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Synthesis and characterization of novel 2-(1-benzyl-3-[4-fluorophenyl]-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives

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Abstract

Novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**. The base catalyzed condensation of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** gave (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e**. On cyclization with dimethyl sulfoxide (DMSO)/I_2, compounds **5a** to **5e** gave 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e**. Structures of all novel compounds were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and mass spectral data. All the synthesized compounds were screened for their antibacterial activities.

1 | INTRODUCTION

Chromones (4*H*-1-benzopyran-4-one, 4*H*-chromen-4-one) are the heterocyclic compound widely distributed in nature.[1] Chromone-containing compounds display various pharmacological properties such as antifungal,[2] antimalarial,[3] anticancer,[4] antibacterial,[5] and are also well known as an antidiabetic and cardiovascular agents.[6,7] Pyrazole-containing compounds show antiangiogenic,[8] antimalarial,[9] antifungal,[10] antitubercular,[11] antimicrobial,[11] and anticancer[12] activities.

Currently, there are more than 200 pharmaceutical drugs available in market containing fluorine atom. Fluorine and fluorine-containing substituent can impart many effects on properties of organic compounds.[13,14] Fluorine-containing compounds exhibit fungicidal,[15] herbicidal,[16] antiviral,[17] antipyretic,[18] and analgesic[19] activities.

Considering the biological importance of chromone, pyrazole, and fluorine nucleus, we have reported the synthesis, characterization, and antibacterial screening of novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**, (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** and 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives **6a** to **6e**.

2 | RESULT AND DISCUSSION

1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via the Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**.[20] (*E*)-3-(1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** were synthesized from the reaction of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** in 10% aq. KOH. The synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-

7-fluoro-4*H*-chromen-4-ones **6a** to **6e** was achieved by reaction of (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** with dimethyl sulfoxide (DMSO)/I_2 (Scheme 1 and Section 3).

Structures of all the synthesized compounds were confirmed by using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and liquid chromatography-mass spectrometry (LC-MS) spectroscopic techniques.

2.1 | Antibacterial activities

All the synthesized compounds were screened for their antibacterial activities. The bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* were used. The zone of inhibition in millimeter was determined by the well diffusion method at 1 mg/mL of concentration, and Ampicillin was used as reference drugs. The results of antibacterial activity are shown in Table 1.

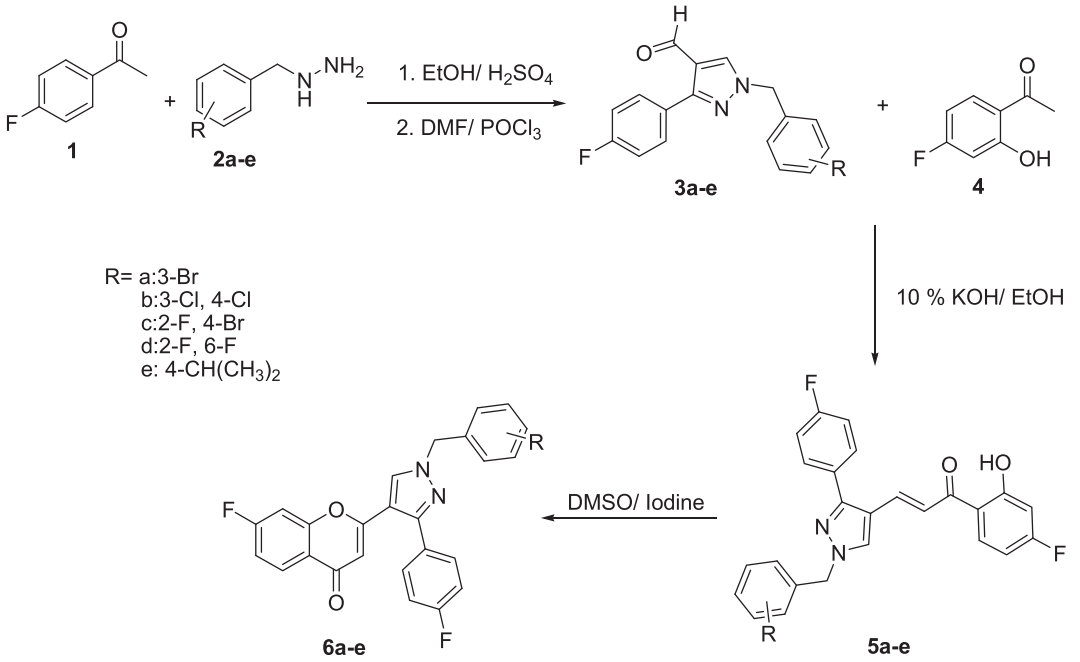
The results given in Table 1 indicated that compounds **3c**, **3d**, **3d**, **6a**, **6b**, **6c**, and **6d** exhibited good antibacterial activity against *E. coli* bacterial strain. Compounds **3c** to **3e**, **5e**, and **6a** to **6e** exhibited good antibacterial activity against *P. aeroginosa*. While compounds **3e** and **6a** to **6d** exhibited good antibacterial activity against *B. subtilis* and *S. aureus* compared with the standard Ampicillin. While other compounds were found to be less to moderately active against all bacterial strains.

3 | EXPERIMENTAL

The melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (attenuated total reflection [ATR]) Fourier transform infrared (FTIR) spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian 400 spectrophotometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent, and chemical shifts were expressed as δ parts per million units. Mass spectra were obtained on Shimadzu (LC-MS) mass spectrometer.

3.1 | General procedure for synthesis of 1-benzyl-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehydes (3a-e)

A mixture of substituted 1-benzylhydrazine (0.01 mol) and catalytic amount of concencentated H_2SO_4 was added to a solution of 1-(4-fluorophenyl)ethanone (0.01 mol) in 20 mL of ethanol. The mixture was refluxed for 1 hour, and the 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine formed was filtered and dried. A mixture of dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) was cooled with constant stirring at 0°C. A solution of 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine in DMF was added dropwise to the reaction mixture and then heated at 70 to 80°C for 5 hours. After completion of reaction, contents were cooled to room temperature and poured onto ice-cold water, and then it was made alkaline with saturated K_2CO_3 solution. The



SCHEME 1 Synthetic approach to the title compounds

TABLE 1 Antibacterial activities of the synthesized compounds (zone of inhibition in millimeter)

Compound	*Escherichia coli*	*Pseudomonas aeroginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
3a	8	10	10	12
3b	9	10	10	11
3c	14	13	12	12
3d	15	14	12	13
3e	16	15	14	17
5a	9	11	12	11
5b	9	10	10	12
5c	8	10	10	9
5d	10	11	10	9
5e	12	14	13	12
6a	16	15	14	16
6b	14	15	14	16
6c	16	14	16	17
6d	14	15	15	16
6e	12	14	9	10
Ampicillin	16	15	17	18

precipitate formed was crystallized from ethanol to get pure 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a-e**.

3.2 | 1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3a)

Yield: 71%, White solid, mp 58-60°C. IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.45 (s, 2H, —CH_2), 7.25-7.35 (m, 4H, Ar—H), 7.52-7.60 (m, 2H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.92, 115.17, 115.38, 120.48, 127.96, 128.36, 130.10, 130.52, 130.61, 130.85, 131.24, 137.09, 138.35, 150.91, 161.21, 163.66, 184.33; MS (LC-MS): *m/z* 358.95 $(M + H)^+$.

3.3 | 1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3b)

Yield: 65%, White solid. mp 190-192°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 7.26-7.36 (m, 3H, Ar—H), 7.64-7.68 (m, 2H, Ar—H), 7.86-7.89 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); MS (LC-MS): *m/z* 349 $(M + H)^+$.

3.4 | 1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3c)

Yield: 69%; White solid; mp 64-66°C; IR (ν_{max}/cm^{-1}): 3113 (═C—H), 2822 (aldehyde C—H), 1673 (C═O), 1656 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 7.29 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.35 (t, 1H, *J* = 8 Hz, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.66, 115.40, 115.62, 116.20, 116.42, 119.34, 119.58, 121.08, 121.23, 123.26, 123.35, 127.44, 127.85, 128.02, 128.05, 130.53, 130.61, 131.57, 131.60, 131.77, 131.86, 134.57, 152.82, 159.01, 161.53, 161.97, 164.45, 184.20; MS (LC-MS): *m/z* 376.95 $(M + H)^+$.

3.5 | 1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3d)

Yield: 61%; White solid; mp 68-70°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2824 (aldehyde C—H), 1677 (C═O), 1654 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 2H, —CH_2), 7.18 (t, 2H, *J* = 8 Hz, Ar—H), 7.26 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.50 (t, 1H, *J* = 8 Hz, Ar—H), 7.83 (m, 2H, Ar—H), 8.66 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.32, 111.38, 111.57, 111.75, 112.00, 115.17, 115.38, 120.24,

127.96, 130.49, 130.57, 131.43, 131.53, 131.64, 138.50, 150.59, 159.75, 161.20, 162.15, 163.64, 184.38; MS (LC-MS): *m/z* 317.05 $(M + H)^+$.

3.6 | 1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3e)

Yield: 64%; White solid; mp 52-54°C; IR (ν_{max}/cm^{-1}): 3111 (=C—H), 2821 (aldehyde C—H), 1672 (C=O), 1656 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.1 (d, 6H, —CH_3), 2.8 (m, 1H, —CH), 5.4 (s, 2H, —CH_2), 7.23-7.30 (m, 6H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); MS (LC-MS): *m/z* 323.05 $(M + H)^+$.

3.7 | General procedure for synthesis of (E)-3-(1-Benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-ones (5a-e)

A mixture of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** (0.005 mol) with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** (0.005 mol) was stirred in ethanolic KOH (10%) for 16 hours at room temperature. After completion of reaction, contents were poured onto ice-cold water and then acidified with concentrated hydrochloric acid (HCl). The precipitate formed was filtered off, washed with water, and crystallized from ethanol to get the pure product **5a-e**.

3.8 | (E)-3-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5a)

Yield: 74%; Yellow solid; mp 80-82°C; IR (ν_{max}/cm^{-1}): 1637 (C=O), 1590 (C=N), 1569 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.33-7.39 (m, 4H, Ar—H), 7.53-7.61 (m, 4H, Ar—H), 7.70-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =C—H), 8.21 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.75 (s, 1H, pyrazolyl-H), 13.09 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.73, 104.12, 104.36, 106.79, 107.02, 115.65, 115.86, 117.58, 119.62, 121.84, 126.97, 128.52, 130.36, 130.44, 130.63, 130.90, 132.31, 133.04, 133.16, 135.87, 139.10, 151.29, 161.01, 163.46, 164.46, 164.60, 165.14, 167.67, 192.09; MS (LC-MS): *m/z* 495.10 $(M + H)^+$.

3.9 | (E)-3-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5b)

Yield: 72%; Yellow solid; mp 158-160°C; IR (ν_{max}/cm^{-1}): 1641 (C=O), 1594 (C=N), 1524 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.81-6.87 (m, 2H, Ar—H), 7.33-7.44 (m, 3H, Ar—H), 7.59 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.66-7.68 (m, 2H, Ar—H), 7.69-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.19 (t, 1H, *J* = 8 Hz, Ar—H), 8.73 (s, 1H, pyrazolyl-H), 13.07 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.34, 104.98, 105.22, 106.86, 107.08, 115.76, 115.97, 116.83, 118.83, 127.23, 128.22, 129.90, 129.97, 130.48, 130.56, 131.06, 131.49, 131.60, 132.92, 133.22, 135.43, 136.10, 152.44, 166.03, 166.18, 192.06; MS (LC-MS): *m/z* 485.05 $(M + H)^+$.

3.10 | (E)-3-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5c)

Yield: 71%; Yellow solid; mp 118-120°C; IR (ν_{max}/cm^{-1}): 1638 (C=O), 1587 (C=N), 1574 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.48 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.32-7.40 (m, 3H, Ar—H), 7.48 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.57 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.63 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.69-7.82 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.23 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 13.10 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.07, 104.13, 104.37, 106.82, 107.03, 115.66, 115.74, 115.87, 117.60, 118.92, 119.16, 119.67, 121.97, 122.07, 122.64, 122.79, 128.00, 128.46, 130.39, 130.47, 132.29, 132.38, 132.43, 133.12, 133.23, 135.80, 151.35, 158.82, 161.02, 161.32, 163.47, 164.47, 164.60, 165.16, 167.68, 192.13; MS (LC-MS): *m/z* 515 $(M + H)^+$.

3.11 | (E)-3-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5d)

Yield: 74%; Yellow solid; mp 184-186°C; IR (ν_{max}/cm^{-1}): 1640 (C=O), 1596 (C=N), 1568 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.17 (t, 2H, *J* = 8 Hz, Ar—H), 7.33 (t, 2H, *J* = 8 Hz, Ar—H), 7.48-7.56 (m, 3H, Ar—H), 7.7 (d, 1H, *J* = 15.8 Hz, =C—H), 7.83 (d, 1H, *J* = 15.6 Hz, =C—H), 8.26 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.14 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.47, 104.09, 104.32, 106.73, 106.95, 111.37, 111.56,

111.75, 111.93, 111.99, 115.59, 115.65, 115.81, 117.45, 119.49, 128.45, 128.48, 130.37, 130.45, 131.37, 131.47, 131.57, 132.10, 133.17, 133.28, 135.82, 151.32, 159.71, 159.79, 161.02, 162.20, 162.27, 163.47, 164.63, 164.77, 165.19, 167.71, 193.20; MS (LC-MS): m/z 453.15 $(M + H)^+$.

3.12 | (E)-3-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5e)

Yield: 77%; Yellow solid; mp 130-132°C; IR (ν_{max}/cm^{-1}): 1635 (C═O), 1595 (C═N), 1567 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 1.17 (d, 6H, CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.25-7.37 (m, 6H, Ar—H), 7.57-7.61 (m, 2H, Ar—H), 7.70-7.81 (AB quartet, 2H, J = 15.8 Hz, ═C—H), 8.23 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.13 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.75, 33.12, 55.41, 104.13, 104.36, 106.79, 107.01, 115.63, 115.75, 115.84, 117.56, 119.36, 126.06, 127.92, 128.63, 130.35, 130.43, 132.01, 133.06, 133.17, 133.90, 136.05, 148.22, 151.04, 160.98, 163.42, 164.49, 164.63, 165.14, 167.67, 192.13; MS (LC-MS): m/z 459.15 $(M + H)^+$.

3.13 | General procedure for synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-ones (6a-e)

Compound **5a** to **5e** (0.002 mol) was dissolved in 15-mL DMSO. To this solution, catalytic amount of iodine was added. The reaction mixture was heated to 140°C for 2 hours. After completion of reaction (checked by thin-layer chromatography [TLC]), content were cooled and poured over crushed ice. The product obtained was filtered, washed with cold water and 10% sodium thiosulphate solution followed by cold water, and crystallized from ethanol to get the pure product **6a** to **6e**.

3.14 | 2-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6a)

Yield: 77%; White solid; mp 200-202°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 1641 (C═O), 1622 (C═N), 1597 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (dd, 1H, J = 8 and 2 Hz, Ar—H), 7.30-7.62 (m, 9H, Ar—H), 8.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.71 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.87, 104.56, 104.82, 107.24, 110.95, 112.30, 113.82, 115.32, 115.54, 116.69, 119.55, 120.72, 122.07, 127.24, 127.74, 127.84, 129.20, 130.97, 131.12, 133.66, 139.25, 149.39, 158.12, 158.50, 158.89, 159.28, 159.63, 163.82, 175.80; MS (LC-MS): m/z 495.10 $(M + H)^+$.

3.15 | 2-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6b)

Yield: 65%; White solid; mp 148-150°C; IR (ν_{max}/cm^{-1}): 3059 (═C—H), 1645 (C═O), 1620 (C═N), 1598 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (d, 1H, J = 8 Hz, Ar—H), 7.27-7.70 (m, 8H, Ar—H), 8.19 (t, 1H, J = 8 Hz, Ar—H), 8.70 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.13, 104.83, 107.23, 110.87, 113.74, 115.32, 115.54, 116.61, 120.59, 127.80, 128.53, 129.00, 130.25, 131.06, 131.39, 133.71, 137.48, 157.96, 158.34, 158.73, 159.10, 175.70; MS (LC-MS): m/z 483.10 $(M + H)^+$.

3.16 | 2-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6c)

Yield: 69%; White solid; mp 220-222°C; IR (ν_{max}/cm^{-1}): 3065 (═C—H), 1643 (C═O), 1620 (C═N), 1594 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.31 (s, 1H), 7.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 7.25-7.78 (m, 8H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.46, 104.43, 104.69, 107.01, 111.87, 113.66, 113.89, 115.14, 115.35, 118.85, 119.09, 120.41, 121.87, 121.96, 122.62, 122.77, 127.48, 127.59, 127.96, 128.77, 130.43, 130.83, 130.91, 132.24, 133.50, 149.04, 156.26, 156.40, 158.73, 159.23, 161.01, 161.24, 163.46, 165.97, 175.44; MS (LC-MS): m/z 513.10 $(M + H)^+$.

3.17 | 2-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6d)

Yield: 72%; White solid; mp 140-142°C; IR (ν_{max}/cm^{-1}): 3110 (═C—H), 1648 (C═O), 1622 (C═N), 1594 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.51 s (2H, —CH_2), 6.31 (s, 1H), 7.16-7.57 (m, 9H, Ar—H), 8.04 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.66 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.31, 104.41, 104.66, 106.95, 111.43, 111.70, 111.75, 111.93, 113.58, 113.80, 115.09, 115.30, 120.38, 127.43, 127.54, 128.80, 130.81, 130.89, 131.44, 131.54, 133.25, 148.96, 156.23, 156.37, 159.17, 159.74, 161.00, 162.16, 163.44, 165.94, 175.41; MS (LC-MS): m/z 451.05 $(M + H)^+$.

3.18 | 2-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6e)

Yield: 67%; White solid; mp 280-282°C; IR (ν_{max}/cm^{-1}): 3066 (=C—H), 1644 (C=O), 1620 (C=N), 1592(C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18 (d, 6H, —CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.30 (s, 1H), 7.18-7.36 (m, 8H, Ar—H), 7.58-7.62 (m, 2H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.68 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.76, 33.12, 55.20, 104.44, 104.70, 106.90, 111.81, 113.67, 113.90, 115.16, 115.37, 120.44, 126.57, 127.52, 127.98, 128.98, 130.85, 130.93, 133.17, 133.83, 148.22, 148.76, 156.30, 156.43, 159.46, 161.00, 163.44, 165.99, 175.46; MS (LC-MS): m/z 457.15 $(M + H)^+$.

4 | CONCLUSION

In conclusion, we have synthesized a series of novel 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e** from 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**. All synthesized compounds are characterized by using spectral methods and screened for their antibacterial activities.

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SUPPORTING INFORMATION

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Microwave Assisted Synthesis and Antibacterial Activity of New 1,3,4-Thiadiazoles and 1,2,4-Triazoles Derived from 2-{2-[2-(4-Fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide

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Abstract—A series of novel derivatives of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide, 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol and 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]-imidazol-1-yl}methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine have been synthesized by the conventional method as well as using MW irradiation. All newly synthesized compounds have been tested for antibacterial activity. Several products have demonstrated moderate activity against gram positive and gram negative bacterial strains.

Keywords: 1,3,4-thiadiazole, 1,2,4-triazole, microwave irradiation, antibacterial activity

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Antimycobacterial and antimicrobial activities have been well established and studied in depth for benzimidazole [1, 2], thiazole [3, 4], 1,3,4-thiadiazole [5–7], and 1,2,4-triazole [8, 9] derivatives.

Pharmacological importance associated with those compounds inspired us to synthesize novel benzimidazole and thiazole containing 1,3,4-thiadiazoles and 1,2,4-triazoles under conventional and MW irradiation. All newly synthesized compounds were evaluated for their antibacterial activity.

RESULTS AND DISCUSSION

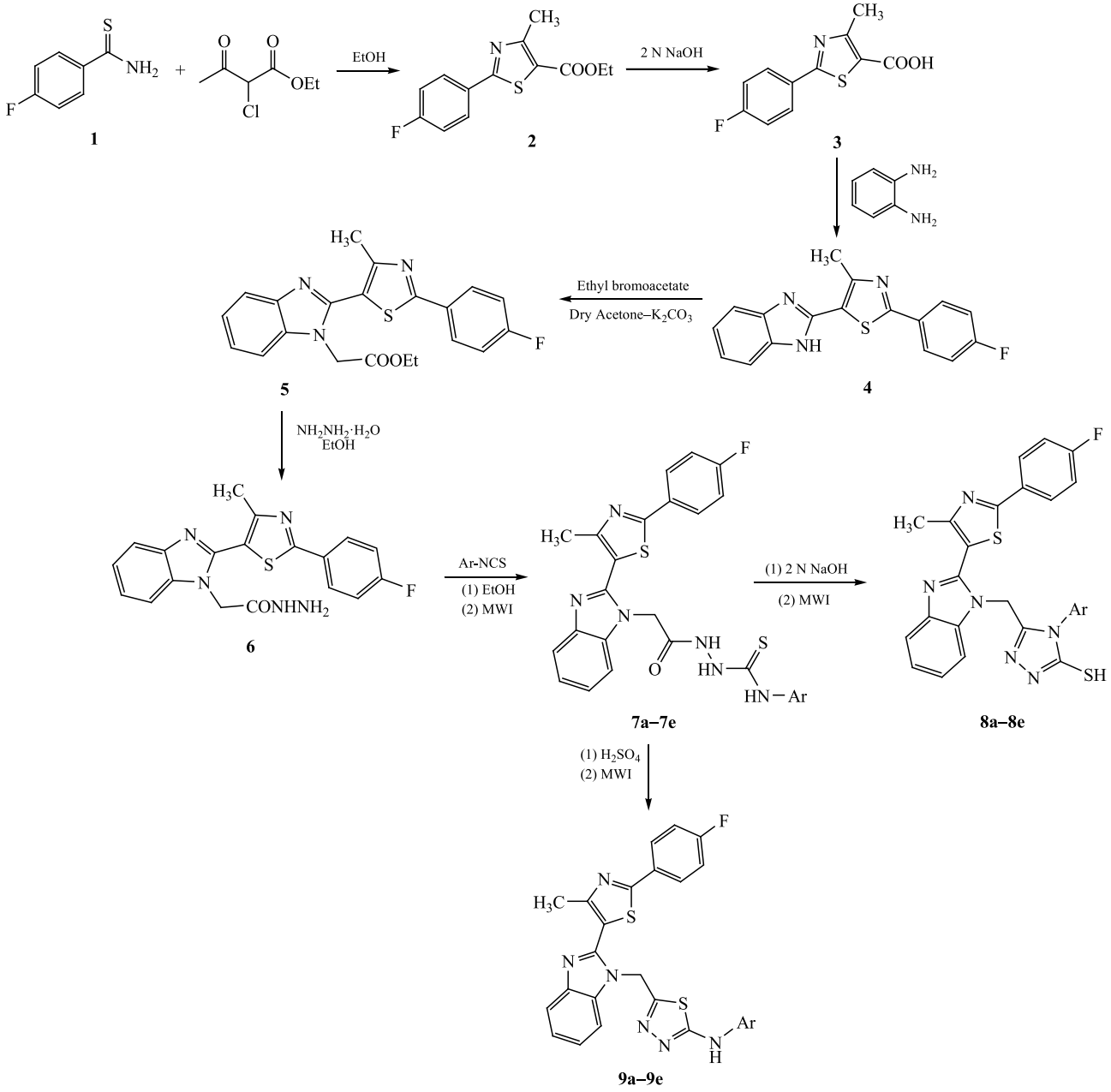
Synthesis of 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide **6** was carried out by the known method (Scheme 1) [10–12].

A novel series of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide **7a**–**7e** was synthesized from the intermediate **6** and substituted aryl isothiocyanates by conventional method and under MW irradiation [10, 13]. Their molecular structures were supported by IR, ^{1}H and ^{13}C NMR spectra. Reaction of compounds **7a**–**7e** in presence of NaOH under conventional conditions or MW irradiation gave 1,2,4-triazole derivatives **8a**–**8e** [10, 13]. In IR spectra of the products **8a**–**8e** no bands at ca. 3100 cm^{-1} characteristic for –NH group were recorded. In ^{1}H NMR spectra of those compounds characteristic singlets of S–H were recorded at ca. 14.00 ppm. Similar reaction of compounds **7a**–**7e** in acidic media under conventional conditions or MW irradiation gave 1,3,4-thiadiazoles **9a**–**9e** [10, 13]. The NH group of compound **9a** was recorded in IR spectrum by the band at 3201 cm^{-1} and in ^{1}H NMR spectrum by a singlet at 9.50 ppm.

The MW irradiation method proved to be more efficient in the synthesis of thiosemicarbazides **7a**–**7e**, 1,2,4-triazoles **8a**–**8e** and 1,3,4-thiadiazoles **9a**–**9e** derivatives than the conventional heating. It reduced the reaction time from hours to 5–10 min and increased the products yield up to 77–88% over the conventional method (60–74%) (Table 1).

***In vitro* antibacterial activity.** All the synthesized compounds were tested against gram positive bacterial

Scheme 1. Synthesis of derivatives of thiosemicarbazide (**7a**–**7e**), 1,2,4-triazole (**8a**–**8e**), and 1,3,4-thiadiazole (**9a**–**9e**).



Ar: 3-Chlorophenyl (**a**), 2-chlorophenyl (**b**), 2,4-dichlorophenyl (**c**), 4-chlorophenyl (**d**), 3,4-dichlorophenyl (**e**).

strains *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2063), and gram negative bacterial strains *Escherichia coli* (NCIM 2810)*, Salmonella abony* (NCIM 2257). The zone of inhibition in mm was determined by the well diffusion method at concentration of 1 mg/ mL, and Ciprofloxacin was used as the reference drug (Table 2). Compounds **7a**, **7d**, **7e**, **8d**, and **9e** demonstrated moderate activity against both gram positive and gram negative bacteria while other compounds were characterized by low activity or none.

EXPERIMENTAL

All organic solvents and reagents were acquired from commercial sources and used as received. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in a Raga's synthetic microwave oven.

Table 1. Synthesis data for the products

Comp. no.	Ar	Conventional method		Microwave method	
		time, min	yield, %	time, min	yield, %
7a	3-Chlorophenyl	90	74	7.0	88
7b	2-Chlorophenyl	90	70	6.5	85
7c	2,4-Dichlorophenyl	90	75	7.5	84
7d	4-Chlorophenyl	90	68	8.0	82
7e	3,4-Dichlorophenyl	90	72	9.5	87
8a	3-Chlorophenyl	150	65	8.5	80
8b	2-Chlorophenyl	150	68	9.0	78
8c	2,4-Dichlorophenyl	150	62	8.0	81
8d	4-Chlorophenyl	150	66	7.5	83
8e	3,4-Dichlorophenyl	150	70	8.5	79
9a	3-Chlorophenyl	240	68	9.0	77
9b	2-Chlorophenyl	240	62	9.5	85
9c	2,4-Dichlorophenyl	240	67	8.5	83
9d	4-Chlorophenyl	240	60	8.5	78
9e	3,4-Dichlorophenyl	240	66	8.0	81

Table 2. Antibacterial tests data for the synthesized compounds

Compound	Zone of inhibition, mm			
	S. aureus	*B. subtilis*	*E. coli*	*S. abony*
7a	16	15	14	17
7b	15	11	–	15
7c	15	14	–	13
7d	15	13	14	15
7e	16	16	17	16
8a	–	–	–	12
8b	–	–	11	10
8c	–	–	13	–
8d	15	17	13	18
8e	–	–	10	10
9a	11	12	12	16
9b	13	12	14	13
9c	12	12	14	–
9d	11	12	12	13
9e	13	15	14	16
Ciprofloxacin	23	28	26	40

FTIR spectra were recorded on a Shimadzu IR Affinity 1S (ATR) spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Advance 400 spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a Waters, Q-TOF micromass (ESI-MS) mass spectrometer.

Synthesis of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide (7a–7e). *Conventional method.* Equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanate **5** were dissolved in 15 mL of ethanol and refluxed for 90 min. Reaction progress was monitored by TLC. Upon completion of the reaction the solid product was filtered off and crystallized from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 1).

Microwave method. The mixture of equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanates **5** was dissolved in 15 mL of ethanol and subjected to MW irradiation for 5 to 10 min at 350 W. Reaction progress was monitored by TLC. Upon completion of the reaction the precipitated product was filtered off and crystallized

from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 2).

4-(3-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7a). White solid, mp 194–196°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3277 (N–H), 3248 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 9.99 s (1H, NH), 9.80 s (1H, NH), 8.05 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.58 d (2H, *J* = 8 Hz, ArH), 7.19–7.40 m (7H, ArH), 5.07 s (2H, CH_2), 2.51 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 162.25, 155.01, 145.38, 142.48, 140.42, 135.87, 132.21, 129.76, 129.14, 128.64, 128.55, 123.14, 122.52, 119.29, 118.91, 116.50, 116.27, 110.98, 45.56, 16.47. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3365 (N–H), 3277 (N–H), 3245 (N–H), 1674 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.55 s (1H, NH), 9.98 s (1H, NH), 9.60 s (1H, NH), 8.05 d. d (2H, *J* = 5.2 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.29–7.57 m (9H, ArH), 5.06 s (2H, CH_2), 2.52 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 155.01, 145.37, 142.48, 135.87, 129.39, 129.14, 128.66, 128.57, 127.21, 123.09, 122.51, 119.27, 118.94, 116.48, 116.26, 111.01, 45.50, 16.48. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7c), White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3366 (N–H), 3275 (N–H), 3246 (N–H), 1671 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.52 s (1H, NH), 10.03 s (1H, NH), 9.58 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.4 Hz, ArH), 7.71 d (1H, *J* = 8 Hz, ArH), 7.66 s (1H, ArH), 7.25–7.52 m (7H, ArH), 5.02 s (2H, CH_2), 2.48 s (3H, CH_3). LC-MS: *m/z*: 585 $[M + H]^+$.

4-(4-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7d). White solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3278 (N–H), 3247 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.46 s (1H, NH), 9.89 s (1H, NH), 9.74 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.71 d (1H, *J* = 7.6 Hz, ArH), 7.54 d (1H, *J* = 8 Hz, ArH), 7.41 d (2H, *J* = 7.6 Hz, ArH), 7.25–7.36 m (6H, ArH), 5.04 s (2H, CH_2), 2.48 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.25, 162.28, 155.02, 145.42, 142.49, 137.91, 135.88, 129.16, 128.67, 128.58, 128.09, 123.18, 122.54, 119.31, 118.94, 116.51, 116.29, 110.98, 45.57, 16.48. LC-MS: *m/z*: 551 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7e). White solid, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3276 (N–H), 3244 (N–H), 1671 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 10.07 s (1H, NH), 9.88 s (1H, NH), 7.29–8.05 m (11H, ArH), 5.07 s (2H, CH_2), 2.50 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.21, 164.73, 162.25, 154.99, 145.38, 142.48, 139.09, 135.84, 129.95, 129.10, 128.62, 128.53, 123.14, 122.52, 119. 29, 118.90, 116.47, 116.25, 110.95, 45.55, 16.45. LC-MS: *m/z*: 585 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8a–8e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 10 mL of 2 N NaOH solution was refluxed for 2.5 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice and acidified with acetic acid. The product was filtered off and crystallized from ethanol to give the corresponding pure compound **8a**–**8e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 2 N NaOH solution was subjected to MW irradiation at 350W for 5–10 min. Progress of the reaction was monitored by TLC. After completion of the process, the mixture was poured onto crushed ice and acidified with dilute acetic acid. The product was filtered off and crystallized from DMF/water to afford the corresponding pure compound **8a**–**8e** (Table 1).

4-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8a). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2939 (=C–H), 1640 (C=N), 1218 (C–F). ^{1}H NMR spectrum, δ, ppm: 6.99–8.01 m (12H, ArH), 5.50 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.42, 165.99, 162.27, 154.71, 146.50, 144.53, 142.42, 135.27, 135.13, 133.19, 130.51, 128.94, 128.63, 128.54, 127.65, 126.28, 123.15, 122.51, 119.22, 118.71, 116.55, 116.32, 111.21, 40.50, 16.62. LC-MS: *m/z*: 533.11 $[M + H]^+$.

4-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-4*H*-1,2,4-triazole-3-thiol (8b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 2936 (=C–H), 1638 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 7.13–7.99 m (12H, ArH), 5.31 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.87, 154.76, 142.49, 130.81, 129.92, 128.51, 127.92, 122.43, 119.16, 116.57, 116.35, 111.35, 40.12, 16.63. LC-MS: *m/z*: 532.98 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8c). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1635 (C=N), 1221 (C–F). ^1H NMR spectrum, δ, ppm: 7.23–7.97 m (11H, ArH), 5.38 s (2H, CH_2), 2.40 s (3H, CH_3). LC-MS: *m/z*: 567.00 $[M + H]^+$.

4-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4*H*-1,2,4-triazole-3-thiol (8d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2935 (=C–H), 1639 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm**:** 168.51, 166.04, 154.75, 147.24, 144.53, 142.39, 135.16, 134.44, 131.49, 129.41, 129.31, 129.03, 128.65, 128.56, 123.29, 122.65, 119.33, 118.58, 116.59, 116.37, 111.09, 38.88, 16.57. LC-MS: *m/z*: 533.05 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8e). White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1637 (C=N), 1222 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.53, 166.09, 162.30, 154.68, 146.94, 144.47, 142.35, 135.08, 132.63, 131.74, 131.15, 129.54, 129.03, 128.67, 128.59, 127.86, 123.25, 122.67, 119.32, 118.57, 116.55, 116.33, 111.09, 16.64. LC-MS: *m/z*: 567.05 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (9a–9e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 5 mL of conc. H_2SO_4 was stirred for 4 h at RT. After completion of process, the mixture was poured onto crushed ice and neutralized with liquid NH_3, a solid product was formed. It was filtered off and washed with methanol to afford the corresponding pure compound **9a**–**9e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 5 mL of conc. H_2SO_4 was subjected to MW irradiation for 5 to 10 min at 350 W. After completion of the process the mixture was poured onto crushed ice and neutralized with liquid NH_3. The precipitated solid was filtered off and crystallized from water–DMF to afford the corresponding pure thiadiazole **9a**–**9e** (Table 1).

***N*-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9a).** White solid, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3039 (=C–H), 1606 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.5 s (1H, NH), 7.05–8.18 m (12H, ArH), 5.85 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.80, 165.01, 154.67, 144.15, 142.18, 134.57, 129.11, 128.54, 128.19, 127.31, 123.71, 123.02, 122.35, 121.10, 118.99, 118.11, 116.07, 115.85, 110.74, 42.31, 15.98. LC-MS: *m/z*: 533.15 $[M + H]^+$.

***N*-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-1,3,4-thiadiazol-2-amine (9b).** White solid, mp 140–142°C. IR spectrum, ν, cm^{-1}: 3203 (N–H), 3038 (=C–H), 1607 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.17 d (1H, *J* = 8.8 Hz, ArH), 8.01–8.02 m (2H, ArH), 7.72 d. d (2H, *J* = 13.2 and 8 Hz, ArH), 7.26–7.44 m (6H, ArH), 7.03 t (1H, *J* = 7.2 Hz, ArH), 5.84 s (2H, CH_2), 2.47 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.51, 162.30, 155.75, 155.17, 144.65, 142.69, 136.91, 135.08, 129.61, 129.05, 128.69, 128.61, 127.81, 124.22, 123.52, 122.86, 122.70, 121.61, 119.50, 118.61, 116.57, 116.35, 111.25, 42.81, 16.48. LC-MS: *m/z*: 533.10 $[M + H]^+$.

***N*-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9c).** White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3037 (=C–H), 1608 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.29 d (1H, J = 8.4 Hz, ArH), 8.04 m (2H, ArH), 7.74 d. d (2H, *J* = 14.8 and 7.2 Hz, ArH), 7.60 s (1H, ArH), 7.32–7.38 m (5H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.04, 156.19, 155.16, 144.64, 142.68, 136.09, 135.06, 128.89, 128.69, 128.61, 127.80, 126.60, 123.52, 123.02, 122.86, 122.12, 119.50, 118.59, 116.57, 116.35, 111.25, 42.78, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

***N*-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-1,3,4-thiadiazol-2-amine (9d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3039 (=C–H), 1605 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 10.2 s (1H, NH), 8.04 m (1H, ArH), 7.73 d. d (2H, J = 17 and 7.6 Hz, ArH), 7.56 d (1H, J = 8 Hz, ArH), 7.33–7.50 m (4H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 164.66, 162.29, 155.16, 154.64, 144.63, 142.68, 139.13, 135.06, 129.01, 128.84, 128.68, 128.59, 125.41, 123.50, 122.84, 119.49, 118.89, 118.60, 116.55, 116.33, 111.23, 42.80, 16.48. LC-MS: *m/z*: 533.05 $[M + H]^+$.

***N*-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9e).** White solid, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3035 (=C–H), 1604 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 10.5 s (1H, NH), 6.5–8.4 m (11H, ArH), 5.86 s (2H, CH_2), 2.4 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.29, 164.39, 162.35, 155.23, 144.65, 142.69, 140.07, 135.08, 131.25, 130.71, 128.65, 123.50, 123.13, 119.50, 118.56, 117.52, 116.51, 111.20, 42.77, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

CONCLUSIONS

The new series of derivatives of 1,2,4-triazole **8a**–**8e** and 1,3,4-thiadiazole **9a**–**9e** have been synthesized by conventional as well as MW irradiation methods from 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide. MW irradiation at 350 W reduces the reaction time from hours to 5–10 min and increases the yield of products from 60–74 to 77–88%. All the newly synthesized compounds have been tested for their antibacterial activity. Compounds **7a**, **7d**, **7e**, **8d**, and **9e** are characterized by moderate activity against both gram positive and gram negative bacterial strains.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY MATERIAL

Supplementary material are available for this article at https://doi.org/10.1134/S1070363220090200 and are accessible for authorized users.

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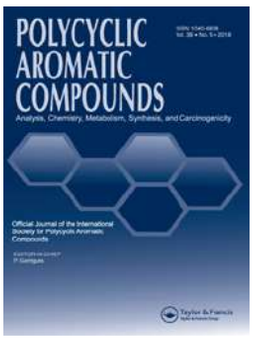

Polycyclic Aromatic Compounds

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Design, Synthesis and Biological Evaluation of Novel Furan & Thiophene Containing Pyrazolyl Pyrazolines as Antimalarial Agents

Hemantkumar N. Akolkar[a], Sujata G. Dengale[b], Keshav K. Deshmukh[b], Bhausaheb K. Karale[a], Nirmala R. Darekar[a], Vijay M. Khedkar[c], and Mubarak H. Shaikh[a]

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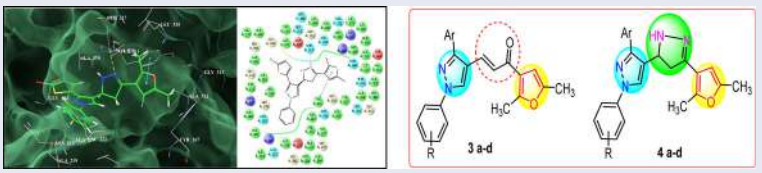
ABSTRACT

In search for novel compounds targeting Malaria, based on the *in silico* molecular docking binding affinity data, the novel furans containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized. The formation of the synthesized compound were confirmed by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Compounds with thiophene and pyrazoline ring **4b** (0.47 μM), **4c** (0.47 μM) and **4d** (0.21 μM) exhibited excellent anti-malarial activity against *Plasmodium falciparum* compared with standard antimalarial drug Quinine (0.83 μM). To check the selectivity furthermore, compounds were tested for antimicrobial activity and none of the synthesized compound exhibited significant potency compared with the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin respectively. So, it can be resolved that the produced compounds show selectively toward antimalarial activity and have the potential to be explored further.



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Introduction

Life-threatening disease Malaria is caused by *Plasmodium* parasites that are spread to people through the bites of infected female Anopheles mosquitoes. Out of five *Plasmodium* Parasites *Plasmodium falciparum* produces high levels of blood-stage parasites that sequester in critical organs in all age groups.[1] As per the World Health Organization report in 2018, in sub Saharan Africa 11 million pregnant women were infected with malaria and 872 000 children were born with a low birth weight. Around 24 million children estimated to be infected with the *P. falciparum* parasite in the region; out of these, 1.8 million had severe anemia and 12 million had

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moderate anemia.[2] Mortality and morbidity caused by malaria are continually increasing. This subject is the consequence of the ever-increasing development of parasite resistance to drugs and also increased mosquito resistance to insecticides which is one of the most critical complications in controlling malaria over recent years.[3]

P. falciparum enoyl-acyl carrier protein (ACP) reductase (ENR) is an enzyme in type II fatty acid synthesis (FAS II) pathway which catalyzes the NADH-dependent reduction of trans-2-enoyl-ACP to acyl-ACP and plays important role in completion of the fatty acid elongation cycles. Due to its role in the parasite's fatty acid pathway, *Pf*ENR has been known as one of the most promising antimalarial targets for structure-based drug design.[4–6] Triclosan, a broadly used antibiotic, is effective inhibitor of *Pf*ENR enzyme activity. Several efforts have been taken in the recent past in the direction of the identification of new antimalarials using pharmacophore modeling, molecular docking and MD simulations.[7–12]

Pyrazole is a well-known class of nitrogen containing heterocyclic compounds and play important role in agricultural and medicinal field. Pyrazole and its derivatives are known to possess antibacterial,[13] antipyretic,[14] fungistatic,[15] anticonvulsant,[16] antitubercular,[17] antipyretic,[18] insecticides,[19] and anti-inflammatory[20] activities. Pyrazoline containing compounds are recognized to possess various pharmacological activities like antimalarial,[21,22] anticancer,[23] anti-inflammatory,[24] analgesic,[24] antitumor,[25] antimicrobial[26] and antidepressant activities.[27] Furan containing compounds possess lipoxygenase inhibitor,[28] urotensin-II receptor antagonists,[29] fungicidal,[30] epidermal growth factor receptor inhibitors and anticancer[31] etc. activities. Chalcone is a natural pigment found in plant and is an important intermediate for the synthesis of flavonoids. Varieties of biological activities are associated with chalcones and their derivatives such as antiplasmodial,[32] nematicide,[33] antiallergenic,[34] antimalarial,[35] anti-HIV,[36] anti-cancer,[37] anti-inflammatory[38] and anti-tuberculosis.[39]

So, considering the biological importance of pyrazoles, furan and chalcone, herein we report the design of a small library of furan containing pyrazolyl pyrazoline derivatives by molecular hybridization approach targeting *Pf*ENR using the *in silico* molecular docking technique. The promising results obtained from this *in silico* study served the basis for the synthesis of these molecules followed by evaluation of their antimalarial potential.

Molecular docking technique plays significant role in lead identification/optimization and in the mechanistic study by predicting the binding affinity and the thermodynamic interactions leading the binding of a ligand to its biological receptor. Thus, with the objective to identify novel leads targeting the crucial antimalarial target *Plasmodium falciparum enoyl-ACP reductase* (*Pf*ENR or FabI) (pdb code: 1NHG), molecular docking was carried out using the GLIDE (Grid-based LIgand Docking with Energetics) program of the Schrodinger Molecular modeling package.[40–42] A small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-3d**, **4a-4d**) was docked against *Pf*ENR. The ensuing docking conformation revealed that these molecules changed a binding mode which is corresponding with the active site of pfENR and were found to be involved in a series of bonded and non-bonded interactions with the residues lining the active site. Their docking scores varied from −6.979 to −8.222 with an average docking score of −7.563 signifying a potent binding affinity to *Pf*ENR. In order to get a quantitative insight into the most significantly interacting residues and their associated thermodynamic interactions, a detailed per-residue interaction analysis was carried out (Table S1, Supporting Information). This analysis showed that the furan containing pyrazolyl chalcones (**3a-d**) (Figure 1) were deeply embedded into the active site of *Pf*ENR engaging in a sequence of favorable *van der Waals* interactions observed with Ile:C369, Phe:C368, IleA323, Ala:A320, Ala:A319, Arg:A318, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Met:A281, Tyr:A277, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110 and Asp:A107 residues through the 1,3-substituted-1*H*-pyrazol-4-yl scaffold while the 1-(2,5-Dimethylfuran-3-yl) prop-2-en-1-one

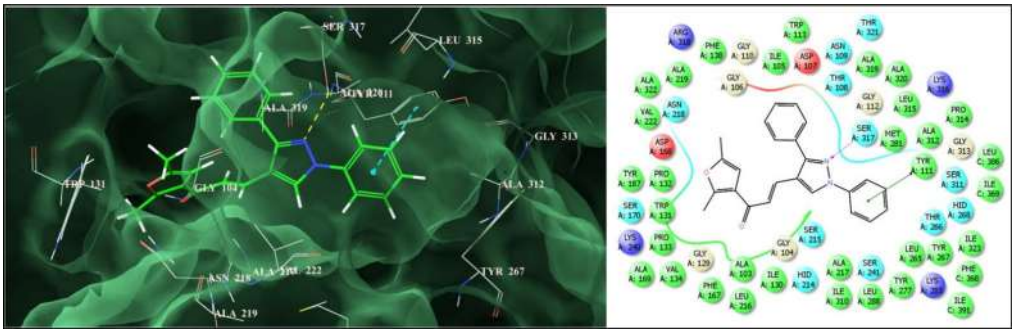


Figure 1. Binding mode of **3a** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

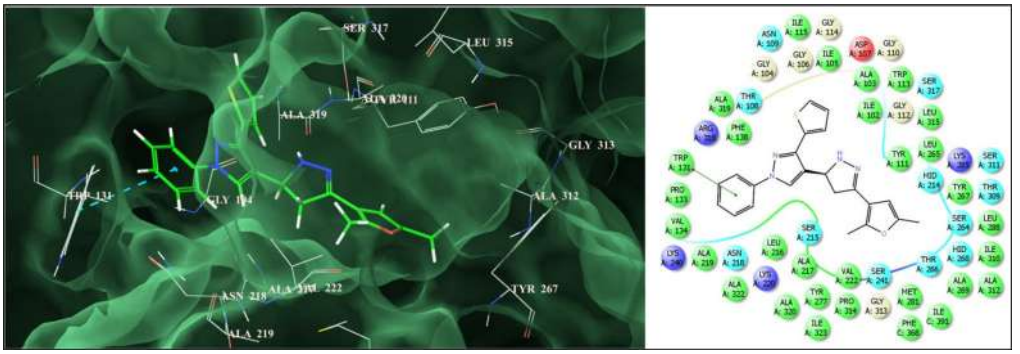
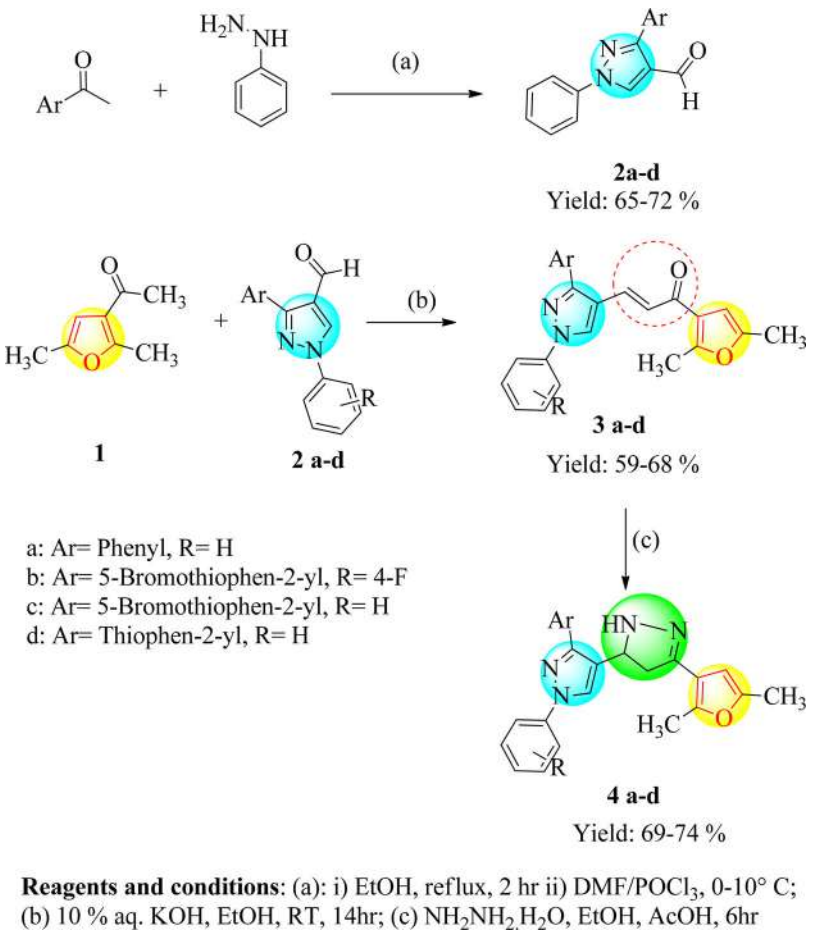


Figure 2. Binding mode of **4d** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

component of the molecules was seen to be involved in similar interactions with Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Gly:A106, Ile:A105, Gly:A104 residues of the active site.

Furthermore the enhanced binding affinity of these molecule is also attributed to significant electrostatic interactions observed with Arg:A318, Ser:A317, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107, Gly:A104 residues lining the active site. On the other hand, the furan containing pyrazoline derivatives (**4a-d**) (Figure 2) were also seen to be stabilized into the active of *Pf*ENR through a network of significant *van der Waals* interactions observed with (2,5-dimethylfuran-3-yl)-1*H*-pyrazolyl scaffold *via* Ile:C369, Phe:C368, Ala:A320, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110, Gly:A106 and Ile:A105 while other half of the molecule i.e., 2-thiophenyl-1-phenyl-1*H*-pyrazole showed similar type of interactions with IleA323, Ala:A319, Arg:A318, Met:A281, Tyr:A277, Val:A222, Ala:A219, Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Ile:A130, Trp:A113, Asp:A107, Gly:A104 residues.

Further the enhanced binding affinity of the molecules is also attributed to favorable electrostatic interactions observed with Arg:A318, Ser:A317, Glu:A289, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107 and Gly:A104. While these non-bonded interactions (*van der Waals* and electrostatic) were observed to be the major driving force for the mechanical interlocking of these novel furan containing pyrazolyl pyrazoline derivatives into the active site *Pf*ENR, the enhanced binding affinity of these molecules is also contributed by very prominent hydrogen bonding interaction observed for **3a** (Ser:A317(2.708 Å)), **4a** (Ser:A317(2.783 Å)), **4b** (Ser:A317(2.462 Å)) and **4c** (SerA317(2.462 Å)). Furthermore these



Scheme 1. Synthesis of pyrazolyl chalcones (**3a-d**) and pyrazolyl pyrazolines (**4a-d**).

molecules were also engaged in a very close π-π stacking interactions: **3a**: Tyr: A111(2.669 Å), **3b**: Tyr:A267(2.529 Å), **3c**: Tyr:A267(2.541 Å), **3d**: Tyr:A267(2.335 Å), **4a**: Tyr:A111(2.602 Å), **4b**: Trp:A131(2.073 Å), **4c**: TyrA:111(2.073 Å) and **4d**: TrpA131(2.538 Å) (Figures S1–S6, Supporting Information).

This type of bonded interactions i.e., hydrogen bonding and π-π stacking are known to serve as an "anchor" to guide the alignment of a molecule into the 3D space of enzyme's active site and facilitate the non-bonded interactions (*Van der Waals* and electrostatic) as well. Overall, the in-silico binding affinity data suggested that these furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) could be developed as novel scaffold to arrive at compounds with high selectivity and potency *Plasmodium falciparum*.

Results and discussion

Chemistry

The novel series of furan containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized from commercially available starting materials (Scheme 1). Initially, pyrazole aldehyde **2a-d** was formed by the condensation between substituted acetophenone and phenyl

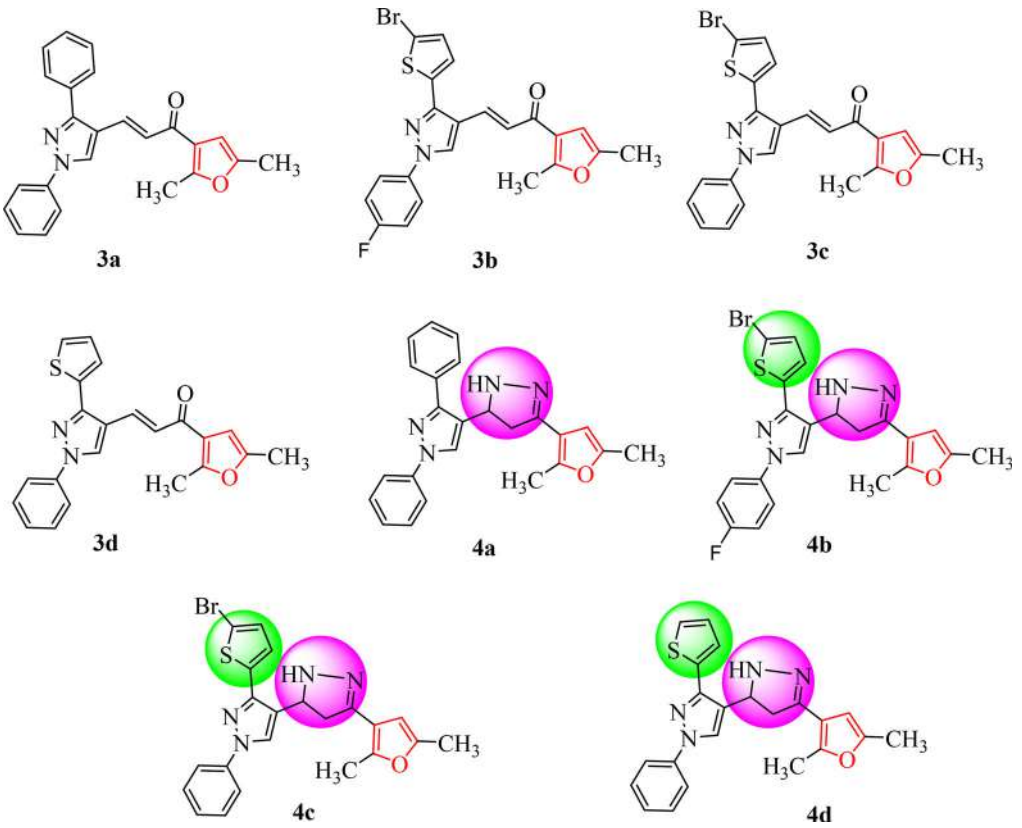


Figure 3. The newly synthesized compounds structure **3a-d** & **4a-d**.

hydrazine followed by Vilsmeier-Haack formylation reaction (Scheme 1). Then furan containing pyrazolyl chalcones **3a-d** were synthesized by base-catalyzed Claisen-Schmidt condensation of 1-(2,5-dimethylfuran-3-yl)ethanone **1** and substituted pyrazole aldehyde **2a-d**.[43] Finally, the furan containing pyrazolyl chalcones **3a-d** and hydrazine hydrate in ethanol solvent using catalytic amount of acetic acid at reflux condition for 6 hr afforded the corresponding pyrazolyl pyrazolines (**4a-d**) in quantitative isolated yield (69–74%) (Scheme 1).

The newly synthesized compounds structures were shown in Figure 3. The newly synthesized compound's structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data. For compound **3a**, in IR spectrum the stretching band for C = O was detected at 1657 cm^{-1}. In the ^{1}H NMR spectrum of compound **3a**, the proton of pyrazole and furan ring resonate as a singlet at δ 9.31 and δ 6.60 ppm respectively. Also, singlet for two $-CH_3$ were observed at δ 2.27 and δ 2.50 ppm. The ^{13}C NMR spectrum of compound **3a** showed signal at δ 184.41 ppm due to C = O and δ 12.89 and δ 13.93 ppm is due to two $-CH_3$. Mass spectrum confirms the formation of compound **3a** showed m/z = 369 $(M+H)^{+}$.

Secondly, in the IR spectrum of compound **4a**, –N–H stretching band observed at 3252 cm^{-1}. The 1H NMR spectrum of compound **4a**, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 2.88 ppm and 3.35 ppm. The CH proton appeared as triplet at δ 4.87 ppm due to vicinal coupling with two protons of the methylene group. In the ^{13}C NMR spectra of the compound **4a** carbons of the pyrazoline ring were observed at δ 41.97 ppm and 54.67 ppm. All the other aromatic and aliphatic protons and carbons were observed at expected regions. Mass spectrum confirms the formation of compound **4a** showed m/z = 383 $(M+H)^{+}$.

Table 1. Antimalarial (μM), Antibacterial (MIC in μg/mL) & Antifungal (MIC in μg/mL) activity.

Cpd	Antimalarial activity Plasmodium falciparum	Antibacterial activity				Antifungal activity			Molecular Docking Score
		EC	PA	SA	SP	CA	AN	AC	
3a	1.46	200	200	250	250	500	500	500	−7.814
3b	3.93	100	250	250	200	1000	500	500	−7.032
3c	2.16	62.5	200	125	250	500	>1000	>1000	−7.192
3d	3.07	100	100	200	200	1000	500	500	−7.118
4a	6.31	125	100	100	100	500	500	500	−6.979
4b	0.47	100	200	100	100	250	500	500	−8.157
4c	0.47	125	125	200	200	1000	>1000	>1000	−8.222
4d	0.21	200	100	125	100	500	500	500	−7.988
Chloroquine	0.06	–	–	–	–	–	–	–	–
Quinine	0.83	–	–	–	–	–	–	–	–
CP	–	50	50	50	50	–	–	–	–
NS	–	–	–	–	–	100	100	100	–

Cpd: Compound; EC: Escherichia coli; PA: Pseudomonas aeruginosa; SA: Staphylococcus aureus; SP: Streptococcus pyogenes; CA: Candida albicans; AN: Aspergillus niger; AC: Aspergillus clavatus; CP: Chloramphenicol; NS: Nystatin.

Biological evaluation

In vitro antimalarial screening

All the synthesized novel compounds were tested for antimalarial activities. The *in vitro* antimalarial assay was carried out according to the micro assay protocol of Rieckmann and coworkers with minor modifications.[44–47] The results were recorded as the minimum inhibitory concentrations (μM MIC) chloroquine and quinine were used as the reference drug (Table 1).

Herein, we have synthesized four chalcone and pyrazoline derivatives respectively. Structure activity relationship (SAR) plays very important role while displaying the antimalarial activity. All the synthesized chalcone derivatives (**3a-d**) exhibited less potency compared to the standard drug. But pyrazoline derivatives exhibited excellent antimalarial activity compared to the standard drug. In compound **4a**, thiophene ring was absent and pyrazoline ring is present, so, the compound **4a** exhibited less potency compared to the standard drug. Now, in compound **4b**, bromo substituted thiophene and pyrazoline rings are present along with the fluorine at the para position on benzene ring. Interestingly, this compound **4b** (0.47 μM), exhibited excellent activity compared to the standard drug quinine (0.83 μM). Again, in compound **4c**, bromo substituted thiophene and pyrazoline rings are present but no fluorine at the para position of benzene ring. Though fluorine is absent on benzene ring in compound **4c** (0.47 μM), it exhibited same potency as that of compound **4b** compared to the standard drug quinine (0.83 μM). Finally, in compound **4d**, there were no substitution on the thiophene and benzene ring. In compound **4d** plane thiophene, plane benzene ring and pyrazoline ring constructed in a single molecular framework. Compound **4d** (0.21 μM), exhibited four-fold more antimalarial activity compared to the standard drug quinine (0.83 μM). From SAR, we can conclude that for the antimalarial activity thiophene, pyrazoline and benzene ring were very important in a single molecular framework.

Antimicrobial activities

Further, all the novel synthesized compounds were also screened for antimicrobial activities against the bacterial strains *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 1688), *Streptococcus pyogenes* (MTCC 442) and fungal strains *Aspergillus clavatus* (MTCC 1323), *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282). The minimum inhibitory concentration (MIC) was determined by the broth dilution method. Chloramphenicol and Nystatin were used as reference drugs for antibacterial and antifungal activity, respectively. The results of antibacterial and antifungal activity were given in Table 1.

The results given in Table 1 indicated that none of the synthesized compound exhibited significant potency toward the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin. Hence, from above result we can conclude that the synthesized compounds show selectively antimalarial activity and negligible antimicrobial activity.

Conclusion

In conclusion, Considering the importance of enoyl-ACP reductase (*Pf*ENR) in *Plasmodium*, a small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) was designed and docked against *Pf*ENR. Based on the *in silico* binding affinity data, synthesis was carried out for these novel furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) and was evaluated for activity against *Plasmodium falciparum*. The synthesized compounds shown selectively antimalarial activity with minimal antimicrobial activity. Compounds (**3a-d**) exhibited less antimalarial activity compared to the standard drug. From the series of compounds (**4a-d**), compound **4b** (0.47 µM), **4c** (0.47 µM) and **4d** (0.21 µM) exhibited more antimalarial activity compared to the standard drug quinine (0.83 µM). Compound 4d shows four-fold more activity compared to the standard drug quinine. From the SAR, we have distinguished areas of the pyrazolyl chalcones and pyrazolyl pyrazolines framework where variations can be made to expand the pharmacokinetic profile as well as features required to improve inhibitor effectiveness. This innovative molecular scaffold presents breakthrough for optimization to develop effective *Pf*ENR inhibitors.

Experimental

General

All the reagents, solvents and chemicals were taken from commercial sources found to be and used as such without purification. The physical constant like melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Advance II 400 spectrophotometer using TMS as an internal standard and DMSO-d6 as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Waters, Q-TOF micro mass (ESI-MS) mass spectrometer.

General procedure for the synthesis of pyrazolyl chalcones (3a-d)

A mixture of 1-(2,5-dimethylfuran-3-yl)ethanone 1 (0.05 mol), substituted pyrazole aldehyde **2** (0.05 mol) and 10% aqueous potassium hydroxide (10 mL) in ethanol (50 mL) was stirred at room temperature for 14 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice and neutralized by dil. HCl. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3a)

Yield: 61%, yellow solid; mp: 80–82 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1657 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.31 (s, 1H, Pyrazole-H), 7.93 (d, 2H, J = 7.9 Hz), 7.38–7.68 (m, 10H, Ar–H), 6.60 (s, 1H, Furan-H), 2.53 (s, 3H, –CH_3), 2.27 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4 (C = O), 159.9, 152.8, 149.7, 138.9, 132.2, 132.0, 129.6, 128.8, 128.5, 128.6, 128.4, 127.1, 123.8, 122.1, 118.6, 117.6, 105.9, 13.9 (CH_3), 12.9 (CH_3); MS(ESI-MS): m/z 369.11 (M + H).$^{+}$

(E)-3-(3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran -3-yl) prop-2-en-1-one (3b)

Yield: 59%, yellow solid, mp: 112–114 °C; IR (νmax, cm^{-1}): 2923 (=C–H), 2856 (C–H), 1656 (C = O), 1455 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.25 (s, 1H, Pyrazole-H), 7.90 (dd, 2H, J = 4.7 & 9.0 Hz, Ar–H), 7.64 (d, 1H, J = 15.4 Hz, olefinic-H), 7.39–7.45 (m, 3H, Ar–H), 7.34 (d, 1H, J = 3.8 Hz, Ar–H), 7.25 (d, 1H, J = 3.8 Hz, Ar–H), 6.61 (S, 1H, Furan-H), 2.55 (s, 3H, $-CH_3$), 2.28 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.2, 162.0, 159.6, 157.1, 149.7, 145.7, 135.4, 135.1, 131.4, 130.8, 128.9, 127.3, 124.6, 122.0, 120.7, 120.6, 117.3, 116.6, 116.3, 112.5, 105.9, 13.9, 12.9; MS (ESI-MS): m/z 472.89 $(M + H)^{+}$.

(E)-3-(3-(5-Bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran-3-yl)prop -2-en-1-one (3c)

Yield: 68%, yellow solid, mp120–114 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1699 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.14 (s,1H, Pyrazole-H), 7.87 (d, 2H, J = 7.8 Hz, Ar–H), 7.70 (d, 1H, J = 15 Hz, olefinic-H), 7.52 (t, 2H, J = 8 Hz, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.20 (s, 2H, Ar–H), 6.55 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.3, 157.1, 149.7, 145.7, 138.6, 135.5, 131.4, 130.9, 129.7, 128.8, 127.3, 127.3, 124.6, 122.0, 118.6, 117.4, 112.5, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 454.57 $(M + H)^{+}$.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)prop-2-en-1-one (3d)

Yield: 62%, yellow solid, mp 124–126 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2715 (C–H), 1652 (C = O),1456 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, Pyrazole-H), 7.91 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 1H, J = 15.4 Hz, olefinic-H), 7.60 (d, 1H, J = 5.1 Hz, Ar–H), 7.54 (t, 2H, J = 8.2 Hz, Ar–H), 7.35–7.44 (m, 3H, Ar–H), 7.21 (dd, 1H, J = 5.0 & 3.7 Hz, Ar–H), 6.59 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4, 157.0, 149.7, 146.8, 138.7, 133.5, 131.5, 129.7, 128.7, 128.1, 127.3, 127.2, 126.8, 124.3, 122.1, 118.6, 117.4, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 375.10 $(M + H)^{+}$.

General procedure for synthesis of pyrazolyl-pyrazoline (4a-d)

A mixture of chalcone **3a-d** (0.001 mol) and hydrazine hydrate (0.004 mol) in solvent ethanol (10 ml) was refluxed in presence of catalytic amount of glacial acetic acid for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol to get pure pyrazolines.

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (4a)

Yield: 74%, white solid, mp 102–104 °C; IR (νmax, cm^{-1}): 3306 (N–H), 3049 (Ar–H), 1592 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, pyrazole-H), 7.90 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 2H, J = 8.3 Hz, Ar–H), 7.47–7.52 (m, 4H, Ar–H), 7.41 (t, 1H, J = 7.3 Hz, Ar–H), 7.31 (t, 1H, J = 7.4 Hz, Ar–H), 7.20 (s, 1H, N–H), 6.19 (s, 1H, furan-H), 4.87 (t, 1H, J = 10.7 Hz, pyrazoline-H), 3.34 (dd, 1H, J = 10.5 & 15.6 Hz, pyrazoline-H), 2.88(dd, 1H, J = 11.1 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 150.4, 149.3, 147.6, 145.1, 139.5, 132.9, 129.5, 128.6, 127.9, 127.2, 126.2, 123.2, 118.1, 115.2, 105.9, 54.7, 41.9, 13.3, 12.9; MS (ESI-MS): m/z 383.04 $(M + H)^{+}$.

3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1H-pyrazole (4b)

Yield: 69%, white solid, mp 98–100 °C; IR (νmax, cm^{-1}):3310 (N–H), 3046 (Ar–H), 1594 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.54 (s, 1H, pyrazole-H), 7.88 (m, 2H, Ar–H), 7.35 (t, 2H, J = 8.7 Hz, Ar–H), 7.28 (dd, 2H, J = 3.8 Hz, Ar–H), 7.21 (s, 1H, N–H), 6.20 (s, 1H, furan-H), 4.93 (t, 1H, J = 10.68 Hz, pyrazoline-H), 3.37 (dd, 1H, J = 10.7 & 16.5 Hz, pyrazoline-H), 2.86 (dd, 1H, J = 10.9 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 161.6, 159.1, 149.3, 147.7, 145.3, 144.1, 136.9, 135.6, 131.2, 128.0, 126.6, 122.6, 120.2, 120.2, 116.4, 116.2, 115.1, 111.5, 105.9, 54.3, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 486.93 $(M + H).^{+}$

3-(5-Bromothiophen-2-yl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole (4c)

Yield: 72%, white solid, mp 122–124 °C; IR (ν max, cm^{-1}): 3303 (N–H), 3096 (Ar–H), 1593 (C = N), ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.55 (s, 1H, pyrazole-H), 7.84 (d, 2H, J = 7.9 Hz, Ar–H), 7.51 (t, 2H, J = 7.6 Hz, Ar–H), 7.22–7.34 (m, 4H, Ar–H), 6.20 (s, 1H, furan-H), 4.94 (t, 1H, J = 10.6 Hz, pyrazoline-H), 3.38 (m, 1H, pyrazoline-H), 2.88 (dd, 1H, J = 12.1 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.2, 144.0, 139.0, 137.0, 131.2, 129.6, 127.8, 126.6, 126.5, 122.5, 118.0, 115.1, 111.4, 105.9, 54.4, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 468.95 $(M + H).^{+}$

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (4d)

Yield: 70%, white solid, mp 96–98 °C; IR (ν max, cm^{-1}): 3336 (N–H), 3067 (Ar–H), 1501 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.53 (s, 1H, pyrazole-H), 7.86 (d, 1H, J = 8 Hz, Ar–H), 7.58 (d, 1H, J = 4.9 Hz, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.31 (t, 1H, J = 7.3 Hz, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 6.21 (s, 1H, furan-H), 4.98 (t, 1H, J = 10.5 Hz, pyrazoline-H), 3.42 (m, 1H, pyrazoline-H), 2.89 (dd, 1H, J = 10.7 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.1, 144.9, 139.2, 135.0, 129.6, 127.9, 127.4, 126.3, 126.0, 125.8, 122.6, 118.1, 115.1, 105.9, 54.5, 41.3, 13.3, 12.9; MS (ESI-MS): m/z 389.03 $(M + H).^{+}$

Experimental protocol for biological activity

Antimalarial assay

The antimalarial activity of the synthesized compounds was carried out in the Microcare laboratory & TRC, Surat, Gujarat. According to the micro assay protocol of Rieckmann and coworkers the *in vitro* antimalarial assay was carried out in 96 well microtiter plates. To maintain *P. falciparum* strain culture in medium Roswell Park Memorial Institute (RPMI) 1640 supplemented with 25 mM (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. To obtain only the ring stage parasitized cells, 5% D-sorbitol treatment required to synchronized the asynchronous parasites of *P. falciparum*. To determine the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+}) an initial ring stage parasitaemia of 0.8 to 1.5% at 3% hematocrit in a total volume of 200 µl of medium RPMI-1640 was carried out for the assay. A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. To the test wells to obtain final concentrations (at five-fold dilutions) ranging between 0.4 µg/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation the diluted samples in 20 µl volume were added. In a candle jar, the culture plates were incubated at 37 °C. Thin

blood smears from each well were prepared and stained with Jaswant Singh-Bhattacharji (JSB) stain after 36 to 40 h incubation. To record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents the slides were microscopically observed. The minimum inhibitory concentrations (MIC) was recorded as the test concentration which inhibited the complete maturation into schizonts. Chloroquine was used as the reference drug.

After incubation for 38 hours, and percent maturation inhibition with respect to control group, the mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells.

Molecular docking

The crystal structure of *Plasmodium Falciparum Enoyl-Acyl-Carrier-Protein Reductase* (*Pf*ENR or FabI) in complex with its inhibitor Triclosan was retrieved from the protein data bank (PDB) (pdb code: 1NHG) and refined using the protein preparation wizard. It involves eliminating all crystallographically observed water (as no conserved interaction is reported with co-crystallized water molecules), addition of missing side chain/hydrogen atoms. Considering the appropriate ionization states for the acidic as well as basic amino acid residues, the appropriate charge and protonation state were assigned to the protein structure corresponding to pH 7.0 followed by thorough minimization, using OPLS-2005 force-field, of the obtained structure to relieve the steric clashes due to addition of hydrogen atoms. The 3D structures of the furan containing pyrazolyl chalcones (**3a-d**) were sketched using the build panel in Maestro and were optimized using the Ligand Preparation module followed by energy minimization using OPLS-2005 force-field until their average root mean square deviation (RMSD) reached 0.001 Å. The active site of *Pf*ENR was defined using receptor grid generation panel to include residues within a 10 Å radius around the co-crystallized ligand. Using this setup, flexible docking was carried using the extra precision (XP) Glide scoring function to gauze the binding affinities of these molecules and to identify binding mode within the target. The obtained results as docking poses were visualized and analyzed quantitatively for the thermodynamic elements of interactions with the residues lining the active site of the enzyme using the Maestro's Pose Viewer utility.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Nanostructured N doped TiO_2 efficient stable catalyst for Kabachnik–Fields reaction under microwave irradiation†

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Herein, we report nitrogen-doped TiO_2 (N-TiO_2) solid-acid nanocatalysts with heterogeneous structure employed for the solvent-free synthesis of α-aminophosphonates through Kabachnik–Fields reaction. N-TiO_2 were synthesized by direct amination using triethylamine as a source of nitrogen at low temperature and optimized by varying the volume ratios of $TiCl_4$, methanol, water, and triethylamine, under identical conditions. An X-ray diffraction (XRD) study showed the formation of a rutile phase and the crystalline size is 10 nm. The nanostructural features of N-TiO_2 were examined by HR-TEM analysis, which showed they had rod-like morphology with a diameter of ~7 to 10 nm. Diffuse reflectance spectra show the extended absorbance in the visible region with a narrowing in the band gap of 2.85 eV, and the high resolution XPS spectrum of the N 1s region confirmed successful doping of N in the TiO_2 lattice. More significantly, we found that as-synthesized N-TiO_2 showed significantly higher catalytic activity than commercially available TiO_2 for the synthesis of a novel series of α-amino phosphonates *via* Kabachnik–Fields reaction under microwave irradiation conditions. The improved catalytic activity is due to the presence of strong and Bronsted acid sites on a porous nanorod surface. This work signifies N-TiO_2 is an efficient stable catalyst for the synthesis of α-aminophosphonate derivatives.

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1 Introduction

In recent years, organophosphorus compounds have received much attention due to their widespread applications in medicinal and agriculture industries.[1,2] α-Aminophosphonates are one such biological important framework that are structural mimics of amino acids. For example, glyphosate (*N*-(phosphonomethyl)glycine) is extensively utilized in agriculture as a systemic herbicide and Alafosfalin is used as an antibacterial agent[3] (Fig. 1). The bioactivity of these molecules such as antimicrobial,[4] antioxidant,[5] anti-inflammatory,[6] enzyme inhibitors[7] and antibacterial[8] is one of the reasons for them to be of immense interest in synthetic organic chemistry. It has been demonstrated that on incorporation of heterocycles such as thiophene,[9] benzothiazoles,[10] thiadiazoles,[11] and pyrazole[12] into the α-aminophosphonates scaffold, the resulting compounds exhibited interesting biological activities. Pyrazole derivatives of α-aminophosphonates have been rarely reported in the literature,[13,14] thus synthesis of novel pyrazole derivatives of α-aminophosphonates is important to research.

Although several protocols for the synthesis of α-aminophosphonates are reported, one of the most important is the Kabachnik–Fields reaction.[15,16] This involves a one-pot three-component coupling of a carbonyl compound, an amine and alkylphosphite. These protocols has been accomplished in presence of a variety of catalyst such as $TiCl_4$,[17] CuI,[18] hexanesulphonic sodium salt,[19] trifluoroacetic acid (TFA),[20] $In(OTf)_3$,[21] $BiCl_3$,[22] $Cu(OTf)_2$,[23] $SbCl_3/Al_2O_3$,[24] $InCl_3$,[25] $LiClO_4$,[26] $ZrOCl_2$,[27] TsCl,[28] $Mg(ClO_4)_2$,[29] and Na_2CaP_2O[30] in presence or

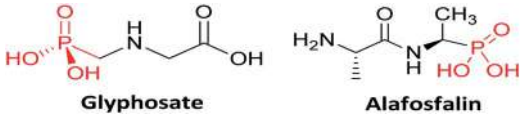

Fig. 1 Some biological active α-aminophosphonate.

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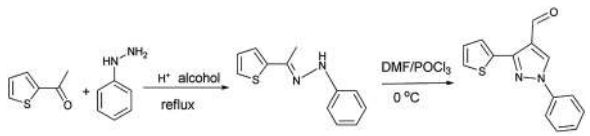


Scheme 1 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde.

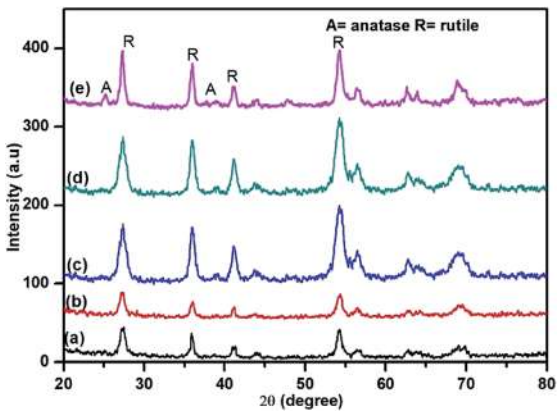


Fig. 2 X-ray diffraction patterns of (a) TN0 (TiO_2), (b) TN1, (c) TN2 (d) TN3 (e) TN4.

even in the absence of a solvent. However, most of these existing procedures are sluggish, require long reaction times, use of strong acidic conditions, give unsatisfactory yields and also suffer from the formation of many side products. Moreover, in all alternatives microwave reaction proved to be a kind of promising medium for such reaction.[31]

In the last few years, the application of transition metal oxides gained particular interest as a heterogeneous catalyst for various organic synthesis.[32] Among all transition metal oxides the use of nanocrystalline titania (TiO_2) has been grown extensively owing to their outstanding physiochemical properties, which furnished their wide applications in sensors,[33] pigments,[34] photovoltaic cells,[35] and catalysis.[36] Also, the use of potential titania catalyst attracted in organic synthesis due to its environmental compatibility, inexpensive, safe, stable, reusable and earth-abundant. It has been proven the desired property of TiO_2 was attained by fulfilling requirements in terms of unique morphology, high crystallinity and mixed-phase composition, the ability of oxidizing and reducing ability under suitable irradiation makes promising greener alternative approach towards important organic transformations compared to other expensive, toxic, transition metal oxides. Moreover, the phase composition and the degree of crystallinity of the titania sample plays an important role in catalytic activity.[8] In the past several organic transformations such as oxidation of primary alcohols,[37] synthesis of xanthenes,[38] Friedel–Crafts alkylation,[39] Beckmann rearrangement[40] efficiently utilizes TiO_2 as a heterogeneous reusable catalyst. In the literature several reports have been debated to influence nitrogen doping on photocatalytic activity of nanocrystalline TiO_2. However, the effect is unrevealed for catalytic applications in organic synthesis. Recently, Hosseini-Sarvari explored the use of commercial TiO_2 in the synthesis of α-aminophosphonates *via* Kabachnik–Fields reactions.[41]

In present investigation, we have prepared nanostructured N doped TiO_2 and also investigation emphasis was given on the synthesis of a series of a novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamin) methylphosphonates under microwave irradiation.

Table 1 Phase composition and crystallite size of as-prepared samples from analysis of XRD

Sample	Rutile	Anatase	Crystallite size (nm)
TN0	100	0	25
TN1	98	2	19
TN2	94	6	16
TN3	95	5	12
TN4	91	9	9

2 Experimental sections

2.1 Synthesis of N doped TiO_2 nanorods

The nanostructured N-TiO_2 were synthesized by previously reported method with some modification.[42,43] In a typical procedure, 0.5 mL of titanium tetrachloride ($TiCl_4$) was added in absolute methanol (25 mL) with constant stirring at room temperature. To this solution requisite quantity a 0.1–2 M aqueous triethylamine solution is injected rapidly. The resulting solution was refluxed for 24 h with constant stirring. The white precipitate formed was collected and washed with ethanol several times followed by centrifugation (10 000 rpm for 20 min). The precipitate was dried at 473 K for 24 h. To control the final morphologies of samples, the sample were synthesized as function of volume ratio of $TiCl_4$, methanol, water, and triethylamine. The sample prepared in volume ratio 1 : 10 : 50 : 0, 1 : 10 : 50 : 1, 1 : 10 : 50 : 2, 2 : 10 : 50 : 2, and 2 : 10 : 50 : 4 were denoted as TN0 (pure TiO_2), TN1, TN2, TN3 and TN4 respectively.

2.2 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde

1-Phenyl-5-(thiophene-2-yl)-1*H*-pyrrole-3-carbaldehyde were obtained *via* the Vilsmeier–Haack reaction of the appropriate phenylhydrazones, derived from the reaction of 2-acetyl thiophene with phenylhydrazine[44] (Scheme 1).

2.3 Synthesis of diethyl(1-phenyl-3-(thiophene-2-yl)-1*H*-pyrazole-4-yl)(phenylamino)methylphosphonates

In a typical procedure, the pyrazolealdehyde **1** (1 mmol), aniline **2** (1 mmol), triethyl phosphite **3** (1.1 mmol) and N-TiO_2 (12 mol%) were taken in a round bottom flask equipped with a condenser and subjected to microwave irradiation for (10–15 min) using 420 W (RAGA's Microwave system) (Scheme 3). The

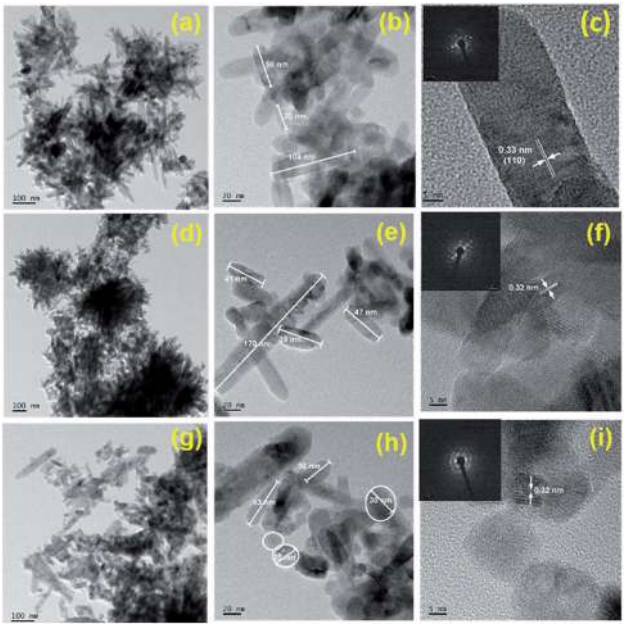


Fig. 3 HR-TEM images of (a–c) TN0, (d–f) TN1, and (d–f) TN2; inset c, f and h SAED pattern of TN0, TN2 and TN3 respectively.

progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture extracted using ethyl acetate and insoluble catalyst separated by filtration. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate as eluent. The product structure was determined by FTIR, ^{1}H NMR, and LS-MS.

2.4 Samples characterization

The phase purity and crystallinity were examined by X-ray diffraction (XRD) technique (Advance, Bruker AXS D8) using Cu Kα1 (1.5406 Å) radiation with scanning 2θ range from 20 to 80°. For FETEM analysis samples were prepared by evaporating dilute solution on carbon-coated grids. FE-TEM measurements were carried using the JEOL SS2200 instrument operated at an accelerating voltage of 300 kV. The Brunauer–Emmett–Teller (BET) surface area of nanocatalysts was examined using the Quantachrome v 11.02 nitrogen instrument. The optical properties of the powder samples were studied using UV-vis diffuse reflectance absorption spectra (UV-DRS) were recorded on the Perkin-Elmer Lambada-950 spectrophotometer in the wavelength range of 200–800 nm. Powder samples were used for XPS measurements. The XPS measurements of powdered samples were carried out on a VG Microtech ESCA3000 instrument. Fourier transform infrared (FTIR) spectra of prepared samples were recorded on a Shimadzu Affinity 1-S spectrophotometer in over a range of 400–4000 cm^{-1}. ^{1}H NMR was recorded in DMSO-d_6 solvent on a Bruker Advance-400 spectrometer with tetramethylsilane (TMS) as an internal reference.

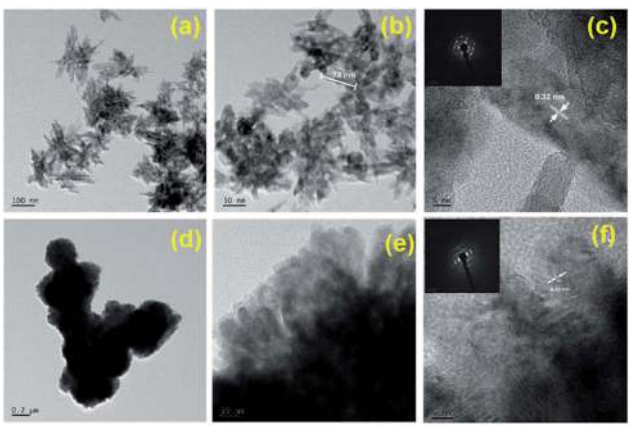


Fig. 4 HR-TEM images of (a–c) TN3 and (d–f) TN4; inset c, and f SAED pattern of TN3, and TN4 respectively.

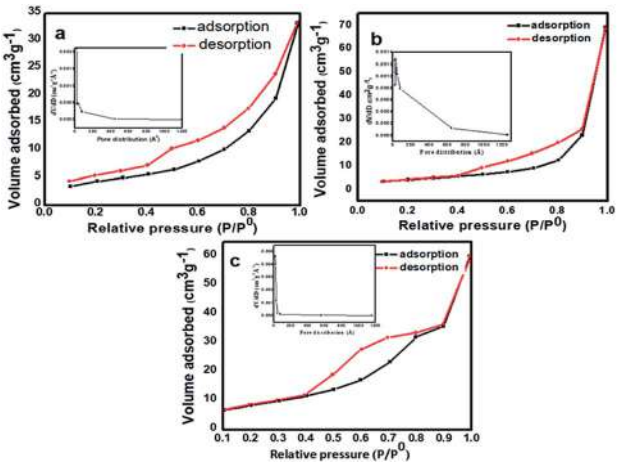


Fig. 5 Nitrogen (N_2) adsorption–desorption isotherms of (a) TN0 (TiO_2), (b) TN2 (N-TiO_2), (c) TN4 (N-TiO_2). Insets shows their corresponding pore size distributions.

3 Results and discussions

3.1 Structural study

Nanostructured TiO_2 and N doped TiO_2 were synthesized by a simple refluxing method. The phase purity and phase formation of as-synthesized material were analysed by powder X-ray diffraction pattern. Fig. 2 compares powder XRD patterns of TiO_2 and N doped TiO_2 samples. The peak position and peak intensity of the pure TiO_2 powder can be indexed into rutile phases (Fig. 2). Further, it is observed that an increase in the amount N-dopant (triethylamine) the intensity of the diffraction

Table 2 BET specific surface area and pore size distribution of TiO_2 and N-TiO_2

Sample	Surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})	Pore radius (Å)
TN0	21.956	0.051	18.108
TN2	40.359	0.215	30.811
TN4	53.589	0.101	18.041

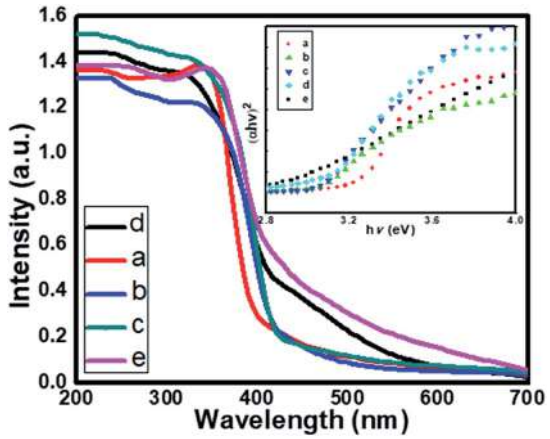


Fig. 6 UV-DRS spectra of (a) TN0 (TiO_2), (b) TN1 (c) TN2 (d) TN3 (N-TiO_2), (e) TN4. Insets shows Tauc plot of TiO_2 and N-TiO_2 samples.

peaks of the rutile phase decreases, while that of anatase phase increases, indicating that the fraction of the anatase phase gradually increases at the expense of the rutile phase during this condition (sample TN2–TN4). The phase composition of rutile and anatase phase of TiO_2 evaluated from the peak intensity using the following equation,

$$f_A = \frac{1}{1+\frac{1}{K}\frac{I_R}{I_A}} \quad K = 0:79; f_A > 0.2; K_{1/4}0:68; f_A \leq 0.2$$

where f_A is the fraction of the anatase phase, and I_A and I_R are the intensities of the anatase (1 0 1) and rutile (1 1 0) diffraction peaks, respectively. The higher molar concentration of triethylamine is favourable for the transformation from rutile to anatase.[45,46] Therefore, the phase composition of TiO_2 samples, *i.e.* the fraction of anatase and rutile, can be facilely controlled through adjusting the concentration of triethylamine. The slight shift of rutile (1 1 0) diffraction peaks towards a higher angle with an increase in the amount of N dopant suggesting

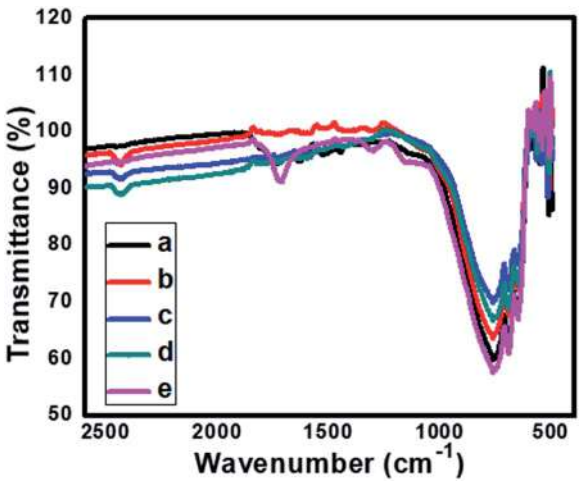


Fig. 7 FTIR spectra of (a) TN0 pure (TiO_2), (b) TN1 (N-TiO_2), (c) TN2, (d) TN3 and (e) TN4.

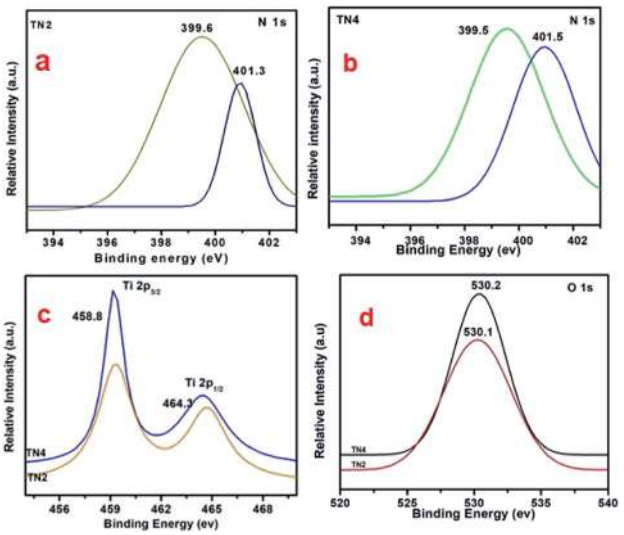
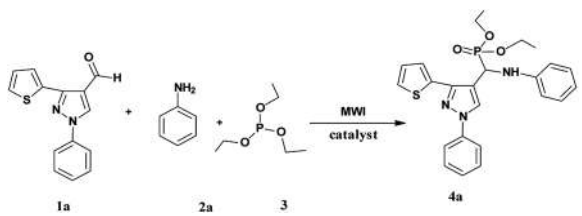


Fig. 8 (a and b) High resolution spectrum of N 1s region (c) high resolution spectrum of Ti 2p region (d) high resolution spectrum of O 1s region.

the incorporation of nitrogen in the TiO_2 crystal structure. The crystallite size is calculated from each (1 1 0) peak in the XRD pattern using the Sherrer formula.[39] The average crystalline size are 25, 19, 16, 12 and 9 nm for TN0, TN1, TN2, TN3, and TN4 respectively (Table 1). From, XRD analysis it is clear that with an increase in the concentration of nitrogen in TiO_2, fraction of anatase increases phase and crystalline size decreases.

3.2 Surface and morphological study

Transmission electron microscopy (TEM) and high-resolution transmission electron microscopy (HRTEM) analysis were performed to study morphology and crystallinity of as-synthesized pure and N doped TiO_2 materials (Fig. 3). The pure TiO_2 (TN0) sample seems flowerlike nanostructures (Fig. 3a). At high-resolution it reveals that each flower microstructure consisting several nanorods. The length of nanorods are in the range of 50–70 nm and diameter is about 10–15 nm (Fig. 3b). Fig. 3c shows the lattice fringes of the material with interplanar spacing *d* spacing 0.33 nm matches well (1 0 0) plane of rutile TiO_2. Fig. 3c inset shows a selected area diffraction pattern in which bright spots observed that confirm the TiO_2 nanorods are in nanocrystalline nature. It was observed that addition of N dopant, resulting sample TN1 and TN2 grows into new superstructure consisting nanorods of length 30–50 nm and spheres



Scheme 2 Standard model reaction.

Table 3 Comparative study of catalysts used for the synthesis of α-aminophosphonate[a]

Entry	Catalyst	Time (minutes)	Yield[b] (%)
1	—	20	Trace
2	Acetic acid	20	30
3	Commercial ZnO	15	20
4	Commercial TiO_2	15	30
5	TN0	10	72
6	TN1	10	73
7	TN2	10	76
8	TN3	10	85
9	TN4	10	95

[a] Reaction condition: aldehyde(**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), catalyst, MW power 420 watt. [b] Isolated yield.

of diameter 20–30 nm, particles size is obviously smaller than TN0 (Fig. 3d and h). HRTEM results are consistent with XRD results. The *d*-spacing is about 0.325 Å between adjacent lattice planes of the N doped TiO_2.

It was revealed that with doubling concentration of $TiCl_4$, sample TN3 and TN4 were grown into very fine agglomerated nanorods (Fig. 4). Further, it is observed that these nanorods having size in length 30–40 nm and diameter is around 7–10 nm which is lower than pure TiO_2. Fig. 4f inset shows selected area diffraction pattern shows, surprisingly, ring-like pattern unlike TiO_2, indicates N-TiO_2 nanorods are in polycrystalline nature. From HR-TEM results it is concluded that increase in concentration of $TiCl_4$ and triethylamine reduces the size of the nanorods.

The specific surface area of as-prepared samples was studied by (N_2) nitrogen gas adsorption–desorption measurement at 77 K using the Brunauer–Emmett–Teller (BET) method. The N_2 adsorption–desorption isotherm of N-TiO_2 nanoparticles is shown in Fig. 5. The pure TiO_2 shows type IV isotherm according to IUPAC classification,[47] which are typical characteristics of a material with pore size in the range of 1.5–100 nm Fig. 5a. The shape of the hysteresis loop is H_3 type may associates due to the agglomeration of nanoparticles forming slit-like pores, reflected in TEM images. At higher relative pressure (p/p^0) the slope shows increased uptake of adsorbate as pores become filled; inflection point typically occurs near

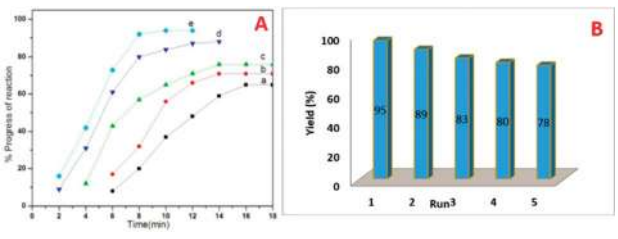


Fig. 9 (A) Progress of reaction (a) TN0 (b) TN1 (c) TN2 (d) TN3 and (e) TN4. (B) Reusability of catalyst TN4; reaction condition: aldehyde (**1a**) (1 mmol), aniline (**2a**) (1 mmol), triethylphosphite **3** (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt.

Table 4 Optimization of the concentration of catalyst[a]

Sr. no.	Concentration of catalyst (mol%)	Yield[b] (%)
1	3	69
2	6	76
3	9	86
4	12	95
5	15	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, MW power 420 watt. [b] Isolated yield.

completion of the first monolayer. The BET surface area of pure TiO_2 is found to be 21.956 $m^2\ g^{-1}$. The pore size distribution of prepared samples was investigated by Barrett–Joyner–Halenda (BJH) method Fig. 5(a)–(c) insets. The average pore diameter of pure TiO_2 nanoparticles is 18 nm which demonstrates the material is mesoporous nature. Further, it is observed that the incorporation of nitrogen in TiO_2 nanoparticles the surface area shifts towards higher values. The adsorption–desorption isotherms of nitrogen-doped TiO_2 samples display the type II isotherm according to IUPAC classification.[46] The specific BET surface area of samples TN_2 and TN_4 are 40.359 $m^2\ g^{-1}$ and 53.589 $m^2\ g^{-1}$ respectively (Fig. 5b and 4c). This observation specifies a decrease in the particle size of TiO_2 nanoparticles specific surface area increases which are in consisting of XRD and TEM results. The Brunauer–Emmett–Teller (BET) specific surface areas, pore volumes and mean pore and mean pore diameters of samples TN0, TN2, and TN4 are summarized in Table 2.

3.3 Optical and electronic property studies

The optical property of the as-synthesized material was analyzed by UV-Vis diffuse absorbance spectra as shown in Fig. 6. Fig. 6 displays the comparative UV-DRS spectra of pristine TiO_2 and a series of N doped TiO_2 samples. The absorption edge for the pure TiO_2 (TN0) is observed at around 410 nm (Fig. 6a), which is consistent with the band gap of the rutile phase.[45] The N doped TiO_2 nanostructures show strong absorption in the visible region (410–600 nm). The redshift clearly indicates the

Table 5 Screening of solvents[a]

Entry	Solvent	Yield (%)[b]
1	Ethanol	85
2	Methanol	87
3	Dichloromethane	55
4	THF	58
6	Toluene	60
7	Neat	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, solvent, MW power 420 watt. [b] Isolated yield.

successful doping of N in the lattice of TiO_2. Moreover, as the concentration of triethylamine increases redshift of N-TiO_2 also increases which confirms higher nitrogen doping and a higher fraction of absorption of photons from the visible region. The band gap of as-synthesized material calculated by using the Tauc plot shown in Fig. 6 (insets). The band gap (E_g) for the sample TN0, TN1, TN2, TN3, and TN4, were observed to 3.15, 3.09, 3.07, 3.03 and 2.85 eV respectively. The decrease in the band gap is attributed to higher mixing of the (O/N) 2p level is developed in the Ti-3d level falls at the top of the VB, therefore, band gap reduced compared to the pristine TiO_2 nanostructure.

3.4 FT-IR spectroscopy

Fig. 7 shows comparative FTIR spectra for pure and N doped TiO_2. The absorption peak signal in the range of 400–1100 cm^{-1} is characteristic of the formation of O–Ti–O lattice. The absorption at 668 cm^{-1}, 601 cm^{-1}, 546 cm^{-1} and 419 cm^{-1} corresponds to Ti–O vibrations.[48,49] Further, for the sample TN1–TN3 the IR bands centred at 1400–1435 cm^{-1} indicates nitrogen doping in the TiO_2 sample. The band located at 1070 cm^{-1} is attributed to Ti–N bond vibrations. Also, it is observed that the band at 1335 cm^{-1} for pure TiO_2 is shifted towards longer wavenumber 1430 cm^{-1} supports for the claim of N doping in TiO_2 lattice. Further it is also observed that some of the minor the peaks of pure TiO_2 are rather different than the N-doped TiO_2, this indicates the incorporation of nitrogen in TiO_2 lattices. The peak centered at 1600–2180 cm^{-1} is ascribed due to –OH stretching frequency. From, IR spectra it is clear that N is successfully incorporated in the lattice of TiO_2.

3.5 X-ray photoelectron spectroscopy

The XPS were used for chemical identification and electronic state of dopant nitrogen in sample TN2 and TN4. The high resolution XPS spectra of N 1s on deconvolution shows two different peaks at 399.6 and 401.5 eV indicates nitrogen present in two different electronic state (Fig. 8a and b). The peak at 399.6 is attributed to presence of interstitial N or N–Ti–O linkage. The result is consistent with previous reports.[43] The peak at 401.5 is attributed to presence of N in oxidized state as NO or NO_2. The concentration of nitrogen on surface of TN2 and TN4 are 2.8% and 3.4% respectively. Fig. 8c shows the peak at 458.8 and 458.3 is attributed to Ti $2p_{3/2}$ and Ti $2p_{\frac{1}{2}}$, in good agreement the presence of Ti(IV) in TiO_2. The peak at binding energy 530.1 and 530.2 eV of sample are attributed to O 1s (Fig. 8d).

3.6 Catalytic study in synthesis of α-aminophosphonates

In order to find out the best experimental condition, the reaction of pyrazolaldhyde **1a**, aniline **2a** and triethylphospite **3** under microwave irradiation is considered as standard model reaction (Scheme 2).

In the absence of a catalyst, the standard model reaction gave a small amount of product (Table 3 entry 1). These results specify catalyst is required to occur reaction. In order to check the catalytic utility, the model reaction carried out in the presence of a variety of catalysts (Table 3 entry 2–9). The N-TiO_2 NRs gave better results than acetic acid, commercial ZnO and commercial TiO_2.

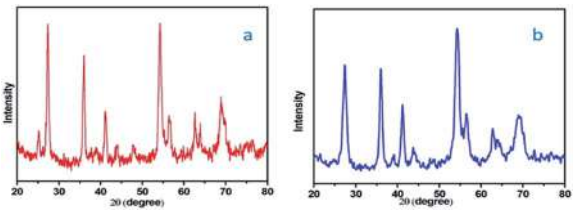


Fig. 10 XRD of sample TN4 (a) before reaction (b) after reaction.

Inspiring these results, we further studied the progress of reaction at different time intervals, we observed the sample N-doped TiO_2 catalyzes efficiently than undoped TiO_2, and this may be attributed to the higher surface area (Fig. 9A).

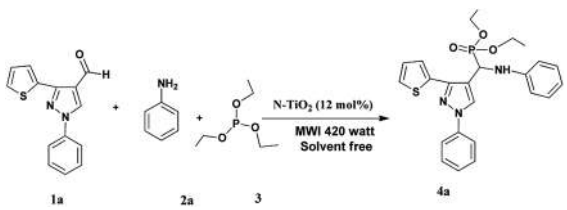
The optimum concentration of the catalyst was investigated by performing the model reaction at different concentrations such as 3, 6, 9, 12 and 15 mol%. The reaction yielded in 69, 76, 86, 95 and 95% yields respectively (Table 4). This shows that 12 mol% of TN_4 is adequate for the reaction by considering the yield of the product.

To evaluate the effect of solvents, different solvents such as ethanol, methanol, dichloromethane, THF, 1,4-dioxane and toluene were used for the model reaction in presence of N-TiO_2 catalyst. The reaction proceed with better yield in polar protic solvent (Table 5, entries 1, 2). However it was observed that the usage of solvents slows down the rate of reaction and gives the desired product in lower yields than that for neat condition (Table 5, entries 1–6).

The recyclability of the catalyst was then examined and the outcomes are shown in Fig. 9B. After the completion of reaction, the reaction mixture was extracted with ethyl acetate. The residual catalyst was washed with acetone, dried under vacuum at 100 °C and reused for consequent reactions. The recovered catalyst could be used for 5 times without obvious loss of catalytic activity.

The difference between the XRD of fresh catalyst and reused catalyst shown in Fig. 10.

The usefulness of optimized reaction condition for model reaction (12 mmol % of catalyst, solvent-free, MWI) was extended for the synthesis of a series of novel α-amino-phosphonates (**4a–l**) by reacting pyrazoldhyde (**1a–c**), anilines (**2a–d**) and triethylphosphite (**3**) in excellent yields (Scheme 3).



Scheme 3 Optimized reaction condition for synthesis of diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino) methylphosphonates

Table 6 Microwave assisted synthesis of novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino)methylphosphonates[a]

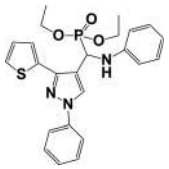
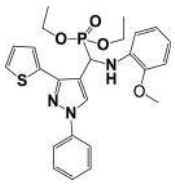
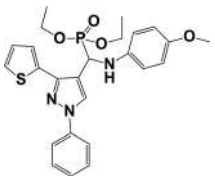
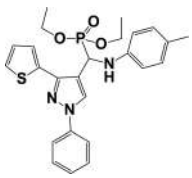
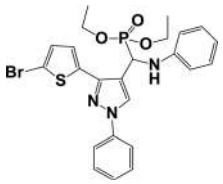
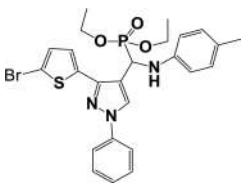
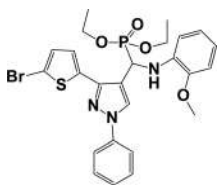
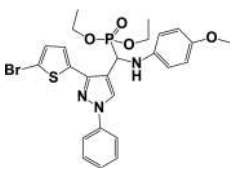
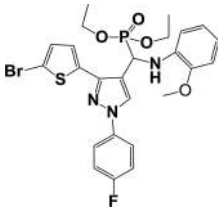
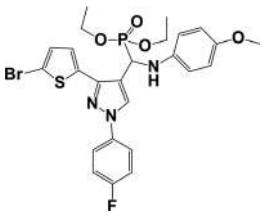
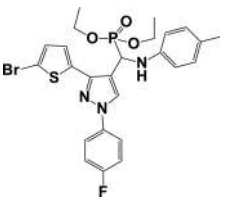
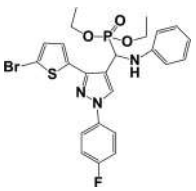
Entry	Product	M.P. (°C)	Yield[b] (%)
4a		218	95
4b		220	79
4c		208	92
4d		216	79
4e		180	86
4f		200	82
4g		162	85
4h		190	71

Table 6 (*Contd.*)

Entry	Product	M.P. (°C)	Yield[b] (%)
4i		195	81
4j		120	76
4k		210	89
4l		190	75

[a] Reaction condition: aldehyde (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt. [b] Isolated yield.

The obtained product **4a–l** was characterized by spectroscopic techniques (Table 6).

The spectroscopic data of synthesized compounds are given in ESI (S-2 to S-26).†

4 Conclusions

In summary, we have prepared N doped TiO_2 nanorods by thermal hydrolysis method using triethylamine as the source of nitrogen at relatively low temperatures. The XRD analysis showed that with varying composition molar ratios of $TiCl_4$, CH_3OH, H_2O, and $(C_2H_5)_3N$, phase composition of rutile to anatase also tunes. FTIR spectra show the chemical environment of doping by the formation of the N–Ti–O and Ti–O–Ti bond. The morphological study performed by the FE-TEM technique shows the formation of well-developed nanorods of size in length 30–40 nm and diameter is around 7–10 nm, which is lower than pure TiO_2. Further, BET analysis N-TiO_2 shows the maximum specific surface area 53.4 $m^2\ g^{-1}$ which is 2.5 times

higher than pure TiO_2. The as-synthesized materials were employed for the synthesis of α-aminophosphonates *via* Kabachnik–Fields reaction under microwave irradiation. The N-TiO_2 shows remarkable catalytic activity for aminophosphonate derivatives compared with TiO_2 and other similar nanocatalysts.

Conflicts of interest

There are no conflicts to declare.

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

Perfluoro-alkylated and trifluoro-methylated pyrazoles represent pharmacologically related core structures that are present in many important drugs and agrochemicals, such as fluazolate (herbicide), penthiopyrad (fungicide), razaxaban (anticoagulant), deracoxib, celecoxib (anti-inflammatory), and penflufen (fungicidal) (Figure 1).[16] So, the modern trend is moving more in the direction of the synthesis of a collection of fluorine-containing molecules in order to find excellent biological activity.

Ultrasonic irradiation is a new technology that has been widely used in chemical reactions. When ultrasonic waves pass through a liquid medium, a large number of microbubbles form, grow, and collapse in very short times, about a few microseconds. The formation and violent collapse of small vacuum bubbles takes place due to the ultrasonication waves generated in alternating high pressure and low pressure in liquids, and the phenomenon is known as cavitation. It causes high-speed imposing liquid jets and strong hydrodynamic shear forces. The deagglomeration of nanometer-sized materials was carried out using these effects. In this aspect, for high-speed mixers and agitator bead mills, ultrasonication is an alternative.[17]

In the preparative chemist's toolkit, microwave heating is a valuable technique. Due to a modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way.[18] In recent years, microwave-assisted organic synthesis (MAOs)[19] has been emerged as a new "lead" in organic synthesis. Important advantages of this technology include a highly accelerated rate of the reaction and a decrease in reaction time, with an increase in the yield and quality of the product. The current technique is considered an important method toward green chemistry as this technique is more environmentally friendly. The conventional method of organic synthesis usually needs a longer heating time; tedious apparatus setup, which results in the higher cost of the process; and the excessive use of solvents/reagents, which leads to environmental pollution. This growth of green chemistry

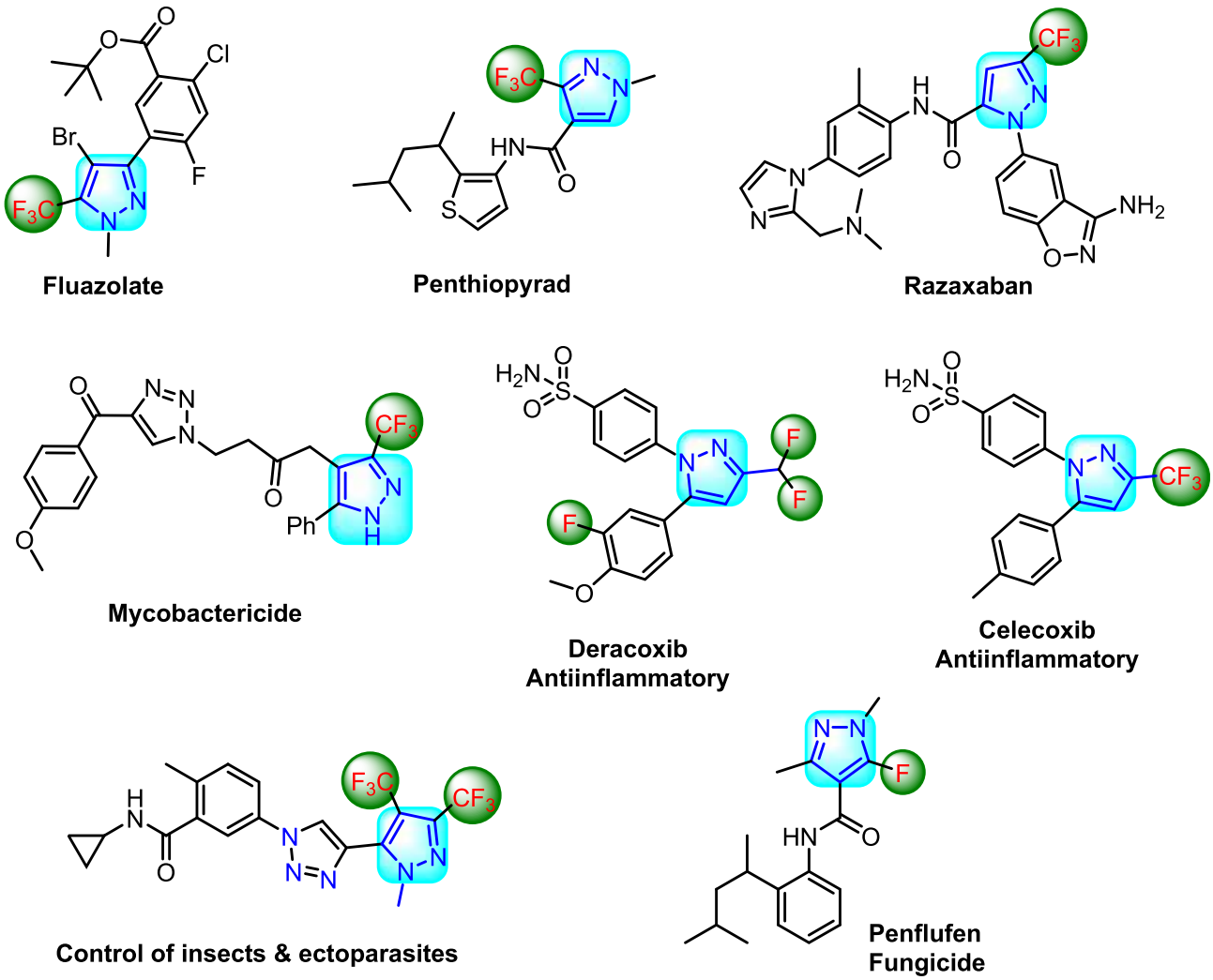


FIGURE 1 Structure of pyrazole- and fluorine-containing commercially available drugs

holds significant potential for a reduction of the byproduct, a reduction in waste production, and lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and bypass thermal conductivity, leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[20] Knoevenagel condensation reactions are carried out by the condensation of aldehyde and the active methylene group using different catalysts such as piperidine, $InCl_3$, $TiCl_4$, LiOH, $ZnCl_2$, and $NbCl_5$.[20,21] They are also carried out using $NaAlO_2$-promoted mesoporous catalysts,[22] ionic liquid,[23] monodisperse carbon nanotube-based NiCu nanohybrids,[24] and MAOs.[25] This is one of the most important methodologies used in synthetic organic chemistry for the formation of a C—C double bond.

From our study, the results demonstrated that green methodologies are less hazardous than classical synthesis methods, as well more efficient and economical and environmentally friendly; short reaction times and excellent yields are observed for those reactions in which conventional heating is replaced by microwave irradiation. Keeping in mind the 12 principles of green chemistry, in continuation of our research work,[26] and the advantages of microwave irradiation and activities associated with pyrazole and fluorine, we construct pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional, as well as microwave, irradiation and ultrasonication and evaluated their anti-inflammatory and antioxidant activity. In addition to this, we have also performed in silico absorption, distribution, metabolism, and excretion (ADME) predictions for the synthesized compounds.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A facile, economic, and green protocol for the cyclocondensation of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) with different aldehydes has been achieved.

The key starting material 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (**3**) was synthesized by the condensation of 1-(perfluorophenyl)hydrazine (**1**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in ethanol[27] (Scheme 1).

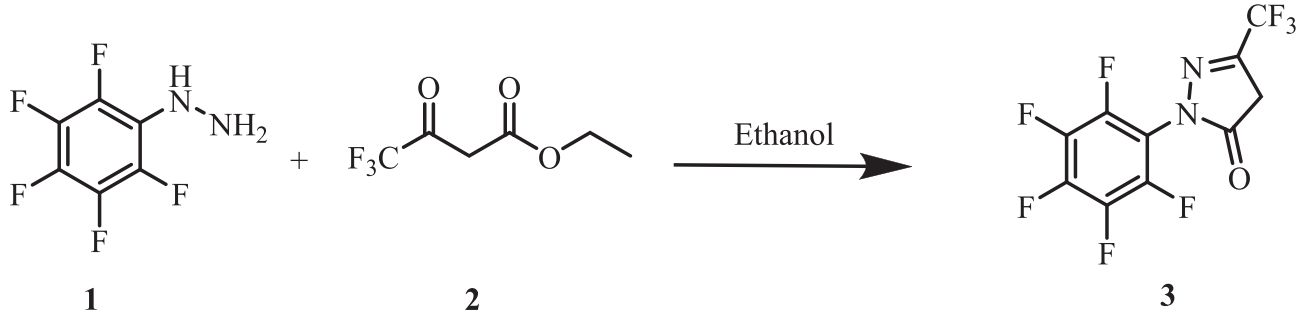
Initially, we carried out the reaction between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) (**3**) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid as a model reaction (Scheme 2). Initially, the model reaction was carried out in ethanol without using acetic acid, and it was observed that a very low yield of product (20%) was obtained even after 2 hr. Therefore, improving the yield intervention of the catalyst was thought to be necessary. So, we decided to use acetic acid as a catalyst to promote this transformation at room temperature. At room temperature, the yield of product (45%) was found to be increased in 3 hr, so we decided to provide heating to the reaction mixture to achieve maximum product yield.

When the reaction mixture refluxed in acetic acid, product formation took place after 2 hr, and the yield of the product was 72% (Table 1).

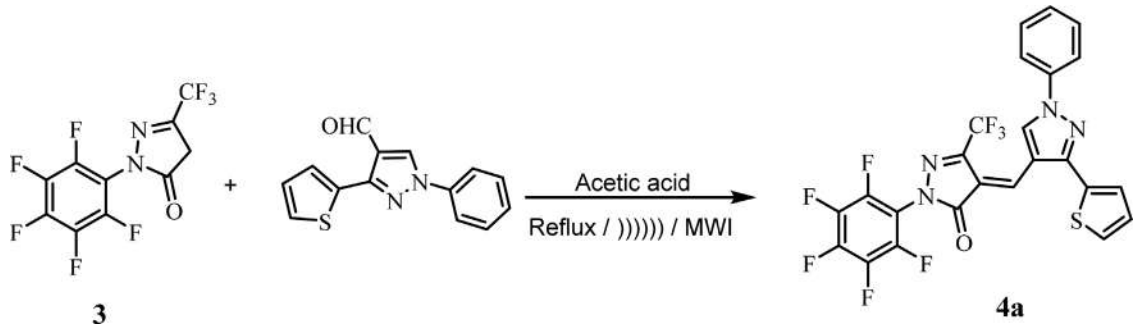
To check the ultrasonication's specific effect on this reaction, under ultrasound irradiation at 35–40°C, we carried out the model reaction using the optimized reaction conditions in hand to check whether the reaction could be accelerated with further improved product yield within a short reaction time (Scheme 2).

It was observed that, under ultrasonic conditions, the conversion rate of a reactant to product increased with less time (Table 1). Thus, when considering the basic green chemistry concept, ultrasonic irradiation was found to have a beneficial effect on the synthesis of Knoevenagel derivatives (**4a-d**, **5a-f**, and **6a-e**), which was superior to the traditional method with respect to yield and reaction time (Table 1).

To accomplish the goal and significance of green chemistry, the model reaction was carried out under



SCHEME 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one **3**



SCHEME 2 Model reaction for conventional, ultrasonication, and microwave irradiation methods

TABLE 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**)

						Conventional method[a]		Ultrasound method[b]		Microwave method[c]	
Cpd	R_1	R_2	R_3	R_4	m. p. (°C)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
4a	H	H	-	-	224–226	120	72	20	81	6.5	84
4b	Br	F	-	-	232–234	120	75	18	78	6.5	81
4c	Cl	H	-	-	216–218	120	70	20	76	6.0	80
4d	Br	H	-	-	230–232	120	64	16	70	6.5	76
5a	H	H	OMe	-	202–204	120	70	21	76	5.5	84
5b	H	H	H	-	186–188	120	66	17	72	6.0	80
5c	F	H	OMe	-	180–182	120	68	16	75	7.0	82
5d	H	H	Me	-	206–208	120	65	16	71	6.5	79
5e	H	H	OCF_3	-	142–144	120	62	18	70	6.5	76
5f	H	Cl	Cl	-	212–214	120	70	19	80	5.5	84
6a	Me	Cl	Me	H	188–190	120	66	18	76	6.0	78
6b	H	Cl	Me	H	180–182	120	62	17	72	7.5	75
6c	H	Cl	H	H	176–178	120	59	18	79	7.0	80
6d	H	Cl	H	Cl	212–214	120	64	20	72	7.0	78
6e	H	H	Me	H	180–182	120	60	18	80	7.5	82

Abbreviation: Cpd, compound.

[a]Reaction conditions: Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid.

[b]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under ultrasound irradiation.

[c]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under microwave irradiation.

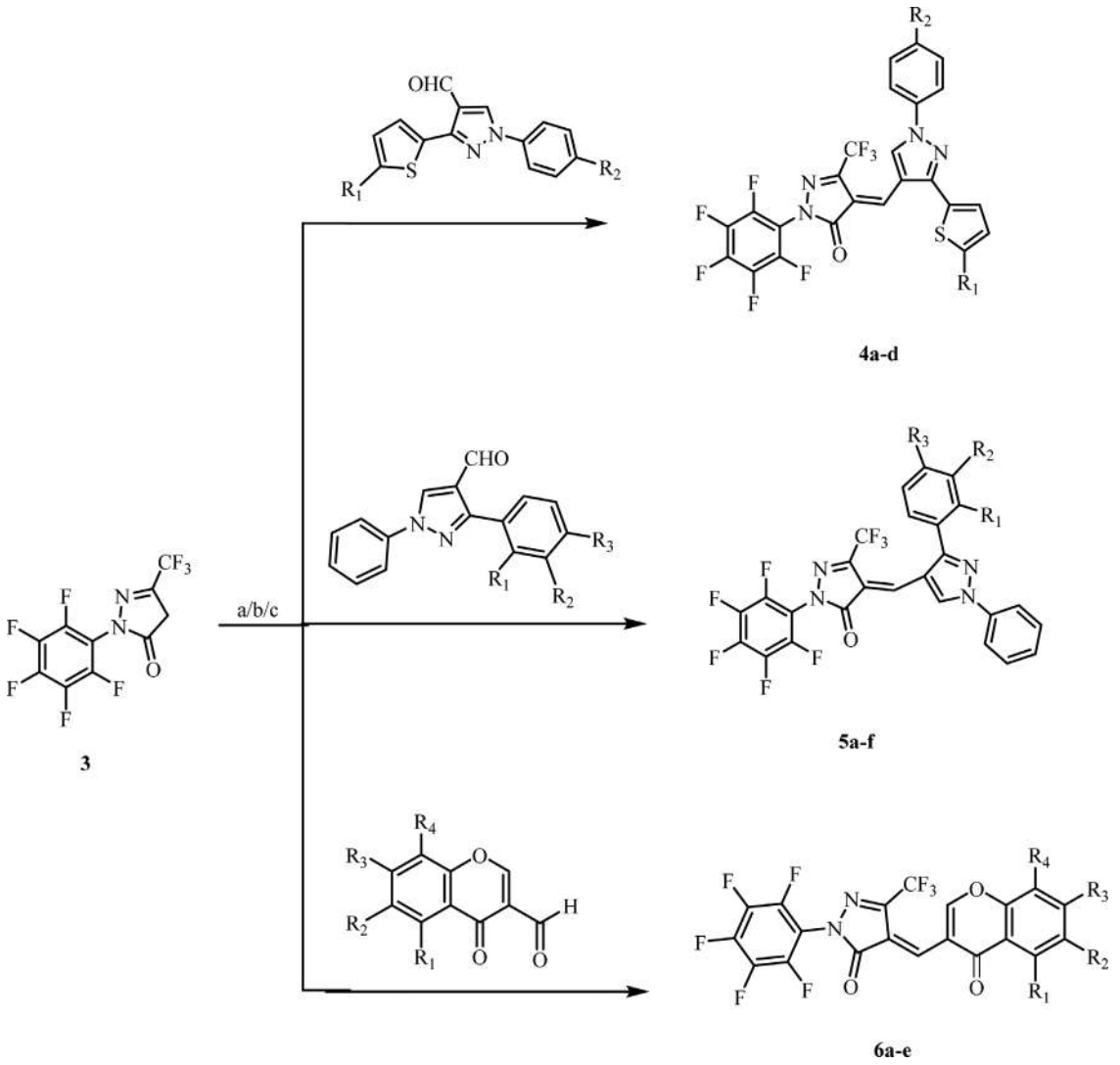
[d]Isolated yield. m.p.: melting point.

microwave irradiation for a period of time indicated in Table 1 at 350 W (Scheme 2). Fortunately, the product formation occurred in 6.5 min, with an 84% increase in yield .

So, from the above experiments, it can be concluded that, when the reaction was carried out under the conventional method, it gave comparatively low yields of products with longer reaction times, while the same reaction carried out under the influence of ultrasonic irradiation and microwave irradiation gave excellent yields of the products in short reaction times.

Finally, we assessed the scope and generality of this method for the Knoevenagel condensation between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) and different aldehydes (Scheme 3), achieved under conventional and nonconventional methods like the ultrasound and microwave methods, respectively. With respect to the substituent present on the aromatic ring of aldehyde, under the optimized conditions, the corresponding products were obtained in high to excellent yields (Table 1).

More importantly, hetero aryl aldehydes were observed to be well tolerated under optimized conditions,



SCHEME 3 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**). Reaction conditions: **a** = Refluxed in acetic acid. **b** = Under ultrasound irradiation in acetic acid. **c** = Under microwave irradiation using acetic acid as a solvent

furnishing the product in good yields. All the synthesized compounds (**4a-d**, **5a-f**, and **6a-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

The formation of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **4a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. In the IR spectrum of compound **4a**, the peaks observed at 1,681 cm^{-1} indicate the presence of C═O group. In the ^{1}H NMR spectrum of compound **4a**, two singlets were observed at δ 8.11 and 10.10 ppm for pyrazolyl and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **4a** revealed that the peak appearing at δ 161.4 ppm is due to the presence of carbonyl carbon. The structure of compound **4a** was also confirmed by a molecular ion peak at *m*/*z* 555.01 $(M + H)^+$. Similarly, the synthesis of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-ones **5a-f** was also confirmed by spectral techniques. In the IR spectrum of compound **5a**, the peak observed at 1,701 cm^{-1} corresponded to the C═O group. In the ^{1}H NMR spectrum of compound **5a**, the three singlets observed at δ 3.92, 8.11, and 10.10 ppm confirm the presence of ─OCH_3, pyrazolyl proton, and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **5a** showed peaks at δ 162.5 and 55.5 ppm, confirming the presence of carbonyl carbon and methoxy carbon, respectively. Furthermore, the structure of compound **5a** was also confirmed by a molecular ion peak at *m*/*z* 573.21 $(M + H)^+$.

Furthermore, the formation of (*Z*)-4-([4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **6a-e** was

confirmed by various spectral techniques. The IR spectrum of compound **6a** showed absorption peaks at 1,707 and 1,666 cm^{-1} corresponding to two carbonyl groups present in the molecules. The ^{1}H NMR spectrum of compound **6a** showed four singlets at δ 2.54 and δ 3.01 ppm for two —CH_3, δ 8.50 ppm for chromone ring proton, and δ 10.54 ppm for olefinic proton. The ^{13}C NMR spectrum of compound **6a** showed that two signals appear at δ 175.4 and 164.2 ppm for the carbonyl carbon of chromone and pyrazolone ring, respectively. In addition, two signals for methyl carbon appear at δ 22.2 and 18.6 ppm. The structure of compound **6a** was also confirmed by mass spectra and by a molecular ion peak observed at m/z 537.11 $(M + H)^+$. Similarly, all the synthesized compounds were characterized by the spectral analysis. Structures of all the synthesized derivatives are shown in Figure S1 (Supporting Information).

2.2 | Biological activity

2.2.1 | Anti-inflammatory activity

The newly synthesized 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) (EC_{50} range = 0.6483 ± 0.221–0.8519 ± 0.281 μg/ml) exhibited moderate anti-inflammatory activity compared to the standard drug diclofenac sodium. Among all the synthesized compounds, except compounds **4c**, **5c**, **5e**, **6d**, and **6e**, all other compounds exhibited a minimum inhibitory concentration (MIC) of 200 μg/ml compared to the standard drug diclofenac sodium (Table 2).

The percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 2. Furthermore, the comparative percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 3.

TABLE 2 Anti-inflammatory and antioxidant activity of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (MIC in μg/ml)

Compound	Anti-inflammatory	Antioxidant
4a	200	>100
4b	200	>400
4c	400	>200
4d	200	>200
5a	200	<100
5b	200	>200
5c	NT	NT
5d	200	<100
5e	800	<100
5f	200	<100
6a	200	<100
6b	200	<100
6c	200	>200
6d	800	>100
6e	400	<100
Diclofenac sodium	50	-
Ascorbic acid	-	<50

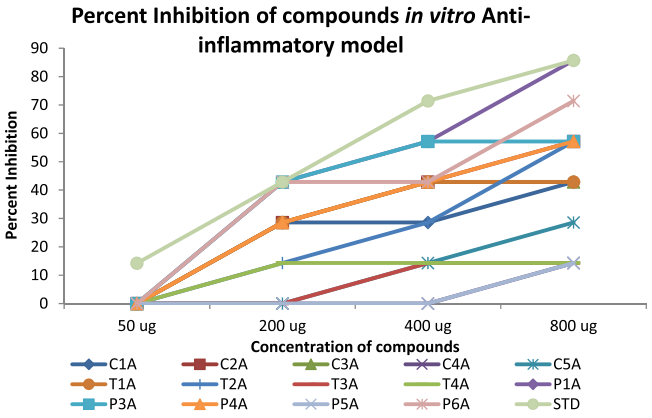


FIGURE 2 The percent inhibition of compounds in an in vitro anti-inflammatory model

2.2.2 | Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed in vitro by the DPPH radical scavenging assay.[28] Ascorbic acid (AA) has been used as a standard drug for the comparison of antioxidant activity, and the observed results are summarized in Table 2.

According to the DPPH assay, compounds **5a**, **5d**, **5e**, **5f**, **6a**, **6b**, and **6e** (IC_{50} = <100 μg/ml) exhibited excellent antioxidant activity compared to the standard antioxidant drug AA (IC_{50} = <50 μg/ml). The remaining synthesized compounds display comparable antioxidant activity than the standard drug butylated hydroxytoluene (Table 2). The percent inhibition of compounds in the in vitro antioxidant model is shown in Figure 4.

2.3 | Computational study

2.3.1 | In silico ADME

An important task for the lead compounds is early prediction of drug likeness properties as it resolves the cost

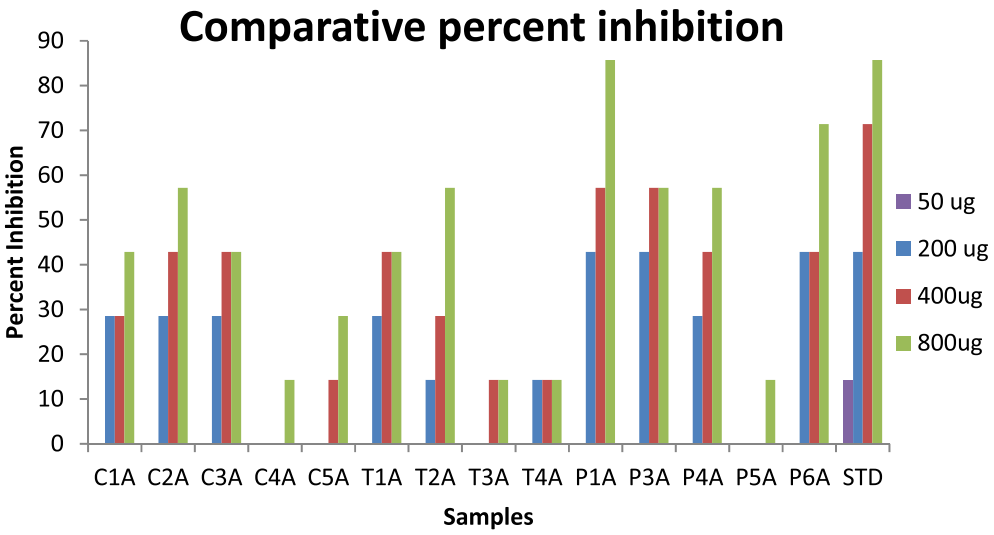


FIGURE 3 The comparative percent inhibition of compounds in an in vitro anti-inflammatory model

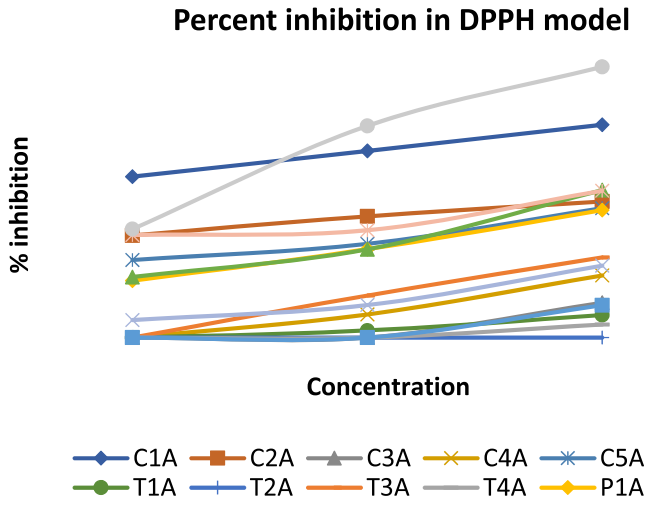


FIGURE 4 The percent inhibition of compounds in an in vitro antioxidant model

and time issues of drug development and discovery. Due to the inadequate drug likeness properties of many active agents with a significant biological activity, these compounds have failed in clinical trials.[29] On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using the Molinspiration online property calculation toolkit,[30] and data are summarized in Table 3.

All the compounds exhibited noteworthy values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants, which characterized these agents to be likely orally active. For the synthesized compound **6e**, the data obtained were within the range of accepted values. Parameters such as the number of rotatable bonds and total polar surface area are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which are reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules.

3 | EXPERIMENTAL SECTION

All organic solvents were acquired from Poona Chemical Laboratory, Pune and Research-Lab Fine Chem Industries, Mumbai and were used as such without further purification. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in *Raga's* synthetic microwave oven. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) fourier transform infrared spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Advance neo 500 spectrophotometers using tetramethylsilane as an internal standard, and $CDCl_3$ and dimethyl sulphoxide-d_6 as solvent and chemical shifts, respectively, were expressed as δ ppm units. Mass spectra were obtained on Waters quadrupole time-of-flight micromass (ESI-MS) mass spectrometer.

3.1 | General procedure for the synthesis of synthesize new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (4a-d, 5a-f and 6a-e)

Conventional method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-

TABLE 3 Pharmacokinetic parameters of (**4a-d**, **5a-f**, and **6a-e**) compounds

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	-
4a	90.81	52.72	5	397.75	554.42	5.83	5	0	2	−0.68
4b	90.81	52.72	5	420.56	651.31	6.92	5	0	2	−0.84
4c	90.81	52.72	5	411.28	588.87	6.63	5	0	2	−0.25
4d	90.81	52.72	5	415.63	633.32	6.76	5	0	2	−0.56
5a	87.62	61.96	6	432.58	578.42	6.10	6	0	2	−0.46
5b	90.81	52.72	5	407.04	548.39	6.04	5	0	2	−0.80
5c	87.62	61.96	6	437.51	596.41	6.19	6	0	2	−0.22
5d	90.81	52.72	5	423.60	562.42	6.49	5	0	2	−0.51
5e	87.62	61.96	7	447.32	632.39	7.01	6	0	2	−0.45
5f	90.81	52.72	5	434.11	617.28	7.33	5	0	2	−0.36
6a	86.53	65.11	3	374.21	536.76	6.25	5	0	2	−0.53
6b	86.53	65.11	3	357.65	522.74	5.87	5	0	2	−0.36
6c	86.53	65.11	3	341.09	508.71	5.49	5	0	2	−0.32
6d	86.53	65.11	3	354.62	543.15	6.10	5	0	2	−0.93
6e	86.53	65.11	3	344.11	488.29	5.26	5	0	1	−0.81

Abbreviations: % ABS, percentage absorption; TPSA, topological polar surface area; n-ROTB, number of rotatable bonds; MV, molecular volume; MW, molecular weight; milogP, logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors, number of hydrogen bond acceptors; n-OHNH donors, number of hydrogen bonds donors.

one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask using glacial acetic acid (5 ml) as a solvent and were refluxed for the period of time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Ultrasound method: A mixture of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) in acetic acid (5 ml) was taken in a 50-ml round-bottom flask. The mixture was irradiated in the water bath of an ultrasonic cleaner at 35–40°C for a period of time indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water, and the obtained solid was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Microwave irradiation method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask (RBF) using glacial acetic acid (5 ml) as a solvent, and the contents of RBF were subjected to MW irradiation for the period of time indicated in Table 1 at 350 W. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

3.1.1 | (4*E*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) methylene)-1*H*-pyrazol-5(4*H*)-one (4a)

Orange solid; Wt. 930 mg, Yield 84%; IR(ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,598 (C=N), 1,519 (C=C), 1,234 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.35–7.91 (m, 8H, Ar—H), 8.11 (s, 1H, pyrazolyl-H), 10.10 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 161.4 (C=O), 151.7, 140.1, 137.8, 134.9, 131.1, 130.0, 129.6, 129.1,

128.70, 128.6, 119.7, 115.7, 113.5; MS (ESI-MS): *m/z* 555.01 $(M + H)^+$.

3.1.2 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4b)

Orange solid; Wt. 1.05 g; Yield 81%; IR (ν_{max}/cm^{-1}): 2,927 (=C—H), 1,680 (C=O), 1,598 (C=N), 1,516 (C=C), 1,231 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, J = 3.50 Hz, Ar—H), 7.26–7.19 (m, 3H, Ar—H), 7.84 (dd, 2H, *J* = 5.00 Hz and 9.00 Hz, Ar—H), 8.10 (s, 1H, pyrazole-H), 10.11 (s, 1H, =C—H); MS: *m/z* 651.03 $(M + H)^+$.

3.1.3 | (4*E*)-4-((3-[5-Chlorothiophen-2-yl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4c)

Orange solid; Wt. 873 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,682 (C=O), 1,597 (C=N), 1,518 (C=C), 1,232 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 1H, Ar—H), 7.26–7.18 (s, 1H, Ar—H), 7.44 (d, 1H, *J* = 6.00 Hz, Ar—H), 7.52 (m, 2H, Ar—H), 7.86 (d, 2H, *J* = 7.00 Hz, Ar—H), 8.11 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 151.3, 139.5, 138.3, 135.0, 133.5, 130.8, 130.0, 128.8, 127.6, 127.4, 120.0, 116.3, 114.6; MS: *m/z* 547.11 $(M + H)^+$.

3.1.4 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4d)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,597 (C=N), 1,520 (C=C), 1,235 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, *J* = 4.00 Hz, Ar—H), 7.21 (d, 1H, *J* = 3.50 Hz, Ar—H), 7.44 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.75–7.86 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.47 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 183.2 (C=O), 162.3, 151.2, 143.2, 142.9, 139.4, 138.3, 134.9, 133.7, 133.4, 131.2, 130.6, 129.8, 129.1, 128.8, 128.5, 128.2, 120.6, 119.9, 119.6, 116.2, 115.9, 114.6; MS: *m/z* 633.05 (M + H).

3.1.5 | (4*Z*)-3-(Trifluoromethyl)-4-((3-[4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5a)

Orange solid; Wt. 971 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,141 (=C—H), 1,703 (C=O), 1,595 (C=N), 1,514 (C=C), 1,224 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.92 (s, 3H, —OCH_3), 7.10 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.51 (t, 2H, *J* = 8.50 Hz, Ar—H), 7.62 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.90 (d, 2H, *J* = 9.00 Hz, Ar—H), 7.99 (s, 1H, pyrazole-H), 10.19 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 161.1, 158.7, 143.3, 141.4, 138.6, 134.9, 130.7, 129.7, 128.5, 122.6, 120.1, 116.8, 114.7, 113.7, 55.5 (OCH_3); MS: *m/z* 579.21 $(M + H)^+$.

3.1.6 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1H-pyrazol-5(4*H*)-one (5b)

Orange solid; Wt. 876 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,142 (=C—H), 1,701 (C=O), 1,595 (C=N), 1,510 (C=C), 1,223 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42 (m, 1H, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.57–7.58 (m, 3H, Ar—H), 7.68 (dd, 2H, *J* = 7.50 and 2.00 Hz, Ar—H), 7.90 (d, 2H, *J* = 8.00 Hz, Ar—H), 8.00 (s, 1H, pyrazole-H), 10.22 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 158.8, 143.0, 141.2, 138.6, 134.9, 130.3, 129.9, 129.7, 129.4, 129.2, 128.6, 120.0, 116.8, 114.0; MS: *m/z* 549.19 $(M + H)^+$.

3.1.7 | (4*Z*)-4-((3-[2-Fluoro-4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5c)

Orange solid; Wt. 1.06 g; Yield 82%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,702 (C=O), 1,596(C=N), 1,512 (C=C), 1,221 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.91 (s, 3H, —OCH_3), 6.82 (dd, 1H, *J* = 2.50 and 12.00 Hz, Ar—H), 6.91 (dd, 1H, *J* = 2.00 and 8.50 Hz, Ar—H), 7.42 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.58–7.49 (m, 2H, Ar—H), 7.79 (d, 1H, *J* = 2.50 Hz, Ar—H), 7.88 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.52 (s, 1H, pyrazole-H), 10.20 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.7 (C=O), 162.6, 162.5, 154.1, 141.2, 138.6, 134.7, 132.5, 129.7, 128.5, 120.0, 117.6, 113.9, 111.2, 110.3, 102.2, 102.0, 55.8 (OCH_3); MS: *m/z* 653.26 $(M + H)^+$.

3.1.8 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-one (5d)

Orange solid; Wt. 887 mg; Yield 79%; IR (ν_{max}/cm^{-1}): 3,143 (=C—H), 1,701 (C=O), 1,594 (C=N), 1,511 (C=C), 1,220 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.44 (s, 3H, —CH_3), 7.45 (d, 1H, J = 7.50 Hz, Ar—H), 7.51 (t, 1H, J = 7.50 Hz, Ar—H), 7.62 (d, 1H, J = 8.00 Hz, Ar—H), 7.65 (d, 1H, J = 8.00 Hz, Ar—H), 9.90 (s, 1H, pyrazole-H), 11.96 (s, 1H, =C—H); MS: m/z 563.08 $(M + H)^+$.

3.1.9 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(4-[trifluoro methoxy]phenyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (5e)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,700 (C=O), 1,595 (C=N), 1,517 (C=C), 1,225 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42–7.44 (m, 3H, Ar—H), 7.51–7.54 (m, 2H, Ar—H), 7.71 (d, 1H, J = 2.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.00 Hz, Ar—H), 7.88 (d, 1H, J = 2.00 Hz, Ar—H), 7.90 (d, 1H, J = 3.50 Hz, Ar—H), 7.92 (s, 1H, pyrazole-H), 10.21 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 157.3, 150.5, 143.2, 142.9, 140.3, 138.5, 134.9, 130.9, 129.8, 129.0, 128.7, 121.5, 120.6, 120.0, 118.4, 116.6, 114.4; MS: m/z 633.23 $(M + H)^+$.

3.1.10 | (4*Z*)-4-((3-[3,4-Dichlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5f)

Orange solid; Wt. 1.03 g; Yield 84%; IR (ν_{max}/cm^{-1}): 3,144 (=C—H), 1,701 (C=O), 1,596 (C=N), 1,517 (C=C), 1,227 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.44 (m, 1H, Ar—H), 7.48 (d, 1H, J = 2.00 Hz, Ar—H), 7.50 (d, 1H, J = 2.00 Hz, Ar—H), 7.53 (d, 1H, J = 7.50 Hz, Ar—H), 7.67 (d, 1H, J = 8.50 Hz, Ar—H), 7.83 (d, 1H, J = 2.00 Hz, Ar—H), 7.87–7.89 (m, 2H, Ar—H), 7.89 (s, 1H, pyrazole-H), 10.18 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.3 (C=O), 156.1, 143.2, 142.9, 139.7, 138.4, 135.0, 134.5, 133.7, 131.2, 131.1, 130.3, 129.8, 128.8, 128.3, 120.0, 116.4, 114.7; MS: m/z 617.15 $(M + H)^+$.

3.1.11 | (*Z*)-4-([6-Chloro-5,7-dimethyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6a)

Orange solid; Wt. 900 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,666 (C=O), 1,624 (C=N), 1,508 (C=C), 1,192 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 3.01 (s, 3H, —CH_3), 7.26 (s, 1H, Ar—H), 8.50 (s, 1H, chromone-H), 10.54 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 175.4 (C=O), 164.2 (C=O), 162.3, 155.1, 144.5, 143.4, 143.3, 139.7, 134.7, 120.9, 120.2, 119.4, 118.3, 118.2, 118.1, 22.2 (—CH_3), 18.6 (—CH_3); MS: m/z 537.11 $(M + H)^+$.

3.1.12 | (*Z*)-4-([6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6b)

Orange solid; Wt. 783 mg; Yield 75%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,705 (C=O), 1,664 (C=O), 1,627 (C=N), 1,508 (C=C), 1,192 (C—F);^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 7.47 (s, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 8.48 (s, 1H, chromone-H), 10.62 (s, 1H, =C—H); MS: m/z 523.08 $(M + H)^+$.

3.1.13 | (*Z*)-4-([6-Chloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6c)

Orange solid; Wt. 812 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,662 (C=O), 1,621 (C=N), 1,509 (C=C), 1,193 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.55 (d, 1H, J = 9.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.50 and 9.00 Hz, Ar—H), 8.26 (d, 1H, J = 2.50 Hz, Ar—H), 8.47 (s, 1H, chromone-H), 10.63 (s, 1H, =C—H); MS: m/z 509.08 $(M + H)^+$.

3.1.14 | (*Z*)-4-([6,8-Dichloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6d)

Orange solid; Wt. 845 mg; Yield 78%; IR (ν_{max}/cm^{-1}): 3,078 (=C—H), 1,707 (C=O), 1,665 (C=O), 1,626 (C=N), 1,506 (C=C), 1,194 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.83 (d, 1H, J = 2.50 Hz, Ar—H), 8.17 (d, 1H, J = 2.50 Hz, Ar—H), 8.40 (s, 1H, chromone-H), 10.66 (s, 1H, =C—H); MS: m/z 543.07 $(M + H)^+$.

3.1.15 | (*Z*)-4-([7-Methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6e)

Orange solid; Wt. 800 mg; Yield 82%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,703 (C=O), 1,666 (C=O), 1,627 (C=N), 1,510 (C=C), 1,193 (C—F);^{1}H NMR spectrum, δ, ppm: 2.51 (s, 3H, —CH_3), 7.48 (d, 1H, J = 8.00 Hz, Ar—H), 7.60 (dd, 1H, J = 8.00 and 2.00 Hz, Ar—H), 8.08 (d,1H, J = 1.50 Hz), 8.54 (s, 1H, chromone-H), 10.64 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 174.5 (C=O), 165.5 (C=O), 162.4, 154.2, 143.4, 142.4, 137.5, 136.3, 126.2, 120.9, 123.3, 120.2, 118.6, 118.5, 118.2, 118.1, 21.1 (—CH_3); MS: m/z 489.14 $(M + H)^+$.

3.2 | Anti-inflammatory activity

All the synthesized compounds were screened for their in vitro anti-inflammatory activities against the standard drug diclofenac sodium. The minimum inhibitory concentration was determined by the well diffusion method at 1 mg/ml of concentration. (Table 2). A volume of 1 ml of diclofenac sodium at different concentrations (50, 100, 200, 400, 800, and 1,000 μg/ml) was homogenized with 1 ml of aqueous solution of bovine serum albumin (5%) and incubated at 27°C for 15 minutes. The mixture of distilled water and bismuth sulphite agar constituted the control tube. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 minutes at 70°C. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 255 nm. Each test was conducted thrice. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = \text{absorbance of control} - \text{absorbance of sample} / \text{absorbance of control} \times 100.$$

3.3 | In silico ADME

In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[31] using the Molinspiration online property calculation toolkit.[30] Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA).[32] Drug likeness model score (a collective property of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound that is represented by a numerical value) was computed by MolSoft software.[33]

4 | CONCLUSIONS

In conclusion, we have constructed pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional and nonconventional methods like microwave irradiation and ultrasonication, respectively, via Knoevenagel condensation and evaluated their biological activity. Ultrasonication and microwave irradiation can shorten the reaction time from a few hours to a few minutes and increases the product yield (74–84%) compared to the conventional method (59–75%). The synthesized compounds exhibited promising anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, the synthesized compound displayed promising antioxidant activity compared to the standard drug. Furthermore, an analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as an oral drug candidate, thus suggesting that compounds from the present series can be further optimized and developed as a lead molecule.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Microwave-assisted Synthesis, Characterization, and Antibacterial Screening of Some Pyrazolone Derivatives

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ABSTRACT 1-(4-(4-Chlorophenyl)thiazol-2-yl)-3-propyl-1*H*-pyrazol-5(4*H*)-one **5** was prepared by the reaction of 1-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine and ethyl 3-oxohexanoate. Compound **5** was condensed with different 4-formylpyrazoles **8a-f** to give product **9a-f** through Knoevenagel condensation. The reaction was carried out by both conventional and non-conventional methods. The structures of all the newly synthesized compounds were confirmed with the help of spectral techniques. All the compounds were screened for antibacterial activity. Compounds **9a**, **9d**, and **9e** exhibited good antibacterial activity against *Bacillus subtilis*.

KEYWORDS Knoevenagel condensation. Pyrazolone. Thiazoles. Thiophene.

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INTRODUCTION

The Knoevenagel condensation reaction has been widely employed for C-C bond formation in organic synthesis[1] and their products are the key intermediates for the synthesis of various natural and therapeutic drugs, polymer, and perfumes.[2,3] Lewis bases and acids have been reported as catalysts in the Knoevenagel condensation, including Ni-SiO_2,[4] synthetic phosphate $Na_2CaP_2O_7$,[5] $Ca_2P_2O_7$,[5] and natural phosphate ([NP]/KF or NP/$NaNO_3$).[6] Ionic liquids[7] have been also used as catalysts in Knoevenagel condensation.

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities such as anti-inflammatory,[8] antitubercular,[9] antimicrobial,[10] angiogenesis,[11] and neuroprotective.[12] Various pyrazole derivatives exhibit anti-inflammatory,[13] analgesic,[13] antiproliferative,[14] and antihepatotoxic[15] activities.

Thiophene is sulfur-containing a five-membered heterocyclic compound. Various biological activities associated with thiophene derivatives are BACEI inhibitors,[16] HIV protease inhibitor,[17] antibreast cancer,[18] acetylcholinesterase inhibitors,[19] and antidepressant.[20]

The pyrazolone skeleton exists in the core structure of several biologically active compounds and natural products.[21] Antipyrine[22] was the first synthetic drug containing pyrazolone ring as the main framework which has been used as an analgesic and antipyretic. Pyrazolone derivatives show a broad spectrum of biological activities such as severe acute respiratory syndrome-coronavirus 3C-like protease inhibitors,[23] cytotoxic,[24] antitubulin,[24] anaplastic lymphoma kinase inhibitors,[25] anti-inflammatory,[26] and analgesic.[26] Some of the chlorine-containing compounds exhibit anti-inflammatory,[27] analgesic,[28] antibacterial,[29] and antifungal[30] activities.

The application of microwave (MW) and ultrasound irradiation as a non-conventional energy source for the activation of reactions has now become a very popular and useful technology in organic chemistry.[31-33] These methods lead to enhanced conversion rates, higher yields, and easier work-up.

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Synthesis and Antibacterial Screening of Some New Pyrazolylchromones and Pyrazolylcoumaran-3-ones

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ABSTRACT Some new pyrazolylchromones **4a-e** (flavone analogs) and pyrazolylcoumaran-3-ones **5a-e** (aurone analogs) were synthesized by refluxing chalcones **3a-e** in dimethyl sulfoxide/I_2 and Pyridine/$Hg(OAc)_2$, respectively. Spectral techniques such as infrared, proton nuclear magnetic resonance, and mass spectrometry were used to confirm the structures of newly synthesized compounds. These compounds were studied for their antibacterial activities toward *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Salmonella typhi*. Some of these compounds showed promising activity against test organisms.

KEYWORDS: Pyrazoles, Flavones, Aurones, Antibacterial activity.

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INTRODUCTION

Treatment of various diseases is a worldwide serious issue. The emergence of newer infectious diseases, multidrug resistance developing in microbial strains, diseases due to homeostatic disturbances, toxicity associated with existing drugs have created a need of selective, potential therapeutic agents. In search of potential therapeutic agents, many natural and synthetic compounds have been investigated. Many of the natural products are heterocycles which possess medicinal properties and serve as lead molecules for drug discovery.[1] Lead modification is an important step in drug design and development.

Pyrazole containing compounds are medicinally useful because of their various therapeutic properties, including antimicrobial,[2,3] anti-inflammatory,[4] antitubercular,[5] antitumor,[6] antidiabetic,[7] and antiviral and antioxidant[8] properties.

Flavonoids are extensively studied plant products for their biological potential. Chalcones are important intermediates in the flavonoid synthetic pathway and also have medicinal properties.[9] These are known to exhibit antibacterial,[10] antitubercular,[11] anti-inflammatory,[12,13] antimalarial,[14] antifungal,[15] and antiviral[16] activities. Synthetic chalcones with heterocyclic rings have been investigated for medicinal properties and are also used in the synthesis of various heterocycles. Pyrazole containing chalcones exhibits potential antimicrobial,[17] antioxidant,[18] and anticancer[19] activities.

Flavones and aurones are medicinally useful members of the flavonoid family. Flavones are widely known for their interesting bioactivities. As a consequence of the

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

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WILEY

ARTICLE

Synthesis and characterization of novel 2-(1-benzyl-3-[4-fluorophenyl]-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives

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Abstract

Novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**. The base catalyzed condensation of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** gave (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e**. On cyclization with dimethyl sulfoxide (DMSO)/I_2, compounds **5a** to **5e** gave 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e**. Structures of all novel compounds were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and mass spectral data. All the synthesized compounds were screened for their antibacterial activities.

1 | INTRODUCTION

Chromones (4*H*-1-benzopyran-4-one, 4*H*-chromen-4-one) are the heterocyclic compound widely distributed in nature.[1] Chromone-containing compounds display various pharmacological properties such as antifungal,[2] antimalarial,[3] anticancer,[4] antibacterial,[5] and are also well known as an antidiabetic and cardiovascular agents.[6,7] Pyrazole-containing compounds show antiangiogenic,[8] antimalarial,[9] antifungal,[10] antitubercular,[11] antimicrobial,[11] and anticancer[12] activities.

Currently, there are more than 200 pharmaceutical drugs available in market containing fluorine atom. Fluorine and fluorine-containing substituent can impart many effects on properties of organic compounds.[13,14] Fluorine-containing compounds exhibit fungicidal,[15] herbicidal,[16] antiviral,[17] antipyretic,[18] and analgesic[19] activities.

Considering the biological importance of chromone, pyrazole, and fluorine nucleus, we have reported the synthesis, characterization, and antibacterial screening of novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**, (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** and 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives **6a** to **6e**.

2 | RESULT AND DISCUSSION

1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via the Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**.[20] (*E*)-3-(1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** were synthesized from the reaction of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** in 10% aq. KOH. The synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-

7-fluoro-4*H*-chromen-4-ones **6a** to **6e** was achieved by reaction of (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** with dimethyl sulfoxide (DMSO)/I_2 (Scheme 1 and Section 3).

Structures of all the synthesized compounds were confirmed by using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and liquid chromatography-mass spectrometry (LC-MS) spectroscopic techniques.

2.1 | Antibacterial activities

All the synthesized compounds were screened for their antibacterial activities. The bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* were used. The zone of inhibition in millimeter was determined by the well diffusion method at 1 mg/mL of concentration, and Ampicillin was used as reference drugs. The results of antibacterial activity are shown in Table 1.

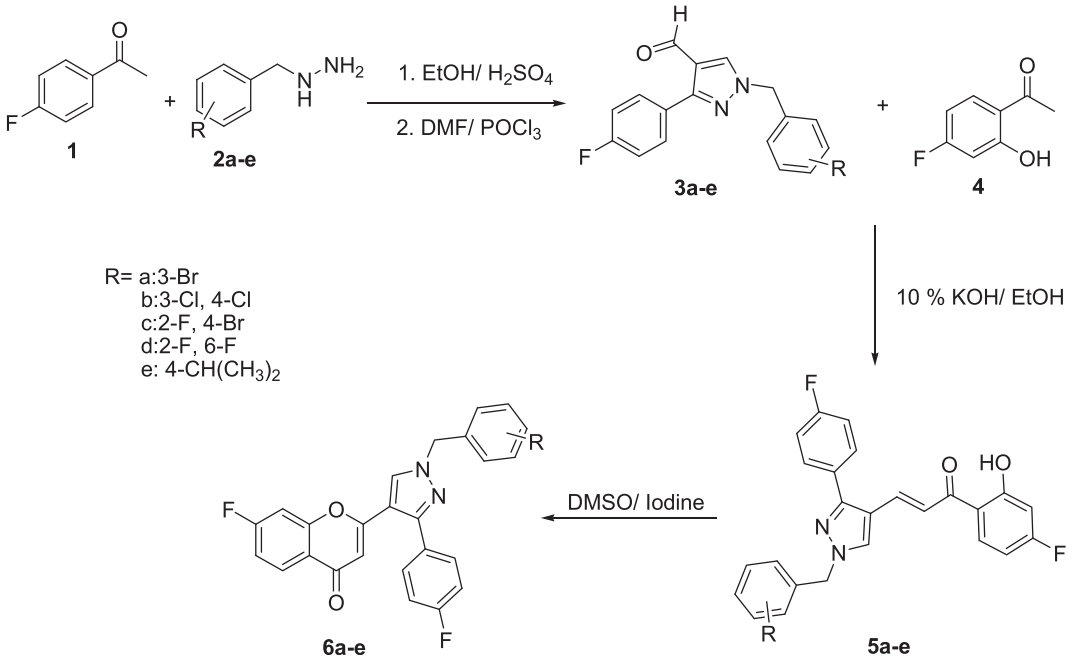
The results given in Table 1 indicated that compounds **3c**, **3d**, **3d**, **6a**, **6b**, **6c**, and **6d** exhibited good antibacterial activity against *E. coli* bacterial strain. Compounds **3c** to **3e**, **5e**, and **6a** to **6e** exhibited good antibacterial activity against *P. aeroginosa*. While compounds **3e** and **6a** to **6d** exhibited good antibacterial activity against *B. subtilis* and *S. aureus* compared with the standard Ampicillin. While other compounds were found to be less to moderately active against all bacterial strains.

3 | EXPERIMENTAL

The melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (attenuated total reflection [ATR]) Fourier transform infrared (FTIR) spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian 400 spectrophotometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent, and chemical shifts were expressed as δ parts per million units. Mass spectra were obtained on Shimadzu (LC-MS) mass spectrometer.

3.1 | General procedure for synthesis of 1-benzyl-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehydes (3a-e)

A mixture of substituted 1-benzylhydrazine (0.01 mol) and catalytic amount of concencentated H_2SO_4 was added to a solution of 1-(4-fluorophenyl)ethanone (0.01 mol) in 20 mL of ethanol. The mixture was refluxed for 1 hour, and the 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine formed was filtered and dried. A mixture of dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) was cooled with constant stirring at 0°C. A solution of 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine in DMF was added dropwise to the reaction mixture and then heated at 70 to 80°C for 5 hours. After completion of reaction, contents were cooled to room temperature and poured onto ice-cold water, and then it was made alkaline with saturated K_2CO_3 solution. The



SCHEME 1 Synthetic approach to the title compounds

TABLE 1 Antibacterial activities of the synthesized compounds (zone of inhibition in millimeter)

Compound	*Escherichia coli*	*Pseudomonas aeroginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
3a	8	10	10	12
3b	9	10	10	11
3c	14	13	12	12
3d	15	14	12	13
3e	16	15	14	17
5a	9	11	12	11
5b	9	10	10	12
5c	8	10	10	9
5d	10	11	10	9
5e	12	14	13	12
6a	16	15	14	16
6b	14	15	14	16
6c	16	14	16	17
6d	14	15	15	16
6e	12	14	9	10
Ampicillin	16	15	17	18

precipitate formed was crystallized from ethanol to get pure 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a-e**.

3.2 | 1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3a)

Yield: 71%, White solid, mp 58-60°C. IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.45 (s, 2H, —CH_2), 7.25-7.35 (m, 4H, Ar—H), 7.52-7.60 (m, 2H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.92, 115.17, 115.38, 120.48, 127.96, 128.36, 130.10, 130.52, 130.61, 130.85, 131.24, 137.09, 138.35, 150.91, 161.21, 163.66, 184.33; MS (LC-MS): *m/z* 358.95 $(M + H)^+$.

3.3 | 1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3b)

Yield: 65%, White solid. mp 190-192°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 7.26-7.36 (m, 3H, Ar—H), 7.64-7.68 (m, 2H, Ar—H), 7.86-7.89 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); MS (LC-MS): *m/z* 349 $(M + H)^+$.

3.4 | 1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3c)

Yield: 69%; White solid; mp 64-66°C; IR (ν_{max}/cm^{-1}): 3113 (═C—H), 2822 (aldehyde C—H), 1673 (C═O), 1656 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 7.29 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.35 (t, 1H, *J* = 8 Hz, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.66, 115.40, 115.62, 116.20, 116.42, 119.34, 119.58, 121.08, 121.23, 123.26, 123.35, 127.44, 127.85, 128.02, 128.05, 130.53, 130.61, 131.57, 131.60, 131.77, 131.86, 134.57, 152.82, 159.01, 161.53, 161.97, 164.45, 184.20; MS (LC-MS): *m/z* 376.95 $(M + H)^+$.

3.5 | 1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3d)

Yield: 61%; White solid; mp 68-70°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2824 (aldehyde C—H), 1677 (C═O), 1654 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 2H, —CH_2), 7.18 (t, 2H, *J* = 8 Hz, Ar—H), 7.26 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.50 (t, 1H, *J* = 8 Hz, Ar—H), 7.83 (m, 2H, Ar—H), 8.66 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.32, 111.38, 111.57, 111.75, 112.00, 115.17, 115.38, 120.24,

127.96, 130.49, 130.57, 131.43, 131.53, 131.64, 138.50, 150.59, 159.75, 161.20, 162.15, 163.64, 184.38; MS (LC-MS): *m/z* 317.05 $(M + H)^+$.

3.6 | 1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3e)

Yield: 64%; White solid; mp 52-54°C; IR (ν_{max}/cm^{-1}): 3111 (=C—H), 2821 (aldehyde C—H), 1672 (C=O), 1656 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.1 (d, 6H, —CH_3), 2.8 (m, 1H, —CH), 5.4 (s, 2H, —CH_2), 7.23-7.30 (m, 6H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); MS (LC-MS): *m/z* 323.05 $(M + H)^+$.

3.7 | General procedure for synthesis of (E)-3-(1-Benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-ones (5a-e)

A mixture of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** (0.005 mol) with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** (0.005 mol) was stirred in ethanolic KOH (10%) for 16 hours at room temperature. After completion of reaction, contents were poured onto ice-cold water and then acidified with concentrated hydrochloric acid (HCl). The precipitate formed was filtered off, washed with water, and crystallized from ethanol to get the pure product **5a-e**.

3.8 | (E)-3-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5a)

Yield: 74%; Yellow solid; mp 80-82°C; IR (ν_{max}/cm^{-1}): 1637 (C=O), 1590 (C=N), 1569 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.33-7.39 (m, 4H, Ar—H), 7.53-7.61 (m, 4H, Ar—H), 7.70-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =C—H), 8.21 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.75 (s, 1H, pyrazolyl-H), 13.09 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.73, 104.12, 104.36, 106.79, 107.02, 115.65, 115.86, 117.58, 119.62, 121.84, 126.97, 128.52, 130.36, 130.44, 130.63, 130.90, 132.31, 133.04, 133.16, 135.87, 139.10, 151.29, 161.01, 163.46, 164.46, 164.60, 165.14, 167.67, 192.09; MS (LC-MS): *m/z* 495.10 $(M + H)^+$.

3.9 | (E)-3-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5b)

Yield: 72%; Yellow solid; mp 158-160°C; IR (ν_{max}/cm^{-1}): 1641 (C=O), 1594 (C=N), 1524 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.81-6.87 (m, 2H, Ar—H), 7.33-7.44 (m, 3H, Ar—H), 7.59 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.66-7.68 (m, 2H, Ar—H), 7.69-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.19 (t, 1H, *J* = 8 Hz, Ar—H), 8.73 (s, 1H, pyrazolyl-H), 13.07 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.34, 104.98, 105.22, 106.86, 107.08, 115.76, 115.97, 116.83, 118.83, 127.23, 128.22, 129.90, 129.97, 130.48, 130.56, 131.06, 131.49, 131.60, 132.92, 133.22, 135.43, 136.10, 152.44, 166.03, 166.18, 192.06; MS (LC-MS): *m/z* 485.05 $(M + H)^+$.

3.10 | (E)-3-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5c)

Yield: 71%; Yellow solid; mp 118-120°C; IR (ν_{max}/cm^{-1}): 1638 (C=O), 1587 (C=N), 1574 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.48 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.32-7.40 (m, 3H, Ar—H), 7.48 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.57 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.63 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.69-7.82 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.23 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 13.10 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.07, 104.13, 104.37, 106.82, 107.03, 115.66, 115.74, 115.87, 117.60, 118.92, 119.16, 119.67, 121.97, 122.07, 122.64, 122.79, 128.00, 128.46, 130.39, 130.47, 132.29, 132.38, 132.43, 133.12, 133.23, 135.80, 151.35, 158.82, 161.02, 161.32, 163.47, 164.47, 164.60, 165.16, 167.68, 192.13; MS (LC-MS): *m/z* 515 $(M + H)^+$.

3.11 | (E)-3-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5d)

Yield: 74%; Yellow solid; mp 184-186°C; IR (ν_{max}/cm^{-1}): 1640 (C=O), 1596 (C=N), 1568 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.17 (t, 2H, *J* = 8 Hz, Ar—H), 7.33 (t, 2H, *J* = 8 Hz, Ar—H), 7.48-7.56 (m, 3H, Ar—H), 7.7 (d, 1H, *J* = 15.8 Hz, =C—H), 7.83 (d, 1H, *J* = 15.6 Hz, =C—H), 8.26 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.14 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.47, 104.09, 104.32, 106.73, 106.95, 111.37, 111.56,

111.75, 111.93, 111.99, 115.59, 115.65, 115.81, 117.45, 119.49, 128.45, 128.48, 130.37, 130.45, 131.37, 131.47, 131.57, 132.10, 133.17, 133.28, 135.82, 151.32, 159.71, 159.79, 161.02, 162.20, 162.27, 163.47, 164.63, 164.77, 165.19, 167.71, 193.20; MS (LC-MS): m/z 453.15 $(M + H)^+$.

3.12 | (E)-3-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5e)

Yield: 77%; Yellow solid; mp 130-132°C; IR (ν_{max}/cm^{-1}): 1635 (C═O), 1595 (C═N), 1567 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 1.17 (d, 6H, CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.25-7.37 (m, 6H, Ar—H), 7.57-7.61 (m, 2H, Ar—H), 7.70-7.81 (AB quartet, 2H, J = 15.8 Hz, ═C—H), 8.23 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.13 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.75, 33.12, 55.41, 104.13, 104.36, 106.79, 107.01, 115.63, 115.75, 115.84, 117.56, 119.36, 126.06, 127.92, 128.63, 130.35, 130.43, 132.01, 133.06, 133.17, 133.90, 136.05, 148.22, 151.04, 160.98, 163.42, 164.49, 164.63, 165.14, 167.67, 192.13; MS (LC-MS): m/z 459.15 $(M + H)^+$.

3.13 | General procedure for synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-ones (6a-e)

Compound **5a** to **5e** (0.002 mol) was dissolved in 15-mL DMSO. To this solution, catalytic amount of iodine was added. The reaction mixture was heated to 140°C for 2 hours. After completion of reaction (checked by thin-layer chromatography [TLC]), content were cooled and poured over crushed ice. The product obtained was filtered, washed with cold water and 10% sodium thiosulphate solution followed by cold water, and crystallized from ethanol to get the pure product **6a** to **6e**.

3.14 | 2-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6a)

Yield: 77%; White solid; mp 200-202°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 1641 (C═O), 1622 (C═N), 1597 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (dd, 1H, J = 8 and 2 Hz, Ar—H), 7.30-7.62 (m, 9H, Ar—H), 8.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.71 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.87, 104.56, 104.82, 107.24, 110.95, 112.30, 113.82, 115.32, 115.54, 116.69, 119.55, 120.72, 122.07, 127.24, 127.74, 127.84, 129.20, 130.97, 131.12, 133.66, 139.25, 149.39, 158.12, 158.50, 158.89, 159.28, 159.63, 163.82, 175.80; MS (LC-MS): m/z 495.10 $(M + H)^+$.

3.15 | 2-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6b)

Yield: 65%; White solid; mp 148-150°C; IR (ν_{max}/cm^{-1}): 3059 (═C—H), 1645 (C═O), 1620 (C═N), 1598 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (d, 1H, J = 8 Hz, Ar—H), 7.27-7.70 (m, 8H, Ar—H), 8.19 (t, 1H, J = 8 Hz, Ar—H), 8.70 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.13, 104.83, 107.23, 110.87, 113.74, 115.32, 115.54, 116.61, 120.59, 127.80, 128.53, 129.00, 130.25, 131.06, 131.39, 133.71, 137.48, 157.96, 158.34, 158.73, 159.10, 175.70; MS (LC-MS): m/z 483.10 $(M + H)^+$.

3.16 | 2-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6c)

Yield: 69%; White solid; mp 220-222°C; IR (ν_{max}/cm^{-1}): 3065 (═C—H), 1643 (C═O), 1620 (C═N), 1594 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.31 (s, 1H), 7.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 7.25-7.78 (m, 8H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.46, 104.43, 104.69, 107.01, 111.87, 113.66, 113.89, 115.14, 115.35, 118.85, 119.09, 120.41, 121.87, 121.96, 122.62, 122.77, 127.48, 127.59, 127.96, 128.77, 130.43, 130.83, 130.91, 132.24, 133.50, 149.04, 156.26, 156.40, 158.73, 159.23, 161.01, 161.24, 163.46, 165.97, 175.44; MS (LC-MS): m/z 513.10 $(M + H)^+$.

3.17 | 2-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6d)

Yield: 72%; White solid; mp 140-142°C; IR (ν_{max}/cm^{-1}): 3110 (═C—H), 1648 (C═O), 1622 (C═N), 1594 (C═C); ^1H NMR (400 MHz, DMSO-d_6): δ = 5.51 s (2H, —CH_2), 6.31 (s, 1H), 7.16-7.57 (m, 9H, Ar—H), 8.04 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.66 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.31, 104.41, 104.66, 106.95, 111.43, 111.70, 111.75, 111.93, 113.58, 113.80, 115.09, 115.30, 120.38, 127.43, 127.54, 128.80, 130.81, 130.89, 131.44, 131.54, 133.25, 148.96, 156.23, 156.37, 159.17, 159.74, 161.00, 162.16, 163.44, 165.94, 175.41; MS (LC-MS): m/z 451.05 $(M + H)^+$.

3.18 | 2-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6e)

Yield: 67%; White solid; mp 280-282°C; IR (ν_{max}/cm^{-1}): 3066 (=C—H), 1644 (C=O), 1620 (C=N), 1592(C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18 (d, 6H, —CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.30 (s, 1H), 7.18-7.36 (m, 8H, Ar—H), 7.58-7.62 (m, 2H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.68 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.76, 33.12, 55.20, 104.44, 104.70, 106.90, 111.81, 113.67, 113.90, 115.16, 115.37, 120.44, 126.57, 127.52, 127.98, 128.98, 130.85, 130.93, 133.17, 133.83, 148.22, 148.76, 156.30, 156.43, 159.46, 161.00, 163.44, 165.99, 175.46; MS (LC-MS): m/z 457.15 $(M + H)^+$.

4 | CONCLUSION

In conclusion, we have synthesized a series of novel 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e** from 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**. All synthesized compounds are characterized by using spectral methods and screened for their antibacterial activities.

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SUPPORTING INFORMATION

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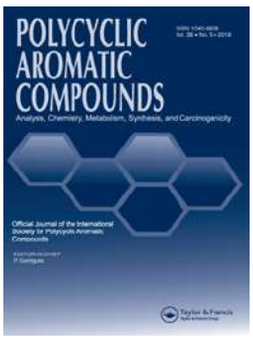

Polycyclic Aromatic Compounds

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Design, Synthesis and Biological Evaluation of Novel Furan & Thiophene Containing Pyrazolyl Pyrazolines as Antimalarial Agents

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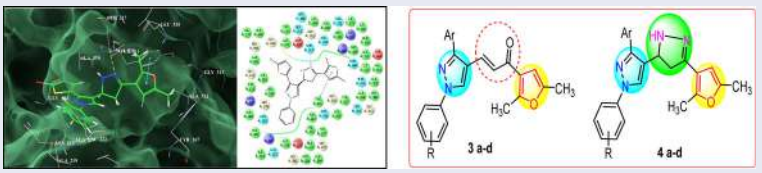
ABSTRACT

In search for novel compounds targeting Malaria, based on the *in silico* molecular docking binding affinity data, the novel furans containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized. The formation of the synthesized compound were confirmed by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Compounds with thiophene and pyrazoline ring **4b** (0.47 μM), **4c** (0.47 μM) and **4d** (0.21 μM) exhibited excellent anti-malarial activity against *Plasmodium falciparum* compared with standard antimalarial drug Quinine (0.83 μM). To check the selectivity furthermore, compounds were tested for antimicrobial activity and none of the synthesized compound exhibited significant potency compared with the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin respectively. So, it can be resolved that the produced compounds show selectively toward antimalarial activity and have the potential to be explored further.



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Introduction

Life-threatening disease Malaria is caused by *Plasmodium* parasites that are spread to people through the bites of infected female Anopheles mosquitoes. Out of five *Plasmodium* Parasites *Plasmodium falciparum* produces high levels of blood-stage parasites that sequester in critical organs in all age groups.[1] As per the World Health Organization report in 2018, in sub Saharan Africa 11 million pregnant women were infected with malaria and 872 000 children were born with a low birth weight. Around 24 million children estimated to be infected with the *P. falciparum* parasite in the region; out of these, 1.8 million had severe anemia and 12 million had

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moderate anemia.[2] Mortality and morbidity caused by malaria are continually increasing. This subject is the consequence of the ever-increasing development of parasite resistance to drugs and also increased mosquito resistance to insecticides which is one of the most critical complications in controlling malaria over recent years.[3]

P. falciparum enoyl-acyl carrier protein (ACP) reductase (ENR) is an enzyme in type II fatty acid synthesis (FAS II) pathway which catalyzes the NADH-dependent reduction of trans-2-enoyl-ACP to acyl-ACP and plays important role in completion of the fatty acid elongation cycles. Due to its role in the parasite's fatty acid pathway, *Pf*ENR has been known as one of the most promising antimalarial targets for structure-based drug design.[4–6] Triclosan, a broadly used antibiotic, is effective inhibitor of *Pf*ENR enzyme activity. Several efforts have been taken in the recent past in the direction of the identification of new antimalarials using pharmacophore modeling, molecular docking and MD simulations.[7–12]

Pyrazole is a well-known class of nitrogen containing heterocyclic compounds and play important role in agricultural and medicinal field. Pyrazole and its derivatives are known to possess antibacterial,[13] antipyretic,[14] fungistatic,[15] anticonvulsant,[16] antitubercular,[17] antipyretic,[18] insecticides,[19] and anti-inflammatory[20] activities. Pyrazoline containing compounds are recognized to possess various pharmacological activities like antimalarial,[21,22] anticancer,[23] anti-inflammatory,[24] analgesic,[24] antitumor,[25] antimicrobial[26] and antidepressant activities.[27] Furan containing compounds possess lipoxygenase inhibitor,[28] urotensin-II receptor antagonists,[29] fungicidal,[30] epidermal growth factor receptor inhibitors and anticancer[31] etc. activities. Chalcone is a natural pigment found in plant and is an important intermediate for the synthesis of flavonoids. Varieties of biological activities are associated with chalcones and their derivatives such as antiplasmodial,[32] nematicide,[33] antiallergenic,[34] antimalarial,[35] anti-HIV,[36] anti-cancer,[37] anti-inflammatory[38] and anti-tuberculosis.[39]

So, considering the biological importance of pyrazoles, furan and chalcone, herein we report the design of a small library of furan containing pyrazolyl pyrazoline derivatives by molecular hybridization approach targeting *Pf*ENR using the *in silico* molecular docking technique. The promising results obtained from this *in silico* study served the basis for the synthesis of these molecules followed by evaluation of their antimalarial potential.

Molecular docking technique plays significant role in lead identification/optimization and in the mechanistic study by predicting the binding affinity and the thermodynamic interactions leading the binding of a ligand to its biological receptor. Thus, with the objective to identify novel leads targeting the crucial antimalarial target *Plasmodium falciparum enoyl-ACP reductase* (*Pf*ENR or FabI) (pdb code: 1NHG), molecular docking was carried out using the GLIDE (Grid-based LIgand Docking with Energetics) program of the Schrodinger Molecular modeling package.[40–42] A small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-3d**, **4a-4d**) was docked against *Pf*ENR. The ensuing docking conformation revealed that these molecules changed a binding mode which is corresponding with the active site of pfENR and were found to be involved in a series of bonded and non-bonded interactions with the residues lining the active site. Their docking scores varied from −6.979 to −8.222 with an average docking score of −7.563 signifying a potent binding affinity to *Pf*ENR. In order to get a quantitative insight into the most significantly interacting residues and their associated thermodynamic interactions, a detailed per-residue interaction analysis was carried out (Table S1, Supporting Information). This analysis showed that the furan containing pyrazolyl chalcones (**3a-d**) (Figure 1) were deeply embedded into the active site of *Pf*ENR engaging in a sequence of favorable *van der Waals* interactions observed with Ile:C369, Phe:C368, IleA323, Ala:A320, Ala:A319, Arg:A318, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Met:A281, Tyr:A277, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110 and Asp:A107 residues through the 1,3-substituted-1*H*-pyrazol-4-yl scaffold while the 1-(2,5-Dimethylfuran-3-yl) prop-2-en-1-one

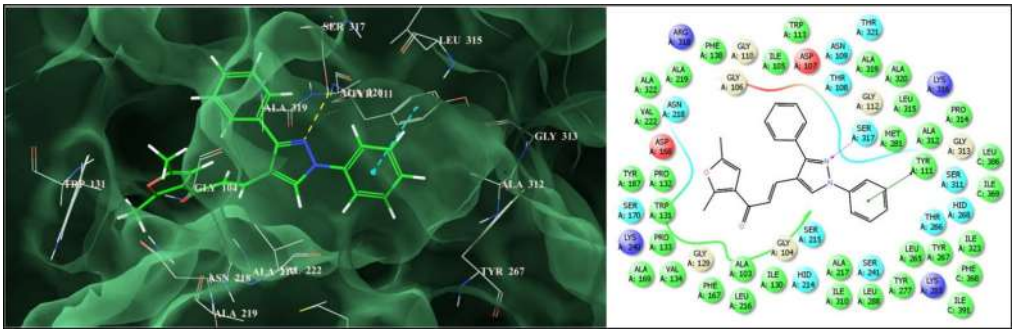


Figure 1. Binding mode of **3a** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

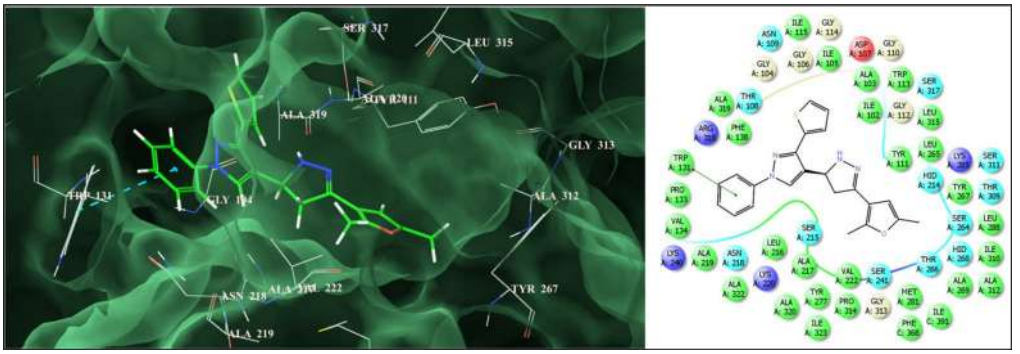
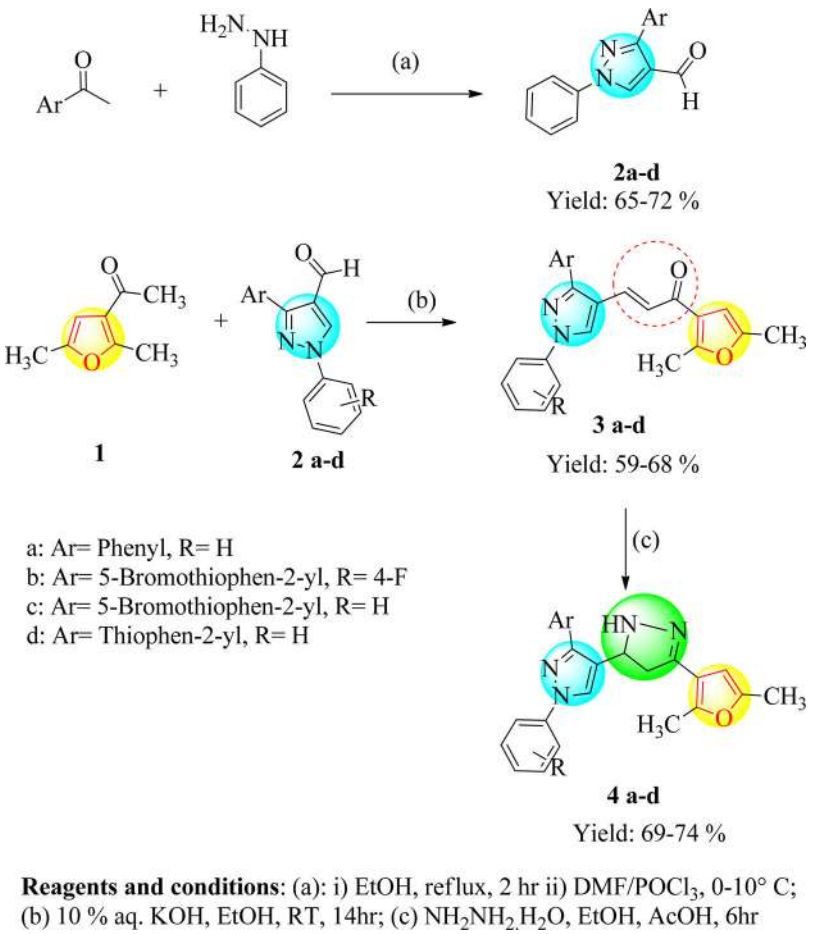


Figure 2. Binding mode of **4d** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

component of the molecules was seen to be involved in similar interactions with Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Gly:A106, Ile:A105, Gly:A104 residues of the active site.

Furthermore the enhanced binding affinity of these molecule is also attributed to significant electrostatic interactions observed with Arg:A318, Ser:A317, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107, Gly:A104 residues lining the active site. On the other hand, the furan containing pyrazoline derivatives (**4a-d**) (Figure 2) were also seen to be stabilized into the active of *Pf*ENR through a network of significant *van der Waals* interactions observed with (2,5-dimethylfuran-3-yl)-1*H*-pyrazolyl scaffold *via* Ile:C369, Phe:C368, Ala:A320, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110, Gly:A106 and Ile:A105 while other half of the molecule i.e., 2-thiophenyl-1-phenyl-1*H*-pyrazole showed similar type of interactions with IleA323, Ala:A319, Arg:A318, Met:A281, Tyr:A277, Val:A222, Ala:A219, Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Ile:A130, Trp:A113, Asp:A107, Gly:A104 residues.

Further the enhanced binding affinity of the molecules is also attributed to favorable electrostatic interactions observed with Arg:A318, Ser:A317, Glu:A289, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107 and Gly:A104. While these non-bonded interactions (*van der Waals* and electrostatic) were observed to be the major driving force for the mechanical interlocking of these novel furan containing pyrazolyl pyrazoline derivatives into the active site *Pf*ENR, the enhanced binding affinity of these molecules is also contributed by very prominent hydrogen bonding interaction observed for **3a** (Ser:A317(2.708 Å)), **4a** (Ser:A317(2.783 Å)), **4b** (Ser:A317(2.462 Å)) and **4c** (SerA317(2.462 Å)). Furthermore these



Scheme 1. Synthesis of pyrazolyl chalcones (**3a-d**) and pyrazolyl pyrazolines (**4a-d**).

molecules were also engaged in a very close π-π stacking interactions: **3a**: Tyr: A111(2.669 Å), **3b**: Tyr:A267(2.529 Å), **3c**: Tyr:A267(2.541 Å), **3d**: Tyr:A267(2.335 Å), **4a**: Tyr:A111(2.602 Å), **4b**: Trp:A131(2.073 Å), **4c**: TyrA:111(2.073 Å) and **4d**: TrpA131(2.538 Å) (Figures S1–S6, Supporting Information).

This type of bonded interactions i.e., hydrogen bonding and π-π stacking are known to serve as an "anchor" to guide the alignment of a molecule into the 3D space of enzyme's active site and facilitate the non-bonded interactions (*Van der Waals* and electrostatic) as well. Overall, the in-silico binding affinity data suggested that these furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) could be developed as novel scaffold to arrive at compounds with high selectivity and potency *Plasmodium falciparum*.

Results and discussion

Chemistry

The novel series of furan containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized from commercially available starting materials (Scheme 1). Initially, pyrazole aldehyde **2a-d** was formed by the condensation between substituted acetophenone and phenyl

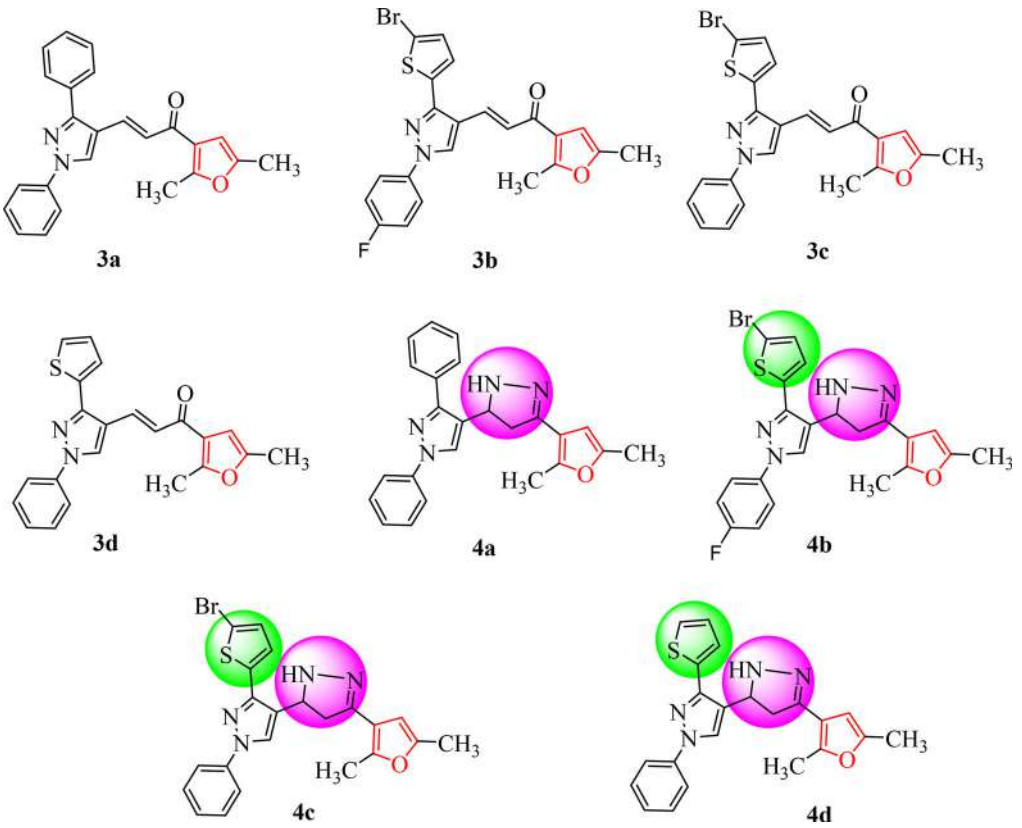


Figure 3. The newly synthesized compounds structure **3a-d** & **4a-d**.

hydrazine followed by Vilsmeier-Haack formylation reaction (Scheme 1). Then furan containing pyrazolyl chalcones **3a-d** were synthesized by base-catalyzed Claisen-Schmidt condensation of 1-(2,5-dimethylfuran-3-yl)ethanone **1** and substituted pyrazole aldehyde **2a-d**.[43] Finally, the furan containing pyrazolyl chalcones **3a-d** and hydrazine hydrate in ethanol solvent using catalytic amount of acetic acid at reflux condition for 6 hr afforded the corresponding pyrazolyl pyrazolines (**4a-d**) in quantitative isolated yield (69–74%) (Scheme 1).

The newly synthesized compounds structures were shown in Figure 3. The newly synthesized compound's structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data. For compound **3a**, in IR spectrum the stretching band for C = O was detected at 1657 cm^{-1}. In the ^{1}H NMR spectrum of compound **3a**, the proton of pyrazole and furan ring resonate as a singlet at δ 9.31 and δ 6.60 ppm respectively. Also, singlet for two $-CH_3$ were observed at δ 2.27 and δ 2.50 ppm. The ^{13}C NMR spectrum of compound **3a** showed signal at δ 184.41 ppm due to C = O and δ 12.89 and δ 13.93 ppm is due to two $-CH_3$. Mass spectrum confirms the formation of compound **3a** showed m/z = 369 $(M+H)^{+}$.

Secondly, in the IR spectrum of compound **4a**, –N–H stretching band observed at 3252 cm^{-1}. The 1H NMR spectrum of compound **4a**, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 2.88 ppm and 3.35 ppm. The CH proton appeared as triplet at δ 4.87 ppm due to vicinal coupling with two protons of the methylene group. In the ^{13}C NMR spectra of the compound **4a** carbons of the pyrazoline ring were observed at δ 41.97 ppm and 54.67 ppm. All the other aromatic and aliphatic protons and carbons were observed at expected regions. Mass spectrum confirms the formation of compound **4a** showed m/z = 383 $(M+H)^{+}$.

Table 1. Antimalarial (μM), Antibacterial (MIC in μg/mL) & Antifungal (MIC in μg/mL) activity.

Cpd	Antimalarial activity Plasmodium falciparum	Antibacterial activity				Antifungal activity			Molecular Docking Score
		EC	PA	SA	SP	CA	AN	AC	
3a	1.46	200	200	250	250	500	500	500	−7.814
3b	3.93	100	250	250	200	1000	500	500	−7.032
3c	2.16	62.5	200	125	250	500	>1000	>1000	−7.192
3d	3.07	100	100	200	200	1000	500	500	−7.118
4a	6.31	125	100	100	100	500	500	500	−6.979
4b	0.47	100	200	100	100	250	500	500	−8.157
4c	0.47	125	125	200	200	1000	>1000	>1000	−8.222
4d	0.21	200	100	125	100	500	500	500	−7.988
Chloroquine	0.06	–	–	–	–	–	–	–	–
Quinine	0.83	–	–	–	–	–	–	–	–
CP	–	50	50	50	50	–	–	–	–
NS	–	–	–	–	–	100	100	100	–

Cpd: Compound; EC: Escherichia coli; PA: Pseudomonas aeruginosa; SA: Staphylococcus aureus; SP: Streptococcus pyogenes; CA: Candida albicans; AN: Aspergillus niger; AC: Aspergillus clavatus; CP: Chloramphenicol; NS: Nystatin.

Biological evaluation

In vitro antimalarial screening

All the synthesized novel compounds were tested for antimalarial activities. The *in vitro* antimalarial assay was carried out according to the micro assay protocol of Rieckmann and coworkers with minor modifications.[44–47] The results were recorded as the minimum inhibitory concentrations (μM MIC) chloroquine and quinine were used as the reference drug (Table 1).

Herein, we have synthesized four chalcone and pyrazoline derivatives respectively. Structure activity relationship (SAR) plays very important role while displaying the antimalarial activity. All the synthesized chalcone derivatives (**3a-d**) exhibited less potency compared to the standard drug. But pyrazoline derivatives exhibited excellent antimalarial activity compared to the standard drug. In compound **4a**, thiophene ring was absent and pyrazoline ring is present, so, the compound **4a** exhibited less potency compared to the standard drug. Now, in compound **4b**, bromo substituted thiophene and pyrazoline rings are present along with the fluorine at the para position on benzene ring. Interestingly, this compound **4b** (0.47 μM), exhibited excellent activity compared to the standard drug quinine (0.83 μM). Again, in compound **4c**, bromo substituted thiophene and pyrazoline rings are present but no fluorine at the para position of benzene ring. Though fluorine is absent on benzene ring in compound **4c** (0.47 μM), it exhibited same potency as that of compound **4b** compared to the standard drug quinine (0.83 μM). Finally, in compound **4d**, there were no substitution on the thiophene and benzene ring. In compound **4d** plane thiophene, plane benzene ring and pyrazoline ring constructed in a single molecular framework. Compound **4d** (0.21 μM), exhibited four-fold more antimalarial activity compared to the standard drug quinine (0.83 μM). From SAR, we can conclude that for the antimalarial activity thiophene, pyrazoline and benzene ring were very important in a single molecular framework.

Antimicrobial activities

Further, all the novel synthesized compounds were also screened for antimicrobial activities against the bacterial strains *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 1688), *Streptococcus pyogenes* (MTCC 442) and fungal strains *Aspergillus clavatus* (MTCC 1323), *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282). The minimum inhibitory concentration (MIC) was determined by the broth dilution method. Chloramphenicol and Nystatin were used as reference drugs for antibacterial and antifungal activity, respectively. The results of antibacterial and antifungal activity were given in Table 1.

The results given in Table 1 indicated that none of the synthesized compound exhibited significant potency toward the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin. Hence, from above result we can conclude that the synthesized compounds show selectively antimalarial activity and negligible antimicrobial activity.

Conclusion

In conclusion, Considering the importance of enoyl-ACP reductase (*Pf*ENR) in *Plasmodium*, a small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) was designed and docked against *Pf*ENR. Based on the *in silico* binding affinity data, synthesis was carried out for these novel furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) and was evaluated for activity against *Plasmodium falciparum*. The synthesized compounds shown selectively antimalarial activity with minimal antimicrobial activity. Compounds (**3a-d**) exhibited less antimalarial activity compared to the standard drug. From the series of compounds (**4a-d**), compound **4b** (0.47 µM), **4c** (0.47 µM) and **4d** (0.21 µM) exhibited more antimalarial activity compared to the standard drug quinine (0.83 µM). Compound 4d shows four-fold more activity compared to the standard drug quinine. From the SAR, we have distinguished areas of the pyrazolyl chalcones and pyrazolyl pyrazolines framework where variations can be made to expand the pharmacokinetic profile as well as features required to improve inhibitor effectiveness. This innovative molecular scaffold presents breakthrough for optimization to develop effective *Pf*ENR inhibitors.

Experimental

General

All the reagents, solvents and chemicals were taken from commercial sources found to be and used as such without purification. The physical constant like melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Advance II 400 spectrophotometer using TMS as an internal standard and DMSO-d6 as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Waters, Q-TOF micro mass (ESI-MS) mass spectrometer.

General procedure for the synthesis of pyrazolyl chalcones (3a-d)

A mixture of 1-(2,5-dimethylfuran-3-yl)ethanone 1 (0.05 mol), substituted pyrazole aldehyde **2** (0.05 mol) and 10% aqueous potassium hydroxide (10 mL) in ethanol (50 mL) was stirred at room temperature for 14 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice and neutralized by dil. HCl. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3a)

Yield: 61%, yellow solid; mp: 80–82 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1657 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.31 (s, 1H, Pyrazole-H), 7.93 (d, 2H, J = 7.9 Hz), 7.38–7.68 (m, 10H, Ar–H), 6.60 (s, 1H, Furan-H), 2.53 (s, 3H, –CH_3), 2.27 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4 (C = O), 159.9, 152.8, 149.7, 138.9, 132.2, 132.0, 129.6, 128.8, 128.5, 128.6, 128.4, 127.1, 123.8, 122.1, 118.6, 117.6, 105.9, 13.9 (CH_3), 12.9 (CH_3); MS(ESI-MS): m/z 369.11 (M + H).$^{+}$

(E)-3-(3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran -3-yl) prop-2-en-1-one (3b)

Yield: 59%, yellow solid, mp: 112–114 °C; IR (νmax, cm^{-1}): 2923 (=C–H), 2856 (C–H), 1656 (C = O), 1455 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.25 (s, 1H, Pyrazole-H), 7.90 (dd, 2H, J = 4.7 & 9.0 Hz, Ar–H), 7.64 (d, 1H, J = 15.4 Hz, olefinic-H), 7.39–7.45 (m, 3H, Ar–H), 7.34 (d, 1H, J = 3.8 Hz, Ar–H), 7.25 (d, 1H, J = 3.8 Hz, Ar–H), 6.61 (S, 1H, Furan-H), 2.55 (s, 3H, $-CH_3$), 2.28 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.2, 162.0, 159.6, 157.1, 149.7, 145.7, 135.4, 135.1, 131.4, 130.8, 128.9, 127.3, 124.6, 122.0, 120.7, 120.6, 117.3, 116.6, 116.3, 112.5, 105.9, 13.9, 12.9; MS (ESI-MS): m/z 472.89 $(M + H)^{+}$.

(E)-3-(3-(5-Bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran-3-yl)prop -2-en-1-one (3c)

Yield: 68%, yellow solid, mp120–114 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1699 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.14 (s,1H, Pyrazole-H), 7.87 (d, 2H, J = 7.8 Hz, Ar–H), 7.70 (d, 1H, J = 15 Hz, olefinic-H), 7.52 (t, 2H, J = 8 Hz, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.20 (s, 2H, Ar–H), 6.55 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.3, 157.1, 149.7, 145.7, 138.6, 135.5, 131.4, 130.9, 129.7, 128.8, 127.3, 127.3, 124.6, 122.0, 118.6, 117.4, 112.5, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 454.57 $(M + H)^{+}$.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)prop-2-en-1-one (3d)

Yield: 62%, yellow solid, mp 124–126 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2715 (C–H), 1652 (C = O),1456 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, Pyrazole-H), 7.91 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 1H, J = 15.4 Hz, olefinic-H), 7.60 (d, 1H, J = 5.1 Hz, Ar–H), 7.54 (t, 2H, J = 8.2 Hz, Ar–H), 7.35–7.44 (m, 3H, Ar–H), 7.21 (dd, 1H, J = 5.0 & 3.7 Hz, Ar–H), 6.59 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4, 157.0, 149.7, 146.8, 138.7, 133.5, 131.5, 129.7, 128.7, 128.1, 127.3, 127.2, 126.8, 124.3, 122.1, 118.6, 117.4, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 375.10 $(M + H)^{+}$.

General procedure for synthesis of pyrazolyl-pyrazoline (4a-d)

A mixture of chalcone **3a-d** (0.001 mol) and hydrazine hydrate (0.004 mol) in solvent ethanol (10 ml) was refluxed in presence of catalytic amount of glacial acetic acid for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol to get pure pyrazolines.

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (4a)

Yield: 74%, white solid, mp 102–104 °C; IR (νmax, cm^{-1}): 3306 (N–H), 3049 (Ar–H), 1592 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, pyrazole-H), 7.90 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 2H, J = 8.3 Hz, Ar–H), 7.47–7.52 (m, 4H, Ar–H), 7.41 (t, 1H, J = 7.3 Hz, Ar–H), 7.31 (t, 1H, J = 7.4 Hz, Ar–H), 7.20 (s, 1H, N–H), 6.19 (s, 1H, furan-H), 4.87 (t, 1H, J = 10.7 Hz, pyrazoline-H), 3.34 (dd, 1H, J = 10.5 & 15.6 Hz, pyrazoline-H), 2.88(dd, 1H, J = 11.1 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 150.4, 149.3, 147.6, 145.1, 139.5, 132.9, 129.5, 128.6, 127.9, 127.2, 126.2, 123.2, 118.1, 115.2, 105.9, 54.7, 41.9, 13.3, 12.9; MS (ESI-MS): m/z 383.04 $(M + H)^{+}$.

3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1H-pyrazole (4b)

Yield: 69%, white solid, mp 98–100 °C; IR (νmax, cm^{-1}):3310 (N–H), 3046 (Ar–H), 1594 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.54 (s, 1H, pyrazole-H), 7.88 (m, 2H, Ar–H), 7.35 (t, 2H, J = 8.7 Hz, Ar–H), 7.28 (dd, 2H, J = 3.8 Hz, Ar–H), 7.21 (s, 1H, N–H), 6.20 (s, 1H, furan-H), 4.93 (t, 1H, J = 10.68 Hz, pyrazoline-H), 3.37 (dd, 1H, J = 10.7 & 16.5 Hz, pyrazoline-H), 2.86 (dd, 1H, J = 10.9 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 161.6, 159.1, 149.3, 147.7, 145.3, 144.1, 136.9, 135.6, 131.2, 128.0, 126.6, 122.6, 120.2, 120.2, 116.4, 116.2, 115.1, 111.5, 105.9, 54.3, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 486.93 $(M + H).^{+}$

3-(5-Bromothiophen-2-yl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole (4c)

Yield: 72%, white solid, mp 122–124 °C; IR (ν max, cm^{-1}): 3303 (N–H), 3096 (Ar–H), 1593 (C = N), ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.55 (s, 1H, pyrazole-H), 7.84 (d, 2H, J = 7.9 Hz, Ar–H), 7.51 (t, 2H, J = 7.6 Hz, Ar–H), 7.22–7.34 (m, 4H, Ar–H), 6.20 (s, 1H, furan-H), 4.94 (t, 1H, J = 10.6 Hz, pyrazoline-H), 3.38 (m, 1H, pyrazoline-H), 2.88 (dd, 1H, J = 12.1 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.2, 144.0, 139.0, 137.0, 131.2, 129.6, 127.8, 126.6, 126.5, 122.5, 118.0, 115.1, 111.4, 105.9, 54.4, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 468.95 $(M + H).^{+}$

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (4d)

Yield: 70%, white solid, mp 96–98 °C; IR (ν max, cm^{-1}): 3336 (N–H), 3067 (Ar–H), 1501 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.53 (s, 1H, pyrazole-H), 7.86 (d, 1H, J = 8 Hz, Ar–H), 7.58 (d, 1H, J = 4.9 Hz, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.31 (t, 1H, J = 7.3 Hz, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 6.21 (s, 1H, furan-H), 4.98 (t, 1H, J = 10.5 Hz, pyrazoline-H), 3.42 (m, 1H, pyrazoline-H), 2.89 (dd, 1H, J = 10.7 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.1, 144.9, 139.2, 135.0, 129.6, 127.9, 127.4, 126.3, 126.0, 125.8, 122.6, 118.1, 115.1, 105.9, 54.5, 41.3, 13.3, 12.9; MS (ESI-MS): m/z 389.03 $(M + H).^{+}$

Experimental protocol for biological activity

Antimalarial assay

The antimalarial activity of the synthesized compounds was carried out in the Microcare laboratory & TRC, Surat, Gujarat. According to the micro assay protocol of Rieckmann and coworkers the *in vitro* antimalarial assay was carried out in 96 well microtiter plates. To maintain *P. falciparum* strain culture in medium Roswell Park Memorial Institute (RPMI) 1640 supplemented with 25 mM (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. To obtain only the ring stage parasitized cells, 5% D-sorbitol treatment required to synchronized the asynchronous parasites of *P. falciparum*. To determine the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+}) an initial ring stage parasitaemia of 0.8 to 1.5% at 3% hematocrit in a total volume of 200 µl of medium RPMI-1640 was carried out for the assay. A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. To the test wells to obtain final concentrations (at five-fold dilutions) ranging between 0.4 µg/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation the diluted samples in 20 µl volume were added. In a candle jar, the culture plates were incubated at 37 °C. Thin

blood smears from each well were prepared and stained with Jaswant Singh-Bhattacharji (JSB) stain after 36 to 40 h incubation. To record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents the slides were microscopically observed. The minimum inhibitory concentrations (MIC) was recorded as the test concentration which inhibited the complete maturation into schizonts. Chloroquine was used as the reference drug.

After incubation for 38 hours, and percent maturation inhibition with respect to control group, the mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells.

Molecular docking

The crystal structure of *Plasmodium Falciparum Enoyl-Acyl-Carrier-Protein Reductase* (*Pf*ENR or FabI) in complex with its inhibitor Triclosan was retrieved from the protein data bank (PDB) (pdb code: 1NHG) and refined using the protein preparation wizard. It involves eliminating all crystallographically observed water (as no conserved interaction is reported with co-crystallized water molecules), addition of missing side chain/hydrogen atoms. Considering the appropriate ionization states for the acidic as well as basic amino acid residues, the appropriate charge and protonation state were assigned to the protein structure corresponding to pH 7.0 followed by thorough minimization, using OPLS-2005 force-field, of the obtained structure to relieve the steric clashes due to addition of hydrogen atoms. The 3D structures of the furan containing pyrazolyl chalcones (**3a-d**) were sketched using the build panel in Maestro and were optimized using the Ligand Preparation module followed by energy minimization using OPLS-2005 force-field until their average root mean square deviation (RMSD) reached 0.001 Å. The active site of *Pf*ENR was defined using receptor grid generation panel to include residues within a 10 Å radius around the co-crystallized ligand. Using this setup, flexible docking was carried using the extra precision (XP) Glide scoring function to gauze the binding affinities of these molecules and to identify binding mode within the target. The obtained results as docking poses were visualized and analyzed quantitatively for the thermodynamic elements of interactions with the residues lining the active site of the enzyme using the Maestro's Pose Viewer utility.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Nanostructured N doped TiO_2 efficient stable catalyst for Kabachnik–Fields reaction under microwave irradiation†

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Herein, we report nitrogen-doped TiO_2 (N-TiO_2) solid-acid nanocatalysts with heterogeneous structure employed for the solvent-free synthesis of α-aminophosphonates through Kabachnik–Fields reaction. N-TiO_2 were synthesized by direct amination using triethylamine as a source of nitrogen at low temperature and optimized by varying the volume ratios of $TiCl_4$, methanol, water, and triethylamine, under identical conditions. An X-ray diffraction (XRD) study showed the formation of a rutile phase and the crystalline size is 10 nm. The nanostructural features of N-TiO_2 were examined by HR-TEM analysis, which showed they had rod-like morphology with a diameter of ~7 to 10 nm. Diffuse reflectance spectra show the extended absorbance in the visible region with a narrowing in the band gap of 2.85 eV, and the high resolution XPS spectrum of the N 1s region confirmed successful doping of N in the TiO_2 lattice. More significantly, we found that as-synthesized N-TiO_2 showed significantly higher catalytic activity than commercially available TiO_2 for the synthesis of a novel series of α-amino phosphonates *via* Kabachnik–Fields reaction under microwave irradiation conditions. The improved catalytic activity is due to the presence of strong and Bronsted acid sites on a porous nanorod surface. This work signifies N-TiO_2 is an efficient stable catalyst for the synthesis of α-aminophosphonate derivatives.

1 Introduction

In recent years, organophosphorus compounds have received much attention due to their widespread applications in medicinal and agriculture industries.[1,2] α-Aminophosphonates are one such biological important framework that are structural mimics of amino acids. For example, glyphosate (*N*-(phosphonomethyl)glycine) is extensively utilized in agriculture as a systemic herbicide and Alafosfalin is used as an antibacterial agent[3] (Fig. 1). The bioactivity of these molecules such as antimicrobial,[4] antioxidant,[5] anti-inflammatory,[6] enzyme inhibitors[7] and antibacterial[8] is one of the reasons for them to be of immense interest in synthetic organic chemistry. It has been demonstrated that on incorporation of heterocycles such as thiophene,[9] benzothiazoles,[10] thiadiazoles,[11] and pyrazole[12] into the α-aminophosphonates scaffold, the resulting compounds exhibited interesting biological activities. Pyrazole derivatives of α-aminophosphonates have been rarely reported in the literature,[13,14] thus synthesis of novel pyrazole derivatives of α-aminophosphonates is important to research.

Although several protocols for the synthesis of α-aminophosphonates are reported, one of the most important is the Kabachnik–Fields reaction.[15,16] This involves a one-pot three-component coupling of a carbonyl compound, an amine and alkylphosphite. These protocols has been accomplished in presence of a variety of catalyst such as $TiCl_4$,[17] CuI,[18] hexanesulphonic sodium salt,[19] trifluoroacetic acid (TFA),[20] $In(OTf)_3$,[21] $BiCl_3$,[22] $Cu(OTf)_2$,[23] $SbCl_3/Al_2O_3$,[24] $InCl_3$,[25] $LiClO_4$,[26] $ZrOCl_2$,[27] TsCl,[28] $Mg(ClO_4)_2$,[29] and Na_2CaP_2O[30] in presence or

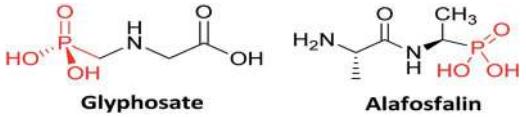

Fig. 1 Some biological active α-aminophosphonate.

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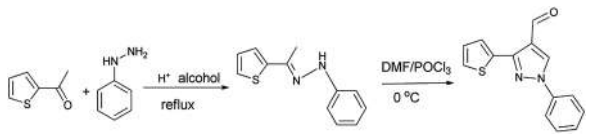
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra04533k



Scheme 1 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde.

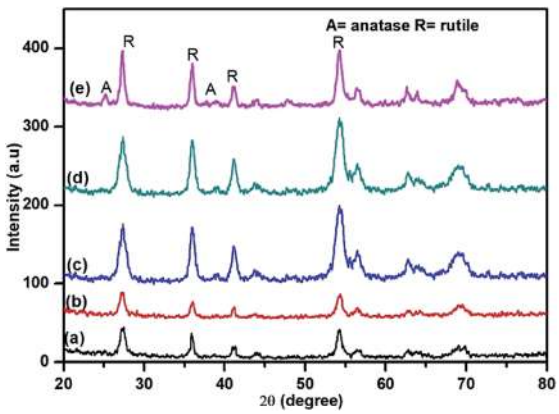


Fig. 2 X-ray diffraction patterns of (a) TN0 (TiO_2), (b) TN1, (c) TN2 (d) TN3 (e) TN4.

even in the absence of a solvent. However, most of these existing procedures are sluggish, require long reaction times, use of strong acidic conditions, give unsatisfactory yields and also suffer from the formation of many side products. Moreover, in all alternatives microwave reaction proved to be a kind of promising medium for such reaction.[31]

In the last few years, the application of transition metal oxides gained particular interest as a heterogeneous catalyst for various organic synthesis.[32] Among all transition metal oxides the use of nanocrystalline titania (TiO_2) has been grown extensively owing to their outstanding physiochemical properties, which furnished their wide applications in sensors,[33] pigments,[34] photovoltaic cells,[35] and catalysis.[36] Also, the use of potential titania catalyst attracted in organic synthesis due to its environmental compatibility, inexpensive, safe, stable, reusable and earth-abundant. It has been proven the desired property of TiO_2 was attained by fulfilling requirements in terms of unique morphology, high crystallinity and mixed-phase composition, the ability of oxidizing and reducing ability under suitable irradiation makes promising greener alternative approach towards important organic transformations compared to other expensive, toxic, transition metal oxides. Moreover, the phase composition and the degree of crystallinity of the titania sample plays an important role in catalytic activity.[8] In the past several organic transformations such as oxidation of primary alcohols,[37] synthesis of xanthenes,[38] Friedel–Crafts alkylation,[39] Beckmann rearrangement[40] efficiently utilizes TiO_2 as a heterogeneous reusable catalyst. In the literature several reports have been debated to influence nitrogen doping on photocatalytic activity of nanocrystalline TiO_2. However, the effect is unrevealed for catalytic applications in organic synthesis. Recently, Hosseini-Sarvari explored the use of commercial TiO_2 in the synthesis of α-aminophosphonates *via* Kabachnik–Fields reactions.[41]

In present investigation, we have prepared nanostructured N doped TiO_2 and also investigation emphasis was given on the synthesis of a series of a novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamin) methylphosphonates under microwave irradiation.

Table 1 Phase composition and crystallite size of as-prepared samples from analysis of XRD

Sample	Rutile	Anatase	Crystallite size (nm)
TN0	100	0	25
TN1	98	2	19
TN2	94	6	16
TN3	95	5	12
TN4	91	9	9

2 Experimental sections

2.1 Synthesis of N doped TiO_2 nanorods

The nanostructured N-TiO_2 were synthesized by previously reported method with some modification.[42,43] In a typical procedure, 0.5 mL of titanium tetrachloride ($TiCl_4$) was added in absolute methanol (25 mL) with constant stirring at room temperature. To this solution requisite quantity a 0.1–2 M aqueous triethylamine solution is injected rapidly. The resulting solution was refluxed for 24 h with constant stirring. The white precipitate formed was collected and washed with ethanol several times followed by centrifugation (10 000 rpm for 20 min). The precipitate was dried at 473 K for 24 h. To control the final morphologies of samples, the sample were synthesized as function of volume ratio of $TiCl_4$, methanol, water, and triethylamine. The sample prepared in volume ratio 1 : 10 : 50 : 0, 1 : 10 : 50 : 1, 1 : 10 : 50 : 2, 2 : 10 : 50 : 2, and 2 : 10 : 50 : 4 were denoted as TN0 (pure TiO_2), TN1, TN2, TN3 and TN4 respectively.

2.2 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde

1-Phenyl-5-(thiophene-2-yl)-1*H*-pyrrole-3-carbaldehyde were obtained *via* the Vilsmeier–Haack reaction of the appropriate phenylhydrazones, derived from the reaction of 2-acetyl thiophene with phenylhydrazine[44] (Scheme 1).

2.3 Synthesis of diethyl(1-phenyl-3-(thiophene-2-yl)-1*H*-pyrazole-4-yl)(phenylamino)methylphosphonates

In a typical procedure, the pyrazolealdehyde **1** (1 mmol), aniline **2** (1 mmol), triethyl phosphite **3** (1.1 mmol) and N-TiO_2 (12 mol%) were taken in a round bottom flask equipped with a condenser and subjected to microwave irradiation for (10–15 min) using 420 W (RAGA's Microwave system) (Scheme 3). The

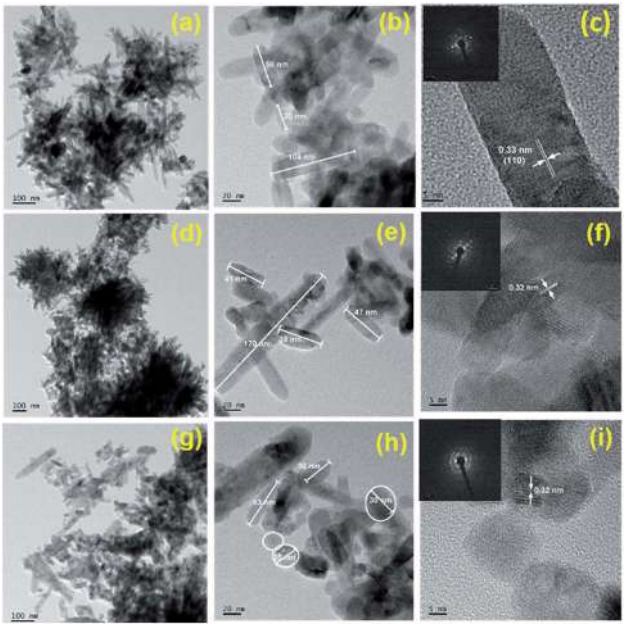


Fig. 3 HR-TEM images of (a–c) TN0, (d–f) TN1, and (d–f) TN2; inset c, f and h SAED pattern of TN0, TN2 and TN3 respectively.

progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture extracted using ethyl acetate and insoluble catalyst separated by filtration. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate as eluent. The product structure was determined by FTIR, ^{1}H NMR, and LS-MS.

2.4 Samples characterization

The phase purity and crystallinity were examined by X-ray diffraction (XRD) technique (Advance, Bruker AXS D8) using Cu Kα1 (1.5406 Å) radiation with scanning 2θ range from 20 to 80°. For FETEM analysis samples were prepared by evaporating dilute solution on carbon-coated grids. FE-TEM measurements were carried using the JEOL SS2200 instrument operated at an accelerating voltage of 300 kV. The Brunauer–Emmett–Teller (BET) surface area of nanocatalysts was examined using the Quantachrome v 11.02 nitrogen instrument. The optical properties of the powder samples were studied using UV-vis diffuse reflectance absorption spectra (UV-DRS) were recorded on the Perkin-Elmer Lambada-950 spectrophotometer in the wavelength range of 200–800 nm. Powder samples were used for XPS measurements. The XPS measurements of powdered samples were carried out on a VG Microtech ESCA3000 instrument. Fourier transform infrared (FTIR) spectra of prepared samples were recorded on a Shimadzu Affinity 1-S spectrophotometer in over a range of 400–4000 cm^{-1}. ^{1}H NMR was recorded in DMSO-d_6 solvent on a Bruker Advance-400 spectrometer with tetramethylsilane (TMS) as an internal reference.

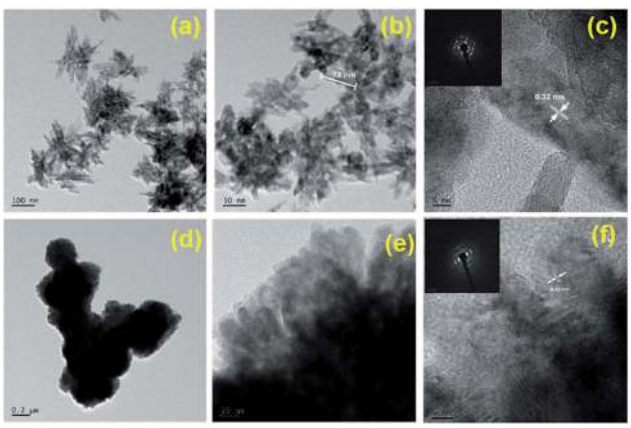


Fig. 4 HR-TEM images of (a–c) TN3 and (d–f) TN4; inset c, and f SAED pattern of TN3, and TN4 respectively.

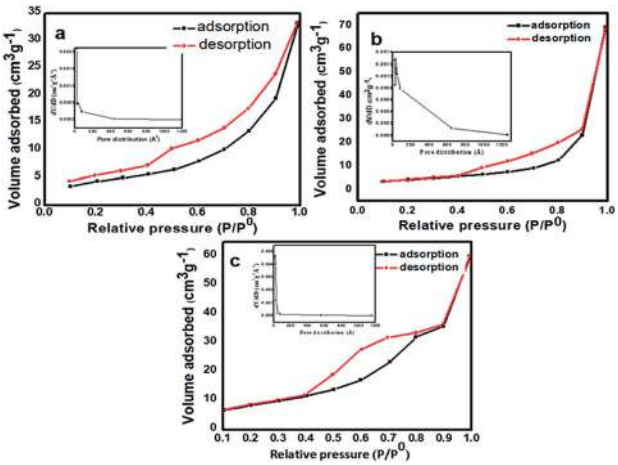


Fig. 5 Nitrogen (N_2) adsorption–desorption isotherms of (a) TN0 (TiO_2), (b) TN2 (N-TiO_2), (c) TN4 (N-TiO_2). Insets shows their corresponding pore size distributions.

3 Results and discussions

3.1 Structural study

Nanostructured TiO_2 and N doped TiO_2 were synthesized by a simple refluxing method. The phase purity and phase formation of as-synthesized material were analysed by powder X-ray diffraction pattern. Fig. 2 compares powder XRD patterns of TiO_2 and N doped TiO_2 samples. The peak position and peak intensity of the pure TiO_2 powder can be indexed into rutile phases (Fig. 2). Further, it is observed that an increase in the amount N-dopant (triethylamine) the intensity of the diffraction

Table 2 BET specific surface area and pore size distribution of TiO_2 and N-TiO_2

Sample	Surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})	Pore radius (Å)
TN0	21.956	0.051	18.108
TN2	40.359	0.215	30.811
TN4	53.589	0.101	18.041

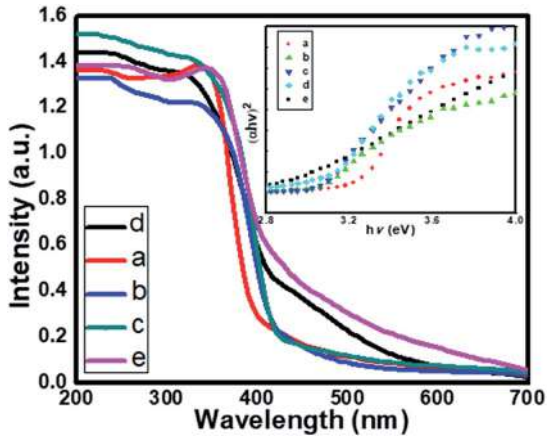


Fig. 6 UV-DRS spectra of (a) TN0 (TiO_2), (b) TN1 (c) TN2 (d) TN3 (N-TiO_2), (e) TN4. Insets shows Tauc plot of TiO_2 and N-TiO_2 samples.

peaks of the rutile phase decreases, while that of anatase phase increases, indicating that the fraction of the anatase phase gradually increases at the expense of the rutile phase during this condition (sample TN2–TN4). The phase composition of rutile and anatase phase of TiO_2 evaluated from the peak intensity using the following equation,

$$f_A = \frac{1}{1+\frac{1}{K}\frac{I_R}{I_A}} \quad K = 0:79; f_A > 0.2; K_{1/4}0:68; f_A \leq 0.2$$

where f_A is the fraction of the anatase phase, and I_A and I_R are the intensities of the anatase (1 0 1) and rutile (1 1 0) diffraction peaks, respectively. The higher molar concentration of triethylamine is favourable for the transformation from rutile to anatase.[45,46] Therefore, the phase composition of TiO_2 samples, *i.e.* the fraction of anatase and rutile, can be facilely controlled through adjusting the concentration of triethylamine. The slight shift of rutile (1 1 0) diffraction peaks towards a higher angle with an increase in the amount of N dopant suggesting

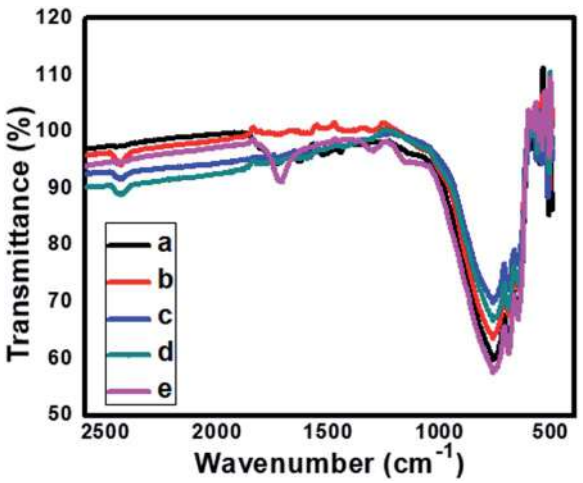


Fig. 7 FTIR spectra of (a) TN0 pure (TiO_2), (b) TN1 (N-TiO_2), (c) TN2, (d) TN3 and (e) TN4.

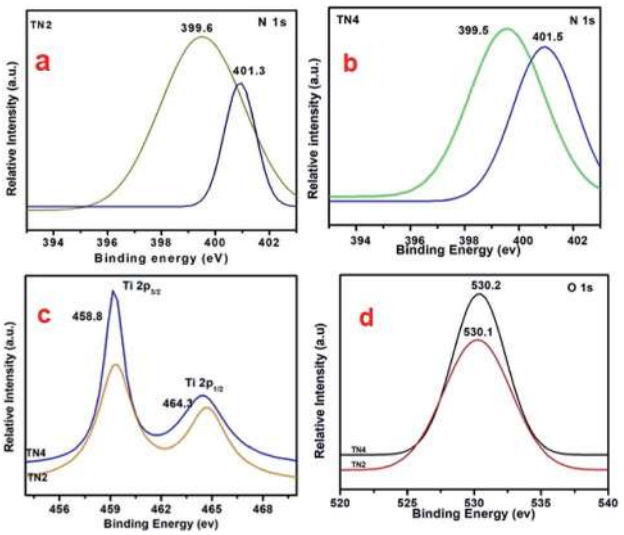
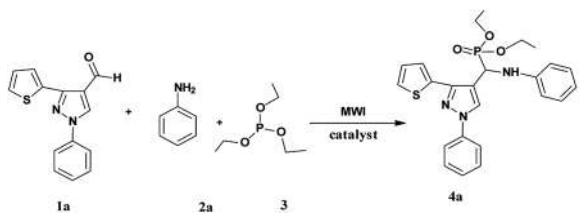


Fig. 8 (a and b) High resolution spectrum of N 1s region (c) high resolution spectrum of Ti 2p region (d) high resolution spectrum of O 1s region.

the incorporation of nitrogen in the TiO_2 crystal structure. The crystallite size is calculated from each (1 1 0) peak in the XRD pattern using the Sherrer formula.[39] The average crystalline size are 25, 19, 16, 12 and 9 nm for TN0, TN1, TN2, TN3, and TN4 respectively (Table 1). From, XRD analysis it is clear that with an increase in the concentration of nitrogen in TiO_2, fraction of anatase increases phase and crystalline size decreases.

3.2 Surface and morphological study

Transmission electron microscopy (TEM) and high-resolution transmission electron microscopy (HRTEM) analysis were performed to study morphology and crystallinity of as-synthesized pure and N doped TiO_2 materials (Fig. 3). The pure TiO_2 (TN0) sample seems flowerlike nanostructures (Fig. 3a). At high-resolution it reveals that each flower microstructure consisting several nanorods. The length of nanorods are in the range of 50–70 nm and diameter is about 10–15 nm (Fig. 3b). Fig. 3c shows the lattice fringes of the material with interplanar spacing *d* spacing 0.33 nm matches well (1 0 0) plane of rutile TiO_2. Fig. 3c inset shows a selected area diffraction pattern in which bright spots observed that confirm the TiO_2 nanorods are in nanocrystalline nature. It was observed that addition of N dopant, resulting sample TN1 and TN2 grows into new superstructure consisting nanorods of length 30–50 nm and spheres



Scheme 2 Standard model reaction.

Table 3 Comparative study of catalysts used for the synthesis of α-aminophosphonate[a]

Entry	Catalyst	Time (minutes)	Yield[b] (%)
1	—	20	Trace
2	Acetic acid	20	30
3	Commercial ZnO	15	20
4	Commercial TiO_2	15	30
5	TN0	10	72
6	TN1	10	73
7	TN2	10	76
8	TN3	10	85
9	TN4	10	95

[a] Reaction condition: aldehyde(**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), catalyst, MW power 420 watt. [b] Isolated yield.

of diameter 20–30 nm, particles size is obviously smaller than TN0 (Fig. 3d and h). HRTEM results are consistent with XRD results. The *d*-spacing is about 0.325 Å between adjacent lattice planes of the N doped TiO_2.

It was revealed that with doubling concentration of $TiCl_4$, sample TN3 and TN4 were grown into very fine agglomerated nanorods (Fig. 4). Further, it is observed that these nanorods having size in length 30–40 nm and diameter is around 7–10 nm which is lower than pure TiO_2. Fig. 4f inset shows selected area diffraction pattern shows, surprisingly, ring-like pattern unlike TiO_2, indicates N-TiO_2 nanorods are in polycrystalline nature. From HR-TEM results it is concluded that increase in concentration of $TiCl_4$ and triethylamine reduces the size of the nanorods.

The specific surface area of as-prepared samples was studied by (N_2) nitrogen gas adsorption–desorption measurement at 77 K using the Brunauer–Emmett–Teller (BET) method. The N_2 adsorption–desorption isotherm of N-TiO_2 nanoparticles is shown in Fig. 5. The pure TiO_2 shows type IV isotherm according to IUPAC classification,[47] which are typical characteristics of a material with pore size in the range of 1.5–100 nm Fig. 5a. The shape of the hysteresis loop is H_3 type may associates due to the agglomeration of nanoparticles forming slit-like pores, reflected in TEM images. At higher relative pressure (p/p^0) the slope shows increased uptake of adsorbate as pores become filled; inflection point typically occurs near

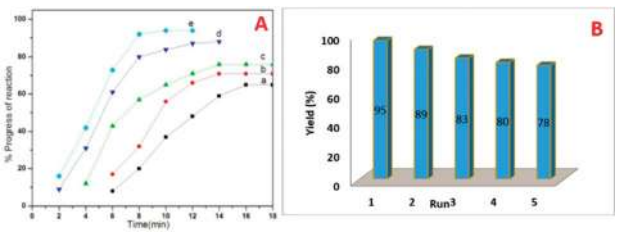


Fig. 9 (A) Progress of reaction (a) TN0 (b) TN1 (c) TN2 (d) TN3 and (e) TN4. (B) Reusability of catalyst TN4; reaction condition: aldehyde (**1a**) (1 mmol), aniline (**2a**) (1 mmol), triethylphosphite **3** (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt.

Table 4 Optimization of the concentration of catalyst[a]

Sr. no.	Concentration of catalyst (mol%)	Yield[b] (%)
1	3	69
2	6	76
3	9	86
4	12	95
5	15	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, MW power 420 watt. [b] Isolated yield.

completion of the first monolayer. The BET surface area of pure TiO_2 is found to be 21.956 $m^2\ g^{-1}$. The pore size distribution of prepared samples was investigated by Barrett–Joyner–Halenda (BJH) method Fig. 5(a)–(c) insets. The average pore diameter of pure TiO_2 nanoparticles is 18 nm which demonstrates the material is mesoporous nature. Further, it is observed that the incorporation of nitrogen in TiO_2 nanoparticles the surface area shifts towards higher values. The adsorption–desorption isotherms of nitrogen-doped TiO_2 samples display the type II isotherm according to IUPAC classification.[46] The specific BET surface area of samples TN_2 and TN_4 are 40.359 $m^2\ g^{-1}$ and 53.589 $m^2\ g^{-1}$ respectively (Fig. 5b and 4c). This observation specifies a decrease in the particle size of TiO_2 nanoparticles specific surface area increases which are in consisting of XRD and TEM results. The Brunauer–Emmett–Teller (BET) specific surface areas, pore volumes and mean pore and mean pore diameters of samples TN0, TN2, and TN4 are summarized in Table 2.

3.3 Optical and electronic property studies

The optical property of the as-synthesized material was analyzed by UV-Vis diffuse absorbance spectra as shown in Fig. 6. Fig. 6 displays the comparative UV-DRS spectra of pristine TiO_2 and a series of N doped TiO_2 samples. The absorption edge for the pure TiO_2 (TN0) is observed at around 410 nm (Fig. 6a), which is consistent with the band gap of the rutile phase.[45] The N doped TiO_2 nanostructures show strong absorption in the visible region (410–600 nm). The redshift clearly indicates the

Table 5 Screening of solvents[a]

Entry	Solvent	Yield (%)[b]
1	Ethanol	85
2	Methanol	87
3	Dichloromethane	55
4	THF	58
6	Toluene	60
7	Neat	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, solvent, MW power 420 watt. [b] Isolated yield.

successful doping of N in the lattice of TiO_2. Moreover, as the concentration of triethylamine increases redshift of N-TiO_2 also increases which confirms higher nitrogen doping and a higher fraction of absorption of photons from the visible region. The band gap of as-synthesized material calculated by using the Tauc plot shown in Fig. 6 (insets). The band gap (E_g) for the sample TN0, TN1, TN2, TN3, and TN4, were observed to 3.15, 3.09, 3.07, 3.03 and 2.85 eV respectively. The decrease in the band gap is attributed to higher mixing of the (O/N) 2p level is developed in the Ti-3d level falls at the top of the VB, therefore, band gap reduced compared to the pristine TiO_2 nanostructure.

3.4 FT-IR spectroscopy

Fig. 7 shows comparative FTIR spectra for pure and N doped TiO_2. The absorption peak signal in the range of 400–1100 cm^{-1} is characteristic of the formation of O–Ti–O lattice. The absorption at 668 cm^{-1}, 601 cm^{-1}, 546 cm^{-1} and 419 cm^{-1} corresponds to Ti–O vibrations.[48,49] Further, for the sample TN1–TN3 the IR bands centred at 1400–1435 cm^{-1} indicates nitrogen doping in the TiO_2 sample. The band located at 1070 cm^{-1} is attributed to Ti–N bond vibrations. Also, it is observed that the band at 1335 cm^{-1} for pure TiO_2 is shifted towards longer wavenumber 1430 cm^{-1} supports for the claim of N doping in TiO_2 lattice. Further it is also observed that some of the minor the peaks of pure TiO_2 are rather different than the N-doped TiO_2, this indicates the incorporation of nitrogen in TiO_2 lattices. The peak centered at 1600–2180 cm^{-1} is ascribed due to –OH stretching frequency. From, IR spectra it is clear that N is successfully incorporated in the lattice of TiO_2.

3.5 X-ray photoelectron spectroscopy

The XPS were used for chemical identification and electronic state of dopant nitrogen in sample TN2 and TN4. The high resolution XPS spectra of N 1s on deconvolution shows two different peaks at 399.6 and 401.5 eV indicates nitrogen present in two different electronic state (Fig. 8a and b). The peak at 399.6 is attributed to presence of interstitial N or N–Ti–O linkage. The result is consistent with previous reports.[43] The peak at 401.5 is attributed to presence of N in oxidized state as NO or NO_2. The concentration of nitrogen on surface of TN2 and TN4 are 2.8% and 3.4% respectively. Fig. 8c shows the peak at 458.8 and 458.3 is attributed to Ti $2p_{3/2}$ and Ti $2p_{\frac{1}{2}}$, in good agreement the presence of Ti(IV) in TiO_2. The peak at binding energy 530.1 and 530.2 eV of sample are attributed to O 1s (Fig. 8d).

3.6 Catalytic study in synthesis of α-aminophosphonates

In order to find out the best experimental condition, the reaction of pyrazolaldhyde **1a**, aniline **2a** and triethylphospite **3** under microwave irradiation is considered as standard model reaction (Scheme 2).

In the absence of a catalyst, the standard model reaction gave a small amount of product (Table 3 entry 1). These results specify catalyst is required to occur reaction. In order to check the catalytic utility, the model reaction carried out in the presence of a variety of catalysts (Table 3 entry 2–9). The N-TiO_2 NRs gave better results than acetic acid, commercial ZnO and commercial TiO_2.

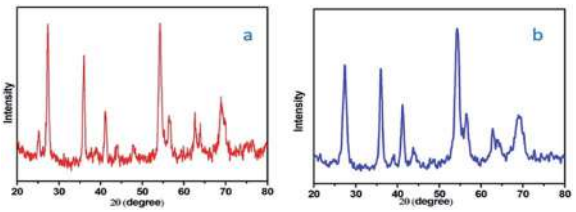


Fig. 10 XRD of sample TN4 (a) before reaction (b) after reaction.

Inspiring these results, we further studied the progress of reaction at different time intervals, we observed the sample N-doped TiO_2 catalyzes efficiently than undoped TiO_2, and this may be attributed to the higher surface area (Fig. 9A).

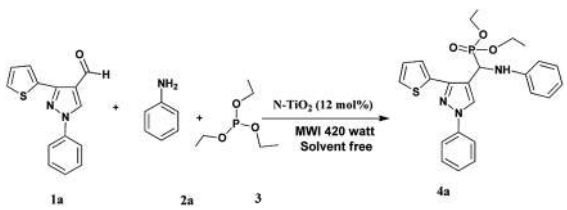
The optimum concentration of the catalyst was investigated by performing the model reaction at different concentrations such as 3, 6, 9, 12 and 15 mol%. The reaction yielded in 69, 76, 86, 95 and 95% yields respectively (Table 4). This shows that 12 mol% of TN_4 is adequate for the reaction by considering the yield of the product.

To evaluate the effect of solvents, different solvents such as ethanol, methanol, dichloromethane, THF, 1,4-dioxane and toluene were used for the model reaction in presence of N-TiO_2 catalyst. The reaction proceed with better yield in polar protic solvent (Table 5, entries 1, 2). However it was observed that the usage of solvents slows down the rate of reaction and gives the desired product in lower yields than that for neat condition (Table 5, entries 1–6).

The recyclability of the catalyst was then examined and the outcomes are shown in Fig. 9B. After the completion of reaction, the reaction mixture was extracted with ethyl acetate. The residual catalyst was washed with acetone, dried under vacuum at 100 °C and reused for consequent reactions. The recovered catalyst could be used for 5 times without obvious loss of catalytic activity.

The difference between the XRD of fresh catalyst and reused catalyst shown in Fig. 10.

The usefulness of optimized reaction condition for model reaction (12 mmol % of catalyst, solvent-free, MWI) was extended for the synthesis of a series of novel α-amino-phosphonates (**4a–l**) by reacting pyrazoldhyde (**1a–c**), anilines (**2a–d**) and triethylphosphite (**3**) in excellent yields (Scheme 3).



Scheme 3 Optimized reaction condition for synthesis of diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino) methylphosphonates

Table 6 Microwave assisted synthesis of novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino)methylphosphonates[a]

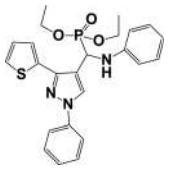
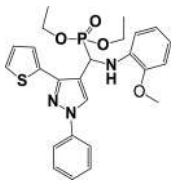
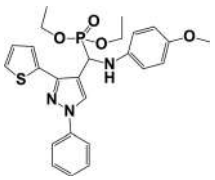
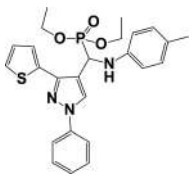
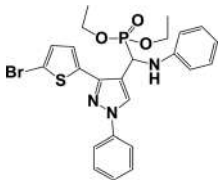
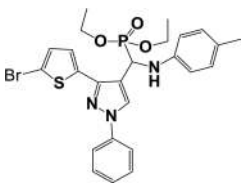
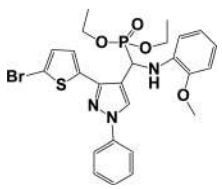
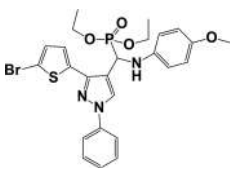
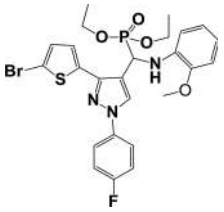
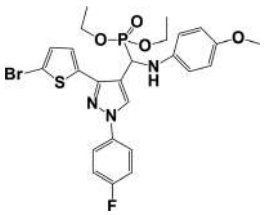
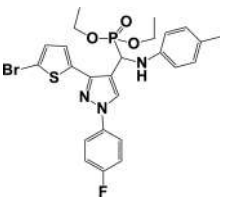
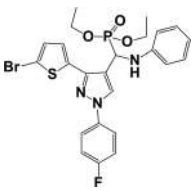
Entry	Product	M.P. (°C)	Yield[b] (%)
4a		218	95
4b		220	79
4c		208	92
4d		216	79
4e		180	86
4f		200	82
4g		162	85
4h		190	71

Table 6 (*Contd.*)

Entry	Product	M.P. (°C)	Yield[b] (%)
4i		195	81
4j		120	76
4k		210	89
4l		190	75

[a] Reaction condition: aldehyde (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt. [b] Isolated yield.

The obtained product **4a–l** was characterized by spectroscopic techniques (Table 6).

The spectroscopic data of synthesized compounds are given in ESI (S-2 to S-26).†

4 Conclusions

In summary, we have prepared N doped TiO_2 nanorods by thermal hydrolysis method using triethylamine as the source of nitrogen at relatively low temperatures. The XRD analysis showed that with varying composition molar ratios of $TiCl_4$, CH_3OH, H_2O, and $(C_2H_5)_3N$, phase composition of rutile to anatase also tunes. FTIR spectra show the chemical environment of doping by the formation of the N–Ti–O and Ti–O–Ti bond. The morphological study performed by the FE-TEM technique shows the formation of well-developed nanorods of size in length 30–40 nm and diameter is around 7–10 nm, which is lower than pure TiO_2. Further, BET analysis N-TiO_2 shows the maximum specific surface area 53.4 $m^2\ g^{-1}$ which is 2.5 times

higher than pure TiO_2. The as-synthesized materials were employed for the synthesis of α-aminophosphonates *via* Kabachnik–Fields reaction under microwave irradiation. The N-TiO_2 shows remarkable catalytic activity for aminophosphonate derivatives compared with TiO_2 and other similar nanocatalysts.

Conflicts of interest

There are no conflicts to declare.

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

Perfluoro-alkylated and trifluoro-methylated pyrazoles represent pharmacologically related core structures that are present in many important drugs and agrochemicals, such as fluazolate (herbicide), penthiopyrad (fungicide), razaxaban (anticoagulant), deracoxib, celecoxib (anti-inflammatory), and penflufen (fungicidal) (Figure 1).[16] So, the modern trend is moving more in the direction of the synthesis of a collection of fluorine-containing molecules in order to find excellent biological activity.

Ultrasonic irradiation is a new technology that has been widely used in chemical reactions. When ultrasonic waves pass through a liquid medium, a large number of microbubbles form, grow, and collapse in very short times, about a few microseconds. The formation and violent collapse of small vacuum bubbles takes place due to the ultrasonication waves generated in alternating high pressure and low pressure in liquids, and the phenomenon is known as cavitation. It causes high-speed imposing liquid jets and strong hydrodynamic shear forces. The deagglomeration of nanometer-sized materials was carried out using these effects. In this aspect, for high-speed mixers and agitator bead mills, ultrasonication is an alternative.[17]

In the preparative chemist's toolkit, microwave heating is a valuable technique. Due to a modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way.[18] In recent years, microwave-assisted organic synthesis (MAOs)[19] has been emerged as a new "lead" in organic synthesis. Important advantages of this technology include a highly accelerated rate of the reaction and a decrease in reaction time, with an increase in the yield and quality of the product. The current technique is considered an important method toward green chemistry as this technique is more environmentally friendly. The conventional method of organic synthesis usually needs a longer heating time; tedious apparatus setup, which results in the higher cost of the process; and the excessive use of solvents/reagents, which leads to environmental pollution. This growth of green chemistry

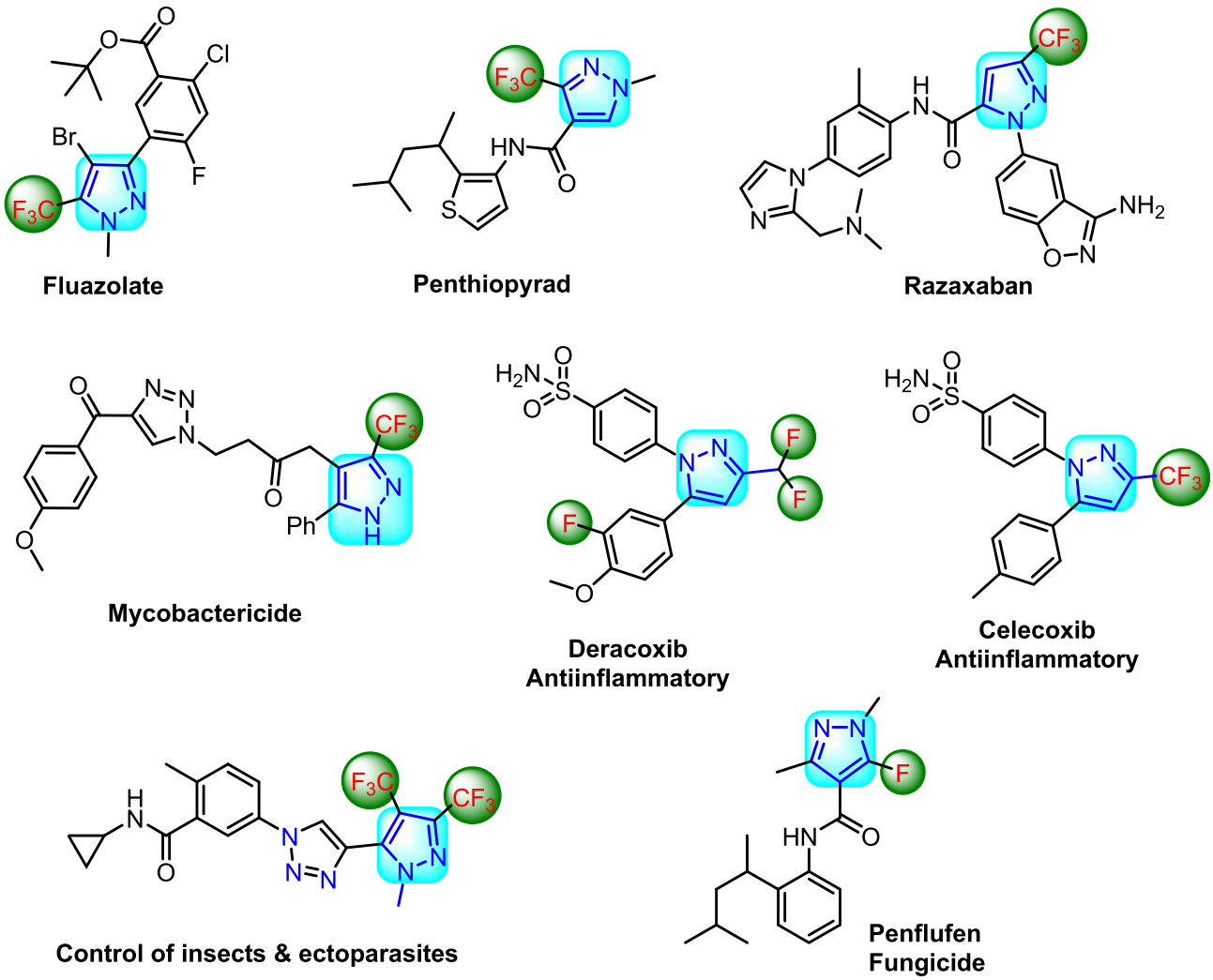


FIGURE 1 Structure of pyrazole- and fluorine-containing commercially available drugs

holds significant potential for a reduction of the byproduct, a reduction in waste production, and lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and bypass thermal conductivity, leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[20] Knoevenagel condensation reactions are carried out by the condensation of aldehyde and the active methylene group using different catalysts such as piperidine, $InCl_3$, $TiCl_4$, LiOH, $ZnCl_2$, and $NbCl_5$.[20,21] They are also carried out using $NaAlO_2$-promoted mesoporous catalysts,[22] ionic liquid,[23] monodisperse carbon nanotube-based NiCu nanohybrids,[24] and MAOs.[25] This is one of the most important methodologies used in synthetic organic chemistry for the formation of a C—C double bond.

From our study, the results demonstrated that green methodologies are less hazardous than classical synthesis methods, as well more efficient and economical and environmentally friendly; short reaction times and excellent yields are observed for those reactions in which conventional heating is replaced by microwave irradiation. Keeping in mind the 12 principles of green chemistry, in continuation of our research work,[26] and the advantages of microwave irradiation and activities associated with pyrazole and fluorine, we construct pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional, as well as microwave, irradiation and ultrasonication and evaluated their anti-inflammatory and antioxidant activity. In addition to this, we have also performed in silico absorption, distribution, metabolism, and excretion (ADME) predictions for the synthesized compounds.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A facile, economic, and green protocol for the cyclocondensation of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) with different aldehydes has been achieved.

The key starting material 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (**3**) was synthesized by the condensation of 1-(perfluorophenyl)hydrazine (**1**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in ethanol[27] (Scheme 1).

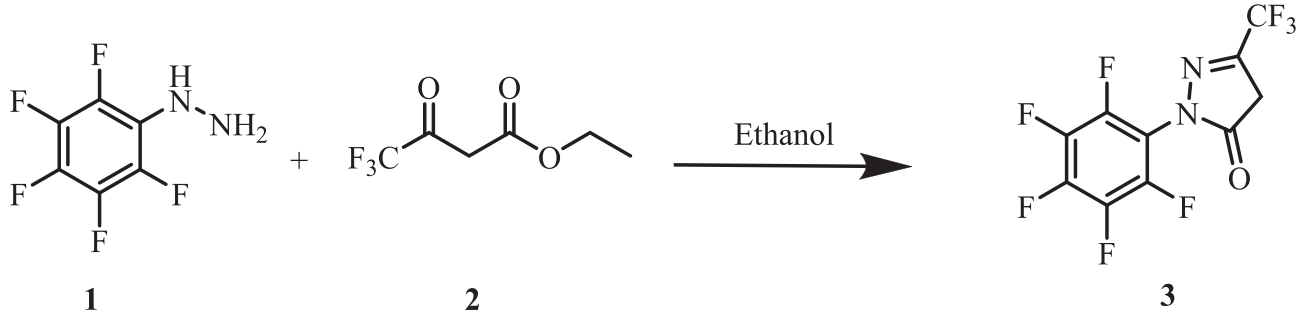
Initially, we carried out the reaction between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) (**3**) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid as a model reaction (Scheme 2). Initially, the model reaction was carried out in ethanol without using acetic acid, and it was observed that a very low yield of product (20%) was obtained even after 2 hr. Therefore, improving the yield intervention of the catalyst was thought to be necessary. So, we decided to use acetic acid as a catalyst to promote this transformation at room temperature. At room temperature, the yield of product (45%) was found to be increased in 3 hr, so we decided to provide heating to the reaction mixture to achieve maximum product yield.

When the reaction mixture refluxed in acetic acid, product formation took place after 2 hr, and the yield of the product was 72% (Table 1).

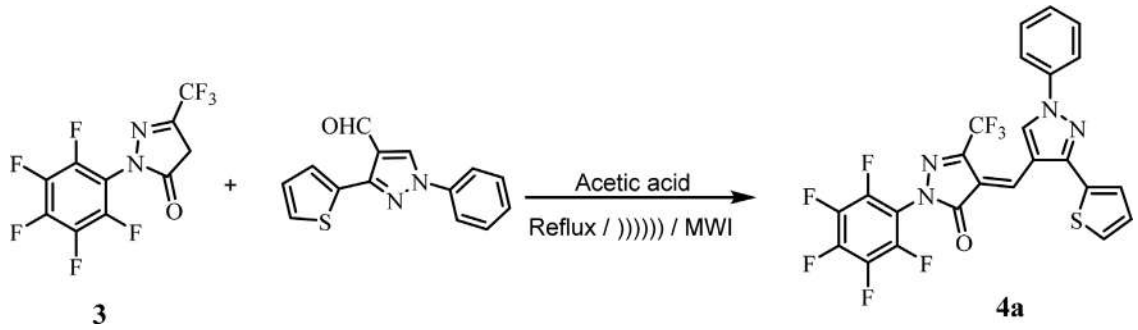
To check the ultrasonication's specific effect on this reaction, under ultrasound irradiation at 35–40°C, we carried out the model reaction using the optimized reaction conditions in hand to check whether the reaction could be accelerated with further improved product yield within a short reaction time (Scheme 2).

It was observed that, under ultrasonic conditions, the conversion rate of a reactant to product increased with less time (Table 1). Thus, when considering the basic green chemistry concept, ultrasonic irradiation was found to have a beneficial effect on the synthesis of Knoevenagel derivatives (**4a-d**, **5a-f**, and **6a-e**), which was superior to the traditional method with respect to yield and reaction time (Table 1).

To accomplish the goal and significance of green chemistry, the model reaction was carried out under



SCHEME 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one **3**



SCHEME 2 Model reaction for conventional, ultrasonication, and microwave irradiation methods

TABLE 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**)

						Conventional method[a]		Ultrasound method[b]		Microwave method[c]	
Cpd	R_1	R_2	R_3	R_4	m. p. (°C)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
4a	H	H	-	-	224–226	120	72	20	81	6.5	84
4b	Br	F	-	-	232–234	120	75	18	78	6.5	81
4c	Cl	H	-	-	216–218	120	70	20	76	6.0	80
4d	Br	H	-	-	230–232	120	64	16	70	6.5	76
5a	H	H	OMe	-	202–204	120	70	21	76	5.5	84
5b	H	H	H	-	186–188	120	66	17	72	6.0	80
5c	F	H	OMe	-	180–182	120	68	16	75	7.0	82
5d	H	H	Me	-	206–208	120	65	16	71	6.5	79
5e	H	H	OCF_3	-	142–144	120	62	18	70	6.5	76
5f	H	Cl	Cl	-	212–214	120	70	19	80	5.5	84
6a	Me	Cl	Me	H	188–190	120	66	18	76	6.0	78
6b	H	Cl	Me	H	180–182	120	62	17	72	7.5	75
6c	H	Cl	H	H	176–178	120	59	18	79	7.0	80
6d	H	Cl	H	Cl	212–214	120	64	20	72	7.0	78
6e	H	H	Me	H	180–182	120	60	18	80	7.5	82

Abbreviation: Cpd, compound.

[a]Reaction conditions: Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid.

[b]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under ultrasound irradiation.

[c]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under microwave irradiation.

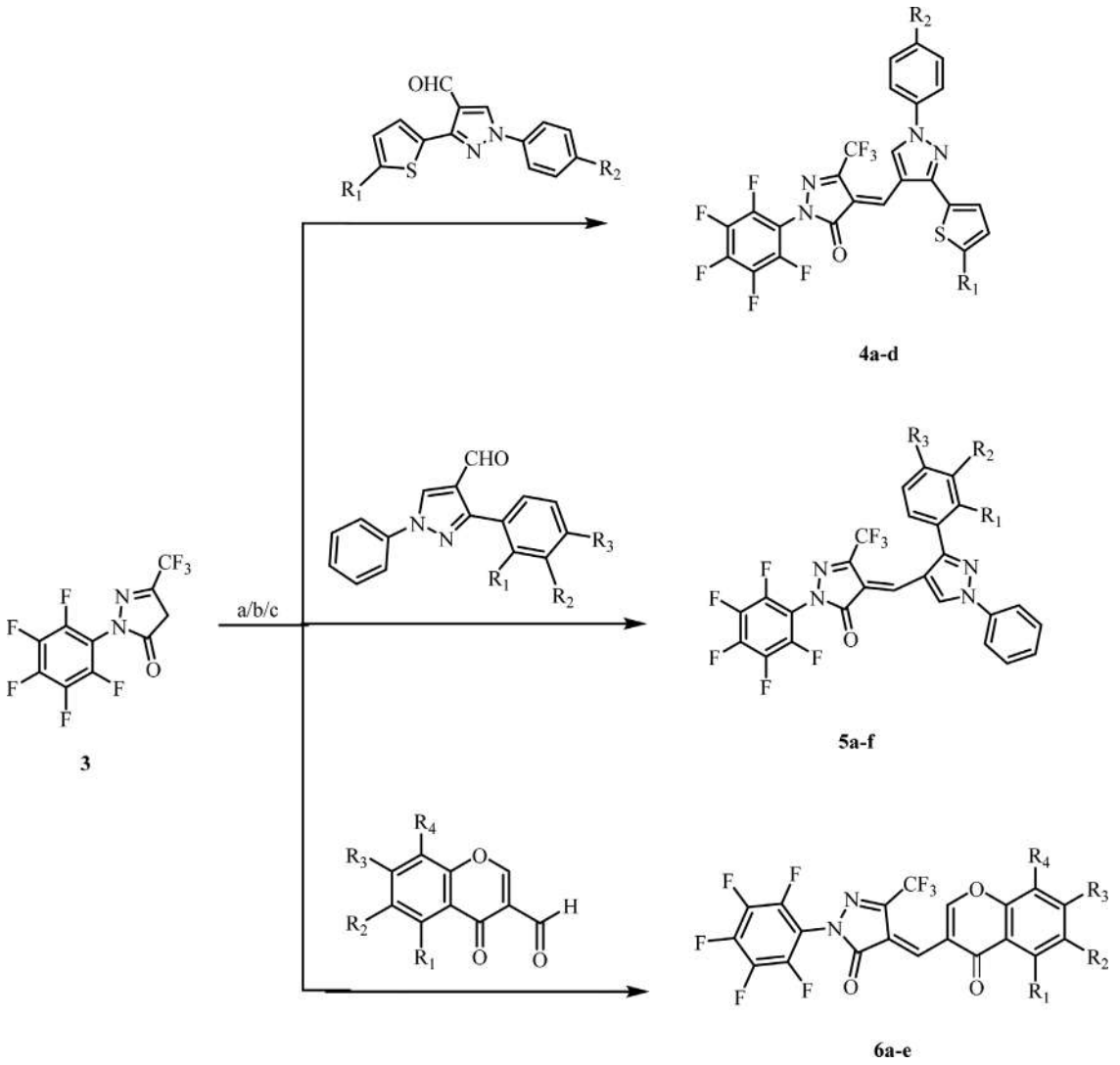
[d]Isolated yield. m.p.: melting point.

microwave irradiation for a period of time indicated in Table 1 at 350 W (Scheme 2). Fortunately, the product formation occurred in 6.5 min, with an 84% increase in yield .

So, from the above experiments, it can be concluded that, when the reaction was carried out under the conventional method, it gave comparatively low yields of products with longer reaction times, while the same reaction carried out under the influence of ultrasonic irradiation and microwave irradiation gave excellent yields of the products in short reaction times.

Finally, we assessed the scope and generality of this method for the Knoevenagel condensation between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) and different aldehydes (Scheme 3), achieved under conventional and nonconventional methods like the ultrasound and microwave methods, respectively. With respect to the substituent present on the aromatic ring of aldehyde, under the optimized conditions, the corresponding products were obtained in high to excellent yields (Table 1).

More importantly, hetero aryl aldehydes were observed to be well tolerated under optimized conditions,



SCHEME 3 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**). Reaction conditions: **a** = Refluxed in acetic acid. **b** = Under ultrasound irradiation in acetic acid. **c** = Under microwave irradiation using acetic acid as a solvent

furnishing the product in good yields. All the synthesized compounds (**4a-d**, **5a-f**, and **6a-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

The formation of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **4a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. In the IR spectrum of compound **4a**, the peaks observed at 1,681 cm^{-1} indicate the presence of C═O group. In the ^{1}H NMR spectrum of compound **4a**, two singlets were observed at δ 8.11 and 10.10 ppm for pyrazolyl and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **4a** revealed that the peak appearing at δ 161.4 ppm is due to the presence of carbonyl carbon. The structure of compound **4a** was also confirmed by a molecular ion peak at *m*/*z* 555.01 $(M + H)^+$. Similarly, the synthesis of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-ones **5a-f** was also confirmed by spectral techniques. In the IR spectrum of compound **5a**, the peak observed at 1,701 cm^{-1} corresponded to the C═O group. In the ^{1}H NMR spectrum of compound **5a**, the three singlets observed at δ 3.92, 8.11, and 10.10 ppm confirm the presence of ─OCH_3, pyrazolyl proton, and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **5a** showed peaks at δ 162.5 and 55.5 ppm, confirming the presence of carbonyl carbon and methoxy carbon, respectively. Furthermore, the structure of compound **5a** was also confirmed by a molecular ion peak at *m*/*z* 573.21 $(M + H)^+$.

Furthermore, the formation of (*Z*)-4-([4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **6a-e** was

confirmed by various spectral techniques. The IR spectrum of compound **6a** showed absorption peaks at 1,707 and 1,666 cm^{-1} corresponding to two carbonyl groups present in the molecules. The ^{1}H NMR spectrum of compound **6a** showed four singlets at δ 2.54 and δ 3.01 ppm for two —CH_3, δ 8.50 ppm for chromone ring proton, and δ 10.54 ppm for olefinic proton. The ^{13}C NMR spectrum of compound **6a** showed that two signals appear at δ 175.4 and 164.2 ppm for the carbonyl carbon of chromone and pyrazolone ring, respectively. In addition, two signals for methyl carbon appear at δ 22.2 and 18.6 ppm. The structure of compound **6a** was also confirmed by mass spectra and by a molecular ion peak observed at m/z 537.11 $(M + H)^+$. Similarly, all the synthesized compounds were characterized by the spectral analysis. Structures of all the synthesized derivatives are shown in Figure S1 (Supporting Information).

2.2 | Biological activity

2.2.1 | Anti-inflammatory activity

The newly synthesized 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) (EC_{50} range = 0.6483 ± 0.221–0.8519 ± 0.281 μg/ml) exhibited moderate anti-inflammatory activity compared to the standard drug diclofenac sodium. Among all the synthesized compounds, except compounds **4c**, **5c**, **5e**, **6d**, and **6e**, all other compounds exhibited a minimum inhibitory concentration (MIC) of 200 μg/ml compared to the standard drug diclofenac sodium (Table 2).

The percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 2. Furthermore, the comparative percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 3.

TABLE 2 Anti-inflammatory and antioxidant activity of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (MIC in μg/ml)

Compound	Anti-inflammatory	Antioxidant
4a	200	>100
4b	200	>400
4c	400	>200
4d	200	>200
5a	200	<100
5b	200	>200
5c	NT	NT
5d	200	<100
5e	800	<100
5f	200	<100
6a	200	<100
6b	200	<100
6c	200	>200
6d	800	>100
6e	400	<100
Diclofenac sodium	50	-
Ascorbic acid	-	<50

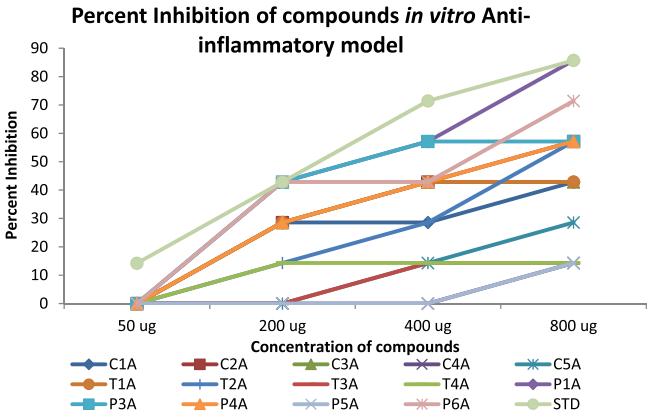


FIGURE 2 The percent inhibition of compounds in an in vitro anti-inflammatory model

2.2.2 | Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed in vitro by the DPPH radical scavenging assay.[28] Ascorbic acid (AA) has been used as a standard drug for the comparison of antioxidant activity, and the observed results are summarized in Table 2.

According to the DPPH assay, compounds **5a**, **5d**, **5e**, **5f**, **6a**, **6b**, and **6e** (IC_{50} = <100 μg/ml) exhibited excellent antioxidant activity compared to the standard antioxidant drug AA (IC_{50} = <50 μg/ml). The remaining synthesized compounds display comparable antioxidant activity than the standard drug butylated hydroxytoluene (Table 2). The percent inhibition of compounds in the in vitro antioxidant model is shown in Figure 4.

2.3 | Computational study

2.3.1 | In silico ADME

An important task for the lead compounds is early prediction of drug likeness properties as it resolves the cost

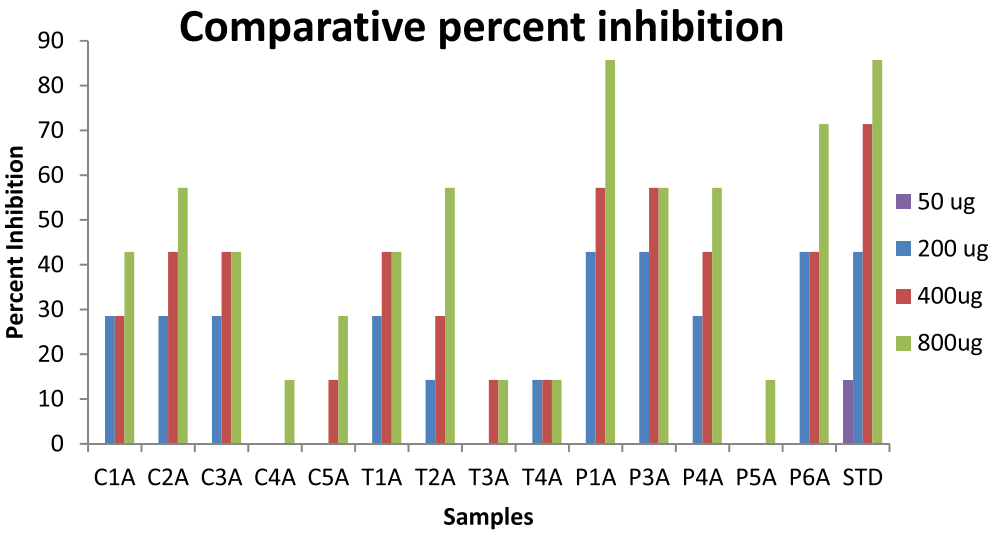


FIGURE 3 The comparative percent inhibition of compounds in an in vitro anti-inflammatory model

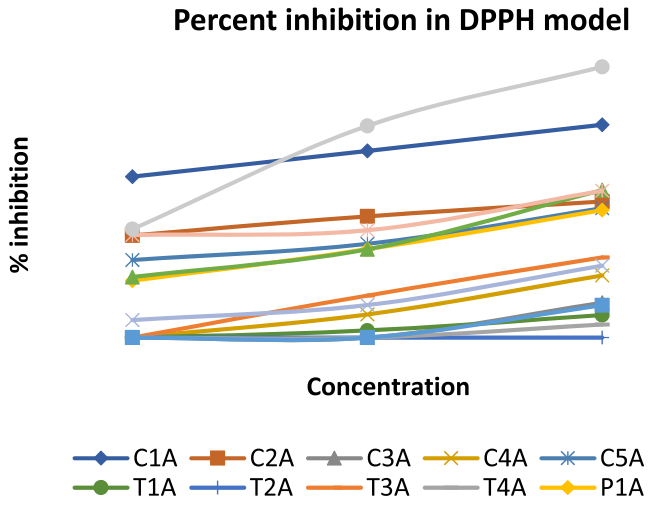


FIGURE 4 The percent inhibition of compounds in an in vitro antioxidant model

and time issues of drug development and discovery. Due to the inadequate drug likeness properties of many active agents with a significant biological activity, these compounds have failed in clinical trials.[29] On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using the Molinspiration online property calculation toolkit,[30] and data are summarized in Table 3.

All the compounds exhibited noteworthy values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants, which characterized these agents to be likely orally active. For the synthesized compound **6e**, the data obtained were within the range of accepted values. Parameters such as the number of rotatable bonds and total polar surface area are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which are reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules.

3 | EXPERIMENTAL SECTION

All organic solvents were acquired from Poona Chemical Laboratory, Pune and Research-Lab Fine Chem Industries, Mumbai and were used as such without further purification. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in *Raga's* synthetic microwave oven. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) fourier transform infrared spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Advance neo 500 spectrophotometers using tetramethylsilane as an internal standard, and $CDCl_3$ and dimethyl sulphoxide-d_6 as solvent and chemical shifts, respectively, were expressed as δ ppm units. Mass spectra were obtained on Waters quadrupole time-of-flight micromass (ESI-MS) mass spectrometer.

3.1 | General procedure for the synthesis of synthesize new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (4a-d, 5a-f and 6a-e)

Conventional method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-

TABLE 3 Pharmacokinetic parameters of (**4a-d**, **5a-f**, and **6a-e**) compounds

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	-
4a	90.81	52.72	5	397.75	554.42	5.83	5	0	2	−0.68
4b	90.81	52.72	5	420.56	651.31	6.92	5	0	2	−0.84
4c	90.81	52.72	5	411.28	588.87	6.63	5	0	2	−0.25
4d	90.81	52.72	5	415.63	633.32	6.76	5	0	2	−0.56
5a	87.62	61.96	6	432.58	578.42	6.10	6	0	2	−0.46
5b	90.81	52.72	5	407.04	548.39	6.04	5	0	2	−0.80
5c	87.62	61.96	6	437.51	596.41	6.19	6	0	2	−0.22
5d	90.81	52.72	5	423.60	562.42	6.49	5	0	2	−0.51
5e	87.62	61.96	7	447.32	632.39	7.01	6	0	2	−0.45
5f	90.81	52.72	5	434.11	617.28	7.33	5	0	2	−0.36
6a	86.53	65.11	3	374.21	536.76	6.25	5	0	2	−0.53
6b	86.53	65.11	3	357.65	522.74	5.87	5	0	2	−0.36
6c	86.53	65.11	3	341.09	508.71	5.49	5	0	2	−0.32
6d	86.53	65.11	3	354.62	543.15	6.10	5	0	2	−0.93
6e	86.53	65.11	3	344.11	488.29	5.26	5	0	1	−0.81

Abbreviations: % ABS, percentage absorption; TPSA, topological polar surface area; n-ROTB, number of rotatable bonds; MV, molecular volume; MW, molecular weight; milogP, logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors, number of hydrogen bond acceptors; n-OHNH donors, number of hydrogen bonds donors.

one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask using glacial acetic acid (5 ml) as a solvent and were refluxed for the period of time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Ultrasound method: A mixture of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) in acetic acid (5 ml) was taken in a 50-ml round-bottom flask. The mixture was irradiated in the water bath of an ultrasonic cleaner at 35–40°C for a period of time indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water, and the obtained solid was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Microwave irradiation method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask (RBF) using glacial acetic acid (5 ml) as a solvent, and the contents of RBF were subjected to MW irradiation for the period of time indicated in Table 1 at 350 W. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

3.1.1 | (4*E*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) methylene)-1*H*-pyrazol-5(4*H*)-one (4a)

Orange solid; Wt. 930 mg, Yield 84%; IR(ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,598 (C=N), 1,519 (C=C), 1,234 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.35–7.91 (m, 8H, Ar—H), 8.11 (s, 1H, pyrazolyl-H), 10.10 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 161.4 (C=O), 151.7, 140.1, 137.8, 134.9, 131.1, 130.0, 129.6, 129.1,

128.70, 128.6, 119.7, 115.7, 113.5; MS (ESI-MS): *m/z* 555.01 $(M + H)^+$.

3.1.2 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4b)

Orange solid; Wt. 1.05 g; Yield 81%; IR (ν_{max}/cm^{-1}): 2,927 (=C—H), 1,680 (C=O), 1,598 (C=N), 1,516 (C=C), 1,231 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, J = 3.50 Hz, Ar—H), 7.26–7.19 (m, 3H, Ar—H), 7.84 (dd, 2H, *J* = 5.00 Hz and 9.00 Hz, Ar—H), 8.10 (s, 1H, pyrazole-H), 10.11 (s, 1H, =C—H); MS: *m/z* 651.03 $(M + H)^+$.

3.1.3 | (4*E*)-4-((3-[5-Chlorothiophen-2-yl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4c)

Orange solid; Wt. 873 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,682 (C=O), 1,597 (C=N), 1,518 (C=C), 1,232 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 1H, Ar—H), 7.26–7.18 (s, 1H, Ar—H), 7.44 (d, 1H, *J* = 6.00 Hz, Ar—H), 7.52 (m, 2H, Ar—H), 7.86 (d, 2H, *J* = 7.00 Hz, Ar—H), 8.11 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 151.3, 139.5, 138.3, 135.0, 133.5, 130.8, 130.0, 128.8, 127.6, 127.4, 120.0, 116.3, 114.6; MS: *m/z* 547.11 $(M + H)^+$.

3.1.4 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4d)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,597 (C=N), 1,520 (C=C), 1,235 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, *J* = 4.00 Hz, Ar—H), 7.21 (d, 1H, *J* = 3.50 Hz, Ar—H), 7.44 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.75–7.86 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.47 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 183.2 (C=O), 162.3, 151.2, 143.2, 142.9, 139.4, 138.3, 134.9, 133.7, 133.4, 131.2, 130.6, 129.8, 129.1, 128.8, 128.5, 128.2, 120.6, 119.9, 119.6, 116.2, 115.9, 114.6; MS: *m/z* 633.05 (M + H).

3.1.5 | (4*Z*)-3-(Trifluoromethyl)-4-((3-[4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5a)

Orange solid; Wt. 971 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,141 (=C—H), 1,703 (C=O), 1,595 (C=N), 1,514 (C=C), 1,224 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.92 (s, 3H, —OCH_3), 7.10 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.51 (t, 2H, *J* = 8.50 Hz, Ar—H), 7.62 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.90 (d, 2H, *J* = 9.00 Hz, Ar—H), 7.99 (s, 1H, pyrazole-H), 10.19 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 161.1, 158.7, 143.3, 141.4, 138.6, 134.9, 130.7, 129.7, 128.5, 122.6, 120.1, 116.8, 114.7, 113.7, 55.5 (OCH_3); MS: *m/z* 579.21 $(M + H)^+$.

3.1.6 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1H-pyrazol-5(4*H*)-one (5b)

Orange solid; Wt. 876 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,142 (=C—H), 1,701 (C=O), 1,595 (C=N), 1,510 (C=C), 1,223 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42 (m, 1H, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.57–7.58 (m, 3H, Ar—H), 7.68 (dd, 2H, *J* = 7.50 and 2.00 Hz, Ar—H), 7.90 (d, 2H, *J* = 8.00 Hz, Ar—H), 8.00 (s, 1H, pyrazole-H), 10.22 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 158.8, 143.0, 141.2, 138.6, 134.9, 130.3, 129.9, 129.7, 129.4, 129.2, 128.6, 120.0, 116.8, 114.0; MS: *m/z* 549.19 $(M + H)^+$.

3.1.7 | (4*Z*)-4-((3-[2-Fluoro-4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5c)

Orange solid; Wt. 1.06 g; Yield 82%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,702 (C=O), 1,596(C=N), 1,512 (C=C), 1,221 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.91 (s, 3H, —OCH_3), 6.82 (dd, 1H, *J* = 2.50 and 12.00 Hz, Ar—H), 6.91 (dd, 1H, *J* = 2.00 and 8.50 Hz, Ar—H), 7.42 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.58–7.49 (m, 2H, Ar—H), 7.79 (d, 1H, *J* = 2.50 Hz, Ar—H), 7.88 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.52 (s, 1H, pyrazole-H), 10.20 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.7 (C=O), 162.6, 162.5, 154.1, 141.2, 138.6, 134.7, 132.5, 129.7, 128.5, 120.0, 117.6, 113.9, 111.2, 110.3, 102.2, 102.0, 55.8 (OCH_3); MS: *m/z* 653.26 $(M + H)^+$.

3.1.8 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-one (5d)

Orange solid; Wt. 887 mg; Yield 79%; IR (ν_{max}/cm^{-1}): 3,143 (=C—H), 1,701 (C=O), 1,594 (C=N), 1,511 (C=C), 1,220 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.44 (s, 3H, —CH_3), 7.45 (d, 1H, J = 7.50 Hz, Ar—H), 7.51 (t, 1H, J = 7.50 Hz, Ar—H), 7.62 (d, 1H, J = 8.00 Hz, Ar—H), 7.65 (d, 1H, J = 8.00 Hz, Ar—H), 9.90 (s, 1H, pyrazole-H), 11.96 (s, 1H, =C—H); MS: m/z 563.08 $(M + H)^+$.

3.1.9 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(4-[trifluoro methoxy]phenyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (5e)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,700 (C=O), 1,595 (C=N), 1,517 (C=C), 1,225 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42–7.44 (m, 3H, Ar—H), 7.51–7.54 (m, 2H, Ar—H), 7.71 (d, 1H, J = 2.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.00 Hz, Ar—H), 7.88 (d, 1H, J = 2.00 Hz, Ar—H), 7.90 (d, 1H, J = 3.50 Hz, Ar—H), 7.92 (s, 1H, pyrazole-H), 10.21 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 157.3, 150.5, 143.2, 142.9, 140.3, 138.5, 134.9, 130.9, 129.8, 129.0, 128.7, 121.5, 120.6, 120.0, 118.4, 116.6, 114.4; MS: m/z 633.23 $(M + H)^+$.

3.1.10 | (4*Z*)-4-((3-[3,4-Dichlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5f)

Orange solid; Wt. 1.03 g; Yield 84%; IR (ν_{max}/cm^{-1}): 3,144 (=C—H), 1,701 (C=O), 1,596 (C=N), 1,517 (C=C), 1,227 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.44 (m, 1H, Ar—H), 7.48 (d, 1H, J = 2.00 Hz, Ar—H), 7.50 (d, 1H, J = 2.00 Hz, Ar—H), 7.53 (d, 1H, J = 7.50 Hz, Ar—H), 7.67 (d, 1H, J = 8.50 Hz, Ar—H), 7.83 (d, 1H, J = 2.00 Hz, Ar—H), 7.87–7.89 (m, 2H, Ar—H), 7.89 (s, 1H, pyrazole-H), 10.18 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.3 (C=O), 156.1, 143.2, 142.9, 139.7, 138.4, 135.0, 134.5, 133.7, 131.2, 131.1, 130.3, 129.8, 128.8, 128.3, 120.0, 116.4, 114.7; MS: m/z 617.15 $(M + H)^+$.

3.1.11 | (*Z*)-4-([6-Chloro-5,7-dimethyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6a)

Orange solid; Wt. 900 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,666 (C=O), 1,624 (C=N), 1,508 (C=C), 1,192 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 3.01 (s, 3H, —CH_3), 7.26 (s, 1H, Ar—H), 8.50 (s, 1H, chromone-H), 10.54 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 175.4 (C=O), 164.2 (C=O), 162.3, 155.1, 144.5, 143.4, 143.3, 139.7, 134.7, 120.9, 120.2, 119.4, 118.3, 118.2, 118.1, 22.2 (—CH_3), 18.6 (—CH_3); MS: m/z 537.11 $(M + H)^+$.

3.1.12 | (*Z*)-4-([6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6b)

Orange solid; Wt. 783 mg; Yield 75%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,705 (C=O), 1,664 (C=O), 1,627 (C=N), 1,508 (C=C), 1,192 (C—F);^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 7.47 (s, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 8.48 (s, 1H, chromone-H), 10.62 (s, 1H, =C—H); MS: m/z 523.08 $(M + H)^+$.

3.1.13 | (*Z*)-4-([6-Chloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6c)

Orange solid; Wt. 812 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,662 (C=O), 1,621 (C=N), 1,509 (C=C), 1,193 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.55 (d, 1H, J = 9.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.50 and 9.00 Hz, Ar—H), 8.26 (d, 1H, J = 2.50 Hz, Ar—H), 8.47 (s, 1H, chromone-H), 10.63 (s, 1H, =C—H); MS: m/z 509.08 $(M + H)^+$.

3.1.14 | (*Z*)-4-([6,8-Dichloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6d)

Orange solid; Wt. 845 mg; Yield 78%; IR (ν_{max}/cm^{-1}): 3,078 (=C—H), 1,707 (C=O), 1,665 (C=O), 1,626 (C=N), 1,506 (C=C), 1,194 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.83 (d, 1H, J = 2.50 Hz, Ar—H), 8.17 (d, 1H, J = 2.50 Hz, Ar—H), 8.40 (s, 1H, chromone-H), 10.66 (s, 1H, =C—H); MS: m/z 543.07 $(M + H)^+$.

3.1.15 | (*Z*)-4-([7-Methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6e)

Orange solid; Wt. 800 mg; Yield 82%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,703 (C=O), 1,666 (C=O), 1,627 (C=N), 1,510 (C=C), 1,193 (C—F);^{1}H NMR spectrum, δ, ppm: 2.51 (s, 3H, —CH_3), 7.48 (d, 1H, J = 8.00 Hz, Ar—H), 7.60 (dd, 1H, J = 8.00 and 2.00 Hz, Ar—H), 8.08 (d,1H, J = 1.50 Hz), 8.54 (s, 1H, chromone-H), 10.64 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 174.5 (C=O), 165.5 (C=O), 162.4, 154.2, 143.4, 142.4, 137.5, 136.3, 126.2, 120.9, 123.3, 120.2, 118.6, 118.5, 118.2, 118.1, 21.1 (—CH_3); MS: m/z 489.14 $(M + H)^+$.

3.2 | Anti-inflammatory activity

All the synthesized compounds were screened for their in vitro anti-inflammatory activities against the standard drug diclofenac sodium. The minimum inhibitory concentration was determined by the well diffusion method at 1 mg/ml of concentration. (Table 2). A volume of 1 ml of diclofenac sodium at different concentrations (50, 100, 200, 400, 800, and 1,000 μg/ml) was homogenized with 1 ml of aqueous solution of bovine serum albumin (5%) and incubated at 27°C for 15 minutes. The mixture of distilled water and bismuth sulphite agar constituted the control tube. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 minutes at 70°C. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 255 nm. Each test was conducted thrice. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = \text{absorbance of control} - \text{absorbance of sample} / \text{absorbance of control} \times 100.$$

3.3 | In silico ADME

In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[31] using the Molinspiration online property calculation toolkit.[30] Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA).[32] Drug likeness model score (a collective property of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound that is represented by a numerical value) was computed by MolSoft software.[33]

4 | CONCLUSIONS

In conclusion, we have constructed pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional and nonconventional methods like microwave irradiation and ultrasonication, respectively, via Knoevenagel condensation and evaluated their biological activity. Ultrasonication and microwave irradiation can shorten the reaction time from a few hours to a few minutes and increases the product yield (74–84%) compared to the conventional method (59–75%). The synthesized compounds exhibited promising anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, the synthesized compound displayed promising antioxidant activity compared to the standard drug. Furthermore, an analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as an oral drug candidate, thus suggesting that compounds from the present series can be further optimized and developed as a lead molecule.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPORTING INFORMATION

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Microwave Assisted Synthesis and Antibacterial Activity of New 1,3,4-Thiadiazoles and 1,2,4-Triazoles Derived from 2-{2-[2-(4-Fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide

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Abstract—A series of novel derivatives of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide, 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol and 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]-imidazol-1-yl}methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine have been synthesized by the conventional method as well as using MW irradiation. All newly synthesized compounds have been tested for antibacterial activity. Several products have demonstrated moderate activity against gram positive and gram negative bacterial strains.

Keywords: 1,3,4-thiadiazole, 1,2,4-triazole, microwave irradiation, antibacterial activity

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Antimycobacterial and antimicrobial activities have been well established and studied in depth for benzimidazole [1, 2], thiazole [3, 4], 1,3,4-thiadiazole [5–7], and 1,2,4-triazole [8, 9] derivatives.

Pharmacological importance associated with those compounds inspired us to synthesize novel benzimidazole and thiazole containing 1,3,4-thiadiazoles and 1,2,4-triazoles under conventional and MW irradiation. All newly synthesized compounds were evaluated for their antibacterial activity.

RESULTS AND DISCUSSION

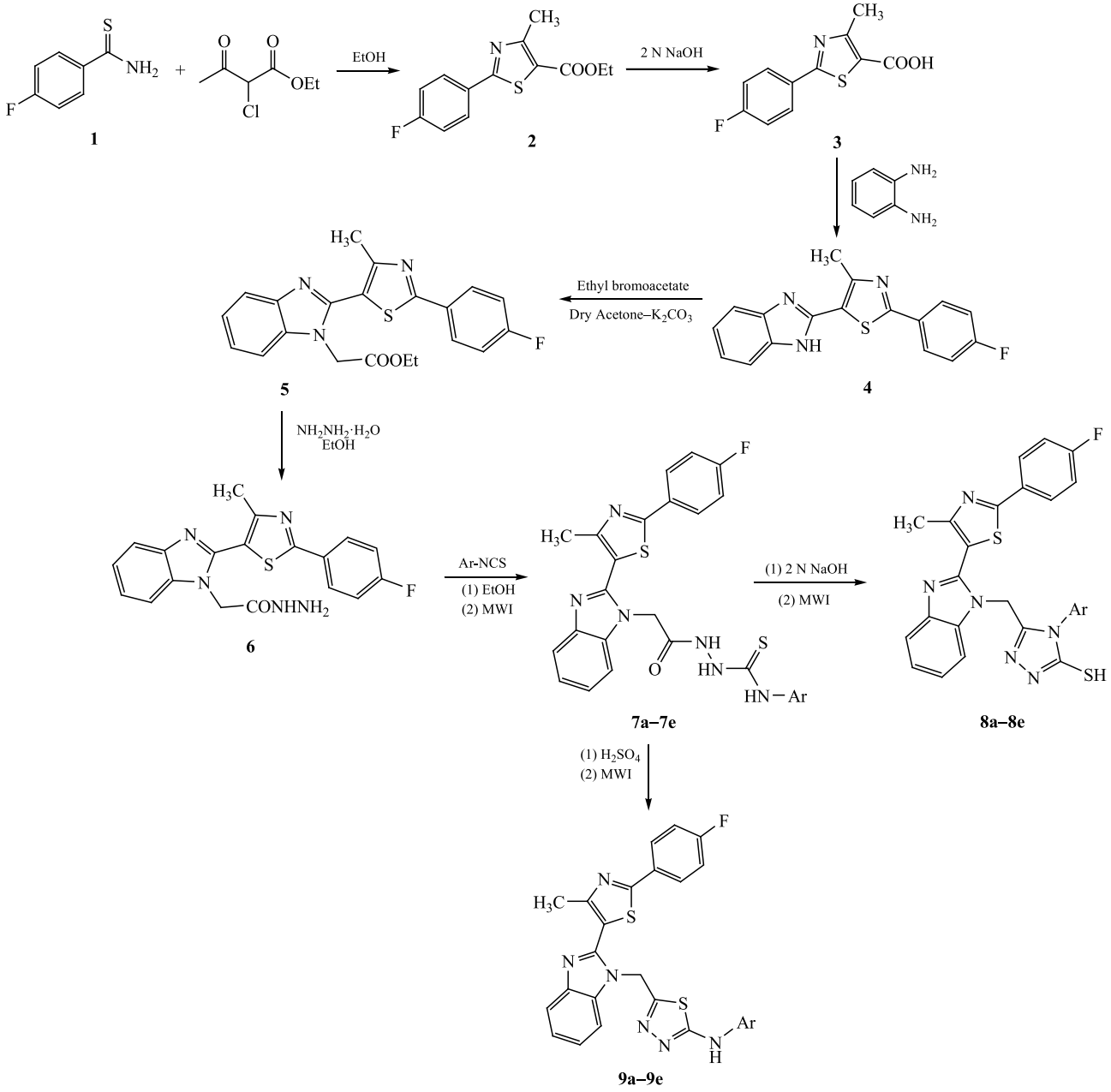
Synthesis of 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide **6** was carried out by the known method (Scheme 1) [10–12].

A novel series of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide **7a**–**7e** was synthesized from the intermediate **6** and substituted aryl isothiocyanates by conventional method and under MW irradiation [10, 13]. Their molecular structures were supported by IR, ^{1}H and ^{13}C NMR spectra. Reaction of compounds **7a**–**7e** in presence of NaOH under conventional conditions or MW irradiation gave 1,2,4-triazole derivatives **8a**–**8e** [10, 13]. In IR spectra of the products **8a**–**8e** no bands at ca. 3100 cm^{-1} characteristic for –NH group were recorded. In ^{1}H NMR spectra of those compounds characteristic singlets of S–H were recorded at ca. 14.00 ppm. Similar reaction of compounds **7a**–**7e** in acidic media under conventional conditions or MW irradiation gave 1,3,4-thiadiazoles **9a**–**9e** [10, 13]. The NH group of compound **9a** was recorded in IR spectrum by the band at 3201 cm^{-1} and in ^{1}H NMR spectrum by a singlet at 9.50 ppm.

The MW irradiation method proved to be more efficient in the synthesis of thiosemicarbazides **7a**–**7e**, 1,2,4-triazoles **8a**–**8e** and 1,3,4-thiadiazoles **9a**–**9e** derivatives than the conventional heating. It reduced the reaction time from hours to 5–10 min and increased the products yield up to 77–88% over the conventional method (60–74%) (Table 1).

***In vitro* antibacterial activity.** All the synthesized compounds were tested against gram positive bacterial

Scheme 1. Synthesis of derivatives of thiosemicarbazide (**7a**–**7e**), 1,2,4-triazole (**8a**–**8e**), and 1,3,4-thiadiazole (**9a**–**9e**).



Ar: 3-Chlorophenyl (**a**), 2-chlorophenyl (**b**), 2,4-dichlorophenyl (**c**), 4-chlorophenyl (**d**), 3,4-dichlorophenyl (**e**).

strains *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2063), and gram negative bacterial strains *Escherichia coli* (NCIM 2810)*, Salmonella abony* (NCIM 2257). The zone of inhibition in mm was determined by the well diffusion method at concentration of 1 mg/ mL, and Ciprofloxacin was used as the reference drug (Table 2). Compounds **7a**, **7d**, **7e**, **8d**, and **9e** demonstrated moderate activity against both gram positive and gram negative bacteria while other compounds were characterized by low activity or none.

EXPERIMENTAL

All organic solvents and reagents were acquired from commercial sources and used as received. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in a Raga's synthetic microwave oven.

Table 1. Synthesis data for the products

Comp. no.	Ar	Conventional method		Microwave method	
		time, min	yield, %	time, min	yield, %
7a	3-Chlorophenyl	90	74	7.0	88
7b	2-Chlorophenyl	90	70	6.5	85
7c	2,4-Dichlorophenyl	90	75	7.5	84
7d	4-Chlorophenyl	90	68	8.0	82
7e	3,4-Dichlorophenyl	90	72	9.5	87
8a	3-Chlorophenyl	150	65	8.5	80
8b	2-Chlorophenyl	150	68	9.0	78
8c	2,4-Dichlorophenyl	150	62	8.0	81
8d	4-Chlorophenyl	150	66	7.5	83
8e	3,4-Dichlorophenyl	150	70	8.5	79
9a	3-Chlorophenyl	240	68	9.0	77
9b	2-Chlorophenyl	240	62	9.5	85
9c	2,4-Dichlorophenyl	240	67	8.5	83
9d	4-Chlorophenyl	240	60	8.5	78
9e	3,4-Dichlorophenyl	240	66	8.0	81

Table 2. Antibacterial tests data for the synthesized compounds

Compound	Zone of inhibition, mm			
	S. aureus	*B. subtilis*	*E. coli*	*S. abony*
7a	16	15	14	17
7b	15	11	–	15
7c	15	14	–	13
7d	15	13	14	15
7e	16	16	17	16
8a	–	–	–	12
8b	–	–	11	10
8c	–	–	13	–
8d	15	17	13	18
8e	–	–	10	10
9a	11	12	12	16
9b	13	12	14	13
9c	12	12	14	–
9d	11	12	12	13
9e	13	15	14	16
Ciprofloxacin	23	28	26	40

FTIR spectra were recorded on a Shimadzu IR Affinity 1S (ATR) spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Advance 400 spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a Waters, Q-TOF micromass (ESI-MS) mass spectrometer.

Synthesis of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide (7a–7e). *Conventional method.* Equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanate **5** were dissolved in 15 mL of ethanol and refluxed for 90 min. Reaction progress was monitored by TLC. Upon completion of the reaction the solid product was filtered off and crystallized from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 1).

Microwave method. The mixture of equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanates **5** was dissolved in 15 mL of ethanol and subjected to MW irradiation for 5 to 10 min at 350 W. Reaction progress was monitored by TLC. Upon completion of the reaction the precipitated product was filtered off and crystallized

from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 2).

4-(3-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7a). White solid, mp 194–196°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3277 (N–H), 3248 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 9.99 s (1H, NH), 9.80 s (1H, NH), 8.05 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.58 d (2H, *J* = 8 Hz, ArH), 7.19–7.40 m (7H, ArH), 5.07 s (2H, CH_2), 2.51 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 162.25, 155.01, 145.38, 142.48, 140.42, 135.87, 132.21, 129.76, 129.14, 128.64, 128.55, 123.14, 122.52, 119.29, 118.91, 116.50, 116.27, 110.98, 45.56, 16.47. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3365 (N–H), 3277 (N–H), 3245 (N–H), 1674 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.55 s (1H, NH), 9.98 s (1H, NH), 9.60 s (1H, NH), 8.05 d. d (2H, *J* = 5.2 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.29–7.57 m (9H, ArH), 5.06 s (2H, CH_2), 2.52 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 155.01, 145.37, 142.48, 135.87, 129.39, 129.14, 128.66, 128.57, 127.21, 123.09, 122.51, 119.27, 118.94, 116.48, 116.26, 111.01, 45.50, 16.48. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7c), White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3366 (N–H), 3275 (N–H), 3246 (N–H), 1671 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.52 s (1H, NH), 10.03 s (1H, NH), 9.58 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.4 Hz, ArH), 7.71 d (1H, *J* = 8 Hz, ArH), 7.66 s (1H, ArH), 7.25–7.52 m (7H, ArH), 5.02 s (2H, CH_2), 2.48 s (3H, CH_3). LC-MS: *m/z*: 585 $[M + H]^+$.

4-(4-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7d). White solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3278 (N–H), 3247 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.46 s (1H, NH), 9.89 s (1H, NH), 9.74 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.71 d (1H, *J* = 7.6 Hz, ArH), 7.54 d (1H, *J* = 8 Hz, ArH), 7.41 d (2H, *J* = 7.6 Hz, ArH), 7.25–7.36 m (6H, ArH), 5.04 s (2H, CH_2), 2.48 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.25, 162.28, 155.02, 145.42, 142.49, 137.91, 135.88, 129.16, 128.67, 128.58, 128.09, 123.18, 122.54, 119.31, 118.94, 116.51, 116.29, 110.98, 45.57, 16.48. LC-MS: *m/z*: 551 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7e). White solid, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3276 (N–H), 3244 (N–H), 1671 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 10.07 s (1H, NH), 9.88 s (1H, NH), 7.29–8.05 m (11H, ArH), 5.07 s (2H, CH_2), 2.50 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.21, 164.73, 162.25, 154.99, 145.38, 142.48, 139.09, 135.84, 129.95, 129.10, 128.62, 128.53, 123.14, 122.52, 119. 29, 118.90, 116.47, 116.25, 110.95, 45.55, 16.45. LC-MS: *m/z*: 585 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8a–8e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 10 mL of 2 N NaOH solution was refluxed for 2.5 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice and acidified with acetic acid. The product was filtered off and crystallized from ethanol to give the corresponding pure compound **8a**–**8e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 2 N NaOH solution was subjected to MW irradiation at 350W for 5–10 min. Progress of the reaction was monitored by TLC. After completion of the process, the mixture was poured onto crushed ice and acidified with dilute acetic acid. The product was filtered off and crystallized from DMF/water to afford the corresponding pure compound **8a**–**8e** (Table 1).

4-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8a). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2939 (=C–H), 1640 (C=N), 1218 (C–F). ^{1}H NMR spectrum, δ, ppm: 6.99–8.01 m (12H, ArH), 5.50 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.42, 165.99, 162.27, 154.71, 146.50, 144.53, 142.42, 135.27, 135.13, 133.19, 130.51, 128.94, 128.63, 128.54, 127.65, 126.28, 123.15, 122.51, 119.22, 118.71, 116.55, 116.32, 111.21, 40.50, 16.62. LC-MS: *m/z*: 533.11 $[M + H]^+$.

4-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-4*H*-1,2,4-triazole-3-thiol (8b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 2936 (=C–H), 1638 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 7.13–7.99 m (12H, ArH), 5.31 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.87, 154.76, 142.49, 130.81, 129.92, 128.51, 127.92, 122.43, 119.16, 116.57, 116.35, 111.35, 40.12, 16.63. LC-MS: *m/z*: 532.98 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8c). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1635 (C=N), 1221 (C–F). ^1H NMR spectrum, δ, ppm: 7.23–7.97 m (11H, ArH), 5.38 s (2H, CH_2), 2.40 s (3H, CH_3). LC-MS: *m/z*: 567.00 $[M + H]^+$.

4-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4*H*-1,2,4-triazole-3-thiol (8d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2935 (=C–H), 1639 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm**:** 168.51, 166.04, 154.75, 147.24, 144.53, 142.39, 135.16, 134.44, 131.49, 129.41, 129.31, 129.03, 128.65, 128.56, 123.29, 122.65, 119.33, 118.58, 116.59, 116.37, 111.09, 38.88, 16.57. LC-MS: *m/z*: 533.05 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8e). White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1637 (C=N), 1222 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.53, 166.09, 162.30, 154.68, 146.94, 144.47, 142.35, 135.08, 132.63, 131.74, 131.15, 129.54, 129.03, 128.67, 128.59, 127.86, 123.25, 122.67, 119.32, 118.57, 116.55, 116.33, 111.09, 16.64. LC-MS: *m/z*: 567.05 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (9a–9e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 5 mL of conc. H_2SO_4 was stirred for 4 h at RT. After completion of process, the mixture was poured onto crushed ice and neutralized with liquid NH_3, a solid product was formed. It was filtered off and washed with methanol to afford the corresponding pure compound **9a**–**9e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 5 mL of conc. H_2SO_4 was subjected to MW irradiation for 5 to 10 min at 350 W. After completion of the process the mixture was poured onto crushed ice and neutralized with liquid NH_3. The precipitated solid was filtered off and crystallized from water–DMF to afford the corresponding pure thiadiazole **9a**–**9e** (Table 1).

***N*-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9a).** White solid, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3039 (=C–H), 1606 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.5 s (1H, NH), 7.05–8.18 m (12H, ArH), 5.85 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.80, 165.01, 154.67, 144.15, 142.18, 134.57, 129.11, 128.54, 128.19, 127.31, 123.71, 123.02, 122.35, 121.10, 118.99, 118.11, 116.07, 115.85, 110.74, 42.31, 15.98. LC-MS: *m/z*: 533.15 $[M + H]^+$.

***N*-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-1,3,4-thiadiazol-2-amine (9b).** White solid, mp 140–142°C. IR spectrum, ν, cm^{-1}: 3203 (N–H), 3038 (=C–H), 1607 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.17 d (1H, *J* = 8.8 Hz, ArH), 8.01–8.02 m (2H, ArH), 7.72 d. d (2H, *J* = 13.2 and 8 Hz, ArH), 7.26–7.44 m (6H, ArH), 7.03 t (1H, *J* = 7.2 Hz, ArH), 5.84 s (2H, CH_2), 2.47 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.51, 162.30, 155.75, 155.17, 144.65, 142.69, 136.91, 135.08, 129.61, 129.05, 128.69, 128.61, 127.81, 124.22, 123.52, 122.86, 122.70, 121.61, 119.50, 118.61, 116.57, 116.35, 111.25, 42.81, 16.48. LC-MS: *m/z*: 533.10 $[M + H]^+$.

***N*-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9c).** White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3037 (=C–H), 1608 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.29 d (1H, J = 8.4 Hz, ArH), 8.04 m (2H, ArH), 7.74 d. d (2H, *J* = 14.8 and 7.2 Hz, ArH), 7.60 s (1H, ArH), 7.32–7.38 m (5H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.04, 156.19, 155.16, 144.64, 142.68, 136.09, 135.06, 128.89, 128.69, 128.61, 127.80, 126.60, 123.52, 123.02, 122.86, 122.12, 119.50, 118.59, 116.57, 116.35, 111.25, 42.78, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

***N*-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-1,3,4-thiadiazol-2-amine (9d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3039 (=C–H), 1605 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 10.2 s (1H, NH), 8.04 m (1H, ArH), 7.73 d. d (2H, J = 17 and 7.6 Hz, ArH), 7.56 d (1H, J = 8 Hz, ArH), 7.33–7.50 m (4H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 164.66, 162.29, 155.16, 154.64, 144.63, 142.68, 139.13, 135.06, 129.01, 128.84, 128.68, 128.59, 125.41, 123.50, 122.84, 119.49, 118.89, 118.60, 116.55, 116.33, 111.23, 42.80, 16.48. LC-MS: *m/z*: 533.05 $[M + H]^+$.

***N*-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9e).** White solid, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3035 (=C–H), 1604 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 10.5 s (1H, NH), 6.5–8.4 m (11H, ArH), 5.86 s (2H, CH_2), 2.4 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.29, 164.39, 162.35, 155.23, 144.65, 142.69, 140.07, 135.08, 131.25, 130.71, 128.65, 123.50, 123.13, 119.50, 118.56, 117.52, 116.51, 111.20, 42.77, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

CONCLUSIONS

The new series of derivatives of 1,2,4-triazole **8a**–**8e** and 1,3,4-thiadiazole **9a**–**9e** have been synthesized by conventional as well as MW irradiation methods from 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide. MW irradiation at 350 W reduces the reaction time from hours to 5–10 min and increases the yield of products from 60–74 to 77–88%. All the newly synthesized compounds have been tested for their antibacterial activity. Compounds **7a**, **7d**, **7e**, **8d**, and **9e** are characterized by moderate activity against both gram positive and gram negative bacterial strains.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY MATERIAL

Supplementary material are available for this article at https://doi.org/10.1134/S1070363220090200 and are accessible for authorized users.

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Microwave-assisted Synthesis, Characterization, and Antibacterial Screening of Some Pyrazolone Derivatives

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ABSTRACT 1-(4-(4-Chlorophenyl)thiazol-2-yl)-3-propyl-1*H*-pyrazol-5(4*H*)-one **5** was prepared by the reaction of 1-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine and ethyl 3-oxohexanoate. Compound **5** was condensed with different 4-formylpyrazoles **8a-f** to give product **9a-f** through Knoevenagel condensation. The reaction was carried out by both conventional and non-conventional methods. The structures of all the newly synthesized compounds were confirmed with the help of spectral techniques. All the compounds were screened for antibacterial activity. Compounds **9a**, **9d**, and **9e** exhibited good antibacterial activity against *Bacillus subtilis*.

KEYWORDS Knoevenagel condensation. Pyrazolone. Thiazoles. Thiophene.

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INTRODUCTION

The Knoevenagel condensation reaction has been widely employed for C-C bond formation in organic synthesis[1] and their products are the key intermediates for the synthesis of various natural and therapeutic drugs, polymer, and perfumes.[2,3] Lewis bases and acids have been reported as catalysts in the Knoevenagel condensation, including Ni-SiO_2,[4] synthetic phosphate $Na_2CaP_2O_7$,[5] $Ca_2P_2O_7$,[5] and natural phosphate ([NP]/KF or NP/$NaNO_3$).[6] Ionic liquids[7] have been also used as catalysts in Knoevenagel condensation.

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities such as anti-inflammatory,[8] antitubercular,[9] antimicrobial,[10] angiogenesis,[11] and neuroprotective.[12] Various pyrazole derivatives exhibit anti-inflammatory,[13] analgesic,[13] antiproliferative,[14] and antihepatotoxic[15] activities.

Thiophene is sulfur-containing a five-membered heterocyclic compound. Various biological activities associated with thiophene derivatives are BACEI inhibitors,[16] HIV protease inhibitor,[17] antibreast cancer,[18] acetylcholinesterase inhibitors,[19] and antidepressant.[20]

The pyrazolone skeleton exists in the core structure of several biologically active compounds and natural products.[21] Antipyrine[22] was the first synthetic drug containing pyrazolone ring as the main framework which has been used as an analgesic and antipyretic. Pyrazolone derivatives show a broad spectrum of biological activities such as severe acute respiratory syndrome-coronavirus 3C-like protease inhibitors,[23] cytotoxic,[24] antitubulin,[24] anaplastic lymphoma kinase inhibitors,[25] anti-inflammatory,[26] and analgesic.[26] Some of the chlorine-containing compounds exhibit anti-inflammatory,[27] analgesic,[28] antibacterial,[29] and antifungal[30] activities.

The application of microwave (MW) and ultrasound irradiation as a non-conventional energy source for the activation of reactions has now become a very popular and useful technology in organic chemistry.[31-33] These methods lead to enhanced conversion rates, higher yields, and easier work-up.

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Synthesis and Antibacterial Screening of Some New Pyrazolylchromones and Pyrazolylcoumaran-3-ones

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ABSTRACT Some new pyrazolylchromones **4a-e** (flavone analogs) and pyrazolylcoumaran-3-ones **5a-e** (aurone analogs) were synthesized by refluxing chalcones **3a-e** in dimethyl sulfoxide/I_2 and Pyridine/$Hg(OAc)_2$, respectively. Spectral techniques such as infrared, proton nuclear magnetic resonance, and mass spectrometry were used to confirm the structures of newly synthesized compounds. These compounds were studied for their antibacterial activities toward *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Salmonella typhi*. Some of these compounds showed promising activity against test organisms.

KEYWORDS: Pyrazoles, Flavones, Aurones, Antibacterial activity.

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INTRODUCTION

Treatment of various diseases is a worldwide serious issue. The emergence of newer infectious diseases, multidrug resistance developing in microbial strains, diseases due to homeostatic disturbances, toxicity associated with existing drugs have created a need of selective, potential therapeutic agents. In search of potential therapeutic agents, many natural and synthetic compounds have been investigated. Many of the natural products are heterocycles which possess medicinal properties and serve as lead molecules for drug discovery.[1] Lead modification is an important step in drug design and development.

Pyrazole containing compounds are medicinally useful because of their various therapeutic properties, including antimicrobial,[2,3] anti-inflammatory,[4] antitubercular,[5] antitumor,[6] antidiabetic,[7] and antiviral and antioxidant[8] properties.

Flavonoids are extensively studied plant products for their biological potential. Chalcones are important intermediates in the flavonoid synthetic pathway and also have medicinal properties.[9] These are known to exhibit antibacterial,[10] antitubercular,[11] anti-inflammatory,[12,13] antimalarial,[14] antifungal,[15] and antiviral[16] activities. Synthetic chalcones with heterocyclic rings have been investigated for medicinal properties and are also used in the synthesis of various heterocycles. Pyrazole containing chalcones exhibits potential antimicrobial,[17] antioxidant,[18] and anticancer[19] activities.

Flavones and aurones are medicinally useful members of the flavonoid family. Flavones are widely known for their interesting bioactivities. As a consequence of the

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

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Microwave Assisted Synthesis and Antibacterial Activity of New 1,3,4-Thiadiazoles and 1,2,4-Triazoles Derived from 2-{2-[2-(4-Fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide

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Abstract—A series of novel derivatives of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide, 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol and 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]-imidazol-1-yl}methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine have been synthesized by the conventional method as well as using MW irradiation. All newly synthesized compounds have been tested for antibacterial activity. Several products have demonstrated moderate activity against gram positive and gram negative bacterial strains.

Keywords: 1,3,4-thiadiazole, 1,2,4-triazole, microwave irradiation, antibacterial activity

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Antimycobacterial and antimicrobial activities have been well established and studied in depth for benzimidazole [1, 2], thiazole [3, 4], 1,3,4-thiadiazole [5–7], and 1,2,4-triazole [8, 9] derivatives.

Pharmacological importance associated with those compounds inspired us to synthesize novel benzimidazole and thiazole containing 1,3,4-thiadiazoles and 1,2,4-triazoles under conventional and MW irradiation. All newly synthesized compounds were evaluated for their antibacterial activity.

RESULTS AND DISCUSSION

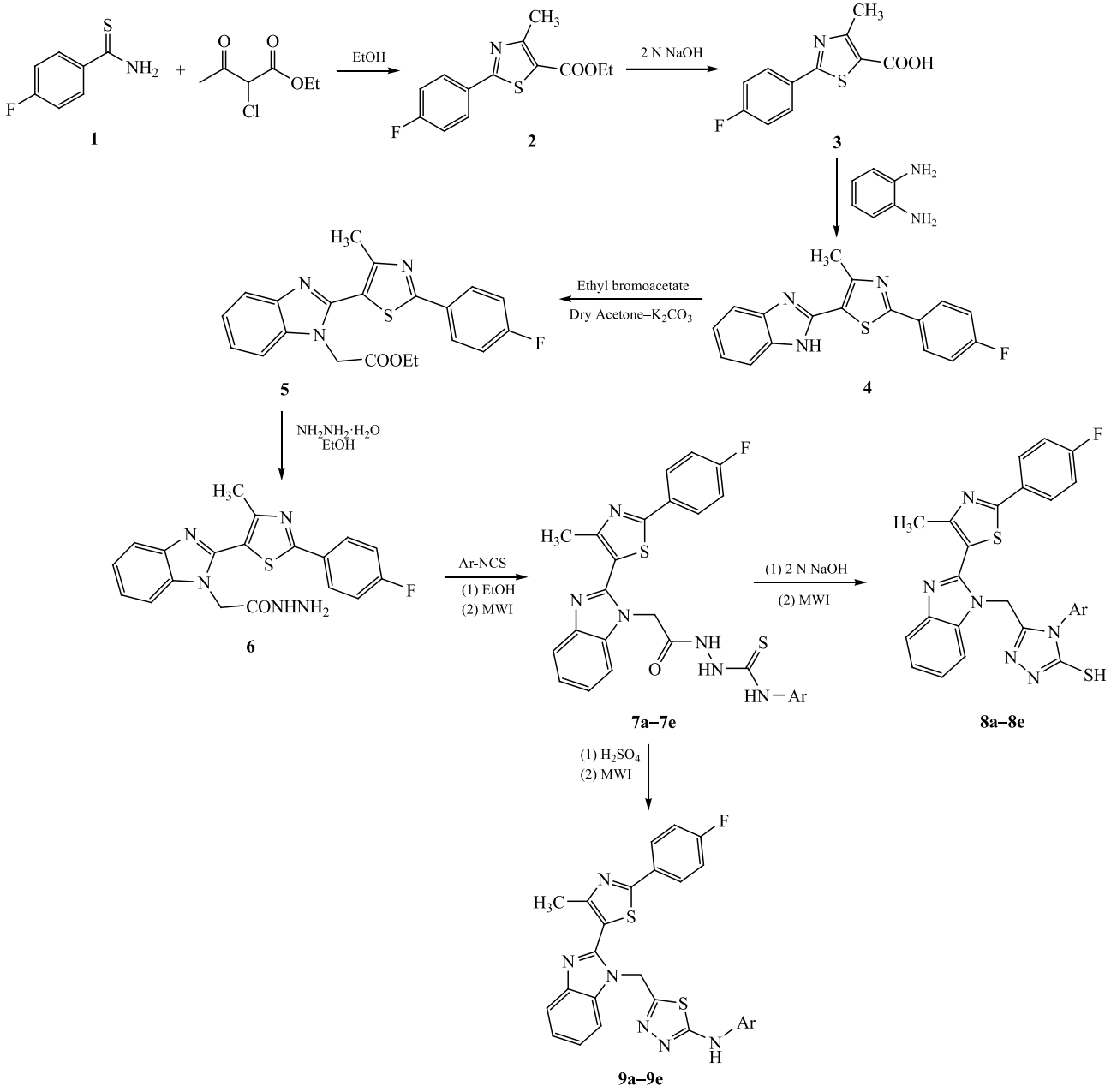
Synthesis of 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide **6** was carried out by the known method (Scheme 1) [10–12].

A novel series of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide **7a**–**7e** was synthesized from the intermediate **6** and substituted aryl isothiocyanates by conventional method and under MW irradiation [10, 13]. Their molecular structures were supported by IR, ^{1}H and ^{13}C NMR spectra. Reaction of compounds **7a**–**7e** in presence of NaOH under conventional conditions or MW irradiation gave 1,2,4-triazole derivatives **8a**–**8e** [10, 13]. In IR spectra of the products **8a**–**8e** no bands at ca. 3100 cm^{-1} characteristic for –NH group were recorded. In ^{1}H NMR spectra of those compounds characteristic singlets of S–H were recorded at ca. 14.00 ppm. Similar reaction of compounds **7a**–**7e** in acidic media under conventional conditions or MW irradiation gave 1,3,4-thiadiazoles **9a**–**9e** [10, 13]. The NH group of compound **9a** was recorded in IR spectrum by the band at 3201 cm^{-1} and in ^{1}H NMR spectrum by a singlet at 9.50 ppm.

The MW irradiation method proved to be more efficient in the synthesis of thiosemicarbazides **7a**–**7e**, 1,2,4-triazoles **8a**–**8e** and 1,3,4-thiadiazoles **9a**–**9e** derivatives than the conventional heating. It reduced the reaction time from hours to 5–10 min and increased the products yield up to 77–88% over the conventional method (60–74%) (Table 1).

***In vitro* antibacterial activity.** All the synthesized compounds were tested against gram positive bacterial

Scheme 1. Synthesis of derivatives of thiosemicarbazide (**7a**–**7e**), 1,2,4-triazole (**8a**–**8e**), and 1,3,4-thiadiazole (**9a**–**9e**).



Ar: 3-Chlorophenyl (**a**), 2-chlorophenyl (**b**), 2,4-dichlorophenyl (**c**), 4-chlorophenyl (**d**), 3,4-dichlorophenyl (**e**).

strains *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2063), and gram negative bacterial strains *Escherichia coli* (NCIM 2810)*, Salmonella abony* (NCIM 2257). The zone of inhibition in mm was determined by the well diffusion method at concentration of 1 mg/ mL, and Ciprofloxacin was used as the reference drug (Table 2). Compounds **7a**, **7d**, **7e**, **8d**, and **9e** demonstrated moderate activity against both gram positive and gram negative bacteria while other compounds were characterized by low activity or none.

EXPERIMENTAL

All organic solvents and reagents were acquired from commercial sources and used as received. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in a Raga's synthetic microwave oven.

Table 1. Synthesis data for the products

Comp. no.	Ar	Conventional method		Microwave method	
		time, min	yield, %	time, min	yield, %
7a	3-Chlorophenyl	90	74	7.0	88
7b	2-Chlorophenyl	90	70	6.5	85
7c	2,4-Dichlorophenyl	90	75	7.5	84
7d	4-Chlorophenyl	90	68	8.0	82
7e	3,4-Dichlorophenyl	90	72	9.5	87
8a	3-Chlorophenyl	150	65	8.5	80
8b	2-Chlorophenyl	150	68	9.0	78
8c	2,4-Dichlorophenyl	150	62	8.0	81
8d	4-Chlorophenyl	150	66	7.5	83
8e	3,4-Dichlorophenyl	150	70	8.5	79
9a	3-Chlorophenyl	240	68	9.0	77
9b	2-Chlorophenyl	240	62	9.5	85
9c	2,4-Dichlorophenyl	240	67	8.5	83
9d	4-Chlorophenyl	240	60	8.5	78
9e	3,4-Dichlorophenyl	240	66	8.0	81

Table 2. Antibacterial tests data for the synthesized compounds

Compound	Zone of inhibition, mm			
	S. aureus	*B. subtilis*	*E. coli*	*S. abony*
7a	16	15	14	17
7b	15	11	–	15
7c	15	14	–	13
7d	15	13	14	15
7e	16	16	17	16
8a	–	–	–	12
8b	–	–	11	10
8c	–	–	13	–
8d	15	17	13	18
8e	–	–	10	10
9a	11	12	12	16
9b	13	12	14	13
9c	12	12	14	–
9d	11	12	12	13
9e	13	15	14	16
Ciprofloxacin	23	28	26	40

FTIR spectra were recorded on a Shimadzu IR Affinity 1S (ATR) spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Advance 400 spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a Waters, Q-TOF micromass (ESI-MS) mass spectrometer.

Synthesis of 1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-4-phenylthiosemicarbazide (7a–7e). *Conventional method.* Equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanate **5** were dissolved in 15 mL of ethanol and refluxed for 90 min. Reaction progress was monitored by TLC. Upon completion of the reaction the solid product was filtered off and crystallized from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 1).

Microwave method. The mixture of equimolar amounts (0.01 mmol) of acid hydrazide **6** and aryl isothiocyanates **5** was dissolved in 15 mL of ethanol and subjected to MW irradiation for 5 to 10 min at 350 W. Reaction progress was monitored by TLC. Upon completion of the reaction the precipitated product was filtered off and crystallized

from ethanol to give the corresponding pure compounds **7a**–**7e** (Table 2).

4-(3-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7a). White solid, mp 194–196°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3277 (N–H), 3248 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 9.99 s (1H, NH), 9.80 s (1H, NH), 8.05 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.58 d (2H, *J* = 8 Hz, ArH), 7.19–7.40 m (7H, ArH), 5.07 s (2H, CH_2), 2.51 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 162.25, 155.01, 145.38, 142.48, 140.42, 135.87, 132.21, 129.76, 129.14, 128.64, 128.55, 123.14, 122.52, 119.29, 118.91, 116.50, 116.27, 110.98, 45.56, 16.47. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3365 (N–H), 3277 (N–H), 3245 (N–H), 1674 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.55 s (1H, NH), 9.98 s (1H, NH), 9.60 s (1H, NH), 8.05 d. d (2H, *J* = 5.2 and 8.8 Hz, ArH), 7.75 d (1H, *J* = 8 Hz, ArH), 7.29–7.57 m (9H, ArH), 5.06 s (2H, CH_2), 2.52 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.22, 155.01, 145.37, 142.48, 135.87, 129.39, 129.14, 128.66, 128.57, 127.21, 123.09, 122.51, 119.27, 118.94, 116.48, 116.26, 111.01, 45.50, 16.48. LC-MS: *m/z*: 551.06 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7c), White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3366 (N–H), 3275 (N–H), 3246 (N–H), 1671 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.52 s (1H, NH), 10.03 s (1H, NH), 9.58 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.4 Hz, ArH), 7.71 d (1H, *J* = 8 Hz, ArH), 7.66 s (1H, ArH), 7.25–7.52 m (7H, ArH), 5.02 s (2H, CH_2), 2.48 s (3H, CH_3). LC-MS: *m/z*: 585 $[M + H]^+$.

4-(4-Chlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)-thiosemicarbazide (7d). White solid, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3278 (N–H), 3247 (N–H), 1672 (C=O), 1232 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.46 s (1H, NH), 9.89 s (1H, NH), 9.74 s (1H, NH), 8.01 d. d (2H, *J* = 5.6 and 8.8 Hz, ArH), 7.71 d (1H, *J* = 7.6 Hz, ArH), 7.54 d (1H, *J* = 8 Hz, ArH), 7.41 d (2H, *J* = 7.6 Hz, ArH), 7.25–7.36 m (6H, ArH), 5.04 s (2H, CH_2), 2.48 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.25, 162.28, 155.02, 145.42, 142.49, 137.91, 135.88, 129.16, 128.67, 128.58, 128.09, 123.18, 122.54, 119.31, 118.94, 116.51, 116.29, 110.98, 45.57, 16.48. LC-MS: *m/z*: 551 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-1-(2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetyl)thiosemicarbazide (7e). White solid, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3367 (N–H), 3276 (N–H), 3244 (N–H), 1671 (C=O), 1231 (C–F). ^{1}H NMR spectrum, δ, ppm: 10.51 s (1H, NH), 10.07 s (1H, NH), 9.88 s (1H, NH), 7.29–8.05 m (11H, ArH), 5.07 s (2H, CH_2), 2.50 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.21, 164.73, 162.25, 154.99, 145.38, 142.48, 139.09, 135.84, 129.95, 129.10, 128.62, 128.53, 123.14, 122.52, 119. 29, 118.90, 116.47, 116.25, 110.95, 45.55, 16.45. LC-MS: *m/z*: 585 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8a–8e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 10 mL of 2 N NaOH solution was refluxed for 2.5 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice and acidified with acetic acid. The product was filtered off and crystallized from ethanol to give the corresponding pure compound **8a**–**8e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 2 N NaOH solution was subjected to MW irradiation at 350W for 5–10 min. Progress of the reaction was monitored by TLC. After completion of the process, the mixture was poured onto crushed ice and acidified with dilute acetic acid. The product was filtered off and crystallized from DMF/water to afford the corresponding pure compound **8a**–**8e** (Table 1).

4-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8a). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2939 (=C–H), 1640 (C=N), 1218 (C–F). ^{1}H NMR spectrum, δ, ppm: 6.99–8.01 m (12H, ArH), 5.50 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.42, 165.99, 162.27, 154.71, 146.50, 144.53, 142.42, 135.27, 135.13, 133.19, 130.51, 128.94, 128.63, 128.54, 127.65, 126.28, 123.15, 122.51, 119.22, 118.71, 116.55, 116.32, 111.21, 40.50, 16.62. LC-MS: *m/z*: 533.11 $[M + H]^+$.

4-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-4*H*-1,2,4-triazole-3-thiol (8b). White solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 2936 (=C–H), 1638 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 7.13–7.99 m (12H, ArH), 5.31 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.87, 154.76, 142.49, 130.81, 129.92, 128.51, 127.92, 122.43, 119.16, 116.57, 116.35, 111.35, 40.12, 16.63. LC-MS: *m/z*: 532.98 $[M + H]^+$.

4-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8c). White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1635 (C=N), 1221 (C–F). ^1H NMR spectrum, δ, ppm: 7.23–7.97 m (11H, ArH), 5.38 s (2H, CH_2), 2.40 s (3H, CH_3). LC-MS: *m/z*: 567.00 $[M + H]^+$.

4-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-4*H*-1,2,4-triazole-3-thiol (8d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2935 (=C–H), 1639 (C=N), 1219 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm**:** 168.51, 166.04, 154.75, 147.24, 144.53, 142.39, 135.16, 134.44, 131.49, 129.41, 129.31, 129.03, 128.65, 128.56, 123.29, 122.65, 119.33, 118.58, 116.59, 116.37, 111.09, 38.88, 16.57. LC-MS: *m/z*: 533.05 $[M + H]^+$.

4-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-4*H*-1,2,4-triazole-3-thiol (8e). White solid, mp 220–222°C. IR spectrum, ν, cm^{-1}: 2938 (=C–H), 1637 (C=N), 1222 (C–F). ^1H NMR spectrum, δ, ppm: 14.00 s (1H, SH), 7.17–8.01 m (12H, ArH), 5.51 s (2H, CH_2), 2.41 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 168.53, 166.09, 162.30, 154.68, 146.94, 144.47, 142.35, 135.08, 132.63, 131.74, 131.15, 129.54, 129.03, 128.67, 128.59, 127.86, 123.25, 122.67, 119.32, 118.57, 116.55, 116.33, 111.09, 16.64. LC-MS: *m/z*: 567.05 $[M + H]^+$.

Synthesis of 5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (9a–9e). *Conventional method.* The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.001 mol) with 5 mL of conc. H_2SO_4 was stirred for 4 h at RT. After completion of process, the mixture was poured onto crushed ice and neutralized with liquid NH_3, a solid product was formed. It was filtered off and washed with methanol to afford the corresponding pure compound **9a**–**9e** (Table 1).

Microwave method. The mixture of an appropriate thiosemicarbazide **7a**–**7e** (0.01 mol) with 5 mL of conc. H_2SO_4 was subjected to MW irradiation for 5 to 10 min at 350 W. After completion of the process the mixture was poured onto crushed ice and neutralized with liquid NH_3. The precipitated solid was filtered off and crystallized from water–DMF to afford the corresponding pure thiadiazole **9a**–**9e** (Table 1).

***N*-(3-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9a).** White solid, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3039 (=C–H), 1606 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.5 s (1H, NH), 7.05–8.18 m (12H, ArH), 5.85 s (2H, CH_2), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 165.80, 165.01, 154.67, 144.15, 142.18, 134.57, 129.11, 128.54, 128.19, 127.31, 123.71, 123.02, 122.35, 121.10, 118.99, 118.11, 116.07, 115.85, 110.74, 42.31, 15.98. LC-MS: *m/z*: 533.15 $[M + H]^+$.

***N*-(2-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}methyl)-1,3,4-thiadiazol-2-amine (9b).** White solid, mp 140–142°C. IR spectrum, ν, cm^{-1}: 3203 (N–H), 3038 (=C–H), 1607 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.17 d (1H, *J* = 8.8 Hz, ArH), 8.01–8.02 m (2H, ArH), 7.72 d. d (2H, *J* = 13.2 and 8 Hz, ArH), 7.26–7.44 m (6H, ArH), 7.03 t (1H, *J* = 7.2 Hz, ArH), 5.84 s (2H, CH_2), 2.47 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.51, 162.30, 155.75, 155.17, 144.65, 142.69, 136.91, 135.08, 129.61, 129.05, 128.69, 128.61, 127.81, 124.22, 123.52, 122.86, 122.70, 121.61, 119.50, 118.61, 116.57, 116.35, 111.25, 42.81, 16.48. LC-MS: *m/z*: 533.10 $[M + H]^+$.

***N*-(2,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9c).** White solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 3037 (=C–H), 1608 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 9.2 s (1H, NH), 8.29 d (1H, J = 8.4 Hz, ArH), 8.04 m (2H, ArH), 7.74 d. d (2H, *J* = 14.8 and 7.2 Hz, ArH), 7.60 s (1H, ArH), 7.32–7.38 m (5H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 165.04, 156.19, 155.16, 144.64, 142.68, 136.09, 135.06, 128.89, 128.69, 128.61, 127.80, 126.60, 123.52, 123.02, 122.86, 122.12, 119.50, 118.59, 116.57, 116.35, 111.25, 42.78, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

***N*-(4-Chlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-

methyl)-1,3,4-thiadiazol-2-amine (9d). White solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3039 (=C–H), 1605 (C=N), 1232 (C–F). ^1H NMR spectrum, δ, ppm: 10.2 s (1H, NH), 8.04 m (1H, ArH), 7.73 d. d (2H, J = 17 and 7.6 Hz, ArH), 7.56 d (1H, J = 8 Hz, ArH), 7.33–7.50 m (4H, ArH), 5.86 s (2H, CH_2), 2.49 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.30, 164.66, 162.29, 155.16, 154.64, 144.63, 142.68, 139.13, 135.06, 129.01, 128.84, 128.68, 128.59, 125.41, 123.50, 122.84, 119.49, 118.89, 118.60, 116.55, 116.33, 111.23, 42.80, 16.48. LC-MS: *m/z*: 533.05 $[M + H]^+$.

***N*-(3,4-Dichlorophenyl)-5-({2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}-methyl)-1,3,4-thiadiazol-2-amine (9e).** White solid, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3202 (N–H), 3035 (=C–H), 1604 (C=N), 1231 (C–F). ^1H NMR spectrum, δ, ppm: 10.5 s (1H, NH), 6.5–8.4 m (11H, ArH), 5.86 s (2H, CH_2), 2.4 s (3H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 166.29, 164.39, 162.35, 155.23, 144.65, 142.69, 140.07, 135.08, 131.25, 130.71, 128.65, 123.50, 123.13, 119.50, 118.56, 117.52, 116.51, 111.20, 42.77, 16.49. LC-MS: *m/z*: 567.05 $[M + H]^+$.

CONCLUSIONS

The new series of derivatives of 1,2,4-triazole **8a**–**8e** and 1,3,4-thiadiazole **9a**–**9e** have been synthesized by conventional as well as MW irradiation methods from 2-{2-[2-(4-fluorophenyl)-4-methylthiazol-5-yl]-1*H*-benzo[*d*]imidazol-1-yl}acetohydrazide. MW irradiation at 350 W reduces the reaction time from hours to 5–10 min and increases the yield of products from 60–74 to 77–88%. All the newly synthesized compounds have been tested for their antibacterial activity. Compounds **7a**, **7d**, **7e**, **8d**, and **9e** are characterized by moderate activity against both gram positive and gram negative bacterial strains.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

SUPPLEMENTARY MATERIAL

Supplementary material are available for this article at https://doi.org/10.1134/S1070363220090200 and are accessible for authorized users.

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

Perfluoro-alkylated and trifluoro-methylated pyrazoles represent pharmacologically related core structures that are present in many important drugs and agrochemicals, such as fluazolate (herbicide), penthiopyrad (fungicide), razaxaban (anticoagulant), deracoxib, celecoxib (anti-inflammatory), and penflufen (fungicidal) (Figure 1).[16] So, the modern trend is moving more in the direction of the synthesis of a collection of fluorine-containing molecules in order to find excellent biological activity.

Ultrasonic irradiation is a new technology that has been widely used in chemical reactions. When ultrasonic waves pass through a liquid medium, a large number of microbubbles form, grow, and collapse in very short times, about a few microseconds. The formation and violent collapse of small vacuum bubbles takes place due to the ultrasonication waves generated in alternating high pressure and low pressure in liquids, and the phenomenon is known as cavitation. It causes high-speed imposing liquid jets and strong hydrodynamic shear forces. The deagglomeration of nanometer-sized materials was carried out using these effects. In this aspect, for high-speed mixers and agitator bead mills, ultrasonication is an alternative.[17]

In the preparative chemist's toolkit, microwave heating is a valuable technique. Due to a modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way.[18] In recent years, microwave-assisted organic synthesis (MAOs)[19] has been emerged as a new "lead" in organic synthesis. Important advantages of this technology include a highly accelerated rate of the reaction and a decrease in reaction time, with an increase in the yield and quality of the product. The current technique is considered an important method toward green chemistry as this technique is more environmentally friendly. The conventional method of organic synthesis usually needs a longer heating time; tedious apparatus setup, which results in the higher cost of the process; and the excessive use of solvents/reagents, which leads to environmental pollution. This growth of green chemistry

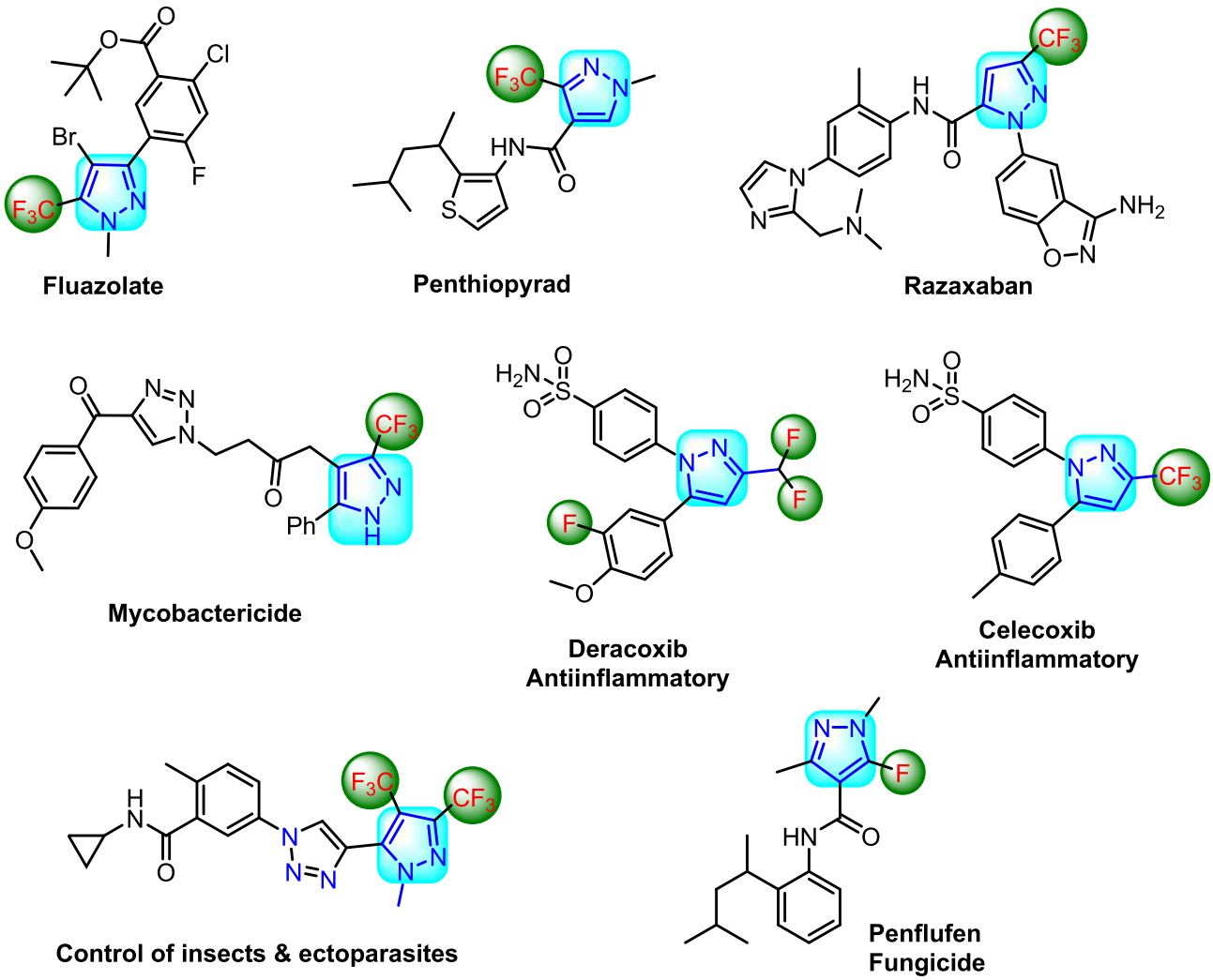


FIGURE 1 Structure of pyrazole- and fluorine-containing commercially available drugs

holds significant potential for a reduction of the byproduct, a reduction in waste production, and lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and bypass thermal conductivity, leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[20] Knoevenagel condensation reactions are carried out by the condensation of aldehyde and the active methylene group using different catalysts such as piperidine, $InCl_3$, $TiCl_4$, LiOH, $ZnCl_2$, and $NbCl_5$.[20,21] They are also carried out using $NaAlO_2$-promoted mesoporous catalysts,[22] ionic liquid,[23] monodisperse carbon nanotube-based NiCu nanohybrids,[24] and MAOs.[25] This is one of the most important methodologies used in synthetic organic chemistry for the formation of a C—C double bond.

From our study, the results demonstrated that green methodologies are less hazardous than classical synthesis methods, as well more efficient and economical and environmentally friendly; short reaction times and excellent yields are observed for those reactions in which conventional heating is replaced by microwave irradiation. Keeping in mind the 12 principles of green chemistry, in continuation of our research work,[26] and the advantages of microwave irradiation and activities associated with pyrazole and fluorine, we construct pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional, as well as microwave, irradiation and ultrasonication and evaluated their anti-inflammatory and antioxidant activity. In addition to this, we have also performed in silico absorption, distribution, metabolism, and excretion (ADME) predictions for the synthesized compounds.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A facile, economic, and green protocol for the cyclocondensation of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) with different aldehydes has been achieved.

The key starting material 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (**3**) was synthesized by the condensation of 1-(perfluorophenyl)hydrazine (**1**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in ethanol[27] (Scheme 1).

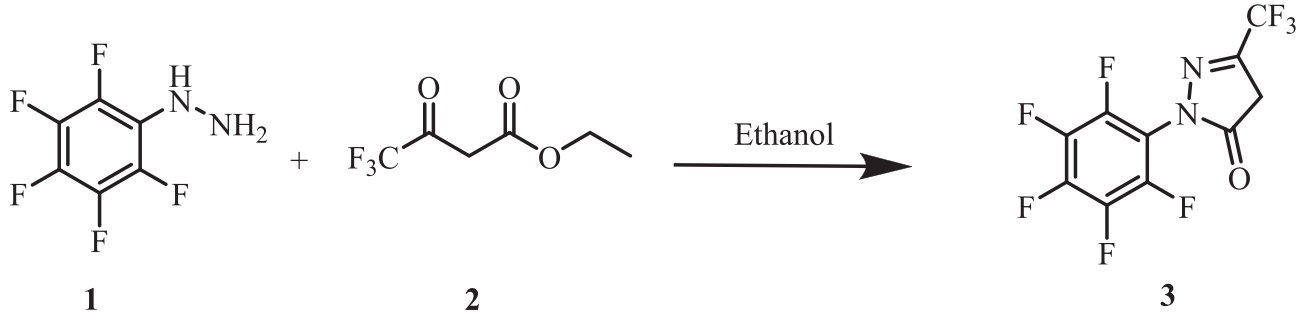
Initially, we carried out the reaction between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) (**3**) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid as a model reaction (Scheme 2). Initially, the model reaction was carried out in ethanol without using acetic acid, and it was observed that a very low yield of product (20%) was obtained even after 2 hr. Therefore, improving the yield intervention of the catalyst was thought to be necessary. So, we decided to use acetic acid as a catalyst to promote this transformation at room temperature. At room temperature, the yield of product (45%) was found to be increased in 3 hr, so we decided to provide heating to the reaction mixture to achieve maximum product yield.

When the reaction mixture refluxed in acetic acid, product formation took place after 2 hr, and the yield of the product was 72% (Table 1).

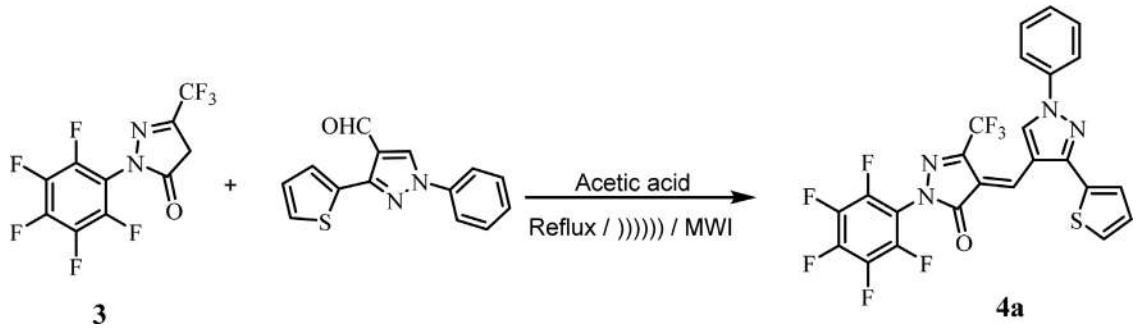
To check the ultrasonication's specific effect on this reaction, under ultrasound irradiation at 35–40°C, we carried out the model reaction using the optimized reaction conditions in hand to check whether the reaction could be accelerated with further improved product yield within a short reaction time (Scheme 2).

It was observed that, under ultrasonic conditions, the conversion rate of a reactant to product increased with less time (Table 1). Thus, when considering the basic green chemistry concept, ultrasonic irradiation was found to have a beneficial effect on the synthesis of Knoevenagel derivatives (**4a-d**, **5a-f**, and **6a-e**), which was superior to the traditional method with respect to yield and reaction time (Table 1).

To accomplish the goal and significance of green chemistry, the model reaction was carried out under



SCHEME 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one **3**



SCHEME 2 Model reaction for conventional, ultrasonication, and microwave irradiation methods

TABLE 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**)

						Conventional method[a]		Ultrasound method[b]		Microwave method[c]	
Cpd	R_1	R_2	R_3	R_4	m. p. (°C)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
4a	H	H	-	-	224–226	120	72	20	81	6.5	84
4b	Br	F	-	-	232–234	120	75	18	78	6.5	81
4c	Cl	H	-	-	216–218	120	70	20	76	6.0	80
4d	Br	H	-	-	230–232	120	64	16	70	6.5	76
5a	H	H	OMe	-	202–204	120	70	21	76	5.5	84
5b	H	H	H	-	186–188	120	66	17	72	6.0	80
5c	F	H	OMe	-	180–182	120	68	16	75	7.0	82
5d	H	H	Me	-	206–208	120	65	16	71	6.5	79
5e	H	H	OCF_3	-	142–144	120	62	18	70	6.5	76
5f	H	Cl	Cl	-	212–214	120	70	19	80	5.5	84
6a	Me	Cl	Me	H	188–190	120	66	18	76	6.0	78
6b	H	Cl	Me	H	180–182	120	62	17	72	7.5	75
6c	H	Cl	H	H	176–178	120	59	18	79	7.0	80
6d	H	Cl	H	Cl	212–214	120	64	20	72	7.0	78
6e	H	H	Me	H	180–182	120	60	18	80	7.5	82

Abbreviation: Cpd, compound.

[a]Reaction conditions: Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid.

[b]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under ultrasound irradiation.

[c]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under microwave irradiation.

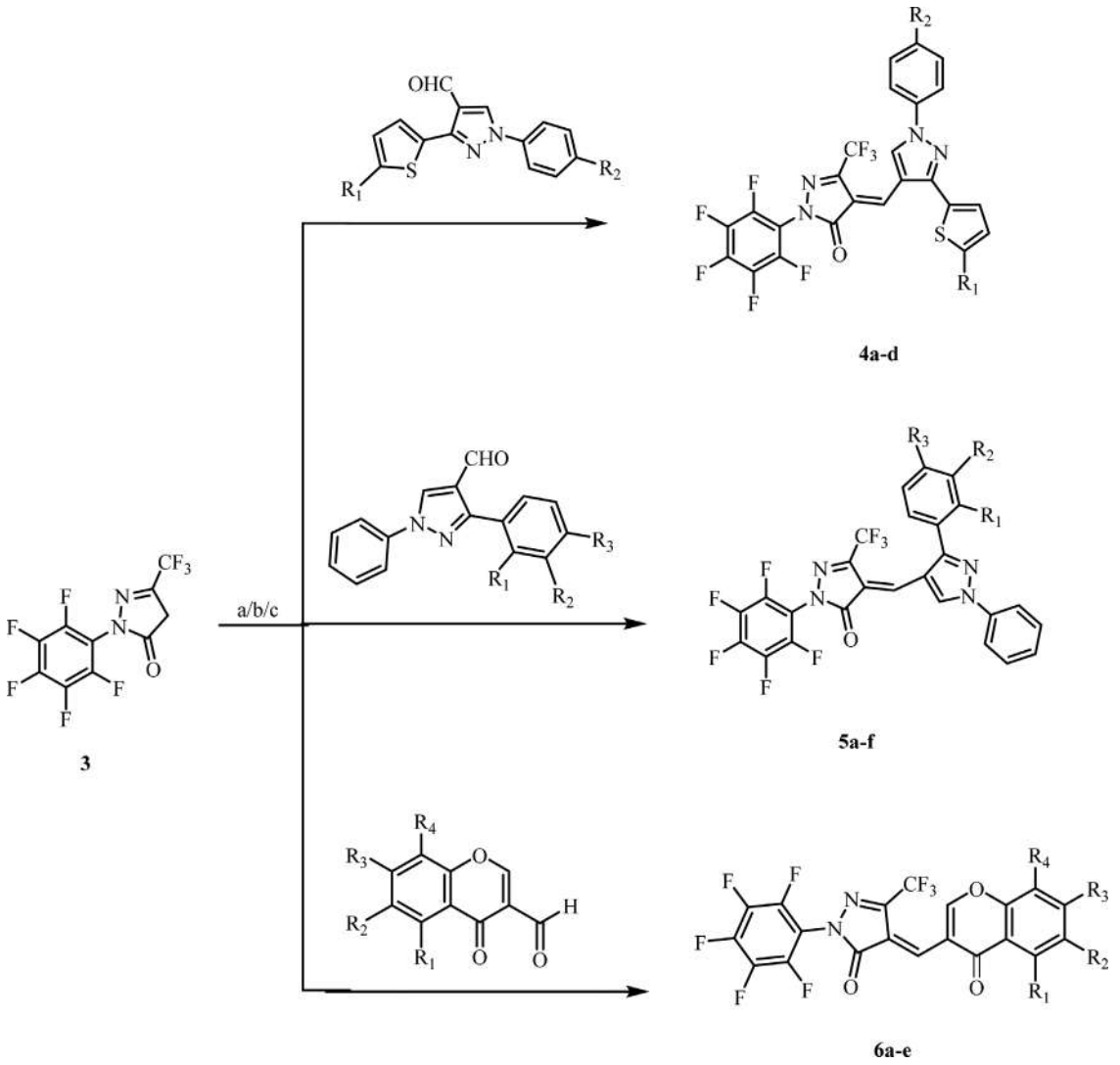
[d]Isolated yield. m.p.: melting point.

microwave irradiation for a period of time indicated in Table 1 at 350 W (Scheme 2). Fortunately, the product formation occurred in 6.5 min, with an 84% increase in yield .

So, from the above experiments, it can be concluded that, when the reaction was carried out under the conventional method, it gave comparatively low yields of products with longer reaction times, while the same reaction carried out under the influence of ultrasonic irradiation and microwave irradiation gave excellent yields of the products in short reaction times.

Finally, we assessed the scope and generality of this method for the Knoevenagel condensation between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) and different aldehydes (Scheme 3), achieved under conventional and nonconventional methods like the ultrasound and microwave methods, respectively. With respect to the substituent present on the aromatic ring of aldehyde, under the optimized conditions, the corresponding products were obtained in high to excellent yields (Table 1).

More importantly, hetero aryl aldehydes were observed to be well tolerated under optimized conditions,



SCHEME 3 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**). Reaction conditions: **a** = Refluxed in acetic acid. **b** = Under ultrasound irradiation in acetic acid. **c** = Under microwave irradiation using acetic acid as a solvent

furnishing the product in good yields. All the synthesized compounds (**4a-d**, **5a-f**, and **6a-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

The formation of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **4a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. In the IR spectrum of compound **4a**, the peaks observed at 1,681 cm^{-1} indicate the presence of C═O group. In the ^{1}H NMR spectrum of compound **4a**, two singlets were observed at δ 8.11 and 10.10 ppm for pyrazolyl and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **4a** revealed that the peak appearing at δ 161.4 ppm is due to the presence of carbonyl carbon. The structure of compound **4a** was also confirmed by a molecular ion peak at *m*/*z* 555.01 $(M + H)^+$. Similarly, the synthesis of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-ones **5a-f** was also confirmed by spectral techniques. In the IR spectrum of compound **5a**, the peak observed at 1,701 cm^{-1} corresponded to the C═O group. In the ^{1}H NMR spectrum of compound **5a**, the three singlets observed at δ 3.92, 8.11, and 10.10 ppm confirm the presence of ─OCH_3, pyrazolyl proton, and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **5a** showed peaks at δ 162.5 and 55.5 ppm, confirming the presence of carbonyl carbon and methoxy carbon, respectively. Furthermore, the structure of compound **5a** was also confirmed by a molecular ion peak at *m*/*z* 573.21 $(M + H)^+$.

Furthermore, the formation of (*Z*)-4-([4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **6a-e** was

confirmed by various spectral techniques. The IR spectrum of compound **6a** showed absorption peaks at 1,707 and 1,666 cm^{-1} corresponding to two carbonyl groups present in the molecules. The ^{1}H NMR spectrum of compound **6a** showed four singlets at δ 2.54 and δ 3.01 ppm for two —CH_3, δ 8.50 ppm for chromone ring proton, and δ 10.54 ppm for olefinic proton. The ^{13}C NMR spectrum of compound **6a** showed that two signals appear at δ 175.4 and 164.2 ppm for the carbonyl carbon of chromone and pyrazolone ring, respectively. In addition, two signals for methyl carbon appear at δ 22.2 and 18.6 ppm. The structure of compound **6a** was also confirmed by mass spectra and by a molecular ion peak observed at m/z 537.11 $(M + H)^+$. Similarly, all the synthesized compounds were characterized by the spectral analysis. Structures of all the synthesized derivatives are shown in Figure S1 (Supporting Information).

2.2 | Biological activity

2.2.1 | Anti-inflammatory activity

The newly synthesized 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) (EC_{50} range = 0.6483 ± 0.221–0.8519 ± 0.281 μg/ml) exhibited moderate anti-inflammatory activity compared to the standard drug diclofenac sodium. Among all the synthesized compounds, except compounds **4c**, **5c**, **5e**, **6d**, and **6e**, all other compounds exhibited a minimum inhibitory concentration (MIC) of 200 μg/ml compared to the standard drug diclofenac sodium (Table 2).

The percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 2. Furthermore, the comparative percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 3.

TABLE 2 Anti-inflammatory and antioxidant activity of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (MIC in μg/ml)

Compound	Anti-inflammatory	Antioxidant
4a	200	>100
4b	200	>400
4c	400	>200
4d	200	>200
5a	200	<100
5b	200	>200
5c	NT	NT
5d	200	<100
5e	800	<100
5f	200	<100
6a	200	<100
6b	200	<100
6c	200	>200
6d	800	>100
6e	400	<100
Diclofenac sodium	50	-
Ascorbic acid	-	<50

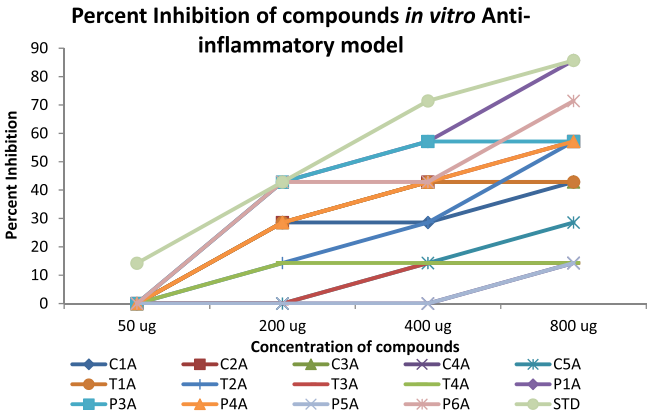


FIGURE 2 The percent inhibition of compounds in an in vitro anti-inflammatory model

2.2.2 | Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed in vitro by the DPPH radical scavenging assay.[28] Ascorbic acid (AA) has been used as a standard drug for the comparison of antioxidant activity, and the observed results are summarized in Table 2.

According to the DPPH assay, compounds **5a**, **5d**, **5e**, **5f**, **6a**, **6b**, and **6e** (IC_{50} = <100 μg/ml) exhibited excellent antioxidant activity compared to the standard antioxidant drug AA (IC_{50} = <50 μg/ml). The remaining synthesized compounds display comparable antioxidant activity than the standard drug butylated hydroxytoluene (Table 2). The percent inhibition of compounds in the in vitro antioxidant model is shown in Figure 4.

2.3 | Computational study

2.3.1 | In silico ADME

An important task for the lead compounds is early prediction of drug likeness properties as it resolves the cost

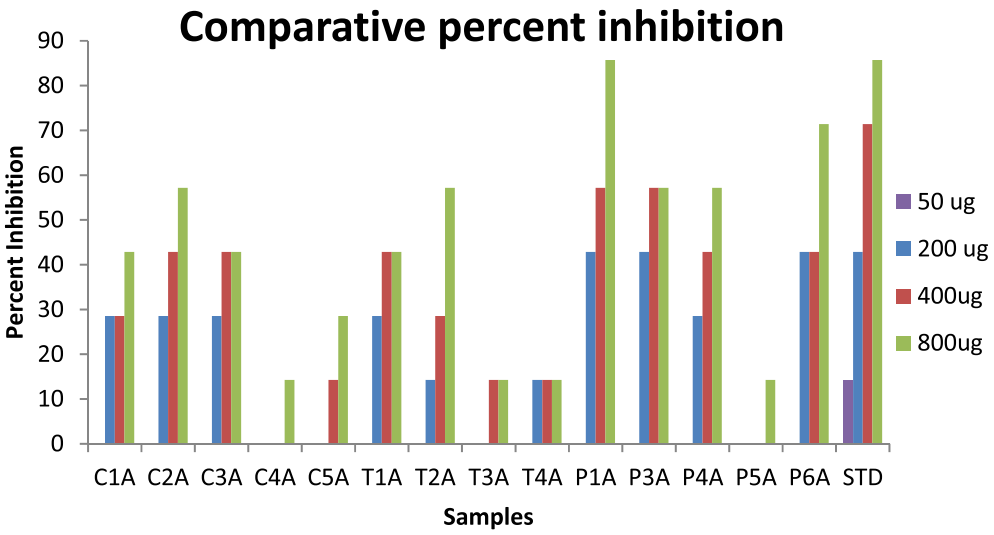


FIGURE 3 The comparative percent inhibition of compounds in an in vitro anti-inflammatory model

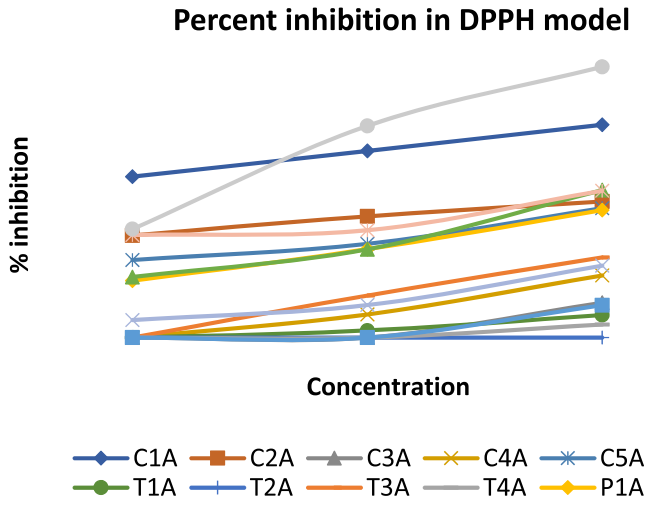


FIGURE 4 The percent inhibition of compounds in an in vitro antioxidant model

and time issues of drug development and discovery. Due to the inadequate drug likeness properties of many active agents with a significant biological activity, these compounds have failed in clinical trials.[29] On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using the Molinspiration online property calculation toolkit,[30] and data are summarized in Table 3.

All the compounds exhibited noteworthy values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants, which characterized these agents to be likely orally active. For the synthesized compound **6e**, the data obtained were within the range of accepted values. Parameters such as the number of rotatable bonds and total polar surface area are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which are reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules.

3 | EXPERIMENTAL SECTION

All organic solvents were acquired from Poona Chemical Laboratory, Pune and Research-Lab Fine Chem Industries, Mumbai and were used as such without further purification. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in *Raga's* synthetic microwave oven. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) fourier transform infrared spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Advance neo 500 spectrophotometers using tetramethylsilane as an internal standard, and $CDCl_3$ and dimethyl sulphoxide-d_6 as solvent and chemical shifts, respectively, were expressed as δ ppm units. Mass spectra were obtained on Waters quadrupole time-of-flight micromass (ESI-MS) mass spectrometer.

3.1 | General procedure for the synthesis of synthesize new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (4a-d, 5a-f and 6a-e)

Conventional method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-

TABLE 3 Pharmacokinetic parameters of (**4a-d**, **5a-f**, and **6a-e**) compounds

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	-
4a	90.81	52.72	5	397.75	554.42	5.83	5	0	2	−0.68
4b	90.81	52.72	5	420.56	651.31	6.92	5	0	2	−0.84
4c	90.81	52.72	5	411.28	588.87	6.63	5	0	2	−0.25
4d	90.81	52.72	5	415.63	633.32	6.76	5	0	2	−0.56
5a	87.62	61.96	6	432.58	578.42	6.10	6	0	2	−0.46
5b	90.81	52.72	5	407.04	548.39	6.04	5	0	2	−0.80
5c	87.62	61.96	6	437.51	596.41	6.19	6	0	2	−0.22
5d	90.81	52.72	5	423.60	562.42	6.49	5	0	2	−0.51
5e	87.62	61.96	7	447.32	632.39	7.01	6	0	2	−0.45
5f	90.81	52.72	5	434.11	617.28	7.33	5	0	2	−0.36
6a	86.53	65.11	3	374.21	536.76	6.25	5	0	2	−0.53
6b	86.53	65.11	3	357.65	522.74	5.87	5	0	2	−0.36
6c	86.53	65.11	3	341.09	508.71	5.49	5	0	2	−0.32
6d	86.53	65.11	3	354.62	543.15	6.10	5	0	2	−0.93
6e	86.53	65.11	3	344.11	488.29	5.26	5	0	1	−0.81

Abbreviations: % ABS, percentage absorption; TPSA, topological polar surface area; n-ROTB, number of rotatable bonds; MV, molecular volume; MW, molecular weight; milogP, logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors, number of hydrogen bond acceptors; n-OHNH donors, number of hydrogen bonds donors.

one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask using glacial acetic acid (5 ml) as a solvent and were refluxed for the period of time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Ultrasound method: A mixture of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) in acetic acid (5 ml) was taken in a 50-ml round-bottom flask. The mixture was irradiated in the water bath of an ultrasonic cleaner at 35–40°C for a period of time indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water, and the obtained solid was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Microwave irradiation method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask (RBF) using glacial acetic acid (5 ml) as a solvent, and the contents of RBF were subjected to MW irradiation for the period of time indicated in Table 1 at 350 W. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

3.1.1 | (4*E*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) methylene)-1*H*-pyrazol-5(4*H*)-one (4a)

Orange solid; Wt. 930 mg, Yield 84%; IR(ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,598 (C=N), 1,519 (C=C), 1,234 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.35–7.91 (m, 8H, Ar—H), 8.11 (s, 1H, pyrazolyl-H), 10.10 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 161.4 (C=O), 151.7, 140.1, 137.8, 134.9, 131.1, 130.0, 129.6, 129.1,

128.70, 128.6, 119.7, 115.7, 113.5; MS (ESI-MS): *m/z* 555.01 $(M + H)^+$.

3.1.2 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4b)

Orange solid; Wt. 1.05 g; Yield 81%; IR (ν_{max}/cm^{-1}): 2,927 (=C—H), 1,680 (C=O), 1,598 (C=N), 1,516 (C=C), 1,231 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, J = 3.50 Hz, Ar—H), 7.26–7.19 (m, 3H, Ar—H), 7.84 (dd, 2H, *J* = 5.00 Hz and 9.00 Hz, Ar—H), 8.10 (s, 1H, pyrazole-H), 10.11 (s, 1H, =C—H); MS: *m/z* 651.03 $(M + H)^+$.

3.1.3 | (4*E*)-4-((3-[5-Chlorothiophen-2-yl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4c)

Orange solid; Wt. 873 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,682 (C=O), 1,597 (C=N), 1,518 (C=C), 1,232 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 1H, Ar—H), 7.26–7.18 (s, 1H, Ar—H), 7.44 (d, 1H, *J* = 6.00 Hz, Ar—H), 7.52 (m, 2H, Ar—H), 7.86 (d, 2H, *J* = 7.00 Hz, Ar—H), 8.11 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 151.3, 139.5, 138.3, 135.0, 133.5, 130.8, 130.0, 128.8, 127.6, 127.4, 120.0, 116.3, 114.6; MS: *m/z* 547.11 $(M + H)^+$.

3.1.4 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4d)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,597 (C=N), 1,520 (C=C), 1,235 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, *J* = 4.00 Hz, Ar—H), 7.21 (d, 1H, *J* = 3.50 Hz, Ar—H), 7.44 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.75–7.86 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.47 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 183.2 (C=O), 162.3, 151.2, 143.2, 142.9, 139.4, 138.3, 134.9, 133.7, 133.4, 131.2, 130.6, 129.8, 129.1, 128.8, 128.5, 128.2, 120.6, 119.9, 119.6, 116.2, 115.9, 114.6; MS: *m/z* 633.05 (M + H).

3.1.5 | (4*Z*)-3-(Trifluoromethyl)-4-((3-[4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5a)

Orange solid; Wt. 971 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,141 (=C—H), 1,703 (C=O), 1,595 (C=N), 1,514 (C=C), 1,224 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.92 (s, 3H, —OCH_3), 7.10 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.51 (t, 2H, *J* = 8.50 Hz, Ar—H), 7.62 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.90 (d, 2H, *J* = 9.00 Hz, Ar—H), 7.99 (s, 1H, pyrazole-H), 10.19 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 161.1, 158.7, 143.3, 141.4, 138.6, 134.9, 130.7, 129.7, 128.5, 122.6, 120.1, 116.8, 114.7, 113.7, 55.5 (OCH_3); MS: *m/z* 579.21 $(M + H)^+$.

3.1.6 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1H-pyrazol-5(4*H*)-one (5b)

Orange solid; Wt. 876 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,142 (=C—H), 1,701 (C=O), 1,595 (C=N), 1,510 (C=C), 1,223 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42 (m, 1H, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.57–7.58 (m, 3H, Ar—H), 7.68 (dd, 2H, *J* = 7.50 and 2.00 Hz, Ar—H), 7.90 (d, 2H, *J* = 8.00 Hz, Ar—H), 8.00 (s, 1H, pyrazole-H), 10.22 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 158.8, 143.0, 141.2, 138.6, 134.9, 130.3, 129.9, 129.7, 129.4, 129.2, 128.6, 120.0, 116.8, 114.0; MS: *m/z* 549.19 $(M + H)^+$.

3.1.7 | (4*Z*)-4-((3-[2-Fluoro-4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5c)

Orange solid; Wt. 1.06 g; Yield 82%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,702 (C=O), 1,596(C=N), 1,512 (C=C), 1,221 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.91 (s, 3H, —OCH_3), 6.82 (dd, 1H, *J* = 2.50 and 12.00 Hz, Ar—H), 6.91 (dd, 1H, *J* = 2.00 and 8.50 Hz, Ar—H), 7.42 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.58–7.49 (m, 2H, Ar—H), 7.79 (d, 1H, *J* = 2.50 Hz, Ar—H), 7.88 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.52 (s, 1H, pyrazole-H), 10.20 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.7 (C=O), 162.6, 162.5, 154.1, 141.2, 138.6, 134.7, 132.5, 129.7, 128.5, 120.0, 117.6, 113.9, 111.2, 110.3, 102.2, 102.0, 55.8 (OCH_3); MS: *m/z* 653.26 $(M + H)^+$.

3.1.8 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-one (5d)

Orange solid; Wt. 887 mg; Yield 79%; IR (ν_{max}/cm^{-1}): 3,143 (=C—H), 1,701 (C=O), 1,594 (C=N), 1,511 (C=C), 1,220 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.44 (s, 3H, —CH_3), 7.45 (d, 1H, J = 7.50 Hz, Ar—H), 7.51 (t, 1H, J = 7.50 Hz, Ar—H), 7.62 (d, 1H, J = 8.00 Hz, Ar—H), 7.65 (d, 1H, J = 8.00 Hz, Ar—H), 9.90 (s, 1H, pyrazole-H), 11.96 (s, 1H, =C—H); MS: m/z 563.08 $(M + H)^+$.

3.1.9 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(4-[trifluoro methoxy]phenyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (5e)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,700 (C=O), 1,595 (C=N), 1,517 (C=C), 1,225 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42–7.44 (m, 3H, Ar—H), 7.51–7.54 (m, 2H, Ar—H), 7.71 (d, 1H, J = 2.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.00 Hz, Ar—H), 7.88 (d, 1H, J = 2.00 Hz, Ar—H), 7.90 (d, 1H, J = 3.50 Hz, Ar—H), 7.92 (s, 1H, pyrazole-H), 10.21 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 157.3, 150.5, 143.2, 142.9, 140.3, 138.5, 134.9, 130.9, 129.8, 129.0, 128.7, 121.5, 120.6, 120.0, 118.4, 116.6, 114.4; MS: m/z 633.23 $(M + H)^+$.

3.1.10 | (4*Z*)-4-((3-[3,4-Dichlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5f)

Orange solid; Wt. 1.03 g; Yield 84%; IR (ν_{max}/cm^{-1}): 3,144 (=C—H), 1,701 (C=O), 1,596 (C=N), 1,517 (C=C), 1,227 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.44 (m, 1H, Ar—H), 7.48 (d, 1H, J = 2.00 Hz, Ar—H), 7.50 (d, 1H, J = 2.00 Hz, Ar—H), 7.53 (d, 1H, J = 7.50 Hz, Ar—H), 7.67 (d, 1H, J = 8.50 Hz, Ar—H), 7.83 (d, 1H, J = 2.00 Hz, Ar—H), 7.87–7.89 (m, 2H, Ar—H), 7.89 (s, 1H, pyrazole-H), 10.18 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.3 (C=O), 156.1, 143.2, 142.9, 139.7, 138.4, 135.0, 134.5, 133.7, 131.2, 131.1, 130.3, 129.8, 128.8, 128.3, 120.0, 116.4, 114.7; MS: m/z 617.15 $(M + H)^+$.

3.1.11 | (*Z*)-4-([6-Chloro-5,7-dimethyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6a)

Orange solid; Wt. 900 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,666 (C=O), 1,624 (C=N), 1,508 (C=C), 1,192 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 3.01 (s, 3H, —CH_3), 7.26 (s, 1H, Ar—H), 8.50 (s, 1H, chromone-H), 10.54 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 175.4 (C=O), 164.2 (C=O), 162.3, 155.1, 144.5, 143.4, 143.3, 139.7, 134.7, 120.9, 120.2, 119.4, 118.3, 118.2, 118.1, 22.2 (—CH_3), 18.6 (—CH_3); MS: m/z 537.11 $(M + H)^+$.

3.1.12 | (*Z*)-4-([6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6b)

Orange solid; Wt. 783 mg; Yield 75%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,705 (C=O), 1,664 (C=O), 1,627 (C=N), 1,508 (C=C), 1,192 (C—F);^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 7.47 (s, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 8.48 (s, 1H, chromone-H), 10.62 (s, 1H, =C—H); MS: m/z 523.08 $(M + H)^+$.

3.1.13 | (*Z*)-4-([6-Chloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6c)

Orange solid; Wt. 812 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,662 (C=O), 1,621 (C=N), 1,509 (C=C), 1,193 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.55 (d, 1H, J = 9.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.50 and 9.00 Hz, Ar—H), 8.26 (d, 1H, J = 2.50 Hz, Ar—H), 8.47 (s, 1H, chromone-H), 10.63 (s, 1H, =C—H); MS: m/z 509.08 $(M + H)^+$.

3.1.14 | (*Z*)-4-([6,8-Dichloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6d)

Orange solid; Wt. 845 mg; Yield 78%; IR (ν_{max}/cm^{-1}): 3,078 (=C—H), 1,707 (C=O), 1,665 (C=O), 1,626 (C=N), 1,506 (C=C), 1,194 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.83 (d, 1H, J = 2.50 Hz, Ar—H), 8.17 (d, 1H, J = 2.50 Hz, Ar—H), 8.40 (s, 1H, chromone-H), 10.66 (s, 1H, =C—H); MS: m/z 543.07 $(M + H)^+$.

3.1.15 | (*Z*)-4-([7-Methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6e)

Orange solid; Wt. 800 mg; Yield 82%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,703 (C=O), 1,666 (C=O), 1,627 (C=N), 1,510 (C=C), 1,193 (C—F);^{1}H NMR spectrum, δ, ppm: 2.51 (s, 3H, —CH_3), 7.48 (d, 1H, J = 8.00 Hz, Ar—H), 7.60 (dd, 1H, J = 8.00 and 2.00 Hz, Ar—H), 8.08 (d,1H, J = 1.50 Hz), 8.54 (s, 1H, chromone-H), 10.64 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 174.5 (C=O), 165.5 (C=O), 162.4, 154.2, 143.4, 142.4, 137.5, 136.3, 126.2, 120.9, 123.3, 120.2, 118.6, 118.5, 118.2, 118.1, 21.1 (—CH_3); MS: m/z 489.14 $(M + H)^+$.

3.2 | Anti-inflammatory activity

All the synthesized compounds were screened for their in vitro anti-inflammatory activities against the standard drug diclofenac sodium. The minimum inhibitory concentration was determined by the well diffusion method at 1 mg/ml of concentration. (Table 2). A volume of 1 ml of diclofenac sodium at different concentrations (50, 100, 200, 400, 800, and 1,000 μg/ml) was homogenized with 1 ml of aqueous solution of bovine serum albumin (5%) and incubated at 27°C for 15 minutes. The mixture of distilled water and bismuth sulphite agar constituted the control tube. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 minutes at 70°C. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 255 nm. Each test was conducted thrice. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = \text{absorbance of control} - \text{absorbance of sample} / \text{absorbance of control} \times 100.$$

3.3 | In silico ADME

In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[31] using the Molinspiration online property calculation toolkit.[30] Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA).[32] Drug likeness model score (a collective property of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound that is represented by a numerical value) was computed by MolSoft software.[33]

4 | CONCLUSIONS

In conclusion, we have constructed pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional and nonconventional methods like microwave irradiation and ultrasonication, respectively, via Knoevenagel condensation and evaluated their biological activity. Ultrasonication and microwave irradiation can shorten the reaction time from a few hours to a few minutes and increases the product yield (74–84%) compared to the conventional method (59–75%). The synthesized compounds exhibited promising anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, the synthesized compound displayed promising antioxidant activity compared to the standard drug. Furthermore, an analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as an oral drug candidate, thus suggesting that compounds from the present series can be further optimized and developed as a lead molecule.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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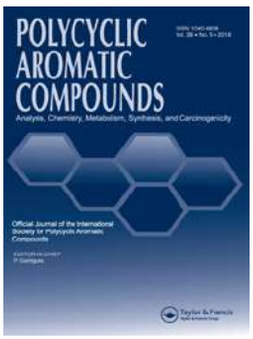

Polycyclic Aromatic Compounds

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Design, Synthesis and Biological Evaluation of Novel Furan & Thiophene Containing Pyrazolyl Pyrazolines as Antimalarial Agents

Hemantkumar N. Akolkar[a], Sujata G. Dengale[b], Keshav K. Deshmukh[b], Bhausaheb K. Karale[a], Nirmala R. Darekar[a], Vijay M. Khedkar[c], and Mubarak H. Shaikh[a]

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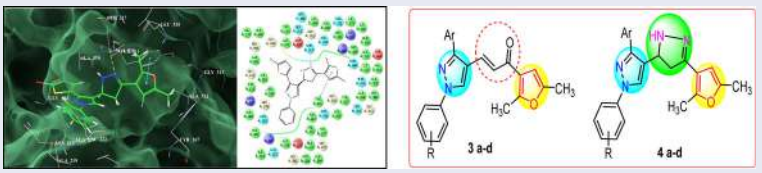
ABSTRACT

In search for novel compounds targeting Malaria, based on the *in silico* molecular docking binding affinity data, the novel furans containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized. The formation of the synthesized compound were confirmed by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Compounds with thiophene and pyrazoline ring **4b** (0.47 μM), **4c** (0.47 μM) and **4d** (0.21 μM) exhibited excellent anti-malarial activity against *Plasmodium falciparum* compared with standard antimalarial drug Quinine (0.83 μM). To check the selectivity furthermore, compounds were tested for antimicrobial activity and none of the synthesized compound exhibited significant potency compared with the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin respectively. So, it can be resolved that the produced compounds show selectively toward antimalarial activity and have the potential to be explored further.



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Introduction

Life-threatening disease Malaria is caused by *Plasmodium* parasites that are spread to people through the bites of infected female Anopheles mosquitoes. Out of five *Plasmodium* Parasites *Plasmodium falciparum* produces high levels of blood-stage parasites that sequester in critical organs in all age groups.[1] As per the World Health Organization report in 2018, in sub Saharan Africa 11 million pregnant women were infected with malaria and 872 000 children were born with a low birth weight. Around 24 million children estimated to be infected with the *P. falciparum* parasite in the region; out of these, 1.8 million had severe anemia and 12 million had

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moderate anemia.[2] Mortality and morbidity caused by malaria are continually increasing. This subject is the consequence of the ever-increasing development of parasite resistance to drugs and also increased mosquito resistance to insecticides which is one of the most critical complications in controlling malaria over recent years.[3]

P. falciparum enoyl-acyl carrier protein (ACP) reductase (ENR) is an enzyme in type II fatty acid synthesis (FAS II) pathway which catalyzes the NADH-dependent reduction of trans-2-enoyl-ACP to acyl-ACP and plays important role in completion of the fatty acid elongation cycles. Due to its role in the parasite's fatty acid pathway, *Pf*ENR has been known as one of the most promising antimalarial targets for structure-based drug design.[4–6] Triclosan, a broadly used antibiotic, is effective inhibitor of *Pf*ENR enzyme activity. Several efforts have been taken in the recent past in the direction of the identification of new antimalarials using pharmacophore modeling, molecular docking and MD simulations.[7–12]

Pyrazole is a well-known class of nitrogen containing heterocyclic compounds and play important role in agricultural and medicinal field. Pyrazole and its derivatives are known to possess antibacterial,[13] antipyretic,[14] fungistatic,[15] anticonvulsant,[16] antitubercular,[17] antipyretic,[18] insecticides,[19] and anti-inflammatory[20] activities. Pyrazoline containing compounds are recognized to possess various pharmacological activities like antimalarial,[21,22] anticancer,[23] anti-inflammatory,[24] analgesic,[24] antitumor,[25] antimicrobial[26] and antidepressant activities.[27] Furan containing compounds possess lipoxygenase inhibitor,[28] urotensin-II receptor antagonists,[29] fungicidal,[30] epidermal growth factor receptor inhibitors and anticancer[31] etc. activities. Chalcone is a natural pigment found in plant and is an important intermediate for the synthesis of flavonoids. Varieties of biological activities are associated with chalcones and their derivatives such as antiplasmodial,[32] nematicide,[33] antiallergenic,[34] antimalarial,[35] anti-HIV,[36] anti-cancer,[37] anti-inflammatory[38] and anti-tuberculosis.[39]

So, considering the biological importance of pyrazoles, furan and chalcone, herein we report the design of a small library of furan containing pyrazolyl pyrazoline derivatives by molecular hybridization approach targeting *Pf*ENR using the *in silico* molecular docking technique. The promising results obtained from this *in silico* study served the basis for the synthesis of these molecules followed by evaluation of their antimalarial potential.

Molecular docking technique plays significant role in lead identification/optimization and in the mechanistic study by predicting the binding affinity and the thermodynamic interactions leading the binding of a ligand to its biological receptor. Thus, with the objective to identify novel leads targeting the crucial antimalarial target *Plasmodium falciparum enoyl-ACP reductase* (*Pf*ENR or FabI) (pdb code: 1NHG), molecular docking was carried out using the GLIDE (Grid-based LIgand Docking with Energetics) program of the Schrodinger Molecular modeling package.[40–42] A small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-3d**, **4a-4d**) was docked against *Pf*ENR. The ensuing docking conformation revealed that these molecules changed a binding mode which is corresponding with the active site of pfENR and were found to be involved in a series of bonded and non-bonded interactions with the residues lining the active site. Their docking scores varied from −6.979 to −8.222 with an average docking score of −7.563 signifying a potent binding affinity to *Pf*ENR. In order to get a quantitative insight into the most significantly interacting residues and their associated thermodynamic interactions, a detailed per-residue interaction analysis was carried out (Table S1, Supporting Information). This analysis showed that the furan containing pyrazolyl chalcones (**3a-d**) (Figure 1) were deeply embedded into the active site of *Pf*ENR engaging in a sequence of favorable *van der Waals* interactions observed with Ile:C369, Phe:C368, IleA323, Ala:A320, Ala:A319, Arg:A318, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Met:A281, Tyr:A277, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110 and Asp:A107 residues through the 1,3-substituted-1*H*-pyrazol-4-yl scaffold while the 1-(2,5-Dimethylfuran-3-yl) prop-2-en-1-one

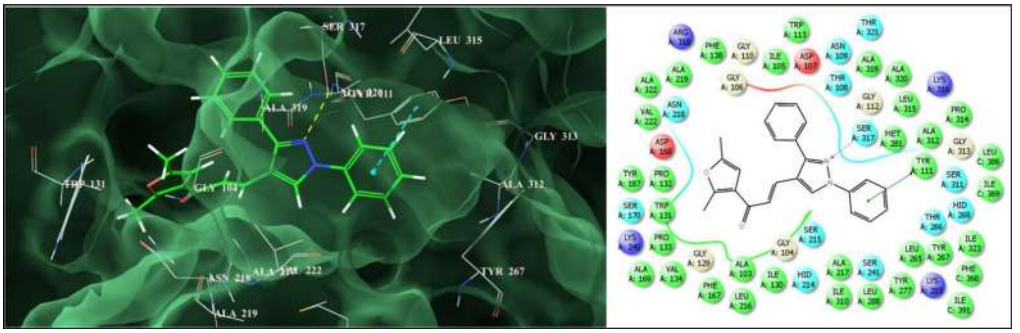


Figure 1. Binding mode of **3a** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

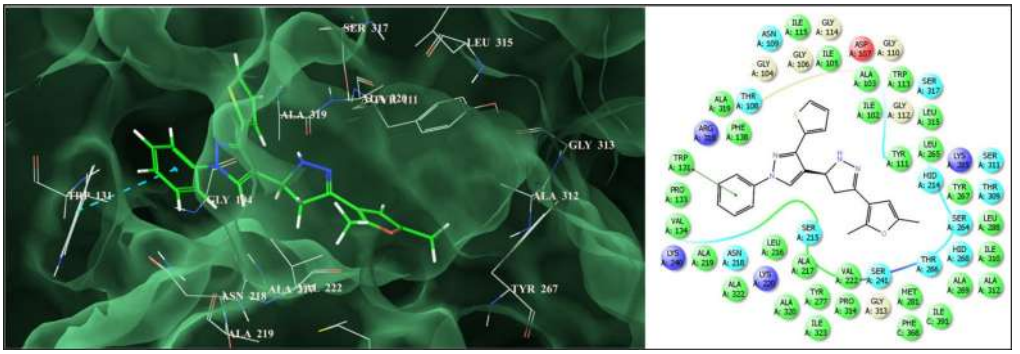
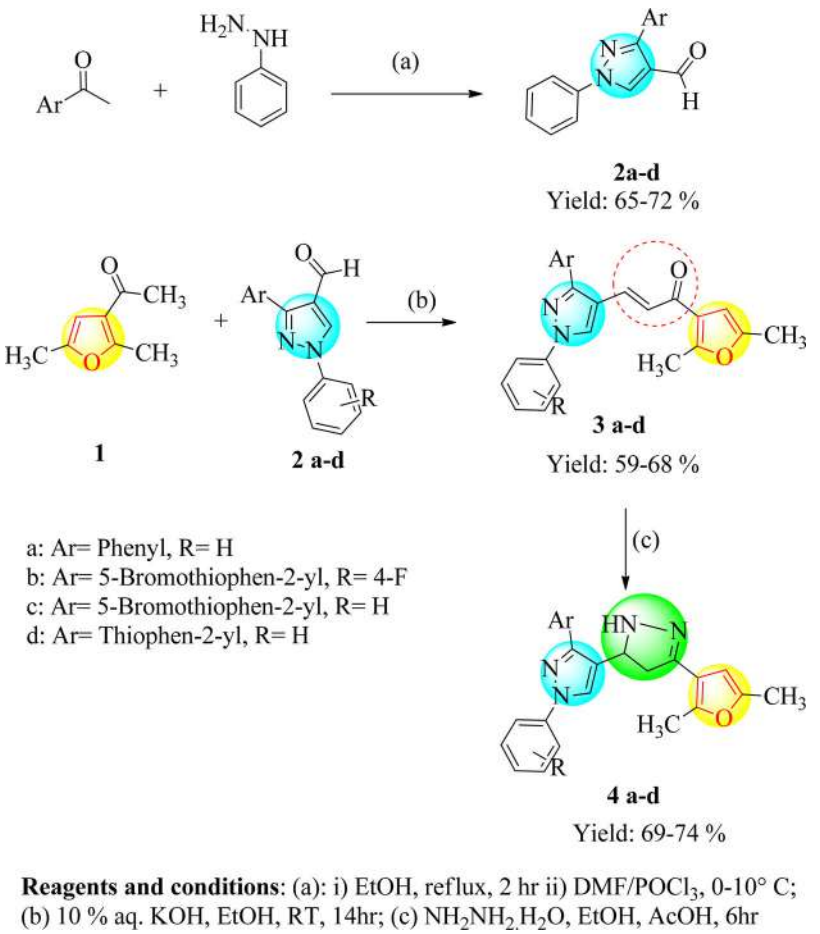


Figure 2. Binding mode of **4d** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

component of the molecules was seen to be involved in similar interactions with Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Gly:A106, Ile:A105, Gly:A104 residues of the active site.

Furthermore the enhanced binding affinity of these molecule is also attributed to significant electrostatic interactions observed with Arg:A318, Ser:A317, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107, Gly:A104 residues lining the active site. On the other hand, the furan containing pyrazoline derivatives (**4a-d**) (Figure 2) were also seen to be stabilized into the active of *Pf*ENR through a network of significant *van der Waals* interactions observed with (2,5-dimethylfuran-3-yl)-1*H*-pyrazolyl scaffold *via* Ile:C369, Phe:C368, Ala:A320, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110, Gly:A106 and Ile:A105 while other half of the molecule i.e., 2-thiophenyl-1-phenyl-1*H*-pyrazole showed similar type of interactions with IleA323, Ala:A319, Arg:A318, Met:A281, Tyr:A277, Val:A222, Ala:A219, Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Ile:A130, Trp:A113, Asp:A107, Gly:A104 residues.

Further the enhanced binding affinity of the molecules is also attributed to favorable electrostatic interactions observed with Arg:A318, Ser:A317, Glu:A289, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107 and Gly:A104. While these non-bonded interactions (*van der Waals* and electrostatic) were observed to be the major driving force for the mechanical interlocking of these novel furan containing pyrazolyl pyrazoline derivatives into the active site *Pf*ENR, the enhanced binding affinity of these molecules is also contributed by very prominent hydrogen bonding interaction observed for **3a** (Ser:A317(2.708 Å)), **4a** (Ser:A317(2.783 Å)), **4b** (Ser:A317(2.462 Å)) and **4c** (SerA317(2.462 Å)). Furthermore these



Scheme 1. Synthesis of pyrazolyl chalcones (**3a-d**) and pyrazolyl pyrazolines (**4a-d**).

molecules were also engaged in a very close π-π stacking interactions: **3a**: Tyr: A111(2.669 Å), **3b**: Tyr:A267(2.529 Å), **3c**: Tyr:A267(2.541 Å), **3d**: Tyr:A267(2.335 Å), **4a**: Tyr:A111(2.602 Å), **4b**: Trp:A131(2.073 Å), **4c**: TyrA:111(2.073 Å) and **4d**: TrpA131(2.538 Å) (Figures S1–S6, Supporting Information).

This type of bonded interactions i.e., hydrogen bonding and π-π stacking are known to serve as an "anchor" to guide the alignment of a molecule into the 3D space of enzyme's active site and facilitate the non-bonded interactions (*Van der Waals* and electrostatic) as well. Overall, the in-silico binding affinity data suggested that these furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) could be developed as novel scaffold to arrive at compounds with high selectivity and potency *Plasmodium falciparum*.

Results and discussion

Chemistry

The novel series of furan containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized from commercially available starting materials (Scheme 1). Initially, pyrazole aldehyde **2a-d** was formed by the condensation between substituted acetophenone and phenyl

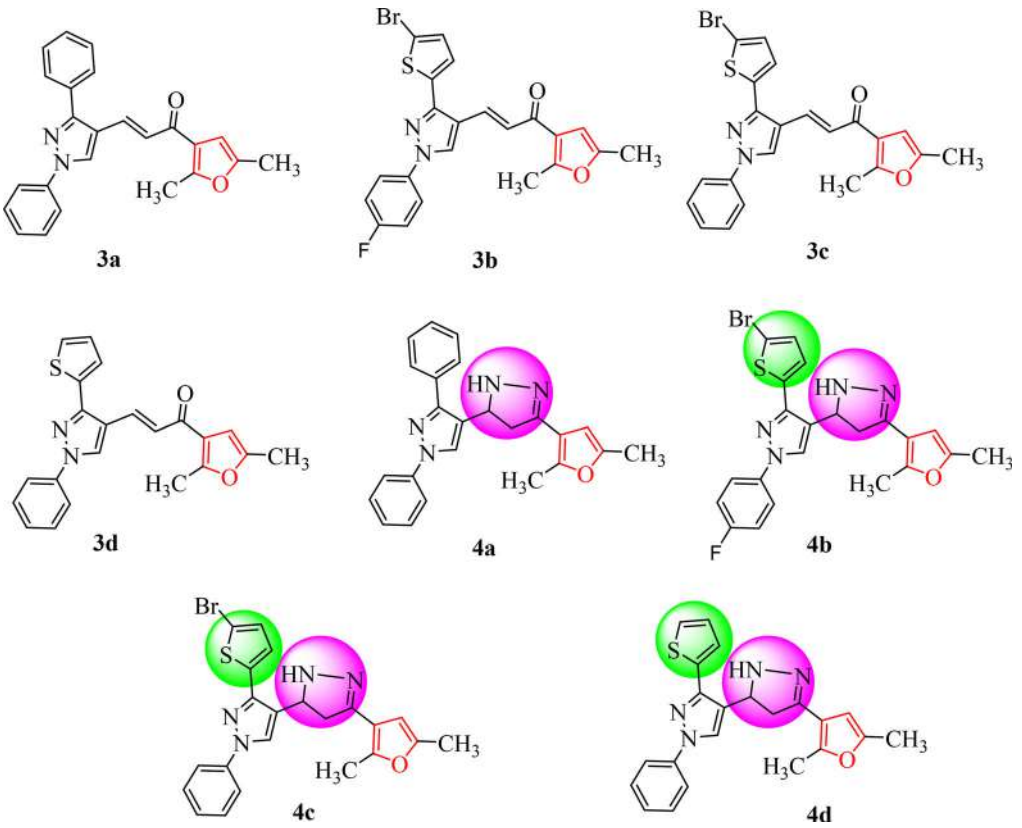


Figure 3. The newly synthesized compounds structure **3a-d** & **4a-d**.

hydrazine followed by Vilsmeier-Haack formylation reaction (Scheme 1). Then furan containing pyrazolyl chalcones **3a-d** were synthesized by base-catalyzed Claisen-Schmidt condensation of 1-(2,5-dimethylfuran-3-yl)ethanone **1** and substituted pyrazole aldehyde **2a-d**.[43] Finally, the furan containing pyrazolyl chalcones **3a-d** and hydrazine hydrate in ethanol solvent using catalytic amount of acetic acid at reflux condition for 6 hr afforded the corresponding pyrazolyl pyrazolines (**4a-d**) in quantitative isolated yield (69–74%) (Scheme 1).

The newly synthesized compounds structures were shown in Figure 3. The newly synthesized compound's structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data. For compound **3a**, in IR spectrum the stretching band for C = O was detected at 1657 cm^{-1}. In the ^{1}H NMR spectrum of compound **3a**, the proton of pyrazole and furan ring resonate as a singlet at δ 9.31 and δ 6.60 ppm respectively. Also, singlet for two $-CH_3$ were observed at δ 2.27 and δ 2.50 ppm. The ^{13}C NMR spectrum of compound **3a** showed signal at δ 184.41 ppm due to C = O and δ 12.89 and δ 13.93 ppm is due to two $-CH_3$. Mass spectrum confirms the formation of compound **3a** showed m/z = 369 $(M+H)^{+}$.

Secondly, in the IR spectrum of compound **4a**, –N–H stretching band observed at 3252 cm^{-1}. The 1H NMR spectrum of compound **4a**, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 2.88 ppm and 3.35 ppm. The CH proton appeared as triplet at δ 4.87 ppm due to vicinal coupling with two protons of the methylene group. In the ^{13}C NMR spectra of the compound **4a** carbons of the pyrazoline ring were observed at δ 41.97 ppm and 54.67 ppm. All the other aromatic and aliphatic protons and carbons were observed at expected regions. Mass spectrum confirms the formation of compound **4a** showed m/z = 383 $(M+H)^{+}$.

Table 1. Antimalarial (μM), Antibacterial (MIC in μg/mL) & Antifungal (MIC in μg/mL) activity.

Cpd	Antimalarial activity Plasmodium falciparum	Antibacterial activity				Antifungal activity			Molecular Docking Score
		EC	PA	SA	SP	CA	AN	AC	
3a	1.46	200	200	250	250	500	500	500	−7.814
3b	3.93	100	250	250	200	1000	500	500	−7.032
3c	2.16	62.5	200	125	250	500	>1000	>1000	−7.192
3d	3.07	100	100	200	200	1000	500	500	−7.118
4a	6.31	125	100	100	100	500	500	500	−6.979
4b	0.47	100	200	100	100	250	500	500	−8.157
4c	0.47	125	125	200	200	1000	>1000	>1000	−8.222
4d	0.21	200	100	125	100	500	500	500	−7.988
Chloroquine	0.06	–	–	–	–	–	–	–	–
Quinine	0.83	–	–	–	–	–	–	–	–
CP	–	50	50	50	50	–	–	–	–
NS	–	–	–	–	–	100	100	100	–

Cpd: Compound; EC: Escherichia coli; PA: Pseudomonas aeruginosa; SA: Staphylococcus aureus; SP: Streptococcus pyogenes; CA: Candida albicans; AN: Aspergillus niger; AC: Aspergillus clavatus; CP: Chloramphenicol; NS: Nystatin.

Biological evaluation

In vitro antimalarial screening

All the synthesized novel compounds were tested for antimalarial activities. The *in vitro* antimalarial assay was carried out according to the micro assay protocol of Rieckmann and coworkers with minor modifications.[44–47] The results were recorded as the minimum inhibitory concentrations (μM MIC) chloroquine and quinine were used as the reference drug (Table 1).

Herein, we have synthesized four chalcone and pyrazoline derivatives respectively. Structure activity relationship (SAR) plays very important role while displaying the antimalarial activity. All the synthesized chalcone derivatives (**3a-d**) exhibited less potency compared to the standard drug. But pyrazoline derivatives exhibited excellent antimalarial activity compared to the standard drug. In compound **4a**, thiophene ring was absent and pyrazoline ring is present, so, the compound **4a** exhibited less potency compared to the standard drug. Now, in compound **4b**, bromo substituted thiophene and pyrazoline rings are present along with the fluorine at the para position on benzene ring. Interestingly, this compound **4b** (0.47 μM), exhibited excellent activity compared to the standard drug quinine (0.83 μM). Again, in compound **4c**, bromo substituted thiophene and pyrazoline rings are present but no fluorine at the para position of benzene ring. Though fluorine is absent on benzene ring in compound **4c** (0.47 μM), it exhibited same potency as that of compound **4b** compared to the standard drug quinine (0.83 μM). Finally, in compound **4d**, there were no substitution on the thiophene and benzene ring. In compound **4d** plane thiophene, plane benzene ring and pyrazoline ring constructed in a single molecular framework. Compound **4d** (0.21 μM), exhibited four-fold more antimalarial activity compared to the standard drug quinine (0.83 μM). From SAR, we can conclude that for the antimalarial activity thiophene, pyrazoline and benzene ring were very important in a single molecular framework.

Antimicrobial activities

Further, all the novel synthesized compounds were also screened for antimicrobial activities against the bacterial strains *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 1688), *Streptococcus pyogenes* (MTCC 442) and fungal strains *Aspergillus clavatus* (MTCC 1323), *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282). The minimum inhibitory concentration (MIC) was determined by the broth dilution method. Chloramphenicol and Nystatin were used as reference drugs for antibacterial and antifungal activity, respectively. The results of antibacterial and antifungal activity were given in Table 1.

The results given in Table 1 indicated that none of the synthesized compound exhibited significant potency toward the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin. Hence, from above result we can conclude that the synthesized compounds show selectively antimalarial activity and negligible antimicrobial activity.

Conclusion

In conclusion, Considering the importance of enoyl-ACP reductase (*Pf*ENR) in *Plasmodium*, a small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) was designed and docked against *Pf*ENR. Based on the *in silico* binding affinity data, synthesis was carried out for these novel furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) and was evaluated for activity against *Plasmodium falciparum*. The synthesized compounds shown selectively antimalarial activity with minimal antimicrobial activity. Compounds (**3a-d**) exhibited less antimalarial activity compared to the standard drug. From the series of compounds (**4a-d**), compound **4b** (0.47 µM), **4c** (0.47 µM) and **4d** (0.21 µM) exhibited more antimalarial activity compared to the standard drug quinine (0.83 µM). Compound 4d shows four-fold more activity compared to the standard drug quinine. From the SAR, we have distinguished areas of the pyrazolyl chalcones and pyrazolyl pyrazolines framework where variations can be made to expand the pharmacokinetic profile as well as features required to improve inhibitor effectiveness. This innovative molecular scaffold presents breakthrough for optimization to develop effective *Pf*ENR inhibitors.

Experimental

General

All the reagents, solvents and chemicals were taken from commercial sources found to be and used as such without purification. The physical constant like melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Advance II 400 spectrophotometer using TMS as an internal standard and DMSO-d6 as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Waters, Q-TOF micro mass (ESI-MS) mass spectrometer.

General procedure for the synthesis of pyrazolyl chalcones (3a-d)

A mixture of 1-(2,5-dimethylfuran-3-yl)ethanone 1 (0.05 mol), substituted pyrazole aldehyde **2** (0.05 mol) and 10% aqueous potassium hydroxide (10 mL) in ethanol (50 mL) was stirred at room temperature for 14 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice and neutralized by dil. HCl. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3a)

Yield: 61%, yellow solid; mp: 80–82 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1657 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.31 (s, 1H, Pyrazole-H), 7.93 (d, 2H, J = 7.9 Hz), 7.38–7.68 (m, 10H, Ar–H), 6.60 (s, 1H, Furan-H), 2.53 (s, 3H, –CH_3), 2.27 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4 (C = O), 159.9, 152.8, 149.7, 138.9, 132.2, 132.0, 129.6, 128.8, 128.5, 128.6, 128.4, 127.1, 123.8, 122.1, 118.6, 117.6, 105.9, 13.9 (CH_3), 12.9 (CH_3); MS(ESI-MS): m/z 369.11 (M + H).$^{+}$

(E)-3-(3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran -3-yl) prop-2-en-1-one (3b)

Yield: 59%, yellow solid, mp: 112–114 °C; IR (νmax, cm^{-1}): 2923 (=C–H), 2856 (C–H), 1656 (C = O), 1455 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.25 (s, 1H, Pyrazole-H), 7.90 (dd, 2H, J = 4.7 & 9.0 Hz, Ar–H), 7.64 (d, 1H, J = 15.4 Hz, olefinic-H), 7.39–7.45 (m, 3H, Ar–H), 7.34 (d, 1H, J = 3.8 Hz, Ar–H), 7.25 (d, 1H, J = 3.8 Hz, Ar–H), 6.61 (S, 1H, Furan-H), 2.55 (s, 3H, $-CH_3$), 2.28 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.2, 162.0, 159.6, 157.1, 149.7, 145.7, 135.4, 135.1, 131.4, 130.8, 128.9, 127.3, 124.6, 122.0, 120.7, 120.6, 117.3, 116.6, 116.3, 112.5, 105.9, 13.9, 12.9; MS (ESI-MS): m/z 472.89 $(M + H)^{+}$.

(E)-3-(3-(5-Bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran-3-yl)prop -2-en-1-one (3c)

Yield: 68%, yellow solid, mp120–114 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1699 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.14 (s,1H, Pyrazole-H), 7.87 (d, 2H, J = 7.8 Hz, Ar–H), 7.70 (d, 1H, J = 15 Hz, olefinic-H), 7.52 (t, 2H, J = 8 Hz, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.20 (s, 2H, Ar–H), 6.55 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.3, 157.1, 149.7, 145.7, 138.6, 135.5, 131.4, 130.9, 129.7, 128.8, 127.3, 127.3, 124.6, 122.0, 118.6, 117.4, 112.5, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 454.57 $(M + H)^{+}$.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)prop-2-en-1-one (3d)

Yield: 62%, yellow solid, mp 124–126 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2715 (C–H), 1652 (C = O),1456 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, Pyrazole-H), 7.91 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 1H, J = 15.4 Hz, olefinic-H), 7.60 (d, 1H, J = 5.1 Hz, Ar–H), 7.54 (t, 2H, J = 8.2 Hz, Ar–H), 7.35–7.44 (m, 3H, Ar–H), 7.21 (dd, 1H, J = 5.0 & 3.7 Hz, Ar–H), 6.59 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4, 157.0, 149.7, 146.8, 138.7, 133.5, 131.5, 129.7, 128.7, 128.1, 127.3, 127.2, 126.8, 124.3, 122.1, 118.6, 117.4, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 375.10 $(M + H)^{+}$.

General procedure for synthesis of pyrazolyl-pyrazoline (4a-d)

A mixture of chalcone **3a-d** (0.001 mol) and hydrazine hydrate (0.004 mol) in solvent ethanol (10 ml) was refluxed in presence of catalytic amount of glacial acetic acid for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol to get pure pyrazolines.

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (4a)

Yield: 74%, white solid, mp 102–104 °C; IR (νmax, cm^{-1}): 3306 (N–H), 3049 (Ar–H), 1592 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, pyrazole-H), 7.90 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 2H, J = 8.3 Hz, Ar–H), 7.47–7.52 (m, 4H, Ar–H), 7.41 (t, 1H, J = 7.3 Hz, Ar–H), 7.31 (t, 1H, J = 7.4 Hz, Ar–H), 7.20 (s, 1H, N–H), 6.19 (s, 1H, furan-H), 4.87 (t, 1H, J = 10.7 Hz, pyrazoline-H), 3.34 (dd, 1H, J = 10.5 & 15.6 Hz, pyrazoline-H), 2.88(dd, 1H, J = 11.1 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 150.4, 149.3, 147.6, 145.1, 139.5, 132.9, 129.5, 128.6, 127.9, 127.2, 126.2, 123.2, 118.1, 115.2, 105.9, 54.7, 41.9, 13.3, 12.9; MS (ESI-MS): m/z 383.04 $(M + H)^{+}$.

3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1H-pyrazole (4b)

Yield: 69%, white solid, mp 98–100 °C; IR (νmax, cm^{-1}):3310 (N–H), 3046 (Ar–H), 1594 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.54 (s, 1H, pyrazole-H), 7.88 (m, 2H, Ar–H), 7.35 (t, 2H, J = 8.7 Hz, Ar–H), 7.28 (dd, 2H, J = 3.8 Hz, Ar–H), 7.21 (s, 1H, N–H), 6.20 (s, 1H, furan-H), 4.93 (t, 1H, J = 10.68 Hz, pyrazoline-H), 3.37 (dd, 1H, J = 10.7 & 16.5 Hz, pyrazoline-H), 2.86 (dd, 1H, J = 10.9 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 161.6, 159.1, 149.3, 147.7, 145.3, 144.1, 136.9, 135.6, 131.2, 128.0, 126.6, 122.6, 120.2, 120.2, 116.4, 116.2, 115.1, 111.5, 105.9, 54.3, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 486.93 $(M + H).^{+}$

3-(5-Bromothiophen-2-yl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole (4c)

Yield: 72%, white solid, mp 122–124 °C; IR (ν max, cm^{-1}): 3303 (N–H), 3096 (Ar–H), 1593 (C = N), ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.55 (s, 1H, pyrazole-H), 7.84 (d, 2H, J = 7.9 Hz, Ar–H), 7.51 (t, 2H, J = 7.6 Hz, Ar–H), 7.22–7.34 (m, 4H, Ar–H), 6.20 (s, 1H, furan-H), 4.94 (t, 1H, J = 10.6 Hz, pyrazoline-H), 3.38 (m, 1H, pyrazoline-H), 2.88 (dd, 1H, J = 12.1 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.2, 144.0, 139.0, 137.0, 131.2, 129.6, 127.8, 126.6, 126.5, 122.5, 118.0, 115.1, 111.4, 105.9, 54.4, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 468.95 $(M + H).^{+}$

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (4d)

Yield: 70%, white solid, mp 96–98 °C; IR (ν max, cm^{-1}): 3336 (N–H), 3067 (Ar–H), 1501 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.53 (s, 1H, pyrazole-H), 7.86 (d, 1H, J = 8 Hz, Ar–H), 7.58 (d, 1H, J = 4.9 Hz, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.31 (t, 1H, J = 7.3 Hz, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 6.21 (s, 1H, furan-H), 4.98 (t, 1H, J = 10.5 Hz, pyrazoline-H), 3.42 (m, 1H, pyrazoline-H), 2.89 (dd, 1H, J = 10.7 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.1, 144.9, 139.2, 135.0, 129.6, 127.9, 127.4, 126.3, 126.0, 125.8, 122.6, 118.1, 115.1, 105.9, 54.5, 41.3, 13.3, 12.9; MS (ESI-MS): m/z 389.03 $(M + H).^{+}$

Experimental protocol for biological activity

Antimalarial assay

The antimalarial activity of the synthesized compounds was carried out in the Microcare laboratory & TRC, Surat, Gujarat. According to the micro assay protocol of Rieckmann and coworkers the *in vitro* antimalarial assay was carried out in 96 well microtiter plates. To maintain *P. falciparum* strain culture in medium Roswell Park Memorial Institute (RPMI) 1640 supplemented with 25 mM (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. To obtain only the ring stage parasitized cells, 5% D-sorbitol treatment required to synchronized the asynchronous parasites of *P. falciparum*. To determine the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+}) an initial ring stage parasitaemia of 0.8 to 1.5% at 3% hematocrit in a total volume of 200 µl of medium RPMI-1640 was carried out for the assay. A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. To the test wells to obtain final concentrations (at five-fold dilutions) ranging between 0.4 µg/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation the diluted samples in 20 µl volume were added. In a candle jar, the culture plates were incubated at 37 °C. Thin

blood smears from each well were prepared and stained with Jaswant Singh-Bhattacharji (JSB) stain after 36 to 40 h incubation. To record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents the slides were microscopically observed. The minimum inhibitory concentrations (MIC) was recorded as the test concentration which inhibited the complete maturation into schizonts. Chloroquine was used as the reference drug.

After incubation for 38 hours, and percent maturation inhibition with respect to control group, the mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells.

Molecular docking

The crystal structure of *Plasmodium Falciparum Enoyl-Acyl-Carrier-Protein Reductase* (*Pf*ENR or FabI) in complex with its inhibitor Triclosan was retrieved from the protein data bank (PDB) (pdb code: 1NHG) and refined using the protein preparation wizard. It involves eliminating all crystallographically observed water (as no conserved interaction is reported with co-crystallized water molecules), addition of missing side chain/hydrogen atoms. Considering the appropriate ionization states for the acidic as well as basic amino acid residues, the appropriate charge and protonation state were assigned to the protein structure corresponding to pH 7.0 followed by thorough minimization, using OPLS-2005 force-field, of the obtained structure to relieve the steric clashes due to addition of hydrogen atoms. The 3D structures of the furan containing pyrazolyl chalcones (**3a-d**) were sketched using the build panel in Maestro and were optimized using the Ligand Preparation module followed by energy minimization using OPLS-2005 force-field until their average root mean square deviation (RMSD) reached 0.001 Å. The active site of *Pf*ENR was defined using receptor grid generation panel to include residues within a 10 Å radius around the co-crystallized ligand. Using this setup, flexible docking was carried using the extra precision (XP) Glide scoring function to gauze the binding affinities of these molecules and to identify binding mode within the target. The obtained results as docking poses were visualized and analyzed quantitatively for the thermodynamic elements of interactions with the residues lining the active site of the enzyme using the Maestro's Pose Viewer utility.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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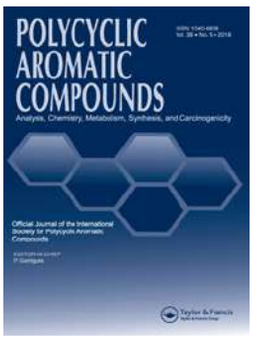

Polycyclic Aromatic Compounds

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Tetrazoloquinoline-1,2,3-Triazole Derivatives as Antimicrobial Agents: Synthesis, Biological Evaluation and Molecular Docking Study

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ABSTRACT

In search of new active molecules, a small focused library of tetrazoloquinoline-based 1,2,3-triazoles has been efficiently prepared *via* click chemistry approach. Several derivatives were found to be exhibiting promising antimicrobial and antioxidant activity characterized by their lower minimum inhibitory concentration values. All the synthesized compounds exhibited excellent antibacterial activity against Gram negative bacteria *E. coli* and *F. devorans* and antifungal activity against *C. albicans* and *A. niger*. Further, these compounds were tested for their antitubercular activity against dormant *MTB H37Ra* and dormant *M. bovis BCG* using XRMA assay protocol and showed no significant activity. Also, the synthesized compounds were found to have potential antioxidant activity with IC_{50} range = 12.48–50.20 μg/mL. Furthermore, to rationalize the observed biological activity data, the molecular docking study also been carried out against the active site of fungal *C. albicans* enzyme P450 cytochrome lanosterol 14α-demethylase, which revealed a significant correlation between the binding score and biological activity for these compounds. The results of the *in vitro* and *in silico* study suggest that the triazole-incorporated tetrazoloquinolines may possess the ideal structural requirements for further development of novel therapeutic agents.

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Introduction

In recent years, life threatening systemic fungal infections have become increasingly common, especially in immunocompromised hosts suffering from tuberculosis, cancer, or AIDS and in organ transplant cases. Development of resistance against available antifungal agents (generally azoles) is also an alarming factor. Commonly used azole antifungal agents are fluconazole, itraconazole, miconazole, and voriconazole displayed broad spectrum antifungal activity.[1] Azoles have broad spectrum activities against most yeasts and filamentous fungi and are the drug of choice for antifungal chemotherapy.[2] These antifungal drugs inhibiting CYP51 in the process of biosynthesis of ergosterol through a mechanism in which the heterocyclic nitrogen atom (*N*-4

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of triazole) binds to the heme iron atom.[3] However, increasing use of these antifungal drugs has led to increase in resistance to these drugs.[4–6]

Heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Quinoline and their derivatives are pharmacologically important heterocyclic compounds because of their wide existence in alkaloids, therapeutics, and synthetic analogues with interesting biological activities such as antimalarial,[7] analgesic,[8] anticancer,[9] anti-inflammatory,[10] antiviral,[11] antihelmintic,[12] anti-protozoal,[13] cardiovascular,[14] hypoglycemic,[15] and antimicrobial activity.[16]

Triazoles are stable to acidic/basic hydrolysis and also reductive/oxidative conditions, indicative of a high aromatic stabilization. This moiety is relatively resistant to metabolic degradation. Over the past two decades 1,2,3-triazole and its derivatives have attracted continued interest in the medicinal field and are reported to possess a wide range of biological activities such as antifungal,[17] antitubercular,[18] antiallergic,[19]a anti-HIV,[19]a antibacterial,[19]b α-glycosidase inhibitor,[20] antimicrobial,[21] anticoccidiostats,[22] anticonvulsant,[23] antimalarial,[24] antiviral,[25] and antimycobacterial.[26] Triazole has been used to improve the pharmacokinetic properties of the desired drug.[27]

Click chemistry is a newer approach for the synthesis of drug-like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. Sharpless[28] and Meldal[29] groups have reported the dramatic rate enhancement (up to 10^7 times) and improved regio-selectivity of the Huisgen 1,3-dipolar cycloaddition reaction of an organic azide and terminal acetylene to afford, regio-specifically, the 1,4-disubstituted-1,2,3-triazole in the presence of Cu (I) catalyst. The Cu (I)-catalyzed azide alkyne cycloaddition (CuAAC) reaction has successfully fulfilled the requirement of "click chemistry" as prescribed by Sharpless and within the past few years has become a premier component of synthetic organic chemistry.[30]

Tetrazoles can act as pharmacophore for the carboxylate group, increasing their utility. Angiotensin II blocker often contain tetrazoles, as Losartan and candesartan. Tetrazoles and its derivatives displays various biological activities such as antibacterial,[31]a,b anti-inflammatory,[31]a,b antinociceptive,[31]a,b hypoglycemic,[31]a,b anticancer[31]a,b antifungal,[31]c antiviral,[31]a antitubercular & antimalarial,[31]d and cyclo-oxygenase inhibitors activities.[31]e They are used as catalyst in the synthesis of phosphonates.[31]a

In recent years, a library of quinoline derivatives conjugated with 1,2,3-triazole were synthesized and proved to possess different bioactivity such as antimicrobial activity[32] (Figure 1, **A**), *β*-haematin inhibitor[33] (Figure 1, **B**), antimalarial agent[33] (Figure 1, **C**), antifungal agent[16] (Figure 1, **D**), antimalarial and cytotoxic activity[34] (Figure 1, **E**), DNA binding and photonuclease activity[35] (Figure 1, **F**).

In continuation of our earlier work[16,36] on synthesis and biological properties of heterocyclic moieties and the importance of tetrazoloquinoline-1,2,3-triazole moieties as a single molecular scaffold, herein we would like to report the design and syntheses of new tetrazoloquinoline-linked triazole hybrids and their evaluation for antimicrobial and antioxidant activities. The computational parameters like docking study for antimicrobial activity and ADME prediction of synthesized tetrazoloquinoline-triazole conjugates **5a-i** were also performed.

Results and discussion

Chemistry

We have described a protocol for the syntheses of a series of new derivatives of 8-methoxy-4-((4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-*a*]quinoline **5a-i** as a potential antimicrobial, antioxidant, and antitubercular agents from commercially available starting materials. These compounds were formed by the fusion of substituted (prop-2-yn-1-yloxy)benzenes **4a-h**,

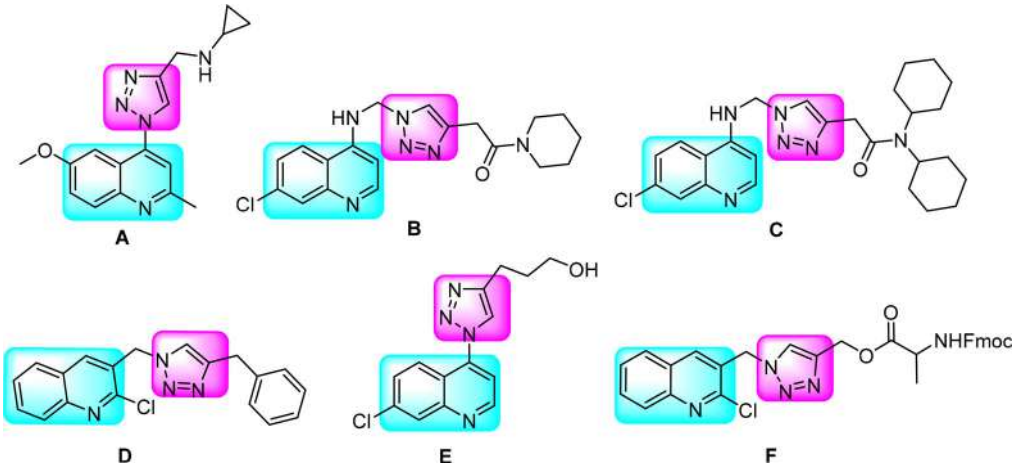
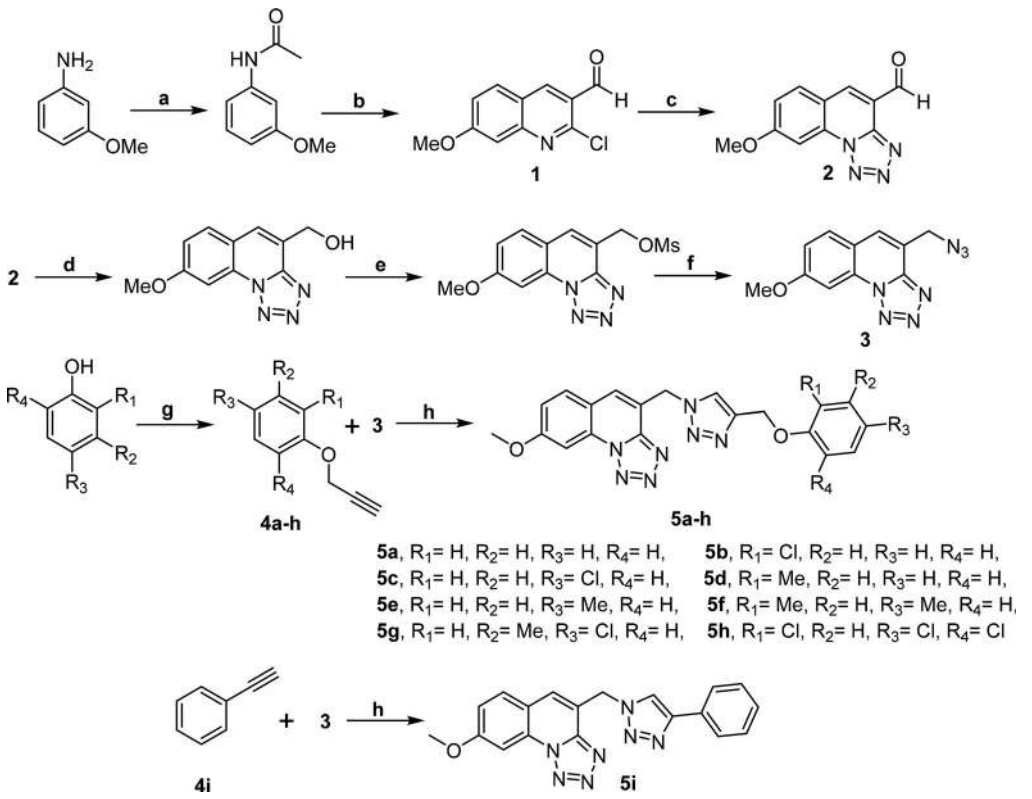


Figure 1. Triazole incorporated quinoline derivatives **A–F**.

phenyl acetylene **4i** and 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** *via* click chemistry approach (Scheme 1). The synthesis of starting material 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** was prepared from 8-methoxytetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** *via* $NaBH_4$ reduction, mesylation followed by nucleophilic substitution reaction of sodium azide (Scheme 1).

The synthesis of methoxytetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** was prepared from 3-methoxyaniline (*m*-anisidine) which on acylation followed by Vilsmeier-Haack formylation at 80 °C for 8 hr to generate 2-chloro-7-methoxyquinoline-3-carbaldehyde **1**, which on further reaction with sodium azide in DMF at 80 °C for 6 hr produces tetrazoloquinoline aldehyde **2** in good yield. The commercially available phenols have been alkylated with propargyl bromide in the presence of K_2CO_3 as a base in *N,N*-dimethylformamide (DMF) afforded the corresponding (prop-2-yn-1-yloxy)benzene derivatives **4a-h** in good to excellent yield (Supporting Information). Finally, the Huisgen's CuAAC reaction has been performed on 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and (prop-2-yn-1-yloxy)benzene derivatives **4a-h** and phenylacetylene **4i** in the presence of $Cu(OAc)_2$ in *t*-BuOH-H_2O (3:1) at room temperature for 16–22 hr gives the corresponding 1,4-disubstituted-1,2,3-triazole based tetrazoloquinoline derivatives **5a-h** and **5i**, respectively, in quantitative isolated yield (86–90%) (Scheme 1). The formation of compounds **3** and **5a-i** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS spectral analysis. In the ^{1}H NMR spectrum of the compound **5a**, the two methylene groups attached to nitrogen and oxygen showed singlet at δ 5.16 and 6.09 ppm, respectively. In addition to this, the signal observed at δ 4.06 ppm indicates the -OCH_3 proton present on the quinoline ring. Similarly signal observed at δ 8.01 ppm indicates the proton present on the triazole ring. In the ^{13}C NMR spectrum for compound **5a**, the signals at δ 61.5 and 66.2 ppm indicates the presence of methylene carbon attached to the nitrogen of triazole ring and oxygen to phenyl ring, respectively, and signal at δ 54 ppm indicates the presence of methoxy carbon.

For compound **5a**, the calculated mass for $[M+H]^+$ is 388.1516 and in HRMS, the $[M+H]^+$ peak observed at 388.1513. Furthermore, to expand the series, 1,4-disubstituted-1,2,3-triazole tetrazoloquinoline derivatives **5 b-i** with various substituent has been prepared by the cycloaddition reaction of 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and alkynes (prop-2-yn-1-yloxy)benzene derivatives **4 b-h** and phenylacetylene **6** (Scheme 1) under similar reaction condition in good to excellent yields.



Scheme 1. Reagents and conditions: (a) acetic acid, 110–120 °C, 6 hr; (b) DMF, $POCl_3$, 0–80 °C, 8 hr, (c) NaN_3, DMF, 80 °C, 6 hr; (d) $NaBH_4$, methanol, 0 °C to rt, 2 hr; (e) MsCl, DCM, 0 °C to rt, 4 hr; (f) NaN_3, DMF, 80 °C, 2 hr; (g) propargyl bromide, K_2CO_3, DMF; (h) $Cu(OAc)_2$ (20 mol%), *t*-BuOH-H_2O (3:1), rt.

Biological evaluation

Antibacterial activity

Minimum inhibitory concentration (MIC) values for bacteria determined according to the two-fold broth micro-dilution method using Muller-Hinton broth in 96-well micro-test plates recommended by National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[37] All the tested tetrazoloquinoline-1,4-disubstituted 1,2,3-triazole based derivatives **5a-i** shows significant antibacterial activity (Table 1). For bacterial strain *S. aureus*, it can be seen that, the compounds **5b**, **5d**, **5e**, **5f**, and **5g** shows excellent inhibitory activity with MIC value 8 µg/mL, which is two-fold more potent than the clinical drug ampicillin and kanamycin (MIC 16 µg/mL) and equivalent to the chloramphenicol (8 µg/mL). However, the compounds **5a**, **5c**, **5h**, and **5i** also possess equivalent antibacterial effect against *S. aureus* with MIC value 16 µg/mL compared to the ampicillin and kanamycin. Compounds **5b**, **5c**, **5d**, **5f**, **5h**, and **5i** with MIC value 16 µg/mL exhibit equivalent antibacterial activity for *M. luteus* compared to the standard drug ampicillin. All the synthesized compounds show considerable activity against *B. cereus*, especially compounds **5e**, **5f**, **5g**, and **5i** with MIC value 4 µg/mL exhibited four-fold more activity compared to the ampicillin and two-fold more potent than kanamycin and chloramphenicol. Compound **5h** shows equivalent activity compared to the standard drug kanamycin and chloramphenicol. Compounds **5b** and **5c** show good activity against *B. cereus* compared to the ampicillin. It can be seen that, all the synthesized tetrazoloquinoline-1,2,3-triazole-based derivatives **5a-i** possess comparable activity against *E. coli* as compared to ampicillin, kanamycin, and chloramphenicol.

Table 1. *In vitro* antimicrobial evaluation of synthesized compounds **3** and **5a-i** MIC values (μg/mL).

	Antibacterial activity											
	Gram + ve bacteria			Gram –ve bacteria			Antifungal activity					
Entry	*SA*	*ML*	*BC*	*EC*	*PF*	*FD*	*CA*	*AN*	*CL*	*PC*	*AF*	*CN*
3	128	128	256	256	256	256	128	128	256	256	256	256
5a	16	32	32	16	16	8	8	8	8	32	32	128
5b	8	16	16	8	8	32	16	16	32	64	16	32
5c	16	16	16	4	8	4	4	8	8	16	16	16
5d	8	16	32	4	128	16	16	32	16	32	16	128
5e	8	32	4	16	16	16	8	8	8	64	16	16
5f	8	16	4	4	16	8	16	8	16	64	32	32
5g	8	32	4	4	4	4	4	8	8	32	8	128
5h	16	16	8	4	4	4	4	8	8	32	128	256
5i	16	16	4	4	128	4	8	16	32	128	256	256
AP	16	16	16	16	16	16	–	–	–	–	–	–
KM	16	8	8	16	16	16	–	–	–	–	–	–
CP	8	8	8	8	8	8	–	–	–	–	–	–
MA	–	–	–	–	–	–	16	16	16	16	16	16
AB	–	–	–	–	–	–	16	8	16	16	8	16
FA	–	–	–	–	–	–	8	8	8	8	8	8

SA, Staphylococcus aureus; ML, Micrococcus luteus; BC, Bacillus cereus; EC, Escherichia coli; PF, Pseudomonas fluorescens; FD, Flavobacterium devorans; AN, Aspergillus niger; PC, Penicillium chrysogenum; CL, Curvularia lunata; CA, Candida albicans; AF, Aspergillus flavus; CN, Cryptococcus neoformans; AP, Ampicillin; KM, Kanamycin; CP, Chloramphenicol; MA, Miconazole; AB; Amphotericin B; FA, Fluconazole.

Compounds **5c**, **5d**, **5f**, **5g**, **5h**, and **5i** with MIC value 4 μg/mL shows four-fold more activity compared to the ampicillin, kanamycin, and two-fold more activity compare to the chloramphenicol against *E. coli*. Compound **5b** with MIC value 8 μg/mL, possesses equivalent activity compared to the standard drug chloramphenicol. Compounds **5g** and **5h** with MIC value 4 μg/mL show four-fold more activity compared to the ampicillin, kanamycin, and two-fold more activity compared to the chloramphenicol against bacterial strain *P. fluorescens*. Compounds **5b** and **5c** shows two-fold more activity compared to the standard ampicillin, kanamycin, and show equivalent activity compared to the chloramphenicol. Compounds **5a**, **5e**, and **5f** show equivalent activity compared to the standard drug ampicillin and chloramphenicol with MIC value 16 μg/mL. Compounds **5c**, **5g**, **5h**, and **5i** with MIC value 4 μg/mL show four-fold more activity compared to the ampicillin, kanamycin, and two-fold more activity compared to the chloramphenicol against bacterial strain *F. devorans*.

Compounds **5a** and **5f** (MIC = 8 μg/mL) show two-fold more activity compared to the standard ampicillin, kanamycin, and shows equivalent activity compared to the chloramphenicol. Compounds **5d** and **5e** show equivalent activity compared to the ampicillin and chloramphenicol with MIC value 16 μg/mL. In general, for Gram positive bacteria, among all the synthesized compounds **3** and **5a-i**, compounds **5e**, **5f**, **5g**, and **5i** show promising antibacterial activity against bacterial strain *B. cereus* and all the synthesized compounds exhibited excellent antibacterial activity against Gram negative bacteria *E. coli* and *F. devorans* compared to the standard drugs.

Antifungal activity

Fungi were subcultured in potato dextrose broth medium. MIC of the synthesized compounds was determined using potato dextrose broth in 96-well micro-test plates recommended by NCCLS guidelines.[37] In case of antifungal activity, all the synthesized 1,4-disubstituted 1,2,3-triazole-based tetrazoloquinoline derivatives **5a-i** show good to moderate activity against *C. albicans*, *A. niger*, *C. lunata*, *P. chrysogenum*, *A. flavus*, and *C. neoformans* strains (Table 1). Compounds **5c**, **5g**, and **5h** with MIC value 4 μg/mL, exhibited four-fold more activity compared to the standard drug miconazole, amphotericin B and two-fold more activity compared to the fluconazole against the fungicidal strain *C. albicans*. Compounds **5a**, **5e**, and **5i** with MIC values 8 μg/mL,

exhibited two-fold more activity compared to the standard drug miconazole, amphotericin B and equivalent potency compared to the standard fluconazole. Compounds **5b**, **5d**, and **5f** with MIC values 16 μg/mL, exhibited equivalent activity compared to the standard drug miconazole and amphotericin B against the fungal strain *C. albicans*. Compounds **5a**, **5c**, **5e**, **5f**, **5g**, and **5h** with MIC values 8 μg/mL, exhibited two-fold more activity compared to the standard drug miconazole, amphotericin B and equivalent activity compared to the fluconazole against the fungicidal strain *A. niger*. Compounds **5b** and **5i** with MIC values 16 μg/mL, exhibited equivalent potency compared to the standard drug miconazole against the fungal strain *A. niger*. Compounds **5a**, **5c**, and **5e** with MIC values 8 μg/mL, exhibited two-fold more activity compared to the standard drug miconazole, amphotericin B and equivalent activity compared to the fluconazole against the fungicidal strain *C. lunata*. Compounds **5d** and **5f** with MIC values 16 μg/mL, exhibited equivalent potency compared to the standard drug miconazole and amphotericin B against the fungal strain *C. lunata*. Compound **5c** with MIC values 16 μg/mL, exhibited equivalent potency compared to the standard drug miconazole and amphotericin B against the fungal strain *P. chrysogenum*. Compound **5g** with MIC values 8 μg/mL, exhibited two-fold more activity compared to the standard drug miconazole and equivalent potency compared to the amphotericin B and fluconazole against the fungal strain *A. flavus*. Compounds **5b**, **5c**, **5d**, and **5e** with MIC value 16 μg/mL exhibited equivalent activity as compared to standard drug miconazole for fungal strain *A. flavus*. Compounds **5c** and **5e** with MIC value of 16 μg/mL, show equivalent antifungal activity against *C. neoformans* as compared to standard drug miconazole and fluconazole. Overall, the starting material 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** exhibited very less antifungal activity but the 1,2,3-triazoles derived from the azide **3** shows excellent antifungal activity compared to the standard antifungal drugs miconazole, amphotericin B and fluconazole.

Antitubercular activity

All the synthesized compounds **5a-i** showed antibacterial activity against both Gram positive and Gram negative bacteria, especially against the Gram negative bacteria. As these compounds have shown significant antibacterial activities, we extended our study for evaluation of antitubercular activity. The newly synthesized 1,4-disubstituted-1,2,3-triazole containing tetrazoloquinoline derivatives **5a-i** were screened for *in vitro* antitubercular activity against *MTB H37Ra* (ATCC 25177) and *M. bovis BCG* (ATCC 35743) in liquid medium. In a preliminary screening (Supporting Information, Table S1), the antimycobacterial activity of these compounds was assessed at concentrations of 30, 10, and 3 μg/mL using an established XTT Reduction Menadione assay (XRMA) anti-tubercular screening protocol[38] using first-line antitubercular drugs rifampicin and isoniazid as reference standards and the MIC and IC_{50} values are presented in Table 2. The MIC, that is, concentration of compounds required to completely inhibit MTB growth, were recorded. The MIC was calculated from a dose response curve. The compounds with more than 90% inhibition of initial primary screening were further assayed for secondary screening, that is, determination of MIC against dormant *MTB H37Ra* and dormant *M. bovis BCG* clinical isolates (drug sensitive and resistant). The tetrazoloquinoline-1,2,3-triazole conjugates **5a-i** (MIC range > 30 μg/mL) were found to be particularly inactive against dormant *MTB H37Ra*, dormant *M. bovis BCG*.

Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed *in vitro* by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay[39] and all the synthesized compounds **5a-i** show good to moderate antioxidant activity as compared to the standard drug BHT (Butylated Hydroxy Toluene) (Table 2). Compounds **5b** and **5d** having *chloro*-substituent at *ortho*- and *para*-position of phenyl ring, respectively, shows potent activity (IC_{50} 12.48 and 16.30 μg/mL, respectively) as compared to the standard drug BHT. However, the compound **5g**

Table 2. *In vitro* antitubercular activity against dormant *MTB H37Ra*, dormant *M. bovis BCG* and DPPH radical scavenging activity of compound **3** and **5a-i**.

	MTB H37Ra dormant		*M. bovis* BCG dormant		
Compounds	MIC	IC_{50}	MIC	IC_{50}	DPPH IC_{50} (μg/mL)
3	>30	>30	>30	>30	50.20
5a	>30	>30	>30	>30	29.43
5b	>30	>30	>30	>30	12.48
5c	>30	>30	>30	>30	16.30
5d	>30	>30	>30	>30	40.41
5e	>30	>30	>30	>30	26.78
5f	>30	>30	>30	>30	32.55
5g	>30	>30	>30	>30	15.19
5h	>30	>30	>30	>30	19.20
5i	>30	>30	>30	>30	33.82
RP	0.043 ± 0.15	0.0018 ± 0.009	0.041 ± 0.01	0.0016 ± 0.002	NT
INH	0.075 ± 0.25	0.0025 ± 0.0007	0.045 ± 0.02	0.0023 ± 0.001	NT
BHT	NT	NT	NT	NT	16.47

RP: Rifampicin; INH: Isoniazid; BHT: Butylated hydroxy toluene; NT: Not tested.

(15.19 μg/mL) with *methyl*-group at *meta*- and *chloro*-group at *para*-position of phenyl ring shows excellent antioxidant activity as compared to the BHT. The starting material 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** exhibited very less antioxidant activity as compared to standard drugs.

Computational study

Molecular docking

Molecular docking is now an established approach in drug discovery for predicting the binding mode of a specified compound within the active site of the protein target of interest and the types of thermodynamic interactions governing the protein-inhibitor complexation especially in the absence of available resources to carry out the enzymatic assays. Thus, with the aim of rationalizing the promising antifungal activity portrayed by the title compounds tetrazoloquinoline-1,2,3-triazole derivatives (**5a-i**) and to gain an insight into the molecular basis of their interactions, a molecular docking study was carried out against the fungal sterol 14α-demethylase (CYP51) as the target enzyme. Sterol 14α-demethylase (CYP51) is an ancestral activity of the cytochrome P450 superfamily. It converts lanosterol into 4,4′-dimethyl cholesta-8,14,24-triene-3-*β*-ol-a step required for ergosterol biosynthesis which is an essential component of the fungal cytoplasmic membrane. Inhibition of CYP51 causes depletion of ergosterol coupled with an accumulation of 14-methyl sterols resulting in impaired cell growth in fungi. This crucial role of CYP51 in fungi makes it an important target for drug design. A perusal of the docking poses obtained for all these tetrazoloquinoline-1,2,3-triazole derivatives revealed that they could snugly fit into the active site of CYP51 with varying degree of binding affinities adopting a very homologous orientation and at co-ordinates very close to that of the native ligand-fluconazole (Figure 2). The resulting enzyme-inhibitor complexation was stabilized through a network of steric and electrostatic interactions with the active site residues.

To gauze the accuracy and reliability of the docking protocol, the co-crystallized ligand (fluconazole) was extracted from the crystal structure and again subjected to dock into the same binding pocket defining the above-mentioned parameters. The docked conformation of fluconazole comparing with the experimental binding mode as in X-ray is shown in Figure 3. The result show that the docking protocol could reproduce the X-ray bound conformation of fluconazole with an RMSD of less than 1.0 Å indicating the reliability of the docking protocol in accurately predicting the binding mode for the title molecules.

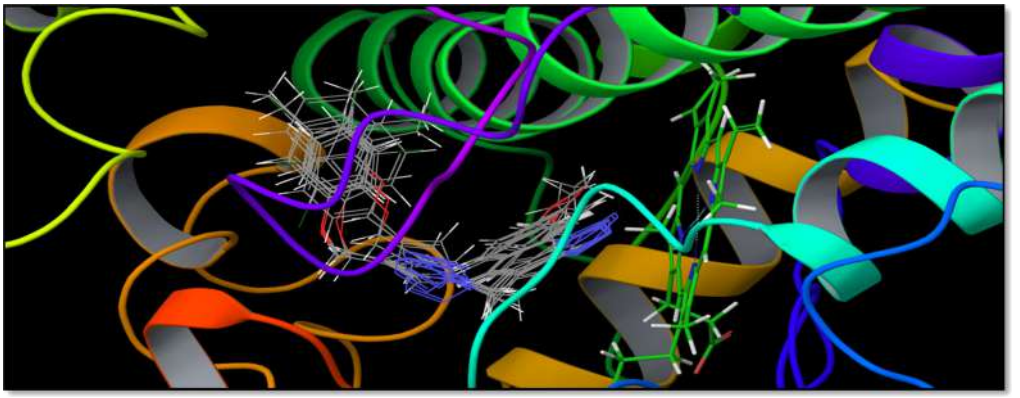


Figure 2. Docking-based binding mode of tetrazoloquinoline-1,2,3-triazole derivatives (**5a-i**) into the active site of fungal sterol 14α-demethylase (CYP51).

The minimum energy (Glide energy) for each of these complexes was observed to be negative ranging from −58.54 kcal/mol to −49.70 kcal/mol while the docking scores ranged from −7.79 to −7.14 with a significant correlation between their docking score and the experimentally observed MIC values—the active compounds possessing higher scores while those with relatively lower activity were also predicted to have lower docking scores. The binding energy for the reference ligand-fluconazole was found to be −52.92 kcal/mol with a docking score of −7.34. The binding energy signifies the energy required for a ligand to cover the entire enzyme surface and its putative interactions with the amino acid residues. A higher negative value for the binding energy (and docking score) signifies a good binding affinity for the ligand toward the target enzyme and vice versa. Furthermore, a detailed analysis of the per-residue interactions between the enzyme and these compounds was carried out to identify the most significantly interacting residues and the type of thermodynamic elements (bonded and non-bonded interactions) governing the binding of these molecules to the target. This analysis is elucidated in the next section for one of the most active compound **5g** while the results for the remaining compounds are summarized in Table 3 and their binding modes are provided in the Supporting Information as Figure 4.

The lowest energy docked conformation of **5 g** into the active site of CYP51 showed that the inhibitor binds at the same co-ordinates as the native ligand with a significantly higher binding affinity resulting in a docking score of −7.79 and a binding energy −58.54 kcal/mol (Figure 4). The higher binding affinity can be explained in terms of the specific bonded and non-bonded per-residue interactions with the residues lining the active site.

The complexation of **5g** with CYP51 is observed to be stabilized through an extensive network of van der Waals interactions with Ala291 (−3.08 kcal/mol), Ala288 (−1.55 kcal/mol), Ala287 (−1.99 kcal/mol), Tyr116 (−3.54 kcal/mol), Phe110 (−1.94 kcal/mol), and Tyr103 (−3.54 kcal/mol) through quinoline-tetrazole backbone while 1,2,3-triazole heterocycle was engaged in similar interactions through Val461 (−3.28 kcal/mol), Met460 (−2.52 kcal/mol), Thr459 (−1.28 kcal/mol), Leu356 (−2.46 kcal/mol), and Met106 (−4.00 kcal/mol) residues in the active site. Furthermore, the substituted aromatic ring connected to 1,2,3-triazole heterocycle also showed favorable van der Waals interactions through His294 (−1.40 kcal/mol), Phe290 (−3.98 kcal/mol), Leu208 (−3.02 kcal/mol), and Glu205 (−1.96 kcal/mol) residues. The compound was also involved in a set of relatively few but significant electrostatic interactions as well through Met106 (−1.50 kcal/mol) and Tyr103 (−1.18 kcal/mol) residues in the active site CYP51. The excellent binding affinity of **5g** toward CYP51 can also be attributed to a very strong van der Waals (−10.62 kcal/mol) as well as electrostatic (−9.425 kcal/mol) interactions with heme moiety in the active site. Furthermore, a prominent π-π stacking interaction was observed through the aromatic ring of quinoline-tetrazole backbone with the Phe110 having a bonding distance of 2.451 Å which as well contributed significantly to the stability of the **5g** in the active site of the

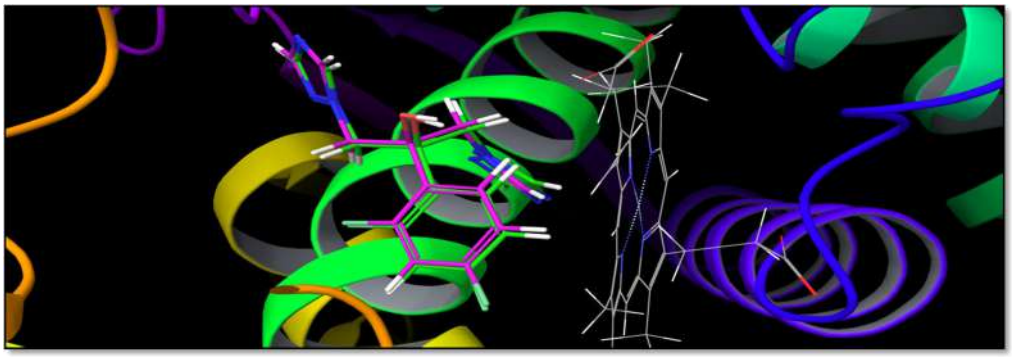


Figure 3. Validation of the molecular docking protocol: super-imposed image of the structures of fluconazole from the crystal structure (orange carbon chain) and the docked conformation (purple carbon chain).

enzyme. Such π-π stacking interactions serve as an "anchor" for channelizing the 3 D orientation of the ligand in its active site and also facilitate the steric and electrostatic interactions thereby contributing to the stability of the enzyme-inhibitor complex.

A similar network of interaction was observed for the other quinoline-tetrazole-1,2,3-triazole derivatives as well but decreasing gradually with their observed antifungal activity. The per-residue interaction analysis revealed that the primary driving forces for mechanical interlocking is the steric complementarity between the ligand and the active site of CYP51 which is evident from the relatively higher number of van der Waals interactions over other components contributing to the binding scores. Interestingly, all the quinoline-tetrazole-1,2,3-triazole derivatives investigated herein were found coordinated to the iron of the heme group present in the active site. This is a very important observation as the native ligand-fluconazole is also coordinated with the metal ion in the active site of CYP51. Thus, these quinoline-tetrazole-1,2,3-triazoles may as well share the same inhibition mechanism as fluconazole making them pertinent starting points for structure-based drug design.

In silico ADME prediction

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism, and excretion) profile. In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[40] using Molinspiration online property calculation toolkit.[41] Absorption (% ABS) was calculated by: % ABS = 109 – (0.345 × TPSA).[42] Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics, and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software.[43]

A computational study of all the synthesized **5a-i** was performed for prediction of ADME properties and the value obtained is presented in Table 4.

It is observed that, the compounds exhibited a good % ABS (% absorption) ranging from 77.16 to 80.35%. Furthermore, none of the synthesized compounds **5a-i** violated Lipinski's rule of five (miLog $P \leq 5$). A molecule likely to be developed as an orally active drug candidate should not show more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) $\leq$ 5, molecular weight $\leq$ 500, number of hydrogen bond acceptors $\leq$ 10 and number of hydrogen bond donors $\leq$ 5.[44] The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Table 3. Quantitative estimate of the per-residue interactions for the tetrazoloquinoline-1,2,3-triazole derivative (**5a-i**) with the *fungal sterol 14α-demethylase (CYP51) enzyme*.

			Per-residue interaction energy analysis		
Cpd	Docking score	Binding energy	van der Waals (kcal/mol)	Electrostatic (kcal/mol)	π-π stacking (Å)
5a	−7.40	−53.57	500(−10.79), Val461(−2.92), Met460(−2.41), Thr459(−1.19), Leu356(−2.21), Ala291(−2.31), Phe290(−2.30), Ala288(−1.24), Ala287(−1.59), Leu208(−1.26), Tyr116(−2.45), Phe110(−1.52), Met106(−3.16), Tyr103(−2.92)	500(−7.37), Met106(−1.25), Tyr103(−1.09)	Tyr116(2.07)
5b	−7.1	−50.77	500(−10.72), Val461(−2.41), Met460(−1.78), Thr459(−1.08), Leu356(−2.10), Ala291(−2.03), Phe290(−2.19), Ala288(−1.14), Ala287(−1.11), Leu208(−1.14), Leu127(−1.04), Tyr116(−1.98), Phe110(−1.27), Met106(−2.92), Tyr103(−3.75)	500(−6.75), Tyr116(−1.32), Met106(−1.10), Tyr103(−1.017)	Tyr116(2.06)
5c	−7.78	−57.71	500(−10.85), Val461(−3.18), Met460(−3.11), Thr459(−1.42), Leu356(−2.10), His294(−1.40), Ala291(−2.91), Phe290(−3.51), Ala288(−1.43), Ala287(−1.96), Leu208(−2.96), Glu205(−1.85), Tyr116(−3.55), Phe110(−1.77), Met106(−3.83), Ile105(−2.63), Tyr103(−3.05)	500(−9.67), Met106(−1.43), Tyr103(−1.19)	Phe110(2.39)
5d	−7.14	−49.70	500(−10.52), Val461(−2.50), Met460(−1.71), Thr459(−1.00), Leu356(−2.16), Ala291(−2.04), Phe290(−2.09), Ala288(−1.14), Ala287(−1.05), Leu208(−1.18), Leu127(−1.00), Tyr116(−1.95), Phe110(−1.25), Met106(−2.59), Tyr103(−2.61)	500(−6.76), Tyr116(−1.11), Met106(−1.19)	Tyr116(2.066)
5e	−7.33	−53.50	500(−10.42), Val461(−2.70), Met460(−2.35), Thr459(−1.13), Leu356(−2.27), His294(−1.11), Ala291(−2.21), Phe290(−2.25), Ala288(−1.24), Ala287(−1.57), Leu208(−1.33), Tyr116(−2.25), Phe110(−1.42), Met106(−3.03), Tyr103(−3.14)	500(−7.29), Tyr116(−0.86), Met106(−1.24), Tyr103(−1.09)	Tr116(2.07)
5f	−7.26	−50.74	500(−10.44), Val461(−2.40), Met460(−1.41), Thr459(−1.07), Leu356(−2.17), His294(−1.34), Ala291(−2.18), Phe290(−2.16), Ala288(−1.06), Ala287(−1.05), Leu208(−1.04), Glu205(−1.67), Tyr116(−1.35), Phe110(−1.15), Met106(−2.29), Tyr103(−2.83)	500(−7.05), Tyr116(−1.22), Met106(−1.12)	Tyr116(1.97)
5g	−7.79	−58.54	500(−10.62), Val461(−3.28), Met460(−2.52), Thr459(−1.28), Leu356(−2.46), His294(−1.40), Ala291(−3.08), Phe290(−3.98), Ala288(−1.55), Ala287(−1.99), Leu208(−3.02), Glu205(−1.96), Tyr116(−3.54), Phe110(−1.94), Met106(−4.00), Tyr103(−3.54)	500(−9.42), Met106(−1.5), Tyr103(−1.18)	Phe110(2.45)
5h	−7.72	−57.51	500(−10.87), Val461(−3.13), Met460(−2.29), Thr459(−1.58), Leu356(−2.58), His294(−1.37), Ala291(−2.94), Phe290(−3.29), Ala288(−1.45), Ala287(−1.84), Leu208(−3.40), Glu205(−1.98), Tyr116(−3.42), Phe110(−1.81), Met106(−3.72), Tyr103(−3.01)	500(−9.41), Tyr116(−1.31), Tyr103(−1.13)	Tyr116(2.07)
5i	−7.42	−51.64	500(−10.26), Val461(−2.78), Met460(−2.53), Thr459(−1.14), Leu356(−2.26), Ala291(−2.33), Phe290(−2.29), Ala288(−1.28), Ala287(−1.67), Leu208(−1.49), Tyr116(−2.29), Phe110(−1.40), Met106(−3.01), Tyr103(−2.81)	500(−7.97), Tyr116(−1.18), Tyr103(−1.016)	Tyr103(2.92), Tyr116(2.01)

Conclusion

We have synthesized new 1,4-disubstituted 1,2,3-triazole-based tetrazoloquinoline derivatives *via* click chemistry approach and evaluated for biological activity. The synthesized compound displays promising antibacterial, antifungal, and antioxidant activity as compared to the respective standard drugs and unfortunately does not show antitubercular activity. Compounds **5g** and **5h** displayed significant antibacterial activity as compared to the standard antibacterial drug. Compounds **5c**, **5g**, and **5h** displayed significant antifungal activity as compared to the standard

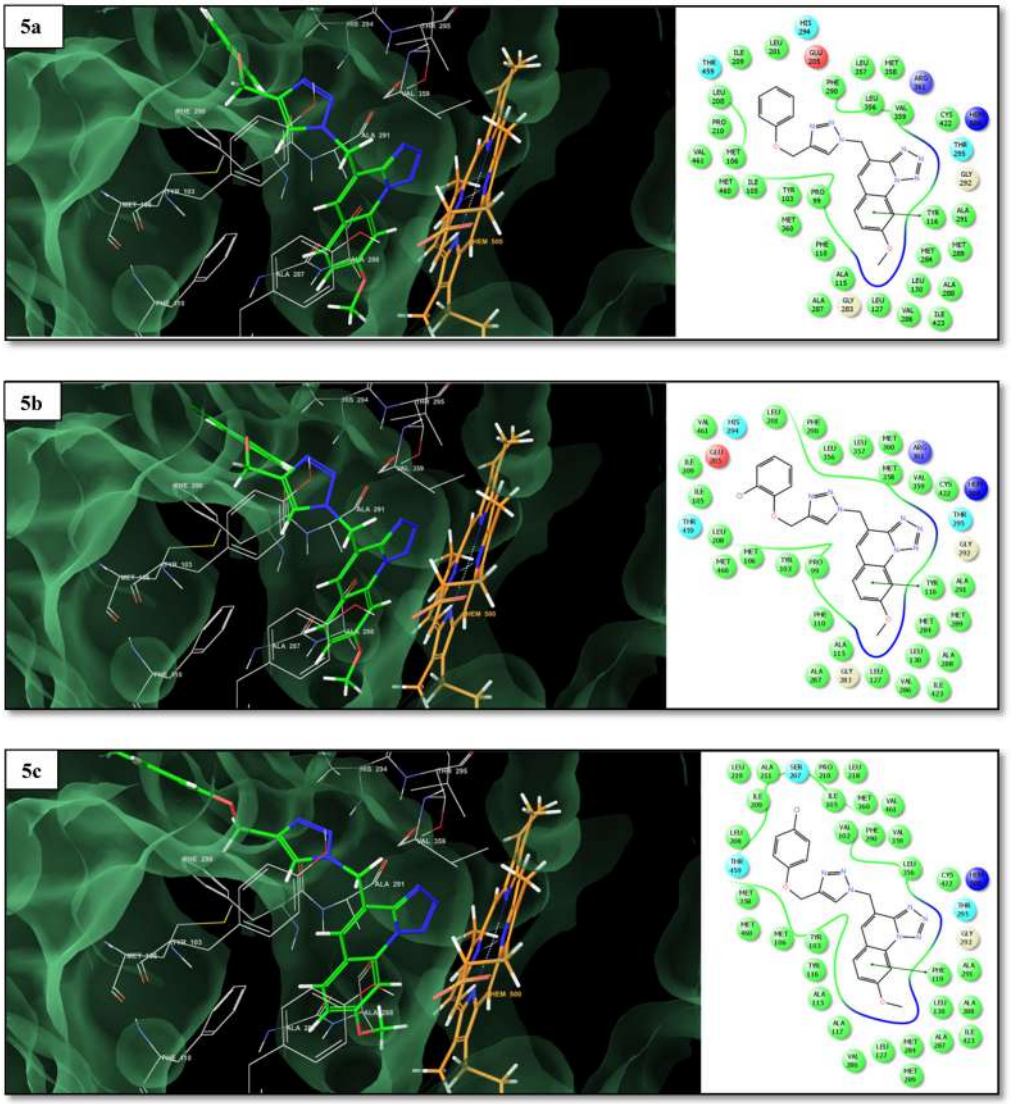


Figure 4. Docking-based binding mode of **5a**, **5b**, **5c**, **5d**, **5e**, **5f**, **5g**, **5h**, and **5i** into the active site of sterol 14α-demethylase (CYP51) (the π-π stacking interaction is represented using the green line).

antifungal drug. Compounds **5b**, **5d**, and **5g** shows potential antioxidant activity when compared with standard BHT. The trend observed in the antifungal activity for these tetrazoloquinoline-1,2,3-triazole derivatives was further rationalized by molecular docking studies with respect to their binding energy toward target enzyme sterol 14α-demethylase (CYP51). The theoretical predictions from molecular docking studies were found to be in agreement with the experimental antifungal data. Furthermore, the quantitative estimation of the per-residue interactions between these tetrazoloquinoline-1,2,3-triazoles and CYP51 enzyme helps to speculate regarding the detailed binding patterns in the cavity and the most significantly interacting the residues as well as the type of thermodynamic interactions governing the binding of these molecules which can provide an ample opportunity for medicinal chemist to design more specific and potent analogues targeting CYP51. Furthermore, analysis of the ADME parameters for synthesized compounds predicted good drug like properties and

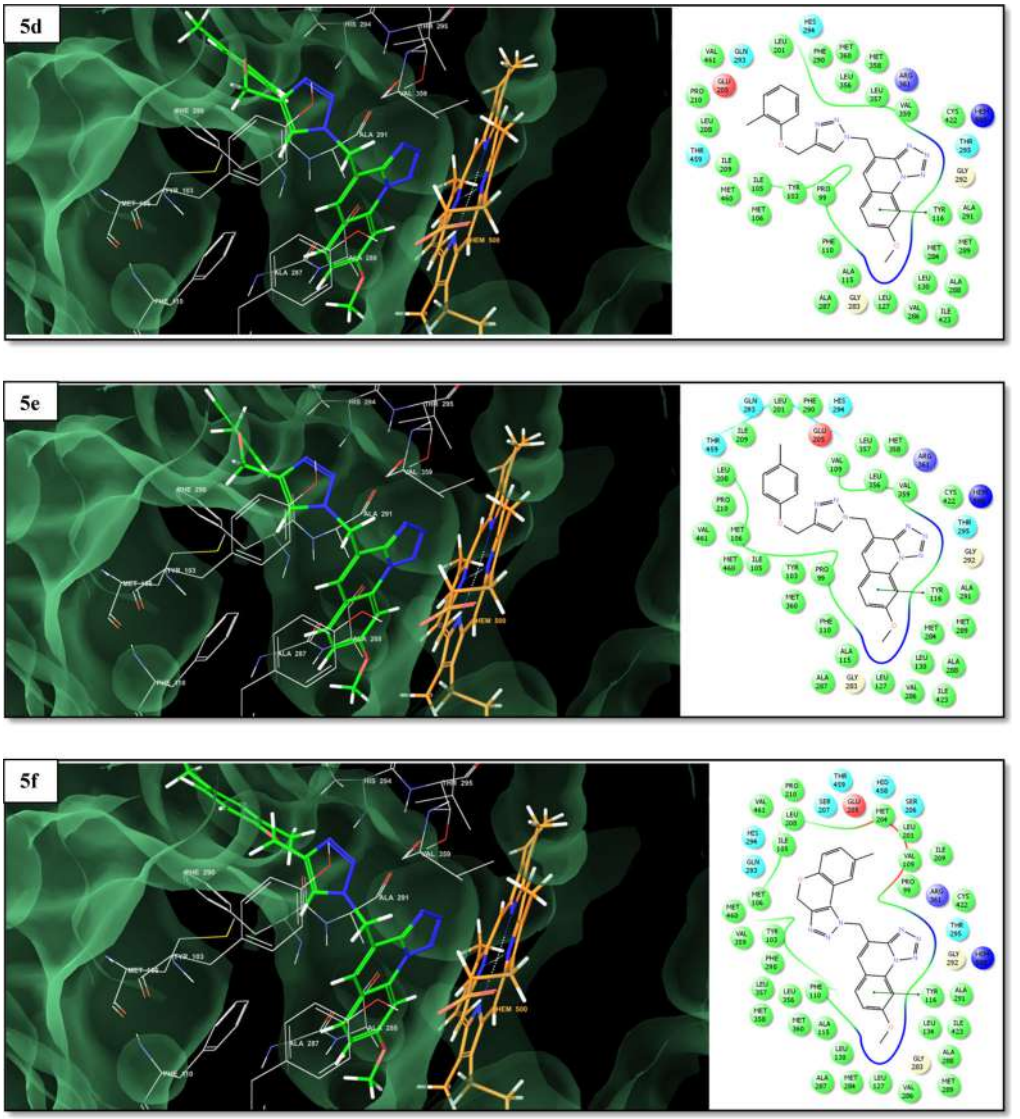


Figure 4. Continued.

can be developed as oral drug candidate. Thus, suggesting that compounds from present series can be further optimized and developed as a lead molecule.

Experimental

General procedure for the synthesis of 1-(prop-2-ynyloxy)benzene or substituted 1-(prop-2-ynyloxy)benzene (4a-h)

To the stirred solution of phenol or substituted phenol (20 mmol) in *N,N*-dimethylformamide (DMF) (20 mL), K_2CO_3 (24 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, which results into the corresponding oxyanion. To this mixture, propargyl bromide (20 mmol) was added and stirred for 2 hr. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction was quenched by crushed ice.

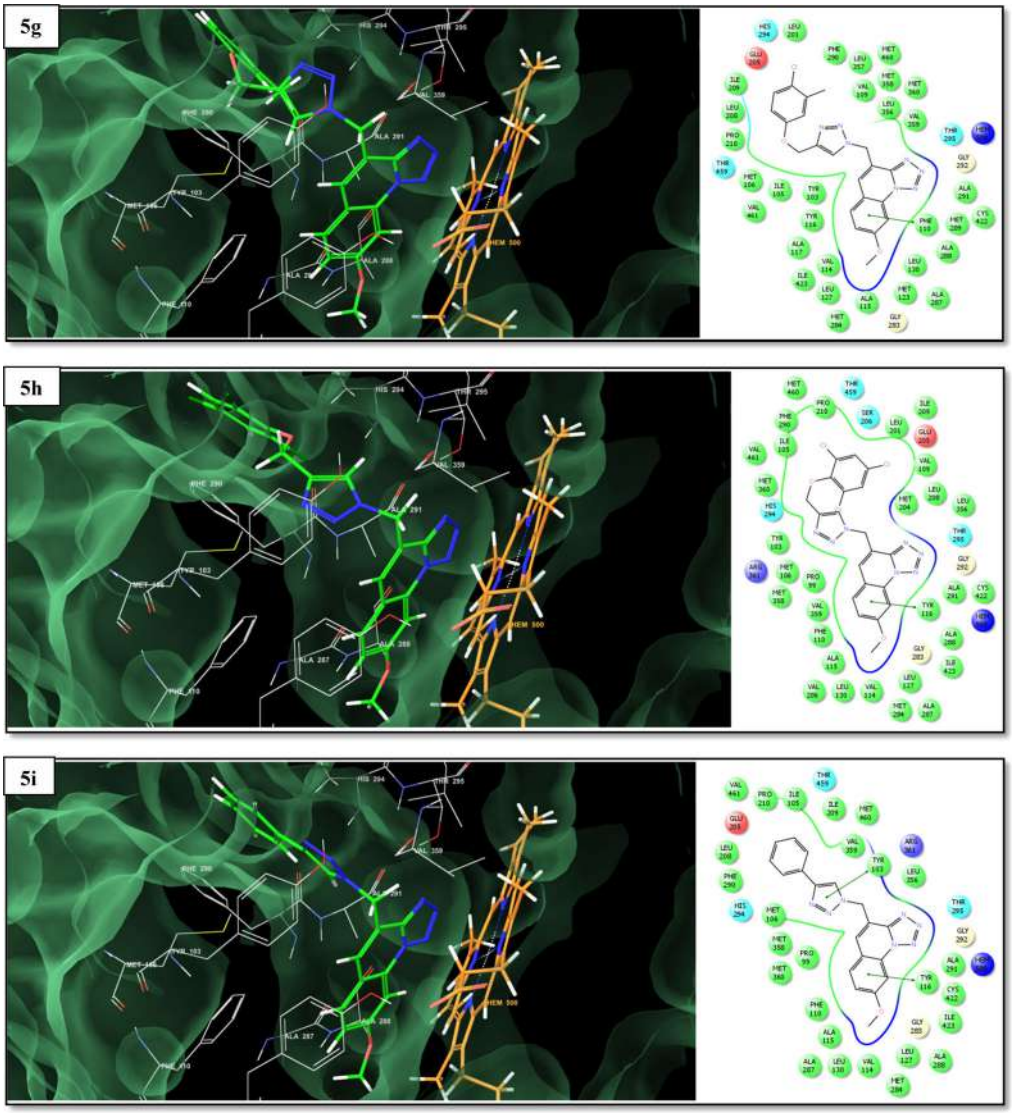


Figure 4. Continued.

In case of solid product, it was filtered and the obtained crude solid product was crystallized using ethanol. The crystallized products were taken for next step. When the products are liquid, it has been extracted in ethyl acetate (20 mL × 3). The combined organic layers were dried over $MgSO_4$. The solvent was removed under a reduced pressure and used for further reaction without purification.

General procedure for the synthesis of 8-methoxy-4-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline 5a-i

To the solution of 1-(prop-2-ynyloxy)benzene and phenyl acetylene **(4a-i)** (0.5 mmol), 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** (0.5 mmol) and copper diacetate ($Cu(OAc)_2$) (20 mole %) in *t*-BuOH-H_2O (3:1, 8 mL) and the resulting mixture was stirred at room temperature for 16–22 hr. The progress of the reaction was monitored by TLC using ethyl acetate:hexane

Table 4. Pharmacokinetic parameters important for good oral bioavailability and its drug likeness model score.

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	–	–	–	–	<500	≤5	<10	<5	≤1	-
5a	77.16	92.28	6	332.93	387.40	3.01	9	0	0	−0.24
5b	77.16	92.28	6	346.47	421.85	3.64	9	0	0	0.18
5c	77.16	92.28	6	346.47	421.85	3.69	9	0	0	0.21
5d	77.16	92.28	6	349.49	401.43	3.42	9	0	0	0.14
5e	77.16	92.28	6	349.49	401.43	3.46	9	0	0	−0.24
5f	77.16	92.28	6	366.05	415.46	3.84	9	0	0	−0.10
5g	77.16	92.28	6	363.03	435.88	4.07	9	0	0	0.32
5h	77.16	92.28	6	373.54	490.74	4.90	9	0	0	0.10
5i	80.35	83.04	4	307.14	357.38	2.80	8	0	0	−0.03

% ABS: Percentage absorption, TPSA: Topological polar surface area, n-ROTB: Number of rotatable bonds, MV: Molecular volume, MW: Molecular weight, miLog *P*: Logarithm of partition coefficient of compound between n-octanol and water, n-ON Acceptors: Number of hydrogen bond acceptors, n-OHNH donors: Number of hydrogen bonds donors.

as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with brine solution (2 × 25 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were crystallized using ethanol and ethyl acetate.

Synthesis of 2-chloro-7-methoxyquinoline-3-carbaldehyde[45]

To a solution of *N*-(3-methoxyphenyl)acetamide (5 mmol) in dry DMF (15 mmol) at 0–5 °C with stirring $POCl_3$ (60 mmol) was added drop wise and the mixture stirred at 80–90 °C for time 8 hr. After the completion of reaction (checked by TLC), the mixture was poured into crushed ice, stirred for 5 min and the resulting solid filtered, washed well with water and dried. The compounds were purified by recrystallization from ethyl acetate.

Synthesis of 8-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde

2-Chloro-7-methoxyquinoline-3-carbaldehyde (5 mmol), sodium azide (10 mmol), and DMF (10 mL) were taken in round bottom flask as per reported procedure.[46] The reaction mixture was slowly heated at 80 °C for 2 hr. After the completion of reaction (checked by TLC), the product was filtered and washed with ethanol. The crude product was purified by crystallization in DMF. Melting point is 240–242 °C.

Synthesis of (8-methoxytetrazolo[1,5-a]quinolin-4-yl)methanol

8-methoxytetrazolo[1,5-*a*]quinoline-4-carbaldehyde (1 equiv) were taken in round bottom flask, methanol used as a solvent and allowed reaction mixture for stirring below 0 °C. Then, $NaBH_4$ (3 equiv.) were added slowly with constant stirring and maintaining the temperature below 0 °C for 2 hr. The progress of the reaction was monitored by thin layer chromatography (TLC) using ethyl acetate:hexane as a solvent system. After completion of the reaction as indicated by TLC, the reaction mixture was then poured on crushed ice and extracted in ethylacetate (3 × 10 mL). The combined organic layer was dried over $MgSO_4$. Solvent was removed under reduced pressure and the (8-methoxytetrazolo[1,5-*a*]quinolin-4-yl)methanol were sufficiently pure to use without further work up.

Synthesis of (8-methoxytetrazolo[1,5-a]quinolin-4-yl)methyl methanesulfonate

To a mixture of (2-chloro quinolin-3-yl)methanol 1 (1 equiv) in acetone, triethyl amine (2 equiv) was added at 0 °C. Methane sulfonyl chloride (1.5 equiv) in acetone was added dropwise in 10 min at 0 °C, and stirred for 4 hr. The progress of the reaction was monitored on TLC. After completion of the reaction, reaction mixture was poured on crushed ice. The solid obtained was extracted with ethylacetate (2 × 20 mL) and washed with brine (2 × 20 mL). Thus, organic layer was separated, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The obtained crude product was crystallized using ethanol/ethylacetate obtain pure compound (8-methoxytetrazolo[1,5-*a*]quinolin-4-yl)methyl methanesulfonate.

Synthesis of 4-(azidomethyl)-8-methoxytetrazolo[1,5-a]quinoline (3)

To a solution of (8-methoxytetrazolo[1,5-*a*]quinolin-4-yl)methyl methanesulfonate (1 equiv) in dry DMF, sodium azide (2 equiv) was added and stirred at 80 °C for 2 hr. The progress of the reaction was monitored on TLC. After completion of reaction, reaction mixture was poured on crushed ice. The solid obtained was extracted with EtOAc (2 × 25 mL). The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product 3, which was purified by crystallization using ethanol/ethylacetate with 92% yield. Mp 133–135 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.05 (*s*, 3H, -OMe), 4.95 (*s*, N-CH_2), 7.40–7.46 (*m*, 1H), 7.98–7.99 (*d*, 1H), and 8.15–8.25 (*m*, 2H). HRMS calculated $[M+H]^+$ for $C_{11}H_{10}N_7O$: 256.0941, found: 256.0935.

8-Methoxy-4-((4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline (5a)

The compound **5a** as a pale pink solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and (prop-2-yn-1-yloxy)benzene **4a** in 17 hr with 90% yield. Mp 150 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 4.06 (*s*, 3H, -OMe), 5.16 (*s*, N-CH_2), 6.09 (*s*, O-CH_2), 6.92–7.06 (*m*, 3H), 7.27–7.35 (*m*, 2H), 7.43–7.47 (*d*, 1H), 8.01 (*s*, 1H), 8.16 (*s*, 1H), 8.20 (*s*, 1H) and 8.44 (*s*, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 49.3, 56.8, 61.8, 99, 117, 117.6, 118.6, 125.1, 126, 129.7, 131.8, 131.9, 133.6, 143, 147.3, 157.4 and 162.3. HRMS calculated $[M+H]^+$ for $C_{20}H_{17}N_7O_2$: 388.1516, found: 388.1513.

4-((4-((2-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-8-methoxytetrazolo[1,5-a]quinoline (5b)

The compound **5b** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1-chloro-2-(prop-2-yn-1-yloxy)benzene **4b** in 19 hr with 88% yield. Mp 139–140 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 4.03 (*s*, 3H, -OMe), 5.14 (*s*, N-CH_2), 6.06 (*s*, O-CH_2), 7.02–7.06 (*m*, 2H), 7.29–7.45 (*m*, 3H), 7.98–7.99 (*d*, 1H), 8.13 (*s*, 1H), 8.17 (*s*, 1H), and 8.41 (*s*, 1H).

4-((4-((4-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-8-methoxytetrazolo[1,5-a]quinoline (5c)

The compound **5c** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1-chloro-4-(prop-2-yn-1-yloxy)benzene **4c** in 20 hr with 87% yield. Mp 180 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 4.06 (*s*, 3H, -OMe), 5.17 (*s*, N-CH_2), 6.09 (*s*, O-CH_2), 7.05–7.09 (*m*, 2H), 7.32–7.37 (*m*, 2H), 7.43–7.48 (*3*, 1H), 8.01–8.02 (*d*, 1H), 8.16 (*s*, 1H), 8.20 (*s*, 1H), and 8.44 (*s*, 1H). ^{13}C NMR (50 MHz,

$CDCl_3$, δ ppm): 48.8, 56.3, 61.3, 98.4, 116.5, 117, 118.1, 124.6, 125.5, 129.2, 131.2, 131.3, 133.1, 142.5, 146.8, 156.8, and 161.8. HRMS calculated $[M+H]^+$ for $C_{20}H_{17}N_7O_2Cl$: 422.1127, found: 422.1123.

8-Methoxy-4-((4-((o-tolyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline (5d)

The compound **5d** as a pale pink solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1-methyl-2-(prop-2-yn-1-yloxy)benzene **4d** in 17 hr with 89% yield. Mp 145 °C.

8-Methoxy-4-((4-((p-tolyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline (5e)

The compound **5a** as a pale pink solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1-methyl-4-(prop-2-yn-1-yloxy)benzene **4e** in 16 hr with 90% yield. Mp 152–153 °C.

4-((4-((2,4-Dimethylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-8-methoxytetrazolo[1,5-a]quinoline (5f)

The compound **5f** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 2,4-dimethyl-1-(prop-2-yn-1-yloxy)benzene **4f** in 18 hr with 90% yield. Mp 135 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 2.06 (*s*, 3H), 2.18 (*s*, 3H), 4.04 (*s*, 3H, -OMe), 5.10 (*s*, N-CH_2), 6.07 (*s*, O-CH_2), 6.93–6.96 (*m*, 3H), 7.39–7.45 (*m*, 1H), 7.99–8.00 (*d*, 1H), 8.13–8.17 (*m*, 2H), and 8.39 (*s*, 1H). HRMS calculated $[M+H]^+$ for $C_{22}H_{22}N_7O_2$: 416.1829, found: 416.1825.

4-((4-((4-Chloro-3-methylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-8-methoxytetrazolo [1,5-a]quinoline (5 g)

The compound **5f** as a pale pink solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1-chloro-2-methyl-4-(prop-2-yn-1-yloxy)benzene **4g** in 21 hr with 86% yield. Mp 150 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 2.27 (*s*, 3H), 4.04 (*s*, 3H, -OMe), 5.13 (*s*, N-CH_2), 6.07 (*s*, O-CH_2), 6.85–7.03 (*m*, 2H), 7.26–7.46 (*m*, 2H), 7.99–8.00 (*d*, 1H), 8.14 (*s*, 1H), 8.18 (*s*, 1H), and 8.41 (*s*, 1H). HRMS calculated $[M+H]^+$ for $C_{21}H_{19}N_7O_2Cl$: 436.1283, found: 436.1283.

8-Methoxy-4-((4-((2,4,6-trichlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)tetrazolo [1,5-a]quinoline (5 h)

The compound **5h** as a off white solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and 1,3,5-trichloro-2-(prop-2-yn-1-yloxy)benzene **4 h** in 22 hr with 86% yield. Mp 143–145 °C.

8-Methoxy-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline (5i)

The compound **5i** as a pale pink solid and was obtained *via* 1,3-dipolar cycloaddition reaction between 4-(azidomethyl)-8-methoxytetrazolo[1,5-*a*]quinoline **3** and phenyl acetylene **4i** in 19 hr

with 88% yield. Mp 175–177 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ ppm): 4.07 (*s*, 3H, -OMe), 6.12 (*s*, N-CH_2), 7.34–7.47 (*m*, 4H), 7.84–7.88 (*m*, 2H), 8.04–8.05 (*d*, 1H), 8.21–8.26 (*m*, 2H), and 8.72 (*s*, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 48.9, 56.3, 98.5, 117, 117.5, 118.1, 122.2, 125.2, 127.9, 128.9, 130.8, 131.3, 131.4, 133.1, 146.4, 146.9, and 161.8.

Experimental protocol for biological activity

Antibacterial activity

The antimicrobial susceptibility testing of newly synthesized compounds were performed *in vitro* against bacterial strains *viz*., Gram positive *Staphylococcus aureus* (ATCC No. 29737), *Micrococcus luteus* (ATCC No. 398), *Bacillus cereus* (ATCC No. 6630), and Gram negative *Escherichia coli* (NCIM No. 2256), *Pseudomonas fluorescens* (NCIM No. 2173), and *Flavobacterium devorans* (ATCC No. 10829), respectively, to find out MIC. The MIC (μg/mL) were defined as the lowest concentrations of compound that completely inhibit the growth of each strain. Serial two-fold dilutions of all samples were prepared in triplicate in micro titer plates and inoculated with suitably prepared cell suspension to achieve the required initial concentration. Serial dilutions were prepared for screening. Dimethyl sulfoxide (DMSO) was used as solvent control. Ampicillin, kanamycin, and chloramphenicol were used as a standard antibacterial drug. The concentration range of tested compounds and standard was 256–0.5 µg/mL. The plates were incubated at 37 °C for all micro-organisms; absorbance at 595 nm was recorded to assess the inhibition of cell growth after 24 hr. The compounds which are showing promising antibacterial activity were selected for MIC studies. The MIC was determined by assaying at 256, 128, 64, 32, 16, 8, 4, 2, 1, and 0.5 µg/mL concentrations along with standards at the same concentrations.

Antifungal activity

The antifungal activity was evaluated against different fungal strains such as *Aspergillus niger* (NCIM No. 1196), *Penicillium chrysogenum* (NCIM No. 723), *Curvularia lunata* (NCIM No. 1131), *Candida albicans* (NCIM No. 3471), *Aspergillus flavus* (NCIM No. 539), and *Cryptococcus neoformans* (NCIM No. 3378). Fluconazole, miconazole, and amphotericin B were used as standard drugs for the comparison of antifungal activity. The plates were incubated at 37 °C for all micro-organisms; absorbance at 410 nm was recorded to assess the inhibition of cell growth after 48 hr. The lowest concentration inhibiting growth of the organisms was recorded as the MIC. DMSO was used as a solvent or negative control. In order to clarify any effect of DMSO on the biological screening, separate studies were carried out with solutions alone of DMSO and showed no activity against any microbial strains. The compounds which are showing promising antifungal activity were selected for MIC studies. The MIC was determined by assaying at 256, 128, 64, 32, 16, 8, 4, 2, 1, and 0.5 µg/mL concentrations along with standards at the same concentrations.

Antitubercular activity protocol

Compounds were tested for their *in vitro* effects against *MTB H37Ra* (ATCC 25177) which is susceptible to control drugs (Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide). Compounds were screened for their inhibitory effect on MTB by *in vitro* according to standard XTT Reduction Menadione Assay (XRMA) protocol as described previously.[38] Dimethyl Sulfoxide (DMSO) was used as a solvent or negative control. In order to clarify any effect of DMSO on the biological screening, separate studies were carried out with solutions alone of DMSO and showed no activity against any mycobacteria. Rifampicin and Isoniazide was used as positive control for assay. Primary screening was done against MTB at 30, 10, and 3 µg/mL concentration of

compound. Those compounds were shown more than 90% inhibition at 30 μg/mL which were selected for dose response. The MIC (in μg/mL) was recorded as the lowest concentration/highest dilution of the compounds/control drugs that completely inhibited the growth of MTB cultures.

The *in vitro* effect of compounds against *M. bovis BCG* (ATCC 35743) was done according to standard NR assay protocol as described previously.[38] Briefly in NR assay, take 80 μL of culture from incubated 96 well plate into another 96 well plate, then add 80 μL of 1% sulfanilic acid in 20% of conc. HCl, incubate it for 10 min at room temperature then add 80 μL of 0.1% NEDD solution in D/W. Finally, the optical density of the suspension was measured at 540 nm using micro plate reader. MIC and IC_{50} values were calculated using origin9 software. The % inhibition of bacilli was measured using following formula,

$$\% \text{ Inhibition} = [(\text{Abs of control}) - (\text{Abs of test sample})/(\text{Abs of control}) - (\text{Abs of blank})] \times 100.$$

Control: cell growth in medium without compound, with DMSO
Test: cell growth in presence of compound
Blank: culture medium without cells.

DPPH radical scavenging activity

The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple-colored methanol solution of 1,1-diphenyl-1-picrylhydrazyl (DPPH).[39] The spectrophotometric assay uses the stable radical DPPH as a reagent. One milliliter of various concentrations of the test compounds (5, 10, 25, 50, and 100 μg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30-min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (I %) of free radical production from DPPH was calculated by the following equation.

$$\% \text{ of scavenging} = [(\text{A control} - \text{A sample})/\text{A blank}] \times 100$$

Where "A control" is the absorbance of the control reaction (containing all reagents except the test compound) and "A sample" is the absorbance of the test compound. Tests were carried at in triplicate.

Molecular docking

To gain an insight into the binding mode of quinoline-tetrazole-1,2,3-triazole derivatives into the active site of fungal sterol 14α-demethylase (CYP51) enzyme and to increase the understanding of their action as antifungal agents, the molecular docking study was performed using the *Glide* (Grid-Based Ligand Docking with Energetics) program of Schrodinger molecular modeling suite.[47] *Glide* is an interactive molecular graphics program for analyzing the enzyme-inhibitor interactions and identifying potential binding site of the bio-macromolecular targets. The algorithm carries out a systematic search for favorable interactions between the ligand(s) and the target enzyme through a complete search of the conformational, orientation, and positional space of the docked ligand by adopting a funnel type approach and eliminates unwanted conformations using a scoring function followed by energy optimization. With this purpose, the starting coordinates of the sterol 14α-demethylase (CYP51) in complex with its inhibitor-fluconazole were retrieved from the Protein Data Bank (PDB) (www.rcsb.org) (PDB code: 3KHM) and further modified to be used for *Glide* docking. The crystal structure was preprocessed the *Protein Preparation Wizard in Glide* which involved eliminating the crystallographically observed water molecules (as none of them were observed to be conserved), assigning the correct bond orders

followed by addition of missing hydrogen atoms corresponding to pH 7.0 (considering the appropriate ionization states for the acidic as well as basic amino acid residues). Following the assignment of appropriate charge and protonation state, the enzyme-inhibitor complex was subjected to energy minimization (until the average root-mean-square deviation (RMSD) of the non-hydrogen atoms reached 0.3 Å) using Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field in order to relieve the steric clashes among the residues due to addition of hydrogen atoms. After ensuring that enzyme-inhibitor complex is in the correct form, the shape and properties of the active site of the enzyme was characterized and setup for the docking study using the *receptor grid generation* panel in *Glide*. With the non-covalently bound native ligand-fluconazole in place, the active site grid was defined by a box of 10X10X10Å dimensions centered on the centroid of fluconazole in the crystal complex which was sufficiently large to explore a bigger surface of the enzyme. The co-crystallized ligand serves as the reference co-ordinate signifying the active site of a ligand with respect to the target.

The 3 D-structures of all the tetrazoloquinoline-1,2,3-triazole derivatives (**3**, **5a-i**) were sketched using the *build* panel within Maestro and were optimized using the *LigPrep* module which involved addition of hydrogens, adjusting realistic bond lengths and angles, correcting the chiralities, ionization states and ring conformations, and generation of tautomers. The partial atomic charges were ascribed for these structures using the OPLS-2005 force-field and finally each of these structures was subjected to energy minimization until energy gradient of 0.001 kcal/mol/Å is reached. The optimized enzyme and ligand structures were then used as input for carrying out docking study utilizing the *extra precision* (XP) Glide scoring function to rank the docking poses and to estimate the binding affinities of these ligands to the target. This scoring function is equipped with force field-based parameters accounting for contributions from van der Waals and coulombic interaction energies along with terms for solvation, repulsive, hydrophobic, hydrogen bonding, and metal-ligand interactions all integrated in an empirical energy functions. The output files in terms of the docking poses of the ligands were visualized and analyzed for the key elements of interaction with the enzyme using the Pose Viewer utility in *Maestro*.

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Disclosure statement

There are no conflicts of interest.

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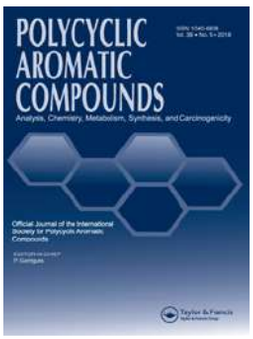

Polycyclic Aromatic Compounds

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Amide-Linked Monocarbonyl Curcumin Analogues: Efficient Synthesis, Antitubercular Activity and Molecular Docking Study

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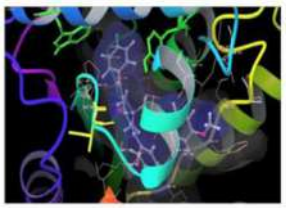
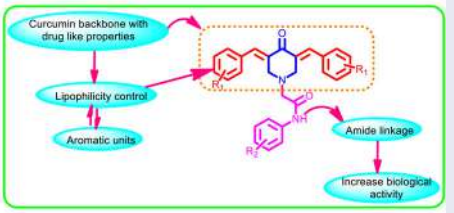
ABSTRACT

An approach toward the synthesis of novel conjugates of 3,5-bis (arylidene)-4-piperidones (DAP) pharmacophore with amide-linkage has been developed *via* one-pot multicomponent reaction of aryl aldehydes, piperidinone and 2-chloro-*N*-phenylacetamide using $[Et_3NH][HSO_4]$ as a catalyst/medium. Both substitutions on arylidene rings and piperidinone nitrogen (substituted 2-chloro-*N*-phenylacetamide) were varied. The synthesized conjugates were evaluated for their *in vitro* antitubercular activity against *M. tuberculosis* $H_{37}Ra$ (*MTB*) and *M. bovis* BCG strains. Among the series, compounds **4f**, **4g, 4i** and **4j** showed remarkable broad spectrum antitubercular activity with low IC_{50} values. Furthermore, computer docking simulations, for the most active conjugates were performed with the active site of mycobacterial enoyl-acyl carrier protein reductase (InhA) support the antitubercular activity. Lower cytotoxicity, high potency and promising activity against *MTB* and *M. Bovis* BCG suggest that amide linked DAP could serve as good leads for further modifications and development.



3D view of binding of compound **4f**



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Introduction

Tuberculosis is the ninth leading cause of death worldwide from a single infectious agent ranking above HIV/AIDS. It is fatal airborne disease caused by *Mycobacterium tuberculosis* (*Mtb*) which affects the lung and also responsible for infection in others sites of body.[1] Global tuberculosis report of 2017 given by World Health Organization (WHO), shows that TB is the leading cause of deaths due to antimicrobial resistance and among people with HIV.[2] Over 6.3 million new TB

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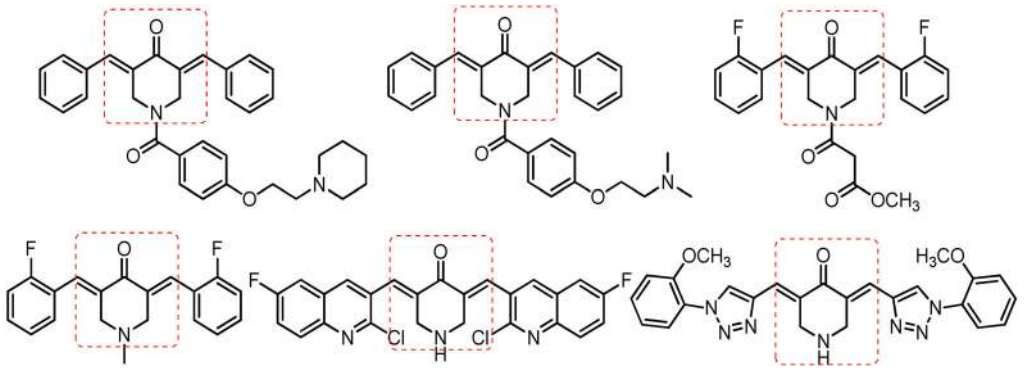


Figure 1. Known MACs as an antimycobacterial agents.

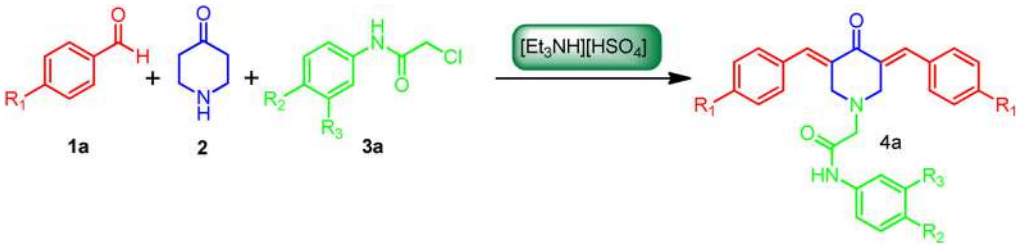
cases were notified to WHO by national authorities. In 2016 WHO estimates that there have been emergence and increasing evidences of extensively drug resistance and multiple drug resistance TB cases which results in global epidemic. Also, 4.9 lacs of new multidrug resistance TB cases were reported as per global tuberculosis report given by WHO. It was also reported that about 6 lacs new TB cases were found to exhibit resistance to most of the front-line drug against TB like rifampicin.[3] Hence, development of new therapeutic agents against TB is the urgent need of time.

In recent years enormous efforts have made by organic chemists across the globe in the development of structurally modified, therapeutically active curcumin analogues/derivatives.[4] Monocarbonyl analogue of curcumin is one of the class of structurally modified and potentially active curcuminoids obtained by removing β-diketone moiety and active methylene group from curcumin.[5,6] Monocarbonyl curcumin analogues exhibit a wide array of biological activities,[7] such as antileishmanial,[8] antiparasitic,[9] anti-inflammatory,[10] antitumor and antioxidant,[11] alzheimer's disease,[12] antibacterial,[13] anticancer[14] and antitubercular activity are well reported[15] (Figure 1).

Owing to the potential importance of curcumin derivatives as a key moieties in life sciences, pharmaceuticals, agriculture, world-wide efforts have made in the last few decades by researchers and various protocols have been developed for their synthesis[16]a using catalysts, such as NaOH/EtOH,[16]b EtOH/KOH,[16]c piperidine/HCl,[16]d AcOH/HCl gas,[16]epiperidine, L-Proline/EtOH[16]f and $MgBr_2.Et_2O/Et_3NH$.[16]g The above methods suffer from one or more limitations such as the use of excess or stoichiometric quantity, corrosive, which are non-recoverable and/or recoverable with tedious separation procedures involving lots of toxic waste generation besides a long reaction time and low yield for the desired product.

Ionic Liquids (ILs) have attracted interest because of alternative green reaction media due to their unique chemical and physical properties such as low vapor pressure, high thermal and chemical stability, good solvating ability, ease of recyclability, and controlled miscibility.[17] Thus, ILs are considered to be a safer alternative to original organic solvents as they are cleaner and safer to use and reuse.[18] The utility of Acidic Bronsted Ionic Liquid (ABIL), particularly $[Et_3NH][HSO_4]$[19] has received considerable attention because, it is an inexpensive, nontoxic catalyst as well as solvent for many organic transformations in excellent yields. Multicomponent reactions (MCRs) are important class of organic transformations and increasing attention due to their, efficiency, atom economy, short reaction times and diversity in organic synthesis.[20] Moreover, use of solvent-free methods in MCRs makes the process safer, cleaner and easier to perform.[21] Thus, the utilization of MCRs coupled with environmentally benign solvent-free condition is highly desirable.

Monocarbonyl analogues of curcumin (MACs) are key constituent and structural backbone of many pharmaceutical and agricultural compounds and the development of more general and cost



Scheme 1. Model reaction.

Table 1. Optimization of solvent and temperature.

Entry	Solvent	Temp	Time (h)	Yield(%)[a]
1	EtOH	rt	6	60
2	MeOH	rt	6	65
3	DMF	rt	6	70
4	THF	rt	6	55
5	CH_3CN	rt	6	50
6	Toluene	rt	6	71
7	Solvent-free	rt	2.5	82

Reaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and 25 mol%. $[Et_3NH][HSO_4]$.
[a]Isolated yield.

effective, one-pot multi-component protocols for their synthesis under more efficient, environment friendly conditions using recyclable, ecofriendly catalysts is still a possibility to explore. Hence keeping in view the potential of MACs as an antitubercular agents and as part of our continuous efforts for the development of bioactive molecules[22] using highly efficient, safer as cost effective protocols,[23,24] we would like to report herein, synthesis and antimycobacterial evaluation of novel MACs by using $[Et_3NH][HSO_4]$ as a medium/catalyst *via* one-pot multicomponent approach.

Results and discussion

Chemistry

In a preliminary experimental investigation of the optimum reaction conditions regarding the solvent, amount of catalyst and temperature. For this, benzaldehyde **1a** (1 mmol), piperidone **2** (1 mmol) and 2-chloro-*N*-phenyl acetamide **3a** (1 mmol) were chosen as standard model substrates for the synthesis of representative compound **4a** *via* Clasien-Schmidt reaction-alkylation as shown in Scheme 1.

The model reaction was carried out with 25 mol% of $[Et_3NH][HSO_4]$ as a catalyst in different solvents (Table 1) at room temperature. In methanol (MeOH) and ethanol (EtOH), the reaction took a longer time (6 h) with a moderate yield of the products (Table 1, entries 1 and 2). In *N*,*N*-Dimethylformamide (DMF), a better yield of the product was obtained (Table 1, entry 3). Further, the reaction carried out in tetrahydrofuran (THF) and acetonitrile (CH_3CN), but again a lower yield of the product (Table 1, entries 4, 5) obtained In Toluene, a good yield of the product was obtained in 6 h (Table1, entry 6). However, when the model reaction was carried out under a solvent-free condition, there is a significant increase in the yield of the product in a shorter period (Table1, entry 7). Thus, solvent-free is the best condition for this Clasien-Schmidt reaction.

To optimize the concentration of catalyst, we further examined the influence of catalyst concentration on the reaction time and percentage yield. So, the model reaction was performed using different concentration of catalyst 5, 10, 15, 20, 25 and 30 mol% of $[Et_3NH][HSO_4]$ at room

Table 2. The effect of catalyst loading on model reaction **4a**.[a]

Entry	Catalyst (mol %)	Yield (%)[b]
1	5	40
2	10	59
3	15	69
4	20	73
5	25	82
6	30	82

[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and 25 mol%. $[Et_3NH][HSO_4]$.
[b]Isolated yield.

Table 3. Reusability of $[Et_3NH][HSO_4]$ in the synthesis of **4a**.[a]

Entry	Reaction cycle	Isolated yield (%)[b]
1	1st (fresh run)	82
2	2nd cycle	80
3	3rd cycle	78
4	4th cycle	78
5	5th cycle	74

[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol) and 25 mol%. $[Et_3NH][HSO_4]$,rt.
[b]Isolated yield of products.

temperature under solvent-free conditions and the product **4a** was obtained in 40, 59, 69, 73, 82 and 82% yields, respectively.

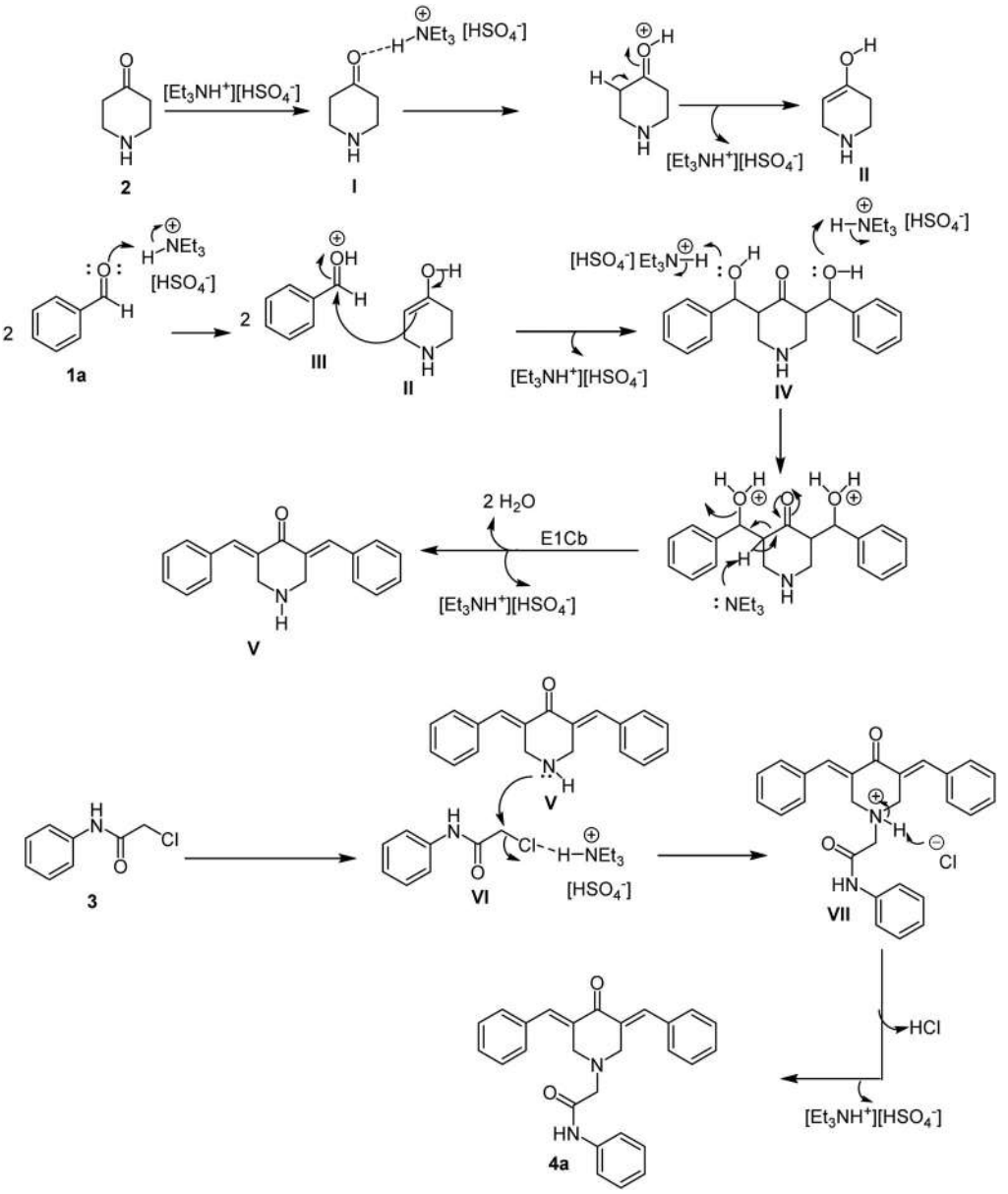
Further, the yield of the product did not improve as the concentration of catalyst increased (Table 2, entry 6). It was therefore concluded that the optimum concentration of catalyst was 25 mol % (Table 2, entry 5). Thus, it is concluded that 25 mol % of $[Et_3NH][HSO_4]$ is sufficient for the best result.

Further, the recyclability of the ionic liquid $[Et_3NH][HSO_4]$was then studied and the results are shown in Table 3. After completion of the reaction, the reaction mixture was poured on ice cold water and the product was extracted using ethyl acetate solvent. The filtrate was subjected for evaporation of water to get viscous liquid, which on cooling afforded ionic liquid. Further, the residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 °C and reused for subsequent reactions. It was then reused at least four consecutive cycles without much appreciable loss in its catalytic activity (Table 3, entries 1–5).

The formation of compound **4a** has been confirmed by IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral study. IR spectrum of **4a** displayed characteristic signals for C = O at 1707 and 1656 cm^{-1}. In the ^{1}H NMR spectrum of compound **4a**, a sharp singlet resonating at around δ 4.47 ppm for four protons, assigned to methylene groups of the piperidine ring. The peak observed at δ 4.12 ppm for the CH_2 group attached to the *N*-phenylacetamide. ^{13}C NMR spectrum was also in agreement with the proposed structure displaying characteristic signals for carbonyl at around δ 187.2 and 169.5 ppm. Similarly, signals resonating at around δ 57.5 and 50.5 have been assigned to methylene carbons of the piperidine and *N*-phenylacetamide ring. The HRMS spectral analysis of the **4a** was also conformity with the proposed structure. Similarly, the structure of other derivatives was confirmed by physical and spectral data (Supplementary information).

A plausible mechanistic pathway is proposed to illustrate the synthesis of monocarbonyl curcumin analogues catalyzed by $[Et_3NH][HSO_4]$ (Scheme 2).

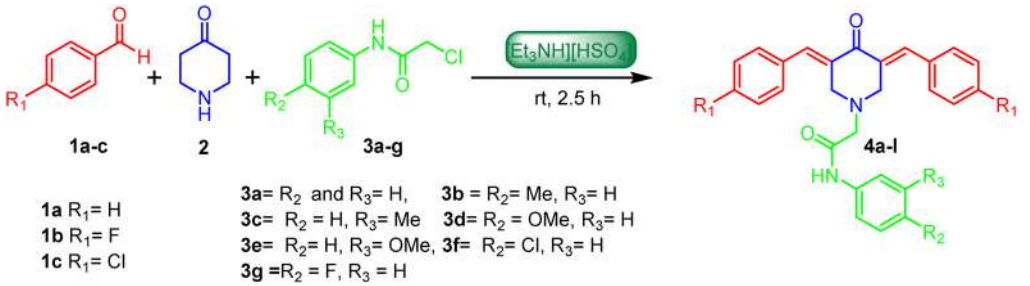
The initial step is believed to be the protonation of the carbonyl carbon of aldehyde **1a** by ionic liquid $[Et_3NH][HSO_4]$ to form intermediate **III** and enolate formation of piperidinone **II** which facilitates the nucleophilic attack of piperidinone to promote the formation of C-C bond to yield intermediate **IV**. The subsequent protonation and elimination of H_2O molecule *via* E_1CB



Scheme 2. Plausible mechanistic catalytic cycle for the synthesis of compound **4a**.

mechanism leads to the formation of intermediate **V**. Ionic liquid increases the electrophilicity of 2-chloro-*N*-phenylacetamide C-Cl carbon shown in structure **VI**. Then nucleophilic substitution of 2-chloro-*N*-phenylacetamide by compound **V** expedite the formation of C-N bond to yield compound **VII**. The final step involves deprotonation of intermediate **VII** leads to regeneration of ionic to yield compound **4a**.

So, having the optimized reaction conditions in hand, the scope and efficiency of this approach were explored for the synthesis of highly functionalized amide linked 3,5-bis (arylidene)-4-piperidones (Scheme 3) and the structures are given in Figure 2. The structures of all the synthesized conjugates were confirmed by their physical data and spectral analysis.



Scheme 3. Synthetic pathway for 3,5-bis (arylidene)-4-piperidones.

Biological activity

Antitubercular activity

In a standard primary screening, all the newly synthesized 3,5-bis (arylidene)-4-piperidones **4a-l** were evaluated for their *in vitro* antitubercular activity against *M. tuberculosis* $H_{37}Ra$ and

M. bovis BCG at concentrations of 30, 10 and 3 μg/mL using an established XTT Reduction Menadione assay (XRMA) method.[25] The drug rifampicin was used as reference.

In general, compounds which showed more than 90% inhibition (SI, Table S1, S2) at 30 μg/mL were confirmed by carrying out dose dependent effect using a range from 50 to 0.39 μg/mL to determine IC_{50} and MIC with serial dilution in DMSO (Table 4).

Among all the prepared xanthene conjugates, compounds **4f, 4h, 4i, 4j, 4k** and **4l** are found prominent antimycobacterial activities against *MTB* and *M. bovis BCG* strain with MIC values 1.89–26.37 and 2.69–29.14 µg/mL, respectively. However, rest of the xanthene conjugates **4a, 4b, 4c, 4d, 4e** and **4g** are inactive against *MTB* and *M. bovis BCG* strain with MIC = >30 µg/mL.

Cytotoxic activity

The most active conjugates **4f, 4h, 4i, 4j, 4k** and **4l** were further evaluated against human cancer cell lines (MCF-7, A549 and HCT 116) for toxicity and results are given in Table 5. The GI_{50}/GI_{90} (>250 µg/mL) values of all the compounds (except **4k**) indicate that the compounds are potent and specific inhibitors against *MTB*. The primary cytotoxic study information is given in supporting information (SI S3, S4 and S5).

Selectivity index (SI)

The selectivity index reflects the concentration of the compound at which it is active against *mycobacteria* but not toxic toward host cells. A higher selectivity index of compounds indicates that the can be used as a therapeutic agent. The compound **4f** (SI > 12) showed very high SI, which is actually good inhibitor of *MTB* and *M. bovis* BCG and the results are shown in Table 6.

Although the selectivity index of rifampicin is very high, it is important to consider the significance of this study with respect to the developing resistance among microorganisms against available antibiotics. According to a study of Hartkoorn et al.[26] on the drug susceptibility of TB, antimycobacterial activity was considered to be specific when the selectivity index was >10. In the current study compound **4f** exhibited highest selectivity index of >10, indicating their potential as an antitubercular agent and should be investigated further.

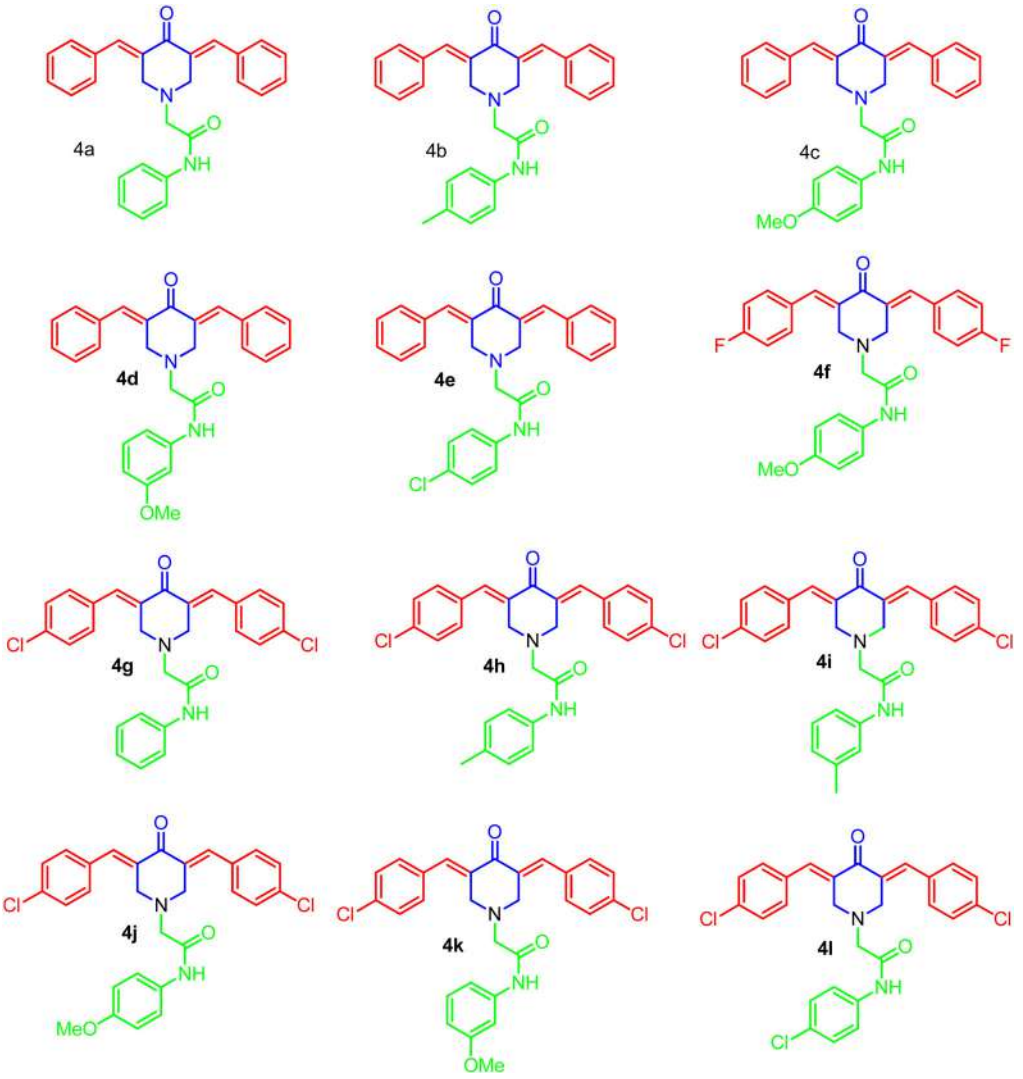


Figure 2. Structures of synthesized MACs.

Table 4. Antitubercular screening results of compounds **4a-l** (μg/mL)[a].

	MTB H37Ra		*M. bovis* BCG	
Compound	MIC	IC_{50}	MIC	IC_{50}
4a	>30	>30	>30	>30
4b	>30	>30	>30	>30
4c	>30	>30	>30	>30
4d	>30	>30	>30	>30
4e	>30	>30	>30	>30
4f	20.57	1.89	22.33	2.69
4g	>30	6.85	>30	7.33
4h	>30	>30	>30	>30
4i	>30	18.33	>30	6.94
4j	28.46	2.37	29.42	2.85
4k	>30	26.37	>30	29.14
4l	>30	27.64	>30	23.4
[b]Rifampicin	0.045	0.0017	0.017	0.0015

[a]MIC in μg/mL. Antitubercular activity of all agents was firm by serial dose dependent dilutions method.
[b]Standard antitubercular drug rifampicin as a positive control. Data were expressed as the means of triplication. SD (±): Standard Deviation.

Table 5. Cytotoxicity activity.

	MCF-7		A549		HCT-116	
Compound	GI_{50}	GI_{90}	GI_{50}	GI_{90}	GI_{50}	GI_{90}
4f	>250	>250	>250	>250	>250	>250
4h	>250	>250	>250	>250	>250	>250
4i	>250	>250	>250	>250	>250	>250
4j	>250	>250	>250	>250	>250	>250
4k	188.58	>250	225.51	>250	219.11	>250
4l	>250	>250	>250	>250	>250	>250
Rifampicin	>100	>100	>100	>100	>100	>100
Paclitaxel	0.0048	0.075	0.0035	0.0706	0.1279	5.715

The GI_{50} (cytotoxicity) values were calculated as the concentration of compounds resulting in 50% reduction of absorbance compared to untreated cells.

Table 6. SI of selected 3,5-*bis* (arylidene)-4-piperidones.

	MCF-7		A549		HCT 116	
Compound	*MTB*	BCG	*MTB*	BCG	*MTB*	BCG
4f	>12	>11	>12	>11	>12	>11
4h	>8	>8	>8	>8	>8	>8
4i	>8	>8	>8	>8	>8	>8
4j	>6	>6	>8	>8	>7	>7
4k	>9	>8	>9	>8	>9	>8
4l	>8	>8	>8	>8	>8	>8
Rifampicin	>133	>123	>133	>123	>133	>123

Table 7. Antibacterial activity of curcumin derivatives (MIC in μg/mL).

Compound	Gram-negative		Gram-positive	
	E. coli	*P. fluorescens*	*S. aureus*	*B. subtilis*
4f	>100	>100	>100	>100
4h	>100	>100	>100	>100
4i	18.54	20.99	20.61	22.48
4j	>100	>100	>100	>100
4k	>100	>100	>100	>100
4l	28.32	22.87	26.57	26.65
Ampicillin	1.46	4.36	1	10.32
Kanamycin	1.62	0.49	>30	1.35

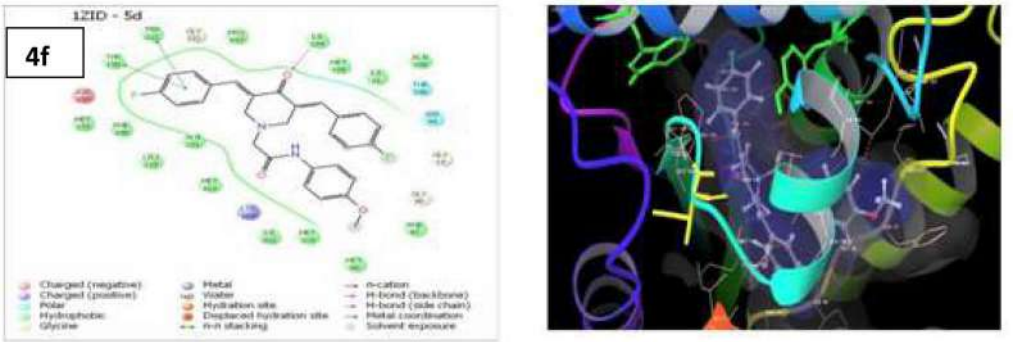
Antibacterial activity

For investigating the specificity of conjugates **4f, 4h, 4i, 4j, 4k** and **4l** were further screened for their anti-bacterial activity against four bacterial strains. All the compounds (except **4i** and **4l**) showed higher specificity toward *MTB*, because they display no anti-bacterial activity upto 100 μg/mL (Tables 6 and 7).

Computational study

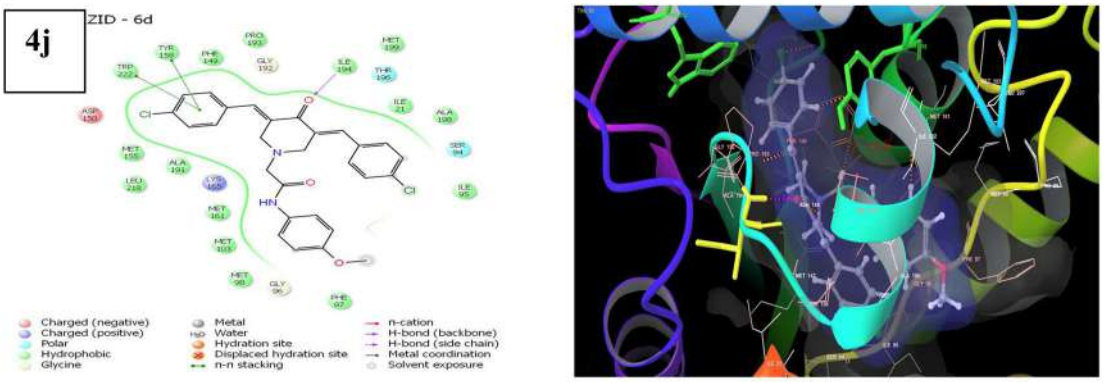
Molecular docking

Studies of whole genome sequence of *MTB* H37Ra showed the presence of genes which encodes the components of the FAS-II system along with enzyme enoyl-acyl carrier protein reductase (InhA) aids in elongation and synthesis of mycolic acids.[27] We have carried out the docking study of benzylidene-4-oxopiperidin-1-yl-*N*-phenylacetamide derivatives against mycobacterial enoyl-acyl carrier protein reductase (InhA) which could give the important leads for treatment of TB.



2D view of binding of compound **5d** 3D view of binding of compound **5d**

Figure 3. 2D and 3D view of binding of compound **4f** with the active site of InhA.



2D view of binding of compound **6d** 3D view of binding of compound **6d**

Figure 4. 2D and 3D view of binding of compound **4j** with the active site of InhA.

All the conjugates were successfully docked into the active site of mycobacterial InhA. The docking score of most active compounds **4f**, **4g** and **4j** were found to be −8.102, −7.960 and −7.816, respectively. The interactions of these molecules with the active site of mycobacterial InhA is shown in Figures 3–5, respectively. The lowest energy docking pose for **4f**, **4g** and **4j** revealed the presence of hydrogen bonding interactions between 4-oxo group of piperidine ring and Ile194 with a distance of 1.966 Å, 2.086 Å and 1.900 Å as observed in Figures 3–5, respectively. These firm hydrogen bonding interactions helps in 3D orientation of these ligands within the active site which increases the steric and electrostatic interactions of ligands with the amino acid residues present within the active site of mycobacterial InhA.

The per residue interaction analysis showed that several strong van der Waals and electrostatic interactions which played an important role for binding of benzylidene-4-oxopiperidin-1-yl-*N*-phenylacetamide derivatives with the active site of mycobacterial InhA. (Data represented in Table S6 in SI.) In addition, one of the 4-fluoro phenyl ring of compound **4f** and 4-chloro phenyl ring of compound **4g** and **4j** showed the two π-π stacking interactions with amino acid Tyr158 and Trp222 which were enclosed in the hydrophobic pocket of the active site of mycobacterial InhA formed by the amino acids Pro193, Trp222, Met155 and Phe149 as observed in Figures 3–5.

Further, the other 4-fluoro phenyl ring of compound **4f** and 4-chloro phenyl ring of compound **4g** and **4j** fits into the hydrophobic pocket formed by the amino acid residues Ile21,

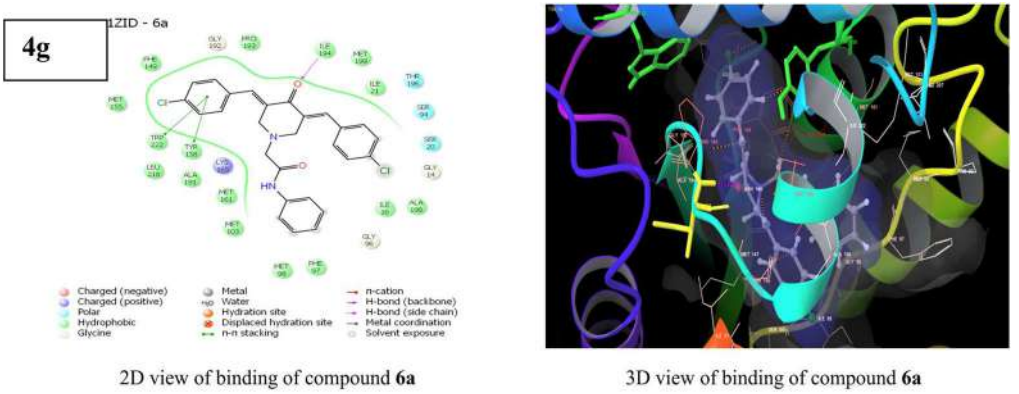


Figure 5. 2D and 3D view of binding of compound **4g** with the active site of InhA.

Ala198, Ile95 and Ile16 present within the active site of mycobacterial InhA. Also, the phenyl ring attached to acetamide group is embedded in the hydrophobic pocket formed by theMet103, Mett98 and Phe97 amino acid residues present within the active site of mycobacterial InhA. Therefore, from the docking studies, it is clear that these compounds have significant binding with the active site of mycobacterial InhA. The hydrophobic substituents on aromatic rings attached to piperidin-4-one ring are necessary for firm binding through π-π stacking interactions with the active site of mycobacterial InhA. The –C = O group attached to the piperidine is essential for firm binding with the active site through strong hydrogen bonding interactions with the Ile194 amino acid residue present within the active site of mycobacterial InhA. Also, the phenyl ring attached to the acetamide group is essential for binding since it perfectly fits into hydrophobic pocket formed by the amino acid residues of active site which helps in the firm binding of these compounds with the active site of mycobacterial InhA. Hence, the mode of action of antitubercular activity for these compounds might be through the inhibition of active site of mycobacterial InhA.

Conclusions

In conclusion, a novel, highly efficient, one-pot multi-component protocol has been developed for the synthesis of 3,5-bis (arylidene)-4-piperidones in excellent yields using $[Et_3NH][HSO_4]$ as a catalyst at room temperature in a short reaction time. These analogues were evaluated for the first time for antitubercular activity against the *MTB* H37Ra and *M. Bovis* BCG strains. However, the compounds **4f**, **4g** and **4j** exhibited IC_{50} values of 1.89, 6.85 and 2.37 µg/ml against *MTB* H37Ra, respectively. Compounds **4f**, **4g, 4i** and **4j** showing excellent antitubercular activity against *M. Bovis* BCG strain with IC_{50} values of 2.69, 7.33, 6.94 and 2.85 µg/mL, respectively. From the docking studies, the most active conjugates **4f**, **4g** and **4j** showed hydrogen binding with the amino acid residue Ile194 and two π-π stacking hydrophobic interactions with the amino acid residue Tyr158 and Trp222 present in the active site of *MTB* InhA. Furthermore, evaluation of the data on the cytotoxicity, antimicrobial activity and docking studies shows that the conjugates **4f**, **4g, 4i** and **4j** are highly selective toward the *MTB* H37Raand *M. Bovis* BCG strain.

Experimental section

Materials and methods

All chemicals and reagents were procured from Sigma Aldrich, S.D. Fine chemical and commercial suppliers and used without further purification. The completion of the reactions was

monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel 60 F_{254}, 0.25 mm thickness (Merck). The detection of the components was made by exposure to iodine vapors or UV light. Melting points were determined by open capillary methods and are uncorrected. The products were characterized using ^{1}H NMR, ^{13}C NMR spectra and HRMS. The NMR spectra of the product were obtained using a Bruker AC-400MHz spectrometer with TMS as the internal standard. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) mass spectrometer.

Experimental procedure for the synthesis of $[Et_3NH][HSO_4]$

The synthesis of ionic liquid was carried out in a 100 mL round-bottom flask, which was immersed in a recirculating heated water-bath and fitted with a reflux condenser. Sulfuric acid (98%) (1.96 g, 0.02 mol) was added drop wise from triethylamine (2.02 g, 0.02 mol) stirring at 60 °C for 1 h. After the addition, the reaction mixture was stirred for an additional period of 1 h at 70 °C to ensure the reaction had proceeded to completion. The traces of water were removed by heating the residue at 80 °C in high vacuum until the weight of the residue remains constant.

Triethylammonium hydrogen sulfate $[Et_3NH][HSO_4]$

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm = 1.16–1.23 (t, 9H, 3 × CH_3), 3.04–3.15 (q, 6H, 3 × CH_2) and 8.85 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 11.03 (CH_3) and 52.6 (CH_2); FT-IR cm^{-1} 3024 (for N-H stretch), 2815.74 (for C-H stretch), 1231.96 (for C-N stretch).

General procedure for one-pot synthesis of 2-((3E,5E)-3,5-dibenzylidene-4-oxopiperidin-1-yl)-N-phenylacetamide (4a-l)

A mixture of the substituted aldehyde (**1a-c**) (1 mmol), piperidinone (**2**) (1 mmol) and various 2-chloro-*N*-phenyl acetamides (**3a-g**) (1 mmol) in 25 mol% $[Et_3NH][HSO_4]$ catalyst was stirred at room temperature for 2.5 h. The progress of the reaction was monitored by TLC. After the completion of reaction confirmed by the TLC using *n*-hexane: ethyl acetate (8:2) as solvent system. After completion of the reaction, the reaction mixture was poured on ice cold water and the product was extracted using ethyl acetate solvent. The organic layer evaporated under vacuum on rotavapor to get crude solid which further crystallized from ethanol to obtain a pure solid product (**4a-l**). The aqueous filtrate was subjected for evaporation of water to get viscous liquid, which on cooling afforded ionic liquid. Further, the residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 °C and reused for subsequent reactions. It was then reused at least four consecutive cycles without much appreciable loss in its catalytic activity.

2-((3E,5E)-3,5-Dibenzylidene-4-oxopiperidin-1-yl)-N-phenylacetamide (**4a**): The compound **4a** was obtained from **1a**, **2** and **3a** as yellow solid; Yield: 82%; Mp: 182–184 °C; IR (cm^{-1}): 3030, 2985, 1707, 1656, 1591, 1555 and 1493; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 9.76 (s, 1H, NH), 7.83 (s, 2H, -C = H), 7.67–7.65 (m, 4H, Ar-H), 7.59–7.30 (m, 10H, Ar-H), 4.47 (s, 4H, -CH_2) and 4.12 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 187.2, 169.5, 145.8, 137.0, 136.6, 132.3, 131.5, 131.0, 130.9, 127.5, 126.7, 125.0, 123.3, 121.9, 119.7, 57.5 and 50.5; HRMS (ESI-qTOF): Calcd for $C_{27}H_{25}N_2O_2$ $[M + H]^+$, 409.2838, found: 409.2842.

2-((3E,5E)-3,5-Dibenzylidene-4-oxopiperidin-1-yl)-N-(p-tolyl)acetamide (**4b**): The compound **4b** was obtained from **1a**, **2** and **3b** as pale yellow solid; Yield: 75%; Mp: 205–207 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.75 (s, 2H, -C = H), 7.59–7.48 (m, 10H, Ar-H), 7.46–7.29 (m, 4H, Ar-H), 4.48 (s, 4H, -CH_2), 4.11 (s, 2H, -CH_2) and 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 183.8, 162.2, 142.2, 134.9, 131.7, 129.9, 129.8, 128.3, 124.2, 123.1, 115.2, 115.0, 114.6, 55.2, 51.3 and 21.1.

2-((3E,5E)-3,5-Dibenzylidene-4-oxopiperidin-1-yl)-N-(4-methoxyphenyl) acetamide (**4c**): The compound **4c** was obtained from **1a**, **2** and **3c** as yellow solid; Yield: 76%; Mp: 181–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.69 (s, 2H, -C = H), 7.54–7.36 (m, 12H, Ar-H), 7.04–703 (m, 2H, Ar-H), 4.57 (s, 4H, -CH_2), 4.37 (s, 2H, -CH_2) and 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 184.9, 155.7, 136.5, 135.2, 132.2, 128.6, 125.6, 125.5, 123.5, 121.8, 121.3, 119.7, 119.1, 111.1, 57.3, 54.5 and 49.9; HRMS (ESI-qTOF): Calcd for $C_{28}H_{27}N_2O_3$ $[M + H]^+$, 439.1555, found: 439.1586.

2-((3E,5E)-3,5-Dibenzylidene-4-oxopiperidin-1-yl)-N-(3-methoxyphenyl) acetamide (**4d**): The compound **4d** was obtained from **1a**, **2** and **3d** as yellow solid; Yield: 71%;Mp: 198–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.84 (s, 2H, -C = H), 7.56–7.08 (m, 11H, Ar-H), 7.02–6.73 (m, 3H, Ar-H), 4.79 (s, 4H, -CH_2), 4.46 (s, 2H, -CH_2) and 3.89 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 185.1, 160.0, 140.3, 137.8, 135.3, 131.5, 129.4, 129.1, 127.8, 127.5, 127.1, 126.2, 124.3, 123.4, 122.6, 119.9, 56.4, 53.7 and 49.2.

N-(4-Chlorophenyl)-2-((3E,5E)-3,5-dibenzylidene-4-oxopiperidin-1-yl) acetamide (**4e**): The compound **4e** was obtained from **1a**, **2** and **3f** as pale yellow solid; Yield: 76%; Mp: 207–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.77 (s, 2H, -C = H), 7.61–7.46 (m, 12H, Ar-H), 7.38–7.36 (m, 2H, Ar-H), 4.53 (s, 4H, -CH_2) and 4.16 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 184.3, 168.1, 141.1, 136.7, 132.5, 131.6, 130.9, 137.3, 126.7, 126.3, 122.6, 122.3, 122.0, 121.8, 119.5, 55.3 and 49.6; HRMS (ESI-qTOF): Calcd for $C_{27}H_{24}ClN_2O_2$ $[M + H]^+$, 443.2032, found: 443.2005

2-((3E,5E)-3,5-Bis(4-fluorobenzylidene)-4-oxopiperidin-1-yl)-N-(4-methoxyphenyl)acetamide (**4f**): The compound **4f** was obtained from **1b**, **2** and **3f** as yellow solid; Yield: 78%; Mp: 232–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.83 (s, 2H, -C = H), 7.60–7.58 (m, 4H, Ar-H), 7.39–7.04 (m, 8H, Ar-H), 4.59 (s, 4H, -CH_2), 4.03 (s, 2H, -CH_2) and 3.91 (s, 3H, OCH_3); ^{13}C NMR (101 MHz, DMSO) δ 183.9, 163.4, 162.1, 160.4, 136.1, 132.4, 130.9, 129.5, 127.5, 125.5, 122.1, 115.83, 57.3, 52.78, 46.58; HRMS (ESI-qTOF): Calcd for $C_{28}H_{25}F_2N_2O_3$ $[M + H]^+$, 475.2342, found: 475.2364

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-phenylacetamide (**4g**): The compound **4g** was obtained from **1c**, **2** and **3g** as pale yellow solid; Yield: 80%; Mp: 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.79 (s, 2H, -C = H), 7.53–7.46 (m, 4H, Ar-H), 7.44–7.16 (m, 9H, Ar-H), 4.40 (s, 4H, -CH_2) and 4.08 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 184.1, 166.7, 160.8, 148.8, 148.2, 142.2, 138.7, 129.9, 129.8, 128.6, 128.4, 124.2, 123.1, 115.2, 115.0, 114.0, 57.4 and 51.5; ESI-MS: Calcd for $C_{27}H_{23}Cl_2N_2O_2$ $[M + H]^+$, 478.1, found: 478.0.

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-(p-tolyl)acetamide (**4h**): The compound **4h** was obtained from **1c**, **2** and **3b** as pale yellow solid; Yield: 82%; Mp: 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.77 (s, 2H, -C = H), 7.49–7.43 (m, 8H, Ar-H), 7.30–7.25 (m, 4H, Ar-H), 4.50 (s, 4H, -CH_2), 3.98 (s, 2H, -CH_2) and 2.37 (s, 3H, CH_3); 184.4, 143.1, 139.5, 135.1, 134.5, 133.5, 130.5, 129.7, 128.4, 125.3, 124.4, 115.3, 57.3, 49.6 and 21.5; ESI-MS: Calcd for $C_{28}H_{25}Cl_2N_2O_2$ $[M + H]^+$, 492.2, found: 492.0.

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-(m-tolyl)acetamide (**4i**): The compound **4i** was obtained from **1c**, **2** and **3c** as pale yellow solid; Yield: 75%; Mp: 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.81 (s, 2H, -C = H), 7.47–7.43 (m, 8H, Ar-H), 7.30–7.02 (m, 4H, Ar-H), 4.48 (s, 4H, -CH_2), 3.90 (s, 2H, -CH_2) and 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 185.8, 167.8, 144.8, 143.6, 139.5, 134.1, 129.3, 120.3, 119.2, 57.9, 55.8 and 21.2; ESI-MS: Calcd for $C_{28}H_{25}Cl_2N_2O_2$ $[M + H]^+$, 492.4, found: 492.0.

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-(4-methoxyphenyl)acetamide (**4j**): The compound **4j** was obtained from **1c**, **2** and **3d** as yellow solid; Yield: 74%; Mp: 217–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.78 (s, 2H, -C = H), 7.49–7.43 (m, 10H, Ar-H), 7.00–6.99 (m, 2H, Ar-H), 4.48 (s, 4H, -CH_2), 3.96 (s, 2H, -CH_2) and 3.86 (s, 3H, OCH_3); ^{13}C

NMR (100 MHz, DMSO-d_6, δppm): 186.4, 161.3, 137.6, 136.7, 132.7, 129.0, 126.2, 126.1, 124.9, 124.8, 124.0, 122.4, 121.7, 120.1, 56.8, 52.7 and 47.4; HRMS (ESI-qTOF): Calcd for $C_{28}H_{25}Cl_2N_2O_3$ $[M+H]^+$, 508.2652, found: 508.2629

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-(3-methoxyphenyl)acetamide (**4k**): The compound **4k** was obtained from **1c**, **2** and **3e** as yellow solid; Yield: 76%; Mp: 221–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 7.95 (s, 2H, -C = H), 7.65–7.53 (m, 9H, Ar-H), 7.11–6.85 (m, 3H, Ar-H), 4.53 (s, 4H, -CH_2), 3.93 (s, 2H, -CH_2) and 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 185.1, 161.7, 136.5, 134.6, 129.7, 129.3, 126.3, 126.0, 125.6, 125.3, 122.9, 122.5, 122.0, 121.2, 120.4, 120.2, 119.8, 119.3, 56.1, 52.4 and 49.0.

2-((3E,5E)-3,5-Bis(4-chlorobenzylidene)-4-oxopiperidin-1-yl)-N-(4-chlorophenyl)acetamide (**4l**): The compound **4l** was obtained from **1c**, **2** and **3f** as yellow solid; Yield: 78%; Mp: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 8.05 (s, 2H, -C = H), 7.84–7.80 (m, 9H, Ar-H), 7.76–7.64 (m, 3H, Ar-H), 4.52 (s, 4H, -CH_2) and 4.26 (s, 2H, -CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δppm): 187.0, 168.9, 146.0, 144.8, 137.7, 136.7, 135.3, 130.4, 129.8, 132.4, 59.1 and 57.0; HRMS (ESI-qTOF): Calcd for $C_{27}H_{22}Cl_3N_2O_2$ $[M+H]^+$, 512.4762, found: 512.4727.

Biological assay

Antitubercular activity

All the chemicals such as sodium salt XTT, DMSO, sulfanilic acid, sodium nitrate, NEED and rifampicin were purchased from Sigma-Aldrich, USA. Dubos medium was purchased from DIFCO, USA. Compounds were dissolved in DMSO and used as stock solution for further antimycobacterial testing. Microbial strains such as Mycobacterium bovis BCG (ATCC 35734) and Mycobacterium tuberculosis H_{37}Ra (ATCC 25177) were obtained from AstraZeneca, India. The stock culture was maintained at −80 °C and sub cultured once in a liquid medium before inoculation into an experimental culture. Cultures were grown in Dubos media (enrichment media). Mycobacterium pheli medium (minimal essential medium) was used for antimycobacterial assay. It contains 0.5 g KH_2PO_4, 0.25 g trisodium citrate, 60 mg $MgSO_4$, 0.5 g aspargine and 2 mL glycerol in distilled water (100 mL) followed by pH adjustment to 6.6. All the newly synthesized compounds were screened *in vitro* against two Mycobacterium species such as Mycobacterium tuberculosis H_{37}Ra and Mycobacterium bovis BCG. Both species of Mycobacterium were grown in Mycobacterium pheli medium. Screening of Mycobacterium tuberculosis H_{37}Ra was done by using XTT reduction menadione assay (XRMA) and Mycobacterium Bovis BCG screening was done by using NR (Nitrate reductase) assay, both of them were developed earlier in our lab.[25] Briefly, 2.5 μl of these inhibitor solutions were added in a total volume of 250 μl of Mycobacterium pheli medium consisting of bacilli. The incubation was terminated on the 8th day for Active and 12 days for Dormant MTB culture. The XRMA and NR was then carried out to estimate viable cells present in different wells of the assay plate. The optical density was read on a micro plate reader (Spectramax plus384 plate reader, Molecular Devices Inc) at 470 nm filter for XTT and at 540 nm filter for NR against a blank prepared from cell-free wells. Absorbance given by cells treated with the vehicle alone was taken as 100% cell growth. Primary screening was done at 30, 10 and 3 μg/ml. Compounds showing 90% inhibition of bacilli, at or lower than 30 μg/mL were selected for further dose response curve. All experiments were performed in triplicates and the quantitative value was expressed as the average ± standard deviation. MIC and IC_{50} values of selected compound were calculated from their dose response curves by using Origin 6 software. % Inhibition was calculated by using following formula: % Inhibition = [(absorbance of compound − absorbance of Test)/(absorbance of Control − absorbance of Blank)] × 100, where control is the medium with bacilli along with vehicle and blank is cell free medium.

Cytotoxicity activity

Three human cancer cell lines, HeLa (human cervical cancer cell line), A549 (human lung adenocarcinoma cell line) and PANC-1 (human pancreas carcinoma cell line) were used to check the cytotoxicity of compounds. The cell lines were obtained from the American Type Culture Collection (ATCC) and maintained in T 25 flasks with 10% (v/v) fetal bovine serum (FBS) containing Dulbecco's Modified Eagle Medium (DMEM). Cell line containing T 25 flasks were maintained at 37 °C under 5% CO_2 and 95% air in a humidified atmosphere. Medium were replaced twice a week. All the compounds were tested for their cytotoxicity against HeLa, A549 and PANC-1 cell line by using modified MTT assay.[28] Briefly, cells were seeded as, 1.5×10^4 cells/ml for HeLa, 1×10^4-cells/well for A549 and PANC-1 in a 96 well plate. The plates were incubated for 24 h into CO_2 incubator (37 °C under 5% CO_2 and 95% air in a humidified atmosphere) to adhere the cells. After incubation, compound was added in such a way that final concentration becomes 30, 10, and 3 µg/ml in the test well. Concentrations ranges of compound were selected as 30, 10 and 3 µg/ml of each. Again, plates were incubated for additional 72 h for HeLa and 48 h for A549 and PANC-1 to see the effect of compound on cells. After that, cell medium was replaced with 100 µl of Glucose-MTT (0.5 mg/ml)-PBS medium and kept the plate for 2–4 h to form the reduced MTT or Formazan crystals. This reduced MTT or Formazan crystals were solubilized by addition of acidified isopropanol. The optical density was read on a micro plate reader (Spectramax plus 384 plate reader, Molecular Devices Inc) at 470 nm filter against a blank prepared from cell-free wells. Absorbance given by cells treated with the vehicle alone was taken as 100% cell growth. All the experiments were performed in triplicates and the quantitative value was expressed as the average ± standard deviation. GI_{50} and MIC values were calculated by plotting the graphs, by using Origin Pro software. The viability and growth in the presence of test material is calculated by using the following formula: % cytotoxicity = [(average absorbance of control-absorbance of compound)/(absorbance of control-absorbance of blank)] × 100, where control is the culture medium with cells and DMSO and blank is the culture medium without cells.

Selectivity index

The selectivity index (SI) was calculated by dividing the 50% growth inhibition concentration (GI_{50}) for cell lines (HeLa, A549 and PANC-1) by the MIC for *in vitro* activity against active/dormant MTB and BCG.[29]

Anti-bacterial activity

All bacterial cultures were first grown in LB media at 37 °C at 180 RPM. Once the culture reaches 1 O.D, it is used for antibacterial assay. Bacterial strains *E. coli* (NCIM 2688), *P. fluorescens* (NCIM 2036) as Gram-negative and *B. subtilis* (NCIM 2079), *S. aureus* (NCIM 2010) as Gram-positive were obtained from NCIM (NCL, Pune) and were grown in Luria Burtony medium from Himedia, India. The assay was performed in 96 well plates after 8 and 12 h. for Gram-negative and Gram-positive bacteria, respectively. 0.1% of 1 OD culture at 620 nm was used for screening.[30] 0.1% inoculated culture was added in to each well of 96 well plate containing the compounds to be tested. Optical density for each plate was measured at 620 nm after 8 h for Gram negative bacteria and after 12 h for Gram-positive bacteria.

Computational study

Molecular docking study

To understand mode of action for antitubercular activity of the synthesized benzylidene-4-oxopiperidin-1-yl-*N*-phenylacetamide derivatives, molecular modeling and docking studies were

performed. Glide 5.8[31] was used to perform docking studies using crystal structure of mycobacterium tuberculosis enoyl-acyl carrier protein reductase (InhA) (PDB id:1ZID).

The structures of the compounds were drawn using 2D-sketcher present in Maestro 9.3[32] and were converted from 2D into 3D representations and saved in maestro format. For further computational studies, compounds were prepared using LigPrep 2.5[33] which gives the low-energy conformers, 3D structures with correct chiralities for each successfully processed input structure. The protein was purified using the protein preparation wizard present in Maestro 9.3. All the water molecules were deleted. Bond order was assigned and H-atoms were added to the protein, including the protons necessary to define the correct ionization and tautomeric states of the amino acid residues. Missing residues of the side chain were added using Prime 3.1.[34] Protein refinement was done in two steps. Initially, orientation of polar hydrogens, flip terminal amides and histidines was optimized and the protonation states were adjusted. Further, steric clashes potentially existing in the protein were relaxed using the OPLS-2005 force field present in the impact refinement module. Minimization was terminated when the energy converged or the root mean square deviation reached a maximum cut off of 0.30 Å.[35] To predict the active site of the receptor, a grid was generated using grid generation panel of glide with the default settings. Grid is generated to define the binding site of co crystallized ligand in the receptor. The ligand was selected to define the position of active site and size of the enclosing box was set to 20 Å to include the significant part of 1ZID.

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Disclosure statement

There are no conflicts of interest.

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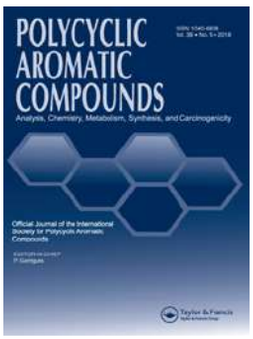

Polycyclic Aromatic Compounds

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Design, Synthesis and Biological Evaluation of Novel Furan & Thiophene Containing Pyrazolyl Pyrazolines as Antimalarial Agents

Hemantkumar N. Akolkar[a], Sujata G. Dengale[b], Keshav K. Deshmukh[b], Bhausaheb K. Karale[a], Nirmala R. Darekar[a], Vijay M. Khedkar[c], and Mubarak H. Shaikh[a]

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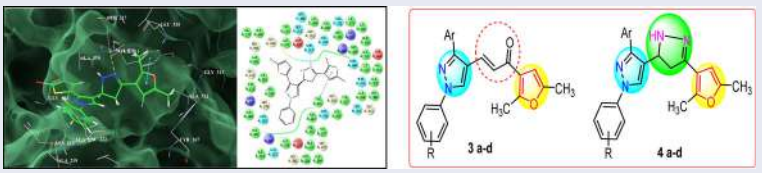
ABSTRACT

In search for novel compounds targeting Malaria, based on the *in silico* molecular docking binding affinity data, the novel furans containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized. The formation of the synthesized compound were confirmed by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Compounds with thiophene and pyrazoline ring **4b** (0.47 μM), **4c** (0.47 μM) and **4d** (0.21 μM) exhibited excellent anti-malarial activity against *Plasmodium falciparum* compared with standard antimalarial drug Quinine (0.83 μM). To check the selectivity furthermore, compounds were tested for antimicrobial activity and none of the synthesized compound exhibited significant potency compared with the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin respectively. So, it can be resolved that the produced compounds show selectively toward antimalarial activity and have the potential to be explored further.



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Introduction

Life-threatening disease Malaria is caused by *Plasmodium* parasites that are spread to people through the bites of infected female Anopheles mosquitoes. Out of five *Plasmodium* Parasites *Plasmodium falciparum* produces high levels of blood-stage parasites that sequester in critical organs in all age groups.[1] As per the World Health Organization report in 2018, in sub Saharan Africa 11 million pregnant women were infected with malaria and 872 000 children were born with a low birth weight. Around 24 million children estimated to be infected with the *P. falciparum* parasite in the region; out of these, 1.8 million had severe anemia and 12 million had

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moderate anemia.[2] Mortality and morbidity caused by malaria are continually increasing. This subject is the consequence of the ever-increasing development of parasite resistance to drugs and also increased mosquito resistance to insecticides which is one of the most critical complications in controlling malaria over recent years.[3]

P. falciparum enoyl-acyl carrier protein (ACP) reductase (ENR) is an enzyme in type II fatty acid synthesis (FAS II) pathway which catalyzes the NADH-dependent reduction of trans-2-enoyl-ACP to acyl-ACP and plays important role in completion of the fatty acid elongation cycles. Due to its role in the parasite's fatty acid pathway, *Pf*ENR has been known as one of the most promising antimalarial targets for structure-based drug design.[4–6] Triclosan, a broadly used antibiotic, is effective inhibitor of *Pf*ENR enzyme activity. Several efforts have been taken in the recent past in the direction of the identification of new antimalarials using pharmacophore modeling, molecular docking and MD simulations.[7–12]

Pyrazole is a well-known class of nitrogen containing heterocyclic compounds and play important role in agricultural and medicinal field. Pyrazole and its derivatives are known to possess antibacterial,[13] antipyretic,[14] fungistatic,[15] anticonvulsant,[16] antitubercular,[17] antipyretic,[18] insecticides,[19] and anti-inflammatory[20] activities. Pyrazoline containing compounds are recognized to possess various pharmacological activities like antimalarial,[21,22] anticancer,[23] anti-inflammatory,[24] analgesic,[24] antitumor,[25] antimicrobial[26] and antidepressant activities.[27] Furan containing compounds possess lipoxygenase inhibitor,[28] urotensin-II receptor antagonists,[29] fungicidal,[30] epidermal growth factor receptor inhibitors and anticancer[31] etc. activities. Chalcone is a natural pigment found in plant and is an important intermediate for the synthesis of flavonoids. Varieties of biological activities are associated with chalcones and their derivatives such as antiplasmodial,[32] nematicide,[33] antiallergenic,[34] antimalarial,[35] anti-HIV,[36] anti-cancer,[37] anti-inflammatory[38] and anti-tuberculosis.[39]

So, considering the biological importance of pyrazoles, furan and chalcone, herein we report the design of a small library of furan containing pyrazolyl pyrazoline derivatives by molecular hybridization approach targeting *Pf*ENR using the *in silico* molecular docking technique. The promising results obtained from this *in silico* study served the basis for the synthesis of these molecules followed by evaluation of their antimalarial potential.

Molecular docking technique plays significant role in lead identification/optimization and in the mechanistic study by predicting the binding affinity and the thermodynamic interactions leading the binding of a ligand to its biological receptor. Thus, with the objective to identify novel leads targeting the crucial antimalarial target *Plasmodium falciparum enoyl-ACP reductase* (*Pf*ENR or FabI) (pdb code: 1NHG), molecular docking was carried out using the GLIDE (Grid-based LIgand Docking with Energetics) program of the Schrodinger Molecular modeling package.[40–42] A small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-3d**, **4a-4d**) was docked against *Pf*ENR. The ensuing docking conformation revealed that these molecules changed a binding mode which is corresponding with the active site of pfENR and were found to be involved in a series of bonded and non-bonded interactions with the residues lining the active site. Their docking scores varied from −6.979 to −8.222 with an average docking score of −7.563 signifying a potent binding affinity to *Pf*ENR. In order to get a quantitative insight into the most significantly interacting residues and their associated thermodynamic interactions, a detailed per-residue interaction analysis was carried out (Table S1, Supporting Information). This analysis showed that the furan containing pyrazolyl chalcones (**3a-d**) (Figure 1) were deeply embedded into the active site of *Pf*ENR engaging in a sequence of favorable *van der Waals* interactions observed with Ile:C369, Phe:C368, IleA323, Ala:A320, Ala:A319, Arg:A318, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Met:A281, Tyr:A277, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110 and Asp:A107 residues through the 1,3-substituted-1*H*-pyrazol-4-yl scaffold while the 1-(2,5-Dimethylfuran-3-yl) prop-2-en-1-one

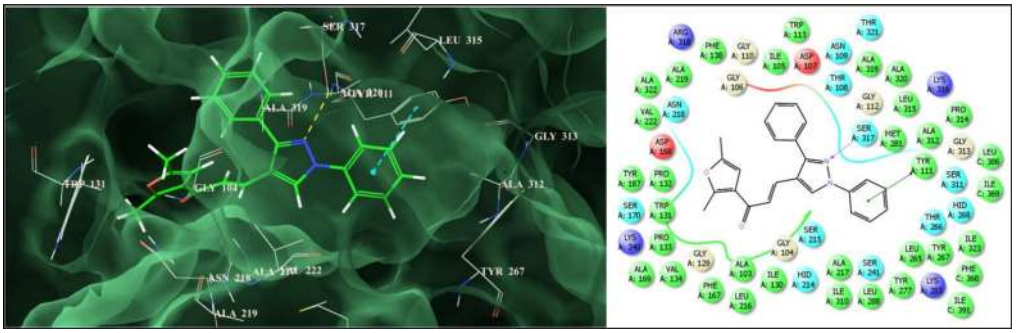


Figure 1. Binding mode of **3a** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

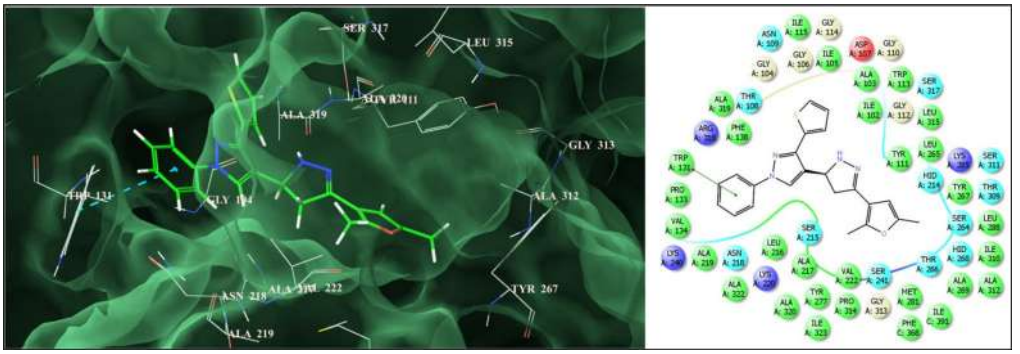
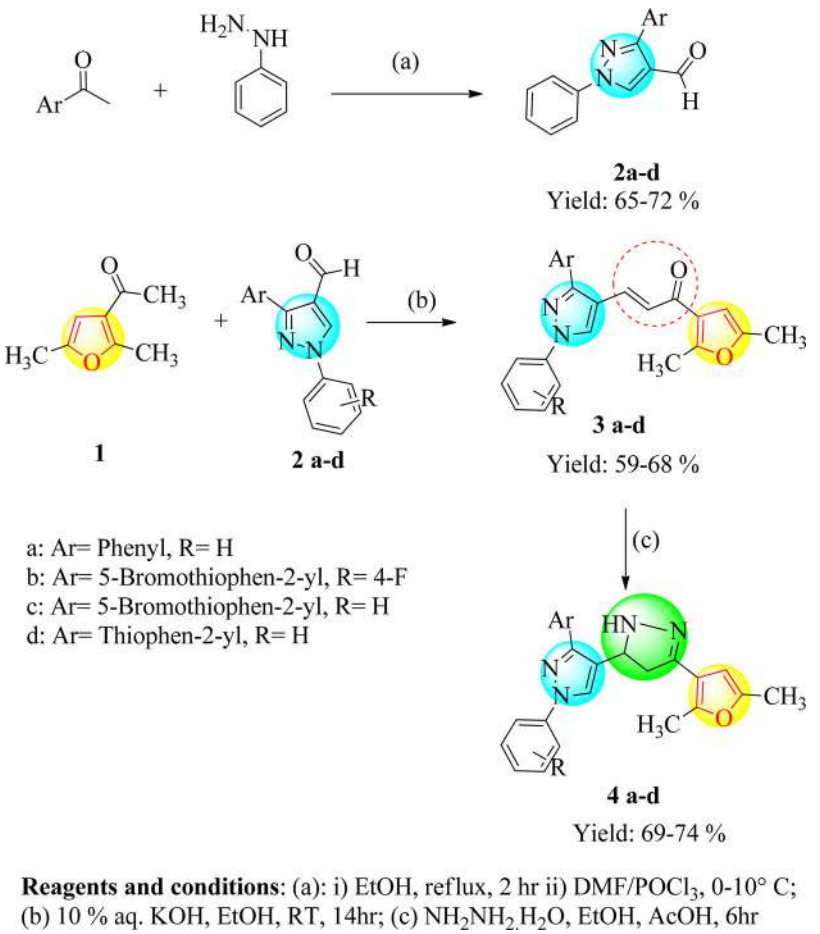


Figure 2. Binding mode of **4d** into the active site of *Plasmodium falciparum enoyl-ACP reductase* (on right side: pink lines represent the hydrogen bond while green lines signify π-π stacking interactions).

component of the molecules was seen to be involved in similar interactions with Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Gly:A106, Ile:A105, Gly:A104 residues of the active site.

Furthermore the enhanced binding affinity of these molecule is also attributed to significant electrostatic interactions observed with Arg:A318, Ser:A317, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107, Gly:A104 residues lining the active site. On the other hand, the furan containing pyrazoline derivatives (**4a-d**) (Figure 2) were also seen to be stabilized into the active of *Pf*ENR through a network of significant *van der Waals* interactions observed with (2,5-dimethylfuran-3-yl)-1*H*-pyrazolyl scaffold *via* Ile:C369, Phe:C368, Ala:A320, Ser:A317, Leu:A315, Pro:A314, Gly:A313, Ala:A312, Lys:A285, Tyr:A267, Thr:A266, Leu:A265, Gly:A112, Tyr:A111, Gly:A110, Gly:A106 and Ile:A105 while other half of the molecule i.e., 2-thiophenyl-1-phenyl-1*H*-pyrazole showed similar type of interactions with IleA323, Ala:A319, Arg:A318, Met:A281, Tyr:A277, Val:A222, Ala:A219, Asn:A218, Ala:A217, Leu:A216, Ser:A215, Trp:A131, Ile:A130, Trp:A113, Asp:A107, Gly:A104 residues.

Further the enhanced binding affinity of the molecules is also attributed to favorable electrostatic interactions observed with Arg:A318, Ser:A317, Glu:A289, Lys:A285, Asp:A236, Asn:A218, Ala:A217, Ser:A215, Tyr:A111, Gly:A110, Asp:A107 and Gly:A104. While these non-bonded interactions (*van der Waals* and electrostatic) were observed to be the major driving force for the mechanical interlocking of these novel furan containing pyrazolyl pyrazoline derivatives into the active site *Pf*ENR, the enhanced binding affinity of these molecules is also contributed by very prominent hydrogen bonding interaction observed for **3a** (Ser:A317(2.708 Å)), **4a** (Ser:A317(2.783 Å)), **4b** (Ser:A317(2.462 Å)) and **4c** (SerA317(2.462 Å)). Furthermore these



Scheme 1. Synthesis of pyrazolyl chalcones (**3a-d**) and pyrazolyl pyrazolines (**4a-d**).

molecules were also engaged in a very close π-π stacking interactions: **3a**: Tyr: A111(2.669 Å), **3b**: Tyr:A267(2.529 Å), **3c**: Tyr:A267(2.541 Å), **3d**: Tyr:A267(2.335 Å), **4a**: Tyr:A111(2.602 Å), **4b**: Trp:A131(2.073 Å), **4c**: TyrA:111(2.073 Å) and **4d**: TrpA131(2.538 Å) (Figures S1–S6, Supporting Information).

This type of bonded interactions i.e., hydrogen bonding and π-π stacking are known to serve as an "anchor" to guide the alignment of a molecule into the 3D space of enzyme's active site and facilitate the non-bonded interactions (*Van der Waals* and electrostatic) as well. Overall, the in-silico binding affinity data suggested that these furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) could be developed as novel scaffold to arrive at compounds with high selectivity and potency *Plasmodium falciparum*.

Results and discussion

Chemistry

The novel series of furan containing pyrazolyl chalcones (**3a-d**) and pyrazoline derivatives (**4a-d**) were synthesized from commercially available starting materials (Scheme 1). Initially, pyrazole aldehyde **2a-d** was formed by the condensation between substituted acetophenone and phenyl

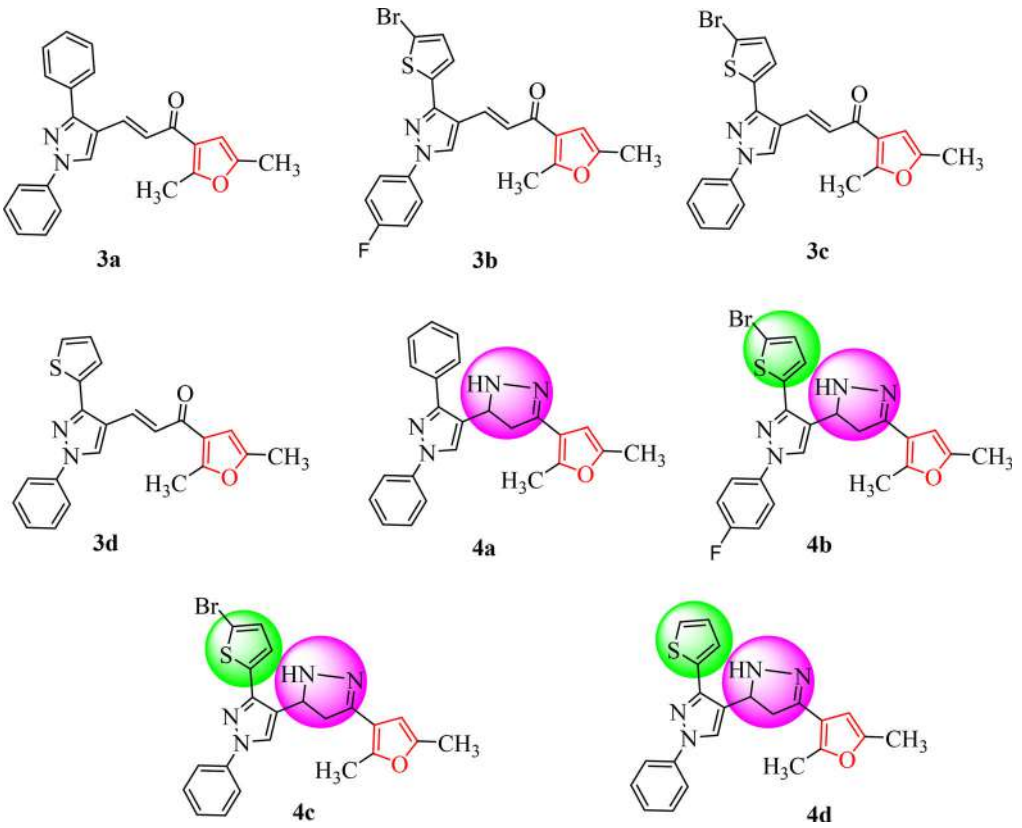


Figure 3. The newly synthesized compounds structure **3a-d** & **4a-d**.

hydrazine followed by Vilsmeier-Haack formylation reaction (Scheme 1). Then furan containing pyrazolyl chalcones **3a-d** were synthesized by base-catalyzed Claisen-Schmidt condensation of 1-(2,5-dimethylfuran-3-yl)ethanone **1** and substituted pyrazole aldehyde **2a-d**.[43] Finally, the furan containing pyrazolyl chalcones **3a-d** and hydrazine hydrate in ethanol solvent using catalytic amount of acetic acid at reflux condition for 6 hr afforded the corresponding pyrazolyl pyrazolines (**4a-d**) in quantitative isolated yield (69–74%) (Scheme 1).

The newly synthesized compounds structures were shown in Figure 3. The newly synthesized compound's structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data. For compound **3a**, in IR spectrum the stretching band for C = O was detected at 1657 cm^{-1}. In the ^{1}H NMR spectrum of compound **3a**, the proton of pyrazole and furan ring resonate as a singlet at δ 9.31 and δ 6.60 ppm respectively. Also, singlet for two $-CH_3$ were observed at δ 2.27 and δ 2.50 ppm. The ^{13}C NMR spectrum of compound **3a** showed signal at δ 184.41 ppm due to C = O and δ 12.89 and δ 13.93 ppm is due to two $-CH_3$. Mass spectrum confirms the formation of compound **3a** showed m/z = 369 $(M+H)^{+}$.

Secondly, in the IR spectrum of compound **4a**, –N–H stretching band observed at 3252 cm^{-1}. The 1H NMR spectrum of compound **4a**, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 2.88 ppm and 3.35 ppm. The CH proton appeared as triplet at δ 4.87 ppm due to vicinal coupling with two protons of the methylene group. In the ^{13}C NMR spectra of the compound **4a** carbons of the pyrazoline ring were observed at δ 41.97 ppm and 54.67 ppm. All the other aromatic and aliphatic protons and carbons were observed at expected regions. Mass spectrum confirms the formation of compound **4a** showed m/z = 383 $(M+H)^{+}$.

Table 1. Antimalarial (μM), Antibacterial (MIC in μg/mL) & Antifungal (MIC in μg/mL) activity.

Cpd	Antimalarial activity Plasmodium falciparum	Antibacterial activity				Antifungal activity			Molecular Docking Score
		EC	PA	SA	SP	CA	AN	AC	
3a	1.46	200	200	250	250	500	500	500	−7.814
3b	3.93	100	250	250	200	1000	500	500	−7.032
3c	2.16	62.5	200	125	250	500	>1000	>1000	−7.192
3d	3.07	100	100	200	200	1000	500	500	−7.118
4a	6.31	125	100	100	100	500	500	500	−6.979
4b	0.47	100	200	100	100	250	500	500	−8.157
4c	0.47	125	125	200	200	1000	>1000	>1000	−8.222
4d	0.21	200	100	125	100	500	500	500	−7.988
Chloroquine	0.06	–	–	–	–	–	–	–	–
Quinine	0.83	–	–	–	–	–	–	–	–
CP	–	50	50	50	50	–	–	–	–
NS	–	–	–	–	–	100	100	100	–

Cpd: Compound; EC: Escherichia coli; PA: Pseudomonas aeruginosa; SA: Staphylococcus aureus; SP: Streptococcus pyogenes; CA: Candida albicans; AN: Aspergillus niger; AC: Aspergillus clavatus; CP: Chloramphenicol; NS: Nystatin.

Biological evaluation

In vitro antimalarial screening

All the synthesized novel compounds were tested for antimalarial activities. The *in vitro* antimalarial assay was carried out according to the micro assay protocol of Rieckmann and coworkers with minor modifications.[44–47] The results were recorded as the minimum inhibitory concentrations (μM MIC) chloroquine and quinine were used as the reference drug (Table 1).

Herein, we have synthesized four chalcone and pyrazoline derivatives respectively. Structure activity relationship (SAR) plays very important role while displaying the antimalarial activity. All the synthesized chalcone derivatives (**3a-d**) exhibited less potency compared to the standard drug. But pyrazoline derivatives exhibited excellent antimalarial activity compared to the standard drug. In compound **4a**, thiophene ring was absent and pyrazoline ring is present, so, the compound **4a** exhibited less potency compared to the standard drug. Now, in compound **4b**, bromo substituted thiophene and pyrazoline rings are present along with the fluorine at the para position on benzene ring. Interestingly, this compound **4b** (0.47 μM), exhibited excellent activity compared to the standard drug quinine (0.83 μM). Again, in compound **4c**, bromo substituted thiophene and pyrazoline rings are present but no fluorine at the para position of benzene ring. Though fluorine is absent on benzene ring in compound **4c** (0.47 μM), it exhibited same potency as that of compound **4b** compared to the standard drug quinine (0.83 μM). Finally, in compound **4d**, there were no substitution on the thiophene and benzene ring. In compound **4d** plane thiophene, plane benzene ring and pyrazoline ring constructed in a single molecular framework. Compound **4d** (0.21 μM), exhibited four-fold more antimalarial activity compared to the standard drug quinine (0.83 μM). From SAR, we can conclude that for the antimalarial activity thiophene, pyrazoline and benzene ring were very important in a single molecular framework.

Antimicrobial activities

Further, all the novel synthesized compounds were also screened for antimicrobial activities against the bacterial strains *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 1688), *Streptococcus pyogenes* (MTCC 442) and fungal strains *Aspergillus clavatus* (MTCC 1323), *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282). The minimum inhibitory concentration (MIC) was determined by the broth dilution method. Chloramphenicol and Nystatin were used as reference drugs for antibacterial and antifungal activity, respectively. The results of antibacterial and antifungal activity were given in Table 1.

The results given in Table 1 indicated that none of the synthesized compound exhibited significant potency toward the standard antibacterial drug Chloramphenicol and antifungal drug Nystatin. Hence, from above result we can conclude that the synthesized compounds show selectively antimalarial activity and negligible antimicrobial activity.

Conclusion

In conclusion, Considering the importance of enoyl-ACP reductase (*Pf*ENR) in *Plasmodium*, a small library of 8 molecules comprising furan containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) was designed and docked against *Pf*ENR. Based on the *in silico* binding affinity data, synthesis was carried out for these novel furans containing pyrazolyl pyrazoline derivatives (**3a-d**, **4a-d**) and was evaluated for activity against *Plasmodium falciparum*. The synthesized compounds shown selectively antimalarial activity with minimal antimicrobial activity. Compounds (**3a-d**) exhibited less antimalarial activity compared to the standard drug. From the series of compounds (**4a-d**), compound **4b** (0.47 µM), **4c** (0.47 µM) and **4d** (0.21 µM) exhibited more antimalarial activity compared to the standard drug quinine (0.83 µM). Compound 4d shows four-fold more activity compared to the standard drug quinine. From the SAR, we have distinguished areas of the pyrazolyl chalcones and pyrazolyl pyrazolines framework where variations can be made to expand the pharmacokinetic profile as well as features required to improve inhibitor effectiveness. This innovative molecular scaffold presents breakthrough for optimization to develop effective *Pf*ENR inhibitors.

Experimental

General

All the reagents, solvents and chemicals were taken from commercial sources found to be and used as such without purification. The physical constant like melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Advance II 400 spectrophotometer using TMS as an internal standard and DMSO-d6 as solvent and chemical shifts were expressed as δ ppm units. Mass spectra were obtained on Waters, Q-TOF micro mass (ESI-MS) mass spectrometer.

General procedure for the synthesis of pyrazolyl chalcones (3a-d)

A mixture of 1-(2,5-dimethylfuran-3-yl)ethanone 1 (0.05 mol), substituted pyrazole aldehyde **2** (0.05 mol) and 10% aqueous potassium hydroxide (10 mL) in ethanol (50 mL) was stirred at room temperature for 14 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice and neutralized by dil. HCl. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3a)

Yield: 61%, yellow solid; mp: 80–82 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1657 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.31 (s, 1H, Pyrazole-H), 7.93 (d, 2H, J = 7.9 Hz), 7.38–7.68 (m, 10H, Ar–H), 6.60 (s, 1H, Furan-H), 2.53 (s, 3H, –CH_3), 2.27 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4 (C = O), 159.9, 152.8, 149.7, 138.9, 132.2, 132.0, 129.6, 128.8, 128.5, 128.6, 128.4, 127.1, 123.8, 122.1, 118.6, 117.6, 105.9, 13.9 (CH_3), 12.9 (CH_3); MS(ESI-MS): m/z 369.11 (M + H).$^{+}$

(E)-3-(3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran -3-yl) prop-2-en-1-one (3b)

Yield: 59%, yellow solid, mp: 112–114 °C; IR (νmax, cm^{-1}): 2923 (=C–H), 2856 (C–H), 1656 (C = O), 1455 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.25 (s, 1H, Pyrazole-H), 7.90 (dd, 2H, J = 4.7 & 9.0 Hz, Ar–H), 7.64 (d, 1H, J = 15.4 Hz, olefinic-H), 7.39–7.45 (m, 3H, Ar–H), 7.34 (d, 1H, J = 3.8 Hz, Ar–H), 7.25 (d, 1H, J = 3.8 Hz, Ar–H), 6.61 (S, 1H, Furan-H), 2.55 (s, 3H, $-CH_3$), 2.28 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.2, 162.0, 159.6, 157.1, 149.7, 145.7, 135.4, 135.1, 131.4, 130.8, 128.9, 127.3, 124.6, 122.0, 120.7, 120.6, 117.3, 116.6, 116.3, 112.5, 105.9, 13.9, 12.9; MS (ESI-MS): m/z 472.89 $(M + H)^{+}$.

(E)-3-(3-(5-Bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethylfuran-3-yl)prop -2-en-1-one (3c)

Yield: 68%, yellow solid, mp120–114 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2855 (C–H), 1699 (C = O), 1454 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 9.14 (s,1H, Pyrazole-H), 7.87 (d, 2H, J = 7.8 Hz, Ar–H), 7.70 (d, 1H, J = 15 Hz, olefinic-H), 7.52 (t, 2H, J = 8 Hz, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.20 (s, 2H, Ar–H), 6.55 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.3, 157.1, 149.7, 145.7, 138.6, 135.5, 131.4, 130.9, 129.7, 128.8, 127.3, 127.3, 124.6, 122.0, 118.6, 117.4, 112.5, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 454.57 $(M + H)^{+}$.

(E)-1-(2,5-Dimethylfuran-3-yl)-3-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)prop-2-en-1-one (3d)

Yield: 62%, yellow solid, mp 124–126 °C; IR (νmax, cm^{-1}): 2921 (=C–H), 2715 (C–H), 1652 (C = O),1456 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, Pyrazole-H), 7.91 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 1H, J = 15.4 Hz, olefinic-H), 7.60 (d, 1H, J = 5.1 Hz, Ar–H), 7.54 (t, 2H, J = 8.2 Hz, Ar–H), 7.35–7.44 (m, 3H, Ar–H), 7.21 (dd, 1H, J = 5.0 & 3.7 Hz, Ar–H), 6.59 (s, 1H, Furan-H), 2.57 (s, 3H, $-CH_3$), 2.29 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 184.4, 157.0, 149.7, 146.8, 138.7, 133.5, 131.5, 129.7, 128.7, 128.1, 127.3, 127.2, 126.8, 124.3, 122.1, 118.6, 117.4, 105.9, 13.9, 12.9; MS(ESI-MS): m/z 375.10 $(M + H)^{+}$.

General procedure for synthesis of pyrazolyl-pyrazoline (4a-d)

A mixture of chalcone **3a-d** (0.001 mol) and hydrazine hydrate (0.004 mol) in solvent ethanol (10 ml) was refluxed in presence of catalytic amount of glacial acetic acid for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was transferred into crushed ice. The precipitation observed, filtered it, washed with water and dried. The crystallization of product carried out in ethanol to get pure pyrazolines.

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1,3-diphenyl-1H-pyrazole (4a)

Yield: 74%, white solid, mp 102–104 °C; IR (νmax, cm^{-1}): 3306 (N–H), 3049 (Ar–H), 1592 (C = N); ^{1}H-NMR (400 MHz, DMSO-d6, δ, ppm): 8.56 (s, 1H, pyrazole-H), 7.90 (d, 2H, J = 7.8 Hz, Ar–H), 7.76 (d, 2H, J = 8.3 Hz, Ar–H), 7.47–7.52 (m, 4H, Ar–H), 7.41 (t, 1H, J = 7.3 Hz, Ar–H), 7.31 (t, 1H, J = 7.4 Hz, Ar–H), 7.20 (s, 1H, N–H), 6.19 (s, 1H, furan-H), 4.87 (t, 1H, J = 10.7 Hz, pyrazoline-H), 3.34 (dd, 1H, J = 10.5 & 15.6 Hz, pyrazoline-H), 2.88(dd, 1H, J = 11.1 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 150.4, 149.3, 147.6, 145.1, 139.5, 132.9, 129.5, 128.6, 127.9, 127.2, 126.2, 123.2, 118.1, 115.2, 105.9, 54.7, 41.9, 13.3, 12.9; MS (ESI-MS): m/z 383.04 $(M + H)^{+}$.

3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1H-pyrazole (4b)

Yield: 69%, white solid, mp 98–100 °C; IR (νmax, cm^{-1}):3310 (N–H), 3046 (Ar–H), 1594 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.54 (s, 1H, pyrazole-H), 7.88 (m, 2H, Ar–H), 7.35 (t, 2H, J = 8.7 Hz, Ar–H), 7.28 (dd, 2H, J = 3.8 Hz, Ar–H), 7.21 (s, 1H, N–H), 6.20 (s, 1H, furan-H), 4.93 (t, 1H, J = 10.68 Hz, pyrazoline-H), 3.37 (dd, 1H, J = 10.7 & 16.5 Hz, pyrazoline-H), 2.86 (dd, 1H, J = 10.9 & 16.1 Hz, pyrazoline-H), 2.38 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 161.6, 159.1, 149.3, 147.7, 145.3, 144.1, 136.9, 135.6, 131.2, 128.0, 126.6, 122.6, 120.2, 120.2, 116.4, 116.2, 115.1, 111.5, 105.9, 54.3, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 486.93 $(M + H).^{+}$

3-(5-Bromothiophen-2-yl)-4-(4,5-dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole (4c)

Yield: 72%, white solid, mp 122–124 °C; IR (ν max, cm^{-1}): 3303 (N–H), 3096 (Ar–H), 1593 (C = N), ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.55 (s, 1H, pyrazole-H), 7.84 (d, 2H, J = 7.9 Hz, Ar–H), 7.51 (t, 2H, J = 7.6 Hz, Ar–H), 7.22–7.34 (m, 4H, Ar–H), 6.20 (s, 1H, furan-H), 4.94 (t, 1H, J = 10.6 Hz, pyrazoline-H), 3.38 (m, 1H, pyrazoline-H), 2.88 (dd, 1H, J = 12.1 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.2, 144.0, 139.0, 137.0, 131.2, 129.6, 127.8, 126.6, 126.5, 122.5, 118.0, 115.1, 111.4, 105.9, 54.4, 41.1, 13.3, 12.9; MS (ESI-MS): m/z 468.95 $(M + H).^{+}$

4-(4,5-Dihydro-3-(2,5-dimethylfuran-3-yl)-1H-pyrazol-5-yl)-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole (4d)

Yield: 70%, white solid, mp 96–98 °C; IR (ν max, cm^{-1}): 3336 (N–H), 3067 (Ar–H), 1501 (C = N); ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm): 8.53 (s, 1H, pyrazole-H), 7.86 (d, 1H, J = 8 Hz, Ar–H), 7.58 (d, 1H, J = 4.9 Hz, Ar–H), 7.47–7.52 (m, 3H, Ar–H), 7.31 (t, 1H, J = 7.3 Hz, Ar–H), 7.15–7.20 (m, 2H, Ar–H), 6.21 (s, 1H, furan-H), 4.98 (t, 1H, J = 10.5 Hz, pyrazoline-H), 3.42 (m, 1H, pyrazoline-H), 2.89 (dd, 1H, J = 10.7 & 16.1 Hz, pyrazoline-H), 2.39 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 149.3, 147.7, 145.1, 144.9, 139.2, 135.0, 129.6, 127.9, 127.4, 126.3, 126.0, 125.8, 122.6, 118.1, 115.1, 105.9, 54.5, 41.3, 13.3, 12.9; MS (ESI-MS): m/z 389.03 $(M + H).^{+}$

Experimental protocol for biological activity

Antimalarial assay

The antimalarial activity of the synthesized compounds was carried out in the Microcare laboratory & TRC, Surat, Gujarat. According to the micro assay protocol of Rieckmann and coworkers the *in vitro* antimalarial assay was carried out in 96 well microtiter plates. To maintain *P. falciparum* strain culture in medium Roswell Park Memorial Institute (RPMI) 1640 supplemented with 25 mM (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES), 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. To obtain only the ring stage parasitized cells, 5% D-sorbitol treatment required to synchronized the asynchronous parasites of *P. falciparum*. To determine the percent parasitaemia (rings) and uniformly maintained with 50% RBCs (O^{+}) an initial ring stage parasitaemia of 0.8 to 1.5% at 3% hematocrit in a total volume of 200 µl of medium RPMI-1640 was carried out for the assay. A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. To the test wells to obtain final concentrations (at five-fold dilutions) ranging between 0.4 µg/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation the diluted samples in 20 µl volume were added. In a candle jar, the culture plates were incubated at 37 °C. Thin

blood smears from each well were prepared and stained with Jaswant Singh-Bhattacharji (JSB) stain after 36 to 40 h incubation. To record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents the slides were microscopically observed. The minimum inhibitory concentrations (MIC) was recorded as the test concentration which inhibited the complete maturation into schizonts. Chloroquine was used as the reference drug.

After incubation for 38 hours, and percent maturation inhibition with respect to control group, the mean number of rings, trophozoites and schizonts recorded per 100 parasites from duplicate wells.

Molecular docking

The crystal structure of *Plasmodium Falciparum Enoyl-Acyl-Carrier-Protein Reductase* (*Pf*ENR or FabI) in complex with its inhibitor Triclosan was retrieved from the protein data bank (PDB) (pdb code: 1NHG) and refined using the protein preparation wizard. It involves eliminating all crystallographically observed water (as no conserved interaction is reported with co-crystallized water molecules), addition of missing side chain/hydrogen atoms. Considering the appropriate ionization states for the acidic as well as basic amino acid residues, the appropriate charge and protonation state were assigned to the protein structure corresponding to pH 7.0 followed by thorough minimization, using OPLS-2005 force-field, of the obtained structure to relieve the steric clashes due to addition of hydrogen atoms. The 3D structures of the furan containing pyrazolyl chalcones (**3a-d**) were sketched using the build panel in Maestro and were optimized using the Ligand Preparation module followed by energy minimization using OPLS-2005 force-field until their average root mean square deviation (RMSD) reached 0.001 Å. The active site of *Pf*ENR was defined using receptor grid generation panel to include residues within a 10 Å radius around the co-crystallized ligand. Using this setup, flexible docking was carried using the extra precision (XP) Glide scoring function to gauze the binding affinities of these molecules and to identify binding mode within the target. The obtained results as docking poses were visualized and analyzed quantitatively for the thermodynamic elements of interactions with the residues lining the active site of the enzyme using the Maestro's Pose Viewer utility.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Nanostructured N doped TiO_2 efficient stable catalyst for Kabachnik–Fields reaction under microwave irradiation†

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Herein, we report nitrogen-doped TiO_2 (N-TiO_2) solid-acid nanocatalysts with heterogeneous structure employed for the solvent-free synthesis of α-aminophosphonates through Kabachnik–Fields reaction. N-TiO_2 were synthesized by direct amination using triethylamine as a source of nitrogen at low temperature and optimized by varying the volume ratios of $TiCl_4$, methanol, water, and triethylamine, under identical conditions. An X-ray diffraction (XRD) study showed the formation of a rutile phase and the crystalline size is 10 nm. The nanostructural features of N-TiO_2 were examined by HR-TEM analysis, which showed they had rod-like morphology with a diameter of ~7 to 10 nm. Diffuse reflectance spectra show the extended absorbance in the visible region with a narrowing in the band gap of 2.85 eV, and the high resolution XPS spectrum of the N 1s region confirmed successful doping of N in the TiO_2 lattice. More significantly, we found that as-synthesized N-TiO_2 showed significantly higher catalytic activity than commercially available TiO_2 for the synthesis of a novel series of α-amino phosphonates *via* Kabachnik–Fields reaction under microwave irradiation conditions. The improved catalytic activity is due to the presence of strong and Bronsted acid sites on a porous nanorod surface. This work signifies N-TiO_2 is an efficient stable catalyst for the synthesis of α-aminophosphonate derivatives.

1 Introduction

In recent years, organophosphorus compounds have received much attention due to their widespread applications in medicinal and agriculture industries.[1,2] α-Aminophosphonates are one such biological important framework that are structural mimics of amino acids. For example, glyphosate (*N*-(phosphonomethyl)glycine) is extensively utilized in agriculture as a systemic herbicide and Alafosfalin is used as an antibacterial agent[3] (Fig. 1). The bioactivity of these molecules such as antimicrobial,[4] antioxidant,[5] anti-inflammatory,[6] enzyme inhibitors[7] and antibacterial[8] is one of the reasons for them to be of immense interest in synthetic organic chemistry. It has been demonstrated that on incorporation of heterocycles such as thiophene,[9] benzothiazoles,[10] thiadiazoles,[11] and pyrazole[12] into the α-aminophosphonates scaffold, the resulting compounds exhibited interesting biological activities. Pyrazole derivatives of α-aminophosphonates have been rarely reported in the literature,[13,14] thus synthesis of novel pyrazole derivatives of α-aminophosphonates is important to research.

Although several protocols for the synthesis of α-aminophosphonates are reported, one of the most important is the Kabachnik–Fields reaction.[15,16] This involves a one-pot three-component coupling of a carbonyl compound, an amine and alkylphosphite. These protocols has been accomplished in presence of a variety of catalyst such as $TiCl_4$,[17] CuI,[18] hexanesulphonic sodium salt,[19] trifluoroacetic acid (TFA),[20] $In(OTf)_3$,[21] $BiCl_3$,[22] $Cu(OTf)_2$,[23] $SbCl_3/Al_2O_3$,[24] $InCl_3$,[25] $LiClO_4$,[26] $ZrOCl_2$,[27] TsCl,[28] $Mg(ClO_4)_2$,[29] and Na_2CaP_2O[30] in presence or

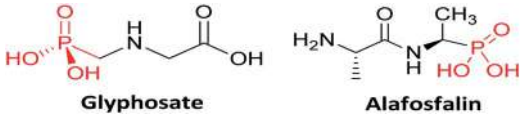

Fig. 1 Some biological active α-aminophosphonate.

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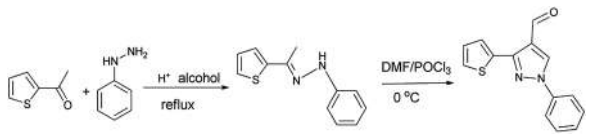


Scheme 1 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde.

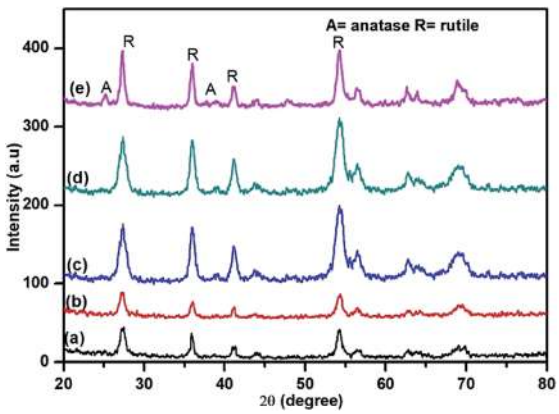


Fig. 2 X-ray diffraction patterns of (a) TN0 (TiO_2), (b) TN1, (c) TN2 (d) TN3 (e) TN4.

even in the absence of a solvent. However, most of these existing procedures are sluggish, require long reaction times, use of strong acidic conditions, give unsatisfactory yields and also suffer from the formation of many side products. Moreover, in all alternatives microwave reaction proved to be a kind of promising medium for such reaction.[31]

In the last few years, the application of transition metal oxides gained particular interest as a heterogeneous catalyst for various organic synthesis.[32] Among all transition metal oxides the use of nanocrystalline titania (TiO_2) has been grown extensively owing to their outstanding physiochemical properties, which furnished their wide applications in sensors,[33] pigments,[34] photovoltaic cells,[35] and catalysis.[36] Also, the use of potential titania catalyst attracted in organic synthesis due to its environmental compatibility, inexpensive, safe, stable, reusable and earth-abundant. It has been proven the desired property of TiO_2 was attained by fulfilling requirements in terms of unique morphology, high crystallinity and mixed-phase composition, the ability of oxidizing and reducing ability under suitable irradiation makes promising greener alternative approach towards important organic transformations compared to other expensive, toxic, transition metal oxides. Moreover, the phase composition and the degree of crystallinity of the titania sample plays an important role in catalytic activity.[8] In the past several organic transformations such as oxidation of primary alcohols,[37] synthesis of xanthenes,[38] Friedel–Crafts alkylation,[39] Beckmann rearrangement[40] efficiently utilizes TiO_2 as a heterogeneous reusable catalyst. In the literature several reports have been debated to influence nitrogen doping on photocatalytic activity of nanocrystalline TiO_2. However, the effect is unrevealed for catalytic applications in organic synthesis. Recently, Hosseini-Sarvari explored the use of commercial TiO_2 in the synthesis of α-aminophosphonates *via* Kabachnik–Fields reactions.[41]

In present investigation, we have prepared nanostructured N doped TiO_2 and also investigation emphasis was given on the synthesis of a series of a novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamin) methylphosphonates under microwave irradiation.

Table 1 Phase composition and crystallite size of as-prepared samples from analysis of XRD

Sample	Rutile	Anatase	Crystallite size (nm)
TN0	100	0	25
TN1	98	2	19
TN2	94	6	16
TN3	95	5	12
TN4	91	9	9

2 Experimental sections

2.1 Synthesis of N doped TiO_2 nanorods

The nanostructured N-TiO_2 were synthesized by previously reported method with some modification.[42,43] In a typical procedure, 0.5 mL of titanium tetrachloride ($TiCl_4$) was added in absolute methanol (25 mL) with constant stirring at room temperature. To this solution requisite quantity a 0.1–2 M aqueous triethylamine solution is injected rapidly. The resulting solution was refluxed for 24 h with constant stirring. The white precipitate formed was collected and washed with ethanol several times followed by centrifugation (10 000 rpm for 20 min). The precipitate was dried at 473 K for 24 h. To control the final morphologies of samples, the sample were synthesized as function of volume ratio of $TiCl_4$, methanol, water, and triethylamine. The sample prepared in volume ratio 1 : 10 : 50 : 0, 1 : 10 : 50 : 1, 1 : 10 : 50 : 2, 2 : 10 : 50 : 2, and 2 : 10 : 50 : 4 were denoted as TN0 (pure TiO_2), TN1, TN2, TN3 and TN4 respectively.

2.2 Synthesis of 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde

1-Phenyl-5-(thiophene-2-yl)-1*H*-pyrrole-3-carbaldehyde were obtained *via* the Vilsmeier–Haack reaction of the appropriate phenylhydrazones, derived from the reaction of 2-acetyl thiophene with phenylhydrazine[44] (Scheme 1).

2.3 Synthesis of diethyl(1-phenyl-3-(thiophene-2-yl)-1*H*-pyrazole-4-yl)(phenylamino)methylphosphonates

In a typical procedure, the pyrazolealdehyde **1** (1 mmol), aniline **2** (1 mmol), triethyl phosphite **3** (1.1 mmol) and N-TiO_2 (12 mol%) were taken in a round bottom flask equipped with a condenser and subjected to microwave irradiation for (10–15 min) using 420 W (RAGA's Microwave system) (Scheme 3). The

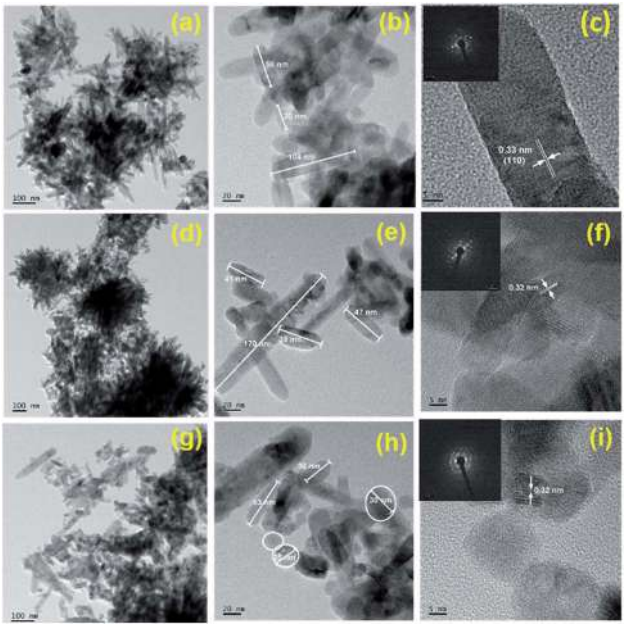


Fig. 3 HR-TEM images of (a–c) TN0, (d–f) TN1, and (d–f) TN2; inset c, f and h SAED pattern of TN0, TN2 and TN3 respectively.

progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture extracted using ethyl acetate and insoluble catalyst separated by filtration. The crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate as eluent. The product structure was determined by FTIR, ^{1}H NMR, and LS-MS.

2.4 Samples characterization

The phase purity and crystallinity were examined by X-ray diffraction (XRD) technique (Advance, Bruker AXS D8) using Cu Kα1 (1.5406 Å) radiation with scanning 2θ range from 20 to 80°. For FETEM analysis samples were prepared by evaporating dilute solution on carbon-coated grids. FE-TEM measurements were carried using the JEOL SS2200 instrument operated at an accelerating voltage of 300 kV. The Brunauer–Emmett–Teller (BET) surface area of nanocatalysts was examined using the Quantachrome v 11.02 nitrogen instrument. The optical properties of the powder samples were studied using UV-vis diffuse reflectance absorption spectra (UV-DRS) were recorded on the Perkin-Elmer Lambada-950 spectrophotometer in the wavelength range of 200–800 nm. Powder samples were used for XPS measurements. The XPS measurements of powdered samples were carried out on a VG Microtech ESCA3000 instrument. Fourier transform infrared (FTIR) spectra of prepared samples were recorded on a Shimadzu Affinity 1-S spectrophotometer in over a range of 400–4000 cm^{-1}. ^{1}H NMR was recorded in DMSO-d_6 solvent on a Bruker Advance-400 spectrometer with tetramethylsilane (TMS) as an internal reference.

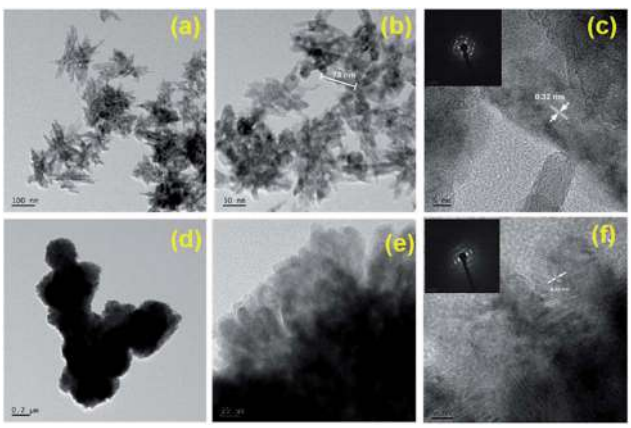


Fig. 4 HR-TEM images of (a–c) TN3 and (d–f) TN4; inset c, and f SAED pattern of TN3, and TN4 respectively.

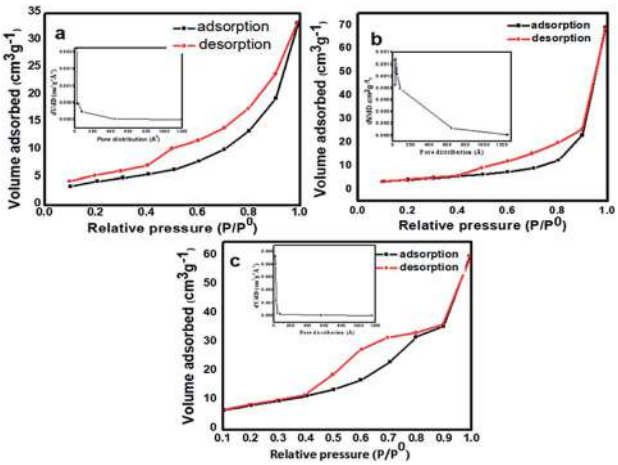


Fig. 5 Nitrogen (N_2) adsorption–desorption isotherms of (a) TN0 (TiO_2), (b) TN2 (N-TiO_2), (c) TN4 (N-TiO_2). Insets shows their corresponding pore size distributions.

3 Results and discussions

3.1 Structural study

Nanostructured TiO_2 and N doped TiO_2 were synthesized by a simple refluxing method. The phase purity and phase formation of as-synthesized material were analysed by powder X-ray diffraction pattern. Fig. 2 compares powder XRD patterns of TiO_2 and N doped TiO_2 samples. The peak position and peak intensity of the pure TiO_2 powder can be indexed into rutile phases (Fig. 2). Further, it is observed that an increase in the amount N-dopant (triethylamine) the intensity of the diffraction

Table 2 BET specific surface area and pore size distribution of TiO_2 and N-TiO_2

Sample	Surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})	Pore radius (Å)
TN0	21.956	0.051	18.108
TN2	40.359	0.215	30.811
TN4	53.589	0.101	18.041

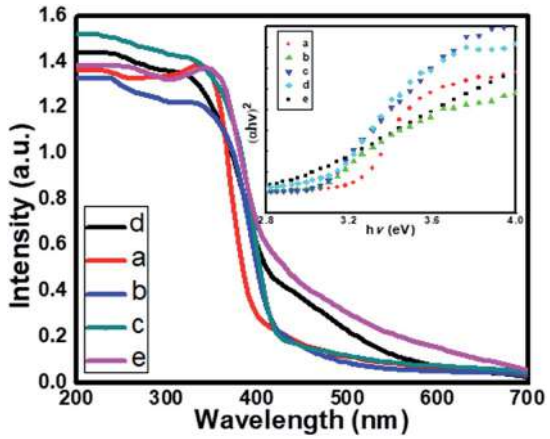


Fig. 6 UV-DRS spectra of (a) TN0 (TiO_2), (b) TN1 (c) TN2 (d) TN3 (N-TiO_2), (e) TN4. Insets shows Tauc plot of TiO_2 and N-TiO_2 samples.

peaks of the rutile phase decreases, while that of anatase phase increases, indicating that the fraction of the anatase phase gradually increases at the expense of the rutile phase during this condition (sample TN2–TN4). The phase composition of rutile and anatase phase of TiO_2 evaluated from the peak intensity using the following equation,

$$f_A = \frac{1}{1+\frac{1}{K}\frac{I_R}{I_A}} \quad K = 0:79; f_A > 0.2; K_{1/4}0:68; f_A \leq 0.2$$

where f_A is the fraction of the anatase phase, and I_A and I_R are the intensities of the anatase (1 0 1) and rutile (1 1 0) diffraction peaks, respectively. The higher molar concentration of triethylamine is favourable for the transformation from rutile to anatase.[45,46] Therefore, the phase composition of TiO_2 samples, *i.e.* the fraction of anatase and rutile, can be facilely controlled through adjusting the concentration of triethylamine. The slight shift of rutile (1 1 0) diffraction peaks towards a higher angle with an increase in the amount of N dopant suggesting

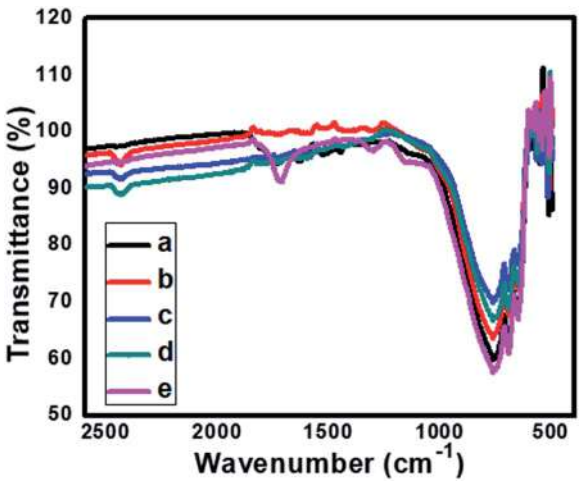


Fig. 7 FTIR spectra of (a) TN0 pure (TiO_2), (b) TN1 (N-TiO_2), (c) TN2, (d) TN3 and (e) TN4.

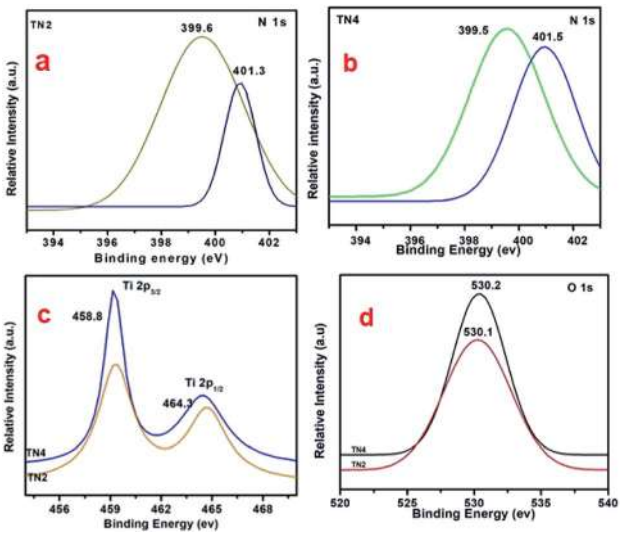
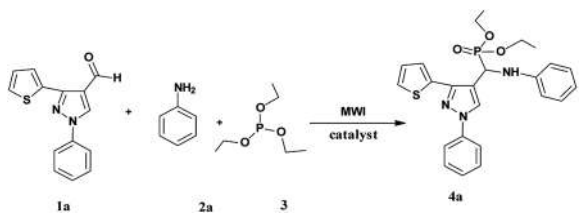


Fig. 8 (a and b) High resolution spectrum of N 1s region (c) high resolution spectrum of Ti 2p region (d) high resolution spectrum of O 1s region.

the incorporation of nitrogen in the TiO_2 crystal structure. The crystallite size is calculated from each (1 1 0) peak in the XRD pattern using the Sherrer formula.[39] The average crystalline size are 25, 19, 16, 12 and 9 nm for TN0, TN1, TN2, TN3, and TN4 respectively (Table 1). From, XRD analysis it is clear that with an increase in the concentration of nitrogen in TiO_2, fraction of anatase increases phase and crystalline size decreases.

3.2 Surface and morphological study

Transmission electron microscopy (TEM) and high-resolution transmission electron microscopy (HRTEM) analysis were performed to study morphology and crystallinity of as-synthesized pure and N doped TiO_2 materials (Fig. 3). The pure TiO_2 (TN0) sample seems flowerlike nanostructures (Fig. 3a). At high-resolution it reveals that each flower microstructure consisting several nanorods. The length of nanorods are in the range of 50–70 nm and diameter is about 10–15 nm (Fig. 3b). Fig. 3c shows the lattice fringes of the material with interplanar spacing *d* spacing 0.33 nm matches well (1 0 0) plane of rutile TiO_2. Fig. 3c inset shows a selected area diffraction pattern in which bright spots observed that confirm the TiO_2 nanorods are in nanocrystalline nature. It was observed that addition of N dopant, resulting sample TN1 and TN2 grows into new superstructure consisting nanorods of length 30–50 nm and spheres



Scheme 2 Standard model reaction.

Table 3 Comparative study of catalysts used for the synthesis of α-aminophosphonate[a]

Entry	Catalyst	Time (minutes)	Yield[b] (%)
1	—	20	Trace
2	Acetic acid	20	30
3	Commercial ZnO	15	20
4	Commercial TiO_2	15	30
5	TN0	10	72
6	TN1	10	73
7	TN2	10	76
8	TN3	10	85
9	TN4	10	95

[a] Reaction condition: aldehyde(**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), catalyst, MW power 420 watt. [b] Isolated yield.

of diameter 20–30 nm, particles size is obviously smaller than TN0 (Fig. 3d and h). HRTEM results are consistent with XRD results. The *d*-spacing is about 0.325 Å between adjacent lattice planes of the N doped TiO_2.

It was revealed that with doubling concentration of $TiCl_4$, sample TN3 and TN4 were grown into very fine agglomerated nanorods (Fig. 4). Further, it is observed that these nanorods having size in length 30–40 nm and diameter is around 7–10 nm which is lower than pure TiO_2. Fig. 4f inset shows selected area diffraction pattern shows, surprisingly, ring-like pattern unlike TiO_2, indicates N-TiO_2 nanorods are in polycrystalline nature. From HR-TEM results it is concluded that increase in concentration of $TiCl_4$ and triethylamine reduces the size of the nanorods.

The specific surface area of as-prepared samples was studied by (N_2) nitrogen gas adsorption–desorption measurement at 77 K using the Brunauer–Emmett–Teller (BET) method. The N_2 adsorption–desorption isotherm of N-TiO_2 nanoparticles is shown in Fig. 5. The pure TiO_2 shows type IV isotherm according to IUPAC classification,[47] which are typical characteristics of a material with pore size in the range of 1.5–100 nm Fig. 5a. The shape of the hysteresis loop is H_3 type may associates due to the agglomeration of nanoparticles forming slit-like pores, reflected in TEM images. At higher relative pressure (p/p^0) the slope shows increased uptake of adsorbate as pores become filled; inflection point typically occurs near

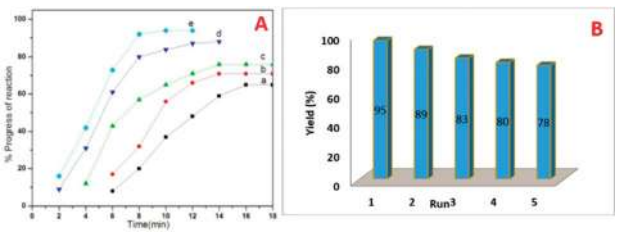


Fig. 9 (A) Progress of reaction (a) TN0 (b) TN1 (c) TN2 (d) TN3 and (e) TN4. (B) Reusability of catalyst TN4; reaction condition: aldehyde (**1a**) (1 mmol), aniline (**2a**) (1 mmol), triethylphosphite **3** (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt.

Table 4 Optimization of the concentration of catalyst[a]

Sr. no.	Concentration of catalyst (mol%)	Yield[b] (%)
1	3	69
2	6	76
3	9	86
4	12	95
5	15	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, MW power 420 watt. [b] Isolated yield.

completion of the first monolayer. The BET surface area of pure TiO_2 is found to be 21.956 $m^2\ g^{-1}$. The pore size distribution of prepared samples was investigated by Barrett–Joyner–Halenda (BJH) method Fig. 5(a)–(c) insets. The average pore diameter of pure TiO_2 nanoparticles is 18 nm which demonstrates the material is mesoporous nature. Further, it is observed that the incorporation of nitrogen in TiO_2 nanoparticles the surface area shifts towards higher values. The adsorption–desorption isotherms of nitrogen-doped TiO_2 samples display the type II isotherm according to IUPAC classification.[46] The specific BET surface area of samples TN_2 and TN_4 are 40.359 $m^2\ g^{-1}$ and 53.589 $m^2\ g^{-1}$ respectively (Fig. 5b and 4c). This observation specifies a decrease in the particle size of TiO_2 nanoparticles specific surface area increases which are in consisting of XRD and TEM results. The Brunauer–Emmett–Teller (BET) specific surface areas, pore volumes and mean pore and mean pore diameters of samples TN0, TN2, and TN4 are summarized in Table 2.

3.3 Optical and electronic property studies

The optical property of the as-synthesized material was analyzed by UV-Vis diffuse absorbance spectra as shown in Fig. 6. Fig. 6 displays the comparative UV-DRS spectra of pristine TiO_2 and a series of N doped TiO_2 samples. The absorption edge for the pure TiO_2 (TN0) is observed at around 410 nm (Fig. 6a), which is consistent with the band gap of the rutile phase.[45] The N doped TiO_2 nanostructures show strong absorption in the visible region (410–600 nm). The redshift clearly indicates the

Table 5 Screening of solvents[a]

Entry	Solvent	Yield (%)[b]
1	Ethanol	85
2	Methanol	87
3	Dichloromethane	55
4	THF	58
6	Toluene	60
7	Neat	95

[a] Reaction condition: aldehyde (**1a**) (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 catalyst, solvent, MW power 420 watt. [b] Isolated yield.

successful doping of N in the lattice of TiO_2. Moreover, as the concentration of triethylamine increases redshift of N-TiO_2 also increases which confirms higher nitrogen doping and a higher fraction of absorption of photons from the visible region. The band gap of as-synthesized material calculated by using the Tauc plot shown in Fig. 6 (insets). The band gap (E_g) for the sample TN0, TN1, TN2, TN3, and TN4, were observed to 3.15, 3.09, 3.07, 3.03 and 2.85 eV respectively. The decrease in the band gap is attributed to higher mixing of the (O/N) 2p level is developed in the Ti-3d level falls at the top of the VB, therefore, band gap reduced compared to the pristine TiO_2 nanostructure.

3.4 FT-IR spectroscopy

Fig. 7 shows comparative FTIR spectra for pure and N doped TiO_2. The absorption peak signal in the range of 400–1100 cm^{-1} is characteristic of the formation of O–Ti–O lattice. The absorption at 668 cm^{-1}, 601 cm^{-1}, 546 cm^{-1} and 419 cm^{-1} corresponds to Ti–O vibrations.[48,49] Further, for the sample TN1–TN3 the IR bands centred at 1400–1435 cm^{-1} indicates nitrogen doping in the TiO_2 sample. The band located at 1070 cm^{-1} is attributed to Ti–N bond vibrations. Also, it is observed that the band at 1335 cm^{-1} for pure TiO_2 is shifted towards longer wavenumber 1430 cm^{-1} supports for the claim of N doping in TiO_2 lattice. Further it is also observed that some of the minor the peaks of pure TiO_2 are rather different than the N-doped TiO_2, this indicates the incorporation of nitrogen in TiO_2 lattices. The peak centered at 1600–2180 cm^{-1} is ascribed due to –OH stretching frequency. From, IR spectra it is clear that N is successfully incorporated in the lattice of TiO_2.

3.5 X-ray photoelectron spectroscopy

The XPS were used for chemical identification and electronic state of dopant nitrogen in sample TN2 and TN4. The high resolution XPS spectra of N 1s on deconvolution shows two different peaks at 399.6 and 401.5 eV indicates nitrogen present in two different electronic state (Fig. 8a and b). The peak at 399.6 is attributed to presence of interstitial N or N–Ti–O linkage. The result is consistent with previous reports.[43] The peak at 401.5 is attributed to presence of N in oxidized state as NO or NO_2. The concentration of nitrogen on surface of TN2 and TN4 are 2.8% and 3.4% respectively. Fig. 8c shows the peak at 458.8 and 458.3 is attributed to Ti $2p_{3/2}$ and Ti $2p_{\frac{1}{2}}$, in good agreement the presence of Ti(IV) in TiO_2. The peak at binding energy 530.1 and 530.2 eV of sample are attributed to O 1s (Fig. 8d).

3.6 Catalytic study in synthesis of α-aminophosphonates

In order to find out the best experimental condition, the reaction of pyrazolaldhyde **1a**, aniline **2a** and triethylphospite **3** under microwave irradiation is considered as standard model reaction (Scheme 2).

In the absence of a catalyst, the standard model reaction gave a small amount of product (Table 3 entry 1). These results specify catalyst is required to occur reaction. In order to check the catalytic utility, the model reaction carried out in the presence of a variety of catalysts (Table 3 entry 2–9). The N-TiO_2 NRs gave better results than acetic acid, commercial ZnO and commercial TiO_2.

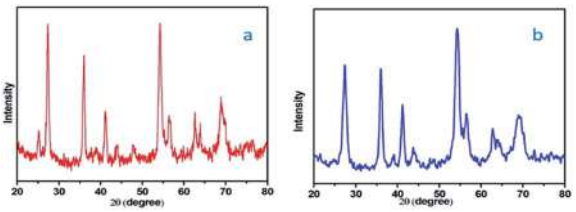


Fig. 10 XRD of sample TN4 (a) before reaction (b) after reaction.

Inspiring these results, we further studied the progress of reaction at different time intervals, we observed the sample N-doped TiO_2 catalyzes efficiently than undoped TiO_2, and this may be attributed to the higher surface area (Fig. 9A).

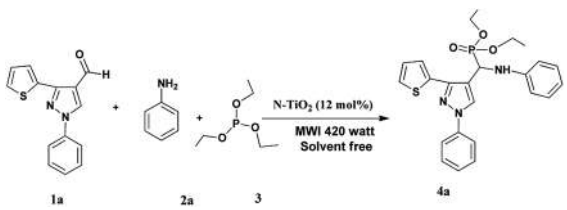
The optimum concentration of the catalyst was investigated by performing the model reaction at different concentrations such as 3, 6, 9, 12 and 15 mol%. The reaction yielded in 69, 76, 86, 95 and 95% yields respectively (Table 4). This shows that 12 mol% of TN_4 is adequate for the reaction by considering the yield of the product.

To evaluate the effect of solvents, different solvents such as ethanol, methanol, dichloromethane, THF, 1,4-dioxane and toluene were used for the model reaction in presence of N-TiO_2 catalyst. The reaction proceed with better yield in polar protic solvent (Table 5, entries 1, 2). However it was observed that the usage of solvents slows down the rate of reaction and gives the desired product in lower yields than that for neat condition (Table 5, entries 1–6).

The recyclability of the catalyst was then examined and the outcomes are shown in Fig. 9B. After the completion of reaction, the reaction mixture was extracted with ethyl acetate. The residual catalyst was washed with acetone, dried under vacuum at 100 °C and reused for consequent reactions. The recovered catalyst could be used for 5 times without obvious loss of catalytic activity.

The difference between the XRD of fresh catalyst and reused catalyst shown in Fig. 10.

The usefulness of optimized reaction condition for model reaction (12 mmol % of catalyst, solvent-free, MWI) was extended for the synthesis of a series of novel α-amino-phosphonates (**4a–l**) by reacting pyrazoldhyde (**1a–c**), anilines (**2a–d**) and triethylphosphite (**3**) in excellent yields (Scheme 3).



Scheme 3 Optimized reaction condition for synthesis of diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino) methylphosphonates

Table 6 Microwave assisted synthesis of novel diethyl(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)(phenylamino)methylphosphonates[a]

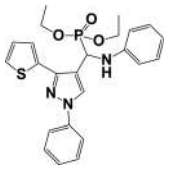
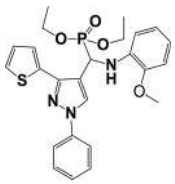
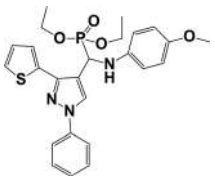
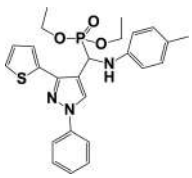
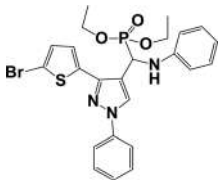
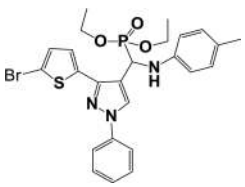
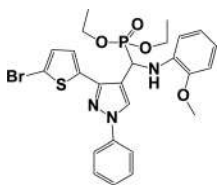
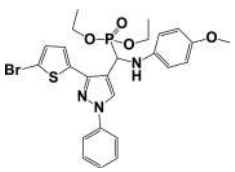
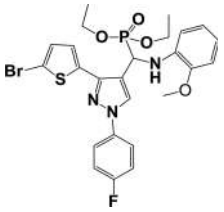
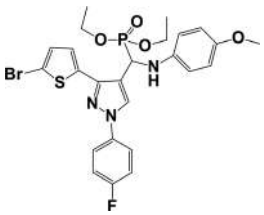
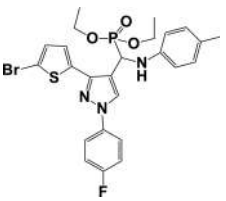
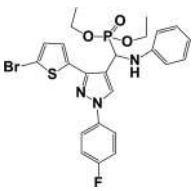
Entry	Product	M.P. (°C)	Yield[b] (%)
4a		218	95
4b		220	79
4c		208	92
4d		216	79
4e		180	86
4f		200	82
4g		162	85
4h		190	71

Table 6 (*Contd.*)

Entry	Product	M.P. (°C)	Yield[b] (%)
4i		195	81
4j		120	76
4k		210	89
4l		190	75

[a] Reaction condition: aldehyde (1 mmol), aniline (1 mmol), triethylphosphite (1.1 mmol), N-TiO_2 (12 mol%), MW power 420 watt. [b] Isolated yield.

The obtained product **4a–l** was characterized by spectroscopic techniques (Table 6).

The spectroscopic data of synthesized compounds are given in ESI (S-2 to S-26).†

4 Conclusions

In summary, we have prepared N doped TiO_2 nanorods by thermal hydrolysis method using triethylamine as the source of nitrogen at relatively low temperatures. The XRD analysis showed that with varying composition molar ratios of $TiCl_4$, CH_3OH, H_2O, and $(C_2H_5)_3N$, phase composition of rutile to anatase also tunes. FTIR spectra show the chemical environment of doping by the formation of the N–Ti–O and Ti–O–Ti bond. The morphological study performed by the FE-TEM technique shows the formation of well-developed nanorods of size in length 30–40 nm and diameter is around 7–10 nm, which is lower than pure TiO_2. Further, BET analysis N-TiO_2 shows the maximum specific surface area 53.4 $m^2\ g^{-1}$ which is 2.5 times

higher than pure TiO_2. The as-synthesized materials were employed for the synthesis of α-aminophosphonates *via* Kabachnik–Fields reaction under microwave irradiation. The N-TiO_2 shows remarkable catalytic activity for aminophosphonate derivatives compared with TiO_2 and other similar nanocatalysts.

Conflicts of interest

There are no conflicts to declare.

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Synthesis, evaluation and molecular docking of 1,2,3-triazolyl chalcones as potential antifungal and antioxidant agents

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Abstract: A series of new 1,2,3-triazolyl chalcones were efficiently synthesized and screened for in *vitro* antifungal activity against five different fungal strains such as *Candida albicans*, *Fusarium oxysporum, Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. All the synthesized chalcones displayed potential antifungal activity against most of the tested fungal strains. Especially, compounds **9b, 9c, 9d** and **9g** are the most active chalcones and displayed excellent MIC values as compared to standard antifungal drug Miconazole. Based on the structural similarity to known triazole inhibitors of sterol 14α-demethylase (CYP51), molecular docking study was performed to gauze the binding affinity of these chalcones and gains an insight into the plausible mechanism of antifungal action. The synthesized chalcones were also evaluated for in *vitro* antioxidant activity. All compounds exhibited moderate to excellent antioxidant activity, particularly compounds **9e, 9f, 9g** and **9h** exhibited excellent antioxidant activity in comparison with standard butylated hydroxytoluene (BHT). Furthermore, the synthesized chalcones were analyzed for ADME properties and showed the potential to build up as good oral drug candidates.

Keywords: 1,2,3-triazole, Chalcone, Antifungal activity, Antioxidant activity, Molecular docking study, ADME prediction.

1. Introduction

The incidences of multidrug-resistant fungal infections in recent years have increased dramatically and commonly seen in patients with weak immune systems [1]. An increasing number

of infections with stem cell transplantation, organ transplantation, chemotherapy, and human immunodeficiency virus increases invasive fungal infections [2]. The major pathogenic strains responsible for systematic fungal infections are *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigates* [3]. Fluconazole, Voriconazole, Itraconazole and Miconazole are some of the widely used azole based broad-spectrum antifungal drugs [4] **(Figure 1).** They displayed broad-spectrum antifungal potential against most of the filamentous fungi, however, some of them are not effective against invasive aspergillosis and also suffered from severe drug resistance [5]. Moreover, the broad use of existing antifungal drugs has caused severe drug resistance. Therefore, it is urgent to develop new antifungal agents with excellent activity against a variety of clinical fungal strains.

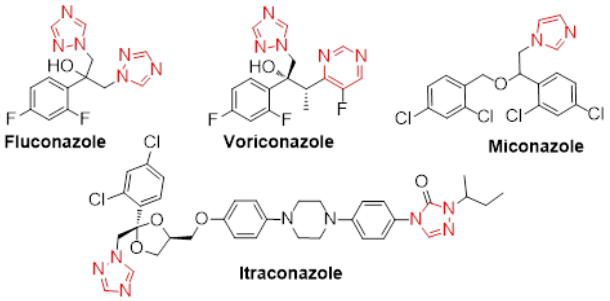


Figure 1. Known azole containing antifungal drugs

Many natural enzymatic and non-enzymatic antioxidants present in the human body that counteract the harmful effect of free radicals and other oxidants [6]. Although reactive oxygen species (ROS) are essential for various complex mechanisms of the organism's body in various diseases, the excessive production of ROS causes various diseases and oxidative stress. Antioxidant protects the cell from oxidative injury by neutralizing free radicals. Recently, it has been observed that reactive oxygen species participates in the mechanism of action of triazole containing antifungals [7]. It is important to elucidate possible association among oxidative stress response and antifungal mechanism of action for developing new targets for novel antifungal agents by rational development of antifungal drugs.

Chalcones i.e. α-β unsaturated ketones are important pharmacophore in many natural and synthetic biologically active compounds [8–12]. It is used as an effective template in medicinal chemistry and drug discovery process [13,14]. The double bond in conjugation to carbonyl group is considered as responsible for the pharmacological effect in chalcones. Literature revealed that chalcones exhibited broad spectrum of biological activities like anticancer[15], antimalarial[16], antimicrobial[17], antioxidant[18], anti-inflammatory[13] etc.

1,2,3-triazole based natural and synthetic compounds are privileged scaffold in the drug discovery process with a broad spectrum of biological activities [19–25]. Molecular hybridization of chalcones with 1,2,3-triazole can be an efficient strategy to synthesize chemically diverse and biologically active conjugates. Recent literature revealed that 1,2,3-triazolyl chalcones displayed a broad spectrum of pharmacological activities [17,22,26–31] **(Figure 2)**.

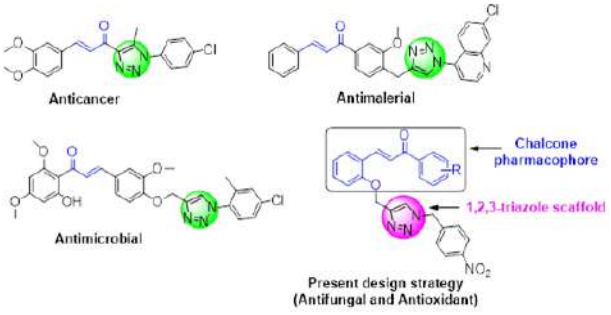


Figure 2. Known 1,2,3-triazolyl-chalcones and our design strategy

In search of the development of new active antifungal and antioxidant agents, combinatorial synthesis of 1,2,3-triazolyl chalcones has

been efficiently carried out by click chemistry and Aldol type condensation reaction. We were encouraged to design and synthesize 1,2,3-triazolyl chalcones from commercially available starting materials with high overall yield and evaluation of their antifungal and antioxidant activities.

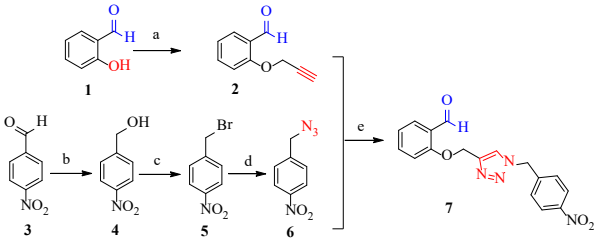
Hence, keeping in view the urgent need of potential antifungal and antioxidant agents and in continuation to our earlier work on 1,2,3-triazole based bioactive compounds [21,23,24] and α,β-unsaturated compounds [32–34], we report herein design, synthesis, molecular docking, ADME prediction and bio evaluation of some new 1,2,3-triazolyl chalcones as potential antifungal and antioxidant agents.

2 Result and discussion

2.1 Chemistry

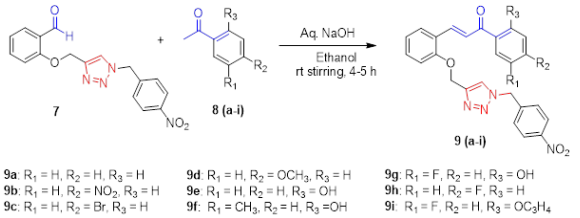
In present work, we have described the syntheses of new substituted 1,2,3-triazolyl chalcones **9a-i** from commercially available starting materials **(Scheme 2)**. 1,2,3-triazole based benzaldehyde **7** was formed by the fusion of benzyl azide and the terminal alkyne group of substituted benzaldehyde *via* the click chemistry approach **(Scheme 1).**

The treatment of *o*-hydroxy benzaldehyde **1** with propargyl bromide in the presence of K_2CO_3 as a base in *N, N*-dimethylformamide (DMF) at room temperature afforded 2-(prop-2-yn-1-yloxy)benzaldehyde **2** in 89% yield (**Scheme 1**). The *p*-nitrobenzyl azide **6** was prepared from the *p*-nitrobenzaldehyde *via* $NaBH_4$ reduction, bromination, and nucleophilic substitution reaction of sodium azide, according to the reported procedure [35]. **(Scheme 1).** Furthermore, 1, 3-dipolar cycloaddition reaction of benzyl azide **6** and terminal alkyne group of benzaldehyde **2** using a catalytic amount of copper diacetate $Cu(OAc)_2$ in *t*-BuOH-H_2O (3:1) at room temperature for 20 h afforded regioselective 1,4-disubstituted-1,2,3-triazole incorporated benzaldehyde **7** in 88% yield **(Scheme 1).**



Scheme 1. Reagents and conditions: (a) Propargyl bromide, K_2CO_3, DMF, r.t., 2.5 h; (b) $NaBH_4$, methanol, 0 °C to r.t., 2 h; (c) PBr_3, CH_2Cl_2, 0 °C, 0.5 h; (d) NaN_3, acetone:H_2O (3:1), r.t., 24 h; (e) $Cu(OAc)_2$ (20 mol%), *t*-BuOH/H_2O (3:1), r.t., 19-27 h.

Finally, newly synthesized 1,2,3-triazole based benzaldehyde **7** was condensed with various substituted acetophenone (**8a-i)** in aqueous NaOH, resulted into the corresponding 1,2,3-triazolyl chalcones **(9a-i)** in quantitative isolated yield (85-90%) **(Scheme 2).**



Scheme 2. Synthesis of 1,2,3-triazolyl-chalcones

The structures of 1,2,3-triazolyl-chalcones **9a-i** were confirmed by FT-IR, ^1H NMR, ^{13}C NMR and LC/ESI-MS analysis. Structures of the synthesized 1,2,3-triazolyl-chalcones are given below in **Figure 3.**

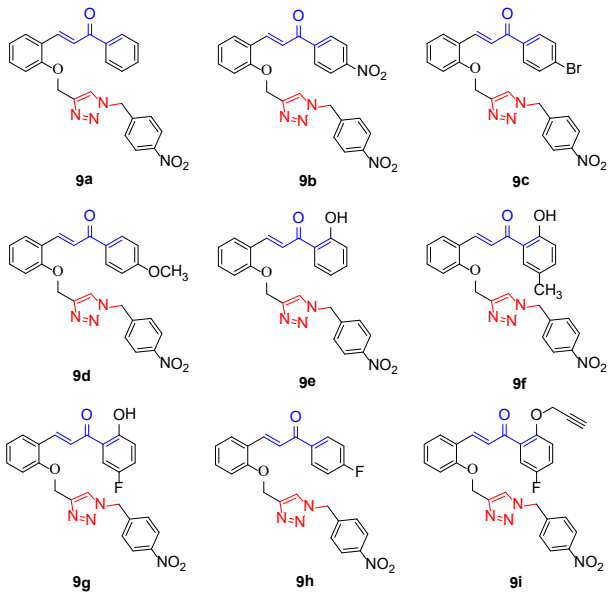


Figure 3. Structures of 1,2,3-triazolyl chalcones

Entry	Antifungal Activity MIC (µg/mL)					Antioxidant activity IC_{50} (µg/mL)	Molecular Docking Score
	CA	*FO*	*AF*	*AN*	*CN*		
9a	**25**	**25**	25	**25**	**6.25**	50.17± 0.35	-7.944
9b	**6.25**	**12.5**	**12.5**	**25**	**12.5**	40.32± 0.46	**-8.947**
9c	**12.5**	50	**12.5**	50	**12.5**	27.11± 0.25	-8.154
9d	**12.5**	**12.5**	25	**25**	**12.5**	21.12 ± 0.19	-8.447
9e	**25**	**12.5**	50	50	**12.5**	**16.34 ± 0.91**	-7.902
9f	**12.5**	**25**	50	75	**12.5**	**15.66± 0.45**	-8.015
9g	**25**	**25**	50	50	50	**16.37± 0.87**	-7.458
9h	**25**	**25**	75	50	100	**16.06 ± 0.18**	-7.263
9i	75	50	75	50	50	31.46 ± 0.88	-7.039
MA	**25**	**25**	**12.5**	**25**	**25**	-	-
BHT	-	-	-	-	-	**16.47± 0.18**	-

CA-*Candida albicans,* FO-*Fusarium oxysporum,* AF-*Aspergillus flavus*, AN-*Aspergillus Niger,* CN-*Cryptococcus neoformans,* MA- Miconazole, BHT- Butoxy hydroxy tolune, Values are the average of three readings (n=3) ± standard deviation

2.2 Antifungal activity

All the synthesized 1,2,3-triazolyl-chalcones were screened for their *in vitro* antifungal activity. The antifungal activity was evaluated against five different pathogenic fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, and *Cryptococcus neoformans*. Minimum inhibitory concentration (MIC) values were determined using a standard agar plate method [36,37]. MIC value of an antimicrobial compound is its lowest concentration that prevents visible growth of the microorganism. It is a measure of the effective ability of the antimicrobial against the concerned microbe. Miconazole was used as a standard for the comparison of antifungal activity. Dimethyl sulfoxide was used as solvent control.

Table 1. In *vitro* antifungal, antioxidant data and *in silico* molecular docking score of 1,2,3-triazolyl chalcones (**9a-i**).

MIC values of the tested compounds are presented in **Table 1**. Most of the newly synthesized 1,2,3-triazolyl chalcones were found to show excellent antifungal activity as compared to standard antifungal drug Miconazole. From the antifungal activity data **(Table 1)**, it is observed that almost all the synthesized chalcones were displayed promising antifungal activity against fungal strain *C. Albicans*. Particularly, chalcones **9b, 9c, 9d,** and **9g** are the most active among all tested compounds against most of the fungal strains. Structure-activity relationship revealed that introduction of nitro (-NO_2) group at *para*- position of acetophenone moiety in compound **9b** showed a significant rise in activity as compared to **9a** (activity increases by two-fold as reflected in lowered MIC value). Compound **9a** is equipotent to Miconazole against *C. albicans* (MIC value 25 µg/mL), *A. Niger* (MIC value 25 µg/mL**)**, *F. oxysporum* ***(***MIC value 25 µg/mL***)***, *A. flavus* (MIC value 25 µg/mL***)*** and most active than Miconazole in case of fungal strain *C. neoformans* (MIC value 12.5

µg/mL*)*. Introduction of alkyne group in case of **9i** reduces the antifungal activity compared to other tested compounds. Introduction of electron-withdrawing groups and halogens on acetophenone shows a significant enhancement in an activity. Graphical representation of antifungal activity data of the synthesized compounds is represented in **figure 4**.

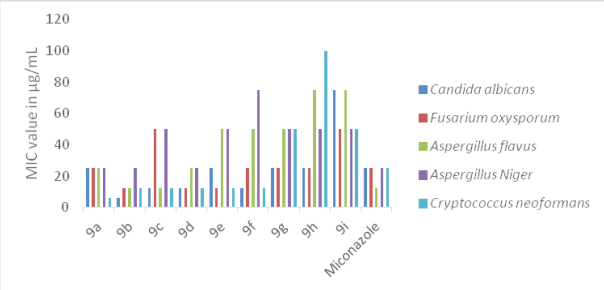


Figure 4. Antifungal activity of synthesized analogues as compared to standard Miconazole

2.3 Antioxidant activity

All the synthesized chalcones displayed good to moderate radical scavenging activity when compared with the standard drug BHT **(Table 1).** Particularly compounds **9e, 9f, 9g** and **9h** exhibit significant IC_{50} values (IC_{50} =16.34 ± 0.91, 15.66 ± 0.45, 16.37 ± 0.87, 16.06 ± 0.18 in µg/mL respectively) as compared to standard antioxidant BHT. Structure-activity data revealed that the hydroxy group is important for the enhancement of antioxidant potential as reflected in IC_{50} values. Also, the substitution of electron-donating groups on acetophenone increases the antioxidant activity of 1,2,3-triazole substituted chalcones as compared to standard antioxidant BHT. The antioxidant activity of these compounds may be related to their redox properties, which allow them to act as reducing agents or hydrogen atom donors and scavenge-free radicals.

2.4 Molecular docking

Molecular docking study revealed the binding orientations of 1,2,3-triazolyl-chalcones in the active sites of CYP51. It was observed that all the synthesized chalcones could snuggly fit into the active site of CYP51 with varying degrees of affinities at co-ordinates close to a native ligand. Their docking scores varied from -8.947 for the most active analogue to -7.039 for moderately active with average docking score of -7.907 signifying a promising binding affinity towards CYP51 (**Table 2, Fig 5** and **Fig 6-13**). To gain a better understanding on the potency and types of interactions contributing to the enhanced binding affinity towards the target, a detailed investigation of the per-residue interactions for the most active analogues (**9b, 9c, 9d** and **9f**) was carried out which is elaborated in detail for one of the most active compound **9b** while it summarized in **Table 2** for other active compounds (**9c-Fig 6, 9d- Fig 7** and **9f- Fig 9**).

The best-docked conformation of **9b** was seen to be deeply embedded into the active pocket of sterol 14α-demethylase (CYP51). The lower interaction energy (Glide binding energy -62.896 kcal/mol, Glide score of from -8.947) rationalizes the tighter binding of this chalcone analogue (**Figure. 5**) into the CYP51 active site.

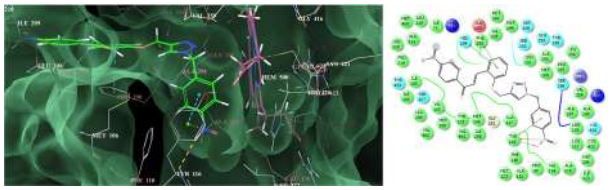


Figure 5: Binding mode of **9b** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

The per-residue interaction analysis revealed that the enzyme-inhibitor complex was stabilized by a series of favourable van der Waals interactions observed with Hem500 (-6.776 kcal/mol), Val461 (-2.929 kcal/mol), Val359 (-2.431 kcal/

Table 2. The per-residue interaction analysis based on molecular docking for 1,2,3-triazolyl-chalcones with sterol 14α-demethylase (CYP51).

Code	Docking Score	Glide Interaction Energy (kcal/mole)	Per-Residues interactions			
			Van der Waals (kcal/mol)	Columbic (kcal/mol)	H-bond (Å)	π-π / Cation-π Stacking
9b	-8.947	-62.896	Hem 500(-6.776), Val461 (-2.929), Met460 (-3.151), Thr459 (-2.898), His458 (-2.543), Met360 (-3.233), Val359 (-2.431), Met358 (-2.981), Leu356 (-2.779), Thr295 (-2.358), His294 (-2.277), Ala291 (-3.531), Phe290 (-3.236), Ala287 (-2.528), Pro210 (-2.614), Ile209 (-2.643), Leu208 (-3.157), Glu205 (-2.827), Leu127 (-2.789), Tyr116 (-3.788), Phe110 (-2.735), Met106 (-3.434), Ile105 (-2.742), Tyr103 (-2.39), Val102 (-2.825)	Hem500 (-3.959), Arg361 (-2.414), Phe290 (-2.362), Leu208 (-2.522), Glu205 (-3.569), Arg124 (-2.223), Ile105 (-2.293), Val102 (-3.201)	Tyr116 (2.65)	π-π Stacking: His294 (2.168), Phe290 (2.374),Tyr116 (2.651) Cation- π Stacking: Tyr116 (2.651)
9c	-8.154	-60.358	Hem500 (-6.458), Val461 (-2.463), Met460 (-2.793), Thr459 (-2.264), His458 (-2.129), Met360 (-2.233), Val359 (-2.143), Met358 (-2.280), Leu356 (-2.261), Thr295 (-2.157), His294 (-2.082), Ala291 (-2.191), Phe290 (-2.467), Ala287 (-2.269), Pro210 (-2.600), Ile209 (-2.204), Leu208 (-3.072), Glu205 (-2.523), Leu127 (-2.114), Tyr116 (-2.878), Phe110 (-2.034), Met106 (-3.247), Ile105 (-2.558), Tyr103 (-2.095), Val102 (-2.216)	Hem500 (-3.548), Arg361 (-2.239), Phe290 (-2.203), Leu208 (-2.136), Glu205 (-3.122), Arg124 (-2.183), Ile105 (-2.150), Val102 (-2.872)	Tyr116 (2.50)	π-π Stacking: His294 (2.271), Phe290 (2.303),Tyr116 (2.498) Cation- π Stacking: Tyr116 (2.498)
9d	-8.447	-61.216	Hem500 (-6.702), Val461 (-2.751), Met460 (-2.901), Thr459 (-2.727), His458 (-2.241), Met360 (-2.929), Val359 (-2.230), Met358 (-2.328), Leu356 (-2.388), Thr295 (-2.377), His294 (-2.191), Ala291 (-2.796), Phe290 (-2.866), Ala287 (-2.324), Pro210 (-2.628), Ile209 (-2.315), Leu208 (-3.096), Glu205 (-2.617), Leu127 (-2.187), Tyr116 (-2.892), Phe110 (-2.128), Met106 (-3.338), Ile105 (-2.729), Tyr103 (-2.123), Val102 (-2.221)	Hem500 (-3.667), Arg361 (-2.548), Phe290 (-2.226), Leu208 (-2.254), Glu205 (-3.417), Arg124 (-1.110), Ile105 (-2.025), Val102 (-2.442)	Tyr116 (2.63)	π-π Stacking: His294 (2.175), Phe290 (2.369),Tyr116 (2.632) Cation- π Stacking: Tyr116 (2.632)
9f	-8.015	-59.091	Hem500 (-5.137), Val461 (-2.644), Met460 (-2.481), Thr459 (-2.282), His458 (-2.230), Met360 (-2.233), Val359 (-1.834), Met358 (-1.928), Leu356 (-2.037), Thr295 (-2.171), His294 (-1.871), Ala291 (-1.897), Phe290 (-2.569), Ala287 (-2.022), Pro210 (-1.911), Ile209 (-1.798), Leu208 (-2.316), Glu205 (-1.899), Leu127 (-2.017), Tyr116 (-2.838), Phe110 (-1.969), Met106 (-2.010), Ile105 (-2.167), Tyr103 (-2.154), Val102 (-2.111)	Hem500 (-2.299), Arg361 (-1.324), Phe290 (-1.732), Leu208 (-2.001), Glu205 (-2.970), Arg124 (-1.537), Ile105 (-2.023), Val102 (-2.219)	--	π-π Stacking: His294 (2.126), Phe290 (2.549),Tyr116 (3.176) Cation- π Stacking: Tyr116 (3.176)

mol), Leu356 (-2.779 kcal/mol), Thr295 (-2.358 kcal/mol), Ala291 (-3.531 kcal/mol), Ala287 (-2.528 kcal/mol), Leu127 (-2.789 kcal/mol), Tyr116 (-3.788 kcal/mol), Phe110 (-2.735 kcal/mol) and Met106 (-3.434 kcal/mol) residues through 1-(4-nitrobenzyl)-1*H*-1,2,3-triazole core while the other half of the molecule i.e. 4-nitro-phenylprop-2-en-1-one was seen to be engaged significant van der Waals interactions with Met460 (-3.151 kcal/mol), Thr459 (-2.898 kcal/mol), His458 (-2.543 kcal/mol), Pro210 (-2.614 kcal/mol), Ile209 (-2.643 kcal/mol), Leu208 (-3.157 kcal/mol), Ile105 (-2.742 kcal/mol), Tyr103 (-2.39 kcal/mol) and Val102 (-2.825 kcal/mol) residues. The central phenyl ring linking these two halves of the molecule also showed very favourable van der Waals interactions with Met360 (-3.233), Met358 (-2.981), His294 (-2.277), Phe290 (-3.236) and Glu205 (-2.827) residues. The enhanced binding affinity observed for **9b** is also attributed to significant electrostatic interactions observed with Hem500 (-3.959 kcal/mol), Arg361 (-2.414 kcal/mol), Phe290 (-2.362 kcal/mol), Leu208 (-2.522 kcal/mol), Glu205 (-3.569 kcal/mol), Arg124 (-2.223 kcal/mol), Ile105 (-2.293 kcal/mol) and Val102 (-3.201 kcal/mol) residues of active site. Since CYP51 is a Heme enzyme, it is expected for a ligand to show significant steric and electrostatic interactions with Heme moiety and in the present study, it was consistently observed for all the chalcone analogues investigated. Furthermore, **9b** showed a very prominent hydrogen bonding interactions via the nitro (-NO_2) functional group with Tyr116 residue having a bonding distance of 2.65Å. The compound was also seen to be engaged in very close pi stacking interactions, firstly a pi-pi stacking interaction was observed between the central phenyl ring and His294 (2.168Å), Phe290 (2.374Å) residues and secondly through the 4-nitro phenyl ring and Tyr116 (2.651Å) residue. A Cation-Pi stacking type of interaction was also observed through the same nitro functional group and Tyr116 (2.651Å) residue. While the non-bonded interactions (steric and electrostatic) were observed to be the major driving force for mechanical interlocking of the chalcone analogues, the high binding affinity was strongly facilitated by these hydrogen bonding and Pi-stacking interactions which serve as an ″anchor″ to guide the orientation of inhibitor into the 3D space of enzyme's active site.

Overall, the binding affinity data derived from the docking study suggest that the 1,2,3-triazolyl chalcones possess a promising affinity for the fungal CYP51 enzyme qualifying them as a pertinent starting point for structure-based lead optimization to generate compounds with high selectivity and potency against CYP51.

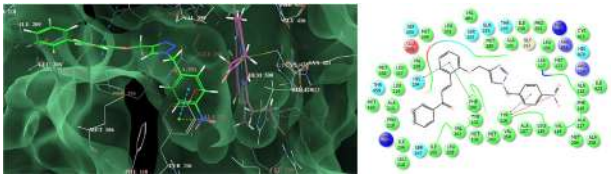


Figure 6: Binding mode of **9a** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

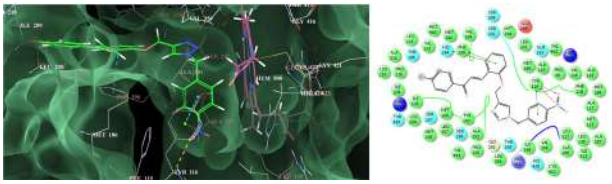


Figure 7: Binding mode of **9c** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

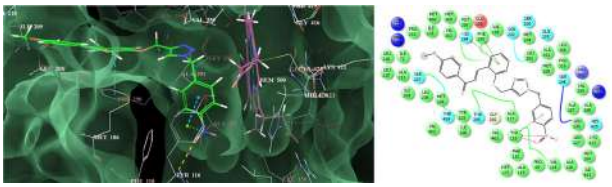


Figure 8: Binding mode of **9d** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

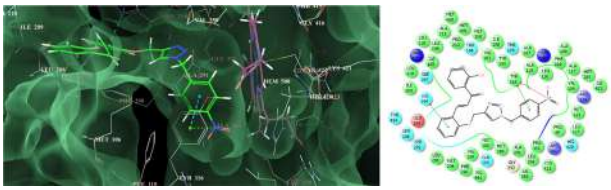


Figure 9: Binding mode of **9e** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

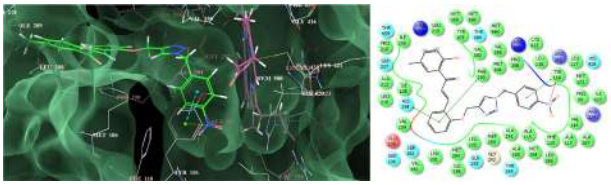


Figure 10: Binding mode of **9f** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

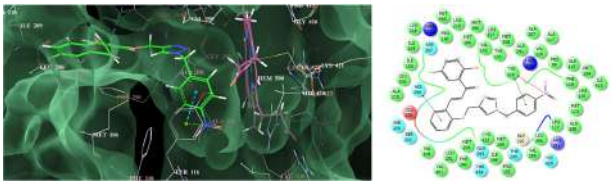


Figure 11: Binding mode of **9g** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

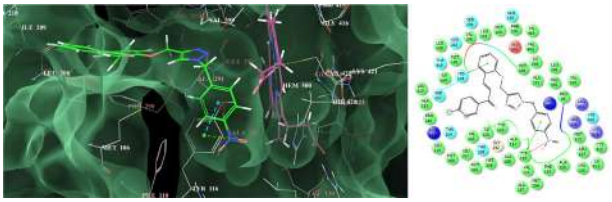


Figure 12: Binding mode of **9h** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

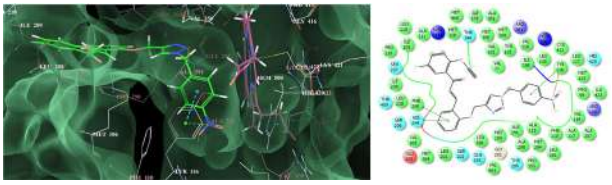


Figure 13: Binding mode of **9i** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen bonding interaction, green lines signify π-π stacking while red line represent cation-pi stacking interactions)

2.5 ADME Properties

Pharmacokinetic parameters of the synthesized 1,2,3-triazolyl-chalcones are summarised in **table 3**. It is observed that only compounds **9c** and **9i** violated Lipinski's rule of five (miLogP ≤ 5), remaining all other compounds did not show more than one violation of Lipinski's rule of five. Also, compounds exhibited a good % ABS (% absorption) ranging from 57.70% to 73.51%. Hence, All the tested compounds except **9c** and **9i** followed the criteria for orally active drug and therefore, these newly synthesized 1,2,3-triazolyl-chalcones may have a good potential to develop as good oral active drug candidates.

Table 3. Pharmacokinetic parameters important for good oral bioavailability

Entry	%ABS	n-atoms	TPSA (A^2)	n-ROTB	MV	MW	milog p	n-ON	n-OHNH	Lipinski's violations	Drug-likeness model score
Rule	-	-	-	-	-	<500	≤5	<10	<5	≤1	-
9a	73.51	33	102.85	09	387.65	440.46	4.94	8	0	0	-0.50
9b	57.70	36	148.67	10	410.98	485.46	4.90	11	0	1	-0.44
9c	73.51	34	102.85	09	405.53	519.36	5.75	08	0	2	-0.35
9d	70.33	35	112.08	10	413.19	470.49	5.00	09	0	1	-0.35
9e	66.54	34	123.08	09	395.66	456.46	4.88	09	1	0	+0.25
9f	66.54	35	123.08	09	412.23	470.49	5.31	09	1	1	+0.00
9g	66.54	35	123.08	09	400.60	474.45	5.02	09	1	1	+0.16
9h	73.51	34	102.85	09	392.58	458.45	5.11	08	0	1	-0.19
9i	70.33	38	112.08	11	440.62	512.50	5.23	09	0	2	-0.03

ABS: absorption; TPSA: topological polar surface area; n-ROTB: number of rotatable bonds; MV: molecular volume; MW: molecular weight; lmiLog P: logarithm of partition coefficient; n-ON: number of hydrogen bond acceptors; n-OHNH: number of hydrogen bonds donors.

3 Conclusion

In conclusion, we have synthesized some new 1,2,3-triazolyl-chalcones and subsequently screened for their in *vitro* antifungal and antioxidant activity. Most of the synthesized chalcones were displayed potential antifungal activity against most of the fungal strain used in the experiment which indicates the broad-spectrum antifungal activity of the synthesized chalcones. Molecular docking studies further supported the strong inhibitory activity which was further enriched using per-residue interaction analysis that could provide a deeper insight into the specific residues and their associated type of thermodynamic interactions influencing the binding affinity for the crucial fungal enzyme CYP51. Also, synthesized 1,2,3-triazolyl-chalcones showed potential antioxidant properties. Furthermore, ADME prediction shows better chances of these derivatives to evolve as a potential antifungal and antioxidant drug candidates. This inference derived from the in *vitro*/ in *silico* experiments is now fruitfully utilized to carry out site-specific modifications around the scaffold to improve the selectivity and potency of the 1,2,3-triazolyl-chalcones.

4 Experimental

4.1 Analytical methods

All chemicals and reagents used were of analytical grade. The progress of the reactions was monitored by thin-layer chromatography (TLC) on aluminium plates coated with silica gel 60 F_{254}, 0.25 mm thickness (Merck). The detection of the components was made by exposure to iodine vapours or UV light. Melting points were determined by an open capillary method and are uncorrected. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-200 MHz spectrometer. ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-100 MHz instrument. IR spectra were recorded using a Bruker ALPHA ECO-ATR FTIR spectrometer. Mass spectra were recorded on

LC/ESI-MS spectrometer.

4.2 Chemistry

General procedure for the preparation of 1,2,3-triazolyl-chalcones:

A mixture of 1,2,3-triazole incorporated benzaldehyde **7** (1 mmol) and various substituted acetophenone (**8a-i)** (1 mmol) in ethanolic NaOH was taken in a 50 mL round bottom flask, equipped with a mechanical stirrer. The reaction mixture was stirred at room temperature for 4-5hrs. The progress of the reaction was monitored by TLC. The reaction mixture was poured into 50 mL ice-water and the obtained solid was filtered, dried and recrystallized from ethanol-DMF to obtain a dark brown solid product **(Scheme 2, 9a-i)**.

Spectral data of synthesized compounds:

4.2.1 (E)-3-(2-((1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1-phenylprop-2-en-1-one (9a):

Yellow colored solid, Yield: 86%, mp. 178-180 °C; IR (cm^{-1}): 1655 (C=O), 1588 (C=C), 1506 (C=C Ar), 1341 (N-O), 999 (N-N); ^{1}H NMR (200 MHz, DMSO-d_6 ppm): 8.83 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 8.0 Hz, 5H), 7.96 (d, *J* = 8.0 Hz, 4H), 7.66 (d, *J* = 8.0 Hz, 4H), 6.24 (s, 2H), 5.72 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 191.0, 158.3, 148.3, 144.9, 143.7, 140.9, 138.3, 133.0, 130.4, 128.8, 128.5, 124.5, 125.0, 122.3, 122.2, 121.9, 115.7, 58.0 and 50.2; ESI-MS: Calcd for $C_{25}H_{20}N_4NaO_4$ $[M+Na]^+$, 463.4, found: 463.0

4.2.2 (E)-3-(2-((1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1-(4-nitrophenyl)prop-2-en-1-one (9b):

Yellow colored solid, Yield: 85%, mp. 182-184 °C; IR (cm^{-1}): 1592 (C=O), 1511 (C=C), 1392 (C=C Ar), 1339 (N-O), 1009 (N-N); ^{1}H NMR (200 MHz, DMSO-d_6 ppm): 8.88 (s, 1H), 8.72 (d, *J* = 8.0 Hz, 3H), 8.35 (d, *J* = 8.0 Hz, 4H), 8.01 (d, *J* = 8.0 Hz, 3H), 7.70 (d, *J* = 8.0 Hz, 4H), 6.28 (s, 2H), 5.76 (s, 2H)**;** ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 191.6, 158.9, 151.3, 148.9, 145.5, 144.3, 143.8, 141.5, 129.7, 129.4, 129.2, 125.1, 124.6, 122.8, 116.3, 58.6 and 50.8**;** LC-MS: Calcd for $C_{25}H_{20}N_5O_6$ $[M+H]^+$, 486.5, found: 486.2

4.2.3 (E)-1-(4-Bromophenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one (9c):

Yellow colored solid, Yield: 85%, mp. 190-193 °C; IR (cm^{-1}): 1655 (C=O), 1587 (C=C), 1407 (C=C Ar), 1343 (N-O), 998 (N-N); ^{1}H NMR (200 MHz, DMSO-d_6 ppm): 8.79 (s, 1H), 8.43 - 8.35 (m, 4H), 7.93-7.73 (m, 9H), 7.48 (t, *J* = 8.0 Hz, 1H) 6.08 (s, 2H), 5.72 (s, 2H)**;** ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 188.0, 155.3, 137.9, 133.6, 129.1, 127.4, 126.7, 125.8, 125.7, 125.6, 125.4, 121.5, 119.4, 119.2, 118.9, 112.7, 55.0 and 47.2; ESI-MS: Calcd for $C_{25}H_{19}BrN_4NaO_4$ $[M+Na]^+$, 542.3, found: 542.0

4.2.4 (E)-1-(4-Methoxyphenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one (9d):

Yellow colored solid, Yield: 87%, mp. 175-178 °C; IR (cm^{-1}): 1655 (C=O), 1588 (C=C), 1477 (C=C Ar), 1340 (N-O), 1014 (N-N); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 187.8, 160.5, 155.1, 145.1, 141.7, 140.5, 137.7, 127.6, 125.6, 125.4, 121.3, 119.2, 119.0, 112.5, 110.7, 54.8, 52.8 and 47.0**;** LC-MS: Calcd for $C_{26}H_{23}N_4O_5$ $[M+H]^+$, 471.5, found: 471.2

4.2.5 (E)-1-(2-Hydroxyphenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one (9e):

Yellow colored solid, Yield: 86%, mp. 198-200 °C; IR (cm^{-1}): 1766 (C=O), 1594 (C=C), 1402 (C=C Ar), 1343 (N-O), 1008 (N-N); ^{1}H NMR (200 MHz, DMSO-d_6 ppm): 8.83 (s, 1H), 8.67 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 4H), 7.65 (d, *J* = 8.0 Hz, 6H),

6.23 (s, 2H), 5.71 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 190.0, 158.7, 155.1, 145.1, 141.7, 140.5, 136.7, 132.3, 127.2, 126.8, 125.6, 125.5, 125.3, 121.3, 119.8, 119.1, 119.0, 116.6, 114.7, 112.5, 54.7 and 47.0; LC-MS: Calcd for $C_{25}H_{21}N_4O_5$ $[M+H]^+$, 457.5, found: 457.2

4.2.6 (E)-1-(2-Hydroxy-5-methylphenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl) methoxy)phenyl)prop-2-en-1-one (9f):

Yellow coloured solid, Yield: 88%, mp. 188-192 °C; IR (cm^{-1}): 1660 (C=O), 1515 (C=C), 1433 (C=C Ar), 1344 (N-O), 1044 (N-N); ^{1}H NMR (200 MHz, DMSO-d_6 ppm): 8.41 (s, 1 H), 8.25 (d, J = 8.0 Hz, 3H), 7.88 (d, J = 8.0 Hz, 4H), 7.54 (d, J = 8.0 Hz, 3H), 7.24 (d, J = 8.0 Hz, 3H), 5.81 (s, 2H), 5.29 (s, 2H), 1.90 (s, 3H)**;** ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 186.4, 153.0, 152.2, 142.2, 138.8, 137.6, 133.8, 128.9, 124.9, 124.3, 123.3, 122.7, 122.6, 122.5, 118.4, 117.4, 116.9, 116.3, 116.1, 112.5, 109.6, 51.9, 44.1 and 15.1**;** LC-MS: Calcd for $C_{26}H_{23}N_4O_5$ $[M+H]^+$, 471.5, found: 471.2

4.2.7 (E)-1-(5-Fluoro-2-hydroxyphenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl) methoxy)phenyl)prop-2-en-1-one (9g):

Yellow coloured solid, Yield: 87%, mp. 177-180 °C; IR (cm^{-1}): 1659 (C=O), 1593 (C=C), 1440 (C=C Ar), 1337 (N-O), 1026 (N-N); ^{1}H NMR (400 MHz, DMSO-d_6 δ ppm): 8.60 (d, J = 8.0 Hz, 3H), 8.34-8.21 (m, 4H), 7.90 (d, J = 8.0 Hz, 4H), 7.51 (d, J = 8.0 Hz, 3H), 6.15 (s, 2H), 5.68 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 192.5, 158.3, 157.8, 155.5, 148.3, 144.9, 143.7, 139.9, 130.4, 128.8, 128.5, 124.5, 123.0, 122.3, 121.8, 120.7, 119.7, 118.3, 115.7, 58.0 and 50.2**;** ESI-MS: Calcd for $C_{25}H_{20}FN_4O_5$ $[M+H]^+$, 475.4, found: 476.0

4.2.8 (E)-1-(4-Fluorophenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy) phenyl)prop-2-en-1-one (9h):

Yellow colored solid, Yield: 90%, mp. 197-200 °C; IR (cm^{-1}): 1655 (C=O), 1597 (C=C), 1445 (C=C Ar), 1333 (N-O), 1008 (N-N); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 191.0, 165.9, 163.8, 158.3, 148.3, 144.9, 143.7, 140.9, 134.9, 131.0, 130.4, 128.8, 128.5, 124.5, 122.3, 121.9, 116.0, 115.7, 58.0 and 50.2; LC-MS: Calcd for $C_{25}H_{19}FN_4O_4$ $[M]^+$, 458.4, found: 458.1

4.2.9 (E)-1-(5-Fluoro-2-(prop-2-yn-1-yloxy) phenyl)-3-(2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one (9i):

Yellow colored solid, Yield: 86%, mp. 200-204 °C; IR (cm^{-1}): 1674 (C=O), 1564 (C=C), 1412 (C=C Ar), 1341 (N-O), 1008 (N-N); ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 190.6, 160.9, 158.8, 158.3, 154.0, 148.3, 144.9, 143.7, 139.9, 130.4, 128.8, 128.5, 126.8, 124.5, 123.0, 122.3, 120.1, 119.6, 118.6, 115.7, 80.0, 78.8, 59.7, 58.0 and 50.2; ESI-MS: Calcd for $C_{28}H_{21}FN_4NaO_5$ $[M+Na]^+$, 535.5, found: 535.0

4.3 Antifungal activity assay

Antifungal activity was determined by standard agar dilution method as per CLSI (formerly, NCCLS) guidelines[38]. The synthesized compounds and standard Miconazole were dissolved in DMSO solvent. The medium yeast nitrogen base was dissolved in phosphate buffer pH 7 and it was autoclaved at 110°C for 10 min. With each set a growth control without the antifungal agent and solvent control DMSO were included. The fungal strains were freshly sub cultured onto Sabouraud dextrose agar (SDA) and incubated at 25°C for 72 h. The fungal cells were suspended in sterile distilled water and diluted to get 105cells/mL. Ten microliters of standardized suspension was inoculated onto the control plates and the media incorporated with the antifungal agents. The inoculated plates were incubated at 25°C for 48 h. The readings were taken at the end of 48 and 72 h. The MIC was the lowest concentration of drug preventing growth of macroscopically visible colonies on drug containing plates when there was visible

growth on the drug free control plates.

4.4 Antioxidant activity assay

Antioxidant activity of the synthesized compounds has been assessed in *vitro* by the 1, 1-diphenyl-2picrylhydrazyl (DPPH) radical scavenging assay [39]. Results were compared with standard antioxidant BHT (Butylated Hydroxy Toluene). The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple coloured methanol solution of 1, 1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 mg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The per cent inhibition (I %) of free radical production from DPPH was calculated by the following equation.

% of scavenging = [(A control-A sample)/A blank] X 100

Where 'A control' is the absorbance of the control reaction (containing all reagents except the test compound) and 'A sample' is the absorbance of the test compound. Tests were carried at in triplicate.

4.5 Molecular docking

To gain insight into the plausible mechanism of action by which the 1,2,3-triazolyl-chalcones studied herein could exhibit the antifungal activity and guide further SAR based on our experimental studies, molecular docking against sterol 14α-demethylase (CYP51) was performed. Molecular docking has emerged as a reliable tool to identify the biological target for the bioactive molecules and gain an insight into crucial ligand-protein thermodynamic interactions. Especially in the absence of available resources to perform enzyme-based assays, molecular docking is considered as complementary to the *in vivo* and *in vitro* biological study for understanding the ligand-receptor interactions at the atomic level. With this purpose, the 3D X-ray crystal structure of sterol 14α-demethylase (CYP51) enzyme complexed with its inhibitor-Miconazole (pdb code: 3KHM) was retrieved from the Protein Data Bank (PDB) (http: //www.rcsb. org/pdb). Sterol 14α-demethylase (CYP51) is a crucial fungal enzyme that catalyses the conversion of lanosterol to ergosterol in the cell and thus its inhibition could lead to accumulation of 14α-methyl sterols in the cell causing impaired cell growth. The GLIDE (Grid-based Ligand Docking with Energetics) program integrated into the Schrödinger Molecular modelling package (Schrodinger, LLC, New York, NY, 2018) [40–43] was used to perform the docking study. The preliminary crystal structure of CYP51 was refined using with the protein preparation wizard to remove the experimental errors in the structure. This involved eliminating the crystallographic water molecules since no conserved interactions with the enzyme are reported; adding the missing hydrogen/side-chain atoms corresponding to pH 7.0, assignment of appropriate charge and protonation state followed by energy minimization (applying the OPLS-2005 force field) of the obtained structure to relieve the steric clashes among the amino acid residues till RMSD for the heavy atoms reached 0.30Å. The 3D structures of the 1,2,3-triazole incorporated chalcone were sketched using the build panel and optimized using Ligand Preparation tool in Maestro which involves adjusting realistic bond lengths and angles, ascribing the partial charges using OPLS-2005 force-field followed by energy minimization until its average RMSD reached 0.001Å. The active site of CYP51 enzyme for docking was defined using Receptor Grid Generation panel

wherein a grid box of 10X10X10Å dimensions centred on centroid of the co-crystallized ligand was generated. With this automatic setup, the lowest energy conformation of each ligand was docked against defined active site of CYP51 using extra precision (XP) Glide scoring function to gauze the binding affinities of triazole analogues towards CYP51. For each compound, the most stable docking pose was selected according to best-scored conformation and analysed quantitatively for the most significant interactions with residues lining the active site using Maestro's Pose Viewer utility.

4.6 ADME Prediction

All the synthesized 1,2,3-triazolyl-chalcones were tested for Lipinski's rule of five. According to this rule, a molecule likely to be developed as an orally active drug should not exhibit more than one violation of following four criteria: molecular weight ≤ 500, number of hydrogen bond donors ≤ 5, miLogP (octanol-water partition coefficient) ≤ 5, number of hydrogen bond acceptors ≤ 10. ADME properties were predicted by using molinspiration online property calculation toolkit. A collective property of physicochemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value known as the drug-likeness model score was computed by using MolSoft software.

Conflict of interest

The authors declare that they have no conflict of interest.

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Propargylated monocarbonyl curcumin analogues: synthesis, bioevaluation and molecular docking study

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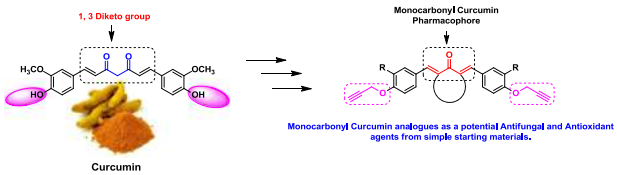
Abstract

In the current experimental study, we have synthesised new monocarbonyl curcumin analogues bearing propargyl ether moiety in their structure and evaluated for in vitro antifungal and radical scavenging activity. The antifungal activity was carried out against five human pathogenic fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. Most of the curcumin analogues displayed excellent to moderate fungicidal activity when compared with standard drug Miconazole. Also, synthesised analogues exhibited potential radical scavenging activity as compared with standard antioxidant Butylated hydroxyl toluene (BHT). Based on biological data, structure-activity relationship (SAR) were also discussed. Furthermore, in silico computational study was carried out to know binding interactions of synthesised analogues in the active sites of enzyme sterol 14α-demethylase (CYP51).

Graphical Abstract



Keywords Monocarbonyl curcumin analogues · Antifungal activity · Antioxidant activity · SAR · Molecular docking study

Introduction

Curcumin is the principal curcuminoid of the turmeric plant of the family *Zingiberaceae*. It has been used to treat many health conditions in India and other parts of Asia since ancient times. According to recent literature, curcumin is the multi-target pleiotropic agent displaying a wide spectrum of biological activities (Goel et al. 2008; Marchiani et al. 2013; Bairwa et al. 2014; Shetty et al. 2015). Curcumin has been evaluated in clinical trials for the treatment of various diseases like cancer, liver diseases, infectious diseases and rheumatoid arthritis (Hatcher et al. 2008; Bairwa et al. 2014). However, clinical use of the curcumin is restricted due to poor bioavailability, poor

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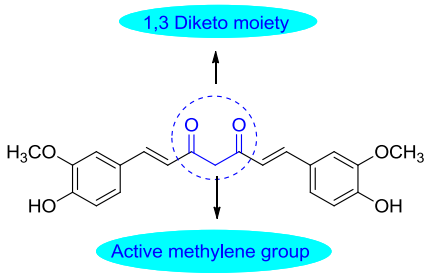


Fig. 1 Curcumin and groups responsible for the instability

pharmacokinetics and rapid in vivo metabolism (Anand et al. 2008). It was observed that, presence of the β-diketone and active methylene groups are responsible for the instability of curcumin (Anand et al. 2007; Wang et al. 1997) (Fig. 1).

Structural modification on curcumin by replacing β-diketone moiety as well as an active methylene group with single keto-functionality leads to the formation of therapeutically active, stable monocarbonyl analogues of curcumin (MACs) (Shetty et al. 2015). The literature survey revealed that, MACs were displayed a wide spectrum of biological activities which are found to be superior to curcumin itself. MACs shows potential anticancer (Kerru et al. 2017), anti-inflammatory (Wang et al. 2017), antioxidant (Zheng et al. 2017), antibacterial (Sanabria-Rios et al. 2015), anti-Alzheimer's activity (Chen et al. 2011), antiparasitic (Carapina da Silva et al. 2019), antileishmanial (Tiwari et al. 2015), topoisomerase II alpha inhibitors (Paul et al. 2014), antiobesity (Buduma et al. 2016), anti-tubulin (Singh et al. 2016), anti-invasive chemotypes (Roman et al. 2015), lipoxygenase and proinflammatory cytokines (Ahmad et al. 2014), anti-tubercular (Subhedar et al. 2017), antifungal activity (Sahu et al. 2012) etc.

In recent years, invasive fungal infections are a major concern due to an increase in organ transplantation, stem cell transplantation, chemotherapy and human immunodeficiency virus. Candidosis, aspergillosis and cryptococcosis, are three major fungal infections responsible for clinical infections in patients having a weak immune system. Although, there are several drugs available to treat fungal diseases, multidrug-resistant strain development among the fungal species against existing amphotericin B, triazoles, and echinocandins based antifungal drugs (Pappas et al. 2015) become a critical problem for therapeutic strategies (Seufert et al. 2018). Also, existing antifungal drugs have many side effects. Long term use of the existing antifungal drugs can induce many side effects such as cough, bad taste, nausea, hepatotoxicity, liver toxicity, hypokalemia, fever, gastrointestinal, endocrinologic, metabolic, carcinogenic, chills and drug-drug interactions between azole and other drug classes that are metabolised *via* similar pathways in the liver (Bodey 1992; Shehaan et al. 1999).

These limitations emphasise the need to develop new and more effective antifungal agents. Martins et al. (Martins et al. 2009) evaluated the potential of curcumin against various fungal strains as an effective antifungal as compared with commercial drug fluconazole. Very recently, anti-infective properties of curcumin have been reviewed (Praditya et al. 2019). Hence, curcumin and its analogues can be the new scaffold in the search of new antifungal agents. Covalent modification by prenylation have been recognised as a mechanism for promoting membrane interactions and biological activity of a variety of cellular proteins (Casey 1992).

It was observed that, reactive oxygen species were involved in the mechanism of action of antifungal drugs (Da Silva et al. 2014). Therefore, new antifungals with antioxidant potential can be a good choice. Literature revealed that, curcumin moiety is responsible for antioxidant activity (Masuda et al. 2001; Sokmen, Khan 2016). Considering the antioxidant activity of curcumin analogues (Li et al. 2015; Sahu et al. 2016a, b; Lal et al. 2016; Zheng et al. 2017), many attempts were made to develop new curcumin based molecules as an antioxidant agents. Some of the representative structures of the molecules as an antioxidant agents were shown in Fig. 2.

Under this context and as a part of our ongoing research in the synthesis and biological evaluation of monocarbonyl curcumin analogues (Deshmukh et al. 2020; Subhedar et al. 2017; Nagargoje et al. 2019, 2020), we report herein, synthesis, antifungal and antioxidant evaluation of new propargylated monocarbonyl curcumin analogues. Furthermore, to understand the binding mechanism of newly synthesised analogues into the active sites of cytochrome P450, molecular docking study was also performed.

Results and discussion

Chemistry

In the present work, we have described the synthesis of new propargylated monocarbonyl curcumin analogues by the Claisen–Schmidt type condensation (Fine, Pulaski 1973; Ziani et al. 2013) of propargylated benzaldehydes with monoketone linkers like cyclohexanone, cyclopentanone, acetone and 4-methyl piperidone by literature method. The reaction of benzaldehyde **1a–c** with propargyl bromide in the presence of an alkaline condition resulted in the corresponding substituted prop-2-yn-1-yloxy-benzaldehydes **2a–c** in excellent yields (Scheme 1). The condensation of these benzaldehydes **2a–c** with respective monoketone **3a–d** using aq. NaOH and ethanol at room temperature resulted into corresponding propargylated monocarbonyl curcumin analogues **4a–i** in a good yield. (Scheme 1).

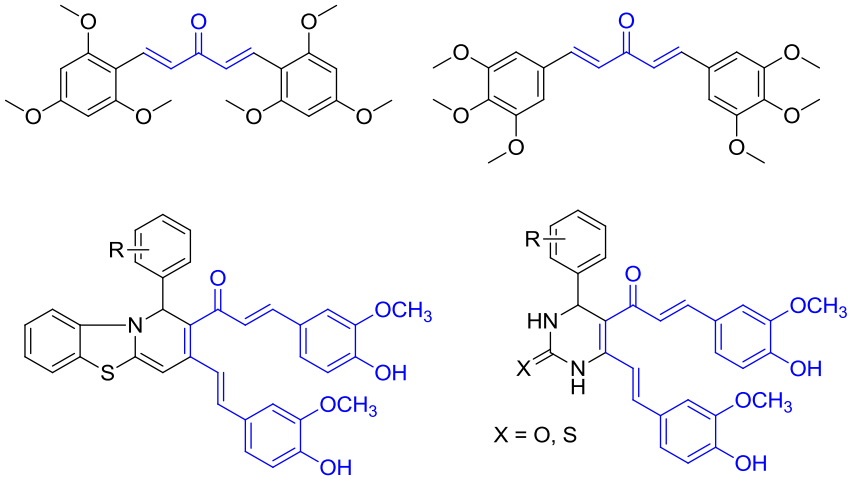
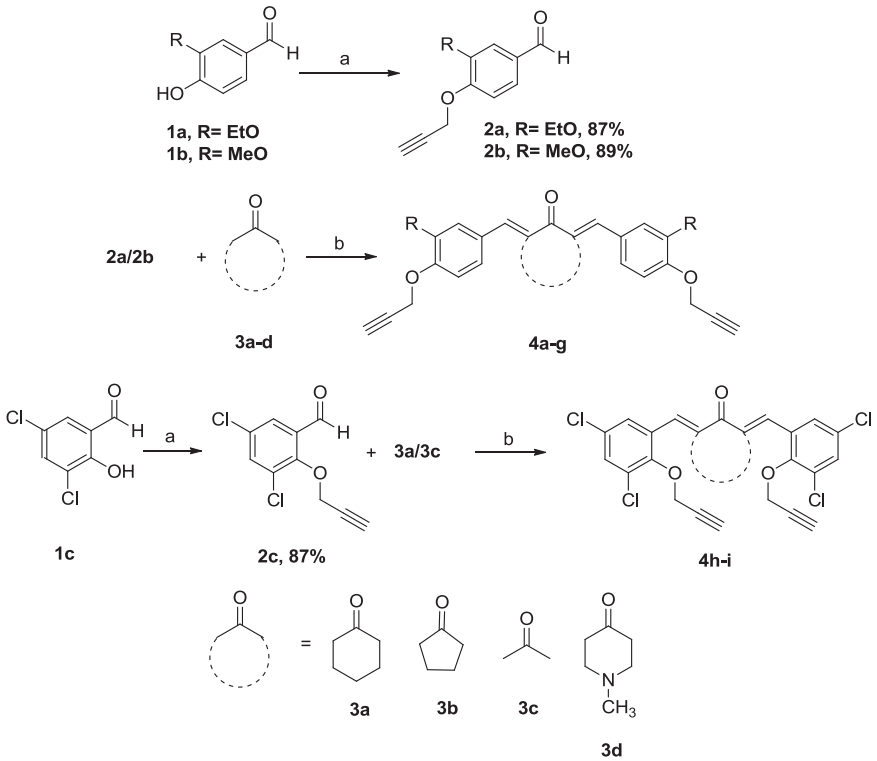


Fig. 2 Known MACs with antioxidant activity



Scheme 1 Synthesis of propargylated monocarbonyl curcumin analogues. Reagent and conditions: (a) Propargyl bromide, K_2CO_3, DMF, rt, 3–4 h; (b) Aq. NaOH, EtOH, rt, 4–5 h

The formation of propargylated monocarbonyl curcumin analogues **4a–i** has been confirmed by physical data and spectroscopic methods such as FT-IR, ^{1}H NMR, ^{13}C NMR and LC/ESI-MS. According to the FT-IR spectrum of compound **4a**, the peaks observed at 3262 cm^{-1}, 2120 cm^{-1} indicate the presence of the alkyne group and 1660 cm^{-1} for the presence of a carbonyl group. In the ^{1}H NMR spectrum of compound **4a**, the triplet at 1.47 ppm is observed for methyl group adjacent to a methylene group present on the benzene ring, multiple ranging in between 1.84 and 1.78 ppm, and triplet at 2.93 ppm is observed for methylene groups of cyclohexanone ring, triplet at 2.53 ppm with coupling constant 2.4 Hz for two alkyne protons (This indicates coupling of acetylinic proton with methylene protons adjacent to oxygen and alkyne group), the quartet at 4.12 ppm for four methylene protons adjacent to oxygen and methyl group on benzene rings, a doublet at 4.81 ppm with coupling constant 2.4 Hz (This indicates coupling of these protons with terminal acetylene protons) for the presence of two methylene protons adjacent to oxygen and alkyne group on a benzene ring. In addition to this, the signal appeared at 7.03 and 7.08 ppm for six aromatic protons of benzene rings. The signal appeared at 7.73 ppm is for two alkene protons. These alkene protons are benzylidine protons, and also in β position to the carbonyl group, hence due to resonance effect and –I effect of the

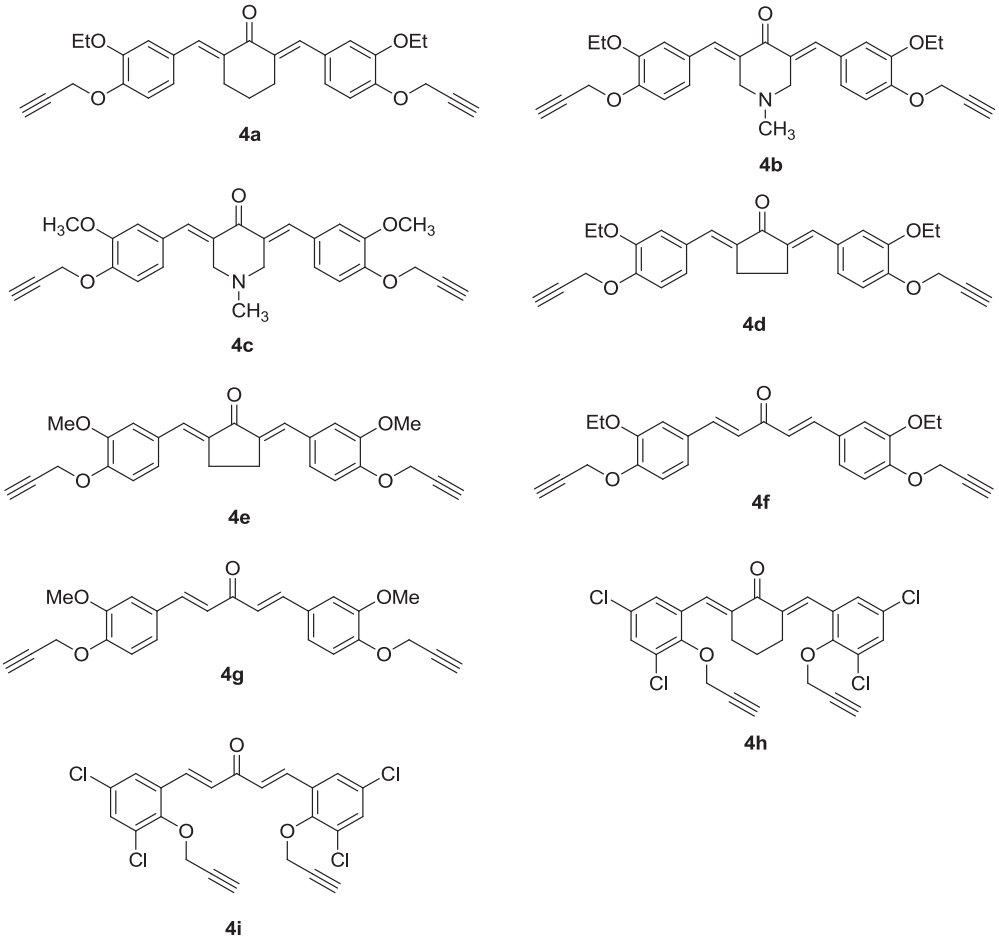


Fig. 3 Structures of synthesised monocarbonyl curcumin analogues

carbonyl group and benzene ring this signal is shifted to downfield region. In the ^{13}C NMR spectrum of compound **4a**, the signal at 14.8 ppm is observed for the methyl carbon and the signals at 23.0 and 28.5 ppm indicate the presence of two methylene carbon of cyclohexanone ring. The signals at 56.8 and 64.6 ppm indicate the presence of methylene carbons adjacent to oxygen. The signal at 76.0 and 78.4 ppm shows the presence of alkyne carbons. Furthermore, the peak observed at 190.1 ppm for carbonyl carbon. The formation of compound **4a** has been further confirmed by mass spectrometry. The calculated $[M\text{-}H]^+$ for compound **4a** is 469.2093 and observed $[M\text{-}H]^+$ in the mass spectrum at 469.2143. Similarly compounds **4b–i** were characterised by the spectral analysis. The structures of all the synthesised MACs are given in Fig. 3.

In vitro antifungal activity

The synthesised MACs were evaluated for in vitro antifungal activity against various fungal strains like *Cryptococcus neoformans*, *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, *Fusarium oxysporum* etc. The minimum inhibitory potential of synthesised analogues were compared against the standard antifungal drug Miconazole. The *MIC* values in µg/mL were estimated and the results are summarised in Table 1.

Most of the synthesised MACs exhibited excellent to moderate antifungal potential against most of the pathogenic fungal strains, which is reflected by their *MIC* values. Antifungal activity of synthesised MACs compare to standard Miconazole is represented graphically in Fig. 4. Among the series, compound **4a** displayed equivalent or two/three fold more potency as compared with positive control Miconazole, which reflects its broad-spectrum nature. Compound **4a** demonstrates excellent inhibitory activity against *Candida albicans, Fusarium oxysporum* and *Cryptococcus neoformans* (*MIC* 12.5 µg/mL, *MIC* 12.5 µg/mL and *MIC* 12.5 µg/mL, respectively) with compared with Miconazole. Also, **4a** is equipotent against *Aspergillus flavus and Aspergillus niger* (*MIC* 25 µg/mL each) with compared with Miconazole. Furthermore, compound **4b** and **4c** exhibited almost equal potency as

Table 1 In vitro antifungal and antioxidant evaluation of propargylated monocarbonyl curcumin analogues

Entry	Antifungal activity (MIC in μg/mL)					Molecular docking score	Antioxidant activity (IC_{50} in μg/mL)
	CA[a]	FO[b]	AF[c]	AN[d]	CN[e]		
4a	12.5	12.5	25	25	12.5	−8.939	24.28 ± 0.45
4b	25	12.5	25	25	50	−8.559	16.17 ± 0.11
4c	62.5	25	37.5	12.5	25	−8.097	15.78 ± 0.47
4d	37.5	87.5	25	50	62.5	−8.534	40.34 ± 0.14
4e	25	25	75	50	100	−7.490	13.18 ± 0.34
4f	75	75	12.5	25	75	−7.762	28.36 ± 0.43
4g	100	75	75	100	175	−7.338	27.81 ± 0.05
4h	12.5	25	75	100	25	−7.637	41.42 ± 0.67
4i	150	125	150	175	100	−7.088	12.78 ± 0.71
MA	25	25	12.5	25	25	–	–
BHT	–	–	–	–	–	–	16.47 ± 0.18

MA miconazole, *BHT* butoxy hydroxy tolune

[a]Candida albicans

[b]Fusarium oxysporum

[c]Aspergillus flavus

[d]Aspergillus niger

[e]Cryptococcus neoformans

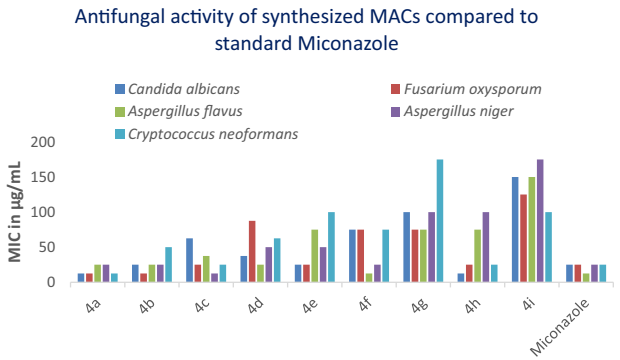


Fig. 4 Antifungal activity of synthesised MACs compared with Miconazole

compared with standard. Compound **4e**, **4f** and **4h** displayed moderate potential to act as an antifungal agent. Also, antifungal activity data showed that **4a**, **4b** and **4f** were the most active against *Aspergillus flavus*. The trends in the *MIC* values of the synthesised analogues help to establish some sort of structure-activity relationship (SAR). From the minimum inhibitory concentration values of the synthesised propargylated monocarbonyl curcumin analogues against different fungal strains, it was observed that curcumin analogues with cyclic linkers like cyclohexanone and *N*-methyl piperidone enhances antifungal potential. To be more specific, analogues with cyclohexanone linker displayed better antifungal activity. Comparing *MIC* values of compound **4a** and **4h** it was observed that cyclohexanone linker played an important role in enhancing antifungal activity. Analogues with ethoxy (-OEt) group on the aromatic side-chain have better antifungal potential than other analogues having a methoxy (-OMe) and chloro (-Cl) group. Furthermore, antifungal potential is found to decrease when cyclopentanone and acetone were used as a linker molecule. Also, it was observed that most of the curcumin analogues showed strong potential against all fungal strains except *Cryptococcus neoformans*. In contrast, curcumin analogues **4g** and **4i** do not show significant antifungal activity against any tested pathogenic fungal strains, which also revealed that open space linker like acetone found to decrease antifungal activity.

In vitro antioxidant activity

All synthesised propargylated monocarbonyl curcumin analogues were further evaluated for in vitro radical scavenging activity. It was observed that the compound **4i** with acetone linker and 3,5-chloro substitution on the aromatic ring displayed potential antioxidant activity (IC_{50} = 12.78 ± 0.71) when compared with the standard drug BHT (IC_{50} = 16.47 ± 0.18) (Table 1). Furthermore, analogues **4b**, **4c** and **4e** displays almost greater or equal antioxidant potential as compared with BHT. Trends in antioxidant and antifungal activity data revealed that analogues **4b**, **4c** and **4e** exhibited potential antifungal and antioxidant activity as reflected in their *MIC* and IC_{50} values. Also, analogue **4i** which was inactive against fungal strains were found to exhibit strong antioxidant activity. It was observed that

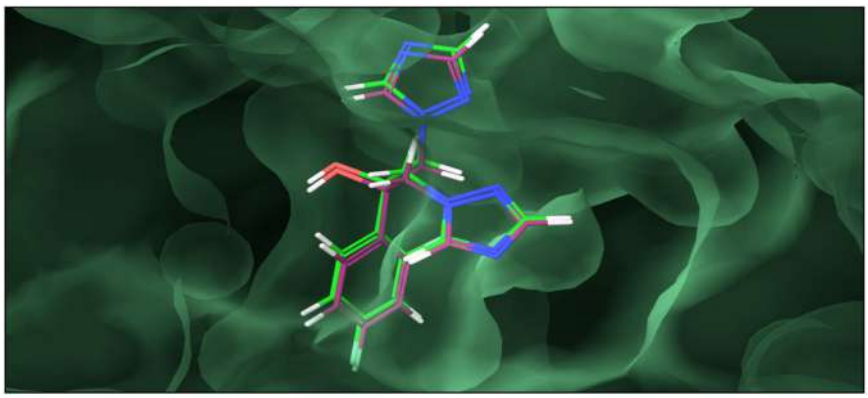


Fig. 5 Superimposition of the best scoring pose for Fluconazole obtained from docking (green carbon) against the X-ray bound conformation (pink carbon)

acetone linker enhances antioxidant activity than cyclic linker.

Molecular docking study

Promising levels of activities demonstrated by the propargylated monocarbonyl curcumin analogues investigated herein against the various fungal strains prompted us to carry out molecular docking studies against the crucial sterol 14α-demethylase (CYP51) enzyme (PDB code: 3KHM) to elucidate their plausible mechanism of antifungal activity. Within the framework of in silico structure-based drug design approaches, molecular docking has evolved an inevitable tool to predict the potential biological target with a substantial degree of accuracy especially in the absence of available resources to do the experimental enzyme assay. Sterol 14α-demethylase (CYP51) is an ancestral activity of the cytochrome P450 superfamily and is essential for ergosterol biosynthesis in fungi where it catalyzes the conversion of lanosterol to ergosterol. Inhibition of CYP51 leads to accumulation of 14α-methyl sterols and depletion of ergosterol in the fungal cell wall, resulting in altered cell membrane properties and function with subsequently increased permeability and inhibition of cell growth and replication.

Molecular docking protocol was validated by extracting the co-crystallised ligand (Fluconazole) and re-docking using the experimental set up described in the experimental part of docking analysis (Fig. 5).

From the ensuing docked conformations, it is revealed that all the propargylated monocarbonyl curcumin analogues could bind to the active site of CYP51 with varying degrees of affinities at co-ordinates close to the native structure by formation of a network of close interactions. The docking scores for the series varied from −8.939 for the most active to −7.088 for moderately active with an average docking score of −7.963 signifying a promising binding affinity towards CYP51. Furthermore, a detailed per-residue interaction analysis was carried out to identify the most significantly interacting residues and their associated thermodynamic interactions. This analysis is discussed in detail for one of the most active molecule **4a** and summarised in Table 2 for other active compounds **4b, 4c, 4f** and **4h** as well (SI-1 to SI-4, Supplementary Information).

The lowest energy docked conformation of **4a** (Fig. 6) revealed that it could snugly fit into the active site of CYP450 at co-ordinates similar to native ligand (Fig. 7) engaging in a network of bonded and non-bonded (steric and electrostatic) interactions.

The compound was found to be stabilised through most significant van der Waals interactions observed with Val461 (−3.246 kcal/mol), Phe290 (−2.953 kcal/mol), Ala287 (−2.954 kcal/mol), Glu205 (−2.741 kcal/mol), Tyr116 (−4.431 kcal/mol), Phe110 (−2.871 kcal/mol), Met106 (−3.155 kcal/mol), Tyr103 (−3.098 kcal/mol) residues *via* the central cyclohexanone nucleus while the 3-ethoxy-4-(prop-2-yn-1-yloxy) benzylidene side chains flanking both side of the nucleus engaged in similar van der Waals interactions with Hem500 (−5.738 kcal/mol), Met460 (−4.355 kcal/mol), Thr459 (−3.486 kcal/mol), Leu356 (−3.261 kcal/mol), Thr295 (−2.918 kcal/mol), Ala291 (−2.972 kcal/mol), Pro210 (−3.197 kcal/mol), Ile209 (−2.977 kcal/mol), Leu208 (−3.232 kcal/mol) and Ile105 (−3.288 kcal/mol) residues lining the active site. The enhanced binding affinity of **4a** is also attributed to very significant electrostatic interactions observed through Hem500 (−3.185 kcal/mol), Ile209 (−2.896 kcal/mol), Glu205 (−2.867 kcal/mol) and Tyr103 (−2.712 kcal/mol) residues.

Furthermore, **4a** also exhibited a very close hydrogen-bonding interactions with Tyr103(1.989 Å) residue through the ketone function of the central cyclohexanone nucleus which serve as an ″anchor″ to stabilise the 3D orientation of a ligand into the active site and also guide the steric and electrostatic (non-bonded) interactions. A similar network of bonded (H-bond) and non-bonded (steric and electrostatic) interactions were observed for other active analogues. It is noteworthy that all the active molecules,

Table 2 The per-residue interaction analysis based on docking study for propargylated monocarbonyl curcumin analogues with sterol 14α-demethylase (CYP51)

Code	Docking score	Glide interaction energy (kcal/mole)	Per-residues interactions	
			Coulombic (kcal/mol)	H-bond (Å)
4a	−8.939	−49.907	Hem500 (−3.185), Ile209 (−2.896), Glu205 (−2.867), Tyr103 (−2.712)	Tyr103 (1.989)
4b	−8.559	−48.324	Hem500 (−3.077), Ile209 (−2.596), Glu205 (−2.367), Tyr103 (−2.429)	–
4c	−8.097	−46.877	Hem500 (−2.939), Ile209 (−2.292), Glu205 (−2.349), Tyr103 (−2.392)	Tyr103 (2.088)
4f	−7.762	−47.954	Hem500 (−2.850), Ile209 (−2.196), Glu205 (−2.267), Tyr103 (−2.128)	Tyr103 (1.899)
4h	−7.637	−45.814	Hem500 (−2.739), Ile209 (−1.432), Glu205 (−2.139), Tyr103 (−2.092)	–
Fluconazole	−7.34	−52.92	Hem500 (−5.862), Ile209 (−2.896), Glu205 (−2.929), Tyr103 (−2.35)	Tyr116 (2.11)

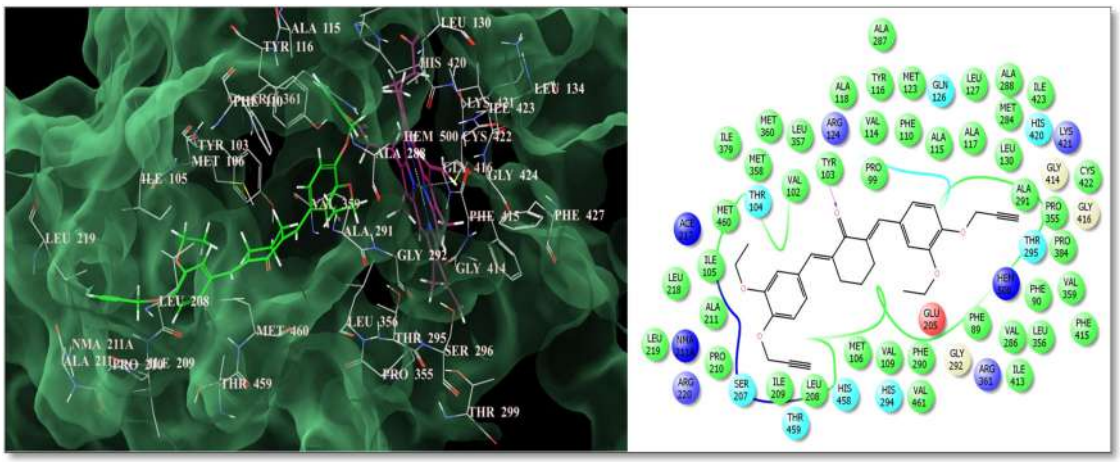


Fig. 6 Binding mode of **4a** into the active site of sterol 14α-demethylase (CYP51) (on the right side: the pink lines signify hydrogen-bonding interaction)

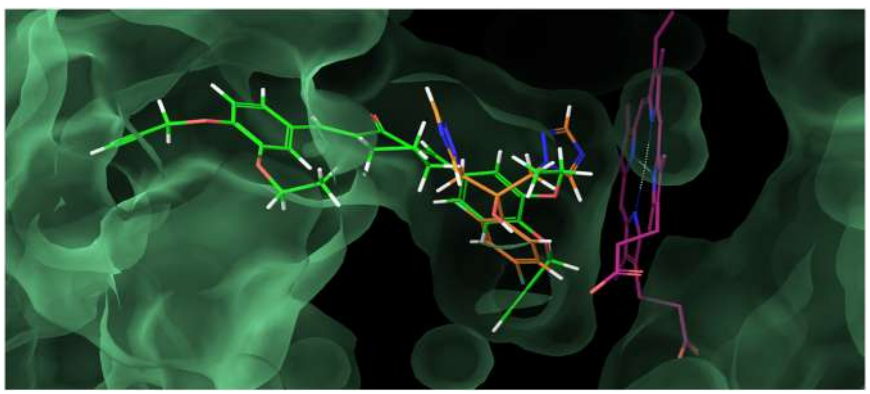


Fig. 7 Superimposition of the **4a** against the X-ray bound conformation of Fluconazole (Green backbone: **4a**, Orange backbone: Fluconazole; Pink backbone: Hem)

including **4a**, showed a very strong steric as well as electrostatic interaction with the Hem moiety (iron metal) of CYP51 which is crucial for antifungal activity knowing the experimental evidence that Miconazole is also coordinated with CYP51 through this Hem moiety. This suggests that the propargylated monocarbonyl curcumin analogues investigated herein may also exhibit their antifungal activity through CYP51 inhibition.

Materials and methods

General

All chemicals and reagents were procured from Sigma Aldrich, S.D. Fine chemical and commercial suppliers and used without further purification. TLC was performed on 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}). The components were identified by exposure to iodine vapours or UV light. The melting point was decided by using an open capillary technique and are uncorrected. The products were characterised using ^{1}H NMR, ^{13}C NMR spectra and MS. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 MHz spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-100 MHz instrument. TMS was used as the internal standard. IR spectra were recorded using a Bruker ALPHA ECO-ATR FTIR spectrometer. Mass spectra were recorded on LC/ESI-MS spectrometer.

General procedure for the preparation of prop-2-yn-1-yloxy benzaldehydes (2a–c)

An appropriate mixture of hydroxybenzaldehyde **1a–c** (1 mmol), propargyl bromide (1 mmol) and K_2CO_3 (2 mmol) in DMF (9–10 mL) was stirred at room temperature for 2–3 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the reaction mixture was poured in ice-cold water. The separated solid was filtered washed with water, dried and recrystallised from ethanol resulted in the corresponding propargylated benzaldehydes in good yields (87–89%).

General procedure for the preparation of propargylated monocarbonyl curcumin analogues (4a–i)

A mixture of appropriate propargylated benzaldehydes **2a–c** (1 mmol), appropriate monoketone linker (1 mmol) and aq. NaOH in ethanol (10 mL) was stirred at room temperature for about 3–4 h. The progress of the reaction was monitored using TLC. The precipitate was washed with water, dried and recrystallised using ethyl acetate-chloroform as a solvent.

(2*E*,6*E*)-2,6-Bis(3-ethoxy-4-(prop-2-yn-1-yloxy)benzylidene) cyclohexanone (4a)

Yellow coloured crystal; yield 82%; mp: 150–153 °C; IR (KBr) ν_{max} 3262, 2120, 1660, 1589, 1503 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.73$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.08 (4H, s, Ar-H, H-5, H-5′, H-9, H-9′), 7.03 (2H, s, Ar-H, H-8, H-8′), 4.81 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 4.12 (4H, q, $J = 8.0$ Hz, -OC<u>H</u>$_2$CH$_3$), 2.93 (4H, t, $J = 8.0$ Hz, -C<u>H</u>$_2$-CH$_2$-C<u>H</u>$_2$), 2.53 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 1.84–1.78 (2H, m, -CH$_2$-C<u>H</u>$_2$-CH$_2$), 1.47 (6H, t, $J = 8.0$ Hz, -OCH$_2$-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 190.1$ (C = O, C-1), 148.6 (Ar-C, C-7, C-7′), 147.6 (Ar-C, C-6, C-6′), 136.7 (Ar-<u>C</u>H = C-, C-3, C-3′), 134.8 (Ar-CH = <u>C</u>-, C-2, C-2′), 130.2 (Ar-C, C-4, C-4′), 123.5 (Ar-C, C-9, C-9′), 115.7 (Ar-C, C-8, C-8′), 114.2 (Ar-C, C-5, C-5′), 78.4 (-<u>C</u> ≡ CH-), 76.0 (-C ≡ <u>CH</u>-), 64.6 (-O<u>C</u>H$_2$), 56.8 (-O<u>C</u>H$_2$CH$_3$), 28.5 (-<u>C</u>H$_2$), 23.0 (-<u>C</u>H$_2$) and 14.8 (OCH$_2$-<u>C</u>H$_3$); HRMS: Calcd for $C_{30}H_{29}O_5$ $[M\text{-}H]^+$, 469.2093, found: 469.2143

(3*E*,5*E*)-3,5-Bis(3-ethoxy-4-(prop-2-yn-1-yloxy)benzylidene)-1-methylpiperidin-4-one (4b)

Yellow coloured crystal; yield 84%; mp: 152–154 °C; IR (KBr) ν_{max} 3241, 2117, 1660, 1574, 1502 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.76$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.11 (2H, d, $J = 8.4$ Hz, Ar-H, H-9, H-9′), 7.02 (2H, d, $J = 1.6$ Hz, Ar-H, H-5, H-5′), 6.99 (2H, d, $J = 8.4$ Hz, Ar-H, H-8, H-8′), 4.83 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 4.14 (4H, q, $J = 8.0$ Hz, -OC<u>H</u>$_2$CH$_3$), 3.80 (4H, s, -C<u>H</u>$_2$-N-C<u>H</u>$_2$-), 2.56 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 2.5 (3H, s, -N-C<u>H</u>$_3$), 1.50 (6H, t, $J = 8.0$ Hz, -OCH$_2$-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 186.7$ (C = O, C-1), 148.8 (Ar-C, C-7, C-7′), 148.0 (Ar-C, C-6, C-6′), 136.3 (Ar-<u>C</u>H = C-, C-3, C-3′), 131.8 (Ar-CH = <u>C</u>-, C-2, C-2′), 129.5 (Ar-C, C-4, C-4′), 123.4 (Ar-C, C-9, C-9′), 115.8 (Ar-C, C-8, C-8′), 114.3 (Ar-C, C-5, C-5′), 78.4 (-<u>C</u> ≡ CH-), 76.1 (-C ≡ <u>CH</u>-), 64.6 (O<u>C</u>H$_2$-CH$_3$), 56.8 (Ar-O<u>C</u>H$_2$), 45.8 (-<u>C</u>H$_2$-N-<u>C</u>H$_2$), 29.7 (-N-<u>C</u>H$_3$), 14.8 (OCH$_2$-<u>C</u>H$_3$); LC-MS: Calcd for $C_{30}H_{32}NO_5$ $[M + H]^+$, 486.2, found: 486.2

(3*E*,5*E*)-3,5-Bis(3-methoxy-4-(prop-2-yn-1-yloxy) benzylidene)-1-methylpiperidin-4-one (4c)

Yellow coloured crystal; yield 80%; mp: 159–161 °C; IR (KBr) ν_{max} 3227, 2117, 1660, 1569, 1503 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.75$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.08 (2H, d, $J = 8.4$ Hz, Ar-H, H-9, H-9′), 7.01 (2H, d, $J = 1.2$ Hz, Ar-H, H-5, H-5′), 6.97 (2H, d, $J = 8.4$ Hz, Ar-H, H-8, H-8′), 4.81 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 3.90 (6H, s, -OC<u>H</u>$_3$), 3.78 (4H, s, -C<u>H</u>$_2$-N-C<u>H</u>$_2$-), 2.54 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 2.48 (3H, s, -N-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 186.7$ (C = O, C-1), 149.3 (Ar-C, C-7, C-7'), 147.7 (Ar-C, C-6, C-6′), 136.2 (Ar-<u>C</u>H = C-, C-3, C-3′), 131.9 (Ar-CH = <u>C</u>-, C-2, C-2′), 129.4 (Ar-C, C-4, C-4′), 123.3 (Ar-C, C-9, C-9′), 114.3 (Ar-C, C-8, C-8′), 113.6 (Ar-C, C-5, C-5′), 78.1 (-<u>C</u> ≡ CH-), 76.2 (-C ≡ <u>CH</u>-), 57.1 (Ar-O<u>C</u>H$_2$), 56.6 (O<u>C</u>H$_3$), 56.0 (-<u>C</u>H$_2$-N-<u>C</u>H$_2$), 45.8 (-N-<u>C</u>H$_3$); LC-MS: Calcd for $C_{28}H_{28}NO_5$ $[M + H]^+$, 458.5, found: 458.5

(2*E*,5*E*)-2,5-Bis(3-ethoxy-4-(prop-2-yn-1-yloxy)benzylidene) cyclopentanone (4d)

Yellow coloured crystal; yield 81%; mp: 177–179 °C; IR (KBr) ν_{max} 3253, 2119, 1672, 1581, 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.53$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.23 (2H, dd, $J = 8.4$ Hz and 1.6 Hz, Ar-H, H-9, H-9′), 7.15 (2H, d, $J = 1.6$ Hz, Ar-H), 7.11 (2H, d, $J = 8.4$ Hz, Ar-H), 4.83 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 4.15 (4H, q, $J = 7.2$ Hz, -OC<u>H</u>$_2$CH$_3$), 3.10 (4H, s, -C<u>H</u>$_2$), 2.53 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 1.49 (6H, t, $J = 7.2$ Hz, -OCH$_2$-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 196.1$ (C = O, C-1), 148.9 (Ar-C, C-7, C-7′), 148.3 (Ar-C, C-6, C-6′), 135.8 (Ar-<u>C</u>H = C-, C-3, C-3′), 133.6 (Ar-CH = <u>C</u>-, C-2, C-2′), 130.2 (Ar-C, C-4, C-4′), 124.0 (Ar-C, C-9, C-9′), 115.6 (Ar-C, C-8, C-8′), 114.4 (Ar-C, C-5, C-5′), 78.3 (-<u>C</u> ≡ CH-), 76.1 (-C ≡ <u>C</u>H-), 64.7 (O<u>C</u>H$_2$-CH$_3$), 56.7 (Ar-O<u>C</u>H$_2$), 26.5 (-<u>C</u>H$_2$), 14.8 (OCH$_2$-<u>C</u>H$_3$); LC-MS: Calcd for $C_{29}H_{29}O_5$ $[M + H]^+$, 457.5, found: 457.2.

(2*E*,5*E*)-2,5-Bis(3-methoxy-4-(prop-2-yn-1-yloxy) benzylidene)cyclopentanone (4e)

Yellow coloured crystal; yield 83%; mp: 178–180 °C; IR (KBr) ν_{max} 3251, 2117, 1671, 1580, 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.78$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.10 (2H, d, $J = 8.4$ Hz, Ar-H, H-9, H-9′), 7.03 – 6.98 (4H, m, Ar-H, H-5, H-5′, H-8, H-8′), 4.84 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 3.93 (6H, s, -OC<u>H</u>$_3$), 2.57 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 2.50 (4H, s, -C<u>H</u>$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 196.4$ (C = O, C-1), 149.1 (Ar-C, C-7, C-7′), 148.5 (Ar-C, C-6, C-6′), 136.0 (Ar-<u>C</u>H = C-, C-3, C-3′), 133.9 (Ar-CH = <u>C</u>-, C-2, C-2′), 130.4 (Ar-C, C-4, C-4′), 124.3 (Ar-C, C-9, C-9′), 115.8 (Ar-C, C-8, C-8′), 114.6 (Ar-C, C-5, C-5′), 78.5 (-<u>C</u> ≡ CH-), 76.4 (-C ≡ <u>C</u>H-), 64.8 (Ar-O<u>C</u>H$_2$), 56.8 (-O<u>C</u>H$_3$), 26.5 (-<u>C</u>H$_2$); ESI-MS: Calcd for $C_{27}H_{25}O_5$ $[M + H]^+$, 429.5, found: 430.0

(1*E*,4*E*)-1,5-Bis(3-ethoxy-4-(prop-2-yn-1-yloxy)phenyl)penta-1,4-dien-3-one (4f)

Yellow coloured crystal; yield 85%; mp: 144–146 °C; IR (KBr) ν_{max} 3263, 2120, 1645, 1579, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.67$ (2H, d, $J = 16$ Hz, Ar-C<u>H</u> = C-, H-3, H-3′), 7.20 (2H, dd, $J = 8.4$ Hz and 2 Hz, Ar-H, H-9, H-9′), 7.16 (2H, d, $J = 2$ Hz, Ar-H, H-5, H-5′), 7.06 (2H, d, $J = 8.4$ Hz, Ar-H, H-8, H-8′), 6.95 (2H, d, $J = 16$ Hz, Ar-CH = C<u>H</u>-, H-2, H-2′), 4.82 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 4.15 (4H, q, $J = 7.2$ Hz, -OC<u>H</u>$_2$CH$_3$), 2.54 (2H, d, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 1.50 (6H, t, $J = 7.2$ Hz, -OCH$_2$-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 188.8$ (C = O, C-1), 149.3 (Ar-C, C-7, C-7′), 149.2 (Ar-C, C-6, C-6′), 143.0 (Ar-<u>C</u>H = CH-, C-3, C-3′), 129.0 (Ar-C, C-4, C-4′), 124.0 (Ar-CH = <u>C</u>H-, C-2, C-2′), 122.5 (Ar-C, C-9, C-9′), 114.4 (Ar-C, C-8, C-8′), 112.2 (Ar-C, C-5, C-5′), 78.3 (-<u>C</u> ≡ CH-), 76.3 (-C ≡ <u>C</u>H-), 64.7 (O<u>C</u>H$_2$-CH$_3$), 56.8 (Ar-O<u>C</u>H$_2$), 14.9 (OCH$_2$-<u>C</u>H$_3$); LC-MS: Calcd for $C_{27}H_{27}O_5$ $[M + H]^+$, 431.5, found: 431.1

(1*E*,4*E*)-1,5-Bis(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) penta-1,4-dien-3-one (4g)

Yellow coloured crystal; yield 82%; mp: 155–157 °C; IR (KBr) ν_{max} 3253, 2109, 1660, 1571, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.71$ (2H, d, $J = 16$ Hz, Ar-C<u>H</u> = C-, H-3, H-3′), 7.22 (2H, d, $J = 8.4$ Hz, Ar-H, H-9, H-9′), 7.17 (2H, s, Ar-H, H-5, H-5′), 7.07 (2H, d, $J = 8$ Hz, Ar-H, H-8, H-8′), 6.98 (2H, d, $J = 16$ Hz, Ar-CH = C<u>H</u>-, H-2, H-2′), 4.84 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 3.96 (6H, s, -OC<u>H</u>$_3$), 2.57 (2H, t, $J = 2.4$ Hz, -C ≡ C<u>H</u>); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 188.6$ (C = O, C-1), 149.8 (Ar-C, C-7, C-7′), 149.0 (Ar-C, C-6, C-6′), 143.0 (Ar-<u>C</u>H = CH-, C-3, C-3′), 129.0 (Ar-C, C-4, C-4′), 124.0 (Ar-CH = <u>C</u>H-, C-2, C-2′), 122.5 (Ar-C, C-9, C-9′), 113.7 (Ar-C, C-8, C-8′), 110.5 (Ar-C, C-5, C-5′), 78.0 (-<u>C</u> ≡ CH-), 76.3 (-C ≡ <u>C</u>H-), 56.6 (Ar-O<u>C</u>H$_2$), 56.0 (O<u>C</u>H$_3$); LC-MS: Calcd for $C_{25}H_{23}O_5$ $[M + H]^+$, 403.4, found: 403.1

(2*E*,6*E*)-2,6-Bis(3,5-dichloro-2-(prop-2-yn-1-yloxy) benzylidene)cyclohexanone (4h)

Yellow coloured crystal; yield 84%; mp: 146–148 °C; IR (KBr) ν_{max} 3243, 2109, 1661, 1560, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 7.87$ (2H, s, Ar-C<u>H</u> = C-, H-3, H-3′), 7.42 (2H, d, $J = 2.4$ Hz, Ar-H, H-7, H-7′), 7.22 (2H, d, $J = 2.4$ Hz, Ar-H, H-5, H-5′), 4.71 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 2.78 (4H, t, $J = 8.0$ Hz, -C<u>H</u>$_2$-CH$_2$-C<u>H</u>$_2$), 2.54 (2H, t, $J = 2.4$ Hz, -C ≡ C<u>H</u>), 1.82-1.76 (2H, m, -CH$_2$-C<u>H</u>$_2$-CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz,): $\delta = 189.0$ (C = O, C-1), 151.3 (Ar-C, C-9, C-9′), 138.8 (Ar-<u>C</u>H = C-, C-3, C-3′), 133.3 (Ar-CH = <u>C</u>-, C-2, C-2′), 131.3 (Ar-C, C-7, C-7′), 130.2 (Ar-C, C-6, C-6′), 129.7 (Ar-C, C-5, C-5′), 129.5 (Ar-C, C-8, C-8′), 128.5 (Ar-C, C-4, C-4′), 77.8 (-<u>C</u> ≡ <u>C</u>H-), 61.0 (Ar-O<u>C</u>H$_2$), 28.5 (-<u>C</u>H$_2$), 22.7 (-<u>C</u>H$_2$); LC-MS: Calcd for $C_{26}H_{18}Cl_4O_3$ $[M]^+$, 520.2, found: 520.0

(1*E*,4*E*)-1,5-Bis(3,5-dichloro-2-(prop-2-yn-1-yloxy)phenyl) penta-1,4-dien-3-one (4i)

Yellow coloured crystal; yield 80%; mp: 181–183 °C; IR (KBr) ν_{max} 3285, 2126, 1664, 1599, 1554 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 8.03$ (2H, d, $J = 16$ Hz, Ar-C<u>H</u> = C-, H-3, H-3′), 7.57 (2H, d, $J = 2.4$ Hz, Ar-H, H-7, H-7′), 7.45 (2H, d, $J = 2.4$ Hz, Ar-H, H-5, H-5′), 7.12 (2H, d, $J = 16$ Hz, Ar-CH = C<u>H</u>-, H-2, H-2′), 4.78 (4H, d, $J = 2.4$ Hz, Ar-OC<u>H</u>$_2$), 2.57 (2H, t, $J = 2.4$ Hz, -C ≡ C<u>H</u>); ^{13}C NMR

($CDCl_3$, 100 MHz,): $\delta = 188.4$ (C = O, C-1), 151.8 (Ar-C, C-9, C-9′), 136.9 (Ar-CH = CH-, C-3, C-3′), 132.3 (Ar-CH = CH-, C-2, C-2′), 131.7 (Ar-C, C-7, C-7′), 130.7 (Ar-C, C-6, C-6′), 129.8 (Ar-C, C-5, C-5′), 127.9 (Ar-C, C-8, C-8′), 125.9 (Ar-C, C-4, C-4′), 77.6 (-C ≡ CH-), 61.5 (Ar-OCH_2); ESI-MS: Calcd for $C_{23}H_{14}Cl_4KO_3$ $[M + K]^+$, 519.3, found: 520.0

Bioactivity assay

Antifungal activity assay

Standard agar dilution method as per CLSI (formerly, NCCLS) was used to determine in vitro antifungal activity of synthesised analogues (Collins 1967; Duraiswamy et al. 2009). Synthesised analogues and standard drug Miconazole were dissolved in DMSO solvent. A phosphate buffer solution of pH 7 was used to dissolve medium yeast nitrogen base furthermore, it was autoclaved at 110 °C for 10 min. A growth control without an antifungal agent and solvent control DMSO were included with each set. On Sabouraud dextrose agar, fungal strains were freshly subcultured and incubated at 25 °C for 72 h. Fungal cells were suspended and diluted to get 105 cells/mL in sterile distilled water. Ten microliters of standardised suspension were inoculated onto the control plates and the antifungal agents were integrated with the media. The inoculated plates were incubated at 25 °C for 48 h. At the end of 48 and 72 h readings were taken. The *MIC* values (Minimum inhibitory concentration of drugs preventing the growth of macroscopically visible colonies on drug-containing plates when there was visible growth on the drug-free control plates) was calculated.

Antioxidant activity assay

Synthesised curcumin analogues were screened for in vitro antioxidant activity by using 1, 1-diphenyl-2- picrylhydrazyl (DPPH) radical scavenging assay. The results were compared with standard antioxidant drug BHT (Butylated Hydroxy Toluene).

Radical scavenging activity of the synthesised compounds has been carried out in vitro by the 1, 1-diphenyl-2picrylhydrazyl (DPPH) radical scavenging assay (Burits and Bucar 2000). The obtained results were compared with standard antioxidant BHT (Butylated Hydroxy Toluene). The hydrogen atom or electron donation ability of the compounds was calculated from the bleaching of the purple-coloured methanol solution of 1, 1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 mg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (I %) of free radical production from DPPH was calculated by the following equation.

$$\% \text{ of scavenging} = [(\text{A control} - \text{A sample})/\text{A blank}] \times 100,$$

where 'A control' is the absorbance of the control reaction (containing all reagents except the test compound) and 'A sample' is the absorbance of the test compound. Tests were carried at in triplicate.

Molecular docking

To gauze the binding affinity and the mode of interaction of the new propargylated monocarbonyl curcumin analogues to the critical fungal enzyme sterol 14α-demethylase (CYP51), molecular docking study has been performed using the GLIDE (Grid-based Ligand Docking with Energetics) module of the Schrodinger Molecular modelling package (Schrodinger, LLC, New York, NY, 2015) (Halgren et al. 2004; Friesner et al. 2006). The 3D X-ray crystal structure of sterol 14α-demethylase (CYP51) complexed with its inhibitor-fluconazole (pdb code: 3KHM) was obtained from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb) and cleaned using with the *protein preparation wizard* applying the OPLS-2005 force field. This includes deletion of the crystallographic water molecules as there are no conserved interactions with receptor; addition of the missing protons/side-chain atoms corresponding to pH 7.0 and assignment of the appropriate charge and protonation state. The refined structure thus obtained was subjected to energy minimisation to relieve the steric clashes among the amino acid residues till RMSD for the heavy atoms reached 0.30 Å. The 3D structures of the curcumin analogues were sketched using the *build* panel in *Maestro* and further optimised using *Ligand Preparation* tool. This involves adjusting realistic bond lengths and angles, assignment of the partial charges using the OPLS-2005 force-field followed by energy minimisation until the RMSD of heavy atoms reached 0.001 Å. Next, using the *Receptor Grid Generation* panel, shape and properties of the active site of the CYP51 enzyme were defined for which a grid box of 10 × 10 × 10 Å dimensions centred on the centroid of the co-crystallised ligand was generated. Before submitting the calculations for the synthesised dataset, the molecular docking protocol was validated by extracting the co-crystallised ligand (Fluconazole) and re-docking using the above setup which could produce an RMSD of <0.29 Å (Fig. 7).

With this setup, molecular docking was performed to determine the binding affinities and modes of binding of

the propargylated monocarbonyl curcumin analogues towards CYP51 using the extra precision Glide scoring function. The outputs files i.e. docking poses were visualised and investigated for the most significant elements of thermodynamic interactions using the Maestro's Pose Viewer utility.

Conclusion

In conclusion, we have synthesised a small, focused library of propargylated monocarbonyl curcumin analogues and screened for their in vitro antifungal and antioxidant activity. Most of the synthesised analogues especially **4a**, **4b** and **4c** were found to display excellent antifungal potential and can be further developed as lead molecules in search of new antifungal agents. Furthermore, the antioxidant activity of synthesised analogues was studied using DPPH assay and BHT as a positive control. Compound **4b**, **4c**, **4e** and **4i** displayed stronger antioxidant potential as compared with BHT. Furthermore, molecular docking study could provide valuable insight into the binding affinity and the mode of interactions of these compounds into the active site of crucial fungal enzyme CYP51. The per-residue interaction analysis could highlight the bonded (hydrogen bonding) and non-bonded (steric and electrostatic) interactions that influence their binding affinity towards the target. This information is being fruitfully utilised to optimise these propargylated monocarbonyl curcumin analogues to identify and optimise new antifungal and antioxidant agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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FULL PAPER

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New *N*-phenylacetamide-linked 1,2,3-triazole-tethered coumarin conjugates: Synthesis, bioevaluation, and molecular docking study

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Abstract

A series of new 1,2,3-triazole-tethered coumarin conjugates linked by *N*-phenylacetamide was efficiently synthesized *via* the click chemistry approach in excellent yields. The synthesized conjugates were evaluated for their in vitro antifungal and antioxidant activities. Antifungal activity determination was carried out against fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. Compounds **7b**, **7d**, **7e**, **8b** and **8e** displayed higher potency than the standard drug miconazole, with lower minimum inhibitory concentration values. Also, compound **7a** exhibited potential radical scavenging activity as compared with the standard antioxidant butylated hydroxytoluene. In addition, a molecular docking study of the newly synthesized compounds was carried out, and the results showed a good binding mode at the active site of the fungal (*C. albicans*) P450 cytochrome lanosterol 14α-demethylase enzyme. Furthermore, the synthesized compounds were also tested for ADME properties, and they demonstrated potential as good candidates for oral drugs.

KEYWORDS

ADME properties, antifungal activity, antioxidant activity, molecular docking, triazole–coumarin conjugates

1 | INTRODUCTION

The incidence of systemic fungal infection has increased dramatically in recent years due to an increase in the number of patients undergoing anticancer chemotherapy and organ transplantation, and AIDS patients.[1] Fungi are vital opportunistic human pathogens that have become drug-resistant to many approved compounds, especially *Cryptococcus neoformans*, *Candida*, and *Aspergillus* species, with serious potential consequences. The commonly used azole-based antifungal agents are miconazole, fluconazole, voriconazole, and itraconazole, which showed a wide range of antifungal activity.[2] Azoles, especially triazole-based antifungal agents (e.g., voriconazole, fluconazole, and posaconazole) are widely used for the prevention and treatment of fungal infections (Figure 1). These antifungal drugs inhibit CYP51 (P450 cytochrome lanosterol 14α-demethylase), a key enzyme in ergosterol biosynthesis.[3] However, extensive use of these drugs has resulted in severe drug resistance.[4] Therefore, the development of more potent, broad-spectrum antifungal agents with fewer side effects and improved efficiency to cure fungal infections is urgently required.

To counteract the harmful effects of free radicals and other oxidants, the human body has a complex system of natural enzymatic and nonenzymatic antioxidants. Free radicals are unstable chemical species having unpaired electrons that are extremely reactive toward other species. The action of reactive oxygen species (ROS) results in

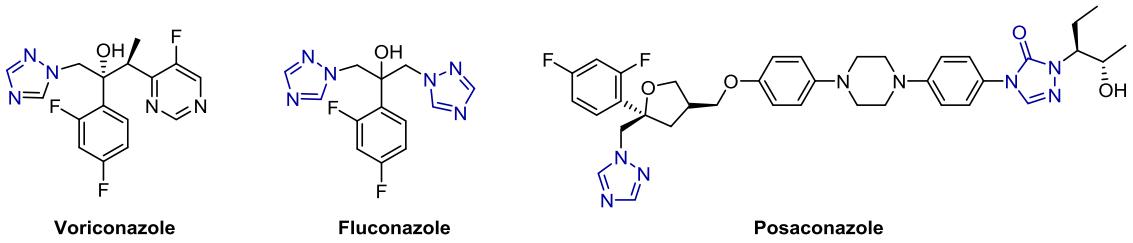


FIGURE 1 1,2,4-Triazole-based antifungal drugs

key biomolecules being altered and modulated in function. There is a delicate balance between producing and removing free radicals in healthy organisms. Triazole–coumarin conjugates have unique potential to scavenge ROS such as hydroxyl and superoxide radicals.[5] Therefore, the synthesis and development of new antioxidants having the triazole–coumarin pharmacophore have enormous significance in medicinal chemistry.

Diversely functionalized 1,2,3-triazole derivatives have attracted great attention due to their extensive biological properties such as antioxidant,[5] antifungal,[6,7] antitubercular,[8] antibacterial,[9] anticancer,[10] anti-HIV,[11] antimicrobial,[12] and antimalarial activity.[13] The 1,4-disubstituted-1,2,3-triazoles were synthesized *via* copper-catalyzed azide–alkyne cycloaddition reaction, well known as a click chemistry reaction.[14] In the field of medicinal chemistry and drug discovery, 1,2,3-triazoles have received[15–19] increasing attention since Sharpless group introduced the "click chemistry" concept. The promising properties of the 1,2,3-triazole ring, such as hydrogen bonding capability, rigidity, stability under in vivo conditions, and moderate dipole character, could be helpful for binding of biomolecular targets and increasing solubility.[15,20,21] Moreover, 1,2,3-triazoles have become increasingly useful and important in the construction of bioactive and functional molecules as attractive linker units that could connect two pharmacophores to provide innovative bifunctional drugs.[22–24] Many drugs available in the market contain 1,2,3-triazole core in their structure, such as cefatrizine (antibiotic), carboxyamidotriazole (anticancer agent), rufinamide (anticonvulsant) and tazobactam (antibacterial agent; Figure 2).

Synthesis of new heterocycles with multiple biological activities remains an interest of the researchers. Among the oxygen heterocycles, coumarins are the privileged structural motifs commonly found in many natural products. Literature reveals that coumarin and its derivatives are isolated from plant-associated endophytes and display potential biological activities.[25–29] In recent years, coumarin-based hybrid molecules have attracted intense interest due to their diverse biological properties.[30,31] Different nitrogen-containing heterocycles (e.g., triazole, thiazolidine, thiazole, etc.) in conjunction with coumarin backbone significantly increase the antimicrobial efficiency and also broaden antimicrobial spectrum of these compounds.[32–34]

Due to the rapid and effective distribution of privileged systems with relatively improved biological properties as compared with individual entities, the molecular hybridization approach has established eminence over the past few years.[35] With strong drug-like properties and desirable binding interactions, these hybrid molecules have emerged for further chemical modifications as structurally novel chemotypes with several exploitable sites. In recent years, a library of coumarin–triazole conjugates was synthesized and proved to enhance biological activity.[36–39] There are various reports on the synthesis of coumarin–triazole conjugates with antifungal activity.[32,38,40,41] Therefore, the design and synthesis of coumarin–triazole conjugates is crucial for the enhancement of activity.

In continuation of our previous works[40,42–51] on the synthesis and biological evaluation of heterocycles, and the significance of coumarin and 1,2,3-triazole moieties in a single molecular framework, herein, we would like to report the design and syntheses of new *N*-phenylacetamide-linked coumarin–triazole conjugates by using the molecular hybridization approach (Figure 3).

The 1,2,3-triazole moiety is good for antifungal activity, and coumarin derivatives have been well reported for the antioxidant activity. Thus, we have evaluated the synthesized compounds for their antifungal and antioxidant activities. The computational parameters like docking study for antifungal activity and ADME (absorption, distribution, metabolism, and elimination) prediction of synthesized coumarin–triazole conjugates were also performed.

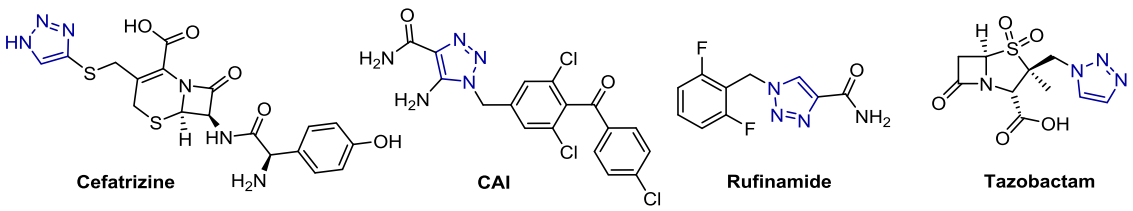


FIGURE 2 Marketed drugs containing the 1,2,3-triazole unit

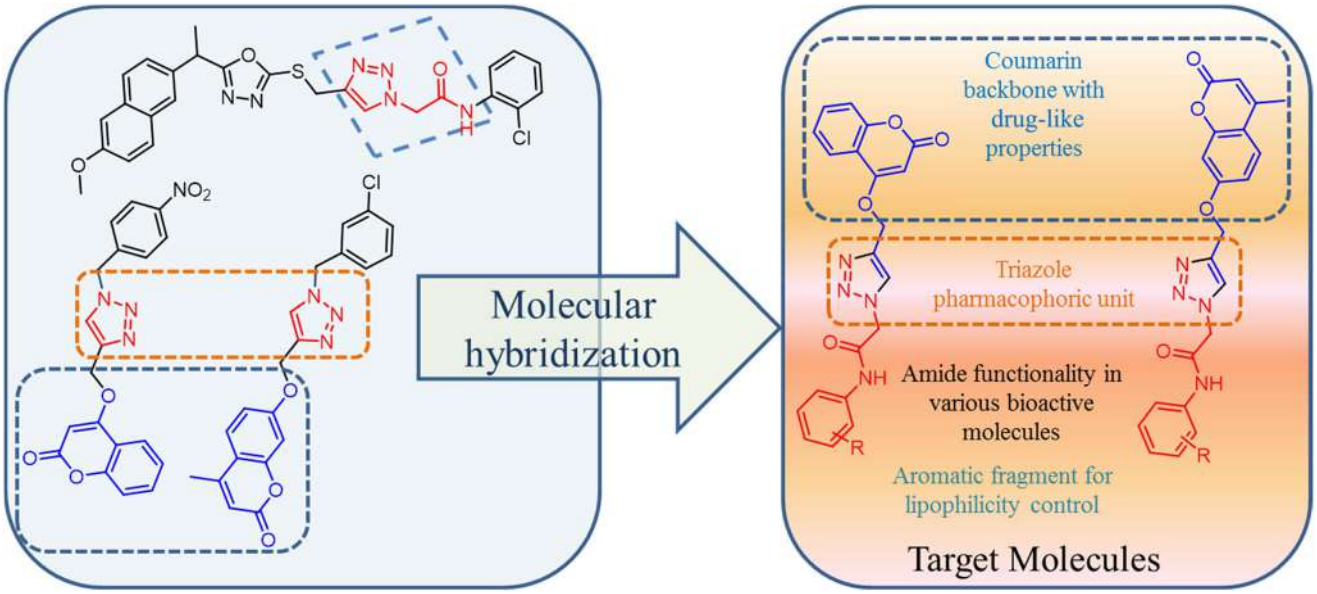


FIGURE 3 The design strategy for the synthesis of new *N*-phenylacetamide-linked 1,2,3-triazole–coumarin conjugates

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

1,4-Disubstituted-1,2,3-triazoles bearing amide functionality displayed several biological activities.[52–55] On the basis of these reports and molecular hybridization concept, we have designed and synthesized coumarin–triazole conjugates with amide linkage in their structures. A library of substituted 2-(4-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides **7a**–**g** and substituted 2-(4-{[(2-oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides **8a**–**g** was synthesized from commercially available starting materials. These compounds were constructed by the fusion of coumarin-based alkynes and substituted 2-azido-*N*-phenylacetamides *via* the click chemistry approach (Scheme 1).

The starting materials, 2-azido-*N*-phenylacetamides **3a**–**g**, were prepared by a previously reported method[45,51] from corresponding anilines in excellent yields (Scheme 1). The 7-hydroxy-4-methyl coumarin **5a** has been synthesized *via* acid-catalyzed Pechmann condensation between resorcinol and ethyl acetoacetate in 80% yield (Scheme 1). Compounds **6a** and **6b** were prepared by a previously reported method.[44] Compounds **5a** and **5b** were treated with propargyl bromide in the presence of K_2CO_3 as a base in *N*,*N*-dimethylformamide (DMF) at room temperature, resulting in 4-methyl-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one **6a** and 4-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one **6b**, respectively, in excellent yields (Scheme 1).

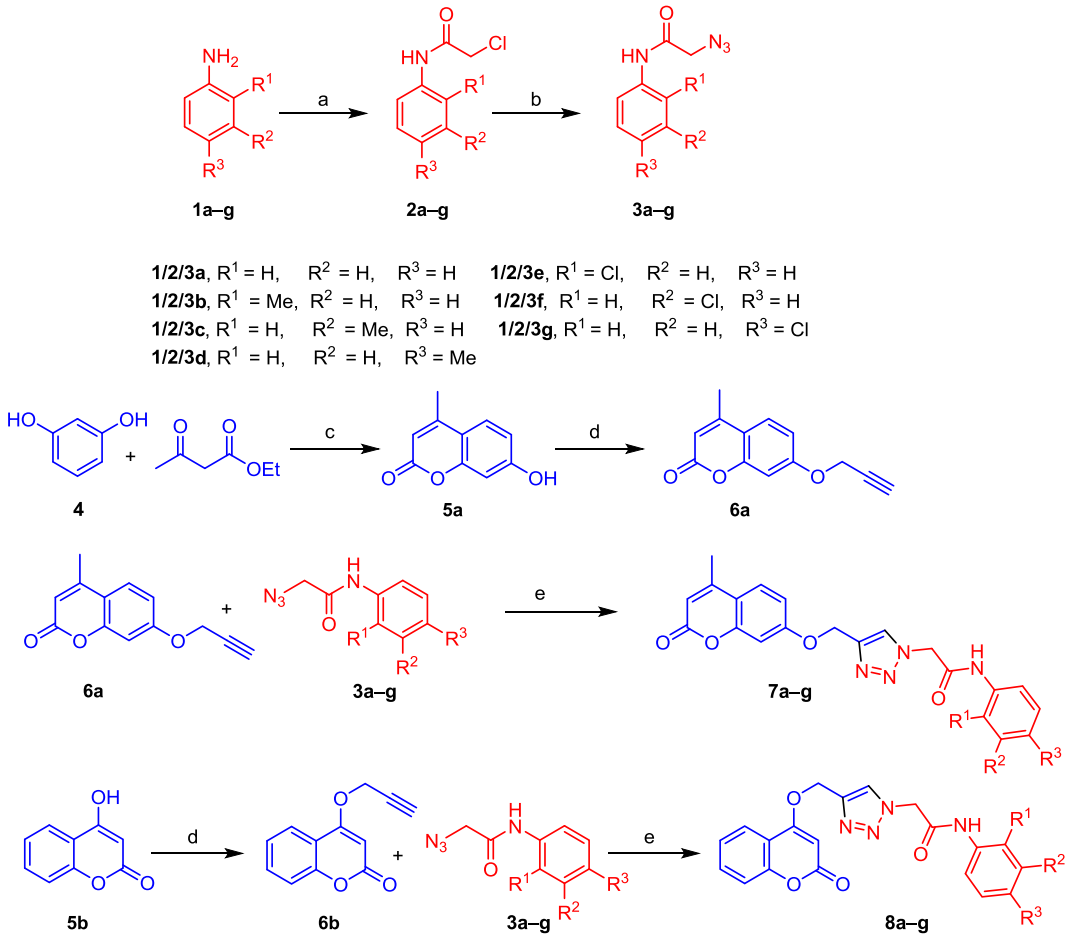
Finally, the click reaction of compounds **6a**,**b** with azides **3a**–**g** in the presence of $Cu(OAc)_2$ in *t*-BuOH-H_2O (3:1) at room temperature for 8–10 hr gave the corresponding 1,4-disubstituted-1,2,3-triazole–coumarin conjugates **7a**–**g** and **8a**–**g**, respectively, in good-to-excellent yield (88–94%; Scheme 1).

Regioselective formation of 1,4-disubstituted 1,2,3-triazole–coumarin conjugates **7a**–**g** and **8a**–**g** has been confirmed by physical data and spectroscopic techniques such as Fourier-transform infrared spectroscopy (FTIR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and high-resolution mass spectra (HRMS). According to the FTIR spectrum of compound **7a**, the peaks observed at 3,275 cm^{-1} indicate the presence of N–H group, and the peaks observed at 1,698 and 1,670 cm^{-1} indicate the presence of two carbonyl groups. In the ^{1}H NMR spectrum of compound **7a**, the signal at 2.41 ppm indicates the methyl group present on the coumarin ring, and signals at 5.32 and 5.37 ppm are for two protons each and they indicate the presence of two methylene groups attached with nitrogen and oxygen heteroatom, respectively. In addition to this, the signal appearing at 8.32 ppm for one proton clearly indicates the formation of the 1,4-disubstituted 1,2,3-triazole ring. In the ^{13}C NMR spectrum of compound **7a**, the signal at 18.6 ppm indicates methyl carbon, and the signals at 52.7 and 62.1 ppm indicate the presence of two methylene groups attached to the nitrogen of triazole and oxygen attached to the coumarin ring, respectively. Furthermore, the peak observed at 161.6 ppm indicates amide carbonyl carbon and the peak at 164.6 ppm indicates the presence of carbonyl carbon (lactone carbon) in the coumarin ring. The formation of compound **7a** has been further confirmed by mass spectrometry. The calculated $[M+Na]^+$ for compound **7a** is at 413.1226, and observed $[M+Na]^+$ in mass spectrum is at 413.1171. Similarly, compounds **7b**–**g** and **8a**–**g** were characterized by the spectral analysis. The structures of synthesized triazole–coumarin conjugates are represented in Figure 4.

2.2 | Biological activity

2.2.1 | Antifungal activity

The synthesized compounds were screened for their in vitro antifungal activities against five different fungal strains such as *Candida*



SCHEME 1 The synthesis of coumarin–triazole conjugates. Reagents and conditions: (a) Chloroacetyl chloride, NEt3, CH_2Cl2, 0°C at room temperature (rt), 3–5 hr, 85–95%; (b) NaN_3, toluene, reflux, 5–7 hr, 88–96%; (c) H_2SO_4, 0°C, 80%; (d) propargyl bromide, K_2CO_3, *N*,*N*-dimethylformamide, 2 hr, 93–95%; (e) $Cu(OAc)_2$ (10 mol%), *t*-BuOH/H_2O (3:1), rt, 8–10 hr, 88–94%

albicans, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger* and *C. neoformans*. The minimum inhibitory concentration (MIC, μg/ml) values of all the newly synthesized compounds were determined by the standard agar dilution method as per the Clinical & Laboratory Standards Institute (CLSI; formerly NCCLS) guidelines.[56] Miconazole was used as the standard antifungal drug for the comparison of antifungal activities and dimethyl sulfoxide (DMSO) was used as negative control. The data on the antifungal activity are presented in Table 1. Most of the compounds from the series exhibited a good-to-excellent antifungal activity against all the fungal strains with MIC values ranging from 12.5 to 25 μg/ml.

Without substitution on the phenyl ring, compound **7a** exhibited a two fold antifungal activity against *A. niger* and an equipotent activity against *C. albicans* and *F. oxysporum*, with MIC values of 12.5, 25, and 25 μg/ml, respectively, as compared with the standard antifungal drug miconazole. Compound **7b** having methyl group at *ortho* position of the phenyl ring was two fold more potent than the standard miconazole against *F. oxysporum*, *A. niger* and *C. neoformans*, with an MIC value of 12.5 μg/ml; it was also equipotent against the fungal strain *C. albicans* with an MIC value of 25 μg/ml. Compound **7c** with methyl substituent at *meta* position of the phenyl ring is equipotent to miconazole against fungal strains *A. niger* and *C. neoformans*, with an MIC value of 25 μg/ml, and it is two fold more potent than miconazole against *C. albicans*, with an MIC value of 12.5 μg/ml. Compound **7d** with methyl group at *para* position shows two fold potency than the miconazole against *A. niger*, with an MIC value of 12.5 μg/ml, and it is equipotent against *C. albicans* (MIC: 25 μg/ml), *F. oxysporum* (MIC: 25 μg/ml), *A. flavus* (MIC: 12.5 μg/ml), and *C. neoformans* (MIC: 25 μg/ml). Compound **7e** (chloro group at *ortho* position) exhibited a two fold activity against *C. albicans* and *A. niger* (MIC: 12.5 μg/ml). Compound **7e** also displayed an equivalent activity against *F. oxysporum* and *C. neoformans*, with an MIC value of 25 μg/ml. Compounds **7f** and **7g** displayed an equipotent activity against *A. niger*, *C. neoformans*, *C. albicans* and *F. oxysporum*, with an MIC value of 25 μg/ml. In addition, compounds **8a–g** are equivalent or more potent than the standard miconazole. Among the compounds, **8b**, **8c**, **8e**, and **8f** showed an equivalent or two fold activity against all the fungal strains, with MIC values of 12.5–25 μg/ml. The activity results clearly indicate that most of the triazole–coumarin conjugates are

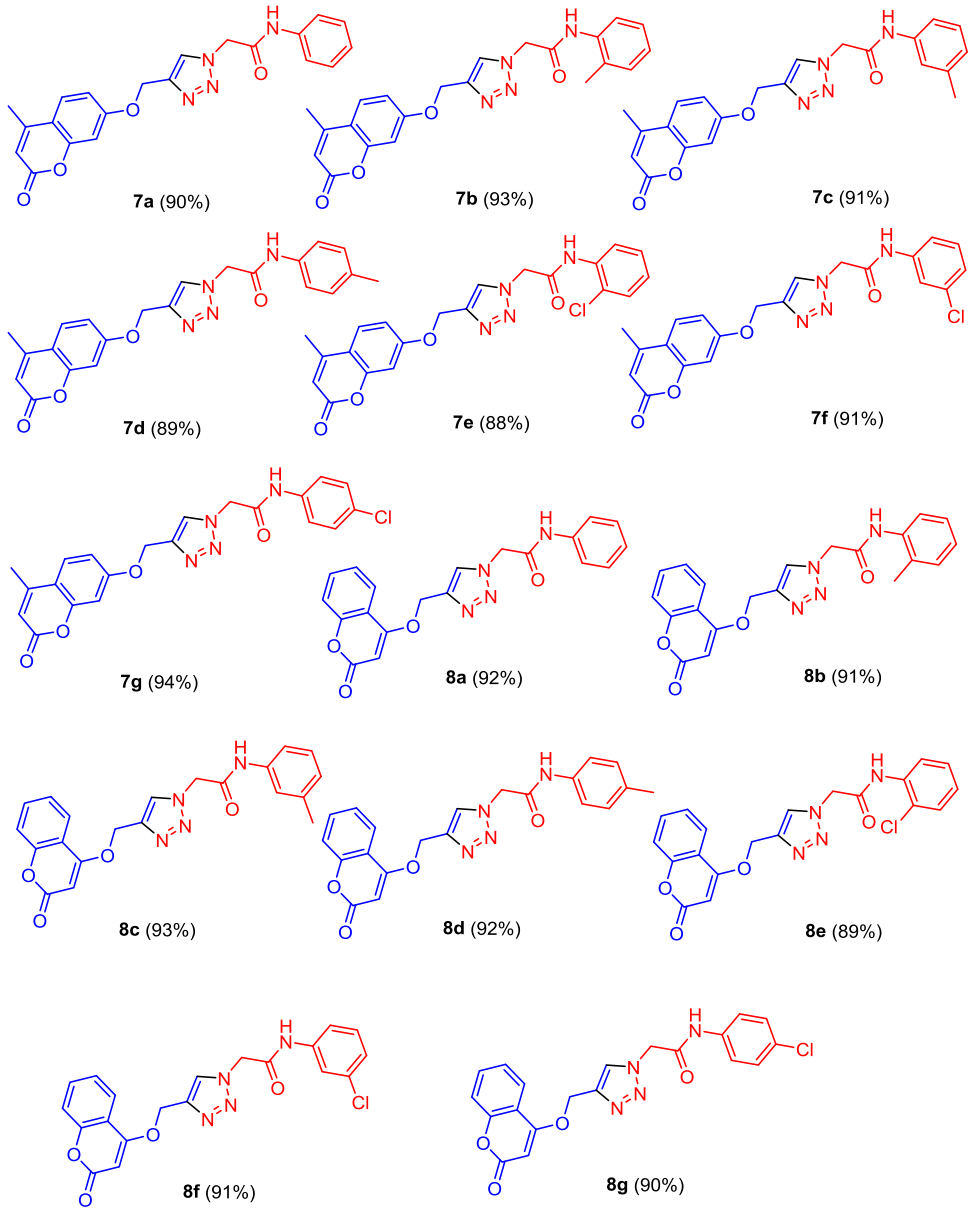


FIGURE 4 Structures of triazole–coumarin conjugates

more potent or equipotent as compared with the miconazole, as shown in the graphical representation (Figure 5).

2.2.2 | Antioxidant activity

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was used to screen the antioxidant activities of the synthesized compounds **7a**–**g** and **8a**–**g**. The DPPH radical scavenging assay is the most widely used tool for screening the antioxidant activity of various natural and synthetic compounds. A lower IC_{50} value indicates more activity against antioxidants. The IC_{50} (concentration required to scavenge 50% of the radicals) values were calculated to assess the potential antioxidant activities. Butylated hydroxytoluene (BHT) has been used as the standard drug to compare antioxidant activities; the findings obtained are summarized in Table 1. In comparison to the synthetic antioxidant BHT, compound **7a** exhibited excellent radical scavenging activities, with an IC_{50} value of 15.01 μg/ml, and remaining compounds showed good-to-moderate activities.

2.3 | Computational study

2.3.1 | Comparative modeling

The sequence identity and atomic resolution are two key parameters while selection of the template structure, which were 44% and 2.8 Å, respectively, which satisfy the basic criterion for comparative modeling. The final model was subjected to structure validation tool such as Procheck, ProSA, SPDBV and were found that 99.7 percent of the

TABLE 1 In vitro biological evaluation of the synthesized triazole–coumarin conjugates **7a–g** and **8a–g**

Compound	Antifungal activity (MIC in μg/ml)					DPPH IC_{50} (μg/ml)	Molecular docking score
	CA	FO	AF	AN	CN		
7a	25	25	25	12.5	50	15.01 ± 0.26	−7.0932
7b	25	12.5	50	12.5	12.5	19.24 ± 0.19	−7.3901
7c	12.5	50	25	25	25	21.14 ± 0.97	−6.8629
7d	25	25	12.5	12.5	25	24.37 ± 0.34	−7.7256
7e	12.5	25	25	12.5	25	38.25 ± 0.24	−7.9245
7f	50	50	37.5	25	25	29.34 ± 0.19	−6.8669
7g	25	25	75	75	50	38.18 ± 0.54	−6.7934
8a	37.5	25	25	37.5	25	36.59 ± 0.64	−6.2456
8b	12.5	25	12.5	12.5	12.5	27.44 ± 0.31	−7.1950
8c	25	12.5	25	12.5	25	67.30 ± 0.05	−6.2411
8d	37.5	25	12.5	75	25	44.31 ± 0.99	−7.4214
8e	12.5	12.5	12.5	12.5	25	89.32 ± 0.76	−7.2302
8f	25	12.5	12.5	12.5	25	71.08 ± 0.26	−6.6233
8g	37.5	50	62.5	37.5	12.5	57.16 ± 0.79	−6.7248
MA	25	25	12.5	25	25	NA	−5.26
BHT	NA	NA	NA	NA	NA	16.47 ± 0.18	NA

Abbreviations: AF, *Aspergillus flavus*; AN, *Aspergillus niger*; BHT, butylated hydroxytoluene; CA, *Candida albicans*; CN, *Cryptococcus neoformans*; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FO, *Fusarium oxysporum*; MA, miconazole; MIC, minimum inhibitory concentration; NA, not applicable.

residue followed in the allowed region. Also, overall model quality was assessed using Prosa where Z score is −3.2 and Cα deviation is 0.45 Å, respectively. The validation study of the model suggested that it was perfect for further computation study.

2.3.2 | Molecular docking study

The molecular docking study of all synthesized triazole–coumarin conjugates, **7a–g** and **8a–g**, was performed against modeled three-dimensional structure of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* to understand the binding affinity and binding interactions of enzyme and synthesized derivatives. The synthesized triazole–coumarin conjugates (**7a–g**, **8a–g**) and the standard drug miconazole were docked in the active site of modeled CACYP51 using the AutoDock Vina docking tool. The results of docking are shown in Table 1. The analysis of docking interaction revealed that the triazole ring was mainly responsible for the interaction.

The triazole–coumarin conjugates **7b**, **7d**, **7e**, **8b** and **8e** reproduced a similar result as that of in vitro activity data. All active

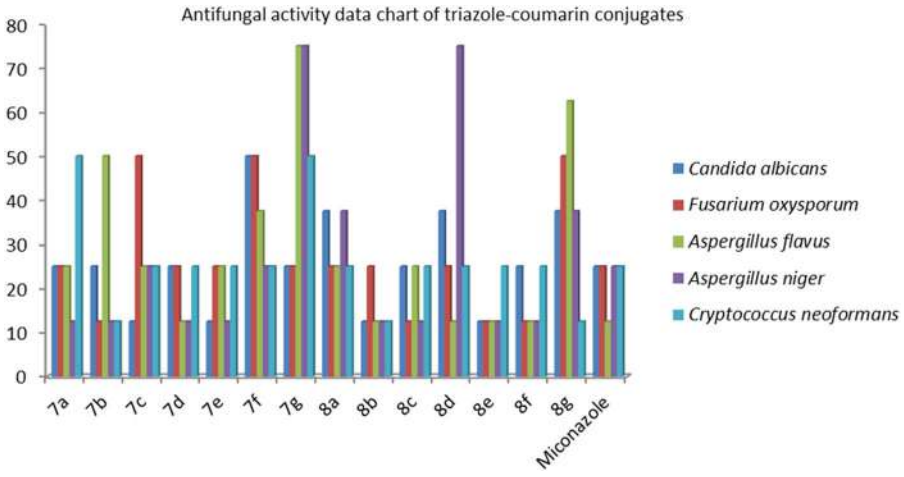


FIGURE 5 A comparison of the antifungal activities of triazole–coumarin conjugates with miconazole

compounds efficiently interact with the active-site residues like Tyr105, Phe108, Phe121, Val130, Tyr168, Tyr154, Phe162, Leu412, Phe246, Met342, Ala343, Cys439, Ser414, Leu412 and Met544. The triazole–coumarin conjugates having *ortho* substitution on the phenyl ring partially replicate in vitro antifungal results, that is, **8b** and **8e**.

The *ortho*-substituted (–CH_3) phenyl ring derivative **8b** (−7.19) interacts with polar and nonpolar amino acids of the active site. The polar amino acid Ser414 interacts with the nitrogen atom of the triazole ring to form conventional hydrogen bond interactions with a distance of 2.37 Å. The sulfur atom of polar amino acid Cys439 interacts with π electron cloud of the phenyl ring to form π–sulfur interactions. The aliphatic and hydrophobic amino acids Leu412, Tyr105, Phe108, Phe121, and Val130 interact with π electron cloud of aromatic ring to form π–π T-shaped, π–π stacked, and π–sulfur interactions with various distance values shown in Figure 6a.

The *ortho*-substituted (–Cl) phenyl ring derivative **8e** (−7.23) interacts with aliphatic and hydrophobic amino acid residues Ala342 and Tyr168, where it interacts with carbonyl oxygen atom and nitrogen atom of the triazole ring with a distance of 2.21 and 2.08 Å to form conventional hydrogen bond interactions. The polar amino acid residue Met342 and hydrophobic amino acid Phe264 form a carbon–hydrogen bond and π interaction with *ortho*-substituted chlorine atom with a distance of 2.08 and 3.77 Å. However, aliphatic and hydrophobic amino acids Leu412, Phe264, Phe162, Tyr154, and Met342 interact with π electron cloud of aromatic phenyl rings to form π–π stacked, amide–π stacked, alkyl and π–alkyl interactions shown in Figure 6b.

2.3.3 | In silico ADME prediction

Early prediction of druglikeness properties of lead compounds is an important task, as it decides the time and cost of drug discovery and development. Many of the active agents with a significant biological activity have failed in clinical trials due to inadequate druglikeness properties.[57] The druglikeness properties were predicted by analyzing ADME parameters based on Lipinski's rule of five. We had calculated and analyzed various physical descriptors and pharmaceutical relevant properties for ADMET prediction by using FAFDrugs2, and data are summarized in Table 2.

All the compounds showed significant values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants that characterized these agents to be likely orally active. The data obtained for all the

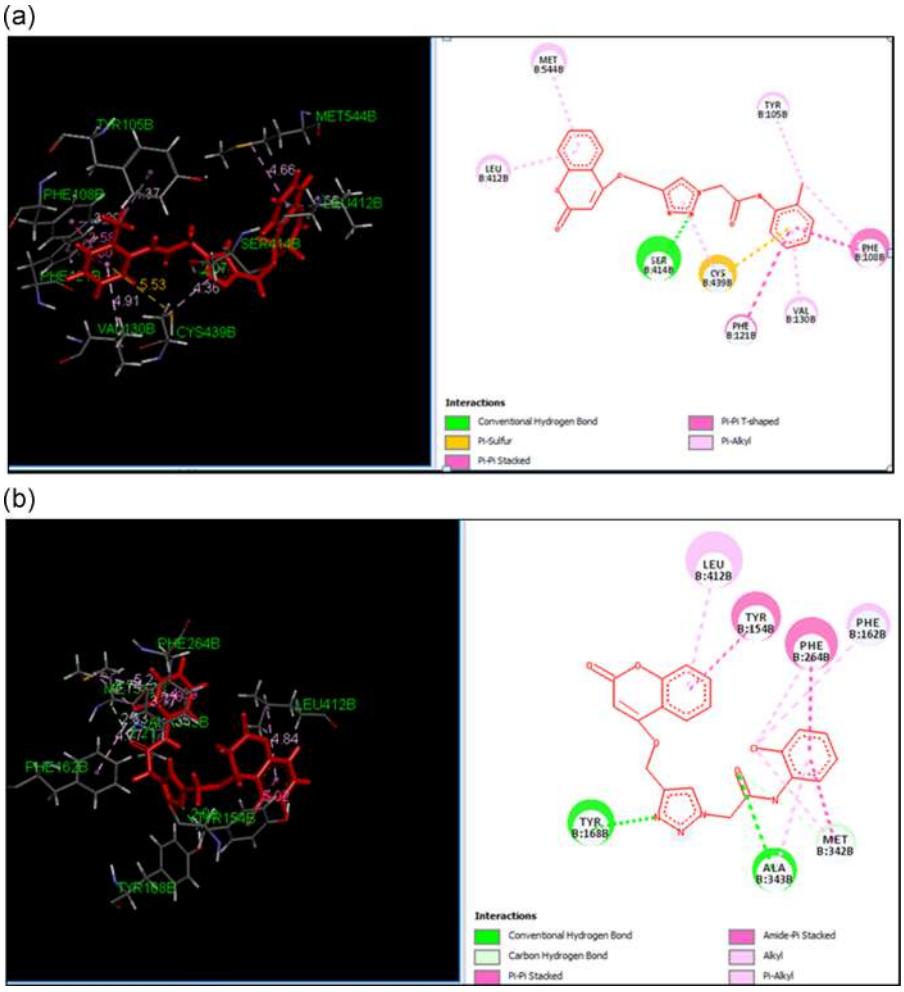


FIGURE 6 Binding pose and molecular interactions of (a) **8b** and (b) **8e** in the active site of cytochrome P450 lanosterol 14α-demethylase (CYP51)

TABLE 2 Pharmacokinetic parameters of triazole–coumarin conjugates (**7a–g** and **8a–g**)

Entry	%ABS	MW	Log*P*	PSA	RotB	RigidB	HBD	HBA	Ratio H/C	Lipinski violation	Toxicity
7a	74.76	390.39	2.98	99.25	6	25	1	6	0.4	0	Nontoxic
7b	74.76	404.42	3.29	99.25	6	25	1	6	0.4	0	Nontoxic
7c	74.76	404.42	3.29	99.25	6	25	1	6	0.4	0	Nontoxic
7d	74.76	404.42	3.29	99.25	6	25	1	6	0.4	0	Nontoxic
7e	74.76	424.84	3.64	99.25	6	25	1	6	0.4	0	Nontoxic
7f	74.76	424.84	3.64	99.25	6	25	1	6	0.4	0	Nontoxic
7g	74.76	424.84	3.64	99.25	6	25	1	6	0.4	0	Nontoxic
8a	76.11	378.38	2.56	95.34	6	25	1	6	0.4	0	Nontoxic
8b	76.11	392.41	2.87	95.34	6	25	1	6	0.4	0	Nontoxic
8c	76.11	392.41	2.87	95.34	6	25	1	6	0.4	0	Nontoxic
8d	76.11	392.41	2.87	95.34	6	25	1	6	0.4	0	Nontoxic
8e	76.11	412.83	3.21	95.34	6	25	1	6	0.5	0	Nontoxic
8f	76.11	412.83	3.21	95.34	6	25	1	6	0.5	0	Nontoxic
8g	76.11	412.83	3.21	95.34	6	25	1	6	0.5	0	Nontoxic

Abbreviations: HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; MW, molecular weight; PSA, polar surface area; RotB, rotatable bonds; RigidB, rigid bonds; %ABS, percentage absorption.

synthesized compounds were within the range of accepted values. None of the synthesized compounds had violated the Lipinski's rule of five. The value of polar surface area, log*P*, and H/C ratio of synthesized compounds **7a–g** and **8a–g** indicated good oral bioavailability. The parameters like the number of rotatable bonds and number of rigid bonds are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. All the synthesized compounds were found to be nontoxic. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which is reflected in their physicochemical values, thus ultimately enhancing pharmacological properties of these molecules.

3 | CONCLUSIONS

In conclusion, we have synthesized new triazole–coumarin conjugates *via* the click chemistry approach, which were evaluated for their in vitro antifungal and antioxidant activity. The synthesized compounds displayed a promising antifungal activity as compared with the standard drug miconazole. Compounds **7b**, **7d**, **7e**, **8b**, and **8e** displayed an excellent antifungal activity as compared with the standard antifungal drug miconazole. Compound **7a** displayed a potential antioxidant activity when compared with standard BHT. In addition, molecular docking study of these synthesized triazole–coumarin conjugates reveals that they have a high affinity toward the active site of enzyme P450 cytochrome lanosterol 14α-demethylase, which offers a strong platform for new structure-based design efforts. Furthermore, the analysis of the ADME parameters for the synthesized compounds predicted good drug-like properties and potential for development as oral drug candidates. Thus, we suggest that compounds **7a** (antioxidant activity), **7b**, **7d**, **7e**, **8b** and **8e** (antifungal activity) can be developed as an important lead moiety, as they replicate in vitro activity in the inhibition assay and in silico molecular docking study. They can be used in scaffolds, hoping for the design and development of new lead compounds as antifungal agents.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All the solvents and reagents were purchased from commercial suppliers, Sigma-Aldrich, Rankem India Ltd., and Spectrochem Pvt. Ltd., and were used without further purification. The completion of the reactions was monitored by thin-layer chromatography (TLC) on aluminum plates coated with silica gel 60 F_{254}, with 0.25 mm thickness (Merck). The detection of the components was done by exposure to iodine vapors or UV light. Melting points were determined by open capillary methods and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker DRX-400 and 500-MHz spectrometer. Infrared (IR) spectra were recorded using a Bruker ALPHA Eco-ATR FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6520 (QTOF) mass spectrometer.

The original spectra of the investigated compounds, together with their InChI codes and some biological activity data, are provided as Supporting Information Data.

4.1.2 | General procedure for the synthesis of substituted 2-(4-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)-oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide derivatives 7a–g and 8a–g

To the stirred solution of alkyne **6** (1 mmol), azide **3** (1 mmol) and copper diacetate ($Cu(OAc)_2$; 10 mol%) in *t*-BuOH-H_2O (3:1) were added, and the resulting mixture was stirred at room temperature for 8–10 hr. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction mixture was quenched with crushed ice, and the obtained solid was filtered and washed with water. The crude solid was crystallized in ethanol to afford the corresponding pure product. The synthesized compounds **7a**–**g** and **8a**–**g** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

*2-(4-{[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**7a**)*

Compound **7a** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3a** and alkyne **6a** in 8.5 hr as a white solid, mp: 149–151°C; FTIR (cm^{-1}): 3,275 (N–H stretching), 1,698 and 1,670 (C═O stretching); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.41 (s, 3H, $-CH_3$), 5.32 (s, 2H, $-NCH_2CO-$), 5.37 (s, 2H, $-OCH_2$), 6.23 (s, 1H, Ar-H), 7.07 (dd, J = 8.0, 3.0 Hz, 1H, Ar-H), 7.10 (d, J = 8.0 Hz, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 7.34 (t, J = 8.0 Hz, 2H, Ar-H), 7.58 (d, J = 8.0 Hz, 2H, Ar-H), 7.71 (d, J = 8.0 Hz, 1H, Ar-H), 8.32 (s, 1H, triazole), and 10.48 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 18.6, 52.7, 62.1, 102.1, 111.8, 113.1, 113.9, 119.7, 124.3, 127.0, 127.1, 129.4, 138.9, 142.3, 153.9, 155.2, 160.6, 161.6, and 164.6; mass calculated for $C_{21}H_{18}N_4O_4Na$ $[M+Na]^+$: 413.1226 and found: 413.1171.

*2-(4-{[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(o-tolyl)acetamide (**7b**)*

Compound **7b** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3b** and alkyne **6a** in 9.5 hr as an orange solid, mp: 195–197°C; FTIR (cm^{-1}): 3,276 (N–H stretching), 1,690 and 1,670 (C═O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.95 (s, 3H, $-CH_3$), 2.12 (s, 3H, $-CH_3$), 5.04 (s, 4H, $-NCH_2CO-$ and $-OCH_2$), 5.84 (s, 1H, Ar-H), 6.67–6.68 (m, 4H, Ar-H), 7.25 (s, 3H, Ar-H), 7.75 (s, 1H, triazole), and 9.07 (s, 1H, NH); mass calculated for $C_{22}H_{20}N_4O_4Na$ $[M+Na]^+$: 427.1382 and found: 427.1334.

*2-(4-{[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(m-tolyl)acetamide (**7c**)*

Compound **7c** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3c** and alkyne **6a** in 8 hr as a white solid, mp: 190–192°C; FTIR (cm^{-1}): 3,291 (N–H stretching), 1,678 (C═O stretching); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.27 (s, 3H, $-CH_3$), 2.39 (s, 3H, $-CH_3$), 5.31 (s, 2H, $-NCH_2CO-$), 5.36 (s, 2H, $-OCH_2$), 6.21 (s, 1H, Ar-H), 6.91 (d, J = 8.0, Hz, 1H, Ar-H), 7.05 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 7.17 (d, J = 4.0 Hz, 1H, Ar-H), 7.21 (t, J = 8.0 Hz, 1H, Ar-H), 7.37 (d, J = 8.0 Hz, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.69 (d, J = 8.0 Hz, 1H, Ar-H), 8.31 (s, 1H, triazole) and 10.40 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 17.9, 20.9, 52.1, 61.4, 101.4, 111.1, 112.4, 113.2, 116.3, 119.6, 124.3, 126.3, 126.4, 128.6, 138.0, 138.1, 141.6, 153.2, 154.5, 160.0, 160.9, and 163.9; HRMS calculated for $C_{22}H_{21}N_4O_4$ $[M+H]^+$: 405.1563 and found: 405.1571.

*2-(4-{[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide (**7d**)*

Compound **7d** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3d** and alkyne **6a** in 9 hr as a red solid, mp: 216–218°C; FTIR (cm^{-1}): 3,248 (N–H stretching), 1,698 and 1,659 (C═O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$), 5.31 (s, 2H, $-NCH_2CO-$), 5.34 (s, 2H, $-OCH_2$), 6.22 (s, 1H, Ar-H), 7.06 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 7.13 (d, J = 8.0 Hz, 2H, Ar-H), 7.17 (d, J = 4.0 Hz, 1H, Ar-H), 7.46 (d, J = 8.0 Hz, 2H, Ar-H), 7.70 (d, J = 8.0 Hz, 1H, Ar-H), 8.31 (s, 1H, triazole), and 10.40 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 18.5, 20.8, 52.5, 61.9, 101.9, 111.6, 113.0, 113.7, 119.6, 126.9, 127.0, 129.6, 133.1, 136.2, 142.1, 153.8, 155.0, 160.5, 161.4, and 164.2; HRMS calculated for $C_{22}H_{19}N_4O_4$ $[M-H]^+$: 403.1412 and found: 403.1424.

*N-(2-Chlorophenyl)-2-(4-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**7e**)*

Compound **7e** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3e** and alkyne **6a** in 9.5 hr as a white solid, mp: 206–208°C; FTIR (cm^{-1}): 3,118 (N–H stretching), 1,664 and 1,600 (C═O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, $-CH_3$), 5.31 (s, 2H, $-NCH_2CO-$), 5.48 (s, 2H, $-OCH_2$), 6.22 (s, 1H, Ar-H), 7.05 (d, J = 8.0, Hz, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.22 (t, J = 8.0 Hz, 1H, Ar-H), 7.34 (t, J = 8.0 Hz, 1H, Ar-H), 7.52 (d, J = 8.0 Hz, 1H, Ar-H), 7.69 (d, J = 8.0 Hz, 1H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 8.32 (s, 1H, triazole), and 10.09 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 18.1, 52.0, 61.6, 101.6, 111.3, 112.6, 113.4, 125.9, 126.3, 126.5, 126.7, 126.8, 127.6, 129.6, 134.1, 141.8, 153.4, 154.7, 160.1, 161.1, and 164.9; HRMS calculated for $C_{21}H_{16}ClN_4O_4$ $[M-H]^+$: 423.0866 and found: 423.0880.

*N-(3-Chlorophenyl)-2-(4-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**7f**)*

Compound **7f** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3f** and alkyne **6a** in 10 hr as a yellow solid, mp: 218–220°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.39 (s, 3H, $-CH_3$), 5.31 (s, 2H, $-NCH_2CO-$), 5.38 (s, 2H, $-OCH_2$), 6.21 (s, 1H, Ar-H), 7.05 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 7.36 (t, J = 8.0 Hz, 1H, Ar-H), 7.44 (d, J = 8.0 Hz, 1H, Ar-H), 7.69 (d, J = 8.0 Hz, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 8.31 (s, 1H, triazole), and 10.68 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 18.2, 52.2, 61.6, 101.6, 111.3, 112.6, 113.4, 117.7, 118.8, 123.6, 126.5, 126.7, 130.7, 133.2, 139.8, 141.8, 154.7, 160.2, 161.1, and 164.7; HRMS calculated for $C_{21}H_{16}ClN_4O_4$ $[M-H]^+$: 423.0866 and found: 423.0872.

*N-(4-Chlorophenyl)-2-(4-{[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]-methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**7g**)*

Compound **7g** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3g** and alkyne **6a** in 8.5 hr as a yellow solid,

mp: 210–212°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, –CH_3), 5.30 (s, 2H, –NCH_2CO–), 5.36 (s, 2H, –OCH_2), 6.23 (s, 1H, Ar-H), 7.05 (dd, J = 8.0, 4.0 Hz, 1H, Ar-H), 7.17 (d, J = 4.0 Hz, 1H, Ar-H), 7.39 (d, J = 8.0 Hz, 2H, Ar-H), 7.60 (d, J = 8.0 Hz, 2H, Ar-H), 7.70 (d, J = 8.0 Hz, 1H, Ar-H), 8.31 (s, 1H, triazole), and 10.63 (s, 1H, NH); HRMS calculated for $C_{21}H_{16}ClN_4O_4$ $[M-H]^+$: 423.0866 and found: 423.0878.

*2-(4-{[(2-Oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**8a**)*

Compound **8a** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3a** and alkyne **6b** in 10 hr as a white solid, mp: 216–218°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.40 (s, 2H, –NCH_2CO–), 5.47 (s, 2H, –OCH_2), 6.20 (s, 1H, Ar-H), 7.09 (t, J = 8.0, Hz, 1H, Ar-H), 7.33 (t, J = 8.0 Hz, 3H, Ar-H), 7.40 (d, J = 8.0 Hz, 1H, Ar-H), 7.59 (d, J = 8.0 Hz, 2H, Ar-H), 7.65 (t, J = 8.0 Hz, 1H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 8.43 (s, 1H, triazole), and 10.51 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 52.3, 62.8, 91.4, 115.1, 116.5, 119.3, 122.8, 123.8, 124.3, 127.1, 128.9, 132.8, 138.4, 152.8, 164.2, and 164.4; HRMS calculated for $C_{20}H_{15}N_4O_4$ $[M-H]^+$: 375.1099 and found: 375.1080.

*2-(4-{[(2-Oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(o-tolyl)acetamide (**8b**)*

Compound **8b** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3b** and alkyne **6b** in 8.5 hr as a white solid, mp: 170–172°C; FTIR (cm^{-1}): 3,248 (N–H stretching), 1,698 and 1,659 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.24 (s, 3H, –CH_3), 5.45 (s, 2H, –NCH_2CO–), 5.47 (s, 2H, –OCH_2), 6.20 (s, 1H, Ar-H), 7.11 (t, J = 8.0, Hz, 1H, Ar-H), 7.17 (t, J = 8.0 Hz, 1H, Ar-H), 7.23 (d, J = 8.0 Hz, 1H, Ar-H), 7.33 (t, J = 8.0 Hz, 1H, Ar-H), 7.42 (d, J = 8.0 Hz, 2H, Ar-H), 7.65 (t, J = 8.0 Hz, 1H, Ar-H), 7.73 (d, J = 8.0 Hz, 1H, Ar-H), 8.43 (s, 1H, triazole), and 9.83 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 17.8, 52.0, 62.8, 91.4, 115.1, 116.5, 122.8, 124.2, 124.8, 125.6, 126.1, 127.0, 130.5, 131.6, 132.8, 135.5, 152.8, 161.6, 164.3, and 164.4; HRMS calculated for $C_{21}H_{17}N_4O_4$ $[M-H]^+$: 389.1255 and found: 389.1311.

*2-(4-{[(2-Oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(m-tolyl)acetamide (**8c**)*

Compound **8c** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3c** and alkyne **6b** in 9 hr as a yellow solid, mp: 211–213°C; FTIR (cm^{-1}): 3,307 (N–H stretching), 1,703 and 1,666 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.27 (s, 3H, –CH_3), 5.40 (s, 2H, –NCH_2CO–), 5.47 (s, 2H, –OCH_2), 6.20 (s, 1H, Ar-H), 6.90 (d, J = 8.0, Hz, 1H, Ar-H), 7.21 (t, J = 8.0, Hz, 1H, Ar-H), 7.30–7.44 (m, 4H, Ar-H), 7.65 (t, J = 8.0 Hz, 1H, Ar-H), 7.73 (d, J = 8.0 Hz, 1H, Ar-H), 8.43 (s, 1H, triazole) and 10.44 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 21.4, 52.5, 63.0, 91.6, 115.3, 116.6, 116.7, 120.0, 123.3, 124.4, 124.7, 127.3, 129.0, 133.0, 138.4, 138.5, 153.0, 161.8, 164.3, and 164.6; HRMS calculated for $C_{21}H_{17}N_4O_4$ $[M-H]^+$: 389.1255 and found: 389.1346.

*2-(4-{[(2-Oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-*N*-(p-tolyl)acetamide (**8d**)*

Compound **8d** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3d** and alkyne **6b** in 8.5 hr as a white solid, mp: 247–249°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, –CH_3), 5.38 (s, 2H, –NCH_2CO–), 5.47 (s, 2H, –OCH_2), 6.20 (s, 1H, Ar-H), 7.13 (d, J = 8.0, Hz, 2H, Ar-H), 7.34 (t, J = 8.0, Hz, 1H, Ar-H), 7.41 (d, J = 8.0 Hz, 1H, Ar-H), 7.47 (d, J = 8.0 Hz, 2H, Ar-H), 7.66 (t, J = 8.0 Hz, 1H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 8.41 (s, 1H, triazole), and 10.41 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 20.5, 52.3, 62.8, 91.4, 116.5, 119.2, 122.8, 124.2, 127.0, 129.3, 132.8, 135.9, 140.6, 152.8, 161.6, 163.9, and 164.4; HRMS calculated for $C_{21}H_{17}N_4O_4$ $[M-H]^+$: 389.1255 and found: 389.1314.

*N-(2-Chlorophenyl)-2-(4-{[(2-oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**8e**)*

Compound **8e** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3e** and alkyne **6b** in 9.5 hr as a brown solid, mp: 217–219°C; FTIR (cm^{-1}): 3,254 (N–H stretching), 1,709 and 1,673 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.47 (s, 2H, –NCH_2CO–), 5.51 (s, 2H, –OCH_2), 6.19 (s, 1H, Ar-H), 7.20–7.76 (m, 8H, Ar-H), 8.43 (s, 1H, triazole), and 10.12 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 52.0, 62.7, 91.4, 115.0, 116.5, 122.8, 124.2, 125.9, 126.3, 126.8, 127.1, 127.6, 129.6, 132.8, 134.1, 152.8, 161.5, 164.3, and 164.8; HRMS calculated for $C_{20}H_{14}ClN_4O_4$ $[M-H]^+$: 409.0709 and found: 409.0722.

*N-(3-Chlorophenyl)-2-(4-{[(2-oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**8f**)*

Compound **8f** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3f** and alkyne **6b** in 10 hr as a red solid, mp: 218–220°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.42 (s, 2H, –NCH_2CO–), 5.47 (s, 2H, –OCH_2), 6.20 (s, 1H, Ar-H), 7.15 (d, J = 8.0, Hz, 1H, Ar-H), 7.32–7.41 (m, 3H, Ar-H), 7.45 (d, J = 8.0 Hz, 1H, Ar-H), 7.65 (t, J = 8.0 Hz, 1H, Ar-H), 7.73 (d, J = 8.0 Hz, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 8.43 (s, 1H, triazole), and 10.71 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 52.3, 62.8, 91.4, 115.1, 116.5, 117.7, 118.8, 122.8, 123.6, 124.2, 127.0, 130.7, 132.8, 133.2, 139.8, 140.8, 152.8, 161.6, 164.4, and 164.6; HRMS calculated for $C_{20}H_{14}ClN_4O_4$ $[M-H]^+$: 409.0709 and found: 409.0724.

*N-(4-Chlorophenyl)-2-(4-{[(2-oxo-2*H*-chromen-4-yl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)acetamide (**8g**)*

Compound **8g** was obtained *via* the 1,3-dipolar cycloaddition reaction between azide **3g** and alkyne **6b** in 8 hr as a white solid, mp: 240–242°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 5.40 (s, 2H, –NCH_2CO–), 5.46 (s, 2H, –OCH_2), 6.19 (s, 1H, Ar-H), 7.30–7.44 (m, 4H, Ar-H), 7.57–7.68 (m, 3H, Ar-H), 7.74 (d, J = 8.0 Hz, 1H, Ar-H), 8.41 (s, 1H, triazole), and 10.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 52.8, 63.2, 91.8, 115.6, 117.0, 121.3, 123.3, 124.7, 127.5, 127.9, 129.3, 133.3, 137.8, 141.3, 153.3, 162.0, and 164.8; HRMS calculated for $C_{20}H_{14}ClN_4O_4$ $[M-H]^+$: 409.0709 and found: 409.0715.

4.2 | Biological activity assays

4.2.1 | Antifungal activity

The antifungal activity was determined by the standard agar dilution method as per the CLSI (formerly NCCLS) guidelines.[56] The newly synthesized compounds were screened against five human pathogenic fungal strains, including *C. albicans* (NCIM 3471), *F. oxysporum* (NCIM 1332), *A. flavus* (NCIM 539), *A. niger* (NCIM 1196), and *C. neoformans* (NCIM 576). The standard miconazole and synthesized compounds were dissolved in DMSO. In phosphate buffer of pH 7, the medium yeast nitrogen base was dissolved and autoclaved for a duration of 10 min at 110°C. With each set, a growth control without the antifungal agent and solvent control DMSO were included. The fungal strains were freshly subcultured on Sabouraud dextrose agar and incubated at 25°C for 72 hr. The fungal cells were suspended in sterile distilled water and diluted to get 10^5 cells/ml. Then, 10 ml of the standardized suspension was inoculated on the control plates and the media were incorporated with the antifungal agents. The inoculated plates were incubated at 25°C for 48 hr. The readings were taken at the end of 48 and 72 hr. MIC is the lowest concentration of the drug preventing the growth of macroscopically visible colonies on the drug-containing plates when there is visible growth on the drug-free control plates.

4.2.2 | Antioxidant activity

Synthesized triazole–coumarin conjugates were screened for in vitro radical scavenging potential by using the DPPH radical scavenging assay. The results were compared with the standard synthetic antioxidant BHT.

The antioxidant activity of the synthesized compounds was assessed in vitro by the DPPH radical scavenging assay.[58] Results were compared with the standard antioxidant BHT. The hydrogen atom or electron-donating ability of the compounds was measured from the bleaching of the purple-colored methanol solution of DPPH. The spectrophotometric assay uses the stable radical DPPH as a reagent. Furthermore, 1 ml of various concentrations of the test compounds (5, 10, 25, 50, and 100 mg/ml) in methanol was added to 4 ml of 0.004% (w/v) methanol solution of DPPH. After a 30-min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (*I*%) of free radical production from DPPH was calculated by the following equation:

$$\% \text{ scavenging} = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound. Tests were carried out in triplicate.

4.3 | Molecular modeling study

4.3.1 | Homology modeling

The homology modeling technique was employed to build a 3D model structure of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* with the help of VLifeMDS 4.3 Promodel molecular modeling tool. The protein sequence was retrieved from UniprotKB database (accession number: P10613). The homologs' template sequence search was carried out against the protein structure database (http://www.rcsb.org/) by using BlastP. The appropriate template crystal structure of human lanosterol 14α-demethylase (CYP51) complexes with miconazole (3LD6 B) which was based on default parameters, identity and positive criteria. The secondary structure assignment and sequence realignment were carried out to build the final modeled structure of fungal CYP51.

4.3.2 | Molecular docking study

The model protein structure and 3D structure of sketched synthesized compound were prepared for molecular docking using AutoDock Vina docking tool. The molecular docking study of synthesized compounds **7a–g** and **8a–g** was carried out using the final modeled structure of fungal CYP51. To understand this mechanism of action of inhibitors, molecular interactions were analyzed.

4.3.3 | ADMET testing

The ADMET properties of synthesized compounds **7a–g** and **8a–g** and standard drug were tested using FAFDrug2 tool, which is run on the Linux operating system.[59] The FAFDrug2 tool works on assumptions of Lipinski's rule of five and Veber's rule, which was widely followed in filtering lead compounds that would likely be further developed in drug design programs.[60] In addition to this, some other parameters were also considered to test ADMET properties, such as the number of rotatable bonds (>10), the number of rigid bonds, and percentage absorption (%ABS), which significantly contribute to good oral bioavailability and good intestinal absorption.[61]

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

Perfluoro-alkylated and trifluoro-methylated pyrazoles represent pharmacologically related core structures that are present in many important drugs and agrochemicals, such as fluazolate (herbicide), penthiopyrad (fungicide), razaxaban (anticoagulant), deracoxib, celecoxib (anti-inflammatory), and penflufen (fungicidal) (Figure 1).[16] So, the modern trend is moving more in the direction of the synthesis of a collection of fluorine-containing molecules in order to find excellent biological activity.

Ultrasonic irradiation is a new technology that has been widely used in chemical reactions. When ultrasonic waves pass through a liquid medium, a large number of microbubbles form, grow, and collapse in very short times, about a few microseconds. The formation and violent collapse of small vacuum bubbles takes place due to the ultrasonication waves generated in alternating high pressure and low pressure in liquids, and the phenomenon is known as cavitation. It causes high-speed imposing liquid jets and strong hydrodynamic shear forces. The deagglomeration of nanometer-sized materials was carried out using these effects. In this aspect, for high-speed mixers and agitator bead mills, ultrasonication is an alternative.[17]

In the preparative chemist's toolkit, microwave heating is a valuable technique. Due to a modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way.[18] In recent years, microwave-assisted organic synthesis (MAOs)[19] has been emerged as a new "lead" in organic synthesis. Important advantages of this technology include a highly accelerated rate of the reaction and a decrease in reaction time, with an increase in the yield and quality of the product. The current technique is considered an important method toward green chemistry as this technique is more environmentally friendly. The conventional method of organic synthesis usually needs a longer heating time; tedious apparatus setup, which results in the higher cost of the process; and the excessive use of solvents/reagents, which leads to environmental pollution. This growth of green chemistry

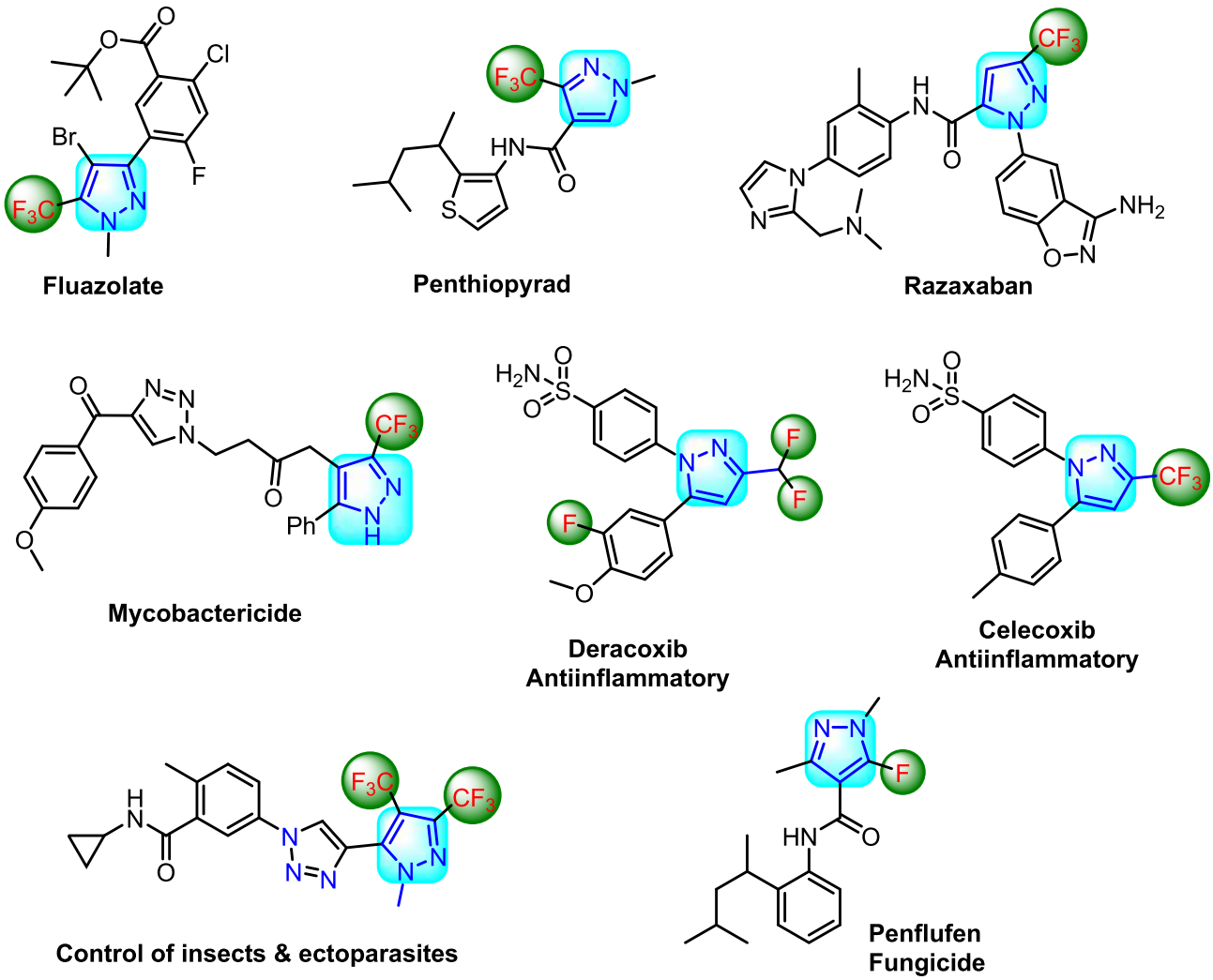


FIGURE 1 Structure of pyrazole- and fluorine-containing commercially available drugs

holds significant potential for a reduction of the byproduct, a reduction in waste production, and lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and bypass thermal conductivity, leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[20] Knoevenagel condensation reactions are carried out by the condensation of aldehyde and the active methylene group using different catalysts such as piperidine, $InCl_3$, $TiCl_4$, LiOH, $ZnCl_2$, and $NbCl_5$.[20,21] They are also carried out using $NaAlO_2$-promoted mesoporous catalysts,[22] ionic liquid,[23] monodisperse carbon nanotube-based NiCu nanohybrids,[24] and MAOs.[25] This is one of the most important methodologies used in synthetic organic chemistry for the formation of a C—C double bond.

From our study, the results demonstrated that green methodologies are less hazardous than classical synthesis methods, as well more efficient and economical and environmentally friendly; short reaction times and excellent yields are observed for those reactions in which conventional heating is replaced by microwave irradiation. Keeping in mind the 12 principles of green chemistry, in continuation of our research work,[26] and the advantages of microwave irradiation and activities associated with pyrazole and fluorine, we construct pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional, as well as microwave, irradiation and ultrasonication and evaluated their anti-inflammatory and antioxidant activity. In addition to this, we have also performed in silico absorption, distribution, metabolism, and excretion (ADME) predictions for the synthesized compounds.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A facile, economic, and green protocol for the cyclocondensation of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) with different aldehydes has been achieved.

The key starting material 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (**3**) was synthesized by the condensation of 1-(perfluorophenyl)hydrazine (**1**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in ethanol[27] (Scheme 1).

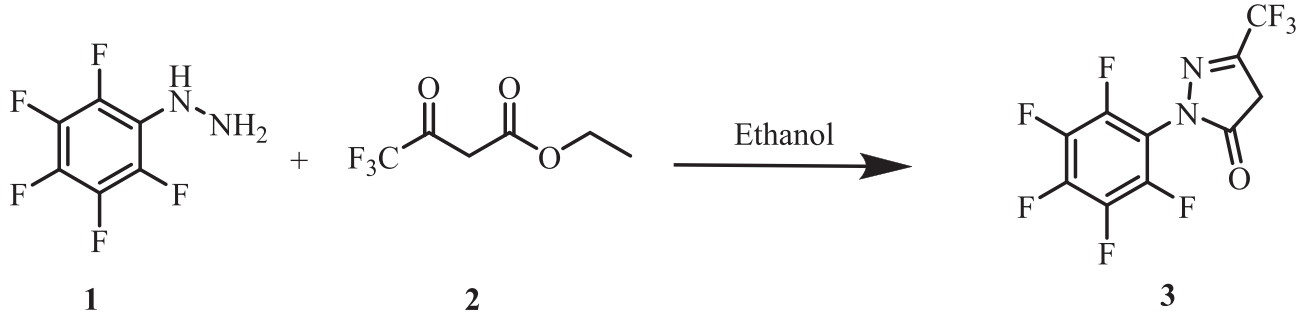
Initially, we carried out the reaction between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) (**3**) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid as a model reaction (Scheme 2). Initially, the model reaction was carried out in ethanol without using acetic acid, and it was observed that a very low yield of product (20%) was obtained even after 2 hr. Therefore, improving the yield intervention of the catalyst was thought to be necessary. So, we decided to use acetic acid as a catalyst to promote this transformation at room temperature. At room temperature, the yield of product (45%) was found to be increased in 3 hr, so we decided to provide heating to the reaction mixture to achieve maximum product yield.

When the reaction mixture refluxed in acetic acid, product formation took place after 2 hr, and the yield of the product was 72% (Table 1).

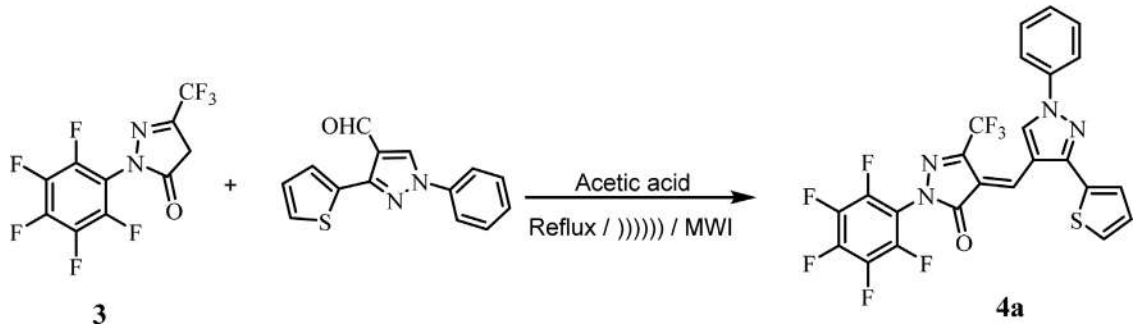
To check the ultrasonication's specific effect on this reaction, under ultrasound irradiation at 35–40°C, we carried out the model reaction using the optimized reaction conditions in hand to check whether the reaction could be accelerated with further improved product yield within a short reaction time (Scheme 2).

It was observed that, under ultrasonic conditions, the conversion rate of a reactant to product increased with less time (Table 1). Thus, when considering the basic green chemistry concept, ultrasonic irradiation was found to have a beneficial effect on the synthesis of Knoevenagel derivatives (**4a-d**, **5a-f**, and **6a-e**), which was superior to the traditional method with respect to yield and reaction time (Table 1).

To accomplish the goal and significance of green chemistry, the model reaction was carried out under



SCHEME 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one **3**



SCHEME 2 Model reaction for conventional, ultrasonication, and microwave irradiation methods

TABLE 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**)

						Conventional method[a]		Ultrasound method[b]		Microwave method[c]	
Cpd	R_1	R_2	R_3	R_4	m. p. (°C)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
4a	H	H	-	-	224–226	120	72	20	81	6.5	84
4b	Br	F	-	-	232–234	120	75	18	78	6.5	81
4c	Cl	H	-	-	216–218	120	70	20	76	6.0	80
4d	Br	H	-	-	230–232	120	64	16	70	6.5	76
5a	H	H	OMe	-	202–204	120	70	21	76	5.5	84
5b	H	H	H	-	186–188	120	66	17	72	6.0	80
5c	F	H	OMe	-	180–182	120	68	16	75	7.0	82
5d	H	H	Me	-	206–208	120	65	16	71	6.5	79
5e	H	H	OCF_3	-	142–144	120	62	18	70	6.5	76
5f	H	Cl	Cl	-	212–214	120	70	19	80	5.5	84
6a	Me	Cl	Me	H	188–190	120	66	18	76	6.0	78
6b	H	Cl	Me	H	180–182	120	62	17	72	7.5	75
6c	H	Cl	H	H	176–178	120	59	18	79	7.0	80
6d	H	Cl	H	Cl	212–214	120	64	20	72	7.0	78
6e	H	H	Me	H	180–182	120	60	18	80	7.5	82

Abbreviation: Cpd, compound.

[a]Reaction conditions: Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid.

[b]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under ultrasound irradiation.

[c]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under microwave irradiation.

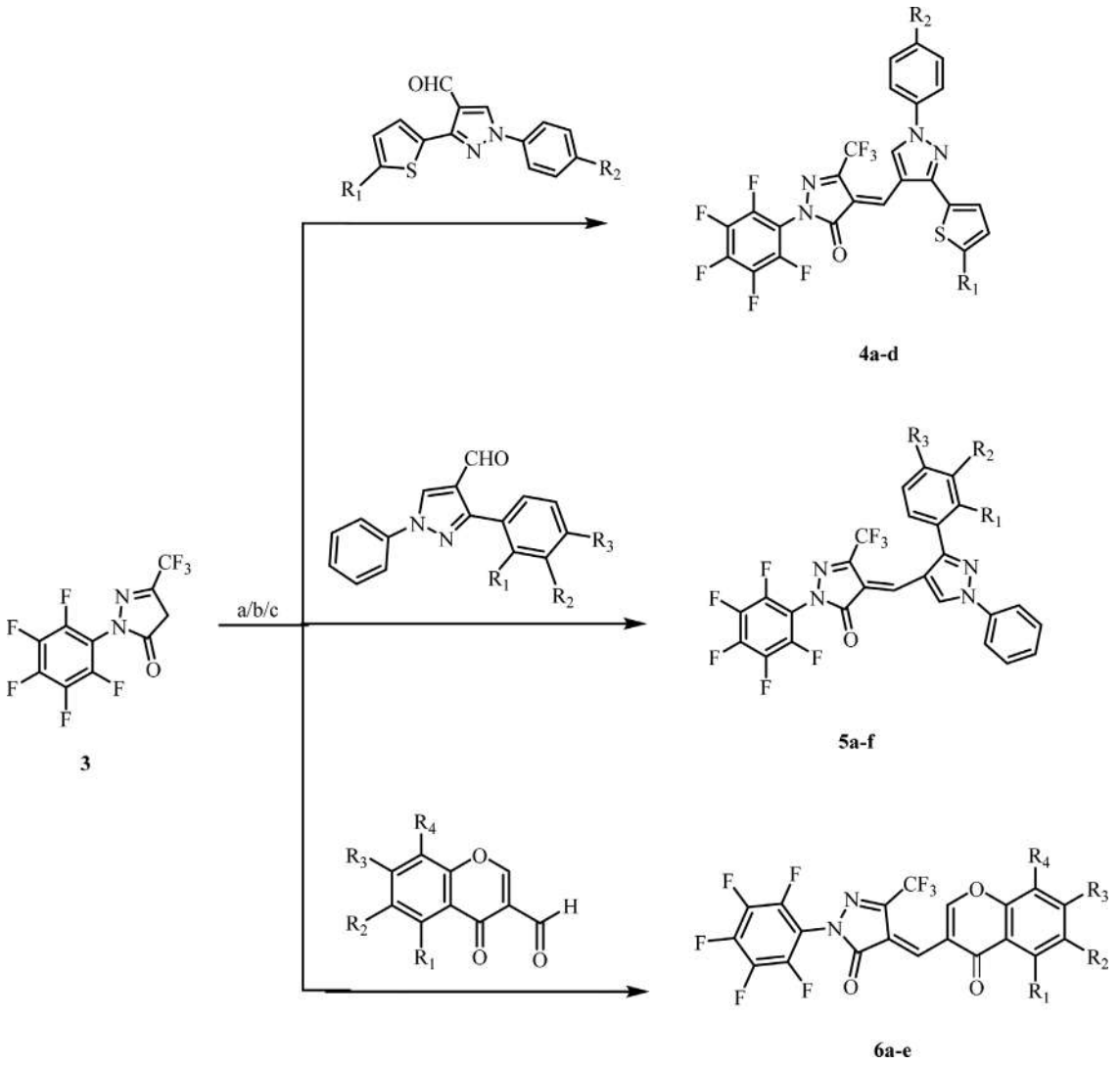
[d]Isolated yield. m.p.: melting point.

microwave irradiation for a period of time indicated in Table 1 at 350 W (Scheme 2). Fortunately, the product formation occurred in 6.5 min, with an 84% increase in yield .

So, from the above experiments, it can be concluded that, when the reaction was carried out under the conventional method, it gave comparatively low yields of products with longer reaction times, while the same reaction carried out under the influence of ultrasonic irradiation and microwave irradiation gave excellent yields of the products in short reaction times.

Finally, we assessed the scope and generality of this method for the Knoevenagel condensation between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) and different aldehydes (Scheme 3), achieved under conventional and nonconventional methods like the ultrasound and microwave methods, respectively. With respect to the substituent present on the aromatic ring of aldehyde, under the optimized conditions, the corresponding products were obtained in high to excellent yields (Table 1).

More importantly, hetero aryl aldehydes were observed to be well tolerated under optimized conditions,



SCHEME 3 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**). Reaction conditions: **a** = Refluxed in acetic acid. **b** = Under ultrasound irradiation in acetic acid. **c** = Under microwave irradiation using acetic acid as a solvent

furnishing the product in good yields. All the synthesized compounds (**4a-d**, **5a-f**, and **6a-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

The formation of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **4a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. In the IR spectrum of compound **4a**, the peaks observed at 1,681 cm^{-1} indicate the presence of C═O group. In the ^{1}H NMR spectrum of compound **4a**, two singlets were observed at δ 8.11 and 10.10 ppm for pyrazolyl and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **4a** revealed that the peak appearing at δ 161.4 ppm is due to the presence of carbonyl carbon. The structure of compound **4a** was also confirmed by a molecular ion peak at *m*/*z* 555.01 $(M + H)^+$. Similarly, the synthesis of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-ones **5a-f** was also confirmed by spectral techniques. In the IR spectrum of compound **5a**, the peak observed at 1,701 cm^{-1} corresponded to the C═O group. In the ^{1}H NMR spectrum of compound **5a**, the three singlets observed at δ 3.92, 8.11, and 10.10 ppm confirm the presence of ─OCH_3, pyrazolyl proton, and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **5a** showed peaks at δ 162.5 and 55.5 ppm, confirming the presence of carbonyl carbon and methoxy carbon, respectively. Furthermore, the structure of compound **5a** was also confirmed by a molecular ion peak at *m*/*z* 573.21 $(M + H)^+$.

Furthermore, the formation of (*Z*)-4-([4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **6a-e** was

confirmed by various spectral techniques. The IR spectrum of compound **6a** showed absorption peaks at 1,707 and 1,666 cm^{-1} corresponding to two carbonyl groups present in the molecules. The ^{1}H NMR spectrum of compound **6a** showed four singlets at δ 2.54 and δ 3.01 ppm for two —CH_3, δ 8.50 ppm for chromone ring proton, and δ 10.54 ppm for olefinic proton. The ^{13}C NMR spectrum of compound **6a** showed that two signals appear at δ 175.4 and 164.2 ppm for the carbonyl carbon of chromone and pyrazolone ring, respectively. In addition, two signals for methyl carbon appear at δ 22.2 and 18.6 ppm. The structure of compound **6a** was also confirmed by mass spectra and by a molecular ion peak observed at m/z 537.11 $(M + H)^+$. Similarly, all the synthesized compounds were characterized by the spectral analysis. Structures of all the synthesized derivatives are shown in Figure S1 (Supporting Information).

2.2 | Biological activity

2.2.1 | Anti-inflammatory activity

The newly synthesized 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) (EC_{50} range = 0.6483 ± 0.221–0.8519 ± 0.281 μg/ml) exhibited moderate anti-inflammatory activity compared to the standard drug diclofenac sodium. Among all the synthesized compounds, except compounds **4c**, **5c**, **5e**, **6d**, and **6e**, all other compounds exhibited a minimum inhibitory concentration (MIC) of 200 μg/ml compared to the standard drug diclofenac sodium (Table 2).

The percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 2. Furthermore, the comparative percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 3.

TABLE 2 Anti-inflammatory and antioxidant activity of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (MIC in μg/ml)

Compound	Anti-inflammatory	Antioxidant
4a	200	>100
4b	200	>400
4c	400	>200
4d	200	>200
5a	200	<100
5b	200	>200
5c	NT	NT
5d	200	<100
5e	800	<100
5f	200	<100
6a	200	<100
6b	200	<100
6c	200	>200
6d	800	>100
6e	400	<100
Diclofenac sodium	50	-
Ascorbic acid	-	<50

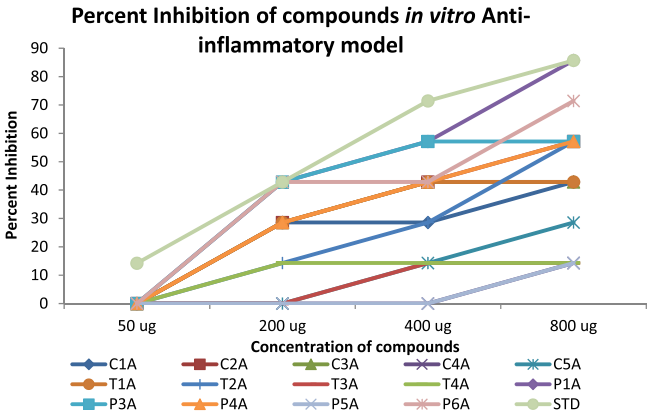


FIGURE 2 The percent inhibition of compounds in an in vitro anti-inflammatory model

2.2.2 | Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed in vitro by the DPPH radical scavenging assay.[28] Ascorbic acid (AA) has been used as a standard drug for the comparison of antioxidant activity, and the observed results are summarized in Table 2.

According to the DPPH assay, compounds **5a**, **5d**, **5e**, **5f**, **6a**, **6b**, and **6e** (IC_{50} = <100 μg/ml) exhibited excellent antioxidant activity compared to the standard antioxidant drug AA (IC_{50} = <50 μg/ml). The remaining synthesized compounds display comparable antioxidant activity than the standard drug butylated hydroxytoluene (Table 2). The percent inhibition of compounds in the in vitro antioxidant model is shown in Figure 4.

2.3 | Computational study

2.3.1 | In silico ADME

An important task for the lead compounds is early prediction of drug likeness properties as it resolves the cost

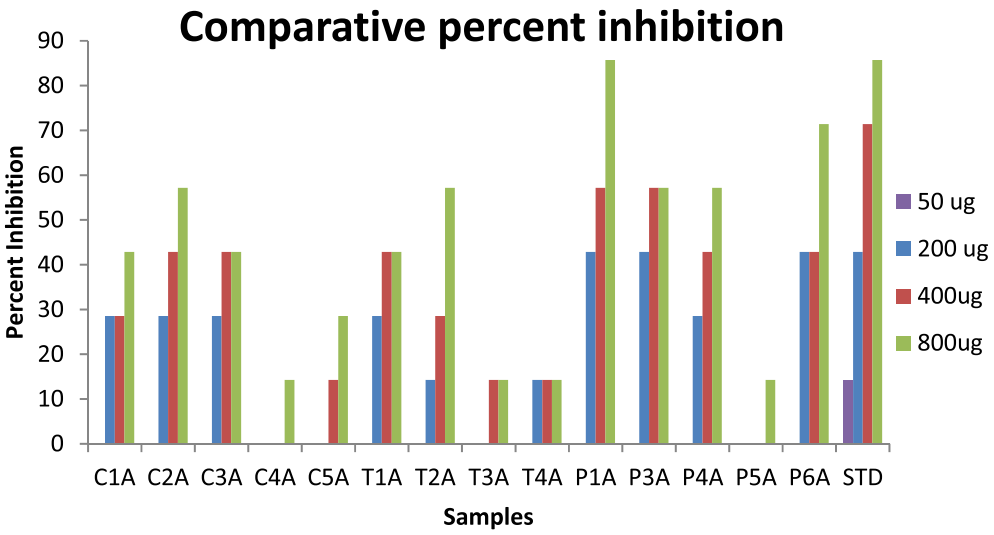


FIGURE 3 The comparative percent inhibition of compounds in an in vitro anti-inflammatory model

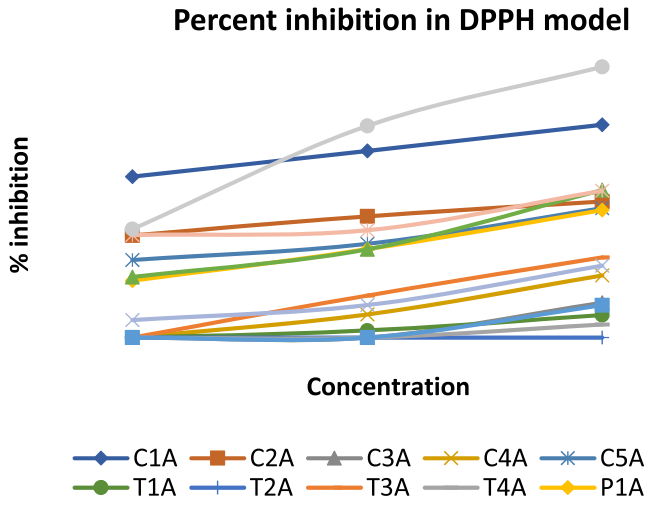


FIGURE 4 The percent inhibition of compounds in an in vitro antioxidant model

and time issues of drug development and discovery. Due to the inadequate drug likeness properties of many active agents with a significant biological activity, these compounds have failed in clinical trials.[29] On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using the Molinspiration online property calculation toolkit,[30] and data are summarized in Table 3.

All the compounds exhibited noteworthy values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants, which characterized these agents to be likely orally active. For the synthesized compound **6e**, the data obtained were within the range of accepted values. Parameters such as the number of rotatable bonds and total polar surface area are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which are reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules.

3 | EXPERIMENTAL SECTION

All organic solvents were acquired from Poona Chemical Laboratory, Pune and Research-Lab Fine Chem Industries, Mumbai and were used as such without further purification. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in *Raga's* synthetic microwave oven. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) fourier transform infrared spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Advance neo 500 spectrophotometers using tetramethylsilane as an internal standard, and $CDCl_3$ and dimethyl sulphoxide-d_6 as solvent and chemical shifts, respectively, were expressed as δ ppm units. Mass spectra were obtained on Waters quadrupole time-of-flight micromass (ESI-MS) mass spectrometer.

3.1 | General procedure for the synthesis of synthesize new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (4a-d, 5a-f and 6a-e)

Conventional method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-

TABLE 3 Pharmacokinetic parameters of (**4a-d**, **5a-f**, and **6a-e**) compounds

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	-
4a	90.81	52.72	5	397.75	554.42	5.83	5	0	2	−0.68
4b	90.81	52.72	5	420.56	651.31	6.92	5	0	2	−0.84
4c	90.81	52.72	5	411.28	588.87	6.63	5	0	2	−0.25
4d	90.81	52.72	5	415.63	633.32	6.76	5	0	2	−0.56
5a	87.62	61.96	6	432.58	578.42	6.10	6	0	2	−0.46
5b	90.81	52.72	5	407.04	548.39	6.04	5	0	2	−0.80
5c	87.62	61.96	6	437.51	596.41	6.19	6	0	2	−0.22
5d	90.81	52.72	5	423.60	562.42	6.49	5	0	2	−0.51
5e	87.62	61.96	7	447.32	632.39	7.01	6	0	2	−0.45
5f	90.81	52.72	5	434.11	617.28	7.33	5	0	2	−0.36
6a	86.53	65.11	3	374.21	536.76	6.25	5	0	2	−0.53
6b	86.53	65.11	3	357.65	522.74	5.87	5	0	2	−0.36
6c	86.53	65.11	3	341.09	508.71	5.49	5	0	2	−0.32
6d	86.53	65.11	3	354.62	543.15	6.10	5	0	2	−0.93
6e	86.53	65.11	3	344.11	488.29	5.26	5	0	1	−0.81

Abbreviations: % ABS, percentage absorption; TPSA, topological polar surface area; n-ROTB, number of rotatable bonds; MV, molecular volume; MW, molecular weight; milogP, logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors, number of hydrogen bond acceptors; n-OHNH donors, number of hydrogen bonds donors.

one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask using glacial acetic acid (5 ml) as a solvent and were refluxed for the period of time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Ultrasound method: A mixture of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) in acetic acid (5 ml) was taken in a 50-ml round-bottom flask. The mixture was irradiated in the water bath of an ultrasonic cleaner at 35–40°C for a period of time indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water, and the obtained solid was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Microwave irradiation method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask (RBF) using glacial acetic acid (5 ml) as a solvent, and the contents of RBF were subjected to MW irradiation for the period of time indicated in Table 1 at 350 W. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

3.1.1 | (4*E*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) methylene)-1*H*-pyrazol-5(4*H*)-one (4a)

Orange solid; Wt. 930 mg, Yield 84%; IR(ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,598 (C=N), 1,519 (C=C), 1,234 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.35–7.91 (m, 8H, Ar—H), 8.11 (s, 1H, pyrazolyl-H), 10.10 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 161.4 (C=O), 151.7, 140.1, 137.8, 134.9, 131.1, 130.0, 129.6, 129.1,

128.70, 128.6, 119.7, 115.7, 113.5; MS (ESI-MS): *m/z* 555.01 $(M + H)^+$.

3.1.2 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4b)

Orange solid; Wt. 1.05 g; Yield 81%; IR (ν_{max}/cm^{-1}): 2,927 (=C—H), 1,680 (C=O), 1,598 (C=N), 1,516 (C=C), 1,231 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, J = 3.50 Hz, Ar—H), 7.26–7.19 (m, 3H, Ar—H), 7.84 (dd, 2H, *J* = 5.00 Hz and 9.00 Hz, Ar—H), 8.10 (s, 1H, pyrazole-H), 10.11 (s, 1H, =C—H); MS: *m/z* 651.03 $(M + H)^+$.

3.1.3 | (4*E*)-4-((3-[5-Chlorothiophen-2-yl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4c)

Orange solid; Wt. 873 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,682 (C=O), 1,597 (C=N), 1,518 (C=C), 1,232 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 1H, Ar—H), 7.26–7.18 (s, 1H, Ar—H), 7.44 (d, 1H, *J* = 6.00 Hz, Ar—H), 7.52 (m, 2H, Ar—H), 7.86 (d, 2H, *J* = 7.00 Hz, Ar—H), 8.11 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 151.3, 139.5, 138.3, 135.0, 133.5, 130.8, 130.0, 128.8, 127.6, 127.4, 120.0, 116.3, 114.6; MS: *m/z* 547.11 $(M + H)^+$.

3.1.4 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4d)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,597 (C=N), 1,520 (C=C), 1,235 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, *J* = 4.00 Hz, Ar—H), 7.21 (d, 1H, *J* = 3.50 Hz, Ar—H), 7.44 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.75–7.86 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.47 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 183.2 (C=O), 162.3, 151.2, 143.2, 142.9, 139.4, 138.3, 134.9, 133.7, 133.4, 131.2, 130.6, 129.8, 129.1, 128.8, 128.5, 128.2, 120.6, 119.9, 119.6, 116.2, 115.9, 114.6; MS: *m/z* 633.05 (M + H).

3.1.5 | (4*Z*)-3-(Trifluoromethyl)-4-((3-[4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5a)

Orange solid; Wt. 971 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,141 (=C—H), 1,703 (C=O), 1,595 (C=N), 1,514 (C=C), 1,224 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.92 (s, 3H, —OCH_3), 7.10 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.51 (t, 2H, *J* = 8.50 Hz, Ar—H), 7.62 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.90 (d, 2H, *J* = 9.00 Hz, Ar—H), 7.99 (s, 1H, pyrazole-H), 10.19 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 161.1, 158.7, 143.3, 141.4, 138.6, 134.9, 130.7, 129.7, 128.5, 122.6, 120.1, 116.8, 114.7, 113.7, 55.5 (OCH_3); MS: *m/z* 579.21 $(M + H)^+$.

3.1.6 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1H-pyrazol-5(4*H*)-one (5b)

Orange solid; Wt. 876 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,142 (=C—H), 1,701 (C=O), 1,595 (C=N), 1,510 (C=C), 1,223 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42 (m, 1H, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.57–7.58 (m, 3H, Ar—H), 7.68 (dd, 2H, *J* = 7.50 and 2.00 Hz, Ar—H), 7.90 (d, 2H, *J* = 8.00 Hz, Ar—H), 8.00 (s, 1H, pyrazole-H), 10.22 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 158.8, 143.0, 141.2, 138.6, 134.9, 130.3, 129.9, 129.7, 129.4, 129.2, 128.6, 120.0, 116.8, 114.0; MS: *m/z* 549.19 $(M + H)^+$.

3.1.7 | (4*Z*)-4-((3-[2-Fluoro-4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5c)

Orange solid; Wt. 1.06 g; Yield 82%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,702 (C=O), 1,596(C=N), 1,512 (C=C), 1,221 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.91 (s, 3H, —OCH_3), 6.82 (dd, 1H, *J* = 2.50 and 12.00 Hz, Ar—H), 6.91 (dd, 1H, *J* = 2.00 and 8.50 Hz, Ar—H), 7.42 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.58–7.49 (m, 2H, Ar—H), 7.79 (d, 1H, *J* = 2.50 Hz, Ar—H), 7.88 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.52 (s, 1H, pyrazole-H), 10.20 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.7 (C=O), 162.6, 162.5, 154.1, 141.2, 138.6, 134.7, 132.5, 129.7, 128.5, 120.0, 117.6, 113.9, 111.2, 110.3, 102.2, 102.0, 55.8 (OCH_3); MS: *m/z* 653.26 $(M + H)^+$.

3.1.8 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-one (5d)

Orange solid; Wt. 887 mg; Yield 79%; IR (ν_{max}/cm^{-1}): 3,143 (=C—H), 1,701 (C=O), 1,594 (C=N), 1,511 (C=C), 1,220 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.44 (s, 3H, —CH_3), 7.45 (d, 1H, J = 7.50 Hz, Ar—H), 7.51 (t, 1H, J = 7.50 Hz, Ar—H), 7.62 (d, 1H, J = 8.00 Hz, Ar—H), 7.65 (d, 1H, J = 8.00 Hz, Ar—H), 9.90 (s, 1H, pyrazole-H), 11.96 (s, 1H, =C—H); MS: m/z 563.08 $(M + H)^+$.

3.1.9 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(4-[trifluoro methoxy]phenyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (5e)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,700 (C=O), 1,595 (C=N), 1,517 (C=C), 1,225 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42–7.44 (m, 3H, Ar—H), 7.51–7.54 (m, 2H, Ar—H), 7.71 (d, 1H, J = 2.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.00 Hz, Ar—H), 7.88 (d, 1H, J = 2.00 Hz, Ar—H), 7.90 (d, 1H, J = 3.50 Hz, Ar—H), 7.92 (s, 1H, pyrazole-H), 10.21 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 157.3, 150.5, 143.2, 142.9, 140.3, 138.5, 134.9, 130.9, 129.8, 129.0, 128.7, 121.5, 120.6, 120.0, 118.4, 116.6, 114.4; MS: m/z 633.23 $(M + H)^+$.

3.1.10 | (4*Z*)-4-((3-[3,4-Dichlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5f)

Orange solid; Wt. 1.03 g; Yield 84%; IR (ν_{max}/cm^{-1}): 3,144 (=C—H), 1,701 (C=O), 1,596 (C=N), 1,517 (C=C), 1,227 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.44 (m, 1H, Ar—H), 7.48 (d, 1H, J = 2.00 Hz, Ar—H), 7.50 (d, 1H, J = 2.00 Hz, Ar—H), 7.53 (d, 1H, J = 7.50 Hz, Ar—H), 7.67 (d, 1H, J = 8.50 Hz, Ar—H), 7.83 (d, 1H, J = 2.00 Hz, Ar—H), 7.87–7.89 (m, 2H, Ar—H), 7.89 (s, 1H, pyrazole-H), 10.18 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.3 (C=O), 156.1, 143.2, 142.9, 139.7, 138.4, 135.0, 134.5, 133.7, 131.2, 131.1, 130.3, 129.8, 128.8, 128.3, 120.0, 116.4, 114.7; MS: m/z 617.15 $(M + H)^+$.

3.1.11 | (*Z*)-4-([6-Chloro-5,7-dimethyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6a)

Orange solid; Wt. 900 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,666 (C=O), 1,624 (C=N), 1,508 (C=C), 1,192 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 3.01 (s, 3H, —CH_3), 7.26 (s, 1H, Ar—H), 8.50 (s, 1H, chromone-H), 10.54 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 175.4 (C=O), 164.2 (C=O), 162.3, 155.1, 144.5, 143.4, 143.3, 139.7, 134.7, 120.9, 120.2, 119.4, 118.3, 118.2, 118.1, 22.2 (—CH_3), 18.6 (—CH_3); MS: m/z 537.11 $(M + H)^+$.

3.1.12 | (*Z*)-4-([6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6b)

Orange solid; Wt. 783 mg; Yield 75%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,705 (C=O), 1,664 (C=O), 1,627 (C=N), 1,508 (C=C), 1,192 (C—F);^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 7.47 (s, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 8.48 (s, 1H, chromone-H), 10.62 (s, 1H, =C—H); MS: m/z 523.08 $(M + H)^+$.

3.1.13 | (*Z*)-4-([6-Chloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6c)

Orange solid; Wt. 812 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,662 (C=O), 1,621 (C=N), 1,509 (C=C), 1,193 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.55 (d, 1H, J = 9.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.50 and 9.00 Hz, Ar—H), 8.26 (d, 1H, J = 2.50 Hz, Ar—H), 8.47 (s, 1H, chromone-H), 10.63 (s, 1H, =C—H); MS: m/z 509.08 $(M + H)^+$.

3.1.14 | (*Z*)-4-([6,8-Dichloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6d)

Orange solid; Wt. 845 mg; Yield 78%; IR (ν_{max}/cm^{-1}): 3,078 (=C—H), 1,707 (C=O), 1,665 (C=O), 1,626 (C=N), 1,506 (C=C), 1,194 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.83 (d, 1H, J = 2.50 Hz, Ar—H), 8.17 (d, 1H, J = 2.50 Hz, Ar—H), 8.40 (s, 1H, chromone-H), 10.66 (s, 1H, =C—H); MS: m/z 543.07 $(M + H)^+$.

3.1.15 | (*Z*)-4-([7-Methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6e)

Orange solid; Wt. 800 mg; Yield 82%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,703 (C=O), 1,666 (C=O), 1,627 (C=N), 1,510 (C=C), 1,193 (C—F);^{1}H NMR spectrum, δ, ppm: 2.51 (s, 3H, —CH_3), 7.48 (d, 1H, J = 8.00 Hz, Ar—H), 7.60 (dd, 1H, J = 8.00 and 2.00 Hz, Ar—H), 8.08 (d,1H, J = 1.50 Hz), 8.54 (s, 1H, chromone-H), 10.64 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 174.5 (C=O), 165.5 (C=O), 162.4, 154.2, 143.4, 142.4, 137.5, 136.3, 126.2, 120.9, 123.3, 120.2, 118.6, 118.5, 118.2, 118.1, 21.1 (—CH_3); MS: m/z 489.14 $(M + H)^+$.

3.2 | Anti-inflammatory activity

All the synthesized compounds were screened for their in vitro anti-inflammatory activities against the standard drug diclofenac sodium. The minimum inhibitory concentration was determined by the well diffusion method at 1 mg/ml of concentration. (Table 2). A volume of 1 ml of diclofenac sodium at different concentrations (50, 100, 200, 400, 800, and 1,000 μg/ml) was homogenized with 1 ml of aqueous solution of bovine serum albumin (5%) and incubated at 27°C for 15 minutes. The mixture of distilled water and bismuth sulphite agar constituted the control tube. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 minutes at 70°C. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 255 nm. Each test was conducted thrice. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = \text{absorbance of control} - \text{absorbance of sample} / \text{absorbance of control} \times 100.$$

3.3 | In silico ADME

In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[31] using the Molinspiration online property calculation toolkit.[30] Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA).[32] Drug likeness model score (a collective property of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound that is represented by a numerical value) was computed by MolSoft software.[33]

4 | CONCLUSIONS

In conclusion, we have constructed pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional and nonconventional methods like microwave irradiation and ultrasonication, respectively, via Knoevenagel condensation and evaluated their biological activity. Ultrasonication and microwave irradiation can shorten the reaction time from a few hours to a few minutes and increases the product yield (74–84%) compared to the conventional method (59–75%). The synthesized compounds exhibited promising anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, the synthesized compound displayed promising antioxidant activity compared to the standard drug. Furthermore, an analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as an oral drug candidate, thus suggesting that compounds from the present series can be further optimized and developed as a lead molecule.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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COLLEGE CAMPUS AS A ROLE MODEL FOR ENVIRONMENTAL CONSCIOUSNESS

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ABSTRACT:

India is a young country. College is the place where this youth come to learn and spend lot of time. These students are the future and part of the society. As our planet earth faces many environmental issues, college is the best place for sensitization of students regarding environment. Students propagate this to their locality also. This paper deals with measures the college can adopts for ecofriendly campus and to become a role model for environmental consciousness like green audit, e governance, vermicompost plant, rainwater harvesting project, biogas plant, botanical garden, hydroponics, use of renewable energy, waste management, biodiversity posters & environmental slogans, students projects based on environment and offering compulsory course on environmental education.

Key words: - *Campus, College, Consciousness, Environment.*

INTRODUCTION:

The human society is facing many environmental issues like pollution, population explosion, deforestation, resource depletion, loss of biodiversity etc. Sustainable development is a significant social, economic or environmental challenge for any country (Wynn Calder, 2003). The youth should get sensitive about environment. Education is one solution to solve environmental problem. The teaching and learning must begin to reflect environmental issues; there is an emerging consensus that institutions must also model sustainable practices (Erin Redman, 2013). Students take with them the green practices and approaches they were involved with at their institution (Will Toor, 2003). Environmental education becomes integral part in syllabus. National Assessment and Accreditation Council an autonomous institution of the University Grants Commission play important role in periodic assessment and accreditation of higher education institutions also gives importance to environment consciousness and sustainability. In Criteria 7 Institutional Values and Best Practices of NAAC manual for the college, environmental consciousness and sustainability is incorporated which includes metrics regarding use of alternate energy sources, management of waste, water conservation facilities, green campus initiatives and quality audits on environment. Eco friendly college means "environmental sustainability within the college". Eco friendly college campus mainly focuses on the efficient uses of energy and water, minimize waste generation or pollution and also economic efficiency. Eco friendly college focuses on the reduction of the emissions of green house gases, more use of renewable energy, rainwater harvesting, encourages staff and student for environmental issues, to have significant environmental impacts. Following measures and activities can be adopted by college to make campus ecofriendly.

Vermicompost Plant: Construction of vermicompost pit for the waste from gardens

and office can be converted to vermicompost which is used as compost for plants in campus.

Rainwater harvesting: Collection of rain water in ponds and using it for laboratory purpose.

Biogas plant: Construction of biogas plant for the biodegradable waste from hostel can be converted to biogas.

Solar Panels: Installation of solar panels at prominent places to utilize renewable solar energy for laboratory work.

Botanical Garden: Maintenance of botanical garden for aesthetic purpose and to attract insects specially butterflies which help in biodiversity study.

Green campus: Plantation programme for green campus so that more carbon dioxide can be fixed and tree attract many birds for their nesting and green initiatives like observation of no vehicle day, environment days etc.

E-waste management: E-waste produced by Information Technology Department is managed by recycling and by doing annual maintenance contract.

Green audit: Green audit of the college should be done regularly.

Biodiversity Posters & Environmental Slogans: Local Biodiversity posters and environmental slogans at prominent places in campus should be displayed which aware students and staff.

Dust bin: Separate dust bin for liquid and solid waste should be placed and properly used.

Hydroponics: Plants can be cultivated in mineral rich water without soil.

E governance: Use of mobile applications, SMS and email for admission and governance.

LED and CFL: To decrease the energy consumption use of CFL and LED should be promoted, five star electronic appliances can be preferred and students and staff should be promoted to switch off appliances after use.

Organization of environmental awareness activities like poster presentation, environmental related day celebration, plays, seminar, conference etc. and involvement of students and staff.

To frame various college level committees related to environment like water management committee, green audit committee, energy conservation committee, waste recycling committee.

CONCLUSION:

College is the place where students spend more time. These young students are the future of any nation. Awareness of these students regarding environmental issues is very important. Eco friendly college campus can be a very good model to learn and sanitizes the students regarding environment that can be passed to society also. For that, college can establish eco friendly college committee to look and implement eco-friendly measures

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OCCURRENCE OF *TENODERA SUPERSTITIOSA SUPERSTITIOSA* (FABRICIUS, 1781) (INSECTA: MANTODEA: MANTIDAE: MANTINAE) FROM THE DECCAN PLATEAU OF MAHARASHTRA STATE, INDIA.

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ABSTRACT

Tenodera superstitiosa superstitiosa (Fabricius, 1781) has been reported for the first time from Kolhapur and Satara Districts of Maharashtra. Present record adds to its geographical distribution apart from Andaman, Bihar, Kerala, Punjab and Uttar Pradesh.

Key words: *Tenodera superstitiosa superstitiosa,* first record, Deccan Plateau.

Praying Mantids are well known predators with about 56 species reported from Maharashtra state (Ghate et. al. 2012). Out of these, *Tenodera superstitiosa superstitiosa* is distributed in Andaman, Bihar, Kerala, Punjab and Uttar Pradesh (Mukherjee et. al. 1995). Later on it was reported in Maharashtra by Mukherjee et. al. (2014) without mentioning specimen examined or deposition records. This leads to a question mark on its distribution in Maharashtra state. Present communication reports collection of this species from Kolhapur district along with brief description.

Material and Methods

The specimen was collected from Karveer Tehsil of Kolhapur district, and Dahiwadi region of Satara district, of Maharashtra state. The nymphs and adults were collected from Panchganga river bank, Karveer, reared in laboratory at the Department of Zoology, Shivaji University, Kolhapur till adult stage. Specimens were properly spread, dried, preserved and deposited at the Department of Zoology, Shivaji University, Kolhapur and Western Regional Centre, Zoological Survey of India,, Pune. The specimens were observed under microscope and photographed. The identification and nomenclature was done following Mukherjee et al. (1995).

Material Examined: 7 nymphs, Karveer, Kolhapur. 18.08.2014, NZC,ZSI,WRC, Ent.-12/106, coll. G.A. Raut. 1 male, Karveer, Kolhapur. 10.09.2015, NZC,ZSI,WRC,Ent.-12/107, coll. G.A. Raut, 1 Female, Dahiwadi, Satara. 12.vii. 2018, ZSUK.MANT.F221, coll. Raut G. A.

Diagnosis: Male (Figure1) and female greenish straw colored. Frontal sclerite 2X wide than high; upper edge sinus on each side. Pronotum long, supra coxal dilation little, the metazona depressed, lateral edges carinated strongly in female, little in male, much longer than the fore coxa; prosternum with small band at the junction of coxa. In fore legs, coxa smooth; femora with 4 external, 4 discoidal, 15 internal spines in which 8 small and 7 large; tibia with 13 internal and 9 external spines; all spines black at the tip. Elytra acute, longer than abdomen, costal area opaque remaning hyaline; in hind wings. costal and discoidal areas crossed by line of dark smoky patches on veins.

Both male and females are in faint brown in the middle and at the lateral green; males were brownish than females. In rainy season both male and female having much green shade while in dry season it become

more brownish; nymphs mostly green in colour.

Measurements: Body length: M-82.78, F-92.67; Pronotum: M-28.41, F-39.1; Fore wing: M-59.3, F-68.7.(M: Male, F: Female)

Distribution: India: Andaman, Bihar, Kerala, Punjab, Uttar Pradesh (Mukherjee et al. 1995) and Maharashtra (present record)

Distribution Elsewhere: Singapore, Angola, Java, Malay, Africa (Mukherjee et al. 2014).

The species has been reported for the first time from Deccan Plateau of Maharashtra. The present record extends its known geographical range notably from Andaman, Bihar, Kerala, Punjab, Uttar Pradesh towards western India and adds information on its known distributional range.

Due to limited literature on this species, misidentifications and confusion, *T. superstitiosa superstitiosa* is frequently reported as *T. fasciata*. However, present study will enable its correct identification and distribution pattern.

Acknowledgements:

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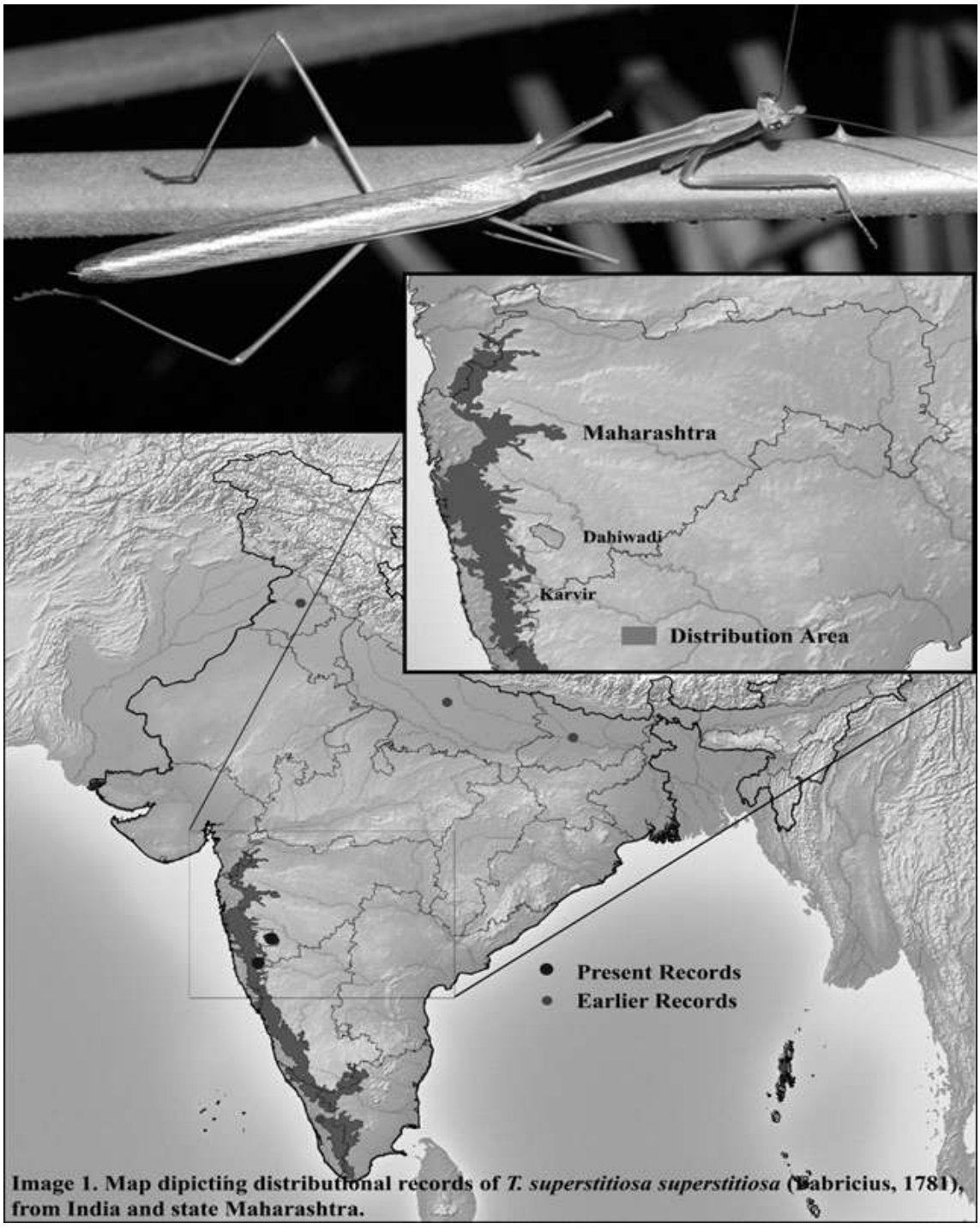

Image 1. Map dipicting distributional records of *T. superstitiosa superstitiosa* (Fabricius, 1781), from India and state Maharashtra.

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OCCURRENCE OF *TENODERA SUPERSTITIOSA SUPERSTITIOSA* (FABRICIUS, 1781) (INSECTA: MANTODEA: MANTIDAE: MANTINAE) FROM THE DECCAN PLATEAU OF MAHARASHTRA STATE, INDIA.

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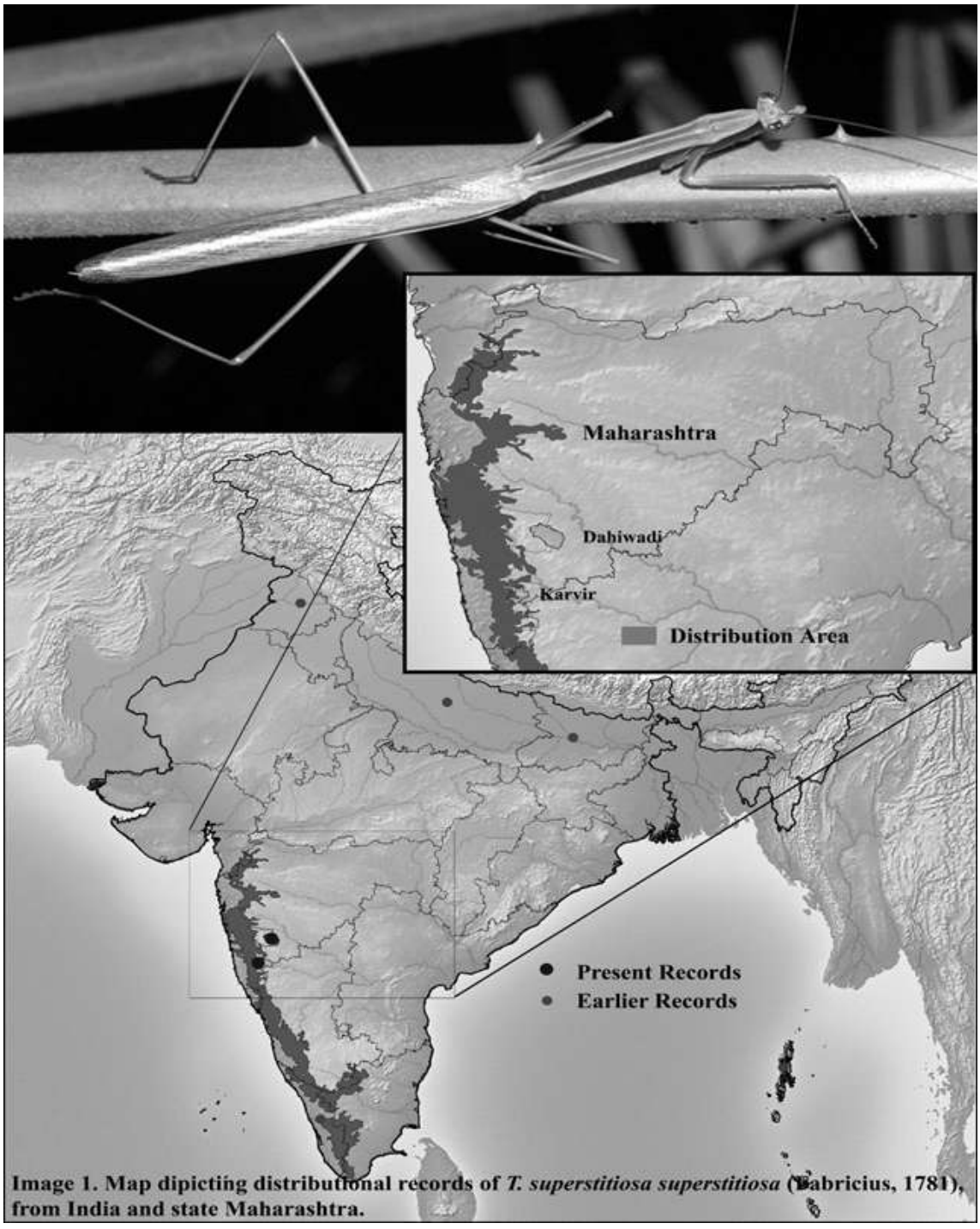

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NUTRITIONAL STATUS OF BASIDIOMYCETOUS FUNGI ASSOCIATED WITH CASUARINA FROM TAMILNADU

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ABSTRACT:
Present study dealt with study of nutritional status of Basidiomycetous fungi associated with Casuarina. During the investigation various carbon and nitrogen sources were used and the basidiomycetous fungi such as Podaxis pistillaris and Clavaria species were grown invitro. It was found that Podaxis pistillaris flourishes best with xylose and Raffinose sugars as carbon sources and sodium nitrate and sodium ammonium nitrate as nitrogen sources. Clavaria sp. grows best with the carbon sources like mannitol and maltose. Glutamine and sodium ammonium nitrate as nitrogen sources for the growth of Clavaria. The inorganic sources help in faster growth of fungus. The effect of growth is positive when the sources are used in combinations.

Key words: - *Podaxis pistillaris, Clavaria*

INTRODUCTION:

Casuarina, a member of the family Casuarinaceae, is a native of Australia. They are successfully introduced in the east coast of Indian Peninsula in 1960s and then cultivated in all parts of the country. Species of *Casuarina* is planted on a large scale in different parts of our country where there is longer dry season and less water contents. Casuarinas are salt tolerant and adaptable to poor soils with least requirements for their growth. In South India they are grown on coastal areas with sandy soils as well as in interiors with loam soils. The *Casuarina* plantations are abundant along the seashores of Tamilnadu. The plant is a multipurpose tree in Agro-forestry. The tree gives diffused shade, improves physical and chemical properties of soil, suppresses the weeds, helps in maintaining the fertility of soil, used as food, fuel and fodder and acts as good wind breaker.

Fungi utilize dead plant tissues and the soluble substrates including root exudates and develop themselves in rhizoplane and rhizosphere. Members of Ascomycetes and Basidiomycetes are reported to be present in rhizosphere. *Casuarina* plants from different localities were surveyed for Basidiomycetous fungi and their ectomycorrhizal association. During the study, *Podaxix pistilaris*, *Clavaria* sp., *Lycoperdon* sp., *Calvatia* sp. and some mushrooms were found associated with *Casuarina* plantations. These forms did not have any Ectomycorrhizal association with the plants.

Present investigation dealt with studies on Basidiomycetous fungi occurring in the rhizosphere of *Casuarina* from Tamilnadu and their nutritional requirements.

MATERIAL AND METHODS:

In the present study the material of basidiomycetous fungi *Podaxix pistilaris*, *Clavaria* species associated with *Casuarina* was collected from sites of Chennai, Mahabalipuram and Trichur (Tamilnadu

state). The species of *podaxis* and *Clavaria* were selected for nutritional studies. The work was undertaken in following steps:

1. Two fungi *Podaxis* and *Clavaria* were selected for study. The fungal spores were collected and grown in axenic cultures on Malt agar plates incubated at 27^0 C for 48 hours.
2. After the growth of hyphae, the hyphal mat was punched with the help of corn borer and used as a source of inoculum.
3. The inoculums was added to the agar plates with different nitrogen and carbon sources were inoculated at 27^{0}C for 48 hours till 144 hours in diffused light conditions and recorded in tables (Table – I & II).
4. The different nitrogen sources included Cysteine, Alanine, Glutamine, Sodium nitrate, Threonine, Ammonium oxalate, Sodium nitrate and Sodium ammonium nitrate which were added in the concentrations of 0.05% in the basal medium (Modified Pridham & Gottlieb medium ;1948).
5. Different carbon sources included were Sorbitol, Lactose, Xylose, Mannitol, Galactose, Maltose and Raffinose which were added in the concentrations of 3.5% in the basal medium.

OBSERVATIONS AND RESULTS:

Based on the nutritional requirements it is concluded that

1. *Podaxis pistillaris* flourishes best with xylose and Raffinose sugars as carbon sources and sodium nitrate and sodium ammonium nitrate as nitrogen sources.
2. *Clavaria* sp. grows best with the carbon sources like mannitol and maltose as well as Glutamine and sodium ammonium nitrate as nitrogen sources.
3. The inorganic sources help in faster growth of fungus.
4. The effect of growth is positive when the sources are used in combinations.
5. Structurally the fungi belonged to gastromycetes group and the nutritional analysis indicated the use of inorganic nitrogen sources and disaccharides as carbon sources either single or in combination has helped in better growth of fungi.
6. The *Casuarina* plant litter and residue provides the inorganic sources of carbon and nitrogen for the growth of the fungi around them.

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TABLE: I

A. Carbon nutrition studies - *Podaxis*

Diameter of colony in cms							
Hours	Sorbitol	Lactose	Xylose	Mannitol	Galactose	Maltose	Raffinose
48	1.0	1.8	2.7	1.0	2.0	2.8	2.4
72	1.9	3.0	3.5	3.0	2.1	3.2	3.4
96	1.9	3.0	4.5	4.0	2.8	3.9	4.0
120	2.0	3.9	5.8	5.5	3.0	3.9	5.0
144	2.3	4.1	6.5	5.5	3.8	4.1	5.9
Mean	1.8± 0.9	3.1±0.1	**4.6±0.9**	3.8±0.2	2.7±0.9	3.5±0.2	**4.1±0.1**
Type of growth	Scanty	Scanty	**Normal**	Moderate	Scanty	Scanty	**Normal**

B. Carbon nutrition studies - *Clavaria*

Diameter of colony in cms							
Hours	Sorbitol	Lactose	Xylose	Mannitol	Galactose	Maltose	Raffinose
48	2.0	3.4	2.5	2.5	2.0	4.4	1.9
72	2.7	4.4	4.2	4.6	3.6	5.7	3.5
96	3.0	5.6	5.3	7.5	5.2	7.5	3.5
120	3.4	6.3	5.7	8.4	7.0	8.8	3.7
144	4.0	6.8	6.0	9.3	7.2	10.0	4.0
Mean	3.0± 0.4	5.3±0.8	4.7±0.9	**6.4±0.1**	5.0±0.3	**7.2±0.1**	3.3±0.1
Type of growth	Scanty	Scanty	Scanty	**Normal**	Scanty	**Normal**	Scanty

TABLE: II

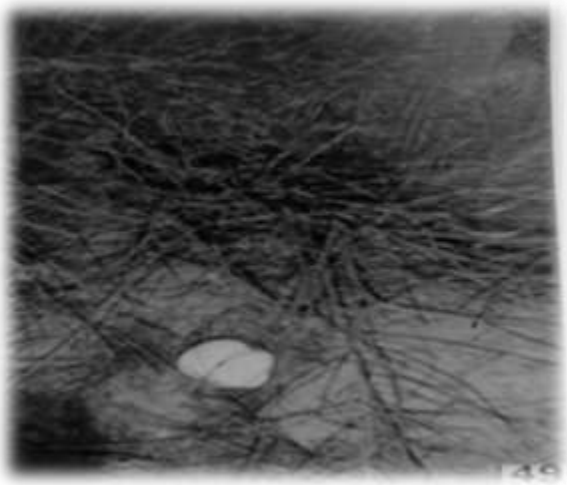
A. Nitrogen nutrition studies - *Podaxis*

Diameter of colony in cms							
Hours	Cystiene	Alanine	Glutamine	Threonine	Amm. oxalate	Na nitrate	$NaNH_4$ nitrate
48	1.2	1.5	1.5	1.4	1.5	1.5	1.5
72	1.7	2.1	2.1	2.0	2.0	2.4	2.4
96	2.5	2.7	2.7	2.6	2.4	3.0	3.0
120	3.1	3.4	3.0	3.0	3.1	3.6	3.6
144	3.3	3.6	3.1	3.0	3.3	4.1	4.1
Mean	2.3± 0.9	2.6±0.1	2.4±0.1	2.4±0.1	2.4±0.1	**2.9±0.2**	**2.9±0.2**
Type of growth	Scanty	Scanty	Scanty	Scanty	Scanty	**Normal**	**Normal**

B. Nitrogen nutrition studies - *Clavaria*

Diameter of colony in cms							
Hours	Cystiene	Alanine	Glutamine	Threonine	Amm. Oxalate	Na nitrate	$NaNH_4$ nitrate
48	0.7	3.2	4.2	4.9	4.5	1.9	3.5
72	0.7	5.4	6.0	6.4	6.0	4.4	5.8
96	0.7	6.4	7.4	7.0	7.0	6.0	7.2
120	0.7	7.5	8.5	8.0	7.5	6.7	9.0
144	0.8	8.5	9.0	8.5	8.0	7.9	9.5
Mean	$0.7\pm^{0.2}$	$6.2\pm^{0.1}$	**$7.0\pm^{0.2}$**	$6.9\pm^{0.8}$	$6.8\pm^{0.2}$	$5.3\pm^{0.2}$	**$7.0\pm^{0.2}$**
Type of growth	Scanty	Moderate	**Normal**	Moderate	Moderate	Scanty	**Normal**

Podaxis pistillaris



Clavaria sp.

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Online Teaching and Learning: Threat or Opporurtity

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Abstract

We are seeing education institutions adapting these developments into their systems And relying on group resources and mechanisms to improve the student life. The use of social media in education provides students with the ability to get more useful information, to connect with learning groups and other educational systems that make education convenient.

Key Words:Online Teaching Threat, opportunity.

Introduction:

Social network tools afford students and institutions with multiple opportunities to improve learning methods. Through these networks, you can incorporate social media plugins that enable sharing and interaction. Students can benefit from online tutorials and resources that are shared through social networks and LMS's.There is valuable knowledge to be gained through social media such as analytics and insights on various topics or issues for study purposes.

Connecting with experts on topics via social media

The great thing about using social media is that you soon learn who the experts are in particular fields and subjects. When you start following these experts you learn more and gain useful content from them, this empowers you to produce great results.Social media has the ability to broaden your perspective on various subjects and gives illuminating, instant content that is new. You have the opportunity of engaging experts to get answers on topics that you may need help in.Institutions communicate with students via YouTube and Facebook

Learning colleges have the ability to connect with students through social media networks such as Facebook, Google Plus groups, and YouTube. These channels can be used to communicate campus news, make announcements and provide students with useful information. This builds engagement between the College and students which help tackle many student issues through the group interactions.

It helps in Research process

Social media offers audience and subject monitoring tools that are useful and it is one of the best platforms to extract data. You can find out how the majority people feel about a particular topic or how experts perceive and advice on specific issues.

Positive effects of Social Media:

Encourage Online Learning: With the advance use of Social Media platforms in boarding school Dehradun, the students get encouraged and motivated to learn. Educational videos on YouTube, The use of YouTube to watch educational videos, easy access to e-books, online notes, learning via video calling are some of the major aspects which contribute to educational development.

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लोककला विशेषांक

साहित्य, कला आणि लोकसंस्कृतीला वाहिलेले त्रैमासिक

तिफण

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अनुक्रमणिका

अ.क्र.	शीर्षक / लेखक	पृ.क्र.
*	लोककला विशेषांकाच्या निमित्ताने... - डॉ. शिवाजी हुसे	
*	संपादकीय - प्रा. डॉ. चंद्रशेखर कणसे (अतिथी संपादक)	
१.	'कीर्तन' समाजप्रबोधनाचे प्रभावी माध्यम: एक अभ्यास - डॉ. चंद्रशेखर कणसे (परळी वैजनाथ, बीड)	९
२.	महाराष्ट्रातील लोककला : कीर्तन - प्रा. डॉ. सोमनाथ महादेव दडस (दापोडी, पुणे)	१८
३.	वारकरी दिंडी लोककला : एक आनंदयात्रा - धन्यकुमार प्रल्हाद तारळकर (ता. फलटण जि. सातारा)	२४
४.	'सोंगी भारूडी भजन' - डॉ. आनंद बल्लाळ (आजरा, कोल्हापूर)	३२
५.	प्रयोगात्मक लोककलाप्रकार - 'भारूड' - डॉ. नाना झगडे (पुरंदर)	३९
६.	विदर्भातील झाडीपट्टी येथील लोककला 'दंडार' - प्रा. अमृता डोरलीकर (नागपूर)	४७
७.	महाराष्ट्रातील लोककला 'बोहडा' - डॉ. भास्कर शेळके (अकोले)	५२
८.	गोमंतकीय लोककला : विशेष संदर्भ 'धालोत्सव' - डॉ. नीता तोरणे (पेडणे, गोवा)	५५
९.	'गोंधळ : स्वरूप आणि आविष्कार' - डॉ. पांडुरंग भोसले (हडपसर, पुणे)	६७
१०.	महाराष्ट्रातील लोककला : 'गोंधळ' - डॉ. पद्माकर तामगाडगे (मुंबई) व प्रा. राजू शनवार (ठाणे)	७१
११.	महाराष्ट्राचे विधिनाट्य 'गोंधळ' आणि 'जांभूळ आख्यान' - प्रा. शिल्पा नेवे (मुंबई)	७५
१२.	'गोंधळ' कला प्रकाराचे बदलते स्वरूप - डॉ. जयदेवी पवार (बाभळगाव, ता. जि. लातूर)	८९
१३.	गोंधळ : महाराष्ट्राची लोककला - डॉ. वैशाली श्रीकृष्ण भालसिंग (अहमदनगर)	९५

१४. 'जागरण' - डॉ. राखी सलगर (औरंगाबाद) १०२
१५. गोवा येथील लोककला 'जागर' - प्रा. विनय मडगांवकर (गोवा) १०६
१६. महाराष्ट्रातील लोककला : 'दशावतार व नमन' - प्रा. प्रियंका कुंभार (तासगाव, जि. सांगली) ११४
१७. महाराष्ट्रातील लोकनाट्याचा आविष्कार - 'लळीत' - प्रा. पुरुषोत्तम महाजन (भुसावळ) १२१
१८. 'लळीत' - डॉ. प्रतिभा सोनी (शिक्रापूर, शिरूर) १२८
१९. सर्वांना एकत्र बांधून ठेवणारा सांस्कृतिक ठेवा - 'भोंडला' - प्रा. तारळेकर (सांगली) १३३
२०. 'लोककला तमाशा'- एक अभ्यास - प्रा. डॉ. रामहारी मायकर (वडवणी जि. बीड) १३८
२१. 'लोकरंगभूमीवरील डाका विधीनाट्य' - डॉ. सुनिल टाक (औरंगाबाद) १४३
२२. 'लोकसाहित्यातील लोककला प्रकार' - डॉ. भाऊसाहेब गव्हाणे (केडगाव, ता. दौंड, जि. पुणे) १४८
२३. लोककला : स्वरूप व वाटचाल - प्रा. डॉ. विजय विष्णूपंत केसकर (कळंब, जि. उस्मानाबाद) १५५
२४. 'महाराष्ट्रातील लोककला : एक चिंतन' - कु. वर्षा तांदळे (कोल्हापूर) व प्रा. बाळासाहेब चव्हाण (कोरेगाव) १६०
२५. आदिवाशी यांच्या लोककला - प्रा. चिंतामण धिंदळे (नगर) १६५
२६. महाराष्ट्रामधील आदिवाशी लोककलांचे विवेचन - डॉ. सुनिल घनकुटे (अकोले जि. नगर) १७१
२७. महाराष्ट्र लोकसंस्कृती उपासकांचे कलाविष्कार : वासुदेव आणि पोतराज - डॉ. किरण नामदेव पिंगळे (नाशिक) १७८
२८. लोकसंस्कृतीचे लोककलेतून सहज सुंदर आविष्कार घडविणारा 'वासुदेव' - डॉ. नानासाहेब पवार (हडपसर, पुणे) १८४
२९. पोतराजाची आराधना : एक लोककला - डॉ. नितीन मोटे (वडगाव, पुणे) १९४
३०. महाराष्ट्राच्या लोककलेचा सहजसुंदर आविष्कार - लावणी - डॉ. धबडगे (औरंगाबाद) २००

महाराष्ट्रातील आदिवासींच्या लोककला

- प्रा. चिंतामण धिंदळे
(मराठी विभागप्रमुख)
राधाबाई काळे महिला महाविद्यालय, अहमदनगर

प्रस्तावना :-

भारतीय आदिवासी हा स्वातंत्र्योतर काळात अनेकांच्या आकर्षणाचा विषय झाला होता. उदा. भारतात येणारे हौसी पर्यटक आदिवासी क्षेत्राला आवर्जून भेट देत. आदिवासी लोककलांच्या महोत्सवी कार्यक्रमात हौशी पर्यटकांची उपस्थिती लक्षणीय प्रमाणात वाढत असल्याचे दिसून येते. महाराष्ट्रात जवळजवळ ४७ आदिवासी जमाती आहेत. प्रत्येक आदिवासी जमातीचा अभ्यास करता, त्यांची संस्कृती, वेगळी असल्याचे जाणवते. त्यांची बोलीभाषा, सण-उत्सव, लग्न समारंभ पद्धतीमध्ये साम्यआढळत असले तरी, ते वेगळे आहेत. आदिवासींच्या जीवनातील समान गुणधर्म जर काय असेल तर तो प्रत्येक आदिवासी जमाती या निसर्गपूजक आहेत. निसर्गालाच त्या देव मानतात. निसर्गाच्या सानिध्यात ते आपले जीवन जगत असतात. आयुष्यभर काबाडकष्टाचे जीवन वाट्याला आलेला आदिवासी माणूस लोककलांच्या माध्यमातून आपल्या जीवनात विरंगुळा शोधत असतो. जवळपास प्रत्येक जमातीची एक स्वतंत्र लोककलाआज अस्तित्वात आहे. कलेच्या माध्यमातून ते आपल्या समाजाची संस्कृती दुसऱ्या समाजासमोर मांडण्याचा प्रयत्न करतांना दिसतात. नृत्य, गाणे, वाद्य, अशा प्रमुख कलांबरोबरच तमाशा, वगनाट्य, भारूड, दशावतार, बोहाडा, जत्रा अशा माध्यमातून ते आपल्या उपजत कलागुणांना वाव देताना दिसतात. काळाच्या ओघात बहुतांशी जमातींच्या कला कालबाह्य होण्याच्या मार्गावर आहेत. शासन दरबारी ह्या कला संवर्धनकरण्याचेजोरदार प्रयत्न चालू आहेत. मात्र औपचारिकपणामुळे त्यात यश येताना दिसत नाही. साक्षरता वाढली पण आपली उपजत कला मात्र हा समाज विसरत चालला आहे. तरूण पिढीला ह्या कलांविषयी फारशी आस्ता नाही. एकूणच काय तर या कला जतन करायला हव्यात. या कलांचे संवर्धन व्हायला हवे. सरकारी दरबारी असणारी उदासीनता दूर व्हायला हवी. आदिम संस्कृती नष्ट होऊ पाहात आहे. लोककलांच्या माध्यमातून आदिवासी संस्कृती टिकविणे आज काळाची गरज आहे. आदिवासींच्या लोककला म्हणजे पांढरपेशीय समाजाच्या मनोरंजनाचा उपक्रम नव्हे तर त्यांच्या कला त्यांच्या जगण्याचा मूलाधार व्हावा ही संकल्पना त्यांच्या ठायी रुजवणे काळाची गरज आहे.

आदिवासी संकल्पना :-

आदिवासीबाबत विविध अभ्यासकानी, संशोधकांनी विविध व्याख्या मांडल्याचे दिसते. त्या व्याख्यांच्या अनुषंगाने आपल्याला आदिवासी म्हणजे काय, व त्याविषयीची संकल्पना स्पष्ट करता येईल. डॉ. घुर्ये यांनी आदिवासींना 'मागासलेले हिंदू' असे संबोधले आहे. काही अभ्यासक आदिवासी हे मुळचे रहिवासी आहेत असे मानतात. आंतरराष्ट्रीय श्रम संघटनेने कोणत्याही देशातील मूळ रहिवाश्यांना संबोधण्यासाठी आदिवासी ही संज्ञा वापरावी असे म्हटले आहे. अजून काही अभ्यासकांनी विविध व्यापाराच्या द्वारे आदिवासी संकल्पना स्पष्ट केल्या आहेत.

१. **बोआम :-** यांच्या मते जगात म्हणजे आर्थिकदृष्ट्या असा स्वातंत्र लोकसमूह की जो एक भाषा बोलतो व बाह्य आक्रमणापासून स्वताःचे संरक्षण करण्यासाठी संघटीत झालेला असतो.

२. **गिलीन व गिलीन :-** यांचे मते एका विशिष्ट भूप्रदेशावर राहणारा, समान बोली भाषा बोलणारा व समान सांस्कृतिक जीवन जगणारा पण अक्षर ओळख नसलेल्या स्थानीय समूहाला आदिवासी समाज असे म्हणतात.

३. **डॉ. मुजुमदार :-** यांच्या मते आदिवासी समुदाय म्हणजे नातेदारीने संबधित असणाऱ्या अनेक कुटूबांचा असा समुच्च्य होय की ज्याचे एक सामान्य नाव व समान भाषा असते. हा समुदाय एका विशिष्ट भूप्रदेशावर वसलेला असतो. तसेच या समुदायाला सभासद विवाह व व्यवसायाबद्दल समान नियमांचे पालन करतात.

४. १९६२ साली शिलाँगमध्ये आदिवासी समितीच्या परिषदेने आदिवासी समुदायाची व्याख्या पुढीलप्रमाणे केली आहे. 'आदिवासी समुदाय हा एकाच पूर्वजापासून उत्पत्ती सांगणारा असा एक सजातीय गट आहे की, ज्यातील सभासद एक भाषा किंवा बोली बोलतात. त्यांचे एका विशिष्ट भूप्रदेशात वास्तव्य असते. हे लोक विज्ञान व तंत्रज्ञानाच्या दृष्टीने मागासलेले असतात. अक्षर ओळख नसलेल्या व रक्तसंबधावरआधारित सामाजिक व राजकीय रीतिरिवाजांचे प्रामाणिक पालन करणाऱ्या एकजिनसी गटाला आदिवासी समुदाय असे म्हणतात.'

आदिवासी जमात, आदिवासी समाज, आदिवासी समुदाय अशा संज्ञांच्याव्याख्या विचारवंतानी केल्या आहेत. या सर्व व्याख्यामधून आदिवासी जमात या शब्दाचा अर्थ स्पष्ट करण्याचा प्रयत्न केला आहे. एकूणच आदिवासी समाज ह्या भूमीवरचा प्रथम समाज आहे, असा निकष लावता येऊ शकेल. कोणत्याही देशाचा मूळ रहिवाशी आदिवासी समाज असा अर्थ लावता येऊ शकेल.

महाराष्ट्रातील आदिवासी जमाती:-

महाराष्ट्रात आजमितीस जवळ-जवळ ४५ आदिवासी जमाती आहेत. सह्याद्री, सातपुडा, ब्रह्मगिरी, भीमाशंकर, महादेवाच्या टेकड्या या डोंगररांगाच्या पायथ्याशी आदिवासी जमातींची वस्ती आढळून येते. औधोगिकरणाचापरिणाम त्यांच्या जीवनरहाटीवर पडलेला दिसून येतो. डोंगरदऱ्यातून वस्ती करून राहणाऱ्या या जमाती आता सपाट प्रदेशात, शहराच्या जवळ यायला लागल्या आहेत. शिक्षणाचा झालेला प्रसार आणि प्रचार यामुळे आदिवासी समाज शिकून नोकरी व्यवसायानिमित्त, रोजगाराच्या शोधात शहरात राह्यला येऊ लागला आहे. आदिवासी जमतींची नावे भिन्न अशी आहेत. उदा. गोंड, भिल्ल, कोलम, कोरकू, माडिया, अंध, इत्यादी. आदिवासींच्या वसतीस्थानाचा विचार करता उदा. कोळी महादेव, ठाकर ह्या जमाती पुणे, अहमदनगर, ठाणे, रायगड, नाशिक या जिल्यात आढळतात. कोरकू, वापेची, भावासी, वापी व निहाल ह्या जमाती अमरावती जिल्यातील मेळघाट भागातच आढळून येतात. थोडक्यात आदिवासी जमातींची विशिष्ट भाषा, प्रदेश, चालीरीती-रिवाज, संस्कृती असे वेगळेपण आपणास जाणवते. आदिवासी जमातींचा मुख्य व्यवसाय शेती करणे व त्याबरोबरच पशुपालन हा पूरक व्यवसाय करणाऱ्या काही आदिवासी जमाती आहेत. तर अजूनही बहुतांशी जमाती या जंगल व त्यातून मिळणारे वनउपज, मजुरी, यावर अवलंबून आहेत. पूर्वी शेती व्यवसायाकडे वळण्याअगोदर जंगलात जाऊन शिकार करणे, जंगलातील सरपण, फळे, हिरडा, बेहडा, गोळा करून आपला उदरनिर्वाह करीत असत. शिक्षणाने समाज बदला व सुधारित तशीच पारंपारिक शेती करणे, गुरे पाळणे, शहरात जाऊन रोजगार मिळविणे, नोकरी, व्यवसाय करणे, हा बदल झाल्याचे दिसते.

आर्थिकदृष्ट्या मागास असलेला हा समाज मात्र सांस्कृतिकदृष्ट्या संपन्न आहे. निसर्गाला देव मानणारा, निसर्गाच्या नियमांप्रमाणे जीवन जगणारा हा समाज आपल्या कला-गुणांसाठी प्रसिद्ध आहे. जवळ-जवळ सर्वच आदिवासी जमातीमध्ये काहीना काही कला ह्या उपजतच असतात. त्यांच्या विवाहप्रसंगी, शेतीच्या कामाच्या वेळी, कामे संपल्यावर रिकाम्यावेळी मनाला विरंगुळा मिळावा, श्रम कमी व्हावेतम्हणून नाच-गाण्यांचा कार्यक्रम हमखास होत असतो. लग्नविधी, जत्रा विशेषतः सामुदायिक कार्यक्रमात स्त्रियांची नृत्ये होतात, प्रत्येक आदिवासी जमातीत अशाप्रकारची नृत्ये होत असतात. मात्र स्त्रियांच्या नृत्याला विशेष महत्त्व असते. आदिवासींचा भूप्रदेश हा शहरापासून दूर असल्याने नागर संस्कृतीचे विशेष अजूनही त्यांच्यापर्यंत पोहचले नाहीत, थोड्याफार प्रमाणात शहरातील संस्कृती आज आदिवासी समाजाची झाल्याचे दिसते. परंतु सगळ्या आदिवासी जमाती आपल्या पारंपारिक लोककला जतन करून आहेत. देशातील इतर राज्यांचा विचार करता

ज्या ठिकाणी आदिवासी समूह आहे, त्यांची आजची स्थिती पाहता महाराष्ट्र, पूर्वांचल, दक्षिण भारत या राज्यातील आदिवासी जमाती मुख्य प्रवाहामध्ये आल्या आहेत. मात्र मध्यप्रदेश, छत्तीसगड, गुजरात, हिमाचलप्रदेश, ओरिसा, प. बंगाल, तेलंगाना, बिहार, झारखंड या राज्यातील आदिवासींची स्थिती वाईट आहे. राज्यस्थान मधील मीना नावाच्या जमातीचा जितका विकास झालेला दिसतो तितका विकास इतर जमातींचा झालेला नाही.

आदिवासींच्या लोककला:-

आदिवासी समाज म्हटला की कला ही आलीच. कारण आदिवासींचे जगणे कलेशिवाय अधुरे आहे. लोकलेमधून आदिवासींची जीवनरहाटी, संस्कृती व एकूणच जगण्याचा आशय त्यातून व्यक्त होत असतो. उदा. नृत्य, वाद्य, गायन, चित्रकला, विनकाम इ. कला आढळून येतात. त्यातही'नृत्य' ही लोककला सर्वच आदिवासी जमतीमध्ये आढळून येते. उदा. ठाकर जमातीचा कांबडनाच, ठाकर स्त्रियांची 'फुगडी'ह्या कला इतर जमातीत दिसून येत नाहीत. फुगडी हा नाच सर्वच जमातीत असला तरी ठाकर स्त्रिया फुगडी बसून घालतात, बाकी जमातीच्या स्त्रिया फुगडी उभ्याने खेळतात. कोळी महादेव जमातीत 'घेवडा' व 'वरमाई' हे दोन नाच प्रमुंख आहेत. वाध्यांचा विचार करता पावा, बासरी, ढोल, ढोलकी, झांज, इत्यादी वाद्यंचा समावेश होतो. सर्वच आदिवासी जमातींना गायनाची कला अवगत असते. किंबहुना ती कला त्यांना निसर्गतःच मिळालेली देणगी आहे. चित्रकलेचा विचार करता वारली चित्रकला जगप्रसिद्ध म्हणून मान्यता पावली आहे. विणकाम ही कला सर्वच आदिवासी जमातींना अवगत असते. जंगलात मिळणाऱ्या बांबूपासून गृह उपयोगी वस्तू ते बनवित असतात. उदा. टोपल्या, कुरकुले, हारा, किरकिंडा, कणगा, कणगी, काठवळा, मळई, बोक्सी, सुपाट, इरले, चटया जवळजवळ सर्व उपयोगी वस्तू ते घरच्या घरी बनवितात. मासेमारीसाठी बऱ्याच वस्तू बनवितात. ससे मारण्यासाठी वाघुर बनवितात. एकूणच आदिवासी जमातीमध्ये कलेचा वारसा दिसून येतो. आदिवासींच्या कला ह्या केवळ कला नसून त्या उपयोजित कला म्हणून त्यांचा विचार व्हायला हवा.

१. आदिवासी नृत्य :- महाराष्ट्रामध्ये एकूण ४७ आदिवासी जमाती आहेत. प्रत्येक आदिवासी जमातीचा एक वेगळा नृत्य प्रकार आहे. नाच संस्कृती आदिवासींची आहे. त्यांच्या नाच संस्कृतीनेच त्यांचे जीवन समृद्ध केले आहे. आनंदाच्या प्रसंगी हा समाज एकत्र येतो आणि बेधुंद रात्रभर नाचतो. नाचताना सर्व दुःख विसरून नाचतो. निसर्गाच्या साथीने, निसर्गाच्या संगतीने तो नृत्य करीत असतो. सह्याद्रीच्या पायथ्याशी व कोकणात 'ठाकर'नावाची जमात वास्तव्य करून राहते. ठाकर आदिवासींमध्ये'कांबड'नाच विशेष प्रसिद्ध आहे. दहा ते पंधरा पुरुष मंडळी एकत्र येतात, मोठे (कोंडोळे) रिंगण केले जाते,

मध्येढोल वाजवणारा एक ढोल्या असतो. त्याच्या समोर ढोलाला पकडून राहणारा एक व गाणे म्हणणारा असा हा कांबड नाच सुरु होतो. शेतीची कामे आटोपल्यावर रात्री चांदण्यात ही मंडळी एकत्र जमते व कांबड नाच सुरु होतो. वेशभूषा अशी विशेष नसते मुळातच अंगभर कपडे नसणारा हा समाज डोक्याला मुंडास, अंगात कोपरी, किंवा बंडी पायात मात्र चाळ (घुंगरू), हाताला (मनगटाला) फुलांचा गजरा बांधून आपला नाच सुरु करतात. त्यांच्या गीतात उत्साह असतो. नाचणे हा त्यांचा छंद आहे. बेफाम होऊन नाचणे, त्यांचा हा नाच रांगडा आहे, वेगात नाचले जाते. म्होरक्या मध्येच शिळ घालून इशारे करतो, कुठे मुरडायचे, वळायचे कुठे, कुठे आवाज काढून नाचायचे हे ठरलेले असते. मर्दानी अशा नाचातून ठाकरांचा चपळपणा, काटकपना जाणवतो. ज्या पद्धतीने पुरुष मंडळी कांबडा नाच सादर करतात, त्याचप्रमाणे स्त्रिया सुद्धा फुगडी नाच सादर करतात. १० ते १५ स्त्रिया रिंगण करून गोलाकार उभ्या राहतात. कधी पायाच्या चवड्यावर बसून गाणी म्हणत फुगडी नाच करतात. या नृत्यात तरून मुली, वृद्ध स्त्रिया, मध्यम वयाच्या स्त्रिया नाचत सहभागी होतात. या नाचासाठी कोणत्याही वाद्याची गरज नसते. टाळ्यांच्या तालावर गाणी म्हणत फुगडी नाच सादर केला जातो.

२. आदिवासी कोळी महादेव जमातीचा घेवडानृत्य :- कोळी महादेव ही जमातमहाराष्ट्रातील सहा जिल्यात वास्तव्य करून राहत आहे. पुणे, अहमदनगर, नाशिक, ठाणे, रायगड, पालघरसह्याद्रीच्या कुशीत व कोकणच्या पायथ्याशी राहणारी ही जमात शेती, पशुपालन, मजुरी करून आपला उदरनिर्वाह करतांना दिसते आहे. जागतिकीकरणात बहुतांशी शिकलेला तरुण शहरात नोकरी, रोजगारानिमित्त गेला आहे. कोळी महादेव या जमातीची एक वेगळी अशी बोली प्रचलित आहे. त्या बोलीस 'डांगाणी' व 'मावळी' बोली असे संबोधले जाते. पुणे जिल्यात 'मावळी' बोली म्हणून प्रसिद्ध आहे. तर अहमदनगर, नाशिक जिल्ह्यात 'डांगानि' बोली म्हणून प्रसिद्ध आहे. या जमातीचे दोन नृत्य प्रसिद्ध आहेत. ती दोन्ही नृत्य लग्ना प्रसंगी नाचली जातात. एक आहे 'वरमाई'नृत्य व दुसरे आहे 'घेवडा' नृत्य. हळदीच्या दिवशी आदिवासी स्त्रिया वरमाई नृत्य नाचतात. वाजंत्री वाजवितात, व या स्त्रिया हातात आहेर घेऊन नाचविण्याच्या नृत्यला वरमाई नृत्य म्हणतात. वरातीच्या रात्री नवऱ्या मुलीला व नवऱ्या मुलाला कडेवर घेऊन दोन पुरुष वाजंत्र वाजवतील त्या तालावर वधु-वराला नाचविले जाते. त्या नृत्याला 'घेवडा' नृत्य म्हणतात. नवरा. नवरीच्या हातात, कपड्याचे चाबूक तयार करून दिले जातात. त्या चाबकाने एकमेकाला मारण्याचा कार्यक्रम होत असतो. अतिशय गमतीशीर हे नृत्य असते. प्रत्येक आदिवासी जमातीचे असे स्वतंत्र बोली व नृत्य असते.

आदिवासी जमाती त्यांच्या कलांनी ओळखल्या जातात. आदिवासी संस्कृती ही

अतिशय समृद्ध आहे. त्यांच्या लोककलांमधून त्यांचे जीवन, संस्कृतीचे दर्शन होत असते. या लेखामध्ये आदिवासी ठाकर व कोळी महादेव या जमातींच्या लोककलांचा परिचय करून देण्याचा प्रयत्न केला आहे.

मूलभूत संदर्भ :-

अकोले तालुक्यातील 'चाळीसगाव डांगण' आंबेगाव तालुक्यातील 'घोडनयार' जुन्नर तालुक्यातील 'कुकडेनयार' इगतपुरी तालुक्यातील 'महालदेश' मूळनयार, पेहरा, या प्रदेशातील आदिवासी जमातीच्या लोककलांचा अभ्यास करून वरील नोंदी केल्या आहेत.

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आदिवासी साहित्य, संस्कृती आणि अस्मितेचे प्रतीक

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संपादक- डॉ. मारुती आढळ । देवराम आढळ

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* कोरोना काळी भुकेचे बळी-तुकाराम चौधरी ३
* कोरोनाविषयी आदिवासींची धारणा -श्री.संजय घोरपडे ९
* सिंदीचा काला-प्रा.चिंतामण धिंदळे ११
* प्रतिकारशक्ती वाढवा,आरोग्य जपा -वाहरु सोनवणे १५
* कोरोना प्रादुर्भावामुळे जव्हार तालुक्यातील आदिवासींच्या जीवनावर झालेला परिणाम -प्रा. राजू शंकर शनवार २१
* वाडीतला कोरोना- कैलास धिंदळे २३
* समाजाचा दुष्मन- मारूती कोंडू आढळ २५

कविता * कोरोना म्हणत्यात मला-प्रशांत गायकवाड ८/काळजी घ्या-श्वेता आवारी १४/कोरोना आला विमानात बसून-वाहरु सोनवणे २०/संवसांर मूडी पडणा-प्रमोद (पोम्या) कोंडेसावल बागूल ३१/मजबूर मी मजदूर-संजय इधे ३२/हिदगी ज आगोंही (डांगी भाषेत)-भावेश बागूल ३२/भरलंय कोरोनाचं वारं-देवदत्त चौधरी ३३/चल ना वं आये, घरला आता -संजय दोबाडे ३३/गर्दी करणं टाळ-पंकजकुमार गवळी ३४/कोरोनाचे वारे-वैजनाथ अनमुलवाड ३४/चला हरवुया या कोरोनाला- देवदत्त चौधरी ३५/ड्रॅगन मामा-वैजनाथ अनमुलवाड ३५/आला आला कोरोना-किरण निरवार ३६/नाव माझे मयत नोंदल्यावर-किशोर डोके ३६/पायपीट-विठ्ठल निरवारे ३७/पसरू देवू नका कोरोना-रोशनी आवारी ३७/विषाणू- कोरोना-सोनाली डगळे ३७/लॉकडाऊन काळातील आदिवासी हायकू -मधुचंद्र भुसारे ३८

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'कोरोना' म्हणजे 'कोविड-१९' या नव्या रोगाची लागण प्रथम चीनमधील 'वुहान' या शहरात झाल्याचे निदर्शनास आले. 'कोरोना' हा संसर्गजन्य आजार चीनमध्ये फोफावला. वुहान शहरात जवळजवळ ९०% लोकांना 'कोरोनाची' बाधा झाल्याचे जगासमोर आले. आजमीतीस कोरोनामुळे चीनमध्ये ४५०० च्या वर लोकांचा बळी गेल्याचा आकडा समोर आला आहे. डिसेंबर २०१९ ते मार्च २०२०पर्यंत हा आजार हळूहळू कमी झाल्याचे चीनने नमूद केले आहे. असे असले तरी मे २०२० ला पुन्हा काही रुग्ण आढळल्याचा दावा चीनने केला आहे. चीनमधून तो आजार थेट युरोप, अमेरिका, इराक, इराण व संपूर्ण जगभर आज कोरोनाचे ३५ लाख रुग्ण आहेत. संपूर्ण जगभर २ लाखाच्यावर मृतांचा आकडा पोहोचला आहे. इटली, स्पेन, अमेरिका सारख्या देशाने तर अक्षरशः हात टेकले आहेत. सध्य:स्थित एकट्या अमेरिकेत ९० हजार व्यक्तींचे बळी गेले आहेत. साधारणतः फेब्रुवारीच्या शेवटच्या आठवड्यात 'कोरोना' भारतात दाखल झाला. पहिला रुग्ण केरळमध्ये सापडल्याची नोंद आहे. आजच्या तारखेला भारतात कोरोनाग्रस्तांची संख्या ९८ हजारावर गेली आहे. मृतांचा आकडा कमी असला तरी, बाधितांची संख्या दर २४ तासाला ५००० ते ५२०० अशा पटीने वाढते आहे. बऱ्या होणाऱ्या रुग्णांचा दर ३८.१२% च्या आसपास आहे.

'कोरोना' या आजाराची लक्षणे उशिरा दिसत असल्याने संसर्ग झालेल्या व्यक्तीला किमान १४ दिवसानी रोगाची लक्षणे जाणवू लागतात. झपाट्याने वाढणारा हा संसर्ग भारतातील सर्वच राज्यात दाखल झाला आहे. त्यातही महाराष्ट्रात बाधितांची संख्या ३६ हजारांवर जाऊन पोहोचली आहे. देशातील सर्वात गर्दीची शहरे मुंबई, ठाणे, पुणे, नागपूर, नाशिक (मालेगाव) ही महाराष्ट्रात आहेत. एकट्या मुंबईत कोरोना बाधितांची संख्या २६ हजारांवर पोहोचली आहे. सरकारने यावर प्रतीबंधात्मक उपाययोजना म्हणून संपूर्ण देशात 'टाळेबंदी' घोषित केली आहे. पहिली टाळेबंदी १७ मार्च २०२० ते २४ मार्च २०२० अशी जाहीर केली होती. ती पुढे वाढवून ३१ मार्च २०२० पर्यंत करण्यात आली. रुग्णाची संख्या वाढत असल्याने टाळेबंदी १४ एप्रिल २०२० पर्यंत वाढविली, पुढे ३ मे २०२०, त्याही पुढे १८ मे आणि आता ३१ मे २०२० पर्यंत टाळेबंदी वाढविण्यात आली आहे. रुग्णांचा वाढता दर हा शहरात ज्यास्त आहे,त्या मानाने खेडी अजून सुरक्षित आहेत. परंतु सध्य:स्थिती पाहता सरकारने शहरात अडकलेले परराज्यातील, परजिल्ह्यातील मजुरांना आप-आपल्या गावी जाण्यास परवानगी दिली आहे. केवळ मुंबई, ठाणे, पुणे या महानगरातील कोरोना संसर्ग रोखता यावा म्हणून ही उपाययोजना करण्यात येत आहे. जर हाच निर्णय दीड महिन्यापूर्वी घेतला गेला असता तर कोरोनाचा संसर्ग टाळता आला असता. परदेशातून आलेले नागरिक घरीच न राहता ते इतर गर्दीच्या ठिकाणी जात होते, त्यामुळेही संसर्ग वाढला. दुसरी अत्यंत महत्त्वाची घटना म्हणजे दिल्ली येथील 'मरकज' या धार्मिक कार्यक्रमासाठी गेलेले 'तबलिगि' जमातीच्या २२०० लोकांना कोरोनाची बाधा झाली. हे सर्व लोक आपापल्या राज्यात गेल्याने त्याठिकाणी कोरोनाचा संसर्ग झपाट्याने वाढल्याचे समोर आले आहे. पहिल्या स्टेपमधील कोरोना संपून आता तो गर्दीच्या ठिकाणी जाऊन पोहोचला आहे. आतापर्यंत देशात २ हजाराच्या आसपास मृतांचा आकडा समोर आला आहे.मृत व्यक्तींमध्ये वृद्धांची संख्या अधिक आहे. त्याखालोखाल दुर्धर आजार असणारे रुग्ण आहेत, म्हणजेच ज्या व्यक्तींची रोगप्रतिकार शक्ती कमी आहे अशा लोकांचा समावेश जास्त आहे. युरोप अमेरिकेत मृतांचा व बाधितांचा आकडा वाढण्याचे प्रमुख कारण म्हणजे

तेथील लोकांची जीवनशैली हा महत्त्वाचा घटक आहे. युरोप अमेरिकेतील लोक 'वातानुकुलीत' जागेत काम करतात व 'वातानुकुलीत' घरात राहतात. तसेच जेवणात पिझ्झा, बर्गर, न्यूडल अशा पदार्थांचा समावेश असतो. या आहारामुळे व्यक्तीमध्ये रोगप्रतिकार शक्ती कमी होते. सदरच्या लेखात आपण आदिवासी लोकांच्या रोगप्रतिकार शक्ती व जीवनशैली याविषयावर भाष्य करणार आहोत. 'कोरोना' सारख्या जागतिक महामारीत या आजाराला आपल्यापासून आदिवासी लोक कसे दूर ठेवू शकतात ? अपवाद, बाधित व्यक्ती व त्यांच्या संपर्कात आल्यास हा संसर्ग होऊ शकतो. परंतु त्यांच्याकडे असणारी नैसर्गिक रोगप्रतिकार शक्तीमुळे या संसार्गावर मात करू शकतील.

आदिवासी लोकांची रोगप्रतिकार शक्ती इतर लोकांपेक्षा २० ते ३० टक्के जास्त असण्याची करणे त्यांची जीवनशैली व आहार यावर अवलंबून आहे. भारतात फेब्रुवारी महिन्यात 'कोरोना' आला याविषयी समजताच सगळ्या आदिवासी जमातींनी जंगलात सापडणारे कंदमुळे आणून सेवन करायला सुरुवात केली. चाळीसगाव डांगानातील आदिवासी लोकांनी सिंदीचा काला शिरपुंजे येथील मुडाच्या डोंगरावर जाऊन आणून प्रत्येक माणसाला देण्यात आला. सिंदीचा काला खाऊन, साथीच्या आजारात डोंगरावर राहून माणसे जिवंत राहिल्याचे दाखले या भागात उपलब्ध आहेत. साधारणतः १८५६ सालाच्या आसपास मानमोडी,पटकी,प्लेग असे साथीचे आजार आले होते. त्यावेळी या आदिवासींनी डोंगरचा रस्ता धरला व जंगलात डोंगरावर मिळणाऱ्या रानभाज्या, रानकंद यांचे सेवन करून साथींपासून आपला बचाव केल्याचे दाखले उपलब्ध आहेत. महामारीच्या साथीत 'सिंद' नावाच्या झाडाचा कंद 'काला' खाऊन माणसे जिवंत राहिली होती. सह्याद्रीच्या पट्ट्यात डोंगरावर 'सिंद' जातीची झाडे मुबलक प्रमाणात आढळतात. खजुराच्या झाडाच्या जातकुळीची ही वनस्पती आहे. खजुराच्या चवीची फळे या झाडाला लागतात. या झाडाचा 'गर्भ' म्हणजे आतील 'गर' काला काढून बारीक तुकडे करून खातात. तसेच तुकडे पिण्याच्या पाण्यात टाकून आठ दिवस ते पाणी संपूर्ण कुटुंब पिते. त्या काल्याचा संपूर्ण अर्क पाण्यात उतरतो. काल्यामुळे फुफुस स्वच्छ राहते.साधारणतः पुढील तीन महिने फुप्फुसाला संसर्ग होत नाही. कोरोनाचा विषाणू प्रथम हल्ला करतो तो श्वसन यंत्रणेवर म्हणजे घसा आणि फुफ्फुसावर. थोडक्यात, श्वसन यंत्रणा सुरक्षित राहिली तर अशा विषाणूची बाधा व्यक्तीला होण्याची शक्यता नसते. त्याचबरोबर आदिवासी भागात महुचे फूल मिळते. त्यापासून ही माणसे दारू तयार करतात. महूच्या फुलांसोबत जंगलातील काही औषधी वनस्पतींच्या मुळ्या उकळून ही दारू तयार केली जाते. जांभूळ या फळापासून सुद्धा दारू तयार केली जाते. महूच्या दारूमुळे कफ,खोकला बरा होतो. श्वसन यंत्रणा चांगल्या प्रकारे कार्यरत राहते. जांभळा पासून तयार केलेली दारू सेवनामुळे मधुमेहासारखे आजार बरे होतात. पोट साफ करण्याचे उत्तम औषध म्हणून जांभळ्याची दारू उपयुक्त ठरते. अशा प्रकारची मद्ये आदिवासी आपल्या घरात नेहमी ठेवतात. करवंदापासून सुद्धा दारू तयार करतात. या दारूमुळे पित्ताचे आजार होत नाहीत. रोगप्रतिकार शक्ती वाढते. वरील सर्व प्रकारच्या दारू आदिवासी, औषध म्हणून वापरतात. आदिवासी आणि जंगल यांचे नाते अतूट आहे. जंगलातील प्रत्येक वनस्पती मानवी शरीरास काही ना काही प्रतिजैविके देत असते. यांचे ज्ञान आदिवासींना आहे. प्रत्येक ऋतूमध्ये जंगलात उगवणाऱ्या रानभाज्या, रानकंद हे आदिवासी सेवन करीत असतात. सृष्टीचे व आयुर्वेदाचे ज्ञान त्यांना आहे. महामारीचा आजार, साथीचे आजार हे उन्हाळयात व पावसाच्या पहिल्या सत्रात जास्त फैलावतात. त्यामुळे त्यापूर्वी नेमके काय प्रतिबंधात्मक उपाय आदिवासींना माहीत आहेत ?

मकरसंक्रारातीच्या दुसऱ्या दिवशी 'कर' असते. करीच्या दिवशी हे लोक जंगलात जातात व 'आणीव' नावाचा कंद खणून आणतात. 'आणीव' हा संजीवनी देणारा रानकंद आहे. चविष्ट असणारा हा कंद सर्वात जास्त रोगप्रतिकार शक्ती वाढवितो. संपूर्ण वर्षभर रोगप्रतिकार शक्ती टिकवून ठेवणारा हा कंद आहे, म्हणून आदिवासी त्याला संजीवनी म्हणतात.

याबरोबरच अजून बरेच रानकंद आहेत की ज्यामुळे प्रतिकारशक्ती टिकून राहते. हायंदा, चाय, खुरपुडी हे कंद शरीरातील वेगवेगळ्या अवयवाना संजीवनी देत असतात, तसेच त्या अवयवांची प्रतिकारशक्ती वाढवतात. पावसाळ्यात 'हायंदा' खणून आणला जातो व त्याच्या फोडीपासून कालवण, सुकी भाजी करतात. त्याच्या फुलांची सुद्धा भाजी केली जाते. हायंदा खाल्यामुळे पोटाचे विकार बरे होतात. चायचा कंद किंवा चाविंद हा कंद चिकट असतो. तो भूजून अथवा शिजवून खातात. त्याच्या चिकट गुणधर्मामुळे घसा साफ होतो, मल मार्ग स्वच्छ होतो. 'खुरपुडी' हा कंद चवीला अत्यंत कडू आहे.तो भाजून किंवा शिजवून खातात. त्याच्या कडू गुणधर्मामुळे पित्त, कफ असे विकार बरे होतात. श्रावण महिन्यात जंगलात अनेक फळभाज्या असतात, त्या कच्च्या किंवा कमी शिजवून खातात. 'करटूली', 'गोमेटा' या भाज्या सेवन केल्याने भूक वाढते. पहिल्या पावसात चाईची भाजी, कोंबड्याची भाजी, कुरडूची भाजी, भात्याची भाजी, बडद्याची भाजी, बरकीची, कौल्याची,तांदुरड्याची भाजी, घायपताची भाजी आदिवासी लोक खातात. यामुळे पचनसंस्था चांगले कार्य करते. भाज्यांमधून मिळणारे 'क' जीवनसत्त्वे प्रतिकारशक्ती वाढवितात. पावसाळ्यात आदिवासींचे आवडते खाद्य म्हणजे किरवे, चिंबोरी, गींधोडी, मुरे मासे. हे अन्न यांच्या जेवणात वर्षभर असते.या अन्नापासून त्यांना भरपूर प्रमाणात प्रथिने मिळतात. खेकड्यांपासून कॅल्शियम मिळते. माशांच्या सेवनामुळे दृष्टी कमजोर होत नाही. निसर्गातून मिळणाऱ्या रानभाज्या, रानकंद, खेकडे, मासे यांच्या सेवनाने त्यांची प्रतिकारशक्ती चांगली राहते. कार्तिक महिन्यात 'चिचूरडा' नावाचे वांग्याच्या जातीचे बारीक फळ येते. त्याची भाजी आदिवासी लोक आवर्जून खातात. चवीला अत्यंत कडू असणारी ही भाजी खाल्यामुळे कफ,पित,वात यांचा त्रास होत नाही. जवळजवळ सहा महिने पित्ताचा त्रास होत नाही. अशा रानभाज्या खाल्यामुळे आदिवासी माणसे सुदृढ राहतात. चैत्र,ज्येष्ठ महिन्यात 'कुसर' नावाच्या फळांची भाजी खातात. कुसरे अतिशय कडू असतात. कुसरे आणून उखळात कांडतात, मग शिजवून त्यातील कडू पाणी काढून टाकले जाते व मग तव्यावर 'खुरसनी' तेलात, कांद्याबरोबर परतून भाजी केली जाते. पावसाळ्यात डोंगराच्या कुशीत उगवलेले 'पंदा' नावाचा कंद शिजवून, कधी दळून भाकरी करून खातात. पूर्वी अन्नधान्य मुबलक प्रमाणात होत नव्हते, तेव्हा हा कंद अन्न म्हणून आदिवासी खात असत. या कंदाच्या सेवनाने भरपूर कर्बोदके मानवी शरीरास मिळतात. रानकेळी, त्यास आदिवासी 'कवदरा' असे म्हणतात. तो कंद सुद्धा शिजवून भातासारखा लागतो. तसेच 'हमर-कंद' यास आदिवासी संजीवनी म्हणतात. आदिवासी हे कष्टाची कामे करतात, कंबरदुखीवर अत्यंत रामबाण औषध असणारा हा कंद आदिवासी लोक पावसाळ्यात भाजी करून खातात. बाळंत स्त्रीला खारीक, खोबरे व हमरकंद यांचे कूट खायला देतात. त्यामुळे बाळंतपनात स्त्रीला कमरेचा त्रास होत नाही. असे अनेक कंद आहेत, ज्यांचे सेवन आदिवासी अन्न म्हणून उपयोग करतात. त्यामुळे त्यांची प्रतिकारशक्ती व रोगप्रतिकारशक्ती उत्तम असते. उन्हाळयात काही खास रानभाज्या हे लोक जाणूनबुजून खातात. त्यात भोकराची भाजी, सायरधोडे, रान निरगुडीच्या फुलांची भाजी खातात, ज्यामुळे उन्हाळयात येणाऱ्या साथीच्या,तापसरीच्या रोगापासून बचाव होऊ शकेल. लहान मुलांना या ऋतूत कांजण्या, गोवर हे साथीचे आजार होतात. त्याला जलसंजीवनी म्हणून उंबराच्या झाडाच्या मुळीचे पाणी पाजतात.

डोकेदुखीवर रामबाण उपाय म्हणून एक छोटीशी वनस्पती आदिवासी भागात सापडते, ती म्हणजे 'चित्रुक'. चित्रुकाचे दोन प्रकार आहेत. एक कांड्या चित्रुक व दुसरे पताड्याचित्रुक. या चित्रुकाचा लेप कपाळावर देतात. सर्दी पडसे झाल्यावर गरम-गरम नाचण्याची (नागल्याची) भाकरी, गरम उडीदाची डाळ, लसणाची लाल मिरची, विशेषतः खुरसणी तेलात तळलेली, असा आहार घेतल्यास अर्ध्या तासात सर्दी पडसे गायब होते. आदिवासी जीवन आणि निसर्ग हे एकमेकांवर अवलंबून आहेत. निसर्ग चक्राप्रमाणे आदिवासींचे

जीवन आहे. त्यांच्या आहारापासून ते दैनंदिन जीवनापर्यंत निसर्ग आणि त्यातील वनस्पती यांचे नाते अतूट आहे. आदिवासी भागात साथीचा आजार आल्यास संपूर्ण गाव, घरे, रस्ते 'निरगुडी' च्या फांद्याचा झाडू करून सात दिवस स्वच्छता केली जाते. 'निरगुडी' ही वनस्पती निर्जंतुकीकरना (सानिटाईझर) चे कार्य करते. या विषयीचे ज्ञान आदिवासींना पूर्वीपासूनच आहे. 'विलगीकरण' ही संकल्पना आदिवासींना माहीत आहे. 'कोरोना' सारख्या साथीच्या आजारात बाहेरून आलेल्या व्यक्तीला 'मरीआईच्या' देवळात क्वारंटाईन केले जात असे. साथीच्या आजराव्यतिरिक्त 'क्षय' सारख्या आजारी रुग्णास बकरीच्या गोठ्यात रात्रभर झोपवले जाते. बकरीचे गोमुत्र उपासीपोटी प्यायला देतात. त्यामुळेही ज्यांची रोगप्रतिकारशक्ती चांगली आहे, असे रुग्ण बरे झाले आहेत. प्रत्येक आदिवासीच्या वाडग्यात पूर्वी 'कोरपड' असायचे, जे पित्तावर अत्यंत गुणकारी आहे. उन्हाळ्यात लहान मुलांना डांग्या खोकला होत असे. त्यावर उपाय म्हणून हिरड्याची पूड मधात कालवून चाटण दिले जायचे. त्यामुळे खोकला बरा होत असे. जंगलाचे ज्ञान,आयुर्वेदाचे ज्ञान असणारे आदिवासी इतर लोकांपेक्षा आरोग्याने सुदृढ आहेत. त्यांच्या राहायच्या घरापासून ते शेतीच्या आवजारासाठी लागणारे लाकूड सुद्धा विशिष्ट झाडाचे असायचे. उदा.घराचा 'उंबरा' भुस्कूटाच्या झाडाचा असायचा. बुस्कुट ही वनस्पती जंतुनाशक आहे. तसेच वास नष्ट करणारी आहे. जंगलात एखाद्या विषारी जातीच्या सापावर चुकून पाय पडला अथवा त्याचा स्त्राव पायाला चिकटला तर तो साप घरापर्यंत येत असे, परंतु तो उंबरा (उमतरा) कधीच ओलांडत नसे. भुस्कुटाच्या उंबऱ्यामुळे सापाचा स्त्राव गंदहिन होऊन जातो. त्यामुळे तो साप घरात प्रवेश करीत नसे.

'कोरोना' या विषाणूने जगभर थैमान माजवले आहे. संपूर्ण जग या महामारीने हतबल झालेले आहे. मात्र आदिवासी लोक बिनधास्त आहेत. त्यांना माहीत आहे की, अशा महामारीला रोखण्यासाठी आपले शरीर सक्षम आहे. 'कोरोना' मुळे आदिवासी लोक बाधित होतील, परंतु त्यांची रोगप्रतिकार शक्ती चांगली असल्यामुळे त्यावर ते मात करू शकतील. सामाजिक अंतर म्हणजेच 'सोशल डीस्टन्स' कसे पाळावे याचे ज्ञान त्यांना आहे. क्वारनटाईण,सानिटायझर याविषयी पुरेसे ज्ञान त्यांना आहे. साथीच्या आजारात विहिरीवरून 'दुडीने' हंडे आणायचे नाहीत याचे ज्ञान त्यांना आहे. खनिजयुक्त पाणी, सेंद्रिय अन्न यामुळे आदिवासी लोक 'कोरोना' सारख्या दुर्धर साथीच्या आजाराचा सामना नक्कीच करतील. कारण रानमेवा,कंदमुळे आणि शुद्ध हवा,निसर्ग हे घटक आदिवासींच्या जीवनाचा अविभाज्य भाग आहेत.

संदर्भ:- अकोले तालुक्यातील चाळीसगाव डांगाणातील (शिरपुंजे गाव)आदिवासी लोकांकडून मिळालेली माहिती.

***

काळजी घ्या...

पाऊस वारे गाती छान
सृष्टी हिरवळ आहे ना
हे जग किती सुंदर
पण आला एक व्हायरस असा
भारतातून जाणार कसा ?
त्याच्यावर एकच उपाय... घरात बसा
मानव पशु-पक्षी कसे राहणार
घरात राहून आंबे कसे खाणार ?
घरात बसून व्हायरसला सामोरे जाणार
बाहेरून आल्यावर स्वच्छ हात धुवू
भारतातून कोरोनाला पळवून लावू
हँडवॉश आणि सॅनिटायझर घरात ठेवू
भरातवासीयांना कोरोनाचा आला कंटाळा
त्यामुळे घराबाहेर पडायचे टाळा
नाहीतर पोलीस मारून करतील काळा निळा

– **श्वेता आवारी** (इ. ९ वी)

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Volume 01

Sr.No.	Name of the Aurhor	Title of Paper	Page No.
1.	Mr. S.D. Rajratna	Socio-Political Issues in Margie Orford's Crime Novel, Like Clockwork	1
2.	Chandrakant K. Chavan	The struggle and suffering in Hemingway's *'The old man and the sea'*	5
3.	Dr. Madhavi Pawar	The Fractured Identity That Long Silence	8
4.	Dr. Uttam Ramchandra Patil	Literature: A Gateway to Social Change	10
5.	Dr. Prashant Kale	A Study of Reading Habits of B.Ed. Teacher Trainees	13
6.	Dr. A. S. Arbole	Society and Symbols Depicted in the Novel *Train to Pakistan*	17
7.	Mrs. Jadhav Jyoti Mohan	Provincial Customs and Attitudes Dictate the Future of Children in Anita Desai's Novel Fasting, Feasting: A Social Study	20
8.	Mr. Sorate J.B.	Role Of Literature in Social Change	23
		Marathi Language	
9.	प्रा.डॉ.आनंद वारके	सामाजिक चळवळी आणि राजन गवस यांच्या कादंबऱ्या	25
10.	प्रा. डॉ. सुभाष पाटील	मराठीतील आदिवासी साहित्य प्रवाह	31
11.	डॉ. कुंडलिक चिंधू पारधी	सामाजिक चळवळी आणि आदिवासी साहित्य	38
12.	डॉ. लता पां. मोरे	'ज्याचा त्याचा प्रश्न'मधील स्त्रीवादी दृष्टिकोन	42
13.	प्रा.चिंतामण दुंदा घिंदळे	सामाजिक चळवळी आणि आदिवासी कविता	47
14.	डॉ. योगिता मारुती रांधवणे	नव्वदोत्तर ग्रामीण कादंबरीतील बदलेली ग्रामीण मानसिकता	52
15.	प्रा. आशालता नारायण खोत	मराठी कादंबरीतील बदलते चित्रण (बनगरवाडी)	55
16.	प्रा. सुजाता संजय चोपडे	'सूड' कथेची नायिका जानकी चा ज्वालाप्रसाद पर्यंतचा प्रवास	60
17.	प्रा. मोहन बाबुराव चव्हाण	सामाजिक चळवळी आणि ग्रामीण कथा	65

सामाजिक चळवळी आणि आदिवासी कविता

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प्रास्ताविक

महाराष्ट्रातील ख्रिस्ती मिशनरीतर्फे संस्थेचे शैक्षणिक व आरोग्यविषयक कार्य, ठाणे जिल्हयातील 'कल्याण' चर्च ऑफ ब्रेदेरेन मिशन' या अमेरिकन संस्थेतर्फे रेव्हरंड ॲडॅम एबी यांनी इ.स.१९०३ साली वारली आदिवासींकरीता दवाखाना उघडला होता. याच मिशनतर्फे शिक्षणाचे कार्य सुरू झाले. याशिवाय पुणे,नाशिक,धुळे,विदर्भातील चंद्रपूर, गडचिरोली या सर्व प्रादेशिक भूभागात ख्रिस्ती मिशनरींनी सेवाभावी वृत्तीनी आदिम जमातींची सामाजिक गरज लक्षात घेऊन त्यांच्या उत्थानाचे कार्य केले. या सर्व प्रक्रियेतून कळत-नकळत आदिवासी जागृतीची चळवळ अधिक विकसित होत गेली. एतदेशियांपैकी नामदार गोपाळ कृष्ण गोखले (भारत सेवक समाज) पू. ठक्करबाप्पा (भिल्ल सेवा मंडळ) पालघरचे वि.वा ऊर्फ बाबासाहेब दांडेकर, बोडीचे आचार्य भिसे (आदिवासी सेवा मंडळ, मुंबई) बाळासाहेब खेर, म. गांधीजींची समाजसेवेची प्रेरणा घेऊन काकासाहेब बर्वे, शंकरराव ठकार, दादासाहेब बिडकर, भाऊसाहेब हिरे, डॉ. ए. के. मोरे, कोंडू मारती बोकड (जून्नर) गोपाळराव कडू, ओंकार होळक्या पाडवी, मारोती महादेव केंगले, नागपूर विदर्भाकडील पंचमबाबू मडावी.

भारतीय संविधानाने भारतीय नागरिकांना जे संरक्षण आणि हक्क दिले ते सर्वसामान्य आदिवासीलाही प्राप्त झाले. विशेष म्हणजे आदिवासींची विशिष्ट परिस्थिती लक्षात घेता त्यांना संविधानाव्दारे विशेष संरक्षण व अधिकारही मिळाले. डॉ. बाबासाहेब आंबेडकर व पू. ठक्करबाप्पा यांच्यासारख्या द्रष्ट्या नेत्याचे हे ऋण आदिवासी कधीही उतराई होऊ शकणार नाही. आदिवासी जंगली आणि अशिक्षित, अडाणी आहेत. त्यांना सर्व हक्क व आधिकार प्रदान करावेत की नाहीत ? त्यांना त्यांचा वापर करता येईल का नाही ? असाही त्याकाळी एक विचार प्रवाह होता. परंतु थोर नेत्यांच्या प्रयत्नांमुळे हा विचार प्रवाह निर्माण झाला तिथेच संपला. परिणामता संविधानाव्दारे आदिवासींची शैक्षणिक, आर्थिक आणि सामाजिक मागासलेपणातून सोडवणूक करण्याचे सर्व थरावर प्रयत्न सुरू झाले. हे जरी खरे असले तरी आदिवासींचे जे जटिल प्रश्न होते, विशेषत: जमीन,जंगल,सावकारी शोषण त्यांची तातडीने सोडवणूक होण्यासारखी परिस्थिती निर्माण होऊ न शकल्याने देशभर आदिवासींनी चळवळी, लढे आणि संस्था संघटनांव्दारे जन आंदोलने सुरू केली. जंगल आणि जमिनीवरील हक्क प्रस्थापित करण्यासाठी व अन्याय, अत्याचार आणि शोषणा विरूध्द आवाज उठविण्यासाठी स्वातंत्र्यपूर्व काळात अनेक चळवळी आणि लढे उभे राहिले. या चळवळीचा इतिहास आणि त्यावर आधारीत ललित साहित्याची निर्मिती हा खरं म्हणजे आदिवासी साहित्याचा ठेवाच ठरेल. त्यात प्रामुख्याने बिरसा मुंडाची चळवळ, बिहारमधील ताना भगत चळवळ, बस्तरच्या आदिवासींचा लढा, तेलंगणातील आदिवासी लढा, गोंड आणि कोलामांचा आदिलाबादमधील लढा, कोयांचा लढा, ओरिसातील कोरापूटचा लढा, नागाचा लढा, मुंडा आदिवासींची सरदारी चळवळ,मनिपूरचा लढा,मुंबई राज्यातील वारली लढा, सावकार जमीनदारांविरूध्द लाल बावटयांची चळवळ, जुआंग रिबेल्ट, जोरिया नाईक रिहोल्ट, १९३७ सालचा जंगल सत्याग्रह, गुजरातमधील भगत मुव्हमेंट आणि आप की जय अस्तीत्ववादी चळवळ, संताळ परगण्यातील संताळी लढे, लुशाई टेकडयातील मिझोंच्या चळवळी, चणकापूरचे बंड इत्यादींचा प्रामुख्याने उल्लेख करता येईल. विसाव्या शतकाच्या पूर्वार्धात झालेल्या या चळवळी आणि लढयांनी आदिवासींचे प्रश्न सुटले असे नाही. परंतु स्वातं स्वातंत्र्यानंतरच्या पूर्वार्धात हया चळवळीचा शोषभाग आणि नव्याने चळवळी उभ्या राहिल्या. अनेक आंदोलने झाली. त्यात आदिवासींची अस्मिता, अस्तित्व आणि प्रादेशिक स्वातंत्र्यतेचे लढे आणि चळवळी अग्रस्थानी होत्या. याशिवाय अलीकडील काळात आदिवासी जमातीत जन्म घेऊन समाजसेवेचा वसा घेणारे अनेक समाजसेवक व कार्यकर्ते यांनी आदिम जमातींना शैक्षणिक सुविधा पुरविल्या आहेत. महाराष्ट्रातील शासन संस्थेनेही आदिवासी उपाय योजनेच्या माध्यमातून त्यांचा

जीवनस्तर उंचावण्याचा प्रयत्न केला आहे. याशिवाय महाराष्ट्रातील डाव्या विचारसरणीच्या आश्रयाखाली येऊन धुळे येथील कॉ. शरद पाटील यांच्या मार्गदर्शनाखाली नजूबाई गावीत व वाहरू सोनवणेसारखी प्रतिभावंत लेखक मंडळी उदयास आली आहेत. वरील सर्वांच्या अथक परिश्रमातून, समाजसेवेतून आदिवासी मुक्ती चळवळ आणि पर्यायाने आदिवासी कविता निर्माण झाली आहे.

मराठी साहित्यात १९६० नंतर दलित व ग्रामीण असे साहित्य प्रवाह निर्माण झाले. त्यांच्याकडून आदिवासींच्या खूप अपेक्षा होत्या परंतु ते साहित्य त्या पूर्ण करु शकले नाही. त्यामुळेच आदिवासींची आपला वेगळा प्रवाहा निर्माण करण्याच्या दृष्टीने पावूल उचलून १० व ११ नोव्हेंबर १९७९ साली प्रा. विनयाक तुमराम यांच्या पुढाकाराने व भराणी दुर्गावती' वाचनालयाच्या वतीने पहिले आदिवासी साहित्य संमेलन चंद्रपूर जिल्यात भद्रावती' या गावी भरविण्यात आले. व या निमित्ताने आदिवासी साहित्याचे स्वतंत्र दालन मराठी साहित्यात उघडले गेले. त्यानंतर दुसरे आदिवासी साहित्य संमेलन श्री राजाभाऊ राजगडकर यांच्या पुढाकाराने २३ मे १९८२ रोजी यवतमाळ जिल्हयात भवणी' या गावी घेण्यात आले. या साहित्य संमेलनाच्या उदघाटन प्रसंगी चळवळी विषयी शिवाजीराव मोघे म्हणतात की, ''निसर्गाशी समरस होऊन आदिवासी आनंदात राहतो. वाघाशी मुकाबला करताना भित नाही. पण शहरातील उच्चभ्रू अधिकाऱ्यांची त्याला भिती वाटते. शेकडो वर्षापासून जपलेला साहित्यसाठा रानावनात आहे. साहित्य संमेलनापासून प्रेरणा घेऊन त्यातील अनिष्ट ते काढून सोज्वळ व चांगले साहित्य प्रकाशात आले पाहिजे आदिवासी साहित्य चळवळ ही केवळ साहित्यापुरती मर्यादित नाही तर ती आदिवासींच्या सर्वांगीण विकासासाठी आहे. त्याव्दारे मार्गदर्शन मिळाले पाहिजे.''१ स्वातंत्र्यनंतरच्या काळातच आदिवासीतींच्या शैक्षणिक विकासाचा वेग खऱ्या अर्थाने वाढलेला दिसतो. शिक्षणाचे महत्त्व पटल्यावरुन म्हणा अथवा सामाजिक सर्वकष मदतीसाठी ज्या शिक्षणसंस्था उभारलया त्या संस्थातून म्हणा, अनेक आदिवासी कार्यकर्त्यांनी शिक्षणसंस्था उभारल्या. त्या संस्थांमधून शिक्षण घेऊन बाहेर पडलेले शेकडो आदिवासी तरुण उच्च पदांवर असलेले आज पाहावयास मिळतात. डॉ. विनायक तुमराम हयांनी १९७८ साली ग्रंथाल्याची चळवळ उभारुन भद्रावती, जिल्हा चंद्रपूर येथे भराणी दर्गावती वाचनालय' नावाचे पहिले वहिले वाचनालय सुरु केले. तर १९८१ साली भएकलव्य शिक्षण प्रसारक मंडळ' स्थापन केले. १९८५ साली तेलवार येथे भगवान पेरसापेन ग्रंथालय' स्थापन केले. महिलांसाठी १९८६ साली,आदिवासी महिला विकास ग्रंथालय'अशा अनेक संस्था स्थापन करण्यात आल्यामुळे आदिवासी तरुणवर्ग वाचन आणि लेखनाकडे वळल्याचे दिसून येतो. यानंतर पाच वर्षांनी ६ व ७ जून १९८७ साली तिसरे आदिवासी साहित्य संमेलन नांदेडजिल्हयात किनवट' या गावी श्री. राम भिराशे यांनी आयोजित केले होते. त्यानंतर चौथेआदिवासी साहित्य समेलन १९८९ यावर्षी आदिवासी साहित्यिकांचे दोन मेळावे गडचिरोली येथे डॉ. सुभाष सावरकर यांचे अध्यक्षतेखाली १८ व १९ फेब्रुवारी १९८९ रोजी भरविला होता. तर दुसरा मेळावा पांदरकवडा येथे ८ मे १९८९ रोजी आदिम' चे लेखक डॉ. भाऊ मांडकर यांचे अध्यक्षतेखाली संपन्न झाला. या दोन्ही मेळाव्यांचे अध्यक्ष बिगर आदिवासी साहित्यिक व अभ्यासक होते. दुसऱ्या मेळाव्याचे उदघाटकही डॉ. जयंतराव धावडे हे बिगर आदिवासी होते. त्यामुळे ६ व्या आदिवासी साहित्य संमेलनाच्या अध्यक्षीय भाषणात कवी भुंजग मेश्राम म्हणतात की, ''आपल्याला आपली वाट, आपली दिशा निश्चत करणे महत्त्वाचे आहे. आदिवासी साहित्य कृतीशील बनवून त्यास आत्मसन्मानाच्या चळवळीशी जोडणे आवश्यक आहे. आम्हांला आदिवासीच्या आत्मसन्माची चळवळ तीव्र करायची आहे. आदिवासी साहित्य हे तिचे अविभाज्य अंग आहे.''२ भुजंग मेश्राम यांनी जे मत व्यक्त केले आहे त्याचा परिणाम आदिवासी कवितेवर नक्कीच झालेला आहे. त्यामुळेच वाहरु सोनवणे' यांच्या स्टेज' नावाच्या कवितेतून मांडलेले आहे. ते लिहितात.

''आम्ही स्टेजवर गेलो नाही.
आणि आम्हाला बोलावलही नाही
बोटाच्या इशाऱ्याने
आमची पायरी आम्हाला दाखवून दिली
आम्ही तिथंच बसलो.....
ते आले नि स्टेजवर गेले
आमचेच दुःख आम्हाला सांगत राहिले
आम्ही चुळबुळलो.....

गप्प रहा नाहीतर
ते आले न स्टेज घेऊन गेले ''३

कवी वाहरु सोनवणे हे स्वत: चळवळीतील कार्यकर्ते असल्यामूळे त्यांनी चळवळीचा विचार स्विकारुन मांडणी केलेली आहे. असे वरील कवितेतून दिसून येते.आदिवासी साहित्य संमेलनाची सुरुवात विदर्भापासून झाली. पहिली तीनही साहित्य संमेलने विदर्भ व मराठवाडयात झाली.चौथे आदिवासी साहित्य संमेलन मात्र खानदेशात झाले. पाचव्या आदिवासी साहित्य संमेलनाचा मोर्चा पश्चिम महाराष्ट्राकडे वळला. ठाणे जिल्हयात पालघर या तालुक्याच्या ठिकाणी पाचवे आदिवासी साहित्य संमेलन २३ ते २५ डिसेंबर १९९० रोजी संपन्न झाले. या समेलनात आदिवासी साहित्यीक वाहरु सोनवणे हे अध्यक्ष होते. या समेलनाचा परीणाम होऊन अनेक आदिवासी कवी लिहू लागले. वाहरु सोनवणे यांचा गोधड' हा काव्यसंग्रह प्रकाशित झाला. त्याच बरोबर विनायक तुमराम यांचा गोंडवन पेटले आहे' हा काव्यसंग्रहप्रकाशित झाला भुंजग मेश्राम याचा उलगुलान' काव्यसंग्रह प्रकाशित झाला. त्याच बरोबर विविध नियतकालीकातून नवोदित आदिवासी कवी लिहू लागले. त्यामध्ये प्रभु राजगडकर, वामन शेळमाके, सोपान सुरकुले, मारुती कुळमेथे, उषाकिरण आत्राम, कुसुम आलाम, यासारख्या कवींचा समावेश होता. त्यानंतर ९ वे आदिवासी साहित्य समेलन ७ व ८ मे रोजी नागपूर येथे संपन्न झाले त्या साहित्य समेलनाच्या अध्यक्ष होत्या उषाकरिण आत्राम तर स्वागताध्यक्ष मधुकररावजी पिचड, होते. २०११ पर्यत झालेल्या आदिवासी साहित्य समेलनाचे अध्यक्ष हे आदिवासी कवी असल्यामुळे वरील अभ्यासातून दिसून येते. संजय लोहकरे व तुकाराम रोंगटे यांच्या मार्गदर्शनातून आदिवासी फडकी फाऊण्डेशन' च्या वतीने वेगवेगळी जिल्हास्तरीय साहित्य समेलने आयोजित करण्यात आली. त्यामुळेच सिता भोजने सारख्या कवयित्री आदिवासी समाज्याला आणि मराठी साहित्याला दिल्या आहेत. तर डॉ. तुकाराम रोंगटे व डॉ. राधाकृष्ण पेढेकर यांनी स्थापन केलेल्याआदिवासी विचारमंच' यांच्या आगळया वेगळया उपक्रमातून आदिवासी सामाजिक कार्यकत्यांना जीनगौरव पुरस्काराने संन्मानित करण्यात आले आहे. त्यामुळेआदिवासी समाजात जागृती होऊन अनेक कवी पुढे आलेले आहे. त्याच बरोबर फडकी' सारख्या मासिकातून अनेक कविनी आपले काव्यलेखन करुन समाजातील प्रश्न, चळवळीचे विचार मांडलेले आहे. त्यामूळेच साहित्य हे एकाव वेळी व्यक्तिनिष्ठ आणि समूहाचे कसे असते याविषयी चळवळीच्या अंगाने मांडणी करतांना काळूराम धोदडे म्हणतात. की, ''लोकसमूहाचं साहित्य हे त्यांच्या निर्मितीक्षमता, सर्जनशक्तिचं प्रतिक असते. एकाबाजूने ते अत्यंत वैयक्तिक, व्यक्तिनिष्ठ असते पण व्यक्त होतांना वस्तुनिष्ठ जाणीवांच्या आधारानेच जन्म घेते आणि हया संदर्भाची बंधनं तोडून वेगळया पातळीवर पोहचंत. साहित्य एकाच वेळेला संस्कृतीची जाणीव देते आणि त्याच वेळी ते संस्कृतीचा एक भाग असते. हया जाणीवांना जाग आणताना आपल्या सर्जनशीलता दुसऱ्या पर्यत पोहचवण्यासाठी ते अर्थाचा एक नविनच आकृतिबंध तयार करते. साहित्य लोकसमूहाने घडवलेले असते आणि लोकसमूहही साहित्याने घडतो.''४अन्यातूनच साहित्य निर्मिती कशी होते आणि त्याला आदिवासी साहित्य चळवळ अपवाद नसल्याचे सांगताना विनायक तुमराम म्हणतात. की, '' जेव्हा जेव्हा, विषमता कायम ठेवून शोषणचा पिंड उरीपोटी कवटाळून, मानवमुक्ति व साहित्यपीठ निर्माण करण्याचा ज्यांनी ज्यांनी प्रयत्न केला, तेव्हा तेव्हा त्यांनी त्यांनी अप्रत्यक्षपणे कोणत्या ना कोणत्या वर्गावर अन्यायच केला आहे, हे ध्यानात ठेवलं पाहिजे ! कोणतंही साहित्य हेसमाजवादी दृष्टीने वाटचाल करणारं हवं. अशा साहित्याचा धर्म विभू आणि शाश्वत असावा लागतो. तो सर्वजीवनस्पर्शीही असावा लागतो. पण आजच्या काळात तो तसा नाही. महाराष्ट्रात ज्या अनेक साहित्यिक चळवळी अस्तित्वात आल्या त्या सर्व चळवळींच्या उदयाला कारण म्हणजे मराठी साहित्यातील, मानवकेंद्री वृत्तीचा अभाव होय. तथापि सगळयाच चळवळीतून आदिवासी जीवन लुप्तच होत गेलं आहे; हा आरोप हया संदर्भात चूकीचा नाही. तेव्हा बदलत्या काळाला अनुलक्षून, आदिवासी म्हणून रानावनात जगणाऱ्या वंचितांना साहित्याच्या दालनात न्यायाचा वाटा मिळावा, हयाच भूमिकेतू आदिवासी साहित्यपीठ निर्माण करावं लागलं, मराठी साहित्याचा तोच तो पणा झुगारुन बादळी निर्णयाने पुढे आलेल्या दलित साहित्यासारख्या ज्या इतरही चळवळी महाराष्ट्रात निर्माण झाल्या, आदिवासी साहित्याची चळवळ ही त्यापैकीच एक होय.''५ पुढेते म्हणतात.''आदवासींच्या चळवळींना संघर्षाच्या विविध छटा आहेत. एकाच प्रकारच्या सामाजिक आणि राजकीय जाचातून त्यांचा विद्रोह जन्माला आलेला नाही. काही आदिवासी जमातींनी आत्मसन्मानाच्या चळवळी राबविल्या, काहींनी आपल्या धर्म- संस्कृतीवर होणारे परकीयांचे आक्रमण थोपविण्यासाठी उठाव केले, तर काहींनी शोषणाविरूध्द, विषमतेविरूध्द लढे उभारले. त्यावरून, आदिवासींच्या ध्येय – धोरणांचा व अस्मितेच्या दिशेने झेपावणाऱ्या त्यांच्या युध्दस्वी प्रवृत्तीचा

आपणास परिचय होतो. हे ऐतिहासिक वास्तव विसरून चालणार नाही.''६ असे मत आदिवासी अभ्यासक विनायक तुमराम नोंदवतात वरील अभ्यासकांच्या मताचा विचार करुन आदिवासी काव्यातून चळवळीचे सूर येतात. आदिवासीच्या शिक्षणातील समस्या मांडतानां, कधी तरी भरणाऱ्या शाळेचे वर्णन पुरुषोत्तम आगाशे' आपल्या कवितेत करतात.

''ऐसी इथली शाळा
नाही खडू नाही फळा
हवेशीर इथल्या भिंती
छपराला लागते गळती
पोर इथं शिकायला जाती
कधीतरी मास्तर आल्यावरती..''७

आदिवासींच्या समस्या कवितेतून मांडण्यामागील प्रेरणा हया चळवळीच्याच असल्याचे लक्षात येते. म्हणूनच कवितेतून आदिवासी कुपोषन, दारिद्रय, आरक्षण, स्त्रियांवरील अन्याय, अत्याचाराचे चित्रण कविनी केल्याचे पाहावयास मिळते. आदिवासी कविता हा आदिवासी हा आदिवासी जीवनाचा आरसाच आहे. कवितेतून आदिवासी कवींनी सूचकपणे यथार्थवादी दृष्टिकोनातून आदिम भावना मांडून नवआदवासी कवींनी एक दिशाव प्रेरणा देण्याचे काम केले आहे. आदिवासी कवींची कविता अस्सल आदिमत्व प्रकट करते व ती विविध भाषिक सौंदर्यांनी नटलेली आहे. आदिवासी साहित्याबरोबरच आदिवासी संस्कृतीचे जतन व संवर्धन आदिवासी चळवळीने आवश्यक आहे. त्यासाठी आदिवासी कविनी प्रयत्न केले आहे. आदिवासींच्या शोषण मुक्तीचा विचार आदिवासी चळवळीनी मांडलेला आहे. त्याचा परिणाम, प्रभाव कवितेवर असल्याचे दिसून येते. नवसमाज निर्माण करण्यासाठीचे सामर्थ्य आदिवासी साहित्य परिषद व आदिवासी चळवळीत प्राप्त झाले आहे. त्यामुळे नवोदीत आदिवासी कविच्या काव्यातून नवा विचार पुढे येतो आहे. आदिवासी समाजातील मुक्या भावंनाना व्यक्त स्वरुप देण्यासाठी चळवळीनी प्रयत्नं केले आहे. अशा प्रकारे आदिवासी चळवळी आणि कवितेचा सहसंबध असल्याचे दिसून येते.

आदिवासी साहित्याची निर्मिती ही स्वातंत्र्योत्तर काळातील आहे. त्याअगोदर आदिवासी साहित्य नव्हते, असे नाही. मात्र, मुळातच हा समाज आणि साहित्य स्वातंत्र्यापूवी आणि स्वातंत्र्यानंतरही मोठया प्रमाणात उपेक्षित राहिला आहे. अर्थातच जाणूनबुजून उपेक्षित ठेवले, हे या उपेक्षित राहण्यामागचे कारण आहे. १९७५ पासून आदिवासी साहित्य खऱ्याअर्थाने पावले टाकत आलेला पहावयास मिळतो. आदिवासींच्या धार्मिक व सामाजिक रूढी परंपरागत निसर्गपूजेतून निर्माण झाल्या आहेत. निसर्गातील जे जे निरनिराळे गूढ, अनाकलनीय ते सर्व पूजनीय असं ते मानतात. आकाशात चमकणारी वीज, चंद्र, सूर्य, प्रचंड वृक्ष, वाघ, सिंह, साप, विंचू अशा निसर्गनिर्मित सजीव-निर्जीव वस्तुंची आणि प्राण्यांची ते पुजा करतात, त्यांच्यात हिरवा, हिमाई, वनदेव, बडादेव, गावदेव, कणसरी, धरतरी, वाघदेव, वाघिया, चित्ता, डोंगरदेव अशा निसर्गातून झालेल्या देवतांचीही पूजा केली जाते. त्यामुळेवास्तविक 'आदिवासी साहित्य' हे खऱ्या अर्थाने. साहित्याचे मूळ आहे. त्याचा कर्ता कोण हे कोणाला सांगता येत नाही. वेदाचा कर्ता कोण हे कुठे सांगता येते कुणाला ?वेद ब्रहम्याच्या मुखातून प्रगट झाले असे सांगतात, म्हणून ते परिपूर्ण आहे असे मानले जाते. 'वेद वाक्य प्रमाण' असे मानण्याचा प्रघात जनमाणसांत त्यामुळेच रूढ झालेला आहे. आदिवासींच्या अभिजात जनसाहित्याच्या विशेषत: आदिवासींच्या लोककथा, लोकगीते, जानपदगीते, गुराखी गीते, देव-देवतांच्या, मनुष्य - प्राण्याच्या उत्पत्ती आणि मरण्याच्या कथा, जनव्यवहाराचे वाद संवाद, घात-प्रघात, बोलण्या-चालण्याचे अडाखे, म्हणी आणि वाक्प्रचार हा आदिवासी साहित्याचा आद्य प्रकार म्हणता येईल. त्यांचा उगम कुठे झाला, केव्हा झाला, त्याचा कर्ता कोण हे कुणाला सांगता येणार नाही. आदिवासी मात्र अनादी काळापासून या साहित्यावर जगाला आहे. अनादी काळापासून त्यांचे हे मौखिक साहित्य एका पिढीकडून दुसऱ्या पिढीकडे केवळ मौखिक परंपरेने चालत आलेले आहे. खरेतर त्यांचे हे साहित्य अक्षरवाड्मय आहे. परंतु आजचे आदिवासी साहित्यिक त्याला विसरून गेले आहेत. या निमित्ताने त्याची आठवण मी करून देऊ इच्छितो. या मौखिक वाड्मयाचा शोध घेण्याची, विकास करण्याची, त्यातील शब्द सौंदर्य, लालित्य, भावना प्रधानता, शृंगार, प्रेम आणि निसर्गाशी विलीन होण्याची व त्यात स्वत:ला विसरून जाण्याची किमया

साहित्य प्रेमींना सुस्पष्ट झाली पाहिजे आणि हे उत्तरदायित्व आजच्या आदिवासी साहित्य संमेलनाला जमणाया साहित्यिकांवर आहे.आदिवासी कवितेच्या प्रेरणा शोधतांना,निसर्ग हीच पहिली प्रेरणा असल्याचे सांगता येईल. प्रस्थापित भौतकदृष्ट्या प्रगत अशा संस्कृतीपासून अलिप्त असलेला, निसर्ग ज्याच्या जीवनाचा अविभाज्य भाग आहे, कृत्रिम, तथाकथित सुसंस्कृत वातावरणापासून दूर राहून स्वाभाविक नैसर्गिक जीवन व्यतीत करणारा आणि किमान प्राथमिक गरजांपासून वंचित ठेवण्यात आलेला जो आदिवासी समाज आहे त्या समाजातून जिद्दीने प्राप्त परिस्थितीशी संघर्ष करीत आदिवासींच्या व्यथा-वेदनांची दाहकता आदिवासी कविते तून मांडली आहे.

समारोप-

स्वातंत्र्योत्तर सामाजिक चळवळीचा विचार केला असता. आदिवासी साहित्य प्रवाहाची सुरुवात ही आदिवासी कवितेनी झालेली आहे. नव्या जगाची नवीन अनुभवविश्वाची भर घातली गेली आहे. अन्याय, अत्याचार विरुध्द आवाज उठवला आहे. आदिवासी कला, संस्कृती, निसर्ग यांची ओळख येथील प्रस्थापित समाजाला करून देण्याचे काम कथा, कविता, कादंबरी आणि नियतकालिकांनी केले आहे. त्यामुळे मराठी साहित्य समृद्ध होण्यास नक्कीच मदत झाली आहे.

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Volume 01

Sr.No.	Name of the Aurhor	Title of Paper	Page No.
1.	Mr. S.D. Rajratna	Socio-Political Issues in Margie Orford's Crime Novel, Like Clockwork	1
2.	Chandrakant K. Chavan	The struggle and suffering in Hemingway's *'The old man and the sea'*	5
3.	Dr. Madhavi Pawar	The Fractured Identity That Long Silence	8
4.	Dr. Uttam Ramchandra Patil	Literature: A Gateway to Social Change	10
5.	Dr. Prashant Kale	A Study of Reading Habits of B.Ed. Teacher Trainees	13
6.	Dr. A. S. Arbole	Society and Symbols Depicted in the Novel *Train to Pakistan*	17
7.	Mrs. Jadhav Jyoti Mohan	Provincial Customs and Attitudes Dictate the Future of Children in Anita Desai's Novel Fasting, Feasting: A Social Study	20
8.	Mr. Sorate J.B.	Role Of Literature in Social Change	23
		Marathi Language	
9.	प्रा.डॉ.आनंद वारके	सामाजिक चळवळी आणि राजन गवस यांच्या कादंबऱ्या	25
10.	प्रा. डॉ. सुभाष पाटील	मराठीतील आदिवासी साहित्य प्रवाह	31
11.	डॉ. कुंडलिक चिंधू पारधी	सामाजिक चळवळी आणि आदिवासी साहित्य	38
12.	डॉ. लता पां. मोरे	'ज्याचा त्याचा प्रश्न'मधील स्त्रीवादी दृष्टिकोन	42
13.	प्रा.चिंतामण दुंदा घिंदळे	सामाजिक चळवळी आणि आदिवासी कविता	47
14.	डॉ. योगिता मारुती रांधवणे	नव्वदोत्तर ग्रामीण कादंबरीतील बदलेली ग्रामीण मानसिकता	52
15.	प्रा. आशालता नारायण खोत	मराठी कादंबरीतील बदलते चित्रण (बनगरवाडी)	55
16.	प्रा. सुजाता संजय चोपडे	'सूड' कथेची नायिका जानकी चा ज्वालाप्रसाद पर्यंतचा प्रवास	60
17.	प्रा. मोहन बाबुराव चव्हाण	सामाजिक चळवळी आणि ग्रामीण कथा	65

नव्वदोत्तर ग्रामीण कादंबरीतील बदलेली ग्रामीण मानसिकता

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प्रास्ताविक

ग्रामीण अर्थव्यवस्थेचा कणा असलेली शेती ही सुरुवातीपासूनच संकटात आहे. शेतकऱ्याचे वर्षाचे उत्पन्न आणि शेतीचा व जगण्याचा खर्च याचा ताळेबंद आजपर्यंत जुळलेला दिसत नाही. याशिवाय खाऊजा अर्थनीतीमुळे ग्रामीण शेतकऱ्यांच्या जीवनावर अनिष्ट परिणाम झाले आहेत.याचाच परिणाम मराठी ग्रामीण कादंबरीतून येणाऱ्या समकालीन शेतकरी जीवन चित्रणावर झालेले आहे. आत्महत्येच्या वाटेवर चालणारा शेतकरी, वांझोटया ठरलेल्या शेतकरी चळवळी, शहर खेडे यांच्यात रुंदावलेली दरी गावातील नवतरुणांत वाढत चाललेले शहराचे आकर्षण, यामुळे मोडत चाललेली ग्रामसंस्कृती, नात्यात येत असलेला फोलपणा स्वत:पुरते पाहण्याची वाढत चाललेली वृत्ती, प्रामाणिक माणंसाची होणारी दमछाक, पैशाला आलेले देवपण हे सारे जागतिकीकरणाचे देणे असून त्याचा परिणाम ग्रामजीवनावर खूपच पडलेला आहे. या सर्व घडामोडीचा प्रभाव मराठी ग्रामीण कादंबरीवरही पडलेला असून त्याचे प्रतिबिंब या दशकातील कादंबरीत रेखाटले आहे.

नव्वदोत्तरग्रामीण कांदबरी वाटचाल व वेगळेपण :-

भारतासारख्या कृषीप्रधान देशाने १९९१ मध्ये नवे आर्थिक धोरण स्वीकारले. त्याचा ग्रामीण साहित्यातील कथा, कविता, नाटक साहित्याप्रमाणे मराठी, ग्रामीण कादंबरीवरही जागतिकीकरणाचा प्रभाव पडलेला आहे. त्याचे कारण म्हणजे ग्रामीण लेखक ग्रामीण समाजजीवनात वावरत असताना त्यांना अलेले अनुभव, ग्रामीण संस्कृती, रूढी, परंपरा, ग्रामनिष्ठा कृषिसंस्कृती, ग्रामीण माणसांचे राहणीकमान, त्याची केशभूषा, वेशभूषा, त्याचे सण-उत्सव खेडयाची रचना, व्यापार, उद्योग, रोजगार अशा विविधांगी घटकांचे ग्रामीण कादंबरीच्या माध्यमातून चित्रण केले आहे. मुक्त अर्थव्यवस्थेची स्वीकार व त्यामुळे जगाला आलेले एक मोठया खेडयाचे स्वरुप या शहरी आणि ग्रामीण माणसाच्या जगण्यात अमुलाग्र बदल झाले. शहरे बदलली तशी खेडीही बदलली याचे प्रतिबिंब तत्कालीन साहित्यात बरोबरच कांदबरीत पहावयास मिळते. १९९० नंतर रा.रं बोराडे, बाबाराव मुसळे, संदानंद देशमुख, अशोक कोळी, राजन गवस, रंगनाथ पठारे, विश्वास पाटील, किशोर सानप, पुरुषोत्तम बोरकर, प्रवीण दशरथ बांदेकर, जी. के. ऐनापुरे यांच्या ग्रामीण कादंबऱ्यातून खाजगीकरण, उदारीकरण आणि जागतिकीकरणाचे होणारे चांगले, वाईट परिणाम मांडण्यात आलेले आहेत. याशिवाय मराठी ग्रामीण कादंबरीकाराच्या कादंबऱ्यातून 'खाऊजा' अर्थनींतीचे आजतागायत चित्रण केले जात आहे. त्यामुळे जागतिकीकरण आणि मराठी ग्रामीण कादंबरीची वाटचाल आज २१ व्या शतकातही सुरुच आहे. सदानंद देशमुख यांच्या 'बारोमास ' या कादंबरीतील जागतिकीकरण संदर्भात प्रा. शेटकार रामशेट्टी असे म्हणतात की, "बारोमास या कादंबरीत जागतिकीकरणामुळे शेतकऱ्याच्या मुलाला म्हणजे एकनाथाला दु:खाचे जीवन जगावे लागत आहे. तो एम.ए . बी. एड प्रथम श्रेणीत उत्तीर्ण होऊनही त्याला नौकरी मिळत नाही. तो शेतीत काम करीत असल्यामुळे त्याची पत्नी त्याच्यासोबत राहत नाही. त्याच्या स्वप्नांच्या चुराडा होतो. 'बारोमास' या कादंबरीत मांडलेल्या एकनाथ या एका शेतकऱ्याच्या मुलाची कहाणी नसून संबंध देशातील शेतकरी मुलांची कहाणी आहे. प्रत्येक शेतकऱ्यांच्या नशिबी बेकारीचा प्रश्न 'आ' वासून उभा राहिलेला आहे. म्हणजेच, सर्वसामान्य शेतकरी हा आर्थिक विवंचनेत दिवस काढत आहे."[१]

शेतकऱ्याच्या मुलांची होणारी फरफट ग्रामीण कादंबरीतून चित्रित होताना दिसून येते.राजन गवस यांनी 'कळप' व 'तणकट' या कादंबरीतून शहर व गाव यातील नेमके अंतर प्रभाविपणे व्यक्त केले आहे. किशोर सानप यांच्या 'पांगुळवाडा' या कादंबरीतून खेडयातून शहराकडे जाणाऱ्या लोकांची मानसिकता, ग्रामीण जीवनाचे होणारे 'स्थित्यंतर' या कादंबरीत टिपले आहे. तर रमेश इंगळे यांनी 'निशाणी डावा अंगठा' २००५ या कादंबरीतून आजची बदलत चालेली ग्रामव्यवस्था, शाळा, दवाखाने याचे यथार्थ चित्रण केलेले आहे. तर प्रतिमा इंगोल यांची बुढाई, अप्पासाहेब खोत यांची गाव पांढरीच्या वाटेवरी, प्रशांत पोखरकर यांची गाव ढासळत आहे, भारत काळे यांची ऐसे कुणबी भूपाळ, प्रकाश देशपांडे यांची बारदान, कृष्णात खोत यांची रौंदाळा, अशोक कोळी - कुंधा, महेंद्र कदम- धुळपावल, कैलास दौंड – कापूस काळ, पांडुरंग कुंभार– गावकूस, पाणधुई, मोहन पाटील- साखरपेरा, हया कादंबऱ्या नव्वदोत्तरी ग्रामीण कादंबरीची वाटचाल सांगणाऱ्या आहेत.

बदलेली ग्रामीण मानसिकता :-

पारंपरिक ग्रामीण अर्थव्यवस्थेत ग्रामीण माणूस, ग्रामीण शेतकरी हा सुखी-समाधानी होता. परंतु जागतिकीकरणाने ग्रामीण पारंपरिक अर्थव्यवस्था बदलून नवी अर्थव्यवस्था वसत आहे. आज शेती करणे परवडण्याजोगी राहिली नाही. जागतिकीकरणामुळे सामान्य माणसाच्या हातात नवे तंत्रज्ञान आले. मोबाईलव्दारे घरात बसून शेतीतील मोटरपंप चालु किंवा बंद करता येईल, असे तंत्रज्ञान विकसित झाले. शिक्षणाच्या माध्यमातून नोकरी उद्योगात शिरकाव झाल्यामुळे खेडेगावातील नव्या पिढीचे राहणीमान बदलले. गावातील प्रत्येक घरावर टि. व्हि. डिश. लावलेल्या दिसू लागल्या, मॉल संस्कृती वाढीस लागली, प्रसारमाध्यमाच्या प्रसारामुळे जगात घडणारी प्रत्येक गोष्ट क्षणात सर्वत्र पसरु लागली. दुसरीकडे बहुराष्ट्रीय कंपन्यांच्या मुक्त संचारामुळे शेतकऱ्यांच्या शेतात पिकलेली फळे, भाजीपाला, धान्य हे कवडीमोल भावाने विकले जाऊ लागले. तोच माल आकर्षक पॅकिंगमध्ये या कंपन्या बाजारात आणून जास्त किंमतीत विकून मोठया होऊ लागल्या. नव्या तंत्रज्ञानाच्या आगमनासोबत अवर्षणासारख्या आपत्तीमुळे अपेक्षाभंगाचे दु:ख वाढून कर्जाचे ओझे शेतकऱ्यांच्या मानगुटीवर वाढायला लागले. असह्य होणाऱ्या ताणाची परिणीती शेतकऱ्यांच्या आत्महत्येस होऊ लागली. "शेती नीट पिकत नसेल तर ती विकून टाकावी आणि त्या पैशात पोटापाण्यासाठी दुसरा उद्योगधंदा बघावा दुकान टाकावे किंवा पाण्याची व्यवस्था करुन बागाईत करावी अर्थात बागायती शेती करुन शेतीमालाला भाव मिळत नसेल तर मग सरळच विकून टाकावी. अशीही भयंकर मानसिकता ग्रामीण भागातील शेतकरी कुटुंबातून निर्माण झाली"[२] आधुनिकीकरण व जागतिकीकरणाची ही दुसरी बाजूही विचारात घ्यावी लागेल. या सर्वाचे दर्शन या कालखंडातील ग्रामीण कादंबरीतून घडत गेले. अशोक कोळी यांच्या 'पाडा' (२००६) सुरेंद्र पाटील यांच्या चिखलवाटा (२००७) अशा काही कादंबऱ्यातून हे नव्या यंत्राचे आधुनिकतेचे वारे आणि त्याच्या झंझावात वाहून जाणारा ग्रामीण समाज याचे चित्रण आलेले आहे.

भ्रष्टाचाराचा भंयकर विळखा :-

ग्रामीण भागात या कालखंडात भ्रष्ट व्यवस्थेचा शिरकाव होत गेला. शिक्षण संस्थामधून नवशिक्षतांची पिळवणूक होऊ लागली. साखर कारखाने, दुध संस्था, सहकारी सोसायटयां मध्ये मक्तेदारी वाढीस लागली. या संस्था आपल्याकडे टिकवून ठेवण्यासाठी राजकारण गलिच्छ थरावर पोहोचले पैशातून सत्ता व सत्तेतून पैसा असे नवे समीकरण उद्यास आले. गुंडाचा शिरकाव झाल्यामुळे राजकारणातील स्वच्छ चारित्र्याची माणसे बाजूला गेली. सामान्य माणूस या भ्रष्ट व्यवस्थेत भरडला गेला. शेती करणारे, व्यवसाय करणारे नोकरी करणारे असे सारेच या व्यवस्थेतील सत्तास्थानाचे गुलाम झाले. या सगळया परिस्थितीचा परिणाम म्हणजे शेतकऱ्यांची आर्थिक स्थिती कमालीची खालावली. त्यामुळे यांचे पडसात ग्रामीण कादंबरीवरती पडणे साहाजिक होते. शेतकऱ्याच्या आर्थिक परिस्थिती विषयी लिहिताना देशपांडे म्हणतात की, " ग्रामीण जनतेवरील म्हणजे मुख्यत्वे शेतकऱ्यांवरील कर्जाचे

ओझे वाढले. भारतातील बहुसंख्य शेतकऱ्यांना दारिद्र्यामुळे विविध गरजा भागविण्यासाठी वेळोवेळी कर्ज काढावे लागले. मग त्या गरजा कृषीसंबधी असोत की अनुत्पादक स्वरुपाच्या (लग्न ,धार्मिक सणसभारंभ अथवा कार्य) असोत कर्जाचा उपयोग उत्पादक कार्यासाठी करुनही त्यांची आर्थिक स्थिती विशेष न सुधारल्यामुळे कर्जाचा व त्यावरील व्याजाचा भार सतत वाढतच जाऊन ग्रामीण जनता ऋणग्रस्त होते."[३] तसेच राजकीय लोक स्वार्थासाठी समाजाची विभागणी गटागटात करतात. त्यामुळे सामान्य माणूस आपआपसात भांडत बसतो. देश स्वतंत्र होऊनही त्याच्या नशिबी पारतंत्र्यच आहे. "स्वातंत्र्यानंतरचा समतेचा लढा इथेच उभारला गेला. शेतकऱ्यांच्या हक्कासाठी संघर्ष घडले ते इथेच अमेरिकन मिशनंन इथ शैक्षणिक व सामाजिक सेवेचा आदर्श उभा केला. इथल्या सेवाभावी कार्यकर्त्यांनी शिक्षण संस्थाचे जाळ गुफलं आणि खेडयापाडयापर्यत ज्ञानाचे पाझर पोहोचले"[४] आर्थिक दारिद्रय त्यातून व्यसनाधिनता आजार अशा समस्यांच्या गर्तेत ग्रामीण समाज ओढला गेला. सारी ग्रामव्यवस्थाच रसातळाला जाऊ लागल. एकविसाव्या शतकातील ग्रामीण कादंबरीत हेच चत्रित व्हायला लागले. व. बा. बोधे यांची 'पाननिवळी' (२००७) आणि सुरेशकुमार लोंढे यांची 'शाळा आणि माती' (२००७) अशा काही कादंबऱ्या यादृष्टीने महत्त्वाच्या ठरतात.

वाढती बेकारी :-

ग्रामीण भागात शिक्षणाचा प्रसार वाढल्यामुळे नवीन पिढी शिक्षित झाली. शिक्षणाच्या काळात त्यांची शेतीकामाची सवय मोडते. पदवीधर झालेले हे तरुण शेतीकाम करीत नाही. दुसरीकडे एवढे शिक्षण घेतलेल्या या तरुणांना नोकऱ्या मिळत नाहीत. त्यांनी घेतलेले शिक्षण निकामी ठरते. शिकवण्यासाठी आई बापांनी केलेल्या खर्च वाया जातो. अनेकांनी शेती विकून कर्ज काढून मुलांना शिकवलेले असते. काहीनी कष्ट करुन मुलांना शिकवलेले असते. त्यांच्याही आशा फोल ठरतात. नवशिक्षितांची ही नवी पिढी सैरभैर झालेली आहे. मुले शिकली तरी नोकरी मिळत नसल्यामुळे बेकारी वाढते. काही शेतात काम करतात. उपवर मुलींचे बाप आपल्या मुलींचे लग्न अशा नोकरी नसलेल्या मुलांबरोबर करण्यास तयार होत नाहीत. लग्नासाठी नोकरी मिळणे महत्त्वाचे होऊ लागले आहे. सदानंद देशमुख यांच्या (बारोमास) २००२ या कादंबरीत याचे चित्रण येते.

समारोप :-

शेतकऱ्याला बारा महिने शेतात राबावे लागते. श्रम हेच त्यांचे भांडवल असते व त्याचीच गुंतवणुक करावी लागते. नवी पिढी शिकल्यामुळे तिला हे श्रम नको वाटतात त्यातून आर्थिक समस्या निर्माण होतात व त्यांना आत्महत्येसारख्या वाईट मार्गाला जावे लागते. वाढता खर्च कमी उत्पन्न यामुळे ग्रामीण भागातील माणसाला संसाराचा भार सहन होत नाही. तो आत्महत्येकडे वळतो. आज नवनविन तंत्रज्ञान येत आहे परंतु त्यासाठी पैसा शिल्लक राहत नाही. निसर्गाची अवकृपा, अतिवृष्टी, दुष्काळ शेतमालाला भाव न मिळणे, वाढती महागाई यामुळे शेतकरी हवादिल झालेला दिसतो व या सर्व परिस्थितीचे वर्णन या कालंखडातील कादंबऱ्यातून आलेले आहे.

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INDEX

Sr. No.	Title	Author Name	Page No.
1	Study of Muscular Endurance of School Students from Nashik District	Dr. Sopan Kangane Dr. Sunil More	1
2	Comparison of Psychological Barriers Among Competitive and Amateur Players	Dr. Yogesh Bodke Dr. Santosh Pawar	4
3	A Comparative Study Of Motion Examination Of Forehand Overhead Clear Stroke And Relationship Of Anthropometric Estimations At The time of Contact Stage in Badminton	Mr. Vijay B. Singh Dr. Balwant Singh	8
4	A Study On Speed And Strength Variables Of Indian Male Long Jumpers In Relation To Performance	Dr. Nilima Deshpande Dr.R. Subramanian Dr. Neha Ms Chaitaly Nandy	16
5	Comparative Study of Selected Physiological and Physical Variables of Inter Collegiate Level Baseball and Softball Players	Mr. Ravindra A. Kadane Dr. Bhaskar Reddy S. N.	21
6	Effect Of Meditation And Yogic Pranayama On Selected Physical And Physiological Variables	Mrs.S.Anbu Nisha Jeba Soundar Dr.S.Saroja	25
7	A Comparative Study Of Agility Ability Among The Kho-Khoand Football Players	Mr. Rupesh Vasant Rupwate	29
8	A Comparative Study On Body Composition And Physical Fitness Of Amature, State And National Level Adolescent Archers Residing In Mumbai.	Urmi Hariya Subhadra Mandalika	32
9	A Comparative Study on Selected Physical Fitness Components of Karate and Taekwondo Male School Players	Shiva Raj Bhatt	39
10	A Study on Injuries during Badminton Sports	Dr. Rajendra S. Raykar	43
11	Effect of Integrated Training Program on Selected Social Variables of Degree College Male Students	Dr. Aditya Anil Kulkarni Vishal Prakash Gaikwad	47
12	Effect of Pranayama on Recovery of Students undergoing Police Recruitment Training at Maharashtriya Mandal Vyayamshala, Pune	Dr. Ameet Dattaram Prabhu	52
13	A Study of Anthropometrical, Physical fitness and Skills of Indian Roll Ball players participating at the International Level	Mr. Anand Mohan Yadav Dr. Sharad Shankarrao Aher	55
14	Study of Attitude towards and Physical Fitness Knowledge of Physical education Teachers of Elementary School Ahmednagar District	Mr. Satish D. Chormale Dr. Bhaskar Reddy S. N.	62
15	Effect of Yoga Training Program on Selected Skill Related Physical Fitness Factor & Shooting Performance of Inter School Male Basketball Players	Mr. Navanath M. Sarode Dr. D. K. Kamble	68
16	Assessment Tools for Physical Literacy Self Perception amongChildren and Adolescents: A Review	Beulah Sebastian Savio Viegas	72

95	Effect of Acupressure Program on Selected Fitness Variable of Kho-Kho Players Aged Between 14 to 18 Years	Dr. Shirish More Dr. Yogesh Bodke	436
96	Effect of Suryanamaskar on Selected Physical Fitness Variables of Stay at Home Peoples of Nashik City	Ravindra R. Chavan Dr. Vishwasrao. K. Kadam	439
97	Health Related Fitness And Its Impact On Sports Performance	Dr. Vijay L. Mhaske Prof. Vilas Uttam Elke	444
98	The Study of Exercise Adherence Ttechniques Used by Male Exercise participants at Maharashtriya Mandal	Mr. Kumar Krishnanand Upadhyay Dr.Balaji Satwaji Pote	449
99	Caparison of Health-Related Physical Fitness Factors of Pune City and Pune District First Year Under-Graduate Girl Students of Savitribai Phule Pune University	Dr. Shrikant Mahadik	452
100	Psychological Effect of Injury on the Athlete	Ulhas V. Bramhe	456
101	Relationship Of Yoga, Immunity, Diet And Corona Virus-19 (Covid-19)	Dr. Rahul Rajan Bhosale	460
102	A Brief Study on new innovative factors to analyze coaching patterns for Indian Sports	Dr. Pradeep S Patil	464
103	Study of Health-Related Physical Fitness and Teaching Ability of Male Teacher Trainer	Dr. Balaji S. Pote	475
104	The Super Food Daliya Upma, theNutritionally Dense Recipe for Fueling & Nourishing Athlete	Samarth Mahesh Deshpande Dr. Mahesh Deshpande	478
105	To Study the Health Effects of Slum Area in Pune City	Dr. Sheetal Laxman Shendkar	485
106	Analysis of Motor Fitness Components Between Different Sports	Dr. Yogesh Bodke Mr. Sachin Kamble	488

HEALTH RELATED FITNESS AND ITS IMPACT ON SPORTS PERFORMANCE

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ABSTRACT

Regular exercise and physical activity promotes strong muscles and bones. It improves respiratory, cardiovascular health, and overall health. Staying active can also help you maintain a healthy weight, reduce your risk for type 2 diabetes, heart disease, and reduce your risk for some cancers.Aerobic exercise, like running and swimming, appears to be best for brain health. That's because it increases a person's heart rate, "which means the body pumps more blood to the brain," says Okonkwo. But strength training, like weight lifting, may also bring benefits to the brain by increasing heart rate. Health related physical fitness is primarily oriented towards systematic development of motor abilities and their manifestation through sports skills. Health related physical fitnessis help to improve sports performance. In Sports performance stamina, muscle strength, and body movement is important. It is develop by physical fitness training. Health-related components focus on factors that promote optimum health and prevent the onset of disease and problems associated within activity.

INTRODUCTION

To improve health and fitness effectively through physical activity or exercise, we need to understand how this comes about. For many of these changes, the stimulus has been grossly defined in terms of type, intensity, duration, and frequency of exercise, but for others a dose-response relationship has not been determined. Physical activity that appears to provide the most diverse health benefits consists of dynamic, rhythmical contractions of large muscles that transport the body over distance or against gravity at a moderate intensity relative to capacity for extended periods of time during which 200 to 400 kilocalories (or 4 kilocalories per kilogram of body weight) are expended. For optimal health benefits, such activity should be performed daily or at least every other day and should be supplemented with some heavy resistance and flexibility exercises. The greatest benefits are achieved when the least active individuals become moderately active; much less benefit is apparent when the already active individual becomes extremely active. Overexertion or inappropriate exercise can produce significant health risks. Research is needed to characterize better the health-promoting features of physical activity and exercise.

Sports performance is to enhance one's performance in competition and increase one's potential for success in a chosen sport or everyday activity.Sports performance is the execution of specific physical routines or acts by an athlete while participating in a sport or activity.

Components of health related fitness :

Health related fitness divided into five parts

Cardiovascular Endurance

Cardiovascular fitness is the ability of the heart (cardio) and circulatory system (vascular) to supply oxygen to muscles for an extended period of time. Cardiovascular is also called cardiorespiratory (lungs) fitness. Usually the mile run or some other type of continuous fitness activity (12 minute run, cycling, step-test, etc.) is used to assess

Cardiovascular fitness.Cardiovascular, which is synonymous with cardiopulmonary exercise or "Cardio", is aerobic physical activities that last longer than 90 seconds.Cardiovascular or cardiopulmonary endurance is your physical ability to maintain aerobic exercise for prolonged periods of time.Physiologically, cardiovascular endurance deals with the efficiency of your body's (heart, lunges and vascular system) ability to transfer oxygen rich blood to your working muscles during activities that last longer than 90 seconds.

Important of Cardiovascular Endurance

Life without exercise or physical Fitness contributes to the early onset and progression of life style disease such as cardiovascular disease, hypertension, diabetes and obesity.

The importance of cardiovascular fitness to health for all individuals has been well documented. Physical fitness is a required element for all the activities in our life. Cardiovascular fitness of an individual is mainly dependent on lifestyle related factors such as daily physical activity levels. It was believed that the low cardiovascular fitness level of an individual is associated with higher mortality rate. (jourkhesh et.al.2012).Cardiovascular endurance is very important because the more cardiovascular fit you are, the healthier your lungs, heart and vascular system is. While exercising this may be obvious to you but there is more. If you demonstrate high levels of cardiovascular endurance during exercise you also have more efficient heart, lungs and vascular system while at rest which takes up the bulk of your time. This means less stress is put on your heart and lungs around the clock which enables you to avoid illness and live a long healthy life. Many argue that cardiovascular endurance is the most important of the 5 components to physical fitness.

In sports cardiovascular endurance is important for improves your posture and health, Enhances stamina which improves your performance ability, Boosts your immune system and reduces the risk of injury, Increases oxygen supply to muscles – efficient functioning Improves your anaerobic ability, Reduces the risk of fatigue, enhances concentration and reduces stress levels.

MUSCULAR STRENGTH

Muscular strength refers to the maximum amount of force a muscle can exert against an opposing force. Fitness testing usually consists of a one-time maximum lift using weights (bench press, leg press, etc.). Muscular strength is the amount of force your muscle can exert against resistance for short duration, anaerobic (without oxygen) activities. Resistance includes external objects such as free weights or household objects as well as your own body weight.Physiologically, muscular strength it is the ability to your body to supply ATP (Adenosine Tri-Phosphate or muscle energy) to your muscle fibers for concentric, eccentric and isometric contractions in short times, which range from 0 to around 15 seconds.

IMPORTANT OF MUSCULAR STRENGTH

While muscular strength may be subjective, the primary reason why muscular strength is important is your efficiency at Activities of Daily Living (ADLs). ADLs one of the most important reasons why being proficient at all 5 components of physical fitness is important. At the very least, to be physically fit for in the muscular strength department, you should demonstrate the basic muscular strength needed to efficiently your ADLs. While ADLs vary from person to person, you can also consider activities such as push-ups, pull-ups and carrying heavy objects as ADLs. Even though each of the 5 components of fitness depends on one another, poor muscular strength can also affect aerobic fitness and muscular endurance negatively.

Muscular strength can enhance the ability to perform general sport skills such as jumping, sprinting, and change of direction tasks. Muscular strength allows an individual to potentiate earlier and to a greater extent, but also decreases the risk of injury.Greater muscular strength when it comes to improving an individual's performance across a wide range of both general and sport specific skills while simultaneously reducing their risk of injury when performing these skills.

In sports muscular strength is important forincrease your ability to do performance in sports without getting tired, Reduce the risk of injury, Help you keep a healthy body weight, Lead to healthier, stronger muscles and bones and Improve confidence and how you feel about yourself.

MUSCULAR ENDURANCE

Muscular endurance refers to the ability of the muscle to work over an extended period of time without fatigue. Performing pushups and sit-ups or crunches for one minute is commonly used in fitness testing of muscular endurance. While muscular strength deals with short duration muscle contractions muscle endurance deals with sustained muscle contractions and other anaerobic activities lasting less than about 90 seconds.Muscular endurance is the bridge between muscular strength and cardiovascular endurance. In order to be cardiovascular fit, you must demonstrate muscular endurance.Physiologically while muscle strength deals primarily with type II, fast twitch muscle fibers, muscular endurance deals with primarily type I, slow twitch muscle fibers. Your body contains both but only anaerobic exercises which last longer than around 15 seconds and less than 90 seconds strengthen your type I muscle fibers.

In sports muscular endurance is important forhelping maintain good posture and stability for longer periods, improving the aerobic capacity of muscles, improving the ability to carry out sports performance activities, increasing athletic performance in endurance-based sports.

FLEXIBILITY

Flexibility is the range of motion possible for each of your joints or groups of joints. To some degree, your flexibility determines how efficiently your muscles are. Increased flexibility has also been associated with decreased risk of acute and chronic (overuse) injuries. Poor flexibility can directly affect cardiovascular endurance, muscle strength and muscular endurance. Physiologically flexibility can include extra-muscular (range of motion at a joint) and intramuscular factors such as hyper tonicity (knots) within the muscles themselves.

Flexibility is important for completing sports activities with ease, increased joint mobility, better posture, decreased back pain and a lower risk of injury. Improved performance of daily sport performance activities, Improved performance in sport, Enhanced joint health, Relief of pains.Relief of muscle cramps, Relaxation and stress relief (mental and physical), Improved posture and balance.

BODY COMPOSITION

Body composition is the percentage of your body's tissues which you exhibit. The easiest way to look at body composition is with a 2 compartment analysis which estimates the amount of body fat you have with lean body mass which includes muscle, bone, water, and organs. It takes expensive equipment for a 3 compartment analysis which isolates bone mass which can also be considered an important part of body composition. You could say body composition depends on the other components of physical fitness. Having a poor body composition has many negative physical and psychological effects such as increased chance of a host of chronic diseases and depression. As mentioned previously, improper exercise habits and choices can not only lead to being overweight and obesity, but decreased bone mass associated with osteopenia and osteoporosis.

NEED OF PHYSICAL FITNESS

Regular physical activity can improve your muscle strength and boost your endurance. Exercise delivers oxygen and nutrients to your tissues and helps your cardiovascular system work more efficiently. And when your heart and lung health improve, you have more energy to tackle daily chores. Regular physical activity can help children and adolescents improve cardio respiratory fitness, build strong bones and muscles, control weight, reduce symptoms of anxiety and depression, and reduce the risk of developing health conditions. Exercise can help provide: Sharper memory and thinking. The same endorphins that make you feel better also help you concentrate and feel mentally sharp for tasks at hand. Exercise also stimulates the growth of new brain cells and helps prevent age-related decline

IMPACT ON SPORTS PERFORMANCE

Health related physical fitness training can improve stamina, strength, body movement and body posture. Physical fitness leads to better athletic performance, and persistent training will usually develop physical fitness. Ability of the endurance athlete to use oxygen is related to circulatory and respiratory capacity, but in sprints, weight lifting, and swimming there are many other important specifics. In sports, good physical fitness can increase the efficiency of learning sports skills, but also can reduce the incidence of injuries and accidents caused by the movement.Maintain and improve sports performance by health related physical fitness training.

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CONTENTS OF ENGLISH

S. No.	Title & Author	Page No.
1	Strategic Location of Bhaje Caves with Respect to Ancient Trade Routes in Western India **Samir Vasant Mankar**	1-9
2	Hostel Movement in Solapur **Dr. Dhanaji B. Masal**	10-16
3	Review of Literature on Lokmanya Bal Gangadhar Tilak **Dr. Nalini Avinash Waghmare**	17-24
4	Tilak Views on Nationalism **Dr. Suma. S. Nirni**	25-29
5	Political Ideas of Bal Gangadhar Tilak's **Dr. Nivedita Swami**	30-36
6	Mesolithic Culture of Karha Basin, Pune District, Maharashtra **Dr. Kshirsagar Shivaji Dadaso**	37-42

CONTENTS OF MARATHI PART - II

अ.क्र.	शोधनिबंध आणि लेखकाचे नाव	पृष्ठ क्र.
१	अण्णाभाऊ साठे यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदान **डॉ. गंगणे जीवन सुदामराव**	१-५
२	सत्यशोधकीय विचारवंत आण्णाभाऊ साठे **प्रा. डॉ. सावंत जे. सी.**	६-९
३	साहित्यिक अणाभाऊ साठे यांचे योगदान **डॉ. उर्मिला क्षीरसागर**	१०-१४
४	अण्णाभाऊ साठे यांच्या निवडक कथात्मक साहित्यातील स्त्री चित्रण **प्रा. डॉ. सौ. कल्पना राजीव मोहिते**	१५-२१
५	आण्णाभाऊ साठे यांच्या साहित्यातील मानवतावाद संघर्ष आणि स्थानिक इतिहासाचे वास्तववादी चित्रण **प्रा. डॉ. वंदना रा. लोंढ**	२२-२५
६	खिरविरे येथील सावकारांच्या वह्यांची होळी (७ नोव्हेंबर १९४९) **डॉ. गणेश शंकर विधाटे**	२६-२८
७	दुसऱ्या महायुद्धातील यशवंत घाडगे यांची कामगिरी **किरण गणपत कुंभार**	२९-३१
८	प्रजाहितदक्ष जयसिंगराव घाटगे **राजेंद्र मा. घाडगे**	३२-३६
९	घारापुरी लेणीचा एक ऐतिहासीक अभ्यास **डॉ. भानुदास धोंडिबा शिंदे**	३७-४१
१०	डॉ. संजीवनी सतीष केळकर यांचे कार्य **डॉ. एस. एन. गायकवाड**	४२-४५
११	उत्तर पेशवेकालीन तुरुंग व्यवस्था **प्रिया ब्रिजेश कुलकर्णी**	४६-४८
१२	शेतकऱ्यांच्या व्यथा व महात्मा फुले यांचे उपाय **प्रा. कोकाटे अनिल दत्तात्रय**	४९-५२

CONTENTS OF MARATHI PART - II

अ.क्र.	शोधनिबंध आणि लेखकाचे नाव	पृष्ठ क्र.
१३	इ.व्ही. रामासामी पेरीयार यांनी केलेल्या अस्पृश्योद्धार कार्याचा चिकित्सक अभ्यास - एक ऐतिहासिक आढावा **प्रा. अरूण वसंत अवसरमल**	५३-५९
१४	भारताची आण्विक नीती **प्रा. सुनिल लक्ष्मण परदेशी**	६०-६४
१५	महाराष्ट्राच्या जडणघडणीत अण्णाभाऊ साठे यांचे योगदान **प्रा. किशोर शेषराव चौरे**	६५-६८
१६	तलासरी तालुक्यातील आदिवासी 'वारली' समाजाची लोकगिते **डॉ. सौ. हेमलता यु. मुकणे**	६९-७४
१७	महात्मा गांधी आणि अस्पृश्यता जातीभेदाच्या विशेष संदर्भात **प्रा. मनिषा श्रेणिककुमार पाटील**	७५-७९
१८	संयुक्त महाराष्ट्र चळवळीत अण्णाभाऊ साठे यांचे योगदान **डॉ. माणिक सोनावणे**	८०-८५

1. Strategic Location of Bhaje Caves with Respect to Ancient Trade Routes in Western India

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Abstract

In between 2nd century B.C.E. to 2 ndcentury C.E. trade of India with Roman empire reached to zenith. Coincidently same period also considered as golden period of Buddhism. Both men and women from various strata of society like rulers, warriors, farmers, monks , Indian as well as Yavana merchants donated caves, cisterns to Buddhist and Jain monks. Majority of caves are located in western ghat along theancient trade routes connecting to ports. Bhaje cave complex is considered to be one of the oldest caves in Maharashtra. The purpose of this study is to reveal the importance of the location of Bhaje caves with respect to trade routes of ancient India.It also aims to trace ancient trade route network leading to harbours of coastal Maharashtra with the help of existing ancient cave complexes in Western Maharashtra.

Keywords:- mainland caves, hinterland caves, port caves

Objectives

1. To study the strategic importance of the location of Bhaje caves with respect to trade routes connecting western coastal ports of contemporary Maharashtra to rest of India.
2. To trace thenetwork of ancient trade routes in Western Maharashtra with help of ancient cave temples.

Introduction

Bhajecave complex is a group of 22 rock cut caves dedicated to Hinayana Sect of Buddhism located 65 km north west to Pune (18.7284 ^{0} N,73.4815 ^{0}E)on old Pune- Mumbai highway in Mavaltaluka of Pune district in Maharashtra.In these caves one isChaitya and all other are viharas. These cavesdates back to circa 2nd century B.C.E.Eleveninscriptions havebeen recorded at Bhaje caves .A medieval fort Visapur is located 3 km south west of Bhaje caves (18.7199 ^{0} N,73.4880 ^{0} E) . 6 DonativeBrahmiinscriptions of Satavahana period have been recorded on this fortby ShobhanaGokhale.Bhaje caves are surrounded by other Buddhist caves i.e. Karle caves (18.78333 ^{0} N ' 73.4704 ^{0}E), Bedse caves (18.78333 ^{0} N ' 73.4704 ^{0}E)Patan caves (18.7329 ^{0} N ' 73.5001 ^{0} E) andLohgad caves (18.6943 ^{0} N ' 73.4873 ^{0} E). Chain of caves can be

observed at places like Ghorawadi, Bhandara, Bhamchandra, Pale, Uksan, Kambre, Kondane, Tikona fort caves etc.Within sphere of 20 km from Bhaje-Bedse-Karle cave complexes.All these caves are located in Mavaltaluka of Pune district. Cluster of cave complexes were once certainly interconnected with each other which could be the part of ancient trade routes.Inscriptions tells us that merchants made huge donations to those cave complexes. Cells or Viharas were not only used by monks but also by merchants to take halt. In Maharashtra about 200 such caves complexes exists. Majority of caves are located in western ghat i.e. in Kokan and Western Maharashtra.

Methodology

Research Design

Research paper is based on primary sources collected by field visits to some location sites and study ofBrahmi inscriptions on actual locations. Research paper is also based on secondary sources, electronic media, Google images, Blogs.

Area of study

Ancient cave complexes located in Pune, Satara, Raigad and Thane districts of Maharashtra.

Analysis

Location sites of ancient cave complexes,are analyzed. The collected data is presented in tabular form and analyzed in descriptive format.

Descriptions

Bhaje complex is dates back to circa 2nd century B.C.E. It is one of the oldest cave complex in Maharashtra [1].Recently early Brahmi inscription related to Jainism have been recorded on Lohgad fort[2].This inscription also dates back to circa 2nd century B.C.E. Other cave complexes i.e. Bedse, Karle, Ghorawadi, etc excavated later i.e. probably in circa 1st century C.E. Chain of cave complexes can be traced in Pune,Satara, Raigad, Mumbai, Thane districts of Maharashtra. veteran historian D.D.Kosambi stated that these cave complexes were located along the trade routes and this opinion is widely accepted by historians .Those cave complexes were not remote as they are today.In few donative inscriptions of cave complexes native place of donor merchants is also mentioned.

For convenience we can classify ancient cave complexes into 3 types based on their location, and area.

1. **Mainland cave complexes -** These cave complexes are large in area and size. Generally caves of these complexes are of 2 types.- a) Multi pillar , intricately carved

chaityas. b) Small cells or Viharsas. e.g. Bhaje , Karle, Bedse, Kondane, Manmodi, Lenyadri, Ghorawadi, Tulja etc.

2. **Hinterland caves** – These cave complexes are small in size. Generally these were viharas meant for taking rest e.g. Pale, Uksan, Kambre, Gadad, Tikona caves, Lohgadcaves, Nadsur, Khadsamble, Pataleshwar, Parvati, Bhamchndra, Bhandara, Patan, Shirwal caves etc.
3. **Port caves** – This type of caves were located near to ancient sea ports of Maharashtra. e.g. Kuda, Ganhdarpale, Kanheri, Mandapeshwar, Bahrotcaves etc.

Observations

Observations regarding Chain of cave complexes are presented in following table no. 1

No	Mainland Caves	Hinterlad Cave network	Port Caves
1	Bhajecaves, Bedse caves	Visapurfort, Lohagad caves, Tikona caves, Yelghol Caves, (Mavaltaluka, Puneditrict) Thanale caves (Sudhagadtaluka, Raigad district.)	Hingulja Devi cave temple [3] (Thane dist.
No	Mainland Caves	Hinterlad Cave network	Port Caves
2	Bhaje caves, Bedse caves	Tikona caves, Yelghol Caves, Khadsamble caves (Sudhagadtal, Raigad district.)	Kuda caves (Talataluka, Raigad dist.)
3	Bhaje caves, Bedse caves	Tikona caves, Yelghol Caves, Thanale caves Khadsamble caves,	Gandharpale caves (Mahadtal, Raigad dist.)
4	Bhaje caves, Karle caves	Sai caves, Pal caves, Uksan caves, Kambre caves, Kondane caves (Sudhagadtaluka, Raigad district.)	Lonad caves (Bhivandital. Thane dist.)
5	Bhaje caves, Karle caves	Sai caves, Pal caves, Uksan caves, Kambre caves, Ambivali caves (Karjattaluka, Raigad dist.)	Kanheri caves ,Baronda Devi caves [4]
6	Bhaje caves, Karle caves	Sai caves, Pal caves, Uksan caves, Kambre caves, Ambivali caves (Karjattal. Raigad dist.)	bahrot caves [5]

Contemporary donors who made donations of cisterns, cells, chaityasetc and alsomentioned their native places in cave inscriptions. These are inscribed in Brahmi script and Maharattiprakrit language. From these inscriptions connection of these caves with contemporary towns and ports can be traced. Further information is presented infollowing table no. 2(Courtesy-Cave Temples In Western India.)

No	Cave Location, and Inscription no.	Description
1	Kuda 20	कर्हाकडस[6] लोहवणियसमहिकसदेयधमलेणं
2	Bedase 3	नासिकानं [7] आनंदससेठीसपुतसपुसणकदानम
3	Karle 1	वैजयंतीता [8] सेठीनाभूतपलेनासेलघरंपरिनिथापितंजम्बुदीपम्हीउत्तम
4	Karle 11	धेनुकाकता[9]उसभपुतसमितदेवनकसथभोदानम
5	Karle 9	सोपारका[10]भयतांनघमुतारीयानामभानकसनांदापुतीससातीमितस सहतुयथभोदानमुलं
6	Junnar 1	भरुकच्छनम[11]लंकुडियानंभातुनंआसमसपुताणबुद्धमितसबुधराखि तसचविभागंदेयधम
7	Junnar 28	कल्लिअनकस [12] कुदीरपुतससुवणकारससंघकसपोढीदेयधम

(Courtesy- Cave Temples of Western India by BhagawanlalIndraji and James Burgesse)

Conclusive Remarks

Strategic location of Bhaje caves can be studied with the help of table no. 1 . From the above observations of cave locations, hypothetically following ancient trade routes can be traced.

1. Bhaje caves were connected to contemporary prosperous port Chaul which was described as Symulla or Chymulla in Ptolemy's Geographia andalso in the travel book Periplus of ErythraenSea.This route was perhaps leading to Chaul viaLohgad caves, Visapur fort, Bedasecaves,Tikona caves Yelghol caves. Thereafter crossing Tail-Bail fort and Sawashnighat[13] it leaded to Thanale caves and then from present Pali inRaigad district to Chaul port.Sawashnighat also leaded to Khadsamble caves near Sudhagad fort in Raigad district. This route leads to Mandad which is identified as ancient port Mandagora[14] situated on Rajapuri creek.Ptolemy's Geographia and Periplus of Erythraen Seadescribes port Mandagora located south to Chaul.Kuda caves are situated near Mandad town.Another route from Khadsamble cavesalso leads to Gandharpale caves. Village Pale is situated on Savitririver which is navigable till Bankot creek.

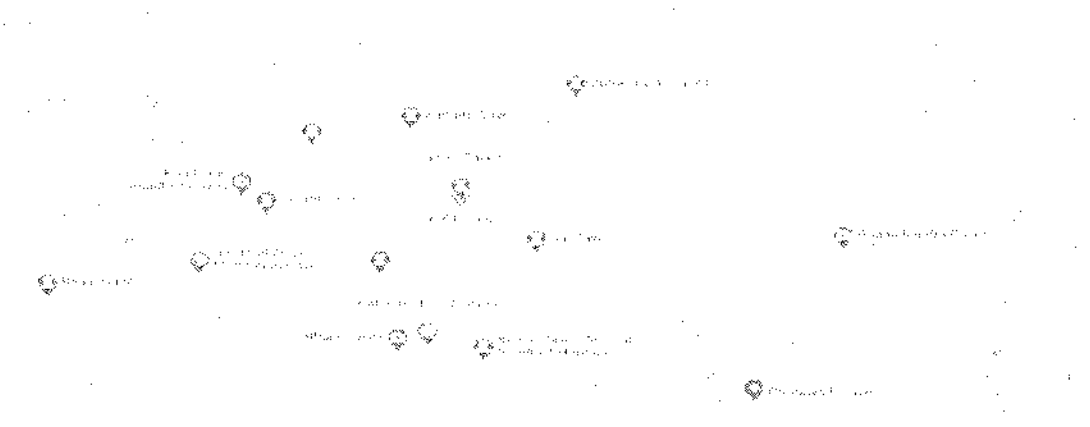
2. Prosperous port Calliana or Kalyan was connected to Bhaje caves via Karle caves that are seven kilometers north-west from Bhaje. Karle caves dates back to2ndC.E.. Cluster of caves at Sai, Pale, Uksan, Kambrewere connectingBhaje-Karle caves to Kusurghat[15].Itfurther leaded to Kondane caves and then to Kalyan port via karjat. Another route from Kusurghat leaded to

Ambivali caves, Bhivapuri,Gadad caves,Gorakhgad caves finally connected to Naneghat to reach flourishing ports Sopare, Dahanu, Sanajn,Bhadoch and also to Junnar.

3. Another chain of caves that can be traced from Bhaje caves is Ghorawadi caves,Bhandara caves, Bhamchandra caves (Mavaltaluka,Pune ditrict).This route was proceeding towards Junnar, earlier capital of Shakasandalso to Nasik,Ujjain .South to Ghorawadi caves, other caves can be traced vizBaner caves, Pataleshwar caves, Parvati caves, Sinhgad caves, (Haveli tal, Pune dist,) Shirwal caves, Patan caves, Wai caves Karhad caves (Satara dist.) . It shows connection of Bhaje caves to ancient towns Karhad, Banavasi via Ghorawadi caves.

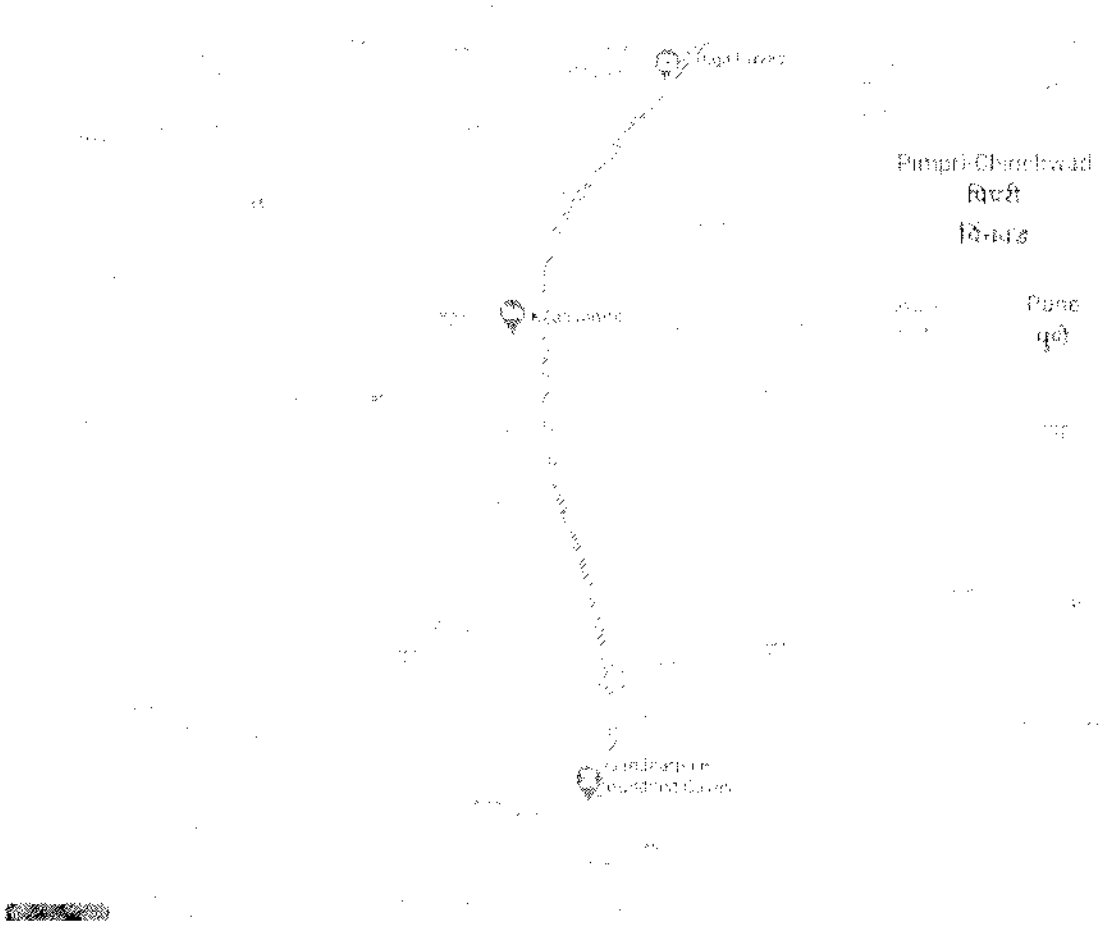
Thus hypothetically Bhaje cave complex was a junction, connecting ancient towns of Maharashtraand rest of India to the Ports in Kokan. It was playing pivotal role in Indo-Roman trade.A small village is located at base of fortVisapur and Bhaje named Patan. This name seems to be derived from sanskrit word Pattani.e.town.

(From right to left) Donative inscription of KosikiputtaVenhudatta at Bhaje caves (first).Donative inscription of same donor (second) onancient trade route (third) connecting Visapur fort to Chaul and Mandad port viaBedasecaves,Tikonacaves,Thanale caves, Khadsamble caves.

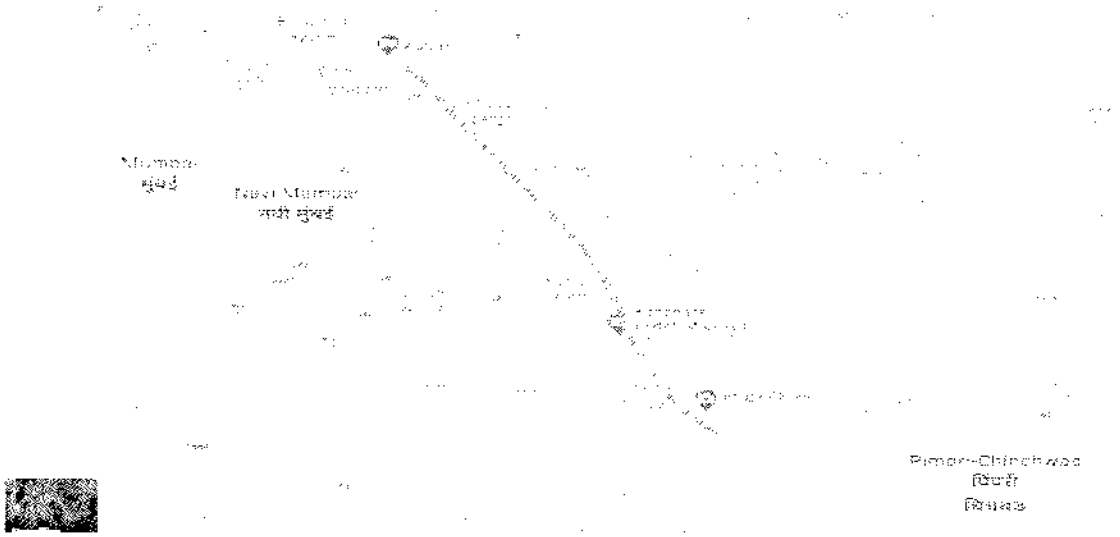


Cave complexes around Bhaje caves. (Above)

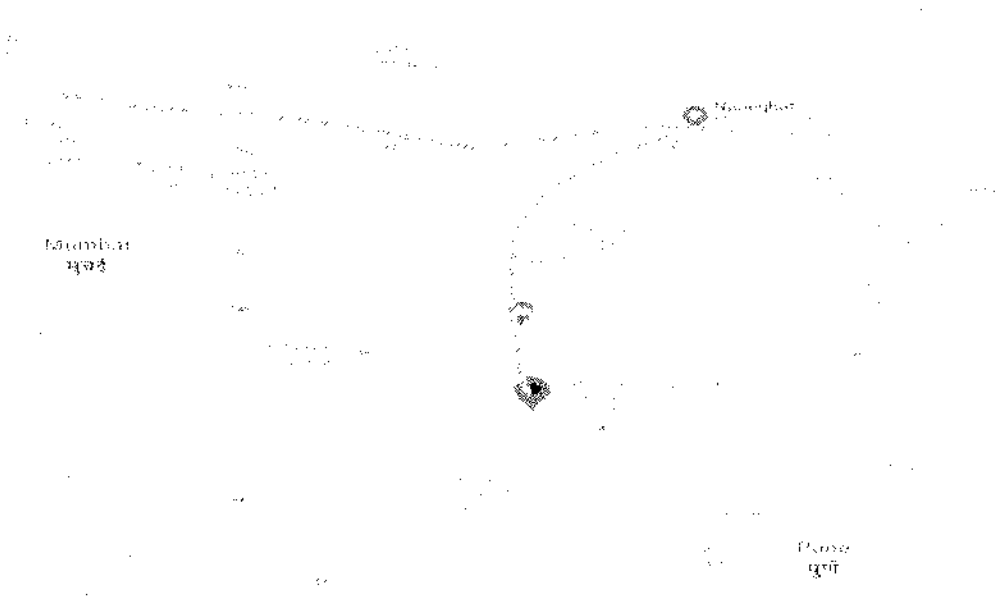
Route connecting Bhaje caves to Kuda caves or Mandad (Above)



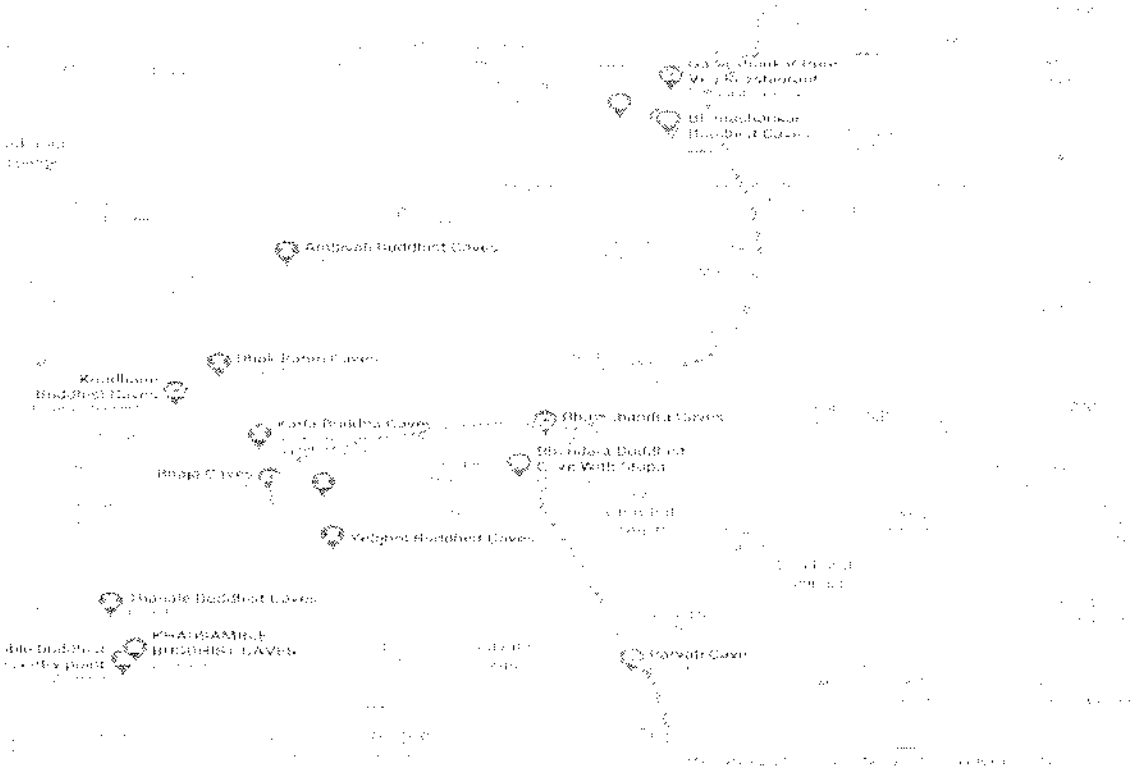
Route connecting Bhaje caves to Gandharpale caves via Khadsamble caves (Above)



Bhaje caves to Kalyan via Pale,Uksan, Kambre and Kondane caves. (Above)



Karle to Nallasopare,Dahanu,viaKusurghat and Naneghat. (Above)



Parvaticaves,Ghorawadi caves,Bhaje caves to Junnar ,Nasik and Ujjain

(Courtesy – Google Map)

1. Pitalkhora caves in Jalgaon district is considered as the oldest cave complex in Maharashtra.
2. Recently Noticed Inscription from Lohagadwadi, Fort Lohagad District Pune Maharashtra India – By ShrikantPradhan .Published in Ancient India Journal of the society of South Asian Archaeology. Jan. 2020.
3. Rock cut caves at Chaul (Thane district) now the temple of Hingulija Devi.
4. Rock cut caves at Nallasopara (Thane district) now the temple of Baronda Devi.
5. Rock cut caves at Dahanu (Talasarital. Palghar district) now the ParsiAgyari.
6. Karhad (Maharashtra),
7. Nashik (Maharashtra)
8. Banavasi (Karnataka),
9. According to some historian it is present Dharanikota (A.P.) While some says it is Benakat (Maharashtra) and it is also considered to be present Dahanu (Maharashtra)

10. Nallasopara (Maharashtra),
11. Bhadoch (Gujarath)
12. Kalyan (Maharashtra)
13. Connects Pune district to Raigad district via Tail-Bail fort and Sudhagad fort.
14. "The Hippocampus of Kuda: A Mediterranean Motif which Validates the Identification of the Indo-Roman Port of Mandagora."Published in Journal of INDIAN OCEAN ARCHAEOLOGY Number 13-14, 2017-18. Town Mandad-Kuda, Tal.Tala, district Raigad in Maharashtra is identified as ancient port Mandagora.
15. Starts from Kusur in Mavaltaluka in Pune district and ends at Bhivapuri in Karjattaluka in Raigad dist.

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2. Hostel Movement in Solapur

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Keywords: Talim Master, Digamber Jain, Religious education, Moral Sciences, Musthi Fund, Rao Bahadur, Dharmaday Nidhi, Female Education.

Introduction

Education flourished with the auxiliary institutions like hostels, boarding, library, etc. Out of the auxiliary institutions hostels are essentials in the period British Reign. In those days caste system was so rigid and the students came from the rural areas in the city for the education. There was no lodging and boarding facilities available for them. It was the hindrance in the educational developments. In Solapur Christian Missionaries took a lead in the field of education. Thereafter other communities started their educational activities. When the various communities started their educational activities. The students felt the need of lodging and boarding facilities. Thus the absence of hostels and rigidity in caste system became hindrance in the educational development. The people from Hindu, Christian, Muslim Bouddh, Jain, Shikh, Padmshali, Lingayat, etc. communities are in the large scale. Amongst them the first hostel was started by Jain community and were followed by the Lingayat, Christian, Padmshali, Maratha, Brahmin, Backward Communities and others.

Hypothesis of the Study

The present study will endeavor to test the following hypothesis. The Hostel movement is essential for the spread of education in all strata of the society and rural areas. Because of the hostel movement, the citizens of good characters are created for the nation building from the students. The hostel movement of Solapur growing on without any common leadership, but the many leaders of the particular castes and communities came forward for the upliftment of their own community and Hostel movement came into existence.

Objectives of the Present Study

The major objectives of the present study are listed below:

1. To study the efforts of the eminent personalities of the educational field of the city, who were took lead for the hostel movement in the city.

2. To focus on the hostel movement in the city, which came into existence without any common leadership.
3. To focus on the communal harmony of the city in the field of education.
4. To study the role of the hostels in the freedom movement of India.

Methodology and Resources

The present study is basically library based and fully relies on the primary and secondary data. The data is collected by the visited to the hostels and boardings of the Solapur city. The data is collected from the souvenirs, periodicals, proceedings, annuals and notebooks of the related various hostels of the city. Some unpublished Ph. D. thesis, newspaper clippings from Daily Anandvritta Ani Kalptaru as well as Solapur Samachar are also used for this study. Interview of the eminent personality of the education field of the city is helpful for the cross checking and the lacuna of the information. Bombay Legislative Council Debates, Files of the Education Department from the Bombay Archives are also used for the data collection. All this collected data interpreted in the light of the hypothesis and objectives of the study.

Gandhi Natha Rangaji Digamber Jain Boarding

The Hirachand Gumanji Jain Boarding, Bombay was the first Jain Boarding in the Presidency. Ramchand Natha Gandhi of Akluj created a 'Gandhi Natha Rangaji Digamber Jain Unnati fund' in 1905, for investment towards the development of the Jain community. He came into contact with Manikchand Hirachand of Bombay and on his suggestion decided to start a boarding at Solapur with the help of Hirachand Nemchand Doshi. They started 'Gandhi Natha Rangaji Digamber Jain Boarding on 12th March 1908. He handed over the Jain Unnati fund of Rs. 25,000 to the boarding trustees. In its establishment and all activities Hirachand Nemchand Doshi took initiation.[1]

At first the boarding was started at Mangalwarpeth in a rented house. Then the trustees purchased land near Bale Ves and constructed a building of 24 rooms in 1913. The trustees appointed a Superintendent, a Panditji, a Talim Master and women workers for the kitchen for its management.[2] In 1933, its sister unit 'Gandhi Ramchand Natha Digamber Jain Boarding Chatralaya' was started by the 'Gandhi Ramchand Natha Memorial Committee'. It provided only accommodation facilities to Digamber Jain students. Its students took their education in the Jain Pathashala and meals in the Jain boarding[3]

In 1924, there were 70 students but they decreased to 41 in 1930, because of Martial Law during the Civil Disobedience movement. After the 1st World War and the Economic Depression (1929) the financial conditions of the merchants and commercial communities was in a bad situation, which had its effects on education. The students took part in the freedom movement and sacrificed everything in the freedom struggle. Most of the leading political personalities arranged their meetings in the boarding premises and took important decisions. During the Civil Disobedience Movement when martial law was enforced, Ranade, a student of this hostel died in police firing.[4] Due to the terrorist activities of the Razakars in 1948, some of these fugitives were given asylum on the premises of the Jain Boarding. The boarding also took a lead in the cultural movement by arranging mass physical training, lezim and games for exercise.[5]

Shri Madveershaiv Mahajan Sabha

Appasaheb Warad an eminent personality from the Lingayat community. He was influenced by the work of the 'K. L. E. Society' Belgum, which was doing valuable educational work in Karnataka. He organised the third conference of 'Veershaiv Mahajan Sabha' in 1907 under the Presidentship of Pattanshetti. The conference decided that an educational institution should be established for the education of Maharashtrian Lingayats.[6] Eminent Lingayat personalities of the city such as Appasaheb Warad, Annarao Patil, Mahalingappa Vajirkar, Mallikarjun Zunje, Mallikarjun Shete, Baslingappa Shetti etc., who were made efforts more than two years, then they established 'Madveershaiv Mahajan Sabha' on 9th May 1909.[7]

The institution collected a Musthi Fund and made necessary financial provision for the opening of the boarding. Appasaheb Warad died in 1911 and the work of institution slackened. Estimated educational work lagged behind and only the boarding was managed. The foundation stone of the building was laid down at the hands of Ranjan Berul Swami on 18th May 1921, near Gandhi Natha Rangaji Digamber Jain Boarding.[8] The object behind the opening of the boarding was to provide lodging and boarding facilities to the poor students particularly from the Lingayat community. This boarding made them complete men ready to take on the world boldly. Many students from this institution' earned name and fame in various fields of life. Among them were C.S. Mulage, M.C. Antad, Satling Shatgar etc. One of the leading Journalists P.J.Buwa remarked that "The hostels are cultural centres and this boarding was doing good work in this context."9

Maratha Boarding

The awareness of the importance of education among the Maratha community took place much later than the Jain and Lingayat communities. Eminent personalities from the Maratha community came together and established 'Maratha Shikshan Prasarak Mandal' in 1917, under the presidentship of Krishnajipant Manjrekar with the purpose of providing help to the poor students of the Maratha caste. Prominent Maratha members who worked for the educational upliftment were Ambadas Gavane, Jaysingrao Pawar, Narayan Pawar, etc.

The institution started 'Maratha Boarding' from June 1921, in order to provide lodging and boarding facilities in Solapur to poor Maratha students coming from rural areas seeking education. The Municipality donated more than an acre of land without any cost on the request of Mr. Narayanrao Jadhav in 1932 and the expenditure for the construction of the Hostel was made from the contribution of the people of the Maratha community. On 17th August 1946, the Maratha Boarding in Solapur was placed under the control of the Maratha Mandir, Bombay.10 This boarding was later on closed due to mismanagement. Many students from this hostel made a name for themselves in society. Honourable Sushil Kumar Shinde, today's member of Parliament and minister of Home department in the central Government and G. M. Pawar, former Head of the Marathi Department, Shivaji University Kolhapur etc. were ex-students of this boarding.11

Dr. Chati Ananth Vidyarthi Gruh

The Brahmin community in the city was comparatively less in number. Like the Jain, Lingayat and Maratha community the Brahmins also started their own boarding in 1923 for providing free accommodation to the students from their community. Dr. Chati made valuable contribution in the starting of the hostel and also donated a piece of land for the building at Dufferin Chowk. Therefore the Hostel was named as 'Dr. Chati Anath Vidyarthi Gruh'.12 The Municipal President Rao Bahadur Dr. V.V. Mulay donated Rs.5,000 to the building fund. He was the trustee of the boarding and played a vital role in its development. In 1933, 12 students appeared for the School Leaving Certificate examination, and they received Rs. 30 monthly as a scholarship from the institution.13 It also encouraged students for vocational education. The institutions gave some rooms to the 'Kulkarni's Shorthand and Typewriting Institute' and it provided free typing education to 10 students of the boarding for each year.14

Bahishkrit Anath Vidyarthi Ashram

After returning from abroad in 1923, Dr. Ambedkar started work for their development. He reformed the 'Bahishkrit Hitkarni Sabha' in July 1924 and through it with the help of Jivappa Eidale he started a hostel in Solapur on 4th January 1925.15 The Hostel provided free accommodation only to the students from the Backward Communities. The number of students rose from 15 to 71 between 1925 to 1944.16

Shri Siddheshwar Devasthan Vastigruh

It was with a philanthropic motive that Kadadi family established the 'Kadadi Veershaiv Dharmaday Nidhi' in 1932 with a view to encourage charitable works. Through it they started the' Kadadi Free Boarding House' and later on its name was changed to 'Shri Siddheshwar Devasthan Vastigruh'. The intense desire of the Kadadi brothers to serve the community in the field of education prompted them to make effort for the upliftment of the economically backward communities especially from the Lingayats.17 Nowadays this hostel stands near Tuljapur ves on a spacious land and serves the Lingayat community in the field of education.

Other Hostels

In addition to the above hostels and boardings, the government, other communities and private institutions also started Hostels in the city. The Northcote Highschool is the oldest and the first highschool not only in the city but also in the district. Therefore the students from all over the district came to Solapur for secondary education. These students needed for accommodation and mess facility for which the government gave a grant of Rs.64,500 for the construction of hostel attached to the highschool by order of 18th September 1913.18 Other educational institutions like the American Marathi Mission, Australian Christian Mission, Dayanand Anglo-Vedic College, Solapur College, Solapur Social Association, Muslim education society, Padmashali Shikshan Sanstha, Dr. Ambedkar Memorial Fund Samiti, Magas Samaj Seva Mandal, etc. started their own hostels attached to their educational institutions and provided accommodation facilities.

Ladies Hostels

The missionaries took a lead in the field of female education and started schools. They also provided accommodation facilities. The American Marathi Mission took the lead in female education in the Presidency as well as in the city. In Solapur City it started a school and hostel for girls. The Saraswati Mandir started its boarding for girls in 1899.19 The Australian Christian

Mission was established only for the upliftment of girls. It adopted girls and took responsibility of their education and career, it started its boarding in 1907. The Shravika Sanstha Nagar maintained two hostels one for students named as 'Kshu. Rajulmati Digamber Jain Shravikashram' (1923) and the other for working women named as 'Nawalbai Working Women's Hostel' (1983). The Sevasadan Society also established a hostel for girls in 1938 named as 'Gajarabai Doshi Girls Hostel.' The 'Bahishkrit Hitkarini Sabha' too started a hostel for girls in the premises of Sevasadan Society in 1938. Dr.V. V. Mulay played a vital role in its development.20 For the Backward community girls another hostel managed by the Dr. Ambedkar Memorial Fund Samiti named as 'Ramabai Kanya Kshatralaya' (1964).

Major Conclusions

Through this study it is clear that now a days there are more than forty hostels in the city, which are served in the field of education. Major conclusions are as under:

1. In the nineteenth century there was no single hostel in the city.
2. The missionaries took a lead in the field of education and started their hostels in the city.
3. Among all the local communities the Jain community started their first hostel in the city.
4. The awareness of the importance of education among the Maratha community took place much later than the Jain and Lingayat communities.
5. The Jain and Lingayat communities were financially strong because they were mostly connected with industry and commerce.
6. The Maratha community was financially weak as they were dependent on agriculture.
7. There is no single example of the communal crisis in the field of education.
8. At first these hostels started for the students of their own community by the particular community. But in the course of time all hostels started to admit the students all castes and creeds.

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3. Review of Literature on Lokmanya Bal Gangadhar Tilak

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Introduction

Lokmanya the title confered to Bal Gangadhar Tilak tells, that a leader of masses has evolved. He lived the title and instill the spirit of Nationalism among the young and old. His call for Swaraj , Swadeshi, Boycott and National Education shaped the struggle and challenges that he foresaw. The National Education shaped the much required learned men to lead the Nation towards Independence. His contributions to Social and Cultural, awaken the people for a noble cause which we are the beneficiaries.The Nationalism instill pride to fought the mighty British Empire. The Philsophy and Ideology of the Lokmanya gave direction to the people for their intellectual existence. The Media was a means to so read knowledge and information about the unjust rule of the time as well as to create awareness in the freedom struggle.

Lokmanya Tilak, his magnetic and all encompassing personality is indeed an ideal for the Indian Youth to emulate. He is a true example of how much a man of determination, vision, conscience and courage can become in this lifetime. A scholar in astro, mathematics, inspiration for the revolutionaries, a commentator on the Shrimad Bhagwat Gita , an exemplary journalist, the father of the Indian unrest, a leader of the common downtrodden people, a student of history, and many more words and phrases have been used to praise and describe him. But the most appropriate description was made by Mahatma Gandhi when he called him "The Maker of Modern India".

Tilak was the scholar of eminence. He was so visionary that, his articles are still considered to be very relevant in the present social, political, religious, academic, and economical sphere of our life.The Orion and the Arctic Home in the Vedas established his reputation as a research scholar and author in the western world of learning and scholarship.He had written a very popular as well as famous book known as "Gita Rahasya" that is Secrets of Gita which is a sacred book for Hindus. He came to the conclusion that the Gita was not a book

of cold philosophy, but a guide to everyday life to all human beings, a treatise on the science and art of Karmayoga.

He was a editor of two newspaper Kesari and The Mahratta.' Mahrattha' in English on 1st of January 1881 edited by Tilak and ' Kesari' on 4th January 1881 edited by Agarkar. The Kesari addressed the needs of the common men and came to have a large reader base and was written in a simple and direct style. The Mahrattha by its very language (English) was addressed to a mere educated and prosperous people. Being a man of the highest integrity and fearlessness, he challenged the Westernizing social reformers as well as the spirit of inert orthodoxy. In seeking to awaken the people of India, he became the Lion of Maharashtra and the leader of the Nationalists. He challenged the Moderates for control of the Congress and the might of the British Empire with his famous cry, "Swaraj is my brithright, and I shall have it". He was the chief architect of the political philosophy of the Indian independence movement, and he was one of the most important leaders of India in many centuries.

During his earlier political career, Tilak pioneered popular movements on two types of issues and causes.One type was cultural, based on historico – religious situational factors. The other type was economic or constitutional - cum – administrative.The Ganesh and Shivaji festivals piloted by Tilak during the nineties of the last century represented the first type of causes. The people's movements Tilak roused in Poona and the countrywide round about on their oppression during the plague epidemic and the sufferings due to successive famine respectively, illustrated the second type of causes.

The present study highlights Review of Literature on Lokmanya Bal Gangadhar Tilak. Mostly the major books on Tilak in Marathi, a translation into English will help the readers.The present study covers all aspects in one platform in English language. Here both Marathi and English book reviewed for paper , which will he helpful to higher studies.

Major existing research works reviewed

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- Lion's Road Swaraj is my Birth Right and I shall have it, Article by Dr. Deepak. J. Tilak Geeta Rahasya (Essence of Bhagavad Geeta) Path way for freedom (Swarajya) to Mankind, Tilak Maharashtra, Vidyapeeth, Pune, 2016. This book focuses on Eminent authors article on Lokmanya Tilak's view on National Education,Economic freedom, food, Geeta Rahasya, women satatus and Lokamaya dream. And Tilak thoughts relevance to Modern Times mentioned in detail.
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Kesari, Marahtta, The Hindu, The Statesman, Deccan Herald, The Times of India, The Hindustan Times,

Conclusion

The study covers the life of Lokmanya Tilak in different phases. As an educationalist, journalist, Nationalist , and as a leader of Mass Movement. Lokmanya Tilak's history and ideology will be brought to light and his cultural contribution will be seen in a broader view.It aids in writing the political and cultural history.In order to document the socio-economic, political, religious views of Tilak the study will be helpful.This research will help rewrite the political history.

Apart from above books also referred Samagra Tilak Volumes, Tilak's own written books and articles in Marathi and English for writing paper. To support the claim many Marathi literature on Lokmanya Tilak will be translated and enrich the availability of literature. The multi dynamic personality reveals his ability to master in the many subject. This becomes the base on which we can research the interdisciplinary or multidisciplinary aspects of the present students. Tilak history sources available in other languages like Kannada, Hindi, Bengali, Gujarati, Sanskrit. The only thing is to do research and rewrite the history of great person of Modern India.The above review is a brief one which will be helpful to scholars who are interested to do

research on Tilak.This paper will be useful for academicians, scholars, researchers, historians, economist, politicians , indologist, journalist, writers and Nationalist for further research.

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4. Tilak Views on Nationalism

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Abstract

Lokamanya Tilak was a great national leader who contributed much to the rise of Indian Nationalism. He was one of those leaders who asserted ever since the beginning of the freedom struggle, Indian's right to swaraj of national self determination. He recognized the basic conflict between the interest of British imperialism and the aspiration of the people of India and that conflict cannot be resolved unless the Indians have the right to shape their own destiny and conduct the affairs of the country.Tilak's Nationalism was also influenced by the western theories of national independence and self determination. Tilak was one of the dominant political figures who gave to the people of India the first lessons in the consciousness of the right of swaraj .He himself represented a new wave of nationalist movement that created an automatic space for it by providing the most powerful and persuasive critique of moderate philosophy.Tilak being visionary, studied every minute details about nationalism .He tried to find ancient foundation of Nationalism.

This versatile man achieved not only India wide but also worldwide fame as a patriot, a politician, an educationist, a scholar and a philosopher which no other personality equaled or excelled. Through his dynamism, dedication and versatile genius, he could be the pathfinder of India's freedom. Tilak was nationalist par excellence of Vedanta philosophy and orthodox Hindu rituals and practices. Tilak's nationalism had to some extent, a revivalist orientation .He wanted to bring to the front the message of the Vedas and Gita for providing spiritual energy and moral enthusiasm to the nation. Tilak was perhaps the most articulate militant leader of this phase of freedom struggle.

The present paper is an attempt to bring out the views of Lokamanya Tilak and Nationalism which states that India was never one country ruled one king or dynasty before British rule.

Key words: Lokamanya Tilak, Visionary, Nationalism, Swaraj, Modern India.

Introduction

Lokamanya Tilak as a political philosopher has given us a theory of Nationalism. His theory of Nationalism. is a synthesis of both the teachings eastern and western thinkers. Tilak's nationalism had a revivalist orientation .He wanted to bring to the foreforn the message of the Vedas and the Gita for providing spiritual energy and moral enthusiasm to the nation .M.N.Ray pointed out that Shivaji and Ganpati festivals had been encouraged by Tilak to link contemporary events and movements with historical traditions .Because of his spiritual approach. He also gave a moral and spiritual meaning of swarajya. His philosophy of Nationalism was a synthesis of the vedantic idea of the spirit as self contained freedom and western conception of the Mazzini and Burke, Mill and later on of Wilson.

Programmes of Tilak

Tilak presented the nation with a threetold programme or techniques for effective practical and political action. The three principals were boycott, swadeshi, and national education.

Tilaks thoughts about Boycott

Boycott initially involved the refusal of the people to purchase British manufactured goods. It was started as admeasure designed to bring economic pressure on the British business interests, both in India and abroad. Tilak was an advocate of swadeshi movement. Tilak supported the swadeshi resolution and spelled out the economic foundations of Indian Nationalism. The quite Tilak. "To recognize the land of the aryas as mother earth is the swadeshi movment". It was an economic, political and spiritual weapon. Tilak believed that emphasis on economic issues and the demands for removal of poverty would give a fillip to the struggle of swaraj.

Tilak through his writings in newspaper and speeches, made Indians aware about their history. Need of swaraj, their role in socity, and their political rights. And showed them the path towards achieving it. Boycott was a negative weapon and swadeshi was its positive side. It these two were faithfully followed swaraj would certainly be attained people from all walks of life rejected the British government and boycotted the various institutions. Indian people boycotted the British manufactured goods, school, colleges, offices, etc. It was started as a measure designed to bring economic pressure on the British business interests both in India and abroad.

It was expected to help the cause of Indian nationalism in three ways. Firstly, it would hit at one of the primary motives of the imperialists I,e exploitation. Secondly, it would create determination among the Indian people to sacrifice their immediate interests for the good of the nation. This would help foster the feeling of Nationalism among them, and Thirdly, it would help Indian industry, trade and craft to regain their place in the Indian life and economy and develop rapidly under the stimulating influence of Nationalism.

Tilak thoughts about swaraj

Tilak was the first political leader to break through the routine methods of the Indian congress which was dominated by the moderates. In his view, swaraj was more than a law and order mechanism. It was also more that an economic order providing the necessities of life or the luxuries of a pleasurable life. He was against the western culture and tradition. He had a great inclination for Indian culture and tradition and made all round efforts to preserve it. Tilak gave a moral and spirited meaning to the term swaraj. Tilak said that swaraj is natural to an individual. It is only in swaraj that an individual can acquire manhood. To Tilak, the concept of swaraj does not have only a negative meaning that is only to be free from the foreign yoke .He was of the opinion that the society must be governed by the people for the interest and welfare of the people than only could it be called free. Tilak's views on nationalism in the context of his conceptual understanding and evalvation of the concept and phenomenon of Nationalism , in its various aspects.

The political goal of Tilak was atain swaraj or government for the people of India. Usually swaraj is translated to mean self rule or independence for foreign political domination. It did not imply the negation of the ultimate British sovereignty.

Tilak thoughts about National Education

The western system of education introduced in India aimed at creating a class of people who were Indian by blood . Tilak and his associates held the view that the education imparted through government school and colleges encouraged amongst the students attendance to imitate the westerners in all aspects of life. Tilak desired the new generation of students to cultivate the qualities of self-respect, hard work, sincerity of purpose and above all the willingness to sacrifice the comforts of family life and worldly career for the sake of the motherland.

Tilak said, "Only to read and write is not education. An education should enable us to earn our livelihood and teach us about our ancestors". Only English could not do that. Thus,

under the scheme of National Education, the modern scientific and technological knowledge of the best was to be combined with the knowledge of all that was best and worth retaining in our own heritage. Tilak was in favor of giving education in mother language. He wanted to give moral and religion to the students. Thus Tilak was the greatest supporter of moral education. Tilak had strong belief that Indian should be given national education so that Indian could get freedom from western education and they could become independent.

Tilak thoughts about swadeshi

Swadeshi was the positive part of boycott which was only a negative weapon. The swadeshi movement also included in it a plan to train Indians in the art of industry and commerce. Swadeshi was thus a positive programmed to reconstruct Indian industry, trade and craft and rescue it From its dilapidated condition.

Tilak views about Nationalism

Tilak did not look upon Nationalism as some spiritual phenomenon. It is true that Tilak himself was an ardent believer in the Advaita philosophy; it is also true that he was proud of Hindu philosophical heritage. Tilak, a feeling of oneness and solidarity among a people arising mainly from their common heritage was the vital force of Nationalism. Knowledge of a common heritage and pride in it fosters Psychological unity.

Tilak's Nationalism had, to some extract a revivalist orientation. Tilak wanted to bring to the front the message of the Vedas and the Gitas for providing spiritual energy and moral enthusiasm to the nation. Tilak's concept of Nationalism was based on the synthesis of vedantic spirit as self contained freedom and the Wilson, it is interesting to note that Tilak was only aware that Nationalism is a secular concept, but Tilak also perceived That the awareness of a separate national identity is, many times, a consequence of some political calamity, e.g., period of subjugation.

Brief asessment

This research has helped to understand the Tilak's through process about foundation of our Nation. Tilak, as a visionary, planned a roadmap for development of modern India .Tilak as a political leader has been the subject of controversy and misunderstandings. He believed in the inevitability of reforms in society with the progress and enlightenment of human consciousness.

Tilak was one of the dominant political figures who gave to the people of India the first lessons in the consciousness of the right of swaraj .He himself represented a new wave of

nationalist movement that created an automatic space for it by providing the most powerful and persuasive critique of moderate philosophy .Tilak being a visionary, studied every minute details about Nationalism .He tried to find ancient foundation of Nationalism .This versatile man achieved not only India wide but also worldwide fame as a patriot ,a politician ,an educationist , a scholar and a philosopher which no other personality equaled or excelled . Through his dynamism, dedication and versatile genius, he could be the pathfinder of India's freedom.

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5. Political Ideas of Bal Gangadhar Tilak's

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Introduction

Among the many great figures of the British Period of Indian History there is none more impressive of distinctive than Bal Gangadhar Tilak's the only Lokmanya of India. In the course of his career of 64 years this versatile man achived not only India wide but also world- wide fame as a patriot, a politician, an educationist, a scholar and a philosopher which no other personality equalled or excelled.

Shri Bal Gangadhar Tilak popularly know as the Lokmanya, was one of the greated personalities in the political history of Modern Asia. He was a great scholar, journalist, educator, partriot and the leader of the Extremist Sections of the Indian National Congress. Tilak was the first who converted the Indian National Congress in to a mass organization. In the words of Pandit Jawahar Lal Nehru, "The early founders of the National Congress were great man but the rather made the intellectual foundation in the early stages of the freedom Movement. I don't think that it is unfair to them to say that they were not massleader in the sense that some subsequent great leaders becomes. I think the first mass leader of this new state of our revolutionary movement was lokmanya Tilak." He was the great guide and the leader of the nationalist movement in contemporary India. In the words of T.L. Sahay:' For Gandhiji and the congress he left a philosophy of struggle and a clearly demarcated goal, for free India he left the broad outlines of a new political philosophy integreated with the value system of his people. However, a study of the works and speeches of Tilak does provide us with an insight into the fundamentals of the xtremist school of political thought in Modern India.

Influences on Tilak

Bal Gangadhar Tilak was influenced by many sources. He was born in an orthodox Chitpavan Brahman family and as such he was the product of Indian culture and civilization. He led a simple life. Tilak was highly influenced by his father. The

Lokmanya was not only a front rank politician and patriot, Tilak was also a great Orientalist, a great Sanskrit scholar and the author of one of the most famous, comprehensive

and original commentaries on the Gita. The Gita contains the essence of Indian Spirituality and applies it to human life and action, it places before manking a philosophy of life which inspires us to heroic action in a spirit of dedication to the lord. It is this philosophy which underlay the thinking and activities of Tilak and which he sought to infuse in Indian politics. Tilak was an a embodiment of the teachings the Gita: he bore his sufferings and sacrifices calmly and quietly and as a metter of course.

Tilak also come under the influence of Swami Dayanand Saraswati Swami Rama Krishna Parmhansa and Swami Vivekanand. Tilak appreciated the views and philosophy of Justice M. G. Ranande. Another influence on Tilak was a Vishnu Shastri Chiplunkar. In the words of Tilak, the development of our language is a principle means of the country's regeneration and it is an accepted fact that no one did this work as fully as Vishno Shartri did- During the last 25 years there have been movements like that of the Indian National Congress but it is indisputable that Shastri Buura, Chiplunkar, removed the chaos and stupor which had come with the first drought of English education and every impartial person will have to admit that it is not a small matter to turn the peoples mind towards good behavior and religious patriotism arresting with his pen the undesirable tendency that was the result of early English education and that the men who did this before completion of 32 years, cannot be counted as of the common kind.

Tilak was also influenced by British liberals and western Ideas. Moreover, Tilak in his educational career had devoted much time to the study of the western thinkers, Hegel, Kant, Spencer, Mill, Bentham, Voltaire, Rouseau etc. But he combined western influences with the influence of ancient India. Tilak was a great scholar of the Vedas. Tilak believed in the superiority of Indian culture and civilization.

Tilak's political philosophy has its roots both in the Indian tradition as well as in some of the currents of contemporary western political and legal thought. It should not be forgotten that he was a graduate of the Bombay university and had a first class Bachelor's Degree in law. But Tilak was also nurtured in a great Sanskritic tradition and cultural environment permeated with old Hindu values. The Mahabharata had a great influence on Tilak's thought . In his writings in the Kesari, Tilak's has at a few places, quoted the Manusmriti, and Nitishataka of Bhartuhari. Their realism come to Tilak's support. Tilak was deeply rooted in the Hindu tradition. For his religious traditionalism he did draw sustenance and support from the writings of the large number of Maratha Saints, including people like Dnganeshwar, Tukaram and Ramadas.

Basis of Tilak's Political Thought

Bal Gangadhar was not an idealistic thinker like Plato or Aristotle. Tilak never depicted any picture of the ideal State. His main aim was the political mancipation of India. Tilak was realistic in his political thought. Tilak was a Vedantist and believed in metaphysical assumptions. Tilak was of the view that metaphysics of the Vedanta, was the political conception of natural rights. All men have the same autonomous spiritual potentiality. Tilak regarded freedom as a divine attribute, without which on spiritual and moral life was possible. That is way he regarded Swarajya as Dharma. Politicaly, Swarajya, according to Tilak meant Home Rule and morally, it meant the attainment of the perfection of self control. For Tilak, Swaraj was a moral necessity. It was the duty of every men to achieve Swaraj or self rule. In his own words: "it is a life centered in self- rule. There is Swarajya in this world as well as in the world here after.The Rishis who laid down the law of duty be took themseleves t because the people were already enjoying Swarajya or people's dominion which was administered and defended in the first instance by the Kshatriya Kings." Tilak was a deeply religious man and held the conviction that India must be re-created on the foundations of her own greatnes in the past.

Tilak as A Revivalist

Tilak was a revivalist in the sense that he wanted to revive all that was good and noble in India's past culture and civilization. Tilak never wanted to have a complete break with the past. In his own words, ... a proper knowledge of the old traditions and philosophies must be imported the newly educated classes, and the Pandits and Shastris must be given information about the newly changed and changing circumstances. Tilak' criticized and repudiated the blind imitation of the west by the Indian moderates. Lokmanya Tilak was partially, a revivalist, it must not be thought that he was a more Hindu nationalist. As a person, Tilak had intense pride in Hindu religion and culture. As a Political leader he wanted to preserve the legitimate interests of the Hindu people and would not sanction cowardice and surrender. The moderates like Ghokhale and Ranade were of the opinion that the only way on the lines of western society. They wanted to reform Indian society of the moderates. However Tilak was not a narrow-minded person. Tilak appreciated the introduction of English education in India and he himself propagated in favour of the some. Tilak also studies the works of western liberal thinkers like Hegel, Kant, Spencers, Mill and Rousseaio.

Tilak's Political Method Passive Resistance

Bal Gangadhar Tilak substituted the use of passive resistance for constitutional method to attain Swaraj. Tilak declared, 'the congress agitation based on the so called constitutional method is sheer-waste of time. Tilak was of the opinion that the constitutional method used by the Moderates was not at all applicable under the conditions then prevailing in India. The constitutional method was applicable only where the people enjoyed the power of over throwing a government by the use of ballot box , a government of whose policies the people disapproved and where there existed a strong and virile public opinion. In the words of Tilak, there is no constitution in India. The government in India is irresponsible and non-constitutional. Constituted authorities in India are irresponsible and we have to take our rights from them. The legality of our action is decided by this government. Tilak wanted the people to appose these laws which were against justice and morality. But Tilak ruled out the use of violence in attaining self rule. However, he was not a preacher of Ahisnsa a or non-violence. He said, 'passive resistance was the means to an end but was not the goal in itself.' To Tilak non- violent resistance was at best a policy, a matter of convenience.

Tilak and Violence

As mentioned earlier, Tilak ruled out the use of violence in India's struggle for self rule. However, Tilak was not a preacher of Ahimsa or non-violence. Some people are of the opinion that Lokmanya Tilak was a revolutionary as he wished to awaken the people of India so that they could rise in revolt against the British. Some foreign critics of Tilak's philosophy also regarded him as a revolutionary. There is no doubt that Tilak was in touch with some of the revolutionaries of those days, Tilak also supported the action of Shivaji in Killing Afzal Khan and some people believe that Tilak had a hand in the setting up of an Arms Factory in Nepal in 1903. In spite of all that , Tilak was not a revolutionary. He felt that the conditions in the country were not fit for revolutionary activies.

Gandhiji was an apostle of non-violence, But Tilak did not have the same faith non-violence, Tilak did not rule out the possibility of resorting to violence as a means of achieving independence. As a practical politician Tilak relised that it was never wise to restrict onself to the employment of one single method only for the achievement of freedom, one should have more than string to one's bow. Tilak did not encourage crimes of violence and sought to restrain the young revolutionaries but was not opposed to the use of violence on principle, Tilak thought that

the conditions in India were not favourable for its employment. He relised the necessity of having some devoted revolutionaries who could devote themselves to the work of preparing the country for an eventual issurrection. But Tilak did not want that the two activities, awakening the spirit of the people for passive resistance and preparing the ground for armed revolt should be mixed up. If they were mixed together, the government would get a pretext to repress the civic rising also. Tilak's attitude in this matter was wholly pragmatic, it was not theoretic or philosophical.

Tilak's Concepts of Swaraj

The political goal of Bal Gangadhar Tilak was to atain Swaraj or self government for the people of India. Tilak was the most significant and And dominant political personality of the early years of the 20 century who gave to the people of the country the first lesson in the form of the consciousness of the right of Swaraj are Home Rule. Tilak gave the slogan, Swaraj is my birth right, I shall have it. At the lucknow session of the Indian Naitional Congress 1916 Tilak declared: 'Swaraj is the birth right of the Indians.' To Tilak, Swaraj meant Home Rule or self-government for the people of India. Usually Swaraj is translated to mean self rule or independence for foreign political domination. It did not imply the negation of the ultimate British Sovereignty.

Tilak: Nationalism

The word nation from the latin terms nasci and natio. Immediate English congrates would be words like natal or nature, some of which figure obliquely in nationalist discourse. The initial commonplace sense of nation is thus concerned with people related by birth or birthplace. One important connotation is that such a birthplace provide the basis for a natural form of human association.45 Most scholars writing on nationalism are faced with a number of primary cognate words to nationalism , which are tied etymologically to the same root. Words like nationality, nation, national character, national self-determination, and national interest proliferate and occasionally directly overlap.

Nationalism is often seem as an ideology which makes national self- consciousness, ethnic or linguistic identity, into central planks of a doctrine which seeks political expression.

The idea of Nationalism reached the Indian soil in the 19th century.Exposed to the invigorating and modernizing ideologies of the west and eager to learn the secrets of western ascendency, the educated Indians were too Willing to receive the ideology of Nationalism.

Evidently, Tilak also shared the view that awareness of nationhood acts as a foundation necessary for progress in to days terminology modernization Tilak, naturally, felt it necessary to investigate into the nature and character of 'Nationalism' and to identify the essential components a 'Nation'.

Tilak's nationalism had , to some extract a revivalist orientation. Tilak wanted to bring to the front the message of the Vedas and the Gita for providing spiritual energy and moral enthusiasm to the nation. A recovery of the healthy and vital traditions of the old culture India was essential. Tilak said:" a true nationalist desires to build on old

Foundations reform based on utter disrespect for the old does not appeal to be as constructive work...we do not want to anglicize our Institutions and denationalize them in the name of social and political reforms." Hence to pointed out that the Shivaji and the Ganapti festivals had been encourage by him because they served to link contemporary events and movements was historical traditions. Tilak's concept of nationalism was based on the synthesis of Vedantic spirit as self contained freedom and the western conception of Mazzini, Burke, Mill and Wilson. His nationalism was not devoid of revivalism. Tilak's nationalism was also influenced by the western theories of national independence and self- determination. In the famous trial speech of 1908, Tilak quotes with approval John Stuart Mill's definition of nationality.

In 1919 and 1920, he accepted the wilsonian concept or self determination and pleaded for its application to India. Hence Tilak's philosophy of nationalism was a synthesis of the Vedantic ideas of the spirit as supreme freedom ovn and later on of Wilson. This synthesis Tilak expressed in terms of Swarajya, a Vedic term which was used in Maharashtra to indicate of Maratha polity of Shivaji.

It is interesting to note that Tilak was only aware that nationalism is a secular concept, but Tilak also perceived that the awareness of a separate national identity is, many times, a consequence of some political calamity, e.g., period of subjugation. Tilak further observed that the concept of nationalism would not have emerged in the history of mankind if no nation on this earth had suffered from the foreign subjugation or had been living under such threat. Tilak did not elaborate this point. Yet his arguments clearly indicate that for him, Nationalism was a secular phenomenon. As Nevinson has so rightly pointed out, ''To Tilak nationalism was mainly a political agent, a means of material improvement."

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6. Mesolithic Culture of Karha Basin, Pune District, Maharashtra

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Abstract

Geoarcheological exploration is carried out by author in Karha Basin, Paleolithic and Mesolithic culture sites are recovered. Tandulwadi, Undewad village area in primary context on the stony waste, hilly deserted area and pastoral land on Gojubai Odha, Medad village site is located on the right bank of Karha river and North West of Baramati Tehsil, District Pune, Maharashtra. Mesolithic Culture site are recovered. Blades, Flakes, scrapers, Cores etc. stone tools types are made on the Chalcedony, Agate etc. raw material are used.

Key Word: - Mesolithic- Karha River - Pune- Maharashtra

Introduction

Karha river is rich in archaeological cultural material of various period. Karha river origination at Garade Village, Saswad Tehsil, District Pune, Mharashtra. Karha river is tributary of Nira Basin in the Upper reaches of Bhima Basin. Karha River is flowing through the cities of Baramati, Saswad and Jejuri. Karha river and Nira river confluence at Songaon Village, Baramati Tehsil.

Study Area

The origin of river Karha River is near the Garade Village in Saswad Taluka and merges with the Nira River near Songaon in the Baramati Tehsil. Karha River is left tributary of Nira River. Total length of the river is 98 Km. Karha River lies in Scarcity zone of Pune district. The study area of Karha river basin is taken about 1196.98 km2. The latitudinal and longitudinal extent of the Karha river basin under study lies between 18.05 N to 18.43 N and 74.00 E to 74.65 E. It receives the rain mostly from the southwest monsoon curing June to October. The study area lies in well rainfall occurring areas as the annual average rainfall is about 556.4 mm. The soil are brown to black calcareous soil with varying depth and Texture. Average rainfall occurs

in June to October. Crops cultivated in this area Jawar, Cotton, Wheat, and Gram, Groundnut and Sunflower and also sugarcane in canal areas Fig. 1 (Deshmukh Satish S. and Abhaykumar S. Wayal, 2018[1], Lohar and Awatade, 2020[2]). Geology of study area is Cretaceous Eocene (60-65 Ma) age Deccan Trap basalt (GSI 2001[3]). Soil is medium and low deep.

(Fig. 1) Study area map of Karha Basin (After-Deshmukh Satish S. and Abhaykumar S. Wayal, 2018. Lohar and Awatade 2020).

Previous Work

Karha basin is rich in cultural material of Prehistory, Protohistory, Early Historic and Medievel period and scholars are contributing on the various cultural aspects if Karha Basin from 6 decades. Deo et, al. IAR (1964-65[4]), Songaon Excavation of Chalcolithic and Mesolithic culture site. Kale et, al. IAR (1988-89[5]). Paleolithic tools finding at Morgaon. Kale et, al. (1993[6]), Thepra finding. Shirvalkar, (2002)[7], Geomorphology of Prehistoric sites of Karha river. Rajaguru et, al. (2004)[8]. Banarji was carried out at Morgaon site Mesolithic tools study. Morgaon Acheulian sites Site Excavation (Mishra et al. 2008[9]), Mammalian fossils study (Sathe, 2008[10]). Deo, Sushama and Sheila Mishra 2013[11], Banaraji was carried out at Morgaon site Mesolithic tools study.

Aims and Objective

1. To study the Mesolithic Culture of Karha Basin.
2. To study of Mesolithic culture sequence of study area.
3. To study tool typology of Mesolithic culture of Karha Basin.
4. To understand Geoarchaeological study Mesolithic cultue site of Karha Basin.

Methodology

1. Village and river Bank survey of Karha Basin with the help of Survey India Toposheets (SOI) 1:50000 and Google Earth, Bhuvan2D, 3D, Bhuvan Panchayat 03.
2. Finding of Tool types and raw material outcrops location.
3. Geoarchaeological study of Karha Basin with previous work carried out by various scholars

Field work and Findings

Field work is carried out in the Bararmati Tehsil area Undewadi Kade Pathar villege is (Lat- N 18^{O} 14' 54" Long- E 74^{O} 32' 42") North West of Baramati Tehsil and right bank or Gojubavi Odha. Mesolithic Culture Site is SE of Village and Gojubavi-Undewadi road Right

side Fig. 2 A. Tandulwadi village (Lat- N 18^{O} 11' 52" Long- 74^{O} 35' 18") is north of Baramati Tehsil and left bank of Gojubavi Odha and right side of Tandulwadi to Katphal road Fig. 2 B. Medad village (Lat- N 18^{O} 14' 01" Long- 74^{O} 32' 16") is located on right bank of Karha river and west of Baramati Tehsil. North East of the Khodad Village near of Brige Mesolitic Culture stone tools are recovered in secondary deposit of the sandy gravels (Fig. 1 A, B and C) Location map of Sites. (Fig. 2 A, B, C, D, E, F)

Conclusion

Mesolithic Culture sites are previously dated at Morgon Village Ostrich Eggs (<20k) and compare with this date and tool types are possible same period. Raw material

Acknowledgement

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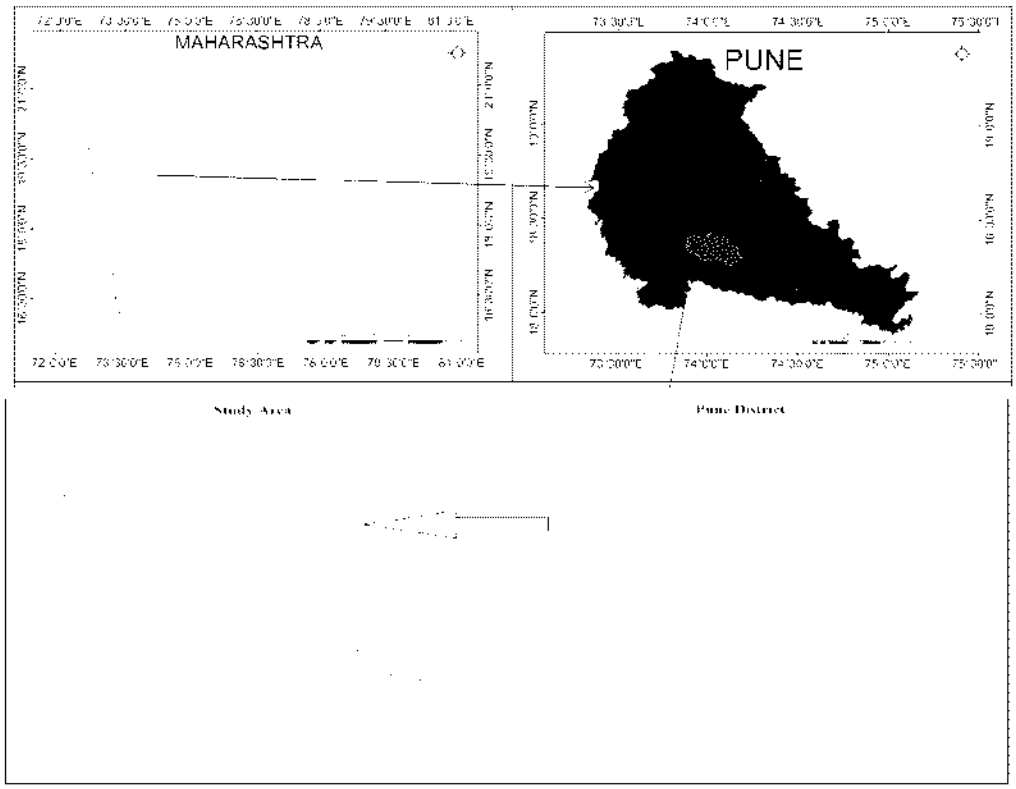


Fig.1 Study Area Location Map of Karha Basin, District Pune.

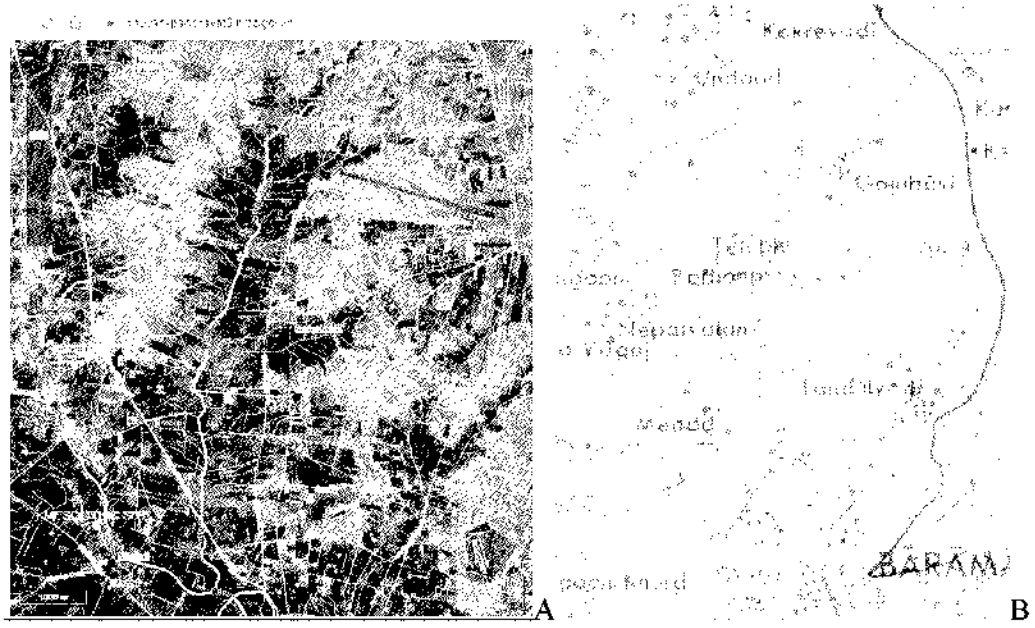


Fig. 1 A and B Location Map of Sites

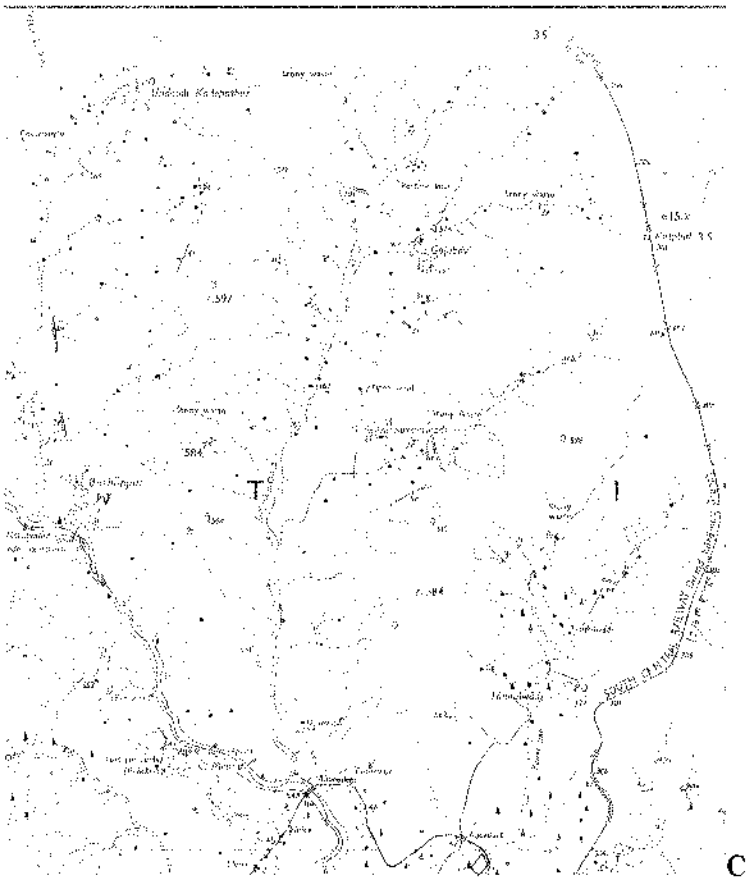
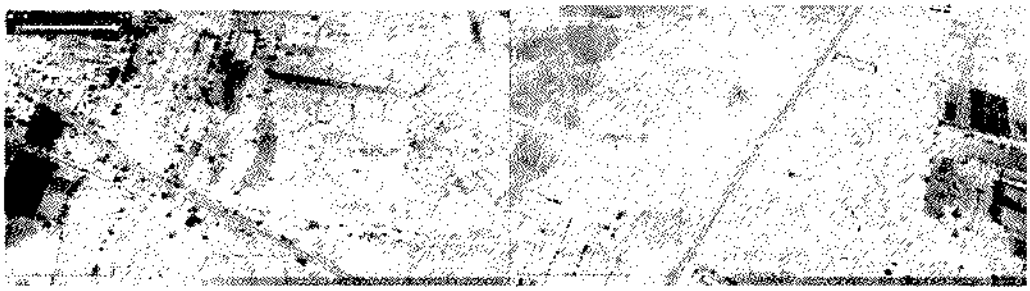
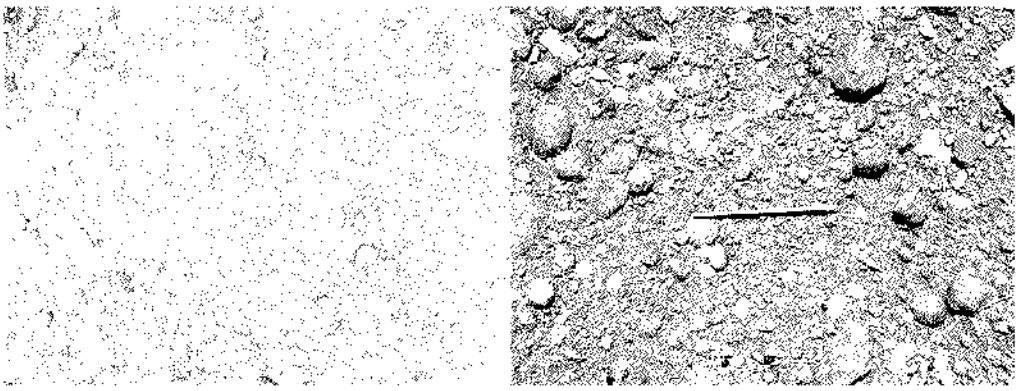


Fig. 1 C- Location Map of Undewadi Kadepathar, Tandulwadi and Medad (SOI) Sites



A **B**

Fig.2. A- Location of Undewadi Kade Pathar. B- Location of Tandulwadi Mesolithic Site



C **D**

Fig. 2 C – Undewadi Mesolithic Tools **D- Tandulwadi Mesolithic Tools**

C **D**

Fig. 2 E, F- Location of Medad Mesolithic Site.

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१. अण्णाभाऊ साठे यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदान

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प्रस्तावना

अण्णा भाऊ साठे एक असे नाव जे केवळ दिड दिवस शाळेत गेले मात्र आपल्या कार्यकर्तृत्वाच्या जोरावर त्यांनी सातासमुद्रापार भारताची कीर्ती स्थापन केली. श्री रणजित ल. चौगुले हे मात्र अण्णा भाऊ साठे यांचे शिक्षण चौथीपर्यंत झाले असल्याचे नोंदवतात.[1] जातीयता आणि कमालीचे दारिद्रय, यामुळे त्यांना कोणत्याही प्रकारचे औपचारिक शिक्षण घेता आले नाही. आपल्या उपजत प्रतिभेच्या जोरावर त्यांनी साहित्य सारस्वतात मोठी भर घातली. ते वास्तववादी लेखक होते. त्यांनी कधीही आपल्या साहित्यामध्ये कल्पनेला वाव दिला नाही.

मुख्य शब्द - अण्णा भाऊ साठे, महाराष्ट्राची जडणघडण, संयुक्त महाराष्ट्र, इतिहास, शाहिरी, पोवाडा.

समस्यासुत्रण

अण्णा भाऊ साठे यांच्यावर आजपर्यंत विपूल लिखाण झाले आहे मात्र ते त्यांच्या संयुक्त महाराष्ट्राच्या लढ्यातील भूमिकेला न्याय देणारे नाही. असे आपणास वाटत नाही काय? एक डाव्या चळवळीचा, साम्यवादी विचारवंत म्हणून त्यांनी खूप दिलंय देशाला. आज आपण जे स्वतंत्र महाराष्ट्रात महाराष्ट्राचं वाटोळं करत फिरत आहोत; यासाठीच 105 जण हुतात्मा झाले आहेत का? पुन्हा मुंबई महाराष्ट्रापासून तोडण्याचे मनसुबे यशस्वी होणार आहेत का? अण्णांनी आपल्या असामान्य प्रतिभेचा वापर संयुक्त महाराष्ट्र चळवळीसाठी कसा केला? याचा अचंबा वाटल्याशिवाय राहत नाही.

संशोधनाची उद्दिष्ट

1. संयुक्त महाराष्ट्राच्या निर्मितीत अण्णा भाऊ साठे यांच्या योगदाणावर प्रकाश टाकणे, यासंदर्भातील अधिकच्या संशोधनाची आवश्यकता प्रतिपादन करणे.
2. अण्णा भाऊ साठे यांच्या कलापथकातील संयुक्त महाराष्ट्राशी संबधित शाहिरीचा आढावा घेणे.
3. संयुक्त महाराष्ट्राच्या आंदोलनात अण्णा भाऊ साठे यांच्या साहित्याचा कोणत्या स्वरूपात परिणाम झाला, हे अभ्यासणे.

संशोधन पध्दती

सदरच्या संशोधनासाठी ऐतिहासिक संशोधन पद्धतीचा अवलंब करण्यात आला आहे. हा संशोधन पेपर द्वितीयक स्रोतांवर आधारित आहे. विविध ग्रंथांमधील, आंतरजालावरील संयुक्त महाराष्ट्राचा लढा, अण्णा

अण्णा भाऊ साठे यासंबंधीचे वर्णन कामी आले आहे. महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळाचे ग्रंथ, आधुनिक महाराष्ट्रातील परिवर्तनाचा इतिहास आदी ऐतिहासिक ग्रंथ, विविध संशोधन पेपर, लेख, वर्तमानपत्र, वर्तमानपत्र, नियतकालिके तसेच शासकीय प्रकाशनांचा अवलंब करण्यात आला आहे.

गृहीतक

1. संयुक्त महाराष्ट्राच्या निर्मितीसाठी सर्वसामान्यांमध्ये जनजागृती करण्यात अण्णा भाऊ साठे यांचे योगदान अनन्यसाधारण आहे.
2. तत्कालीन सरकारच्या जाचास न कंटाळता अण्णा भाऊ साठे यांनी क्रांतीचे रणशिंग फुंकले.
3. 'अण्णा भाऊ साठे यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदान' याबाबत अधिक संशोधन होण्याची आवश्यकता नाही.

शाहीर म्हणजे केवळ डफ आणि तुणतुणे नव्हे तर अज्ञान आणि अंधश्रद्धेच्या गर्तेत रुतलेल्या निद्रिस्त समाजाला मनोरंजनाच्या माध्यमातून लोकशिक्षण देऊन त्यांना जागं करण्याचं एक पारंपरिक व प्रभावी माध्यम शाहिरी होय. संयुक्त महाराष्ट्राच्या लढ्यात सहभागी झालेले वर्ग प्रामुख्याने शेतकरी व कामगार वर्ग होता, तो अशिक्षित होता. त्यांच्यात जागृती निर्माण करण्याचे कार्य दृकश्राव्य अशा पोवाडा या कलाप्रकाराने केले. अण्णा भाऊ साठे यांनी आपली शाहिरी लेखणी समाजहितासाठी झिजविली.

"पहा पर्व पातले आजचे । संयुक्त महाराष्ट्राचे ।।
साकार स्वप्न करण्याचे । करी कंकण बांधून साचे ।।
पर्वत उलथून यत्नाचे । सांधू या खंड की त्याचे ।।
या सत्यास्तव मैदानी शिंग फुंकाया ।
महाराष्ट्रावरूनी टाकू ओवाळूनी काया ।।"[2]

त्यांच्या रगारगात राष्ट्रप्रेम ओतप्रोत भरलेले होते. ते लोकशाहीर होते. कृष्णा, कोयना, वारणा आणि पंचगंगा या नद्यांच्या खोऱ्यातील म्हणजेच सातारा, सांगली, कोल्हापूर परिसरातील लोकपरंपरा, लोकरूढी, गावगाढा आणि स्वातंत्र्य चळवळ याबरोबरच संयुक्त महाराष्ट्राची चळवळ अण्णा भाऊ साठे यांनी आपल्या साहित्यातून सातासमुद्रापालिकडे पोहचवली. त्यांनी आपल्या साहित्यातून समाजातील जातीय विषमता, वर्गसंघर्ष, दारिद्रय, कामगारांचे जीवन या महत्त्वपूर्ण गोष्टीवर प्रकाश टाकण्याचे काम केले आहे. त्यांचे संयुक्त संयुक्त महाराष्ट्राच्या निर्मितीमध्ये महत्त्वपूर्ण योगदान आहे. कित्येक शाहिरांनी जिल्ह्याजिल्ह्यात जागल्याचं जागल्याचं काम केलं.[3] संयुक्त महाराष्ट्राची चळवळ आणि अण्णा भाऊ या दोघांना एकमेकांपासून वेगळे केलेच जाऊ शकत नाही. अण्णांच्या शाहिरीचं सर्वसामान्यांच्या वेदनेशी नातं होत. त्यांच्या शाहिरीने दलितांचा, दिनदुबळ्यांचा कळवळा घेतला आणि अशा कनवाळूपणामुळेच ती सताधारी वर्गापासून लांब गेली. गेली. कडेपारी आणि वंचित वस्त्यांत तिने आपले बस्तान थाटले. हे बस्तान साधे-सुदे नव्हते तर या बस्तानाने निर्माण केलेला चळवळीचा मार्ग थेट एकीकडे कम्युनिस्ट तर त्याच वेळेस प्रगतीकडे जाणारा

होता. अण्णांच्या कर्तृत्वाचा, वैचरिकतेचा आणि साहित्यिकतेचाही कस शाहिरी रुपात पुढे आला, तो संयुक्त महाराष्ट्राच्या चळवळीमध्ये.[4] आधुनिक महाराष्ट्राच्या जडण घडणीमध्ये संयुक्त महाराष्ट्र चळवळीचे योगदान योगदान अनन्यसाधारण आहे. मराठी भाषिकांसाठी मुंबई शहरासह स्वतंत्र महाराष्ट्र राज्य निर्माण झाले पाहिजे अशी मराठी जनतेची मागणी होती. संयुक्त महाराष्ट्र चळवळ दहा वर्षे चालली.

समाजजागृतीचे प्रभावी माध्यम म्हणून अण्णा भाऊ साठे यांनी शाहिरीचा अवलंब केला. त्यांनी हा मार्ग अवलंबला नसता तर आज कदाचित मुंबईसह महाराष्ट्र दिसला नसता. कोणत्याही चळवळीच्या यशाच्या मुळाशी जनतेची साथ असते. संयुक्त महाराष्ट्राची चळवळ अण्णाभाऊनी यशस्वी करून दाखवली. संतोष जाधव म्हणतात, 'संयुक्त महाराष्ट्राच्या स्थापनेसाठी मराठी जनतेने दिलेल्या प्रदीर्घ लढ्यात अनेकांचा सिंहाचा वाटा आहे. विशेषतः अण्णा भाऊ साठे यांचे उल्लेखनीय योगदान राहिले आहे.'[5] संयुक्त महाराष्ट्राचे आंदोलन आणि अण्णा भाऊ साठे याबाबत श्री अर्जुन डांगळे लिहीतात, 'इंडियन पिपल्स थिएटर असोसिएशनशी आलेला त्यांचा संबंध; संयुक्त महाराष्ट्राच्या आंदोलनात त्यांचा सक्रिय सहभाग यातून अण्णा भाऊंच्या प्रतिभेचे विविध पैलू जनतेसमोर आले आणि अण्णा भाऊंचे एक विकसित, प्रगल्भ, तेजाने तळपणारे आणि स्वतंत्र व्यक्तिमत्व साकार झाले.'[6] जनसामान्यांनी मनावर घेतल्याशिवाय कुठलीही क्रांती होऊ शकत नाही हे ओळखून त्यांनी महाराष्ट्रातील प्रत्येक व्यक्तीच्या मनात मुंबईसह संयुक्त महाराष्ट्र निर्माण झाला पाहिजे यासाठी आपल्या घरावर तुळशीपत्र ठेवले.

लाल बावटा पथक

टिटवाळा येथे 1944 मध्ये झालेल्या शेतकरी परुषदेत अमर शेख, अण्णा भाऊ साठे, द. ना. गव्हाणकर यांनी 'लाल बावटा कला पथका'ची स्थापना केली. घरादारावर निखारे ठेवून हे शाहीर तन-मन-धन अर्पून या लढ्यात उतरले. संयुक्त महाराष्ट्र चळवळीत शाहिरांच्या वाणी, लेखणीने समाजमनात क्रांतीच्या ठिणग्या पडत होत्या. म्हणूनच अण्णा भाऊ साठे यांचे संयुक्त महाराष्ट्र चळवळीतील योगदान लक्षणीय आहे. शाहिरीतून अण्णा संघर्षाच्या ठिणग्या पेरतात. याबाबत इतिहास लेखक प्रा. दिनेश मोरे लिहितात, 'पण मुंबई हे महाराष्ट्राचे हृदय आहे. संयुक्त महाराष्ट्राच्या पुरस्कर्त्यांनी याबाबतीत कोणतीही तडजोड स्वीकारण्यास नकार दिला. तशातच अण्णा भाऊ साठेंसारखे शाहीर आपल्या कवनातून लोकांना पेटवीत असत.[7] याची धास्ती घेतलेल्या देसाई सरकारने पुढे या पथकावर बंदी घातली. 'आमचं लक्ष थोर म्हणून साठे, तुम्ही मुक्त आहात नाहीतर तुमची खरी जागा तुरंगातच आहे.'[8] तत्कालीन मुंबई राज्याचे नेते नेते मोरारजी देसाई यांचे हे उद्गार अण्णांनी किती बिकट स्थितीत संयुक्त महाराष्ट्रासाठी कष्ट उपसले याचा याचा ईतिहास जागृत करतात. सरकारच्या या विरोधास जराही न जुमानता या त्रिकुटाने आपले पोलिसांची नजर चुकवून, शासनाचा बंदीहुकूम मोडून समाजमन जागृतीचे कार्य सातत्यपूर्ण चालू ठेवले. 'माझी मैना गावावर राहिली' याच लावणीत त्यांनी संयुक्त महाराष्ट्राच्या निर्मितीसाठी सर्वांनी एकतेने लढाण्याचे आवाहन आवाहन केले.[9] 'मुंबईची लावणी' अर्थात मुंबई कुणाची या वगनाट्यामुळे व त्यातील 'माझी मैना गावावर

राहिली, माझ्या जीवाची होतीया काहिली' या शाहिरीमुळे व इतर साहित्यामुळे त्यांचे संयुक्त महाराष्ट्र चळवळीत महत्वपूर्ण योगदान राहिले आहे. अण्णा शहाण्यास शब्दाचा मार देत.

संयुक्त महाराष्ट्राच्या चळवळीतील अण्णा भाऊ साठे यांच्या योगदानाबद्दल **श्री माधव वाघमारे** म्हणतात, 'अण्णा भाऊ साठे हे एक साहित्यिक म्हणून परिचित आहेत. परंतु त्यांचे संयुक्त महाराष्ट्राच्या चळवळीमध्ये योगदान महत्वाचे असूनही ते दुर्लक्षित राहिले आहे.'[10]

गृहितकांची पडताळणी

1. 'संयुक्त महाराष्ट्राच्या निर्मितीसाठी जनजागृती करण्यात अण्णा भाऊ साठे यांचे योगदान अनन्यसाधारण आहे'. हे गृहितक सत्य सिद्ध झाले आहे. शाहिरी, तमाशा ही पारंपरिक समाजमाध्यम त्यांनी परिणामकारकपणे वापरली. जनमानसांच्या हृदयात असलेल्या संयुक्त महाराष्ट्राच्या इच्छेला त्यांनी साद घातली.
2. 'तत्कालीन सरकारच्या जाचास न कंटाळता अण्णा भाऊ साठे यांनी क्रांतीचे रणशिंग फुंकले'. हे गृहितक सत्य सिद्ध झाले आहे. 'यह आझादी झुठी है देश की जनता भुखी है' असे म्हणत त्यांनी सर्वसामान्यांसाठी सरकारविरुद्ध शिंग उपसले.
3. 'अण्णा भाऊ साठे यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदान' याबाबत अधिक संशोधन होण्याची आवश्यकता नाही'. हे गृहितक असत्य सिद्ध झाले आहे. प्रत्यक्षात याबाबतीत अधिक संशोधन होण्याची आवश्यकता आहे. 'अण्णा भाऊ साठे यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदान' हा भाग प्रचंड दुर्लक्षिला गेला आहे. याबाबतीत अधिक खोलात जाऊन ऐतिहासिक संशोधन होण्याची आवश्यकता आहे.

निष्कर्ष व शिफारशी

1. 'संयुक्त महाराष्ट्राच्या चळवळीत अण्णा भाऊ साठे यांचे योगदान' याविषयीच्या संशोधनाबाबत आजपर्यंत मोठ्या प्रमाणात दुर्लक्ष झाले आहे. स्वतंत्र अध्यासन, शोध मोहीमा हाती घेण्याची आवश्यकता आहे.
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3. 'राष्ट्रभक्ती आणि शाहिरी वाङ्मय' या व अशा विषयांवर सामाजिक न्याय विभागामार्फत राष्ट्रीय चर्चासत्र आयोजित करण्यात येणे आवश्यक.
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२. सत्यशोधकीय विचारवंत आण्णाभाऊ साठे

प्रा. डॉ. सावंत जे. सी.
शंकरराव जगताप आर्ट्स ॲण्ड कॉमर्स कॉलेज, वाघोली, ता. कोरेगांव, जि. सातारा.

सत्यशोधक ही एक वैचारिक परंपरा आहे.या परंपरेचे महात्मा जोतीराव फुले हे निर्माते असून त्यांनी स्थापन केलेल्या सत्यशोधक समाज व सत्यशोधक चळवळीतून एका नव्या समाजाचा अभ्युदय झाला.भारताला फार मोठी ऐतिहासीक परंपरा आहे.प्राचीन काळापासून भारतात राजकीय, आर्थिक, सामाजिक, धार्मिक आणि सांस्कृतिक आदी बाबींचा विकास झाला.मात्र या विकासात सामाजिक वर्गवारी महत्वपुर्ण झाली.भारत खेड्यांचा देश आहे असे संबोधले जाते.आणि ही खेडी प्राचीन काळापासून स्वयंपूर्ण होती असे मानतात.एवढेच नव्हे तर आपल्या भारतीय इतिहासाची मांडणी करत असताना आपली खेडी स्वयंपूर्ण कशा प्रकारे होती याचे विवेचन अत्यंत उत्कृष्टरित्या करण्यात येते.मात्र या स्वयंपुर्णतेच्या पाठीमागे अशी सामाजिक वर्ग वारी होती की ज्या वर्गवारीमध्ये कोणत्याही वर्गातील व्यक्तीला आपला वर्ग बदलून वरिष्ठ वर्गात पात्रता असूनही जाता येत नसे.जर कोणी असा प्रयत्न केला तर त्याला जातीबहिष्कृत करण्यात येत असे.अशा या सामाजिक व धार्मिक बंधनात अडकलेल्या समाजात सर्वप्रथम सत्यशोधक दृष्टी दाखवण्याचे कार्य गौतम बुध्दांनी केले.ज्या परंपरेने बहुसंख्य स्त्रियांना व शुद्रांना अस्पृश्य ठरविले होते .'बहुजन हिताय-बहुजन सुखाय' अशी घोषणा करून सर्वप्रथम बुध्दांनी अमानवी रूढी-परंपरांच्या जोखडातून समाजाची मुक्तता केली.अशा लोकांच्या मुक्तिची चळवळ म्हणजे सत्यशोधक चळवळ असे ढोबळ मानाने म्हणता येई ल.

सत्यशोधक विचारांचा मागोवा घेतला असता काही प्रमुख गोष्टी आपणासमोर येतात.गौतम बुध्द, महात्मा फुले आणि डॉ.आंबेडकर हे सत्यशोधक परंपरेतील आहेत.या प्रत्येक महापुरूषाने आपला स्वतःचा ठसा उमटवलेला आहे. गौतम बुध्दांनी धार्मिक क्षेत्रात क्रांती केली आणि धार्मिक क्षेत्रात आपला स्वतःचा एक नवा प्रवाह सुरू केला.महात्मा फुल्यांनी विशेषतः सामजिक, शैक्षणिक क्षेत्रात क्रांती केली आणि तिथून पुढे सामाजिक व शैक्षणिक क्षेत्रात एक नवीन प्रवाह निर्माण झाला.डॉ.आंबेडकरांनी मुख्यत्वे राजकिय क्षेत्रात क्रांती केली आणि भारताच्या राजकिय क्षेत्रात एक नवा आंबेडकरी प्रवाह सुरू झाला.अगदी याचप्रमाणे आण्णा भाऊ साठे यांनी साहित्य आणि लोककलेच्या क्षेत्रात नवा विचारप्रवाह प्रवाहीत केला.आण्णा भाऊ साठे या सत्यशोधक परंपरेचे पाईक ठरतात .आण्णाभाऊंचे एकूण साहित्य आणि त्यांची विचारधारा पाहिली असता, आण्णा भाऊ साठे हे सत्यशोधक विचारपरंपरेतील ठरतात.अण्णा भाऊ साठे यांच्या जीवनाचे चार टप्पे आहेत. वारणेच्या खो-यात डोंगरद-यात वाढणारे भाऊ, दुसरा टप्पा म्हणजे वाटेगाव येथून मुंबईस चालत आलेले व पोटापाण्यासाठी नोकरी

शोधणारे भाऊ, त्यांच्या आयुष्याचा तिसरा आणि महत्वपुर्ण टप्पा म्हणजे,पद्दलित शोषित जनतेची दुखेः आपल्या लेखणीतून मांडणारे भाऊ.आण्णा भाऊंच्या आयुष्याच्या चौथा आणि अखेरचा टप्पा संयुक्त महाराष्ट्राच्या चळवळीनंतर मृत्यूपर्यतचा आहे.

आण्णा भाऊ साठेंनी पोवाडे, लावणी, गीते, कथा, कादंबरी, प्रवासवर्णन, नाटक, लोकनाटय असे साहित्यातील विविध प्रकार हातळले.वैचारीक व सामाजिक बांधिलकी हे त्यांच्या लिखाणाचे सूत्र आहे.उपेक्षित वंचित दलितांच्या बाजूने त्यांची सत्यपरिस्थितीची मांडणी आण्णा भाऊ साठेंनी केली.त्यांच्या कोणत्याही साहित्यकृतीतील नायक, नायीका हे आपल्या हक्कांसाठी सन्मानासाठी निष्ठापूर्वक झगडताना दिसतात. शरद पाटील यांच्या मते, "कोणत्याही साहित्य निर्मितीची कारणे फक्त वाङःमयीन नसतात,तर त्याला सामाजिक-राजकिय परिस्थितीही कारणीभूत असते."[१]

महात्मा जोतीबा फुले व डॉ.आंबेडकरांनी ज्याप्रमाणे ब्राम्हणशाहीस विरोध केला त्याप्रमाणे आण्णा भाऊ साठेंनीही ब्राम्हणशाहीस विरोध केल्याचे दिसते.ब्राम्हणशाही ही मनुस्मृती समर्थकांची संस्कृती असून हा मनुवाद किंवा ही भटशाही आण्णा भाऊ साठेंनी मुळापासून नाकारली आहे. महाराष्ट्र दलित साहित्य संघाच्या वतीने २ मार्च १९५८ रोजी आयोजित पहिल्या साहित्य संमेलनाच्या उद्घाटन भाषणात ते म्हणतात, "आम्हाला गंगेसारखे निर्मळ साहित्य हवे आहे. आम्हाला मांगल्य हवे आहे. आम्हाला मराठी साहित्याच्या थोर परंपरेचा अभिमान आहे.कारण मराठी साहित्याची नांदी आमच्याच जीवन-संघर्षाने झडली आहे.जेव्हा दलितांची सावली असहय होती तेव्हा महानुभावपंथीय साहित्यिकांनी सर्वांना ज्ञान मिळाले पाहीजे, ज्ञान हे मोक्ष असे समजून त्यांनी बंड केले.ते आमचे साहित्यिक,माणसाला माणूस म्हणून जगता आले पाहिजे असा दावा मांडून ज्यांनी दलितांच्या भाषेत महाराष्ट्राला सुंदर ज्ञानेश्वरी दिली ते आमचे साहित्यिक आणि चूकलेले महाराचे मुल कडेवर घेऊन जाणारे ते एकनाथ, ते आमचे साहित्यिक.आम्ही आपल्या वर्गाचे इमान पटवून त्याचा उपमर्द होणार नाही याची काळजी घेऊन त्याचे साहित्य निर्माण करूया.या दलितांचे जिवन सुखी व संमृध्द कसे होईल याची काळजी करूया,या दलिताला नि त्याच्या जीवनाला वरच्या पातळीवर नेण्याचा आपल्या कलेतून प्रयत्न करूया".[२]

आण्णा भाऊ साठे यांनी आपल्या 'पंजाब-दिल्लीचा पोवाडया' मध्ये 'देव, धर्म आणि संस्कृतीचा खोटा बुरखा घातलेल्या लोकांना देशाचे वैरी म्हणून संबोधले आहे'.[३] आण्णा भाऊ साठे यांचे हे विचार सत्यशोधकी विचारपरंपरेशी अगदी घट्टपणे बसतात.'वारणेच्या खो-यात' या कादंबरीत आण्णा भाऊ साठे भटशाहीचे वाभाडे काढतात, 'मंगलाचे लग्न ठरवण्यासाठी भटजीकडे नावरसनाव पाहण्याचा सल्ला बहीरू देतो तेंव्हा आण्णा भाऊ नारूमामच्या तोंडून म्हणतात, 'पाच तिथे परमेश्वर मग भटजीची काय जरूरी आहे? आणि भटजीला व पंचांगात पाहूनच जर सर्व करायचे तर माणसाला काहीच करता येत नाही.लग्नच काय; परंत मुहूर्ताशिवाय ऊसाला पाणीसुध्दा पाजता येत नाही.आम्हाला मुहूर्ताची वाट पातह बसावे लागेल.कारण विहीर काढायला, मोट जुंपायला, नांगरायला, कुळवाला, पेरणी करायला, कुपाण घालायला सा-यालाच मुहूर्त लावून ठेवला आहे.आणि रोज उठून मुहूर्त पाहायचा म्हटलं तर;आमचे बारा वाजतील.अहो मरायसाठी देखिल पंचांग चाळाव लागेल.म्हणून म्हणतो, आता नविन कायदा सूरू करा.....' वास्तविक भटशाहीने आणि ब्राम्हणशाहीने सत्यनारायण,पूजा-अर्चा ,स्वर्ग-नरक,जन्म-पुर्नजन्म,पाप-पुण्य आणि पंचांगासारख्या फालतू कल्पनांनी बहुजनांच्या जीवनात हजारो वर्षे बाराच वाजवले

आहेत.हा भटाचा कायदा रद्द करण्याचा आग्रह आण्णा भाऊ साठे धरतात आणि नविन कायदा सूरू करण्याचा सल्ला देतात... हा नवा कायदा जो विज्ञानवादी विचारांनी प्रेरित असला पाहिजे, असा त्याचा गर्भित अर्थ आहे.[४] याच कादंबरीत पुढे आण्णा भाऊ एका प्रसंगात लिहीतात, 'माणूस मेल्यावर माणसं त्याची जाळून राख करतात.मग त्याची हाडे आणि ते सर्व काही पाण्यात नेऊन टाकतात आणि सांगतात,आता म्हणे तो पुण्यवान झाला,त्याच्या आत्म्याला शांती मिळाली.खरे म्हटले तर तसे काहीच नसते.ही राख होण-याची आणि पाण्यात टाकणा-याची नुसती फसवणूक आहे.कारण राख पाण्यात टाकून पुण्य मिळत नाही आणि शांतीही मिळत नाही'.[५] आण्णा भाऊ साठे डॉ.बाबासाहेब आंबेडकर यांच्या विचार चळवळीकडे आकृष्ट झाले होते.जातीयवादी आणि धर्माध भटशाहीने दलितांना छळले आहे.जन्मजन्मांतरीच्या जाळयात अडकवून त्यांना कलंकीत केले. आण्णा भाऊ साठेंचा 'दलित' जातवाचक नव्हता.त्यापलिकडे तो ऊभा होता.शोषित,श्रमजीवी मग तो कोणिही असो,तो दलित,अशी आण्णा भाऊ साठेंची व्याख्या होती.त्याला जातापात-पंथ-धर्मभेद याची कसलीच बंधने नव्हती.[६]

आण्णा भाऊ साठे यांच्या कथांमधूनही त्याचे विचार स्पष्टपणे दिसतात.त्यांच्या 'मरीआईचा गाडा' या कथेत गावात आलेल्या प्लेगच्या साथीच्या पार्श्वभूमीवर जे नाटय घडते ते आण्णा भाऊ दाखवतात.गावात अचानक लोक आजारी पडू लागतात तेव्हा 'मरीआई' गावात शिरल्यामुळेच हे सारे घडते आहे असा निष्कर्ष गावातील काही लोक काढतात.यावेळी या अंधश्रध्देला बळी न पडता गावातील नाना पाटील हा तरूण विरोध करतो .आजार रोगराई ही मरीआईमुळे होत नसून अस्वच्छता व घाणीमुळे होते हे पटवून देतो.[७] आणि गावाला अंधश्रध्देच्या विळख्यातून बाहेर काढतो हे आण्णा भाऊ दर्शवतात.एकुणच अंधश्रध्दा व अनिष्ट रूढी परंपरांना नाकारून विज्ञानवादी सत्यशोधक भूमीका येथे आण्णा भाऊ दाखवतात. आण्णा भाऊ साठे त्याची दुसरी कथा 'बरबाद्या कंझारी' या कथेत आण्णा भाऊ साठे पतीनिधनानंतर विधवा स्त्रीने दुसरा विवाह केला तर समाज किती विरोध करतो हे दर्शवले आहे.या कथेची निल्ली ही नायीका व तिचा पिता बरबाद्या समाज लादत असणारी बंधने झुगारून देतात.जातपंचायतीच्या विरोधात जाणारी ही आण्णा भाऊंची भूमीका नक्कीच सत्यशोधक विचारांशी जूळणारी आहे.[८] 'सापळा' या कथेत आण्णा भाऊ अस्पृश्यांना कराव्या लागणा-या हीन कामांवर टीका करतात.जातीव्यवस्थेवर कठोर प्रहार करताना या कथेतील नायक हरिबा महार गावातील मरत जनावरे ओढण्यास नकार देतो आणि ज्यांची जनावरे आहेत त्यांनी त्यांची विल्हेवाट लावावी असे स्पष्टपणे सांगतो.[९] 'उपकाराची फेड' या कथेतही आण्णा जातिव्यवस्थेवर टीका करतात आणि एकुण समाजव्यवस्थेत दलितांचे स्थान काय आहे याची दलितांना जाणिव करून देतात.जात हे या देशातील वास्तव आहे वर्ण श्रेष्ठत्वाचा प्रभाव दलितांर्गतही कसा पसरलेला असून वर्ग व्यवस्थेतील श्रेष्ठ-कनिष्ठत्वाचा परीणाम समाजात कसा खोलवर रूजलेला आहे व आपण तो कसा दुर केला पाहीजे हे त्यांनी या कथेत मांडलेले आहे.[१०] याशिवाय 'अकलेची गोष्ट' आणि 'शेटजीचं इलेक्शन' या लोकनाटयांमधून आण्णा सावकार शेतकरीवर्गाचे शोषण का व कसे करतात याचे उत्तम दर्शन घडवतात.[११]

समारोप : आण्णा भाऊ साठे हे सत्यशोधक आहेत.महात्मा फुल्यांनी ज्या समाजातील अनिष्ठ प्रथा परंपरांवर टीका केली आणि त्याचा त्याग करा असे समाजाला सुचवले.अगदी त्याच प्रथांवर आपल्या साहित्यातून आण्णा भाऊंनी टीका केली

आहे.बहुजन वर्गाचे स्वातंत्र अत्यंत महत्वाचे असल्याचे प्रतिपादन त्यांनी केले.त्यांच्या बहुतांश साहित्यातून हे स्पष्टपणे दिसते.सामाजिक,आर्थिक समानतेचा पूरस्कार त्यांनी केला.त्यांनी सर्व प्रकारची गुलामगिरी नाकारलेली आहे,अंधश्रध्दा नाकारली आहे, ब्राम्हणशाही नाकारलेली आहे, शोषण नाकारले आहे. 'पृथ्वी शेषाच्या मस्तकावर तरली नसून दलितांच्या तळहातावर तरली आहे.' आणि "जग बदल घालुनिय घाव | मला सांगून गेले भिमराव" या त्यांच्या दोन विधानांमधूनच त्यांची समाजकडे पाहण्याची दृष्टी स्पष्ट होते.म्हणूनच लोकशिक्षण, लोकजागृती करणारे अण्णा हे एक प्रबोधनकार तर होतेच शिवाय स्वदेशी, अब्राम्हणी आणि सत्यशोधकी विचारपरंपरेतील फुले,आंबेडकरांच्यानंतरचे अण्णा भाऊ साठे हे एक सत्यशोधक होते.

संदर्भ साधने

१. पाटील शरद अब्राम्हणी साहित्याचे सौंदर्यशास्त्र,सुगावा प्रकाशन,पुणे,१९८८ पृष्ट क्र.१३९

२. डांगळे अर्जुन (संपा.)लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय,'पंजाब-दिल्लीचा पोवाडा' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ,मुंबई,तृतिय आवृत्ती २००६, पृष्ठ क्र.०४

३. डांगळे अर्जुन (संपा.)लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय,'पंजाब-दिल्लीचा पोवाडा' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ,मुंबई,१९९८, पृष्ठ क्र.५१

४. सकटे मच्छिंद्र,आण्णा भाऊ साठे -एक सत्यशोधक प्रज्ञा प्रकाशन कोल्हापूर २००५ पृष्ट क्र.१९७

५. साठे आण्णा भाऊ,वारणेच्या खो-यात, विद्यार्थीगृह प्रकाशन पुणे-९

६. भोसले एस. एस., डांगळे अर्जुन (संपा.) लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय, 'प्रातिनिधिक कथा-प्रस्तावना' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ, मुंबई, तृतिय आवृत्ती २००६, पृष्ठ क्र.१९५६

७. डांगळे अर्जुन (संपा.)लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय,'मरीआईचा गाडा' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ, मुंबई, तृतिय आवृत्ती २००६, पृष्ठ क्र.२५२ ते ३६०

८. साठे आण्णा भाऊ, बरबाद्या कंझारी, विद्यार्थीगृह प्रकाशन पुणे-९

९. डांगळे अर्जुन (संपा.) लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय,'सापळा' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ,मुंबई,तृतिय आवृत्ती २००६, पृष्ठ क्र.३३५ ते ३४६

१०. डांगळे अर्जुन (संपा.) लोकशाहीर आण्णा भाऊ साठे निवडक वाङःमय,'उपकाराची फेड' महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ, मुंबई,तृतिय आवृत्ती २००६, पृष्ठ क्र.३९४ ते ३९९

११. सकटे मच्छिंद्र, आण्णा भाऊ साठे -एक सत्यशोधक प्रज्ञा प्रकाशन कोल्हापूर २००५ पृष्ठ क्र.२१३

३. साहित्यिक अण्णाभाऊ साठे यांचे योगदान

डॉ. उर्मिला क्षीरसागर
श्रीमती मथुबाई गरवारे कन्या महाविद्यालय, सांगली.

प्रस्तावना

मराठी साहित्याला व संस्कृतीला चैतन्य प्राप्त करून देण्याचे काम या मराठी साहित्यिक कलावंतांनी केले ,त्यात अण्णाभाऊ साठे यांचे नाव अग्रक्रमाने घेतले पाहिजे .त्यांच्या साहित्याचे विचार विश्व व्यापक होते. महाराष्ट्राच्या ग्रामीण जीवनाचे व संस्कृतीचे पहिले चित्रणकर्तेम्हणून अण्णाभाऊंचा उदय झाला कारण त्यांना या जीवनाचे संस्कृतीचे प्रत्यक्ष ज्ञान होते ,तसेच अनुभवही होता .आपल्या आत्मविश्वासाच्या बळावर सुमारे तीस कादंबऱ्या व बारा कथासंग्रह त्यांनी लिहिले. त्याच्या अनेक आवृत्त्या निघाल्या.(१) त्यांच्या साहित्याचे केवळ भारतातच नव्हे तर जगातील अनेक देशात कौतुक झाले

शोधनिबंधाचा हेतू

अण्णाभाऊ हेसाहित्यिक व समाजसुधारक होते. महाराष्ट्राच्या सामाजिक व सांस्कृतिक क्षेत्रात त्यांनी मोलाचे योगदान दिले. भारतीय इतिहासात त्यांच्या साहित्याला महत्त्वाचे स्थान आहे. मराठी साहित्यातील अनेक प्रकार त्यांनी कुशलतेने हाताळले. त्यांच्या साहित्याचे विविध पैलू आजच्या तरुण पिढीस समजावे यासाठी हा शोधनिबंध लिहिला आहे.

साधने

प्रस्तुत शोधनिबधासाठी अण्णाभाऊंच्या जीवनावरील विविध लेख, चरित्रग्रंथ, विश्वकोश, वर्तमानपत्रे इत्यादी साधनांचा वापर केलेला आहे

पुर्वचरित्र

महाराष्ट्राच्या सामाजिक आणि सांस्कृतिक परिघातील एक कृतिशील आणि उमदा साहित्यिकम्हणजे अण्णाभाऊ साठे होय .अखंड महाराष्ट्रासाठी व मराठी भाषेच्या सन्मानासाठी लढलेला एक ओजस्वी शाहीयांच्या चेहऱ्यावर जो करारीपणा दिसतो, तोच करारीपणा प्रत्यक्षत्यांच्या जीवनातही तेवढाच तीव्र होता. संयुक्त महाराष्ट्राचा लढा असू दे किंवा लोकशाहीसाठी ची झुंज, त्यांची धगधगती वाणी आणि टिपेचा सूर जनमानसाचा अगदीठाव घेत असे. अण्णाभाऊंचे सारे साहित्य, वांग्मययाअद्वैतयातआहे त्यांच्या साहित्याच्या निर्मितीची बीजे आणि प्रेरणा चिंतनाच्या मूठभर कक्षा आणि आकलनाचा आवेग, साम्यवादी विचार प्रणालीची बांधिलकी दारिद्र्याच्या निशाणाखाली एकत्रित होऊन जगण्यासाठी पत्करावे लागणारेहौतात्म्य आणि माणूस म्हणून जगण्याविषयी चे आवाहन आदि साऱ्या गोष्टींची उकल या द्वैतात आहे(२),अण्णाभाऊंचा जन्म 1 ऑगस्ट 1920 रोजी वाटेगाव, जिल्हा सांगली येथे झाला(३).

भाकरीची गरज पुरी होत नसल्यामुळे ते शिक्षण घेऊन सुसंस्कृत होण्याचे स्वप्न सुद्धा पाहू शकत नसत, मग वांग्मयीन जाण तर दूरच राहिली.त्यांचे मूळ नाव तुकाराम होते. भाऊ हे वडिलांचे तर वालुबाई हे आईचे नाव.तुकाराम ज्येष्ठपुत्र असल्याने लोक आदराने त्यांना अण्णा म्हणत. त्यांचे शिक्षण किती यावर मतभेद आहेत, ते दुसरीपर्यंत शिकले असावेत

जडणघडण

बालपणातील त्यांच्या घडणीमध्ये मोठ्या प्रमाणात त्यांच्या स्वतःच्या शारीरिक व मानसिक सवयींचा वाटा आहे 1932 ते 1936 या काळात लोकगीते, कवने, पोवाडे पाठ करणे ते वरच्या पट्टीत गाणे, अशी त्यांना आवड होती .क्रांतिसिंह नाना पाटील यांच्या भाषणांचा प्रभाव पाहून त्यांनी स्वातंत्र्यलढ्यात उडी घेतली. कार्ल मार्क्सच्या साम्यवादी विचारांकडेही ते आकर्षित . त्यांनी आंबेडकरी प्रेरणेने आणि मार्क्सवादी जाणिवांनी लेखन केले .मराठी साहित्यातील अनेक प्रकार त्यांनी सारख्याच कुशलतेने हाताळले आहेत. चरित्रपर ग्रामीण आणि दलित या तिन्ही प्रवाहामध्ये त्यांच्या कादंबऱ्यांनी इतिहास घडविला.

साहित्यिक योगदान

जातीय तणाव आणि आर्थिक शोषण यांच्याविरुद्ध जगणारा शोषित माणूस त्यांच्या साहित्याच्या केंद्रस्थानी आहे. त्यामुळे मराठी साहित्याचा चेहरामोहरा खऱ्या अर्थाने अण्णाभाऊंच्या साहित्यकृती मुळे बदलला. भारतीय साहित्य क्षेत्रात अण्णाभाऊ हे खऱ्या अर्थाने अष्टपैलू लेखक आहेत की ज्यांनी साहित्याचे सर्व प्रकार यशस्वीपणे हाताळले आहेत. ते महाराष्ट्रातील एक प्रतिभावंत साहित्यिकहोय, व जागतिक क्षेत्रातील इत्यंभूत माहिती त्या देशातील सामाजिक राजकीय स्थित्यंतरे त्याचा होणारा चांगला-वाईट परिणाम याची सांगोपांग मांडणी त्यांच्या साहित्यात पहावयास मिळते. त्यांचे लिखाण म्हणजे सामान्य माणसाला सामान्य भाषेत केलेला उपदेश होय. साहित्यातून त्यांनी सामाजिक जीवन सामाजिक समस्या ,अन्याय-अत्याचार इत्यादींची मांडणी केली आहे.

आपल्या अनेक कथांमधून सामाजिक-राजकीय, धार्मिक, कौटुंबिक समस्यांना त्यांनी तोंड फोडले. महाराष्ट्राचे एक पारंपारिक लोकजीवन त्यांच्या कथात्म साहित्यात दिसून येते .पुरोगामी महाराष्ट्राच्या जडणघडणीमध्ये त्यांच्या साहित्याचा अतिशय मोलाचा उपयोग झाला आहे. त्यांच्या विचारातून लेखन विषयक भूमिका, बांधिलकी जशी व्यक्त होते तशीच समाजपरिवर्तनाची असलेली तळमळ ,देशाची सुख समृद्धी व देशभक्ती यांचाही प्रत्यय येतो.(४) त्यांनी श्रीमंत कष्टकऱ्यांना शोषितांना आपल्या साहित्यातून नायक बनवण्याचे ऐतिहासिक कार्य अगदी सहजपणे पेलूनमार्क्सवादआलापर्यायाने परिवर्तनवादी आंबेडकरवादी साहित्याचा गती देण्याचे कार्य केले. मानवजातीच्या कल्याणाची कामना करणारे प्रभावी लेखन त्यांनी केले. आपल्या लिखाणातून मराठी साहित्याचे विश्व विशिष्ट घटका पुरते मर्यादित नसून त्या देशातील तळागाळातील व्यक्ती ही एक नायकच आहे हे त्यांनी दाखवून दिले .समाज परिवर्तन व्हावे या हेतूने फकीरा, वैजयंता ,वारणेचा वाघ अलगुज ,चंदन गुलाम, रूपा, रानबोका, धुंद ,चित्रा, मथुरा ,अहंकार, फुलपाखरू ,केवढ्याचे कणीस, माकडीचा माळ, रानगंगा

,आवडी, अग्निदिव्य इत्यादीसारख्या कादंबऱ्यांमधून समाजातील विषमता, स्त्रियांविषयी असलेला दृष्टिकोन, गावगाड्यातील राजकारण आणि शोषण व्यवस्था इत्यादी विषयी विस्तृत लिखाण केले .अनेक वगनाट्य तून समाजातील वास्तविकता मोठ्या ताकतीने मांडली आहे व मानवतावादाचा प्रचार केला.

कार्ल मार्क्सच्या विचाराप्रमाणे श्रमिकांचे राज्य अस्तित्वात यावे या हेतूने सामान्यांचे दुःख साहित्यातून मांडले .त्यांनी सुंदर प्रेम कथा लिहिल्या. मराठी कथेचे पांढरपेशा वळण बदलले. विषयवआशयाच्याकक्षा रुंदावल्या. त्यांची सगळी महाराष्ट्र गीते पाहिल्यानंतर मराठी माणूस ,त्याचा गौरवशाली इतिहास, झुंजण्याचे सामर्थ्य ,लढाऊ बाणा वीरवृत्ती ,आवेश यांचे स्वाभिमानी चित्र या सर्व गीतांमधून त्यांनी रेखाटले आहे(५). महाराष्ट्राच्या ग्रामीण जीवनाचे व संस्कृतीचे ते पहिले प्रमुख इतिहासकार होय.साहसाचेचित्रण करणाऱ्या कादंबऱ्या (वारणेच्या खोऱ्यात), महिलांच्या समस्या वरील कादंबऱ्या(चित्रा, वैजयंता))प्रेमाचे चित्रण करणाऱ्या कादंबऱ्या(रानगंगा, अहंकार) ग्रामीण जीवनाचे चित्रण करणाऱ्या (रानबोका) इत्यादी अनेक साहित्य प्रकार त्यांनी हाताळले, तरी त्यांची अंगभूत प्रतिभा ही एका कथा लेखकाची होती .त्यांच्या कथांचे साधारणता पुढील प्रकारात वर्गीकरण होईल–कलात्मक, विनोदी कथा ,सामाजिक राजकीय ऐतिहासिक जीवनावरील कथा, आत्मचरित्रात्मक कथा, शोकांत व हृदयद्रावक कथा,गुन्हेगारी जीवनाचे वर्णन करणाऱ्या कथा ,कौटुंबिक कथा, अंधश्रद्धा विरुद्ध च्या कथा इत्यादी.(६)

आधुनिक मराठी साहित्यात एक प्रगतिशील व वैज्ञानिक विचारसरणी चे लेखक म्हणून त्यांना महत्त्वाचे स्थान आहे .आपल्या काव्य लेखनाच्या कारकिर्दीत त्यांनी पोवाडा, लावणी ,पदे ,गीते, गण छक्कडइत्यादी लोकगीतांचे प्रकार हाताळले. अनुभवालाही अनुभूती दाखविणारे लिखाण हे त्यांचे खास वैशिष्ट्य होय .त्यांच्या समग्र साहित्यातत्यांनी जीवन संघर्षातून प्रचंड वाचन, चिंतन आणि मननातून स्वतःच स्वतःच्या प्रयत्नांनी कमावलेली स्वतंत्र अशी जीवनदृष्टी अभिव्यक्त झाली आहे. त्यामुळे त्यांचे साहित्य वाचकांच्या हृदयाला भिडते. त्यांच्या जाणिवा उन्नत करते आणि त्याला जीवनाकडे बघण्याची एक नवी दृष्टी देते.(७) त्यांनी तमाशाच्या कलेला समृद्ध केले .लोकरंजन यासाठी लोकनाट्य नावाने आजही ते महाराष्ट्राच्या कानाकोपऱ्यात गर्जत आहे, याचे कारण वीर रस, शृंगार रस, कोमलता, क्रौर्य या सर्वांचे समीकरण म्हणजे अण्णाभाऊ होय. समाज केवळ भौतिक दृष्टीने समृद्ध होऊन चालत नाही तर नैतिक दृष्ट्या अधिक अधिष्ठान असावे लागते ही त्यांची धारणा होती. त्यांच्या साहित्यातील एकही पात्र असे नाही की जे दुर्गुणी बनले आहे, उलट दुर्गुणी पात्र सद्गुणी बनावीत आणि समाजाच्या उपयोगी ठरावीत असाच त्यांचा प्रयत्न होता. सत्तू, चंदन ,फकीरा, विष्णुपंत कुलकर्णी अशी कितीतरी पात्रे केवळ सौंदर्य दर्शना कडे नव्हे तर समृद्ध जीवन दर्शना कडे जाताना . अन्यायावर तुटून पडतात, या सगळ्या प्रक्रियेतून आदर्श जीवन व्यवस्थेसाठी दलित जनतेच्या मर्मभेदक आक्रोशाचा आविष्कार होतो.

अमृता,आबी, कृष्णाकाठच्या कथा, पिसाळलेला माणूस ,फरारी, बरबाद्या कंजारी ,भुताचा मळा ,रानवेली, राम रावण युद्ध ,निखारा इत्यादी 250 ते 300 कथा त्यांनी लिहिल्या. या कथा मराठी साहित्य पुरत्या मर्यादित न राहता त्या अनुवादातून सर्व प्रमुख भारतीय भाषांमध्ये पोहोचल्या. त्याचप्रमाणे जर्मन इंग्रजी पोलीस रशियन स्लोव्हाक इत्यादी विदेशी भाषांतही अनुवाद झाले. कथा लेखन करताना जी व्यक्तिचित्रे रेखाटली आहेत ती प्रत्यक्ष

त्यांना कुठे ना कुठे भेटली आहेत. ्या माणसांच्या जीवनातील दुःख, गरिबी, असहाय्यता, व्यसने, धाडसे ,संघर्ष ,अंधश्रद्धा या सर्व बाबी जवळून त्यांनी पाहिल्या होत्या म्हणून त्यांचे साहित्य हे वास्तवाशी सामना करताना दिसून येते. अकलेची गोष्ट ,खापर्‍या, देशभक्त घोटाळे, माझी मुंबई, पुढारी मिळाला, इनामदार, बिलंदर बुडवे, पेंग्याचं लगीन इत्यादी लोकनाट्य ,वगनाट्य त्यांनी लिहिली जाणीवपूर्वक तमाशा सुसंस्कृत लोककलेला लोकनाट्याचे रूप त्यांनी दिले. त्यांनी लिहिलेल्या लावणीत माझी मैना गावावर राहिली आणि मुंबईची लावणी या अविस्मरणीय आहेत.(८) गण लेखनाला त्यांनी वेगळे स्वतंत्र रूप दिले. संयुक्त महाराष्ट्राची गीते ही त्यांची मोलाची गीत संपदा होय. स्टालिनग्राडचा पोवाडा, बंगालची हाक ,बर्लिनचा पोवाडा, पंजाब-दिल्लीचा दंगा इत्यादी पोवाड्यांच्या माध्यमातून त्यांनी जनजागृती केली .लाल बावटा या कलापथकाच्या माध्यमातून राष्ट्रीय विचारांचा प्रसार केला.

अण्णाभाऊंच्या साहित्यावर आधारित साहित्य अनेक लेखकांनी निर्माण केले .सदा कराडे, आसाराम गायकवाड ,बाबुराव गुरव, किशोर जाधव, दिनकर साठे ,बजरंग कोरडे इत्यादींनी लेखन केले .त्यांनी विविध पुस्तकांना प्रस्तावना लिहिल्या. कमीत कमी शब्दात जास्तीत जास्त आशय कसा ठासुन भरावा याचा, या प्रस्तावना आदर्श आहेत. त्यातून त्यांची जीवनदृष्टी वांग्मयीन दृष्टिकोण याचे प्रत्यंतर येते. अण्णाभाऊ सामाजिक बांधिलकी मानणारे जीवन सन्मुख साहित्यिक होते. नाट्यमयता हा त्यांच्या लेखनशैलीचा खास गुण होता. त्यांनी मराठी कथेचे एक वेगळे रूप वाचकांसमोर आणली. मराठी भाषा, प्रदेश, संस्कृती यासंबंधी अलोट प्रेम त्यांच्या साहित्यातून व्यक्त होते. महाराष्ट्राच्या अव्वल व्यक्तिमत्त्वाचा आविष्कार हे त्यांच्या वांगमायचे खास वेगळेपण आहे. त्यांच्यापासून प्रेरणा घेऊन दलित लेखकांची एक प्रतिभावान पिढी निर्माण झाली, त्यात बाबूराव बागूल ,नामदेव ढसाळ ,लक्ष्मण माने यशवंत मनोहर, दया पवार ,केशव मेश्राम ,शरणकुमार लिंबाळे इत्यादीचा अंतर्भाव होतो .अण्णाभाऊंच्या काही कादंबऱ्यांवर चित्रपटही निघाले उदा. वैजयंता ,टिळा लावते मी रक्ताचा, डोंगरची मैना, चित्रा, फकीरा, वारणेचा वाघ इत्यादी(९).त्यांच्या वागमयानेएकूणच मराठी वाङ्ममयाला विषय,आशय,जीवन प्रश्न आणि मांडणीच्या संदर्भात वेगळेपणा बहाल केला, त्यांनी साहित्य सर्वसामान्य वाचकांपर्यंत नेले

निष्कर्ष

1. अण्णाभाऊ हे आधुनिक मराठीतीलवैविध्यपूर्ण आणि विपुल लेखन करणारे सिद्धहस्त व समर्थ लेखक होय.
2. ते स्वतंत्र स्वयंभू आणि उत्तर कालीनयावर खोलवर प्रभाव टाकणारे ललित लेखक आहेत.
3. त्यांनी कथा-कादंबरी ,लावणी ,पोवाडा ,नाटक, लोकनाट्य ,प्रवासवर्णन,छक्कड, पदे, गण असे विविध प्रकारचे लेखन यशस्वीरित्या केले असले तरी त्यांचा पिंड मूलतः कथाकाराचाआहे.
4. त्यांनी आधुनिक मराठी वाङ्मयातआशयविषयाचे नवे प्रवाह आणले. ते मराठीतील पहिले समर्थ दलित लेखक आहेत .पुढील दलित लेखक समीक्षकांना नवी वाट निर्माण करून देणारे हे आघाडीचे शिलेदारहोय.

5. **तमाशा कलेचे उद्धार करते व श्रेष्ठ कलावंत होय.**
6. **लोककला, लोकसमूह, लोकसंघर्ष, लोकरूची यांनी युक्त अण्णाभाऊंची भाषाशैली हे मराठीतील एक आकर्षक सौंदर्यस्थळ आहे.**

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४. अण्णाभाऊ साठे यांच्या निवडक कथात्मक साहित्यातील स्त्री चित्रण

प्रा. डॉ. सौ. कल्पना राजीव मोहिते
प्रोफेसर इतिहास विभाग प्रमुख, यशवंतराव चव्हाण कॉलेज इस्लामपूर, जि. सांगली.

प्रस्तावना

आधुनिक भारताच्या इतिहासात विसाव्या शतकात महाराष्ट्राच्या मातीत विविधांगी क्षेत्रात आपल्या कार्याचा ठसा उमटवणारी अनेक व्यक्तिमत्वे जन्मास आली. महाराष्ट्राच्या साहित्य विश्वात आपल्या लेखणीने सातासमुद्रापार अजरामर झालेले साहित्यातील एक अलौकिक व्यक्तिमत्व म्हणजेच साहित्यरत्न लोकशाहीर अण्णाभाऊ साठे. अण्णाभाऊंचे साहित्य म्हणजे मराठी साहित्य विश्वाला मिळालेली देणगी होय.

महाराष्ट्राच्या स्वातंत्र्यपूर्व सातारा जिल्ह्यातील सद्याच्या सांगली जिल्ह्यातील वाळवे तालुक्यातील वाटेगाव या गावी मातंग जातीत भाऊराव व वालूबाई यांच्या पोटी १ ऑगस्ट १९२० रोजी तुकाराम उर्फ अण्णा यांचा जन्म झाला.[१]

तत्कालीन सामाजिक विषमता, जातीयता, भेदभावाचे चटके यामुळे केवळ दीड दिवस शाळेत गेलेल्या अण्णा भाऊंनी साहित्याच्या क्षेत्रात अजरामर असे साहित्य लेखन केले. कादंबऱ्या, कथा, नाटके, पोवाडे,लोकनाट्य, कविता,प्रवास वर्णने इत्यादी विपुल अशी साहित्य संपदा त्यांच्या लेखणीतून निर्माण झाली.म्हणुन अण्णा भाऊंचे साहित्य म्हणजे महाराष्ट्राच्या साहित्यातील अमुल्य असा वाड्मयीन ठेवा. प्रस्तुतच्या शोधनिबंधात अण्णा भाऊंच्या निवडक कथात्मक साहित्यातील स्त्रीचित्रणाचा अभ्यास करण्याचा प्रयत्न केलेला आहे.

पूर्वचरित्र

गरिबी व अस्पृश्यतेचे चटके यामुळे स्वातंत्र्यपूर्व काळात वयाच्या १२ व्या वर्षी ते वडिलांबरोबर २२७ मैलांचा पायी प्रवास करत वाटेगांवहून मुंबईला आले.चरितार्थासाठी, पोटासाठी लहान वयात पडेल ती कामे त्यांनी केली.झाडूवाला,हमाली,मोलमजुरी इ.कामे करुन उदरनिर्वाहास सुरुवात केली.[२] या काळात वयाच्या १५-१६ व्या वर्षीच ते कामगार चळवळीकडे झुकले व कम्युनिस्ट पक्षाचे क्रियाशील कार्यकर्ते झाले. कॉ. श्रीपाद अमृत डांगे डॉ. बाबासाहेब आंबेडकर, कार्ल मार्क्स यांच्या विचारांनी ते प्रभावित झाले, याच काळात मुंबईतील गिरणी कामगारांचे प्रश्न,समाजाचे विदारक दृष्य,दुःख,संघर्ष या गोष्टी लहानपणी अनुभवल्या.

पुढे १९४२ स्वातंत्र्य चळवळीत ते सामील झाले.१९४४ ला शाहीर अमर शेख,शाहीर गवाणकर व अण्णा भाऊंनी "लाल बावटा" या कलापथकाची स्थापना केली.पोवाडे,लावण्या,वगनाट्ये या माध्यमातुन त्यांनी स्वातंत्र्य आंदोलन, संयुक्त महाराष्ट्राची चळवळ,गोवा मुक्ति आंदोलनात महाराष्ट्रभर जनजागृती केली.संपुर्ण महाराष्ट्र ढवळून काढला.[३] "माझी मैना गावाकडं राहिली माझ्या जीवाची होतीया काहिली" त्यांची ही लावणी संयुक्त महाराष्ट्राचे प्रेरणागीत बनली.

१९४२ नंतर अण्णा भाऊंनी साहित्य लेखनाकडे विशेष लक्ष दिले. त्यांनी उपेक्षित माणसांचे आणि श्रमाचे मुल्य राखुन मानवी जीवनाला नवा विचार देणारे,वास्तववादी लिखाण अत्यंत सुक्ष्म अशा निरीक्षणातुन तळमळीने केले.

लोकवाङःमय,लोकनाट्य,कथा,कादंबऱ्या,नाट्य,चित्रपट,पोवाडे,लावण्या,गीतं,पदे,गवळण,वग,तमाशा इ.अनेक साहित्यातील प्रकारात त्यांनी लिखाण केले.पोवाडा व लावणी या लोककथात्मक शैलीच्या वापराने ते विशेष लोकप्रिय झाले.मॅक्झिम गोर्कीच्या साहित्य वाचनाने त्यांना लिखाणाची उर्मी दिली.

अण्णा भाऊंचे साहित्य

अण्णां भाऊंनी एकुण ३५ कादंबरीचे लिखाण केले.त्यामध्ये चित्रा ही त्यांची पहिली कादंबरी. फकिरा, वारणेचा वाघ,माकडीचा माळ, आवडी,अलगुज,चिखलातील कमळ, गुलाम,मथुरा,रत्ना, रुपा, वैजयंता या काही कादंबऱ्या.त्यांच्या कादंबरीवर सात चित्रपटही निघाले.१९६१ साली "फकिरा" या त्यांच्या कादंबरीला महाराष्ट्र शासनाचा उत्कृष्ट कादंबरीचा पुरस्कार मिळाला.[४]

त्यांचे २२ कथासंग्रह आहेत. त्यातील खुळंवाडी, बरबाद्या कंजारी, स्मशानातील सोनं,आबी, भानामती,चिरागनरची भुतं, नवती, निखारा, कृष्णाकाठच्या कथा, गुऱ्हाळ, लाडी, पिसाळलेला माणुस, ठासलेल्या बंदुका, स्वप्नसुंदरी, रानगा, फरारी, भोमक्या आणि इतर कथा, भुताचा मळा, रानवेली, राम रावण युद्ध, जिवंत काडतूस, गजाआड हे काही कथासंग्रह. याचबरोबर पटकथा, पोवाडा शैलीतील दहा गाणी त्यांनी गायिली. इनामदार, पेंग्याचं लगीन, सुलतान ही नाटके त्यांनी लिहली. त्याचबरोबर अकलेची गोष्ट, कापऱ्या चोर, कलंत्री,देशभक्त घोटाळे, निवडणूतील घोटाळे, शेटजींचे इलेक्शन, बेकायदेशीर, पुढारी मिळाला, माझी मुंबई, मूक मिरवणूक, लोकमंत्र्यांचा दौरा, इ. लोकनाट्ये त्यांनी लिहली. अमळनेरचे अमर हुतात्मे,पंजाब दिल्लीचा दंगा या त्यांच्या काव्यरचनाही १९४८ साली प्रसिध्द झाल्या.

१९४३ साली त्यांनी लिहलेला स्टॅलिनग्राडचा पोवाडा "पार्टी" या मासिकात प्रसिध्द झाला.रशियाच्या इंडो सोविएत कल्चरल सोसायटीच्या निमंत्रणावरुन ते १९६१ साली रशियाला गेले होते.छत्रपती शिवरायांचे चरित्र पोवाड्यातुन त्यांनी रशियात सांगितले.

"कविता आणि माझा रशियाचा प्रवास" हे त्यांच्या प्रवासवर्णनाचे नाव.डॉ.बाबासाहेब आंबेडकरांच्या विचारांचे संस्कार त्यांच्यावर झाले होते.म्हणुनच "जग बदल घालुनी घाव।सांगुनी गेले मज भीमराव। हे त्यांचे गीत खुप गाजले.[५]

विलक्षण अशी प्रतिभा लाभलेल्या अण्णा भाऊंचे लिखाण भारतीय व इतर २७ भाषांत भाषांतरीत झाले अशालेखक,साहित्यिक,शाहीर,कथा कादंबरीकार अण्णा भाऊंनी अलौकिक साहित्याने समाजमनात आपले वेगळे स्थान निर्माण केले.त्यांच्या समृध्द लेखणीतून उपेक्षित वर्गाला जीवनाचा मार्ग प्राप्त झाला. जातीव्यवस्थेने किडलेल्या समाजात अस्पृश्यांना,दबलेल्यांना,दुःखीतांना,कष्टकऱ्यांना,पुरुषप्रधान समाज व्यवस्थेत दुय्यम स्थान असलेल्या स्त्रियांना जगण्याचं बळ दिलेलं होतं.त्यांच्या साहित्यात उपेक्षित,शोषित,गरीब वर्गाचं जिणं, वास्तव

जगणं त्यांनी मांडलेले आहे.पोटासाठी धडपडणाऱ्या ,संघर्ष करणाऱ्या अठरा विश्व दारिद्र्य असणाऱ्या ,उपाशीपोटी दिवस काढणाऱ्या गोरगरीब व सामान्य जनतेच्या लोकजीवनाचे दर्शन आणि जगण्यासाठी स्वाभीमान व संघर्ष अण्णाभाऊंच्या कथा, कादंबऱ्यातून पहायला मिळतो.

अण्णा भाऊंचे कथालेखन

अण्णा भाऊंनी १९४९ पासुन कथालेखनाला सुरुवात केली ते आयुष्याच्या अखेर पर्यत१९६९ पर्यत लिहीतच होते.[६] त्यांनी प्रारंभीचे कथालेखन युगांतर,मशाल,आशा इ.नियतकालिकातून केले.त्यांनी अनेक कथा प्रकारामध्ये कथालेखन केले.[७] त्यामध्ये सामाजिक, राजकीय, ऐतिहासिक, दलित, विनोदी, कलात्मक, हृदयद्रावक, शोकांत, आत्मचरित्रात्मक याबरोबरच गुन्हेगारी जीवनाचे चित्रण करणाऱ्या कथा, प्रेमकथा, कौटूंबीक, अंधःश्रध्दांच्या विरुध्दच्या कथा अशा अनेक कथा त्यांनी लिहल्या.[८]

अण्णा भाऊंच्या निवडक कथात्मक साहित्यातील स्त्रीचित्रण

अण्णा भाऊंच्या कांही निवडक कथात्मक साहित्यातील स्त्रीव्यक्ती रेखांचे चित्रण पाहता त्या झोपड पट्टीत राहणाऱ्या,काबाडकष्ट करणाऱ्या,मुरळी,वेश्या समजल्या गेलेल्या पोटासाठी, कुटूंबासाठी, प्रामाणिकपणे राबणाऱ्या इ.स्त्रीजीवनाचे दर्शन त्यांच्या साहित्यातून होते.[९] या सर्व स्त्रिया सोशीक आहेत कष्टाळू, त्यागी आहेत..समकालीन परिस्थितीत पुरुषप्रधान संस्कृतीत समाजव्यवस्थेत दुय्यम स्थान असणाऱ्या स्त्रिया अण्णा भाऊंच्या साहित्यात या स्त्रिया खंबीरपणे धाडसाने निर्णय घेत असलेल्या दिसतात.हे यातील निवडक कथां चित्रणावरुन समजते.

बिलवरी

"बरबाद्या कंजारी" या अण्णा भाऊंच्या कथा संग्रहातील बिलवरी ही एक स्त्रीप्रधान नायिका असलेली कथा.या कथेत बिलवरी पोटासाठी तमाशा ही लोककला सादर करुन आपला व जमातीचा चरितार्थ चालविणारी वीस वर्षाची तरुण सुंदर स्त्री. सुगीच्या दिवसात आपल्या जमातीतील लोकांना बरोबर घेऊन गावोगावी पालं घेऊन जाणारे हे लोक.तांड्यातील शे-दोनशे लोकांची देखभाल करण्याची जबाबदारी बिलवरीच असते.त्यांच्या कुटूंबाची गुजराण या तमाशावरच चालत असते.बिलवरी या जमातीची म्होरक्या असते.

येळापूर गावात तमाशासाठी ती आपली पालं गावच्या देशमुखाच्या मर्जीविरुध्द त्याच्या शेतात उतरते.त्यांना शेतात राहायला देशमुख विरोध करतो पण सुंदर बिलवरीला बघुन मात्र तिच्या जमातीला शेतात राहायची परवानगी देशमुखांकडून मिळते. ती तमाशा करण्यासाठी देशमुखाच्या वाड्यावर जाते तेव्हा देशमुखाची बिलवरीवर वाईट नजर जाते.देशमुखाच्या वाड्यावर काम करणारा गरीब पण धन्याशी इमान असणाऱ्या अमीनचे व तिचे प्रेम जुळते.तेव्हा देशमुखाने प्रचंड संपत्ती देऊ केली तरी गरीबीतही आपलं चारित्र्य जपणारी बिलवरी, नैतिकतेचे सुंदर स्त्रीचित्रण अण्णा भाऊंनी या कथेत उभे केले आहे.

त्याचबरोबर तिची अब्रु घ्यायल्या आलेल्या देशमुखाच्या तावडीतून आपला जीव धोक्यात घालून तिच्या वडिलांना व तिला वाचवणारा गरीब कामगार अमीन.एक कणखर निर्णयक्षम,चारित्र्यवान प्रामाणिक,गरीब कष्टाळू,अन्यायाविरुध्द पेटून उठणारी,देशमुखाशी टक्कर देऊन आपल्या जमातीचेही रक्षण करणारी धाडसी

बिलवरी या कथेत पहायला मिळते.पुरुषप्रधान भारतीय संस्कृतीत अण्णा भाऊंच्या साहित्यात स्त्रियांचं शील जपणं हा अमुल्य ठेवा व तो जपल्याचं चित्रण या कथेमध्ये दिसते.बिलवरीच्या अब्रुलाच हात घालणाऱ्या देशमुखाच्या विरुध्द म्हणजे आपल्या धन्याविरुध्द दंड थोपटलेला अमीन व गरीबीतही अन्याया विरुध्द लढा देणाऱ्या,पेटून उठणाऱ्या आपले शील जपणाऱ्या बिलवरी सारख्या नायिका अण्णा भाऊंनी आपल्या कथेत आणल्या.[१०]

डोळं

अण्णा भाऊंच्या "स्मशानातील सोनं" या कथासंग्रहातील 'डोळं' ही नैतिक मुल्यांची जाणीव कशी जागविली जाते याचे चित्रण करणारी एक हृदयद्रावक कथा.या कथेची नायिका गीता ही नवऱ्याला देवासमान मानणारी सुंदर स्त्री,विशेषतःतिचे डोळे खुपच सुंदर असतात.तिचे हे सुंदर डोळेच तिच्या दुःखाचे कारण ठरतात.नवरा व सासरचे लोक तिचा संशयाने छळ करतात.वास्तविक गीताचे मन व हृदय निर्मळ असते पण संशयामुळे घरच्यांना ते गढूळ दिसते.स्वतःच्या चारित्र्याबद्दल तापलेल्या तेलातून पैसा काढण्याची अग्निपरीक्षा देण्याची वेळ गीतावर येते तेव्हा ठामपणे नकार देणारी गीता पापी ठरवली जाते.क्षणाक्षणाला उत्कंठा वाढवून काळजाचा ठाव घेणारी ही कथा शेवटी माहेरी घालवलेल्या गीताने आपल्या दुःखाचे कारण असणारे स्वतःचे हे सुंदर डोळे, म्हणुन ती डोळ्यात शेंडाचा चीक घालून स्वतःची दृष्टी घालवून बसते.डोळ्यांचं सौंदर्य हा तिच्यासाठी शापच ठरला.[११]

नैतिकता ही केवळ उच्चवर्णिय अथवा श्रीमंत लोकांकडेच असते असे नाही तर समकालीन,गरीब,उपेक्षित पददलित या स्त्रिया प्रसंगी जीव देतील पण आपल्या शीलाचं रक्षण करणाऱ्या,गरीबीतही नीतीमतेला धक्का लागू न देणाऱ्या आहेत हे गीताच्या डोळं कथेतून प्रत्ययाला येते.

निखारा

अण्णा भाऊंच्या "निखारा" या कथासंग्रहातील निखारा ही कथा फुला या गरीब, प्रामाणिक मुलीची आहे. देवभक्ती,भजन,कीर्तन करणाऱ्या गरीब विठोबा डंगारणेची फुला ही आईविना वाढलेली पोर.सुंदर दिसणारी फुला वयात आल्यानंतर तिच्या लग्नाची काळजी असलेले वडील.

स्त्री म्हणजे उपभोग्य वस्तु असे समजणारे व त्यांच्या गरीबीचा फायदा घेणारे अनेक गावगुंड समकालीन परिस्थितीत समाजात असतात. फुलाच्या गावातील गुंग्या पाटलांसारखे काही लांडगे स्त्री शोषण करण्यासाठी टपलेले असतात.

गुंग्या पाटलाला फुलाने दाद न दिल्याने चिडून त्याने विठोबावरती घरात गांजा ठेवल्याचा खोटा आळ आणून त्याला पोलिसात पकडून दिले.झालेल्या मानहानीत विठोबाचा मृत्यु होतो.तेव्हा आपल्या कुटूंबावर ,वडिलांवर झालेल्या अन्यायाची धग मनात ठेवून फुला बदला घेते.गावगुंड गुंगा पाटलासह त्याचे घर निखाऱ्याने पेटवून देते अशी ही कथा.[१२]

अन्यायाचा प्रतिकार करणाऱ्या,असहाय्य परिस्थितीतही धैर्याने मुकाबला करणाऱ्या फुलासारख्या धाडसी स्त्रियांचे अण्णा भाऊंनी आपल्या कथेत चित्रण केले आहे.अण्णा भाऊंच्या "खुळंवाडी" या कथासंग्रहाच्या

प्रस्तावनेमध्ये अण्णा भाऊंच्या कथा विषयी आचार्य अत्रे म्हणतात,"अण्णा भाऊंच्या कथा या जगण्यासाठी लढणाऱ्या माणसांच्या कथा आहे" हे सार्थ वाटते.[13]

काडीमोड

असहाय्य परिस्थितीत, ऐन तारुण्यात वैधव्याची कुऱ्हाड कोसळलेल्या एकाकी जिनं जगणाऱ्या सखुच्या जीवनातील काडीमोड ही कथा.औताड्याची देखणी सुंदर सखु वीस वर्षाची असताना नवरा मेला.पदरी एक दोन वर्षाचे मुल.तेव्हा विधवेपणानं जगायचं कसं नि अब्रुदार म्हणुन मरायचं कसं हा प्रश्न भेडसावणारी सखु खंबीरपणे दुःख विसरते.भाऊबंदानी घर,शेत लुबाडू नये म्हणुन मोठ्या जिद्दीनं ,धडपडीनं मुलगा भीमाला मोठं करणाऱ्या कष्टाळू सखुचं चित्रण अण्णा भाऊंनी काडीमोड या कथेत केले आहे.

पुढे जाऊन ही कथा वेगळ्या वळणावर येते.वयात आलेल्या भीमाचे लग्न ठरावे म्हणुन सखु भैरुबाला नवस बोलते.भीमाचे हरणा नावाच्या मुलीशी लग्न होते पण नवस जोपर्यत फेडत नाही तोपर्यत ती नवविवाहीत सुन व मुलाला एकत्र येऊ देत नाही.शेवटी दोघांत काडीमोड होतो.[14]

नवस बोलणं ,त्यातुन गैरसमज मग काडीमोड.रुढी परंपरांच्या,अंधःश्रध्दांच्या भोवऱ्यात अडकलेला समाज त्यातून झालेला भीमाचा काडीमोड. पण अण्णा भाऊंनी आपल्या कथांत अंधःश्रध्दांचे समर्थन कधीच केले नाही. शेवटी अंधःश्रध्देच्या विरोधात असणारी ही कथा सखु मुलाचा संसार पुन्हा जोडून देते.थोडक्यात समाजात असणाऱ्या अनिष्ठ चालीरिती,रुढीपरंपरा,अंधःश्रध्दा यांच्या भोवऱ्यात लोक अडकले होते यातून समाजाला मुक्त करण्याच्या जाणिवेतुन निर्माण झालेली काडीमोड ही कथा.

आबी

"आबी" या कथासंग्रहातील आबी ही कथा, आबी या ग्रामीण मुलीच्या जीवनाची कथा आहे.आवडी गावच्या आबा भोसल्याची आबी ही देखणी मुलगी. तिला त्रास देणाऱ्या,तिच्या विषयी वाईट नजर ठेवणाऱ्या व तिचे ठरलेले लग्न मोडणाऱ्या बक्याचा अत्यंत धाडसी वृतीने आबी बदला घेते याचे चित्रण या कथेत आहे..पण पुढे तडजोड म्हणुन ती सांगून आलेल्या मुलाशी लग्न करते पण तेही गुन्हेगारी प्रवृतीच्या माणसाशी आपले लग्न झाले,आपण फसले गेलो हे समजताच नवऱ्याचे घर सोडून येणारी,त्याच्याकडे नांदण्यास नकार देणारी करारी,निश्चयी आबीचे चित्रण या कथेत आहे.अत्यंत कष्टप्रद परिस्थितीतही ती आपल्यावरील अन्यायाचा बदला घेते.[15]

स्त्री ही अबला नाही तर ती सबला आहे याचे उदाहरण म्हणजे आबी .ती ज्या धैर्याने अन्याचाचा प्रतिकार करते.स्त्रिया जेवढ्या सोशिक असतात तेवढ्याच त्या अन्यायाचा प्रतिकार करताना आक्रमकही होतात, दुर्गेचा अवतार धारण करतात हे आबीच्या चित्रणातून समजते.परिस्थितीनेच त्या तशा बनतात.करारी,धाडसी आबीचे चित्रण अण्णा भाऊंनी या कथेत केले आहे.

समारोप

अण्णा भाऊंच्या कथात्मक साहित्याचे चित्रण पाहता त्यांच्या साहित्यात कष्टकरी,कामगार,झोपडपट्टीत राहणाऱ्या,दलित,सामान्य गोरगरीब कुटूंबातील स्त्रिया आहेत.त्या उदार आहेत,प्रामाणिक,मायाळू ,कष्टाळू,सोशिक

व आत्मविश्वासू आहेत पण प्रसंगी फुला व आबी सारख्या अन्यायाचा प्रतिकार करताना त्या दुर्गेचा अवतार देखील धारण करतात.त्या धाडसी व करारी आहेत. अण्णा भाऊंनी आपल्या साहित्यातील या क्रांतीकारी व्यक्तिरेखांना मानाचे,आदराचे स्थान दिलेले दिसते.त्या सर्व स्त्रिया सुंदर आहेत,त्यांच्या साधेपणातील सौंदर्याचे वर्णन वाचताना त्यात कुठेही भपकेबाज पणा नाही तर त्यांच्या सौंदर्यात निखळ शालीनता जाणवते ती वाचकांच्या मनाला भावते.

आपल्या कथेतून त्यांनी बिलवरी,गीता,फुला,मानकी,आबी,लाडी,सखु,आवडी अशा कितीतरी स्त्री व्यक्तिरेखांना अमर केले. या व्यक्तिरेखा अण्णा भाऊंनी पाहिलेल्या होत्या,अनुभवलेल्या होत्या.म्हणुनच १९६० साली अभिनव प्रकाशनने "बरबाया कंजारी" हा त्यांचा कथासंग्रह प्रकाशीत केला तेव्हा त्याच्या प्रस्तावनेत अण्णा भाऊ म्हणतात," मी जे जीवन जगतो,पाहतो,अनुभवतो तेच मी लिहतो.मला कल्पनेची पंखं लावून भरारी मारता येत नाही.त्याबाबतीत मी स्वतःला बेडूक समजतो.यातील सारी पात्रं माझ्या आयुष्यात या ना त्या कारणाने येऊन गेलेली आहेत.[१६] अण्णा भाऊ ज्या परिसरात वावरले त्याठिकाणच्या उपेक्षित,दलित,पीडितांचा जो संघर्ष त्यांनी अनुभवला, पाहिला तो कथेतून चित्रित केला. पुरुषप्रधान भारतीय संस्कृतीत अण्णा भाऊंच्या साहित्यातील या नायिकांना बरोबरीचे ,आदराचे,स्थान दिलेले दिसते.

अण्णा भाऊंचे समकालीन वाटेगाव येथील लोकशाहीर अण्णा भाऊ साठे शिल्पसृष्टी समितीचे (महाराष्ट्र शासन) संचालक श्री.बाबासाहेब कृष्णाजी पाटील हे अण्णा भाऊंविषयी आपल्या आठवणी सांगताना म्हणतात,"अण्णा भाऊ मुंबईहून जेव्हा जेव्हा वाटेगावला येत तेव्हा मी कै.जंगले गुरुजी व अण्णा भाऊ तिघे एकत्र भेटत असे.अण्णा भाऊ त्यांच्या कथा आम्हाला ऐकवत.वाचकाच्या भूमिकेतून आमची प्रतिक्रिया ऐकण्यास ते ऊत्सुक असत.पुढे ते म्हणतात, त्यांच्या कथा कादंबऱ्यातील पात्रं ही याच वाटेगाव परिसरातील,वारणेच्या खोऱ्यापासुन ते तारळी खोऱ्यापर्यंतची आहेत.ती वास्तव आहेत फक्त काही पात्रांची नावे बदलली असतील पण माकडीचा माळ ,खुळंवाडी हा सगळा परिसर व यातील माणसांचे चित्रण आपल्या सुक्ष्म निरीक्षण शैलीतून अण्णा भाऊंनी आपल्या कथातून केले आहे.[१७]

अण्णा भाऊंनी आपल्या कथातून अन्यायाविरुध्द पेटून उठणाऱ्या धाडसी,कणखर,तितक्याच मृदू पण करारी अशा स्त्री व्यक्तिरेखांचे चित्रण केले आहे. लढणाऱ्यांना या व्यक्तिरेखा नेहमीच बळ देतील.

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५. आण्णाभाऊ साठे यांच्या साहित्यातील मानवतावाद संघर्ष आणि स्थानिक इतिहासाचे वास्तववादी चित्रण

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अण्णांच्या समग्र साहित्यातून दलित, उपेक्षित आणि ग्रामीण या तिन्ही प्रवाहाचे लेखन झालेले दिसून येते. मानवाने मानसाशी कसे वागावे, दलितांचे सामाजिक, उपेक्षित जिवन किती कष्टाचे आहे यांचे स्थानिक सामाजिक जीवन किती वंचित आहे हे त्यांच्या साहित्यातुन दिसून येते.

आण्णा भाऊराव साठे उर्फ तुकाराम भाऊराव साठे यांचा जन्म सांगली जिल्हयातील वाटेगांव येथे १ ऑगस्ट १९२० रोजी झाला. त्यांचे समग्र साहित्य दलित साहित्याच्या प्रवाह या संकल्पनेच्या अंगाने येत असले तरी त्यांचे लेखन हे मानवतावादी संघर्षाने भरलेले दिसते.

दलितांच्या जगण्याच वास्तवदर्शी चित्रण

अण्णाभाऊ साठेंनी आपल्या कादंबरी वाःङमयातून ग्रामिण उपेक्षित आणि दलितांच्या जगण्याच वास्तवदर्शी चित्रण केले आहे . अण्णांनी हे लेखन काळाची गरज म्हणून लिहीलेले नसून समस्त मानवजातीसाठीची शिकवन या भुमिकेतून लिहिलेले आहे. त्यांच्या कादंबऱ्यातून उपेक्षितांचा सामाजिक प्रश्न बलुतेदार, शेनमजुर, भटक्याजाती–जमाती व त्यांच्या स्त्रिया मुले या घटकांना अनुसरुन येतो. त्यामध्ये वारणेच्या खोऱ्यात, गुलाम, रानगंगा चित्रा, वैर, माकडीचा माळ या कादबंऱ्यातील स्त्रिया, देवदासी, शेतकरी, कामगार, कलाकार, व्यवसनाधीन यांच्या जगण्याविषयीचे सामाजिक, आर्थिक, सांस्कृतिक प्रश्न का? आणि कसे? निर्माण झालेले प्रश्न सोडविण्यासाठी ज्या — त्या कादंबरीतील पात्रे आपापल्या परीने जसा जमेल तसा प्रयत्न करताना दिसतात. 'वारणेचा वाघ' या कांदबरीत शेतकऱ्यांचे शोषण करणाऱ्या सावकार, भांडवलदार आणि पर्यायाने सरकारविरूध्द बंड पुकारणाऱ्या हिंदुरावांचे दर्शन घडते. ज्या सावकारांनी दस्तखत करून गरिबांच्या जमिनी बळकावल्या होत्या, त्यांच्याविरूध्द बंड थोपटून त्यांनी लिहिलेली गहाणखते फाडतो. गरीब शेतकऱ्यांना त्यांच्या जमिनी परत मिळवून देतो. 'रानगंगा' या कांदबरीतून नदीचे पाणी अडविल्यामुळे जाधवांच्या शेतीची व घराची झालेली उध्वस्त अवस्था चित्रित झालेली आहे.[१]

अण्णांच्या कांदबऱ्यातून येणाऱ्या ग्रामीण भागातिल उपेक्षित समाज कोणाचा व्देष करत नाही तर त्याला संपत्ती आणि श्रीमंती पेक्षा समाजात माणसासारखे जगायचे आहे पण त्यांच्या जगण्यावर जर घाला घालायचा प्रयत्न केलाच तर तो त्यांच्याविरुद्ध संघर्ष करतो. 'वारणेचा वाघ' कादंबरितील सत्तु भोसले सरकारविरुध्द् बंड पुकारुन त्यांना धारेवर धरतो. वारणा खोऱ्यात 'प्रतिसरकार' स्थापन करुन दीन, दलित, शोषित, पिडीत, गाव कुसा बाहेरील लोकांवरिल अन्याय — अत्याचारांविरुध्द् दंड थोपटतो. तो म्हणतो, ''हे

कुंभकरणाच्या अवलादिचं राज हाय, आपुन तलवार घेऊनच त्यांच्या उगवर नाचले पाहिजे.[२] असाा अन्यायाविरुदध् पेटून उटनाग नायक अण्णांनी उभा केलेला आहे.

मानवतावाद

अण्णाभाऊंच्या साहित्यामध्ये मानवतावाद दिसून येतो. त्यांच्या साहित्यातून ग्रामीण जीवन, दलितांचे भावविश्व, शोषण, मार्क्सवादी, साम्यवाद, डॉ. बाबासाहेब आंबेडकर यांचे समतेचे, मानवतेचे जीवन प्रतिबिंबीत झालेले दिसून येते. आपल्या साहित्यातील प्रेरणांचा अविष्कार करताना अण्णा भाऊ म्हणतात, ''जग बदल घालुनी घाव सांगुनी गेले आम्हा भिमराव''.[३] यातून माणसाने मानवतेने वागल पाहिजे. गोर गरिबांवार अन्याय अत्याचार करून त्यांचे दमन करण्यापेक्षा त्यांना समतेने जीवन जगू दया असा संदेश दिलेला आहे. म. फुले, राजर्षी शाहू महाराज आणि डॉ. आंबेडकरांनी समतेचा लढा दिला तर अण्णा भाऊंनी आपल्या साहित्यातून जातीव्यवस्था विषमता, उपेक्षित जीवनाचा कमालीचा विरोध केला आणि मानवतावादी समाजव्यवस्था निर्माण होण्यासाठी आटोकाट प्रयत्न केला. अण्णा भाऊ भिंती नसलेल्या शाळेत शिकले, त्यांनी जिवंत माणसे वाचली, दारिद्रयावरती मात करण्यासाठी मुंबई गाठली पण तिथे ही मिळालेले काम आणि पडेल ते दाम घेऊन अण्णांनी कामे केली. कधी घरगडी म्हणून, कोळसा वाहणारा हमाली करणारा, कुत्रे सांभाळणारा, डोअर किपर, खाणकामगार, सोगांडया, रंगारी मजूर, तमाशातील झिलकारी अशी असंख्य काम पोटासाठी करावी लागली.[४] पण त्यांना खरे प्रत्येक ठिकाणी मानवतेसाठी संघर्ष करावा लागला.

स्थानिक इतिहासाचे वास्तववादी चित्रण

अण्णाभाऊंना पोट भरण्यासाठी मुंबईला कामगार म्हणून जावे लागले. पण तेथील वास्तव जीवन अतिशय हलाकीचे होते. मुंबई यंत्रांची तंत्राची बेकारांची, जगणाऱ्यांची, चोरांची, भांडवलदारांची आहे असे वर्णन अण्णाभाऊ करतात. वाटेगांवात जातीयतेचे चटके त्यांना बसले होते. तसेच मुंबईच्या गल्ली बोळातून फिरणाऱ्या अण्णाभाऊंना वर्ग विषमतेचे चटके बसले. एका बाजूला गिरणीत राहणारे बकाल वस्तीत रहाणारे आणि दुसऱ्या बाजुला मुंबईच्या एका ठिकाणी राहणारे श्रीमंत लोक[५] त्यांचे जीवन यांचे चित्रण लावणीतून, साहित्यातून केले आहे.

'मुंबईची लावणी' मध्ये याचे वर्णन त्यांनी केले आहे.

मुंबईत उंचावरी । मलबार हिल इंद्रपूरी।
कुबेरांची वस्ती तिथं सुख भोगती।
नायगांव, धरावीला माटुंग्याच्या शेजारला।
बेकारांची पारं घाणीमध्ये लोळती ।।

अण्णा भाऊंनी केलेले हे मुंबईचे वर्णन वास्तववादी आहे. माणसाला अंतर्मुख करणारे आहे. मुंबईतील वास्तविक आहे. माणसाला अंतर्मुख करणारे आहे. मुंबईतील वास्तविक भीषण चित्र लोकांपुढे आणण्यासाठी त्यांनी ही लावणी रचली होती.

पौराणिक कथामध्ये राम सीताला जे वनवासी जीवन भोगावे लागले. त्यापेक्षा वाईट जीवन आजच्या वर्तमानकाळातील, कामगार पती–पत्नीला भोगावे लागते हे अण्णाभाऊंनी आपल्या लावणीतून रचले आहे.

''माझी मैना गावाकडे राहिली
माझ्या जीवाची होतीया काहिली।।
ओतीव बांधा । रंग गव्हाळा, कोर चंद्राची।
उदात्त गुणाची । मोठया मनाची। सीता
ती माझी रामाची ।

झोंपडपट्टीत कामगारांच्या पती–पत्नीला पोटाची खळगी भरण्यासाठी वेगळे राहावे लागते. कष्टकरी, कामगार, दलित समाजाचे जीवनसुखी नसून वनवासात राहण्यासारखेच आहे.

अण्णाभाऊ साठेचे लहानपण जातीय संघर्षातच गेले. व मोठेपणी वर्गशोषणाला बळी पडत होते. त्यांचे साहित्य या सर्वांचे वास्तविक चित्रण करते. त्यांच्या साहित्यावर कार्लमार्क्स व डॉक्टर बाबासाहेब आंबेडकर यांच्या विचारांचा प्रभाव जाणवतो. या दोन्ही तत्वज्ञानाच्या मुल्यातून त्याचे साहित्य आकार पावलेले आहे.[६]

कार्लमार्क्सने संघर्षाचे मुळच वर्गसंघर्ष सांगितले आहे. याचे उदाहरण म्हणून 'गुलाम' या कांदबरीकडे पाहता येते. या कांदबरीचा नाथ अनाथ 'वासू' आहे. त्याचे आई वडील इथल्या व्यवस्थेचे बळी ठरले आणि त्यांचा मुलगा वासू हा गुलाम झाला. या कांदबरीतील ग्रामीण भागातून येणारी शोषणाची वृत्ती किती हीन पातळीवर जाते. तसेच या गरीब, कष्टकरी लोकांचे जिवंतपणच कसे नाहीसे केले जाते. शिवाय त्याच्याच जमिनीत गुलाम म्हणून मरेस्तोवर राबावे लागते. हे राबनेच आपल्या जीवनाचे एक अंग बनवायचे असा 'गुलाम' अण्णांनी उभा केला. त्याच्या दु:खाने कड गाठलेली आहे. दु:खाला वाचा फोडण्याचे अन्य मार्ग संपलेले आहेत. हा वासू याच गर्तेत अडकलेला आहे. सामाजात जो कोणी वर्ग सत्ताधारी असतो. तो आपल्या हितसंबंधाच्या सोयीचे असेल तर त्यात बदल घडवून आणावा असे त्या सत्ताधीश वर्गाला वाटत नाही. त्यामुळे शोषितांचा संसार गाडग्या–मडक्याचाच राहातो.[७] सतत पोटाची खळगी भरण्याची चिंता करण्यात आयुष्य संपते. ते कशी भविष्याची उभारणी करणार? असा प्रश्न यातून निर्माण होतो.

अण्णाभाऊ यांच्या साहित्यातील तत्वज्ञान कसे होते. याविषयी रा. ग. जाधव म्हणतात, 'अण्णाभाऊंच्या वाङ:मयातील कम्युनिझम हा प्राकृतिक कम्युनिझम होता. अण्णाभाऊंच्या घडण काळातील मानवाच्या विशाल जाणिवेचा तो नवा धर्म होता. त्यांच्या साहित्याची प्रेरणा कार्ल मार्क्स व डॉ. बाबासाहेब आंबेडकर अशी मिश्र स्वरूपाची होती. या दोन्ही तत्वज्ञानाच्या मुल्यातून त्यांचे साहित्य आकार पावलेले आहे''[८]

अण्णांच्या साहित्यातून दलित, उपेक्षित यांचा मानव म्हणून जगण्याचा संघर्ष वास्तववादी चित्रित केलेला आढळून येतो. स्थानिक बडया लोकांशी संघर्ष करत आपले जीवन व्यतीत करतो. तो कोणाचा द्वेष करत नाही. श्रीमंताविषयी मत्सरभाव नाही तर सत्ता, संपत्ती आणि श्रीमंतीपेक्षा समाजात माणसासारखे

जगायचे आहे. यासाठी सर्वसामान्यांचा लढा आहे. दलित शोषित समाजाच्या व्यथा—वेदनांना वाचा त्यांनी फोडली. अण्णांच्या साहित्य लेखणीतून मानवतावाद संघर्ष आणि स्थानिक समाजाचे सामाजिक चित्रण, आर्थिक चित्रण स्पष्ट दिसून येते. या साहित्यातून स्थानिक इतिहासाचं महत्वही समजते. स्थानिक लोकांवर उच्चवर्णियाकडून होणारा अन्याय, अत्याचार, त्याविरूध्दची झुंज दिसते. अन्यायाची जाणीव व झालेला माणूस वर्ग संघर्षाचा पाईक बनतो. हेही साहित्यातून त्यांनी दाखवून दिलेले आहे.

तत्वज्ञानातून खरा मानवतावाद संघर्ष दिसून येतो. अण्णांनी आपल्या साहित्यातून विषमतावादी व्यवस्थेबद्दल कमालीचा निषेध केला आणि समतावादी समाजव्यवस्था निर्माण होण्यासाठी आटोकाट प्रयत्न केला. आपल्या साहित्यातून मानवतावाद संघर्षाचे वास्तववादी चित्रण केले. जे आजच्या काळानुसार प्रासंगिक आहे.

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६. खिरविरे येथील सावकारांच्या वह्यांची होळी (७ नोव्हेंबर १९४९)

डॉ. गणेश शंकर विधाटे
इतिहास विभाग, राधाबाई काळे महिला महाविद्यालय, अहमदनगर, ता. जि. अहमदनगर.

महत्वाचे शब्द :— रोखेफाडी, गहाणखते, खरेदीखते, सालखते, लाल बावटा

प्रस्तावना

अहमदनगर जिल्हा हा जहाल शेतकऱ्यांचा जिल्हा म्हणून ओळखला जातो. 'शेतकरी आम्ही झालो समदं लाल बावटेवालं' असे अहमदनगर जिल्हयातील कम्युनिस्ट विचारांचे शेतकरी अभिमानाने म्हणत असत. जिल्हयातील कम्युनिस्ट पक्ष मजबूत करण्याचे काम या शेतकरी चळवळीच्या माध्यमातून झालेले दिसून येते. अशा या शेतकऱ्यांची नगर जिल्हयातील संघटित चळवळ खऱ्या अर्थाने सुरू झाली ती कम्युनिस्ट पक्षाच्या नेतृत्वाखाली किसान सभेची स्थापना झाल्यापासून. किसान सभेच्या अजेंड्यावर असलेला महत्त्वाचा कार्यक्रम म्हणजे सावकारशाही विरोधी दस्तऐवज ताब्यात घेऊन ती फाडणे अगर नष्ट करणे होय. या सावकारशाही विरोधी चळवळीचा महत्वाचा भाग म्हणजे नगर जिल्हयातील खिरविरे येथील सावकारांच्या वहयांची होळी होय.

१. **खिरविरे गावातील सावकारांची पूर्वपीठिका :—** सावकारशाहीला विरोध हा कम्युनिस्टांचा एक प्रभावी कार्यक्रम होता. अहमदनगर जिल्हयातील अकोले तालुक्याच्या वायव्य भागात खिरविरे हे एक दुर्गम गाव आहे. गावातील बहुसंख्य लोक आदिवासी शेतकरी होते.[१] या गावात शहा, मेहता या आडनावांची व्यापारी सावकारांची ७—८ कुटुंबे मोठमोठया वाड्यात वास्तव्य करून होती. डांग, टोकद, घोटी, इगतपूरी, समशेरपूर इत्यादी गावांमध्ये त्यांची मोठी सावकारी होती. ते लोकांच्या निरक्षरता, अडचणीचा गैरफायदा घेऊन कर्जाच्या बदल्यात खोटी दस्तऐवज लिहून घेत असत. फसवला गेलेला शेतकरी न्यायालयात गेला असता तेथे त्याचा टिकाव लागत नसे. अनेक शेतकऱ्यांच्या जमिनी या सावकारांनी गिळंकृत केलेल्या होत्या. त्यामुळे या शेतकऱ्यांमध्ये मोठा असंतोष होता.[२]

२. **सावकारी दस्तऐवज बाहेर काढून त्याची होळी करण्याचा कार्यक्रम** :— महाराष्ट्र राज्य किसान सभेची पहिली परिषद ठाणे जिल्हयातील टिटवाळयाला १२ जानेवारी १९४५ रोजी भरली. महाराष्ट्रातील किसान सभेची अध्वर्यू होते कॉ.शामराव परूळेकर आणि गोदूताई परूळेकर. ऐतिहासिक कम्युनिस्ट पक्षाच्या नेतृत्वाखालील वारली आदिवासींचे बंड सुरू झाले ते किसान सभेच्या या परिषदेतून स्फूर्ती घेवूनच. मे १९४५ मध्ये ठिणगी पडलेल्या या बंडाचा वणवा सर्व आदिवासी भागात दोन वर्षात पसरला. या वणव्यात सर्व प्रकारची वेठबिगारी आणि गुलामगिरी

जळून राख झाली.[३] या परिषदेतील कार्यक्रमानुसार सन १९४६ साली गुहा, राहुरी येथील शिबीरामध्ये कॉ.शामराव परूळेकर व गोदूताई परूळेकर यांनी सावकारांचे दस्तऐवज बाहेर काढून त्यांची सार्वजनिक ठिकाणी होळी करावयाची, आदिवासी कर्जमुक्त झाला असे घोषित करावयाचे असा विचार मांडला होता.[४]

३. **सावकारशाही विरोधी चळवळीची कार्यवाही** :— कॉ. मुरलीधर नवले, कुशाबा नवले, भाऊसाहेब थोरात, कॉ. धर्मा कमा भांगरे, कॉ. सक्रुभाई मेंगाळ यांनी अकोले व संगमनेर तालुक्यातील कार्यकर्त्यांची एक बैठक बोलावली. बैठकीत सावकारांच्या घरावर मोर्चा काढून त्यांच्या ताब्यातील शेतकऱ्यांची गहाणखते, खरेदीखते, सालखते ताब्यात घेऊन त्यांची भर चौकात होळी करावे असा कार्यक्रम ठरला.[५]

या मोहिमेचे नेतृत्व कॉ. मुरलीधर नवले यांनी करावे असे ठरले. ७ नोव्हेंबर हा रशियन राज्यक्रांतीचा स्मृतीदिन. सावकारांजवळची कागदपत्रे जाळण्यासाठी कार्यकर्त्यांनी हा दिवस जाणीवपूर्वक निवडला. राजूर, अकोले, राजापूर, संगमनेर, खिरविरे इत्यादी गावातील १०० कार्यकर्त्यांनी लाल बावटयाचा जयजयकार करीत खिरविरे गावात प्रवेश केला व सावकारांच्या घराला वेढा घातला. आपल्याकडील सर्व कागदपत्रे जमा करण्याचे सावकारांना आवाहन केले. सावकारांनी त्याच्याकडे दुर्लक्ष करून दरवाजे बंद केले. अखेर बळजबरीने एकएका सावकाराच्या घरात प्रवेश करून तिजोरीतील कर्जाचे दस्तऐवज गोळा केले आणि गावातील मंदिरासमोर उपस्थित लोकांसमोर त्यांची जाहीर होळी केली. यावेळी सावकारांच्या घरातील बायकामुलांना कोणत्याही प्रकारचा त्रास कार्यकर्त्यांनी दिला नाही. तसेच त्यांच्या रोकड व दागिन्यांना हातही लावला नाही. जमलेल्या जमावाला उद्देशून कॉ. मुरलीधर नवले म्हणाले, ''भावा—बहिणींनो सावकारांच्या जाचातून तुम्ही आता मुक्त झाला आहात. तुमच्या जमिनींचे खोटे दस्तऐवज तुमच्या सर्वांच्या साक्षीने आगीच्या भक्षस्थानी पडले आहेत. आता तुम्ही घाबरायचे कारण नाही. तुम्ही कर्जमुक्त झालात. तुमच्या जमिनी जर सावकारांनी ताब्यात घेतल्या असतील, तर लगेच आजपासून तुम्ही कसायला सुरूवात करा. किसान सभा सदैव तुमच्या पाठीशी आहे. सावकारांनी अरेरावी व अत्याचार केले तर आम्हाला बोलवा. बोला लाल बावटे की जय.''[६]

४. **सरकारी दडपशाही** :— खिरविरे प्रकरणाची बातमी जिल्हयात वाऱ्यासारखी पसरली. कॉ.बुवासाहेब नवले, कॉ. कुशाभाऊ नवले, कॉ. मुरलीधर नवले यांच्याकडे बंदुका असूनही त्यांनी त्याचा प्रत्यक्ष वापर केला नाही.[७] मात्र एका सावकाराने पोलीस स्टेशनला या नेत्यांच्या विरोधात खून आणि दरोड्याची तक्रार केली. परंतु पोलिसांची धाड पडण्याआधीच प्रमुख नेते भूमिगत झाले. मात्र काहींना अटक करण्यात आली. अटक झालेल्यांमध्ये निवृत्ती गोडसे, विठ्ठल हासे यांचा समावेश होता. सरकारने या घटनेनंतर कॉ. मुरलीधर नवले, रावसाहेब शिंदे, भाऊसाहेब थोरात, कॉ. धर्मा कमा भांगरे यांच्यावर हजारो रूपयांची बक्षिसे लावली. अहोरात्र त्यांच्या मागे पोलिसांचा ससेमारा लागला. त्यांना आश्रय देणाऱ्यांचा पोलिसांनी छळ आरंभला. पोलिसांच्या दडपशाहीचा सर्वत्र वरवंटा फिरू लागला.[८]

खिरविरे प्रकरण हे दक्षिणेतील रेखेफाडीच्या (दख्खनचे दंगे) चळवळीशी साधर्म्य दाखविणारी चळवळ होती. सावकारांच्या वह्यांची होळी करण्याची घटना ही आदिवासी भागातील एक क्रांतिकारी घटना ठरली. या घटनेचा निर्णय स्थानिक नेत्यांनी घेतलेला होता. आपल्यावर अन्याय करणाऱ्यांना कम्युनिस्टांनी धडा शिकवल्याचे उदगार जनतेच्या मुखातून निघत होते. त्यामुळे त्यांनी या कृतीचे भरभरून समर्थन केले अशी नोंद रावसाहेब शिंदे आपल्या 'ध्यासपर्व' या आत्मचरित्रात करतात.[९]

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५. https://mr.wikipedia.org/wiki%E0%A4%AD%E0%A4%BE%E0%A4%B8%E0%A4%8D%E0%A4%95%E0%A4%B0%E0%A4%B0%E0%A4%BE%E0%A4%B5_%E0%A6%E0%A5%81%E0%A4%B0%E0%A5%8D%E0%A4%B5%E0%A5%87, last seen at 02/09/2020

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९. शिंदे रावसाहेब, ध्यासपर्व. A Rebel for a cause, उपरोक्त, पृ.क्र.२२७.

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७. दुसऱ्या महायुद्धातील यशवंत घाडगे यांची कामगिरी

किरण गणपत कुंभार
इतिहास विभाग, प्रा. डॉ. एन. डी. पाटील महाविद्यालय, मलकापूर, पेरीड.

प्रस्तावना

दुसरे महायुद्ध

(१सप्टेंबर १९३९ ते २सप्टेंबर १९४५)हे युद्ध मुख्यत: युरोप व आशियामध्ये दोस्त राष्ट्रे व अक्ष राष्ट्रे यांच्या मध्ये झाले. जर्मनीने पोलंडवर केलेल्या हल्ल्याने हे युद्ध १ सप्टेंबर १९३९ रोजी अधिकृतपणे सुरू झाले. यानंतर फ्रांस, युनायटेड किंग्डम आणि इतर राष्ट्रांनी जर्मनी विरुद्ध युद्ध पुकारले. जपान व इटलीने जर्मनीच्या बाजुने युद्धात पदार्पण केले. डिसेंबर १९४१ मध्ये जपानने अमेरिकेवर हल्ला केल्यावर अमेरिकेने युद्धात सक्रीय भाग घेतला व येथून युद्ध जगभर पसरले. दोस्त राष्ट्रांमध्ये चीन, रशिया, इंग्लंड, अमेरिका व इतर राष्ट्रांचा समावेश होता, तर अक्ष राष्ट्रांमध्ये जर्मनी, इटली व जपान हे देश होते. जवळ जवळ ७०देशांचे सैन्य यात सहभागी झाले होते. या युद्धात सहा कोटींच्यावर जीवित हानी झाली. मानवी इतिहासातील ही सर्वात मोठी जीवित हानी आहे. या युद्धामध्ये दोस्त राष्ट्रांचा विजय झाला.

मित्र राष्ट्रांच्या विजयात भारतीय सैनिकांचा मोठा वाटा आहे. या सैनिकांनी युरोप, आफ्रिका आणि पूर्व आशियात अनेक मोहिमांमध्ये भाग घेतला, आणि ब्रिटिशांना विजय मिळवून दिला. ब्रिटीश भारताच्या सुमारे ४०००सैनिकांना त्यांच्या पराक्रमासाठी शौर्य पदके मिळाली. त्यातील ३१सैनिकांना विक्टोरिया क्रॉस हे सर्वोच्च शौर्य पदक मिळाले.

भारतीय सैनिकांचा समावेश

भारतीय सैनिक इथिओपियात इटालियन सैन्याशी, इजिप्त, लिबिया, ट्युनिशिया आणि खुद्द इटलीमध्ये इटालियन आणि जर्मन सैन्याशी लढले. पण भारतीय सैनिकांच्या लढाया मुख्य करून जपानी सैनिकांशी मलाया, सिंगापूर आणि ब्रम्हदेश येथे झाल्या. भारतीय भूसेनेने उत्तर आफ्रिका, (ईजिप्त धरून) इराक, इराण, ईशान्य हिंदुस्थान, ग्रीस, ब्रह्मदेश व मलाया येथील युध्दांत लढाया मारल्या. युध्दोत्तर काळात मलाया, इंडोनेशिया व इंडोचायना येथील अस्तिर परिस्थितीला मार्गावर आणण्याची कामगिरी त्यांनी केली.

ब्रिटिश सैन्य हे जर्मन आघाडीवर लढत होत व पराभूत होत होते. या पार्श्वभूमीवर पूर्व आफ्रिकेत भारताच्या चौथ्या व पाचव्या डिव्हिजनने उत्कृष्ट पराक्रम दाखवून विजयश्री प्राप्त केली. 'सिदीबरानी'च्या लढाईत फोर्थ इन्फन्ट्री डिव्हिजन व सेव्हंथ आर्म्ड डिव्हिजननी आपल्या संयुक्त कारवाईत आपल्या शौर्याने इटलीच्या सैन्याचा पाडाव केला व या एकाच लढाईत १,३०,०००सैनिकांना कैद केले आणि ४०० टँक्स व १२४० तोफा हस्तगत केल्या. नंतर 'अलअमीन व इटली येथील युद्ध आघाड्यवर भारतीय सैन्याने मोठे

विजय मिळविले. भारताच्या चौदाव्या इन्फन्ट्री डिव्हिजनने ब्रह्मदेशाचा मोठा प्रदेश जपानी सैन्याकडून जिंकून घेतला. दुसऱ्या महायुद्धाच्या समाप्तीच्या वेळी भारतीय सैन्य संख्या वीस लाख होती व अधिकाऱ्यांची संख्या १५००० होती. भारतीय सैन्याच्या पराक्रमाविना ब्रिटिशांना जर्मनी व जपान विरुद्ध विजय मिळविता आला नसता. या युद्धात ३१भारतीयांना 'व्हिक्टो रियाक्रॉस' हा सर्वोच्च वीर सन्मान मिळाला. यात महाराष्ट्रातील यशवंत घाडगे व नामदेव जाधव या दोघांचा समावेश आहे. हे दोन्ही वीर मराठा इन्फन्ट्री रेजिमेंटचे होते. ब्रिटिश ईस्ट इंडिया कंपनीच्या अधीन असलेल्या एका लहान स्थानिक सैनिकांच्या तुकडी चेदुसऱ्या महायुद्धा अखेर जगातील एका मोठ्या सैन्यात रूपांतर झाले होते.[1]

सैनिकांची प्राण हानी

महायुध्दात झालेली भू सैनिकांची प्राण हानी व इतर हानी पुढील प्रमाणे आहेत : मृत्यू : १५,२९१ जखमी : १०,३७१. युध्द बंदी : ७२,८५८. जपान विरूध्दच्या लढायांत, इतर लढायां पेक्षा सैनिकांची हानी (मृत्यू, जखमी, युध्द बंदी व बेपत्ता) फार मोठी झाली. ती अशी : (अ) मलाया : ६२, १७५ (सैनिक) (आ) ब्रह्मदेश : ४०,४५८ (सैनिक) (इ) इटली : २२,४९७ (सैनिक) (ई) ऊत्तर आफ्रिका १५,२४८ (सैनिक) (उ) सूदान व एरीट्रिया : ४,७८५ (सैनिक) (ऊ) इराक व इराण : ५४१ (सैनिक) (ए) ग्रीस : ३१४ (सैनिक). समुद्रावर एकूण ४९९ सैनिक मृत्यू, जखमी व युध्द बंदी झाले.[2]

इंग्रजांच्या राज्यात व्हिक्टोरिया क्रॉस या पदकाला खूप महत्व आहे. ब्रिटिश सैन्यातील अतुलनीय शौर्य धाडस दाखवणाऱ्या सैनिकांना हे पदक दिले जात असे. या पदकाची सुरवात व्हिक्टोरिया राणीने २९ जानेवारी १८५६ साली केली. वर्णभेदामुळे सुरवातीला हा पुरस्कार फक्त गोऱ्या लोकांना देण्यात येई. पण भारतीय उपखंडातील सैनिकांची कामगिरी पाहून १९११ पासून या पुरस्कारासाठी काळ्या लोकांना म्हणजे भारतीयांनाही (भारतीय उपखंड) ग्राह्य धरण्यात येईल अशी घोषणा करण्यात अली. आणि १९१४ दरवान सिंग नेगी नावाच्या भारतीयान भारतातील प्रथम व्हक्टोरिया क्रॉस पटकावले. तेहि फ्रान्स मध्ये झालेल्या युद्धासाठी.

मराठा लाईट इन्फन्टरी मधील २ योध्यांनी व्हिक्टोरिया क्रॉस पटकावले त्यापैकी एक म्हणजे यशवंत घाडगे. यशवंत घाडगे यांचा जन्म १६नोव्हेंबर १९२१रोजी पासल गाव सातारा येथे झाला. १९४१ साली घाडगे ५ मराठा लाईट इन्फन्टरी मध्ये शिपाई म्हणून भरती झाले. यशाची एक एक पायरी चढत वयाच्या २२ वर्षाचे असताना ते नाईक पदा पर्यंत पोहचले. त्यांचा ९१९२ क्रमांक होता. दुसऱ्या महायुद्धात भारताने ब्रिटिशांच्या बाजूने उडी घेतली. आणि ब्रिटिश सैन्याच्या भारतातील बऱ्याच तुकड्या युरोप, आणि मध्य पूर्व आणि पूर्व भागात युद्धासाठी उतरल्या त्यावेळी यशवंत घाडगे यांची ५ मराठा लाईट इन्फन्टरी युरोपात होती.[3]

यशवंत घाडगे यांची कामगिरी

१० जुलै १९४४ रोजी जर्मन सैन्याच्या ताब्यात असलेली छावणी ताब्यात घेण्यासाठी, यशवंत घाडगे आणि त्यांची तुकडी अप्पर टिम्बर व्हॅली इटली येथे दाखल झाली. ब्रिटिश सैन्याने जर्मन छावणीवर हल्ला केला. या हल्ल्याच्या वेळेला यशवंत घाडगे रायफल तुकडीचे नेतृत्व करत होते. त्यांच्या या हल्ल्याला जर्मन पोस्टकडून कडवा प्रतिकार मिळत होता. जर्मन सैन्याकडून होणारा मशीनगनचा प्रतिकार एवढा जबरदस्त होता

कि घाडगे यांच्या तुकडीतील बहुतांश सैनिक शाहिद झाले वा जबर जखमी झाले. यशवंत घाडगे एकटेच त्या पोस्ट समोर लढत उभे राहिले. अशाही परिस्थितीत माघार न घेता ते कडवी झुंज देत राहिले. त्यांनी सर्वात आधी हात गोळा त्या पोस्टवरील मशीनगनच्या दिशेने भिरकावला. त्यात अचूक हल्यात माशिनगन आणि ती चालवणारा गार झाले. त्यानंतर त्यांनी हातातील टॉमी गनच्या साहाय्याने अजून दोन शत्रू टिपले. शेवटी टॉमीगनची मॅगझीन संपली ती भरण्यात, बदलण्यात वेळ न दवडता. त्यांनी ती रिकामी गन घेऊन पोस्टवर धावुन गेले आणि राहिलेल्या दोघांना रिकाम्या गनच्या दस्त्यान ठार केले. एकट्याने एक हाती पोस्ट घेतली पण तेवढ्यात शत्रूच्या स्नाइपरने त्यांचा लांबुन अचूक वेध घेतला. यशवंत घाडगेना पाठीत व छातीत गोळ्या लागल्या आणि त्यांनी जिंकलेल्या पोस्टवर त्यांनी देह ठेवला. त्यांच्या या अतुलनीय पराक्रमा बद्दल त्यांना १९४४ साली मरणोपरांत व्हिक्टोरिया क्रॉस बहाल केला गेला.[४]

समारोप

दुसऱ्या महायुध्दाच्या काळात भारताने इंग्लंडला सर्व प्रकारची मदत केली. भारतीय सैन्याच्या पराक्रमाविना ब्रिटिशांना जर्मनी व जपान विरुद्ध विजय मिळविता आला नसता. भारतीय सैनिक इथिओपियात इटालियन सैन्याशी, इजिप्त, लिबिया, ट्युनिशिया आणि खुद्द इटलीमध्ये इटालियन आणि जर्मन सैन्याशी लढले. ब्रिटीश भारताच्या सुमारे ४००० सैनिकांना त्यांच्या पराक्रमासाठी शौर्य पदके मिळाली. त्यातील ३१ सैनिकांना विक्टोरिया क्रॉस हे सर्वोच्च शौर्य पदक मिळाले. त्यापैकी एक यशवंत घाडगे होय. त्यांच्या या अतुलनीय पराक्रमा बद्दल त्यांना १९४४ साली मरणोपरांत व्हिक्टोरिया क्रॉस बहाल केला गेला. ३१ ऑक्टोबर १९४४ रोजी छापलेल्या लंडन गॅझेट मध्ये त्यांची शौर्य कथा छापून अली होती. त्यात पुढील गौरवउद्गार काढले आहेत. "जीवंत राहण्याची अशा अगदी धूसर दिसत असतानाही धैर्य, जिद्द आणि कर्तव्यनिष्ठा या मूल्यांच्या आधारावर यशवंत घाडगे लढत राहिले." यशवंत घाडगे यांच्या सारख्या असंख्य सैनिकांनी आपल्या प्राणांची पर्वा न करता आपले कर्तव्य पार पाडले. म्हणूनच भारतीयांच्या शैर्याची ओळख संपूर्ण जगाला झाली.

संदर्भ

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८. प्रजाहितदक्ष जयसिंगराव घाटगे

राजेंद्र मा. घाडगे
प्रशासकीय अधिकारी (सातारा)

थोर समाजक्रांतीकारक राजर्षी शाहू महाराजांचे जीवनकार्य अनेकांना ज्ञात आहे. परंतु या महामानवाच्या जडणघडणीमध्ये ज्यांचा सिंहाचा वाटा होता ते त्यांचे जनक पिता जयसिंगराव घाटगे यांचे व्यक्तिमत्व आणि कार्य हे उपेक्षितच राहिले. त्यासंबंधी काही संशोधित माहिती ज्ञात करून देत आहे.

घाटगे घराण्याचा इतिहास

चौदाव्या शतकात कामराज राठोड नांवाचा पराक्रमी सरदार बिदरशाहीमध्ये पराक्रम गाजवत होता. राठोड हे रजपूतच, सुर्यवशी घराण्यातले. राजपुतान्यातून जे काही पराक्रमी सरदार दक्षिणेत आले त्यापैकीच हे एक घराणे. एकदा एक उंचावर टांगलेली भलीमोठी घाट म्हणजे घंटा वाजविण्यासाठी अनेक सरदार प्रयत्न करीत असता कित्येकांना यश येत नव्हते. तेव्हा कामराज या सरदारानं हवेत उडया मारून ती घंटा वाजविली. तेव्हा 'घाट' वाजविणारे ते घाटगे अशी त्यांची ओळख निर्माण झाली. पुढे यांस घाटगे हेच नामाभिधान मिळाले. 'घाटगे' या नावाची दुसरी उत्पत्ती म्हणजे याच घराण्यातील लखमोजी व रामाजी हे सरदार रसद घेउन बेदरास चालले होते. शत्रूसैन्याने त्यांना एका घाटात अडविले. रामोजी आणि लखमोजी यांनी जीवाची बाजी लावून शत्रूचा दारूण पराभव केला आणि घाटावर कब्जा मिळविला. तो घाट घेणारे ते 'घाट घे, 'घाटगे', तर काही ठिकाणी अपभ्रंश होउन 'घाडगे' असे आडनांव प्राप्त झाले. आपल्या पराक्रमाच्या आणि मुत्सद्देगिरीच्या बळावर घाटगे घराण्यातील वंशजांनी मोठा लौकिक प्राप्त केला असे सुप्रसिध्द इतिहासकार फेरीस्त याने नमूद केले आहे. कालांतराने बिदर व गुलबर्गा ही राज्ये नष्ट झाली. घाटगे सरदार हे आदिलशाहीत रूजू झाले. इ.स. 1572 च्या दरम्यान कागलचा जहागिरदार देसाई रयतेला उपद्रव देत होता. तेव्हा आदिलशाहीच्या वतीने भानजी घाटगे या सरदाराने कागलवर हल्ला चढवून देसायाचा दारूण पराभव केला. भानजीची तो पराक्रम पाहून आदिलशहाने भानजीस कागलचा परगणा बहाल केला व त्यास कागलचा जहागिरदार बनविला. तेव्हा निजामशाहीचा एक रजपूत सरदार दुधा सर्जेराव हा कागलवर चालून आला. पराक्रमी भानजी घाटगे यांनी दुधा सरदाराचाही दारूण पराभव केला आणि त्याचा 'सर्जा' नांवाचा घोडा आपल्या ताब्यात घेतला. एवढा मोठा पराक्रम पाहून आदिलशहाने भानजीस सर्जेराव हा किताब बहाल केला. पुढे छत्रपती शिवरायांनी कागल घराण्यातील पराक्रमी सरदार विठोजीरावे घाटगे यांना अभय त्यांचे सुपुत्र पिराजीराव घाटगे यांच्या नांवे सनद बहाल केली आणि कागल परगण्याचा कारभार सांगितला. ही घटना 1667 सालातील होय.[1]

छत्रपती शिवरायांचे द्वितीय पुत्र राजाराम महाराज यांची तिसरी पत्नी राजसबाई या याच घाटगे घराण्यातील होत्या. कोल्हापूरचे दुसरे शिवाजी महाराज यांनी आऊबाई ह्या आपल्या कन्येचा याच घाटगे घराण्यातील यशवंतराव यांच्याशी घडवून आणला. आणि भोसले व घाटगे या दोन घराण्यात रक्ताचे संबंध प्रस्थापित

प्रस्थापित केले.[2] 1731च्या तहाने मराठा साम्राज्याच्या सातारा आणि करवीर अशा दोन वेगवेगळया गादया अस्तित्वात आल्या. आणि त्यावेळेपासून कागलचे जहागिरदार हे करवीरच्या छत्रपतींचे जहागिरदार बनले. मात्र करवीरचे तत्कालिन जहागिरदार हिंदूराव घाटगे हे दिल्लीस वास्तव्यास गेले. ते परत आलेच नाहीत. त्यामुळे 1815 ते 1878 अशी 63 वर्षे कागलची जहागिर नोकरशाहीच्या ताब्यात होती.हिंदूरावाच्या मृत्यूनंतर त्यांच्या पत्नी पार्वतीबाई यांनी 14 वर्षीय मुलगा दत्तक घेतला. त्याचे नांव सखाराम बापूसाहेब ठेवले. परंतु तो चारच वर्षात निधन पावला. तेव्हा त्यांच्या पत्नी सुंदराबाई ह्यांनी बायजाबाई नारायणराव घाटगे यांचा 12 वर्षीय सुपुत्र दत्तक घेतला. व व त्याचे नाव जयसिंगराव उर्फ आबासाहेब असे ठेवले. हेच जयसिंगराव कागल जहागिरीचे उध्दारकर्ते होत. जयसिंगराव घाटगे यांचा जन्म 1 मार्च 1856 रोजी कोल्हापुर येथे झाला. बायजाबाई हया करवीरचे तत्कालिन छत्रपती बाबासाहेब महाराज यांच्या भगिनी होत.[3]

जयसिंगरावांचे शिक्षण व संस्कार

वयाने सज्ञान झाल्यावर आबासाहेब हे कागलच्या जहागिरीचे अधिपती म्हणून कारभार पाहणार होते. तत्पूर्वी त्यांचे शिक्षण पूर्ण होणे महत्वाचे होते. बाबासाहेब महाराजांनी कुशाग्र बुध्दीच्या जयसिंगरावांच्या जडण-घडणीकडे सुरूवातीपासूनच विशेश लक्ष दिले होते. त्यांच्या शिक्षणासाठी यशवंत आठल्ये आणि कृष्णाजी गोखले यांची एक निश्णात टयूटर आणि शिक्षक म्हणून नेमणूक केलेली होती. आबासाहेबांची बुध्दी तल्लख होती. त्यांना वाचनाचा छंद फार होता. इंग्रजी व मराठी ग्रंथांचे वाचन आबासाहेबांनी चांगल्याप्रकारे केले होते. त्यामुळे ते अस्खलित इंग्रजीत सुध्दा चांगले बोलू शकत होते. तसेच त्यांना कुस्ती, क्रिकेट या खेळांची विलक्षण आवड होती. शिकारीचाही छंद होता. आबासाहेबांच्या शिक्षणाचाच एक भाग म्हणून हिंदूस्थानातील विविध ठिकाणच्या सहलीचे नियोजन करण्यात आले. पहिली सहल 1874 साली उत्तर हिंदूस्थानची आयोजित करण्यात आली. त्यावेळी त्यांच्यासोबत त्यांचे जनक पिता नारायणराव घाटगे हे होते. दुसरी सहल वर्षभरातच म्हणजे 1875 साली आयोजित करण्यात आली. या दोन्ही सहलींमध्ये आबासाहेबांनी दिल्ली, मथुरा, राजकोट, पंजाब, लाहोर, पेशावर, मुलतान, प.बंगाल तसेच हैद्राबाद आदि ठिकाणच्या ऐतिहासिक व धार्मिक स्थळांना भेटी दिल्या. तेथील लोकजीवनाचा, लोकसंस्कृतीचा, शेतीविशयक सुधारणांचा अभ्यास केला. देशाच्या विविध भागातील भिन्न संस्कृती तसेच भौगोलिक रचना, पिण्याच्या व शेतीच्या पाण्याच्या सुविधा, वेगवेगळया जमिनीतील वेगवेगळया पिकांची लागवड आदि गोष्टी त्यांनी डोळस नजरेने पाहिल्या. त्यामुळे सामाजिक विकासाकडे व लोकहिताकडे पाहण्याची त्यांची दृष्टी विशाल बनली.[4]

सुसूत्र कारभार व शेती विषयक पायाभूत विकास

वयाने सज्ञान व शिक्षणाने सक्षम झाल्यावर आबासाहेबांनी कागलच्या कारभाराची सुत्रे हाती घेतली. त्यावेळी कारभारात प्रचंड अनागोंदी माजलेली होती. गांवागांवात चोऱ्यामाऱ्या, दरोडे पडत होते. अवघी रयत हैराण झालेली होती. रयतेला कुणी वालीच उरला नव्हता. तेव्हा आबासाहेबांनी सर्वप्रथम नागरी वसाहतीमधील पोलीस, फौजदार तसेच गांवागांवच्या पोलीस पाटलांना सक्त ताकीद दिली आणि सर्वत्र शांतता निर्माण केली. स्वतः

आबासाहेबांनी जहागिरीचा इलाखा पिंजून काढला. गांव, पेठा, वाडीवस्तीवर जावून तेथील गोरगरीब लोकांसोबत आबासाहेबांनी बैठका घेतल्या. त्यांचे दु:ख, अडीअडचणी जाणून घेतल्या. तेव्हा सरकारी व दरबारी लोक रयतेला हकनाक पिळत असल्याचे आणि दुखावत असल्याचे आबासाहेबांना समजले. लोकांनी दरबारी नोकरांच्या मनमानी कारभाराला वाचा फोडली. आबासाहेबांनी अशा मतलबी आणि स्वार्थी अधिकारी लोकांची कानउघाडणी केली आणि त्यांना वठणीवर आणले. आणि गांवागांवात सर्वप्रथम शांतता प्रस्थापित करून गोरगरीब रयतेच्या आणि बायाबापडयांच्या मनातील भीती कायमची दूर केली. सर्वच क्षेत्रात लोकांच्या मनांत विश्वास निर्माण केला. शासकीय कारभारात सुसुत्रता आणीत असतानाच जयसिंगराव घाटगे यांनी गांव खेडी, वाडी वस्तीवर स्वतः आपल्या सेवेतील कर्मचारी, वनअधिकारी, पोलीसपाटील यांना सोबत घेउन दौरे काढले. आणि शेतीमध्ये चांगले उत्पन्न घेणार्या शेतकर्यांसोबत चर्चा केल्या. तसेच कसदार जमिनी, कमी पाण्याच्या शेत जमिनी, कोरडवाहू शेतीची पाहणी केली. शेतकर्याच्या पिकाच्या पाण्यासाठी सोयाी सुविधा उपलब्ध व्हाव्यात म्हणून विहिरी, तलाव खोदले. सर्वात म्हणजे शेतकर्याला जो शेतफाळा भरावा लागत होता तो जमिनीसोबतच पिकांची पाहणी व एकूण उत्पन्न पाहूनच फाळा आकारण्याची सोय केली. त्यामुळे शेतकर्यांचे केवळ आर्थिक नुकसानच थांबले नाही तर मधल्या मध्ये जो भ्रश्टाचार होत होता तो थांबला आणि गरीब शेतकर्यांची पिळवणूक थांबविली. सहाजिकच शेतकर्यांचे राहणीमान उंचावण्यास मदत झाली. रयतेमध्ये मिळून मिसळून आबासाहेब लोकांची गार्हाणी ऐकू लागले, त्यांना न्याय देवू लागले. त्यामुळे शेकडो वर्षांपासून गलितगात्र झालेली रयत आबासाहेबांना दुवा देवू लागली. महत्वाचे म्हणजे आबासाहेबांचे वय हे त्यावेळी केवळ 23 वर्शांचे होते. शेतीचा विकास हा सर्व समाजाच्या कल्याणाचा उत्तम मार्ग आहे. आहे. शेती म्हणजे आर्थिक विकासाचा कणा आहे. हे आबासाहेबांनी एवढया लहान वयात हेरले होते. आणि म्हणूनच आबासाहेबांनी शेतकरयांचे उत्पन्न जसे वाढविले. तसेच त्यांच्या शेतमालाला बाजारपेठ मिळावी म्हणून शेतकर्यांच्या मालांचे प्रदर्शन भरविले. बैल, गायी, म्हैशी आणि शेळया, कोंबडया, मेंढया आदि पाळीव प्राण्यांचे प्रदर्शन भरविले. त्याकारणे शेतकर्यांना खरेदी विक्री म्हणजे व्यापार कसा करावा, शेतमालाचा दर्जा कसा असावा, पाळीव प्राण्यांची निगा कशी राखावी या मूलभूत गोश्टींचे व्यवहार ज्ञान व सामान्य ज्ञानही प्राप्त झाले. या माध्यामातून अशिक्षित माणसाच्या सुध्दा बुध्दीचा विकास होत गेला. त्यांची मने आणखी सजग आणि जागृत होण्यास मदत झाली. थोडक्यात शेतजमिनीच्या मशागतीसोबतच आबासाहेबांनी माणसांच्या मनाची सुध्दा चांगल्या प्रकारची मशागत केली असे म्हटले तर वावगे ठरू नये.[5]

शालेय शिक्षण व तांत्रिक शिक्षण विकास

माणसाचा सर्वांगिण विकासाचा पाया हा शेतीसोबतच शिक्षणावरही अवलंबून आहे हे आबासाहेबांना चांगलेच उमगले होते. मनुश्याचा बोध्दिक विकास हा बालपणापासूनच झाला पाहिजे. याची जाण सुध्दा आबासाहेबांना होती. बाजारहाट करताना शेतकर्यांना नीटसा हिशेब करता येत नव्हता. यामध्ये अनेक तरूण शेतकरी होते. बाजारहाट करण्यात स्त्रियांचा वाटा हा नेहमीच मोठा असतो. परंतु, हिशेबाच्या अज्ञानामुळे त्याकाळच्या स्त्रियांची व शेतकाऱ्यांची होणारी फसवणूक आबासाहेबांच्या लक्षात आली होती. त्यामुळे शिक्षण ही उज्वल भविश्याची

भविश्याची व काळाची गरज असल्याचे आबासाहेबांच्या लक्षात आले. खेडयापाडयातील गोरगरीब शेतकऱ्यांच्या मुलामुलींचा बौध्दिक विकास व्हावा. ही जाणीव ठेवून आबासाहेबांनी आपल्या जहागिरीत मुलांसोबतच मुलींच्या शिक्षणाची सोय केली. महात्मा जोतिराव फुले यांच्यानंतर मुलींसाठी खेडयामध्ये शाळा सुरू करणारे जयसिंगराव घाटगे हे पहिले व्यक्तिमत्व असावे. कागलच्या जहागिरीचं क्षेत्रफळ केवळ 115 मैलांइतकं लहान असूनही आबासाहेबांनी मुलांसाठी अकरा तर मुलींसाठी दोन शाळा सुरू केल्या. कागल व माणगांव येथे एकेक इंग्रजी माध्यमाची शाळा सुरू केली. शिवाय करवीर दरबारच्या तत्कालिन शिक्षणाधिकारी मिस लिट्ल यांच्यावर मुलींच्या शिक्षणाची काळजी घेण्याची जबाबदारी त्यांनी सोपविली. प्रजेच्या मनातला आणि जीवनातला अंधार दूर करण्याचं अतिशय महत्वाचं काम एक तेवीस वर्शाचा युवा जहागिरदार करतो ही गोश्ट अभूतपूर्वच म्हटली पाहिजे. ज्ञानाचा प्रकाश दूरवर खेडयापाडयात पोहचविणारा महाराश्ट्रातला हा असा पहिला समाजसुधारक जहागिरदार होता. शालेय शिक्षणासोबतच आबासाहेबांनी तांत्रिक शिक्षणही महत्वाचे मानले. कागलच्या जहागिरीमध्ये एक होतकरू व मेहनती तरूण होता. त्याच्या अंगी चांगली कलाकुसर होती. नरहरी भीमराव सुतार असे त्याचे नांव. त्याच्यातील गुणांची पातळी उच्चदर्जाची होती हे आबासाहेबांनी जाणले. आणि त्यास मुंबईच्या जे.जे. स्कूल आॅफ आर्टस येथे शिक्षणासाठी स्वतःहून पाठविले. त्यास खास विद्यावेतन देण्याची सोय आबासाहेबांनी स्वतः केली. जातपात रहित प्रजेच्या उत्कर्शाचे कार्य करण्याचाही आदर्श आबासाहेबांनी जपला होता.

वाचन चळवळीला प्रोत्साहन व लोकोपयोगी सोयी सुविधा

आबासाहेब हे स्वतः ग्रंथप्रेमी होते. असंख्य इंग्रजी व मराठी ग्रंथांचे वाचन त्यांनी केले होते. एवढंच नाही तर ''वाईल्ड स्पोर्ट्स ऑफ इंडिया", ''ट्रॅव्हल्स इन इंग्लड" व "हिस्टरी ऑफ इंडिया अैण्ड इंग्लंड'' अशा विविध ग्रंथांचा त्यांनी सखोल अभ्यासही केला होता. शालेय शिक्षणासोबतच तरूण मुलामुलींचे अवांतर वाचन वाढावे. 'माणूस शिक्षणाने साक्षर होईल परंतु, ग्रंथवाचनाने तो ज्ञानी होईल' असा सद्विचार आबासाहेबांनी जनमानसात रूजविला. ज्ञानप्रसाराचे उत्तम माध्यम म्हणून आबासाहेब विविध ग्रंथांकडे पहात होते. त्यासाठीच आबासाहेबांनी कागल येथे 1880 साली ''नेटीव्ह लायब्ररी'' सुरू केली. या ग्रंथालयाची ओळख पुढे 'महात्मा गांधी वाचनालय' अशी निर्माण झाली. या ग्रंथालयासाठी येणार्या सर्व खर्चाची तरतूद आबासाहेबांनी आपल्या जहागिरीतून केली. आबासाहेबांनी रयतेच्या आरोग्याचीही काळजी घेतली. कागल येथे फार जुनाट एक दवाखाना होता. त्या दवाखान्याची इमारत ढासळत चालली होती. तिथे कुणी तज्ञ डाक्टर सुध्दा फिरकत नव्हता. आबासाहेबांनी तातडीने आपल्या जहागिरीतील स्वतःच्या मालकीच्या जागेत नवीन सुसज्ज इमारत बांधून तिथे दवाखाना सुरू केला. करवीर दरबारचे सेवेत डॉ. सिंक्लेअर हे सर्जन होते. कागल येथे येवून रूग्णसेवा देण्यासाठी यांच्यावर आबासाहेबांनी ती जबाबदारी टाकली. तसेच दवाखान्याची स्वच्छता व देखबाल करण्यासाठी नरसूलिंग नांवाच्या इसमाची नेमणूक केली. केवळ दवाखानाच नव्हे तर उत्तम प्रतीची औशधे सुध्दा कागलमध्ये मिळण्यासाठी सोय निर्माण केली. हा सगळा खर्चाचा भाग आबासाहेबांनी आपल्या जहागिरीच्या खर्चातून करण्याची तरतूद केली. याशिवाय आबासाहेबांनी रस्ते व पूर बांधून दळणवळणाची सोय केली. लोकांना पिण्याचे स्वच्छ पाणी मिळावे म्हणून विहिरी खोदल्या.

करवीरच्या रिजंटपदी नेमणूक

अवघ्या चार वर्षांमध्ये कागलसारख्या छोटया जहागिरीमध्ये लोकोपयोगी विकासकामे केली. ते पाहून इंग्रज सरकारने आबासाहेबांची करवीर संस्थानच्या रिजंटपदी नेमणूक केली. रयतेची अशी निस्पृह भावनेने सेवा करीत असताना आबासाहेबांचे कौटुंबिक जीवन मात्र जणू उध्वस्तच झाले होते. त्यांच्या पत्नी राधाबाई अचानक आजारपणामुळे निधन पावल्या. आबासाहेब स्वतः त्यावेळी केवळ तेवीस वर्शांचे होते. तर त्यांचे दोन लहान मुले थोरला यशवंत हा केवळ तीन व पिराजी हा दीड वर्षांचा होता. आबासाहेबांनी आई व बाप म्हणून आपल्या या दोन्ही मुलांची जबाबदारी मोठया कौशल्याने व काळजीने पार पाडली होती. करवीर संस्थानच्या रीजंट पदाची जबाबदारी स्विकारल्यानंतर आबासाहेबांनी या संस्थानांतर्गत देखिल विविध सोयी सुविधा नव्याने निर्माण केल्या. मलकापूर, पन्हाळा येथे मुलामुलींसाठी शाळा सुरू केल्या. कोल्हापूर ते जोतिबाेगर हा रस्ता नव्यानेच बांधला. तसेच शिरोळ ते नरसोबावाडी या रस्त्याचे बांधकाम केले. रंकाळा टावरचे काम हाती घेतले. तसेच रंकाळा व कळंबा तलावात ज्यांच्या जमिनी गेल्या होत्या त्या भूमीपुत्रांचे पुनर्वसन केले. भोगावती नदीवर दानवडे येथे नवा पूल बांधला.[6]

याच दरम्यान करवीरचे छत्रपती चौथे शिवाजी महाराज यांना इंग्रजसरकारने अटक करून त्यांना नगरच्या किल्ल्यात त्यांना डांबून ठेवले. तिथेच त्यांची हत्या झाली. करवीर संस्थानावर दुःखाचा डोंगर कोसळला. करवीर संस्थान आता बरखास्त होणार की काय? अशी लोकांना भीती वाटू लागली. तेव्हा जयसिंगरावांनी करवीरचा तत्कालिन पोलिटिकल एजंट कर्नल रीव्हजला सोबत घेउन करवीर संस्थानचा दौरा केला आणि लोकांच्यात शांतता निर्माण केली. चौथ्या शिवाजी महाराजांच्या पत्नी 17 वर्षाच्या आनंदीबाईना अपत्य नव्हते. त्यांनी इंग्रज गव्हर्नरकडून करवीर संस्थानसाठी दत्तक वारस मंजूर करून घेतला. आबासाहेबांचा थोरला सुपुत्र यशवंत यास आनंदीबाईना सर्वसंमतीने दत्तक घेतले. 17 मार्च 1884 रोजी यशवंतरावांचा शास्त्रोक्त विधीने दत्तक समारंभ पार पडला. या यशवंतरावांचेच नांव " शाहू छत्रपती." असे ठेवण्यात आले. शाहू त्यावेळी केवळ दहा वर्षाचे होते. तेव्हा अनेकजण शाहूंना इंग्लंडला शिक्षणासाठी पाठविण्यासाठी आग्रही होते. परंतु जयसिंगरावांसारख्या जाणत्या पित्याने स्वतः युरोपला जावून तेथील शिक्षणाची व्यवस्था, लोकसंस्कृती व राहणीमान पाहिले. आणि आपल्या मुलांना हिंदूस्थानातच शिकविण्याची निर्णय घेतला. त्यानंतर आबासाहेबांचे 20 मार्च 1886 रोजी वयाच्या अवघ्या तिसाव्या वर्षी निधन झाले. प्रजातहितदक्ष लोकराजा घडविणारा पिता काळाने ओढून नेला. त्यावेळी त्यांची दोन्ही मुले केवळ 10-12 वर्षांची होती.[7]

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९. घारापुरी लेणीचा एक ऐतिहासीक अभ्यास

डॉ. भानुदास धोंडिबा शिंदे
महात्मा फुले ए.एस.सी. कॉलेज पनवेल.

लेणीचा काळ

घारापूरी लेणी कोणी व केव्हा कोरली या बाबत एवढे मतभेद आहेत. इ.स ६ व्या शतकात कलचूरी घराण्याच्या काळात कोरली असावी. बदामी चालुक्याच्या काळात कोरली असावी अशी मते आहेत. वाकाटक व शिलाहारांनी कोरली असावी. परंतू याला दुजोरा मिळत नाही. फर्ग्युसनच्या मते ही लेणी ६ व्या शतकात कोरली असावी. याला पंडीत भगवानलाल इंद्रजी यांनी दुजोरा दिला आहे. अमेरिकन संशोधन वाल्टर स्पिंकच्या मते कलचूरी कृष्णराज यांच्या काळात ६ व्या शतकात कोरली असावी.

घारापूरी लेणी सकल व निष्कल ही दोन्ही स्वरूपात शिव आहे. शिवलिंग असलेल्या मंडपात मात्र पूर्वाभिमूख सर्वतोभद्र प्रकारच्या (चारही दिशेला प्रवेशव्दार असलेल्या) गाभा-यात शिवलिंग असून म्हणजे शिवाजी निष्कल प्रतिमा (अरूपी व निराकार प्रतिमा) असून मंडपाच्या मागील भिंतीच्या मधल्या देवकोष्ठात आहे. ती शिवाची प्रचंड मूर्ती आहे. सकल प्रकारची देहरूपातली म्हणजे साकार किंवा रूपवान अशी लेणीत व मंदिरातील गाभा-यात एकाच वेळी सकाल व निष्कल अशा दोन्ही प्रकारात शिवाचे अस्तित्व असणे हे फक्त घारापुरीतच आढळतो. इतरत्र कोठेही नाही.

मुख्य लेणी

समुद्रसपाटीपासून ७६.७५ मी उंचीवर उत्तराभिमुख लेणी आहे. पूर्वेस व पश्चिमेस प्रवेशव्दारे असून १.२२ मी रचनेची वळचण आहे. लेणीच्या आतील मंडपामध्ये उत्तमोत्तम शिल्पे आहेत. २६ स्तंभावर मंडप आधारलेला असून ४० मी मंडप आहे. मंडपाच्या पश्चिमेश असलेल्या गाभा-यासमोर स्तंभाच्या चार जोड्या चार ओळीत उभारलेल्या आहेत. उत्तराभिमुख असलेल्या दक्षिण भिंतीत कोरलेल्या सदासिव मूर्तीसमोर आठ जोडया दोन ओळीत आहेत. स्तंभ खाली अयतस्त्र मध्यभागी निमूळत्या अंगावर उभ्या पन्हाळया कोरलले शीर्षभागी आमलकाच्या (उशीच्या) आकाराची रचना असलेले आणि सर्वातवर हस्त (ब्रॅकेटस) असलेले आहेत.

मंडपाच्या पश्चिम बाजूस पूर्वाभिमुख शिवमंदिर १९.५ चौरस मीटर व छतापर्यत भिडलेले आहेत. त्याच्या बाजूस व्दारपाल आहेत. चेह-यावरील भाव सात्विक आहेत. मंदिरात उंच चौकोनी शाळूंका असून त्याच्या मधोमध शिवलिंगाची स्थापना केलेली आहे. मंडपाच्या रचनेतील प्रमाणबध्दता पाहता शिवलिंगने गाभाराच केंद्रस्थानी वाटतो. लेणीतच शिवची सकल व निष्कल अशी दोन्ही रूपे एक समयावच्छेदे करून आढळतात.

लकुलीश (योगीश्वर शीव)

उत्तरेकडून प्रवेश केल्यास प्रथम लकुलीशची मूर्ती आढळते. ती शिल्पपटात कोरलेली असून अनेक लहान मोठ्या प्रतिमा आहेत. केंद्रस्थानी पद्मासनात बसलेला शिव आहे. हात तूटलेले आहे. आजूबाजूस हंसरूढ ब्रम्हा, गरूड विष्णू, अश्वरूढ सूर्य, गजारूढ इंद्र, अमृतकुंभधारी चंद्र आहे. आकाशात गंधर्व व अप्सराही आढळतात. शिवाय २८ वा अवतार लकुलीशचा आहे.

रावणानुग्रहमूर्ती (कैलासोत्तोलन)

या शिल्प कलामध्ये पुराणात सांगीतलेल्या कथेत शिवाने रावणाचे गर्वहरण केलेले शिल्प कोरलेले आहे. मुख्यप्रवेशव्दारातून प्रवेश केल्यास डाव्या हाताकडे पश्चिमाभिमुख शिल्पा आहे. शिव - पार्वती कैलासावर बसलेले. एका हाताने पार्वतीला सावरले तर दुस-या हाताने त्रिशूळ धरलेला आहे. गणेश शिव पार्वती आजूबाजूस व्दारपाल व वरच्या बाजूस अनेक गंधर्व-अप्सरा,ऋषीगण सहकुटूंब आहेत. कैलासाचे खाली नष्टप्रायबैठा रावण आहे. पतिपत्नी भाव विश्वातला हा प्रसंग विलक्षण आहे. व्दारपाल,गण गणेश, भृंगी आणि अन्य मंडळी एका वर्तुळात दिसतात. मध्यात रावणानुग्रहण उठावदार प्रसंग कोरलेला आहे.

शिव-पार्वती अक्षक्रीडा (सारीपाट खेळताना)

घारापुरीच्या मुख्यलेणीतील शिव-पार्वती अक्षक्रीडा हा प्रसंग शिल्पपटावर कोरलेला आहे. कैलास पर्वतावर शिव-पार्वती समोरासमोर अर्धपर्यंकासनात बसलेले आहेत. त्याच्या मध्यात सरीपाट मांडलेला आहे. दोघांचे पाय मांडलेले आहेत. शिवाच्या बाजूस चामरधर तर पार्वतीचे मागे कडेवर मुल घेतलेली ललना आहे. शिवाच्या पायाशी अस्थिपंजर भृंगी तर पार्वतीच्या खालच्याबाजूस नंदी आहे. दोघांच्या वरच्या बाजूस गंधर्व अप्सरा त्यांच्यावर पुष्पवृती करीत असल्याचे दाखिवले आहे. सरीसपाट खेळताना लबाडी करून आपण डाव जिंकल्याची बतावनी शिवा करतो. त्यावेळी पार्वती रागावते व निघून जाते. तेव्हा शिवा तिचा हात धरून एक डाव खेळण्याचा आग्रह करतो. अशा वेळी त्याने उजव्या हाताचे एक बोट ताठ केलेले आसते. याचा अर्थ हे जग हा संसाराचा खेळ हे मिथ्या आहे. माया आहे. सत्य एकच आहे. हसत खेळत अंतिम सत्य सांगण्याची ही कथा आहे.

अर्धनारीश्वर शिव

मंडपाच्या दक्षिणेकडील भिंतीत तीन शिल्पपट आहेत. सदाशिवच्या पूर्वबाजूस ५.१० मी. उंचीची अर्धनारीश्वराची भव्य मूर्ती आहे. अर्धनारीश्वर म्हणजे अर्धा भाग पुरूषाचा (शिवाचा) आणि अर्धा भाग पार्वतीचा आहे. पृथ्वीच्या निर्मितील पुरूष व प्रकृती म्हणजेच शिवशक्त्यैक्य कारणीभूत आहे. स्त्री व पुरूष हे प्राण्यामध्ये मादी व नर यांची प्रतिक मानले आहे. सर्व सृष्टीत व्यापणारी सांख्य तत्वज्ञानाप्रमाणे पुरूष व त्रिगूणात्मिका प्रकृति यांची ही जोडी आह. यांचे यथार्थ ज्ञान म्हणजेच ब्रम्हाकाय याचे ज्ञान होय. ते ज्ञान प्राप्ती म्हणजे मोक्षप्राप्ती होय. ही मूर्ती म्हणजे तत्वज्ञानाचे सुत्ररूप मानावे लागते.

शिवाच्या जटाभारात चंद्रकोर कोरलेली आहे. तर पार्वतीच्या केशसंभार घनदाट आहे. उजव्या कानात बाळी तर डाव्या कानात जडावाच्या कर्ण फुलांची जोडी आहे. नंदीला आवरणा-या शिवाच्या हातात व पार्वतीच्या वस्त्र सावणाच्या हातात समतोल राखलेला आहे. चेह-यावरील भावही वेगळे असून उजवीकडे गांभीर्य तर डावीकडे सात्विकता दाखविले आहेत.

अर्धनारीश्वराच्या बाजूस आधी कार्तिकेय व भृंगी आहेत. कार्तिकेच्या हाती भाला आहे. वरच्याबाजूस हंस वाहनारूढ चार हातांचा व चार तोंडाचा ब्रम्हदेव आहे. कमळ कमंडलू अमुक (पळी) व वेदग्रंथ त्यांच्या हातात आहेत.बाजूलाच ऐशवतावर आरूढ झालेला.हाती वज्र व अंकूश धारण केलेला इंद्र आहे. पार्वतीच्या बाजूस गरूडा आरूढ विष्णू आहे. खालच्या बाजूस दोन दासी उभ्या आहेत.एका चामरधारिणी व दुसरी मंजुषा आहे. वरच्या बाजूस पश्चिमाधिपती मकरवाहण वरून आहे. या मुर्तीच्या मागे वरच्या बाजूस गंधर्व अ अप्सरा आहे.

सदाशिव (महेशमूर्ती)

मुख्य मंडपात सर्वाधिक आकर्षण म्हणजे त्रिमूर्ती शिवप्रतिमा होय. त्रिमुर्ती म्हणजे ब्म्हा विष्णू आणि शिव यांची त्रिमूती. या मुर्तीच्या तीन तोडापैकी ब्रम्ह व विष्णूच्या सौम्य आणि उग्र शिवाचे वदने आहे. गोपिनाथरावच्या मते ही मूर्ती महेशमुर्ती आहे.पंडिता स्टेला क्रॅमरिश यांच्यामते ती शिवाचीच आहे. हे खरे पण ती महेशमुर्ती नसून सदाशिवाची आहे. जितेंद्रनाथ बॅनर्जीच्या मते तीन तोंडापैकी समोरचे व उजवीकडचे तोंड शिवाच्या सौम्य व उग्र अवस्था दाखवितात. महाभारतात त्याला व्दितनू असे म्हटले आहे.तिसरे स्त्रैण दिसते ते पार्वतीचे आहे.

उत्तराभिमुख गाभा-यात सदाशिवाची प्रतिमा आहे.गाभा-याच्या प्रवेशव्दाराच्या दोन्ही बाजूस व्दारपाल आहे.भक्तीची खात्री पटावी यासाठी व्दारपालांची नेमणूक केलेली आहे.गाभा-याची लांबी व रूंदी ६.६० मीटर असून खोली ३.९९ मी आहे. ७६ सेमी उंचीच्या आसनावर सदाशिवाची आवक्ष प्रतिमा आहे. मूर्तीची उंची ५.४६ मी.आहे.शैद्रमुख १.५३ मी त्याच्या विरूध्द बाजूस मुख १.२२ मी.उंचीचे असून तिन्ही मुखांच्या भिवयांच्या पातळीचा घेर ६.९८ मी आहे. घारापुरीच्या मूख्य लेणीतील गाभा-यातल्या मूर्तीस तीन दृष्ये वदने आहेत.यामध्ये अघोर म्हणजे भैरव, तत्पुरूष म्हणजे महादेव, वामदेव म्हणजे उमा, सघोजात म्हणजे नंदीकेश्वर आणि ईशान म्हणजे सदासिव होय.म्हणजे क्रमाने अग्नि, वायू, आप, पृथ्वी आणि आकाश अशा पंचमहाभुतांचे आकार आहेत.ही प्रतिमा शिवाचे सर्वसाक्षीत्व आणि सर्वव्यापित्व आहे. संपूर्ण महाराष्ट्रात सर्व प्रथम कोरलेली मुर्ती आहे.

गंगावतरण

सदासिव मुर्तीच्या डावीकडे (पश्चिमेकडे) गंगावतरणाचा भव्य देखावा आहे.यालाच शिव-पार्वती म्हटले आहे.शिवपुराणात वर्णन केल्याप्रमाणे सगर राजाच्या साठ सहस्त्र पुत्रीची क्रोधदग्ध कपिल मुषीच्या शापाने राख झाली. त्यांना मुक्ती मिळायची तर गंगाजल पाहिजे होते.गंगा तर स्वर्गात होती.स्वर्गातून आणण्याचा निश्चय सगराचा नातू भागीरथ याचे तपश्चर्चीच्या बळास आणली.गंगेचा प्रचंड स्त्रोत पृथ्वीवरील लोकांना सहन करता येणार नसल्यामुळे तिचा वेग कुणीतरी सामर्थाने अडविला पाहिजे अशी अट होती.शिव महादेव हे कार्य करण्यास तत्परतेने तयार होते. त्यानंतर स्वर्गस्थ गंगा पृथ्वीवर येण्यास निघाली हा प्रसंग म्हणजे गंगावतरण होय.

या शिल्पामध्ये ५ मी उंचीचा शिव आणि ३.७५ उंचीचा पार्वती अत्यंत प्रमाणबध्द कोरलेले आहे.शिवाय येथे दोन कामगि-या पार पाडाव्या लागतात. एकीकडे दिलेले वचन मुर्तीसाठ गंगेला मस्तकी धारण करायचे दुसरे म्हणजे पार्वतीची नाराजी

दुरर करायची म्हणून शिवा डावा हात लांब करून पार्वतीच्या जवळ घेण्याचा प्रयत्न करतो. त्याला नकार देण्याचे चेहऱ-यावर भाव प्रकट झालेले आहे.

गंगा स्वर्गातून खाली येताना शिवाच्या जटाभाराकडे झेपावताना दिसते. तील तीन मुख दाखिवलेले आहेत.गंगेला त्रिपथगा म्हणतात.ती स्वर्गात मंदाकीनी, पृथ्वीवर भागीरथी आणि पाताळात भोगावती असते. पार्वतीच्या बाजूस मंजूषा घेवून तिची सखी उभी आहे. शिवाने बाजूला गुडघ्यावर वाकलेला भगिरथ आहे. इतस्त्र शिवगण आहे. वरच्या बाजूस देवता असून वाहनावर ब्रम्ह ऐशवतावर ईद्र गरूडा रूढ विष्णू ही आहे.

कल्याणसुंदरमूर्ती (शिवपार्वती विवाह)

हिमवान व मेना या जोडप्याची कन्या पार्वती असून तिला शिवासमोर विवह करावयाचा असतो.पण शिवाजे ब्रम्हचारी राहायचे ठरवले होते. पार्वती शिवाच्या प्राप्तीसाठी पंचाग्नीतप करीत होती.सर्व देवांच्या सांगण्यावरून शिवाचे ब्रम्हचर्याव्रत भंग करण्याचा प्रयत्न सुरू झाला.त्यात पार्वतीला यश मिळाले व दोघांचा विवाह ठरला.विष्णूने कन्यादान केले. ब्रम्हाने पौरोहिताचे कार्य केले. या विवाह प्रसंगी सर्व प्रतिष्ठित देवता मंडळी उपस्थित होती.

या शिल्पपटात मध्यभागी शिव-पार्वती आहे. शिवाच्या चार हातांपैकी तीन हात तुटलेले आहेत पार्वतीची प्रतीमा २.५ मी उंचीची आहे. तिच्या डोक्यावर मुक्ताजाल असून त्यावर करंडमुकूट आहे.तीच्यामागे पिता हिमवान असून तिचा दंडावर हात आहे.ब्रम्हदेवाच्या मागे चतुर्भज विष्णू उभा आहे. पार्वतीच्या बाजूस माता मेना, चामरधारिणी व अमृतकुंभधारी चंद्र आहे.शिव-पार्वतीच्या वरच्या बाजूस गंधर्व अप्सरा ऋषीमुनी आहेत.

अंधकासुरवधमुती

शिवाच्या मुर्ती अनेक प्रकारच्या आहेत.अनुग्रह दर्शन संहारपवित्र, दक्षिणमुर्ती,भैरवमुर्ती इ.प्रकारच्या मुर्ती आहेत.संहार प्रकारच्या गजहा, त्रिपुरान्तक, कालारी,अंधकासुरवध मुर्तीची गनना केली जाते.पार्वतीच्या अभिलाषाने अंधकासुशल आंधळे बनविले होते.त्याला शिवसामर्थ्याची कल्पना नव्हती. वराहपुराण प्रमाणेच कुर्म व वामनपुराण तरी अंधकासुरवधाची कथा दिलेली आहे. ब्रम्हदेवाच्या वरामुळे हा राक्षस उत्पन्न झालेला होता. शिवाची त्याच्याशी झुंज झाली. शिवाने मोठ्या चपळतेने अंधकाच्या पोटात त्रिसूळ खुपसून त्याला आकाशात भिरकावतो. तो शरण आल्यानंतर शिवाने आपल्या गणांचे अधिपत्य त्याच्याकडे सोपवतो. तेव्हापासून अंधकभृंगी किवा भृगीस म्हणून ओळखला जातो.

हे शिल्पपटात शिव अष्टभूज आहे.मागील वरच्या दोन हातांनी गजचर्म शिरोभागी धरलेले आहे. एका डाव्या व उजव्या हातात त्रिशुळाने अंधकाच्या पोटात खुपसलेला आहे.अंधकाच्या जमीनीवर पडलेला रक्ताच्या थेंबागणिक राक्षस निर्माण होत असतो.तो होवू नये म्हणून शिव रक्त भांडयात गोळा करून ते गिळण्यासाठी योगेश्वरी नावाची एक मातृका निर्माण करतो.शिवाच्या झोपेतून व चेहऱ-यावरील रौद्रभावातून तो कर्दनकाळ झाला आहे हे स्पस्ट दिसते. सुमारे ३.५६ मी उंचीची ही विजीगीषू प्रतिमा पराक्रमाची द्योतक आहे.शिवाच्या मस्तकाचे वरील बाजूस मधोमध शिवलींग असून त्याचे दोन्ही बाजूस भक्तगण, विद्याधर वगैरेच्या प्रतिमा आहेत.

नटराज शिव

मुख्य प्रवेशव्दाराच्या उजवीकडे ३.४५मी ४मी आकाराच्या शिल्पपटात शिवाची तांडवनृत्य करणारी ३.५0 मी उंचीची मुर्ती आहे.गायन, वादन, नर्तन, नाटक यांची अधिष्टाती देवता म्हणजे शिव होय. दोन प्रकारचे नृत्य मानली जातात. सर्जनाच्या नृत्याला लास्य म्हणतात.संहार नृत्याला तांडवनृत्य म्हणतात. तांडवाचे प्रमूख सात भाग मानतात. पण १0८ प्रकार आहेत. याची सविस्तर माहिती भरताच्या नाटयशास्त्रात ताण्डव लक्षणम् या ग्रंथात आढळते.हे सर्व प्रकारचे नृत्य चिदंबरम (तामिळनाडू) येथील नटराज मंदिराच्या गोपुरावर आणि तंजावर येथील बृहदीश्वर मंदिराच्या गाभा-याच्या वरच्या भूमीवर शिल्पांकित केले आहेत.

ब्रम्हांड हि शिवाची नृत्यशाळा होय. त्याच्या नृत्यासवे सर्व विश्वव्यापाराला गती मिळते. आणि नृत्य जेव्हा विराम पावते तेव्हा चराचर विश्वाला आपल्यात सामवून घेऊन आत्मनंदात घतो.हे नृत्य सृष्टी,स्थिती,संहार, तिरोभाव आणि अनुग्रह या पाच क्रियांचे घोतक आहे.शिवाच्या वरच्या उजव्या हातीच्या डमरूव्दारे सृष्टी निर्मिती दर्शविली आहे. आश्वासनाकडे संकेत आहे.डाव्या वरील हाती अग्नी संहाराचा निदर्शक असतो तर डावा खालचा हात छातीवर आडवा धरलेला असतो त्याला गजहस्त म्हणतात. डावा पाय वर उचलेला असतो.भक्ताला मोक्ष मोकळा आहे हे सुचित करतो.४ मीटर उंचीचा शिल्पपटात शिवाची ३.३0 मी उंचीची व पार्वतीची २.७ मी प्रतिमा आहे.शिव, पार्वती,गणेश, कार्तिकेय इतर तसेच ब्रम्ह, विष्णू, इंद्र, भृंगी, वादक, गण इ.शिवा भोवती फेर धरून आहेत असे दिसते.

संदर्भ साधने

१. नागराजू एस बुध्दिस्ट आर्किटेक्चर ऑफ वेस्टर्न इंडिया -आगम कला प्रकाशन दिल्ली १९८१
२. दळवीकर म.के 'लेट हिनायन केन्हज ऑफ वेस्टर्न इंडिया' डेक्कन कॉलेज पोस्टग्रॅज्युएट रिसर्च इन्स्टिटयूट, पुणे १९८४
३. जेम्स बर्जेस बॉम्बे ऑर्किऑलॉजिकल सर्वे ः सेरपेट मॅम्टलेट.१0
४. देव
५. कुलाबा गॅझेटिअर १८८३
६. कुलावा गॅझेटिार -१८६३ पृ.८३१
७. कार्ल खंडाळावाला पाषाण गुहातील देवळै - महाराष्ट्र मार्ग पब्लिकेशनस १९८५
८. जेम्स फर्ग्यसन जेम्स बर्जेस केव्ह टेंपल्स ऑफ इंडिया
९. पर्सी ब्राऊन इंडिया ऑर्किटेक्चर बुध्दिस्ट ॲडण पिरिअड पृ.क्र.३

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१०. डॉ. संजीवनी सतीष केळकर यांचे कार्य

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प्रस्तावना

पुण्यासारख्या शहरी भागातून सोलापूर जिल्ह्यातील सांगोल्यासारख्या ग्रामीण भागच्या सासुरवाशीण झालेल्या डॉ. संजीवनी केळकर या तिथल्या पहिल्या महिला डॉक्टर आहेत. या भागातील दु:ख, दारिद्रय यामुळे या भागाचे जे भयावह चित्र त्यांच्यासमोर आले त्यातून त्यांना विधायक कामाची प्रेरणा मिळाली. त्यांनी आपल्या काही मैत्रिणींना एकत्रित करून सुरवातीला 'महिला सहविचार केंद्र' सुरु केले, त्यातून 'माता-बालक उत्कर्ष प्रतिष्ठान', 'जिजामाता बाल संस्कार वर्ग', 'उत्कर्ष बालक मंदिर', 'महिला अन्याय निवारण समिती', 'आरोग्य दूत योजना' अशा विविध संस्था उभ्या करून ग्रामीण भागातील स्त्रीला सक्षम केले. माणदेशातील दुष्काळी भागात असे काम करणाऱ्या महिलांची या कालखंडात कमतरताच होती. असे काम करण्यासाठी फारसे कोणी प्रयत्न केलेले दिसत नाहीत. डॉ. संजीवनी केळकर यांनी हे काम जोमाने करून आपल्या मात्रिणींनाही यात सहभागी करून घेतले.

जन्म बालपण आणि शिक्षण

संजीवनी केळकर यांचा जन्म विद्येचे माहेरघर असणाऱ्या पुणे येथे गोडबोले कुटुंबात झाला.[१] त्यांची कौटुंबिक पार्श्वभूमी सुशिक्षित व सुसंस्कृत अशी आहे. त्यांचे बालपण संवेदनशील अशा माता-पित्यांच्या सानिध्यात गेले. संजीवनी केळकर या सुरवातीपासूनच हुशार व हरहुन्नरी विद्यार्थीनी म्हणून ओळखल्या जात. त्यांनी आपल्या विध्यार्थी जीवनात अनेक सन्मान व पारितोषिके मिळविली आहेत. आपल्या विद्वत्येच्या जोरावर त्यांनी वैद्यकीय क्षेत्रातील एमबीबीएस ही मनाची पदवी संपादन केली. १९७३ मध्ये त्यांचा विवाह सांगोल्याच्या डॉ. सतीश केळकर यांच्या बरोबर झाला. येथे आल्यानंतर वैद्यकीय व्यवसायाबरोबर इतर अनेक सामाजिक कार्यामध्ये हिरीरेने भाग घेवून त्यांनी आपल्या कामाचा ठसा उमटविलेला दिसतो.

महिला सहविचार केंद्र

ग्रामीण भागामध्ये राहून, सर्व प्रकारांच्या अभावांना, पुरुषकेंद्रित ग्रामीण रूढी परंपरांना, पुरुषांच्या व्यसनांना, दारिद्रयाला, शाररीक कष्टांना, समाजातील गुंडगिरीला तोंड देत असणाऱ्या स्त्रीबद्दल फारसा कळवला कोणास दिसत नव्हता. १९७५ - १९७७ या खालखंडात देशात आणीबाणी होती.[२] आपण काहीतरी करावं या विचारांनी संजीवनी केळकर यांनी आपल्या मैत्रिणी नीला देशपांडे, माधवी देशपांडे, माधवी देशपांडे, कै. निर्मला वांगीकर, कै. नलिनी ठोंबरे, प्रतिभा पुजारी, वसुधा डबीर, वसुंधरा कुलकर्णी, प्रा.

शालिनी कुलकर्णी, प्रा. चित्रा जांभळे, श्रीदेवी बिराजदार यांना बरोबर घेवून इ. स. १९७८ - १९७९ मध्ये 'महिला सहविचार केंद्र' सुरु केले.[३] हे केंद्र म्हणजे या महिलांचा 'पाणवठाच' बनला. दर आठवड्यातून एकदा या सर्व महिला एकत्र जमत असत. या केंद्रात सर्व जातीधर्माच्या, सर्व वयोगटातील, अशिक्षित, अर्धशिक्षित, सुशिक्षित, पदवीधर महिला सहभागी होत असत. या महिलांमध्ये सर्व आर्थिक स्तरांमधील महिलांचा समावेश होता. या महिला या सहविचार केंद्रात मनमोकळेपणाने आपली दु:खे मांडू लागल्या, एकमेकींचे अश्रू पुसू लागल्या, एकमेकींना आधार देऊ लागल्या. त्यामुळे त्या परिस्थीचा विचार करायला शिकल्या, विचार करून समस्यांवर उपाय शोधायला शिकल्या आणि तो उपाय अमलात आणायलाही शिकल्या. ही सर्व किमया महिला सहविचार केंद्रामुळे साध्य झाली.

माता बालक उत्कर्ष प्रतिष्ठान

कालपर्यंत मानही वर न काढणाऱ्या महिलांना, महिला सहविचार केंद्राच्या कार्यामुळे त्यांच्यात आत्मविश्वास वाढला. त्यांनी परिसरातील लहान बालकांचा सर्वांगीण विकास करण्यासाठी 'माता बालक उत्कर्ष प्रतिष्ठान' ही संस्था स्थापन केली.[४] त्यांनी या संस्थेच्या माध्यमातून १९७९ मेध्ये 'जिजामाता बाल संस्कार' वर्ग सुरु केला. त्यातूनच पुढे १९८० मध्ये बालवाडी सुरु करण्याची कल्पना पुढे आली आणि सर्वांनी मिळून तालुक्याच्या इतिहासात प्रथमच एक चॅरिटी शो आयोजित केला. त्यातून बालवाडीसाठी लागणारा निधी उपलब्ध झाला आणि १९८० मध्ये डॉ. केळकर हॉस्पिटलच्या आवारात 'उत्कर्ष बालक मंदिर' सुरु झाले. त्यासाठी शिक्षिका व सेविका म्हणून महिला सहविचार केंद्रातील सभासदांनी काम केले. १९८१ मध्ये पालकांच्या आग्रहाने उत्कर्ष प्राथमिक विद्यालयाचा पहिलीचा वर्ग सुरु झाला. सहविचार केंद्रातून निष्ठावान कार्यकर्त्या मिळत गेल्या, त्यांनाच प्रशिक्षित केले आणि त्यांनी उत्कर्ष प्राथमिक आणि पूर्व प्राथमिक विद्यालय उभे केले. इ.स. २०१३ पर्यंत या शाळेतील विद्यार्थी संख्या एकून ७५० होती. जून २०१२ पासून ५ वी चा वर्ग सुरु झाला आहे आणि दरवर्षी एक इयत्ता वाढवत शाळा दहावीपर्यंत वाढविण्याचा त्यांचा मानस आहे. मन, मनगट आणि मेंदू यांचा मिलाफ साधून ग्रामीण विद्यार्थ्यांचा सर्वांगीण विकास साधणारी शाळा असा नावलौकिक या शाळेने मिळवला आहे. वनस्थळी आणि निर्मला पुरंदरे यांचे मोलाचे सहकार्य या कामात असते. शाळेतील औपचारिक शिक्षणाबरोबर ग्रामीण मुलांसाठी विविध छंदवर्ग, व्यक्तिमत्व विकास शिबिरे, मुक्त विद्या केंद्र, छोट्या - मोठ्या सहली, यासारखे बहुआयामी उपक्रम संस्था आयोजित करत असते.

महिला अन्याय निवारण समिती

महिलांवर होणाऱ्या अन्याला वाचा फोडण्यासाठी या भागात कोणत्याही स्वरूपाचे खंबीर असे मध्यम या भागात उपलब्ध नव्हते, त्यामुळे त्यांनी १९९० मध्ये महिला अन्याय निवारण समितीची स्थापना केली. या समितीच्या माध्यमातून जुलै २०१३ पर्यंत १८७० अन्यायग्रस्त महिलांच्या तक्रारी नोंद झाल्या. यातील ४०% अर्जाबाबत यशस्वी तोडगा होऊ शकला.[५] आज सांगोला येथे भारतीय स्त्री-शक्तीच्या

सहकार्याने केंद्रीय समाज कल्याण बोर्डाचे 'मैत्रीण कुटुंब सल्ला केंद्र' व मंगळवेढा येथे महाराष्ट्र शासनाच्या सहकार्याने महिला समुपदेशन केंद्र सुरु केले आहे. यांच्या माध्यमातून अन्यायग्रस्त महिलांना न्याय मिळवून देण्याचा प्रयत्न केले जातो.

प्रशिक्षण व्यवसाय

ग्रामीण महिलांना आर्थिकदृष्ट्या स्वयंपूर्ण बनण्यासाठी या भागात व्यवसायाभिमुख असे शिक्षण उपलब्ध नव्हते, परिणामी महिलांना व्यवसाय करण्याची इच्छा असतानाही योग्य प्रशिक्षणाअभावी त्या चांगल्या प्रकारे व्यवसाय करू शकत नव्हत्या. त्यामुळे १९९२ मध्ये त्यांनी विविध प्रकारचे व्यवसाय प्रशिक्षण देण्यास सुरवात केली. शेळीपालन, गांडूळखत निर्मितीपासून ते संगणक आणि ब्यूटीपार्लर प्रशिक्षणापर्यंत ३८ प्रकारची व्यवसाय प्रशिक्षणे घेऊन जवळपास ३१०३ महिला प्रशिक्षित झाल्या.[६] त्यातून स्वत:चे छोटे-छोटे व्यवसाय सुरु करण्याचे प्रमाण ५० टक्क्यांहून अधिक आहे. या प्रशिक्षणांसाठी कोल्हापूर येथील कांचन परुळेकर यांच्या 'स्वयंसिध्दा' चे उस्फूर्त मार्गदर्शन मिळाले.

महिला बचत गट

व्यवसायाभिमुख झालेल्या ग्रामीण स्त्रीला पतपुरवठा मिळावा आणि त्यामुळे तिचे तिच्या कुटुंबातील स्थान सन्मानाचे व्हावे यासाठी १९९५ मध्ये भारतीय स्त्री शक्तीच्या सहाय्याने पाच महिला बचत गटांची स्थापना केली. आज २६५ गटांपैकी १४० गट स्वयंपूर्ण झालेले आहेत. १२५ गटांचे व्यवस्थापन सध्या केले जाते. बचत गटांमुळे ग्रामीण महिला स्वतः सक्षम, सबल झाल्या आणि त्यांनी त्यांची कुटुंबेही तेवढीच सक्षम केली.

मेडलरी चरख्यावर लोकरीचे सुत कातण्याचे दिलेले प्रशिक्षिण घेऊन निरक्षर शकुंतला खडतरेने स्वत:च्या क्षमता वाढवीत सुरु केलेला चप्पल कारखाना, नवनिर्वाचित ग्रामपंचायत सदस्यांसाठी दिलेले प्रशिक्षण घेऊन आत्मनिर्भर झालेल्या सरपंच शारदा रणदिवेने संस्थेच्या अर्थसहाय्यातून तिच्या गावातील ओढयामध्ये बांधलेला बंधारा, खाटिक व्यवसाय करणाऱ्या हसीना मुलाणीने बचत गटातून नेतृत्व विकासाचे प्रशिक्षण घेऊन गावच्या उपसरपंच पदापार्यात बिनविरोध मारलेली भरारी, शेळीपालनाच्या प्रशिक्षणातून एका शेळीपासून १० दुभत्या जनावरांच्या गोटयापर्यंत मजल मारणारी समाबाई गडदे, बालवाडी प्रशिक्षणातून प्रथम बालवाडी सुरु करून आपल्या नाकर्त्या पतीला मिळवते करून आपला आणि शेजारपाजारच्या बायाबापडयांचाही संसार सावरणारी शारदा बोत्रे, शिलाई प्रशिक्षणातून स्वतःची शिलाई मशीन घेऊन शिलाई करणाऱ्या २९० हून अधिक महिला, भाजी विक्री, फळ विक्री, चहाची टपरी, बांगडयांचे दुकान, किरण दुकान, कापड दुकान, मालाची ने-आण करण्याचा वाहन व्यवसाय अशा छोटया-मोठया अनेक व्यवसायातून २००० हून अधिक महिला व त्यांची कुटुंबे विकसित झाली आहेत. समाजात प्रतिष्ठित झाली आहेत. यासाठी काही बँका व इतर सहकारी संस्था यांनी महत्वाचे योगदान दिले आहे.

आरोग्यदूत योजना

ग्रामीण भागामध्ये मातामृत्यू व बालमृत्यूचे प्रमाण दिवसेंदिवस चिंताजनक बनत होते. त्याच्यावर मात करण्यासाठी २००८ मध्ये 'आरोग्यदूत योजना' सुरु केली. या योजनेच्या मध्यातून १० गावातील ग्रामीण महिलांना प्रसूतिपूर्व आणि नवजात शिशूंच्या तपासणी व धोक्याचे प्रशिक्षण दिले. आज त्या आपापल्या गावांमध्ये 'आरोग्यदूत' म्हणून जबाबदारीने काम करीत आहेत. त्यामुळे सबंधित गावातील महिलांमध्ये जागृती होण्यास मदत झाली. त्यामुळे तेथील मातामृत्युचे प्रमाण त्यांनी जवळ जवळ शून्य टक्यांवर आणले असून नवजात शिशूंच्या मृत्यूचा दरही परिणामकारक घटलेला आहे. एकंदरीत विचार करता ग्रामीण भागातील महिलांना या योजनेचा चांगला फायदा झाला असे आपणास म्हणता येते.

मूल्यमापन

ग्रामीण महिलांचे सक्षमीकरण आणि त्यातून स्वावलंबी समाजानिर्मितीचा संकल्प हे उद्दिष्ट ठेवून शिक्षण, आरोग्य, अन्याय-अत्याचाराविरूध्द संघर्ष, आर्थिक स्वावलंबन, आणि पर्यावरण साक्षरता या पंचसूत्रीचा अवलंब डॉ. सांजीवणी केळकर यांनी केला. १९७८ पासून आजपर्यंत त्यांच्या सर्व मैत्रिणी व त्यांनी आपापले संसार व व्यवसाय सांभाळून, गुण्यागोविंदाने आणि एकदिलाने, ग्रामीण समाजाचा एक भाग होऊन ग्रामीण स्त्रीला आणि तिच्या कुटुंबाला सक्षम करण्याचा प्रयत्न केला आहे. या कामासाठी प्रसंगी अर्थसहाय्य समाजाकडून मिळाले आहे व मिळत आहे. काम करीत असताना त्यांना नैराश्यांचे अनेक क्षण आले पण त्यात समाधानाचे पारडे मात्र नेहमीच जड राहिले. त्यांच्या कुटुंबीयांनी या कामात नेहमीच त्यांना साथ दिली. हे काम पुढे चालवण्यासाठी त्यांच्या टीममधील दुसरी फळी पुढे येत आहे.

संदर्भ

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११. उत्तर पेशवेकालीन तुरुंग व्यवस्था

प्रिया ब्रिजेश कुलकर्णी
पीएच.डी. विद्यार्थिनी, टिळक महाराष्ट्र विद्यापीठ, पुणे.

प्रस्तावना

सतराव्या शतकातील हिंदवी स्वराज्याची स्थापना ही विचारवंतांना विचार करण्यास भाग पाडणारी एक घटना आहे. हिंदवी स्वराज्याचे शिवरायांनी या कठीण परिस्थितीतून निर्माण कार्य केले, त्याला जागतिक पातळीवरही ग्राह्य धरले जाते .स्वराज्य निर्मिती ही पराक्रम आणि धाडस या जोरावर शिवरायांनी केलेली होती, मात्र हे स्वराज्य मजबुतीसाठी व टिकण्यासाठी प्रशासनाची घट्ट चौकट गरजेची आहे, हे जाणणारे छत्रपती शिवाजी महाराज होते. कारण राज्य निर्माण होते ,ते तलवारीच्या जोरावर पण टिकते ते प्रशासनाच्या काटेकोर नियमांमुळे हेच जणू शिवरायांनी हिंदवी स्वराज्याची प्रशासकीय व्यवस्था निर्माण करून सिद्ध केलेले होते. प्रशासकीय व्यवस्थेचे विविध घटक त्यांनी निर्माण केले होते. उदा: अष्टप्रधान मंत्रिमंडळ, आरमार, लष्कर ,महाल, कारखाने ,न्यायदान व्यवस्था, तुरुंग व्यवस्था इत्यादी. शिवरायांच्या हिंदवी स्वराज्याचा उत्तरार्ध म्हणजेच इ.स. १७०७ला सुरू झालेला पेशवे कालखंड होय. पेशव्यांनी नर्मदे पलीकडे मराठी साम्राज्याचा विस्तार केला. शिवरायांची तत्वे अमलात आणण्याचा आटोकाट आणि कसोशीने प्रयत्न केला. पण बऱ्याच व्यवस्थेत काळपरत्वे पेशव्यांना बदल करावे लागले. त्यामध्ये पेशवेकालीन तुरुंग व्यवस्था हा एक घटक येतो. या तुरुंगात व्यवस्थेवर चिकित्सक प्रकाश टाकण्याचा प्रयत्न या शोधनिबंधाद्वारे केला जात आहे .

1. तुरुंग

तुरुंग याचा अर्थ कारागृह ,बंदिशाळा किंवा कारा असा होतो. सामान्य किंवा गंभीर गुन्ह्यांसाठी गुन्हा सिद्ध झाल्यानंतर शारीरिक दृष्टीने शिक्षा भोगण्याचे ठिकाण म्हणून तुरुंग व्यवस्था निर्माण केली होती. तुरुंग म्हणजे गुन्हेगार व कैदी यांना डांबून ठेवण्याचे ठिकाण, असा सरळ अर्थ होता. राज्य व्यवस्थेचा एक महत्त्वाचा भाग म्हणूनही बंदी शाळेकडे पाहिले जाई. प्राचीन काळापासून यासंदर्भात बरेच संदर्भ मिळतात. कौटिल्याने आपल्या अर्थशास्त्रात न्याय ,गुन्हेगार ,दंड, शिक्षा या संदर्भातील वर्णन केलेले आहे. गुन्हेगार म्हणजेच समाजकंटक आणि त्यांनी केलेल्या अपराधाची शिक्षा याबाबतीतही आर्य चाणक्य या ग्रंथात माहिती मिळते.(१) प्राचीन काळाचा हाच दंडक मध्ययुगीन काळातही चालू होता. स्वराज्यामध्ये व पेशवाईमध्ये देखील गुन्हेगार, दंड व शिक्षा हे विषय होते .दंडामध्ये आर्थिक भरपाई असेल तर गुन्हेगारांकडून रक्कम वसूल केली जाई आणि शारीरिक दृष्टिकोनातून शिक्षा दिली असेल तर ती तुरूंगामध्ये भोगावी लागत असे. म्हणजे स्वतंत्र तुरुंग व्यवस्था होती, मात्र आधुनिक काळाप्रमाणे तुरुंगाच्या स्वतंत्र व मोठमोठ्या इमारती मात्र अस्तित्वात नव्हत्या. मराठ्यांकडे तर किल्ल्यामध्येच तुरुंग

व्यवस्था होती. पेशवे काळात किल्ल्यांना फारसे महत्त्व राहिलेले नव्हते. या किल्ल्यांना तुरुंगाची कळा आली होती. किल्ल्यांवरील अशा तरुणांना कारागृह किंवा बंदीखाना आणि गुन्हेगारास कैदी किंवा बंदी असे म्हणले जाई. परंपरेवर आधारित असाच न्याय व शिक्षा होती. यासाठी ठराविक नियम वा कायदे पेशवाईत नसावेत. फितुरी आणि राजद्रोह हे गंभीर स्वरूपाचे गुन्हे होते, तर जात विषयक व अनैतिक वर्तनाचे गुन्हे जास्त घडत असत. (२) थोडक्यात पेशवे काळातही तुरुंग व्यवस्था अस्तित्वात होती, हे स्पष्ट होते.

2. गुन्ह्यांची विविधता व शिक्षा

पेशवे काळामध्ये, किल्ल्यामध्येच काही ठराविक भागात तुरुंगाची व्यवस्था करीत असल्याचे पाहिले आहे. तुरुंगाचा एक भाग म्हणून अंधार कोठडी ही बहुतांशी सर्व किल्ल्यावर असेच. जसे गुन्हे विविध प्रकारचे असत, तसेच शिक्षाही त्यानुसार दिली जात असे .मुख्य म्हणजे तत्कालीन काटेकोर जातिव्यवस्थेचा गंभीर पगडा न्याय-निवाडा यावर पडलेला दिसतो. एकच गुन्हा ब्राह्मण, क्षत्रिय, वैश्य आणि क्षुद्र या वर्णांमध्ये घडला असेल तर शिक्षा कमी जास्त प्रमाणात दिली जाई. ब्राह्मण जातीस शक्यतो देहदंडाची शिक्षा होत नसे. क्षुद्र व्यक्ती ,अनैतीक वर्तन करणाऱ्या स्त्रिया तसेच पुरुष यांना मात्र फारच मोठी शिक्षा दिली जाई. शक्यतो अशी सक्तमजुरीची शिक्षा म्हणून त्यांना जिथे-जिथे बांधकाम चालत असे तिथे-तिथे हे बांधकामासाठी नेमले जाई. शिक्षेचे प्रकार कठीण भीतीदायक असत. गुन्हेगारास शिक्षा म्हणून रोख दंड आकारणे त्याची मालमता सरकार जमा करणे ,त्याचे वतन आणि पद काढून घेणे. (३) गुन्हेगार स्त्रीला मात्र फार मोठ्या शिक्षा दिल्या जात असत, असे दिसते. त्यातही स्त्री हलक्या जातीतील असेल तर आणि तिने बदकर्म केले असेल तर शिक्षा मोठ्या प्रमाणात होत असे. थोरल्या माधवराव पेशव्यांच्या काळामध्ये एक गुन्हा असा घडला की एक ब्राह्मण पुरुष व एक देशमुख बाई जिचे नाव 'सई चीकोडीकर' असे होते, त्यांच्या हातून बदकर्म घडले. त्यावेळेस तिने मद्यपान केलेले होते. गुन्हा सिद्ध झाल्यानंतर दोघांनाही ही अटक करून शिवनेरी किल्ल्यात कैदेत ठेवण्यात आले होते. (४) एक गुन्हा तर असा होता की त्यामध्ये स्त्रीस फटके मारण्याची शिक्षा दिलेली होती. एका हिंदू स्त्रीने चोरी केली व मुद्देमाल लपवून ठेवला म्हणून तिला १९ फटके मारण्याची शिक्षा मुद्देमाल सापडेपर्यंत देण्यात आली होती. (५)अशा रीतीने गुन्ह्यांची व शिक्षेची विविधता दिसून येते.

3. कैद्यांचे दैनंदिन जीवन

तुरुंग व्यवस्थेचा हादेखील एक महत्वाचा भाग होता कि जिथे- जिथे स्त्री व पुरुष कैदी ठेवले जात तिथे- तिथे त्यांचे दैनंदिन जीवन कसे होते? याची माहिती घेणे. यामध्ये कैद्यांची राहण्याची, अन्न- वस्त्रांची वस्त्रांची व्यवस्था इत्यादी विषय असत. तसेच कैद्यांना हाता-पायात बेड्या ठोकणे व त्या विशिष्ट वेळी, काही काळ काढणे. हेही प्रकार होते.काही विशिष्ट प्रसंगी कैदेचा कालावधी संपला नसतानाही कैद्यास काही दिवसांसाठी सोडणे व पुन्हा कैदे मध्ये ठेवणे इत्यादी बाबी असत. या सर्व गोष्टींची इत्यंभूत माहिती लेखक लेखक चिमणाजी वाड यांच्या "पेशवा डायरीज" या ग्रंथांमधून प्राप्त होते.(६) गुन्ह्यानुसार दंड व कैद

झालेल्या कैद्यांना वेळ प्रसंगी चांगली वागणूक दिली जात असे. उदा: कैद्याच्या आरोग्याची काळजी घेणे ,त्यांना विशिष्ट धार्मिक कामासाठी द्रव्य देणे, ज्या किल्ल्यावर कैद्यास ठेवले आहे तेथील हवामान निरोगी नसेल तर कैद्यांना दुसरीकडे हलविले जात होते .सर्वसामान्य गुन्ह्यांसाठी फारशी काटेकोर बंधने नव्हती. मात्र राजकीय गुन्ह्यांसाठी कडक बंधने होती. शक्यतो सामान्य जनतेला कोणताही उपद्रवही होऊ नये आणि त्यांना जीवित, वित्त व अब्रू यासाठी सरकारी संरक्षण मिळावे ,अशी प्रशासकीय तरतुदींच्या मागे उद्दिष्टे होती.

4. निष्कर्ष/ परीक्षण

उत्तर पेशवेकालीन तुरुंग व्यवस्था हि जनतेच्या स्थैर्यासाठी होती.आधुनिक काळाप्रमाणे तुरुंगाच्या स्वतंत्र इमारतीत व स्वतंत्र काम खास पद्धतीने नसली, तरीही जनतेवर आणि गुन्हेगारांवर तुरुंग व्यवस्थेचा पगडा होता.तुरुंगातील कैद्यांची एक माणूस या नात्याने काळजी घेतली जात असे.तत्कालीन कैद्यांना हाता-पायात बेड्या ठोकल्या जात असत. मात्र जेव्हा त्यांना जेवण दिले जाई, तेव्हा काही काळ त्यांच्या बेड्या काढल्या जात असत. उदा: तुळाजी आंग्रे हा सोलापूर किल्ल्यात काही होता त्याचा बेड्या जेवणाच्या वेळी काढल्या जायची माहिती मिळते..जर कैदी म्हणून स्त्री गुन्हेगार ठरली तर स्त्रियांना वर्षाकाठी दोन लुगडी व खण पेशवे दरबारातून दिले जात असत. यावरून स्त्रियांची तुरुंगामध्ये उत्तम काळजी घेतली जात असे व एक स्त्री म्हणून त्यांचे स्थान अबाधित ठेवले जात असे.गुन्हेगारांना वर्णव्यवस्थेनुसार शिक्षा ठोठावल्या जात असत. मात्र आधुनिक काळात कायदे व्यवस्थेत जातीयता आणि येत नाही. कितीही मोठा गुन्हा केला तरी ब्राह्मण गुन्हेगारास देहदंडाची शिक्षा होत नसे. यावरून चातुर्वर्ण्य व्यवस्थेतील ब्राह्मणांच्या स्थानावर प्रकाश पडतो.शिव काळाप्रमाणे किल्ल्याचे महत्व पेशवेकाळात उरले नव्हते. अनेक किल्ल्यांना पेशवाईमध्ये तुरुंगाची कळा आली होती.पानिपतनंतर मराठे- शाहीचा संपूर्ण ऱ्हास झालेला नव्हता, हे तुरुंग व्यवस्थेसारख्या अनेक प्रशासकीय बाबींवरून स्पष्ट होते.

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१२. शेतकऱ्यांच्या व्यथा व महात्मा फुले यांचे उपाय

प्रा. कोकाटे अनिल दत्तात्रय
इतिहास विभाग, छत्रपती शिवाजी कॉलेज, सातारा.

विसाव्या शतकात भारतात झाल्या तशा महाराष्ट्रातही समाजसुधारणाविषयक विविध चळवळी घडून आल्या. या चळवळी घडून येण्याची जी विविध कारणे होती. त्यामध्ये प्रामुख्याने भारतातील इंग्रजी सत्तेची स्थापना, इंग्रजांनी येथे सुरू केलेले इंग्रजी शिक्षण व त्यातून आपणास पाश्चात्य समाज तेथील आधुनिक संकल्पना, त्यांनी केलेली वैज्ञानिक प्रगती यांचे झालेले ज्ञान यांचा समावेश होतो. या शतकात जे काही सुधारक महाराष्ट्रात होऊन गेले. त्यामध्य उक्तीप्रमाणे कृती करणारे व स्वत:च्या कार्याने बहुजन समाजाच्या उन्नतीसाठी प्रेरक ठरलेले व्यक्तिमत्व म्हणजे महात्मा फुले होय.

जोतीराव फुले यांचे कुलपुरूष आताच्या सातारा जिल्हयातील कटगुण या गावी राहत असत. त्यांचे घराणे क्षत्रिय माळी जातीचे होते. जोतीरावांचा जन्म १८२७ साली झाला. बालपणीच आईचे निधन झाल्यामुळे त्यांचा सर्व सांभाळ वडील गोविंदरावांनी केला. जोतीरावांच्या जन्मापूर्वीच पुण्यातून पेशवाई नष्ट झाली असली तरी राजसत्ता आणि धार्मिक सत्ता ब्राम्हणांच्या हाती असल्यामुळे शिक्षण ही ब्राम्हणांखेरीज समाजातील कनिष्ठ वर्गातील लोकांनी संपादन करावयाची गोष्ट नाही, अशी त्याकाळी समजूत होती. त्यावेळची परिस्थिती अशी असली तरी गोविंदरावांनी जोतीला वयाच्या सातव्या वर्षी प्राथमिक मराठी शाळेत घातले होते.[१] ही गोष्ट खरोखरच धैर्यद्योतक आणि प्रशंसनीय होती. जोतीराव हे बुद्धीमान व उत्साही होते. त्यामुळे अल्पकाळात त्यांनी अभ्यासात प्रगती केली. त्यांनी प्राथमिक शाळेतील अभ्यास पूर्ण केला होता. आता त्यांना चांगले लिहिता वाचता येऊ लागले होते व हिशेबही करता येऊ लागले होते. नेमके याच वेळी गोविंदरावांनी आपला मुलगा जोतीरावला शाळेतून काढून टाकले. याचे मुख्य कारण म्हणजे गोविंदरावाच्या दुकानातील ब्राम्हण कारकुनाने त्यांचे कान फुंकून जोतीला शाळेतून काढण्याविषयी त्यांना कुसल्ला दिला असे जोतीरावांचा दत्तक मुलगा यशवंतने लिहून ठेवले आहे.[२] त्यामुळे जोतीरावांचे शिक्षण थांबले. याचा सरळ अर्थ असा होतो की त्या काळात वरिष्ठ वर्गातील लोकांना कनिष्ठ वर्गातील लोकांनी शिकू नये असे वाटे. हे कनिष्ठ शिकले तर नोकरीधंद्यात ते आपले भागीदार होतील. लोकहितवादी गोपाळरावांनी १८४८ साली शतपत्रात लिहिले की, एखादा मराठा किंवा इतर जातीचा कारकून ब्राम्हणांनी पाहिला म्हणजे त्यांचे अंगाचे तिळपापड होतात, हे काय?[३]

जोतीरावांना शाळेतून काढल्यानंतर ते वडिलांच्या फुलबागेत आणि भाजीच्या मळयात तन्मयतेने काम करू लागले. आपल्या मुलाची सुदृढता, प्रामाणिकपणा, उत्साह आणि अंगची अखंड उद्योगशीलता पाहून

गोविंदरावांना परम संतोष वाटे. त्याकाळच्या रीतीरिवाजाप्रमाणे जोतीरावांचे लग्न वयाच्या १३ व्या वर्षी पुण्याजवळील धनकवडी गावातील झगडेपाटीलांची मुलगी सावित्रीबाई हिच्याशी मोठया थाटात गोविंदरावांनी लावून दिला. शिक्षणात खंड पडला तरी शिक्षणाबद्दलची जोतीरावांची ओढ कमी झाली नव्हती. दिवसभर काम केल्यानंतर ते रात्री मिणमिणत्या समईजवळ वाचत बसत. साहजिकच त्यांच्या शेजाऱ्यांतील दोन विद्वान गृहस्थांचे लक्ष त्यांच्याकडे वेधले गेले. ते दोन सद्गृहस्थांपैकी एक होते उर्दू व पर्शियन भाषेचे पंतोजी गफव्हार बेग मुनशी व दुसरे होते ख्रिस्ती धर्मोपदेशक लिजीट साहेब. या परधर्मातील दोन विद्वानांच्या आग्रहावरून गोविंदरावांनी ३ वर्षाच्या खंडानंतर जोतीबांना १८४१ मध्ये एका स्कॉटिश मिशनरी इंग्रजी शाळेत घातले. जोतीबांनी सन १८४७ साली आपला इंग्रजी शाळेतील अभ्यास पूर्ण केला. या शैक्षणिक काळात जोतीरावांना असे अनेक मित्र लाभले ज्यांनी जोतीरावांच्या पुढील अलौकीक कार्यात त्यांना प्रचंड अशी साथ दिली. या मित्रांपैकी सदाशिव गोवंडे यांच्याबरोबर त्यांनी छत्रपती शिवाजी आणि जॉर्ज वॉशिंग्टन यांची चरित्रे अभ्यासली होती. या दोघांच्या मनावर थॉमस पेन याच्या 'राइटस ऑफ मॅन' या आणखी एका ग्रंथाने मोठा परिणाम घडवून आणला होता.[४] त्या काळी सामान्य माणसाचे 'बायबल' असे त्या ग्रंथाचे वर्णन केले जाई. या शिक्षण व वाचनामुळे जोतीराव आता मानवी समता, मानवी हक्क आणि मानवी स्वातंत्र्य यांचे कैवारी बनले. पुढील काळात जे अद्वितीय कार्य त्यांनी केले त्यासाठी आवश्यक असलेले शारीरिक सामर्थ्य त्यांनी या काळातच लहुजीबुवा मांग या गृहस्थाच्या मार्गदर्शनाखाली मिळविले होते. खरेतर जोतीराव जी परीक्षा उत्तीर्ण झाले होते तीच परीक्षा गोपाळ हरी देशमुखही उत्तीर्ण झाले होते. परंतु जोतीरावांनी लोकहितवादी व इतर समकालीनांपैकी बाळशास्त्री जांभेकर व कृष्णशास्त्री चिपळूणकरांप्रमाणे सरकारी नोकरी केली नाही तर ते समाजसुधारणेच्या क्षेत्राकडे वळले.

जोतीरावांनी सामाजिक अन्यायाविरूद्ध लढून समाजक्रांती करण्याचे ठरविण्यास त्यांच्या आयुष्यात १८४८ साली घडून आलेली अपमानकारक घटना कारणीभूत ठरली. आपल्या एका ब्राम्हण मित्राच्या लग्नाच्या मिरवणुकीत ते ब्राम्हण मंडळीबरोबर चालत होते. एका माळयाच्या मुलाने आपल्या बरोबरीने चालावे हे सनातनी ब्राम्हणांना न आवडल्याने ते बेभान झाले. त्यांनी जोतीरावांचा कनिष्ठ जातीवरून अपमान केला व सर्वांच्या मागून चालण्यास सांगितले. या भयंकर अपमानामुळे जोतीरावांनी तत्कालीन सामाजिक स्थितीवर खूप विचार करून जी क्रांती घडण्याची त्यांची इच्छा होती ती शस्त्राने साध्य होणार नाही हे त्यांच्या लक्षात आले. त्यांचे असे मत झाले की, 'राजकीय गुलामगिरीपेक्षा सामाजिक गुलामगिरी अधिक वाईट होय' आणि म्हणूनच असा निष्कर्ष काढता येऊ शकतो की, त्यांच्या ब्राम्हण मित्राच्या विवाह मिरवणुकीत त्यांना जी सामाजिक अप्रतिष्ठा अनुभवाला आली त्यातूनच त्यांच्या पुढील आयुष्यातील चळवळीची सुरूवात झाली.

जोतीरावांच्या आयुष्यात जातीमुळे जी अपमानकारक घटना घडली तशाच प्रकारची घटना म. गांधीजींना दक्षिण आफ्रीकेत इंग्रजांच्या वंशश्रेष्टत्वाच्या भावनेतून अनुभवाला आली व या घडलेल्या अपमानास्पद घटनेमुळे दोघांच्यातील बंडखोर जागा झाला. दोघेही कांतीकार्याकडे वळले. म.गांधीनी राजकीय क्षेत्रात कार्य केले तर जोतीराव फुल्यांनी सामाजिक क्षेत्रात क्रांती घडवून आणली. जोतीरावांच्या चिंतनाचे,

लेखनाचे आणि कार्याचे प्रमुख केंद्र म्हणजे उपेक्षितांचा वर्ग होय. या उपेक्षित वर्गात अर्थातच जसे शूद्र व स्त्रिया होत्या तसेच शेतकऱ्यांचाही समावेश होता. १९ व्या शतकात इंग्रजांनी महाराष्ट्रात सत्ता स्थापून नवी रचना येथे निर्माण करण्याचा प्रयत्न केला. परंतु हया नव्या रचनेतही परंपरागत प्रस्थापित पुन्हा नव्याने प्रस्थापित झाले व उपेक्षित वर्गाचे हाल वाढतच गेले. अर्थात इंग्रजी सत्तेचे काही फायदे नंतर भारतीयांना झाले. जोतीरावांनी उपेक्षितांसाठी केलेल्या कार्याचा सन्मान म्हणून जनतेने त्यांना 'महात्मा' ही उपाधी दिली.

महात्मा फुल्यांनी स्त्रीया व शूद्रांच्या उन्नतीसाठी तर कार्य केलेच पण त्याबरोबर त्यांनी येथील शेती व शेतकऱ्यांचा सूक्ष्मपणे अभ्यास करून त्यांच्या समस्या व त्यांच्या उन्नतीसाठीचे उपाय अतिशय पोटतिडकीने मांडले जे आजच्या सरकारलाही मार्गदर्शक ठरू शकतात. फुल्याांच्या समकालीन सुधारकांना शेतकऱ्यांच्या प्रश्नांचे एव्हढे महत्वाचे वाटले नाहीत. परंतु महात्मा फुलेंनी मात्र सन १८८३ साली 'शेतकऱ्यांचा आसूड' या ग्रंथातून शेतकऱ्यांची परिस्थिती, शेतकऱ्यांच्या दारिद्रयाची कारणे व त्यांच्या समस्यांचे उपाय सूचवून शेतकऱ्यांबद्दलची आपली बांधिलकी व सूक्ष्म निरीक्षण दाखवून दिले. खरे तर प्राचीन काळापासून हा शेतकरी किंवा कष्टकरी समाजाचे पोषण करत आला आहे. त्यांच्या दु:खाचा विचार करताना इतिहासात शिरल्यानंतर फुल्यांच्या असे लक्षात येते की अनेक शतकांपासून शेतकरी दैन्यावथेतच जगतो आहे. पेशवाईत शेतकऱ्यावर होणाऱ्या अन्यायाचे चित्रण त्यांनी 'इशारा' या आपल्या ग्रंथातही केले आहे.

शेतकऱ्यांच्या तत्कालिन स्थितीची व दैन्यावस्थेची कारणे सांगताना महात्मा फुले म्हणतात की, भटब्राम्हण अडाणी शेतकऱ्यास धर्माची भीती घालून किंवा धर्मग्रंथातील दाखले देऊन आईच्या तुप्राप्तीपासून, गर्भधारनादि संस्कार ते शेतकरी मरेपर्यंत व मृत्यूनंतरही विविध विधी करावयास लावून भोजने व दक्षिणांच्या माध्यमातून शेतकऱ्यांची यथेच्छ लूट करत होता. ब्रिटिशांचे राज्य आल्यामुळे पेशव्यांच्या सैन्यातील लोक बेकार झाले व त्यांचा भार शेतजमिनीवर पडला. कुटुंबातील वाटपामुळे शेतजमिनीचे लहान तुकडे पडले. या लहान तुकडेवाल्या शेतकऱ्यांनी आपल्या जमीनी ज्या शेतकऱ्यांजवळ नांगर व बैल होते त्यांना कसायला दिल्या व ते स्वत: सुतार, लोहारांकडे कामासाठी फिरू लागले. परंतु इंग्लडमधून यंत्रावर तयार झालेला माल भारतात आयात झाल्याने देशी उद्योग खालावले व यातून कष्टकरी विपन्न होत गेले. इंग्रजांनी जंगल खाते निर्माण करून कुरणे नष्ट केली. त्यामुळे शेळया मेंढयास चरण्यास जागा राहिली नाही. शेतकऱ्यांना पडीक जमीन उरली नाही व एकाच शेतात पीक घेतल्यामुळे तिची सुपीकता कमी झाली. यामुळे शेतकरी गव्हाच्या व तांदळाच्या कोंडयावर व आंब्याचा कोयांवर जगण्याचा प्रयत्न करत होता. याच्या उलट इंग्रज नोकर मात्र चांगले कपडे, उत्कृष्ट दारू, पाव, बिस्किटे यांचा उपभोग घेत होते. शेतकऱ्यांच्या दैन्यावस्थेचे पुढचे कारण महात्मा फुले सांगतात की, बहुतेक इंग्रज अधिकारी ऐषारामात गुंग असल्याने सर्व सरकारी खात्यात ब्राम्हण कामगार शेतकऱ्यांना इतके लुटतात की त्यांना पोटभर अन्न व अंगभर वस्त्र मिळू शकत नाही.[५]

शेतकऱ्यांच्या व्यथा व विपन्नावस्थेची कारणे महात्मा फुले यांनी 'शेतकऱ्यांचा आसूड' या ग्रंथातून अतिशय मार्मिकपणे मांडली. हा ग्रंथ त्यांनी बडोद्याचे महाराज सयाजीराव गायकवाड यांना वाचून दाखविल्यानंतर महाराजांनी जोतीरावांना आर्थिक सहाय्य तर केलेच पण त्याबरोबर शाल पागोटे देऊन त्यांचा

सत्कार केला यावरून त्या ग्रंथात शेतकऱ्यांच्या यथार्थ स्थितीचे चित्रण महात्मा फुले यांनी केल्याचे प्रकर्षाने जाणवते. शेतकऱ्यांच्या या व्यथांवर महात्मा फुले यांनी अभ्यासपूर्ण उपाय सांगितले. याबाबत ते सांगतात की, शेतीवर वाजवी कर आकारावा, शेतीसाठी काढलेल्या कालव्याचे पाणी शेतकऱ्यांना वेळेवर मिळावे, इंग्रजांनी राज्यकारभारावरचा खर्च कमी करावा, मोठया पगाराचे अधिकारी कमी करावेत. महात्मा फुल्यांना शिक्षणाची ताकद समजलेली होती म्हणून त्यांनी सरकारला अशी एक सूचना केली होती की, सरकारने शेतकऱ्यांच्या मुलांना सक्तीचे प्राथमिक शिक्षण द्यावे, कनिष्ठ वर्गातील शिक्षक निवडावेत कारण उच्चवर्णिय शिक्षकांना शेतकऱ्यांच्या मुलांबद्दल प्रेम किंवा आस्था वाटत नाही. शेतकऱ्यांच्या मुलांकरिता खास वसतिगृहांची सोय करावी. त्यांच्या या सूचना काळाच्या पुढच्या असल्याचे जाणवते. कारण नंतरच्या काळात राजर्षी शाहू महाराज व कर्मवीर भाऊराव पाटील यांनी ग्रामीण भागातील मुलांसाठी शहरात वसतिगृहांची सोय केल्याचे दिसते. त्यांची सरकारला पुढील सूचना होती की, सरकारने शेतकऱ्यांच्या मुलांना पाटया, पुस्तके व कपडे पुरवावेत. सरकारी नोकरीत ब्राम्हणांना त्यांच्या लोकसंख्येच्या प्रमाणात नोकऱ्या द्याव्यात जेणेकरून नंतर शिकलेल्या शेतकऱ्यांच्या मुलांनाही नोकऱ्या मिळतील. महात्मा फुले यांनी फक्त सरकारलाच उपाय सुचविले नाहीतर शेतकऱ्यांनाही टणकावून सांगितले की, त्यांनी एकापेक्षा अधिक लग्ने करू नयेत व आपल्या मुलांची लग्ने बालपणी करू नयेत.[६]

महात्मा फुले यांनी शेतकऱ्यांच्या उन्नतीसाठी असे मुलभूत उपाय सुचविले. यानुसार ते पुढे सुचवितात की, भारतात कायद्याने गोमांस बंदी व्हावी म्हणजे शेतकऱ्यांना शेतीसाठी बैलांचा भरपूर पुरवठा होईल. सरकारने सैन्य व पोलीस दलाच्या मदतीने नदीवर धरणे बांधावित. पाऊस जमिनीत मुरवला जावा, जमिनीची० धूप न होण्याची काळजी घ्यावी. तलाव व नद्यातील गाळ शेतकऱ्यांना विनामूल्य द्यावा, वृक्षतोडीविरोधी कायदा करावा, शेतकऱ्यांसाठी कृषीप्रदर्शने भरवावीत. उत्तम पीक काढल्याबद्दल शेतकऱ्यांना बक्षिसे द्यावी. शेतीविषयी ज्ञान देणारी पुस्तके द्यावीत इ. या व अशा प्रकारचे उपाय शेतकऱ्यांची दयनीय अवस्था संपावी व शेतकऱ्यांना चांगले दिवस यावेत यासाठी महात्मा फुल्यांनी सुचविले

शेतकऱ्यांच्या श्रमाला योग्य मूल्य मिळाले पाहीजे असे महात्मा फुले सांगतात. त्या काळातील महात्मा फुले हे असे एकमेव सुधारक होते की ज्यांनी शेतकऱ्यांचे प्रश्न फक्त समजावून घेतले नाहीत तर त्या प्रश्नांवर मानवतावादी दृष्टिकोणातून उपायही सुचविले. ज्यातील बरेच उपाय स्वातंत्र्यानंतर भारत सरकारने अवलबिंले व बरेच स्वीकारण्याचे बाकी आहेत.

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प्रा. अरूण वसंत अवसरमल
इतिहास विभाग सामाजिक शास्त्रे प्रशाळा, कवयित्री बहिणाबाई चौधरी उत्तर महाराष्ट्र विद्यापीठ, जळगाव.

प्रस्तावना

वैदीक कालखंडात कर्मावर आधारित वर्णव्यवस्था उदयास आली तर उत्तरवैदीक काळात वर्णव्यवस्थेचे स्वरुप बदलून जन्म आणि जाती आधारित झाले. यात शुद्रातिशुद्रांना उपेक्षित आणि दुर्लक्षित स्थान वर्णव्यवस्थेमुळे समाजात दिले गेले. शुद्र हे जीवंत मानव असूनही सवर्ण आणि धर्मअभ्यासकांनी त्यांना मानवतेची वागणुक दिली नाही, हजारो वर्षे शूद्रातिशुद्र वर्ग हा हीनवागणुकीत खितपत पडलेला होता. मध्ययुगीनकाळातही त्यांना हीन, विटाळ, भेदाभेद आणि कनिष्ठ वागणुक मिळाली. आधुनिककाळात भारतात ब्रिटिश अंमल सुरू झाल्याने सुधारणावादी चळवळीचा उदय झाल्याने अनेक समाजसुधारकांनी शुद्रातिशुद्र, अस्पृश्य म्हणून गणल्या जाणाऱ्यांच्या सामाजिक प्रश्नांकडे लक्ष केंद्रित केले होते. यात महात्मा फुले, शाहूमहाराज, डॉ. बावासाहेब आंबेडकर, गोपाळबाबा वलंगकर, शिवराम जाणवा कांबळे, महर्षी वि. रा. शिंदे, नारायण गुरू यांच्यासारख्या उच्चविचारसरणीच्या महापुरुषांनी परंपरागत जातीव्यवस्था आणि वर्णव्यवस्थेवर कडाडून हल्ला करून मनुवादी जातीव्यवस्थेचा मनोरा खिळखिळा केला. याच धाटनीतील एक नास्तिक आणि वादळी व्यक्तिमत्त्व म्हणजे इ. व्ही. रामासामी पेरीयार हे होते.

उद्देश

१. रामासामी पेरीयार यांनी केलेल्या अस्पृश्यतानिर्मुलन कार्याचे विश्लेषण करणे.
२. रामासामी पेरीयार यांनी दक्षिण भारतात उभारलेल्या ब्राह्मणेत्तर चळवळीची माहिती घेणे.
३. रामासामी पेरीयार यांच्या नास्तिकवादाचा सविस्तर परामर्ष घेणे.
४. रामासामी पेरीयार यांच्याकार्याचा तत्कालीन व्यवस्थेवर झालेल्या प्रभावाचा अभ्यास करून त्यांचे कार्य इतिहास संशोधक आणि अभ्यासकांच्या समक्ष मांडणे.

संशोधन पद्धत

सदरील संशोधन कार्यामध्ये ऐतिहासिक संशोधनत्मक पद्धत आणि विश्लेषणात्मक संशोधन पद्धतीचा अवलंब केलेला आहे.

विषय विवेचन

प्रारंभिक जीवन

रामासामी पेरियार यांचे पूर्ण नाव इरोडे वेंकटप्पा रामासामी नायकर असे होते त्यांचा जन्म १७ सप्टेंबर १८७९मध्ये मद्रासमधील कोइंबतूर जिल्ह्यातील इरोडे येथे वैष्णव पंथीय हिंदू कुटुंबात झाला. त्यांचे वडील एक श्रीमंत

व्यापारी होते रामासामी यांनी अवघे तीन वर्षे शिक्षण घेतले आणि वयाच्या बाराव्या वर्षी आपल्या वडिलांना उद्योगात हातभार लावू लागले, कन्नड ही त्यांची मातृभाषा असून त्यांना मल्याळम, तामिळ, तेलगू या द्रविडियन भाषाही अवगत होत्या. १९०४मध्ये रामासामी पेरीयार यांनी हिंदू धर्मीयांचे पवित्र तीर्थस्थळ काशीची यात्रा केली, तेथे त्यांना ब्राह्मण्यवादाचे खरे रूप ज्ञात झाले. कारण काशी विश्वनाथ मंदिराच्या शेजारीच उपेक्षित अपंग, भुकेने व्याकूळलेले भिकारी, पाण्यावर तरंगणारे मृतदेह, धर्म पंडीतांकडून भोळे भाबळ्या श्रद्धाळूंची होणारी लुबाडणूक अशा अनेक अनैतिक आचरणांमुळे काशी तीर्थस्थळ पूर्णतः विटले होते. पेरीयार म्हणतात कि, 'काशी हे तीर्थक्षेत्र कमी, पण ब्राह्मणांचे शोषणक्षेत्रच ज्यास्त आहे'. काशी येथे एका दक्षिणात्य ब्रह्मणेत्तर व्यापाऱ्याने यात्रेकरूंसाठी उपहारगृह उभारलेले होते परंतु त्यावर ब्राह्मण पंडितांनी मक्तेदारी करून ब्रह्मणेत्तर व्यक्तींना उपहारगृहात प्रवेशास मनाई होती, पेरीयार यांना सुद्धा सदरील उपहार गृहातून अपमान करून बाहेर काढले होते, त्यांनी खरकटे अन्न ग्रहण करून आपली भुक शमवली होती. काशीतील अपमानास्पद अनुभवांचा त्यांच्या मनावर खोलवर परीणाम होवून त्यांची विचारसरणी पुरती बदलली होती, ब्राह्मण्यवादाला मुळापासून नेस्तानाबूत करण्याचा ठाम निश्चय केला होता, "काशी यात्रेला आस्तिक म्हणून रवाना झालेले पेरीयार परतीच्या प्रवासात नास्तिक म्हणून स्वगृही परतले होते"

काँग्रेस पक्ष प्रवेश

अस्पृश्यांची दयनीय अवस्था पाहून पेरीयार यांचे मन क्षुब्ध झाले होते त्यांनी हिंदूधर्माचा चिकित्सक अभ्यास केल्यानंतर त्यांची हिंदू धर्मावरील श्रद्धा डळमळीत झाली, म्हणून त्यांनी सामाजिक समतेचा पुरस्कार करून अस्पृश्योद्धाराचे कार्य हाती घेतले. १९१९ला चक्रवर्ती राजगोपालाचारींच्या सल्ल्यावरून त्यांनी काँग्रेसमध्ये प्रवेश केला. कारण राष्ट्रीय व्यासपीठावरून अस्पृशतानिर्मूलनमुद्द्याला परिणामकारक मांडून काँग्रेसच्या आधारे अस्पृश्यतानिर्मुलन करण्याचा रामसामी नायकर यांचा मानस होता. काँग्रेसने आखलेल्या १९२०च्या असहकार चळवळीत त्यांनी सक्रीय सहभाग घेवून मद्रास प्रांतातील असहकार आंदोलनाचे नेतृत्व केले होते. खादीचा प्रचार प्रसार, दारूबंदीसाठी धरणे, सत्याग्रह आंदोलनांमध्ये त्यांना अनेकवेळा तुरुंगवासही भोगला होता.

वायकोम मंदिर सत्याग्रह

तामिळनाडू मध्ये इंझावा आणि पुलैय्या या अस्पृश्य जाती होत्या त्यांना सवर्णांपासून अनुक्रमे १६ व ३२ फुट हे संरक्षित अंतर ठेवूनच राहावे लागत होते. कारण त्यांच्या स्पर्शानेच नव्हेतर सावलीने सुद्धा आपणास विटाळ होऊन धर्मभ्रष्ट होईल असे भावडे तत्वज्ञान धर्मग्रंथ रचनाकारांनी निर्मित केले होते. त्रावणकोर जिल्ह्यात वायकोम येथील शीवमंदिर प्रसिद्ध आहे, मंदिराच्या चारही बाजूंनी रहदारीचे मुख्य रस्ते असून ते मंदिराच्या खाजगी मालकीचे होते. त्या रस्त्यांवरून सुद्धा अस्पृश्यांना चालण्याचा हक्क पुजाऱ्यांनी नाकारला होता, तर अस्पृश्यांना मंदिर प्रवेश आणि देवदर्शन तर खूप दूरचीच बाब होती. याविरुद्ध अनेक समाजसुधारकांनी आवाज उठवला होता.

अस्पृश्य समुदायाला सर्व मंदिरांमध्ये प्रवेश मिळावा यासाठी १९२२ ला पेरीयार यांनी काँग्रेसमध्ये ठराव मांडला परंतु तत्कालीन तामिळनाडू काँग्रेसमध्ये सवर्ण आणि ब्राह्मण समुदायाचे वर्चस्व असल्याने काँग्रेसने त्यांचा ठराव अमान्य केला. १९२४ साली काँग्रेसने वायकोम मंदिरात अस्पृश्यांना प्रवेश मिळवण्यासाठी चळवळ उभारली. वायकोम मंदिरप्रवेश सत्याग्रहात पेरीयार यांनी अग्रणीची भूमिका स्वीकारून मदुराई तुकडीचे नेतृत्व केले, या आंदोलनात त्यांना

तुरुंगवासही भोगावा लागला परंतु त्यांनी आपल्या कार्यात कदापि खंड पडू दिला नाही. त्यांच्या कार्यकर्त्यांनी त्यांच्या या भरीव कार्याबद्दल त्यांना 'वायकोमवीरन' ही पदवी दिली होती.

गुरुकुलम प्रकरण

ब्रिटिश धोरणांना विरोध करण्यासाठी सुरु केलेल्या १९२०च्या असहकार चळवळीमध्ये काँग्रेसने राष्ट्रीय शिक्षण आणि राष्ट्रीय शाळांची निर्मिती करणे हा कार्यक्रम आखला होता त्याअनुषंगाने भारतासोबत तामिळनाडूमध्ये राष्ट्रीय शिक्षणासाठी काँग्रेस प्रणित गुरुकुलामार्फत राष्ट्रीय शाळा स्थापन केली होती. गुरुकुललाचे अध्यक्ष व्ही. व्ही. एस. अय्यर हे होते ते सनातनी ब्राम्हण्यवादाचे पुरस्कर्ते असून गुरुकुलातील ब्राह्मण व ब्राह्मणेत्तर विद्यार्थ्यांमध्ये शिक्षण, अन्न, वस्त्रे तसेच विविध बाबतीत भेदभाव करून खालच्या दर्जाची कामे ब्राह्मणेत्तर व अस्पृश्य विद्यार्थांकडून करवून घेत असत. व्ही. व्ही. एस. अय्यर यांच्या ब्राह्मण-अब्राह्मण जातीयवादाचा पेरीयार यांनी तीव्र विरोध करून त्यांची तक्रार काँग्रेस पक्षश्रेष्ठींकडे केली, परंतु काँग्रेसवर ब्राह्मण समुदायाचे वर्चस्व असल्याने काँग्रेसने पेरीयार यांची तक्रार फेटाळून अय्यर यांच्यावर कोणत्याही प्रकारची कारवाई केली नाही. त्यामुळे पेरीयार यांच्या मनात काँग्रेस आणि ब्राह्मण समुदायावद्दलची चीड निर्माण झाली होती.

१२ नोव्हेंबर १९२५मध्ये रामासामी पेरीयार यांनी महात्मा गांधी यांची बेंगलोर येथे भेट घेऊन काँग्रेसने अस्पृश्योद्धार आंदोलन उभारून जाती निर्मूलन आणि अस्पृश्यांना आरक्षण मिळवून देण्यासंदर्भात मागणी केली, परंतु गांधीजींनी पेरियार यांची मागणी फेटाळून लावल्याने पेरियार यांना गांधीजींच्या हिंदू धर्मावाबतची निष्ठा आणि त्यांचा वर्णाश्रमव्यवस्थेवरील विश्वास याची प्रचिती आल्याने पेरीयार हे महात्मा गांधी आणि काँग्रेसपासून दूर गेल्याचे दिसून येते. काँग्रेस आणि पेरियार यांच्यात राजकीय स्वातंत्र्य आणि सामाजिक स्वातंत्र्य यावरून मतभेद होते. काँग्रेसचे मत होते की ब्रिटीशांना भारतातून हुसकावून सत्ता भारतीयांच्या हातात येताच सामाजिक स्वातंत्र्य देता येवू शकेल म्हणून काँग्रेसने सामाजिक स्वातंत्र्याला दुय्यम स्थान दिले, तर सामाजिक स्वातंत्र्याशिवाय राजकीय स्वातंत्र्य हे कवडीमोल ठरेल अशी भूमिका पेरियार यांची होती. "From now on it should be my secrete duty to destroyed the Congress which is close to the preservation to Brahmanism".म्हणजे "काँग्रेस ही ब्राह्मण्यवादाला चालना देण्याचे कार्य करीत असल्याने आतापासून काँग्रेसला नेस्तनाबूत करणे हे माझे कर्तव्य आहे". अशी घोषणा करून पेरियार यांनी नोव्हेंबर १९२५ रोजी काँग्रेसला सोडचिठ्ठी दिली होती.

स्वाभिमानी चळवळ

स्वतःतील स्वाभिमान व आत्मसम्मान गमावल्याने माणूस हा दुसऱ्याचा गुलाम होतो म्हणून ही जातीयतेची गुलामगिरी मुळासकट उपटून काढण्यासाठी आपल्यातील स्वाभिमान जागृत असणे अपरिहार्यअसते असा विचार मांडून त्यांनीपददलित, दुर्लक्षित समाजाच्या हक्कांचे संरक्षण करण्यासाठी १९२५ला स्वाभिमानी आंदोलन उभारले होते.यात मुख्य उद्दिष्ट अस्पृश्यता समुळ नष्ट करणे, पददलित समाजाला मानाचे स्थान प्राप्त करून देवून त्यांच्या हक्कांचे संरक्षण करणे हे होते. धर्म हा मानवाने त्याच्या उपयोगीतेसाठी साठी स्थापन केलेला असून त्यांची उपयोगिता सद्यकाळात संपलेली असल्याने मानवा मानवा मधील भेदभाव आणि जातीयता नष्ट करायची असेल तर सर्वात आधी धर्माला नष्ट करणे अनिवार्य ठरते असे मत रामसामी पेरियार यांनी मांडून त्यांनी स्वाभिमानी चळवळ त्यामार्फत स्त्री-पुरुष समानता, विधवा पुनर्विवाह, देवदासी प्रथेचे निर्मुलन करणे,आंतरजातीय विवाहास उत्तेजन देणे, अस्पृश्य समुदायाला आरक्षण देणे असे विविध उपक्रम पेरियार यांनी आपल्या स्वाभिमानी चळवळी मार्फत राववलेले दिसतात. स्वाभिमानी चळवळीच्या प्रचार प्रसारासाठी त्यांनी १९२५मध्ये "कुडी अरासू" तामिळ साप्ताहिक सुरु केले तर पाश्चात्य इंग्रजी भाषेतून शिक्षण मिळावे या प्रचारासाठी १९२८मध्ये "Revolt" इंग्रजी जर्नल सुरु केले होते.

मानवाने आपल्या जातीचे संकेत मिळावे यासाठी आडनावांचा वापर केला आणि सध्याही आडनाव हाच जातीचा संकेतांक ठरत असल्याचे विधान करून रामास्वामी नायकर यांनी १९२९मध्ये चेंगलपट्टू येथील स्वाभिमानी चळवळीच्या प्रांतीय परिषदेत आपले आडनाव नायकर हे त्यागले होते कारण नायकर ही कन्नड जमातीतील एक कर्मठ हिंदू जात होत. तेव्हापासून त्यांना सर्व पेरियार म्हणजेच महान व्यक्ती किंवा महान आत्मा असे संबोधू लागले होते. १९२९मध्ये पेरीयार यांनी त्रावणकोरच्या महाराजांशी संवाद साधून तामिळनाडूतील अस्पृश्य समाजाला आरक्षण मिळवून दिले होते. परंतु भारताला स्वातंत्र्य मिळाल्यानंतर येथील सनातनी समुदायाने सर्वोच्च न्यायालयाकडून संबंधित आरक्षण असंवैधानिक असल्याचा आदेश आणून तामिळनाडूतील अस्पृश्यांचे आरक्षण रद्द केले होते. त्यामुळे पेरियार यांनी चौफेर आक्रमक आंदोलन उभारून राज्य आणि केंद्रसरकारला जेरीस आणले होते त्यामुळे सरकारला १९५१मध्ये संविधानामध्ये पहिली घटनादुरुस्ती करून वंचित, मागाससमुदायाला आरक्षण देण्याचा अधिकार राज्यसरकारकडे सुपूर्द करण्यात येईल अशी घटनादुरुस्ती करावी लागली होती.

१९३७ मध्ये मद्रास प्रेसिडेंसीचे मुख्यमंत्री म्हणून राजगोपालाचारी यांची निवड होताच हिंदी भाषा अनिवार्य करण्याची घोषणा केली त्यास पेरीयार यांनी तीव्र विरोध केला. हिंदी भाषा अनिवार्य करणे म्हणजे उत्तरभारतीयांची संस्कृती दक्षिणेवर लादण्याचा हा प्रकार आहे तसेच उत्तर भारतीयांच्या हिंदीला प्रथम भाषेचा दर्जा देणे म्हणजे आपल्या दक्षिणात्य द्रविडीयन भाषा दुय्यम आहेत का? असा प्रतिप्रश्न पेरीयार यांनी उपस्थित केला.हिंदी भाषेला विरोध म्हणून त्यांनी तमिळनाडूतील हिंदी भाषेत असणाऱ्या पाट्या काढून त्यावर डांबर फासण्याचे आंदोलन उभारले होते.

द्रविड कझगम

१९२३ला त्यांनी कॉंग्रेसमध्ये राहून जस्टीस पार्टीच्या सुधारणावादी ध्येय्य धोरणांना जाहीर पाठींबा दिलेला दिसतो. २८ ऑगस्ट १९४४ रोजी पेरीयार यांनी जस्टीस पार्टीचे नामकरण द्रविड कझगम असे केले आणि द्रविड कझगम निवडणुका लढवणार नाही, तर सामाजिक सुधारणा आणि सामाजिक प्रश्नांचे निर्मुलनासाठी पूर्णवेळ काम करेल ही क्रांतीकारक घोषणा त्यांनी केली होती. त्यांचे पूर्वाश्रमीचे सहकारी अण्णा दुराई यांनी द्रविड मुन्नेत्र कझगम या राजकिय पक्षाची स्थापना केली आणि प्रत्यक्ष निवडणूकांमध्ये सहभाग घेऊन पददलितांच्या राजकिय आणि सामाजिक हक्कांसाठी आवाज उठवला होता.

पेरीयार यांनी अनेक देशांचे दौरे केले, साम्यवादी नेत्यांशी सलगी वाढवण्याचा प्रयत्न केला. १९३०मध्ये कार्ल मार्क्सलिखित साम्यवादाचा जाहीरनामा (Communist Manifesto) ग्रंथाचे तामिळ भाषांतर आपल्या 'कुडी अरासू' जर्नलमध्ये प्रकाशित केले. वैचारिक तफावतीमुळे साम्यवादी आणि पेरीयार यांचा संयोग घडून आला नाही, कारण मार्क्सवादी तत्वज्ञान हे आर्थिक संघर्षाला आणि आर्थिक समानतेला ज्यास्त महत्व देतात तर पेरियार हे सामाजिक समानता, जातीभेद निर्मुलनाला सर्वोच्चस्थान देत असल्याने साम्यवादी आणि पेरियार यांचे विचार जुळून आलेले नव्हते. भारतीय राजकारण, संस्कृती आणि धर्म यावरील उत्तर भारताच्या वर्चस्वाला रामासामी पेरीयार यांनी कडवा विरोध दर्शवून द्रविडीन चळवळ सुरू केली होती. दक्षिणभारतामध्ये तामिळ, तेलगू, कन्नड आणि मल्याळम या द्रविडीयन भाषिक प्रदेशांचा मिळून स्वतंत्र, सार्वभौम असा वेगळा देश म्हणून 'द्रविडनाडू' स्थापन करण्याची मागणी करून तीव्र आंदोलन छेडले होते.

नास्तिकवाद

"असे काही तर्कहीन तत्त्वे असतात कि त्यांना पूर्णतः नष्ट करणे समाजहितासाठी आवश्यक असतात, जर धर्म तर्कहीन असेल तर त्यालासुद्धा नष्ट करण्यात यावे"असे मत पेरीयार मांडतात. पेरियार हे हिंदूधर्म तत्वज्ञानाला तर्कहीन म्हणून संबोधतात. परमेश्वर एकच असेल तर इतके धर्म कशासाठी? धर्माधर्मांमध्ये भेदभाव का? देवाचा संचार सर्वत्र असेल तर त्याच्यासाठी मंदिरे का उभारलीत? असे अनेक प्रश्न उपस्थित करून रामास्वामी पेरियार यांनी आपले तत्वज्ञान जगासमोर मांडले होते. हिंदूधर्म थोतांड मुर्खतेचे मूर्तिमंत उदाहरण असून हिंदुधर्माला मूर्ख तर त्यास मानणाऱ्यांना महामूर्ख म्हणून पेरीयार संबोधतात.

हिंदूधर्मग्रंथ आणि हिंदू देवीदेवतांचे मंदिरे हे सामाजिक भेदभाव, उच्चनीचता आणि असमानतेचे वातावरण निर्मितीस कारणीभूत असल्याचे त्यांनी प्रतिपादन करून हिंदू धर्मग्रंथ आणि हिंदू देवीदेवता नष्ट करण्यावर भर दिला. १९५५मध्ये पेरीयार यांनी भररस्त्यात राम आणि कृष्ण यांच्या प्रतिमांचे दहन केल्याने त्यांना अटक करण्यात आली होती रामसामी पेरीयार यांच्या नास्तिकवादी आंदोलनाला उत्तरभारतातील पंडित नेहरूसारखे लोक रानटी आणि मूर्तीभंजक म्हणून टिप्पणी करीत असत तरीही पेरीयार यांनी आपला नास्तिकवाद तसूभरही कमी होऊ दिला नव्हता.

विनोबा भावे यांनी पेरीयार यांना मूर्ती-भंजकतेवरून आणि धार्मिक तत्वज्ञानावरून शिष्टाई करतांना सांगितले की, 'प्रत्येक धर्मात चांगल्या आणि वाईट बाबींचा अंतर्भाव असतोच तर आपण त्यातील चांगल्या गोष्टींचा स्वीकार का करत नाही'? यावर रामास्वामी पेरियार यांनी उत्तर दिले की, 'जर आपणास साखर कालवून विष दिले तर आपण त्यातील विष बाजूला सारून साखर ग्रहण करू शकतो काय'? असा तार्किकतेवर आधारित प्रतिप्रश्न पेरीयार यांनी विनोबा भावे यांना केलेला दिसून येतो. थिना-थंती (Thina Thanti) या Tamil Daily News Paper मध्ये विनोबा भावे आणि पेरियार यांच्यातील चर्चेतील संवाद छापून आला होता.

मृत्यू

रामासामी पेरीयार यांनी समाजकार्य, अस्पृश्योद्धार आणि अस्पृश्यांना त्यांचे हक्क व अधिकार मिळवून देण्यासाठी आपले संपूर्ण जीवन खर्च केले. सततच्या कामाचा ताण, विविध सभा, दौरे, वाढते वय, यामुळे पेरियार पूर्णत: खंगले होते. दिनांक २४ डिसेंबर १९७३ रोजी त्याचे निधन तामिळनाडूतील वेल्लोर येथे वयाच्या ९४व्या वर्षी निधन झाले. त्यांनी वर्णव्यवस्था, बालविवाह, सक्तीचे वैधव्य या विरोधात प्रबोधन आणि आंदोलन केले राम, कृष्णाच्या प्रतिमांची होळी करून रामलीला ऐवजी रावणलीला करण्याची प्रेरणा द्रविडीयन जनतेला दिली त्यांच्या मृत्यूनंतरही आजतागायत त्यांचे कार्यकर्ते तामिळनाडूमध्ये दसऱ्याच्या दिवशी रावनप्रतिमेची मिरवणुक काढून रावणलीला साजरी करतात.

गौरव

रामासामी पेरीयार यांच्या कार्याची दखल घेऊन यूनेस्कोने २७ जानेवारी १९७०मध्ये त्यांचा गौरव करतांना म्हटले कि, "नवयुगाचे दूत, सामाजिक सुधारणा चळवळीचे जनक, आशियाखंडाचे सॉक्रेटिस असून अज्ञान, अंधश्रद्धा, अर्थहीन व नीती मूल्यांना डावलुन देणाऱ्या कनिष्ठ वागणुकीचा कट्टर वैरी रामासामी पेरीयार हे आहेत." अशा शब्दात युनेस्कोने पेरीयार यांचा गौरव केला. २४ सप्टेंबर १९७४ ला तामिळनाडूचे तत्कालीन मुख्यमंत्री एम. करुणानिधी यांनी रामासामी पेरीयार यांच्या जन्म दिवसाचे औचित्य साधून तामिळनाडूत Periyar's Rationalist Library &Research Library Research Institute ची स्थापना करून त्यांना मानवंदना दिली. भारत सरकाराने रामासामी पेरीयार यांच्या

स्मृतीत टपाल तिकिट काढले, मलेशिया सरकारने २०१४ मध्ये रामासामी पेरीयार यांच्या १३७व्या जन्मवर्षाचे औचित्य साधून क्वालालांपूर येथे टपाल तिकिटाचे अनावरण केले होते. तंजावर विद्यापीठाला रामासामी पेरीयार यांचे नाव देण्यात आले आहे, तामिळनाडूमध्ये पेरीयार यांच्या नावाने ४० शैक्षणिक संस्था सध्या ज्ञानदानाचे कार्य करीत आहेत. रामासामी पेरीयार यांचे कार्यकर्ते त्यांना 'पेरीयार', 'थंथाई', 'वायकोमवीरन्' अशा अनेक नावांनी संबोधतात.

निष्कर्ष

वरील विवेचनावरून असा निष्कर्ष निघतो की, रामासामी पेरियार यांच्या अस्पृश्योद्धार आणि ब्राह्मणेतर चळवळीचे फलित म्हणजे दक्षिण भारतातील अस्पृश्यांना सामाजिक आर्थिक धार्मिक अधिकारांसोबतच अस्पृश्यांमधून राजकीय नेतृत्व निर्माण झाले. द्रविड कझघम आणि द्रविड मुन्नेत्र कझघम पक्ष पेरियार यांच्या विचारांनी प्रभावित होऊन त्यांनी सामाजिक, राजकीय क्षेत्रात भरीव कामगिरी केलेली दिसते.

रामस्वामी पेरीयार यांच्या अस्पृश्योद्धाराचे क्रांतिकारी कार्य अस्पृश्यांच्या सर्वांगीण प्रगतीसाठी आणि उन्नतीसाठी एक मैलाचा दगड ठरले आहे म्हणून रामासामी पेरियार यांना दक्षिण भारताचे प्रती आंबेडकर असेही म्हटले जाते. रामासामी पेरीयार यांचे सामाजिक चळवळींमधील योगदान हे अत्यंत महत्त्वाचे असून त्यांना इतिहासामध्ये मानाचे स्थान आहे.

सारांश

कीटक, प्राणी, पक्षी यांच्यात एखाद्या जातीत जन्मावरून भेद दिसत नाही, पण धर्मग्रंथ रचनाकारांनी जन्म व जाती आधारित वर्णव्यवस्था निर्माण करून आपल्या सारख्याच दिसणाऱ्या मानवाला तुच्छ लेखून त्याच्यावर अनेक निर्बंध घालून त्यांच्या हक्क आणि अधिकारांचे हनन करून त्यांची प्रगती खुंटवली आहे. भारतातील उत्तरेकडील इंडो-आर्यनांनी वर्णाश्रम, जातीयवाद, भेदाभेद ही देणगी दक्षिण भारताला दिलेली आहे असे मत रामासामी पेरीयार यांनी मांडले. पेरीयार यांना जातीनिर्मूलन करून समुळ वर्णव्यवस्था नष्ट करणे अभिप्रेत होते म्हणून त्यांनी काँग्रेस पक्षात प्रवेश केला होता, परंतु काँग्रेसमध्ये उच्चवर्णीय ब्राह्मण्यवादधार्जीणे विचारांच्या सदस्यांचा दबदबा तसेच त्यांची स्वार्थी ध्येय्यधोरणे असल्याने काँग्रेस सुद्धा अस्पृश्योद्धारावाबत निर्णायक पाऊल उचलण्यास कचरत होती यामुळे रामासामी पेरीयार यांना काँग्रेस सुद्धा हतवल आणि नकोशी वाटत होती म्हणून त्यांनी गुरुकुलमप्रकरणानंतर काँग्रेसला १९२५मध्ये सोडचिठ्ठी दिली होती.

स्वतःतील स्वाभिमान व आत्मसन्मान गमावल्याने माणूस हा दुसऱ्याचा गुलाम होतो म्हणून अस्पृश्यांमध्ये आत्मसन्मान निर्माण करण्यासाठी व त्यांचे हक्क मिळवून देण्यासाठी रामासामी पेरीयार यांनी १९२५ मध्ये स्वाभिमानी चळवळ उभारली, या चळवळीच्या माध्यमातून ते सनातन विचारसरणी, ब्राह्मण वर्ग व हिंदुधर्म यावर परखड टीकास्त्र करत. हिंदू धर्म हे ब्राह्मणांच्या वर्चस्वाचे व मक्तेदारीचे एक साधन असून मनुस्मृती ही अमानुष आहे आणि पुराणे म्हणजे परिकथा होय अशी त्यांची मते आहे त्यास कारण म्हणजे धर्मग्रंथ व पुराणांनी अस्पृश्य समाज व स्त्रियांना त्यांच्या मानवी हक्काचे अवमूल्यन करून त्यांना त्यांच्या मूळ हक्कापासून वंचित केलेले आहे याचा राग रामासामी पेरियार यांच्या मनात खदखदतांना दिसतो. चळवळीत अस्पृश्य व स्त्रियांना हक्काचे हनन करणाऱ्या अनिष्ट सनातनी रूढी-परंपरांना मूठमाती देणे, सर्वांना शिक्षण देवून समता निर्माण करण्यासाठी विश्वबंधुत्व यावर आधारित समाज रचना करणे हे या चळवळीचे मुख्य उद्दिष्ट होते चळवळीच्या प्रचारार्थ त्यांनी कुडी अरासू हे साप्ताहिक सुरू केले. रामासामी पेरियार यांनी डॉ बाबासाहेब आंबेडकर यांच्यासोबत कधीही आपली तुलना केलेली नाही. दिनांक १० जुलै १९४७रोजी मायावरम येथे

आयोजित बहिष्कृत समाज परिषदेत यांनी बोलताना सांगितले की, "डॉ. बाबासाहेब आंबेडकर हे आमचे राष्ट्रीय नेते असून त्यांच्या अस्पृश्योद्धार कार्याला आणि चळवळीला आमच्या स्वाभिमानी चळवळीचा तसेच द्रविड कझगम पक्षाचा सदैव पाठिंबा राहील" असे जाहीर केले होते.

रामासामी पेरियार हे ब्राह्मण्यवादाचे कट्टर विरोधक होते त्यांनी हिंदू धर्मग्रंथ देव-देवता यांची खिल्ली उडवून राम कृष्ण यांच्या प्रतिमा व रामायणाची होळी केली, तसेच त्यांनी अनेक मुर्त्या फोडल्या, देवतांनाही चपलेने बनवले कारण ज्या देवता माणसामाणसांमध्ये भेदभाव करून त्यांना दर्शन देत नाही त्यासाठी एकमेव पर्याय म्हणजे त्यांना नष्ट करणे हा होय असे मत मांडले.जाती नष्ट करणे ही काळाची गरज असून त्याद्वारेच अस्पृश्यतानिर्मूलन सहज शक्य होईल असे मत मांडून त्यांनी हिंदूधर्म व देव-देवतांची खिल्ली उडवून असे प्रतिपादित केले की, काही तत्त्वे असेच असतात त्यात सुधारणा होऊ शकत नाही तर त्यांचा केवळ आपणास अंतच करावा लागतो त्यापैकी ब्राह्मण्यवाद आणि हिंदुधर्म हे सुद्धा असेच तत्व आहे कारण ३% असणारा ब्राह्मण वर्ग ९७%द्रविडीयन लोकांवर वर्चस्व गाजवतो हे समीकरण त्यांना मान्य नव्हते.

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१४. भारताची आण्विक नीती

प्रा. सुनिल लक्ष्मण परदेशी
महात्मा फुले कला विज्ञान व वाणिज्य महाविद्यालय, पनवेल, जि. रायगड.

अणुऊर्जा

युरेनियम सारख्या मोठया वस्तुमानाच्या (भारी)अणुकेंद्रांच्या भंजनामुळे (फुटण्यामुळे)किंवा ड्युटेरियम वा ट्रिटियम या सारख्या लहान वस्तुच्या (हलक्या) अणुकेंद्रांच्या संघटणेमुळे (संयोग झाल्यामुळे) प्राप्त होना-या ऊर्जेस अणुऊर्जा म्हनतात.[१]

भारतीय अणुऊर्जा आयोग

भारतात १४ एप्रिल १९४८ रोजी अणुऊर्जाविषयक कायदा होऊन १0 ऑगष्ट १९४८ रोजी भारताच्या अणुआयोगाची स्थापना करण्यात आली.या आयोगाने सुरूवातीपासून अण्वस्त्रे तयार करणार नाही असे धोरण ठरविले.शेती,जीर्वविज्ञान, उद्योगधंदे,वैद्यकीय उपचार,विद्युत निर्मिती यांसाठी अणुऊर्जावापरण्याचे आयोगाचे धोरण आहे.

भारतातील अणुऊर्जेच्या दृष्टीने उपयुक्त असलेल्या खनिजांचे सर्वकर्ष संशोधन करणे,या खनिजांचे मोठया प्रमाणात उत्पादन करणे ,अणुऊर्जेचा शांततामय कार्यासाठी उपयोग करण्याच्या दृष्टीने आवश्यक अशा शास्त्रीय व तांत्रिक विषयातील संशोधन करणे ,अशा संशोधनाची जबाबदारी पेलू शकणारा शास्त्रज्ञांचा वर्ग तयार करणे,आपल्या प्रयोगशाळेमधून अणुकेंद्र विषयक मुलभूत संशोधणावर भर देणे,विद्यापीठे ,महाविद्यालये व राष्ट्रीय संशोधनामधन संस्थामधून अशा संशोधनास उत्तेजन देणे या योजना आयोगाणे प्राथमिक स्वरूपाचा म्हणून हाती घेतल्या भारत सरकारणे अणुऊर्जा विषयक विविध कार्याचा समन्वय साधण्यासाठी एक स्वतंत्र खाते उघडले .पंडित जवाहरलाल नेहरू हे या खात्याचे मंत्री व डॉ.भाभा मुख्य सचिव होते.[२]

अणुऊर्जाविषयक धोरण

दुस-या महायुध्दाच्या अखेरीस ६ ऑगष्ट १९४५ ला अमेरिकेने अणुबॉम्बचा पहिला प्रयोग हिरोशीमावर केला.जपानला शरणागती पतकरावयास लावली.त्याच वेळी अशा अस्त्रांची भयंकर संहारक्षमता पाहून जगातील विचारवंताना धक्का बसला.अशा अस्त्रांच्या नियंत्रणाबाबत आंतरराष्ट्रीय पातळीवर काही योजना करणे आवश्यक आहे,एवढ्यापुरतेच जगातील सर्व प्रमुख राजकीय नेत्यांचे एकमत झाले.अणुऊर्जेची संहारक्षमता प्रंचड असली तरी मानवी सुखसमृध्दीसाठी तिचा पृष्कळ उपयोग करता येण्यासारखा आहे.

शांततामय कार्यासाठी अणुऊर्जेचा विनोयोग करावा हे उदिष्ट सर्व राष्ट्राचे आहे परंतु सर्वच राष्ट्रांजवळ त्यासाठी आवश्यक असणारे तांत्रिक ज्ञान व साधनसामुग्री असणे शक्य नाही त्यासाठी आंतरराष्ट्रीय सहकार्यावर अशा राष्ट्रांवर अवलंबून राहिले पाहिजे.हया दृष्ट्रीने जुलै १९५७ मध्ये संयुक्त राष्ट्रांनी व्हिएन्ना येथे आंतरराष्ट्रीय अणुऊर्जा–मंडळ (इंटर नॅशनल

ॲटॉमिक एनर्जी एजन्सी) स्थापन केले.अणुऊर्जेचा शांततामय कार्यासाठी जास्तीत जास्त वापर कसा करता येईल व त्यासाठी सभासद राष्ट्रानी उपतब्ध केलेल्या साधन सामुग्रीचे योग्य वाटप कसे करावे त्या संबधी हे मंडळ विचार करते.आज या संघटनेचे शंभरहून अधिक सभासद आहेत.

अण्वस्त्रासंबधी भारताचे धोरण

अण्वस्त्र संबधाचे भारताचे धोरण स्पष्ट आहे.अण्वस्त्रांवर संपूर्ण बंदी घातली पाहिजे असे भारताने संयुक्त राष्ट्रसंघात व बाहेरही आग्रहाने प्रतिपादन केले आहे.हया तत्वानुसार भारताने अणुऊर्जेचा उपयोग संहारक शस्त्रांच्या निर्मितीसाठी केलेला नाही व तसा तो केला जानार नाही ,असे भारतीय नेत्यांनी पुन्हा पुन्हा स्पष्ट केले आहे. तथापी जगात अण्वस्त्रनिर्मितीची स्पर्धा अशीच चालू राहिली आणि चीन,पाकिस्थान या सारख्या शेजारी राष्ट्रांनी निराळी धोरण अंगीकारली ,तर भारताला आपल्या धोरणाचा पुर्नविचार करावा लागेल.

अण्वस्त्र –प्रसारणबंदी ठरावासंबधी विचार विनिमय करण्यासाठी अण्वस्त्र रहित अशा ९२ राष्ट्राची परिषद संयुक्त राष्ट्रातर्फे ऑगष्ट–सप्टेबर १९६८ मध्ये जिनिव्हा येथे भरविण्यात आलीहोती.परिषदेनंतर निघालेल्या पत्रकात असे म्हटले आहे की,अणुयुगात प्रत्यक राष्ट्रास संरक्षणाची हमी मिळणे अगत्याचे आहे.जागतीक शांतताा व आर्थिक प्रगतीसाठी शस्त्राची स्पर्धा बंद झाली पाहिजे अण्वस्त्र प्रसारबंदी ठरावानंतर संपूर्ण निःशस्त्रीकरणाची योजनाही कार्यवाहीत केले पाहिजे.सर्व राष्ट्रांना अणु–ऊजेचा शांततामय कार्यासाठी उपयोग कसा करावा हयाचे शास्त्रीय ज्ञान व साधने मिळाले पाहिजे.त्यासाठी अण्वस्त्रधारी राष्टांनी आर्थिक व अन्य मदत देऊन आंतरराष्ट्रीय सहकार्य केले पाहिजे ३.

सर्व समावेशक अण्वस्त्र चाचणी बंदी करार

ऑगष्ट १९४५ मध्ये अमेरिकेने जपानवर टाकलेल्या अणुबॉम्बमुळे झालेल्या विनाशाची पार्श्वभूमिवर अण्वस्त्रचाचण्यावर बंदी घालण्याचा प्रस्ताव जागतिक संघटनेसमोर ठेवला आणि अशी अंशतः बंदी घालण्याच्या आंशिक अण्वस्त्र चाचणी बंदी (Partial Test Ban Treaty-PT B) करारावर भारताने स्वाक्षरी केली .१८ मे १९७४ रोजी पोखरण येथे भारताने पहिली भूमिगत चाचणी केली,तेव्हापासून भारताने भूमिगत अण्वस्त्र चाचणी संबंधीचे धोरण खुले ठेवले.

अण्वस्त्र चाचण्यावर बंदी घालण्यात यावी असा प्रस्ताव अणवस्त्रधारी राष्ट्रानी समंत करावयाचे ठरविले.त्यानुसार निर्ब धीत अण्वस्त्र बंदी करार (Nuclear Non-Proliferation -NPT) 1९६८ संमत करण्यात आला व १९७0 पासूण तो प्रत्यक्ष अमलात आला.

एन.पी.टी.ची प्रमुख कलमे खालील प्रमाणे

१. अण्वस्त्रधारी राष्ट्रांनी विना अण्वस्त्रधारी राष्टांना अण्वस्त्रे देऊ नयेत किंवा त्यासंबंधीचे तंत्रज्ञान देऊ नये.

२. विना अण्वस्त्रधारी राष्ट्रांनी अण्वस्त्रे घेऊ नयेत वा स्वतःतयार करू नयेत.

३. मात्र विना अण्वस्त्रधारी राष्ट्रांनी अणुशक्तीचा वापर शांततेसाठी करावयाचे ठरविल्यास तसे अणुतंत्रज्ञान अण्वस्त्रधारी राष्ट्रांनी देण्यास हरकत नाही.

४. एन.पी.टी २५ वर्ष अमलात राहील.

एनपीटीची मुदत संपत आल्यावर त्याची मुदत वाढविण्यासाठी ११मे १९९५ रोजी जागतीक परिषद बोलाविण्यात आली या परिषदेत एनपीटी कायम स्वरूपात अमलात राहील.तसेच फक्त पाच अण्वस्त्रधारी राष्ट्रांना – अमेरिका,रशिया,इंग्लंड,फ्रान्स,चिन यांना कायदेशीरपने अण्वस्त्रे ब्वाळगण्याचा अधिकार राहील असे सूचविणारा अमेरिकेचा प्रस्ताव मंजूर करण्यात आला एनपीटी करारास प्रथमपासूण भारत ,पाकिस्तान आणि इस्त्रायल इत्यादी राष्ट्राचा विरोध होता.

जगातील बहुतेक विनअण्वस्त्रधारी राष्टांनी या करारावर स्वाक्षरी केल्या मात्र एनपीटी पक्षपाती करार असून अणुतंत्रज्ञान बळावर मिळविना-या राष्ट्रांना अण्वस्त्रे बनविण्याचा अधिकार काढून घेण्यात आला.या भूमिकेतून १९७0 नंतर अण्वस्त्रधारी झालेल्या भारताने एनपीटीवर स्वाक्षरी केली नाही.भारताने अणुस्फोट करण्याचा हक्क राखून ठेवला.मे १९७४ मध्ये अणुस्फोट घडवून आणला.त्यावेळी अणुस्फोट तंत्रज्ञानाचा उपयोग शांततेसाठी केला जाईल असेही भारताने जाहीर केले.

अण्वस्त्र चाचणी बंदी करार

(Nuclear Test Ban Treaty -NTBT) हा करार १९६३ मध्ये करण्यात आला.या करारान्वये भूपृष्ठ,वातावरण,आणि सागरतळ या ठिकाणी कोनत्याही प्रकारच्या अणुचाचण्या घेतल्या जाऊ नये.या करारावर अमेरिका,रशिया आणि इंग्लंड या राष्ट्रांसहीत १0५ राष्टांनी स्वाक्ष-या केल्या पण फ्रान्स व चीन यांनी एनबीटी वर स्वाक्षरी करण्यास नकार दिला.त्यांनी अण्वस्त्रचाचणी चालू ठेवल्या.एनपीटी किंवा एनटीबीटी करार होउन देखील अण्वस्त्रचाचण्या पूर्ण ता बंद झाल्या नाही.साहजीकच या दोन्ही करारांचा उद्देश सफल झाला नाही.भारताने या करारावर सही केली नाही.

सी.टी.बी.टी.(Comprehensive Test Ban Treaty- CTBT)

जानेवारी १९९४ मध्ये जिनिव्हा येथे अण्वस्त्र निर्मितीवर बंदी घालण्यासाठी निःशस्त्रीकरण परिषद सुरू झाली .युनोच्या आमसभेपुढे सादर केला.सीटीबीटीचा बाजूने १५८ राष्ट्रे आणि विरोधात भारत,भूतान आणि लिबिया राष्ट्रानी मतदान होऊन प्रस्ताव मंजूर झाला.

भारताचा युनोतील प्रतिनिधी श्रीमती अरूथती घोष यांनी आमसभेत असे जाहिर केले की,भारत अशा असमान करारावर आताही आणि कधीही स्वाक्षरी करनार नाही.

सी.टी.बी.टी. मधील वादग्रस्त तरतुदी अशा आहेत.

१. भूमिगत किंवा वातावरणात अण्वस्त्रचाचणी करण्यास बंदी घालण्यात आली आहे. अशी चाचणी कोणत्या राष्ट्राने केलीच,तर त्या राष्ट्राची सत्यता पडताळून पाहण्यासाठी आंतराष्ट्रीय अणुऊर्जा समिती (AEA) नियुक्त करण्यात आले आहे.

२. प्रयोगशाळेत संगणकाव्दारे किंवा अन्य मार्गाने चाचणी करण्यास बंदी नाही.

वादग्रस्त तरतुदीना भारतासहित काही राष्ट्रानी विरोध केला. प्रयोगशाळेत संगणकाव्दारे अण्वस्त्र चाचणी करण्यावर बंदी नसल्यामुळे अण्वस्त्रराष्ट्रांना क्षेपणास्त्रांची सुधारण्याकरण्यास किंवा त्याची क्षमता वाढविण्याचे कार्य चालू ठेवता येईल त्यातून अमेरिका,रशिया,चीन ,ब्रिटन,फ्रान्स या अण्वस्त्र सज्ज राष्ट्रांची मक्तेदारी निर्माण होण्याचा धोका आहे.या राष्ट्रावर निबर्ध घालण्यासाठी करारातील त्रुटी व पळवाटा दुर करण्याची मागणी भारताने केली.

सी.टी.बी.टी. बाबत भारताची भूमिका

भारताने सी.टी.बी.टी. कराराच्या मसुद्याला जोरदार विरोध केला .भारताचे सी.टी.बी.टी.वर प्रामुख्याने चार आक्षेप होते.

१. पाच अण्वस्त्रधारी राष्ट्रांनी (अमेरिका, रशिया,ब्रिटन, फ्रान्स, चीन)आपली अण्वस्त्रे पूर्णतः नष्ट करण्याच्या कृतीस निश्चीत कालमर्यादा घातलेली नाही.(भारताने त्या साठी १० वर्षाची कालमर्यादा सुचविली आहे)

२. करार प्रत्यक्ष अंमलात आणणा-या कलमास युनोने कोनतेही कायदेशीर तरतूदी केली नसल्यास हे कलम भारतास अमान्य आहे.

३. पाच अण्वस्त्रधारी राष्ट्रांना माघार घेण्याची तरतूद त्यांना अण्वस्त्र निर्मिती करण्याची इच्छा मोकळीक आहे. अशी माघार घेताना करारावर स्वाक्ष-या करना-या संमतीचीआवश्यकता नाही .या तरतुदीचा फायदा घेऊनही पाच राष्ट्रे आपला अण्वस्त्र कार्यक्रम आणि प्रयोगशाळेतील संशोधन तसेच पुढे चालू ठेवतील .

४. ख-या अर्थाने करार सर्वसमावेशक नाही .कारण या करारान्वये फक्त अण्वस्त्रचाचण्यावर बंदी घातली आहे.अगोदर अण्वस्त्रे आहेत

अशा राष्ट्रांच्या संगणकाचा उपयोग करून ती राष्ट्रे आपला अण्वस्त्र निर्मितीचा कार्यक्रम अनिर्बधपने चालू ठेवतील.

भारताच्या या आक्षेपांना कोनत्याही राष्टाने - पाच अण्वस्त्रधारी राष्ट्रानीही उत्तर दिले नाही. १९४५ पासून अण्वस्त्रधारी म्हनून पाच राष्ट्रांनी स्थापन केला.त्यांची इतर कोणत्याही राष्ट्रांणी अण्वस्त्रसंबंधीची मक्तेदारी नष्ट करू नये म्हणुनच सी.टी.बी.टी. सारखा करार घडवून आणला.

१९७४ साली भारताने अणुस्फोट घडवून आणल्यानंतर 'अणुमंडळ'चा सहाव सदस्य म्हनुन पाच राष्ट्रानी भारतास मान्यता देण्यास नकार दिला.भारतानेही एन.पी.टी.वरही साक्षरी केली नाही.त्या पाठीमागेही पाच अण्वस्त्रधारी राष्ट्रांची मक्तेदारी नष्ट करावी असाच हेतू होता.

भारताच्या ११व १३ मे १९९८ पोखर-२ अणुस्फोटाचा नंतर परिस्थितीत बदल घडवून आणला. भारताच्या अणुस्फोटामुळे भारतीय जनतेच्या मनामध्ये आंनदाची लरत उमटली तर अमेरिका,फ्रान्स,जपान इ.राष्ट्रांनी आर्थिक मदत अन्य तंत्रज्ञान भारताला

देण्यास बंदी घातली.जगातील बहुतेक सर्व राष्ट्रांनी भारताच्या अणुस्फोटाच्या कृतीचा निषेध केला. भारत सरकाने जनतेच्या पाठिंब्यामुळे सी.टी.बी.टी. बाबत ठाम भुमिका घेतली.

पक्षपाती तरतुदीमुळे भारताने सी.टी.बी.टी.वर स्वाक्षरी करावी,असा अण्वस्त्रधारी राष्ट्रांना कोणताही नैतिक अधिकार नाही.या बडयाा अण्वस्त्रधारी राष्ट्रांची अण्वस्त्र क्षमता लक्षात घेतल्यास त्यांचे म्हनने किती विसंगती आहे लक्षात येईल.गेल्या काही वर्षात अमरिकेने १०३२,रशिया ७१५,फ्रान्स २१०,ब्रिटन ४५,चिनने ४५ आण्विक चाचण्या घेतल्या. मे १९९८पर्यत अमेरिकेजवळ १२०७,रशियाजवळ २२५०,फ्रान्स ५००,ब्रिटन ३८० ,चिन ४५० अण्वस्त्रे होती.

भारत -पाकिस्थान संबंधातील काश्मिरप्रश्न हाच एकमेव मुद्दा असून भारताशी युध्द अटळ असूनवेळ पडल्यास पाकिस्थान संभाव्य युध्दात अण्वस्त्र वापरण्यास कचरणार नाही. अशी धमकी भारताला पाकिस्थाने दिली.याच प्रकारची धमकी उत्तर कोरियाने अमेरिकेला दिलेली आहे.

सारांश

अणुचाचणी बंदी करार सी.टी.बी.टी. अस्तित्वात येऊ देण्यास भारताचा विरोध नाही,पण आण्विक सत्तांनी आधी विनाअट या करारावर शिक्कामोर्तब केले पाहिजे.अशी जोरदार मागणी पंतप्रधान वाजपेयी यांनी संयुक्त राष्ट्रसंघाच्या सहस्त्रक परिषदेत केली.तसेच भारत स्वतःहून आण्विक चाचण्या करणार नाही,भारत पहिल्यादा आण्विकअस्त्राचा वापर करणार नाही अशी भूमिका भारताने मांडली

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१५. महाराष्ट्राच्या जडणघडणीत अण्णाभाऊ साठे यांचे योगदान

प्रा. किशोर शेषराव चौरे
इतिहास विभाग प्रमुख, म. ज्यो. फुले महाविद्यालय, बल्लारपूर, जि. चंदपूर.

प्रस्तावना

महाराष्ट्राला पारतंत्र्याच्या गुलामीतून बाहेर काढून मराठी राज्याची स्थापना लोकराजा शिवाजी महाराजांनी केली, तर महात्मा फुले यांनी बहुजन समाजाच्या गळ्यातील हजारो वर्षे धार्मिक, मानसिक, अंधश्रद्धा, विषमता व गुलामगिरीच्या श्रृंखला तोडून त्यांच्यात आधुनिक विचारांची बिजे पेरली. महात्मा फुले यांचे कार्य राजर्षी शाहू महाराजांनी पुढे कार्यरत ठेवले. महात्मा फुले व शाहू महाराज यांचे कार्य पुढे डॉ. बाबासाहेब आंबेडकर यांनी सुरू ठेवले. माणगाव परिषदेमुळे शाहू महाराज आणि डॉ. बाबासाहेब आंबेडकर ही नवीन जोडी महाराष्ट्राच्या क्षितिजावर अवतीर्ण झाली. शाहू महाराज माणगावात भाषण करतात, "तुमचा खरा पुढारी तुम्ही निवडला; माझी खात्री आहे की, डॉ. आंबेडकर तुमचा उद्धार केल्याशिवाय राहणार नाहीत. इतकेच नव्हे, तर एक वेळ अशी येईल की, ते सर्व हिंदूस्थानचे पुढारी होतील. अशी माझी मनोदेवता मला सांगते." शाहू महाराजांची ही भविष्यवाणी पुढे खरीही ठरते. अशा ज्या-ज्या महापुरूषांचे महाराष्ट्राच्या जडणघडणीत योगदान आहे. त्या महापुरूषांच्याच पंक्तिमध्ये अण्णाभाऊ साठे यांच्या नावाचा आवार्जून उल्लेख करावा लागतो. महाराष्ट्राच्या ग्रामीण मातीतील बोली आणि कलांचा संस्कार घेऊन विविध कथा, कादंब-या, लोकनाट्ये या साहित्य प्रकारात त्यांनी आपली छाप उमटविली. या साहित्यातून श्रीमंतांच्या, सताधा-यांच्या शोषण व्यवस्थेविरूद्ध वैचारिक बंड उभारले, या साहित्यातून गुलामगिरीत खितपत पडलेल्या लोकांमध्ये स्वाभिमान जागृत करण्याचे कार्य केले. तसेच संयुक्त महाराष्ट्राच्या चळवळीतून निर्माण झालेल्या मराठी भाषिक महाराष्ट्र राज्याच्या नवनिर्मितीत अण्णाभाऊ साठे यांचे मोलाचे योगदान होते. प्रस्तुत शोधनिबंधात महाराष्ट्राच्या जडणघडणीत अण्णाभाऊ साठे यांच्या योगदानाचा शोध घेण्याचा अल्पसा प्रयत्न केलेला आहे.

अण्णाभाऊ साठे यांचे जीवन चरित्र

अण्णाभाऊ साठे यांचा जन्म १ ऑगस्ट १९२० रोजी सांगली जिल्ह्यातील वाटेगाव येथे मांगवाड्यात श्री. भाऊ भाऊ शिघोजी साठे व सौ. वालुबाई साठे यांच्या पोटी झाला. "मांग जात ही शूद्र जातीपैकी एक होती. त्या जातीतील लोकांना उत्पन्नाचे कुठलेही खात्रीशीर साधन नव्हते. ब्रिटिश सरकारच्या नोंदीनुसार मांग ही जात एक गुन्हेगार जात म्हणून ओळखली जात असे." परिसरात कुठेही दरोडा पडला किंवा चोरी झाली की पोलीस लगेच अण्णाभाऊच्या वस्तीत येऊन लोकांची धरपकड करायचे. पोरगा शिकावा म्हणून अण्णाभाऊंच्या वडिलांनी अण्णा भाऊंना वाटेगावच्या शाळेत दाखल केले होते. अण्णाभाऊ पहिल्यांदा वाटेगावच्या शाळेची पायरी चढले; पण शिक्षकांच्या निर्दयी मारामुळे दिड दिवसातच त्यांनी कायमची शाळा सोडली. सगळ्याच संधी नाकारलेल्या

जन्मलेल्या अण्णाभाऊ साठे यांनी मुंबईला आल्यावर अक्षरशः मिळेल ते काम केले. झाडू मारणे, कोळसे वेचने, बुटपॉलिस, हमाली, वेटर, घरगडी अशी अनेक प्रकारची कामे केली. ही कामे करीत असतानांच रस्त्यावरील दुकानाचे बोर्ड वाचून आपले ज्ञान वाढविले. या सगळ्यातूनच त्यांच अनुभवविश्व घडत गेलं. मुंबईतल्या शहरी वातावरणात अण्णा झपाटून गेले. नवनवीन लोकांशी त्यांचा संपर्क होत गेला. त्याकाळी मुंबईत अनेक घडामोडी होत्या. इथेच अण्णाभाऊंची नाळ कम्युनिस्ट पक्षाशी जोडली गेली. मुंबईमध्ये त्यांचा पिंड ज्या वातावरणात विकसीत झाला. ज्या सामाजिक राजकीय संघर्षाच्या चळवळीत वाढला, त्या चळवळीने त्यांच्यात एक वेगळा साहित्यिक पिंड निर्माण झाला. माटुंग्याच्या लेबर रेस्टॉरेंटमध्ये जो राजकीय पक्षांच्या कार्यकर्त्यांचा अड्डा होता तेथे अण्णाभाऊंनी डासावर पहिला पोवाडा लिहिला. जन्मजातच उपजत गुण असल्यामुळे कोणत्याही प्रकारचे औपचारिक शिक्षण घेऊ न शकलेल्या अण्णाभाऊंनी साहित्य क्षेत्रात नावलौकिक केले. शाहिर, कामगार, नेता, कथाकार, कादंबरीकार, समाजसुधारक अशा विविध भूमिका त्यांनी आपल्या जीवनात पार पाडलेल्या दिसतात.

महाराष्ट्राच्या जडणघडणीत योगदान

महाराष्ट्र राज्याच्या जडणघडणीत जा-ज्या महापुरूषांचे योगदान आहे. मग ते महात्मा फुले असतील, डॉ. बाबासाहेब आंबेडकर असतील, लोकमान्य टिळक असतील या महापुरूषांच्याच बरोबरीचेच योगदान अण्णाभाऊ साठे यांचे दिसून येते. अण्णाभाऊंनी 'वैचारिक क्रांती शिवाय समाजक्रांती शक्य नाही.' हे सूत्र डोळ्यासमोर ठेवून त्यांनी अनेक साहित्याची निर्मिती केली. त्यात सुमारे ३५ कादंब-या, १३ कथासंग्रह, १४ लोकनाट्य, ३ नाटके, १ प्रवास वर्णन, १ शाहिरी पुस्तक, ७ चित्रपट कथा आणि १५ प्रसिद्ध पोवाडे इतका प्रचंड साहित्याचा खजिना अण्णाभाऊ आपल्यासाठी ठेवून गेले. या साहित्यातून तळागाळातील माणसाच्या अवस्थेच्या वेदनेचे हुंकार व्यक्त केले. सामान्य कष्टकरी जनतेत याद्वारे समाजातील विषमतेवर विचार करावयास भाग पाडले.

अण्णानी दारिद्रय फार कोवळ्या वयात अनुभवले, समाजाच्या उपेक्षेचे चटके सहन केले, वेठबिगारीतील अमानुष पिळवणूक भोगली, गिरणीकामगाराच्या हालअपेष्टा आणि शोषण सोसले आणि झोपडपट्टीतील बालपणाची सोबतही केली. इतके अपार दुःख भोगलेल्या अण्णांच्या साहित्यात कठेही आक्रस्ताळा तळतळाट, समाजाला शिव्याशाप किंवा अन्याय करणा-यांना खलास करण्याची भाषा आढळत नाही, हे त्यांचे ठसठसीत वैशिष्ट्ये प्रकर्षाने जाणवणारे आहे. भारतातील व जगातील २७ भाषांमध्ये त्यांच्या साहित्याची भाषांतरित झाली आहेत. साधारणता ४९ वर्षे आयुर्मान मिळालेला माणूस इतके अद्वितीय लिखान करतो. त्यांच्या कादंब-यातून ब्रिटिशांविरूद्ध लढणारे देशभक्त येतात. त्याप्रमाणे स्वकीयांच्या शोषणाविरूद्ध, वासनेविरूद्ध लढणारे, स्त्री-पुरूष येतात, मुंबईतील वेश्यांचे जीवन, गिरणी कामगारातील कामगारांचे जीवन, तमाशा कलावंतांचे, जीवन, मुंबईतील झोपडपट्टी आणि चाळीतील माणसाचा संघर्ष, महाराष्ट्रातील मुरळी सारख्या अनिष्ट प्रथा, मुंबईतील कारखाण्याचे मालक आणि कामगार

कामगार संघर्ष, गावातील उच्चवर्णीय (श्रीमंत) माणसाकडून उपेक्षित जातीतील लोकांचे होणारे शोषण इत्यादी तत्कालीन महाराष्ट्रातील ज्वलंत समस्या अण्णाभाऊंनी आपल्या या कथा कादंब-यातून रेखाटले. कथा कादंब-यातील व्यक्तिरेखा अन्यायाविरूद्ध लढावू वृतीने जीवन जगताना दिसतात.

वारणेच्या खो-यात, फकिरा, वारणेचा वाघ, मास्तर, अग्निदिव्य या कादंब-यामधून अण्णाभाऊंने महाराष्ट्रातील पुरूषांच्या साहसाचे, पराक्रमाचे चित्रण केले. महिलांच्या समस्येवरील महत्वाच्या कादंब-या चित्रा, वैजयंता, चंदन, चिखलातील कमळ, फुलपाखरू, आवडी आणि रत्ना या कादंब-यातून महाराष्ट्रातील महिलांच्या साहसाचे, संघर्षाचे चित्रण केले. ज्याला माणूस म्हणून जगण्याचा कोणताही हक्क धर्माने नाकारलेला होता, त्या गरीब, कष्टकरी, दलित शूद्र, अतिशूद्र समाजातील घटकांना अण्णाभाऊंनी आपल्या साहित्यात स्थान दिले, त्यांना नायक बनविले.

स्वातंत्र्यपूर्व आणि स्वातंत्र्यानंतरच्या काळात राजकीय प्रश्नाविषयी महाराष्ट्रात त्यांनी मोठी जागृती केली. संयुक्त महाराष्ट्राच्या चळवळीतून निर्माण झालेल्या मराठी भाषिक महाराष्ट्र राज्याच्या नवनिर्मितीत त्यांचे योगदान मोलाचे आहे. संयुक्त महाराष्ट्राच्या चळवळीत अण्णाभाऊंनी सांस्कृतिक आघाडीद्वारे लालबावटा कलापथकातून स्वतःला झोकून दिले. मुंबई सरकारने 'लालबावटा' या कला पथकावर बंदी घातली होती. पुढे तमाशावरही बंदी आली. तमाशातील कलाकारांचे संसार देशोधडीला लागले. अण्णाभाऊंनी तमाशा या कलेला लोकनाथाचे वैभव मिळवून दिल्याचे सरकारची बंदी कुचकामी ठरली. संयुक्त महाराष्ट्राची राजकीय अंगाणी सुरू झालेली चळवळ नंतर साहित्यिक आणि सांस्कृतिक विचारांनी पुढे आली. मुंबई महाराष्ट्राला मिळू नये यासाठी सरदार वल्लभभाई पटेल, मोरारजी देसाई यांचे प्रयत्न होते. या प्रतिष्ठीत नेत्याविरोधात सर्व मराठी भाषीकांनी एकत्र येऊन केलेला हा महान संघर्ष होता. महाराष्ट्राची परंपरा, मुंबईचा गिरणी कामगार, अमळनेरचे हुतात्मे या पोवाड्यातून तसेच मुंबईची लावणी आणि माझी मैना गावावर राहिली. यातून त्यांनी महाराष्ट्राचा भौगोलिक, सामाजिक, राजकीय, सांस्कृतिक इतिहास कथन केला. शेतकरी, कामगार, तत्कालीन चळवळी संयुक्त महाराष्ट्र चळवळीचा इतिहास अशा कित्येक घडामोडीचा अण्णाभाऊंने शाहिरी वाङमयात वेध घेतलेला दिसून येतो. त्यांच्या सोबतीला दत्ता गव्हाणकर, महेबूक हुसेन पटेल उर्फ शाहीर अमर शेख हे होते. संयुक्त महाराष्ट्राच्या चळवळीचा इतिहास लिहितांना या त्रिमूर्तीच्या नावाचा उल्लेख करावाच लागेल.

सारांश

महाराष्ट्रातील अनेक साहित्यिक होऊन गेले. त्यापैकी एक अण्णाभाऊ साठे होत. त्यांनी आपल्या साहित्यातून वास्तववादाचे चित्रण केले. बहुजनवादी साहित्य निर्माण केले. अण्णाभाऊच्या 'माझी मैना' या लावणीने अख्ख्या संयुक्त महाराष्ट्र जागा केला. अण्णाभाऊंचा संघर्ष एका व्यवस्थेविरूद्ध होता. राबराब राबणा-या कष्टकरी वर्गाला न्याय मिळावा यासाठी आयुष्यभर झगडत राहिले. साहित्यातून त्यांनी

विषमतेवर हल्ला चढविला. त्यांचा संघर्ष पूर्णत्वास नेण्याकरिता समस्त बहुजनांनी त्यांना समजून घेणे गरजेचे आहे. अशा या महान साहित्यिक, समाजसुधारकास माझे त्रिवार अभिनंदन।

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१६. तलासरी तालुक्यातील आदिवासी 'वारली' समाजाची लोकगिते

डॉ. सौ. हेमलता यु. मुकणे
असिस्टंट प्रोफेसर, इतिहास विभाग, श्री. एम.डी. शाह महिला महाविद्यालय, मालाड (प) मुंबई.

भारताचा सारख्या खंडप्राय देशात जगातल्या सर्व प्रकारच्या गोष्टी थोड्याफार प्रमाणात भारतीय समाजात दिसून येतात त्यामुळे भारताला जगाची छोटी प्रतिकृति असे म्हटले जाते . आपला देश अनेक घटक राज्य अनेक केंद्रशासीत प्रदेश मिळून एक संघराज्य बनला आहे . भारतातील अनेक राज्यातील महाराष्ट्र एक अग्रेसर राज्य आहे . निसर्गाची कृपा सर्वच भूप्रदेशांना लाभते असे नाही . मात्र ज्या भुभागाला ती लाभते तो निसर्ग सौंदर्याने श्रीमंत हातो अशी श्रीमंती महाराष्ट्राला लाभली आहे . महाराष्ट्रातील कोकण हा एक प्रशासकीय विभाग आहे . " कोकण विभागात ठाणे , पालघर , रायगड , रत्नागिरी , सिंधुदुर्ग हे जिल्हे आहेत . मुंबई व नवी मुंबई हे जिल्हे प्रशासकीय दृष्टया कोकण विभागात असेल तरी कोकणची खरी संस्कृती वरील जिल्हयामध्ये दिसून येते . कोकण हे भारताचे नंदनवन म्हणून संबोधले जाते . कोकणातील सर्वच जिल्हयांना विस्तीर्ण समुद्र किनारे लाभले आहे.

या देशात फार प्राचीन काळापासुन आदिवासी जमातीची मूळ वस्तीस्थान आहे . देशाच्या उत्तर व पूर्व भागात आधप्रदेश , बिहार , झारखंड , गुजरात , मध्यप्रदेश , छत्तीसगड , ओडीसा , राजस्थान आणि महाराष्ट्र या राज्यात मोठया प्रमाणात आदिवासी लोक राहतात एकूण लोकसंख्येत आदिवासींचे प्रमाण ९% इतके आहे . २१ व्या शतकातही हा समाज बराच मागासलेला आहे तरीसुध्दा जीवनाचा प्रत्येक क्षण हा आनंदाभिमुख व्हावा यासाठी तो प्रयत्नशील असतो . मानवी समाजाच्या विकासाबरोबरच कलानिर्मितीला वेगळे परिणाम लाभत गेले कोणतीही कला एखाद्या रोपा सारखी असून तिला निष्ठेचे खत आणि मनाच्या एकाग्रतेचे पाणी मिळाले तर ती वाढते . कला म्हणजे सौंदर्य , संस्कृती , राग , आनंद , लोभ , तिरस्कार , सुखदुःख , वेदना या सर्व भावना कलेतून व्यक्त करता येतात . प्रत्येक कलेचा जन्म कोणत्या ना कोणत्या संस्कृतीतुन होत असतो अशीच महाराष्ट्रातील पालघर ' या आदिवासी जिल्हयातील तलासरी तालुक्यातील वारली ' समाजाची लोकगीते अत्यंत लोकप्रिय आहेत.

भारतीय आदिवासी हा स्वातंत्र्योत्तर काळात अनेकांच्या आकर्षणाचा विषय झाला आहे . उदा . भारतात येणारे हौशी पर्यटक आदिवासी क्षेत्राला आवर्जून भेट देतात . महाराष्ट्रात जवळ जवळ ४५ आदिवासी जमाती आहेत . प्रत्येक जमातीचा अभ्यास करता त्याची संस्कृती वेगळी असल्याचे जाणवते आदिवासींच्या जीवनातील समान गुणधर्म जर काय असेल तर तो प्रत्येक आदिवासी जमाती हया निसर्ग पूजक आहेत . " लिखित वाङःमयाचा संपूर्ण अभाव असल्यामुळे त्याची संस्कृती ही त्याच्या पिढ्यानपिढ्याचालत आलेल्यागीताच्या आणि कहाण्याच्या द्वाराच टिकून राहिलेली आहे . " त्यांच्या सर्व आशा - आकांक्षा त्यांच्या लोकगीतांतून व्यक्त झालेल्या आढळतात . " कोणत्याही समाजामध्ये मनोरंजनाला महत्वाचे स्थान असते . व्यक्तिगत किंवा सामाजिक जीवनातील धावपळ , संघर्ष , थकवा कमी होण्यासाठी मनोरंजनाची अनन्य साधारण गरज असते . "

ती गीते वारली स्त्रिया एकटया गात नाही पाच सहा स्त्रिया मिळूनच गातात ज्या प्रसगांना अनुसरुन गीते रचलेली असतात ती त्याच प्रसंगी गायली जातात . व्यापक दर्शन या लोग गीतांमधुन घडते समाजातील घडामोडींची व इतर समाज घटकांकडून त्यांना कशी वागणूक मिळते हे तर या गाण्यामधुन दिसतेच . शिवाय गावातील पाटील , जमीनदार , पोलिस , वनाधिकारी यांनी त्यांची केलेली पिळवणूक पिढयान्पिढया करावी लागणारी वेठबिगारी याचे देखील दर्शन यातून होते . पारंपारिक व्यवसाय , स्त्रियांची कामे यांचा उल्लेख अनेक गीतामधून येतो . त्याचप्रमाणे समाज जीवनात भगत , भूत , सुईण अशा घटकांनाही एक वेगळे व मानाचे स्थान प्राप्त झालेले या गीतामधुन दिसुन येते .

त्याशिवाय त्यांची दैनंदिन कामे , स्त्रियांचे विविध प्रकारचे स्वभाव , त्यांच्या भावना , शृंगार , व्याभिचार तसेच त्यांचे शौर्य आणि कौर्य याचं ही दर्शन घडते . आत्मविश्वास , स्वशक्तीची जाणीव निर्भयता आणि निष्ठूरता ही या गीतांमधुन दिसते . सासु , जावा , ननंद , सासरा , मोठा धाकटा दीर , अशी सासरची नाती , आई - वडील , बहीण , भावजय , भाऊ , काका - काकी , मामा - मामी ही माहेरची नाती विविध दृष्टीकोनातुन ती लोकगीतातुन मांडताना आढळतात . आपल्या भावना व विचार प्रकट करताना ते विनोदाचा , उपरोधाचा , टिंगळटवाळीचा , हसत खेळत , कधी कठोर शब्दाचा वापर करण्यासाठी कचरत नाही . गाण्याचे जे विभाग केले आहेत त्यांची सुरुवात अर्थातच ' जन्मा ' पासून ते मृत्युपर्यंत वेगवेगळया विधींची गाणी गायली जातात .

उदा. १) " पाचवी'ची गाणी - पाचवी हा विधी मुल जन्माला आल्यानंतर पाचव्या दिवशी करण्याचा आहे दिवशी मुलाचं नावही ठेवल जाते . वेगळा नामकरणविधी नसतो . पाचव्या दिवशी संध्याकाळी आजुबाजुच्या लोकांच्या घरी जाऊन ' पाचवी ' साठी येण्याचे आमंत्रण दिले जाते . रात्री आठच्या सुमारात लोक जमतात त्यावेळी जिने बाळंतपण केल ती सुईण देखील आलेली असते दगडी पाटा किंवा जमीन स्वच्छ करुन त्याच्यावर तांदळाने ' बाहुल " पाडतात म्हणजेच मानवाकृती काढल्या जातात . भिंतीच्या कुडावर गोल आकारात शेंदूर , गुलाल , अबीर , हळद , कुंकु यांचे ठिपके देतात , कुडावरी दोन बाहुले रंगवले जातात . सुईणबाई बाळाला घेऊन जमिनी वरील तांदळाच्या बाहुल्यावर ठेवते एका हातात थाळी घेत ती थाळी वाजवत दुसऱ्या हाताने बाळाच्या डोक्यापासून पाया पर्यंत पाणी शिंपडते . पाणी शिपडताना ती पुढील ओळी म्हणते –

" ॲस हाक देल ते धाव घेत ये
बास हाक दे लते धाव घेत पल
गाज विजल भीऊ नको
वारा - पाण्याल भीऊ नको "

त्यानंतर टॉवेल किंवा साडीची झोळी बनवून बाळाला त्यात ठेवून त्या झोळीला पाच झोके घालतात , मग बाळाची आई बाळाला घेत त्यानंतर सर्वांना घुगऱ्या , (उकडलेले चणे) देऊन बाळाचे नाव सांगतात हा विधी संपल्यानंतर उपस्थितांना दारु , ताडी दिली जाते तसेच जेवण दिले जाते . जेवणानंतर बायकांना पाचवीची गाणी गाण्यास सांगितले जाते . पाचवीच्या रात्री बारा वाजल्यानंतर ' सटी ' येऊन बाळाच्या कपाळावर तीन अक्षरे लिहुन

जाते असा समज आहे . सटीची एक कथाही सांगितली जाते रात्री अपरात्री लोकांचे भविष्य लिहिण्यासाठी बाहेर पडणारी " कुटुंबवत्सल स्त्री " अशाा रुपात तिचे चित्रण केलेले आहे .

२) अंगाईगीत , खेळ गीत , बडबडगीत- " अंगाई गीतांचे प्रमाण वारली लोकगीतांमध्ये अत्यल्प दिसते . मुलांना सांभाळण्याचे काम घरातील मोठी मुलेच करतात . अंगाई गाण्याचे कामही त्यांचेच असते ही गाणी त्यांना घरातील वृध्द स्त्रियांकडून ऐकण्यास , शिकण्यास मिळतात . खेळगीत असलेला मुख्य खेळ म्हणजे फुगडी , फुगडीचे दोन - तीन प्रकार आहेत . त्यापैकी ' बसफुगडी ' या भागात प्रामुख्याने खेळली जाते . बडबड गीत ही बऱ्याचदा प्रासंगिक व तात्कालीक असतात . मुल सहज सुचेल ते व मोठयांच्या तोंडून एकल जाईल ते अशा दोन्ही प्रकारांचे मिश्रण करत बडबड गीते गातात . ती जितकी सहज निर्माण होतात तशीव विरुनही जातात .

३) लग्नाची गाणी- एकूण विधिगीतांच्या तुलनेत लग्न विधीची गाणी संख्येत विपुल आढळतात , कालानुसार त्यांत बदलही फार मोठया प्रमाणात व ठसठसीत जाणवण्यासारखे होतात तरीही मंगलप्रसंगाची आनंददायी गाणी असल्याने ती गुणगुणावशी , ऐकावीशी वाटतात . खालील गाण्यामध्ये विवाहाच्या आदर्शाची कल्पना मांडली आहे .

" जा बोलवा कुणी एका देवाला
जा बोलवा कणसरी मातेला
कणसरी माता घोडयावर बसली
तुम्ही यावे लग्नाच्या दारी
लग्नाची घटका भरत आली
जा बोलवा धरती ' मातेला ' (अपूर्ण)

लग्नाच्या गाण्यांचे काही उपप्रकार करता येतील

अ) धवलेरी - लग्न लावताना म्हणतले ते मुख्य गीत हे पारंपारिकच असते . त्यात नवा बदल पटवून घेतला जात नाही . धवलेरीचे गाणे आकाराने प्रदीर्घ असुन अनेकदा पाच - सात तास देखील चालतं .

ब) विधींशी निगडित पारंपरिक गाणी -यात तेलवाणीची , हळदीची गाणी येतात .

क) चढाची गाणी - या गाण्यांत बदलत्या काळाचं प्रतिबिंब दिसतं याच स्वरुप उखाण्याच असत . दोन दोन ओळीची ही गाणी असतात ती अतिश्योक्ती पूर्ण काही वेळा चावट अर्थाची उपहासपूर्ण टिंगलटवाळी करणारी असतात .

ड) प्रासंगिक गाणी - लग्न , माहेर , सासर , कुटुंब , मुले , सवती , स्त्रियांची व्याभिचार प्रवृत्ती , माते संबंध अशा विविध विषयांवरील गाणी या प्रकारात येतात .

इ) कथा / गीत - लग्नाच्या गाण्यात काही कथा गीतही असतात . ती आकराने फारशी मोठी नसतात . त्यातील कथा साधारणत : कौटुंबिक , सामाजिक व पौराणिक असतात . लग्नाआधी हळदीप्रसंगी पुष्कळ गाणी

म्हटली जातात . त्यानंतर लग्न लागताना व नंतर चढाची गाणी सुरु होतात . मेव्हणील उद्देशुन गाणी म्हणतात त्यात रुसवे , फुगवे , भांडण ही होतात नवरीच्या पाठवणीच्या वेळीही गाणी गायली जातात .

" चालत लक्ष्मी घरात आली / चालत लक्ष्मी घरात आली /

काय ग लक्ष्मी पाहतेस / काय ग लक्ष्मी पाहतेस .

मी त पाहेत्या सासु - सासरा / मी त पाहेत्या सासु - स -सासरा "

स्वयंपाकघरात जाऊन प्रथम कुलदेवतेच्या पाया पडतात त्यावेळी सुध्दा गाणी म्हणतात .

४) गौरी नाचाची गाणी .

५) नागपंचमीची गाणी

६) कोंबडी नाचाची गाणी

७) मांदल नाचाची गाणी

८) होळीची गाणी

९) घोर नाचाची गाणी

१०) देवी , गोवर हे आजार झाल्यास त्याची गाणी .

या आजरांची लक्षणे दिसु लागल्यापासुन ते आजार पूर्ण बरा होईपर्यंत विविध विधी केले जातात . या विधीच्या प्रसंगी गाणी गायली जातात .

११) श्रमगीत - वारल्याच्या श्रमगीताना ' हैदाची गाणी ' असे संबोधले जाते ही गाणी पुरुष गातात . जंगलातुन मोठमोठी झाडे तोडुन त्यांचे ओडके वाहुन आणताना ही गाणी म्हटले जातात काम वेगाने होण्यास ही गाणी पूरक ठरतात .

१२) दारुचे महात्म्य गाण्यातून –

"आंबट आंबाडी खालली / आंबट आंबाडी खाली ई

गळा माझा बसेला रं / गलां माझा बसेलारं

गला माझा सुटेल / गला माझा सुटेल "

दारु त्यांच्या जीवनातील अविभाज्य घटक आहे . दारु शिवाय त्यांच्या आयुष्याची परिपुर्ती होत नाही .

१३) लाडक्या भावाची आठवण येते तेव्हा- ती भाव व्यक्त करण्यास गाणे म्हणते .

"आंब्या मोपुरा मोपुरा कधी येतो ?

भाऊ नवरा कधी होसी "

वरील गीता वरुन आपल्या निदर्शनास असे येते की मोहराने आंब्याचे झाड पिवळे कधी होईल अन् माझा भाऊ हळद लावून पिवळा धमक कधी होईल विचार तिच्या मनात येतो .

१४) दिवसाची गाणी - घरातील व्यक्तीच्या मृत्युनंतर अकराव्या बाराव्या रात्री जागरण करुन गाणी म्हटली जातात . या गाण्यामध्ये जीवन मृत्यु विषयक तत्वज्ञान असते . ही गाणी बहुतेक वेळा प्रदीर्घ कथागीते असतात . प्रेत

दहन केल्यानंतरच्या तिसऱ्या दिवशी ' खांदे उतरवण्याचा ' विधी होतो . त्या दिवशी उत्तर कार्याचा दिवस निश्चीत ठरवला जातो . डाक्या भगताला ' सुपारी ' देऊन बोलवल जाते तो रात्री जाग भरतो , बात लावतो , बाराव्या दिवशी नदीवर किंवा ओठ्यावर जाऊन पिंड पाडतात . पिंडदानाच्या वेळी गावली म्हटली जाते .

ही लोकगीत वेगाने बदलणाऱ्या समाजात अदयापही तग धरुन आहेत . त्याचे मुख्य कारण म्हणजे या समाजात अजुन ' सामुहिकता ' टिकलेली आहे . व्यक्ती - व्यक्तीमधील अंतर वाढत गेले . समाज व्यक्ती होऊ लागला की लोकवाङ्मयावर त्याचा विपरीत परिणाम होऊ लागतो . वारली जीवनातील गाणी बहुतेक अंगाना स्पर्श करुन जाणारी जीवनाभिमुख असल्यामुळे त्यात व्यक्तीनिष्ठेपेक्षा सामुहिकता मोठ्या प्रमाणात दिसते . वारली लोकगीतांचा अभ्यास करण्यासाठी क्षेत्रीय पाहणी हाच उपाय आहे .

आदिवासी लोककलांचे वैशिष्टये

सर्व लोककलांचे उगम स्थान पाहता ते आदिवासी जमातीत दिसते निसर्गच्या सानिध्यात हा समाज रानावनात भटकतांना पानांच्या सळसळीचा आवाज आपल्या गीतात घेतो जंगलातील पशुपक्ष्यांचे विविध आवाजातुन आपले संगीत तयार करतो . वीजांचा कडकडाट , ढगांचा गड - गडाट , पावसाच्या ठिबकणाऱ्या थेंबावर आपल्या वादयाचे अवाज निश्चीत करतो आदिवासींच्या लोककला ह्या नागर समाजापेक्षा वेगळया आहेत कारण त्यांच्या कला सादरीकरणासाठी कुठलाही रंगमंच नसतो , प्रकाश योजना नसते , वातावरण निर्मिती ही गोष्ट त्याच्या दृष्टीने महत्वाची नसते , वाद्यांच्या बाबतीत साधी - सुधीच वाद्य ते वापरतात , त्याचा ठेका चूकत नाही , वेशभूषा आणि केशभूषा यावर फार लक्ष नसते . निसर्गाच्या नियमानुसार पुसत जाणारी ही जमात निसर्गातील प्रत्येक गोष्टीला बरोबर घेऊन चालत असते .

आदिवासी लोककलांना आज जागतीक पातळीवर फार महत्व प्राप्त झाले आहे . आदिवासी कलामध्ये असणारा संदेश आज जगभर पसरत आहे . साधेपणा , सुंदरता , रेखीवपणा व उपयोगिता ही त्यांच्या कलेची वैशिष्टये आहेत . कलेच्या कक्षा त्यांच्या सांस्कृतिक जीवनापासून वेगळया करता येत नाही . शासनाने आदिवासींच्या विकासासाठी काही ठोस पावले उचलली आहेत . उदा . शिक्षण , आरोग्य , व्यवस्थापन , रोजगार इ . त्याचप्रमाणे आदिवासींची लोककला विषयी शासनाने काही ध्येय धोरण जाहीर केली आहेत तरी सुध्दा आदिवासींच्या लोककला नामशेष होतायेत कारण ज्या जंगलाचे राजे ते ऐक काळी होते ते जंगले त्याची आता राहिली नाही . जगण्याचा प्रश्न समोर असल्याने कला काय जतन करणार असे असेल तरी आदिवासींच्या लोककला म्हणजे त्यांचे जगणे होय . त्याशिवाय आनंदात राहु शकत नाहीत .

आजच्या माहिती तंत्रज्ञानाच्या व संगणकाच्या युगात त्यांची संस्कृती व कलेला पुर्नजीवन प्राप्त करुन देण्याकरिता आजच्या तरुण पिढीने पुढाकार घ्यायला हवा . त्याच्या कलांचा व संस्कृतीचा ऐतिहासिक व राष्ट्रीय अंगाने अभ्यास झाल्यास भारतीय संस्कृती समृध्द झाल्या शिवाय राहणार नाही . वारली समाजाच्या विविध कलांच्या आविष्काराला मुक्त संधी मिळावी या करिता केंद्र सरकार व राज्यसरकार यांनी प्रयत्न करायला हवेत .

त्यांच्या कलेचा स्वतंत्रपणे व स्थानिक पातळीवर अध्ययन करण्याची गरज आहे . परंतु हे करीत असताना त्यांच्या केलेला बाजारी स्वरुप न येण्याची खबरदारी घ्यायला हवी . लोककला जोपासणारी माणसे हळुहळु कमी होत आहेत .

संदर्भ सूची

१. **महाजन कवीता- वारली लोकगिते .**
२. **अधेर महादेव - आम्ही आदिवासी वारली .**
३. **ॲन्डयु रॉडीग्ज-उंबराचे फुल.**
४. **डॉ . बाबर सरोजिनी - आदिवासींचे सण आणि उत्सव .**
५. **डॉ . फडके सुधीर – महाराष्ट्रातील आदिवासी आणि त्यांचे प्रश्न .**
६. **सोनावणे उत्तमराव - आदिवासी कलाविश्व .**
७. **गारे गोविंद - आदिवासी समस्या विचार आणि विश्लेषण .**
८. **गारे गोविंद - आदिवासी लोकगिते .**
९. **गारे गोविंद – ठाणे जिल्हयातील आदिवासींची लोकनृत्ये आणि त्यांचे लोकसंगीत .**
१०. **डॉ . गिरधारी भास्कर - आरसा आदिवासी जीवनशैलींचा .**
११. **नारगोलकर कुसूम - जंगलचे राजे .**
१२. **लोटलीकर द . ता - वारल्यांचे शेंडीधर्म .**
१३. **कॉ.परुळेकर गोदावरी- जेव्हा माणुस जागा होतो .**
१४. **वाघ अनुताई - कोसबाडच्या टेकडीवरुन .**
१५. **सावे खंडेराव - वारली .**
१६. **ठाणकर संपद- वारली हृदय .**
१७. **डॉ. हेमलता यु. मुकणे यांनी तलासरी तालुक्यातील आदिवासी वारली समाजाला प्रत्यक्ष भेट देऊन ही माहिती मिळवली आहे.**

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१७. महात्मा गांधी आणि अस्पृश्यता जातीभेदाच्या विशेष संदर्भात

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के. बी. पी. कॉलेज इस्लामपूर.

महात्मा गांधी हे देशभक्ती बरोबरच त्यांच्या जाती धर्म सहिष्णू ते बद्दलही सर्वज्ञात आहेत. परंतु त्यांच्या जाती व अस्पृश्यताविषयक विचारांबद्दल बरेचदा उलटसुलट चर्चा केली जाते. बाबासाहेब आंबेडकर आणि पुणे करार, हिंदु महासभा आणि गांधीजी, गांधीजींच्या रामराज्य विचाराविषयक चर्चा केली जाते. त्यांच्या हरीजन शब्दावरही आक्षेप घेतला जातो. इतिहास लेखनाचे काही नियमही आहेत. त्यानुसार दोन वेगवेगळया, कालखंडातील व्यक्ती, प्रसंगांचे तौलनिक संशोधन करणे संशोधनात अडथळा ठरू शकते. कालखंड, चालीरिती, व्यक्तिचे रहाणीमान त्याच्यावरील संस्कार, भवताल याचाही विचार इतिहास संशोधकाने करणे गरजेचे असते. नाविन्याच्या ओढीने नवीन संशोधन प्रस्तुत करण्याच्या नादात संशोधक वहावत जातो आणि इतिहासातील प्रसिध्द व्यक्तीच्या योग्य, महत्वपूर्ण कार्याकडे कानाडोळा करून त्याचे दोष दाखवित त्याची प्रतिमा डागाळण्याचा प्रयत्न करतो. महात्मा गांधी एक अतुलनीय व्यक्तिमत्व परंतु त्यांच्या चरित्रावरही उलटसुलट चर्चा होते. त्यांचे जातीसंदर्भात व अस्पृश्यता विषयक विचाराबाबत अशी चर्चा केली जाते. त्यामुळे परिस्थिती विचारात घेणे आवश्यक आहे.

गांधीजीचे बालपण आणि संस्कार

गांधीजीचे सत्याचे प्रयोग किंवा माझी आत्मकथा या पुस्तकात बापूजी त्यांच्या लहानपणीच्या गोष्टी वर्णन करतात. म.गांधीचे घराणे वैष्णवसंप्रदायी होते. रामनाम हे त्यांची दाईरंभा, त्याचा चुलतभाऊ रामरक्षा म्हणणारा, आणि घरातील रामभक्त वातावरणाचा त्यांच्या मनावर प्रभाव होता. त्यांच्या घरी विविध जातीधर्माची आचार्य येत असत. त्यामुळे धार्मिक वातावरणात गांधीजीचे बालपण गेले.[१] उचनीचतेचा भेदाभेद असल्याचे दिसत नाही.

हिंदूमहासभा डॉ.बाबासाहेब आंबेडकर व अस्पृश्यतेचा प्रश्न याबाबत गांधीजीचे विचार असा अभ्यास ही केला जातो. महात्मा गांधी यांच्या 'हरीजन' शब्दासही आक्षेप घेतला जातो. सर्वच देवाची लेकरे या उक्तीप्रमाणे फक्त अस्पृश्यानाच का हरीजन संबोधन असा प्रश्न उपस्थित केला जातो. फ्रेंच लेखक रॉंश फुको याने दांभिकतेची व्याख्या केली आहे. ती 'अशी दांभिकता म्हणजे अनैतिकतेने नैतिकतेला केलेले अभिवादन असते.'[२] महात्मा गांधी आणि राष्ट्रीय स्वयंसेवक संघ यांच्यातील संबंध अधोरेखित करणे गरजचे आहे.

महात्मा गांधी आणि रा.स्व.संघ

महात्मा गांधींच्या समग्र साहित्याच्या ८७ व्या खंडात संघाचा उल्लेख येतो. गांधीजी संघटनेच्या पारदर्शीपणाबद्दल आग्रही असल्याचे दिसून येते. गांधीजीना संघाकडून पहिले पत्र गांधीजीच्या प्रार्थना सभेत

गीता व कुराण यातील ओळी एकत्र न म्हणण्याबद्दल होते. मुस्लिमांबद्दल संघाचे मत फारसे चांगले नसल्याचे गांधीजीना समजले होते. १९४७ मधील हिंदु मुस्लिम दंग्याच्या वेळी गांधीजी उपोषणास बसले त्यावेळी संघाच्या 'ऑर्गनायझर' हे मुखपत्रात लेख आला. ''जेव्हा रोम जळत होते. तेंव्हा निरो फिड्ल वाजवत होता.'' इस्लामी अल्ला हो अकबरचा नारा देत हिंदूंवर अत्याचार करत असताना गांधीजी इस्लामची वाहवाह करीत आहेत असे संघाचे म्हणणे होते. ९ सप्टेंबर रोजी गांधीजी सरसंघचालक गोळवलकराना भेटले होते. त्यावेळी गोळवलकर म्हणाले होते की मुस्लिमांच्या हत्यांशी संघाचा काही संबंध नाही. संघ मुस्लिमांचा शत्रु नाही. परंतु यामध्ये काहीच तथ्य नसल्याचे गांधीजींच्या लवकरच लक्षात आले.[३] गांधीजी कधीच हिंदूत्ववादी किंवा कट्टर नव्हते. संघाने नंतरच्या काळात गांधीजींची प्रतिमा मलिन करण्याचा प्रयत्नच केला. सप्टेंबर १९४७ ते १९४८ निर्णायक काळात दिल्ली पोलिसांची कागदपत्रे तपासता हे लक्षात येते की मुस्लिम व गांधीजी यांची संघाने विखारी भाषेत टीकाच केली आहे.[४]

सर्वधर्मसमभाव आणि म.गांधी

भारत पाक फाळणीच्या वेळी हिंदू मुस्लिम दंगली उसळल्या. मुस्लिमांच्या शिरकाणाची मोहिम राबविली तरच ते भारत सोडतील असे संघ कार्यकर्त्यांना वाटत होते. भारतीय कॉंग्रेस समितीसमोरील भाषणात गांधीजी म्हणतात. (दिल्ली—दंगल काळात) ''कॉंग्रेस पक्षाच्या सदस्यानी हिंदू मुस्लिम एकतेसाठी लढत राहीले पाहीजे. मुस्लिमाना भारतात सुरक्षित वाटेल यासाठी प्रयत्न करायला हवेत तसेच 'हिंसक दंगखोरीने हिंदू किंवा शीख यापैकी कुटल्याच धर्माचे रक्षण होणार नाही.[५] गांधीजी जरी एका रूढीवादी घरात वाढले असते. तरी त्यांच्या मनात कोणत्याही जाती धर्माबद्दल तेढ किंवा आकस नव्हता. हिंदूत्ववादी असणाऱ्या रा.स्व संघाचे विचार त्यांना पटले नाहीत. आणि पुढे ते म्हणतात की जनमतात हजार तलवारीपेक्षा अधिक बळ असते. हिंदू धर्माचे रक्षण हिंसक तांडवाच्या बळावर होवू शक्त नाही. असे गांधीजीचे मत होते. प्रार्थनासभेत गांधीजी म्हणाले होते. की, 'धार्मिक ध्रुवीकरण मुस्लिम लीगकडून घडवून आणले जात आहे. त्यांना हिंदूमहासभा सहकार्य करीत आहे. भारतातून मुस्लिमाना हाकलून देण्याचे हे षड्यंत्र आहे. या गांधीजींच्या मतामुळे हिंदुत्ववादी संघटनांच्या रोष गांधीजीनी ओढवून घेतला. आणि गांधीजी संघाची दिशाभूल करू शकत नाहीत. यावरही आमच्याकडे उपाय आहेत. कॉंग्रेसच्या फायदयासाठी गांधीजी मुस्लिमाना भारतात ठेवू इच्छितात असे मत संघाचे होते. मुस्लिम व हिंदू यांच्यात शांती निर्माण व्हावी म्हणून गांधीजी दिल्लीत उपोषणास बसले. पाकिस्तानातील हिंदू आणि शीख समुदायाच्या सुरक्षिततेसाठी पाकिस्तानात जाण्याचेही त्यांचे नियोजन होते. परंतु ३० जानेवारी १९४८ रोजी संघकार्यकर्ता नथुराम गोडसे याने गांधीजींचा गोळी मारून खून केला.[६] आपल्या सर्वधर्म समभाव या विचाराचे सुदृढीकरण करण्यासाठी गांधीजीनी त्यांचे प्राण गमवावे लागले. 'भारत हे हिंदू राष्ट्र नसुन या देशावर इतर धर्मियांचाही समान हक्क आहे.' या तत्वासाठी गांधीजीनी आपले आयुष्य समर्पित केले.

स्वातंत्र्यानंतर त्यानी स्वत:ला कोणतेच पद मागितले नाही. धार्मिक भेदाभेद त्यांनी अमान्य केला. तरीही गांधीजींवर अशी टीका केली जाते. की गांधीजीनी धर्माच्या माध्यमातून लोकांना इंग्रजांशी लढण्यास

प्रवृत्त केले आणि भारताला ब्राम्हण आणि बनिया व्यापारी लोकांच्या हाती दिले.'' या टीकेत तथ्य नाही. असे असते तर गांधीजींना आपला जीव गमवावा लागला नसता.

गांधीजी आणि अस्पृश्यता

ब्राम्हण असणाऱ्या हिंदूत्ववादाच्या पुरस्कार करणाऱ्या नथुराम गोडसेंनी गांधीजींचा खुन केला. हे धर्माबाबत म्हणावे लागेल. पण अस्पृश्यता आणि जातीभेदाबद्दल ही गांधीजींवर अनेक मते मांडली जातात. स्वातंत्र्यपूर्व काळात लो. टिळकांच्या मृत्यूनंतर राष्ट्रीय कॉंग्रेस मवाळमतवादी झाली. म्हणजेच राष्ट्रीय चळवळीत गांधीजींचा उदय झाला होता. गांधीजीना 'महात्मा' व 'बापूजी' अशी हाक मारली जात होती. परंतु डॉ. बाबासाहेब आंबेडकर त्यांना ''मिस्टर गांधी'' असे संबोधन वापरत असत. त्यामुळे त्यांनी गांधीजीनी अछूत अस्पृश्यता' या विरोधी आवाज उठविला. पुणे करार पूर्वी गांधीजींनी उपोषण केले होते. पण अस्पृश्याना गुलाम बनवून ठेवण्याची त्यांची खेळी होती असा त्यांच्यावर आरोप केला जातो.[७] डॉ. आंबेडकर सरकारकडून फक्त दलितांसाठी आरक्षण मागत नव्हते. तर स्वतंत्र मतदार संघ मागत होते. त्यामुळे हिंदुत्ववादी संघटनाना ही डॉ. बाबासाहेब आंबेडकर भारताचे पंतप्रधान होतील अशी भीती होती. यावेळी गांधीजीनी केलेल्या उपोषणला या संघटनानीही पाठींबा दिला होता.

इंग्लंडमध्ये दुसरी गोलमेज परिषद १९३२ मध्ये भरली यामध्ये गांधीजी व डॉ.आंबेडकर यांचा समावेश होता. बाबासाहेबांनी अस्पृश्यांसाठी राखीव मतदार संघ मागणी केली. गांधीजींचा यास विरोध होता. परंतु तो निष्प्रभ ठरला. भारतात आल्यावर याविरोधात आंदोलन होणार होते. परंतु गांधीना अटक झाली. त्यांना येरवडा जेल मध्ये ठाकण्यात आले. ब्रिटिश पंतप्रधान रॅम्से मॅकडोनाल्ड यानी जातीय निवडा जाहीर केला. गांधीजींनी त्यास विरोध केला. आणि उपोषण सुरू केले. जातीय निवाडयात स्वतंत्र मतदारसंघात फक्त अस्पृश्यच मतदान करू शकत होते. सर्वसाधारण मतदारसंघातही अस्पृश्य मतदान करू शकत होते. त्यांना दुबार मतदानाचा हक्क मिळणार होता. यामुळे हिंदू समाजाचे विभाजन होते. असे सांगून गांधीजीनी उपोषण सुरू केले. (२१ दिवस) तेव्हा डॉ. आंबेडकरानी राखीव मतदार संघाचा स्विकार केला. हाच तो पुणे करार होता.[८] दलितांचे खरे नेतृत्व पुढे येणार नाही याची गांधीनी दक्षता घेतली. असा गांधीजींवर आरोप केला जातो. याची दुसरी बाजूही लक्षात घेतली पाहीजे. हे आपण हिंदू समाजाच्या ऐक्यासाठी करीत आहोत असे गांधीजीनी पी.एन.राजभोज यांना लिहिलेल्या पत्रात नमुद केले आहे. सरदार पटेलांना ते म्हणतात. ''अस्पृश्याना स्वतंत्र मतदार संघ मिळाल्यास अस्पृश्य आणि मुस्लिम गुंड एकत्र येतील सवर्ण हिंदुना ठार करतील. महादेव देसाईनी हे बोलणे त्यांच्या डायरीत पृष्ठ क्र. ३११ वर लिहून ठेवले आहे. तसेच मंदीर प्रवेशाच्या बाबतीत गांधीजी उदासिन होते आणि डॉ. आंबेडकरानी गोलमेज परिषदेच्या वेळी गांधीना सविस्तर सांगितल्यावर त्यांनी समर्थन केले असे म्हणतात. प्राचीन काळापासून ज्यांच्या स्पर्शाचा विटाळ मानला गेला त्यांच्यावर सामाजिक, सांस्कृतिक बहिष्कार घातला गेला त्यांचे कल्याण स्वतंत्र मतदार संघामुळे होईल असा दावा बाबासाहेब आंबेडकरानी केला. ब्रिटनमधील कायदेतज्ञ आणि लोक प्रतिनिधीनी आंबेडकरांची बाजू उचलून धरली.[९] परंतु गांधीजीच्या प्राणोतिक उपोषणामुळे आणि गांधींचे प्राण ही महत्वाचे असल्याचे सांगत डॉ. बाबासाहेब आंबेडकरानी पुणे करारावर सही केली.

गांधीजींचे उपोषण पं.नेहरूना ही फारसे रूचले नव्हते. ते म्हणतात. ''गांधीजींचा राजकारणाकडे पहाण्याचा जो भावनिक आणि धार्मिक दृष्टिकोण आहे तो चीड आणण्यासारखा आहे.[१०]

गांधीजींचे उपोषण आणि स्वत:च त्रास करून घेणे हे एखादया गोष्टीचा अट्टाहास असे त्यावेळी काही राजकीय नेत्यांना वाटत होते. परंतु गांधीजी हिंदुत्व वादी किंवा मुस्लिम धर्म विरोधी होते असे म्हणू शकत नाही. कारण मुस्लिम, शीख दंगयांच्यावेळी ही त्यांनी उपोषणाचा निर्णय घेतला होता. हिंदूत्ववादी संघाचे कधीही समर्थक केले नाही.

गांधीजीच्या विचारांवर अध्यात्माचे वलय होते. लहानपणातील संस्कार जैन, हिंदू, पारसी धर्मातील गुरूंचा त्यांच्या घरातील वावर आणि दयाभाव संकल्पना मनात रूजली होती. तरीही उपोषण हे जैन धर्मातील 'उपसर्ग' या प्रकारामध्ये येते. ते त्यानी कोणाच्या हितास बाधा यावी म्हणून केले नव्हते. त्यांच्या खान अब्दुल गफार खान यांच्या मैत्रीबद्दल ही चर्चा हेते. त्यांना हिंदूत्ववादी संघाने नाकारले त्यांच्यावर टीका केली. आणि यामध्ये गांधीजीनी त्यांचे प्राणही गमवावे लागले. त्यांनी स्वातंत्र्यानंतर कोणतेही पदही स्विकारले नाही तरीही त्यांच्यावर बायस असण्याचा आरोप केला जातो. जातीभेदाच्या बाबतीत गांधीजींचा दृष्टीकोण विशाल होता. तसेच ते सहिष्णू होते. आदर्शाचा अतिरेक झाला असेही काहीचे म्हणणे आहे. अस्पृश्यता जातीभेद याबाबतील गांधीचे विचार आदर्शवत आणि पुरोगामीच होते.

निष्कर्ष

१. इतिहास पुरूषांच्या व्यक्तिमत्वातील एखादया प्रसंगावरून त्यांचे अवलोकन म्हणजे त्यांच्यावरील अन्यायच आहे.

२. महात्मा गांधीजींचे जातीभेद, अस्पृश्यता विषयक विचार पुरोगामीच होते.

३. गांधीजीनी हिंदूत्ववादाचा उदो—उदो केल्याचे आरोप खोटेच आहेत.

४. म.गांधी व बाबासाहेब आंबेडकर यांचा वैचारिक अभ्यास करताना गांधीजींचे विचार मागासच होते असे म्हणता येणार नाही.

५. तौलनिक अभ्यास करताना इतिहासकाराने व्यक्ती पुजा व पूर्व ग्रह नाकारला पाहिजे. अन्यथा ऐतिहासिक घटना आणि व्यक्ति यांचा इतिहास चूकीचा मांडला जातो. याचे उत्तम उदाहरण म्हणजे गांधीजी आणि बाबासाहेब आंबेडकर संबंध होय.

संदर्भ

१. गांधी मो.क — सत्याचे प्रयोग/आत्मकथा — माणिक प्रकाशन कोल्हापूर — प्रथमावृत्ती — मार्च २०१० — पृष्ट क्र. ३५ व ३६

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३. कित्ता पृ.क्र. ६

४. कित्ता पृ.क्र. ६

५. कित्ता पृ.क्र. ७

६. किल्ला पृ.क्र. ८

७. डॉ. वाघमारे एन. जे. अनुवादक/प्रकाशक/संशोधक — गोडसेने गांधीहत्या क्यों की? — बुध्दभूमी प्रकाशन — नागपूर (धंतोली) — द्वितीय आवृत्ती १४ ऑक्टो. २००१— पृष्ठ क्र. १३

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९. डॉ. बाबासाहेब आंबेडकर गौरव ग्रंथ — संपादक मंडळ — दया पवार (निमंत्रक) — महाराष्ट्र राज्य साहित्य आणि संस्कृती मंडळ पुणे — ४०००३२ —प्रथमावृत्ती २५ डिसे. १९९३ — पृष्ठ क्र. ८३, ८४, ८५

१०. किल्ला — पृष्ठ क्र. २२३ व २२४

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१८. संयुक्त महाराष्ट्र चळवळीत अण्णाभाऊ साठे यांचे योगदान

डॉ. माणिक सोनावणे
टिळक महाराष्ट्र विद्यापीठ, १२४२, सदाशिव पेठ, पुणे.

प्रस्तावना

मराठी साहित्यविश्वात ज्यांच्या साहित्याला जगभर मिळाली आहे, अशा मोजक्या साहित्यीकांमध्ये अण्णाभाऊ साठे यांचे नाव अत्यंत आदराने घेतले जाते. त्यांनी लिहिलेल्या कथा, कादंबऱ्या, लावण्या, पोवाडे, वग आणि प्रवासवर्णने ईत्यादी साहित्य प्रकारातून सामान्य माणसाच्या जीवनाचे वास्तववादी चित्र रेखाटले आहे. समकालीन साहित्य विश्वात रंजनवाद आणि काल्पनिकतेवर भर दिलेला आहे. तथापि अण्णाभाऊ साठे यांचे साहित्य याला अपवाद आहे. त्यांनी वस्तुस्थितीचे जसेच्यातसे चित्र रेखाटण्यावर भर दिला आहे. त्यांचे साहित्य समाज व्यवस्थेतील वाईट चालीरीती व परंपरांवर घाव घातले. त्यांनी आपल्या साहीत्यातून उभ्या केलेले वोद्रोही नायक - नायीकांच्या माध्यमातून समाज परिवर्तनाच्या लडाईत सामान्य माणूसही महत्वाची भूमिका बजावू शकतो, याचे आशावादी चित्र रेखाटले आहे. दुसरीकडे त्यांनी गोर-गरीव जनतेच्या दु:खाला कारणीभूत ठरलेल्या अज्ञान आणि अंधश्रद्धावर घाव घालविण्याचा प्रयत्न केला आहे. तसेच समाजातील विषमतेचे विदारक चित्र जागाच्या समोर आणले आहे. यांच्या साहित्यात 'वेदना' आणि 'विद्रोह' या नाण्याच्या दोन्ही बाजूंचे दर्शन होते. त्यांनी सामान्य माणसाला समाजक्रांतीचे नायक बनवले, पोटाची खळगी भरण्यासाठी जमीनदारांचा अन्याय अत्याचार सहन करणारा समाज त्यांनी आपल्या साहित्यातून रेखाटला आहे. ग्रामीण जीवनातील अन्याय–अत्याचाराचे, दारिद्र्य व शोषणाचे, विषमता आणि भेदभावाचे विश्लेषण त्यांनी त्यांच्या साहित्यातून केले आहे. म्हणूनच नारायण सुर्वे हे जेष्ठ साहित्यीक म्हणतात की, "अण्णाभाऊ साठे केवळ दलित आणि शोषीतांबावत लिखाण करणारे लेखक नव्हते तर जगातील सर्व अन्यायाविरुद्ध लढणार्या समग्र मानवजातीचे लेखक होते, मानवतावादी आणि शोषणमुक्तीचा ध्यास घेऊन साहित्य लिहणारे साहित्यिक होते, त्यांनी साहित्यातून पृथ्वी वरील सर्व कष्टकरी आणि शोषितांचे शोषण संपविण्यासाठी आयुष्यभर लढा दिला, त्यांनी वर्गविरहित समाजाचे स्वप्न पाहिले आणि मानवमुक्तीच्या व शोषण विरहीत समाज निर्मितीच्या कार्यात संपूर्ण आयुष्य पणाला लावले".

अण्णाभाऊंनी त्यांच्या जीवनात चित्रपटातील 'हिरो' पासून घरगडी, खाण कामगार, कोळसेवाला, डोअर किपर, हमाल, रंग कामगार, मजूर, तमाशातला सोंगाड्या अशा विविध भूमिका बजावल्या. त्यांच्या साहित्तीकाच्या कारकीर्दीत जवळपास २१ कथासंग्रह, ३० पेक्षा अधिक कादंबऱ्या लिहिल्या, त्यातील ७ कादंबऱ्यांवर मराठीतून चित्रपट निघाले. १९६१ साली महाराष्ट्र राज्य शासनाचा उत्कृष्ट कादंबरीचा पुरस्कार त्यांच्या 'फकिरा' या कादंबरीला मिळाला. आण्णाभाऊंनी त्यांची ही कादंबरी डॉ. वावासाहेव आंबेडकरांच्या झुंजार लेखणीला अर्पण केली. 'वैजयंता' नामक

कादंबरीत त्यांनी तमाशात काम करणाऱ्या स्त्रियांच्या शोषनाचे स्वरूप दाखविण्याचा प्रयत्न केला आहे. 'माकडीचा माळ' ही भटक्या-विमुक्त समाजाच्या भटक्या जीवनावर लिहिलेली पहिली कादंबरी आहे. या कादंबरीने भटक्या-विमुक्त समाजाच्या जीवनाचे चित्रण करून अण्णाभाऊंनी भटक्या समाजाला भोगाव्या लागत असलेल्या यातना व चव्हाट्यावर आणल्या आहेत.

अण्णाभाऊ साठे एक साहित्यिक म्हणून परिचित आहेत परंतु त्यांचे संयुक्त महाराष्ट्राच्या चळवळीसाठी दिलेले योगदान दुर्लक्षित राहिले आहे. साहित्याचा संयुक्त महाराष्ट्राच्या आंदोलनामध्ये अण्णाभाऊ साठे यांच्या कार्याचा प्रभाव दिसून येतो. त्यांच्या लावण्या, पोवाडे आणि शाहिरी आणि गीतांच्या माध्यमातून सामान्य जाणतेमध्ये चेतना निर्माण झाली व त्यांनी संयुक्त महाराष्ट्राच्या चळवळीत लोकांनी हिररीने सहभाग घेतला. अण्णाभाऊ साठे यांनी लिहिलेल्या कथा, कादंबर्या आणि शाहिरी-पोवाडे यांच्या माध्यमातून संयुक्त महाराष्ट्राच्या चळवळीत अण्णाभाऊंचे महत्त्वाचे योगदान दिसून येते. त्यांच्या साहित्याकडे केवळ साहित्य म्हणून न पाहता त्याचे सामाजिक व राजकीय परिपेक्षात विश्लेशान होणे आवश्यक आहे. या पार्श्वभूमीवर अण्णाभाऊं साठें त्यांचे संयुक्त महाराष्ट्राच्या चळवळीतील योगदानचा पुढील संशोधन प्रश्नांच्या चौकटीत आढावा घेतला आहे.

१) अण्णाभाऊं साठें त्यांनी त्यांच्या लावण्या तमाशे, वग, गौळणी, पोवाडे, शाहिरी आणि साहित्याचा संयुक्त महाराष्ट्राच्या चळवळीसाठी कसा उपयोग केला?

२) संयुक्त महाराष्ट्र निर्मितीच्या पार्श्वभूमीवर अण्णाभाऊं साठें त्यांनी त्यांच्या साहित्यातून मुंबई शहराचे महत्व पटवून दिले, ते संयुक्त महाराष्ट्र चळवळीच्या कार्यात कसे उपयोगी ठरले?

३) अण्णाभाऊ साठे यांच्या साहित्यातून आणि लेखणीतून जन सामान्यांच्या मनावर कोणते सकारात्मक परिणाम झाले?

वरील संशोधन प्रश्नांच्या चौकटीत संयुक्त महाराष्ट्राच्या चळवळीत अण्णाभाऊं साठें यांच्या योगदानाचा अभ्यास करताना एतिहासिक व ग्रंथालयीन पद्धतीचा अवलंब केला असून त्यांनी लिहलेले साहित्य आणि त्यांच्या साहित्यावर उपलब्ध असलेल्या साहित्याचा प्राथमिक आणि दुय्यम साधने म्हणून उपयोग केला आहे.

अण्णाभाऊ साठे यांनी आपल्या पोवाडे, लावण्या, वगनाट्य, शाहिरीच्या माध्यमातून मुंबईसह संयुक्त महाराष्ट्र झालाच पाहिजे हे जन-माणसाच्या मनावर विंबवले. या पार्श्वभूमीवर मुंबईसह महाराष्ट्राची निर्मिती झाली पाहिजे यासाठी अण्णाभाऊ साठे यांचे साहित्य महत्त्वाचे ठरले आहे. साहित्य, कला, कवणे ही केवळ मनोरंजनाची साधणे नसून ती राष्ट्रनिष्ठा, देशप्रेम आणि देशभक्ती जागविणारे साधने आहेत हे अण्णाभाऊ साठे यांनी त्यांच्या विचार, कृती आणि साहित्यातून दाखवून दिले आहे. साहित्य आणि कला यांच्या माध्यमातून सामाजिक, वैचारिक आणि मानसिक प्रगल्भ जाणिवा तयार करता येतात, तसेच समाजप्रबोधनाचे, ज्ञानदानाचे आणि परिवर्तनाचे सर्जनशील साधन म्हणूनही कार्य

करू शकतात हे त्यांनी निदर्शनास आणून दिले आहे. अण्णाभाऊ साठे मार्क्सवादी विचाराने प्रभावीत झालेले होते, त्यांच्या साहित्यात समतावादी विचार ओतप्रोत भरलेले दिसतात. श्रीपाद अमृत डांगे यांच्या सान्निध्यात आल्यानंतर त्यांचे विचार खर्या अर्थाने मार्क्सवादी चौकटीत विस्तारले आणि त्यांच्या शोषण विषयक जाणीवा विकसित झाल्या व त्यांनी मुंबईतील कामगार वर्गाचे जीवन समजून घेतले त्यातूनच कामगार चळवळ, संप, मोर्चे यावाबतच्या अनुभवातून अण्णाभाऊंच्या विचार प्रगल्भ होत गेले आणि त्यातूनच सामान्य गरीब, शोषित आणि कामगार वर्गाचे जीवन त्यांच्याकडून रेखाटले जाऊ लागले. त्यांनी १९४२ मध्ये स्टॅलिनग्राडचा पोवाडा लिहिला. त्या पोवाड्याने कम्युनिस्ट पार्टीच्या वर्तुळात कम्युनिस्ट शाहीर म्हणून प्रसिद्ध झाले. शाहीर अमर शेख, द. न. गव्हाणकर यांच्या सहकार्याने 'लाल बावटा' कलापथक काढले. लाल बावट्याच्या माध्यमातून साम्यवादी विचार त्यांनी महाराष्ट्रातील जनतेला समजावण्याचा प्रयत्न केला. भारतीय स्वातंत्र्यलढा, गोवा मुक्ती संग्राम आणि संयुक्त महाराष्ट्राचे आंदोलन यामध्ये मोलाचे योगदान दिले.

संयुक्त महाराष्ट्राचा लढा त्यांनी आपल्या शाहिरीच्या माध्यमातून जनमानसात पर्यंत पोहोचवला आणि मुंबई बद्दलचे प्रेम, मराठी भाषेबावतची आस्मिता महाराष्ट्राच्या कानाकोपऱ्यात पोहोचवण्याचा आहोरात्र प्रयत्न केला. 'भाषवार प्रांत रचनेनंतरचा महाराष्ट्र मुंबईसहीतच व्हायला हवा' यासाठी त्यांनी अस्सल ग्रामीण भाषेत लावण्या – गीते लिहली, पोवाडे लिहिले. महाराष्ट्र राज्याच्या सर्व दूर जनजागृतीचे कार्यक्रम केले. लोकानाट्याच्या व वगाच्या माध्यमात्यून महाराष्ट्रभर संयुक्त महाराष्ट्र निर्मीतीचा विचार पोहचविला. संयुक्त महाराष्ट्र निर्मीतीचा लढा त्यांनी आपल्या शाहिरीच्या माध्यमातून जनमानसापर्यंत पोहोचवला. त्याच्या परिणामातून मराठवाड्यापासून कर्नाटकव्याप्त भागातील मराठी भाषिक लोकांपर्यंत एकात्मतेची भावना वाढीस लागली आणि संयुक्त महाराष्ट्र निर्मीतीचा लढा अधिक तीव्र होण्यास हातभार लागला.

साहित्याच्या माध्यमातून सामाज वास्तवावर प्रहार करतानाच प्रस्थापित राजकारणावर त्यांनी टीका केली होती. त्यांनी १९५२ साली 'लोकमंत्र्यांचा दौरा' हे वगनाट्यात समकालीन राजकारणातील वाईट प्रवृतींवर सडेतोड टीका केली. तत्कालीन शासन–प्रशासन व राजकारण्यांवर केलेल्या टीकेमुळे हे वगनाट्य प्रेक्षकांना अतिशय आवडले. तथापि शासनावर केलेल्या टीकेमुळे तत्कालीन शासनाने त्यांच्यावर पकड वॉरंट काढले. १९५७ मध्ये 'माझी मैना गावावर राहिली माझ्या जीवाची होतेय काहिली' हे लोकनाट्य लिहिले या लोकनाट्याचा प्रयोग होताच महाराष्ट्र शासनाने पुन्हा त्यांच्यावर बंदी घातली. परंतु आणाभाऊ साठे थांबले नाहीत. त्यांनी अनेक वगनाट्य, शाहिरी पोवाडे, लावण्या लिहिल्या आणि संयुक्त महाराष्ट्राच्या लढ्यामध्ये लोकसहभाग वाढविण्याचा च्या प्रयत्न केला. त्यातूनच 'तमाशा' या शब्दाऐवजी 'लोकनाट्य' हा नवीन पर्यायी शब्द देऊन तमाशा या कला प्रकाराला सन्मान मिळवून दिला. अण्णाभाऊ साठे यांनी लोकनाट्याच्या माध्यमातून समाजातील दुःख आणि विदारक चित्र चव्हाट्यावर आणले. गीते आणि कवणे

गाऊन अण्णाभाऊ साठेंनी संयुक्त महाराष्ट्र निर्मीतीसाठीचा विचार संपूर्ण महाराष्ट्रभर पोहचविला. 'अकलेची गोष्ट', 'निवडणुकीत घोटाळे', 'बेकायदेशीर', 'माझी मुंबई', 'शेटजींचे इलेक्षण' इत्यादी गाजलेल्या लोकनाट्यातून 'मुंबईसह संयुक्त महाराष्ट्र झालाच पाहिजे', अशी आग्रही मागणी आण्णाभाऊंनी केली. त्यासाठी सामान्य माणसांमध्ये जनजागृती करण्याचे महत्त्वाचे कार्य अण्णाभाऊ साठे यांनी केले. त्यातूनच संयुक्त महाराष्ट्राची चळवळ ही मराठी भाषिकांच्या अस्मितेचा हुंकार बणली. परिणामी अंतर्गत मतभेद विसरून महाराष्ट्रातील जनतेने एकजुटीने संयुक्त महाराष्ट्राच्या लढ्यात सहभाग घेतला. त्यासाठी त्यांनी लोकागीतांच्या माध्यमातून संयुक्त महाराष्ट्राची चळवळ सामान्य माणसाला समजावून सांगितली. तसेच त्यांनी कॉम्रेड डांगे, आचार्य अत्रे, सेनापती बापट, एस. एम. जोशी, प्रबोधनकार ठाकरे आणि दादासाहेब गायकवाड यांच्यासारख्या नेत्यांचे विचार सर्वसामान्य जनतेपर्यंत पोहचविले आणि संयुक्त महाराष्ट्राचा लढा सतत तेवत ठेवला.

भारताच्या स्वातंत्र्य चळवळीतही अण्णाभाऊ साठे यांनी सहभाग घेतला होता. १९४२ च्या चलेजाव आंदोलनात सहभाग घेतला म्हणून त्यांच्यावर पकड वॉरंट काढण्यात आले होते. पुढे भारत स्वातंत्र्य झाल्याच्या दुसर्याच दिवशी म्हणजे १६ ऑगष्ट १९४७ साली भारतीय स्वातंत्र्यामध्ये सामान्य माणसाचे स्थान काय? हे विचारण्यासाठी मुंबई येथे भला मोठा मोर्चा काढला. स्वातंत्र्य भारतातील हा पहिला मोर्चा आहे, या मोर्चात स्वातंत्र्य भारतात सामान्य माणसाचे स्थान काय? असे मुलाभूत प्रश्न अण्णाभाऊ साठे यांनी उपस्थीत केले आणि "ये आझादी जुठी है, देश कि जनता भुकी है" हे सांगण्याचे धाडस केले. त्या दिवशी मुंबईमध्ये प्रचंड पाऊस पडत होता, तरीही अण्णाभाऊ साठे आणि त्यांचे सहकारी मागे हटले नाहीत.

१९५० ते १९६० चा कालावधी जनजागृती आणि समाजप्रबोधनाच्या आंदोलनांनी ओतप्रोत भरलेला होता, सर्व स्तरातील लोक संयुक्त महाराष्ट्राच्या चळवळीसाठी लढा देत होते. राजकीय नेते कार्यकर्ते विचारवंत आपल्या जीवाची पर्वा न करता या आंदोलनासाठी कार्य करत होते. अशावेळी अण्णाभाऊ साठे यांनी आपल्या लावणी पोवाडे शाहीर लोकनाट्य इत्यादी साहित्य प्रकारातून जनमानसामध्ये संयुक्त महाराष्ट्राच्या लढ्यात बाबतची जागृती निर्माण करण्याचे महत्त्वाचे कार्य केले. या लढ्यात काम करणाऱ्या कार्यकर्त्यांना उत्साहित करण्याचे त्यांनी आपल्या असामान्य प्रतिभेने केले आहे. त्यांनी शाहीर अमरशेख व दो.ना.गवाणकर यांच्या सहकार्याने 'लालबावटा' पथकाच्या माध्यमातून लोकाजागृतिचे कार्य केले आणि संयुक्त महाराष्ट्राच्या चळवळीत लढणाऱ्या कार्यकर्त्यांना प्रेरणा दिली. यांच्या साहित्याने प्रभावित होऊन संयुक्त महाराष्ट्राच्या आंदोलनामध्ये सामान्य कष्टकरी जनतेपासून शेतकरी व कामगार या चळवळीत सहभागी झाले.

अण्णाभाऊ साठे यांनी शायरी, काव्य, पोवाडे, लावण्या आणि वगाची नव्याने मांडणी केली आणि महाराष्ट्राच्या देशभक्ती आणि थोर परंपरेला सन्मान मिळवून देण्याचा प्रयत्न केला. त्यांनी 'गणेश वंदन' या स्तवना ऐवजी छत्रपती

शिवाजी महाराज आणि अन्य क्रांतिकारकांचे स्मरण करून हुतात्मे आणि देशभक्तांना मानाचा मुजरा केला. त्यांनी शिवजी महाराज, लोकमान्य टिळक, महात्मा फुले, डॉ. बाबासाहेब आंबेडकर, सेनापती बापट, क्रांतिसिंह नाना पाटील, कॉम्रेड श्रीपाद डांगे आणि संयुक्त महाराष्ट्रासाठी बलिदान दिलेल्या १०५ हुतात्म्यांनांचे स्मरण करून जन-सामान्यांमध्ये स्फूर्ती निर्माण करण्याचा प्रयत्न केला. अण्णाभाऊ साठे यांना देशाच्या वैभवशाली इतिहासाबाबत आदर होता. त्यांच्या मनात देशप्रेम, राष्ट्रभक्ती ओतप्रोत भरलेली होती. त्यांनी 'महाराष्ट्राची परंपरा' या पोवाड्यातून महाराष्ट्राचा गुणगौरव केला आहे. कवणातून आणि पोवाड्यांच्या माध्यमातून महाराष्ट्राचे वैभव स्पष्ट करून मुंबईसह संयुक्त महाराष्ट्र झालाच पाहिजे असा आग्रह धरला, मराठवाड्यावर असलेली निजामाची सत्ता उलथून मराठवाडा महाराष्ट्रात सामील करावा असा विचार मांडला. अठरा पगड जातीचा संयुक्त महाराष्ट्र करण्यासाठी बारली, कातकरी, भिल्ल आणि कोळी या सर्वांनी एकत्र येण्याचा सल्लाही त्यांनी आपल्या शाहिरी - पोवाडे आणि साहित्यकृतीतून दिला. १८ ऑक्टोबर १९४८ रोजी संयुक्त महाराष्ट्र चळवळीची संबंधित परिषद भरली होती त्यात अण्णाभाऊ साठें यांनी लिहलेला 'महाराष्ट्राचा पोवाडा' शाहीर अमर शेखांनी सादर केला. या पोवाडयात अण्णाभाऊंनी महाराष्ट्राच्या संस्कृतिक इतिहासाचे वर्णन केलेले आहे. अण्णाभाऊ द्वारा लिखित 'महाराष्ट्राचा पोवाडा' हा जणू काही १९५६च्या संयुक्त महाराष्ट्र चळवळीची नांदीच होती. 'महाराष्ट्र माय-भू आमची/ मराठी भाषिकांची /संत-महंतांची' असा शब्दप्रयोग असलेला पोवाडा अण्णाभाऊ साठेंनी लिहिला व शाहीर अमर शेखांनी गायला त्यामुळे हा पोवाडा अजरामर झाला आहे.

सारांश

अण्णाभाऊ साठे यांनी महाराष्ट्रातील जनतेच्या मनात महाराष्ट्र आणि देशाप्रती प्रेम निर्माण करण्याचे महत्वाचे कार्य आनाभाऊ साठे यांनी त्यांच्या कवितेतून केले आहे. 'माझी मैना गावावर राहिली' या लावणीतून त्यांनी मुंबईसह संयुक्त महाराष्ट्राचे वर्णन केले आहे. मुंबईशिवाय महाराष्ट्र निर्माण केला किंवा मुंबईला महाराष्ट्रापासून वेगळे केले तर पती पत्नीला विभक्त केल्यासारखे होईल, विभक्त केल्यामुळे ज्याप्रमाणे पती पत्नीला विरहाचे जीवन जगावे लागते त्याच प्रकारे मुंबईला महाराष्ट्रापासून वेगळे केले तर पती पत्नीला विरहा प्रमाणे होईल, ही बाब त्यांनी स्पष्ट करून दाखवली. "माझी मैना गावावर राहिली माझ्या जीवाची होतीया काहीली" या लावणीतील मैना म्हणजे वेळगाव, कारवार, डांग, उंबरगाव आणि तेथील जनतेक्या मनात होत असलेल्या दु:खाचे वर्णन करून अण्णाभाऊ साठे यांनी सीमा प्रश्नाविषयीचा प्रश्न किती महत्वाचा आहे हे लक्षात आणून दिले आहे. आशा प्रकारे अण्णाभाऊ साठे यांचे साहित्य हा केवळ साहित्य प्रकार नसून एक विचारधारा आहे. ही विचारधारा समतावादी आणि लोकशाही मुल्यांनी ओतप्रोत भरलेली आहे. सर्व समाज घटकांत समानतेची जोपासना करणारी आहे. परंतु प्रस्थापित इतिहासकरांनी आणि साहित्य समीक्षकांनी याकडे अक्षम्य दुर्लक्ष केले आहे. शोषणमुक्ती हा त्यांचा ध्यास होता. कष्टकरी, दलित, शोषित, पीडित यांचे शोषण संपविण्यासाठी त्यांनी आयुष्यभर लढा दिला. अनेक नामवंत साहित्यिकांच्या वाट्याला त्यांच्या हयातीत उपेक्षाच आली. जशी महात्मा

जोतीराव फुले यांच्या वाङ्मयाची त्यांच्या काळात उपेक्षा झाली, तशीच उपेक्षा अण्णाभाऊ साठे यांचीही झाली असली तरी संयुक्त महाराष्ट्राच्या चळवळीत अण्णाभाऊ साठे व यांच्या साहित्याचे योगदान अनन्यसाधारण आहे ही बाब अधोरेखित होते.

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अहमदनगर जिल्ह्यातील कम्युनिस्ट पक्षाचा जमीन बळकाव लढा

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प्रास्ताविक

आशिया खंडात सहकार चळवळीची पायाभरणी करणाऱ्या अहमदनगर जिल्ह्यास महाराष्ट्रातील कम्युनिस्ट चळवळीच्या इतिहासात महत्त्वाचे स्थान आहे. कारण कष्टकरी शेतकरी समुदायात व ग्रामीण भागात कम्युनिस्ट पक्षाने याच जिल्ह्यात भक्कमपणे पाय रोवले. स्वातंत्र्योत्तर काळात अहमदनगर जिल्ह्यातील शेतकऱ्यांच्या जमीन विषयक प्रश्नावर कम्युनिस्ट पक्षाने केलेल्या चळवळीमध्ये जमीन बळकाव लढ्याच्या चळवळीस अनन्यसाधारण महत्त्व असल्याचे दिसून येते. या चळवळीच्या माध्यमातून स्वकीय सरकारच्या शोषक व जुलमी धोरणांचे जिल्ह्यातील कम्युनिस्ट पक्षाने हिडीस स्वरूप दर्शवून वंचित घटकांच्या प्रति आपली बांधिलकी स्पष्ट केल्याचे दिसते.

महत्त्वाचे शब्द : *सिलिंग. लाल बावटा, कॉंग्रेड, च्या जमीन धारणा कमाल कायदा, जबरन जोत,*

शोधनिबंधाचा उद्देश :

१. जमीन बळकाव लढ्याची पार्श्वभूमी समजून घेणे.
२. भारतीय कम्युनिस्ट पक्षाचा जमीन बळकाव लढ्याच्या हेतूचा मागोवा घेणे.
३. कॉंग्रेस सरकारची जमीन बळकाव लढयासंबंधीची प्रतिक्रिया जाणून घेणे.
४. १९६२ च्या महाराष्ट्र सरकार जमीन धारणा कमाल मर्यादा ठरविणाऱ्या कायद्याची वस्तुस्थिती जाणून घेणे.
५. भारतीय कम्युनिस्ट पक्षाच्या सिलिंग कायद्यामागच्या भूमिकेचा आढावा घेणे
६. अहमदनगर जिल्ह्यातील कम्युनिस्ट पक्षाच्या जमीन बळकाव लढ्यातील कामगिरीचा आढावा घेणे.

1. जमीन बळकाव लढ्याच्या पार्श्वभूमी :

१९५२ च्या दुष्काळाच्या पार्श्वभूमीवर अहमदनगर जिल्ह्यात कम्युनिस्ट पक्ष, रिपब्लिकन पक्ष व लाल निशाण पक्षाने सरकारकडे असलेली हजारो एकर जमीन आदिवासी, हरिजन भूमिहीनांना मिळावी या करिता भूमिहीनांच्या चळवळीची यशस्वी मुहूर्तमेढ रोवली होती. या चळवळीतील जमीन बळकाव लढा हा पुढचा महत्वाचा टप्पा होता. भारतीय कम्युनिस्ट पक्षाने संपूर्ण देशामध्ये सिलींगचा कायदा झाला पाहिजे याकरिता १९७० साली अखिल भारतीय पातळीवर एक मोठा जमीन बळकाव लढ्याचा कार्यक्रम हाती घेण्याचा निर्णय घेतला. कारण कम्युनिस्ट पक्षाच्या मते स्वातंत्र्य मिळून २३ वर्षे होऊनही कॉंग्रेस सरकार शेतकऱ्यांना त्यांच्या उदरनिर्वाहाचे साधन (शेतकीचे मालकी हक्क) उपलब्ध करून देण्यात अपयशी ठरले होते. राज्यांतील कॉंग्रेस सरकारने शेतीबाबत अनेक कायदे केले. शेती विकासावर प्रचंड पैसा खर्च केला. तरीही ग्रामीण भागातील ८० टक्के शेतमजूर, गरीब शेतकरी दरिद्री जीवन जगत होते. खेड्यातील ४० टक्के जनता भूमिहीन होती. जे शेतकरी भूमालक होते त्यांच्याकडे तुटपुंजी जमीन होती. याउलट ८ टक्के लोक असे होते, की त्यांच्याकडे लागवडीखाली असलेल्या जमिनीचा ३६ टक्के मालकी भाग होता. त्यात जुने राजेरजवाडे, वडे जमीनदार, पूर्वीचे जहागीरदार, बडे उद्योगपती आदींचा समावेश होता. त्यामुळे जमिनीवरची ही प्रस्थापितांची मक्तेदारी नष्ट करून त्यांच्याकडील जमिनी भूमिहीनांना दिल्या जात नाही, तोपर्यंत शेतमजूर आणि गरीब शेतकऱ्यांचे जीवनमान सुधारणे शक्य नाही असे कम्युनिस्टांचे मत होते.१ कॉंग्रेस सरकार मात्र देशात पुरेशी जमीनच नाही, आहे त्या जमिनीचे आम्ही वाटप करून टाकले आहे अशा थापा मारीत होते. एम. एस. दांतवालांसारखे सरकारधार्जिणे अर्थशास्त्रज्ञ जमीन मालकी संबंधाबाबत पंजाब, तामिळनाडू व आंध्रप्रदेश या राज्यात पुरोगामी कायदे झालेले नसतानाही तेथे हरितक्रांतीने अपेक्षेपेक्षा जास्त यश प्राप्त केल्याचे दिसून येते. याउलट महाराष्ट्र व गुजरातसारख्या राज्यात जमीनविषयक विशेषत: कुळांच्या बाबत प्रगत कायदे झालेले आहेत त्या राज्यात शेती उत्पादनक्षमतेची वाढ बेताचीच आहे असा निष्कर्ष काढण्यात मश्गुल होते. शेती उत्पादनाला आणि उत्पादनक्षमतेला हानीकारक अशा जमीनविषयक सुधारणा सरकारने टाळाव्यात असे त्यांचे मत होते. सरकारनेही हरितक्रांतीला, वाढत्या शेतीउत्पादनाला महत्व देऊन त्यामागे जमीनवाटप व जमीनसुधारणा घडवून आणून शेती उत्पादनात वाढ करण्याचा मार्ग अवरूद्ध करून टाकला. कॉ. डांगे सरकारच्या या धोरणावर टिका करताना म्हणतात, "जमीनमालकी संबंधात सामाजिक जीवनात, शासनसंस्थेत एकूण समाज व अर्थव्यवस्थेत रचनात्मक बदल न करता शेती व्यवस्थेतील तांत्रिक प्रगतीवर दिलेला एकांगी भर हा प्रगतीविरोधाचा धोका वाढवीत आहे." अमेरिकन अर्थतज्ञ सोलोन बारक्लोभ भारत सरकारच्या जमीन सुधारणेवर भाष्य करतांना म्हणतो, "शेती मालकी संबंधात फेरबदल करण्याच्या प्रश्नाला बगल दिली तरी त्या प्रश्नाशी चार डोळे करण्याचा क्षण टळत नाही आणि राज्यकर्त्यांनी टाळाटाळ केली तरी अविकसीत देशातील कष्टकरी जनता तो अशा पद्धतीने सोडविल की ती सुखावलेल्या जमीनदारांना सुखावह

होणार नाही."२ त्यातच जमीनधारणेच्या कमाल मर्यादेच्या कायद्यात सरकारने अनेक पळवाटा करून ठेवल्या होत्या. उदा: १९६२ साली महाराष्ट्र सरकारने जमीन धारणेची कमाल मर्यादा ठरविणारा कायदा केला. हा कायदा म्हणजे जमीन मालकी संबंध सुधारणेचा अखेरचा टप्पा व जमीन मालकी संबंधात विषमता नष्ट करणारा कायदा होय असे कॉंग्रेसजन आत्मप्रौढीने सांगू लागले. मात्र वस्तुस्थिती वेगळीच होती. महाराष्ट्रात ३० एकर जमिनीवर ११ टक्के खातेदार आहेत व शेतकऱ्यांच्या ६ टक्के खातेदार आहेत. परंतु त्यांच्याजवळ ४२ टक्के जमीन आहे. ह्याउलट ५ एकरपर्यंत ३७ टक्के खातेदार व १५ टक्के शेतकरी असून फक्त ७ टक्के जमीन त्यांच्याजवळ आहे. त्यामुळे ही जमीन मालकी संबंधात विषमता नव्हे तर आणखी काय असा सवाल कम्युनिस्ट सरकारला विचारू लागले. या कायद्यात जमीनदारांना पळवाटा असल्यामुळे आणि मर्यादेचे क्षेत्र अधिक ठेवल्यामुळे जमिनीचे केंद्रीकरण अबाधित राहिले. उदा: १९५६ सालच्या भाऊसाहेब हिरे यांच्या कुळ कायद्यातील तरतुदींनुसार बारमाही पाणी, दोन व एका हंगामातील पाणीपुरवठा जमिनीसाठीचे प्रमाण व कोरडवाहू जमीनसाठीचे कमाल जमीन धारण प्रमाण अनुक्रमे १२, २४, २७ व ४८ एकर असे ठेवण्यात आले. याउलट १९६२ च्या जमीन धारणा कमाल कायद्यानुसार बारमाही पाणी, दोन व एका हंगामातील पाणीपुरवठा जमिनीसाठीचे प्रमाण व कोरडवाहू जमीनसाठीचे कमाल जमीन धारण प्रमाण अनुक्रमे १८, २७, ३० व ६६ ते १२६ एकर (व्यक्तीगत मालकीच्या जमिनीवर व कुटुंबाला सवलत) असे ठेवण्यात आले. त्याचा फायदा घेऊन मक्तेदार, जमीनदार, उच्च अधिकारी, मंत्री यांनी लाखो शेतकऱ्यांना त्यांच्या हक्काच्या जमिनीपासून वंचित ठेवले.३

1.भारतीय कम्युनिस्ट पक्षाची जमीन बळकाव लढ्याची भूमिका व उद्देश :भारतीय कम्युनिस्ट पक्षाने कॉंग्रेस सरकारचा हा धूर्त डाव ओळखून जनतेचे या प्रश्नावर प्रबोधन करावयास सुरुवात केलीएकीकडे जनतेला समाजवादाचे डोस पाजावयाचे . तर दुसरीकडे जमीनदारशाही नष्ट करून भूमिहीनांना हक्काची जमीन मिळवू द्यावयाची नाही असा धूर्त खेळ सरकार वाटप करायला पडजमीनच शिल्लक नाही असा प्रचा .आपल्याशी खेळत आहे हे जनतेने ओळखलेर प्रस्थापित सरकार, जनसंघ व हितसंबंधी करीत असतांना देशात ९ कोटी एकर सरकारी पडजमीन, ३ कोटी एकर जंगलाची जमीन व ९ कोटी एकर वरकड जमीन अशी एकूण २१ कोटी एकर जमीन वाटपासाठी उपलब्ध आहे हे कम्युनिस्ट पक्षाने दाखवून दिले व सरकारचा हा प्रचार धादांत खोटा असल्याचे जनतेच्या निदर्शनास आणून दिलेच्या निवडणुकीच्या काळात १९६७ . कम्युनिस्ट पक्षाने मक्तेदार, जमीनदार, सरकारी मंत्री, बडे अधिकारी आणि त्यांचे पाठीराखे सरकार यांच्या विरुद्ध प्रचार करून १९६९ च्या सुरुवातीला जमीन बळकाव लढा उभारण्याचा निश्चय केला.४

2.भारतीय कम्युनिस्ट पक्षाचा सरकारी पडजमिनी ताब्यात घेण्याचा अहमदनगर जिल्ह्यातील कार्यक्रम :१९६९ मध्ये भाकप, भारतीय खेत मजदूर युनियन आणि अखिल भारतीय किसान सभा या संघटनांनी एकत्र येऊन लागवडीस लायक अशा सरकारी पडजमिनी ताब्यात घेण्याची मोहीम हाती घेतलीसप्टेंबर . १९६९ मध्ये भारतीय कम्युनिस्ट पक्षाच्या राष्ट्रीय कौन्सिलने एक ठराव पास केला" .सरकारी जमिनी ताब्यात घेण्याची मोहीम हिरहिरीने हाती घ्या; आपल्या पक्षाशी सहकार्य करून ज्या ज्या जनसंघटना आपल्याबरोबर यायला तयार असतील त्यांना बरोबर घेऊन या मोहिमेला हात घाला ही .सत्याग्रहाची लक्षणात्मक मोहीम आहे, या दृष्टीने तिच्याकडे न पाहता सरकारी जमिनीचा प्रत्यक्ष ताबा घेऊन तेथे पिके काढवयाची आहेत या दृष्टीने या मोहिमेकडे आपण पहिले पाहिजे", असा सर्व पक्षघटकांना आदेश दिला.५ भारतीय कम्युनिस्ट पक्षाच्या आदेशानुसार दिफेब्रुवा ८ .री १९७० रोजी अहमदनगर जिल्ह्यातील श्रीरामपूर येथे भारतीय कम्युनिस्ट पक्ष, मार्क्सवादी कम्युनिस्ट पक्ष, लाल निशाण पक्ष व, संयुक्त समाजवादी पक्ष यांच्या वतीने भूमिहीन शेतकरी, शेतमजूर व आदिवासींची एक परिषद कॅाडांगे .दत्ता देशमुख यांच्या अध्यक्षतेखाली व कॅा ., कॅागोदूताई परुळेकर ., साथी एसपरिषदेत महाराष्ट्रातील लागवडी लायक जंगल व पडीक जमीन .जोशी यांच्या उपस्थितीत संपन्न झाली .एम . ना कसण्यास द्यावीभूमिहीन शेतकऱ्यां, जमीनदार व बागायतदार शेतकऱ्यांचे जमिनीवरील केंद्रीकरण नष्ट करून जमिनीचे फेरवाटप व्हावे, आदिवासींनी वहितास आणलेल्या 'जंगल जमिनी' काढून घेऊ नये इत्यादी मागण्यांचे ठराव पास करण्यात आले.मार्च रोजी विधानसभेवर भव्य मोर्चा नेण्याचा निर्णय घेण्यात आला ४च्या प्रश्नावर तसेच भूमिहीन शेतकऱ्यां .६ श्रीरामपूर परिषदेतील निर्णयानुसार ४ मार्च रोजी कॅाडांगे यांच्य .ा अध्यक्षतेखाली २५ हजार शेतकऱ्यांचा भव्य मोर्चा विधानसभेवर नेण्यात आला" .एप्रिल पर्यंत जमिनीचे फेरवाटप केले नाही तर २० हजार भूमिहीन शेतकरी जमिनीत नांगर घालून तिचा कब्जा करतील .असा निर्णायक इशारा कॅा "सारा महाराष्ट्र पेटविल्याशिवाय आम्ही गप्प राहणार नाही .डांगे यांनी सरकारला दिला.७ सरकारने मात्र बहिरेपणाचे सोंग घेऊन भूमिहीनांच्या मागण्यांना वाटाण्याच्या अक्षता लावल्या . रोजी १९७०एप्रिल १४ .त्यामुळे भाकप व महाराष्ट्र राज्य शेतमजूर संघ यांच्या आवाहनाला प्रतिसाद देऊन दि जिल्ह्यातील हजारो भूमि १५महाराष्ट्रातील हीन व आदिवासींनी लालबावट्याच्या जयघोषात पडित जमिनीत नांगर

घातले व २३ हजार एकर जमिनीवर कब्जा केला या .'जबरन जोत' आंदोलनात सुमारे ५ हजार भूमिहीन व आदिवासींना अटक करून त्यांना दिर्घ मुदतीच्या शिक्षा ठोठावण्यात आल्या.८ अहमदनगर जिल्ह्यात संगमनेर तालुक्यातील ८, अकोले तालुक्यातील ०५, श्रीरामपूर तालुक्यातील ०५ व राहुरी तालुक्यातील ०६ केंद्रांवर भूमिहीनांनी जमिनीत नांगर फिरवून सत्याग्रह केलाकडू .बी .पी .या सत्याग्रहात कॉ ., आमदार कॉदेशमुख .के .बी ., कॉसहाणे मास्तर ., कॉरामभाऊ नागरे ., कॉबाबुराव थोरात यांनी स .हभाग घेतलाया .भूमिहीनांच्या प्रश्नावर झालेला हा पहिलाच राज्यव्यापी भव्य लढा होता . लढ्याने गरीब जनतेच्या जमिनीच्या मागणीबाबत सरकारचे धोरण बदल्याखेरीज आपणास जमीन मिळू शकणार नाही ही जाणीव भूमिहीनांना झाल्यामुळे या लढ्याला प्रचंड पाठिंबा मिळाला असे आपल्या मुल०खती दरम्यान कॉपंढरीनाथ . .सहाणे मास्तर यांनी सांगितले९

३. भूमिहीनांच्या लढ्यासंबंधी इंदिरा गांधींची भूमिका :

भूमिहीनांची लढाऊ चळवळ आणि जमिनीची भूक लक्षात घेऊन प्रधानमंत्री इंदिरा गांधी यांनी सर्व मुख्यमंत्र्यांना एक पत्र लिहिले. 'सरकारी पडजमिनी गरीब भूमिहीन शेतकऱ्यांना लवकर वाटून द्या, कुळ कायद्यात योग्य त्या दुरुस्त्या करण्यासाठी आणि त्या अंमलात आणण्यासाठी उपाय योजा', असे आदेश या पत्रान्वये देण्यात आले. पंतप्रधानांच्या नेतृत्वाखाली 'आम्ही मूलगामी जमीनसुधारणा कायदे करणार आहोत, जमिनीचे वाटप करणार आहोत अशा घोषणा कॉंग्रेसकडून केल्या गेल्या.१० भाकपचे अहमदनगर जिल्ह्यातील अकोल्याचे आमदार कॉ. बी. के. देशमुख यांनी विधानसभेत सरकारच्या शेतजमीन (जमीनधारणेची कमाल मर्यादा) (तृतीय सुधारणा) विधेयकाची चिरफाड करतांना ४ मे १९७० च्या भाषणात शेतकऱ्यांची वस्तुनिष्ठ व्याख्या करून सरकारच्या दुटप्पी धोरणाचे सातत्याने वाभाडे काढले. ते म्हणाले, "ज्याने कधी शेतात नांगर धरला नाही, नांगर कसा धरायचा याची ज्याला माहिती नाही, तो शेतकरी झाला आहे. अध्यक्षमहाराज, जो स्वतः शेती करतो, थोडीफार मजुरी लावून कष्ट करतो, राबतो त्याला शेतकरी समजले पाहिजे. असा जो शेतकरी आहे तो जी जमीन कसतो तेवढी जमीन त्याला देण्यात यावी. तशी दुरूस्ती कायद्यामध्ये केली तरच आपल्याला जी हरितक्रांती करावयाची आहे, ती यशस्वी होऊ शकेल. तरच गोरगरिबांचे प्रश्न सुटतील. अन्नधान्याची गरज भागेल. पण अध्यक्षमहाराज ह्या गोष्टी करण्याच्या दृष्टीने शासन कधीही पाऊल टाकणार नाही. कारण मध्यमवर्ग व वरच्या वर्गाचे विशिष्ट लोक यांचे-संरक्षण हे सरकार करते. कारण ते लोक निवडणुकीत शासनाला मदत करतात. त्यामुळे त्यांच्या हिताचे संरक्षण करणे ही शासनाची जबाबदारी समजली जाते. तेव्हा आपण सिलींगचा कायदा करून योग्य ते पाऊल उचलावे. तसा कायदा केला तरच देशाचे उत्पादन वाढू शकेल व भूमिहीनांना आणि शेतकऱ्यांना जमिनी कसण्यास मिळू शकतील. परंतु अशा प्रकारचे पाऊल सरकार उचलणार नाही याची मला खात्री आहे."११

४. भारतीय कम्युनिस्ट पक्षाचा जमीन बळकाव लढ्याचा कार्यक्रम :

दि. ८ ते १३ मे १९७० या काळात भारतीय कम्युनिस्ट पक्षाच्या राष्ट्रीय कौन्सिलची बैठक दिल्ली येथे पार पडली. या बैठकीत आजचे बिनबुडाचे सिलिंगचे कायदे सुधारण्याच्या प्रश्नावर कॉंग्रेस, अकाली-जनसंघ, डी.एम.के, स्वतंत्र पक्षाचे मुख्यमंत्री मूग गिळून बसले आहेत. सिलिंगच्या कायद्यात सुधारणा करण्याचा प्रश्नच उद्भवत नाही असे ही काही मुख्यमंत्री उघडपणे बोलत आहेत. त्यामुळे प्रधानमंत्री व काही राज्यांच्या मुख्यमंत्र्यांनी कितीही चांगल्या घोषणा केल्या तरी गरीब शेतकरी, शेतमजूर आणि आदिवासींनी लढाऊ आंदोलने उभारल्याशिवाय या घोषणांमधून फारसे काही निष्पन्न होणार नाही असा बैठकीत निष्कर्ष काढण्यात आला. म्हणून सिलिंगच्या कायद्यात मूलभूत सुधारणा करून सरकारी जमिनींचे वाटप व्यवस्थित घडवून आणणे यासाठी भूमिहीनांच्या खालील मागण्यांवर अखिल भारतीय पातळीवर जमीन बळकाव लढ्याची भारतीय कम्युनिस्ट पक्षाने हाक दिली.

१. सर्व सरकारी जमिनी, लागवडी लायक पडजमिनी, जंगल जमिनी सोडून ग्रामपंचायतीच्या ताब्यातील उपजाऊ जमिनी, जमीनदार, मक्तेदार आदींच्या ताब्यात असलेल्या सरकारी जमिनी भूमिहीन गरीबांना देण्यात याव्यात. ज्या भूमिहीनांच्या ताब्यात सरकारी जमिनी आहेत त्यांचा होणारा छळ बंद करून त्यांचे पट्टे त्यांना करून देण्यात यावेत.

२. कुळांच्या ताब्यातील जमिनीवरून त्यांना बेदखल करण्याचे सर्व मार्ग बेकायदेशीर घोषित करून त्यांचे उल्लंघन करणाऱ्या जमिनदारांना दंड ठोठावले पाहिजेत. कुळ कायद्यात योग्य त्या दुरुस्त्या करणारे कायदे केले पाहिजेत. खंडाचा भरमसाठ दर कमी करून त्याचे प्रमाण निश्चित केले पाहिजे. सरंजामी जमीनदारी नष्ट करून कुळांना जमिनीचे मालक ठरविले पाहिजे. ३. आजचे सिलिंगचे कायदे पूर्णतः बदलावेत. त्यात खालील मुद्यांचा समावेश करावा. साखर कारखान्यांच्या मालकीचे फार्म्स, गवताळ जमिनी, फळबागा आणि देवस्थानांच्या जमिनी यांना मिळणाऱ्या सवलती बंद कराव्यात. काही कायद्यांमध्ये सिलिंगचा कायदा व्यक्तींना लागू आहे. त्यामुळे हा कायदा कुटुंबाला लागू केला पाहिजे. जमिनदारांच्या मालकीच्या जमिनीवर आज जी कमालमर्यादा आहे ती कमी केली पाहिजे. जमिनीची परिस्थिती आणि

चळवळीची तीव्रता या बाबी लक्षात घेऊन भिन्नभिन्न राज्यात सिलिंगच्या मर्यादा खाली आणल्या पाहिजेत. ४. आदिवासींच्या बळकावलेल्या जमिनी त्यांना परत करून त्यासंदर्भात कडक कायदा करावा. त्यांना जंगलाच्या जमिनी दिल्या जाव्यात आणि बिबड (भटक्या पद्धतीने) शेती कसण्याचे त्यांनी सोडून देऊन कायम शेती करावी म्हणून त्यांना आर्थिक व तांत्रिक मदत दिली जावी. ५. जमीनदारांच्या मालकीच्या गावठाणाच्या जमिनीवर वस्ती करून राहणाऱ्या लोकांना या जमिनीचे मोफत मालकी हक्क दिले पाहिजेत. ६. सिलिंग कायद्याची अंमलबजावणी केल्यानंतर वरकड, सरकारी पडजमीन व जंगलाची जमीन भूमिहीन शेतकऱ्यांना वाटून द्यावी किंवा त्यांची सहकारी शेते स्थापन करावीत. ७. जमिनीचे योग्य वाटप व्हावे या करिता ज्या वेगवेगळ्या भूमीसमित्या केल्या जातील त्यात भूमिहीनांच्या संघटनांना योग्य प्रतिनिधित्व मिळाले पाहिजे.[१२] १४ एप्रिलच्या लढ्यानंतर सरकारने '१९७० च्या आत आम्ही हा प्रश्न सोडवू' अशी घोषणा केली असली व त्याप्रमाणे हालचाली सुरू केल्या असल्या तरी १४ एप्रिल सरकारची व ७ जून आपली! या जिद्दीने आपण पुढील लढ्याची तयारी केली पाहिजे. १४ एप्रिलच्या लढ्यात जी जंगल, वरकड व पडजमीन आपण सरकारकडे मागितली आहे ती "७ जून नंतर मृग नक्षत्राचा पाऊस पडल्यावर आम्ही पेरणार, त्याचे पीक घेणार व त्याचे प्रत्यक्ष फायदे भूमिहीन शेतकऱ्यांना मिळवून देणार". म्हणून या लढ्याच्या तयारीला त्वरित सुरुवात करून '७ जून नंतर पेरते व्हा' असा संदेश देऊन जमिन बळकाव लढ्याचा कार्यक्रम सर्व राज्यांत पावसाळा सुरू होताच हाती घेण्याचा आदेश कम्युनिस्ट पक्षाने दिला.[१३]

5.अहमदनगर जिल्ह्यातील कम्युनिस्ट पक्षाचे जमीन बळकाव लढ्यातील योगदान व कामगिरी:

दि. १ जुलै १९७० रोजी भाकप, अ. भा. किसान सभा व आदिवासी भूमिहीन शेतमजूर संघ यांच्या नेतृत्वाखाली राहुरी तालुक्यात सहा केंद्रांवर जमीन पेरणी सत्याग्रह करण्यात आला. त्याचे नेतृत्व जिल्हा किसान सभेचे अध्यक्ष कॅ. बाबुराव थोरात, कॅ. गंगाधर जाधव यांनी केले.[१४] १४ जुलै रोजी महाराष्ट्र राज्य कम्युनिस्ट पक्षाच्या सभेत जमीन बळकाव लढा तीव्र करण्याचा निर्णय घेण्यात आला. कम्युनिस्ट पक्षाच्या आदेशानुसार १५ ऑगस्ट १९७० रोजी भाकप, किसान सभा, लाल निशाण पक्ष, प्रजा समाजवादी पक्ष, संयुक्त समाजवादी पक्ष व भूमिहीन शेतमजूर संघटना यांच्या नेतृत्वाखाली संपूर्ण भारतात व महाराष्ट्रभर बड्या बागायतदारांकडील जमिनी ताब्यात घेण्याचा सत्याग्रह करण्याचा निर्णय घेण्यात आला.[१५]

अहमदनगर जिल्ह्यात श्रीरामपूर तालुक्यात खाजगी साखर कारखानदारी व बड्या बागायतदारांचे मोठे प्रस्थ होते. त्यामुळे सर्वपक्षीय नेतृत्वाने या तालुक्यात ४ केंद्रांवर जमीन बळकाव लढा कार्यक्रम घेण्याचा निर्णय घेतला. तालुका मॅजिस्ट्रेटने या भागाच्या आसपास १४४ कलम जारी केले. त्याचा भंग करून सत्याग्रह करण्याचा सर्वांनी निश्चय केला. अहमदनगर जिल्ह्यात सोमय्या (९०० एकर जमीन) यांच्या श्रीरामपूर तालुक्यातील फार्मवरील सत्याग्रहात अहमदनगर बीड व औरंगाबाद जिल्ह्यातील ८०० सत्याग्रहींनी भाग घेतला. त्याचे नेतृत्व कॅ. चंद्रगुप्त चौधरी व कॅ. निवृत्ती उगले यांनी केले. कॅ. बाळासाहेब नागवडे, कॅ. वकीलराव लंघे, कॅ. नामदेवराव आव्हाड, कॅ. जगनाथ सोनवणे, कॅ. बाबुराव थोरात, कॅ. अचपळराव लांडे पाटील, कॅ. सातपुते पाटील, कॅ. लक्ष्मणराव लांडे, कॅ. शांतीलिंग आप्पा लोहकरे, कॅ. विनायकराव औटी आदी कम्युनिस्ट पुढाऱ्यांनी या सत्याग्रहात भाग घेतला. फार्म भोवती पोलिस व एस. आर. पी. चा कडक पहारा ठेवण्यात आला होता. फार्ममधील शेतमजुरांनी १५ ऑगस्ट रोजी एक दिवसांचा लाक्षणिक संप करून सत्याग्रहाला आपला पाठिंबा व्यक्त केला. सत्याग्रहींनी सिलींग मर्यादेपेक्षा जादा जमीन काढून घ्या, भूमिहीन व आदिवासींना जमीन मिळालीच पाहिजे, जान देंगे जमीन लेंगे अशा घोषणा देत फार्ममध्ये घुसण्याचा प्रयत्न केला. पोलिसांनी १४४ कलमाचा भंग केल्यावद्दल सर्व सत्याग्रहींना अटक केली. स्त्रियांना २०० रु. दंड अगर दोन दिवसांची शिक्षा ठोठावण्यात आली. श्रीरामपूर तालुक्यातील जमीनदार खटोड (१३०० एकर जमीन) यांच्या मालुंजा येथील फार्ममध्ये कॅ. एकनाथ भागवत व आमदार दराडे यांच्या नेतृत्वाखाली ६०० भूमिहीन सत्याग्रहींनी जबरदस्तीने जमीन बळकावण्याचा प्रयत्न केला. पोलिसांनी त्यांनाही ताब्यात घेतले. स्टेट फार्म हरेगाव येथे सुमारे ७६ सत्याग्रहींनी जमीन ताब्यात घेण्याचा प्रयत्न केला. या तुकडीचे नेतृत्व कॅ. माँधवराव गायकवाड, आमदार कॅ. बी. के. देशमुख व कॅ. पी. बी. कडू पाटील यांनी केले. १६ कोल्हार येथे केंद्रीय मंत्री अण्णासाहेब शिंदे यांच्या ६० एकर शेतीत २२३ सत्याग्रही घुसल्याबद्दल त्यांना १८८ कलमाखाली अटक करण्यात आली. या सत्याग्रहाचे नेतृत्व कॅ. गंगाधर ओगले यांनी केले.[१७]

6.जमीन बळकाव लढ्याचे मूल्यमापन :

१५ ऑगस्टचा जमीन बळकाव लढा संपूर्ण भारतभर झाला. या लढ्यात ३१,१८३ सत्याग्रहींना अटक झाली व १, ६१, ९९० एकर जमीन ताब्यात घेण्यात आली. महाराष्ट्रातील २६ पैकी २२ जिल्ह्यातील २० हजारापेक्षा जास्त सत्याग्रहींनी लढ्यात भाग घेतला. त्यात १२०० स्त्रिया होत्या. ७५०० जणांना अटक झाली व ४ हजारापेक्षा जास्त सत्याग्रहींना ७

दिवस ते ४॥ महिन्यांची शिक्षा झाली. या लढ्यात १२ हजार एकर पडजमिनीचा कब्जा घेण्यात आला.१८ महाराष्ट्रात अहमदनगर जिल्हा हा या लढ्यामध्ये सर्वात आघाडीवर होता. जिल्ह्यात १७०० सत्याग्रहींना अटक करण्यात आली. ११६७ जणांना १ महिन्याची शिक्षा झाली. या लढ्यामुळे जिल्ह्यातील बड्या बागायतदारांनी आज ना उद्या आपल्या ताब्यातील जमीन जाणार याची धास्ती घेतली. ठेच स्वत:कडे हजारो एकर जमीन ठेवून त्या जमिनीवर राबणाऱ्या कुळांना उपाशी मारणारे व शेतमजुरांची पिळवणूक करणारे शासकीय व खासगी भांडवलदारांचे लुटारू शोषक स्वरूप समोर आले. भूमिहीनांना वाटण्यासाठी थोडीच जमीन शिल्लक आहे ह्या प्रचारातील फसवेपणा दिसून आला. बड्या जमीनदार व भांडवलदारांनी हजारो एकर जमीन बेकायदेशीर मार्गाने बळकावली आहे हे या लढ्यामुळे स्पष्ट झाले.१९ या लढ्याच्या परिणामस्वरूप केंद्र सरकारच्या सूचनेनुसार महाराष्ट्र सरकारने १९६१ च्या भूमीधारणेची मर्यादा कमी करण्यासंबंधीचा वटहुकूम १९७१ साली काढला. त्यानुसार बागायतीची कमालमर्यादा १० ते १८ एकर, विहीरीच्या पाण्याखालील जमिनीची २७ एकर व कोरडवाहू जमिनीची कमालमर्यादा ५४ एकर एवढी निश्चित केली. गरीब शेतकरी, शेतमजूर व आदिवासी शेतकऱ्यांच्या परिषदेत कम्युनिस्ट पक्षाचे सेक्रेटरी कॉ. एकनाथ भागवत यांनी या वटहुकूमला विरोध करून जमीनधारणेची कमाल मर्यादा निम्यावर आणून ही मर्यादा साधारण जमिनीसाठी ३० एकर, हलक्या जमीनिसाठी ५० एकर व ओलीताखालील जमिनीसाठी ८ एकरपेक्षा अधिक न ठेवण्याची मागणी केली. तसेच जमिनीची कालमर्यादा ठरवितांना जमिनीच्या मालकीऐवजी त्या जमिनीत किती उत्तपन्न निघते हा निकष लावण्याची मागणी केली. सिलींगची अंमलबजावणी सप्टेंबर १९७० ऐवजी जानेवारी १९७१ पासून करण्याच्या सूचनेला कम्युनिस्टांनी विरोध केला. कारण अनेक बागायतदारांनी आपल्या लाखो एकर जमिनी नातेवाईकांच्या नावे केल्या होत्या. शेतकरी कोणाला म्हणावे याची स्पष्ट व्याख्या न केल्याने सधन व्यापारी, दलाल, सरकारी अधिकारी, काळा पैसेवाले यांना एक प्रकारे अभय मिळून त्यांना जमीन ठेवण्याची मुभा मिळाली. त्यामुळे कम्युनिस्ट पक्षाने जमीन धारणेची कमाल मर्यादा ठरविणाऱ्या वटहुकूमाला विरोध करण्याची भूमिका चालूच ठेवली.२० पुढे १९७५ साली देशात आणीबाणी जाहीर झाल्यानंतर पंतप्रधान इंदिरा गांधी यांनी २० कलमी कार्यक्रम घोषित केला आणि त्यामध्ये कम्युनिस्ट पक्षाच्या धोरणानुसार सिलींग कायदा करून त्यात मोठ्या जमीनदारांकडील अतिरिक्त जमिनी भूमिहीन शेतमजुरांना देण्याची तरतूद केली.२१ अशा प्रकारे कम्युनिस्ट पक्षाने देशपातळीवर जमीन बळकाव लढ्याच्या माध्यमातून उभी केलेली चळवळ यशस्वी करण्यात अहमदनगर जिल्ह्यातील कम्युनिस्ट पक्षाने मोठी भागीदारी केलेली दिसते.

संदर्भ ग्रंथ सूची

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कला एवं धर्म शोध संस्थान, वाराणसी द्वारा संचालित

कला सरोवर (त्रैमासिक)

(Kala Sarovar Quarterly Journal Approved by UGC Care List)

भारतीय कला एवं संस्कृति की विशिष्ट शोध पत्रिका

प्रिय महोदय/महोदया,

रचना के लिए धन्यवाद! सुविधानुसार शीघ्र ही अंक वर्ष 24 संख्या-2-2021 में प्रकाशित करने की व्यवस्था करूँगा। इसे इस विश्वास पर स्वीकृत किया गया है कि यह आपकी अपनी मौलिक रचना है और कहीं अन्यत्र प्रकाशित नहीं हुई है।

आपकी रचना जायकवाडीबांध आंदोलन मे जिलाअहमदनगर के साम्यवादीदल का योगदान

प्रा.विघाटे गणेश शंकर डॉ. राजाराम काळडे की स्वीकृति संख्या कला सरोवर वर्ष 24/43 है। पत्र व्यवहार करते समय इसका उल्लेख अवश्य करें।

भवदीय :
प्रधान सम्पादक :
कला सरोवर (त्रैमासिक), वाराणसी
डॉ. प्रेमशंकर त्रिवेदी

आफिस - कला सरोवर (त्रैमासिक) बी. 33/33 ए-1, न्यू माकेंत कालोनी, बी.एच.यू., वाराणसी-5 दूरभाष : 0542-2310682

जायकवाडी बांध आंदोलन में जिला अहमदनगर के साम्यवादी दल का योगदान

★ प्रा.डॉ. विधाटे गणेश शंकर ★★डॉ.राजाराम कानडे

सारांशः

जायकवाडी जलसिंचन परियोजना में सरकार की भूमिका और विस्थापित लोगों पर हुए सितम के कारण, विस्थापितों का पुनर्वास संबंधी प्रश्नों की ओर सरकार का नजरअंदाज की वजह से उभरा जन आंदोलन को सही अंजाम देने की भूमिका में अहमदनगर जिले के साम्यवादी दल के योगदान को उजागर करने के प्रयोजन में प्रस्तुत शोध आलेख पाठक, संशोधक को आंदोलन के प्रति सजग करेगा। इसमें जन आंदोलन के बढ़ते प्रभाव के कारण सरकार द्वारा पारित विभिन्न अधिनियम की जानकारी है। साथ ही आंदोलन कर्मियों का विश्वास कायम रखने के प्रयास में साम्यवादी अनुयायियों का अथक प्रयास ही मानवतावादी विचारधारा की तरफ पाठक को ले जाता है।

महत्त्वपूर्ण शब्दः

महाराष्ट्र राज्य सरकार तथा साम्यवादी भूमिका की फल निष्पत्ति.

उद्देश्यः

1. जायकवाडी जलसिंचन परियोजना निर्माण में सरकार की भूमिका पर प्रकाश डालना।
2. बांध निर्माण कार्य में पीड़ितों की मानसिकता को उजागर करना एवं जन आंदोलन के विषय पर प्रकाश डालना।
3. साम्यवादी विचारकों की भूमिका और उनका मानवतावादी प्रयास की दिशा पर प्रकाश डालना।
4. जायकवाडी बांध निर्माण एवं जन आंदोलन की शुरूआत और पुनर्वास संबंधी अधिनियम के प्रति वाचक कोसजग करना।
5. बांध पीड़ितों के आंदोलन की दिशा और फलनिष्पत्ति का अध्ययन करना।

प्रस्तावनाः

महाराष्ट्र की मशहूर नदी गोदावरीके तट पे स्थित 'पैठण' के समीप स्थापितजायकवाडी बांध के कारण विस्थापित हुए किसान, खेती मजदूरों के आवास के प्रश्नों पर अहमदनगर के साम्यवादी विचार दलने बांध पीड़ितों के आंदोलन हेतु बिगुल बजाया जो अहमदनगर जिले के किसान आंदोलन एक यशस्वी आंदोलन के रूप में समझा जाता है। बेघरं भूमिहीन किसान

तथा मजदूरों की विपन्न अवस्था में वे बांध के वास्ते मृत्यु' को गले लगान सके, पुनर्वासके साथ बांध योजना इस तत्व के अनुसरण में अहमदनगर के साम्यवादी दल के अनुयायियों ने 'गोदावरी बांध परिषद' की सहयोग में राज्यव्यापी आंदोलन जारी रखने का ऐलान किया और उसे जिम्मेदारी के साथ निभाया।

1. जायकवाडी बांध योजना का ऐलान

तत्कालीन जलसंधारण मंत्री शंकरराव चौहान ने जनवरी 1965 में ख्यातनाम नदी गोदावरी एवं पैठण के पश्चिम दिशा में स्थित 'कावसन' गांव में जायकवाडी बांध निर्माण करने का ऐलान किया। जायकवाडी बांध की ऊंचाई 120 फीट और लंबाई 7मीलथी। इसकी बृहददीवारलगभग 120 फीट की थी। इस बांध से उपलब्ध पानी लगभग 25 मील दूर और 12 से लेकर 15 मील चौड़ाई के अहाते में रहनेवाला था।बांध का कुल खर्चा 70 करोड़ था। बांध की एक ओर 115 मील तथा दूसरी ओर 178 मील की दो नहरे निकालने का ऐलान किया गया।[1] सामान्यतः यह बांध मराठवाड़ा के अकाल को दूर करके वहां

★ इतिहास विभागाध्यक्ष,राधाबाई काळे महिंला महाविंद्यालय, अहमदनगर

★ ★ हिंदी विभागाध्यक्ष एस.एस.जी.एम.कॉलेज,कोपरगांव, जि. अहमदनगर

शैक्षिक, व्यवसायिक, औद्योगिक विकास की दृष्टि के तहत बांध निर्माण किया जा रहा था।''इस बांध परियोजना से मराठवाड़ा की 7.5 लाख एकड़ जमीन जलसिंचनमें आने वाली थी।''[2]इसलिए जायकवाडी बांध परियोजना मराठवाड़ा के चहुँमुखी विकास की एक मौलिक चाबी प्रतीत हो रही थी।

2.जायकवाडी बांध पीड़ितों के सत्याग्रह आंदोलन की नींव

महाराष्ट्र केतत्कालीन मुख्यमंत्री यशवंतराव चौहान ने 7 दिसंबर 1960 में स.गो.बर्वे की अध्यक्षता में समिति गठित की थी।[3]प्रस्तुत समिति ने पुनर्वास के बारे में निम्न सूचनाएं दी–बांध परियोजना में जिन किसानों की जमीन शासन ने अपने कब्जे में की हैं, उनके लिंये पुनर्वास योजना तैयार करना और परियोजना के साथ ही मंजूर होना अनिवार्य है।[4]गुल्हाटी समिति के सम्मुख महाराष्ट्र की ओर से महाराष्ट्र शासन ने अकाल से पीड़ितों को इस योजना में सबसे पहले हक देने का मुद्दा प्रस्तुत किया था। लेकिन जायकवाडी बांध के ऐलान में शासन ने इसके बारे में कोई भी प्रारूपण प्रस्तुत नहीं किया।अतः 1962 की बर्वे सिंचन समिति की सिफारिशों को रोकने की संभावनाएं किसानों में तीव्र होने लगी। इस बांध के कारण शेवगांव, नेवासा, पैठण तथा गंगापुर जैसे चार तहसीलों के 66 गांव, 7 लाख क्विंटल से ज्यादा जवार फसल देने वाली 92 हजार एकड उपजाऊ जमीन और लगभग एक लाख से ज्यादा लोग बेघर होने वाले थें। इनमें से शेवगांव तहसील के 20 और नेवासा तहसील के 24 गांव बांध में डूबने वाले थें।[5] स्वातंत्र्योत्तर महाराष्ट्र में वीर, पानशेत तथा कोयना इन बांध पीडितों के ढेर सारे प्रश्नों को सरकार ने अनदेखा किया था। इसलिए कई लोग दिशाहीन हो गए थे अतः 'वीर' बांध परियोजना परिषद के सामने भारतीय कम्युनिस्ट दल के कॉमरेड वसंतराव तुळपुळे ने 'पहले पुनर्वास फिर बांध' यह नारा देकर बांधों के आंदोलन का बिगुल बजाया था।[6]

बांध परियोजना निर्माण और उससे संबंधित प्रश्नों के कारणविपन्न किसानों ने नापसंदगी दिखाई। पैठण में आयोजित कांग्रेस की सभा में अहमदनगर के कांग्रेस अध्यक्षघुले पाटील ने शंकरराव चव्हाण की निंदा की। उनकी राय द्रष्टव्य है,''जायकवाडी बांध परियोजना की जगह जब निश्चित की गई तब शंकर चव्हाण और बाळासाहेब भारदे ने बांध की जगह यदि बदलने का प्रस्ताव भी सामने आया तो वे उसका जमकर विरोध करते क्योंकि शेवगांव, नेवासा तथा पैठण इन तहसीलों में साम्यवादी दल का काफी प्रभाव था और उनका प्रभाव या असर कम करने हेतु उनकी धनयुक्त जमीन को जल परियोजना में डूबने पर उन्हें बेघर करने का एक सुअवसर प्राप्त हो रहा था। इसलिए सत्ताधारियों ने अपनी पूरी शक्ति इस कार्य में लगाई।[7]

साम्यवादियोंने 1 मार्च 1965 में शेवगांव तहसीलके'आगरनांदुर' में बांध पीड़ितों की एक सभा कॉमरेड नाना पाटीलकीअगुवाई में आयोजिंत की। इस परिषद में 'गोदावरी बांध परिषद' की स्थापना की गई।इस संगठन केसचिव कॉमरेड वसंतराव तुळपुळे, अध्यक्ष कॉमरेड विश्वनाथ कर्डिले थे।पुनर्वास प्रश्नके बारे में 'गोदावरी बांध परिषद' में कई मांगे स्वीकृत की गईं।

1. पुनर्वास का आलेखन तैयार करके उसे बांध परियोजना में स्थान मिलना चाहिए।
2. बांध में जिनकी जमीन जाने वाली है, उन्हें उतनी ही जमीन नहर पानी की मिलनी चाहिए।
3. जमीन का कब्जा लेते समय नई जमीन हक का ठहराव शीघ्र तैयार होना चाहिए।
4. पुनर्वास बांध योजना में गैर किसान को समाकर उन्हें उचित आर्थिक मदद करनी चाहिए।
5. बांध विकास में तबाह हो गई जमीन पर जितना भी कर्ज का बोझ हो उसे मिटाया जाए।
6. सरकार बांध पीड़ितों की संतानों को मुफ्त में शिक्षा देने का ऐलान करें।

सरकार ने उपर्युक्त बातों की ओर गौर करके उनपर यथाशीघ्र अमल करके उन्हें पूर्ण किया जाए।[8] साथ इन माँगों की पूर्ति हेतु किसानों ने आंदोलन के लिए तैयार होने का नारा दिया।

3.जायकवाडी बांध और सत्याग्रह आंदोलन का प्रारंभ:

संगमनेरकाकॉमरेड दत्ता देशमुख ने जायकवाडी बांध पीड़ितों के असंतोष का अध्ययन करके 'गोदावरी परियोजना व महाराष्ट्र शासन' इस प्रकाशित निबंध में जायकवाडी बांध योजनाअशासकीय होने तथा गलत जगह पर निर्माण करने के प्रति मुहर लगाई।[9] सरकार ने इस खयाल की ओर अनदेखा किया। इसलिए कॉमरेड विश्वनाथ पाटील कर्डिले एवं कॉमरेड एकनाथ भागवत केमोरचा में तत्कालीन मुख्यमंत्री वसंतराव नाईक बांध स्थल को देखने हेतु पधारे उस वक्त साम्यवादियों ने 2000 किसानों के मोर्चा में उन्हें आवेदन दिया।

महाराष्ट्र राज्य के सब बांध पीड़ितों की सभा का आयोजन दिनांक 26 तथा 27 जून 1965 को हुआ। जिसकी अध्यक्षता कॉमरेड डांगे ने की और यह सभा 'महाराष्ट्र राज्य बांध और पुनर्वास परिषद' तथा साम्यवादी दल के निर्देशन में हुई। इसमें काकासाहेब गाडगीळ ने जायकवाडी बांध योजनाका सबसे ज्यादा फायदा महाराष्ट्र के अलावा आंध्र प्रदेश को होने वाली बात कहकर इस योजना पर प्रश्नचिह्न लगाने का प्रयास किया। इसलिए गोदावरी घाटमें बन रहे महाराष्ट्र केबांधों का अधिक खर्चा उठाने संबंधी प्रस्ताव यदि आ भी जाता है तो उसे मंजूर करने का सवाल निर्माण न हो इस लिंयें तत्कालीन केंद्रीय जलसंधारन मंत्री के.एल.राव नेजायकवाड़ी बांध को अतिशीघ्र मंजूरी दी। परिणामतः गोदावरी का ज्यादातर पानी आंध्र प्रदेश को ही मिलने वाला है यह निश्चितहो गया।''[10]

बाँध और पुनर्वास परिषदकेआदेश मुताबिक 29 जुलाई 1965 में मुंबई कोअहमदनगर जिले के हजारों बांध पीड़ित किसानों का विधानसभा पर मोरचानिकाला। उन्होंने सरकार को यह इशारा दिया कि पुनर्वास के प्रश्नों को कानून के तौर पर हक प्रदान नहीं किया तो प्रस्तुत बांध योजना को रोका जाएगा। महाराष्ट्र शासन ने इस बात की ओर अनदेखा करके जायकवाडी बांध परियोजना निर्माण हेतु भूमिपूजन समारोह को 18 अक्तूबर 1965 में प्रधानमंत्री लाल बहादुर शास्त्री के कर कमलों से निश्चित किया। साम्यवादी दल ने इस समारोह के खिलाफ बिगुल बजाया। पुलिसों की सजगता में भूमि पूजन के पहले कॉमरेड एकनाथ भागवत, कॉमरेड अचपळराव लांडेपाटील, कॉमरेड शशिकांत कुलकर्णी आदि साम्यवादी अनुयायियों को गिरफ्तार कर नासिक के हरसुल नामक कारागृह में बंद किया और भूमि पूजा समारोह संपन्न होने पर उन्हें रिहा किया।[11] इससे यह स्पष्ट होता है कि सरकार की ऐसी मनचाही भूमिका में कहीं ना कहीं उनकी तानाशाही भूमिका प्रतीत होती है।गोदावरी बांध परिषद व्दारा नियुक्त सभासद मंडल नेभुतपूर्व प्रधानमंत्री लाल बहादुर शास्त्री के सामने बांध पीड़ितों के प्रश्न प्रकट किए जिसे प्रधानमंत्री लाल बहादुर शास्त्री ने अपनी स्वीकृति दी।''जिन बांध पीडितों को जिस गांव में पुनर्वासके लिए जमीन मिलेगी वहाँ जलसिंचन तथा पीने के लिए यथा योग्य पानी की सुविधा मिले।'' उन्होंने इसकी सूचना महाराष्ट्र शासन को दी।[12]इसके बावजूद महाराष्ट्र सरकार ने परियोजना पीड़ितों के लिए यथा योग्य सुविधाएं न देने के कारण 18 मार्च 1966 में हो गई महाराष्ट्र राज्य बांध परिषद की कार्यकारी मंडल की सभा में पुनर्वास के अधिनियम के लिए गोदावरी बांध परिषद ने सत्याग्रह की राह पर कूच करके गोदावरी बांध कार्य रोकने का निर्णय लिया।[13]

ऊपरी फैसले के मुताबिक 14 मई 1966 को कॉमरेड रामराव पाटील थोरात के अगुवाई में, 19 मई को एरंडगांव के सरपंच कॉमरेड चंद्रभान पाटील के अगुआपन में; 26 मई को नेवासा तहसील के वकीलराव लंघे, 2 जून 1966 को कॉमरेड विश्वनाथ पाटील कर्डीले के आगुआपन में सत्याग्रह किए जिसमें क्रमशः 29, 77, 130, 114 अनुयायी प्रतिभागी हुए थे और इन्हें कई दिनों का कारावास भी हुआ था।[14] 9 जून कों श्रमिक महिला परिषद की अध्यक्षा वत्सलाबाई भागवत, अंजनाबाई दादा पाटील, सीताबाई काशीनाथ कर्डिले और सत्यभामा विश्वनाथ पाटील के आगुआपन में 101 किसान महिला सत्याग्रही की टुकडी ने सत्याग्रह करके बांध का कारोबार पूर्ण रूप से बंद किया। हालाँकि क्रेन वाहक डोजर तथा रोडरोलर को अपने कब्जे में करने वाली 24 महिलाओं को पुलिस ने हिरासत में लिया था। शेष महिलाओं

ने पूरा दिन क्रेन वाहक के सम्मुख बैठकर अपना आंदोलन किया। शाम पाँच बजे आयोजित की गई सभा में अगले आंदोलन के स्वरूप की दिशा तय करने में अपने पारिवारिक सदस्यों को भी इस आंदोलन में प्रतिभागी करने का नारा दिया गया।[15] महिलाओं के इसी प्रयास में आंदोलन को एक मौलिक दिशा मिल गई।

4.जायकवाडी बांध और पुनर्वास में सरकार की भूमिका:

महाराष्ट्र शासन ने 'जायकवाडी बांध परियोजना' के ऐलान के पश्चात बांध पीड़ितों के पुनर्वास संबंधी एकयोजनाबनाई। जिसके अनुसारसरकार ने 1884 के भूसंपादन अधिनियम के तहत 1000 रुपये की क्षतिपूर्ति की रकम देनी चाही।मंगर यह मदद विलंब से मिलने के कारण बांध पीड़ितों का असंतोष बढ़ गया ।इसलिए सन 1965 में सरकार ने 'पुनर्वास मंडल' की स्थापना की। इसका कार्यक्षेत्र केवल बांध पीड़ितों को क्षतिपूर्ति के लिए आर्थिक बँटवारा ही थाना कीपुनर्वास की कानूनी योजना बनाना। उसमें उन्होंने 1 एकड़ के लिए 1000रुपये के बदले 2000 रुपये कर दिए थे फिर भी महंगाई के परिप्रेक्ष्य में यह रकम काफी न थी इसलिए आंदोलन जारी रहा।[16]

'महाराष्ट्र राज्य बांध एवं पुनर्वास परिषद' का दूसरा अधिवेशन अहमदनगर में 18 मार्च 1969 में कॉमरेड डांगे की अध्यक्षता में संपन्न हुआ। इस अधिवेशन के परिणाम स्वरूप सरकार ने किसानों की क्षतिपूर्ति की केवल नाममात्र रकम बढ़ाकर विद्रोही लोगों को खुश करने की कोशिश की। इसमें किसानों के जमीन का उचित साक्ष्यपत्र न देना, भ्रष्टाचार तथा किसानों के अज्ञान का नाजायद फायदा लेकर किसानों के कानूनी हक को नकारने कार्य प्रशासकीय अधिकारी कर रहेथेयह इल्जाम कॉमरेड डांगे नेकिया। डांगे की राय से किसानों के लिए 'पुनर्वासकानून'ही एकमात्र राहत देने में सक्षम है। उसके लिए आवश्यक अधिनियम की आवश्यकता है और बांधपीडितों पर हो रहे सितम को रोकने हेतु उन्होंने एक कार्यक्रम सप्ताह का नारा दिया। इसके अनुसार 2 से लेकर 9 अप्रैल तक महाराष्ट्र में जहां कहीं पुनर्वास के प्रश्न है उन तहसिलों में सप्ताह में हर रोज सैकड़ों किसानों का जमघट तहसीलदार कार्यालय या कचहरी के सामनें करने का ऐलान किया।[17]यदि सरकार इसकी ओर अनदेखा करेगी तब महाराष्ट्र के प्रशासकीय अधिकारी तथा मंत्रीगण को रोकने की बात तय हो गई।

परिषद के आदेश के अनुसार शेवगांव में 9 अप्रैल को कॉमरेड विश्वनाथ कर्डिले के आगुआपन में पहले 98 और बाद में 68 किसानों ने 144 दफा खारिज करके कचहरी के सम्मुख सत्याग्रह किया।पी.बी. कडुपाटील की आगुआपन में राहुरी में 45 किसानों के सहयोग में सत्याग्रह किया। उन्हें 7 दिनों का कारावास मिला। जिन्हें कारावास मिला उनमें पुणे की कॉमरेड कमलाबाई भागवत, कॉमरेड विश्वनाथ कर्डिले, कॉमरेड बाबासाहेब नागवडे, कॉमरेड वकील राव लंघे, कॉमरेड पी.बी. कडु, कॉमरेड चंद्रभान थोरात आदि का समावेश था।[18] इन्हें येरवड़ा कारागृह में भेज दिया गया।इस तरह क्षतिपूर्ति के प्रयास में सरकार की ओर से केवल नाममात्र प्रयास हुआ जिसका खंडन साम्यवाद के अनुयायियों ने बलपूर्वक करके आंदोलन को योग्य दिशा दी।

5.बांध पीड़ितों को जमीन और आर्थिक क्षतिपूर्ति करने का अधिनियम:

जायकवाडी बांध पीडितों के निरंतर आंदोलन केकारण महाराष्ट्र सरकार को इसकी ओर ध्यान आकृष्ट करना पड़ा। जायकवाडी बांध में भूमिहीन हुए किसानों, मजदूरों अथवा वंचितों को जमीन देने का फैसला लिया गया।नये पुनर्वास में पाठशाला, बिजली, पीने का पानी, अस्पताल आदि अत्यावश्यक सुविधाएँ नए गांव में स्थापित करने में सरकारके कटिबद्ध होने का ऐलान है। अगले छह माह में शेवगांव,नेवासा तहसील के बांध को 30 हजार एकड़ जमीन का बँटवारा किया जाएगा। इसकी घोषणा तत्कालीन राज्य पुनर्वासमंत्री माननीय शरद पवार ने 20 जुलाई 1974 को शेवगांव में आयोजित सभा में की।[19]

नेवासा तहसील के भूतपूर्व विधायक कॉमरेड वकीलराव लंघे की आगुआपनमें स्थापित समिति ने माननीय शरद पवार के सम्मुख बांध पीड़ितों को सीलिंग की सीमा तक जमीन उपलब्ध कराने की माँग की। शरद पवारजी ने अतिशीघ्र बांध पीड़ितों का पुनर्वास के संबंधी अधिनियम करने का विश्वास व्यक्त किया।[20]

सन 1976 में महाराष्ट्र सरकार ने बांध पीड़ितों के 'पुनर्वास अधिनियम' को मंजूरी दी। इसके अनुसार

1. बांध पीड़ितों कोसीलिंग सीमा के तहत सरकार की ओर जमीन प्रदान की जाएगी।
2. यदि किसानों को जमीन के बदले आर्थिक क्षतिपूर्ति की चाहत है तो उसे आर्थिक भुगतान दिया जाए।
3. ग्रामस्थल के गृह निर्माण के तहत किसान को उसके पारिवारिक सदस्य संख्या के मुताबिक भूखंड प्रदान किए जाएं। भूमिहीन किसान मजदूर व्यापारी अथवा उद्योजक को 186 से 280 चौरस मीटर केभूखंडदेने का प्रावधान हो।

सन 1976 के अधिनियम को कानूनी दर्जा प्राप्त हुआ औरपुनर्वास परियोजना के निर्वाह हेतु नेक प्रणाली तैयार करने की बात तय हो गई।[21]मगर प्रावधान में कुछ समस्याएँ निर्माण हो गई। बाढ़ पीड़ितों को जमीन देने का प्रावधान अधिनियम में करने पर भी सरकार पर इसका बंधन न था।पुनर्वास गाँव में वहाँ केबड़े जमींदार जमीन देने में आनाकानी कर रहे थे। इसलिए अनेक किसानों को आर्थिक रूप में सहायता देने का प्रयास रहाजिसे बांध पीड़ितों ने ठुकराया।अतः गोदावरी बांध परिषद के नेताओं ने बांध पीडितों के सुशिक्षित युवकों को नौकरी में 10 प्रतिशत आरक्षण देने, बेघरों को 1500 रुपयों में मकान देने, खेतीकार्य के लिए मुफ्त में बिजली, आंतरिक सड़क, सुजल एवं पाठशालाओं का इंतजाम करने की माँग पुनर्वास मंत्री प्रतापराव भोसले के सम्मुख रखी थी जिसपर यथायोग्य अमल करने का विश्वास परिषद के नेताओं कोप्रतापराव भोसले ने दिया।[22]

6.जायकवाडी बांध प्रथम के आंदोलन की फल निष्पत्तिः

सन 1976के पुनर्वासअधिनियम के तहत कई बांध पीडितों का मूल गाँव के नजीकपुनर्वास कियागया। जायकवाड़ी बांध निर्माण में शेवगांव तथा नेवासा के जो गाँवडूब गए थेवहाँके रास्ते, पाठशाला एवं अस्पतालकी 70 प्रतिशत तक की कार्यपूर्ति सन 1978 ई. तक पूरी की गई।[23]बांध पीड़ितों को सन 1979 तक मकान के लिए 94 लाख तथा जमीन खरीदी के लिए 4.8 करोड रुपये दिए गए।बांध पीडितोंकी संतानों के लिए सरकारी नौकरी में 10 प्रतिशत जगह आरक्षित की।[24]शेवगांव तहसील केबांध पीडितों को जिस गाँव में जमीन मिली, उन जमीनों के सिंचन की सुविधाहेतुजायकवाड़ी बांध योजना से पानीउठाकर ताजनापुरगाँव सेलिफ्ट के माध्यम से कर देने की माँग की गई थी।सरकार ने'ताजनापुर' लिफ्ट योजना को मंजूरी दी लेकिन यह योजना शुरू होने में विलंब हुआ।[25]

1976 के पुनर्वास अधिनियम से बांध पीडित असंतुष्टथे। जिनकिसानोंकी जमीनबांधमें गई उन किसानों की बहुत कम क्षतिपूर्ति होने का इल्जाम साम्यवादियों ने किया। कुछ किसानों ने कोर्ट कचहरी के जरिए यथा योग्य क्षतिपूर्ति कर ली थी। साथ ही कुछ किसानों कोपुनर्वास के आहाते में जमीन प्राप्त नहीं हो सकी।उपरी दिक्कतों के अलावा 1976 में महाराष्ट्र सरकार ने पुनर्वासकानून के जरिए जायकवाडी बांध पीडितों के पुनर्वासकरने का जो प्रयास किया, उससे बांध सरकार के प्रति का क्रोधभाव कम होने में मदद हो गई। बांध के प्रारुपण के साथ ही पुनर्वास प्रारूप तैयार हो जाना चाहिए। जमीन के बदले जमीन और मकान के बदले मकान देने के कानूनी अधिकार मिलने चाहिए। इस तरह की साम्यवादी नेताओं की दृढता एवं तद्संबंधी के आंदोलन को अनुपम सफलता मील गई। यह साम्यवादी दल को प्राप्त हुई सबसे बड़ी कामयाबी समझी जाती है।

निष्कर्षः

1. जायकवाडी बांध परियोजना की कार्य गतिविधियों के स्पष्ट प्रारूपण को विशद न करके उसका ऐलानबांध पीडितों को धोखा देने के समान प्रतीत होता है।
2. साम्यवादियोंका अकालग्रस्त मराठवाड़ा के विकास के खातिर सरकारी योजनाओं के प्रति विरोध न था।बांध के जरिए एक प्रदेश के विकास के साथ–साथ वहां के अनगिनत लोगों का विस्थापनसाम्यवादियोंको नामंजूर था।
3. कोयना और वीर बांध योजना में पुनर्वासके दर्द को पूरी तरह मिटाया नहीं था। इसलिए 'पहले पुनर्वास फिर बांध योजना' इस खयाल को सम्मुख रखकर 'गोदावरी बांध परिषद' के माध्यम से बांध पीडितों का भव्य मोर्चा मार्क्सवादियों ने खड़ा करके लगभग दो शतक तक सरकार के साथ अथक संघर्ष करने का ऐलान ही उनके योगदान पर प्रकाश डालता है।
4. सन 1894 ई. के भूमिअधिग्रहण अधिनियम की तहत सरकार का बांध परियोजना ग्रस्त या पीडितों को मराठवाड़ा के विकास के नाम पर सितम करने का प्रयास शुरूसे देखा जाता है। साम्यवाद के दबाव तथा जन आंदोलन के परिणाम स्वरुप 1976 के पुनर्वास अधिनियम के प्रावधानों के अनुसार पीड़ितों को अपने गाँव के नजीक पुनर्वास की सुविधा देकर महाराष्ट्र सरकार ने लोगों केअसंतोष को कम जरूर किया है, इसमें कोई संदेह नहीं है।

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Book 1

RELIGIOUS FUNDAMENTALISM: CONCEPT, CAUSES, AND REALITY

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Preface: Fundamentalism is defined as 'forming a foundation or Basis'. Yet the word today resonates with destruction and annihilation. It evokes strong emotions and impulses. Originally characteristic of American conservative Protestantism, Fundamentalism is now associated with violence and terror. Fundamentalism was a world problem. In this complex world there are so many peoples lived which belongs to different race, religion, cast and community. Each community rewards its religious superiority with furioso. Love of religion is the main element of nationalism. But extreme religiosity is the cause of hatred of other religions. This creates an atmosphere of unrest and instability in society. The present research paper discusses various factors related to fundamentalism.

1. Concept and meaning of Fundamentalism: Fundamentalism is a words which seem to have a curious charge to them an emotional, spiritual, religious charge. Fundamentalism usually has a religious connotation that indicates unwavering attachment to a set of irreducible beliefs.[1] However, fundamentalism has come to be applied to a tendency among certain groups – mainly, although not exclusively, in religion – that is characterized by a markedly strict literalism as it is applied to certain specific scriptures, dogmas, or ideologies, and a strong sense of the importance of maintaining ingroup and outgroup distinctions.[2] The term is used to refer to extremism, fanaticism, and literal thinking in connection with a religious faith. When used by the West with reference to Muslim groups, religious fundamentalism also implies terrorism and oftentimes evokes a powerful image of persons who are irrational, immoderate, and violent.[3] Fundamentalism, type of conservative religious movement characterized by the advocacy of strict conformity to sacred texts. Indeed, in the broad sense of the term, many of the major religions of the world may be said to have fundamentalist movements. It has a close commitment to religion.[4] Karen Armstrong underscores the meaning of Fundamental and the power it evokes:

> One of the most startling developments of the Twentieth century has been the emergence within every major religious tradition of a militant piety popularly known as "fundamentalism." Its manifestations are sometimes shocking. Fundamentalists have gunned down worshipers in a mosque, have killed doctors and nurses who work in abortion clinics, have shot their presidents, and have even toppled a powerful government. It is only a small minority of fundamentalists who commit such acts of terror, but even the most peaceful and law-abiding are perplexing, because they seem so adamantly opposed to many of the most positive values of modern society. Fundamentalists have not time for democracy, pluralism, religious toleration, peace-keeping, free speech, or the separation of church and state.[5]

2. Causes of Fundamentalism: The main causes of Fundamentalism are modernism and Secularism. But religions fundamentalism also stimulate the wave of the fundamentalist movements. **Modernization has undermined religion in at least three ways:**

- Social life has become separated from religious life.
- In a Rationalist view people are more likely to seek scientific explanations for behavior rather than religious explanations.
- In certain societies 'religious traditionalist' feel as if their way of life is under threat, and so they take steps to defend their traditions against the erosive influence of modernization.
- **Where there is 'ideological cohesion'** around a single God and sacred text Fundamentalism seems to be stronger in Christianity and Islam, not so strong in Hinduism and Buddhism.
- **When there is a common enemy to unite against** Islamic Fundamentalism is often united against the USA.
- **The existence of marginalized individuals facing oppression** Fundamentalism needs recruits, and if a Fundamentalist group emerges with claims that it can provide a better life for people if they just adhere to the faith, it is more likely to grow
- The nature of Fundamentalism is shaped by how the political institutions deal with Fundamentalist movements where they are blocked access to political representation, movements are more likely to turn to violence.
- The specific histories of Christianity and Islam have affected the way the see politics. Christianity spent much of its early life as an obscure sect, on the political fringes, so is more concerned with 'day to day' (non-political) life, whereas Islam quickly came to dominate states in its early history – thus Islam is more concerned with politics than Christianity.
- Christianity tends to emphasize the importance of belief, while Islam emphasizes the importance of actions, thus Islam is more likely to develop violent forms of fundamentalism compared to Christianity.[6]
- Religious fundamentalism serves to reduce anxiety by promising justice. Indeed, structural conditions, over which the individual has little or no control, bring about many frustrations hard to bear with. The powerful use the underprivileged, some exercise power over others. In most parts of the world, economic and social conditions are such that some enjoy prosperity and well-being, while some others hardly survive. Thus, in the face of earthy injustices, religion functions as a palliative pill by promising that justice will be done and all sins will be punished eventually.[7]

3. Origin of Fundamentalism: The growth of fundamentalism represents a culture war – a clash between the sacred and the secular. Religious fundamentalism first appeared in the 1880s in the USA. At that time, liberal Protestants attempted to adapt their views to the modern world, while conservative Protestants opposed. The conservative Protestants believed that the bible must be understood literally and wrote a set of pamphlets named 'The Fundamentals'.[8]

4. Founder of Fundamentalism: The term fundamentalist was coined in 1920 to describe conservative Evangelical Protestants who supported the principles expounded in The Fundamentals: A Testimony to the Truth (1910–15), a series of 12 pamphlets that attacked modernist theories of biblical criticism and reasserted the authority of the Bible. There is no single founder of Fundamentalism. American Evangelist Dwight L. Moody (1837–99) and British preacher and father of dispensationalism11 John Nelson Darby (1800–1882). Also associated with the early beginnings of Fundamentalism were Cyrus I.[9]

5. Teaching of Fundamentalism:

- Supremacy of own religion
- Creates motivation to sacrifice for Dharma
- The doctrine of monotheism
- Only one particular religion will exist in the world in the future. Fundamentalism therefore denies religious freedom to other religions and opposes their existence
- The Fundamentalists teach a violent way to destroy the existence of opposing religions through traditional thinking and religious fanatic.
- The deities of other religions and their mention are also not tolerated. According to the essence of Islam, Allah is the only supreme power. Christian fundamentalists say that Jesus is the deity of all mankind, not Allah. At the same time, they worship the gods of other religions as Devil. Occasionally there is an emphasis on forcible conversion by the force of the sword or by financial temptation.[10]

5. Characteristics of Fundamentalism:

- Religious texts are seen as perfect. As such, they might be read literally be it the Bible, the Quran, Bhagvadgita or the Torah. One consequence of this is that fundamentalism rejects religious pluralism.
- There is a profound rejection of modern society. Modern society is seen as morally corrupt. Living in the modern world is seen as problematic because of the variety of choice. Fundamentalists reject the idea of choice and assert the value of tradition.
- Chauvinism is another defining characteristic of fundamentalism. While a fundamentalist of a religious type talks in the power of God, he is one who denies himself the power of God; while he makes a full cry of equality, he is, by nature, a patriarchialistic; while he claims all life based around faith, he declares all science 10 be wrong. While he pays a great deal of lip service to the ideals, he ignores them in practice and occasionally is contemptuous of them in private. He plays foul with ideology for which he claims to live and die, if necessary.
- Activism is strongly encouraged. Fundamentalists are vocal in their struggle of good against evil e.g. media images often focus on fundamentalists protesting against modernity.
- Fundamentalism reinforces nationalism. Fundamentalists often appeal to deep-seated fears of 'strangers'

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- Fundamentalism is always without a base. It starts with a conclusion and, thereafter, searches for evidence of support for the conclusion and if the fundamentalist does not find any, he creates one.
- Fundamentalists have a political agenda. Absolute opposition to homosexuals, abortion and birth control.[11]

The specific histories of Christianity and Islam have affected the way the see politics. Christianity spent much of its early life as an obscure sect, on the political fringes, so is more concerned with 'day to day' (non-political) life, whereas Islam quickly came to dominate states in its early history – thus Islam is more concerned with politics than Christianity.

6. Features of Fundamentalism:

- Dualism: The fundamentalist divide the world into binary categories: good/evil, right/wrong
- Paranoia: A deep feeling of suspicion towards those on the wrong side of the dualistic dividing lines.
- An Apocalyptic orientation: An obsession with the ultimate endpoint for society or humanity. Usually positively disposed to bring about that ultimate end.
- Charismatic leadership: A commitment or devotion to Charismatic leader. Often accompanied with a cult of leadership.
- Totalized conversion experience: Once the fundamentalist converts or embrace the ideology, they do so completely.[12]

7. Comparing Fundamentalism: Religions like ideologies vary. They differ in their potential for becoming fundamentalistic. 'The more monolithic a religion or ideology is, the more are the chances of it turning to fundamentalism. Islam and the evangelical Protestant strand of Christianity are monolithic religions; they believe that there is just one God; they are also dogmatic; they believe il is possible to express his nature and will in specific propositions both these things arc the necessary pre-conditions for fundamentalism.[13]

Hinduism as a religion, in the context of Islam and Protestant Christianity as they are, is less monolithic and dogmatic and hence, less fundamentalistic. There are a number of reasons for that: there is diffuseness ill Hinduism, different deities, a variety of gods. So diffused is the society as well: a variety of traditions, groups, sects. It might be, Bruce says, "better described riot as a religion, but as a loose collection of religions: that of the Shaivites, the Vaishnavas, the Shalcras, the Smartas, and others - that share some common themes but they tolerate a huge variety of expressions of these themes. As those expressions can vary from village to village and caste to caste, there is a little scope for enforcing conformity, criticizing laxity, or vigorously rejecting moderate reconstructions of the tradition. Instead of the single Bible or Quran, there are a large numbers of holy books and holy traditions." Hindu fundamentalism is rare and arises only when anti-Hindu fundamentalism challenges it. Within itself, revivalistic attempts have been at work in Hinduism: sometimes in the forms of Buddhism, Jainism or Sikhism at an early period of history or in the forms of Brahmo Samaj, Arya Samaj, Ramakrishna Mission or Ved-Samaj during the greater part of the nineteenth century. Orthodoxy has always been

met with revivalism in Hinduism. To that extent and arguably, monolithic religions such as Judaism, Christianity and Islam offer relatively more fertile soil for fundamentalism than Hinduism.[14]

Protestantism and Islam have much in common. Their potentials are the same. Both can generate fundamentalism; their aims are similar. Each wishes to assert the primacy of its religious belief systems and the patterns of behavior each belief system requires. But both differ in their methods. The Islamic fundamentalists believe that coercion is proper; most of them believe that it is necessary as well, while others feel that it is required, declaring 'Jihad' literally. The Protestant fundamentalists do not believe so. Christ preached against the old law of 'eye for an eye' and instead recommended to offer another check to the person who has already hit the first check. Though radical Protestants have created militant sects, the Protestants are relatively pacifists. Protestants and Islamists differ in1 their attitudes to toleration. By and large, the Protestants are tolerant while the Islamists are less so; the USA, for example, permits freedom of religious expression and attempts to prevent the state promoting one religion as superior to any other. As against this, most of the Muslim countries are far less tolerant. Referring to this, Bruce writes: 'Note that this is a matter of description and not value judgement. Nothing about what I have said requires us to believe that permissiveness is better than authoritarianism." Differences in the two monolithic religions can be cited in abundance. But that apart, what is more significant here is that Islamic fundamentalism is more potent, and more severe than Christian fundamentalism. We can turn to them briefly. Christianity and politics, for most of the time stayed apart. It became official religion of the Roman Empire in only AD 373, though it was officially tolerated from sixty years before, i.e., 313 AD. During the Middle Ages, the theory of the two the swords kept the two domains, temporal and ecclesiastical, distinct from each other. The Reformation not only brought to the fore the two sects, Catholics and Protestants, it made religion a private affair of the individual. Liberalism, in the West, is not due to Christianity but due to its absence. Lewis says: "The distinction between the church and the state is rooted in Christendom". This is not to say that Christians are not religious. They are as religious minded as the followers of any other religions: many of them live a life-style which is particularly godly. Bruce says, "The core of Protestantism is correct belief, not correct action; orthodoxy rather than ortho-praxis." With the emergence of the modern state, century after century, Christianity remained aloof from the state, though most of the citizens in the western nations were Christians. Christian fundamentalists, in relation to the state and the law, operate in a more legitimate manner and largely .in secular countries.[15]

Islamic fundamentalism is more pronounced, more vocal and more action-oriented. From the beginning, Islam, unlike Christianity, remained political. The Prophet and the subsequent Caliphs were both spiritual and political leaders. The founder of the Muslim Brotherhood, an Islamic fundamentalist organization, puts it as: "Politics is part of religion. Caesar and what belongs to Caesar is for God Almighty alone. "The Islamic fundamentalist promotes a life- style which is not only conformity to the creed, it demands actions also in conformity with what the fundamentalist wants. A hostage, held by Hezbollah, puts the case of Islamic fundamentalism, saying: "All our activities, from the way we slept to the way we entered a lavatory, were watched so that we could not violate the laws of Islam. Khomeini had written that on entering a lavatory, a believer must put his left foot forward first. We were taken to task for violating that rule." And Bruce adds: "For Islam, religion is a matter of obeying the Holy Law, As what God requires is obedience to the Law, then its imposition is not just acceptable but necessary."

Most of the Muslim countries, especially in the Middle East, have not been able to shed their religion which is Islam, despite all their efforts to westernize themselves. Islam, for them, is more than a religion: it is their eye, it is their way. The Islamic fundamentalists in relation to the state, operate largely intheocratic countries and seek Muslim brotherhood and Islamic unity.[16]

Thus the religious and cultural conflict among various nations creates threat among various community in the world. Religion is such situations offers support and a sense of cultural identity in an uncertain or hostile environment. Defending a community against a threat often gives religion a prominent role in politics. Fundamentalism happens in monotheistic religions with one God. There is a comparison of fundamentalism in the West and in the Third World; West; fundamentalism is a reaction to change in modern society, either because of increasing diversity or postmodernity. Third world; fundamentalism is a reaction to outside values being thrust upon them.

Conclusion: Although the terms *fundamentalism* and *fundamentalist* have entered common parlance and are now broadly applied, it should not be forgotten that the myriad movements so designated vary greatly in their origins, character, and outlook. Thus, Islamic fundamentalist movements differ from their Christian and Jewish counterparts in having begun as essentially defensive responses to European colonial domination. Early Islamic fundamentalists were reformers who wished to affirm the value of their religion by returning to what they sought to portray as its pristine original form; their movements only gradually acquired the militancy characteristic of much religious fundamentalism today. On the other hand, these movements share with Christian and Jewish fundamentalism

an antipathy to secularism, an emphasis on the importance of traditional religiosity as their members understand it, and a strict adherence to sacred texts and the moral codes built upon them. Although these and other common features are important as sources of insight, each fundamentalist movement is in fact unique and is best understood when viewed in its own historical and cultural context.

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