Optimized Synthesis of Novel Pyrazole Based Thiazole Derivatives and their Antimicrobial Evaluation

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Abstract. A series of nitro pyrazole based thiazole derivatives compounds were synthesized by using solid base catalyst. The process was further optimized by setting up the solvent and catalyst ratio. The structures of these compounds were elucidated by spectral (IR, ¹H NMR, ¹³C NMR, mass spectra) analysis. Synthesized compounds were screened for their in vitro antibacterial activity against the representative panel of Gram-positive (Staphylococcus aureus, Streptococcus pyogenes) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa) bacteria. These compounds were tested for their inhibitory action against strains of fungi (Candida albicans, Aspergillus niger, Aspergillus clavatus).

1. Introduction
As rate of microbial infections is increasing and microorganisms are resisting the known antimicrobial agents, designing novel, potent and broad spectrum antimicrobial agents are still remained a major challenge for medicinal chemists.

Pyrazoles belong to the family of five-member azoles, Pyrazole ring has attracted much attention as it has become fairly accessible and showed diverse properties. Pyrazoles and its derivatives are well known for their biological and medicinal, applications, such as antimicrobial [1], antitumor [2], antileukemia [3], antidepressant [4], anticonvulsant [5], antifungal [6] and antitubercular [7]. Pyrazole analogues can selectively inhibit (cyclooxygenase enzyme) COX-2 [8] they are also expressing anti-inflammatory, analgesic, anti-hypertensive, antipyretic, sedatives, and antidiabetic activities [9,10].

Pyrazolines are dihydro-pyrazole derivatives. They are also found to be equally pharmacologically interesting characteristic. Pyrazolines displayed a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules. Some of major activities are listed as anti-inflammatory [11], anti-parasitary [12], anticonvulsant [13], antimicrobial [14], antinociceptives [15], antimalarial [16], antiviral [17], antioxidant [18], antiamoebic [19], cytotoxic [20], antidiabetic [21], antifungal [22], antinociceptive [23], antimycobacterial [24], antihepatotoxic [25] and pesticidal properties [26]. Edaravone is a neuroprotective agent and used for brain ischemia. Phenazone is an analgesic and antipyretic drug.

Thiazole derivatives are known to exhibit diverse bioactivities [27-30] such as antibiotic, anthelmintic, fungicidal, analgesic, anti-inflammatory, psychotropic, antioxidant, selective adenosine receptor antagonists, antipyretic etc. 4-Thiazolidones are undergoing different stages of clinical trials as potential thyromimetic, [31] antimicrobial, anti-HIV, anti-ischaemic, cardiovascular, anticancer, thrombolytic drugs.
Figure 1 Structural resemblance between marketed drugs and targeted compounds

2. Results and discussion

2.1. Chemistry

To compare the efficiency of the catalyst, we had carried out a set of experiments by varying the reaction time, amounts of the catalysts and various solvents. The optimized conditions to prepare compound (3a-o) was achieved with 20 mmol catalyst and dry methanol as solvent. The details are given below in Table 1 and Table 2. The final compounds (5a-o) can be synthesized in three main reaction steps. According to Scheme 1, the key chalcone derivatives (3a-o) are used as precursors for the synthesis of title compounds (5a-o). These chalcone derivatives were prepared from 1 (3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde) and derivatives of acetophenone (2a-o). This reaction is modified Claisen Schmidt reaction which was further optimized. In second step, these chalcones (3a-o) were cyclise with thiosemicarbazide to get pyrazoline compounds (4a-o). In the last step, compounds (4a-o) were further cyclized using ethyl bromoacetate in order to get targeted compounds (5a-o).

2.2. Spectral characterization of synthesized compound (5a-o)

IR spectrum of the compound 5a showed stretching vibrations at 3068, 3042 cm⁻¹ due to the C-H stretching of aromatic ring. Aromatic carbon having C-H stretching of methylene group appeared at 2860 cm⁻¹. >C=O stretching of thiazolidinone ring appeared at 1690 cm⁻¹. Stretching vibration at 1578 cm⁻¹ revealed the presence of >C=N- group in the compound 5a. >C=C- stretching of aromatic ring appeared at 1532 cm⁻¹. Asymmetric and symmetric stretching appeared at 1485 cm⁻¹ and 1351 cm⁻¹ is due to the -NO₂ group.

¹H NMR spectra of compound 5a showed a singlet at δ = 8.32 ppm which is the proof of =CH-N< proton in pyrazoline ring. Aromatic proton expressed multiplet values between δ=6.86-8.21 ppm. Functional group =CH-N< of pyrazoline ring appeared as doublet of doublet at δ=6.09 ppm. Protons of -S=CH₂- gave a sharp singlet at δ=4.11 ppm. Lastly-CH₂- protons of pyrazoline ring appeared as two different doublet of doublet signals at δ=3.91 ppm and at δ=3.42 ppm.

¹³C NMR spectra of compound 5a showed distinct values of differently functionalized carbon atom. At δ = 187.4 ppm shows the presence of ketonic carbon in thiazolidinone ring (-CH₂-CO-N-). While carbon attached to nitrogen and sulphur in thiazolidinone ring (-CO-N=će-N-) appeared at δ = 178.0 ppm. Carbon attached to the phenyl ring in pyrazoline (-N=C-Ph) reveals its presence at δ = 152.6 ppm. Carbon of 4-nitrophenyl ring attached to nitro group (Ar-će-NO₂) gave signal at δ = 148.2 ppm. Different aromatic carbons had given chemical shifts between δ = 115.4-151.3 ppm. Chiral carbon of pyrazoline ring (-N-CH₂-CH₂-) is responsible for chemical shift at δ = 60.4 ppm. Methylene carbon of pyrazoline ring (-N-CH₂-CH₂-CH₂-Ph) had given chemical shift at δ = 42.3 ppm. Methylene carbon of thiazolidinone ring (-S-CH₂-CO-N-) gave shift at δ = 39.0 ppm.
Table 1 Effect of solvent on synthesis of compound 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Timeb (min)</th>
<th>Yieldc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>360</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol (96%)</td>
<td>300</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>280</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>250</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>300</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>Methanol</td>
<td>280</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>Methanol Dry</td>
<td>360</td>
<td>70</td>
</tr>
</tbody>
</table>

a. Indole-3-carbaldehyde (0.75 mol), ethyl acetoacetate (0.75 mol) and thiourea (0.5 mol)
b. All reactions were refluxed in ethanol till completion as indicated by TLC.
c. Isolated yield.

Table 2 Optimization of catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of catalyst (mmol)</th>
<th>Timeb (min)</th>
<th>Isolated yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>NaOH</td>
<td>20</td>
<td>480</td>
<td>89</td>
</tr>
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<td>2</td>
<td>KOH</td>
<td>25</td>
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<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Cs2CO3</td>
<td>20</td>
<td>480</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>Cs2CO3, Recycled</td>
<td>18</td>
<td>480</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>CaO</td>
<td>20</td>
<td>360</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>ZnO</td>
<td>20</td>
<td>600</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>Hydrotelsite</td>
<td>25</td>
<td>900</td>
<td>10</td>
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<tr>
<td>8</td>
<td>RbOH</td>
<td>15</td>
<td>600</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)2</td>
<td>20</td>
<td>480</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>K2CO3</td>
<td>15</td>
<td>360</td>
<td>35</td>
</tr>
</tbody>
</table>

a. 3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.75 mol) and acetophenone (0.75 mol).
b. All reactions were refluxed in ethanol till completion as indicated by TLC.

Scheme 1 Synthetic route for preparation of title compounds (5a-o)
2.3. Antibacterial activity

From the Table 3 it has been clearly seen that synthesized compounds (5a-o) showed significant activity against bacterial strains along with MIC values of reference compounds ciprofloxacin. Compound containing electron donating groups at para position (compound 5j, 5m and 5o) had shown optimum activity against the bacterial strains. When para position is replaced by electron withdrawing group (compound 5e and 5h) the activity was slightly decreased.

2.4. Antifungal activity

In comparison of the antifungal activity the case was altered. Compound containing electron withdrawing group at para position (compound 5e) had expressed excellent overall activity as compared to the standard drug nystatin. While compound 5m containing electron donating group at para position found to be a bit less active then compound 5e.

The remaining compounds of the series possessed feeble antimicrobial activity.

Table 3 Antimicrobial evaluation of synthesized compounds*

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-R</th>
<th>Minimal bactericidal concentration (μg/mL)</th>
<th>Minimal fungicidal concentration (μg/mL)</th>
</tr>
</thead>
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<tr>
<td>5a</td>
<td>-H</td>
<td>500</td>
<td>500</td>
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<tr>
<td>5b</td>
<td>-4-Br</td>
<td>100</td>
<td>150</td>
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<tr>
<td>5c</td>
<td>-2-Br</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>5d</td>
<td>-4-F</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>5e</td>
<td>-3.5-(F)₂</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>5f</td>
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<td>150</td>
</tr>
<tr>
<td>5g</td>
<td>-2-Cl</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>5h</td>
<td>-2,4-(Cl)₂</td>
<td>25</td>
<td>500</td>
</tr>
<tr>
<td>5i</td>
<td>-3,4-(Cl)₂</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>5j</td>
<td>-4-CH₃</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
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<td>500</td>
</tr>
<tr>
<td>5l</td>
<td>-3-NO₂</td>
<td>250</td>
<td>50</td>
</tr>
<tr>
<td>5m</td>
<td>-4-OCH₃</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5n</td>
<td>-3-OCH₃</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>5o</td>
<td>-2-OCH₃</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Nystatin</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* The protocol for the bio-activity measurement is as per literature method. [32-33]

E.c.- Escherichia coli MTCC 443; P.a.- Pseudomonas aeruginosa MTCC 1688, S.a.- Staphylococcus aureus MTCC 96; S.p.- Staphylococcus pyogenes MTCC 442; C.a.- Candida albicans MTCC 227; A.n.- Aspergillus niger MTCC 282; A.c.- Aspergillus clavatus MTCC 1323.

3. Experimental

3.1. Materials and method

The essential chemicals were purchased from E. Merck. Melting points were recorded on Gallenkamp apparatus and were left uncorrected. The completion of reaction was checked on aluminum-coated TLC plates 60, F₂₅₄ (E. Merck) using various solvent systems as mobile phase and visualized under ultraviolet (UV) light, or iodine vapor. Elemental analysis (% C, H, N) was carried out by a Perkin-Elmer 2400 CHN analyzer. IR spectra were also recorded on Perkin Elmer FT-IR L1280002 spectrophotometer. 1H NMR and spectra were recorded on Varian Gemini 400 MHz and 13C NMR spectra on Varian Mercury-400, 100 MHz in DMSO-d₆ as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer.
3.2. Synthesis of 3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1)

3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1) was prepared according to the literature method [34].

3.3. Synthesis of 3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-arylprop-2-en-1-ones (3a-o)

A mixture of 3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1) (0.01 mol) and different derivatives of acetophenone (2a-o) (0.01 mol) were stirred in presence of CsCO3 (20 mol%) as a catalyst using 45 mL dry methanol for 6 h at 55-60 °C on a heating pan with magnetic stirrer (Complete optimization is shown in Table 1 and 2). Product was filtered off, washed with water and crystallized from ethanol (95%).

3.4. Synthesis of 3’-(4-nitrophenyl)-1’-phenyl-5-(aryl)-3,4-dihydro-1’H,2H-[3,4’-bipyrrozole]-2-carbothioamides (4a-o)

3’-(4-nitrophenyl)-1’-phenyl-5-(aryl)-3,4-dihydro-1’H,2H-[3,4’-bipyrrozole]-2- carbothioamide (4a-o) were prepared according to the literature method [34].

3.5. General synthesis of 2-(3’-(4-nitrophenyl)-1’-phenyl-5-(aryl)-3,4-dihydro-1’H,2H-[3,4’-bipyrrozol]-2-yl)thiazol-4(5H)-ones (5a-o)

To suspension of compound (4a-o) (0.01 mol) in ethanol (95%), ethyl bromoacetate (0.01 mol) was added and refluxed for 3 h. After cooling, the separated product was filtered and washed. Product was crystallized from ethanol (95%).

2-(3’-(4-nitrophenyl)-1’-5-diphenyl-3,4-dihydro-1’H,2H-[3,4’-bipyrrozol]-2-yl)thiazol-4(5H)-one (5a)

Yield: 64%; m.p.: 263-265 °C; IR (KBr, cm⁻¹): 3068, 3042 (C-H, aromatic), 2860 (C-H, methylene), 1690 (C=O), 1578 (C=N), 1532 (C=C), 1485, 1351 (N-O asymmetric, symmetric, -NO₂); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.42 (dd, 1H, J = 17.50 Hz, 3.11 Hz, C₄-H pyrazoline), 3.91 (dd, 1H, J = 17.52 Hz, 11.10 Hz, C₄-H pyrazoline), 4.11 (s, 2H, thiazolone-C₅-H), 6.09 (dd, 1H, J = 11.15 Hz, 3.11 Hz, C₅-H pyrazoline), 6.86-8.21 (m, 14H, Ar-H), 8.32 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.0 (C₅ of thiazoline), 42.3 (C₄ of pyrazoline), 60.4 (C₅ of pyrazoline), 115.4-151.3 (Ar-C), 159.5 (C=N of pyrazoline), 178.0 (C=N of thiazoline), 125.0 (C=O of thiazoline); LCMS (m/z): 508.13 (M⁺); Anal. Calcd. For C₇₇H₅₉N₆O₃S: C-63.77, H-3.96, N-16.53; Found: C-63.59, H-3.84, N-16.44%.  

2-(5-(4-bromophenyl)-3’-(4-nitrophenyl)-1’-phenyl-3,4-dihydro-1’H,2H-[3,4’-bipyrrozol]-2-yl)thiazol-4(5H)-one (5b)

Yield: 62%; m.p.: 191-193 °C; IR (KBr, cm⁻¹): 3065, 3040 (C-H, aromatic), 2866 (C-H, methylene), 1694 (C=O), 1574 (C=N), 1530 (C=C), 1488, 1354 (N-O asymmetric, symmetric, -NO₂), 664 (C-Br); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.39 (dd, 1H, J = 17.52 Hz, 3.15 Hz, C₄-H pyrazoline), 3.91 (dd, 1H, J = 17.51 Hz, 11.11 Hz, C₄-H pyrazoline), 4.12 (s, 2H, thiazolone-C₅-H), 6.09 (dd, 1H, J = 11.13 Hz, 3.13 Hz, C₅-H pyrazoline), 6.92-8.17 (m, 13H, Ar-H), 8.34 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.4 (C₅ of thiazoline), 42.6 (C₄ of pyrazoline), 60.4 (C₅ of pyrazoline), 115.1-151.5 (Ar-C), 159.5 (C=N of pyrazoline), 178.4 (C=N of thiazoline), 187.1 (C=O of thiazoline); LCMS (m/z): 586.04 (M⁺); Anal. Calcd. For C₇₇H₅₉Br₆N₆O₃S: C-55.20, H-3.26, N-14.31; Found: C-55.36, H-3.40, N-14.22%. 

2-(5-(2-bromophenyl)-3’-(4-nitrophenyl)-1’-phenyl-3,4-dihydro-1’H,2H-[3,4’-bipyrrozol]-2-yl)thiazol-4(5H)-one (5c)

Yield: 58%; m.p.: 175-177 °C; IR (KBr, cm⁻¹): 3068, 3039 (C-H, aromatic), 2869 (C-H, methylene), 1690 (C=O), 1571 (C=N), 1535 (C=C), 1480, 1351 (N-O asymmetric, symmetric, -NO₂), 669 (C-Br); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.35 (dd, 1H, J = 17.48 Hz, 3.08 Hz, C₄-H pyrazoline), 3.94 (dd, 1H, J = 17.50 Hz, 11.07 Hz, C₄-H pyrazoline), 4.10 (s, 2H, thiazolone-C₅-H), 6.01 (dd, 1H, J = 11.11 Hz, 3.17 Hz, C₅-H pyrazoline), 6.98-8.20 (m, 13H, Ar-H), 8.41 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.7 (C₅ of thiazoline), 42.9 (C₄ of pyrazoline), 60.2 (C₅ of pyrazoline), 114.7-151.4 (Ar-C), 159.1 (C=N of pyrazoline), 178.0 (C=N of thiazoline); LCMS (m/z): 587.04 (M⁺); Anal. Calcd. For C₇₅H₅₉Br₅N₅O₃S: C-55.20, H-3.26, N-14.31; Found: C-55.36, H-3.40, N-14.22%. 

2-(5-(2-bromophenyl)-3’-(4-nitrophenyl)-1’-phenyl-3,4-dihydro-1’H,2H-[3,4’-bipyrrozol]-2-yl)thiazol-4(5H)-one (5d)
thiazolone), 187.4 (C=O of thiazolone); LCMS (m/z): 586.04 (M⁺); Anal. Calcd. For C₂₇H₁₉BrN₆O₃S: C-55.20, H-3.26, N-14.31; Found: C-55.48, H-3.37, N-14.46%.

2-(5-(4-fluorophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5d)

Yield: 66%; m.p.: 200-202 °C; IR (KBr, cm⁻¹): 3066, 3037 (C-H, aromatic), 2862 (C-H, methylene), 1695 (C=O), 1570 (C=N), 1531 (C=C), 1493, 1354 (N-O asymmetric, symmetric, -NO₂), 1118 (C-F); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.40 (dd, 1H, J = 17.49 Hz, 3.05 Hz, C₄-H pyrazoline), 3.94 (dd, 1H, J = 17.48 Hz, 11.07 Hz, C₅-H pyrazoline), 4.15 (s, 2H, thiazolone-C₃-H), 6.00 (dd, 1H, J = 11.21 Hz, 3.09 Hz, C₅-H pyrazoline), 7.01-8.24 (m, 13H, Ar-H), 8.40 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.1 (C₅ of thiazolone), 42.2 (C₄ of pyrazoline), 60.3 (C₃ of pyrazoline), 114.5-151.5 (Ar-C), 159.0 (C=N of pyrazoline), 178.7 (C=N of thiadiazole), 187.4 (C=O of thiazolone); LCMS (m/z): 526.12 (M⁺); Anal. Calcd. For C₂₇H₁₉F₆N₆O₆S: C-61.59, H-3.64, N-15.96; Found: C-61.64, H-3.71, N-15.84%.

2-(5-(3,5-difluorophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5e)

Yield: 67%; m.p.: 252-254 °C; IR (KBr, cm⁻¹): 3067, 3041 (C-H, aromatic), 2869 (C-H, methylene), 1705 (C=O), 1577 (C=N), 1535 (C=C), 1494, 1350 (N-O asymmetric, symmetric, -NO₂), 1125 (C-F); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.49 (dd, 1H, J = 17.48 Hz, 3.11 Hz, C₄-H pyrazoline), 3.97 (dd, 1H, J = 17.40 Hz, 11.01 Hz, C₅-H pyrazoline), 4.18 (s, 2H, thiazolone-C₃-H), 6.08 (dd, 1H, J = 11.20 Hz, 3.17 Hz, C₅-H pyrazoline), 7.10-8.20 (m, 12H, Ar-H), 8.41 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.0 (C₅ of thiazolone), 42.0 (C₄ of pyrazoline), 61.3 (C₃ of pyrazoline), 114.7-152.7 (Ar-C), 158.1 (C=N of pyrazoline), 178.6 (C=N of thiadiazole), 187.5 (C=O of thiazolone); LCMS (m/z): 544.11 (M⁺); Anal. Calcd. For C₂₇H₁₈F₄N₅O₆S: C-59.55, H-3.33, N-15.43; Found: C-59.62, H-3.24, N-15.36%.

2-(5-(4-chlorophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5f)

Yield: 75%; m.p.: 274-276 °C; IR (KBr, cm⁻¹): 3067, 3041 (C-H, aromatic), 2869 (C-H, methylene), 1705 (C=O), 1577 (C=N), 1535 (C=C), 1494, 1350 (N-O asymmetric, symmetric, -NO₂), 748 (C-Cl); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.44 (dd, 1H, J = 17.44 Hz, 3.14 Hz, C₄-H pyrazoline), 3.94 (dd, 1H, J = 17.45 Hz, 11.04 Hz, C₅-H pyrazoline), 4.15 (s, 2H, thiazolone-C₃-H), 6.07 (dd, 1H, J = 11.14 Hz, 3.15 Hz, C₅-H pyrazoline), 7.00-8.22 (m, 13H, Ar-H), 8.35 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.5 (C₅ of thiazolone), 42.8 (C₄ of pyrazoline), 61.1 (C₃ of pyrazoline), 114.5-151.8 (Ar-C), 158.7 (C=N of pyrazoline), 178.4 (C=N of thiazolone), 187.0 (C=O of thiazolone); LCMS (m/z): 542.09 (M⁺); Anal. Calcd. For C₂₇H₁₈ClN₅O₆S: C-59.72, H-3.53, N-15.48; Found: C-59.63, H-3.45, N-15.34%.

2-(5-(2-chlorophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5g)

Yield: 70%; m.p.: 207-209 °C; IR (KBr, cm⁻¹): 3069, 3040 (C-H, aromatic), 2867 (C-H, methylene), 1709 (C=O), 1570 (C=N), 1534 (C=C), 1497, 1351 (N-O asymmetric, symmetric, -NO₂), 740 (C-Cl); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.40 (dd, 1H, J = 17.40 Hz, 3.10 Hz, C₄-H pyrazoline), 3.90 (dd, 1H, J = 17.41 Hz, 11.07 Hz, C₅-H pyrazoline), 4.13 (s, 2H, thiazolone-C₃-H), 6.05 (dd, 1H, J = 11.14 Hz, 3.15 Hz, C₅-H pyrazoline), 7.01-8.24 (m, 13H, Ar-H), 8.37 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.8 (C₅ of thiazolone), 42.4 (C₄ of pyrazoline), 61.2 (C₃ of pyrazoline), 115.2-151.7 (Ar-C), 158.1 (C=N of pyrazoline), 178.7 (C=N of thiazolone), 187.4 (C=O of thiazolone); LCMS (m/z): 542.09 (M⁺); Anal. Calcd. For C₂₇H₁₈ClN₅O₆S: C-59.72, H-3.53, N-15.48; Found: C-59.65, H-3.48, N-15.39%.

2-(5-(2,4-dichlorophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5h)

Yield: 69%; m.p.: 240-242 °C; IR (KBr, cm⁻¹): 3074, 3044 (C-H, aromatic), 2869 (C-H, methylene), 1700 (C=O), 1577 (C=N), 1536 (C=C), 1498, 1353 (N-O asymmetric, symmetric, -NO₂), 754 (C-
Cl); 1H NMR (400 MHz, DMSO-$d_6$, $\delta$, ppm): 3.48 (dd, 1H, $J = 17.45$ Hz, 3.04 Hz, C4-H pyrazoline), 3.86 (dd, 1H, $J = 17.42$ Hz, 11.19 Hz, C4-H pyrazoline), 4.10 (s, 2H, thiazolone-C5-H), 6.01 (dd, 1H, $J = 11.16$ Hz, 3.17 Hz, C5-H pyrazoline), 7.03-8.28 (m, 12H, Ar-H), 8.34 (s, 1H, pyrazole-H); 13C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 39.5 (C5 of thiazoline), 42.7 (C4 of pyrazoline), 61.4 (C5 of pyrazoline), 115.0-151.1 (Ar-C), 158.4 (C=N of pyrazoline), 178.5 (C=N of thiazolone), 187.2 (C=O of thiazolone); LCMS (m/z): 576.05 (M$^+$); Anal. Calcd. For C27H18Cl2N6O5S: C=56.16, H=3.14, N=14.55; Found: C=56.28, H=3.26, N=14.68%.

2-(5-(3,4-dichlorophenyl)-3'--(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5i)

Yield: 73%; m.p.: 144-146 ºC; IR (KBr, cm$^{-1}$): 3077, 3046 (C-H, aromatic), 2872 (C-H, methylene), 1704 (C=O), 1579 (C=N), 1537 (C=C), 1487, 1350 (N-O asymmetric, symmetric, -NO2), 759 (C-Cl); 1H NMR (400 MHz, DMSO-$d_6$, $\delta$, ppm): 3.44 (dd, 1H, $J = 17.40$ Hz, 3.05 Hz, C4-H pyrazoline), 3.87 (dd, 1H, $J = 17.40$ Hz, 11.08 Hz, C4-H pyrazoline), 4.14 (s, 2H, thiazolone-C5-H), 6.04 (dd, 1H, $J = 11.15$ Hz, 3.15 Hz, C5-H pyrazoline), 7.01-8.20 (m, 12H, Ar-H), 8.36 (s, 1H, pyrazole-H); 13C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 39.7 (C5 of thiazoline), 42.5 (C4 of pyrazoline), 61.7 (C5 of pyrazoline), 115.1-152.3 (Ar-C), 158.5 (C=N of pyrazoline), 178.0 (C=N of thiazolone), 187.1 (C=O of thiazolone); LCMS (m/z): 576.05 (M$^+$); Anal. Calcd. For C27H18Cl2N6O5S: C=56.16, H=3.14, N=14.55; Found: C=56.30, H=3.22, N=14.43%.

2-(3'-(4-nitrophenyl)-1'-(phenyl-5-(p-tolyl))-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5j)

Yield: 67%; m.p.: 225-227 ºC; IR (KBr, cm$^{-1}$): 3077, 3046 (C-H, aromatic), 2930 (C-H, CH3), 2872 (C-H, methylene), 1704 (C=O), 1579 (C=N), 1537 (C=C), 1487, 1350 (N-O asymmetric, symmetric, -NO2); 1H NMR (400 MHz, DMSO-$d_6$, $\delta$, ppm): 2.46 (s, 3H, CH3), 3.41 (dd, 1H, $J = 17.41$ Hz, 3.01 Hz, C4-H pyrazoline), 3.85 (dd, 1H, $J = 17.44$ Hz, 11.02 Hz, C4-H pyrazoline), 4.11 (s, 2H, thiazolone-C3-H), 6.03 (dd, 1H, $J = 11.15$ Hz, 3.14 Hz, C5-H pyrazoline), 7.12-8.27 (m, 13H, Ar-H), 8.42 (s, 1H, pyrazole-H); 13C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 21.4 (CH3), 39.5 (C5 of thiazoline), 42.4 (C4 of pyrazoline), 61.6 (C5 of pyrazoline), 115.6-152.9 (Ar-C), 158.6 (C=N of pyrazoline), 178.7 (C=N of thiazolone), 187.5 (C=O of thiazolone); LCMS (m/z): 522.15 (M$^+$); Anal. Calcd. For C29H22N6O5S: C=64.35, H=4.24, N=16.08; Found: C=64.32, H=4.19, N=16.15%.

2-(3',5-bis(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5k)

Yield: 56%; m.p.: 235-237 ºC; IR (KBr, cm$^{-1}$): 3072, 3045 (C-H, aromatic), 2870 (C-H, methylene), 1695 (C=O), 1574 (C=N), 1535 (C=C), 1490, 1351 (N-O asymmetric, symmetric, -NO2); 1H NMR (400 MHz, DMSO-$d_6$, $\delta$, ppm): 3.40 (dd, 1H, $J = 17.42$ Hz, 3.07 Hz, C4-H pyrazoline), 3.81 (dd, 1H, $J = 17.42$ Hz, 11.02 Hz, C4-H pyrazoline), 4.10 (s, 2H, thiazolone-C5-H), 6.00 (dd, 1H, $J = 11.13$ Hz, 3.12 Hz, C5-H pyrazoline), 7.14-8.30 (m, 13H, Ar-H), 8.41 (s, 1H, pyrazole-H); 13C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 39.0 (C5 of thiazoline), 41.9 (C4 of pyrazoline), 61.4 (C3 of pyrazoline), 114.9-153.1 (Ar-C), 158.2 (C=N of pyrazoline), 178.4 (C=N of thiazolone), 187.5 (C=O of thiazolone); LCMS (m/z): 553.12 (M$^+$); Anal. Calcd. For C29H19N6O5S: C=58.58, H=3.46, N=17.71; Found: C=58.65, H=3.35, N=17.86%.

2-(5-(3-nitrophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5l)

Yield: 61%; m.p.: 259-261 ºC; IR (KBr, cm$^{-1}$): 3075, 3042 (C-H, aromatic), 2872 (C-H, methylene), 1696 (C=O), 1571 (C=N), 1533 (C=C), 1493, 1352 (N-O asymmetric, symmetric, -NO2); 1H NMR (400 MHz, DMSO-$d_6$, $\delta$, ppm): 3.43 (dd, 1H, $J = 17.40$ Hz, 3.02 Hz, C4-H pyrazoline), 3.82 (dd, 1H, $J = 17.43$ Hz, 11.01 Hz, C4-H pyrazoline), 4.12 (s, 2H, thiazolone-C5-H), 5.99 (dd, 1H, $J = 11.15$ Hz, 3.10 Hz, C5-H pyrazoline), 7.12-8.35 (m, 13H, Ar-H), 8.40 (s, 1H, pyrazole-H); 13C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 39.6 (C5 of thiazoline), 42.0 (C4 of pyrazoline), 61.7 (C3 of pyrazoline), 114.1-153.2 (Ar-C), 157.8 (C=N of pyrazoline), 178.3 (C=N of thiazolone), 187.2
(C=O of thiazolone); LCMS (m/z): 553.12 (M⁺); Anal. Calcd. For C₂₇H₁₉N₅O₅S: C-58.58, H-3.46, N-17.71; Found: C-58.47, H-3.56, N-17.65%. 

2-(5-(4-methoxyphenyl)-3'-4(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-one (5m)

Yield: 67%; m.p.: 225-227 °C; IR (KBr, cm⁻¹): 3071, 3050 (C-H, aromatic), 2870 (C-H, methylene), 2840 (-OCH₃), 1710 (C=O), 1571 (C=N), 1533 (C=C), 1488, 1352 (N=O asymmetric, symmetric, -NO₂; ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.38 (dd, 1H, J = 17.40 Hz, 3.00 Hz, C₄-H pyrazoline), 3.82 (dd, 1H, J = 17.44 Hz, 11.00 Hz, C₄-H pyrazoline), 3.88 (s, 3H, OCH₃), 4.12 (s, 2H, thiazolone-C₅-H), 6.02 (dd, 1H, J = 11.10 Hz, 3.14 Hz, C₅-H pyrazoline), 7.00-8.20 (m, 13H, Ar-H), 8.43 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 39.1 (C₃ of thiazolone), 42.0 (C₄ of pyrazoline), 55.7 (-OCH₃), 61.2 (C₅ of pyrazoline), 115.1-153.2 (Ar-C), 158.7 (C=N of pyrazoline), 178.9 (C=N of thiazolone), 187.1 (C=O of thiazolone); LCMS (m/z): 538.14 (M⁺); Anal. Calcd. For C₂₈H₂₂N₆O₅S: C-62.44, H-4.12, N-15.60; Found: C-62.35, H-4.23, N-15.65%.

Conclusion

The comparative study of these catalytic synthesis had shown that Cs₂CO₃ is the best suitable heterogeneous catalyst for the synthesis of 2-(3'-4(4-nitrophenyl)-1'-phenyl-5-(aryl)-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-2-yl)thiazol-4(5H)-ones moieties. Synthesized compounds had shown significant activity. It may be visualized from the activity results that halogen derivatives are identified as the most potential agents against bacterial strains and fungal strains.

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References


