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, ^{13}C 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-1*H*-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 cyclised with thiosemicarbazide to get pyrazoline compounds (**4a-o**). In the last step, compounds (**4a-o**) were further cyclised 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 -NO_2 group.

^1H NMR spectra of compound **5a** showed a singlet at $\delta = 8.32$ ppm which is the proof of $=\text{CH-N}<$ proton in pyrazoline ring. Aromatic proton expressed multiplet values between $\delta = 6.86$ –8.21 ppm. Functional group $=\text{CH-N}<$ of pyrazoline ring appeared as doublet of doublet at $\delta = 6.09$ ppm. Protons of $-\text{S-CH}_2-$ gave a sharp singlet at $\delta = 4.11$ ppm. Lastly $-\text{CH}_2-$ protons of pyrazoline ring appeared as two different doublet of doublet signals at $\delta = 3.91$ ppm and at $\delta = 3.42$ ppm.

^{13}C NMR spectra of compound **5a** showed distinct values of differently functionalized carbon atom. At $\delta = 187.4$ ppm shows the presence of ketonic carbon in thiazolidinone ring ($-\text{CH}_2-\text{CO-N-}$). While carbon attached to nitrogen and sulphur in thiazolidinone ring ($-\text{CO-N=C-N-}$) appeared at $\delta = 178.0$ ppm. Carbon attached to the phenyl ring in pyrazoline ($-\text{N=C-Ph}$) reveals its presence at $\delta = 152.6$ ppm. Carbon of 4-nitrophenyl ring attached to nitro group (Ar-C-NO_2) gave signal at $\delta = 148.2$ ppm. Different aromatic carbons had given chemical shifts between $\delta = 115.4$ –151.3 ppm. Chiral carbon of pyrazoline ring ($-\text{N-CH-CH}_2-$) is responsible for chemical shift at $\delta = 60.4$ ppm. Methylene carbon of pyrazoline ring ($-\text{N-CH-CH}_2-\text{CH-Ph}$) had given chemical shift at $\delta = 42.3$ ppm. Methylene carbon of thiazolidinone ring ($-\text{S-CH}_2-\text{CO-N-}$) gave shift at $\delta = 39.0$ ppm.

Table 1 Effect of solvent on synthesis of compound **3a**^a

Entry	Solvent	Time ^b (min)	Yield ^c (%)
1	Acetonitrile	360	47
2	Ethanol (96%)	300	54
3	DMF	280	40
4	THF	250	35
5	DMSO	300	61
6	Methanol	280	67
7	Methanol Dry	360	70

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^a

Entry	Catalyst	Amount of catalyst (mmol)	Time ^b (min)	Isolated yield (%)
1	NaOH	20	480	89
2	KOH	25	360	88
3	Cs ₂ CO ₃	20	480	94
4	Cs ₂ CO ₃ Recycled	18	480	90
5	CaO	20	360	52
6	ZnO	20	600	55
7	Hydrotelsite Mg ₆ Al ₂ (CO ₃)(OH) ₁₆ 4H ₂ O	25	900	10
8	RbOH	15	600	87
9	Pd(OAc) ₂	20	480	70
10	K ₂ CO ₃	15	360	35

a. 3-(4-nitrophenyl)-1-phenyl-1*H*-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 than compound **5e**.

The remaining compounds of the series possessed feeble antimicrobial activity.

Table 3 Antimicrobial evaluation of synthesized compounds*

Sr. No.	Minimal bactericidal concentration (µg/mL)					Minimal fungicidal concentration (µg/mL)		
	-R	<i>E. c.</i>	<i>P. a.</i>	<i>S. a.</i>	<i>S. p.</i>	<i>C. a.</i>	<i>A. n.</i>	<i>A. c.</i>
5a	-H	500	500	250	500	500	500	500
5b	-4-Br	100	150	500	250	1000	1000	1000
5c	-2-Br	500	500	250	250	500	1000	1000
5d	-4-F	250	500	250	100	1000	500	500
5e	-3,5-(F) ₂	25	50	25	50	25	25	50
5f	-4-Cl	100	150	500	250	1000	>1000	>1000
5g	-2-Cl	500	500	250	250	500	500	500
5h	-2,4-(Cl) ₂	25	500	250	500	1000	1000	>1000
5i	-3,4-(Cl) ₂	500	500	250	500	500	1000	1000
5j	-4-CH ₃	12.5	12.5	25	25	1000	1000	>1000
5k	-4-NO ₂	500	500	250	250	100	250	250
5l	-3-NO ₂	250	50	250	100	1000	1000	1000
5m	-4-OCH ₃	50	50	25	12.5	50	50	50
5n	-3-OCH ₃	100	150	50	50	1000	1000	>1000
5o	-2-OCH ₃	50	50	50	50	1000	500	500
Ciprofloxacin	-	25	25	50	50	-	-	-
Nystatin	-	-	-	-	-	100	100	100

* 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, F₂₄₅ (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-*d*₆ 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 derivative 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'-bipyrazole]-2-carbothioamides (4a-o)

3'-(4-nitrophenyl)-1'-phenyl-5-(aryl)-3,4-dihydro-1'H,2H-[3,4'-bipyrazole]-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'-bipyrazol]-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'-bipyrazol]-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-*d*₆, 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-*d*₆, δ, ppm): 39.0 (C₅ of thiazolone), 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 thiazolone), 187.4 (C=O of thiazolone); LCMS (m/z): 508.13 (M⁺); Anal. Calcd. For C₂₇H₂₀N₆O₃S: 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'-bipyrazol]-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-*d*₆, 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), 8.38 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-*d*₆, δ, ppm): 39.4 (C₅ of thiazolone), 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 thiazolone), 187.1 (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-55.36, H-3.40, N-14.22%.

2-(5-(2-bromophenyl)-3'-(4-nitrophenyl)-1'-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazol]-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-*d*₆, 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-*d*₆, δ, ppm): 39.7 (C₅ of thiazolone), 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

thiazolone), 187.4 (C=O of thiazolone); LCMS (m/z): 586.04 (M^+); Anal. Calcd. For $C_{27}H_{19}BrN_6O_3S$: 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, $-NO_2$), 1118 (C-F); 1H NMR (400 MHz, DMSO- d_6 , 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, C₄-H pyrazoline), 4.15 (s, 2H, thiazolone-C₅-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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.1 (C₅ of thiazolone), 42.2 (C₄ of pyrazoline), 60.3 (C₅ of pyrazoline), 114.5-151.5 (Ar-C), 159.0 (C=N of pyrazoline), 178.7 (C=N of thiazolone), 187.4 (C=O of thiazolone); LCMS (m/z): 526.12 (M^+); Anal. Calcd. For $C_{27}H_{19}FN_6O_3S$: 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, $-NO_2$), 1125 (C-F); 1H NMR (400 MHz, DMSO- d_6 , 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, C₄-H pyrazoline), 4.18 (s, 2H, thiazolone-C₅-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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.0 (C₅ of thiazolone), 42.0 (C₄ of pyrazoline), 61.3 (C₅ of pyrazoline), 114.7-152.7 (Ar-C), 158.1 (C=N of pyrazoline), 178.6 (C=N of thiazolone), 187.5 (C=O of thiazolone); LCMS (m/z): 544.11 (M^+); Anal. Calcd. For $C_{27}H_{18}F_2N_6O_3S$: 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, $-NO_2$), 748 (C-Cl); 1H NMR (400 MHz, DMSO- d_6 , 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, C₄-H pyrazoline), 4.15 (s, 2H, thiazolone-C₅-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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.5 (C₅ of thiazolone), 42.8 (C₄ of pyrazoline), 61.1 (C₅ 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 $C_{27}H_{19}ClN_6O_3S$: 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, $-NO_2$), 740 (C-Cl); 1H NMR (400 MHz, DMSO- d_6 , 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, C₄-H pyrazoline), 4.13 (s, 2H, thiazolone-C₅-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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.8 (C₅ of thiazolone), 42.4 (C₄ of pyrazoline), 61.2 (C₅ 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 $C_{27}H_{19}ClN_6O_3S$: 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, $-NO_2$), 754 (C-

Cl); ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 3.48 (dd, 1H, $J = 17.45$ Hz, 3.04 Hz, C₄-H pyrazoline), 3.86 (dd, 1H, $J = 17.42$ Hz, 11.10 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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.5 (C₅ of thiazolone), 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 C₂₇H₁₈Cl₂N₆O₃S: 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 °C; 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 , δ , 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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.7 (C₅ of thiazolone), 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 C₂₇H₁₈Cl₂N₆O₃S: 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 °C; 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 , δ , 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-C₅-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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 21.4 (-CH₃), 39.5 (C₅ of thiazolone), 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 C₂₈H₂₂N₆O₃S: 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 °C; 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 , δ , 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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.0 (C₅ of thiazolone), 41.9 (C₄ of pyrazoline), 61.4 (C₅ 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 C₂₇H₁₉N₇O₅S: 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 °C; 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 , δ , 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); ^{13}C NMR (100 MHz, DMSO- d_6 , δ , ppm): 39.6 (C₅ of thiazolone), 42.0 (C₄ of pyrazoline), 61.7 (C₅ 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 $C_{27}H_{19}N_7O_5S$: 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-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-*d*₆, 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-*d*₆, δ, ppm): 39.1 (C₅ 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 $C_{28}H_{22}N_6O_4S$: C-62.44, H-4.12, N-15.60; Found: C-62.35, H-4.23, N-15.65%.

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

Yield: 68%; m.p.: 229-231 °C; IR (KBr, cm^{-1}): 3074, 3052 (C-H, aromatic), 2877 (C-H, methylene), 2844 (-OCH₃), 1711 (C=O), 1572 (C=N), 1534 (C=C), 1485, 1355 (N-O asymmetric, symmetric, -NO₂); ¹H NMR (400 MHz, DMSO-*d*₆, δ, ppm): 3.37 (dd, 1H, *J* = 17.42 Hz, 3.04 Hz, C₄-H pyrazoline), 3.80 (dd, 1H, *J* = 17.41 Hz, 11.02 Hz, C₄-H pyrazoline), 3.86 (s, 3H, OCH₃), 4.11 (s, 2H, thiazolone-C₅-H), 6.05 (dd, 1H, *J* = 11.12 Hz, 3.11 Hz, C₅-H pyrazoline), 7.03-8.27 (m, 13H, Ar-H), 8.45 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-*d*₆, δ, ppm): 39.3 (C₅ of thiazolone), 42.4 (C₄ of pyrazoline), 55.0 (-OCH₃), 61.5 (C₅ of pyrazoline), 114.8-153.4 (Ar-C), 158.4 (C=N of pyrazoline), 178.4 (C=N of thiazolone), 187.0 (C=O of thiazolone); LCMS (m/z): 538.14 (M^+); Anal. Calcd. For $C_{28}H_{22}N_6O_4S$: C-62.44, H-4.12, N-15.60; Found: C-62.40, H-4.26, N-15.63%.

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

Yield: 63%; m.p.: 208-210 °C; IR (KBr, cm^{-1}): 3075, 3055 (C-H, aromatic), 2875 (C-H, methylene), 2840 (-OCH₃), 1712 (C=O), 1571 (C=N), 1533 (C=C), 1481, 1357 (N-O asymmetric, symmetric, -NO₂); ¹H NMR (400 MHz, DMSO-*d*₆, δ, ppm): 3.34 (dd, 1H, *J* = 17.47 Hz, 3.08 Hz, C₄-H pyrazoline), 3.81 (dd, 1H, *J* = 17.42 Hz, 11.07 Hz, C₄-H pyrazoline), 3.88 (s, 3H, OCH₃), 4.12 (s, 2H, thiazolone-C₅-H), 6.03 (dd, 1H, *J* = 11.10 Hz, 3.13 Hz, C₅-H pyrazoline), 7.10-8.26 (m, 13H, Ar-H), 8.42 (s, 1H, pyrazole-H); ¹³C NMR (100 MHz, DMSO-*d*₆, δ, ppm): 39.6 (C₅ of thiazolone), 42.8 (C₄ of pyrazoline), 55.5 (-OCH₃), 61.7 (C₅ of pyrazoline), 114.7-153.5 (Ar-C), 158.1 (C=N of pyrazoline), 178.2 (C=N of thiazolone), 187.2 (C=O of thiazolone); LCMS (m/z): 538.14 (M^+); Anal. Calcd. For $C_{28}H_{22}N_6O_4S$: C-62.44, H-4.12, N-15.60; Found: C-62.34, H-4.12, N-15.54%.

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-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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