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Synthesis and Antimicrobial Evaluation of Some New Pyrazole Derivatives Containing Thiazole Scaffold †

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Abstract: In present work one pot synthesis of some new 2,4-disubstitued thiazolyl pyrazole derivatives was carried out. The reaction of different pyrazole 4-carbalaldehydes, thiosemicarbazide and α-haloketones in one pot afforded the target molecules. The synthesis was carried out by two ways, one by conventional method in which pyrazole 4-carbaldehyde, thiosemicarbazide and α-haloketones were refluxed in ethanol and second way in which the reaction mixture was grinded at R.T. Rate of the reaction, yield of the products and purity of the products were compared for both the methods. All the synthesized compounds were tested for their antimicrobial activities. It was found that most of the compounds showed good to moderate antibacterial as well as antifungal activities.

Keywords: 2,4-disubstituted thiazolyl pyrazole; pyrazole 4-carbaldehydes; α-haloketones thiosemicarbazide; one pot; antimicrobial activities

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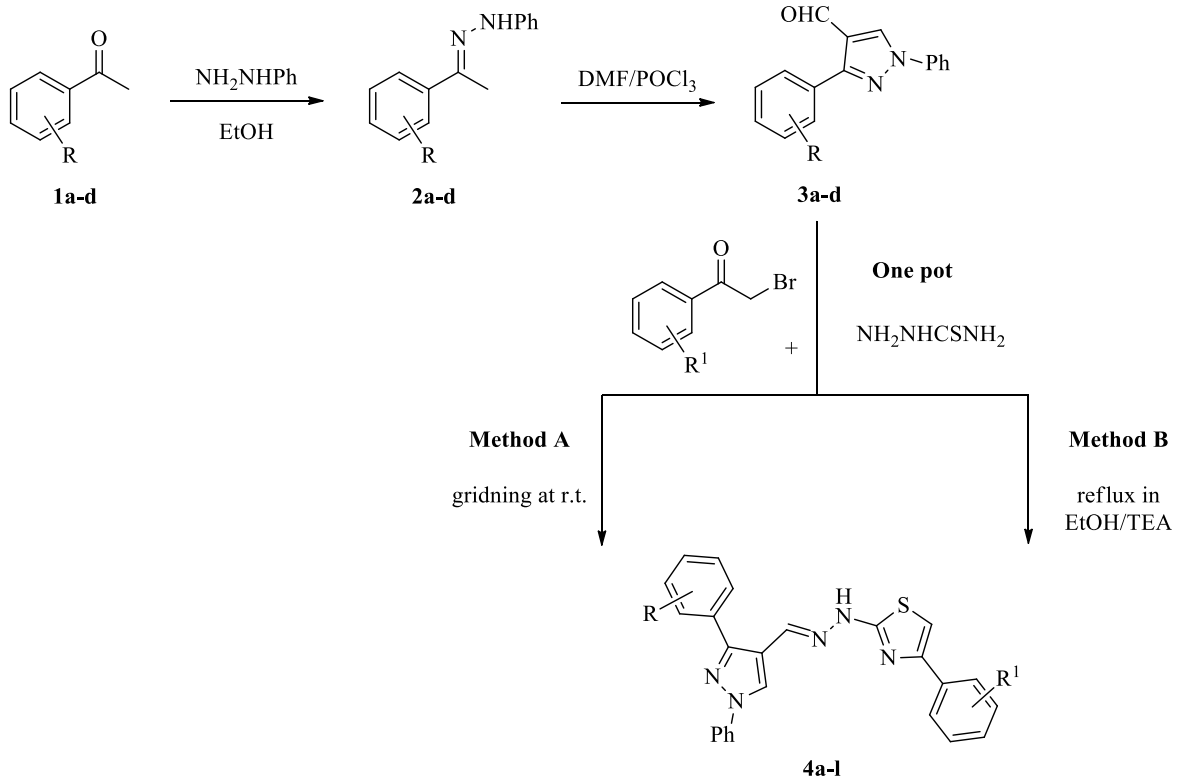
1. Introduction

Importance of new biological active molecules in pharma industry encouraged the chemists for its capable and fast synthesis which would be useful for the society. Now a days modern and fast technologies have motivated the scientists and researchers to synthesize and develop new effective drug molecules. The synthesis and designing of pyrazole and thiazole derivatives are of great interest due to their extensive applications in pharmaceutical and agrochemical industry. The curiosity in study of pyrazole chemistry is still ongoing due to its broad spectrum of biological activities like antibacterial [1–6], antiviral [7,8], antiproliferative, proapoptotic [9], antitumor [10], anti-inflammatory [11,12] and herbicidal activities [13]. Furthermore, thiazole heterocycles are noteworthy class of heterocyclic compounds which is present in several important biologically dynamic drug molecules like Ritonavir as antiretroviral drug, Sulfathiazole as antimicrobial drug, Tiazofurin as antineoplastic drug and Abafungin as an antifungal drug [14]. Thiazole containing heterocycles showed various biological activities like antifungal [15], anticancer [16–20], anti-HIV [21] and as metabotropic glutamate receptor 1 (mGluR1) antagonist [22]. On other hand it was observed that when thiazole is in combination with pyrazole nucleus, it exposed different biological activities like Antitubercular [23–28], anti-inflammatory, antimicrobial [29,30] and protein synthase III (FabH) inhibitors [31].

All these observations inspired us about to design and synthesize new effective drug molecule which contain thiazole and pyrazole nuclei together and asses their antibacterial and antifungal activities expecting that these new moieties could be the effective heterocycle in the library of recognized drug molecules. Thus, in our target we synthesized a new derivative of heterocycles containing pyrazole and thiazole molecules in one component which may show more effective biological activities.

In extension of our work [32–35] on preparation of new products with combination of dissimilar heterocyclic moieties as possible antimicrobial agents, we are reporting here the synthesis of some new pyrazole derivatives containing thiazole scaffold. The intermediate pyrazole carbaldehyde **3a-d** was synthesized by the known literature method [36,37]. A series of pyrazole containing thiazole derivatives **4a-l** synthesized and all the synthesized compounds were screened for their antimicrobial activity.



Compound	R	R¹	Compound	R	R¹
4a	3,5-bis(CF_3)	4-NO_2	**4g**	3-NO_2	4-NO_2
4b	3,5-bis(CF_3)	3-NO_2	**4h**	3-NO_2	3-NO_2
4c	3,5-bis(CF_3)	4-Cl	**4i**	3-NO_2	4-Cl
4d	4-NO_2	4-NO_2	**4j**	4-Br	4-NO_2
4e	4-NO_2	3-NO_2	**4k**	4-Br	3-NO_2
4f	4-NO_2	4-Cl	**4l**	4-Br	4-Cl

Scheme 1. Synthetic route of **4a-l**.

2. Results and Discussion

The structure of all the synthesized compounds **4a-l** was characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. IR band at 3300–3340, 1545–1550, 1620–1640 cm^{-1} showed presence of NH, C=C and C=N. In the ^{1}H NMR spectra, broad signal appeared at 12.1 ppm due to NH, a singlet at 9.1–9.2 ppm due to pyrazolyl proton, singlet at 7.68 ppm due to thiazolyl proton and multiplet at 7.4 to 8.3 ppm due to aromatic protons. The molecular ion peaks of all the synthesized compounds were obtained from EI-MS while the presence of M+2 peaks were characteristic for the compounds with chlorine, bromine and sulphur atoms. Analogously, all other compounds were characterized by spectroscopic and analytical data which is presented in the experimental part.

The grinding of aldehyde with thiosemicarbazide and α-haloketone was carried out at room temperature to afford the corresponding 2,4-disubstituted thiazole derivatives in

high yield (80–90%). In a typical procedure, pyrazole aldehyde reacts with thiosemicarbazide and α-haloketone to provide excellent yields of 2,4- disubstituted thiazoles after just a few minutes of grinding. To optimize the reaction conditions, the reaction between 3-(3,5-bis(trifluoromethyl) phenyl 1)-1-phenyl-1H-pyrazole-4-carbaldehyde thiosemicarbazide and 4-chloro phenacyl bromide was chosen as a model reaction. The reaction completed after grinding for 4 min and afforded 2,4 disubstituted thiazole derivative with 85% yield. After optimizing the conditions, we next examined the scope and generality of this method using different pyrazole 4-caradehydes. It was observed that all reactions completed in 5–10 min by grinding without any catalyst or solvent at ambient temperature. Highly efficient grinding was however required for the success of these reactions. When attempts were made to carry out the synthesis of thiazole derivatives by conventional method in ethanol under reflux temperature, it required more time, and the yield of the products was in the range 60–70% (Table 1). In general, reactions under solvent-free condition were clean, rapid and afforded higher yield than those obtained by conventional method in ethanol.

Table 1. Table showing difference between conventional and solvent free method.

Compound	Yield (%)		Time	
	Solvent Free	Conventional	Conventional (h)	Solvent Free (min)
4a	85	65	4	6
4b	81	62	4.3	7
4c	86	63	4.4	6–7
4d	87	68	3.4	3
4e	89	70	3.2	3–4
4f	92	72	3.4	3
4g	90	70	4	3
4h	85	69	3.1	4
4i	88	69	3.2	4
4j	85	65	4	4–5
4k	84	67	4.1	5
4l	86	66	4.3	5

3. Biological Results and Discussion

All the synthesized compounds were screened for their antibacterial and antifungal activities and the results are shown in Table 2. It was found that, most of the compounds showed good to moderate activity against both the Gram positive as well as Gram negative bacteria. It was noted that substituent R on phenyl ring does not affect the biological activity to a large extent but substituent R^1 was found to play important role in deciding the biological activity. It was observed that when R^1 is strong electron withdrawing like NO_2 (compound **4a**, **4d**, **4g** and **4j**) showed enhancement in antifungal as well as antibacterial activities as compared to compound **4c**, **4f**, **4i** and **4l** where the substituent R^1 is 4-Cl. The derivatives in which R^1 group is at position 3 (compound **4b**, **4e**, **4h** and **4k**) showed less antimicrobial activities.

Table 2. Antimicrobial screening of synthesized compounds **4a-l**.

Compound	*S. aureus*	*E. coli*	*B. subtilis*	*P. aeruginosa*	*A. niger*	*C. albicans*
4a	18.5	16.0	17.2	13.0	11.3	-
4b	12.2	-	11.1	7.5	-	4.8
4c	16.4	14.0	-	-	9.3	8.3
4d	18.0	-	17.1	15.6	11.1	10.1
4e	11.6	-	10.5	-	5.9	-

4f	-	12.1	14.5	10.2	8.5	7.4
4g	18.2	15.3	-	15.7	10.8	-
4h	12.0	-	11.5	-	5.6	-
4i	15.0	12.3	-	10.3	8.4	7
4j	17.6	14.0	16.4	12.1	-	10
4k	-	7.0	9.6	5.7	4.3	3.9
4l	15.2	13.1	-	10.0	-	7.5
Nystatin	NA	NA	NA	NA	21.12	21.96
Chloramphenicol	32.8	29.1	30.1	24.6	NA	NA

Chloromphenicol (100 μg/disc), Nystatin (100 μg/disc) were used as reference; synthesized compounds (100 μg/disc); NA = Not Applicable; (-) = Inactive.

4. Experimental

*4.1. General Procedure for the Synthesis of Phenyl Hydrazone Derivatives **2a-d***

A mixture of substituted acetophenone **1a-d** (1 mol), phenyl hydrazine (1 mol) and acetic acid (1 mL) in ethanol (20 mL) was refluxed for 30 min. After the completion of the reaction, as monitored on TLC, the reaction mixture was cooled at room temperature. The product was filtered, washed with water, dried and re-crystallized from ethanol.

Table 3. Physical data of compounds **2a-d**.

Compound	Colour	mp (°C)	R_f Value/Solvent System (Hexanes: Ethyl Acetate)	Yield (%)
2a	Brown	140-43	0.1/6:4	85
2b	Pale yellow	132-35	0.15/6:4	80
2c	Pale yellow	135-38	0.18/6:4	84
2d	Brown	126-29	0.1/6:4	86

*4.2. General Procedure for the Synthesis of 1-phenyl-3-(substituted -phenyl)-1H-pyrazole-4-carbaldehyde **3a-d***

To a well stirred and cooled (0 °C) DMF (12 mL), $POCl_3$ (6 mL) was added drop wise during 1h. After complete addition of $POCl_3$, the reaction mixture was further stirred at 0 °C for 1h. To this well stirred and cooled reaction mixture a solution of **2a-d** (1 mol) in anhydrous DMF (10 mL) was added drop wise for one hour, after complete addition, reaction mixture was heated at 65–70 °C for 2h. The reaction mixture was poured into crushed ice and left overnight in a refrigerator during which product separates out as solid mass. The product was filtered, washed with Na_2CO_3 (5%, 30 mL), water and re-crystallized from DMF-ethanol mixture.

Table 4. Physical data of compounds **3a-d**.

Compound	Colour	mp (°C)	R_f Value/Solvent System (Hexanes: Ethyl Acetate)	Yield (%)
3a	Brown	135-38	0.27/7:3	78
3b	Pale yellow	147-50	0.31/7:3	73
3c	Pale yellow	137-40	0.2/7:3	75
3d	Brown	150-155	0.24/7:3	77

*4.3. General Procedure for the Synthesis of 2,4-disubstitutde Thiazole Derivatives **4a-l***

4.3.1. Method A

A mixture of pyrazole aldehyde (1 mmol), thiosemicarbazide (1 mmol) and α-haloketone (1 mmol) was grinded thoroughly by pestle in mortar at room temperature for 5–

10 min. The progress of reaction was monitored by TLC (Ethyl acetate/hexanes 3:7). After completion of reaction, the mixture was washed with water and re-crystallized from ethanol to afford the pure product.

4.3.2. Method B

A mixture of pyrazole aldehyde (1 mmol), thiosemicarbazide (1 mmol) and α-haloketone (1 mmol) in ethanol was refluxed for 3h. The reaction mixture was cooled at room temperature and poured into crushed ice. The separated solid was filtered, washed with ice cold water and purified by column chromatography (Ethyl acetate/hexanes 2:8).

5. Spectral Data

1-((3-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (**4a**) mp: 236–238 °C; IR (KBr, cm^{-1}): 3340(NH), 1545(C=C), 1620(C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1(bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.68(s, 1H, thiazolyl-H), 8.4(s, 1H, CH=N), 7.4–7.8(m, 5H, Ar-H, Phenyl ring), 8.4(s, 2H, Ar-H), 8.3(s, 1H Ar-H), 8.2(d, J = 7.9Hz, 2H), 8.3(d, J = 7.9 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 168.1, 150.1, 148.5, 146.4, 140.5, 137.7, 109.1, 116.0, 119.2(2C), 130.1(2C), 126.3, 139.5, 126.6(2C), 131.8(2C), 130.7, 128.7, 129.5(2C), [133.5, 133.9, 134.4, 134.8(q, J = 34.5 Hz, 2C)], 127.8, [124.1, 120.5, 116.8, 113.2(q, J = 272 Hz, 2C)]; MS (EI, 70 eV): *m*/*z* (%): 602(M^+, 100); Analysis calcd. for $C_{27}H_{16}F_6N_6O_2S$: C, 53.82; H, 2.68; N, 13.95; found: C, 53.43; H, 2.32; N, 14.15.

1-((3-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(3-nitrophenyl)thiazol-2-yl)hydrazine (**4b**) mp: 230–235 °C; IR (KBr, cm^{-1}): 3350 (NH), 1550(C=C), 1625(C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1(bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.7 (s, 1H, thiazolyl-H), 8.4 (s, 1H, CH=N), 7.4–7.8(m, 5H, Ar-H, Phenyl ring), 8.4(s, 2H, Ar-H), 8.3(s, 1H Ar-H), 7.7–8.6(m, 4H, m-NO_2 phenyl protons); MS (EI, 70 eV): *m*/*z* (%): 602(M^+, 100); Analysis calcd. for $C_{27}H_{16}F_6N_6O_2S$: C, 53.82; H, 2.68; N, 13.95; found: C,53.55; H,2.38; N,14.25.

1-((3-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (**4c**) mp: 238–240 °C; IR (KBr, cm^{-1}): 3340 (NH), 1545(C=C), 1620(C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H, NH), 9 (s, 1H, pyrazolyl-H), 7.7 (s, 1H, thiazolyl-H), 8.3 (s, 1H, CH=N), 7.4–7.8(m, 5H, Ar-H, Phenyl ring), 8.4(s, 2H, Ar-H), 8.3(s, 1H Ar-H), 7.9(d, J = 8.3Hz, 2H), 8.2(d, J = 8.3 Hz, 2H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 168.0, 150.0, 148.4, 146.5, 140.1, 136.0, 109.0, 116.0, 119.3(2C), 129.0(2C), 126.4, 139.4, 125.6(2C), 130.1(2C), 129.4, 128.7, 129.6(2C), [133.5, 133.9, 134.4, 134.8 (q, J = 34.5 Hz, 2C)], 128.0, [124.1, 120.5, 116.8, 113.2(q, J = 272 Hz, 2C)]; MS (EI, 70 eV): *m*/*z* (%): 591(M^+, 100); Analysis calcd. for $C_{27}H_{16}ClF_6N_5S$: C, 54.78; H, 2.72; N, 11.83; found: C, 54.57; H, 2.48; N, 12.04.

1-((3-(4-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (**4d**) mp: 213–216 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.7(s, 1H, thiazolyl-H), 8.4(s, 1H, CH=N), 7.4–7.8(m, 5H, Ar-H, Phenyl ring), 8.2(d, J = 7.9Hz, 2H), 7.9(d, J = 7.9Hz, 2H), 8.3(d, J = 8.1Hz, 2H), 8.1(d, J = 8.1Hz, 2H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.2, 150.0, 149.1, 147.0, 141.4, 138.0, 136.1, 109.4, 118.0, 120.0(2C), 130.1(2C), 128.0, 125.5(2C), 129.0(2C), 129.1(2C), 136.0(2C), 136.5(2C), 136.2, 125.4(2C); MS (EI, 70 eV): *m*/*z* (%): 511(M^+, 100); Analysis calcd. for $C_{25}H_{17}N_7O_4S$: C, 58.70; H, 3.35; N, 19.17; found: C, 58.58; H, 4.11; N, 19.63.

1-((3-(4-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(3-nitrophenyl) thiazol-2-yl)hydrazine (**4e**) mp: 222–225 °C; IR (KBr, cm^{-1}): 3350(NH), 1560(C=C), 1600(C=N), 1350, 1540(NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1(bs, 1H, NH), 9.0(s, 1H, pyrazolyl-H), 7.5 (s, 1H, thiazolyl-H), 8.4 (s, 1H, CH=N), 7.9–8.4(m, 4H, m-NO_2), 8.4(d, J = 7.9 Hz, 2H), 8.2(d, J = 7.9Hz, 2H), 7.5–7.7(m, 5H, Ar-H phenyl); MS (EI, 70 eV): *m*/*z* (%): 511(M^+, 100); Analysis calcd. for $C_{25}H_{17}N_7O_4S$: C, 58.70; H, 3.35; N, 19.17; found: C, 58.35; H, 3.61; N, 19.52.

1-((3-(4-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-chlorophenyl) thiazol-2-yl)hydrazine (**4f**) mp: 234–239 °C; IR (KBr, cm^{-1}): 3300(NH), 1555(C=C), 1615(C=N), 3322, 3022(Ar-H), 1355, 1550 (NO_2), 965; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.0(bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.6(s, 1H, thiazolyl-H), 8.4(s, 1H, CH=N), 7.4–7.8(m, 5H, Ar-H, Phenyl ring), 7.9(d, J = 8.2 Hz, 2H), 8.1(d, J = 8.2Hz, 2H), 8.3(d, J = 8 Hz, 2H), 8.2(d, J = 8 Hz, 2H); MS (EI, 70 eV): *m*/*z* (%): 500(M^+, 100); Analysis calcd. for $C_{25}H_{17}ClN_6O_2S$: C, 59.94; H, 3.42; N, 16.78; found: C, 60.11; H, 3.62; N, 16.50.

1-((3-(3-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (**4g**) mp: 230–235 °C; IR (KBr, cm^{-1}): 3350(NH), 1550(C=C), 1620(C=N), 3315, (Ar-H), 1330, 1540(NO_2) 950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.4 (s, 1H, thiazolyl-H), 8.3 (s, 1H, CH=N), 7.8–8.3(m, 4H, m-NO_2), 8.2(d, J = 8.2 Hz, 2H), 8.3(d, J = 8.2 Hz, 2H), 7.5–7.8(m, 5H, Ar-H phenyl); MS (EI, 70 eV): *m*/*z* (%): 511(M^+, 100); Analysis calcd. for $C_{25}H_{17}N_7O_4S$: C, 58.70; H, 3.35; N, 19.17; found: C, 58.54; H, 3.60; N, 19.01.

1-((3-(3-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-(4-(3-nitrophenyl) thiazol-2- yl)hydrazine (**4h**) mp: 224–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H, NH), 9.1(s, 1H, pyrazolyl-H), 7.3 (s, 1H, thiazolyl-H), 8.2 (s, 1H, CH=N), 7.9–8.6(m, 8H, m-NO_2 phenyl rings), 7.4–7.8(m, 5H, Ar-H phenyl); ^{13}C NMR(75 MHz, $CDCl_3$): δ 149.5, 140.7, 118.7(2C), 129.7(2C), 126.4, 135.0, 117.0, 146.3, 168.0, 146.5, 108.8, 133.9(2C), 132.8(2C), 130.4(2C), 120.9(2C), 148.9(2C), 122.4(2C); MS (EI, 70 eV): *m*/*z* (%): Analysis calcd. for $C_{25}H_{17}N_7O_4S$: C, 58.70; H, 3.35; N, 19.17; found: C, 58.64; H, 3.50; N, 19.08.

1-((3-(3-Nitro-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene]-2-(4-(4-chloro-phenyl) thiazol-2-yl)hydrazine (**4i**) mp: 220–225 °C; IR (KBr, cm^{-1}): 3350(NH), 1545(C=C), 1622(C=N), 3320 (Ar-H), 1345, 1545(NO_2) 950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1(bs, 1H, NH), 9(s, 1H, pyrazolyl-H), 7.5 (s, 1H, thiazolyl-H), 8.6 (s, 1H, CH=N) 7.9–8.3(m, 4H, m-NO_2), 8.0(d, J = 8.2 Hz, 2H), 7.9(d, J = 8.2Hz, 2H), 7.4–7.7(m, 5H, Ar-H phenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 129.5(2C), 129.0(2C), 131.1, 149.6, 140.7, 118.8(2C), 129.7(2C), 126.4, 135.1, 117.0, 146.3, 168.5, 108.5, 148.6, 134.0, 132.0, 130.5, 121.0, 140.5, 122.5; MS (EI, 70 eV): *m*/*z* (%): 500(M^+, 100); Analysis calcd. for $C_{25}H_{17}ClN_6O_2S$: C, 59.94; H, 3.42; N, 16.78; found: C, 60.10; H, 3.12 ; N, 16.45.

1-((3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene]-2-(4-(4-Nitro-phenyl)thiazol-2-yl)hydrazine (**4j**) mp: 230–233 °C; IR (KBr, cm^{-1}): 3355(NH), 1555 (C=C), 1610(C=N), 3320, (Ar-H), 950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0(bs, 1H, NH), 8.9(s, 1H, pyrazolyl-H), 7.6 (s, 1H, thiazolyl-H), 8.0 (s, 1H, CH=N), 7.8(d, J = 8.3 Hz, 2H), 8.2(d, J = 8.3Hz, 2H), 7.9(d, J = 8.1Hz, 2H), 8.3(d, J = 8.1 Hz, 2H), 7.3–7.6(m, 5H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 150.0, 148, 146.2, 140.7, 138.0, 135.0, 109.1, 117.2, 119.0(2C), 129.9(2C), 126.0, 125.5(2C), 129.6(2C), 136.4, 128.8, 124.0(2C), 127.0(2C), 132.2; MS (EI, 70 eV): *m*/*z* (%): 544(M^+, 100).

1-((3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene]-2-(4-(3-Nitro-phenyl)thiazol-2-yl)hydrazine (**4k**) mp: 212–215 °C; IR (KBr, cm^{-1}): 3350(NH), 1550 (C=C), 1620(C=N), 3315, (Ar-H), 1330, 1540(NO_2) 950; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1(bs, 1H, NH), 9.0(s, 1H, pyrazolyl-H), 7.5 (s, 1H, thiazolyl-H), 8.4 (s, 1H, CH=N), 8.3–8.5(m, 4H, m-NO_2 phenyl ring), 7.9(d, J = 8.3 Hz, 2H), 8.1(d, J = 8.3 Hz, 2H), 7.4–7.6(m, 5H, Ar-H phenyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.8, 131.5(2C), 129.1(2C), 131.9, 149.4, 140.7, 118.7(2C), 129.7(2C), 126.4, 135.0, 117.2, 146.3, 167.9, 108.5, 148.5, 134.0, 132.0, 130.2, 121.1, 139.9, 122.5; MS (EI, 70 eV): *m*/*z* (%): 544(M^+, 100); Analysis calcd. for $C_{25}H_{17}BrN_6O_2S$: C, 55.05; H, 3.14; N, 15.41; found: C, 55.25; H, 3.35; N, 15.15.

1-((3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene]-2-(4-(4-chloro-phenyl)thiazol-2-yl)hydrazine (**4l**) mp: 235–237 °C; IR (KBr, cm^{-1}): 3350(NH), 1550 (C=C), 1610(C=N), 3323, 3021(Ar-H), 960, 850, 720; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0(bs, 1H, NH), 8.9(s, 1H, pyrazolyl-H), 7.7 (s, 1H, thiazolyl-H), 8.1 (s, 1H, CH=N), 7.9(d, J = 8.2 Hz, 2H), 8.1(d, J = 8.2 Hz, 2H), 7.7(d, J = 8.3Hz, 2H), 8.2(d, J = 8.3 Hz, 2H), 7.4–7.6(m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 149.6, 148.6, 146.3, 140.7, 139.0, 135.1, 108.5, 117.0, 118.8(2C), 129.7(2C), 126.4, 125.3(2C), 131.5(2C), 130.6, 128.7, 124.2(2C), 127.1(2C), 132.0; MS (EI, 70

eV): *m*/*z* (%): 533(M^+,100); Analysis calcd. for $C_{25}H_{17}BrClN_5S$: C, 56.14; H, 3.20; N, 13.09; found: C, 56.54; H, 3.64; N, 12.89.

6. Conclusions

In conclusion we have developed a new series of pyrazole derivatives containing thiazole heterocyclic rings. In vitro antimicrobial assay showed that most of the synthesized compounds showed good activity as compared to standard drugs. From the biological activity report it can be concluded that pyrazole and thiazole heterocyclic rings play an important role in deciding the biological activity. It was therefore of interest to explore these azoles for additional modification in order to design new heterocycles as a potent drugs.

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