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

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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, thiosemicarbazides and α-haloketones in one pot afforded the target molecules. The synthesis was carried out via two methods: one conventional method, whereby pyrazole 4-carbaldehydes, thiosemicarbazides, and α-haloketones were refluxed in ethanol; and a second way, where the reaction mixture was ground at RT. The rate of the reaction, yield of the products, and purity of the products were compared for both methods. All of 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; thiosemicarbazides; one pot; antimicrobial activities

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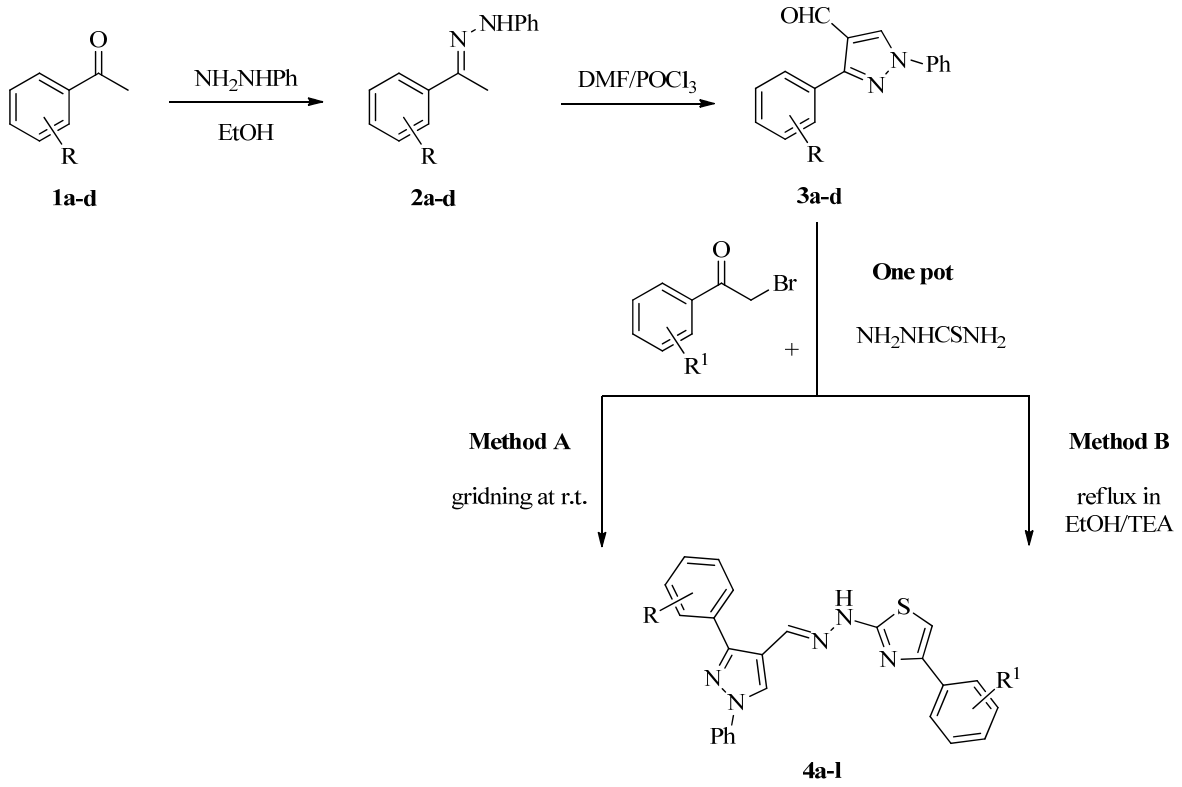
1. Introduction

The importance of new biologically active molecules in the pharmaceutical industry has encouraged chemists to engage in their capable and fast synthesis, so as to provide useful benefits for society. Today, modern and fast technologies have motivated scientists and researchers to synthesize and develop new effective drug molecules. The synthesis and design of pyrazole and thiazole derivatives are of great interest due to their extensive applications in the pharmaceutical and agrochemical industries. The interest in the study of pyrazole chemistry is still ongoing due to its broad spectrum of biological activities, such as antibacterial [1–6], antiviral [7,8], antiproliferative, proapoptotic [9], antitumor [10], anti-inflammatory [11,12], and herbicidal activities [13]. Furthermore, thiazole heterocycles are a noteworthy class of heterocyclic compounds that are present in several important biologically dynamic drug molecules, such as the antiretroviral drug ritonavir, the antimicrobial drug sulfathiazole, the antineoplastic drug tiazofurin, and the antifungal drug abafungin [14]. Thiazole-containing heterocycles show various biological activities, such as antifungal [15], anticancer [16–20], and anti-HIV activity [21], as well as acting as a metabotropic glutamate receptor 1 (mGluR1) antagonist [22]. On the other hand, it has been observed that when thiazole is in combination with the pyrazole nucleus, it exhibits different biological activities, including antitubercular [23–28], anti-inflammatory, and antimicrobial effects [29,30], as well as acting as a protein synthase III (FabH) inhibitor [31].

All of these observations inspired us to design and synthesize new effective drug molecules containing thiazole and pyrazole nuclei together, and to assess 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 study we synthesized a new derivative of heterocycles containing pyrazole and thiazole molecules in one component, which may show more effective biological activities.

In an extension of our work [32–35] on the preparation of new products with combinations of dissimilar heterocyclic moieties as possible antimicrobial agents, we report here the synthesis of some new pyrazole derivatives containing thiazole scaffolds. The intermediate pyrazole carbaldehydes **3a–d** were synthesized by a known method from the literature [36,37]. A series of pyrazole-containing thiazole derivatives **4a–l** (Scheme 1) were synthesized, and all of 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 of the synthesized compounds **4a–l** was characterized by analysis of IR, ^{1}H NMR, ^{13}C NMR, mass, and elemental spectra. The IR bands at 3300–3340, 1545–1550, and 1620–1640 cm^{-1} showed the presence of NH, C=C, and C=N, respectively. In the ^{1}H NMR spectra, a broad signal appeared at 12.1 ppm due to NH, a singlet appeared at 9.1–9.2 ppm due to a pyrazolyl proton, a singlet appeared at 7.68 ppm due to a thiazolyl proton, and a multiplet appeared at 7.4 to 8.3 ppm due to aromatic protons. The molecular ion peaks of all of the synthesized compounds were obtained from EI-MS, while the

presence of M+2 peaks were characteristic for the compounds with chlorine, bromine, and sulfur atoms. Analogously, all other compounds were characterized by spectroscopic and analytical data, which are presented in the Experimental Section.

The grinding of aldehydes with thiosemicarbazides and α-haloketones was carried out at room temperature to afford the corresponding 2,4-disubstituted thiazole derivatives at a high yield (80–90%). In a typical procedure, pyrazole aldehydes react with thiosemicarbazides and α-haloketones 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 as shown in Table 1. The reaction was completed after grinding for 4 min, and afforded a 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-carbaldehydes. It was observed that all reactions were completed within 5–10 min by grinding without any catalyst or solvent at ambient temperature. However, highly efficient grinding was required for the success of these reactions. When attempts were made to carry out the synthesis of thiazole derivatives by conventional methods in ethanol under reflux temperature, it required more time, and the yield of the products was in the range of 60–70% (Table 1). In general, reactions under solvent-free conditions were clean, rapid, and afforded higher yields than those obtained via conventional methods in ethanol.

Table 1. Table showing the differences between the conventional and solvent-free methods.

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 of 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 Gram-positive and Gram-negative bacteria. It was noted that the substituent R on the phenyl ring does not affect the biological activity to a large extent, but the substituent R^1 was found to play important role in determining the biological activity. It was observed that when R^1 was a strong electron-withdrawing compound similar to NO_2 (i.e., compounds **4a**, **4d**, **4g**, and **4j**), it showed enhancements in antifungal as well as antibacterial activities, as compared to compounds **4c**, **4f**, **4i**, and **4l**, where the substituent R^1 was 4-Cl. The derivatives in which the R^1 group was at position 3 (i.e., compounds **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

Chloramphenicol (100 µg/disc) and nystatin (100 µg/disc) were used as references; synthesized compounds (100 µg/disc); NA = not applicable; (-) = inactive.

4. Experimental Section

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

A mixture of substituted acetophenones **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 via TLC, the reaction mixture was cooled at room temperature. The product was filtered, washed with water, dried, and recrystallized from ethanol. Physical data of compound **2a–d** is mentioned in Table 3.

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

Compound	Color	m.p. (°C)	R_f Value/Solvent System (Hexanes: Ethyl Acetate)	Yield (%)
2a	Brown	140–143	0.1/6:4	85
2b	Pale yellow	132–135	0.15/6:4	80
2c	Pale yellow	135–138	0.18/6:4	84
2d	Brown	126–129	0.1/6:4	86

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

To a well-stirred and cooled (0 °C) DMF solution (12 mL), $POCl_3$ (6 mL) was added dropwise for 1 h. After complete addition of $POCl_3$, the reaction mixture was further stirred at 0 °C for 1 h. To this well-stirred and cooled reaction mixture, a solution of **2a–d** (1 mol) in anhydrous DMF (10 mL) was added dropwise for one hour; after complete addition, the reaction mixture was heated at 65–70 °C for 2 h. The reaction mixture was poured onto crushed ice and left overnight in a refrigerator, during which time the product separated out as a solid mass. The product was filtered, washed with Na_2CO_3 (5%, 30 mL) and water, and recrystallized from the DMF–ethanol mixture. Physical data of compound **3a–d** is mentioned in Table 4.

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

Compound	Color	m.p. (°C)	R_f Value/Solvent System (Hexanes: Ethyl Acetate)	Yield (%)
3a	Brown	135–138	0.27/7:3	78
3b	Pale yellow	147–150	0.31/7:3	73
3c	Pale yellow	137–140	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 ground thoroughly with a pestle and mortar at room temperature for 5–10 min. The progress of the reaction was monitored by TLC (ethyl acetate/hexanes 3:7). After completion of the reaction, the mixture was washed with water and recrystallized from ethanol to yield 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 3 h. The reaction mixture was cooled at room temperature and poured onto 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**) m.p.: 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* = 7.9 Hz, 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 calculated 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**) m.p.: 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 calculated 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**) m.p.: 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* = 8.3 Hz, 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 calculated 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**) m.p.: 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* = 7.9 Hz, 2H), 7.9 (d, *J* = 7.9 Hz, 2H), 8.3 (d, *J* = 8.1 Hz, 2H), 8.1 (d, *J* = 8.1 Hz, 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 calculated 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**) m.p.: 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* = 7.9 Hz, 2H), 7.5–7.7 (m, 5H, Ar-H phenyl); MS (EI, 70 eV): *m*/*z* (%): 511 (M^+, 100); Analysis calculated 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**) m.p.: 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* = 8.2 Hz, 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 calculated 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**) m.p.: 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 calculated 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**) m.p.: 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 calculated 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**) m.p.: 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 calculated 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**) m.p.: 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* = 8.3 Hz, 2H), 7.9 (d, *J* = 8.1 Hz, 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**) m.p.: 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 calculated 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**) m.p.: 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* = 8.3 Hz, 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 calculated 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 developed a new series of pyrazole derivatives containing thiazole heterocyclic rings. The 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 determining the biological activity. It was therefore of interest to explore these azoles for additional modification in order to design new heterocycles for use as potent drugs.

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