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Synthesis, characterization and antimicrobial activity of pyrazole derivatives

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This study synthesized pyrazole derivatives from pyrazoline and evaluated them for antibacterial activity. From benzofuran-5-carbaldehyde and 1-(1,2,3,4-thiatriazol-5-yl)hydrazine, compound **1** is formed under reflux. Then DMF and $POCl_3$ is added at 70°C for 5 h to the compound **1** to get compound **2**. To a mixture of compound **2**, acetophenone in ethanol and KOH is added and stirred under reflux for 6 h to get compound **3**. From the compound **3**, different pyrazole derivatives have been synthesized. All the desired compounds have been successfully synthesized and characterized by ^{1}H and ^{13}C NMR and LCMS. The antimicrobial activity has been tested using a serial dilution approach against several Gram-positive and Gram-negative bacteria. Compounds **1**, **3**, **5**, **6**, **8** and **9** show greater antimicrobial activity against several Gram-positive and Gram-negative bacteria.

Keywords: Benzofuran, Pyrazole, Thiatriazole, Antimicrobial activity

The study of heterocyclic compounds is still a developing area in organic chemistry[1]. Pyrazole is one of the heterocyclic compounds. A crucial group of manufactured and naturally occurring compounds, pyrazoles reveal a wide range of biological activities[2-3]. Pyrazoles have a wide range of medicinal uses, including herbicides, antitumor, hypoglycemia, antimicrobial, antidepressant, analgesic, anti-inflammatory, anti-cancer and enzyme inhibitor[4-10]. Pyrazole derivatives have been the subject of a great deal of research because of their widespread biological activity varied chemical reactivity, and pivotal role in the development of heterocyclic chemistry[11].

Where as triazoles, which are heterocyclic molecules with three adjacent nitrogen atoms, exhibit unexpected stability[12]. The chemical, pharmaceutical, supra-molecular, agricultural and materials science industries have shown great interest in triazole derivatives due to their many purportedly useful uses[13-16]. When it comes to drug design and heterocyclic chemistry, thiotriazoles and bis-heterocycles are two of the most significant moieties[17]. The thiotriazole motif is present in many pharmaceutically active chemicals and in naturally occurring molecules. In keeping with our continuing research on interesting new and synthetic protocols, as well as the preparation of diverse biologically active heterocyclic compounds[18-21]. This study can successfully accomplish a simple synthetic procedure for the synthesis of novel series of heterocycles[22]. Based on the aforementioned information, pyrazole-thiotriazole based hybrids were designed and synthesized. The compounds that were produced were identified using ^{1}H and ^{13}C NMR, and mass spectrometry. This study details the results of an evaluation of their antimicrobial effects.

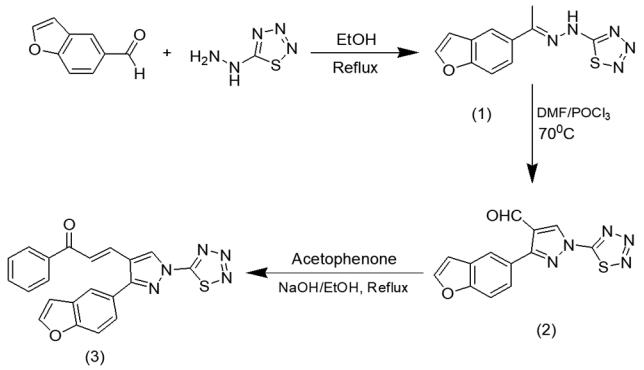
Results and Discussion

According to the designed structures nine pyrazole derivatives was synthesized. The synthesis of compound **1** was carried out by refluxing 1-(1,2,3,4-thiatriazol-5-yl)hydrazine and the substituted benzofuran-5-carbaldehyde in 100% ethanol. The first a compound was converted into the corresponding 4-carboxaldehyde-functionalized pyrazoles **2** under 70°C in a DMF-$POCl_3$ conditions. The acetophenone undergo a reaction with the EtOH–H_2O, KOH/NaOH solution, resulting in the formation of the significant intermediate **3** (Scheme 1).

Subsequently, the compounds **3** underwent treatment with the reagents NH_2NH_2, ethanol, reflux will give compound **4**. Then the compound **3** is treated with NH_2NH_2/AcOH ethanol, reflux it will give the derivative of pyrazole **5**. Forthermore the the pyrazole derivatives (**6**, **7**, **8**, **9**) are formed when the compound **3** is treated with NH_2NH_2/HCO_2H, and benzohydrazide, ethanol, reflux semicarbazide hydrochloride, ethanol, reflux and add thiosemicarbazide, ethanol, reflux at 70°C (Scheme 2).

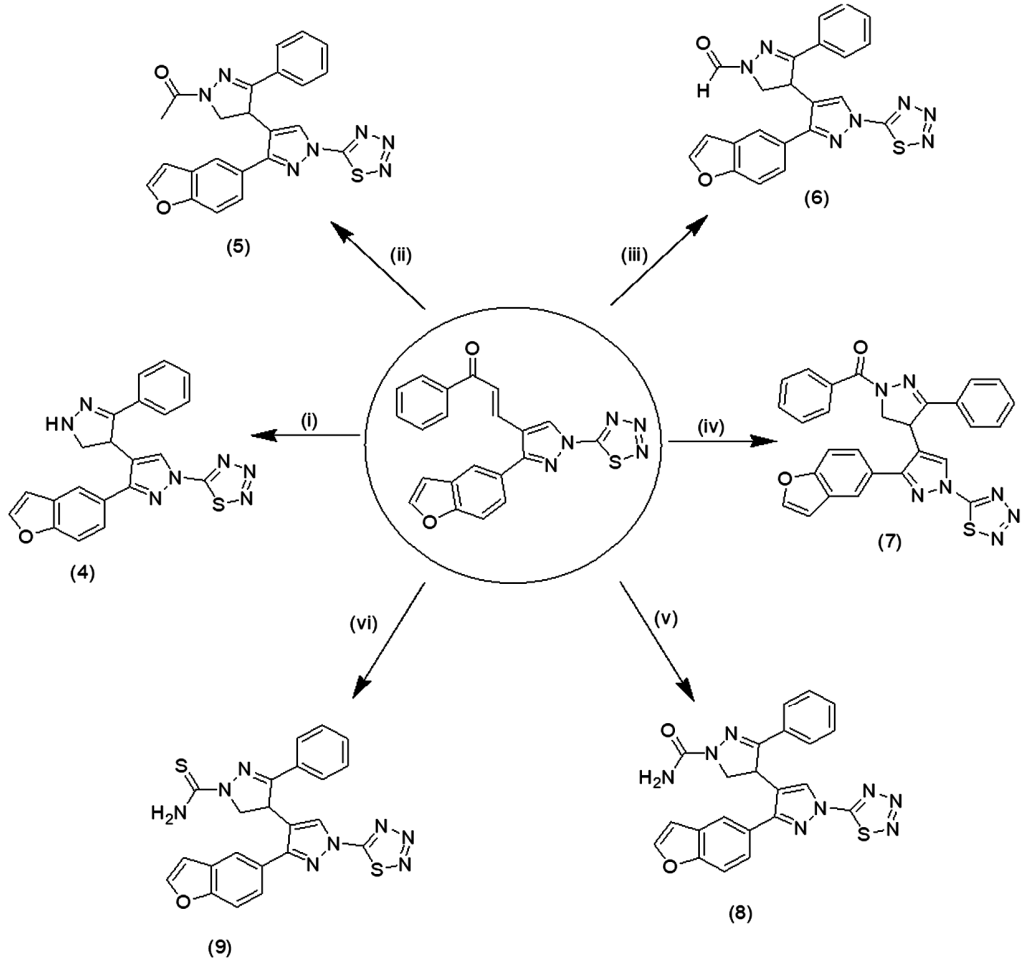
Antimicrobial activity

The anti-bacterial activity of all target compounds was tested *in vitro* using a serial dilution approach. The minimum inhibitory concentration (MIC) was determined against a variety of bacterial strains, including Gram-positive and Gram-negative. Penicillin and Norfloxacin were employed as positive controls (Fig. 1).



Scheme 1 — The synthetic route to intermediate **3**

The antimicrobial screening findings are reported as MIC values in Table 1. The antibacterial activity of all compounds was greater when tested against some strains with MIC values. The Gram-positive and Gram-negative bacteria including Staphylococcus aureus and Enterococcus faecalis, Bacillus subtilis, Pseudomonas aeruginosa, were more susceptible to the majority of the substances. The compounds (**1**, **3**, **5**, **6**, **8**, **9**) Showed greater activity compared to the other compounds. Similarly, the inhibitory action of the reference medicines penicillin and norfloxacin was examined using the same conditions. Clearly our compounds showed far better inhibitory action than penicillin and norfloxacin.



Reagents and Conditions: (i) NH_2NH_2, ethanol, reflux, (ii) NH_2NH_2, AcOH, ethanol, reflux, (iii) NH_2NH_2, HCO_2H, ethanol, reflux, (iv) Benzohydrazide, ethanol, reflux, (v) Semicarbazide hydrochloride, ethanol, reflux, (vi) Thiosemicarbazide, ethanol, reflux.

Scheme 2 — The synthesis of target compounds **4**, **5**, **6**, **7**, **8** and **9**

Experimental Section

All compounds were of analytical grade and they were distilled before use in accordance with conventional procedure. The melting points were measured in uncorrected open capillary tubes. An AV-300 spectrometer from Bruker was used to record ^{1}H and ^{13}C NMR spectra and all chemical shifts were expressed as parts per million relative to tetramethylsilane. Elemental analysis CHN was done using Elementar Vario EL III analyzer. The KBr pellets used to record the FT-IR spectra were analyzed using a Thermo Nicolet Avatar370 spectrophotometer. Mass spectra were recorded on SHIMADZU LCMS 2020 mass spectrometers. The progress of reactions was monitored by TLC (Silica gel, aluminium sheets 60 F254, Merck).

General procedure for the synthesis of compounds

The compounds that were investigated have been synthesized by following the steps outlined in Scheme 1 and Scheme 2. Benzofuran-5-carbaldehyde (1.08 g, 0.01 M) and acetophenone (1.20 g, 0.01 M) were combined in absolute ethanol and heated under reflux for 6 hours. The progress of the reaction was monitored using TLC with a developing system of 20% EtOAc in ether. Compound **1** was obtained through the process of cooling and subsequently crystallized from absolute ethanol, resulting in a yield of 88%.

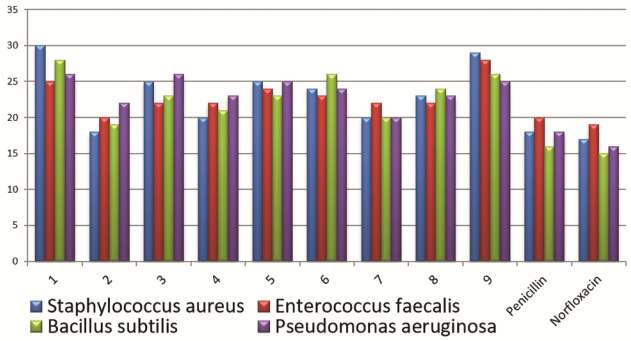


Fig. 1 — Graphical representation of antimicrobial activities of compounds

Compound **1** was added drop-wise to ice-cooled N,N-Dimethyl formamide (18.25 g, 250 mmol) along with $POCl_3$ (6.12 g, 40 mol). The mixture was then agitated at 70°C for 5 hours while TLC monitored the reaction using a developing solution of 30% CH_2Cl_2 in ether. The reaction mixture was poured into crushed ice to obtain a crude product. This product was then filtered and crystallized from ethanol, resulting in the compound **2** with a yield of 81%.

The reagent **2** (1.24 g, 5 mmol) and acetophenone (0.60 g, 5 mmol) in 40 mL of pure ethanol were combined with 8 mL of a 40% KOH solution. The combination was then agitated under reflux for 6 hours while TLC monitored the reaction using a developing system of 30% CH_2Cl_2 in ether. We obtained compound **3** with a yield of 78% by filtering the precipitated solid after cooling, rinsing it with water and then recrystallizing it from ethanol.

Add 80% hydrazine hydrate (4 mmol) to a solution of compound **3** (0.70 g, 2 mmol) in 20 mL of absolute ethanol, and reflux for 1 hour while using a TLC apparatus that monitored the reaction with a 15% EtOAc in ether developing system. Compound **4** was obtained with a yield of 75% by filtering the precipitated solid after cooling and recrystallizing it from ethanol. To get compounds (**5**, **6**, **7**, **8** and **9**) respectively, the reagents NH_2NH_2/AcOH, benzohydrazide, semicarbazide hydrochloride, and thiosemicarbazide were used in place of 80% of the hydrozine hydrate, following a process similar to that of compound **3**. The following sections include a list of spectral data.

(E)-1-(1-(Benzofuran-5-yl)ethylidene)-2-(1,2,3,4-thiatriazol-5-yl)hydrazine, 1: Yield 88%. m.p. 180-182°C. IR (KBr): 1616 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.48 (s, 3H-CH_3), 7.07 (s, 1H-

Table 1 — Inhibitory activity (MIC, µM) of compounds

Compd	*Staphylococcus aureus*	*Enterococcus faecalis*	*Bacillus subtilis*	*Pseudomonas aeruginosa*
1	30	25	28	26
2	18	20	19	22
3	25	22	23	26
4	20	22	21	23
5	25	24	23	25
6	24	23	26	24
7	20	22	20	20
8	23	22	24	23
9	29	28	26	25
Penicillin	18	20	16	18
Norfloxacin	17	19	15	16

CH), 7.62 (d, *J*=0.9Hz, 2H-ArH), 7.85 (s, 1H-CH), 8.00 (s, 1H-ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 15.45, 105.97, 114.81, 121.49, 124.94, 126.89, 133.52, 146.35, 148.35, 156.47, 181.47. LCMS: *m/z* 259.10. Found: 259.49. Anal. Calcd for $C_{11}H_9N_5OS$: C, 50.95; H, 3.50; N, 27.01. Found: C, 50.97; H, 3.52; N, 27.03%.

3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazole-4-carbaldehyde, 2: Yield 81%. m.p. 185-187°C. IR (KBr): 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.05 (s, 1H-CH), 7.54 (d, *J*=1.9Hz, 2H-ArH), 8.07 (m, 2H-ArH), 9.69 (s, 1H-CHO); ^{13}C NMR (DMSO-d_6, 75MHz): δ 105.97, 115.98, 120.05, 124.40, 124.72, 126.32, 13.0.50, 132.50, 146.35, 156.34, 164.35, 179.42, 185.82. LCMS: *m/z* 297.12. Found: 297.52. Anal. Calcd for $C_{13}H_7N_5O_2S$: C, 52.52; H, 2.37; N, 23.56. Found: C, 52.55; H, 2.38; N, 23.59%.

(E)-3-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one, 3: Yield 78%. m.p. 180-182°C. IR (KBr): 1615 (C=N), 1680 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.28 (s, 1H-CH), 7.78 (m, 3H-ArH), 8.04 (m, 4H-ArH), 8.12 (s, 4H-ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 105.97, 115.83, 120.52, 122.61, 124.85, 126.79, 128.94, 130.05, 133.00, 138.10, 146.35, 158.23, 158.23, 169.16, 179.42, 191.43. LCMS: *m/z* 399.62. Found: 399.20. Anal. Calcd for $C_{21}H_{13}N_5O_2S$: C, 63.15; H, 3.28; N, 17.53. Found: C, 63.20; H, 3.30; N, 17.55%.

5-(3-(Benzofuran-5-yl)-4-(4,5-dihydro-3-phenyl-1*H*-pyrazol-4-yl)-1*H*-pyrazol-1-yl)-1,2,3,4-thiatriazole, 4: Yield 75%. m.p. 186-188°C. IR (KBr): 1620 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.11 (s, 2H-CH_2), 3.88 (s, 1H-CH), 6.87 (s, 1H-NH), 7.16 (m, 3H-ArH), 7.36 (m, 3H, ArH), 7.73 (m, 3H, ArH), 7.85 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 48.36, 57.39, 105.97, 115.83, 122.61, 124.72, 126.79, 127.32, 128.06, 128.78, 130.05, 132.08, 140.68, 146.35, 153.78, 158.23, 167.73, 179.42. LCMS: *m/z* 413.70. Found: 413.50. Anal. Calcd for $C_{21}H_{15}N_7OS$: C, 61.00; H, 3.66; N, 23.71. Found: C, 61.02; H, 3.69; N, 23.74%.

1-(4-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-3-phenylpyrazol-1-yl)ethanone, 5: Yield 78%. m.p. 184-186°C. IR (KBr): 1620 (C=N), 1650 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.04 (s, 3H-CH_3), 3.73 (s, 2H-CH_2), 4.16 (s, 1H-CH), 7.09 (m, 2H-CH), 7.51 (m, 3H, ArH), 7.78 (m, 4H, ArH), 8.00 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 22.12, 50.84, 105.97, 115.83, 122.61, 125.61, 126.79, 127.73, 128.85, 130.05, 132.24, 140.90, 146.35, 155.41, 158.23, 166.12, 167.73, 179.42. LCMS: *m/z* 455.12. Found: 455.51. Anal. Calcd for $C_{23}H_{17}N_7OS$: C, 60.65; H, 3.76; N, 21.53. Found: C, 60.68; H, 3.79; N, 21.54%.

4-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-3-phenylpyrazole-1-carbaldehyde, 6: Yield 76%. m.p. 185-187°C. IR (KBr): 1650 (C=N), 1750 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50 (s, 2H-CH_2), 4.52 (s, 1H-CH), 7.46 (m, 2H-CH), 7.72 (m, 3H-ArH), 7.89 (m, 3H, ArH), 8.40 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 52.19, 54.86, 105.97, 115.83, 122.61, 125.16, 126.79, 127.73, 128.85, 130.05, 132.24, 140.90, 146.35, 154.87, 158.23, 166.20, 167.73, 179.42. LCMS: *m/z* 444.15. Found: 444.70. Anal. Calcd for $C_{22}H_{15}N_7O_2S$: C, 59.85; H, 3.42; N, 22.21. Found: C, 59.89; H, 3.46; N, 22.25%.

(4-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-3-phenylpyrazol-1-yl)(phenyl)methanone, 7: Yield 73%. m.p. 183-185°C. IR (KBr): 1616 (C=N), 1650 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.73 (s, 2H-CH_2), 4.60 (s, 1H-CH), 7.10 (m, 2H-CH), 7.27 (m, 4H-ArH), 7.57 (m, 3H, ArH), 7.68 (m, 3H, ArH), 8.26 (m, 4H-ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 50.88, 52.80, 105.97, 115.83, 122.61, 125.16, 126.79, 127.83, 129.11, 130.05, 131.73, 132.24, 140.90, 146.35, 150.81, 158.23, 163.14, 167.73, 179.42. LCMS: *m/z* 517.12. Found: 517.42. Anal. Calcd for $C_{28}H_{19}N_7O_2S$: C, 64.98; H, 3.70; N, 18.94. Found: C, 64.99; H, 3.72; N, 18.96%.

4-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-3-phenylpyrazole-1-carboxamide, 8: Yield 76%. m.p. 182-184°C. IR (KBr): 1605 (C=N), 1750 (C=O), 3450 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70 (s, 2H-CH_2), 4.68 (s, 1H-CH), 5.97 (s, 2H-NH_2), 6.11 (m, 3H-ArH), 7.26 (m, 3H, ArH), 7.41 (m, 3H, ArH), 7.57 (m, 2H-ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 47.29, 50.88, 105.97, 115.83, 122.61, 125.16, 126.79, 127.83, 128.85, 130.05, 132.24, 140.90, 146.35, 153.62, 157.80, 158.23, 167.33, 179.42. LCMS: *m/z* 456.26. Found: 456.42. Anal. Calcd for $C_{22}H_{16}N_8O_2S$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.92; H, 3.56; N, 24.57%.

4-(3-(Benzofuran-5-yl)-1-(1,2,3,4-thiatriazol-5-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-3-phenylpyrazole-1-carbothioamide, 9: Yield 78%. m.p. 185-187°C. IR (KBr): 1030 (C=S), 3500 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.92 (s, 2H-CH_2), 4.40 (s, 2H-CH), 6.87 (s, 2H-NH_2), 7.06 (s, 1H-CH), 7.32 (m, 3H, ArH), 7.67 (m, 3H, ArH), 7.83 (m, 2H-ArH); ^{13}C NMR (DMSO-d_6, 75MHz): δ 48.60, 50.88, 105.97, 115.83, 122.61, 125.16, 126.79, 127.73, 128.85, 130.05, 132.24, 140.90, 146.95, 158.23, 160.80, 167.73, 179.36. LCMS: *m/z* 472.30. Found: 472.24. Anal. Calcd for $C_{22}H_{16}N_8OS_2$: C, 55.92; H, 3.41; N, 23.71. Found: C, 55.94; H, 3.45; N, 23.75%.

Conclusion

In conclusion, pyrazole derivatives were developed and tested for their antibacterial properties. A series of dilution method was used to assess the antibacterial activity against a variety of Gram-positive and Gram-negative bacteria. As far as antibacterial activity against various Gram-positive and Gram-negative bacteria is concerned, compounds (**1**, **3**, **5**, **6**, **8**, **9**) exhibit somewhat higher levels. Component **3** was used to create a number of pyrazole derivatives. All of the compounds that were generated were characterized using ^1H and ^{13}C NMR, and LCMS.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Conflict of interest

The authors of this work do not have any conflicting interests that might be affected by the publishing of this work.

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