AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Carbohydrazides as Precursors for the Synthesis of Heterocycles Having Pyrazole Benzofuran Moiety and their Biological Evaluation

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ABSTRACT

5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides **1a-b** on reaction with phenylisothiocyanate, potassium thiocyanate, carbon disulphide in pyridine and carbon disulphide in KOH followed by hydrazine hydrate afforded nitrogenous, sulphur bridgehead heterocycles **2-5a-d** respectively. The structures of the newly synthesized compounds were elucidated by elemental analysis and spectral data such as IR, ^{1}H NMR, ^{13}C NMR and mass spectra. In addition the *in vitro* antibacterial and antifungal properties were tested for these synthesized compounds against *B. subtilis, S. aureus, E. coli, P. aeruginosa* and *A. niger* compared with ampicillin and clotrimazole as reference drugs. Synthesized compounds were found to possess moderate to excellent activity against selected strains.

Keywords: Phenylthiosemicarbazides, thiosemicarbazide, 4-amino-[1, 2, 4]triazole-thione, 1,3,4-oxadiazole-thione

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Received 08 December 2014, Accepted 12 December 2014

Please cite this article as: Siddiqui NJ *et al.*, Carbohydrazides as Precursors for the Synthesis of Heterocycles Having Pyrazole Benzofuran Moiety and their Biological Evaluation. American Journal of PharmTech Research 2015.

INTRODUCTION

Several benzofuran ring systems bearing various substituents at C-2 and C-3 positions are widely distributed in nature, [1] e.g. ailanthoidol,[2] amiodarone[3] etc. On the other hand compounds consisting pyrazole nucleus are known to possess various pharmacological activities.[4] During last three decades organo-sulfur chemistry has developed at a faster stride than any other branches of organic chemistry.[5] The synthetic potential of the functional group $–CONHNH_2$ in substituted pyrazoles has been utilized as the building blocks for the synthesis of a variety of nuclei of various oxygen, nitrogen and / or sulphur containing heterocycles such as thiosemicarbazides,[6] mercapto and thione-substituted 1,2,4-triazoles.[7-11] Triazole units have attracted substantial attention in fields such as medicinal and agrochemical research as well as in the material sciences due to their unique structure and properties.[12] 1, 2, 4-triazole ring is a pervasive structural feature of many synthetic compounds with diversified therapeutic competency such as analgesic,[13] antitubercular,[14] anticonvulsant and antidepressant.[15] In view of these findings and in continuation to our previous work[16] we have reported here synthesis of some novel nitrogenous, sulphur bridgehead heterocycles such as substituted/unsubstituted thiosemicarbazides, 1,3,4-oxadiazole-thiones and 4-amino[1,2,4]triazole-3-thiones from 5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides by adopting the reported procedures[7] with the purpose of investigating their possible antibacterial and antifungal activities.

MATERIALS AND METHOD

The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, v max in cm^{-1}). ^1H NMR and ^{13}C NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 and $CDCl_3$ as solvent. Chemical Shifts are given in parts per million (ppm). Positive-ion electrospray ionisation (ESI) mass spectra were obtained with a Waters Micromass Q–TOF Micro, Mass Spectrophotometer. Elemental analysis (CHN) was done using Elemental analyzer, Vario EL III. All the chemicals used for the synthesis were of AR grade of Merck, S.D.Fine and Aldrich. The reactions were monitored by E.Merck TLC aluminum sheet silica $gel_{60}F_{254}$ and visualizing the spot in UV Cabinet and iodine chamber. The compounds were analyzed for carbon, hydrogen, nitrogen and sulphur and the results were in good agreement with the calculated values.

Experimental Procedure

General procedure for the synthesis of 5-(substituted/unsubstituted benzofuran-2-yl)-1-

phenyl-1*H*-pyrazole-3-carbohydrazides (1a-d).[16]

General procedure for the synthesis of 1-(5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazides (2a-d): A mixture of **1a** (10 mmol) and phenylisothiocyanate (11 mmol) in chloroform (30 mL) was refluxed for 1.5h. The reaction mixture was cooled, excess of chloroform was evaporated, solid obtained was washed with water, filtered and further purified by recrystallization using 1,4-dioxane to give **2a**. Similarly, **2b-d** were synthesized from **1b-d** by extending the same procedure followed for **2a** and their structural demarcation were further proved by spectral and analytical measurements.

General procedure for the synthesis of 1-(5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbonyl) thiosemicarbazides (3a): A mixture of **1a** (10 mmol), potassium thiocyanate (20 mmol), water (50 mL) and conc. HCl (10 mL) was refluxed for 4h. The reaction mixture was then cooled then, poured in water, filtered, washed and further purified by recrystallization using 1,4-dioxane to give **3a**. Similarly, **3b-d** were synthesized from **1b-d** by adopting the same procedure as adopted for **3a** and their structural characterization proved by spectral and analytical records.

General procedure for the synthesis of 5-(5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thiones (4a-d): A mixture of **1a** (10 mmol), CS_2 (30 mL) and pyridine (100 mL) was refluxed on water bath for 6h. The reaction mixture was cooled and the residue obtained was triturated with ice-water mixture and neutralized with dilute HCl. The solid obtained was filtered and further recrystallized from ethanol to afford **4a.**

Similarly, **4b-d** were synthesized from **1b-d** by extension of the same procedure adopted for **4a** and their structural capability were proved by spectral and analytical techniques.

General procedure for the synthesis of 4-amino-5-(5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thiones (5a-d): This can be synthesised by two different ways.

Method 1: This is a two-step reaction.

Step I: Synthesis of potassium-3-[substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-yl carbonyl]-dithiocarbazates: CS_2 (15 mmol) was added drop wise to a solution of **1a** (10 mmol) in absolute ethanol (20 mL) containing KOH (15 mmol). To this absolute ethanol (15 mL) was added and the reaction mixture was agitated for 12h. To it dry ether (25 mL) was added, product was filtered off and dried at 65 $^{\circ}$C to obtain the potassium salt which was used for further without purification.

Step II: Synthesis of 4-amino-5-(5-(substituted/ unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thiones (5a-d): A suspension of potassium salt (20 mmol), 95% hydrazine hydrate (40 mmol) and water (2 mL) was refluxed with stirring for 1h. The colour of the reaction mixture changed to green, H_2S was evolved and the resultant homogeneous solution was added to ice cold water. The solid **5a** was separated out by acidification with conc. HCl, filtered and washed by cold water (2 x 30 mL) and recrystallized from ethanol.

Method 2: This is a one-step reaction

A mixture of **4a** (1 mmol), hydrazine hydrate (3 mL) and ethanol (10 mL) was refluxed on water bath for 6h. The reaction mixture was cooled and the residue obtained was triturated with water, the solid obtained was filtered and further recrystallized from ethanol to afford **5a.**

Similarly, **5b-d** were synthesized from **1b-d** and **4b-d** by extending the same procedure followed for **5a** and their structural characterization were proved by spectral and analytical techniques.

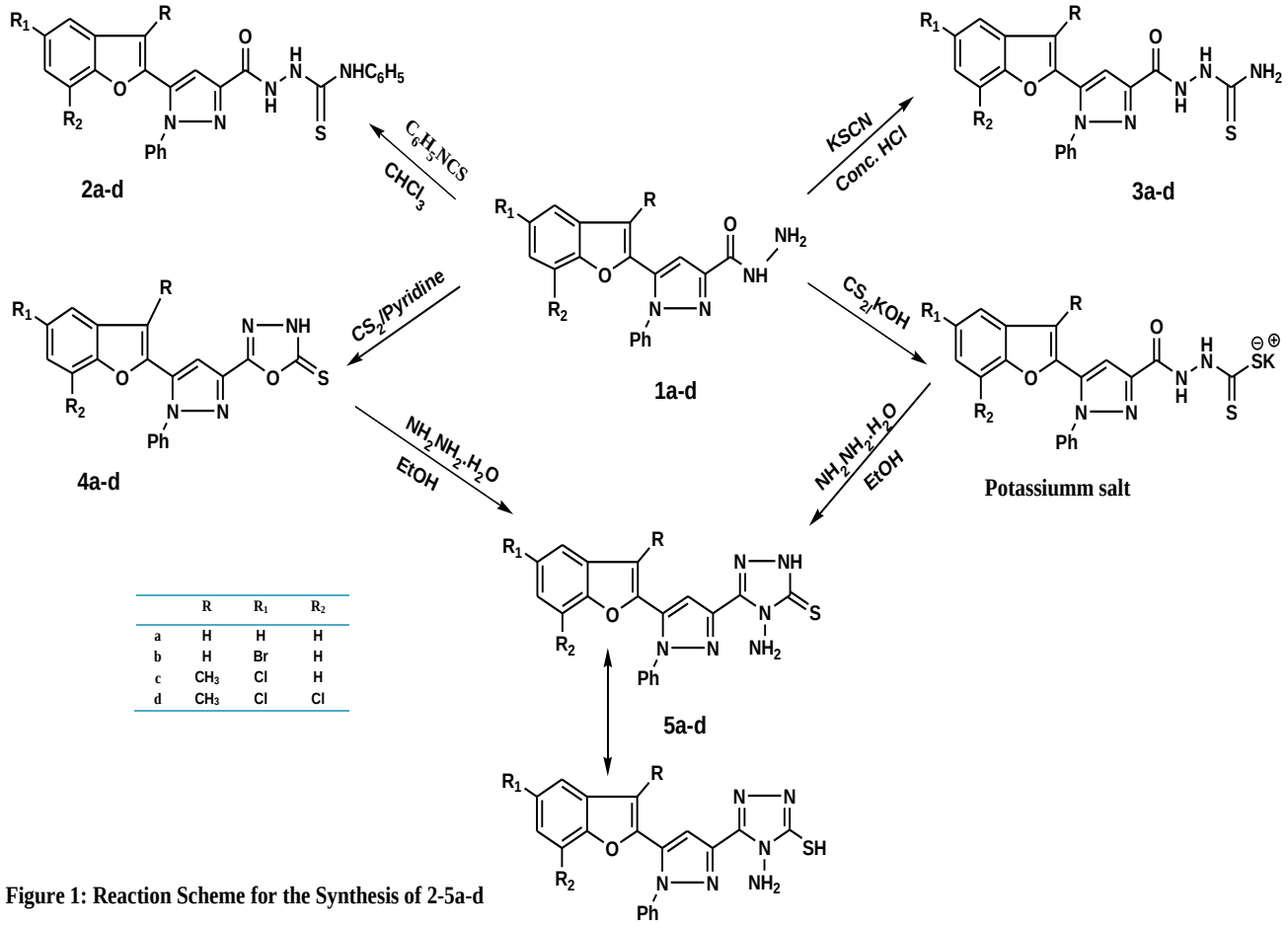
Antimicrobial Activity

All the novel synthesized compounds from **2-5a-d** have been screened for their *in vitro* antibacterial activity against two gram positive strains i.e. *Bacillus subtilis* (NCIM 2439) and *Staphylococcus aureus* (NCIM 2079) and two gram negative strains i.e. *Escherichia coli* (NCIM 2064) and *Pseudomonas aeruginosa* (NCIB 8650) by using Mueller Hinton Agar and antifungal activity against a fungus *Aspergillus niger* (NCIM 501) using Sabouraud Dextrose agar using cup plate agar diffusion method[17,18] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1mg/mL using Dimethyl Sulphoxide (DMSO) as negative control. Ampicillin was used as standard for antibacterial and Clotrimazole for antifungal activity. 10ml of this sterilized agar media were poured into petridishes and allowed to solidify. On the surface of media microbial suspension were spread with the help of sterilized triangular loop. A stainless steel cylinder of 10mm diameter (pre-sterilized) was used to bore the cavity. Into these wells were added 0.1mL portion of the test compound in the solvent. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37°C for 24 hours for bacteria and 28°C for 72-96 hrs for fungus. Zone of inhibition observed around the cup after respective incubation was measured in four directions with the help of Vernier Calipers. The results of antibacterial and antifungal activities are given in the Table 1.

RESULTS AND DISCUSSION

The synthesis of the title compounds **2–5a-d** is described in reaction scheme **1**. The reactions were monitored by TLC. The identities of the newly synthesized compound have been established on

the basis of their elemental analysis and spectral data[19] such as IR, ^{1}H NMR, ^{13}C NMR and Mass spectral studies. The analytical data of the compounds are mentioned below. These compounds were screened for their antimicrobial activities. The synthesis of the starting compounds 5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides **1a-b** were prepared recently[16]. Condensation of carbohydrazides **1a-d** with phenyl isothiocynate in chloroform afforded phenyl thiosemicarbazides **2a-d** while their reaction with potassium thiocyanate in conc. HCl yielded thiosemicarbazides **3a-d** in good yields. The structural individuality of these products has been proved by spectral techniques and molecular mass confirmation by mass spectrum at 454 $[M+H]^{+}$ for **2a** and at 426 $[M+H]^{+}$ for **3c** which is in good agreement with corresponding molecular formula. The reaction of **1a-d** with carbon disulfide in boiling pyridine gave corresponding **4a-d**. The IR spectra of **4a** showed characteristic absorption band at 1255cm^{-1} due to C=S and stretch at 3405 cm^{-1} is due to NH. ^{1}H NMR of **4a** revealed an exchangeable imino proton at δ 14.79 ppm in oxadiazole ring and absence of SH signal indicates its existence as the thione tautomer.



	R	R_1	R_2
a	H	H	H
b	H	Br	H
c	CH_3	Cl	H
d	CH_3	Cl	Cl

Figure 1: Reaction Scheme for the Synthesis of 2-5a-d

Figure 1: Reaction Scheme for the Synthesis of 2-5a-d

5a-d were prepared using two different methods, first was a two-step reaction in which **1a-d** was reacted with CS_2/KOH in ethanol to afford the potassium salt; followed by treating salt with hydrazine hydrate afforded **5a-d**. Second method was a single step process in which oxadiazolinethione **4a-d** on reacting with hydrazine hydrate furnished **5a-d,** that exists as thiol-thione tautomers as indicated by their IR and ^{1}H NMR spectra. The disappearance of C=O stretching band as in **1a** and appearance of C=S stretch at 1189 cm^{-1} in IR spectra of **5b**, and two characteristics singlet in ^{1}H NMR at δ 5.78 and δ 13.91 ppm due to NH_2 at 4-position and NH at 2-position, proves closure of the triazole thione ring. Percentage yield of the product was found to be more by adopting the first method against the second method.

Table 1 – Inhibition zone in (mm) of the compounds 2-5a-d

Compound*	***Antibacterial***				***Antifungal***
	***B. subtilis* (NCIM 2439)**	***S. aureus* (NCIM 2079)**	***E. coli* (NCIM 2064)**	***P. aeruginosa* (NCIB 8650)**	***A. niger* (NCIM 501)**
2a	-	-	09	11	17
2b	13	15	09	-	19
2c	15	13	12	13	18
2d	17	18	13	13	21
3a	-	-	16	17	16
3b	10	15	-	-	18
3c	18	18	16	16	22
3d	18	17	18	18	21
4a	-	-	10	-	18
4b	13	14	-	-	18
4c	10	13	17	16	17
4d	12	12	16	16	18
5a	18	17	18	15	21
5b	17	18	18	17	20
5c	17	19	19	17	19
5d	18	18	17	18	19
Ampicillin	20	22	20	20	-
Clotrimazole	-	-	-	-	25
DMSO	-	-	-	-	-

Analytical data

5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides (1a-d).[16]

1-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazide (2a): White crystalline solid; mp 242-244 °C; yield 96 %; M. F. $C_{25}H_{19}O_2N_5S$; IR: 3317, 3239, 3158 (NH), 3059 (ArH), 1650 (C=O), 1625, 1600 (C=N), 1237 (C=S); ^{1}H NMR: 6.4480 (s, 1H, pyrazole CH), 7.1164-7.6131 (m, 15H, ArH), 9.7317 (s, 2H, NH-CS-NHC_6H_5), 10.4350 (s, 1H,

NHCO); ^{13}C NMR: 105, 107, 110, 121, 123, 124, 125, 127, 129, 134, 139, 144, 145 (Ar C_1-C_{13}), 153 (C=O), 181 (C=S); MS: *m/z* 454 $[M+H]^+$, 476 $[M+Na]^+$;

Calculated: C, 66.23; H, 4.19; N, 15.45; S, 7.06 Found: C, 66.11; H, 4.34; N, 15.43; S, 7. 00

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazide (2b): White crystalline solid; mp 255-257 °C; yield 92%; M. F. $C_{25}H_{18}O_2N_5SBr$; Calculated: C, 56.39; H, 3.38; N, 13.16; S, 6.02 Found: C, 56.12; H, 3.32; N, 13.14; S, 6.02.

1-(5-(5-chloro-3-methylbenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazide (2c): White crystalline solid; mp 150-152 °C; yield 90%; M. F. $C_{26}H_{20}O_2N_5SCl$; Calculated: C, 62.15; H, 3.98; N, 13.94; S, 6.37 Found: C, 62.05; H, 3.72; N, 13.99; S, 6.31.

1-(5-(5,7-dichloro-3-methylbenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazide (2d): White crystalline solid; mp 208-210 °C; yield 89 %; M. F. $C_{26}H_{19}O_2N_5SCl_2$; Calculated: C, 58.21; H, 3.54; N, 13.06; S, 5.97 Found**:** C, 58.00; H, 3.42; N, 13.00; S, 5.58.

1-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl) thiosemicarbazide (3a): White crystalline solid; mp 226-228 °C; yield 76%; M. F. $C_{19}H_{15}O_2N_5S$; Calculated: C, 60.40; H, 3.98; N, 18.57; S, 8.49 Found: C, 60.38; H, 3.96; N, 18.54; S, 8.40

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl) thiosemicarbazide (3b): White crystalline solid; mp 222-224 °C; yield 70%; M. F. $C_{19}H_{14}O_2N_5SBr$; Calculated: C, 50.00; H, 3.07; N, 15.35; S, 7.02 Found: C, 50.11; H, 2.99; N, 15.16; S, 7.45.

1-(5-(5-chloro-3-methylbenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl) thiosemicarbazide (3c): White crystalline solid; mp 216-218 °C; yield 79%; M. F. $C_{20}H_{16}O_2N_5SCl$; IR: 3373, 3275, 3231, 3186 (NH, NH_2), 3039 (ArH), 2974 (CH_3), 1688 (C=O), 1609 (C=N), 1226 (C=S); ^{1}H NMR: 2.1390 (s, 3H, CH_3), 7.2660 (s, 2H, NH_2), 7.2712-7.6026 (m, 7H, ArH), 9.5460 (s, 1H, NH), 10.4993 (s, 1H, NH); ^{13}C NMR: 8(CH_3), 66, 110, 112, 115, 119, 123, 125, 127, 128, 130, 132, 139, 141, 145 (Ar C_1-C_{14}), 152 (C=O), 182 (C=S); MS: *m/z* 426 $[M+H]^+$, 448 $[M+Na]^+$, 450 $[(M+Na)^+,{}^{37}Cl]$; Calculated: C, 56.47; H, 3.76; N, 16.47; S, 7.53 Found: C, 56.11; H, 3.89; N, 16.18; S, 7.50.

1-(5-(5,7-dichloro-3-methylbenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl) thiosemicarbazide (3d): White crystalline solid; mp 226-228 °C; yield 72%; M. F. $C_{20}H_{15}O_2N_5SCl_2$; Calculated: C, 52.17; H, 3.26; N, 15.22; S, 6.96 Found: C, 52.01; H, 3.21; N, 15.23; S, 6.95.

5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione (4a)[20]: White crystalline solid; mp 249-250 °C; yield 95%; M. F. $C_{19}H_{12}O_2N_4S$; IR: 3405(-NH), 3070, 3019 (ArH), 1636, 1594 (C=N-N=C), 1518, 1497 (C=C), 1255 (C-O-C), 1230 (C=S) ^{1}H NMR: 6.5607 (s, 1H pyrazole CH), 7.225-7.6236 (m, 10H, ArH), 14.7986 (s, 1H, -NH); ^{13}C NMR: 105, 106, 110, 121, 123, 125, 127, 129, 135, 136, 138, 144 (Ar C_1-C_{12}), 153, 155 (C-O), 177 (C=S); MS: *m/z* 361 $[M+H]^+$, 383 $[M+Na]^+$; Calculated: C,63.33; H,3.33; N,15.55; S,8.88 Found: C,63.42; H,3.30; N,15.61; S,8.94.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione (4b): White crystalline solid; mp 258-260 °C; yield 80%; M. F. $C_{19}H_{11}O_2N_4SBr$; Calculated: C, 51.94; H, 2.51; N, 12.76; S, 7.28 Found: C, 51.12; H, 2.48; N, 12.70; S, 7.24.

5-(5-(5-chloro-3-methylbenzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione (4c): White crystalline solid; mp 222-224 °C; yield 86%; M. F. C_{20} $H_{13}O_2N_4S$ Cl; Calculated: C, 58.67; H, 3.18; N, 13.69; S, 7.82 Found: C, 58.74; H, 3.25; N, 13.72; S, 7.82.

5-(5-(5,7-dichloro-3-methylbenzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2(3*H*)-thione (4d): White crystalline solid; mp 208-210 °C; yield 86%; M. F. $C_{20}H_{12}O_2N_4SCl_2$; Calculated: C, 54.17; H, 2.71; N, 12.64; S, 7.22 Found**:** C, 54.13; H, 2.88; N, 12.56; S, 7.02.

4-Amino-5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thione (5a): White crystalline solid; mp 222-224 °C; yield 68%; M. F. $C_{19}H_{14}ON_6S$; ^{1}H NMR: 5.8907 (s, 2H, NH_2), 6.3924 (s, 1H pyrazole CH), 7.2063-7.6373 (m, 10H, ArH), 13.9184 (s, 1H, NH); ^{13}C NMR: 105, 107, 110, 121, 123, 125, 127, 129, 134, 139, 143, 144(Ar-C_1-C_{12}), 153(C-O), 165(C=S); MS: *m/z* 375 $[M+H]^+$, 397[$(M+Na)^+$, ^{35}Cl]; Calculated: C, 60.96; H, 3.74; N, 22.45: S, 8.56 Found: C, 60.84; H, 3.68; N, 22.42; S, 8.40.

4-Amino-5-(5-(bromobenzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thione (5b): White crystalline solid; mp 246-248 °C; yield 72%; M. F. $C_{19}H_{13}ON_6SBr$ IR: 3268, 3154 (NH), 3062 (ArH), 1628, 1596 (C=N), 1512, 1499, 1475, 1455 (C=C), 1258 (C-O-C), 1189 (C=S); ^{1}H NMR: 5.7872 (s, 2H, NH_2), 6.3613 (s, 1H, pyrazole CH), 7.2630-7.6977 (m, 9H, ArH), 13.9121 (s, 1H, NH); Calculated: C, 50.33; H, 2.87; N, 15.54; S, 7.06 Found: C, 50.26; H, 2.66; N, 15.74; S, 7.00.

4-Amino-5-(5-(5-chloro-3-methylbenzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thione (5c): White crystalline solid; mp 225-226 °C; yield 70%; M. F. $C_{20}H_{15}ON_6SCl$; ^{1}H NMR: 2.1501 (s, 3H, CH_3), 5.9125 (s, 2H, NH_2), 7.2784-7.6027 (m, 9H, pyrazole CH +ArH), 13.9424 (s, 1H, NH); Calculated: C, 56.74; H, 3.55; N, 19.86; S, 7.56 Found: C, 56.92; H, 3.39; N, 19.96; S, 7.43.

4-Amino-5-(5-(5,7-dichloro-3-methylbenzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-yl)-2*H*-1,2,4-triazole-3(4*H*)-thione (5d): White crystalline solid; mp 210-212 °C; yield 65%; M. F. $C_{20}H_{14}ON_6SCl_2$; Calculated: C, 52.52; H, 3.06; N, 18.38: S, 7.00 Found: C, 52.52; H, 3.00; N, 18.29; S, 6.99.

Antimicrobial Activity

The results indicate that the synthesized compounds showed moderate to strong activity against these bacterial strains (Table **1**). Compounds **2d, 3c, 3d** and **5a-d** showed good activity against B. subtilis and S. aureus, **3a, 3c, 3d, 4c, 4d, 5a-d** showed strong activity against E. coli, and P. aeruginosa. While rest of the compounds are found to be poor or inactive against *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa*. Similarly, all the synthesized compounds showed good activity against the fungus, *A. niger*. From the above observations it is clear that the 4-amino-[1, 2, 4] triazole-3-thione derivatives are more active and play a protuberant role in the biological activity.

CONCLUSION

In conclusion, we have reported herein synthesis of some new nitrogenous and sulphur heterocycles synthesized from 5-(substituted/unsubstituted benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides **1a-b** such as phenylthiosemicarbazides 2a-b, thiosemicarbazides 3a-d, oxadiazole-3-thiones 4a-d and 4-amino-[1,2,4]triazole-3-thiones 5a-d**.** Synthesized compounds were found to possess moderate to strong activity against selected strains of bacteria and fungus.

ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Applied Chemistry, Priyadarshini College of Engineering, Nagpur for providing Laboratory facilities, to the Director, SAIF, Punjab University, Chandigarh for providing ^{1}H-NMR, ^{13}CNMR and Mass Spectra, RSIC, CDRI, Lucknow, India for providing CHN analysis. The authors are also thankful to Ms. Farheen Siddiqui for antimicrobial screening of the compound.

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