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Synthesis of Some Novel 1,3,4-Thiadiazoles: Acid Catalyzed Cyclodehydration of Thiosemicabazides bearing Benzofuran and Pyrazole Moiety and their Antibacterial Screening

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ABSTRACT

Two new series of sixteen compounds of thiosemicarbazide and 1,3,4-thiadiazole derivatives containing benzofuran and pyrazole moieties were synthesised in order to study the effect of such combinations on the expected antimicrobial activity. In first series synthesis of eight novel 1-(5-(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-substituted/ unsubstituted phenyl thiosemicarbazides ***(3a-h)*** *have been achieved through an interaction of 5(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbohydrazides* ***(1a-b)*** *with different arylisothiocyanates* ***(2a-h).*** *Second series comprise of eight novel derivatives of 5-(5-(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-substituted / unsubstituted phenyl-1,3,4-thiadiazol-2-amine* ***(4a-h)*** *have also been synthesised by cyclo-dehydration of* ***(3a-h)*** *with cold concentrated sulfuric acid. The structures of the newly synthesized compounds were assigned on the basis of elemental analysis and spectral studies like IR, ^{1}H NMR and Mass spectra. The novel synthesized title compounds were screened for their in-vitro antimicrobial activity at different concentrations and have shown their potent activity against tested bacterial strain.*

Keywords: 1,3,4-Thiadiazole,acylthiosemicarbazide, arylisothiocyate, carbohydrazides

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INTRODUCTION

Researchers always prefer to synthesize and characterize heterocyclic compounds because of their interesting pharmacological properties. Compounds containing benzofuran substituted at 2 and 3 positions have attracted much more importance because of their profound physiological and pharmaceutical properties such as insect anti-feedant, cannabimimetic [1], reductase inhibitory [2] and metallo thioneinogenic activities [3]. Similarly pyrazole ring have great therapeutic activity in class of nitrogen heterocycles system and their derivative showed excellent antiviral, anti-tumor [4], anti-inflammatory, analgesic [5], herbicidal [6] and insecticidal [7] activities.

In addition, it is known that acylthiosemicarbazides, the versatile key intermediates itself has various pharmacological activities like analgesic [8], antibacterial [9], antifungal [10-11], antitubercular [12] etc.

Most of the researcher have adopted common route to synthesize 1,3,4-thiadiazoles derivatives from cyclodehydration of acylthiosemicarbazides derivatives with a variety of acidic reagents, such as sulphuric acid [13,17], phosphoric acid [13,16], polyphosphoric acid, phosphorous oxychloride [14], ethanolic hydrochloric acid [15,17] and anhydrous acetic acid [17] etc.

It is not surprising that compounds containing 1,3,4-thiadiazole rings in their structure has attracted widespread attention, mainly in connection with their wide range of biological properties possibly due the combination of nitrogen and sulphur heteroatom. The 1,3,4-thiadiazoles derivatives are found to exhibit a variety of applications

such as antibacterial, antifungal [18], radioprotective, investigational antitumor, gastroprotective [19], anticancer [20], corrosion inhibitors [21], ulcer inhibitors [22], in photography [23], diuretic [24], antitubercular [25], antiviral [26], insecticidal [27] and anti-inflammatory agents [28].

According to the synthetic strategy, we thought to utilize acylthiosemicarbazides bearing benzofuran and pyrazole moieties to synthesize some novel 1,3,4-Thiadiazole and that might be a good combination for enhancing their biological activity. Hence, present work is focused on to synthesize 1,3,4-Thiadiazole derivatives via cyclodehydration of acylthiosemicarbazides in acidic condition and to evaluate their antimicrobial activity.

MATERIALS AND METHODS

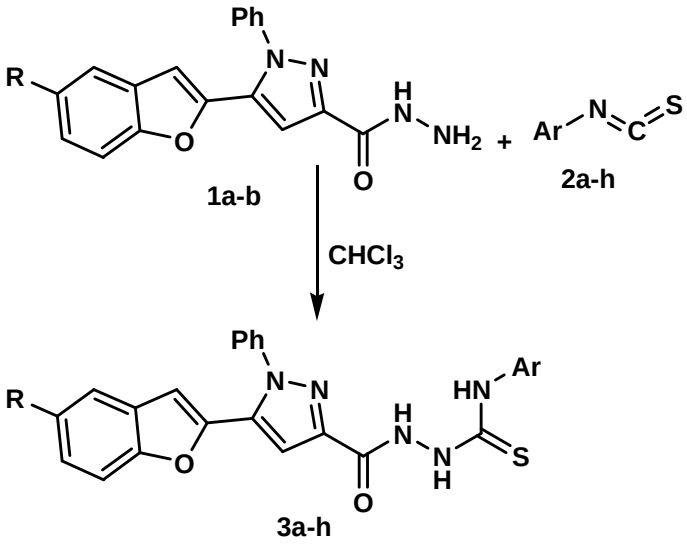
The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, v max in cm^{-1}). ^1H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as solvent. Chemical shifts are given in parts per million (ppm). Positive-ion Electro Spray Ionization (ESI) mass spectra were obtained with a Waters Micromass Q–TOF Micro, Mass Spectrophotometer. Elemental (CHN) analysis was done using Thermo Scientific (Flash-2000). The compounds were analysed for carbon, hydrogen, nitrogen and sulphur and the results obtained are in good agreement with the calculated values. 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.

Experimental

General procedure for the synthesis of 1-(5-(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-substituted/unsubstituted phenyl thiosemicarbazides (3a-h):

Synthesis of 3a: A mixture of **1a** (10 mmol) and phenyl isothiocyanate **2a** (11 mmol) in chloroform (30 mL) was refluxed for 1.5h. The reaction mixture was cooled, excess of solvent was removed under reduced pressure, solid obtained was washed with water, filtered and further purified by recrystallization using 1,4-Dioxane to give **3a** (Scheme **1**).

Reaction Scheme 1:



Entry	R	Ar
a	H	4-CH_3-C_6H_4
b	Br	4-Br-C_6H_4
c	Br	4-Cl- C_6H_4
d	Br	3-Cl- C_6H_4
e	Br	2-CH_3-C_6H_4
f	Br	3-CH_3-C_6H_4
g	Br	4-CH_3-C_6H_4
h	Br	-C_6H_5

Similarly, **3b-h** were synthesised from **1b** and **2a-h** by extending the same procedure followed for **3a.**

1-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-p-tolylthiosemicarbazide (3a): White crystalline solid; solvent for recrystallization, 1,4-Dioxane; mp, 224-226°C; yield, 94%; IR (KBr v max in cm^{-1}): 3114, 3146, 3227, 3312 (NH), 3035, 3066 (ArH), 1650 (C=O), 1234(C=S), 1481, 1513, 1561(C=C), 1261,1063 (C-O-C); ^1H NMR(DMSO-d_6) δ (ppm): 2.28 (s, 3H, Ar-CH_3), 6.60 (s, 1H, pyrazole CH), 7.1164-7.6131 (m, 14H, ArH), 9.735 (s, 1H, NH-CS-N<u>H</u>C_6H_5),9.776 (s, 1H, N<u>H</u>-CS-NHC_6H_5), 10.4350 (s, 1H, -CON<u>H</u> NH-CS-NHC_6H_5); MS: *m/z* 468$[M+H]^+$, 469$[M+2]^+$, 470$[M+3]^+$, 490$[M+Na]^+$, 491 $[(M+H)+Na]^+$. Elemental Anal.Calcd: for $C_{26}H_{21}O_2N_5S$; C, 66.79; H, 4.53; N, 14.98; S, 6.86; Found: C, 66.12; H, 4.24; N, 14.33; S,6.23.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-(4-bromophenyl)thiosemicarbazide (3b): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp, 255-257°C; yield, 89%; Elemental Anal. Calcd: for $C_{25}H_{17}Br_2N_5O_2S$; N, 11.46; S, 5.25; Found: N, 11.03;S,5.11.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-(4-chlorophenyl) thiosemicarbazide (3c): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,246-250°C; yield, 82%; Elemental Anal. Calcd: for $C_{25}H_{17}BrClN_5O_2S$; N, 12.35; S, 5.66; Found: N, 12.17; S, 5.02.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-(3-chlorophenyl) thiosemicarbazide (3d): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,260-262°C; yield, 80%; .Elemental Anal. Calcd: for $C_{25}H_{17}Br_2N_5O_2S$; N, 12.35; S, 5.66; Found: N, 12.40; S, 5.36.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-o-tolyl thiosemicarbazide (3e): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,243-245°C; yield, 86%; Elemental Anal. Calcd: for $C_{26}H_{20}BrN_5O_2S$; N, 12.82; S, 5.87; Found: N, 12.26; S, 5.54.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-m-tolyl thiosemicarbazide (3f): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,236-240°C; yield, 84%; Elemental Anal.Calcd: for $C_{26}H_{20}BrN_5O_2S$; N, 12.82; S, 5.87; Found: N, 12.31; S, 5.38.

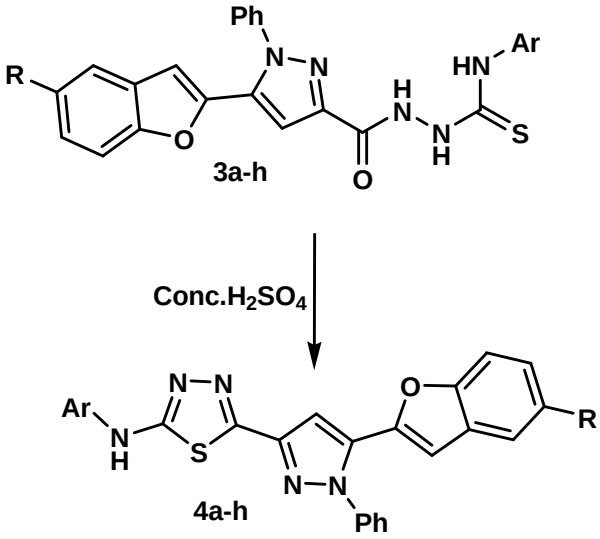
1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-p-tolyl thiosemicarbazide (3g): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,238-240°C; yield, 78%; Elemental Anal.Calcd: for $C_{26}H_{20}BrN_5O_2S$; N, 12.82; S, 5.87; Found: N, 12.13; S, 5.46.

1-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-phenyl thiosemicarbazide (3h): White crystalline solid; recrystallization solvent, 1,4-Dioxane; mp,243-245°C; yield, 86%; Elemental Anal. Calcd: for $C_{25}H_{18}BrN_5O_2S$; N, 13.15; S, 6.02; Found: N, 12.94; S, 5.86.

General procedure for the synthesis of 5-(5-(H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-substituted/unsubstituted phenyl-1,3,4-thiadiazol-2-amine (4a-h):

Synthesis of 4a: A mixture of **3a** (1 mmol) were dissolved ice cold conc. H_2SO_4 (5 mL) and kept at room temperature with occasional stirring for 3h. The reaction mixture was poured into crushed ice, ammonium hydroxide was then added to obtain the solid which was filtered, washed, dried and further recrystallized from ethanol to get **4a** (Scheme **2**).

Similarly, **4b-h** were synthesised from **3b-h** by following the same procedure for **4a. Reaction Scheme 2:**



Entry	R	Ar
a	H	4-CH_3-C_6H_4
b	Br	4-Br-C_6H_4
c	Br	4-Cl- C_6H_4
d	Br	3-Cl- C_6H_4
e	Br	2-CH_3-C_6H_4
f	Br	3-CH_3-C_6H_4
g	Br	4-CH_3-C_6H_4
h	Br	-C_6H_5

5-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-p-tolyl-1,3,4-thiadiazol-2-amine (4a): White crystalline solid; recrystallization solvent, ethanol; mp,142-144°C; yield, 82%; M. F. $C_{26}H_{19}N_5OS$. Elemental Anal. Calcd: for $C_{26}H_{19}N_5OS$; N, 15.58; S, 7.13; Found: N, 15.22; S, 7.03.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-N-(4-bromophenyl)-1,3,4-thiadiazol-2-amine (4b): White crystalline solid; recrystallization solvent, ethanol; mp, above 280°C; yield, 82%; IR (KBr v max in cm^{-1}):

3393, 3252, 3190 (NH), 3038 (ArH), 1563, 1497 (C=C), 1619, 1598 (C=N), 692 (C-S-C in Thiadiazole).^{1}H NMR(DMSO-d_6) δ (ppm): 6.60 (s, 1H, pyrazole CH), 10.68 (broad, 1H, NH),7.35-8.27 (m, 13H, ArH).MS: *m/z* 593$[M]^+$, 594$[M+H]^+$, 595$[M+2]^+$, 616$[M+Na]^+$, 618$[(M+2)+Na]^+$. Elemental Anal. Calcd: for M. F. $C_{25}H_{15}N_5Br_2OS$ required: C, 50.61; H, 2.55; N, 11.80; S, 5.40; Found: C, 50.12; H, 2.24; N, 11.30;S, 5.12.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (4c):
White crystalline solid; recrystallization solvent, ethanol; mp, 148-150°C; yield, 73%; Elemental Anal.Calcd: for $C_{25}H_{15}BrClN_5OS$; N, 12.76; S, 5.84; Found: N, 12.38; S, 5.28.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine (4d):
White crystalline solid; recrystallization solvent, ethanol; mp, 152-154°C; yield, 75%; Elemental Anal.Calcd: for $C_{25}H_{15}BrClN_5OS$; N, 12.76; S, 5.84; Found: N, 12.53; S, 5.39.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-o-tolyl-1,3,4-thiadiazol-2-amine (4e):
White crystalline solid; recrystallization solvent, ethanol; mp, 140-142°C; yield, 78%; Elemental Anal.Calcd: for $C_{26}H_{18}BrN_5OS$; N, 13.25; S, 6.07; Found: N, 13.06; S, 5.88.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-m-tolyl-1,3,4-thiadiazol-2-amine (4f):
White crystalline solid; recrystallization solvent, ethanol; mp,148-150°C; yield, 80%; Elemental Anal.Calcd: for $C_{26}H_{18}BrN_5OS$; N, 13.25; S, 6.07; Found: N, 13.11; S, 5.96.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-p-tolyl-1,3,4-thiadiazol-2-amine (4g):
White crystalline solid; recrystallization solvent, ethanol; mp,142-144°C; yield, 81%; Elemental Anal.Calcd: for $C_{26}H_{18}BrN_5OS$; N, 13.25; S, 6.07; Found: N, 13.03; S, 5.79.

5-(5-(5-bromobenzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-N-phenyl-1,3,4-thiadiazol-2-amine (4h):
White crystalline solid; recrystallization solvent, ethanol; mp,165-168°C; yield, 78%; Elemental Anal.Calcd: for $C_{26}H_{16}BrN_5OS$; N, 13.61; S, 6.23; Found: N, 13.23; S, 6.02.

Antibacterial activity
The novel synthesized heterocyclic compounds were screened for their *in-vitro* antimicrobial activity using cup plate agar disc-diffusion method against two Gram positive bacterial strains, *B. thurengienesis* and *S. aureus* and two Gram negative strains, *E. coli* and *E. aerugenes.* Chloramphenicol was used as standard drug for bacteria.

General procedure: Determination of zone of inhibition by agar disc-diffusion method:
Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant concentration of 31-1000µg/mL. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. *In-vitro* antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. Petri plates were prepared by pouring 10mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The discs were then applied and the plates were incubated at 37°C for 24h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean. The results were compared using Chloramphenicol as a standard antibacterial agent. The results of antibacterial activity (zone of inhibition in mm) of some of the synthesized compounds are given in the Table **1**.

RESULTS AND DISCUSSION

The synthesis of the novel compound **3a-h** and **4a-h** is described in the reaction schemes **1** and **2**. At every stage purity of the compounds were monitored by TLC technique. The newly synthesized compounds have been established on the basis of their elemental and spectral analysis such as IR, ^{1}H NMR and Mass. The synthesis of the starting compound, 5-(5-H/Br benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazides **(1a-b)** achieved in quantitative yields by the reference method [29]. The reaction of **1a-b** with substituted phenyl isothiocynate **2a-h** in chloroform as a solvent afforded **3a-h.**The IR spectrum of **3a** showed -NH stretch of amine at 3312 cm^{-1} and C=O stretching in amide group at 1650 cm^{-1}. The ^{1}H NMR spectrum showed singlet at δ 2.3 ppm for ($-CH_3$) group, hence it confirms that substituted phenyl isothiocynate has condensed with 5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide to afford 1-(5-(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-substituted/ unsubstituted phenyl thiosemicarbazide **3a-h.** The elemental analysis of this product gave C, 66.12; H, 4.24; N, 14.33 and S, 6.23. The mass spectra of the products revealed a molecular ion peak at *m/z* 468 $[M+H]^+$ which is in agreement with the molecular formula $C_{26}H_{21}O_2N_5S$.

The reaction of 1-(5-(5-H/Br benzofuran-2-yl)-1-phenyl-1H-pyrazole-3-carbonyl)-4-substituted/unsubstituted phenyl thiosemicarbazide **3a-h** with conc. sulphuric acid yielded substituted/unsubstituted phenyl-1,3,4-thiadiazol-2-amine derivatives **4a-h.** The IR spectrum of **4b** reveals that C=O stretching in amide group has disappeared and C-S-C stretch has appeared at 692 cm^{-1}. This was further confirmed from its ^1H NMR spectrum which showed expected signals for aromatic and aliphatic proton. Appearance of a singlet at δ 10.68 ppm for -NH proton, and disappearance of the two singlet's of –NH protons as obtained in thiosemicarbazides confirms that cyclization has occurred to get the target molecule. Its elemental analysis reveals that % of C, H, N and S are 50.12, 2.24, 11.30 and 5.12 respectively, while its mass spectrum shows a molecular ion peak at *m/z* 593 $[M]^+$ matches with the molecular formula $C_{25}H_{15}N_5Br_2OS$.

Antibacterial activity

It could be seen from antimicrobial data the test compound **3a** and **4b** are highly active against the *E.coli.* **4b** is highly active while **3a** moderately active against *B. thurengienesis* as well as *E. Areogenes* while both shows moderate activity against *S. aureus.* On the basis of data it is clear that both acylthiosemicarbazide and 1,3,4-Thiadiazole shows antibacterial activity against all the test organisms at each concentration.

Figures showing zone of inhibition of test compound 3a and 4b at different conc. and bacterial strain

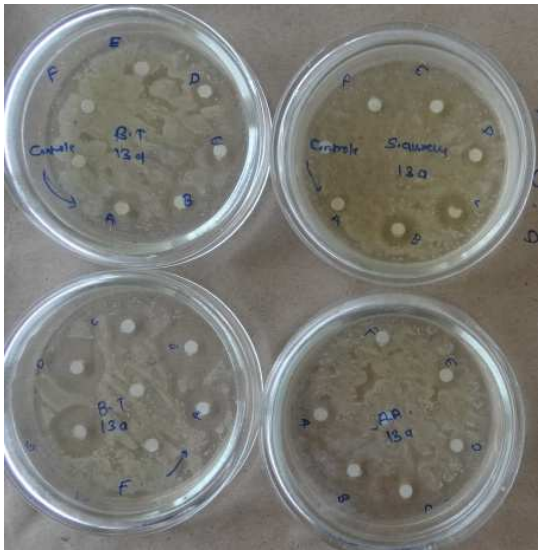


Figure 1: 3a

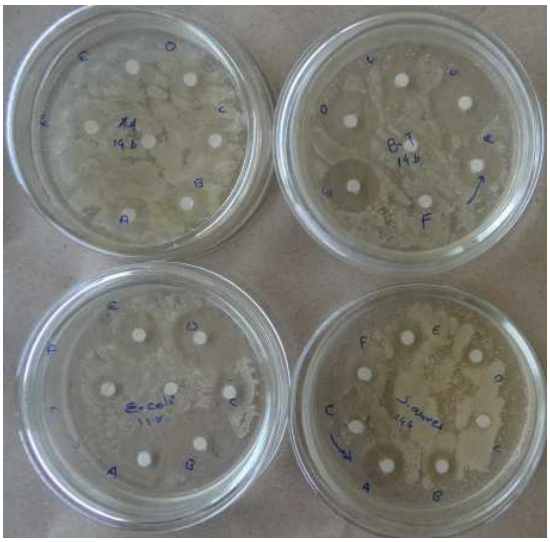


Figure 2: 4b

Table 1: Antibacterial Activity of 3a and 4b

Sr. No.	Conc. (µg/mL)	Zone of Inhibition in mm			
		Gram +ve		Gram -ve	
		B. thurengienesis	*S. aureus*	*E. coli*	*E. areogenesis*
		3a			
1.	**1000**	16	8	15	10
2.	**500**	12	15	22	12
3.	**250**	10	14	15	15
4.	**125**	10	8	24	8
5.	**63**	8	10	22	8
6.	**31**	6	8	8	6
		4b			
1.	**1000**	16	18	28	18
2.	**500**	26	15	30	20
3.	**250**	18	5	15	10
4.	**125**	25	8	30	14
5.	**63**	24	15	18	10
6.	**31**	8	8	12	8
		Standard Chloramphenicol			
1.	**1000**	22	26	24	16
2.	**500**	20	30	20	16
3.	**250**	21	27	18	17
4.	**125**	16	21	17	16
5.	**63**	15	18	17	15
6.	**31**	16	20	21	15

CONCLUSION

A series of novel 1,3,4-Thiadiazoles **(4a-h)** and acylthiosemicarbazides **(3a-h)** were successfully synthesized in good yields. Their purity and confirmation was checked by physical, analytical and spectral data. Antibacterial screening of these compounds was found to possess high to moderate activity against selected strains of bacteria.

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