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Synthesis of some New Thiosemicarbazide and 1,3,4-Thiadiazole Heterocycles Bearing Benzo[b]Thiophene Nucleus as a Potent Antitubercular and Antimicrobial Agents

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Abstract

Reaction of 2-hydrazinocarbonyl-3-chloro-5-phenoxy-benzo[b] thiophene with different substituted phenyl isothiocyanate gave N-substituted arylthiosemicarbazide derivatives **(1a-h)**. 1,3,4-Thiadiazole derivatives **(2a-h)** were prepared by the cyclization of arylthiosemicarbazides **(1a-h)** with concentrated sulphuric acid. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$) and antimicrobial activity against various microorganisms.

Keywords: Benzo[b]thiophene; 1,3,4-Thiadiazole; Arylthiosemicarbazide; Antitubercular and antimicrobial activity

Introduction

The thiadiazoles have occupied an important place in drug industry. 1,3,4-Thiadiazoles have wide applications in many fields. The earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs. Some of the later uses are as antitumor and anti-inflammatory agents, pesticides, dyes, lubricants and analytical reagents.

1,3,4-Thiadiazole and its derivatives possess wide range of therapeutic activities like anticonvulsant [1], herbicidal [2], pesticidal [3], amoebicidal [4], CNS depressant [5], antibacterial [6], antiviral [7]. In continuation of our work on benzo[b]thiophene nucleus [8], it was contemplated to synthesize some new 1,3,4-thiadiazoles derivatives bearing benzo[b]thiophene moiety.

The N-substituted arylthiosemicarbazide derivatives **(1a-h)** were prepared by the reaction of 2-hydrazinocarbonyl-3-chloro-5-phenoxy-benzo[b]thiophene with different substituted phenyl isothiocyanate. 1,3,4-Thiadiazole derivatives **(2a-h)** were prepared by the reaction of arylthiosemicarbazide with concentrated sulphuric acid.

The structures of the synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}HNMR and Mass spectral data. The compounds were screened for their antitubercular and antimicrobial activities.

Experimental

Thin layer chromatography was used to access the reactions and purity of the compounds synthesized. The melting points were determined in open capillary tubes

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and presented uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 instrument in KBr disk. ^{1}H NMR spectra were recorded on Bruker AC-300 MHz FT NMR using TMS as an internal standard, chemical shift in δppm. Mass spectra were recorded on Jeol-D300 spectrometer. All the compounds gave satisfactory elemental analyses.

Preparation of N^1-(3'-Chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N^4-aryl thiosemicarbazide (1a-h)

An ethanolic solution of 2-hydrazinocarbonyl-3-chloro-5-phenoxy benzo[b]thiophene (4.81 g, 0.01 M) and arylisothiocyanate (0.01 M) was refluxed for 6 h. The resulting solution was cooled and the solid separated was crystallized from ethanol to give **1g**: (60%), m.p. 222-223°C, Anal. Calcd. for $C_{23}H_{18}N_3O_3S_2Cl$ Calcd. C, 57.08; H, 3.72; N, 8.68 %. Found: C, 57.05; H, 3.70; N, 8.66 %. IR (KBr νmax cm^{-1}): 3060 (-CH=CH str., vinyl), 2922 (-CH_3, sym.), 1624 (-C=O str., ketone), 1232(C-O-C str.), 750 (C-S-C str.). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) (δ ppm): 3.84 (s, 3H, -OCH_3), 6.89 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H), 7.12 (m, 4H, Ar-H), 7.24 (d, 2H, Ar-H), 7.82 (d, 2H, Ar-H). MS=m/z (483 M^+).

Other thiadiazoles were prepared similarly. The physical constants are recorded in Table 1.

Preparation of 2-(3'-Chloro-5'-phenoxy-benzo[b]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazole (2a-h)

A mixture of N^1-(3′-chloro-5′-phenoxy benzo[b]thiophen-2′-yl)-N^4-aryl thiosemicarbazide (4.65 g, 0.01 M) and concentrated sulphuric acid (10 ml) was refluxed for half an hour and kept at room temperature for 24 h. The content was poured into cold water and neutralized with diluted sodium carbonate solution. The product was isolated and crystallized from ethanol **2g**: Yield 59%, m.p. 197-198°C, Anal. Calcd. for $C_{23}H_{16}N_3O_2S_2Cl$ Calcd. C, 59.29; H, 3.43; N, 9.02 %. Found: C, 59.27; H, 3.40; N, 9.00 %. IR (KBr νmax cm^{-1}): 3060 (-CH=CH str., vinyl), 2922 (-CH_3 sym.), 1624 (-C=N str.), 1232 (C-O-C str.), 750 (C-S-C str.). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) (δppm): 3.83 (s, 3H, -OCH_3), 6.85 (d, 2H, Ar-H), 6.92 (d, 2H, Ar-H), 7.20 (m, 4H, Ar-H), 7.32 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H). MS=m/z (465 M^+).

Other thiadiazoles were prepared similarly. The physical constants are recorded in Table 1.

Results and Discussion

Antimicrobial Activity

Antimicrobial activity was assayed by using the cup-plate agar diffusion method [9] against bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus megaterium*, *Staphylococcus aureus* and fungus *Aspergillus niger* at 40 μg/ml concentration using amoxycillin, benzyl penicillin, ciprofloxacin, erythromycin and griseofulvin as standards. The data of compounds are recorded in Table 2. It was observed that compounds 1b, 1d, 1g, 2c and 2e showed good activity against *E. coli*. Compounds 1d, 1g were active against *P. vulgaris* while compounds 1b, 1d, 1e, 1f, 1g, 2b and 2c, had moderate activities against *B. mega.* Compounds 1d, 1e, 1f, 1g, 2a and 2h were active against *S. aureus* and compounds 1b, 1d, 1g, 1h, 2a, 2g, 2h active against *A. niger*.

Antitubercular Activity

The antitubercular evaluations of the compounds were carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) USA. Antitubercular activity was evaluated at 6.25 μg/ml concentration against Mycobacterium *tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the ALAMAR radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 μg/ml concentration which showed 98% inhibition. Compounds having 2-(3′-chloro-5′-phenoxy-benzo[b]thiophen-2′-yl)-5-(p-methoxyphenyl) amino-1,3,4-thiadiazole and 2-methyl, 2-methoxy derivatives showed higher activity than the others. The data of compounds are recorded in Table 3.

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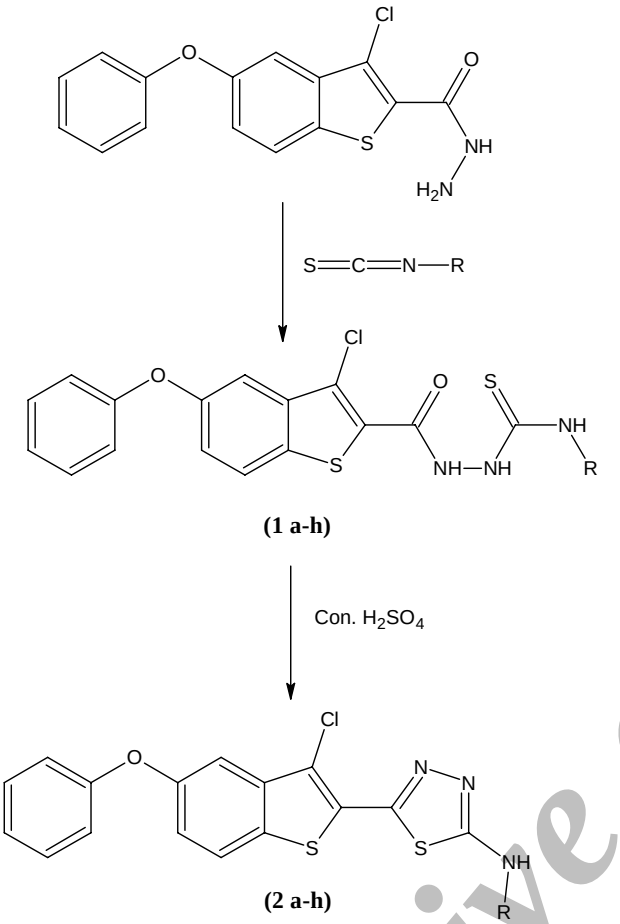
Table 1. Physical data of compounds **1a-h** and **2a-h**

Compounds	R	Molecular formula	m.p. (°C)	Yield (%)	% of N	
					Calcd.	Found
1a	C_6H_5	$C_{22}H_{16}N_3O_2S_2Cl$	231	58	9.26	9.22
1b	3-Cl, C_6H_4	$C_{22}H_{15}N_3O_2S_2Cl_2Br$	215	60	8.60	8.57
1c	4-Cl, C_6H_4	$C_{22}H_{15}N_3O_2S_2Cl_{2222}$	209	65	8.60	8.55
1d	2-CH_3, C_6H_4	$C_{23}H_{18}N_3O_2S_2Cl$	169	62	8.98	8.95
1e	4-CH_3, C_6H_4	$C_{23}H_{18}N_3O_2S_2Cl$	179	61	8.98	8.95
1f	2-OCH_3, C_6H_4	$C_{23}H_{18}N_3O_3S_2Cl$	216	54	8.68	8.64
1g	4-OCH_3, C_6H_4	$C_{23}H_{18}N_3O_3S_2Cl$	223	60	8.68	8.66
1h	2-NO_2, C_6H_4	$C_{22}H_{15}N_4O_4S_2Cl$	256	64	11.23	11.20
2a	C_6H_5	$C_{22}H_{14}N_3OS_2Cl$	216	55	9.64	9.61
2b	3-Cl, C_6H_4	$C_{22}H_{13}N_3OS_2Cl_2$	203	58	8.93	8.90
2c	4-Cl, C_6H_4	$C_{22}H_{13}N_3OS_2Cl_2$	196	60	8.93	8.88
2d	2-CH_3, C_6H_4	$C_{23}H_{16}N_3OS_2Cl$	219	61	9.34	9.34
2e	4-CH_3, C_6H_4	$C_{23}H_{16}N_3OS_2Cl$	211	54	9.34	9.32
2f	2-OCH_3, C_6H_4	$C_{23}H_{16}N_3O_2S_2Cl$	220	58	9.04	9.00
2g	4-OCH_3, C_6H_4	$C_{23}H_{16}N_3O_2S_2Cl$	198	59	9.02	9.00
2h	2-NO_2, C_6H_4	$C_{22}H_{13}N_4O_3S_2Cl$	235	65	11.65	11.63

Table 2. Antimicrobial screening results of compounds **1a-h** and **2a-h**

Compounds	Antibacterial activity (zones of inhibition in mm)				Antifungal activity
	E. coli	*P. aeruginosa*	*B. mega*	*S. aureus*	*A. niger*
1a	18	19	20	17	23
1b	20	17	21	19	27
1c	21	14	19	16	24
1d	20	25	22	29	30
1e	14	12	24	31	21
1f	12	16	26	24	14
1g	20	25	22	29	30
1h	15	14	20	17	30
2a	16	18	20	25	24
2b	19	14	22	20	23
2c	20	18	21	19	22
2d	14	16	14	18	20
2e	21	14	16	17	19
2f	14	13	19	20	18
2g	18	14	20	15	20
2h	13	18	19	22	21
Benzyl penicillin penicillin	17	25	16	22	0
Amoxycillin	16	15	15	18	0
Ciprofloxacin	20	28	15	28	0
Erythromycin	25	26	20	18	0
Griseofulvin	0	0	0	0	22

Reaction Scheme



R = Aryl

Table 3. Antitubercular-screening result of compounds which shows high percentage of inhibition

Compounds	MIC (µg/ml)	% Inhibition
1b	>6.25	21
2c	>6.25	29
2d	>6.25	60
2f	>6.25	60
2g	>6.25	91

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