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Heterocyclic systems containing S/N regioselective nucleophilic competition: facile synthesis, antitubercular and antimicrobial activity of thiohydantoins and iminothiazolidinones containing the benzo[*b*]thiophene moiety

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Abstract: The required compounds *N*-aryl-*N'*-(3-chloro-2-benzo[*b*]thenoyl)–thioureas **1a–k** were prepared by condensing 3-chloro-2-benzo[*b*]thenoyl chloride with different arylamines using ammonium thiocyanate, which in turn when treated with chloroacetic acid, yielded 1-aryl-3-(3-chloro-2-benzo[*b*]thenoyl)thiohydantoins **2a–k**, while in the presence of sodium acetate treated with chloroacetic acid, yielded 2-arylimino-3-(3-chloro-2-benzo[*b*]thenoyl)-4-thiazolidinones **3a–k**. All the synthesized compounds were screened for their antitubercular and antimicrobial activities. Some selected compounds were selected for their further antitubercular screening.

Keywords: iminothiazolidinone, thiohydantoin, antitubercular activity, antimicrobial activity.

INTRODUCTION

Thioureas are verstile synthetic intermediate for the preparation of many heterocyclic entities. In the literature, many research workers have reported an S/N regioselective nucleophilic competition in the synthesis of heterocyclic compounds by intermolecular and intramolecular cyclisation reactions. A change in the reaction conditions might favor S-attack or N-attack to afford different cyclic products from the same reaction precursor. Thioureas have been used as intermediates for a great variety of heterocyclic products, such as thiohydantoin, iminothiazolidinone, thioxopyrimidindione, *etc.* Therefore, it was planned to investigate a system, which combines these thiourea systems for screening the pharmacological properties of the formed compounds. The synthetic potential and biological activity of nitrogen and sulphur containing heterocycles has been explored to the

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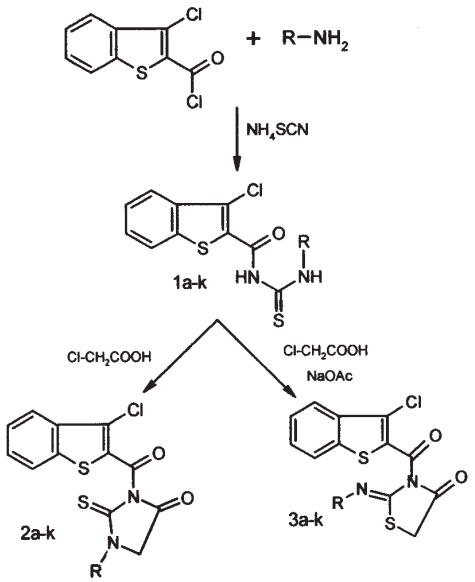
maximum extent and several heterocyclic analogues of thioureas have been reported in recent years.[1,2]

There is considerable interest in the chemotherapeutic activity of thiohydantoins and iminothiazolidinone nucleus bearing a benzo[*b*]thiophene moiety. This

REACTION SCHEME



R = Aryl

1,2,3 a	: C_6H_5-	1,2,3 g	: 4-OCH_3-C_6H_4-
1,2,3 b	: 2-Cl-C_6H_4-	1,2,3 h	: 2-NO_2-C_6H_4-
1,2,3 c	: 3-Cl-C_6H_4-	1,2,3 i	: 4-NO_2-C_6H_4-
1,2,3 d	: 4-Cl-C_6H_4-	1,2,3 j	: $C_4H_3N_2$-
1,2,3 e	: 2,6-$(CH_3)_2$-C_6H_3-	1,2,3 k	: C_3H_2NS-
1,2,3 f	: 2-CH_3-5-Cl-C_6H_3-		

➢ In case of 1,2 and 3 the structure of j and k are as under:

	R	Structure
j	-$C_4H_3N_2$	
k	-C_3H_2NS	

Scheme 1.

includes anticancer,[3] antiviral,[4] anticonvulsant,[5] anti-inflammatory,[6] antitubercular,[7] *etc.* agents. Thioureas have been extensively used to synthesize thiohydantoins and iminothiazolidinone derivatives.[8] In the present study, this strategy was used for the synthesis of these compounds in the hope that they may possess different biological activities.

The starting compound *N*-aryl-*N'*-(3-chloro-2-benzo[*b*]thenoyl)thioureas **1a–k** were prepared by condensing 3-chloro-2-benzo[*b*]thenoyl chloride with different arylamines using ammonium thiocyanate, which in turn when treated with chloroacetic acid, yielded the 1-aryl-3-(3-chloro-2-benzo[*b*]thenoyl)thiohydantoins **2a–k**, while in the presence of sodium acetate treated with chloroacetic acid, the 2-arylimino-3-(3-chloro-2-benzo[*b*]thenoyl)-4-thiazolidinones **3a–k**, were formed (Scheme 1).

The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H-NMR and mass spectral data. The compounds were screened for their *in vitro* antitubercular and antimicrobial activities.

EXPERIMENTAL

Thin layer chromatography was used to access the reactions and purity of the compound synthesized. The melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400 instrument as KBr discs and only noteworthy absorption levels (cm^{-1}) are listed. ^{1}H-NMR spectra were recorded on a Bruker AC-300 MHz FT NMR spectrometer using TMS as the internal standard, chemical shift in δ ppm. Mass spectra were recorded on a Jeol D-300 spectrometer. All the compounds gave satisfactory elemental analyses.

Preparation of N-*(3-chloro-2-benzo*[b]*thenoyl*)-N'-*(2,6-dimethylphenyl)*thiourea ***1e***

Ammonium thiocyanate (0.76 g, 0.01 mol) in acetone (25 ml) was added dropwise to a solution of 3-chloro-2-benzo[*b*]thenoyl chloride (2.31 g, 0.01 mol) in acetone (25 ml). 2,6-Dimethylaniline (1.21 g, 0.01 mol) in acetone (25 ml) was then added to the above reaction mixture in small portions; after completion of addition, the reaction mixture was refluxed for 3 h. The excess acetone was then distilled off, the resulting solid was washed with water and crystallized from ethanol. Yield 48 %, m.p. 181 °C. *Anal*: Calcd. for $C_{18}H_{15}ClN_2OS_2$. Requires: C, 57.67; H, 4.00; N, 7.47, Found: C, 57.59; H, 3.97; N, 7.45 %. ν_{max}: 3425 (N–H), 1728 (C=O), 748 (C–Cl), 721 (C–S–C). δ ppm 2.61 (6H, *s*, CH_3), 6.71–7.06 (7H, *m*, Ar–H), 6.98 (1H, *s*, –NH). The mass spectrum indicated a molecular ion peak at *m*/*z* 391.

The other *N*-aryl-*N'*-(3-chloro-2-benzo[b]thenoyl)thioureas **1a-d**, **f-k** were prepared in a similar manner. The physical data are recorded in Table I.

Synthesis of 3-(3-chloro-2-benzo[b]*thenoyl)-1-(2,6-dimethylphenyl)-2-thiohydantoin **2e***

A mixture of *N*-(3-chloro-2-benzo[*b*]thenoyl)-*N'*-(2,6-dimethylphenyl)thiourea (3.74 g, 0.01 mol) was dissolved in the minimum quantity of pyridine. To this solution, chloroacetic acid (1.88 g, 0.02 mol) and 15 ml of dioxane were added. The resulting reaction mixture was refluxed for 12 h. The contents were cooled, poured into ice-cold water, the solid mass was separated, filtered, washed with water and crystallized from benzene. Yield 55 %, m.p. 173 °C *Anal*: Calcd. for $C_{20}H_{15}ClN_2O_2S_2$; Requires: C, 57.90; H, 3.61; N, 6.75 %; Found: C, 57.89; H, 3.62; N, 6.72 %. ν_{max}: 1722 (C=O), 752 (C–Cl), 721 (C–S–S) cm^{-1}. δ ppm: 2.57 (6H, *s*, CH_3), 6.84–7.99 (7H, *m*, Ar–H). The mass spectrum indicated a molecular ion peak at *m*/*z* 431.

TABLE I. Physical data of compounds **1a–k**, **2a– k** and **3a–k**

Compd.	R	M.F.	M.p./°C	Yield/%	% of nitrogen	
					Calcd.	Found
1a	C_6H_5–	$C_{16}H_{11}ClN_2OS_2$	121	44	8.08	8.06
1b	2-Cl-C_6H_4–	$C_{16}H_{10}Cl_2N_2OS_2$	80	55	7.34	7.33
1c	3-Cl-C_6H_4–	$C_{16}H_{10}Cl_2N_2OS_2$	109	59	7.34	7.32
1d	4-Cl-C_6H_4–	$C_{16}H_{10}Cl_2N_2OS_2$	58	51	7.34	7.32
1e	2,6-$(CH_3)_2$-C_6H_3–	$C_{18}H_{15}ClN_2OS_2$	181	48	7.47	7.45
1f	2-CH_3-5-Cl-C_6H_3–	$C_{17}H_{12}Cl_2N_2OS_2$	139	50	7.08	7.07
1g	4-OCH_3-C_6H_4–	$C_{17}H_{13}ClN_2O_2S_2$	165	59	7.43	7.40
1h	2-NO_2-C_6H_4–	$C_{16}H_{10}ClN_3O_3S_2$	178	55	10.70	10.69
1i	4-NO_2-C_6H_4–	$C_{16}H_{10}ClN_3O_3S_2$	180	57	10.70	10.67
1j	$C_4H_3N_2$–	$C_{14}H_9ClN_4OS_2$	169	51	16.07	16.06
1k	C_3H_2NS–	$C_{13}H_8ClN_3OS_3$	151	49	11.81	11.79
2a	C_6H_5–	$C_{18}H_{11}ClN_2O_2S_2$	156	54	7.24	7.21
2b	2-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	132	67	6.65	6.62
2c	3-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	190	49	6.65	6.61
2d	4-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	168	61	6.65	6.63
2e	2,6-$(CH_3)_2$-C_6H_3–	$C_{20}H_{15}ClN_2O_2S_2$	173	55	6.75	6.72
2f	2-CH_3-5-Cl-C_6H_3–	$C_{19}H_{12}Cl_2N_2O_2S_2$	153	57	6.43	6.42
2g	4-OCH_3-C_6H_4–	$C_{19}H_{13}ClN_2O_3S_2$	150	62	6.72	6.74
2h	2-NO_2-C_6H_4–	$C_{18}H_{10}ClN_3O_4S_2$	192	51	9.73	9.74
2i	4-NO_2-C_6H_4–	$C_{18}H_{10}ClN_4O_2S_2$	128	54	9.73	9.71
2j	$C_4H_3N_2$–	$C_{16}H_9ClN_4O_2S_2$	215	59	14.41	14.39
2k	C_3H_2NS–	$C_{15}H_8ClN_3O_2S_3$	198	67	10.72	10.71
3a	C_6H_5–	$C_{18}H_{11}ClN_2O_2S_2$	178	59	7.24	7.21
3b	2-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	163	73	6.65	6.62
3c	3-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	183	68	6.65	6.61
3d	4-Cl-C_6H_4–	$C_{18}H_{10}Cl_2N_2O_2S_2$	179	61	6.65	6.65
3e	2,6-$(CH_3)_2$-C_6H_3–	$C_{20}H_{15}ClN_2O_2S_2$	160	59	6.75	6.72
3f	2-CH_3-5-Cl-C_6H_3–	$C_{19}H_{12}Cl_2N_2O_2S_2$	143	64	6.43	6.41
3g	4-OCH_3-C_6H_4–	$C_{19}H_{13}ClN_2O_3S_2$	153	68	6.72	6.74
3h	2-NO_2-C_6H_4–	$C_{18}H_{10}ClN_3O_4S_2$	171	64	9.73	9.72
3i	4-NO_2-C_6H_4–	$C_{18}H_{10}ClN_3O_4S_2$	188	59	9.73	9.71
3j	$C_4H_3N_2$–	$C_{16}H_9ClN_4O_2S_2$	213	65	14.41	14.37
3k	C_3H_2NS–	$C_{15}H_8ClN_3O_2S_3$	182	61	10.72	10.70

The other 1-aryl-3-(3-chloro-2-benzo[*b*]thenoyl)thiohydantoins **2a–d, f–k** were prepared in a similar manner. The physical and spectral data are recorded in Tables I and II, respectively.

Synthesis of 3-(3-chloro-2-benzo[b]*thenoyl)-2-*[*(2,6-dimethylphenyl)imino*]*-4-thiazolidinone 3e*

A mixture of *N*-(3-chloro-2-benzo[*b*]thenoyl)N'-(2,6-dimethylphenyl)thiourea (3.74 g, 0.01 mol) (**1e**), chloroacetic acid (1.88 g, 0.02 mol) and anhydrous sodium acetate was refluxed in DMF (50 ml) for 10 h. The reaction mixture was cooled, poured onto crushed ice and left overnight. The precipitate thus obtained was filtered, washed with water, dried and crystallized from benzene. Yield 64 %, m.p. 171 °C. *Anal*: Calcd. for $C_{20}H_{15}ClN_2O_2S_2$; Requires: C, 57.90; H, 3.61; N, 6.75 %; Found: C, 57.89; H, 3.62; N, 6.72 %. ν_{max}: 1716 (C=O), 752 (C–Cl), 725 (C–S–C) cm^{-1}. δ/ppm: 2.62 (6H, *s*, CH_3), 6.90–7.89 (7H, *m*, Ar–H). The mass spectrum indicated a molecular ion peak at *m*/*z* 431.

TABLE II. Spectral characterization of the synthesized compounds **2a–k** and **3a–k**

Compd.	R	IR (cm^{-1})		NMR	
		C=O str. Ring	C=O str. Amide	X	Ar–H
2a	C_6H_5–	1724	1666	–	6.91– 7.74 (*m,* 9H)
2b	2-Cl-C_6H_4–	1722	1668	–	6.88 – 7.69 (*m,* 8H)
2c	3-Cl-C_6H_4–	1721	1669	–	6.41–7.72 (*m,* 8H)
2d	4-Cl-C_6H_4–	1722	1666	–	6.90–8.04 (*m*, 8H)
2e	2,6-$(CH_3)_2$-C_6H_3–	1724	1668	2.57 (*s,* 6H, –CH_3)	6.84–7.99 (*m,* 7H)
2f	2-CH_3-5-Cl-C_6H_3–	1728	1668	2.52 (*s,* 3H, –CH_3)	6.82–7.95 (*m,* 7H)
2g	4-OCH_3-C_6H_4–	1724	1669	3.90 (*s,* 3H, –OCH_3)	6.92–7.89 (*m*, 8H)
2h	2-NO_2-C_6H_4–	1722	1666	–	7.01–7.96 (*m,* 8H)
2i	4-NO_2-C_6H_4–	1724	1668	–	7.00–8.02 (*m,* 8H)
2j	$C_4H_3N_2$–	1725	1666	–	6.98–7.99 (*m,* 6H)
2k	C_3H_2NS–	1722	1664	–	7.00–8.02 (*m,* 5H)
3a	C_6H_5–	1716	1662	–	6.92–7.89 (*m,* 9H)
3b	2-Cl-C_6H_4–	1712	1658	–	7.01–8.03 (*m,* 8H)
3c	3-Cl-C_6H_4–	1716	1655	–	6.83–7.68 (*m,* 8H)
3d	4-Cl-C_6H_4–	1716	1662	–	7.11–8.12 (*m,* 8H)
3e	2,6-$(CH_3)_2$-C_6H_3–	1715	1661	2.62 (*s,* 6H, –CH_3)	6.90–7.89 (*m*, 7H)
3f	2-CH_3-5-Cl-C_6H_3–	1711	1660	2.59 (*s,* 3H, –CH_3)	6.94–8.01 (*m,* 7H)
3g	4-OCH_3-C_6H_4–	1716	1659	3.91 (*s,* 3H, –OCH_3)	7.22–8.15 (*m,* 8H)
3h	2-NO_2-C_6H_4–	1712	1662	–	6.98–8.02 (*m,* 8H)
3i	4-NO_2-C_6H_4–	1715	1663	–	6.99–7.98 (*m,* 8H)
3j	$C_4H_3N_2$–	1716	1664	–	7.24–7.92 (*m,* 6H)
3k	C_3H_2NS–	1716	1662	–	6.94–7.95 (*m,* 5H)

The other 2-arylimino-3-(3-chloro-2-benzo[*b*]thenoyl)-4-thiazolidinones **3a–d, f–k** were prepared in a similar manner. The physical and spectral data are recorded in Tables I and II, respectively.

RESULTS AND DISCUSSION

Antitubercular activity

The antitubercular evaluation of the compounds was carried out at the Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) U.S.A. Primary screening of the compounds for antitubercular activity was conducted at the minimum inhibition concentration of 6.25 μg/ml against *Mycobacterium tuberculosis* H_{37}Rv in BACTEC 12B medium using an ALAMAR radiometric system. The antimycobacterial activity data were compared with the standard drug rifampin at a 0.25 μg/ml concentration, which showed 98 % inhibition (Table III).

TABLE III. Antitubercular-screening result of compounds **1a–k**, **2a–k** and **3a–k** at concentration > 6.25 μg/ml.

Compd.	Assay	MTb strain	% Inhibition
1a	Alamar	H_{37}Rv	44
1b	"	"	31
1c	"	"	22
1d	"	"	43
1e	"	"	16
1f	"	"	18
1g	"	"	10
1h	"	"	19
1i	"	"	33
1j	"	"	69
1k	"	"	24
2a	"	"	26
2d	"	"	55
2e	"	"	13
2f	"	"	21
2g	"	"	27
3h	"	"	32
3i	"	"	34
3k	"	"	35

Antimicrobial activity

The anitmicrobial activity was assayed using the cup-plate agar diffusion method[9] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains, such as *Escherichia coli*, *Proteus vulgaris*, *Bacillus megaterium, Staphylococcus aureus* and fungi *Aspergillus niger* at 40 μg/ml concentration. Standard drugs, such as amoxicillin, ampicillin, ciprofloxacin, erythromycin and griseofulvin were used for comparison purposes (Table V).

TABLE IV. Antimicrobial activity of the compounds **1a–k**, **2a–k** and **3a–k**

Compd.	Zones of inhibition in mm				
	Antibacterial activity				Antifungal activity
	E. coli	*P. vulgaris*	*B. megaterium*	*S. aureus*	*A. niger*
1a	9	15	16	24	15
1b	18	25	11	11	16
1c	16	21	16	16	18
1d	12	19	16	20	19
1e	17	17	14	25	15
1f	14	15	12	30	21
1g	6	14	13	17	14
1h	12	13	14	20	19
1i	16	21	12	19	16
1j	13	18	19	23	17
1k	21	17	16	23	12
2a	15	24	14	20	14
2b	6	9	12	28	16
2c	1	15	20	22	18
2d	15	24	18	31	21
2e	14	21	16	18	18
2f	9	23	17	30	23
2g	20	14	15	23	24
2h	22	16	19	18	17
2i	16	12	14	31	16
2j	14	19	13	26	24

TABLE IV. Continued

Compd.	Zones of inhibition in mm				
	Antibacterial activity				Antifungal activity
	E. coli	*P. vulgaris*	*B. megaterium*	*S. aureus*	*A. niger*
2k	16	12	20	20	9
3a	15	19	19	16	24
3b	8	15	17	26	12
3c	16	20	20	15	19
3d	8	5	16	10	15
3e	18	14	19	18	24
3f	9	12	12	16	17
3g	16	11	15	19	16
3h	14	17	13	15	18
3i	13	19	14	12	21
3j	8	12	12	17	25
3k	21	23	15	21	14
Ampicillin	17	25	16	22	0
Amoxicillin	16	15	15	18	0
Ciprofloxacin	20	28	15	28	0
Erythromycin	25	26	20	18	0
Griseofulvin	0	0	0	0	22

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ИЗВОД

ХЕТЕРОЦИКЛИЧНИ СИСТЕМИ СА S/N РЕГИОСЕЛЕКТИВНОМ НУКЛЕОФИЛНОМ КОМПЕТИЦИЈОМ: ЛАКА СИНТЕЗА, АНТИТУБЕРКУЛОЗНА И АНТИБАКТЕРИЈСКА АКТИВНОСТ ТИОХИДАНТОИНА И ИМИНОТИАЗОЛИДИНОНА КОЈИ САДРЖЕ ДЕРИВАТЕ БЕНЗО[b]ТИОФЕНА

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Потребна једињења *N*-арил-*N'*-(3-хлоро-2-бензо[*b*]теноил)-тиоурее **1a–k** добијена су кондензовањем 3-хлоро-2-бензо[*b*]теноил-хлорида са различитим арил-аминима и амонијум-тиоцијанатом. Накнадним третирањем хлорсирћетном киселином ова једињења дају 1-арил-3-(3-хлоро-2-бензо[*b*]теноил)-тиохидантоине **2a–k**, док третирањем истом киселином у присуству натријум-ацетата дају 2-арилимино-3-(3-хлоро-2-бензо[*b*]теноил)-4-тиазолидиноне **3a–k**. Свим синтетисаним једињењима испитана је антитуберкулозна и антибактеријска активност. Нека од ових једињења издвојена су за даље праћење њихове антитуберкулозне активности.

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