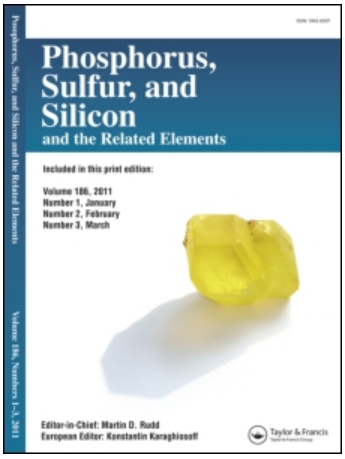

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New Biologically Active N-(Tetrahydrobenzothienopyrimidin-4-YL)-Amino Acids, Thiourethane, Sulfonamides and Related Compounds

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NEW BIOLOGICALLY ACTIVE N-(TETRAHYDROBENZOTHIENO-PYRIMIDIN-4-YL)-AMINO ACIDS, THIOURETHANE, SULFONAMIDES AND RELATED COMPOUNDS

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Some derivatives of thieno[2,3-d]pyrimidine containing amino acids **3a-i**, imidazoles **4a-f**, isothiocyanate **5**, thiourethane **6**, triazine **8**, pyrimidine **10**, sulphonamides **13a-d**, **14**, pyrazole **16** and pyrazolone **17** were synthesized. The structural assignments of the new compounds were based on analytical, spectroscopic measurements and chemical reactions. Some of the obtained compounds showed interesting antimicrobial activities.

Keywords: Amino acids; thiourethane; sulfonamides; antimicrobial activity

INTRODUCTION

Derivatives of thieno[2,3-d]pyrimidine are known to be potential bioactive molecules. They have various biological activities including antibacterial[1], antifungal[2], antimicrobial[3], antitumor[4], radioprotection[5], antiallergic[6], analgesic[7] and CNS[8] activities. Also, compounds having amino acid moieties are known to possess a wide rang of biological and pharmacological activity[9]. In addition sulphonamides have been widely used as bacteriostatic agents[10,11]. In the present paper I report the synthesis of some compounds combining amino acids, imidazoles, thiourethane, sulfonamides,

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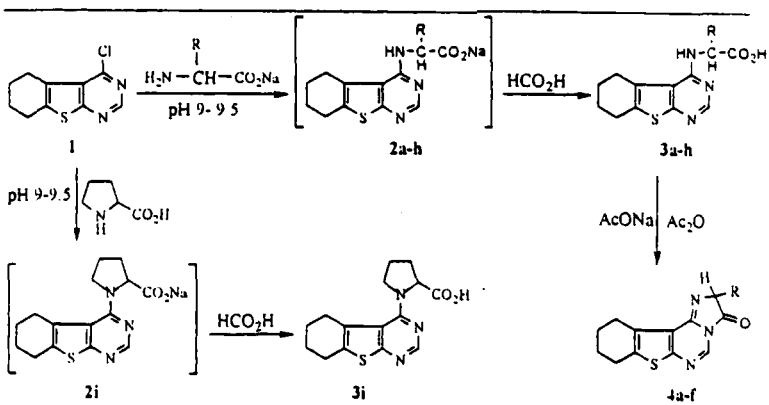
pyrazole, and pyrazolone with the thienopyrimidine moiety to evaluate their antimicrobial activities against Gram positive and Gram negative bacteria and yeast.

RESULTS AND DISCUSION

The present work was aimed at synthesizing new thienopyrimidine derivatives expected to have antimicrobial activity. When the chloro derivative **1**[12] was allowed to react with the sodium salt of various amino acids under reflux at pH 9–9.5, the corresponding N-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yl)-amino acids **3a-i** were afforded (Scheme 1). The structure of products which showed ν NH and νC=O in the 3430–3250 and 1750–1700 cm^{-1} regions respectively, in addition to another band in the 1254–124 cm^{-1} region for a -COOH group[13].

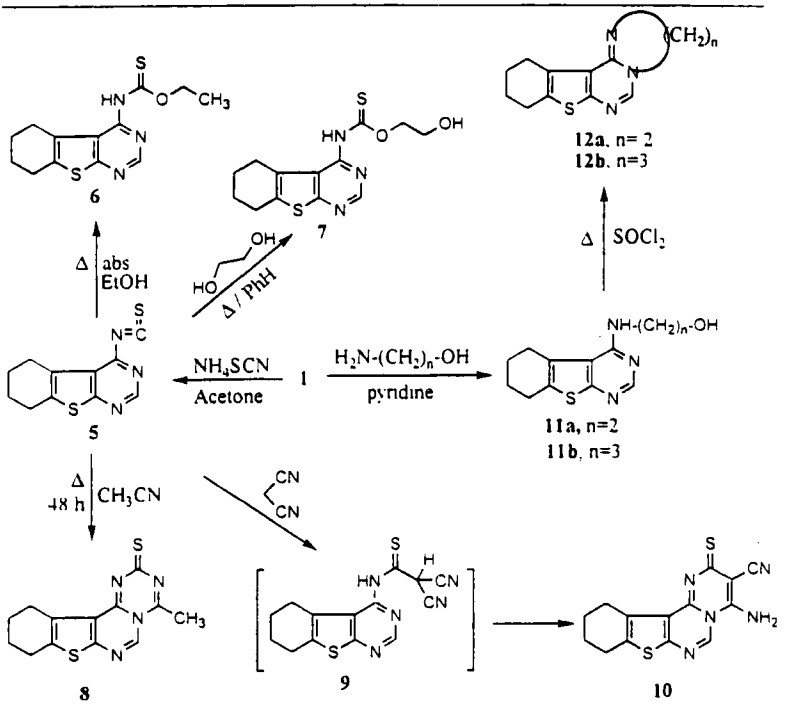


3,4	R	3,4	R
a	H	e	$CH_2CH_2SCH_3$
b	CH_3	f	CH_2Ph
c	$CH(CH_3)_2$	g	CH_2OH
d	$CH_2CH(CH_3)_2$	h	CH_2CO_2H

SCHEME 1

The amino acid derivatives **3a-f** were then cyclized with acetic anhydride in the presence of anhydrous sodium acetate[14] to give the imidazol derivatives **4a-f**, its IR spectra showed the absence of (NH) band. The pos-

tulated structures were confirmed by IR, ^{1}HNMR, mass spectral data (Table I) and elemental analysis. The 5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yl-isothiocyanate **5** was obtained via reaction of the chloro derivative **1** with ammonium sulfocyanide in dry acetone. The IR spectrum showed a strong absorption band at 2165 cm^{-1} due to (-N=C=S), (Scheme 2).



SCHEME 2

The thiourethane **6** was readily obtained upon heating the isothiocyanate **5** in absolute ethanol. The reactivity of isothiocyanate group in compound **5** was further investigated through reaction with ethylene glycol to give the corresponding hydroxy derivative **7**. Structure of **6** was established based on ^{1}H NMR which showed a triplet at 1.4 ppm and a quartet at 4.4 ppm due to the OCH_2CH_3 moiety and confirmed by mass spectrum which showed m/z (%): 293 (8.12, M^+); (Table I).

TABLE I Physical and spectral data of the synthesized compounds 3–17

Compd. No.	M.P. (°C) Yield(%)	Mol. Formula (Mol. Wt)	Elemental analyses Calculated/Found			IR (cm^{-1})	^{1}HBMR (δ ppm)
			C%	H%	N%		
3a	230–232	$C_{12}H_{13}N_3O_2S$	54.69	4.93	15.95	3423 (NH), 2930 (CH aliph), 1730 (C=O), 1244 (CO_2H)	1.6, 2.8 (2s, 8H, $4CH_2$ cyclo), 4.1 (s,2H,α-CH_2), 7.7 (s, 1H, NH), 8.1 (s, 1H, CH pyrimidine-H).
	85	(263.3)	54.50	4.70	15.80		
3b	215–217	$C_{13}H_{15}N_3O_2S$	56.25	5.41	15.14	3415 (NH), 2938 (CH aliph), 1700 (C=O), 1241 (CO_2H)	1.7, 2.6 (2s, 8H, $4CH_2$ cyclo), 3.4 (d, 3H, CH_3), 4.9 (m, 1H, α-CH), 7.6 (s,1H,NH), 8.4(s,1H, CH pyrimidine-H).
	79	(277.3)	56.40	5.20	15.30		
3c	164–166	$C_{15}H_{19}N_3O_2S$	58.97	6.22	13.76	3430 (NH), 2948 (CH aliph), 1700 (C=O), 1250 (CO_2H)	1.1(t, 6H, γ-CH_3) 1.5, 2.8(2s,8H,$4CH_2$ cyclo), 2.4(m, 1H, β-CH), 4.1 (m,1H,α-CH), 7.5 (s, 1H, NH), 8.0 (s, 1H, CH pyrimidine-H).
	80	(305.2)	58.90	6.10	13.50		
3d	152–154	$C_{16}H_{21}N_3O_2S$	60.11	6.57	13.15	3392 (NH), 2946 (CH aliph), 1740 (C=O), 1254 (CO_2H)	0.7(d,6H,$2CH_3$), 1.5, 2.6(2s, 8H, $4CH_2$ cyclo), 2.2 (t,2H,β-CH_2), 4.3(m,1H,β-CH), 5.8 (t,1H,α-CH), 7.7(s, 1H, NH), 8.0(s,1H,CH pyrimidine-H)
	81	(319.4)	60.30	6.80	13.40		
3e	196–198	$C_{15}H_{19}N_3O_2S_2$	53.35	5.63	12.44	3390(NH), 2927(CH aliph), 1720 (C=O), 1249 (CO_2H)	1.5, 2.8 (2s, 8H, $4CH_2$ cyclo), 2.1 (s,3H, SCH_3), 2.3 (m, 2H,β-CH_2), 2.6(m, 2H,γ-CH_2), 4.5(m,1H,α-CH), 7.6 (s, 1H, NH), 8.2(s,1H,CH pyrimine-H).
	84	(337.4)	53.60	5.80	12.20		
3f	174–176	$C_{19}H_{19}N_3O_2S$	64.51	5.37	11.88	3250 (NH), 2940 (CH aliph),	1.6, 2.8(2s, 8H, $4CH_2$ cyclo), 3.3 (d,2H, β-CH_2),
	77	(353.4)	64.30	5.20	11.60	1710 (C=O), 1248 (CO_2H)	4.9(q,1H,α-CH), 7.0–7.6 (m,5H, arom), 7.8 (s, 1H, NH), 8.1 (s, 1H, CH pyrimidine-H).
3g	229–231	$C_{13}H_{15}N_3O_3S$	53.18	5.11	14.32	3500 (OH), 3420 (NH), 2920 (CH aliph), 1730 (C=O), 1248 (CO_2H)	1.6, 2.7 (2s, 8H, $4CH_2$ cyclo), 2.3 (m,2H, β-CH_2), 3.2 (m, 1H, α-CH), 7.0(s, 1H, NH), 7.6 (s, 1H, OH), 8.3 (s, 1H, CH pyrimidine-H)
	72	(293.3)	53.40	5.30	14.20		

Compd. No.	M.P. (°C) Yield(%)	Mol. Formula (Mol. Wt)	Elemental analyses Calculated/Found			IR (cm^{-1})	^{1}HBMR (δ ppm)
			C%	H%	N%		
3h	252–254	$C_{14}H_{15}N_3O_4S$	52.28	4.66	13.07	3390 (NH), 2910 (CH aliph), 1700 (C=O), 1254 (CO_2H)	1.6, 2.7 (2s, 8H,4CH_2 cyclo), 2.9 (d,2H, β-CH_2), 4.9 (m, 1H, α-CH), 7.7(s, 1H, NH), 8.2(s,1H, CH pyrimidine-H).
	62	(321.3)	52.50	4.40	13.20		
3i	170–172	$C_{15}H_{17}N_3O_2S$	59.34	5.60	13.84	1720 (C=O), 1630 (C=N), 1251 (CO_2H).	1.7, 2.8 (2s, 8H, 4CH_2 cyclo), 2.0 (m, 2H, γ-CH_2), 2.4 (m,2H, β-CH_2), 3.9 (m,2H δ-CH_2), 4.3 (m,1H,δ-CH), 8.1(s, 1H, CH pyrimidine-H).
	68	(303.3)	59.10	5.40	13.90		
4a	280–282	$C_{12}H_{11}N_3OS$	58.70	4.48	17.12	1700 (C=O), 1630 (C=N)	1.8, 2.6 (2s, 8H,4CH_2 cyclo), 3.2 (s,2H, CH_2), 8.0 (s,1H, CH pyrimidine-H).
	86	(245.3)	58.50	4.70	17.30		
4b	186–188	$C_{13}H_{13}N_3OS$	60.16	5.01	16.19	1690 (C=O), 1610 (C=N)	1.6, 2.8 (2s, 8H,4CH_2 cyclo), 2.4 (d, 3H, CH_3), 5.4 (q, 1H, α-CH), 8.3 (s, 1H, CH pyrimidine-H).
	69	(259.3)	60.30	5.20	16.30		
4c	174–176	$C_{15}H_{17}N_3OS$	62.65	5.91	14.61	1680 (C=O), 1600 (C=N)	0.9(d, 6H, 2CH_3), 1.9,2.8 (2s, 8H, 4CH_2 cyclo), 5.2 (m,1H,β-CH), 5.6(d,1H,α-CH), 8.3 (s,1H, CH pyrimidine-H).
	70	(287.3)	62.40	5.60	14.40		
4d	146–148	$C_{16}H_{19}N_3OS$	63.70	6.30	13.93	1700 (C=O), 1640 (C=N)	
	59	(301.4)	63.90	6.10	14.10		
4e	127–129	$C_{15}H_{17}N_3OS_2$	56.35	5.32	13.15	1705 (C=O), 1620 (C=N)	1.7, 2.8 (2s, 8H, 4CH_2 cyclo), 2.0 (1,2H, CH_2S-),
	64	(319.4)	56.60	5.10	13.30		2,2(s,3H,SCH_3), 2.2 (s, 3H, SCH_3), 2.6(m,2H,β-CH_2), 5.8(s, 1H,α-CH), 8.3(s,1H,CH pyrimidine-H).
4f	134–136	$C_{19}H_{17}N_3OS$	67.99	5.07	12.52	1710 (C=O), 1630 (C=N)	1.8, 2.8(2s, 8H, 4CH_2 cyclo), 3.7(d,2H, β-CH_3), 4.8(t,1H,α-CH), 7.2–7.6 (m, 5H,arom.), 8.2(s,1H, CH pyrimidine-H).
	68	(335.3)	67.70	5.20	12.70		

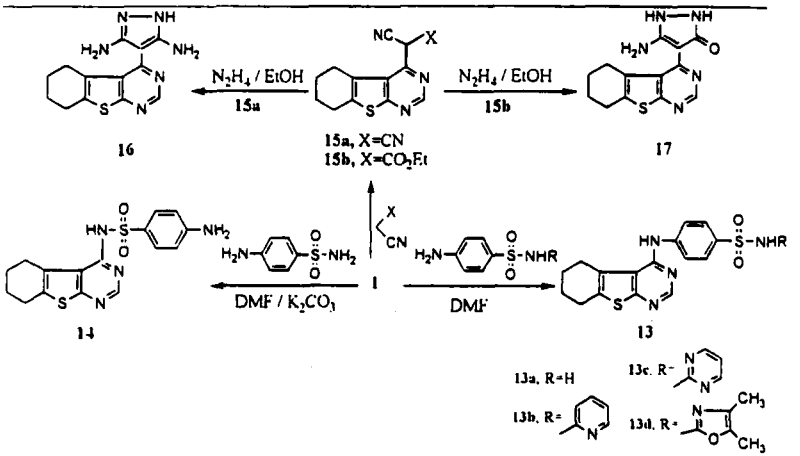
Compd. No.	M.P. (°C) Yield(%)	Mol. Formula (Mol. Wt)	Elemental analyses Calculated/Found			IR (cm^{-1})	^{1}HBMR (δ ppm)
			C%	H%	N%		
5[a]	154–156	$C_{11}H_9N_3S_2$	53.37	3.64	16.98	2165 (-N=C=S), 1610 (C=N)	1.5, 2.6 (2s, 8H, $4CH_2$ cyclo), 8.4(s, 1H, CH pyrimidine-H).
	84	(247.3)	53.20	3.90	16.70		
6[a]	210–212	$C_{13}H_{15}N_3OS_2$	53.17	5.11	14.31	3200(NH), 2900(CH aliph), 1608 (C=N), 1280 (C=S)	1.4(t,3H,CH_3), 1.9, 2.8 (2s,8H,$4CH_2$cyclo), 4.41.4(t,3H,CH_3), 1.9, 2.8 (2s,8H,$4CH_2$cyclo), 4.4 1.4(t,3H,CH_3), 1.9, 2.8 (2s,8H,$4CH_2$cyclo), 4.4 (q,2H,CH_2), 7.9(s,1H,NH),8.3 (s,1H, CH pyrimidine-H).
	76	(293.4)	53.40	5.30	14.10		
7	205–207	$C_{13}H_{15}N_3O_2S_2$	50.42	4.84	13.57	3500(OH), 3310(NH), 2920 (CH aliph), 1620 (C=N), 1320 (C=S)	1.6,2.7(2s,8H,$4CH_2$ cyclo), 2.1 (t,2H,OCH_2), 3.6 (m, 2H, $HOCH_2$), 7.8 (s,1H,NH), 8.2 (s,1H, CH pyrimidine-H), 8.4(s,1H,OH).
	69	(309.4)	50.60	4.70	13.30		
8[a]	216–218	$C_{13}H_{12}N_4S_2$	54.11	4.16	19.42	1610, 1630 (C=N), 1310 (C=S)	1.7, 2.8(2s,8H,$4CH_2$ cyclo), 2.2 (s,3H, CH_2), 8.3(s,1H, pyrimidine-H).
	44	(288.3)	54.30	4.40	19.10		
10[a]	212–214	$C_{14}H_{11}N_5S_2$	53.60	3.51	22.33	3210, 3170 (NH_2), 2210 (C≡N), 1600 (C=N), 1280 (C=S)	
	66	(313.4)	53.30	3.20	22.50		
11a	80–82	$C_{12}H_{15}N_3OS$	57.76	6.01	16.84	3500 (OH), 3220 (NH), 1620 (C=N)	1.9, 2.9(2s,8H,$4CH_2$ cyclo), 3.7 (m,2H,-NCH_2), 4.9 (t,2H,OCH_2), 6.4 (t,1H,NH), 8.2 (s,1H, CH pyrimidine-H)
	82	(249.3)	57.50	6.20	16.60		
11b	180–182	$C_{13}H_{17}N_3OS$	59.24	6.45	15.95	3500 (OH), 3310 (NH), 1630 (C=N)	1.7, 2.7(2s,8H,$4CH_2$ cyclo), 3.3 (m,4H,-NCH_2CH_2), 4.5 (t,2H,OCH_2), 6.4(t,1H,NH), 8.1(s,1H, CH pyrimidine-H)
	89	(263.3)	59.50	6.60	15.70		

Compd. No.	M.P. (°C) Yield(%)	Mol. Formula (Mol. Wt)	Elemental analyses Calculated/Found			IR (cm^{-1})	^{1}HBMR (δ ppm)
			C%	H%	N%		
12a	176–178	$C_{12}H_{13}N_3S$	62.25	5.62	18.15	1607 (C=N)	1.6. 2.7(2s,8H,4CH_2 cyclo), 4.2 (m,4H,-CH_2CH_2-), 8.3 (s, 1H, CH pyrimidine-H)
	78	(231.3)	62.50	5.30	18.40		
12b	>280	$C_{13}H_{15}N_3S$	63.59	6.11	17.12	1620 (C=N)	
	61	(245.3)	63.40	6.30	17.40		
13a[b]	> 280	$C_{16}H_{16}N_4O_2S_2$	53.27	4.44	15.53	3430, 3338, 3253 (NH, NH_2), 1607 (C=N)	1.7, 2.6 (2s,8H,4CH_2 cyclo), 5.7(s,2H,-NH_2), 7.1–7.8 (m, 4H, arom),8.2(s,1H, CH pyrimidine-H), 9.0 (s, 1H, NH).
	83	(360.4)	53.50	4.20	15.20		
13b	225–227	$C_{21}H_{19}N_5O_2S_2$	57.60	4.34	16.00	3350, 3270(NH), 1610 (C=N)	1.6, 2.8(2s,8H,4CH_2 cyclo), 7.1–7.9 (m, 8H, arom.), 8.2 (s, 1H, CH pyrimidine-H) 8.4 (s,1H,NH), 11.5 (s, 1H, NH).
	59	(437.5)	57.30	4.10	16.20		
13c	>280	$C_{20}H_{18}N_6O_2S_2$	54.73	4.10	19.15	3380, 3290 (NH), 1630 (C=N)	1.8, 2.8(2s,8H,4CH_2 cyclo), 7.0–8.0 (m, 7H,arom.), 8.2 (s, 1H, CH pyrimidine-H) 8.5 (s,1H,NH), 11.7 (s, 1H, NH).
	61	(438.5)	54.90	4.30	19.40		
13d	230–232	$C_{21}H_{21}N_5O_3S_2$	55.32	4.61	15.36	3410, 3350 (NH), 1620 (C=N)	1.8, 2.9 (2s,8H,4CH_2 cyclo), 2.0, 2.2 (2s,6H,2CH_3), 7.1–7.6 (m,4H,arom.), 8.2 (s,1H,CH pyrimidine-H) 8.4 (br, 2H, 2NH).
	54	(455.5)	55.60	4.40	15.10		
14	250–252	$C_{16}H_{16}N_4O_2S_2$	53.27	4.44	15.53	3353 3230 (NH_2), 1600 (C=N)	1.5, 2.7(2s,8H,4CH_2 cyclo), 5.4 (s,2H,NH_2), 7.0–7.9 (m, 4H,arom.), 8.3 (s,1H, CH pyrimidine-H), 9.2 (s, 1H, NH).
	78	(360.4)	53.50	4.60	15.70		
15 a	230–232	$C_{13}H_{10}N_4S$	61.34	3.93	22.02	2192,2185 (2C≡N), 1630 (C=N)	1.6, 2.8 (2s, 8H, 4CH_2 cyclo), 6.7 (s, 1H, CH), 8.2 (s, 1H, CH pyrimidine-H).
	68	(254.3)	61.60	4.20	22.20		

Compd. No.	M.P. (°C) Yield(%)	Mol. Formula (Mol. Wt)	Elemental analyses Calculated/Found			IR (cm^{-1})	^{1}HBMR (δ ppm)
			C%	H%	N%		
15b	218–220	$C_{15}H_{15}N_3O_2S$	59.74	4.97	13.94	2200 (C≡N), 1740 (C=O), 1640	1.2 (t, 3H (CH_3), 1.7, 2.8 (2s, 8H, 4CH_2 cyclo), 4.3 (q, 2H, CH_2), 6.5 (s, 1H, CH), 8.3(s,1H, CH pyrimidine-H).
	63	(301.3)	59.80	4.60	13.70	(C=N).	
16	259–261	$C_{13}H_{14}N_6S$	54.48	4.89	29.34	3361, 3329, 3130 (NH, NH_2), 1645 (C=N)	1.8, 2.6 (2s, 8H, 4CH_2 cyclo), 5.8 (s, 4H, 2NH_2), 8.2 (s, 1H, CH pyrimidine-H), 9.5 (s,1H,NH).
	54	(286.3)	54.70	4.60	29.60		
17	> 280	$C_{13}H_{13}N_5OS$	54.29	4.52	24.36	3330, 3248, 3215 (NH, NH_2), 1680 (C=O), 1630 (C=N)	1.6, 2.7 (2s, 8H, 4CH_2 cyclo), 5.6 (s,2H, NH_2), 8.1 (s, 1H, CH pyrimidine-H), 9.2, 9.4 (2s, 2H, 2NH).
	60	(287.3)	54.60	4.30	24.10		

a. MS: m/z (%) for compound **5**; 247 (100, M^+); **6**: 293 (8.12, M^+), 69 (100); **8**: 289 (18.3, M+1), 59 (100); **10**: 313 (0.8, M^+), 222 (100)
b. MS: m/z (%) for compound **13a**: 360 (100, M^+).

Fusion of the isothiocyanate **5** with methyl cyanide proceedes through [4+2]cycloadition[15] to furnish the triazine derivative **8**. The IR spectrum of **8** showed the absence of (-N=C=S) band in the parent compound. The ^{1}HNMR of **8** was characterized by the methyl protons at 2.2 ppm. The mass spectrum of **8**showed m/z (%): 289 (18.3, M+1). It was reported that the condensation of isothiocyanate with active methylene (malononitrile or ethyl cyanoacetate) was exploited in the synthesis of heterocyclic derivatives[16]. Thus, interaction of the isothiocyanate **5** with malononitrile in presence of sodium ethoxide gave the pyrimidine derivative **10** through the intermediate **9**. The IR spectrum of **10** exhibited bands at 3360, 3280, 2210 due to (NH_2) and (C≡N). Interaction of the chloro derivative **1** with ethanolamine or 3-amino propanol in pyridine yielded the hydroxy compounds **11a,b**, which cyclized by action of thionyl chloride to give the imidazole or pyrimidine derivatives **12a** or **12b**, respectively. The IR spectra of **11a,b** showed the presence of (OH) band at 3500 cm^{-1}and (NH) band at 3310, 3220 cm^{-1}. The IR spectra of **12a,b** showed the disappearance of (OH) and (NH) bands (Table I). ^{1}H NMR spectra of **11a,b** showed the presence of methylene protons. Condensation of the chloro derivative **1** with some sulpha drugs in N,N-dimethyl-formamide (DMF) only gave the sulfonamide derivatives **13a-d**, whereas, conducting this reaction in presence of anhydrous K_2CO_3[17] afforded sulfanilamide derivative **14** (Scheme 3).



SCHEME 3

Compound **1** reacted with active methylene compounds (malononitrile or ethyl cyanoacetate) in pyridine to afford the corresponding 4-alkylthienopyrimidine derivative **15a,b**. The IR spectrum of **15a** showed absorption bands at 2192, 2185 (2 C≡N), IR spectrum of **15b** exhibited bands at 2200 (C≡N), 1740 (C=O) ^{1}H NMR of **15b**showed a triplet at 1.2 ppm and a quartet at 4.3 ppm due to the -$COOCH_2CH_3$ moiety. Treatment of **15a,b** with hydrazine hydrate in boiling ethanol furnished the pyrazole **16** and pyrazolone **17**. The IR spectra showed the disappearance of (C≡N) and presence of (NH, NH_2) bands at 3361–3130 cm^{-1}; (Table I).

BIOLOGICAL ACTIVITY

The prepared compounds were evaluated for their antimicrobial activity using the agar diffusion technique[18]. A 1 mg/ ml solution in dimethylformamide was used. The test organisms were Gram positive bacteria (*Bacillus ceraus* and *Staphylococcus aureus)*, Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and yeast (Candida albicans) (local isolate). DMF showed no inhibition zones. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured using the two fold serial dilution method. Amikin was taken (in a concentration of 30 μg/ml) as a reference antibiotic.

Results (Table II) revealed that compounds **3c, 3i, 4c, 4f, 13d** and **15a** are highly active against Gram positive bacteria and their (MIC values were < 25 μg/ml). Compounds **3a, 3e, 3f, 3i and 4f** possess high potency against Gram negative bacteria and their (MIC values were < 50 μg/ml). These active compounds showed a considerable antimicrobial activity compared to the antibiotic Amikin. On the other hand compounds **3a, 3c, 3d, 3e, 3f, 4b, 4c, 4f** and **15a** showed the highest activity against yeast (Candida albicans) and their (MIC values were < 50 μg/ml). The other tested compounds showed mild activities against the tested micro-organisms.

EXPERIMENTAL

All m.p.'s are uncorrected. IR spectra (cm^{-1}) were taken with a Perkin Elmer FT-IR spectrophotometer as KBr pellets. ^{1}HNMR spectra were

recorded on a varian EM-390 (90 MHz) spectrophotometer using DMSO-d_6 as a solvent. Mass spectra were recorded on a HP MODEL MS-5988 instrument at 70 eV. Microanalytical data were obtained from the microanalytical data unit at Cairo University, Egypt.

TABLE II Antimicrobial activity of the prepared compounds

Compd. No.	*Bacillus ceraus*	*Staphylococcus aureus*	*Eschericha coli*	*Pseudomonas aeruginosa*	*Candida albicans*
3a	++++	++++	+	++++	+++
3b	++++	++++	+	+++	++
3c	++++	+++++	+	+++	+++
3d	+++	++++	+++	++	+++
3e	+++	+++	+++	+++	+++
3f	+++	++++	+++	+++	+++
3g	+++	++++	++	++	+
3h	++	+++	+	+++	++
3i	+++++	++++	+++	++++	++
4a	++	+++	+	++	+
4b	+++	++++	+	+++	+++
4c	+++	++++	+	++	+++
4d	+++	++++	+++	++	+
4e	+++	+++	++	++	+
4f	+++	++++	+++	+++	+++
5	++	+++	+	++	++
6	++	+++	+	+	++
7	+	+	++	+	++
8	++	+++	++	+	++
10	+++	+++	++	+	++
11a	+++	++++	+	+	++
11b	+++	++++	+	+	+
12a	+++	++	+	+	++
12b	+++	++	+	+	++
13a	+++	+++	+	++	++
13b	+++	+++	+	++	+
13c	++	++++	+	++	+

Compd. No.	*Bacillus ceraus*	*Staphylococcus aureus*	*Eschericha coli*	*Pseudomonas aeruginosa*	*Candida albicans*
13d	+++	++++	+	++	++
14	++++	++++	+	++	++
15a	+++++	+++++	++	++	+++
15b	++++	++++	++	+	++
16	++	++	+	+	++
17	++	+	+	++	+
Amikin	++++	++++	++	++	-

+: 1 to 1.5 cm; ++: 1.5 to 2 cm; +++: 2 to 3 cm; ++++: 3 to 4 cm; +++++: 4 to 5 cm.

Synthesis of N-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d] pyrimidin-4-yl)amino acids 3a-i

The amino acid (9.60 mmol) and sodium carbonate (5.40 mmol) were dissolved in water (10 ml), then adjusted to pH 9–9.5. The chloro derivative **1** (4.80 mmol) was then added and the mixture was stirred at 100°C for 6 h with control of pH. The reaction mixture was left overnight at room temperature, then treated with formic acid (88%). The solid product obtained was filtered off, washed with water and crystallized from dioxane to give **3a-i**; (Table I).

Synthesis of 2-Substituted-3-oxo-8,9,10,11-tetrahydro[1]benzothieno [2',3':4,5]pyri-mido[6,1-c]imidazole 4a-f

A mixture of **3a-f** (10 mmol), acetic anhydride (5 ml), and anhydrous sodium acetate (10 mmol) was heated under reflux for 3 h. The solvent was removed and the residue washed with water, filtered, dried and crystallized from DMF-EtOH; (Table I).

Synthesis of 5,6,7,8-Tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4-yl-isothiocyanate 5

A mixture of the chloro derivative **1** (10 mmol) and NH_4SCN (10 mmol) was refluxed in dry acetone (30 ml) for 1 h. The solvent was then removed and the residue was crystallized from acetone to give **5**; (Table I).

Synthesis of 4-(Ethoxythiocarbonylamino)-5,6,7,8,-tetrahydrobenzo [b]thieno[2,3-d]-pyrimidine 6

A solution of the isothiocyanate derivative **5** (10 mmol) in absolute ethanol (20 ml) was refluxed for 5 h. The solvent was then removed and the residue was washed with ethanol, then crystallized from ethanol to give **6**; (Table I).

Synthesis of 4-[(2-Hydroxyethyloxy)thiocarbonylamino]-5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidine 7

To a solution of **5** (10 mmol) in benzene (20 ml), ethylene glycol (10 mmol) was added and the mixture was heated under reflux for 8 h, then left overnight at room temperature. The precipitated product was collected by filtration and crystallized from dioxane to give **7**; (Table I).

Synthesis of 4-Methyl-6-thioxo-9,10-,11,12-tetrahydro[1] benzothieno[2',3':4,5]-pyrimido-[6,1-c][1,3,5]triazine 8

The isothiocyanate derivative **5** (10 mmol) was added to acetonitrile (5 ml) and the reaction mixture was refluxed for 48 h, cooled and the obtained product was crystallized from dioxane to give **8**; (Table I).

Synthesis of 4-Amino-5-cyano-2-thioxo-9,10,11,12-tetrahydro[1] benzothieno-[2',3':4,5]pyrimido[6,1-c]pyrimidine 10

To a solution of sodium ethoxide (0.23 g Na in 10 ml absolute C_2H_5OH). compound **5** (10 mmol) and malononitrile (10 mmol) were added and the reaction mixture was refluxed for 6 h, cooled and neutralized with dilute HCl (10%). The obtained product was filtered, washed with ethanol and crystallized from DMF-H_2O to give **10**; (Table I).

Synthesis of 2-(5,6,7,8-Tetrahydrobenzo[b]thieno[2,3-d] pyrimidinylamino)-1-ethanol 11a and 3-(5,6,7,8-tetrahydrobenzo[b] thieno[2,3-d]pyrimidinylamino)-1-propanol 11b

A mixture of **1** (10 mmol) and ethanolamine or 3-aminopropanol (10 mmol) in 20 ml of pyridine was refluxed for 12 h, then cooled and

poured into an ice/HCl mixture. The separated solid was filtered off, washed with water, and crystallized from ethanol to give **11a,b**; (Table I).

Synthesis of 2,3,8,9,10,11-hexahydro[1]benzothieno[2',3':4,5] pyrimido[6,1-c]-imidazole 12a and 2,3,4,9,10,11,12-hepta[1] benzothieno[2',3':4,5]pyrimido[6,1-c] pyrimidine 12b

A solution of **11a,b** (10 mmol) in thionyl chloride (5ml) was refluxed for 8 h. The precipitated solid after cooling was crystallized from ethanol to give **12a,b**; (Table I).

Synthesis of N^4-(4,5,6,7-Tetrahydrobenzo[b]thieno[2,3-d] pyrimidinyl)sulfonamide 13a-d

A mixture of the chloro derivative **1** (10 mmol) and sulpha drugs (10 mmol) in N,N-dimethylformamide (20 ml) was heated under reflux for 12 h, poured into crushed ice. The solid product was collected and crystallized from DMF-EtOH to give **13a-d**; (Table I).

Synthesis of N^1-(4,5,6,7-Tetrahydrobenzo[b]thieno[2,3-d]pyrimidinyl) sulfanilamide 14

A mixture of **1** (10 mmol), sulfanilamide (10 mmol) and anhydrous K_2CO_3 (lg) was refluxed in DMF (30 ml) for 12 h, then cooled and poured into crushed ice. The solid product was collected and crystallized from DMF/H_2O; (Table I).

Synthesis of 1-Dicyano-1-(5,6,7,8-tetrahydrobenzo[b]thieno [2,3-d]pyrimidine) 15a and ethyl-2-cyano-2-(5,6,7,8-tetrahydrobenzo [b]thieno[2,3-d]pyrimidinyl)acetate 15b

A solution of **1** (10 mmol) and an active methylene compound (malononitrile or ethyl cyanoacetate) (10 mmol) in pyridine (20 ml) was refluxed for 5 h, then cooled and poured into ice/HCl mixture. The separated solid was filtered off, washed with water and crystallized from ethanol to give **15a,b**; (Table I).

Synthesis of 3,5-Diamino-4-(5,6,7,8-tetrahydrobenzo[b]thieno [2,3-d]pyrimidinyl)-1H-pyrazole 16 and 5-amino-4-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]pyrimidinyl)-2,3-dihydro-1H-3-pyrazolone 17

A mixture of **15a,b** (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (20 ml) was refluxed for 6 h, then allowed to cool. The solid product was collected and crystallized from ethanol to give **16,17**; (Table I).

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References

[1] M.M. Ghorab, H.I. Heiba, M.A. El-Gawish; Phosphorus Sulfur and Silicon, **106**, 85 (1995).

[2] M.M. Ghorab, S.G. Abdel-Hamide; Phosphorus Sulfur and Silicon, **106**, 9 (1995).

[3] H.I. Heiba, M.M. Ghorab, M.A. El-Gawish; Phosphorus Sulfur and Silicon, **131**, 197 (1997).

[4] M.M. Ghorab, O.M. Nassar, A.Y. Hassan; Phosphorus Sulfur and Silicon, **134/135**, 57 (1998).

[5] M.M. Ghorab, A.Y. Hassan, O.M. Nassar, Phosphorus Sulfur and Silicon, **134/135**, 447 (1998).

[6] E. Gillespie, K.W. Dungan, A.W. Gomoll, R.J. Seidehamel; J. Immunopharmacol. **7**, 655 (1985).

[7] R. Bohm, R. Muller, R. Pech; Pharmazie **41**, 661 (1986).

[8] M.B. Devani, C.J. Shishoo, U.S. Pathak, S.H. Parikh, G.F. Shah, A.C. Padhya; J. Pharm., Sci. **65**, 660 (1976).

[9] P.A. Petynin, M.S. Khodyeva; Chemical Structure and Biological Activity in the Series of Amides of Some Carboxylic Acids. Zh. Obshch. Khim, **33**, 755 (1963).

[10] R. Shankar, A.R. Devendra, E.R. Jayasene, V.M. Reddy, V.K. Saxena and R. Srivastava; J. Ind. Chem. Soc. **60**, 61 (1983).

[11] V.S. Misra, V.K. Saxena, R. Srivastava; J. Ind. Chem. Soc. **59**, 781 (1982).

[12] J.R. Vishnu, K.P. Hrishi, J.V. Arnold; J. Heterocyclic Chem., **18**, 1277 (1981).

[13] L.J. Bellamy; The Infra-red Spectra of Complex Molecules, Wiely, New York, 275 (1975).

[14] A.A. Afify, S. El-Nagdy, M.A. Sayed, I. Mohey; Indian J. Chem., **27B**, 920 (1988).

[15] S. Patai; The Chemistry of Cyanates and Their Thio Derivatives, part 2, John Wiely & Sons, chapter 22, page 1003 (1977).

[16] R.M. Mohareb, A. Habash, N.S. Ibrahim, S.M. Sherief; Synthesis 228 (1987).

[17] M.B. Hogale, A.R. Shelar, D.S. Kachare and V.K. Salunkhe; J. Indian Chem. Soc., **64**, 314 (1987).

[18] S.R. Jain, A. Kar; Planta Med. **20**, 118 (1971).