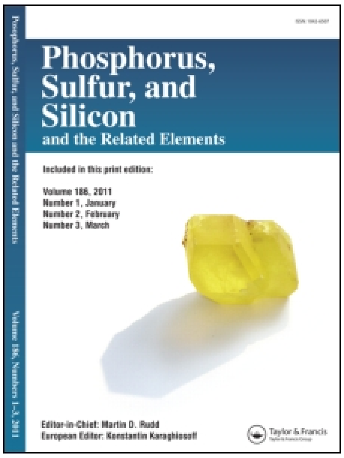

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Synthesis and Reactions of Some Tetrahydrobenzothieno[2,3- d]Pyrimidine Derivatives with Biological Interest

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SYNTHESIS AND REACTIONS OF SOME TETRAHYDROBENZOTHIENO[2,3-*d*]PYRIMIDINE DERIVATIVES WITH BIOLOGICAL INTEREST

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Hetetrocyclic substituted rings were prepared from 1-amino-2-carboxamido-4,5,6,7-tetrahydrobenzothiophene and carbon disulphide, chloroacetic acid, or arylidene with different active methylene groups. The antimicrobial activity of synthesized compounds is discussed.

INTRODUCTION

Many tetrahydrobenzothiophenes possess a wide span of medical activities including hypoglycemic,[1] antifibrillatory,[2] and antitumor characteristics.[3] Furthermore, divers biological properties have been associated with numerous thienopyrimidines and thiazolothienopyrimidines comprising hypnotic,[4] antivirol,[5,6] and plant bactericidal effects.[7]

Based on the foregoing, the synthesis of certain novel thieopyrimidines and thiazolothienopyrimidines were undertaken in and endeavor to produce heterocylic compounds of possible pharmacological activity.

Results and Discussion

Condensation of cyclohexanone with cyano(thio)acetamide and elemental sulfur in presence of morpholine afforded 2-amino-4,5,6,7-terahydrobenzothiophen-3-[carbo(thio)oxamide] **1a**,**b**. The reaction with cyanothioacetamide proceeded via a Gewald reaction,[8] followed by a condensation with another mole of cyclohexanone to yield **1a**. This structure was indicated via its mass spectrum where a molecular ion appeared at *m/z* 292 [M^+, 73.8%].

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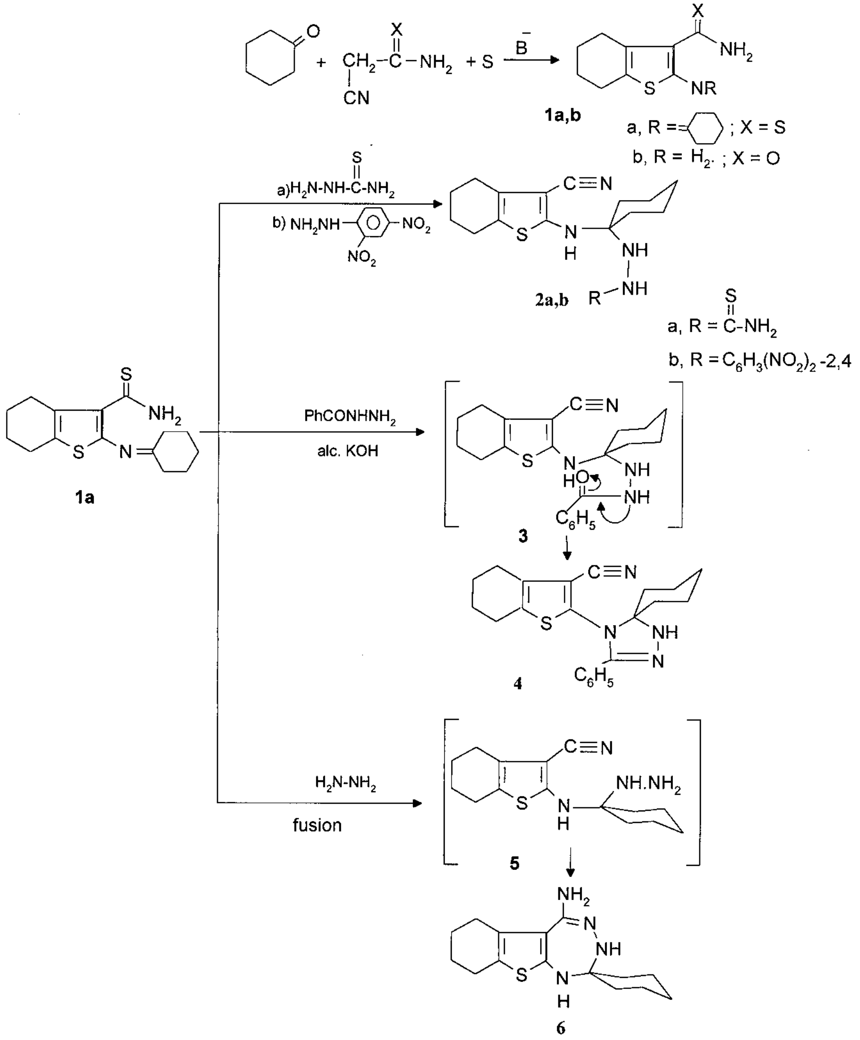


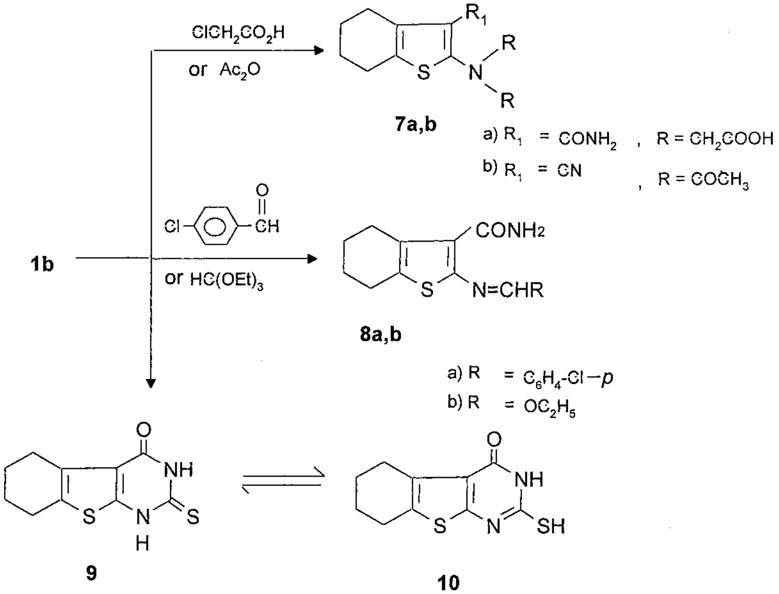
SCHEME 1

Interaction (Scheme 1) of 2-(*N*-cyclohexyl)-4,5,6,7-tetrahydrobenzothiophen-3-carbothioamide **1a** with thiosemicarbazide or 2,4-dinitrophenyl-hydrazine in the presence of alcoholic potassium hydroxide generated an adduct from which H_2S evolved to produce compounds **2a**,**b**. The infrared spectra showed the appearance of cyano group at 2199 cm^{-1}.

While the reaction **1a** with benzoyl hydrazide under the same conditions caused an evolution of H_2S to form the carbonitrile **3** as the intermediate, the latter lost one molecule of water to form triazolo derivative **4**. The IR spectrum of **4** showed the disappearance of the carbonyl group of benzoyl hydrazide and the appearance of a cyano group. On the other hand, fusion of thioamide derivative **1a** with hydrazine hydrate caused a loss of H_2S to yield the carbonitrile intermediate **5**, which underwent intermolecular cyclization to yield triazepine derivative **6** (Scheme 1).

Interaction of 2-amino-4,5,6,7-tetrahydrobenzothiophen-3-carboxamide **1b** with a equivalent of chloroacetic acid or acetic anhydride afforded *N,N*-disubstituted derivatives **7a,b.** However in the case of acetic anhydride, dehydration took place to give carbonitrile derivative **7b**, which was in agreement with spectral data where the mass spectrum of **7a** showed a molecular ion peak at 312. This was compatible with molecular formula $C_{13}H_{16}N_2O_5S$, and the IR spectrum of **7b** showed a cyano group at 2213 cm^{-1}.

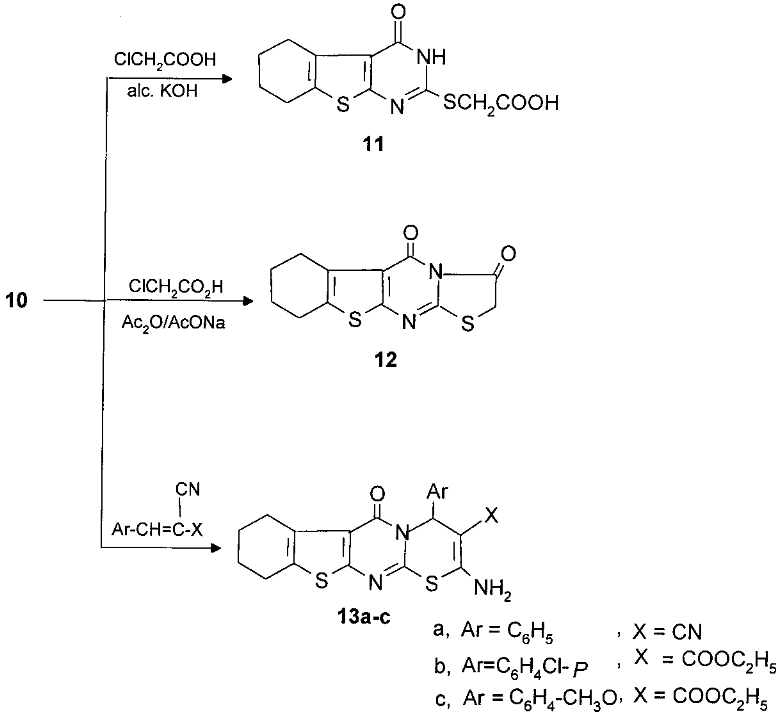
The Schiff's base **8a,b** were obtained through the condensation of **1b** with *p*-chlorobenzaldehyde in presence of triethylamine or triethylorthoformate in dimethylformamide respectively. Structures were assigned from mass spectral analysis. For example **8a** exhibited a molecular ion peak at *m/z* 318. The ^{1}H-NMR spectrum of **8a** showed a singlet at δ 7.8 which revealed a CH=N group and peaks of ethoxy at δ 1.0 (t, 3H, CH_3) and 3.6 (q, 2H, CH_2). Treatment of **1b** with



SCHEME 2

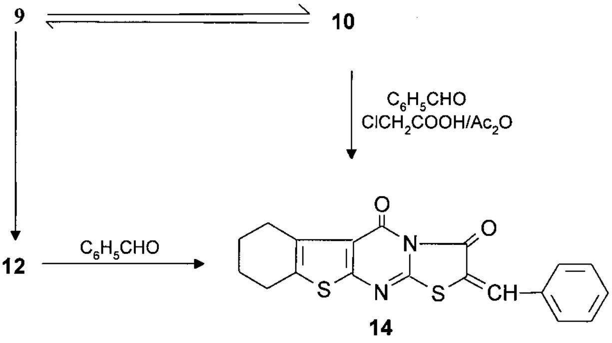
carbon disulphide yielded 2-thioxo-5,6,7-8-tetrahydrobenzothieno-[2,3-*d*]pyrimidin-4-(3H)one, either **9** or the possible isomer **10**. The mass spectrum of **9** revealed a molecular ion peak at *m*/*z* 238 [M^+, 100%] and this was compatible with the molecular formula $C_{10}H_{10}N_2OS_2$which was analogous to previous work.[9]

Condensation of 2-mercaptothieno[2,3-*d*]pyrimidin-4-one **10** with chloroacetic acid in presence of alcoholic potassium hydroxide caused alkylation of the thiol group to give thienopyrimidine derivative **11**. The interaction of **10** with chloroacetic acid in acetic anhydride in presence of anhydrous sodium acetate alkylation occurred, followed by cyclodehydration to produce thiazolopyrmidine derivative **12**. The IR spectrum of **11** showed a broad band of an OH, and a C=O of a carboxylic acid. The ^{1}H-NMR spectrum of **12** showed the presence of a CH_2 group of the thiazolidinone moiety at δ 4.0. Interaction of 2-mercaptothieno-[2,3-*d*]pyrimidin-4-(3H)one **10** with arylidene malonnitrile or ethylcyanoacetate led to the formation of the corresponding 2-amino-4-(aryl)-6-oxo-7,8,9,10-tetrahydro-1,3-thiazino-[3,2-*a*]-thieno-[2,3-*d*]-pyrimidine–3-carbonitrile (or carbethoxy, **13a–c**, Scheme 3).



SCHEME 3

Compound **12** that contained an active methylene group condensed with benzaldehyde to yield 2-(phenylmethylene)–3,5-dioxo-6,7,8,9-tetrahydrobenzo-1,3 thiazolo[3,2-*a*]thieno[2,3-*d*]pyrmidine **14**. The latter also could be conveniently prepared through reaction of **10** with chloroacetic acid and benzaldehyde in acetic anhydride in presence of anhydrous sodium acetate (Scheme 4).



SCHEME 4

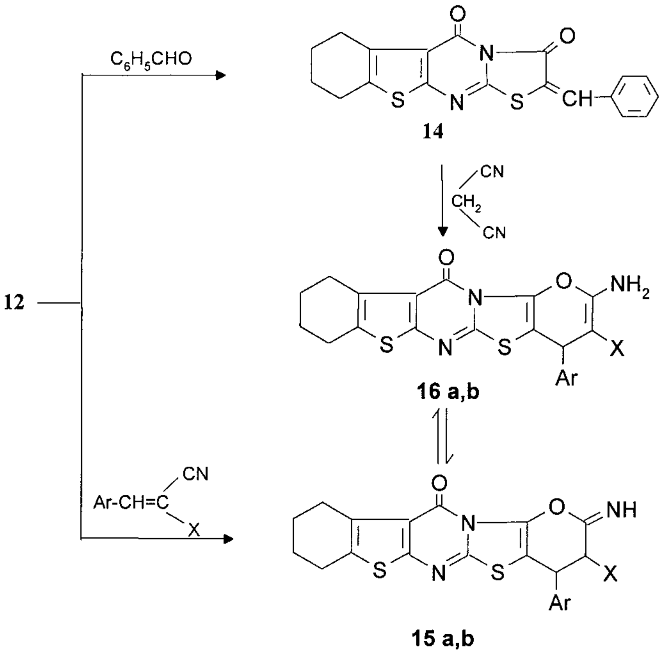
On the other hand, reaction of **12** with arylidene malononitrle or ethylcyanoacetate afforded **15a**,**b** or the possible isomer **16a**,**b**. The structure of **15a** was confirmed by elementary analysis and spectroscopic data wherein the ^{1}H-NMR spectrum showed signals at δ 5.6 (s, 1H, H_4 pyran moiety) and δ 7.3–7.6 (m, 7H, Ar—H + NH_2). The mass spectrum exhibited a molecular ion peak at 432 which is compatible with the molecular formula $C_{22}H_{16}N_4O_2S_2$. The ^{1}H-NMR spectrumof **15b** revealed a signal for the ethoxy group at δ 1.3 (t, 3H, CH_3) and δ 4.4 (q, 2H, CH_2) (Scheme 5).

EXPERIMENTAL

All melting points were uncorrected. The IR spectra were recorded in KBr on a unicam SP200 spectrophotometer. The ^{1}H-NMR ($CDCl_3$ or DMSO) spectra were obtained using a Geol DFF 100 (270 NH_2) with TMS as an internal reference. Mass spectra were recorded on a Varian mat. CH-48 spectrometer.

2-(*N*-Cyclohexyl)-4,5,6,7-tetrahydrobenzothiophene–3-thioamide (1a)

A mixture of cyclohexanone (0.1 mmol) cyanothioacetamide (0.1 mmol) and sulfur (0.1 mmol) in ethanol (30 ml) and morpholine (5 ml) was



15,16 a, Ar = C_6H_5 , X = CN

b, Ar = C_6H_4 OCH_3, X = COOEt

SCHEME 5

refluxed for 4 h. The reaction mixture was left to cool, and the solid formed was recrystallized from ethanol (Tables I and II). The **1b** was previously prepared.[9,10]

Mass spectrum of **1a**: *m/z* 292 (M^+ 73.8%), 263 (22%), 259 (33.4%) with base peak 249.

2-*N*-Cyclohexyl-4,5,6,7-tetrahydrobenzothiophene Hydrazide Derivatives (2a,b)

Compound **1a** (0.01 mmol) was refluxed with thiosemicarbazide or 2,4 dinitrophenylhydrazine (0.01 mmol) in ethanol for 6 h. The reaction mixture was left to cool, and the precipitate formed was filtered off and crystallized from a suitable solvent to give derivatives **2a**,**b** respectively.

2a Mass: *m/z* 349 [M^+, 1.05%], 300 [M^+-17(NH_3)], 259 (M^+-HCNS 59%), 236 (M^+-96 (⬡N)).

2b ^{1}H-NMR: δ 8.3 (s, 1H, NH), 7.8–7.0 (m, 8H, aromatic H's), 4.7$^{(DMSO)}$ (br. s, 1H, NH_2), 2.6–1.2 (2m, 18H, two cyclohexyl H's).

TABLE I Physical Properties of New Compounds

Comp. no.	m.p. °C	Solvent color	Yield %	Mol. form./m.wt.	Analysis calcd/found				
					C	H	N	S	Cl
1a	230	EtOH	60	$C_{15}H_{20}N_2S_2$	61.60	6.89	9.57	21.92	
		White		292.44	61.71	6.95	9.62	22.00	
2a	200	EtOH	65	$C_{16}H_{23}N_5S_2$	54.98	6.63	20.03	18.34	
		Gray		349.49	54.78	6.43	19.99	18.21	
2b	170	EtOH	60	$C_{21}H_{25}N_6O_4S$	55.12	5.50	18.36	17.00	
		Green		457.50	55.25	5.62	18.43	7.13	
4	165	EtOH	50	$C_{22}H_{24}N_4S$	70.17	6.42	14.88	8.51	
		Orange		376.50	70.27	6.51	14.91	8.61	
6	265	EtOH	55	$C_{15}H_{22}N_4S$	62.03	7.63	19.29	11.03	
		Brown		290.41	62.13	7.72	19.35	11.18	
7a	210	EtOH	70	$C_{13}H_{16}N_2O_5S$	49.99	5.16	8.96	10.26	
		Brown		312.32	50.1	5.22	9.10	10.35	
7b	140	EtOH	70	$C_{13}H_{14}N_2O_2S$	59.52	5.37	10.67	12.22	
		Gray		262.31	59.61	5.45	10.72	12.33	
8a	235	EtOH	60	$C_{16}H_{15}N_2OSCl$	60.27	4.74	8.78	10.65	11.12
		Green		318.79	60.11	4.62	8.77	10.55	11.00
8b	240	EtOH	90	$C_{12}H_{16}N_2O_2S$	57.11	6.39	11.10	12.70	
		Yellow		252.32	57.25	6.45	11.21	12.82	
10	245	EtOH	70	$C_{10}H_{10}N_2OS_2$	50.39	4.21	11.75	26.90	
		Brown		238.30	50.31	4.31	11.82	26.91	
11	200	EtOH	75	$C_{12}H_{12}N_2O_3S_2$	48.63	4.08	9.45	21.63	
		Brown		296.32	48.69	4.17	9.60	21.72	
12	165	EtOH	60	$C_{12}H_{10}N_2O_2S_2$	51.78	3.62	10.06	23.04	
		Brown		278.33	51.81	3.72	10.14	23.16	
13a	200	EtOH	75	$C_{20}H_{16}N_4OS_2$	61.20	41.6	14.27	16.33	
		Green		392.46	61.15	4.14	14.20	16.23	
13b	90	EtOH	60	$C_{22}H_{20}N_3O_3S_2Cl$	55.74	4.25	8.86	13.52	7.48
		Brown		473.94	55.54	4.20	8.66	13.42	7.38
13c	170	EtOH	60	$C_{23}H_{23}N_3O_4S_2$	58.83	4.93	8.95	13.65	
		Brown		469.50	58.91	5.07	9.10	13.72	
14	>300	EtOH	85	$C_{19}H_{14}N_2O_2S_2$	62.27	3.85	7.64	17.49	
		Brown		366.43	62.15	3.96	7.73	17.54	
15a	200	EtOH	75	$C_{22}H_{16}N_4O_2S_2$	61.09	3.72	12.95	14.82	
		Green		432.47	61.20	3.61	13.00	14.72	
15b	90	EtOH	60	$C_{25}H_{23}N_3O_5S_2$	58.92	4.55	8.24	12.60	
		Orange		509.57	59.05	4.61	8.30	12.52	

2-(*N*-Cyclohexyl)-4,5,6,7-tetrahydrobenzothiophene-3-(2-phenyl-1,2,4-triazol) (4)

Compound **1a** (0.01 mmol) was refluxed with benzoylhydrazide (0.01 mmol) for 4 h. The reaction mixture was left to cool. The crystals formed was recrystallized from a suitable solvent.

^{1}H-NMR: δ 8.2 (s, 1H, NH), 7.5–7.2 (m, 5H, aromatic H's), 3–1.8 (m, 18H, two cyclohexyl H's).

TABLE II IR Spectroscopic Data for the Prepared Compounds

Comp. no.	IR (KBr) cm^{-1}
1a	3141 (NH), 2923, 2844 (CH-aliphatic), 1539 (C=N) and 1224 (C=S)
2a	Broad band at 3189 (NH_2/NH), 2926, 2852 (CH-aliphatic 2199 (C≡N) and 1221 (C=S)
2b	Strong broad band at 3143 (NH), 2928, 2851 (CH-aliphatic and 2199 (C≡N)
4	3140 (NH), 2920, 2848 (CH-aliphatic), 2197 (C≡N) and 1521(C=N)
6	3378, 3299, 3176 (H_2N/NH), 2931, 2853 (CH-aliphatic) and 1623 (C=N)
7a	Broad band 3405 (HO/NH_2), 2930 (CH-aliphatic) and very strong band at 1657 (C=O)
7b	2934 (CH-aliphatic), 2213 (C≡N) and 1743, 1693 (C=O)
8a	Broad band 3100 (NH_2), 2924 (CH-aliphatic) and 1654 (C=O)
8b	2931 (CH-aliphatic) and 1631 (C=O)
10	3427 (NH), 1664 (C=O) and 1205 (C=S)
11	Broad band (3226–2300) OH of carboxylic) and 1689 (C=O)
12	3433 (OH), 2928 (CH-aliphatic) and 1663 (C=O)
13a	3320, 3181 (NH_2), 2931 (CH-aliphatic), 2195 (C≡N) and 1653 (C=O)
13b	3373, 3182 (NH_2), 2930 (CH-aliphatic) and 1637 (C=O)
13c	3371, 3186 (NH_2), 2931 (CH-aliphatic) and 1635 (C=O)
15a	3385 (NH), 2933, 2855 (CH-aliphatic), 2205 (C≡N) and 1686 (C=O)
15b	3373, 3182 (NH_2), 2930, 2855 (CH-aliphatic) and 1637 (C=O)

2-Cyclohexyl-4amino-6,7,8,9,-tetrahydrobenzothiophene-1,3,4-triazepine (6)

A mixture of **1a** (0.1 mmol) and excess hydrazine hydrate was fused for 1/2 h. The solid obtained was crystallized from suitable solvent (Tables I and II).

2-*N*-Diacetic Acid-3 Carboxamido-4,5,6,7-tetrahydrobenzothiophene (7a)

Compound **1b** (0.01 mmol) was refluxed with chloroacetic acid (0.01 mmol) in the presence of alcoholic KOH (20 ml) for 6 h. The mixture was cooled, and then acidified with dilute hydrochloric acid. The crystals formed were washed with water and crystallized from a suitable solvent.

Mass: *m/z* at 312 (M^+), 314 ($M^+ + 2$, 29.6%), 254 (51.9%), and a base peak at 192.

2-*N*-Diacetyl-3-cyano-4,5,6,7-tetrahydrobenzothiophene (7b)

Acetic anhydride (20 mmol) and compound **1b** (0.01 mmol) were refluxed for 8 h. The reaction mixture was allowed to cool, and then poured into water, the solid was filtered off, washed with H_2O, and recrystallized from a suitable solvent.

Mass: *m*/*z* at 262 (M^+, 3%), 220 [(M^+-43 ($COCH_3$), 90.4%], 197 (75.5%), and a base peak at 192.

SCHIFF'S BASES 8a,b

8a: *p*-Chlorobenzaldehyde (0.01 mmol) and compound **1b** (0.01 mmol) in ethanol (20 ml) and two drops of triethylamine were refluxed for 6 h. The reaction was cooled and acidified with dilute HCl. The solid formed was filtered and washed with water and recrystallized from a suitable solvent.

Mass: *m*/*z* at 318 (M^+, 1%), 283 (24%), and base peak at 62.

8b: Triethylorthoformate (0.04 mmol) in acetic anhydride (20 ml) and compound **1b** (0.01 mmol) were refluxed for 4 h. Cooling the reaction gave a solid which was filtered and recrystallized from a suitable solvent.

Mass: *m*/*z* at 252 (M^+, 4.861%) and a base peal at 62.

^{1}H-NMR: δ 7.8 (s, 1H, CH=N), 3.6 (q, 2H, CH_2), 2.8, 2.4, 1.4 $^{(CDCl_3)}$ (m, 10H, tetrahydrobenzo + NH_2) 1.0 (t, 3H, CH_3).

^{13}C: 170 (C=O), 143, 133, 131, 127, 125, 120 (4 thiophen C'S + 1 $^{(DMSO)}$ CH=N), 36,27 (2-aliphatic C'S) 26, 25, 23, 22 (4 tetrahydrobenzo C'S).

2-Thioxo-4,5,6,7-tetrahydrobenzothieno-(2,3,d)pyrimidine-4-(3H) one (10)

A mixture of compound **1b** (0.01 mmol), carbon disulphide (10 ml), and KOH (3.6 gm) in ethanol (50 ml) was refluxed in a water bath at 60–80°C for 24 h. The reaction mixture was acidified with dilute acetic acid, the solid formed was washed with water, filtered off, and recrystallized from a suitable solvent.

Mass: *m*/*z* at 238 (M^+ 100%), 210 (18,97%), 178 (62.4%) 151 (44.0 %).

2-*S*-Acetic-4-oxo-4H-4,5,6,7-tetrahydrobenzothiopheno-[3,2-e)pyrmidine (11)

A mixture of compound 10 (0.01 mmol) and chloroacetic acid (0.01 mmol) in acetic acid (20 ml) in presence of sodium acetate (0.01 mmol) were refluxed for 6 h. The reaction was cooled and the solid obtained was washed with water and recrystallized from a suitable solvent.

Mass: *m/z* at 296 (M^+,15.8%), 278 [(M-18 (H_2O), 100%].

Tetrahydrobenzothien(1,3)thiazolo(5,1-*b*)pyrimidine-3,4-dione (12)

A mixture of compound **10** (0.01 mmol) and chloroacetic acid (0.01 mmol) in acetic anhydride (30 m) in presence of sodium acetate (0.01 mmol were refluxed for 4–6 h. The mixture was cooled and then a poured into H_2O. The solid obtained was filtered and washed with H_2O several times and crystallized from a proper solvent.

Mass: *m/z* at 277 (M^+, 1%) and base peak at 238.

^{13}C: 169, 167(2C=O), 131, 126, 125, 124, 123, 120 [4-thiophene C'S + $^{(DMSO)}$ (1-pyrimidine + 1 thiazole C'S)], 26, 25, 24, 23, 22 (4-tetrahydrobenzo C'S).

^1H-NMR: δ 4.0–1.8 ppm (m, 10H, tetrahydrobenzo + CH_2 of $^{(DMSO)}$ thiazolidinone moiety).

2-Amino-4-(4-aryl)-6-oxo-7,8,9,10-tetrahydrobenzo-1,3-thiazine[3,2-*a*]-thieno[2,3-d]pyrimidin-3-carbonitrile or carboxylate (13a–c)

Compound **10** (0.01 mmol) and benzylidene malononitrile or *p*-chloro (*p*-methoxy)benzylidene ethylcyanoacetate (0.01 mmol) in ethanol (20 ml) and 2 drops of piperidine were refluxed for 8–10 h. The solid obtained was recrystallized from a suitable solvent to give **13a–c**.

13a: mass: *m/z* at 392 (M^+, 5.6%) 368 (9.05%), 320 (15.09%), 302 (38.79%).

13b: mass: *m/z* at 473 (M^+, 1.74%), 399 [M-73 (COOEt)] and a base peak at 318.

13c: ^1H-NMR δ 12.2 (s, 2H, NH_2, D_2O exchangeable), 8.3 (d, 1H, H_3 of thiazine moiety), 8.1–7.1 [d-d (A-B), 4H, aromatic] 4.2 (q, 2H, CH_2), 3.8 (s, 3H, OCH_3), 3.4 (d, 1H, H_4 of thiazine moiety), 2.7–1.6 (m, 8H, cyclohexyl H's), 1.2 (t, 3H, CH_3).

2-(Phenylmethylen)-3,5,dioxo-6,7,8,9-tetrahydrobenzo-1,3-thizolo[3,2-*a*]-thieno[2,3-*d*]pyrimidine (14)

Compound **12** (0.01 mmol) and benzaldehyde (0.01 mmol) in acetic anhydride and acetic acid (20 ml) were refluxed for 6 h. The mixture was cooled and poured into water. The solid obtained was filtered and was crystallized from a suitable solvent to give compound **14**.

Mass: *m/z* at 366 (M^+, 1.0%), 277 (2.5%), 238 (100%), 210 (14.3%).

2-Amino-4-(4-chlorophenyl)-12-oxo-8,9,10,11-tetrahydrobenzo-pyrano[2,3:4,5]thiazolo[3,2-*a*]thieno-[2,3-*d*]pyrimidine-3-carbonitril or Carboxylate (15a,b)

Compound **12** (0.01 mmol) was refluxed with benzylidene malononitirile of *p*-methoxybenzylidene ethylcyanoacetate (0.01 mmol) in ethanol (20 ml) in presence of piperidine for 6 h. The mixture was cooled and acidified with dilute hydrochloric acid. The solid formed was filtered and washed with water and recrysallized from a proper solvent to give **15a**,**b** respectively.

Compound **15a** also was obtained by refluxing compound **14** (0.01 mmol) with malononitrile (0.01 mmol) in presence of piperidine in ethanole (20 ml) for 4 h. The solid formed was recrystalized from ethanol (m.p. and mixed m.p.).

15a: Mass : *m/z* at 432 (M^+ , 25%), 369 (43.75%), 312 (35.5%), 257 (89.58%), 5.1 and base peak at 119.

^{1}H-NMR: δ 7.6–7.2 (m, 7H, aromatic H's + NH_2), 5.1 (s, 1H, H_4 $^{(DMSO)}$ pyran moiety, 2.8–1.4 (m, 8H, cyclohexyl H'S).

15b: ^{1}H-NMR δ 7.2–7.5 (m, 6H, aromatic H'S + NH_2), 5.4 (s, 1H, H_4 $^{(DMSO)}$ pyran moiety), 4.4. (q, 2H, CH_2), 4.0 (d, 1H, H_4 pyran moiety), 3.8 (s, 3H, OCH_3), 2.8–1.8 (m, 8H, cyclohexyl H's), 1.3 (t, 3H, CH_3).

TABLE III Gram (+ve)

Comp. no.	Conc.	*Slaphylococcus aureus*	*Bacillus subtillis*
1b	5	+++	++
	2.5	++	++
	1	++	++
2a	5	+	+
	2.5	+	+
	1	+	+
8a	5	+	+
	2.5	+	+
	1	+	+
8b	5	+	+
	2.5	+	+
	1	+	−
10	5	+	++
	2.5	+	++
	1	+	+
12	5	+	+
	2.5	+	+
	1	+	+

TABLE IV Gram (−ve)

Comp. no.	Conc.	*Pseudomonas aeruginosa*	*Escherichia coli*
1b	5	++	+
	2.5	++	+
	1	++	+
2a	5	++	+
	2.5	++	+
	1	++	+
8a	5	+	++
	2.5	+	++
	1	++	+
8b	5	+++	+
	2.5	++	++
	1	++	+
10	5	++	+
	2.5	+	+
	1	+	+
12	5	+	+
	2.5	+	+
	1	+	+

+: less activity (0.1–0.5 cm).
++: moderate activity (0.6–1.0 cm).
+++: high activity (1.1–1.5).
−: no activity.

ANTIBACTERIAL ACTIVITY

Compounds **1b**, **2a**, **8a**, **8b**, **10**, and **12** were tested for their antimicrobial activity using the gram positive bacteria *Staphylococcus aureus* and *Bacillus subrllis* and gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* at different concentrations of the sample.

The test was done using the diffusion agar technique.[11]

The relation of the different concentrations of the active compounds against the growth of bacteria was recorded in Tables III and IV.

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