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SYNTHESIS AND APPLICATION OF SOME NEW THIENOPYRIMIDINE DERIVATIVES AS ANTIMICROBIAL AGENTS

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Abstract: The paper describes the synthesis of new ring system 5-phenylthieno[2,3-d]pyrimidine-4(3H)one (2). Chlorination of (2) with PCl_5, $POCl_3$ gave the corresponding 4-chloro derivative (4). Several derivatives of the latter compound have been synthesised and tested for antimicrobial activity.

The derivatives (1 - 25) were tested against strains of bacteria (*Serratia rhodnii, Bacillus cereus, Staphylococcus citreus & Pseudomonas aeraginose*) and fungai (*Aspergillus flavus, Pencillium chrysogenum & Alternaria alternata*).

Different biological activities of condensed pyrimidines as sedative, antibacterial and antimalarials are well documented[1-3]. The isosteric properties of benzene and thiophene[4] are in general of interest to medicinal chemists. So, in addition to the above mentioned properties of condensed pyrimidines, many thienopyrimidines have been evaluated pharmacologically and used as analgesic, antiinflammatory, anticonvulant and antimicrobial[2]. For example Manhas *et al.*[5] reported a significant antiinflammatory activity for substituted thieno[2,3-d]pyrimidinones as well as for triazolothienopyrimidines[6,7]

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These observations motivated us to undertake the synthesis and test the title compounds bearing the biologically active thieno- and pyrimidino-moieties in a biological screening.

The main objective of the present work in the synthesis of thienopyrimidine containing heterocycles with the anticipated biological activities. The target compounds were prepared through a series of reactions starting with ethyl-2-amino-4-phenyl-thiophene 3-carboxylate (1). Compound (1) was obtained from the interaction of arylidenecyanoacetate and sulfur in basic medium, morpholine, according to the Gewald method[8]. Cyclization of (1) with formamide gave 5-phenylthieno [2,3-d] pyrimidin-4(3H)one (2). Confirmation of structure of (2) was achieved by alkylation with methyl iodide in alkaline medium to the N-methyl derivative (3), beside the microanalytical and the spectroscopic data (Table 1).

Chlorination of (2) with phosphorus pentachloride in the presence of phosphorus oxychloride gave the expected chloro derivatives (4) in good yield (74%). Substitution reaction, with different nucleophiles such as hydrazine hydrate, aryl amines, aryl thioles and heterocyclic amines produced the corresponding hydrazino, arylamino- and mercapto-thieno[2,3-d]pyrimidines (5 - 7) respectively. The structures of compounds (4 - 7) were confirmed by elemental analysis, ^{1}HNMR and IR spectra (Table 1).

Reaction of 4-chloro-5-phenylthienopyrimidine (4) with thiourea in ethanol gave 4-mercapto-5-phenylthienopyrimidine (8) after working up with alkali. Attempts to prepare (8) by the usual method (P_2S_5/pyrdine) were unsuccessful. Interaction of (8) with ethyl chloroacetate gave the corresponding ethyl 5-phenylthieno[2,3-d]pyrimidine-4-yl-thio-acetate (9). The structures of the produced compounds were established by elemental analysis, ^{1}HNMR and IR spectra.

Hydrazinolysis of (9) with hydrazine hydrate gave the derivative (5a) and ethyl 4-thioacetate was regenerated. This indicates that nucelophilic attack of hydrazine nitrogen on C4 is much more favored than hydrazide formation (10).

The broad utility of heterocyclic hydrazines as precursors for the synthesis of several condensed systems containing triazole and tetrazole nuclei has received increasing

Table (1)

Compd. No.	Yield (%)	M.P. (C)	Solvent of cryst	Mol. Formula (M.Wt)	Microanalysis (Calcd/Found) %				
					C	H	N	S	Cl
2	63	227	EtOH	$C_{12}H_8N_2SO$	63.14	3.53	12.27	14.05	-
				(228.27)	63.29	3.40	12.35	14.25	-
3	69	186	EtOH	$C_{13}H_{10}N_2SO$	64.44	4.16	11.56	13.23	-
				(242.30)	64.19	4.49	11.86	13.51	-
4	74	128-30	C_6H_6	$C_{12}H_7N_2SCl$	58.42	2.86	11.35	12.99	14.39
				(246.72)	58.70	2.74	10.97	13.40	14.41
5a	68	165-80	EtOH	$C_{12}H_{10}N_4S$	59.48	4.16	23.12	13.23	-
				(242.30)	59.64	4.40	23.36	13.09	-
5b	64	158-60	EtOH	$C_{18}H_{13}N_3S$	71.26	4.32	13.85	10.57	-
				(303.39)	71.66	4.22	14.20	10.72	-
5c	57	157	EtOH	$C_{14}H_{13}N_3SO$	61.97	4.83	15.49	11.82	-
				(271.34)	61.79	4.53	15.79	11.73	-
6a	78	155-7	EtOH	$C_{16}H_{15}N_3SO$	64.62	5.08	14.13	10.78	-
				(297.38)	64.48	5.15	13.99	11.20	-
6b	80	143	EtOH	$C_{17}H_{17}N_3S$	69.16	5.80	14.23	10.86	-
				(295.24)	69.24	5.83	14.00	11.28	-
7a	82	180	AcOH	$C_{18}H_{12}N_2S_2$	67.92	3.77	8.74	20.01	-
				(320.44)	67.84	4.07	8.27	20.28	-
7b	85	173	AcOH	$C_{18}H_{11}N_2S_2Cl$	60.92	3.12	7.89	18.07	9.99
				(354.88)	61.15	3.26	7.74	17.84	9.94
7c	84	178-80	AcOH	$C_{19}H_{14}N_2S_2$	68.23	4.22	8.38	19.17	-
				(334.46)	68.15	4.13	8.15	19.00	-
7d	44	150	AcOH	$C_{19}H_{11}N_3S_2O$	63.14	3.07	11.63	17.74	-
				(361.45)	63.28	3.23	11.85	17.74	-

(continued)

Contd: Table (1)

Compd. No.	Yield (%)	M.P. (°C)	Solvent of cryst	Mol. Formula (M.Wt)	Microanalysis (Calcd/Found) %				
					C	H	N	S	Cl
7e	45	200	AcOH	$C_{19}H_{11}N_3S_3$ (377.51)	60.45 60.44	2.94 2.91	11.13 11.30	25.48 25.84	- -
8	71	225-8	AcOH	$C_{12}H_8N_2S_2$ (244.34)	58.99 58.64	3.30 3.34	11.47 11.16	26.25 26.31	- -
9	66	105	C_6H_6 Dioxane (2:1)	$C_{16}H_{14}N_2S_2O_2$ (330.43)	58.16 58.48	4.27 4.60	8.48 8.32	19.41 19.03	- -
11a	75	180-4	C_6H_5- Dioxane (2:1)	$C_{19}H_{14}N_4S$ (330.41)	69.07 69.07	4.27 4.58	16.96 16.96	9.70 10.03	- -
11b	78	173-5	C_6H_5- Dioxane (2:1)	$C_{19}H_{13}N_4SCl$ (364.86)	62.55 62.37	3.59 3.49	15.36 15.01	8.79 9.17	9.72 9.78
11c	81	233	C_6H_5- Dioxane (1:1)	$C_{19}H_{14}N_5SO_2$ (376.42)	60.63 60.60	3.75 3.60	18.61 18.83	8.52 8.25	- -
11d	70	>360	C_6H_5	$C_{19}H_{14}N_4SO$ (346.41)	65.88 65.88	4.07 4.36	16.17 15.71	9.26 9.03	- -
11e	79	135-7	C_6H_5	$C_{21}H_{19}N_5S$ (373.48)	67.54 67.33	5.84 5.71	18.75 19.17	8.59 8.65	- -
11f	72	120	C_6H_5- pet-ether	$C_{20}H_{16}N_4SO$ (360.44)	66.65 66.66	4.47 4.49	15.54 15.61	8.90 8.53	- -
12a	70	172-7	Dioxane	$C_{19}H_{12}N_4S$ (328.40)	69.49 69.15	3.68 3.68	17.06 17.43	9.76 9.36	- -
12b	74	117.2	pet-ether C_6H_5 (1:1)	$C_{19}H_{11}N_4SCl$ (362.84)	62.90 62.55	3.06 2.75	15.44 14.95	8.84 8.53	9.77 9.89

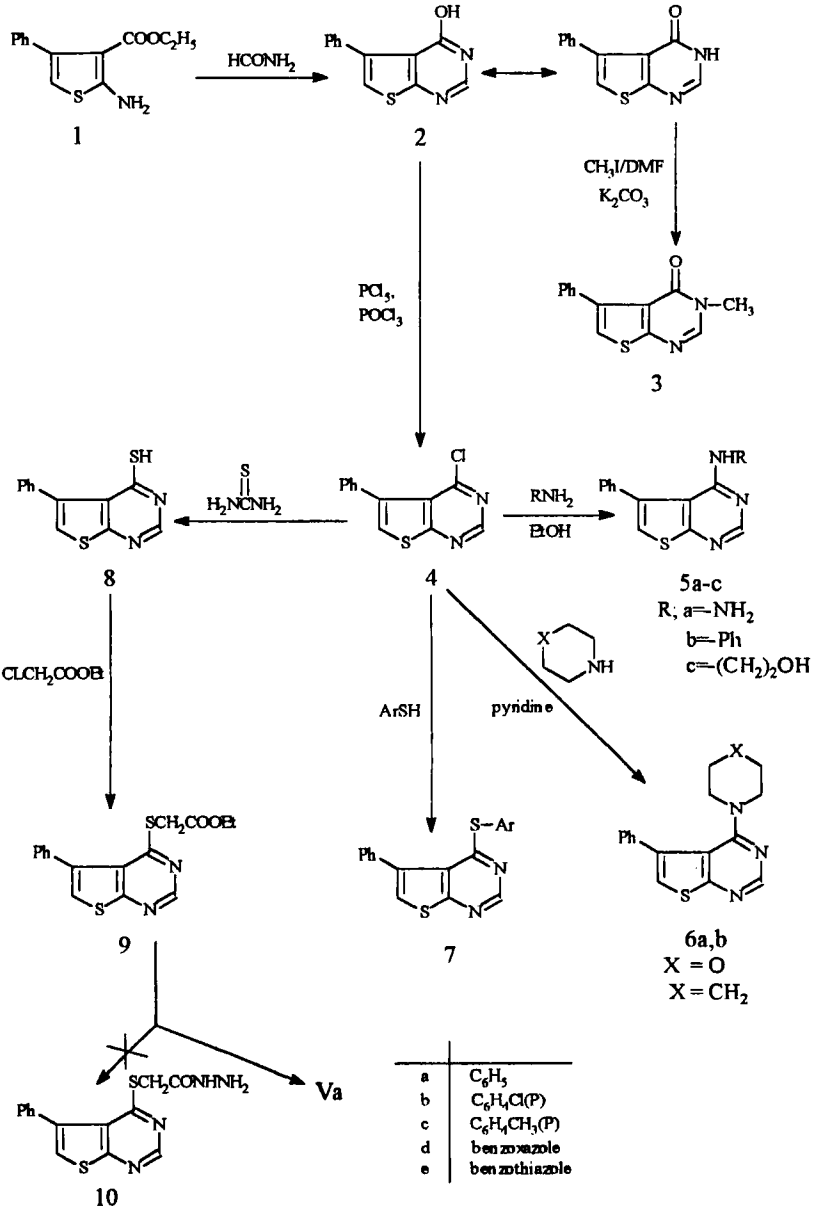
Contd: Table (1)

Compd. No.	Yield (%)	M.P. (°C)	Solvent of cryst	Mol. Formula (M.Wt)	Microanalysis (Calcd/Found) %				
					C	H	N	S	Cl
12c	70	195	pet-ether-C_6H_5	$C_{19}H_{11}N_5SO_2$ (373.39)	61.11 61.19	3.24 3.26	18.76 18.83	8.59 8.63	- -
12d	71	230-3	C_6H_5-Dioxane (1:1)	$C_{19}H_{12}N_4SO$ (344.40)	66.26 66.71	3.51 3.91	16.27 16.27	9.31 9.59	- -
12e	68	195-7	Dioxane	$C_{21}H_{17}N_5S$ (371.47)	67.90 67.63	4.61 4.49	18.85 18.59	8.63 8.60	- -
12f	71	99-102	C_6H_6	$C_{20}H_{14}N_4SO$ (358.42)	67.02 67.28	3.94 3.70	15.63 15.31	8.95 8.90	- -
13	66	227-30	AcOH	$C_{13}H_8N_4S$ (252.30)	61.89 61.40	3.20 3.27	22.21 22.54	12.72 13.76	- -
14	77	200-2	EtOH	$C_{12}H_7N_5S$ (253.27)	56.90 56.71	2.79 2.71	27.65 27.50	12.66 12.65	- -
15	71	278	AcOH	$C_{13}H_8N_4S_2$ (284.36)	54.91 54.93	2.84 3.09	19.70 19.80	22.55 22.66	- -
16a	70	175	EtOH	$C_{14}H_{10}N_4S_2$ (298.39)	56.35 56.47	3.38 3.40	18.78 18.55	21.49 21.35	- -
16b	55	135-8	EtOH	$C_{15}H_{12}N_4S_2$ (312.42)	57.67 57.55	3.87 3.77	17.93 17.20	20.53 20.96	- -
16c	66	133-4	EtOH	$C_{20}H_{14}N_4S_2$ (374.49)	64.15 64.51	3.77 3.94	14.96 14.68	17.12 17.43	- -
17a	68	143	EtOH	$C_{19}H_{19}N_5S_2$ (381.52)	59.82 59.07	5.02 5.01	18.36 18.46	16.81 16.61	- -
17b	75	163	EtOH	$C_{18}H_{17}N_5S_2O$ (383.50)	56.37 56.77	5.00 5.37	18.34 18.45	16.72 16.62	- -
17c	73	155	EtOH	$C_{21}H_{17}N_5S_2$ (403.53)	62.51 62.50	4.25 4.50	17.36 17.14	15.89 15.98	- -

(continued)

Contd: Table (1)

Compd. No.	Yield (%)	M.P. (°C)	Solvent of cryst	Mol. Formula (M.Wt)	Microanalysis (Calcd/Found) %				
					C	H	N	S	Cl
17d	72	175-8	MeOH	$C_{15}H_{13}N_5S_2$	55.02	4.40	21.39	19.59	-
				(327.43)	55.14	4.00	21.61	19.58	-
18	52	100-2	C_6H_6	$C_{15}H_{14}N_4SO_2$	57.31	4.49	17.82	10.20	-
				(314.37)	57.37	4.71	17.92	10.19	-
19	54	135-8	Dioxane C_6H_5 (2:1)	$C_{14}H_{10}N_4S$	63.14	3.78	21.04	12.04	-
				(266.33)	63.10	3.81	20.75	12.42	-
20a	49	195	EtOH	$C_{21}H_{15}N_5S$	68.27	4.00	18.96	8.68	-
				(369.45)	68.28	4.10	18.60	8.86	-
20b	52	205-7	EtOH	$C_{21}H_{14}N_5SCl$	62.39	3.49	17.34	7.94	8.77
				(403.89)	62.00	3.80	17.33	7.72	8.78
21a	62	235-7	AcOH	$C_{16}H_{10}N_6S$	60.36	3.16	26.39	10.07	-
				(318.34)	60.77	3.23	25.90	10.07	-
21b	60	200	EtOH	$C_{18}H_{15}N_5SO_2$	59.16	4.14	19.17	8.77	-
				(365.42)	59.70	4.63	19.21	8.36	-
22	68	135-7	C_6H_6	$C_{18}H_{18}N_4SO_2$	61.00	4.90	15.81	9.05	-
				(354.43)	61.13	5.12	16.06	9.48	-
23	67	140-5	C_6H_6	$C_{17}H_{14}N_4S$	66.64	4.61	18.29	10.47	-
				(306.39)	66.94	4.27	18.67	10.71	-
24	52	135	C_6H_6	$C_{17}H_{14}N_4SO_2$	60.32	4.17	16.56	9.48	-
				(338.29)	60.48	4.44	16.52	9.84	-
25	77	265	EtOH	$C_{19}H_{15}N_5S_2$	60.45	4.01	18.55	16.98	-
				(377.49)	60.53	3.80	18.64	17.09	-



Scheme 1

attention[9,10]. From this view, it was of interest to examine the chemistry of 4-hydrazino-5-phenylthieno[2,3-d]pyrimidine (5a) as a key intermediate in this work.

Condensation of hydrazino derivative (5a) with selected aromatic aldehydes in ethanol, in the presence of few drops of piperidine, afforded arylidene hydrazino derivatives (11a-f). Treatment of (11a-f) with thionyl chloride at reflux for 3 hours gave aryl-1,2,4-triazolothienopyrimidine derivatives (12a-f). Interestingly, reaction of (5a) with benzoyl chloride also gave product (12a). The structure of these compounds were confirmed by m.p., mixed m.p., TLC, elemental analysis, IR and ^{1}HNMR spectra (Tables 1&2).

Also, the hydrazino derivative (5a) easily underment ring closure with triethyl ortho formate and gave the cyclization product 9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]-pyrimidine (13). The reaction proceeds through N-2-acylation followed by thermal cyclization at N-3 of the diazine to form the angular structure (13)[9,11,12]. The tetrazole derivative (14) was also obtained, 9-phenyl-1,2,3,4-tetrazolo[5,1-f]thieno[2,3-d]pyrimidine (14) was isolated via treatment of (5a) with nitrous acid in good yield (77%). The chemical structure of (14) was confirmed on the basis of analytical and spectroscopic data (Tables 1&2). The condensation tricyclic triazolo[3,4-f]thieno[2,3-d]pyrimidine-3(2H)thione derivative (15) could be synthesised by refluxing of the hydrazino compound (5a) with carbon disulfide in dry pyridine. Chemical confirmation of the suggested structure is derived from its reaction with reagents such as methyl iodide, ethyl iodide and benzyl chloride to give S-alkylated products. On the other hand, reaction of (15) with heterocyclic, secondary aliphatic and/or primary aliphatic amines and formaldehyde in methanol gave the expected N-substituted Mannich's bases (17a-d).

Refluxing of (5a) with ethyl chloroformate at 120°C gave 4-(ethoxycarbonyl hydrazino)-5-phenylthieno[2,3-d]pyrimidine (18) (Tables 1&2). Attempts for ring closure by heating over its melting point were unsuccessful. Conversely, reaction of (5a) with acetic acid at refluxing for 6 hours gave the corresponding 3-methyl-9-phenyl-1,2,4-triazolo[3,4-f] thieno[2,3-d]pyrimidine (19).

Table (2)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
1	3400-3300(NH_2), 3150-3100(CH arom), 2900-2990(CH aliph), 1625(C=O), 1575(C=C).	δ1.30(t,3H,CH_3); 4.50(q,2H, CH_2); 6.50 (s,2H,NH_2); 7.60-7.75(s,6H,arom); 5H + 1H thiophene).
3	3050-3100(CH arom), 2900(CH aliph), 1660(C=N).	δ3.65(s,3H,CH_3); 7.25(s,1H, thiophene), 7.30-7.70(m,5H,arom); 8.20(s,1H, pyrimidine).
5a	3300(NH),3250-3100(NH_2), 3100 (CH aliph), 1520(C=N).	δ3,30(s,2H,NH_2); 5.50(s,1H,NH); 6.40 (s,1H,NH); 6.40(s,1H, thiophene); 6.80 (s,5H,arom), 7.80(s,1H, pyrimidine).
5c	3400(OH), 3200(NH), 3050-3100 (CH arom), 2900-2950(CH aliph), 1560(C=N).	δ3.50-3.70(d,4H,2CH_2); 5.50(s,1H,NH); 7.15(s,1H, thiophene); 7.53(s,5H, arom); 8.50(s,1H, pyrimidine).
6a	3100(CH arom), 2850-2950(CH aliph), 1510(C=N).	δ3.50(s,8H, morphline); 7.50(s,1H, thiophene); 7.70(s,5H, arom); 8.80(s,1H, pyrimidine).
6b	3020-3090(CH arom), 2820-2920 (CH aliph), 1510(C=N).	δ1.20(m,4H, metaN-piper); 1.50(m,2H, para N-piper); 3.20(t,4H, ortho N-piper); 7.20(s,1H, thioph); 7.40(m,5H, arom); 8.63 (s,1H,pyrim.).
7c	3100(CH arom), 2900-3000(CH aliph), 1490(C=N).	δ2.55(s,3H,CH_3);7.50-7.80(d,10H,(9H arom protons + 1H thiophene)); 8.80 (s,1H, pyrimidine).
9	3050-3100(CH arom), 2950(CH aliph), 1715(C=O), 1595(C=N).	δ1.55(t,3H,CH_3); 4.20(s,2H,CH_2); 4.30-4.50(q,2H,CH_2); 7.60(s,1H, thioph); 7.80 (s,5H, arom); 9.00(s,1H, pyrim.).

(continued)

Contd. Table (2)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
11a	3300(NH), 3050(CH arom), 2890-2900(CH aliph), 1582(C=N).	δ3.67(s,1H,CH); 7.25-8.40(m,14H, (10H, arom, 1H(CH), 1H(thioph), 1H(pyrim.), 1H(NH)).
11c	3300(NH), 3100(CH arom), 2900 (CH aliph), 1590(C=N).	δ7.30-8.30(m,13H (9H arom, 1H(CH), 1H(NH), 1H(thioph), 1H(pyrim.)).
11f	3400(NH), 3050(CH arom), 2900 (CH aliph), 1683(C=N), 1600 (C=C).	δ3.80(s,3H,OCH_3); 7.20(s,1H,CH), 7.60-8.60(m,11H (1H(NH), 1H(thioph), 9H arom); 8.70(s,1H,pyrim.)).
12a	3100(CH arom), 2900(CH aliph), 1600(C=N), 1510(NO_2).	δ7.30-7.80(m,10H, 9H arom, 1H(thioph)); 8.80(s,1H, pyrim).
12f	3400(NH), 3050(CH arom), 2900 (CH aliph), 1600(C=N).	δ4.10(s,3H,CH_3); 7.50(s,1H (thioph)); 7.60-7.80(m,9H, arom); 9.40(s,1H, pyrim).
14	3100(CH arom), 1596(N=N), 1490(C=N)	(DMSO-D_6): δ7.30-7.90(m,6H,(5H arom + 1H(thioph); 10.00(s,1H,pyrim).
16c	3050-3100(CH arom), 2950-2900 (CH aliph), 1690(C=N).	(DMSO-D_6): δ4.45(s,2H,CH_2); 7.28 (s,1H, thioph); 7.40-7.90(m,10H arom); 8.89(s,1H,pyrim).
17a	3100-3050(CH arom), 2900(CH aliph), 1600(C=N).	δ1.50(m,6H,piper.); 2.70(m,4H,piper); 5.20(s,2H,CH_2); 7.20-7.80(m,6H(5 arom + 1H(thioph); 9.10(s,1H,pyrim.).
17b	3090(CH arom), 2990(CH aliph), 1600(C=N).	δ2.80(t,4H, morph.); 3.70(t,4H, morph.)' 5.30(s,2H,CH_2); 7.50(s,1H, thioph); 7.60-7.80(m,5H, arom); 9.25(s,1H,pyrim).

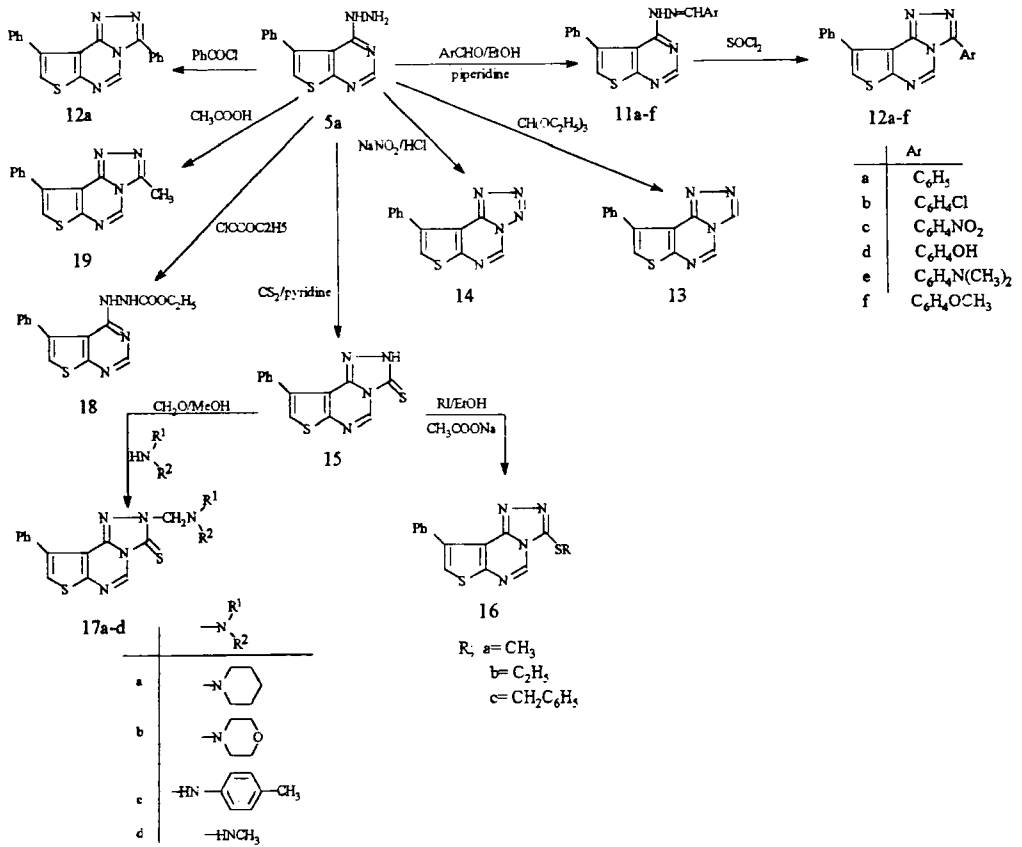
Contd. Table (2)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
18	3400-3200(NH_2), 3100-3080(CH arom), 1710(C=O), 1580(C=N)	δ1.50(t,3H,CH_3); 4.50(m,2H,CH_2); 7.60-7.80(m,9H,5H arom, 2H(2NH), 1H (thioph), 1H pyrim).
21a	3400-3295(NH_2), 3100(CH arom), 2200(C≡N), 1620(C=N).	(DMSO-d_6): δ3.20(s,2H,NH_2); 6.90-7.60 (m,6H(5H arom, 1H thioph); 8.90(s,1H, pyrazole); 9.20(s,1H, pyrim).
21b	3450-3350(NH_2), 3090(CH arom), 2990(CH aliph), 1687(C=O), 1610 (C=N).	δ1.35(t,3H,CH_3); 4.30(q,2H,CH_2); 6.65 (s,2H,NH_2); 6.95(s,1H, thioph); 7.10-7.30(m,5H, arom); 7.55(s,1H, pyraz); 8.95(s,1H, pyrim).
22	3350(NH), 3100(CH arom), 2995 (CH aliph), 1720(C=O), 1613 (C=N).	δ1.20(t,6H,2CH_3); 3.40(s,2H,CH_2); 4.20 (q,2H,CH_2); 7.20(s,1H, thioph); 7.50-7.70 (m,5H, arom); (8.75(s,1H, pyrim).
23	3000-3100(CH arom), 2980(CH aliph), 1590(C=N).	δ1.40(s,3H,CH_3); 2.30(s,3H,CH_3); 7.40 (s,1H, thioph); 7.60(s,1H,pyrazole); 7.80 (s,5H, arom); 8.80(s,1H, pyrim).
24	3100(CH arom), 2995(CH aliph), 1715(C=O), 1600(C=N).	δ1.30(t,3H,CH_3); 4.15(s,2H,CH_2); 4.30 (q,2H,CH_2); 7.50-8.00(m,6H(5H arom, 1H thioph); 9.30(s,1H, pyrim).

* The solvent used is $CDCl_3$ except otherwise indicated.

The noncondensed tricyclic 4-[5-amino-3-arylpyrazol-1-yl]-5-phenylthieno[2,3-d]-pyrimidine (20a,b) were synthesized by interaction of the hydrazino compound (5a) with phenacylnitrile derivatives in ethanol.

It has been reported[13] that some substituted hydrazines react with ethoxymethylene malononitrile giving the corresponding amino cyano pyrazoles are potential purine



Scheme 2

antagonnists. In light of these result, it was of interest to use the hydrazino compound (5a) for the preparation of the 4-(5-amino-4-substituted pyrazol-1-yl)-5-phenylthieno[2,3-d]-pyrimidines (21a,b). The structure of these compounds were confirmed by elemental analysis as well as by spectrosopical methods (Tables 1&2).

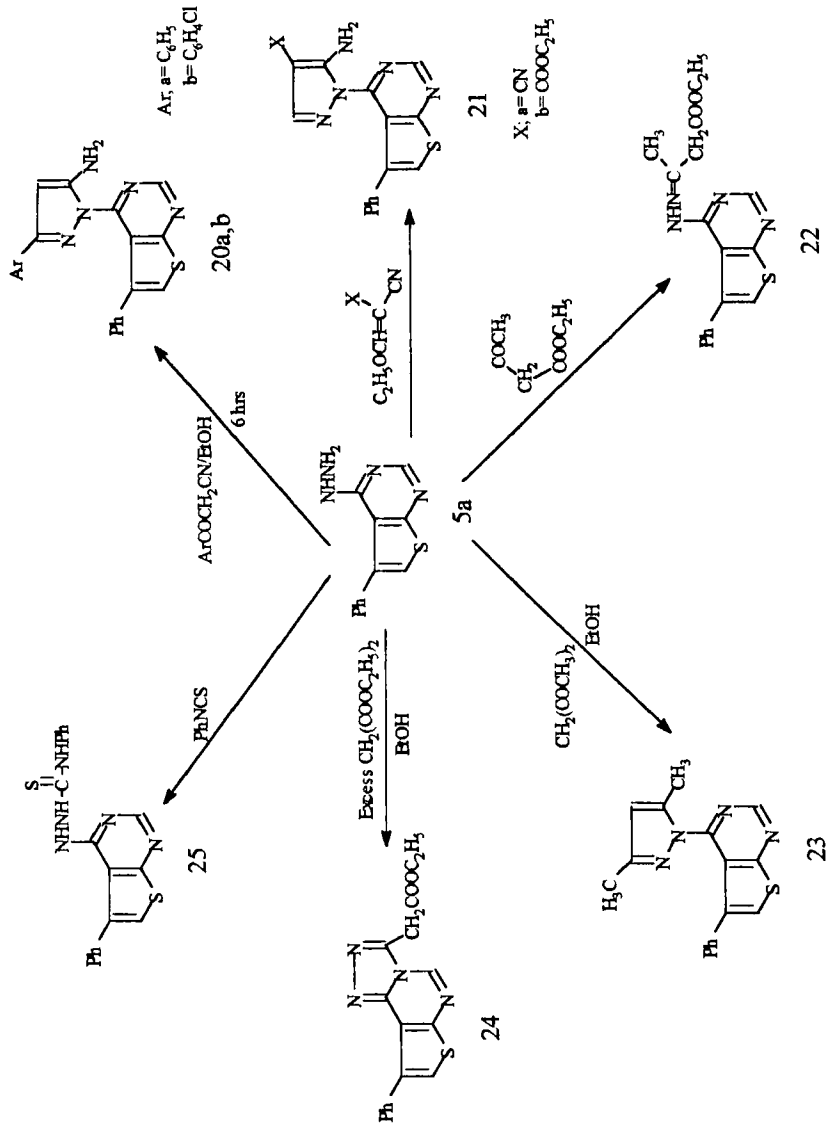
Reaction of (5a) with active methylene compounds such as ethyl acetoacetate, acetylacetone and diethyl malonate in ethanol afforded hydrazonoacetoacetate (22 & 23) and thieno[2,3-d]pyrimdine-3-acetate (24) respectively. Also, the reaction of (5a) with phenylisothiocyanate in pyridine gave the thiosemicarbazide (25). The structure of these compounds were confirmed by elemental analysis, ^{1}HNMR & IR spectral data.

From the antimicrobial results shown in (Table 3), it is clear that 4-hydrazino-5-phenylthieno[2,3-d]pyrimidine (5a) is potent against all of the fungus and bacteria used except *Serratia rhodnii* and *Staphylocococcus citreus*. The cyclized products derived from (5a) have different potency according to the type of the heterocyclic moiety and the organism under investigation. Thus, the five membered heterocyclic fused as tricyclic derivatives, e.g. tetrazolothienopyrimdine (14), has higher activity against all the fungus and bacteria used. Similarly, the Schiff bases (11a and b) have high activity against all of the fungus and bacteria used except against *Pseudomonas aeraginose*. The noncondensed tricyclic systems derived from (5a) revealed different activities according to the type of substitutent and the organism used, for example, (20b) is quite active only against *Pseudomonasaeraginose*, but 4-(3,5-dimethyl-pyrazol-4-yl)-5-phenylthieno[2,3-d]-pyrimidine (23) as higher activity against all of the tested organism.

Experimental

Ethyl 2-amino-4-phenylthiophene-3-carboxylate 1:

A mixture of arylidene ethyl cyanoacetate (10.5 g, 0.05 mol) and sulphur (1.3 g, 0.05 mol) in (20 mL) of absolute ethanol in the presence of (10 mL) of morpholine (0.011 mol) was



Scheme 3

heated at 40-60°C for 4 h. After cooling the mixture was poured into ice/water and the solid product was filtered off and recrystallized from ethanol to give 1 as a yellow crystals m.p. 98°C (Lit.[8], m.p. 98°C) (80% yield).

Analysis for $C_{13}H_{13}NSO_2$: (247.32)

Calcd %: C, 63.13; H, 5.30; N, 5.66; S, 12.96.

Found %: C, 63.35; H, 5.26; N, 5.75; S, 13.05.

IR : 3346, 3240 (NH_2); 1646 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): 1.30 (t, 3H, CH_3), 4.50 (q, 2H, CH_2); 6.50 (s, 2H, NH_2); 7.60-7.75 (m, 6H, 5H, Ar + 1H Thiophene).

Synthesis of 5-phenylthieno[2,3-d]pyrimidine-4(3H)one 2:

A mixture of 1 (2.47 g, 0.01 mol) in (20 mL) of formamide was refluxed for 4h. On cooling, a white precipitate was formed, which was filtered off and recrystallized from ethanol.

Synthesis of 3-methyl-5-phenylthieno[2,3-d]pyrimidine-4-one 3:

A mixture of 2 (0,456 g, 0.002 mol) and methyl iodide (0.6 mL, 0.008 mol) was stirred in DMF (20 mL) in the persence of fused potassium carbonate (1 gm, 0.07 mol) for 1.5 h. The solid product obtained an addition of ice was filtered off and recrystallized from ethanol.

Synthesis of 4-chloro-5-phenylthieno[2,3-d]pyrimidine 4:

A mixture of 2 (2.28 g, 0.01 mol) was refluxed with phosphorus pentachloride (2.54 g, 0.012 mol) and phosphorus oxychloride (7 mL) for 3h. After cooling the mixture was carefully poured over ice and ammonia solution. The solid products was filtered off and recrystallized from benzene as brown crystals.

Table (3)

	Antibacterial activity				Antifungal activity		
	gram positive		gram negative				
	Serratia Rhodnii	Bacillus cereus	Staphylo-coccus citreus	Pseudomonas aeraginosa	Aspergillus flavus	Pencillium chrysogenum	Alternaria alternata
1	8	10	-	8	-	1	3
2	10	8	-	7	-	3	2
3	-	-	-	-	5	6	4
4a	-	8	-	8	5	6	3
5b	-	-	-	-	5	4	-
6a	7	7	-	7	4	3	6
6b	-	-	7	7	-	2	4
7a	-	-	-	7	4	-	-
7b	-	-	-	7	5	-	6
7c	-	7	-	8	-	-	-
9	-	8	-	8	-	3	4
11a	7	8	7	-	5	5	6
11b	8	9	8	-	3	5	4
11c	7	-	-	-	3	4	-
11d	9	7	-	-	-	-	-
11e	-	7	-	7	6	5	-
11f	8	10	-	-	4	4	4
12a	8	7	-	7	4	-	-
12b	-	7	-	-	3	4	3
12c	8	7	8	-	3	5	3
12d	8	8	-	-	-	4	4
12e	-	-	-	7	-	2	5
12f	-	-	-	-	3	-	3
13	-	-	8	-	4	4	3
14	13	15	16	8	15	7	8
15	-	-	-	7	4	3	-

Contd.: Table (3)

	Antibacterial activity				Antifungal activity		
	gram positive		gram negative				
	Serratia Rhodnii	Bacillus cereus	Staphylo-coccus citreus	Pseudomonas aeraginosa	Aspergillus flavus	Pencillium chrysogenum	Alternaria alternata
16a	8	8	7	-	4	-	5
16b	8	7	-	-	3	5	5
16c	9	7	-	-	4	5	3
17a	8	8	-	11	6	-	3
17b	8	9	-	7	5	4	3
17c	7	-	8	12	4	-	-
18	-	9	-	7	5	3	5
19	7	-	-	8	-	3	3
20b	-	-	-	10	-	-	-
21a	-	-	-	-	5	-	3
21b	10	7	8	7	4	-	2
22	12	13	-	7	4	-	3
23	7	7	8	7	10	8	3
24	-	7	-	-	3	3	-
25	-	-	-	8	-	3	-

Synthesis of 4-(N-substituted amino)-5-phenylthieno[2,3-d]pyrimidine 5a-c:

General procedure:

A solution of 4 (5 g, 0.02 mol), hydrazine hydrate (7 mL), aniline and/or ethanol amine (2 mL) in ethanol (30 mL) was refluxed for 2h. On cooling, the solid product was filtered off and recrystallized from the appropriate solvent (Table 1).

Analysis of $C_{12}H_{10}N_4S$ (5a): (242.30).

Calcd.% : C, 59.48; H, 4.15; N, 23.12; S, 13.23.

Found %: C, 59.64; H, 4.40; N, 23.36; S, 13.09.

IR : 3300 (NH); 3250-3300 (NH_2); 3100 (CH aliph).

^{1}H-NMR: 3.30 (s, 2H, NH_2); 5.50 (s, 1H, NH); 6.40 (s, 1H, thiophene)[14], 6.80 (m, 5H, Ar); 7.80 (s, 1H, pyrimidine)[14].

Synthesis of 4-(N-substituted amino)-5-phenylthieno[2,3-d]pyrimidine 6a,b:

A mixture of 4 (0.494 g, 0.002 mol), morpholine and/or piperidine (2mL, 0.014 mol) was heated under reflux in (10 mL) ethanol for 3 h. The mixture was poured into ice and the solid product was filtered off and recrystallized from ethanol to give 6a,b as a pale yellow crystals.

Synthesis of 4(Arylthio)-5-phenylthieno[2,3-d]pyrimidine 7a-e:

General procedure:

A mixture of 4 (0,247 g, 0.001 mol) and aryl or heterocyclic thiol (0.01 mol) was refluxed in pyridine (10 mL) for 2 h. After cooling, the mixture was poured on ice, filtered and the solid residue recrystallized from the suitable solvent (Table 1).

Synthesis of 4-Mercapto-5-phenylthieno[2,3-d]pyrimidine 8:

A mixture of 4 (0,494, 0.002 mol) and thiourea (0.24 g, 0.025 mol) in dry methanol was heated under reflux for 2 h. The separated yellow crystalline solid was collected, washed with ethanol, heated with 10% aqueous sodium hydroxide (20 mL) and the solution acidified with acetic acid at pH (5.6-5.8) to give 8 as yellow crystals from acetic acid.

Synthesis of Ethyl -5-phenylthieno[2,3-d]pyrimidine-4-yl-thioacetate 9:

To a solution of 8 (0.244 g, 0.001 mol) in ethanol (20 mL) was added fused sodium acetate (1 g) and ethyl chloroacetate (0.1 mL, 0.02 mol). The mixture was heated under reflux for 2h. The solid product was filtered off to give 9 as a pale yellow crystals from benzene.

Synthesis of 4-(Arylidene-hydrazino)-5-phenylthieno[2,3-d]pyrimidines 11a-f:

General procedure:

A mixture of 5a (0.24 g, 0.001 mol) and selected aromatic aldehydes (0.001 mol) refluxed in ethanol (20 mL) in the presence of few drops of piperidine for 3h. After cooling the solid precipitate was filtered off and recrystallized from the suitable solvent (Table 1).

Synthesis of 3-Aryl-9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidines 12a-f:

General procedure:

A mixture of 11 (0.01 mol) and thionyl chloride (15 mL) was heated on a water bath for 2 h. The excess thionyl chloride was removed by distillation under reduced pressure, the residue was triturated with petroleum ether (60-80°C) and the product was filtered off and recrystallized from the suitable solvent (Table 1). Also, compound 12a was obtained in a single step upon reflux of 5a (0.24 g, 0.001 mol) and benzoyl chloride (5 mL, 0.036 mol) for 2 h as a pale yellow crystals, after vacuum removal of the unreacted benzoyl chloride.

Synthesis of 9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidine 13:

A mixture of 5a (0.24 g, 0.001 mol) and (6 mL) of formic acid (or 5 mL of triethyl orthoformate) was refluxed for 3 h. After cooling, the reaction mixture was poured into ice. The solid obtained was filtered off then recrystallized from acetic acid to give a pale yellow crystals.

Synthesis of 9-phenyl-1,2,3,4-tetrazolo[5,1-f]thieno[2,3-d]pyrimidine 14:

A mixture of 5a (0.24 g, 0.001 mol) and sodium nitrite solution (7 mL, 5%) was added dropwise in the presence of 5 mL of HCl at 0°C for 30 mins with stirring. The solid product obtained was filtered off and washed several times with water and recrystallized from ethanol to give brown crystals.

Synthesis of 9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidine 3(2H)thione 15:

A mixture of 5a (0.48 g, 0.002 mol) and carbon disulphide (10 mL) was refluxed in dry pyridine (15 mL) for 4 h. After cooling, water (10 mL) was added and the solid precipitate was filtered off and recrystallized from acetic acid to give yellow crystals.

Synthesis of 9-phenyl-3-(alkylthio)-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidine 16a-c:

General procedure:

A mixture of 15 (0.28 g, 0.001 mol) and alkylhalide (0.002 mol) was stirred in ethanol (20 mL) in the presence of fused sodium acetate for 30 min. The solid product obtained an addition of water was filtered off and recrystallized from ethanol as white crystals.

Synthesis of 2-(N,N-dialkylamino)methyl-9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]-pyrimidine-3 (2H)thione 17:

General procedure:

To a suspension of 15 (0.28 g, 0.001 mol) in ethanol (20 mL), formalin solution (37%, 1 mL) and selected amines (0.1 mol) were added. The contents were stirred for one h. and left over night at room temperature. The product thus formed was filtered off and recrystallized from the appropriate solvent as colorless fine crystals.

Synthesis of 4-(Ethoxycarbonyl hydrazino)-5-phenylthieno[2,3-d]pyrimidine 18:

A mixture of 5a (0.24 g, 0.001 mol) and chloro ethyl formate (3 mL, 0.03 mol) was refluxed in dry pyridine (10 mL) for 5 h. After cooling and addition of water, the solid precipitate was filtered off and recrystallized from benzene to give pale brown crystals.

Synthesis of 3-Methyl-9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidine 19:

A mixture of 5a (0.24 g, 0.001 mol) was refluxed in acetic acid for 6 h. After cooling, the reaction mixture was poured into ice and the precipitate was filtered off and recrystallized from dioxane-benzene (2:1) to give 19 as brown crystals.

Synthesis of 4-(5-amino-3-arylpyrazol-1-yl)-5-phenylthieno[2,3-d]pyrimidine 20a,b:

A mixture of 5a (0.24 g, 0.001 mol) and phenacyl cyanide (or p-chlorophenacyl cyanide) (0.01 mol) was refluxed in ethanol (30 mL) for 6h. After cooling, the solid product was filtered off and recrystallized from ethanol to give 20a (or 20b) as brown crystals.

Synthesis of 4-(5-amino-4-substituted pyrazol-1-yl)-5-phenylthieno[2,3-d]pyrimidine 21a,b:

A mixture of the hydrazino compound 5a (0.24 g, 0.001 mol) and ethoxy methylene malononitrile (or ethoxymethylene ethyl cyanoacetate) (0.01 mol) in ethanol (20 mL) was refluxed for 3h. After cooling, the solid product was filtered off and recrystallized from acetic acid & ethanol to give 21a as white crystals (or 21b) as yellow crystals, respectively.

Synthesis of Ethyl 5-phenylthieno[2,3-d]pyrimidine-4-yl-hydrazonoacetate 22:

A mixture of hydrazino compound 5a (0.24 g, 0.001 mol) and ethyl acetoacetate (0.3 mL, 0.002 mol) was refluxed in ethanol for 3h. On cooling, the solid product was filtered off and recrystallized from benzene as a yellow crystals.

Synthesis of 4-[3,5-dimethylpyrazol-1-yl]-5-phenylthieno[2,3-d]pyrimidine 23:

A mixture of the hydrazino compound 5a (0.24 g, 0.001 mol) and acetylactone (0.4 mL, 0.002 mol) was refluxed in ethanol (20 mL) for 3h. The product was separated by filteration and recrystallized from benzene to give 23 as brown crystals.

Synthesis of Ethyl (9-phenyl-1,2,4-triazolo[3,4-f]thieno[2,3-d]pyrimidine)-3-acetate 24:

A mixture of 5a (0.24 g, 0.001 mol) and diethyl malonate was refluxed for 3h. After cooling, the solid precipitate was filtered off and recrystallized from benzene to give brown crystals.

Synthesis of 1-(5-phenylthieno[2,3-d]primidine-4-yl)-4-phenylthiosemicarbazide 25:

A mixture of 5a (0.24 g, 0.001 mol) and phenylisothiocyanate (0.4 mL, 0.003 mol) was refluxed in dry pyridine (15 mL) for 3h. After cooling, (20 mL) water was added and the precipitate was filtered off and recrystallized from ethanol to give 25 as yellow crystals.

Antimicrobial activity:

The anitmicrobial activities of the synthesized compounds (at a concentration of 5 mg per disc) were determined by the usual disc assay method against some bacteria and fungi[15]. Nutrient agar medium with the following composition in gdm^{-3}: beef extract, 3; peptone, 5; NaCl 5 and agar 20, were used for bacterial cultures. Fungi were grown on Sabouraud's dextrose agar which contained (gdm^{-3}): glucose, 40; peptone, 10 and agar 20. Inhibition zones (in mm) around filter paper discs (3 mm in diameter) were measured and the average of three readings was considered.

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