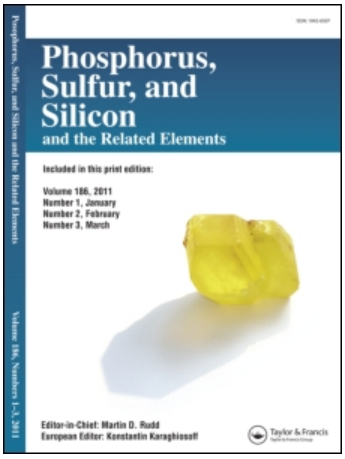

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Synthesis of Novel Pyrrylthieno[2,3-d]Pyrimidines and Related Pyrrolo[1",2":1",6"]Pyrazino[2",3":4,5]Thieno[2,3-d]Pyrimidines

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SYNTHESIS OF NOVEL PYRRYLTHIENO-[2,3-d]PYRIMIDINES AND RELATED PYRROLO[1″,2″:1′,6′]PYRAZINO-[2′,3′:4,5]THIENO[2,3-d]PYRIMIDINES

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(Received February 7 2001.)

*4-Methyl-2-phenyl-5-(1-pyrryl)-6-substituted-thieno[2,3-d]pyrimidines (**3a–c**, **4a–c**, **5a**,**b**, and **6**) have been synthesized. Some of the substituents in position 6 were used to build up different sulfur-, nitrogen- and/or oxygen-containing heterocyclic rings at that position. The 4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine-6-carboazide (**20**) was also used as a key intermediate in the synthesis of the target pyrrolo[1″,2″:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidines.*

Keywords: Pyrrolopyrazinothienopyrimidines; pyrrylthienopyrimidines; thienopyrimidines

INTRODUCTION

Many thieno[2,3-d]pyrimidines have been investigated in relation with their pharmacological activities. Some of them proved to possess antituberculosis,[1] antianaphylactic,[2] immunostimulating,[3] analgesic, and antiinflammatory[4] activities. Others are useful as herpsvirus inhibitors[5] and as endothelin antagonists.[6] Very recently,[7] certain thieno[2,3-d]pyrimidine derivatives were prepared as immunosuppressants for the treatment of reversible obstructive airway diseases such as asthma, bronchitis, and rhinitis. In view of these observations and in continuation to our program directed to the synthesis of new pyrazines fused to aza- and diaza analogs of benzothiophene,[8–10] we report herein the synthesis of the hitherto unknown pyrrylthieno[2,3-d]pyrimidines and related tetracyclic systems; pyrrolopyrazinothienopyrimidines.

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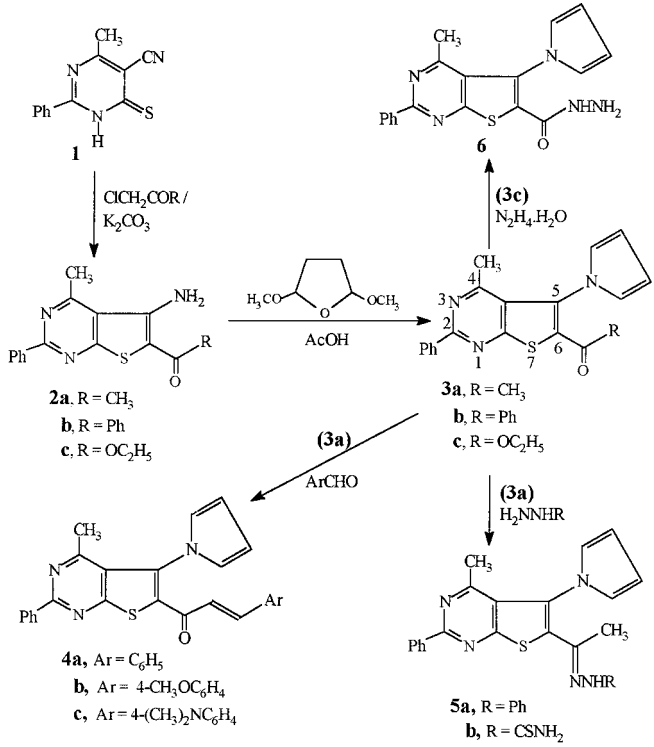
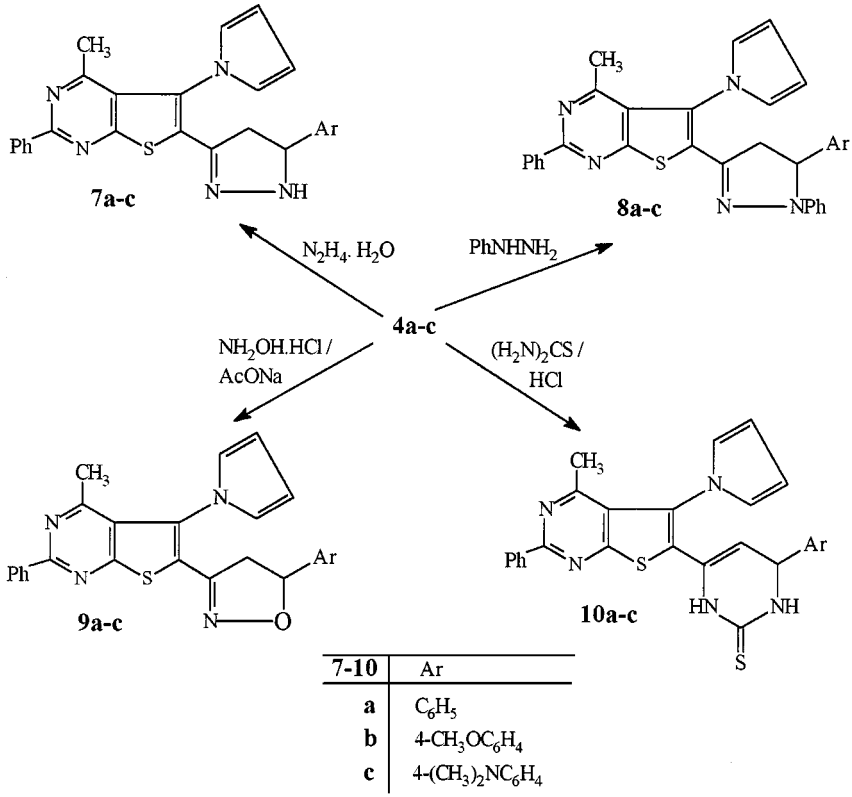
RESULTS AND DISCUSSION

5-Cyano-6-methyl-2-phenylpyrimidine-4(3*H*)-thione (**1**)[11] was reacted with some halo compounds, viz chloroacetone, phenacyl bromide, or ethyl chloroacetate, by refluxing in ethanol containing anhydrous potassium carbonate, to give the corresponding 5-amino-4-methyl-2-phenyl-6-substituted-thieno[2,3-d]pyrimidines (**2a–c**). The amino group of the latter compounds was easily transformed into a pyrryl moiety via the reaction with 2,5-dimethoxytetrahydrofuran in boiling acetic acid[12,13] to give the pyrryl derivatives **3a–c**. The acetyl compound **3a** was easily converted into the chalcones **4a–c**, phenylhydrazone **5a**, and also into thiosemicarbazone **5b** upon treatment with aromatic aldehydes, phenylhydrazine, or thiosemicarbazide respectively. Treatment of the ester **3c** with hydrazine hydrate resulted in the formation of 4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine-6-carbohydrazide (**6**) (Scheme 1).



SCHEME 1

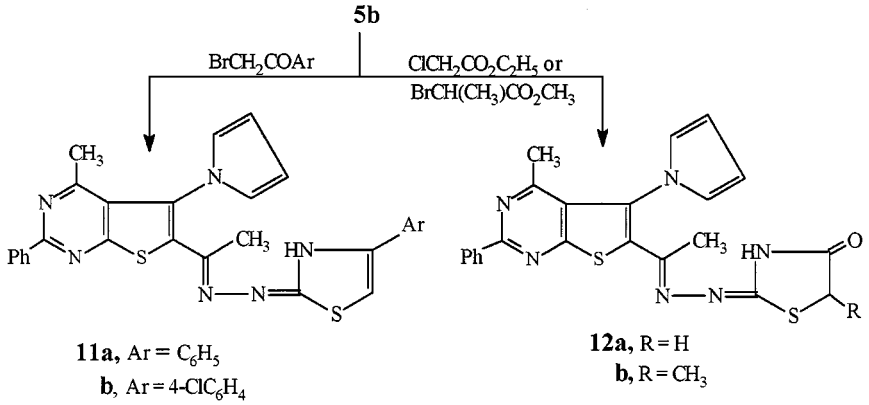
The compounds **4a–c**, **5b**, and **6** served as useful intermediates for the synthesis of pyrrylthienopyrimidines containing different heterocyclic residues at position 6. Thus, when the chalcones **4a–c** were interacted with hydrazine hydrate or phenylhydrazine, the products were identified as pyrazolinyl derivatives **7a–c** and **8a–c** respectively. However, their reaction with hydroxylamine led to the formation of isoxazolinyl derivatives **9a–c**. On the other hand, the interaction of **4a–c** with thiourea in boiling ethanol in the presence of catalytic amounts of HCl produced the pyrimidinethiones **10a–c** (Scheme 2).



7-10	Ar
a	C_6H_5
b	4-$CH_3OC_6H_4$
c	4-$(CH_3)_2NC_6H_4$

SCHEME 2

The thiosemicarbazone **5b** was reacted with phenacyl bromide, *p*-chlorophenacyl bromide, ethyl chloroacetate, or methyl 2-bromopropionate by refluxing in ethanol containing fused sodium

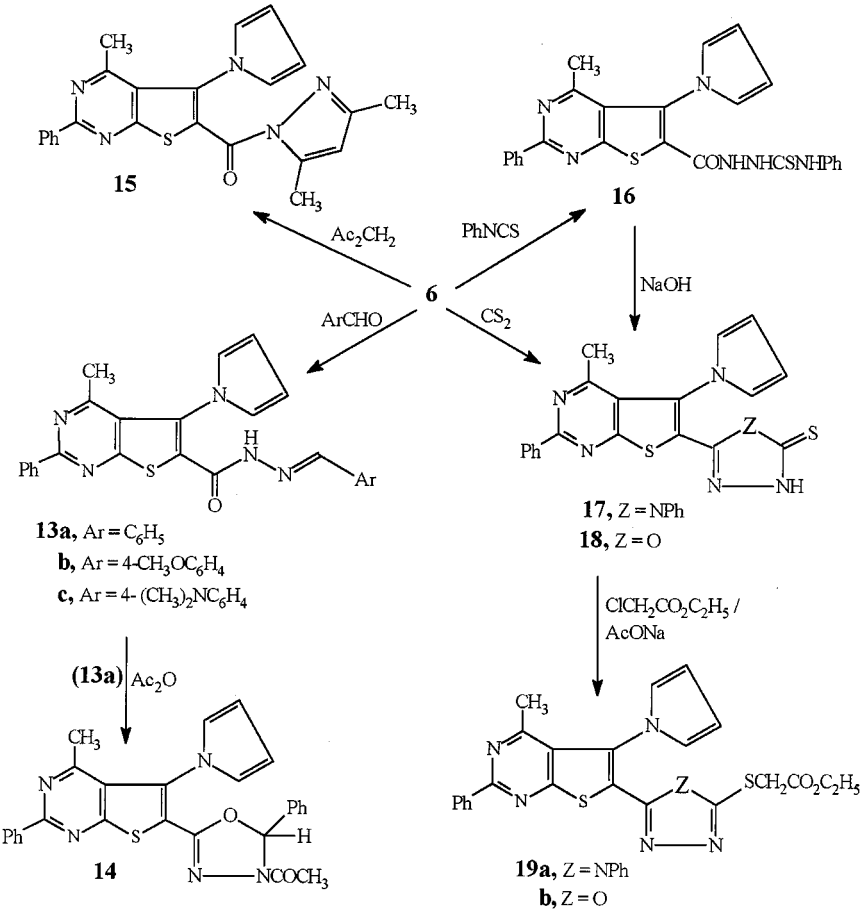


SCHEME 3

acetate to furnish the thiazolines **11a**,**b** and thiazolidinones **12a**,**b** respectively (Scheme 3).

The condensation of carbohydrazide **6** with some aromatic aldehydes yielded the expected hydrazones **13a–c**. On treatment of **13a** with acetic anhydride at reflux temperature, the acetyloxadiazolinyl derivative **14** was isolated. The pyrazolyl derivative **15** was obtained upon fusion of **6** with acetylacetone. Compound **6** was also reacted with phenyl isothiocyanate to afford the thiosemicarbazide **16** which was cyclized into *s*-triazole derivative **17** upon heating in aqueous sodium hydroxide solution. The 1,3,4-oxadiazole-5(4*H*)-thione **18** was prepared by reacting **6** with carbon disulfide in the presence of potassium hydroxide. When the thiones **17** and **18** were allowed to react with ethyl chloroacetate, the corresponding esters **19a**,**b** were obtained (Scheme 4).

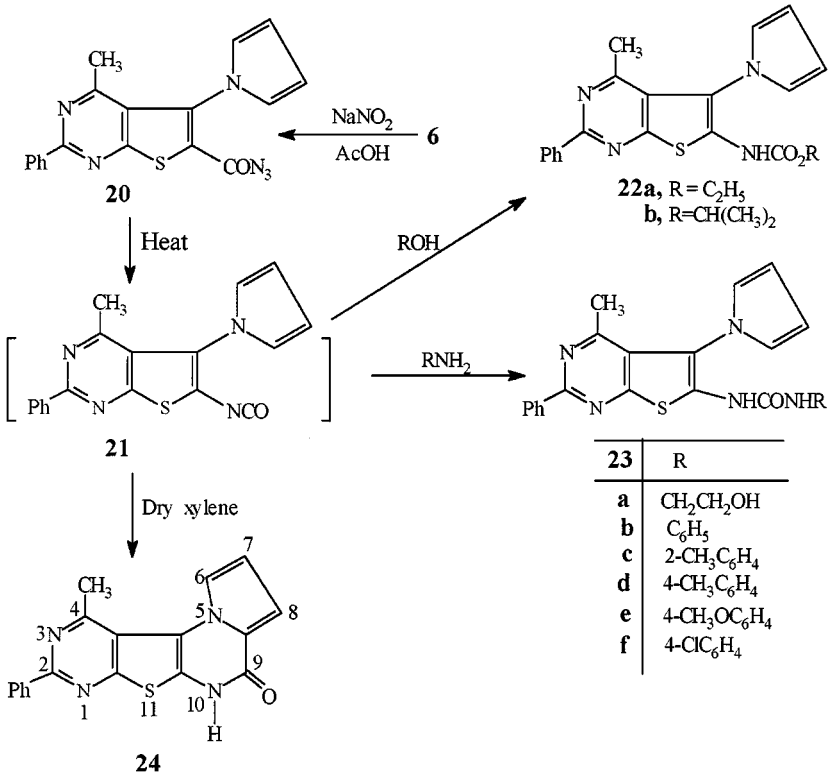
The treatment of a solution of **6** in glacial acetic acid with sodium nitrite solution at low temperature resulted in the formation of 4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine-6-carboazide (**20**). This azide served as a point of departure into other pyrrylthienopyrimidines and also it was used as a key intermediate in the synthesis of new tetracyclic heterocycles, pyrrolopyrazinothienopyrimidines. Thus, when **20** was heated in alcohols, Curtius rearrangement occurred and the formed isocyanate **21** reacted concomitantly with alcohols used to give the corresponding N-alkyl carbamates **22a**,**b**. Similarly, fusion of **20** with different amines led to the formation of the urea derivatives **23a–f**. However, when the acid azide **20** was heated in an inert high boiling point solvent such as dry xylene and in absence of any reactive entity, Curtius rearrangement



SCHEME 4

took place with subsequent intramolecular ring closure to give the 4-methyl-2-phenylpyrrolo[1″,2″:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidine-9(10*H*)-one (**24**) (Scheme 5).

The pyrazinethione **25** was obtained by heating **24** with phosphorus pentasulfide in dry pyridine. This thione was easily reacted with *p*-chlorophenacyl bromide or ethyl chloroacetate to furnish pyrrolopyrazinothienopyrimidines **26a**,**b**. It is worthy to mention that when **26b** was treated with hydrazine hydrate in ethanol at room temperature, the product was the acethydrazide **27**, however, when the reaction was carried out by fusion of the two reactants, the hydrazino derivative **29** was obtained. The latter compound was obtained unequivocally by chlorinating **24** followed by nucleophilic



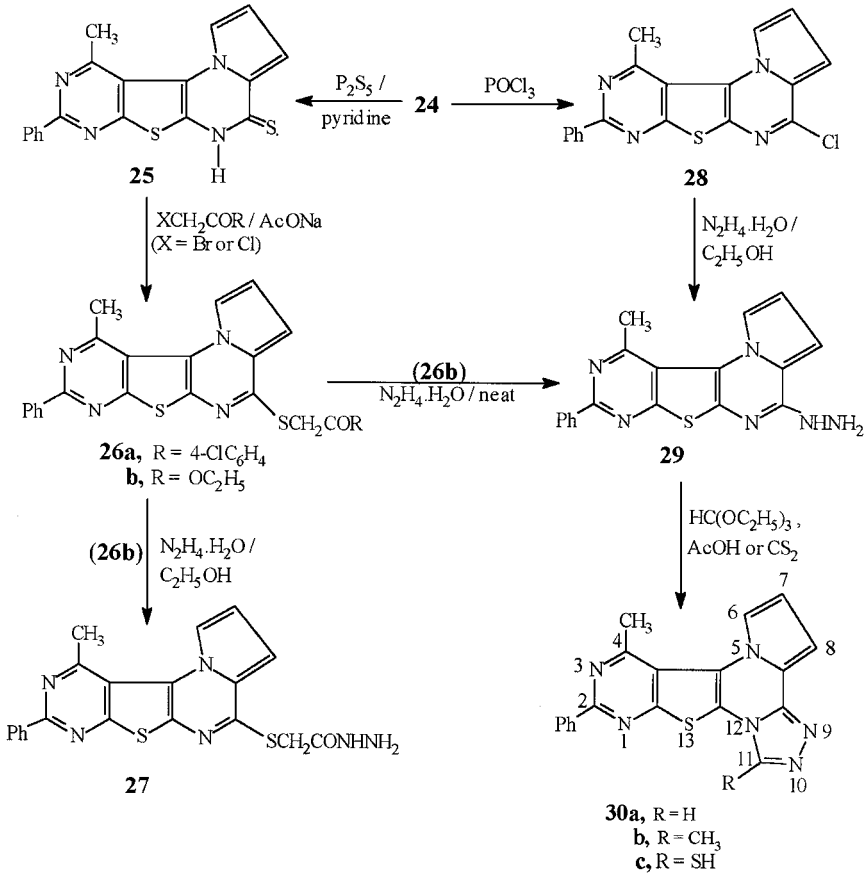
SCHEME 5

displacement of the labile chlorine with hydrazine hydrate. The compound **29** underwent some cyclization reactions upon treatment with triethyl orthoformate, acetic acid and/or carbon disulfide to give s-triazolo[4‴,3‴:4′,5′]pyrrolo[1″,2″ :1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d] pyrimidine derivatives **30a–c** (Scheme 6).

Elemental analyses and spectroscopic data of all compounds prepared are shown in Tables I and II respectively.

EXPERIMENTAL

All melting points are uncorrected and measured on a Fisher-John apparatus. IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer (KBr; υ_{max} in cm^{-1}); ^{1}H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as an internal standard (δ in ppm). Elemental analyses (C, H, N) were carried out on a Perkin-Elmer 240C elemental analyser. Sulfur and chlorine analyses were obtained



SCHEME 6

using oxygen flask method by the microanalytical Unite at Assiut University.

5-Cyano-6-methyl-2-phenylpyrimidine-4(3*H*)-thione (1)

It was prepared by the reported method.[15]

Reaction of Compound 1 with Chloroacetone, Phenacyl Bromide or Ethyl Chloroacetate; Formation of Thieno[2,3-d]pyrimidines 2a–c

To a suspension of **1** (4.54 g, 0.02 mol) and anhydrous potassium carbonate (8.28 g, 0.06 mol) in ethanol (80 mL), the respective halo

TABLE I Physical Properties and Analytical Data (Calc./Found %) of the Prepared Compounds

Comp.	Sol. of cryst. color	m.p. (°C) yield (%)	Mol. formula (M.Wt.)	C	H	N	S
2a	Ethanol	221–222	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83	11.31
	Yellow	77	283.4	63.19	4.79	14.62	11.50
2b	Ethanol	235–238	$C_{20}H_{15}N_3OS$	69.54	4.38	12.16	9.28
	Yellow	86	345.4	69.35	4.42	12.00	9.43
2c[a]	Ethanol	175–176	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41	10.23
	Yellow	80	313.37	61.49	4.76	13.52	10.00
3a	Ethanol	186–187	$C_{19}H_{15}N_3OS$	68.45	4.53	12.60	9.62
	White	76	333.41	68.66	4.50	12.39	9.91
3b	Ethanol	163–164	$C_{24}H_{17}N_3OS$	72.89	4.33	10.63	8.11
	White	79	395.5	72.97	4.37	10.86	8.03
3c	Ethanol	175–176	$C_{20}H_{17}N_3O_2S$	66.10	4.71	11.56	8.82
	White	81	363.4	66.33	4.43	11.50	9.09
4a	Dioxane	182–184	$C_{26}H_{19}N_3OS$	74.09	4.54	9.97	7.61
	Yellow	65	421.5	73.80	4.56	10.17	7.52
4b	Dioxane	238–239	$C_{27}H_{21}N_3O_2S$	71.82	4.69	9.31	7.10
	Yellow	71	451.5	71.77	4.59	9.53	7.34
4c	Dioxane	176–177	$C_{28}H_{24}N_4OS$	72.39	5.21	12.06	6.90
	Red	70	464.6	72.28	5.25	12.11	6.75
5a	Acetic acid	>300	$C_{25}H_{21}N_5S$	70.90	5.00	16.54	7.57
	Yellow	90	423.5	70.69	5.11	16.48	7.40
5b	Acetic acid	243–244	$C_{20}H_{18}N_6S_2$	59.09	4.46	20.67	15.77
	Yellow	83	406.5	58.92	4.37	20.51	16.00
6	Ethanol	220–221	$C_{18}H_{15}N_5OS$	61.88	4.33	20.04	9.18
	White	79	349.4	62.02	4.45	19.77	9.32
7a	Ethanol	205–206	$C_{26}H_{21}N_5S$	71.70	4.86	16.08	7.36
	Pale yellow	80	435.6	71.83	4.70	16.25	7.19
7b	Ethanol	221–222	$C_{27}H_{23}N_5OS$	69.66	4.98	15.04	6.89
	Pale yellow	73	465.6	69.50	5.16	14.93	6.70
7c	Ethanol	254–255	$C_{28}H_{26}N_6S$	70.27	5.48	17.56	6.70
	Pale yellow	76	478.6	70.19	5.63	17.72	6.93
8a	Dioxane	179–180	$C_{32}H_{25}N_5S$	75.12	4.93	13.69	6.27
	Yellow	82	511.6	75.28	5.05	13.55	6.04
8b	Dioxane	260–261	$C_{33}H_{27}N_5OS$	73.17	5.02	12.93	5.92
	Yellow	81	541.7	73.10	5.26	12.87	5.81
8c	Dioxane	274–275	$C_{34}H_{30}N_6S$	73.62	5.45	15.15	5.78
	Red	86	554.7	73.89	5.62	15.00	5.57
9a	Ethanol	173–174	$C_{26}H_{20}N_4OS$	71.54	4.62	12.83	7.34
	Pale yellow	69	436.5	71.64	4.67	12.71	7.61
9b	Ethanol	170–171	$C_{27}H_{22}N_4O_2S$	69.51	4.75	12.01	6.87
	Pale yellow	66	466.6	69.52	4.62	11.95	7.11
9c	Ethanol	158–159	$C_{28}H_{25}N_5OS$	70.12	5.25	14.60	6.68
	Yellow	65	479.6	70.03	5.44	14.87	6.79
10a	Acetic acid	197–198	$C_{27}H_{21}N_5S_2$	67.62	4.41	14.60	13.37
	Yellow	65	479.6	67.38	4.56	14.70	13.21
10b	Acetic acid	220–221	$C_{28}H_{23}N_5OS_2$	65.99	4.55	13.75	12.56
	Yellow	70	509.64	66.17	4.42	13.67	12.69

TABLE I Physical Properties and Analytical Data (Calc./Found %) of the Prepared Compounds *(Continued)*

Comp.	Sol. of Cryst. Color	m.p. (°C) Yield (%)	Mol. formula (M. Wt.)	C	H	N	S
10c	Acetic acid	182–184	$C_{29}H_{26}N_6S_2$	66.64	5.01	16.08	12.27
	Yellow	67	522.7	66.90	5.17	15.97	12.34
11a	Dioxane	211–212	$C_{28}H_{22}N_6S_2$	66.38	4.38	16.59	12.66
	Yellow	83	506.6	66.41	4.26	16.72	12.59
11b[b]	Dioxane	234–235	$C_{28}H_{21}ClN_6S_2$	62.15	3.91	15.53	11.85
	Yellow	85	541.1	62.28	3.04	15.31	12.00
12a	Dioxane	235–236	$C_{22}H_{18}N_6OS_2$	59.17	4.06	18.82	14.36
	White	89	446.5	60.11	4.09	18.96	14.60
12b	Dioxane	242–243	$C_{23}H_{20}N_6OS_2$	59.98	4.38	18.25	13.92
	White	84	460.6	59.83	4.54	18.37	14.15
13a	Ethanol	259–261	$C_{25}H_{19}N_5OS$	68.63	4.38	16.01	7.33
	White	88	437.5	67.88	4.26	16.17	7.51
13b	Ethanol	295–296	$C_{26}H_{21}N_5O_2S$	66.79	4.53	14.99	6.84
	White	87	467.6	66.83	4.76	15.27	7.15
13c	Ethanol	297–298	$C_{27}H_{24}N_6OS$	67.48	5.03	17.49	6.67
	Yellow	91	480.6	67.44	5.11	17.65	7.02
14	Ethanol	218–219	$C_{27}H_{21}N_5O_2S$	67.62	4.41	14.60	6.69
	White	72	479.6	67.75	4.47	14.54	6.84
15	Ethanol	170–171	$C_{23}H_{19}N_5OS$	66.81	4.63	16.94	7.75
	White	76	413.5	67.12	4.56	16.75	7.63
16	Dioxane	289–291	$C_{25}H_{20}N_6OS_2$	61.96	4.16	17.34	13.23
	White	90	484.6	62.17	4.15	17.65	13.07
17	Ethanol	286–287	$C_{25}H_{18}N_6S_2$	64.36	3.89	18.01	13.74
	White	75	466.6	64.20	3.73	18.22	13.67
18	Ethanol	293–294	$C_{19}H_{13}N_5OS_2$	58.30	3.35	17.89	16.38
	White	83	391.5	58.33	3.42	17.98	16.21
19a	Methanol	210–211	$C_{29}H_{24}N_6O_2S_2$	63.02	4.38	15.21	11.60
	White	87	552.7	62.81	4.56	15.43	11.77
19b	Methanol	192–193	$C_{23}H_{19}N_5O_3S_2$	57.85	4.01	14.66	13.43
	White	84	477.6	57.50	4.09	14.41	13.48
20	Not cryst.	163–165	$C_{18}H_{12}N_6OS$	59.99	3.36	23.32	8.90
	White	75	360.4	60.17	3.56	23.19	8.77
22a	Ethanol	245–246	$C_{20}H_{18}N_4O_2S$	63.47	4.79	14.80	8.47
	White	67	378.5	63.40	4.65	14.73	8.69
22b	Iso-propanol	251–252	$C_{21}H_{20}N_4O_2S$	64.27	5.14	14.28	8.17
	White	78	392.5	64.20	5.00	14.43	8.32
23a	Methanol	235–236	$C_{20}H_{19}N_5O_2S$	61.05	4.87	17.80	8.15
	White	90	393.5	60.86	4.67	17.95	8.34
23b	Ethanol	>300	$C_{24}H_{19}N_5OS$	67.75	4.50	16.46	7.53
	White	81	425.5	67.94	4.47	16.81	7.50
23c	Ethanol	>300	$C_{25}H_{21}N_5OS$	68.32	4.82	15.93	7.29
	White	82	439.5	68.34	4.65	15.71	7.16
23d	Ethanol	>300	$C_{25}H_{21}N_5OS$	68.32	4.82	15.93	7.29
	White	80	439.5	68.63	4.78	16.09	7.45

(Continued on next page)

TABLE I Physical Properties and Analytical Data (Calc./Found %) of the Prepared Compounds *(Continued)*

Comp.	Sol. of cryst. color	m.p. (°C) yield (%)	Mol. formula (M.Wt.)	C	H	N	S
23e	Dioxane	>300	$C_{25}H_{21}N_5O_2S$	65.92	4.65	15.37	7.04
	White	79	455.5	65.71	4.72	15.51	7.32
23f[c]	Dioxane	>300	$C_{24}H_{18}ClN_5OS$	62.67	3.94	15.23	6.97
	White	81	460.0	62.90	4.15	15.00	7.18
24	DMF	>300	$C_{18}H_{12}N_4OS$	65.05	3.64	16.86	9.65
	Pale yellow	65	332.4	65.17	3.51	16.69	9.53
25	DMF	>300	$C_{18}H_{12}N_4S_2$	62.05	3.47	16.08	18.40
	Yellow	66	348.4	62.29	3.39	16.30	18.56
26a[d]	Dioxane	159–160	$C_{26}H_{17}ClN_4OS_2$	62.33	3.42	11.18	12.80
	Pale yellow	81	501.0	62.14	3.68	11.05	13.10
26b	Ethanol	150–151	$C_{22}H_{18}N_4O_2S_2$	60.81	4.18	12.89	14.76
	Pale yellow	74	434.5	60.75	4.53	12.66	14.95
27	Dioxane	271–272	$C_{20}H_{16}N_6OS_2$	57.13	3.84	19.99	15.25
	Pale yellow	63	420.5	57.42	3.80	19.87	15.31
28[e]	Chloroform	287–288	$C_{18}H_{11}ClN_4S$	61.63	3.16	15.97	9.14
	Pale yellow	81	350.8	61.76	3.22	16.06	9.10
29	Dioxane	>300	$C_{18}H_{14}N_6S$	62.41	4.07	24.26	9.25
	Yellow	71	346.4	62.29	4.15	24.45	9.18
30a	Dioxane	275–276	$C_{19}H_{12}N_6S$	64.03	3.39	23.58	9.00
	Pale yellow	80	356.4	64.25	3.36	23.70	9.18
30b	Dioxane	271–272	$C_{20}H_{14}N_6S$	64.85	3.81	22.69	8.65
	Pale yellow	69	370.4	64.72	3.71	22.93	8.69
30c	Acetic acid	293–294	$C_{19}H_{12}N_6S_2$	58.75	3.11	21.63	16.51
	Yellow	70	388.5	58.82	3.27	21.51	16.79

[a] Lit.[11] m.p. 174–176°C.
[b] Calcd. Cl = 6.55%; Found = 6.40%.
[c] Calcd. Cl = 7.71%; Found = 7.90%.
[d] Calcd. Cl = 7.08%; Found = 6.93%.
[e] Calcd. Cl = 10.11%; Found = 10.32%.

compound (0.02 mol) was added. The resulting mixture was heated under reflux for 3 h and then left to cool. The precipitate that formed was filtered off, washed thoroughly with water, and recrystallized to give **2a–c**.

Reaction of Compounds 2a–c with 2,5-Dimethoxytetrahydrofuran; Formation of Pyrrylthieno[2,3-d]pyrimidines 3a–c

A mixture of **2a–c** (0.02 mol) and 2,5-dimethoxytetrahydrofuran (2.6 mL, 0.02 mol) in glacial acetic acid (40 mL) was heated under reflux for 1 h. The solid product was collected and recrystallized to give **3a–c**.

TABLE II IR and ^{1}H NMR Spectral Data of the Prepared Compounds

Compd.	IR [cm^{-1}]	^{1}H NMR [ppm]
2a	3470, 3300 (NH_2); 1630 (C═O)	($CDCl_3$): 8.0–8.2 (m, 2H, ArH's); 7.2–7.5 (m, 3H, ArH's); 6.3–6.7 (br, 2H, NH_2); 2.5 (s, 3H,CH_3); 2.3 (s, 3H, CH_3)
2b	3470, 3300 (NH_2); 1630 (C═O)	($CDCl_3$): 8.1–8.4 (m, 2H, ArH's); 7.0–7.6 (m, 8H, ArH's); 6.4–6.7 (br, 2H, NH_2); 2.4 (s, 3H, CH_3)
2c	3480, 3300 (NH_2); 1660 (C═O)	($CDCl_3$): 8.1–8.3 (m, 2H, ArH's); 7.2–7.5 (m, 3H, ArH's); 5.6 (s, 2H, NH_2); 4.3 (q, 2H, OCH_2); 2.6 (s, 3H, CH_3); 1.3 (t, 3H, CH_3)
3a	1680 (C═O)	($CDCl_3$): 8.1–8.3 (m, 2H, ArH's); 7.2–7.5 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.8 (s, 3H, CH_3); 2.5 (s, 3H, CH_3)
3b	1650 (C═O)	($CDCl_3$): 8.2–8.5 (m, 2H, ArH's); 7.0–7.7 (m, 8H, ArH's); 6.6 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 2.4 (s, 3H, CH_3)
3c	1680 (C═O)	($CDCl_3$): 8.0–8.2 (m, 2H, ArH's); 7.3–7.6 (m, 3H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.3 (q, 2H, OCH_2); 2.5 (s, 3H, CH_3); 1.2 (t, 3H, CH_3)
4a	1650 (C═O); 1590 (C═C)	(DMSO-d_6): 7.0–8.2 (m, 12H, ArH's, CH═CH); 6.8 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 2.6 (s, 3H, CH_3)
4b	1650 (C═O); 1590 (C═C)	(DMSO-d_6): 6.7–8.2 (m, 11H, ArH's, CH═CH); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 3.9 (s, 3H, OCH_3); 2.5 (s, 3H, CH_3)
4c	1650 (C═O); 1590 (C═C)	(DMSO-d_6): 6.8–8.3 (m, 11H, ArH's, CH═CH); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 3.0 (s, 6H, $N(CH_3)_2$); 2.5 (s, 3H, CH_3)
5a	3370 (NH)	(DMSO-d_6): 9.8 (s, 1H, NH); 6.9–8.3 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 2.4 (s, 3H, CH_3); 2.1 (s, 3H, CH_3)
5b	3400-3130 (NH_2, NH); 1230 (C═S)	(DMSO-d_6): 10.3 (s, 1H, NH); 8.4 (s, 2H, NH_2); 8.0–8.2 (m, 2H, ArH's); 7.5–7.7 (m, 3H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.5 (s, 3H, CH_3); 2.0 (s, 3H, CH_3)
6	3450-3120 ($NHNH_2$); 1640 (C═O)	($CDCl_3$): 9.6 (s, 1H, NH); 8.1–8.3 (m, 2H, ArH's); 7.2–7.5 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.5 (s, 2H, NH_2); 2.5 (s, 3H, CH_3)
7a	3200 (NH); 1600 (C═N)	($CDCl_3$): 7.0–8.2 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.3 (m, 2H, CH_2 pyrazoline); 2.9 (s, 1H, NH) and 2.6 (s, 3H, CH_3)
7b	3240 (NH); 1600 (C═N)	($CDCl_3$): 6.8–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.9 (s, 3H, OCH_3); 3.3 (m, 2H, CH_2 pyrazoline); 2.9 (s,1H, NH); 2.6 (s, 3H, CH_3)

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TABLE II IR and ^{1}H NMR Spectral Data of the Prepared Compounds *(Continued)*

Compd.	IR [cm^{-1}]	^{1}H NMR [ppm]
7c	3200 (NH); 1600 (C═N)	($CDCl_3$): 6.8–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.0 (s, 6H, N $(CH_3)_2$); 3.3 (m, 2H, CH_2 pyrazoline); 2.9 (s,1H, NH); 2.6 (s, 3H, CH_3)
8a	1620 (C═N)	(DMSO-d_6): 6.9–8.3 (m,15H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.3 (m, 2H, CH_2 pyrazoline); 2.6 (s, 3H, CH_3)
8b	1610 (C═N)	(DMSO-d_6): 6.7–8.3 (m,14H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.8 (s, 3H, OCH_3); 3.3 (m, 2H, CH_2 pyrazoline); 2.6 (s, 3H, CH_3)
8c	1620 (C═N)	($CDCl_3$): 6.6–8.2 (m, 14H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH pyrazoline); 3.1 (s, 6H, $N(CH_3)_2$); 3.3 (m, 2H, CH_2 pyrazoline); 2.6 (s, 3H, CH_3)
9a	1600 (C═N)	($CDCl_3$): 6.9–8.2 (m,10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.6 (t, 1H, CH isoxazoline); 3.2 (m, 2H, CH_2 isoxazoline); 2.7 (s, 3H, CH_3)
9b	1600 (C═N)	($CDCl_3$): 6.6–8.3 (m, 9H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.8 (t, 1H, CH isoxazoline); 3.8 (s, 3H, OCH_3); 3.3 (m, 2H, CH_2 isoxazoline); 2.6 (s, 3H, CH_3)
9c	1610 (C═N)	($CDCl_3$): 6.7–8.2 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 4.7 (t, 1H, CH isoxazoline); 3.1 (s, 6H, $N(CH_3)_2$); 3.4 (m, 2H, CH_2 isoxazoline); 2.7 (s, 3H, CH_3)
10a	3180 (NH); 1640 (NCS)	(DMSO-d_6): 9.8 (s, 1H, NH); 9.2 (s, 1H, NH); 6.9–8.2 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 5.3 (m, 1H, CH pyrimidine); 4.5 (d, 1H, CH pyrimidine); 2.7 (s, 3H, CH_3)
10b	3180 (NH); 1640 (NCS)	(DMSO-d_6): 9.9 (s, 1H, NH); 9.3 (s, 1H, NH); 6.8–8.3 (m, 9H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 5.4 (m, 1H, CH pyrimidine); 4.6 (d, 1H, CH pyrimidine); 3.8 (s, 3H, OCH_3); 2.6 (s, 3H, CH_3)
10c	3180 (NH); 1640 (NCS)	($CDCl_3$): 9.6 (s, 1H, NH); 9.3 (s, 1H, NH); 7.0–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 5.4 (m, 1H, CH pyrimidine); 4.6 (d, 1H, CH pyrimidine); 3.0 (s, 6H, $N(CH_3)_2$); 2.7 (s, 3H, CH_3)
11a	3420 (NH)	(TFA): 6.9–8.2 (m,11H, ArH's, CH thiazoline); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.6 (s, 3H, CH_3); 2.1 (s, 3H, CH_3)
11b	3420 (NH)	(TFA): 6.9–8.4 (m, 10H, ArH's, CH thiazoline); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.6 (s, 3H, CH_3); 2.2 (s, 3H, CH_3)

TABLE II IR and 1H NMR Spectral Data of the Prepared Compounds *(Continued)*

Compd.	IR [cm^{-1}]	^1H NMR [PPM]
12a	3100 (NH); 1710 (C═O)	(TFA): 8.0–8.3 (m, 2H, ArH's); 7.5–7.8 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 4.1 (s, 2H, CH_2 thiazolidinone); 2.5 (s, 3H, CH_3); 2.0 (s, 3H, CH_3)
12b	3100 (NH); 1710 (C═O)	(TFA): 8.1–8.3 (m, 2H, ArH's); 7.5–7.8 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 4.0 (q, 1H, CH thiazolidinone); 2.6 (s, 3H, CH_3); 2.1 (s, 3H, CH_3); 1.7 (d, 3H, CH_3)
13a	3300 (NH); 1680 (C═O)	(TFA): 6.9–8.3 (m, 11H, ArH's, and N═CH); 6.6 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 2.6 (s, 3H, CH_3)
13b	3300 (NH); 1680 (C═O)	(TFA): 6.8–8.3 (m, 10H, ArH's, and N═CH); 6.6 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 3.3 (s, 3H, OCH_3); 2.6 (s, 3H, CH_3)
13c	3300 (NH); 1680 (C═O)	(TFA): 6.8–8.3 (m, 10H, ArH's, and N═CH); 6.6 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 3.8 (s, 6H, $N(CH_3)_2$); 2.6 (s, 3H, CH_3)
14	1650 (C═O)	($CDCl_3$): 6.9–8.3 (m, 10H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.3 (m, 2H, 2CH pyrrole); 3.0 (s, 1H, CH oxadiazoline); 2.6 (s, 3H, CH_3); 2.3 (s, 3H, CH_3CO)
15	1660 (C═O)	($CDCl_3$): 8.0–8.3 (m, 2H, ArH's); 7.1–7.4 (m, 3H, ArH's); 6.6 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 6.1 (s, 1H, CH pyrazole); 2.7, 2.5,2.3 (3s, 9H, $3XCH_3$)
16	3350–3160 (NH); 1650(C═O)	(DMSO-d_6): 9.8 (s, 1H, NH); 9.6 (s, 1H, NH); 7.0–8.2 (m, 11H, ArH's and NH); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.7 (s, 3H, CH_3)
17	3100 (NH); 1600 (C═N)	(DMSO-d_6): 13.3 (s, 1H, NH); 7.0–8.2 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.7 (s, 3H, CH_3)
18	3300 (NH); 1600 (C═N)	($CDCl_3$):13.0 (s, 1H, NH); 8.0–8.3 (m, 2H, ArH's); 7.1–7.4 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.7 (s, 3H, CH_3)
19a	1720 (C═O)	($CDCl_3$):7.1–8.3 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 4.3 (q, 2H, OCH_2); 3.9 (s, 2H, SCH_2); 2.7 (s, 3H, CH_3); 1.2 (t, 3H, CH_3)
19b	1720 (C═O)	($CDCl_3$): 8.0–8.3 (m, 2H, ArH's); 7.1-7.4 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 4.4 (q, 2H, OCH_2); 4.1 (s, 2H, SCH_2); 2.7 (s, 3H, CH_3); 1.3 (t, 3H, CH_3)
20	3150 (N_3); 1660 (C═O)	($CDCl_3$): 8.1–8.3 (m, 2H, ArH's); 7.1–7.4 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 2.6 (s, 3H, CH_3)
22a	3400 (NH); 1720 (C═O)	(TFA): 8.1–8.3 (m, 2H, ArH's); 7.4–7.7 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 4.3 (q, 2H, OCH_2); 2.5 (s, 3H, CH_3); 1.3 (t, 3H, CH_3)

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TABLE II IR and 1H NMR Spectral Data of the Prepared Compounds *(Continued)*

Compd.	IR [cm^{-1}]	^1H NMR [ppm]
22b	3400 (NH); 1720 (C═O)	(TFA): 8.0–8.3 (m, 2H, ArH's); 7.5–7.8 (m, 3H, ArH's); 6.9 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 5.5 (m, 1H, OCH); 2.4 (s, 3H, CH_3); 1.6 (d, 6H, 2XCH_3)
23a	3500–3100 (OH, NH); 1630 (C═O)	($CDCl_3$): 8.5 (s, 1H, NH); 8.0–8.3 (m, 3H, ArH's NH); 7.2–7.5 (m, 3H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.5 (m, 2H, 2CH pyrrole); 3.2–3.8 (m, 5H, $(CH_2)_2$ and OH); 2.4 (s, 3H, CH_3)
23b	3400–3100 (NH); 1640 (C═O)	(DMSO-d_6): 9.7 (s, 1H, NH); 8.9 (s,1H, NH); 6.8–8.3 (m, 10H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.4 (s, 3H, CH_3)
23c	3400–3100 (NH); 1640 (C═O)	(DMSO-d_6): 9.7 (s, 1H, NH); 8.8 (s,1H, NH); 6.9–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.5 (s, 3H, CH_3); 2.3 (s, 3H, CH_3)
23d	3400–3100 (NH); 1640 (C═O)	(DMSO-d_6): 9.8 (s,1H, NH); 9.0 (s,1H, NH); 6.9–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.5 (s, 3H, CH_3); 2.2 (s, 3H, CH_3)
23e	3400–3100 (NH); 1640 (C═O)	(DMSO-d_6): 9.8 (s,1H, NH); 8.9 (s,1H, NH); 6.9–8.3 (m, 9H, ArH's); 6.7 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 3.8 (s, 3H, OCH_3); 2.5 (s, 3H, CH_3)
23f	3400–3100 (NH); 1650 (C═O)	(DMSO-d_6): 9.7 (s, 1H, NH); 8.9 (s,1H, NH); 6.8–8.3 (m, 9H, ArH's); 6.8 (m, 2H, 2CH pyrrole); 6.4 (m, 2H, 2CH pyrrole); 2.4 (s, 3H, CH_3)
24	3200–2400 (NH); 1640 (C═O)	(TFA): 8.0–8.4 (m, 3H, ArH's and CH pyrrole); 7.6 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m, 1H, CH pyrrole); 2.9 (s, 3H, CH_3)
25	3400–3200 (NH); 1250 (C═S)	(TFA): 8.1–8.3 (m, 3H, ArH's, CH pyrrole); 7.5 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m, 1H, CH pyrrole); 2.8 (s, 3H, CH_3)
26a	1680 (C═O); 1600 (C═N)	(DMSO-d_6): 8.0–8.4 (m, 3H, ArH's, CH pyrrole); 7.6 (d, 1H, CH pyrrole); 7.0–7.3 (m, 7H, ArH's); 6.9 (m, 1H, CH pyrrole); 5.4 (s, 2H, SCH_2); 2.9 (s, 3H, CH_3)
26b	1730 (C═O); 1600 (C═N)	(DMSO-d_6): 8.0–8.4 (m, 3H, ArH's, CH pyrrole); 7.6 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m, 1H, CH pyrrole); 4.2–4.5 (q, 2H, OCH_2); 4.0 (s, 2H, SCH_2); 2.9 (s, 3H, CH_3); 1.1–1.4 (t, 3H, CH_3)
30a	1600 (C═N)	(TFA): 9.4 (s, 1H, CH triazole); 8.1–8.4 (m, 3H, ArHs, CH pyrrole); 7.5 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m,1H, CH pyrrole); 2.8 (s, 3H, CH_3)
30b	1600 (C═N)	(TFA): 8.1–8.4 (m, 3H, ArH's, CH pyrrole); 7.5 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m,1H, CH pyrrole); 3.0 (s, 3H, CH_3); 2.8 (s, 3H, CH_3)
30c	3400 (NH); 1600 (C═N)	(TFA): 8.1–8.4 (m, 3H, ArH's, CH pyrrole); 7.5 (d, 1H, CH pyrrole); 7.0–7.3 (m, 3H, ArH's); 6.9 (m, 1H, CH pyrrole); 2.8 (s, 3H, CH_3)

Condensation of Compound 3a with Aromatic Aldehydes; Formation of Chalcones 4a–c

A mixture of **3a** (3.33 g, 0.01 mol) and the respective aldehyde (0.01 mol) in an ethanolic sodium hydroxide solution 8% (50 mL) was stirred at room temperature for 2 h. The solid that precipitated was collected and recrystallized to give **4a–c**.

Condensation of Compound 3a with Phenylhydrazine or Thiosemicarbazide; Formation of Phenylhydrazone 5a or Thiosemicarbazone 5b

A mixture of **3a** (3.33 g, 0.01 mol) and phenylhydrazine or thiosemicarbazide (0.01 mol) in glacial acetic acid (30 mL) was heated under reflux for 1 h. The precipitate that formed after cooling was collected and recrystallized to give **5a** or **5b** respectively.

4-Methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidine-6-carbohydrazide (6)

A mixture of the ester **3c** (3.63 g, 0.01 mol) and hydrazine hydrate 99% (2 mL, 0.04 mol) in pyridine (30 mL) was heated under reflux for 3 h. The reaction mixture was cooled and diluted with ice-water (30 mL) whereby a white solid precipitated. It was collected by filtration and crystallized to give **6**.

6-(5-Aryl-2-pyrazolin-3-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidines (7a–c)

A suspension of **4a–c** (0.005 mol) and hydrazine hydrate 99% (1 mL, 0.02 mol) in ethanol (35 mL) was heated under reflux for 4 h. The precipitate that formed on cooling was collected and recrystallized to give **7a–c**.

6-(5-Aryl-1-phenyl-2-pyrazolin-3-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidines (8a–c)

A mixture of **4a–c** (0.005 mol) and phenylhydrazine (0.54g, 0.005 mol) in glacial acetic acid (25 mL) was heated under reflux for 3 h. The precipitate that formed after cooling was collected and recrystallized to give **8a–c**.

6-(5-Aryl-2-isoxazolin-3-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidines (9a–c)

To a suspension of **4a–c** (0.01 mol) and hydroxylamine hydrochloride (0.7 g, 0.01 mol) in ethanol (35 mL), anhydrous sodium acetate (1.64 g, 0.02 mol) was added. The resulting mixture was heated under reflux for 4 h, cooled, and poured onto ice water (30 mL). The precipitated solid was collected and recrystallized to give **9a–c**.

6-(6-Aryl-1,2,3,6-tetrahydro-2-thioxopyrimidin-4-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidines (10a–c)

To a suspension of **4a–c** (0.005 mol) and thiourea (0.35 g, 0.005 mol) in ethanol (30 mL), few drops of concentrated HCl was added. The resulting mixture was heated under reflux for 4 h and then left to cooled. The precipitated solid was collected and recrystallized to give **10a–c**.

Reaction of Thiosemicarbazone 5b with Phenacyl Bromide, *p*-Chlorophenacyl Bromide, Ethyl Chloroacetate or Methyl 2-bromopropionate; Formation of Thiazolines 11a,b and Thiazolidinones 12a,b

To a mixture of **5b** (2.03 g, 0.005 mol) and the respective halocompound (0.005 mol) in ethanol (25 mL), fused sodium acetate (0.82 g, 0.01 mol) was added. The resulting mixture was heated under reflux for 4 h and then allowed to cool. The solid that formed was collected and recrystallized to give **11a**,**b** or **12a**,**b** respectively.

N^1-Arylmethylene-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine-6-carbohydrazides (13a–c)

A mixture of carbohydrazide **6** (1.75 g, 0.005 mol) and the respective aldehyde (0.005 mol) in ethanol (20 mL) was heated under reflux for 3 h. The precipitate that separated after cooling was collected and recrystallized to give **13a–c**.

6-(4-Acetyl-4,5-dihydro-5-phenyl-1,3,4-oxadiazol-2-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidine (14)

Compound **13a** (0.87 g, 0.002 mol) in redistilled acetic anhydride (20 mL) was heated under reflux for 4 h. The reaction mixture was

cooled, diluted with water (20 mL), and then allowed to stand at room temperature for 3 h. The white solid that formed was collected and recrystallized to give **14**.

6-(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine (15)

A mixture of carbohydrazide **6** (1.75 g, 0.005 mol) and acetylacetone (5 mL, 0.05 mol) was heated under reflux for 30 min, then triturated with ethanol (10 mL), and left to cool. The precipitate that formed was collected and recrystallized to give **15**.

1-(4-Methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidin-6-yl)carbonyl-4-phenylthiosemicarbazide (16)

A mixture of carbohydrazide **6** (2.09 g, 0.006 mol) and phenyl isothiocyanate (0.72 mL, 0.006 mol) in ethanol (25 mL) was heated under reflux for 3 h. The precipitate that separated after cooling was collected and recrystallized to give **16**.

6-(4-Phenyl-5-thioxo-s-triazolin-3-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]pyrimidine (17)

A suspension of thiosemicarbazide **16** (2.42 g, 0.005 mol) in sodium hydroxide solution 8% (20 mL) was heated under reflux on a steam bath for 4 h, cooled, and filtered. The clear filtrate was acidified with dilute HCl at 5–10°C. The solid that separated was collected and crystallized to give **17**.

6-(4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)-4-methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidine (18)

A mixture of carbohydrazide **6** (1.75 g, 0.005 mol) and carbon disulfide (3 mL) in ethanol (40 mL) containing potassium hydroxide (0.45 g, 0.008 mol) was heated under reflux on a steam bath for 5 h. The reaction mixture was concentrated, diluted with water, and filtered. The clear filtrate was acidified with dilute HCl at 5–10°C. The precipitated solid was collected and crystallized to give **18**.

Reaction of Thiones 17 and 18 with Ethyl Chloroacetate; Formation of Esters 19a,b

To a mixture of **17** or **18** (0.002 mol) and ethyl chloroacetate (0.22 mL, 0.002 mol) in ethanol (20 mL), sodium acetate trihydrate (0.68 g, 0.005 mol) was added. The resulting mixture was heated under reflux for 2 h, cooled, and diluted with water (10 mL). The solid that formed was filtered off, washed thoroughly with water, and recrystallized to give **19a** or **19b** respectively.

4-Methyl-2-phenyl-5-(1-pyrryl)-thieno[2,3-d]-pyrimidine-6-carboazide (20)

To a chilled suspension of carbohydrazide **6** (3.49 g, 0.01 mol) in glacial acetic acid (25 mL), a cold solution of sodium nitrite 33% (10 mL) was added dropwise with stirring. After completion of addition, the stirring was continued for additional 1 h. The precipitate that formed was collected by filtration, dried in air, and applied in the next reactions without purification.

Reaction of Acid Azide 20 with Alcohols; Formation of Alkyl Carbamate 22a,b

The acid azide **20** (0.72 g, 0.002 mol) in ethanol or iso-propanol (20 mL) was heated under reflux for 5 h, concentrated, and then allowed to cool. The precipitated solid was collected and recrystallized to give **22a** or **22b** respectively.

Reaction of 20 with Different Amines; Formation of Urea Derivatives 23a–f

A mixture of acid azide **20** (0.72 g, 0.002 mol) and an excess amount of the respective amine (ethanolamine, aniline, *o*-toluidine, *p*-toluidine, *p*-anisidine or *p*-chloroaniline) (0.01 mol) was heated gently for 2 h, triturated with ethanol (15 mL), and then allowed to cool. The precipitated solid was collected and recrystallized to give **23a–f**.

4-Methyl-2-phenylpyrrolo[1″,2″:1′,6′]pyrazino-[2′,3′:4,5]thieno[2,3-d]pyrimidine-9(10*H*)-one (24)

A suspension of **20** (3.6 g, 0.01 mol) in dry xylene (50 mL) was heated under reflux for 2 h. The solid that formed while hot was collected and recrystallized to give **24**.

4-Methyl-2-phenylpyrrolo[1′′,2′′:1′,6′]pyrazino-[2′,3′:4,5]thieno[2,3-d]pyrimidine-9(10*H*)-thione (25)

A mixture of **24** (1.66 g, 0.005 mol) and phosphorus pentasulfide (1.11 g, 0.005 mol) in dry pyridine (20 mL) was heated under reflux for 5 h. The reaction mixture was cooled, diluted with ice-water (40 mL), and acidified with dilute acetic acid. The precipitate that formed was collected and crystallized to give **25**.

4-Methyl-2-phenyl-9-substituted methylthiopyrrolo-[1′′,2′′:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]-pyrimidines (26a,b)

To a mixture of **25** (0.70 g, 0.002 mol) and *p*-chlorophenacyl bromide or ethyl chloroacetate (0.002 mol) in ethanol (25 mL), sodium acetate trihydrate (0.54 g, 0.004 mol) was added. The resulting mixture was heated under reflux for 2 h and then left to cool. The solid that formed was filtered off, washed thoroughly with water, and recrystallized to give **26a** or **26b** respectively.

4-Methyl-2-phenylpyrrolo[1′′,2′′:1′,6′]pyrazino-[2′,3′:4,5]thieno[2,3-d]pyrimidin-9-ylthioacethydrazide (27)

A mixture of compound **26b** (0.87 g, 0.002 mol) and hydrazine hydrate 99% (0.3 mL, 0.006 mol) in ethanol (15 mL) was allowed to stand overnight at room temperature. The solid that formed was filtered off, washed thoroughly with water and recrystallized to give **27**.

9-Chloro-4-methyl-2-phenylpyrrolo[1′′,2′′:1′,6′]-pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidine (28)

Compound **24** (3.32 g, 0.01 mol) in an excess amount of phosphorus oxychloride (60 mL) was heated under reflux for 4 h and then left to cool. The reaction mixture was poured gradually onto ice water (180 mL) with stirring. The solid that formed was filtered off, washed thoroughly with water, and crystallized to give **28**.

9-Hydrazino-4-methyl-2-phenylpyrrolo[1′′,2′′:1′,6′]-pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidine (29)

A mixture of the ester **26b** (0.87 g, 0.002 mol) and hydrazine hydrate 99% (3 mL, 0.06 mol) was heated under reflux for 3 h. The solid that formed while hot was collected and recrystallized to give **29**.

A mixture of chlorocompound **28** (1.75 g, 0.005 mol) and hydrazine hydrate 99% (1 mL, 0.02 mol) in ethanol (30 mL) was heated under reflux for 3 h. The solid that formed while hot upon recrystallization was identical to that described the method above (yield: 93%).

4-Methyl-2-phenyl-s-triazolo[4′′′,3′′′:4′,5′]pyrrolo-[1′′, 2′′:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidine (30a)

A suspension of hydrazino compound **29** (0.35 g, 0.001 mol) in triethyl orthoformate (10 mL) was heated under reflux for 3 h. The solid that formed while hot was collected and recrystallized to give **30a**.

4,11-Dimethyl-2-phenyl-s-triazolo[4′′′,3′′′:4′,5′]-pyrrolo[1′′,2′′:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]-pyrimidine (30b)

A suspension of hydrazino compound **29** (0.35 g, 0.001 mol) in glacial acetic acid (15 mL) was heated under reflux for 3 h. The solid that formed on cooling was collected and recrystallized to give **30b**.

4-Methyl-2-phenyl-s-triazolo[4′′′,3′′′:4′,5′]pyrrolo-[1′′,2′′:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-d]pyrimidine-11-thiol (30c)

A mixture of hydrazino compound **29** (0.35 g, 0.001 mol) and carbon disulfide (1 mL) in pyridine (10 mL) was heated under reflux on a steam bath for 8 h. The solid that formed on cooling was collected and recrystallized to give **30c**.

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