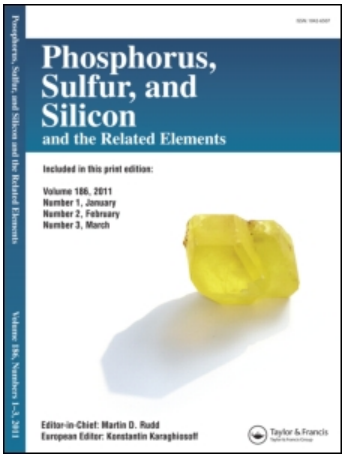

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Reactions of Some New Thienopyrimidines

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SYNTHESIS AND REACTIONS OF SOME NEW THIENOPYRIMIDINES

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*4-Methyl-6-mercapto-2-phenylpyrimidine-5-carbonitrile (**1**) was reacted with different halo compounds, namely ethylchloroacetate, chloroacetone, bromoacetanilide, p-chlorobromoacetanilide, and* p*-methoxy chloroacetanilide in ethanol in the presence of sodium acetate yielded the corresponding S-alkylated derivatives (**2a–e**). The latter compounds underwent cyclization into thienopyrimidines (**4a–e**) upon treatment with sodium ethoxide in ethanol. The reaction of (**4a**) with hydrazine hydrate led to the formation of 5-amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-2-carbohydrazide (**5**). Compound (**5**) was reacted with a variety of reagents to produce other new thienopyrimidines as well as oxadiazolylthienopyrimidines (**6, 11**).*

Thienopyrimidines and pyrimidothienopyrimidines have been subject to chemical and biological studies due to their interesting pharmacological effects,[1] which includes analgesic,[2] antipyretic,[3] and anti-inflammatory[4,5] properties. In view of the above activities, we report on the synthesis of some new thienopyrimidines and pyrimidothienopyrimidines hoping to get compounds with high biological activity or medicinal applications.

RESULTS AND DISCUSSION

The starting compound 4-methyl-6-mercapto-2-phenylpyrimidine-5-carbonitrile (**1**) was prepared according to literature procedures.[6] The reaction of (**1**) with some halo-compounds, namely ethylchloroacetate,

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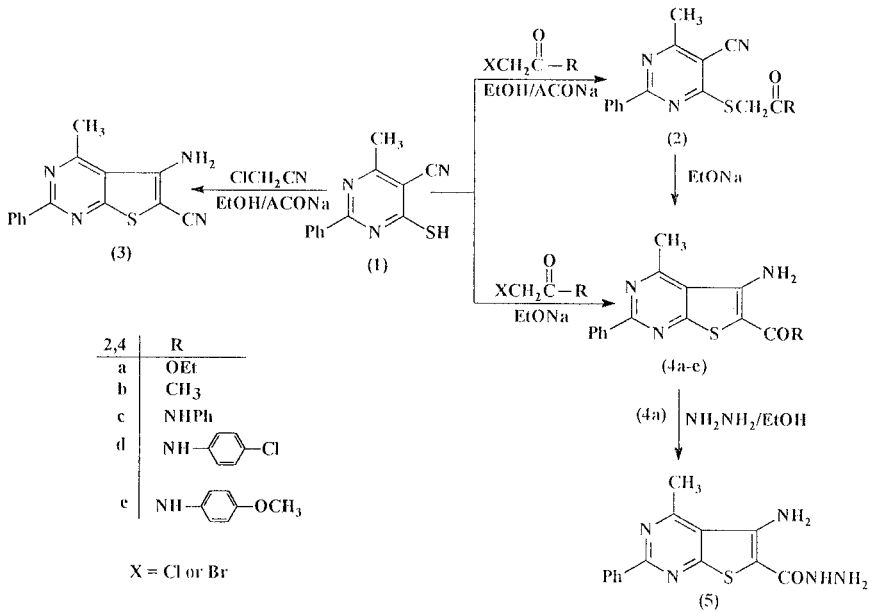
chloroacetone, and N-arylchloroacetamide, on refluxing ethanol in the presence of sodium acetate, afforded the S-alkylated derivatives (**2a–e**), respectively, in excellent yields (Scheme 1). On the other hand, the reaction of (**1**) with chloroacetonitrile under the above conditions yielded the cyclized product 5-amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carbonitrile (**3**). Compounds (**2a–e**) underwent ring closure by refluxing in ethanol containing sodium ethoxide to give thieno[2,3-d]-pyrimidines (**4a–e**). Synthesis of thienopyrimidine derivatives (**4a–e**) were achieved in one step by subjecting pyrimidine (**1**) to react with above halo compounds in ethanol in the presence of sodium ethoxide (Scheme 1).



SCHEME 1

Hydrazinolysis of ethyl 5-amino-4-methyl-2-phenylthieno-[2,3-d]-pyrimidine-6-carboxylate (**4a**) with hydrazine hydrate in absolute ethanol afforded the corresponding 6-carbohydrazide derivative (**5**). The latter compound (**5**) was used as precursor intermediate to produce other fused heterocyclic compounds. Refluxing **5** with carbon disulfide in pyridine yielded oxadiazolyl derivative (**6**) instead of pyrimidothieno-pyrimidine derivative (**7**). The formation of compond **6** was established

chemically by its reaction with dimethoxy tetrahydrofurane, to afford pyrrolyl derivative **8**. Compound **8** was prepared by another route from compound **4a**, which was converted into the corresponding pyrrolyl derivative **9**, followed by its hydrazinolysis to give carbohydrazide **10**; the latter compound was cyclized using CS_2 in pyridine to afford compound **8** which recently was reported by El-Kashef et al.[7] Alkylation of compound (**6**) with ethylchloroacetate in ethanol in presence of sodium acetate gave the S-alkylated derivative (**11**).

Compound (**5**) was allowed to react with nitrous acid yielded the corresponding carboazide (**12**), which upon boiling in dry xylene underwent Curtius rearrangment to give 4-methyl-2-phenylimidazo [4′,5′:4,5]thieno[2,3-d]pyrimidine-(6H,7H)one (**13**). Carbohydrazide derivative **5** was reacted with acetylacetone in ethanol to produce pyrazolyl derivative **14**. Also, compound **5** undergoes ring closure followed by formaylation or N acylation upon treatment with formic acid or acetic anhydride to afford compounds (**15**) and (**16**) respectively (Scheme 2).

Condensation of carbohydrazide derivative (**5**) with various aromatic aldehydes in refluxing ethanol yielded the corresponding carbohydrazone derivatives (**17a–c**). Refluxing each of compounds (**17a–c**) with carbon disulfide in pyridine for long time gave 9-methyl-7-phenyl-4-oxo-2-thioxo-1,2,3-trihydro-pyrimido-[5′,4′:4,5]thieno[2,3-d]thiazine (**18**) instead of the expected pyrimidothienopyrimidine (**19**).

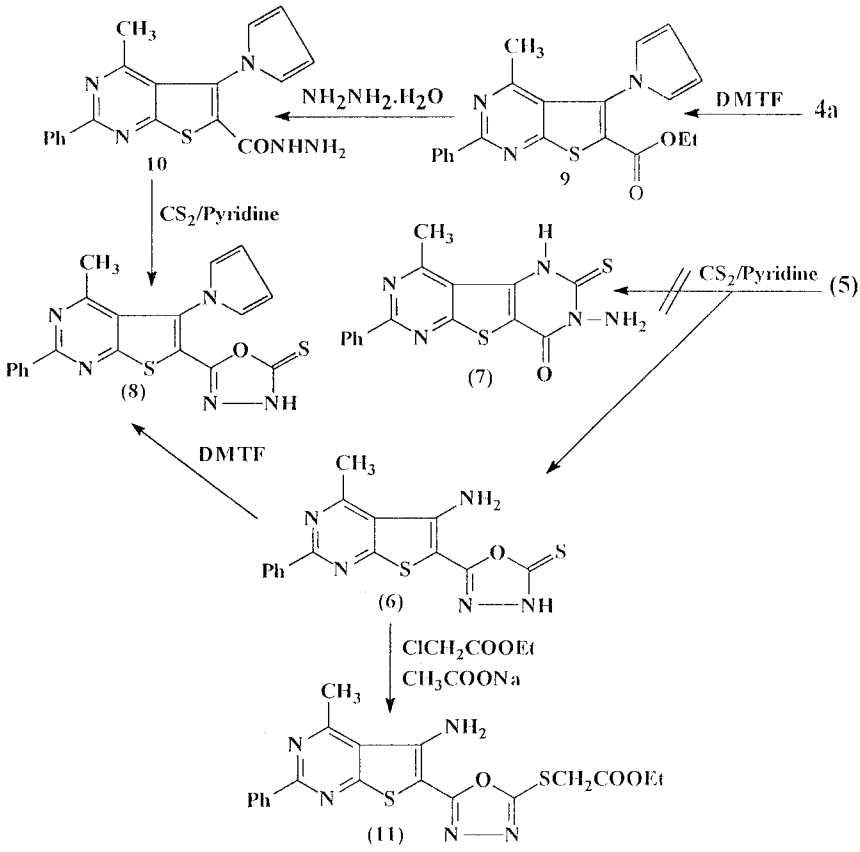
We postulate that the mechanism of this reaction was proceeded as reported previously[8,9] as follows.

o-Amino ester (**4a**) was used as a starting material for synthesis of some unreported new heterocyclic compounds, thus it's reaction with formamide and phenylisothiocyanate afforded the pyrimidothienopyrimidine derivatives (**20, 21**) respectively.

Saponification of (**4a**) using 10% sodium hydroxide gave the corresponding sodium salt (**22**), which upon treatment with orthophosphoric acid, at room temperature, decarboxylation was occurred to give 4-methyl-2-phenylthieno[2,3-d] pyrimidine-5(6H)-one (**23**) (Scheme 4).

Thienopyrimidine-5-one derivative **23** was reacted with aromatic aldehydes in ethanol in the presence of catalytic amount of piperidine to give 6-aryledinethienopyrimidine-5-one **24a,b** (Scheme 5). The latter compound was reacted with malononitrile in ethanol in the presence of triethylamine to give pyranothienopyrimidine derivatives **25a,b**. It is worthy to mentioned that **25a,b** also could be obtained by the reaction of **21** with aryledinemalononitrile in ethanol in the presence of triethylamines.

On the other hand, the active methylene compound **23** was spontaneously oxidized to produce the indigo like compound **26** when exposed



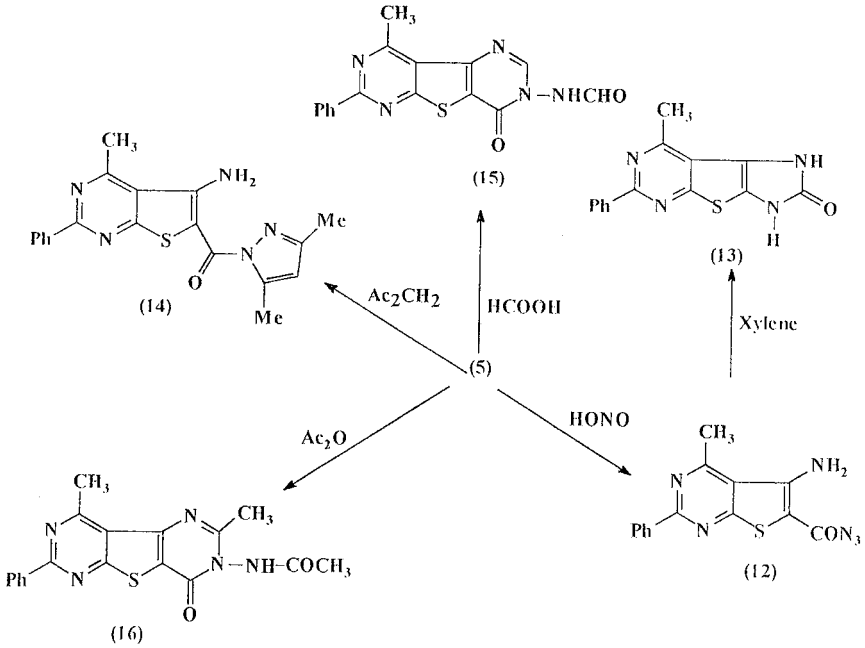
DMTF = Dimethoxytetrahydrofuran

SCHEME 2

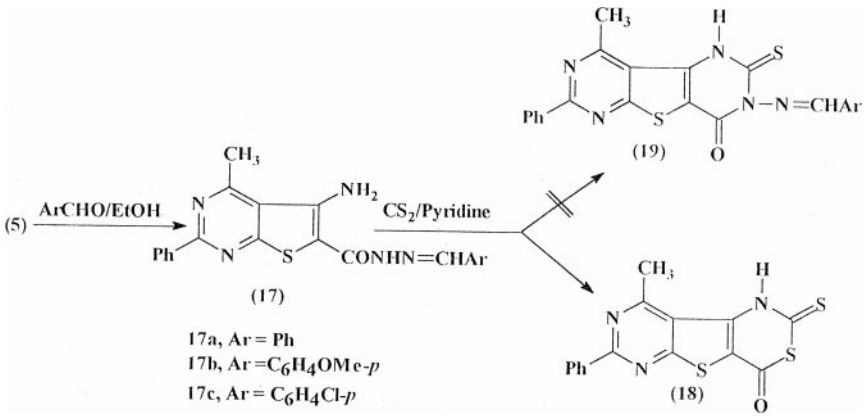
to air, which its suspension in ethanol was changed from white to red. Also the dimmer compound **26** was produced when we try to react α,β-unsaturated compounds **24a,b** with hydrazines to synthesize pyrazolo compound **27** (Scheme 5).

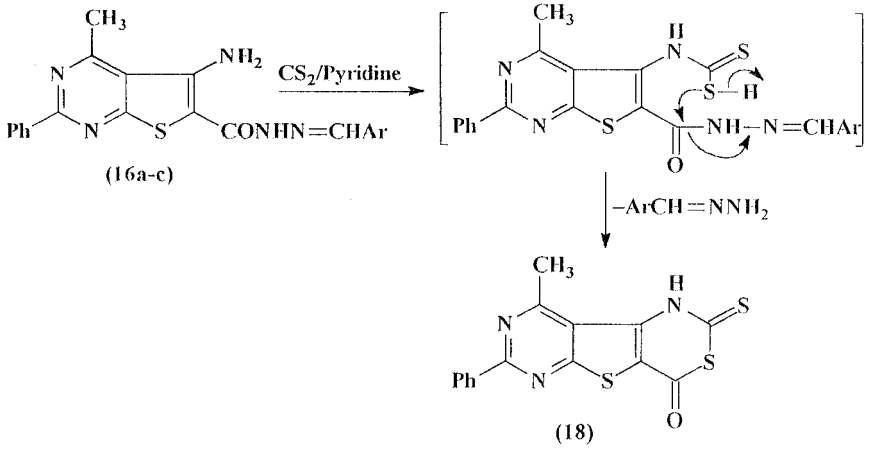
EXPERIMENTAL

Melting point are uncorrected and were measured on a Fisher-John apparatus. IR spectra were recorded on a Shimaduz 470 IR



spectrophotometer using KBr discs, ^{1}H-NMR spectra in a Varian EM 390 90 MHz NMR spectrometer using TMS as internal reference and MS on Jeol JMS-600 apparatus. Elemental analysis were determined on a Perkin-Elmer 240 C elemantel analyzer and the results were in an acceptable range. All physical properties and spectral data of the synthesized compounds are listed in Tables I and II.





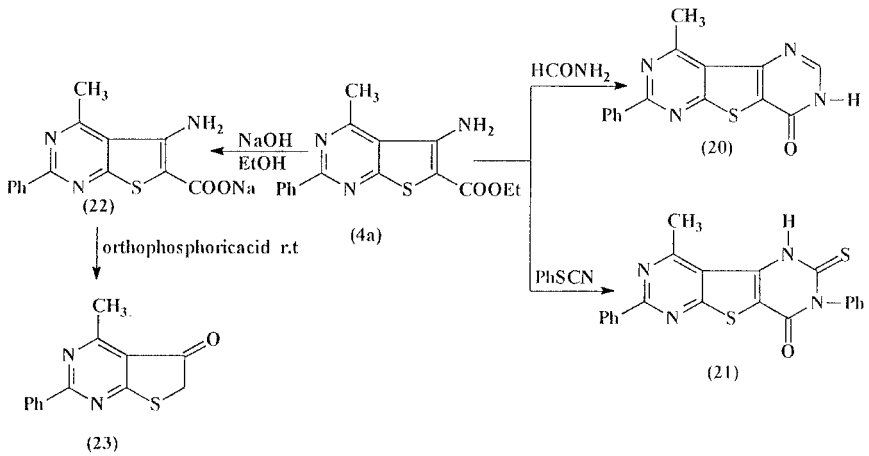
4-Methyl-6-mercapto-2-phenylpyrimidine-5-carbonitrile (1)

The above compound was prepared according to literature procedure.[6]

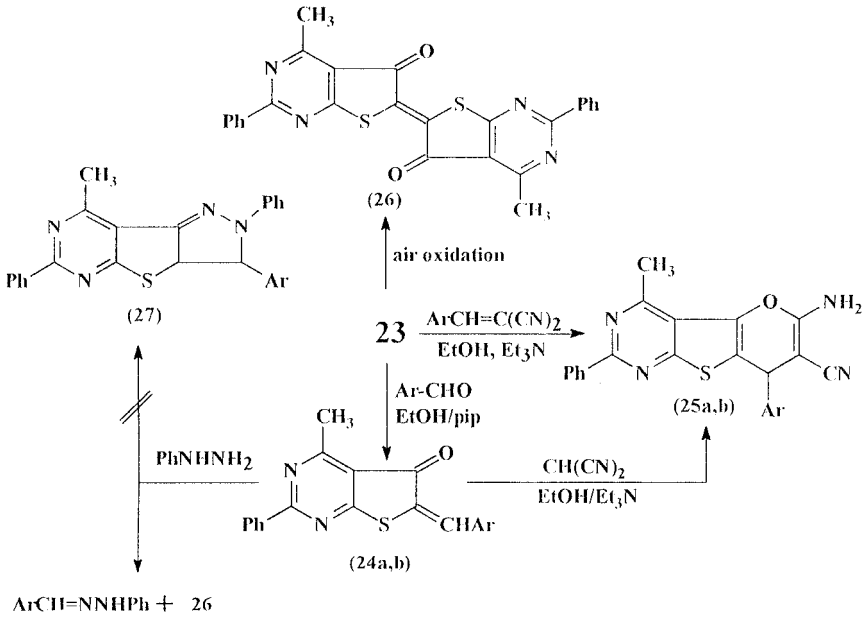
4-Methyl-6-substituted Mercapto-2-phenylpyrimidine-5-carbonitrile (2a–e)

General Procedure

To a suspension of **1** (0.01 mmol) and sodium acetate (0.02 mmol) in ethanol (100 ml), the respective halo-compound (0.01 mmol) was added. The resulting mixture were refluxed for 3 h and then allowed to cool.



SCHEME 4



SCHEME 5

The precipitated product was collected by filtration, washed with water, and recrystallized from ethanol to give **2a–e** in the form of white fine needles.

5-Amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carbonitrile (3)

A mixture of **1** (0.01 mmol) and chloroacetonitrile (0.01 mmol) in ethanol (50 ml) containing sodium acetate (0.02 mmol) was refluxed for 1 h. The solid product was formed during refluex was filtered off and recrystallized from dioxane as yellow crystalls.

Cyclization of Compounds (2a–e); Synthesis of Compounds (4a–e)

General Procedure: and Method A

A suspension of (**2a–e**) (0.05 mmol) in absolute ethanol (50 ml) containing sodium (250 mg) was heated under reflux for 1 h. The products was collected by filtration, washed thoroughly with water, and recrystallized from ethanol to give **4a–e** as yellow crystals.

TABLE I Physical Properties and Analytical Data of Compounds **2–23**

Comp. no.	m.p.°C	Yield %	Formula mol. wt	Calculated/Found C	H	N	S
2a	124–126	83	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41	10.23
			313.38	61.06	4.53	13.11	10.03
2b	160	85	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83	11.32
			283.35	63.43	4.25	14.69	11.19
2c	242–245	81	$C_{20}H_{16}N_4SO$	66.65	4.47	15.54	8.90
			360.34	66.47	4.52	15.82	9.12
2d[a]	270	82	$C_{20}H_{15}ClN_4OS$	60.83	3.83	14.19	8.12
			394.88	60.55	3.77	14.02	7.89
2e	253–255	81	$C_{21}H_{18}N_4O_2S$	64.60	4.65	14.35	8.21
			390.46	64.34	4.55	14.07	8.32
3	260	70	$C_{14}H_{10}N_4S$	63.14	3.78	21.04	12.04
			266.32	63.38	3.49	19.78	11.86
4a	164–165	(76)	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41	10.23
			313.38	61.56	5.06	13.68	10.46
4b	202	(77)	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83	11.32
			283.35	63.73	4.38	15.06	11.53
4c	240	(73)	$C_{20}H_{16}N_4SO$	66.65	4.47	15.54	8.90
			360.34	66.38	4.66	15.28	8.62
4d[a]	250	(76)	$C_{20}H_{15}ClN_4OS$	60.83	3.83	14.19	8.12
			394.88	60.59	3.56	13.93	7.86
4e	230	(74)	$C_{21}H_{18}N_4O_2S$	64.60	4.65	14.35	8.21
			390.46	64.35	4.52	14.19	8.11
5	235	(86)	$C_{14}H_{13}N_5OS$	56.17	4.38	23.40	10.71
			299.35	56.46	4.21	23.16	10.52
6	>360	(64)	$C_{15}H_{11}N_5OS_2$	52.77	3.25	20.51	18.78
			341.41	52.52	3.43	20.78	19.05
8	298	78	$C_{19}H_{13}N_5OS_2$	58.29	3.35	17.89	16.83
			391.47	58.42	3.18	18.08	17.12
11	210	(60)	$C_{19}H_{17}N_5O_3S_2$	53.38	4.01	16.38	15.00
			427.50	52.12	4.24	16.41	15.22
12	170	(82)	$C_{14}H_{10}N_6OS$	54.18	3.25	27.08	10.33
			310.34	54.00	3.09	27.36	10.02
13	>360	(76)	$C_{14}H_{10}N_4OS$	59.56	3.57	19.85	11.36
			282.32	59.75	3.77	19.63	11.04
14	258–261	(65)	$C_{19}H_{17}N_5OS$	62.79	4.71	19.27	8.82
			363.12	63.69	4.54	19.42	8.99
15	290	(78)	$C_{16}H_{11}N_5O_2S$	56.96	3.29	20.76	9.51
			337.36	56.78	3.08	20.56	9.34
16	330	(77)	$C_{18}H_{15}N_5O_2S$	59.16	4.14	19.17	8.78
			365.41	59.17	4.26	19.02	8.52
17a	290	(88)	$C_{21}H_{17}N_5OS$	65.10	4.42	18.08	8.28
			387.12	64.86	4.13	17.84	8.03
17b	297–300	(86)	$C_{22}H_{19}N_5O_2S$	63.29	4.59	16.78	7.68
			417.48	63.56	4.24	16.55	7.44
17c[b]	296	(85)	$C_{21}H_{16}ClN_5OS$	59.78	3.82	16.60	7.60
			421.5	59.52	4.57	16.42	7.33

(Continued on next page)

TABLE I Physical Properties and Analytical Data of Compounds **2–23** *(Continued)*

Comp. no.	m.p.°C	Yield %	Formula mol. wt	Calculated/Found C	H	N	S
18	>300	(68)	$C_{15}H_9N_3OS_3$	52.46	2.64	12.23	28.01
			343.45	52.22	3.47	18.23	27.79
20	260	(62)	$C_{15}H_{10}N_4OS$	61.21	3.42	19.04	10.89
			294.06	61.44	3.19	18.84	10.73
21	280	(50)	$C_{21}H_{14}N_4OS_2$	62.67	3.51	13.92	15.93
			402.49	62.40	3.76	14.08	16.18
23	157–160	(63)	$C_{13}H_{10}N_2OS$	64.44	4.16	11.56	13.23
			242.05	64.17	4.00	11.70	13.03
24a	223	(73)	$C_{20}H_{14}N_2OS$	72.70	4.27	8.48	9.71
			330.40	72.48	4.00	7.72	9.42
24b	216	(77)	$C_{21}H_{16}N_2O_2S$	69.98	4.47	7.77	8.88
			360.43	69.77	4.32	7.52	8.81
25a	291	(71)	$C_{23}H_{16}N_4OS$	69.68	4.07	14.13	8.09
			396.47	69.44	3.89	13.85	7.87
25b	279	(83)	$C_{24}H_{18}N_4O_2S$	67.59	4.25	13.14	7.52
			426.49	67.34	3.98	13.42	7.27
26	300	(65)	$C_{26}H_{16}N_4O_2S_2$	64.98	3.36	11.66	13.35
			480.07	64.81	3.05	12.83	13.09

[a]Cl (Cal. 8.99, Found 8.72).
[b]Cl (Cal. 8.40, Found 8.12).

Method B

A mixture of **1** (0.005 mmol) and the respective halo-compound in absalute ethanol (50 ml) containing sodium (0.5 g) was refluxed for 1 h. The solid was collected by filtration, washed with water, and recrystallized from ethanol to give (**4a–e**). The products were identical with those reported in method A.

5-Amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carbohydrazid (5)

A mixture of compound **4a** (0.01 mmol) and hydrazine hydrate (3 ml) was refluxed in ethanol (20 ml) for 4 h. The solid product which formed in hot was filtered off and recrystallized from dioxane as pale yellow crystals.

5-Amino-6[4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-3-yl]-4-methyl-2-phenylthieno[2,3-d]pyrimidine (6)

A sample of compound **5** (0.5 g) and carbondisulfide (2 ml) in pyridine (20 ml) was refluxed for 4 h in a steam bath. The solid was collected and recrystallized from dioxane as yellow crystals.

TABLE II Spectroscopic Data of Compounds **2–26**

Compd. no.	IR (υ cm^{-1})/^{1}H-NMR δ (ppm)
2a	IR: $\nu = 2950$ cm^{-1} (CH-aliphatic), 2200 cm^{-1} (C≡N) and 1720 cm^{-1} (C=O); ^{1}HNMR ($CDCl_3$): $\delta = 1.3$ (t, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 4.5 (q, 2H, SCH_2), 7.7–8.5 (m, 5H, Ar-H)
2b	IR: $\nu = 2910$ cm^{-1} (CH-aliphatic), 2210 cm^{-1} (C≡N) and 1715 cm^{-1} (C=O); ^{1}HNMR ($CDCl_3$): $\delta = 2.4$ (s, 3H, CH_3), 3.2 (s, 3H, OCH_3) 3.5 (s, 2H, CH_2), 7.8–8.5 (m, 5H, Ar-H)
2c	IR: $\nu = 3250$ cm^{-1} (NH), 2200 cm^{-1} (C≡N) and 1650 cm^{-1} (C=O): ^{1}HNMR (DMSO-d_6): $\delta = 2.6$ (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.3–7.7 (m, 9H, Ar-H), 8.6 (s, 1H, NH)
2d	IR: $\nu = 3240$ cm^{-1} (NH), 2205 cm^{-1} (C≡N) and 1660 cm^{-1} (C=O); ^{1}HNMR ($CDCl_3$): $\delta = 2.7$ (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.5–8.3 (m, 9H, Ar-H) and 8.8 (s, 1H, NH)
2e	IR: $\nu = 3245$ cm^{-1} (NH), 2210 cm^{-1} (C≡N) and 1655 cm^{-1} (C=O)
3	IR: $\nu = 3320$–3220 cm^{-1} (NH_2), 2200 cm^{-1} (C≡N) and 1590 cm^{-1} (C=N); ^{1}HNMR (CF_3CO_2D): $\delta = 3.2$ (s, 3H, CH_3), 4.5 (s, 2H, NH_2) and 7.7–8.4 (m, 5H, Ar-H)
4a	IR: $\nu = 3450$, 3350 cm^{-1}(NH_2), 3050 cm^{-1} (CH-aliphatic), 1660 cm^{-1} (C=O) and 1590 cm^{-1} (C=N); ^{1}HNMR (DMSO-d_6): $\delta = 1.1$–1.4 (t, 3H, CH_3 ethyl), 2.9 (s, 3H, $-CH_3$), 4.1–4.3 (q, 2H, CH_2), δ 6.9 (s, 2H, NH_2), and 7.3–8.3 (m, 5H, Ar-H)
4b	IR: $\nu = 3400$, 3300 cm^{-1} (NH_2), 1650 cm^{-1} (C=O) and 1600 cm^{-1} (C≡N). ^{1}HNMR (DMSO-d_6): $\delta = 2.4$ (s, 3H, $-CH_3$ pyrimidine), 3 (s, 3H, —C=O—CH_3), 7.8 (s, 2H, NH_2), and 7.7–8.7 (m, 5H, Ar-H)
4c	IR: $\nu = 3480$ cm^{-1} (NH), 3400–3350 cm^{-1} (NH_2), 1630 cm^{-1} (C=O), 1590 cm^{-1} (C=N). m/e = 359.76
4d	IR: $\nu = 3475$ cm^{-1} (NH), 3400, 3300 cm^{-1} (NH_2), 1640 cm^{-1} (C=O), 1590 cm^{-1} (C=N)
4e	IR: $\nu = 3450$ cm^{-1} (NH), 3400, 3300 cm^{-1} (NH_2) and 1630 cm^{-1} (C=O). ^{1}HNMR ($CDCl_3$): $\delta = 3$ (s, 3H, CH_3 pyrimidine), 3.8 (s, 3H, OCH_3), 6.5 (s, 2H, NH_2), 6.9–7.4 (m, 9H, Ar-H), 8.5 (s, 1H, NH)
5	IR: $\nu = 3400$, 3300, 3200 cm^{-1} (NH, NH_2), 1640 cm^{-1} (C=O—) and 1590 cm^{-1} (C=N); ^{1}HNMR (DMSO-d_6): $\delta = 3.2$ (s, 3H, CH_3), 4.6 (s, 2H, NH_2), 7.2 (s, 2H, NH_2), 7.6–8.7 (m, 5H, Ar-H), and 9.5 (s, 1H, NH)
6	IR: $\nu = 3400$, 3300 cm^{-1} (NH_2), 2900 cm^{-1} (SH), 1620 cm^{-1} (C=N)
8	IR: $\nu = 3300$ cm^{-1} (NH), 1600 cm^{-1} (C=N). ^{1}HNMR ($CDCl_3$): $\delta = 2.7$ (s, 3H, CH_3 pyrimidine), 6.6 (m, 2H, pyrrolyl-H), 6.8 (m, 2H, pyrrolyl-H), 8.0–8.3 (m, 9H, Ar-H), 13.0 (s, 1H, NH)
11	IR: $\nu = 3450$, 3350 cm^{-1} (NH_2), 2950 cm^{-1} (CH aliphatic) and 1610 cm^{-1} (C=N). ^{1}HNMR ($CDCl_3$): $\delta = 1.2$–1.3 (t, 3H, CH_3), 2.9 (s, 3H, CH_3), 4.1 (q, 2H, CH_2), 4.6 (s, 2H, SCH_2), 6.1 (s, 2H, NH_2), 7.5–8.5 (m, 5H, Ar-H)
12	IR: $\nu = 3500$, 3400 cm^{-1} (NH_2), 2125 cm^{-1} (N_3), 1650 cm^{-1} (C=O) and 1590 cm^{-1} (C=N)
13	IR: $\nu = 3200$ cm^{-1} (NH), 1680 cm^{-1} (C=O) and 1590 cm^{-1} (C=N). ^{1}HNMR (DMSO-d_6): $\delta = 2.7$ (s, 3H, CH_3), 7.5–8.4 (m, 5H, Ar-H), 11.3 (s, 2H, 2NH)

(Continued on next page)

TABLE II Spectroscopic Data of Compounds **2–26** *(Continued)*

Compd. no.	IR (υ cm^{-1})/^{1}H-NMR δ (ppm)
14	IR: ν = 3450, 3350 cm^{-1} (NH_2), 1680 cm^{-1} (C═O) and 1620 cm^{-1} (C═N). ^{1}HNMR ($CDCl_3$): δ = 2.1, 2.3 (2s, 6H, $2CH_3$), 2.6 (s, 3H, CH_3), 5.8 (s, 2H, NH_2) and 7.24–7.26 (m, 6H, Ar-H, CH pyrazoline)
15	IR: ν = 3450 cm^{-1} (NH), 1710 cm^{-1}, 1670 cm^{-1} (2 C═O) and 1590 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.4 (s, 3H, CH_3), 7.5–8.4 (m, 5H, Ar-H), 8.5 (s, 1H, CH-pyrimidine), 8.6–8.7 (d, 1H, CHO), 8.8 (d, 1H, NH)
16	IR: ν = 3250 cm^{-1} (NH), 1710, 1670 cm^{-1} (2 C═O) and 1590 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 7.49–7.54, 8.4–8.42 (2m, 5H, Ar-H), 11.34 (s, 1H, NH)
17a	IR: ν = 3480, 3370, 3300 cm^{-1} (NH, NH_2), 1640 cm^{-1} (C═O) and 1595 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.9 (s, 3H, CH_3), 7.4 (s, 2H, NH_2), 7.9–8.6 (m, 6H, 5 Ar-H, N═CH), 11.7 (s, 1H, NH)
17b	IR: ν = 3500, 3400, 3300 cm^{-1} (NH, NH_2), 1645 cm^{-1} (C═O) and 1595 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.9 (s, 3H, CH_3), 3.8 (s, 3H, CH_3), 7.07–7.72 (2d, 4H, Ar-H), 7.5–8.4 (m, 5H, Ar-H), 7.6 (s, 2H, NH_2) and 8 (s, 1H, CH═N)
17c	IR: ν = 3500–3300 (NH, NH_2), 1640 (C═O), 1590 (C═N)
18	IR: ν = 3310 cm^{-1} (NH), 1680 cm^{-1} (C═O) and 1600 (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.7 (s, 3H, CH_3), 7.3–8.3 (m, 5H, Ar-H), 9.5 (s, 1H, NH)
20	IR: ν = 3350 cm^{-1} (NH) and 1660 cm^{-1} (C═O). ^{1}HNMR (CF_3CO_2D): δ = 2.7 (s, 3H, CH_3), 7.7–8.0, 8.3–8.5 (2m, 5H, Ar-H) and 8.8 (s, 1H, N═CH)
21	IR: ν = 3400 (NH), 1680 (C═O), 1600 (C═N). ^{1}HNMR (CF_3CO_2D) δ = 3.3 (s, 3H, CH_3) and 7.5–8.6 (m, 10 H aromatic)
23	IR: ν = 1680 cm^{-1} (C═O) and 1600 cm^{-1} (C═N) ($CDCl_3$) δ 2.8 (s, 3H, CH_3), δ 3.8 (s, 2H, CH_2), δ 7.3–8.5 (2m, 5H, aromatic)
24a	1665 cm^{-1} (C═O) and 1600 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.8 (s, 3H, CH_3), 7.5–7.7 (m, 5H, aromatic), 7.81–8.0 (2d, 4H, Ar-H) and 8.2 (s, 1H, CH)
24b	IR: ν = 1660 cm^{-1} (C═O) and 1590 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.9 (s, 3H, CH_3), 3.5 (s, 3H, OCH_3), 7.5–7.6 (m, 5H, Ar-H), 7.81, 7.83, 8.48, 850 (2d, 4H, Ar-H) and 8 (s, 1H, ─CH)
25a	IR: ν = 3400, 3300 cm^{-1} (NH_2), 2200 cm^{-1} (C≡N) and 1600 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6) δ = 2.9 (S, 3H, CH_3), 5.1 (s, 1H, CH pyrane), 6.9 (s, 2H, NH_2), δ 7.2–7.7 and 8.0–8.5 (2m, 9H, Ar-H)
25b	IR: ν = 3400, 3300 cm^{-1} (NH_2), 2200 cm^{-1} (C≡N) and 1590 cm^{-1} (C═N). ^{1}HNMR (DMSO-d_6): δ = 2.9 (s, 3H, CH_3), 3.4 (s, 3H, ─OCH_3), 4.9 (s, 1H, CH pyrane), 6.8 (s, 2H, NH_2), and 7.0–7.6, 8.3–8.5 (2m, 10H, Ar-H)
26	IR: ν = 1680 cm^{-1} (C═O), 1600 cm^{-1} (C═N). ^{1}HNMR (CF_3CO_2D): δ = 2.35 (s, 6H, $2CH_3$) and 7.3–7.5, (m, 10H, Ar-H). m/e = 479.78

6-[4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-3-yl]-4-methyl-2-phenyl-5-[1-pyrrolyl]-thieno[2,3-d]pyrimidine (8)

A mixture of compound **5** (0.01 mmol) and dimethoxytetrahydrofuran (0.01 mmol) in acetic acid (20 ml) was refluxed for 1 h, allowed to cool,

and poured into cold water (100 ml). The solid product was collected, washed several times with water, and recrystallized from ethanol as white crystals.

Ethyl 4-Methyl-2-phenyl-5-[pyrrol-1-yl]thieno[2,3-d]-pyrimidine-6-carboxylate (9)

Title compound was prepared according to literature procedure, m.p. 176°C; Lit.[7] m.p. 175–176°C.

4-Methyl-2-pheny-5-[pyrrol-1-yl]thieno[2,3-d]pyrimidine-6-carbohydrazid (10)

Title compound was prepared according to literature procedure, m.p. 221°C; Lit.[7] m.p. 220–221°C.

5-Amino-6[2-ethoxycarbonylmethylmercaptooxadiazol-5-yl]-4-methyl-2-phenylthieno-[2,3-d] pyrimidine (11)

A mixture of compound **6** (0.01 mmol), ethylchloroacetate (0.01 mmol) and sodium acetate (0.012 mmol) in ethanol (30 ml) was heated under reflux for 3 h, and allowed to cool to room temperature. The solid product was collected by filtration, washed well with water, and recrystallized from ethanol as yellow crystals.

5-Amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carboazide (12)

To a cooled solution of compound **5** (0.01 mmol) in glacial acetic acid (20 ml), sodium nitrite solution (0.69 g in 5 ml H_2O) was added dropwise with stirring. The stirring was continued for additional 2 h, then the reaction mixture was allowed to stand 5 h. The solid product separated was filtered off, washed severel times with water, and air dried to give pale yellow crystals. This compound was subjected to the next step without further purefication.

4-Methyl-2-phenylimidazo[4′,5′:4,5]thieno[2,3-d]-pyrimidine-(6H,7H)-one (13)

A sample of compound **10** (0.5 g) in dry xylene (10 ml) was heated under reflux for 3 h, then allowed to cool to the room temperature. The solid product was collected and recrystallized from dioxane into pale brown crystals.

5-Amino-6[carbonyl-3′,5′-dimethylpyrazol]-4-methyl-2-phenylthieno-[2,3-d]pyrimidine (14)

A mixture of hydrazide **5** (0.01 mmol) and acetyl acetone (0.012 mmol) in ethanol (40 ml) was refluxed for 3 h, then allowed to cool. The solid product was collected and recrystallized from ethanol as yellow needles.

7-N-Formylamino-4-methyl-2-phenylpyrimido-[4′,5′:4,5]thieno[2,3-d]-pyrimidine 8 (7H) one (15)

A sample of compound **5** (0.5 g) in formaic acid (5 ml) was refluxed for 5 h, then allowed to cool to the room temperature. The solid product was collected and recrystallized from dioxane as pale yellow crystals.

7-N-Acetylamino-4,6-dimethyl-2-phenylpyrimido-[4′,5′:4,5]thieno-[2,3-d]pyrimidine-8(7H) one (16)

A sample of compound **5** (0.5 g) was refluxed in acetic anhydride (10 ml) for 2 h, then allowed to cool and poured into cold water. The solid product was collected and recrystallized from dioxane as pale yellow crystals.

6-Aryledine carbohydrazone-5-amino-4-methyl-2-phenylthieno[2,3-d]-pyrimidine (17a–c)

General Procedure

A mixture of thienopyrimidine carbohydrazide **5** (0.01 mmol) and appropriate aromatic aldehyde (0.01 mmol) in ethanol (30 ml) was refluxed for 4 h, then allowed to cool to the room temperature. The solid product was collected and recrystallized from dioxane.

9-Methyl-7-phenyl-1,2,4-trihydro-4-oxo-2-thioxopyrimido[4′,5′:4,5][1,3]thiazine (18)

A mixture of each 6-aryledinecarbohydrazone derivatives (**17a–c**) (2 g) and carbondisulfide (2 ml) in pyridine (20 ml) was heated on water bath for 50 h, then allowed to cool to room temperature. The solid product was collected and recrystallized from dioxane as yellow crystals.

4-Methyl-2-phenylpyrimido[4′,5′:4,5]thieno[2,3-d]-pyrimidine 8(7H)-one (20)

A sample of compound **4a** (1 g) in formamide (10 ml) was refluxed for 3 h. The solid product which separated from the hot mixture was filtered off and recrystallized from dioxane as pale green crystals.

2,7-Diphenyl-5,6,7,8-tetrahydro-8-oxo-4-methylpyrimido[4′,5′:4,5]-thieno[2,3-d]-pyrimidine-6-thion (21)

A mixture of compound **4a** (0.01 mmol) and phenylisothiocyanate (0.01 mmol) in 30 ml pyridine was refluxed for 10 h, then allowed to cool to room temperature. The solid product was collected by filtration and recrystallized from D.M.F as yellow crystals.

4-Methyl-2-phenylthieno[2,3-d]pyrimidine-5-one (23)

A mixture of compound (**22**) (0.01 mmol) and o-phosphoric acid (10 ml) was stirred at room temperature for 3 h, then cooled and neutralized by ammonium hydroxide the white precipitate was filtered off as white crystalls. This compound used without crystallization.

4-Methyl-3-phenyl-6-aryledinethieno[2,3-d]pyrimidine-5-one (24a,b)

General Procedure

A mixture of **23** (0.01 mmol) and the respective aromatic aldehyde (0.01 mmol) in ethanol (50 ml) containing catalytic amount of piperidine was refluxed for 3 h. The solid product, which formed after cooling, was filtered off and recrystallized from ethanol as yellow crystalls.

6-Amino-8-aryl-7-cyano-4-methyl-2-phenylpyrano-[2′,3′:4,5]thieno[2,3-d]pyrimidine (25a,b)

Method A

A mixture of compound (**24a,b**) (0.01 mmol) and malononitrile (0.01 mmol) in ethanol (50 ml) containing triethylamine was refluxed for 4 h. The precipitated thus formed during reflux was collected by filteration and crystallized from dioxane as yellow crystalls.

Method B

A mixture of **23** (0.01 mmol) and aryledinemalononitrile (0.01 mmol) in ethanol (50 ml) containing triethylamine was refluxed for 5 h. The preciptated thus formed during refluex was collected by filtration, washed well with ethanol, and crystallized from dioxane as yellow crystalls. The products were identical with those reported in method A.

4,4′-Dimethyl-2,2′-diphenyl[2,2′]bi[thieno[2,3-d] pyrimidinylidene-3,3′-dione (26)

Method A

A sample of compound **23** (0.5 gm) was heated in ethanol (20 ml) until dissolved, then allowed to exposed to atmospheric air for 2 days. The solution was turned into red and the solid product was collected and identified as a dimmer **26** in 65% yield

Method B

A mixture of compound **24a** or **24b** (0.01 mmol) and phenyl hydrazine (0.01 mmol) in ethanol (20 ml) was heated under reflux for 3 h. The red solid crystals which was separated on hot was identified as a dimmer **26** in 55% yield. The mother liquer was evaporated and the residue was identified as arylidene phenylhydrazone.

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