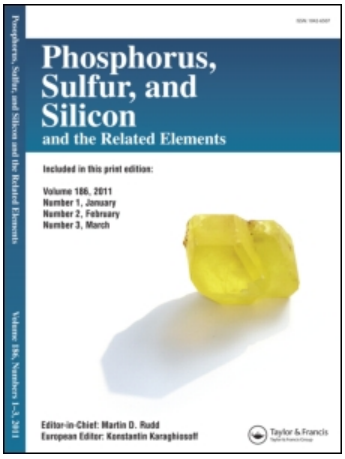

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The Synthesis of Some New Derivatives Derived from 1,2,3,4-Tetrahydrocyclohepteno[4,5]thieno-[2,3-d]pyrimidine

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The Synthesis of Some New Derivatives Derived from 1,2,3,4-Tetrahydrocyclohepteno[4,5]thieno-[2,3-*d*]pyrimidine

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*Polynuclear thieno[2,3-d]pyrimidone derivatives had been synthesized by an intermolecular reaction of 2-hydrazino-thieno[2,3-d]pyrimidin-4-one (**1**) with each of the aliphatic acids, and carbon disulfide afforded thienotriazolepyrimidin-5-one derivatives. On the other hand, compound **1** that condensed with α-haloketone yielded thienopyrimidotriazine, and with β-diketones and β-ketoesters formed 2-(1-pyrazolyl) derivatives. Also, the condensation of compound **1** with aromatic aldehydes gave arylhydrazones. The purpose of synthesis the thienopyrimidine derivatives is due to high biological activities. 4-chloro derivatives exhibited spasmodic and antiviral activity, and also 4-amino derivatives showed antimicrobial, insecticidal, pesticidal, and acaricidal activity.*

Keywords ^{1}H NMR spectra; azolopyrimidine; mass spectra; thienopyrimidine

DISCUSSION

Pyrimidines, being an integral part of nucleic acids and many chemotherapeutic agents, display a wide range of pharmacological activities as a phosphodiesterase inhibitor,[1] fungicide,[2] viricide,[3] bactericide,[4] and leishmanicide.[5] This aroused considerable interest to design and synthesize pyrimidines compounds profound leishmanicidal activity. Sulfur-containing derivatives are important in the pyrimidine chemistry because their different reactions make them convenient intermediates.[6,7] Among these reactions, the alkylation of mercaptopyrimidines is a very useful synthetic procedure for the pyrimidine ring functionalization.[8] 2-hydrazinopyrimidine **1** can be synthesized by the nucleophilic displacement of the alkylthio

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group with hydrazine hydrate.[9,10] Therefore, 2-hydrazinothieno[2,3-d]pyrimidine **1** is a good source to synthesize several new azolothienopyrimidines, thienopyrimido-as-triazines, and pyrazolyl-thienopyrim-idines derivatives. Thus, heating under reflux 2-hydrazino **1** with formic acid yielded 1H-cyclohepteno[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(5H)-one (**2**).

Beside the correct values in elemental analyses, the IR, ^{1}H NMR, and mass spectra of **2** are in agreement with the assigned structure, experimental (See Experimental Section).

Surprisingly, heating under reflux compound **1** with acetic acid yielded the 2-acethydrazido derivative **3**. The IR spectrum of **3** displayed absorption bands at 3277 cm^{-1}, 3115 cm^{-1} 2(NH) and 1680 and 1650 cm^{-1} 2 (CO).

Compound **1** reacted with carbon disulphide in ethanolic potassium hydroxide solution and afforded 3(3H)-thioxo-1,2-dihydrocyclohepteno[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(5H)-one (**4**).

The IR spectrum of **4** displayed absorption bands at 3404 cm^{-1}, 3122 cm^{-1} 2(NH), and 1664 cm^{-1} (CO). Its ^{1}H NMR spectrum (DMSO-d_6) showed signals at δ 1.65 ppm (m, 4H, 2CH_2), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 12.65 (brs, 1H, NH, D_2O exchangeable), and 13.85 (brs, 1H, NH, D_2O exchangeable). Mass spectra of **4** showed the molecular ion peak at m/z 292.

It is reported in the literature that the cyclization of 2-hydrazino derivatives with formic acid and carbon disulphide takes place at the N-3 nitrogen atom[11] to give azolo[4,3-a]-pyrimidines.

Also, 2-hydrazino derivative **1** was used for the preparation of the thieno-pyrimidotriazine derivative, **5**. Thus, heating under reflux compound **1** with chloroacetone in dry xylene yielded directly 3-methyl-1H,4H,6H-cycloheptenothieno-[2′,3′:4,5] pyrimido[2,1-c][1,2,4]triazine-6-one (**5**). The previously discussed reaction may proceed via the intermediate (5′ or 5″), as shown in Scheme 1. Also the 2-hydrazino derivative **1** reacted with potassium thiocyanate in boiling acetic acid to give compound **6**. Beside the correct values in elemental analyses, the spectral data of **6** is in agreement with the assigned structure, (c.f. Experimental section).

The 2-hydrazino derivative **1** reacted with β-ketoesters, β-cyanoesters, and β-diketones to form 2-(1-pyrazolyl) derivatives. Thus, heating under reflux compound **1** with ethyl acetoacetate afforded the hydrazone derivative **7**, which was cyclized by heating it in ethanolic sodium hydroxide solution to give **8**. Also, compound 8 can be achieved directly from compound **1** by heating it with ethyl acetoacetate in ethanolic sodium hydroxide solution. The ^{1}H NMR spectrum ($CDCl_3$)

of **7** showed signals at δ 1.25 ppm (t, 3H, CH_3), 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.00 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 3.20 (m, 2H, CH2), 3.25 (s, 2H, CH2), 4.18 (q, 2H, CH_2), 8.45 (brs, 1H, NH, D_2O exchangeable), and 9.55 (brs, 1H, NH, D_2O exchangeable). Its ^{13}C NMR spectrum showed 9 sp^3 and 8 sp^2 carbon atoms, and its IR spectrum displayed absorption bands at 3279, 3206 cm^{-1} 2(NH), 1741, and 1643 cm^{-1} 2(CO). Also, the ^1H NMR spectrum (DMSO-d_6) of **8** showed no signals corresponding to ethyl group protons (see the Experimental section).

Compound **8** behaved typically as an active methylene containing compounds. It coupled with aromatic diazonium salts to afford the corresponding azo derivatives **9a,b**. The IR spectra of **9a** displayed absorption bands around 3450 cm^{-1} (OH), 3180 cm^{-1} (NH) and 1656 cm^{-1} (CO). The ^1H NMR spectrum (DMSO-d_6) of **9**a, as an example, showed signals at δ 1.65 ppm (? m, 4H, $2CH_2$), 1.85 (m, 4H, $2CH_2$), 2.30 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 7.45 (d, 2H, aromatic protons), 7.75 (d, 2H, aromatic protons), 11.55 (brs, 1H, NH, D_2O exchangeable), and 13.00 (brs, 1H, OH, D_2O exchangeable). Its mass spectrum showed the molecular ion at peak m/z 454.

Similarly, 2-hydrazino derivative **1** reacted with ethyl cyanoacetate in ethanolic sodium ethoxide solution to afford 2-(3-amino-5-hydroxy-4H-pyrazol-l-yl) derivative **10**. The IR spectrum of **10** displayed absorption bands at 3340 cm^{-1} (NH_2), 3260 cm^{-1} (NH), and 1674 cm^{-1} (CO). Its ^1H NMR spectrum (DMSO-d_6) showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), (4.50–5.40) (brs, 2H, NH_2, D_2O exchangeable), 7.95 (s, 1H, pyrazole proton), and 8.25 (brs, 1H, NH, D_2O exchangeable).

When equimolar amounts of **1** and pentane-2,4-dione or 3-chloropentane-2,4-dione were heated under ruflux in absolute ethanol, 2-pyrazolyl-thieno[2,3-d]pyrimidinone **11a,b** were obtained in a good yield. The ^1H NMR spectrum (DMSO-d_6) of **11a**, as an example, showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 6.15 (s, 1H, CH), and 11.65 (brs, 1H, NH, D_2O exchangeable). Its IR spectrum displayed absorption bands at 3131 cm^{-1} (NH) and 1685 cm^{-1} (CO). Its mass spectrum showed the molecular ion peak at m/z 314. Surprisingly, heating compound **1** under reflux with 1,1,1-trifluoro-pentan-2,4-dione in absolute ethanol led to the formation of compound **12**. Beside the correct values in elemental analyses, the spectral data of **12** is in agreement with the assigned structure (see Experimental section).

Compound **1** gave arylhydrazone derivatives **13a–c** when it was treated with the appropriate aldehyde in boiling dioxane in the presence of catalytic amounts of piperidine. Compounds **13a–c** gave compatible

spectral and analytical data (see Experimental section). Trials to cyclize **13** under different conditions had failed (Scheme 1).

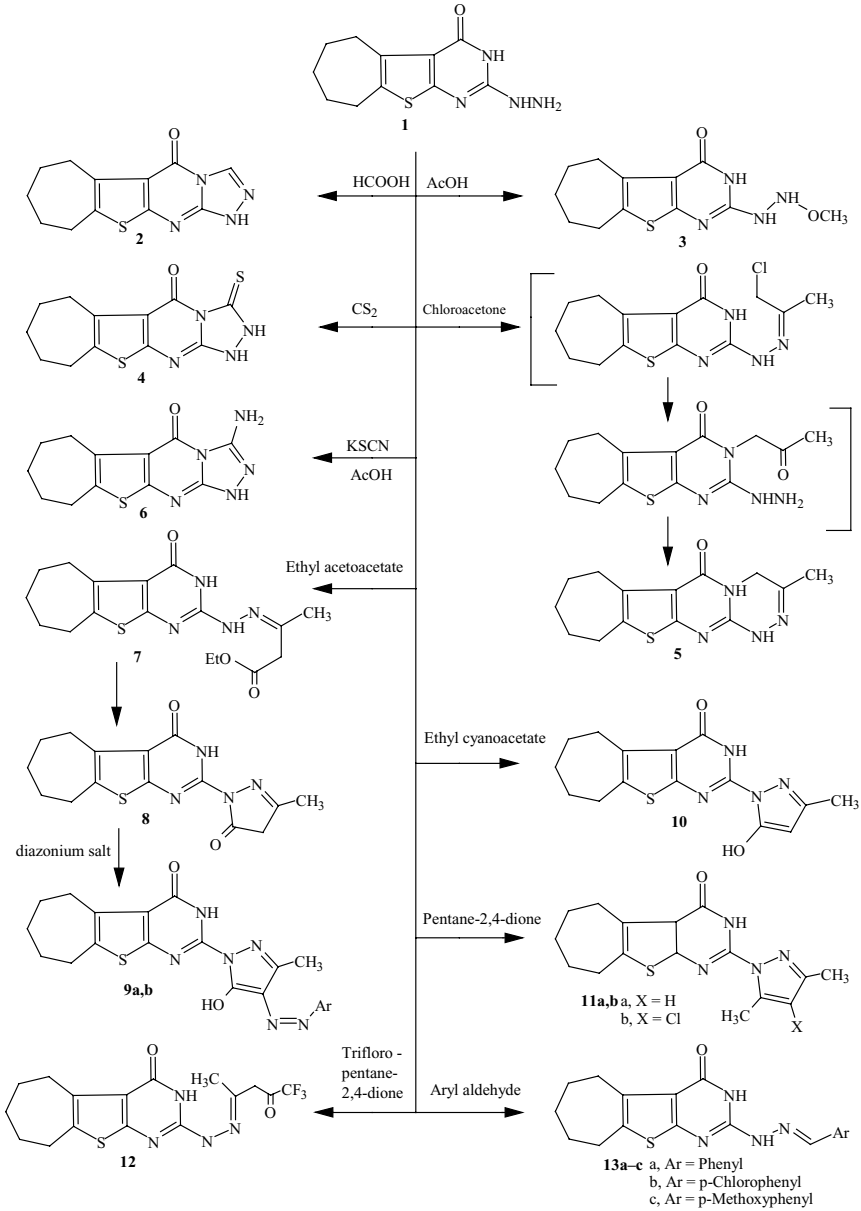
On surveying the literature it is observed that publications dealing with azolo[-,a]pyrimidines out number those of azolo[-,c]pyrimidines. Therefore, we oriented our program to the synthesis of azolo[-,c]thieno[3,2-c]pyrimidines. The reaction of the S-methylthienopyrimidone **14** with phosphorus oxychloride, in dry dioxane, yielded the corresponding 4-chloro derivative **15**. The IR spectrum of **15** revealed the absence of any absorption bands in the carbonyl region. Its ^{1}H NMR spectrum ($CDCl_3$) showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), 1.75 (m, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.86 (m, 2H, CH_2), and 3.20 (m, 2H, CH_2).

It is well known in pyrimidine chemistry that position 4 in pyrimidines and fused pyrimidines shows distinct activity toward nucleophiles. Therefore, the chlorine atom at position 4 in compound **15** is active. Its reactions with some nucleophiles, such as primary aromatic amine, anthranilic acid, and hydrazine hydrate, were investigated. Thus, heating under reflux compound **15** with aniline or *p*-toluidine, in dry dioxane, afforded the 4-arylamine derivatives **16a,b**. The IR spectrum of **16a** displayed an absorption band around 3430 cm^{-1} (NH). The ^{1}H NMR spectrum ($CDCl_3$) of **16a**, as an example, showed signals at δ 1.85 ppm (m, 6H, $3CH_2$), 2.45 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.09 (m, 2H, CH_2), 7.05 (t, 1H and 1H, NH, D_2O exchangeable), 7.25 (t, 2H, aromatic protons), and 7.55 (d, 2H, aromatic protons) (Scheme 2).

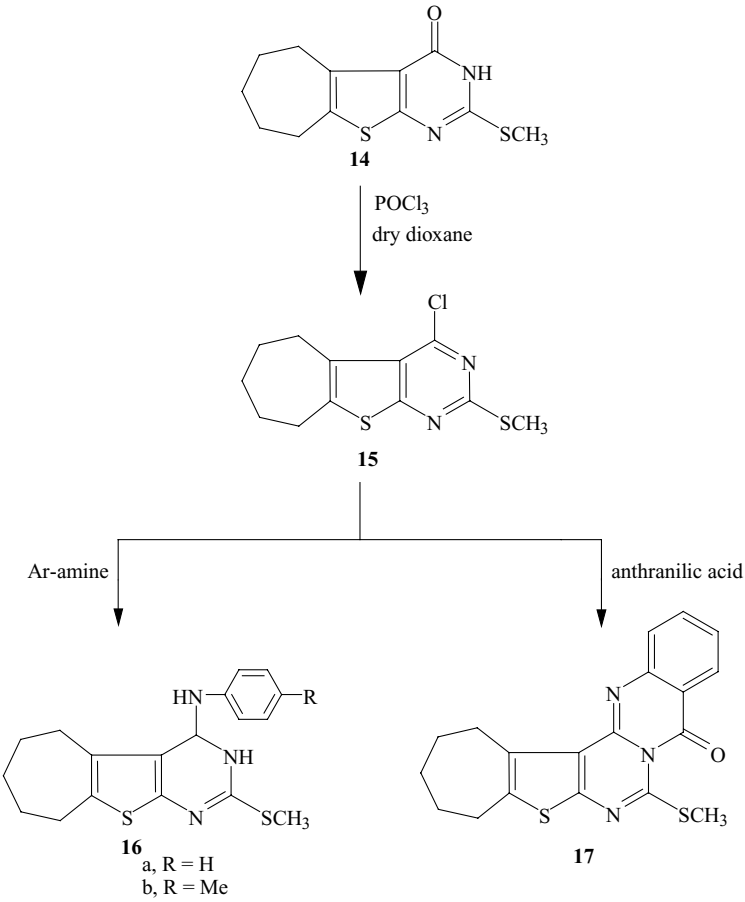
When **15** was fused with anthranilic acid at 180°C, it gave 8-methylthiocyclo-hepteno[4′,5′]thieno[2′,3′:4,5]pyrimido[6,1-b]quinazolin-10-one (**17**). The IR spectrum of **17** revealed the absence of any absorption bands in the (NH) region and displayed an absorption band at 1690 cm^{-1} (CO). Its ^{1}H NMR spectrum ($CDCl_3$) showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.70 (m, 2H, CH_2), 7.45 (t, 1H, aromatic proton), 7.60 (d, 1H, aromatic proton), 7.65 (t, 1H, aromatic proton), and 8.25 (d, 1H, aromatic proton).

The hydrazinepyrimidine **18** can be synthized by the nucleophilic displacement of a labile halogen atom of the corresponding compound **15** by hydrazine hydrate. The IR spectrum of **18** displayed an absorption band at 3283 cm^{-1} (NH). Its ^{1}H NMR spectrum ($CDCl_3$) showed signals at δ 1.70 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.56 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 4.15 (brs, 2H, NH_2, D_2O exchangeable), and 6.57 (s, 1H, NH, D_2O exchangeable).

The 4-hydrazino derivative **18** was used as a starting material for the syntheses of some azolo[-,c]thieno[3,2-e]pyrimidines. Thus, heating under reflux compound **18** with some aliphatic carboxylic acids,



SCHEME 1



SCHEME 2

namely formic acid or acetic acid in the presence of catalytic amounts of hydrochloric acid, yielded 3-alkyl-5-methylthiocyclohepteno-[4,5]thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine **19a,b**. The IR spectra of **19a,b** revealed the absence of any absorption bands in the (NH) region. The ^{1}H NMR spectrum ($CDCl_3$) of compound **19b**, as an example, showed signals at δ 1.75 ppm (m, 4H, $2CH_2$), 2.95 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.15 (s, 3H, CH_3), and 3.50 (m, 2H, CH_2). Its mass spectrum showed the molecular ion peak at m/z 304. Also, compound **18** reacted with carbon disulphide in ethanolic potassium hydroxide solution to afford 5-methylthio-2H-cyclohepteno[4,5]thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimi-dine-3(3H)-thione (**20**). The ^{1}H NMR spectrum ($CDCl_3$) of compound **20** showed

signals at δ 1.65 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.85 (m, 4H, $2CH_2$), and 9.00 (brs, 1H, NH, D_2O exchangeable).

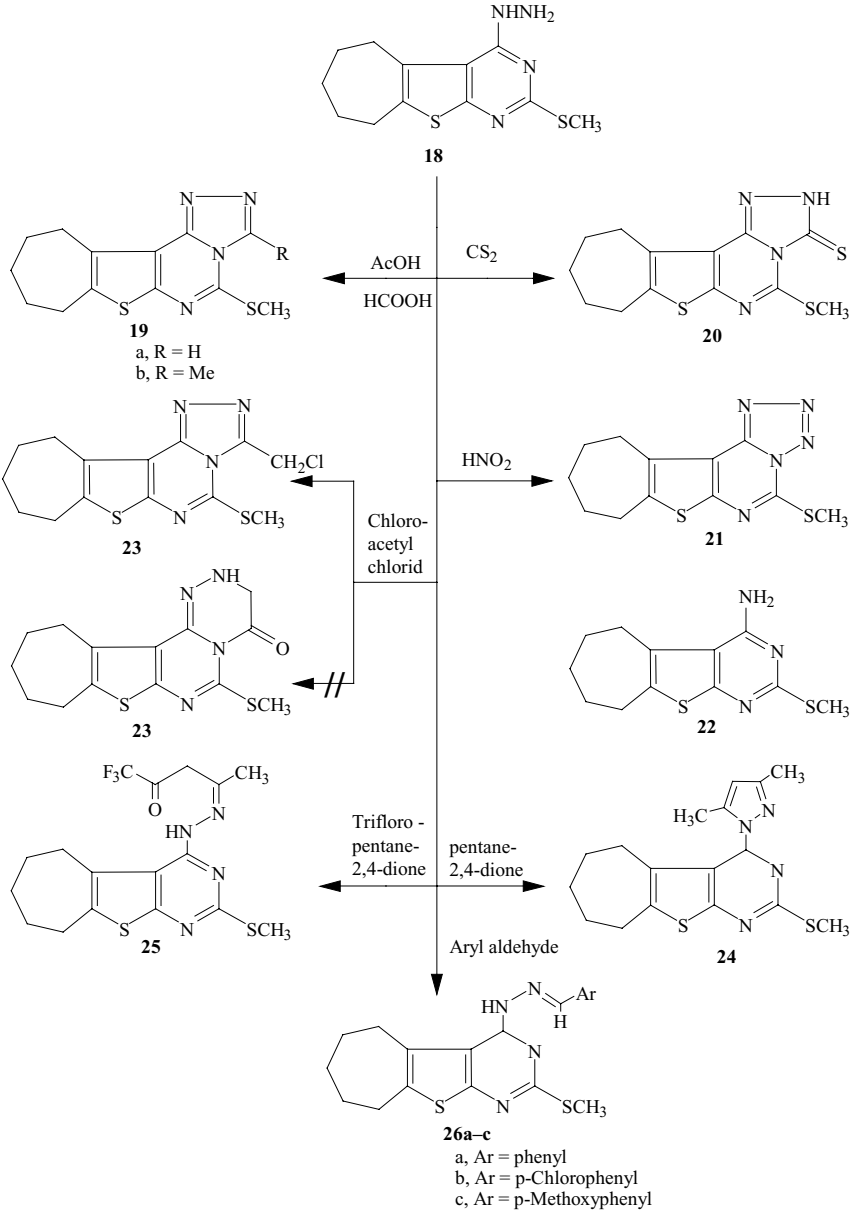
Its mass spectrum showed the molecular ion peak at m/z 322.

The treatment of compound **18** with nitrous acid at 0°C led to the formation of 5-methylthiotetrazolo[1,5-c]cyclohepteno[4,5]thieno[3,2-e]pyrimidine (**21**). The ^{1}H NMR spectrum ($CDCl_3$) of **21** showed signals at δ 1.75 ppm (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.95 (m, 2H, CH_2), and 3.45 (m, 2H, CH_2). The latter compound was reduced into 4-amine-2-methylthiocyclohepteno[4,5]thieno[2,3-d]pyrimidine (**22**) by zinc dust in acetic acid. The ^{1}H NMR spectrum ($CDCl_3$) of compound **22** showed signals at δ 1.75 ppm (m, 4H, $2CH_2$), 1.96 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), and 5.30 (brs, 2H, NH_2, D_2O exchangeable). Its IR spectrum displayed an absorption band at 3494 cm^{-1} (NH_2).

Surprisingly, when heating under reflux compound **18** with chloroacetyl chloride in dry dioxane, it gave compound **23**. The formation of **23** from the reactants may proceed as shown in Scheme 3. The ^{1}H NMR spectrum ($CDCl_3$) of compound **23** showed signals at δ 1.60 ppm (m, 4H, $2CH_2$), 1.75 (? m, 2H, CH_2), 2.59(s, 3H, CH_3), 2.70 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), and 5.15 (s, 2H, CH_2). Its ^{13}C NMR showed 7 SP^3 and 7 SP^2. Its mass spectrum showed the molecular ion peak at m/z 338 (M^+, 100%).

The reaction of 4-hydrazino derivative **18** with pentane-2,4-dione in absolute ethanol led to the formation of 4-(3,5-dimethyl-1H-pyrazol-1-yl)-2-methylthiocyclohepteno[4,5]thieno[2,3-d]pyrimidine (**24**). The ^{1}H NMR spectrum ($CDCl_3$) of **24** showed signals at δ 1.65 ppm (m, 2H, CH_2), 1.70 (m, 2H, CH_2), ?1.80 (m, 2H, CH_2), ?2.15 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), and 6.05 (s, 1H, pyrazolo proton). Its IR spectrum revealed the absence of any absorption bands in the (NH) region. However, compound **18** gave **25** when it was heated with 1,1,1-Trifluoropentan-2,4-dione in absolute ethanol. Beside the correct values in elemental analyses, the spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectra) of **25** are in agreement with the assigned structure (see Experimental section).

Finally, 4-hydrazino derivative **18** gave the corresponding arylhydrazone derivatives **26a–c**, when it was treated with a proper aromatic aldehyde in boiling dioxane in the presence of catalytic amounts of piperidine. The IR spectra of **26a–c** displayed an absorption band around 3320 cm^{-1} (NH). The ^{1}H NMR spectrum ($CDCl_3$) of **26a**, as an example, showed signals at δ 1.70 ppm (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.35 (m, 2H, CH_2), 7.40 (m, 3H, aromatic protons), 7.70 (m, 2H, aromatic protons), and 8.35 (brs, 1H, NH, D_2O exchangeable) (Scheme 3).



SCHEME 3

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were carried out at the Microanalytical units, National Research Center and Faculty of Science, Cairo University. IR spectra were carried out at a FT/IR-300 E Jasco using KBr discs. ^{1}H NMR spectra were measured in DMSO or $CDCl_3$, using a JEOL-JNM-Ex270 NMR spectrometer. Mass spectra were recorded on a Finnigan SSQ 7000 spectrometer. All reactions were followed by TLC.

1H-cyclohepteno[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5 (5H)-one (2)

A mixture of compound **1** (2.50 g, 0.01 mole), formic acid (10 mL), and a catalytic amount of concentrated hydrochloric acid solution was heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t. and poured into water. The solid product so precipitated was filtered off and recrystallized from dioxane to produce **2** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3121 (NH), 2924 (CH aliphatic), and 1689 (CO). ^{1}H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 9.18 (s, 1H, CH), and 14.00 (s, 1H, NH, D_2O exchangeable). MS (m/z): 260.0 (M^+) 100%.

2-(Acethydrazido)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4 (4H)-one (3)

A mixture of compound **1** (2.50 g, 0.01 mole) and glacial acetic acid (30 mL) was refluxed for 5 h. The reaction mixture was allowed to cool to r.t. and poured into water. The precipitate was collected by filtration, dried, and recrystallized from acetic acid to produce **3** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3277 (NH), 3115 (NH), 2985 (CH aliphatic) 1681 (CO) and 1651 (CO). ^{1}H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.75 (m, 2H, CH_2), 1.85 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 8.55 (br s, 1H, NH, D_2O exchangeable), 9.75 (br s, 1H, NH, D_2O exchangeable) and 11.20 (br s, 1H, NH, D_2O exchangeable). MS (m/z): 292.0 (M^+) 100%.

3(3H)-Thioxo-1,2-dihydrocyclohepteno[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(5H)-one (4)

To a warmed ethanolic sodium hydroxide solution [prepared by dissolving sodium hydroxide (0.40 g, 0.01 mole) in ethanol (50 mL)], compound **1** (2.50 g, 0.01 mole) and carbon disulphide (10 mL) was added. The

TABLE I Physical Data for Products 2–26

Compound No.	M.P. °C	Yield (%)	M.F. (M. wt.)	Elemental Analyses Calcd./Found			
				C	H	N	S
2	238–240	67	$C_{12}H_{12}N_4SO$	55.36	4.64	21.52	12.31
	melted		(260.31)	55.56	4.82	21.39	12.30
3	303–305	65	$C_{13}H_{16}N_4SO_2$	53.40	5.51	19.16	—
	melted		(292.35)	54.00	5.00	19.00	
4	?350	60	$C_{12}H_{12}N_4S_2O$	49.29	4.13	19.16	—
	dec		(292.38)	49.00	4.10	19.10	
5	240–242	68	$C_{14}H_{16}N_4SO$	58.31	5.59	19.42	11.11
	melted		(288.37)	38.00	5.50	19.40	11.13
6	294–296	65	$C_{12}H_{13}N_5SO$	52.34	4.75	25.43	—
	melted		(275.33)	52.09	5.00	25.00	
7	164–166	70	$C_{17}H_{22}N_4SO_3$	56.33	6.11	15.45	—
	melted		(362.45)	56.68	5.97	15.64	
8	?310	60	$C_{15}H_{16}N_4SO_2$	56.94	5.09	17.70	10.13
			(316.38)	56.76	5.29	17.00	10.12
9a	270–272	70	$C_{21}H_{19}N_6SO_2Cl$	55.44	4.20	18.47	—
	melted		(454.94)	55.00	4.66	18.00	
9b	280–282	65	$C_{22}H_{22}N_6SO_3$	58.65	4.92	18.65	—
	melted		(450.52)	58.00	4.90	17.99	
10	290–292	63	$C_{14}H_{15}N_5SO_2$	52.98	4.76	22.06	—
	melted		(317.37)	52.60	5.06	21.90	
11a	252–254	70	$C_{16}H_{18}N_4SO$	61.12	5.77	17.81	10.19
	melted		(314.41)	60.90	5.00	17.50	10.17
11b	244–246	70	$C_{16}H_{17}N_4SOCl$	55.08	4.91	16.05	—
	melted		(348.85)	55.80	4.30	16.00	
12	230–232	60	$C_{16}H_{17}N_4SO_2F_3$	49.47	4.43	14.50	—
	melted		(386.36)	49,90	4.80	14.00	
13a	310–312	70	$C_{18}H_{18}N_4SO$	63.88	5.36	16.55	—
	dec		(338.43)	63.96	5.57	16.36	
13b	305–307	75	$C_{18}H_{17}N_4SOCl$	57.98	4.59	15.02	—
	melted		(372.85)	58.20	4.50	15.11	
13c	289–291	78	$C_{19}H_{20}N_4SO_2$	61.93	5.47	15.20	8.70
	melted		(368.45)	61.87	5.32	15.29	8.68
15	90–92	65	$C_{12}H_{13}N_2S_2Cl$	50.60	4.60	9.83	22.51
	melted		(284.83)	50.80	4.40	9.80	22.50
16a	177–179	65	$C_{18}H_{19}N_3S_2$	63.30	5.60	12.30	—
	melted		(341.49)	63.06	5.78	12.22	
16b	168–170	70	$C_{19}H_{21}N_3S_2$	64.18	5.95	11.81	—
	melted		(355.52)	63.90	5.95	11.73	
17	193–195	60	$C_{19}H_{18}N_3S_2O$	62.09	4.66	11.43	—
	melted		(367.49)	61.80	4.83	11.19	
18	168–170	70	$C_{12}H_{16}N_4S_2$	51.40	5.75	19.97	—
	melted		(280.41)	51.60	5.50	19.22	
19a	185–187	65	$C_{13}H_{14}N_4S_2$	53.76	4.85	19.29	—
	melted		(290.40)	53.35	5.00	19.14	

(*Continued*)

TABLE I Physical Data for Products 2–26 (*Continued*)

Compound No.	M.P. °C	Yield(%)	M.F. (M. wt.)	Elemental Analyses Calcd./Found C	H	N	S
19b	151–153	75	$C_{14}H_{16}N_4S_2$	55.23	5.29	18.40	—
	melted		(304.43)	55.50	4.90	18.00	
20	190–192	68	$C_{13}H_{14}N_4S_3$	48.42	4.37	17.37	29.82
	melted		(322.47)	48.00	4.00	17.00	29.80
21	165–167	60	$C_{12}H_{13}N_5S_2$	49.46	4.49	24.03	22.00
	melted		(291.39)	49.94	4.43	24.22	22.00
22	177–179	69	$C_{12}H_{15}N_3S_2$	54.30	5.69	15.83	24.16
	melted		(265.40)	54.33	5.76	15.72	24.15
23	214–216	70	$C_{14}H_{15}N_4S_2Cl$	49.61	4.45	16.52	—
	melted		(338.93)	50.49	4.68	16.71	
24	119–121	65	$C_{17}H_{20}N_4S_2$	59.27	5.85	16.26	—
	melted		(344.50)	59.54	5.71	16.37	
25	124–126	77	$C_{17}H_{19}N_4S_2OF_3$	49.02	4.59	13.45	—
	melted		(416.48)	49.24	4.50	13.47	
26a	145–147	80	$C_{19}H_{20}N_4S_2$	61.92	5.47	15.20	—
	melted		(368.52)	62.70	5.00	15.00	
26b	177–179	75	$C_{19}H_{19}N_4S_2Cl$	56.63	4.75	13.90	—
	melted		(402.96)	56.80	4.35	13.80	
26c	150–152	70	$C_{20}H_{22}N_4S_2O$	60.27	5.56	14.05	—
	melted		(398.55)	60.49	5.70	14.00	

mixture was heated on a water bath at 80°C under reflux for 10 h, it was poured into water and neutralized by diluted acetic acid, and the formed precipitate was filtered off. The product was recrystallized from dioxane to produce **4** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3404 (NH), 3122 (NH), 2929 (CH aliphatic) and 1664 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 12.65 (brs, 1H, NH, D_2O exchangeable) and 13.85 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 292 (M^+) 100%.

3-Methyl-1H-cyclohepteno[4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-c][1,2,4]triazin-(4H)-5(5H)-one (5)

A mixture of compound **1** (2.50 g, 0.01 mole) and chloroacetone (0.93 g, 0.01 mole) was heated under reflux for 6 h in dry xylene (30 mL). The solid product so precipitated was filtered off and recrystallized from dioxane to produce **5** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3373 (NH), 2918 (CH aliphatic) and 1688 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.85 (s, 3H, CH_3), 3.15 (m, 2H, CH_2) and 10.25 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 288(M^+) 64.19%, 273 (M-Me) 17.84%.

3-Amino-1H-cyclohepteno[4,5]thieno[2,3-d][1,2,4]triazolo[4′,3′-a]pyrimidin-5(5H)-one (6)

A mixture of compound **1** (2.50 g, 0.01 mole) and potassium thiocyanate (0.97 g, 0.01 mole) was heated under reflux in acetic acid for 6 h. The reaction mixture was allowed to cool to r.t. and poured into water. The precipitate so-formed was collected by filtration, dried, and recrystallized from acetic acid to produce **6** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3284 (NH) and 1653 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 8.85 (brs, 1H, NH, D_2O exchangeable) and 9.90 (brs, 1H, NH, D_2O exchangeable).

2-Ethylacetoacetatehydrazon-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (7)

A mixture of compound **1** (2.50 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) was heated under reflux in absolute ethanol for 5 h. The reaction mixture was allowed to cool to r.t. and poured into water. The precipitate so-formed was collected by filtration, dried and recrystallized from ethanol to produce **7** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3279 (NH), 3206 (NH), 2975 (CH aliphatic), 1741 (CO) and 1643 (CO). ^1H NMR ($CDCl_3$) δ ppm: 1.25 (m, 3H, CH_3), 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.00 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.25 (s, 2H, CH_2), 4.15 (q, 2H, CH_2), 8.45 (brs, 1H, NH, D_2O exchangeable), and 9.55 (brs, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ ppm: 14.1, 15.9, 24.2, 27.2, 27.8, 29.5, 32.4, 44.0, 61.2 (seven CH_2 + Two CH_3); 117.5, 132.1, 136.5, 146.2, 148.9 and 158.6 (thieno pyrimidine carbon atoms); 163.6 and 169.4 (two CO). MS (m/z): 362.1 (M^+) 47.70%, 316 (M-EtOH) 12.00%.

2-(3-Methyl-5-oxo-4H-pyrazol-1-yl)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (8)

Method A

A solution of compound **1** (2.50 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) in sodium ethoxide solution [prepared by dissolving sodium metal (0.23 g, 0.01 mole) in absolute ethanol (30 mL)] was heated under reflux for 5 h. The reaction mixture was allowed to cool to r.t., poured into water, and neutralized by diluted acetic-acid solution. The solid product so-precipitated was filtered off, dried, and recrystallized from dimethylformamide to produce **8** as colorless crystals.

Method B

A solution of compound **7** (3.62 g, 0.01 mole) was heated under reflux with sodium ethoxide solution [prepared by dissolving sodium metal (0.23 g, 0.01 mole) in absolute ethanol (30 mL)] for 5 h. The reaction mixture was allowed to cool to r.t. and poured into water and neutralized by diluted acetic-acid solution .The precipitate so-formed was collected by filtration, dried, and recrystallized from dimethylformamide to produce **8** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3446 (OH), 2922 (CH aliphatic), and 1654 (CO). ^1H NMR ($CDCl_3$-TFA) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), and 5.55 (s, 1H, CH). MS (m/z): 316 (M^+) 100%, 301 (M-Me) 15.90%.

Coupling 8 with Aryldinediazonium Salts: The Preparation of 9a,b

To an ice-cold solution of the appropriate aromatic amine (0.01 mole) in [-38pt]Au: Colon ok? concentrated hydrochloric acid (3 mL) was added dropwise a solution of sodium nitrite (1.03 g, 0.01 mole) dissolved in the least amount of water, in an ice bath at -5°C. This previously prepared diazonium salt was added dropwise to a mixture of **8** (3.16 g, 0.01 mole) and anhydrous sodium acetate in ethanol. The reaction mixture was allowed to stand overnight at r.t., and then it was poured into water. The formed solid was filtered off, washed with water, dried, and recrystallized from dioxane to produce **9a,b**.

Coupling 8 with Diazotized-4-chloroaniline: The Preparation of 9a

Compound **9a** was obtained from compound **8** (3.16 g, 0.01 mole) and diazotized-4-chloroaniline (1.27 g, 0.01 mole). The product was recrystallized from dioxane to produce **9a** as orange crystals. IR spectrum (KBr) cm^{-1}: 3450 (OH), 3180 (NH), 2913 (CH aliphatic) and 1656 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 7.45 (d, 2H, aromatic protons), 7.75 (d, 2H, aromatic protons), 11.55 (br s, 1H, NH, D_2O exchangeable) and 13.00 (br s, 1H, OH, D_2O exchangeable). MS (m/z): 454 (M^+) 100%.

Coupling 8 with Diazotized-4-methoxyaniline: The Preparation of 9b

Compound **9b** was obtained from compound **8** (3.16 g, 0.01 mole) and diazotized-4-methoxyaniline (1.13 g, 0.01 mole). The product was

recrystallized from dioxane to produce **9b** as orange crystals. IR spectrum (KBr) cm^{-1}: 3443 (OH), 3212 (NH), 2920 (CH aliphatic) and 1660 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.7 (m, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.9 (m, 2H, CH_2), 3.2 (m, 2H, CH_2), 3.8 (s, 3H, CH_3), 7.0 (d, 2H, aromatic protons), 7.7 (d, 2H, aromatic protons), 11.6 (br s, 1H, NH, D_2O exchangeable) and 13.2 (brs, 1H, OH, D_2O exchangeable). MS (m/z): 450 (M^+) 100%.

2-(3-Amino-5-oxo-4H-pyrazol-1-yl)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one (10)

To a warmed ethanolic sodium ethoxide solution [prepared by dissolving sodium metal (0.23 g, 0.01 mole) in absolute ethanol (30 mL)] was added compound **1** (2.50 g, 0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole). The heating was continued for 5 h. The reaction mixture was allowed to cool to r.t., poured into water, and neutralized by diluted acetic acid solution. The solid product so precipitated was filtered off, dried, and recrystallized from dimethylformamide to produce **10** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3340 (NH_2), 3260 (NH), 2975 (CH aliphatic) and 1674 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 4.50–5.40 (br, 2H, NH_2, D_2O exchangeable), 8.95 (s, 1H, CH), and 8.25 (br, 1H, NH, D_2O exchangeable).

2-(3-Methyl-4-(un)substituted-5-substituted-pyrazol-1-yl)-3H-cyclohepteno[4,5]-thieno[2,3-d]pyrimidin-4(4H)-one (11a,b): General Procedure

A mixture of compound **1** (2.50 g, 0.01 mole) and the appropriate β-diketone (0.01 mole) was heated under reflux in absolute ethanol (30 mL) for 5 h. The reaction mixture was allowed to cool to r.t. The precipitate solid was collected by filtration, dried, and recrystallized from dioxane to produce **11a,b**.

2-(3,5-Dimethyl-pyrazol-1-yl)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (11a)

Compound **11a** was obtained from compound **1** (2.50 g, 0.01 mole) and pentane-2,4-dione (1.00 g, 0.01 mole). The product was recrystallized from dioxane to produce **11a** as pale yellow crystals. IR spectrum (KBr) cm^{-1}: 3131 (NH), 2919 (CH aliphatic) and 1685 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 6.15 (s, 1H, CH) and 11.65 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 314 (M^+) 100%.

2-(3,5-Dimethyl-4-chloropyrazol-1-yl)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimi-din-4(4H)-one (11b)

Compound **11b** was obtained from compound **1** (2.50 g, 0.01 mole) and 3-chloropentane-2,4-dione (1.34 g, 0.01 mole). The product was recrystallized from dioxane to produce **11b** as orange crystals. IR spectrum (KBr) cm^{-1}: 3124 (NH), 2920 (CH aliphatic) and 1683 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.85 (m, 2H, CH_2) and 3.25 (m, 2H, CH_2). MS (m/z): 348 (M^+) 100%.

2-(1,1,1-Trifluoropentane-2,4-dione-hydrazone)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (12)

A mixture of compound **1** (2.50 g, 0.01 mole) and 1,1,1-trifluoro-2,4-pentandione (1.54 g, 0.01 mole) was heated under reflux in absolute ethanol (30 mL) for 5 h. The reaction mixture was allowed to cool to r.t. The precipitated solid was collected by filtration, dried, and recrystallized from dioxane to produce **12** as pale yellow crystals. IR spectrum (KBr) cm^{-1}: 3110 (NH), 2925 (CH aliphatic) and 1670 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 3.30–3.65 (m, 2H, CH_2), 8.00 (s, 1H, NH, D_2O exchangeable) and10.80 (s, 1H, NH, D_2O exchangeable). MS (m/z): 386 (M^+) 100%.

2-(Arylmethylenehydrazone)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (13a–c): General Procedure

A mixture of compound **1** (2.50 g, 0.01 mole) and the appropriate aromatic aldehyde (0.01 mole), dioxane (30 mL), and a catalytic amount of piperidine were heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t., and then it was poured into water. The formed precipitate was filtered off, washed with water, dried, and recrystallized from dimethylformamide to produce **13a,b**.

2-(Phenylmethylenehydrazone)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (13a)

Compound **13a** was obtained from compound **1** (2.50 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **13a** as pale yellow crystals. IR spectrum (KBr) cm^{-1}: 3375 (NH), 3140 (NH), 3044 (CH aromatic), 2919 (CH aliphatic) and 1667 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 7.35

(m, 3H, aromatic protons), 7.85 (m, 2H, aromatic protons), 8.00 (s, 1H, CH), 11.25 (brs, 1H, NH, D_2O exchangeable), and 11.55 (br s, 1H, NH, D_2O exchangeable). MS (m/z): 338.20 (M^+) 100%.

2-(4-Chlorophenylmethylenehydrazone)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (13b)

Compound **13b** was obtained from compound **1** (2.50 g, 0.01 mole) and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dimethylform-amide to produce **13b** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3375 (NH), 3140 (NH), 3044 (CH aromatic), 2920 (CH aliphatic) and 1668 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 7.50 (d, 2H, aromatic protons), 8.00 (t, 3H, aromatic protons + CH), 11.35 (br s, 1H, NH, D_2O exchangeable), and 11.65 (br s, 1H, NH, D_2O exchangeable). MS (m/z): 372 (M^+) 100%.

2-(4-Methoxyphenylmethylenehydrazone)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (13c)

Compound **13c** was obtained from compound **1** (2.50 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **13c** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3376 (NH), 3163 (NH), 3045 (CH aromatic), 2919 (CH aliphatic) and 1667 (CO). ^1H NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 6.85 (d, 2H, aromatic protons), 7.90 (d, 2H, aromatic protons), 8.00 (s, 1H, CH), 11.15 (br s, 1H, NH, D_2O exchangeable) and 11.50 (brs, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ ppm: 27.0, 27.3, 27.6, 28.9, 32.1 and 55.3 (5 $CH_2 + OCH_3$); 114.0, 116.1, 127.0, 129.0, 129.8, 136.0, 142.9, 149.7, 158.8 and 160.8 (thienopyrimidine aromatic carbon atoms); 163.8 (CO). MS (m/z): 368.20 (M^+) 100%.

4-Chloro-2-methylthio–cyclohepteno[4,5]thieno[2,3-d]pyrimidine (15)

A solution of compound **14** (2.66 g, 0.01 mole) in dry dioxane was treated with phosphorus oxychloride (9 mL) and stirred under reflux for 3 h. The reaction mixture was allowed to cool to r.t. and poured into cold water. The solid product so precipitated was filtered off and recrystallized from absolute ethanol to produce **15** as colorless crystals. IR spectrum (KBr) cm^{-1}: 2996 (CH aliphatic), 1554 (C=N) and 1467 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.75 (m, 2H, CH_2), 2.58 (s, 3H,

CH_3), 2.85 (m, 2H, CH_2) and 3.20 (m, 2H, CH_2). MS (m/z): 284.0 (M^+) 100%.

4-Arylamino-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (16a,b): General Procedure

An equimolar amount of **15** (2.84 g, 0.01 mole) and the appropriate aromatic amine (0.01 mole) were heated under reflux in dry dioxane for 6 h. The solid that separated during reflux was collected by filtration, washed, dried, and recrystallized from ethanol to produce **16a,b**.

2-Methylthio-4-phenylamino-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (16a)

Compound **16a** was obtained from compound **15** (2.84 g, 0.01 mole) and aniline (0.93 g, 0.01 mole). The product was recrystallized from ethanol to produce **16a** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3436 (NH), 3028 (CH aromatic), and 2963 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.85 (m, 6H, $3CH_2$), 2.45 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.09 (m, 2H, CH_2), 7.05 (t, 1H, CH and 1H, NH, D_2O exchangeable), 7.25 (t, 2H, aromatic protons) and 7.55 (d, 2H, aromatic protons). MS (m/z): 341 (M^+) 100%.

2-Methylthio-4-(4-methylphenylamino)-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (16b)

Compound **16b** was obtained from compound **15** (2.84 g, 0.01 mole) and 4-methylaniline (1.07 g, 0.01 mole). The product was recrystallized from ethanol to produce **16b** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3437 (NH) and 2909 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 7.15 (d, 2H, aromatic protons), 7.65 (d, 2H, aromatic protons) and 8.85 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 355 (M^+) 100%.

8-Methylthio-cyclohepteno[4,5]thieno[2′,3′:4,5]pyrimido[6,1-b]quinazolin-10-one (17)

A mixture of compound **15** (2.84 g, 0.01 mole) and anthranilic acid (1.37 g, 0.01 mole) was fused at 170–180°C for 3 h. Cooling and an addition of methanol solidified the product. The precipitate so formed was collected by filtration and recrystallized from dioxane to produce **17** as yellow crystals. IR spectrum (KBr) cm^{-1}: 2922 (CH aliphatic) and

1690 (CO). ^{1}H NMR ($CDCl_3$) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.70 (m, 2H, CH_2), 7.45 (t, 1H, aromatic proton), 7.60 (d, 1H, aromatic proton), 7.65 (t, 1H, aromatic proton) and 8.25 (d, 1H, aromatic proton). MS (m/z): 367.10 (M^+) 100%, 339 (M-CO) 39.52.

4-Hydrazino-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (18)

A mixture of compound **15** (2.84 g, 0.01 mole) and hydrazine hydrate (99–100%) (7 mL, 0.03 mole) in dioxane (30 mL) and ethanol (5 mL) was heated under reflux for 5 h. The reaction mixture was allowed to cool to r.t. The precipitated solid was collected by filtration, washed, dried, and recrystallized from ethanol to produce **18** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3283 (NH), 3186 (NH) and 2986 (CH aliphatic). ^{1}H NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.95 (m, 2H, CH_2), 4.15 (brs, 2H, NH_2, D_2O exchangeable) and 6.55 (br s, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ ppm: 14.1 (CH_3); 26.4, 27.0, 28.9, 29.8, and 30.7 (Five CH_2); 113.5, 130.2, 135.4, 158.3, 164.7, and 164.8 (thienopyrimidine carbon atoms). MS (m/z): 280 (M^+) 100%.

5-Methylthio-Cyclohepteno[4,5]thieno[3,2-e][1,2,4]triazolo[4′,3′-c]pyrimidine (19a)

A mixture of compound **18** (2.80 g, 0.01 mole), formic acid (10 mL) and a catalytic amount of concentrated hydrochloric acid was heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t. and poured into water. The solid product so precipitated was filtered off, dried, and recrystallized from dioxane to produce **19a** as colorless crystals. IR spectrum (KBr) cm^{-1}: 2919 (CH aliphatic) and 1488 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm: 1.75 (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 3.40 (m, 2H, CH_2) and 8.75 (s, 1H, CH). MS (m/z): 290.0(M^+) 100%.

3-Methyl-5-methylthio-cyclohepteno[4,5]thieno[3,2-e][1,2,4]triazolo[4′,3′-c]pyrimidine (19b)

A solution of compound **18** (2.80 g, 0.01 mole) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t. and poured into water. The solid product so precipitated was filtered off, dried and recrystallized from acetic acid to produce **19b** as colorless crystals. IR spectrum (KBr) cm^{-1}: 2994 (CH

aliphatic). ^{1}H NMR ($CDCl_3$) δ ppm: 1.75 (m, 4H, $2CH_2$), 2.95 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.15 (s, 3H, CH_3), and 3.50 (m, 2H, CH_2). MS (m/z): 304 (M^+) 100%, 289 (M-Me) 40.05%.

5-Methylthio-2H-cyclohepteno[4,5]thieno[3,2-e][1,2,4]triazolo[4′,3′-c]pyrimidine-3(3H)-thione (20)

To a warmed ethanolic sodium hydroxide solution [prepared by dissolving sodium hydroxide (0.40 g, 0.01 mole) in ethanol (50 mL)], compound **18** (2.80 g, 0.01 mole) and carbon disulphide (10 mL) were added. The mixture was heated on a water bath at 80°C under reflux for 10 h, and then it was poured into water, neutralized by diluted acetic acid. The formed precipitate was filtered off. The product was recrystallized from dioxane to produce **20** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3420 (NH), 2922 (CH aliphatic). ^{1}H NMR ($CDCl_3$) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.85 (m, 4H, $2CH_2$) and 9.00 (brs, 1H, NH, D_2O exchangeable).

5-Methylthiotetrazolo[1,5-c]cyclohepteno[4,5]thieno[3,2-e]pyrimidine (21)

To an ice-cold solution of compound **18** (2.80 g, 0.01 mole) in acetic acid (10 mL), a solution of sodium nitrite [prepared by dissolving sodium nitrite (1.03 g, 0.01 mole) in the least amount of water] was added dropwise in an ice bath at –5°C. The reaction mixture was allowed to stand overnight at r.t., and then it was poured into water. The formed solid was filtered off, washed with water, dried, and recrystallized from ethanol to produce **21**. IR spectrum (KBr) cm^{-1}: 2921 (CH aliphatic). ^{1}H NMR ($CDCl_3$) δ ppm: 1.75 (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.95 (m, 2H, CH_2) and 3.45 (m, 2H, CH_2). MS (m/z): 291(M^+) 71.38%.

4-Amino-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (22)

A mixture of compound **21** (2.91 g, 0.01 mole), zinc dust (0.65 g, 0.01 mole), and acetic acid (10 mL) was stirred at r.t. for 2 h, and then it was heated on a water bath at 80°C for 6 h (under TLC control). The reaction mixture was then extracted with benzene. Then benzene was evaporated, and the formed solid was recrystallized from methanol to produce **22** as pale yellow crystals. IR spectrum (KBr) cm^{-1}: 3494 (NH_2) and 2924 (CH aliphatic). ^{1}H NMR ($CDCl_3$) δ ppm: 1.75 (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 2.95 (m, 2H, CH_2) and 5.30 (brs, 2H, NH_2, D_2O exchangeable). MS (m/z): 265 (M^+) 100%.

3-Chloromethyl-5-methylthio-cyclohepteno[4,5]thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (23)

A mixture of compound **18** (2.80 g, 0.01 mole), chloroacetyl chloride (1.13 g, 0.01 mole), was allowed to stand overnight at r.t. in 20 ml of dry dioxane. The solid so formed was filtered, dried, and recrystallized from dioxane to produce **23** as colorless crystals. IR spectrum (KBr) cm^{-1}: 2994 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.60 (m, 4H, $2CH_2$), 1.75 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.70 (m, 2H, CH_2), 3.30 (m, 2H, CH_2) and 5.15 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 14.7 (CH_3), 27.1, 27.6, 28.5, 30.0, 32.2, and 36.0 (Six CH_2) and 116.7, 134.8, 140.3, 142.8, 144.1, 148.7, and 149.2 (thieno-pyrimidine-triazolo carbon atoms). MS (m/z): 338 (M^+) 100%.

4-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-methylthio-cyclohepteno[4,5]thi-eno[2,3-d]pyrimidine (24)

A mixture of compound **18** (2.80 g, 0.01 mole) and pentane-2,4-dione (1.00 g, 0.01 mole) was heated under reflux in absolute ethanol (30 mL) for 6 h. The reaction mixture was allowed to cool to r.t. The precipitated solid was collected by filtration, dried, and recrystallized from ethanol to produce **24** as colorless crystals. IR spectrum (KBr) cm^{-1}: 2927 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.65 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.90 (m, 2H, CH_2) and 6.05 (s, 1H, CH pyrazolo proton). MS (m/z): 344 (M^+) 100%, 330 (M-Me) 69.34 %.

2-Methylthio-4-[1,1,1-trifluoropentane-2,4-dione-4-hydrazone-cyclohepteno[4,5]-thieno[2,3-d]pyrimidine] (25)

A mixture of compound **18** (2.80 g, 0.01 mole) and 1,1,1-trifluoropentane-2,4-dione (1.54 g, 0.01 mole) was heated under reflux in absolute ethanol (30 mL) for 6 h. The reaction mixture was allowed to cool to r.t. The precipitated solid was collected by filtration, dried, and recrystallized from ethanol to produce **25** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3567 (OH), 3159 (NH) and 2996 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.50–2.00 (m, 6H, $3CH_2$), 2.10 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 2.70–2.90 (m, 2H, CH_2), 3.10–3.45 (d-d, 2H, CH_2), and 8.50 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) δ ppm: 14.0, 15.2 (Two CH_3); 26.6, 27.2, 29.6, 29.9, 32.2, and 48.4 (Six CH_2) and 118.9, 121.5, 125.7, 133.3, 138.3, 151.9, 156.3, and 161.8 (thienopyrimidine carbon atoms); 168.9 (CO). MS (EI + Q1MS LMR UP LR): 416 (M^+) 100%, 398 (M-18) 37.19 %

4-(Arylmethylenehydrazone)-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]-pyrimidine 26a–c: General Procedure

A mixture of compound **18** (2.80 g, 0.01 mole) and the appropriate aromatic aldehyde (0.01 mole), dioxane (30 mL), and a catalytic amount of piperidine were heated under reflux for 6 h. The reaction mixture were allowed to cool to r.t., and then it was poured into water. The formed precipitate was filtered off, washed with water, dried, and recrystallized from dioxane to produce **26a,b.**

4-(Phenylmethylenehydrazone)-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (26a)

Compound **26a** was obtained from compound **18** (2.80 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane to produce **26a** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3328 (NH), 3140 (NH) and 2969 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.35 (m, 2H, CH_2), 7.40 (m, 4H, aromatic protons + CH ethylenic proton), 7.70 (m, 2H, aromatic protons) and 8.35 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 368.00 (M^+) 100%.

4-(4-Chlorophenylmethylenehydrazone)-2-methylthio-cyclohepteno[4,5]thieno[2,3-d]pyrimidine (26b)

Compound **26b** was obtained from compound **18** (2.80 g, 0.01 mole) and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dioxane to produce **26b** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3345 (NH) and 2926 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.80 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 7.15 (s, 1H, CH), 7.40 (d, 2H, aromatic protons), 7.70 (d, 2H, aromatic protons) and 8.35 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 402 (M^+) 100%.

4-(4-Methoxyphenylmethylenehydrazone)-2-methylthiocyclohepteno[4,5]thieno-[2,3-d]pyrimidine (26c)

From compound **18** (2.80 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane to produce **26c** as yellow crystals. IR spectrum (KBr) cm^{-1}: 3378 (NH) and 2922 (CH aliphatic). ^1H NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 3.30 (m, 2H,

CH_2), 3.85 (s, 3H, CH_3), 6.90 (m, 3H, aromatic protons + CH ethylenic proton), 7.70 (d, 2H, aromatic protons) and 10.20 (brs, 1H, NH, D_2O exchangeable). MS (m/z): 398 (M^+) 100%.

CONCLUSION

This work deals with the synthesis of polynuclear thieno[2,3-d]pyrimidine derivatives by intermolecular reactions of 2- or 4-hydrazinothieno[2,3-d]pyrimidine with aliphatic acids, functional, and bifunctional groups to give triazolo, pyrazolyl, and triazine derivatives.

REFERENCES

[1] R. E. Weishaar, M. C. Cain, and J. A. Bristol, *J. Mednl. Chem.,* **28,** 537 (1985).
[2] G. Matolcsy, *World Rev. Pest Contr.*, **10,** 50 (1971).
[3] B. Commoner and F. L. Mercer *Nature*, **168,** 113 (1951).
[4] F. L. Mercer, T. E. Lindhorst, and B. Commoner, *Science*, **117,** 558 (1953).
[5] G. N. Pershin, L. I. Sherbakova, T. N. Zykova, and V. N. Sokolova, *Farmakol Ioksikol*, **35,** 466 (1972): *Chem. Abstr.*, **77,** 135580z (1972).
[6] V. J. Ram, U. K. Singha, and P. Y. Guru, *Europ. J. Mednl. Chem.*, **25,** 533 (1990).
[7] A. B. A. El-Gazzar, *Phosphorus, Sulfur, and Silicon*, **180,** 283–293 (2005).
[8] A. B. A. El-Gazzar, M. I. Hegab, S. A. Swelam, and S. A. Aly, *Phosphorus, Sulfur, and Silicon*, **177,** 123 (2002).
[9] A. M. Abdel-Fattah, A. S. Aly, F. A. Gad, M. E. A. Zaki, and A. B. A. El-Gazzar *Phosphorus, Sulfur, and Silicon*, **141,** 263 (1998).
[10] A. M. Abdel-Fattah, A. S. Aly, F. A. Gad, N. A. Hassan, and A. B. A. El-Gazzar, *Phosphorus, Sulfur, and Silicon*, **163,** 1 (2000).
[11] M. B. Devani, C. J. Shisoo, U. S. Pathak, S. H. Parikh, G. F. Shah, and A. C. Padhya, *J. Pharmaceutical Science*, **65,** 660 (1976).