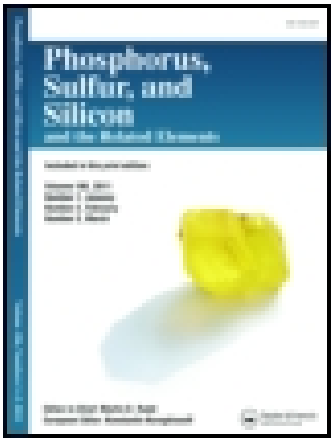

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Synthesis and Reactions of Polynuclear Heterocycles: Azolothienopyrimidines and Thienothiazolopyrimidines

A. B. A. El-Gazzar [a] , H. A. R. Hussein [a] & A. S. Aly [a]
[a] Photochemistry Department (Heterocyclic Unit), National Research Center , Dokki, Cairo, Egypt
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Synthesis and Reactions of Polynuclear Heterocycles: Azolothienopyrimidines and Thienothiazolopyrimidines

A. B. A. El-Gazzar
H. A. R. Hussein
A. S. Aly

Photochemistry Department (Heterocyclic Unit), National Research Center, Dokki, Cairo, Egypt

We prepared a thieno[2,3-d]pyrimidine compound fused with a thiazolo ring to produce biologicaly active compounds. In a one-step reaction, 2-arylmethylene derivative **(3)** *was prepared via the reaction of a ternary mixture of 2-thioxo-1,2,3,4-tetrahydrocyclohepteno[4,5]thieno[2,3-d]pyrimi-dine-4-one* **(2)***, cloroacetic acid, and a proper aldehyde. The reaction of* **2** *with 3-chloropent-2,4-dione in ethanolic potassium hydroxide yielded the S-acetylacetone derivative* **4e***. The latter compound reacted with hydrazine hydrate and phenyl hydrazine to give 2-pyrazolthio derivatives* **8a,b***, respectively. Compound* **4e** *also underwent cyclization on boiling with acetic anhydride/pyridine solution to form 2-acetyl-3-methyl thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d] pyrimidine-5-one* **(9)***. To support the structure* **9***, it gave a characteristic reaction for the 2-acetyl group. The 2-methylthio derivatives* **4a** *underwent further alkylation at N_3 to give* **6a,b***. The purpose of the synthesis of thienopyrimidine derivatives is due to high biological activities. The 4-oxo-thienopyrimidine derivatives acted as inhibitors of adenosine kinase, platelet aggregation, antilukemia, and anticancer activities.*

Keywords Mass spectra; NMR spectra; polynuclear; pyrimidines

DISCUSSION

Our interest in thieno[2,3-d]pyrimidine synthesis emerges from numerous reports on their diverse biological activities. We report here the syntheses of new polynuclear heterocyclic thienopyrimidine derivatives, starting with 2-thioxo-1,2,3,4-tetrahydrocyclopenteno[4,5]thieno[2,3-d]pyrimidine-4-one **(2)**, which is a versatile intermediate for the preparation of polyheretocycles due to the presence of reactive functional groups.

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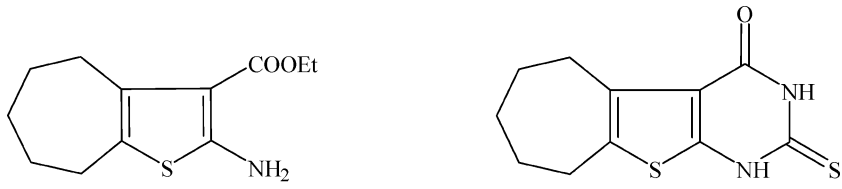
Address correspondence to A. S. Aly, National Research Center, Photochemistry Department (Heterocyclic Unit), Dokki, Cairo, Egypt. E-mail: a_s_aly@yahoo.com



1 **2**

SCHEME 1

Thus heating under reflux ethyl 2-amino-cyclohepteno[b]thiophene-3-carboxylate **(1)**, prepared according to Karl Gewald method,[1–3] with potassium thiocyanate in dry dioxane in the presence of hydrochloric acid, followed by cyclization with acetic acid, yielded compound **2** in a good yield (Scheme 1).

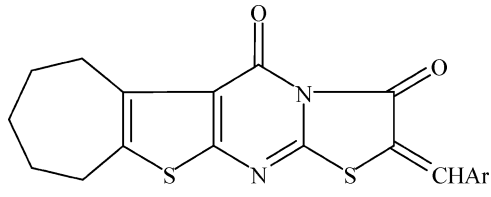
The IR spectrum of **2** displayed absorption bands at 3414 cm^{-1} (NH) and 1660 cm^{-1} (CO).

Its ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 1.65 ppm (m, 4H, 2CH_2), δ 1.85 (m, 2H, CH_2), δ 2.90 (m, 2H, CH_2), δ 3.20 (m, 2H, CH_2), δ 12.30 (br, s, 1H, NH, D_2O exchangeable), and δ 13.30 (br, s, 1H, NH, D_2O exchangeable). The mass spectrum of 2 showed the molocular ion peak at m/z 252.

On heating under reflux a mixture of compound **2**, chloroacetic acid, aromatic aldehyde in acetic acid, and acetic anhydride in the presense of anhydrous soduim acetate, heterocycles **3a–c** were obtained in a good yield (Scheme 2).

The assignment of structure **3** to the reaction products was based on

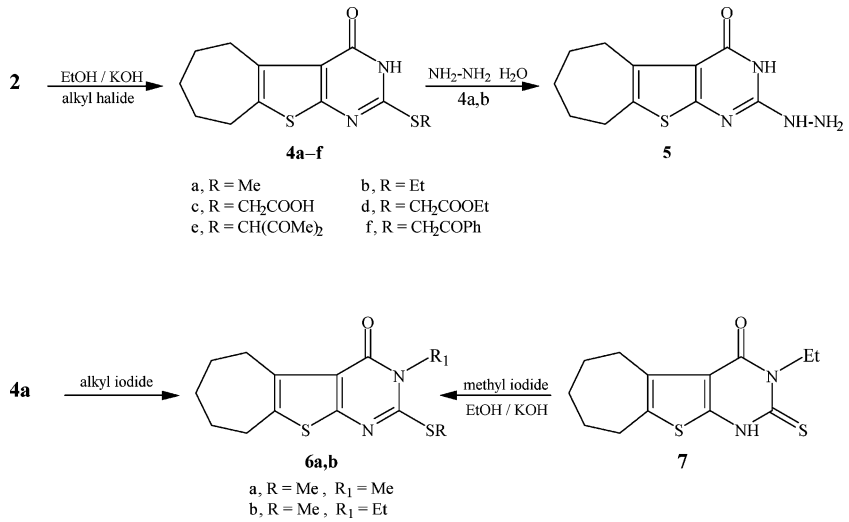
1. correct values in elemental analyses and compatible IR spectral data (Experimental);



3

Ar , a = Ph
b = C_6H_4Cl-p
c = C_6H_4OMe-p

SCHEME 2



SCHEME 3

2. ^{1}H-NMR and mass spectra (Experimental); and
3. it is reported in the literature that the N-3 nitrogen atom[4,5] and not the N-1 nitrogen atom is involved in the cyclization.

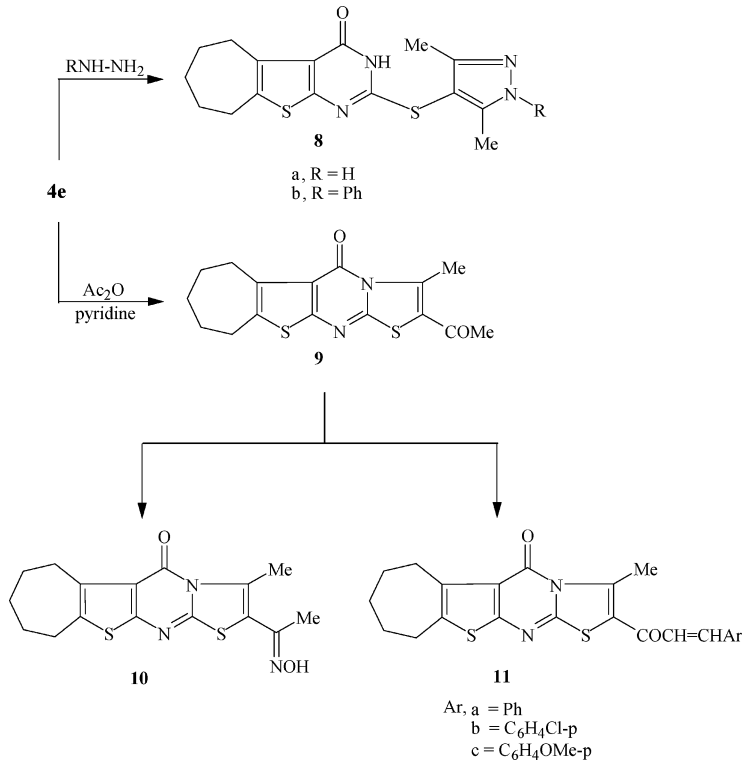
The alkylation of compound **2** in ethanolic potassium hydroxide solution or chloro-compounds yielded the 2-alkythio derivatives **4a–f** (Scheme 3). With hydrazine hydrate, compounds **4a,b** gave the 2-hydrazino derivative **5**. This is conclusive for structures **4a,b**.

The 2-alkylthio derivatives **4a,b** underwent further alkylation on treatment with alkyl iodide in aqueous ethanolic potassium ethoxide, the N-3 alkylated products **6a,b** (Scheme 3). The structural assignment of **6** is based on an independent preparation of **6b** by the methylation of compound **7** with methyl iodide.[4]

On the other hand, compound **4e** reacted as 1,3-diketone with hydrazine hydrate and phenyl hydrazine to afford the cyclized products **8a,b** (Scheme 4).

IR spectra of these compounds displayed absorption bands around 1660 cm^{-1} (CO). The ^{1}H-NMR spectrum (DMSO-d_6) of **8a** showed signals at δ 1.65 ppm (m, 4H, 2CH_2), δ 1.85 (m, 2H, CH_2), δ 2.20 (s, 6H, 2CH_3), δ 2.90 (m, 2H, CH_2), δ 3.20 (m, 2H, CH_2), and δ 12.60 (br, s, 1H, NH, D_2O exchangeable).

Heating **4e** in a mixture of acetic anhydride/pyridine led to the formation of the cyclic product **9**. The IR spectrum of **9** displayed two

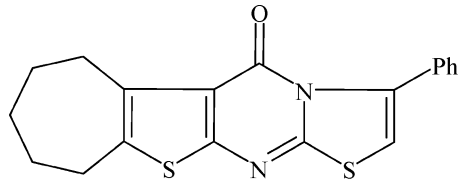


SCHEME 4

carbonyl absorption bands at 1694 and 1671 cm^{-1}. Its ^{1}H-NMR spectrum (DMSO-d_6) showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), δ 1.85 (m, 2H, CH_2), δ 2.60 (s, 3H, CH_3), δ 2.90 (m, 2H, CH_2), δ 3.10 (s, 3H, CH_3), and δ 3.20 (m, 2H, CH_2).

Ketone compound **9** formed an oxime **10**. Moreover, the condensation of **9** with aromatic aldehydes furnishes the derivatives **11a–c** (Scheme 4). The IR of **11** displayed two carbonyl absorption bands around 1700 and 1650 cm^{-1} (2CO). The ^{1}H-NMR spectrum ($CDCl_3$) of **11b** showed signals at δ 1.70 ppm (m, 4H, $2CH_2$), δ 1.90 (m, 2H, CH_2), δ 2.80 (m, 2H, CH_2), δ 3.20 (s, 3H, CH_3), δ 3.30 (m, 2H, CH_2), δ 7.10 (d, 1H, ethylenic proton), δ 7.45 (d, 2H, aromatic protons), δ 7.65 (d, 2H, aromatic protons), and δ 7.85 (d, 1H, ethylenic proton).

Also, when compound **4f** was heated with polyphosphoric acid, it afforded 3-phenylthiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidine-5(5H)-one (**12**) (Scheme 5). The IR spectrum of **12** displayed an absorption band at 1695 cm^{-1}(CO). Its ^{1}H-NMR spectrum



12

SCHEME 5

(DMSO-d_6) showed signals at δ 1.65 ppm (m, 4H, $2CH_2$), δ 1.85 (m, 2H, CH_2), δ 2.90 (m, 2H, CH_2), δ 3.30 (m, 2H, CH_2), δ 7.20 (s, 1H, thiazolo proton), and δ 7.55 (m, 5H, aromatic protons). The mass spectrum of 12 showed the molecular ion peak at m/z 352.

EXPERIMENTAL

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus. Microanalyses were carried out at the microanalytical units, National Research Center and Faculty of Science, Cairo University (Table I). 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. Signals were measured with reference to TMS as an internal standard. The mass spectra were recorded on Finnigan SSQ 7000 spectrometer. All solid compounds were recrystallized to produce constant melting points.

2-Thioxo-1,2,3,4-tetrahydrocyclohepteno[4,5]thieno[2,3-d]pyrimidin-4-one (2)

A mixture of **1** (2.39 g, 0.01 mole), potassium thiocyanate (0.97 g, 0.01 mole), and concentrated hydrochloric acid (30 mL) was refluxed in dioxane (30 mL) for 5 h (the reaction was followed by TLC). The reaction mixture was cooled and poured into water. The deposited precipitate was filtered off and recrystallized from dioxane. The precipitate that formed was cyclized by heating in glacial acitic acid and anhydrous sodium acetate to afford a colorless precipitate. The formed precipitate was collected by filtration, washed with water, and recrystallized from dioxane to produce a colorless powder **2**; IR spectrum (KBr) cm^{-1}: 3414 (NH); 2920 (CH aliphatic) and 1660 (CO); ^{1}H-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), 12.30 (br s, 1H, NH, D_2O exchangeable) and 13.30 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 252.0 (M^+) 100%.

TABLE I Physical Data for Products 2–12

Compound No.	M.P.°C	Yield %	M.F. (M. Wt.)	Elemental analyses (Calcd./Found) %C	%H	%N
2	308–310°C	70	$C_{11}H_{12}N_2S_2O$	52.35	4.79	11.10
			252.34	52.40	4.75	11.10
3a	288–290°C	80	$C_{20}H_{16}N_2S_2O_2$	63.13	4.23	7.36
			380.48	63.40	4.90	7.36
3b	298–300°C	80	$C_{20}H_{15}N_2S_2O_2Cl$	57.89	3.64	6.75
			414.94	57.90	3.60	6.75
3c	300–302°C	80	$C_{21}H_{18}N_2S_2O_3$	61.44	4.41	6.82
			410.51	61.42	4.50	6.82
4a	257–259°C	65	$C_{12}H_{14}N_2S_2O$	54.10	5.29	10.51
			266.38	54.60	5.00	10.50
4b	212–214°C	67	$C_{13}H_{16}N_2S_2O$	55.68	5.75	9.98
			280.41	56.08	5.56	10.10
4c	243–245°C	62	$C_{13}H_{14}N_2S_2O_3$	50.30	4.54	9.02
			310.39	50.29	4.85	9.00
4d	180–182°C	65	$C_{15}H_{18}N_2S_2O_3$	53.23	5.36	8.27
			338.44	53.00	5.40	8.27
4e	237–239°C	85	$C_{16}H_{18}N_2S_2O_3$	54.83	5.17	7.99
			350.46	54.90	5.00	7.90
4f	224–226°C	72	$C_{19}H_{18}N_2S_2O_2$	61.59	4.89	7.56
			370.49	61.70	4.60	7.56
5	300–302°C	73	$C_{11}H_{14}N_4SO$	52.78	5.63	22.38
			250.32	52.90	5.70	22.35
6a	145–147°C	82	$C_{13}H_{16}N_2S_2O$	55.68	5.75	9.98
			280.41	55.70	4.90	9.50
6b	150–152°C	67	$C_{14}H_{18}N_2S_2O$	57.11	6.16	9.51
			294.43	56.70	5.90	9.78
8a	299–301°C	82	$C_{16}H_{18}N_4S_2O$	55.46	5.23	16.17
			346.47	55.33	5.28	16.10
8b	223–225°C	58	$C_{22}H_{22}N_4S_2O$	62.53	5.24	13.25
			422.57	62.30	5.30	13.15
9	189–191°C	81	$C_{16}H_{16}N_2S_2O_2$	57.80	4.85	8.42
			332.44	57.79	4.98	8.40
10	260–62°C	67	$C_{16}H_{17}N_3S_2O_3$	55.30	4.93	12.09
			347.45	55.80	5.10	12.00
11a	245–147°C	61	$C_{23}H_{20}N_2S_2O_2$	65.68	4.79	6.66
			420.55	65.60	4.50	6.60
11b	230–132°C	59	$C_{23}H_{19}N_2S_2O_2Cl$	60.71	4.20	6.15
			454.99	60.70	4.30	6.10
11c	215–217°C	58	$C_{24}H_{22}N_2S_2O_3$	63.97	4.92	6.21
			450.58	63.90	5.04	6.28
12	214–216°C	63	$C_{19}H_{16}N_2S_2O$	64.74	4.57	7.94
			352.47	64.66	4.29	8.02

2-Arylmethylene-2H-thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidine-3(3H), 5(5H)dione 3a–c

General Procedure: Method A

A mixture of compound **2** (2.52 g, 0.01 mole), chloroacetic acid (0.95 g, 0.01 mole), appropriate aromatic aldehyde (0.01 mole), and anhydrous sodium acetate (0.02 mole) was refluxed in 30 mL of glacial acetic acid and 15 mL of acetic anhydride for 5 h. The reaction mixture was cooled and poured into water. The deposited precipitate was filtered-off and recrystallized from dimethylformamide to produce **3a–c**.

Method B

Compound **4c** (3.10 g, 0.01 mole) was heated under reflux with the proper aldehyde in acetic acid (30 mL) and acetic anhydride (15 mL), in the presence of anhydrous sodium acetate (0.02 mole), for 5 h. The reaction mixture was then cooled and poured into water. The deposited precipitate was filtered-off and recrystallized from dimethylformamide to yield the title product.

2-(Phenylmethylene)-2H-thiazolo[3,2-a]cyclohepteno[4,5]-thieno[2,3-d]pyrimidine-3(3H), 5(5H)-dione (3a)

Compound **3a** was obtained from **2** (2.52 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The compound was recrystallized from dimethylformamide to produce **3a** as pale yellow crystals; IR spectrum (KBr) cm^{-1}: 2921 (CH); 1758 (CO) and 1697 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 7.50–7.70 (m, 5H, phenyl protons) and 8.00 (s, 1H, CH); MS (m/z): 379.9 (M^+) 100%.

2-(4-Chlorophenylmethylene)-2H-thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidine-3(3H), 5(5H)-dione (3b)

Compound **3b** was obtained from **2** (2.52 g, 0.01 mole) and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **3b** as yellow crystals; IR spectrum (KBr) cm^{-1}: 2913 (CH), 1758 (CO) and 1685 (CO); ^{1}H-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), 7.75 (d, 2H, aromatic protons), 7.85 (d, 2H, aromatic protons) and 8.00 (s, 1H, ethylenic proton); MS (m/z): 414.0 (M^+) 100%.

2-(4-Methoxyphenylmethylene)-2H-thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidine-3(3H),5(5H)-dione (3c)

Compound **3c** was obtained from **2** (2.52 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The compound was recrystallized from dimethylformamide to produce **3c** orange crystals; IR spectrum (KBr) cm^{-1}: 2900 (CH), 1749 (CO) and 1675 (CO); MS (m/z): 410 (M^+) 100%.

2-(Alkylthio)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one 4a–f

General Method

To a warmed ethanolic potassium hydroxide solution [prepared by dissolving potassium hydroxide (0.56 g, 0.01 mole) in ethanol (50 mL)] was added compound **2** (2.52 g, 0.01 mole); it was heated for 30 min, and the mixture was allowed to cool to r.t. the proper halo compound (0.01 mole) was added. The mixture was heated under reflux, filtered off, recrystallized from appropriate solvent to for 5 h, and then cooled and poured into water. The solid product so-precipitated produced **4a–f**.

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

Compound **4a** was obtained from **2** (2.52 g, 0.01 mole) and methyl iodide (1.72 g, 0.013 mole). The compound was recrystallized from dioxane to produce **4a** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3448 (NH); 2917 (CH aliphatic) and 1654 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), and 12.60 (br s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6) δ ppm: 31.9, 28.8, 27.3, 27.1, 26.8, and 12.8 (five CH_2+ one CH_3); 119.4, 134.3, 136.1, 155.9, and 158.5 (thienopyrimidine carbon atoms); MS (m/z): 266.0 (M^+) 100%.

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

Compound **4b** was obtained from **2** (2.52 g, 0.01 mole) and ethyl iodide (1.86 g, 0.012 mole). The compound was recrystallized from ethanol to produce **4b** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3567 (NH); 2928 (CH) and 1670 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.40 (t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.40 (m, 2H, CH_2) and 10.90 (br s, 1H, NH, D_2O exchangeable). MS (m/z): 280.1 (M^+) 100%.

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

Compound **4c** was obtained from **2** (2.52 g, 0.01 mole) and chloroactetic acid (1.14 g, 0.01 mole). The compound was recrystallized from dimethylformamide to produce **4c** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3444 (OH); 1690 (CO) and 1655 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 4.00 (s, 2H, CH_2) and 12.60 (br s, 2H, 2(OH), D_2O exchangeable); MS (m/z): 310.0 (M^+).

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

Compound **4d** was obtained from **2** (2.52 g, 0.01 mole) and ethyl chloroacetate (1.22 g, 0.01 mole). The compound was recrystallized from ethanol to produce **4d** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3458 (NH); 2981 (CH aliphatic), 1741 (CO) and 1655 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.40 (t, 3H, CH_3), 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.90 (s, 2H, CH_2), 4.30 (q, 2H, CH2) and 11.70 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 338.1 (M^+) 100%.

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

Compound **4e** was obtained from **2** (2.52 g, 0.01 mole) and chloroacetylacetone (1.61 g, 0.012 mole). The compound was recrystallized from dioxane to produce **4e** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3444 (broad NH and OH); 2979 (CH aliphatic), 1683 (CO) and 1653 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.55 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 6H, $2CH_3$), 2.75 (m, 2H, CH_2), 3.10 (m, 2H, CH_2) and 12.80 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 350.0 (M^+) 32.6% and 332 (M-18) 100%.

2-(Benzoylmethylthio)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one(4f)

Compound **4f** was obtained from **2** (2.52 g, 0.01 mole) and ω–bromoacetophenone (2.38 g, 0.012 mole). The compound was crystallized from dioxane to produce **4f** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3447 (broad OH); 3062 (CH aromatic), 2917 (CH aliphatic), 1683 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 4.80 (s, 2H, CH2), 7.40–8.15 (m, 5H, aromatic protons) and 12.70 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 370 (M^+) 100%.

2-Hydrazino-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one (5)

A mixture of **4a** (2.66 g, 0.01 mole) and hydrazine hydrate (99–100%) (7 mL, 0.03 mole) in dioxane and ethanol was heated under reflux for 5 h. The reaction mixture was cooled, filtered off, and recrystallized from dimethylformamide to produce **5** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3341; 3178 [(NH_2), (NH)]; 2914 (CH aliphatic) and 1657 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 4.60 (br, 1H, NH, D_2O exchangeable) and 8.20 (br s, 1H, NH, D_2O exchangeable); ^{13}C-NMR(DMSO-d_6) δ ppm: 27.0, 27.3, 27.6, 28.8, and 32.0 (five CH_2); 114.7, 128.5, 135.6, 154.3 and 158.4 (thienopyrimidine carbon atoms) and 165.1 (CO); MS (m/z): 250.1 (M^+) 100%.

2-Alkylthio-3-alkyl-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one 6a,b

General Procedure

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving (0.56 g, 0.01 mole in 50 mL of ethanol) was added compound **4a** (0.01 mole). Heating was continued for 30 min, and the mixture was allowed to cool; the proper alkyl iodide (0.012 mole) was added. The mixture was heated under reflux for 4 h, cooled at r.t., poured into cold water. The solid so-precipitated was filtered off, washed with water, and recrystallized from the appropriate solvent to produce **6a,b**.

2-Methylthio-3-methyl-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one(6a)

Compound **6a** was obtained from **4a** (2.66 g, 0.01 mole) and methyl iodide (1.72 g, 0.012 mole). The compound was recrystallized from ethanol to produce compound **6a** as colorless crystals; IR spectrum (KBr) cm^{-1}: 2916 (CH aliphatic) and 1667 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.30 (m, 2H, CH_2) and 3.65 (s, 3H, CH_3); MS (m/z): 280 (M^+) 100%.

2-Methylthio-3-ethyl-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one(6b)

Compound **6b** was obtained from **4a** (2.66 g, 0.01 mole) and ethyl iodide (1.86 g, 0.012 mole). The compound was recrystallized from ethanol to produce compound **6b** as colorless crystals; IR spectrum (KBr) cm^{-1}:

2918 (CH aliphatic) and 1664 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.30 (t, 3H, CH_3), 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.30 (m, 2H, CH_2) and 4.20 (q, 2H, CH_2); MS (m/z): 294 (M^+) 100%.

2-(3,5-Dimethyl–1-(un)substitutedpyrazol-4-ylthio)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one 8a,b

General Procedure

A mixture of compound **4e** (3.50 g, 0.01 mole) and hydrazine hydrate (99–100%) or phenyl hydrazine hyrochloride (0.01 mole) in dioxane and ethanol was stirred under reflux for 10 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 **8a,b**.

2-(3,5-Dimethyl–1H-pyrazol-4-ylthio)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidine-4(4H)-one (8a)

Compound **8a** was obtained from a mixture of **4e** (3.50 g, 0.01 mole) and hydrazine hydrate (10 mL). The compound was recrystallized from dioxane to produce compound **8a** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3447 (NH), 3230 (NH), 2920 (CH aliphatic) and 1662 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.20 (s, 6H, $2CH_3$), 2.80 (m, 2H, CH_2), 3.20 (m, 2H, CH_2) and 12.60 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 346 (M^+) 100%.

2-(3,5-Dimethyl–1-phenylpyrazol-4-ylthio)-3H-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-4(4H)-one (8b)

Compound **8b** was obtained from a mixture of **4e** (3.50 g, 0.01 mole) and phenyl hydrazine hydrochloride (1.45 g, 0.01 mole). The compound was recrystallized from dioxane to produce compound **8b** as light yellow crystals; IR spectrum (KBr) cm^{-1}: 3286 (NH), 2913 (CH aliphatic) and 1683 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 2.95 (s, 3H, CH_3), 3.30 (m, 2H, CH_2), 6.85–7.30 (m, 5H, aromatic protons) and 9.70 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 422 (M^+) 100%.

2-Acetyl-3-methylthiazolo[3,2-a]-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one (9)

A solution of compound **4e** (3.50 g, 0.01 mole) in (10 mL) acetic anhydride and (20 mL) of pyridine was heated under reflux for 5 h. The reaction mixture was cooled, and the deposited precipitate was filtered-off and recrystallized from dioxane to produce **9** as yellow crystals; IR spectrum (KBr) cm^{-1}: 2930 (CH aliphatic), 1694 (CO) and 1671 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.10 (s, 3H, CH_3) and 3.20 (m, 2H, CH_2); MS (m/z): 332 (M^+) 100%.

2-(Acetoxime)-3-methylthiazolo[3,2-a]-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one (10)

A mixture of **9** (3.32 g, 0.01 mole), hydroxylamine hydrochloride (0.70 g, 0.01 mole), and a catalytic amount of piperidine was refluxed in dioxane (30 mL) for 6 h. The reaction mixture was allowed to cool to r.t. and was poured into water. The solid product so-precipitated was filtered off and recrystallized from dioxane to produce **10** as yellow crystals; IR spectrum (KBr) cm^{-1}: 3250 (OH), 2917 (CH aliphatic) and 1685 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 2.90 (m, 2H, CH_2), 3.20 (m, 2H, CH_2) and 11.80 (s, 1H, OH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6) δ ppm: 14.4 and 17.1 (two CH_3); 26.8, 27.1, 27.3, 29.0 and 32.0 (five CH_2); 117.5, 118.8, 133.3, 134.3, 136.3, 148.2 and 157.0 (thiazolothienopyrimidine carbon atoms); 157.4 (C=NOH); 160.2 (CO); MS (m/z): 347.0 (M^+) 100%.

2-Cinnamoyl(derivatives)-3-methylthiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one 11a–c

General Procedure

A mixture of compound **9** (3.32 g, 0.01 mole), the proper aromatic aldehyde (0.01 mole), and a catalytic amount of piperidine was fused at 170–180°C for 3 h. The product was solidified by cooling and an addition of methanol. The precipitate so-formed was collected by filtration and recrystallized from dioxane to produce **11a–c**.

2-Cinnamoyl-3-methyl-thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one (11a)

Compound **11a** was obtained from **9** (3.32 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The compound was recrystallized from dioxane

to produce **11a** as pale yellow crystals; IR spectrum (KBr) cm^{-1}: 2923 (CH); 1698 (CO) and 1655 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.30 (m, 2H, CH_2), 7.15 (d, 1H, CH), 7.40–7.70 (m, 5H, aromatic protons) and 7.8 (d, 1H, CH); MS (m/z): 420.1 (M^+) 100%.

2-(4-Chlorocinnamoyl)-3-methylthiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one (11b)

Compound **11b** was obtained from **9** (3.32 g, 0.01 mole) and 4-chlorobenzaldehyde (1.41 g, 0.01 mole). The compound was recrystallized from dioxane to produce **11b** as yellow crystals; IR spectrum (KBr) cm^{-1}: 2916 (CH); 1701 (CO) and 1655 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.90 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.30 (m, 2H, CH_2), 7.10 (d, 1H, CH), 7.45 (d, 2H, aromatic protons), 7.65 (d, 2H, aromatic protons) and 7.85 (d, 1H, CH); MS (m/z): 454.01 (M^+) 100%.

2-(4-Methoxycinnamoyl)-3methyl-thiazolo[3,2-a]cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5(5H)-one (11c)

Compound **11c** was obtained from **9** (3.32 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The compound was recrystallized from dioxane to produce **11c** as yellow crystals; IR spectrum (KBr) cm^{-1}: 2919 (CH); 1698 (CO) and 1654 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.30 (s, 3H, CH_3), 3.60 (m, 2H, CH_2), 3.90 (s, 3H, CH_3), 7.00 (d, 1H, CH), 7.00 (d, 2H, aromatic protons), 7.60 (d, 2H, aromatic protons) and 7.80 (d, 1H, CH).

3-Phenylthiazolo[3,2-a]-cyclohepteno[4,5]thieno[2,3-d]pyrimidin-5 (5H)-one (12)

A mixture of compound **4f** (3.70 g, 0.01 mole) and polyphosphoric acid was heated at 170–180°C for 2 h. The reaction mixture was allowed to cool to r.t. and was poured into water. The solid product so-precipitated was filtered off and recrystallized from dioxane to produce **12** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3079 (CH aromatic) and 1695 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.65 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 7.20 (s, 1H, CH) and 7.55 (m, 5H, aromatic protons); MS (m/z): 352.0 (M^+) 100%.

CONCLUSION

This work is concerned with the synthesis and reactions of thieno[2,3-d]pyrimidone with functional and bifunctional groups to give pyrazolothieno and thiazolothieno derivatives. The work involves carrying out transformations, which in one or two steps add a new heterocyclic ring to the molecule.

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