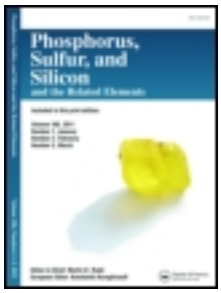

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Studies with Polyfunctionality Substituted Heterocycles: Novel Syntheses of Thienopyrimido-1,2,4-triazoles

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STUDIES WITH POLYFUNCTIONALITY SUBSTITUTED HETEROCYCLES: NOVEL SYNTHESES OF THIENOPYRIMIDO-1,2,4-TRIAZOLES

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*Several 3-substituted-(un)-cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazoles **10**, **11**, **12**, **13**, and **14** were prepared by reaction of an appropriate substituted 2-amino-3-cyanothiophene **1** with aliphatic acids or benzoyl chloride. Also the fusion of **1** with urea, thiourea to give the corresponding 2-oxo or thioxo-4-aminopyrimidine derivatives **6a**, **b** and other reactions of compound **1** are reported.*

Keywords: β-diketone; ^{1}H NMR spectra; *o*-aminonitrile; pyrimidine; mass spectra

The pyrimidine ring is a frequent partner in polycyclic heterocyclic systems of biological significance.[1] Compounds containing a fused pyrimidine ring make up a broad class that has attracted attention in the past few years owing to its wide range of biological activity. Many potential drugs have been modelled on these compounds, particularly in cancer and virus research.[2–4] On the other hand, thienopyrimidine, heterocyclic ring systems, have also attracted attention because of their promising biological activities. These derivatives have analgesic,[5] antipyretic,[6] antianaphilactic,[7,8] and antiinflammatory effects.[9,10] Also, some are clinically effective antialergic,[11] potentially antineoplastic agents,[12] or have a significant hypocholesterolemic activity.[13] This asset prompted us to prepare new polyheterocyclic system with potential biological activity containing the thienopyrimidine moiety in our search for new compounds of pharmacological interest.[14–16]

Syntheses of fused bi- and polycyclic compounds by annelation of a pyrimidine ring to an existing ring are high in number and were recently reviewed.[11] The structure of the required starting compounds is

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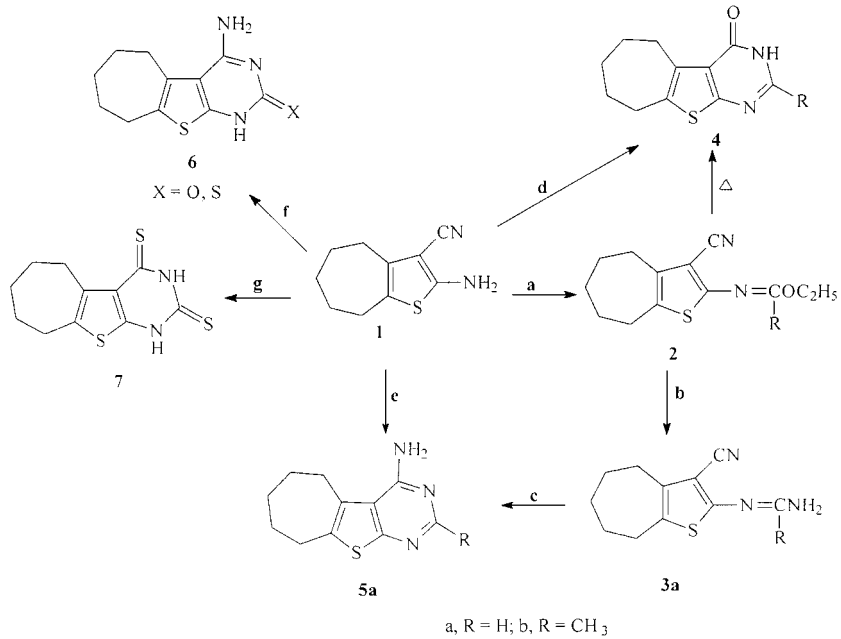
mainly determined by the nature of the substituents on the pyrimidine; as a rule, systems with an amino group next to another functional group are the most widely used.[17] For this purpose the nucleophilic character and structural diversity of amino groups have placed them in a prominent position in synthetic chemistry. Succesive replacement of the hydrogen atoms of the amino group with electrophilic methylene groups, leads to the iminium salts, which can function as a Vilsmeier or Manich reagents. This has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions. This article reports a new method for the preparation of substituted cyclohepta(*b*)thieno[2,3-*d*]pyrimido[3,4-*a*]-1,2,4-triazole (**10**, **11**) by reaction of an appropriately substituted thiophene derivative **1** and an acidic methylene group. The synthetic concept of constructing fused pyrimidines from *o*-aminonitrile and phosegeneiminium salts has already been applied to the synthesis of chloroquinazolines.[18]

The readily available 2-amino thiophene 3-nitrile **1**[19] was employed as the starting material (Scheme 1). The condensation of cycloheptanone with malononitrile in the presence of sulfur afforded the 2-amino-3-cyanocyclohepta(*b*)thiophene derivative **1** in a 87% yield.



SCHEME 1 a. triethylortho formate (acetate). Ac_2O; b. methanol, ammonia solution; c. ethoxide solution; d. formic acid, triethylortho acetate; e. formamide, DMF; f. urea, thiourea; g. CS_2, ethanolic KOH.

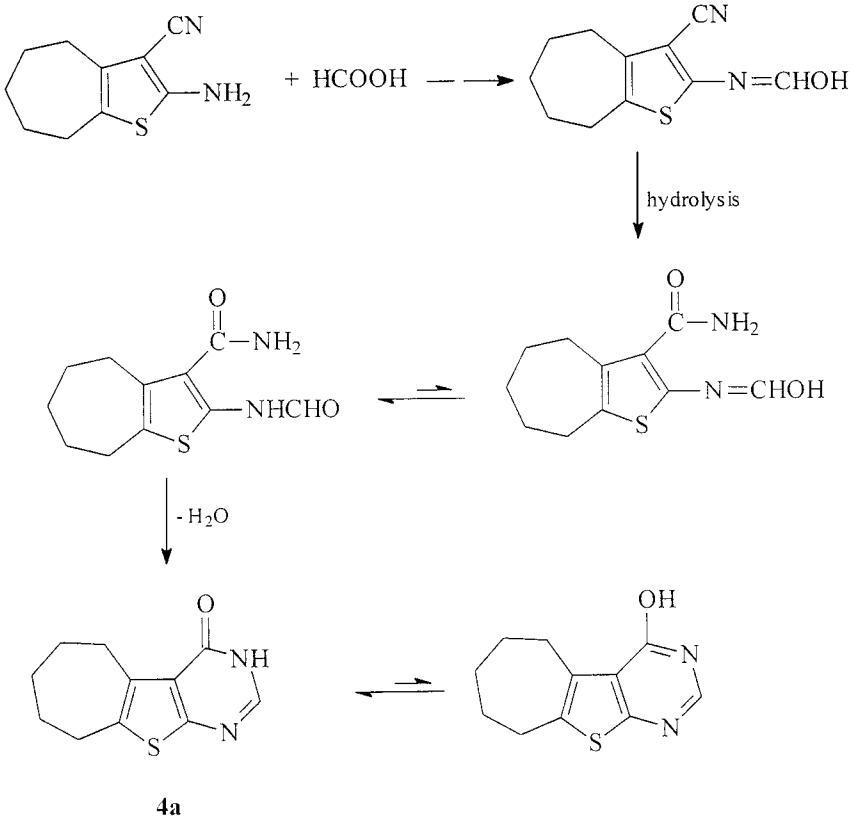
Structural elucidation of compound **1** was accomplished from analytical and spectral data. The mass spectra showed the expected molecular ion peak and the IR spectra exhibited absorption band at $\nu = 2218\ cm^{-1}$ due to the cyano group. Formation of the desired *o*-aminonitrile compound **1** was also confirmed by the ^1H NMR spectrum. Upon treatment with triethylorthoformate at reflux, the corresponding ethoxymethylene amino derivative **2a** was afforded in high yield.

Aminolysis of **2** (R = H) in methanol in the presence of ammonium hydroxide solution yielded the aminomethylene amino derivative **3** as the intermediate structure which cyclized when refluxed in ethanolic sodium ethoxide solution to give the cyclo-form 1-amino cyclohepta(*b*)thieno[2,3-*d*]pyrimidine (**5**). The latter compound was also prepared by the action of formamide and catalytic amount of formic acid, 2-amino-3-cyanocyclohepta(*b*)thiophene (**1**) in refluxing dimethylformamide. Also, the action of triethyortho acetate at room temperature gave the corresponding ethoxymethylene amino derivative **2b**. On the other hand, the refluxing action on the same reaction mixture afforded the 3-methyl cyclohepta(*b*)thieno[2,3-*d*]pyrimidine (**4b**) (R = CH_3) as shown in Scheme 1.

Similarly, compound **1** reacted with formic acid in presence of catalytic amount of hydrochloric acid to afford the corresponding[20] 1,2-dihydro-1-oxo-cyclohepta(*b*)thieno[2,3-*d*]pyrimidine (**4a**). The formation of **4a** from compound **1** and formic acid may proceed as shown in Scheme 2.

When compound **1** was fused with urea or thiourea at 180°C, it gave 1-amino-3-oxo-3*H*-cyclohepta(*b*)thieno[2,3-*d*]pyrimidine (**6a**) or the 3-thioxo derivative **6b**, with compatible spectral data (^1H NMR, mass spectrum) and elemental analysis. On the other hand, when compound **1** was heated with carbon disulfide in ethanolic potassium hydroxide solution, 1,3-dithioxo-1,2,3,4-tetrahydrocyclohepta(*b*)thieno[2,3-*d*]pyrimidine (**7**) was obtained as shown in Scheme 1.

The reaction of hydrazine hydrate with compound **2a** in the cold in ethanol afforded 2-amino-1-imino-1,2-dihydrocyclohepta(*b*)thieno [2,3-*d*]pyrimidine (**8′**), which could be rearranged to 1-hydrazino cycloheta(*b*)thieno[2,3-*d*]pyrimidine (**8**). The latter compound must be formed by the Dimroth rearrangement of intermediate **8′**. If the formation of amino imino (**8′**) is faster than Dimroth rearrangement, the final product is (**8′**). Vice versa, if the Dimroth rearrangement of the intermediate **8′** is faster than the formation of amino imino **8′**, one ends up with the 1-hydrazino derivative **8**. Also the hydrazino derivative **8** was prepared by the action of hydrazine hydrate with the chloro derivative **9**,[20] as shown in Scheme 3.

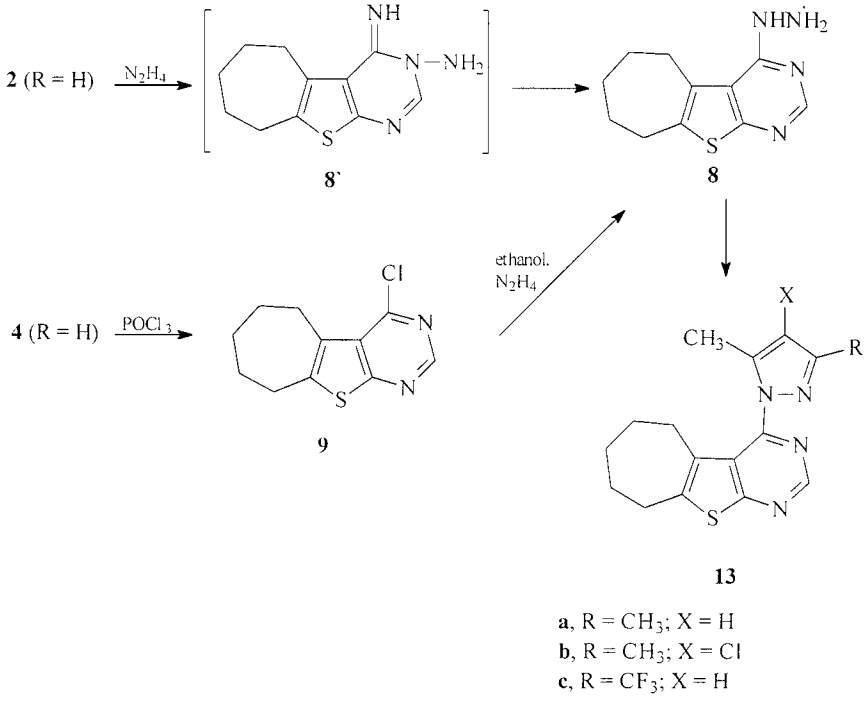


4a

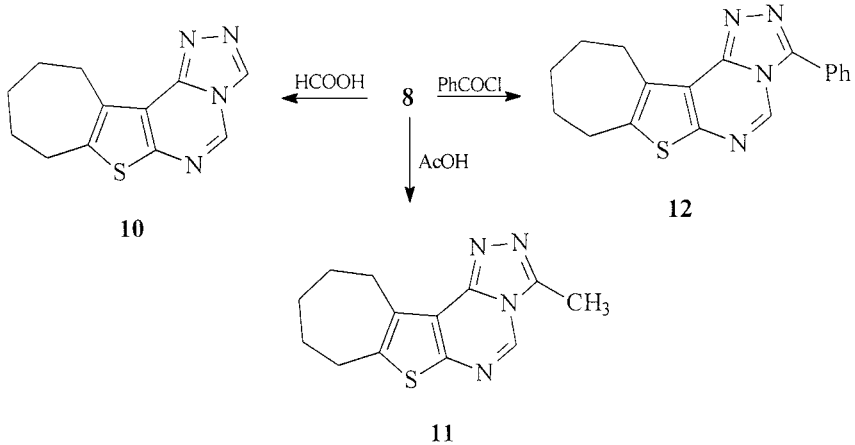
SCHEME 2

The reaction of hydrazino derivative **8** with aliphatic acids such as formic or acetic acid or acid chlorides such as benzoyl choride afforded 3-substituted (un-)cyclohepta(*b*)thieno[2,3-*d*]pyrimido [3,4-*a*]1,2,4-triazoles derivatives **10**, **11**, and **12**, as shown in Scheme 4. The spectral data (^{1}H NMR, mass spectrum) and elemental analysis are compatible with their expected structures. Also, the hydrazino derivative **8** reacted with β-diketones, such as acetyl acetone, chloroacetylacetone and trifluroacetylacetone to form 1-(1-pyrazolyl) derivatives. Thus, heating under reflux compound **8** with each of pentane-2,4-dione, 3-chloropentane-2,4-dione and 1,1,1-trifluropentane-2,4-dione in absolute ethanol yielded 1-(3,5-dimethyl-4-(un-)substituted-1*H*-pyrazol-1- yl)cyclohepta(*b*)thieno[2,3-*d*]pyrimidines **13a–c**. (Scheme 3)

Reaction of **8** with diethyl oxalate at reflux yielded the corresponding 3-ethyl cyclohepta(*b*)thieno[2,3-*d*]pyrimido[3,4-*a*]-1,2,4-triazole carboxylate (**14**), which upon saponification was converted

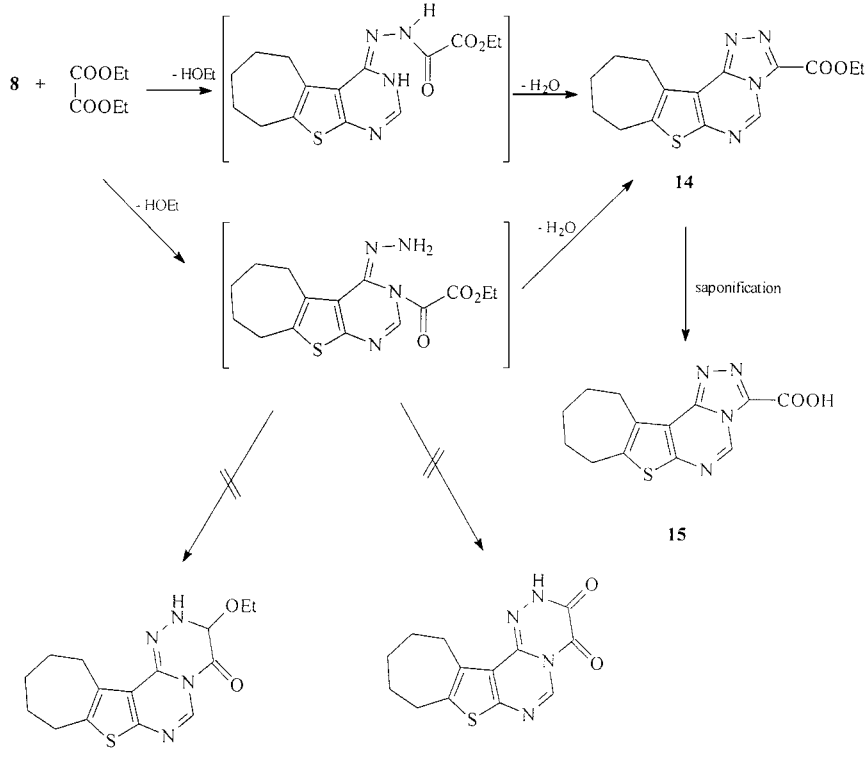


SCHEME 3



SCHEME 4

to the 3-(cyclohepta(*b*)thieno[2,3-*d*]pyrimido[3,4-*a*]-1,2,4-triazole) carboxylic (**15**). The IR spectra showed absorption bands at 3450 cm^{-1} (OH), and 1690 (CO). The ^1H NMR showed the signal for the hydroxyl group at 10.23 ppm. The reaction mechanism may proceed as shown in Scheme 5.



SCHEME 5

CONCLUSION

The prepared compounds seem to be interesting for biological activity studies. Furthermore, the present investigation offers rapid and effective new procedures for the synthesis of the title ring systems.

EXPERIMENTAL

All melting points are uncorrected. The ^1H NMR spectra were recorded on Bruker (WM-250 MHz), Bruker (AC-250 MHz) spectrometers (Faculty of Chemistry, Konstantz University, Germany), and a Varian 1H

Gemini 200 spectrometer (National Research Centre, Egypt) and chemical shifts were expressed as δ values against TMS as internal standards. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 spectrometer, (National Research Centre and Department of Chemistry, Cairo University). Mass spectra were recorded on GCMS-QP 1000 Ex Shimadzu Japan (Gas Chromatography-Mass Spectromer). Microanalytical data were performed by the Microanalytical Centre at Cairo University and National Research Centre (Egypt). All compounds gave satisfactory C, H, N, and S analysis (Table I).

TABLE I Physical Data for the Products **2–15**

Comp. no.	m.p.°C	Yield %	M. F. (m. wt.)	Elemental analyses calcd./found C	H	N
2a	115–118	81	$C_{13}H_{16}N_2OS$	62.87	6.49	11.28
	decom.		(248.34)	62.76	6.51	11.31
2b	81–83	83	$C_{14}H_{18}N_2OS$	64.09	6.91	10.68
	melted		(262.36)	64.13	6.81	10.73
3a	137–139	73	$C_{11}H_{13}N_3S$	60.24	5.97	19.16
	decom.		(219.29)	60.31	5.93	19.21
4a	224–226	67	$C_{11}H_{12}N_2OS$	59.97	5.49	12.72
	decom.		(220.29)	60.02	5.42	12.63
4b	187–188	68	$C_{12}H_{14}N_2OS$	61.51	6.02	11.96
	decom.		(234.31)	61.49	5.98	12.01
5a	231–233	49	$C_{11}H_{13}N_3S$	60.24	5.97	19.16
	decom.		(219.29)	60.19	5.96	19.17
6a	214–216	63	$C_{11}H_{13}N_3OS$	56.15	5.57	17.86
	decom.		(235.29)	56.20	5.48	17.93
6b	271–73	59	$C_{11}H_{13}N_3S_2$	52.56	5.21	16.72
	decom.		(251.35)	52.63	5.81	16.83
7	234–236	63	$C_{11}H_{12}N_2S_3$	49.22	4.51	10.44
	decom.		(268.42)	49.20	4.53	10.39
10	151–153	87	$C_{12}H_{12}N_4S$	58.99	4.95	22.93
	decom.		(244.31)	59.02	4.89	23.01
11	217–219	75	$C_{13}H_{14}N_4S$	60.44	5.46	21.69
	decom.		(258.33)	60.47	5.49	21.61
12	269–271	69	$C_{18}H_{16}N_4S$	67.47	5.03	17.49
	decom.		(320.40)	67.51	4.98	17.47
13a	163–165	81	$C_{16}H_{18}N_4S$	64.40	6.08	18.78
	melted		(298.39)	64.43	6.09	18.84
13b	138–141	73	$C_{16}H_{17}ClN_4S$	57.73	5.15	16.83
	melted		(332.84)	57.81	5.13	16.77
13c	151–153	82	$C_{16}H_{15}F_3N_4S$	54.53	4.29	15.90
	melted		(352.37)	54.61	4.32	15.87
14	206–209	53	$C_{15}H_{16}N_4O_2S$	56.95	5.10	17.71
	decom.		(316.33)	57.07	5.11	17.83
15	273–275	61	$C_{13}H_{12}N_4O_2S$	54.15	4.20	19.43
	decom.		(288.29)	54.18	4.23	19.37

2-Ethoxymethylene amino-3-cyanocyclohepta(b)-thiophene (2a)

A mixture of compound **1** (1.90 g, 10 mmol) and triethyl orthoformate (2.96 g, 20 mmol) was stirred under reflux in acetic anhydride (30 ml) for 6 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml), and neutralized by ammonia solution. The deposited coprecipitate was collected by filtration, washed by water, dried, and crystallized from ethanol in 81% yield, m.p. 115–118°C; ^{1}H NMR ($CDCl_3$) ppm: δ 1.31 (t, 3H, CH_3), 1.60 (m, 4H, 2 CH_2), 1.75 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 3.48 (m, 2H, CH_2), 3.79 (q, 2H, CH_2), 9.18 (s, H, methylenic proton); MS (EI): m/z: 248 (M^+), 249 (MH^+), 234 (MH—CH_3).

2-Ethoxy-2-methylmethylene amino-3-cyanocyclohepta(b)thiophene (2b)

A mixture of compound **1** (1.90 g, 10 mmol) and triethyl orthoacetate (5 ml) was stirred at room temperature for 13 h. The excess solvent was evaporated under reduced pressure. The solid formed was collected and crystallized from cyclohexane in 83% yield, m.p. 81–83°C; ^{1}H NMR ($CDCl_3$) ppm: δ 1.30 (t, 3H, CH_3), 1.70 (m, 4H, 2 CH_2), 1.87 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.75 (m, 2H, CH_2), 4.30 (q, 2H, CH_2); MS (EI): m/z: 261 (M—H), 248 (M—CH_4), 234 (M—C_2H_7).

2-Aminomethylene amino-3-cyanocyclohepta (b)-thiophene (3a)

A mixture of compound **2a** (2.48 g, 10 mmol) and ammonia solution 30–40% (20 ml) was stirred under reflux in methanol (50 ml) for 10 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml), and neutralized by the addition of acetic acid. The deposited coprecipitate was filtered off, washed with water, dried, and crystallized from ethanol in 73% yield, m.p. 137–139°C (dec.), ^{1}H NMR ($CDCl_3$) ppm: δ 1.58 (m, 4H, 2 CH_2), 1.78 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 3.35 (m, 2H, CH_2), 7.40 (s, H, CH), 8.35 (br. s, NH).

1,2-Dihydro-1-oxo-cyclohepta(b)thieno[2,3-d]-pyrimidine (4a)

A mixture of compound **1** (1.90 g, 10 mmol), formic acid (10 ml) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 12 h; the reaction mixture was allowed to cool to room temperature and poured into cold water (100 ml). The formed solid was collected

by filtration, washed by ethanol (20 ml), dried, and crystallized from DMF/ethanol (2:1) in 67% yield, m.p. 224–226°C (lit.,[20] 220–222°C); ^{1}H NMR (DMSO-d_6) ppm: δ 1.60 (m, 4H, 2 CH_2), 1.85 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 3.30 (m, 2H, CH_2), 8.05 (s, H, pyrimidine proton), 12.35 (br. s, NH, exchangeable with D_2O); MS (EI): m/z: 221 (MH^+), 220 (M^+), 205 (MH^+—O).

1,2-Dihydro-3-methyl-1-oxo-cyclohepta(b)thieno-[2,3-d] pyrimidine (4b)

A mixture of compound **1** (1.90 g, 10 mmol) and triethyl orthoacetate (5 ml) was stirred under reflux for 10 h; the reaction mixture was allowed to cool to room temperature and poured into cold water (100 ml). The deposited coprecipitate was collected by filtration, washed by water, dried, and crystallized from DMF/ethanol (2:1) in 68% yield, m.p. 187–188°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.55 (m, 4H, 2 CH_2), 1.75 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.62 (m, 2H, CH_2), 3.35 (m, 2H, CH_2), 11.40 (br. s, NH, exchangeable with D_2O); MS (EI): m/z: 234 (M^+), 220 (MH^+—CH_3).

1,2-Dihydro-1-aminocyclohepta(b)thieno[2,3-d]-pyrimidine (5a)

Method A: To a warmed ethanolic sodium ethoxide solution (0.23 g, 10 mmol sodium metal in 50 ml absolute ethanol), 2.19 g, 10 mmol of compound **3a** was added. The mixture was stirred under reflux for 5 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 ml), and neutralized by the addition of acetic acid. The solid formed was filtered off, dried, and crystallized from DMF in 49% yield, m.p. 231–233°C (dec.).

Method B: A mixture of compound **1** (1.90 g, 10 mmol), formamide (0.45 g, 10 mmol) and formic acid (2 ml) was stirred under reflux in dimethylformamide (20 ml) for 9 h; the reaction mixture was allowed to cool, poured in water (100 ml), and neutralized by ammonia solution. The deposite coprecipitate was collected, washed by water, ethanol, dried, and crystallized from DMF/ethanol (2:1) in 75% yield, m.p. 232–234°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.57 (m, 4H, 2 CH_2), 1.78 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 3.37 (m, 2H, CH_2), 8.08 (S, H, pyrimidine proton).

1-Amino-3-oxo or (thioxo)-3H-cyclohepta(b)-thieno[2,3-d]pyrimidine (6a,b)

General procedure: A mixture of compound **1** (1.90 g, 10 mmol) and urea or thiourea (10 mmol) was heated at 180°C in a test tube on sand

bath for 4 h. The mixture was allowed to cool to room temperature; the product was solidified by cooling and addition of methanol (50 ml). The precipitate formed was collected by filtration and crystallized from the proper solvent to produce **6a**,**b**.

1-Amino-3-oxo-3H-cyclohepta(b)thieno[2,3-d]-pyrimidine (6a)

From compound **1** (1.90 g, 10 mmol) and urea (0.61 g, 10 mmol). The compound was obtained as white crystals, crystallized from dioxane in 63% yield, m.p. 214–216°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.93 (m, 4H, 2 CH_2), 2.85 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.32 (m, 2H, CH_2), 3.89 (br. s, NH), 10.22 (br. s, NH).

1-Amino-3-thioxo-3H-cyclohepta(b)thieno[2,3-d]-pyrimidine (6b)

From compound **1** (1.90 g, 10 mmol) and thiourea (0.77 g, 10 mmol). The compound was obtained as yellow crystals, crystallized from dioxane in 59% yield, m.p. 271–273°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.56 (m, 4H, 2 CH_2), 1.80 (m, 2H, CH_2) 2.75 (m, 2H, CH_2), 3.12 (m, 2H, CH_2), 3.50 (br. s, NH), 3.61 (br. s, NH).

1,3-Dithioxo-1,2,3,4-tetrahydrocyclohepta(b)-thieno[2,3-d]pyrimidine (7)

To a warmed potassium hydroxide solution (prepared by dissolving 0.56 g, 10 mmol of potassium hydroxide in 50 ml ethanol), 1.90 g, 10 mmol of compound **1** was added and excess carbon disulfide (10 ml). The mixture was heated on water bath at 80°C under reflux for 10 h, then allowed to cool to room temperature, poured into cold water (100 ml), and neutralized with diluted acetic acid. The deposited coprecipitate was collected by filtration, washed with water, dried and crystallized from DMF/ethanol (2:1) in 63% yield, m.p. 234–236°C (dec.); ^{1}H NMR (DMSO-d_6) ppm: δ 1.55 (m, 4H, 2 CH_2), 1.77 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 3.60 (m, 2H, CH_2), 13.22 (br. s, NH, exchangeable with D_2O), 13.90 (br. S, NH, exchangeable with D_2O).

1-Chloro cyclohepta(b)thieno[2,3-d]pyrimidine (9)

A solution of compound **4a** (2.20 g, 10 mmol) in dry dioxane (30 ml) was treated with phosphorus oxychloride (7 ml) and the mixture was stirred under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and poured into ice-water (200 g), whereby a solid was

separated, filtered off, and crystallized from petroleum ether in 71% yield, m.p. 68–71°C (dec.) (lit.,[20] 65–67°C).

1-Hydrazino cyclohepta(b)thieno[2,3-d]pyrimidine (8)

Method A: A mixture of compound **2a** (2.45 g, 10 mmol) and hydrazine hydrate 80% (7.5 ml) in ethanol (50 ml) was heated at 50°C for 3 h. The reaction mixture was allowed to cool to room temperature. The deposited so-precipitate was filtered off and crystallized from dioxane in 83% yield, m.p. 195–197°C (dec.) (lit.,[20] 193–194°C).
Method B: A mixture of compound **9** (2.38 g, 10 mmol) and hydrazine hydrate 80% (7.5 ml) was stirred under reflux in dry dioxane (30 ml) for 5 h. The reaction mixture was allowed to cool to 0°C for 5 h. The solid was collected by filtration and crystallized from dioxane/ethanol (2:1) in 79% yield, as same as that of which produced by Method A. ^{1}H NMR (DMSO-d_6) ppm: δ 1.62 (m, 4H, 2 CH_2), 1.82 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 4.51 (br. s, 2H, NH_2, exchangeable with D_2O), 7.31 (s, H, pyrimidine proton), 8.70 (br. s, NH, exchangeable with D_2O); MS (EI): m/z: 234 (M^+), 221 (MH^+—NH_2).

3H-Cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazole (10)

A mixture of compound **8** (2.34 g, 10 mmol), formic acid (10 ml), and a catalytic amount of concentrated hydrochloric acid was heated under reflux for 7 h. The reaction mixture was allowed to cool to room temperature and poured into water (200 ml). The precipitate that was formed was collected by filtration, washed with ethanol (50 ml), dried, and crystallized from dioxane/ethanol (2:1) in 87% yield, m.p. 151–153°C (dec.) (lit.,[20] 153°C); ^{1}H NMR (DMSO-d_6) ppm: δ 1.89 (m, 4H, 2 CH_2), 2.78 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.72 (m, 2H, CH_2), 8.37 (s, H, triazole proton), 8.39 (s, H, pyrimidine proton).

3-Methyl-cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazole (11)

A mixture of compound **8** (2.34 g, 10 mmol), glacial acetic acid (30 ml), was heated under reflux for 15 h; the reaction mixture was allowed to cool to room temperature and poured into water (200 ml). The solid so-formed was collected by filtration, dried, and crystallized from acetic acid in 75% yield, m.p. 217–219°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.91 (m, 4H, 2 CH_2), 2.86 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 8.41 (s, H, pyrimidine proton).

3-Phenyl-cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazole (12)

A mixture of compound **8** (2.34 g, 10 mmol), benzoyl chloride (30 ml), was stirred under reflux for 8 h. The reaction mixture was allowed to cool to room temperature and poured into water (200 ml). The solid formed was filtered off, dried, and crystallized from dioxane/ethanol (2:1) in 69% yield, m.p. 269–271°C (dec.); ^{1}H NMR (DMSO-d_6) ppm: δ 1.60 (m, 4H, 2CH_2), 1.80 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 7.40–7.63 (m, 5H, phenyl protons), 7.95 (s, H, pyrimidine proton); MS (EI): *m/z*: 320 (M^+), 243 (M^+—C_6H_5).

1-(3,5-Dimethyl-4-(un)substituted-1H-pyrazol-1-yl)-cyclohepta(b)thieno-[2,3-d]pyrimidine (13a–c)

General procedure: A mixture of compound **8** (2.34 g, 10 mmol) and β-diketone (10 mmol) in absolute ethanol (30 ml) was stirred under reflux for 5 h. The reaction mixture was allowed to cool to 0°C for 3 h. The deposited coprecipitate was filtered off, dried, and crystallized from appropriate solvent to produce **13a–c** in high yield.

1-(3,5-Dimethyl-4H-pyrazol-1-yl)cyclohepta(b)-thieno[2,3-d]pyrimidine (13a)

From compound **8** (2.34 g, 10 mmol) and pentan-2,4-dione (1.00 g, 10 mmol). The compound was obtained as colorless crystals, crystallized from dioxane in 81% yield, m.p. 163–165°C; IR: ^{1}H NMR ($CDCl_3$) ppm: δ 1.86 (m, 4H, 2 CH_2), 1.95 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.68 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 6.01 (s, H, pyrazole proton), 8.73 (s, H, pyrimidine proton).

1-(3,5-Dimethyl-4-chloropyrazol-1-yl)-cyclohepta(b)thieno[2,3-d]pyrimidine (13b)

From compound **8** (2.34 g, 10 mmol) and 3-chloro-2,4-pentandione (1.34 g, 10 mmol). The compound was obtained as white crystals, crystallized from dioxane/ethanol (1:1) in 73% yield, m.p. 138–141°C; ^{1}H NMR ($CDCl_3$) ppm: δ 1.83 (m, 4H, 2 CH_2), 1.85 (m, 2H, CH_2), 2.11 (s, 3H, CH_3), 2.72 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 3.55 (s, 3H, CH_3), 8.32 (s, H, pyrimidine proton).

1-(3-Methyl-4H-trifluromethylpyrazol-1-yl)-cyclohepta(b)thieno[2,3-d]pyrimidine (13c)

From compound **8** (2.34 g, 10 mmol) and 1,1,1-trifluro-2,4-pentandione (1.54 g, 10 mmol). The compound was obtained as colorless crystals,

crystallized from ethanol in 82% yield, m.p. 151–153°C; ^{1}H NMR ($CDCl_3$) ppm: δ 1.83 (m, 4H, 2 CH_2), 1.85 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.66 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 5.99 (s, H, pyrazolo proton), 8.39 (s, H, pyrimidine proton).

3-Ethyl-(cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazole)carboxylate (14)

A mixture of compound **8** (2.34 g, 10 mmol), diethyloxalate (10 ml) was heated under reflux for 18 h. The reaction mixture was allowed was to cool to room temperature and poured into cold water (100 ml). The solid formed was filtered off, dried, and crystallized from ethanol (50 ml) in 53% yield, m.p. 206–209°C; ^{1}H NMR (DMSO-d_6) ppm: δ 1.20 (t, 3H, CH_3), 1.88 (m, 4H, 2CH_2), 1.92 (m, 2H, CH_2), 2.29 (m, 2H, CH_2), 3.19 (m, 2H, CH_2), 4.18 (q, 2H, CH_2), 7.78 (s, H, pyrimidine proton).

3-(cyclohepta(b)thieno[2,3-d]pyrimido[3,4-a]-1,2,4-triazole) Carboxylicacid (15)

A stirred suspension of compound **13** (2.88 g, 10 mmol) in 5% of sodium hydroxide (3 ml) was stirred under reflux for 45 min. The cold mixture was acidified to pH 5–6 with dilute hydrochloric acid and the white precipitate was filtered off, washed with water, dried, and crystallized from dioxane/ethanol (1:1) in 61% yield, m.p. 273–275°C (dec.); ^{1}H NMR (DMSO-d_6) ppm: δ 1.91 (m, 4H, 2CH_2), 2.78 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 3.56 (m, 2H, CH_2), 8.37 (s, H, pyrimidine proton), 10.23 (br. s, OH); MS (EI): m/z: 289 (MH^+), 243 (MH^+—COOH).

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