Synthesis and biological activity of new functionalised cyclohepta[4,5]-thieno[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidin-5-ones

Ahmad S. Shawali[a]*, Nasser A. H. Ali[b], Ahmed S. Ali[b] and Dalia A. Osman[b]

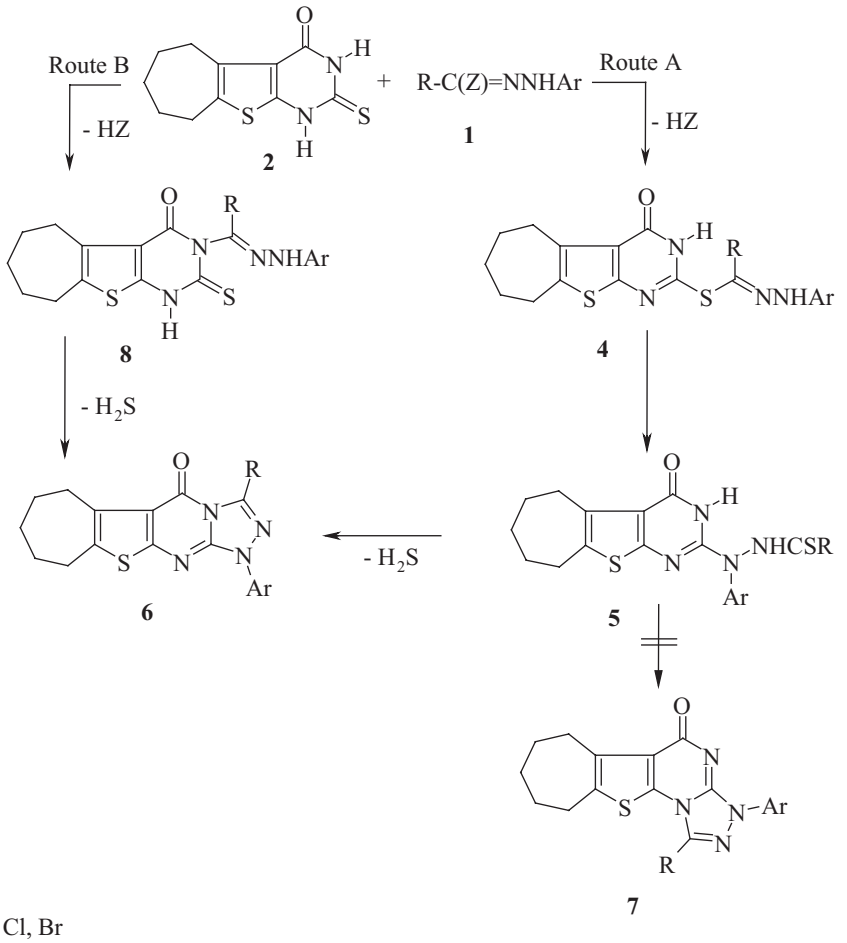
[a]*Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt*

[b]*Department of Photochemistry, National Research Centre, Dokki, Giza, Egypt*

Various functionalised derivatives of 5*H*-cyclohepta[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one were synthesised *via* reaction of hydrazonoyl halides (**1**) with either 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta-[4,5]thieno[2,3-*d*]pyrimidin-4-one (**2**) or its methylthio derivative (**3**). The mechanism and the regioselectivity of the studied reactions are investigated and discussed.

Keywords: hydrazonoyl halides, fused thiophenes, pyrimidines, 1,2,4-triazoles, thiohydrazonates

For a long time our research group has been interested in the chemistry of hydrazonoyl halides (**1**) with the aim of exploring their utility as precursors in the synthesis of various functionalised monoheterocylic and annelated heterocyclic derivatives and elucidating their regio-, site- and peri-selectivities.[1-5] As part of this work, we here report a new synthetic strategy for the preparation of functionalised cycloh epta[4,5]thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidin-5-ones (**6**) *via* reactions of hydrazonoyl halides (**1**) with 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*] pyrimidin-4-one (**2**) and its 2-methylthio derivative (**3**). The study was carried out with the following objectives in mind. On the one hand, it was thought interesting to elucidate the regiochemistry of the reactions of **1** with **2** as such reactions can lead to **6** and/or **7** (Scheme 1), and on the other, we wished to examine the biological activity of the products.



Z= Cl, Br

1,4-7: R/X: **a**, CH_3CO / H; **b**, CH_3CO / 4-Me; **c**, CH_3CO / 4-Cl; **d**, CH_3CO / 4-NO_2; **e**, EtOCO / H; **f**, EtOCO / 4-Me; **g**, EtOCO / 4-Cl; h, EtOCO / 4-NO_2; **i**, PhNHCO / H; **j**, PhNHCO / 4-Me; **k**, PhNHCO / 4-Cl; l, PhNHCO / 4-NO_2; **m**, PhCO / H; **n**, PhCO / 4-NO_2; **o**, Ph / H.

Scheme 1 Synthesis of 3-substituted 1-aryl-1,6,7,8,9,10-hexahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*] pyrimidin-5-ones (**6**).

* Correspondent. E-mail: as_shawali@mail.com

This is because many thieno[2,3-*d*]pyrimidines (purine analogues) have been reported to exhibit various biological,[6-10] bactericidal[11] and medicinal[12,13] activities. Also, various derivatives of 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one have been reported to be useful as calcium channel blocking vasodilators; some have antihypertensive,[14] cardiovascular[15,16] and anxiolytic activities[17] and others are used as components in photographic materials.[18]

Results and discussion

The hydrazonoyl halides **1**[19] and 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one **2**[20] and its 2-methylthio derivative **3**[21] were prepared by literature methods. Reaction of **2** with each of **1** in refluxing ethanol in the presence of sodium ethoxide gave, in each case, one isolable product as evidenced by tlc analysis of the crude product. This finding indicates that the studied reaction is regioselective. On the basis of elemental analyses and IR, ^{1}H and ^{13}C NMR spectra which showed all the expected signals (see Experimental), the isolated products were assigned structures of 3-substituted 1-aryl-1,6,7,8,9,10-hexahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones (**6**) rather than the isomeric 1-substituted 3-aryl-7,8,9,10-tetrahydro-6*H*-cyclohepta[4,5]thieno[2,3-*d*]-1,2,4]triazolo[4,3-*b*]pyrimidin-5(3*H*)-ones (**7**) (Scheme 1).

The assigned structure of compounds **6** was confirmed by an alternative synthesis and by X-ray crystallography. Thus, treatment of the 2-methylthio derivative **3** with each of the hydrazonoyl halides **1** in ethanol in the presence of sodium ethoxide under reflux, yielded products that proved identical in all respects (m.p., mixed m.p., IR and ^{1}H and ^{13}C NMR spectra) with those obtained from **1** and **2** (Scheme 2).

The ORTEP drawing of product **6e**, taken as a representative example of the series prepared, is shown in Fig. 1.[22] As shown, the crystal of compound **6e** is triclinic with four molecules per unit cell. The seven-membered ring is puckered, in a chair-like form, as expected. The study indicates that the structure of the products isolated from the reactions of **1** with **2** is **6** and not **7**. This finding indicates that such reactions are regioselective.

Formation of compounds **6** from **1** and **2** could be accounted for by one of the two pathways indicated in Scheme 1. It is suggested that, as depicted, the studied reactions start with the hydrazonoylation of **2** to give the respective thiohydrazonate esters **4**. This is followed by Smiles-type rearrangement[23] of the latter esters to form the respective thiohydrazides **5**, which in turn undergo cyclisation to give **6** as end products (Route A, Scheme 1). All attempts to isolate these proposed intermediates failed under the conditions employed. However, by varying the reaction conditions, we succeeded in isolation of the intermediates **4**. For example, when **2** was treated with each of **1a**, **1e**, **1i** and **1o** in ethanol in the presence of triethylamine at room temperature, it gave the respective **4a, 4e, 4i** and **4o**. The structures of these esters were established on the basis of their microanalyses and spectra (IR, MS and ^{1}H NMR) (see Experimental) and their conversion into the corresponding **6a,e,i,o** on refluxing each in ethanolic sodium ethoxide. Alternatively, the formation of **6** from **1** and **2** involves the initial formation of the amidrazones **8** as intermediates which in turn undergo cyclisation to give **6** as end products (Route B, Scheme 1). This latter alternative pathway is contra-indicated, however, since alkylation and acylation of 2-thiouracil derivatives are known to give *S*-alkyl and *S*-acyl derivatives, respectively.[24]

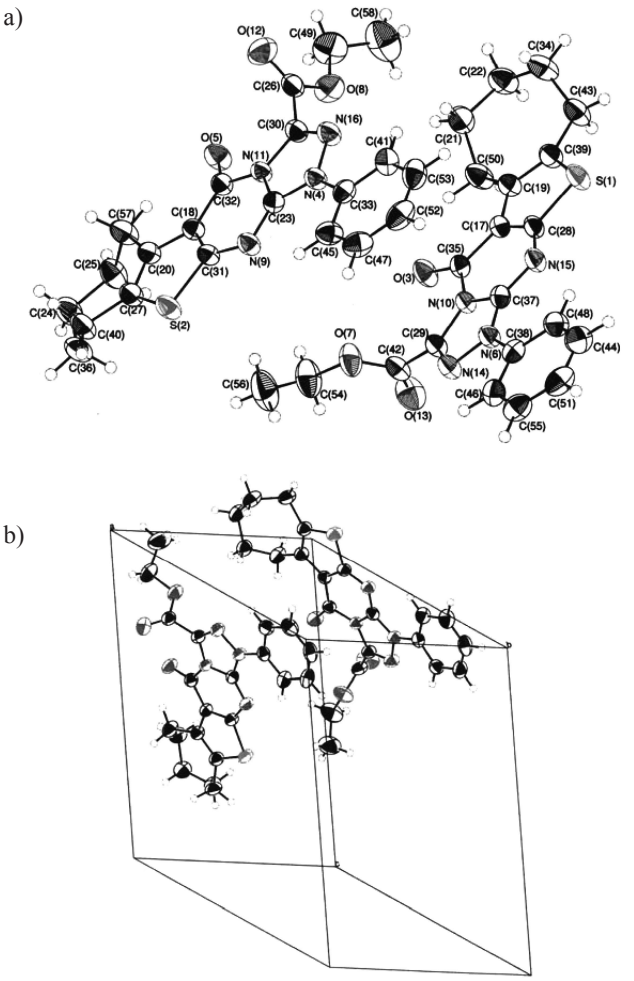
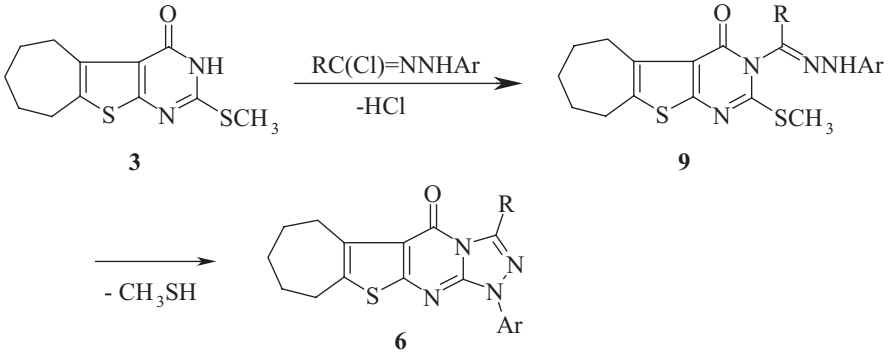
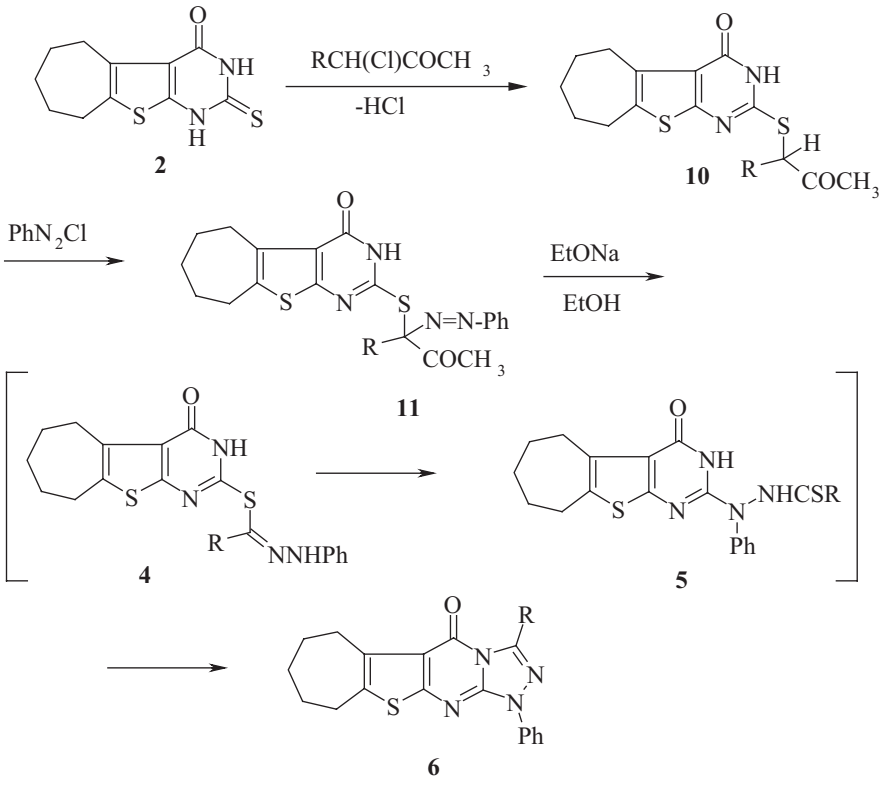


Fig. 1 **a**, Crystal structure of **6e**; the crystallographic numbering does not represent the systematic numbering. **b**, Arrangement of molecules of **6e** in the unit cell.



Scheme 2 Reaction of compounds **1** and **3**.



4-11: R :**a**, CH_3CO; **e**, EtOCO; **i**, PhNHCO

Scheme 3 Alternative synthesis of **6**.

The involvement of **4** and **5** as intermediates in the formation of **6** was further evidenced by alternative synthesis of **8a, 6e** and **8i** (Scheme 3). Thus, treatment of **2** with each of 3-chloro-2,4-pentanedione, ethyl 2-chloro-3-oxobutanoate and *N*-phenyl 2-chloro-3-oxobutanamide in ethanol in the presence of sodium ethoxide afforded the respective substituted products **10a,e,i**. Coupling of these last with benzenediazonium chloride in ethanol in the presence of sodium acetate yielded the coupling product **11a,e,i** (Scheme 3).

Treatment of compounds **11** with sodium ethoxide in refluxing ethanol, in an attempt to effect Japp-Klingemann cleavage[25] of the acetyl group to give the respective thiohydrazonate **4a,e,i**, was found to give the corresponding **6a,e,i** directly as end product (Scheme 3). This finding substantiates our previous suggestion that **4** and **5** are intermediates in the studied reactions and they are consumed *in situ* as soon as they are formed.

Finally, our finding that the site of cyclisation of the thiohydrazide intermediates **5** involves N-3 to give **6** and not N-1 to form **7** is consistent with literature data. For example, it has been reported that cyclisation of 2-substituted-uracil derivatives having no substituent at N-3 proceeds regio-selectively to give the respective 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones.[26]

The compounds **6** were tested for their antimicrobial activities against two fungal species, namely *Aspergillus niger* and *Candida albicans*, as well as two bacterial species, *Bacillus subtilis* and *Escherichia coli*. Techniques and results will be reported elsewhere.

Experimental

Melting points were determined on an Electrothermal apparatus. IR spectra were recorded in potassium bromide using a PU 9712 spectrophotometer. EI Mass spectra were recorded at 75 eV using a Kratos spectrometer. X-ray was recorded using a single-crystal diffractometer Kappa CCD 590 Enraf Nonius; all diagrams and calculations were performed using maXus (Bruker Nonius, Delft MacScience, Japan). Elemental analyses were carried out at the Microanalytical Laboratory. All of the above data were recorded in National Research Centre, Giza, Egypt. ^1H and ^{13}C NMR spectra were recorded in the appropriate deuterated solvents using a Varian Gemini 300 MHz apparatus in Cairo University, Giza, Egypt and some were recorded using a Varian 500 MHz apparatus in Konstanz University, Germany.

The hydrazonoyl halides **1**[19] and 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one **2**[20] and its 2-methylthio derivative **3**[21] were prepared by literature methods.

The crystallographic study of **6e** was undertaken to establish its three-dimensional structure. Geometries are tabulated below.[22]

Crystal data

Chemical formula $C_{21}H_{20}N_4O_3S$, $M_w = 408.480$ $D_x = 1.407$ Mgm^{-3}
Symmetry cell setting 'Triclinic', Symmetry space group name H-M 'P -1

Cell length	Cell angle
a 11.8403(3) Å	Alpha (α) 62.034(2)°
b 13.1388(4) Å	Beta (β) 90.087(2)°
c 14.0316(4) Å	Gamma (γ) 89.9677(12)°
Cell volume	1927.95(9) Å3
Cell formula units	Z = 4

Preparation of compounds **4**

To a stirred solution of equimolar quantities of the appropriate hydrazonoyl halide **1** and 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one (**2**) (10 mmole each) in absolute ethanol (30 ml) and few drops of DMF, triethylamine was added (1.4 ml, 10 mmole). The mixture was stirred for 45 min at room temperature, and then poured into cold water. The precipitate formed was filtered off and washed with cold ethanol and finally crystallised from chloroform-petroleum ether (60–80 ºC) mixture to give the corresponding thiohydrazonate **4a, 4e, 4i** and **4o**.

S-(4,5,6,7,8,9-Hexahydro-4-oxo-3H-cyclohepta[4,5]thieno[2,3-d] pyrimidin-2-yl) N-phenyl-2-oxopropanethiohydrazonate (**4a**): Pale

yellow solid (0.28 g, 68 %), m.p. 165–167 ºC. IR: ν_{max} 3237, 3075, 2917, 2842, 1716, 1676 cm^{-1}. MS: *m/z* (%) 412 (M^+, 100), 413 (M^+ + 1, 65), 414 (M^+ + 2, 22), 252 (23), 91 (30), 77 (21), 64 (21). ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 4H, $2CH_2$), 1.85 (q, 2H, CH_2), 2.49 (s, 3H, CH_3) 2.84 (t, 2H, CH_2), 3.23 (t, 2H, CH_2), 7.24–7.75 (m, 5H, Ar–H), 8.50 (s, 1H, NH), 11.13 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{20}N_4O_2S_2$ (412.5): C, 58.23; H, 4.89; N, 13.58; S, 15.54. Found: C, 58.45; H, 4.75; N, 13.43; S, 15.50 %.

S-(4,5,6,7,8,9-Hexahydro-4-oxo-3H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl N-phenyl-2-ethoxycarbonylmethanethiohydrazonate (**4e**): Pale buff powder (0.27 g, 63 %), m.p. 174–175 ºC. IR: ν_{max} 3385, 2976, 2919, 2846, 1749, 1700 cm^{-1}. MS: *m/z* (%) 442 (M^+, 20), 443 (M^+ + 1, 12), 273 (44), 275 (19.5), 237 (31), 252 (14), 135 (100), 119 (83), 91 (88), 77 (85). ^{1}H NMR ($CDCl_3$): δ 1.45 (t, 3H, CH_3), 1.60 (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 4.45 (q, 2H, CH_2), 7.40 (m, 5H, Ar–H), 12.23 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{18}N_2O_3S_2$ (442): C, 56.99; H, 5.01; N, 12.66; S, 14.49. Found: C, 57.11; H, 5.00; N, 12.53; S, 14.30 %.

S-(4,5,6,7,8,9-Hexahydro-4-oxo-3H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl) N-phenyl-2-oxo-2-phenyl aminoethane thiohydrazonate (**4i**): Buff powder (0.29 g, 61 %), m.p. 156–157 °C. IR: ν_{max} 3216, 3060, 2939, 1715, 1645 cm^{-1}. MS: *m/z* (%) 489 (M^+, 13), 252 (14), 91 (73), 77 (70). ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 4H, $2CH_2$), 1.92 (q, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.21 (t, 2H, CH_2), 7.00–7.70 (m, 10H, 2Ar–H), 8.25 (s, 1H, NH), 9.75 (s, 1H, NH), 11.9 (br, 1H, NH). Anal. Calcd. for $C_{25}H_{23}N_5O_2S_2$ (489.6): C, 61.33; H, 4.73; N, 14.30; S, 13.10. Found: C, 60.93; H, 4.57; N, 14.00; S, 12.86 %.

S-(4,5,6,7,8,9-Hexahydro-4-oxo-3H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl) N-phenyl-benzenecarbthiohydrazonate (**4o**): Buff powder (0.3 g, 69 %), m.p. 147–148 °C. IR: ν_{max} 3222, 3160, 2939, 1685 cm^{-1}. MS: *m/z* (%) 445 (M^+, 100), 63 (31), 118 (21.6), 164 (23.2), 206 (25), 311 (23), 326 (50), 371 (27). ^{1}H NMR ($CDCl_3$): δ 1.66 (m, 4H, $2CH_2$), 1.88 (q, 2H, CH_2), 2.82 (t, 2H, CH_2), 3.23 (t, 2H, CH_2), 7.41–7.85 (m, 10H, 2Ar–H), 12.40 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{22}N_4OS_2$ (446.60): C, 64.55; H, 4.97; N, 12.55; S, 14.36. Found: C, 64.95; H, 4.80; N, 12.33; S, 14.3 %.

Preparation of compounds **10**

To 3-chloro-2,4-pentanedione (10 mmole) and 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one **2** (10 mmole) in absolute ethanol was added triethylamine (1.4 ml, 10 mmole). The mixture was stirred for 3–5 h at room temperature. The solvent was then distilled off under reduced pressure in a rotatory evaporator, the residue left was treated with methanol and left in refrigerator for 2 h where a solid formed. This was filtered off and crystallised from EtOH/dioxan mixture to give **10a**. Repetition of the above procedure using ethyl 2-chloroacetoacetate and 2-chloroacetoacetanilide in place of 3-chloro-2,4-pentanedione yielded **10e** and **10i**, respectively.

3-[(4,6,7,8,9,10-Hexahydro-4-oxo-3H-cyclohepta[4,5]thieno-[2,3-d]pyrimidin-2-yl)thio]pentane-2,4-dione (**10a**): White powder (0.3 g, 91 %), m.p. 238–239 °C. IR: ν_{max} 3446, 2922, 2848, 1660 cm^{-1}. MS: *m/z* (%) 350 (M^+, 90), 351.1 (M^+ + 1, 27), 352.1 (M^+ + 2, 12), 308.1 (28), 291.1 (35), 265 (100), 250 (27), 193.1 (40), 91 (20). ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.91 (q, 2H, CH_2), 2.35, s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.83 (t, 2H, CH_2), 3.29 (t, 2H, CH_2), 9.15 (br, 1H, NH). Anal. Calcd. for $C_{16}H_{18}N_2O_3S_2$ (350): C, 54.83; H, 5.17; N, 7.99; S, 18.30. Found: C, 54.90; H, 5.00; N, 7.90; S, 18.00 %.

Ethyl 3-[(3,5,6,7,8,9-hexahydro-4-oxocyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl)thio]butanoate (**10e**): White powder (0.34 g, 91 %), m.p. 259–260 °C (EtOH/dioxan). IR: ν_{max} 3418, 2921, 1649, 1587 cm^{-1}. MS: *m/z* (%) 380 (M^+, 100), 381.1 (M^+ + 1, 27), 382.1 (M^+ + 2, 12), 334 (72), 292 (40), 265 (52), 251 (20). ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.90 (q, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.80 (t, 2H, CH_2), 3.26 (t, 2H, CH_2), 4.25 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 6.53 (s, 1H, CH), 9.23 (br, 1H, NH), 14.10 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{20}N_2O_4S_2$ (380): C, 53.67; H, 5.30; N, 7.36; S, 16.85. Found: C, 53.71; H, 4.89; N, 7.22; S, 16.80 %.

N-Phenyl 3-oxo-2-[(3,5,6,7,8,9-hexahydro-4-oxocyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl)thio]butanamide (**10i**): Pale yellow powder (0.38 g, 90 %), m.p. 179–180 °C (EtOH/dioxan). IR: ν_{max} 3248, 2847, 1645, 1536 cm^{-1}. MS: *m/z* (%) 427.2 (M^+, 14), 428.2 (M^+ + 1, 4.3), 429.2 (M^+ + 2, 1.9), 334.1 (90), 306.1 (28), 93 (100), 65 (33). ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.88 (q, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.83 (t, 2H, CH_2), 3.26 (t, 2H, CH_2), 5.00 (s, 1H, CH), 7.17–7.58 (m, 5H, Ar–H), 7.95 (s, 1H, NH), 8.44 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{21}N_3O_3S_2$ (427.55): C, 59.00; H, 4.95; N, 9.83; S, 15.00. Found: C, 59.12; H, 4.80; N, 9.8; S, 15.01 %.

Preparation of compounds **11e** *and* **11i**

To **10e** (10 mmole) in EtOH (50 ml) was added sodium acetate trihydrate (3 g), and the mixture was stirred and cooled in an ice bath (0–5 °C). To the resulting solution was added portionwise a cold solution of benzenediazonium chloride, prepared from aniline (10 mmole) in hydrochloric acid (6 ml, 6M) and sodium nitrite (0.7 g, 10 mmole) in water (3 ml). After the addition was complete the reaction mixture was stirred for 1 h while cooling in ice bath and left overnight in the refrigerator. The solid that precipitated was filtered off, washed with water, air-dried and crystallised from ethanol/dioxan to give the arylazo derivative **11e**.

Repetition of the above procedure using **10i** in place of **10e** yielded the product **11i**. However, when the above procedure was repeated using **10a** in lieu of **10e** or **10i**, work up of the reaction mixture gave **6a** directly.

Ethyl 2-(phenylazo)-3-oxo-2-[(3,5,6,7,8,9-hexahydro-4-oxocyclohepta-[4,5]thieno[2,3-d]pyrimidin-2-yl)thio]butanoate (**11e**): Pale yellow powder (0.35 g, 74 %), m.p. 239–240 °C. IR: ν_{max} 3420, 2923, 1659, 1590 cm^{-1}. MS: *m/z* (%) 485 (M^+, 0.05), 326 (24), 325 (100), 268 (16), 256 (28), 243 (37), 216 (45). ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.89 (q, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.82 (t, 2H, CH_2), 3.28 (t, 2H, CH_2), 4.25 (t, 3H, CH_3), 4.32 (q, 2H, CH_2), 7.88 (m, 5H, Ar–H), 9.18 (br, 1H, NH), 14.10 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{24}N_4O_4S_2$ (484.59): C, 57.01; H, 4.99; N, 11.56; S, 13.23. Found: C, 57.23; H, 4.87; N, 11.48; S, 13.22 %.

N-Phenyl 3-oxo-2-[(3,5,6,7,8,9-hexahydro-4-oxocyclohepta[4,5]thieno[2,3-d]pyrimidin-2-yl)thio]-2-(phenylazo)butanamide (**11i**): Pale yellow powder (0.47 g, 90 %), m.p. 200–201 °C (EtOH/dioxan). IR: ν_{max} 3252, 2921, 2849, 1652, 1597, 1537 cm^{-1}. MS: *m/z* (%) 529.5 (M^+, 19.5), 93.1 (100), 77 (23), 66.1 (27). ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 4H, $2CH_2$), 1.87 (q, 2H, CH_2), 2.07 (s, 3H, CH_3), 2.80 (t, 2H, CH_2), 3.25 (t, 2H, CH_2), 7.55 (m, 10H, Ar–H). Anal. Calcd. for $C_{27}H_{25}N_5O_3S_2$ (531.66): C, 61.00; H, 4.74; N, 13.17; S, 12.06. Found: C, 61.17; H, 4.80; N, 13.11; S, 12.00 %.

Synthesis of compounds **6a–o**

Method A: To a stirred ethanolic sodium ethoxide solution, prepared by dissolving sodium metal (0.046 g, 0.002 mol) in absolute ethanol (30 ml), was added 1,2,3,5,6,7,8,9-octahydro-2-thioxo-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one (**2**) (0.504 g, 0.002 mol) and stirred until complete dissolution. To the resulting mixture was added the appropriate hydrazonoyl halide **1** (0.002 mol) portionwise. After complete addition, the reaction mixture was refluxed until hydrogen sulfide ceased to be evolved. The reaction mixture was then evaporated in a rotatory evaporator and the residue was treated with methanol. The solid that precipitated was filtered, washed with water and dried and finally crystallised from ethanol–dioxan to give the respective cyclohepta[4,5]thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidin-5-one derivatives **6a–o**.

Method B: To a stirred ethanolic sodium ethoxide, prepared from sodium metal (0.23 g, 10 mmole) and absolute ethanol (20 ml), was added 2-methylthio-3,5,6,7,8,9-hexahydro-4*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-one (**3**) (2.66 g, 10 mmole). To the resulting solution was added each of the hydrazonoyl halides **1a** and **1o** (2.3 g, 10 mmole) portionwise while stirring the mixture, after the addition was complete, the reaction mixture was refluxed for 2 h, then cooled. The solid that precipitated was filtered off, washed, air dried and finally crystallised from ethanol/dioxan mixture to give the respective triazolopyrimidine **6a** and **6o** in 80–85 % yield.

Method C: To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 0.01 mol) and absolute ethanol (20 ml), was added the appropriate arylazo derivative **11e** or **11i** and the mixture was refluxed with stirring until hydrogen sulfide ceased to evolve (2 h). The mixture was then cooled and poured into water. The precipitated solid was filtered off, washed with water and air-dried. Crystallisation from ethanol–dioxan gave the respective products **6e** and **6i** which proved identical in all respects with those obtained by method A.

Method D: To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 0.01 mol) and absolute ethanol (20 ml), was added the appropriate thiohydrazonate ester **4** and the mixture was refluxed with stirring until hydrogen sulfide ceased to be evolved (1 h). The mixture was then cooled and poured onto water. The precipitate was filtered off, washed with water and air-dried. Crystallisation from ethanol–dioxan gave the respective products **6** which proved identical in all respects with those obtained by method A.

3-Acetyl-1-phenyl-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6a**): Pale yellow crystals (0.29 g, 78 %), m.p. 208–209 °C. IR: ν_{max} 2915, 2846, 1720, 1693 cm^{-1}. MS: *m/z* (%) 378.1 (M^+, 100), 379 (M^++1, 26), 380 (M^++2, 10), 77.1 (24); ^{1}H NMR (DMSO-d_6): δ 1.66 (m, 4H, $2CH_2$), 1.85 (q, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.24 (t, 2H, CH_2), 2.55 (s, 3H, $COCH_3$), 7.41–8.09 (m, 5H, Ar–H); ^{13}C NMR (DMSO-d_6) δ ppm: 26.7, 27.3, 27.5, 28.9, 29.9, 31.4, 114.8, 120.7, 127.4, 129.3, 132.7, 135.4, 136.5, 141.6, 145.4, 151.8, 164.5. Anal. Calcd. for $C_{20}H_{18}N_4O_2S$ (378.1): C, 63.47; H, 4.79; N, 14.80; S, 8.47. Found: C, 63.61; H, 4.67; N, 14.77; S, 8.47 %.

3-Acetyl-1-p-tolyl-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6b**): Pale yellow crystals (0.31 g, 80 %), m.p. 202–203 °C. IR: ν_{max} 2917, 2846, 1727, 1689 cm^{-1}. MS: *m/z* (%) 392.1 (M^+, 100), 393 (M^+ + 1, 24), 394 (M^+ + 2, 8), 364.1 (32), 350.1 (20), 91.1 (26); ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.85 (q, 2H, CH_2), 2.78 (t, 2H, CH_2), 3.29 (t, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.70 (s, 3H, $COCH_3$), 7.26–8.03 (dd, 4H, *p*-Ar–H). ^{13}C NMR ($CDCl_3$): δ: 21.1, 27.2, 27.7, 27.9, 29.8, 32.5, 67.1, 115.5, 120.5, 129.9, 134.1, 136.3, 137.6, 141.3, 144.9, 152.1, 164.7, 186.7. Anal. Calcd. for $C_{21}H_{20}N_4O_2S$ (392.1): C, 64.27; H, 5.14; N, 14.27; S, 8.17. Found: C, 64.34; H, 5.11; N, 14.00; S, 8.20 %.

3-Acetyl-1-(p-chlorophenyl)-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6c**): Pale yellow crystals (0.28 g, 70 %), m.p. 187–188 °C. IR: ν_{max} 2921, 2848, 1729, 1698 cm^{-1}. MS: m/z (%) 412.1 (M^+, 100), 413.1 (M^+ + 1, 28), 414.1 (M^+ + 2, 36), 370.1 (40). ^{1}H NMR ($CDCl_3$): δ 1.62 (m, 4H, $2CH_2$), 1.89 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.25 (t, 2H, CH_2), 2.54 (s, 3H, CH_3), 7.36–8.27 (m, 4H, p-Cl-Ar–H). Anal. Calcd. for $C_{20}H_{17}ClN_4O_2S$ (412): C, 58.18; H, 4.15; Cl, 8.59; N, 13.57; S, 7.77. Found: C, 58.01; H, 4.40; Cl, 8.50; N, 13.49; S, 7.74 %.

3-Acetyl-1-(p-nitrophenyl)-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6d**): Yellow crystals (0.30 g, 73 %), m.p. 170–171 °C. IR: ν_{max} 2919, 2846, 1707, 1677 cm^{-1}. MS: *m/z* (%) 423 (M^+, 100), 424 (M^+ + 1, 22), 425 (M^+ + 2, 6), 394.9 (14), 380.9 (64); ^{1}H NMR (DMSO-d_6): δ 1.63 (m, 4H, $2CH_2$), 1.85 (q, 2H, CH_2), 2.78 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 2.75 (s, 3H, CH_3), 7.77–8.23 (dd, 4H, Ar–H). Anal. Calcd. for $C_{20}H_{17}N_5O_4S$ (423.4): C, 56.73; H, 4.05; N, 16.54; S, 7.57. Found: C, 56.77; H, 4.04; N, 16.42; S, 7.51 %.

Ethyl 5-oxo-1-phenyl-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (**6e**): White crystals (0.31 g, 78 %), m.p. 183–185 °C. IR: ν_{max} 2977, 2846, 1751, 1700 cm^{-1}. MS: *m/z* (%) 408.1 (M^+, 100), 409.1 (M^+ + 1, 26.4), 410.1 (M^+ + 2, 8.3), 380.1 (9.59), 336.1 (7.4), 91.1 (24.9), 77.1 (34.82). ^{1}H NMR ($CDCl_3$): δ 1.55 (t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 1.90 (m, 2H, CH_2), 2.81 (t, 2H, CH_2), 3.28 (t, 2H, CH_2), 4.59 (q, 2H, CH_2), 7.25–8.20 (m, 5H, Ar–H). Anal. Calcd. for $C_{21}H_{20}N_4O_3S$ (408.1): C, 61.75; H, 4.94; N, 13.72; S, 7.85. Found: C, 61.66; H, 5.00; N, 13.81; S, 7.79 %.

Ethyl 5-oxo-1-p-tolyl-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (**6f**): White crystals (0.33 g, 80 %), m.p. 199–200 °C. IR: ν_{max} 2984, 2927, 2849, 1758, 1701 cm^{-1}. MS: m/z (%) 422.1 (M^+, 100), 423.1 (M^+ + 1, 26), 424.1 (M^+ + 2, 8). ^{1}H NMR ($CDCl_3$): δ 1.50(t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 1.89 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.79 (t, 2H, CH_2), 3.30 (t, 2H, CH_2), 4.59 (q, 2H, CH_2), 7.26–8.01 (dd, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 14.0, 21.1, 27.3, 27.7, 27.9, 29.8, 32.4, 63.8, 115.1, 120.3, 129.8, 133.8, 135.4, 136.1, 137.4, 144.3, 151.9, 157.2, 165.2. Anal. Calcd. for $C_{22}H_{22}N_4O_3S$ (422.1): C, 62.54; H, 5.25; N, 13.26; S, 7.59. Found: C, 62.61; H, 5.10; N, 13.11; S, 7.62 %.

Ethyl 1-(p-chlorophenyl)-5-oxo-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (**6g**): Yellow crystals (0.32 g, 73 %), m.p. 228–229 °C. IR: ν_{max} 3104, 2987, 2923, 2851, 1735, 1705 cm^{-1}. MS: m/z (%) 442 (M^+, 100), 443 (M^+ + 1, 12), 444 (M^+ + 2, 44), 370 (14); ^{1}H NMR ($CDCl_3$): δ 1.51 (t, 3H, CH_3), 1.68 (m, 4H, $2CH_2$), 1.88 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.29 (t, 2H, CH_2), 4.57 (q, 2H, CH_2), 7.45–8.19 (dd, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): 13.9, 27.2, 27.6, 27.9, 29.8, 32.4, 64.00, 115.4, 121.1, 129.4, 132.6, 134.3, 135.1, 135.8, 136.2, 144.1, 151.7, 156.9, 164.7. Anal. Calcd. for $C_{21}H_{19}ClN_4O_3S$ (442.1): C, 56.95; H, 4.32; Cl, 8.00; N, 12.65; S, 7.24. Found: C, 57.1; H, 4.56; Cl, 7.98; N, 12.54; S, 7.23 %.

Ethyl 1-(p-nitrophenyl)-5-oxo-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (**6h**): Fine deep yellow crystals (0.34 g, 75 %) m.p. 222–223 °C. IR: ν_{max} 2921, 2850, 1752, 1705 cm^{-1}. MS: *m/z* (%) 453.1 (M^+, 100), 454.1 (M^+ + 1, 26.35), 455.1 (M^+ + 2, 9.15), 425.1 (12). ^{1}H NMR ($CDCl_3$): δ 1.50 (t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.77 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 4.65 (q, 2H, CH_2), 8.45 (dd, 4H, Ar–H). Anal. Calcd. for $C_{21}H_{19}N_5O_5S$ (453.1): C, 55.62; H, 4.22; N, 15.44; S, 7.07. Found: C, 55.70; H, 4.43; N, 15.50; S, 7.00 %.

N-Phenyl 5-oxo-1-phenyl-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxamide (**6i**): Pale yellow cotton-like solid (0.33 g, 74 %), m.p. 313–315 °C. IR: ν_{max} 3312, 2921, 2845, 1716, 1697 cm^{-1}. MS: *m/z* (%) 455.1 (M^+, 100), 456.1 (M^+ + 1, 26.5), 457.2 (M^+ + 2, 7.8), 91 (14.3), 77 (27.3). ^{1}H NMR ($CDCl_3$): δ 1.69 (m, 4H, $2CH_2$), 1.90 (q, 2H, CH_2), 2.82 (t, 2H, CH_2), 3.24 (t, 2H, CH_2), 7.15–8.23 (m, 10H, 2Ar–H), 12.77 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 27.2, 27.6, 28.2, 29.9, 32.3, 115.1, 120.7, 121.3, 125.2, 127.8, 129.1, 129.3, 135.2, 136.1, 136.6, 137.8, 139.6, 145.3, 151.6, 154.8, 165.8. Anal. Calcd. for $C_{25}H_{21}N_5O_2S$ (455.1): C, 65.92; H, 4.65; N, 15.37; S, 7.04. Found: C, 65.78; H, 4.77; N, 15.3; S, 7.00 %.

N-Phenyl 5-oxo-1-p-tolyl-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxamide (**6j**): Pale yellow cotton-like solid (0.37 g, 79 %), m.p. 286–287 °C. IR: ν_{max} 3316, 2916, 2846, 1696 cm^{-1}. MS: *m/z* (%) 469.2 (M^+, 100), 470.2 (M^+ + 1, 28), 471.2 (M^+ + 2, 8.8), 119 (36), 120 (16), 91 (44), 77 (40), 65 (31). ^{1}H NMR (DMSO-d_6): δ 1.64 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.81 (t, 2H, CH_2), 3.24 (t, 2H, CH_2), 7.16–7.98 (m, 9H, 2Ar–H), 10.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 20.5, 26.7, 27.3, 27.5, 28.9, 31.4, 114.4, 120.2, 120.7, 124.7, 128.9, 129.8, 132.6, 134.1, 135.4, 137.1, 137.9, 138.7, 144.9, 151.9, 154.1, 164.8. Anal. Calcd. for $C_{26}H_{23}N_5O_2S$ (469.2): C, 66.51; H, 4.94; N, 14.91; S, 6.83. Found: C, 66.64; H, 4.89; N, 14.89; S, 6.77 %.

N-Phenyl 1-p-chlorophenyl-5-oxo-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxamide (**6k**): Pale yellow cotton-like solid (0.34 g, 71 %), m.p. 258–260 °C. IR: ν_{max} 3292, 2915, 2847, 1685 cm^{-1}. MS: *m/z* (%) 489.1 (M^+, 100), 490.1 (M^+ + 1, 34), 491.1 (M^+ + 2, 43), 119 (18), 77 (24), 65.1 (19). ^{1}H NMR ($CDCl_3$): δ 1.74 (m, 4H, $2CH_2$), 1.90 (q, 2H, CH_2), 2.83 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 7.19–8.25 (m, 10H, 2Ar–H), 12.80 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 27.2, 27.6, 28.2, 29.9, 32.3, 115.3, 120.7, 122.2, 125.3, 129.1, 129.5, 133.6, 135.1, 135.5, 136.2, 137.8, 139.8, 145.1, 151.4, 154.8, 165.6. Anal. Calcd. for $C_{25}H_{20}ClN_5O_2S$ (489.1): C, 61.28; H, 4.11; N, 14.29; S, 6.54; Cl, 7.24. Found: C, 61.11; H, 4.32; N, 14.10; S, 6.04; Cl, 7.13 %.

N-Phenyl 1-p-nitrophenyl-5-oxo-5,6,7,8,9,10-hexahydro-1H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxamide (**6l**): Yellow powder (0.34 g, 69 %), m.p. 290–291 °C. IR: ν_{max} 3300, 2930, 2835, 1691, 1585 cm^{-1}. MS: *m/z* (%) 500 (M^+, 100), 501 (M^+ + 1, 50), 502 (M^+ + 2, 25), 485 (15.7), 63 (12.1). ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 4H, $2CH_2$), 1.90 (q, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.34 (t, 2H, CH_2), 7.27–8.21 (m, 9H, 2Ar–H), 11.28 (s, 1H, NH). Anal. Calcd. for $C_{25}H_{20}N_6O_4S$ (500): C, 59.99; H, 4.03; N, 16.79; S, 6.41. Found: C, 54.90; H, 4.15; N, 16.71; S, 6.43 %.

3-Benzoyl-1-phenyl-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6m**): Pale yellow cotton-like solid (0.34 g, 78 %), m.p. 249–250 °C. IR: ν_{max} 2914, 2843, 1690, 1581 cm^{-1}. MS: m/z (%) 440.1 (M^+, 100), 441.1 (M^+ + 1, 28.7), 442.1 (M^+ + 2, 8.12), 105 (59.2), 77.1 (37.7). ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 4H, $2CH_2$), 1.89 (q, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.25 (t, 2H, CH_2), 7.40–8.29 (m, 10H, 2Ar–H). Anal. Calcd. for $C_{25}H_{20}N_4O_2S$ (440.1): C, 68.16; H, 4.58; N, 12.72; S, 7.28. Found: C, 67.96; H, 4.50; N, 12.74; S, 7.4 %.

3-Benzoyl-1-(p-nitrophenyl)-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6n**): Deep yellow to orange powder (0.38 g, 80 %), m.p. 290–291 °C. IR: ν_{max} 2921, 2845, 1696, 1577 cm^{-1}. MS: *m/z* (%) 485.2 (M^+, 53), 486.2 (M^+ + 1, 17), 487.2 (M^+ + 2, 6), 105 (100), 77 (56). ^{1}H NMR ($CDCl_3$): δ 1.75 (m, 4H, $2CH_2$), 1.89 (q, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 6.65–7.50 (m, 9H, 2Ar–H). Anal. Calcd. for $C_{25}H_{19}N_5O_4S$ (485.1): C, 61.85; H, 3.94; N, 14.42; S, 6.60. Found: C, 61.76; H, 3.99; N, 14.4; S, 6.55 %.

1,3-Diphenyl-1,6,7,8,9,10-hexahydro-5H-cyclohepta[4,5]thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6o**): White crystals (0.30 g,75 %) m.p. 269–271 °C. IR: ν_{max} 3053, 2845, 2909, 1701 cm^{-1}. MS: *m/z* (%) 412.2 (M^+, 100), 413 (M^+ + 1, 30), 414 (M^+ + 2, 8), 384.1 (16), 358.1 (20), 326.2 (26), 308.1 (8), 280 (16), 127 (16), 91 (96), 77 (52); ^{1}H NMR: ($CDCl_3$): δ: 1.58 (m, 4H, $2CH_2$), 1.85 (q, 2H, CH_2), 2.78 (t, 2H, CH_2), 3.22 (t, 2H, CH_2), 7.40–8.19 (m, 10H, Ar–H). Anal. Calcd. for $C_{24}H_{20}N_4OS$ (412.2): C, 69.88; H, 4.89; N, 13.58; S, 7.77. Found: C, 69.97; H, 4.78; N, 13.50; S, 7.69 %.

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