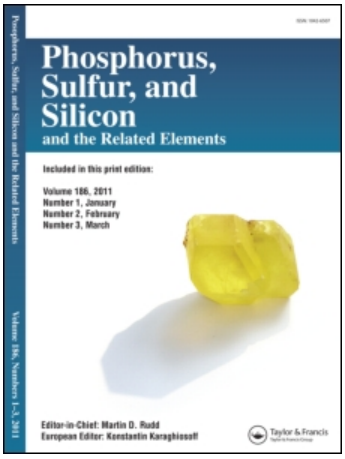

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Synthesis and Reactions of Some Novel Azolothienopyrimidines and Thienopyrimido-As-Triazines Derivatives

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Synthesis and Reactions of Some Novel Azolothienopyrimidines and Thienopyrimido-As-Triazines Derivatives

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Compounds **2** *and* **4** *reacted with nitrous acid to give tetrazolothienopyrimidine* **5** *and* **7***, respectively, which was reduced to aminothienopyrimidone* **6** *and* **8***, respectively. Also, reaction* **2** *and* **4** *with aliphatic acid gave thienotriazolopyrimidine* **9** *and* **10***, respectively. On the other hand, 2-hydrazino derivative* **2** *and 4-hydrazino derivative* **4** *reacted with* α*-haloketone to yield thienopyrimidotriazine* **14** *and* **15***, respectively, and with* β*-diketone and* β*-ketoester to form pyrazolyl derivatives* **16–21**. *Pyrazolinone derivatives* **20** *and* **21** *condensed with aromatic aldehydes afforded arylidene derivatives* **22** *and* **23***, respectively.*

Keywords Azidoazomethine; ^{1}H NMR; mass; pyrimidine

DISCUSSION

Thieno [2,3-d] pyrimidines and fused pyrimidines[1–3] deserve great interest by virtue of their biological,[4–8] bactericidal,[9] and medicinal[10,11] activities, which prompted us to be involved in a program directed to the development of syntheses of various derivatives of pyrimidines and fused pyrimidines. We report here a convenient method for the synthesis of azolothien pyrimidines and thienopyrimido-as-triazines derivatives[12–14] starting from pentenothienopyrimidin-4-one[15] **1** (which was prepared according to karl gewalid method) mostly via corresponding 2-hydrazino **2** and 4-chloro derivatives **3**. This work was carried out by simple transformations, which in one or two steps added a heterocycling ring to the molecule.

It is reported in the literature that aminopyrimidines and condensed aminopyrimidines have exhibited promising antifolate activities. Some

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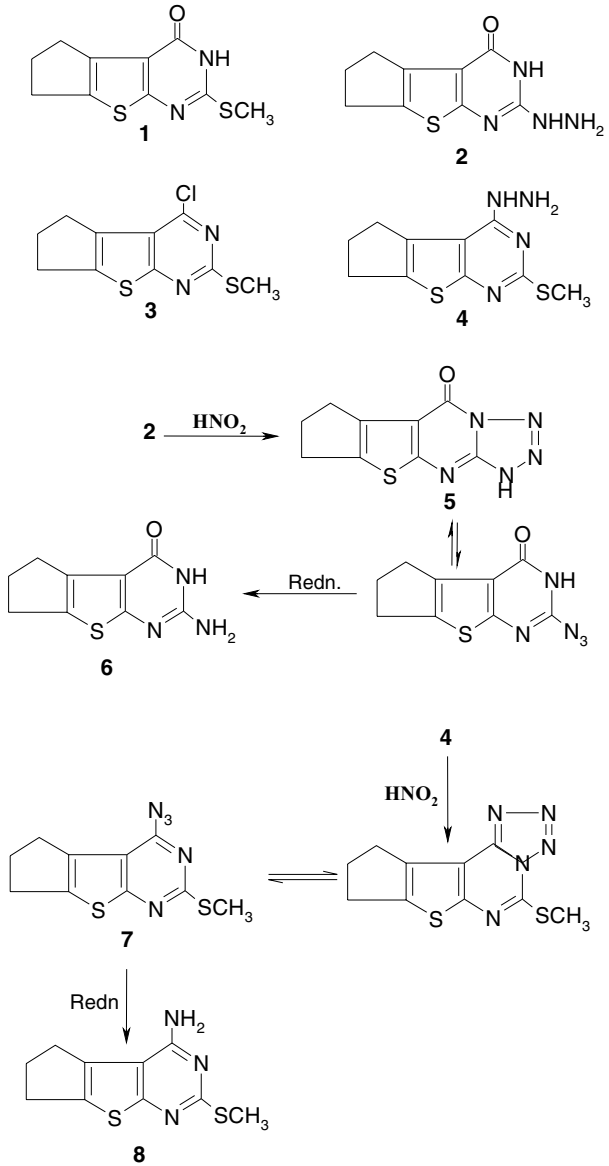
of these antifolate compounds are widely used in therapy as potential anticancer, antibacterial, and antimalarial drugs.

This report describes our approach to the synthesis of aminothieno [2, 3-*d*] pyrimidines **6** and **8** by reduction of the appropriate precursor azido/tetrazolothienopyrmidines **5** and **7** (Scheme 1).

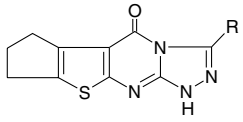


SCHEME 1

Azides and tetrazoles can be viewed as latent amino functionalities. While azides undergo facile reduction to yield amines, tetrazoles are highly resistant to reduction.[16] Heterocyclic azides, especially azidoazomethines, are known to exist in equilibrium with their tetrazolo tautomers. The azidoazomethine–tetrazole equilibrium is the subject of many reviews.[17–19] This equilibrium is influenced by many factors, notably the nature of the substituents around the C=N bond of the azidoazomethine; the nature of the solvent system, PH, and temperature,[14–16] therefore, can be shifted in either direction by manipulating these factors. The well-studied influence of acidic PH to shift the azide–tetrazole equilibrium to the more reactive azido tautomer has been successfully utilized[20–22] not only in reduction reactions to obtain amines, but also in photolysis of tetrazoles to obtain reactive nitrenes. Thus, it is possible to effect the reduction of tetrazoles by shifting this equilibrium to the side of the more labile and reactive azides prior to the reduction step.

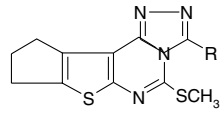
In general, azido/tetrazolopyrimidines **5** and **7** can be obtained through nitrosation of corresponding hydrazinopyrimidines **2** and **4** with nitrous acid. Hydrazinopyrimidines **2** and **4** in turn can be synthesized by nucleophilic displacement alkylthioxy or a labile halogen atom of the corresponding substrate **1** and **3**, respectively, by hydrazine. Azido/tetrazolothienopyrimidines have been synthesized by different routes, and their structural assignments are based on spectral data (c.f. Experimental section).

On the other hand, heating under reflux hydrazino derivatives **2** or **4** with some aliphatic carboxylic acids, namely formic or acetic acid, yielded the corresponding triazolopyrimidine derivatives **9** and **10** respectively (Scheme 2).



9

R = H



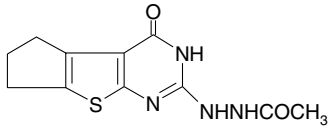
10

a, R = H

b, R = CH_3

SCHEME 2

Surprisingly, heating compound **2** under reflux with acetic acid yielded compound **11** (c.f. Experimental section) (Scheme 3).

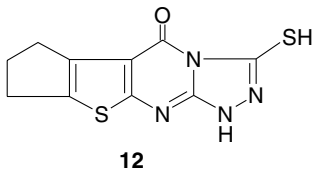


11

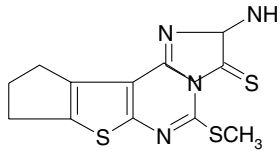
SCHEME 3

Compound **2** or **4** reacted with carbon disulfide in ethanolic potassium hydroxide solution to afford compounds **12** and **13**, respectively (c.f. Experimental section) (Scheme 4).

It is reported in literature that cyclization of 2-hydrazino derivatives **9** and **12** with formic acid or carbon disulfide were placed at N-3 nitrogen to give azolo [4,3-a] pyrimidines.[23–25]



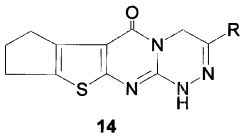
12



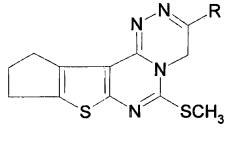
13

SCHEME 4

When compounds **2** or **4** were heated under reflux with α-haloketones, namely chloroacetone or phenacyl bromide in dry xylene, they yielded compounds **14a,b** and **15a,b**, respectively (Scheme 5).



14



15

a,R = CH_3

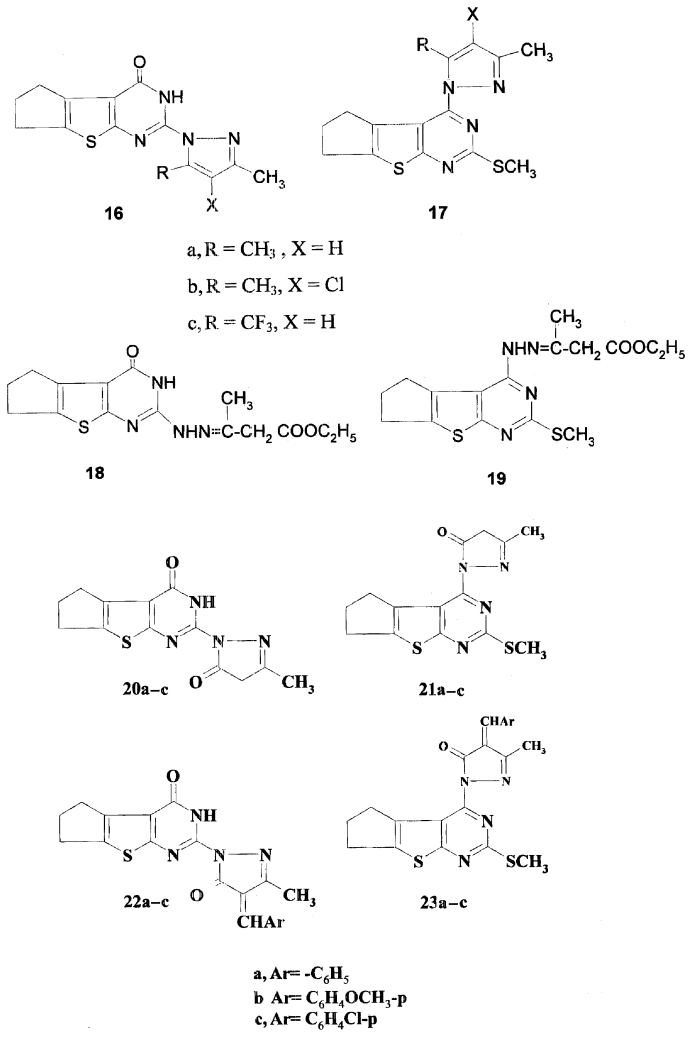
b,R = C_6H_5

SCHEME 5

2-hydrazino and 4-hydrazino derivatives reacted with β-diketones and β-ketoesters to from 2-(1-pyrazoyl) and 4-(1-pyrazoyl) derivatives, respectively. Thus, heating under reflux compounds **2** or **4** with each of pentane 2, 4-dione, 3-chloropentane-2, 4-dione, and 1,1,1-trifluoropentene-2, 4-dione in absolute ethanol yielded compounds **16a–c** and **17a–c**, respectively. Compound **2** or **4** condensed with ethyl

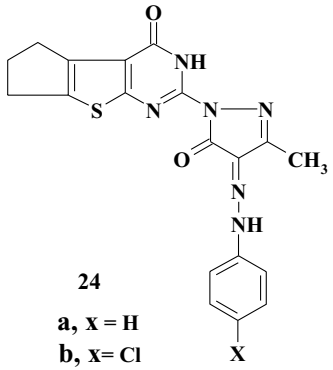
acetoacetate, upon heating in boiling ethanol for 2 h, afforded hydrazone derivatives **18** and **19**, respectively, which could be cyclized either by prolonged heating in ethanol or by heating in ethanolic sodium ethoxide solution to give compounds **20** and **21**, respectively.

Compounds **20** and **21** behaved typically as active methylene-containing compounds. They condensed with aromatic aldehydes in acetic acid in the presence of anhydrous sodium acetate to afford corresponding arylidene derivatives **22a–c** and **23a–c** (Scheme 6).



SCHEME 6

Compound **20** coupled with diazotized aromatic amines to afford **24a,b** (Scheme 7).

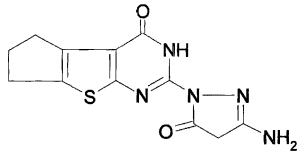


24

a, X = H
b, X= Cl

SCHEME 7

Similarly, the reaction of **2** with ethyl cyanoacetate in ethanolic sodium ethoxide solution led to the formation of compound **25** (Scheme 8).

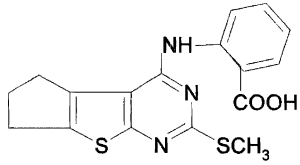


25

SCHEME 8

On the other hand, heating **4** with anthranilic acid in acetic acid gave 4-(O-carboxy phenylamino) derivative **26** (Scheme 9).

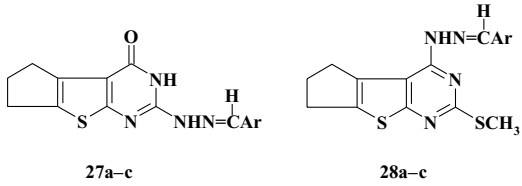
Trials to cyclize **26** under different experimental conditions failed.



26

SCHEME 9

The interaction of **2** or **4** with proper aldehydes in boiling dioxane in the presence of catalytic amounts of piperidine afforded arylhydrazones **27a–c** and **28a–c**, respectively (Scheme 10).



27a–c **28a–c**

a, Ar = C_6H_5

b, Ar = C_6H_4Cl-p

c, Ar = $C_6H_4OCH_3$-p

SCHEME 10

Also, trails to cyclize **27** under different experimental conditions failed.

EXPERIMENTAL

Solid compounds were recrystallized to constant melting points and dried in a vacuum in a drying pistol containing sodium hydroxide.

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp apparatus.

Microanalyses were carried out at the Micro Analytical Unit, National Research Centre and Faculty of Science, Cairo University.

IR spectra were carried out on an FTIR 300 E Jasco using KBr discs.

^1H and ^{13}C-NMR spectra were measured in DMSO or $CDCl_3$ using Ex. 270 FT NMR spectrometer. Signals were measured with reference to TMS as an internal standard.

Mass spectra were recorded on a Finnigan SSQ 7000 spectrometer.

All reactions were followed up by TLC using $CHCl_3$/MeOH (9:1, v/v) and/or ethyl acetate/Benzene (7:3) and detected under a UV Lamp.

2-Hydrazino-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d]pyrimidin-4(4H) One (2)

A mixture of compound **1a** (2.24 g, 0.01 mole) and hydrazine hydrate (99–100%) (7 mL, 0.03 mole) in dioxane (20 mL) and ethanol (10 mL) was heated under reflux for 4 h. The solid that separated upon cooling the reaction mixture was filtered off and recrystallized from dioxane-dimethylformamide (4:1, 25 mL) to yield the title compound as a colorless crystals (1.44 g, 65%), m.p. >300°C.

Analyses and Spectral Data

[$C_9H_{10}N_4SO$] (222.26). Required: C, 48.63%; H, 4.54%; N, 25.21%. Found: C, 48.51%; H, 4.46%; N, 24.91%.

IR (K.Br) cm^{-1}: 3322 (NH_2), 3245 (NH), 2913 (CH alkyl) and 1666 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$) and 8.20 (br s, 1H, NH, D_2O exchangeable). MS (EI+Q1MS LMR UP LR): 222.0 (M^+) 100%.

2-Methylthio-4-chloro-5H, 6H, 7H-Cyclopentenothieno[2,3-d]-pyrimidine (3)

A solution of compound **1** (2.38 g, 0.01 mole) in dry dioxane (30 mL) was treated with phosphorus oxychlolride (7 mL) and stirred under reflux for 3 h. The reaction mixture was allowed to cool to r.t. and then poured into cold water (100 mL). The solid precipitate so-formed was filtered off, dried, and recrystallized from ethanol (25 mL) to yield the title compound as a colorless powder (1.66 g, 65%); m.p. 134–136°C.

Analyses and Spectral Data

[$C_{10}H_9N_2S_2Cl$] (256.7). Required: C, 46.77%; H, 3.53%; N, 10.91%. Found: C, 46.47%; H, 3.71%; N, 10.94%. IR (K.Br) cm^{-1}: 2921 (CH alkyl), 1556 (C=N) and 1467 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.45 (m, 2H, CH_2), 3.00 (m, 4H, CH_2) and 3.30 (s, 3H, SCH_3). ^{13}C-NMR: ($CDCl_3$) δ ppm: 14.3 (CH_3), 27.1, 29.2 and 29.5 (CH_2) and 121.7, 133.2, 135.7, 138.3, 141.3 and 152.3 (thieno pyrimidine carbon atoms).

2-Methylthio-4-hydrazino-5H, 6H, 7H-Cyclopentenothieno [2,3-d]pyrimidine (4)

A mixture of compound **3** (2.56 g, 0.01 mole) and hydrazine hydrate (99–100%) (5 mL) was stirred under reflux in dioxane (25 mL) and ethanol (5 mL) for 6 h. The reaction mixture was allowed to cool to r.t. The solid so-formed was collected by filtration, washed with ethanol, and recrystallized from ethanol-dioxane (25:5 mL) to yield the title compound as a pale yellow crystals (1.70 g, 67%); m.p. 190–192°C.

Analyses and Spectral Data

[$C_{10}H_{12}N_4S_2$] (252.3). Required: C, 47.59%; H, 4.79%; N, 22.20%. Found: C, 47.30%; H, 4.51%; N, 22.11%. IR (K.Br) cm^{-1}: 3305, 3200 (NH) and 2958 (CH alkyl). ^1H NMR ($CDCl_3$) δ ppm: 2.40 (m, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 3.30 (s, 3H, SCH_3), 4.50 (br s, 2H, NH_2 D_2O exchangeable) and 8.20 (br s, 1H, NH, D_2O exchangeable) ^{13}C

NMR ($CDCl_3$) δ ppm: 13.6 (CH_3), 26.7, 27.5 and 28.9 (CH_2) and 108.5, 132.4, 134.4, 135.6, 142.7 and 156.9 (thieno-pyrimidine carbon atoms). MS (EI + Q1MS MR UP LR): 252.5 (M^+); 100%.

1,6,7,8-Tetrahydrotetrazolo[1,5-a]cyclopentenothieno[2,3-d] Pyrimidin-5 (5H)-one (5)

To an ice-cold solution of compound **2** (2.22 g, 0.01 mole) in acetic acid (10 mL) was added dropwise a solution of sodium nitrite (prepared by dissolving sodium nitrite [1.04 g, 0.015 mole] in the least amount of water) 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 (100 mL). The solid so-precipitated was filtered off and recrystallized from acetic acid to yield the title product as a pale yellow crystals (1.60 g, 68%), m.p. 232–233°C.

Analyses and Spectral Data

[$C_9H_7N_5SO$] (233.2). Required: C, 46.34%; H, 3.03%; N, 13.75%. Found: C, 45.81%; H, 3.10%; N, 13.45%. IR (K.Br) cm^{-1}: 3410 (NH), 2930 (CH alkyl), 2235 (N_3) and 1678 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$) and 12.68 (br s, 1H, NH, D_2O exchangeable).

2-Amino-3,5,6,7-tetrahydrocyclopentano Thieno [2,3-d]pyrimidin-4-(4H)-one (6)

To a well-stirred solution of compound **5** (2.33 g, 0.01 mole) in glacial acetic acid (30 mL) was added portionwise activated zinc dust (5.00 g) at r.t. over a period of 30 min. Stirring was continued for an additional 3 h. Therefore, the reaction mixture was heated on a water bath (80–90°C) for 3 h. Progress of reduction was monitored by TLC. After allowing the reaction mixture to cool to r.t., it was poured into cold water (100 mL). The insoluble solid, which separated, was filtered, washed with water, and dried. The crude solid was extracted with hot benzene, and the solid obtained after removal of benzene under reduced pressure was re-crystallized from acetic acid to yield the title product as yellow crystals (1.30 g, 61%), m.p. 239–241°C.

Analyses and Spectral Data

[$C_9H_9N_3SO$] (207.2) Required: C, 52.16%; H, 4.37%; N, 20.27%. Found: C, 52.3%; H, 4.10%; N, 20.11%. IR (K.Br) cm^{-1}: 3400 (NH_2), 3140 (NH), 2890 (CH alkyl) and 1660 (CO). ^1H NMR (DMSO-d_6) δ ppm:

2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 6.45 (br s, 2H, NH_2, D_2O exchangeable) and 10.82 (br s, 1H, NH, D_2O exchangeable).

5-Methylthio-8H, 9H, 10H-Tetrazolo [3, 2-e] Cyclopentenothieno [2,3-d] Pyrimidine (7)

To an ice-cold solution of compound **4** (2.52 g, 0.01 mole) in acetic acid (10 mL) was added dropwise a solution of sodium nitrite (prepared by dissolving sodium nitrite [1.03 g, 0.015 mole] in the least amount of water) 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 and recrystallized from acetic acid (25 mL) to yield the title compound as yellow crystals (1.48 g, 64%); m.p. 199–201°C.

Analyses and Spectral Data

$[C_{10}H_6N_5S_2]$ (231.3). Required: C, 45.61%; H, 3.44%; N, 26.59%. Found: C, 45.70%; H, 3.50%; N, 26.11%. IR (K.Br) cm^{-1}: 2922 (CH alkyl), 1601 (C=N) and 1534 (C=C). ^1H NMR (DMSO-d_6) δ ppm: 2.55 (m, 2H, CH_2), 2.80 (s, 3H, CH_3) and 3.20 (m, 4H, $2CH_2$).

4-Amino-2-methylthio-5H, 6H, 7H-Cyclopentenothieno[2,3-d] Pyrimidine (8)

A mixture of compound **7** (2.31 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. The reaction mixture was then extracted with benzene, and after the removal of benzene under reduced pressure, the formed solid was recrystallized from, benzene to produce **8** as a pale yellow powder (1.45 g, 61%); m.p. 186–187°C.

Analyses and Spectral Data

$[C_{10}H_{11}N_3S_2]$ (237.3). Required: C, 50.61%; H, 4.67%; N, 17.71%. Found: C, 50.60%; H, 4.61%; N, 17.22%. IR (K.Br) cm^{-1}: 3484 (NH) and 2915 (CH alkyl). ^1H NMR (DMSO-d_6) δ ppm: 2.40 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2) and 6.95 (br s, 2H, NH_2, D_2O exchangeable).

1,6,7,8-Tetrahydrocyclopentenothieno[2,3-d][1,2,4]traizolo[4,3-a] Pyrimidin-5(5H)-one (9)

A mixture of compound **2** (2.22 g, 0.01 mole), formic acid (10 mL), and a catalytic amount of concentrated hydrochloric acid solution was heated

under reflux for 5 h. The reaction mixture was allowed to cool to r.t. and poured into water (100 mL). The formed solid was collected by filtration, washed with ethanol (20 mL), dried, and recrystallized from dioxane (25 mL) to yield the title compound as colorless crystals (1.42 g, 61%), m.p. 281–282°C.

Analyses and Spectral Data

[$C_{10}H_8N_4SO$] (232.2). Required: C, 51.71%; H, 3.47%; N, 24.12%. Found: C, 51.50%; H, 3.31%; N, 23.86%.

IR (K.Br) cm^{-1}: 3100 (NH), 2922 (CH alkyl) and 1681 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 9.05 (s, 1H, CH) and 14.05 (br s, 1H, NH, D_2O exchangeable).

8,9-Dihydro-5-methylthio-10H-cyclopentenothieno[3,2-e][1,2,4] Triazolo [4,3-c] Pyrimidine (10a)

A mixture of compound **4** (2.52 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 cold water (100 mL). The formed solid was collected by filtration, washed with water, dried, and recrystallized from dioxane to yield the title compound as a colorless crystals (1.73, 66%); m.p. 200–201°C.

Analyses and Spectral Data

[$C_{11}H_{10}N_4S_2$] (262.3). Required: C, 50.35%; H, 3.84%; N, 21.35%. Found: C, 50.10%; H, 3.73%; N, 21.00%. IR (K.Br) cm^{-1}: 2900 (CH alkyl), 1601 (C=N) and 1482 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.50 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 3.10 (t, 2H, CH_2), 3.30 (t, 2H, CH_2) and 8.80 (s, 1H, triazolo-H4 proton).

8,9-Dihydro-3-methyl-5-methylthio-10H-cyclopentenothieno[3,2-c] [1,2,4] Triazolo [4,3-c] Pyrimidine (10b)

A solution of compound **4** (2.52 g, 0.01 mole) in glacial acid (40 mL) was stirred under reflux for 6 h. The reaction mixture was allowed to cool and poured into cold and water (100 mL), and the solid so-produced was filtered off and crystallized from acetic acid to yield the title product as colorless crystals (1.90 g, 70%); m.p. 244–246°C.

Analyses and Spectral Data

[$C_{12}H_{12}N_4S_2$] (276.3). Required: C, 52.14%; H, 4.37%; N, 20.27%. Found: C, 52.30%; H, 4.11%; N, 20.13%. IR (K.Br) cm^{-1}: 2929 (CH alkyl),

1604 (C=N) and 1535 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm: 2.55 (m, 2H, CH_2), 2.70 (s, 3H, CH_3), 3.05 (t, 2H, CH_2), 3.10 (s, 3H, CH_3) and 2.25 (t, 2H, CH_2).

2-Acetylhydrazin-3, 3, 6,7-tetrahydrocyclopentenothieno Thieno[2,3-d] Pyrimidin-4 (4H)-one (11)

A mixture of compound **2** (2.22 g, 0.01 mole) and glacial acetic acid (25 mL) was refluxed for 4 h. The reaction mixture was allowed to cool to r.t. and poured into water (100 mL), and the solid so-formed was collected by filtration, dried, and recrystallized from acetic acid (25 mL) to yield the title compound as a colorless crystals (2.04 g, 77%), m.p. 287–288°C.

Analyses and Spectral Data

$[C_{11}H_{12}N_4SO_2]$ (264.36). Required: C, 49.97%; H, 4.58%; N, 21.19%. Found: C, 50.03%; H, 4.51%; N, 21.49%.

IR (K.Br) cm^{-1}: 3290 (NH), 2920 (CH alkyl) and 1690, 1655 (2CO), ^{1}H NMR (DMSO-d_6) δ ppm: 1.90 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 8.65 (br s, 1H, NH, D_2O exchangeable), 9.70 (br s, 1H, NH, D_2O exchangeable) and 11.35 (br s, 1H, NH, D_2O exchangeable), MS (EI + Q1MS LMR UP LR): 264 (M^+) 69% and 222 (m/z) 100%.

3-Mercapto-1,6,7,8-tetrhydrocyclopentenothieno[2,3-d][1,2,4]triazolo [4,3-a] Pyrimidin-5(5H)-one (12)

To a warmed ethanolic sodium hydroxide solution (prepared by dissolving sodium hydroxide [0.40 g, 0.01 mole] in ethanol [50 mL], compound **2** (2.22 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 8 h, and then it was allowed to cool to r.t., poured into water (100 mL), and neutralized by diluted acetic acid. The formed precipitate was filtered-off, dried, and recrystallized from dioxane (30 mL) to yield the title product as a pale yellow powder (1.70 g, 64%), m.p. >300°C.

Analyses and Spectral Data

$[C_{10}H_8N_4S_2O]$ (264.3). Required: C, 45.44%; H, 3.05%; N, 21.19%. Found: C, 45.10%; H, 3.30%; N, 20.82%, IR (K.Br) cm^{-1}: 3451 (NH), 2930 (CH alkyl) and 1670 (CO), ^{1}H NMR (DMSO-d_6) δ ppm: 2.40 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$) and 12.65 (br s, 1H, NH, D_2O exchangeable).

5-Methylthio-2,8,9,10-tetrahydrocyclopentenolthieno[3,2-e][1,2,4] Triazolo [4,3-c] Pyrimidine-(3H)-thione (13)

To a warmed ethanolic sodium hydroxide solution (prepared by dissolving sodium hydroxide [0.4 g, 0.01 mole] in ethanol (50 mL]) were added compound **4** (2.52 g, 0.01 mole) and carbon disulphide (10 mL). The mixture was heated on a water bath at 80°C under reflux for 8 h. The reaction mixture was allowed to cool to r.t., poured into water (100 mL), and neutralized by dilute acetic acid, and the formed precipitate was filtered off, washed with water, dried, and recrystllizaed from dioxane (35 mL) to yield the title product as yellow powder (1.94 g, 66%); m.p. 285–286°C.

Analyses and Spectral Data

[$C_{11}H_{10}N_4S_3$] (294.4). Required: C, 44.87%; H, 3.42%; N, 19.03%. Found: C, 45.00%; H, 3.30%; N, 18.87%. IR (K.Br) cm^{-1}: 3445 (NH) and 2919 (CH alkyl).^{1}H NMR (DMSO-d_6) δ ppm: 2.40 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.90 (m, 4H, $2CH_2$) and 11.10 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1 MS LMR UP LR): 294 (M^+); 100%.

1,4,6,7,8,9-Hexahydro-3-(methyl)-cyclopentenothieno[2′,3′:4,5] Pyrimido [2,1-c] [1,2,4] Triazin-6-one (14a)

Compound **14a** was obtained from compound **2** (2.22 g, 0.01 mole) and chloroacetone (0.93 g, 0.01 mole). The compound was recrystallized from dioxane (25 mL) to yield the title product as pale yellow crystals (2.00 g, 77%); m.p. 265–266°C.

Analyses and Spectral Data

[$C_{12}H_{12}N_4SO$] (207.3). Required: C, 55.36%; H, 4.65%; N, 21.52%. Found: C, 55.13%; H, 4.70%; N, 21.46%. IR (K.Br) cm^{-1}: 3450 (NH), 2961 (CH alkyl) and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ ppm: 2.25 (s, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.70 (s, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.05 (t, 2H, CH_2) and 10.30 (br s, 1H, NH, D_2O exchangeable).

1,4,6,7,8,9-Hexahydro-3-(phenyl)-cyclopentenothieno[2′,3′:4,5]pyrimido [2,1-c] [1,2,4] Triazin-6-one (14b)

Compound **14b** was obtained from compound **2** (2.22 g, 0.01 mole) and phenacylbromide (1.99 g, 0.01 mole). The compound was recrystallized from dioxane (25 mL) to yield the title product as orange crystals (2.28 g, 71%); m.p. >300°C.

Analyses and Spectral Data

[$C_{17}H_{14}N_4SO$] (322.3). Required: C, 63.33%; H, 4.34%; N, 17.38%. Found: C, 62.77%; H, 3.91%; N, 17.11%. IR (K.Br) cm^{-1}: 3250 (NH), 3050 (CH aromatic), 2920 (CH, alkyl) and 1670 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.45 (s, 2H, CH_2), 2.90 (m, 4H, $2CH_2$), 7.40–7.85 (m, 5H, phenyl protons), and 11.03 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1M LMR UP LR): 322.1 (M^+) 100%.

5-Methylthiosubstituted-1,4,8,9-tetrahydro[2,1-f][1,2,5]traizin-10H-cyclopentenothieno [2,3-d] Pyrimidine (15 a,b): General Procedure

A mixture of compound 4 (2.52 g, 0.01 mole) with chloroacetone or phenacyl bromide (0.01 mole) was heated under reflux for 5 h in dry xylene (30 mL). The solid precipitated that separated upon cooling was filtered off, dried, and recrystallized from an appropriate solvent to produce **15a,b**.

5-Methylthio-3-methyl-1,4,8,9-tetrahydro[2,1-f][1,2,5]triazin-10H-cyclopentenothieno [2,3-d] Pyrimidine (15a)

Compound **15a** was obtained from compound 4 (2.52 g, 0.01 mole) and chloroacetone (0.93 g, 0.01 mole). The product was recrystallized from ethanol (25 mL) to yield the title compound as colorless crystals (1.91 g, 66%); m.p. 159–161°C.

Analyses and Spectral Data

[$C_{13}H_{14}N_4S_2$] (290.4). Required: C, 53.76%; H, 4.85%; N, 19.29%. Found: C, 53.71%; H, 4.70%; N, 19.12%. IR (K.Br) cm^{-1}: 2919 (CH alkyl), 1580 (C=N) and 1474 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.30 (s, 2H, CH_2), 2.40 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.65 (S, 3H, CH_3), 2.90 (t, 2H, CH_2) and 3.00 (t, 2H, CH_2) MS (EI + QIMSLMRUPLR): 290.4 (M^+) 33%.

5-Methylthio-3-phenyl-1,4,8,9-tetrahydro[2,1-f][1,2,5]triazin-10H-cyclopentenothieno [2,3-d] Pyrimidine (15b)

Compound **15b** was obtained from compound **4** (2.52 g, 0.01 mole) and phenacyl bromide (1.99 g, 0.01 mole). The product was recrystallized from an ethanol–dioxane mixture (25–5 mL) to yield the title compound as pale yellow crystals (2.25 g, 64%); m.p. 198–200°C.

Analyses and Spectral Data

[$C_{18}H_{16}N_4S_2$] (352.5). Required: C, 61.33%; H, 4.57%; N, 15.89%. Found: C, 61.00%; H, 4.31%; N, 15.63%. IR (K.Br) cm^{-1}: 3010 (CH aromatic) and 2909 (CH alkyl). ^1H NMR (DMSO-d_6) δ ppm: 2.35 (s, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.75 (m, 4H, $2CH_2$), 2.95 (s, 3H, CH_3) and 7.35–7.65 (m, 5H, phenyl protons). MS (EI + Q1MS LMR UP LR): 352.4 (M^+) 14%.

2-(3,5-Dimethyl-4H-pyrazol-1-yl)-3,5,6,7-tetrahydrocyclopenteno-thieno [2,3-d] Pyrimidin-4(4H)-one (16a)

Compound **16a** was obtained from compound **2** (2.22 g, 0.01 mole) and pentan-2,4-dione (1.00 g, 0.01 mole). The product was recrystallized from dioxane (25 mL) to yield the title product as pale yellow crystals (2.11 g, 73%); m.p. 204–206°C.

Analyses and Spectral Data

[$C_{14}H_{16}N_4SO$] (288.3) Required: C, 58.30%; H, 5.59%; N, 19.43%. Found: C, 58.20%; H, 5.60%; N, 19.11%. IR (K.Br) cm^{-1}: 3230 (NH), 2860 (CH alkyl) and 1680 (CO).

^1H NMR (DMSO-d_6) δ ppm: 2.20 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.90 (m, 4H, $2CH_2$) and 6.25 (s, 1H, CH, pyrazol-H4).

2-(3,5-Dimethyl-4-chloropyrazol-1-yl)-3,5,6,7-tetrahydrocyclopenteno-thieno[2,3-d] Pyrimidin-4(4H)-one (16b)

Compound **16b** was obtained from compound **2** (2.22 g, 0.01 mole) and 3-chloropentane-2,4-dione (1.34 g, 0.01 mole). The product was recrystallized from dimethyl- formamide (25 mL) to yield the title compound as yellow crystals (2.25, 70%); m.p. 255–257°C.

Analyses and Spectral Data

[$C_{14}H_{15}N_4SOCl$] (248.3). Required: C, 52.08%; H, 4.68%; N, 17.35%. Found: C, 51.84%; H, 4.30%; N, 17.11%. IR (K.Br) cm^{-1}: 3370 (NH), 2910 (CH alkyl) and 1699 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.20 (s, 3H, CH_3), 2.30 (t, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.85 (t, 2H, CH_2), 2.95 (t, 2H, CH_2) and 11.30 (br s, 1H, NH, D_2O exchangeable).

2-(3-Methyl-4H-5-trifluoromethylpyrazol-1-yl)-3,5,6,7-tetrahydrocyclo-pentenothieno [2,3-d] Pyrimidin-4 (4H)-one (16c)

Compound **16c** was obtained from compound **2** (2.22 g, 0.01) mole and 1,1,1-trifluoro-2,4-pentandione (1.54 g, 0.01 mole). The product was

recrystallized from dioxane (30 mL) to yield title compound as pale yellow crystals (2.15 g, 63%); m.p. 250–252°C.

Analyses and Spectral Data

$[C_{14}H_{13}N_4SOF_3]$ (342.3) Required: C, 49.11%; H, 3.82%; N, 16.36%. Found: C, 48.77%; H, 4.10%; N, 16.00%. IR (K.Br) cm^{-1}: 3320 (NH), 2880 (CH alkyl) and 1689 (CO). ^1H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 7.85 (s, 1H, CH, pyrazol-H4) and 10.85 (br s, 1H, NH, D_2O exchangeable).

2-Methylthio-4-(3,5-dimethyl-4-chloro-1H-pyrazol-1-yl)-5H, 6H, 7H-Cyclopentanothieon [2,3-d] Pyrimidine (17a)

Compound **17a** was obtained from compound **4** (2.52 g, 0.01 mole) and pentane-2,4-dione (1.00 g, 0.01 mole). The product was recrystallized from ethanol (30 mL) to afford the title compound as colorless crystals (1.93 g, 61%); m.p. 140–142°C.

Analyses and Spectral Data

$[C_{15}H_{16}N_4S_2]$ (316.4). Required: C, 56.93%; H, 5.09%; N, 17.71%. Found: C, 57.10%; H, 4.73%; N, 17.31%. IR (K.Br) cm^{-1}: 2930 (CH alkyl), 1555 (C=N) and 1484 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.30 (s, 3H, CH3), 2.40 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2) and 6.05 (s, 1H, CH). MS (EI + Q1MS LMR UR LR): 316 (M^+), 78%.

2-Methylthio-4-(3,5-dimethyl-4-chloro-1H-pyrazol-1-yl)-5H,6H, 7H-Cyclopentenothieno[2,3-d]pyrimidine (17b)

Compound **17b** was obtained from compound **4** (2.52 g, 0.01 mole) and 3-chloropentan-2,4-dione (1.30 g, 0.01 mole). The product was recrystallized from ethanol (30 mL) to afford the title compound as pale yellow crystals (2.25 g, 64%); m.p. 187–188°C.

Analyses and Spectral Data

$[C_{15}H_{16}N_4S_2Cl]$ (351.8). Required: C, 51.19%; H, 4.58%; N, 15.92%. Found: C, 51.10%; H, 4.31%; N, 15.57%. IR (K.Br) cm^{-1}: 2930 (CH alkyl), 1600 (C=N) and 1530 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.30 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.95 (t, 2H, CH_2), 3.05 (t, 2H, CH_2).

2-Methylthio-4-(3-methyl-5-trifluoromethyl-4H, 1H-Pyrazol-1-yl)-5H, 6H, 7H-Cyclopentenothieno[2,3-d]pyrimidine (17c)

Compound **17c** was obtained from compound 4 (2.52 g, 0.01 mole) and 1,1,1-trifluoropentane-2,4-diones (1.54 g, 0.01 mole). The product was recrystallized from an ethanol–dioxane mixture (25–5 mL) to afford the title compound as colorless crystals (2.22 g, 60%); m.p. 182–184°C.

Analyses and Spectral Data

$[C_{15}H_{13}N_4S_2F_3]$ (370.4). Required: C, 48.64%; H, 3.53%; N, 15.12%. Found: C, 48.80%; H, 3.60%; N, 14.86%. IR (K.Br) cm^{-1}: 2859 (CH alkyl), 1513 (C=N) and 1488 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm: 2.10 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2) and 8.40 (s, 1H, CH).

2-Ethylacetoacetatehydrazon-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d] Pyrimidin-4 (4H)-one (18)

A mixture of compound **2** (2.22 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) was refluxed in absolute ethanol (30 mL) for 5 h. The reaction mixture was allowed to cool to r.t., and the solid precipitate so-produced was filtered off and recrystallized from benzene (30 mL) to yield the title compound (2.50 g, 75%); m.p. 192–193°C.

Analyses and Spectral Data

$[C_{15}H_{18}N_4SO_3]$ (334.3). Required: C, 53.87%; H 5.42%; N, 16.75%. Found: C, 54.09%; H 5.26%; N, 16.90%. IR (K.Br) cm^{-1}: 3309, 3224 (2NH), 2931 (CH alkyl) and 1728, 1665 (2CO). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.30 (t, 3H, CH_3), 1.65 (s, 2H, CH_2), 2.00 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 4.20 (q, 2H, CH_2), 8.00 (br s, 1H, NH, D_2O exchangeable) and 9.50 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 333.9 (M^+) 100%.

4-Ethylacetoacetatehydrazone-2-methylthio-5H, 6H, 7H-Cyclopentenothieno[2,3-d]pyrimidine (19)

A mixture of compound **4** (2.52 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) was refluxed in absolute ethanol (30 mL) for 5 h. The reaction mixture was allowed to cool to r.t., and the solid precipitate so-produced was filtered off and recrystallized from benzene (30 mL) to yield the title compound as colorless crystals (2.44 g. 67%); m.p. 150–151°C.

Analyses and Spectral Data

[$C_{16}H_{20}N_4S_2O_2$] (364.5). Required: C, 52.72%; H, 5.53%; N, 15.37%. Found: C, 52.60%; H, 5.60%; N, 15.11%. IR (K.Br) cm^{-1}: 3253 (NH), 2289 (CH alkyl) and 1716 (CO), ^1H NMR ($CDCl_3$) δ ppm: 1.30 (t, 3H, CH_3), 1.60 (s, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.95 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 3.40 (s, 2H, CH_2), 4.20 (q, 2H, CH_2) and 8.05 (br s, 1H, NH, D_2O exchangeable).

2-(3-Methyl-4H-pyrazol-5-one-1yl)-3,5,6,7-tetrahydrocyclopentenothieno-[2,3-d] Pyrimidin-4(4H)-one (20)

Method (A)

A solution of compound **2** (2.22 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 cold water (100 mL), and neutralized by acetic acid solution, whereby a solid was precipitated, which was filtered off and crystallized from dioxane to produce the title compound as colorless crystals (2.02 g, 70%); m.p. 295–296°C.

Method (B)

A solution of compound **18** (3.34 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 4 h. The reaction mixture was allowed to cool to r.t. and then poured into water (100 mL), and neutralized by acetic acid solution. The formed precipitate was filtered off, dried, and recrystallized from dioxane to afford the title product **20**.

Analyses and Spectral Data

[$C_{13}H_{12}N_4SO_2$] (288.3). Required: C, 54.15%; H 4.19%; N, 19.43%. Found: C, 54.10%; H 3.87%; N, 18.83%. IR (K.Br) cm^{-1}: 3220 (NH), 2924 (CH alkyl) and 1697, 1660 (2CO).^1H NMR (DMSO-d_6) δ ppm: 2.25 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.55 (s, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 5.3 (s, 1H, OH, D_2O exchangeable) and 12.65 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 288.1 (M^+) 100%.

2-Methylthio-4-(5-hydroxy-3-methyl-1H-pyrazol-5-one-1-yl)5H, 6H, 7H-Cyclopentenothieno [2,3-d] Pyrimidine (21)

Method (A)

A solution of compound **4** (2.52 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 with stirring for 6 h. The reaction mixture was allowed to cool to r.t., poured into cold water (100 mL), and neutralized by acetic acid solution, whereby a solid was precipitated, which was filtered off, washed with water, dried, and recrystallized from ethanol to yield compound **21**.

Method (B)

A solution of compound **19** (3.64 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 4 h. The reaction mixture was allowed to cool to r.t., poured into water (100 mL), and neutralized by acetic acid solution, whereby a solid precipitated. The solid so-formed was collected by filtration, washed with water, dried, and recrystallized from ethanol (30 mL) to afford the title compound as buff crystals (1.85 g, 58%); m.p. 188–189°C.

Analyses and Spectral Data

$[C_{14}H_{14}N_4S_2O]$ (318.4). Required: C, 52.80%; H, 4.43%; N, 17.59%. Found: C, 53.1%; H, 4.71%; N, 17.13%. IR (K.Br) cm^{-1}: 2918 (CH alkyl), 1623 (CO), 1550 (C=N) and 1480 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 2.20 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.95 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 3.65 (br s, 1H, OH, D_2O exchangeable) and 3.95 (s, 2H, CH_2).

2-(3-Methyl-4-phenylmethylene-pyrazol-5-one-1-yl)-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d] Pyrimidin-4-(4H)-one (22a)

a

Compound **22a** was obtained from compound **20** (2.88 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.50 g, 68%); m.p. 297–298°C.

b

Compound **22a** was obtained from compound **18** (3.34 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.40 g, 64%); m.p. 297–298°C.

Analyses and Spectral Data

$[C_{20}H_{16}N_4SO_2]$ (376.4) Required: C, 63.81%; H 4.28%; N, 14.88%. Found: C, 63.53%; H 3.81%; N, 14.53%. IR (K.Br) cm^{-1}: 3240 (NH), 3050 (CH aromatic), 2930 (CH alkyl) and 1699, 1683 (2CO). ^1H-NMR

(DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.90 (m, 4H, $2CH_2$), 7.25–7.35 (m, 5H, phenyl protons), 7.45 (s, 1H, ethylenic proton) and 12.70 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR):376 (M^+) 19% and 288 (m/z) 100%.

2-(3-Methyl-4-p-chlorophenylmethylene)-pyrazol-5-one-1-yl)-3,5,6,7-tetrahydrocyclopentenothieno [2,3-d]pyrimidin-4(4H)-one (22b)

a

Compound **22b** was obtained from compound **20** (2.88 g, 0.01 mole) and p-chlolobenzal-dehyde (1.41 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to afford the title compound as yellow crystals (2.70 g, 66%); m.p. >300°C.

b

Compound **22b** was obtained from compound **18** (3.34 g, 0.01 mole) and p-chlorobenzaldehyde (1.49, 0.01 mole). The product was crystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.50 g, 61%); m.p. >300°C.

Analyses and Spectral Data

[$C_{20}H_{15}N_4SO_2Cl$] (410.8). Required: C, 58.46%; H; 3.68%; N, 13.64%. Found: C, 58.11%; H, 3.54%; N, 12.98%. IR (K.Br) cm^{-1}: 3255 (NH), 3015 (CH aromatic), 2900 (CH alkyl) and 1700, 1680 (2CO). ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.85 (m, 4H, $2CH_2$), 7.25–7.35 (m, 4H, aromatic protons), 7.45 (s, 1H, ethylenic proton) and 12.60 (br s, 1H, NH, D_2O exchangeable).

2-(3-Methyl-4-p-methoxyphenylmethylene)-pyrazol-5-one-1-yl)-3,5,6,7-tetrahydrocyclopentenothieno [2,3-d] Pyrimidin-4 (4H)-one (22c)

a

Compound **22c** was obtained from compound **20** (2.88 g, 0.01 mole) and 4-methoxy-benzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as orange crystals (2.60 g, 0.01 mole); m.p. 288–289°C.

b

Compound **22c** was obtained from compound **18** (3.34 g, 0.01 mole) and 4-methoxy-benzaldehyde (1.36 g, 0.01 mole). The product was

recrystallized from dioxane (30 mL) to produce the title compound as orange crystals (2.40, 60%); m.p. 288–289°C.

Analyses and Spectral Data

$[C_{21}H_{18}N_4SO_3]$ (406.4) Required: C, 62.05%; 4.46%; N, 13.78%. Found: C, 61.73%; H 4.07%; N, 13.55%. IR (K.Br) cm^{-1}: 3240 (NH), 3020 (CH aromatic), 2900 (CH alkyl) and 1690, 1683 (2CO). ^1H NMR ($CDCl_3$) δ ppm: 2.35 (s, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.05 (t, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.05 (d, 2H, J=10 Hz, aromatic protons), 7.50 (s, 1H, CH, ethylenic proton), 8.55 (d, 2H, J = 10Hz, aromatic protons) and 11.75 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 406 (M^+) 12%.

2-Methylthio-4-(5-hydroxy-4-arylmethylene-3-methyl-1H-pyrazol-5-one-1-yl)-5H, 6H, 7H-Cyclopentenothieno[2,3-d]pyrimidine (23a–c)

A mixture of compound **4** (3.18 g, 0.01 mole), the appropriate aromatic aldehyde (0.01 mole), dioxane (40 mL), and a catalytic amount of piperidine was stirred under reflux for 5 h. The reaction mixture was allowed to cool to r.t. and poured into water (100 mL), whereby a solid precipitate was formed. The solid precipitate so-formed was filtered off, washed with water, dried, and recrystallized from the proper solvent to produce compounds (**23a–c**).

2-Methylthio-4-(5-hydroxy-4-phenylmethylene-3-methyl-1H-pyrazol-5-one-1-yl)-5H, 6H, 7H-Cyclopentano[2,3-d]thienopyrimidine (23a)

Compound **23a** was obtained from compound **4** (3.18 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane (35 mL) to yield the title compound as reddish brown powder (2.51 g, 58%); m.p. 250–252°C.

Analyses and Spectral Data

$[C_{21}H_{18}N_4S_2O]$ (406.5). Required: C, 62.04%; H, 4.46%; N, 13.78%. Found: C, 61.86%; H, 4.92%; N, 13.70%. IR (K.Br) cm^{-1}: 3030 (CH aromatic), 2918 (CH alkyl) and 1668 (CO). ^1H-NMR ($CDCl_3$) δ ppm: 2.10 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 3.01 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 7.15 (s, 1H, CH) and 7.25–7.30 (m, 5H, phenyl protons). MS (EI + Q1MS LMR UP LR): 406 (M^+); 74%.

2-Methylthio-4-(5-hydroxy-4-(4-chlorophenylmethylene)-3-methyl1H-pyrazol-5-one-1-yl)-5H, 6H, 7H-Cyclopentenothieno [2,3-d]pyrimidine (23b)

Compound **23b** was obtained from compound **4** (3.18 g, 0.01 mole) and 4-chlorobenzaldehyde (2.66 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as greenish yellow powder (3.30 g, 60%); m.p. 255–257°C.

Analyses and Spectral data

$[C_{21}H_{17}N_4S_2OCl]$ (440.9). Required: C, 57.19%; H, 3.88%; N, 12.71%. Found: C, 57.10%; H, 3.75%; N, 12.65%. IR (K.Br) cm^{-1}: 3010 (CH aryl), 2880 (CH alkyl) and 1677 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.20 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.70 (t, 2H, CH_2), 2.80 (t, 2H, CH_2), 7.25–7.50 (m, 4H, aromatic protons) and 8.25 (s, 1H, CH). MS (EI + Q1 MS LMR UP LR): 440.9 (M^+); 100%.

2-Methylthio-4-(5-hydroxy-4-(4-methoxyphenylmethylene)-3-methyl-1H-pyrazol-5-on-1-yl)-5H,6H, 7H-Cyclopentenothieno[2,3-d] Pyrimidine (23c)

Compound **23c** was obtained from compound **4** (3.18 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow powder (2.44, 56%); m.p. 237–238°C.

Analyses and Spectral Data

$[C_{22}H_{20}N_4S_2O_2]$ (436.5). Required: C, 60.52%; H, 4.62%; N, 12.83%. Found: C, 60.45%; H, 4.55%; N, 12.77%. IR (K.Br) cm^{-1}: 3050 (CH aryl), 2900 (CH alkyl) and 1690 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.25 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.60 (s, 3H, SCH_3), 2.75 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 3.45 (s, 3H, OCH_3), 7.35 (d, 2H, J = 10Hz, aromatic protons), 7.55 (d, 2H, J = 10Hz, aromatic protons) and 8.35 (s, 1H, CH). MS (EI + Q1 MS LMR UP LR): 436.1 (M^+); 36%.

Condensation of 20 with Aromatic Amines: Preparation of (24a,b): General Method

To an ice-cold solution of the proper aromatic amine (0.01 mole) in 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, which was in an ice bath at −5°C. This previously prepared diazonium salt was added dropwise to a mixture of **20** (2.88 g, 0.01 mole) and anhydrous sodium acetate. The reaction mixture was allowed to stand

overnight at r.t., and then it was poured into water (100 mL). The formed solid was filtered off, washed with water, dried, and recrystallized from the proper solvent to produce **33a,b**.

Condensation of 20 with Ailin: Preparation of (24a)

Compound **24a** was obtained from compound **20** (2.88 g, 0.01 mole) and aniline (0.39 g, 0.01 mole). The product was recrystallized and from dimethylformamide (25 mL) to yield the title compound as orange crystals (2.30 g, 66%); m.p. >300°C.

Analyses and Spectral Data

$[C_{19}H_{16}N_6SO_2]$ (392.4) Required: C, 58.15%; H 4.11%; N, 21.42%. Found: C, 57.88%; H 3.74%; N, 21.23%. IR (K.Br) cm^{-1}: 3220 (NH), 3050 (CH aromatic), 2920 (CH alkyl) and 1680, 1660 (2CO). ^{1}H-NMR ($CDCl_3$) δ ppm: 2.25 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2) and 7.40–7.55 (m, 5H, phenyl protons). MS (EI + Q1MS LMR UP LR): 392 (M^+) 12% and 288 (m/z) 100%.

Condensation of 20 with P-chloroaniline: Preparation of (24b)

Compound **24b** was obtained from compound **20** (2.88 g, 0.01 mole) and 4-chloroaniline (1.27 g, 0.01 mole). The product was recrystallized from dimethylformamide (25 mL) to yield the title compound as orange crystals (2.68 g, 63%); m.p. >300°C.

Analyses and Spectral Data

$[C_{19}H_{15}N_6SO_2Cl]$ (426.8). Required: C, 53.45%; H 3.54%; N, 19.69%. Found: C, 52.92%; H 3.99%; N, 19.20%. IR (K.Br) cm^{-1}: 3180 (NH), 3015 (CH aromatic), 2950 (CH alkyl) and 1680, 1660 (2CO). ^{1}H NMR ($CDCl_3$) δ ppm: 2.45 (m, 2H, CH_2), 2.95 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.15 (s, 3H, CH_3), 7.45 (d, 2H, J = 13.5 Hz; aromatic protons), 7.65 (d, 2H, J = 13.5 Hz, aromatic protons) and 13.20 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 426.4 (M^+) 9% and 288 (m/z) 100%.

2-(3-Amino-4H-pyrazol-5-one-1-yl)-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d] Pyrimidin-4(4H)-one (25)

To a warmed ethanolic sodium ethoxide solution (prepared by dissolving [0.23 g, 0.01 mole] sodium metal in absolute ethanol [30 mL] was added compound **2** (2.22 g, 0.01 mole) and ethyl cyanoacetate (1.13 g, 0.01 mole). The heating was continued for 4 h. The reaction mixture

was allowed to cool to r.t. and was poured into water (100 mL) and neutralized with acetic acid. The solid so-precipitated was filtered off, washed with water, dried, and recrystallized from dimethylformamide (25 mL) to yield the title compound as yellow crystals (1.76 g, 61%); m.p. >300°C.

Analyses and Spectral Data

$[C_{12}H_{11}N_5SO_2]$ (289.3). Required: C, 49.81%; H 3.83%; N, 24.21%. Found: C, 49.37%; H 3.74%; N, 24.11%. IR (K.Br) cm^{-1}: 3450 (broad OH), 3405 (NH), 2860 (CH alkyl) and 1709, 1617 (2CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.25 (m, 2H, CH_2), 2.75 (m, 4H, $2CH_2$), 4.59 (br s, 1H, OH, D_2O exchangeable) 7.95 (br s, 2H, NH_2, D_2O exchangeable), 8.00 (s, 1H, pyrazole proton) and 11.40 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 289 (M^+) 16%, 272 (m/z) 27% and 191 (m/z) 100%.

2-Methylthio-4-(0-carboxyphenyl) Amino-5H, 6H, 7H-Cyclopentenothieno[2,3-d]pyrimidine (26)

A mixture of compound **3** (2.56 g, 0.01 mole) and anthranilic acid (1.37 g, 0.01 mole) was stirred under reflux in glacial acetic acid (30 mL) for 5 h. The reaction mixture was allowed to cool to 0°C, whereby a solid was formed. The solid formed was filtered off, dried, and recrystallized from acetic acid to yield the title compound as pale yellow crystals (2.28 g, 64%); m.p. 273–74°C.

Analyses and Spectral Data

$[C_{17}H_{15}N_3S_2O_2]$ (357.4). Required: C, 57.12%; H, 4.23%; N, 11.75%. Found: C, 50.83%; H, 3.77%; N, 11.54%. IR (K.Br) cm^{-1}: 3446 (broad NH), 3040 (CH aromatic), 2836 (CH alkyl) and 1661 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.45 (s, 3H, SCH_3), 2.85 (m, 4H, $2CH_2$), 7.10–8.85 (m, 4H, aromatic protons), 11.25 (br s, 1H, NH, D_2O exchangeable) and 12.65 (br s, 1H, COOH, D_2O exchangeable). MS (EI + Q1MS MR UP LR): 355 (M-2); 12.5%.

2-(Arylmethylenehydrazone)-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d] Pyrimidin-4(4H)-one (27a–c): General Procedure

A mixture of compound **2** (2.22 g, 0.01 mole), the appropriate aromatic aldehyde (0.01 mole), dioxane (30 mL), and a catalytic amount of piperidine was heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t., and then it was poured into water (100 mL). The formed precipitate was filtered off, washed with water, dried, and recrystallized from a proper solvent to yield **(27a–c)**.

2-(Phenylmethylenehydrazone)-3,5,6,7-tetrahydrocyclopentenothieno [2,3-d] pyrimidin-4(4H)-one (27a)

Compound **27a** was obtained from compound **2** (2.22 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as pale yellow crystals (2.20 g, 71%); m.p. 279–280°C.

Analyses and Spectral Data

[$C_{16}H_{14}N_4SO$] (310.36). Required: C, 61.91%; H 4.55%; N, 18.05%. Found: C, 61.80%; H 5.00%; N, 18.11%. IR (K.Br) cm^{-1}: 3358 (NH), 3037 (CH aromatic), 2909 (CH alkyl) and 1675 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 7.40–7.90 (m, 5H, phenyl protons), 8.05 (s, 1H, CH, ethylenic proton), 11.4 (br s, 1H, NH, D_2O exchangeable) and 11.6 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 310 (M^+) 100%.

2-(4-Chlorophenylmethylenehydrazone)-3,5,6,7-tetrahydrocyclopentenothieno [2,3-d] Pyrimidin-4 (4H)-one (27b)

Compound **27b** was obtained from compound **2** (2.22 g, 0.01 mole) and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.34 g, 68%); m.p. >300°C.

Analyses and Spectral Data

[$C_{16}H_{13}N_4SOCl$] (344.81). Required: C, 55.73%; H 3.79%; N, 16.25%. Found: C, 56.10%; H 3.50%; N, 16.11%. IR (K.Br) cm^{-1}: 3361 (NH), 3032 (CH aromatic), 2907 (CH alkyl) and 1672 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 7.45 (d, 2H, J = 10Hz, aromatic protons), 8.00 (s, 1H, CH, ethylenic proton), 8.05 (d, 2H, J = 10Hz, aromatic protons), 11.6 (br s, 1H, NH, D_2O exchangeable) and 11.7 (br s, 1H, NH, D_2O exchangeable).

2-(4-Methoxyphenylmethylenehydrazone)-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d] Pyrimidin-4(4H)-one (27c)

Compound **27c** was obtained from compound **2** (2.22 g, 0.01 mole) and 4-methoxybenzalde-hyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.48 g, 73%); m.p. >300°C.

Analyses and Spectral Data

[$C_{17}H_{16}N_4SO_2$] (340.1). Required: C, 60.02%; H 4.74%; N, 16.47%. Found: C, 59.30%; H 4.90%; N, 16.31%. IR (K.Br) cm^{-1}: 3140 (NH), 3034 (CH aromatic), 2907 (CH alkyl) and 1672 (CO). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 3.80 (s, 3H, OCH_3), 6.85 (d, 2H, J = 13Hz, aromatic protons), 7.80 (d, 2H, J = 13Hz, aromatic protons), 8.00 (s, 1H, CH, ethylenic proton), 11.35 (br s, 1H, NH, D_2O exchangeable) and 11.55 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 340.1 (M^+) 100%.

Compound **27d** was obtained from compound **2** (2.22 g, 0.01 mole) and acetaldehyde (0.44 g, 0.01 mole). The product was recrystallized from ethanol (30 mL) to yield the title compound as yellow crystals (1.60, 64); m.p. 162–164°C.

Analyses and Spectral Data

[$C_{11}H_{12}N_4SO$] (248.30). Required: C, 53.20%; H, 4.87%; N, 22.56%. Found: C, 53.14%; H, 4.94%; N, 21.82%. IR (K.Br) cm^{-1}: 3127 (NH), 2855 (CH alkyl) and 1675 (CO).

^{1}H-NMR ($CDCl_3$) δ ppm: 2.00 (d, 3H, CH_3); 2.35 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 2.95 (t, 2H, CH_2), 7.25 (m, 1H, CH) and 8.15 (br s, 1H, NH, D_2O exchangeable). MS (EI + Q1MS LMR UP LR): 247.98 (M^+) 100%.

4-(Arylmethylenehydrazone)-2-methylthio-5H, 6H, 7H, Cyclopenteno Thieno[2,3-d] Pyrimidines (28a–c): General Procedure

A mixture of compound **41** (2.52 g, 0.01 mole), the proper aromatic aldehyde (0.01 mole), dioxane (30 mL), and a catalytic amount of piperidine was heated under reflux for 6 h. The reaction mixture was allowed to cool to r.t. and then was poured into water (100 mL), whereby a solid precipitate was formed. The solid precipitate so-formed was filtered off, washed with water, dried, and recrystallized from the appropriate solvent to produce **(28a–c)**.

4-(Phenylmethylenehydrazone)-2-methylthio-5H, 6H, 7H-Cyclopentenothieno [2,3-d]pyrimidine (28a)

Compound **28a** was obtained from compound **4** (2.52 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane (30 mL) to yield the title compound as yellow crystals (2.50 g, 74%); m.p. 127–128°C.

Analyses and Spectral Data

[$C_{17}H_{16}N_4S_2$] (340.4). Required: C, 59.97%; H, 4.73%; N, 16.45%. Found: C, 60.00%; H, 4.57%; N, 61.41%. IR (K.Br) cm^{-1}: 3020 (CH aryl)

and 2920 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.55 (s, 3H, SCH_3), 2.90 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 7.45 (t, 3H, phenyl protons), 7.70 (d, 2H, phenyl protons), 8.30 (s, 1H, ethylenic proton) and 11.20 (br s, 1H, NH, D_2O exchangeable).

4-(4-chlorophenylmethylenehydrazone)-2-methylthion-5H,6H,7H-cyclopentenothieno[2,3-d]pyrimidine (28b)

Compound **28b** was obtained from compound **4** (2.52 g, 0.01 mole) and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dioxane to afford the title compound as yellow crystals (2.66 g, 71%); m.p. 214–216°C.

Analyses and Spectral Data

[$C_{17}H_{15}N_4S_2Cl$] (374.8). Required: C, 54.46%; H, 4.03%; N, 14.94%. Found: C, 54.19%; H, 3.77%; N, 14.88%. IR (K.Br) cm^{-1}: 3250 (NH), 3035 (CH aryl) and 2924 (CH aryl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.95 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 7.50 (d, 2H, J = 7.50 Hz, aromatic protons), 7.70 (d, 2H, J = 7.50Hz, aromatic protons), 8.30 (s, 1H, CH, ethylenic proton) and 11.25 (br s, 1H, NH, D_2O exchangeable).

4-(4-Methoxyphenylmethylenehydrazone)-2-methylthio-5H, 6H, 7H-Cyclopentenothieno [2,3-d] Pyrimidine (28c)

Compound **28c** was obtained from compound **4** (2.52 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane to yield the title product as yellow crystals (2.75 g, 74%); m.p. 180–181°C.

Analyses and Spectral Data

[$C_{18}H_{18}N_4S_2$](370.4). Required: C, 58.35%; H, 4.89%; N, 15.12%. Found: C, 57.83%; H, 5.10%; N, 15.01%. IR (K.Br) cm^{-1}: 3200 (NH), 3040 (CH alkyl) and 2927 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 2.90 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.8 (s, 3H, OCH_3), 7.00 (d, 2H, J = 10Hz, aromatic protons), 7.60 (d, 2H, J = 10Hz, aromatic protons), 8.20 (s, 1H, CH, ethylenic proton) and 11.10 (br s, 1H, NH, D_2O exchangeable).

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