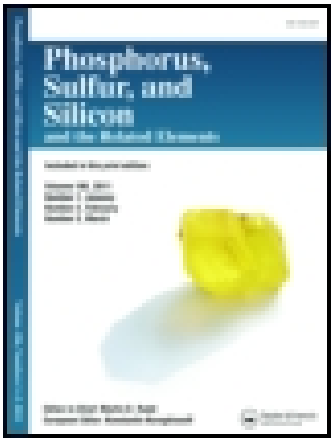

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Reactions of Novel Thienopyrimidine and Thiazolothienopyrimidine Derivatives

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Published online: 16 Jul 2007.

To cite this article: Kh. M. Abu-Zied (2007) Synthesis and Reactions of Novel Thienopyrimidine and Thiazolothienopyrimidine Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 182:9, 2179-2191, DOI: 10.1080/10426500701407714

To link to this article: http://dx.doi.org/10.1080/10426500701407714

Phosphorus, Sulfur, and Silicon, 182:2179–2191, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701407714

Synthesis and Reactions of Novel Thienopyrimidine and Thiazolothienopyrimidine Derivatives

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*In a one-pot reaction, 2-arylidine-6,7,8,9-tetrahydrohexenothieno[2,3-*d*]pyrimidine-3(3H),5(5H)-diones* **2a**,**b** *were prepared by the reaction of a ternary mixture of 2-thioxo-5,6,7,8-tetrahydrohexenothieno[2,3-*d*]pyrimidin-4(4H)-one* [1] (***1***), *chloroacetic acid, and a proper aldehyde. Compound* ***2a*** *react with hydroxyl amine hydrochloride to give corresponding oxime derivative* ***4***. *Reaction of* ***1*** *with 3-chloropent-2, 4-dione in ethanolic sodium hydroxide solution yielded S-acetyl acetone derivative* ***5b***. *The latter compound reacted with hydrazines affording the 2-pyrazolthio* ***6***. *Compound* ***5b*** *reacted with urea and thiourea to give* ***7a***, ***b***. *Also, compound* ***5b*** *underwent cyclization on boiling with acetic anhydride / pyridine mixture to yield thiazolopyrimidine derivative* ***8***. *Ketone compound* ***8*** *formed an oxime* ***9***. *Moreover, condensation of* ***8*** *with aromatic aldehyde furnished the derivative* ***11***.

Keywords ^{1}H-NMR; Mass spectra; pyrimidine; pyrazolothienopyrimidine

DISCUSSION

Our interest in thieno [2, 3-*d*] pyrimidine synthesis emerges from the numerous reports on their diverse biological activity.[2–7]

A part of our program is the synthesis of various pyrimidines and fused pyrimidines, such as thiazolothienopyrimidine and pyrazolothienopyrimidine derivatives.

Upon heating under reflux a mixture of 2-thioxo-5, 6,7,8-tetrahydrohexenothie-no[2,3-*d*]pyrimidin-4(4H)-one **1**, chloroacetic acid and aldehyde in acetic acid and acetic anhydride in presence of anhydrous sodium acetate, heterocycles **2a**,**b** were obtained in a good yields scheme 1.

The structure assignment is based on an independent preparation of **2a**,**b** by condensation of **3** with each of p-chloro benzaldehyde and

Received December 21, 2006; accepted April 2, 2007.
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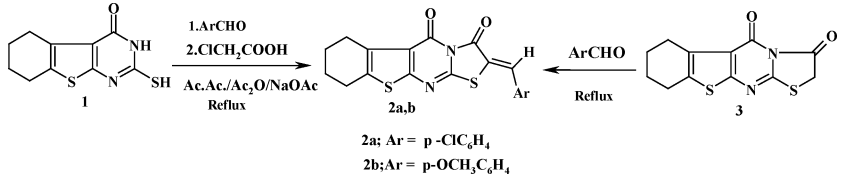
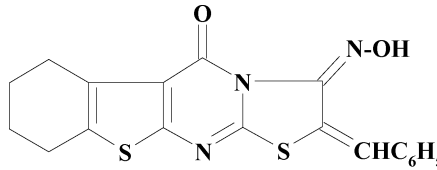


SCHEME 1

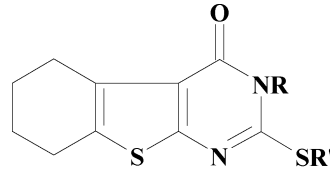
p-methoxy benzaldehyde in acetic acid in the presence of anhydrous sodium acetate.

Compound **2a** react with hydroxyl amine hydrochlorid to give corresponding oxime derivative **4**.



4

Alkylations of compound **1** in ethanolic potassium hydroxide solution with alkyl halide or choloro compound yielded alkylthio derivatives **5a–c**.



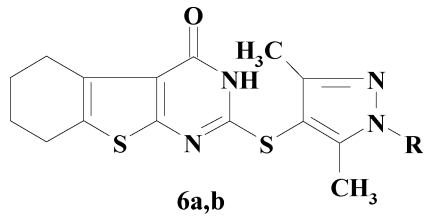
5

5a;R=H ,R'= -CH_3

5b;R=H ,R'= -$CH(COCH_3)_2$

5c;R=H ,R'= -CH_3CH_2

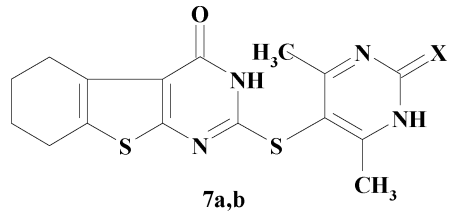
Compound **5b**, as a typical 1, 3-diketones, reacted with hydrazine hydrate and phenyl hydrazine to give the corresponding 2-(3, 5-dimethyl-1-pheny-1H-pyrazol-4-ylthio) derivatives **6a**, **b**, respectively.



6a,b

6a;R=H , 6b;R=C_6H_5

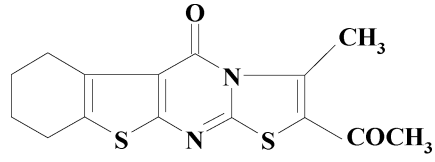
Also, compound **5b** was reacted with urea and thiourea to give **7a**, **b** derivatives, respectively.



7a,b

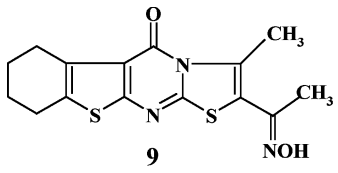
7a ; X= O , 7b ; X= S

Compound **5b** underwent cyclization on boiling with acetic anhydride/pyridine mixture to yield thiazolopyrimidine derivative **8**.

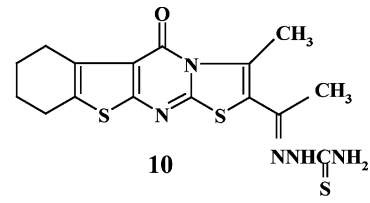


8

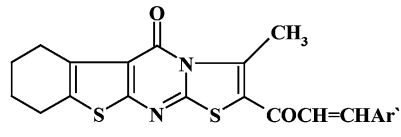
Ketone compound **8** formed an oxime **9** and thiosemicarbazide **10**. Also, condensation of **7** with aldehydes gave the derivatives **11a**, **b**. The IR spectrum of **11a** displayed two carbonyl absorption bands around 1734 and 1690 cm^{-1}.



9



10

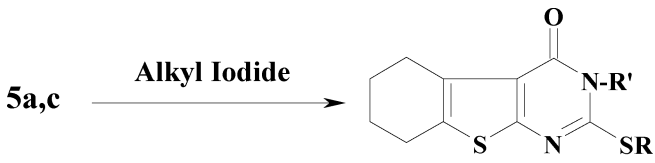


11a,b

11a; Ar`= -C_6H_5

11b; Ar`= p-ClC_6H_4

The 2-alkylthio derivatives **5a**, **c** underwent further alkylations on treatment with alkyl iodide in an ethanolic potassium ethoxide solution, the N-3 alkylated products **12**. Scheme 2.



12 a,b

12a ; R = -CH_3 , R' = -C_2H_5

12b ; R = -C_2H_3 , R' = -CH_3

SCHEME 2

EXPERIMENTAL

Solid compounds were recrystallized to constant melting points and dried under vacuum in 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 Microanalytical unit, National Research Centre and Faculty of Science, Cairo University. IR spectra were carried out on FT/IR 300 E Jasco using KBr discs. ^{1}H-NMR spectra were measured in DMSO or $CDCl_3$,

using Joel Ex. 270 NMR spectrometer. Signal was measured with reference to TMS as an internal standard. The Mass spectra were recorded on 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 UV Lamp.

2-Arylmethylene-6,7,8,9-tetrahydrothiazolo[3,2-*a*]-cyclohexenothieno [2,3,-*d*]pyrimidin-(5H)-3,5-dione 2a,b—General Procedure

Method (A)

A mixture of compound **1** (2.38 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol), appropriate aromatic aldehyde (0.01 mol), and anhydrous sodium acetate (0.02 mol) was stirred under reflux in glacial acetic acid (30 ml) and acetic anhydride (15 ml) for 3 h. The reaction mixture was cooled and poured into water (100 ml). The deposited precipitate was filtered-off and recrystallized from appropriate solvent to yield the title product.

Method (B)

A mixture of compound **3** (2.78 g, 0.01 mol), the appropriate aromatic aldehyde (0.01 mol) and anhydrous sodium acetate (0.02 mol) was stirred under reflux in glacial acetic acid (30 ml) and acetic anhydride (15 ml) for 2 h. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml). The deposited precipitate was filtered off, dried, and recrystallized from appropriate solvent to yield the title product.

*2-(p-Chlorophenylmethylene)-4,6,7,8,9-hexahydrothiazolo [3,2-*a*] cyclohexenothieno[2,3-*d*] pyrimidin-(5H)-3,5-dione 2a*

A mixture of compound **1** and p-chlorobenzaldehyde (1.06 g, 0.01 mol).The product was recrystallized from dimethylformamide (25 ml) to yield the title product as yellow crystals (2.63 g, 72%); m.p. 298–300°C. [$C_{19}H_{13}N_2S_2O_2Cl$] (400.3); Required: C, 56.92%; H, 3.26%; N, 6.98%; S, 15.99%. Found C, 56.85%; H, 3.45%; N, 6.87; S, 15.76%. IR (KBr) cm^{-1} 3028 (CH), 2900 (CH alkyl) and 1760, 1710 (2CO)^{1}H-NMR (CF_3 COOD: $CDCl_3$/1:1) δ ppm. 1.85 (m, 4H, $2CH_2$), 2.75 (t, 2H, $2CH_2$), 2.95 (t, 2H, $2CH_2$), 7.50 (d, 2H, J = 13Hz, phenyl protons), 7.75 (d, 2H, J = 13Hz, phenyl protons) and 8.10 (s, 1H, ethylenic proton).^{13}C-NMR(CF_3COOD: $CDCl_3$/1:1) δ ppm: 26.38, 28. 77, 30.08, and 32.40 ($4CH_2$); 68.00 (CH); 113.00, 115.00, 116.80, 119.44, 125.11, 126.87, 129.00, 130.10, 131.36, 134.60, 143.15, and 144.00 (thiophene carbon atoms, pyrimidine carbon atom, thiazol carbon atom, and phenyl carbon

atoms), 170.77 and 173.80 (2CO). MS (EI + Q1MS LMR UP LR): 400.3 (M^+) 100%.

2-(4-Methoxyphenylmethylene)-6,7,8,9-hexahydrothiazolo[3,2-a]cyclohexenothie-no[2,3-d]pyrimidin-(5H)-3,5-dione 2b

A mixture of compound **1** and 4-methoxy benzaldehyde (1.36 g, 0.01 mol). The compound was recrystallized from dimethylformamide (30 ml) to yield the title product as yellow needles crystals (3.17 g, 77%); m.p. 287–389°C.[$C_{20}H_{16}N_2S_2O_3$](396.49). Required: C, 60.58%; H, 4.06%; N, 7.06%. Found: C, 60.51%; H, 3.66%; N, 6.79%. IR (KBr) cm^{-1} 3028 (CH), 2930 (CH) and 1747, 1695 (2CO).^{1}H-NMR (CF_3 COOD: $CDCl_3$/1:1) δ ppm: 1.70 (m, 4H, $2CH_2$), 3.05 (m, 4H, $2CH_2$), 3.96 (s, 3H, OCH_3), 7.26 (d, 2H, J = 13Hz, aromatic protons), 7.61 (d, 2H, J = 13Hz, aromatic protons), and 8.20 (s, 1H, CH, ethylenic proton).^{13}C-NMR(CF_3COOD: $CDCl_3$/1:1) δ ppm:28.70, 29.50, 29.80, and 30.20 (CH_2); 56.50 (CH_3); 67.60 (CH); 108.40, 113.00, 133.80, 116.30, 117.50, 118.30, 122.00, 126.30, 134.80, 142.00, 142.50, 142.70, 155.60, and 157.20 (thiophene ring carbon atoms, pyrimidine ring carbon atom, thiazol ring carbon atom, and aromatic carbon atoms) and 170.8, 175.0 (2CO). MS (EI+MS/70 ev/T: 230°C): 396(M^+) 97.5%, 367 (M-HCO) 12.5%, 205 (M-$C_{10}H_8SO_2$) 10.42% and 160 (C_9H_8CO) 100%.

2,3,4,6,7,8-Hexahydro-5H-thiazolo[3,2-a]cyclohexenothieno-[2,3-d]pyrimidin-3,5-diones 3

A mixture of compound **1** (2.38 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol) and anhydrous sodium acetate (1.64 g, 0.01 mol) was heated gently, with stirring on a water bath (60°C) for 2 h. The reaction mixture was allowed to cool to room temperature and poured into water (100 ml). The deposited precipitate was filtered off and recrystallized from dimethylformamide (20 ml) to afford the title product as a colorless powder (1.61 g, 61%), m.p. >300 °C. [$C_{12}H_{10}N_2S_2O_2$] (278.35). Required: C, 51.78%; H, 3.62%; N, 10.08%. Found: C, 51.66%; H, 3.53%; N, 10.22%. IR (KBr) cm^1: 2930 (CH) and 1686, 1700 (2CO).^{1}H-NMR (DMSO-d_6)) δ ppm: 1.70 (m, 4H, $2CH_2$), 2.65 (t, 2H, CH_2) 2.80 (t, 2H, CH_2), and 3.45 (s, 2H, CH_2). ^{13}C- NMR (DMSO-d_6)δ ppm: 24.50, 25.00, 26.60, 27.20 and 28.80 (CH_2); 116.5, 135.3, 139.3, 156.2, and 157.7 (Thienopyrimidone carbon atoms) and 164.30, 168.03 (2CO). MS (EI + Q1MS LMR UP LR): 278(M^+) (Base peak) 100%.

2-Phenylmethylene-3-oxime-2,3,5,6,7,8-hexahydrocyclohexenothieno[2,3-d]pyrim-idine-(4H)-4-one 4

A mixture of compound **2a** (3.81 g, 0.01 mol), hydroxylamine hydrochloride (0.70 g, 0.01 mol), and anhydrous sodium acetate (1.64 g,

0.02 mol) was stirred under reflux in glacial acetic acid (30 ml) for 8 h. The reaction mixture was allowed to cool to room temperature and poured into water (100 ml.). The deposited precipitate was filtered-off and recrystallized from dioxane/dimethyl formamide (20/5 ml) to yield the title product as colorless powder (2.19 g, 57%), m.p. 297–298°C. [$C_{19}H_{15}N_3S_2O_2$] (381.48). Required: C, 59.82%; H, 3.96%; N, 11.01%; Found: C, 59.71%; H, 3.67%; N, 10.81%; IR (K.Br) cm^{-1}:3433 (broad NH), 3038 (CH), 2928 (CH alkyl) and 1696 (CO).^{1}H-NMR (DMSO-d_6)) δ ppm: 1.77 (m, 4H, $2CH_2$), 2.68 (t, 2H, CH_2) 2.83 (t, 2H, CH_2), 3.87 (br s, 1H,OH, D_2O exchangeable), 7.60–7.75 (m, 5H, phenyl protons), and 8.01 (s, 1H, CH, ethylenic protons). MS (EI + Q1MS LMR UP LR): 381.4 (M^+) 100%.

2-(S-Alkyl)-3,4,5,6,7,8-hexahydrocyclohexenothieno[2,3-*d*]pyrimidin-4-one 5a–c—General Method

To a warmed ethanolic potassium hydroxide solution [prepared by dissolving potassium hydroxide (0.56 g, 0.01 mol) in ethanol (50 ml)] was added compound **1** (2.38 g, 0.01 mol), the heating was continued for 30 min, and the mixture was allowed to cool to room temperature, and the proper halo-compound (0.012 mol) was added. The mixture was stirred under reflux for 5 h, then cooled to room temperature and poured into water (100 ml). The solid product so-precipitated was filtered-off, washed with water, dried, and recrystallized from appropriate solvent to produce **5a–c**.

*2-(Methylthio)-3,4,5,6,7,8-hexahydrocyclohexenothieno-[2,3-*d*]pyrimidin-4-one 5a*

From compound **1** (2.38 g, 0.01 mol) and methyl iodide (1.82 g, 0.012 mol). The compound was recrystallized from dioxane (35 ml) to yield the title product as a colorless crystals (1.80 g, 71%), m.p. 298–302°C. [$C_{11}H_{12}N_2S_2O$] (252.35). Required; C, 52.35%; H, 4.79%; N, 11.09%; S, 25.41%. Found: C, 51.73%; H, 4.51%; N, 10.77; S, 25.11%. IR (KBr) cm^{-1}:3400 (broad NH), 2920 (CH alkyl) and 1680 (CO).^{1}H-NMR (DMSO-d_6)) δ ppm: 2.35 (m, 4H, $2CH_2$), 2.45 (s, 3H, SCH_3), 2.85 (m, 4H, $2CH_2$), and 11.25 (br. s, 1H, NH, D_2O exchangeable). MS (EI-MS/70 ev/T = 230°C):252(M^+) 100%.

*2-(Acetylacetonethio)-3,4,5,6,7,8-hexahydrocyclohexenothieno[2,3-*d*]pyrimidin-4-one 5b*

From compound **1** (2.38 g, 0.01 mole) and chloroacetylacetone (1.61 g, 0.012 mol). The compound was recrystallized from dioxane (30 ml) to yield the title product as yellow crystals (2.72 g, 81%), m.p.

298–300°C. [$C_{15}H_{16}N_2S_2O_3$] (336.44). Required: C, 53.55%; H, 4.79%; N, 8.33%; S, 19.06%. Found: C, 53.11%; H, 4.37%; N, 7.86%; S, 18.31%. IR (KBr) cm^{-1}:3415 (broad NH and OH), 2930 (CH alkyl) and 1700, 1668 (CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.78 (m, 4H, $2CH_2$), 2.42 (s, 6H, $2CH_3$), 2.85 (t, 2H, CH_2), 2.93 (t, 2H, CH_2), 5.61 (s, 1H, CH), and 11.88 (br s, 1H, NH, D_2O exchangeable).^{13}C-NMR (DMSO-d_6)δ ppm: 13.90, 16.34, 18.55, 22.48, 26.06, and 38.86 (sp^2 carbon atoms), 118.70, 128.60, 136.44, 149.95, and 154.39 (Thienopyrimidone carbon atoms) and 158.44 and 168.6 (CO). MS (EI-MS/70 ev/T = 230°C): 336.4(M^+) 87.89%.

*2-(Ethylthio)-3,4,5,6,7,8-hexahydrocyclohexenothieno-[2,3-*d*]pyrimidin-4-one 5c*

From compound **1** (2.38 g, 0.01 mol) and ethyl iodide (1.86 g, 0.012 mol). The compound was recrystallized from ethanol to yield the title product as a colorless crystals (1.70 g, 63%), m.p. 188–189°C. [$C_{12}H_{14}N_2S_2O$] (266.38). Required: C, 52.35%; H, 4.79%; N, 11.10%. Found: C, 51.73%; H, 4.51%; N, 10.77%. IR (KBr) cm^{-1}: 3400 (broad NH), 2925 (CH alkyl) and 1660 (CO).^{1}H-NMR (DMSO-d_6)) δ ppm: 1.40 (t, 3H, CH_3), 2.45 (m, 4H, $2CH_2$), 2.76 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.05 (q, 2H, CH_2), and 9.70 (br s, 1H, NH, D_2Oexchangeable). MS (EI+Q1 MS LMR UPLR):266 (M^+) 100%.

2-(3, 5-Dimethyl-1H-or(1-phenyl)pyrazol-4-ylthio)-3,4,5,6,7,8-hexahydrocyclohex-enothieno [2, 3-*d*] pyrimidin-4-one 6a,b—General Procedure

A mixture of compound **5b** (3.36 g, 0.01 mol) and hydrazine hydrate (99–100%) or phenyl hydrazine hydrochloride (0.01 mol) in dioxane (20 ml), and ethanol (10 ml) was stirred under reflux for 6 h. The reaction mixture was allowed to cool to room temperature and then poured into cold water (100 ml). The deposited precipitate was collected upon filtration and recrystallized from appropriate solvent to produce **6a**, **b**.

*2-(3,5-Dimethyl-1H-pyrazol-4-ylthio)-3,4,5,6,7,8-hexahydrocyclohexenothieno[2,3-*d*] pyrimidin-4-one 6a*

From compound **5b** (3.36 g, 0.01 mol) and hydrazine hydrate (12 ml). The compound was recrystallized from dioxane (35 ml) to yield the title product as yellow crystals (2.25 g, 68%), m.p. 300–302°C. [$C_{15}H_{16}N_4S_2O$] (332.46) Required: C, 54.19%; H, 4.84%; N, 16.85%. Found: C, 53.55%; H, 4.61%; N, 16.64%. IR (KBr) cm^{-1}:3420 (NH), 2880 (CH alkyl) and 1660 (CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.76 (m, 4H, $2CH_2$), 2.60 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.73 (t, 2H, $2CH_2$), 2.88

(t, 2H, CH_2), and 9.05 (br s, 1H, NH, D_2O exchangeable).MS (EI+Q1 MS LMR UP LR): 332.4 (M^+) 86.70%.

*2-(3,5-Dimethyl-1-phenylpyrazol-4-ylthio)-3,4,5,6,7,8-hexahydrocyclohexeno[2,3-*d*]pyrimidin-4-one 6b*

From compound **5b** (3.36 g, 0.01 mol) and phenyl hydrazine hydrochloride (1.51 g, 0.01 mol). The compound was recrystallized from dioxane/dimethyl formamide (30 ml/5 ml) to yield the title product as yellow crystals (2.89 g, 71%); m.p. 283–285°C. [$C_{21}H_{20}N_4S_2O$] (408.55). Required: C, 61.73%; H, 4.93%; N, 13.71%. Found: C, 61.53%; H, 4.55%; N, 13.45%. IR (KBr) cm^{-1}:3443 (broad NH), 3043 (CH), 2926 (CH alkyl), and 1670 (CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.74 (m, 4H, $2CH_2$), 2.15 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.77 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 7.40–7.55 (m, 5H, phenyl protons), and 11.33 (br s , 1H , NH , D_2O exchangeable).^{13}C-NMR (DMSO-d_6)δ ppm: 16.40 and 18.06 (CH_3); 26.77, 27.4, 28.6 and 28.9 (CH_2); 104.02, 116.11, 126.00, 127.18, 130.02, 134.49, 138.84, 140.05, 144.37, 152.81, 153.07, 155.16, and 157.21 (thienopyrimidone carbon atoms, pyrazol ring carbon atoms and phenyl carbon atoms) and 166.70 (CO).MS (EI+Q1 MS LMR UP LR): 408.5 (M^+) 91.63%.

2-(4,6-Dimethyl-2-oxo-our(2-thioxo)-1,2-dihydropyrimidin-5-ylthio)-3,4,5,6,7,8-exahydrocyclohexenothieno[2,3-*d*] pyrimidin-4-one 7a,b—General Procedure

A mixture of compound **5b** (3.36 g, 0.01 mol) and urea (0.48 g, 0.01 mol) or thiourea (0.76 g,0.01 mol) was stirred under reflux in dioxane (30 ml) in the presence of a catalytic amount of piperidine for 8 h .The reaction mixture was allowed to cool to room temperature and poured into water (100 ml). The formed precipitate was filtered-off, washed withed water, and recrystallized from suitable solvent to give compounds **7a**, **b** in a good yield.

*2-(4,6-Dimethyl-2-oxo-1,2-dihydropyrimidin-5-ylthio)-3,4,5,6,7,8-hexahydrocyclo-hexenothieno [2, 3-*d*] pyrimidin-4-one 7a*

From compound **5b** (3.36 g, 0.01 mol) and urea (0.48 g, 0.01 mol).The product was recrystallized from dioxane (30 ml) to yield **7a** as yellow powder (2.40 g, 66%), m.p. 271–273°C. [$C_{16}H_{16}N_4S_2O_2$] (360.47). Required: C, 53.31%; H, 4.47%; N, 15.54%. Found: C, 53.01%; H, 4.28%; N, 14.88%.IR (K.Br) cm^{-1}:3450 (broad NH), 2928 (CH alkyl) and 1660, 1666 (2CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.75 (m, 4H, $2CH_2$), 2.15 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.75 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 9.35 (br s,

1H, NH, D_2O exchangeable), and 11.02 (br s, 1H, NH, D_2O exchangeable). MS (EI+Q1 MS LMR UP LR): 360.4 (M^+) 100%.

*2-(4,6-Dimethyl-2-thioxo-1,2-dihydropyrimidin-5-ylthio)-3,4,5,6,7,8-hexahydrocycl-ohexenothieno[2,3-**d**] pyrimidin-4-one 7b*

From compound **5b** (3.36 g, 0.01 mol) and thiourea (0.48 g, 0.01 mol).The product was recrystallized from dioxane (30 ml) to yield **7b** as yellow crystal (2.50 g, 67%), m.p. 278–280°C. [$C_{16}H_{16}N_4S_3O$] (376.54). Required: C, 51.03%; H, 4.28%; N, 14.88%. Found: C, 50.61%; H, 3.55%; N, 14.54%.IR (KBr) cm^{-1}:3443 (broad NH), 2930 (CH alkyl) and 1668 (CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.70 (m, 4H, $2CH_2$), 2.08 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.71 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 8.55 (br s, 1H, NH, D_2O exchangeable), and10.65 (br s, 1H, NH, D_2O exchangeable). MS (EI+Q1 MS LMR UP LR): 376.5 (M^+) 100%.

*2-Acetyl-3-methylthiazolo [3′, 2′-**a**]-5,6,7,8-tetrahydrocyclohexenothieno[2,3-**d**] pyri-imidin-5-one 8*

A solution of compound **5b** (3.36 g, 0.01 mol) in a mixture of acetic anhydride-pyridine (20 ml: 10 ml) was stirred under reflux for 6 h. The reaction mixture was allowed to cool to room temperature, then the deposited precipitate was filtered-off, dried, and recrystallized from dioxane (30 ml) to yield the title product as a light yellow crystals (2.48, 77%), m.p. 211–213°C. [$C_{15}H_{14}N_2S_2O_2$] (318.42). Require: C, 56.34%; H, 4.42%; N, 9.21%. Found: C, 55.57%; H, 3.89%; N, 8.81%. IR (KBr) cm^{-1}:2944 (CH alkyl) and 1700, 1666 (2CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.73 (m, 4H, $2CH_2$), 2.56 (s, 3H, CH_3), 2.70 (t, 2H, CH_2), 2.80 (t, 2H, CH_2), and 3.06 (s, 3H, CH_3).^{13}C-NMR (DMSO-d_6)δ ppm: 18.03 and 26.90 (CH_3), 28.90, 30.03, 30.17, and 30.67 (CH_2), 113.09, 121.42, 137.11, 139.76, 142.4, 156.60, and 156.86 (Thiazolothienopyrimidone carbon atoms) and 170.00, 185.45 (2CO). MS (EI+Q11.33 1 MS LMR UP LR): 318.4(M^+) 100%.

*2-(Acetoxime)-3-methylthiazolo[3′,2′-**a**]-6,7,8,9-tetrahydrocyclohexenothieno[2,3-**d**]- pyrimidin-(5H)-5-one 9*

A mixture of compound **8** (3. 18 g, 0.01 mol) and hydroxylamine hydrochloride (0.70 g, 0.01 mol) in dioxane (30 ml) and a catalytic amount of pipridine was added. The reaction mixture was stirred under reflux for 8 h, and then it was allowed to cool to room temperature and poured into water (100 ml). The deposited precipitate was collected upon filtration and recrystallized from dioxane/dimethylformamide (20 ml/10 ml) to yield the title product as yellow crystals (1.94 g, 61%), m.p. 251–253°C. [$C_{15}H_{15}N_3S_2O_2$] (333.44). Required: C, 54.03%; H, 4.53%; N,

12.60%. Found: C, 53.71%; H, 4.35%; N, 12.51%.IR (KBr) cm^{-1}:3455 (broad OH and NH), 2930 (CH alkyl) and 1691 (CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.73 (m, 4H, $2CH_2$), 2.25 (s, 3H, CH_3), 2.70 (t, 2H, CH_2), 2.80 (s, 3H, CH_3), and 2.85 (t, 2H, CH_2) and 10.25 (br s, 1H, NH, D_2O exchangeable). MS (EI+Q1 MS LMR UP LR): 332 (M-1) 100%.

*2-(Acetothiosemicarbazone)-3-methylthiazolo [3′, 2′-*a*]-6, 7,8,9-tetrahydrocyclohexeno-thieno [2,3-*d*] pyrimidin-(5H)-5-one 10*

A mixture of compound **8** (3.36 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in dioxane (30 ml) and catalytic amount of piperidine was added. The reaction mixture was stirred under reflux for 8 h, and then it was allowed to cool to room temperature and poured into water (100 ml). The deposited precipitate was filtered-off, dried, and recrystallized from dimethylformamide (30 ml) to yield the title product as yellow crystals (3.36 g, 68%), m.p. 247–249°C. [$C_{15}H_{15}N_5S_3O$] (391.54). Required: C, 49.08%; H, 4.37%; N, 17.88%. Found: C, 48.70%; H, 4.11%; N, 17.56%. IR (KBr) cm^{-1} 3344 (NH_2), 3150 (NH), 2929 (CH alkyl) and 1690 (CO).^{1}H-NMR (DMSO-d_6)δ ppm:1.70 (m, 4H, $2CH_2$), 2.30 (s, 3H, CH_3), 2.70 (t, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.85 (t, 2H, CH_2) , 8.15 (br s, 2H , NH_2, D_2O exchangeable), and 11.65(br s, 1H, NH, D_2O exchangeable). MS (EI+Q1 MS LMR UP LR): 390.5 (M^+); 100%.

2-Cinnamoyl (derivatives)-3-methylthiazolo [3′, 2′-*a*]-6, 7, 8,9-tetrahydrocyclohexeno-thieno [2, 3-*d*] pyrimidin-(5H)-5-one 11a,b—General Procedure

A mixture of compound **8** (3.36 g, 0.01 mol), the proper aromatic aldehyde (0.01 mol), and a catalytic amount of piperidine was heated at 170–180°C in a test tube for 3 h. The product was solidified by cooling and addition of methanol (50 ml). The precipitate so-formed was collected by filtration and recrystallized from the proper solvent to produce **11a**,**b**.

*2-Cinnamoyl-3-methyl-thiazolo[3′,2′-*a*]-6,7,8,9-tetrahydrocyclohexenothieno[2,3-*d*]-pyrimidin-(5H)-5-one 11a*

From compound **8** (3.18 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mol).The compound was recrystallized from dioxane (30 ml) to yield the title compound as yellow crystals (2.40 g, 59%), m.p. 253–255°C. [$C_{22}H_{18}N_2S_2O_2$] (406.52). Required: C, 65.00%; H, 4.46%; N, 6.89%. Found: C, 64.71%; H, 4.33%; N, 6.54%. IR (KBr) cm^{-1} 3030 (CH

aromatic), 2926 (CH alkyl) and 1710, 1680 (2CO).^{1}H-NMR ($CDCl_3$)δ ppm: 1.76 (m, 4H, $2CH_2$), 2.75 (t , 2H , CH_2), 2.88 (t , 2H , CH_2), 3.15 (s , 3H , CH_3), 7.15 (d, 1H, J = 10Hz , ethylenic proton), 7.55–7.86 (m , 5H, phenyl protons), and 7.90 (d, 1H , J = 10Hz , ethylenic proton). MS (EI + Q1 MS LMR UP LR): 406.5 (M^+) 100%.

2-(p-Methoxycinnamoyl)-3-methylthiazolo [3′, 2′-a]-6,7,8,9-tetrahydrocyclohexeno-thieno [2,3-d] pyrimidin-(5H)-5-one 11b

From compound 8 (3.18 g, 0.01 mol) and 4-methoxy benzaldehyde (1.36 g, 0.01 mol). The compound was recrystallized from dioxane (30 ml) to yield the title product as yellow crystals (2.58 g, 61%), m.p. 246–248°C. [$C_{23}H_{20}N_2S_2O_3$] (436.55) Required: C, 62.54%; H, 4.29%; N, 6.63. Found: C, 62.31%; H, 3.91%; N, 6.50%. IR (KBr) cm^{-1}:3025 (CH), 2929 (CH alkyl) and 1693, 1680 (2CO).^{1}H-NMR (DMSO-d_6)δ ppm: 1.70 (m , 4H , $2CH_2$), 2.22 (s, 3H , CH_3), 2.77(t , 2H CH_2), 2.90 (t, 2H, CH_2), 3.45 (s , 3H, CH_3) 7.05 (d, 1H, J = 13Hz, ethylenic proton), 7.60–7.80 (m, 4H , phenyl protons), and 7.77 (d, 1H, J = 13Hz, ethylenic proton). MS (EI + Q1 MS LMR UP LR): 436.5 (M^+) 89.60%.

2-Alkylthio-3-alkyl-5,6,7,8-tetrahydrocyclohexenothieno[2,3-*d*]pyrimidin-(4H)-4- one 12a,b—General Procedure

To a warmed ethanolic sodium ethoxide solution (prepared by dissolving (0.23 g, 0.01 mol) of sodium metal in absolute ethanol (30 ml)) was added each of compound **5a** or **5c** (0.01 mol), the heating was continued for 30 min, and the mixture was allowed to cool to room temperature and the proper alkyl iodide (0.012 mol) was added. The mixture was stirred under reflux for 3 h, and then cooled to room temperature and poured into cold water (100 ml). The solid so-precipitated was filtered-off, washed with water, dried, and recrystallized from appropriate solvent to produce **12a**,**b**.

2-Methylthio-3-ethyl-5,6,7,8-tetrahydrocyclohexenothieno-[2,3-d]pyrimidin-(4H)-4-one 12a

From compound **5a** (2.52 g, 0.01 mol) and ethyl iodide (2.10g, 0.012 mol). The compound was recrystallized from ethanol (30 ml) to yield the title product as a colorless crystals (2.30 g, 82%), m.p. 211–213°C. [$C_{13}H_{16}N_2S_2O$] (280.41). Required: C, 55.68 %; H , 5.75 % ; N, 9.98 % ;S , 22.86% .Found: C, 55.55%; H, 5.61%; N, 9.70%;S , 22.70 %. IR (KBr) cm^{-1}2922 (CH alkyl) and 1675 (CO).^{1}H-NMR ($CDCl_3$)δ ppm: 1.40 (t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 2.64 (s, 3H, CH_3), 2.80 (t, 2H,

CH_2), 2.86 (t, 2H, CH_2), and 4.15 (q, 2H, CH_2). MS (EI + Q1 MS LMR UP LR): 280.4 (M^+) 86.20%.

*2-Ethylthio-3-methyl-5,6,7,8-tetrahydrocyclohexenothieno-[2,3-*d*]pyrimidin-(4H)-4-one 12b*

From compound **5c** (2.66 g, 0.01 mol) and methyl iodide (1.82 g, 0.012 mol). The compound was recrystallized from ethanol (25 ml) to yield the title product as a colorless crystals (2.04 g, 78.40%), mp. 193–195°C. [$C_{13}H_{16}N_2S_2O$] (280.41). Required: C, 55.68%; H, 5.75%; N, 9.89%; S, 22.87 %. Found: C, 55.53%; H, 5.49%; N, 9.64%, S; 22.67%. IR (KBr) cm^{-1} 2930 (CH alkyl) and 1668 (CO).^{1}H-NMR ($CDCl_3$)δ ppm: 1.43 (t, 3H, CH_3), 1.75 (m, 4H, $2CH_2$), 2.66 (s, 3H, CH_3), 2.75 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), and 4.20 (q, 2H, CH_2). MS (EI + Q1 MS LMR UP LR): 279 (M^+) 93.10%.

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