Synthesis of Novel Pyridothienopyrimidines, Pyridothienopyrimidothiazines, Pyridothienopyrimidobenzthiazoles and Triazolopyridothienopyrimidines

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The reaction of 3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide (**1a)** or its N-aryl derivatives **1b-d** with carbon disulphide gave the pyridothienopyrimidines **2a-d**, whilst when the same reaction was carried out using N^1-arylidene-3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbohydrazides (**1e-h)**, pyridothienothiazine **3** was obtained. Also, refluxing of **1b-d** with acetic anhydride afforded oxazinone derivative **4**. Compounds **2a** and **2b-d** were also obtained by the treatment of thiazine **3** with ammonium acetate or aromatic amines, respectively. When compound **2a** was allowed to react with arylidene malononitriles or ethyl α-cyanocinnamate, novel pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*][1,3] thiazines **5a-c** were obtained. Treatment of **2b-d** with bromine in acetic acid furnished the disulphide derivatives **6a-c**. U.V. irradiation of **2b-d** resulted in the formation of pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*]benzthiazoles **7a-c**. The reaction of **2a-d** with some halocarbonyl compounds afforded the corresponding *S*-substituted thiopyrido thienopyrimidines **8a-j**. Compound **8b** was readily cyclized into the corresponding thiazolo[3″,2″-*a*]-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine **9** upon treatment with conc. sulphuric acid. Heating of **2a,b** with hydrazine hydrate in pyridine afforded the hydrazino derivatives **11a,b**. Reaction of ester **8c** with hydrazine hydrate in ethanol gave acethydrazide **10**. Compounds **10** and **11a,b** were used as versatile synthons for other new pyridothienopyrimidines **12-15** as well as [1,2,4] triazolopyridothienopyrimidines **16-19**.

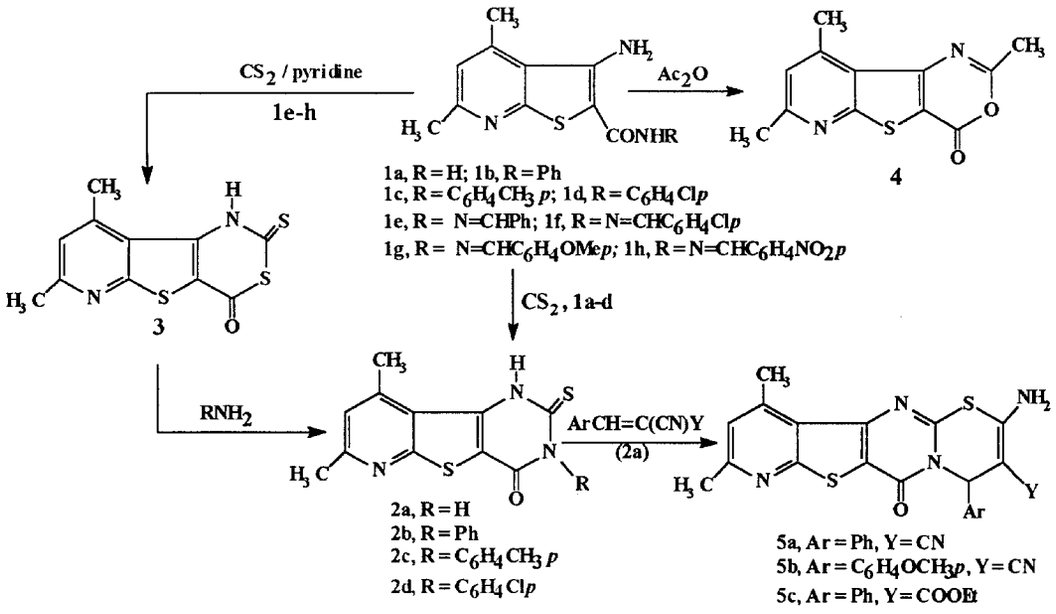
INTRODUCTION

The biological activities of condensed pyrimidines as sedatives, antibacterials and antimalarials are well documented.[1,2] In particular, many thienopyrimidines have been evaluated pharmacologically and used as analgesic, anti-inflammatory, anticonvulsant and antimicrobial agents.[1] Also, some thienopyrimidines have been found to show activity against many organisms.[3,4] 1,3-Disubstituted-2,4-dioxo-thieno[2,3-*d*]pyrimidine-1-acetic acids were evaluated as aldose reductase inhibitors and show significant AR inhibitory activity *in vitro*.[5] Vega et al.[6,7] found that some thieno-[2,3-*d*]pyrimidines have analgesic, antipyritic and anti-inflammatory activity at concentrations lower than 50 mg/kgip and have effect on the inhibition of Hellacell growth. Moreover, pyridothienopyrimidines have been the subject of chemical and biological studies on account of their interesting pharmacological properties. Such derivatives have analgesic,[8] antipyretic[9] and antiinflammatory[10,11] properties. Encouraged by all these facts and as a continuation of our previous work on annelated thieno[2,3-*b*]pyridines,[12-18] we report herein the synthesis of novel heterocyclic compounds containing pyridothienopyrimidine moiety of anticipated biological and medicinal importance.

RESULTS AND DISCUSSION

The reaction of 3-amino-4,6-dimethylthieno[2,3-*b*]-pyridine-2-carboxamide (**1a**)[12] or its *N*-aryl derivatives **1b-d** with carbon disulphide when heated in pyridine gave the promising pyridothienopyrimidines **2a-d**,[12,14] whilst when the latter reaction under the same condition was carried out using N^1-arylidene-3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbohydrazides (**1e-h)**[12] instead of the carboxamide derivatives **1b-d**, pyridothienothiazine **3** was obtained. Also, refluxing of thienopyridines **1b-d**[12] with acetic anhydride led to the formation of oxazinone derivative **4**. The formation of thiazino compound **3** occurred through the addition of an amino group on carbon disulphide to give dithiocarbamic acid followed by departure of a arylidenehydrazone molecule,[13] and the formation of oxazinone derivative **4** took place *via* acetylation of the amino group followed by departure of aromatic amine. Compounds **2a** and **2b-d** were also obtained upon treatement of thiazine derivative **3** with ammonium acetate in acetic acid or with the respective aromatic amines in ethanol, respectively. When compound **2a** was allowed to react with arylidene malononitrile and/or ethyl α-cyanocinnamate in refluxing ethanol containing a catalytic amount of triethylamine, the Michael addition occurred followed by

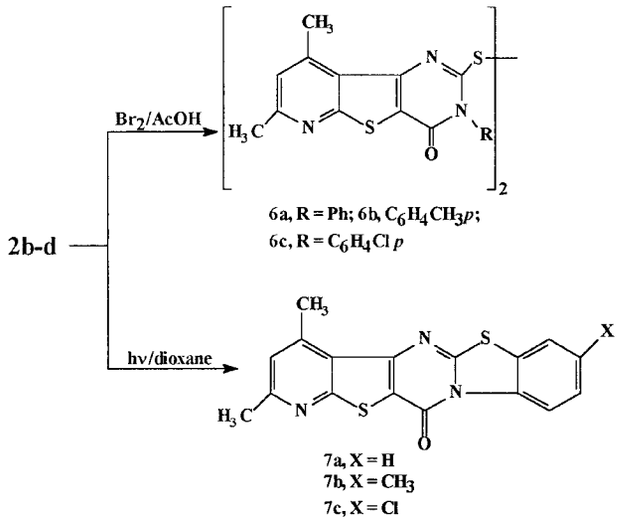
Scheme I



addition of SH on the nitrile group to afford novel pyrido-[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*][1,3]thiazines **5a-c** (Scheme I).

On treatment of pyridothienopyrimidinethiones **2b-d** with bromine in acetic acid, oxidation occurred and disulphide derivatives **6a-c** were isolated. An attempt to synthesize novel heterocyclic systems containing pyrido[3″,2″:4′,5′]-thieno[3′,2′:4,5]pyrimido[2,1-*b*]benzthiazole moiety involved U.V. irradiation of compounds **2b-d** in dioxane under aerobic conditions whereby a cyclodehydrogenation reaction took place and the target compounds **7a-c** were obtained (Scheme II).

Scheme II

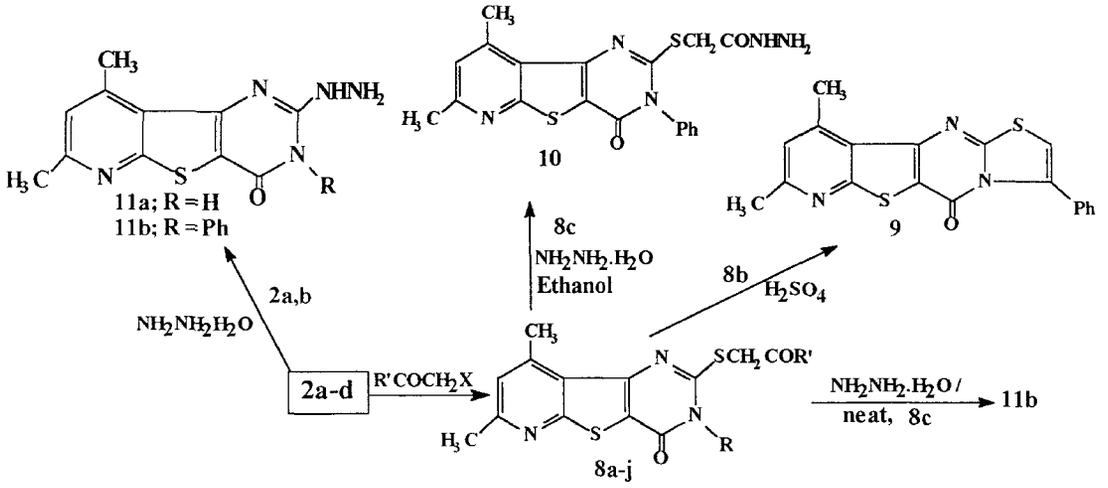


The reaction of compound **2a** with an equimolar quantity of ethyl chloroacetate or phenacyl bromide by refluxing in acetone in the presence of anhydrous K_2CO_3 gave *S*-alkylated products **8a** and **8b,** respectively. Similarly, compounds **2b-d** were reacted with some halocompounds like ethyl chloroacetate, ω-bromoacetophenones, chloroacetamide or chloro-*N*-arylacetamides by refluxing in ethanol containing sodium acetate to afford the corresponding *S*-substituted thiopyridothienopyrimidines **8c-j**. Compound **8b** was readily cyclized into the corresponding thiazolo[3″,2″-*a*]pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine **9** upon treatment with conc. sulphuric acid at room temperature. Heating compounds **2a,b** with hydrazine hydrate in pyridine resulted in the formation of the hydrazino derivatives **11a,b**. Compound **11b** was also obtained by refluxing the ester derivative **8c** with hydrazine hydrate under neat condition. When the latter reaction was performed in refluxing ethanol, the corresponding acethydrazide **10** was produced (Scheme III).

Acethydrazide **10** was condensed with benzaldehyde in ethanol to give the hydrazone **12** and with acetylacetone in acetic acid to afford the corresponding pyrazolyl derivative **13** (Scheme IV).

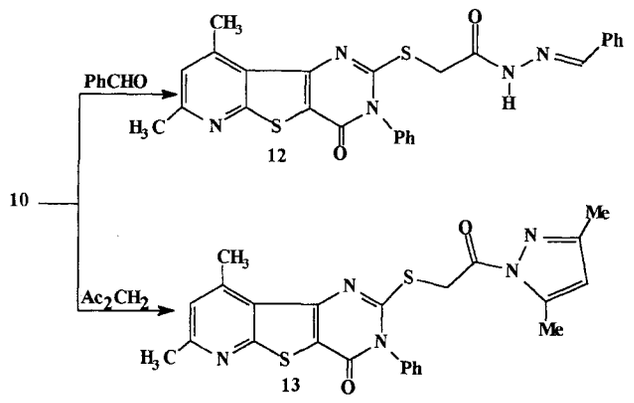
Hydrazino compounds **11a,b** proved to be versatile synthons for other new pyridothienopyrimidines as well as [1,2,4]triazolopyridothienopyrimidines. Thus, the reaction of **11b** with benzaldehyde or with acetylacetone in refluxing ethanol gave the corresponding hydrazone **14** and pyrazolyl derivative **15**. Also when compounds **11a,b** were allowed to react with triethyl orthoformate in the presence of a catalytic amount of acetic acid, the triazolo derivatives **16, 17** were ob-

Scheme III



Compd.	R'	R	Compd.	R'	R
8a	OEt	H	8g	$C_6H_4Cl\,p$	Ph
8b	Ph	H	8h	NH_2	Ph
8c	OEt	Ph	8i	NHPh	Ph
8d	OEt	$C_6H_4CH_3p$	8j	$NHC_6H_4Cl\,p$	Ph
8e	OEt	$C_6H_4Cl p$			
8f	Ph	Ph			

Scheme IV



tained. Other triazole compounds **18, 19** were synthesized by heating compounds **11a,b** with carbon disulphide in pyridine (Scheme V).

The structural formulas of all newly synthesized compounds were elucidated and confirmed by elemental and spectroscopic analysis (*cf.* Experimental).

EXPERIMENTAL

All melting points were measured on a Fisher-John apparatus and are uncorrected. IR spectra were run on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}); ^1H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer, TMS as the internal standard (δ in ppm). All elemental analyses were carried out on a Perkin-Elmer 240C elemental analyser; the results of the analysis were in good agreement with the calculated values.

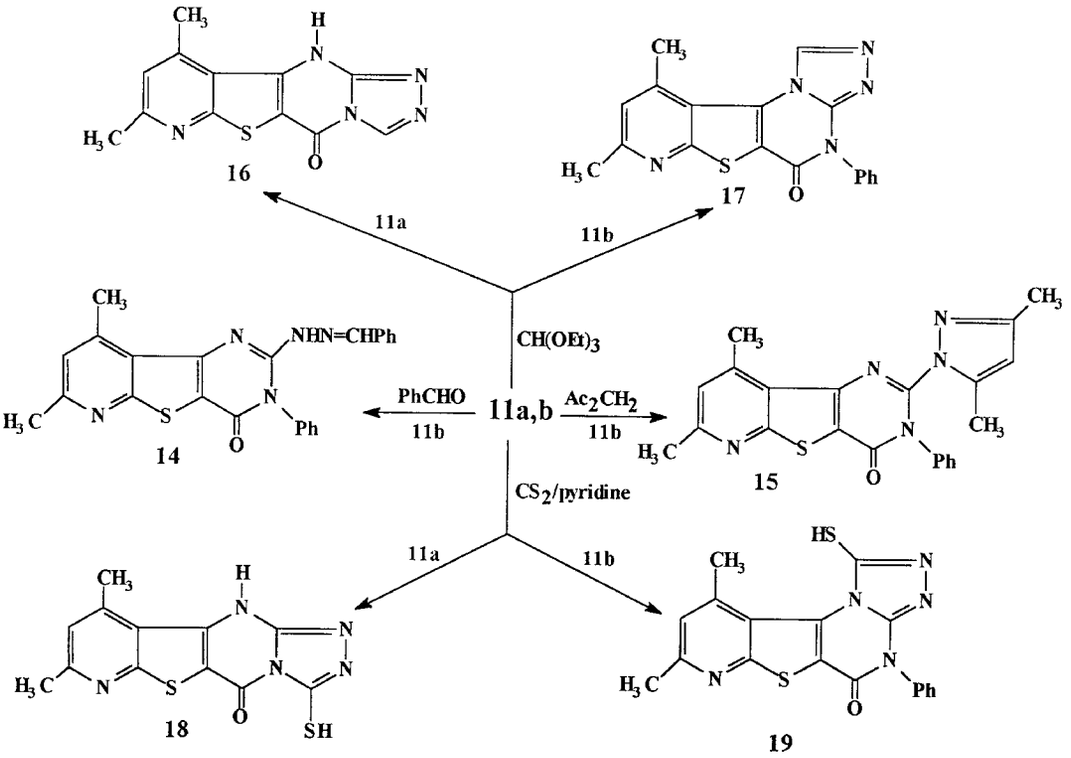
7,9-Dimethyl-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-4-one (2a)

A) Prepared according to reported methods.[14] B) A mixture of **3** (0.28 g, 0.001 mol) and ammonium acetate (0.77 g, 0.01 mol) in 20 mL acetic acid was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from dioxane to give **2a** as yellow crystals. yield: 0.19 g (72%); m.p.: >300 °C. Anal. Calcd. for $C_{11}H_9N_3OS_2$ (263.33): C, 50.17; H, 3.44; N, 15.96; S, 24.35%; Found: C, 50.39; H, 3.68; N, 16.03; S, 24.16%.; IR: ν = 3220 (NH), 2950-2800 (SH), 1680 (CO); ^1H NMR (DMSO-d_6): δ = 2.5, 2.95 (2s, 6H, $2CH_3$), 7.05 (s, 1H, CH pyridine), 9.1 (br, 1H, NH), 11.0 (s, 1H, NH) ppm.

3-Aryl-7,9-dimethyl-1,2,3,4-tetrahydro-2-thioxopyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-one (2b-d); general procedures

A) These compounds were prepared according to re-

Scheme V



ported procedures.[12,14]

B) A mixture of **3** (0.28 g, 0.001 mol) and the apropriate aromatic amine (0.01 mol) in ethanol (20 mL) was refluxed for 3 h, then allowed to cool. The solid product was collected and recrystallized from dioxane.

7,9-Dimethyl-3-phenyl-1,2,3,4-tetrahydro-2-thioxopyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-one (2b)

Prepared from **3** and aniline; yield: 84%; m.p.: 262 °C; Lit.[12] m.p.: 263 °C; Anal. Calcd. for $C_{17}H_{13}N_3OS_2$ (339.43): C, 60.16; H, 3.86; N, 12.38; S, 18.89%.; Found: C, 60.24; H, 4.03; N, 12.50; S, 18.96%.; IR: ν = 3220 (NH), 1670 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5,3.1 (2s, 6H, $2CH_3$), 7.1 (s, 1H, CH pyridine), 7.3-7.6 (m ,5 H, ArH), 11.0 (s, 1H, NH) ppm.

7,9-Dimethyl-1,2,3,4-tetrahydro-2-thioxo-3-*p*-tolylpyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4-one (2c)

Prepared from **3** and *p*-toluidine; yield: 72%; m.p.: 252 °C; Anal. Calcd. for $C_{18}H_{15}N_3OS_2$ (353.46): C, 61.17; H, 4.28; N, 11.89; S, 18.14%.; Found: C, 60.91; H, 4.08; N, 12.00; S, 17.96%.; IR: ν = 3220 (NH), 1670 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.1, 3.3 (3s, 9H, $3CH_3$), 7.0 (s, 1H, CH pyridine), 7.4-7.8 (dd, 4H, ArH), 10.5 (s, 1H, NH) ppm.

3-(*p*-Chlorophenyl)-7,9-dimethyl-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-one (2d)

Prepared from **3** and *p*-chloroaniline; yield: 65%; m.p.: >300 °C, Lit.[14] m.p.: >300 °C; Anal. Calcd. for $C_{17}H_{12}ClN_3OS_2$ (373.87): C, 54.61; H, 3.24 ;Cl, 9.48; N, 11.24; S, 17.15; Found: C, 54.82; H, 3.44 ; Cl, 9.55; N, 11.09; S, 17.00; IR: ν = 3220 (NH), 1670 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.1 (2s, 6H, $2CH_3$), 7.2 (s, 1H, CH pyridine), 7.6-8.0 (dd, 4H, ArH), 10.5 (s, 1H, NH) ppm.

1,2-Dihydro-7,9-dimethyl-2-thioxopyrido[3′,2′:4,5]thieno-[3,2-*d*][1,3]thiazine-4-one (3)

A sample of compounds **1e-h**[14] (0.005 mol) was refluxed on a steam bath with 1 mL carbon disulphide in 20 mL pyridine for 45 h. The solid product which precipitated while refluxing was separated by filtration and recrystallized from dioxane as yellow crystals of **3**. yield: 0.70-0.91 g (50-65%); m.p.: 255 °C; Anal.Calcd. for $C_{11}H_8N_2OS_3$ (280.38): C, 47.12; H, 2.88; N, 9.99; S, 34.30%; Found: C, 47.02; H, 3.00; N, 10.11; S, 34.45%; IR: ν = 3250 (NH), 1700 (C=O), 1250

(C=S); ^{1}H NMR (DMSO-d_6): δ = 2.4 , 2.9 (2 s, 6H, 2 CH_3), 7.05 (s, 1H, CH pyridine), 10.5 (s, 1H, NH) ppm.

2,7,9-Trimethylpyrido[3′,2′:4,5]thieno[3,2-*d*][1,3]oxazin-4-one (4)

A sample of compounds **1b-d** (0.002 mol) was heated in 20 mL acetic anhydride for 4 h, then concentrated and allowed to cool. The solid product was collected, recrystallized from xylene and identified as oxazinone derivative **4** by comparison of its elemental and spectral analyses with an authentic sample prepared previously.[15] yield: 60-68%; m.p.: 208-210 °C; Lit.[15] m.p.: 208-210 °C.

Reaction of 7,9-dimethyl-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-one (2a) with arylidene malononitrile or ethyl α-cyanocinnamate; formation of pyridothienopyrimidothiazines 5a-c; general procedure

To a mixture of **2a** (0.52 g, 0.002 mol) and arylidene malononitrile or ethyl α-cyanocinnamate (0.002 mol) in 30 mL ethanol, a few drops of triethylamine were added. The resulting mixture was refluxed for 6 h and left to cool. The solid product was collected and recrystallized from the proper solvent to give **5a-c** in the form of yellow crystals.

2-Amino-3-cyano-9,11-dimethyl-4-phenyl-4*H*-pyrido-[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*][1,3]thiazine-6-one (5a)

Prepared from **2a** and benzylidenemalononitrile; yield; 63%; m.p.: >300 °C (dioxane); Anal. Calcd. for $C_{21}H_{15}N_5OS_2$ (417.50): C, 60.41; H, 3.62; N, 16.77; S, 15.36%; Found: C, 60.62; H, 3.60; N, 16.58; S, 15.18%; IR, ν = 3300, 3200 (NH_2), 2220 (CN), 1700 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.1 (2s, 6H, 2CH_3), 5.6 (s, 1H, CH thiazine), 6.4 (br, 2H, NH_2), 7.0 (s, 1H, CH pyridine), 7.4-7.7 (m, 5H, ArH) ppm.

2-Amino-3-cyano-9,11-dimethyl-4-*p*-methoxyphenyl-4*H*-pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*][1,3]-thiazine-6-one (5b)

Prepared from **2a** and *p*-methoxybenzylidenemalononitrile; yield: 67%; m.p.: >300 °C (dioxane), Anal. Calcd. for $C_{22}H_{17}N_5O_2S_2$ (447.53): C, 59.04; H, 3.83; N, 15.65; S, 14.33%; Found: C, 59.12; H, 3.71; N, 15.60; S, 14.18%; IR: ν = 3350, 3250 (NH_2), 2220 (CN), 1690 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.0 (2s, 6H, 2 CH_3), 3.85 (s, 3H, OCH_3), 5.65 (s, 1H, CH thiazine), 6.2 (br, 2H, NH_2), 7.1 (s, 1H, CH pyridine), 7.4 -7.8 (dd, 4H, ArH) ppm.

2-Amino-9,11-dimethyl-3-ethoxycarbonyl-4-phenyl-4*H*-pyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido[2,1-*b*][1,3]-thiazine-6-one (5c)

Prepared from **2a** and ethyl α-cyanocinnamate; yield: 67%; m.p.: >300 °C (ethanol); Anal. Calcd. for $C_{23}H_{20}N_4O_3S_2$ (464.56): C, 59.47; H, 4.34; N, 12.06; S, 13.80%; Found: C, 59.29; H, 4.18; N, 12.03; S, 14.00%; IR: ν = 3350, 3200 (NH_2), 1720, 1700 (2 C=O); ^{1}H NMR (DMSO-d_6): δ = 1.5 (t, 3H, CH_3 ester), 3.8 (q, 2H, CH_2), 2.55, 3.1 (2s, 6H, 2CH_3), 5.6 (s,1H, CH thiazine), 6.4 (br, 2H, NH_2), 7.0 (s, 1H, CH pyridine), 7.4-7.7 (m, 5H, ArH) ppm.

Di(3-aryl-3,4-dihydro-7,9-dimethyl-4-oxopyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-2-yl)disulphides (6a-c); general procedure

To a stirred suspension of **2b-d** (0.001 mol) in 20 mL acetic acid, bromine (0.001 mol) in 5 mL acetic acid was added dropwise during 10 min. After completion of addition the stirring was continued for 1 h, then allowed to stand at room temperature for other 2 h. The solid product was collected and recrystallized from dioxane to give **6a-c** in the form of yellowish white crystals.

Di(3,4-dihydro-7,9-dimethyl-4-oxo-3-phenylpyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2-yl)disulphide (6a)

Prepared from **2b** and bromine; yield: 78%; m.p.: > 300 °C; Anal. Calcd. for $C_{34}H_{24}N_6O_2S_4$ (676.84): C, 60.34; H, 3.57; N, 12.42; S, 18.95%; Found: C, 60.20; H, 3.72; N, 12.22; S, 19.12%; IR: ν = 1600 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.5 (2s, 12H, 4 CH_3), 7.5 (s, 2H, 2 CH pyridine), 7.6-8.0 (m, 10H, ArH) ppm.

Di(3,4-dihydro-7,9-dimethyl-4-oxo-3-*p*-tolylpyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2-yl)disulphide (6b)

Prepared from **2c** and bromine; yield: 78%; m.p.: > 300 °C; Anal. Calcd. for $C_{36}H_{28}N_6O_2S_4$ (704.90): C, 61.34; H, 4.00; N, 11.92; S, 18.19%; Found: C, 61.17; H, 3.76; N, 12.02; S, 18.00%; IR: ν = 1600 (C=N); ^{1}H NMR (CF_3CO_2D): δ = 2.9, 3.4, 3.55 (3s, 18H, 6 CH_3), 7.5 (s, 2H, 2 CH pyridine), 7.6-8.0 (m, 8H, ArH) ppm.

Di(3-*p*-chlorophenyl-3,4-dihydro-7,9-dimethyl-4-oxopyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2-yl)disulphide (6c)

Prepared from **2d** and bromine; yield: 78%; m.p.: > 300 °C; Anal. Calcd. for $C_{34}H_{22}Cl_2N_6O_2S_4$ (745.37): C, 54.76; H, 2.97; N, 11.27; S, 17.20%; Found): C, 55.00; H, 3.21; N, 11.07; S, 17.00%; IR: ν = 1600 (C=N); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.4 (2s, 12H, 4 CH_3), 7.5 (s, 2H, 2 CH pyridine),

7.6-8.0 (m, 8H, ArH) ppm.

Cyclization of thioxopyrimidineones 2b-d; formation of pyridothienopyrimidobenzthiazoles 7a-c; general procedure

A sample of **2b-d** (0.001 mol) in 60 mL dioxane was irradiated at room temperature with a Hanovia high-pressure mercury lamp (450 W) in an open topped pyrex beaker. The reaction speed followed up by T.L.C. When the starting material disappeared, the solid product which precipitated during irradiation time was collected and recrystallized from dioxane as white crystals of **7a-c**.

2,4-Dimethylpyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido-[2,1-*b*]benzthiazole-12-one (7a)

Obtained by cyclization of **2b**; yield: 92%; m.p.: >300 °C; Anal. Calcd. for $C_{17}H_{11}N_3OS_2$ (337.41): C, 60.52; H, 3.29; N, 12.45; S, 19.00%; Found): C, 60.55; H, 3.12; N, 12.27; S, 18.82%; IR: ν = 1600 (C=N); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.15 (2s, 6H, $2CH_3$), 7.6 (s, 1H, CH pyridine), 7.7-7.9 (m, 2 H, ArH), 8.1-8.35 (m, 1H, ArH), 8.7-9.0 (m, 1H, ArH) ppm.

2,4,9-Trimethylpyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]pyrimido-[2,1-*b*]benzthiazole-12-one (7b)

Obtained by cyclization of **2c**; yield: 92%; m.p.: >300 °C; Anal. Calcd. for $C_{18}H_{13}N_3OS_2$ (351.44): C, 61.52; H, 3.73; N, 11.96; S, 18.24%; Found): C, 61.27; H, 3.96; N, 12.07; S, 18.00%; IR: ν = 1600 (C=N); ^{1}H NMR (CF_3CO_2D): δ = 2.9, 3.1, 3.3 (3s, 9H, $3CH_3$), 7.5 (s, 1H, CH pyridine), 7.7-7.9 (m, 1H, ArH), 8.1-8.35 (m, 1H, ArH), 8.7-9.0 (s, 1H, ArH) ppm.

9-Chloro-2,4-dimethylpyrido[3″,2″:4′,5′]thieno[3′,2′:4,5]-pyrimido[2,1-*b*]benzthiazole-12-one (7c)

Obtained by cyclization of **2d**; yield: 88%; m.p.: >300 °C; Anal. Calcd. for $C_{17}H_{10}ClN_3OS_2$ (371.86): C, 54.91; H, 2.71; Cl, 9.53; N, 11.30; S, 17.24%; Found): C, 55.11; H, 2.96; Cl, 9.73; N, 11.07; S, 17.00%; IR: ν = 1600 (C=N); ^{1}HNMR (CF_3CO_2D): δ = 2.9, 3.1 (2s, 6H, $2CH_3$), 7.5 (s, 1H, CH pyridine), 7.7-7.9 (m, 1H, ArH), 8.1-8.35 (m, 1H, ArH), 8.7-9.0 (s, 1H, ArH) ppm.

Reaction of thioxopyrimidineone 2a with ethyl chloroacetate or phenacyl bromide; formation of compounds 8a,b; general procedure

A mixture of **2a** (0.52 g, 0.002 mol) and anhydrous K_2CO_3 (0.55 g, 0.004 mol) in 30 mL acetone was refluxed for 1 h, while the potassium salt was precipitated, then the respective halocompound (0.002 mol) was added and refluxed for an additional 1 h. The solid product that separated on cooling was collected, dissolved in water (40 mL) and filtered. The clear filterate was acidified with HCl (0.1 N) at 0 °C to pH 7 whereby a white solid precipitated. It was collected and recrystallized from ethanol to give **8a,b**. The physical constants and spectral data of compounds **8a,b** are listed in Tables

Table 1. Physical Constants of Compounds **8a-j**

No.	R	R'	M.P. °C	Yield %	Molecular Formula (Mol. Wt)	Analytical Data C	H	N	S	Cl
8a	H	OEt	270	74	$C_{15}H_{15}N_3O_3S_2$	51.56	4.33	12.03	18.35	
					(349.42)	51.67	4.18	11.80	18.39	
8b	H	Ph	>300	72	$C_{19}H_{15}N_3O_2S_2$	59.82	3.96	11.02	16.81	
					(381.47)	60.00	4.18	10.21	17.00	
8c	Ph	OEt	220	82	$C_{21}H_{19}N_3O_3S_2$	59.28	4.50	9.87	15.07	
					(425.52)	59.04	4.68	10.03	14.92	
8d	$C_6H_4CH_3$-*p*	OEt	210	78	$C_{22}H_{21}N_3O_3S_2$	60.12	4.82	9.56	14.59	
					(439.55)	59.88	5.00	9.78	14.32	
8e	C_6H_4Cl-*p*	OEt	182	80	$C_{21}H_{18}ClN_3O_3S_2$	54.84	3.94	9.14	11.94	7.71
					(459.97)	55.00	4.05	8.96	12.18	7.60
8f	Ph	Ph	>300	84	$C_{25}H_{19}N_3O_2S_2$	65.62	4.19	9.18	14.01	
					457.56	65.68	3.96	8.94	13.90	
8g	Ph	C_6H_4Cl-*p*	242	86	$C_{25}H_{18}ClN_3O_2S_2$	61.03	3.69	8.54	13.03	7.21
					(492.01)	60.84	3.81	8.74	12.80	7.00
8h	Ph	NH_2	258	78	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13	16.17	
					(396.48)	57.77	4.00	13.95	16.00	
8i	Ph	NHPh	284	82	$C_{25}H_{20}N_4O_2S_2$	63.54	4.27	11.86	13.57	
					(472.58)	63.70	4.25	12.12	13.70	
8j	Ph	NH C_6H_4Cl-*p*	260	84	$C_{25}H_{19}ClN_4O_2S_2$	59.22	3.78	11.05	12.65	6.99
					(507.02)	59.00	4.00	10.82	12.68	7.18

Table 2. Spectral Data of Compounds **8a-k**

No.	IR (ν)	^{1}H NMR (δ)
8a	3250 (NH), 1710-1650 (2C=O)	DMSO-d_6: 1.3 (t,3H,CH_3), 2.5 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 4.1 (q, 2H,CH_2), 5.1 (s, 2H, SCH_2), 7.0 (s, 1H, CH), 11.55 (s,1H, NH).
8b	3250 (NH), 1680, 1650 (2C=O)	DMSO-d_6: 2.3 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 5.0 (s, 2H, SCH_2), 7.0 (s, 1H, CH), 7.4-7.85, 8.0-8.2 (2m, 5H, ArH), 12.0 (s, 1H, NH).
8c	3050 (CH aromatic), 2950, 2900 (CH aliphatic), 1720, 1690 (2CO).	DMSO-d_6: 1.5 (t, 3H, CH_3), 2.5, 3.0 (2s, 6H, $2CH_3$), 3.95 (q,2H, CH_2), 4.2 (s, 2H, CH_2), 7.1 (s, 1H, CH-pyridine), 7.3-7.9 (m, 5H, ArH).
8d	1720, 1670 (2C=O)	DMSO-d_6: 1.4 (t, 3H, CH_3), 2.5, 3.0, 3.3 (3s, 9H, $3CH_3$), 4.0 (q, 2H, CH_2), 4.4 (s, 2H, CH_2), 7.0 (s, 1H, CH-pyridine), 7.2,7.9 (2d, 4H, ArH).
8e	1710, 1670 (2C=O)	DMSO-d_6: 1.3 (t, 3H, CH_3), 2.5, 3.1 (2s, 6H, $2CH_3$), 4.1 (q, 2H, CH_2), 4.4 (s, 2H, CH_2), 7.0 (s, 1H, CH-pyridine), 7.2,7.9 (2d, 4H, ArH).
8f	1690, 1670 (2C=O)	DMSO-d_6: 2.5 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 7.2 (s, 1H, CH-pyridine), 7.3-7.8 (m, 10H, ArH).
8g	3050 (CH Aromatic) 1690-1670 (2CO).	DMSO-d_6: 2.6 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 4.4 (s, 2H, CH_2), 7.2 (s, 1H, CH-pyridine), 7.3-8.2 (m, 9H, ArH).
8h	3300, 3150 (NH_2), 1690-1660 (2CO).	DMSO-d_6: 2.5 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 7.15 (s, 2H, NH_2), 7.25 (s, 1H, CH-pyridine), 7.3-7.8 (m, 5H, ArH).
8I	3290 (NH), 1690-1670 (br, 2CO).	DMSO-d_6: 2.5 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 7.1 (s, 1H, CH-pyridine), 7.3-7.8 (m, 10H, ArH), 11.5 (s, 1H, NH).
8j	3300 (NH), 1700-1660 (br, 2CO).	DMSO-d_6: 2.5 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 7.2 (s, 1H, CH-pyridine), 7.3-8.3 (m, 9H, ArH), 12.0 (s, 1H, NH).

1 and 2.

Reaction of thioxopyrimidineones 2b-d with halocompounds; formation of compounds 8c-j; general procedure

A mixture of **2b-d** (0.001 mol), halocompound (0.001 mol) and sodium acetate (1.0 g, 0.012 mol) in ethanol (30 mL) was refluxed for 1 h and then allowed to cool. The solid product was collected by filtration, washed well with water and recrystallized from ethanol to give **8c-j** in the form of white crystals. The physical constants and spectral data of compounds **8c-j** are listed in Tables 1 and 2.

3-Phenyl-8,10-dimethylthiazolo[3″,2″-*a*]pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-5-one (9)

A sample of **8b** (0.38 g, 0.001 mol) in conc. H_2SO_4 (6 mL) was stirred at room temperature for 6 h, then poured into cold water (25 mL). The solid product was collected and recrystallized from dioxane as yellow crystals of **9**. yield: 0.28 g (78%); m.p.: > 300 °C; Anal. Calcd. for $C_{19}H_{13}N_3OS_2$ (363.45): C, 62.79; H, 3.61; N, 11.56; S, 17.64%; Found: C, 62.83; H, 3.60; N, 11.48; S, 17.80%; IR: ν= 1700 (C=O), and revealed disappearance of bands characteristic for NH and C=O groups of compound **8b**. ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.4 (2s, 6H, $2CH_3$), 7.3 (s, 1H, CH pyridine), 7.4-7.7 (m, 5H, ArH), 7.8 (s, 1H, CH thiazole) ppm.

(3,4-Dihydro-7,9-dimethyl-4-oxo-3-phenylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidin-2-ylthio)acethydrazide (10)

A mixture of **8c** (0.85 g, 0.002 mol) and 99% hydrazine hydrate (0.2 mL, 0.004 mol) in 25 mL ethanol was refluxed for 3 h and allowed to cool. The solid product was collected and recrystallized from ethanol to give **10** as white crystals. yield: 0.61g (75%); m.p.: 265-267 °C; Anal. Calcd. for $C_{19}H_{17}N_5O_2S_2$ (411.50): C, 55.46; H, 4.16; N, 17.02; S, 15.58%; Found: C, 55.62; H, 4.00; N, 16.81; S, 15.78%; IR: ν = 3400-3200 (NH_2, NH), 1690, 1670 (2C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 2.8 (2s, 6H, $2CH_3$), 3.9 (s, 2H, SCH_2), 4.3 (br, 2H, NH_2), 7.25 (s, 1H, CH pyridine), 7.4-7.8 (m, 5H, ArH), 9.35 (s, 1H, NH) ppm.

3,4-Dihydro-7,9-dimethyl-2-hydrazino-4-oxopyrido-[3′,2′:4,5′]thieno[3,2-*d*]pyrimidine (11a)

A mixture of **2a** (1.31 g, 0.005 mol) and 99% hydrazine hydrate (2 mL, 0.02 mol) in pyridine (10 mL) was heated under reflux for 10 h, or till the H2S gas ceased, then allowed to cool. The solid product was collected, washed well with ethanol and recrystallized from pyridine to give **11a** white crystals. yield: 0.98 g (75%); m.p.: >300 °C; Anal. Calcd. for $C_{11}H_{11}N_5OS$ (261.30): C, 50.56; H, 4.24; N, 26.80; S, 12.27%; Found: C, 50.62; H, 4.04; N, 26.68; S, 12.21%; IR: ν = 3400-3200 (2NH, NH_2), 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 2.9 (2s, 6H, $2CH_3$), 4.3 (br, 2H, NH_2), 7.2 (s, 1H, CH

pyridine), 9.45, 10.7 (2s, 2H, 2 NH) ppm.

3,4-Dihydro-7,9-dimethyl-2-hydrazino-4-oxo-3-phenylpyrido[3′,2′:4,5′]thieno[3,2-*d*]pyrimidine (11b)

Prepared by reaction of **2b** with hydrazine hydrate in pyridine analogous to the method described above for **11a**. Yield: 1.35g (80%), m.p.: 272-274 °C (pyridine); Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337.40): C, 60.52; H, 4.48; N, 20.76; S, 9.50%; Found: C, 60.62; H, 4.64; N, 20.68; S, 9.78%; IR: ν = 3400-3200 ($NHNH_2$), 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 2.9 (2s, 6H, $2CH_3$), 4.3 (b, 2H, NH_2), 7.2 (s, 1H, CH pyridine), 7.3-7.7 (m, 5H, ArH), 9.45 (s, 1H, NH) ppm.

N^1-Benzylidene-(3,4-dihydro-7,9-dimethyl-4-oxo-3-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2-ylthio)-acethydrazide (12)

A mixture of **10** (0.37 g, 0.001 mol) and benzaldehyde (0.01 mL, 0.001 mol) in ethanol (20 mL) was refluxed for 2 h and left to cool. The solid product was collected and re-crystallized from dioxane to give **12** as white crystals.yield: 0.37 g (70%); m.p.: >300 °C; Anal. Calcd. for $C_{26}H_{21}N_5O_2S_2$ (499.61): C, 62.51; H, 4.24; N, 14.02; S, 12.83%; Found: C, 62.27; H, 3.90; N, 14.28; S, 12.76%; IR: ν = 3350 (NH), 1670 (2 C=O); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.0 (2s, 6H, $2CH_3$), 4.3 (s, 2H, CH_2), 7.1 (s, 1H, CH pyridine), 7.3-7.7 (m, 10H, ArH), 8.65 (s, 1H, CH=N), 12.2 (s, 1H, NH) ppm.

3,4-Dihydro-7,9-dimethyl-2-(3,5-dimethylpyrazol-1-ylcarbonylmethylthio)-4-oxo-3-phenylpyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine (13)

A mixture of **10** (2.05 g, 0.005 mol) and acetylacetone (1 mL, 0.01 mol) in acetic acid (20 mL) was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **13** as white crystals. yield: 1.66 g (70%); m.p.: 255 °C; Anal. Calcd. for $C_{24}H_{21}N_5O_2S_2$ (475.58): C, 60.61; H, 4.45; N, 14.73; S, 13.48%; Found: C, 60.87; H, 4.60; N, 14.68; S, 13.18%; IR: ν = 1680 (2 C=O); ^{1}H NMR (DMSO-d_6): δ = 1.9, 2.3, 2.5, 3.0 (4s, 12H, $4CH_3$), 4.5 (s, 2H, SCH_2), 6.0 (s, 1H, CH pyrazole), 7.2 (s, 1H, CH pyridine), 7.3-7.7 (m, 5H, ArH) ppm.

2-Benzylidenehydrazino-3,4-dihydro-7,9-dimethyl-4-oxo-3-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (14)

A mixture of **11b** (0.67 g, 0.002 mol) and benzaldehyde (0.02 mL, 0.002 mol) in ethanol (25 mL) was refluxed for 3 h. The solid product that precipitated on cooling was collected and recrystallized from dioxane to give **14** as white crystals. yield: 0.64 g (75%); m.p.: 233 °C; Anal. Calcd. for $C_{24}H_{19}N_5OS$ (425.51): C, 67.75; H, 4.50; N, 16.46; S, 7.53%; Found: C, 67.69; H, 4.34; N, 16.68; S, 7.83%; IR: ν = 3250 (NH); ^{1}H NMR (DMSO-d_6): δ = 2.5, 3.1 (2s, 6H, $2CH_3$), 7.1 (s, 1H, CH pyridine), 7.3-7.7 (m, 10H, ArH), 8.65 (s, 1H, CH=N), 12.2 (s, 1H, NH) ppm.

3,4-Dihydro-7,9-dimethyl-2-(3,5-dimethylpyrazol-1-yl)-4-oxo-3-phenylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (15)

A mixture of **11b** (0.67 g, 0.002 mol) and acetylacetone (0.4 mL, 0.004 mol) in ethanol (20 mL) was refluxed for 4 h and left to cool. The precipitated solid was collected and recrystallized from ethanol to give **15** as white crystals. yield: 0.64 g (80%); m.p.: 205 °C; Anal. Calcd. for $C_{22}H_{19}N_5OS$ (401.49): C, 65.82; H, 4.77; N, 17.44; S, 7.99%; Found: C, 65.69; H, 4.58; N, 17.68; S, 7.78%; IR: ν = 1680(C=O) and revealed the disappearance of bands characteristic of the $NHNH_2$ group of compound **11b**; ^{1}H NMR (DMSO-d_6): δ = 1.9, 2.3, 2.65, 2.95 (4s, 12H, $4CH_3$), 5.8 (s, 1H, CH pyrazole), 7.15, (s, 1H, CH pyridine), 7.2-7.45 (m, 5H, ArH) ppm.

8,10-Dimethyl[1,2,4]triazolo[4″,3″-*a*]pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidine-5(11*H*)-one (16)

To a mixture of **11a** (0.52 g, 0.002 mol) and triethyl orthoformate (4 mL), a few drops of acetic acid were added. The mixture was refluxed for 2 h and left to cool. The precipitated solid was collected and recrystallized from dioxane to give **16** as white crystals. yield: 0.46 g (85%); m.p.: > 300 °C; Anal. Calcd. for $C_{12}H_9N_5OS$ (271.30): C, 53.13; H, 3.34; N, 25.81; S, 11.82%; Found: C, 53.02; H, 3.24; N, 25.68; S, 11.68%; IR: ν = 3250(NH), 1670 (C=O); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.3 (2s, 6H, $2CH_3$), 7.7 (s, 1H, CH pyridine), 9.2 (s, 1H, CH triazole) ppm.

8,10-Dimethyl-4-phenyl[1,2,4]triazolo[3″,4″-*b*]pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-5-one (17)

This compound was prepared from compound **11b** instead of **11a** in the above procedure. yield: 0.56 g (80%); m.p.: 296 °C; Anal. Calcd. for $C_{18}H_{13}N_5OS$ (347.39): C, 62.23; H, 3.77; N, 20.16; S, 9.23%; Found: C, 62.11; H, 4.00; N, 20.28; S, 9.18%; IR: ν = 1670 (C=O); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.3 (2s, 6H, $2CH_3$), 7.7 (s, 1H, CH pyridine), 7.8-8.4 (m, 5H, ArH), 9.2 (s, 1H, CH triazole) ppm.

8,10-Dimethyl-3-mercapto[1,2,4]triazolo[4″,3″-*a*]pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-5(11*H*)-one (18)

A mixture of **11a** (0.52 g, 0.002 mol) and carbon disulfide (2 mL) in pyridine (10 mL) was refluxed on a water bath for 8 h, then the solid product which precipitated was separated by filtration and recrystallized from dioxane to give **18** as yellow crystals. yield: 0.49 g (81%); m.p.: > 300 °C ; Anal. Calcd. for $C_{12}H_9N_5OS_2$ (303.36): C, 47.51; H, 2.99; N, 23.09; S, 21.14%; Found: C, 47.43; H, 2.74; N, 22.28; S, 21.27%; IR:

ν = 3250 (NH), 1670 (C=O); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.3 (2s, 6H, $2CH_3$), 4.75 (br, 1H, SH), 7.7 (s, 1H, CH pyridine) ppm.

8,10-Dimethyl-1-mercapto-4-phenyl[1,2,4]triazolo[3″,4″-*b*]-pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-5-one (19)

This compound was prepared from compound **11b** instead of **11a** in the above procedure. yield: 0.56 g (74%); m.p.: >300 °C; Anal. Calcd. for $C_{18}H_{13}N_5OS_2$ (379.45): C, 56.98; H, 3.45; N, 18.46; S, 16.60%; Found: C, 57.21; H, 3.24; N, 18.28; S, 16.51%; IR: ν = 1670 (C=O); ^{1}H NMR (CF_3CO_2D): δ = 3.0, 3.3 (2s, 6H, $2CH_3$), 4.85 (br, 1H, SH), 7.7 (s, 1H, CH-pyridine), 7.8-8.4 (m, 5H, ArH) ppm.

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Key Words

Disulphides; Pyridothienopyrimidines; Pyridothienothiazine; Pyridothienopyrimidothiazines; Pyridothienopyrimidobenzthiazoles; Triazolopyridothienopyrimidines; Triazolopyridothienopyrimidines.

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