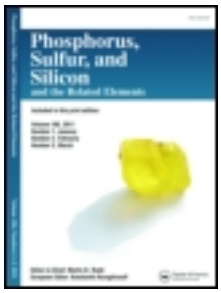

Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis of Some New Pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidines and Related Fused Heterocycles

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# SYNTHESIS OF SOME NEW PYRIDO[4′,3′:4,5]THIENO[2,3-d]PYRIMIDINES AND RELATED FUSED HETEROCYCLES

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*A highly efficient and versatile synthetic approach to the synthesis of pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidines (**3**, **7a–c**), pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidines (**8**, **10–12**), (**15**, **16**), pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3]thiazine (**9**), and polymethylene condensed (e.g., pyrrolo-, piperidino-, azepino-)-pyridothienopyrimidines (**18a–c**) is described utilizing diethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1** as the starting material.*

*Keywords:* BMMA reagents; fused S,N-heterocycles; pyrimidine annelations

Work in our laboratories recently has been concerned with the discovery and development of synthesis of new tetracyclic systems containing pyrimidine moiety in order to search for new pharmacological or biological active compounds. We have reported previously on the synthesis of novel tetracyclic ring systems, containing the thienopyrimidine skeleton with potential pharmaceutical activity.[1–6] Pyridothienopyrimidines represent an important class of heterocyclic compounds owing to their medicinal interest. A number of syntheses for substituted derivatives of this triheterocyclic ring system, which feature a variety of pharmacological activities have been reported in a number of articles. Such derivatives have analgesic,[7] antipyretic,[8,9] antianaphylactic,[10,11] and antiinflammatory[12–14] activity. Also, some of these compounds are clinically effective antiallergic[15] and a few possess signifficant hypocholesterolenic[16] activity. As a part of our continuing study on the synthesis of such system,[1–3] here we report on efficient syntheses of some fused pyridothienopyrimidines utilizing diethyl 2-amino-4,5,6,

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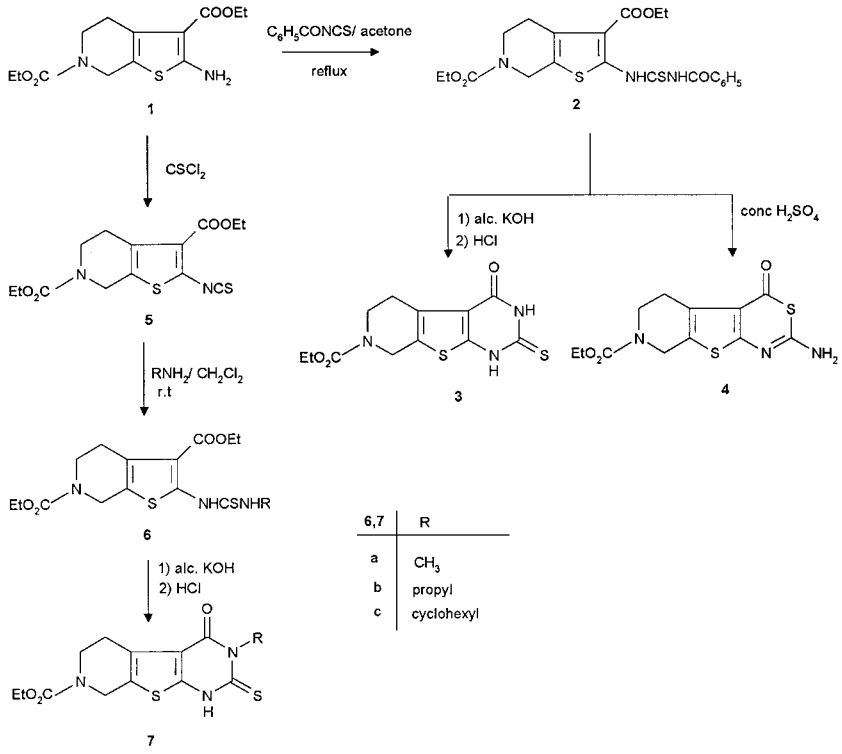
7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1**[17] as the starting material.

Diethyl 2({[(benzoyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **2** was obtained from diethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1** by treatment with ammonium thiocyanate and benzoyl chloride in acetone at reflux. This was subjected to cyclization reactions under different reaction conditions to afford pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine or pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazine derivatives. Thus, treatment of **2** in alkaline medium, resulted in the formation of ethyl 4-Oxo-2-thioxo-1,2,3,4,5,6,7,8-octahyropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7-carboxylate **3** through cyclization and debenzoylation, while in acidic medium **2** yield ethyl 2-amino-4-oxo-5,6,7,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazine-7-carboxylate **4**. The N3-substituted pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidines **7a–c** were synthesized from the isothiocyanate **5**[2] and methylamine, propylamine and cyclohexylamine in dichloromethane at room temperature, with subsequent heating of the (hydrazinothioxomethyl)amino derivatives **6a–c** with an ethanolic potassium hydroxide solution. Acidification of an aqueous solution of the 3-substituted pyridothienopyrimidine potassium salts gave the thioxo compounds **7a–c**. Whose structures were substantiated by elemental analysis and spectral data which were found to be in good agreement with the assigned structures (Scheme 1).

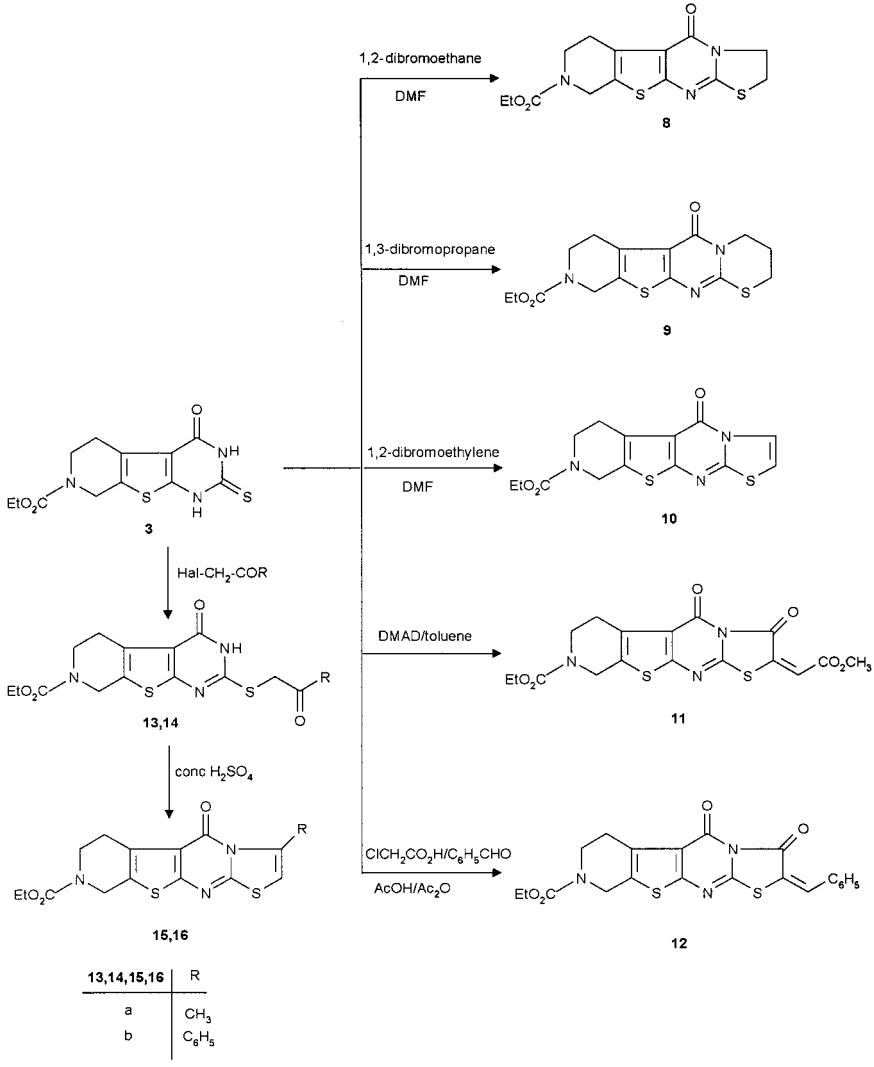
Our interest in developing synthetic approaches with a view to synthesize new derivatives of interesting heterocycles pyrido[4′,3′:4,5]-thieno[2,3-d] [1,3] thiazolo [3,2-a] pyrimidines, compound **3** was thus investigated as a good precursor for this purpose. Reaction of **3** with 1,2-dibromoethane afforded ethyl 5-Oxo-2,3,6,9-tetrahydro-5*H*-pyrido [4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8(7H)-carboxylate **8**. Similary, the condensation of **3** with 1,3-dibromopropane and 1,2-dibromoethylene in dimethyl formamide yielded the corresponding ethyl 6-Oxo-3,4,7,10-tetrahydro-2H,6Hpyrido [4″,3″:4′,5′]thieno [2′,3′:4,5] pyrimido [2,1-b] [1,3] thiazine-9(8H)-carboxylate (**9**) and ethyl 5-Oxo-6,9-dihydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8(7H)-carboxylate (**10**), respectively. Condensation of compound **3** with dimethylacetylene dicarboxylate provided ethyl 2-methoxycarbonylmethylidene-3,5-dioxo-2,3,6,9-tetrahydro-5H-pyrido-[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2a]pyrimidine 8(7H)-carboxylate **11**. The reaction of **3** with benzaldehyde and chloroacetic acid, in the presence of acetic acid and acetic anhydride gave ethyl 2-benzylidene-3,5-dioxo-2,3,6,9-tetrahydro-5H-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo [3,2-a]-pyrimidine-8(7H)-carboxylate **12** (Scheme 2).




**SCHEME 1**

The ethyl (3-substituted)-5-oxo-6,9-dihydro-5*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7H)-carboxylates **15**, **16** were prepared by a simple acid cyclodehydration in 98% sulphuric acid of the ethyl 2-[(2-substituted) sulfanyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylates **13**, **14** at room temperature for 2–3 days. The intermediates **13**, **14** were prepared by stirring the compound **3** with $\alpha$-haloketone, in anhydrous acetone/ potassium carbonate.

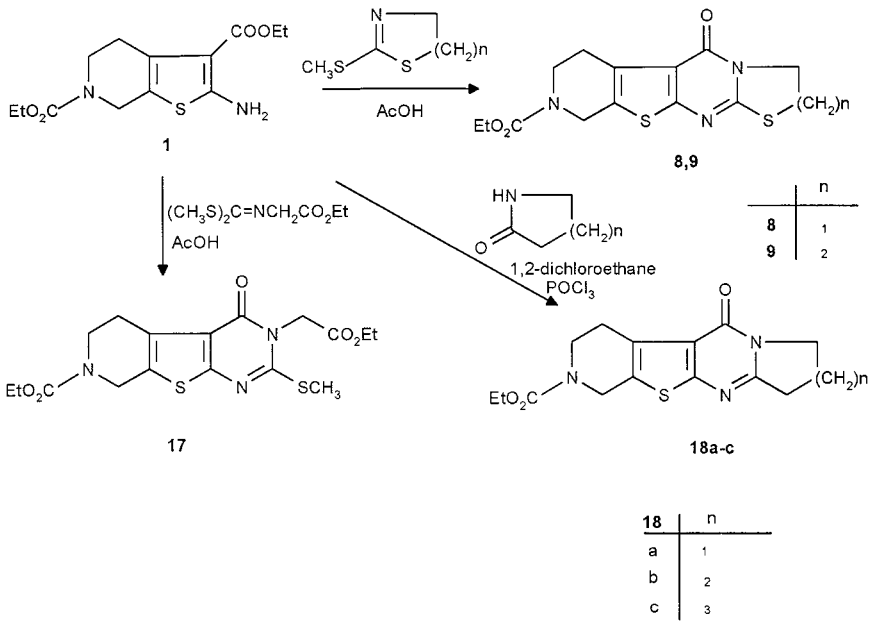
As the preparation of novel tetracyclic systems is the main target of this synthetic program, the diethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1** was selected as a model compound for studying all the reactions leading to the construction of various heterocyclic systems incorporating a pyrimidine, thiazolopyrimidine, pyrimidothiazine, and polymethylene condensed (e.g., pyrrolo-, piperidino-, azepino-)pyrimidine in addition to the thienopyridine moiety.




**SCHEME 2**

It is worth mentioning that ethyl N-[bis(methylthio) methylene]-glycinate (BMMA)[18] is known as a reagent for the synthesis of a variety of heterocycles.[19] To the best of our knowledge, its utility in the synthesis of pyridothienopyrimidines derivatives is unknown. We recently[5] reported on the use of ethyl N-[bis(methylthio)methylene]-glycinate for the direct one-pot annelation

of a fused pyrimidine moiety when starting from 2-amino-4,7-dihydro-5*H*-thieno[2,3-c]thiopyran-3-carboxylic acid ethyl ester. In order to shed further light on the synthetic ability of this reagent, we report herin its reaction with the aminoester **1**. Thus it has been found that in an one-pot reaction of **1** with ethyl N-[bis(methylthio)methylene]-glycinate (BMMA), ethyl 3-(2-ethoxy-2-oxoethyl)-2-(methylsulfanyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7-carboxylate **17** is formed. A variety of novel, structurally related linear tetracyclic systems, were approached either by reacting **1** with the cyclic BMMA reagents such as 2-(methylthio)-2-thiazoline[20] and 2-methylthio-dihydro-1,3-thiazine[21] to yield **8** and **9** (both of which are products of a one-pot double annelation at a thiazolopyrimido- or a thiazinopyrimido moiety respectively) or by reacting **1** with 5-, 6-, and 7-membered lactams to obtain **18a–c** (both of which are products of a double annelation at a pyrrolopyrimido-, a pyridopyrimido-, and an azepinopyrimido-moiety respectively). The incorporation of lactams into our annelation studies was done with the intention to compare the results thus obtained with those realized by BMMA reagents and to access via these means the novel target compounds **18a–c** (Scheme 3).




**SCHEME 3**

## EXPERIMENTAL

All m.p.s were recorded on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were performed at the Microanalytical Data Unit, Cairo University. $^{13}C$ and $^{1}H$ NMR spectra were recorded on a Bruker AC 300 ($^{1}H$: 300.13 MHz, $^{13}C$: 75.5 MHz). The solvent were deuterated dimethyl sulfoxide and chloroform respectively; $\delta$-values are given in ppm, the internal standard TMS ($\delta = 0$ ppm). IR spectra were recorded on a Shimadzu 470 Spectrophotometer in KBr pellets.

### Diethyl 2({[(Benzoyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (2)

To a solution of ammonium thiocyanate (0.76 g, 0.01 mmol) in anhydrous acetone (15 ml) was added benzoyl chloride (1.40 g, 0.01 mmol). To the resulting suspension, after being refluxed for 15 min, was added a solution of amino ester **1** (2.98 g, 0.01 mmol) in anhydrous acetone (50 ml). The mixture was refluxed for another 15 min and filtered while hot. After cooling, the solid product was collected by filtration, poured into water, and filtered to give by recrystallization from ethanol. Yield 3.7 g (80.4%) of compound **2** as yellow microcrystals, m.p. 222–224°C; (found: C, 54.55; H, 5.10; N, 9.26; S, 13.97. $C_{21}H_{23}N_3O_5S_2$ (461.56) requires C, 54.64; H, 5.02; N, 9.10; S, 13.89%); $\nu_{max}/cm^{-1}$: 3240 (NH), 3110–3045 (Ar-CH), 2980 (aliph. CH), 1720, 1685, 1675 (3 CO), 1250 (CS); $\delta_H$ (DMSO-$d_6$): 1.15 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.10 (q, 2H, $COOCH_2CH_3$), 4.35 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-7), 7.40–7.90 (m, 5H, Ar-H), 11.90 (s, 1H, NH), 13.80 (s, 1H, NH).

### Ethyl 4-Oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido-[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (3)

A solution of compound **2** (0.92 g, 0.002 mmol) dissolved in 2*N* methanolic sodium hydroxide (10 ml) was refluxed for 6 h then filtered. The clear solution was acidified (pH = 5.6) with 10% hydrochloric acid, and the mixture was stirred at room temperature for 30 min. The solid was collected by filtration, washed with water, dried, and recrystallized from DMF/water. Yield 0.48 g (77.4%) of compound **3** as colorless crystals, m.p. 288–290°C; (found: C, 46.20; H, 4.11; N, 13.38; S, 20.50. $C_{12}H_{13}N_3O_3S_2$ (311.38) requires: C, 46.28; H, 4.20; N, 13.49; S, 20.59%); $\nu_{max}/cm^{-1}$: 3150 (NH), 1710, 1685 (2 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 12.40 (s, 1H, NH), 13.60 (s, 1H, NH);

$\delta_c$ (DMSO-$d_6$): 14.20 (q, $COOCH_2CH_3$), 24.75 (t, C-5), 40.20 (t, C-6), 42.35 (s, C-8), 60.95 (t, $COOCH_2CH_3$), 115.85 (s, C-4a), 124.60 (s, C-4b), 129.45 (s, C-8a), 150.80 (s, C-9a), 154.85 (s, C-4), 156.68 (s, CO), 172.90 (s, C-2).

## Ethyl 2-Amino-4-oxo-5,6,7,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,3]thiazine-7-carboxylate (4)

A suspension of compound 2 (0.6 g, 0.0013 mmol) in 98% sulphuric acid (5 ml) was left at room temperature for 2 days. The resultant clear solution was slowly added to ice water (30 ml) and the solid residue was collected, washed with 5% sodium bicarbonate solution and cold water, dried and recrystallized from ethanol. Yield 0.33 g (81.6%) of compound **4** as pale yellow crystals, m.p. 250–252°C; (found: C, 46.40; H, 4.21; N, 13.43; S, 20.66. $C_{12}H_{13}N_3O_3S_2$ (311.38) requires: C, 46.28; H, 4.20; N, 13.49; S, 20.59%); $\nu_{max}/cm^{-1}$: 3340 ($NH_2$), 1720, 1660 (2 CO), 1630 (C=N); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 8.35 (s, 2H, $NH_2$). $\delta_c$ (DMSO-6): 14.42 (q, $COOCH_2CH_3$), 25.80 (t, C-5), 40.20 (t, C-6), 42.21 (t, C-8), 60.90 (t, $COOCH_2CH_3$), 112.45 (s, C-4a), 121.04 (s, C-4b), 128.38 (s, C-8a), 154.59 (s, C-9a), 163.01 (s, C-2), 170.13 (s, C-4), 174.86 (s, CO ester).

## General Procedure for the Synthesis of 6a–c

A solution of isothiocyanate **5** (0.34 g, 0.001 mmol) in dichloromethane (5 ml) was added under stirring to a solution of an equimolar amount of respective amine (0.001 mmol) in dichloromethane (5 ml) and the mixture was stirred at room temperature for 1–2 h. The solvent was removed under reduced pressure and the solid collected by filtration, washed with dichloromethane, dried, and recrystallized from an appropriate solvent.

### *Diethyl 2({[(Methyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (6a)*

Colorless crystals from EtOH. Yield 86.4%, m.p. 178–180°C; (found: C, 46.40; H, 4.21; N, 13.43; S, 20.66. $C_{15}H_{21}N_3O_4S_2$ (371.49) requires: C, 48.49; H, 5.69; N, 11.31; S, 17.26%); $\nu_{max}/cm^{-1}$: 3340–3240 (NH), 2995 (aliph. —CH), 1710, 1680 (2 CO), 1220 (CS); $\delta_H$ ($CDCl_3$): 1.20 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-4), 3.10 (d, 3H, —$CH_3$), 3.60 (t, 2H, H-5), 4.15 (q, 2H, $COOCH_2CH_3$), 4.25 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 5.30 (s, 1H, NH), 6.55 (s, 1H, NH). $\delta_c$ (DMSO-$d_6$): 4.22 (q, $COOCH_2CH_3$), 14.64 (q, $COOCH_2CH_3$), 26.36 (t, C-4), 30.83 (q, $CH_3$), 41.09 (t, C-5), 42.53 (t, C-7), 60.85

(t, $COOCH_2CH_3$), 61.60 (t, $COOCH_2CH_3$), 111.30 (s, C-3), 122.25 (s, C-7a), 129.23 (s, C-3a), 155.12 (s, CO), 155.51 (s, CO), 167.11 (s, C-2), 177.89 (s, CS).

### *Diethyl 2({[(Propyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (6b)*

Colorless crystals from EtOH. Yield 87.7%, m.p. 148–150°C; (found: C, 51.21; H, 6.39; N, 10.43; S, 15.92. $C_{17}H_{25}N_3O_4S_2$ (399.54) requires: C, 51.10; H, 6.30; N, 10.51; S, 16.05%); $\delta_H$ ($CDCl_3$): 0.93 (t, 3H, $CH_3$), 1.20 (t, 3H, $COOCH_2CH_3$), 1.35 (t, 3H, $COOCH_2CH_3$), 1.60–176 (m, 2H, $CH_2$), 2.85 (t, 2H, H-4), 3.45 (t, 2H, $CH_2$), 3.60 (t, 2H, H-5), 4.15 (q, 2H, $COOCH_2CH_3$), 4.25 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 6.50 (br s, 1H, NH), 1.90 (br s, 1H, NH). $\delta_c$ (DMSO-$d_6$): 11.35 (q, $CH_2CH_2CH_3$), 14.19 (q, $COOCH_2CH_3$), 14.61 (q, $COOCH_2CH_3$), 21.90 (t, $CH_2CH_2CH_3$), 26.23 (t, C-4), 41.08 (t, C-5), 42.51 (t, C-7), 46.01 (t, $-NHCH_2$), 60.79 (t, $COOCH_2CH_3$), 61.57 (t, $COOCH_2CH_3$), 115.30 (s, C-3), 122.19 (s, C-7a), 129.08 (s, C-3a), 154.45 (s, CO), 155.55 (s, CO), 167.01 (s, C-2), 177.01 (s, CS).

### *Diethyl 2({[(Cyclohexyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (6c)*

Colorless crystals from EtOH. Yield 79.7%, m.p. 206–208°C; (found: C, 54.74; H, 6.73; N, 9.43; S, 14.69. $C_{20}H_{29}N_3O_4S_2$ (439.60) requires: C, 54.64; H, 6.64; N, 9.55; S, 14.58%); $\delta_H$ ($CDCl_3$): 1.20 (t, 3H, $COOCH_2CH_3$), 1.35 (t, 3H, $COOCH_2CH_3$), 1.45–1.95 (m, 11H, cyclohexane-H), 2.80 (t, 2H, H-4), 3.60 (t, 2H, H-5), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 6.30 (br s, 1H, NH), 11.95 (br s, 1H, NH).

### Ethyl 3-Methyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (7a)

Compound **6a** (0.37 g, 0.001 mmol) was added to a solution of potassium hydroxide (0.07 g, 0.0012 mmol) in absolute ethanol (10 ml), and the mixture was refluxed under stirring for 10–30 min. The potassium salt of compound **7a** was collected by filtration then dissolved in water and neutralized (to pH = 4) with hydrochloric acid. The product was collected by filtration, washed with water and recrystallized from ethanol. Yield 0.26 g (80.2%) of compound **7a** as colorless crystals, m.p. 304–306°C; (found: C, 47.91; H, 4.60; N, 12.84; S, 19.59. $C_{13}H_{15}N_3O_3S_2$ (325.41) requires: C, 47.98; H, 4.64; N, 12.91; S, 19.70%); $\nu_{max}/cm^{-1}$:

3240 (NH), 2980 (aliph. —CH), 1710, 1680 (2 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.60 (t, 2H, H-6), 3.70 (s, 3H, $CH_3$), 4.10 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 13.40 (s, 1H, NH). $\delta_c$ (DMSO-$d_6$): 14.47 (q, $COOCH_2CH_3$), 25.73 (t, C-5), 40.78 (t, C-6), 42.65 (t, C-8), 55.93 (q, $CH_3$), 60.87 (t, $COOCH_2CH_3$), 113.17 (s, C-4a), 120.04 (s, C-4b), 128.67 (s, C-8a), 154.68 (s, C-9a), 159.63 (s, C-4), 164.71 (s, CO), 176.11 (s, C-2).

In a similar manner the following compounds were obtained.

### Ethyl 3-Propyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (7b)

Colorless crystals from EtOH. Yield 85.7%, m.p. 220–222°C; (found: C, 50.89; H, 5.49; N, 11.80; S, 18.25. $C_{15}H_{19}N_3O_3S_2$ (353.47) requires: C, 50.97; H, 5.41; N, 11.88; S, 18.14%); $\delta_H$ (DMSO-$d_6$): 0.95 (t, 3H, $CH_3$), 1.25 (t, 3H, $COOCH_2CH_3$), 1.60–1.76 (m, 2H, $CH_2$), 2.90 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (t, 2H, $CH_2$), 4.60 (t, 2H, H-8), 13.45 (s, 1H, NH).

### Ethyl 3-Cyclohexyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (7c)

Colorless crystals from EtOH. Yield 78.9%, m.p. 228–230°C; (found: C, 54.88; H, 5.83; N, 10.77; S, 16.38. $C_{18}H_{23}N_3O_3S_2$ (393.53) requires: C, 54.93; H, 5.89; N, 10.67; S, 16.29%); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 1.45–1.97 (m, 11H, cylohexane-H), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 13.50 (s, 1H, NH).

### Ethyl 5-Oxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7*H*)-carboxylate (8)

#### *Method A (from Compound 3)*

1,2-Dibromoethane (0.19 g, 0.001 mmol) in DMF (5 ml) was added dropwise to a stirred solution containing **3** (0.31 g, 0.001 mmol), water (10 ml), and sodium hyroxide (0.05 g). The mixture was heated at 80°C for 1 h and then stirred at room temperature for an additional 1 h. The solid product was washed with water and then triturated with ethanol to give a colorless solid which was crystallized from ethanol. Yield 0.24 g (71.6%) of compound **8** as colorless crystals, m.p. 174–176°C;

(found: C, 49.78; H, 4.42; N, 12.36; S, 19.13. $C_{14}H_{15}N_3O_3S_2$ (337.43) requires: C, 49.83; H, 4.48; N, 12.45; S, 19.00%); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-6), 3.55–3.70 (m, 4H, H-7, H-2), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (t, 2H, H-3), 4.60 (s, 2H, H-9). $\delta_c$ (DMSO-$d_6$): 14.15 (q, $COOCH_2CH_3$), 25.12 (t, C-6), 26.80 (t, C-2), 40.70 (t, C-7), 42.70 (s, C-9), 48.16 (t, C-3), 61.06 (t, $COOCH_2CH_3$), 117.48 (s, C-5a), 127.03 (s, C-5b), 128.92 (s, C-9a), 154.70 (s, C-10a), 156.18 (s, C-11a), 160.76 (s, C-5), 163.43 (S, CO ester).

### *Method B (from Compound 1)*

A mixture of **1** (0.6 g, 0.002 mmol) and 2-methylthio-2-thiazoline (0.28 g, 0.0021 mmol) in dry AcOH (3 ml) was heated at 80°C for 4 h. After cooling the separated solid product was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol. Yield 0.44 g (64.8%) of compound **8** as colorless crystals, m.p. 175–176°C. The compound is identical to that obtained according to method A.

## Ethyl 6-Oxo-3,4,7,10-tetrahydro-2*H*,6*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3]-thiazine-9(8*H*)-carboxylate (9)

### *Method A (from Compound 3)*

1,3-Dibromopropane (0.22 g, 0.0011 mmol) in DMF (10 ml) was added dropwise to a stirred solution containing compound **3** (0.31 g, 0.001 mmol), water (10 ml), and sodium hydroxide (0.05 g). The mixture was heated at 80–90°C for 2.5 h and then stirred at room temperature for an additional 1 h. The solid product was washed with water and then triturated with ethanol to give a yellow solid which was crystallized from ethanol. Yield 0.23 g (65.9%) of compound **9** as yellow crystals, m.p. 148–150°C; (found: C, 51.19; H, 4.81; N, 11.86; S, 18.13. $C_{15}H_{17}N_3O_3S_2$ (351.45) requires: C, 51.26; H, 4.87; N, 11.95; S 18.24%); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.20 (m, 2H, H-3), 2.80 (t, 2H, H-7), 3.30 (t, 2H, H-2), 3.60 (t, 2H, H-8), 4.10 (q, 2H, $COOCH_2CH_3$), 4.35 (t, 2H, H-4), 4.60 (s, 2H, H-10).

### *Method B (from Compound 1)*

A mixture of **1** (0.6 g, 0.002 mmol) and 2-methylthio-dihydro-1,3-thiazine (0.31 g, 0.0021 mmol) in dry AcOH (4 ml) was heated at at 80°C for 3 h. After cooling the separated solid product was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol. Yield 0.45 g (63.7%) of compound **9** as yellow crystals, m.p. 149–150°C. The compound is identical to that obtained according to method A.

### Ethyl 5-Oxo-6,9-dihydro-5*H*-pyrido[4′,3′:4,5]thieno-[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7*H*)-carboxylate (10)

1,2-Dibromoethylene (0.19 g, 0.001 mmol) in DMF (10 ml) was added dropwise to a stirred solution containing compound **3** (0.31 g, 0.001 mmol), water (10 ml), and sodium hydroxide (0.04 g). The mixture was heated at 80°C for 1 h and then stirred at room temperature for an additional 1 h. The solid product was washed with water and then triturated with ethanol to give a yellow solid which was crystallized from ethanol. Yield 0.26 g (78.7%) of compound **10** as yellow crystals, m.p. 230–232°C; (found: C, 50.25; H, 3.98; N, 12.69; S, 19.21. $C_{14}H_{13}N_3O_3S_2$ (335.41) requires: C, 50.13; H, 3.90; N, 12.52; S, 19.11%); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-6), 3.60 (t, 2H, H-7), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-9), 7.55 (d, 1H, H-3), 8.10 (d, 2H, H-2).

### Ethyl 2-Methoxycarbonylmethylidene-3,5-dioxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo-[3,2-a]pyrimidine-8(7*H*)-carboxylate (11)

A mixture of **3** (0.31 g, 0.001 mmol) and dimethyl acetylenedicarboxylate (0.16 g, 0.0011 mmol) in 15 ml of toluene was refluxed for 2 h. After cooling, the reaction mixture was filtered and the resulting solid was recrystallized from ethyl acetate. Yield 0.28 g (66.8%) of compound **11** as orange crystals, m.p. 224–226°C; (found: C, 48.36; H, 3.52; N, 9.86; S, 15.12. $C_{17}H_{15}N_3O_6S_2$ (421.46) requires: C, 48.44; H, 3.58; N, 9.97; S, 15.21%); $\nu_{max}/cm^{-1}$: 1720, 1710, 1700, 1685, (4 CO), 1620 (C=N); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-6), 3.65 (t, 2H, H-7), 3.88 (s, 3H, $OCH_3$), 4.10 (q, 2H, $COOCH_2CH_3$), 4.65 (s, 2H, H-9), 7.10 (s, 1H, C=CH).

### Ethyl 2-Benzylidene-3,5-dioxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8(7*H*)-carboxylate (12)

A mixture of **3** (3.1 g, 0.01 mmol), chloroacetic acid (0.94 g, 0.01 mmol), benzaldehyde (1.1 g, 0.01 mmol), anhydrous sodium acetate (0.82 g, 0.01 mmol), acetic anhydride (6 ml), and acetic acid (8 ml) was refluxed for 5 h. The mixture was poured into ice-water. The precipitate was separated and dissolved in dichloromethane. The organic layer was washed using 6% sodium bicarbonate solution, then was evaporated under reduced pressure. The crude product was recrystallized from ethanol. Yield 3.3 g (75.5%) of compound **12** as yellow crystals, m.p.

248–250°C; (found: C, 57.29; H, 3.81; N, 9.45; S, 14.48. $C_{21}H_{17}N_3O_4S_2$ (439.51) requires: C, 57.38; H, 3.89; N, 9.56; S, 14.59%); $\nu_{max}/cm^{-1}$: 3060–3000 (Ar-CH), 1720, 170, 1685 (3 CO), 1620 (C=N), $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-6), 3.65 (t, 2H, H-7), 4.20 (q, 2H, $COOCH_2CH_3$), 4.65 (s, 2H, H-9), 7.1–7.5 (m, 5H, Ar-H), 8.15 (s, 1H, =C–H). $\delta_c$ (DMSO-$d_6$): 14.10 (q, $COOCH_2CH_3$), 25.72 (t, C-6), 40.16 (t, C-7), 42.22 (t, C-9), 61.63 (t, $COOCH_2CH_3$), 115.60 (s, C-5a), 117.48 (s, C-2), 127.13 (s, C-5b), 128.30 (Ph, C-4), 128.83 (Ph C-2,6), 128.88 (Ph C-3,5), 131.22 (Ph C-1), 132.80 (s, C-9a), 140.27 (s, =C–Ph), 152.93 (s, C-10a), 160.72 (s, C-5), 161.62 (s, C-11a), 164.64 (s, CO ester), 165.49 (s, CO thiazole).



## Ethyl 2-[(2-Oxopropyl)sulfanyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (13)

A mixture of compound **3** (0.31 g, 0.001 mmol), chloroacetone (0.11 g, 0.0012 mmol) and potassium carbonate (0.14 g, 0.001 mmol) in anhydrous acetone (10 ml) was gently warmed under stirring for 2 h. The mixture was then poured into water (50 ml) and the resulting solid was collected by filtration, dried, and crystallized from ethanol/water. Yield 0.26 g (71.2%) of compound **13** as colorless crystals, m.p. 158–160°C; (found: C, 49.12; H, 4.75; N, 11.52; S, 17.56. $C_{15}H_{17}N_3O_4S_2$ (367.45) requires: C, 49.03; H, 4.66; N, 11.43; S, 17.45%); $\nu_{max}/cm^{-1}$: 3180 (NH), 2900 (aliph. –CH), 1720, 1690, 1680 (3 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.25 (s, 3H, $CH_3$), 2.90 (t, 2H, H-5), 3.60 (t, 2H, H-6), 3.85 (s, 2H, $-SCH_2$), 4.10 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 12.25 (s, 1H, NH).

## Ethyl 2-[(2-Phenyl-2-oxoethyl)sulfanyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (14)

To a stirred suspension of compound **3** (0.31 g, 0.001 mmol) and potassium carbonate (0.14 g, 0.001 mmol) in anhydrous acetone (15 ml) a saturated phenacylbromide solution (0.2 g, 0.001 mmol) was slowly added for 2 h. The mixture was then stirred for an additional 20 h and the solid was collected by filtration, washed with water, dried, and recrystallized from acetic acid. Yield 0.29 g (67.9%) of compound **14** as colorless crystals, m.p. 216–218°C; (found: C, 55.85; H, 4.38; N, 9.67; S, 14.82. $C_{20}H_{19}N_3O_4S_2$ (429.52 ) requires: C, 55.92; H, 4.45; N, 9.78; S, 14.93%); $\nu_{max}/cm^{-1}$: 3160 (NH), 3018–3000 (Ar-CH), 1720, 1695, 1685 (3 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85

(t, 2H, H-5), 3.65 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 4.85 (s, 2H, $SCH_2$), 7.40–7.80 (m, 3H, Ar-H), 7.90–8.10 (m, 2H, Ar-H), 12.70 (br s, 1H, NH).

### Ethyl 3-Methyl-5-oxo-6,9-dihydro-5*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7*H*)-carboxylate (15)

A suspension of compound **13** (0.36 g, 0.001 mmol) in 98% sulphuric acid (3 ml) was stirred for 1 h, then left at room temperature for 2 days. The clear solution was then poured into water (100 ml) and the resulting solid was collected, dried, and recrystallized from ethanol/water. Yield 0.22 g, (64.7%) of compound **15** as yellow crystals, m.p. 168–170°C; (found: C, 51.42; H, 4.27; N, 12.12; S, 18.26. $C_{15}H_{15}N_3O_3S_2$ (349.44) requires: C, 51.55; H, 4.32; N, 12.02; S, 18.35%); $\nu_{max}/cm^{-1}$: 2980 (aliph. CH), 1720, 1680 (2 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.65 (s, 3H, $CH_3$), 2.80 (t, 2H, H-6), 3.65 (t, 2H, H-7), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-9), 6.90 (s, 1H, H-2).

### Ethyl 3-Phenyl-5-oxo-6,9-dihydro-5*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7*H*)-carboxylate (16)

A suspension of compound **14** (0.52 g, 0.0012 mmol) in 98% sulphuric acid (4 ml) was stirred for 1 h, then left at room temperature for 3 days. The clear solution was then poured into water (50 ml) and the resulting solid was collected, dried, and recystallized from DMF/water. Yield 0.29 g (58.2%) of compound **16** as colorless crystals, m.p. 198–200°C; (found: C, 58.49; H, 4.21; N, 10.29; S, 15.69. $C_{20}H_{17}N_3O_3S_2$ (411.50) requires: C, 58.37; H, 4.16; N, 10.21; S, 15.58%); $\nu_{max}/cm^{-1}$: 3055–3006 (Ar-CH), 1720, 1680 (2 CO); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-6), 3.60 (t, 2H, H-7), 4.10 (q, 2H, $COOCH_2CH_3$), 4.65 (s, 2H, H-9), 6.80 (s, 1H, H-2), 7.30–7.50 (m, 3H, Ar-H), 7.60–7.75 (m, 2H, Ar-H).

### Ethyl 3-(2-Ethoxy-2-oxoethyl)-2-methylsulfanyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7-carboxylate (17)

A mixture of **1** (0.72 g, 0.0024 mmol), N-(bis-(methylthio)-methylene)-glycine ethyl ester (0.51 g, 0.0024 mmol) in dry acetic acid (5 ml) was heated at 60–70°C for 5 h under nitrogen. On cooling, the separated solid product was filtered, washed with ethanol, dried, and recrystallized from ethanol. Yield 0.62 g (62.6%) of compound **17** as colorless

crystals, m.p. 133–134°C; (found: C, 49.75; H, 5.19; N, 10.08; S, 15. 64. $C_{17}H_{21}N_3O_5S_2$ (411.51) requires: C, 49.61; H, 5.14; N, 10.21; S, 15.58%); $\nu_{max}/cm^{-1}$ : 2985 (aliph.–CH), 1720, 1700, 1680 (3 CO); 1620 (C=N); $\delta_H$ (DMSO-$d_6$): 1.2 (t, 3H, $-CO_2CH_2CH_3$), 1.25 (t, 3H, $CO_2CH_2CH_3$), 2.60 (s, 3H, $SCH_3$), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.20 (q, 2H, $CO_2CH_2CH_3$, 4.35 (q, 2H, $CO_2CH_2CH_3$), 4.60 (s, 2H, H-8), 4.85 (s, 2H, $CH_2CO_2Et$); $\delta_c$ (DMSO-$d_6$): 13.7 (q, $SCH_3$), 13.9 (q, $-CO_2CH_2CH_3$), 14.3 (q,$-CO_2CH_2CH_3$), 24.9 (t, C-5), 40.2 (t, C-6), 42.6 (t, C-8), 44.3 (t, $NCH_2$), 60.9 (t, $CO_2CH_2CH_3$), 61.3 (t, $CO_2CH_2CH_3$), 116.7 (s, C-4a), 127.5 (s, C-4b), 129.0 (s, C-8a), 154.5 (s, C-2), 156.0 ( s, C-9a), 158.0 (s, C-4), 162.0 (s, CO), 166.6 ( s, CO); ms: m/z 411 ($M^+$).

## Ethyl 1,3,4,7,8,9-Hexahydro-5-oxo-5*H*,*10H*-pyrido[4′,3′:4,5]thieno[2,3-d]pyrrolo[1,2-a]pyrimidine-2-carboxylate (18a)

To a mixture of **1** (0.3 g, 0.001 mmol) and 2-pyrrolidone (0.094 g, 0.0011 mmol) in 1,2-dichloromethane (5 ml) was added 5 drops of phosphorous oxychloride and refluxed for 1 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in water, alkalinized with dilute potassium hydroxide solution, and extracted with chloroform. The extract was evaporated and the residue was crystallized from ethanol. Yield 0.22 g (68.7%) of compound **18a** as pale yellow crystals, m.p. 129–130°C; (found: C, 56.49; H, 5.43; N, 13.23; S, 10.13. $C_{15}H_{17}N_3O_3S$ (319.38) requires: C, 56.41; H, 5.36; N, 13.15; S, 10.03%); $\nu_{max}/cm^{-1}$: 2990 (aliph.–CH), 1720, 1685 (2 CO), 1630 (C=N); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 2.25 (m, 2H, H-8), 2.85 (t, 2H, H-4), 3.15 (t, 2H, H-9), 3.65 (t, 2H, H-3), 4.02 (t, 2H, H-7), 4.10 (q, 2H, $COOCH_2CH_3$), 4.65 (s, 2H, H-1). $\delta_c$ (DMSO-$d_6$): 14.20 (q, $COOCH_2CH_3$), 18.86 (t, C-8), 25.55 (t, C-4), 31.42 (t, C-9), 40.22 (t, C-3), 42.51 (t, C-1), 45.96 (t, C-7), 60.83 (t, $COOCH_2CH_3$), 118.92 (s, C-4b), 127.22 (s, C-11a), 128.74 (s, C-4a), 154.54 (s, C-5), 156.55 (s, C-10a), 160.75 (s, C-9a), 163.65 (s, CO ester).

## Ethyl 3,4,7,8,9,10-Octahydro-5-oxo-1*H*,5*H*-pyrido-[4′,3′:4,5]thieno[2,3-d]pyrido[1,2-a]pyrimidine-2-carboxylate (18b)

Molar portions of amino ester **1** and valerolactam were treated as described for the preparation of **18a**. The yield of the crystallized compound was 62.6%, m.p. 194–195°C; yellow crystals; (found: C, 57.56; H, 5.68; N, 12.51; S, 9.53. $C_{16}H_{19}N_3O_3S$ (333.41) requires: C, 57.64; H, 5.74; N, 12.60; S, 9.61%); $\delta_H$ (DMSO-$d_6$): 1.09 (t, 2H, H-10), 1.20

(t, 3H, $COOCH_2CH_3$), 1.95–2.10 (m, 4H, H-8, H-9), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-3), 3.95 (t, 2H, H-7), 4.20 (q, 2H, $COOCH_2CH_3$), 4.65 (s, 2H, H-1). $\delta_c$ (DMSO-$d_6$): 14.15 (q, $COOCH_2CH_3$), 18.43 (t, C-9), 21.32 (t, C-8), 25.53 (t, C-4), 31.33 (t, C-10), 40.50 (t, C-3), 42.40 (t, C-1), 44.55 (t, C-7), 60.95 (t, $COOCH_2CH_3$), 119.42 (s, C-4b), 127.15 (s, C-4a), 130.13 (s, C-12a), 156.03 (s, C-11a), 157.66 (s, C-10a), 160.65 (s, C-5), 164.55 (s, CO).

### Ethyl 1,3,4,7,8,9,10,11-Octahydro-5-oxo-5*H*-pyrido-[4′,3′:4,5]thieno[2,3-d]azepino[1,2-a]pyrimidine-2-carboxylate (18c)

Upon treatment of amino ester **1** with caprolactam as described for the preparation of **18a**, 57.3% yield of recrystallized **18c** was obtained; m.p. 260–262°C, yellow crystals; (found: C, 58.69; H, 5.99; N, 12.21; S, 9.34. $C_{17}H_{21}N_3O_3S$ (347.44) requires: C, 58.76; H, 6.09; N, 12.09; S, 9.22%); $\delta_H$ (DMSO-$d_6$): 1.20 (t, 3H, $COOCH_2CH_3$), 1.55–1.88 (m, 6H, H-8, H-9, H-10), 2.85 (t, 2H, H-4), 3.10 (t, 2H, H-11), 3.65 (t, 2H, H-3), 4.20 (q, 2H, $COOH_2CH_3$), 4.36 (t, 2H, H-7), 4.65 (s, 2H, H-1).

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