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Synthesis of 3-Substituted Pyrido[4′,3′:4,5]-thieno[2,3-*d*]pyrimidines and Related Fused Thiazolo Derivatives

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ABSTRACT: *Convenient syntheses of 3-substituted ethyl 4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylates* **3a, b, 6, 11–13**, *ethyl 3-methyl-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 (**4**), and ethyl 2-methyl-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**) from diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**1**) are reported.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:201–207, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10131

INTRODUCTION

Compounds containing a fused pyrimidine ring have received considerable attention over the past years because of their wide range of biological activity. As an example, pyridothienopyrimidines have long been used for their antiinflammatory [1–3], antipyretic [4,5], analgesic [6], and antianaphylactic [7,8] activity. On the other hand, thiazoles represent a very intersting class of compounds because of their wide applications in pharmaceutical, phytosanitary, analytical, and industrial aspects, e.g. as fungicides, anthelmintics, and herbicides [9]. Because of these findings, our interest was focused on investigating efficient and convenient routes to construct the titled novel ring systems. In continuation of our interest in the synthesis of pharmacologically interesting new heterocyclic systems containing the thienopyrimidine moiety [10–16], we now succeeded in the synthesis of new derivatives of pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine and pyrido[4′,3′:4,5]thieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidine with expected potential biological activity.

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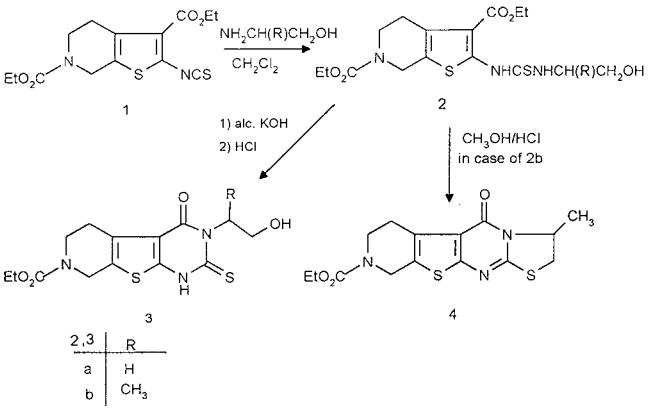
RESULTS AND DISCUSSION

In the syntheses presented in this paper, the conveniently available diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**1**) [11] was employed as the starting material. Reaction of compound **1** with aminoalcohols under mild conditions provided the thioureido derivatives **2a,b**. Compound **2b** could be cyclized to ethyl 3-methyl-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 (**4**) in good yield by heating in methanolic hydrogen chloride to reflux. No intermediate pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine derivative was isolated. In a separate reaction, pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine derivatives **3a,b** were synthesized by heating **2a,b** in ethanolic potassium hydroxide solution. Structures **4** and **3a,b** were confirmed by the results of elemental analysis and spectroscopic data (Scheme 1).

For the synthesis of ethyl 2-methyl-5-oxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-*d*][1,3]-

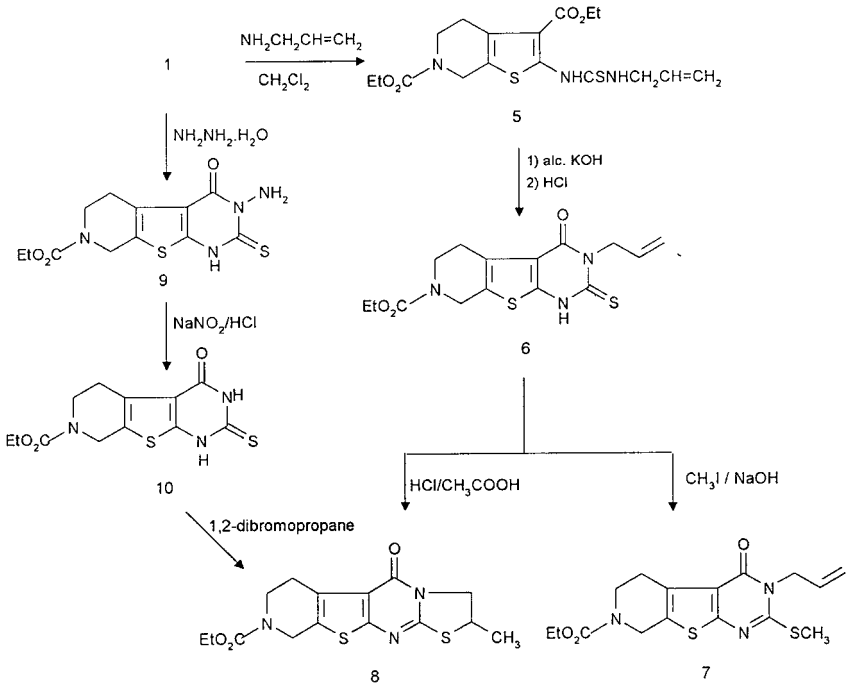


SCHEME 1

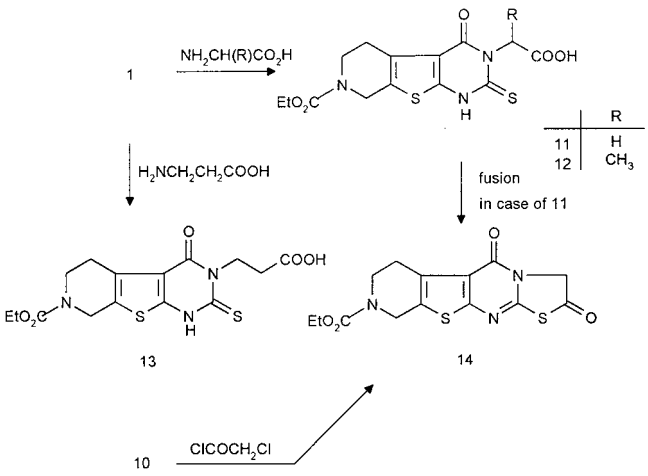
thiazolo[3,2-*a*]pyrimidine-8(7*H*)-carboxylate (**8**), compound **1** was reacted with allylamine to give ethyl 2-{[(2-propenyl)aminothioxomethyl]amino}-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (**5**), which could be cyclized to ethyl 3-(2-propenyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**6**) by heating to reflux in potassium hydroxide solution. The structure of **6** was substantiated by elemental analysis and spectroscopic data. The IR spectrum showed absorption bands due to NH, ester CO, and pyrimidine ring CO. The ^{1}H NMR spectrum showed signals assignable to the allyl substituent and to pyrimidine NH (Experimental section). Treatment of **6** with methyl iodide under basic conditions afforded the S-methylated compound **7** in excellent yield. The target product **8** was prepared in 68% yield by ring closure of **6** in a mixture of hydrochloric and acetic acid. Compound **8** was alternatively obtained from **1** by initial conversion to ethyl 3-amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(2H)-carboxylate (**9**) [16], followed by deamination with nitrous acid to yield 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 (**10**) and the subsequent reaction with 1,2-dibromopropane (Scheme 2).

For the synthesis of more pyridothienopyrimidine derivatives, we investigated the reaction of **1** with amino acids glycine, L-alanine, and β-alanine in a mixture of dioxane and water (pH 8–9) under mild conditions, which gave ethyl 3-carboxymethyl, 3-[(*S*)-1-carboxyethyl], and 3-(2-carboxyethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]-thieno[2,3-*d*]pyrimidine-7-carboxylate **11,12,13**, respectively. The structures of **11–13** were established on the basis of their elemental and spectral data.

Ethyl 2,5-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 (**14**) could be obtained either by



SCHEME 2



SCHEME 3

thermal fusion of compound **11** or by reaction of compound **10** with chloroacetyl chloride in DMF (Scheme 3).

EXPERIMENTAL

Melting points were recorded on a GallenKamp 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; solvent: DMSO-d_6 and $CDCl_3$, respectively). Chemical shifts δ are given relative to the internal standard TMS. IR spectra were recorded on a Shimadzu 470 spectrophotometer in KBr pellets.

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

To a stirred solution of **1** (0.34 g, 0.001 mol) in dichloromethane (8 ml), 2-aminoethanol (0.07 g, 0.0011 mol) was added and stirred at room temperature for 20 min. After evaporation of the solvent at reduced pressure, the solid product was collected and crystallized from ethanol. Yield: 0.28 g (70%) **2a** as colorless crystals, m.p. 158–160°C. IR: ν = 3500 (OH), 3200 (NH), 2990 (aliph. CH), 1720, 1690 (2CO, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.20 (t, 3H, CH_2CH_3), 1.30 (t, 3H, CH_2CH_3), 2.80 (t, 2H, H-4), 3.60 (t, 2H, H-5), 3.70 (q, 2H, $-NCH_2$), 3.90 (t, 2H, $-CH_2OH$), 4.10 (q, 2H, CH_2CH_3), 4.50 (s, 2H, H-7), 4.80–4.90 (t, 1H, CH_2OH), 9.60 (s, 1H, NH), 11.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 14.1 (q, CH_2CH_3), 14.4 (q, CH_2CH_3), 25.9 (t, C-4), 41.0 (t, C-5), 42.6 (t, C-7), 46.9 (t, $NHCH_2$), 58.6 (t, CH_2OH), 60.3 (t, CH_2CH_3), 60.9 (t, CH_2CH_3), 110.0 (s, C-3), 121.3 (s, C-7a), 130.0 (s, C-3a), 154.8 (s, CO), 165.7 (s, CO), 175.1 (s, C-2), 177.4 (s, CS). $C_{16}H_{23}N_3O_5S_2$ (401.51) calcd.: C, 47.86; H, 5.77; N, 10.46; S, 15.97. Found: C, 47.65; H, 5.83; N, 10.59; S, 15.87.

*Diethyl 2-({[(2-hydroxy-1-methylethyl)amino]-carbothioyl}amino)-4,5,6,7-tetrahydrothieno-[2,3-c]pyridine-3,6-dicarboxylate (**2b**)*

This compound was obtained from **1** (0.34 g, 0.001 mol) and 2-aminopropanol (0.08 g, 0.0011 mol) in dichloromethane (5 ml) and stirred at room temperature for 30 min. After evaporation of the solvent at reduced pressure the solid product was collected and crystallized from ethanol. Yield: 0.37 g, (89%) **2b** as pale yellow crystals, m.p. 166–168°C. IR: ν = 3500 (OH), 3220 (NH), 2980 (aliph. CH), 1710, 1690 (2CO), 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.10 (d, 3H, CH_3CH-), 1.20 (t, 3H, CH_2CH_3), 1.35 (t, 3H, CH_2CH_3), 2.80 (t, 2H, H-4), 3.40–3.55 (m, 2H, $-CH_2OH$), 3.65 (t, 2H, H-5), 4.10 (q, 2H, CH_2CH_3), 4.20–4.35 (m, 3H, CH_2CH_3, $NHCH(CH_2OH)CH_3$), 4.40 (s, 2H, H-7), 4.70–4.85 (t, 1H, $-CH_2OH$), 9.40–9.50 (br s, 1H, NH), 11.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 14.1 (q, CH_2CH_3), 14.4 (q, CH_2CH_3), 16.2 (q, CH_3), 25.8 (t, C-4), 40.7 (t, C-5), 42.1 (t, C-7), 51.9 (d, CH), 60.2 (t, CH_2CH_3), 60.9 (t, CH_2CH_3), 63.3 (t, CH_2OH), 109.9 (s, C-3), 121.3 (s, C-7a), 128.3 (s, C-3a), 154.5 (s, CO), 165.3 (s, CO), 176.5 (s, C-2), 179.3 (s, CS), $C_{17}H_{25}N_3O_5S_2$ (415.54) calcd.: C, 49.13; H, 6.06; N, 10.11; S, 15.43. Found: C, 49.32; H, 6.18; N, 10.30; S, 15.29.

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

Compound **2a** (0.4 g, 0.001 mol) was added to a solution of potassium hydroxide (0.06 g, 0.0011 mol) in absolute ethanol (10 ml), and the mixture was refluxed with stirring for 15 min. The potassium salt of compound **3a** was collected by filtration and then dissolved in water and neutralized (to pH 4) with hydrochloric acid. The product was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield: 0.27 g (77%) **3a** as colorless crystals, m.p. 177–179°C. IR: ν = 3550 (OH), 3180 (NH), 2850 (aliph. CH), 1720 (CO ester), 1680 (CO pyrimidine ring), 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.20 (t, 3H, CH_2CH_3), 2.90 (t, 2H, H-5), 3.60–3.80 (m, 4H, H-6, $-NCH_2CH_2OH$), 4.10 (q, 2H, CH_2CH_3), 4.40 (s, 2H, H-8), 4.65 (t, 2H, $-NCH_2CH_2OH$), 4.70 (t, 1H, $-CH_2OH$), 11.85 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 14.5 (q, CH_2CH_3), 25.3 (t, C-5), 40.2 (t, C-6), 42.6 (t, C-8), 46.7 (t, NCH_2), 58.4 (t, CH_2OH), 60.8

(t, CH_2CH_3), 113.6 (s, C-4a), 120.3 (s, C-4b), 128.7 (s, C-8a), 152.7 (s, C-9a), 154.7 (s, C-4), 164.7 (s, CO), 175.8 (s, C-2). $C_{14}H_{17}N_3O_4S_2$ (355.44) calcd.: C, 47.31; H, 4.81; N, 11.82; S, 18.04. Found: C, 47.18; H, 4.89; N, 11.60; S, 18.26.

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

Compound **2b** (0.41 g, 0.001 mol) was added to a solution of potassium hydroxide (0.06 g, 0.0011 mol) in absolute ethanol (10 ml), and the mixture was refluxed under stirring for 1 h. The potassium salt of compound **3b** was collected by filtration and then dissolved in water and neutralized (to pH 4) with hydrochloric acid. The product was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield: 0.25 g (69%) **3b** as colorless crystals, m.p. 188–190°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 1.40 (d, 3H, CH_3CH—), 2.90 (t, 2H, H-5), 3.55 (t, 2H, H-6), 3.80–3.95 (m, 2H, —CH_2OH), 4.10–4.20 (m, 6H, CH_2CH_3, $CH(CH_3)CH_2OH$), 4.55 (s, 2H, H-8), 4.80–4.90 (br, 1H, CH_2OH), 11.80 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.6$ (q, CH_2CH_3), 18.7 (q, CH_3), 25.5 (t, C-5), 40.7 (t, C-6), 42.7 (t, C-8), 61.8 (t, CH_2CH_3), 64.4 (d, CH), 68.9 (t, CH_2OH), 116.6 (s, C-4a), 121.4 (s, C-4b), 128.7 (s, C-8a), 151.6 (s, C-9a), 155.7 (s, C-4), 165.6 (s, CO), 174.8 (s, C-2). $C_{15}H_{19}N_3O_4S_2$ (369.47) calcd.: C, 48.76; H, 5.18; N, 11.37; S, 17.35. Found: C, 48.89; H, 5.10; N, 11.50; S, 17.22.

*Ethyl 3-methyl-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 (***4***)*

Compound **2b** (0.4 g, 0.001 mol) was dissolved in 10 ml of methanolic hydrogen chloride and stirred at reflux temperature for 10 h. After evaporation of the solvent under reduced pressure the yellow residue was dissolved in 10 ml of water and neutralized to pH 7.5 with aqueous ammonia and extracted with chloroform. The organic layer was dried (magnesium sulfate) and evaporated to yield the solid, which was recrystallized from ethanol. Yield: 0.21 g (62%) **4** as yellow crystals, m.p. 136–138°C. IR: $\nu =$ 2955 (aliph. CH), 1720 (CO ester), 1680 (CO pyrimidine ring), 1590 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 1.45 (d, 3H, CH_3CH—), 2.90 (t, 2H, H-6), 3.20–3.30 (d, 2H, H-2), 3.65 (t, 2H, H-7), 4.15 (q, 2H, CH_2CH_3), 4.60 (s, 2H, H-9), 5.10–5.20 (m, 1H, H-3). $C_{15}H_{17}N_3O_3S_2$ (351.45) calcd.: C, 51.26; H, 4.87; N, 11.95; S, 18.24. Found: C, 51.10; H, 4.79; N, 11.80; S, 18.36.

*Ethyl 2-{[(2-propenyl)-aminothioxomethyl]-amino}-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate (***5***)*

A solution of **1** (0.34 g, 0.001 mol) in dichloromethane (10 ml) was added under stirring to a solution of an equimolar amount of allylamine (0.06 g, 0.001 mol) in dichloromethane (10 ml), and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the solid product collected by filtration, washed with dichloromethane, dried, and recrystallized from ethanol. Yield: 0.36 g (91%) **5** as pale yellow crystals, m.p. 148–150°C. IR: $\nu = 3190$ (NH), 2982 (aliph. CH), 1720 (CO), 1690 (CO), 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 1.35 (t, 3H, CH_2CH_3), 2.80 (t, 2H, H-4), 3.65 (t, 2H, H-5), 3.85 (d, 2H, —CH_2—CH=CH_2), 4.20 (q, 2H, CH_2CH_3), 4.55 (s, 2H, H-7), 4.95–5.40 (m, 2H, —CH_2—CH=CH_2), 5.70–5.90 (m, 1H, —CH=CH_2), 6.55–6.65 (br, 1H, NH), 11.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.2$ (q, CH_2CH_3), 14.6 (q, CH_2CH_3), 26.3 (t, C-4), 41.1 (t, C-5), 42.5 (t, C-7), 46.7 (t, $NHCH_2$), 60.8 (t, CH_2CH_3), 61.6 (t, CH_2CH_3), 111.2 (s, C-3), 115.9 (t, —CH=CH_2), 122.20 (s, C-7a), 131.8 (s, C-3a), 134.0 (d, —CH=CH_2), 153.6 (s, CO), 166.5 (s, CO), 170.0 (s, C-2), 177.7 (s, CS). $C_{17}H_{23}N_3O_4S_2$ (397.52) calcd.: C, 51.36; H, 5.83; N, 10.57; S, 16.13. Found: C, 51.18; H, 5.92; N, 10.41; S, 15.95.

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

Compound **5** (0.4 g, 0.001 mol) was added to a solution of potassium hydroxide (0.07 g, 0.0012 mol) in absolute ethanol (10 ml), and the mixture was refluxed under stirring for 10 min. The potassium salt of compound **6** was collected by filtration and then dissolved in water and neutralized (to pH 4) with hydrochloric acid. The product was collected by filtration, washed with water dried, and recrystallized from ethanol. Yield: 0.3 g (86%) **6** as pale yellow crystals, m.p. 178–180°C. IR: $\nu = 3150$ (NH), 2990 (aliph. CH), 1710 (CO ester), 1680 (CO pyrimidine ring), 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta =$ 1.20 (t, 3H, CH_2CH_3), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.10 (q, 2H, CH_2CH_3), 4.55 (s, 2H, H-8), 4.90–5.12 (m, 2H, —CH_2—CH=CH_2), 5.15–5.30 (m, 2H, —CH_2—CH=CH_2), 5.80–6.10 (m, 1H, —CH=CH_2), 13.70 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.4$ (q, CH_2CH_3), 24.9 (t, C-5), 40.2 (t, C-6), 42.4 (t, C-8), 47.1 (t, NCH_2), 61.0 (t, CH_2CH_3), 114.9 (t, CH=CH_2), 116.9 (s, C-4a), 124.5 (s, C-4b), 129.6 (s, C-8a), 134.5 (d, —CH=CH_2), 149.5 (s, C-9a), 154.6 (s, C-4), 160.0

(s, CO), 173.5 (s, C-2). $C_{15}H_{17}N_3O_3S_2$ (351.45) calcd.: C, 51.26; H, 4.87; N, 11.95; S, 18.24. Found: C, 51.39; H, 4.95; N, 12.11; S, 18.38.

*Ethyl 3-(2-propenyl)-2-(methylsulfanyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno-[2,3-*d*]pyrimidine-7-carboxylate (**7**)*

A solution of **6** (0.35 g, 0.001 mol) in 1 M aqueous sodium hydroxide (1.5 ml) was treated with methyl iodide (0.16 g, 0.0011 mol) and the mixture was stirred at room temperature. Compound **7** started to crystallize almost immediately. After 30 min, it was filtered, washed with water, dried, and recrystallized from ethanol. Yield: 0.32 g (89%) **7** as colorless crystals, m.p. 130–132°C. IR: $\nu = 2990$ (aliph. CH), 1710 (CO ester), 1680 (CO pyrimidine ring), 1600 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 2.65 (s, 3H, SCH_3), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.20 (q, 2H, CH_2CH_3), 4.60 (s, 2H, H-8), 4.80–5.10 (d, 2H, $-CH_2-CH=CH_2$), 5.25–5.55 (m, 2H, $-CH_2-CH=CH_2$), 5.80–6.10 (m, 1H, $-CH=CH_2$). ^{13}C NMR (DMSO-d_6): $\delta = 14.4$ (q, CH_2CH_3), 15.7 (q, SCH_3), 25.1 (t, C-5), 40.2 (t, C-6), 42.6 (t, C-8), 45.2 (t, NCH_2), 61.0 (t, CH_2CH_3), 114.3 (t, $-CH=CH_2$), 116.8 (s, C-4a), 127.0 (s, C-4b), 129.1 (s, C-8a), 134.3 (d, $-CH=CH_2$), 151.2 (s, C-9a), 154.6 (s, C-4), 158.1 (s, C-2), 161.9 (s, CO). $C_{16}H_{19}N_3O_3S_2$ (365.48) calcd.: C, 52.58; H, 5.23; N, 11.49; S, 17.54. Found: C, 52.47; H, 5.18; N, 11.40; S, 17.41.

*Ethyl 2-methyl-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. A mixture of **6** (0.35 g, 0.001 mol) in acetic acid (1 ml) and concentrated hydrochloric acid (2 ml) was refluxed for 1 h. After cooling to room temperature, the solid formed by neutralizing the mixture with 10% sodium hydroxide was collected by filtration and washed with water (20 ml), affording 0.32 g of crude product, which was recrystallized from 15% aqueous ethanol. Yield: 0.24 g (69%) **8** as yellow crystals, m.p. 138–140°C. IR: $\nu = 2980$ (aliph. CH), 1700 (CO ester), 1670 (CO pyrimidine ring), 1610 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 1.60 (d, 3H, CH_3), 2.90 (t, 2H, H-6), 3.60 (t, 2H, H-7), 3.95–4.10 (d, 2H, H-3), 4.20 (q, 2H, CH_2CH_3), 4.40–4.55 (m, 1H, H-2), 4.65 (s, 2H, H-9). $C_{15}H_{17}N_3O_3S_2$ (351.45) calcd.: C, 51.26; H, 4.87; N, 11.95; S, 18.24. Found: C, 51.17; H, 4.95; N, 11.82; S, 18.13.

Method B. 1,2-Dibromopropane (0.22 g, 0.0011 mol) in DMF (5 ml) was added to a stirred solution containing **10** (0.31 g, 0.001 mol), water (5 ml), and sodium hydroxide (0.05 g). The mixture was heated to 90°C for 1 h and then stirred at room temperature for an additional hour. The reaction mixture was poured into cold water; the precipitated product was collected by filtration, dried, and recrystallized from 15% aqueous ethanol. Yield: 0.24 g (69%) **8** as yellow crystals, m.p. 139–140°C. The product is identical to that obtained according to Method A.

*Ethyl 3-amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine-7(2*H*)-carboxylate (**9**)*

A solution of **1** (0.6 g, 0.0017 mol) in benzene (10 ml) was added dropwise at room temperature to a stirred solution of hydrazine hydrate (0.6 g, 0.0018 mol) in benzene (5 ml). The suspension was refluxed under stirring for 8 h. After cooling, the solid product was collected by filtration, washed with ethanol, dried, and recrystallized from dioxane. Yield: 0.57 g (91%) **9** as yellow crystals, m.p. 232–234°C (dec). IR: $\nu = 3400$, 3320, 3180 (NH_2, NH), 1720 (CO ester), 1680 (CO pyrimidine ring), 1200 (C=S). ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7$ Hz, 3H, CH_2CH_3), 2.90 (t, $J = 5.6$ Hz, 2H, H-5), 3.60 (t, $J = 5.6$ Hz, 2H, H-6), 4.20 (q, $J = 7$ Hz, 2H, CH_2CH_3), 4.50 (s, 2H, H-8), 6.30–6.50 (br, 2H, NH_2), 13.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.6$ (q, CH_2CH_3), 25.3 (t, C-5), 40.7 (t, C-6), 46.8 (t, C-8), 61.0 (t, CH_2CH_3), 113.3 (s, C-4a), 128.3 (s, C-4b), 141.0 (s, C-8a), 154.8 (s, C-4), 157.6 (s, C-9a), 161.6 (s, CO), 168.8 (s, C-2). $C_{12}H_{14}N_4O_3S_2$ (326.40) calcd.: C, 44.15; H, 4.32; N, 17.16; S, 19.64. Found: C, 44.07; H, 4.30; N, 17.01; S, 19.50. MS: $m/z = 326$ (M^+).

*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 (**10**)*

To a suspention of **9** (0.32 g, 0.001 mol) in acetic acid (2 ml) and water (10 ml), a solution of sodium nitrite (0.27 g, 0.0039 mol) in 1 ml of water was added. After stirring for 15 min at room temperature, 5 ml of a 40% sodium hydroxide solution was added and warmed to obtain a clear solution. After cooling it was acidified with a 50% solution of sulfuric acid to give colorless crystals. The crystals were washed with cold water, dried, and recrystallized from ethanol. Yield: 0.2 g (66%) **10** as colorless crystals, m.p. 287–289°C. IR: $\nu = 3200$ (NH), 2980 (aliph. CH), 1720 (CO ester), 1680 (CO pyrimidine ring), 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7$ Hz, 3H, CH_2CH_3), 2.90 (t, $J = 5.6$ Hz, 2H, H-5), 3.70 (t, $J = 5.6$ Hz, 2H, H-6), 4.10 (q, $J = 7$ Hz,

2H, CH_2CH_3), 4.60 (s, 2H, H-8), 12.40 (s, 1H, NH), 13.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.3$ (q, CH_2CH_3), 24.7 (t, C-5), 40.2 (t, C-6), 42.3 (s, C-8), 60.9 (t, CH_2CH_3), 115.7 (s, C-4a), 124.5 (s, C-4b), 129.4 (s, C-8a), 150.7 (s, C-9a), 154.8 (s, C-4), 156.6 (s, CO), 172.9 (s, C-2). $C_{12}H_{13}N_3O_3S_2$ (311.38) calcd.: C, 46.28, H, 4.20; N, 13.49; S, 20.59. Found: C, 46.18; H, 3.15; N, 13.32; S, 20.52.

*Ethyl 3-carboxymethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylate (**11**)*

To a solution of glycine (0.08 g, 0.001 mol) in a mixture of water (5 ml), dioxane (5 ml), and sodium hydroxide (1 M, 5 ml), **1** (0.34 g, 0.001 mol) was added and the mixture was stirred at 50°C for 5 h. The volatile components were evaporated in vacuo, water was added to the solid residue, and the mixture was acidified with hydrochloric acid (18%) to pH 3. The precipitate was collected by filtration, dried, and recrystallized from DMF/water. Yield: 0.26 g (71%) **11** as yellow crystals, m.p. 280–282°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 2.80 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.10 (q, 2H, CH_2CH_3), 4.60 (s, 2H, H-8), 5.10 (s, 2H, $-NCH_2$), 13.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.5$ (q, CH_2CH_3), 24.7 (t, C-5), 40.4 (t, C-6), 42.43 (t, C-8), 46.0 (t, $-NCH_2$), 60.8 (t, CH_2CH_3), 115.8 (s, C-4a), 125.1 (s, C-4b), 129.5 (s, C-8a), 150.1 (s, C-9a), 154.6 (s, C-4), 166.4 (s, CO), 169.3 (s, C-2), 173.8 (s, COOH). $C_{14}H_{15}N_3O_5S_2$ (369.43) calcd.: C, 45.51; H, 4.09; N, 11.37; S, 17.35. Found: C, 45.39; H, 4.19; N, 11.24; S, 17.48.

*Ethyl 3-[(*S*)-1-carboxyethyl]-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno-[2,3-*d*]pyrimidine-7-carboxylate (**12**)*

To a stirred solution of L-alanine (0.09 g, 0.001 mol) in a mixture of water (5 ml), dioxane (5 ml), and sodium hydroxide (1 M, 5 ml), **1** (0.34 g, 0.001 mol) was added and the mixture was stirred at 50°C for 10 h. The volatile components were evaporated in vacuo, water was added to the solid residue, and the mixture was acidified with hydrochloric acid (18%) to pH 3. The precipitate was collected by filtration, dried, and recrystallized from DMF/water. Yield: 0.24 g (63%) **12** as yellow crystals, m.p. 290–292°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.10$ (t, 3H, CH_2CH_3), 1.52 (d, 3H, $CH(CH_3)COOH$), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, CH_2CH_3), 4.60 (s, 2H, H-8), 6.20 (q, 1H, $-CH(CH_3)COOH$), 13.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.5$ (q, CH_2CH_3), 17.4 (q, CH_3), 24.9 (t, C-5), 40.8 (t, C-6), 42.6 (t, C-8), 50.0 (d, CH), 61.1 (t, CH_2CH_3), 115.4 (s, C-4a), 125.5 (s, C-4b), 129.6 (s, C-8a), 150.5 (s, C-9a), 155.7 (s, C-4), 161.7, 170.5 (s, C-2), 174.5 (s, COOH). $C_{15}H_{17}N_3O_5S_2$ (383.45) calcd.: C, 46.98; H, 4.46; N, 10.95; S, 16.72. Found: C, 46.91; H, 4.39; N, 10.82; S, 16.61.

*Ethyl 3-(2-carboxyethyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylate (**13**)*

To a solution of β-alanine (0.09 g, 0.001 mol) in water (5 ml), dioxane (5 ml), and sodium hydroxide (1 M, 5 ml), **1** (0.34 g, 0.001 mol) was added and the mixture was stirred at 50°C for 3 h and then at room temperature for 4 h. The volatile components were evaporated in vacuo, water (10 ml) was added to the residue, and the mixture was acidified with hydrochloric acid (18%) to pH 3. The precipitate was collected by filtration, dried, and recrystallized from DMF/water. Yield: 0.26 g (68%) **13** as yellow crystals, m.p. >300°C. ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 2.65 (t, 2H, $-CH_2CH_2COOH$), 2.85 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, CH_2CH_3), 4.60–4.80 (m, 4H, H-8, $-CH_2CH_2COOH$), 13.60 (br, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.4$ (q, CH_2CH_3), 24.8 (t, C-5), 30.6 (t, $-NCH_2$), 36.7 (t, CH_2COOH), 40.2 (t, C-6), 42.4 (t, C-8), 61.0 (t, CH_2CH_3), 115.8 (s, C-4a), 124.8 (s, C-4b), 129.5 (s, C-8a), 149.5 (s, C-9a), 154.6 (s, C-4), 163.6 (s, CO), 170.1 (C-2), 173.2 (s, COOH). $C_{15}H_{17}N_3O_5S_2$ (383.45) calcd.: C, 46.98; H, 4.46; N, 10.95; S, 16.72. Found: C, 46.84; H, 4.39; N, 10.82; S, 16.59.

*Ethyl 2,5-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 (7H)-carboxylate (**14**)*

Method A. Compound **11** (0.5 g, 0.0013 mol) was heated above its melting point for 15 min; the residue was cooled and crystallized from DMF. Yield: 0.28 g (59%) **14** as yellow crystals, m.p. 260–262°C. IR: $\nu = 1740$, 1710, 1680 (3CO), 1640 (C=N). ^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, CH_2CH_3), 2.85 (t, 2H, H-6), 3.60 (t, 2H, H-7), 3.90 (s, 2H, H-3), 4.20 (q, 2H, CH_2CH_3), 4.60 (s, 2H, H-9). $C_{14}H_{13}N_3O_4S_2$ (351.41) calcd.: C, 47.85; H, 3.72; N, 11.95; S, 18.24. Found: C, 47.76; H, 3.64; N, 11.81; S, 18.33.

Method B. To a solution of **10** (0.31 g, 0.001 mol) in DMF (10 ml) was added chloroacetyl chloride (0.14 g, 0.0012 mol) dropwise under stirring. The reaction mixture was then heated on a water bath for 2 h and after cooling, poured into 100 ml of cold water with vigorous stirring. The precipitate was collected by filtration, washed with water, dried,

and recrystallized from DMF. Yield: 0.21 g (62%) **14** as yellow crystals, m.p. 260–261°C. The product is identical to that obtained by Method A.

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