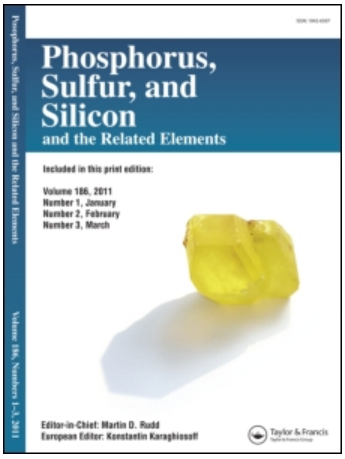

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Synthesis of New Pyrido[4",3":4",5"]thieno[2",3":4,5]pyrimido[2,1-b][1,3,4]thiadiazine Derivatives

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SYNTHESIS OF NEW PYRIDO[4″,3″:4′,5′]THIENO[2′,3′:4,5]PYRIMIDO-[2,1-B][1,3,4]THIADIAZINE DERIVATIVES

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*Ethyl 2-methyl-11-oxo-9, 10-dihydro-1*H*, 11*H*-pyrido[4″,3″:4′,5′]thieno-[2′,3′:4,5]pyrimido[2,1-b][1,3,4]thiadiazine-8(7*H*)-carboxylate* ***7*** *has been synthesised by the reaction of 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* ***2*** *with allylbromide followed by treatment with bromine and subsequent dehydrobromination of the brominated product* ***5*** *with ethanolic sodium hydroxide. Its isomeric ethyl 2-methyl-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b]-[1,3,4]thiadiazine-8(7*H*)-carboxylate* ***8*** *has been obtained by condensation of* ***2*** *with chloroacetone followed by cyclization of the intermediate* ***9*** *with* p*-toulenesulfonic acid. The thiadiazino derivatives* ***11***, ***13***, ***15*** *were prepared through the reaction of* ***2*** *with the appropriate α-halocarbonyl compounds followed by cyclization reactions of the intermediates* ***10***, ***12***, ***14***.

Keywords: Fused S; N-heterocycles; pyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidines; pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazines

Pyridothienopyrimidines have been the subject of chemical and biological studies on account of their interesting pharmacological properties which include antiinflammatory,[1–3] antipyretic,[4,5] analgesic,[6] and anti-anaphylactic,[7,8] activity. Also some are clinically efective antiallergic[9] and a few possess significant hypocholesterolenic[10] activity. In view of the above activities and in continuation of our work in the synthesis of such system,[11–13] this article follows that line of research reporting on a new series of linear fusion reactions of pyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine derivatives, in which thiadiazine moiety was annelated,

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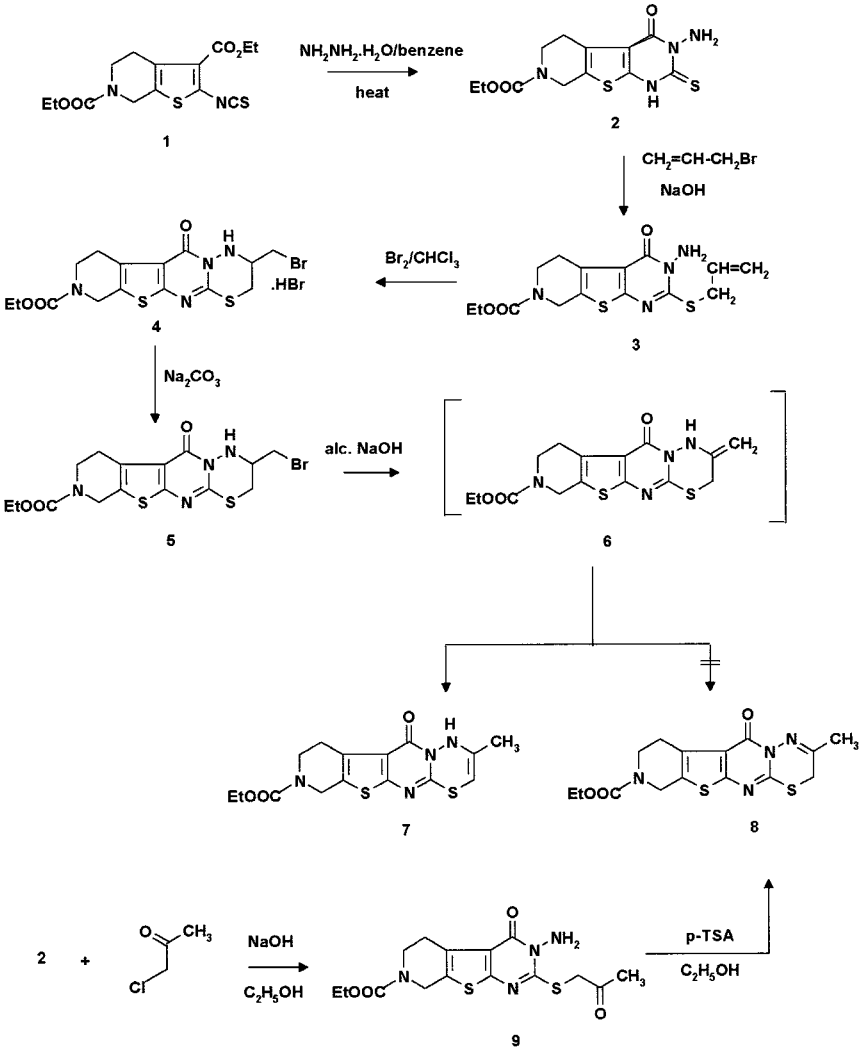
yielding pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]thiadiazines **7**, **8**, **11**, **13**, **15**.

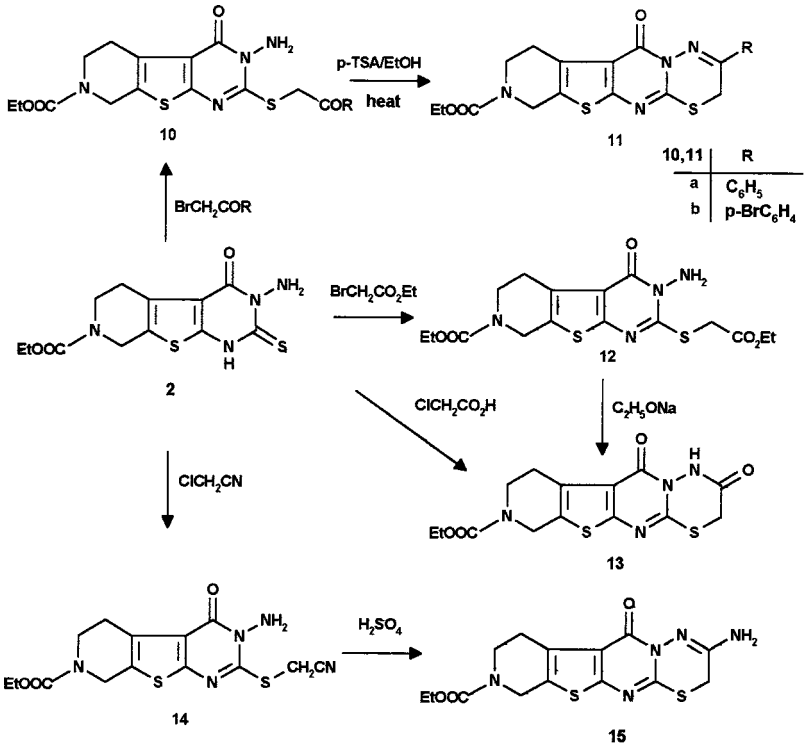
The versatile intermediate ethyl 3-amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(2*H*)-carboxylate (**2**) was prepared by adding a benzene solution of diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1**[12] to hydrazine hydrate and subsequent prolonged heating of the reaction mixture. Reaction of (**2**) with allyl bromide in the presence of sodium hydroxide resulted in the formation of ethyl 2-(allylsulfanyl)-3-amino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (**3**). The structure of **3** has been confirmed on the basis of ^{1}H NMR studies which showed a doulet at 3.90 assignable to two allylic protons (−**CH$_2$**−CH=CH$_2$). It also gave two multiplets at 5.80–6.20 (1H) and at 5.10–5.50 (2H), the former may be assigned to one vinylic protons **CH**=CH$_2$ and −CH=**CH$_2$**. And a singlet at 5.70 (2H) exchangeable with D$_2$O which was assigned to the amino function. Other analytical and spectroscopic data are given in experimental section. Treatment of **3** with bromine in chloroform at 5°C led to the formation of ethyl 2-(bromomethyl)-11-oxo-2,3,9,10-tetrahydro-1*H*,11*H*-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5] pyrimido[2, 1-b]-[1,3,4]thiadiazine-8(7*H*)-carboxylate hydrobromide (**4**) which on basification with 10% sodium carbonate solution librated its free base (**5**).

Compound **5** on treatment with alcoholic sodium hydroxide underwent dehydrohalogenation and gave rise to ethyl 2-methyl-11-oxo-9,10-dihydro-1*H*,11H-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b]-[1,3,4]thiadiazine-8(7*H*)-carboxylate (**7**) instead of the expected product (**6**) this may be due to greater stability of **7** as compared to **6**, the latter might have rearranged to the former. In fact **6** could have undergone rearrangement to (**8**) too but structure **7** has been assigned on the basis of IR and ^{1}H NMR studies. Compound **7** showed no IR absorption band around 890 cm^{-1} due to its exocyclic double bond. Its ^{1}H NMR exhibited a doublet (3H) because of allylic spilitting at δ 3.60 which could be assigned to three methyl protons −CH=C−**CH$_3$**. It also showed a quartet (1H) again because of allylic splitting at δ 4.90 assignable to one vinylic protons −**CH**=C−CH$_3$. The single proton attached to nitrogen appeared as a singlet (1H) exchangeable with D$_2$O at δ 8.90. It was thought desirable to prepare isomeric ethyl 2-methyl-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate **8** by an alternative route by heating in ethanol in the presence of *p*-toluenesulfonic acid the derivative (**9**), previously obtained from **2** and chloroacetone. Structure of **8** is supported by the results of IR and ^{1}H NMR measurements. It gave

an absorption band at 1680 cm^{-1} due to —CO— but the bands at 3420-3350 and 3120 cm^{-1} due to the NH_2 and at 1690 cm^{-1} due to carbonyl of ketone —CH_2—CO— originally present in **9**, disappeared. Its ^1H NMR exhbited a singlet (3H) at δ 2.40 assignable to three methyl protons. Besides it also gave singlet at δ 4.30 due to methylene protons (—S—**CH_2**—). This eliminate the possibility of structure **7** and confirms structure **8** (Scheme 1).



SCHEME 1



SCHEME 2

As illustrated in Scheme 2, the ethyl 2-phenyl(**11a**) and ethyl-2-(4-bromophenyl) (**11b**)-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido[4″,3″:4′,5′]-thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]thiadiazine-8(7*H*)-carboxylate were obtained by cyclizing in refluxing ethanol with a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) the thio derivatives (**10a**,**b**) obtained from amino-thioxo derivative **2** and 2-bromoacetophenone or 2,4′-dibromo-acetophenone in benzene in the presence of triethylamine, respectively.

By reaction of the alkaline solution of the amino-thioxo derivative **2** with ethyl bromoacetate, the ethyl 3-amino-2-[(2-ethoxy-2-oxoethyl)sulfanyl]-4-oxo-3,5,6,8-tetra hydropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7(4*H*)-carboxylate (**12**) was formed. Heating of the ester **12** in ethanol in the presence of sodium ethoxide and subsequent acidification of the resulting mixture with hydrochloric acid or acetic acid afforded the ethyl 2,11-dioxo-2,3,9,10-tetra hydro-1*H*,11*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]thiadiazine-8(7*H*)-carboxylate (**13**), which is identical to the product obtained by

treatment of **2** with chloroacetic acid. The structure of compound **13** was characterized by elemental analysis, IR, and ^{1}H NMR. In particular, the IR spectrum showed a band at 3180 cm^{-1} attributable to N—H stretching and a broad band at 1680 cm^{-1} due to overlapping bands of the two carbonyl groups. Moreover, the ^{1}H NMR spectrum exhibited a broad signal at δ 11.70 confirming the presence of NH group, and a signal at δ 4.30 attributable to the two methylene protons in position 3.

Heating an alcoholic solution of **2** with chloroacetonitrile afforded ethyl 3-amino-2-[cyanomethylsulfanyl]-4-oxo-3,5,6,8-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (**14**). The structure of **14** was confirmed by analytical and spectral data. The IR showed a sharp band at 2220 cm^{-1} characteristic of the stretching frequency of nitrile whereas the ^{1}H NMR spectra showed a singlet at δ 4.40 ppm (2H, CH_2CN) and broad singlet at 5.80 ppm (2H, NH_2). Compound **14** underwent cyclization when treated with concentrated sulfuric acid at room temperature to yield ethyl 2-amino-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b]-[1,3,4]thiadiazine-8(7*H*)-carboxylate (**15**). The cyclization of **14** to **15** involved a nucleophilic addition at the cyano group followed by a proton acquisition, resulting in ring closure and the formation of the amino-substituted heterocycles.

EXPERIMENTAL

All m.p.s were recorded on a Gallenkamp apparatus and are uncorrected. Microanalyses were performed at the Microanalytical Laboratory, Cairo University. ^{13}C and ^{1}H NMR spectra were recorded on a Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz), 5 mm dual ^{1}H/^{13}C-VT probe at 300 K; solvent: DMSO-d_6 and $CDCl_3$, respectively; δ values are given in ppm, internal standard TMS ($\delta = 0$ ppm). IR-spectra were recorded on a Shimadzu 470 Spectrophotometer in KBr pellets.

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 (2)

A solution of diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3,6-dicarboxylate **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, 0.018 mol) in benzene (5 ml). The suspension was refluxed under stirring for 8 hours. After cooling, the solid

product was collected, by filtration washed with ethanol, dried, and recrystallized from dioxane. Yield 0.52 g (91.2%) of compound **2** as yellow crystals, m.p. 232–234°C (dec); (Found: C, 44.07; H, 4.30; N, 17.01; S, 19.50. $C_{12}H_{14}N_4O_3S_2$ (326.40) requires C, 44.15; H, 4.32; N, 17.16; S, 19.64%); ν_{max}/cm^{-1}: 3400, 3320, 3180 (NH_2, NH), 1700, 1680 (CO), 1200 (C=S); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 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, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 6.30–6.50 (br, 2H, NH_2); δ_c (DMSO-d_6): 14.56 (q, $COOCH_2CH_3$), 25.26 (t, C-5), 40.74 (t, C-6), 46.75 (t, C-8), 60.95 (t, $COOCH_2CH_3$), 113.31 (s, C-4a), 128.28 (s, C-4b), 141.03 (s, C-8a), 154.64 (s, C-4), 157.64 (s, C-9a), 161.63 (s, CO), 168.83 (s, C-2).

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

To a solution of **2** (0.32 g, 0.001 mol) in 5% sodium hydroxide solution (1 ml), allyl bromide (0.13 g, 0.001 mol) dissolved in ethanol (2 ml) was added dropwise with stirring at room temperature. There was immediate separation of **3**. After keeping the mixture over night it was diluted with water, the precipitate was collected under suction, washed with water, dried, and crystallized from ethanol. Yield 0.3 g (83.3%) of compound **3** as colorless crystals, m.p. 158–159°C; (Found: C, 48.96; H, 4.79; N, 15.10; S 17.30. $C_{15}H_{18}N_4O_3S_2$ (366.47) requires C, 49.16; H, 4.94; N, 15.28; S, 17.49%); ν_{max}/cm^{-1}: 3380 (NH_2), 1700, 1670 (CO), 1660 (C=N); δ_H (DMSO-d_6): 1.3 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.90 (t, J 5.6 Hz, 2H, H-5), 3.70 (t, J 5.6 Hz, 2H, H-6), 3.90 (d, J 7 Hz, 2H, $\mathbf{CH_2}$–CH=CH_2), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 5.10–5.50 (m, 2H, CH_2–CH=$\mathbf{CH_2}$), 5.70 (s, 2H, NH_2), 5.80–6.20 (m, 1H, $\mathbf{CH}$=CH_2).

Ethyl 2-(bromomethyl)-11-oxo-2,3,9,10-tetrahydro-1*H*, 11*H*-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b]-[1,3,4]thiadiazine-8(7*H*)-carboxylate-hydrobromide (4)

A solution of bromine (0.32 g, 0.002 mol) in chloroform (6 ml) was added dropwise to a solution of **3** (0.73 g, 0.002 mol) in 5 ml chloroform with constant stirring at 5°C. The reaction mixture was kept at room temperature for 4 h until the color of bromine had completly disappeared. On evaporating the solvent, the solid thus obtained was collected and crystallized from dioxane. Yield 0.74 g (71.15%) of compound **4** as yellow crystals, m.p. 260–262°C; (Found: C, 34.11; H, 3.30; N, 10.48; S, 12.10. $C_{15}H_{18}N_4O_3S_2\,Br_2$ (526.26) requires C, 34.23; H, 3.44; N, 10.64; S, 12.18%).

Ethyl 2-(bromomethyl)-11-oxo-2,3,9,10-tetrahydro-pyrido[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido [2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (5)

Compound **4** (0.52 g, 0.001 mol) was treated with 10% sodium carbonate solution, then the precipitate was filtered, washed with water, and crystallized from ethanol. Yield. 0.4 g (90.9%) of compound **5** as colorless crystals, m.p. 192–193°C; (Found: C, 40.32; H, 3.67; N, 12.65; S, 14.22. $C_{15}H_{17}N_4O_3S_2Br$ (445.34) requires C, 40.45; H, 3.84; N, 12.58; S, 14.39%); ν_{max}/cm^{-1}: 3180 (NH), 1710, 1680 (CO), δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-10), 3.40 (t, 2H H-9), 3.60 (d, 2H, CH_2Br), 4.10 (q, 2H, $COOCH_2CH_3$), 4.32 (d, 2H, S–CH_2), 4.60 (s, 2H, H-7), 6.20–6.40 (m, 1H, **CH**–CH_2Br).

Ethyl 2-methyl-11-oxo-9,10-dihydro-1*H*,11*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (7)

To a solution of **5** (0.66 g, 0.0015 mol) in 25% ethanol (20 ml) 2% ethanolic sodium hydroxide (30 ml) was added at 45°C. After 20 min crushed ice (100 g) was added. The separated product was collected by filtration, dried, and recrystallized from ethanol. Yield 0.33 g (61.1%) of compound **7** as colorless crystals, m.p. 187–188°C; (Found: C, 49.50; H, 4.28; N, 15.45; S, 17.70. $C_{15}H_{16}N_4O_3S_2$ (364.43) requires C, 49.43; H, 4.42; N, 15.37; S, 17.59%); ν_{max}/cm^{-1}: 3180 (NH), 2950 (CH aliph.), 1720, 1680 (CO), 1660 (C=N); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-10), 3.40 (t, 2H, H-9), 3.60 (d, 3H, CH_3), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-7), 4.90 (q, 1H, **CH**=C–CH_3), 8.90 (s, 1H, NH).

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

Chloroacetone (0.11 g, 0.0011 mol) was added to a hot suspention of **2** (0.32 g, 0.001 mol) in 5% sodium hydroxide solution (1 ml, 0.04 g, 0.001 mol) and ethanol (10 ml). The mixture was gently warmed under stirring for 2 hours, then poured into water (20 ml) and the resulting solid was collected by filtration, dried, and recrystallized from ethanol/water. Yield 0.22 g (59.4%) of compound **9** as colorless crystals, m.p. 150–152°C; (Found: C, 47.25; H, 4.62; N, 14.51; S, 16.63. $C_{15}H_{18}N_4O_4S_2$ (382.44) requires C, 47.10; H, 4.74; N, 14.65; S, 16.76%); ν_{max}/cm^{-1}: 3420-3350 (NH_2), 2900 (CH aliph.), 1720, 1690, 1680 (CO); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.60 (s, 3H, $COCH_3$), 2.80 (t, J 5.6 Hz, 2H,

H-5), 3.40 (t, J 5.6 Hz, 2H, H-6), 3.57 (s, 2H, CH_2—CO—), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 5.80 (s, 2H, NH_2).

Ethyl 2-methyl-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (8)

A mixture of **9** (0.38 g, 0.001 mol) and *p*-TSA (20 mg) in ethanol (20 ml) was refluxed for 3 h. The solution was then cooled to room temperature. The resulting precipitate was collected by filtration, dried, and recrystallized from ethanol. Yield 0.2 g (55.5%) of compound **8** as yellow needless, m.p. 222–224°C; (Found: C, 49.35; H, 4.30; N, 15.22; S, 17.45. $C_{15}H_{16}N_4O_3S_2$ (364.43) requires C, 49.43; H, 4.42; N, 15.37; S, 17.59%); ν_{max}/cm^{-1}: 2990 (CH aliph.), 1700, 1670 (CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.40 (s, 3H, CH_3), 2.70 (t, J 5.6 Hz, 2H, H-10), 3.40 (t, J 5.6 Hz, 2H, H-9), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, S—CH_2), 4.60 (s, 2H, H-7).

Ethyl 3-amino-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 (10a)

2-bromoacetophenone (0.32 g, 0.0016 mol) was added to a stirred solution of **2** (0.5 g, 0.0015 mol) and triethylamine (8 drops) in benzene (15 ml), and the mixture was stirred at room temperature for 30 min, then diluted with water (50 ml). The resulting solid product was collected by filtration, washed with water, dried, and recrystallized from dioxan/water. Yield 0.55 g (80.9%) of compound **10a** as colorless crystals, m.p. 180–182°C; (Found: C, 54.14; H, 4.65; N, 12.76; S, 14.60. $C_{20}H_{20}N_4O_4S_2$ (444.54) requires C, 54.03% H, 4.53; N, 12.60; S, 14.42%); ν_{max}/cm^{-1}: 3400-3320 (NH_2), 3120 (Ar—CH), 1720, 1690 (CO); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.80 (t, J 5.6 Hz, 2H, H-5), 3.60 (t, J 5.6 Hz, 2H, H-6), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, S—CH_2), 4.60 (s, 2H, H-8), 5.80 (s, 2H, NH_2), 7.50–7.90 (m, 5H, Ar—H).

Ethyl 3-amino-2-{[2-(4-bromophenyl)-2-oxoethyl]-sulfanyl}-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]-thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (10b)

2,4′-dibromoacetophenone (0.31 g, 0.0011 mol) was added to a stirred solution of **2** (0.32 g, 0.001 mol) and triethylamine (5 drops) in benzene (10 ml), and the mixture was stirred at room temperature for 40 min,

then diluted with water (50 ml). The resulting solid product was collected by filtration, washed with water, dried, and recrystallized from dioxane/water. Yield 0.46 g (90.2%) of compound **10b** as yellow crystals, m.p. 220–222°C; (Found: C, 45.70; H, 3.77; N, 10.85; S, 12.34. $C_{20}H_{19}N_4O_4S_2Br$ (523.43) requires C, 45.89; H, 3.65; N, 10.70; S, 12.25%); ν_{max}/cm^{-1}: 3450-3350 (NH_2), 3050 (Ar—CH), 1720, 1690, 1680 (CO); δ_H (DMSO-d_6): 1.30 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.90 (t, J 5.6 Hz, 2H, H-5), 3.60 (t, J 5.6 Hz, 2H, H-6), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, S—CH_2), 4.60 (s, 2H, H-8), 5.70 (s, 2H, NH_2), 7.60 (d, J 7.7 Hz, 2H, Ar—H), 8.08 (d, J 7.7 Hz, 2H, Ar—H).

Ethyl 2-phenyl-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido-[4′′,3′′:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (11a)

The solution of compound **10a** (0.44 g, 0.001 mol) in ethanol (10 ml), *p*-toluenesulfonic acid (20 mg) was refluxed for 2 h. After cooling, the solid product was collected by filtration, washed with warm ethanol, dried, and recrystallized from dioxane. Yield 0.3 g (71.4 %) of compound **11a** as yellow crystals, m.p. 256–257°C; (Found: C, 56.18; H, 4.32; N, 13.05; S, 14.90. $C_{20}H_{18}N_4O_3S_2$ (426.52) requires C, 56.32; H, 4.25; N, 13.13; S, 15.03%); ν_{max}/cm^{-1}: 3050 (Ar—CH), 1710, 1680 (CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.90 (t, J 5.6 Hz, 2H, H-10), 3.70 (t, J 5.6 Hz, 2H, H-9), 4.20 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, S—CH_2), 4.60 (s, 2H, H-7), 7.70–8.10 (m, 5H, Ar–H).

Ethyl 2-(4-bromophenyl)-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido[4′′,3′′:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (11b)

The solution of compound **10b** (0.52 g, 0.001 mol) in ethanol (10 ml), *p*-toluenesulfonic acid (20 mg) was refluxed for 2 h. After cooling, the solid product was collected by filtration, washed with warm ethanol, dried, and recrystallized from dioxane. Yield 0.35 g (70%) of compound **11b** as yellow crystals, m.p. 255–257°C; (Found: C, 47.44; H, 3.28; N, 10.94; S, 12.51. $C_{20}H_{17}N_4O_3S_2Br$ (505.41) requires C, 47.52; H, 3.38; N, 11.08; S, 12.68%); ν_{max}/cm^{-1}: 3080 (Ar—CH), 1730, 1710 (CO); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.80 (t, J 5.6 Hz, 2H, H-10), 3.70 (t, J 5.6 Hz, 2H, H-9), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, CH_2), 4.60 (s, 2H, H-7), 7.70 (d, J 8 Hz, 2H, Ar—H), 7.90 (d, J 8 Hz, 2H, Ar—H).

Ethyl 3-amino-2-[(2-ethoxy-2-oxoethyl)sulfanyl]-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-7(4*H*)-carboxylate (12)

Ethyl bromoacetate (0.19 g, 0.0012 mol) was added to a hot suspension of **2** (0.32 g, 0.001 mol) in ethanolic potassium hydroxide solution (0.15 g KOH in 20 ml ethanol). The mixture was refluxed for 2 h and then filtered while hot. The white solid product separated at room temperature from the ethanolic filtrate was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol. Yield 0.31 g (75.6%) of compound **12** as colorless crystals, m.p. 158–159°C; (Found: C, 46.46; H, 4.64; N, 13.45; S, 15.41. $C_{16}H_{20}N_4O_5S_2$ (412.50) requires C, 46.58; H, 4.88; N, 13.58; S, 15.54%); ν_{max}/cm^{-1}: 3350-3280 (NH_2), 1730, 1710, 1680 (CO); δ_H (DMSO-d_6): 1.10 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 1.30 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.80 (t, J 5.6 Hz, 2H, H-5), 3.60 (t, J 5.6 Hz, 2H, H-6), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.20 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, S—CH_2), 4.60 (s, 2H, H-8), 5.80 (s, 2H, NH_2).

Ethyl 2,11-dioxo-2,3,9,10-tetrahydro-1*H*,11*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (13)

Method A: To a hot solution of sodium (0.026 g, 0.0011 mol) in ethanol (10 ml), the thioacetate derivative **12** (0.41 g, 0.001 mol) was added over 5 min. The solution after refluxing for 30 min, was stirred at room temperature for 1 h and then concentrated under reduced pressure, acidified with glacial acetic acid (0.2 ml) or 10% hydrochloric acid (1.1 ml) and then stirred for 30 min. The resulting solid product was collected by filtration, washed with water, dried, and recrystallized from dioxane/water. Yield 0.2 g (55.5%) of compound **13** as colorless crystals, m.p. 310–312°C; (Found: C, 45.78; H, 3.78; N, 15.15; S, 17.38. $C_{14}H_{14}N_4O_4S_2$ (366.43) requires C, 45.89; H, 3.85; N, 15.29; S, 17.50%); ν_{max}/cm^{-1}: 3180 (NH), 1700, 1680 (CO); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.80 (t, J 5.6 Hz, 2H, H-10), 3.70 (t, J 5.6 Hz, 2H, H-9), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, H-3), 4.60 (s, 2H, H-7), 11.70 (s, 1H, NH).

Method B: A mixture of **2** (0.64 g, 0.002 mol), chloroacetic acid (0.22 g, 0.0022 mol) and anhydrous sodium acetate (0.2 g, 0.0024 mol) in absolute ethanol (15 ml) was refluxed on a steam-bath for 6 h, then cooled and poured into cold water. The resulting solid was collected by filtration, dried, and crystallized from dioxane/water. Yield 0.48 g (66.6%) of compound **13** as colorless crystals, m.p. 311–313°C. The compound is identical to that obtained according to method A.

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

Compound **2** (0.64 g, 0.002 mol) dissolved in 10 ml of absolute ethanol was mixed with chloroacetonitrile (0.3 g, 0.004 mol) and refluxed for 4 h. The solvent was evaporated and the residue dissolved in water. Neutralization with sodium carbonate gave a precipitate which was filtered, washed with cold water, and crystallized from ethanol/water. Yield 0.43 g (60.5%) of compound **14** as pale yellow crystals, m.p. 198–199°C; (Found: C, 45.89; H, 4.25; N, 19.30; S, 17.65. $C_{14}H_{15}N_5O_3S_2$ (365.44) requires C, 46.01; H, 4.13; N, 19.16; S, 17.54%); ν_{max}/cm^{-1}: 3340 (NH_2), 2220 (CN), 1700,1680 (CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.90 (t, J 5.6 Hz, 2H, H-5), 3.60 (t, J 5.6 Hz, 2H, H-6), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.40 (s, 2H, S–CH_2CN), 4.60 (s, 2H, H-8), 5.80 (s, 2H, NH_2).

Ethyl 2-amino-11-oxo-9,10-dihydro-3*H*,11*H*-pyrido-[4″,3″:4′,5′]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3,4]-thiadiazine-8(7*H*)-carboxylate (15)

Compound **14** (0.36 g, 0.001 mol) was dissolved in 5 ml of concentrated sulfuric acid and left for 3 h at room temperature. After dilution with water and neutralization with 20% ammonium hydroxide, the solid product was collected, dried, and recrystallized from ethanol. Yield 0.25 g (69.4%) of compound **15** as brown crystals, m.p. 257–258°C; (Found: C, 46.12; H, 4.35; N, 19.33; S, 17.62. $C_{14}H_{15}N_5O_3S_2$ (365.44) requires C, 46.01; H, 4.13; N, 19.16; S, 17.54); ν_{max}/cm^{-1}: 3400-3340 (NH_2), 1720, 1680 (CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.80 (t, J 5.6 Hz, 2H, H-10), 3.60 (t, J 5.6 Hz, 2H, H-9), 3.90 (s, 2H, S–CH_2), 4.10 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-7), 7.20 (s, 2H, NH_2).

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