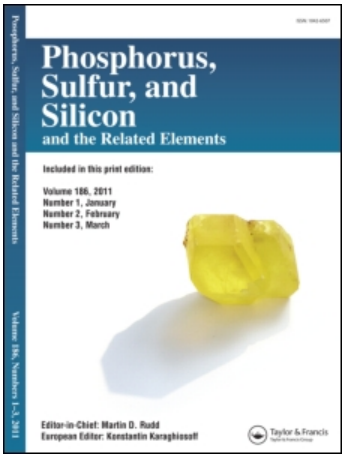

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A Convenient Synthesis for Some New Pyrido[4',3':4,5]thieno[2,3-d]pyrimidines and Related Fused 1,2,4-Triazolo and 1,3,4-Thiadiazolo-derivatives

Essam Kh. Ahmed[a]
[a] Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt

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A CONVENIENT SYNTHESIS FOR SOME NEW PYRIDO[4′,3′:4,5]THIENO[2,3-d]PYRIMIDINES AND RELATED FUSED 1,2,4-TRIAZOLO AND 1,3,4-THIADIAZOLO-DERIVATIVES

Essam Kh. Ahmed
Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt

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Diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate ***1*** *is a convenient and useful starting matrial for the constructions of heterocyclic systems. It was utilized to synthesize derivatives of the novel heterocyclic systems pyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine* ***4,10****, pyrido[4′,3′:4,5]thieno[2,3-d]-[1,2,4]triazolo-[1,5-a]pyrimidine* ***7,11a–e*** *and pyrido[4′,3′:4,5]thieno[2,3-d][1,3,4]-thiadiazolo[3,2-a]pyrimidine* ***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-d][1,2,4]triazolo[1,5-a]pyrimidines; pyrido[4′,3′:4,5]thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidines; thieno[2,3-c]pyridines

A literature survey revealed that pyridothienopyrimidines possess a broad spectrum of biological activity. They proved to be analgesic,[1] antipyretic,[2,3] antianaphylactic,[4,5] and antiinflammatory[6–8] activity. Also, some of these compounds are clinically effective antiallergic[9] and a few possess signifficant hypocholesterolenic[10] activity. On the other hand, 1,2,4-triazoles are considered a very interesting heterocyclic ring system because of their therapeutic importance. Recently derivatives of 1,2,4-triazole have been found to have significant analgesic[11] and antiseptic[12] activity. It was also found that some thiadiazole derivatives showed diverse biological activities e.g. they are used as antitumour agents, pesticides, dyes lubricants, and analytical reagents.[13] From all of the forgoing facts, and as a continuation of our interest in the synthesis of fused heterocycles with thienopyrimidines.[14–19] We reported herein the synthesis of the title compounds which might show enhanced

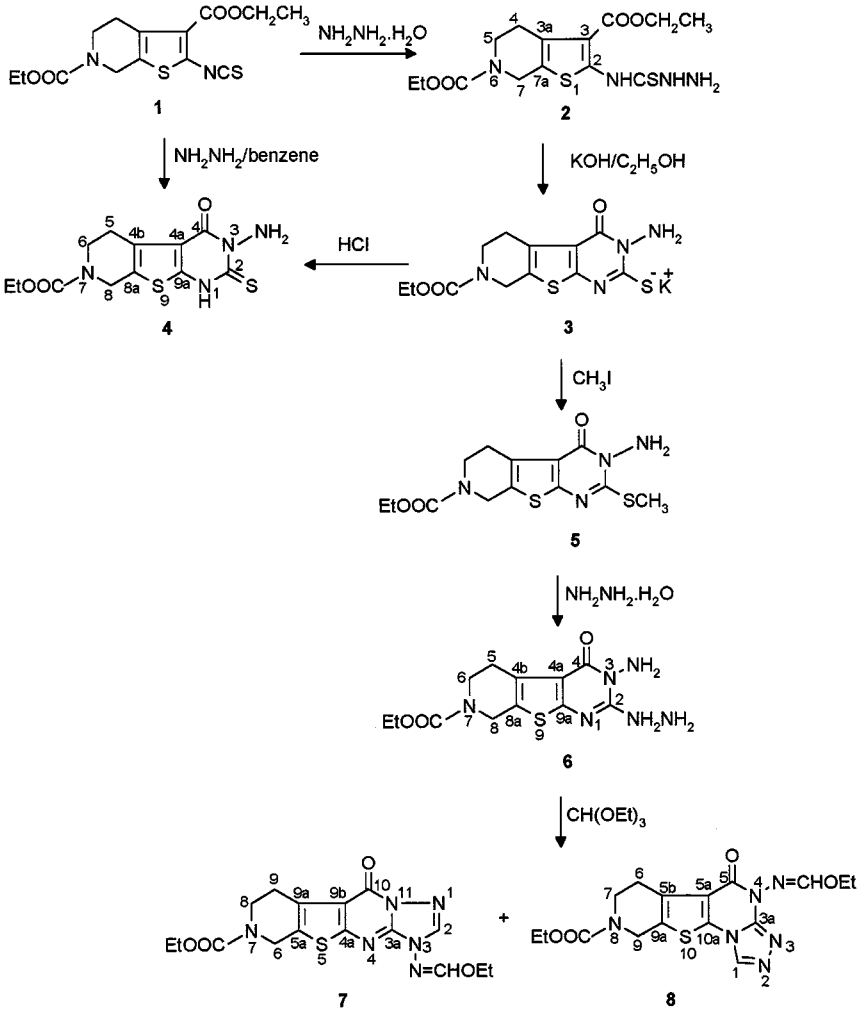
Address correspondence to E. K. Ahmed, Department of Chemistry, Faculty of Science, El-Minia University, El-Minia 61519, Egypt. E-mail: essamkhaala24@yahoo.com

biological activity due to the presence of fused pyridothienotriazolopyrimidine and pyridothienothiadiazolopyrimidine.

It has been found that dropwise addition at room temperature of a solution of hydrazine hydrate in dichloromethane to a stirred solution of diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3,6-dicarboxylate **1**[15] in dichloromethane afforded diethyl-(4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-y1)thiosemicarbazide- 3,6-dicarboxylate **2**, which by subsequent heating under reflux in ethanolic potassium hydroxide solution, gave the potassium salt of ethyl 3-amino-4-oxo-2-thioxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-7(4*H*)-carboxylate **3**. Acidification of an aqueous solution of the potassium salt **3**, the amino-thioxo derivative **4** was obtained. Compound **4** was also prepared by adding hydrazine hydrate to isothiocyanate **1** in benzene and subsequent prolonged heating of the reaction mixture. Reaction of compound **3** with methyl iodide gave methylthio derivative **5**. Treatment of **5** with hydrazine hydrate gave the hydrazino derivative **6**, which by cyclocondensation with triethyl orthoformate afforded two isomeric pyrido[4′,3′:4,5]thieno[2,3-d]-[1,2,4]triazolo[1,5-a]pyrimidine **7** and pyrido[4′,3′:4,5]thieno[2,3-e]-[1,2,4]triazolo[4,3-a]pyrimidine **8**, dependent on the cyclization which took place either to nitrogen at position 1 or at position 3. The structure determination of both systems is based on the ^{1}H NMR spectra. The chemical shifts of H-1 in triazolo[4,3-a] fused system (**8**) appear at lower field $\delta = 9.80$ than H-2 in triazolo[1,5-a]fused system $\delta = 9.30$ (**7**) (Scheme 1).

As an extension of our studies, we have been interested in preparing the interesting tetracyclic system **11** by another route. Thus, pyrido[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidines **11a–e** were prepared by cycling the corresponding ethyl 3-amino-2-ary-laminopyrido[4′,3′:4,5]thieno[2,3-d]pyrimidin-4(3H)-one-7-carboxylate **10a–e** with triethyl orthoformate in the presence of *p*-toluenesulfonic acid. The starting derivatives **10a–e** were synthesized by reaction of hydrazine hydrate with the appropriate diethyl 2-({[(aryl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2, 3-c]-pyridine-3,6-dicarboxylate **9a–e** obtained from the isothiocyanate **1** with commercially available substituted arylamines (Scheme 2).

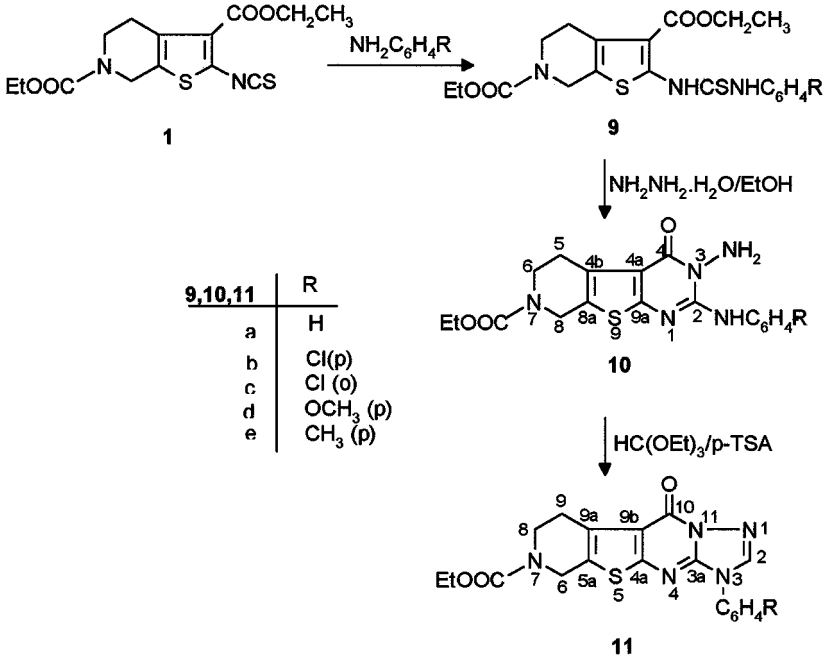
With a view to expand the scope of our investigation, ethyl 3-amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(2*H*)-carboxylate **4** was used as a key intermediate to synthesize tetracyclic ring system pyrido[4′,3′:4,5][2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidine. Thus compound **4** was converted to the ethyl 10-oxo-8,9-dihydro-10*H*-pyrido[4′,3′:4,5][2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidine-7-(6*H*)carboxylate **12** and 2-methyl analog **13** by



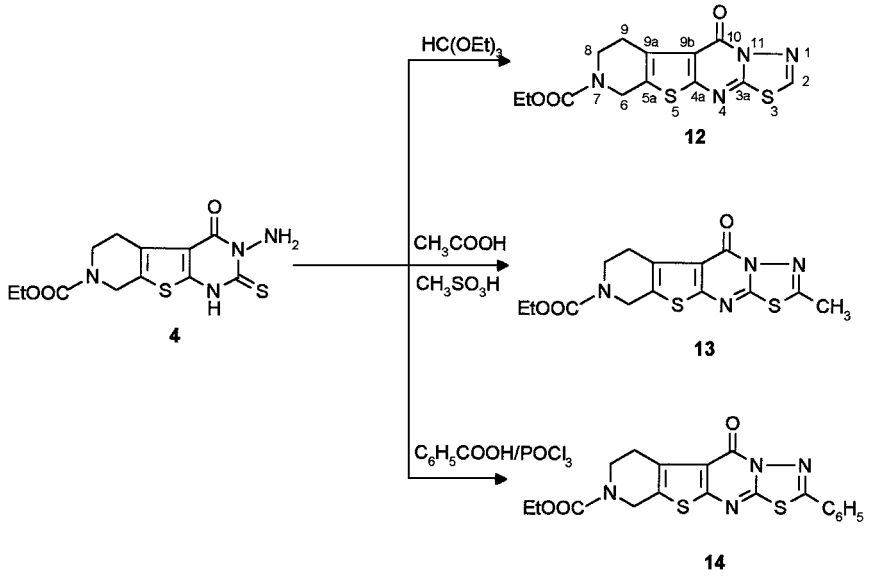
SCHEME 1

reaction with triethyl orthoformate and acetic acid, respectively. The ethyl 2-phenyl-10-oxo-8, 9-dihydro-10*H*-pyrido[4′,3′:4,5][2,3-d]-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7(6*H*)-carboxylate **14** was obtained by reaction of **4** with benzoic acid/$POCl_3$ mixture. (Scheme 3).

Structural assignments of all novel compounds were made on the basis of elemental analyses, nmr and infrared spectra (see Experimental section).



SCHEME 2



SCHEME 3

EXPERIMENTAL

All m.p.s were recorded on a Gallen kamp 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 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 Mhz), 5 mm dual $^{1}H/^{13}C$-VT probe at 300K; 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.

Diethyl-(4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-thiosemicarbazide-3,6-dicarboxylate (2)

To a stirred solution of isothiocyanate **1** (0.6 g, 0.0017 mol) in dichloromethane (10 ml) a solution of hydrazine hydrate (0.07 g, 0.0021 mol) in dichloromethane (10 ml) was added dropwise at room temperature. The suspension was stirred at room temperature for 2 h and then the solid was collected, washed with dichloromethane, dried, and recrystallized from ethanol. Yield 0.64 g (70.7%) of compound **2** as colorless crystals, m.p. 172–173°C (found: C, 45.07; H, 5.38; N, 14.90; S, 17.18. $C_{14}H_{20}N_4O_4S_2$ requires C, 45.14; H, 5.4; N, 15.04; S, 17.21%); ν_{max}/cm^{-1}: 3360,3200 and 3150 (NH, NH_2), 1690, 1710 (2 CO); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 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), 5.40 (brs, 2H, NH_2), 9.90 (s, 1H, NH), 12.60 (s, 1H, NH); δ_c (DMSO-d_6): 14.07 (q, $COOCH_2CH_3$), 14.15 (q, $COOCH_2CH_3$), 25.94 (t, C-4), 41.23 (t, C-5), 42.17 (t, C-7), 60.25 (t, $COOCH_2CH_3$), 60.93 (t, $COOCH_2CH_3$), 110.76 (s, C-3), 121.79 (s, C-7a), 128.90 (s, C-3a), 150.20 (s, CO), 154.64 (s, CO), 164.65 (s, C-2), 176.70 (s, CS).

Potassium Salt of Ethyl 3-Amino-4-oxo-2-thioxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4*H*)-carboxylate (3)

To a hot ethanolic solution (5 ml) of potassium hydroxide (0.07 g, 0.0012 mol), compound **2** (0.37 g, 0.001 mol) was added and the resulting mixture was refluxed for 30 min. The hot suspension was then filtered and the solid was collected, washed with warm dioxane, and dried to give 0.32 g (88.8% yield) of **3** as pale yellow crystals, m.p. 282–284°C (dec.) (found: C, 39.32; H, 3.74; N, 15.20; S, 17.40. $C_{12}H_{13}N_4O_3S_2K$ requires C, 39.54; H, 3.59; N, 15.37; S, 17.59%); ν_{max}/cm^{-1}: 3240 (NH_2), 1710, 1680 (2 CO), 1640 (C=N);

δ_H (DMSO-d_6): 1.30 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.30 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 6.40 (s, 2H, NH_2). δ_c (DMSO-d_6): 14.54 (q, $COOCH_2CH_3$), 25.24 (t, C-5), 42.74 (t, C-6), 46.76 (t, C-8), 60.94 (t, $COOCH_2CH_3$), 113.27 (s, C-4a), 128.62 (s, C-4b), 140.92 (s, C-8a), 154.65 (s, C-4), 157.64 (s, C-9a), 161.86 (s, CO), 167.90 (s, C-2).

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 (4)

Method A (from Compound 1)

A solution of hydrazine hydrate (0.6 g, 0.018 mol) in benzene (5 ml) was added dropwise at room temperature to a stirred solution of isothiocyanate **1** (0.6 g, 0.0017 mol) in benzene (10 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 0.52 g (91.2%) of compound **4** as yellow crystals, m.p. 232–234°C (dec.) (found: C, 44.07; H, 4.30; N, 17.01; S, 19.50. $C_{12}H_{14}N_4O_3S_2$ requires C, 44.15; H, 4.32; N, 17.16; S, 19.64%); ν_{max}/cm^{-1}: 3400, 3320, 3180 (NH_2, NH), 1710, 1680 (2 CO), 1200 (C=S); δ_H(DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.20 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 6.30–6.50 (br, 2H, NH_2), 13.40 (s, 1H, NH); 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).

Method B (from Compound 3)

To a stirred solution of potassium salt **3** (3.6 g, 0.01 mol) in water (50 ml) 37% hydrochloric acid (0.9 ml) was added dropwise, a white solid separated. The solid product was collected by filtration, washed with water, dried, and recrystallized from dioxane. Yield 2 g (62.5%) of compound **4** as yellow crystals. m.p. 231–233 (dec.). The compound is identical to that obtained according to Method A.

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

A mixture of **3** (0.22 g, 0.0006 mol) and methyl iodide (0.15 ml, 99%, d = 2.27) in water (10 ml) was stired at room temperature. The methylthio compound **5** started to crystallize almost immediately.

After 1 h, it was filtered off, washed with petroleum ether, dried, and crystallized from 2-propanol. Yield 0.18 g (90%) of compound **5** as white needles, m.p. 187–188°C (found: C, 45.83; H, 4.67; N, 16.45; S, 18.82. $C_{13}H_{16}N_4O_3S_2$ requires C, 45.86; H, 4.73; N, 16.45; S, 18.83%); ν_{max}/cm^{-1}: 3230 (NH_2), 1710, 1680 (2 CO), 1640 (C=N); δ_H(DMSO-d_d): 1.20 (t, 3H, $COOCH_2CH_3$), 2.30 (s, 3H, SCH_3), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.30 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 5.70 (s, 2H, NH_2); δ_c(DMSO-d_6): 14.30 (q, $COOCH_2CH_3$), 15.20 (q, SCH_3), 25.20 (t, C-5), 40.74 (t, C-6), 46.15 (t, C-8), 60.95 (t, $COOCH_2CH_3$), 113.30 (s, C-4a), 127.55 (s, C-4b), 141.03 (s, C-8a), 154.64 (s, C-4), 156.76 (s, C-9a), 161.63 (s, CO), 167.83 (s, C-2).

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

A mixture of **5** (0.34 g, 0.001 mol), hydrazine hydrate (1.5 ml 98%, d = 1.032) and 2-propanol (5 ml) was refluxed for 6 h. After cooling, the resulting solid was collected, dried, and crystallized from ethanol. Yield 0.28 g (87.5%) of compound **6** as colorless needless, m.p. 243–245°C (found: C, 44.60; H, 4.90; N, 25.86; S, 9.80. $C_{12}H_{16}N_6O_3S$ requires C, 44.43; H: 4.97; N, 25.90; S, 9.88%); ν_{max}/cm^{-1}: 3330, 3150 (NH_2, NH), 1710, 1680 (2 CO), 1640 (C=N); δ_H (DMSO-d_6): 1.30 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, H-8), 4.70 (s, 2H, NH_2), 5.30 (s, 2H, NH_2), 8.30 (s, 1H, NH).

Ethyl 3-Ethoxymethyleneamino-10-oxo-3,8,9,10-tetrahydropyrido[4′,3′:4,5]thieno[3,2-d][1,2,4]-triazolo[1,5-a]pyrimidine-7(6*H*)-carboxylate (7) and Ethyl 4-Ethoxymethyleneamino-5-oxo-4,5,6,9-tetrahydropyrido-[4′,3′:4,5]thieno[3,2-e][1,2,4]triazolo[4,3-a]pyrimidine-8-(7*H*)-carboxylate (8)

A mixture of **6** (0.39 g, 0.001 mol) and triethyl orthoformate (10 ml) was heated under reflux for 8 h. The precipitate was, after cooling, collected by filtration, dissolved in ethanol (3 ml), and separated by column chromatography (Kiesegel 60, E. Merk, and chloroform/methanol (9:1 as solvent) into two fractions. The first fraction gave, after evaporation of solvent in vacuo, 0.2 g (42.6% yield) of compound **7** as colorless crystals, m.p. 200–202°C (found: C, 48.99; H, 4.48; N, 21.38; S, 8.18. $C_{16}H_{18}N_6O_4S$ requires C, 49.22; H, 4.64; N, 21.52; S, 8.21%); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.40 (t, 3H, OCH_2CH_3), 2.95

(t, 2H, H-9), 3.70 (t, 2H, H-8), 4.10 (q, 2H, $COOCH_2CH_3$)), 4.40 (q, 2H, OCH_2CH_3), 4.80 (s, 2H, H-6), 8.60 (s, 1H, N=CH), 9.30 (s, 1H, H-2).

The second fraction gave, after evaporation of solvent in vacuo, 0.12 g (25.5% yield) of compound **8** as colorless crystals, m.p. 240–242°C (found: C, 48.95; H, 4.50; N, 21.42; S, 8.10. $C_{16}H_{18}N_6O_4S$ requires C, 49.22; H, 4.64; N, 21.52; S, 8.21%); δ_H (DMSO-d_6) 1.20 (t, 3H, —$COOCH_2CH_3$), 1.40 (t, 3H, OCH_2CH_3), 3.00 (t, 2H—H-6), 3.70 (t, 2H, H-7), 4.20 (q, 2H, $COOCH_2CH_3$), 4.40 (q, 2H, OCH_2CH_3), 4.60 (s, 2H, H-9), 9.00 (s, 1H, N=CH), 9.80 (s, 1H, H-1).

General Procedure for the Synthesis of (9a–e)

To a solution of the substituted arylamine (0.001 mol) in dichloromethane (5 ml) a solution of isothiocyanate **1** (0.001 mol) in dichloromethane (5 ml) was added with stirring. The solution was stirred at room temperature for 1–3 h and then the solid was filtered off, washed with ethanol, dried, and recrystallized from an appropriate solvent.

Diethyl 2-({[(Phenyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (9a)

Colorless crystals from EtOH. Yield 83.7%, m.p. 178–180°C (found: C, 55.20; H, 5.38; N, 9.62; S, 14.68. $C_{20}H_{23}N_3O_4S_2$ requires C, 55.40; H, 5.34; N, 9.69; S, 14.79%); δ_H (DMSO-d_6): 1.10 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 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), 7.30–7.50 (m, 5H, Ar—H), 11.10 (s, 1H, NH), 11.90 (s, 1H, NH).

Diethyl 2-({[(p-Chlorophenyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (9b)

Colorless crystals from EtOH. Yield 91.3%, m.p. 186–188°C (found: C, 51.15; H, 4.79; N, 8.88; S, 13.59. $C_{20}H_{22}N_3O_4S_2Cl$ requires C, 51.33; H, 4.73; N, 8.97; S, 13.70%); ν_{max}/cm^{-1}: 3200 (NH), 1710, 1670 (2 CO); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.70 (t, 2H, H-4), 3.60 (t, 2H, H-5), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-7), 7.40–7.70 (m, 4H, Ar—H), 11.20 (s, 1H, NH), 11.95 (s, 1H, NH); δ_c (DMSO-d_6): 14.25 (q, —$COOCH_2CH_3$), 14.50 (q, $COOCH_2CH_3$), 25.91 (t, C-4), 40.74 (t, C-5), 42.13 (t, C-7), 60.56 (t, $COOCH_2CH_3$), 61.35 (t, $COOCH_2CH_3$), 111.19 (s, C-3), 122.74 (s, C-7a), 128.26 (Ph C-3,5), 129.78 (Ph C-2,6), 137.28 (s, C-3a), 142.12 (Ph C-1), 150.45 (s, CO ester). 154.62 (s, CO ester), 165.39 (s, C-2), 175.50 (s, CS).

Diethyl 2-({[(o-Chlorophenyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (9c)

Colorless crystals from EtOH. Yield 74.9%, m.p. 181–183°C (found: C, 51.20; H, 4.60; N, 8.80; S, 13.61. $C_{20}H_{22}N_3O_4S_2Cl$ requires C, 51.33; H, 4.73; N, 8.97; S, 13.70%); δ_H (DMSO-d_6): 1.10 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-4), 3.60 (t, 2H, H-5), 4.10 (q, 2H, $COOCH_2CH_3$), 4.35 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 7.40–7.80 (m, 4H, Ar—H), 10.90 (s, 1H, NH), 11.80 (s, 1H, NH).

Diethyl 2-({[(p-Methoxyphenyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (9d)

Colorless crystals from EtOH. Yield 71.7%, m.p. 188–190°C (found: C, 54.20; H, 5.35; N, 8.90; S, 13.60. $C_{21}H_{25}N_3O_5S_2$ requires C, 54.40; H, 5.43; N, 9.06; S, 13.83%); ν_{max}/cm^{-1}: 3200 (NH), 1710, 1680 (2 CO); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-4), 3.60 (t, 2H, H-5), 3.80 (s, 3H, OCH_3), 4.10 (q, 2H, $COOCH_2CH_3$), 4.30 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 7.15–7.60 (m, 4H, Ar—H), 10.60 (s, 1H, NH), 11.50 (s, 1H, NH); δ_c (DMSO-d_6): 13.92 (q, $COOCH_2CH_3$), 14.50 (q, $COOCH_2CH_3$), 25.90 (t, C-4), 40.76 (t, C-5), 42.12 (t, C-7), 55.26 (s, OCH_3), 60.43 (t, $COOCH_2CH_3$), 61.20 (t, $COOCH_2CH_3$), 114.87 (s, C-3), 122.20 (s, C-7a), 127.40 (Ph C-3,5), 128.74 (Ph C-2,6), 130.49 (s, C-3a), 142.20 (Ph C-1), 150.80 (s, CO ester), 154.65 (s, CO ester), 165.21 (s, C-2), 175.87 (s, C=S).

Diethyl 2-({[(p-Tolyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (9e)

Colorless crystals from EtOH. Yield 73.9%, m.p. 199–200°C (found: C, 56.20; H, 5.55; N, 9.30; S, 14.20. $C_{21}H_{25}N_3O_4S_2$ requires C, 56.35; H, 5.63; N, 9.38; S, 14.32%); ν_{max}/cm^{-1}: 3220 (NH), 1710, 1680 (2 CO); δ_H (DMSO-d_6): 1.15 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.30 (s, 3H, CH_3), 2.70 (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), 7.20–7.50 (m, 4H, Ar—H), 11.00 (s, 1H, NH), 11.90 (s, 1H, NH).

General Procedure for the Synthesis of (10a-e)

To a suspention of the arylthioureas **9a–e** (0.001 mol) in ethanol (10 ml), hydrazine hydrate (0.04 mol) was added. The mixture was heated under reflux for 3–4 h. After cooling the precipitated was collected, washed with ethanol, dried, and recrystallized from a suitable solvent.

Ethyl 3-Amino-2-phenylamino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (10a)

Colorless crystals from EtOH. Yield 63.1%, m.p. 220–221°C (found: C, 56.23; H, 5.18; N, 18.42; S, 8.42. $C_{18}H_{19}N_5O_3S$ requires C, 56.09; H, 4.96; N, 18.16; S, 8.31%); δ_H ($CDCl_3$): 1.30 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6) 4.20 (q, 2H, —$COOCH_2CH_3$), 4.60 (s, 1H, H-8), 5.40 (s, 2H, NH_2), 7.30–7.80 (m, 4H, Ar—H), 8.60 (s, 1H, NH); δ_c ($CDCl_3$): 14.62 (q, $COOCH_2CH_3$), 25.45 (t, C-5), 41.06 (t, C-6), 42.91 (t, C-8), 61.59 (t, $COOCH_2CH_3$), 114.46 (s, C-4a), 123.81 (s, C-4b), 128.28 (Ph C-4), 128.57 (Ph C-3,5), 129.90 (Ph C-2,6), 131.40 (Ph C-1), 134.62 (s, C-8a), 147.74 (s, C-9a), 155.49 (s, C-2), 158.08 (s, C-4), 165.46 (s, CO ester).

Ethyl 3-Amino-2-p-chlorophenylamino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (10b)

Colorless crystals from EtOH. Yield 75.6%, m.p. 204–206°C (found: C, 51.53; H, 4.42; N, 16.51; S: 7.75. $C_{18}H_{18}N_5O_3SCl$ requires C, 51.49; H, 4.32; N, 16.67; S, 7.63%); ν_{max}/cm^{-1}: 3350, 3200 (NH_2, NH), 1710, 1670 (2 CO); δ_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, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 5.60 (s, 2H, NH_2), 7.20–7.70 (m, 4H, Ar—H), 9.50 (s, 1H, NH); δ_c (DMSO-d_6): 14.53 (q, $COOCH_2CH_3$), 25.17 (t, C-5), 40.75 (t, C-6), 42.65 (t, C-8), 61.02 (t, $COOCH_2CH_3$), 114.17 (s, C-4a), 126.93 (s, C-4b), 128.32 (Ph C-3,5), 129.08 (Ph C-2,6), 133.88 (s, C-8a), 148.87 (s, C-9a), 154.74 (s, C-2), 157.66 (s, C-4), 165.78 (s, CO ester).

Ethyl 3-Amino-2-o-chlorophenylamino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (10c)

Colorless crystals from EtOH. Yield 68.3%, m.p. 210–212°C (found: C, 51.60; H, 4.40; N, 16.80; S, 7.72. $C_{18}H_{18}N_5O_3SCl$ requires C, 51.49; H, 4.32; N, 16.67; S, 7.63%); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.20 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 5.70 (s, 2H, NH_2), 7.20–7.70 (m, 4H, Ar—H), 9.60 (s, 1H, NH).

Ethyl 3-Amino-2-p-methoxyphenylamino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4H)-carboxylate (10d)

Colorless crystals from EtOH. Yield 63.4%, m.p. 226–228°C (found: C, 54.86; H, 5.22; N, 16.44; S, 7.60. $C_{19}H_{21}N_5O_4S$ requires C, 54.92;

H, 5.09; N, 16.85; S, 7.71%); ν_{max}/cm^{-1}: 3340, 3150 (NH_2, NH), 1710, 1670 (2 CO); δ_H ($CDCl_3$): 1.30 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.60 (t, 2H, H-6), 3.85 (s, 3H, OCH_3), 4.30 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 5.40 (s, 2H, NH_2), 7.20–7.60 (m, 4H, Ar—H), 9.40 (s, 1H, NH); δ_c ($CDCl_3$): 14.62 (q, $COOCH_2CH_3$), 25.40 (t, C-5), 40.95 (t, C-6), 42.95 (t, C-8), 55.44 (s, OCH_3), 61.58 (t, $COOCH_2CH_3$), 115.78 (s, C-4a), 125.41 (s, C-4b), 129.47 (Ph C-3,5), 129.86 (Ph C-2,6), 130.31 (Ph C-1), 133.45 (C-8a), 152.10 (s, C-9a), 153.08 (s, C-2), 160.20 (s, C-4), 165.40 (s, CO ester).

*Ethyl 3-Amino-2-p-tolylamino-4-oxo-3,5,6,8-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(4***H***)-carboxylate** *(10e)*

Colorless crystals from EtOH. Yield: 69.2%, m.p. 206–208°C (found: C, 56.96; H, 5.10; N, 17.35; S, 7.90. $C_{19}H_{21}N_5O_3S$ requires C, 57.12; H, 5.29; N, 17.53; S, 8.02%); ν_{max}/cm^{-1}: 3350, 3150 (NH_2, NH), 1710, 1675 (2 CO); δ_H ($CDCl_3$): 1.30 (t, 3H, $COOCH_2CH_3$), 2.40 (s, 3H, CH_3), 2.90 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.20 (q, 2H, —$COOCH_2CH_3$), 4.65 (s, 2H, H-8), 5.40 (s, 2H, NH_2), 7.20–7.60 (m, 4H, Ar—H), 9.50 (s, 1H, NH); δ_c ($CDCl_3$): 14.59 (q, $COOCH_2CH_3$), 21.14 (s, CH_3), 25.36 (t, C-5), 40.85 (t, C-6), 42.92 (t, C-8), 61.57 (t, $COOCH_2CH_3$), 115.17 (s, C-4a), 120.20 (s, C-4b), 128.22 (Ph C-3,5), 129.44 (Ph C-2,6), 131.60 (Ph C-1), 134.71 (C-8a), 148.10 (s, C-9a), 151.80 (s, C-2), 158.35 (s, C-4), 164.27 (s, CO ester).

General Proceedure for the Synthesis of (11a-e)

A mixture of the 3-amino derivatives **10a–e** (0.001 mol), *p*-toluenesulfonic acid (p-TSA) (0.0015 mol) and triethyl orthoformate (10 ml) was heated at reflux with stirring for 6–8 h. After cooling, the solid was filtered off, washed with ethanol, dried, and recrystallized from a suitable solvent.

Ethyl 3-Phenyl-10-oxo-6,8,9,10-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylate (11a)

Yellow crystals from EtOH. Yield 66.8%, m.p. 240–242°C (found: C, 57.60; H, 4.22; N, 17.59; S, 8.22. $C_{19}H_{17}N_5O_3S$ requires C, 57.70; H, 4.33; N, 17.71; S, 8.10%); δ_H (DMSO-d_d): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-9), 3.60 (t, 2H, H-8), 4.20 (q, 2H, $COOCH_2CH_3$), 4.70 (s, 2H, H-6), 7.70–7.90 (m, 4H, Ar—H), 9.20 (s, 1H, H-2).

Ethyl 3-p-Chlorophenyl-10-oxo-6,8,9,10-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo-[1,5-a]pyrimidine-7-carboxylate (11b)

Yellow crystals from EtOH. Yield 61.9%, m.p. 232–233°C (found: C, 53.12; H, 3.82; N, 16.37; S, 7.60. $C_{19}H_{16}N_5O_3SCl$ requires C, 53.08; H, 3.75; N, 16.29; S, 7.45%); δ_H (DMSO-d_d): 1.20 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-9), 3.40 (t, 2H, H-8), 4.10 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-6), 7.60–7.90 (m, 4H, Ar—H), 9.20 (s, 1H, H-2); δ_c (DMSO-d_6): 14.07 (q, $COOCH_2CH_3$), 25.36 (t, C-9), 40.75 (t, C-8), 42.74 (t, C-6), 61.04 (t, $COOCH_2CH_3$), 114.59 (s, C-9b), 124.81 (s, C-9a), 128.63 (Ph C-3,5), 128.80 (Ph C-2,6), 129.02 (Ph C-1), 130.43 (s, C-5a), 145.05 (s, C-4a), 151.44 (s, C-3a), 153.27 (s, C-2), 154.73 (s, C-10), 164.10 (s, CO ester).

Ethyl 3-o-Chlorophenyl-10-oxo-6,8,9,10-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylate (11c)

Yellow crystals from EtOH. Yield 59.6%, m.p. 250–252°C (found: C, 53.20; H, 3.86; N, 16.35; S, 7.66. $C_{19}H_{16}N_5O_3SCl$ requires C, 53.08; H, 3.75; N, 16.29; S, 7.45%); δ_H (DMSO-d_d): 1.30 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-9), 3.70 (t, 2H, H-8), 4.20 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 7.70–7.90 (m, 4H, Ar—H), 9.20 (s, 1H, H-2).

Ethyl 3-p-Methoxyphenyl-10-oxo-6,8,9,10-tetrahydropyrido[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo-[1,5-a]pyrimidin-7-carboxylate (11d)

Yellow crystals from EtOH. Yield 64.4%, m.p. 246–248°C (found: C, 56.63; H, 4.60; N, 16.95; S, 7.68. $C_{20}H_{19}N_5O_4S$ requires C, 56.45; H, 4.50; N, 16.46; S, 7.53%); δ_H (DMSO-d_d): 1.20 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-9), 3.60 (t, 2H, H-8), 3.80 (s, 3H, OCH_3), 4.20 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 7.50–7.80 (m, 4H, Ar—H), 9.20 (s, 1H, H-2).

Ethyl 3-p-Tolyl-10-oxo-6,8,9,10-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylate (11e)

Yellow crystals from EtOh. Yield 73.3%, m.p. 260–262°C (found: C, 58.8; 1H, 4.77; N, 17.27; S, 7.98. $C_{20}H_{19}N_5O_3S$ requires C, 58.66; H, 4.67; N, 17.10; S, 7.83%); ν_{max}/cm^{-1}: 1710, 1680 (2 CO), 1640 (C=N); δ_H (DMSO-d_d): 1.30 (t, 3H, $COOCH_2CH_3$), 2.40 (s, 3H, CH_3), 2.80 (t, 2H, H-9), 3.30 (t, 2H, H-8), 4.20 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 7.50–7.80 (m, 4H, Ar—H), 9.20 (s, 1H, H-2).

Ethyl 10-Oxo-8,9-dihydro-10*H*-pyrido[4′,3′:4,5]thieno-[2,3-d]-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7(6*H*)-carboxylate (12)

A mixture of **4** (0.32 g, 0.001 mol) and triethyl orthoformate (10 ml) was refluxed for 2 hours. After cooling, the solid was collected, washed with warm dioxane, and recrystallized from dioxane. Yield 0.24 g (72.7%) of compound **12** as white crystals, m.p. 228–230°C (found: C, 46.20; H, 3.70; N, 16.48; S, 18.97. $C_{13}H_{12}N_4O_3S_2$ requires C, 46.41; H, 3.59; N, 16.65; S, 19.06%); ν_{max}/cm^{-1}: 1710, 1680 (2 CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-9), 3.70 (t, 2H, H-8), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 9.30 (s, 1H, H-2).

Ethyl 2-Methyl-10-oxo-8,9-dihydro-10*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidine-7(6*H*)-carboxylate (13)

A mixture of **4** (0.32 g, 0.001 mol), phosphorus pentoxide (0.18 g, 0.0012 mol), acetic acid (0.3 ml, 0.005 mol) and methanesulfonic acid (1.3 ml, 0.019 mol) was heated at 80°C on an oil bath for 6 h. After cooling, the mixture was treated with water and 10% sodium hydroxide and the resulting solid was collected, washed with water, dried, and recrystallized from ethanol. Yield 0.18 g (52.94%) of compound **13** as colorless crystals, m.p. 194–195°C (found: C, 47.77; H, 3.90; N, 15.77; S, 18.10. $C_{14}H_{14}N_4O_3S_2$ requires C, 47.98; H, 4.02; N, 15.98; S, 18.30%); ν_{max}/cm^{-1}: 1700, 1680 (2 CO); δ_H ($CDCI_3$): 1.30 (t, 3H, $COOCH_2CH_3$), 2.70 (s, 3H, CH_3), 3.20 (t, 2H, H-9), 3.90 (t, 2H, H-8), 4.20 (q, 2H, $COOCH_2CH_3$), 4.70 (s, 2H, H-6).

Ethyl 2-Phenyl-10-oxo-8,9-dihydro-10*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3,4]thiadiazolo[3,2-a]pyrimidine-7(6*H*)-carboxylate (14)

A mixture of **4** (0.33 g, 0.001 mol), benzoic acid (0.24 g, 0.002 mol) and phosphorus oxychloride (2 ml, 0.02 mol) was refluxed for 20 min. After cooling, phosphorous oxychloride was evaporated under reduced pressure and the residue was treated with 10% sodium hydroxide. The resulting solid was collected, washed with water, dried, and recrystallized from dioxane. Yield 0.38 g (91.1%) of compound **14** as yellow microcrystals, m.p. 248–250°C (found: C, 55.48; H, 3.80; N, 13.39; S, 15.41. $C_{19}H_{16}N_4O_3S_2$ requires C, 55.32; H, 3.91; N, 13.58; S, 15.54%); ν_{max}/cm^{-1}: 3100 (arom. protons), 1710, 1680 (2 CO); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.90 (t, 2H, H-9), 3.70 (t, 2H, H-8), 4.10

(q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 7.30–7.60 (m, 5H, Ar—H); δ_c (DMSO-d_6): 14.56 (q, $COOCH_2CH_3$), 25.30 (t, C-9), 40.75 (t, C-8), 42.79 (t, C-6), 61.13 (t, $COOCH_2CH_3$), 117.40 (s, C-9b), 127.20 (s, C-9a), 128.30 (Ph C-4), 128.51 (Ph C-2,6), 128.88 (Ph C-3,5), 131.22 (Ph C-1), 132.80 (C-5a), 152.53 (s, C-4a), 153.60 (s, C-3a), 154.74 (s, C-2), 157.30 (s, C-10), 167.27 (s, CO ester).

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