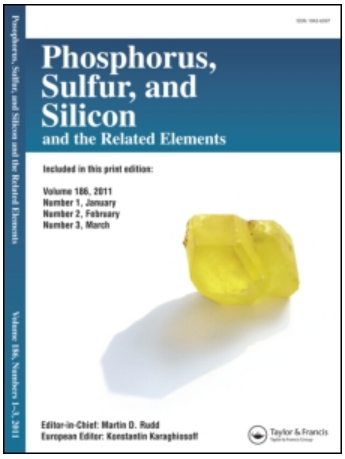

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A Novel Synthetic Routes to New 3-Substituted4-oxo-3,4,5,6,7,8-hexahydropyrido[[4], [4], [5]] thieno[[2], [3]]pyrimidine-7-carboxylic Acid Ethyl Ester Derivatives

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A Novel Synthetic Routes to New 3-Substituted-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′,4,5]-thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester Derivatives

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*Orthoaminoester **1** was investigated by the reaction with ethylchloroformate, 5-phenyl-oxadiazol-2-thione and triethylorthoformate to afford the open structures, **2**, **13** and **15**. These compounds were subjected to ensuing cyclization in one step or more yielding 3-substituted-5,6-dihydro-8*H*-4-oxopyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7(6*H*)-carboxylic acid ethyl ester derivatives.*

Keywords 5-Phenyloxadiazol-2-thione; cyclization; ethylchloroformate; key-intermediate; orthoaminoester; triethylorthoformate

Pyridothienopyrimidine and its derivatives show marked biological activities such as anti-inflammatory, anti-pyretic, and analgesic properties.[1–6] These interesting activities make it desirable to our work during the last few years in which we have been interested in synthesis of substituted heterocycles containing a thienopyrimidine moiety.[7–13] 2-Amino–3-carbethoxy thiophene derivatives have been found to be important intermediates in the chemistry of pyrimidine. Therefore they attracted much attention during recent years.[14–19] The present paper follows that line of research by reporting on a new series of reactions led to the formation of 3-substituted-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester derivatives starting from the bi-functional *o*-aminoester compound.

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RESULTS AND DISCUSSION

Based upon the aforementioned, we decided to investigate our new target pyridothienopyrimidines. Esterification of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrothieno[2,3-*c*]pyrido-6-carboxylic acid ethyl ester (**1**),[20] led to the formation of compound **2**. On ring closure of **2** using hydrazine hydrate in presence of alcoholic KOH, gave **3**. Neutralization of **3** using HCl aqueous afforded 3-amino-pyridothienopyrimidine **4** in 71% yield (Scheme 1).

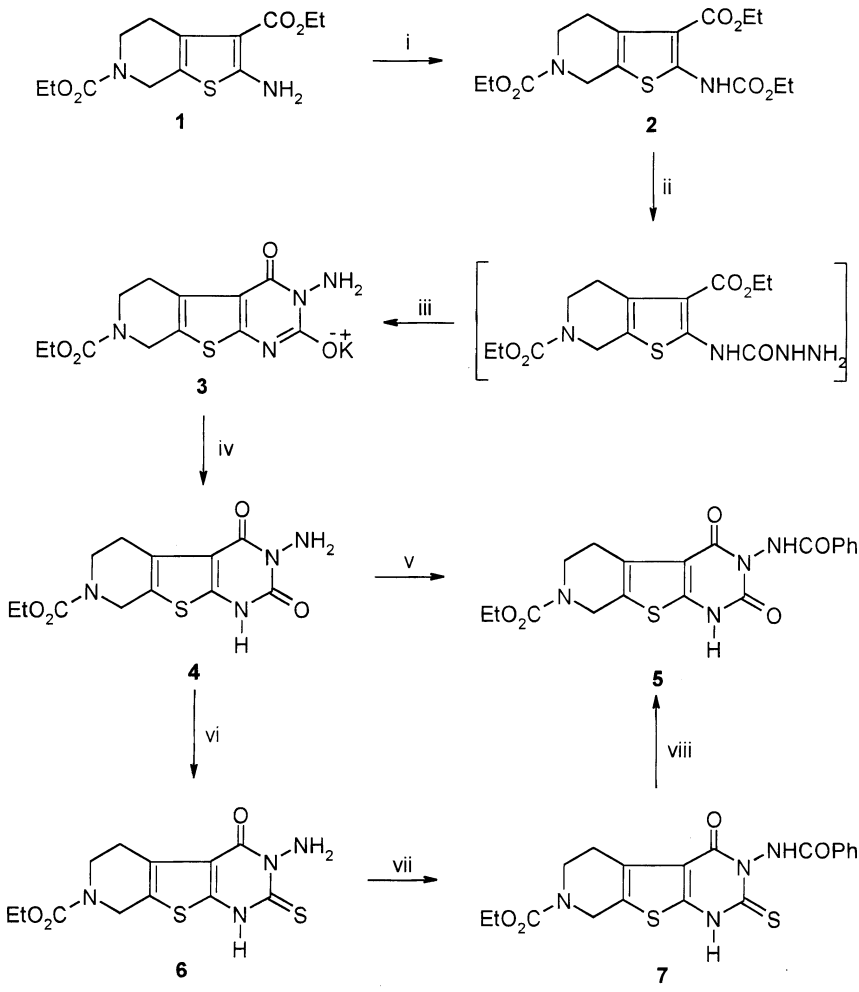
Benzoylation of **4** using benzoyl chloride in THF led to the formation of 3-benzoylamino-1,2,3,4,5,6,7,8-octahydro-2,4-dioxopyrido-[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**5**). The same strategy to obtain compound **5** can be achieved by converting the carbonyl group in **4** into C=S group using P_2S_5 in pyridine to yield our published compound **6**.[10] Subsequently benzoylation of **6** gave compound **7**, which on oxidation by H_2O_2 afforded the target compound **5** (Scheme 1).

The structural feature of our target compound **5** was elucidated by ^{1}H, ^{13}C-NMR and IR spectra as well as elemental analysis. Elemental analysis proved with satisfactory evidence that the molecular formula of **5** is $C_{19}H_{18}N_4O_5S$. The IR spectroscopy of **5** showed absorption bands at 3250 and 1680 cm^{-1} related to the NH and carbonyl group. The ^{1}H-NMR showed broad singlet at $\delta_H = 10.95$ ppm arise to the NH-amide proton. The ^{13}C-NMR confirmed the ^{1}H-NMR spectroscopy by the appearing of four signals at $\delta_C = 146.65$, 154.25, 157.12, and 164.86 ppm corresponding to the carbonyl groups present in compound **5**.

The amino group of compound **4** was chemically investigated by the deamination or the reaction with some electrophiles such as acetic anhydride, chloroacetyl chloride, or benzaldehyde affording **8**, **9**, **10**, and **11** respectively (Scheme 2).

Analytical data and spectroscopic properties were found to be in a good agreement with these assigned structures (See Experimental Section).

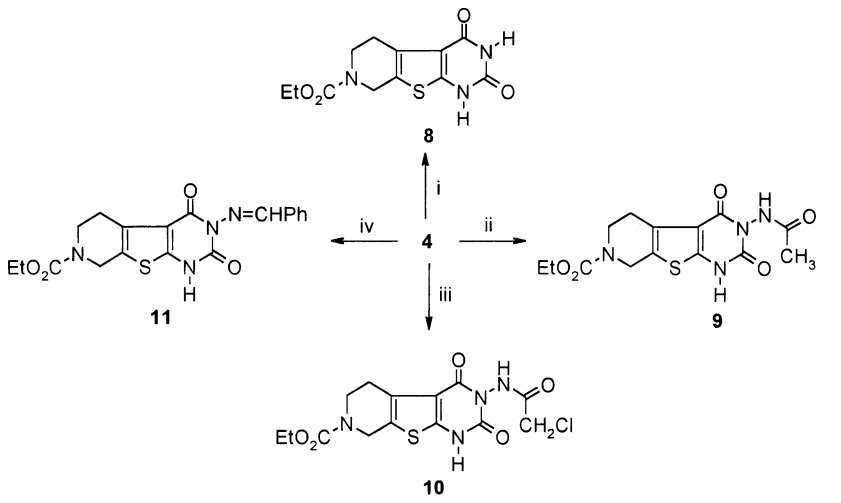
The amino group located in *ortho* position relative to an ester group is considered a versatile site for preparation of thioxopyrimidonone **7** by the reaction of compound **1** with 5-phenyloxadiazol-2-thione (**12**) to give compound **13**, followed by ensuing cyclization in alcoholic potassium hydroxide. The obtained product was identical in all aspects with that described in Scheme 1. S-methylation of compound **7** with iodomethane afforded the final product 3-benzoylamino-2-thiomethyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**14**) (Scheme 3).



Reagents and conditions: i; $ClCO_2Et$, reflux 2 h; **ii**; $N_2H_4.H_2O$: **iii**; alc. KOH, reflux 4 h; **iv**; 2N HCl; **v**; PhCOCl, THF, r.t.; **vi**; P_2S_5, pyridine, reflux 5 h; **vii**; PhCOCl, THF, r.t.; **viii**; H_2O_2, 5% NaOH, r.t.

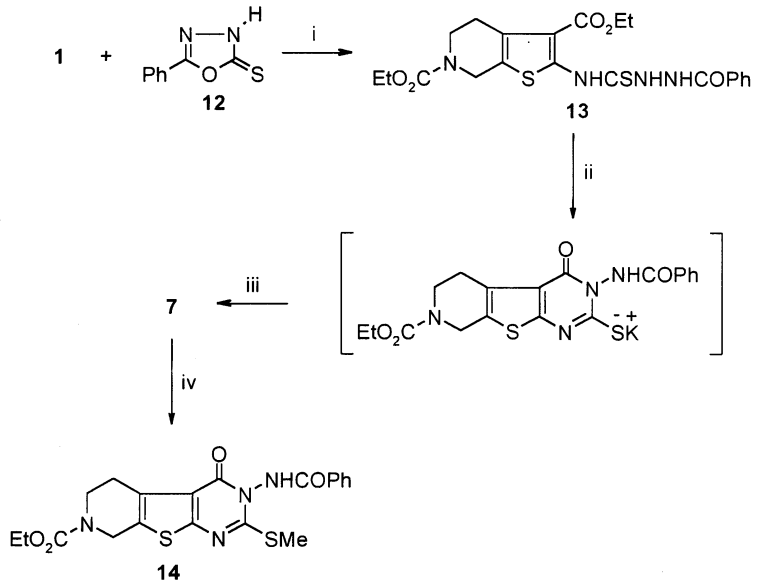
SCHEME 1

The structure of compound **14** was undoubtly proved by the help of the ^{1}H-NMR and IR spectra as well as elemental analysis. Elemental analysis of **14** is in accordance to its molecular formula as $C_{20}H_{20}N_4O_4S_2$. The ^{1}H-NMR spectrum of **14** showed triplet and quartet corresponding to ester-protons. The methyl protons were resonated as a singlet at $\delta_H = 2.55$ ppm, whereas the NH proton appeared at



Reagents and conditions: **i**; $NaNO_2$, CH_3COOH. r.t.; **ii**; Ac_2O, r.t.; iii; $ClCOCH_2Cl$, $CHCl_3$, r.t.; **iv**; PhCHO, piperidine, EtOH, reflux 2 h.

SCHEME 2

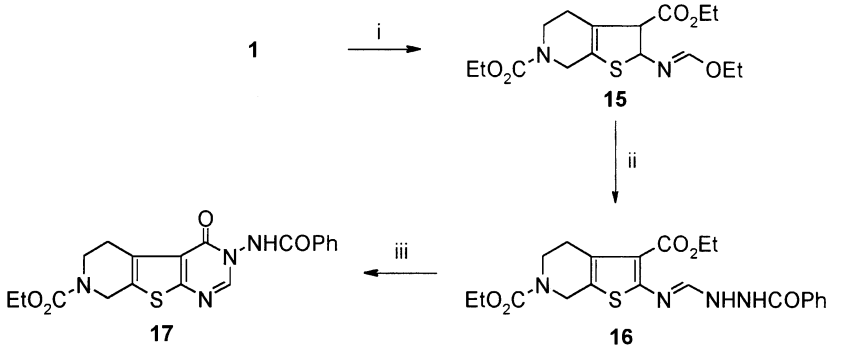


Reagents and conditions: **i**; *m*-cresol, heating at 150°C for 5 h; **ii**; alc. KOH, reflux 2 h; **iii**; 2N HCl; **iv**; MeI, 1N NaOH, r.t.

SCHEME 3

$\delta_H = 10.95$ ppm (see the experimental). The IR spectroscopy of **14** showed the absorption of the NH and the carbonyl groups at 3250 and 1710–1680 cm^{-1}, respectively. With these spectral and analytical data, compound **14** was identified as 3-benzoylamino-2-thiomethyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester.

Analogously, compound **1** was proved to be a key intermediate for other subsequent conversions. Thus, when it allowed to react with triethylorthoformate, the reaction performed to produce compound **15**, which was triturated with benzohydrazide to give 2-[(*N*-benzoylhydrazinomethylene)-amino]-3-carbethoxy-4,5,6,7-tetrahydrothieno-[2,3-*c*]pyrido-6-carboxylic acid ethyl ester (**16**). The pyrimidine ring was built up when the open structure product was subjected to cyclization yielding 3-benzoylamino-4-oxo-3,4,5,6,7,8-hexahydropyrido-[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**17**) (Scheme 4).



Reagents and conditions: **i**; $CH(OEt)_3$, reflux 7 h.; **ii**; $PhCONHNH_2$, EtOH, r.t.; **iii**; KOH, EtOH, reflux 2 h.

SCHEME 4

Our target molecule **17** was proved using ^{1}H-NMR and IR spectra as well as elemental analysis. Elemental analysis of **17** is in accordance on the proposed molecular formula $C_{19}H_{18}N_4O_4S$. The ^{1}H-NMR spectrum of **17** revealed the —N=CH-proton at $\delta_H = 8.50$ ppm, whereas the NH-proton appeared at $\delta_H = 11.00$ ppm. The IR spectroscopy of **17** indicated the absorption of the NH and the carbonyl groups at 3250 and 1710–1680 cm^{-1}, respectively. It is interesting to mention that the products obtained were satisfactorily analyzed with the help of both the elemental analysis and the spectroscopic data.

In conclusion and by the results available, we are assisted in the synthesis new classes of pyridothienopyrimidines using efficient, facile, and elegant methods of preparations rather than those suffering from low yields due to the multiple steps described in their preparation.

EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Carol Erba CHN-S Elemental Analyzer 1108. The ^{13}C and ^{1}H nmr spectra were obtained using sa Bruker AC 300 (^{1}H: 300.13 MHZ, ^{13}C: 75.5 MHZ). The solvents were deuterated dimethyl sulfoxide and chloroform. The δ-values are given in ppm and the internal standard was tetramethylsilane. The IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer as potassium bromide pellets.

Synthesis of 2-Ethoxycarbonylamino-3-carbethoxy-4,5,6,7-tetrahydrothieno[2,3-*c*]pyrido-6-carboxylic Acid Ethyl Ester (2)

A mixture of **1** (2.98 g, 10 mmol) and ethylchloroformate (20 ml) was refluxed for 2 h. The solvent was removed in vacuum. The resulting solid product was recrystallized from ethanol as colorless needles.

Yield 93%, mp. 118–120°C, (Found: C, 52.12: H, 6.02: N, 9.21, S, 8.44 Calc for $C_{16}H_{22}N_2O_6S$ (370.42): C, 52.33: H, 6.08: N, 9.39, S, 8.64), IR (KBr) $\nu = 3250$ (NH), 1720 (ester C=O), 1710 (ester C=O), 1700 (ester C=O) cm^{-1}, ^{1}H NMR (DMSO): $\delta_H = 1.21$ (t, 9H, $COOCH_2CH_3$), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 6H, $3COOCH_2CH_3$), 4.55 (s, 2H, H-7), 10.25 (s, 1H, NH), ^{13}C NMR (DMSO): $\delta_C = 13.80$ (CH_3), 14.02 (CH_3), 14.38 (CH_3), 25.72 (C-4), 41.03 (C-5), 42.10 (C-7), 60.38 (CH_2), 60.85 (CH_2), 62.08 (CH_2), 114.68 (C-3), 121.67 (C-7a), 128.63 (C-3a), 148.62 (C=O), 152.10 (C=O), 154.51 (C=O), 165.10 (C-2).

Synthesis of 3-Amino-1,2,3,4,5,6,7,8-octahydro-2,4-dioxopyrido[3′,4′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (4)

To a solution of **2** (3.7 g, 10 mmol) in ethanol (20 ml), potassium hydroxide (0.56 g, 10 mmol) dissolved in water (5 ml) and hydrazine hydrate (2 ml, were added. The reaction mixture was refluxed for 4 h. The precipitate formed was filtered off, dried well to give the potassium salt of **3**. The salt **3** was dissolved in hot water and neutralized with

HCl 2N. The resulting product was filtered off, dried, and crystallized from ethanol as colorless needles. Yield 71%, mp. 185–187°C, (Found: C, 46.31: H, 4.51: N, 17.94, S, 10.23 Calc for $C_{12}H_{14}N_4O_4S$ (310.3): C, 46.44: H, 4.55: N, 18.05, S, 10.31), IR (KBr) $\nu = 3350–3250$ (NH_2, NH), 1710 (ester C=O), 1690 (C=O) cm^{-1}, ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 5.85 (s, 2H, NH_2), 8.35 (s, 1H, NH), ^{13}C NMR (DMSO): $\delta_C = 14.28$ (CH_3), 24.78 (C-5), 40.51 (C-6), 42.21 (C-8), 60.79 (CH_2), 110.94 (C-4a), 115.59 (C-4b), 121.65 (C-8a), 129.14 (C-9a), 149.16 (C=O), 154.50 (C=O), 156.17 (C=O).

Synthesis of 3-Benzoylamino-1,2,3,4,5,6,7,8-octahydro-2,4-dioxopyrido[4′,3′,4,5]thieno[2,3-*d*] pyrimidine-7-carboxylic Acid Ethyl Ester (5)

Method A

Compound **7** (2.15 g, 5 mmol) was dissolved in 5% NaOH solution (10 ml) at room temperature. Then 30% H_2O_2 (10 ml) was added dropwise and the mixture neutralized with acetic acid. Stirring continued for 30 min. The precipitate isolated by suction filtration, washed with water, dried, and recrystallized from ethanol as pale yellow crystals, in 90% yield.

Method B

Synthesis of 5 and 7 (General procedures). To a suspension of **4** or **6** (10 mmol) in THF (20 ml), Triethylamine (0.95 g, 10 mmol) was added and then benzoyl chloride (1.4 g, 10 mmol) in THF (5 ml) added dropwise with stirring in ice path over a period of 20 min. The mixture stirred at room temperature for 3 h. The solvent was distilled off at atmospheric pressure and the residue treated with ethanol. The solid product so formed was collected by filtration, dried, and crystallized from suitable solvent.

Synthesis of 3-Benzoylamino-1,2,3,4,5,6,7,8-octahydro-2,4-dioxopyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (5)

Yield 76%, mp 193–195°C, (Found: C, 55.01: H, 4.26, N, 13.46, S, 7.61 Calc for $C_{19}H_{18}N_4O_5S$ (414.42):C, 55.06: H, 4.38: N, 13.52, S, 7.72), IR (KBr) $\nu = 3250$ (NH), 3000 (arom. CH), 1710 (ester C=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 7.11–8.00 (m, 5H, Ar-H), 10.95 (s, 1H, NH). ^{13}C NMR (DMSO): $\delta_C = 14.23$

(CH_3), 24.87 (C-5), 40.21 (C-6), 41.20 (C-8), 60.79 (CH_2), 110.94 (C-4a), 114.63 (C-4b), 121.45 (C-8a), 127.11, 128.11, 129.87, 130.98 (Ar-C) 131.69 (C-9a). 146.65 (C=O), 154.25 (C=O), 157.12 (C=O), 164.86s (C=O).

Synthesis of 3-Benzoylamino-1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxopyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (7)

Yield 72%, mp. 160–162°C, (Found: C, 52.91: H, 4.09: N, 12.93. S, 14.64 Calc for $C_{19}H_{18}N_4O_4S_2$ (430.48): C, 53.01: H, 4.21: N, 13.0, S, 14.87) IR (KBr) $\nu = 3250$ (NH), 3000 (arom. CH), 1700 (ester C=O), 1680 (C=O) cm^{-1}. ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 7.11–8.00 (m, 5H, Ar-H), 10.50 (s, 2H, NH), 12.15 (s, 1H, NH).

Synthesis of 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 (6)

To a solution of **4** (0.62 g, 2 mmol) in pyridine (10 ml), P_2S_5 (0.45 g, 2 mmol) was added. The reaction mixture was refluxed for 6 h. The mixture was filtered off. The filtrate was concentrated and then, the residue extracted with diethyl ether. The obtained solid product was recrystallized from methanol to give pale yellow crystals in 83% yield. (Lit [10]).

Synthesis of 1,2,3,4,5,6,7,8-Octahydro-2,4-dioxopyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (8)

To a suspension of **4** (0.31 g, 1 mmol) in acetic acid (2 ml) and water (10 ml), a solution of $NaNO_2$ (0.28 g, 4 mmol) in water (1 ml) was added. After stirring for 15 min at room temperature, 40% sodium hydroxide solution was added (3 ml). The reaction mixture was warmed to clear solution. After cooling 50% H_2SO_4 added dropwise till pH 2. The precipitated product was filtered off, washed with water, dried, and crystallized from ethanol as pale yellow crystals.

Yield 92%, mp. 271–272°C, (Found: C, 48.73: H, 4.32: N, 14.08. S, 10.64 Calc for $C_{12}H_{13}N_3O_4S$ (295.3): C, 48.81: H, 4.44: N, 14.23, S, 10.84), IR (KBr) $\nu = 3250$ (NH), 1710 (ester C=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 10.99 (s, 1H,

NH), .99 s, H, H). ^{13}C NMR (DMSO): $\delta = 14.40$ (CH_3), 24.64 (C-5), 40.96 (C-6), 42.21 (C-8), 60.91 (CH_2), 112.11 (C-4a), 121.63 (C-4b), 136.94 (C-8a), 150.32 (C-9a), 151.72 (C=O), 154.13 (C=O), 159.39 (C=O).

Synthesis of 3-Acetylamino-2,4-dioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (9)

A mixture of **4** (0.62 g, 2 mmol) and acetic anhydride (5 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into water. The precipitate formed was filtered off, dried, and crystallized from ethanol as colorless needles.

Yield 92%, mp. 182–183°C (Found: C, 47.63: H, 4.47: N, 15.81, S, 9.14, Calc for $C_{14}H_{16}N_4O_5S$ (352.35): C, 47.72: H, 4.58: N, 15.90, S, 9.08), IR (KBr) $\nu = 3250$ (NH), 1710 (ester C=O), 1680 (C=O) cm^{-1}. ^{1}H NMR (DMSO): $\delta = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.03 (s, 3H, CH_3), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (1, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 10.37 (s, 1H, NH), .70 s, H, H), ^{13}C NMR (DMSO): $\delta = 14.28$ (CH_3, ester), 20.10 (CH_3), 24.74 (C-5), 40.20 (C-6), 42.22 (C-8), 60.83 (CH_2), 111.44 (C-4a), 122.61 (C-4b), 124.51 (C-8a), 148.59 (C-9a), 150.07 (C=O), 156.55 (C=O), 167.87 (C=O), 171.63 (C=O).

Synthesis of 3-(2-Chloro-acetylamino)-2,4-dioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′,4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid Ethyl Ester (10)

Compound **4** (0.62 g, 2 mmol) was dissolved in dry chloroform (5 ml). To this solution chloroacetyl chloride (0.6 g, 5.35 mmol) in dry chloroform (2 ml) was added dropwise with stirring at room temperature over a period of 1.5 h. The solvent was distilled on vacuum and the residue treated with ethanol. The solid product so formed was collected by filtration, dried and crystallized from ethanol as colorless powder.

Yield 83%, mp. 185–187°C, (Found: C, 43.34: H, 3.83: N, 14.36. S, 8.24, Calc for $C_{14}H_{15}ClN_4O_5S$ (386.79): C, 43.47: H, 3.91: N, 14.48, S, 8.27), IR (KBr) $\nu = 3250$ (NH), 3000 (aliph. CH), 1700 (ester C=O), 1680 (C=O) cm^{-1}, ^{1}H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, CH_2) 4.55 (s, 2H, H-8), 10.83 (s, 1H, NH), 2.43 (s, 1H, NH), ^{13}C NMR (DMSO): $\delta_C = 14.41$ (CH_3), 24.81 (C-5), 40.20 (C-6), 40.51 (CH_2), 42.31 (C-8), 60.98 (CH_2, ester), 111.42 (C-4a), 122.94 (C-4b), 129.65 (C-8a), 148.41 (C-9a), 150.16 (C=O), 154.60 (C=O), 156.16 (C=O), 165.01 (C=O).

Synthesis of 3-Benzylidineamino-2,4-dioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′,4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid Ethyl Ester (11)

To a mixture of **4** (0.62 g, 2 mmol) and benzaldehyde (0.22 g, 2 mmol) in ethanol (10 ml), a catalytic amount of piperidine was added. The reaction mixture was refluxed for 2 h. After concentration and cooling at room temperature, the precipitated product was filtered off, dried, and recrystallized from methanol as colorless powder.

Yield 87%, mp. 280–282°C, (Found: C, 57.20: H, 4.51: N, 14.00, S, 8.13, Calc for $C_{19}H_{18}N_4O_4S$ (398.42): C, 57.28: H, 4.55: N, 14.06, S, 8.03), IR (KBr) $\nu = 3250$ (NH), 3000 (arom. CH), 1710 (ester C=O), 1680 (C=O), 1635 (C=N) cm^{-1}. ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 7.11–8.00 (m, 5H, Ar-H), 8.65 (s, 1H, CH), 12.35 (s, 1H, NH). ^{13}C NMR (DMSO): $\delta_C = 14.37$ (CH_3), 24.78 (C-5), 40.13 (C-6), 42.22 (C-8), 60.80 (CH_2), 111.64 (C-4a), 115.48 (C-4b), 122.22 (C-8a), 147.29 (C-9a), 127.11, 128.11, 129.87, 130.91 (Ar-C) 149.01 (C=O), 154.51 (C=O), 155.27 (C=O), 170.75 (CH=N).

Synthesis of 2-(3-Benzoylamino-thioureido)-3-carbethoxy-4,5,6,7-tetrahydrothieno[2,3-*c*]pyrido-6-carboxylic Acid Ethyl Ester (13)

A mixture of compound **1** (0.6 g, 2 mmol) and 5-phenyloxadiazol-2-thione (12) (0.36 g, 2 mmol) in *m*-cresol (10 ml) was heated at 150°C for 5 h. The solvent was distilled off at atmospheric pressure and the residue treated with *n*-hexane. Then the solid product so formed was filtered off, dried, and crystallized from methanol as yellow crystals.

Yield 71%, mp. 181–183°C, (Found: C, 52.82: H, 5.00: N, 11.62, S, 13.24 Calc for $C_{21}H_{24}N_4O_5S_2$ (476.55): C, 52.93: H, 5.08: N, 11.76, S, 13.43), IR (KBr) $\nu = 3250$ (3NH), 3000 (arom. CH), 1700 (ester 2=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 6H, $2COOCH_2CH_3$), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 4H, $2COOCH_2CH_3$), 4.55 (s, 2H, H-7), 7.11–8.00 (m, 5H, Ar-H), 10.55 (s, 1H, NH), 11.00 (s, 1H, NH), 12.45 (s, 1H, NH). ^{13}C NMR (DMSO): $\delta_C = 13.82$ (CH_3), 14.27 (CH_3), 25.63 (C-4), 40.55 (C-5), 41.45 (C-7), 60.38 (CH_2), 60.73 (CH_2), 111.44 (C-3), 122.36 (C-7a), 127.11, 128.11, 129.87, 130.98 (Ar-C).148.72 (C-3a), 154.46 (C-2). 165.37 (C=O), 166.58 (C=O), 176.80 (C=O), 178.86 (C=S).

3-Benzoylamino-1,2,3,4,5,6,7,8-octahydro-4-oxo-2-thioxopyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7- carboxylic Acid Ethyl Ester (7)

Method A

A mixture of **13** (0.48 g, 1 mmol) and solution of KOH (0.11 g, 2 mmol), in ethanol (10 ml) was refluxed for 2 h. After removing the solvent, the residue diluted with water and acidified with HCl 2*N*. The product was collected by filtration, washed with water, dried, and recrystallized from DMF/water as pale yellow crystals in 75% yield.

Synthesis of 3-Benzoylamino-2-thiomethyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid Ethyl Ester (14)

To a suspension of **7** (1.29 g, 3 mmol) in sodium hydroxide 1*N* (12 ml), methyl iodide (0.72 g, 5 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The solid precipitate was collected by filtration, washed with water, dried, and crystallized from methanol as pale yellow crystals.

Yield 81%, mp. 152°C, (Found: C, 54.15: H, 4.56: N, 12.46, S, 14.34 Calc for $C_{20}H_{20}N_4O_4S_2$ (444.53): C, 54.04: H, 4.53: N, 12.60, S. 14.40), IR (KBr) $\nu = 3250$ (NH), 3000 (arom. CH), 1710 (ester C=O), 1680 (C=O) cm^{-1}, ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.55 (s, 3H, SCH_3), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 7.11–8.00 (m, 5H, Ar-H), 10.95 (s, 1H, NH).

Synthesis of 2-Ethoxymethyleneamino 3-carbethoxy-4,5,6,7-tetrahydrothieno[2,3-*c*]pyrido-6-carboxylic Acid Ethyl Ester (15)

A mixture of **1** (2.98 g, 10 mmol), triethylorthoformate (20 ml) and few drops of acetic anhydride was refluxed for 7 h. The solvent was removed under reduced pressure. The resulting solid product was crystallized from benzene/petroleum ether as colorless needles.

Yield 69%, mp. 110°C, (Found: C, 53.87: H, 6.11: N, 7.75, S, 9.14, Calc for $C_{16}H_{22}N_2O_5S$ (354.42): C, 53.92: H, 6.18: N, 7.86, S, 9.02), IR (KBr) $\nu = 1710$ (ester C=O), 1690 (ester C=O), 1625 (C=N) cm^{-1}, ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 6H, $2COOCH_2CH_3$), 1.35 (t, 3H, OCH_2CH_3), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 4H, $2COOCH_2CH_3$), 4.35 (q, 2H, OCH_2CH_3), 4.55 (s, 2H, H-7), 8.55 (s, 1H, CH). ^{13}C NMR (DMSO): $\delta_C = 13.80$ (CH_3), 14.02 (CH_3), 14.38 (CH_3), 25.72 (C-4), 41.03 (C-5),

42.10 (C-7), 60.38 (CH_2), 60.85 (CH_2), 62.08 (CH_2), 111.45 (C-3), 122.35 (C-7a), 128.32 (C-3a), 144.62 (C=O), 154.10 (C=O), 158.54 (CH=N), 163.78 (C-2).

Synthesis of 2-[(*N*-Benzoyl-hydrazinomethylene)-amino]-3-carbethoxy-4,5,6,7-tetrahydrothieno[2,3-*c*]-pyrido-6-carboxylic Acid Ethyl Ester (16)

To a solution of **15** (1.1 g, 3 mmol) in ethanol (10 ml), benzohydrazide (0.408 g, 3 mmol) was added. The reaction mixture was stirred at room temp. for 1 h. The precipitate formed was filtered off, dried, and recrystallized from ethanol as colorless needles.

Yield 74%, mp. 192–194°C, (Found: C, 56.70: H, 5.36: N, 12.50, S, 7.11, Calc for $C_{21}H_{24}N_4O_5S$ (444.49) C, 56.74: H, 5.44: N, 12.60, S. 7.20), IR (KBr) $\nu = 3250$ (2NH), 3000 (arom. CH), 1710 (C=O), 1690 (ester C=O), 1625 (C=N) cm^1. ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 1.35 (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-4), 3.65 (t, 2H, H-5), 4.11 (q, 2H, $COOCH_2CH_3$), 4.35 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-7), 7.11–8.00 (m, 5H, Ar-H), 8.55 (s, 1H, CH), 10.55 (s, 1H, NH), 11.45 (s, 1H, NH). ^{13}C NMR (DMSO): $\delta_C = 13.80$ (CH_3), 14.02 (CH_3), 25.72 (C-4), 41.03 (C-5), 42.10 (C-7), 60.38 (CH_2), 60.85 (CH_2), 108.13 (C-3), 120.72 (C-7a), 127.11, 128.11, 129.87, 130.98 (Ar-C), 132.74 (C-3a), 142.52 (CH=N), 149.37 (C=O), 154.57 (C=O), 161.90 (C=O), 164.66 (C-2).

Synthesis of 3-Benzoylamino-4-oxo-3,4,5,6,7,8-hexahydropyrido[4′,3′,4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic Acid Ethyl Ester (17)

A mixture of 16 (0.89 g, 2 mmol) and solution of potassium hydroxide (0.17 g, 3 mmol) dissolved in ethanol (10 ml) was refluxed for 2 h. The reaction mixture was acidified with HCl 2*N*. The product was collected by filtration, washed with water, dried, and crystallized from DMF/water as yellow crystals.

Yield 65%, mp. 96–98°C, (Found: C, 57.17: H, 4.43: N, 14.02, S, 8.14 Calc for $C_{19}H_{18}N_4O_4S$ (398.42) C, 57.28: H, 4.55: N, 14.06, S, 8.03), IR (KBr) $\nu = 3250$ (NH), 3000 (arom. CH), 1710 (ester C=O), 1680 (C=O), 1625 (C=N) cm^{-1}. ^1H NMR (DMSO): $\delta_H = 1.21$ (t, 3H, $COOCH_2CH_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.11 (q, 2H, $COOCH_2CH_3$), 4.55 (s, 2H, H-8), 7.11–8.00 (m, 5H, Ar-H), 8.50 (s, 1H, CH), 11.85 (s, 1H, NH), ^{13}C NMR (DMSO): $\delta_C = 13.80$ (CH_3), 25.72 (C-5), 41.03 (C-6), 42.10 (C-8), 60.38 (CH_2), 115.19 (C-4a), 126.68 (C-4b), 130.82 (C-8a), 127.11, 128.11, 129.87, 130.98 (Ar-C) 149.18 (C-2), 154.62 (C-9a).155.10 (C=O), 161.00 (C=O), 166.25 (C=O).

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