

# Microwave-Assisted Synthesis of Novel Imidazo- and Pyrimidopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines

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It is reported on the microwave-assisted synthesis of imidazo- and pyrimidopyrido [4',3':4,5]thieno[2,3-*d*]pyrimidines from 2-ethoxymethylene-amino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester and 4-chloro-pyridothieno[2,3-*d*]pyrimidine.

**Key words:** Microwave Irradiation, Amino Alcohol, Fused Pyrimidines

## Introduction

Bronchial asthma is a chronic debilitating disease, which in its severe forms can even threaten life. It is, in general, characterized by both broncho-constriction and airway inflammation which leads to bronchial hyper responsiveness [1]. Although different classes of drugs have been employed, methylxanthines continue to enjoy significant status as drugs of choice in asthma therapy, despite a narrow therapeutic index. Currently, new tricyclic heterocyclic compounds designed on the basis of the xanthine skeleton are being investigated as possible bronchodilators with a wider margin of safety. While reviewing the recent perspectives in the design of anti-asthmatic agents [2] we observed that different angularly fused heterocyclic ring systems like imidazoquinolines [3] imidazonaphthyridines [4] benzimidazolo-quinazolines, [5, 6] imidazoquinazolines [7] and benzimidazolopyridopyrimidines [8] have been identified as potentially useful compounds. The encouraging broncho-dilatory activity of these compounds led us to attempt the isosteric replacement of benzene by thiophene [9].

The source of regulation of energy has not normally received proper recognition in synthetic organic chemistry. Microwaves have the capacity to alter that, because of the fact that the energy is directly transferred and concentrated in the reaction mixture and also because of the convenience in performing organic transformation with microwave apparatus [10]. In recent years, reagents impregnated on mineral solid support and assisted by microwaves have gained popularity in the synthesis of various heterocyclic com-

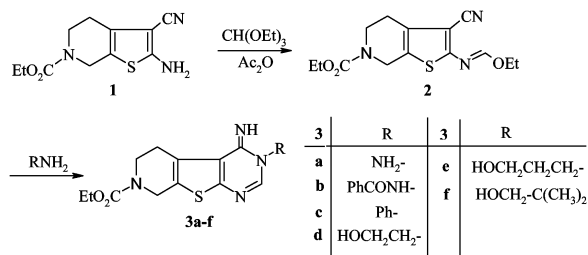
pounds like quinoxalinones [11], triazoles [12], quinolines [13, 14], benzofurans [15], quinazolines [16], imidazoles [17] etc. This is probably due to the enhanced selectivity, improved reaction rates, associated ease of manipulation, and above all, the eco-friendliness of this method.

## Results and Discussion

Microwave irradiation (MWI) is well known to promote the synthesis of a variety of compounds [18, 19] where chemical reactions are accelerated because of selective absorption of microwaves by polar molecules. Recently, the coupling of MWI with solid supports under solvent free conditions has received notable attention [17, 19]. A literature survey reveals examples of specific reactions, which do not occur under conventional heating/sonication, but could be made possible by microwave irradiation coupled with a solid support [20].

We report here a simple and novel synthetic route involving a microwave-assisted cyclization reaction using silica gel as solid support catalyst during the synthesis of imidazo- and pyrimidopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines **7a,b**.

The synthesis of **7a,b** was started by the reaction of compound **1** with triethyl orthoformate in the presence of a catalytic amount of acetic anhydride to give 2-ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester (**2**). Thereafter, on reacting **2** with hydrazine hydrate, benzohydrazide or aniline in dioxane at room temperature, the pyrimidine moiety was built in one



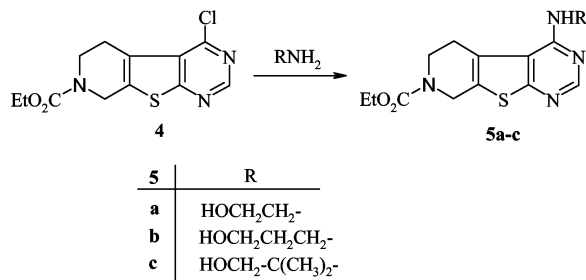
Scheme 1.

step affording the 3-substituted-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**3a–c**) in high yields (Scheme 1).

The structural assignment of the obtained products **3a–c** was made by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectra as well as elemental analyses. The IR spectra of **3a** showed absorption bands at 3360–3280 and 1708 cm<sup>−1</sup> related to the NH<sub>2</sub>, NH and carbonyl group, respectively. The <sup>1</sup>H NMR showed two broad singlets at  $\delta$  = 5.60 and 7.93 ppm, corresponding to the NH<sub>2</sub> and NH-imino protons, respectively. The <sup>13</sup>C NMR spectral data of **3a** supported the <sup>1</sup>H NMR assignments by the appearance of three signals at  $\delta$  = 151.31, 154.62, and 156.09 ppm related to C-2, C=NH and C=O.

The above mentioned promising results prompted us to attempt the preparation of the key intermediates **3d–f**. Compounds **3d–f** were obtained by one-pot reaction of compound **2** with amino alcohol (2-aminoethanol, 1-aminopropanol and 2-amino-2-methyl-propanol) in absolute ethanol at room temp. The reaction mechanism was described as due to addition of a secondary amine to the highly reactive enmino system followed by intermolecular heterocyclization across the electrophilic cyano functionality (Scheme 1).

As an example, elemental analysis of **3d** is in accordance to its molecular formula as C<sub>14</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>S. The IR spectroscopy of **3d** showed the absorption of the OH, NH and the carbonyl group at 3500–3400, 3280 and 1705 cm<sup>−1</sup>, respectively. The <sup>1</sup>H NMR spectrum of **3d** showed a triplet and a quartet corresponding to ester-protons. The H of ethyl protons of the side chain were found to resonate as triplet and quartet at  $\delta$  = 3.91 and 4.09 ppm, whereas the OH and NH protons appeared as two singlets at  $\delta$  = 3.45 and 5.61 ppm, respectively. Three distinctive carbon signals were detected in the <sup>13</sup>C NMR spectrum of **3d** at  $\delta$  = 62.55, 64.45 and 156.20 ppm corresponding to



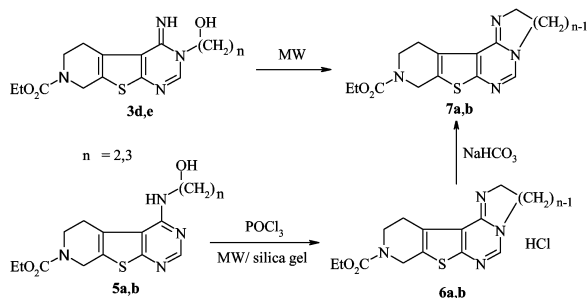
Scheme 2.

the two methylene groups of ethyl and C=NH (see Experimental Section). Accordingly, compound **3d** was identified as 3-(2-hydroxyethyl)-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester.

With the aim to explore the synthesis of 4-substituted aminothieno[2,3-*d*]pyrimidines **5a–c**, we reacted equimolar amounts of 2-aminoethanol, 1-aminopropanol or 2-amino-2-methyl-propanol with 4-chlorothieno[2,3-*d*]pyrimidine **4** [21] in absolute ethanol for 3–7 h. The reaction performed to yield the desired products in 79–83% (Scheme 2).

The structural features of compounds **5a–c** were established by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectra as well as elemental analysis. For example the IR spectrum of compound **5b** showed a broad absorption band at 3500–3400 cm<sup>−1</sup> for a hydroxyl group, and another one at 3290 cm<sup>−1</sup> for the secondary amino group. In the <sup>1</sup>H NMR spectrum, a broad singlet of the amino-proton was observed at  $\delta$  = 6.62 ppm, which disappeared on addition of D<sub>2</sub>O. Additionally, a multiplet and two triplets for the methylene protons of amino-propanol at  $\delta$  = 1.94, 3.75–3.86 ppm were easily detected.

Encouraged by the recent focus on the green chemical theme of eliminating the use of solvents, we extended our studies to neat reactions, since the reaction using solid support catalysis increases the adsorption of reactants on its surface, thereby raising the possibility towards product formation. We used microwave to assist the synthesis of **7a,b** which was established using two pathways. The first one involved cyclization of compounds **3d,e** under microwave irradiation to result in the protected pyrido compounds **7a,b**. The second methodology took attention of the presence of the hydroxyl group in compounds **5a,b**, which upon reaction with phosphorus oxychloride over silica gel under microwave irradiation, were transformed into salts **6a,b** in quantitative yields. Neutralization of **6a,b** with sodium



Scheme 3.

bicarbonate afforded the same target compounds **7a,b** (Scheme 3).

Both IR and  $^1\text{H}$  NMR spectra of **7a,b** did not display peaks for the NH and OH groups. The four dihydroimidazolyl methylene protons of the corresponding imidazo derivative appeared as two triplets at  $\delta = 3.52$  and  $3.92$  ppm. On the other side, trihydropyrimidolyl methylene protons of the corresponding pyrimido derivative **7b** exhibited an upfield shift ( $\delta = 1.91$ ,  $3.07$  and  $3.57$  ppm). Mass spectroscopy and elemental analysis of **7a,b** is in accordance to their molecular formula as  $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$  and  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ , respectively. Based on the spectral and analytical data, compounds **7a,b** were identified as imidazopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine (**7a**) and pyrimidopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine (**7b**).

In conclusion, we might serve in the synthesis of new classes of fused pyridothienopyrimidines using efficient, facile and elegant methods. Thus, the present microwave-assisted route, besides being advantageous in simple reaction conditions and easy work-up procedures, has resulted in improved yields over the conventional methods [22].

## Experimental Section

Melting points were determined on a Boetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Carle Erba CHN-S Elemental Analyzer 1108. The  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra were obtained using a Bruker AC 300 instrument ( $^1\text{H}$ : 300.13 MHz;  $^{13}\text{C}$ : 75.5 MHz). The  $\delta$ -values are given in ppm, and the internal standard was tetramethylsilane. Mass spectra were obtained on a spectrometer Perkin-Elmer SCIEX API-300 (by ion spray using heated nebulizer). The IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer on potassium bromide pellets. Microwave heating was carried out using a domestic oven, BPL 700T (600 Watt).

### 2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carboxylic acid ethyl ester (**2**)

A mixture of **1** (2.51 g, 10 mmol) together with few drops of acetic anhydride in triethyl orthoformate (20 ml) was refluxed for 8 h. The crystalline product separated on cooling at room temp. Yield of **2**: 2.4 g (80%); colorless plates (ethanol); m.p.  $90-92^\circ\text{C}$ . – IR (KBr):  $\nu = 2215$  (CN),  $1715$  (ester C=O),  $1618$  (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([ $\text{D}_6$ ]-DMSO):  $\delta = 1.21$  (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ),  $1.35$  (t, 3H,  $\text{OCH}_2\text{CH}_3$ ),  $2.85$  (t, 2H, 4-H),  $3.65$  (t, 2H, 5-H),  $4.11$  (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ),  $4.35$  (q, 2H,  $\text{OCH}_2\text{CH}_3$ ),  $4.55$  (s, 2H, 7-H),  $8.55$  (s, 1H, CH). –  $^{13}\text{C}$  NMR ([ $\text{D}_6$ ]-DMSO):  $\delta = 14.38$  ( $2\text{CH}_3$ ),  $23.39$  (C-4),  $40.93$  (C-5),  $42.02$  (C-7),  $60.86$  ( $\text{CH}_2$ ),  $60.97$  ( $\text{CH}_2$ ),  $113.38$  (CN),  $123.99$  (C-3),  $129.60$  (C-7a),  $146.09$  (C-3a),  $154.55$  (C=O),  $159.07$  (CH=N),  $163.58$  (C-2).

### Synthesis of **3a–c**

#### General procedure

To a stirred suspension of **2** (0.61 g, 2 mmol) in dioxane (10 ml), an appropriate amine (2.5 mmol) was added. The reaction mixture was stirred at room temperature for 2–4 h. The precipitate was filtered off, washed with cold ethanol and recrystallized from methanol.

### 3-Amino-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]-thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**3a**)

White needles; yield 0.49 g (85%); m.p.  $152-154^\circ\text{C}$  – IR (KBr):  $\nu = 3360-3280$  ( $\text{NH}_2$ , NH),  $1708$  (ester C=O),  $1615$  (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([ $\text{D}_6$ ]-DMSO):  $\delta = 1.21$  (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ),  $3.00$  (t, 2H, 5-H),  $3.65$  (t, 2H, 6-H),  $4.11$  (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ),  $4.55$  (s, 2H, 8-H),  $5.60$  (b, 2H,  $\text{NH}_2$ ),  $7.93$  (b, 1H, NH),  $8.35$  (s, 1H, CH). –  $^{13}\text{C}$  NMR ([ $\text{D}_6$ ]-DMSO):  $\delta = 14.42$  ( $\text{CH}_3$ ),  $26.09$  (C-5),  $40.87$  (C-6),  $42.79$  (C-8),  $60.92$  ( $\text{CH}_2$ ),  $119.68$  (C-4a),  $127.95$  (C-4b),  $129.84$  (C-8a),  $148.22$  (C-2),  $151.31$  (C-9a),  $154.62$  (C=NH),  $156.09$  (C=O). –  $\text{C}_{12}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$  (293.35): calcd. C 49.13, H 5.15, N 23.87; found C 49.02, H 5.01, N 23.63.

### 3-Benzoylamino-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**3b**)

Yellow crystals; yield 0.69 g (87%); m.p.  $169-171^\circ\text{C}$ . – IR (KBr):  $\nu = 3290$  (NH),  $3040$  (arom. CH),  $1710$  (ester C=O),  $1680$  (C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([ $\text{D}_6$ ]-DMSO):  $\delta = 1.20$  (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ),  $2.88$  (t, 2H, 5-H),  $3.62$  (t, 2H, 6-H),  $4.16$  (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ),  $4.51$  (s, 2H, 8-H),  $7.18-7.62$  (m, 5H, Ar-H),  $7.91$  (b, 1H, NH),  $8.35$  (s, 1H, CH).  $10.95$  (b, 1H, NH).

*3-Phenyl-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (3c)*

Pale yellow crystals; yield 0.64 g (91%); m.p. 174–176 °C. – IR (KBr):  $\nu$  = 3260 (NH), 3060 (arom. CH), 1711 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ([D<sub>6</sub>]-DMSO):  $\delta$  = 1.23 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 2.92 (t, 2H, 5-H), 3.72 (t, 2H, 6-H), 4.14 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.63 (s, 2H, 8-H), 7.22–7.54 (m, 5ArH), 6.84 (b, 1H, NH), 8.45 (s, 1H, CH).

*Synthesis of 3d–f*

*General procedure*

To a stirred suspension of **2** (0.61 g, 2 mmol) in absolute ethanol (10 ml), an appropriate amino alcohol (2.5 mmol) was added. The reaction mixture was stirred at room temperature for 3–5 h. After removing the solvent, the residue was subjected to column chromatography (dichloromethane/methanol (9:1)) followed by recrystallization from ethanol/diisopropylether (1:1).

*3-(2-Hydroxyethyl)-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (3d)*

Puff crystals; yield 0.37 g (57%); m.p. 117–119 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3280 (NH), 1705 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.24 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 3.05 (t, 2H, 5-H), 3.45 (b, 1H, OH), 3.72 (t, 2H, 6-H), 3.91 (t, 2H, N-CH<sub>2</sub>), 4.09 (q, 4H, CH<sub>2</sub>OH,  $\text{COOCH}_2\text{CH}_3$ ), 4.65 (s, 2H, 8-H), 5.61 (b, 1H, NH), 7.62 (s, 1H, CH). –  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 14.65 (CH<sub>3</sub>), 26.07 (C-5), 40.75 (C-6), 43.32 (C-8), 61.90 (CH<sub>2</sub>), 62.55 (N-CH<sub>2</sub>), 64.45 (CH<sub>2</sub>-OH), 115.21 (C-4a), 119.42 (C-4b), 126.24 (C-8a), 146.77 (C-2), 155.29 (C-9a), 156.20 (C=NH), 158.16 (C=O). –  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$  (322.39): calcd. C 52.16, H 5.63, N 17.38; found C 52.01, H 5.52, N 17.26.

*3-(3-Hydroxypropyl)-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (3e)*

Colorless needles; yield 0.35 g (51%); m.p. 128–130 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3270 (NH), 1706 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.22 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 1.85–2.10 (m, 2H, CH<sub>2</sub>-propyl), 3.15 (b, 1H, OH), 3.25 (t, 2H, 5-H), 3.42 (t, 2H, N-CH<sub>2</sub>), 3.73 (t, 2H, 6-H), 4.10 (q, 4H, CH<sub>2</sub>OH,  $\text{COOCH}_2\text{CH}_3$ ), 4.76 (s, 2H, 8-H), 6.22 (b, 1H, NH), 8.42 (s, 1H, CH).

*3-(1,1-Dimethyl-2-hydroxyethyl)-4-imino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (3f)*

Colorless crystals; yield 0.34 g (48%); m.p. 147–149 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3240 (NH), 1708 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.29 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 1.65 (s, 6H, 2CH<sub>3</sub>), 3.08 (t, 2H, 5-H), 3.31 (b, 1H, OH), 3.76 (t, 2H, 6-H), 4.08 (d, 2H, CH<sub>2</sub>), 4.18 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.65 (s, 2H, 8-H), 6.42 (b, 1H, NH), 8.14 (s, 1H, CH).

*Synthesis of 5a–c*

*General procedure*

A mixture of 4-chloro-pyridothienopyrimidine **4** (0.6 g, 2 mmol) and an aminoalcohol (2 mmol) was refluxed in absolute ethanol (15 ml) for 3–7 h. After removal of the solvent, the residual extracted with diethyl ether. The solid product was collected, washed with cold ethanol and recrystallized from n hexane- $\text{CHCl}_3$ .

*4-(2-Hydroxyethyl)amino-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (5a)*

Yellow crystals; yield 0.53 g (83%); m.p. 157–159 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3295 (NH), 1712 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.24 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 3.02 (t, 2H, 5-H), 3.42 (b, 1H, OH), 3.72 (t, 2H, 6-H), 3.84 (m, 4H, CH<sub>2</sub>OH, N-CH<sub>2</sub>), 4.12 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.74 (s, 2H, 8-H), 6.01 (b, 1H, NH), 8.38 (s, 1H, CH). –  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$  (322.39): calcd. C 52.16, H 5.63, N 17.38; found C 52.03, H 5.43, N 17.21.

*4-(3-Hydroxypropyl)amino-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid ethyl ester (5b)*

Pale yellow needles; yield 0.53 g (79%); m.p. 143–145 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3290 (NH), 1707 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.26 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 1.94 (m, 2H, CH<sub>2</sub>-propyl), 3.06 (t, 2H, 5-H), 3.38 (b, 1H, OH), 3.67 (t, 2H, 6-H), 3.75–3.86 (m, 4H, CH<sub>2</sub>OH, N-CH<sub>2</sub>), 4.15 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.76 (s, 2H, 8-H), 6.62 (b, 1H, NH), 8.31 (s, 1H, CH). –  $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$  (336.42): calcd. C 53.55, H 5.99, N 16.65; found C 53.41, H 5.83, N 16.51.

4-(1,1-Dimethyl-2-hydroxyethyl)amino-5,6,7,8-tetrahydro-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylic acid ethyl ester (**5c**)

Pale yellow crystals; yield 0.57 g (81%); m.p. 101–103 °C. – IR (KBr):  $\nu$  = 3500–3400 (OH), 3285 (NH), 1712 (ester C=O)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.26 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 1.63 (s, 6H, 2 $\text{CH}_3$ ), 3.04 (t, 2H, 5-H), 3.34 (b, 1H, OH), 3.76 (t, 2H, 6-H), 4.05 (d, 2H,  $\text{CH}_2$ ), 4.16 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.64 (s, 2H, 8-H), 6.87 (b, 1H, NH), 8.23 (s, 1H, CH). –  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 11.47 ( $\text{CH}_3$ ), 14.48 ( $\text{CH}_3$ ), 14.68 ( $\text{CH}_3$ ), 25.66 (C-5), 34.82 (C-6), 43.30 (C-8), 53.91 ( $\text{CH}_2\text{-OH}$ ), 61.87 ( $\text{CH}_2$ ), 77.46 (NH-C), 115.22 (C-4a), 126.23 (C-4b), 146.50 (C-8a), 152.77 (C-2), 155.50 (C-9a), 165.31 (C-4), 165.35 (C=O).

Synthesis of **7a,b**

General procedure

Method A

Compounds **3d,e** (2 mmol) were placed in a tube and subjected to microwave irradiation operating at 50% power for 5 min in a domestic oven (600 Watt, BPL, 700 T), then allowed to reach r.t. The solid product obtained was recrystallized from benzene/*n*-hexane to give compounds **7a,b**.

2,3,7,8,9,10-Hexahydropyrldo[4',3':4,5]thieno[2,3-*d*]imidazo[2,1-*f*]pyrimidine-8-carboxylic acid ethyl ester (**7a**)

Yellow needles; yield 0.47 g (78%); m.p. 71–73 °C. – IR (KBr):  $\nu$  = 1705 (ester C=O), 1625 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.17 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 2.51 (t, 2H, 10-H), 3.23 (t, 2H, 9-H), 3.52 (t, 2H, 2-H), 3.92 (t, 2H, 3-H), 4.09 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.25 (s, 2H, 7-H), 7.65 (s, 1H, CH). –

MS:  $m/z$  = 304 ( $\text{M}^+$ ). –  $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$  (304.37): calcd. C 55.25, H 5.30, N 18.41; found C 55.12, H 5.11, N 18.28.

2,3,4,,8,9,11-Hexahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimido[2,1-*f*]pyrimidine-9(10H)-carboxylic acid ethyl ester (**7b**)

Colorless needles; yield 0.45 g (71%); m.p. 126–127 °C. – IR (KBr):  $\nu$  = 1695 (ester C=O), 1615 (C=N)  $\text{cm}^{-1}$ . –  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.13 (t, 3H,  $\text{COOCH}_2\text{CH}_3$ ), 1.91 (m, 2H, 3-H), 2.16 (t, 2H, 11-H), 2.97 (t, 2H, 10-H), 3.07 (t, 2H, 2-H), 3.57 (t, 2H, 4-H), 3.89 (q, 2H,  $\text{COOCH}_2\text{CH}_3$ ), 4.05 (s, 2H, 8-H), 7.55 (s, 1H, CH). – MS:  $m/z$  = 318 ( $\text{M}^+$ ). –  $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$  (318.40): calcd. C 56.59, H 5.70, N 17.60; found C 56.42, H 5.51, N 17.43.

Method B

Compounds **5a,b** (2 mmol) and phosphorus oxychloride (0.46 g, 3 mmol) were adsorbed on silica gel, placed in a tube and subjected to microwave heating for 12 min in a domestic oven (600 Watt), then allowed to reach r.t. The obtained solid hydrochloride salt was dissolved in water, extracted with chloroform and then the organic layer washed successfully with 5%  $\text{NaHCO}_3$ . The solvent was dried over anhydrous sodium sulfate and removed. The solid product obtained was recrystallized from benzene/*n*-hexane to give compounds **7a,b**. The compounds are identical to those obtained according to method A.

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