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Hussein El-Kashef, Abdel-Rahman Farghaly, Ahmed Al-Hazmi, Thierry Terme, Patrice Vanelle. Pyridine-Based Heterocycles. Synthesis of New Pyrido [4',3':4,5]thieno[2,3-d]pyrimidines and Related Heterocycles. *Molecules*, 2010, 15 (4), pp.2651–2666. 10.3390/molecules15042651 . hal-01460203

HAL Id: hal-01460203

<https://hal.science/hal-01460203>

Submitted on 21 Jun 2023

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Article

Pyridine-Based Heterocycles. Synthesis of New Pyrido [4',3':4,5]thieno[2,3-*d*]pyrimidines and Related Heterocycles

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Received: 11 March 2010; in revised form: 31 March 2010 / Accepted: 6 April 2010 /

Published: 12 April 2010

Abstract: The synthesis of the title compounds was achieved using ethyl 2-amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (**1**) as starting material. The reaction of the amino ester **1** with phenylisothiocyanate in boiling ethanol afforded the thiourea derivative **5**. The cyclization reactions of **5** under different reaction conditions led to different pyridothienopyrimidine derivatives. Other reactions of the latter derivatives leading to pyrido[4',3':4,5]thieno[2,3-*d*]triazolo[1,5-*a*]pyrimidines are also presented.

Keywords: pyrimidines; pyridines; thienopyrimidines; fused pyrimidines; fused pyridines

1. Introduction

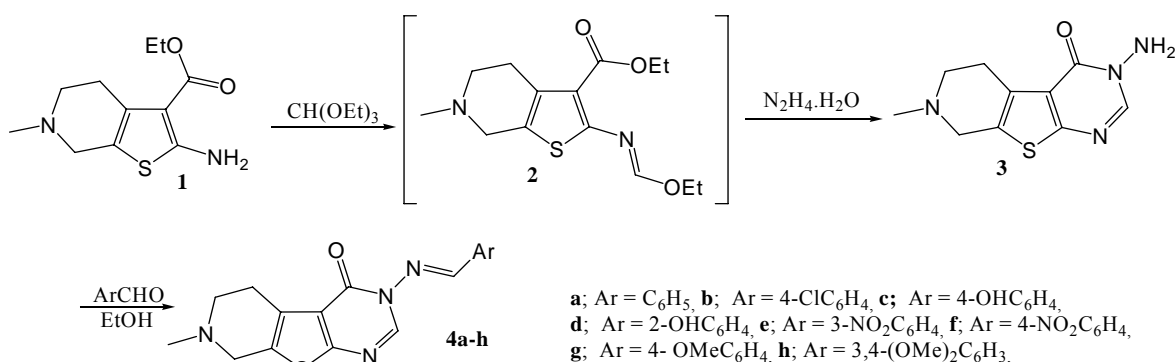
Fused pyridine ring systems have received considerable attention due to their diverse biological activity. In particular, pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones were reported to be used for the prophylaxis and therapy of cerebral ischemia [1,2], and as central nervous system agents [3]. Other derivatives also act as 5-HT_{1A} receptor antagonists and serotonin reuptake inhibitors [4], β-lactamase inhibitors, analgesics, anti-inflammatory [5] and antimalarial agents [6]. Moreover, this triheterocyclic

system showed highly potent dual 5-HT_{1A} and 5-HT_{1B} antagonists as potential antidepressant drugs [7]. The synthesis of other derivatives of this class of heterocycles were reported [8,9].

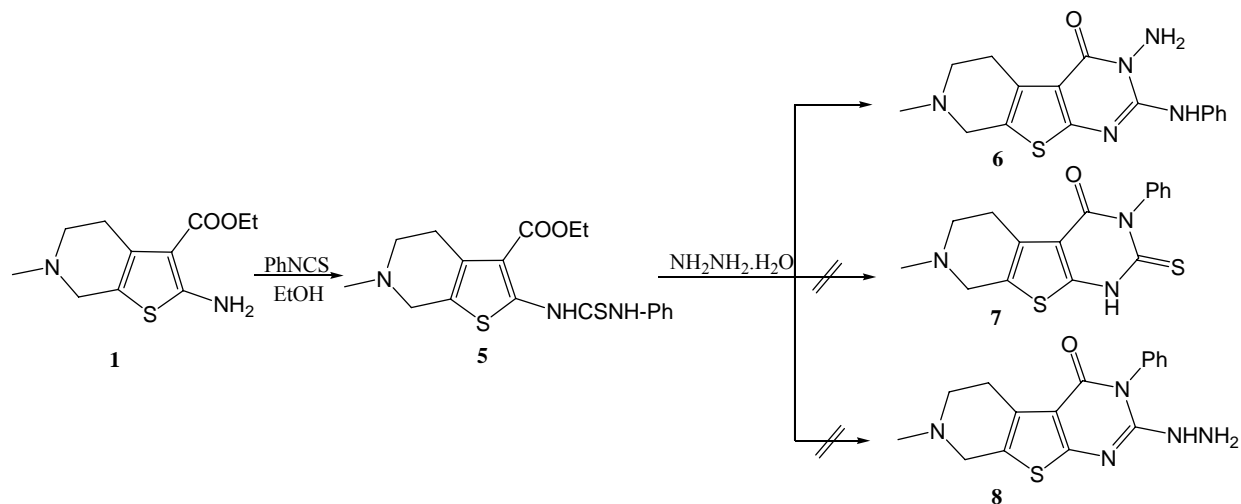
2. Results and Discussion

In view of the above findings and in continuation to our interest in the synthesis of polyfused heterocycles of biological importance [10–23], the synthesis of the title compounds was deemed of interest. Thus when the thienopyridine aminoester **1**, which is easily accessible via the Gewald reaction between 1-methylpiperidin-4-one, elemental sulfur and ethylcyanoacetate [7], was reacted with triethyl orthoformate, the corresponding ethoxymethyleneamino intermediate **2** was obtained as a reddish brown oil. This oil was reacted directly without any purification with hydrazine hydrate to give 3-amino-7-methyl-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**3**). Condensation of **3** with aromatic aldehydes in boiling ethanol gave the corresponding arylidene derivatives **4a–h** (Scheme 1).

Scheme 1. Synthesis of 3-arylideneamino-7-methyl-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**4a–h**).



Scheme 2. Synthesis of 3-amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**6**) from the aminoester **1**.

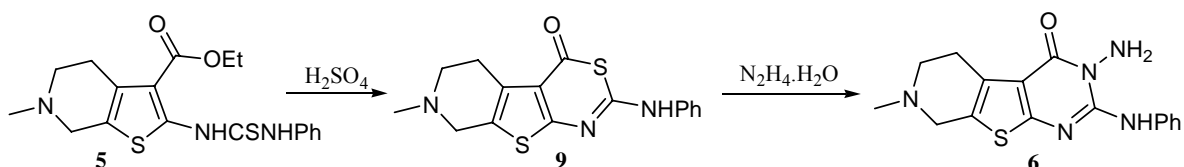


The reaction of the amino ester **1** with phenylisothiocyanate in boiling absolute ethanol gave the corresponding thiourea derivative **5**. When **5** was allowed to react with hydrazine hydrate, the three

possible structures **6** [24,25], **7** [5] and **8** [5] could be proposed for the reaction product (Scheme 2). Interestingly, in our hands this reaction gave one product only. The IR spectrum of this reaction product showed bands corresponding to primary NH₂ functionality, thus from at first glance structure **7** could be ruled out.

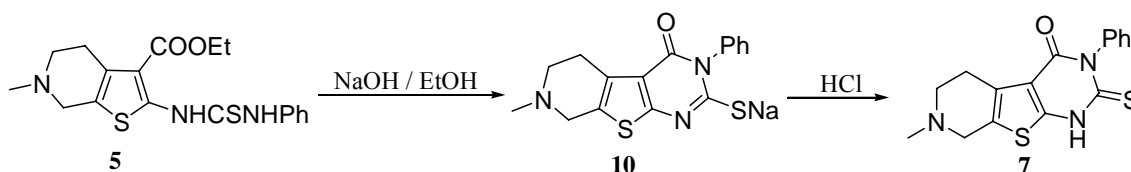
An unequivocal synthesis was carried out to prove whether **6** or **8** is the structure of the reaction product. Thus compound **5** was treated with concentrated sulfuric acid it gave the thiazinone derivative **9** which was then reacted with hydrazine hydrate, whereby an extrusion of the sulfur atom with its replacement by an *N*-amino nitrogen atom occurred, giving 3-amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**6**) having the same melting point, mixed melting point and spectral data as those of our reaction product (Scheme 3).

Scheme 3. Synthesis of 3-amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**6**) from the thioureido ester **5**.

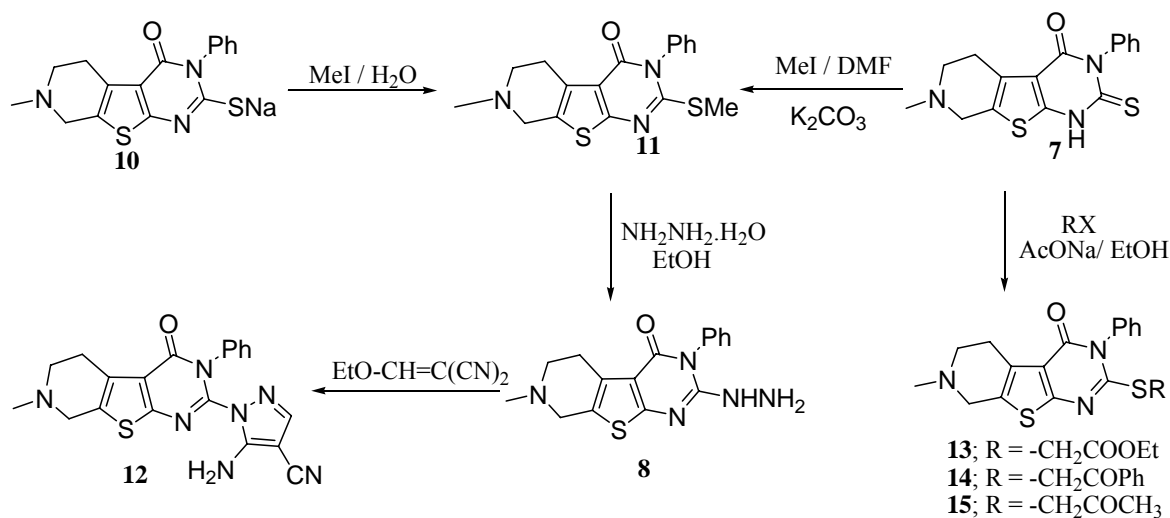


On the other hand, compounds **7** and **8** could be obtained following different reaction pathways *via* the procedure reported by El-Baih *et al.* [26]. Thus, **7** could be obtained when the thiourea derivative **5** was heated under reflux in ethanolic sodium hydroxide giving the sodium salt **10** which gave **7** upon acidification with hydrochloric acid (Scheme 4).

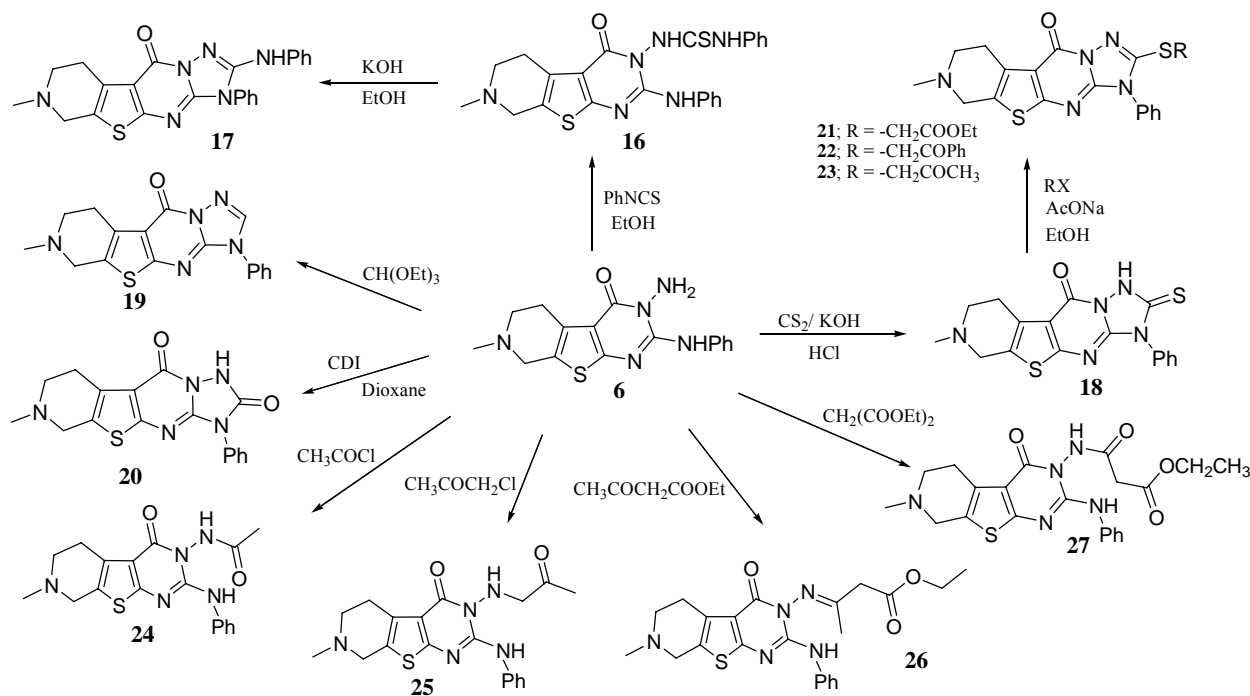
Scheme 4. Synthesis of the pyridothienopyrimidinonethione **7** from **5**.



Compound **8** was easily obtained by treatment of the 2-methylthio derivative **11** with hydrazine hydrate in boiling ethanol. It is to be mentioned that compound **11** was obtained by methylation of either the thione **7** in DMF, or by methylation of the sodium thiolate **10** in an aqueous solution as shown in Scheme 5. Other alkylations of the thione **7** with ethyl chloroacetate, phenacyl bromide and chloroacetone gave the corresponding products **13–15** respectively. When **8** was allowed to react with ethoxymethylene malononitrile the reaction product was identified as 5-amino-1-(7-methyl-3-phenyl-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-on-2-yl)-1*H*-pyrazole-4-carbonitrile (**12**) (Scheme 5).

Scheme 5. Synthesis of different pyridothienopyrimidines.

Compound **6** proved to be a key intermediate and served for the preparation of several new fused heterocycles related to pyridothienopyrimidine ring system (Scheme 6).

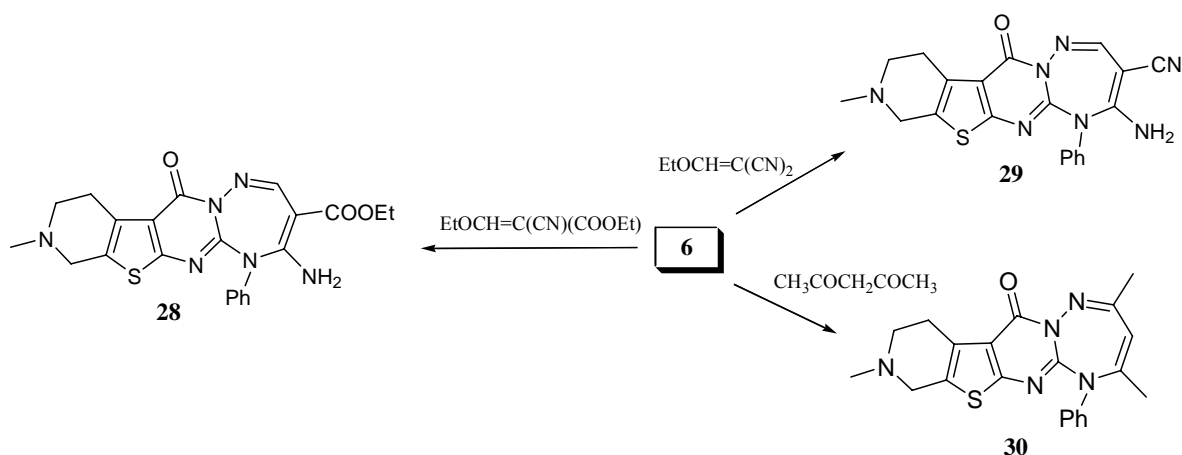
Scheme 6. Pyridothienopyrimidine **6** as a versatile key intermediate.

Thus the triazolo derivative **17** could be obtained via the reaction of **6** with phenylisothiocyanate in boiling ethanol to give the thiourea derivative **16**, which underwent a cyclodehydrosulfurization when heated in ethanolic KOH under reflux to afford 7-methyl-2-phenylamino-3-phenyl-6,7,8,9-tetrahydro-3*H*-pyrido[4,3':4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-10-one (**17**). Other triazolo derivatives could be obtained by the reaction of compound **6** with carbon disulfide, triethyl orthoformate and 1',1'-carbonyldiimidazole (CDI), giving compounds **18–20** respectively. The thione **18** was alkylated with ethyl chloroacetate, phenacyl bromide and chloroacetone in boiling ethanol in

the presence sodium acetate to give the corresponding products **21-23** respectively. Compound **6**, when treated with acetyl chloride also gave *N*-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-on-3-yl)acetamide (**24**). The reaction of **6** with chloroacetone in boiling ethanol afforded the corresponding 7-methyl-2-phenylamino-3-(2-oxopropylamino)-5,6,7,8-tetrahydro-3*H*-pyrido- [4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (**25**). When **6** was reacted with ethyl acetoacetate, a condensation reaction took place only between the keto carbonyl group of the ketoester and the primary amino group of compound **6** giving ethyl 3-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-on-3-ylimino)butanoate (**26**), whereas, the reaction of **6** with diethyl malonate gave ethyl 3-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3*H*-pyrido[4',3':4,5]thieno [2,3-*d*]pyrimidin-4-on-3-ylamino)-3-oxopropanoate (**27**) (Scheme 6).

It is worth mentioning that the reaction of **6** with ethyl ethoxymethylene cyanoacetate and ethoxymethylenemalononitrile gave the triazepines **28** and **29** respectively (Scheme 7). Another triazepine derivative was obtained when **6** was reacted with acetylacetone in boiling ethanol to give 5-phenyl-2,4,9-trimethyl-8,9,10,11-tetrahydro-5*H*-pyrido[4'',3'':4',5']thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4]-triazepin-12-one (**30**) (Scheme 7).

Scheme 7. Synthesis of pyridothienopyrimidotriazepines from **6**.



3. Experimental

3.1. General

All melting points are uncorrected and were measured on a Gallankamp melting point apparatus. The IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer using the KBr wafer technique. The ¹H-NMR spectra were measured on a Jeol LA 400 MHz FT-NMR, Varian Unity-plus 300 (200 MHz) or Varian EM-390 (90 MHz) spectrometers with TMS as internal standard (δ values in ppm). Elemental analyses were carried out using a Perkin-Elmer 240C Microanalyzer, and the results were within an acceptable range.

*3-Amino-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one* (**3**). A mixture of **1** (0.480 g, 2 mmol) and triethyl orthoformate (5 mL) was heated under reflux for 6 h. After cooling, the solvent was removed *in vacuo* and the brownish red oil obtained was used directly without

purification in the next step. A mixture of the latter intermediate (0.592 g, 2 mmol) and excess of hydrazine hydrate (5 mL) in ethanol (10 mL) was refluxed for 1 h. The solvent was then removed under reduced pressure. The solid product obtained was triturated with water, filtered and recrystallized from ethanol as pale buff crystals, yield 0.48 g (81%), m.p. 194–196 °C. IR: ν cm^{-1} = 3,450, 3,300 (NH_2), 2,910 (CH aliph.), 1,670 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.50 (s, 3H, NCH_3), 2.80 (m, 2H, CH_2), 3.20 (m, 2H, CH_2), 3.67 (s, 2H, CH_2), 5.13 (bs, 2H, NH_2), 8.20 (s, 1H, CH pyrimidine). $\text{C}_{10}\text{H}_{12}\text{N}_4\text{OS}$ (236.30) Calcd.: C, 50.83; H, 5.12; N, 23.71; S, 13.57. Found: C, 50.93; H, 4.92; N, 23.41; S, 13.87.

3.2. General procedure for the synthesis of 3-arylideneamino-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-ones **4a–h**

A mixture of compound **3** (0.236 g, 1 mmol) and the appropriate aromatic aldehyde (0.001 mol) in ethanol (10 mL) was refluxed for 2 h. After cooling, the solid precipitate was collected and recrystallized from appropriate solvent to give **4a–h**.

3-(Benzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (4a). This compound was obtained from ethanol as yellow crystals, yield 0.30 g (92%), m.p. 166–168 °C. IR: ν cm^{-1} = 3,050 (CH arom.), 2,920 (CH aliph.), 1,670 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.43 (s, 3H, NCH_3), 2.67 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.80 (s, 2H, CH_2), 6.83 (m, 3H, Ar-H), 7.76 (m, 2H, Ar-H), 8.10 (s, 1H CH, pyrimidinone), 9.20 (s, 1H, N=CH). $\text{C}_{17}\text{H}_{16}\text{N}_4\text{OS}$ (324.40) Calcd.: C, 62.94; H, 4.97; N, 17.27; S, 9.88. Found: C, 62.72; H, 4.82; N, 16.94; S, 9.95.

3-(4-Chlorobenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d] pyrimidin-4-one (4b). This compound was obtained from ethanol as pale yellow crystals, yield 0.21 g (85%), m.p. 198–200 °C. IR: ν cm^{-1} = 3,030 (CH arom.), 2,950 (CH aliph.), 1,675 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.43 (s, 3H, NCH_3), 2.70 (t, 2H, CH_2), 3.07 (t, 2H, CH_2), 3.56 (s, 2H, CH_2), 7.36 (d, 2H, J = 8 Hz, Ar-H), 7.69 (d, 2H, J = 8 Hz, Ar-H), 8.14 (s, 1H, CH pyrimidinone), 9.54 (s, 1H, N=CH). $\text{C}_{17}\text{H}_{15}\text{ClN}_4\text{OS}$ (358.85) Calcd.: C, 56.90; H, 4.21; Cl, 9.88; N, 15.61; S, 8.94. Found: C, 56.68; H, 4.03; Cl, 9.38; N, 15.30; S, 8.66.

3-(4-Hydroxybenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d] pyrimidin-4-one (4c). This compound was obtained from ethanol as yellow crystals, yield 0.21 g (62%), m.p. 224–226 °C. IR: ν cm^{-1} = 3,350 (OH), 3,050 (CH arom.), 2,900 (CH aliph.), 1,670 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.32 (s, 3H, NCH_3), 2.61 (t, 2H, CH_2), 2.93 (t, 2H, CH_2), 3.49 (s, 2H, CH_2), 6.89 (d, 2H, J = 8.5 Hz, Ar-H), 7.72 (d, 2H, J = 8.5 Hz, Ar-H), 8.37 (s, 1H, CH pyrimidinone), 8.87 (s, 1H, N=CH), 11.02 (s, 1H, OH). $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ (340.41) Calcd.: C, 59.98; H, 4.74; N, 16.46; S, 9.42. Found: C, 59.68; H, 4.55; N, 16.16; S, 9.23.

3-(2-Hydroxybenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d] pyrimidin-4-one (4d). This compound was obtained as white powder from ethanol, yield: 0.29 g (86%), m.p. 200–202 °C. IR: ν cm^{-1} = 3,320 (OH), 3,090 (CH arom.), 2,930 (CH aliph.), 1,670 (C=O). $^1\text{H-NMR}$

(CDCl₃): δ = 2.34 (s, 3H, NCH₃), 2.93 (t, 2H, CH₂), 3.17 (t, 2H, CH₂), 3.67 (s, 2H, CH₂), 7.33 (m, 4H, Ar-H), 8.21 (s, 1H, CH pyrimidine), 9.45 (s, 1H, N=CH), 10.90 (s, 1H, OH). C₁₇H₁₆N₄O₂S (340.40) Calcd.: C, 59.98; H, 4.74; N, 16.46; S, 9.42. Found: C, 59.66; H, 4.49; N, 16.69; S, 9.81.

3-(3-Nitrobenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (4e). This compound was obtained from ethanol as yellow crystals, yield: 0.30 g, (81%), m.p. 208–210 °C. IR: ν cm⁻¹ = 3,020 (CH arom.), 2,960 (CH aliph.), 1,675 (C=O), 1,520, 1,350 (NO₂). ¹H-NMR (DMSO-d₆): δ = 2.47 (s, 3H, NCH₃), 2.77 (t, 2H, CH₂), 3.13 (t, 2H, CH₂), 3.62 (s, 2H, CH₂), 7.61 (m, 1H, Ar-H), 8.16 (m, 1H, Ar-H), 8.30 (m, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 8.60 (s, 1H, CH pyrimidine), 9.83 (s, 1H, N=CH). C₁₇H₁₅N₅O₃S (369.40) Calcd.: C, 55.27; H, 4.09; N, 18.96; S, 8.68. Found: C, 54.98; H, 3.81; N, 18.88; S, 8.95.

3-(4-Nitrobenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (4f). This compound was obtained from ethanol as yellowish crystals, yield 0.34 g (92%), m.p. 218–220 °C. IR: ν cm⁻¹ = 3,020 (CH arom.), 2,950 (CH aliph.), 1,670 (C=O), 1,530, 1,330 (NO₂). ¹H-NMR (CDCl₃): δ = 2.91 (s, 3H, NCH₃), 3.18 (t, 2H, CH₂), 3.44 (t, 2H, CH₂), 4.39 (s, 2H, CH₂), 8.27 (m, 3H, Ar-H + CH pyrimidinone), 8.37 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.79 (s, 1H, N=CH). C₁₇H₁₅N₅O₃S (369.40) Calcd.: C, 55.27; H, 4.09; N, 18.96; S, 8.68. Found: C, 54.99; H, 3.81; N, 18.18; S, 7.95.

3-(4-Methoxybenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (4g). This compound was obtained from ethanol as yellowish crystals, yield 0.21 g (59%), m.p. 168–170 °C. IR: ν cm⁻¹ = 3,050 (CH arom.), 2,900 (CH aliph.), 1,665 (C=O). ¹H-NMR (CDCl₃): δ = 2.43 (s, 3H, NCH₃), 2.70 (t, 2H, CH₂), 3.09 (t, 2H, CH₂), 3.56 (s, 2H, CH₂), 3.79 (s, 3H, OCH₃), 6.89 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.71 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.13 (s, 1H, CH pyrimidinone), 9.24 (s, 1H, N=CH). C₁₈H₁₈N₄O₂S (354.43) Calcd.: C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.15; H, 4.31; N, 15.55; S, 8.85.

3-(3,4-Dimethoxybenzylideneamino)-7-methyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (4h). This compound was obtained from ethanol as yellow crystals yield 0.22 g (57%), m.p. 162–164 °C. IR: ν cm⁻¹ = 3,090 (CH arom.), 2,940 (CH aliph.), 1,665 (C=O). ¹H-NMR (CDCl₃): δ = 2.47 (s, 3H, NCH₃), 2.74 (t, 2H, CH₂), 3.13 (t, 2H, CH₂), 3.61 (s, 2H, CH₂), 3.91 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 6.99 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.24 (dd, 1H, *J* = 2.5, 8.5 Hz, Ar-H), 7.36 (d, 1H *J* = 2.5, Ar-H), 8.19 (s, 1H, CH pyrimidinone), 9.23 (s, 1H, N=CH). C₁₉H₂₀N₄O₃S (384.45) Calcd.: C, 59.36; H, 5.24; N, 14.57; S, 8.34. Found: C, 59.05; H, 4.94; N, 14.85; S, 8.30.

Ethyl 6-methyl-2-(3-phenylthioureido)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (5). A mixture of **1** (7.2 g, 30 mmol) and phenylisothiocyanate (4.1 g, 30 mmol) in absolute ethanol (20 mL) was heated under reflux for 2 h. After cooling, the solid product was collected, dried and recrystallized from ethanol to give yellow crystals, yield 7.01 g (62%), m.p. 201–202 °C. IR: ν cm⁻¹ = 3,180 (NH), 2,900 (CH aliph.), 1,670 (C=O), 1,190 (C=S). ¹H-NMR (DMSO-d₆): δ = 1.24 (t, 3H, *J* = 7.1 Hz, CH₂CH₃), 2.31 (s, 3H, NCH₃), 2.57 (t, 2H, CH₂), 2.75 (t, 2H, CH₂), 3.54 (s, 2H, CH₂), 4.19 (q, 2H,

$J = 7.1$ Hz, CH₂CH₃), 7.21 (m, 3H, Ar-H), 7.38 (m, 2H, Ar-H), 8.45 (s, 1H, NH), 12.07 (s, 1H, NH). C₁₈H₂₁N₃O₂S₂ (375.51) Calcd.: C, 57.57; H, 5.64; N, 11.19; S, 17.08. Found: C, 57.33; H, 5.36; N, 10.96; S, 16.80.

3-Amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (6): A mixture of the arylthiourea **5** (3.75 g, 10 mmol) and excess hydrazine hydrate (5 mL) was heated under reflux for 12 h. After cooling, the precipitate formed was filtered, dried and recrystallized from ethanol/dioxane (1:2) to give white crystals, yield: 2.03 g (62%), m.p. 252–254 °C. IR: ν cm⁻¹ = 3,350, 3,300 (NH₂), 3,200 (NH), 3,050 (CH arom.), 2,900 (CH aliph), 1,660 (C=O). ¹H-NMR (DMSO-d₆): δ = 2.41 (s, 3H, NCH₃), 2.64 (t, 2H, CH₂), 2.98 (t, 2H, CH₂), 3.40 (s, 2H, CH₂), 4.79 (bs, 2H, NH₂), 7.32 (m, 2H, Ar-H), 7.61 (m, 3H, Ar-H), 8.51 (bs, 1H, NH). MS : m/z (rel. int.) 329 (M⁺, 91%), 328 (40), 327 (100), 253 (22.8), 77 (20). C₁₆H₁₇N₅OS (327.40) Calcd.: C, 58.69; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.59; H, 4.95; N, 21.11; S, 9.89.

7-Methyl-3-phenyl-2-thioxo-1,2,5,6,7,8-hexahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (7). *Method (a)*: A suspension of compound **5** (3.75 g, 10 mmol) in an ethanolic solution of sodium hydroxide (2N, 5 mL) was heated under reflux for 2 h. The reaction mixture was cooled and acidified with hydrochloric acid (2N), whereupon a solid product was separated out. The solid product formed was filtered and recrystallized from ethanol as yellow crystals, yield 3.1 g (94%), m.p. 296–298 °C. IR: ν cm⁻¹ = 2900 (CH aliph.), 2400 (SH), 1680 (C=O). ¹H-NMR (DMSO-d₆): δ = 2.33 (s, 3H, NCH₃), 2.83 (m, 4H, 2CH₂), 3.33 (s, 2H, CH₂), 7.13 (m, 3H, Ar-H), 7.33 (m, 2H, Ar-H). MS : m/z (rel. int.) 329 (M², 57%), 324.35 (13.5), 299.22 (24.8), 285.25 (41.9), 252.70 (24.5), 76.83 (33), 17.96 (24.4). C₁₆H₁₅N₃OS₂ (329.44) Calcd.: C, 58.33; H, 4.59; N, 12.75; S, 19.47. Found: C, 58.45; H, 4.35; N, 12.88; S, 19.25. *Method (b)*: An aqueous solution of compound **10** (3.83 g, 10 mmol) was acidified with concentrated hydrochloric acid whereupon a solid product was separated out which was filtered, washed with water and recrystallized from ethanol to give as yellow crystals, yield: 3.28 g (86%).

2-Hydrazino-7-methyl-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (8). A mixture of **11** (0.37 g, 1 mmol) and hydrazine hydrate (5 mL) in ethanol (10 mL) was heated under reflux for 2 h. The reaction mixture was then allowed to cool and the solid product obtained was collected and recrystallized from ethanol as white crystals, yield 0.17 g (52%), m.p. 148–150 °C. IR: ν cm⁻¹ = 3,300, 3,250 (NHNH₂), 3,050 (CH arom.), 2,910 (CH aliph.), 1,670 (C=O). ¹H-NMR (CDCl₃): δ = 2.46 (s, 3H, NCH₃), 2.75 (t, 2H, CH₂), 3.03 (t, 2H, CH₂), 3.61 (s, 2H, CH₂), 3.90 (bs, 2H, NH₂), 5.35 (bs, 1H, NH), 7.25 (m, 3H, Ar-H), 7.56 (m, 2H, Ar-H). C₁₆H₁₇N₅SO (327.41) Calcd.: C, 58.69; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.45; H, 4.99; N, 21.27; S, 9.58.

7-Methyl-2-phenylamino-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-d][1,3]thiazin-4-one (9). A mixture of the compound **5** (3.75 g, 10 mmol) and concentrated sulfuric acid (5 mL) was stirred for 6 h. The reaction mixture was then poured cautiously into cold sodium bicarbonate solution. The solid product obtained was filtered, washed with water and recrystallized from ethanol/dioxane (2:3) to give yellow crystals, yield 3.2 g (97%), m.p. 282–284 °C. IR: ν cm⁻¹ = 3400 (NH), 1640 (C=O). ¹H-NMR (DMSO-d₆): δ = 2.50 (s, 3H, NCH₃), 2.67 (t, 2H, CH₂), 3.03 (t, 2H, CH₂), 4.40 (bs, 1H, NH), 7.40 (m,

2H, Ar-H), 7.67 (m, 3H, Ar-H). C₁₆H₁₅N₃OS₂ (329.44). Calcd.: C, 58.33; H, 4.59; N, 12.76; S, 19.47. Found: C, 58.13; H, 4.24; N, 12.53; S, 19.70.

Sodium salt of 2-mercapto-7-methyl-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (10). To a solution of sodium hydroxide (0.40 g, 10 mmol) in absolute ethanol (30 mL) compound **5** (3.75 g, 10 mmol) was added and the resulting mixture was heated under reflux for 2 h. The precipitate that was formed on hot was filtered, washed with boiling ethanol and dried to give yellow powder, yield 2.8 g (80%), m.p. >300 °C. IR: ν cm⁻¹ = 3,030 (CH arom.), 2,900 (CH aliph.), 1,640 (C=O).

7-Methyl-2-(methylthio)-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (11). *Method (a)*: To a solution of compound **10** (3.51 g, 10 mmol) in water (15 mL) methyl iodide (1.8 g, 13 mmol) was added under stirring at room temperature. After complete addition, the reaction mixture was stirred for 2 h further. The solid product thus formed was filtered and recrystallized from dioxane to give white crystals, yield 3.21 g (93%), m.p. 202–204 °C. IR: ν cm⁻¹ = 2,990 (CH aliph.), 1,680 (C=O). ¹H-NMR (CDCl₃): δ = 2.40 (s, 3H, NCH₃), 2.51 (s, 3H, SCH₃), 2.74 (t, 2H, CH₂), 3.07 (t, 2H, CH₂), 3.78 (s, 2H, CH₂), 7.31 (m, 3H, Ar-H), 7.55 (m, 2H, Ar-H). MS: *m/z* (rel. int.) 343 (M⁺, 80.7%), 338 (50), 300 (100), 253 (78.8), 150 (17.8), 76.83 (33), 58 (97.9). C₁₇H₁₇N₃OS₂ (343.47) Calcd.: C, 59.45; H, 4.99; N, 12.23; S, 18.67. Found: C, 59.11; H, 4.75; N, 12.17; S, 18.35. *Method (b)*: To a mixture of **7** (3.29 g, 10 mmol) and potassium carbonate (0.5 g) in dimethylformamide (15 mL), methyl iodide (2 mL) was added and the reaction mixture was gently heated on a water bath at 60 °C for 2 h. After cooling, the reaction mixture was poured on water, and the solid product was filtered, washed with water and recrystallized from dioxane to give white crystals, yield 0.97g (28%).

5-Amino-1-(7-methyl-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-on-2-yl)-1H-pyrazole-4-carbonitrile (12). A mixture of compound **8** (0.65 g, 2 mmol) and ethoxymethylenemalononitrile (0.254 g, 2 mmol) in absolute ethanol (10 mL) was heated under reflux for 8 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol to give yellow crystals, yield 0.46 g (57%), m.p. 228–230 °C. IR: ν cm⁻¹ = 3,300, 3,150 (NH₂), 2,900 (CH aliph.), 2,200 (C≡N), 1,640 (C=O). ¹H-NMR (DMSO-d₆): δ = 2.57 (s, 3H, NCH₃), 2.83 (t, 2H, CH₂), 3.17 (t, 2H, CH₂), 4.17 (s, 2H, CH₂), 4.47 (bs, 2H, NH₂), 7.53 (m, 6H, Ar-H + CH pyrazole). C₂₀H₁₇N₇SO (403.46) Calcd.: C, 59.54; H, 4.25; N, 24.30; S, 7.95. Found: C, 59.25; H, 4.19; N, 24.28; S, 7.77.

3.3. General procedure for the synthesis of compounds **13–15** (from **7**) and **21–23** (from **18**) with appropriate RX

A mixture of **7** (0.66 g, 2 mmol) or **18** (0.74 g, 2 mmol), appropriate RX (2 mmol) and sodium acetate (5 mmol for reaction with **7** or 10 mmol for reaction with **18**) in ethanol (10 mL) was heated under reflux for 3 h. After cooling, the solid product was collected by filtration, washed with water and recrystallized from appropriate solvent.

Ethyl (7-methyl-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-on-2-yl)-thioacetate (13). yellow crystals, yield 0.51 g (61%), m.p. 204–206 °C (ethanol/water 3/1). IR: ν cm^{-1} = 3,040 (CH arom.), 2,950 (CH aliph.), 1,730 (C=O), 1,650 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.53 (s, 3H, NCH_3), 2.79 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.67 (s, 2H, CH_2), 3.85 (s, 2H, SCH_2), 4.23 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.33 (m, 2H, Ar-H); 7.55 (m, 3H, Ar-H). MS: m/z (rel. int.) 415 (M^+ , 70%), 372 (75), 328 (73), 285 (24), 253 (72), 122 (24), 77 (40). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3\text{S}_2$ (415.53) Calcd.: C, 57.81; H, 5.09; N, 10.11; S, 15.43. Found: C, 57.63; H, 5.17; N, 9.97; S, 15.35.

7-Methyl-2-(phenacylthio)-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (14). yellow crystals, yield 0.75 g (84%), m.p. 220–222 °C (ethanol). IR: ν cm^{-1} = 1,690 (C=O), 1,665 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.48 (s, 3H, NCH_3), 2.74 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.60 (s, 2H, CH_2), 4.55 (s, 2H, SCH_2), 7.35 (m, 3H, Ar-H), 7.53 (m, 5H, Ar-H), 8.02 (m, 2H, Ar-H). $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2\text{S}_2$ (447.57) Calcd.: C, 64.40; H, 4.37; N, 9.39; S, 14.33. Found: C, 64.05; H, 4.22; N, 9.33; S, 14.12.

7-Methyl-2-[(2-oxopropyl)thio]-3-phenyl-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d] pyrimidin-4-one (15). white crystals, yield: 0.52 g (68%), m.p. 215–217 °C (ethanol). IR: ν cm^{-1} = 2,900 (CH aliph.), 1,710 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.50 (s, 3H, COCH_3), 2.67 (s, 3H, NCH_3), 2.95 (t, 2H, CH_2), 3.23 (t, 2H, CH_2), 3.81 (s, 2H, CH_2), 4.03 (s, 2H, SCH_2), 7.45 (m, 2H, Ar-H), 7.68 (m, 3H, Ar-H). $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}_2$ (385.51) Calcd.: C, 59.19; H, 4.97; N, 10.90; S, 16.64. Found: C, 59.03; H, 4.79; N, 10.87; S, 16.60.

Ethyl (7-methyl-3-phenyl-6,7,8,9-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidin-10-on-2-yl)thioacetate (21). pale yellow crystals, yield 0.53 g (58%), m.p. 178–180 °C (water/methanol 2/1). IR: ν cm^{-1} = 3,050 (CH arom.), 2,910 (CH aliph.), 1,730 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.29 (t, J = 7.1 Hz, 3H, $\text{CH}_2\text{-CH}_3$), 2.73 (s, 3H, NCH_3), 2.92 (t, 2H, CH_2), 3.27 (t, 2H, CH_2), 3.59 (s, 2H, CH_2), 3.82 (q, J = 7.1 Hz, 2H, $\text{CH}_2\text{-CH}_3$), 4.27 (s, 2H, SCH_2), 7.61 (m, 5H, Ar-H). $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}_3\text{S}_2$ (455.56) Calcd.: C, 55.37; H, 4.65; N, 15.37; S, 14.08. Found: C, 55.55; H, 4.57; N, 15.56; S, 14.27.

7-Methyl-2-phenacylthio-3-phenyl-6,7,8,9-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4] triazolo[1,5-a]pyrimidin-10-one (22). yellowish crystals, yield 0.13 g (33%), m.p. 200–202 °C (water/methanol 2/1). IR: ν cm^{-1} = 3,050 (CH arom.), 2,910 (CH aliph.), 1,720 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.48 (s, 3H, NCH_3), 2.72 (t, 2H, CH_2), 3.08 (t, 2H, CH_2), 3.63 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 7.34 (m, 3H, Ar-H), 7.47 (m, 5H, Ar-H), 7.79 (m, 2H, Ar-H). $\text{C}_{25}\text{H}_{21}\text{N}_5\text{O}_2\text{S}_2$ (487.60) Calcd.: C, 61.58; H, 4.34; N, 14.36; S, 13.15. Found: C, 61.49; H, 4.35; N, 14.19; S, 12.99.

7-Methyl-2-[(2-oxopropyl)thio]-3-phenyl-6,7,8,9-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4] triazolo[1,5-a]pyrimidin-10-one (23). yellow crystals, yield 0.61 g (72%). m.p. 194–196 °C (water/methanol 3/2). IR: ν cm^{-1} = 2,910 (CH aliph.), 1,730 (C=O), 1,690 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.29 (s, 3H, COCH_3), 2.48 (s, 3H, NCH_3), 2.74 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 3.64 (s, 2H, CH_2),

4.11 (s, 2H, SCH₂), 7.45 (m, 5H, Ar-H). C₂₀H₁₉N₅O₂S₂ (425.53) Calcd.: C, 56.45; H, 4.50; N, 16.46; S, 15.07. Found: C, 56.25; H, 4.25; N, 16.27; S, 15.25.

7-Methyl-2-phenylamino-3-(3-phenylthioureido)-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidine-4-one (16). A mixture of **6** (1.64 g, 5 mmol) and phenyl isothiocyanate (0.68 g, 5 mmol) in absolute ethanol (10 mL) was refluxed for 4 h. After cooling, the solid precipitate obtained was filtered and recrystallized from ethanol/dioxane (2:1) as reddish crystals, yield: 2.04 g (88%), m.p. 209–210 °C. IR: ν cm⁻¹ = 3,350, 3,300, (NH), 3,050 (CH arom.), 2,900 (CH aliph.), 1,680 (C=O), 1,220 (C=S). ¹H-NMR (CDCl₃): δ = 2.47 (s, 3H, NCH₃), 3.27 (m, 6H, 3CH₂), 7.31 (m, 10H, Ar-H), 9.25 (bs, 1H, NH), 9.55 (bs, 1H, NH), 9.94 (bs, 1H, NH). C₂₃H₂₂N₆OS₂ (462.59) Calcd.: C, 59.72; H, 4.79; N, 18.17; S, 13.86. Found: C, 59.55; H, 4.62; N, 18.35; S, 13.65.

7-Methyl-2-phenylamino-3-phenyl-6,7,8,9-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidin-10-one (17). A solution of compound **16** (0.463 g, 1 mmol) in ethanolic KOH (2N, 5 mL) was heated under reflux for 2 h. The reaction mixture was cooled and acidified with hydrochloric acid (2N), whereupon a solid product was separated out. This solid was filtered, washed with water and recrystallized from ethanol as buff crystals, yield 0.23 g (54%), m.p. 178–180 °C. IR: ν cm⁻¹ = 3,200 (NH), 3,120 (CH arom.), 2,900 (CH aliph.), 1,675 (C=O). ¹H-NMR (CDCl₃): δ 2.50 (s, 3H, NCH₃), 2.86 (t, 2H, CH₂), 3.19 (t, 2H, CH₂), 6.68 (s, 2H, CH₂), 6.92 (m, 5H, Ar-H), 7.68 (m, 5H, Ar-H), 7.92 (bs, 1H, NH). C₂₃H₂₀N₆OS (428.51) Calcd.: C, 64.47; H, 4.70; N, 19.61; S, 7.48. Found: C, 64.22; H, 4.79; N, 19.50; S, 7.33.

7-Methyl-3-phenyl-2-thioxo-1,2,6,7,8,9-hexahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidin-10-one (18). A mixture of the thienopyrimidine compound **6** (0.327 g, 1 mmol), carbon disulfide (3 mL) and potassium hydroxide (0.5 g, 9 mmol) in absolute ethanol (10 mL) was heated under reflux for 5 h. The solvent and the excess of carbon disulfide were removed *in vacuo*. The residue was treated with cold water (100 mL) and the resulting mixture was stirred then acidified with hydrochloric acid (2N). The precipitate thus formed was filtered and recrystallized from ethanol to give yellow crystals, yield 0.27 g (84%), m.p. 235–237 °C. IR: ν cm⁻¹ = 3,300 (NH), 3,050 (CH arom.), 2,900 (CH aliph.), 1,670 (C=O), 1,210 (C=S). ¹H-NMR (CDCl₃): δ = 2.40 (s, 3H, NCH₃), 2.70 (t, 2H, CH₂), 2.90 (t, 2H, CH₂), 3.50 (s, 2H, CH₂), 5.11 (bs, 1H, NH), 7.16 (m, 5H, Ar-H). MS: *m/z* (rel. int.) 367.75 (M⁺, 36.7%), 325 (39.5), 28 (29.4), 18 (100), 17 (22). C₁₇H₁₅N₅S₂O (369.47) Calcd.: C, 55.26; H, 4.09; N, 18.96; S, 17.37. Found: C, 54.98; H, 3.94; N, 18.65; S, 17.30.

7-Methyl-3-phenyl-6,7,8,9-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidin-10-one (19). A mixture of **6** (1.25 g, 3.8 mmol) and triethyl orthoformate (8 mL) was maintained at reflux for 4 h. After cooling, the excess of triethyl orthoformate was removed under reduced pressure. The residue obtained was recrystallized from petroleum ether/ethanol (9:2) to give white crystals, yield 0.85 g (66%), mp 243–245 °C. IR: ν cm⁻¹ = 3,050 (CH arom.), 2,910 (CH aliph.), 1,680 (C=O). ¹H-NMR (DMSO-d₆): δ = 2.19 (s, 3H, NCH₃), 2.96 (t, 2H, CH₂), 3.17 (t, 2H, CH₂), 4.55 (s, 2H, CH₂), 7.44 (m, 3H, Ar-H), 7.55 (m, 2H, Ar-H), 9.36 (s, 1H, CH triazole). C₁₇H₁₅N₅SO (337.4) Calcd.: C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.42; H, 4.22; N, 20.69; S, 9.33.

7-Methyl-3-phenyl-1,2,6,7,8,9-hexahydro-3H-pyrido[4',3':4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a] pyrimidine-2,10-dione (20). A mixture of the thienopyrimidine compound **6** (0.65 g, 2 mmol) and *N,N*-carbonyldimidazole (CDI) (0.64 g, 4 mmol) in dry dioxane (20 mL) was refluxed for 6 h. After cooling, the solvent was removed and the residue was triturated with cold water. The solid product was filtered, dried and recrystallized from water/ethanol (2:3) to give brown crystals, yield 0.61 g (86%), m.p. 280–282 °C. IR: ν cm^{-1} = 3,200 (NH), 3,050 (CH arom.), 2,910 (CH aliph.), 1,720 (C=O triazolo), 1,680 (C=O pyrimidinone). $^1\text{H-NMR}$ (DMSO- d_6): δ = 2.34 (s, 3H, NCH₃), 2.48 (s, 2H, CH₂), 2.87 (t, 2H, CH₂), 3.53 (t, 2H, CH₂), 7.43 (m, 2H, Ar-H), 7.53 (m, 3H, Ar-H), 11.95 (bs, 1H, NH). C₁₇H₁₅N₅SO₂ (353.40) Calcd.: C, 57.78; H, 4.28; N, 19.82; S, 9.07; Found: C, 57.69; H, 4.07; N, 19.91; S, 8.89.

N-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-on-3-yl)acetamide (24). To a solution of **6** (0.33 g, 1 mmol), in pyridine (5 mL), acetyl chloride (0.08 mL, 1.1 mmol) was added with stirring. The reaction mixture was stirred at room temperature for 7 h further. After removal of the solvent, the solid residue was treated with cold diluted HCl, filtered, washed with water and recrystallized from ethanol/dioxane (2:3) to give fine yellow crystals, yield 0.27 g (73%), m.p. 143–145 °C. IR: ν cm^{-1} = 3,390 (NH), 3,050 (CH arom.), 2,910 (CH aliph.), 1,730 (C=O), 1,690 (C=O). $^1\text{H-NMR}$ (CDCl₃): δ = 2.10 (s, 3H, COCH₃), 2.50 (s, 3H, NCH₃), 2.73 (t, 2H, CH₂), 3.00 (t, 2H, CH₂), 3.57 (s, 2H, CH₂), 4.73 (bs, 2H, NH), 7.37 (m, 2H, Ar-H); 7.47 (m, 3H, Ar-H). C₁₈H₁₉N₅SO₂ (369.44) Calcd.: C, 58.52; H, 5.18; N, 18.96; S, 8.68. Found: C, 58.35; H, 4.99; N, 18.69; S, 8.41.

7-Methyl-2-phenylamino-3-(2-oxopropylamino)-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-one (25). A mixture **6** (0.66 g, 2 mmol), and chloroacetone (0.19 mL, 2.2 mmol) in ethanol (10 mL) was heated under reflux for 3 h. After cooling, the solvent was removed *in vacuo* and the solid residue obtained was recrystallized from ethanol to give white crystals, yield 0.42 g (55%), m.p. 278–280 °C. IR: ν cm^{-1} = 3,300 (NH), 3,100 (CH arom.), 2,910 (CH aliph.), 1,720 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl₃): δ = 1.88 (s, 3H, COCH₃), 2.10 (s, 3H, NCH₃), 2.43 (t, 2H, CH₂), 2.66 (t, 2H, CH₂), 2.96 (s, 2H, CH₂), 3.54 (s, 2H, CH₂CO), 7.37 (m, 2H, Ar-H), 7.50 (m, 3H, Ar-H), 9.03 (bs, 1H, NH), 9.72 (s, 1H, NH). C₁₉H₂₁N₅O₂S (383.47) Calcd.: C, 59.51; H, 5.52; N, 18.26; S, 8.36. Found: C, 59.41; H, 5.35; N, 17.98; S, 8.39.

Ethyl 3-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-on-3-ylimino)butanoate (26). A mixture of **6** (0.82 g, 2.5 mmol) and ethyl acetoacetate (0.33 mL, 2.5 mmol), and sodium acetate (0.82 g, 10 mmol) in absolute ethanol (20 mL) was heated under reflux for 5 h. The reaction mixture was then triturated with diethyl ether (10 mL) and the precipitate thus formed was collected and recrystallized from ethanol to give buff crystals, yield 0.56 g (68%), m.p. 150–152 °C. IR: ν cm^{-1} = 3,350 (NH), 3,050 (CH arom.), 2,910 (CH aliph.), 1,730 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl₃): δ = 1.17 (t, J = 7.1 Hz, 3H, CH₂CH₃), 1.93 (s, 3H, CH₃), 2.48 (s, 3H, NCH₃), 2.81 (t, 2H, CH₂), 3.02 (t, 2H, CH₂), 3.39 (s, 2H, CH₂), 3.65 (s, 2H, CH₂), 4.09 (q, J = 7.1 Hz, 2H, CH₂CH₃), 7.43 (m, 5H, Ar-H), 8.41 (bs, 1H, NH). C₂₂H₂₅N₅O₃S (439.53) Calcd.: C, 60.12; H, 5.73; N, 15.93; S, 7.30. Found: C, 60.18; H, 5.05; N, 15.95; S, 6.40.

Ethyl 3-(7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3H-pyrido[4',3':4,5]thieno[2,3-d]pyrimidin-4-on-3-ylamino)-3-oxopropanoate (27). A mixture of **6** (1.64 g, 5 mmol) and diethyl malonate (5 mL) was heated under reflux for 5 h. After cooling, the excess of diethylmalonate was removed *in vacuo* and the solid residue was recrystallized from ethanol to give white platelets, yield: 1.3 g, (59%), m.p. 194–196 °C. IR: ν cm^{-1} = 3,300 (NH), 3,050 (CH arom.), 2,950 (CH aliph.), 1,730 (C=O), 1,690 (C=O), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 1.24 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.45 (s, 3H, NCH_3), 2.70 (t, 2H, CH_2), 3.30 (t, 2H, CH_2), 3.33 (s, 2H, CH_2), 3.57 (s, 2H, CH_2), 4.16 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.36 (m, 2H, Ar-H), 7.52 (m, 3H, Ar-H), 8.98 (bs, 1H, NH), 10.09 (bs, 1H, NH). $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_4\text{S}$ (441.51) Calcd.: C, 57.13; H, 5.25; N, 15.86; S, 7.26. Found: C, 57.05; H, 4.98; N, 15.65; S, 6.99.

Ethyl 4-amino-9-methyl-12-oxo-5-phenyl-8,9,10,11-tetrahydro-5H-pyrido[4'',3''':4',5']thieno[2',3':4,5]pyrimido[1,2-b][1,2,4]triazepine-3-carboxylate (28). A mixture of **6** (0.33 g, 1 mmol) and ethyl ethoxymethylenecyanoacetate (0.17 g, 1 mmol) in absolute ethanol (10 mL) was heated under reflux for 8 h. After cooling, the solvent was removed under reduced pressure and the solid residue obtained was recrystallized from ethanol/dioxane (3:1) as yellow crystals, yield: 0.39 g (87%), m.p. 214–217 °C. IR: ν cm^{-1} = 3,400, 3,290 (NH_2), 3,100 (CH arom.), 2,910 (CH aliph.), 1,680 (C=O), 1,630 (C=O). $^1\text{H-NMR}$ (DMSO-d_6): δ = 1.14 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.44 (s, 3H, NCH_3), 2.67 (t, 2H, CH_2), 3.02 (t, 2H, CH_2), 3.64 (s, 2H, CH_2), 4.09 (q, 2H, J = 7.1 Hz, CH_2CH_3), 6.08 (bs, 2H, NH_2), 7.26 (m, 5H, Ar-H), 8.29 (s, 1H, CH triazepine). MS: m/z (rel. int.) 450 (M^+ , 87%), 408 (22), 407 (40), 217.91 (100), 361 (29), 337 (85), 336 (45), 294 (98), 293 (19), 267 (34), 254 (13), 253 (55), 163 (13), 122 (17), 94 (13), 77 (34.6), 64 (11), 58 (27), 50.97 (13), 52 (19), 51 (16). $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_3\text{S}$ (450.51). Calcd.: C, 58.65; H, 4.92; N, 18.55; S, 7.12. Found: C, 58.48; H, 4.95; N, 18.40; S, 6.99.

4-Amino-9-methyl-12-oxo-5-phenyl-8,9,10,11-tetrahydro-5H-pyrido[4'',3''':4',5']thieno[2',3':4,5]pyrimido[1,2-b][1,2,4]triazepin-3-carbonitrile (29). A mixture of **6** (0.33 g, 1 mmol) and ethoxymethylenemalononitrile (0.13 g, 1 mmol) in absolute ethanol (10 mL) was heated under reflux for 4 h. After cooling, the solvent was removed *in vacuo* and the solid residue was recrystallized from ethanol/dioxane (2:1) to give reddish crystals, yield: 0.33 g (82%), m.p. 214–216 °C. IR: ν cm^{-1} = 3,400, 3,300 (NH_2), 3,100 (CH arom.), 2,910 (CH aliph.), 2,210 (CN), 1,680 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.75 (s, 3H, NCH_3), 2.86 (t, 2H, CH_2), 3.12 (t, 2H, CH_2), 3.24 (s, 2H, CH_2), 5.60 (bs, 2H, NH_2), 7.35 (m, 5H, Ar-H), 8.59 (s, 1H, CH triazepine). $\text{C}_{20}\text{H}_{17}\text{N}_7\text{OS}$ (403.46). Calcd.: C, 59.54; H, 4.25; N, 24.30; S, 7.95. Found: C, 59.35; H, 4.15; N, 24.03; S, 7.88.

5-Phenyl-2,4,9-trimethyl-8,9,10,11-tetrahydro-5H-pyrido[4'',3''':4',5']thieno[2',3':4,5]pyrimido[1,2-b][1,2,4]triazepin-12-one (30). Compound **6** (0.33 g, 1 mmol) in excess acetyl acetone (6 mL) was heated under reflux for 4 h, then the reaction mixture was concentrated and left to cool. The solid precipitate was triturated with ethanol, filtered and recrystallized from isopropanol to give buff crystals, yield 0.24 g (61%), m.p. 196–198 °C. IR: ν cm^{-1} = 2,900 (CH aliph.), 1,690 (C=O). $^1\text{H-NMR}$ (CDCl_3): δ = 2.11 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.51 (s, 3H, NCH_3), 2.90 (t, 2H, CH_2), 3.21 (t, 2H,

CH₂), 3.71 (s, 2H, CH₂), 5.81 (s, 1H, CH triazepine), 7.26 (m, 5H, Ar-H). C₂₁H₂₁N₅OS (391.49)
Calcd.: C, 64.43; H, 5.41; N, 17.89; S, 8.19. Found: C, 64.25; H, 5.35; N, 17.82; S, 8.15.

4. Conclusions

New pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines were obtained using ethyl 2-amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate (**1**) as starting material. The reaction of **1** with phenylisothiocyanate in boiling ethanol afforded the thiourea derivative **5** as the key intermediate which was reacted under different cyclization reaction conditions to form different pyridothienopyrimidine derivatives. Moreover, the cyclization reactions of the intermediate **6** led to pyrido[4',3':4,5]thieno[2,3-*d*]triazolo[1,5-*a*]pyrimidine or pyrido[4'',3''':4',5']thieno[2',3':4,5]pyrimido-[1,2-*b*][1,2,4]triazepine derivatives. In continuation of our program directed toward the preparation of new bioactive compounds as anti-infectious agents [27–31], the pharmacological evaluation of these synthesized compounds is under active investigation in this area.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique, the Assiut University and the Université de la Méditerranée.

References and Notes

1. Steiner, G.; Schellhaas, K.; Lubisch, W.; Holzenkamp, U.; Starck, D.; Knopp, M.; Szabo, L.; Emling, F.; Garcia-Ladona, F.J.; Hofmann, H.-P.; Unger, L. Preparation of thienopyrimidines for use in the prophylaxis and therapy of cerebral ischemia. German Patent 19900545, 1999; [*Chem. Abstr.* **2000**, *133*, 89541].
2. Steiner, G.; Schellhaas, K.; Szabo, L.; Behl, B.; Garcia-Ladona, F.J.; Unger, L. Preparation of 5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones for the treatment of cerebral ischemia. Patent WO 2002002569, 2002; [*Chem. Abstr.* **2002**, *136*, 85831].
3. Abbott GmbH & Co. Kg, Germany. 3-Substituted 3,4-dihydrothieno[2,3-*d*]pyrimidine-4-one derivatives, production and use thereof. German Patent 10259382, 2002; [*Chem. Abstr.* **2004**, *141*, 89095].
4. Steiner, G.; Lubisch, W.; Bach, A.; Emling, F.; Wicke, K.; Teschendorf, H.-J.; Behl, B.; Kerrigan, F.; Cheetham, S. Preparation of 3-substituted pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines as 5-HT_{1A} receptor antagonists and serotonin reuptake inhibitors. German Patent 19636769, 1996; [*Chem. Abstr.* **1998**, *128*, 217381].
5. Sakr, S.M.; Kadry, A.M.; El-Sayed, A.M.M.; Al Ashmawi, M.I. Condensed thieno[2,3-*d*]pyrimidines: synthesis and biological activity. *Egypt. J. Chem.* **1992**, *34*, 147–155.
6. Eichenberger, K.; Schmidt, P.; Schweizer, E. Antimalarial 5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidins. German Patent 1937459, 1969; [*Chem. Abstr.* **1970**, *72*, 100743].
7. Kling, A.; Lange, U.E.W.; Mack, H.; Bakker, M.H.M.; Drescher, K.U.; Hornberger, W.; Hutchins, C.W.; Möller, A.; Müller, R.; Schmidt, M.; Unger, L.; Wicke, K.; Schellhaas, K.;

- Steiner, G. Synthesis and SAR of highly potent dual 5-HT_{1A} and 5-HT_{1B} antagonists as potential antidepressant drugs. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5567–5573.
- Ahmed, E.K. Synthesis of 3-substituted pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines and related fused thiazolo derivatives. *Heteroatom Chem.* **2003**, *14*, 201–207.
 - Lalezari, I.; Jabari-Sahbari, M.H. New polyheterocyclic series based on 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (1). *J. Heterocycl. Chem.* **1978**, *15*, 873–875.
 - Robba, M.; Touzot, P.; El-Kashef, H. [1]Benzothienopyrimidines. I. Study of 3*H*-benzothieno[3,2-*d*]pyrimidin-4-one. *J. Heterocycl. Chem.* **1980**, *17*, 923–928.
 - El-Kashef, H.; Rault, S.; Cugnon de Sevrécourt, M.; Touzot, P.; Robba, M. [1]Benzothienopyrimidines. II. Study of the electrophilic substitutions of [1]benzothieno[3,2-*d*]pyrimidine and [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one. *J. Heterocycl. Chem.* **1980**, *17*, 1399–1404.
 - El-Dean, A.M.K.; El-Kashef, H.S. Synthesis of some imidazopyrazolopyrimidine derivatives. *Pharmazie* **1996**, *51*, 155–158.
 - Bakhite, E.A.; Geies, A.A.; El-Kashef, H.S. Synthesis of novel pyrrolylthieno[2,3-*d*]pyrimidines and related pyrrolo[1'',2'':1',6']pyrazino[2',3':4,5]thieno[2,3-*d*]pyrimidines. *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 303–323.
 - Baraldi, P.G.; Fruttarolo, F.; Tabrizi, M.A.; Preti, D.; Romagnoli, R.; El-Kashef, H.; Moorman, A.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P.A. Design, synthesis, and biological evaluation of C9- and C2-substituted pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines as new A_{2A} and A₃ adenosine receptors antagonists. *J. Med. Chem.* **2003**, *46*, 1229–1241.
 - Baraldi, P.G.; El-Kashef, H.; Farghaly, A.; Vanelle, P.; Fruttarolo, F. Synthesis of new pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines and related heterocycles. *Tetrahedron* **2004**, *60*, 5093–5104.
 - Baraldi, P.G.; Tabrizi, M.A.; Romagnoli, R.; El-Kashef, H.; Preti, D.; Bovero, A.; Fruttarolo, F.; Gordaliza, M.; Borea, P.A. Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine template: organic and medicinal chemistry approach. *Curr. Org. Chem.* **2006**, *10*, 259–275.
 - Farghaly, A.; El-Kashef, H. Synthesis of imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines derived from indole and related heterocycles. *Monatsh. Chem.* **2006**, *137*, 1195–1202.
 - Baraldi, P.G.; Fruttarolo, F.; Tabrizi, M.A.; Romagnoli, R.; Preti, D.; Ongini, E.; El-Kashef, H.; Carrion, M.D.; Borea, P.A. Synthesis of a new series of pyrazolo[1,5-*a*]pyrimidines structurally related to zaleplon. *J. Heterocycl. Chem.* **2007**, *44*, 355–361.
 - Baraldi, P.G.; Romagnoli, R.; El-Kashef, H.; Tabrizi, M.A.; Preti, D.; Pavani, M.G.; Zanella, L.; Fruttarolo, F. Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and linked heterocycles as template for the adenosine receptor antagonism: medicinal chemistry approach and SAR considerations. *Targets Heterocycl. Syst. Chem. Prop.* **2006**, *10*, 175–196.
 - Roubaud, C.; Vanelle, P.; Maldonado, J.; Crozet, M.P. Synthesis and unimolecular radical nucleophilic substitution reactions in the 3-nitroimidazo[1,2-*a*]pyrimidine series. *Tetrahedron* **1995**, *51*, 9643–9656.
 - El-Kashef, H.S.; El-Emary, T.I.; Gasquet, M.; Timon-David, P.; Maldonado, J.; Vanelle, P. New pyrazolo[3,4-*b*]pyrazines: synthesis and biological activity. *Pharmazie* **2000**, *55*, 572–576.

22. Rathelot, P.; Azas, N.; El-Kashef, H.; Delmas, F.; Di Giorgio, C.; Timon-David, P.; Maldonado, J.; Vanelle, P. 1,3-Diphenylpyrazoles: synthesis and antiparasitic activities of azomethine derivatives. *Eur. J. Med. Chem.* **2002**, *37*, 671–679.
23. Vanelle, P.; Maldonado, J.; Madadi, N.; Gueiffier, A.; Chapat, J.-P.; Crozet, M.P. S_{RN1} reactions in imidazo[1,2-*a*]pyridine series. *Tetrahedron Lett.* **1990**, *31*, 3013–3016.
24. El-Subbagh, H. Synthesis and antitumor activity of certain thienopyridine and pyridothienopyrimidine derivatives. *S. Pharm. J.* **1997**, *5*, 23–28.
25. El-Subbagh, H. Antitumor screening of new cyclopenteno[*b*]thiophene, benzo[*b*]thiophene, thieno[2,3-*c*]pyridine and pyrido[4',3':4,5]thieno[2,3-*d*]pyrimidine analogs. *S. Pharm. J.* **1999**, *7*, 34–38.
26. El-Baih, F.E.M.; Al-Blowy, H.A.S.; Al-Hazimi, H.M. Synthesis of some thienopyrimidine derivatives. *Molecules* **2006**, *11*, 498–513.
27. Vanelle, P.; De Meo, M.P.; Maldonado, J.; Nouguier, R.; Crozet, M.P.; Laget, M.; Dumenil, G. Genotoxicity in oxazolidine derivatives—Influence of the nitro group. *Eur. J. Med. Chem.* **1990**, *25*, 241–250.
28. Vanelle, P.; Crozet, M.P.; Maldonado, J.; Barreau, M. S_{RN1} synthesis of new 5-nitroimidazoles highly active against protozoa and anaerobes. *Eur. J. Med. Chem.* **1991**, *26*, 167–178.
29. Jentzer, O.; Vanelle, P.; Crozet, M.P.; Maldonado, J.; Barreau, M. New 5-nitroimidazoles bearing lactame nucleus – Synthesis and antibacterial properties. *Eur. J. Med. Chem.* **1991**, *26*, 687–697.
30. Delmas, F.; Gasquet, M.; Timon-David, P.; Madadi, N.; Vanelle, P.; Vaille, A.; Maldonado, J. Synthesis and *in vitro* anti-protozoan activity of new 5-nitrothiophene oxime ether derivatives. *Eur. J. Med. Chem.* **1993**, *28*, 23–27.
31. Upcroft, J.A.; Dunn, L.A.; Wright, J.M.; Benakli, K.; Upcroft, P.; Vanelle, P. 5-Nitroimidazole drugs effective against metronidazole-resistant. *Trichomonas vaginalis* and *Giardia duodenalis*. *Antimicrob. Agents Chemother.* **2006**, *50*, 344–347.

Sample Availability: Available from the authors.

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