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Synthesis of 1,3-dipropyl-1*H*,3*H*-pyrazino, pyrido, pyrimido and pyrrolo[2,1-*f*]purine-2,4-diones, starting from 5,6-diamino-1,3-dipropylpyrimidine-2,4-dione **1** and 6-chloro-1,3-dipropylpyrimidine-2,4-dione **14** is described. A new synthetic approach to 1,3-dipropyl-1*H*,3*H*-pyrido(or pyrazino)[1',2'-1,2]pyrimido[4,5-*d*]pyrimidine-2,4,5-triones **19 e, f, h** has been also developed.

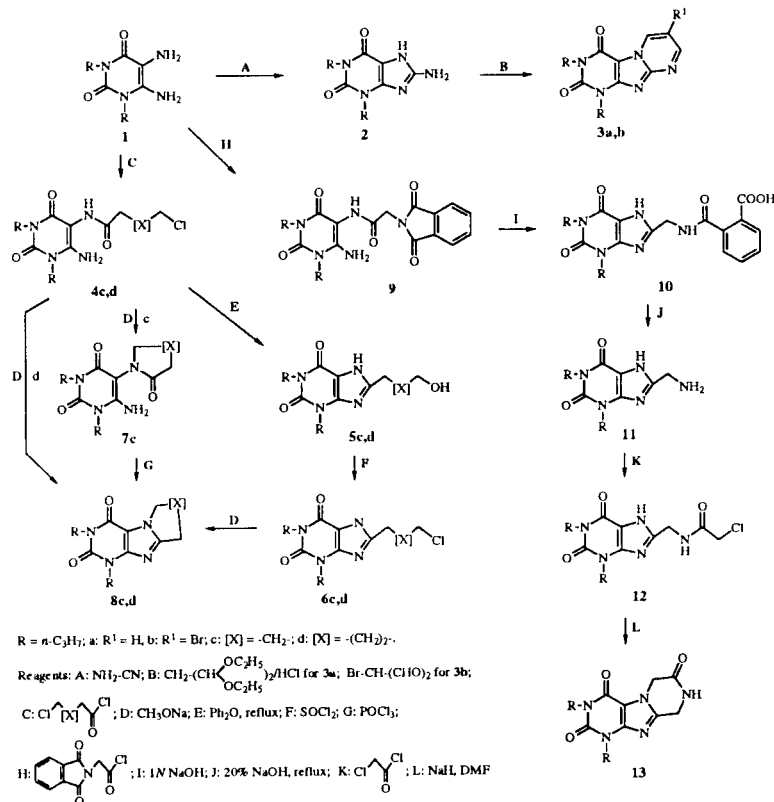
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Substituted xanthines, with theophylline as the prototype, inhibit many of the pharmacological and physiological effects of the adenosine, by acting as competitive antagonists at A₁- and A₂-adenosine receptor subtypes [1]. In recent years, considerable efforts have been dedicated to synthesize functionalized xanthine congeners, as selective antagonists for one or the other type of adenosine receptor [2,3]. Moreover, it is noteworthy that the replacement of 1,3-dimethyl groups of theophylline with *n*-propyl groups generates compounds that have been found to possess more potent antagonistic properties [4,5].

to our previous work on the preparation of new A₂-adenosine receptor antagonists [6], we describe here the synthesis of some tricyclic 1,3-dipropylxanthine derivatives, in order to study their abilities to bind to adenosine receptors.

The 5,6-diamino-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione (**1**) prepared as reported in the literature [7] was the key intermediate to the syntheses outlined in Scheme 1. Compound **1**, by fusion with an excess of cyanamide and in presence of *p*-toluenesulfonic acid at 160°, provided a 68% yield of the 8-amino derivative **2**, which by reaction with 1,1,3,3-tetraethoxypropane or bromomalonald-

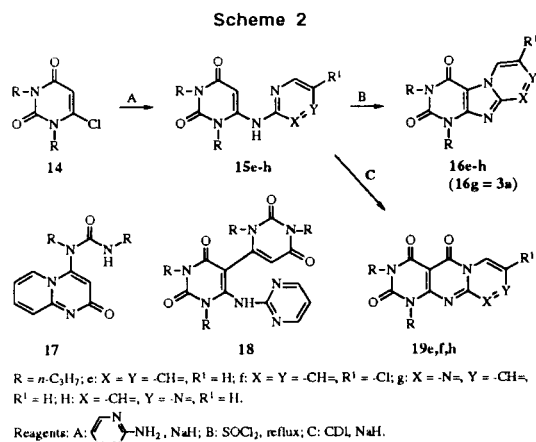
Scheme 1



As a result of this current pharmacological interest in the chemistry of xanthines, and as a further development

hyde afforded the expected 1,3-dipropyl-1*H*,3*H*-pyrimido[2,1-*f*]purine-2,4-diones **3a,b**. Compound **3a** was also

obtained according to the synthetic pathway described in Scheme 2.



Our one-step synthesis of **2** proved to be much more convenient than those reported for the 8-aminotheophylline, prepared either by reduction of the 8-nitro compound [8] or by treatment of the 8-benzylamino derivative with concentrated sulfuric acid [9].

The more nucleophilic 5-amino group of **1** was selectively acylated by using the appropriate carboxylic acid chloride, forming the 5-(acylamino)-6-aminouracils **4** and **9**.

Crude compounds **4**, in refluxing diphenyl ether, were cyclized to 8-(hydroxyalkyl)xanthines **5**. Reaction of **5** with thionyl chloride, followed by ring closure of the resulting chloro derivatives **6** with sodium methoxide gave, in good to excellent yields, the 1,3-dipropyl-7,8-dihydro-1*H*,3*H*,6*H*-pyrrolo[2,1-*f*]purine-2,4-dione **8c** and the 1,3-dipropyl-6,7,8,9-tetrahydro-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **8d**. Treatment of **4c** with sodium methoxide afforded only the pyrrolidinone **7c**, while the homologous **4d**, in the same conditions, led directly to the pyridoxanthine **8d** in 60% yield. The cyclocondensation of **7c** to **8c** was achieved in refluxing phosphorus oxychloride, in very poor yield (18%). The uv absorption spectra of compounds **8** confirmed unambiguously the assigned structures; in fact they showed two maxima at 207-208 nm and 275 nm, in full agreement with those previously observed for analogous moieties [10, 11].

The 5-(phthalimidoacetyl)-6-aminouracil **9**, was cyclized with diluted sodium hydroxide to **10**, which was then hydrolyzed, with hot 20% sodium hydroxide solution, to 8-(aminomethyl)xanthine **11**. The latter one was found to react with chloroacetyl chloride in acetic acid to give **12**; ring closure to 8,9-dihydro-1*H*,3*H*,6*H*-pyrazino[2,1-*f*]purine-2,4,7-trione **13** was then accomplished by sodium hydride in anhydrous dimethylformamide.

The 6-chloro-1,3-dipropyluracil **14**, prepared from 1,3-dipropylbarbituric acid according to the procedure previously described for the corresponding 1,3-dimethyl-derivative [12], was the starting material for the syntheses

of tricyclic compounds **16** and **19**, summarized in Scheme 2.

Compound **14** was treated in anhydrous tetrahydrofuran with sodium hydride and 2-aminopyridine, 2-amino-5-chloropyridine, 2-aminopyrimidine or 2-aminopyrazine to give compounds **15e-h**, then cyclized to **16** by simple heating in thionyl chloride. The reaction of **14** with 2-aminopyridine afforded also the 4-[*N*-propyl-*N*-(propylcarbamoyl)amino]-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**17**), in about 1:3 ratio with **15e**, while the reaction with 2-aminopyrimidine gave the 1,3-dipropyl-5-(1,3-dipropyl-1*H*,3*H*-pyrimidin-2,4-dion-6-yl)-6-(pyrimidin-2-yl)amino-1*H*,3*H*-pyrimidine-2,4-dione **18**, in about 1:1 ratio with **15g**.

The structure of **17** was supported by uv, ¹H-nmr and mass spectra. The uv spectrum was practically the same as that of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one [13]; the ¹H-nmr spectrum in dimethyl sulfoxide showed a triplet at δ 5.76 ppm, exchangeable with deuterium oxide, for the NH group, a sharp singlet at 4.75 for the methinic CH at the 3 position and an apparent quartet at 2.98 assigned to the methylene next to NH; finally, the mass spectrum showed the molecular ion at m/z 288 and a significant peak at 146, corresponding to the loss of the side-chain.

The structure of **18** was confirmed and characterized by ¹H-nmr spectrum (broad NH signal at δ 11.95 ppm, sharp singlet for the methinic proton at 5.50 and presence of four propyl groups) and mass spectrum (molecular ion at m/z 483).

Compounds **15e,f,h**, by reaction with sodium hydride and 1,1'-carbonyldiimidazole in anhydrous tetrahydrofuran were easily cyclized to the triones **19** in yields ranging from 60 to 74%; under the same conditions, compound **15g** did not afford **19g**.

Although compounds **19** are not purine derivatives, they are structurally related to the tricyclic xanthines **16** and have been prepared by a new synthetic pathway. In fact, in the chemical literature only a synthesis of **19e** analogues, obtained by a different route [14], has been reported, and there is no data about **19h** ring system.

The compounds described herein have shown negligible affinity for A₁- and A₂-adenosine receptors (IC₅₀ > 10 μ M) and very low selectivity. Further studies to establish their potential inhibitory effects on phosphodiesterase are in progress.

In the experimental, spectral data of the most significant compounds, except the chemical shifts of the propyl protons, are reported.

EXPERIMENTAL

Melting points are uncorrected. The ¹H- and ¹³C-nmr spectra were determined on a Bruker AMX 400 spectrometer; uv spec-

tra were recorded on a Perkin-Elmer 554 spectrophotometer; electron ionization mass spectra were determined on a Finnigan 5100 apparatus. Column chromatography was carried out using Merck silica gel (70-230 mesh). Purity of each compound was checked by Carlo Erba 60 F₂₅₄ silica gel plates. Sodium sulphate was used as drying agent. Elemental analyses were performed by the Microanalytical Section of our Institute.

8-Amino-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione 2.

The 5,6-diamino-1,3-dipropyluracil **1** (11.3 g, 50 mmol) [7] was finely ground in a mortar with cyanamide (4.2 g, 100 mmol) and *p*-toluenesulfonic acid monohydrate (19 g, 100 mmol). The mixture was stirred and heated in an oil bath at 150-160° for 2 hours. The mass melted at once with loss of water and ammonia, then solidified. After cooling, the residue was triturated and dissolved in 200 ml of 20% potassium hydroxide solution. The alkaline solution was shaken with charcoal, filtered and the filtrate, acidified with concentrated hydrochloric acid to pH 5-6, afforded **2** as a cream-colored solid (8.5 g, 68%) which was filtered, washed with water and methanol, then dried. An analytical sample was obtained by recrystallization from methanol, mp 290-293°; ¹H-nmr (DMSO-*d*₆): δ 11.13 (bs, 1H, deuterium oxide-exchangeable, NH), 6.44 (bs, 2H, deuterium oxide exchangeable, NH₂).

Anal. Calcd. for C₁₁H₁₇N₅O₂: C, 52.57; H, 6.82; N, 27.87. Found: C, 52.45; H, 6.89; N, 27.70.

1,3-Dipropyl-1*H*,3*H*-pyrimido[2,1-*f*]purine-2,4-dione 3a.

A solution of **2** (2.5 g, 10 mmol) and 1,1,3,3-tetraethoxypropane (3.3 g, 15 mmol) in ethanol (50 ml) containing concentrated hydrochloric acid (1 ml) was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue, made basic with 10% ammonium hydroxide, was exhaustively extracted with ethyl acetate. After removal of the solvent, the crude residue was chromatographed on a silica gel column by eluting with ethyl acetate. Recrystallization from methanol gave 1.9 g (66%) of **3a**, mp 143-145°; uv (methanol): λ max 240.8 nm (ε 33900), 262.4 nm (ε 13800), 330.4 nm (ε 7800); ¹H-nmr (DMSO-*d*₆): δ 9.24 (dd, 1H, J_{7,8} = 6.4 Hz, J_{6,8} = 1.6 Hz, H-8), 8.77 (dd, 1H, J_{6,7} = 4.4 Hz, J_{6,8} = 1.6 Hz, H-6), 7.36 (dd, 1H, J_{7,8} = 6.4 Hz, J_{6,7} = 4.4 Hz, H-7); ¹³C-nmr (DMSO-*d*₆): 154.1 (C-4), 153.9 (C-8), 151.1 (C-2), 150.6 and 149.6 (C-9a, C-10a interchangeable), 135.2 (C-6), 110.9 (C-7), 99.3 (C-4a), 44.6, 41.9, 20.8, 11.1 and 10.9 (propyl carbons).

Anal. Calcd. for C₁₄H₁₇N₅O₂: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.52; H, 6.00; N, 24.39.

7-Bromo-1,3-dipropyl-1*H*,3*H*-pyrimido[2,1-*f*]purine-2,4-dione 3b.

A solution of **2** (2.5 g, 10 mmol) and bromomalondialdehyde (2.3 g, 15 mmol) [15] in ethanol (50 ml) was refluxed for 8 hours. The solvent was removed and the residue crystallized from ethanol; mp 136-138°, yield 2.2 g, 60%; ¹H-nmr (DMSO-*d*₆): δ 9.33 (d, 1H, J_{6,8} = 2.8 Hz, H-8), 8.89 (d, 1H, J_{6,8} = 2.8 Hz, H-6); ¹³C-nmr (DMSO-*d*₆): 154.1 (C-4), 153.9 (C-8), 151.2 (C-2), 150.4 and 148.0 (C-9a and C-10a, interchangeable), 134.6 (C-6), 105.5 (C-7), 99.5 (C-4a), 44.7, 41.9, 20.7, 11.0 and 10.9 (propyl carbons).

Anal. Calcd. for C₁₄H₁₆BrN₅O₂: C, 45.92; H, 4.40; N, 19.12. Found: C, 45.81; H, 4.44; N, 18.79.

General Procedure for the *N*-5 acylation of 5,6-Diamino-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione 1.

The appropriate carboxylic acid chloride (4-chlorobutyrylchloride for **4c**, 5-chlorovaleroyl chloride for **4d** and phthalimidoacetyl chloride for **9**) (75 mmol) was added portionwise to a stirred and cooled solution of **1** (11.3 g, 50 mmol) in a mixture of acetic acid (75 ml) and a saturated sodium acetate solution (25 ml). The mixture was allowed to stir for 2 hours at room temperature. The solvent was removed *in vacuo* at temperatures not exceeding 40° and the residue, alkalized with 10% sodium hydroxide solution, was extracted with chloroform.

6-Amino-5-(4-chlorobutyryl)amino-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione **4c** (12.0 g, 73%) and 6-amino-5-(5-chlorovaleroyl)amino-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione **4d** (10.5 g, 61%) were used without further purification.

6-Amino-1,3-dipropyl-5-(phthalimidoacetyl)amino-1*H*,3*H*-pyrimidine-2,4-dione **9** (13.0 g, 63%) had mp 134-136° (methanol).

Anal. Calcd. for C₂₀H₂₃N₅O₅·H₂O: C, 55.67; H, 5.84; N, 16.23. Found: C, 55.37; H, 5.82; N, 15.97.

1,3-Dipropyl-8-(3-hydroxypropyl)-1*H*,3*H*,7*H*-purine-2,4-dione 5c. 1,3-Dipropyl-8-(4-hydroxybutyl)-1*H*,3*H*,7*H*-purine-2,4-dione 5d.

Each compound **4** (20 mmol) and diphenyl ether (100 ml) were placed in a flask fitted with a Dean-Stark trap. The mixture was heated rapidly to reflux temperature with vigorous stirring, then maintained until the starting material had disappeared (about 1 hour). The reaction mixture was allowed to cool to room temperature and *n*-hexane (200 ml) was added. The solid was collected by filtration and thoroughly washed with additional *n*-hexane.

Compound **5c**, obtained from **4c** in 80% yield, had mp 184-186° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₄H₂₂N₄O₃: C, 57.12; H, 7.53; N, 19.04. Found: C, 57.27; H, 7.59; N, 19.03.

Compound **5d**, obtained from **4d** in 69% yield, had mp 178-180° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₅H₂₄N₄O₃: C, 58.42; H, 7.85; N, 18.17. Found: C, 58.15; H, 7.98; N, 17.92.

8-(3-Chloropropyl)-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione 6c. 8-(4-Chlorobutyl)-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione 6d.

Each compound **5** (20 mmol) was heated at reflux in thionyl chloride (50 ml) for 2 hours. The excess of thionyl chloride was distilled at reduced pressure. Finely crushed ice (20 g) was added and the resulting suspension, made alkaline with diluted sodium hydroxide, was extracted with chloroform. The solvent was removed and the residue crystallized.

Compound **6c**, obtained from **5c** in 86% yield, had mp 185-187° (ethyl acetate).

Anal. Calcd. for C₁₄H₂₁ClN₄O₂·H₂O: C, 50.83; H, 7.01; N, 16.94. Found: C, 50.56; H, 7.00; N, 16.68.

Compound **6d**, obtained from **5d** in 79% yield, had mp 138-140° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₅H₂₃ClN₄O₂: C, 55.13; H, 7.09; N, 17.14. Found: C, 55.48; H, 7.17; N, 16.88.

1,3-Dipropyl-7,8-dihydro-1*H*,3*H*,6*H*-pyrrolo[2,1-*f*]purine-2,4-dione **8c**. 1,3-Dipropyl-6,7,8,9-tetrahydro-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **8d**.

Method A.

Each compound **6** (20 mmoles) was added to a stirred solution of sodium (0.5 g, 22 mmoles) in anhydrous methanol (50 ml). The mixture was heated at reflux for 2 hours. After cooling, the reaction mixture was diluted with water (200 ml) and extracted with chloroform. The solvent was evaporated, and the crude product was purified by column chromatography, by elution with ethyl acetate/*n*-hexane (1:1), then crystallized.

Compound **8c**, obtained from **6c** in 77% yield, had mp 115–117° (ethyl acetate/*n*-hexane); uv (methanol): λ max 208.0 nm (ϵ 26900), 275.2 nm (ϵ 10200); ^1H -nmr (DMSO- d_6): δ 4.12 (t, 2H, H-6), 2.85 (t, 2H, H-8), 2.55 (m, 2H, H-7); ^{13}C -nmr (DMSO- d_6): 159.2 (C-4), 153.5 (C-2), 151.4 (C-9a), 150.4 (C-8a), 104.9 (C-4a), 41.8 (C-6), 25.1 (C-8), 23.2 (C-7), 45.2, 44.2, 20.8, 11.0 and 10.9 (propyl carbons).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.90; H, 7.57; N, 20.14.

Compound **8d**, obtained from **6d** in 80% yield, had mp 104–106° (methanol); uv (methanol): λ max 208.0 nm (ϵ 26300), 275.2 nm (ϵ 10700); ^1H -nmr (DMSO- d_6): δ 4.26 (t, 2H, H-6), 2.81 (t, 2H, H-9), 1.94 and 1.88 (m, 4H, H-7 and H-8); ^{13}C -nmr (DMSO- d_6): 153.8 (C-4), 150.5 and 150.4 (C-2 and C-10a, interchangeable), 147.4 (C-9a), 105.6 (C-4a), 41.6 (C-6), 24.2 (C-9), 21.4 (C-7), 19.1 (C-8), 44.3, 43.9, 20.7, 11.0 and 10.8 (propyl carbons).

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_4\text{O}_2$: C, 62.04; H, 7.64; N, 19.30. Found: C, 62.34; H, 7.69; N, 19.49.

Method B.

Compounds **4c,d** were treated with sodium methoxide according to the above procedure.

Compound **4d** directly afforded **8d** in 60% yield.

Compound **4c** gave instead the 1,3-dipropyl-5-(pyrrolidin-2-one-1-yl)-1*H*,3*H*-pyrimidine-2,4-dione **7c** in 82% yield, mp 172–174° (ethyl acetate/*n*-hexane); ^1H -nmr (DMSO- d_6): δ 6.77 (s, 2H, deuterium oxide-exchangeable, NH_2), 3.42 and 3.25 (m, 2H, H-5'), 2.26 and 2.20 (m, 2H, H-3'), 2.04 and 1.95 (m, 2H, H-4'); ^{13}C -nmr (DMSO- d_6): 175.4 (C-2'), 158.2 (C-4), 151.6 (C-2), 150.2 (C-6), 88.3 (C-5), 41.8 (C-5'), 30.2 (C-3'), 17.7 (C-4'), 47.1, 43.7, 20.8, 11.2 and 10.7 (propyl carbons); ms: (m/z) 294 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{N}_4\text{O}_3$: C, 57.12; H, 7.53; N, 19.04. Found: C, 56.89; H, 7.68; N, 18.95.

Compound **7c** (2.9 g, 10 mmoles) was continuously added with stirring to phosphorus oxychloride (30 ml), cooling externally with an ice/water bath. The mixture was then refluxed for 2 hours and evaporated to dryness under reduced pressure. The residue was made alkaline with diluted sodium hydroxide and extracted with chloroform. Removal of the solvent gave 0.5 g (18%) of **8c**.

8-[(2-Carboxybenzamido)methyl]-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione **10**.

Compound **9** (8.3 g, 20 mmoles) was refluxed in a mixture of 1*N* sodium hydroxide (50 ml) and ethanol (20 ml) for 1 hour. The hot solution was acidified with diluted hydrochloric acid, giving the formation of a precipitate after cooling. The precipi-

tate (6.2 g, 72%) was collected and recrystallized from methanol, mp 130–132°; ^1H -nmr (DMSO- d_6): δ 13.25 (bs, 1H, COOH), 8.90 (t, 1H, $J = 5.0$ Hz, NH), 7.76 (d, 1H, aromatic), 7.61–7.50 (m, 3H, aromatic), 4.48 (d, 2H, $J = 5.0$ Hz, CH_2); ^{13}C -nmr (DMSO- d_6): 168.8 and 160.8 (phthalic CO), 153.8 (C-6), 151.2 (C-2), 150.6 (C-4), 147.7 (C-8), 137.6, 131.1, 130.8, 129.4, 129.1, 127.8 (aromatic), 106.3 (C-5), 37.3 (CH_2), 44.1, 42.0, 20.8 and 11.0 (propyl carbons).

Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_5 \cdot \text{H}_2\text{O}$: C, 55.67; H, 5.84; N, 16.23. Found: C, 55.80; H, 5.88; N, 16.26.

8-(Aminomethyl)-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione **11**.

A solution of **10** (4.3 g, 10 mmoles) in 20% sodium hydroxide (50 ml) was refluxed for 3 hours. After cooling, the pH was adjusted to 7–8 with diluted hydrochloric acid and the solid, which was formed, was collected by filtration. The crude product was chromatographed on a silica gel column, by eluting with 10% methanol/ethyl acetate, to afford 2.2 g (83%) of **11**, mp 172–174° (benzene/*n*-hexane).

Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{N}_5\text{O}_2$: C, 54.32; H, 7.22; N, 26.40. Found: C, 54.41; H, 7.17; N, 26.14.

8-[(2-Chloroacetamido)methyl]-1,3-dipropyl-1*H*,3*H*,7*H*-purine-2,4-dione **12**.

Chloroacetyl chloride (1.6 ml, 20 mmoles) was dropwise added with stirring to a cooled solution of **11** (2.6 g, 10 mmoles) in glacial acetic acid (50 ml). The mixture was stirred at room temperature for 3 hours, then poured into water (100 ml) and extracted with ethyl acetate. The organic phase was washed with 8% sodium hydroxide solution, and then with water. The solvent was evaporated and the solid residue (3.1 g, 91%), crystallized from ethyl acetate, had mp 205–207°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{ClN}_5\text{O}_3$: C, 49.20; H, 5.90; N, 20.49. Found: C, 49.50; H, 5.78; N, 20.38.

1,3-Dipropyl-8,9-dihydro-1*H*,3*H*,6*H*-pyrazino[2,1-*f*]purine-2,4,7-trione **13**.

To a stirred suspension of sodium hydride (0.75 g of 50% oil dispersion, 15 mmoles) in anhydrous dimethylformamide (30 ml), a solution of **12** (3.4 g, 10 mmoles) in dimethylformamide (20 ml) was added dropwise. After 2 hours stirring at room temperature, the reaction mixture was poured into water and the solid, which was formed, was filtered to afford 1.7 g (56%) of **13**, mp >300° (methanol). Compound **13** was insoluble in dimethylsulfoxide and in trifluoroacetic acid, so its nmr spectra couldn't be recorded; ms: (m/z) 305 (M^+).

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_5\text{O}_3 \cdot \text{H}_2\text{O}$: C, 52.00; H, 6.55; N, 21.66. Found: C, 52.23; H, 6.33; N, 21.47.

6-Chloro-1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dione **14**.

This compound was prepared from 1,3-dipropyl-1*H*,3*H*,5*H*-pyrimidine-2,4,6-trione [16], according to the synthetic pathway described for the corresponding 1,3-dimethyl derivative [12]. Compound **14** was obtained in 68% yield, mp 66–68° (ethanol/water).

Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{ClN}_2\text{O}_2$: C, 52.06; H, 6.55; N, 12.14. Found: C, 51.69; H, 6.66; N, 12.07.

General Procedure for the Reaction of **14** with 2-Aminopyridine, 2-Amino-5-chloropyridine, 2-Aminopyrimidine and 2-Aminopyrazine.

To a stirred suspension of sodium hydride (1.1 g of 50% oil dispersion, 22 mmoles) in anhydrous tetrahydrofuran (30 ml), was added, in several portions during 15-20 minutes, the appropriate amino derivative (22 mmoles). After 1 hour stirring at room temperature, compound **14** (4.6 g, 20 mmoles) was gradually added and the mixture stirred overnight at room temperature. The suspension was concentrated *in vacuo* (maximum bath temperature 40°) and, after water addition, the pH was adjusted to 6 with diluted hydrochloric acid. The mixture was extracted with ethyl acetate, the solvent evaporated and the residue chromatographed on a silica gel column. Compounds **15e** and **15f** were obtained by elution with an ethyl acetate/*n*-hexane 2:1 mixture whereas compounds **15g** and **15h** were eluted with ethyl acetate.

Compound **15e** and compound **18** eluted first, followed by **17** and **15g**, respectively.

1,3-Dipropyl-6-(pyridin-2-yl)amino-1*H*,3*H*,5*H*-pyrimidine-2,4-dione **15e**.

This compound was obtained in 34% yield, mp 132-134° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₅H₂₀N₄O₂: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.76; H, 7.22; N, 19.43.

6-(5-Chloropyridin-2-yl)amino-1,3-dipropyl-1*H*,3*H*,5*H*-pyrimidine-2,4-dione **15f**.

This compound was obtained in 62% yield, mp 168-170° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₅H₁₉ClN₄O₂: C, 55.81; H, 5.93; N, 17.36. Found: C, 55.76; H, 6.05; N, 17.22.

1,3-Dipropyl-6-(pyrimidin-2-yl)amino-1*H*,3*H*,5*H*-pyrimidine-2,4-dione **15g**.

This compound was obtained in 29% yield, mp 120-122° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₄H₁₉N₅O₂: C, 58.12; H, 6.62; N, 24.20. Found: C, 58.05; H, 6.81; N, 23.95.

1,3-Dipropyl-6-(pyrazin-2-yl)amino-1*H*,3*H*,5*H*-pyrimidine-2,4-dione **15h**.

This compound was obtained in 70% yield, mp 151-153° (ethyl acetate/*n*-hexane).

Anal. Calcd. for C₁₄H₁₉N₅O₂: C, 58.12; H, 6.62; N, 24.20. Found: C, 58.41; H, 6.79; N, 23.99.

4-[*N*-Propyl-*N*-(propylcarbamoyl)amino]-2*H*-pyrido[1,2-*a*]pyrimidine **17**.

This compound was obtained in 12% yield, mp 129-131° (diethyl ether); uv (methanol): λ max 202.4 nm (ε 26900), 269.6 nm (ε 22400); ¹H-nmr (DMSO-*d*₆): δ 8.61 (dd, 1H, J_{6,7} = 4.6 Hz, J_{6,8} = 1.2 Hz, H-6), 8.01 (m, 1H, J_{8,9} = 8.2 Hz, J_{7,8} = 7.4 Hz, J_{6,8} = 1.2 Hz, H-8), 7.55 (m, 1H, J_{7,8} = 7.4 Hz, J_{6,7} = 4.6 Hz, J_{7,9} = 0.4 Hz, H-7), 7.51 (dd, 1H, J_{8,9} = 8.2 Hz, J_{7,9} = 0.4 Hz, H-9), 5.76 (t, 1H, deuterium oxide-exchangeable, NH), 4.75 (s, 1H, H-3); ¹³C-nmr (DMSO-*d*₆): 161.7 (N-CO-N), 152.1 (C-2), 151.0 (C-9a), 149.9 (C-6), 147.9 (C-4), 139.4 (C-8), 125.4 (C-7), 124.8 (C-9), 73.1 (C-3), 43.6, 41.1, 20.8, 11.1 and 11.0 (propyl carbons); ms: (m/z) 288 (M⁺), 246, 218, 204, 175, 146, 121, 78.

Anal. Calcd. for C₁₅H₂₀N₄O₂: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.39; H, 7.20; N, 19.31.

1,3-Dipropyl-5-(1,3-dipropyl-1*H*,3*H*-pyrimidine-2,4-dion-6-yl)-6-(pyrimidin-2-yl)amino-1*H*,3*H*-pyrimidine-2,4-dione **18**.

This compound was obtained in 37% yield, mp 214-217° (ethyl acetate); ¹H-nmr (DMSO-*d*₆): δ 11.95 (s, 1H, deuterium oxide-exchangeable, NH), 8.50 (d, 2H, J = 5.0 Hz, pyrimidine H-4 and H-6), 6.93 (t, 1H, J = 5.0 Hz, pyrimidine H-5), 5.50 (s, 1H, methinic proton); ¹³C-nmr (DMSO-*d*₆): 162.0 (C-4), 161.2 (C-4'), 160.0 (pyrimidine C-2), 158.1 (pyrimidine C-4 and C-6), 151.2 (C-6), 150.6 (C-2, C-2'), 146.7 (C-6'), 113.7 (pyrimidine C-5), 103.0 (C-5'), 102.7 (C-5), 50.7, 48.4, 41.7, 20.6, 20.2, 11.1 and 10.9 (propyl carbons); ms: (m/z) 483 (M⁺).

Anal. Calcd. for C₂₄H₃₃N₇O₄: C, 59.61; H, 6.88; N, 20.28. Found: C 59.90; H, 7.17; N, 20.38.

General Procedure for the Preparation of Tricyclic Xanthines **16e-f**.

Each compound **15** (10 mmoles) was refluxed in thionyl chloride (30 ml) for 2 hours. Excess of thionyl chloride was removed *in vacuo* and the residue was treated with crushed ice and water and extracted with ethyl acetate. The solvent was evaporated and the residue crystallized.

Compound **16g** was obtained from **15g** in 51% yield and was identical to **3a**.

1,3-Dipropyl-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **16e**.

This compound was obtained from **15e** in 74% yield, mp 112-114° (ethyl acetate/*n*-hexane); uv (methanol): λ max 240.8 nm (ε 37200), 256.8 nm (ε 16600 nm), 300.0 nm (ε 12600); ¹H-nmr (DMSO-*d*₆): δ 8.93 (dd, 1H, J_{6,7} = 6.4 Hz, J_{6,8} = 1.2 Hz, H-6), 7.74 (dd, 1H, J_{8,9} = 8.8 Hz, J_{7,9} = 1.2 Hz, H-9), 7.65 (m, 1H, J_{7,8} = 8.0 Hz, J_{8,9} = 8.8 Hz, J_{6,8} = 1.2 Hz, H-8), 7.23 (m, 1H, J_{7,8} = 8.0 Hz, J_{6,7} = 6.4 Hz, J_{7,9} = 1.2 Hz, H-7); ¹³C-nmr (DMSO-*d*₆): 154.1 (C-4), 150.7 (C-2), 150.1 and 147.0 (C-9a and C-10a, interchangeable), 130.4 (C-6), 127.0 (C-8), 115.9 (C-9), 114.4 (C-7), 100.8 (C-4a), 44.4, 41.8, 20.8, 11.1 and 10.9 (propyl carbons); ms (m/z): 286 (M⁺).

Anal. Calcd. for C₁₅H₁₈N₄O₂: C, 62.92; H, 6.34; N, 19.57. Found: C, 62.71; H, 6.41; N, 19.56.

7-Chloro-1,3-dipropyl-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **16f**.

This compound was obtained from **15f** in 70% yield, mp 154-156° (methanol).

Anal. Calcd. for C₁₅H₁₇ClN₄O₂: C, 56.16; H, 5.34; N, 17.47. Found: C, 56.36; H, 5.09; N, 17.31.

1,3-Dipropyl-1*H*,3*H*-pyrazino[2,1-*f*]purine-2,4-dione **16h**.

This compound was obtained from **15h** in 58% yield, mp 117-119° (ethyl acetate); ¹H-nmr (DMSO-*d*₆): δ 9.24 (d, 1H, J_{7,9} = 1.2 Hz, H-9), 8.88 (dd, 1H, J_{6,7} = 4.0 Hz, J_{7,9} = 1.2 Hz, H-7), 8.25 (d, 1H, J_{6,7} = 4.0 Hz, H-6); ¹³C-nmr (DMSO-*d*₆): 154.4 (C-4), 150.6 (C-2), 149.8 (C-10a), 141.4 (C-9), 140.7 (C-9a), 131.9 (C-7), 119.7 (C-6), 101.9 (C-4a), 44.6, 42.0, 20.7, 11.1 and 10.9 (propyl carbons).

Anal. Calcd. for C₁₄H₁₇N₅O₂: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.61; H, 5.75; N, 24.33.

General Procedure for the Preparation of Compounds **19 e,f,h**.

Each compound **15** (10 mmoles) was added under stirring to a suspension of sodium hydride (0.6 g of 50% oil dispersion, 12 mmoles) in anhydrous tetrahydrofuran (30 ml). After 1 hour,

1,1'-carbonyldiimidazole (1.9 g, 12 mmol) was added and the mixture was stirred at room temperature for 2 hours. After evaporation of the solvent, water was added to the residue and the solid was collected by filtration. The crude products were purified by chromatography on a silica gel column by eluting with ethyl acetate.

1,3-Dipropyl-1*H*,3*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidine-2,4,5-trione **19e**.

This compound was obtained from **15e** in 66% yield, mp 201–203° (ethyl acetate); uv (methanol): λ max 216.0 nm (ϵ 20000), 251.2 nm (ϵ 31600), 276.0 nm (ϵ 13800), 347.2 nm (ϵ 14100), 361.6 nm (ϵ 12000); ^1H -nmr (DMSO- d_6): δ 8.96 (d, 1H, $J_{7,8}$ = 6.8 Hz, H-7), 8.11 (dd, 1H, $J_{8,9}$ = 6.8 Hz, $J_{9,10}$ = 8.8 Hz, H-9), 7.62 (d, 1H, $J_{9,10}$ = 8.8 Hz, H-10), 7.38 (t, 1H, $J_{7,8}$ = 6.8 Hz, $J_{8,9}$ = 6.8 Hz, H-8); ^{13}C -nmr (DMSO- d_6): 158.4 (C-4), 155.3 (C-5), 153.8 (C-2), 151.5 (C-11a), 150.5 (C-10a), 141.4 (C-7), 128.4 (C-9), 125.1 (C-10), 116.4 (C-8), 89.4 (C-4a), 43.5, 41.8, 20.6, 11.1 and 11.0 (propyl carbons); ms: (m/z) 314 (M^+).

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 61.34; H, 5.74; N, 17.72.

8-Chloro-1,3-dipropyl-1*H*,3*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidine-2,4,5-trione **19f**.

This compound was obtained from **15f** in 74% yield, mp 216–219° (methanol).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{ClN}_4\text{O}_3$: C, 55.10; H, 4.91; N, 16.06. Found: C, 55.14; H, 5.10; N, 15.90.

1,3-Dipropyl-1*H*,3*H*-pyrazino[1',2':1,2]pyrimido[4,5-*d*]pyrimidine-2,4,5-trione **19h**.

This compound was obtained from **15h** in 60% yield, mp 175–177° (methanol/diethyl ether); ^1H -nmr (DMSO- d_6): δ 9.12 (s, 1H, H-10), 8.70 (d, 1H, $J_{7,8}$ = 4.4 Hz, H-8), 8.31 (d, 1H, $J_{7,8}$ = 4.4 Hz, H-7); ^{13}C -nmr (DMSO- d_6): 158.0 (C-4), 156.4 (C-5), 152.8 (C-10a), 152.2 (C-10), 150.2 (C-2), 144.8 (C-11a), 132.6 (C-8), 118.1 (C-7), 91.9 (C-4a), 43.9, 42.1, 20.9, 20.4, 11.1 and 11.0 (propyl carbons).

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_3$: C, 57.13; H, 5.43; N, 22.21. Found: C, 56.87; H, 5.41; N, 21.94.

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REFERENCES AND NOTES

- [1] K. A. Jacobson, P. J. M. van Galen and M. Williams, *J. Med. Chem.*, **35**, 407 (1992) and references therein.
- [2] M. T. Shamim, D. Ukena, W. L. Padgett, O. Hong and J. W. Daly, *J. Med. Chem.*, **31**, 613 (1988).
- [3] J. Shimada, F. Suzuki, H. Nonaka, A. Ishii and S. Ichikawa, *J. Med. Chem.*, **35**, 2342 (1992).
- [4] R. F. Bruns, J. W. Daly and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.*, **80**, 2077 (1983).
- [5] E. A. Martinson, R. A. Johnson and J. N. Wells, *Mol. Pharmacol.*, **31**, 247 (1987).
- [6] F. Gatta, M. R. Del Giudice, A. Borioni, P. Borea, S. Dionisotti and E. Ongini, *Eur. J. Med. Chem.*, **28**, 569 (1993).
- [7] J. N. Wells, J. E. Garst and G. L. Kramer, *J. Med. Chem.*, **24**, 954 (1981).
- [8] J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **82**, 3773 (1960).
- [9] M. Pawlowski and M. Gorczyca, *Pol. J. Chem.*, **55**, 837 (1981).
- [10] A. Lefebvre, R. Rips, A. Martine and C. Lespagnol, *J. Heterocyclic Chem.*, **22**, 105 (1985).
- [11] G. L. Regnier, C. G. Guillonnet, J. L. Duhault, F. P. Tisserand, G. Saint-Romas and S. M. Holstorp, *Eur. J. Med. Chem.*, **22**, 243 (1987).
- [12] W. Pfeleiderer and K.-H. Schündehütte, *Liebigs Ann. Chem.*, **612**, 158 (1958).
- [13] R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
- [14] B. Kokel, J. Guillaumel and R. Royer, *J. Heterocyclic Chem.*, **20**, 575 (1983).
- [15] S. Trofimenko, *J. Org. Chem.*, **28**, 3243 (1963).
- [16] A. Kreutzberger, E. Kreutzberger, S. Leyke-Roeling, *Arch. Pharm.*, **312**, 115 (1979).