Synthesis of Pyrido[2,1-*b*]- and Thiazolo[2,3-*b*]purines

Maria Rosaria Del Giudice*, Anna Borioni, Carlo Mustazza and Franco Gatta

Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanita,
Viale Regina Elena 299, 00161-Roma, Italy

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Some pyrido[2,1-*b*]- and thiazolo[2,3-*b*]purines, tricyclic compounds structurally related to [1,2,4]triazolo[1,5-*c*]quinazolines **1** have been synthesized with a view to study their possible adenosine and benzodiazepine receptors affinity.

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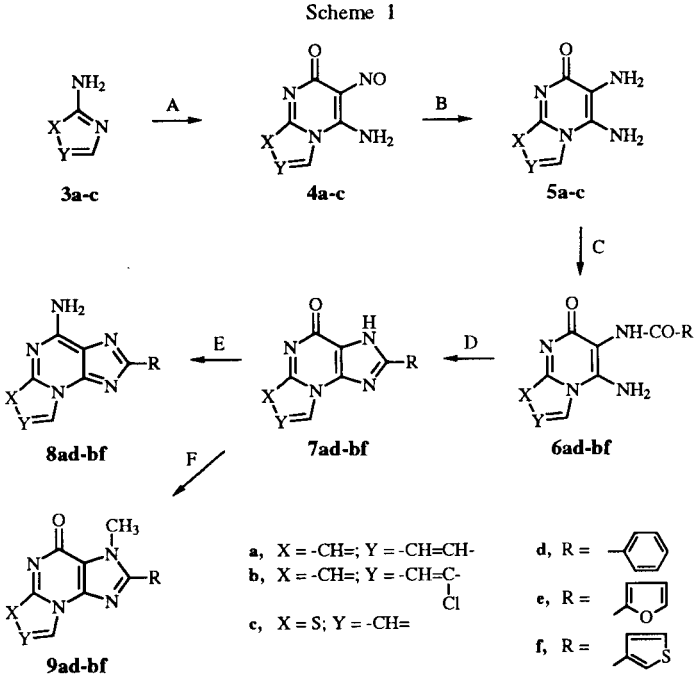
In recent years considerable effort has been dedicated to the development of non-xanthine and non-benzodiazepine classes of compounds with antagonistic properties at either adenosine or benzodiazepine receptors. Particularly, the discovery that some compounds containing the triazoloquinazoline ring were found to possess remarkable adenosine and benzodiazepine receptor affinity, the most potent ligands being respectively the 5-amino-9-chloro-2-(2-furyl)[1,2,4]triazolo[1,5-*c*]quinazoline **1a** (CGS 15943) [1] and 9-chloro-2-(2 fluorophenyl)[1,2,4]triazolo[1,5-*c*]-quinazolin-5(6*H*)-one **1b** [2] (Figure 1), led us to investigate new classes of tricyclic compounds bearing structures isosteric or related to compounds **1**, in order to study their interactions with adenosine and benzodiazepine receptors.

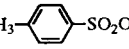
Recently we have reported a series of **1a** and **1b** analogues, in which the benzene ring was replaced by a heterocycle such as pyrazole and imidazole [3] or pyridine, pyrazine and pyrimidine [4].

In this paper we describe the synthesis of some pyrido-[2,1-*b*]-, and thiazolo[2,3-*b*]purines **2** shown in Figure 1.

2-Aminopyridine **3a**, 2-amino-5-chloropyridine **3b** and 2-aminothiazole **3c** served as starting materials for the syntheses outlined in Scheme 1. Compounds **3** were refluxed in anhydrous ethanol with the sodium salt of ethyl oximinocyanoacetate [5] to give, after acidification with diluted hydrochloric acid to *p*H 6, the isonitroso derivatives **4** in good to satisfactory yields. The oximino group was easily reduced by sodium dithionite in 30% aqueous ammonium hydroxide at 70-80°, to provide the key intermediate diamines **5**, in good yields. Compounds **5** were acylated to **6** by the appropriate carboxylic acid chloride in a different way: the acylation of **5a,b**, compounds showing a very poor solubility in pyridine, was accomplished in acetic acid/saturated sodium acetate solution, while acylation of **5c** was easily carried out in pyridine. Also the resulting acylamino derivatives **6**, were cyclized to the [*b*]-fused purino derivatives **7** by different methods: the pyrido-[2,1-*b*]purin-10(1*H*)-ones **7ad-bf** were prepared by refluxing in a solution of sodium methoxide in methanol, while the thiazolo[2,3-*b*]purin-9(1*H*)-ones **7cd-cf** were obtained only by heating in polyphosphoric acid at 100-110°.

Scheme 1



Reagents: A: NC-C (=NOH)-COOEt/C_2H_5ONa; B: $Na_2S_2O_4$/30% NH_4OH, 70-80°; C: R-COCl; D: CH_3ONa/MeOH reflux or PPA 110°; E: 1) $POCl_3$, reflux; 2) CH_3OH/NH_3; F: CH_3-  -SO_2OCH_3/NaH, DMF.

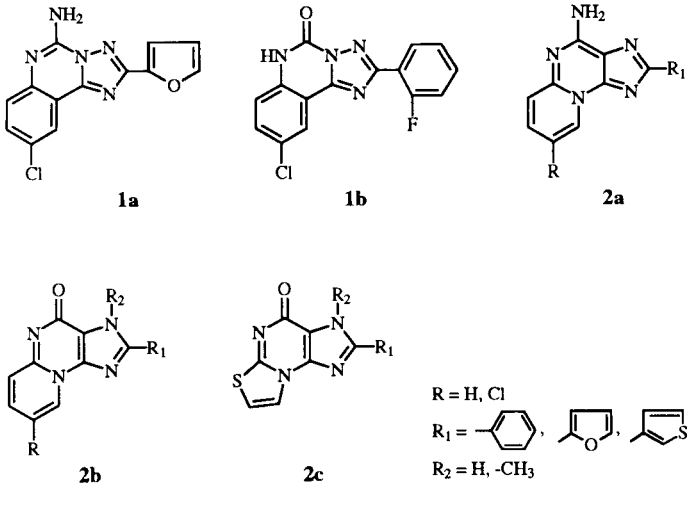


Figure 1

Compounds **7ad-bf** by reaction with phosphorus oxychloride followed by substitution of crude chloro derivatives with methanolic ammonia, afforded the expected 10-aminopyrido[2,1-*b*]purines **8ad-bf**. Attempts to prepare the corresponding 9-aminothiazolo[2,3-*b*]purines **8cd-cf** were unsuccessful owing to the high instability of the 9-chloro intermediates. Finally, methylation of **7** with methyl 4-toluenesulfonate/sodium hydride in dimethylformamide proceeded selectively at N-1 to give the *N*-methylated compounds **9** as sole products. The *N*-methylation in the compounds **9**, was confirmed by ir, ^{13}C-nmr and mass spectral data: in fact ir spectra showed the stretching band of the amide linkage at about 1620 cm^{-1}; ^{13}C-nmr spectra exhibited the chemical shift of the methyl group at about 35 ppm (δ) and the mass spectral fragmentation clearly showed the peak corresponding to the loss of the carbonyl group (M$^+$-28).

Binding studies for compounds **8** and **9** are in progress either on rat whole brain and striatum or on membrane preparations from rabbit brain cortex, in order to evaluate the interactions with A_1 and A_2 adenosine and benzodiazepine receptors. Further functional assays and *in vivo* experiments will be performed and the related biochemical and pharmacological results will be published elsewhere, if interesting.

In the Experimental ir, ^{1}H-nmr, ^{13}C-nmr and mass spectral data of the most significant compounds are reported.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were determined on a Perkin Elmer 580 spectrophotometer; ^{1}H and ^{13}C-nmr spectra were recorded on a Varian Gemini 200 MHz instrument; electron ionization mass spectra were determined at 70 eV on a HP 59980 B spectrometer. The purity of each compound was checked on silica gel Carlo Erba 60 F_{254} plates and spots were located by uv light. Sodium sulfate was used to dry organic solutions.

General Procedure for the Preparation of the Isonitroso Derivatives **4**.

Ethyl oxyminocyanoacetate [5] (28.4 g, 0.2 mole) and the appropriate amine **3** (0.2 mole) were added to a stirred solution of sodium ethoxide (from sodium, 13.8 g, 0.6 mole) in anhydrous ethanol (400 ml), at 5-10°. The mixture was refluxed for 3 hours and after cooling the obtained sodium salt was filtered; the solid was taken up in water (100 ml) and the resulting solution was acidified to *p*H 6 with diluted hydrochloric acid. The isonitroso derivatives **4** which had separated were collected by filtration, washed with water and crystallized.

4-Imino-3-isonitrosopyrido[1,2-*a*]pyrimidin-2-one **4a**.

This compound was obtained from **3a** in 52% yield, mp 262-265° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 14.50 and 10.24 (bs, 2H, NH and NOH), 8.36 (d, 1H, H-6), 8.00 (d, 1H, H-9), 7.86 (t, 1H, H-8), 7.20 (t, 1H, H-7).

Anal. Calcd. for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.29; H, 3.44; N, 29.20.

4-Imino-7-chloro-3-isonitrosopyrido[1,2-*a*]pyrimidin-2-one **4b**.

This compound was obtained from **3b** in 51% yield, mp 255-257° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 14.80 and 10.53 (bs, 2H, NH and NOH), 8.43 (s, 1H, H-6), 7.99 (m, 2H, H-8 and H-9).

Anal. Calcd. for $C_8H_5ClN_4O_2$: C, 42.78; H, 2.24; N, 24.94. Found: C, 42.52; H, 2.22; N, 24.78.

5-Imino-6-isonitrosothiazolo[3,2-*a*]pyrimidin-7-one **4c**.

This compound was obtained from **3c** in 92% yield, mp 274-276° (methanol); ^{1}H-nmr (DMSO-d_6): δ 13.60 (bs, 2H, NH and NOH), 7.53 (d, 1H, H-3), 7.26 (d, 1H, H-2).

Anal. Calcd. for $C_6H_4N_4O_2S$: C, 36.73; H, 2.06; N, 28.56. Found: C, 36.55; H, 2.12; N, 28.27.

General Procedure for the Preparation of Diamino Derivatives **5**.

To a stirred solution of each compound **4** (20 mmoles) in aqueous 30% ammonium hydroxide (250 ml) heated at 70° a solution of sodium dithionite (10.5 g, 60 mmoles) in water (200 ml) was added dropwise at such a rate as to maintaining the internal temperature at 70-80°. Heating and stirring were continued for 30 minutes; the mixture was then concentrated *in vacuo* to 150 ml and the slow-forming precipitate was filtered off after an hour to give compounds **5** which were used without further purification. For analytical purposes they were recrystallized from the appropriate solvent.

3,4-Diaminopyrido[1,2-*a*]pyrimidin-2-one **5a**.

This compound was obtained from **4a** in 90% yield, mp 235-237° (water); ^{1}H-nmr (DMSO-d_6): δ 8.25 (d, 1H, H-6), 7.49 (t, 1H, H-8), 7.18 (d, 1H, H-9), 7.03 (t, 1H, H-7), 5.78 (s, 2H, 4-NH_2), 4.75 (bs, 2H, 3-NH_2); ms: (m/z) 176 (M$^+$).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.62; H, 4.80; N, 31.52.

7-Chloro-3,4-diaminopyrido[1,2-*a*]pyrimidin-2-one **5b**.

This compound was obtained from **4b** in 66% yield, mp 250-252° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 8.40 (d, 1H, H-6), 7.56 (d, 1H, H-8), 7.17 (d, 1H, H-9), 5.88 (s, 2H, 4-NH_2), 4.89 (bs, 2H, 3-NH_2); ms: (m/z) 210 (M$^+$).

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; N, 26.60. Found: C, 45.77; H, 3.66; N, 26.42.

5,6-Diaminothiazolo[3,2-*a*]pyrimidin-7-one **5c**.

This compound was obtained from **4c** in 89% yield, mp 245-248° dec (water); ^{1}H-nmr (DMSO-d_6): δ 7.81 (d, 1H, H-3), 7.33 (d, 1H, H-2), 6.07 (bs, 2H, 5-NH_2), 4.00 (bs, 2H, 6-NH_2); ms: (m/z) 182 (M$^+$).

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75. Found: C, 39.82: H, 3.50; N, 30.47.

General Procedure for the Preparation of 3-Acylamino-4-aminopyrido[1,2-*a*]pyrimidin-2-ones **6ad-bf.**

Diamino compound **5a** (1.8 g, 10 mmoles) or **5b** (2.1 g, 10 mmoles) was suspended in a solution of glacial acetic acid (30 ml) and saturated aqueous sodium acetate (10 ml). The reaction mixture was stirred at room temperature for 15-20 minutes, after which time almost complete solution occurred. The appropriate acyl chloride (10 mmoles) in anhydrous dioxane (2 ml) was then added dropwise at 0°. The reaction mixture was stirred at room

temperature for a further 4 hours, then poured into water (50 ml) and carefully neutralized with diluted ammonium hydroxide. The solid which had formed was collected by filtration, washed with methanol and crystallized.

4-Amino-3-benzoylaminopyrido[1,2-*a*]pyrimidin-2-one **6ad**.

This compound was obtained from **5a** in 70% yield, mp 255-257° (water); ^{1}H-nmr (DMSO-d_6): δ 9.30 (bs, 1H, NH), 8.30 (d, 1H, H-6), 8.01 (m, 2H, phenyl protons), 7.71-7.48 (m, 4H, H-8 and phenyl protons), 7.15 (d, 1H, H-9), 6.98 (t, 1H, H-7), 6.74 (bs, 2H, NH_2); ms: (m/z) 280 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.32; H, 4.57; N, 19.79.

4-Amino-3-(2-furoylamino)pyrido[1,2-*a*]pyrimidin-2-one **6ae**.

This compound was obtained from **5a** in 68% yield, mp 268-270° (water); ^{1}H-nmr (DMSO-d_6): δ 9.10 (bs, 1H, NH), 8.27 (d, 1H, H-6), 7.90 (d, 1H, H-5'), 7.61 (t, 1H, H-8), 7.30 (d, 1H, H-3'), 7.14 (d, 1H, H-9), 6.99 (t, 1H, H-7), 6.79 (bs, 2H, NH_2), 6.67 (dd, 1H, H-4'); ms: (m/z) 270 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73. Found: C, 57.88; H, 3.99; N, 20.54.

4-Amino-3-(3-thenoylamino)pyrido[1,2-*a*]pyrimidin-2-one **6af**.

This compound was obtained from **5a** in 70% yield, mp 276-278° (water); ^{1}H-nmr (DMSO-d_6): δ 9.16 (bs, 1H, NH), 8.33 (s, 1H, H-2'), 8.28 (d, 1H, H-6), 7.65-7.57 (m, 3H, H-8, H-4' and H-5'), 7.14 (d, 1H, H-9), 6.97 (t, 1H, H-7), 6.71 (bs, 2H, NH_2); ms: (m/z) 286 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_4O_2S$: C, 54.54; H, 3.52; N, 19.57. Found: C, 54.70; H, 3.59; N, 19.67.

4-Amino-3-benzoylamino-7-chloropyrido[1,2-*a*]pyrimidin-2-one **6bd**.

This compound was obtained from **5b** in 60% yield, mp 239-241° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.32 (bs, 1H, NH), 8.52 (s, 1H, H-6), 8.00 (m, 2H, phenyl protons), 7.68 (d, 1H, H-8), 7.52 (m, 3H, phenyl protons), 7.17 (d, 1H, H-9), 6.84 (bs, 2H, NH_2); ms: (m/z) 314 (M^+).

Anal. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.42; H, 3.59; N, 17.49.

4-Amino-7-chloro-3-(2-furoylamino)pyrido[1,2-*a*]pyrimidin-2-one **6be**.

This compound was obtained from **5b** in 49% yield, mp 198-200° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.13 (bs, 1H, NH), 8.50 (d, 1H, H-6), 7.89 (d, 1H, H-5'), 7.68 (dd, 1H, H-8), 7.29 (d, 1H, H-3'), 7.17 (d, 1H, H-9), 6.90 (bs, 1H, NH_2), 6.67 (dd, 1H, H-4'); ms: (m/z) 304 (M^+).

Anal. Calcd. for $C_{13}H_9ClN_4O_3$: C, 51.24; H, 2.98; N, 18.39. Found: C, 51.33; H, 3.14; N, 18.12.

4-Amino-7-chloro-3-(3-thenoylamino)pyrido[1,2-*a*]pyrimidin-2-one **6bf**.

This compound was obtained from **5b** in 55% yield, mp 218-220° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.18 (bs, 1H, NH), 8.51 (d, 1H, H-6), 8.33 (dd, 1H, H-2'), 7.68 (dd, 1H, H-8), 7.62 (m, 2H, H-4' and H-5'), 7.17 (d, 1H, H-9), 6.81 (s, 2H, NH_2); ms: (m/z) 320 (M^+).

Anal. Calcd. for $C_{13}H_9ClN_4O_2S$: C, 48.68; H, 2.83; N, 17.47. Found: C, 48.79; H, 2.99; N, 17.29.

General Procedure for the Preparation of 6-Acylamino-5-aminothiazolo[3,2-*a*]pyrimidin-7-ones **6cd-cf**.

To a stirred suspension of **5c** (3.6 g, 20 mmoles) in anhydrous pyridine (25 ml), a solution of the appropriate acyl chloride (22 mmoles) in anhydrous dioxane (10 ml) was added dropwise at 0-5°. The mixture was allowed to react overnight at room temperature. The solid which had formed was filtered, washed with water and methanol, then crystallized.

5-Amino-6-benzoylaminothiazolo[3,2-*a*]pyrimidin-7-one **6cd**.

This compound was obtained from **5c** in 80% yield, mp 287-289° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.14 (s, 1H, NH), 8.00 (m, 3H, H-3 and phenyl protons), 7.51 (m, 3H, phenyl protons), 7.35 (d, 1H, H-2), 6.97 (s, 2H, NH_2); ms: (m/z) 286 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_4O_2S$: C, 54.54; H, 3.52; N, 19.57. Found: C, 54.63; H, 3.50; N, 19.51.

5-Amino-6-(2-furoylamino)thiazolo[3,2-*a*]pyrimidin-7-one **6ce**.

This compound was obtained from **5c** in 79% yield, mp 275-277° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.94 (s, 1H, NH), 7.89 (d, 1H, H-3), 7.87 (s, 1H, H-5'), 7.34 (d, 1H, H-2), 7.27 (dd, 1H, H-3'), 6.91 (s, 2H, NH_2), 6.65 (dd, 1H, H-4'); ms: (m/z) 276 (M^+).

Anal. Calcd. for $C_{11}H_8N_4O_3S \cdot H_2O$: C, 44.89; H, 3.43; N, 19.04. Found: C, 44.93; H, 3.23; N, 18.87.

5-Amino-6-(3-thenoylamino)thiazolo[3,2-*a*]pyrimidin-7-one **6cf**.

This compound was obtained from **5c** in 61% yield, mp 283-285° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 8.99 (s, 1H, NH), 8.30 (dd, 1H, H-2'), 7.90 (d, 1H, H-3), 7.61 (m, 2H, H-4' and H-5'), 7.34 (d, 1H, H-2), 6.85 (bs, 2H, NH_2); ms: (m/z) 292 (M^+).

Anal. Calcd. for $C_{11}H_8N_4O_2S_2$: C, 45.19; H, 2.76; N, 19.17. Found: C, 44.93; H, 3.03; N, 18.87.

General Procedure for the Preparation of 2-Substituted pyrido[2,1-*b*]purin-10(1*H*)-ones **7ad-bf.**

A suspension of each compound **6** (10 mmoles) in a solution of sodium (0.7 g, 30 mmoles) in methanol (50 ml) was refluxed for 2 hours. After cooling to room temperature, water (150 ml) was added and the solution was brought to *p*H 6 with diluted hydrochloric acid. The precipitate was collected by filtration, washed with water and crystallized.

2-Phenylpyrido[2,1-*b*]purin-10(1*H*)-one **7ad**.

This compound was obtained from **6ad** in 64% yield, mp >300°(dimethylformamide/methanol); ir (nujol): ν CO 1709 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 9.28 (d, 1H, H-5), 8.37 (t, 1H, H-7), 8.26 (m, 2H, phenyl protons), 8.06 (d, 1H, H-8), 7.73 (t, 1H, H-6), 7.57 (m, 3H, phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 153.2 (C-10), 151.4 (C-8a), 145.3 (C-3a), 141.1 (C-2), 131.3 (C-5), 129.9 (C-1'), 129.7 (C-7), 129.3 (C-3' and C-5'), 127.9 (C-4'), 127.0 (C-2' and C-6'), 118.4 (C-10a), 117.8 (C-6), 116.7 (C-8); ms: (m/z) 262 (M^+).

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.79; H, 3.99; N, 21.20.

2-(2-Furyl)pyrido[2,1-*b*]purin-10(1*H*)-one **7ae**.

This compound was obtained from **6ae** in 52% yield, mp >300° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 8.83 (d, 1H, H-5), 7.91 (d, 1H, H-5'), 7.81 (t, 1H, H-7), 7.39 (d,

1H, H-8), 7.29 (d, 1H, H-3'), 7.18 (t, 1H, H-6), 6.71 (dd, 1H, H-4'); ms: (m/z) 252 (M^+).

Anal. Calcd. for $C_{13}H_8N_4O_2$: C, 61.90; H, 3.20; N, 22.21. Found: C, 61.99; H, 3.42; N, 22.00.

2-(3-Thienyl)pyrido[2,1-*b*]purin-10(1*H*)-one **7af**.

This compound was obtained from **6af** in 68% yield, mp >300° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 8.73 (d, 1H, H-5), 7.62 (d, 1H, H-2'), 7.52 (t, 1H, H-7), 7.22 (d, 1H, H-8), 6.95 (t, 1H, H-6), 6.85 (d, 1H, H-4'), 6.53 (dd, 1H, H-5'); ms: (m/z) 268 (M^+).

Anal. Calcd. for $C_{13}H_8N_4OS$: C, 58.20; H, 3.01; N, 20.88. Found: C, 58.00; H, 2.92; N, 20.67.

6-Chloro-2-phenylpyrido[2,1-*b*]purin-10(1*H*)-one **7bd**.

This compound was obtained from **6bd** in 64% yield, mp >300° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 8.85 (d, 1H, H-5), 8.26 (m, 2H, phenyl protons), 7.79 (dd, 1H, H-7), 7.53 (m, 3H, phenyl protons), 7.37 (d, 1H, H-8); ms: (m/z) 296 (M^+).

Anal. Calcd. for $C_{15}H_9ClN_4O$: C, 60.72, H, 3.06; N, 18.88. Found: C, 60.62; H, 3.30; N, 18.67.

6-Chloro-2-(2-furyl)pyrido[2,1-*b*]purin-10(1*H*)-one **7be**.

This compound was obtained from **6be** in 62% yield, mp >300° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 8.81 (d, 1H, H-5), 7.96 (d, 1H, H-5'), 7.82 (dd, 1H, H-7), 7.40-7.36 (m, 2H, H-8 and H-3'), 6.74 (dd, 1H, H-4'); ms: (m/z) 286 (M^+).

Anal. Calcd. for $C_{13}H_7ClN_4O_2$: C, 54.47; H, 2.46; N, 19.54. Found: C, 54.70; H, 2.47; N, 19.39.

6-Chloro-2-(3-thienyl)pyrido[2,1-*b*]purin-10(1*H*)-one **7bf**.

This compound was obtained from **6bf** in 65% yield, mp >300° (dimethylformamide/methanol); ^{1}H-nmr (DMSO-d_6): δ 8.81 (d, 1H, H-5), 8.41 (dd, 1H, H-2'), 7.88-7.76 (m, 3H, H-7, H-4' and H-5'), 7.37 (d, 1H, H-8); ms: (m/z) 302 (M^+).

Anal. Calcd. for $C_{13}H_7ClN_4OS$: C, 51.58, H, 2.33; N, 18.51. Found: C, 51.29; H, 2.37; N, 18.40.

General Procedure for the Preparation of 2-Substitutedthiazolo-[2,3-*b*]purin-9(1*H*)-ones **7cd-cf.**

A mixture of the appropriate compound **6** (3.0 g) and polyphosphoric acid (30 ml) was heated under stirring at 100-110° for 6 hours. After cooling, ice water (200 ml) was added and the solution was carefully made alkaline with concentrated ammonium hydroxide. The precipitated solid was collected, washed with water and methanol, then crystallized.

2-Phenylthiazolo[2,3-*b*]purin-9(1*H*)-one **7cd**.

This compound was obtained from **6cd** in 40% yield, mp 221-222° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.17 (d, 1H, H-5), 8.03 (m, 2H, phenyl protons), 7.57 (m, 3H, phenyl protons), 7.44 (d, 1H, H-6); ^{13}C-nmr (DMSO-d_6): δ 161.2 (C-9), 156.6 (C-7a), 147.0 (C-3a and C-2), 131.2 (C-5), 129.3 (C-3' and C-5'), 126.5 (C-1'), 126.2 (C-2' and C-6'), 122.6 (C-4'), 114.9 (C-9a), 111.4 (C-6); ms: (m/z) 268 (M^+).

Anal. Calcd. for $C_{13}H_8N_4OS$: C, 58.20; H, 3.01; N, 20.88. Found: C, 58.11; H, 3.13; N, 20.62.

2-(2-Furyl)thiazolo[2,3-*b*]purin-9(1*H*)-one **7ce**.

This compound was obtained from **6ce** in 54% yield, mp 224-226° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.16 (d, 1H, H-5), 7.99 (dd, 1H, H-5'), 7.43 (d, 1H, H-6), 7.28 (dd, 1H, H-3'), 6.76 (dd, 1H, H-4'); ms: (m/z) 258 (M^+).

Anal. Calcd. for $C_{11}H_6N_4O_2S$: C, 51.15; H, 2.34; N, 21.69. Found: C, 51.27; H, 2.39; N, 21.56.

2-(3-Thienyl)thiazolo[2,3-*b*]purin-9(1*H*)-one **7cf**.

This compound was obtained from **6cf** in 35% yield, mp 232-234° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.30 (dd, 1H, H-2'), 8.15 (d, 1H, H-5), 7.94 (bs, 1H, NH), 7.77 (dd, 1H, H-5'), 7.62 (dd, 1H, H-4'), 7.43 (d, 1H, H-6); ms: (m/z) 274 (M^+).

Anal. Calcd. for $C_{11}H_6N_4OS_2$: C, 48.16; H, 2.20; N, 20.42. Found: C, 47.95; H, 2.11; N, 20.16.

General Procedure for the Preparation of 2-Substituted-9-amino-pyridin[2,1-*b*]purines **8ad-bf**.

The appropriate compound **7** (10 mmoles) was added with stirring to phosphorus oxychloride (20 ml) and the mixture was heated to reflux for 2 hours, then evaporated to dryness under reduced pressure. Ice water (100 ml) was cautiously added and the mixture was neutralized with saturated aqueous sodium bicarbonate. The solid was filtered and dried *in vacuo* at 40° overnight. The crude chloroderivatives were treated with a saturated methanolic ammonia solution (40 ml) and the mixture was stirred at room temperature for 36 hours. By concentration to about 15 ml under reduced pressure at no more than 40° a solid was obtained, which was filtered, washed with water and crystallized.

10-Amino-2-phenylpyrido[2,1-*b*]purine **8ad**.

This compound was obtained from **7ad** in 81% yield, mp >300° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 9.07 (d, 1H, H-5), 8.27 (m, 2H, phenyl protons), 8.08 (s, 2H, NH_2), 7.87 (t, 1H, H-7), 7.62 (d, 1H, H-8), 7.45-7.36 (m, 4H, H-6 and phenyl protons); ^{13}C-nmr (DMSO-d_6): δ 159.4 (C-10), 153.6 (C-8a), 145.9 (C-3a), 144.1 (C-2), 135.1 (C-5), 134.9 (C-1'), 128.4 (C-3' and C-5'), 128.3 (C-7), 128.1 (C-4'), 126.5 (C-2' and C-6'), 123.4 (C-6), 120.6 (C-10a), 115.4 (C-8); ms: (m/z) 261 (M^+).

Anal. Calcd. for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.80. Found: C, 69.13; H, 4.27; N, 26.59.

10-Amino-2-(2-furyl)pyrido[2,1-*b*]purine **8ae**.

This compound was obtained from **7ae** in 75% yield, mp >300° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 9.01 (d, 1H, H-5), 8.09 (bs, 2H, NH_2), 7.87 (t, 1H, H-7), 7.75 (d, 1H, H-5'), 7.61 (d, 1H, H-8), 7.38 (t, 1H, H-6), 6.95 (d, 1H, H-3'), 6.61 (dd, 1H, H-4'); ms: (m/z) 251 (M^+).

Anal. Calcd. for $C_{13}H_9N_5O$: C, 62.15; H, 3.61; N, 27.87. Found: C, 62.01; H, 3.66; N, 27.78.

10-Amino-2-(3-thienyl)pyrido[2,1-*b*]purine **8af**.

This compound was obtained from **7af** in 70% yield, mp >300° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.02 (d, 1H, H-5), 7.98 (m, 3H, H-2' and NH_2), 7.84 (t, 1H, H-7), 7.74 (m, 1H, H-4'), 7.59 (m, 2H, H-6 and H-5'), 7.34 (t, 1H, H-8); ms: (m/z) 267 (M^+).

Anal. Calcd. for $C_{13}H_9N_5S$: C, 58.41; H, 3.39; N, 26.20. Found: C, 58.33; H, 3.41; N, 26.08:

10-Amino-6-chloro-2-phenylpyrido[2,1-*b*]purine **8bd**.

This compound was obtained from **7bd** in 72% yield, mp >300° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.05 (d, 1H, H-5), 8.28 (m, 2H, phenyl protons), 8.17 (bs, 2H, NH_2), 7.89 (dd, 1H, H-7), 7.61 (d, 1H, H-8), 7.45 (m, 3H, phenyl protons); ms: (m/z) 295 (M^+).

Anal. Calcd. for $C_{15}H_{10}ClN_5$: C, 60.92; H, 3.41; N, 23.68. Found: C, 61.00; H, 3.66; N, 23.70.

10-Amino-6-chloro-2-(2-furyl)pyrido[2,1-*b*]purine **8be**.

This compound was obtained from **7be** in 68% yield, mp >300° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.00 (bs, 1H, H-5), 8.25 (bs, 2H, NH_2), 7.89 (dd, 1H, H-7), 7.75 (d, 1H, H-5'), 7.60 (d, 1H, H-8), 6.95 (d, 1H, H-3'), 6.60 (dd, 1H, H-4'); ms: (m/z) 285 (M^+).

Anal. Calcd. for $C_{13}H_8ClN_5O$: C, 54.65; H, 2.82; N, 24.51. Found: C, 54.79; H, 3.05; N, 24.22.

10-Amino-6-chloro-2-(3-thienyl)pyrido[2,1-*b*]purine **8bf**.

This compound was obtained from **7bf** in 81% yield, mp >300° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.00 (d, 1H, H-5), 8.09 (bs, 2H, NH_2), 8.01 (dd, 1H, H-2'), 7.77 (dd, 1H, H-7), 7.78 (dd, 1H, H-4'), 7.62-7.56 (m, 2H, H-8 and H-5'); ms: (m/z) 301 (M^+).

Anal. Calcd. for $C_{13}H_8ClN_5S$: C, 51.74; H, 2.67; N, 23.21. Found: C, 51.88; H, 2.66; N, 23.08.

General Procedure for the Preparation of 1-Methyl-2-substituted-pyrido[2,1-*b*]-and Thiazolo[2,3-*b*] purinones **9**.

Each compound **7** (10 mmoles) was added portionwise to a cooled and stirred suspension of sodium hydride (0.5 g, 50% oil dispersion, 11 mmoles) in anhydrous dimethylformamide (50 ml). The reaction mixture was allowed to warm to room temperature and was stirred for 30 minutes. Methyl 4-toluenesulfonate (2.0 g, 11 mmoles) was added and the mixture was stirred for 2 hours at 60° to obtain **9ad-bf**, or at room temperature to obtain **9cd-cf**. After cooling, ice water (200 ml) was added and the resulting precipitate was collected by filtration, washed with water and crystallized.

1-Methyl-2-phenylpyrido[2,1-*b*]purin-10-one **9ad**.

This compound was obtained from **7ad** in 40% yield, mp 250-252° (ethyl acetate); ir: ν CO 1624 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.84 (d, 1H, H-5), 7.92 (m, 2H, phenyl protons), 7.77 (t, 1H, H-7), 7.61 (m, 3H, phenyl protons), 7.34 (d, 1H, H-8), 7.13 (t, 1H, H-6), 4.18 (s, 3H, N-CH_3); ^{13}C-nmr (DMSO-d_6): δ 160.2 (C-10), 150.6 (C-8a), 147.3 (C-3a), 141.9 (C-2), 136.2 (C-5), 130.4 (C-7), 129.3 (C-3' and C-5'), 128.8 (C-2' and C-6'), 128.4 (C-1'), 127.5 (C-4'), 122.8 (C-6), 116.3 (C-10a), 113.2 (C-8), 33.6 (N-CH_3); ms: (m/z) 276 (M^+), 248, 199.

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.72; H, 4.38; N, 20.08.

2-(2-Furyl)-1-methylpyrido[2,1-*b*]purin-10-one **9ae**.

This compound was obtained from **7ae** in 35% yield, mp 267-270° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 8.78 (d, 1H, H-5), 8.05 (d, 1H, H-5'), 7.76 (t, 1H, H-7), 7.31 (m, 2H, H-8 and H-3'), 7.12 (t, 1H, H-6), 6.81 (dd, 1H, H-4'), 4.32 (s, 3H, N-CH_3); ms: (m/z) 266 (M^+), 238, 199, 171.

Anal. Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15, H, 3.79; N, 21.04. Found: C, 62.89; H, 3.85; N, 20.91.

2-(3-Thienyl)-1-methylpyrido[2,1-*b*]purin-10-one **9af**.

This compound was obtained from **7af** in 42% yield, mp 203-205° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.82 (d, 1 H, H-5), 8.38 (d, 1H, H-2'), 7.77 (m, 3H, H-7, H-4' and H-5'), 7.37 (d, 1H, H-8), 7.16 (t, 1H, H-6), 4.15 (s, 3H, N-CH_3); ms: (m/z) 282 (M^+), 254, 199, 142.

Anal. Calcd. for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.84. Found: C, 59.77; H, 3.3 1 ; N, 19.72.

6-Chloro-1-methyl-2-phenylpyrido[2,1-*b*]purin-10-one **9bd**.

This compound was obtained from **7bd** in 37% yield, mp 211-213° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 9.35 (d, 1H, H-5), 8.34 (m, 2H, phenyl protons), 8.17 (dd, 1H, H-7), 8.04 (d, 1 H, H-8), 7.43 (m, 3H, phenyl protons), 4.27 (s, 3H, N-CH_3); ms: (m/z) 310 (M^+), 288, 276, 155, 142.

Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.57; H, 3.62; N, 17.91.

6-Chloro-2-(2-furyl)-1-methylpyrido[2,1-*b*]purin-10-one **9be**.

This compound was obtained from **7be** in 39% yield, mp 170-172° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 8.80 (d, 1H, H-5), 8.06 (d, 1H, H-5'), 7.85 (dd, 1H, H-7), 7.35 (m, 2H, H-8 and H-3'), 6.81 (dd, 1H, H-4'), 4.32 (s, 3H, N-CH_3); ms: (m/z) 300 (M^+), 272, 265, 186, 142.

Anal. Calcd. for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; N, 18.63. Found: C, 56.08; H, 3.14; N, 18.39.

6-Chloro-1-methyl-2-(3-thienyl)pyrido[2,1-*b*]purin-10-one **9bf**.

This compound was obtained from **7bf** in 37% yield, mp 270-272° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 8.81 (dd, 1H, H-5), 8.33 (dd, 1H, H-2'), 7.84-7.78 (m, 2H, H-7 and H-5'), 7.75 (dd, 1H, H-4'), 7.35 (d, 1H, H-8), 4.27 (s, 3H, N-CH_3); ms: (m/z) 316 (M^+), 281, 253, 233, 144.

Anal. Calcd. for $C_{14}H_9ClN_4OS$: C, 53.08; H, 2.86; N, 17.69. Found: C, 52.97; H, 2.89; N, 17.51.

1-Methyl-2-phenylthiazolo[2,3-*b*]purin-9-one **9cd**.

This compound was obtained from **7cd** in 79% yield, mp 209-211° (methanol); ir: ν CO 1622 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.90 (m, 2H, phenyl protons), 7.54 (m, 3H, phenyl protons), 7.49 (d, 1H, H-5), 6.97 (d, 1H, H-6), 3.61 (s, 3H, CH_3); ^{13}C-nmr (DMSO-d_6): δ 161.5 (C-9), 158.9 (C-7a), 151.8 (C-3a and C-2), 130.3 (C-5), 130.0 (C-4'), 129.1 (C-3' and C-5'), 125.9 (C-1'), 125.1 (C-2' and C-6'), 115.2 (C-9a), 105.1 (C-6), 35.0 (N-CH_3); ms: (m/z) 282 (M^+), 254, 239, 202, 141.

Anal. Calcd. for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.84. Found: C, 59.59; H, 3.28; N, 19.85.

2-(2-Furyl)-1-methylthiazolo[2,3-*b*]purin-9-one **9ce**.

This compound was obtained from **7ce** in 77% yield, mp 225-226° (methanol); ^{1}H-nmr (DMSO-d_6): δ 7.93 (d, 1H, H-5'), 7.48 (d, 1H, H-5), 7.07 (d, 1H, H-3'), 6.96 (d, 1H, H-6), 6.73 (dd, 1H, H-4'), 3.60 (s, 3H, CH_3); ms: (m/z) 272 (M^+), 244, 192, 163, 141.

Anal. Calcd. for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.58. Found: C, 52.88; H, 3.12; N, 20.39.

1-Methyl-2-(3-thienyl)thiazolo[2,3-*b*]purin-9-one **9cf**.

This compound was obtained from **7cf** in 71% yield, mp 198-200° (methanol); ^{1}H-nmr (DMSO-d_6): δ 8.08 (dd, 1H, H-2'), 7.75 (dd, 1H, H-5'), 7.52 (dd, 1H, H-4'), 7.48 (d, 1H, H-5), 6.96 (d, 1H, H-6), 3.60 (s, 3H, CH_3); ms: (m/z) 288 (M^+), 260, 208, 175, 141.

Anal. Calcd. for $C_{12}H_8N_4OS_2$: C, 49.99; H, 2.80; N, 19.43. Found: C, 50.10; H, 2.87; N, 19.26.

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