Synthesis of 2,8-Disubstituted 1,2,4-Triazolo[5,1-*i*]purines

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

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

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This paper describes the preparation of 2-aryl-8-fluorobenzyl-1,2,4-triazolo[5,1-*i*]purines **2**, starting from 2-aryl-7,8-diamino-1,2,4-triazolo[1,5-*c*]pyrimidines **9**. Our synthetic procedure represents the first example of a feasible approach for the synthesis of 2,8-disubstituted triazolo[5,1-*i*]purines. New syntheses of 5-amino-3-arylpyrimido[5,4-*e*]1,2,4-triazines **12** and 8-fluorobenzyl-6-hydrazinopurines **15** are also reported.

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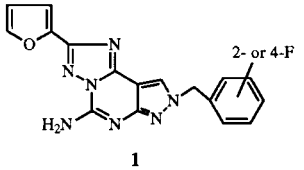
Over the past few years several non-xanthine classes of compounds with antagonistic properties at either A_1 or A_2 adenosine receptors have been identified. Of particular interest are some triazoloquinazolines [1], triazoloquinoxalines [2], and imidazoquinolines [3]. More recently, as reported in a publication from our laboratory [4], 5-amino-2-(2-furyl)–pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]-pyrimidines, with a fluorobenzyl group at the 8 position, **1**, were discovered to be very potent adenosine-A_2 receptor antagonists. In particular, the 4-fluorobenzyl derivative, when compared with other potential A_2 antagonists, possessed the highest activity [5].

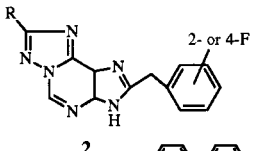
Within the framework of our chemical and pharmacological interest in this field, the present study is concerned with the development of an appropriate synthetic procedure, aimed at preparing 2-aryl-8-fluorobenzyl-1,2,4-triazolo[5,1-*i*]purines **2**, which are expected to bind to adenosine and/or benzodiazepine receptors.

It seems worth mentioning that no 2,8-disubstituted 1,2,4-triazolo[5,1-*i*]purines have been previously reported.

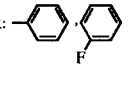
Two different approaches to compounds **2** were explored. While the first approach was entirely successful, the second one failed in the last step, *i.e.*, the ring closure of the triazolopyrimidine moiety.



1



2



4-Amino-6-chloro-5-nitropyrimidine **3**, prepared according to the literature [6], was the starting material for the syntheses outlined in Scheme 1. According to the first synthetic pathway (route 7 → 8 → 9 → 10), compound **3** was allowed to react with benzhydrazide or 2-fluorobenzhydrazide in anhydrous dioxane to give 4-amino-6-aroylhydrazino-5-nitropyrimidines **4** in excellent yields. Attempted cyclization to the corresponding triazolopyrimidines **8**, by heating **4** in polyphosphoric acid (PPA) at 120-130°, resulted in the ring opening of the pyrimidine part to afford 2-(3-aryl-1,2,4-triazol-5-yl)-2-nitro-1,1-ethenediamines **7**. The same treatment was repeated on the 6-aroylhydrazino-4-fluorobenzylamino-5-nitropyrimidines **6**, obtained from the chloro derivative **5** following the procedure described for **4**. Our goal was the preparation of 7-fluorobenzylamino-8-nitro-1,2,4-triazolo[1,5-*c*]pyrimidines as starting materials for the synthesis of 2-aryl-9-fluorobenzyl-1,2,4-triazolo[5,1-*i*]purines. Unfortunately the reaction led only to **7**, because of the unexpected *N*-debenzylation of **6**.

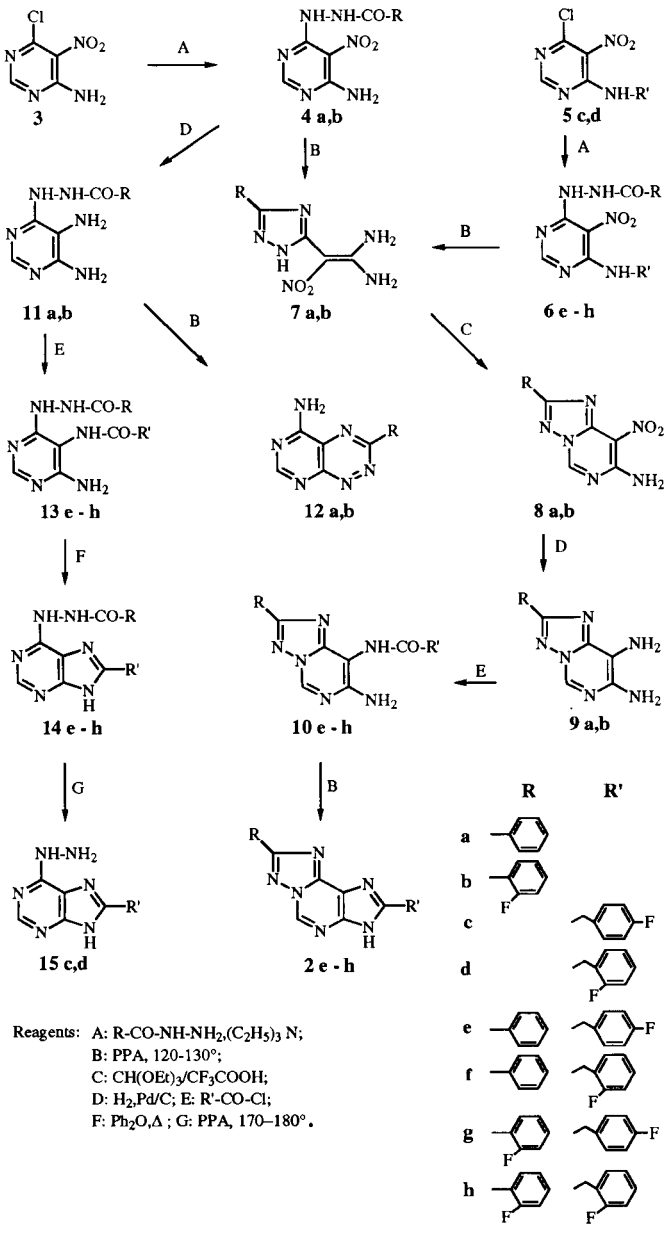
No cyclization took place by reaction of **7**, either with carbonyldiimidazole in anhydrous tetrahydrofuran or by refluxing ethyl urethane or with cyanamide and *p*-toluenesulfonic acid in *N*-methylpyrrolidone at 160°. In contrast, **7** in a refluxing mixture of triethyl orthoformate and trifluoroacetic acid afforded the expected 7-amino-2-aryl-8-nitro-1,2,4-triazolo[1,5-*c*]pyrimidines **8** in essentially quantitative yield.

The reduction of compounds **8** to their related diamino derivatives **9** was difficult. The reduction, effected by using sodium dithionite, either in warm 4% sodium hydroxide or in diluted ammonium hydroxide at 50°, induced cleavage of the pyrimidine ring and formation of **7**. Standard catalytic hydrogenation with Raney nickel or platinum dioxide in methanol or tetrahydrofuran yielded a lot of dark tarry material, presumably by rapid air oxidation of the obtained diamino compound.

We found the hydrogenation with palladium on charcoal in acetic acid to be the most effective hydrogenation method for our purpose. Nevertheless the yields of **9** were moderate (25-30%), the limiting factors being the poor solubility of the nitro adduct in acetic acid and the formation of the corresponding 8-acetylaminoderivatives in 10-15% yields (reaction by-products).

The more nucleophilic 8-amino group of **9** was selectively acylated to the acylamino derivatives **10** by using the appropriate fluorophenylacetyl chloride in pyridine.

Scheme 1



Finally ring closure to the expected compounds **2** was carried out by heating **10** in polyphosphoric acid at 120-130°.

We planned a second, alternative synthetic pathway to compounds **2** (route 11 → 13 → 14). Although the preparation of the desired tricyclic compounds was unsuccessful, we encountered interesting and unreported reactions deserving to be described here. Compounds **4** were hydrogenated in the presence of palladium on charcoal in methanol to give the diamino compounds **11**. On heating in polyphosphoric acid at 120-130°, **11** were directly cyclized and readily air oxidized [7] to 5-amino-3-arylpyrimido[5,4-*e*]1,2,4-triazines **12**, while on treatment with fluorophenylacetyl chlorides in anhydrous dioxane they were converted to **13** in good to excellent yields.

The intermediate **13** gave easily the 6-aroylhydrazino-8-fluorobenzylpurines **14** in boiling diphenyl ether. Contrary to our expectations, cyclization of **14** with polyphosphoric acid at 120-130° resulted in the recovery of the starting material. Under forcing conditions, in polyphosphoric acid at 170-180°, the only isolated products were 6-hydrazino-8-fluorobenzylpurines **15**.

In the experimental, the spectral data on the synthesized compounds, with R = phenyl and R' = 4-fluorobenzyl, will be reported.

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian Gemini 200 instrument. Chemical shifts (δ) are in ppm relative to tetramethylsilane. Electron ionization mass spectra were obtained with an HP 59980 B spectrometer operating at 70 eV. Column chromatography was performed on silica gel Merck (70-230 mesh). Purity of each compound was checked on silica gel Carlo Erba 60 F_{254} plates, and the spots were located by uv light. Sodium sulfate was used to dry organic solutions. Elemental analyses were performed by the Microanalytical Section of our Institute.

The synthesis of **3** [6] has been reported elsewhere.

4-Amino-6-benzoylhydrazino-5-nitropyrimidine **4a**.
4-Amino-6-(2-fluorobenzoylhydrazino)-5-nitropyrimidine **4b**.

To a stirred solution of 4-amino-6-chloro-5-nitropyrimidine (**3**, 8.7 g, 50 mmoles) and triethylamine (5.0 g, 50 mmoles) in anhydrous dioxane (150 ml), benzhydrazide (6.8 g, 50 mmoles, to obtain **4a**) or 2-fluorobenzhydrazide (7.7 g, 50 mmoles, to obtain **4b**) was added. After about 1 hour of stirring at room temperature, a yellow precipitate began to separate from the clear solution. The mixture was stirred for an additional 2 hours, then the solid was collected by filtration, washed with ethanol and used without further purification. An analytical sample was obtained by recrystallization from methanol.

Compound **4a**, obtained in 88% yield, had mp 236-238°; ^{1}H-nmr (DMSO-d_6): δ 10.70 (broad, 2H, deuterium oxide-exchangeable, NH-NH), 8.68 (bs, 2H, deuterium oxide-exchangeable, NH_2), 8.02 (s, 1H, H-2), 7.92 (m, 2H, aromatic protons), 7.54 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{11}H_{10}N_6O_3.H_2O$: C, 45.20; H, 4.14; N, 28.76. Found: C, 45.10; H, 4.23; N, 29.00.

Compound **4b**, obtained in 79% yield, had mp 241-243°.

Anal. Calcd. for $C_{11}H_9FN_6O_3$ C, 45.21; H, 3.10; N, 28.76. Found: C, 45.32; H, 3.38; N, 28.52.

6-Chloro-4-(4-fluorobenzylamino)-5-nitropyrimidine **5c**.
6-Chloro-4-(2-fluorobenzylamino)-5-nitropyrimidine **5d**.

To a stirred solution of 4,6-dichloro-5-nitropyrimidine [8] (19.4 g, 100 mmoles) in 150 ml of anhydrous dioxane (200 ml), a solution of the appropriate fluorobenzylamine (10 g, 80 mmoles) and triethylamine (10.1 g, 100 mmoles) in anhydrous dioxane (100 ml) was added dropwise at room temperature over 50-60 minutes. The reaction was complete after 2 hours. The

solvent was removed *in vacuo* (maximum bath temperature 40°), water was added and the mixture was extracted with ethyl acetate. The residue, obtained after solvent evaporation, was purified by chromatography on a silica gel column, by eluting with an ethyl acetate/*n*-hexane (1:4) mixture, then crystallized from ethyl acetate/*n*-hexane.

Compound **5c**, obtained in 70% yield, had mp 102-104°; ^{1}H-nmr (DMSO-d_6): δ 9.02 (t, 2H, deuterium oxide-exchangeable, NH_2), 8.44 (s, 1H, H-2), 7.35 (t, 2H, aromatic protons), 7.13 (t, 2H, aromatic protons), 4.64 (d, 2H, CH_2).

Anal. Calcd. for $C_{11}H_8ClFN_4O_2$: C, 46.73; H, 2.85; N, 19.82.Found: C, 46.70; H, 2.66; N, 19.59.

Compound **5d**, obtained in 62% yield, had mp 188-190°.

Anal. Calcd. for $C_{11}H_8ClFN_4O_2$: C, 46.73; H, 2.85; N, 19.82. Found: C, 47.01; H, 2.74; N, 19.67.

General Procedure for the Reaction of Pyrimidines **5** with Benzhydrazides.

Pyrimidines **5** were allowed to react with benzhydrazide or 2-fluorobenzhydrazide according to the procedure described for the pyrimidines **4**.

6-(Benzoylhydrazino)-4-(4-fluorobenzylamino)-5-nitropyrimidine **6e**.

This compound, obtained by reaction of **5c** with benzhydrazide in 58% yield, had mp 207-209° (dimethylformamide/ethanol); ^{1}H-nmr (DMSO-d_6): δ 10.91 (bs, 1H, deuterium oxide-exchangeable, NH), 10.73 (bs, 1H, deuterium oxide-exchangeable, NH), 9.86 (t, 2H, deuterium oxide-exchangeable, NH_2), 8.11 (s, 1H, H-2), 7.93 (m, 2H, aromatic protons), 7.58 (m, 3H, aromatic protons), 7.46 (t, 2H, aromatic protons), 7.14 (t, 2H, aromatic protons), 4.76 (d, 2H, CH_2).

Anal. Calcd. for $C_{18}H_{15}FN_6O_3$: C, 56.54; H, 3.95; N, 21.98. Found: C, 56.37; H, 3.84; N, 22.17.

6-(Benzoylhydrazino)-4-(2-fluorobenzylamino)-5-nitropyrimidine **6f**.

This compound, obtained by reaction of **5d** with benzhydrazide in 66% yield, had mp 199-201° (dimethylformamide/ethanol).

Anal. Calcd. for $C_{18}H_{15}FN_6O_3$: C, 56.54; H, 3.95; N, 21.98. Found: C, 56.48; H, 3.77; N, 22.09.

6-(2-Fluorobenzoylhydrazino)-4-(4-fluorobenzylamino)-5-nitropyrimidine **6g**.

This compound, obtained by reaction of **5c** with 2-fluorobenzhydrazide in 52% yield, had mp 278-281° (dimethylformamide).

Anal. Calcd. for $C_{18}H_{14}F_2N_6O_3$: C, 54.00; H, 3.52; N, 20.99. Found: C, 53.78; H, 3.44; N, 20.76.

6-(2-Fluorobenzoylhydrazino)-4-(2-fluorobenzylamino)-5-nitropyrimidine **6h**.

This compound, obtained by reaction of **5d** with 2-fluorobenzhydrazide in 60% yield, had mp 246-248° (dimethylformamide) .

Anal. Calcd. for $C_{18}H_{14}F_2N_6O_3$: C, 54.00; H, 3.52; N, 20.99. Found: C, 53.81; H, 3.42; N, 21.05.

2-Nitro-2-(3-phenyl-1,2,4-triazol-5-yl)-1,1-ethenediamine **7a**. 2-[3-(2-Fluorophenyl)-1,2,4-triazol-5-yl]-2-nitro-1,1-ethenediamine **7b**.

One of the pyrimidines **4** or **6** (5 g) respectively was suspended in polyphosphoric acid (80 g) and the mixture was heated at 120-130° with mechanical stirring for 3 hours. After cooling, ice water (200 ml) was added and the suspension was centrifuged (10,000 rpm for 10 minutes). The separated solid was suspended in 10% potassium hydroxide (100 ml). The insoluble material was filtered off and the filtrate was carefully adjusted to *p*H 6 by dropwise addition of diluted hydrochloric acid. The white solid which had been formed was collected by filtration, washed successively with water, ethanol and diethyl ether, and then recrystallized from acetic acid.

Compound **7a**, obtained from **4a** in 83% yield, had mp 283-285°; ^{1}H-nmr (DMSO-d_6): δ 13.81 (bs, 1H, deuterium oxide-exchangeable, NH), 9.98 (bs, 2H, deuterium oxide-exchangeable, NH_2), 8.06 (m, 2H, aromatic protons), 7.81 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.44 (m, 3H, aromatic protons); ms: (m/z) 246 (M^+), 216, 201, 170, 139, 115, 104.

Anal. Calcd. for $C_{10}H_{10}N_6O_2$ C, 48.78; H, 4.09; N, 34.14. Found: C, 48.55; H, 4.14; N, 34.10.

Compound **7b**, obtained from **4b** in 72% yield, had mp 292-295°.

Anal. Calcd. for $C_{10}H_9FN_6O_2$ C, 45.46; H, 3.43; N, 31.81. Found: C, 45.19; H, 3.17; N, 31.60.

7-Amino-2-phenyl-8-nitro-1,2,4-triazolo[1,5-*c*]pyrimidine **8a**. 7-Amino-2-(2-fluorophenyl)-8-nitro-1,2,4-triazolo[1,5-*c*]pyrimidine **8b**.

A solution of a pyrimidine **7** (5 g) in triethyl orthoformate (100 ml) and trifluoroacetic acid (10 ml) was refluxed for 5 hours. The mixture was concentrated to dryness at reduced pressure and the residue directly crystallized from dimethylformamide/ethanol.

Compound **8a**, obtained from **7a** in 94% yield, had mp 236-238°; ^{1}H-nmr (DMSO-d_6): δ 9.49 (s, 1H, H-5), 8.68 and 8.55 (bs, 2H, deuterium oxide-exchangeable NH_2), 8.17 (m, 2H, aromatic protons), 7.54 (m, 3H, aromatic protons); ms: (m/z) 256 (M^+), 239, 199, 172, 128, 104.

Anal. Calcd. for $C_{11}H_8N_6O_2.H_2O$: C, 48.17; H, 3.68; N, 30.65. Found: C, 48.14; H, 3.73; N, 30.36.

Compound **8b**, obtained from **7b** in 90% yield, had mp 259-261°.

Anal. Calcd. for $C_{11}H_7FN_6O_2$: C, 48.19; H, 2.57; N, 30.66. Found: C, 47.92; H, 2.58; N, 30.40.

General Procedure for the Catalytic Hydrogenation of Compounds **8**.

Each pyrimidine **8** (5 g) in acetic acid (150 ml) was hydrogenated over 10% palladium on charcoal (0.5 g) at 3 atmospheres and room temperature for 12 hours. After filtration under nitrogen, the solvent was evaporated *in vacuo* at 35-40° and the residue immediately chromatographed on silica gel by eluting with ethyl acetate. The fractions containing **9,** which formed characteristic blue spots on the tlc plate upon brief exposure to the atmosphere, were evaporated *in vacuo* at no more than 30°. Compounds **9** were eluted first, followed by their corresponding 8-acetyl derivatives.

7,8-Diamino-2-phenyl-1,2,4-triazolo[1,5-*c*]pyrimidine **9a**.

This compound, obtained from **8a** in 28% yield, had mp 216-218° (ethyl acetate/*n*-hexane); ^{1}H-nmr (DMSO-d_6): δ 8.86 (s, 1H, H-5), 8.17 (m, 2H, aromatic protons), 7.50 (m, 3H, aromatic

protons), 5.92 (bs, 2H, deuterium oxide-exchangeable 7-NH_2), 4.97 (bs, 2H, deuterium oxide-exchangeable, 8-NH_2); ms: (m/z) 226 (M^+), 199, 172, 145, 104.

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.39; H, 4.46; N, 37.15. Found: C, 58.12; H, 4.54; N, 37.27.

8-Acetylamino-7-amino-2-phenyl-1,2,4-triazolo[1,5-*c*]pyrimidine.

This compound, obtained from **8a** in 15% yield, had mp 286-288° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 9.48 (bs, 1H, deuterium oxide-exchangeable, NH), 9.27 (s, 1H, H-5), 8.13 (m, 2H, aromatic protons),7.50 (m, 3H, aromatic protons), 6.55 (bs, 2H, deuterium oxide-exchangeable, NH_2), 2.09 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. Found: C, 57.98; H, 4.37; N, 31.51.

7,8-Diamino-2-(2-fluorophenyl)-1,2,4-triazolo[1,5-*c*]pyrimidine **9b**.

This compound, obtained from **8b** in 25% yield, had mp 217-219° (ethyl acetate).

Anal. Calcd. for $C_{11}H_9FN_6$ C, 54.09; H, 3.71; N, 34.41. Found: C, 53.89; H, 3.52; N, 34.20.

8-Acetylamino-7-amino-2-(2-fluorophenyl)-1,2,4-triazolo[1,5-*c*]pyrimidine.

This compound, obtained from **8b** in 12% yield, had mp 273-275° (ethyl acetate).

Anal. Calcd. for $C_{13}H_{11}FN_6O{\bullet}H_2O$: C, 51.31; H, 4.31; N, 27.62. Found: C, 51.60; H, 4.35; N, 27.36.

General Procedure for the *N*-8 Acylation of 2-Aryl-7,8-diamino-1,2,4-triazolo[1,5-*c*]pyrimidines **9**.

To a stirred solution of **9** (10 mmoles) in pyridine (50 ml), under nitrogen, the appropriate fluorophenylacetyl chloride (2.1 g, 12 mmoles) was added dropwise at room temperature. The mixture was stirred for a further 2 hours, then poured into water and extracted with ethyl acetate. After the solvent evaporation, the resulting residue was chromatographed on a silica gel column by eluting with an ethyl acetate/*n*-hexane (2: 1) mixture.

7-Amino-8-(4-fluorophenylacetylamino)-2-phenyl-1,2,4-triazolo[1,5-*c*] pyrimidine **10e**.

This compound, obtained by reaction of **9a** with 4-fluorophenylacetyl chloride in 68% yield, had mp 256-258° (ethanol); ^{1}Hnmr (DMSO-d_6): δ 9.73 (bs, 1H, deuterium oxide-exchangeable, NH), 9.28 (s, 1H, H-5), 8.12 (m, 2H, aromatic protons), 7.51 (m, 5H, aromatic protons), 7.17 (t, 2H, aromatic protons), 6.53 (s, 2H, deuterium oxide-exchangeable, NH_2), 3.75 (s, 2H, CH_2).

Anal. Calcd. for $C_{19}H_{15}FN_6O{\bullet}H_2O$: C, 59.99; H, 4.51; N, 22.10. Found: C, 59.69; H, 4.34; N, 21.88.

7-Amino-8-(2-fluorophenylacetylamino)-2-phenyl-1,2,4-triazolo[1,5-*c*]pyrimidine **10f**.

This compound, obtained by reaction of **9a** with 2-fluorophenylacetyl chloride in 59% yield, had mp 259-261° (ethanol).

Anal. Calcd. for $C_{19}H_{15}FN_6O{\bullet}H_2O$: C, 59.99; H, 4.51; N, 22.10. Found: C, 60.14; H, 4.26; N, 21.90.

7-Amino-2-(2-fluorophenyl)-8-(4-fluorophenylacetylamino)-1,2,4-triazolo[1,5-*c*]pyrimidine **10g**.

This compound, obtained by reaction of **9b** with 4-fluorophenylacetyl chloride in 62% yield, had mp 236-238° (ethanol).

Anal. Calcd. for $C_{19}H_{14}F_2N_6O$: C, 59.99; H, 3.71; N, 22.10. Found: C, 60.24; H, 3.64; N, 21.90.

7-Amino-2-(2-fluorophenyl)-8-(2-fluorophenylacetylamino)-1,2,4-triazolo[1,5-*c*]pyrimidine **10h**.

This compound, obtained by reaction of **9b** with 2-fluorophenylacetyl chloride in 50% yield, had mp 266-268° (methanol).

Anal. Calcd. for $C_{19}H_{14}F_2N_6O{\bullet}H_2O$: C, 57.29; H, 4.05; N, 21.10. Found: C, 57.50; H, 4.00; N, 21.34.

General Procedure for the Preparation of 2-Aryl-8-fluorobenzyl-1,2,4-triazolo[5,1-*i*]purines **2**.

A suspension of each compound **10** (5 g) in polyphosphoric acid (100 g) was heated at 120-130° for 2 hours with mechanical stirring. After cooling, ice water (300 ml) was added and the resulting suspension was centrifuged (10,000 rpm for 10 minutes). The solid which had been separated was collected by filtration and recrystallyzed from dimethylformamide.

8-(4-Fluorobenzyl)-2-phenyl-1,2,4-triazolo[5,1-*i*]purine **2e**.

This compound, obtained from **10e** in 68% yield, had mp >300°; ^{1}H-nmr (DMSO-d_6): δ 13.95 (broad, 1H, deuterium oxide-exchangeable, NH), 9.55 (s, 1H, H-5), 8.24 (m, 2H, aromatic protons), 7.55 (m, 3H, aromatic protons), 7.40 (t, 2H, aromatic protons), 7.19 (t, 2H, aromatic protons), 4.25 (s, 2H, CH_2); ms: (m/z) 345 (M^++1), 325, 267, 225, 199, 172, 134, 104.

Anal. Calcd. for $C_{19}H_{13}FN_6{\bullet}1/2\ H_2O$: C, 64.58; H, 3.99; N, 23.79. Found: C, 64.83; H, 3.86; N, 23.73.

8-(2-Fluorobenzyl)-2-phenyl-1,2,4-triazolo[5,1-*i*]purine **2f**.

This compound, obtained from **10f** in 50% yield, had mp 286-289°.

Anal. Calcd. for $C_{19}H_{13}FN_6$: C, 66.27; H, 3.81; N, 24.41. Found: C, 66.08; H, 3.77; N, 24.29.

8-(4-Fluorobenzyl)-2-(2-fluorophenyl)-1,2,4-triazolo[5,1-*i*]-purine **2g**.

This compound, obtained from **10g** in 61% yield, had mp 266-268°.

Anal. Calcd. for $C_{19}H_{12}F_2N_6$: C, 62.98; H, 3.34; N, 23.20. Found: C, 63.11; H, 3.56; N, 22.99.

8-(2-Fluorobenzyl)-2-(2-fluorophenyl)-1,2,4-triazolo[5,1-*i*]-purine **2h**.

This compound, obtained from **10h** in 59% yield, had mp 252-254°.

Anal. Calcd. for $C_{19}H_{12}F_2N_6$: C, 62.98; H, 3.34; N, 23.20. Found: C, 62.68; H, 3.30; N, 23.10.

6-Benzoylhydrazino-4,5-diaminopyrimidine **11a**.
4,5-Diamino-6-(2-fluorobenzoylhydrazino)pyrimidine **11b**.

A suspension of each compound **4** (10 g) in methanol (200 ml) was hydrogenated over 10% palladium on charcoal (0.5 g) at 3 atmospheres and room temperature for 12 hours. The filtered solution was concentrated under vacuum and the residue crystallized from methanol/diethyl ether.

Compound **11a**, obtained from **4a** in 65% yield, had mp 204-206°; ^{1}H-nmr (DMSO-d_6): δ 10.30 (broad, 1 H, deuterium

oxideexchangeable, NH), 7.92 (m, 3H, H-2 and 2 aromatic protons), 7.49 (m, 4H, 1H deuterium oxide-exchangeable, NH and 3 aromatic protons), 5.85 (bs, 2H, deuterium oxide-exchangeable, 4-NH_2), 4.15 (broad, 2H, deuterium oxide-exchangeable, 5-NH_2).

Anal. Calcd. for $C_{11}H_{12}N_6O$•1/2 H_2O: C, 52.16; H, 5.17; N, 33.18. Found: C, 52.37; H, 5.12; N, 33.23.

Compound **11b**, obtained from **4b** in 58% yield, had mp 111-113°

Anal. Calcd. for $C_{11}H_{11}FN_6O$•H_2O: C, 47.13; H, 4.67; N, 29.99. Found: C, 46.90; H, 4.52; N, 30.03.

5-Amino-3-phenylpyrimido[5,4-*e*]-1,2,4-triazine **12a**. 5-Amino-3-(2-fluorophenyl)–pyrimido[5,4-*e*]-1,2,4-triazine **12b.**

A mixture of each compound **11** (5 g) with polyphosphoric acid (80 g) was heated at 120-130° for 2 hours. After cooling ice water (200 ml) was added and the solution was cautiously made alkaline with 25% ammonium hydroxide. The resulting precipitate was collected by filtration, washed with water and ethanol, then crystallized.

Compound **12a**, obtained from **11a** in 78% yield, had mp >300° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 9.08 and 8.89 (bs, 2H, deuterium oxide-exchangeable, NH_2), 8.71 (m, 2H, aromatic protons), 8.62 (s,1H, H-7), 7.62 (m, 3H, aromatic protons); ms: (m/z) 225 (M^++1), 196, 169, 141, 104.

Anal. Calcd. for $C_{11}H_8N_6$: C, 58.92; H, 3.60; N, 37.48. Found: C, 59.04; H, 3.46; N, 37.71.

Compound **12b**, obtained from **11b** in 69% yield, had mp 282-285° (dimethylformamide/ethanol).

Anal. Calcd. for $C_{11}H_7FN_6$: C, 54.54; H, 2.91; N, 34.70. Found: C, 54.64; H, 2.67; N, 34.40.

General Procedure for the *N*-5 Acylation of Compounds **11**.

To a stirred solution of **11a** (7.3 g, 30 mmoles) or **11b** (7.9 g, 30 mmoles) in anhydrous dioxane (200 ml), the appropriate fluorophenylacetyl chloride (5.2 g, 30 mmoles) in anhydrous dioxane (50 ml) was dropwise added at room temperature. The mixture was allowed to react for 2 hours, then was evaporated to dryness *in vacuo* at no more than 30-35°. Water was added to the obtained residue, and the aqueous suspension was thoroughly extracted with ethyl acetate. After removal of the solvent, the resulting crude product was purified by column chromatography on silica gel eluting with 10% methanol/ethyl acetate.

4-Amino-6-benzoylhydrazino-5-(4-fluorophenylacetylamino)-pyrimidine **13e**.

This compound, obtained by reaction of **11a** with 4-fluorophenylacetyl chloride in 75% yield, had mp 256-258° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 10.26, 8.93, 8.34 (bs, 3H, deuterium oxide-exchangeable, 3NH), 7.92 (m, 2H, aromatic protons), 7.84 (s, 1 H, H-2), 7.42 (m, 5H, aromatic protons), 7.13 (t, 2H, aromatic protons), 6.07 (bs, 2H, deuterium oxide-exchangeable, NH_2), 3.72 (s, 2H, CH_2).

Anal. Calcd. for $C_{19}H_{17}FN_6O_2$: C, 59.99; H, 4.51; N, 22.10. Found: C, 59.82; H, 4.78; N, 22.13.

4-Amino-6-benzoylhydrazino-5-(2-fluorophenylacetylamino) pyrimidine **13f**.

This compound, obtained by reaction of **11a** with 2-fluorophenylacetyl chloride in 66% yield, had mp 236-238° (ethyl acetate/*n*-hexane) .

Anal. Calcd. for $C_{19}H_{17}FN_6O_2$: C, 59.99; H, 4.51; N, 22.10. Found: C, 59.75; H, 4.36; N, 22.38.

4-Amino-6-(2-fluorobenzoylhydrazino)-5-(4-fluorophenylacetylamino)pyrimidine **13g.**

This compound, obtained by reaction of **11b** with 4-fluorophenylacetyl chloride in 55% yield, had mp 248-250° (methanol).

Anal. Calcd. for $C_{19}H_{16}F_2N_6O_2$•H_2O: C, 54.80; H, 4.36; N, 20.18. Found: C, 54.52; H, 4.23; N, 20.86.

4-Amino-6-(2-fluorobenzoylhydrazino)-5-(2-fluorophenylacetylamino)pyrimidine **13h**.

This compound, obtained by reaction of **11b** with 2-fluorophenylacetyl chloride in 60% yield, had mp 253-255° (methanol).

Anal. Calcd. for $C_{19}H_{16}F_2N_6O_2$ C, 57.28; H, 4.05; N, 21.10. Found: C, 57.04; H, 3.81; N, 21.05.

General Procedure for the Preparation of Compounds **14**.

Each compound **13** (5 g) 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 and then maintained at the temperature until the starting material had disappeared (about 2 hours). The reaction was followed by tlc (ethyl acetate). The reaction mixture was allowed to cool to room temperature and *n*-hexane was added. The crude solid was collected by filtration, thoroughly washed with additional *n*-hexane, then purified by column chromatography on silica gel eluting with ethyl acetate.

6-Benzoylhydrazino-8-(4-fluorobenzyl)purine **14e**.

This compound, obtained from **13e** in 82% yield, had mp 300-303° (dimethylformamide/ethanol); ^{1}H-nmr (DMSO-d_6): δ 11.95 (bs, 1H, deuterium oxide-exchangeable, heterocyclic NH), 8.09 (s, 1H, H-2), 7.93 (m, 2H, aromatic protons), 7.59 (m, 3H, aromatic protons), 7.26 (m, 4H, 2H deuterium oxide-exchangeable, 2 NH and 2 aromatic protons), 7.11 (t, 2H, aromatic protons), 4.10 (s, 2H, CH_2); ms: (m/z) 362 (M^+), 257, 242, 225, 215, 157, 141, 134.

Anal. Calcd. for $C_{19}H_{15}FN_6O$: C, 62.97; H, 4.17; N, 23.19. Found: C, 62.85; H, 4.32; N, 23.31.

6-Benzoylhydrazino-8-(2-fluorobenzyl)purine **14f**.

This compound, obtained from **13f** in 64% yield, had mp 264-266° (methanol) .

Anal. Calcd. for $C_{19}H_{15}FN_6O$: C, 62.97; H, 4.17; N, 23.19. Found: C, 63.09; H, 4.22; N, 22.90.

6-(2-Fluorobenzoylhydrazino)-8-(4-fluorobenzyl)purine **14g.**

This compound, obtained from **13g** in 77% yield, had mp 279-282° (ethyl acetate).

Anal. Calcd. for $C_{19}H_{14}F_2N_6O$•H_2O: C, 57.28; H, 4.05; N, 21.10. Found: C, 56.99; H, 3.95; N, 21.14.

6-(2-Fluorobenzoylhydrazino)-8-(2-fluorobenzyl)purine **14h**.

This compound, obtained from **13h** in 60% yield, had mp 223-225° (ethyl acetate).

Anal. Calcd. for $C_{19}H_{14}F_2N_6O$: C, 59.99; H, 3.71; N, 22.10. Found: C, 59.70; H, 3.68; N, 22.17.

8-(4-Fluorobenzyl)-6-hydrazinopurine **15c**.
8-(2-Fluorobenzyl)-6-hydrazinopurine **15d**.

A suspension of each compound **14** (**14e** or **14g** to give **15c** and **14f** or **14h** to give **15d**) (3 g) in polyphosphoric acid (60 g) was heated at 170-180° for 2 hours. After cooling, ice water (200 ml) was added and the solution was carefully made alkaline with 25% ammonium hydroxide then extracted with ethyl acetate. The solvent was removed and the crude product was purified by column chromatography on silica gel by eluting with 10% methanol/ethyl acetate.

Compound **15c**, obtained from **14e** in 25% yield, had mp 243-245° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 12.81 (broad, 1H, deuterium oxide-exchangeable, heterocyclic NH), 8.04 (s, 1H, H-2), 7.30 (m, 3H, 1H deuterium oxide-exchangeable, NH and 2 aromatic protons), 7.14 (t, 2H, aromatic protons), 7.01 (bs, 2H, deuterium oxide-exchangeable, NH_2), 4.10 (s, 2H, CH_2); ms: (m/z) 258 (M^+), 242, 224, 215, 163, 148, 109.

Anal. Calcd. for $C_{12}H_{11}FN_6$: C, 55.80; H, 4.29; N, 32.54. Found: C, 55.66; H, 4.08; N, 32.26.

Compound **15d**, obtained from **14f** in 22% yield, had mp 148-150° (dimethylformamide).

Anal. Calcd. for $C_{12}H_{11}FN_6$: C, 55.80; H, 4.29; N, 32.54. Found:C, 55.56; H, 4.00; N, 32.34.

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