New [g]-Fused [1,2,4]Triazolo[1,5-c]pyrimidines: Synthesis of Pyrido[3,2-e] and [4,3-e][1,2,4]triazolo[1,5-c]pyrimidine, Pyrimido[5,4-e][1,2,4]triazolo[1,5-c]pyrimidine and [1,2,4]Triazolo[1,5-c]pteridine Derivatives

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

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

Received June 7, 1994

A number of 2-aryl-substituted pyrido[3,2-*e*] and [4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and [1,2,4]triazolo[1,5-*c*]pteridines **11,12a,b,e**, their corresponding 5-carbonyl derivatives **7,8a,b,e** and some pyrimido[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-ones **7,8c,d** have been synthesized, according to different pathways. The new tricyclic heterocycles were prepared with the aim of studying their possible benzodiazepine receptors affinity.

J. Heterocyclic Chem., **31**, 1503 (1994).

The benzodiazepines are currently the agents of choice in the clinical treatment of anxiety, but undesirable side effects such as ataxia, sedation and psychological dependence has prompted a search for a non-benzodiazepine anxiolytic, which would be free from these effects. The recent discovery that some [1,2,4]triazolo[1,5-*c*]quinazolines showed high affinity for the benzodiazepine receptors and, particularly, that 9-chloro-2-(2-fluorophenyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5(6*H*)-one **1** displayed a very potent activity as a benzodiazepine antagonist [1], led us to investigate tricyclic heterocycles containing fused triazolo systems. Previous work of our group has indeed outlined our interest of such compounds in both synthetic [2,3] and medicinal chemistry [4].

As a further development of our program, we wish to report in this paper the preparation of some 2-aryl-substituted pyrido[3,2-*e*] and [4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines, pyrimido[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and [1,2,4]triazolo[1,5-*c*]pteridines **2** and **3**, in order to verify their potential interaction with benzodiazepine receptors.

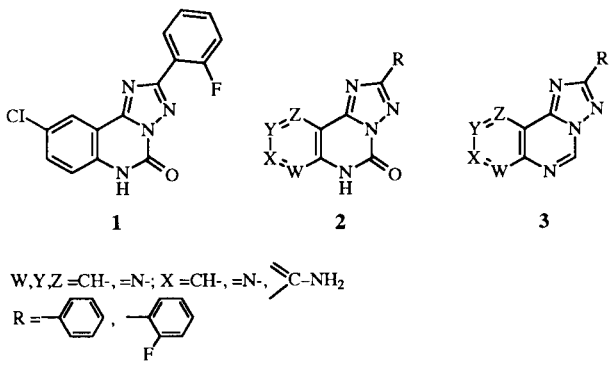
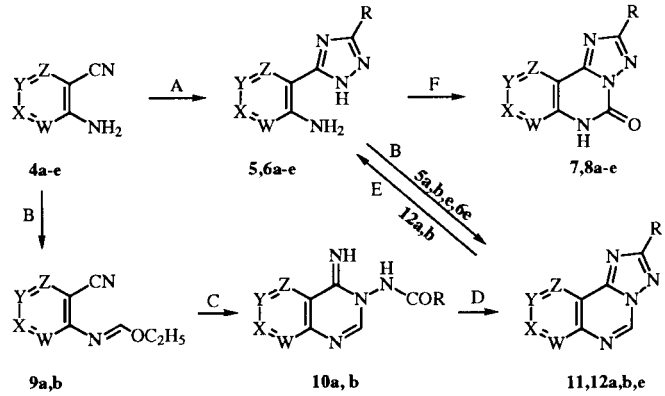


Figure 1

The syntheses are outlined in Scheme 1. Although the synthetic routes were similar to those used in our previous work for the preparation of structurally related compounds [4], we encountered many difficulties in this work owing to the very different reactivity of the various heterocyclic moieties employed as starting materials.

Scheme 1



	W	X	Y	Z
a	-N=	-CH=	-CH=	-CH=
b	-CH=	-N=	-CH=	-CH=
c	-N=	-CH=	-N=	-CH=
d	-N=	C-NH2	-N=	-CH=
e	-N=	-CH=	-CH=	-N=

5,7,11 R =

6,8,10,12 R =

Reagents A, R-CO-NH-NH_2/Ph_2O, reflux; B, $CH(OC_2H_5)_3$, reflux; C, R-CO-NH-NH_2/CH_3O-(CH)-OH, reflux; D, Ph_2O, reflux; E, 10% HCl, reflux; F, CDI/THF or NH_2-$COOC_2H_5$, reflux.

The 2-amino-3-cyanopyridine **4a** was prepared by reaction of 8-cyanotetrazolo[1,5-*a*]pyridine [5] with triphenylphosphine, followed by hydrolysis in 80% acetic acid of the resulting triphenyl-phosphoranylideneamino derivative [6] (see Experimental). The sequence described here represents a novel approach to prepare **4a** and avoids the troublesome high pressure apparatus required for the direct amination of 2-chloro-3-cyanopyridine [7].

The aminocyano compounds **4b** [8], **4c** [9] and **4d** [10] were prepared according to the literature, while the 2-amino-3-cyanopyrazine was obtained and conveniently used as the 1-oxide derivative [11].

Compounds **5a-e** and **6c-e** were directly prepared by condensation of the corresponding aminocarbonitriles with the appropriate arylhydrazide in refluxing diphenyl ether (Route A). This convenient synthetic pathway could not be employed for the preparation of compounds **6a,b**, because of the formation of quantities of decomposition products which afforded very poor yields of the expected amino[3-(2-fluorophenyl)[1,2,4]triazol-5-yl]pyridines.

These latter compounds were obtained by refluxing compounds **4a,b** in triethyl orthoformate to give the *N*-ethoxymethylene derivatives **9a,b** which were found to react with 2-fluorobenzhydrazide to provide **10a,b**; these compounds were easily cyclized in refluxing diphenyl ether to pyrido[3,2-*e*] and [4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **12a,b**. Finally, ring opening of the pyrimidine moiety by refluxing in 10% hydrochloric acid, furnished the desired derivatives **6a,b** (Route B-C-D-E). Compounds **5a-c** and **6c** by reaction with 1,1'-carbonyldiimidazole in refluxing anhydrous tetrahydrofuran were cyclized to [1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones **7a-c** and **8c**; by the same treatment, the remaining compounds **5** and **6** did not afford the corresponding carbonyl compounds **7** and **8** which were instead obtained by heating **5d,e** and **6a,b,d,e** in ethyl carbamate.

Ring closure of amino(3-phenyl[1,2,4]triazol-5-yl)-pyridines **5a,b**, 4-amino and 2,4-diamino-5-(3-aryl-[1,2,4]triazol-5-yl)pyrimidines **5,6c,d** and 2-amino-3-(3-aryl[1,2,4]triazol-5-yl)pyrazines **5,6e** to the corresponding tricyclic derivatives **11a-e** and **12c-e** in refluxing triethyl orthoformate took place only for the pyridines **5a,b** and the pyrazines **5,6e**, while attempts to cyclize the aminotriazolyl pyrimidines **5c,d** and **6c,d** under the same conditions only resulted in the recovery of the starting materials.

In the Experimental ir, ^{1}H-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-nmr spectra were recorded on a Varian Gemini 200 MHz instrument and peak assignments for aromatic protons were also based on ^{1}H-nmr-COSY spectra; electron ionization mass spectra were determined on an HP 59980 B spectrometer, operating at 70 eV. Column chromatography was performed on Merck silica gel (70-230 mesh). 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.

3-Cyano-2-triphenylphosphoranylideneaminopyridine.

8-Cyanotetrazolo[1,5-*a*]pyridine (13.0 g, 90 mmoles) [5] and triphenylphosphine (23.5 g, 90 mmoles) were heated under reflux for 3 hours in chlorobenzene (150 ml). The solvent was evaporated *in vacuo* and the residue was crystallized from benzene/cyclohexane, yield 90%; mp 217-219°, ^{1}H-nmr (DMSO-d_6): δ 7.94 (dd, 1H, H-6), 7.90-7.70 (m, 7H, H-4 and phenyl protons), 7.68-7.46 (m, 9H, phenyl protons), 6.54 (dd, 1H, H-5).

Anal. Calcd. for $C_{24}H_{18}N_3P$: C, 75.98; H, 4.78; N, 11.08. Found: C, 76.04; H, 4.76; N, 10.95.

2-Amino-3-cyanopyridine **4a**.

A mixture of 3-cyano-2-triphenylphosphoranylideneamino-pyridine (15 g, 40 mmoles) in 80% acetic acid (500 ml) was allowed to reflux for 0.5 hours. After cooling, the solution was partially concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The aqueous layer was evaporated *in vacuo* and the residue crystallized from benzene/cyclohexane, yield 80%, mp 130-132° (lit [7] 131-133°).

General Procedure for the Preparation of Amino[1,2,4]triazol-5-yl Derivatives **5a-e** and **6c-e**.

A mixture of the appropriate aminonitrile **4** (20 mmoles) and benzhydrazide (3.3 g, 24 mmoles, to obtain **5a-e**) or 2-fluorobenzhydrazide (3.7 g, 24 mmoles, to obtain **6c-e**) in diphenyl ether (50 ml), was stirred at reflux temperature. The reaction was monitored by tlc, and stopped when starting material had disappeared (3-6 hours). The mixture was allowed to cool to room temperature and *n*-hexane (150 ml) was added. The precipitate was collected by filtration, washed with additional *n*-hexane then treated by different procedures. To obtain compounds **5a,b,e** and **6c-e** the precipitate was extracted with ethyl acetate (**5a,b,e** and **6e**) or methanol (**6c,d**) and the residue, obtained after evaporation of the solvent, was directly crystallized (**5a,b**) or chromatographed by eluting with ethyl acetate (**6c**), or with 10% methanol/ethyl acetate (**6d**), or with an ethyl acetate/*n*-hexane (1:1) mixture (**5,6e**). To obtain compounds **5c,d** the solid which had formed after *n*-hexane addition to the reaction mixture, was first rinsed with hot ethyl acetate then crystallized (**5c**) or purified by chromatography eluting with 10% methanol/ethyl acetate (**5d**).

2-Amino-3-(3-phenyl-1*H*-[1,2,4]triazol-5-yl)pyridine **5a**.

This compound was obtained from **4a** in 40% yield, mp 255-257° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.60 (bs, 1H, deuterium oxide-exchangeable, NH), 8.22 (dd, 1H, H-6), 8.10-8.06 (m, 3H, H-4 and phenyl protons), 7.57-7.48 (m, 3H, phenyl protons), 7.28 (bs, 2H, deuterium oxide-exchangeable, NH_2), 6.69 (dd, 1H, H-5).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.98; H, 4.51; N, 29.27.

3-Amino-4-(3-phenyl-1*H*-[1,2,4]triazol-5-yl)pyridine **5b**.

This compound was obtained from **4b** in 44% yield, mp 215-217° (methanol/ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 14.75 (bs, 1H, deuterium oxide-exchangeable, NH), 8.24 (s, 1H, H-2), 8.10 (d, 1H, H-6), 7.92 (d, 1H, H-5), 7.83-7.79 (m, 2H, phenyl protons), 7.60-7.48 (m, 3H, phenyl protons), 6.70 (bs, 2H, deuterium oxide-exchangeable, NH_2).

Anal. Calcd. for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.95; H, 4.42; N, 29.37.

4-Amino-5-(3-phenyl-1*H*-[1,2,4]triazol-5-yl)pyrimidine **5c**.

This compound was obtained from **4c** in 38% yield, mp 317-318° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.80 (bs, 1H, deuterium oxide-exchangeable, NH), 8.95 (s, 1H, H-6), 8.44 (s, 1H, H-2), 8.08 (m, 2H, phenyl protons), 7.88 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.52 (m, 3H, phenyl protons).

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.48; H, 4.12; N, 34.97.

2,4-Diamino-5-(3-phenyl-1*H*-[1,2,4]triazol-5-yl)pyrimidine **5d**.

This compound was obtained from **4d** in 39% yield, mp 225-227° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.20 (bs, 1H, deuterium oxide-exchangeable, NH), 8.56 (s, 1H, H-6), 8.07-8.03 (m, 2H, phenyl protons), 7.60-7.40 (m, 5H, 3H after deuterium oxide exchange, 2-NH_2 and phenyl protons), 6.43 (bs, 2H, deuterium oxide-exchangeable, 4-NH_2).

Anal. Calcd. for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.71. Found: C, 57.08; H, 4.19; N, 38.42.

2-Amino-3-(3-phenyl-1*H*-[1,2,4]triazol-5-yl)pyrazine **5e**.

This compound was obtained from **4e** *N*-oxide in 35% yield, mp >320° (ethyl acetate/methanol); ^{1}H-nmr (DMSO-d_6): δ 14.87 (bs, 1H, deuterium oxide-exchangeable, NH), 8.19 (d, 1H, H-5), 8.14-8.10 (m, 2H, phenyl protons), 7.95 (d, 1H, H-6), 7.71 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.56-7.45 (m, 3H, phenyl protons).

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.61; H, 4.06; N, 34.98.

4-Amino-5-[3-(2-fluorophenyl)-1*H*-[1,2,4]triazol-5-yl]pyrimidine **6c**.

This compound was obtained from **4c** in 16% yield, mp 282-284° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.68 (bs, 1H, deuterium oxide-exchangeable, NH), 8.94 (s, 1H, H-6), 8.47 (s, 1H, H-2), 8.12 (t, 1H, phenyl H-3), 7.82 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.70-7.32 (m, 3H, phenyl protons).

Anal. Calcd. for $C_{12}H_9FN_6$: C, 56.25; H, 3.54; N, 32.80. Found: C, 56.44; H, 3.57; N, 32.74.

2,4-Diamino-5-[3-(2-fluorophenyl)-1*H*-[1,2,4]triazol-5-yl]-pyrimidine **6d**.

This compound was obtained from **4d** in 22% yield, mp 184-186° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.22 (s, 1H, deuterium oxide-exchangeable, NH), 8.54 (s, 1H, H-6), 8.05 (t, 1H, phenyl H-3), 7.55-7.20 (m, 5H, 3H after deuterium oxide exchange, 2-NH_2 and phenyl protons), 6.40 (bs, 2H, deuterium oxide-exchangeable, 4-NH_2).

Anal. Calcd. for $C_{12}H_{10}FN_7$: C, 53.13; H, 3.72; N, 36.15. Found: C, 53.10 H, 3.82; N, 35.94.

2-Amino-3-[3-(2-fluorophenyl)-1*H*-[1,2,4]triazol-5-yl]pyrazine **6e**.

This compound was obtained from **4e** in 15% yield, mp 261-263° (ethyl acetate/methanol); ^{1}H-nmr (DMSO-d_6): δ 15.00 (bs, 1H, deuterium oxide-exchangeable, NH), 8.18 (d, 1H, H-5), 8.12 (t, 1H, phenyl H-3), 7.95 (d, 1H, H-6), 7.72 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.58-7.30 (m, 3H, phenyl protons).

Anal. Calcd. for $C_{12}H_9FN_6$: C, 56.25; H, 3.54; N, 32.80. Found: C, 56.41; H, 3.46; N, 32.55.

N-Ethoxymethylene-2-amino-3-cyanopyridine **9a**. *N*-Ethoxymethylene-3-amino-4-cyanopyridine **9b**.

A solution of **4a** or **4b** (2.4 g, 20 mmoles) in triethyl orthoformate (60 ml) was refluxed for 24 hours. Excess orthoformate was removed *in vacuo* and the resulting nearly pure solid **9** was used without further purification. An analytical sample was purified by column chromatography eluting with ethyl acetate/*n*-hexane (1:1) mixture.

Compound **9a** was obtained from **4a** in 82% yield, mp 49-51°; ^{1}H-nmr (DMSO-d_6): δ 8.57 (dd, 1H, H-6), 8.25 (dd, 1H, H-4), 7.34 (dd, 1H, H-5), 4.37 (q, 2H, -CH_2), 1.34 (t, 3H, -CH_3).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.59; H, 5.23; N, 23.85.

Compound **9b** was obtained from **4b** in 80% yield, mp 69-71°.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.68; H, 5.25; N, 23.78.

3-(2-Fluorobenzoylamino)-4-iminopyrido[2,3-*d*]pyrimidine **10a**. 3-(2-Fluorobenzoylamino)-4-iminopyrido[3,4-*d*]pyrimidine **10b**.

A suspension of **9a** or **9b** (2.1 g, 12 mmoles) and 2-fluorobenzhydrazide (2.2 g, 14 mmoles) in ethylene glycol monomethyl ether (60 ml), was refluxed for 2 hours. The solvent was removed and the residue was rinsed with hot methanol to give a pure sample.

Compound **10a** was obtained from **9a** in 48% yield, mp 298-300° (methanol); ^{1}H-nmr (DMSO-d_6): δ 11.90 (bs, 1H, deuterium oxide-exchangeable, imino NH), 11.00 (bs, 1H, deuterium oxide-exchangeable, NHCO), 8.51 (dd, 1H, H-7), 8.28 (dd, 1H, H-5), 8.02 (s, 1H, H-2), 7.95 (t, 1H, phenyl H-3), 7.67-7.32 (m, 4H, H-6 and phenyl protons).

Anal. Calcd. for $C_{14}H_{10}FN_5O$: C, 59.36; H, 3.56; N, 24.72. Found: C, 59.50 H, 3.56; N, 24.39.

Compound **10b** was obtained from **9b** in 54% yield, mp 305-307° (methanol); ^{1}H-nmr (DMSO-d_6): δ 12.10 (bs, 1H, deuterium oxide-exchangeable, imino NH), 10.88 (bs, 1H, deuterium oxide-exchangeable, NHCO), 8.64 (s, 1H, H-8), 8.50 (d, 1H, H-6), 8.14 (s, 1H, H-2), 7.92 (t, 1H, phenyl H-3), 7.83 (d, 1H, H-5), 7.68-7.31 (m, 3H, phenyl protons).

Anal. Calcd. for $C_{14}H_{10}FN_5O$: C, 59.36; H, 3.56; N, 24.72. Found: C, 59.47 H, 3.53; N, 24.56.

2-(2-Fluorophenyl)pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **12a**. 2-(2-Fluorophenyl)pyrido[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine **12b**.

A suspension of **10a** or **10b** (2.8 g, 10 mmoles) in diphenyl ether (40 ml) was refluxed for 8 hours. After cooling, *n*-hexane (100 ml) was added to the reaction mixture and the resulting solid was filtered, thoroughly washed with *n*-hexane, and crystallized.

Compound **12a** was obtained from **10a** in 90% yield, mp 215-217° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.90 (s, 1H, H-5), 9.15

(dd, 1H, $J_{8,9}$ = 4.5 Hz, $J_{8,10}$ = 1.9 Hz, H-8), 8.95 (dd, 1H, $J_{9,10}$ = 8.0 Hz, $J_{8,10}$ = 1.9 Hz, H-10), 8.30 (t, 1H, phenyl H-3), 7.87 (dd, 1H, $J_{9,10}$ = 8.0 Hz, $J_{8,9}$ = 4.5 Hz, H-9), 7.72-7.38 (m, 3H, phenyl protons); ms: (m/z) 265 (M^+), 249, 157, 140, 119.

Anal. Calcd. for $C_{14}H_8FN_5 \cdot 1/2H_2O$: C, 61.31; H, 3.31; N, 25.54. Found: C, 61.43; H, 3.11; N, 25.24.

Compound **12b** was obtained from **10b** in 85% yield; mp 276-278° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 9.32 (s, 1H, H-5), 9.19 (s, 1H, H-7), 8.91 (d, 1H, $J_{9,10}$ = 5.2 Hz, H-9), 8.42 (d, 1H, $J_{9,10}$ = 5.2 Hz, H-10), 7.90 (t, 1H, phenyl H-3), 7.80-7.40 (m, 3H, phenyl protons); ms: (m/z) 265 (M^+).

Anal. Calcd. for $C_{14}H_8FN_5$: C, 63.39; H, 3.04; N, 26.40. Found: C, 63.65; H, 2.76; N, 26.55.

2-Amino-3-[3-(2-fluorophenyl)-1*H*-[1,2,4]triazol-5-yl]pyridine **6a**. 3-Amino-4-[3-(2-fluorophenyl)-1*H*-[1,2,4]triazol-5-yl]pyridine **6b**.

A suspension of **12a** or **12b** (2.6 g, 10 mmoles) in 10% hydrochloric acid (100 ml), was heated at reflux temperature for 2 hours. After cooling, the solution was adjusted to *p*H 6 by dropwise addition of diluted sodium hydroxide then extracted with ethyl acetate. The solid resulting from solvent evaporation was crystallized.

Compound **6a** was obtained from **12a** in 95% yield, mp 268-270° (ethyl acetate); ^{1}H-nmr (DMSO-d_6): δ 14.54 (bs, 1H, deuterium oxide-exchangeable, NH), 8.23 (d, 1H, H-6), 8.09 (m, 2H, H-4 and phenyl H-3), 7.64-7.10 (m, 5H, 3H after deuterium oxide exchange, NH_2 and phenyl protons), 6.71 (dd, 1H, H-5).

Anal. Calcd. for $C_{13}H_{10}FN_5$: C, 61.17; H, 3.95; N, 27.44. Found: C, 61.20; H, 4.05; N, 27.37.

Compound **6b** was obtained from **12b** in 92% yield, mp 236-238° (methanol); ^{1}H-nmr (DMSO-d_6): δ 14.64 (bs, 1H, NH), 8.24 (s, 1H, H-2), 8.12 (t, 1H, phenyl H-3), 7.84 (d, 1H, H-6), 7.77 (d, 1H, H-5), 7.65-7.30 (m, 3H, phenyl protons), 6.69 (bs, 2H, deuterium oxide-exchangeable, NH_2).

Anal. Calcd. for $C_{13}H_{10}FN_5$: C, 61.17; H, 3.95; N, 27.44. Found: C, 60.86; H, 3.85; N, 27.10.

General Procedure for the Preparation of [*g*]-Fused 2-Aryl-[1,2,4]triazolo[1,5-*c*]pyrimidines **11a,b,e** and **12e**.

A suspension of each compound **5** or **6** (10 mmoles) in triethyl orthoformate (80 ml) was refluxed for 24 hours. Excess triethyl orthoformate was removed *in vacuo* and the residue crystallized.

2-Phenylpyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **11a**.

This compound was obtained from **5a** in 72% yield, mp 252-254° (ethanol); ^{1}H-nmr (DMSO-d_6): δ 9.84 (s, 1H, H-5), 9.13 (d, 1H, $J_{8,9}$ = 4.6 Hz, H-8), 8.93 (d, 1H, $J_{9,10}$ = 7.6 Hz, H-10), 8.27 (m, 2H, phenyl protons), 7.84 (dd, 1H, $J_{9,10}$ = 7.6 Hz, $J_{8,9}$ = 4.6 Hz, H-9), 7.57 (m, 3H, phenyl protons), ms: (m/z) 247 (M^+), 219, 191, 164.

Anal. Calcd. for $C_{14}H_9N_5$: C, 68.01; H, 3.67; N, 28.32. Found: C, 68.16; H, 3.44; N, 27.95.

2-Phenylpyrido[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **11b**.

This compound was obtained from **5b** in 96% yield, mp 245-247° (dimethylformamide); ^{1}H-nmr (DMSO-d_6): δ 9.81 (s, 1H, H-5), 9.41 (s, 1H, H-7), 8.91 (d, 1H, $J_{9,10}$ = 5.3 Hz, H-9), 8.39 (d, 1H, $J_{9,10}$ = 5.3 Hz, H-10), 8.29 (m, 2H, phenyl protons), 7.59 (m, 3H, phenyl protons), ms: (m/z) 247 (M^+).

Anal. Calcd. for $C_{14}H_9N_5$: C, 68.01; H, 3.67; N, 28.32. Found: C, 68.25; H, 3.54; N, 28.44.

2-Phenyl[1,2,4]triazolo[1,5-*c*]pteridine **11e**.

This compound was obtained from **5e** in 72% yield, mp 296-298° (methanol); ^{1}H-nmr (DMSO-d_6): δ 9.97 (s, 1H, H-5), 9.21 (d, 1H, $J_{8,9}$ = 2.1 Hz, H-9), 9.15 (d, 1H, $J_{8,9}$ = 2.1 Hz, H-8), 8.30 (m, 2H, phenyl protons), 7.60 (m, 3H, phenyl protons); ms: (m/z) 248 (M^+), 207, 166, 139.

Anal. Calcd. for $C_{13}H_8N_6$: C, 62.90; H, 3.25; N, 33.85. Found: C, 62.70; H, 3.07; N, 33.81.

2-(2-Fluorophenyl)[1,2,4]triazolo[1,5-*c*]pteridine **12e**.

This compound was obtained from **6e** in 65% yield, mp 270-272° (methanol); ^{1}H-nmr (DMSO-d_6): δ 10.01 (s, 1H, H-5), 9.21 (d, 1H, $J_{8,9}$ = 2.1 Hz, H-9), 9.15 (d, 1H, $J_{8,9}$ = 2.1 Hz, H-8), 8.33 (m, 1H, phenyl H-3), 7.60-7.41 (m, 3H, phenyl protons); ms: (m/z) 266 (M^+), 247, 212, 184, 157.

Anal. Calcd. for $C_{13}H_7FN_6$: C, 58.65; H, 2.65; N, 31.57. Found: C, 58.74; H, 2.47; N, 31.31.

General Procedure for the Preparation of [*g*]-Fused 2-Aryl-[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones **7a-c** and **8c**.

A mixture of the appropriate compound **5** or **6** (5 mmoles) and 1,1'-carbonyldiimidazole (1.0 g, 6 mmoles) in anhydrous tetrahydrofuran (30 ml) was refluxed overnight. After cooling, the solvent was removed *in vacuo* and the residue crystallized.

2-Phenylpyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **7a**.

This compound was obtained from **5a** in 64% yield, mp >320° (methanol); ir: υ CO 1723 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 12.82 (s, 1H, deuterium oxide-exchangeable, NH), 8.68 (d, 1H, $J_{8,9}$ = 4.5 Hz, H-8), 8.60 (d, 1H, $J_{9,10}$ = 7.6 Hz, H-10), 8.21 (m, 2H, phenyl protons), 7.52 (m, 3H, phenyl protons), 7.45 (dd, 1H, $J_{9,10}$ = 7.6 Hz, $J_{8,9}$ = 4.5 Hz, H-9); ms: (m/z) 263 (M^+), 235, 207, 180.

Anal. Calcd. for $C_{14}H_9N_5O$: C, 63.87 H, 3.45; N, 26.60. Found: C, 63.93; H, 3.20; N, 26.71.

2-Phenylpyrido[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **7b**.

This compound was obtained from **5b** in 72% yield, mp >320° (ethanol); ir: υ CO 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 12.62 (bs, 1H, deuterium oxide-exchangeable, NH), 8.77 (s, 1H, H-7), 8.54 (d, 1H, $J_{9,10}$ = 5.1 Hz, H-9), 8.20 (m, 2H, phenyl protons), 8.09 (d, 1H, $J_{9,10}$ = 5.1 Hz, H-10), 7.54 (m, 3H, phenyl protons); ms: (m/z) 263 (M^+).

Anal. Calcd. for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.60. Found: C; 63.68; H, 3.35; N, 26.31.

2-Phenylpyrimido[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **7c**.

This compound was obtained from **5c** in 60% yield, mp 319-320° (methanol); ir: υ CO 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.40 (bs, 1H, deuterium oxide-exchangeable, NH), 9.17 (s, 1H, H-8), 8.87 (s, 1H, H-10), 8.22 (m, 2H, phenyl protons), 7.49 (m, 3H, phenyl protons); ms: (m/z) 264 (M^+), 236, 209, 197.

Anal. Calcd. for $C_{13}H_8N_6O$: C, 59.09; H, 3.05; N, 31.80. Found: C, 58.85; H, 2.99; N, 31.72.

2-(2-Fluorophenyl)pyrimido[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **8c**.

This compound was obtained from **6c** in 65% yield, mp >320° (methanol); ir: υ CO 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.60 (bs, 1H, deuterium oxide-exchangeable, NH), 9.49 (s, 1H, H-8), 9.18 (s, 1H, H-10), 8.19 (t, 1H, phenyl H-3), 7.70-7.37 (m, 3H, phenyl protons); ms: (m/z) 282 (M^+), 256, 227, 192, 182, 176, 159, 131.

Anal. Calcd. for $C_{13}H_7FN_6O$: C, 55.32; H, 2.50; N, 29.78. Found: C, 55.30; H, 2.47 N, 29.93.

General Procedure for the Preparation of [g]-Fused 2-Aryl-[1,2,4]triazolo[1,5-c]pyrimidin-5(6*H*)-ones **7d,e** and **8a,b,d,e**.

A suspension of each compound **5** or **6** (2.5 mmoles) in ethyl carbamate (1.1 g, 12 mmoles), was refluxed for 24 hours. The reaction mixture was allowed to cool at room temperature, then vigorously stirred in water (30 ml) for **7e** and **8a,b,c,e** or hot methanol (30ml) for **7,8d**, for 1 hour to dissolve residual ester. The solid was filtered, washed with water or methanol, then crystallized.

8-Amino-2-phenylpyrimido[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **7d**.

This compound was obtained from **5d** in 40% yield, mp >320° (methanol); ir: υ CO 1735 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 12.52 (bs, 1H, deuterium oxide-exchangeable, NH), 9.00 (s, 1H, H-10), 8.17 (m, 2H, phenyl protons), 7.54 (m, 5H, 3H after deuterium oxide exchange, NH_2 and phenyl protons); ms: (m/z) 279 (M^+).

Anal. Calcd. for $C_{13}H_9N_7O$: C, 55.91; H, 3.25; N, 35.11. Found: C, 55.87; H, 3.28; N, 35.06.

2-Phenyl[1,2,4]triazolo[1,5-*c*]pteridin-5(6*H*)-one **7e**.

This compound was obtained from **5e** in 50% yield, mp >320° (methanol); ir: υ CO 1737 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.15 (bs, 1H, deuterium oxide-exchangeable, NH), 8.74 (d, 1H, $J_{8,9}$ = 2.3 Hz, H-9), 8.71 (d, 1H, $J_{8,9}$ = 2.3 Hz, H-8), 8.25 (m, 2H, phenyl protons), 7.60 (m, 3H, phenyl protons); ms: (m/z) 264 (M^+), 257, 239, 197, 169, 163.

Anal. Calcd. for $C_{13}H_8N_6O$: C, 59.09; H, 3.05; N, 31.80. Found: C, 59.11; H, 2.98; N, 31.89.

2-(2-Fluorophenyl)pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **8a**.

This compound was obtained from **6a** in 58% yield, mp >320° (methanol); ir: υ CO 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 12.84 (bs, 1H, deuterium oxide-exchangeable, NH), 8.70 (dd, 1H, $J_{8,9}$ = 4.8 Hz, $J_{8,10}$ = 1.8 Hz, H-8), 8.61 (dd, 1H, $J_{9,10}$ = 7.9 Hz, $J_{8,10}$ = 1.8 Hz, H-10), 8.18 (t, 1H, phenyl H-3), 7.58-7.41 (m, 4H, H-9 and phenyl protons); ms: (m/z) 281(M^+), 263, 253, 145, 136.

Anal. Calcd. for $C_{14}H_8FN_5O$: C, 59.79; H, 2.87; N, 24.90. Found: C, 59.64; H, 2.70; N, 25.18.

2-(2-Fluorophenyl)pyrido[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one **8b**.

This compound was obtained from **6b** in 55% yield, mp >320° (dimethylformamide); ir: υ CO 1725 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.15 (bs, 1H, deuterium oxide-exchangeable, NH), 8,79 (s, 1H, H-7), 8.55 (d, 1H, $J_{9,10}$ = 5.14 Hz, H-9), 8.20 (t, 1H, phenyl H-3), 8.10 (d, 1H, $J_{9,10}$ = 5.14 Hz, H-10), 7.60-7.37 (m, 3H, phenyl protons); ms: (m/z) 281 (M^+).

Anal. Calcd. for $C_{14}H_8FN_5O$: C, 59.79; H, 2.87; N, 24.90. Found: C, 59.53; H, 2.61; N, 24.96.

8-Amino-2-(2-fluorophenyl)pyrimido[5,4-*e*][1,2,4]triazolo[5,1-*c*]pyrimidin-5(6*H*)-one **8d**.

This compound was obtained from **6d** in 35% yield, mp >320° (water); ir: υ CO 1720 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 12.52 (bs, 1H, deuterium oxide-exchangeable, NH), 8.98 (s, 1H, H-10), 8.16 (t, 1H, phenyl H-3), 7.56-7.34 (m, 5H, 3H after deuterium oxide exchange, NH_2 and phenyl protons); ms: (m/z) 297 (M^+), 264, 178.

Anal. Calcd. for $C_{13}H_8FN_7O$: C, 52.53; H, 2.71; N, 32.98. Found: C, 52.61; H, 2.65; N, 32.68.

2-(2-Fluorophenyl)[1,2,4]triazolo[1,5-*c*]pteridin-5(6*H*)-one **8e**.

This compound was obtained from **6e** in 55% yield, mp >320° (methanol); ir: υ CO 1735 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.18 (bs, 1H, deuterium oxide-exchangeable, NH), 8.77 (d, 1H, $J_{8,9}$ = 2.4 Hz, H-9), 8.73 (d, 1H, $J_{8,9}$ = 2.4 Hz, H-8), 8.23 (t, 1H, phenyl H-3); 7.70-7.39 (m, 3H, phenyl protons); ms: (m/z) 282 (M^+), 254, 227, 136.

Anal. Calcd. for $C_{13}H_7FN_6O.H2O$: C, 52.00; H, 3.02; N, 27.99. Found: C, 52.20; H, 2.87; N, 27.83.

Acknowledgements.

We wish to thank Dr. L. Turchetto for the mass spectra, Mr. R. Lecce for microanalyses and Mr. A. Puccio for technical assistance. This paper has been supported by the National Research Council (CNR) Grant 93.02921.PF72.

REFERENCES AND NOTES

[1] J. E. Francis, W. D. Cash, B. S. Barbaz, P. S. Bernard, R. A. Lovell, G. C. Mazzenga, R. C. Friedmann, J. L. Hyun, A. F. Braunwalder, P. S. Loo and D. A. Bennett, *J. Med. Chem.*, **34**, 281 (1991).

[2] F. Gatta, M. R. Del Giudice and A. Borioni, *J. Heterocyclic Chem.*, **30**, 11 (1993).

[3] F. Gatta, M. R. Del Giudice, A. Borioni, C. Mustazza and C. Fazio, *J. Heterocyclic Chem.*, in press.

[4] F. Gatta, M. R. Del Giudice, A. Borioni, P. A. Borea, S. Dionisotti and E. Ongini, *Eur. J. Med. Chem.*, **28**, 569 (1993).

[5] A. Pollack, S. Polanc, B. Stanovnik and M. Tisler, *Monatsh. Chem.*, **103**, 1591 (1972).

[6] N. Haider, G. Heinisch and D. Laßnigg, *J. Heterocyclic Chem.*, **25**, 119 (1988).

[7] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

[8] J. L. LaMattina and R. L. Taylor, *J. Org. Chem.*, **46**, 4179 (1981).

[9] J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

[10] H. W. Schmidt, G. Koitz and H. Junek, *J. Heterocyclic Chem.*, **24**, 1305 (1987).

[11] E. C. Taylor, K. L. Perlman, Y. H. Kim, I. P. Sword and P. A. Jacobi, *J. Am. Chem. Soc.*, **95**, 6413 (1973).