7-(2-Fluorobenzyl)-4-(substituted)-7*H*-imidazo[4,5-*d*]-1,2,3-triazines and -7*H*-pyrazolo[3,4-*d*]-1,2,3-triazines. Synthesis and Anticonvulsant Activity

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The imidazo[4,5-*d*]-1,2,3-triazine and pyrazolo[3,4-*d*]-1,2,3-triazine analogues of the potent anticonvulsant purine, BW 78U79 (9-(2-fluorobenzyl)-6-methylamino-9*H*-purine, **1**), were synthesized and tested for anticonvulsant activity. The imidazo[4,5-*d*]-1,2,3-triazines **11-13** were prepared in four steps from 5-aminoimidazole-4-carboxamide (**2**) and the pyrazolo[3,4-*d*]-1,2,3-triazines **18-21** were synthesized starting with 5-amino-1-(2-fluorobenzyl)pyrazole-4-carbonitrile (**14**). The intermediate 1,2,3-triazin-4-ones **6** and **16** were converted to the 4-substituted targets *via* the 4-(4-dimethylaminopyridinium) salts **10** and **17**. Imidazotriazine **11** had potent anticonvulsant activity against maximal electroshock-induced seizures, but its propensity to cause emesis precluded further development.

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Although a variety of drugs are available for the treatment of epilepsy, many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects [1-3]. The potent anticonvulsant purine, BW 78U79 (9-(2-fluorobenzyl)-6-methylamino-9*H*-purine, **1**), emerged from a program initiated to discover and develop improved antiepileptic agents [4-8]. Structure-activity studies showed that optimum activity was associated with a 9-(2-fluorobenzyl) and 6-alkylamino substitution pattern [7,8]. Analogues of **1** that contained nitrogenous, isosteric substitutions in the pyrimidine [9] or imidazole [10] rings did not exhibit improved anticonvulsant activity. We have further modified the structure of **1** by preparing imidazo[4,5-*d*]-1,2,3-triazine and pyrazolo[3,4-*d*]-1,2,3-triazine analogues. Their synthesis and anticonvulsant activity are reported.

Chemistry.

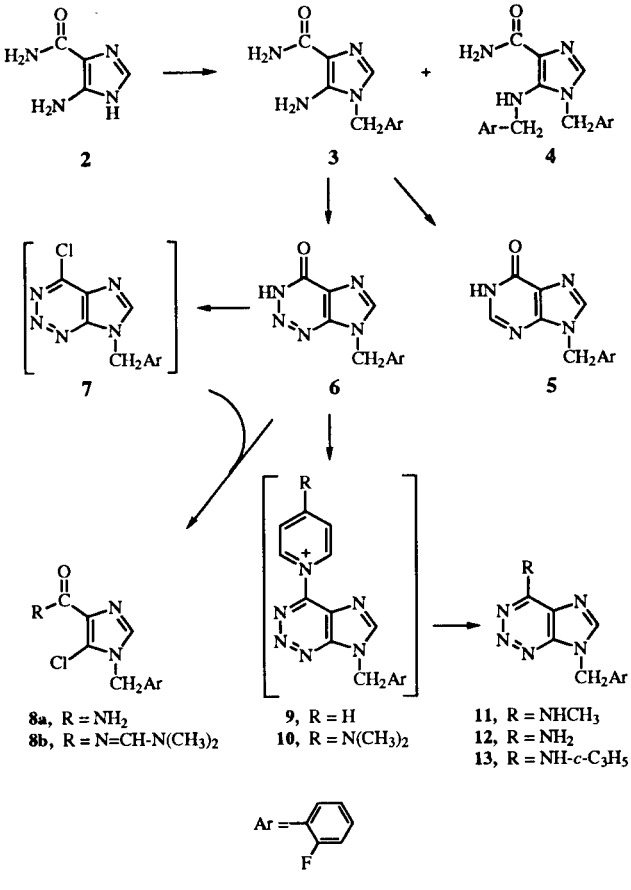
Imidazo[4,5-*d*]triazines

Compounds **11**, **12** and **13** were prepared from 5-aminoimidazole-4-carboxamide (**2**) as outlined in Scheme 1. The sodium salt of **2** was alkylated with 2-fluorobenzyl bromide to give **3** in 42% yield [11]. The *bis*-benzylated byproduct **4** was also formed in about 10% yield. The structure of **3** was confirmed by condensation with ethyl formate [12] to give **5**, which was identical with **5** prepared from 6-chloro-9-(2-fluorobenzyl)-9-*H*-purine [7,13].

The 2-azapurine **6** was prepared from **3** in 84% yield by nitrosation with sodium nitrite in dilute hydrochloric acid [14,15]. Attempts to prepare the chloro intermediate **7** by using phosphorous oxychloride, thionyl chloride-dimethylformamide, and oxalyl chloride-dimethylformamide were unsuccessful due to triazine ring instability, a known property of some triazine derivatives [16-19]. The major degradation products were assigned structures **8a** and **8b** based on physical data. Imidazole **8a** was obtained conveniently by hydrolysis of **8b**, which was isolated in modest yield from reaction of **6** with Vilsmeier reagent. These chloroimidazoles may have formed by Michael addition of chloride to the imidazotriazinone [16].

Several known procedures for converting lactams to amino derivatives *via* pyridinium intermediates [20-22]

Scheme 1

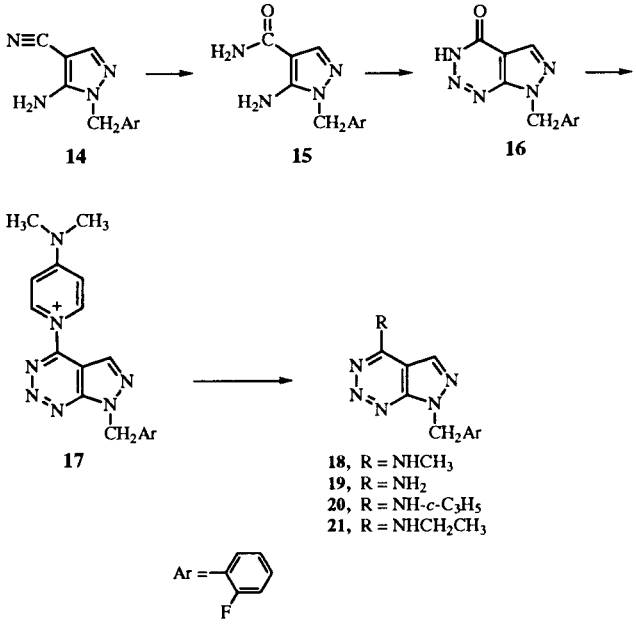


were investigated to convert **6** to **11**, but the desired product was not detected. The pyridinium intermediate **9** was prepared from **6** and 4-chlorophenylphosphorodichloridate in pyridine. When **9** was reacted *in situ* with methylamine, 4-aminoimidazotriazine **12** was formed *via* a Zincke [22,23] ring-cleavage mechanism, which involved nucleophilic attack at the pyridinium α-carbons. The Zincke reaction was circumvented by using 4-dimethylaminopyridine (DMAP) rather than pyridine to form the reactive intermediate **10**. When **10** was treated with methylamine or cyclopropylamine, substitution occurred at the 4-position of the triazine to give **11** and **13** in good yield.

Pyrazolo[3,4-*d*]triazines.

The pyrazolo derivatives **18-21** were prepared in four steps from **14** [10] as outlined in Scheme 2. Hydrolysis of **14** with cold sulfuric acid gave carboxamide **15** in high yield. The pyrazolotriazinone **16** was prepared from **15** in high yield by nitrosation with sodium nitrite in concentrated hydrochloric acid-acetic acid [15,24]. The triazinone **16** was converted to **18-21** *via* the DMAP procedure. In this case the DMAP adduct **17** was sufficiently stable to allow it to be isolated, recrystallized and characterized. The pyridinium intermediate **17** was treated with the appropriate amine or ammonium hydroxide to give **18-21** in good yields. Due to restricted rotation about the C4-N bond, the *syn*- and *anti*-rotomers of the 4-substituent were observed in the proton NMR for **18**, **20** and **21**.

Scheme 2



Biological Results.

Compounds **11-13** and **18-21** were tested for their ability to protect male rats against maximal electroshock-induced seizures (MES) under conditions where **1** had an i.p. ED_{50} of 1.7 ± 0.4 mg/kg and on oral ED_{50} of 2.5 ± 0.4 mg/kg [5,6]. Only the 4-(methylamino)imidazo[4,5-*d*]-1,2,3-triazine **11** had potent activity against MES with i.p. and oral ED_{50}s of 4 mg/kg. Compound **18** had an oral ED_{50} greater than 50 mg/kg, and the other compounds had i.p. ED_{50}s greater than 25 mg/kg. Thus, substitution of a nitrogen for the 2-carbon of **1** gave analogue **11**, which had potent oral anticonvulsant activity. However, **11** caused emesis in dogs when administered at 40 mg/kg, which precluded further consideration of this compound as a potential antiepileptic agent.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. The uv spectra were recorded with a Varian DMS-100 spectrophotometer. The ^{1}H nmr spectra were recorded using a Varian XL-200 spectrometer. Chemical shift values are reported in parts per million on the δ scale. The nmr spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on thin layer chromatography (tlc). Analysis (tlc) was performed on Whatman 200 μ MK6F plates of silica gel with fluorescent indicator; spots were detected with uv light. Preparative column chromatography was done using the flash chromatography technique [25] on Silica Gel 60 (40-63 μm, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc. The 5-aminoimidazole-4-carboxamide hydrochloride (**2**) was purchased from Chemalog.

5-Amino-1-(2-fluorobenzyl)imidazole-4-carboxamide (**3**).

To a stirred dispersion of hexane-washed sodium hydride (50% dispersion in mineral oil) (2.95 g, 123 mmoles) in dry dimethylformamide (150 ml) was added **2** (10.0 g, 61.5 mmoles) in portions over 15 minutes. After gas evolution had ceased (30 minutes), 2-fluorobenzyl bromide (12.8 g, 67.6 mmoles) was added dropwise over 15 minutes. The reaction mixture was stirred under a nitrogen atmosphere at ambient temperature for 3 hours. The solid was collected by filtration, washed with water and dried to give 4.51 g (31%) of crude **3**, which was essentially one spot on tlc. Additional material was obtained by extracting the mother liquors with ethyl acetate (3 x 200 ml) and evaporating the combined extracts to give 1.56 g (42% total) of pure **3** as white crystals, mp 245-250° dec; ^{1}H nmr (DMSO-d_6): δ 5.14 (s, 2H, CH_2), 5.83 (br s, 2H, NH_2), 6.70 (br d, 2H, NH_2), 6.9-7.4 (m, 5H, Ar).

Anal. Calcd. for $C_{11}H_{11}FN_4O$: C, 56.41; H, 4.73; N, 23.92. Found: C, 56.32; H, 4.74; N, 23.86.

9-(2-Fluorobenzyl)-1,9-dihydro-6*H*-purin-6-one (**5**).

To a stirred mixture of **3** (0.234 g, 1.00 mmole) and sodium methoxide (0.320 g, 6.00 mmoles) in ethanol (10 ml) at reflux under a nitrogen atmosphere was added ethyl formate (0.370 g, 5.00 mmoles). After 1 hour the reaction was poured over crushed ice (75 ml), and the mixture was neutralized by drop-

wise addition of glacial acetic acid. The white solid was collected by filtration, washed with water (2 x 30 ml) and dried to give 0.21 g (86%) of **5**, mp 269-274° dec; ^{1}H nmr (DMSO-d_6): δ 5.42 (s, 2H, CH_2), 7.1-7.4 (m, 4H, Ar), 8.03 (s, 1H, purine), 8.14 (s, 1H, purine).

Anal. Calcd. for $C_{12}H_9FN_4O \cdot 0.2H_2O$: C, 58.16; H, 3.82; N, 22.61. Found: C, 58.23; H, 3.73; N, 22.47.

7-(2-Fluorobenzyl)-3,7-dihydro-4*H*-imidazo[4,5-*d*]-1,2,3-triazin-4-one (**6**).

To a stirred solution of **3** (0.468 g, 2.00 mmoles) in 6 *N* hydrochloric acid (20 ml) cooled in an acetonitrile-dry ice bath (-45°) was added a solution of sodium nitrite (0.145 g, 2.10 mmoles) in water (5 ml) dropwise over 5 minutes under a nitrogen atmosphere. A thick precipitate formed, and ethanol (5 ml) was added dropwise to facilitate stirring. After 30 minutes the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction mixture was neutralized by dropwise addition of ammonium hydroxide, and the ethanol was removed by spin evaporation. The residual yellow solid was collected, washed with water, and dried to give 0.410 g (84%) of **6**, mp 150-155° efforescence; uv (0.1 *N* sodium hydroxide): λ_{max} 250 nm (ε 6400), 292 nm (ε 6900); uv (0.1 *N* hydrochloric acid): λ_{max} 268 nm (ε 4300), 285 nm (ε 4800); ^{1}H nmr (DMSO-d_6): δ 5.66 (s, 2H, CH_2), 7.2-7.4 (m, 4H, Ar), 8.55 (s, 1H, C-6 H), 14.05 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_8FN_5O \cdot H_2O$: C, 50.19; H, 3.83; N, 26.61. Found: C, 50.11; H, 3.85; N, 26.45.

5-Chloro-1-(2-fluorobenzyl)imidazole-4-carboxamide (**8a**).

A mixture of **8b** (100 mg, 0.324 mmole) in 95% ethanol (5 ml) was stirred under nitrogen and treated with cyclopropylamine (217 mg, 3.80 mmoles), which added in one portion. After stirring at ambient temperature 24 hours, the reaction mixture was spin-evaporated to a residue, which was mixed with 1 *N* sodium hydroxide (5 ml). The resulting solid was collected by filtration, washed (water) and dried to 73 mg (89%) of **8a** as a beige solid, mp >205° gradual dec; ir (potassium bromide pellet): 3280 (amide NH), 1625 and 1590 (amide CO) cm^{-1}: ms: (CI) m/z 256 (31%), 254 (100), 237 (23), 109 (12); ms: (EI) m/z 255 (63%), 253 (81), 236 (41), 109 (100); ^{1}H-nmr (DMSO-d_6): δ 5.32 (s, 2H, Ar-CH_2), 7.1-7.5 (m, 6H, Ar-H and NH_2), 7.97 (s, 1H, C2-H); ^{13}C-nmr (DMSO-d_6): δ 119 (C5), 129 (C4), 137 (C2, $J_{C2,H}$ = 216 Hz; comparable to data for *N*-methylimidazole, δ C2 = 137 ppm, $J_{C2,H}$ = 206 Hz); hplc: k' = 2.3 on a Supelco LC-8 5 micron column with 50% methanol/water.

Anal. Calcd. for $C_{11}H_9ClFN_3O$: C, 52.09; H, 3.58; N, 16.57; Cl, 13.98. Found: C, 52.12; H, 3.60; N, 16.56; Cl, 13.98.

5-Chloro-*N*-[(dimethylamino)methylene]-1-(2-fluorobenzyl)imidazole-4-carboxamide (**8b**).

To a stirred mixture of **6** (1.91 g, 7.79 mmoles) in cold dichloromethane (75 ml, ice bath) under nitrogen was added dropwise during 10 minutes thionyl chloride (3.24 g, 27.3 mmoles) in cold, dry dimethylformamide (1.71 g, 23.4 mmoles). After 24 hours the reaction mixture was spin-evaporated to a brown residue, which was partitioned between ethyl acetate and saturated sodium bicarbonate (50 ml each). The aqueous phase was separated and extracted with ethyl acetate (1 x 50 ml). The combined extracts were washed with water (1 x 100 ml), dried (magnesium sulfate), filtered spin-evaporated and dried to give a brown residue (1.80 g). Recrystallization from ethyl acetate gave 377 mg (16%) of **8b** as brown crystals; ms: (CI) m/z 311 (34%), 309 (100); ^{1}H-nmr (DMSO-d_6): δ 3.05 and 3.14 (2s, 6H, $N(CH_3)_2$), 5.31 (s, 2H, CH_2), 7.1-7.5 (m, 4H, Ar-H), 7.93 (s, 1H, C2), 8.50 (s, 1H, N-CH=N); hplc: k' = 3.4 on a Supelco LC-8 5 micron column with 50% methanol/water, 0.1% triethylamine.

Anal. Calcd. for $C_{14}H_{14}ClFN_4O$: C, 54.46; H, 4.57; N, 18.15; Cl, 11.48. Found: C, 54.17; H, 4.55; N, 17.83; Cl, 11.33.

7-(2-Fluorobenzyl)-4-(methylamino)-7*H*-imidazo[4,5-*d*]-1,2,3-triazine Hydrochloride (**11**).

This compound was prepared from **6** (2.12 g, 8.64 mmoles) and 40% aqueous methylamine (20 ml) as described for **13** to give 1.45 g (57%) of **11** as a white solid, mp >170° dec; uv (methanol): λ_{max} 206 nm (ε 22400), 261 nm (ε 10600), 307 nm (ε 6700); ^{1}H nmr (DMSO-d_6): δ 3.11 (br s, 3H, CH_3), 5.64 (s, 2H, CH_2), 7.1-7.4 (m, 4H, Ar), 8.53 (br s, 1H, NH), 8.62 (s, 1H, C-6 H).

Anal. Calcd. for $C_{12}H_{11}FN_6 \cdot HCl \cdot H_2O$: C, 46.09; H, 4.51; N, 26.87; Cl, 11.34. Found: C, 46.27; H, 4.49; N, 26.81; Cl, 11.40.

4-Amino-7-(2-fluorobenzyl)-7*H*-imidazo[4,5-*d*]-1,2,3-triazine Hydrochloride (**12**).

To a stirred solution of **6** (4.82 g, 19.7 mmoles) in dry pyridine (50 ml), which was cooled at 0° under a nitrogen atmosphere, was added 4-chlorophenyl phosphorodichloridate (7.24 g, 29.5 mmoles) during 5 minutes. The mixture was allowed to warm to ambient temperature. After 20 hours the reaction was poured into ice water (400 ml) and stirred for 30 minutes. The resultant solution was treated dropwise with 40% aqueous methylamine (40 ml). After 1 hour the precipitate was collected and recrystallized from ethanolic hydrochloric acid to give 3.18 g (58%) of **12**, mp 226-236° dec; uv (*p*H 7.0 buffer-methanol): λ_{max} 257 nm (ε 9000), 298 nm (ε 6600); ^{1}H nmr (DMSO-d_6): δ 5.65 (s, 2H, CH_2), 7.2-7.5 (m, 4H, Ar), 8.25 (br s, 2H, NH_2), 8.67 (s, 1H, C-6 H).

Anal. Calcd. for $C_{11}H_9FN_6 \cdot HCl$: C, 47.07; H, 3.59; N, 29.94; Cl, 12.63. Found: C, 46.98; H, 3.61; N, 29.90; Cl, 12.70.

4-(Cyclopropylamino)-7-(2-fluorobenzyl)-7*H*-imidazo[4,5-*d*]-1,2,3-triazine Hydrochloride (**13**).

To a mixture of **6** (4.44 g, 18.1 mmoles) and 4-dimethylaminopyridine (22.1 g, 181 mmoles) in dry acetonitrile (200 ml), which was stirred at 0° under a nitrogen atmosphere, was added dropwise 4-chlorophenyl phosphorodichloridate (13.3 g, 54.3 mmoles) over 2 minutes. The cold bath was removed, and the reaction was stirred at ambient temperature for 2 hours. Cyclopropylamine (10 ml) was added dropwise over 5 minutes to the reaction. After 15 hours the solution was added to Silica Gel 60 (100 g), and the volatiles were removed by spin evaporation. The residue was added to a Silica Gel 60 column (500 g), and the product was eluted with ethyl acetate. The appropriate fractions (product R_f = 0.5, ethyl acetate) were combined and spin-evaporated to give a solid residue, which was recrystallized from ethanolic hydrochloric acid-ethyl ether to give 3.72 g (64%) of **13**, mp >177° gradual dec; uv (methanol): λ_{max} 262 nm (ε 11600), 306 nm (ε 6530); ^{1}H nmr (DMSO-d_6): δ 0.68-0.86 (m, 4H, CH_2CH_2), 3.14 (br s, 1H, CC*H*C), 5.65 (s, 2H, $ArCH_2$), 7.1-7.4 (m, 4H, Ar), 8.66 (s, 1H, C-6 H), 8.89 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}FN_6 \cdot HCl \cdot 0.75H_2O$: C, 50.31; H, 4.67; N, 25.14; Cl, 10.61. Found: C, 50.12; H, 4.83; N, 25.29; Cl, 10.54.

5-Amino-1-(2-fluorobenzyl)pyrazole-4-carboxamide (**15**).

To concentrated sulfuric acid (100 ml) stirred at 0° was added **14** [10] (28.5 g, 0.132 mole) in portions over 30 minutes. The cold bath was removed, and the mixture was stirred at ambient temperature for 2 hours. The reaction was poured cautiously onto crushed ice (500 ml) and stirred for 1 hour. The cooled solution was neutralized by addition of concentrated ammonium hydroxide in portions (10 ml) each with stirring. The resultant precipitate was collected, washed with water (3 x 100 ml), and dried to give 30.4 g (99%) of crude **15**, which was essentialy one spot on tlc. Recrystallization of a sample (1.0 g) from acetonitrile gave 0.81 g of **15** as yellow flakes, mp 207-208°; uv (methanol): λ_{max} 255 nm (ε 9500); ^{1}H nmr (DMSO-d_6): δ 5.17 (s, 2H, CH_2), 6.33 (br s, 2H, NH_2), 6.8-7.4 (m, 6H, Ar and NH_2), 7.68 (s, 1H, C-3 H).

Anal. Calcd. for $C_{11}H_{11}FN_4O$: C, 56.41; H, 4.73; N, 23.92. Found: C, 56.42; H, 4.76; N, 23.88.

7-(2-Fluorobenzyl)-3,7-dihydro-4*H*-pyrazolo[3,4-*d*]-1,2,3-triazin-4-one (**16**).

To a mixture of **15** (28.0 g, 0.120 mole), concentrated hydrochloric acid (50 ml), and glacial acetic acid (50 ml), which was stirred at 0° under a nitrogen atmosphere, was added a solution of sodium nitrite (25.0 g, 0.362 mole) in water (50 ml) over 30 minutes. The cold bath was removed, and the reaction was stirred at ambient temperature for 2 hours. The thick slurry was diluted with water (150 ml). The resultant solid was collected, washed with water (3 x 200 ml), and dried to give 27.4 g (93%) of crude **16**, which was essentially one spot on tlc. Recrystallization of a sample (1.00 g) from methanol gave 0.65 g of **16**, mp >149° gradual dec; uv (methanol): λ_{max} 283 nm (ε 6100); ^{1}H nmr (DMSO-d_6): δ 5.80 (s, 2H, CH_2), 7.1-7.4 (m, 4H, Ar), 8.36 (s, 1H, C-5 H), 15.13 (br s, 1H, NH).

Anal. Calcd. for $C_{11}H_8FN_5O$: C, 53.88; H, 3.29; N, 28.56. Found: C, 53.80; H, 3.32; N, 28.48.

4-(Dimethylamino)-1-[7-(2-fluorobenzyl)-7*H*-pyrazolo[3,4-*d*]-1,2,3-triazin-4-yl]pyridinium Chloride (**17**).

To a mixture of **16** (1.00 g, 4.08 mmoles) and 4-dimethylaminopyridine (4.98 g, 40.8 mmoles) in dry acetonitrile (100 ml), which was stirred at 0° under a nitrogen atmosphere, was added dropwise 4-chlorophenyl phosphorodichloridate (3.00 g, 12.2 mmoles) over 1 minute. The cold bath was removed, and the reaction was stirred at ambient temperature for 2 hours. The resultant precipitate was collected, washed quickly with acetonitrile (20 ml), and dried to give 2.20 g of crude **17** as a white solid mixed with 4-dimethylaminopyridine hydrochloride, which was suitable for use in subsequent reactions. The analytical sample was obtained by recrystallization of a portion (1.0 g) from acetonitrile to yield 0.39 g of pure **17** as white flakes, mp >150° gradual dec; uv (*p*H 7.0 buffer): λ_{max} 225 nm (ε 21500), 260 nm (ε 8100), 350 nm (ε 33200); ^{1}H nmr (DMSO-d_6): δ 3.41 (s, 6H, $N(CH_3)_2$), 6.09 (s, 2H, CH_2), 7.1-7.5 (m, 4H, Ar), 7.31 (d, 2H, J = 8 Hz, pyridinium H), 9.07 (s, 1H, C-5 H), 9.11 (d, 2H, J = 8 Hz, pyridinium H).

Anal. Calcd. for $C_{18}H_{17}FN_7Cl$: C, 56.03; H, 4.44; N, 25.41; Cl, 9.19. Found: C, 55.92; H, 4.47; N, 25.39; Cl, 9.16.

7-(2-Fluorobenzyl)-4-(methylamino)-7*H*-pyrazolo[3,4-*d*]-1,2,3-triazine Hydrochloride (**18**).

This compound was prepared from **17** (5.00 g, 13.0 mmoles) and 40% aqueous methylamine (5.0 g) as described for **20** to give 2.70 g (71%) of **18** as a white solid, mp 209-212° efferescence; uv (methanol): λ_{max} 318 nm (ε 8510); ^{1}H nmr (DMSO-d_6): δ 3.12 (d, 3H, CH_3), 5.78 (s, 2H, CH_2), 7.1-7.4 (m, 4H, Ar), 8.37 (s, 0.75 H, C-5 H), 8.47 (s, 0.25 H, C-5 H), 8.9 and 9.4 (NH).

Anal. Calcd. for $C_{12}H_{11}FN_6$•HCl: C, 48.90; H, 4.10; N, 28.52; Cl, 12.03. Found: C, 48.75; H, 4.11; N, 28.42; Cl, 12.13.

4-Amino-7-(2-fluorobenzyl)-7*H*-pyrazolo[3,4-*d*]-1,2,3-triazine Hydrochloride (**19**).

This compound was prepared from **17** (5.00 g, 13.0 mmoles), and concentrated ammonium hydroxide (10 ml) as described for **20** to give 3.02 g (83%) of **19**, mp 209-211° efferescence; uv (methanol): λ_{max} 309 nm (ε 7590); ^{1}H nmr (DMSO-d_6): δ 5.78 (s, 2H, CH_2), 7.1-7.5 (m, 4H, Ar), 8.35 (s, 1H, C-5 H), 8.48 and 8.83 (2 br s, 2H, NH_2).

Anal. Calcd. for $C_{11}H_9FN_6$•HCl: C, 47.07; H, 3.59; N, 29.94; Cl, 12.63. Found: C, 47.17; H, 3.62; N, 29.93; Cl, 12.71.

4-(Cyclopropylamino)-7-(2-fluorobenzyl)-7*H*-pyrazolo[3,4-*d*]-1,2,3-triazine Hydrochloride (**20**).

To a stirred mixture of **17** (7.00 g, 18.1 mmoles) and dry dimethylformamide (100 ml) was added cyclopropylamine (5 ml). After 1 hour the solution was diluted with water (400 ml), and the precipitate was collected, washed with water (2 x 100 ml) and dried. The white solid was recrystallized from ethanolic-hydrochloric acid to give 3.62 g (61%) of **20**, mp 200-212° efferescence; uv (methanol): λ_{max} 318 nm (ε 7240); ^{1}H nmr (DMSO-d_6): δ 0.68 (m, 2H, CH_2), 0.94 (m, 2H, CH_2), 3.0-3.1 (br m, 1H, CCHC), 5.77 (s, 2H, $ArCH_2$), 7.1-7.4 (m, 4H, Ar), 8.44 (s, 0.35 H, C-5 H), 8.49 (s, 0.65 H, C-5 H), 9.19 (br s, 0.65 H, NH), 9.81 (br s, 0.35 H, NH).

Anal. Calcd. for $C_{14}H_{13}FN_6$•HCl•0.25H_2O: C, 51.70; H, 4.49; N, 25.84; Cl, 10.90. Found: C, 51.53; H, 4.37; N, 25.68; Cl, 10.84.

4-(Ethylamino)-7-(2-fluorobenzyl)-7*H*-pyrazolo[3,4-*d*]-1,2,3-triazine Hydrochloride (**21**).

This compound was prepared from **17** (9.00 g, 23.3 mmoles) and 70% aqueous ethylamine (15 ml) as described for **20** to give 3.52 g (49%) of **21**, mp 208-211° efferescence; uv (methanol): λ_{max} 319 nm (ε 8790); ^{1}H nmr (DMSO-d_6): δ 1.25 (t, 3H, CH_3), 3.64 (br m, 2H, CH_2CH_3), 5.77 (s, 2H, $ArCH_2$), 7.1-7.4 (m, 4H, Ar), 8.33 (s, 0.73 H, C-5 H), 8.41 (s, 0.27 H, C-5 H), 8.94 (br s, 0.27 H, NH), 9.04 (br s, 0.73 H, NH).

Anal. Calcd. for $C_{13}H_{13}FN_6$•HCl: C, 50.57; H, 4.57; N, 27.22; Cl, 11.48. Found: C, 50.50; H, 4.58; N, 27.18; Cl, 11.54.

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