Notes

Synthesis and Anticonvulsant Activity of *N*-Benzylpyrrolo[2,3-*d*]-, -pyrazolo[3,4-*d*]-, and -triazolo[4,5-*d*]pyrimidines: Imidazole Ring-Modified Analogues of 9-(2-Fluorobenzyl)-6-(methylamino)-9*H*-purine

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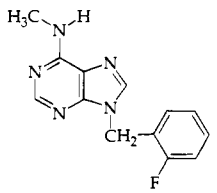
Analogues of 9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine (**1**) containing isosteric replacements of the imidazole ring atoms were synthesized and tested for anticonvulsant activity. The pyrrolo[2,3-*d*]-, pyrazolo[3,4-*d*]-, and triazolo[4,5-*d*]pyrimidines were less active than **1** against maximal electroshock-induced seizures (MES) in rats when given po. The differences in anti-MES activity for these analogues was not explained by differences in pK_a or lipophilicity. However, the four classes of heterocycles have distinctly different calculated electrostatic isopotential maps, which may be related to optimum anticonvulsant activity.

The purine **1** [9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine, 78U79] is an anticonvulsant agent with potent activity against maximal electroshock-induced seizures (MES) in rats and mice.[1,2] Modification of the substituents on the purine ring of **1** showed that optimum activity was associated with a 9-(2-fluorobenzyl) and 6-alkylamino substitution pattern.[2,3] If the 3-nitrogen of **1** was replaced with carbon, the resultant 3-deazapurine **23** was also very active as an anticonvulsant agent.[4] We have further examined the structure–activity relationships of **1** by isosteric replacement of the imidazole ring atoms to give the pyrrolo[2,3-*d*]pyrimidine, pyrazolo[3,4-*d*]pyrimidine, and triazolo[4,5-*d*]pyrimidine ring systems. The synthesis and the anticonvulsant activity of these analogues are reported herein.



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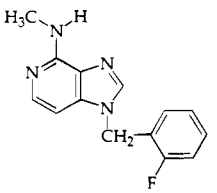

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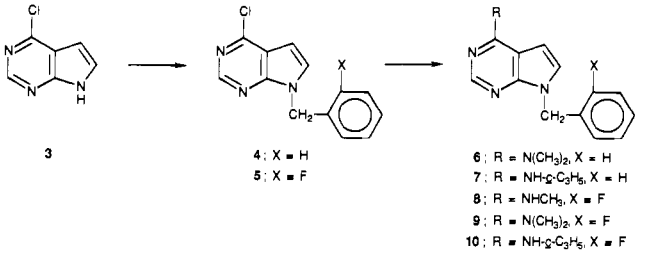
Chemistry

The pyrrolo[2,3-*d*]pyrimidines **6**–**10** were prepared as outlined in Scheme 1. The 4-chloropyrrolopyrimidine **3**[5,6] was alkylated with benzyl chloride or 2-fluorobenzyl chloride in the presence of potassium carbonate to give **4** and **5** in high yield. Amination of **4** and **5** with the appropriate amine gave **6**–**10**.

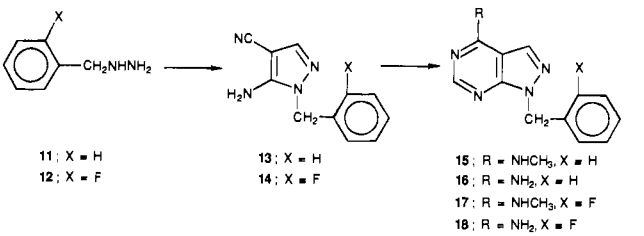
The pyrazolo[3,4-*d*]pyrimidines **15**–**18** were prepared in two steps from the appropriate benzylhydrazine (Scheme 2).[7] Condensation of ethoxymethylenemalononitrile with **11** or **12** gave **13** or **14**, albeit in variable yields. The reaction was best run with pure, distilled benzylhydrazine because *in situ* generation of **11** from the hydrochloride salt gave **13** contaminated with the 2-isomer. Assignment of the structure of **13** as the 1-isomer was established via a NOE experiment. Irradiation of the methylene gave NOE's of 7% and 2% for the aryl and NH_2 protons. When the aminopyrazoles **13** and **14** were refluxed with formamide or *N*-methylformamide, pyrazolo[3,4-*d*]pyrimidines **15**–**18** were formed.[7,8]

The triazolo[4,5-*d*]pyrimidines **21** and **22** were prepared from the diaminopyrimidine **19**.[3] Addition of nitrous acid to **19** gave **20**, which was not isolated but was aminated with ammonia or methylamine to give **21** and **22** (Scheme 3).

Scheme 1



Scheme 2



Biological Results and Discussion

The compounds were tested for anticonvulsant activity against maximal electroshock-induced seizures in

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Scheme 3

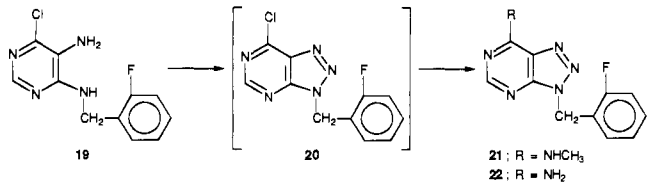

Table 1. Anticonvulsant Activity against Maximal Electroshock-Induced Seizures[a]

no.	R	X	MES ED_{50}, mg/kg[b] ip	po
		Purines		
1[d]	$NHCH_3$	F	1.7 ± 0.4	2.5 ± 0.4
2[d]	NH_2	F	4.5 ± 1.0	12.0 ± 0.4
		Pyrrolo[2,3-*d*]pyrimidines		
6	$N(CH_3)_2$	H	15 ± 1	NT[c]
7	NH-c-C_3H_5	H	36 ± 2	NT
8[d]	$NHCH_3$	F	6 ± 1	12
9	$N(CH_3)_2$	F	11 ± 2	12
10	NH-c-C_3H_5	F	>50	NT
		Pyrazolo[3,4-*d*]pyrimidines		
15[d]	$NHCH_3$	H	7 ± 2	15
16	NH_2	H	>25	NT
17[d]	$NHCH_3$	F	6 ± 2	8 ± 2
18[d]	NH_2	F	8 ± 3	14 ± 1
		Triazolo[4,5-*d*]pyrimidines		
21[d]	$NHCH_3$	F	3 ± 1	8 ± 2
22[d]	NH_2	F	>25	NT
phenytoin			10 ± 2	20 ± 3

[a] The compounds were tested for their ability to protect Wistar male rats obtained from Charles River against maximal electroshock (MES)-induced seizures as described in ref 9. The ED_{50} was the dose needed to protect 50% of the animals against the hind limb extensor component and was calculated using the method of L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.* **1994**, *57*, 261. [b] Where ED_{50} values are presented with a standard error, a minimum of 12 animals were used per dose level with four doses/compound. ED_{50} values without standard error were determined using three doses of compound with six animals/point. [c] NT = not determined. [d] Compounds were tested as the hydrochloride.

Wistar male rats obtained from Charles River, as described previously.[9] The ED_{50}s, which are the doses needed to protect 50% of the animals against the hind limb extensor component of the seizure, are tabulated in Table 1.

The parent purine **1** had an ip ED_{50} of 1.7 mg/kg and an oral ED_{50} of 2.5 mg/kg against MES in male rats.[1,2] Replacement of the imidazole ring N-7 nitrogen with carbon to give **8** resulted in a 4-fold loss in activity. The other pyrrolo[2,3-*d*]pyrimidines were also less active with ip ED_{50}s ranging from **11** to >50 mg/kg. Transposition of the imidazole ring N-7 and C-8 atoms to give the pyrazolo[3,4-*d*]pyrimidine **17** resulted in a 3.5-fold loss in ip activity. By the oral route of administration, **17** was about 3-fold less active than **1**. Substitution of a nitrogen for the C-8 carbon of **1** to give **21** led to a modest loss in ip activity. Compound **21** was about 3 times less active by the oral route. Varying the number or the distribution of the nitrogen and carbon atoms in the imidazole ring of **1** had a significant effect on anticonvulsant activity.

For **1** and its closest analogues, **8**, **17**, and **21**, the ip ED_{50}s were 1.7, 6.2, 6, and 3 mg/kg, respectively. This range of activity is not explained by differences in physicochemical properties attributable to changes in ionization of the heterocycles. The pK_as of **1**, **8**, **17**, and **21** range from 2.49 to 5.56 (Table 2).[10] Thus, all four

Table 2. Physicochemical Properties of Anticonvulsant Agents

compd	ring	pK_a[a]	log *P*[b]
1	purine	3.88 ± 0.02	1.86 ± 0.04
8	pyrrolo[2,3-*d*]pyrimidine	5.56 ± 0.01	2.11 ± 0.06
17	pyrazolo[3,4-*d*]pyrimidine	4.40 ± 0.01	1.94 ± 0.01
21	triazolo[4,5-*d*]pyrimidine	2.49 ± 0.02	2.05 ± 0.01

[a] The pK_as were determined as described in ref 10. [b] The log *P*s were measured in octanol–water using a carbonate-buffered aqueous phase adjusted to pH 10, by Midwest Research Institute, Kansas City, MO.

compounds are unprotonated at physiological pH. The effect of compound lipophilicity would appear to be a potential factor, since compound distribution and central nervous system penetration vary with log *P*.[11] However, although the number of nitrogen atoms is varied from one to three in the five-membered ring, the measured log *P*s range only from **1.86** to **2.11** (Table 2). This small difference in measured log *P* values is probably not significant. Thus, the effect of adding, deleting, or transposing nitrogens in the imidazole ring of purine **1** does not significantly change the lipophilicity of the molecule.

We thought that the differences in activity of **1**, **8**, **17**, and **21** might be related to the electrostatic potential on the surface of the compounds. The electrostatic potentials were calculated from STO-3G wave functions using Gaussian-80 UCSF[12] in a plane through the heterocyclic ring. The molecular structures were deduced from molecular mechanics calculations.[13] The conformations used for subsequent calculations were based on the lowest energy conformer of **1**, calculated from rotation of the torsion angles about the benzyl carbon. The electrostatic isopotential maps of **1**, **8**, **17**, and **21** (Figure 1) reveal distinct differences in the shapes of the electrostatic potential surface that may be recognized at a receptor or binding site.

The major differences in these contour maps are seen in the negative electrostatic potential adjacent to the 7- and 8-positions (purine numbering) of the five-membered ring. Each compound presents a different electrostatic potential surface when viewed from the upper right. Optimum activity may be associated with the electrostatic potential surface presented by **1**. Triazolopyrimidine **21** has a surface somewhat similar to that of **1** and ip activity comparable to that of **1**. Analogues **8** and **17** present quantitatively different surfaces and are less active against MES than **1**.

The 3-deaza analogue of **1**, **23**, has an electrostatic potential surface that is very similar to that of **1** (Figure 2). The anti-MES activity of **23** was reported to be only slightly weaker than that of **1** with an ip ED_{50} of 3 mg/kg and an oral ED_{50} of 4 mg/kg.[4] These observations suggest that other molecules with electrostatic isopotential maps similar to that of **1** may have anti-MES activity similar to that of **1**. Thus, use of electrostatic potential surfaces of proposed synthesis targets in comparison with the surface of **1** could serve as a useful decision branch in selecting targets for synthesis.

The activity profile in rodents of **1** suggested it might be useful in the treatment of seizure disorders in humans.[1] However, phase IA clinical trials were terminated when some subjects experienced dose-related occurrences of nausea and emesis.[14] To identify compounds free of emetic potential, analogues of **1** with good anticonvulsant activity were tested in a dog emesis model.[15] Compound **1** caused significant emesis when

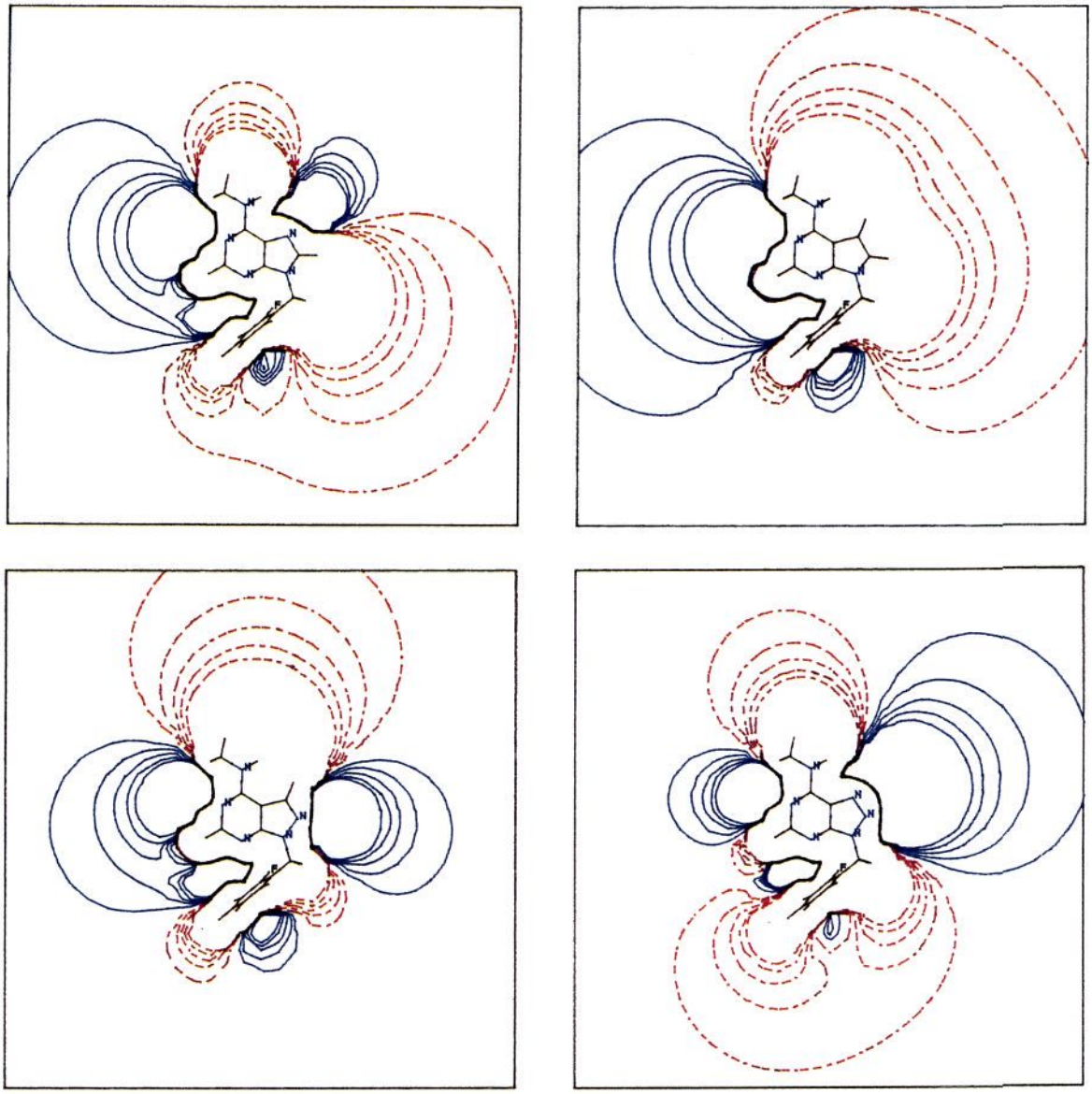

Figure 1. Electrostatic isopotential maps of purine **1** (top left), pyrrolo[2,3-*d*]pyrimidine **8** (top right), pyrazolo[3,4-*d*]pyrimidine **17** (bottom left), and triazolo[4,5-*d*]pyrimidine **21** (bottom right). The positive (red) and negative (blue) contour lines are at sequentially decreasing potentials of 0.005, 0.004, 0.003, 0.002, and 0.001 and −0.001, −0.002, −0.003, −0.004, and −0.005 hartrees.

administered iv at 7.5 mg/kg. Analogues **17** and **21** were tested iv, and emesis was observed with **21** but not with **17**. However, oral **17** at 40 mg/kg caused emesis. Thus, retention of this untoward side effect precluded further development of these compounds as potential antiepileptic agents.

Experimental Section

Melting points were determined with a Thomas Hoover Unimelt or Mel-Temp block and are uncorrected. NMR spectra were recorded using a Varian XL-100-15-FT, a Varian XL-200, or a Hitachi Perkin-Elmer R-24 spectrometer. Chemical shift values are reported in ppm on the δ scale with Me_4Si as the internal reference. The NMR spin multiplicities are indicated by the symbols s (singlet), d (doublet), 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). TLC was done on Whatman (200 μm) MK6GF plates of silica gel with fluorescence indicator. Preparative column chromatography was done using the flash chromatography technique[16] on silica gel 60 (40−63 μm, E. Merck no. 9385). Elemental microanalyses were determined by Atlantic Microlab and gave combustion values for C, H, and N within 0.4% of theoretical values.

7-Benzyl-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (4). A mixture of **3**[5,6] (6.12 g, 39.8 mmol), benzyl chloride (5.25 g, 41.5 mmol), anhydrous potassium carbonate (6.00 g, 43.4 mmol), and dry dimethyl sulfoxide (75 mL) was stirred at ambient temperature for 15 h. Since the reaction was incomplete, the mixture was heated at 70 °C for 3.5 h, cooled to ambient temperature, and diluted with water (250 mL). The solution was extracted with dichloromethane (3 × 75 mL), and the combined extracts were washed with water (5 × 35 mL). The dichloromethane extracts were filtered through glass wool and spin evaporated *in vacuo*. The residue was dissolved in dichloromethane and absorbed on a column (6 cm diameter) of silica gel 60 (50 g) wetted with ethyl acetate:cyclohexane (1:2). The column was eluted with the latter solvent using the flash chromatography technique. The fractions that contained pure product were combined and spin evaporated *in vacuo* to give 9.00 g (92%) of **4**, mp 66−70 °C. Recrystallization of a 0.50 g sample from cyclohexane gave the analytical sample: mp 69−70 °C (lit.[17] mp 66−67 °C); ^{1}H NMR (Me_2SO-d_6) δ 8.48 (s, 1H, C-2), 7.60 (d, 1H, J = 3.6 Hz, C-6), 7.07 (s, 5H, Ar), 6.43 (d, 1H, J = 3.6 Hz, C-5), 5.31 (s, 2H, CH_2). Anal. ($C_{13}H_{10}ClN$) C, H, N.

4-Chloro-7-(2-fluorobenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5). This compound was prepared from **3** and 2-fluorobenzyl chloride on a 40 mmol scale by the method for the

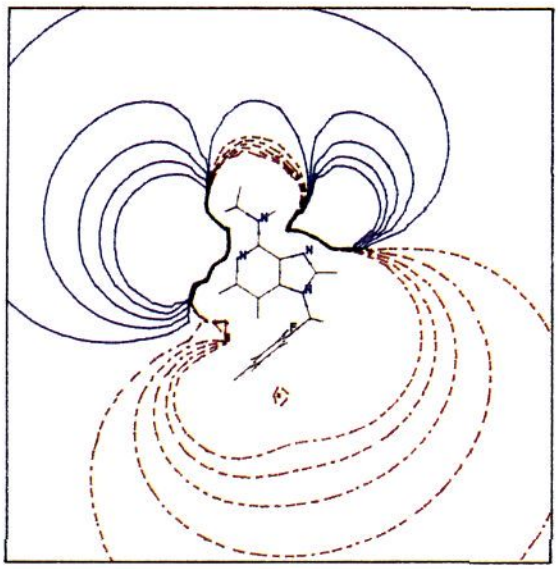

Figure 2. Electrostatic isopotential map of 1-(2-fluorobenzyl)-4-(methylamino)-1*H*-imidazo[4,5-*c*]pyridine (**23**).

preparation of **4**. The compound was eluted from the column with ethyl acetate:cyclohexane (1:10) to give 8.80 g (84%) of **5**, mp 57−60 °C, which was one spot on TLC. The analytical sample was recrystallized from cyclohexane: mp 73−74 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.66 (s, 1H, C-2), 7.79 (d, 1H, J = 3.6 Hz, C-6), 7.3−7.1 (m, 4H, Ar), 6.70 (d, 1H, J = 3.6 Hz, C-5), 5.58 (d, 2H, J = 0.9 Hz, CH_2). Anal. ($C_{13}H_9ClFN_3$) C, H, N.

7-Benzyl-4-(dimethylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine (6). A solution of **4** (3.80 g, 15.6 mmol), ethanol (45 mL), and 40% aqueous dimethylamine (20 mL) was heated on a steam bath for 6 h. The cooled solution was spin evaporated *in vacuo*, and the residue was dispersed in water. The solids were collected and recrystallized from cyclohexane to give 1.78 g (45%) of **6**: mp 82−84 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H, C-2), 7.25 (br s, 5H, Ar), 6.85 (d, 1H, J = 3.6 Hz, C-6) 6.57 (d, 1H, J = 3.6 Hz, C-5), 5.38 (s, 2H, CH_2), 3.37 (s, 6H, $N(CH_3)_2$). Anal. ($C_{15}H_{16}N_4$) C, H, N.

7-Benzyl-4-(cyclopropylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7). A solution of **4** (3.80 g, 15.6 mmol), ethanol (45 mL), and cyclopropylamine (20 mL) was heated on a steam bath for 6 h. The cooled solution was spin evaporated *in vacuo*, and the residue was crystallized from ethyl acetate to give 2.43 g (58%) of **7**: mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H, C-2), 7.26 (s, 5H, Ar), 6.90 (d, 1H, J = 3.6 Hz, C-6), 6.65 (d, 1H, J = 3.6 Hz, C-5), 5.74 (br, 1H, NH), 5.39 (s, 2H, CH_2), 2.96 (br m, 1H, NCH), 0.96−0.69 (m, 4H, CH_2CH_2). Anal. ($C_{16}H_{16}N_4$) C, H, N.

7-(2-Fluorobenzyl)-4-(methylamino)-7*H*-pyrrolo[2,3-*d*]pyrimidine Hydrochloride (8). This compound was prepared from **5** and 40% aqueous methylamine on a 11.4 mmol scale by the method for the preparation of **6** except the reaction mixture was stirred at ambient temperature for 63 h to give 2.70 g (92%) of **8**, mp 145−148 °C. Recrystallization from cyclohexane:ethyl acetate gave 1.51 g (51%) of **8**: mp 149−150 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.15 (s, 1H, C-2), 7.5−6.9 (m, 6H, C-6, NH, Ar), 6.58 (d, 1H, J = 3.5 Hz, C-5), 5.40 (d, 2H, J = 0.7 Hz, CH_2), 2.96 (d, 3H, J = 4.7 Hz, CH_3). Anal. ($C_{14}H_{13}FN_4$) C, H, N.

The hydrochloride of **8** was prepared by dissolution of 5.24 g of the base of **8** in hot absolute ethanol. The solution was diluted with concentrated hydrochloric acid (25 mL). Upon cooling, a white crystalline solid formed, which was collected and recrystallized from absolute ethanol to yield 3.06 g (51%) of **8** hydrochloride: mp 231−235 °C; ^{1}H NMR (Me_2SO-d_6) δ 9.79 (br s, 1H, NH), 8.33 (s, 1H, ring H), 7.48 (d, 1H, J = 3.36 Hz, ring H), 7.40−7.1 (m, 5H, Ar), 6.99 (d, 1H, J = 3.52 Hz, ring H), 5.50 (s, 2H, CH_2), 3.09 (br d, 3H, J = 3.8 Hz, $NHCH_3$). Anal. ($C_{14}H_{13}FN_4$·HCl) C, H, N.

4-(Dimethylamino)-7-(2-fluorobenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9). This compound was prepared from **5** on a 12.5 mmol scale by the method for the preparation of **6** except the reaction mixture was stirred at ambient temperature for 15 h. The solid was recrystallized from cyclohexane to give 2.50 g (74%) of **9**: mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H, C-2), 7.2−6.9 (m, 4H, Ar), 6.92 (d, 1H, J = 3.6 Hz, C-5), 6.58 (d, 1H, J = 3.6 Hz, C-6), 5.44 (d, 2H, J = 0.9 Hz, CH_2), 3.37 (s, 6H, $N(CH_3)_2$). Anal. ($C_{15}H_{15}FN_4$) C, H, N.

4-(Cyclopropylamino)-7-(2-fluorobenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (10). This compound was prepared from **5** on a 11.5 mmol scale by the method for the preparation of **7** except the crude solid was dispersed in water (25 mL), collected, and recrystallized twice from cyclohexane−ethyl acetate (charcoal) to give 1.73 g (53%) of **10**: mp 154−155 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.15 (s, 1H, C-2), 7.60 (br d, 1H, J = 3.4 Hz, NH), 7.4−6.9 (m, 5H, Ar, C-6), 6.67 (d, 1H, J = 3.5 Hz, C-5), 5.41 (s, 2H, CH_2), 2.95 (m, 1H, NCH), 0.83−0.50 (m, 4H, CH_2CH_2). Anal. ($C_{16}H_{15}FN_4$) C, H, N.

(2-Fluorobenzyl)hydrazine (12). To a refluxing solution of hydrazine hydrate (47.4 g, 0.947 mol) in ethanol (200 mL) was added a solution of 2-fluorobenzyl bromide (40.1 g, 0.212 mol) in ethanol (150 mL) dropwise over a 1 h period. The reaction mixture was refluxed for an additional 5 h. The cooled reaction mixture was stirred at ambient temperature for 18 h and then spin evaporated *in vacuo*. The residual liquid was extracted with diethyl ether (3 × 100 mL), and the combined extracts were dried (potassium carbonate) and evaporated. The liquid residue was fractionally distilled under reduced pressure to give 14.2 g (47%) of **12**: bp 76−79 °C (0.8−0.9 mmHg); ^{1}H NMR (DMSO-d_6) δ 6.8−7.4 (m, 4H, Ar), 3.7 (br s, 2H, CH_2), 3.4 (br s, 3H, $NHNH_2$).

5-Amino-1-benzylpyrazole-4-carbonitrile (13). Method 1. To the solution formed by the dropwise addition of ethanol (25 mL) to sodium hydride (50% dispersion in mineral oil) (4.03 g, 84.0 mmol) was added **11** dihydrochloride (7.99 g, 40.9 mmol) in ethanol (60 mL). Ethoxymethylenemalononitrile (5.00 g, 40.9 mmol) was added, and the reaction mixture was refluxed with stirring for 1.75 h. Upon cooling the solid was removed by filtration, and the filtrate was evaporated *in vacuo* to a semisolid residue. This residue was partially dissolved in ethanol, and the crude product was collected. Recrystallization from ethyl acetate gave 1.22 g (15%) of **13**: mp 184−186 °C (lit.[18] mp 184−185.5 °C) (This method gave different results on successive runs. Although a yield as high as 80% was obtained, this reaction sometimes produced low yields of **13** contaminated with the 2-isomer.); ^{1}H NMR (Me_2SO-d_6) δ 7.56 (s, 1H, ring H), 7.38−7.08 (br m, 5H, Ar), 6.71 (br s, 2H, NH_2), 5.16 (s, 2H, CH_2); steady-state NOE (irradiation at δ 5.13) obsd 0.5% NOE at δ 7.56, 7.1% NOE at δ 7.14, 2.8% NOE at δ 6.71. Anal. ($C_{11}H_{10}N_4$) C, H, N.

Method 2. When freshly distilled, pure **11** as the free base was used, and pure **13** precipitated from the cooled reaction mixture in consistent yields of ca. 70%.

5-Amino-1-(2-fluorobenzyl)pyrazole-4-carbonitrile (14). To a mixture of **12** (5.00 g, 35.7 mmol) in ethanol (15 mL) was added ethoxymethylenemalononitrile (4.4 g, 36.0 mmol). The reaction mixture was refluxed with stirring for 1.75 h, cooled, and spin evaporated *in vacuo* to give a bright yellow solid (7.33 g). The solid was dissolved in warm ethyl acetate, added to silica gel 60 (30 g), and spin evaporated *in vacuo*. The residual solids were introduced on a column (75 mm × 200 mm) of silica gel 60 wetted with ethyl acetate:hexane (1:1). The column was eluted with ethyl acetate:hexane (1:1) using the flash chromatography technique. None of the fractions were completely pure. The analytical sample was prepared by spin evaporation of the cleanest fractions and resuspension of the solids in ethyl acetate:hexane (1:1) (25 mL) to give 2.93 g (38%) of **14** as a yellow solid: mp 150−153 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.58 (s, 1H, ring H), 7.32−6.90 (m, 4H, Ar), 6.74 (br s, 2H, NH_2), 5.20 (s, 1H, CH_2). Anal. ($C_{11}H_9FN_4$) C, H, N.

1-Benzyl-4-(methylamino)-1*H*-pyrazolo[3,4-*d*]pyrimidine Hydrochloride (15). A mixture of **13** (1.73 g, 8.73 mmol) and *N*-methylformamide (15 mL) was refluxed with stirring for 26 h. Upon cooling, water (15 mL) was added and the reaction mixture was evaporated *in vacuo*. The semisolid residue was suspended in water (10 mL), and the solids were collected. Recrystallization from ethanol−water gave 0.638 g (32%) of **15** as a yellow solid: mp 173−175 °C; ^{1}H NMR (Me_2-

SO-d_6) δ 8.29 (s, 1H, ring H), 8.10 (s, 1H, ring H), 7.26 (br s, 5H, Ar), 5.50 (s, 2H, CH_2), 3.02 (br m, 4H, $NHCH_3$). Anal. ($C_{13}H_{13}N_5$) C, H, N.

The hydrochloride of **15** was prepared by dissolution of 5.02 g of **15** in hot 2-propanol. The solution was diluted with concentrated hydrochloric acid (15 mL). Upon cooling, a white solid formed, which was collected and recrystallized from 2-propanol to give 3.50 g (60%) of **15** hydrochloride: mp 260–263 °C; ^{1}H NMR (Me_2SO-d) δ 8.50 (s, 1H, ring H), 8.45 (s, 1H, ring H), 7.29 (br s, 5H, Ar), 5.59 (s, 2H, CH_2), 5.08–4.85 (br s, 1H, NH), 3.12 (br d, 3H, CH_3). Anal. ($C_{13}H_{13}N_5$·HCl) C, H, N.

4-Amino-1-benzyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (16). A mixture of **13** (2.3 g, 11.6 mmol) in formamide (15 mL) was refluxed with stirring for 1 h. Upon cooling, the solid cake that formed was dispersed in water (25 mL) and collected by suction filtration. Recrystallization from 70% ethanol gave 1.44 g (55%) of **16**: mp 235–236 °C (lit.[8] mp 232 °C); ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1H, ring H), 8.11 (s, 1H, ring H), 7.71 (br s, 2H, NH_2), 7.26 (br s, 5H, Ar), 5.49 (s, 2H, CH_2). Anal. ($C_{12}H_{11}N_5$) C, H, N.

1-(2-Fluorobenzyl)-4-(methylamino)-1*H*-pyrazolo[3,4-*d*]pyrimidine Hydrochloride (17). A mixture of **14** (6.02 g, 27.8 mmol) in *N*-methylformamide (30 mL) was refluxed with stirring for 22 h. The cooled reaction mixture was diluted with water (15 mL), and the solids were collected and washed with water. Recrystallization from 2-propanol gave 5.37 g (75%) of **17**: mp 213–215 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.30 (br s, 2H, ring H, NH), 8.10 (s, 1H, ring H), 7.3–7.1 (m, 4H, Ar), 5.54 (s, 2H, CH_2), 2.98 (d, 3H, CH_3). Anal. ($C_{13}H_{12}FN_5$) C, H, N.

The hydrochloride was prepared by dissolution of 10.79 g (41.9 mmol) of **17** in hot 2-propanol. Concentrated hydrochloric acid (25 mL) was added, and the solution was allowed to cool to give **17** hydrochloride as a yellow solid: 10.2 g (82%); mp 248–253 °C; ^{1}H NMR (Me_2SO-d_6) δ 10.3 (br s, 1H, NH), 8.48 (s, 1H, ring H), 8.46 (s, 1H, ring H), 7.4–7.1 (m, 4H, Ar), 5.63 (s, 2H, CH_2), 3.10 (d, 3H, NCH_3). Anal. ($C_{13}H_{12}FN_5$·HCl) C, H, N.

4-Amino-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine Hydrochloride (18). Formamide (15 mL) was added to **14** (2.5 g, 11.5 mmol), and the solution was refluxed with stirring for 4 h. The cooled reaction mixture was dispersed in cold water (50 mL). The solids were collected by suction filtration and dissolved in warm ethanol (100 mL). To this solution was added silica gel 60 (20 g), and the mixture was evaporated *in vacuo*. The solids were added to a column (75 mm × 225 mm) of silica gel 60 wetted with ethyl acetate: methanol (10:1). The column was eluted with ethyl acetate: methanol (10:1) using the flash chromatography technique. The appropriate fractions were combined and spin evaporated to give a light green solid. Recrystallization from water gave 0.576 g (20%) of **18** as an off-white crystalline solid: mp 175–176.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.19 (s, 1H, ring H), 8.11 (s, 1H, ring H), 7.71 (br s, 2H, NH_2), 7.3–7.0 (m, 4H, Ar), 5.53 (s, 2H, CH_2). Anal. ($C_{12}H_{10}FN_5$) C, H, N.

The hydrochloride of **18** was prepared by dissolving 4.24 g (17.4 mmol) of **18** in 2-propanol. The solution was diluted with concentrated hydrochloric acid (10 mL) and cooled to give a fine, pale yellow solid. Recrystallization from 2-propanol gave 3.77 g (77%) of **18** hydrochloride as a white solid: mp 216–219 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.52 (s, 2H, ring H), 7.3–7.1 (m, 4H, Ar), 5.63 (s, 2H, CH_2). Anal. ($C_{12}H_{10}FN_5$·HCl) C, H, N.

3-(2-Fluorobenzyl)-7-(methylamino)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine Hydrochloride (21). To an ice-cold solution of **19**[3] (1.00 g, 3.96 mmol), 1 N hydrochloric acid (10 mL), concentrated hydrochloric acid (4 mL), and ethanol (30 mL) was added sodium nitrite (0.328 g, 4.75 mmol). The solution was stirred for 15 min, and 40% aqueous methylamine (25 mL) was added. The reaction mixture was refluxed with stirring for 5 min and cooled, and the solid was collected. The solid was dissolved in hot ethanol (50 mL), and concentrated hydrochloric acid (15 mL) was added to the solution. The solution was cooled, and the white solid was collected to give 0.522 g (45%) of **21**: mp 266–268 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.44 (s, 1H, ring H), 7.4–7.1 (m, 4H, Ar), 5.81 (s, 2H, CH_2), 3.86 (br s, 2H, NH_2^+), 3.04 (d, 3H, CH_3). Anal. ($C_{12}H_{11}FN_6$·HCl) C, H, N.

7-Amino-3-(2-fluorobenzyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine Hydrochloride (22). Sodium nitrite (0.328 g, 4.75 mmol) was added to an ice-cold solution of **19** (1.00 g, 3.96 mmol), 1 N hydrochloric acid (10 mL), concentrated hydrochloric acid (3 mL), and ethanol (30 mL). The solution was stirred for 15 min, ammonium hydroxide (25 mL) was added, and the suspension was refluxed with stirring for 15 min. The reaction mixture was cooled, and the solid was collected and washed with water. The solid was partially dissolved in hot ethanol (200 mL) and then diluted with concentrated hydrochloric acid (15 mL). The solution was cooled, and the white solid was collected to give 0.767 g (76%) of the hydrochloride salt of **22**: mp 260–264 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.44 (s 1H, ring H), 7.5–7.1 (m, 4H, Ar), 6.76 (br s, 2H, NH_2), 5.84 (s, 2H, CH_2). Anal. ($C_{11}H_9FN_6$·HCl) C, H, N.

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