Synthesis and Anticonvulsant Activity of 3*H*-Imidazo[4,5-*c*]-pyridazine, 1*H*-Imidazo[4,5-*d*]pyridazine and 1*H*-Benzimidazole Analogues of 9-(2-Fluorobenzyl)-6-methylamino-9*H*-purine

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The 3*H*-imidazo[4,5-*c*]pyridazine, 1*H*-imidazo[4,5-*d*]pyridazine, and 1*H*-benzimidazole analogues of the potent anticonvulsant purine 9-(2-fluorobenzyl)-6-methylamino-9*H*-purine (**1**, 78U79) were synthesized and tested for anticonvulsant activity. The 3*H*-imidazo[4,5-*c*]pyridazines **8** and **9** were prepared in five stages from 3,4,5-trichloropyridazine (**2**). The 1*H*-imidazolo[4,5-*d*]pyridazine **15** was synthesized in four stages from 5-[(benzyloxy)methyl]-1,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one (**10a**). The benzimidazole analogues **18** and **20** were prepared from 2,6-dinitroaniline in three stages. These compounds were one-tenth or less as active as **1** in protecting rats against maximal electroshock-induced seizures.

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Introduction.

Potent anticonvulsant activity was reported for 9-(2-fluorobenzyl)-6-methylamino-9*H*-purine (**1**, 78U79), but its clinical development was curtailed due to side effects of nausea and emesis [1-3]. Analogues of **1** that contained nitrogenous, isosteric substitutions in the pyrimidine [4] or imidazole [3] ring or both rings [5] were prepared, but none were both anticonvulsant and nonemetic. We have further modified the structure of **1** by synthesis of three analogues with pyrimidine ring modifications, 3*H*-imidazo[4,5-*c*]pyridazine, 1*H*-imidazo[4,5-*d*]pyridazine and 1*H*-benzimidazole ring systems. The synthesis and anticonvulsant activity are reported herein.

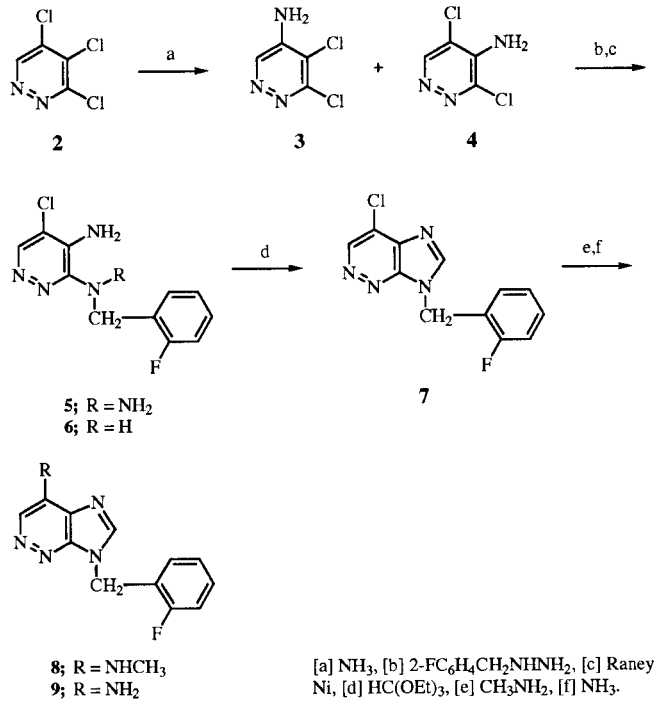
Chemistry.

Imidazo[4,5-*c*]pyridazines.

The imidazo[4,5-*c*]pyridazines **8** and **9** were prepared in five stages from **2** as outlined in Scheme 1. The trichloropyridazine **2** was converted to a mixture of **3** and **4** by modification of a method developed by Kuraishi *et al.* [6,7]. Successive rechromatography of the mixture provided pure **3** and **4** in 26% and 33% yields, respectively. Our melting points for **3** (mp = 177-178°) and **4** (mp = 149-150°) were in agreement with those reported by Kuraishi and Castle [6]; an earlier publication reversed the assignment of melting points [7]. We further substantiated the structural assignments of **3** and **4** by nmr analyses. Irradiation of the NH_2 signal of **3** gave a nuclear Overhauser effect (nOe) enhancement at 8.75 δ. No nOe was observed in a similar experiment with **4**.

Several efforts to aminate **4** with 2-fluorobenzylamine to give **6** in one step were unsuccessful. The low reactivity of **4** contrasts the reactivity of 5-amino-4,6-dichloropyrimidine toward amines [8]. Since alkylhydrazines were known to react with **4** on the secondary nitrogen [6,9], we reacted 2-fluorobenzylhydrazine [3] with **4**, which provided **5** in 29% yield after chromatography on silica gel. The hydrazine N-N bond was cleaved using hydrogen and Raney Ni [10] to provide **6** in high yield. The diaminopyridazine **6** was condensed with triethylorthoformate to give **7** in 62% yield. Amination of **7** with methylamine or ammonia in methanol at 125° provided **8** and **9**, respectively, in about 60% yields.

Scheme 1

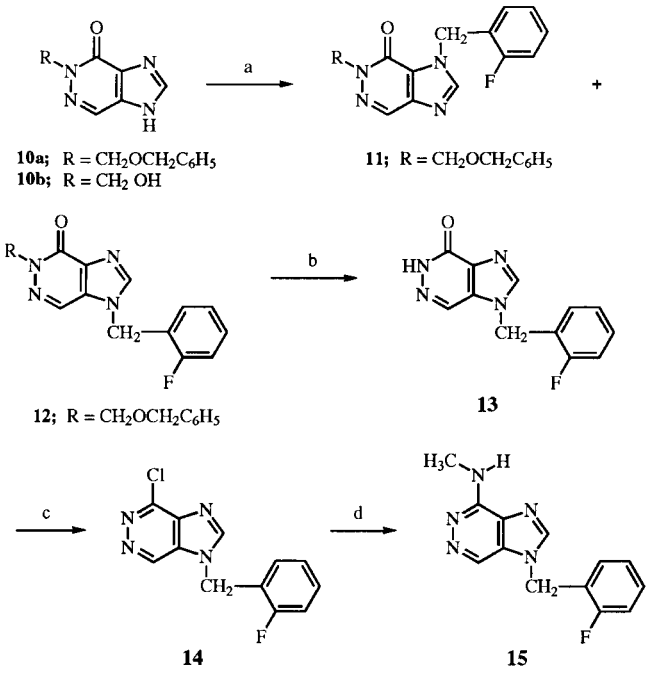


Imidazo[4,5-*d*]pyridazines.

The imidazo[4,5-*d*]pyridazine **15** was prepared in four

stages from **10a** [11] as outlined in Scheme 2. Gagnier *et al.*, reported that **10a** underwent ribosylation at N-1 and N-3 to give a mixture of isomers [11]. We observed a similar mixture of *N*-isomers when **10a** was alkylated with 2-fluorobenzyl bromide. The mixture of isomers was separated by flash chromatography to give **11** and **12** in 47% and 25% yields, respectively. Structural assignments were supported by nmr experiments. Irradiation of the *N*-benzyl CH_2 signal of **11** gave an nOe enhancement of the C-2 hydrogen signal but not of the C-7 hydrogen signal. An nOe was observed for both the C-2 and C-7 hydrogens of **12**.

Scheme 2



[a] $2\text{-}FC_6H_4CH_2Br$, [b] BCl_3, [c] $POCl_3$, [d] CH_3NH_2.

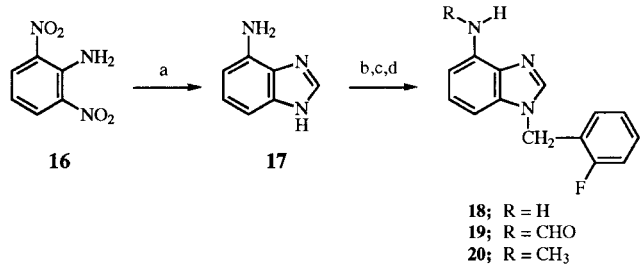
The N-5 protective group was removed with boron trichloride to give **13** in 83% yield. A small amount of **10b** was also isolated. The oxo compound **13** was converted to chloro **14** with phosphorous oxychloride. Amination of **14** with methylamine gave **15**.

Benzimidazoles.

The target 1-(2-fluorobenzyl)benzimidazoles **18** and **20** were prepared from **16** as outlined in Scheme 3. Intermediate 4-aminobenzimidazole **17** was prepared by a literature method from 2,6-dinitroaniline (**16**) [12]. In our hands reduction of **16** in formic acid in the presence of hydrogen and palladium on carbon on a Paar hydrogenator was exothermic, which resulted in a dangerous increase in internal pressure. The modification suggested in the Experimental should be used.

The anion of aminobenzimidazole **17** was alkylated

Scheme 3



[a] HCO_2H, H_2, Pd/C; [b] $2\text{-}FC_6H_4CH_2Br$, NaH; [c] AcOCHO; [d] $BH_3{\cdot}S(CH_3)_2$

with 2-fluorobenzyl bromide to give **18** in 69% yield. A small amount of formamide **19** was also isolated, which probably formed from reaction of **18** with the solvent *N,N*-dimethylformamide. The 4-methylamino compound **20** was prepared from **18** by Krishnamurthy's method for monomethylation of aromatic amines [13]. Amine **18** was formylated to give **19** and then reduced with borane-methyl sulfide to give **20** in 69% yield.

Biological Results.

Compounds **8**, **9**, **15**, **18**, and **20** were tested for their ability to protect male rats against maximal electroshock-induced seizures (MES) under conditions where **1** had an ip ED_{50} of 1.7 ±0.4 mg/kg and an oral ED_{50} of 2.5 ±0.4 mg/kg [1,14] (Table I). Although these compounds had activity against MES with ip ED_{50}s of 13 mg/kg or less, the oral activities were one-tenth or less as active as **1**. Thus, isosteric substitution of the pyrimidine ring nitrogens of **1** to give the imidazo[4,5-*c*]pyridazine, imidazo[4,5-*d*]pyridazine, and benzimidazole systems led to

Table I

Anticonvulsant Activity of Compounds Against Maximal Electroshock-induced Seizures (MES) [a]

Compound [b]	MES ED_{50}, mg/kg [c,d,e]	
	i.p.	p.o.
1	1.7 ±0.4	2.5 ±0.4
8	10	31
9	14	N.D.
15	7	>25
18	7	36
20	13	25

[a] The compounds were tested for their ability to protect Wistar male rats against maximal electroshock-induced seizures (MES) as described in [14]. The ED_{50} was the dose needed to protect 50% of the animals against the hind-limb extensor component and were calculated using the method of L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944). [b] Compounds were tested as the hydrochloride salt. [c] The ED_{50} for phenytoin was 10 ±2 mg/kg i.p. and 20 ±3 mg/kg p.o. [d] Where ED_{50} values are presented with a standard error a minimum of twelve animals were used per dose level with four doses per compound. ED_{50} values without standard error were determined using three doses of compound with six animals per point. [e] N.D. = not determined.

compounds with substantially reduced anticonvulsant activity.

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 nmr spectra were recorded using a Varian XL-200 spectrometer. 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). The tlc was performed on Whatman 200 μ MK6F plates of silica gel with fluorescent indicator; spots were detected with uv light. Analysis (hplc) was performed on a Waters 840 Data System with two Waters Model 510 pumps, a WISP injector, and a Waters 490 UV detector set at 230, 254, 280 nm (maxplot mode) using a Supelco LC-8 (4.6 x 150 mm, 5 micron) or Versapack C_{18} (4.6 x 250 mm, 10 micron) column. Preparative column chromatography was done using the flash chromatography technique [15] on Silica Gel 60 (40-63 μm, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

4-Amino-3,5-dichloropyridazine (**4**).

A mixture of 3,4,5-trichloropyridazine (**2**) (25.0 g, 0.14 mole) [**2** is a skin irritant and may produce severe blisters] and ethanol saturated with ammonia (250 ml) was heated at 125° for 5 hours in a sealed, stainless steel reaction vessel. The reaction was performed six times on a 25 g scale. The combined reaction mixture was concentrated *in vacuo,* and the residual two-component mixture was purified by four successive column chromatographies on Silica Gel 60 (14 cm x 20 cm). The column was eluted with 50% ethyl acetate in hexane.

The first component (R_f 0.66, ethyl acetate) was isolated and crystallized from dichloromethane-methanol-hexane to yield 44.6 g (33%) of **4** as tan crystals, mp 149-150° (dec) (lit [6] 151°, lit [7] 176-178°); hplc: one major peak on Supelco LC-8 with 60% methanol/water/0.1% triethylamine, 99%, k' = 0.79; uv (methanol): λ_{max} 255 nm (ε 10600), λ_{sh} 288 nm (ε 5900); uv (1 *N* hydrochloric acid): λ_{max} 287 nm (ε 11900); uv (0.1 *N* sodium hydroxide): λ_{max} 256 nm (ε 10200), λ_{sh} 287 nm (ε 7100); ^{1}H nmr (DMSO-d_6): δ 8.75 (s,1H, H-6), 7.14 (br s, 2H, NH_2, deuterium oxide exchangeable) irradiation at 7.14 gave no nOe enhancement at 8.75; ms: (CI/methane gas) m/z 164 (100.0, M+1).

Anal. Calcd. for $C_4H_3Cl_2N_3$: C, 29.30; H, 1.84; N, 25.62; Cl, 43.24. Found: C, 29.21; H, 1.87; N, 25.56; Cl, 43.17.

5-Amino-3,4-dichloropyridazine (**3**).

The second component (R_f 0.49, ethyl acetate) was isolated and crystallized from dichloromethane-methanol-hexane to give 34.4 g (26%) of **3** as yellow crystals, mp 177-178° dec (lit [6] 178°; lit [7] 150-151°); hplc: one peak on Supelco LC-8 with 60% methanol/water/0.1% triethylamine, 100%, k' = 1.01; uv (methanol): λ_{max} 258 nm (ε 11700), λ_{sh} 288 nm (ε 4300); uv (1 *N* hydrochloric acid): λ_{max} 286 nm (ε 8000), λ_{sh} 261 nm (ε 5300); uv (0.1 *N* sodium hydroxide): λ_{max} 258 nm (ε 10300), λ_{sh} 287 nm (ε 4500); nmr (DMSO-d_6): δ 8.54 (s, 1H, H-6), 7.25 (br s, 2H, NH_2, deuterium oxide exchangeable) irradiation at 7.25 gave an nOe enhancement at 8.54; ms: (CI/methane gas) m/z 164 (100.0, M+1).

Anal. Calcd. for $C_4H_3Cl_2N_3$: C, 29.30; H, 1.84; N, 25.62; Cl, 43.24. Found: C, 29.20; H, 1.87; N, 25.53; Cl, 43.34.

4-Amino-5-chloro-3-[1-(2-fluorobenzyl)hydrazino]pyridazine (**5**).

A solution of **4** (42.4 g, 0.26 mole) in 2-fluorobenzylhydrazine [3] (156 g, 1.11 moles) was heated under a nitrogen atmosphere at 100° for 13 hours. The mixture was chromatographed on Silica Gel 60. The column (10 cm x 20 cm) was eluted with a gradient of hexane to 40% ethyl acetate in hexane to give 20.0 g of **5** (29%), mp 128-130° (R_f = 0.47, ethyl acetate); hplc: one major peak on Supelco LC-8 with 70% methanol/water/0.1% triethylamine, 98%, k' = 1.1; uv (methanol): λ_{max} 266 nm (ε 2100), λ_{sh} 261 nm (ε 2000); uv (1 *N* hydrochloric acid): λ_{max} 294 nm (ε 4400), 246 nm (ε 7000), λ_{sh} 268 nm (ε 3500); uv (0.1 *N* sodium hydroxide): λ_{max} 306 nm (ε 1300), 248 nm (ε 2000), λ_{sh} 268 nm (ε 1300); nmr (DMSO-d_6): δ 8.35 (s, 1H, H-6), 7.11-7.43 (m, 4H, Ar), 6.89 (br s, 2H, Ar NH_2), 4.79 (s, 2H, CH_2), 4.71 (s, 2H, NNH_2); ms: (CI/methane gas) m/z 268 (100.0, M+1), 251 (4.5, M-NH_2), 158 (5.9, M-$C_6H_4FCH_2$).

Anal. Calcd. for $C_{11}H_{11}ClFN_5$: C, 49.36; H, 4.14; N, 26.16; Cl, 13.24. Found: C, 49.25; H, 4.18; N, 26.09; Cl, 13.15.

4-Amino-5-chloro-3-[(2-fluorobenzyl)amino]pyridazine (**6**).

A mixture of **5** (20.0 g, 74 mmoles) and Raney Ni (W-2, 3 g) [10] in absolute ethanol (650 ml) was shaken in the presence of hydrogen at 40 psi for 3 hours at ambient temperature. The reaction was performed in three batches. The mixture was filtered, and the solvent was removed by spin evaporation *in vacuo* to give 16.5 g (87%) of **6** as yellow crystals (R_f = 0.42, ethyl acetate). The analytical sample was recrystallized from dichloromethane-methanol-hexane, mp 193-195° dec; hplc: one peak on Supelco LC-8 with 60% methanol/water/0.1% triethylamine, 100%, k' = 1.78; uv (methanol): λ_{max} 268 nm (ε 8100), λ_{sh} 295 nm (ε 5700); uv (1 *N* hydrochloric acid): λ_{max} 311 nm (ε 7000), 283 nm (ε 6000), 238 nm (ε 18400); uv (0.1 *N* sodium hydroxide): λ_{max} 296 nm (ε 5500), 267 nm (ε 6900), λ_{sh} 296 nm (ε 5500); ^{1}H nmr (DMSO-d_6): δ 8.13 (s, 1H, H-6), 7.09-7.41 (m, 4H, Ar), 6.66 (t, J = 5 Hz, 1H, NH), 6.24 (br s, 2H, Ar-NH_2), 4.65 (d, J = 5 Hz, 2H, CH_2); ms: (CI/methane gas) m/z 253 (100.0, M+1).

Anal. Calcd. for $C_{11}H_{10}ClFN_4$: C, 52.29; H, 3.99; N, 22.17; Cl, 14.03. Found: C, 52.26; H; 4.00; N, 22.16; Cl, 14.12.

7-Chloro-3-(2-fluorobenzyl)-3*H*-imidazo[4,5-*c*]pyridazine (**7**).

A suspension of **6** (16.1 g, 61 mmoles) in triethylorthoformate (160 ml, 0.96 mole) containing ethanesulfonic acid (0.01 ml, 0.1 mmole) was heated under nitrogen at 75-100° for 4 hours. The dark mixture was concentrated *in vacuo.* The residue was dissolved in ethyl acetate and washed with brine containing sodium bicarbonate. The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and concentrated to a black solid. The solid was chromatographed on Silica Gel 60. The column (8 cm x 15 cm) was eluted with 50% ethyl acetate in hexane to yield 10.4 g (62%) of **7** (R_f = 0.50, ethyl acetate). The analytical sample was recrystallized from ethyl acetate-hexane to give beige crystals, mp 138-139°; hplc: one peak on Supelco LC-8 with 50% methanol/water, 100%, k' = 3.14; uv (methanol): λ_{max} 287

nm (ε 6500), 260 nm (ε 8100); uv (1 *N* hydrochloric acid): λ_{max} 313 nm (ε 6600), 260 nm (ε 6700); uv (0.1 *N* sodium hydroxide): λ_{max} 287 nm (ε 6400), 259 nm (ε 8100); ^{1}H nmr (DMSO-d_6): δ 9.26 (s, 1H, H-6), 9.00 (s, 1H, H-2), 7.14-7.42 (m, 4H, Ar), 5.74 (s, 2H, CH_2); ms: (CI/methane gas) m/z 263 (100.0, M+1), 243 (9.0, M-F), 227 (4.1, M-Cl).

Anal. Calcd. for $C_{12}H_8ClFN_4$: C, 54.87; H, 3.07; N, 21.33; Cl, 13.50. Found: C, 54.86; H, 3.12; N, 21.31; Cl, 13.56.

3-(2-Fluorobenzyl)-7-(methylamino)-3*H*-imidazo[4,5-*c*]pyridazine Hydrochloride (**8**).

A mixture of **7** (4.1 g, 15.6 mmoles) in methanol saturated with methylamine (150 ml) was heated in a stainless steel reaction vessel at 125° for 20 hours. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on Silica Gel 60. The column (7 cm x 20 cm) was eluted with 5% methanol in chloroform to give 4.0 g (99%) of **8**; (R_f = 0.38, 10% methanol in chloroform). The solid was dissolved in 2-propanol (100 ml) and diluted with 1*M* hydrochloric acid in ether (20 ml) to give white crystals of **8** (2.7 g, 59%), mp 184-187°; hplc: one peak on Supelco LC-8 with 50% methanol/water/0.1% triethylamine, 100%, k' = 2.22; uv (methanol): λ_{max} 315 nm (ε 13300), 263 nm (ε 7400); uv (1 *N* hydrochloric acid): λ_{max} 344 nm (ε 10300), λ_{sh} 259 nm (ε 5500); uv (0.1 *N* sodium hydroxide): λ_{max} 315 nm (ε 12400), 262 nm (ε 5400); ^{1}H nmr (DMSO-d_6): δ 8.82 (br s, 2H, H-6 or H-2 and NH), 8.70 (s, 1H, H-6 or H-2), 7.14-7.42 (m, 4H, Ar), 5.65 (s, 2H, CH_2), 3.19 (br s, 3H, CH_3); ms: (CI/methane gas) m/z 258 (100.0, M+1), 238 (8.4, M-F).

Anal. Calcd. for $C_{13}H_{12}FN_5$•HCl: C, 53.16; H, 4.46; N, 23.84; Cl, 12.07. Found: C, 53.15; H, 4.50; N, 23.75; Cl, 12.00.

7-Amino-3-(2-fluorobenzyl)-3*H*-imidazo[4,5-*c*]pyridazine Hydrochloride (**9**).

A mixture of **7** (4.8 g, 18.3 mmoles) in methanol saturated with ammonia (300 ml) was heated in a stainless steel reaction vessel at 125° for 24 hours. Removal of the solvent and chromatography of the residue on Silica Gel 60 (7 cm x 20 cm column; 3% methanol in chloroform) gave 3.3 g (73%) of **9** (R_f = 0.32, 10% methanol in chloroform). The solid was dissolved in 2-propanol (100 ml) and treated with 1*M* hydrochloric acid in ether (20 ml) to give white crystals of **9** hydrochloride (3.3 g, 67%), mp 265-267° dec; hplc: one peak on Supelco LC-8 with 50% methanol/water/0.1% triethylamine, 100%, k' = 1.48; uv (methanol): λ_{max} 305 nm (ε 11900), 260 nm (ε 7600); uv (1 *N* hydrochloric acid): λ_{max} 327 nm (ε 12900), λ_{sh} 260 nm (ε 9200); uv (0.1 *N* sodium hydroxide): λ_{max} 304 nm (ε 11600), 258 nm (ε 6900); ^{1}H nmr (DMSO-d_6): δ 8.84 and 8.62 (s, 2H, H-6 and H-2), 8.30 (br s, 2H, NH_2), 7.14-7.42 (m, 4H, Ar), 5.64 (s, 2H, CH_2); ms: (CI/methane gas) m/z 244 (100.0, M+1).

Anal. Calcd. for $C_{12}H_{10}FN_5$•HCl: C, 51.53; H, 3.96; N, 25.04; Cl, 12.68. Found: C, 51.59; H, 4.00; N, 25.02; Cl, 12.70.

5-[(Benzyloxy)methyl]-3-(2-fluorobenzyl)-3,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one (**11**).

A mixture of 5-[(benzyloxy)methyl]-1,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one (**10a**) [11] (7.8 g, 0.14 mole), potassium carbonate (23.0 g, 0.17 mole), and 2-fluorobenzylbromide (20.1 ml, 0.17 mole) in dimethylformamide (375 ml) was stirred at ambient temperature under nitrogen for 20 hours. The mixture was filtered, and the filtrate was concentrated *in vacuo*. A solution of the residue in ethyl acetate was washed with water, dried (sodium sulfate), and concentrated *in vacuo*. The two component mixtures were separated by chromatography on Silica Gel 60. The column (14 cm x 20 cm) was eluted with a 50% ethyl acetate in hexane to ethyl acetate gradient.

The first component (R_f = 0.53, ethyl acetate) was isolated and crystallized from dichloromethane-hexane to give 23.6 g (47%) of cream-colored crystals of **11**, mp 79-81°; hplc: one peak on Versapack C_{18} with 60% methanol/water/0.1% trifluoroacetic acid, 99.7%, k' = 2.27; uv (methanol): λ_{max} 262 nm (ε 6100); uv (1 *N* hydrochloric acid): λ_{max} 262 nm (ε 6000); uv (0.1 *N* sodium hydroxide): λ_{max} 244 nm (ε 30200); ^{1}H nmr (DMSO-d_6): δ 8.49 (s, 1H, H-2), 8.47 (s, 1H, H-7), 7.15-7.36 (m, 9H, Ar), 5.75 (s, 2H, $ArCH_2N$), 5.52 (s, 2H, NCH_2O), 4.60 (s, 2H, $ArCH_2O$); irradiation at 5.75 gave an nOe enhancement at 8.49 (H-2), but not at 8.47 (H-7); ms: (CI/methane gas) m/z 365 (75.1, M+1), 335 (13.5, M-29), 257 (100.0, M-107).

Anal. Calcd. for $C_{20}H_{17}FN_4O_2$: C, 65.93; H, 4.70; N, 15.38. Found: C, 66.00; H, 4.72; N, 15.35.

5-[(Benzyloxy)methyl]-1-(2-fluorobenzyl)-1,5-dihydro-4*H*-imidazo[4,5-*d*]pyridazin-4-one (**12**).

The second component (see above; R_f = 0.20, ethyl acetate) was isolated as a white solid to give 12.8 g (25%) of **12**, mp 110-112°; hplc: one peak on Versapack C_{18} with 60% methanol/water/0.1% trifluoroacetic acid, 99.9%, k' = 1.36; uv (methanol): λ_{max} 268 nm (ε 5500); uv (1 *N* hydrochloric acid): λ_{max} 262 nm (ε 5800); uv (0.1 *N* sodium hydroxide): λ_{max} 268 nm (ε 5200); ^{1}H nmr (DMSO-d_6): 8.41 and 8.49 (s, 1H each, H-2 and H-7), 7.21-7.38 (m, 9H, Ar), 5.63 (s, 2H, $ArCH_2N$), 5.54 (s, 2H, OCH_2N), δ 4.61 (s, 2H, $ArCH_2O$); irradiation at 5.63 gave an nOe enhancement at 8.41 and 8.49; ms: (CI/methane gas) m/z 365 (100.0, M+1), 335 (10.9, M-29), 257 (77.9, M-107).

Anal. Calcd. for $C_{20}H_{17}FN_4O_2$: C, 65.93; H, 4.70; N, 15.38. Found: C, 65.91; H, 4.73; N, 15.31.

1,5-Dihydro-5-(hydroxymethyl)-4*H*-imidazo[4,5-*d*]pyridazin-4-one (**10b**).

To a stirred solution of **12** (12.1 g, 33 mmoles) in dichloromethane (600 ml) at -78° (dry ice/acetone) under nitrogen was added 1 *M* boron trichloride in dichloromethane (266 ml, 266 mmoles). The mixture was stirred at -78° for 4 hours, and then 75% methanol in dichloromethane (1 l) was added dropwise. The resultant solution was stirred for 2 hours at -78° and allowed to warm to ambient temperature. The mixture was concentrated, the residue was dissolved in methanol (0.7 l), and the solution was concentrated *in vacuo*. The residue was triturated with hot 2-propanol (0.2 l), and the insoluble, reddish-brown solid was collected. Recrystallization from methanol gave 0.15 g, (2.7%) of cream-colored crystals of **10b**, mp >250°; hplc: one peak on Supelco LC-8 with 60% methanol/water/0.1% trifluoroacetic acid, 100%, k' = 0.84; uv (methanol): λ_{max} 250 nm (ε 5400), λ_{sh} 262 nm (ε 4700); uv (1 *N* hydrochloric acid): λ_{max} 256 nm (ε 5700); uv (0.1 *N* sodium hydroxide): λ_{max} 263 nm (ε 5300), 224 nm (ε 44800); ^{1}H nmr (DMSO-d_6): δ 8.36 and 8.41 (s, 1H each, H-2 and H-7), 7.00 (br s, 2H, OH and NH), 5.43 (s, 2H, NCH_2O); ms: (CI/methane gas) m/z 167 (17.4, M+1), 149 (14.5, M-17), 137 (100.0, M-29).

Anal. Calcd. for $C_6H_6N_4O_2$•0.1HCl: C, 42.45; H, 3.62; N, 33.00; Cl, 2.09. Found: C, 42.38; H, 3.70; N, 32.92; Cl, 2.13.

1-(2-Fluorobenzyl)-1,5-dihydro-4*H*-imidazo[3,4-*d*]pyridazin-4-one (**13**).

The 2-propanol filtrate (from synthesis of **10b** above) was concentrated and chromatographed on Silica Gel 60. The column (8 cm x 17 cm) was eluted with chloroform-acetone-methanol/7:2:1, and the appropriate fractions (R_f = 0.23, chloroform-acetone-methanol/7:2:1) were evaporated to give 6.9 g (83%) of **13**. The analytical sample was recrystallized from 2-propanol to give tan crystals, mp 205-207°; hplc: one peak on Versapack C_{18} with 30% methanol/water/0.1% trifluoroacetic acid, 100%, k' = 3.76; uv (methanol): λ_{max} 268 nm (ε 5500), 253 nm (ε 5300), λ_{sh} 276 nm (ε 4700), 247 nm (ε 5200); uv (1 *N* hydrochloric acid): λ_{max} 268 nm (ε 6000), 253 nm (ε 5800), λ_{sh} 248 nm (ε 5300); uv (0.1 *N* sodium hydroxide): λ_{max} 282 nm (ε 6400), 256 nm (ε 5900); ^{1}H nmr (DMSO-d_6): δ 12.69 (br s, 1H, NH), 8.38 and 8.39 (s, 1H each, H-2 and H-7), 7.16-7.46 (m, 4H, Ar), 5.62 (s, 2H, $ArCH_2N$); ms: (CI/methane gas) m/z 245 (100.0, M+1).

Anal. Calcd. for $C_{12}H_9FN_4O$: C, 59.02; H, 3.71; N, 22.94. Found: C, 58.92; H, 3.74; N, 22.86.

4-Chloro-1-(2-fluorobenzyl)-1*H*-imidazo[4,5-*d*]pyridazine (**14**).

A mixture of **13** (2.5 g, 10 mmoles) and phosphorous oxychloride (25 ml, 270 mmoles) was refluxed for 4.5 hours under nitrogen. The reaction was concentrated *in vacuo*; the resultant black tar was stirred for 1 hour with a mixture of dichloromethane and ice-water. The aqueous phase was separated and extracted with dichloromethane. The combined organic layers were washed with dilute sodium bicarbonate, dried, and concentrated to an orange solid. The residue was chromatographed on Silica Gel 60. The column (9 cm x 14 cm) was eluted with chloroform-acetone-methanol/150:20:5. The appropriate fractions were concentrated to give **14** as a yellow solid (1.6 g, 61%), mp 182-184° dec; hplc: one major peak on Supelco LC-8 with 40% methanol/water, 99.6%, k' = 6.92; ^{1}H nmr (DMSO-d_6): δ 9.64 (s, 1H, H-7), 8.85 (s, 1H, H-2), 7.17-7.50 (m, 4H, Ar), 5.76 (s, 2H, $ArCH_2N$); ms: (CI/methane gas) m/z 263 (100.0, M+1).

Anal. Calcd. for $C_{12}H_8ClFN_4$: C, 54.87; H, 3.07; N, 21.33; Cl, 13.50. Found: C, 54.81; H, 3.12; N, 21.25; Cl, 13.59.

1-(2-Fluorobenzyl)-4-(methylamino)-1*H*-imidazo[4,5-*d*]pyridazine (**15**).

A mixture of **14** (1.4 g, 5 mmoles) in methanol saturated with methylamine (100 ml) was heated in a stainless steel pressure vessel at 125° for 24 hours. Removal of the solvent and chromatography of the residue on silica gel 60 (8 cm x 12 cm) using a chloroform to chloroform-acetone-methanol/75:20:5 gradient gave a yellow foam (R_f = 0.39, chloroform-acetone-methanol/7:2:1). The foam was dissolved in 1.2*M* hydrochloric acid in ethanol (5 ml), filtered, and concentrated. Crystallization of the residue from 2-propanol gave **15** (0.9 g, 72%) as a white solid, mp 225-227°; hplc: one peak on Versapack C_{18} with 30% methanol/water/0.1% trifluoroacetic acid, 100%, k' = 2.82; uv (methanol): λ_{max} 296 nm (ε 4700), 261 nm (ε 8800), λ_{sh} 267 nm (ε 7800); uv (1 *N* hydrochloric acid): λ_{max} 260 nm (ε 11900), λ_{sh} 255 nm (ε 11700); uv (0.1 *N* sodium hydroxide): λ_{max} 295 nm (ε 3800), 260 nm (ε 7800), λ_{sh} 267 nm (ε 6900); ^{1}H nmr, (DMSO-d_6): δ 9.58 (br s, 1H, NH), 8.81 and 9.07 (s, 1H each, H-2 and H-7), 7.18-7.51 (m, 4H, Ar); 5.78 (s, 2H, $ArCH_2N$), 3.11 (d, J = 4.45 Hz, 3H, NMe); ms: (CI/methane gas) m/z 258 (100.0, M+1).

Anal. Calcd. for $C_{13}H_{12}FN_5$•HCl: C, 53.16; H, 4.46; N, 23.84; Cl, 12.07. Found: C, 53.06; H, 4.49; N, 23.82; Cl, 12.14.

4-Aminobenzimidazole Hydrochloride (**17**).

To a mixture of 10% Pd on carbon (1.35 g) and formic acid (140 ml) under a stream of nitrogen in a Parr bottle was cautiously added a slurry of 2,6-dinitroaniline (**16**) (25.0 g, 0.14 mole) in formic acid. The addition caused a mildly exothermic reaction. The mixture was shaken in the presence of hydrogen. After 0.5 hour at 49 psi, a very exothermic reaction occurred, which resulted in a large increase in pressure. [**Warning**: The reaction should be run as follows: 1) slowly add 2,6-dinitroaniline suspended in formic acid to the catalyst-solvent mixture under a blanket of nitrogen with occasional swirling; 2) let the mixture stand for at least one hour before placing it on the hydrogenator; 3) monitor the reaction continuously and be prepared to alleviate pressure above 35 psi or to cool the bottle with dry ice if the temperature exceeds 50°]. The reaction was vented, cooled in a dry ice bath, and filtered. The filtrate was concentrated *in vacuo*, and the hydrogenation was repeated on the residue. When no further hydrogen uptake was observed, the mixture was filtered through a Celite pad. The filtrate was spin evaporated, and the residue was refluxed with 10% aqueous hydrochloric acid (300 ml) for 6 hours. The mixture was concentrated *in vacuo* to give a black residue. A mixture of the residue and Darco was boiled with methanol (500 ml) and filtered through Celite. The filtrate was diluted with ether (1 l) to give **17** as a gray powder (20.3 g, 73%), mp 245-248°; ^{1}H nmr (DMSO-d_6): δ 11.1 (s, NH_3^+), 9.5 (s, 1H, H-2), 6.7-7.5 (m, 3H, Ar).

Anal. Calcd. for $C_7H_7N_3$•2HCl: C, 40.80; H, 4.40; N, 20.39; Cl, 34.41. Found: C, 40.88; H, 4.45; N, 20.38; Cl, 34.33.

1-(2-Fluorobenzyl)-4-formamido-1*H*-benzimidazole (**19**).

To an ice-cold, stirred solution of **17** (13.7 g, 66 mmoles) in dimethylformamide (100 ml) under nitrogen was added a 50% oil dispersion of sodium hydride (9.6 g, 200 mmoles). The mixture was stirred for 2 hours at 0°, and 2-fluorobenzyl bromide (13.2 g, 70 mmoles) was added. Stirring was continued at room temperature for 16 hours, and the mixture was concentrated *in vacuo* (20°/0.05 mm Hg). The residue was partitioned between chloroform and water. The chloroform layer was dried (sodium sulfate), filtered, and spin evaporated to a brown solid (20.8 g). Two components were separated by column chromatography (silica gel 60, ethyl acetate). The first component (R_f = 0.23, ethyl acetate) was crystallized from dichloromethane-hexane to yield straw-colored crystals of **19** (0.4 g, 2%), mp 144-145°; hplc: one major peak on Supelco LC-8 with 60% methanol/water/0.1% triethylamine, 97.8%, k' = 2.79; ^{1}H nmr (DMSO-d_6): δ 9.7 (s, 1H, CHO), 8.3 (s, 1H, H-2), 6.8-7.5 (m, 7H, arom), 5.5 (s, 2H, benzylic CH_2); ms: (CI/methane gas) m/z 270 (100.0, M+1), 241 (14.0, M-CO); ir (nujol): 1680 cm^{-1} (C=O). Hydrolysis of **19** (1 mmole/ml of 50% 2 *N* sodium hydroxide in ethanol, reflux, 2 hours) gave a compound identical to **18** by nmr.

Anal. Calcd. for $C_{15}H_{12}FN_3O$•0.2H_2O: C, 66.02; H, 4.58; N, 15.40. Found: C, 65.98; H, 4.66; N, 15.36.

4-Amino-1-(2-fluorobenzyl)-1*H*-benzimidazole Hydrochloride (**18**).

The second component (see above, R_f = 0.15, ethyl acetate) was dissolved in a minimum of methanol, diluted with ether, and

treated with excess ethereal hydrogen chloride. The resulting precipitate was collected and crystallized from absolute ethanol to give white crystals of **18** (11.0 g, 69%), mp 229-232° dec; hplc: one peak on Supelco LC-8 with 60% methanol/water/0.1% trifluoroacetic acid, 99.9%, k' = 1.73; ^{1}H nmr (DMSO-d_6): δ 9.64 (s, 1H, H-2), 7.20-7.54 (m, 6H, NH_2, Ar), 6.95 (d, J = 8 Hz, 1H, H-7), 6.74 (d, J = 8 Hz, 1H, H-5), 5.72 (s, 2H, CH_2); ms: (CI/methane gas) 242 (100.0, M+1).

Anal. Calcd. for $C_{14}H_{12}FN_3$•1.0HCl: C, 60.55; H, 4.72; N, 15.13; Cl, 12.77. Found: C, 60.48; H, 4.73; N, 15.12; Cl, 12.82.

1-(2-Fluorobenzyl)-4-methylamino-1*H*-benzimidazole Dihydrochloride (**20**).

To acetic anhydride (5.4 g, 53 mmoles) stirred under nitrogen at 0° was added dropwise 98% formic acid (3.1 g, 53 mmoles). The mixture was heated at 50° for 1 hour, cooled to -20°, and diluted with tetrahydrofuran (5 ml) before **18** (4.8 g, 20 mmoles) in tetrahydrofuran (20 ml) was added dropwise with stirring. After 30 minutes, the mixture was concentrated *in vacuo* to give **19** as a solid residue. A stirred solution of the residue in tetrahydrofuran (20 ml) was cooled to 0° and treated dropwise with 2*M* borane:methyl sulfide in tetrahydrofuran (25 ml). After vigorous evolution of gas had subsided, the mixture was refluxed 3 hours in a nitrogen atmosphere. The mixture was cooled to 0°, diluted with methanol (10 ml), and acidified to *p*H 2 with ethereal hydrogen chloride. The resulting suspension was refluxed an hour, cooled, diluted with methanol (45 ml), and spin evaporated. The solid residue was treated with aqueous saturated sodium chloride solution and basified to *p*H 12 with 50% sodium hydroxide solution. The milk-colored solution was extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated to a pale lavendar solid (5.5 g). Excess ethereal hydrogen chloride was added to a solution of the solid in methanol at 0° to give a white precipitate (5.6 g). Recrystallization from methanol-ether gave off-white crystals of **20** (4.5 g, 69%), mp 208-210°; hplc: one peak on Supelco LC-8 with 60% methanol/water/0.1% trifluoroacetic acid, 100%, k' = 4.37; nmr (DMSO-d_6): δ 9.65 (s, 1H, H-2), 7.18-7.54 (m, 6H, NH, Ar), 6.80 (d, J = 8 Hz, 1H, H-7), 6.57 (d, J = 8 Hz, 1H, H-5), 5.72 (s, 2H, CH_2), 2.85 (s, 3H, NCH_3); ms: (CI/methane gas) 256 (100.0, M+1).

Anal. Calcd. for $C_{15}H_{14}FN_3$•2.0HCl: C, 54.89; H, 4.91; N, 12.80; Cl, 21.60. Found: C, 55.14; H, 4.96; N, 12.83; Cl, 21.48.

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REFERENCES AND NOTES

[1] J. L. Kelley and F. E. Soroko, *J. Med. Chem.*, **29**, 1133 (1986).

[2] J. L. Kelley, M. P. Krochmal, J. A. Linn, E. W. McLean, and F. E. Soroko, *J. Med. Chem.*, **31**, 1005 (1988).

[3] J. L. Kelley, R. G. Davis, E. W. McLean, M. Notrica, F. E. Soroko, B. R. Cooper, and R. C. Glen, unpublished results.

[4] J. L. Kelley, J. A. Linn, J. L. Rideout, and F. E. Soroko, *J. Heterocyclic Chem.*, **25**, 1255 (1988).

[5] J. L. Kelley, D. C. Wilson and V. L. Styles, unpublished results.

[6] T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, **1**, 42 (1964).

[7] T. Kuraishi, *Pharm. Bull. (Tokyo)*, **4**, 497 (1956).

[8] J. L. Kelley, M. P. Krochmal, J. A. Linn, E. W. McLean, and F. E. Soroko, *J. Med. Chem.*, **31**, 606 (1988).

[9] D. K. Chesney and R. N. Castle, *J. Heterocyclic Chem.*, **11**, 167 (1974).

[10] *Org. Synth.*, Coll. Vol **3**, 181 (1955).

[11] R. P. Gagnier, M. J. Halat, and B. A. Otter, *J. Heterocyclic Chem.*, **21**, 481 (1984).

[12] E. Lebenstedt and W. Schunack, *Arch. Pharm. (Weinheim)*, **310**, 455 (1977).

[13] S. Krishnamurthy, *Tetrahedron Letters*, **23**, 3315 (1982).

[14] N. B. Mehta, C. A. R. Diuguid, and F. E. Soroko, *J. Med. Chem.*, **24**, 465 (1981).

[15] W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).