hydroxyphthalimide, 524-38-9; triethyl methanetricarboxylate, 6279-86-3; 2-(hydroxymethyl)propane-1,3-diol, 4704-94-3; 9-[3-[(*tert*-butyldimethylsilyl)oxy]propoxy]-2-formamidopurine, 123240-75-5; 2,6-diamino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine, 114778-44-8; 2-amino-9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]purine, 114778-42-6; 9-[3-(benzyloxy)propoxy]adenine, 123240-77-7; 9-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]adenine, 123240-78-8.

Benzodiazepine Receptor Binding Activity of 8-Substituted-9-(3-substituted-benzyl)-6-(dimethylamino)-9*H*-purines

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A series of 8-substituted analogues of 9-(3-aminobenzyl)-6-(dimethylamino)-9*H*-purine (**8**) were synthesized and tested for their ability to bind to the benzodiazepine receptor (BZR) in rat brain tissue. The most active compound was the 8-bromo-9-(3-formamidobenzyl) analogue **16** (IC_{50} = 0.011 μM), which was 1000-fold more active than the parent 9-benzyl-6-(dimethylamino)-9*H*-purine (**1**) and nearly as active as diazepam. Although substitution of a *m*-formamido group and an 8-bromo substituent on **1** imparted potent BZR binding activity, neither **16** nor 11 analogues exhibited significant anxiolytic activity on a modified Geller–Seifter conflict schedule.

High-affinity binding sites or receptors through which benzodiazepines exert their pharmacological activities have been identified in the central nervous system.[1-3] Compounds of diverse structure bind to the benzodiazepine receptor (BZR).[4] Purines were proposed as possible endogenous ligands,[5,6] and several papers describe structure–activity studies on the interaction of purines with the BZR.[7-9] We recently reported the BZR binding activity of a series of 6,9-disubstituted purines;[10] one of the most active compounds was 9-(3-aminobenzyl)-6-(dimethylamino)-9*H*-purine (**8**) which had an IC_{50} = 0.9 μM. We report the structure–activity relationships for binding to the BZR of a series of 8-substituted analogues of **8**; the most potent compounds have BZR binding affinity comparable to that of diazepam.

Chemistry

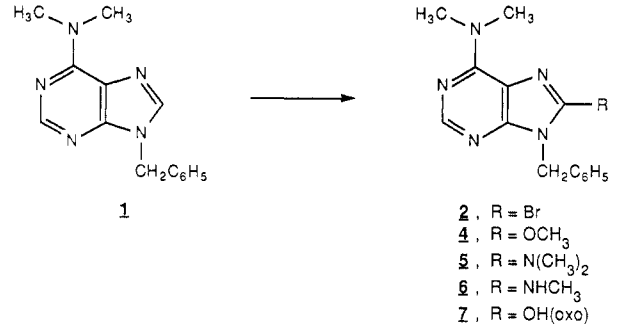
The 9-benzyl-8-substituted-purines **2** and **4–7** were prepared from **1** as outlined in Scheme I. Bromination of **1** with aqueous bromine in sodium acetate buffer gave **2**, which was converted to **4** with sodium methoxide, to **5** with aqueous dimethylamine, and to **6** with aqueous methylamine. The 8-oxopurine **7** was formed as a byproduct in the preparation of **4**.

The 8-methylpurine **3** was prepared in four steps from 4,6-dichloro-5-nitropyrimidine (**27**) as outlined in Scheme II. Amination of **27** with benzylamine gave **28**, which was reacted with dimethylamine to give **29** in fair yield. The nitro group was reduced with palladium on carbon to give **30**, which was cyclized with triethyl orthoacetate to give **3** in low overall yield.

The 8-bromopurine **9** was prepared as outlined in Scheme III. The 9-(3-nitrobenzyl)purine **31** was brominated by using a modification of the method for preparation of **2** to give **20** in high yield. The use of tetrahydrofuran as a cosolvent gave a homogeneous reaction, and the shorter reaction time circumvented formation of a monomethylamino side product. The nitro group of **20** was reduced with Raney nickel without detectable dehalogenation to give the 8-bromopurine **9** in good yield.

The 8-chloropurine **10** was prepared in three steps from 6,8-dichloropurine (**32**) (Scheme IV). Alkylation of **32** with 3-nitrobenzyl chloride gave **33**, which was selectively aminated to give the 6-(dimethylamino)purine **34**. The

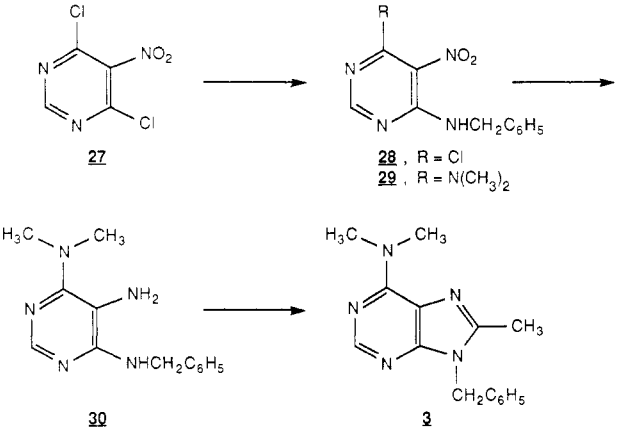
Scheme I



1

2, R = Br
4, R = OCH_3
5, R = $N(CH_3)_2$
6, R = $NHCH_3$
7, R = OH(oxo)

Scheme II



27

28, R = Cl
29, R = $N(CH_3)_2$

30 **3**

structures of **33** and **34** were confirmed by reaction of **34** with methylamine to give **37**, which was identical with **37**

† Division of Organic Chemistry.
‡ Division of Pharmacology.

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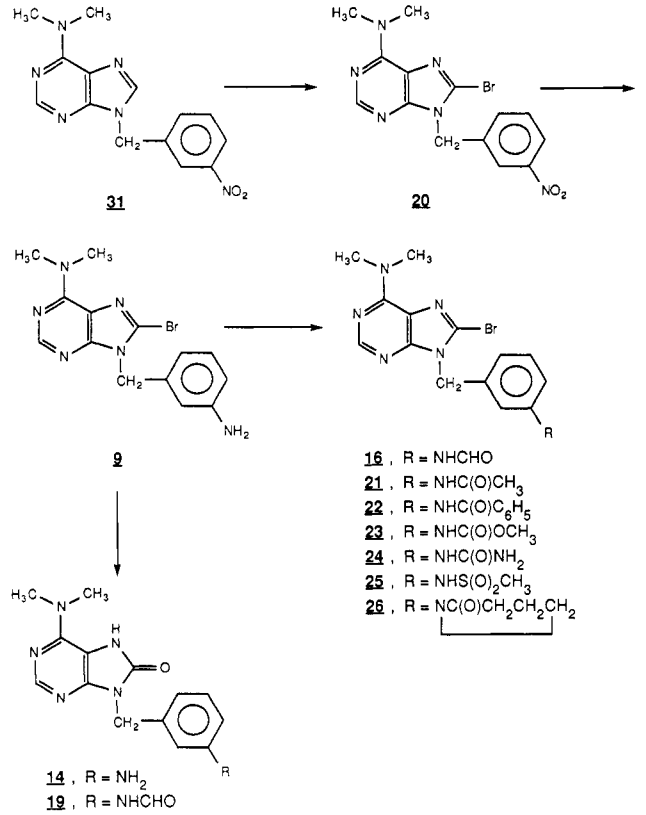
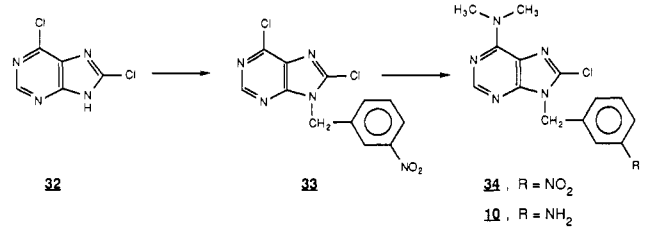
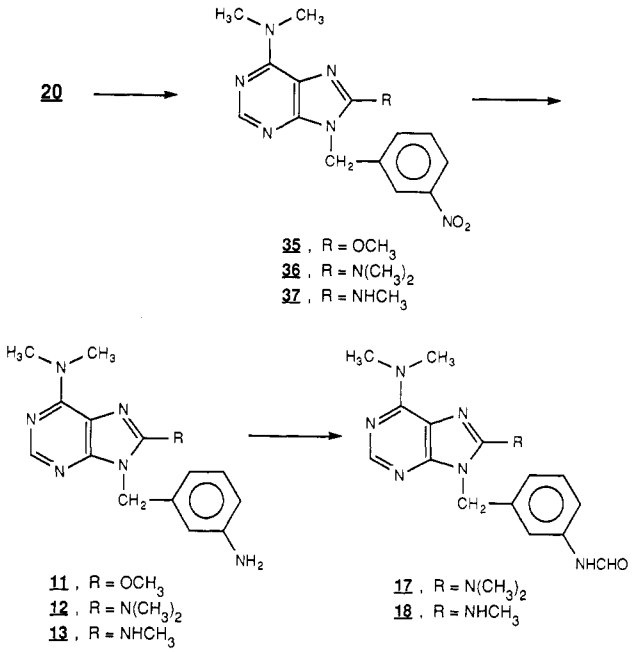
Scheme III



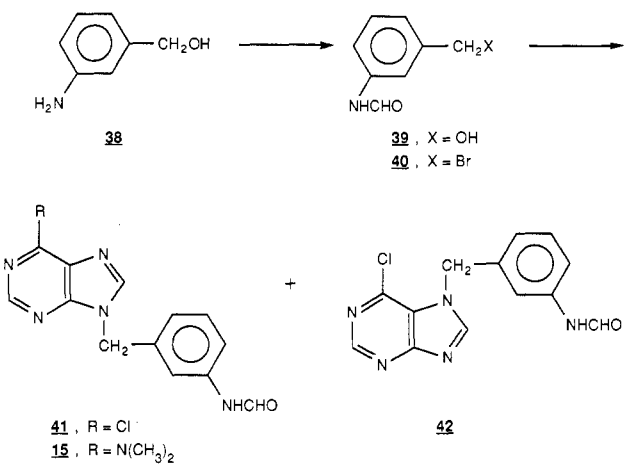
Scheme IV



Scheme V



Scheme VI



prepared from **20** (Scheme V). The nitro group was reduced with Raney nickel to give **10** in 77% yield.

The various 8-substituted-3-(aminobenzyl)purines **11–13** were prepared in two steps from **20** by displacement of the 8-bromo group with sodium methoxide, ethanolic dimethylamine, or methylamine to give **35–37**, respectively (Scheme V). These nitro intermediates were in turn reduced with palladium on carbon to give **11–13**. The 8-oxopurine **14** was prepared from **9** (Scheme III) by hydrolysis of the 8-bromo group with concentrated hydrochloric acid.

Although **15** could be prepared directly from **8** by formylation, an alternative approach was developed that allows the substituent at C-6 to be varied. The versatile intermediate 6-chloropurine **41** was prepared in three steps from 3-aminobenzyl alcohol (**38**) (Scheme VI). Bisformylation of **38** with ethyl formate followed by cleavage of the formate ester gave **39**. The ^{1}H NMR spectrum for **39** shows doublets at δ 8.70 (J = 11.2 Hz) and δ 8.25 (J = 1.8 Hz) corresponding, respectively, to the CHO signals of the E and Z rotamers of the formamide moiety. The corresponding amide NH doublets are overlapping and appear as a very broad multiplet at δ 10.07. The observation of rotamers of formanilide by NMR is well documented[11] and is characteristic of the formamide compounds **15–19** and **39–42**. The benzyl alcohol **39** was converted to the bromide **40**, which was reacted with 6-chloropurine to give a mixture of the 9- and 7-isomers, **41** and **42**. Chromatographic separation of the isomers gave pure **41**, which was reacted with aqueous dimethylamine to give **15** in good yield. The UV spectrum of **15** was compatible with a 9-substituted-6-(dimethylamino)-purine.[12-14]

The other 3-formamidobenzyl purines **16–19** were prepared by formylation of the 3-amino precursors **9** and **12–14** with ethyl formate (Schemes III and V). The N-acyl derivatives **21** and **22** were prepared from **9** with the appropriate anhydride and 4-(dimethylamino)pyridine in dichloromethane (Scheme III). Reaction of **9** with methyl chloroformate, sodium cyanate, or methanesulfonyl chloride gave **23–25**, respectively. The pyrrolidinone **26** was

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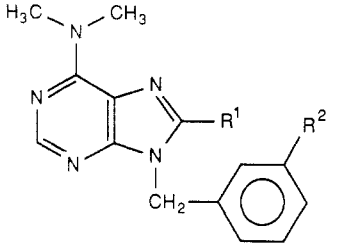
Table I. Benzodiazepine Receptor (BZR) Binding and Conflict Responding Activity of 8-Substituted-9-benzyl-9*H*-purines



compd	R^1	R^2	BZR[a] IC_{50}, μM	% change in conflict responding[b]
1[c]	H	H	13	−17 ± 44
2	Br	H	3	
3	CH_3	H	8.5	
4	OCH_3	H	5.4	
5	$N(CH_3)_2$	H	5.7	
6	$NHCH_3$	H	17	
7	OH(oxo)	H	(43)	
8[d]	H	NH_2	0.9	+4 ± 9
9	Br	NH_2	0.11 ± 0.01	+2 ± 7
10	Cl	NH_2	0.19	+15 ± 5
11	OCH_3	NH_2	1.0	+13 ± 9
12	$N(CH_3)_2$	NH_2	0.6	−3 ± 7
13	$NHCH_3$	NH_2	7.3	
14	OH(oxo)	NH_2	1.8	
15	H	NHCHO	0.034 ± 0.012	−2 ± 21
16	Br	NHCHO	0.011 ± 0.002	+9 ± 9
17	$N(CH_3)_2$	NHCHO	0.11	0 ± 7
18	$NHCH_3$	NHCHO	0.36	
19	OH(oxo)	NHCHO	0.13	−15 ± 13
20	Br	NO_2	(9)	
21	Br	$NHCOCH_3$	0.84	+3 ± 28
22	Br	$NHCOC_6H_5$	8.0	
23	Br	$NHCOOCH_3$	5.3	
24	Br	$NHCONH_2$	0.025 ± 0.018	+9 ± 3
25	Br	$NHSO_2CH_3$	1.5	
26	Br	$NCOCH_2CH_2CH_2$	(47)	
chlordiazepoxide			0.2	+67 ± 10[e]
diazepam			0.006 ± 0.001	

[a] The IC_{50}s were determined by the method described in ref 10. The IC_{50} is the concentration of compound that decreased specific binding of 1.5 nM [^{3}H]diazepam to rat brain receptors by 50%. The values in parentheses are percent inhibition of [^{3}H]diazepam binding by 100 μM compound. The mean ± SEM is given for the most active compounds. [b] The compounds were tested in Long-Evans rats as described in ref 10 on a modified Geller–Seifter conflict schedule. Compounds were administered by oral gavage in a 0.5% methylcellulose suspension at 25 mg/kg. [c] Synthesis: see ref 14. [d] Synthesis: see ref 13. [e] Chlordiazepoxide was administered at 20 mg/kg.

prepared in a two-step process from 4-chlorobutyryl chloride.

Biological Results and Discussion

The compounds in Table I were tested for activity in the BZR binding assay.[10] The percent inhibition of specific binding of 1.5 nM [^{3}H]diazepam to rat brain receptors by 100 μM compound was measured initially. An IC_{50} value was determined if the percent inhibition was greater than 75%. Increased potency of a compound as an inhibitor of [^{3}H]diazepam binding was assumed to reflect its increased affinity for the receptor.

The 9-benzylpurine **1** was reported to inhibit specific binding of [^{3}H]diazepam to rat brain receptors with an IC_{50} = 13 μM.[10] Substitution of an amino group in the meta position of **1** to give **8** enhanced the BZR binding affinity by 14-fold (Table I). To further increase the BZR binding affinity of analogues of **1**, the effect of various substituents at the 8-position was examined. Of six substituents (**2–7**) with orthogonal physicochemical properties, the 8-bromo analogue **2** was the most active with an IC_{50} 4-fold lower than that of **1**.

A similar selection of substituents was introduced at the 8-position of **8** in hopes of gaining an additive effect on receptor binding. Indeed, when the *m*-amino and 8-bromo groups were combined to form **9**, the favorable interactions were additive. Compound **9** had an IC_{50} = 0.11 μM, which was a 100-fold increase in binding over the parent **1**. The other 8-substituted analogues (**10–14**) of **8** were less active than **9**, although the 8-chloro analogue **10** was also highly active, with an IC_{50} = 0.19 μM.

Formylation of the amino group of **8** gave **15**, which had a strong affinity for the BZR with an IC_{50} = 0.034 μM. Several 8-substituted analogues of **15** were prepared, and the 8-bromo analogue **16** was the most potent receptor binder, with an IC_{50} = 0.011 μM. Compound **16** had an affinity for the BZR over 1000-fold greater than that of the parent 9-benzylpurine **1** and over 7000-fold greater than that of 6-(dimethylamino)purine.[7,10] Compound **16** binds to BZR with potent affinity. It is nearly as potent as diazepam (IC_{50} = 0.006 μM) and 18-fold more active than chlordiazepoxide.

The effect of several other nitrogenous substituents on receptor binding were examined. The nitro (**20**) analogue was inactive at 10 μM. Increasing the size of the group by substituting the formyl hydrogen with methyl (**21**), phenyl (**22**), methoxy (**23**), or amino (**24**) resulted in 2- to 800-fold losses in binding affinity. The *m*-(formylamino) substituent appears to be the optimal substituent for enhancing the BZR affinity of analogues of **1**.

Thus, substitution of a *m*-formamido group and an 8-bromo substituent on 9-benzyl-6-(dimethylamino)-9*H*-

purine (1) led to over a 1000-fold increase in BZR binding affinity. Compound 16 had an IC_{50} only half that of diazepam and represents a unique structure for evaluation as an anxiolytic agent.

Twelve of the most active BZR binding purines were tested for activity on a modified Geller–Seifter conflict schedule.[10,15,16] In a typical group of rats used for evaluating the effect of the purines, chlordiazepoxide (CDP) produces significant dose-related increases in responding during the conflict portion of the operant schedule. None of the purines tested at 25 mg/kg po produced any significant change in conflict responding (Table I). Compounds 11, 15, 16, and 24 were also inactive over the dose range of 12.5–50 mg/kg po, and compound 9 was inactive when tested at 20–320 mg/kg po and when tested at 5–200 mg/kg ip.

In another series of experiments, the IC_{50} values of 9, 15, 16, Ro 15-1788, and diazepam as inhibitors of [^{3}H]-flunitrazepam binding to rat brain cortex were determined according to the procedures of Ehlert et al.[17] At 37 °C in the presence of 100 mM sodium chloride, the addition of 10 μM γ-aminobutyric acid (GABA) increased the inhibitory potency of the BZR agonist diazepam by 3.5-fold, while the inhibitory potency of the BZR antagonist Ro 15-1788 was not significantly altered. The IC_{50} values of 9, 15, and 16 were also unaltered in the presence of 10 μM GABA, suggesting that, like Ro 15-1788, these benzylpurines are antagonists of the BZR.[17-19]

A series of 8-substituted-9-benzylpurines was developed that bind to the BZR with potency comparable to the benzodiazepines. However, no activity was observed when several of these compounds were tested for anxiolytic activity in the Geller–Seifter conflict test. In contrast to agonists of the BZR, antagonists are not active in the Geller–Seifter conflict test in vivo. These in vivo data, coupled with the GABA experiments, lend support to the concept that these compounds are antagonists of the BZR. The data do not, however, rule out the possibility that the absence of activity in the conflict paradigm may be due to lack of absorption, lack of penetration into CNS, or rapid metabolism of the compounds.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian XL-100-15-FT, a Varian FT-80A, a Varian T-60, or a Hitachi Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Ultraviolet absorption spectra were measured on a Unicam SP 800 or Cary 118 UV–vis spectrophotometer. TLC's were developed on Whatman 200-μm MK6F plates of silica gel with fluorescent indicator. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. Preparative flash chromatography[20] was performed on silica gel 60 (40–63 μm, E. Merck no. 9385). The analytical samples gave combustion values for C, H, and N within ±0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc.

9-Benzyl-8-bromo-6-(dimethylamino)-9*H*-purine (2). A mixture of 1 (3.00 g, 11.8 mmol), 0.5 M sodium acetate (90 mL), and bromine-saturated water (63 mL) was stirred at ambient temperature for 6 days. The resultant solid was collected and purified by column chromatography on silica gel. Elution with 16% ethyl acetate in hexane gave a solid that was recrystallized from heptane to give 1.65 g (42%) of 2: mp 144–146 °C; NMR (Me_2SO-d_6) δ 8.22 (s, 1 H, purine H), 7.27 (s, 5 H, ArH), 5.37 (s, 2 H, CH_2), 3.42 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{14}BrN_5$) C, H, N.

9-Benzyl-6-(dimethylamino)-8-methyl-9*H*-purine (3). A mixture of 29 (5.30 g, 19.4 mmol), ethanol (250 mL), and 5% palladium on carbon (0.60 g) was shaken in the presence of hydrogen at 2–3 atm for 3 h. The reaction mixture was heated on a steam bath and filtered through Celite (Preiser Scientific, Inc.). The filtrate was spin evaporated in vacuo, and the residue was recrystallized from methanol (charcoal) to give 2.50 g (53%) of 30, mp 181–185 °C, which was used without further purification. The crude 30 (2.50 g, 10.2 mmol), triethyl orthoacetate (70 mL), and ethanesulfonic acid (9 drops) were stirred at ambient temperature for 9 days. The solution was spin evaporated in vacuo. The residual oil was dissolved in dichloromethane (100 mL), washed with 5% aqueous sodium bicarbonate (25 mL) and water (2 × 25 mL), and spin evaporated in vacuo. The residual solid was recrystallized from heptane to give a solid that was further purified by flash chromatography to give 0.35 g (12%) of 3: mp 96–100 °C; NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, purine H), 7.4–7.1 (m, 5 H, ArH), 5.38 (s, 2 H, CH_2), 3.44 [s, 6 H, $N(CH_3)_2$], 2.42 (s, 3 H, CH_3). Anal. ($C_{15}H_{17}N_5$) C, H, N.

9-Benzyl-6-(dimethylamino)-8-methoxy-9*H*-purine (4). A mixture of 2 (5.00 g, 15.1 mmol), sodium methoxide (3.26 g, 60.4 mmol), and methanol (35 mL) was refluxed with stirring with protection from moisture for 55 h. The pH of the cooled solution was adjusted to 5–6 with acetic acid, and the solvent was spin evaporated in vacuo. The residue was triturated with water (10 mL) and collected by suction filtration. The solid was dispersed in dichloromethane (400 mL) and extracted with 1 N sodium hydroxide (2 × 175 mL). The organic phase was spin evaporated in vacuo, and the white residue was recrystallized from cyclohexane to give 1.19 g (27%) of 4: mp 94–94.5 °C; UV (pH 7) λ_{max} 276 nm (ε 20500); NMR (60 MHz, Me_2SO-d_6) δ 8.14 (s, 1 H, purine H), 7.27 (s, 5 H, ArH), 5.13 (s, 2 H, CH_2), 4.07 (s, 3 H, OCH_3), 3.37 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{17}N_5O$) C, H, N.

9-Benzyl-6,8-bis(dimethylamino)-9*H*-purine (5). A mixture of 2 (3.65 g, 11.0 mmol), 20% aqueous dimethylamine (23 g, 102 mmol), and ethanol (25 mL) was heated in a stainless steel reaction vessel at 102 °C for 16 h. The cooled solution was spin evaporated in vacuo, and the residue was triturated with water. The solids were collected and recrystallized from pentane–cyclohexane to give 2.27 g (69%) of 5: mp 110–111 °C; UV λ_{max} (pH 7) 289 nm (ε 22500); NMR (Me_2SO-d_6) δ 8.10 (s, 1 H, purine H), 7.25 (m, 5 H, ArH), 5.30 (s, 2 H, CH_2), 3.42 [s, 6 H, 6-$N(CH_3)_2$], 2.82 [s, 6 H, 8-$N(CH_3)_2$]. Anal. ($C_{16}H_{20}N_6$) C, H, N.

9-Benzyl-6-(dimethylamino)-8-(methylamino)-9*H*-purine (6). This compound was prepared from 2 (3.60 g, 10.8 mmol) and 40% aqueous methylamine (17.6 g, 227 mmol) as described for the preparation of 5 to give 2.20 g (71%) of 6: mp 134–136 °C; UV λ_{max} (pH 7) 290.5 nm (ε 20800); NMR (Me_2SO-d_6) δ 8.01 (s, 1 H, purine H), 7.25 (s, 5 H, ArH), 6.71 (q, 1 H, J = 4.8 Hz, NH), 5.19 (s, 2 H, CH_2), 3.37 [s, 6 H, $N(CH_3)_2$], 2.88 (d, 3 H, J = 4.8 Hz, $NHCH_3$). Anal. ($C_{15}H_{18}N_6$) C, H, N.

9-Benzyl-6-(dimethylamino)-7,9-dihydro-8*H*-purin-8-one (7). The 1 N sodium hydroxide (350 mL) wash from preparation of 4 was acidified to pH 6 with acetic acid. The solid was collected, dried, and recrystallized from ethanol to give 1.68 g (39%) of 7: mp 256–257 °C; UV λ_{max} (pH 7) 282.5 nm (ε 18000); NMR (Me_2SO-d_6) δ 10.88 (br s, 1 H, NH), 8.08 (s, 1 H, purine H), 7.30 (s, 5 H, ArH), 4.94 (s, 2 H, CH_2), 3.13 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{15}N_5O$) C, H, N.

9-(3-Aminobenzyl)-8-bromo-6-(dimethylamino)-9*H*-purine Dihydrochloride (9). A mixture of 20 (6.0 g, 16 mmol) and acetic acid (200 mL) in a 500-mL hydrogenation vessel was warmed to effect solution and then cooled to 40 °C on an ice bath. Three grams of washed (water and acetic acid) Raney nickel (Grace no. 28) was added to the solution, and the mixture was shaken in the presence of hydrogen at 2–3 atm of hydrogen. After 23 min the uptake of hydrogen was complete. The catalyst was removed by filtration and washed with ethanol. The filtrate and wash were diluted with concentrated hydrochloric acid (20 mL) and spin evaporated in vacuo. The white solid was recrystallized from ethanol–water to give 4.85 g (72%) of 9 that moved as a single

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spot on TLC (EtOAc). Recrystallization of a sample from EtOH–H_2O gave the analytical sample: mp 250 °C dec; UV λ_{max} (pH 7) 282 nm (ϵ 21 200); NMR (Me_2SO-d_6) δ 9.9 (s, 4 H, NH_3^+ + H^+), 8.38 (s, 1 H, purine H), 7.4 (m, 4 H, ArH), 5.50 (s, 2 H, CH_2), 3.56 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{15}BrN_6$·2HCl) C, H, N.

9-(3-Aminobenzyl)-8-chloro-6-(dimethylamino)-9*H*-purine Dihydrochloride (10). A mixture of **34** (0.822 g, 2.47 mmol), Raney nickel (0.5 g, Grace no. 28), and acetic acid (50 mL) was shaken in the presence of hydrogen at 2–3 atm for 25 min. The catalyst was removed by filtration and was washed with ethanol. The filtrate and wash were combined, diluted with 2 mL of concentrated hydrochloric acid, and spin evaporated in vacuo. The white residue was recrystallized from ethanol–water to give 0.711 g (77%) of **10**: mp 246–248 °C; NMR (Me_2SO-d_6) δ 8.50 (br s, 4 H, NH_3^+ + H^+), 8.33 (s, 1 H, purine H), 7.1–7.6 (m, 4 H, ArH), 5.47 (s, 2 H, CH_2), 3.47 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{15}ClN_6$·2HCl) C, H, N.

9-(3-Aminobenzyl)-6-(dimethylamino)-8-methoxy-9*H*-purine (11). A mixture of **35** (0.85 g, 2.59 mmol), 5% palladium on carbon (0.10 g), and acetic acid (125 mL) was shaken in the presence of hydrogen at 2–3 atm for 30 min. The catalyst was removed by filtration, and the filtrate was evaporated. The residual oil was dissolved in methanol and diluted with water to give a solid. The solid was collected and recrystallized from methanol–water to give 0.49 g (63%) of **11**: mp 151–153 °C (partial melt at 139 °C with resolidification); NMR (Me_2SO-d_6) δ 8.13 (s, 1 H, purine H), 7.0–6.3 (t + m, 4 H, ArH), 5.07 (s, 2 H, NH_2), 4.98 (s, 2 H, CH_2), 4.08 (s, 3 H, OCH_3), 3.39 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{18}N_6O$) C, H, N.

9-(3-Aminobenzyl)-6,8-bis(dimethylamino)-9*H*-purine Dihydrochloride (12). A mixture of **36** (0.65 g, 1.9 mmol), 5% palladium on carbon (0.02 g), and acetic acid (50 mL) was shaken in the presence of hydrogen at 2–3 atm for 30 min. The catalyst was removed by filtration and was washed with ethanol. The filtrate and wash were combined, diluted with 2 mL of concentrated hydrochloric acid, and spin evaporated in vacuo. The white residue was recrystallized from 2-propanol–water to give 0.38 g (52%) of **12**: mp 354 °C dec; NMR (Me_2SO-d_6) δ 10.9 (br s, 4 H, NH_3^+ + H^+), 8.29 (s, 1 H, purine H), 7.1–7.6 (m, 4 H, ArH), 5.48 (s, 2 H, CH_2), 3.59 [s, 6 H, $N(CH_3)_2$], 2.93 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{16}H_{21}N_7$·2HCl) C, H, N.

9-(3-Aminobenzyl)-6-(dimethylamino)-8-(methylamino)-9*H*-purine (13). To a solution of **37** (0.414 g, 1.26 mmol) and acetic acid (125 mL) was added 5% palladium on carbon (0.065 g). The mixture was shaken in the presence of hydrogen at 2–3 atm for 30 min. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was dissolved in hot heptane–dichloromethane (50:1) and allowed to cool to give 0.20 g (53%) of **13**: mp 152–154 °C; NMR (Me_2SO-d_6) δ 7.98 (s, 1 H, purine H), 7.0–6.2 (t + q + m, 5 H, NH + ArH), 5.03 (s + br s, 4 H, CH_2 + NH_2), 3.39 [s, 6 H, $N(CH_3)_2$], 2.88 (d, 3 H, NCH_3). Anal. ($C_{15}H_{19}N_7$) C, H, N.

9-(3-Aminobenzyl)-6-(dimethylamino)-7,9-dihydro-8*H*-purin-8-one (14). A mixture of **9** (1.0 g, 2.38 mmol) and concentrated hydrochloric acid (20 mL) was heated on a steam bath for 2 days. The solution was spin evaporated in vacuo, and the residual solid was dissolved in water (50 mL). This solution was neutralized with 37% aqueous ammonium hydroxide, and the resultant solid was collected and washed with cold water. The wet solid was recrystallized twice from ethanol to give 0.413 g (61%) of **14**: mp 264–265.5 °C; NMR (Me_2SO-d_6) δ 10.86 (br s, 1 H, NH), 8.08 (s, 1 H, purine H), 6.90 (m, 1 H, ArH), 6.45 (m, 3 H, ArH), 5.04 (br s, 2 H, NH_2), 4.78 (br s, 2 H, CH_2), 3.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{16}N_6$) C, H, N.

6-(Dimethylamino)-9-(3-formamidobenzyl)-9*H*-purine (15). A mixture of **41** (0.483 g, 1.68 mmol) and 40% aqueous dimethylamine (5 mL) was stirred in a sealed flask for 2 h. The reaction mixture was spin evaporated in vacuo to remove the volatile substances. The residual solids were dissolved in water (50 mL) and extracted with ethyl acetate (4 × 100 mL). The organic extracts were combined, washed with water (10 mL), and spin evaporated in vacuo. The residual solids were recrystallized from ethanol–water to give 0.307 g (61%) of **15**: mp 148–150 °C; NMR (Me_2SO-d_6) δ 10.16 (br m, 1 H, NH), 8.75 [d, 0.09 H, (*E*)-NHC*H*O, J = 11.0 Hz], 8.25 (s, 1 H, purine H), 8.22 (s, 1 H, purine H), 8.15 [d, 0.91 H, (*Z*)-NHC*H*O, J = 2.0 Hz], 6.8–7.6 (m, 4 H, ArH), 5.37 (s, 2 H, CH_2), 3.45 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{16}N_6O$) C, H, N.

8-Bromo-6-(dimethylamino)-9-(3-formamidobenzyl)-9*H*-purine (16). A mixture of **9** (0.5 g, 1.44 mmol) and ethyl formate (100 mL) was refluxed for 4 days. The mixture was spin evaporated in vacuo, and the residual solids were recrystallized from ethyl acetate to give 0.364 g (67%) of **16**: mp 213–214 °C; NMR (Me_2SO-d_6) δ 10.17 (br m, 1 H, NH), 8.74 [d, 0.2 H, (*E*)-NHC*H*O, J = 11.0 Hz], 8.23 [m, 1.8 H, purine H + (*Z*)-NHC*H*O], 6.75–7.60 (m, 4 H, ArH), 5.35 (s, 2 H, CH_2), 3.43 [s, 6 H, $N(CH3)_2$]. Anal. ($C_{15}H_{15}BrN_6O$) C, H, N.

6,8-Bis(dimethylamino)-9-(3-formamidobenzyl)-9*H*-purine (17). A mixture of **12** (0.33 g, 0.85 mmol), triethylamine (0.33 g, 2.04 mmol), and ethyl formate (50 mL) was refluxed for 3 days. Additional ethyl formate (25 mL) was added and reflux was continued for 4 h. The resultant mixture was spin evaporated in vacuo, and the residual solids were dissolved in water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with water (20 mL), and spin evaporated in vacuo. The residual solids were recrystallized from diethyl ether to give 0.183 g (63%) of **17**: mp 138–139 °C; NMR (Me_2SO-d_6) δ 10.0–10.2 (br m, 1 H, NH), 8.73 [d, 0.22 H, (*E*)-NHC*H*O, J = 11.2 Hz], 8.21 [d, 0.88 H, (*Z*)-NHC*H*O, J = 1.8 Hz], 8.08 (s, 1 H, purine H), 6.70–7.64 (m, 4 H, ArH), 5.27 (s, 2 H, CH_2), 3.42 [s, 6 H, 6-$N(CH_3)_2$], 2.84 [s, 6 H, 8-$N(CH_3)_2$]. Anal. ($C_{17}H_{21}N_7O$) C, H, N.

6-(Dimethylamino)-9-(3-formamidobenzyl)-8-(methylamino)-9*H*-purine (18). This compound was prepared from **13**·HCl by the method for preparation of **17** to give 0.248 g (71%) of **18**, which contained 0.05 molar equiv of ethyl acetate that was not removed by drying at 100 °C at 1 Torr for 24 h: mp 214–216 °C; NMR (Me_2SO-d_6) δ 10.15 (br s, 1 H, NH), 8.72 [d, 0.21 H, (*E*)-NHC*H*O, J = 11.1 Hz], 8.21 [d, 0.79 H, (*Z*)-NHC*H*O, J = 0.16 Hz], 8.00 (s, 1 H, purine H), 5.7–6.7 (m, 4 H, ArH), 5.18 (s, 2 H, CH_2), 4.04 [q, 0.1 H, CH_2 (EtOAc)], 3.40 [s, 6 H, $N(CH_3)_2$], 2.73 (d, 3 H, NCH_3, J = 4.6 Hz), 2.00 [s, 0.15 H, CH_3 (EtOAc)], 1.18 [t, 0.15 H, CH_2CH_3 (EtOAc)]. Anal. ($C_{16}H_{19}N_7O \cdot {}^1/_{20}C_4H_8O_2$) C, H, N.

6-(Dimethylamino)-9-(3-formamidobenzyl)-7,9-dihydro-8*H*-purin-8-one (19). This compound was prepared from **14** by the method for preparation of **16**. The product was recrystallized from dichloromethane–methanol to give 0.172 g (74%) of **19**: mp 253–257 °C; NMR (Me_2SO-d_6) δ 10.92 (s, 1 H, purine NH), 10.00–10.25 (br m, 1 H, NH), 8.73 [d, 0.18 H, (*E*)-NHC*H*O, J = 11.4 Hz], 8.23 [d, 0.82 H, (*Z*)-NHC*H*O, J = 1.8 Hz], 6.95–7.70 (m, 4 H, ArH), 4.93 (s, 2 H, CH_2), 3.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{16}N_6O_2$) C, H, N.

8-Bromo-6-(dimethylamino)-9-(3-nitrobenzyl)-9*H*-purine (20). To a stirred solution of **31** (15.0 g, 50.0 mmol) in tetrahydrofuran (700 mL) and pH 4 acetate buffer (600 mL), which was prepared from sodium acetate (24.6 g, 0.30 mol) and water with addition of acetic acid to pH 4, was added bromine (28 mL, 82 g, 0.51 mol). The solution was stirred for 5 min, and then a concentrated solution of sodium sulfate (70 g) in a minimum of water was added to reduce the excess bromine. The two layers were separated, and the aqueous layer was washed with ethyl acetate (3 × 200 mL). The tetrahydrofuran and ethyl acetate solutions were combined and spin evaporated to dryness. Water was added to the residue, and the mixture was spin evaporated to remove the residual organic solvent. The solids were collected and washed with water to give 16.2 g (85%) of **20**: mp 203–205 °C; NMR (Me_2SO-d_6) δ 8.25 (s, 1 H, purine H), 7.9–8.2 (m, 2 H, ArH), 7.5–7.7 (m, 2 H, ArH), 5.55 (s, 2 H, CH_2), 3.45 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{13}BrN_6O_2$) C, H, N.

9-(3-Acetamidobenzyl)-8-bromo-6-(dimethylamino)-9*H*-purine (21). A mixture of **9** (0.5 g, 1.44 mmol), acetic anhydride (0.19 g, 1.87 mmol), 4-(dimethylamino)pyridine (0.20 g, 1.65 mmol), and dichloromethane (5 mL) was stirred for 20 min. Additional dichloromethane (45 mL) was added, and the solution was washed with 5% aqueous sodium bicarbonate (5 mL) and brine (5 mL) and dried (magnesium sulfate). The volatile substances were removed by spin evaporation in vacuo, and the residual solids were recrystallized from dichloromethane–hexane to give 0.40 g (66%) of **21**: mp 206.5–207 °C; NMR (Me_2SO-d_6) δ 9.89 (br s, 1 H, NH), 8.23 (s, 1 H, purine H), 6.75–7.65 (m, 4 H, ArH), 5.33 (s, 2 H, CH_2),

3.42 [s, 6 H, $N(CH_3)_2$], 1.98 (s, 3 H, CH_3). Anal. ($C_{16}H_{17}BrN_6O$) C, H, N.

9-(3-Benzamidobenzyl)-8-bromo-6-(dimethylamino)-9*H*-purine (22). This compound was prepared from **9** and benzoic anhydride by the method for preparation of **21** to give 0.393 g (60%) of **22**: mp 167–168 °C; NMR (Me_2SO-d_6) δ 10.24 (br s, 1 H, NH), 8.24 (s, 1 H, purine H), 6.8–7.9 (m, 9 H, ArH), 6.92 (s, 2 H, CH_2), 3.42 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{21}H_{19}BrN_6O$) C, H, N.

8-Bromo-6-(dimethylamino)-9-[3-[(methoxycarbonyl)amino]benzyl]-9*H*-purine (23). A mixture of **9** (0.30 g, 0.71 mmol), triethylamine (0.22 g, 2.17 mmol), methyl chloroformate (0.071 g, 0.75 mmol), and dichloromethane (20 mL) was stirred for 3 h. To this solution was added additional methyl chloroformate (1.22 g, 12.9 mmol), and stirring was continued for 30 min. The solution was spin evaporated in vacuo. The residual solids were dissolved in dichloromethane (40 mL), washed with 5% aqueous sodium bicarbonate, water, and brine, and then dried (magnesium sulfate). The volatile components were spin evaporated in vacuo, and the residual solids were recrystallized from ethanol–water to give 0.113 g (39%) of **23**: mp 164.5–165.5 °C; NMR (Me_2SO-d_6) δ 9.60 (br s, 1 H, NH), 8.23 (s, 1 H, purine H), 6.8–7.5 (m, 4 H, ArH), 5.33 (s, 2 H, CH_2), 3.63 (s, 3 H, OCH_3), 3.43 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{16}H_{17}BrN_6O_2$) C, H, N.

8-Bromo-6-(dimethylamino)-9-(3-ureidobenzyl)-9*H*-purine (24). A mixture of **9** (0.20 g, 0.476 mmol), sodium cyanate (0.065 g, 1.0 mmol), acetic acid (10 mL), and water (20 mL) was warmed to 40 °C for 20 min. To this mixture was added additional sodium cyanate (0.10 g, 1.54 mmol). The reaction was stirred for 30 min and then cooled in an ice bath. The product was collected, washed with cold water, and recrystallized from ethanol to give 0.111 g (57%) of **24**: mp 250–251 °C; NMR (Me_2SO-d_6) δ 8.50 (br s, 1 H, NH), 8.23 (s, 1 H, purine H), 6.6–7.5 (m, 4 H, ArH), 5.77 (br s, 2 H, NH_2), 5.13 (s, 2 H, CH_2), 3.43 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{16}BrN_7O$) C, H, N.

8-Bromo-6-(dimethylamino)-9-[3-(methanesulfonamido)benzyl]-9*H*-purine (25). A solution of **9** (0.30 g, 0.714 mmol) in pyridine (5 mL) was stirred at 0 °C, and methanesulfonyl chloride (6 drops) was added dropwise. The reaction was complete after a few minutes. The volatiles were removed by spin evaporation in vacuo. The residual solids were dissolved in ethyl acetate (50 mL), and the solution was washed with 5% aqueous sodium bicarbonate and water and then spin evaporated in vacuo. The residual solids were recrystallized from ethanol–water to give 0.279 g (89%) of **25**: mp 124–125.5 °C; NMR (Me_2SO-d_6) δ 9.76 (s, 1 H, NH), 8.23 (s, 1 H, purine H), 6.8–7.4 (m, 4 H, ArH), 5.35 (s, 2 H, CH_2), 3.42 [s, 6 H, $N(CH_3)_2$], 2.96 (s, 3 H, CH_3). Anal. ($C_{15}H_{17}BrN_7O_2S$) C, H, N.

8-Bromo-6-(dimethylamino)-9-[3-(2-oxo-1-pyrrolidinyl)benzyl]-9*H*-purine (26). To a stirred mixture of **9** (0.30 g, 0.714 mmol), pyridine (0.5 mL), and dichloromethane (10 mL) was added dropwise 4-chlorobutyryl chloride (0.120 g, 0.86 mmol). After 3 h, 37% aqueous ammonium hydroxide (3 mL) was added, and the reaction was stirred for 18 h. The biphasic mixture was separated, and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined extracts were washed with dilute aqueous acetic acid and water. The volatile components were removed by spin evaporation in vacuo to give an oil that was dissolved in ethyl acetate (50 mL), added to silica gel 60 (10 g), and spin evaporated in vacuo. The residual solids were introduced onto a column of silica gel 60 that had been wetted with ethyl acetate. The column was eluted with ethyl acetate by the flash chromatography technique. The appropriate fractions were combined and concentrated by spin evaporation in vacuo. The residual solids were recrystallized from dichloromethane–cyclohexane and then from methanol to give 0.055 g (20%) of **26**: mp 182–183 °C; NMR (Me_2SO-d_6) δ 8.23 (s, 1 H, purine H), 6.8–7.8 (m, 4 H, ArH), 5.37 (s, 2 H, CH_2), 3.77 (t, 2 H, NCH_2), 3.42 [s, 6 H, $N(CH_3)_2$], 2.3–2.6 (m, 2 H, $COCH_2$, partially obscured by solvent), 1.85–2.25 (m, 2 H, $CH_2CH_2CH_2$). Anal. ($C_{18}H_{19}BrN_6O_2$) C, H, N.

4-(Benzylamino)-6-(dimethylamino)-5-nitropyrimidine (29). To a stirred dispersion of **27** (20.0 g, 103.1 mmol) in ethanol (750 mL) was added a solution of benzylamine (11.14 g, 104.0 mmol) and triethylamine (10.72 g, 106.0 mmol) in ethanol (50 mL). The resultant solution was stirred at ambient temperature for 60 h, and then the volatiles were removed by spin evaporation in vacuo. The residual solids were dispersed in water (500 mL) and collected on a Büchner funnel. The crude 4-(benzylamino)-6-chloro-5-nitropyrimidine (**28**) was dissolved in 2.2 M dimethylamine in ethanol (400 mL) and heated at reflux for 24 h. The solution was evaporated to remove the volatiles, and the residual solid was recrystallized from methanol to give 6.30 g (22%) of product, mp 72–82 °C. The mother liquors were evaporated to give an additional 13.9 g of crude product, which was dissolved in ethyl acetate. This solution was absorbed on a column (5 cm × 15 cm) of silica gel (200 g) wetted with 10% ethyl acetate in hexane. The column was eluted with ethyl acetate by gravity elution, and the appropriate fractions were combined and spin evaporated in vacuo. The solid was recrystallized from methanol to give 8.24 g (29%) of **29**: mp 88–90 °C; NMR (Me_2SO-d_6) δ 8.93 (br t, 1 H, NH), 8.00 (s, 1 H, pyrimidine H), 7.28 (s, 5 H, ArH), 4.73 (d, 2 H, CH_2), 3.00 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{13}H_{15}N_5O_2$) C, H, N.

6,8-Dichloro-9-(3-nitrobenzyl)-9*H*-purine (33). A mixture of 6,8-dichloropurine (**32**) (5.0 g, 26.5 mmol), 3-nitrobenzyl chloride (5.4 g, 31.8 mmol), powdered anhydrous potassium carbonate (4.55 g, 33.0 mmol), and dry dimethylformamide (50 mL) was stirred with protection from moisture (calcium chloride drying tube) for 4 days. The reaction was diluted into ice water (400 mL) and extracted with ethyl acetate (6 × 100 mL). The ethyl acetate extracts were combined, washed with brine (3 × 25 mL), and spin evaporated in vacuo. The isomeric products were separated on a Waters Prep 500 silica gel cartridge by elution with ethyl acetate–hexanes (1:4). The fractions containing the higher R_f product were combined and concentrated by spin evaporation in vacuo. The residual oil crystallized under cyclohexane to give 2.77 g (32%) of **33**: mp 158–159 °C; NMR (Me_2SO-d_6) δ 8.87 (s, 1 H, purine H), 8.4–8.8 (m, 2 H, ArH), 7.6–7.9 (m, 2 H, ArH), 5.71 (s, 2 H, CH_2). Anal. ($C_{12}H_7Cl_2N_5O_2$) C, H, N.

9-(3-Nitrobenzyl)-8-chloro-6-(dimethylamino)-9*H*-purine (34). A mixture of **33** (1.5 g, 4.6 mmol) and 2.2 M ethanolic dimethylamine (50 mL) was stirred for 45 min at ambient temperature. The volatile components were removed by spin evaporation in vacuo. The residual oil was dissolved in ethyl acetate (50 mL), added to silica gel 60 (10 g), and spin evaporated in vacuo. The residual solids were introduced onto a column of silica gel 60, which had been wetted with ethyl acetate–hexane (1:1). The column was eluted with ethyl acetate–hexane (1:1) by using the flash chromatography technique. The fractions containing the product were combined and concentrated by spin evaporation in vacuo. The residual solids were recrystallized from ethanol to give 1.1 g (71%) of **34**: mp 167.5–169 °C; NMR (Me_2SO-d_6) δ 8.28 (s, 1 H, purine H), 8.1–8.25 (m, 2 H, ArH), 7.6–7.75 (m, 2 H, ArH), 5.55 (s, 2 H, CH_2), 3.41 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{14}H_{13}N_6ClO_2$) C, H, N.

6-(Dimethylamino)-8-methoxy-9-(3-nitrobenzyl)-9*H*-purine (35). This compound was prepared from **20** on a 7.95-mmol scale as described for preparation of **4**. The crude product was crystallized from methanol to give **35** in two different solid forms: 0.52 g (20%) of orange crystals, mp 140–143 °C; and 0.66 g (45% total) of a yellow, fluffy solid, mp 132–143 °C. Both samples moved as one spot on TLC in ethyl acetate–hexane (1:1) and had identical spectral properties: NMR (Me_2SO-d_6) δ 8.18 (s, 1 H, purine H), 8.2–7.6 (2 m, 4 H, ArH), 5.32 (s, 2 H, CH_2), 4.12 (s, 3 H, OCH_3), 3.34 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{16}N_6O_3$) C, H, N.

9-(3-Nitrobenzyl)-6,8-bis(dimethylamino)-9*H*-purine (36). A mixture of **20** (1.0 g, 2.65 mmol) and 2.2 M ethanolic dimethylamine (100 mL) was heated in a stainless steel reaction vessel at 130 °C for 3 days. The reaction was cooled, and the volatiles were removed by spin evaporation in vacuo. The residual solids were dissolved in ethyl acetate and washed with water. The ethyl acetate layer was concentrated by spin evaporation in vacuo, and the residue was recrystallized from ethanol–water to give red crystals. The crystalline product was dissolved in ethyl acetate (50 mL), added to silica gel 60 (10 g), and spin evaporated in vacuo. The residual solids were introduced onto a column of silica gel 60, which had been wetted with ethyl acetate. The column was eluted with ethyl acetate by using the flash chromatography technique. The appropriate fractions were combined and concentrated by spin evaporation in vacuo. The residual solids were

recrystallized from ethanol–water to give 0.820 g (90%) of **36** as red crystals: mp 125–126 °C; NMR (Me_2SO-d_6) δ 8.0–8.2 (m, 2 H, ArH), 8.10 (s, 1 H, purine H), 7.4–7.8 (m, 2 H, ArH), 5.44 (s, 2 H, CH_2), 3.42 [s, 6 H, 6-$N(CH_3)_2$], 2.83 [s, 6 H, 8-$N(CH_3)_2$]. Anal. ($C_{16}H_{19}N_7O_2$) C, H, N.

6-(Dimethylamino)-8-(methylamino)-9-(3-nitrobenzyl)-9*H*-purine (37). Method A. A mixture of **20** (3.00 g, 7.95 mmol), 40% aqueous methylamine (400 mL), and ethanol (50 mL) was refluxed with stirring for 3 days. The cooled reaction was spin evaporated in vacuo. The residue was collected and washed with methanol. Recrystallization from methanol gave 0.58 g (22%) of **37**: mp 190–192 °C; NMR (Me_2SO-d_6) δ 8.02 (s, 1 H, purine H), 8.2–7.6 (2 m, 4 H, ArH), 6.85 (q, 1 H, NH), 5.33 (s, 2 H, CH_2), 3.39 [s, 6 H, $N(CH_3)_2$], 2.89 (d, 3 H, NCH_3). Anal. ($C_{15}H_{17}N_7O_2$) C, H, N.

Method B. A mixture of **34** (0.070 g, 0.21 mmol) and 40% aqueous methylamine was heated in a stainless steel reaction vessel at 130 °C for 3 days. TLC (methanol–dichloromethane, 1:10) of the solution revealed a single, new spot (R_f = 0.5), which was chromatographically identical with **37** prepared by method A.

3-Formamidobenzyl Alcohol (39). A mixture of 3-aminobenzyl alcohol (**38**) (30.0 g, 0.236 mol) and ethyl formate (400 mL) was heated in a steel bomb at 105 °C for 3 days. The reaction was cooled, and the volatile components were removed by spin evaporation in vacuo. A solution of the residual oil, 37% aqueous ammonium hydroxide (150 mL), and methanol (150 mL) was stirred at ambient temperature for 5 h. The volatile components were removed by spin evaporation in vacuo, and the residual oil was added to a column (5 cm × 200 cm) of silica gel 60, which had been wetted with ethyl acetate. The column was eluted with ethyl acetate, and the fractions containing product were combined and concentrated by spin evaporation in vacuo to give an oil that crystallized. The crystals were washed with cold ethanol and collected by suction filtration to give 12.3 g (33%) of **39**: mp 69.5–70 °C; NMR (Me_2SO-d_6) δ 10.07 (br m, 1 H, NH), 8.70 [d, 0.25 H, (*E*)-NHC*H*O, *J* = 11.2 Hz], 8.25 [d, 0.75 H, (*Z*)-NHC*H*O, *J* = 1.8 Hz], 6.8–7.7 (m, 4 H, ArH), 5.20 (t, 1 H, OH, *J* = 9.4 Hz), 4.48 (d, 2 H, CH_2, *J* = 9.4 Hz). Anal. ($C_8H_9NO_2$) C, H, N.

3-Formamidobenzyl Bromide (40). To a stirred solution of **39** (28.0 g, 0.185 mol) in tetrahydrofuran (100 mL) was added a solution of phosphorous tribromide (18.35 g, 67.8 mmol) in tetrahydrofuran (50 mL). After 30 min the reaction was concentrated by spin evaporation in vacuo. The residue was dissolved in ethyl acetate (400 mL) and washed sequentially with water, 5% aqueous sodium bicarbonate, and water. The ethyl acetate layer was passed through a pad (30 mm × 30 mm) of silica gel 60 in a fritted glass funnel, and the pad was washed with ethyl acetate. The filtrate and wash were combined and concentrated by spin evaporation in vacuo to give 37 g (93%) of **40** as an oil, which solidified and was used without further purification: NMR (Me_2SO-d_6) δ 10.20 (br m, 1 H, NH), 8.73 [d, 0.14 H, (*E*)-NHC*H*O, *J* = 11.2 Hz], 8.29 [d, 0.86 H, (*Z*)-NHC*H*O, *J* = 1.8 Hz], 7.0–7.8 (m, 4 H, ArH), 4.65 (s, 2 H, CH_2).

6-Chloro-9-(3-formamidobenzyl)-9*H*-purine (41). A mixture of 6-chloropurine (3.0 g, 19.4 mmol), **40** (4.8 g, 22.3 mmol), anhydrous potassium carbonate (4.5 g, 32.6 mmol), and dry dimethylformamide (10 mL) was stirred with protection from moisture for 42 h. The reaction was poured into water (200 mL) and extracted with ethyl acetate (4 × 200 mL). The extracts were combined, washed with water, and then evaporated in vacuo. The isomeric products were separated on a Waters Prep 500 silica gel cartridge by elution with dichloromethane (500 mL) followed by elution with 3% 2-propanol in dichloromethane (15 L). The fractions containing the higher R_f product were combined and concentrated by spin evaporation in vacuo. The residue was crystallized from ethyl acetate to give 1.18 g (21%) of **41**: mp 157.5–158.5 °C; NMR (Me_2SO-d_6) δ 10.15 (br m, 1 H, NH), 8.83 (s, 1 H, purine H), 8.79 (s, 1 H, purine H), 8.76 [d, 0.21 H, (*E*)-NHC*H*O, *J* = 11.2 Hz], 8.23 [d, 0.79 H, (*Z*)-NHC*H*O, *J* = 1.6 Hz], 6.9–7.6 (m, 4 H, ArH), 5.53 (s, 2 H, CH_2). Anal. ($C_{13}H_{10}ClN_5O$) C, H, N.

6-Chloro-7-(formamidobenzyl)-7*H*-purine (42). From a reaction essentially the same as for preparation of **41** on a 64-mmol scale, fractions containing the lower R_f product were combined, concentrated, and crystallized from ethyl acetate to give 2.01 g (11%) of **42**: mp 161–162 °C; NMR (Me_2SO-d_6) δ 10.12 (br m, 1 H, NH), 8.97 (s, 1 H, purine H), 8.80 (s, 1 H, purine H), 8.73 [d, 0.21 H, (*E*)-NHC*H*O, *J* = 11.2 Hz], 8.22 [d, 0.79 H, (*Z*)-NHC*H*O, *J* = 1.8 Hz], 6.7–7.7 (m, 4 H, ArH), 5.73 (s, 2 H, CH_2). Anal. ($C_{13}H_{10}ClN_5O$) C, H, N.

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