H); FABMS m/e 747 $(M + H)^+$, 294.

N-[(8-Isobutyl-6-phenyl-1,2,4-triazolo[4,3-a]pyrazin-3-yl)acetyl]-ACDFOPA-Leu Pyridin-2-ylmethylamide (19a). The Dess-Martin periodinane[11] (390 mg, 1.57 mmol) was added to a solution of **18a** (317 mg, 0.42 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 2.5 h. A solution of $Na_2S_2O_3$ (200 mg, 2.98 mmol) in saturated $NaHCO_3$ (5 mL) was added and the mixture was stirred vigorously for 0.5 h. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The compound organic solutions were washed with H_2O (10 mL) and saturated brine (10 mL) and dried ($MgSO_4$). The solvent was removed by evaporation and the residue was purified by flash chromatography, eluting with $MeOH/CH_2Cl_2$ (1:19 v/v), to give **19a** (158 mg, 50%), as a white powder: mp 90–95 °C (after trituration with ether); ^1H NMR (DMSO-d_6, CD_3CO_2D) δ 0.7–1.8 (complex m, 28 H), 2.5 (m, 1 H), 3.15 (d, 2 H), 4.2–4.5 (complex m, 6 H), 4.9 (dd, 1 H), 7.25 (m, 2 H), 7.5 (m, 3 H), 7.7 (m, 1 H), 8.1 (dd, 1 H), 8.45 (dd, 1 H), 8.8 (s, 1 H); FABMS m/e calcd for $C_{40}H_{51}F_2N_8O_4$ + 1 745.4001, found 745.4067. Anal. ($C_{40}H_{50}F_2N_8O_4 \cdot 0.5H_2O$) C, H; N: calcd, 14.9; found, 14.2.

Boc-ACDFHPA (S)-2-Methylbutylamide (15b). A solution of 14b[8a] (300 mg, 0.79 mmol), (S)-2-methylbutylamine (172 mg, 1.97 mmol), and 1,1,3,3-tetramethylguanidine (91 mg, 0.79 mmol) in $CHCl_3$ (5 mL) was heated under reflux for 2 h. Volatile material was removed by evaporation and the residue was purified by flash chromatography, eluting with EtOAc/hexane (3:7 v/v), to give **15b** (338 mg, 83%), as a foam: ^1H NMR ($CDCl_3$) δ 0.9–1.9 (complex m, 31 H), 3.2 (m, AB X, 2 H), 3.8–4.1 (m, 2 H), 4.7 (br d, 1 H), 6.9 (br, 1 H); FABMS m/e 421 $(M + H)^+$, 365, 321.

N-[(8-Propyl-6-pyridin-3-yl-1,2,4-triazolo[4,3-a]pyrazin-3-yl)acetyl]-ACDFHPA (S)-2-Methylbutylamide (18b). By an analogous procedure to that described for the preparation of 11, compound **15b** (263 mg, 0.63 mmol) was deprotected and the resulting intermediate **16b** was acylated with carboxylic acid sodium salt **17b**[1a] (201 mg, 0.63 mmol) and Et_3N (64 mg, 0.63 mmol), HOBT (84.5 mg, 0.63 mmol), and EDC (120 mg, 0.63 mmol). This provided **18b** (143 mg, 38%), as a foam: ^1H NMR (DMSO-d_6, CD_3CO_2D) δ 0.7–1.8 (complex m, 25 H), 2.0 (m, 2 H), 2.9 (dd, 1 H), 3.1 (dd, 1 H), 3.3 (t, 2 H), 4.0 (dt, 1 H), 4.2 (m, 1 H), 4.3 (m, CH_2CO partially exchanged with CD_3CO_2D), 7.55 (dd, 1 H), 8.45 (dt, 1 H), 8.65 (m, 1 H), 8.95 (s, 1 H), 9.3 (m, 1 H); FABMS m/e 600 $(M + H)^+$.

N-[(8-Propyl-6-pyridin-3-yl-1,2,4-triazolo[4,3-a]pyrazin-3-yl)-acetyl]-ACDFOPA (S)-2-Methylbutylamide (19d). By an analogous procedure to that described for the preparation of **19a**, oxidation of **18b** gave **19d** in 55% yield, as a white powder: mp 79–81 °C (after trituration with ether); ^1H NMR (DMSO-d_6, CD_3CO_2D) δ 0.7–1.8 (complex m, 25 H), 2.0 (m, 2 H), 2.95 (m, AB X, 2 H), 3.3 (t, 2 H), 4.3 (dd, 2 H), 4.9 (dd, 1 H), 7.6 (dd, 1 H), 8.45 (dt, 1 H), 8.65 (m, 1 H), 9.0 (s, 1 H), 9.3 (m, 1 H); ^{13}C NMR (DMSO-d_6, CD_3CO_2D) δ 11.3, 14.2, 17.1, 20.0, 25.9, 26.2, 26.4, 26.8, 31.6, 33.9, 34.1, 34.5, 36.0, 45.1, 52.6, 110.6 (t, J = 184 Hz, CF_2), 112.8, 124.4, 132.2, 134.3, 135.6, 145.0, 147.5, 150.0, 155.8, 160.9 (t, J = 18 Hz, CF_2CONH), 167.3, 197.8 (t, J = 18 Hz, $CHCOCF_2$); ^{13}C NMR (DMSO-d_6): additional signal at 94.9 (t, J = 18 Hz, $CHC(OH)_2CF_2$) and closely spaced line doubling of many other signals; FABMS, m/e calcd for $C_{31}H_{42}F_2N_7O_3$ + 1 598.3317, found 598.3339. Anal. ($C_{31}H_{41}F_2N_7O_3 \cdot 0.5H_2O$) C, H; N: calcd, 16.2; found, 15.6.

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Synthesis and Antirhinovirus Activity of 8-Substituted Analogues of 6-(Dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine

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Several 8-substituted analogues of 6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (1) were synthesized and tested for activity against rhinovirus type 1B. Among 16 8-substituted analogues, the 8-amino (3) and 8-bromo (2) analogues were most active with IC_{50}s of 0.36 and 1.4 μM, respectively, under conditions where 1 had an IC_{50} of 0.03 μM.

Introduction

The rhinoviruses, which are recognized as the most important causative agents of the common cold,[1] are inhibited in vitro by a wide variety of chemical structures.[2-4] Despite the many reports of in vitro antirhinovirus activity, no agent has consistently exhibited significant clinical efficacy.[2,3,5] We previously reported the potent in vitro antirhinovirus activity of a series of 9-benzyl-6-(dimethylamino)purines.[6-9] One of the most active compounds against rhinovirus serotype 1B was 6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (1), which had an IC_{50} of 0.03 μM.

Structure-activity studies addressed the effects of substituent variation at the purine 2-position,[8] on the 9-benzyl moiety,[9] and at the purine 6-substituent.[10] In an effort to develop an agent with a broad spectrum of antirhinovirus serotype activity, a series of 6-anilino-9-benzyl-2-chloro- or 2-(trifluoromethyl)purines were studied,[11,12] but the best compound—6-(3-fluoroanilino)-9-(3-fluorobenzyl)-2-(trifluoromethyl)-9*H*-purine—exhibited in vivo properties incompatible with further drug development.[12] To explore further the structure-activity relationship of

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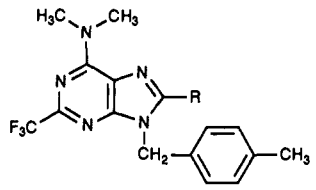
Table I. Antirhinovirus 1B Activity of 8-Substituted Analogues of 6-(Dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine



no.	R	IC_{50},[a] μM	no.	R	IC_{50},[a] μM
1[b]	H	0.03	10	SCH_3	(15%)[c]
2	Br	1.4	11	$SOCH_3$	(27%)[e]
3	NH_2	0.36	12	SO_2CH_3	(37%)[e]
4	$NHCH_3$	2.9	13	$SCH_2C_6H_5$	(25%)[e]
5	$N(CH_3)_2$	(40%)[c]	14	OH (oxo)	(25%)[e]
6	$NHCH_2CH_2OH$	8.6[d]	15	OCH_3	(17)[c]
7	$NHCH_2C_6H_5$	(20%)[e]	16	OC_6H_5	(16)[c]
8	$NHCOCH_3$	(22%)[e]	17	OH (oxo)	15[d]
9	SH (thiono)	20		(7-CH_3)	
				4′,6-dichloroflavan[f]	0.007

[a] The 50% inhibitory concentration (IC_{50}) was measured as described in ref 6. In many cases the exact IC_{50} could not be determined due to limited solubility; the activity is denoted as percent inhibition in parentheses at the concentration in the footnote. [b] For synthesis, see ref 8. [c] Percent inhibition at 8 μM. [d] Estimated by extrapolation. [e] Percent inhibition at 40 μM. [f] See ref 14.

these 9-benzylpurines we prepared a series of 8-substituted analogues of 1. The synthesis and antirhinovirus activity of these compounds are reported herein.

Chemistry

The compounds in Table I were prepared from intermediate **2**, which was synthesized by alkylation of 8-bromo-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine[13] with 4-methylbenzyl bromide. That **2** was the 9-isomer was established by removal of the 8-bromo group by catalytic hydrogenolysis[7] to give **1**.[8] When **2** was treated with ammonia in methanol at 135 °C, with aqueous methylamine in ethanol at 120 °C, with dimethylamine in ethanol at reflux, with 2-hydroxyethylamine in ethanol at 120 °C, or with benzylamine in ethanol at 120 °C, the 8-aminopurines **3–7** were obtained in 39–82% yields. 8-Acetamidopurine **8** was prepared by acetylation of **3** with acetic anhydride and 4-(dimethylamino)pyridine in dichloromethane.

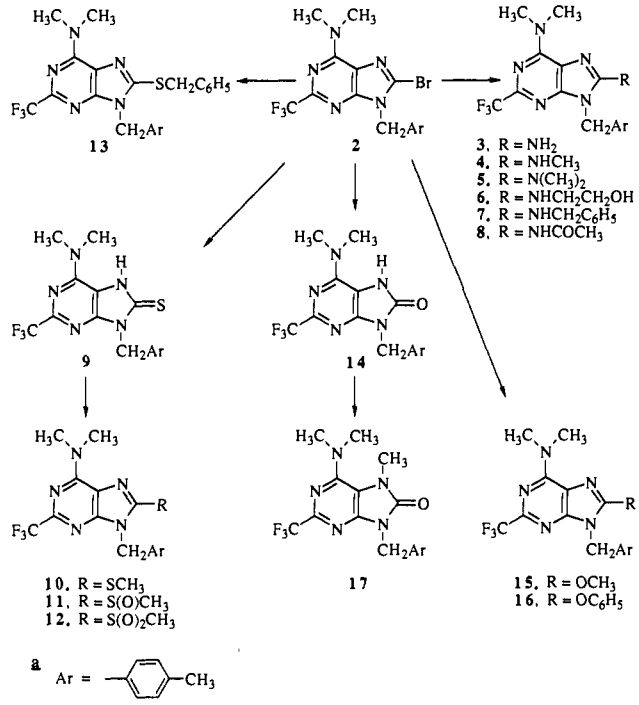
Purine-8-thione **9** was prepared from **2** with thiourea in refluxing ethanol. Thione **9** was selectively S-methylated with dimethylformamide dimethyl acetal to give **10**. (Methylthio)purine **10** was oxidized with peroxyacetic acid to a mixture of sulfoxide **11** and sulfone **12**, which were separated by column chromatography. Reaction of **2** with benzyl mercaptan and sodium methoxide in dimethylformamide at elevated temperature provided **13**.

8-Oxopurine **14** was synthesized from **2** with sodium acetate in acetic acid, which was N-alkylated with methyl iodide and sodium hydride to give **17**. The bromo substituent of **2** was displaced with sodium methoxide in refluxing methanol or with the anion of phenol in dimethylformamide to give **15** and **16**, respectively.

Biological Results and Discussion

The compounds in Table I were tested initially in a plaque-inhibition assay at 50 μg per disk using monolayers of M-HeLa cells. The 50% inhibition concentrations (IC_{50}) were determined for **1–4**, **6**, **9**, and **17** under conditions

Scheme I[a]



where 4′,6-dichloroflavan[14] had an IC_{50} of 0.007 μM. The other compounds were not sufficiently soluble for IC_{50} determination; however, the percent inhibition at the highest concentration tested is tabulated. The plaque-inhibition and plaque-reduction assays were performed as described previously.[6]

The parent 8-H purine **1** is the most potent 2-substituted 9-benzylpurine with activity against rhinovirus type 1B.[8,9] However, the IC_{50}s for **1** against 19 serotypes ranged from 0.03 to >8 μM. To try to improve the serotype profile of **1**, we investigated the effect of 8-substituents on antirhinovirus 1B activity.

The parent 8-H purine **1** had an IC_{50} = 0.03 μM against serotype 1B. Substitution at the 8-position with Br (**2**) led to a 46-fold loss in activity. 8-Amino analogue **3** was $^1/_{12}$ as active as **1**. Thus, neither the lipophilic, electronegative Br, nor the polar, electron-donating NH_2 substituent were compatible with optimum antirhinovirus 1B activity. The 8-$NHCH_3$ (**4**), 8-$N(CH_3)_2$ (**5**), and 8-$NH(CH_2)_2OH$ (**6**) analogues were also less active, with IC_{50}s ranging from 2.9 to about 10 μM. Other 8-*N*-substituted compounds (**7** and **8**) exhibited only modest activity at 40 μM.

Several 8-thio analogues were tested but were appreciably less active. The 8-thiono analogue **9** had an IC_{50} of 20 μM, some 600-fold less active than **1**. The 8-SCH_3 (**10**), 8-$SOCH_3$ (**11**), 8-SO_2CH_3 (**12**), and 8-$SCH_2C_6H_5$ (**13**) analogues were appreciably less active than **9**. The 8-oxy analogues **14–17** were also uniformly less active than the 8-H compound **1**.

These results illustrate that there is limited bulk tolerance for an 8-substituent on purine **1**. Thus, among analogues of 6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (**1**), the parent 8-H purine **1** is the most active against rhinovirus 1B.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. NMR

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data were recorded on a Varian FT-80A spectrometer with Me_4Si as an internal standard. The mass spectra were obtained from Oneida Research Services, Whitesboro, NY, using a Finnegan 4500 TFQ mass spectrometer. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLC's were developed on Whatman 200 μm MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[15] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385). All compounds were analyzed for C, H, N and gave combustion values within 0.4% of the theoretical values. Elemental analyses were performed by Atlantic Microlab, Inc. UV and mass spectra of all compounds were consistent with their assigned structures.

8-Bromo-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (2). A mixture of 8-bromo-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine[13] (6.37 g, 20.5 mmol), 4-methylbenzyl bromide (4.65 g, 24.6 mmol), anhydrous potassium carbonate (3.40 g, 24.6 mmol), and dry dimethylformamide (75 mL) was stirred at ambient temperature for 16 h. The reaction was poured into water (400 mL). The pH of the mixture was adjusted to 5.5 with acetic acid. The precipitate was collected by suction filtration and washed with water (50 mL). The aqueous filtrate was extracted with ether (2 × 200 mL), and the combined ether extract was washed with water (300 mL). The collected solid was dissolved in ether–ethyl acetate (300 mL:200 mL), and this solution was combined with the ether extract (400 mL) of the aqueous filtrate, which was dried with sodium sulfate. The solution was spin evaporated in vacuo to give 8.91 g of crude **2**, which was dissolved in ethyl acetate and added to silica gel 60 (60 g). This mixture was spin evaporated in vacuo, and the residual solid was introduced onto a column (5.0 cm × 18 cm) of silica gel 60 wetted with ethyl acetate–hexane (1:3). The column was eluted with ethyl acetate–hexane (1:3), and the appropriate fractions were combined and spin evaporated in vacuo. The solid residue was triturated with hexane (50 mL) and collected by suction filtration to give 6.77 g (80%) of **2**, which was a single spot on TLC. Recrystallization of 0.30 g of **2** from ethanol gave the analytical sample: mp 153.5–154.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.12 (m, 4 H, ArH), 5.35 (s, 2 H, CH_2), 3.45 (br s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, CH_3); MS *m/e* 413/415 (M^+), 334 (M^+ – Br), 308/310 ($M^+ - C_8H_9$), 105 ($C_8H_9^+$). A sample of **2** was hydrogenolyzed as described in method D of ref 7 to give a product that was identical with 1[8] by TLC, mixed melting points, UV, and NMR. Anal. ($C_{16}H_{15}BrF_3N_5$) C, H, N.

8-Amino-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (3) Hydrochloride. A mixture of **2** (2.00 g, 4.84 mmol) and saturated methanolic ammonia (100 mL) was heated in a stainless steel vessel at 135 °C for 16 h. The reaction was cooled, recharged with saturated methanolic ammonia (100 mL), and heated at 135 °C for 22 h. The reaction was cooled to ambient temperature, and the pH was adjusted to 6.4 with 6 N hydrochloric acid. The white precipitate was collected by suction filtration, dispersed in ethanol, and spin evaporated in vacuo to give a white solid, which was dissolved in ethanol (25 mL). Ethereal hydrochloric acid was added, and the resultant solid was collected by suction filtration and combined with the solids obtained from spin evaporation of the filtrate. The combined solids were triturated with ether (50 mL), collected by suction filtration, and recrystallized from ethanol–water to give 0.76 g (41%) of **3**·HCl: mp 252–255 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.16 (m, 4 H, ArH), 5.19 (s, 2 H, CH_2), 4.99 (br s, 3 H, NH_2·HCl), 3.35 (s, 6H, $N(CH_3)_2$), 2.26 (s, 3 H, CH_3). Anal. ($C_{16}H_{18}ClF_3N_6$) C, H, N.

6-(Dimethylamino)-8-(methylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (4). A mixture of **2** (0.50 g, 1.21 mmol), 40% aqueous methylamine (65 mL), and ethanol (20 mL) was heated in a stainless steel vessel at 120 °C for 16 h. The reaction was cooled, and the solids were collected by suction filtration. The filtrates were reduced in volume to 10 mL, and the resultant solids were collected by suction filtration. The combined solids were recrystallized from ethanol–water to give 0.298 g (68%) of **4**: mp 170–171 °C; ^{1}H NMR (DMSO-d_6) δ 7.03 (m, 4 H, ArH), 5.18 (s, 2 H, CH_2), 3.42 (s, 6 H, $N(CH_3)_2$), 2.90 (d, 3 H, NCH_3), 2.24 (s, 3 H, CH_3). Anal. ($C_{17}H_{19}F_3N_6$) C, H, N.

6,8-Bis(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (5). A solution of **2** (0.500 g, 1.21 mmol) and 2.2 M ethanolic dimethylamine (60 mL) was heated at reflux for 40 h. The solvent volume was reduced to 10 mL by spin evaporation, and water (30 mL) was added. The resultant mixture was reduced in volume to 10 mL. The solid was collected by suction filtration and recrystallized from ethanol–water to give 0.376 g (82%) of **5**: mp 114.5–115.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.05 (AB q, 4 H, ArH), 5.30 (s, 2 H, CH_2), 3.44 (s, 6 H, 6-$N(CH_3)_2$), 2.87 (s, 6 H, 8-$N(CH_3)_2$), 2.24 (s, 3 H, CH_3). Anal. ($C_{18}H_{21}F_3N_6$) C, H, N.

6-(Dimethylamino)-8-[(2-hydroxyethyl)amino]-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (6). This compound was prepared from **2** and 2-hydroxyethylamine by a method analogous to that employed for preparation of **4**. The crude product was recrystallized from hexane–ethyl acetate to give 0.236 g (49%) of **6**: mp 117–118.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.10 (m, 4 H, ArH), 7.03 (br s, 1 H, NH), 5.21 (s, 2 H, CH_2), 4.74 (br s, 1H, OH), 3.15–3.75 (s and m, 10 H, $N(CH_3)_2$ and NCH_2CH_2), 2.25 (s, 3 H, CH_3). Anal. ($C_{18}H_{21}F_3N_6O$) C, H, N.

8-(Benzylamino)-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (7). A mixture containing **2** (0.50 g, 1.21 mmol), benzylamine (3.89 g, 36.3 mmol), and ethanol (50 mL) was heated in a stainless steel reaction vessel at 120 °C for 16 h. The reaction was recharged with benzylamine (1.30 g, 12 mmol) and reheated at 115 °C for 20 h. The reaction was cooled on ice, and the volume was reduced to 10 mL by spin evaporation. The solution was diluted with 50 mL of water, and the volume was reduced to 20 mL. The aqueous solution was extracted with ethyl acetate (50 mL) and back-washed with 0.1 N hydrochloric acid (3 × 50 mL), and the volatiles were removed by spin evaporation to give an amber oil. The oil was adsorbed to 5 g of silica gel 60 and purified by flash chromatography using ethyl acetate–hexane (1:5) as eluant. The fractions that contained pure product were combined and evaporated in vacuo to give a solid that was recrystallized from hexane to give 0.209 g (39%) of **7**: mp 164–165 °C; ^{1}H NMR (DMSO-d_6) δ 7.63 (t, 1 H, NH), 7.28 (m, 5 H, ArH), 7.10 (m, 4 H, ArH), 5.25 (s, 2 H, $^9NCH_2$), 4.56 (d, 2 H, CH_2), 3.39 (br s, 6 H, $N(CH_3)_2$), 2.26 (s, 3 H, CH_3). Anal. ($C_{23}H_{23}F_3N_6$) C, H, N.

8-Acetamido-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (8). Acetic anhydride (0.127 mL, 1.34 mmol) was added to a mixture of **3**·HCl (0.400 g, 1.03 mmol), 4-(dimethylamino)pyridine (0.273 g, 2.21 mmol), and dry dichloromethane (10 mL). After magnetic stirring for 1 h, additional acetic anhydride (0.127 mL) was added and the reaction stirred for 18 h. The volatiles were removed by spin evaporation in vacuo, and the residue was adsorbed to 3 g of silica gel 60 and purified by flash chromatography using ethyl acetate–hexane (1:2) as eluant. The fractions that contained pure product were combined and spin evaporated in vacuo to give a solid that was recrystallized from ethanol–water to give 0.306 g (76%) of **8**: mp 216–217.5 °C; ^{1}H NMR (DMSO-d_6) δ 10.60 (br s, 1 H, NH), 7.06 (AB, q, 4 H, ArH), 5.28 (s, 2 H, CH_2), 3.46 (br s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, CH_3), 2.07 (s, 3 H, $C(O)CH_3$). Anal. ($C_{18}H_{19}F_3N_6O$) C, H, N.

7,9-Dihydro-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-8*H*-purine-8-thione (9). A mixture of **2** (2.00 g, 4.83 mmol), thiourea (3.68 g, 48.3 mmol), and ethanol (50 mL) was refluxed with stirring for 20 h. The solvent was evaporated, and the solids were dispersed in water (200 mL) and collected by suction filtration. The solids were dispersed in dichloromethane (250 mL), and the mixture was extracted with two portions of 1 N sodium hydroxide (400, 250 mL). The pH of the combined sodium hydroxide extracts was adjusted to 5 with acetic acid, the resultant mixture was stirred for 0.5 h, and the solids were collected by suction filtration. Recrystallization from ethanol–water gave 0.543 g (30%) of **9**: mp 265–267 °C; ^{1}H NMR (DMSO-d_6) δ 13.52 (br s, 1 H, NH), 7.19 (AB q, 4 H, ArH), 5.34 (s, 2 H, CH_2), 3.27 (s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, CH_3). Anal. ($C_{16}H_{16}F_3N_5S$) C, H, N.

6-(Dimethylamino)-9-(4-methylbenzyl)-8-(methylthio)-2-(trifluoromethyl)-9*H*-purine (10). A mixture of **9** (1.00 g, 3.00 mmol) and toluene (20 mL) was stirred at 60 °C, and di-

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methylformamide dimethyl acetal (0.62 mL) was added. The solution was heated at reflux for 1 h. The solvent was removed by spin evaporation in vacuo, and the solid residue was dissolved in ether (100 mL) and stirred with 10 mL of 0.1 N hydrochloric acid. The mixture was washed with 75 mL of saturated aqueous sodium bicarbonate. The ether phase was separated and washed with 50 mL of water and 50 mL of brine; the combined aqueous phases were extracted with 50 mL of ether, and the ether was back-washed with 25 mL of brine. The combined ether extracts were dryed with sodium sulfate and filtered, and the solvent was removed by spin evaporation in vacuo to give 0.944 g (83%) of crude **10**. The solid (0.350 g) was recrystallized from ethanol–water to give 0.297 g (85%) of **10**: mp 147–148 °C; ^{1}H NMR (DMSO-d_6) δ 7.12 (m, 4 H, ArH), 5.25 (s, 2 H, CH_2), 3.49 (br s, 6 H, $N(CH_3)_2$), 2.68 (s, 3 H, SCH_3), 2.25 (s, 3 H, CH_3). Anal. ($C_{17}H_{18}F_3N_5S$) C, H, N.

6-(Dimethylamino)-9-(4-methylbenzyl)-8-(methylsulfinyl)-2-(trifluoromethyl)-9*H*-purine (11). This compound was prepared by analogy with ref 16. A mixture of 0.550 g (1.44 mmol) of **10** was reacted with excess (9 equiv) acetic anhydride/30% hydrogen peroxide in glacial acetic acid. After 20 h the reaction was quenched with saturated sodium sulfite. The mixture was reduced to 10 mL by spin evaporation in vacuo and partitioned between water–ethyl acetate. The organic phase was washed with water and saturated brine and dried over sodium sulfate. The volatiles were removed by spin evaporation in vacuo, and the solids were adsorbed to 3.5 g of silica gel 60. Two components were isolated by flash chromatography using first ethyl acetate–hexane (1:2), followed by ethyl acetate–hexane (3:2). The fractions containing the lower R_f component of the two products were combined and concentrated by spin evaporation in vacuo to give 0.326 g of crude **11**. Recrystallization with ethanol–water gave 0.299 g (50%) of **11**: mp 133–134 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (m, 4 H, ArH), 5.61 (s, 2 H, CH_2), 3.70 (br s, 6 H, $N(CH_3)_2$), 3.06 (s, 3 H, $S(O)CH_3$), 2.26 (s, 3 H, CH_3). Anal. ($C_{17}H_{18}F_3N_5OS$) C, H, N.

6-(Dimethylamino)-9-(4-methylbenzyl)-8-(methylsulfonyl)-2-(trifluoromethyl)-9*H*-purine (12). Compound **12** was obtained as the higher R_f product from the flash chromatographic separation of **11**. Crude **12** was recrystallized from ethanol–water to give 0.157 g of a white solid: mp 148–149 °C; ^{1}H NMR (DMSO-d_6) δ 7.14 (m, 4 H, ArH), 5.66 (s, 2 H, CH_2), 3.74 (br s, 6 H, $N(CH_3)_2$), 3.45 (s, 3 H, SO_2CH_3), 2.26 (s, 3 H, CH_3). Anal. ($C_{17}H_{18}F_3N_5O_2S$) C, H, N.

8-(Benzylthio)-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (13). α-Toluenethiol (0.156 mL, 1.33 mmol) was added to a stirred mixture of sodium methoxide (0.072 g, 1.33 mmol) in dry dimethylformamide (10 mL). After 15 min, **2** (0.500 g, 1.21 mmol) was added and the reaction was stirred at ambient temperature for 20 h. Next, additional α-toluenethiol (0.156 mL, 1.33 mmol) and sodium methoxide (0.072 g, 1.33 mmol) were added, and the reaction was stirred for 24 h at ambient temperature and then at 80 °C for 18 h. The reaction was poured into an ice–water slurry (100 mL) and the mixture was extracted with ether (2 × 100 mL). The combined organic phase was washed with 1 N sodium hydroxide (2 × 75 mL), water (2 × 75 mL), and brine (75 mL) and dried with sodium sulfate. The organic phase was concentrated to an oil under reduced pressure and then adsorbed to 5 g of silica gel 60. Crude **13** was purified by flash chromatography using ethyl acetate–hexane (1:8) as the eluant. The fractions that contained pure product were combined and concentrated to an oil (0.447 g) which solidified. The solid was recrystallized from hexane to yield 0.223 g (40%) of **13**: mp 107–108 °C; ^{1}H NMR (DMSO-d_6) δ 7.08–7.44 (m, 9 H, ArH), 5.22 (s, 2 H, $^9NCH_2$), 4.54 (s, 2 H, SCH_2), 3.52 (br s, 6 H, $N(CH_3)_2$), 2.25 (s, 3H, CH_3). Anal. ($C_{23}H_{22}F_3N_5S$) C, H, N.

7,9-Dihydro-6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-8*H*-purin-8-one (14). A mixture of **2** (0.37 g, 0.89 mmol), anhydrous sodium acetate (0.73 g, 8.9 mmol), and glacial acetic acid (18 mL) was refluxed with stirring for 64 h. The reaction was spin evaporated in vacuo; the residual solids were triturated with water (50 mL) and collected by suction filtration. The white solid was recrystallized from ethanol to give 0.245 g (78%) of **14**: mp 277.5–279 °C; ^{1}H NMR (DMSO-d_6): δ 11.24 (br s, 1 H, NH), 7.16 (m, 4 H, ArH), 4.92 (s, 2 H, CH_2), 3.18 (s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, CH_3). Anal. ($C_{16}H_{16}F_3N_5O$).

6-(Dimethylamino)-8-methoxy-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (15). To 0.14 g (6.0 mmol) of sodium metal was added 10 mL of methanol with magnetic stirring under a nitrogen atmosphere. After 15 min, 0.500 g (1.21 mmol) of **2** was added and the mixture was refluxed for 1 h, after which 0.10 g of sodium methoxide was added and the reaction was refluxed for 64 h. The reaction was poured into an ice–water slurry (100 mL) and the pH was adjusted to 4 with glacial acetic acid. The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate extract was washed with water (1 × 75 mL) and saturated brine (1 × 50 mL) and then dried with sodium sulfate, filtered, and spin evaporated in vacuo to give a yellow, solid residue. This residue was adsorbed to 5 g of silica gel 60 and purified by flash column (35 mm diameter) chromatography on a 17-cm bed of silica gel 60 using ethyl acetate–hexane (1:9) as eluant. The product was collected in fractions 6–10 (25-mL fractions), and the solvent was removed by spin evaporation in vacuo to yield a white solid. Recrystallization from hexane gave the analytically pure compound: yield, 0.208 g (47%); mp 146–146.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.11 (m, 4 H, ArH), 5.12 (s, 2 H, CH_2), 4.10 (s, 3 H, OCH_3), 3.42 (s, 6 H, $N(CH_3)_2$), 2.24 (s, 2 H, CH_3). Anal. ($C_{12}H_{18}F_3N_5O$) C, H, N.

6-(Dimethylamino)-9-(4-methylbenzyl)-8-phenoxy-2-(trifluoromethyl)-9*H*-purine (16). To a stirred mixture containing 58 mg (1.45 mmol) of 60.2% sodium hydride (oil dispersion) in 5 mL of dimethylformamide was added 0.136 g (1.45 mmol) of phenol. After 15 min, 0.500 g (1.21 mmol) of **2** was added and the mixture was heated at 140 °C with an oil bath for 1 h. The cooled reaction mixture was poured over an ice–water slurry (50 mL), and the aqueous mixture was extracted with diethyl ether (3 × 35 mL). The combined ether extract was washed once with water (50 mL) and once with saturated brine (50 mL), dried with sodium sulfate, and filtered, and the solvent was removed by spin evaporation in vacuo. The resultant solid residue was recrystallized from hexane to give 0.255 g (44%) of the analytically pure material: mp 120–121 °C; ^{1}H NMR (DMSO-d_6) δ 7.19–7.40 (m, 9 H, ArH), 5.31 (s, 2 H, CH_2), 3.33 (s, 6 H, $N(CH_3)_2$), 2.26 (s, 3 H, CH_3). Anal. ($C_{22}H_{20}F_3N_5O$) C, H, N.

7,9-Dihydro-6-(dimethylamino)-7-methyl-9-(4-methylbenzyl)-2-(trifluoromethyl)-8*H*-purin-8-one (17). A mixture of **14** (0.500 g, 1.42 mmol), sodium hydride (60.2% dispersion in oil) (0.068 g, 1.70 mmol), and dimethylformamide (10 mL) was stirred for 15 min when solution was complete. Methyl iodide (0.241 g, 1.70 mmol) was added and the solution was stirred for 18 h. The reaction was poured over an ice–water slurry (75 mL), brought to pH 4 with acetic acid, and extracted with two portions of ether (2 × 80 mL). The combined ether extract was backwashed with 1 N sodium hydroxide (50 mL), water (75 mL), and saturated brine (50 mL), dried with sodium sulfate, and spin evaporated in vacuo to yield an oil (0.474 g). This oil was adsorbed on silica gel 60 (3.5 g). This material was introduced onto a column (3.5 cm × 18 cm) of silical gel 60, and eluted with ethyl acetate–hexane (1:1) by using the flash chromatography technique. The fractions that contained product were combined and evaporated to give a clear oil (0.395 g). The oil was triturated with pentane to give a solid, which was recrystallized from pentane to give 0.224 g (43%) of **17**: mp 86–87 °C; ^{1}H NMR (DMSO-d_6) δ 7.18 (m, 4 H, ArH), 4.97 (s, 2 H, CH_2), 3.49 (s, 3 H, $^7NCH_3$), 3.01 (s, 6 H, $N(CH_3)_2$), 2.25 (s, 3 H, CH_3). Anal. ($C_{17}H_{18}F_3N_5O$) C, H, N.

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