$H_{15}N_3O_5$) C, H, N.

The diformylprolinol (40 mg, 0.142 mmol) was treated with 3 M NH_4OH (10 mL) at room temperature for 0.5 h. The solvent was removed in vacuo, and recrystallization from methanol–ether gave 30.5 mg (84.9%) of **16**: mp 225–226 °C; UV λ_{max} 208 nm (ϵ 14000) and 271 (ϵ 9200) at pH 7,214 (ϵ 15200) and 271 (ϵ 7200) at pH 12; ^{1}H NMR (DMSO-d_6) δ 1.77 (s, CH_3), 2.0–2.6 (m, 3-H), 3.1–3.7 (m, 5-H and 2-H), 3.93 (bs, CH_2O), 4.9–5.2 (m, 4-H), 7.62 (s, pyrimidine), 8.18 (s, aldehyde); MS (FAB) *m/e* 254 (M + 1), 126 (Thy + H). Anal. ($C_{11}H_{15}N_3O_4 \cdot {}^1/_2H_2O$) C, H, N.

Acknowledgment. This work was supported at The Salk Institute by Grant GM-13435-21 from the National Institutes of Health, and at The University of Texas Health Science Center by a grant from the Anne Guttentag Memorial Research Fund. We thank Dr. Douglas D. Richman (School of Medicine, University of California, San Diego, and Veteran's Administration Medical Center, La Jolla) and Dr. Daniel D. Von Hoff (The University of Texas Health Science Center at San Antonio and Cancer Therapy and Research Foundation of South Texas) for carrying out the bioassays, Aubrey Hill, Jr., for drawing the figures, and Sylvia Bailey for manuscript preparation.

Synthesis and Antirhinovirus Activity of 6-(Dimethylamino)-2-(trifluoromethyl)-9-(substituted benzyl)-9*H*-purines

James L. Kelley,*,† James A. Linn,† and J. W. T. Selway‡

Division of Organic Chemistry, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709, and Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, U.K. *Received October 31, 1988*

A series of 6-(dimethylamino)-2-(trifluoromethyl)-9-(substituted benzyl)purines was synthesized and tested for antirhinovirus activity. Most of the compounds were synthesized by alkylation of 6-chloro-2-(trifluoromethyl)-9*H*-purine with the appropriate benzyl halide followed by displacement of the chloro group with dimethylamine. Alternatively, 6-(dimethylamino)-2-(trifluoromethyl)purine was alkylated with the appropriate benzyl halide. Although several different aryl substituents provided compounds with IC_{50}'s = 0.03 μM against rhinovirus serotype 1B, no congener was significantly more active than the parent **2**. Twenty-three compounds were tested against 18 other serotypes, but none exhibited a uniform profile of activity.

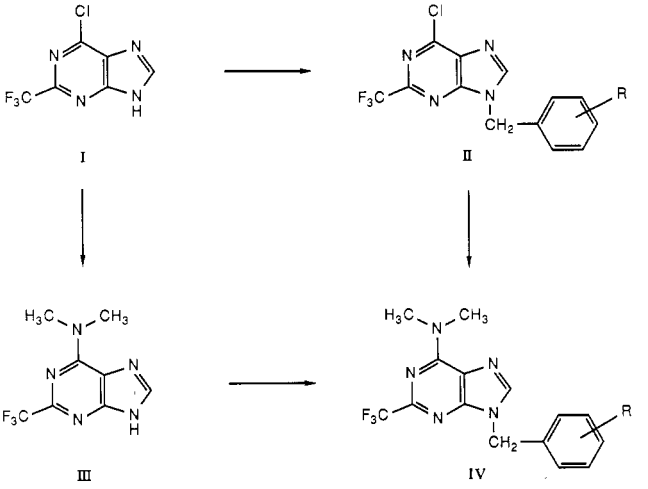
Recently, we reported the structure–activity relationships of some 6-(dimethylamino)-9-benzyl-9*H*-purines with activity against rhinovirus in vitro.[1-3] The most active compounds had a lipophilic, electron-withdrawing 2-substituent.[3] The 2-CF_3 analogue **1** was the most potent compound with an IC_{50} = 0.03 μM against serotype 1B. Although **1** had potent in vitro activity against rhinovirus 1B, most other serotypes were less sensitive.[3] To develop an agent with a broader spectrum of activity, we investigated the effect of various aryl substituents on the antirhinovirus activity of **1**. The synthesis and antirhinovirus activity of aryl-substituted analogues of **1** are reported.

Chemistry

Most of the compounds in Table I were prepared in two steps from 6-chloro-2-(trifluoromethyl)-9*H*-purine (I) and the appropriate benzyl halide (Scheme I). The (trifluoromethyl)purine I was prepared from 5-aminoimidazole-4-carboxamide by a modification of the literature procedure.[4,5] Condensation of 5-aminoimidazole-4-carboxamide with trifluoroacetamide gave 1,9-dihydro-2-(trifluoromethyl)-6*H*-purin-6-one (**67**),[4] which was converted to I by the Vilsmeier–Haack method.

Alkylation of I with the appropriate benzyl halide gave a mixture of the 9-benzylpurine II and the 7-isomer.[6] The 9-isomers were easily separated by flash chromatography and were usually used without further purification. The chloro group in II was displaced with ethanolic dimethylamine to give the target purines **1**, **3–10**, **12**, **15**, **17**, **26**, **30**, **36–40**, **42–45**, **49–54**, and **57–60** (methods A and B). Alternatively, I was treated first with ethanolic dimethylamine to give the 6-(dimethylamino)-2-(trifluoromethyl)purine III, which was alkylated with the appropriate benzyl halide to give purines **1**, **2**, **11**, **14**, **16**, **25**, **27**, **28**, **32**, and **33** (method C).

Scheme I



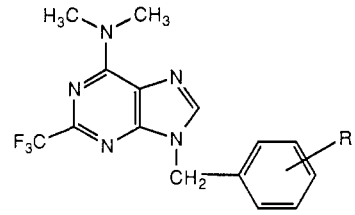
The 9-(aminobenzyl)purines **21**, **35**, **41**, **46**, and **55** were prepared from the nitro precursors by catalytic hydrogenation (method D). Several 9-[(dimethylamino)benzyl] analogues (**18**, **34**, **47**, and **61**) were prepared from the amines by Borch reductive alkylation (method E).[7] Re-

† Burroughs Wellcome Co.
‡ Wellcome Research Laboratories.

(1) Kelley, J. L.; Miller, C. A.; Selway, J. W. T.; Schaeffer, H. J. *Eur. J. Med. Chem.* **1988**, *23*, 319.
(2) Kelley, J. L.; Linn, J. A.; Krochmal, M. P.; Selway, J. W. T. *J. Med. Chem.* **1988**, *31*, 2001.
(3) Kelley, J. L.; Linn, J. A.; Selway, J. W. T. *J. Med. Chem.* **1989**, *32*, 218.
(4) Giner-Sorolla, A.; Bendich, A. *J. Am. Chem. Soc.* **1958**, *80*, 5744.
(5) Nagano, H.; Inoue, S.; Saggiomo, A.; Nodiff, E. *J. Pharm. Med. Chem.* **1964**, *7*, 215.
(6) Kelley, J. L.; Linn, J. A. *J. Org. Chem.* **1986**, *51*, 5435.
(7) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

0022-2623/89/1832-1757$01.50/0

Table I. Physical Properties and Antirhinovirus 1B Activity of 6-(Dimethylamino)-2-(trifluoromethyl)-9-(substituted benzyl)-9*H*-purines



compd no.	R	method[a]	yield, %	mp, °C	formula	IC_{50}, μM
1	4-CH_3	C	72[b]	101–102	$C_{16}H_{16}F_3N_5$	0.03
2	4-H	C	47[c]	107–107.5	$C_{15}H_{14}F_3N_5$	0.04
3	4-Cl	A, B	31, 52[d]	103–105	$C_{15}H_{13}ClF_3N_5$	0.03
4	4-SCH_3	A,[e] B	55, 59[d]	119–120	$C_{16}H_{16}F_3N_5S$	0.07
5	4-CF_3	A, B	38, 44[d]	75–76.5	$C_{16}H_{13}F_6N_5$	0.11
6	4-$OCH(CH_3)_2$	A,[f] B	21, 34[d]	75–76	$C_{18}H_{20}F_3N_5O$	1
7	4-NO_2	A, B	64, 79[g]	168–169	$C_{15}H_{13}F_3N_6O_2$	0.07
8	4-SO_2CH_3	A,[h] B	48, 85[g]	193–194	$C_{16}H_{16}F_3N_5O_2S$	0.5
9	4-F	A, B	61, 50[i]	86–87	$C_{15}H_{13}F_4N_5$	0.05
10	4-C_4H_9	A,[j] B	54, 74[d]	76.5–77.5	$C_{19}H_{22}F_3N_5$	0.78
11	4-C_6H_5	C[k]	53[l]	154–155	$C_{21}H_{18}F_3N_5$	14[m]
12	4-$CO_2C_2H_5$	A,[n] B	44, 72[l]	139.5–141	$C_{18}H_{18}F_3N_5O_2$	5.0
13	4-CO_2H	exp	66[l]	268–275 dec	$C_{16}H_{14}F_3N_5O_2$	4.6
14	4-CN	C	94	195–196[l]	$C_{16}H_{13}F_3N_6$	0.3
15	4-Br	A, B	47, 70[c]	120.5–121.5	$C_{15}H_{13}BrF_3N_5$	0.03
16	4-$OCH_2C_6H_5$	C	89	105.5–106.5[c]	$C_{22}H_{20}F_3N_5O$	4.4
17	4-OC_4H_9	A,[o] B	45, 78[b]	67.5–68.5	$C_{19}H_{22}F_3N_5O$	2.1
18	4-$N(CH_3)_2$	E	45[p]	128–128.5	$C_{17}H_{19}F_3N_6$	0.29
19	4-OH	G	63[l]	167–168	$C_{15}H_{14}F_3N_5O$	0.17
20	4-CH_2OH	exp	60[q]	144–145.5	$C_{16}H_{16}F_3N_5O$	0.2
21	4-NH_2	D	63	169.5–171[r]	$C_{15}H_{15}F_3N_6$	0.13
22	4-CH_2NH_2	exp	12[s]	274.5–276.5	$C_{16}H_{17}F_3N_6 \cdot HCl \cdot {}^1/_2H_2O$	0.2
23	4-NHCHO	F	28[g]	202.5–204	$C_{16}H_{15}F_3N_6O$	0.18
24	4-$NHCOCH_3$	exp	63[l]	206–207	$C_{17}H_{17}F_3N_6O$	0.37
25	3-Br	C	68[t]	123.5–124.5	$C_{15}H_{13}BrF_3N_5$	0.06
26	3-F	A, B	57, 60[i]	96.5–97.5	$C_{15}H_{13}F_4N_5$	0.03
27	3-OCH_3	C	65[t]	101.5–103	$C_{16}H_{16}F_3N_5O$	0.1
28	3-$OCH_2C_6H_5$	C[u]	58[l]	128.5–130	$C_{22}H_{20}F_3N_5O$	1.1
29	3-OH	G[v]	51[w]	188–190	$C_{15}H_{14}F_3N_5O$	0.95
30	3-CO_2CH_3	A, B	43, 58[d]	101–102	$C_{17}H_{16}F_3N_5O_2$	2.6
31	3-CO_2H	exp	46[l]	202–203	$C_{16}H_{14}F_3N_5O_2$	4.6
32	3-NO_2	C	72	172–173[l]	$C_{15}H_{13}F_3N_6O_2$	0.13
33	3-NHCHO	C[x]	80[l]	164.5–165	$C_{16}H_{15}F_3N_6O$	0.74
34	3-$N(CH_3)_2$	E	20[b]	102–103	$C_{17}H_{19}F_3N_6$	0.25
35	3-NH_2	D	45	235 dec[s]	$C_{15}H_{16}ClF_3N_6$	0.3
36	2-CH_3	A, B	48, 65[c]	101–102	$C_{16}H_{16}F_3N_5$	0.29
37	2-Cl	A, B	47, 32[i]	107–108	$C_{15}H_{13}ClF_3N_5$	0.2
38	2-F	A, B	61, 75[c]	124–125	$C_{15}H_{13}F_4N_5$	0.15
39	2-OCH_3	A,[y] B	40, 31[c]	118.5–120	$C_{16}H_{16}F_3N_5O$	5.6
40	2-NO_2	A, B	51, 84[g]	186–186.5	$C_{15}H_{13}F_3N_6O_2$	280[m]
41	2-NH_2	D	64[l]	153.5–154	$C_{15}H_{15}F_3N_6$	1.7
42	2-CH_3,4-Cl	A,[z] B	46, 80[c]	127–128.5	$C_{16}H_{15}ClF_3N_5$	0.12
43	2,4-Cl_2	A,[aa] B	36, 66[i]	137–138	$C_{15}H_{12}Cl_2F_3N_5$	0.12
44	2-OCH_3,4-Cl	A,[bb] B	43, 41[l]	157.5–158.5	$C_{16}H_{15}ClF_3N_5O$	135[m]
45	2-NO_2,4-Cl	A,[cc] B	88,[dd] 63[g]	173.5–174.5	$C_{15}H_{12}ClF_3N_6O_2$	0.53
46	2-NH_2,4-Cl	D[ee]	46	157–158.5[m]	$C_{15}H_{14}ClF_3N_6$	0.47
47	2-$N(CH_3)_2$,4-Cl	E	46[l]	149.5–150.5	$C_{17}H_{18}ClF_3N_6$	180[m]
48	2-NHCHO,4-Cl	F	27[l]	214–215	$C_{16}H_{14}ClF_3N_6O$	6.9
49	2,4-$(CH_3)_2$	A,[ff] B	70, 48[d]	138.5–139.5	$C_{17}H_{18}F_3N_5$	0.11
50	2-OCH_3,4-CH_3	A,[gg] B	22, 60[g]	147–148.5	$C_{17}H_{18}F_3N_5O$	70[m]
51	3-CH_3,4-Cl	A,[hh] B	40, 59[i]	114–115	$C_{16}H_{15}ClF_3N_5$	0.12
52	3,4-Cl_2	A, B	38, 39[ii]	109.5–110.5	$C_{15}H_{12}Cl_2F_3N_5$	0.12
53	3-OCH_3,4-Cl	A,[jj] B	47, 65[l]	160–161	$C_{16}H_{15}ClF_3N_5O$	0.68
54	3-NO_2,4-Cl	A,[kk] B	54, 75[g]	156–157	$C_{15}H_{12}ClF_3N_6O_2$	2.1
55	3-NH_2,4-Cl	D	79	143.5–144.5[l]	$C_{15}H_{14}ClF_3N_6$	0.17
56	3-NHCHO,4-Cl	F	67[l]	184–185	$C_{16}H_{14}ClF_3N_6O$	0.56
57	3,4-$(CH_3)_2$	A,[ll] B	22, 76[g]	115–116	$C_{17}H_{18}F_3N_5$	0.17
58	3-CH_3,4-OCH_3	A,[mm] B	36, 48[c]	117–118	$C_{17}H_{18}F_3N_5O$	0.2
59	3,5-$(CH_3)_2$	A,[nn] B	48, 72[g]	141.5–142	$C_{17}H_{18}F_3N_5$	>1.3
60	3-OCH_3,4-CH_3	A,[oo] B	28, 91[g]	123–124	$C_{17}H_{18}F_3N_5O$	>1
61	3-$N(CH_3)_2$,4-Cl	E	48[i]	147–148	$C_{17}H_{18}ClF_3N_6$	>0.2

[a] Method A: See preparation of 6-chloro-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine in ref 6. Method B: See preparation of 6-(dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine in ref 3. [b] Recrystallized from pentane. [c] Recrystallized from hexane. [d] Recrystallized from pentane–ethyl acetate. [e] The 4-(methylthio)benzyl bromide was prepared from 4-(methylthio)benzoic acid according to methods H and I. [f] The 4-isopropoxybenzyl bromide was prepared by alkylation of ethyl 4-hydroxybenzoate with isopropyl bromide (see Experimental Section, 72), followed by Vitride reduction of the ester (see Experimental Section, 73) and bromination of the alcohol according to method I. [g] Recrystallized from ethanol–water. [h] The 4-(methylsulfonyl)benzyl bromide was obtained from 4-(methylsulfonyl)-

Table I. *Footnotes Continued*

benzoic acid according to methods H and I. [i]Recrystallized from pentane–hexane. [j]The 4-butylbenzyl bromide was obtained by hydrolysis of 4-butylbenzoyl chloride to give the acid **71**,[9] followed by reduction of the acid and bromination of the alcohol according to methods H and I. [k]The 4-phenylbenzyl bromide was obtained from 4-biphenylmethanol according to method I. [l]Recrystallized from hexane–ethyl acetate. [m]Estimated by extrapolation. Compound **11** inhibited 36% at 8 μM. [n]The 4-carbethoxybenzyl bromide was obtained by esterification of 4-toluoyl chloride with ethanol (method J), followed by bromination of the aryl methyl using *N*-bromosuccinimide (method L). [o]The 4-butoxybenzyl bromide was obtained from 4-butoxybenzyl alcohol according to method I. [p]Recrystallized from cyclohexane. [q]Recrystallized from hexane–toluene. [r]Recrystallized from ethanol. [s]Recrystallized from 2-propanol. [t]Recrystallized from pentane–ether. [u]The 3-(benzyloxy)benzyl bromide was obtained from 3-(benzyloxy)benzyl alcohol according to method I. [v]Acetic acid–methanol (1:3) was used as the solvent. [w]Recrystallized from hexane–ether. [x]3-Formamidobenzyl alcohol (see J. L. Kelley, E. W. McLean, R. M. Ferris, and J. L. Howard, in press) was brominated according to method I. [y]The 2-methoxybenzyl bromide was obtained from 2-methoxybenzyl alcohol according to method I. [z]The 4-chloro-2-methylbenzyl bromide was prepared from 4-chloro-2-methylbenzoic acid according to methods H and I. [aa]the 2,4-dichlorobenzyl bromide was prepared from 2,4-dichlorobenzyl alcohol according to method I. [bb]The 4-chloro-2-methoxybenzyl bromide was prepared from 4-chloro-2-methoxybenzoic acid according to methods H and I. [cc]The 4-chloro-2-nitrobenzyl bromide was obtained from 4-chloro-2-nitrobenzyl alcohol according to method I. [dd]The product was contaminated with 12 mol % of the 7-isomer. [ee]Platinum oxide was used instead of 5% palladium on carbon. [ff]The 2,4-dimethylbenzyl bromide[13] was prepared by bromination of 2,4-dimethylbenzyl alcohol using pyridinium bromide perbromide.[10] [gg]The 2-methoxy-4-methylbenzyl bromide was obtained from 2-methoxy-4-methylbenzoic acid according to methods H and I. [hh]The 4-chloro-3-methylbenzyl bromide was obtained from 4-chloro-3-methylbenzoic acid according to methods H and I. [ii]Recrystallized from pentane–hexane–ethyl acetate. [jj]The 4-chloro-3-methoxybenzyl bromide was obtained in several steps from 4-chloro-3-nitrobenzaldehyde by (1) reduction of the nitro group with stannic chloride,[11] (2) formation of the diazonium salt with nitrous acid,[12] (3) hydrolysis of the diazonium salt with 70% sulfuric acid[8] to give 4-chloro-3-hydroxybenzaldehyde,[13] (4) methylation with dimethyl sulfate,[8] (5) reduction of the aldehyde with sodium borohydride, and (6) bromination of the benzylic alcohol[21] using method I. [kk]The 4-chloro-3-nitrobenzyl bromide was obtained from 4-chloro-3-nitrobenzyl alcohol according to method I. [ll]The 3,4-dimethylbenzyl chloride (**68**) was prepared from 3,4-dimethylbenzyl alcohol by using thionyl chloride (see Experimental Section). [mm]The 4-methoxy-3-methylbenzyl bromide was prepared by borohydride reduction of 3-methyl-4-methoxybenzaldehyde (as in footnote *jj*), followed by bromination of the alcohol using method I. [nn]The 3,5-dimethylbenzyl bromide was obtained by bromination of 3,5-dimethylbenzyl alcohol using pyridinium bromide perbromide.[10] [oo]The 3-methoxy-4-methylbenzyl bromide was obtained from 3-methoxy-4-methylbenzoic acid according to methods H and I.

action of the appropriate amine with ethyl formate gave the (formamidobenzyl)purines **23**, **48**, and **56** (method F). The phenols **19** and **29** were prepared by hydrogenolytic debenzylation (method G). The carboxylic acid derivative **13** was prepared from nitrile **14** with sulfuric acid. Lithium aluminum hydride reduction of ester **12** gave the hydroxymethyl derivative **20**. Reduction of nitrile **14** with diborane provided [(aminomethyl)benzyl]purine **22**. Acylation of **21** with acetic anhydride gave acetamide **24**. Base hydrolysis of ester **30** provided carboxylic acid **31**. The intermediate benzyl halides that were not commercially available were prepared from benzyl alcohols with phosphorus tribromide or thionyl chloride. The precursor alcohols were made by various standard methods as exemplified under Experimental Section or in footnotes to Table I.[8-13]

Biological Results and Discussion

Antiviral Activity. The compounds in Table I were tested initially for activity against serotype 1B in a plaque inhibition assay using monolayers of M-HeLa cells. Only compounds **11**, **40**, **44**, **47**, and **50** were inactive at 50 μg per disk. For most compounds the 50% inhibition concentration (IC_{50}) was measured with the plaque reduction assay; the IC_{50}'s are tabulated in Table I. The IC_{50}'s for five compounds were estimated by extrapolation. The plaque inhibition and plaque reduction assays were performed as described previously.[1]

Subsequent to discovery of the potent activity of the 2-chloro-9-benzylpurines,[2] a series of 2-substituted analogues were prepared and tested for antirhinovirus activity.[3] A structure–activity analysis showed that optimum activity was associated with 9-benzylpurines like **1**, which contained a lipophilic, electron-withdrawing 2-substituent. To improve the serotype profile of this new class of antiviral agents, we prepared a set of 6-(dimethylamino)-2-(trifluoromethyl)-9-benzylpurines with various aryl substituents in the benzyl moiety and tested them for activity against rhinovirus serotype 1B.

The parent, unsubstituted benzylpurine **2** had an IC_{50} = 0.04 μM. Substitution in the para position with a CH_3 (**1**), Cl (**3**), SCH_3 (**4**), NO_2 (**7**), F (**9**), or Br (**15**) substituent had no significant effect on activity (IC_{50}'s ranged from 0.03 to 0.07 μM), despite the range of lipophilic and electronic properties of these six substituents. Compounds with larger substituents were generally less active as was evident with the C_6H_5 (**11**) and $OCH_2C_6H_5$ (**16**) substituents (IC_{50}'s = 14 and 4.4 μM, respectively). A similar trend was found for substituents in the meta position, where the most active compounds were **25** (3-Br) and **26** (3-F) with IC_{50}'s = 0.06 and 0.03 μM, respectively. Ortho-substituted analogues were generally less active, with several compounds exhibiting very weak activity (**40**, **44**, **47**, and **50**). Among 60 analogues of **2**, which contained 25 aryl substituents possessing a spread of physicochemical parameters, no congener was significantly more active than the parent **2** against rhinovirus serotype 1B.

Twenty-three compounds were tested for activity against 18 other rhinovirus serotypes (Table II). Serotype 1B was the most sensitive to inhibition, with IC_{50}'s ranging from 0.03 to 1.0 μM. Serotype 5 was the least sensitive, with IC_{50}'s = 8 μM or higher for all compounds tested. Several compounds had potent activity against serotype 1B, but the IC_{50}'s against other serotypes were from 5- to 200-fold higher for serotypes sufficiently sensitive to allow IC_{50} values to be determined. Thus, although several of these agents had potent activity against serotype 1B, other serotypes were less sensitive.

Conclusion

The effect of various aryl substituents on the antirhinovirus 1B activity of 2-(trifluoromethyl)-9-benzylpurines was studied via synthesis and antiviral evaluation of the compounds in Table I. A variety of different substituents were tolerated in the para and meta positions of the benzyl

(8) Faith, H. E.; Bahler, M. E.; Florestano, H. J. *J. Am. Chem. Soc.* **1955**, *77*, 543.
(9) Heeger, A. J.; Yoshida, H.; Naito, K.; Kobayashi, Y. Eur. Patent 106 175, 1984.
(10) Olah, G. A.; Gupta, B. G. B.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638.
(11) Woodward, R. B. *Org. Synth.* **1945**, *25*, 55.
(12) DuBois, G. E.; Crosby, G. A.; Stephenson, R. A. *J. Med. Chem.* **1981**, *24*, 408.
(13) Bernhardt, G.; Petersen, E. N.; Daum, G. Ger. *Patent* 2 948 058, 1981.

Table II. Activity of 9-Benzylpurines against Nineteen Rhinovirus Serotypes[a]

	serotypes																		
compd	1A	1B	2	3	4	5	8	9	12	13	14	15	16	18	19	21	29	30	31
1	0.1	0.03	5.7	(43)[b]	(41)[b]	(18)[c]	(41)[b]	0.35	2.6	2.6	1.2	1.0	(12)[d]	1.8	6.7	(40)[c]	4.2	2.2	1.2
2	1.1	0.04	(33)[c]	(20)[c]	8.8	(33)[c]	8.0	0.46	3.8	(22)[c]	8.0[e]	4.8	0.96	10	(32)[c]	(28)[c]	3.2	(19)[c]	(37)[c]
3	0.73	0.03	6.6	6.9	6.1	8[e]	5.7	0.9	7.4	>8	4.3	3.3	NT	>8	6.5	7.4	2.5	6.5	5.3
4	0.57	0.07	4.5[e]	(39)[c]	3.8	>8	7.2	1.0	5.2	(35)[c]	7.6	4.5	0.81	10[e]	2.5	(35)[c]	2.6	7.9	8.6[e]
5	0.91	0.11	(23)[f]	(44)[c]	6.0	>8	>8	2.2[e]	5.2	(22)[c]	7.0	4.2	1.2	6.6	5.2	8.2[e]	7.2	(40)[c]	6[e]
6	2.8	1.0	5.2	8[e]	3.7	11[e]	10[e]	1.5	10	(39)[c]	(22)[c]	(40)[c]	2.1	6.8	(33)[c]	(40)[c]	2.5	6.6	4.2
7	(38)[f]	0.07	8.3	(43)[c]	4.1	(32)[g]	8.1	5.6[e]	8.0	(13)[c]	8.6	(31)[c]	1.5	5.9	8.8[e]	(28)[c]	10	(28)[c]	(37)[c]
8	2.3	0.5	(36)[c]	4.7	8.8[e]	(40)[c]	(36)[c]	3.7	6.0	4.2	(16)[c]	(47)[c]	2.3[e]	(29)[c]	9[e]	9[e]	3.0	(32)[c]	4.3
9	1.3	0.05	(27)[c]	(35)[c]	3.8	(11)[c]	8	0.87	8[e]	(42)[c]	7.1	8.7	1.3	8.9	(22)[c]	(34)[c]	4.0	9[e]	(47)[c]
15	0.76	0.03	7.3	8[e]	7.6	(37)[c]	8.3	0.7	9.5[e]	(40)[c]	8.1	5.7	1.2	7.5	(27)[c]	5.0	3.2	4.6	5.5
18	1.2	0.29	11[e]	(33)[c]	6.1	(39)[c]	(37)[c]	4.6	4.0	(45)[c]	(46)[c]	(30)[c]	1.9	8.9	(23)[c]	(27)[c]	4.7	(35)[c]	(41)[c]
26	0.57	0.03	15[e]	(35)[c]	(34)[c]	(34)[c]	(45)[c]	0.3	2.3	(30)[c]	7.1	3.2	0.8	8.0	(28)[c]	10[e]	2.7	(28)[c]	(43)[c]
36	8[e]	0.29	(31)[c]	7.5	(22)[c]	(40)[c]	(44)[c]	1.9	6.5	(33)[c]	(31)[c]	(14)[c]	1.9	7.7	(19)[c]	(18)[c]	6.2	9[e]	(47)[c]
37	4.0	0.2	9.4	9[e]	10[e]	(24)[c]	7.9	1.9	8.1	(24)[c]	8[e]	(30)[c]	4.3	13[e]	(27)[c]	(38)[c]	4.2	(31)[c]	(38)[c]
42	0.82	0.13	9[e]	(29)[c]	(25)[c]	>8	9.5[e]	2.0	7.8	(23)[c]	9[e]	(11)[c]	1.9	10[e]	10[e]	(22)[c]	(32)[c]	(28)[c]	12[e]
43	0.58	0.13	6.9	(17)[c]	(25)[c]	>8	8.5[e]	0.93	11	(20)[c]	(35)[c]	(10)[c]	0.85	(32)[c]	(40)[c]	(30)[c]	(15)[c]	11[e]	(28)[c]
49	0.83	0.11	2.8	(40)[c]	7.6	>8	>8	0.95	7.2	(13)[c]	11[e]	(30)[c]	1.2	6.1	(36)[c]	(16)[c]	(20)[c]	(33)[c]	13[e]
51	1.4	0.12	5.2	(44)[c]	7.6	>8	>8	1.0	3.3	(13)[c]	8	6.1	0.84	(28)[c]	7.7	6.3	7.0	(31)[c]	9[e]
52	0.73	0.12	6.1	(40)[c]	8.4	>8	11[e]	0.71	5.1	(23)[c]	10[e]	3.7	0.74	8.1	5.4	(29)[c]	4.8	7.5	13[e]
55	2.4[e]	0.19	6.5	14[e]	7.2	>8	6.2	1.5	5.2	(18)[c]	7.1	5.8	1.6	14[e]	(40)[c]	(10)[c]	(26)[c]	(34)[c]	(29)[c]
56	8[e]	0.56	(35)[c]	(40)[c]	(34)[c]	(36)[c]	6.7	1.8	5.0	(43)[c]	9.6	(29)[c]	1.9	8.7	(18)[c]	(20)[c]	6.3	6.5	8.0
57	1.7	0.17	5.0	(39)[c]	6.0	>8	5.1	0.65	4.0	>8	6.6	2.0	0.78	8.2[e]	7.1	(16)[c]	5.0	8.1[e]	13[e]
58	2.6[e]	0.2	8[e]	(28)[c]	5.5	>8	>8	1.3	4.1	(12)[c]	7.5	9[e]	1.9	(35)[c]	8.6[e]	(16)[c]	(27)[c]	(20)[c]	NT

[a] The nonbracketed numbers are the 50% inhibitory concentration (IC_{50}) measured as described in ref 1. In many cases the exact IC_{50} was not determined; the activity is denoted as greater than (>) the concentration or as percent inhibition at the footnoted concentration. NT = not tested. [b] Percent inhibition at 2.5 μM. [c] Percent inhibition at 8 μM. [d] Percent inhibition at 5 μM. [e] IC_{50} estimated by extrapolation. [f] Percent inhibition at 4 μM. [g] Percent inhibition at 10 μM.

moiety although larger substituents were generally less active; none of the analogues were significantly more active than the parent **2**. Although several compounds had potent activity against serotype 1B, the IC_{50}'s against other serotypes were from 5- to 200-fold higher. This lack of uniform antirhinovirus serotype activity suggests that these compounds would be of little clinical interest.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and were uncorrected. UV spectra were measured on a Unicam SP 800 or Cary 118 UV–vis spectrophotometer. NMR data were recorded on a Varian XL-200, 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. Mass spectra were obtained from Oneida Research Service, Whitesboro, NY, using a Finnegan 45 TFQ mass spectrometer. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLCs were developed on Whatman 200-μm MK6F plates of silica gel (SG) with fluorescent indicator. Preparative flash chromatography[14] was performed on silica gel 60 (40–63 μm, E. Merck no. 9385). All compounds were analyzed for C, H, and N and gave combustion values within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. The 5-aminoimidazole-4-carboxamide hydrochloride was purchased from Chemalog.

Method C. 6-(Dimethylamino)-9-(4-methylbenzyl)-2-(trifluoromethyl)-9*H*-purine (1). Alkylation of III. A mixture of III (2.20 g, 9.52 mmol), 4-methylbenzyl bromide (2.11 g, 11.4 mmol), potassium carbonate (1.58 g, 11.4 mmol), and dry dimethylformamide (50 mL) was stirred at ambient temperature for 48 h. The reaction mixture was poured into ice–water (100 mL), and the pH was adjusted to 5 with acetic acid. The mixture was extracted with ether (4 × 100 mL), and the combined organic phase was washed with water (400 mL) and brine (200 mL) and dried. The solution was added to 20 g of silica gel 60 and spin evaporated to dryness. The residual solids were applied to a column (5 cm × 18 cm) of silica gel 60 wetted with hexane. The column was eluted with ethyl acetate–hexane (1:2), and the fractions containing the major product were combined to give 3.16 g (99%) of crude **1**. Recrystallization from pentane gave 2.3 g (72%) of analytically pure **1**, mp 101–102 °C, which was identical with that prepared by method B. Anal. ($C_{16}H_{16}F_3N_5$) C, H, N.

Method D. 9-(2-Aminobenzyl)-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (41). A mixture of **40** (1.00 g, 2.73 mmol), 5% palladium on carbon (0.200 g), and acetic acid (50 mL) was shaken in the presence of hydrogen at 2–3 atm for 1 h. The mixture was filtered through Celite, and the pad was washed with methanol (20 mL). The filtrate was spin evaporated in vacuo; the residue was covered with dichloromethane and spin evaporated. The residue was dissolved in methanol, and 10 g of silica gel 60 was added to the solution. The mixture was spin evaporated in vacuo, and the residual solids were added to a column (3.5 cm × 18 cm) of silica gel 60 wetted with hexane. The column was eluted with ethyl acetate–hexane (1:1). The appropriate fractions were combined and spin evaporated in vacuo to give 0.803 g (88%) of crude **41**. Recrystallization from ethyl acetate–hexane gave 0.587 g (64%) of analytically pure **41**: mp 153.5–154 °C; TLC-SG, ethyl acetate–cyclohexane (1:1), one spot with R_f = 0.60; NMR (DMSO-d_6) δ 8.35 (s, 1 H, H-8), 6.3–7.3 (m, 4 H, ArH), 5.36 (br s, 2 H, NH_2), 5.28 (s, 2 H, CH_2), 3.50 [br s, 6 H, $N(CH_3)_2$]; MS, *m/e* 336 (M^+), 267 ($M^+ - CF_3$), 230 ($M^+ - C_7H_8N$), 106 ($C_7H_8N^+$). Anal. ($C_{15}H_{15}F_3N_6$) C, H, N.

Method E. 9-[4-Chloro-3-(dimethylamino)benzyl]-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (61). A solution of **55** (0.500 g, 1.35 mmol), 36% aqueous formaldehyde (1.44 mL, 27.0 mmol), and acetonitrile (10 mL) was added dropwise to sodium cyanoborohydride (0.424 g, 6.75 mmol). Acetic acid (0.25 mL) was added to the reaction, and after 2 h of stirring additional acetic acid (0.25 mL) was added. After 3 h, additional 36% aqueous formaldehyde (0.75 mL) and then sodium cyanoborohydride (0.212 g) was added to the reaction. After 15 h diethyl ether (35 mL) was added to the reaction, and the liquid phase was decanted from the solids. The organic phase was washed with water (30 mL) and brine (30 mL) and then dried (sodium sulfate) to give a yellow solid (0.6 g). The solid was dissolved in ethyl acetate, and 5 g of silica gel 60 was added to the solution. The volatiles were removed by spin evaporation in vacuo, and the residual solids were added to a column (3 cm × 18 cm) of silica gel 60 wetted with hexane. The column was eluted with ethyl acetate–hexane (1:3), and the appropriate fractions were combined and spin evaporated in vacuo to give 0.416 g (77%) of crude **61**. Recrystallization from ethyl acetate–hexane gave 0.261 g (48%) of analytically pure **61**: mp 147–148 °C; TLC-SG, ethyl acetate–cyclohexane (1:1), one spot with R_f = 0.56; NMR (DMSO-d_6) δ 8.46 (s, 1 H, H-8), 6.8–7.4 (m, 3 H, ArH), 5.39 (s, 2 H, CH_2), 3.50

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[br s, 6 H, $N(CH_3)_2$], 2.70 [s, 6 H, $ArN(CH_3)_2$]; MS, *m/e* 398 (M^+), 369 ($M^+ - 29$), 230 ($M^+ - C_9H_{11}ClN$), 168 ($C_9H_{11}ClN^+$). Anal. ($C_{17}H_{18}ClF_3N_6$) C, H, N.

Method F. 9-(4-Chloro-2-formamidobenzyl)-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (48). A mixture of **46** (0.500 g, 1.35 mmol) and ethyl formate (35 mL) was heated in a glass-lined stainless steel reaction vessel at 75 °C for 18 h and at 110 °C for 66 h. The volatiles were removed by spin evaporation in vacuo, and the residue was dissolved in ethyl acetate. Silica gel 60 (5 g) was added to the solution, and the solvent was evaporated. The residual solids were added to a column (3.5 cm × 18 cm) of silica gel 60 wetted with cyclohexane. The column was eluted with ethyl acetate–cyclohexane (2:3; 1.5 L) and then with ethyl acetate–cyclohexane (1:1). The major product was collected, and the appropriate fractions were combined and spin evaporated in vacuo to give 0.432 g (80%) of crude **48**. Recrystallization from ethyl acetate–hexane gave 0.146 g (27%) of analytically pure **48**: mp 214–215 °C; TLC-SG, ethyl acetate–cyclohexane (1:1), one spot with R_f = 0.26; NMR (DMSO-d_6) δ 10.14 (br s, 1 H, NH), 8.37 (s, 2 H, CHO and H-8), 6.9–7.8 (m, 3 H, ArH), 5.44 (s, 2 H, CH_2), 3.51 [br s, 6 H, $N(CH_3)_2$]; MS, *m/e* 398 (M^+), 370 ($M^+ - CO$), 301 [$M^+ - (CO + CF_3)$], 230 ($M^+ - C_8H_7ClNO$). Anal. ($C_{16}H_{14}ClF_3N_6O$) C, H, N.

Method G. 6-(Dimethylamino)-9-(4-hydroxybenzyl)-2-(trifluoromethyl)-9*H*-purine (19). A mixture of **16** (1.03 g, 2.41 mmol), 5% palladium on carbon (0.200 g), and methanol (50 mL) was shaken in the presence of hydrogen at 2–3 atm for 2 h. The reaction mixture was filtered through Celite, and the filtrate was spin evaporated in vacuo. The residual solid was recrystallized from hexane–ethyl acetate to give 0.514 g (63%) of analytically pure **19**: mp 167–168 °C; TLC-SG, ethyl acetate–cyclohexane (1:1), one spot with R_f = 0.42; NMR (DMSO-d_6) δ 9.43 (s, 1 H, OH), 8.37 (s, 1 H, H-8), 6.94 (AB q, 4 H, ArH), 5.29 (s, 2 H, CH_2), 3.48 [br s, 6 H, $N(CH_3)_2$]. Anal. ($C_{15}H_{14}F_3N_5O$) C, H, N.

Method H. 4-Chloro-2-methoxybenzyl Alcohol (62). A mixture of 4-chloro-2-methoxybenzoic acid (5.00 g, 26.8 mmol) in tetrahydrofuran (15 mL) was stirred at 0 °C under a nitrogen atmosphere. A solution of 1 M diborane in tetrahydrofuran (35.6 mL, 35.6 mmol) was added dropwise, and the mixture was stirred for 1.5 h. The excess hydride was quenched by addition of water–tetrahydrofuran (1:1; 16 mL). Potassium carbonate (6 g) was added, and the mixture was stirred for 10 min. The liquid phase was decanted from the solids. The solution was washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL) and dried (sodium sulfate). The volatiles were removed by spin evaporation in vacuo to give 4.26 g (92%) of an oil. A portion of this oil (0.403 g) was crystallized from pentane to give 0.234 g (58%) of 4-chloro-2-methoxybenzyl alcohol: mp 47–49 °C (lit.[15]); TLC-SG, ethyl acetate–cyclohexane (1:2), one spot with R_f = 0.39; NMR (DMSO-d_6) δ 6.9–7.4 (m, 3 H, ArH), 5.01 (t, 1 H, OH), 4.43 (d, 2 H, CH_2), 3.78 (s, 3 H, OCH_3). Anal. ($C_8H_9ClO_2$) C, H.

Method I. 2-Methoxybenzyl Bromide (63). Phosphorous tribromide[16] (2.04 g, 7.52 mmol) was added to a stirred solution of 2-methoxybenzyl alcohol (3.00 g, 21.5 mmol) and toluene (25 mL) at 40 °C. The solution was heated to 100 °C for 10 min, and the reaction was cooled to ambient temperature. The liquid was decanted and washed with water (2 × 50 mL) and brine (50 mL). The combined aqueous washes were extracted with ether (75 mL), and the combined organic fractions were spin evaporated to give 4.9 g of a semisolid residue. The residue was dissolved in ether (100 mL) and washed with water (2 × 50 mL) and brine (50 mL). The organic phase was spin evaporated to an oil, which was repeatedly coevaporated with toluene to give 4.04 g (94%) of 2-methoxybenzyl bromide[17] as a golden oil: NMR ($CDCl_3$) δ 6.7–7.5 (m, 4 H, ArH), 4.55 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3).

Method J. 4-Carbethoxytoluene (64). A solution of 4-toluoyl chloride (9.80 g, 63.4 mmol) in dichloromethane (10 mL) was added dropwise to a solution of triethylamine (7.05 g, 69.7 mmol) in absolute ethanol (100 mL). The exothermic reaction was moderated with an ice bath and then stirred at ambient temperature for 18 h. The reaction mixture was filtered, and the filtrate was spin evaporated in vacuo. The residue was extracted with ethyl acetate (100 mL), and the combined extracts were washed with water (2 × 100 mL) and brine (75 mL) and dried (sodium sulfate). The volatiles were removed by spin evaporation in vacuo, and the residue was coevaporated several times with dichloromethane to give 10.0 g (96%) of 4-carbethoxytoluene:[18] NMR (DMSO-d_6) δ 7.22 (AB q, 4 H, ArH), 4.00 (q, 2 H, OCH_2), 2.09 (s, 3 H, $ArCH_3$), 1.06 (t, 3 H, CH_3).

Method K. 4-Chloro-3-methoxybenzaldehyde (65). Dimethyl sulfate (2.85 mL, 30.1 mmol) was added to a stirred mixture of 4-chloro-3-hydroxybenzaldehyde (2.95 g, 18.8 mmol), potassium carbonate (2.11 g, 15.3 mmol), and dry acetone (15 mL). The mixture was refluxed with stirring for 1.5 h. Additional dimethyl sulfate (0.50 mL, 5.3 mmol) was added, and the reaction was refluxed for an additional 1 h. The reaction was cooled, and concentrated ammonium hydroxide (5 mL) was added. Ether (50 mL) was added after 0.5 h, and the phases were separated. The ether extract was washed with water (50 mL) and brine (50 mL) and dried (sodium sulfate). The solution was evaporated under reduced pressure, and the residual oil was dissolved in ethyl acetate. To this solution was added 23 g of silica gel 60, and the solvent was removed by spin evaporation in vacuo. The residual solids were added to a column (5 cm × 18 cm) of silica gel 60 wetted with hexane. The column was eluted with ethyl acetate–hexane (1:5), and the appropriate fractions were combined and spin evaporated in vacuo to give 2.13 g (66%) of 4-chloro-3-methoxybenzaldehyde[8] as an oil, which slowly crystallized: NMR (DMSO-d_6) δ 9.92 (s, 1 H, CHO), 7.53 (m, 3 H, ArH), 3.93 (s, 3 H, OCH_3).

Method L. 4-Carbethoxybenzyl Bromide (66). This compound was prepared by the general literature method[19] with *N*-bromosuccinimide: NMR (DMSO-d_6) δ 7.62 (AB q, 4 H, ArH), 4.63 (s, 2 H, CH_2Br), 4.22 (q, 2 H, OCH_2), 1.24 (t, 3 H, CH_3).

6-Chloro-2-(trifluoromethyl)-9*H*-purine (I). A mixture of 1,9-dihydro-2-(trifluoromethyl)-6*H*-purin-6-one (5.00 g, 24.5 mmol) and chloroform (100 mL) was refluxed with stirring. A solution prepared by dropwise addition of thionyl chloride (8.9 mL, 122 mmol) to cold dimethylformamide (8.92 g, 122 mmol) was added to the refluxing mixture. After 1.5 h at reflux, the reaction was poured into ice–water (400 mL). The layers were separated, and the chloroform phase was washed with water (2 × 100 mL). The pH of the aqueous phase was adjusted to 7 with saturated sodium bicarbonate and extracted with ether (3 × 400 mL). The combined ether and chloroform extracts were dried (magnesium sulfate) and concentrated to dryness under reduced pressure to give 4.94 g (91%) of crude I. The solid was recrystallized from ethyl acetate–hexane to give 3.15 g (58%) of I: mp 202–203 °C (lit.[5] mp 200–201 °C); TLC-SG, methanol–dichloromethane (1:9); NMR (DMSO-d_6) δ 14.4 (br s, 1 H, NH), 8.95 (s, 1 H, H-8); MS, *m/e* 222 (M^+), 203 ($M^+ - F$), 187 ($M^+ - Cl$), 153 ($M^+ - CF_3$), 69 (CF_3^+). Anal. ($C_6H_2ClF_3N_4$) C, H, N.

6-(Dimethylamino)-2-(trifluoromethyl)-9*H*-purine (III). A mixture of I (1.18 g, 5.30 mmol) and 1.6 M dimethylamine in ethanol (35 mL, 55 mmol) was stirred for 66 h. The mixture was concentrated to near dryness on a rotary evaporator, and water (20 mL) was added to the residual solid. This mixture was stirred for 1 h, and the solid was collected and dried to give 1.02 g (83%) of crude III. Recrystallization from ethyl acetate–hexane gave analytically pure III: mp 302–303.5 °C; TLC-SG, methanol–dichloromethane (1:9), one spot with R_f = 0.59; NMR (DMSO-d_6) δ 8.24 (s, 1 H, H-8), 3.62 [br s, 6 H, $N(CH_3)_2$]; MS, *m/e* 231 (M^+), 216 ($M^+ - CH_3$), 202 ($M^+ - 29$), 69 (CF_3^+). Anal. ($C_8H_8F_3N_5$) C, H, N.

9-(4-Carboxybenzyl)-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (13). A solution of **14** (0.490 g, 1.41 mmol) was heated on a steam bath with 50% sulfuric acid (100 mL) for 16 h. The reaction was cooled and added dropwise to a magnetically stirred solution of sodium bicarbonate (76 g) and water

(15) Abraham, D. J.; Kennedy, P. E.; Mehanna, A. S.; Patwa, D. C.; Williams, F. L. *J. Med. Chem.* **1984**, *27*, 967.
(16) Boekelheide, V.; Griffin, R. W., Jr. *J. Org. Chem.* **1969**, *34*, 1960.
(17) Carney, R. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2549.
(18) Waugh, K. M.; Berlin, K. D.; Ford, W. T.; Holt, E. M.; Carrol, J. P.; Schomber, P. R.; Thompson, M. D.; Schiff, L. J. *J. Med. Chem.* **1985**, *28*, 116.
(19) Chapman, N. B.; Williams, J. F. A. *J. Chem. Soc.* **1952**, 5044.

(1.1 L). The mixture was diluted with water (700 mL) and filtered. The pH of the filtrate was adjusted to 6 with sodium bicarbonate, and the solids were collected by filtration. The solids were recrystallized from ethyl acetate–hexane to give 0.339 g (66%) of analytically pure **13**: mp 268–275 °C dec; TLC-SG, methanol–dichloromethane (1:9), one spot with R_f = 0.39; NMR (DMSO-d_6) δ 8.46 (s, 1 H, H-8), 7.63 (AB q, 4 H, ArH), 5.52 (s, 2 H, CH_2), 3.51 [br s, 6 H, $N(CH_3)_2$]; MS, m/e 365 (M^+), 336 ($M^+ - 29$), 230 ($M^+ - C_8H_7O_2$), 135 ($C_8H_7O_2^+$), 69 (CF_3^+). Anal. ($C_{16}H_{14}F_3N_5O_2$) C, H, N.

6-(Dimethylamino)-9-[4-(hydroxymethyl)benzyl]-2-(trifluoromethyl)-9*H*-purine (20). A stirred mixture of lithium aluminum hydride (0.031 g, 0.826 mmol) and anhydrous ether (5 mL) was cooled to 3 °C under nitrogen. To this mixture was added a solution of **12** and anhydrous ether (25 mL) dropwise over 30 min. The reaction was refluxed for 1 h. The excess hydride was quenched by the sequential addition of acetone (30 mL) and water (10 mL). The resultant solution was spin evaporated in vacuo to a volume of 5 mL and diluted with water (20 mL). The solids were collected by filtration, washed with water, and dried. The solid was recrystallized from hexane–toluene with the addition of hexane to give 0.175 g (60%) of **20**: mp 144–145.5 °C; TLC-SG, ethyl acetate–cyclohexane (3:2), one spot with R_f = 0.36; NMR (DMSO-d_6) δ 8.44 (s, 1 H, H-8), 7.28 (s, 4 H, ArH), 5.42 (s, 2 H, CH_2), 5.15 (t, 1 H, OH), 4.46 (d, 2 H, CH_2O), 3.48 [br s, 6 H, $N(CH_3)_2$]; MS, m/e 351 (M^+), 322 ($M^+ - 29$), 230 ($M^+ - C_8H_9O$), 121 ($C_8H_9O^+$), 69 (CF_3^+). Anal. ($C_{16}H_{16}F_3N_5O$) C, H, N.

9-[4-(Aminomethyl)benzyl]-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine Hydrochloride (22). A solution of diborane in tetrahydrofuran (4.76 mL, 4.76 mmol) was added to a stirred solution of **14** (1.50 g, 4.33 mmol) and dry tetrahydrofuran (20 mL) under nitrogen. The reaction was refluxed for 2 h. The reaction was cooled to ambient temperature, and the excess hydride was quenched by addition of methanol (10 mL). Hydrogen chloride gas was bubbled through the reaction solution for 0.5 h. The reaction was refluxed for 1 h. The volatiles were removed by spin evaporation in vacuo. Methanol was added to the residue, and it was reevaporated. The residue was diluted with dichloromethane (100 mL), and the volatiles were again removed. The resultant solid was collected and recrystallized from 2-propanol to give 0.210 g (12%) of analytically pure **22**: mp 274.5–276.5 °C; TLC-SG, methanol–dichloromethane (2:8), one spot with R_f = 0.46; NMR (DMSO-d_6) δ 8.46 (s, 1 H, H-8), 8.15 (br s, 2 H, NH_2), 7.40 (AB q, 4 H, ArH), 5.45 (s, 2 H, CH_2), 3.98 (s, 2 H, CH_2NH_2), 3.46 [br s, 6 H, $N(CH_3)_2$]; MS, m/e 350 (M^+), 333 ($M^+ - NH_3$), 320 ($M^+ - CH_2NH_2$), 230 ($M^+ - C_8H_{10}N$), 120 ($C_8H_{10}N^+$). Anal. ($C_{16}H_{17}F_3N_6 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

9-(4-Acetamidobenzyl)-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (24). Acetic anhydride (0.13 mL, 1.35 mmol) was added to a magnetically stirred solution of **21** (0.350 g, 1.04 mmol), 4-(dimethylamino)pyridine (0.148 g, 1.20 mmol), and dichloromethane (5 mL). After 1 h the reaction was diluted with dichloromethane (30 mL) and washed with water (25 mL) and saturated sodium bicarbonate (25 mL). The organic phase was washed with brine (25 mL), dried (sodium sulfate), and concentrated under reduced pressure to give a white solid. The solid was recrystallized from hexane–ethyl acetate to give analytically pure **24**: mp 206–207 °C; TLC-SG, ethyl acetate, one spot with R_f = 0.39; MS, m/e 378 (M^+), 230 ($M^+ - C_9H_{10}NO$), 148 ($C_9H_{10}NO^+$), 106 ($C_7H_8N^+$). Anal. ($C_{17}H_{17}F_3N_6O$) C, H, N.

9-(3-Carboxybenzyl)-6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine (31). A mixture of **30** (0.368 g, 0.970 mmol), 1 N sodium hydroxide (7 mL, 7 mmol), and methanol (20 mL) was magnetically stirred for 5 h. The volatiles were removed by spin evaporation in vacuo, and the residual mixture (2 mL) was diluted with 1 N hydrochloric acid (10 mL). The resultant mixture was extracted with ethyl acetate (25 mL), and the extract was washed with water (25 mL) and brine (25 mL) and dried (sodium sulfate). The volatiles were removed under reduced pressure, and the residue was recrystallized from ethyl acetate–hexane to give 0.163 g (46%) of analytically pure **31**: mp 202–203 °C; TLC-SG, methanol–dichloromethane (1:9), one spot with R_f = 0.38; NMR (DMSO-d_6) δ 12.77 (br s, 1 H, CO_2H), 8.44 (s, 1 H, H-8), 7.3–7.9 (m, 4 H, ArH), 5.52 (s, 2 H, CH_2), 3.51 [s, 6 H, $N(CH_3)_2$]; MS, m/e 365 (M^+), 336 ($M^+ - 29$), 230 ($M^+ - C_8H_7O_2$), 135 ($C_8H_7O_2^+$). Anal. ($C_{16}H_{14}F_3N_5O_2$) C, H, N.

1,9-Dihydro-2-(trifluoromethyl)-6*H*-purin-6-one (67). A mixture of 5-aminoimidazole-4-carboxamide hydrochloride (25.0 g, 0.154 mol) and trifluoroacetamide (174 g, 1.54 mol) was refluxed with stirring on an oil bath (170–180 °C) for 3 h. The reaction was cooled to ambient temperature, and ether (500 mL) was added with stirring to disperse the solid cake. The ether was decanted, and the residual solid was covered with ether (300 mL) and triturated. This was repeated four times to give a uniform solid that was stirred in ether for 2 h and collected by suction filtration. The solid was dispersed in water (2.6 L), stirred for 1 h, and collected by suction filtration. The aqueous filtrate was evaporated to dryness under aspirator vacuum. The residual solids were recrystallized from methanol (1.6 L) by using decolorizing carbon to give two crops of material, 15.0 g (48%). A portion of this material (1.0 g) was recrystallized from methanol to give 0.745 g of the analytically pure product: mp 331–332.5 °C (lit.[4] mp 324–326 °C dec); TLC-SG, methanol–dichloromethane (2:8), one spot with R_f = 0.27; NMR (DMSO-d_6) δ 11.7 (br s, 2 H, NH), 8.40 (s, 1 H, H-8); MS, m/e 204 (M^+), 185 ($M^+ - F$), 135 ($M^+ - CF_3$). Anal. ($C_6H_3F_3N_4O$) C, H, N.

3,4-Dimethylbenzyl Chloride (68). Thionyl chloride (2 mL) was added to a stirred solution of 3,4-dimethylbenzyl alcohol (1.86 g, 13.5 mmol) and toluene (20 mL). The solution was stirred at ambient temperature for 1.5 h, and the volatiles were removed by spin evaporation in vacuo. The residual oil was dissolved in dichloromethane and reevaporated to give 3,4-dimethylbenzyl chloride,[20] which was used without further purification.

4-Chloro-3-methoxybenzyl Alcohol (69). Sodium borohydride (2.21 g, 58.5 mmol) was added to a stirred solution of 4-chloro-3-methoxybenzaldehyde (2.00 g, 11.7 mmol) and absolute ethanol (25 mL). After 2 h the reaction was poured into ice–water (150 mL), and the pH was adjusted to 5 with glacial acetic acid. The aqueous mixture was extracted with ether (2 × 150 mL), and the combined extracts were washed with water (200 mL) and brine (200 mL) and dried (sodium sulfate). The ether solution was evaporated under reduced pressure. The residual oil was dissolved in dichloromethane and reevaporated to give 1.73 g (86%) of 4-chloro-3-methoxybenzyl alcohol[21] as an oil: NMR (DMSO-d_6) δ 6.6–7.3 (m, 3 H, ArH), 4.36 (s, 2 H, CH_2), 3.72 (s, 3 H, OCH_3).

4-Butylbenzoic Acid (71). A mixture of 4-butylbenzoyl chloride (17.6 g, 89.5 mmol), 1 N sodium hydroxide (90 mL, 90 mmol), and sodium hydroxide pellets (3.58 g, 89.5 mmol) was stirred for 10 min. Dichloromethane (50 mL) and tetrabutylammonium chloride (2.48 g, 8.92 mmol) were added, and the reaction was stirred at 10 °C for 15 min. The reaction was refluxed with stirring for 2 h and cooled, and additional sodium hydroxide pellets (28.6 g) were added. The exothermic reaction resulted in formation of a precipitate, which was dissolved in water–ether (500 mL:400 mL). The layers were separated, and the aqueous phase was acidified with 6 N hydrochloric acid. The aqueous mixture was extracted with ether (350 mL), and the extract was washed with water (350 mL) and dried (magnesium sulfate). The ether was evaporated to dryness under reduced pressure to give 7.80 g (48%) of 4-butylbenzoic acid:[9] NMR (DMSO-d_6) δ 12.7 (br s, 1 H, CO_2H), 7.50 (m, 4 H, ArH), 2.57 (t, 2 H, CH_2Ar), 0.6–1.8 (m, 7 H, $CH_2CH_2CH_3$).

Ethyl 4-Isopropoxybenzoate (72). A stirred mixture of ethyl 4-hydroxybenzoate (50.0 g, 301 mmol), potassium carbonate (49.9 g, 361 mmol), and dry dimethylformamide (300 mL) was heated to 55 °C. 2-Bromopropane (54.1 mL, 542 mmol) was added to the mixture after 0.5 h, and the reaction was heated to 75 °C. Additional 2-bromopropane (18 mL, 180 mmol) was added after 4 h, and the reaction was heated at 70 °C for 18 h. The reaction mixture was poured into ice–water (600 mL) with stirring and extracted with ether (2 × 600 mL). The combined ether phase was washed with 1 N sodium hydroxide (700 mL) and water (2 × 700 mL) and dried (magnesium sulfate). The organic extract was evaporated to dryness to give 51.3 g (82%) of ethyl 4-isopropoxybenzoate[22] as an oil: NMR (DMSO-d_6) δ 7.32 (AB q, 4

(20) Daniel, J. K.; Matthews, D. P.; Peet, N. P. U.S. Patent 4 328 244, 1982.
(21) Munavalli, S.; Bhat, G. A.; Viel, C. *Bull. Chim. Soc. Fr.* **1966**, 3311.
(22) Jones, B. *J. Chem. Soc.* **1935**, 1874.

H, ArH), 4.59 (m, 1 H, CH), 4.16 (q, 2 H, CH_2), 1.18 (t, 3 H, CH_3), 1.16 (d, 6 H, 2 × CH_3).

4-Isopropoxybenzyl Alcohol (73). Ethyl 4-isopropoxybenzoate (25.6 g, 123 mmol) was added dropwise over 30 min to a refluxing solution of Vitride (70% solution in toluene) (42 mL, 150 mmol) and toluene (100 mL). After 1 h additional Vitride (25 mL) and toluene (50 mL) were added. After 4 h additional Vitride (50 mL) was added, and the solution was refluxed for 2 h. The reaction was cooled to ambient temperature, added dropwise to 6 N hydrochloric acid (600 mL), and stirred for 16 h. Toluene (200 mL) was added with stirring, and the layers were separated. The aqueous phase was washed with toluene (150 mL), and the combined toluene extracts were washed with water (2 × 450 mL). The organic layer was filtered and concentrated to an oil under reduced pressure. The oil was dissolved in ethanol and reevaporated. The residual oil was dissolved in ethyl acetate and added to 50 g of silica gel 60. The volatiles were removed by spin evaporation in vacuo, and the residual solids were added to a column (7 cm × 18 cm) of silica gel 60 wetted with hexane. The column was eluted with ethyl acetate–hexane (1:30), and the appropriate fractions were combined and spin evaporated in vacuo to give 8.45 g (41%) of 4-isopropoxybenzyl alcohol:[23] NMR (DMSO-d_6) δ 6.94 (AB q, 4 H, ArH), 4.45 (m, 1 H, CH), 4.27 (s, 2 H, CH_2), 3.14 (s, 1 H, OH), 1.09 (d, 6 H, CH_3).

Acknowledgment. We thank Mr. C. J. Bradley and Mr. A. Emmerson for skilled technical assistance in determining the antiviral activities. Dr. B. S. Hurlbert and has staff provided some of the NMR. We acknowledge the assistance of Ms. T. Cozart, S. Paris, and D. Tabon in preparation of the manuscript and thank Mr. Allen Jones for proofreading the manuscript.

(23) Nakagawa, S.; Okajima, N.; Kitahaba, T.; Nishimura, K.; Fujita, T.; Nakajima, M. *Pestic. Biochem. Physiol.* **1982**, *17*, 243.

Nucleic Acid Related Compounds. 57. Synthesis, X-ray Crystal Structure, Lipophilic Partition Properties, and Antiretroviral Activities of Anomeric 3′-Azido-2′,3′-dideoxy-2,6-diaminopurine Ribosides[1]

Morris J. Robins,*[,†] Steven G. Wood,[†] N. Kent Dalley,[2,†] Piet Herdewijn,[‡] Jan Balzarini,[‡] and Erik De Clercq[‡]

Department of Chemistry, Brigham Young University, Provo, Utah 84602, and Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium. *Received January 9, 1989*

Trimethylsilyl triflate-catalyzed transfer glycosylation of 2,6-diacetamidopurine (**2**) with 3′-azido-3′-deoxythymidine (AZT, **1**) as donor followed by deprotection gave 2,6-diamino-9-(3-azido-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranosyl)purines (**3** and **4**) in low yields. Selective 2′-O-tosylation of 2,6-diamino-9-(β-D-ribofuranosyl)purine (2,6-diaminopurine riboside, DAPR, **5**) followed by our lithium triethylborohydride promoted 1,2-hydride rearrangement gave 2,6-diamino-9-(2-deoxy-β-D-*threo*-pentofuranosyl)purine (**7**). Tritylation of **7** followed by mesylation at O3′, deprotection, and displacement of the 3′-mesylate with azide provided a stereodefined synthesis of 2,6-diamino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)purine (AzddDAPR, **4**). X-ray crystallographic analysis of **4** showed two orientations of the azido group, but consistent conformational features in the remainder of the molecule. In contrast, two independent conformations have been found for AZT. The azido function confers enhanced lipophilicity, which could be expected to contribute significantly to nonselective transport across membranes. A large difference in the octanol/water partition coefficients of the α (**3**) and β (**4**) anomers was found. The β anomer (**4**) exerts potent inhibition of HIV-induced cytopathogenicity in human MT-4 cells (ED_{50}: 0.3 μM). This concentration is an order of magnitude lower than that required for ddDAPR, AzddAdo, and AzddGuo. Potent inhibition of Moloney sarcoma virus induced transformation of murine C3H cells by AzddDAPR (**4**) was also observed. The α anomer (**3**) had no observed antiviral activity.

The discovery that 3′-azido-3′-deoxythymidine (AZT, **1**) exerts potent inhibitory activity against the human immunodeficiency virus (HIV), considered to be the causitive agent for acquired immunodeficiency syndrome (AIDS), has stimulated extensive efforts in nucleoside chemistry and biomedical applications.[3] A number of pyrimidine[4,5a] and purine[5] nucleoside analogues with the 2′,3′-dideoxypentofuranosyl skeleton have been prepared and tested. This includes the parent 2′,3′-unsaturated-2′,3′-dideoxy- and 2′,3′-dideoxynucleosides as well as 2′- or 3′-substituted-2′,3′-dideoxynucleoside derivatives. Attachment of an electronegative substituent at C3′,[5a,b] or especially at C2′,[5b,c] enhances the stability of such acid-sensitive purine nucleosides at lower pH values. However, it also markedly reduces the antiviral selectivity relative to that of the parent dideoxynucleoside in most cases, except for substitution of the *pro-S* hydrogen at C3′ by azide.[5a,b]

We have reported potent anti-HIV activity and enzymatic deamination of 2,6-diamino-9-(2,3-dideoxy-β-D-

† Brigham Young University.
‡ Katholieke Universiteit Leuven.

(1) For the previous paper in this series see: Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* In press.
(2) To whom inquiries regarding X-ray crystallography should be addressed.
(3) (a) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096–7100. (b) *AIDS: Modern Concepts and Therapeutic Challenges*; Broder, S., Ed.; Marcel Dekker: New York, 1987.
(4) For example, see: (a) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915. (b) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162–167. (c) Lin, T.-S.; Chen, M. S.; McLaren, C.; Gao, Y.-S.; Ghazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1987**, *30*, 440–444. (d) Kim, C.-H.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. S. *J. Med. Chem.* **1987**, *30*, 862–866; (e) Lin, T.-S.; Guo, J.-Y.; Schinazi, R. F.; Chu, C. K.; Xiang, J.-N.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 336–340; and references cited therein.

0022-2623/89/1832-1763$01.50/0