111380-71-3; **6p**, 111380-39-3; **6p** (free base), 111380-72-4; **6q**, 111380-40-6; **6q** (free base), 111380-73-5; **7a**, 106689-40-1; **7b**, 106689-41-2; **9a**, 111380-45-1; **9b**, 111380-47-3; **11b**, 111380-48-4; **12a**, 111380-49-5; **13a**, 111380-50-8; **13b**, 111380-51-9; **14**, 111380-52-0; **15**, 111380-53-1; **16**, 111380-54-2; **17**, 111380-55-3; **18a**, 111380-56-4; **18b**, 111380-57-5; **18c**, 111380-58-6; **18d**, 111380-59-7; **18e**, 111380-42-8; **18e** (free base), 111380-41-7; **18f**, 111380-44-0; **18f** (free base), 111380-43-9; $H_2NCH_2CH(CH_3)CH_2N(CH_3)_2$, 6105-72-2; $H_2N(CH_2)_3N(CH_3)_2$, 109-55-7; $H_2N(CH_2)_2N(C_2H_5)_2$, 100-36-7; $H_2N(CH_2)_3N(CH_2)_4$, 23159-07-1; $H_2N(CH_2)_4N(C_2H_5)_2$, 27431-62-5; $H_2NCH_2CHOHCH_2N(C_2H_5)_2$, 6322-01-6; 4-methoxycyclohexanone, 13482-23-0.

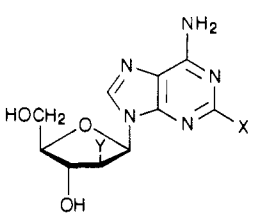
# Synthesis and Biological Evaluations of Certain 2-Halo-2′-Substituted Derivatives of 9-β-D-Arabinofuranosyladenine

John A. Secrist III,* Anita T. Shortnacy, and John A. Montgomery*

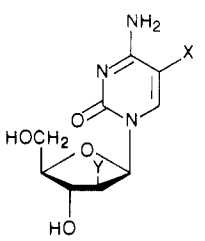
*Kettering-Meyer Laboratory, Southern Research Institute, P.O. Box 55305, Birmingham, Alabama 35255-5305.*
*Received July 8, 1987*

The synthesis of a series of 2-chloro- or 2-fluoro-9-(2-substituted-2-deoxy-β-D-arabinofuranosyl)adenines (**4g–n**) is described. New compounds were prepared from either 2-chloroadenosine or 2-fluoroadenosine by first blocking the 3′- and 5′-hydroxyls as the tetraisopropyldisiloxane derivatives. Activation of O-2′ by formation of a triflate followed by nucleophilic displacement allowed introduction of various groups in the proper configuration at C-2′. Fluoride ion treatment then produced the deblocked nucleosides. All of the new compounds were evaluated as cytotoxic agents against L1210 and H.Ep.-2 cells and as antiviral agents against herpes simplex viruses 1 and 2 and vaccinia virus in culture.

Certain arabinofuranosyl nucleosides have interesting and useful biological activities. Both 9-β-D-arabinofuranosyladenine (araA, **1a**)[1] and 1-β-D-arabinofuranosylcytosine (araC, **2a**)[2] are well known in the areas of viral and cancer chemotherapy, respectively. 9-β-D-




**1a**: X = H; Y = OH
**b**: X = F; Y = OH
**c**: X = H; Y = $N_3$




**2a**: X = H; Y = OH
**b**: X = I; Y = F

Arabinofuranosyl-2-fluoroadenine (2-F-araA, **1b**), administered as the 5′-monophosphate, has completed phase I clinical trials[3,4] and is presently in phase II trials as an anticancer agent,[5,6] and various other arabinofuranosyl nucleosides have received considerable attention. Certain arabinofuranosyl nucleosides with 2′-substituents other than a hydroxyl also have produced marked biological effects. Notable among these compounds are 9-(2-azido-2-deoxy-β-D-arabinofuranosyl)adenine (arazide, **1c**) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (FIAC, **2b**). Arazide has pronounced cytotoxicity in cell culture[7-10] and also has in vivo activity against the P388 mouse leukemia when administered with the potent adenosine deaminase inhibitor pentostatin (2′-deoxycoformycin).[7] This combination is superior to the araA–pentostatin combination on a once-a-day schedule for 6 days, resulting in a significant number of mice that were long-term survivors. Without the pentostatin, arazide did not result in a significant increase in the life span of the leukemic mice. The reduced effectiveness of arazide without pentostatin is presumably caused by a significant deamination of arazide by adenosine deaminase, even though arazide is much less susceptible to deamination than araA itself. Arazide triphosphate has been found to be an inhibitor of DNA polymerase *a*.[11,12] FIAC has in vitro[3,4] and in vivo[15,16] activity against herpes simplex viruses and shows some phase I clinical activity against immunosuppressed patients with herpes simplex virus infections.[15,17]

All of the nucleosides mentioned above require activation in order to exert their effects. Generally, the arabinofuranosyl nucleosides are primarily activated (phos-

(1) North, T. W.; Cohen, S. S. *Pharmacol. Ther.* **1979**, *4*, 81.
(2) Montgomery, J. A.; Johnston, T. P.; Shealy, Y. F. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1979; Part II, Chapter 24, p 611.
(3) Hutton, J. J.; Von Hoff, D. D.; Kuhn, J.; Phillips, J.; Hersh, M.; Clark, G. *Cancer Res.* **1984**, *44*, 4183.
(4) Leiby, J. M.; Grever, M. R.; Staubus, A. E.; Neidhart, J. A.; Malspeis, L. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 169.
(5) Mittelman, A.; Ashikari, R.; Ahmed, T.; Charuvanki, V.; Friedland, M.; Arlin, Z. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 170.
(6) Warrell, R. P., Jr.; Berman, E.; Gee, T. S.; Kempin, S. J. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 179.
(7) Lee, S. H.; Thomas, L. K.; Unger, F. M.; Christian, R.; Sartorelli, A. C. *Int. J. Cancer* **1981**, *27*, 703.
(8) Bobek, M.; Cheng, Y.-C.; Mihich, E.; Bloch, A. *Recent Results Cancer Res.* **1980**, *74*, 78.
(9) Lee, S. H.; Unger, F. M.; Christian, R.; Sartorelli, A. C. *Biochem. Pharmacol.* **1979**, *28*, 1267.
(10) Ranganathan, R.; Larwood, D. *Tetrahedron Lett.* **1978**, 4341.
(11) Allaudeen, H. S.; Kozarich, J. W.; Sartorelli, A. C. *Nucleic Acids Res.* **1982**, *10*, 1379.
(12) Yamaguchi, T.; Saneyoshi, M. *Nucleic Acids Symp. Ser.* **1982**, *11*, 153.
(13) Lopez, C.; Watanabe, K. A.; Fox, J. J. *Antimicrob. Agents Chemother.* **1980**, *17*, 803.
(14) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.
(15) Fox, J. J.; Watanabe, K. A.; Lopez, C.; Philips, F. S.; Leyland-Jones, B. In *Herpesvirus. Clinical, Pharmacological, and Basic Aspects*; Shiota, H., Cheng, Y. C., Prusoff, W. H., Eds.; Excerpta Medica: Amsterdam, 1982; p 135.
(16) Fox, J. J.; Lopez, C.; Watanabe, K. A. *Medicinal Chemistry Advances*; De Las Heras, F. G., Ed.; Pergamon: New York, 1981; p 27.
(17) Young, C.; Jones, B.; Schneider, R.; Armstrong, D.; Tan, C.; Lopez, C.; Watanabe, K.; Fox, J.; Philips, F. *Proc. Am. Assoc. Cancer* Res. **1981**, *22*, 165.

0022-2623/88/1831-0405$01.50/0 

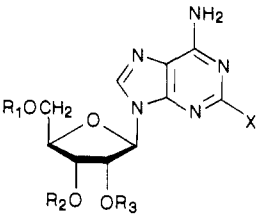
phorylated) by different enzymes than the corresponding ribofuranosyl nucleosides. For example, araA, 2-F-araA, and araC are mainly activated by deoxypyrimidine kinase.[1,18] FIAC is phosphorylated by the virus-specific thymidine kinase of HSV-1.[13] Arazide appears to be an exception to this generalization, because a CCRF-CEM cell line deficient in adenosine kinase is 60-fold more resistant to the arazide–pentostatin combination than a CCRF-CEM line deficient in deoxycytidine kinase. This latter line is only 1.4 times more resistant to the combination than the standard CCRF-CEM cells.[19]

Significant alterations in the metabolism of adenine nucleosides can be effected by incorporating a 2-halo substituent onto the purine ring. Among other effects, such a change significantly reduces the ability of the compound to serve as a substrate for adenosine deaminase relative to the parent compound.[20] In addition to 2-F-araA, 2-bromo-, 2-chloro-, and 2-fluoro-2′-deoxyadenosine, all of which are curative in the L1210 mouse leukemia and other systems on the proper schedule, are examples of useful compounds resulting from such a modification.[21,22]

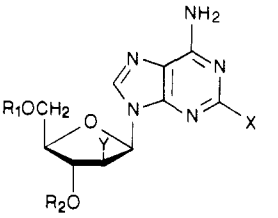
Two of the metabolites identified in animals treated with 2-F-araA phosphate, 2-fluoroadenine and 2-fluoro-ATP, are formed presumably as a result of phosphorylase action on 2-F-araA.[23,24] The initial cleavage product is 2-fluoroadenine, which is then metabolized to the triphosphate of 2-fluoroadenosine, a compound with considerable toxicity but no anticancer activity. Because 2-F-araA is a substrate for *Escherichia coli* purine nucleoside phosphorylase, it seems likely that this enzyme is responsible for the cleavage observed in animals.[25] Substitution of a fluorine or azido group at C-2′ of an inosine derivative while retaining the arabino configuration is known to make these derivatives highly resistant to phosphorolytic cleavage.[26]

On the basis of the foregoing information, we have embarked upon a program of synthesis and biological evaluation of arabinofuranosyl nucleosides with a 2′-substituent other than a hydroxyl and with variously substituted purine rings. This paper presents the results of our investigations of such compounds with either a 2-fluoro or 2-chloropurine heterocyclic ring, and azido, amino, chloro, bromo, and iodo groups at C-2′.

**Chemistry.** Our syntheses of the target structures (**4g–n**) were based upon the selective protection of the 3′- and 5′-hydroxyls of the readily available 2-chloroadenosine (**3a**)[27] and 2-fluoroadenosine (**3d**).[28] Treatment of **3a** or **3d** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[29,30]



**3a**: X = Cl; $R_1 = R_2 = R_3 = H$
**b**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; $R_3 = H$
**c**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; $R_3 = SO_2CF_3$
**d**: X = F; $R_1 = R_2 = R_3 = H$
**e**: X = F; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; $R_3 = H$
**f**: X = F; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; $R_3 = SO_2CF_3$



**4a**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = $N_3$
**b**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = Cl
**c**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = Br
**d**: X = Cl; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = I
**e**: X = F; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = $N_3$
**f**: X = F; $R_1, R_2 = Si(i\text{-}Pr)_2OSi(i\text{-}Pr)_2$; Y = Cl
**g**: X = Cl; $R_1 = R_2 = H$; Y = $N_3$
**h**: X = Cl; $R_1 = R_2 = H$; Y = Cl
**i**: X = Cl; $R_1 = R_2 = H$; Y = Br
**j**: X = Cl; $R_1 = R_2 = H$; Y = I
**k**: X = Cl; $R_1 = R_2 = H$; Y = $NH_2$
**l**: X = F; $R_1 = R_2 = H$; Y = $N_3$
**m**: X = F; $R_1 = R_2 = H$; Y = Cl
**n**: X = F; $R_1 = R_2 = H$; Y = $NH_2$

produced the 3′,5′-substituted compounds **3b** and **3e**. Both compounds were converted into their corresponding 2′-*O*-triflates **3c** and **3f** with trifluoromethanesulfonyl chloride in the presence of 4-(dimethylamino)pyridine.[30] Displacement of the triflate in **3c** was carried out with lithium azide, lithium chloride, lithium bromide, and lithium iodide to afford **4a–d**.[30] Comparable displacements on **3f** with lithium azide and lithium chloride gave **4e** and **4f**. Removal of the silyl protecting group in **4a**, **4b**, **4e**, and **4f** proceeded smoothly by treatment with 1 M tetra-*n*-butylammonium fluoride in THF at room temperature, affording target structures **4g**, 4h, **4l**, and 4m in good yields. Identical treatment of **4c** and **4d**, however, resulted in competing elimination of HX and 2′,3′-epoxide formation. Conducting the desilylation reaction at −20 °C for these two compounds, followed by the addition of acetic acid prior to processing, allowed good yields of both **4i** and **4j** to be obtained without interference from these side reactions. Catalytic reduction of the azido function in **4g** and **4l** in the presence of platinum on charcoal produced the two amino compounds **4k** and **4n**.

**Biological Evaluation.** All of the target compounds were evaluated for their cytotoxicities toward L1210 and H.Ep.-2 cells in culture (see Table I). The 2-chloroadenine nucleosides exhibited little or no cytotoxicity up to the highest levels tested, while the 2-fluoroadenine nucleosides showed some cytotoxicity in both systems, though the cytotoxicity is more pronounced in the colony-counting assay with H.Ep.-2 cells. The most cytotoxic compound against the H.Ep.-2 cell line was the 2-fluoro-2′-amino compound **4n**. Given the cytotoxicity of arazide mentioned

(18) Brockman, R. W.; Cheng, Y.-C.; Schabel, F. M., Jr.; Montgomery, J. A. *Cancer Res.* **1980**, *40*, 3610.
(19) Verhoef, V. L.; Fridland, A. In *Rational Basis for Chemotherapy*; Chabner, B. A., Ed.; Alan R. Liss: New York, 1983, p 261.
(20) Bennett, L. L., Jr.; Chang, C.-H.; Allan, P. W.; Adamson, D. J.; Rose, L. M.; Brockman, R. W.; Secrist, J. A., III; Shortnacy, A.; Montgomery, J. A. *Nucleosides Nucleotides* **1985**, *4*, 107.
(21) Carson, D. A.; Wasson, D. B.; Kaye, J.; Ullman, B.; Martin, D. W., Jr.; Robins, R. K.; Montgomery, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6865.
(22) Huang, M.-C.; Avery, T. L.; Blakley, R. L.; Secrist J. A., III; Montgomery, J. A. *J. Med. Chem.* **1984**, *27*, 800.
(23) Avramis, V. I.; Plunkett, W. *Cancer Drug Delivery* **1983**, *1*, 1.
(24) Noker, P. E.; Duncan, G. F.; El Dareer, S. M.; Hill, D. L. *Cancer Treat. Rep.* **1983**, *67*, 445.
(25) Huang, P.; Plunkett, W. *Biochem. Pharmacol.* **1987**, *36*, 2945.
(26) Stoeckler, J. D.; Bell, C. A.; Parks, R. E., Jr.; Chu, C. K.; Fox, J. J.; Ikehara, M. *Biochem. Pharmacol.* **1982**, *31*, 1723.
(27) Montgomery, J. A.; Hewson, K. *J. Heterocycl. Chem.* **1964**, *1*, 213.
(28) Montgomery, J. A.; Hewson, K. *J. Org. Chem.* **1968**, *33*, 432.
(29) Markiewicz, W. T. *J. Chem. Res. Miniprint* **1979**, 181.
(30) Fukukawa, K.; Uedao, T.; Hirano, T. *Chem. Pharm. Bull.* **1983**, *31*, 1582.
(31) Thayer, P. S.; Himmelfarb, P.; Watts, G. L. *Cancer Chemother. Rep., Part 2* **1971**, *2*, 1.
(32) Ehrlich, J.; Sloan, B. J.; Miller, F. A.; Machamer, H. E. *Ann. N. Y. Acad. Sci.* **1965**, *130*, 5.

**Table I.** Cytotoxicity and Antiviral Data

| compd | 2 substit | 2′ substit | L1210 cells: $IC_{50}$, μM[a] | H.Ep. No. 2 cells: $IC_{50}$, μM[b] | vaccinia virus (Lederle CA/in L929 cells) VR[c] | vaccinia virus (Lederle CA/in L929 cells) $MIC_{50}$[d] |
|---|---|---|---|---|---|---|
| **4g** | Cl | $N_3$ | >120[e] | >120[e] | 0.8 | 187 |
| **4h** | Cl | Cl | >120[e] | >120[e] | 0.7 | 83 |
| 4i | Cl | Br | >110[e] | >110[e] | 0.4 | |
| **4j** | Cl | I | >100[e] | >100[e] | 0 | |
| **4k** | Cl | $NH_2$ | >120[f] | 80 | 0.6 | *g* |
| 4l | F | $N_3$ | 100 | 29 | 2.4 | 14 |
| **4m** | F | Cl | 60 | 100 | 0.6 | 75 |
| **4n** | F | $NH_2$ | 120 | 12 | 0.7 | 68 |

[a] Our procedure is based upon that of Thayer et al.[31] in which rapidly growing L1210 cells in suspension culture are exposed to a range of concentrations of inhibitor, and the reduction in the rate of proliferation of treated cells relative to control cells is determined by means of cell counts 24 and 48 h after addition of the inhibitor. The concentration of inhibitor required to produce a 50% reduction in the rate of cell proliferation is designated $IC_{50}$. [b] $IC_{50}$ is the concentration that produces a 50% inhibition of cloning of H.Ep. No. 2 cells over a 12-day period relative to growth in the controls. [c] VR = virus rating: A measurement of selective antiviral activity which takes into account the degree of inhibition of virus-induced cytopathogenic effects (CPE) and the degree of cytotoxicity produced by the test compound, determined by a modification of the method of Ehrlich et al.[32] In our experience, a VR ≥1.0 indicates definite (+) antiviral activity, a VR of 0.5–0.9 indicates marginal to moderate (±) antiviral activity, and a VR < 0.5 usually indicates no (–) significant antiviral activity. [d] $MIC_{50}$ = minimum inhibitory concentration required for 50% inhibition of virus-induced CPE (in μg/mL). [e] No significant inhibition at the highest level tested. [f] Only slight inhibition at the highest level tested. [g] CPE reduction <50%.

in the introduction, the relatively modest cytotoxicity of **4l** is surprising. In order to determine whether or not **4l–n** are activated in the same manner as arazide, these compounds were examined in several mutant L1210 cell lines by utilizing soft agar cloning and a colony-counting assay.[33,34] Three cell lines were compared with the parent L1210/0 line. One line lacked adenosine kinase, one lacked deoxycytidine kinase, and one lacked both enzymes. The $IC_{50}$ values for all L1210/0 with **4l–n** were in the 65–80 μM range. With all of the mutant lines, the $IC_{50}$ values for all three compounds were in the 80–150 μM range. These relatively small differences suggest that the modest cytotoxicity seen with these compounds is not based upon phosphorylation by either deoxycytidine kinase or adenosine kinase. Neither **4l** nor **4n** exhibited any in vivo activity against the P388 mouse leukemia on a qd 1–5 schedule at doses up to 100 mg/kg. Compounds **4g–n** were examined against herpes simplex virus type 1 (E-377) and herpes simplex virus type 2 (MS) in Vero cell monolayers, and none of the compounds exhibited any antiviral activity. Against vaccinia virus in L929 cells marginal activity was observed with **4g**, **4h**, **4k**, 4m, and **4n**, and good activity was seen with azido compound **4l** (see Table I).

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Nicolet NMC 300NB spectrometer operating at 300.635 MHz for $^1H$ and 75.6 MHz for $^{13}C$ or on a Varian XL-100-15 spectrometer operating at 100.1 MHz for $^1H$ and 25.16 MHz for $^{13}C$. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and by the Molecular Spectroscopy Section of Southern Research Institute. Mass spectra were recorded on a Varian MAT 311A mass spectrometer in the fast atom bombardment (FAB) mode. Ultraviolet absorption spectra were recorded with a Cary 17 spectrophotometer. Each compound was dissolved in dimethyl sulfoxide and diluted 10-fold with 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH. Numbers in parentheses are extinction coefficients (ε × $10^{-3}$), sh = shoulder. HPLC analyses were carried out with a Hewlett-Packard HP 1084B liquid chromatograph with a Waters Associates μBondapak $C_{18}$ column (3.9 mm × 30 cm) with UV monitoring (254 nm). All flash column chromatography used 230–400-mesh silica gel from E. Merck.

**2-Chloro-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (3b).** A solution of 2-chloroadenosine (**3a**; 2 g, 6.63 mmol) in 60 mL of pyridine was treated at room temperature with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.3 g, 7.3 mmol). After the mixture was stirred for 1 h, the reaction was essentially complete as indicated by TLC. At 3 h, the reaction mixture was poured into an ice–water mixture, stirred for 15 min, and then diluted with 200 mL of $CHCl_3$ to give a total volume of 800 mL. The aqueous layer was extracted with $CHCl_3$ (2 × 100 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, and evaporated to dryness. The residue was coevaporated with toluene to remove pyridine and crystallized from EtOH to give crude **3b**, 4.1 g. This solid was recrystallized from EtOH to give 2.5 g (69%) of pure **3b**, mp 203–205 °C. The filtrate was purified on a flash column containing 50 g of silica gel and eluted with $CHCl_3$: yield 425 mg (12%); TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.50; MS, $z/e$ 544 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.09 (m, 28, 4 $CH(CH_3)_2$), 3.65 (d, 1, OH, $J$ = 2 Hz), 4.0–4.2 (m, 3, H-4′, 2 H-5′), 4.60 (m, 1, H-2′), 5.01 (m, 1, H-3′), 5.94 (s, 1 H-1′), 6.49 (br s, 2, $NH_2$), 7.96 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 12.72, 12.76, 13.13, 13.30 ($CH(CH_3)_2$), 17.00, 17.06, 17.08, 17.28, 17.34, 17.37, 17.50 ($CH(CH_3)_2$), 62.39 (C-5′), 71.52, 75.18 (C-2′, C-3′), 82.37, 89.84 (C-1′, C-4′), 119.30 (C-5), 140.08 (C-8), 150.20 (C-4), 154.32 (C-2), 156.40 (C-6). Anal. ($C_{22}H_{38}ClN_5O_5Si_2 \cdot 0.4C_2H_5OH$) C, H, N.

**2-Chloro-2′-*O*-[(trifluoromethyl)sulfonyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (3c).** A solution of **3b** (2.5 g, 4.59 mmol) in 85 mL of sieve-dried $CH_2Cl_2$ was treated with triethylamine (695 μL, 4.98 mmol) and 4-(dimethylamino)pyridine (553 mg, 4.53 mmol) and chilled in an ice bath. To the stirred solution was added trifluoromethanesulfonyl chloride (530 μL, 4.98 mmol) by syringe. The cooling bath was removed, and the reaction was allowed to stir 1.5 h. By TLC (95:5 $CHCl_3$–MeOH, $R_f$ 0.60), the reaction was ~75% complete. Additional trifluoromethanesulfonyl chloride (145 μL, 1.36 mmol) was added in two portions over the next 3 h with cooling prior to the addition. After being stirred at room temperature for 16 h, the reaction mixture was poured into ice water (1 L), stirred for 0.5 h, and then diluted with $CHCl_3$ (300 mL). The layers were separated, and the aqueous layer was extracted with more $CHCl_3$ (2 × 225 mL and then 100 mL). The combined organic layer was washed with water (3 × 200 mL), dried ($MgSO_4$), and evaporated to dryness. This residue was dissolved in 2:1 cyclohexane–ethyl acetate and applied to a flash column containing 100 g of silica gel. The column was eluted with 2:1 cyclohexane–ethyl acetate, and appropriate fractions were combined and evaporated to give essentially pure **3c**: yield 2.9 g (93%); MS, $z/e$ 676 $(M + 1)^+$; exact mass calcd 676.167, found 676.170; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.08 (m, 28, $CH(CH_3)_2$), 4.02–4.24 (m, 3, H-4′, 2 H-5′), 5.10 (dd, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 9 Hz, H-3′), 5.72 (d, 1 H-2′), 6.09 (s, 1, H-1′), 6.46 (br s, 2, $NH_2$), 7.95 (s, 1, H-8); $^{13}C$ NMR (300 MHz) δ 12.80, 12.91, 12.96, 13.24 ($CH(CH_3)_2$), 16.74, 16.80, 16.88, 16.92, 17.25,

(33) Alexander, J. A.; Bowdon, B. J.; Wheeler, G. P. *Cancer Res.* 1986, *46*, 6024.
(34) Bennett, L. L., Jr.; Bowdon, B. J.; Allan, P. W.; Rose, L. M. *Biochem. Pharmacol.* 1986, *35*, 4106.

17.30, 17.41 ($CH(CH_3)_2$), 59.86 (C-5′), 68.49 (C-3′), 81.56 (C-4′), 86.97 (C-2′), 88.02 (C-1′), 112.91, 116.43, 120.65, 124.88 (q, $CF_3$), 119.13 (C-5), 139.33 (C-8), 149.85 (C-4), 154.68 (C-2), 156.33 (C-6).

**2-Fluoro-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (3e).** A solution of 2-fluoroadenosine (**3d**; 7.1 g, 25 mmol) and imidazole (7.5 g, 110 mmol) in 70 mL of dry dimethylformamide was treated at room temperature with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (8.67 g, 27.5 mmol). After the mixture was stirred for 1 h, the reaction was essentially complete as indicated by TLC. At 2 h, the reaction was poured into 2.5 L of ice water and stirred for 3 h, and the solid was collected, washed with cold water, and dried in vacuo at 56 °C to give crude **3e**, 17.5 g. This solid in $CHCl_3$ was purified by flash chromatography (26 g of silica gel/g) with $CHCl_3$ as eluant and then 98:2 $CHCl_3$–MeOH to give essentially pure **3e**, yield 4.0 g (30%). Crystallization of a small sample from acetonitrile gave pure **3e**: mp 205–208 °C; TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.46; MS, $z/e$ 528 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.08 (m, 28, $CH(CH_3)_2$), 3.46 (br s, 1, 2′-OH, $J_{2',OH}$ = 1.7 Hz), 4.02–4.16 (m, 3, H-4′, 2 H-5′), 4.58 (d, 1, $J_{2',3'}$ = 5.5 Hz, H-2′), 5.05 (dd, 1, $J_{3',4'}$ = 7.6 Hz, H-3′), 5.95 (d, 1, H-1′, $J_{1',2'}$ = 1.2 Hz), 6.38 (br s, 2, $NH_2$), 7.92 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 300 MHz) $\delta$ 12.65, 12.74, 13.08, 13.24 ($CH(CH_3)_2$), 16.94, 16.99, 17.01, 17.13, 17.30, 17.47 ($CH(CH_3)_2$), 61.91 (C-5′), 70.98, 74.96 (C-2′,3′), 82.21 (C-4′), 89.65 (C-1′, $J_{C\text{-}1',H\text{-}1'}$ = 167.1 Hz), 118.55 (C-5, $J_{5,F}$ = 4.2 Hz), 139.85 (d, C-8, $J_{8,F}$ = 2.3 Hz), 150.46 (C-4, $J_{4,F}$ = 19.6 Hz), 157.49 (d, C-6, $J_{6,F}$ = 20.1 Hz), 159.03 (d, C-2, $J_{2,F}$ = 211.5 Hz). Anal. ($C_{22}H_{38}FN_5O_5Si_2 \cdot 0.3H_2O$) C, H, N.

**2-Fluoro-2′-*O*-[(trifluoromethyl)sulfonyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (3f).** A solution of **3e** (4.26 g, 8.08 mmol) in 145 mL of sieve-dried $CH_2Cl_2$ was treated with triethylamine (1.24 mL, 8.9 mmol) and 4-(dimethylamino)pyridine (988 mg, 8.08 mmol). To this solution at 0 °C was added trifluoromethanesulfonyl chloride (0.95 mL, 8.9 mmol) in one portion by syringe. After the mixture was stirred at room temperature for 4 h, the reaction was essentially complete. The solution was poured into ice water (2 L) and stirred for 0.5 h, and then $CHCl_3$ (500 mL) was added. The layers were separated, and the aqueous layer was extracted with additional $CHCl_3$ (2 × 250 mL, 200 mL). The combined organic extracts were washed with water (2 × 250 mL), dried ($MgSO_4$), and evaporated to dryness. This residue in $CHCl_3$ was applied to a flash column containing 150 g of silica gel with $CHCl_3$ as eluant. Fractions were combined to give essentially pure **3f**, 4.4 g (83%). A small sample crystallized from $CHCl_3$: mp 175 °C dec; TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.50; MS, $z/e$ 660 (M + 1); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 0.95–1.15 (m, 28, $CH(CH_3)_2$), 3.94–4.14 (m, 3, H-4′, 2 H-5′), 5.23 (dd, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 10 Hz, H-3′), 6.03 (d, 1 H-2′), 6.43 (s, 1, H-1′), 7.97 (v br s, 2, $NH_2$), 8.22 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 12.06, 12.21, 12.28, 12.50 ($CH(CH_3)_2$), 16.52, 16.58, 16.90, 16.98, 17.01, 17.16 ($CH(CH_3)_2$), 59.76 (C-5′), 68.37 (C-3′), 80.26 (C-4′), 85.38 (C-2′), 89.14 (C-1′), 117.60 (d, C-5, $J_{5,F}$ = 4.0 Hz), 117.95 (q, $CF_3$, $J_{CF}$ = 319.4 Hz), 139.96 (d, C-8, $J_{8,F}$ = 2.1 Hz), 149.65 (d, C-4, $J_{4,F}$ = 19.9 Hz), 157.67 (d, C-6, $J_{6,F}$ = 21.2 Hz), 158.44 (d, C-2, $J_{2,F}$ = 205.8 Hz). Anal. ($C_{23}H_{37}F_4N_5O_7SSi_2$) C, H, N.

**2-Chloro-9-[2-azido-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4a).** A solution of **3c** (800 mg, 1.18 mmol) in 5 mL of hexamethylphosphoramide was treated with $LiN_3$ (115 mg, 2.36 mmol) and stirred at room temperature while protected from moisture. A 2-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) indicated complete reaction. The solution was poured into ice water (300 mL) and stirred for 0.5 h. The white solid was collected, washed with water, and dried in vacuo at room temperature to give crude **4a**, 628 mg. This solid in $CHCl_3$ was applied to a flash column containing 30 g of silica gel. The column was eluted with $CHCl_3$, and the pure fractions were combined and crystallized from EtOH to give pure **4a**: yield 373 mg (55%); mp 196–197 °C. The filtrate was plated on silica gel thick plates (Analtech GF, 2000 μm) in 95:5 $CHCl_3$–MeOH to yield more material (85 mg, 13%): TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.60; MS, $z/e$ 569 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 100 MHz) $\delta$ 1.0–1.2 (m, 28, $CH(CH_3)_2$), 3.85–4.2 (m, 3, H-4′, 2 H-5′), 4.35–4.7 (m, 2, H-2′, 3′), 6.40 (d, 1, $J$ = 6 Hz, H-1′), 6.48 (br s, 2, $NH_2$), 8.05 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 12.64, 13.02, 13.07, 13.59 ($CH(CH_3)_2$), 16.86, 16.91, 17.01, 17.33, 17.40, 17.47 ($CH(CH_3)_2$), 60.96 (C-5′), 68.17, 73.44 (C-2′,3′), 82.06, 82.15 (C-1′,4′), 118.59 (C-5), 139.27 (C-8), 150.95 (C-4), 154.35 (C-2), 156.38 (C-6). Anal. ($C_{22}H_{37}ClN_8O_4Si_2$) C, H, N.

**2-Chloro-9-[2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4b).** A solution of **3c** (676 mg, 1 mmol) in 4 mL hexamethylphosphoramide was treated with dry LiCl (85 mg, 2 mmol) and stirred at room temperature while protected from moisture. A 5-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) showed complete reaction. The solution was poured into ice water (200 mL), stirred 15 min, and refrigerated overnight. The white solid that precipitated was collected, washed with cold water, and dried in vacuo at room temperature to give crude **4b**, 576 mg. This solid in $CHCl_3$ was filtered to remove 2-chloroadenine (30 mg). The filtrate was applied to two silica gel thick plates (Analtech, GF, 2000 μm) that were developed in 95:5 $CHCl_3$–MeOH. The extracted product was crystallized from EtOH to give pure **4b**: yield 218 mg (39%); mp 206–207 °C; TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.60; MS, $z/e$ 562 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.0–1.2 (m, 28, $CH(CH_3)_2$), 3.92 (m, 1, H-4′), 4.09, 4.21 (2 dd, 2, $J$ = 3 Hz, $J$ = 13 Hz, 2 H-5′), 4.65 (dd, 1, $J_{1',2'}$ = 6 Hz, $J_{2',3'}$ = 8 Hz, H-2′), 4.74 (apparent t, 1, $J_{3',4'}$ = 8 Hz, H-3′), 6.45 (d, 1, H-1′), 6.49 (br s, 2, $NH_2$), 8.11 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 12.53, 12.99, 13.11, 13.61 ($CH(CH_3)_2$), 16.98, 17.32, 17.36, 17.40, 17.48 ($CH(CH_3)_2$), 61.49 (C-5′), 62.98 (C-2′), 76.22 (C-3′), 82.86, 83.06 (C-1′,4′), 118.46 (C-5), 139.41 (C-8, $J_{C\text{-}8,H\text{-}1'}$ = 3 Hz), 150.95 (C-4), 154.31 (C-2), 156.37 (C-6). Anal. ($C_{22}H_{37}Cl_2N_5O_4Si_2$) C, H, N.

**2-Chloro-9-[2-bromo-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4c).** A solution of **3c** (500 mg, 0.74 mmol) in 3 mL of hexamethylphosphoramide was treated with dry LiBr (133 mg, 1.53 mmol) and stirred at room temperature while protected from moisture. A 5-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) showed complete reaction. The reaction was poured into ice water (200 mL), stirred 15 min, and refrigerated overnight. The white solid that precipitated was collected, washed with cold water, and dried in vacuo at room temperature to give crude **4c**, 440 mg. This material in $CHCl_3$ was applied to a flash column containing 25 g of silica gel. The column was eluted with $CHCl_3$, the pure fractions were combined and crystallized from boiling EtOH, and the solid was dried in vacuo at room temperature to give pure **4c**: yield 295 mg (66%); mp 198–200 °C. The filtrate was applied to two silica gel thick plates (Analtech, GF, 1000 μm), which were developed in 95:5 $CHCl_3$–MeOH, and the product was extracted and crystallized from EtOH to give more material: yield 15 mg (3%); TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.60; MS, $z/e$ 606 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.0–1.2 (m, 28, $CH(CH_3)_2$), 3.91 (m, 1, H-4′), 4.10, 4.23 (2 dd, 2, $J$ = 3 Hz, $J$ = 13 Hz, 2 H-5′), 4.67 (dd, 1, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 8.5 Hz, H-2′), 4.84 (apparent t, 1, $J_{3',4'}$ = 8 Hz, H-3′), 6.40 (s, 1, H-1′), 6.46 (br s, 2, $NH_2$), 8.11 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 12.55, 12.97, 13.12, 13.71 ($CH(CH_3)_2$), 17.08, 17.32, 17.37, 17.40, 17.47 ($CH(CH_3)_2$), 53.60 (C-2′), 61.51 (C-5′), 76.38 (C-3′), 83.08, 83.51 (C-1′,4′), 118.50 (C-5), 139.21 (C-8), 150.90 (C-4), 154.29 (C-2), 156.41 (C-6). Anal. ($C_{22}H_{37}BrClN_5O_4Si_2$) C, H, N.

**2-Chloro-9-[2-deoxy-2-iodo-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4d).** A solution of **3c** (500 mg, 0.74 mmol) in 3 mL of hexamethylphosphoramide was treated with LiI (205 mg, 1.5 mmol) and stirred at room temperature while protected from moisture. A 48-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) indicated complete reaction. The dark-red solution was poured into ice water (200 mL), and the resulting suspended solid was isolated by centrifugation, washed with cold water, collected by filtration, and dried in vacuo at room temperature to give crude **4d**, 455 mg. This solid in $CHCl_3$ was applied to a flash column containing 30 g of silica gel. The column was eluted with $CHCl_3$, and pure fractions were combined and crystallized from EtOH to give pure **4d**: yield 347 mg (72%); mp 170–171 °C; TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.61; MS, $z/e$ 654 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.0–1.25 (m, 28, $CH(CH_3)_2$), 3.87 (m, 1, H-4′), 4.10, 4.24 (2 dd, 2, $J$ = 3.5 Hz, $J$ = 13 Hz, 2 H-5′), 4.71 (dd, 1, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 9.5 Hz, H-2′), 4.92 (apparent t, 1, $J_{3',4'}$ = 8 Hz, H-3′), 6.24 (d, 1, H-1′), 6.30 (br s, 2, $NH_2$), 8.08 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 12.61, 12.92, 13.11, 13.88

($CH(CH_3)_2$), 17.04, 17.09, 17.25, 17.31, 17.38, 17.47 ($CH(CH_3)_2$), 30.60 (C-2'), 61.42 (C-5'), 77.37 (C-3'), 83.99, 84.41 (C-1',4'), 118.65 (C-5), 138.90 (C-8), 150.84 (C-4), 154.28 (C-2), 156.36 (C-6). Anal. ($C_{22}H_{37}ClIN_5O_4Si_2$) C, H, N.

**2-Fluoro-9-[2-azido-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4e).** A solution of **3f** (4.45 g, 6.74 mmol) in 28 mL of hexamethylphosphoramide was treated with $LiN_3$ (660 mg, 13.5 mmol) and stirred at room temperature while protected from moisture. A 2.5-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) indicated complete reaction. The reaction was poured into ice water (1.25 L) and stirred for 1 h, and the white solid was collected, washed with cold water, and dried in vacuo at room temperature to give crude **4e**, 3.82 g. This solid in $CHCl_3$ was applied to a flash column containing 150 g of silica gel. The column was eluted with $CHCl_3$, and the pure fractions were combined and crystallized from EtOH to give pure **4e**: yield 2.02 g (54%); mp 195–198 °C dec; TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.52; MS, $z/e$ 553 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.95–1.2 (m, 28, $CH(CH_3)_2$), 3.90, 3.93 (2 apparent t, 1, H-4'), 4.05, 4.19 (2 dd, 2, $J$ = 3 Hz, $J$ = 13 Hz, 2 H-5'), 4.44 (dd, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 8.5 Hz, H-2'), 4.56 (apparent t, 1, $J_{3',4'}$ = 8.5 Hz, H-3'), 6.35 (d, 1, H-1'), 6.48 (br s, 2, $NH_2$), 8.04 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 300 MHz) δ 12.53, 12.93, 13.00, 13.53 ($CH(CH_3)_2$), 16.79, 16.84, 16.87, 16.96, 17.31, 17.37, 17.45 ($CH(CH_3)_2$), 60.70 (C-5'), 67.96 (C-2'), 73.03 (C-3'), 81.93, 81.98 (C-1',4'), 117.78 (d, C-5, $J_{5,F}$ = 3.8 Hz), 138.94 (C-8), 151.15 (d, C-4, $J_{4,F}$ = 19.5 Hz), 157.23 (d, C-6, $J_{6,F}$ = 20.3 Hz), 159.18 (d, C-2, $J_{2,F}$ = 210.9 Hz). Anal. ($C_{22}H_{37}FN_8O_4Si_2$) C, H, N.

**2-Fluoro-9-[2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]purin-6-amine (4f).** A solution of **3f** (660 mg, 1 mmol) in 5 mL of hexamethylphosphoramide was treated with dry LiCl (85 mg, 2 mmol) and stirred at room temperature while protected from moisture. A 4-h HPLC aliquot (linear gradient, 50% → 100% acetonitrile in water, 20 min) showed essentially complete reaction. At 5 h, the solution was poured into ice water (200 mL) and stirred for 0.5 h. The white solid was collected, washed with cold water, and dried in vacuo at room temperature to give crude **4f**, 477 mg. This solid in $CHCl_3$ was chromatographed on two silica gel thick plates (Analtech, GF, 2000 μm) in 1:1 cyclohexane–ethyl acetate. The extracted product was crystallized from hot EtOH and dried in vacuo at 56 °C for 6 h to give pure **4f**: yield 164 mg (30%); mp 188–190 °C. Additional pure **4f** was isolated from the ethanol filtrate by chromatography on a silica gel thick plate (Analtech, GF, 2000 μm) in 95:5 $CHCl_3$–MeOH: yield 18 mg (3%); TLC 95:5 $CHCl_3$–MeOH, $R_f$ 0.52; MS, $z/e$ 546 $(M + 1)^+$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.0–1.2 (m, 28, $CH(CH_3)_2$), 3.94 (m, 1, H-4'), 4.10, 4.22 (2 dd, 2, $J$ = 3.5 Hz, $J$ = 13 Hz, 2 H-5'), 4.65 (dd, 1, $J_{1',2'}$ = 6 Hz, $J_{2',3'}$ = 8 Hz), 4.75 (apparent t, 1, H-3'), 6.41 (d, 1, H-1'), 6.57 (br s, 2, $NH_2$), 8.09 (s, 1, H-8); $^{13}C$ NMR ($CDCl_3$, 300 MHz) δ 12.40, 12.90, 13.04, 13.56 ($CH(CH_3)_2$), 16.92, 16.98, 17.30, 17.33, 17.37, 17.46 ($CH(CH_3)_2$), 61.19 (C-5'), 62.79 (C-2'), 75.66 (C-3'), 82.70, 82.99 (C-1',4'), 117.64 (d, C-5, $J_{5,F}$ = 4.2 Hz), 139.06 (d, C-8, $J_{8,F}$ = 2.6 Hz), 151.15 (d, C-4, $J_{4,F}$ = 19.4 Hz), 157.24 (d, C-6, $J_{6,F}$ = 20.1 Hz), 159.13 (d, C-2, $J_{2,F}$ = 210.8 Hz). Anal. ($C_{22}H_{37}ClF-N_5O_4Si_2$) C, H, N.

**2-Chloro-9-(2-azido-2-deoxy-β-D-arabinofuranosyl)purin-6-amine (4g).** A solution of **4a** (416.7 mg, 0.732 mmol) in 2.5 mL of dry THF (Aldrich, Sure/Seal) was treated at room temperature with 1 M tetra-*n*-butylammonium fluoride in THF (1.46 mL, 1.46 mmol). A 15-min TLC aliquot showed complete reaction. The solution was evaporated to dryness. The residue in MeOH was applied to two silica gel thick plates (Analtech, GF, 2000 μm) that were developed in 4:1 $CHCl_3$–MeOH. The product was extracted with warm EtOH and evaporated, and the residue was crystallized from water (45 mL) to give pure **4g**, which was dried in vacuo at 56 °C for 16 h: yield 199 mg (83%); mp 210 °C dec; TLC 4:1 $CHCl_3$–MeOH, $R_f$ 0.60; HPLC 99%, 90:10 $H_2O$–MeCN; MS, $z/e$ 327 $(M + 1)^+$; IR 2125 $cm^{-1}$ ($N_3$); UV $\lambda_{max}$ pH 1 264.5 (15.3), pH 7 265 (15.9), pH 13 265 (16.3); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 3.62–3.86 (m, 3, H-4', 2 H-5'), 4.37 (m, 1, H-3'), 4.52 (dd, 1, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 8 Hz), 5.18 (t, 1, $J$ = 5 Hz, 5'-OH), 6.03 (d, 1, $J$ = 2 Hz, 3'-OH), 6.34 (d, 1, H-1'), 7.86 (br s, 2, $NH_2$), 8.36 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 100 MHz) δ 59.58 (C-5'), 67.32, 71.47 (C-2',3'), 81.73, 83.26 (C-1',4'), 117.58 (C-5), 139.65 (C-8), 150.24 (C-4), 153.11 (C-2), 156.74 (C-6). Anal. ($C_{10}H_{11}ClN_8O_3$) C, H, N.

**2-Chloro-9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)-purin-6-amine (4h).** A solution of **4b** (175 mg, 0.31 mmol) in 1 mL of dry THF (Aldrich, Sure/Seal) was treated at room temperature with 2 equiv of 1 M tetra-*n*-butylammonium fluoride in THF (0.62 mL). A 0.5-h TLC aliquot showed complete reaction. The solution was evaporated to dryness, and the residue was crystallized from hot water to give crude **4h**, 143 mg. This solid was recrystallized twice from 20 mL of boiling MeOH to give pure material that was dried in vacuo at 78 °C for 16 h: yield 35 mg (33%); mp 250–251 °C dec; TLC 4:1 $CHCl_3$–MeOH, $R_f$ 0.66; HPLC 99%, 90:10 $H_2O$–MeCN; MS, $z/e$ 320 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 264 (16.6), pH 7 264 (17.1), pH 13 264 (18.5), $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 3.66–3.86 (m, 3, H-4', 2 H-5'), 4.43 (broadened dd, 1, H-3'), 4.78 (apparent, t, 1, $J_{1',2'}$ = 6 Hz, H-2'), 5.20 (t, 1, 5'-OH), 6.10 (d, 1, $J$ = 6 Hz, 3'-OH), 6.41 (d, 1 H-1'), 7.86 (br s, 2, $NH_2$), 8.40 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 59.69 (C-5'), 63.50 (C-2'), 73.75 (C-3'), 82.43, 83.46 (C-1',4'), 117.34 (C-5), 139.50 (C-8), 150.11 (C-4), 152.96 (C-2), 156.63 (C-6). Anal. ($C_{10}H_{11}Cl_2N_5O_3{\cdot}0.5H_2O{\cdot}0.5CH_3OH$) C, H, N.

**2-Chloro-9-(2-bromo-2-deoxy-β-D-arabinofuranosyl)-purin-6-amine (4i).** A solution of **4c** (100 mg, 0.165 mmol) in 2.5 mL of dry THF (Aldrich, Sure/Seal) was chilled to −20 °C and treated in one portion with 2 equiv of 1 M tetra-*n*-butylammonium fluoride in THF (0.33 mL). The reaction mixture was kept at −20 °C for 16 h, at which time a TLC aliquot showed the reaction to be complete. Glacial acetic acid (25 μL, 0.435 mmol) was added at −20 °C to prevent elimination of HBr and epoxide formation during workup. The cold solution was evaporated to dryness, and the residue was solidified by MeOH trituration to give crude **4i**: 58 mg. This solid was recrystallized from 30 mL of boiling MeOH to give pure material, which was dried in vacuo at 56 °C for 16 h: yield 37 mg (58%); mp 230 °C dec; TLC 9:1 EtOAc–MeOH, $R_f$ 0.62; MS, $z/e$ 364 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 264 (15.3), pH 7 265 (15.4), pH 13 264 (15.7); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 3.68–3.84 (m, 3, H-4', 2 H-5'), 4.53 (broadened dd, 1, H-3'), 4.81 (overlapping dd, nearly apparent t, 1, H-2'), 5.20 (t, 1, 5'-OH), 6.09 (d, 1, $J$ = 6 Hz, 3'-OH), 6.37 (d, 1, $J$ = 6 Hz, H-1'), 7.86 (br s, 2, $NH_2$), 8.40 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 54.98 (C-2'), 59.68 (C-5'), 73.88 (C-3'), 82.41, 83.88 (C-1',4'), 117.38 (C-5), 139.32 (C-8), 150.08 (C-4), 152.96 (C-2), 156.66 (C-6). Anal. ($C_{10}H_{11}BrClN_5O_3{\cdot}0.8CH_3OH$) C, H, N.

**2-Chloro-9-(2-deoxy-2-iodo-β-D-arabinofuranosyl)purin-6-amine (4j).** A solution of **4d** (87.5 mg, 0.134 mmol) in 2 mL of dry THF (Aldrich, Sure/Seal) was chilled to −20 °C and treated in one portion with 2 equiv of 1 M tetra-*n*-butylammonium fluoride in THF (0.27 mL). After 0.5 h at −20 °C, a TLC aliquot showed 50% reaction. The solution was allowed to warm slowly to 0 °C over the next 2.5 h, at which time TLC indicated complete reaction. Glacial acetic acid (20 μL, 0.348 mmol) was added, and the cold solution was evaporated to dryness. The residue was solidified by trituration with $CH_3OH$ to give crude **4j**, 44 mg. This solid was recrystallized from hot $CH_3OH$ (20 mL) to give pure material that was dried in vacuo at 56 °C for 16 h: yield 30 mg (54%); mp 190 °C dec; TLC 9:1 EtOAc–MeOH, $R_f$ 0.65; HPLC 99%, 90:10 $H_2O$–MeCN; MS, $z/e$ 412 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 265 (15.8), pH 7 265 (15.8), pH 13 265 (16.2); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 3.68–3.85 (m, 3, H-4', 2 H-5'), 4.56 (m, 1, H-3'), 4.73 (dd, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 9 Hz, H-2'), 5.28 (t, 1, 5'-OH), 5.99 (d, 1, $J$ = 6 Hz, 3'-OH), 6.23 (d, 1, H-1'), 7.85 (br s, 2, $NH_2$), 8.38 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) δ 32.29 (C-2'), 59.58 (C-5'), 74.96 (C-3'), 83.34, 84.65 (C-1',4'), 117.50 (C-5), 139.03 (C-8), 150.01 (C-4), 152.92 (C-2), 156.69 (C-6). Anal. ($C_{10}H_{11}ClIN_5O_3{\cdot}0.1C-H_3OH$) C, H, N.

**2-Chloro-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)-purin-6-amine (4k).** To a solution of **4g** (82 mg, 0.25 mmol) in 20 mL of EtOH was added 23 mg of 5% platinum-on-carbon powder (Engelhard), and the mixture was stirred under hydrogen at atmospheric pressure for 48 h. The catalyst was filtered off, and the filtrate was evaporated and crystallized from boiling EtOH to give crude **4k**, 44 mg. This solid in hot MeOH was applied to two silica gel thick plates (Analtech, GF, 1000 μm) that were developed in 4:1 $CHCl_3$–MeOH + 5% $NH_4OH$. The product was eluted with hot EtOH and evaporated. The residue was crystallized from 20 mL boiling EtOH to give pure **4k**: yield 30 mg (40%); mp 235 °C dec; TLC 4:1 $CHCl_3$–MeOH + 5% $NH_4OH$,

$R_f$ 0.30; MS, $z/e$ 301 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 263 (15.2), pH 7 265 (15.4), pH 13 264 (15.7); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 1.53 (br s, 2, 2'-$NH_2$), 3.52 (apparent t, 1, H-2'), 3.63 (dd, 1, $J$ = 4 Hz, $J$ = 12.5 Hz, H-5'), 3.73 (m, 2, $J_{3',4'}$ = 6 Hz, H-4', H-5'), 4.03 (br dd, 1, H-3'), 5.10 (br, 1, 5'-OH), 5.44 (d, 1, $J$ = 5 Hz, 3'-OH), 6.11 (d, 1, $J_{1',2'}$ = 6.5 Hz, H-1'), 7.75 (br s, 2, 6-$NH_2$), 8.30 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 60.20 (C-2',5'), 74.65 (C-3'), 84.10, 84.49 (C-1',4'), 117.44 (C-5), 140.43 (C-8), 150.27 (C-4), 152.61 (C-2), 156.51 (C-6). Anal. ($C_{10}H_{13}ClN_6O_3$) C, H, N.

**2-Fluoro-9-(2-azido-2-deoxy-β-D-arabinofuranosyl)purin-6-amine (4l).** A solution of 4e (220 mg, 0.398 mmol) in 2 mL of dry THF (Aldrich, Sure/Seal) was treated at room temperature with 1 M tetra-*n*-butylammonium fluoride in THF (796 μL, 0.796 mmol). A 0.5-h TLC aliquot showed complete reaction. The solution was concentrated and applied to one silica gel thick plate (Analtech, GF, 2000 μm) that was developed with 4:1 $CHCl_3$–MeOH. The product was extracted with warm MeOH and crystallized from boiling water (20 mL) to give pure 4l, which was dried in vacuo at 56 °C for 22 h: yield 106 mg (86%); mp 212 °C; TLC 4:1 $CHCl_3$–MeOH, $R_f$ 0.55; HPLC 99%, 90:10 $H_2O$–MeCN; MS, $z/e$ 311 $(M + 1)^+$; IR 2120 $cm^{-1}$ ($N_3$); UV $\lambda_{max}$ pH 1 261.5 (14.5), 270 (sh), pH 7 262 (15.2), 270 (sh), pH 13, 262 (15.5), 270 (sh); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 3.62–3.85 (m, 3, H-4', 2 H-5'), 4.37 (m, 1, H-3'), 4.61 (dd, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 8 Hz, H-2'), 5.16 (t, 1, 5'-OH), 6.01 (d, 1, $J$ = 6 Hz, 3'-OH), 6.29 (d, 1, H-1'), 7.93 (br s, 2, $NH_2$), 8.32 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 59.47 (C-5'), 67.20 (C-2'), 71.26 (C-3'), 81.54, 83.08 (C-1',4'), 116.78 (d, C-5, $J_{5,F}$ = 3.8 Hz), 139.37 (d, C-8, $J_{8,F}$ = 2.6 Hz), 150.39 (d, C-4, $J_{4,F}$ = 20.3 Hz), 157.45 (d, C-6, $J_{6,F}$ = 22.3 Hz), 158.51 (d, C-2, $J_{2,F}$ = 204.0 Hz). Anal. ($C_{10}H_{11}FN_8O_3$) C, H, N.

**2-Fluoro-9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)-purin-6-amine (4m).** A solution of 4f (126 mg, 0.23 mmol) in 1 mL of dry THF (Aldrich, Sure/Seal) was treated at room temperature with 2 equiv of 1 M tetra-*n*-butylammonium fluoride in THF (0.46 mL). A 3-h TLC aliquot showed complete reaction. The solution was evaporated, and the residue was crystallized from MeOH to give crude 4m, 70 mg. This solid was recrystallized from hot MeOH (35 mL) to give pure material that was dried in vacuo at 56 °C for 16 h: yield 63 mg (89%); mp 205–207 °C; TLC 5:1 $CHCl_3$–MeOH, $R_f$ 0.45; HPLC 98%, 90:10 $H_2O$–MeCN; MS, $z/e$ 304 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 262 (14.8), 270 (sh), pH 7 261 (15.6), 270 (sh), pH 13 262 (16.1), 270 (sh); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 3.66–3.86 (m, 3, H-4', 2 H-5'), 4.44 (m, 1, H-3'), 4.77 (dd, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 8 Hz, H-2'), 5.20 (t, 1, 5'-OH), 6.07 (d, 1, $J$ = 5.5 Hz, 3'-OH), 6.37 (d, 1, H-1'), 7.88 (br s, 2, $NH_2$), 8.36 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 59.69 (C-5'), 63.48 (C-2'), 73.72 (C-3'), 82.39, 83.40 (C-1',4'), 116.67 (d, C-5, $J_{5,F}$ = 4.1 Hz), 139.31 (d, C-8, $J_{8,F}$ = 2.3 Hz), 150.39 (d, C-4, $J_{4,F}$ = 20.3 Hz), 157.46 (d, C-6, $J_{6,F}$ = 21.4 Hz), 158.46 (d, C-2, $J_{2,F}$ = 204.3 Hz). Anal. ($C_{10}H_{11}ClFN_5O_3 \cdot 0.8CH_3OH$) C, H, N.

**2-Fluoro-9-(2-amino-2-deoxy-β-D-arabinofuranosyl)-purin-6-amine (4n).** To a solution of 4l (60 mg, 0.193 mmol) in 15 mL of EtOH was added 19 mg of 5% platinum-on-carbon powder (Engelhard), and the mixture was stirred under hydrogen at atmospheric pressure and room temperature. A 16-h TLC aliquot showed essentially complete reaction. The catalyst was filtered off and washed with EtOH, and the filtrate was evaporated to dryness. This residue in hot MeOH was applied to two Analtech, GF, 1000 μm layer plates with Celite zones. After one development in 4:1 $CHCl_3$–MeOH + 5% $NH_4OH$, the product band was eluted with 1:1 $CHCl_3$–MeOH + 10% $NH_4OH$. The plate extract was evaporated to dryness, and the residue was crystallized from 20 mL of hot 99:1 EtOH–$H_2O$. The solid was collected after chilling, washed with cold EtOH, and dried in vacuo at 56 °C for 16 h to give pure 4n: yield 25 mg (45%); mp 210 °C dec; TLC 3:1 $CHCl_3$–MeOH + 5% $NH_4OH$, $R_f$ 0.30; HPLC 98%, pH 3.6, 90:10 0.1 M NaOAc–MeCN; MS, $z/e$ 285 $(M + 1)^+$; UV $\lambda_{max}$ pH 1 261 (14.9), 268 (sh), pH 7 262 (15.4), 270 (sh), pH 13 262 (15.4), 270 (sh); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 3.32 (br s, 2, 2'-$NH_2$), 3.62–3.84 (m, 4, H-2', H-4', 2 H-5'), 4.29 (m, 1, H-3'), 5.56 (v br s, 1, 5'-OH), 5.77 (br s, 1, 3'-OH), 6.19 (d, 1, $J_{1',2'}$ = 6 Hz, H-1'), 7.82 (br s, 2, 6-$NH_2$), 8.29 (s, 1, H-8); $^{13}C$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 58.80 (C-2'), 59.82 (C-5'), 72.62 (C-3'), 82.80, 83.96 (C-1',4'), 117.04 (d, C-5, $J_{5,F}$ = 4.0 Hz), 139.94 (C-8), 150.43 (d, C-4, $J_{4,F}$ = 21.3 Hz), 157.38 (d, C-6, $J_{6,F}$ = 20.2 Hz), 158.37 (d, C-2, $J_{2,F}$ = 203.8 Hz). Anal. ($C_{10}H_{13}FN_6O_3 \cdot 0.7H_2O$) C, H, N.

**Acknowledgment.** This investigation was supported by the National Cancer Institute, National Institutes of Health, DHHS, Grant P01 CA34200. We thank Dr. L. L. Bennett, Jr., B. J. Bowdon, and D. A. Adamson for the cytotoxicity data in normal and mutant cell lines, Dr. W. M. Shannon and G. Arnett for the antiviral data, S. Campbell for HPLC analysis, and members of the Molecular Spectroscopy Section of the Southern Research Institute for spectral data.

**Registry No.** **3a**, 146-77-0; **3b**, 111556-90-2; **3c**, 111581-33-0; **3d**, 146-78-1; **3e**, 111556-91-3; **3f**, 111556-92-4; **4a**, 111556-93-5; **4b**, 111556-94-6; **4c**, 111556-95-7; **4d**, 111556-96-8; **4e**, 111556-97-9; **4f**, 111556-98-0; **4g**, 111556-99-1; **4h**, 111615-20-4; **4i**, 111557-00-7; **4j**, 111557-01-8; **4k**, 111557-02-9; **4l**, 111557-03-0; **4m**, 111557-04-1; **4n**, 111557-05-2.

# Structure-Activity Relationship in PAF-acether. 4.[1] Synthesis and Biological Activities of Carboxylate Isosteres

Boguslaw Wichrowski,[†] Simone Jouquey,[‡] Colette Broquet,[†] Françoise Heymans,[†] Jean-Jacques Godfroid,*[,†] Jeanne Fichelle,[‡] and Manuel Worcel[‡]

*Laboratoire de Pharmacochimie Moléculaire, Université Paris 7, 2 Place Jussieu, 75251 Paris Cédex 05, France, and Centre de Recherches Roussel-Uclaf, 102 Route de Noisy, 93230 Romainville, France.* *Received August 3, 1987*

The synthesis and biological characterization of some 3-carboxylate isosteres of PAF-acether structurally modified in positions 1 (ether, carbamate), 2 (acetoyl, ethoxy), and 3 (chain length and polar head group) are reported. All derivatives present antagonist activities against PAF-acether-induced effects in vitro (platelet aggregation) and in vivo (bronchoconstriction and thrombocytopenia in guinea pig and, to a lesser extent, hypotension in rat). The functional modifications presented here do not modify dramatically the potency of antagonist activities, and there is no enantioselectivity. All of the isosteres are specific PAF-acether antagonists, except the 1-carbamoyl analogue, which is also potent against acetylcholine-induced hypotension and bronchoconstriction.

Platelet activating factor (PAF-acether) is a phospholipid mediator[2-4] of anaphylaxis that is released by a number of stimulated cells including platelets, macrophages, basophils, neutrophils, endothelium cells, and isolated tissue preparation (for reviews, see ref 5–8). It

[†] Université Paris 7.
[‡] Centre de Recherches Roussel-Uclaf.

(1) For part 3 and references of previous papers, see ref 21.
(2) Benveniste, J.; Tencé, M.; Varenne, P.; Bidault, J.; Boullet, C.; Polonsky, J. *C. R. Seances Acad. Sci., Ser. D* **1979**, *289*, 1037.

0022-2623/88/1831-0410$01.50/0 