9-(1-Fluoro-5-hydroxypentan-2-yl)-9*H*-guanine: Synthesis and Evaluation of Antiviral Activity

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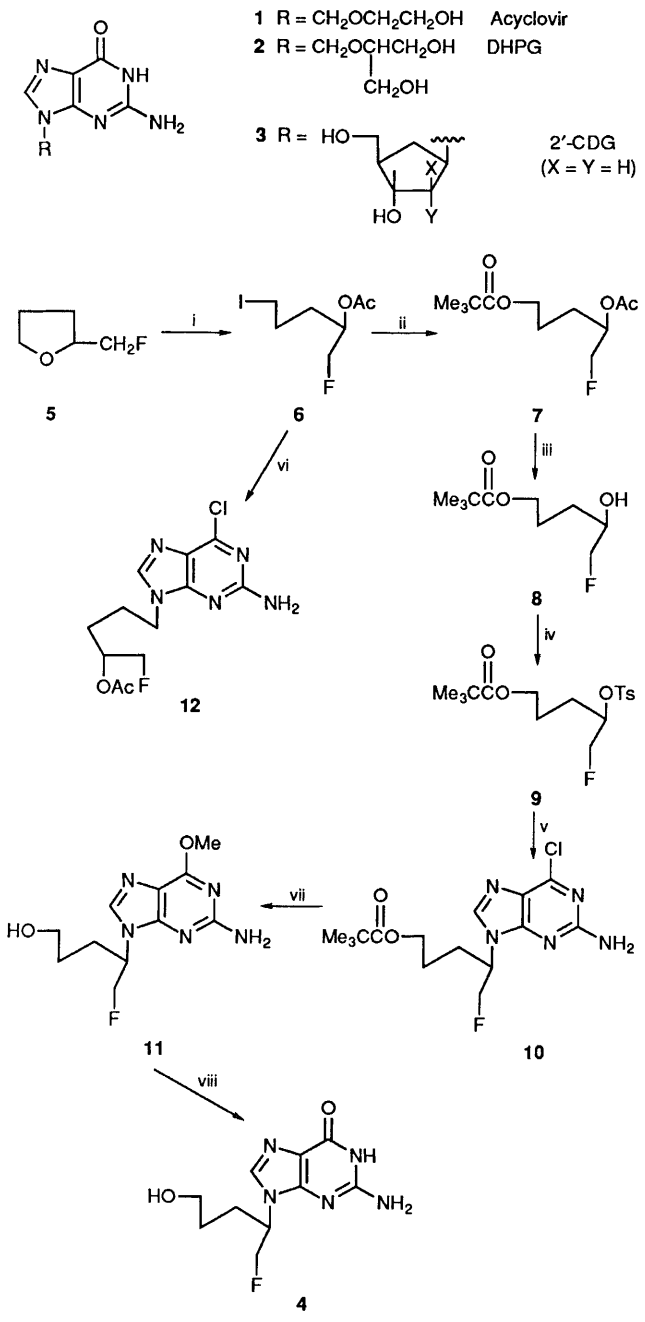
5-Fluoro-4-tosyloxypentyl pivalate has been synthesized in four steps from 2-(fluoromethyl)tetrahydrofuran. Condensation with 2-amino-6-chloropurine gave the N-9 derivative, which was converted *via* the 6-methoxy analogue into 9-(1-fluoro-5-hydroxypentan-2-yl)-9*H*-guanine. The latter was evaluated, and found inactive, in a large variety of antiviral assays.

The acyclic guanosine analogues 9-(2-hydroxyethoxymethyl)-guanine **1** (acyclovir)[1] and 9-[(1,3-dihydroxypropan-2-yloxy)-methyl]guanine **2** (DHPG, ganciclovir)[2] are potent antiviral agents which are in clinical use. Other antivirally active guanine derivatives have alkyl side-chains at N-9 in which the 2′ oxygen atom has been replaced by a methylene group[3] or in which the oxygen has been switched to the 3′ position as in the phosphonate analogues[4] or to the 1′ position as in the 9-alkoxy series.[5] Replacement of a hydrogen atom by fluorine does not produce drastic steric changes in a molecule[6a] but may enhance the biological activity of the molecule. The much greater electronegativity of fluorine has a strong electronic effect on reactions of neighbouring functional groups and the fluorine atom, being a hydrogen-bond acceptor, is often processed by enzymes acting on the corresponding hydroxy compounds.[6b] The carbocyclic analogue of 2′-deoxyguanosine, compound **3** (X = Y = H) (2′-CDG), shows potent anti-herpes activity *in vitro*.[7] Substitution of 2′-H by 2′β-F, **3** (X = F, Y = H), increased the activity one hundred-fold.[8] The 2′α-F derivative **3** (X = H, Y = F) was less active than 2′-CDG. A few examples of fluoroacyclic guanosine analogues have been reported.[9–11] Of those which showed antiviral activity, all were less potent than acyclovir. In this paper we describe the synthesis of racemic 9-(1-fluoro-5-hydroxypentan-2-yl)-9*H*-guanine **4**, the acyclic version of 2′-CDG, lacking C-3′ and with a fluorine substituent at the equivalent of the C-2′ position.

Results and Discussion

Synthesis.—A convergent approach to our target molecule **4** requires, as alkylating moiety, a 1-fluoropentane with a masked hydroxy group at C-5 and a reactive leaving group at C-2. One route to this structure involves regioselective ring opening of the known 2-(fluoromethyl)tetrahydrofuran **5**[12] (Scheme 1). A variety of reagents have been used to cleave the ether link in tetrahydrofuran.[13] With unsymmetrically substituted cyclic ethers as substrates, the products depend on the reagents used and on steric factors. Thus, with acetyl toluene-*p*-sulfonate, 2-methyltetrahydrofuran gave 5-acetoxypentan-2-yl-toluene-*p*-sulfonate (95%),[14] whereas use of pivaloyl chloride–sodium iodide reagent gave 5-iodopentan-2-yl pivalate (88%).[15] Cleavage with acetyl chloride–sodium iodide resulted in a 1:1 mixture of the two possible isomers. In a preliminary investigation the reaction of compound **5** with acetyl toluene-*p*-sulfonate was unsatisfactory. With acetyl chloride–sodium iodide reagent, attack by the iodide ion on compound **5** occurred exclusively at the less hindered position to give 1-fluoro-5-iodopentan-2-yl acetate **6**. Attempts to convert the iodide into the benzyl ether were not successful using the benzyloxy anion, generated by fluorodestannylation of benzyl tributyltin ether.[16] The same procedure with tributyltin pivalate gave a high yield (94%) of the pivalate ester **7**. An equally good yield was later obtained under the conditions described in a more recent publication.[17] The acetate group of the diester **7** was selectively cleaved by methanolic ammonia[18] to yield 5-fluoro-4-hydroxypentyl pivalate **8**. Activation of the secondary hydroxy group by conversion into the tributyltin ether,[19] followed by tosylation of the crude product, gave the required pentane **9** in 79% yield. Direct tosylation of **8** gave a 40% yield of **9**. The overall yield of compound **9** from compound **5** was 52%. Coupling of the tosyl ester **9** with 2-amino-6-chloropurine in dimethylformamide (DMF) with potassium carbonate, and 18-crown-6 as catalyst,[20] gave the N^9-alkylated purine **10** as the major product (64%). A second, more polar, fraction consisted mainly of the N-7 isomer (8%) with two minor contaminants, as shown by ^{1}H NMR spectroscopy. The N-9 and N-7 isomers were distinguished by the characteristic differences in their ^{13}C and ^{1}H NMR spectra.[21] In the case of the N-7 isomer, the 8-H signal and C-8 signal (identified by a ^{13}C DEPT spectrum) appeared downfield and the C-5 signal and NH_2 signal were upfield relative to the corresponding signals of the N-9 isomer **10**. The chemical-shift and ^3J-values in $CDCl_3$ for the fully coupled ^{13}C–^{1}H spectrum of compound **10** agree with those reported for N^9-alkylated 2-amino-6-chloropurine.[22] The C-5 signal at δ_C 124 was a doublet with ^3J 11.5 Hz; the C-4 signal at δ_C 153.4 was a double doublet with ^3J 6 and 3.5 Hz. The ^{1}H and ^{13}C spectra of compound **10** differed from those of its analogue **12**, thus precluding the possibility of a rearrangement of the pentyl chain during the reaction sequence. Comparison of the UV spectrum of the major product **10** with the spectra of N^9- and N^7-alkylated 2-amino-6-chloropurines[23] confirmed it as the N-9 isomer. Hydrolysis of pivalate **10** to compound **4** in the presence of acid (1 mol dm^{-3} HCl; reflux 4 h); or base (2.5 mol dm^{-3} NaOH; reflux 1 h) yielded foams. In both cases UV and NMR spectra were consistent with structure **4** together with contaminants. Attempts to isolate a pure sample were unsuccessful. Conversion of compound **10**, by refluxing it with dry potassium carbonate in methanol, into the 6-methoxy analogue **11** with concomitant removal of the pivaloyloxy protecting group was achieved in 82% yield. The methyl ether was cleaved by treatment of compound **11** with one mole equivalent of bromotrimethylsilane (TMSBr) in DMF to afford a foam with an NMR spectrum consistent with 6-oxo compound **4** and unchanged ether **11**. These were separated by chromatography. When chlorotrimethylsilane (TMSCl)–sodium iodide reagent was used for cleavage of the ether, the isolated product was shown to be the hemi-hydrate of the 1:1 sodium chloride complex of the required compound **4**. The ^{1}H NMR spectrum of the complex showed 8-H as a doublet with $J_{8,F}$ 2.5 Hz. This long-range H • • • F coupling has been observed for β-isomers of



Scheme 1 *Reagents and conditions:* i, NaI, AcCl, MeCN, room temp.; ii, $Me_3CCO_2SnBu_3$, CsF, DMF, 40 °C; iii, NH_3–MeOH, room temp.; iv, $(Bu_3Sn)_2O$, toluene; then *p*-TsCl, DMAP, Et_3N, 65 °C; v, 2-Amino-6-chloropurine, K_2CO_3, 18-C-6, DMF, 65 °C; vi, 2-Amino-6-chloropurine, K_2CO_3, DMSO, room temp.; vii, K_2CO_3, MeOH, 65 °C; viii, TMSBr or TMSCl–NaI, DMF, room temp.

2′-fluoroarabinofuranosylpurines[24] and their carbocyclic analogues.[8] The chemical shifts of ^{1}NH and NH_2 were downfield relative to those of the non-complexed product as a result of hydrogen bonding to the chloride anion.[25] The ^{1}H NMR spectra of the crude material from the acidic or basic aqueous hydrolyses of compound **10** resembled that of the sodium chloride-complexed product.

Evaluation of Antiviral Activity.—9-(1-Fluoro-5-hydroxypentan-2-yl)-9*H*-guanine (compound **4**) was evaluated and found inactive at the highest concentrations (up to 400 μg cm^{-3}) tested, in the following antiviral assay systems: herpes simplex virus type 1 (strain KOS), herpes simplex virus type 2 (strain G), vaccinia virus, vesicular stomatitis virus and thymidine kinase-deficient (TK$^-$) herpes simplex virus type 1 (strain B2006) in human embryonic skin-muscle (ESM) cells; *varicella zoster* virus (strain OKA and strain YS), cytomegalovirus (strain AD-169 and strain Davis) in human embryonic lung (HEL) cells; poliovirus type 1, Coxsackie B4 virus and respiratory syncytial virus (strain Long) in HeLa cells; influenza A (strain Ishikawa) and influenza B (strain Singapore) in Madin–Darby canine kidney (MDCK) cells; reovirus type 1, parainfluenza virus type 3, Sindbis virus, Semliki forest virus, Junin virus and Tacaribe virus in Vero cells; and human immunodeficiency virus (HIV) type 1 (strain III_B/LAI) and type 2 (strain ROD) in MT-4 cells. Compound **4** did not prove cytotoxic (again, at concentrations up to 400 μg cm^{-3}) to any of the host cells used in these studies.

Experimental

M.p.s were determined on a Gallenkamp capillary apparatus and are uncorrected; UV spectra were obtained on a Unicam SP800A spectrometer. NMR spectra were recorded on a Bruker MSL 300 machine at 300.13 MHz for ^{1}H and 75.468 MHz for ^{13}C. $SiMe_4$ was the internal standard; *J*-values are given in Hz. IR spectra were recorded on a Perkin-Elmer 883 spectrometer. FAB–MS was measured at the SERC Mass Spectrometry Service Centre, Swansea using fast xenon atoms at 8 kV and 3-nitrobenzyl alcohol as matrix. GLC was performed on a GOW MAC 552 with 15% DC 200 on CHROM P 90/100 mesh, 4′/$\frac{1}{4}$″. Injector 230 °C, column 175 °C, detector 190 °C. TLC was carried out on Merck silica gel 60F_{254}-coated aluminium sheets and spots were visualised by UV illumination. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh) or 60 (70–230 mesh). Organic extracts were dried over magnesium sulfate and evaporated (rotary evaporator) at 30 °C unless stated otherwise.

1-*Fluoro-5-iodopentan-2-yl Acetate* **6**.—To a stirred mixture of the tetrahydrofuran derivative **5**[12a] (520 mg, 5 mmol) and sodium iodide (1.5 g, 10 mmol) in acetonitrile (5 cm^3) at 0 °C was added gradually a solution of acetyl chloride (600 mg, 7.5 mmol) in acetonitrile (10 cm^3) over a period of 30 min. The mixture was stirred at ambient temperature for 65 h. Crushed ice and saturated aq. sodium hydrogen carbonate (10 cm^3) were then added and the mixture was extracted with diethyl ether (3 × 15 cm^3). The organic layer was washed successively with saturated aq. sodium thiosulfate (2 × 15 cm^3) and brine (2 × 15 cm^3), dried, and evaporated. The product was a pale yellow liquid (1.2 g, 82%). TLC [hexane–chloroform (1:2)] showed a single spot, with R_f 0.7. The product rapidly darkened at ambient temperature but was stable for up to at least six months at −20 °C. It was used without further purification to prepare compound **7**. A *sample* was purified for analysis by column chromatography with hexane–chloroform (1:1) as eluent; ν_{max}(film)/cm^{-1} 1746, 1237, 1070 and 1032; δ_H(CDCl$_3$) 5.07 (1 H, dm, *J* 21.2, C*H*CH$_2$F), 4.47 (1 H, ddd, *J* 47.5, 10.2 and 3.4, CHC*H*^{a}F), 4.42 (1 H, ddd, *J* 47.5, 10.2 and 4.9, CHC*H*^{b}F), 3.20 (2 H, t, *J* 6.7, 5-H$_2$), 2.10 (3 H, s, AcO) and 1.88 and 1.77 (4 H, 2 × m, 3- and 4-H$_2$); δ_C(CDCl$_3$) 170 (C=O), 83.4 (d, *J* 174, C-1), 70.9 (d, *J* 19.7, C-2), 30.5 (d, *J* 5.6, C-3), 28.9 (C-4), 20.9 (Me) and 5.5 (C-5) (Found: C, 31.0; H, 4.0. $C_7H_{12}FIO_2$ requires C, 30.68; H, 4.41%).

4-*Acetoxy-5-fluoropentyl Pivalate* **7**.—Pivalic acid (510 mg, 5 mmol) and bis(tributyltin) oxide (1.5 g, 2.5 mmol) were refluxed in toluene for 3 h using a water separator. The toluene was evaporated off and the residue was dissolved in dry DMF (5 cm^3). Caesium fluoride (760 mg, 5 mmol) was added, followed by a solution of the iodide **6** (1.37 g, 5 mmol) in DMF (5 cm^3) and the mixture was stirred at 40 °C for 40 h with the exclusion of moisture. The solvent was evaporated off and the residue was

stirred with potassium fluoride (750 mg) and ethyl acetate (25 cm^3) for 1 h. The mixture was filtered through a pad of silica gel and eluted with ethyl acetate (100 cm^3). The filtrate was washed with saturated aq. sodium hydrogen carbonate (2 × 50 cm^3), dried, and evaporated. The residue was purified by column chromatography with dichloromethane–methanol (100:1) to yield the *title compound* **7** as a liquid (1.17 g, 94%). GLC showed a single peak, t_R 9.3 min; ν_{max}(film)/cm^{-1} 1750, 1734, 1285, 1237, 1163 and 1041; $\delta_H(CDCl_3)$ 5.07 (1 H, dm, *J* 21.5, C*H*CH_2F), 4.47 (1 H, ddd, *J* 47.5, 10.2 and 3.4, CHC*H*^{a}F), 4.42 (1 H, ddd, *J* 47.5, 10.2 and 4.8, CHC*H*^{b}F), 4.08 (2 H, t, *J* 6, 1-H_2), 2.10 (3 H, s, AcO), 1.73–1.67 (4 H, br m, 2- and 3-H_2) and 1.21 (9 H, s, CMe_3); $\delta_C(CDCl_3)$ 178.4 (C=O), 170.4 (C=O), 83.3 (d, *J* 174, C-5), 71.7 (d, *J* 19.5, C-4) 63.6 (C-1), 38.7 (*C*Me_3), 27.1 (C*Me*$_3$), 26.2 (d, *J* 5.7, C-3), 24.5 (C-2) and 20.9 (*Me*CO) (Found: C, 58.0; H, 8.4. $C_{12}H_{21}FO_4$ requires C, 58.05; H, 8.53%).

5-Fluoro-4-tosyloxypentyl Pivalate **9**.—A solution of the acetate **7** (1.07 g, 4.3 mmol) in methanol saturated with ammonia at 0 °C (40 cm^3) was left at room temperature for 17 h. The solvent was evaporated off and the residue was purified by flash chromatography. Elution with dichloromethane–methanol (100:4) gave the alcohol **8** as a liquid (742 mg, 85%). GLC gave a single peak, t_R 5.3 min; ν_{max}(film)/cm^{-1} 3448, 1731, 1289, 1164 and 1037; $\delta_H(CDCl_3)$ 4.40 (1 H, ddd, *J* 47.5, 9.4 and 3.3, CHC*H*^{a}F), 4.32 (1 H, ddd, *J* 47.5, 9.4 and 6.7, CHC*H*^{b}F), 4.1 (2 H, t, *J* 6.6, 1-H_2), 3.9 (1 H, dm, *J* 16, C*H*CH_2F), 2.3 (1 H, br s, OH), 1.8 and 1.55 (4 H, 2 × m, 2- and 3-H_2) and 1.2 (9 H, s, CMe_3); $\delta_C(CDCl_3)$ 178.6 (C=O), 86.8 (d, *J* 169, C-5), 70.0 (d, *J* 19, C-4), 64.0 (C-1), 38.7 (*C*Me_3), 28.3 (d, *J* 6.6, C-3), 27.2 (C*Me*$_3$) and 24.7 (C-2).

A solution of the alcohol **8** (371 mg, 1.8 mmol) and bis(tributyltin) oxide (596 mg, 1 mmol) in toluene was refluxed for 17 h using a water separator and was then cooled to 65 °C. Toluene-*p*-sulfonyl chloride (684 mg, 3.6 mmol), triethylamine (364 mg, 3.6 mmol) and 4-(dimethylamino)pyridine (DMAP) (244 mg, 2 mmol) were added and the mixture was stirred at 65 °C for 24 h. It was then stirred for 1 h at room temperature with potassium fluoride (200 mg), filtered, and evaporated. The residual oil was purified by flash chromatography. Elution with hexane–dichloromethane (1:2) gave the *title compound* **9** as an oil (510 mg, 79%), ν_{max}(film)/cm^{-1} 1730, 1600, 1368, 1286, 1178, 1048 and 1036; $\delta_H(CDCl_3)$ 7.80 and 7.34 (4 H, AA′BB′q, J_{AB} 8.5, ArH), 4.72 (1 H, dm, *J* 18.6, C*H*CH_2F), 4.49 (1 H, ddd, *J* 47.0, 10.3 and 3.8, CHC*H*^{a}F), 4.34 (1 H, ddd, *J* 47.0, 10.3 and 4.7, CHC*H*^{b}F), 4.00 (2 H, t, *J* 6, 1-H_2), 2.45 (3 H, s, Ar*Me*), 1.8 and 1.6 (4 H, 2 × m, 2- and 3-H_2) and 1.2 (9 H, s, CMe_3); $\delta_C(CDCl_3)$ 178.4 (C=O), 145.0, 133.8 and 127.8 (Ar), 82.9 (d, *J* 176.2, C-5), 79.5 (d, *J* 20.3, C-4), 63.2 (C-1), 38.7 (*C*Me_3), 27.1 (d, *J* 5.3, C-3), 24.1 (C-2) and 21.6 (C*Me*$_3$) (Found: C, 56.7; H, 6.8. $C_{17}H_{25}FO_5S$ requires C, 56.65; H, 6.99%).

2-Amino-6-chloro-9-(1′-fluoro-5′-pivaloyloxypentan-2′-yl)-9H-purine **10**.—A mixture of 2-amino-6-chloropurine (340 mg, 2 mmol), anhydrous potassium carbonate (276 mg, 2 mmol) and 18-crown-6 (528 mg, 2 mmol) in DMF (5 cm^3) was stirred for 1 h at 65 °C. A solution of the tosyl compound **9** (721 mg, 2 mmol) in DMF (5 cm^3) was added and the mixture was stirred for 65 h at 65 °C. The solvent was evaporated off and the residual oil was co-evaporated with water (2 × 5 cm^3) and ethanol (2 × 5 cm^{-3}) and flash chromatographed. Elution with dichloromethane–methanol (100:1.6) gave an oil (510 mg) which showed two spots, R_f 0.50 and 0.33, on TLC with chloroform–ethyl acetate (1:1). The oil was dissolved in diethyl ether–hexane 1:1 and left at −20 °C for 24 h. A solid ether clathrate separated and was air-dried at room temperature, m.p. 35–40 °C (R_f 0.50). This was vacuum-dried at 100 °C to give the *title compound* **10** (458 mg, 64%) as an oil, ν_{max}(MeOH)/nm 230 (ε 7600), 249 (7510) and 312 (8320); $\delta_H[(CD_3)_2SO]$ 8.23 (1 H, s, 8-H), 6.84 (2 H, br s, NH_2), 5.00–4.66 (3 H, m, $CHCH_2F$), 3.97 (2 H, t, *J* 6.3, 5′-H_2), 1.97 and 1.45 (4 H, 2 × m, 3′- and 4′-H_2) and 1.1 (9 H, s, CMe_3); $\delta_C[(CD_3)_2SO]$ 178.6 (C=O), 160.2, 154.6 and 150.4 (Ar), 142.7 (C-8), 124 (C-5), 83.9 (d, *J* 170.8, C-1′), 63.7 (C-5′), 55.5 (d, *J* 18.5, C-2′), 27.4 (C*Me*$_3$), 25.5 (d, *J* 5.2, C-3′) and 25.2 (C-4′); $\delta_C(CDCl_3)$ 159.0 (s, C-2), 153.4 (dd, *J* 6 and 3.5, C-4), 151.1 (s, C-6), 141 (ddd, *J* 210, 4.3 and 2.3, C-8) and 124 (d, *J* 11.5, C-5) (Found: C, 50.2; H, 6.0; N, 19.2. $C_{15}H_{21}ClFN_5O_2$ requires C, 50.35; H, 5.92; N, 19.57%).

Elution of the column with dichloromethane–methanol (100:3.2) gave the impure N-7 isomer of compound **10** as needles (35 mg, 8%), λ_{max}(MeOH)/nm 235 (ε 8950), 250 (4570) and 320 (7550). TLC (ethyl acetate) showed two spots, R_f 0.6 and 0.8; $\delta_H[(CD_3)_2SO]$ of the major constituent: 8.62 (8-H) and 6.73 (NH_2); $\delta_C[(CD_3)_2SO]$ 151.1 (C-8) and 115.1 (C-5). A shorter reaction time of 40 h reduced the yield of the N-9 isomer **10** to 45%.

9-(4′-Acetoxy-5′-fluoropentyl)-2-amino-6-chloro-9H-purine **12**.—A mixture of the iodide **6** (612 mg, 2.2 mmol), 2-amino-6-chloropurine (376 mg, 2.2 mmol) and anhydrous potassium carbonate (304 mg, 2.2 mmol) in dry dimethyl sulfoxide (DMSO) (10 cm^3) was stirred at ambient temperature for 5 h. The solvent was removed at 50 °C, and the residue was triturated with dichloromethane (10 cm^3) and filtered. Evaporation of the filtrate yielded a yellow oil, which was chromatographed. Elution with chloroform–methanol (100:2) gave the *title compound* **12** as a solid (410 mg, 65%), m.p. 122–123 °C. A portion was recrystallised from methanol, m.p. 122–123 °C; λ_{max}(MeOH)/nm 229 (ε 7340), 247 (5270) and 311 (7630); $\delta_H[(CD_3)_2SO]$ 8.15 (1 H, s, 8-H), 6.92 (2 H, s, NH_2), 5.00 (1 H, dm, *J* 22.5, C*H*CH_2F), 4.47 (1 H, ddd, *J* 45.2, 10.4 and 2.9, CHC*H*^{a}F), 4.42 (1 H, ddd, *J* 45.2, 10.4 and 5.2, CHC*H*^{b}F), 4.07 (2 H, t, *J* 7, 1′-H_2), 2.04 (3 H, s, Me) and 1.82 and 1.55 (4 H, 2 × m, 2′- and 3′-H_2); $\delta_C[(CD_3)_2SO]$ 170 (C=O), 159.7, 154.1 and 149.3 (Ar), 143.2 (d, *J* 3.6, C-8), 123.3 (C-5), 83.5 (d, *J* 170, C-5′), 71.3 (d, *J* 18.5, C-4′), 42.7 (C-1′), 26.0 (d, *J* 6.3, C-3′), 24.7 (C-2′) and 20.8 (Me) (Found: C, 45.3; H, 5.0; N, 22.1. $C_{12}H_{15}ClFN_5O_2$ requires C, 45.65; H, 4.79; N, 22.18%). Further elution of the column with the same solvent gave *7-(4′-acetoxy-5′-fluoropentyl)-2-amino-6-chloro-7H-purine*, m.p. 152–154 °C (100 mg, 16%). A portion recrystallised from methanol had m.p. 153–154 °C (decomp.); λ_{max}(MeOH)/nm 234 (ε 9740), 250 (4570) and 323 (6160); $\delta_H[(CD_3)_2SO]$ 8.38 (1 H, s, 8-H), 6.62 (2 H, s, NH_2), 5.00 (1 H, dm, *J* 20, C*H*CH_2F), 4.49 (1 H, ddd, *J* 45.5, 10.4 and 2.9, CHC*H*^{a}F), 4.46 (1 H, ddd, *J* 45.5, 10.4 and 5.1, CHC*H*^{b}F), 4.30 (2 H, *J* 7, 1′-H_2), 2.03 (3 H, s, Me) and 1.82 and 1.56 (4 H, 2 × m, 2′- and 3′-H_2); $\delta_C[(CD_3)_2SO]$ 170 (C=O), 164.3, 159.9 (Ar) 149.4 (d, *J* 3.8, C-8), 142.1 (Ar) 114.7 (C-5), 83.5 (d, *J* 169.6, C-5′), 71.3 (d, *J* 18.4, C-4′), 45.8 (C-1′), 26.5 (C-2′), 25.8 (d, *J* 6.4, C-3′) and 20.7 (Me) (Found: C, 45.5; H, 5.0; N, 22.2%).

2-Amino-9-(1′-fluoro-5′-hydroxypentan-2′-yl)-6-methoxy-9H-purine **11**.—A mixture of compound **10** (180 mg, 0.5 mmol) and anhydrous potassium carbonate (200 mg, 1.45 mmol) in dry methanol (10 cm^3) was stirred and refluxed for 4 h. The solvent was evaporated off and the residue was purified by flash chromatography with dichloromethane–methanol (10:1). The product (112 mg, 82%) was a gum which solidified to give the *title compound* **11** as a solid, m.p. 112–114 °C; λ_{max}(water)/nm pH 7 and pH 12, 217 (5390), 249 (7290) and 281 (ε 8550); $\delta_H[(CD_3)_2SO]$ 7.9 (1 H, s, 8-H), 6.3 (2 H, br s, D_2O exch., NH_2), 4.9–4.6 (3 H, 3 × m, $CHCH_2F$), 4.39 (1 H, dt, D_2O exch., OH), 4.0 (3 H, s, OMe), 3.35 (2 H, dt, D_2O converts to t, *J* 6.2,

5′-H_2), 1.9 (2 H, m, 4′-H_2) and 1.3 (2 H, dm, 3′-H_2); δ_C[$(CD_3)_2SO$] 160.6, 159.7 and 154.3 (Ar), 138.5 (C-8), 113.8 (C-5), 83.7 (d, *J* 170, C-1′), 59.9 (C-5′), 54.2 (d, *J* 18.7, C-2′), 53.1 (OMe), 28.6 (C-4′) and 25.5 (d, *J* 5, C-3′) (Found: C, 48.8; H, 5.9; N, 25.9. $C_{11}H_{16}FN_5O_2$ requires C, 49.06; H, 5.99; N, 26.01%).

9-(1′-*Fluoro*-5′-*hydroxypentan*-2′-*yl*)-9H-*guanine Hydrate* **4**.—A solution of TMSBr (0.03 cm^3, 0.25 mmol) in DMF (2 cm^3) was added to a solution of compound **11** (68 mg, 0.25 mmol) in DMF (2 cm^3) under N_2, and the mixture was stirred for 24 h. The solvent was removed at 40 °C and the residue was co-evaporated with methanol (3 × 5 cm^3). The resulting yellow gum was purified by flash chromatography. Elution with dichloromethane–methanol (10:2) gave unchanged substrate **11** (21 mg). Elution with the same solvents (10:7) gave a foam (42 mg), λ_{max}(water)/nm pH 7, 255 (ε 12 020) and 270 (9380); pH 12, 255 (10 010) and 270 (10 510); δ_H[$(CD_3)_2SO$] 10.65 (1 H, s, D_2O exch., N^1H), 7.79 (1 H, s, 8-H), 6.49 (2 H, s, D_2O exch., NH_2), 4.9–4.6 (3 H, 3 × m, *J* 50.5 and 9.66, $CHCH_2F$), 4.44 (1 H, t, *J* 5.1, D_2O exch., OH), 3.44 after D_2O (2 *H*, *t*, *J* 6.3, 5′-H_2), 1.87 (2 H, m, 4′-H_2) and 1.32 (2 H, dm, 3′-H_2); δ_C[$(CD_3)_2SO$] 156.8, 153.5 and 151.4 (Ar), 136.1 (C-8), 116.5 (C-5), 83.8 (d, *J* 170, C-1′), 59.9 (C-5′), 54.1 (d, *J* 18.7, C-2′), 29.6 (C-4′) and 25.7 (d, *J* 5.0, C-3′).

9-(1′-*Fluoro*-5′-*hydroxypentan*-2′-*yl*)-9H-*guanine*•*Sodium Chloride*.—To a mixture of compound **11** (112 mg, 0.4 mmol) and sodium iodide (62.5 mg, 0.42 mmol) in DMF (4 cm^3), stirred under nitrogen, was added a solution of TMSCl (0.06 cm^3, 0.42 mmol) in DMF (1 cm^3). The mixture was stirred for 22 h. The solvent was removed at 40 °C and the residue co-evaporated with methanol (3 × 5 cm^3). Flash chromatography with dichloromethane–methanol gave the *title product* as a foam (117 mg, 87%), λ_{max}(water)/nm 251 (ε 13 340) and 270 (9930); δ_H[$(CD_3)_2SO$] 10.93 (1 H, D_2O exch., N^1H), 7.78 (1 H, d, *J* 2.5, 8-H), 6.76 (2 H, br s, D_2O exch., NH_2), 4.94–4.55 (3 H, 3 × m, $CHCH_2F$), 4.52 (1 H, t, *J* 5.1, D_2O exch., OH), 3.35 visible after D_2O (2 H, t, *J* 6.3, 5′-H_2), 1.85 (2 H, m, 4′-H_2) and 1.30 (2 H, dm, 3′-H_2); δ_C[$(CD_3)_2SO$] 156.8, 153.7 and 151.3 (Ar), 135.9 (C-8), 116.5 (C-5), 83.8 (d, *J* 169.9, C-1′), 59.9 (C-5′), 53.0 (d, *J* 18.7, C-2′), 28.6 (C-4′) and 25.7 (d, *J* 5, C-3′) (Found: C, 37.2; H, 4.6; N, 21.6; Cl, 11.1; Na, 7.1. $C_{10}H_{14}FN_5O_2$•Na-Cl•0.5H_2O requires C, 37.22; H, 4.69; N, 21.70; Cl, 10.99; Na, 7.12%); +ve FAB–MS *m*/*z*, 278 (M + Na^+), 256 (M + H^+).

Viruses and Antiviral Assays.—The source of the viruses and methodology of the antiviral assays are described in previous publications: for herpes simplex virus [26] and most of the other viruses,[27] *varicella zoster* and cytomegalovirus,[28] human immunodeficiency virus [29] and the myxoviruses.[30]

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