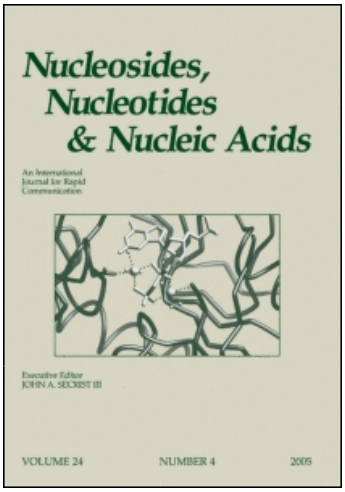

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Fluorinated Carbaacyclonucleosides: Synthesis and Evaluation of Antiviral Activity

Maureen Lewis[a]; T. Brian[a]; H. McMurry[a]; Erik De Clercq[b]
[a] University Chemical Laboratory, Dublin, Ireland [b] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

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FLUORINATED CARBAACYCLONUCLEOSIDES: SYNTHESIS AND EVALUATION OF ANTIVIRAL ACTIVITY.

Maureen Lewis,*[a] T. Brian H. McMurry*, and Erik De Clercq[b].
[a]University Chemical Laboratory, Trinity College, Dublin 2, Ireland.
[b]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium.

Abstract: Two series of fluoroacyclic nucleosides were synthesised by condensation of nucleic acid bases with substituted fluoropentanes. 1-(5'-Fluoro-4'-hydroxypentyl)-cytosine showed a modest activity against cytomegalovirus (MIC_{50}: 12-15 μg/ml). All the other compounds were inactive against all the viruses tested.

The discovery of the antiviral potency of 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir)[1] stimulated the synthesis of a large number of acyclonucleosides with various side chains and aglycones[2,3]. Carbocyclic analogues of nucleosides in which the oxygen of furanose is replaced by a methylene group show increased resistance to phosphorylases while maintaining their biological activity.[4] Replacement of a hydrogen atom by fluorine does not produce drastic steric changes in a molecule[5a] 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.[5b] Pyrimidine and purine nucleosides containing fluorine in the C2' (β) (arabino) configuration show dramatically different biological activity and enhanced chemical and metabolic stability compared to the parent deoxynucleoside.[6] As an extension of previous work[7] we describe the synthesis of two series of fluorinated carbaacyclonucleosides.

Chemistry

The alkylating moieties, 1-fluoro-5-iodopentan-2-yl acetate **1** and 5-fluoro-4-tosyloxypentyl pivalate **2** were obtained through ring opening of 2-(fluoromethyl) tetrahydrofuran as described previously[7] for the preparation of 2-amino-6-chloro-9-(1'-fluoro-5'-pivaloyloxypentan-2'-yl)-9H-purine **6** and 9-(4'-acetoxy-5'-fluoro- pentyl)-2-amino-6-chloro-9H-purine **12**.

The reaction of **2** with 4-methoxy-5-methyl-2-pyrimidinone in dimethylformamide using potassium carbonate as base and 18-crown-6 as catalyst[8], gave a mixture of isomers (see below) from which the required product, **3** was isolated by chromatography. The cytosine analogue **4** was also obtained in the same way, but the yield was improved by use of cesium carbonate in place of potassium carbonate and 18-crown-6[9]. 1-(1'-Fluoro-5' -pivaloxypentan-2'-yl)-O^4-methylthymine **3** was obtained in 30% yield and the isomeric O^2-alkylated product **3a** in 57% yield. The yield of 1-(1'-fluoro-5'-pivaloxypentan-2'-yl)-cytosine **4** was 56% together with 22% of the less polar O^2-isomer **4a**. The position of alkylation of the pyrimidine nucleus in each case was decided by comparison of NMR and UV measurements with literature values.[10] Although there was a marked difference in the R_f values of the N- and O-isomers of the pyrimidine analogues, repeated flash chromatography failed to give a satisfactory separation. The pure isomers were isolated by preparative TLC. Removal of the pivaloyloxy group in **3** and **4** by refluxing in methanol with potassium carbonate (followed by acid hydrolysis of the 4-methoxy group in **3**), afforded compounds **7** and **8**.

The mixture resulting from the alkylation of adenine was separated by flash column chromatography. The main fraction (64%), which showed a single spot on TLC, was separated from an impure more polar fraction (16%). The main fraction was tentatively identified as the N-9 isomer **5** on the basis of ^{13}C NMR evidence. The C-2' signal appeared as a doublet at a higher field 54.9ppm, than the corresponding doublet at 61.5 ppm for the more polar fraction. **5a**. The pivaloyloxy protecting group was removed by refluxing with potassium carbonate in methanol. The N-9 site of alkylation in compound **9** was unambiguously confirmed by ^{13}C NMR[11]. Irradiation of the proton signal at 8.24 ppm showed decoupling with both the C-5 signal at 118.8 ppm[12] and the C-4 signal at 149.6 ppm. Irradiation of the signal at 8.15 showed decoupling with C-4 and with C-6 at

TABLE I ^{1}H NMR Spectral Data[a]

Compd	Base Protons	H_A-1'	H_B-1'	H-2'	H_2-3' H_2-4'	H_2-5'	Other
3[c]	7.31 s	4.7, ddd J,47.1,10.3, 3.4	4.63 ddd J,48.3,10.3,2.3	4.97 dm J,31.7	1.91 m 1.68 m	4.09 t J,6.3	4.00 (s,3H, OMe) 1.97 (d, 3H, J,0.8 Me) 1.2 (s, 9H,CMe_3)
3a[c]	7.96 s	4.63 ddd J,50.0,10.0,5.0	4.58 ddd J,50.0, 10.0,5.0	5.39 dm J,18.7	1.80 m	4.10 dt J,5.9	3.99 (s,3H,OMe) 1.94 (s,3H,Me) 1.19 (s,9H,Me_3)
4[m]	7.60 d 5.71d J,7.2 J.7.2	b	b 4.76 - 4.33 (3H,m)	b	1.70 m 1.47 m	3.98 t J,6.3	7.13 (bd, 2H,J,16.0,NH_2) 1.13 (s,(9H, CMe_3)
4a[m]	7.84d 6.08d J, 5.7 J.5.7	4.58, ddd J.47.6,10.3,3.4	4.54, ddd J,47.2,10.3,5.2	5.21 dm J,22.8	1.67 m	4.02 t J,5.6	6.87 (bs,2H,HN_2) 1.12 (s,9H,CMe_3)
5[c]	8.33 s 7.91 s	b	b 4,98 - 4.61 (3.H,m)	b	2.13 dm 1.63 dm	4.08 t J,5.7	6.10 (s,2H,NH_2) 1.18 (s,9H,CMe_3)
5a[c]	8.13 s 8.02 s	5.11, ddd J 47.1, 10.1,5.7	4.78, ddd J,47.2,10.1,2.7	4.98 dm J,27.0	2.28 dm 1.66 dm	4.08 t J,5.1	6.9 (bs,NH_2) 1.17 (s,9H,CMe_3)
7[m]	7.57 d J, 0.9 11.28 bs	b	b 4.73 - 4.47 (4H,m) 3H after D_2O	b	1.70 m 1.35 m	3,38 t J,6.3	1.79 (d,3H,J,0.9,Me) Obscured OH
8[m]	7.57 d 5.70 d J, 7.3 J.7.3	b	b 4,.74 - 4.41 (4H,m) 3H after D_2O	b	1.70 m 1.32 m	3.37 t J,6.3	7.04 (bd,2H,J,13.2,NH_2) Obscured OH
9[m]	8.24 s 8.15 s	b	b 5.04 - 4.66 (3H,m)	b	1.95 m 1.29 dm	3.37 t H,6.3	7.26 (s,2H,NH_2) 4.45 (t, 1H,J,5.1,0H)

[a]Signals are quoted as s (singlet), d (doublet), bs (broad singlet) , bd (broad doublet) ddd double (double-doublet), t (triplet), dt (apparent double triplet), b Signal overlap. [c]In $CDCl_3$ [m]In DMSO-d_6

TABLE II ^{1}H NMR SPECTRAL DATA[a]

Compd	Base Protons	H_A-5'	H_B-5'	H-4'	H_2-3' H_2-2'	H_2-1'	Other
10[c]	7.18 s J,1.1	4.47 ddd J,47.3.10.3,3.4	4.42 ddd J,47.3,10.3,4.8	5.08 dm J,31.0	1.88- 1.63m	3.84 m	3.98 (s,3H,OMe) 2.11 (s,3H,Ac) 1.95(d,3H.J1.08,Me)
10a[c]	7.98 d J,0.9	4.49 ddd J,47.4,10.2,3.2	4.44 ddd J,47.4,10.2,5.0	5.10 dm J,18.0	1.85 m	4.34 t J,6.2	3.98 (s,3H,OMe) 2.10 (s,3H,Ac) 2.05 (d,3H,J,0.93,Me)
11[m]	8.15 8.14	4.49 ddd J,47.3,10.4,3.0	4.43 ddd J,47.3,10.4,5.2	5.01 dm J,21.3	1.84 m 1.53 m	4.16 t J,6.9	7.17 (s,2H,NH_2) 2.03 (s,3H,Ac)
13[m]	7.82 d J,1.0	4,26 ddd J,47.6,9.3,4.2	4.21 ddd J,47.9,9.3,5.7	3.55 dm J,24.0	1,65 dm 1.33 m	3.74, t J,6.9	5.05 (bs,1H,OH) 3.83 (s,3H,OMe) 1.87 (d,3H,Me)
14[m]	7.54 d J,1.2 11.21 bs,1H	4.27 ddd J,47.5,9.3,4.2	4.22 ddd J,47.9,9.3,5.6	b 3.63 m 3H	1.63 m 1.33 m	b 3.63 m 3H	5.04 (bs,1H,OH) 1.75 (d,3H,J,1.2)
15[m]	7,57 d 5.63d J,7.1 J,7.1	4.27 ddd J,47.5,9.3,4.1	4.21 ddd 47.9,9.3,5.7	b 3.63 m	1.63 dm 1.32 m	b 3.63 m	6.97 (bd,2H,J,18.8) 5.00 (d,1H,J.5.4 OH)
15a[m]	7.84 d 6.07d J,5.8 J,5.8	4.29 ddd J,53.6,9.3,4.2	4.24 ddd J,53.6,9.3,5.7	3.65 m	1.8, m 1.4 m	4.15 t J,6.3	6.86 (bs,2H,NH_2)
16[m]	8.15 s 8.14 s	b 4,35 - 4.10	b 4.35 - 4.10	3.66 dm J,19.5	1.90 dm 1.30 m	b 4.35-4.10	7.20 (s,2H,NH_2) 5.03 (d,1H,OH)
17[m]	7.70 s 10.62 s	4.27 ddd J,47.6,9.4,4.1	4.23 ddd J,47.9,9.4,5.6	3.65 dm J,19.0	1.60 dm 1.35 m	3.95 t J.6.1	6.50 (2H,NH_2) 5.0 (d,1H,OH)

(a) Signals are quoted as s (singlet), d (doublet), bs (broad singlet), bd (broad doublet) ddd (double double-doublet), t (triplet), dt (apparent double triplet), b Signal overlap [c]In $CDCl_3$ [m]In DMSO-d_6

TABLE III ^{13}C NMR SPECTRAL DATA[a]

Compd	C=O	Aromatic	C-5'	C-1'	C-2'	C-3'	C-4'	C-5'	Other
3[c]	178.3	170.3 156.6 141.2,d J,3.5	104.9	84.2 d J,172	55.8 d J,21.6	25.6 d J,4.7	25.1	63.2	54.5 (OMe) 38.7 (CMe$_3$) 27.1 (Me$_3$) 12.2. (d,J,1.7 Me)
3a[c]	178.4	169.7 163.0 156.8,d J,1.2	111.4	83.5 d J,172	73.8 d J,19.8	26.6 d J,5.3	24.4	63.8	53.9 (OMe), 38.6 (CMe$_3$) 27.1 (Me$_3$) 11.7 (d,J,1.2,Me)
4[m]	177.4	165.3 156.0 143.0	94.0	83.9 d J,168	55.0 d J,18.8	24.7 J,4.7	24.6	63.3	38.8 (CMe$_3$) 26.9 (Me$_3$)
4a[m]	177.5	165.5 164.4 156.2	99.6	83.8 d J,168.8	72.6 d J,18.6	26.0 d J,5.8	24.1	63.7	38.8 (CM$_3$) 26.9 (Me$_3$)
5[c]	178.3	155.6 152.8 149.8 139.3	119.5	83.6 d J.173.8	54.9 d J,19.2	26.5 J,5.3	25.1	62.9	38.6 (CMc$_3$) 27.1 (Me$_3$)
5a[c]	178.3	154.7 153.4 150.0 141.5	121.0	82.5 d J,173.8	61.5 d J,18.7	25.2 d J.5.3	25.1	62.8	38.6 (CMe) 27.0 (Me$_3$)
7[m]		163.7 151.4 137.7	109.3	83.3 d J,168	54.4 d J.19.3	24.1 d J,5.8	28.4	59.9	12.1 (Me)
8[m]		165.2 155.5 143.0	93.7	84.0 d J,167.0	55.3 d J.19.0	24.7 J,5.3	28.5	60.0	
9[m]		156.0 152.4 149.6 139.9 d d bd bd ^3J ^1J ^3J ^1J 11.0 209.0 13.0 223	118.8 bd ^3J 8.0	83.67 d J,169.0	54.8 d J.18.0	25.5 d J,5,8	28.6 d	59.9	

[a]Signals are quoted as d(doublet),bd (broad doublet) dm (double multiplet) [c]In $CdCl_3$ [m]In DMSO-d_6

(continued)

TABLE III ^{13}C NMR SPECTRAL DATA[a]

Compd	C=O	Aromatic	C-5'	C-1'	C-2'	C-3'	C-4'	C-5'	Other
10[m]	170.0	169.8 155.3 146.6	102.3	48.4	24.2	25.9 d J,6.4	71.4 d J,18.0	83.6 d J,167	53.9 (OMe) 20.7 (Ac) 11.5 (Me)
10a[m]	170.1	167.0 163.2 157.2 d J,2.9	110.5	66.2	24.2	25.7 d J,6.4	71.5 d J,18.1	83.7 d J,168.5	55.9 (OMe) 20.1 (Ac) 11.5 (Me)
11[m]	170.0	155.9 152.3 149.5 140.8	118.7	42.9	25.2	26.0 J,6.4	71.2 d J,17.5	83.6 d J 168.5	20.7 (Ac)
13[m]		168.9 163.3 157.2	110.3	66.7	24.6	28.7 d J,6.4	68.3 d J.18.7	86.9 d J.168.0	53.7 (OMe) 11.5 Me)
13a[m]		170.0 156.0 146.4	103.3	49.3	25.0	29.1 d J,6.4	68.6 d J,18.7	86.9 d J,167.4	54.4 (OMe) 11.8 (Me)
14[m]		164.3 150.9 141.5	108.41	47.1	24.7	28.9 d J,5.8	68.2 d J,18.7	86.7 d J,168.0	12.0 (Me)
15[m]		165.9 155.9 146.0	93.1	48.5	25.0	29.0 d J,5.8	68.3 d J,18.4	86.7 d J,166.8	
15a[m]		165.4 164.9 156.2	99.3	65.7	24.7	28.8 d J,6.4	68.3 d J,18.3	86.6 d J.167	
16[m]		156.0 152.4 149.6 140.9 d d dm bd ^3J ^1J ^3J ^1J 11.1 119.6 10.5 208.8	118.8 bd ^3J 10.5	42.9	25.7	29.1 d J,7.0	68.1 d J,18.7	86.6 d J,168	
17[m]		156.7 153.4 151.1 137.4	116.5	42.6	25.6	29.1 d J,6.3	68.0 d J,18.9	86.5 d J,168.7	

[a]Signals are quoted as d (doublet), bd (broad doublet) dm (double multiplet)
[c] In $CDCl_3$ [m] In DMSO-d_6

156.0 ppm. A 2-D NMR ^{1}H- ^{13}C correlation experiment connected the signals 8.24 (8-H) with 139.9 (C-8) and 8.15 (2-H) with 152.4 (C-2). The C-8 signal was upfield from the C-2 signal which is characteristic of N-9 alkylated adenines.[11] Irradiation at 4.88 ppm showed decoupling with C-4 and C-8. For compound **16** the separation between signals 8-H and 2-H was too small for selective irradiation. Decoupling at 4.16 ppm showed correlation with C-4 at 149.6 ppm and the signal at 140.9 ppm. Compound **16** was assigned the N-9 structure on the basis of literature values[13] and the similarities of the UV and ^{13}C NMR data with compound **9**.

Condensation of the iodide with nucleic acid bases by stirring with potassium carbonate in DMF at ambient temperature for 24h, gave compounds **10, 11,13** and **16.** Cesium carbonate replaced potassium carbonate in the reaction with cytosine which gave the N- and O- isomers of **15** directly. Hydrolysis with 10% HCl of compounds **10** and **12** gave **14** and **17** respectively.

Evaluation of Antiviral Activity

The antiviral activity and cytotoxicity of the compounds are shown in Table IV. All the compounds were inactive against all viruses, except for compound **15** which showed a modest activity against cytomegalovirus (MIC_{50}: 12-15 μg/ml). This anti-CMV activity must be considered as specific since (1) compound **15** was not inhibitory to the host cell growth unless its concentration was raised to 200 μg/ml and (11) compound **15** did not show activity against any of the other viruses tested.

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 Tables I-III were recorded in ppm on a Bruker MSL300 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. 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).

TABLE IV

Virus (strain)	Cell	MIC_{50}[a,b] (μg/mL) 9	7	8	17	16	14	15	Ribavirin	Ganciclovir	Acyclovir	BVDU
HSV-1 (KOS)	ESM	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	0.002	0.0 7	0.001
HSV-2 (G)	ESM	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	0.007	0.07	200
TK⁻ HSV-1 (B2006)	ESM	> 400	> 400	> 400	> 400	> 400	> 400	> 400	100	20	70	100
VZV (Oka)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	> 50			0.13	0.0001
VZV (YS)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	> 50			0.27	0.0002
TK⁻ VZV (07-01)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	> 50			9	> 50
TK⁻ VZV (YS-R)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	> 50			9	> 50
CMV (AD-169)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	15		0.7		
CMV (Davis)	HEL	> 50	> 50	> 50	> 50	> 50	> 50	12		0.5		
Vaccinia	ESM	> 400	> 200	> 400	> 400	> 400	> 400	> 400	40	> 100	> 400	0.2
Polio-1	HeLa	> 400	> 400	> 400	> 400	> 400	> 400	> 400	70			> 400
Coxsackie B4	HeLa	> 400	> 400	> 400	> 400	> 400	> 400	> 400	70			> 400
Reo-1	Vero	> 400	> 400	> 400	> 400	> 400	> 400	> 400	150			> 400
Parainfluenza-3	Vero	> 400	> 400	> 400	> 400	> 400	> 400	> 400	70			> 400
Sindbis	Vero	> 400	> 400	> 400	> 400	> 400	> 400	> 400	70			> 400
Semliki forest	Vero	> 400	> 400	> 400	> 400	> 400	> 400	> 400	200			> 400
Junin	Vero	> 50	> 200	> 50	> 200	> 50	> 200	> 200	8			
Tacaribe	Vero	> 50	> 200	> 50	> 200	> 50	> 200	> 200	5			
Vesicular stomatitis	ESM	> 400	> 400	> 400	> 400	> 400	> 400	> 400	10	>100	> 400	> 400
HIV-1 (III_B/LAI)	CEM	> 100	> 100	> 100	> 100	> 100	> 100	> 100				
HIV-2(ROD)	CEM	> 100	> 100	> 100	> 100	> 100	> 100	> 100				
Cell growth	HEL				150	100	150	200		> 50	> 200	> 200

[a]Minimal inhibitory concentration required to reduce virus-induced cytopathicity by 50%. Abbreviations for viruses and cells; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; TK⁻, thmidine kinase-deficient; VZV, varicella-zoster virus; CMV, cytomegalovirus; HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; ESM, (human) embryonic-skin muscle (cells); HEL, human embryonic lung (fibroblasts); HeLa, human cervix carcinoma (epithelial) cells; Vero, African green monkey kidney cells; CEM, human T-4 lymphocyte cells.
[b]None of the compounds proved cytotoxic to the cells, as monitored by microscopically visible alteration of normal cell morphology, at the highest concentrations tested.

1-(1'-Fluoro-5'-pivaloyloxypentan-2'-yl)-O^4-methylthymine **3** The tosyl compound **2** (550 mg, 1.5 mmol) was added to a mixture of 4-methoxy-5-methyl-2-pyrimidinone (240 mg, 1.65 mmol), potassium carbonate (700 mg, 5.0 mmol) and 18-crown-6 (370 mg, 1.5 mmol) in DMF (5 cm^3) and stirred at 65°C for 72h. The solvent was evaporated. The residue was triturated with 2 x 50 cm^3 of ethyl acetate, filtered through a pad of silica gel and evaporated. TLC of the crude oil using dichloromethane - ethyl acetate (10:1) gave the 0^2-isomer **3a**, R_f 0.68, as an oil (283 mg, 57%); UV (MeOH)λ_{max} 268 nm. The title compound **3**, R_f 0.34, (149 mg, 30%) was crystallised from hexane :diethyl ether (1:1) to give needles, m.p 94°C; UV(MeOH) λ_{max} 284 nm. Anal. ($C_{16}H_{25}FO_4N_2$) calculated C, 58.52; H, 7.67; N, 8.53. Found: C, 58.52; H, 7.46; N, 8.38.

1-(1'-Fluoro-5'-pivaloyloxypentan-2'-yl)-cytosine. **4**. A mixture of the tosyl ester **2** (360 mg, 1 mmol) cytosine (116 mg, 1.05 mmol) and cesium carbonate (655 mg, 2 mmol) in dry DMF (5 cm^3) was stirred at 75°C for 17 h. The solvent was evaporated. The residue was triturated with ethyl acetate-methanol (5:1, 2 x 50 cm^3), filtered through a pad of silica gel and evaporated. TLC of the crude oil with ethyl acetate gave the 0^2-isomer **4a**, R_f 0.85, as an oil (66 mg, 22%). UV (MeOH) λ_{max} 272 nm. UV (0.01 M H Cl) 262 nm. The title compound **4** R_f 0.35, (170 mg, 56%), after trituration with pentane-acetone 1:1, gave a white powder. UV (MeOH) λ_{max} 275 nm. UV (0.01 HCl) λ_{max} 285 nm. Anal. ($C_{14}H_{22}FN_3O_3$): calculated C, 56.17, H, 7.41; N, 14.04. Found: C, 55.98; H, 7.17, N, 13.89.

9-(1'-Fluoro-5'-pivaloyloxypentan-2'-yl)-9H-adenine **5**. The tosyl ester **2** was condensed with adenine in the same way as described for compound **3**. The crude product was flash chromatographed twice. Elution with dichloromethane-methanol (100:5) gave the title compound **5** (208 mg, 64%) which was recrystallised from dichloromethane-hexane, (1:1). m.p. 125-126°C. UV (MeOH) λ_{max} 262 nm. Anal. ($C_{15}H_{22}$ F N_5 O_2): Calculated C, 55.72; H, 6.86; N, 21.66. Found: C, 55.58; H, 6.78; N, 21.80

Elution of the column with dichloromethane-methanol (100:7) gave the impure N-3 isomer **5a** as a yellow gum. λ_{max} (MeOH) 277 nm.

1-(1-Fluoro-5'-hydroxypentan-2'-yl)-thymine **7**. A mixture of the ester **3** (75 mg, 0.23 mmol) and anhydrous potassium carbonate (200 mg, 1.5 mmol) in methanol (5 cm^3) was refluxed with stirring for 3 h. The mixture was acidified to pH2 with 10% HCl, stirred at ambient temperature for 1 hr and evaporated. The residue was co-evaporated with ethanol (3 x 5 cm^3) and triturated with ethanol (5 cm^3). The ethanol soluble material was purified by TLC using ethyl acetate - methanol (10:1). Elution with ethanol gave a clear oil (40 mg, 76%) which on trituration with diethyl ether gave a white solid. UV (MeOH) λ_{max} 270 nm. Anal. ($C_{10}H_{15}FN_2O_3$ 0.25 H_2O): calculated: C, 51.17; H, 6.66 N, 11.93; found: C, 51.44; H, 6.43; N, 11.65.

1-(1'-Fluoro-5'-hydroxypentan-2'-yl)-cytosine. **8** A mixture of compound **4** (184 mg, 0.62 mmol) and anhydrous potassium carbonate (500 mg, 3.6 mmol) in methanol (5 cm^3) was refluxed with stirring for 3h. The mixture was acidified to pH7 with 10% HCl and the solvent removed in vacuo. The residue was co-evaporated with ethanol (3 x 5 cm^3) and triturated with ethanol. The ethanol soluble material was purified by TLC with ethanol, to give the title compound **8** (55 mg, 41%). Trituration with ethanol-diethyl ether gave a white powder. UV (MeOH) λ_{max} 274 nm. Anal. ($C_9H_{14}FN_3O_2$. 0.5 H_2O). Calculated: C, 48.21; H, 6.74; N, 18.74. Found C, 48.29; H, 6.43; N, 18.60.

9-(1'-Fluoro-5'-hydroxypentan-2'-yl)-adenine **9**. Compound **5** (110 mg, 0.34 mmol) was hydrolysed as described for compound **8.** The ethanol soluble material was flash chromatographed. Elution with dichloromethane-methanol (100:16) gave a clear gum which was triturated with diethyl ether to yield the title compound **9**(58 mg, 71%) as a white powder. UV (MeOH) λ_{max} 263 nm. Anal. ($C_{10}H_{14}N_5OF$. $0.2H_2O$). Calculated: C, 49.46; H, 5.98; N, 28.84. Found: C, 49.10; H, 5.97; N, 28.53.

1-(4'-acetoxy-5'-fluoropentyl)-O^4-methylthymine. **10**. The iodide **1** (276 mg, 1 mmol) was added to a mixture of 4-methoxy-5-methyl-2-pyrimidinone (140 mg, 1 mmol) and anhydrous potassium carbonate (276 mg, 2.0 mmol) in DMF (5 cm^3) and stirred at ambient temperature for 24h. The solvent was evaporated, the residue triturated with ethanol (2 x 50 cm^3) and the ethanol solutions filtered through a pad of silica gel (10 g).

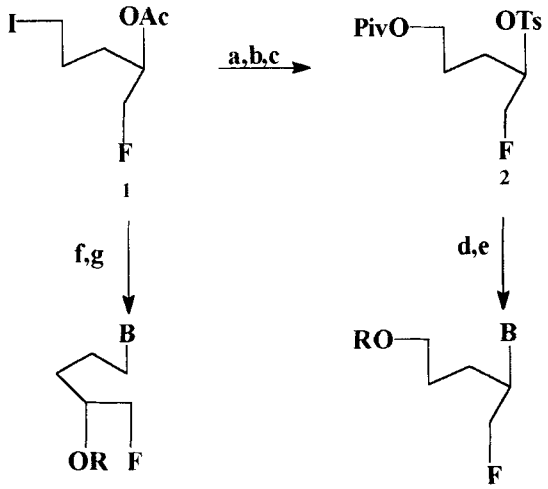
Evaporation of the combined filtrate left an oil which was separated by TLC with dichloromethane-ethyl acetate (10:1) to give the O^2 -isomer of **10a** R_f 0.63 (28 mg, 10%) UV (MeOH) λ_{max} 266 nm and the title compound **10** R_f 0.13. (184 mg, 64%), as a colorless gum, UV (MeOH) λ_{max} 284 nm. Anal. ($C_{13}H_{19}FN_2O_4.0.5H_20$). Calculated: C, 52.88; H, 6.83; N, 9.49. Found: C, 52.86; H, 6.57; N, 9.14.

Partial hydrolysis of the acetate group occurred during work up. 1-(5' -fluoro-4'-hydroxypentyl)-O^4 -methylthymine **13** was isolated by TLC with dichlormethane-methanol (2:1) and recrystallised from ethanol, m.p. 111- 113°C. UV (MeOH) λ_{max} 283 nm. Anal. ($C_{11}H_{17}FN_2O_3.0.5H_20$). Calculated: C, 52.16; H, 7.16; N, 11.06. Found: C, 52.15; H, 6.90; N, 10.94.

1-(5'-Fluoro-4'-hydoxypentyl)-thymine **14**. The acetate **10** (143 mg, 0.5 mmol) was refluxed for 1 h in ethanol: 10% HCl (1:1). The cooled solution was adjusted to pH7 with sodium carbonate and the solvent evaporated in vacuo. The residue was co-evaporated with ethanol (3 x 5 cm^3 and then triturated with ethanol (10 cm^3). TLC of the ethanol soluble material with ethyl acetate-methanol (10:1) gave the title compound **14** as a white powder. (72 mg, 63%). UV (MeOH) λ_{max} 272 nm. Anal. ($C_{10}H_{15}FN_2O_3.0.5H_20$). Calculated: C, 50.20; H, 6.74; N, 11.71. Found: C, 50.35; H, 6.51; N, 11.34.

1-(5'-Fluoro-4'-hydroxypentyl)-cytosine **15**. Cytosine (1 mmol) was alkylated with the iodide (1 mmol) using the same procedure as described for compound **10** except that anhydrous cesium carbonate (652 mg, 2 mmol) replaced potassium carbonate. TLC of the crude product with ethanol gave the O^2-isomer **15a**. R_f 0.85 (37 mg, 17%). UV (MeOH) λ_{max} 272 nm. UV (0.01 HCl) λ_{max} 261 nm. The title compound **15** R_f 0.54 (157 mg, 73%) after trituration with ethanol-diethyl ether was a white powder. UV (MeOH) λ_{max} 273 nm. UV (0.01 HCl) λ_{max} 288 nm. Anal. ($C_9H_{14}FN_3O_2.0.5H_20$). Calculated: C, 48.21; H, 6.74; N, 18.74. Found: C, 47.98; H, 6.33; N, 18.48.

9-(5'-Fluor-4-hydroxypentan-1'-yl)-9H-adenine **16** and 9-(4'-acetoxy-5'-fluoropentyl)-9H-adenine **11**. Adenine (135 mg, 1 mmol) was alkylated with the iodide as described for compound **10**. The crude product was flash chromatographed. Elution with dichloromethane-methanol (10:1) gave the acetate (35 mg, 12%) which crystallised from



10. R=Ac, B= O^4-methylthymin-1-yl
11. R=Ac, B=adenyl-9-yl
12. R=Ac. B=2-amino-6-chloropurin-9-yl
13. R=H, B=O^4-methylthymin-l-yl
14. R=H, B=thymin-l-yl
15.R=H, B=cytosin-l-yl
16 R=H, B=adenin-9-yl
17 R=H, B=guanin-9-yl

3. R=Piv B=O^4-methylthymin-1-yl
4 R=Piv, B=cytosin-1-yl
5 R=Piv, B=adenin-9-yl
6 R=Piv, B=2-amino-6-chloropurin-9-yl
7 R=H; B=thymin-l-yl
8 R=H, B=cytosin-l-yl
9 R=H, B=adenin-9-yl

a. $Me_3CCO_2SnBu_3$, CsF, DMF 40°C; b. NH_3-MeOH, ambient temp.; c, $(Bu_3Sn)_2O$, toluene; then p-TsCl, DMAP, Et_3N, 65°C. d. 5-methyl-4-methoxy-2 pyrimidinone or adenine, K_2CO_3, 18-C-6, DMF, 65°; or cytosine, Cs_2CO_3 DMF, 75°C; e. K_2CO_3, MeOH, 65°C. f. 5-methyl-4-methoxy-2-pyrimidinone or adenine K_2CO_3, DMF ambient temp., or cytosine, Cs_2CO_3, DMF, ambient temp; g. 2M HCl.

ethanol as needles m.p. 143 -145°C. UV (MeOH) λ_{max} 265 nm. Anal. ($C_{12}H_{16}FN_5O_2.0.25H_20$). Calculated: C, 50.93; H, 5.82; N, 24.56. Found: C, 50.64; H, 5.66; N, 24.59. Elution with dichloromethane methanol (7:1) gave the title compound **16** (172 mg, 69%) as a white powder. UV (MeOH) λ_{max} 261. Anal. ($C_{10}H_{14}FN_5O.0.5H_20$). Calculated: C, 48.38; H, 6.09; N, 28.21. Found: C, 48.79; H, 5.97; N, 27.91.

9-(5'-fluoro-4'hydroxypentyl)-9H-guanine **17** Compound **12** (126 mg, 0.34 mmol) was refluxed for 2 hr with 10% HCl. (5cm^3). The mixture was cooled, adjusted to pH7 with sodium carbonate solution and filtered. Recrystallisation of the solid from water gave the title compound m.p. 185-187°C) (93 mg, 83%). UV (H_20) λ_{max} 253 nm. Anal. ($C_{10}H_{14}FN_5O_2$ 1.5 H_20). Calculated: C, 42.55; H, 6.08; N, 24.80. Found: C, 42.38; H, 5.79; N, 24.53.

Viruses and Antiviral Assays

The source of the viruses and methodology of the antiviral assays are described in previous publications for herpes simplex virus[14], and most other viruses[15], varicella zoster and cytomegalovirus[16], human immunodeficiency virus[17] and the myxoviruses[18]

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