Fluoro Carbocyclic Nucleosides: Synthesis and Antiviral Activity of 2′- and 6′-Fluoro Carbocyclic Pyrimidine Nucleosides Including Carbocyclic 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-methyluracil and Carbocyclic 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil[1]

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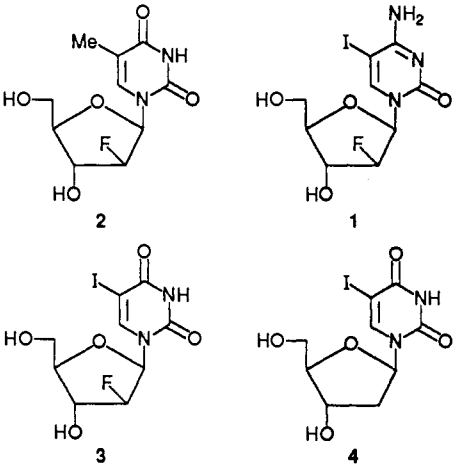
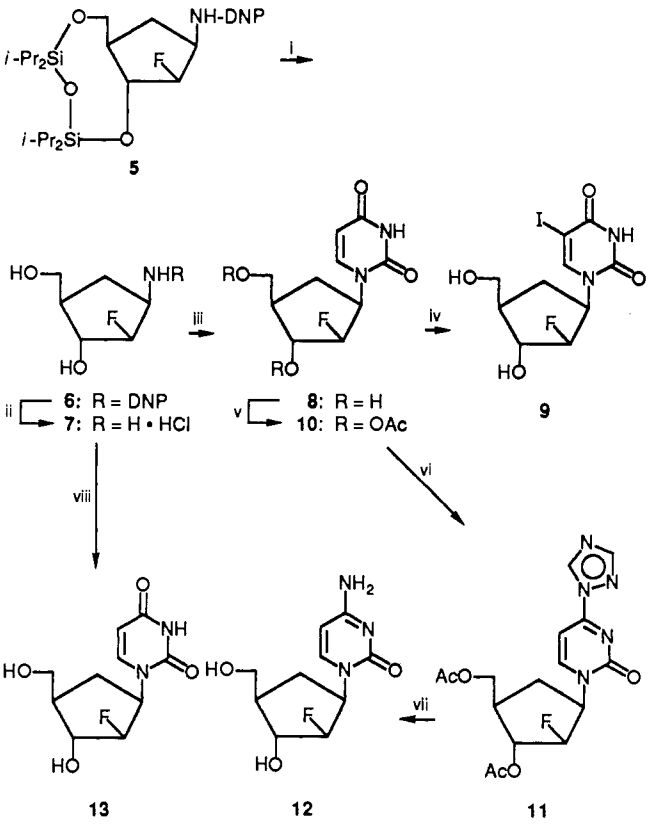
The racemic carbocyclic 2′-fluoroarabinosyl pyrimidine nucleosides **8**, **9** (C-FIAU), **12**, and **13** (C-FMAU) and the 2′-fluororibosyl pyrimidine nucleosides **17**, **20**, and **21** were prepared from their respective protected 2′-fluoro amino diols **5** and **14**. The carbocyclic 2′,2′-difluorothymidine analogue **27** was obtained from the protected difluoro amino diol **24** which was prepared from the ketone **23** and (diethylamino)sulfur trifluoride (DAST). The chiral carbocyclic 2′-deoxy-6′-fluorouridines **33**, **34**, **38**, and **39** were synthesized from the protected 6′-fluoro amino diols **30** and **36**, which were prepared by reduction of the azides **28** and **35**. C-FMAU (**13**) and C-FIAU (**9**) were active in vitro against HSV-1 with ID_{50} values of 4.4 and 11 μg/mL, respectively, but they were inactive against HSV-2. The cytidine analogues **12** and **20** displayed modest activity in vitro against HSV-1 and HSV-2 but were inactive against human influenza A virus.

2′-Fluoroarabinosyl pyrimidine nucleosides are some of the most potent and selective inhibitors of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in cell culture.[2,3] Within this series of compounds 5-iodo-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (FIAC, **1**) and (2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (FMAU, **2**) have emerged as the most potent analogues. Although initial studies[3] showed these compounds to be approximately equipotent in vitro, FMAU appears to demonstrate the greater activity against HSV-1 and HSV-2 in vivo.[4,5] The activity of FIAC in vivo seems to be due to the primary metabolite FIAU.[3,6] Although many carbocyclic derivatives of pyrimidine nucleosides have been described, no 2′-fluoro carbocyclic nucleosides have been reported.



5-Iodo-2′-deoxyuridine (IDU, **4**) was the first nucleoside to be successfully used against herpes infections in humans but was found to be nonselective[9] and mutagenic.[10] Subsequently, numerous 2′-deoxyuridines with different 5-substituents have been found to inhibit the replication of herpes viruses.[8] However, apart from FIAU, modifications to the sugar ring of IDU have resulted in less active compounds.[8] For example, although carbocyclic 5-iodo-2′-deoxyuridine (C-IDU) has similar in vitro activity to IDU against HSV-1, it was found to be an order of magnitude less active against HSV-2.[11] It has been suggested[12] that a fluoromethylene group is a better isostere of oxygen than the methylene group, and therefore carbocyclic de-

Scheme I[a]



[a] (i) $(n\text{-Bu})_4NF$, THF. (ii) Dowex 2 (OH^-), H_2O, Me_2CO, then HCl. (iii) DBU, EtOCH=CHCONCO, then H_2SO_4, Δ. (iv) I_2, HNO_3, $CHCl_3$. (v) Ac_2O, C_5H_5N. (vi) o-$ClC_6H_4OP(O)Cl_2$, C_5H_5N, triazole. (vii) NH_3, MeOH, Δ. (viii) DBU, EtOCH=C(Me)CONCO, then H_2SO_4, Δ.

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(1) A preliminary account of part of this work has appeared: (a) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P.; Slawin, A. M. Z.; Williams, D. R. *J. Chem. Soc., Chem. Commun.* 1987, 251. (b) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P.; Slawin, A. M. Z.; Williams, D. R. *J. Chem. Soc., Chem. Commun.* 1987, 255.
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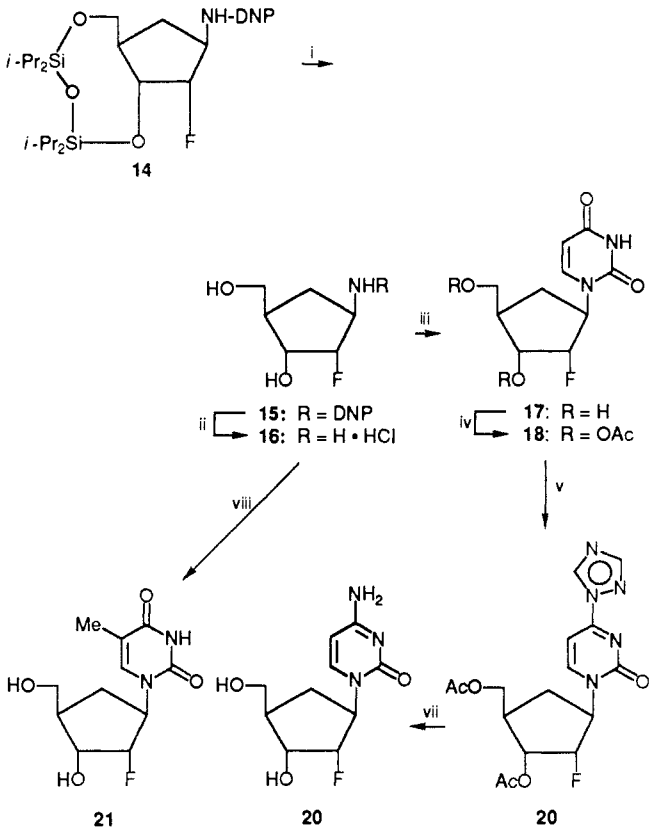
Scheme II[a]

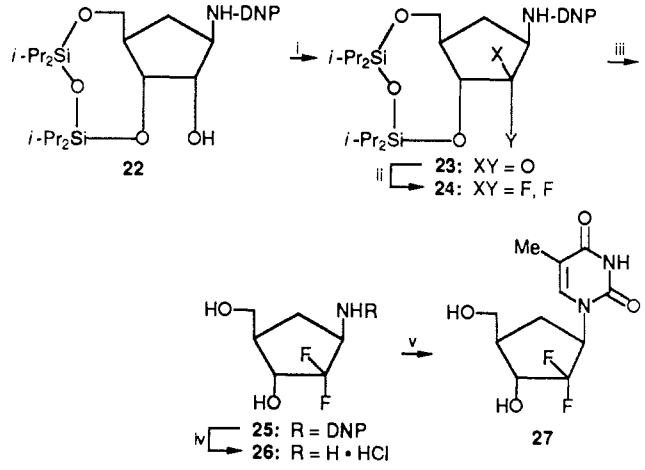


[a] (i) $(n\text{-Bu})_4NF$, THF. (ii) Dowex 2 (OH^-), H_2O, Me_2CO, then HCl. (iii) DBU, EtOCH=CHCONCO, then H_2SO_4, Δ. (iv) Ac_2O, C_5H_5N. (v) $o\text{-}ClC_6H_4OP(O)Cl_2$, C_5H_5N, triazole. (vi) NH_3, MeOH, Δ. (vii) DBU, EtOCH=C(MeCO)NCO, then H_2SO_4, Δ.

rivatives substituted by fluorine at the 6′-position[13] were also attractive targets.

We therefore initiated a program to systematically substitute the 2′- and 6′-positions with fluorine. Our initial targets were the carbocyclic analogues of FMAU, FIAU, and their stereoisomers. Also 2′,2′-difluoro pyrimidine nucleoside derivatives have attracted attention as antiherpes agents,[26] and the synthesis of the corresponding carbocyclic system was therefore of interest.

Scheme III[a]



[a] (i) DCC, DMSO, ortho H_3PO_4. (ii) DAST, CCl_4, $NaHCO_3$. (iii) $(n\text{-Bu})_4NF$, THF. (iv) Dowex 2 (OH^-), H_2O, Me_2CO, then HCl. (v) DBU, EtOCH=C(Me)CONCO, then H_2SO_4, Δ.

Chemistry

For the synthesis of the 2′-fluoro carbocyclic pyrimidine nucleosides (Schemes I and II) we required the fluorocyclopentylamines **7** and **16**. The successful introduction of fluorine into the carbocyclic ring of alcohol **22** by using (diethylamino)sulfur trifluoride (DAST) to give the required protected fluoro amino diols **5** and **14** has been described earlier.[14] Removal of the silyl protection from **5** and **14** with tetrabutylammonium fluoride gave the diols **6** and **15**, which on treatment with basic resin (Dowex 2, OH^-) gave, in high yield, the racemic fluoro amino diols **7** and **16**, which were isolated as their crystalline hydrochloride salts.

The synthetic routes (Scheme I and II) to the uridine and thymidine analogues (**8**, **13**, **17**, **21**) from the fluorocyclopentylamines **7** and **16** were based on a variant[15] of the general methodology for the synthesis of uracils and thymines developed initially by Shaw and Warrener.[16] Treatment of the 2′β-fluoro amino diol hydrochloride **7** in dimethylformamide with 3-ethoxyacryloyl isocyanate in the presence of DBU at −20 °C gave an intermediate acryloylurea, which was cyclized with refluxing dilute sulfuric acid to the uracil **8** in 62% overall yield from **7**. The carbocyclic analogue of FIAU (C-FIAU) **9** was prepared by the method of Prusoff[17] by treatment of the uracil **8** with iodine in chloroform in the presence of nitric acid. The cytidine analogue **12** was prepared according to the procedure of Sung.[18] The diacetate **10** was prepared by reaction of the diol **8** with acetic anhydride in the presence of pyridine. Treatment of **10** with *o*-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine gave the triazole **11**. Reaction of **11** with aqueous ammonia gave the carbocyclic 2′β-fluorocytidine derivative **12** in 79% yield. Carbocyclic FMAU (C-FMAU) **13** was prepared by reacting 2′β-fluoro amino diol hydrochloride **7** with 3-ethoxymethacryloyl isocyanate in dimethylformamide in the presence of DBU and then refluxing the intermediate

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Table I. ^{1}H NMR Parameters of 2′- and 6′-Fluoro Carbocyclic Pyrimidines[a,b]

compd	chemical shifts, δ								coupling constants, Hz				
	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′	H-6	others	$J_{1',F}$	$J_{2',F}$	$J_{3',F}$	$J_{4',F}$	$J_{6',F}$
8	ca. 4.88 dm	4.78 dd	3.90 dd	1.8–2.2 m	3.49 dd, 3.59 dd	1.8–2.2 m	7.63 dd	5.58 d (H-5, J_{56} = 8 Hz), 11.24 bs (NH)	ca. 30	53	25		
9 (C-FIAU)	ca. 4.92 dm	4.75 d	3.87 d	1.8–2.2 m	3.4–3.6 m	1.8–2.2 m	7.99 s	11.2 bs (NH)	ca. 30	53	25		
12	4.91 dm	4.75 dd	3.86 dt	1.7–2.1 m	3.47 dt, 3.58 dt	1.7–2.1 m	7.56 d	5.69 d (H-5, J_{56} = 8 Hz), 5.36 d (3′-OH), 4.75 (5′-OH), 7.05 bs, 7.12 bs (NH_2)	30	53	25		
13 (C-FMAU)	4.87 dm	4.75 dd	3.89 dd	1.8–2.1 m	3.49 dd, 3.59 dd	1.8–2.1 m	7.47 s	1.80 s (5-Me)	ca. 30	53	25		
1 (FMAU)	6.12 dd	5.05 ddd	4.25 dq	3.80 q	3.60 dd, 3.72 dd		7.60 s	1.81 s (5-Me), 5.48 d (3′-OH), 5.08 t (5-OH), 11.00 bs (NH)	16	53	20		
17	ca. 4.88 dm	5.03 dt	3.95 m	2.02 m	3.44 dd, 3.53 dd	1.47 dt, 2.12 dt	7.75 d	5.64 d (5-H, J_{56} = 8 Hz), 5.17 bs (3′-OH)	ca. 30	54			
20	ca. 4.76 m	5.00 dt	3.98 dq	1.9–2.2 m	3.42 dt, 3.55 dt	1.5 m, 1.9–2.2 m	7.67 d	5.71 d (5-H, J_{56} = 7 Hz), 5.06 d (3′-OH), 4.68 t (5′-OH), 7.11 bs (NH_2)	*c*	53	12		
21	ca. 4.74 m	5.00 dt	3.93 dq	1.9–2.2 m	3.42 dt, 3.51 dt	1.42 m, 1.9–2.2 m	7.61 s	1.78 s (5-Me), 5.14 d (3′-OH), 4.74 t (5′-OH), 11.29 bs (NH)	*c*	53	11		
27	5.06		3.82 m	1.7–2.2 m	3.48 dt, 3.57 dt	1.7–2.2 m	7.55 s	1.78 s (5-Me), 5.74 d (3′-OH), 4.78 t (5′-OH), 11.42 bs (NH)	*c*	*c*	*c*		
33	ca. 5.07 m	1.8–2.2 m	4.00 m	1.8–2.2 m	3.5–3.7 m	5.03 dt	7.74 d	5.63 dd (5-H, J_{56} = 8 Hz), 11.30 s (NH)	*c*			*c*	52
34	ca. 5.06 m	1.8–2.2 m	4.00 bs	1.8–2.2 m	3.58 bs	5.07 d	8.26 s	5.01 bs (3′-OH), 5.22 bs (5′-OH), 11.67 bs (NH)	*c*			c	57
38	ca. 5.11 dm	1.92 m, 2.44 m	4.03 m	2.17 dm	3.5–3.7 m	5.11 dt	7.66 dd	5.59 d (5-H, J_{56} = 8 Hz), 5.07 d (3′-OH), 4.63 t (5′-OH), 11.37 bs (NH)	ca. 30			35	55
39	ca. 5.08 dm	1.88, 2.4–2.6 m	4.01 m	2.13 dm	3.5–3.7 m	5.07 d	7.98 s	5.02 d (3′-OH), 4.64 t (5′-OH), 11.76 bs (NH)	ca. 30			32	58
C-IDU	4.94 m	1.4–2.2 m	4.00 m	1.4–2.2 m	3.43 dt, 3.54 dt	1.4–2.2 m	8.14 s	4.69 d (3′-OH), 4.59 t (5′-OH), 11.57 bs (NH)					

[a] The spectra were recorded in Me_2SO-d_6 solutions. Signals are quoted as s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), bs (broad singlet), t (triplet), and m (multiplet), and coupling constants reported are first order. [b] The numbering of positions on the cyclopentane ring is the same as has been used previously (see refs 1 and 13). [c] Coupling not established due to signal overlap.

methacryloylurea with 2 N hydrochloric acid.

The corresponding 2′α-fluorouridine, -cytidine, and -thymidine analogues **17**, **20**, and **21** (Scheme II) were prepared from the 2′α-fluoro amino diol hydrochloride **16** in a similar manner to that used for the synthesis of the 2′β analogues.

Synthesis of the 2′,2′-difluoro carbocyclic nucleoside **27** (Scheme III) required the protected difluoro amino diol **24**. The precursor of **24** is the ketone **23**, but oxidation of the alcohol **22** with chromium trioxide/pyridine, acetic anhydride/dimethyl sulfoxide, or ruthenium tetroxide failed to give the ketone **23**. This conversion was finally achieved in 35% yield with dicyclohexylcarbodiimide (DCC)/dimethyl sulfoxide in the presence of orthophosphoric acid.[19] Reaction of this relatively unstable ketone **23** with (diethylamino)sulfur trifluoride (DAST) in dichloromethane at 5 °C or in carbon tetrachloride at room temperature in the presence of sodium bicarbonate gave the difluoro derivative **24** in 25% yield. Deprotection of **24** with tetrabutylammonium fluoride (TBAF) gave the diol **25**, which on treatment with basic resin (Dowex 2, OH^-) gave the 2′,2′-difluoro amino diol, which was isolated as its hydrochloride salt **26**. The 2′,2′-difluoro carbocyclic thymidine analogue **27** (Scheme III) was prepared in 51% yield from **26** in a similar manner as described for C-FMAU (**13**).

The synthesis of the 2′-deoxy-6′-fluoro carbocyclic pyrimidine nucleosides (Scheme IV) required the fluorocyclopentylamines **30** and **36**, which were obtained from the previously described[14] optically pure fluoro azides **28** and **35**. Reduction of the mixture of the 6′α-fluoro azide **28** and its isomer **29** with hydrogen in the presence of Lindlar catalyst gave a high yield of optically pure fluorocyclopentylamines **30** and **31**, which were separated by column chromatography. Similarly, reduction of **35** gave the 6′β-fluoro amino diol **36** in 93% yield. The 6′-fluoro carbocyclic uridine derivatives **32** and **37** were prepared in high yield from the pure fluoro amines **30** and **36** in a manner analogous to that used for the 2′-fluoro derivatives **8** and **17**. Hydrogenolysis of the benzyl ether derivatives **32** and **37** gave carbocyclic 6′α-fluoro-2′-deoxyuridine (**33**) in 87% yield and carbocyclic 6′β-fluoro-2′-deoxyuridine (**38**) in 94% yield, respectively. Iodination of **33** and **38** using the procedure[17] described above gave the optically pure 6′-fluoro C-IDU derivatives **34** and **39**.

Data from the 250-MHz proton NMR spectra of the fluoro carbocyclic pyrimidines in Me_2SO-d_6 are listed in Table I. The positions of the protons are designated by the numbering system used previously[1,13] for carbocyclic nucleosides.

The configuration of the fluoro substituent could not be unequivocally determined in either the 2′- or 6′-fluoro carbocyclic nucleosides by analysis of the ^{1}H NMR spectra but was eventually confirmed by X-ray crystallography of the 2′β-fluoro intermediate **5** and the 6′β-fluoro derivative **38**.[1] The ^{1}H NMR data reveal that in the 2′-fluoro carbocyclic series the 2′-proton consistently appears at a lower field (Δδ ca. 0.25) in the α-fluoro compounds **17**, **20**, and **21** relative to the corresponding β-fluoro compounds **8**, **12**, and **13**. However, in the 6′-fluoro series the chemical shift of the corresponding 6′-proton is independent of the configuration of the fluoro substituent (compounds **33**, **34**, **38**, and **39**). In both series the H-6 proton of the pyrimidine base appears consistently at slightly lower field in the

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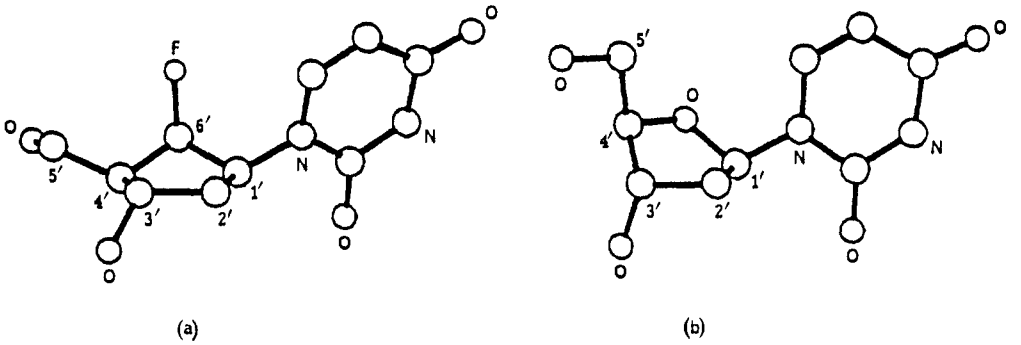
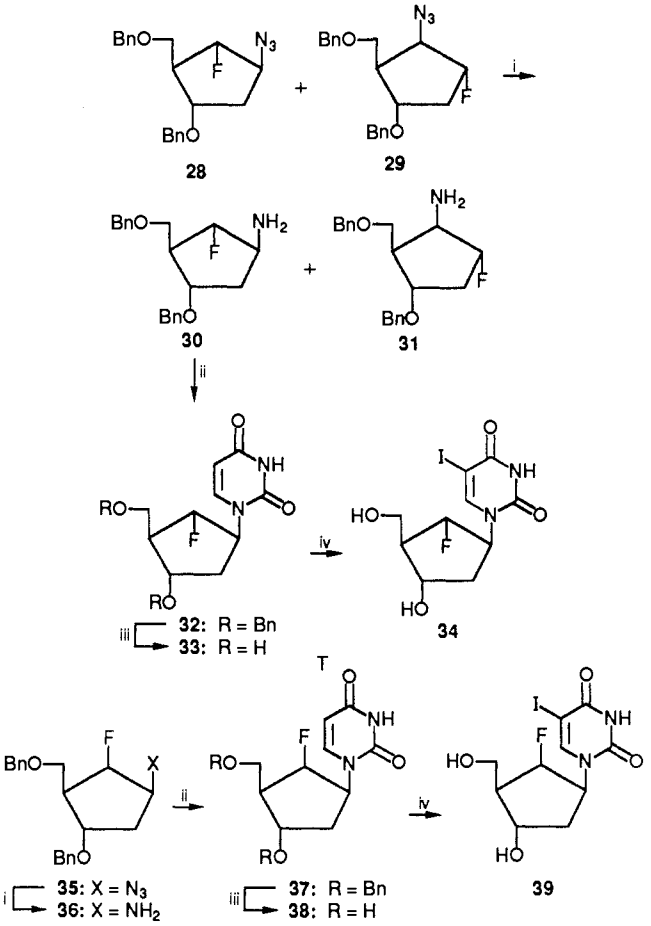


(a) (b)

Figure 1. Computer-generated drawings of (a) carbocyclic 6′β-fluoro-2′-deoxyuridine (**38**)[1] and (b) 2′-deoxyuridine[22] derived from the X-ray coordinates with hydrogens omitted for clarity.

Scheme IV[a]



[a] (i) H_2, LindLar catalyst. (ii) EtOCH=CHCONCO, C_6H_6, then dilute H_2SO_4, Δ. (iii) H_2, Pd/C, aqueous EtOH. (iv) I_2, HNO_3, $CHCl_3$, Δ.

α-fluoro compounds **17**, **20**, **21**, **33**, and **34** relative to their β-fluoro isomers **8**, **12**, **13**, **38**, and **39**.

In the 2′β-fluoro series the vicinal fluorine–proton couplings to H-1′ and H-3′ were both available from the ^1H NMR spectra and were found to be independent of the pyrimidine base (compounds **8**, **9**, **12**, **13**). However, these coupling constants differ from those reported for FMAU and suggest a different conformational equilibrium for the cyclopentane and furanose rings.

It is interesting to compare the crystal conformation of carbocyclic 6′β-fluoro-2′-deoxyuridine (**38**) with that of its furanose parent, 2′-deoxyuridine.[22] Both compounds have

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Table II

molecules/ unit cell			deg	deg	
	2′-Deoxyuridine[22]				
2		*P*	178	173	≡ C2′endo
	glycosyl torsion	*X*	−156	−153	≡ anti
	torsion angle	γ	−74	−69	≡ −sc
	Carbocyclic 6′β-Fluoro-2′-deoxyuridine (**38**)[1]				
2		*P*	84	83	≡ "O4′-endo"
		X	−112	−109	≡ anti
		γ	−172	−178	≡ ap

Table III. Antiherpes Activity of 2′- and 6′-Fluoro Carbocyclic Pyrimidine Nucleosides[a]

	ID_{50}, μg/mL		
compd	HSV-1 strain KOS[b]	HSV-2 strain 186[b]	cytotoxicity[c]
C-FIAU (**9**)	11	>100	>100
C-FMAU (**13**)	4.4	>300	>300
12[d]	13	82	>100
21	>100	>100	>100
20[d]	18	44	>300
27	>100	>100	>100
34, **38**, **39**	>300	>300	>300
FMAU	0.05	0.05	>30
(+)-C-IDU	0.07	97	300
IDU	0.1	0.9	>30

[a] Tested in Vero cells by a plaque reduction assay.[23] [b] Compound concentration required to inhibit HSV cytopathic effect by 50%. [c] Assessed by microscopic examination of cofluent Vero cell monolayers incubated with test compounds for 48 h at 37 °C. [d] Both **12** and **20** were also tested against influenza A virus (H1N1), but neither showed any antiviral activity.

two almost identical molecules per unit cell, and the important conformational parameters are shown in Table II. Although the glycosyl torsion angles are rather different, they both fall in the usual anti range. Perhaps more significant is the conformation of the five-membered ring. Thus, whereas 2′-deoxyuridine has a pseudorotation phase angle of 173°/178° corresponding to a C2′-endo conformation commonly found in 2′-deoxy nucleosides, the fluoro carbocycle adopts an unusual O4′-endo conformation (*P* 83°/84°). This different puckering of the five-membered ring has a marked effect on the relative spatial arrangement of the pyrimidine base and the primary hydroxyl group, the site of initial phosphorylation (Figure 1).

The conformation about the C-4′–C-5′ bond is also different, with the fluoro carbocycle adopting an ap conformation (γ −172°/178°) whereas the natural nucleoside shows a −sc conformation (γ −69°/−74°).

These conformational differences of the 6′β-fluoro carbocyclic ring relative to the furanose ring may be related to the difference in antiviral activity in IDU and its 6′-fluoromethylene isostere **39** (Table III).

Biological Results

The fluoro carbocyclic nucleoside analogues were tested in vitro for selective inhibition of herpes simplex virus (HSV) replication in Vero cells (Table III). A modification of the plaque reduction assay of Lopez et al.[23] was used to evaluate the activity of these analogues against the cytopathic effect of herpes simplex virus type 1 (HSV-1, strain KOS) and herpes simplex virus type 2 (HSV-2, strain 186). The potency of each compound is given by the concentration required for 50% reduction of plaque formation (ID_{50}). The results are summarized in Table III. The nucleoside analogue FMAU and (+)-C-IDU[24] were used as positive controls in these experiments.

The most active of these fluoro carbocyclic nucleosides in the plaque reduction assay was C-FMAU (**13**), with an ID_{50} of 4.4 μg/mL against HSV-1. However, this was 88 times less active than FMAU (**1**). Compound **13** was inactive against HSV-2 unlike FMAU which has an ID_{50} of 0.05 μg/mL. Similarly, C-FIAU (**9**) was only active against HSV-1 (ID_{50} 11 μg/mL) and inactive againt HSV-2. Both cytidine analogues **12** and **20** were moderately active against HSV-1 and HSV-2, and they had similar potencies. As the cytidine derivative **20** can be considered a close analogue of carbodine (C-cytidine), which exhibits activity against the influenza virus,[25] both **20** and its *ara* isomer **12** were tested against influenza A virus (H1N1) in cell culture. However, both **20** and **12** proved to be inactive.

The 2′,2′-difluoro pyrimidine nucleosides have been claimed[26] to have potent antiherpes activity; however, the carbocyclic 2′,2′-difluorothymidine derivative **27** was inactive against both HSV-1 and HSV-2. Similarly, **21** and **34** were inactive against both series types. The chiral 6′α-fluoro and 6′β-fluoro analogues of IDU **34** and **39** were devoid of activity in these assays, indicating that the fluoromethylene group is inferior to the methylene group as a replacement for the ring oxygen of IDU.

Experimental Section[27]

^{1}H and ^{19}F NMR spectra were measured on a Bruker AM250 (250-Hz) spectrometer (by Dr. R. Fletton and his staff). Proton chemical shifts are expressed as δ values with reference Me_4Si. For ^{19}F NMR, the peak positions were determined by reference to $CFCl_3$ as an internal standard. IR spectra were recorded on Perkin-Elmer 580, 257, and 177 spectrophotometers, and UV spectra were measured on a Perkin-Elmer Lambda 5 spectrometer (by Dr. R. Fletton and his staff). Mass spectral data were obtained (by Dr. D. Kelly, University of Cardiff, Cardiff, U.K.) on either a Varion/MAT CH5 spectrometer (for high-resolution spectra) or VG 7070E spectrometer (for low-resolution spectra). Microanalyses were performed by Miss P. J. McDonough and her staff. Preparative HPLC was performed on a Gibson HPLC instrument using a Spherisorb ODS-2 reversed-phase silica column (by Dr. S. Laing and his staff). Column chromatography was performed on Merck Kieselgel 60 (art. 7734). Thin-layer chromatography TLC was performed on Merck silica gel GF254, and developed plates were examined by UV light (254 nm). Optical rotations were measured with a Optical Activity AA-10 polarimeter. Solvents were dried and purified according to standard procedures.[28]

(±)-(1α,2β,3α,4α)-4-[(2,4-Dinitrophenyl)amino]-3-fluoro-2-hydroxycyclopentanemethanol (6). Tetrabutylammonium fluoride (1 M) in THF (75 mL, 75 mmol), was added to a stirred solution of (±)-(6aα,8β,9β,9aβ)-8-[(2,4-dinitrophenyl)amino]-9-fluorohexahydro-2,2,4,4-tetrakis(1-methylethyl)cyclopenta[*f*]-1,3,5,2,4-trioxadisilocin (**5**)[14] (purity ca. 80%, 72.14 g) in alumina-dried THF (280 mL). After 30 min the solvent was evaporated in vacuo and the dark residue was partitioned between water (100 mL) and ethyl acetate (450 mL). The organic phase was separated. The aqueous phase was further extracted with ethyl acetate (3 × 50 mL), and the combined organic phase was concentrated in vacuo to a volume of ca. 150 mL, whereupon the product began to separate into two oils. This mixture was loaded directly onto a column (26 × 12 cm) of silica and eluted with 10:1 chloroform–ethanol. Evaporation of the product containing fractions afforded the title compound **6** as a yellow crystalline solid (29.9 g, ca. 91%), a sample of which was recrystallized from ethyl acetate to give yellow needles: mp 147–149 °C; UV (EtOH) λ_{max} 260.5 (ϵ 10400), 345.5 nm (20600); IR (Nujol) ν_{max} 3620–3060, 1623, 1595, 1526, 1325 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.55, 2.4 (2 H, 2 m, 2 H-6′), 1.95 (1 H, m, H-4′), 3.4–3.6 (2 H, m, 2 H-5′), 4.01 (1 H, dm, J_{HF} = 22 Hz, H-3′), 4.45 (1 H, m, H-1′), 4.90 (1 H, t, 5′-OH), 4.95 (1 H, dm, J_{HF} = 53 Hz, H-2′), 5.43 (1 H, d, 3′-OH), 7.4 (1 H, d, H-6), 8.32 (1 H, dd, H-5), 8.8 (1 H, d, NH), 8.9 (1 H, d, H-3). Anal. ($C_{12}H_{14}FN_3O_6$) C, H, N, F.

(±)-(1α,2β,3α,4α)-4-Amino-3-fluoro-2-hydroxycyclopentanemethanol Hydrochloride Salt (7). Dowex 2 (OH^-) resin (20–50 mesh, 850 g) was added to a solution of (±)-(1α,2β,3α,4α)-4-[(2,4-dinitrophenyl)amino]-3-fluoro-2-hydroxycyclopentanemethanol (**6**) (57.6 g, 182 mmol) in acetone (1.3 L) and water (0.65 L) and the mixture stirred mechanically at room temperature for 24 h. The resin was removed by filtration and washed well with water (0.7 L), and the combined filtrate and washings were concentrated in vacuo to a volume of ca. 0.5 L. Hydrochloric acid (1 N, 175 mL, 0.95 equiv) was then added, and the solution was washed with ethyl acetate (3 × 150 mL). After a charcoal treatment the aqueous phase was concentrated to a colorless syrup which was azeotroped with ethanol (3 × 75 mL) and then seeded to give off-white crystals of **7**, which were dried in vacuo over P_2O_5 (28.9 g, 85%), mp 108–111 °C. Recrystallization of a sample from ethanol afforded colorless prisms: mp 110–112 °C; IR (Nujol) ν_{max} 3700–2260 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.4–1.6, 2.05–2.2 (2 H, 2 m, 2 H-6′), 1.87 (1 H, m, H-4′), 3.3–3.55 (2 H, m, 2 H-5′), 3.63 (1 H, dm, J_{HF} = ca. 25 Hz, H-1′), 3.93 (1 H, dm, J_{HF} = ca. 23 Hz, H-3′), 4.83 (1 H, dm, J_{HF} = ca. 50 Hz, H-2′), 5.47 (1 H, d, 3′-OH), 8.40 (1 H, NH_3^+). Anal. ($C_6H_{12}FNO_2$·HCl) C, H, N, Cl, F.

(±)-1-[(1α,2α,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (8). Compound **7** was treated with DBU and 3-ethoxy-2-propenoyl isocyanate and the product treated with acid according to the procedure described for **16**. The crude product was purified by column chromatography on silica gel, eluting with chloroform–methanol (4:1) to give the title compound **8** (62%) as a white amorphous solid: UV (H_2O) λ_{max} 265 nm; IR (Nujol) ν_{max} 3680–3080, 1680 cm^{-1}; MS, found M^+ 244.0861, $C_{10}H_{13}FN_2O_4$ requires m/z 244.0856.

(±)-1-[(1α,2α,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (9). Compound **8** was iodinated, as described for compound **33**, to give the title compound **9** (21%) as a foam: UV (H_2O) λ_{max} 285 (sh), 291 nm; IR (Nujol) ν_{max} 1685 cm^{-1}; MS, found M^+ 369.9819, $C_{10}H_{11}FIN_2O_4$ requires m/z 369.9823.

(±)-1-[(1α,2α,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione Diacetate (10). Compound **8** was acetylated as described for compound **17**, to give the title compound **10** (89%) as an amorphous white solid, which was used directly in the next stage: UV (MeOH) λ_{max} 264 nm; IR (Nujol) ν_{max} 1740 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.96–2.26

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(2 H, m, H-4′, H-6′), 2.06 (3 H, s, $OCOCH_3$), 2.11 (3 H, s, $OCOCH_3$), 2.42 (1 H, m, H-6′), 4.12 (1 H, m, H-5′), 4.22 (1 H, m, H-5′), 4.75–5.15 (3 H, m, H-1′, H-2′, and H-3′), 5.61 (1 H, d, H-5), 7.72 (1 H, d, H-6), 11.35 (1 H, s, NH).

(±)-1-[(1α,2α,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-4-(1,2,4-triazol-1-yl)-2(1*H*)-pyrimidinone Diacetate (11). The uracil **10** was treated with 1,2,4-triazole and *o*-chlorophenyl phosphorodichloridate according to the procedure described for the preparation of compound **19**, to give the title compound **11** (25%) as a pale yellow solid: mp 175–176 °C; UV (MeOH) λ_{max} 250 (ε 10 300), 315 nm (6100); IR (Nujol) ν_{max} 1743, 1675, 1627, 1550 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.07 (3 H, s, $OCOCH_3$), 2.13 (3 H, s, $OCOCH_3$), 2.15–2.60 (2 H, m, H-4′, H-6′), 4.17–4.27 (2 H, m, 2 H-5′), 4.9–5.30 (3 H, m, H-1′, H-2′, H-3′), 7.00 (1 H, d, H-5), 8.45 (1 H, s, H-3″), 8.53 (1 H, d, H-6), 9.49 (1 H, s, H-5″). Anal. ($C_{16}H_{18}FN_5O_5 \cdot 0.25H_2O$) C, H, N.

(±)-4-Amino-1-[(1α,2α,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2(1*H*)-pyrimidinone (12). Compound **11** was deprotected as described for compound **19** to give the title compound **12** (49%) as colorless crystals: mp 260–262 °C; UV (H_2O) λ_{max} 227 (sh, ε 8500), 273 nm (9600); IR (Nujol) ν_{max} 3660–2500, 1658 cm^{-1}. Anal. ($C_{10}H_{14}FN_3O_3$) C, H, N.

(±)-1-[(1α,2α,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (13). Compound **7** was treated with 3-ethoxy-2-methyl-2-propenoyl isocyanate and the product treated with acid according to the procedure described for the preparation of **27**. The crude product was purified by preparative TLC on silica gel (developing solvent: 5:1 chloroform–methanol). The product band was removed and extracted with methanol. Evaporation of the methanol extract gave the title compound **13** (21%) as a white crystalline solid: mp 211–212 °C; UV (MeOH) λ_{max} 269.4 nm (ε 9600); IR (Nujol) ν_{max} 1710, 1685, 1650, 1625 cm^{-1}. Anal. ($C_{11}H_{15}FN_2O_4$) C, H, N.

(±)-(1α,2β,3β,4α)-4-[(2,4-Dinitrophenyl)amino]-3-fluoro-2-hydroxycyclopentanemethanol (15). Crude compound **14**[14] was deprotected as described for **5** to give the title compound **15** as a yellow foam (21% overall yield for DAST/deprotection sequence), which was used directly in the next stage: ^1H NMR (Me_2SO-d_6) δ 1.46, 2.46 (2 H, 2 m, 2 H-6′), 2.09 (1 H, m, H-4′), 3.4–3.6 (2 H, m, 2 H-5′), 3.96 (1 H, dm, J_{HF} = 18 Hz, H-3′), 4.39 (1 H, m, J_{HF} = 17 Hz, H-1′), 4.81 (1 H, t, 5′-OH), 4.84 (1 H, dt, J_{HF} = 52 Hz, H-2′), 5.08 (1 H, d, 3′-OH), 7.30 (1 H, d, H-6), 8.34 (1 H, dd, H-5), 8.60 (1 H, d, NH), 8.87 (1 H, d, H-3). Anal. ($C_{12}H_{14}FN_3O_6$) C, H, N.

(±)-(1α,2β,3β,4α)-4-Amino-3-fluoro-2-hydroxycyclopentanemethanol Hydrochloride Salt (16). Compound **15** was deprotected as described for **6** to give the title compound **16** (88%) as a white crystalline solid: mp 150–154 °C; IR (Nujol) ν_{max} 3425, 3315 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.34, 2.17 (2 H, 2 m, 2 H-6′), 1.99 (1 H, m, H-4′), 3.3–3.5 (2 H, m, 2 H-5′), 3.60 (1 H, dm, J_{HF} = 20 Hz, H-3′), 3.89 (1 H, m, J_{HF} = 15 Hz, H-1′), 4.76 (1 H, bs, 5′-OH), 4.79 (1 H, dt, J_{HF} = 52 Hz, H-2′), 5.21 (1 H, d, 3′-OH), 8.45 (3 H, bs, NH_3^+). Anal. ($C_6H_{12}FNO_2 \cdot HCl \cdot 0.2H_2O$) C, H, N.

(±)-1-[(1α,2β,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (17). To a solution of fluoro amino diol hydrochloride **16** (370 mg, 2.0 mmol) in dimethylformamide (5 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.3 mL, 2.01 mmol) and 4-Å molecular sieves (1.2 g) at −20 °C was added a solution of 3-ethoxy-2-propenoyl isocyanate (3.33 mmol) in benzene (2 mL) (prepared from silver isocyanate and 3-ethoxy-2-propenoyl chloride according to the procedure of Shaw and Warrener[10,11]). The mixture was stirred at −15 °C for 1 h and then left to warm to room temperature. After 18 h the mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (5:1) to give the intermediate acryloylurea (394 mg, 68%) as a white solid: mp 199–202 °C; ^1H NMR (Me_2SO-d_6) δ 1.22 (1 H, m, H-6′), 1.27 (3 H, t, OCH_2CH_3), 1.95 (1 H, m, H-4′), 2.20 (1 H, m, H-6′), 3.40 (1 H, dd, H-5′), 3.49 (1 H, dd, H-5′), 3.80 (1 H, dm, J_{HF} = 19 Hz, H-3′), 3.98 (2 H, q, OCH_2CH_3), 4.19 (1 H, m, J_{HF} = 19 Hz, H-1′), 4.60 (1 H, dt, J_{HF} = 52 Hz, H-2′), 4.68 (1 H, t, 5′-OH), 4.98 (1 H, d, 3′-OH), 5.53 (1 H, d, $CH{=}CHOCH_2CH_3$), 7.58 (1 H, d, $CH{=}CHOCH_2CH_3$), 8.60 (1 H, d, NHCONHCO), 10.13 (1 H, s, NHCONHCO).

A solution of the acryloylurea (378 mg, 1.30 mmol) in 5% sulfuric acid (9 mL) was refluxed for 3 h. The mixture was cooled to room temperature and adjusted to pH 7 with 2 N sodium hydroxide. The solution was evaporated under reduced pressure and the residue dried and then extracted with ethanol (3 × 10 mL). The combined ethanolic solution was evaporated under reduced pressure and dried in vacuo to give **17** (313 mg, 91%) as a white foam, which was used directly in the next stage: UV (H_2O) λ_{max} 266.5 nm.

(±)-1-[(1α,2β,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione Diacetate (18). Compound **17** (294 mg, 1.2 mmol) was dissolved in acetic anhydride (3.2 mL) containing 4-(*N*,*N*-dimethylamino)pyridine (7 mg), and the mixture was stirred at room temperature for 24 h. The solution was evaporated under reduced pressure and the residue azeotroped with ethanol (3 × 7 mL). The residue was washed with water, filtered, and dried in vacuo over P_2O_5 at room temperature to give, as a white solid, the diacetate **18** (306 mg, 77%), which was used directly in the next stage: mp 190–192 °C; ^1H NMR (Me_2SO-d_6) δ 1.69, 2.20 (2 H, 2 m, 2 H-6′), 2.06 (3 H, s, $OCOCH_3$), 2.11 (3 H, s, $OCOCH_3$), 2.48 (1 H, m, H-4′), 4.10 (1 H, dd, H-5′), 4.19 (1 H, dd, H-5′), 4.76 (1 H, dm, J_{HF} = 28 Hz, H-1′), 5.08 (1 H, d, H-5), 7.8 (1 H, d, H-6), 11.41 (1 H, s, NH).

(±)-1-[(1α,2β,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-4-(1,2,4-triazol-1-yl)-2(1*H*)-pyrimidinone Diacetate (19). To a stirred solution of compound **18** (295 mg, 0.9 mmol) in pyridine (3 mL) was added 1,2,4-triazole (345 mg, 5 mmol) and *o*-chlorophenyl phosphorodichloridate (0.4 mL, 2.43 mmol). The mixture was stirred at room temperature for 72 h, and then the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane (30 mL), and the solution was washed successively with saturated sodium bicarbonate solution (6 mL) and water (6 mL) and then dried over $MgSO_4$. The solution was treated with a small amount of activated charcoal, filtered, and evaporated to leave a dark brown gum (350 mg). The combined aqueous washings were extracted with dichloromethane (10 mL), which was then dried over $MgSO_4$ and evaporated to give a dark orange gum (41 mg). The gums were combined and purified by column chromatography on silica gel, eluting with ethyl acetate to give the title compound **19** (275 mg, 80%) as a white solid: mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 2.10 (3 H, s, $OCOCH_3$), 2.14 (3 H, s, $OCOCH_3$), 2.1–2.4 (2 H, m, 2 H-6′), 2.61 (1 H, m, H-4′), 4.20 (1 H, dd, H-5′), 4.30 (1 H, dd, H-5′), 4.50 (1 H, dm, J_{HF} = 28 Hz, H-1′), 5.28 (1 H, m, J_{HF} = 14 Hz, H-3′), 5.60 (1 H, dt, J_{HF} = 54 Hz, H-2′), 7.08 (1 H, d, H-5), 7.85 (1 H, d, H-6), 8.13 (1 H, s, H-3″), 9.26 (1 H, s, H-5″). This was used directly in the next stage.

(±)-4-Amino-1-[(1α,2β,3β,4α)-2-fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-2(1*H*)-pyrimidinone (20). The diacetate triazole **19** (252 mg, 0.66 mmol) was stirred in 35% aqueous ammonia (7.2 mL) for 27 h at room temperature. The solution was evaporated under reduced pressure to leave an off-white solid (272 mg). This residue was stirred with hot methanol (3 mL) and cooled to room temperature, and the product was collected and dried in vacuo at room temperature to give the title compound **20** (129 mg, 80%) as a white solid: mp 198–201 °C dec; UV (H_2O) λ_{max} 222 (sh, ε 8800), 273 nm (9000); IR (Nujol) ν_{max} 1661, 1630, 1613 cm^{-1}. Anal. ($C_{10}H_{14}FN_3O_3$) C, H, N.

(±)-1-[(1α,2β,3β,4α)-2-Fluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (21). Compound **16** was treated with DBU and 3-ethoxy-2-methyl-2-propenoyl isocyanate, and the product was treated with acid according to the procedure described for the preparation of **27**. The crude product was purified by preparative HPLC (elution with 1:4 MeCN–H_2O, 10 mL/min) and the residue triturated with ethanol to give the title compound **21** (26%) as a white solid: mp 167–174 °C; UV (MeOH) λ_{max} 269.6 nm (ε 10 300). Anal. ($C_{11}H_{15}FN_2O_4$) C, H, N.

(±)-(6aα,8β,9aβ)-8-[(2,4-Dinitrophenyl)amino]hexahydro-2,2,4,4-tetrakis(1-methylethyl)cyclopenta[*f*]-1,3,5,2,4-trioxadisilocin-9-one (23). To a stirred solution of the alcohol **22**[14] (278 mg, 0.5 mmol) and dicyclohexylcarbodiimide (309 mg, 1.5 mmol) in dry dimethyl sulfoxide (2 mL) was added anhydrous orthophosphoric acid (24 mg, 0.25 mmol). The resulting mixture was stirred at room temperature for 3.5 h, and then ethyl acetate (5 mL) was added, followed by a solution of anhydrous

oxalic acid (90 mg, 1 mmol) in methanol (0.5 mL). The mixture was stirred at room temperature for 5 min and was then poured, with stirring, into brine (10 mL). The precipitated dicyclohexylurea was removed by filtration. The organic phase was separated, washed successively with sodium bicarbonate solution and brine, and then dried and evaporated to leave an orange residue (287 mg) which was purified by preparative TLC on silica gel [developing solvent: 3:1 petroleum ether (40–60 °C)–ethyl acetate]. The product band was removed and extracted with ethyl acetate. Evaporation of the ethyl acetate extract gave a yellow foam (96 mg), which was crystallized from hexane to give the title compound **23** as a yellow crystalline solid (46 mg, 17%): mp 136–137 °C; UV (MeOH) λ_{max} 258 (ϵ 9600), 345 nm (12200); IR ($CHBr_3$) ν_{max} 1766, 1620, 1591, 1333 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.2 (28 H, bs, iso-Prx4), 1.82 (1 H, q, H-6′), 2.21 (1 H, m, H-4′), 2.57 (1 H, m, H-6′), 3.94 (1 H, dd, H-5′), 4.05–4.25 (2 H, m, H-1′ and H-5′), 4.30 (1 H, d, H-3′), 7.18 (1 H, d, H-5), 8.28 (1 H, dd, H-4), 8.63 (1 H, d, NH), 9.14 (1 H, d, H-3). Anal. ($C_{24}H_{39}N_3O_8Si_2 \cdot 0.5H_2O$) C, H, N.

(±)-(6aα,8β,9aβ)-9,9-Difluorohexahydro-8-[(2,4-dinitrophenyl)amino]-2,2,4,4-tetrakis(1-methylethyl)cyclopenta[*f*]-1,3,5,2,4-trioxadisilocin (24). A solution of ketone **23** (50 mg, 0.09 mmol) in dichloromethane (1 mL) was added dropwise to a stirred solution of (diethylamino)sulfur trifluoride (0.065 mL, 0.537 mmol) in dichloromethane (1 mL) at 5 °C during 15 min. The mixture was left at 5 °C for 1 h and then added to saturated aqueous sodium bicarbonate (5 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC on silica gel (developing solvent: dichloromethane). The product band was removed and extracted with ethyl acetate. The ethyl acetate extract was evaporated to give **24** (13 mg, 25%) as a yellow solid: mp 95–97 °C; IR ($CHBr_3$) ν_{max} 1619, 1593, 1521, 1336 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.2 (28 H, bs, iso-Prx4), 1.65 (1 H, m, H-6′), 2.07 (1 H, m, H-4′), 2.40 (1 H, m, H-6′), 3.78 (1 H, m, H-5′), 3.96–4.28 (3 H, m, H-1′, H-3′, H-5′), 7.04 (1 H, d, H-5), 8.31 (1 H, dd, H-4), 8.47 (1 H, d, NH), 9.14 (1 H, d, H-3); ^{19}F NMR ($CDCl_3$) δ −109.5 (dt, J_{FF} = 230 Hz, J_{HF} = 16 Hz), −113.2 (dd, J_{FF} = 230 Hz, J_{HF} = 13 Hz). Anal. ($C_{24}H_{39}F_2N_3O_7Si_2$) C, H, N.

Subsequently it was found that a similar yield could be more easily obtained by conducting the reaction in dry carbon tetrachloride at room temperature in the presence of solid sodium bicarbonate (1 equiv) and by using 3–4 equiv of DAST.

(±)-(1α,2β,4α)-4-[(2,4-Dinitrophenyl)amino]-3,3-difluoro-2-hydroxycyclopentanemethanol (25). Compound **24** was deprotected as described for **5** to give the title compound **25** (25%) as a yellow foam: UV (MeOH) λ_{max} 260 (ϵ 8700), 340.2 nm (15900); IR (Nujol) ν_{max} 3700–2500, 1621 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.56 (1 H, m, H-6′), 1.97 (1 H, m, H-4′), 2.37 (1 H, m, H-6′), 3.4–3.6 (2 H, m, 2 H-5′), 3.91 (1 H, m, H-3′), 4.58 (1 H, m, H-1′), 4.93 (1 H, t, 5′-OH), 5.78 (1 H, d, 3′-OH), 7.37 (1 H, d, H-6), 8.36 (1 H, dd, H-4), 8.58 (1 H, d, NH), 8.87 (1 H, d, H-3); ^{19}F NMR (Me_2SO-d_6) δ −109.5 (ddd, J_{FF} = 231 Hz, J_{HF} = 13, 10 Hz), −111.7 (ddd, J_{FF} = 231 Hz, J_{HF} = 15, 11 Hz). Anal. ($C_{12}H_{13}F_2N_3O_6 \cdot 0.6H_2O$) C, H, N.

(±)-(1α,2β,4α)-4-Amino-3,3-difluoro-2-hydroxycyclopentanemethanol Hydrochloride Salt (26). Compound **25** was deprotected as described for **6** to give the title compound **26** (71%) as a pale brown solid: mp 169–170 °C; IR (Nujol) ν_{max} 3680–2350, 2140–2000 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.46 (1 H, q, H-6′), 2.12 (1 H, m, H-6′), 1.85 (1 H, bm, H-4′), 3.35–3.58 (2 H, m, 2 H-5′), 3.62–3.95 (2 H, m, H-1′, H-3′), 4.82 (1 H, 5′-OH), 5.80 (1 H, d, 3′-OH), 8.62 (3 H, bs, NH_3^+); ^{19}F NMR (Me_2SO-d_6) δ −108.9 (ddd, J_{FF} = 235 Hz, J_{HF} = 16, 10 Hz), −111.7 (ddd, J_{FF} = 235 Hz, J_{HF} = 16, 10 Hz). Anal. ($C_6H_{11}F_2NO_2 \cdot HCl$) C, H, N.

(±)-1-[(1α,3β,4α)-2,2-Difluoro-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (27). The difluoro amino diol hydrochloride **26** (210 mg, 1.03 mmol) was dissolved in DMF (20 mL) containing DBU (0.41 mL, 2.7 mmol), and the mixture was stirred at room temperature for 30 min and then cooled to −20 °C. A solution of 3-ethoxy-2-methyl-2-propenoyl isocyanate [prepared from 3-ethoxy-2-methyl-2-propenoyl chloride (297 mg, 2 mmol) and silver cyanate (420 mg, 2.8 mmol) by refluxing in toluene for 30 min and then filtering] was added dropwise to the stirred mixture at −20 °C. When the addition was complete, the mixture was stirred at −20 °C for 30 min and then allowed to attain room temperature. The mixture was stirred at room temperature for $1^1/_2$ h and filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in methanol and the solution adjusted to pH ~7 with Amberlite resin IR 120 [H^+]. The mixture was filtered, and the filtrate was concentrated to a small volume under reduced pressure. Hydrochloric acid (2 N, 70 mL) was added and the mixture heated under reflux for 3 h. The solution was evaporated and the residue azeotroped with ethanol (70 mL). The brown glassy residue (628 mg) was purified by preparative HPLC (elution with 4:1 MeCN–H_2O, 10 mL/min). The major fraction was evaporated under reduced pressure to give the title compound **27** (146 mg, 51%) as a colorless solid: 240–241 °C; UV (MeOH) λ_{max} 267 nm (ϵ 9800); IR (Nujol) ν_{max} 1708, 1695, 1660, 1640 cm^{-1}. Anal. ($C_{11}H_{14}F_2N_2O_4$) C, H, F, N.

[1*S*-(1α,2β,3α,4β)]-2-Fluoro-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]-1-cyclopentanamine (30) and [1*R*-(1α,2α,3β,5β)]-5-Fluoro-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl]-1-cyclopentanamine (31). A mixture of fluoro azides **28** and **29**[14] (10.2 g, 28.7 mmol) in ethanol (50 mL) was hydrogenated over Lindlar catalyst (4 g) at atmospheric pressure for $3^1/_2$ h. The mixture was filtered, the catalyst was washed with ethanol (2 × 15 mL), and the combined filtrate and washings were evaporated. The colorless syrup was purified by column chromatography on silica gel using ethyl acetate–ethanol (7:1) as eluant to give first as a low-melting solid, the fluoro amine **31** (4.25 g, 45%): $[\alpha]^{22}_D$ = +47° (*c* 1.0, $CHCl_3$); IR ($CHBr_3$) ν_{max} 3380, 3320, 1600, 1495, 1070, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (1 H, s, NH_2), 1.76–2.04, 2.4–2.64 (3 H, 2 m, 2 H-2′ and H-4′), 3.45–3.78 (3 H, m, 2 H-5′ and H-6′), 3.96 (1 H, m, H-3′), 4.36–4.64 (4 H, m, 2 PhCH_2), 4.68 (1 H, dm, J_{HF} = 54 Hz, H-1′), 7.2–7.45 (10 H, m, 2 Ph). This was followed by the fluoro amine **30** (3.75 g, 40%): IR ($CHBr_3$) ν_{max} 3380, 3310, 1598, 1595, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (2 H, s, NH_2), 1.63, 2.12 (2 H, 2 m, 2 H-2′), 2.41 (1 H, dm, J_{HF} = 24 Hz, H-4′), 3.60 (2 H, d, 2 H-5′), 3.64 (1 H, m, H-1′), 3.90 (1 H, m, H-3′), 4.44 (1 H, dt, J_{HF} = 54 Hz, H-6′), 4.4–4.6 (4 H, m, 2 PhCH_2), 7.2–7.4 (10 H, m, 2 Ph). Hydrogen chloride was bubbled through a solution of the free amine 30 (700 mg) in ether (50 mL), and the white precipitate was collected, washed with ether, and dried in vacuo to give the hydrochloride salt of **30** (770 mg): mp 116–119 °C; $[\alpha]^{22}_D$ = +10° (*c* 0.5, $CHCl_3$); IR ($CHBr_3$) ν_{max} 3300–2400, 1600, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11–2.56 (3 H, m, H-4′ and 2 H-2′), 3.44–3.58 (2 H, m, 2 H-5′), 3.86–4.08 (2 H, m, H-1′ and H-3′), 4.3–4.6 (4 H, m, 2 PhCH_2), 5.06 (1 H, dm, J_{HF} = 53 Hz, H-6′), 7.16–7.38 (10 H, m, 2 Ph). Anal. ($C_{20}H_{24}FNO_2 \cdot HCl$) C, H, N.

1-[[1*R*-(1α,2β,3α,4β)]-4-(Phenylmethoxy)-3-[(phenylmethoxy)methyl]-2-fluoro-1-cyclopentyl]-2,4-(1*H*,3*H*)-pyrimidinedione (32). To a stirred solution of the fluoro amine **30** (2.965 g, 9 mmol) in dry benzene (40 mL) at 5 °C was added dropwise during 10 min a solution of 3-ethoxy-2-propenoyl isocyanate (10 mmol) (prepared from silver isocyanate and 3-ethoxy-2-propenoyl chloride according to the procedures of Shaw and Warrener[10,11]) in benzene (24 mL). The mixture was allowed to warm to room temperature during 1 h. The mixture was filtered through a pad of Kieselguhr, the filtrate was evaporated, and the residue was purified by column chromatography on silica gel. Elution with ether gave the intermediate acylurea (3.25 g, 77%) as off-white crystals: mp 79–84 °C; IR ($CHBr_3$) ν_{max} 1700, 1685, 1610, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, t, OCH_2CH_3), 1.88, 2.31 (2 H, 2 m, 2 H-2′), 2.41 (1 H, dm, J_{HF} = 25 Hz, H-4′), 3.57 (2 H, m, 2 H-5′), 3.86–4.00 (1 H, m, H-3′), 3.94 (2 H, q, OCH_2CH_3), 4.37–4.64 (5 H, m, 2 $PhCH_2$ and H-1′), 4.78 (1 H, dt, J_{HF} = 53, H-6′), 5.35 (1 H, d, C*H*=$CHOCH_2CH_3$), 7.21–7.44 (10 H, m, 2 Ph), 7.64 (1 H, d, CH=C*H*OCH_2CH_3), 8.86 (1 H, d, N*H*CONHCO), 9.53 (1 H, s, NHCON*H*CO). Anal. ($C_{26}H_{31}FN_2O_5$) C, H, N. To a stirred solution of the acylurea (2.97 g, 6.31 mmol) in dioxane (50 mL) was added 1 N sulfuric acid (50 mL), and the mixture was heated at reflux under a atmosphere of N_2 for $1^1/_4$ h. The mixture was cooled to room temperature and extracted with chloroform (2 × 20 mL). The combined chloroform extract was successively washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL) and then dried (Me_2SO_4) and evaporated. The residue (2.76 g) was purified by column chromatography on silica gel. Elution with 15:1 chloroform–ethanol gave the title compound **32** (2.41 g, 90%) as an off-white hygroscopic

foam: UV (EtOH) λ_{max} 265 nm; IR ($CHBR_3$) ν_{max} 1708, 1685, 1630, 1493 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14–2.30 (2 H, m, 2 H-2′), 2.52 (1 H, dm, J_{HF} = 24 Hz, H-4′), 3.61–3.76 (2 H, m, 2 H-5′), 4.00 (1 H, m, H-3′), 4.50, 4.52 (4 H, 2 s, 2 PhCH_2), 4.96 (1 H, m, H-1′), 5.20 (1 H, dt, J_{HF} = 55 Hz, H-6′), 5.79 (1 H, d, H-6), 7.13 (1 H, d, H-5), 7.24–7.44 (10 H, m, 2 Ph), 8.25 (1 H, s, NH). Anal. ($C_{24}H_{25}FN_2O_4 \cdot 0.6H_2O$) C, H, N.

1-[[1*R*-(1α,2β,3α,4β)]-2-Fluoro-4-hydroxy-3-(hydroxymethyl)-1-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (33). To a solution of the bis benzyl ether **32** (2.4 g, 5.65 mmol) in 95% ethanol (30 mL) was added 2 N hydrochloric acid (4 drops), and the mixture was hydrogenated at atmospheric pressure over 10% Pd/C (540 mg) for 2 h. The catalyst was removed by filtration through Kieselguhr, and the filtrate was evaporated in vacuo. The sticky white residue was dissolved in water (10 mL), stirred with charcoal, and filtered, and the filtrate was freeze-dried to give the title compound **33** (1.29 g, 87%) as a white amorphous solid: $[\alpha]^{22}_D$ = +35° (*c* 1.0, H_2O); UV (EtOH) λ_{max} 266 nm; IR (Nujol) ν_{max} 1720, 1685, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.82–2.16 (3 H, m, 2 H-2′ and H-4′), 3.57 (2 H, m, 2 H-5′), 4.00 (1 H, m, H-3′), 4.97–5.20 (1 H, m, H-1′), 5.02 (1 H, dt, J_{HF} = 52 Hz, H-6′), 5.63 (1 H, d, H-6), 7.74 (1 H, s, H-5), 11.3 (1 H, s, NH). Anal. ($C_{10}H_{13}FN_2O_4 \cdot H_2O$) C, H, F, N.

(+)-1-[[1*R*-(1α,2β,3α,4β)]-2-Fluoro-4-hydroxy-3-(hydroxymethyl)-1-cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (34). To a solution of **33** (244 mg, 0.93 mmol) in 1 N nitric acid (2.2 mL) was added chloroform (1.3 mL) and then iodine (259 mg, 1.02 mmol). The mixture was heated at reflux with stirring for 4 h and then left at 5 °C for 16 h. The precipitated solid was filtered, washed several times with ether, and dried in vacuo (253 mg, 73.5%); mp 201–204 °C. This white solid was recrystallized from water (5 mL), to give **34** (175 mg, 51%): mp 202–204 °C; $[\alpha]^{22}_D$ = +37° (*c* 0.5, Me_2SO); UV (EtOH) λ_{max} 288.5 nm (ε 8700); IR (Nujol) ν_{max} 1715, 1695 cm^{-1}. Anal. ($C_{10}H_{12}FIN_2O_4$) C, H, N.

[1*S*-(1α,2α,3α,4β)]-2-Fluoro-4-(phenylmethoxy)-3-[(phenylmethoxy)methyl]-1-cyclopentanamine (36). Compound **35**[14] was reduced as described for compound **28** to give the title compound **36** (93%) as a colorless syrup, which was used directly in the next stage: IR ($CHBr_3$) 3380, 1620, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (2 H, s, NH_2), 1.77, 2.14 (2 H, 2 m, 2 H-2′), 2.45 (1 H, dm, J_{HF} = 33 Hz, H-4′), 3.52 (1 H, dm, J_{HF} = 28 Hz, H-1′), 3.5–3.75 (2 H, m, 2 H-5′), 3.80 (1 H, m, H-3′), 4.4–4.6 (4 H, m, 2 PhCH_2), 4.85 (1 H, dt, J_{HF} = 55 Hz, H-6′), 7.2–7.4 (10 H, m, 2 Ph). Hydrogen chloride was bubbled through a solution of the free amine **36** (6 mg) in ether (0.5 mL). The mixture was evaporated to give the hydrochloride salt of **36** as a gum: ^1H NMR ($CDCl_3$) δ 2.2–2.4 (3 H, 2 m, 2 H-2′ and H-4′), 3.44–3.7 (2 H, m, 2 H-5′), 3.75–4.0 (2 H, m, H-1′ and H-3′), 4.25–4.55 (4 H, m, 2 PhCH_2), 5.3 (1 H, dm, J_{HF} = 54 Hz, H-6′), 7.15–7.4 (10 H, m, 2 Ph, 8.66 (3 H, bs, NH_3^+).

1-[[1*R*-(1α,2α,3α,4β)]-4-(Phenylmethoxy)-3-[(phenylmethoxy)methyl]-2-fluoro-1-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (37). Compound **36** was treated with 3-ethoxy-2-propenoyl isocyanate and the product treated with acid according to the procedure described for **32**. The crude product was purified by column chromatography on silica gel. Elution with ethyl acetate gave the title compound **37** (72%) as a white hygroscopic foam which was used directly in the next stage: ^1H NMR ($CDCl_3$) δ 2.14–2.34 (2 H, m, 2 H-2′), 2.60 (1 H, dm, J_{HF} = 32 Hz, H-4′), 3.59–3.68 (2 H, m, 2 H-5′), 3.96 (1 H, m, H-3′), 4.43–4.62 (4 H, m, 2 PhCH_2), 5.20 (1 H, dt, J_{HF} = 58 Hz, H-6′), 5.26 (1 H, dm, J_{HF} = 30 Hz, H-1′), 5.69 (1 H, d, H-5), 7.22–7.42 (10 H, m, 2 Ph), 8.25 (1 H, s, NH).

1-[[1*R*-(1α,2α,3α,4β)]-2-Fluoro-4-hydroxy-3-(hydroxymethyl)-1-cyclopentyl]-2,4(1*H*,3*H*)-pyrimidinedione (38). Compound **37** was deprotected as described for compound **33**, to give the title compound **38** (94%) as white crystals: mp 200–203 °C; ^1H NMR (Me_2SO-d_6) δ 1.92, 2.44 (1 H, 2 m, 2 H-2′), 2.17 (1 H, dm, J_{HF} = 35 Hz, H-4′), 3.50–3.70 (2 H, m, 2 H-5′), 4.03 (1 H, m, 2 H-3′), 4.67 (1 H, t, 5-H′), 5.07 (1 H, d, 3′-OH), 5.11 (1 H, dt, J_{HF} = 55 Hz, H-6′), 4.94–5.24 (1 H, m, H-1′), 5.59 (1 H, d, H-5), 7.66 (1 H, d, H-6), 11.37 (1 H, s, NH). Anal. ($C_{10}H_{13}FN_2O_4 \cdot 0.5H_2O$) C, H, N.

1-[[1*R*-(1α,2α,3α,4β)]-2-Fluoro-4-hydroxy-3-(hydroxymethyl)-1-cyclopentyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (39). Compound **38** was iodinated, as described for compound **33**, to give the title compound **39** (51%) as a white amorphous solid: $[\alpha]^{22}_D$ = +4° (*c* 0.5, Me_2SO); UV (EtOH) λ_{max} 286 nm (ε 8100) 289 (sh, ε 8000); IR (Nujol) ν_{max} 1690 cm^{-1}. Anal. ($C_{10}H_{12}FIN_2O_4 \cdot 0.75H_2O$) C, H, N.

Antiviral Activity. (A) Antiherpes Activity. Antiherpes activity was measured in a plaque reduction assay.[23] Confluent monolayers of Vero cells in 24-well plates (Nunc) were infected with 30–40 plaque-forming units of either HSV-1 (strain KOS) or HSV-2 (strain 186). The infected monolayers were incubated at 37 °C for 1 h and then overlaid with maintainence medium containing 0.75% (carboxymethyl)cellulose and various concentrations of test compound. The monolayers were incubated for a further 2 days at 37 °C, after which the cells were fixed and stained, the plaques were counted, and the concentration of compound causing 50% inhibition of plaque formation was calculated.

(B) Cytotoxicity. The cytotoxic effects of the test compounds on Vero cells were determined by examination of mock infected cell monolayers incubated with the compounds. Gross changes in cell staining, number or morphology were noted and scored. Cytotoxic doses quoted were those that caused 50% of the cell monolayer to be affected.

(C) Influenza Activity. Madin-Darby canine kidney (MDCK) cells were infected with influenza A virus (H1N1) at approximately 0.01 PFU/cell in the presence of 1 μg/mL trypsin. The cells were then incubated at 35 °C with 3-fold serial dilutions of compounds prepared in microtiter plates with serum-free EMEM. After incubation for 4 days activity of compounds was assessed by the presence or absence of influenza virus hemagglutinin in the supernatent medium.

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