J. Pharm. Pharmacol. 1998, 50 (Supplement): 130

Isomorphous nucleosides with differing anti-HIV activities

DAN L. RATHBONE, BRENDAN O'CARROLL, MARK P. WALLIS, KAREN C. FARROW, NAHEED MAHMOOD*, CARL H. SCHWALBE AND WILLIAM FRASER

*Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, and *Department of Immunology, Rayne Institute, 123 Cold Harbour Lane, London SE5 9NU*

Our interest in the molecular recognition properties of oligonucleotides containing C4-substituted cytosine bases (Wallis et al 1997) necessitated efficient chemical synthesis of precursors containing a displaceable pentafluorophenyloxy (PfpO) substituent at C4. Chemical synthesis of PfpO-substituted nucleoside (**1**) was achieved in a single step from uridine. Recrystallisation of **1** from methanol gave excellent quality crystals which allowed us to determine the crystal structure (Figure). Sugar pucker is C2'-*endo* with O5'-C5'-C4'-C3' 56.8(4)° and C2-N1-C1'-O4' -125.4(3)°. Steric bulk precludes coplanarity of the PfpO substituent with the heterocycle and strain is relieved by near perpendicular twisting about the phenolic C-O bond. We recently reported on the crystal structure of **2**, the 2'-deoxyribose analogue of **1** (Wallis et al 1995). The unit cell dimensions of **1** and **2** are so similar as to suggest isomorphism yet their anti-HIV activites differ by more than two orders of magnitude (Table). Structural isomorphism is confirmed by successful refinement of **2** starting from the atomic positions of **1** with O2' deleted. The sugar rings of each substance hydrogen bond to their counterparts at equivalent positions i (1-x, 0.5+y, z), linking O2' to $O3'^{i}$ and O3' to $O7^{i}$ in **1** but only the latter in **2**. Although the crystal structures of 6-methyluridine (Saenger & Suck 1972) in space group $P2_1$ and 6-methyl-2'-deoxyuridine (Birnbaum et al 1980) in $P2_12_12_1$ are almost isomorphous, **1** and **2** represent the first case in which crystals of ribose and 2'-deoxyribose nucleosides of the same pyrimidine base are truly isomorphous. Of the compounds synthesised, **1** was the most active against HIV-1 (Table) although none were as active as AZT (**7**). Replacement of the PfpO group by triazole results in a substantial loss in antiviral potency. Substituted cytosine nucleoside (**5**), formed from **2** was moderately active and without cytotoxicity although its methylated analogue (**6**) was inactive. Automated, matrix synthesis of N4-substituted cytosine nucleosides was achieved in a single step by reacting **1** and **2** with a diverse range of amine nucleophiles providing libraries of compounds for biological evaluation.

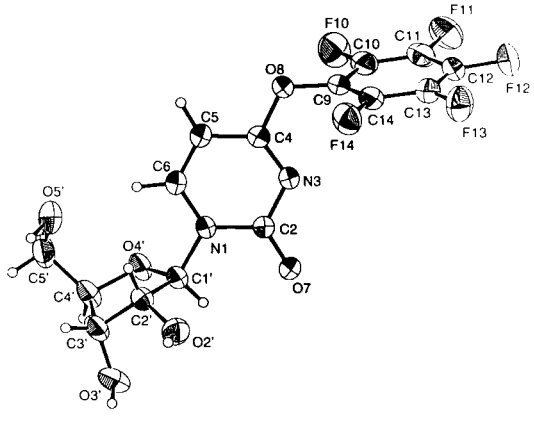

Figure. ORTEP plot of **1**

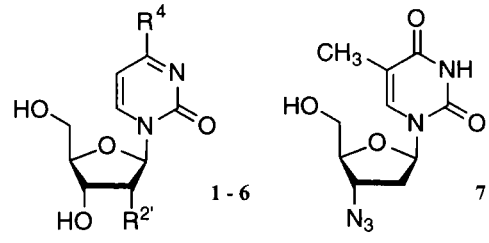

Table. Antiviral Activity and Cytotoxicity of Nucleosides (**1**) to (**7**) Against HIV-1 in C8166 Cells

	$R^{2'}$	R^4	EC_{50} (μM)	TC_{50} (μM)
1	OH	PfpO	1.6	200
2	H	PfpO	400	>1000
3	OH	triazole	100	400
4	H	triazole	>1000	>1000
5	H	$NHCH_2CH_2Ph$	80	>1000
6	H	$NMeCH_2CH_2Ph$	>1000	>1000
7	AZT		0.016	>1000

Birnbaum, G. I. et al (1980) J. Am. Chem. Soc. 102: 5586-5590

Saenger, W. & Suck, D. (1972) J. Am. Chem. Soc. 94: 6520-6526

Wallis, M. P. et al (1997) Nucleosides, Nucleotides 16: 2053-2068

Wallis, M P. et al (1995) Tetrahedron Lett. 36: 3759-3762