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Synthesis and Antiviral Activity of Fluoro Sugar Nucleosides 1: Studies on 4'-Azido-2'-Deoxy-2'-Fluoro-Arabinofuranosyl Nucleosides

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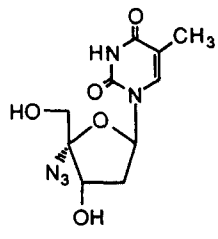
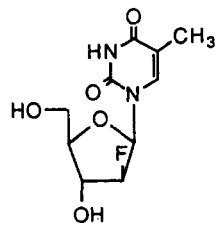
A number of nucleoside derivatives have been developed as potential anti-AIDS drugs. Most of them contain modification in the sugar moiety as exemplied by the clinically important compounds such as 3'-azido-3'-deoxythymidine (AZT, Retrovir), 2',3'-dideoxyinosine (ddI, Videx), 2',3'-dideoxycytidine (ddC, Hivid), 2',3'-didehydro-2',3'-dideoxythymidine (D4T, Stavudine). Recently the 4'-substituted nucleosides have been extensively synthesized to identify novel nucleosides with potent and selective activity against HIV by several groups (Jenkins *et al.*, 1971). Among them 4'-azidonucleosides developed by Syntex group have emerged as the most promising antiviral compounds (Hans *et al.*, 1992). The structure activity relationship of these nucleosides revealed that 4'-azidothymidine (**1**, ADRT) displayed the most potent and selective activity against HIV in A3.01 cells, especially HIV strain resistant to AZT *in vitro* and its analogue lacking a 3'-hydroxy function are devoid of antiviral activity (Maag *et al.*, 1994). Many nucleosides of fluoro sugar, especially 2'-fluoro-arabino configuration like FMAU **2**, FEAU, FIAU and FIAC, have been shown not only significant antiviral activity but also advantage over the corresponding non-fluoro nucleoside in terms of chemical, enzymatical stability.



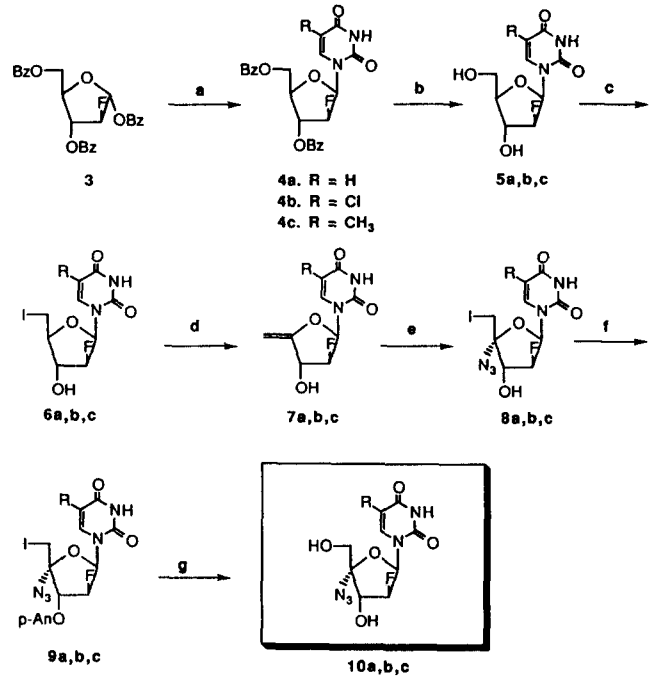
1. 4'-Azidothymidine (ADRT)



2. FMAU

As continuing our program to develop potent and selective antiviral agents from fluoro sugar nucleosides, we decide to synthesize 4'-azido-2'-deoxy-2'-fluoroarabinofuranosyl nucleosides (**10a**: uracil, **10b**: 5-chlorouracil, **10c**: thymine) containing biologically important features, 4'-α-azido and 2'-β-fluoro, of mentioned two active nucleosides.

The synthesis of target compounds was outlined in scheme and started from commercially available 2-deoxy-2-fluoro-1,3,5-tri-O-benzoyl-a-D-arabinofuranose **3**. After reaction of **3** with HBr in acetic acid, the conventional glycosylation procedure was attempted to prepare 2'-deoxy-2'-fluoro-3',5'-di-O-benzoyl-β-D-arabinofuranosyl nucleosides 4 (**4a**: 85%, **4b**: 85%, **4c**: 87%). Benzoyl groups of **4** were deprotected under basic condition to give **5** and then their 5'-primary alcohol was selectively transformed into the correspond-



Reagent: (a) 1) 30% HBr in AcOH ii) silylated base, $CHCl_3$, reflux (85%) (b) NaOMe, MeOH (91%) (c) I_2, Ph_3P, pyridine, 1,4-dioxane (66%) (d) 1N NaOMe, MeOH, reflux (45%) (e) ICl, NaN_3, CH_3CN or DMF (35%) (f) *p*-AnCl, pyridine (80%) (g) i) *m*-CPBA, H_2O-CH_2Cl_2. ii) NaOMe, MeOH (17%-27%).

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ing iodide **6** following literature procedure (I_2, PPh_3, pyridine in dioxane) (Garegg *et al.*, 1980). Elimination reaction of **6** to produce olefin **7** was accomplished by sodium methoxide in methanol (Prisbe *et al.*, 1976). Regioselective introduction of azido group to α-position in **7** with iodine azide (generated in situ from iodinemonochloride and sodium azide) gave desired isomer **8** as a predominant product in a ratio of 20 : 1. The structure of **8** was confirmed utilizing NOE data from ^{1}H-NMR experiments between 5' and anomeric proton (Moffatt *et al.*, 1979). After hydroxyl group at 3' position was protected by 4-methoxybenzoyl group, finally oxidation of 9 to mCPBA, the hypervalent iodine species, in the presence of water (Macdonald *et al.*, 1980) allowed for a successful displacement to afford target compound 10 in moderate yield, respectively (**10a**: 27%, **10b**: 17%, **10c**: 25%). The structures of all target compounds were identified by spectral data.

All prepared compounds (**10a,b,c**) were tested *in vitro* aganist HSV-1 and HSV-2. Preliminary results indicated that none of compounds showed any significant inhibitory activity. Further examination for other biological activities of these compounds is in progress.

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REFERENCES

Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem.* 1971, 93, 4323.

Hans, M.; Robert, M. R.; Mary, J. M.; Diane, C. R.; Julien, P. H.; Verheyden, J. P. H.; Ernest, J. P. *J. Med. Chem.* 1992, 35, 1440.

Maag, H.; Nelson, J. T.; Rios Steiner, J. L.; Prisbe, E. J. *J. Med. Chem.* 1994, 37, 431.

Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans 1*, 1980, 2866.

Prisbe, E. J.; Smejkal, J.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* 1976, 41, 1836.

Moffatt, J. G. In Nucleoside Analogues; Walker, R. T.; De Clercq, E. Eckstein, F. Eds; Plenum Publishing Corp., New York, 1979. pp 71-164.

Macdonald, T. L.; Narasimhan, N.; Burka, L. T. *J. Am. Chem. Soc.* 1980, 102, 7760.

Compound **10a**: 1-(4'-Azido-2'-fluoro-b-D-arabinofuranosyl)uracil ^{1}H NMR (CD_3OD, 400 MHz) δ 7.67 (d, 1 H, H-6), 6.36-6.41 (dd, 1 H, H-1'), 5.61 (d, 1 H, H-5), 4.88-5.2 (m, 1 H, H-2'), 4.38-4.48 (m, 1 H, H-3'), 3.75- 3.83 (m, 2 H, H-5'); IR (neat) 2200 cm^{-1}.

Compound **10b**: 1-(4'-Azido-2'-fluoro-b-D-arabinofuranosyl)chlorouracil ^{1}H NMR (CD_3OD, 400 MHz) δ 6.45-6.56 (dd, 1 H, H-1'), 5.51 (d, 1 H, H-5), 4.98-5.15 (m, 1 H, H-2'), 4.37-4.49 (m, 1 H, H-3'), 3.65-3.73 (m, 2 H,H-5'); IR (neat) 2200 cm^{-1}

Compound **10c**: 1-(4'-Azido-2'-fluoro-b-D-arabinofuranosyl)thymidine ^{1}H NMR (CD_3OD, 400 MHz) δ 7. 49 (s, 1 H, H-6), 6.45-6.56 (dd, 1 H, H-1'), 5.51 (δ, 1 H, H-5), 4.98-5.15 (m, 1 H, H-2'), 4.37-4.49 (m, 1 H, H-3'), 3.65- 3.73 (m, 2 H, H-5'), 1.78 (t, 3 H, CH_3); IR (neat) 2200 cm^{-1}.