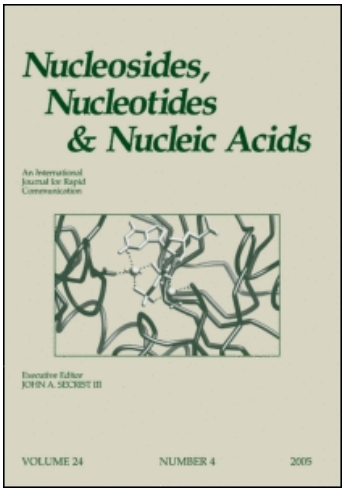

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Synthesis and Antiviral Evaluation of 2′,3′-Dideoxy-2′-fluoro-3′-*C*-hydroxymethyl-β-D-arabinofuranosyl Pyrimidine Nucleosides

Abdalla E. A. Hassan,[1,*] Balakrina S. Pai,[2] Stefania Lostia,[1] Lieven Stuyver,[1] Michael J. Otto,[1] Raymond F. Schinazi,[2] and Kyoichi A. Watanabe[1]

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ABSTRACT

The synthesis and anti-HBV and anti-HIV activity of a number of 2′,3′-dideoxy-2′-fluoro-3′-*C*-hydroxymethyl-β-D-arabinofuranosyl pyrimidine nucleosides are reported.

Key Words: Synthesis; Fluorination; Anti-HBV; Anti-HIV.

We have been interested in the synthesis and the biological activity of novel 1-(2-deoxy-2-fluoro-β-*arabino*-furanosyl) nucleoside analogues related to D/L FMAU, FIAU, ara-C and ara-A. L-FMAU is now in phase II clinical trials for the treatment of chronic hepatitis B virus (HBV) infection.[1] It is now recognized that branched–chain sugar nucleosides can show biological activity. For instance, 2′,3′-dideoxy-3′-*C*-hydroxymethylcytidine (**1**) a simple 3′-homologue of 2′-deoxycytidine, has potent

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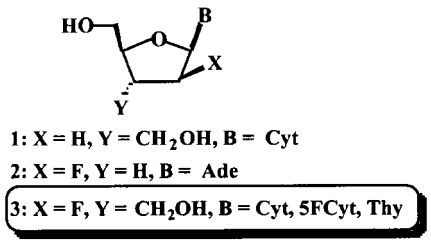
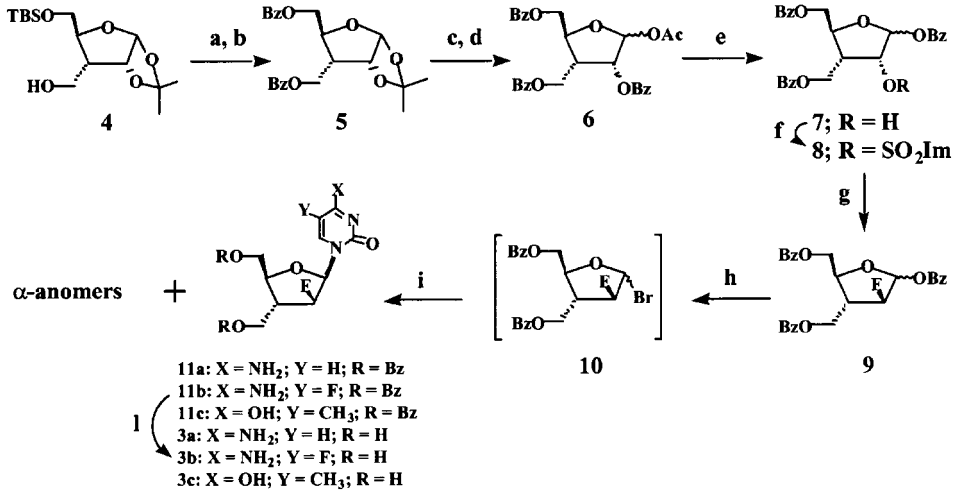


Chart 1.

anti-HIV activity ($EC_{50} = 0.01\,\mu M$).[2] Both α- and β-isomers of 2′,3′-dideoxy-3′-*C*-hydroxy-methylthioguanosine inhibit the growth of WI-L2 human lymphoblastoid cells.[3] Also, 2,3-dideoxy-nucleosides with 2′-fluoro in the *β*-configuration such as 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-adenine (**2**) showed a potent anti-HIV activity.[4] Herein, we report on the synthesis and the antiviral activity of pyrimidine nucleosides **3** that combine both of the 3′-deoxy-3′-*C*-hydroxymethyl and the 2′-β-fluorine moieties (Chart 1).

The key glycon intermediate, 3-deoxy-3-*C*-hydroxymethyl-2-fluoro-*arabino*-furanose derivative **9** was synthesized in 5 steps from the known 3-deoxy-3-*C*-hydroxymethyl-D-ribose derivative **4**[5] (Sch. 1). Conventional transformations of **4** furnished the β-fluorination precursor **8**. Attempts to fluorinate the imidazolyl-sulfonate derivative **8** under several conditions, however were unsuccessful. Direct fluorination of **7** using DAST in the presence of pyridine gave the desired compound



Scheme 1. Reagents and conditions: a) *n*-Bu_4NF, THF, 30 min., r.t., 82%; b) BzCl, Pyr., 0°C, 95%; c) i) 20% HCl, MeOH, 30 min, 55°C; ii) BzCl, Et_3N, DMAP, CH_2Cl_2, 86%; d) conc. H_2SO_4, Ac_2O, AcOH, 0°C-r.t., 3 hr, 77%; e) HCl gas, AcCl, CH_2Cl_2 then H_2O, CH_3CN, 46%; f) DAST, Pyr., CH_2Cl_2, r.t., 20 hr, 78%; g) HBr, AcOH, r.t., 12 hr; h) silylated nucleobase, $CHCl_3$, reflux, 20–30 hr; i) NH_3, MeOH, then HPLC purification.

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9 in good yield. Bromination of **9** with HBr in CH_2Cl_2, gave a bromo derivative **10**, which was coupled with silylated thymine, cytosine, and 5-fluorocytosine in reflux $CHCl_3$ to give the protected nucleosides, **11a–c**, along with the corresponding α-anomers (β : α/3-15 : 1). The protected anomers were treated with NH_3/MeOH and the desired β-anomers (**3a–c**) were purified by HPLC. The newly synthesized nucleosides were evaluated for their anti-HIV in human PBM cells[6] and HBV activity in primary human lymphocytes (PBMC) and in liver cells (HepG2.2.15[8] and/or AD38 cells[9]).

Of the synthesized compounds, 5-fluorocytosine derivative **3b** showed potent and selective anti-HBV in HepG2.2.15 cells and HIV activity in PBM ($EC_{50} = 0.13$ and 3.3 μM, respectively. Compounds **3a–c** did not show cytotoxicity up to 100 μM in PBM, CEM, and Vero cells.

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