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ANTI-HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 (HIV-1) AND ANTI-HEPATITIS B VIRUS (HBV) ACTIVITIES OF (2,3-DIDEOXY-2-FLUORO-β-*L-THREO*-PENTOFURANOSYL)NUCLEOSIDES

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Abstract. 1-or-9-(2,3-Dideoxy-2-fluoro-ß-*L-threo*-pentofuranosyl)- cytosine (F-ß-*L*-ara-ddC) and-adenine (F-ß-*L*-ara-ddA) were synthesized and their anti-HIV and anti-HBV activities were evaluated.

Recently, a number of *L*-nucleosides have been synthesized and some of them showed potent anti-HIV and anti-HBV activities: (-)-(2R,5S)-1-[(2-hydroxymethyl)oxathiolan-5-yl]cytosine (3TC)[1-7] and cis-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (FTC)[8,9], (-)-ß-*L*-dioxolane-cytosine[10-12], 2'-fluoro-5-methyl-ß-*L*-arabinofuranosyluridine (*L*-FMAU)[13] are undergoing various stages of preclinical and clinical evaluations as anti-HIV or anti-HBV agents. 2',3'-Dideoxy-ß-*L*-cytidine (*L*-ddC)[14-15] and 2',3'-dideoxy-ß-*L*-5-fluorocytidine (*L*-FddC)[16,17] have also been synthesized and exhibited anti-HIV and anti-HBV activities. 9-(2,3-Dideoxy-2-fluoro-ß -*D-threo*-pentofuranosyl)adenine (2'-F-ara-ddA)[18], 1-(2,3-dideoxy-2-fluoro-ß-*D-threo*-pentofuranosyl)cytosine (2'-F-ara-ddC)[19,20] and N^6-methyl-9-(2,3-dideoxy-2-fluoro-ß -*D-threo*-pentofuranosyl)adenine (N^6-Me-ara-ddA)[21] have been found to have potent anti-HIV activities and 2'-F-ara-ddA is undergoing clinical trials as an anti-HIV agent. Therefore, it was of interest to synthesize the corresponding *L*-nucleosides as potential antiviral agents. In this communication we wish to report the synthesis of 1-or 9-(2,3-dideoxy-2-fluoro-ß-*L-threo*-pentofuranosyl)-cytosine and -adenine and their preliminary anti-HBV activities. Our synthetic strategy was to prepare the intermediate **11**, which can be condensed with appropriate heterocycles for desired nucleosides **13** and **15**. In order to prepare the intermediate **11**, *L*-xylose was used as the starting material, which was fully protected with isopropylidene groups followed by selective hydrolysis of the 3,5-isopropylidene group to give 1,2-O-isopropylidene-*L*-xylofuranose **3**[22] in 82% yield. The primary hydroxy group of compound **3** was selectively protected by a benzoyl group to 5-benzolylated compound **4**, which was oxidized by pyridinium dichromate in refluxing methylene chloride to give **5** in quantitative yield. Tosyl hydrazone derivative **6** was prepared by the treatment of **5** with p-toluenesulfonhydrazide in absolute ethanol, which was subjected to the Wolff-Kishner conditions[23] to obtain the intermediate **8**. We have also investigated

the Barton-type[24] deoxygenation reaction for intermediate **4**, but observed more side reactions resulting in inferior yields. Other investigators reported similar results with the D-isomers.[25]

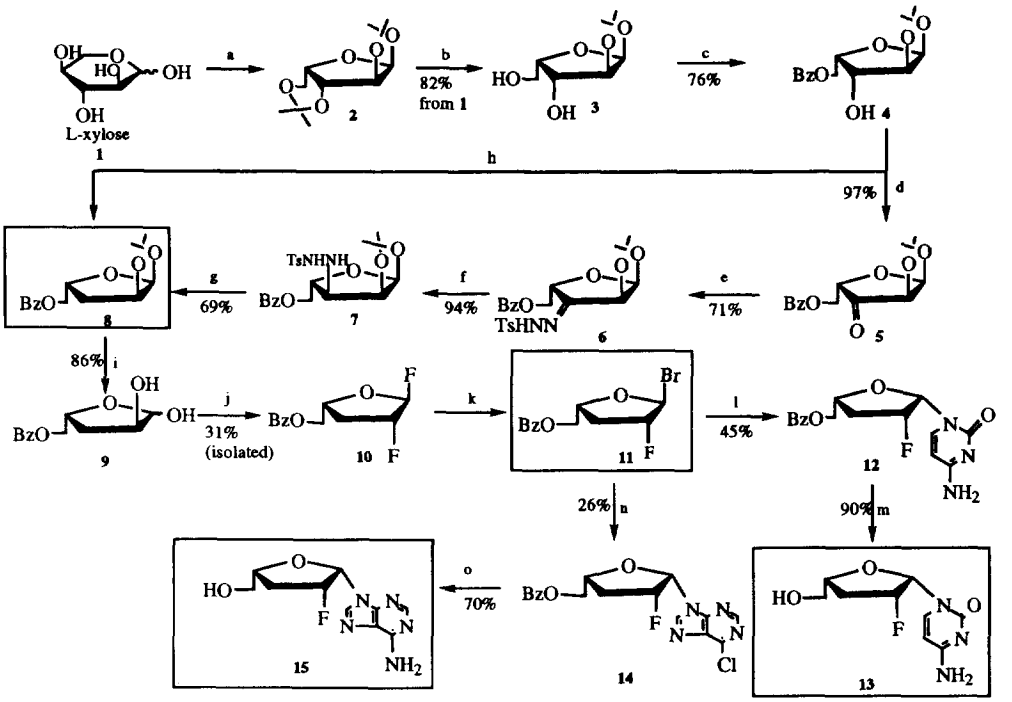
The 1,2-isopropylidene group of **8** was removed by 80% HOAc to obtain the 1,2-dihydroxy derivative **9**, which was treated with diethylaminosulfur trifluoride (DAST) to give the 1,2-difluoro derivative **10** in which the fluorine on the anomeric position is in the trans (ß)-position due to the dipole effects. Since direct the condensation of the D-enantiomer of difluorosugar **10** with a base gave a low yield[21], compound **10** was converted to the bromo derivative **11**, which was then condensed with silylated cytosine to give exclusively the desired ß-isomer **12** in 45% yield. Deprotection of **12** in saturated methanolic ammonia at room temperature gave the desired free nucleoside F-ß-L-ara-ddC **13** in 90% yield[26]. The purine nucleoside analogue **14** was prepared by the sodium salt method[10], in which the bromosugar **11** and sodium salt of 6-chloropurine were reacted in acetonitrile at room temperature to obtain **14** in 52% yield. The protected nucleoside **14** was treated with methanolic ammonia at 100°C for 20 h to obtain the desired F-ß-*L*-ara-ddA **15** in 70% yield[27].

Table 1. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of F-ß-*L*-ara Nucleosides in PBM , CEM, Vero and 2.2.15 cells.

Compound	Anti-HIV activity in PBM cells EC_{50} (μM)	Anti-HBV activity in 2.2.15 cells EC_{50} (μM)	Cytotoxicity in [IC_{50} (μM)] PBM	CEM	Vero	2.2.15
13	16.2	4.0	>100	>100	>100	>200
15	100	>10.0	>100	>100	>100	>200
AZT	0.004	ND	>100	14.0	27.7	ND

The newly synthesized F-ß-L-ara-ddC (**13**) and F-ß-L-ara-ddA (**15**) were evaluated *in vitro* against HIV-1 and HBV in human peripheral blood mononuclear and 2.2.15 cells, respectively (Table 1). In contrast to the D-isomers, the corresponding L-isomers exhibited only moderate to poor anti-HIV activities. Nevertheless, it is interesting to find that the L-isomers exhibited some anti-HIV activities. Furthermore, the cytosine derivative **13** exhibited modest anti-HBV activity and is now considered a lead compound for the synthesis of additional derivatives to search for more potent compounds.

Scheme 1



a. acetone/$CuSO_4$,con. H_2SO_4; b. 0.2%HCl; c. BzCl/Py/CH_2Cl_2; d. PDC/Ac_2O/CH_2Cl_2; e. $TsNHNH_2$; f. $NaBH_3CN$; g. NaOAc.$3H_2O$/EtOH; h. Ph_3P/I_2NaBH_4; i. 80%HOAc; j. DAST/DMAP/CH_2Cl_2; k. 45%HBr/HOAc; l. silylated cytosine/TMSOTf/CH_3CN; m. NH_3/MeOH,r.t.; n. 6-chloropurine/NaH/CH_3CN; o. NH_3/MeOH, 100°C.

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26. Compound **13:** m.p. 142-144°C; $[\alpha]_D^{25}$ -210.7 [c 0.12, MeOH]; UV(H_2O): 272.0 (ε 8140)(pH 2),271.5 (ε 8680)(pH 7), 271.5 (ε 9860)(pH 11);^{1}H NMR(DMSO-d_6): δ 7.67 (d, J=7.6 Hz, 1H, H-6), 7.32 (bs, 2H, NH_2), 5.94 (dd, J=18.5 and 2.6 Hz, 1H, H-1'), 5.72 (d,J=7.6 Hz, 1H, H-5'), 5.21 (dm, J=58.0 Hz, 1H, H-2'), 4.95 (t, J=3.0 Hz, 1H, 5'-OH), 4.09 (m, 1H, H-4'), 3.51 (m, 2H, H-5'), 1.99-2.60 (m, 2H, H-3'); Anal. calcd for $C_9H_{12}FN_3O_3$: C, 47.18; H, 5.24; N, 18.34. Found:C, 46.89; H, 5.27; N, 18.07.
27. Compound **15**: m.p. 225-226°C; $[\alpha]_D^{25}$ -94.6 [c 0.11, MeOH]; UV(H_2O): 258.0 (ε12760) (pH 2), 258.5 (ε 13660)(pH 7), 258.0(ε 12270)(pH 11); ^{1}HNMR(DMSO-d_6): δ 8.14 (s, 1H, H-2), 8.25(d, J=3.0Hz,1H, H-8), 7.33 (bs, 2H, NH_2),6.30 (d, J=3.8 and 16.1Hz, 1H, H-1'), 5.42 (dm, J=54.5Hz, 1H, H-2'), 5.05 (t, J=5.5 Hz, 1H, 5'-OH), 4.16 (m, 1H, H- 4'), 3.59 (2m, 2H, H-5'), 2.14 -2.61(2m, 2H, H-3'); Anal calcd for $C_{10}H_{12}N_5O_2 \cdot 0.25H_2O$:C,46.60; H, 4.88; N, 27.17. Found: C, 46.80; H, 4.78; N, 27.03.

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