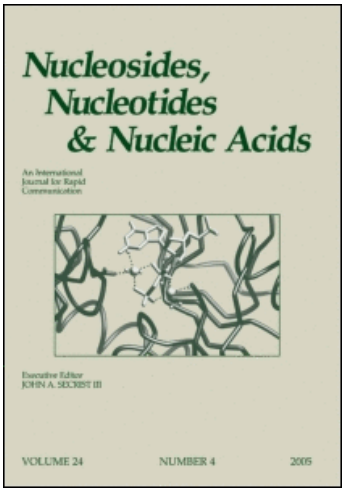

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ANTIVIRAL ACTIVITIES OF β-ENANTIOMERS OF 3'-SUBSTITUTED-3'-DEOXYTHYMIDINE ANALOGS

Abdesslem Faraj[1], M. Abdelaziz El Alaoui[1], Geraldine Pavia[2], Gilles Gosselin[2], Jean-Louis Imbach[2], Raymond F. Schinazi[3] and Jean Pierre Sommadossi*[1].
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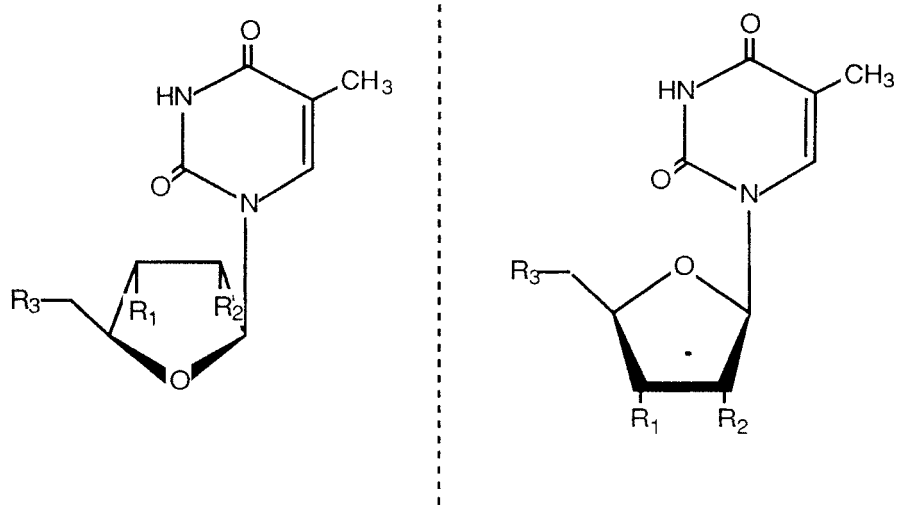
Abstract: Several β-L-3'-substituted-3'-deoxythymidine were stereospecifically synthesized. None of these analogs inhibited HIV-1 nor HBV replication in vitro suggesting that these β-L-pyrimidine derivatives may not be efficiently phosphorylated inside the cells.

Introduction.

Recently, β-L-nucleoside analogs have generated great interest in the field of antiviral chemotherapy as demonstrated by the potent antiviral activity of 3TC, β-L-FTC, β-L-ddC, β-L-FddC, β-L-OddC and β-L-FMAU[1]. However, very few studies were reported with β-L-thymidine analogs. Therefore, novel thymidine analogs with the β-L-sugar configuration were synthesized and tested in vitro against HIV-1 and HBV replication. These compounds, which included β-L-3'-azido-3'-deoxythymidine (β-L-AZT, **1**), β-L-3'-amino-3'-deoxythymidine (β-L-AMT, **3**), β-L-2',3'-didehydro-3'-deoxythymidine (β-L-D4T, **5**), β-L-3'-fluoro-3'-deoxythymidine (β-L-FLT, **7**), β-L-3'-deoxythymidine (β-L-ddT, **9**) were compared to their corresponding natural β-D-analogs (Fig. 1).

Chemistry.

β-D-AZT, β-D-ddT, and β-D-D4T were purchased from Sigma Chemical Co. (St. Louis, Mo.). β-L-AZT (**1**), β-L-D4T (**5**), β-L-FLT (**7**) and β-L-ddT (**9**) were stereospecifically synthesized and their synthesis will be described elsewhere. β-L-AMT and β-D-AMT were synthesized by chemical reduction of the azido function of β-L-AZT and β-D-AZT, respectively.



R_1= N_3, R_2 = H, R_3 = OH; ß-L-AZT (**1**), ß-D-AZT (**2**)
R_1= NH_2, R_2 = H, R_3 = OH; ß-L-AMT (**3**), ß-D-AMT (**4**)
R_1, R_2 = db*, R_3 = OH; ß-L-D4T (**5**), ß-D-D4T (**6**)
R_1= F, R_2 = H, R_3 = OH; ß-L-FLT (**7**), ß-D-FLT (**9**)
R_1= H, R_2 = H, R_3 = OH; ß-L-ddT (**9**), ß-D-ddT (**10**).
(*db = double bound).

Figure 1.

Biological activities.

For anti-HIV assays, human peripheral blood mononuclear (PBM) cells were isolated by Ficoll-Hypaque discontinuous gradient centrifugation from healthy seronegative donors. A prototype strain of HIV-1 (LAV) was used as the standard virus for the antiviral assays. The PBM cells were propagated and used for antiviral assays as described previously[2]. For anti-HBV assays, the HBV transfected human hepatoblastoma-derived HepG2 cell line (2.2.15 cells) was cultured as previously described[3]. Cytotoxicity of the compounds was evaluated by growth inhibition of Hep-G2 cells and measured by the uptake of neutral red dye in 96-wells flat-bottom cell cultures plates as previously reported[3]. Each compound was tested at four concentrations in triplicate cultures and the median inhibitory concentration (IC_{50}) was determined.

Table 1. Effect of β-thymidine analogs against HIV-1 in PBM cells and against HBV in transfected HepG2 (2.2.15) cells.

Compound	EC_{50}[a] (μM)		IC_{50}[b] (μM)
	HBV RI[c]	HIV-1	Hep-G2
β-L-AZT (**1**)	> 10	>100	> 200
β-D-AZT (**2**)	> 10	0.006	> 200
β-L-AMT (**3**)	> 10	>100	> 200
β-D-AMT (**4**)	> 10	>100	120 ± 20
β-L-D4T (**5**)	> 10	>100	> 200
β-D-D4T (**6**)	> 10	0.009	> 200
β-L-FLT (**7**)	> 10	>100	> 200
β-D-FLT (**8**)	0.5	0.002	> 100
β-L-DDT (**9**)	> 10	>10	> 200
β-D-DDT (**10**)	> 10	0.17	> 200

[a] EC_{50} represent drug concentration required to inhibit 50% of viral replication.

[b] IC_{50} represent drug concentration required to inhibit 50% Hep-G2 cells growth.

[c] RI represents the intracellular HBV DNA replicative intermediate.

[d] Values represent mean ± standard deviation.

None of the β-L-nucleoside analogs including β-L-AZT (**1**), β-L-AMT (**3**), β-L-D4T (**5**), β-L-FLT (**7**) and β-L-ddT (**9**) inhibited HIV-1 replication in human PBM cells, up to a concentration of 100 μM (Table 1). In contrast, the corresponding β-D-derivatives **2**, **6** and **9** are well known to be potent anti-HIV agents.

None of the β-L and β-D nucleoside analogs also inhibited HBV replication in 2.2.15 cells up to a concentration of 10 μM, with the exception of β-D-FLT (**8**) which exhibited an EC_{50} value of 0.5 μM (Table 1).

None of the β-D and β-L-nucleosides inhibited Hep-G2 cell proliferation up to 200 μM, except β-D-AMT (**4**) which was toxic to Hep-G2 cells with an IC_{50} of 120 μM (Table 1).

The lack of activity of most β-L-thymidine analogs against HIV and HBV replication in vitro may reflect a limited phosphorylation to their triphosphate derivatives within cell. Studies are in progress to explain the lack of antiviral activities of these β-L-thymidine analogs, and to derive prodrugs that may by-pass the first phosphorylation step.

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