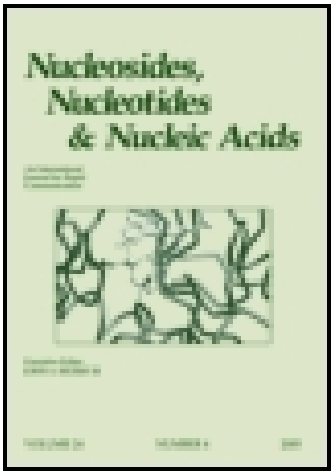


Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

Antiviral Activities of β-Enantiomers of 3′-Substituted-3′-deoxythymidine Analogs

Abdesslem Faraj [a], M. Abdelaziz El Alaoui [a], Geraldine Pavia [b], Gilles Gosselin [b], Jean-Louis Imbach [b], Raymond F. Schinazi [c] & Jean Pierre Sommadossi [a]

[a] University of Alabama at Birmingham, Birmingham, AL, USA
[b] University of Montpellier II, 34095, Montpellier, France
[c] VA Medical Center/Emory University, Decatur, GA, USA

Published online: 16 Aug 2006.

To cite this article: Abdesslem Faraj, M. Abdelaziz El Alaoui, Geraldine Pavia, Gilles Gosselin, Jean-Louis Imbach, Raymond F. Schinazi & Jean Pierre Sommadossi (1997) Antiviral Activities of β-Enantiomers of 3′-Substituted-3′-deoxythymidine Analogs, Nucleosides and Nucleotides, 16:7-9, 1287-1290, DOI: 10.1080/07328319708006172

To link to this article: http://dx.doi.org/10.1080/07328319708006172

NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 1287-1290 (1997)

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].
[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]University of Montpellier II, 34095 Montpellier, France and [3]VA Medical Center/Emory University, Decatur, GA, USA.

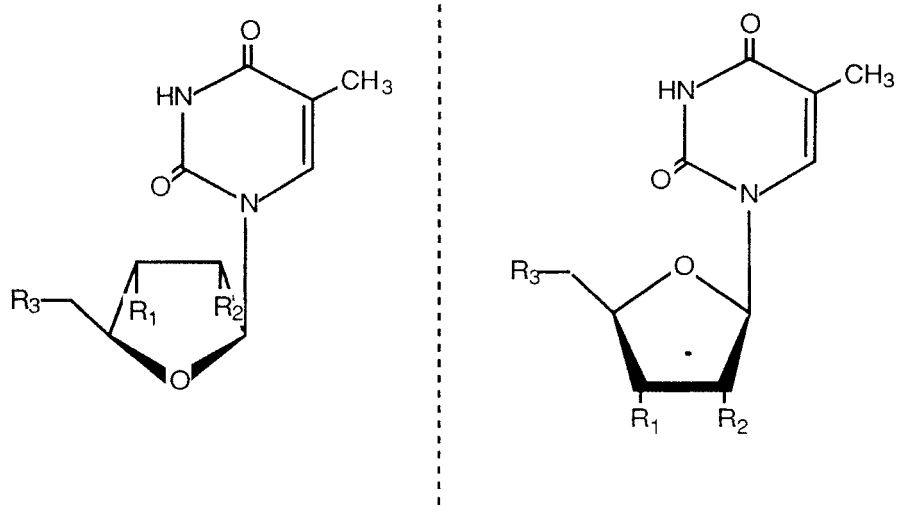
Abstract: Several β-L-3'-substituted-3'-deoxythymidine were stereospecifically synthesized. None of these analogs inhibited HIV-1 nor HBV replication in vitro suggesting that these β-L-pyrimidine derivatives may not be efficiently phosphorylated inside the cells.

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.



ß-L-thymidine analogs ß-D-thymidine analogs

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.

ACKNOWLEDGEMENTS

This work was supported in part by Public Health Service Grants Al-33239 (J.P. Sommadossi), Al-25899 (R.F. Schinazi), the Department of Veterans Affairs, the Georgia RCAHI (R.F. Schinazi) and by grants from the Agence Nationale de Recherche sur le SIDA (ANRS, France)

REFERENCES

1. Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, 39, 1017-1029.
2. Schinazi, R. F., A. McMillan, D. Cannon, R. Mathis, R. M. Lyod, A. Peck, J.-P. Sommadossi, M. St. Clair, J. Wilson, P. A. Furman, G. Painter, W.-B Choi, and D. C. Liotta. *Antimicrob. Agents Chemother.* **1992**, 36, 2423-2431.
5. Schinazi,R. F., G. Gosselin, A. Faraj, B. E. Korba, D.C. Liotta, C. K. Chu, C. Mathe, J.-L. Imbach, and J.-P. Sommadossi. 1994. *Antimicrob. Agents Chemother.* **1994**, 38, 2172-2174.