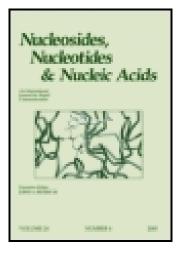
This article was downloaded by: [University of Georgia] On: 18 December 2014, At: 03:49 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lncn19</u>

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

Abdesslem Faraj $^{\rm a}$, M. Abdelaziz El Alaoui $^{\rm a}$, Geraldine Pavia $^{\rm b}$, Gilles Gosselin $^{\rm b}$, Jean-Louis Imbach $^{\rm b}$, Raymond F. Schinazi $^{\rm c}$ & Jean Pierre Sommadossi $^{\rm a}$

^a University of Alabama at Birmingham , Birmingham, AL, USA

^b University of Montpellier II, 34095, Montpellier, France

 $^{\rm c}$ 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: <u>10.1080/07328319708006172</u>

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

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms

& Conditions of access and use can be found at <u>http://www.tandfonline.com/page/</u> terms-and-conditions

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

Abdesslem Faraj¹, M. Abdelaziz El Alaoui¹, Geraldine Pavia², Gilles Gosselin², Jean-Louis Imbach², Raymond F. Schinazi³ and Jean Pierre Sommadossi^{*1}.
¹University of Alabama at Birmingham, Birmingham, AL, USA; ²University of Montpellier II, 34095 Montpellier, France and ³VA 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.

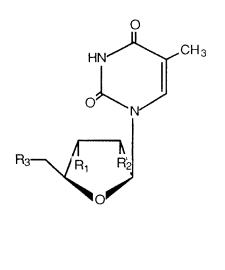
Introduction.

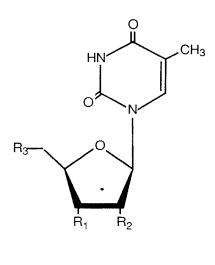
Recently, β -L-nucleoside analogs have generated great interest in the field of antiviral chemotherapy as demonstrated by the potent antiviral activity of 3TC, β -L-FTC, β -L-ddC, β -L-FddC, β -L-OddC and β -L-FMAU¹. However, very few studies were reported with β -L-thymidine analogs. Therefore, novel 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.

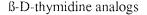
 β -D-AZT, β -D-ddT, and β -D-D4T were purchased from Sigma Chemical Co. (St. Louis, Mo.). β -L-AZT (<u>1</u>), β -L-D4T (<u>5</u>), β -L-FLT (<u>7</u>) and β -L-ddT (<u>9</u>) were stereospecifically synthesized and their synthesis will be described elsewhere. β -L-AMT and β -D-AMT were synthesized by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

1287





B-L-thymidine analogs



 $\begin{array}{l} R_1 = N_3, R_2 = H, R_3 = OH; \ \ \beta \text{-L-AZT} (\underline{1}), \ \ \beta \text{-D-AZT} (\underline{2}) \\ R_1 = NH_2, R_2 = H, R_3 = OH; \ \ \beta \text{-L-AMT} (\underline{3}), \ \ \beta \text{-D-AMT} (\underline{4}) \\ R_1, R_2 = db^*, R_3 = OH; \ \ \beta \text{-L-D4T} (\underline{5}), \ \ \beta \text{-D-D4T} (\underline{6}) \\ R_1 = F, R_2 = H, R_3 = OH; \ \ \beta \text{-L-FLT} (\underline{7}), \ \ \beta \text{-D-FLT} (\underline{9}) \\ R_1 = H, R_2 = H, R_3 = OH; \ \ \beta \text{-L-ddT} (\underline{9}), \ \ \beta \text{-D-ddT} (\underline{10}). \\ (*db = double bound). \end{array}$

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 previously². For anti-HBV assays, the HBV transfected human hepatoblastoma-derived HepG2 cell line (2.2.15 cells) was cultured as previously described³. 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 reported³. Each compound was tested at four concentrations in triplicate cultures and the median inhibitory concentration (IC₅₀) was determined.

Compound	EC ₅₀ ^a (μM)		IC ₅₀ ^b (μM)
	HBV RIC	HIV-1	Hep-G2
B-L-AZT (<u>1</u>)	> 10	>100	> 200
β-D-AZT (<u>2</u>)	> 10	0.006	> 200
β-L-AMT (<u>3</u>)	> 10	>100	> 200
β-D-AMT (<u>4</u>)	> 10	>100	120 ± 20
β-L-D4T (<u>5</u>)	> 10	>100	> 200
β-D-D4T (<u>6</u>)	> 10	0.009	> 200
β-L-FLT (<u>7</u>)	> 10	>100	> 200
β-D-FLT (<u>8</u>)	0.5	0.002	> 100
β-L-DDT (<u>9</u>)	> 10	>10	> 200
β-D-DDT (<u>10</u>)	> 10	0.17	> 200

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

^a EC₅₀ represent drug concentration required to inhibit 50% of viral replication.

^bIC₅₀ represent drug concentration required to inhibit 50% Hep-G2 cells growth. ^cRI represents the intracellular HBV DNA replicative intermediate. ^dValues 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 μ M (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 μ M, with the exception of β -D-FLT (**8**) which exhibited an EC₅₀ value of 0.5 μ M (Table 1). None of the β -D and β -L-nucleosides inhibited Hep-G2 cell proliferation up to 200 μ M, except β -D-AMT (<u>4</u>) which was toxic to Hep-G2 cells with an IC₅₀ of 120 μ M (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.
- 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.
- 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.