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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Synthesis and Biological Evaluation of Polyaminated 2',3'-Dideoxy-3'-thiacytidine Prodrugs

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To cite this Article Camplo, M. , Mourier, N. , Chermann, J-C and Kraus, J-L(1999) 'Synthesis and Biological Evaluation of Polyaminated 2',3'-Dideoxy-3'-thiacytidine Prodrugs', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 879 — 880

To link to this Article: DOI: 10.1080/15257779908041590

URL: <http://dx.doi.org/10.1080/15257779908041590>

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SYNTHESIS AND BIOLOGICAL EVALUATION OF POLYAMINATED 2',3'-DIDEOXY-3'-THIACYTIDINE PRODRUGS

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ABSTRACT : The syntheses and biological evaluation of polyaminated 2',3'-dideoxy-3'-thiacytidine have been performed. A new lead was found to increase the in vitro antiviral potency (syncytia formation on MT-4 cell line) of two order magnitude greater than the parent nucleoside drug. Moreover, the in vitro activity on HIV macrophages was found to be more than 3 log greater than the activity of the parent drug 1.

The most extensively studied anti-HIV agents are the 2',3'-dideoxy nucleoside analogues : AZT (Retrovir[®]), ddC (Zalcitabine[®]), d4T (Zerit[®]), ddI (Videx[®]), 3TC (Epivir[®]), which terminate DNA synthesis during the reverse transcription reaction.^{1,2} As a part of our efforts to design prodrugs of the anti-HIV drug 2',3'-dideoxy-3'-thiacytidine 1 (BCH-189, figure 1), we have previously described some potent inhibitors of the cytopathicity of HIV-1 in MT-4 cells.³

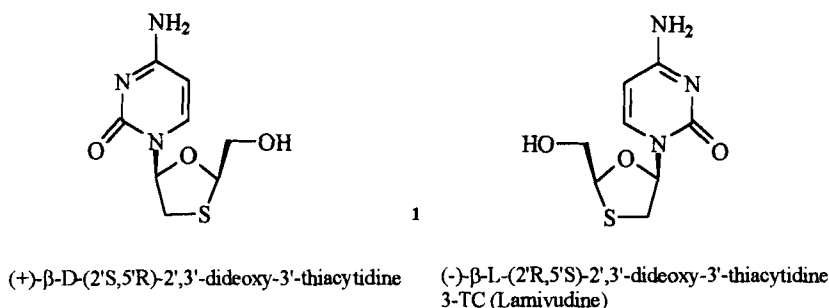


figure 1

We report the synthesis and the structure activity relationship of 2',3'-dideoxy-3'-thiacytidine derivatives obtained by substituting 5'-O positions by various polyamines (figure 2).⁴

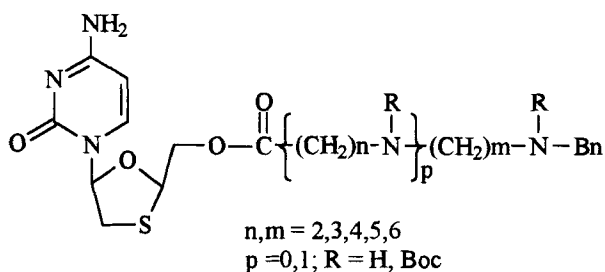


figure 2

Since 3-TC represents the L enantiomer of BCH-189, we preliminary used in this work the racemate mixture **1** represented in figure 1. The incorporation of N-Boc protected monoamine or diamine side arm into the backbone of the 2',3'-dideoxy-3'-thiacytidine **1** (BCH-189) provided an increase of antiviral potency, which could be two order magnitude greater than the parent drug **1**. Several compounds were found to inhibit HIV-1 replication in cell culture with 50% effective concentrations $EC_{50} = 10-50$ nM. A new lead was found to increase the *in vitro* antiviral potency (syncytia formation on MT-4 cell line) of two order magnitude greater than the parent nucleoside drug. Moreover, the *in vitro* activity on HIV macrophages was found to be more than 3 log greater than the activity of the parent drug **1**.

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