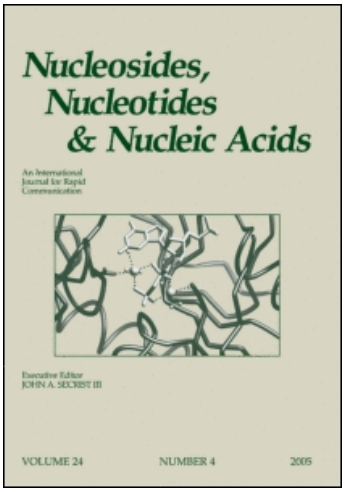

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Synthesis and Biological Evaluation of Polyaminated 2',3'-Dideoxy-3'-thiacytidine Prodrugs

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

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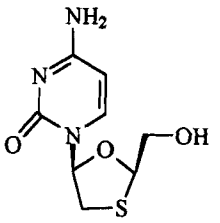
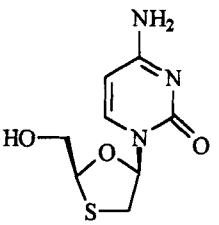
ABSTRACT : The syntheses and biological evaluation of polyaminated 2',3'-dideoxy-3'-thiacytidine have been performed. A new lead was found to increase the in vitro antiviral potency (syncitia formation on MT-4 cell line) of two order magnitude greater than the parent nucleoside drug. Moreover, the in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



(+)-β-D-(2'S,5'R)-2',3'-dideoxy-3'-thiacytidine

1



(-)-β-L-(2'R,5'S)-2',3'-dideoxy-3'-thiacytidine
3-TC (Lamivudine)

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]

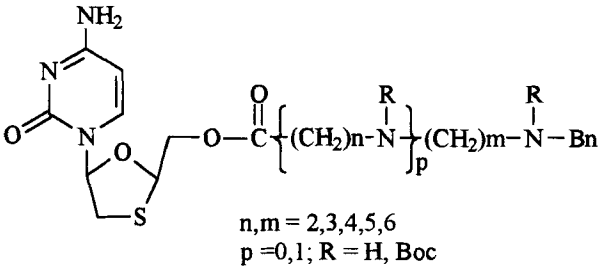


figure 2

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 (syncitia 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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4- Zambon-Inserm patent (1997, M197A000737).