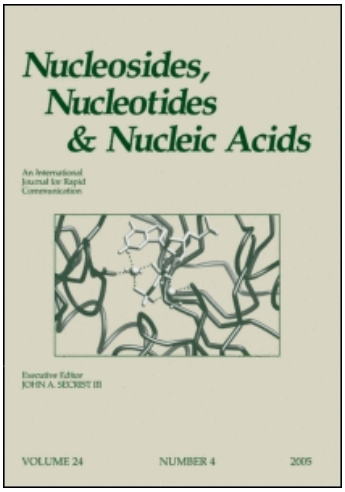

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Stereospecific Synthesis and Antiviral Activities of β-L-2',3'-Dideoxy-5-chloropyrimidine Nucleoside Derivatives

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STEREOSPECIFIC SYNTHESIS AND ANTIVIRAL ACTIVITIES OF β-L-2',3'-DIDEOXY-5-CHLOROPYRIMIDINE NUCLEOSIDE DERIVATIVES

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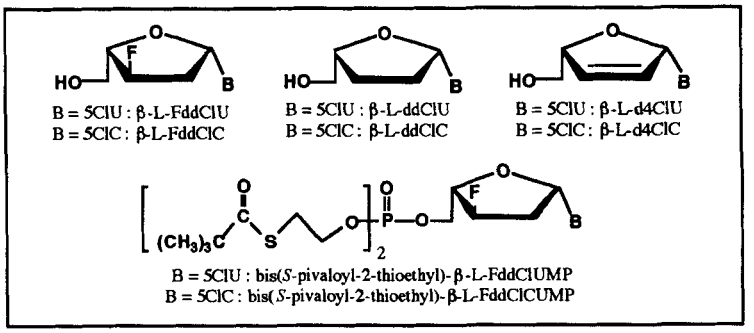
ABSTRACT: Several 5-chlorouracil and 5-chlorocytosine β-L-dideoxynucleosides were stereospecifically synthesized and their activities against human immunodeficiency virus (HIV) and hepatitis B virus (HBV) were examined in cell culture.

Pandemic morbidity and mortality due to HIV and HBV account for intensive efforts in discovering effective agents against these viruses. Among the nucleoside analogs which have been shown to possess potent antiviral activity, 2',3'-dideoxy-3'-fluorothymidine (FddT) had been described as the most effective inhibitor of HIV-1 replication in various cellular systems albeit to the detriment of considerable cytotoxic effects.[1] Subsequently, several 5-halogeno derivatives of FddU have been synthesized,[2] and among them, 2',3'-dideoxy-3'-fluoro-5-chlorouridine (FddClU) emerged as a selective anti-HIV agent.[3,4]

Recently, L-nucleosides have proven to be of great importance as anti-HIV[5] and anti-HBV agents,[6] with a number of these compounds showing promising activity when compared to their corresponding D-enantiomers. Consequently, we decided to synthesize and to study the β-L-enantiomer of FddClU and its *t*-butylSATE pronucleotide,[7] as well as several other 5-chloropyrimidine β-L-nucleoside derivatives ranging from the 5-chlorouracil to the 5-chlorocytosine series (FIG.).

All the presently reported (and hitherto unknown) β-L-nucleosides and pronucleotides were evaluated for their inhibitory effects against HIV and HBV. However, none of these compounds showed significant antiviral activity, except for 2',3'-dideoxy-β-L-5-chlorocytidine and 2',3'-dideoxy-2',3'-didehydro-β-L-5-chlorocytidine which were

endowed with some anti-HBV activity (EC_{50} = 10 and 5 µM, respectively ; CC_{50} > 200 µM in Hep-G2 cells). Unfortunately, no enhancement of the antiviral activities of the two *t*-butylSATE β-L-pronucleotides, in comparison with their parent nucleosides, was observed.



- FIG. -

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