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Synthesis of novel oxathiolane and dithiolane nucleoside analogues possessing anti-HIV activity.

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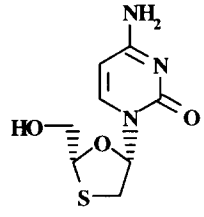
The discovery of **1**, member of novel class of HIV and HBV reverse transcriptase inhibitors led to the clinical development of **3TC**^{TM} for treatment of AIDS and **LAMIVUDINE** for HBV chemotherapy. Novel nucleoside analogues have been synthesized to study the role of the heteroatom in the oxathiolane ring by transposition or by replacing the oxygen with a sulfur giving rise to **2** and **3**. Both classes of compounds were found to possess anti-HIV activity. A description of the synthesis, resolution and biological activities will be presented.



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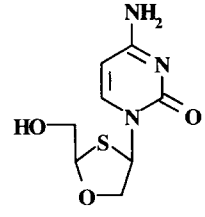

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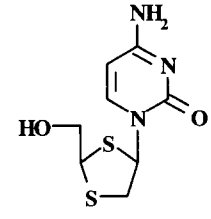

3

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ENANTIOMERIC DDC DERIVATIVES ARE POTENT INHIBITORS OF HIV REPLICATION IN CELL CULTURES

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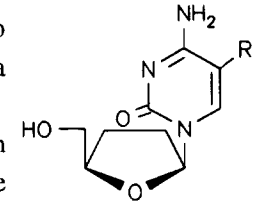
ß-L-DDC (Fig, R = H) and its hitherto unknown 5-fluoro derivative (Fig, R = F) were stereospecifically synthesized by a multi-step reaction sequence from L-xylose.



Figure

The antiviral activities of these compounds were evaluated in several cell lines infected with HIV-1 or HIV-2. In all cases, the fluoro derivative was consistantly more effective than ß-L-DDC in blocking HIV multiplication.

The activity of these compounds was also examined against HIV-1 strains resistant to AZT and to Nevirapine (a nonnucleoside inhibitor). It was shown that the production of virions by CEM-SS or MT-2 cells infected with Nevirapine resistant or AZT resistant virus was greatly reduced in the presence of these L-enantiomers.

Other cross-resistance studies have been carried out and the data will be discussed.