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FTC Inhibition of HIV-1 RT and HBV DNA Polymerase: Differential Activity of Stereoisomers. JE Wilson, JL Martin, K Borrota-Esoda, MG Davis, SE Hopkins, G Painter, D Liotta, and PA Furman. Division of Virology, Burroughs Wellcome Co., 3030 Cornwallis Rd., Research Triangle Park, NC, USA.

(2'R,5'-S)-(-)-1-[2-(hydroxymethyl)-1,3-oxathiolane-5-yl]-5-fluorocytosine, (the (-) enantiomer of 2'-deoxy-3'thia-5-fluorocytosine or FTC), is a potent inhibitor of HIV and HBV *in vitro*. The 5'-triphosphates FTC as well as the (+)-enantiomer [(+)-FTCTP] were synthesized and the mechanism of inhibition with respect to both HIV and HBV was studied. The 5' triphosphates of both enantiomers inhibited equally HIV-1 reverse transcriptase (RT) in both an endogenous HIV-1 reaction carried out in permeablized virus and steady-state assays with purified RT. In the endogenous reaction, IC_{50} values for the inhibition of production of the 9.2 kb, full length genomic minus-strand DNA were calculated of 0.32 μM for FTCTP and 0.45 μM for (+)-FTCTP. Steady-state assays indicated FTCTP and (+)-FTCTP were competitive inhibitors of RT during both RNA-directed and DNA-directed DNA synthesis with respect to dCTP. The K_i values determined for FTCTP and (+)-FTCTP where dCTP was the competing substrate and poly(rI)p(dC)$_{19-24}$ was the primer template were 0.90 μM and 2.5 μM, respectively. Analyzing the inhibition of DNA directed DNA synthesis by the RT using M13mp18HXBRT as the primer template gave a K_i of 4.7 and 1.7 μM for FTCTP and (+)-FTCTP, respectively. FTCTP and (+)-FTCTP were both utilized by the RT as substrates and incorporated into the growing strand of DNA on M13mp18HXBRT, terminating synthesis at stops similar to that found for ddCTP. In contrast to HIV, an HBV endogenous reaction indicated (-)-FTCTP was a more potent inhibitor than (+)-FTCTP during both RNA- and DNA-directed synthesis. The IC_{50} for FTCTP inhibition of dCTP turnover on HBV DNA by the HBV polymerase was 40 fold lower than that found for (+)-FTCTP.

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Semisynthetic antitumor alkaloids derivatives as a antiviral and a potential anti-HIV preparations.

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We have studied antiviral activity of some Chelidonium majus L. alkaloids being thiophosphoric acid triaziridid derivatives. We have shown such derivates activity against infective laryngotracheitis virus, and A and A-2 influenza virus types. Therapeutical effect of preparations has been studied on mice with influenza caused pneumonia, their action being similar to remantadine one. Chelidonium preparations are as low toxicity (200-1700 mg/kg i.p. for mice and rats), therapeutical doses being 0,25- 1 mg/kg. The preparations has no suppressive action upon hematogenesis and has a immunomodulating effect stimulating interleukine 1 but no interleukine 2 production. In vitro one preparation has a selective cytotoxic action against HIV1-infected T-leucosic cells (concentration lower 10-5 M) but no effect on the normal lymphocytes (toxic concentration is upper 10-4 M). This results show the possibility of these compounds application for AIDS therapy.