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2',3',5'-TRIDEOXYURIDINE-5'-METHYLPHOSPHONIC ACID: SYNTHESIS, ANTIVIRAL EVALUATION, AND INTERACTION OF ITS DIPHOSPHATE DERIVATIVE WITH HIV-1 REVERSE TRANSCRIPTASE

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The title compound was chemically synthesized from 2',3'-dideoxyuridine by a five-step reaction sequence. It was evaluated against several DNA and RNA viruses, including HIV, and shown to be inactive in all cases.

The interaction of the diphosphate derivative with HIV-1 reverse transcriptase was studied using methods based primarily on fluorescence spectroscopy. From the variation of intrinsic tryptophan fluorescence of reverse transcriptase, a value of 24 μM for the dissociation constant of the enzyme-diphosphophosphonate complex was found at 25°C. In the presence of a DNA/DNA template/primer of defined sequence, competition experiments with a fluorescent derivative of dTTP confirmed the abscence of incorporation of ddU-5'-methylphosphonic acid. Finally, the reverse transcriptase activity measured with Poly(rA)/$(dT)_{15}$ and [^{3}H]dTTP was lowered to 35% of its value in the presence of 0.5 mM concentration of the diphosphate derivative.

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Synthesis of 2-halo- and 2-aza-adenine analogues of 1,3-oxathiolane nucleoside as potential anti-HIV agents.

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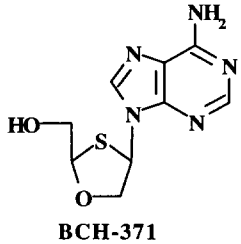
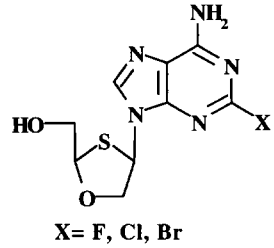
We recently described the synthesis and the anti-HIV activity of a novel class of 1,3-oxathiolane nucleoside analogues. **BCH-371**, the adenine derivative was found to be a potent inhibitor of the HIV replication. It has been reported that the replacement of the 2-carbon of the purine moiety of Oxatanocin-A and ddI by a nitrogen atom resulted in the enhancement of HIV inhibition relative to the parent compounds. Inspired by these finding as well as in the search for ADA-resistance adenine derivatives we have prepared 2-halo- and 2-azaadenine analogues based on **BCH-371**. Details of the synthesis and antiviral activity will be presented.



BCH-371



X= F, Cl, Br