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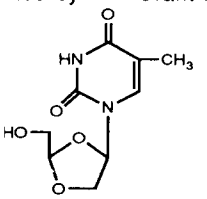
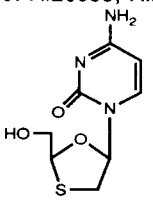
Asynmetric Synthesis of 1,3-Dioxolane Nucleosides and Their Anti-HIV Activities. C. K. Chu,[1] H. O. Kim,[1] S. K. Ahn,[1] A. J. Alves,[1] J. W. Beach,[1] L. S. Jeong,[1] P. Van Roey,[2] and R. F. Schinazi.[3] [1]The University of Georgia, College of Pharmacy, Athens, GA 30602, [2]Medical Foundation of Buffalo, Buffalo, NY 14203, and [3]Emory University/VA Medical Center, Atlanta, GA 30033, U.S.A.

(±)-Dioxolane-T (EC_{50} = 20 μM in ATH8 cells) and (±)-BCH-189 (EC_{50} = 0.05 μM in PBM cells) are unique and interesting anti-HIV nucleosides in which 3'-CH_2 group is substituted by oxygen and sulfur atom, respectively. However, synthesis of enantiomerically pure isomers have not been reported. Thus, it was of interest to synthesize enantiomerically pure dioxolane nucleosides including thymine and cytosine analogues and evaluate their anti-HIV activities. (-)-β-D-dioxolane-thymine and (+)-β-D-dioxolane-cytosine were synthesized from D-mannose which was converted to 1,6-anhydromannose in two steps. 1,6-Anhydro-mannose was converted to 1-acetoxy-5-silyl protected dioxolane which was condensed with silylated thymine or cytosine followed by the separation and subsequent desilylation to obtain the enantiomerically pure thymine and cytosine analogues. Contrary to the (±)-dioxolane-T, the enantiomerically pure (-)-dioxolane-T shows an EC_{50} value of 0.3 μM. The detailed synthesis and anti-HIV activities of several dioxolane nucleosides will be discussed. (Supported by NIH Grant No. AI26055, AI25899 and Veterans Affairs.)



Dioxolane-T



BCH-189

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Novel Modified Nucleosides and Their Phosphorylated Analogues as Potential Anti-HIV Agents.

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Considerable attention has been generated in the last few years in the quest for new nucleosides with therapeutically acceptable anti-HIV activity and special stability properties. In a program in our laboratory directed toward the discovery of novel, hydrolytically stable, strategically modified nucleosides, nucleotides and their pro-drugs as anti-HIV agents, we have synthesized a number of new target dideoxy-nucleosides and their phosphorylated analogues. This paper will describe the biochemically-based design, synthesis, enzymology, and <u>in vitro</u> anti-HIV evaluation of these compounds. The synthetic aspects of this paper will focus on modifications of the carbohydrate, base, and 5'-phosphate components including deoxygenations, specific functionalizations, isosteric modifications, phosphorus group alteration, and pro-drug transformations. Multinuclear high-field NMR studies of the target compounds will be briefly illustrated and explained in terms of structure and stereochemistry. Stability experiments involving the glycosidic bond will be mentioned. Studies pertaining to the behavior of selected compounds towards some key enzymes of purine metabolism will be discussed. The anti-HIV activity of the target compounds will be presented.