2

Synthesis and Anti-HIV and Anti-HBV Activity of Enantiomerically Pure Oxathiolane Nucleosides

C.K. Chu[1], J.W. Beach[1], L.S. Jeong[1], A. Alves[1], R.F. Schinazi[2], C.-N. Chang[3], S.-L. Doong[3], and Y.-C. Cheng[3]. [1]Department of Medicinal Chemistry, The University of Georgia, College of Pharmacy, Athens, GA. 30602, [2]Department of Pediatrics Emory School of Medicine/VA Medical Center, Atlanta, GA. 30033 and [3]Department of Pharmacology Yale School of Medicine, New Haven, CT. 06510, U.S.A.

Dioxolane-thymine and oxathiolane-cytosine are unusual nucleosides which contain oxygen and sulfur atoms at C3' position, respectively. Both nucleosides exhibit an excellent anti-HIV activities in PBM cells. Since these nucleosides have been reported as racemic mixtures, we have synthesized (-)-dioxolane-thymine and (+)-oxathiolane-cytosine. Surprisingly we have discovered that their anti-HIV potencies are lower than that of the racemates. The difference of activity was more pronounced in (+)-oxathiolane-cytosine. Thus, we recently synthesized the enantiomerically pure (-)-oxathiolane-cytosine and determined the anti-HIV activity. From these studies it was found that (-)-oxathiolane-cytosine is the most potent of the four possible oxathiolane cytosines. Furthermore, it was discovered that (-)-isomer exhibits a potent anti-HBV activity. The detailed synthesis and anti-viral activities of above mentioned oxathiolane nucleosides will be discussed (supported by NIH AI25899, AI32351 CA44358 and Veterans Affairs).

3

Optically Active Isodideoxynucleosides: A New Family of Potential Anti-HIV Agents

V. Nair*, Z.M. Nuesca, D.F. Purdy, T.B. Sells and L.B. Zintek, Department of Chemistry, Room 415 CB, The University of Iowa, Iowa City, Iowa 52242, U. S. A.

In the search for unique compounds with therapeutically useful anti-HIV activity, low toxicity, and specific stability properties, we have investigated a family of optically active nucleosides that have an isomeric relationship in the carbohydrate moiety with the anti-HIV active deoxygenated analogs of the natural nucleosides. This paper will describe the design, synthesis, enzymology, and in vitro anti-HIV evaluation of these compounds, their pro-drugs, and their phosphorylated derivatives. Discussion of the synthetic aspects of this investigation will focus on the stereospecific preparation of the altered carbohydrate precursor, the "glycosylation" reaction (phase-transfer and other methods), and specific functionalizations. Establishment of total structure, isomeric arrangement and regiochemistry, and absolute stereochemistry of the target isodideoxynucleosides by spectroscopic methods including high-field NMR data (e.g. selective INEPT, 2D-NOESY, etc.) will be briefly presented. The hydrolytic stability data of this family of compounds will be discussed. Studies pertaining to the behavior of selected compounds towards some key enzymes of nucleoside metabolism will be described. The anti-HIV data of the target compounds will be presented.