41

4(*S*)(6-Amino-9H-purin-9-yl)tetrahydro-2(*S*)-furanmethanol: Synthesis, Enzymology and Anti-HIV Studies

V. Nair, Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, USA
and J. L. Rideout, M. H. St. Clair, H. C. Krasny, J. E. Reardon, R. Dornsife and T. Spector, Burroughs Wellcome Company, Research Triangle Park, N.C. 27709, USA

Within the general family of isomeric dideoxynucleosides (also referred to as isodideoxynucleosides), some of the more interesting compounds have been associated with those regioisomers that arise from the transposition of the base moiety from the natural 1'-position to the adjacent 2'-position. This class of isodideoxynucleosides may also be viewed as involving transposition of the endocyclic oxygen to the 3'-position within the carbohydrate moiety. Of the compounds of this class that we have investigated, the most interesting in the antiviral sense is optically active 4(*S*)(6-amino-9H-purin-9-yl)tetrahydro-2(*S*)-furanmethanol (isoddA). This paper will describe the chemistry, enzymology and anti-HIV studies of this biologically active molecule. The compound has been stereospecifically synthesized in excellent yields from D(+)xylose and its structure and stereochemistry have been studied in both the solid state (X-ray) and solution (NMR). (S,S)-IsoddA is hydrolytically stable with respect to its glycosidic linkage. It is resistant to degradation by mammalian adenosine deaminase. The compound is orally bioavailable; however, it is inefficiently phosphorylated in CEM cells. IsoddA exhibited *in vitro* activity against both HIV-1 and HIV-2 but development of resistance was noted after repeated passages. In addition, isoddA was cross-resistant to variants resistant to either 3TC or AZT. Finally, isoddA inhibited the growth of bone marrow progenitor cells with IC_{50} values similar to the IC_{50} values for antiviral activity.

42

Structure-Activity Relationships Studies in TSAO-T derivatives modified at the 2'- and 5'- positions of the sugar moiety

S.T.Ingate[§], M. J. Camarasa[§], E. De Clercq[+] and J. Balzarini[+]

[§]Instituto de Química Médica (C.S.I.C.). Juan de la Cierva 3, 28006 Madrid, Spain and [+]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium.

Novel analogues of the anti-HIV-1 agents TSAO-T, [1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide) and its 3-methyl counterpart TSAO-m^3T were obtained by modifications at positions 2' or 5' of the sugar moiety. These compounds were evaluated for their inhibitory effect on HIV-1 and HIV-2 replication in cell culture. Introduction of new groups at the 5'-position (i.e. esters, benzylether and silylethers) resulted in compounds that were either inactive or less active than the parent compounds (TSAO-T and TSAO-m^3T). Attempts to introduce small silyl ether groups at this position were not successful since these products decomposed during purification. Similar modifications at the 2'-position had a much less pronounced influence on the anti-HIV-1 activity, the 2'-t-Hexyl and 2'-Benzoyl derivatives for example showed good activities.

Since it was believed that the protecting group at the 5' position could be preventing interactions between parts of the TSAO-T molecule and amino-acids of the reverse transcriptase enzyme of HIV-1, it was of interest to produce compounds in which the configuration at C-4' position was inverted. Hence, the L-*lyxo* and L-*arabino* derivatives of TSAO-T were synthesised from L-arabinose. The stereospecific synthesis of the L-l*yxo* compound was also carried out. Both the L-*lyxo* and L-*arabino* compounds showed poor activities. This can be explained by either the removal of interactions between the enzyme and 5' group or by unfavourable interactions introduced by the proximity of the 5'-*O*-silyl ether and the sulphoxide of the spiro moeity . Derivatives the 5'-deoxy-D-ribo compound (i.e. with a methyl at C-4') were synthesised in order to investigate if the absence of a protecting group would improve activity.