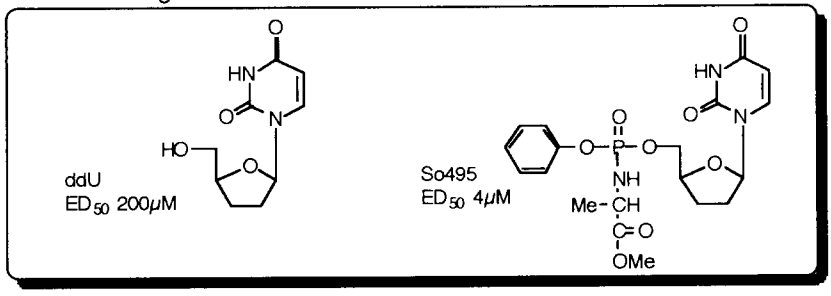
6

Kinase by-pass: A New Strategy for Antiviral Drug Discovery.

C. McGuigan, R.N. Pathirana, P. Bellevergue and M. Davies [Dept. of Chemistry, University of Southampton, Southampton, UK], N. Mahmood [MRC Collaborative Centre, Mill Hill, UK] and A.J. Hay [National Institute for Medical Research, London, UK].

We have demonstrated that certain masked- phosphate pro-drugs of anti-viral nucleoside analogues may act as intracellular delivery forms for the bio-active free phosphates, and that such agents might have improved efficacy over the parent nucleoside. Recently, we have extended this work by noting that chemical phosphorylation of certain inactive, or very poorly active nucleoside analogues leads to the introduction of a selective anti-HIV effect:



Compounds which are poorly phosphorylated by host kinases, but which show good activity as their active [tri]phosphates may benefit from this "kinase by-pass" strategy. Thus, in this presentation we will show how phosphate pro-drugs may improve the performance of known bio-active nucleosides, and may confer activity upon inactive nucleosides. In this way, the scope for structural modification is greatly widened, and an approach to dealing with the emergence of resistance is suggested.

7

Novel Chiral Isomeric Nucleosides and Nucleotides: Synthesis, Enzymology and Anti-HIV Activity

V. Nair*, L. B. Zintek, T. B. Sells, A. L. Jeffery, Z. M. Nuesca, D. F. Purdy, G. S. Jeon, R. B. Hamilton, P. J. Bolon and S. Malany
Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, U.S.A.

Chiral dideoxynucleosides that are isomeric with those that are derived from the natural nucleosides and maintain the same 1,3-*cis* relationship of the nucleic acid base and the primary -CH_2OH as the "natural" systems have evoked interest as potential anti-HIV agents. Over the last few years, we have been involved in the synthesis and collaborative antiviral studies of several families of isomeric deoxygenated nucleosides. This paper will describe recent progress from our laboratory on the molecular design, synthesis, enzymology and *in vitro* anti-HIV evaluation of selected isomeric dideoxynucleosides and their phosphorylated derivatives. Particular attention will be given to isomeric nucleosides bearing the adenine moiety. The syntheses of target compounds, commencing with either a natural chiral pool compound or an optically active precursor generated with the aid of enzymatic reactions, will be discussed in conceptual terms. Isomeric arrangements and both relative and absolute stereochemistry will be explained and structural confirmation for these will be provided. Relevant enzymology will be described. Antiviral data in MT-4 and other cell lines will be presented and analyzed. Structure-activity correlations will be presented.