4

Structure Activity Relationships in a Series of Phosphate Derivatives of AZT.

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Phosphate triester derivatives of 3'-Azido-3'-deoxythymidine (AZT) have been investigated for their activity against the Human Immunodeficiency Virus (HIV 1). Over fifty compounds have been synthesised using phosphate and phosphoramidate methodologies and have been fully characterised. The EC50 values have been evaluated in a lymphoblastoid cell line acutely infected with HIV 1. Many of the triesters show potent inhibition of virus replication with EC50 values below 1μM. The activity of these compounds is dependent upon the phosphate structure, and a number of structure-activity relationships have emerged. In particular, phoshoramidates are especially active: minor structural changes in the amino moiety lead to significant changes in antiviral activity. Almost all of the compounds in the series are non-toxic to uninfected cells at 100μM. These data indicate that the compounds may act as intracellular sources of the bio-active nucleotides, although the precise mechanism is yet to be determined. Structures of this type may be useful as pro-drugs in HIV chemotherapy.

5

Synthesis and Anti-HIV Activities of Diphosphohexose Prodrugs of AZDU (Azddu or CS-87)

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AZDU exhibits a selective and potent anti-HIV activity in peripheral blood mononuclear cells with low toxicity in bone marrow cells. Favorable preclinical toxicological profile in rodents, dogs and monkeys led to the phase I clinical trials in patients with AIDS and AIDS related complex. During the biochemical study AZDU diphosphohexose derivatives were identified. These metabolites may potentially serve as prodrugs of AZDU to generate AZDU-mono-or diphosphate, thereby bypassing the nucleoside kinase. Thus, several diphosphohexose derivatives of AZDU have been synthesized and their anti-HIV activities were determined in vitro. The AZDU monophosphate, prepared from the reaction of cyanoethylphosphate and AZDU in the presence of DCC followed by the treatment with KOH, was condensed with the α-D-glucose-1-phosphate trioctylamine to afford the AZDU-diphos-phoglucose. Similarly, AZDU-diphospho-N-acetyl-glucosamine and AZDU-diphospho-galactosamine have been prepared. The chemical synthesis and anti-HIV activity will be presented. (Supported by NIH grants AI-26055, AI-25899, AI-25784, HL-42125 and VA.)