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Inhibition of HIV- and HBV-Virus Replication by 2,6-Disubstituted Purine 2', 3'-Dideoxynucleosides. G. W. Koszalka, C. L. Burns, M. St. Clair, L. Frick, C. U. Lambe, M. T. Paff, D. J. Nelson, B. Korba+, K. Ayers and T. A. Krenitsky, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709; +Georgetown University, Division of Molecular Biology and Virology, 5640 Fishers Lane Rockville, MD 20852

Twenty-six substituted adenine-9-β-D-2',3'-dideoxyribosides were synthesized using immobilized *E. coli* nucleoside phosphorylases and evaluated as potential anti-HIV agents. The most potent inhibitors of HIV-1 replication in MT4 cells were analogues with either a methyl-, ethyl-, or cyclopropyl- amino group at the purine 6-position. Substitution at the purine 2-position with an amine was preferred over a chloro substituent. Analogs active against HIV and containing a 6-cyclopropylamino group were also evaluated for anti-HBV activity. Only those compounds substituted with a 2-amino substituent were potent inhibitors of HBV replication. 2-Amino-6-cyclopropylaminopurine-9-β-D-2',3'-dideoxyribonucleoside (145U87) was selected for further evaluation. 145U87 was equivalent to ddI in anti-HIV-1 activity, synergistic with ddI, ddC, AZT, and alpha interferon, and cross resistant with ddI-resistant virus. 145U87 was nontoxic to a variety of cultured mammalian cell lines including human bone marrow stem cells. Anabolism studies in both CEM and Molt-4 cells with [^{3}H] 145U87 revealed picomolar levels of ddGTP after 24 h . No other dideoxynucleoside triphosphates were detected. 145U87 was slowly converted by calf intestine adenosine deaminase to ddG and was a substrate for the human placental adenosine phosphotransferase. It was not a substrate for human purine nucleoside phosphorylase, calf thymus deoxycytidine kinase, rabbit liver adenosine kinase, or human placental cytosolic 5'-nucleotidase. In addition, rabbit muscle AMP deaminase did not convert 145U87-monophosphate to ddGMP. Cynomologus monkeys dosed po with 145U87 generated significant levels of aglycone in the plasma. The co-administration of an antacid (2 ml/kg/d) did not affect these plasma levels. No toxicity was observed in monkeys dosed for 30 days at 75 mg/kg/d, po, but at the 150 mg/kg/d dose, slight hematological changes were observed. Monkeys dosed at 300 mg/kg/d displayed appetite suppression, weight loss, diarrhea, lethargy, weakness and moderate anemia. Histopathology studies at this dose revealed vaculolation of the kidney, fatty liver and ulcerative colitis. Although 145U87 had desirable properties for an anti-HIV agent, the overall toxicological profile of this compound was deemed unacceptable for further development.