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L-FMAU, A Novel Anti-HBV and Anti-EBV Agent. Chu, C.K.[1], Ma,T.W.[1], Shanmuganathan, K.[1], Wright, J.D.[1],Boudinot, F.D.[1],Faraj, A.[2] ,Sommadossi,J.-P.[2], Pai,S.B.[3], Yao,G.-Q.[3], Cheng,Y.-C.[3] [1]Dept. of Medicinal Chemistry and Pharmaceutics, Coll. of Pharmacy, The Univ. of Georgia, Athens, GA 30602, [2]Dept. of Clinical Pharmacology, Sch. of Medicine, Univ. of Alabama, Birmingham, AL 35294 and [3]Dept. of Pharmacology, Sch. of Medicine, Yale Univ., New Haven, CT 06510.

As a part of our drug discovery program for novel antiviral agents, we have identified 2'-fluoro-5-methyl-ß-L-arabinofuranosyluridine (L-FMAU) as a potent anti-HBV and anti-EBV agent. Enantiomerically pure L-FMAU was synthesized from L-ribose or L-xylose as the starting material. L-FMAU was evaluated for its anti-HBV and anti-EBV activities in 2.2.15 and P3HR-1 cells, respectively, in which L-FMAU exhibited EC_{50} and EC_{90} values of 0.1μM (in six-day treatment) and 5μM against HBV and EBV, respectively. In nine-day treatment, L-FMAU showed EC_{50} value of 0.02μM against HBV, which is comparable to that of 3TC. *In vitro* cytotoxicities of L-FMAU have been accessed in CEM, MT2, H1, and 2.2.15 cels ,which showed ID_{50} values of 100, >100, 913±70, and >200, respectively. These indicate the therapeutic index range of L-FMAU is 1000 - 9130 in these cells. In contrast , D-FMAU exhibited EC_{50} value of 2.0 μM in 2.2.15 cells and the therapeutic index range is 5-25. Repeated treatments of hepatoma cells (HepG2) with L-FMAU for 9 days at 1μM concentration did not result in any decrease in the total mitochondrial DNA contents. L-FMAU was also evaluated in bone marrow precursor cells. However, no toxicity was detected up to 100 μM. L-FMAU had no effects on the production of the HBV surface antigen. Studies on the recovery of the virus on cessation of the treatment indicated that the viral DNA synthesis returned gradually to control levels with kinetics similar to that shown by other drugs like 3TC. Pharmacokinetics of L-FMAU have been accessed in rats at 10mg/Kg, 26mg/Kg and 50 mg/Kg doses, which indicate that plasma half-lives range from 1.0 to 1.5 h in oral as well as IV dosage. Radiolabeled L-FMAU has been synthesized for the study of mechanism of action, and preclinical toxicology is in progress, which will be presented (Supported by NIH grants AI33655 and AI32351).

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2'-Deoxy-4'-Thio Purine Nucleosides as Potent Inhibitors of HBV and HCMV. G. W. Koszalka, G. A. Freeman, S. A. Short, R. Harvey, R. Jansen, G. Szczech, and N. A. Van Draanen, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park NC 27709

A series of β-D-2'-deoxy-4'-thio purine nucleosides was prepared and tested against hepatitis B virus (HBV), human cytomegalovirus (HCMV), herpes simplex virus (HSV-1 and HSV-2), varicella zoster virus (VZV), and human immunodeficiency virus (HIV-1). Cytotoxicity was determined in a number of cell lines. 2-Amino-6-methoxypurine-2'-deoxy-4'-thio-β-D-ribofuranoside and the 2-amino-6-cyclopropylaminopurine congener were the most potent analogues against HBV (IC_{50} = 0.0025 and 0.0072 μM, respectively) and HCMV (IC_{50} = 0.062 and 0.2 μM, respectively). The B- and T- cell cytoxicity of these two analogues ranged from 2-80 μM. The 2-amino-6-cyclopropylamino analogue was toxic to a beagle dog at a dose of 10 mg/kg/day in a 21-day trial.