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EFFECT OF HUMAN SERUM ON THE *IN VITRO* ANTI-HIV-1 ACTIVITY OF HEPT DERIVATIVES AS RELATED TO THEIR LIPOPHILICITY AND SERUM PROTEIN BINDING CAPACITY M. Baba,[1] S. Yuasa,[2] T. Niwa,[2] H. Takashima,[2] M. Ubasawa,[2] H. Tanaka,[3] T. Miyasaka,[3] R.T. Walker,[4] J. Balzarini,[5] E. De Clercq,[5] and S. Shigeta[1] *[1]Department of Microbiology, Fukushima Medical College, Fukushima 960-12, [2]Mitsubishi Kasei Corporation Research Center, Yokohama 227, [3]Showa University, Tokyo 142, Japan, [4]University of Birmingham, Birmingham B15 2TT, United Kingdom, and [5]Rega Institute, Katholieke Universiteit Leuven, B-3000, Leuven, Belgium*

Several derivatives of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT) were examined for their inhibitory effect on the replication of human immunodeficiency virus type 1 (HIV-1) in MT-4 cells in the presence of varying concentrations (10-50%) of human serum (HS). The binding of the HEPT derivatives to HS proteins and their lipophilicity were also investigated. Although all HEPT derivatives proved to be highly potent inhibitors of HIV-1 in MT-4 cells in the presence of 10% fetal calf serum, some of them were less inhibitory to HIV-1 replication in the presence of 10% HS, and their anti-HIV-1 activity diminished with increasing the HS concentration. The counteracting effects of HS on the anti-HIV-1 activity of the HEPT derivatives differed considerably from one compound to another. Among the HEPT derivatives, 1-benzyloxymethyl-5-ethyl-6-phenylthio-2-thiouracil (E-BPU-S) was most and 1-ethoxymethyl-5-ethyl-6-benzyluracil (E-EBU) was least affected by the presence of HS. Also, the binding capacity of the HEPT derivatives to HS proteins differed considerably from one compound to another. Both the HS protein binding capacity and anti-HIV-1 activity of the compounds appeared to be related to their lipophilicity. These results suggest that HS protein binding capacity and the lipophilicity are important determinants for the anti-HIV-1 activity of HEPT derivatives.

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Preclinical Pharmacokinetic Evaluation of Selected Members of a New Class of Potent HIV-1 Reverse Transcriptase Inhibitors. C. Sahlberg[1], B.-L. Sahlberg[2], K. Frykman[2], M. Clemens[3], J. S. Kasher[3], J. M. Morin, Jr.[3], R. J. Ternansky[3], F. W. Bell[3], C. L. Jordan[3], M. D. Kinnick[3], J. A. Palkowitz[3], C. A. Parrish[3], P. Pranc[3], R. T. Vasileff[3], and S. J. West[3].

[1]Medivir AB, Huddinge, Sweden; Apoteksbolaget Central Laboratory, Stockholm, Sweden; [3]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA.

The oral uptake of selected members of a new class of non-nucleoside HIV-1 RT inhibitors was studied by screening in a rodent model. Peak levels varying between 0.02 μg/ml and 8.55 μg/ml were obtained following an oral dose of 40 mg/kg in acacia vehicle of the selected compounds. The effect of formulation on peak blood levels was also studied. In a more precise study, the oral bioavailability of LY300082 dosed in acacia formulation was determined to be 13-26% of the i.v. dose.