I-44

In Vitro and In Vivo Antiherpes Activity of 4-O-Difluoromethyl-5-substituted Uracil Nucleoside Analogs. J. Reefschläger[1], J.-D. Pein[2], D. Jech[2] and D. H. Krüger[1]. Inst. Med. Virol.[1] and Dept. Chem.[2], Humboldt Univ., 1040 Berlin, German Democratic Republic

Various 4-O-difluoromethyl(CF_2) analogs of 5-substituted(5-X-) 2'-deoxyuridine(dUrd) and 1-ß-D-arabinofuranosyluracil(araU) nucleosides were evaluated for their activity against herpes simplex virus type 1 (HSV-1), type 2(HSV-2), varicella-zoster virus(VZV) and human cytomegalovirus(HCMV) in human embryonic lung fibroblasts(HELF). The introduction of the 4-substituent led to a strong reduction in antiherpes activity for the 5-X-dUrd's but not for the 5-X-araU's. CF_2-(E)-5-(2-bromovinyl)-araU (CF_2BrVaraU) was a strong inhibitor of VZV. CF_2-5-methyl-araU(CF_2araT) showed a high and selective antiherpes effect comparable with that of acyclovir. A lack of activity against HCMV was found for all investigated new 4,5-disubstituted derivatives. In concentrations as high as 500 µM no differences in cytostatic activity of CF_2araT and araT on actively growing HELF cells and BHK suspension cells were observed. Virus strains of HSV-1, HSV-2 and VZV, resistant to different nucleoside analogs, were cross-resistant to CF_2araT. Therapeutic activity of CF_2araT against HSV-2 encephalitis in mice and against HSV-2 keratitis in rabbits was shown.

I-45

Conformation and Antiherpes Activity of 3'- and 5'-Azido and Amino Analogs of 5-Methoxymethyl-2'-deoxyuridine. Guy Tourigny[1], Allan L. Stuart[2] Irena Ekiel[3], Philip J. Aduma[2] and Sagar V. Gupta[2]. Departments of Chemistry[1] and Veterinary Physiological Sciences[2], University of Saskatchewan, Saskatoon, and Division of Biological Sciences[3], National Research Council of Canada, Ottawa, Canada.

The molecular conformations of 3'- and 5'-azido and amino derivatives of 5-methoxymethyl-2'-deoxyuridine (MMdUrd) was investigated by nmr analysis. The glycosidic conformation of 5-methoxymethyl-5'-amino-2',5'-dideoxyuridine (5'-AmMMdUrd) had a considerable population of the Syn form. The 5'-derivatives show a preference for the S conformation of the furanose ring as MMdUrd. In contrast, the 3'-derivatives show preference for the N conformation. For the 3'-amino derivatives, the shift toward the N state is pH dependent (pH 6.3, 52% and pH 10.3, 62%). The preferred conformation for the exocyclic (C4',C5') side chain is g^+ (60%) for all compounds except 5'-AmMMdUrd which has a strong preference for the t rotamer (79%). MMdUrd, 3'-AmMMdUrd, and 5'-AmMMdUrd inhibited HSV-1 replication by 50% at 2, 18 and 70 µg/ml respectively. The compounds were not cytotoxic up to 3,000 uM.