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In Vitro and *In Vivo* Activity of the N-7 Isomeric Acyclic Nucleoside Analogue 2242 Against an Acyclovir/Foscarnet-Resistant Herpes Simplex Virus Type 1 Clinical Isolate

R. Snoeck, M. Helsberg*, G. Jähne*, I. Winkler*, G. Andrei, J. Neyts and E. De Clercq. Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium and *SBU Antiinfectives - Research, G 838, Hoechst AG, D-65926 Frankfurt am Main, Germany

We have evaluated the *in vitro* and *in vivo* anti-herpesvirus activity of 2-amino-7-(1,3-dihydroxy-2-propoxymethyl)purine (2242) against 2 strains of herpes simplex virus type 1 (HSV-1), isolated from an immunocompromised patient with mucositis. The strains are referred to as HU-3, which is sensitive to acyclovir (EC_{50}: 0.024 μg/ml), and HU-10 (isolated after prolonged acyclovir therapy), which is resistant to acyclovir (EC_{50}: > 50 μg/ml). The HU-10 strain also proved resistant to FIAC, BVDU, ara-T and ganciclovir (which depend for their antiviral activity on the viral thymidine kinase) and foscarnet (which is known to act at the viral DNA polymerase level). Compound 2242 was found to inhibit the replication of both strains, with EC_{50} values of 0.8 μg/ml (HU-10) and 0.4 μg/ml (HU-3). We compared the efficacy of compound 2242 and acyclovir against a lethal intracutaneous infection with HU-3 or development of lesions with HU-10 in athymic-nude mice. When compound 2242 was applied topically at 5% in DMSO twice daily for a period of 3 days to HU-3-infected animals, the mean day of death (MDD) was delayed from 8 days (untreated controls) to 24 days. A five-day treatment course with 5% 2242, applied 4 times a day, resulted in 50% survival, whereas only 25% of the animals that had received a similar treatment schedule with ACV survived the infection. In nude mice infected with HU-10, the five-day treatment course with ACV had no effect, whereas 2242 conferred 50% protection. Compound 2242 thus appears to be a promising candidate drug for the treatment of mucocutaneous HSV lesions, particularly in immunocompromised patients infected with acyclovir-resistant virus.

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5-Heteroaromatic substituted 2'-deoxyuridines as anti-HSV-1 agents: synthesis, antiviral activity and structure-activity relationship

P. Herdewijn#, A. Olivier*, L. Wang+, C. Bohman#, I. Creuven*, A. Van Aerschot#, P. Wigerinck#, L. Wiebe+, J. Balzarini#, E. De Clercq# and F. Durant*

#Rega Institute, K.U.Leuven, Belgium
*Facultés Universitaires Notre-Dame de la Paix, Namur, Belgium
+Faculty of Pharmacy, University of Alberta, Edmonton, Canada

Research on the introduction of heteroaromatic substituents in the 5-position of 2'-deoxyuridine has led to the identification of a new series of anti-HSV-1 agents[1]. To establish the structure-activity relationship of this class of compounds, several new 5-thienyl-2'-deoxyuridines were synthesized. The prototype compound, 5-chlorothien-2-yl-2'-deoxyuridine, proved to be an excellent substrate for facilitated diffusion in mammalian cells The substrate specificity for human and viral thymidine kinases was studied. There was no clear correlation between antiviral potency and substrate affinity for HSV-1 thymidine kinase. Theoretical calculations, however, revealed a difference between the molecular electrostatic energy maps of the compounds which are good substrates for the HSV-1 thymidine kinase and those which are poor substrates. Thus a structure-activity relationship was established with regard to the affinity of the compounds for the viral TK.

[1]P. Wigerinck et al. J. Med. Chem. 36, 538 (1993).