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Antiviral Activity and Mechanism of Action of GL-288-C8 on the Replication of Herpes Simplex Viruses (HSV) in Human Cells.
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The purpose of these studies was to establish the antiviral activity of GL-288-C8, a representative of a new class of novel compounds, and to investigate its mechanism of action. When human foreskin fibroblast (HFF) cells were treated for 30-60 minutes prior to infection with HSV-1 or HSV-2, the 50% effective concentration (EC_{50}) was about 7 μg/ml. The 50% inhibitory concentration (IC_{50}) for toxicity was about 300 μg/ml in uninfected stationary cells and was about 50 μg/ml in rapidly dividing cells. Thus, the selectivity index was about 43. In addition, GL-288-C8 was active against three HSV-1 and six HSV-2 isolates that were resistant to Acyclovir. If treatment was delayed until 1 hour post-infection, antiviral activity was lost. The block in HSV-1 replication appeared to be due to an effect of GL-288-C8 on the attachment of HSV-1 to HFF cells. Analysis of early events following HSV-1 infection showed that GL-288-C8 interfered with the adsorption of HSV-1 to the target cells. Immunoblot and in situ hybridization analyses demonstrated a significant inhibition of HSV DNA synthesis and expression of HSV-1-specific capsid and glycoproteins in drug-treated cells. These results indicate that GL-288-C8 inhibits the replication of HSV-1 by blocking one of the early events in the replication cycle, i.e attachment of HSV-1 to treated HFF cells.

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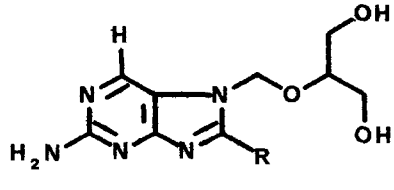
Synthesis, Antiviral Activity, and Pharmacokinetics of an N7-Isomeric 2-Aminopurine Nucleoside Analogue (I). M.Helsberg, G.Jähne, I.Winkler, G.Gross, and Th.Scholl; HOECHST AG, SBU Antiinfectives - Research, G 838, P.O.Box 800320, D-6230 Frankfurt am Main 80, Germany

The synthesis of compound I is described. I is active *in vitro* against HSV-1, HSV-2, VZV, HCMV, MCMV, HHV-6, and Vaccinia Virus. No activity is found against adenovirus and a variety of RNA viruses. Activity is also observed against aciclovir- or ganciclovir-resistant HSV-strains, which were generated in cell culture. Single cycle assays reveal that I acts early in virus replication, although the exact mode of action has not yet been clarified. The efficacy of treatment of HSV infected mice with I is in the same range as with ganciclovir, and both compounds prove to be more active than aciclovir. The cytotoxicity of the compound seems to be low; whereas its cytostatic potential is obvious. In mice, the compound is well tolerated, the only side effect being reversible atrophy of testicles similar to the treatment with ganciclovir. In mice, serum half-life is approx. 45 min. In monkeys, the oral absorption is superior to ganciclovir. The main metabolite is the 8-hydroxy derivative II; this metabolite is not found in dogs. These results reflect data from *in vitro* metabolism studies with liver tissue of different species, including man. From these data low metabolism rates of I are predicted in humans.



I: R = H

II: R = OH