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Mappicine Ketone Is A Novel Non-Nucleoside Inhibitor with in vitro Antiviral Activity against Herpesviruses. D. M. Lambert[1], S. Barney[1], R. Wittrock[1], H. S. Allaudeen[2], M. Massare[1], W. Kingsbury[1], D. Berges[1], G. Gallagher[1], J. Taggart[1], G. Hofmann[1], M. Mattern[1], R. Hertzberg[1], R. Johnson[1] and S. R. Petteway, Jr.[1], [1]SmithKline Beecham Pharmaceuticals, King of Prussia, PA USA and [2]Cytrx Corporation, Norcross, GA USA (current address).

Camptothecin, a potent inhibitor of mammalian topoisomerase I (topo I), inhibits HSV-1 and HSV-2 replication but also displays potent cytotoxicity. Unexpectedly, mappicine ketone, an analog of camptothecin that is devoid of topo I activity, was found to be a potent and selective inhibitor of HSV-1 and HSV-2 replication. Mappicine ketone and its analogs are representative of a novel class of viral inhibitors. These compounds have selective antiviral activity for a broad spectrum of herpes viruses, including HSV-1, HSV-2, HCMV and VZV, while exhibiting no selective inhibition for any of the other DNA or RNA viruses tested. This analog was used to select for resistant isolates of HSV-1 (strain 17) and HSV-2 (MS strain) by multiple rounds of growth in increasing concentrations of inhibitor. Multiple isolates were plaque purified in the absence of inhibitor and the level of resistance was determined by plaque reduction assays. Isolates exhibited >10-fold resistance and did not revert to wild-type (wt) upon passage in the absence of inhibitor. Both resistant isolates were equally sensitive to acyclovir (ACV) compared to parenteral wt HSV-1 and HSV-2 viruses and also were sensitive to the inhibitory effects of camptothecin. Conversely, replication of an ACV-resistant isolate was blocked by mappicine ketone. These results suggest that mappicine ketone inhibits a different viral target than either ACV or camptothecin. Identification of the viral target is underway using marker rescue approaches.

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Inhibitors of *Herpes Simplex* Virus Thymidine Kinases. **G. Wright,[1] H. Xu,[1] G. Maga,[2] J. Gambino,[1] F. Focher,[2] E. Smith[1] and S. Spadari.[2] [1]Department of Pharmacology, University of Massachusetts Medical School, Worcester, MA, USA. [2]Istituto Genetica ed Biochimica Evoluzionistica, Consiglio Nazionale delle Ricerche, Pavia, Italia.**

Two families of selective inhibitors of HSV thymidine kinases (TK) have been developed as potential treatment of recurrent *Herpes simplex* infections. This approach is based on the hypothesis that reactivation of latent herpesvirus infections requires expression of the virus-specific TK in sensory nerve cells. In the first family, compounds related to the potent base analog, N^2-(*m*-trifluoromethylphenyl)guanine (*m*CF_3PG), have been synthesized. Structure-activity relationships for inhibition of HSV1 and HSV2 specific TKs indicate that hydrophobic but electronegative *meta* substituents enhance binding to the enzymes. In the second family, compounds related to the nucleoside, but non-substrate, analog, N^2-phenyl-2'-deoxyguanosine (PhdG), have been synthesized. Derivatives of N^2-phenylguanine with alkyl, hydroxyalkyl and "acyclo-glycosyl" substituents at the 9 position, in place of the glycosyl group of PhdG, retain significant but variable inhibitory potencies against the HSV TKs. Dosing and pharmacokinetic results in mice of certain 9-substituted N^2-phenylguanines possessing high water solubilities and octanol:water partition coefficients will be presented.