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SQ 33,912: A Selective Inhibitor of Varicella-Zoster Virus Replication

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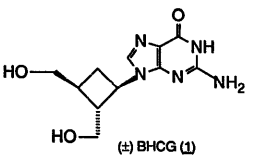
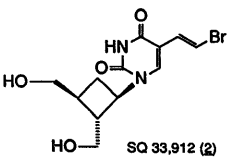
(±)-BHCG (1, also known as SQ 33,054) is a cyclobutane nucleoside analog with potent activity against a bread spectrum of herpesviruses. In vitro evaluation of a number of pyrimidine base analogs of (±)-BHCG reveals that most possess weak to moderate activity against one or more of the herpesviruses tested. SQ 33,912 (2), the 5-(2-bromovinyl)uracil analog of (±)-BHCG, is unique within this class of compounds by displaying potent and selective activity against varicella-zoster virus (ED_{50} = 0.03-0.6μM).



(±) BHCG (1)



SQ 33,912 (2)

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Synthesis and In Vitro Antiviral Activity of Substituted Derivatives of the Potent Antiviral Agent 9-[2-(Phosphonylmethoxy)ethyl]guanine (PMEG).

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The guanine derivative PMEG has exceptional potency against herpesviruses, but also exhibits significant cellular toxicity. As part of a program to identify derivatives of PMEG which have improved selectivity as antiviral agents, we have prepared a series of PMEG analogues bearing methyl substituents at key sites on the side-chain and guanine base. The synthesis of 1'-, 2'-, 4'-, and 8-methyl derivatives of PMEG will be described, along with a comparison of their in vitro antiviral and cellular toxicity effects to those of PMEG and the related guanine derivative HPMPG (9-[3-hydroxy-2-(phosphonylmethoxy)propyl]guanine or 2'-hydroxymethyl-PMEG). Our results show that introduction of a substituent on the side-chain or base generally leads to a decrease in the in vitro potency relative to PMEG.