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4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl Purines and Pyrimidines, a New Class of Anti-herpesvirus Agents

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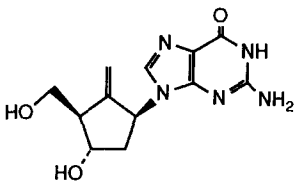
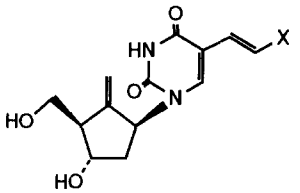
Compounds 1 and 2 are representative members of a new class of anti-herpesvirus agents. The guanine analog 1 (SQ34,676) displays moderate activity *in vitro* against herpes simplex virus (HSV-1 and HSV-2) and varicella virus (VZV) (ID_{50}s in the range 3.6-36 μM). The 5-(2-halovinyl)uracils 2 are at least equivalent to acyclovir against HSV-1, and the bromo- and iodovinyluracil analogs are approximately an order of magnitude more potent against VZV. The potent activity of the 2-bromovinyluracil analog 2 (X=Br, SQ35,223) against VZV (ID_{50} = 0.3-0.6 μM) and low cell toxicity observed indicate a high *in vitro* therapeutic index for SQ35,223.



1 (SQ34,676)



2 (X = Br, I, Cl)

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Comparative Study of Polyamine Pools in HCMV-, MCMV-, and GPCMV- Infected Mammalian Cells

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Human cytomegalovirus (HCMV) infections present a significant medical problem when the function of the immune system is depressed by chemotherapy or by HIV infection. Our approach to develop an effective method of treatment of HCMV infections was to block polyamine biosynthesis, which increases significantly in HCMV-infected cells (A.S.Tyms, et al., Polyamine Res.,4,507,1983) and may be required for HCMV replication. Currently animal models used to evaluate candidate HCMV drugs are the mouse and guinea pig. Information on polyamine pools in cell cultures infected with their species-specific cytomegaloviruses might indicate whether the in vivo mouse and guinea pig models would be predictive for compounds that act on HCMV by reducing the polyamine pools.

Monolayer cultures of human embryonic lung (MRC5) cells, mouse embryo (SC-1) cells or fibroblast-like guinea pig lung (JH4 clone 1) cells were infected (or sham-infected) with HCMV, mouse CMV or guinea pig CMV, respectively. Cells from infected and uninfected cell cultures were harvested days 1-7 postinfection and extracted with cold perchloric acid. The neutralized extracts were derivitized using dansyl chloride according to the reaction conditions described by Kabra and Lee (J Chromatogr.,380,19,1986). The reaction mixtures were extracted with ethyl acetate and analyzed by means of reverse phase HPLC using gradient elution with detection and quantitation by fluorescence. Using these procedures we determined that there were no significant increases in the polyamine pools of CMV species specific infected mouse and guinea pig cell lines as compared to the those of MRC5 cells infected with CMV. These data indicate that the mouse and guinea pig models would not be predictive for compounds that act on HCMV by reducing polyamine pools.

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