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Synthesis and Relationship between Conformation and Antiherpes Activity of N^4-Substituted Analogs of 5-Methoxymethyl-2'-Deoxycytidine (MMdCyd).

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N^4-Substituted analogs of MMdCyd were synthesized to confer resistance to deamination by deaminating enzymes. N^4,N^4-dimethyl, N^4(phenyl, benzyl, methoxy, hydroxy) and 3,4-ethno analogs were inactive against Herpes Simplex Virus type 1 (HSV-1) and also nontoxic to VERO cells up to 512 μM (highest concentration tested). In contrast, N^4-acetyl-MMdCyd (AcMMdCyd), N^4-butanoyl-MMdCyd (BuMMdCyd) and N^4-propanoyl-MMdCyd (PrMMdCyd) were more potent than MMdCyd against HSV-1 in VERO cells. The order of potentiation was: BuMMdCyd > PrMMdCyd > AcMMdCyd > MMdCyd.

The molecular conformation by NMR spectroscopy in solution was determined. Analogs in which the N^4-substituent is proximal to C(5) of the pyrimidine ring are active against HSV-1; whereas when the N^4-substituent is proximal to N(3) of the pyrimidine ring, the compounds are inactive.

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Antiviral Activity of Alkylglycerol Foscarnet Analogs in HIV-1 Infected HT4-6C Cells: Structure-Activity Studies.

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Foscarnet (phosphonoformate, PFA) selectively inhibits viral polymerases and is currently used intravenously to treat HCMV retinitis. Recently we found that the antiviral activity of PFA could be increased by covalent attachment to 1-O-octadecylglycerol at the *sn*-3 hydroxyl by a phosphodiester linkage. 1-O-octadecylglycero-3-phospho-PFA was 93-fold more active than free drug in HCMV-infected cells and 44 times more active than PFA in HIV-1 and HSV-1 infected cells. To elucidate the optimal structure for the alkylglycerols, we synthesized a series of alkylglycerol PFA derivatives having chain lengths varying from 8 to 20 carbons with ether and thioether attachments to glycerol or 1,3-propanediol. The effect of introducing unsaturations into the alkyl chain was also evaluated. Several compounds from this series have *in vitro* anti-HIV activity more than 300 times that of PFA. Mechanism studies suggest that the increase in antiviral activity is due in part to greatly increased cell uptake of the alkylglycerol PFA. Cleavage to PFA occurs in the target cell to release free PFA. Agents of this class are absorbed orally and may be useful in treating human viral disease.