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SYNTHESIS OF ACYCLONUCLEOSIDE PHOSPHONATES AS ANTIVIRAL AGENTS

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3-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9yl)methoxy-4-hydroxybutylphosphonic acid, the isosteric phosphonate analog (SR 3745) of ganciclovir phosphate has been prepared and found to have significant activity against human, murine, and guinea pig cytomegalovirus (CMV) *in vitro*, with therapeutic indices at least equivalent to those of ganciclovir. It also has similar activity *in vitro* against varicella zoster and Epstein Barr viruses. Activity was demonstrated *in vivo* against murine CMV with SR 3745, using doses of 5.6, 16.7, and 50 mg/kg/day administered intraperitoneally twice daily for 5 days, beginning as late as 48 hr post-virus inoculation. No toxicity was observed at these dosages. The chiral enantiomers of SR 3745 have been prepared. The antiviral activity was shown to reside predominantly in the R-enantiomer, corresponding to the natural chirality of guanine nucleosides. The S-enantiomer had only modest activity against HCMV but significant activity against varicella zoster virus. While the anti-CMV activity of SR 3745 is comparable to that observed for ganciclovir, the cytotoxicity as measured by uptake of radiolabeled metabolic precursors appeared to be significantly lower than that of ganciclovir. Thus, SR 3745 and the R-enantiomer appear to be promising candidates for clinical evaluations.

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Calix(n)arene Sulfonates as Novel Antiviral Agents.

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Genelabs' scientists recently discovered that certain calixarene sulfonates inhibit, in-vitro, infections induced by a broad spectrum of enveloped virus such as HIV, HSV, CMV, RSV, and FluAH3. Initial compounds C4, C6, and C8 (respectively n= 4, 6 and 8; R' = H, and R" = OH) were synthesized in one step (50- 70 % yield, > 99 % purity) from commerical materials. C8 has ED_{50} in ~2-20 uM range, whereas C4 has an ED_{50} >100 uM against the above panel of viruses as assayed by plaque reduction or cytopathic effect. Further, C8 retains its potencies against both wild type and Acyclovir resistant strains of HSV-1 and HSV-2. Preliminary structure/ activity relationship (SAR) studies show that, while C8 mediates inhibition against HSV-1 and HSV-2 (ED_{50} ~ 5 uM), its activities were generally lost (ED_{50} >100 uM) when the phenolic R' is replaced with simple alkyl or acyl groups. More SAR studies with HSV and other viruses will be presented.