and weight was stable throughout the 7 day dosing period and the 7 day drug washout even in the 30 mg/kg group. Of the three new compounds tested, ODE-HPMPDAP appears to have no acute oral toxicity and should be evaluated further in view of its 20 nM EC50 against vaccinia virus in vitro.

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Cidofovir: Intratympanic Delivery and Hearing Loss

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Congenital Cytomegalovirus (CMV) is the leading cause of infectious-related sensioneural hearing loss (SNHL) worldwide. Approximately 90% of newborns infected with CMV are asymptomatic at birth, of these 20% exhibit SNHL. Clinicians are developing novel ways to treat SNHL caused by CMV infection. Our lab is exploring the intratympanic route (IT) for delivery of established antivirals to treat CMV related SNHL with promising preliminary results. IT injections provide an advantage over systemic delivery because IT delivery shields the patient from serious side effects. Moreover, the similarities in the anatomy and physiology of the guinea pig (GP) and human ear allows this to be a relevant model to study. Accordingly, viral kinetics studies and auditory brainstem responses (ABR) have shown that direct inoculation of guinea pig CMV (GPCMV) into the bulla of a GP is a consistent and reliable model for CMV infection. Studies are ongoing for IT injections of cidofovir (CDV) for the treatment of GPCMV related hearing loss. Administering CDV at different time points post viral inoculation is proving significant. The viral kinetics show replication begins at day 6 post-surgical inoculation. IT injection of CDV administered at day 7 shows the most impact in hearing improvement. ABR, *realtime* PCR, and histological data confirms that CDV given IT inhibits viral replication and improves hearing without manifesting any side effects. This data demonstrates that CDV given IT prevents the virus from replicating and shows an improvement in hearing loss by day 21. The lab is also exploring a unique application of drug-delivery, a temperature sensitive copolymer used as a transporter of antivirals. *In vitro* data shows that CDV in a temperature sensitive copolymer extends the effective life of the drug. To document the location and migration of these gels *in vivo*, MRI images of guinea pigs ears were taken at different time points post-IT injection of copolymer gels. The MRI data has shown that the gel can be injected IT and is located at the round window. Ongoing *in vivo* studies that include hearing and kinetic data will determine if the temperature sensitive copolymer gel can be used as a transporter for time controlled drug release into the inner ear.

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Toward A More Complete Anti-Herpesvirus SAR for 2nd Generation Methylenecyclopropane Nucleosides

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The discovery of methylenecyclopropane nucleosides (MCPNs) has lead to a large number of promising analogs with potent antiherpesvirus activity. One factor potentially limiting the further development of the MCPNs, however, is a stereocenter included in the first generation compounds (1). In an attempt to synthesize compounds without the problematic stereocenter, Zemlicka developed a second generation of methylenecyclopropane nucleosides that included an additional hydroxymethyl substituent (2). Unlike the thoroughly explored first generation MCPNs, only a few representatives of the second generation MCPNs were synthesized, including the guanine analog ZSM-I-62 (cyclopropavir, CPV), which is now in preclinical development for HCMV. The potent antiherpes activity of CPV and the other second generation MCPNs that were synthesized prompted us to further explore the structure, and elaborate the SAR for this series. Herein, we report the results of our investigations toward expanding the structure–activity relationship within the second generation of MCPNs. Several of the new analogs demonstrated low micromolar activity against HCMV and EBV, and some of the compounds also have moderate activity against HHV-8. We will discuss the relationships between amine, ether, and thioether analogs and the anti-herpes activities thereof.

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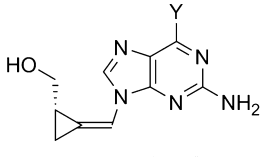
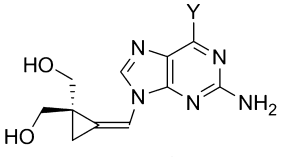


Y = NHR, OR, SR

1, first generation MCPN



Y = NHR, OR, SR

2, second generation MCPN

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Stereoselective Synthetic Strategy to Potentially Antiviral Active Carbocyclic L-Nucleosides and L-Nucleotides

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Since L-nucleosides like 3TC **1** and L-FMAU **2** show potent activity against HBV-replication it would be of interest if this also applies to their carbocyclic analogues. In addition to a higher stability towards phosphorylases the carbocyclic moiety prefers a specific conformation depending on the substituents on the cyclopentane system. This leads to a different structure–activity–relationship (SAR) for carbocyclic compounds which may effect their biological properties in comparison with natural nucleosides.