Oral Session III: Herpesviruses I and Poxviruses I

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Synthesis and Structure–Activity Aspects of Some Cyclic Cidofovir Peptidomimetic Prodrugs

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Cidofovir (HPMPC, Vistide®) is a broad-spectrum antiviral agent that is currently used to treat AIDS-related CMV retinitis. Cidofovir is of particular interest as a potential therapy for orthopox virus infections but is limited by poor oral bioavailability, prompting efforts to create prodrug modifications. We previously reported the synthesis and biological evaluation of cyclic cidofovir phosphonate ester prodrugs incorporating an amino acid attached via an ethylene glycol linker, or else an X-Ser dipeptide C-ester connected via the serine side-chain hydroxyl group. Both types of prodrugs were activated by cellular and tissue homogenates to release the active parent drug, and the ethylene glycol-linked prodrug was 4× more active than ganciclovir in a HCMV plaque reduction assay. However, only the directly conjugated dipeptide prodrugs exhibited enhanced transport properties versus cidofovir. We have now examined structure–activity effects of varying the stereochemistry of the amino acids comprising the dipeptide auxiliary. We have also synthesized a cognate prodrug containing a free serine carboxyl group. The prodrugs were evaluated for pH-dependent and intestinal cell homogenate stability, antiviral activity and transport enhancement.

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Synthesis and Antiviral Activity of 1-(*S*)-[3-Hydroxy-2-(Phosphonomethoxy)Propyl]-5-Azacytosine and its Ester Prodrugs

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Investigation of new acyclic nucleotide analogs as potential antivirals resulted in development of analogs with 5-azacytosine moiety (Krečmerová et al., submitted for publication). 1-(*S*)-[3-Hydroxy-2-(phosphonomethoxy)propyl]-5-azacytosine (1), a 5-azacytosine analog of cidofovir exerts a strong activity against adenoviruses, poxviruses, herpes simplex viruses, VZV and CMV in cell cultures. For all these DNA viruses, 1 showed a 2–16-fold higher antiviral selectivity index compared to cidofovir. Transformation of 1 to appropriate ester prodrugs was carried out on the level of its cyclic phosphonate 2 (Fig. 1). Several types or structurally diverse esters were synthesized: alkyl (octadecyl 3a), acyloxyalkyl (pivaloyloxymethyl 3b) and alkoxyalkyl (Kern et al., 2002) (e.g. hexadecyloxyethyl 3c). The most active prodrug was found ester 3c. The development of other prodrugs is under way.

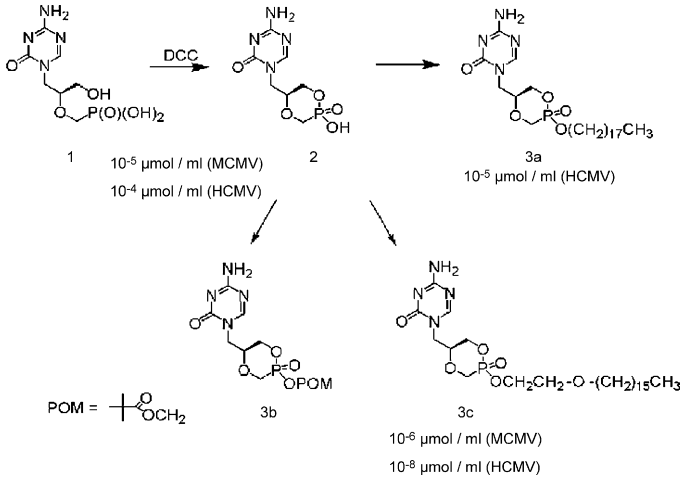

Fig. 1.

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References

Krečmerová, M., Holý, A., et al. J. Med. Chem., submitted for publication.

Kern, E.R., et al., 2002. Antimicrob. Agents Chemother. 46, 991–995.

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In Vivo Antiviral Activity of 1-(*S*)-[3-Hydroxy-2-(Phosphonomethoxy)Propyl]-5-Azacytosine and its Cyclic Form

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