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Intravitreal Alkoxyalkyl Esters of Cyclic Cidofovir for Treatment of Ocular Viral Infections

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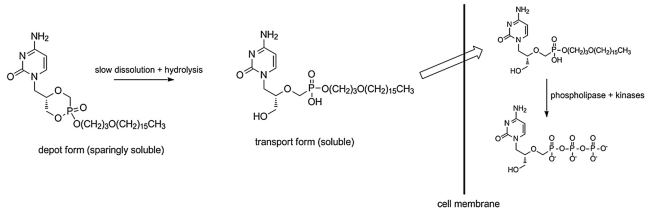
Cytomegalovirus (CMV) retinitis occurs in transplant recipients and other immunosuppressed individuals, such as AIDS patients. Since systemic treatment with the intravenous drug cidofovir (CDV, Vistide®) is hampered by significant toxic side effects, local intervention by intravitreal injection has been investigated. Intravitreal CDV injections can cause a sight-threatening drop in intraocular pressure and are not presently used for anti-CMV therapy. We are investigating sparingly soluble CDV prodrugs as an alternative local treatment for CMV retinitis. Hexadecyloxypropyl cyclic cidofovir (HDP-cCDV), a potent inhibitor of HCMV replication in vitro, forms a slow-release depot in the vitreous that does not adversely affect intraocular pressure or visual clarity. We propose that slow dissolution and hydrolysis of HDP-cCDV converts HDP-cCDV to the more soluble prodrug HDP-CDV which is then taken up by ocular tissues. Metabolism in ocular tissues and retina leads to efficient formation of the active antiviral metabolite, CDV diphosphate (figure). To determine the rate of hydrolysis, HDP-cCDV was suspended in aqueous solution at 37 °C and the rate of appearance of HDP-CDV was determined by HPLC analysis. In a second study, the ocular distribution and clearance of ^{14}C-labeled HDP-CDV was investigated after intravitreal injection (28 μg, rabbits). Through 5 weeks, the drug was detectable in vitreous, retina and ciliary body, and accumulated preferentially in the retina. Overall, our studies suggest that alkoxyalkyl esters of cyclic cidofovir could be useful for local treatment of CMV retinitis, where toxicity and a short half-life has limited the use of unmodified CDV.



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Effect of Molecular Symmetry on Potency in Novel Down-Modulators of the CD4 Receptor

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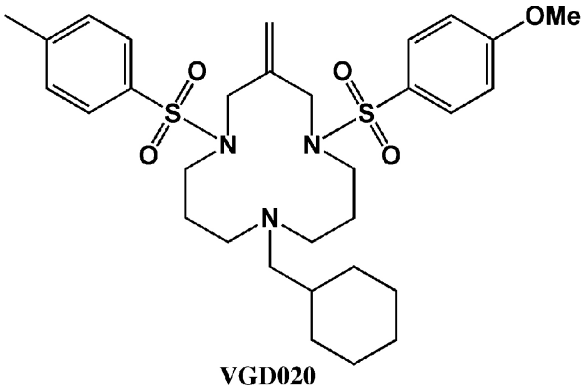
Cyclotriazadisulfonamide (CADA) inhibits the entry of HIV into CD4+ target cells by down-modulating expression of the primary cellular HIV receptor, CD4. Many analogs have been made, and a correlation between CD4 down-modulating and antiviral activities has been observed. Most previously synthesized CADA analogs are symmetrical, with the same arenesulfonyl sidearm on both sides. Exceptions are two compounds with dansyl on one side and tosyl on the other (KKD015 and KKD016). The inactivity of a corresponding symmetrical analog with two dansyl groups suggested that decreased symmetry might increase potency in other cases. By a new synthetic route, new unsymmetrical CADA analogs were prepared and most exhibit CD4 down-modulating activity. The most potent (VGD020), shows a 12-fold increase in potency relative to CADA. The related symmetrical compounds, bearing two tosyl or two methoxybenzenesulfonyl sidearms were found to be 3–4 times less potent than VGD020. The results are consistent with a previous 3D-QSAR model showing that electron-donating groups on sidearms increase potency. They add a new, previously unexplored dimension to the SAR analysis, molecular symmetry. The observation that an unsymmetrical CADA compound can be more potent than either symmetrical analog correlates with the unsymmetrical conformation observed in crystal structures of several CADA analogs and suggests that this may be the bioactive conformation. This information may be of use in designing new analogs for use as tools to identify the cellular target of CADA compounds.



VGD020

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Tripartate Prodrugs of Hydroxy-containing Compounds

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The lymphocyte surface glycoprotein dipeptidyl-peptidase IV enzyme (DPP-IV/CD26), selectively cleaves X-Pro (or X-Ala) dipeptides from the N-terminus of a variety of natural peptides. We have developed a novel enzyme-based prodrug approach that provides conjugates [peptide]–[drug] specifically cleavable by DPP-IV. The approach was applied to a variety of drugs containing a free amino group that was directly coupled with the carboxyl group of amino acids via an amide bond (bipartate prodrug). With these conjugates, it was possible to modulate the hydrolisis rate (half-life) and the physicochemical properties of the compounds by modifying the nature and length of the peptide (di- or tetrapeptides) of the prodrug moiety. (García-Aparicio et al., 2006; Diez-Torrubia et al., 2010).

Recently, we expanded, our prodrug strategy to an hydroxy-containing compound such as the highly potent and selective bicyclic nucleoside analogue (BCNA) inhibitor of Varicella Zoster Virus (VZV), named Cf1743, which exhibit a very low water solubility and poor oral bioavailability. Several of the synthesized prodrugs that contain a dipeptide moiety (cleavable by CD26), a heterobifunctional linker [released by chemical or enzymatic (esterases) hydrolysis of the ester bond] and the drug (tripartate prodrugs)