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Synthesis of Novel CADA Analog Prodrugs Designed as Down-Modulators of the CD4 Receptor

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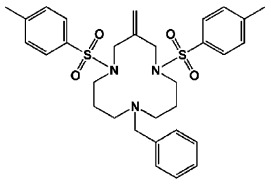
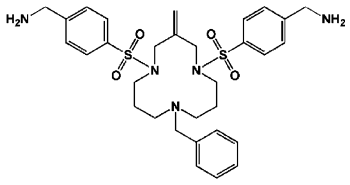
Cyclotriazadisulfonamide (CADA) inhibits HIV replication by specifically down-modulating expression of the of the CD4 receptor protein on host cells. Many analogs of CADA have been synthesized in order to enhance potency, reduce toxicity, and improve physical properties, especially solubility and cell permeability (Bell et al., 2006, J. Med. Chem., 49, 1291). These analogs have also been used to develop a three-dimensional quantitative structure-activity relationship (3D-QSAR) computer model. Current studies are aimed at developing a pro-drug approach involving novel CADA analog ES02. This compound is expected to have a CD4 down-modulation potency that is similar to that of CADA, according to our 3D-QSAR model. ES02 is the parent compound for prodrugs bearing dipeptide chains that are covalently bonded to the two amino groups of the aminomethylbenzenesulfonyl side arms. Cleavage of these chains by dipeptidyl-peptidase IV (Garcia-Aparicio et al., 2006, J. Med. Chem., 49, 5339) is expected to convert the prodrugs into ES02. The synthesis of ES02 uses a new palladium-catalyzed macrocyclization method. Two synthetic routes have been explored, one involving the bis(bromobenzenesulfonyl) analog of CADA, and a new route using the corresponding bis(cyanobenzenesulfonyl) analog as an intermediate. The anti-HIV and CD4 down modulation activities of the novel CADA compounds will be presented.



CADA



ES02

doi:10.1016/j.antiviral.2010.02.468

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Rational Drug Design—Screening and Synthesis of Potential Deoxyhypusine Synthase Inhibitors Targeting HIV-1 Replication

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The introduction of HAART was a key improvement in combating HIV that prolonged patients expectancy of life. However, in order to reduce side-effects and upcoming multidrug resistance in long-term HAART it is mandatory to address new targets and to identify new potential drugs.

Within the HIV replication cycle various host cell-factors play an important role, e.g. the eukaryotic initiation factor 5A (eIF-5A). Activation of eIF-5A involves a unique post-translational modification of a specific lysine residue to the unusual amino acid hypusine. This modification is catalyzed by subsequent action of human deoxyhypusine synthase (DHS) and deoxyhypusine hydroxylase (DOHH). Recently, it was shown that DHS inhibition efficiently prohibits the activation of eIF-5A leading to suppression of HIV replication (Hauber et al., 2005).

Based on X-ray crystal data of DHS and known inhibitors such as GC7 and CNI-1493, structure-based drug design approaches were applied in order to discover novel DHS inhibitors. Using the molecular docking software FlexX in combination with the HYDE scoring function (Reulecke et al., 2008), several suggestions for potential DHS inhibitors were proposed.

Here, we present the synthesis and the biological evaluation of several selected compounds from this set of potential inhibitors. These compounds were tested for inhibition of DHS in an enzymatic assay, inhibition of HIV-1 replication *in vitro* and for potential cytotoxic effects.

References

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doi:10.1016/j.antiviral.2010.02.469

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Lipophilic Nucleoside Diphosphate Prodrugs—Synthesis and Properties

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Nucleoside analogs are commonly used as antiviral and antitumor agents. The antiviral effect of the majority of nucleoside analogs such as 3′-deoxy-3′-azidothymidine (AZT) or 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) depends on their conversion into the ultimately bioactive nucleoside triphosphate (NTP). However, cellular kinases often catalyze the biotransformation via the mono- and diphosphate insufficiently with the result of a loss in antiviral activity.

AZT is very slowly phosphorylated by thymidylate kinase to AZTDP which leads to severe side-effects during AZT treatment. Considering this, it is remarkable that there were only a few attempts made to synthesize lipophilic nucleoside diphosphate prodrugs (NDP prodrugs) in the past. Recently, we reported on the first successful bioreversible protection of nucleoside diphosphates as bis-(acyloxybenzyl) phosphate diesters (Jessen et al., 2008). The pyrophosphate protecting groups is cleaved by esterases/lipases inside cells resulting in the formation of the NDP.

To investigate the structure–activity relationship a series of more lipophilic bis-(4-acyloxy-benzyl)-d4T diphosphates (BAB-d4TDPs) was synthesized with yields up to 65%. We used longer alkyl chains as acyl moieties. The aim of our studies was to identify a correlation between the antiviral activity of the compounds and its lipophilicity.

Very interesting antiviral data found in CEM/TK$^-$ cells will be shown. These data point to a dependence between the alkyl chain