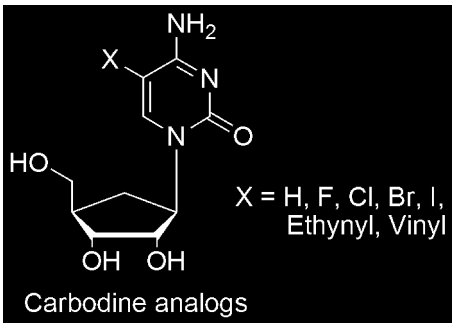


doi:10.1016/j.antiviral.2009.02.150

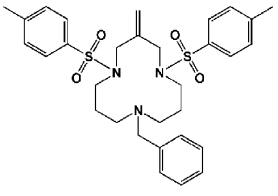
146

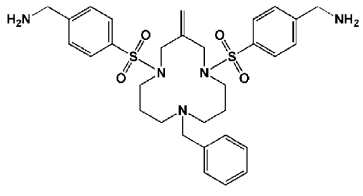
Synthesis of CADA Analog Prodrugs Designed as Novel Down-modulators of the CD4 Receptor

Emily Scarbrough[a,*], Sreenivasa Anugu[a], Kurt Vermeire[b], Dominique Schols[b], Thomas Bell[a]

[a] *Department of Chemistry, University of Nevada, Reno, USA;* [b] *Rega Institute for Medical Research, Department of Microbiology and Immunology, Katholieke Universiteit Leuven, Leuven, Belgium*

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). 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) is expected to convert the prodrugs into ES02. The synthesis of ES02 involves a new macrocyclization method using palladium as a catalyst. This technique avoids large solvent volumes, long reaction times, and polymer side products associated with the conventional, Richman–Atkins macrocyclization method. The anti-HIV and CD4 down-modulation activities of the novel CADA compounds will be presented.





Reference

Bell, et al., 2006. J. Med. Chem. 49, 1291–1312.
Garcia-Aparicio, et al., 2006. J. Med. Chem. 49, 5339–5351.

doi:10.1016/j.antiviral.2009.02.151

147

Bioreversible Protection of Nucleosidediphosphates—Synthesis and Properties

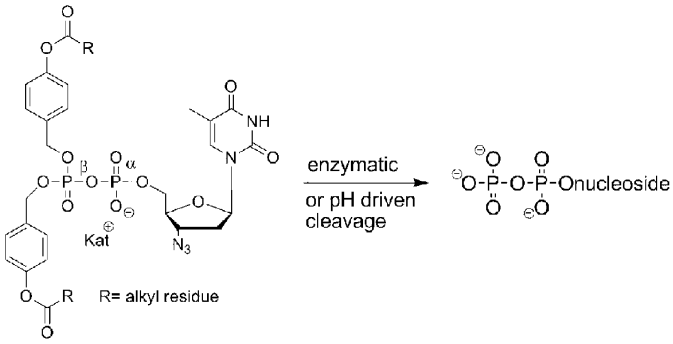
Tilmann Schulz[a,*], Henning J. Jessen[a], Jan Balzarini[b], Chris Meier[a]

[a] *Institue of Organic Chemistry, Department of Chemistry, Faculty of Science, University of Hamburg, Martin-Luther-King Platz 6, D-20146 Hamburg, Germany;* [b] *Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroederstraat 10, B-3000 Leuven, Belgium*

Nucleoside analogs are widely applied in antiviral and antitumor therapy. A severe limitation of these compounds arises from the need of biotransformation to the eventually active nucleoside triphosphates (NTP) by stepwise addition of phosphate groups by kinases which often proceeds insufficient. Prodrugs (e.g. the *cyclo*Sal- or phosphoamidate-approach) can possibly enhance the antiviral or antitumor activity of nucleotide analogs, enabling the nucleotide analogs to penetrate cellular membranes and protecting them from degradation by unspecific plasma phosphatases. They bypass the limited bioactivation of nucleoside kinases, hence rising the intracellular level of nucleoside monophosphates. However the subject of nucleosidediphosphate prodrugs has been addressed very rarely and unsuccessful.

This is remarkable, considering that, e.g. 3′-azido-3′-deoxythymidine (AZT) is only very slowly diphosphorylated by thymidylate kinase resulting in the loss of antiviral activity and unwanted side effects. For these reasons we turned our interest on the bioreversible protection of nucleoside diphosphates. This way of protection might also be very desirable for other nucleotide analogs.

We will present the synthesis and biological properties (pH- and cell extract stability, cytotoxicity, antiviral activity) of newly designed bis-(4-acyloxybenzyl)nucleoside-diphosphates which should act as nucleoside diphosphate prodrugs. Once insight the cell, the pyrophosphate protecting groups should be cleaved by enzymes resulting in a spontaneous release of the nucleotide.



doi:10.1016/j.antiviral.2009.02.152

148

Multivalent Synthetic Lectin Polymers Against HIV

Julie Jay[a,*], Bonnie Lai[b], Patrick Kiser[a]

[a] *University of Utah, Department of Bioengineering, Salt Lake City, USA;* [b] *Duke University, Department of Biomedical Engineering, Durham, USA*

While Phase III trials of microbicides proceed there still remain critical gaps in the therapeutic pipeline. Specifically there is a lack of affordable, and broadly efficacious entry inhibitors that target the HIV ENV complex, and are safe for repeated topical delivery. Cyanovirin-N, one of the most potent anti-HIV agents known, inac-