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## A Heterocyclic Molecule with Significant Activity Against Dengue Virus

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The etiological agents of dengue fever (DF) and dengue hemorrhagic fever (DHF) are four dengue viruses, which are antigenically similar but immunologically distinct serotypes of the family called Flavivirus. Estimates make the number of cases of dengue fever as high as 100 million annually, which makes this arthropod-borne viral infection a serious global health problem. Dengue virus genome is a positive-stranded, 5′-capped RNA of about 11 kD. After fusion and entry, translation of genomic RNA occurs in infected cells. Viral polyprotein processing is apparently catalyzed by both viral and cellular enzymes. For example, the NS3 viral protease is essential for viral replication. The NS5 conserved protein has a methyltransferase motif in the N-terminal domain and an RNA-dependent RNA polymerase in the C-terminal domain. The transferase and polymerase are potential targets in antiviral strategies. However, there are no specific approved drugs or vaccines for the treatment or prevention of DF and DHF. This presentation describes the concise synthesis of a uracil-based multifunctional compound, which has strong activity against dengue virus. Interestingly, this heterocyclic compound also exhibits low activity against a few other RNA viruses, but is highly active against yellow fever virus, a related flavivirus. It is likely that the mechanism of action of the antiviral activity of our compound is through its inhibition of the enzyme, inosine monophosphate dehydrogenase (IMPDH). Molecular modeling studies reveal that the compound can have specific hydrogen bonding interactions with a number of amino acids in the active site of IMPDH, a stacking interaction with the bound natural substrate, IMP, and the ability to interfere with the binding of $NAD^+$ with IMPDH, prior to the hydration step. Details of the chemistry, enzymology and antiviral activity will be discussed.

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## Synthesis and Properties of *Cyclo*Sal-phosphatetriesters of Fluorescent Bicyclic Nucleoside Analogues (BCNAS)

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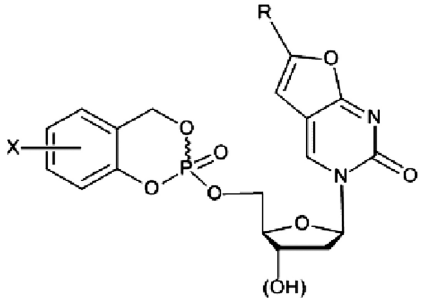
*Cyclo*Sal-pronucleotides are well known for the efficient delivery of nucleoside monophosphates of antivirally active nucleoside analogues inside cells. The *cyclo*Sal-concept is based on the use of substituted salicyl alcohols as lipophilic masking units for the negative charges of the phosphate group and therefore allowing the pronucleotide to diffuse through the cell membrane. Intracellularly, the masking unit is then cleaved by a purely chemically driven hydrolysis mechanism and the nucleoside monophosphate is released. Latest developments include "lock-in"-modifications and enzymatically activated *cyclo*Sal-pronucleotides.

For further development of the concept it is important to acquire information about the cell uptake and the intracellular fate of these pronucleotides. However, for such studies, the compounds should be labelled or should bear a probe. A convenient way for these investigations is the usage of fluorescent probes that show close structural similarity to the antivirally active nucleoside analogues. A class of compounds that may be suitable to act as probes are the bicyclic nucleoside analogues (BCNAs). Originally developed as antiviral agents by the group of *C. McGuigan*, these compounds also exhibit strong intrinsic fluorescence (McGuigan et al., 2007).

Here, we report on the synthesis and properties of the first *cyclo*Sal-phosphatetriesters of these bicyclic nucleoside analogues.

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## Anti-H5N1 Influenza Virus Activity of Carbocyclic Cytosine Nucleosides

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The carbocyclic analog of cytosine (carbodine) was earlier reported as a racemic mixture and has been shown to possess inhibitory activity against human influenza type A virus. Previously, at this meeting in 2008, we have reported enantiomeric D-(−)-carbodine as a potent antiviral agent against various strains of H5N1 influenza virus. This interesting biological result prompts us to synthesize various analogs of carbodine to study the structure-activity relationships against various strains of avian influenza virus (H5N1). Among the synthesized analogs, carbodine and the 5-fluoro-derivative showed potent activity against influenza A/Duck/MN/1525/81 (H5N1), influenza A/Hongkong/213/03 (H5N1) as well as other strains (H1N1, H3N2 and influenza B virus). The 5-fluoro derivative was active in the range of 0.3–2.0 μg/ml against multiple viruses in cytopathic effect inhibition assays. Its potent activity was confirmed by virus yield reduction. No cytotoxicity was evident at 100 μg/ml. Substitution by other groups like Cl, Br, I, vinyl and ethynyl results to the complete loss of activity.

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