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Structure-Activity Relationship Studies of Nucleoside Analogs with Anti-HIV Activity

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The structure-activity relationships of nucleoside analogs with anti-HIV activity have been investigated using molecular similarity analysis and structure-activity maps. Molecular descriptors such as molecular topology number (NAB), maximum common substructure (MaCS), minimum common superstructure (MiCS), and molecular similarity index (MSI) have been used in the molecular similarity analysis. A super-integrated multi-formula approach using these descriptors (NAB, MaCS, MiCS and MSI) to perform quantitative molecular similarity analysis (QMSA) and quantitative structure activity relationship (QSAR) study of the structure and anti-HIV activity of nucleoside analogs is described. Structure-activity maps are also used to examine the structure and anti-HIV activity relationships of nucleoside analogs including dideoxynucleoside analogs and acyclic nucleoside analogs.

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2-Nucleosyl-4H-1,3,2-Benzodioxophosphorine-2-Oxides. A New Concept For Lipophilic Prodrugs Of Biologically Active Nucleoside Monophosphates

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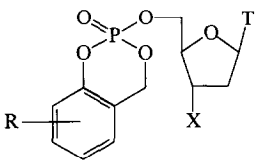
The synthesis of a new class of prodrugs of antivirally active nucleoside analogues based on 4H-1,3,2-benzodioxophosphorine-2-oxide esters of type **1** is presented. As antiviral nucleoside analogues served AZT, d4T, ddT as well as ddU. As a model compound 2'-deoxythymidine was used first. It was shown that these compounds release the nucleoside monophosphate as the sole nucleoside-containing product. The hydrolysis mechanism involves a spontaneous hydrolytic process that affords a tandem-reaction to cleave the phosphotriester derivative **1**. The kinetics of the cleavage as well as direct evidence for the hydrolysis intermediates will be presented. The rate of hydrolysis could be controlled by changing the substituents in the aromatic system. All new compounds showed higher partition coefficients than the parent nucleosides. Several of the compounds were highly inhibitory to HIV-1 and HIV-2 replication. Data on their anti-HIV activity in wild-type CEM/0 and thymidine kinase-deficient CEM/TK$^-$ cells will be presented.



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