viruses. Compounds 05-103227, 05-102300 and 05-102691 yielded effective concentration (EC_{50}) values of 1–9 μM for VV and 6–58 μM for CV. Neutral red uptake and CellTiter-Glo cell viability assays were used to measure cellular cytotoxicity and it was determined that all of the compounds were relatively non-cytotoxic. Thus, these compounds are highly selective agents with 05-103227 and 05-102300 yielding selective indices of >167 and >346, respectively. The chemical structures of these small molecules shared characteristics with the potent antipoxvirus drug ST-246. We hypothesized that the compounds might act by a similar mechanism and tested them against an ST-246 resistant strain of VV. This mutant proved to be highly resistant to both 05-102300 and 05-102691, suggesting that these compounds also inhibited the F13L gene product, p37, which is the target for ST-246. The most effective compound of the three, 05-103227, retained activity against the F13L mutant suggesting that it does not target the same binding site on p37, or that it inhibits a different viral function. Additional experiments are underway to identify the molecular target of this compound and to determine the activity of each of these compounds in experimental animal infections.

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Synthesis and Antiviral Activity of Various N^4-Acyl Derivatives of Cidofovir and its 5-Azacytosine Counterpart, 1-(*S*)-[3-Hydroxy-2-(Phosphonomethoxy)Propyl]-5-Azacytosine

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Investigation of new types of acyclic nucleoside phosphonates (ANPs) as antiviral agents resulted among others in discovery of 1-(*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl]-5-azacytosine (HPMP-5-azaC), its cyclic form and several types of ester prodrugs, compounds active against DNA viruses with activity data similar or better compared to cidofovir and higher index of selectivity *in vitro*. In contrast to cidofovir, HPMP-5-azaC has more complicated metabolic profile due to its chemical and enzymatic instability. In aqueous solutions ring opening between C-6 and N-1 of the triazine moiety occurs and HPMP-5-azaC is successively degraded to 2-{[(2*S*)-3-hydroxy-2-(phosphonomethoxy)propyl]carbamoylguanidine via the intermediary *N*-formyl derivative. The final decomposition product has no cytotoxicity *in vitro* but it is antivirally inactive. Besides chemical decomposition, HPMP-5-azaC undergoes also extensive enzymatic deamination in cell cultures. To improve the stability towards deamination process we tried to transform HPMP-5azaC to diverse N^4-acyl prodrugs on the level of free phosphonic acids as well as on the level of some earlier already prepared ester prodrugs, e.g. hexadecyloxyethyl ester of cyclic HPMP-5-azaC. As acyl groups we selected even number fatty acid residues (e.g. behenoyl, stearoyl). Similar N^4-acyl compounds were prepared also from HPMPC (cidofovir) and some of its esters. Different reactivity of both systems towards acylation reactions and influence of introduction of N^4-acyl groups to stability and antiviral activity of compounds will be discussed.

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Antiviral Effects of Sulfated Exopolysaccharide from the Marine Microalga *Gyrodinium impudicum* Strain KG03

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The sulfated exopolysaccharide p-KG03, which is produced by the marine microalga *Gyrodinium impudicum* strain KG03, exhibited impressive antiviral activity in vitro (EC_{50} = 26.9 mg/ml) against the encephalomyocarditis virus (EMCV). Depending on the p-KG03 concentration, the development of cytopathic effects in EMCV-infected HeLa cells was either inhibited completely or slowed. Moreover, p-KG03 did not show any cytotoxic effects on HeLa cells, even at concentrations up to 1000 mg/ml. The polysaccharide was purified by repeated precipitation in ethanol, followed by gel filtration. The p-KG03 polysaccharide had a molecular weight of 1.87×10^6, and was characterized as a homopolysaccharide of galactose with uronic acid (2.96%, w/w) and sulfate groups (10.32%, w/w). Antiviral activities of p-KG03 against various viruses – various picornaviruses, herpesviruses, influenza viruses and feline coronaviruses and HIV – will be reported. The biological activities of p-KG03 suggest that sulfated metabolites from marine organisms are a rich source of antiviral agents. The p-KG03 polysaccharide may be useful for the development of marine bioactive exopolysaccharides for use in biotechnological and pharmaceutical products.

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Developing a Novel High-throughput Screening Assay against Bluetongue Virus

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Arthropod borne viruses (arboviruses) are important human/animal pathogens that cause acute virus infections with severe diseases and/or death. Several recent human/animal epidemics are caused by arboviruses, including Dengue virus (DNV) in Asia, West Nile virus (WNV) in North America and Bluetongue virus (BTV) in Europe. There are no antiviral drugs available against these diseases. We have designed,