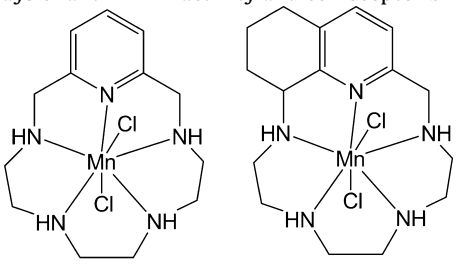
1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (CADA, or cyclotriazadisulfonamide) specifically down-modulates CD4, the principal cellular receptor for HIV. Bicyclams (e.g. AMD3100) and their metal complexes inhibit HIV by a different mechanism, specifically interacting with the cellular co-receptor, CXCR4. SH04 and SH06, the manganese complexes of 3,6,9,12,18-pentaazabicyclo[12,3,1]octadeca-1(18),14,16-triene and 3,4,5,6,7,8,9,10,11,-12,13,13a,14,15,16-pentdecahydro-2,17-etheno-1,4,7,10,13-benzopentaaza-cyclopentadecine, respectively, inhibit HIV replication and also interact with both of the cellular HIV co-receptors, CXCR4 and CCR5. Synthesis of several analogues of these compounds is in progress to decipher in more detail the mechanisms of chemokine receptor interaction and antiviral activity. For example, analogs of SH04 containing copper or zinc, instead of manganese, have been synthesized and tested for activity against HIV and for chemokine receptor interaction. Also, SH06 was previously tested as a racemic mixture, so efforts are also in progress to prepare the pure enantiomers for further assays of anti-HIV-1 activity and co-receptor binding.



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Changes in Human Cytomegalovirus Transcriptional Patterns Induced by Antiviral Drugs

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The expression of herpesvirus genes is temporally regulated and the three kinetic classes of transcripts have been defined in part by transcriptional responses to antiviral drugs, such as phosphonoacetic acid. Since many compounds have been identified that inhibit the replication of human cytomegalovirus (HCMV) by novel mechanisms, we sought to characterize changes in transcriptional patterns that occurred in response to selected antiviral drugs. Compounds evaluated included ganciclovir and cidofovir (inhibitors of DNA polymerase), maribavir (inhibitor of the UL97 kinase), and 1H-β-D-ribofuranosyl-2-bromo-5,6-dichlorobenzimidazole (BDCRB), which inhibits the cleavage/packaging of the viral genome. A quantitative real time RT PCR array was developed that provided a global evaluation of viral transcripts levels. This approach measured levels of 136 viral transcripts at 72 h following infection. Data were normalized to cellular transcripts and ANOVA was used to identify changes that were significant relative to an untreated virus control. This analysis revealed that: (1) distinct kinetic classes of transcripts were less discernable in HCMV than in other herpesviruses, (2) inhibitors of DNA synthesis reduced many viral transcripts and was not restricted to early/late, or late messages, (3) maribavir reduced a subset of transcripts that were also reduced by the DNA synthesis inhibitors, and (4) BDCRB reduced levels of very few viral messages. These data will help to define the complex transcriptional regulation of this virus and will be a useful tool for characterizing the mechanism of action of new compounds that inhibit the virus.

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Antiviral Activity of Acyclic Nucleoside Phosphonates with Branched 2-(2-Phosphonoethoxy)ethyl Chain

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Several drugs that are in current clinical use for the treatment of viral infections belong to the acyclic nucleoside phosphonates (ANPs) (De Clercq and Holý, 2005). Some of the recently prepared ANPs containing the 2-(2-phosphonoethoxy)ethyl function (PEE) were studied as antimalarial compounds (Hocková et al., 2009). When guanine or hypoxanthine is present as the nucleobase in their molecule, they inhibit Plasmodium falciparum hypoxanthine-guanine-xanthine phosphoribosyltransferase and can selectively discriminate between the human and the parasite enzyme (Hocková et al., 2009; Keough et al., 2009). Unexpectedly, some of these ANPs with the PEE-chain branched in the b-position to the phosphonate group exhibit antiviral activity against VZV, CMV, HIV, HSV-1 and HSV-2, although the parent unbranched PEE-ANPs are inactive. The influence of the heterocyclic base and substituent R will be discussed. The cytotoxic and cytostatic activities of the compounds were also evaluated.

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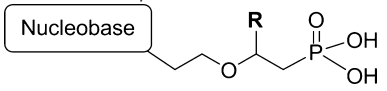

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