vent exchange of the metal ion. New compounds containing zinc(II) and copper(II) were produced, which showed improved binding properties and increased anti-HIV potency. In vitro MT-4 anti-HIV infection assay, average EC_{50} HIV-1 (III_B): SJA-GCV49(Zn) 2.5 nM, SJA5(Cu) 4.3 nM, SJA-GCV18(Cu)26 nM. X-ray crystallographic and spectroscopic data of compounds mimicking the drug binding interactions with CXCR4 allow structure activity relationships to be elucidated with regard to the coordination chemistry of the metal centres.

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West Nile Virus Helicase: Homology Modeling and Docking Studies

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The flaviviridae is a family of at least 66 viruses of which almost half have been associated with human diseases. The most well-known members are Hepatitis C virus, dengue virus, and West Nile virus (WNV). Diseases caused by these viruses are global health problem that put an estimated 2.5 billion people at risk. At present there is no treatment available to prevent or cure most of these diseases. A potential target for the development of therapeutics against the virus is the viral helicase due to its importance in viral replication. In our project we are looking to design inhibitors for different flaviviridae helicases, in particular the HCV, WNV, and Dengue virus enzymes. Considering that the crystal structure of WNV helicase is not reported yet, we have built a homology model of this enzyme using the Yellow Fever helicase as template. The model obtained was further optimized using molecular dynamics. This model can now be used as a tool for the design of novel compounds that target this enzyme and inhibit viral replication.

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Nucleoside Phosphonate Analogues Modified by Lipophilic Cage Moiety as Potential Antiviral Agents

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At the present time analogs of nucleoside phosphonates containing dihydroxypropyl groups (adefovir, cidofovir, tenofovir) are the most perspective antivirus agents. There has been reported cidofovir and its derivatives show good activity against poxvirus on animal models. The most disadvantages of all these compounds are the low level of bioavailability which determines their application by intravenous injection. This disadvantage is determined by the presence in the structure the very polar phosphonate group. But this group is very important for antiviral activity. At this point nucleotide analogs bearing phosphonate group modified by a lipophilic substituent are of the special interest. The modifying lipophilic group can be able easy eliminate in the course of hydrolyses at cytoplasm pH values or cell enzymes action. More lipophilic cidofovir derivatives have been synthesized and they shown better activity due to not only its bioavailability but themselves own structure. For instance hexadecyloxypropyl derivative of cidofovir show very good antiviral activity. We have attempted to modify cidofovir and related structures using lipophilic cage compounds. A number of compounds containing adamantane derivative bonded with phosphonate group by a chain linkage have been prepared (B – heterocyclic base, X – $(CH_2)_n$ or $(CH_2)_nO$, Ad – adamantane derivative): Earlier we have found several oxygen and nitrogen derivatives of cage compounds show high activity against RNA and DNA viruses on cell cultures. And we have used these derivatives as lipophilic modifiers of nucleoside phosphonates analogs in order to raise the activity of the whole structure. This way of modification could allow developing new therapeutic agents having high level of bioavailability and can be able to act on two or more stages of reproductive cycle of DNA viruses

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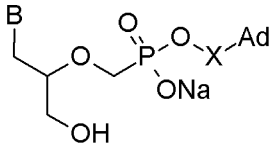

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Antiviral Activity of New Derivatives of Cage Compounds

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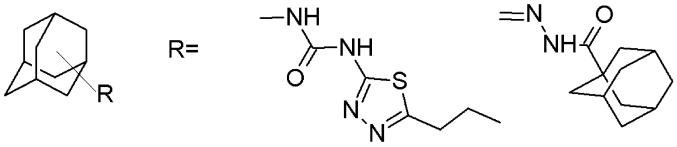
The high pathogenicity influenza A (H5N1) virus has been the cause of large-scale death in poultry and death of over 200 humans. As regards orthopox viruses, discontinuation of vaccination makes population vulnerable to variola and orthopox infections. Functional derivatives of cage structure are as known one of perspective classes of organic compounds for search of antiviral agents. During our investigation we have synthesized series of functional derivatives of adamantane: oxygen, nitrogen, sulphur containing derivatives and wide range of adamantyl substituted heterocycles. Antiviral activity was evaluated against influenza A (H5N1) virus and orthopox viruses: vaccinia, cowpox, mousepox, monkeypox in cell cultures (Vero, MK 2). Biological tests show that most of synthesized compounds reveal antiviral activity to a greater or lesser extent. Among compounds having activity against poxviruses it is necessary to note cage fluoro containing amide, which inhibits reproduction of vaccinia virus in 0.06 mM concentration and derivative of adamantyl substituted 1,3,4-thiadiazole shows good potency against cowpox (IC_{50} = 0.09 mM). Also adamantane containing hydrazide has marked antiviral potency against influenza A virus (H5N1), it inhibits their reproduction at 0.5 mM concentration. Amino derivative, containing adamantylidene unit, suppresses replication of H5N1 virus at 0.7 mM concentration. The presence of great number of high active compounds indicates some common principles of antiviral action of compounds, containing saturated cage moiety. It determines route to new inhibitors of the influenza which block M2 ion channels. Structures of compounds having activity against poxviruses allow to suppose that their action occurs at the later stages of viral reproduction.



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