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Enhanced Antiviral Activity of Hexadecyloxypropyl-PME-N^6-Cyclopropyl-diaminopurine Against Herpesviruses, Hepatitis B Virus and Vaccinia Virus, In Vitro

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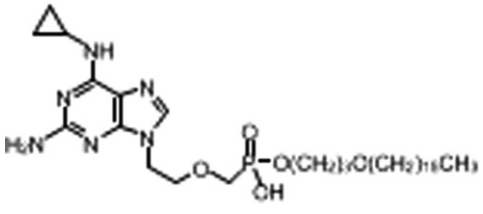
Previous studies from our laboratories showed that esterification of acyclic nucleoside phosphonates (ANPs) increased their antiviral activity, promoted oral bioavailability and reduced nephrotoxicity. Hexadecyloxypropyl (HDP) esters of cidofovir and (*S*)-HPMPA were found to be several logs more active than the unmodified compounds against a variety of DNA viruses. HDP-CDV and HDP-(*S*)-HPMPA are orally active in lethal animal models of poxvirus disease and in animal models of CMV disease. We recently extended this approach by synthesizing the HDP ester of phosphonomethoxyethyl-N^6-cyclopropyl-diaminopurine (HDP-PME-N^6-cPr-DAP) [Fig. 1, right].

The test compound was evaluated in antiviral assays in vitro and had the greatest activity against HCMV and VZV with EC_{50} values of 0.0032 μg/ml and 0.0073 μg/ml. HDP-PME-N^6-cPr-DAP is also active against HSV-1 and HSV-2 with EC_{50} values of 0.32 μg/ml and 0.128 μg/ml, respectively. Notably, the compound retained full activity against TK negative HSV-1 and VZV viruses. It was also active against HBV and vaccinia virus with EC_{50} values of 0.032 and 0.48 μg/ml. Selectivity indexes for HCMV and VZV were >1500 and >600. HDP-PME-N^6-cPr-DAP is also highly active and selective against HIV-1. Alkoxyalkyl esterification of ANPs increases antiviral activity and oral bioavailability and mounting evidence suggests that the technology is generally applicable.



HDP-PME-N^6-cyclopropyl-DAP

Fig. 1.

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Molecular Design of Active Antiherpetic Compounds Using Hierarchic QSAR Technology

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The objective of the present work is QSAR analysis of antiherpetic activity (HSV-1) in the set of nitrogen-containing macroheterocycles, different benzene derivatives and some well-known anti-viral drugs. The compounds ability to inhibit herpetical reproduction on HEP-2 cells was estimated.

QSAR investigation has been carried out using Hierarchic technology based on simplex representation of molecular structure (SiRMS). This method allows providing rational selection of compounds with high specific biological activity. Using PLS-method the models of different level of detailing (2D, 4D, 3D) was obtained. Statistical characteristics of these models were satisfactory ($R^2 = 0.82–0.83$, $Q^2 = 0.55–0.59$).

Using the obtained QSAR models, the influence of different physico-chemical properties of investigated compounds on the changes of antiherpetic activity was studied. These results specify the high role of hydrophobic factors (39–46%) and descriptions of individuality of atoms (33%). Electrostatic descriptions of atoms also have an important role (15%). The shape of molecule (4D and 3D models) also influences on antiherpetic activity (9%).

The influence of different fragments into antiherpetic activity was defined. It is discovered that an important factor for the display of activity is a presence of amino group connected with an aliphatic fragment. Thus, activity of amino group insignificantly falls during substitution of hydrogen atoms on the atoms of carbon. A tendency to improving of compounds activity with improving of acceptor' properties of aromatic ring was found.

As a result of QSAR modeling the molecular design of perspective compounds was carried out. As a result five compounds with high level of antiherpetic activity were obtained: aromatic sulfonate derivatives and nitrous analogues of crown ethers. They are most perspective as antiherpetic preparations and need further detailed researches.

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