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Development of Novel Evaluation Method to Anti-influenza Drug Resistance using Docking Study

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On April 2009, novel swine influenza was occurred in Mexico and was going around all over the world (pandemic). In 2009, more than 600,000 people were infected and 14,000 people were died. Some neuraminidase inhibitor such as oseltamivir is frequently used for treatment. Meanwhile, oseltamivir resistance is one of the problems for treatment recently. For example, His275Tyr (for H1N1) mutation shows oseltamivir resistance.

Against this background, if we can evaluate these kinds of drug resistance rapidly, it contributes an antiviral treatment on site and applies to the prediction of drug resistance in near future. Now we developed a novel evaluation method of antiviral drug resistance in silico.

This method is combination of docking simulation, which calculates a binding affinity between drug and protein, and Boltzmann distribution, which represents an existing probability of molecule. We thought that drug susceptive strains have more suitable docking poses than drug resistant strains. Therefore, all docking poses are converted to the existing probability and expectation value by Boltzmann distribution this can evaluate drug resistance between different complexes.

In this case, we evaluated drug resistance of influenza neuraminidase inhibitor by using structures of neuraminidase and the inhibitor (oseltamivir). We compared to ligand conformations between before and after docking to determine suitable docking pose. The expectation value of drug resistant strains is lower than susceptive strain. It was suggested that our evaluation by comparison with the expectation value of wild type be appropriate since our method agreed with the experimental data.

Our method considers a number of docking poses, the method features more accurate than the method from only top docking score. Therefore, it is useful for appropriate selection of drugs when novel mutant appears.

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Antiviral Properties of New Cage Compounds

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Traditionally, derivatives of adamantane are considered as potential treatments for influenza. The ability of cage structure to interrupt functions of M2 protein, acting as ion channel, allows to suggest that derivatives of polycyclic molecules can be also efficient inhibitors of the replication of other viruses with ion channels. Simultaneously, the same proteins are acting during the assembly of mature viral unit, therefore cage substances can interrupt the late stages of viral reproduction. By sequential search of the viral inhibitors, series of the new compounds has been prepared on the basis of modification of the polycyclic carbonic acids, amines, ketones, alcohols, lactames and also from adamantane alkenes and arenes. Antiviral activity of the prepared substances against the number of RNA viruses (influenza virus type A, H5N1, H1N1, H3N2 pestivirus BVDV as surrogate model of hepatitis C virus) and DNA-viruses (orthopoxviruses vaccinia, cowpox, ectromelia and variola viruses herpes virus) have been investigated on the cell cultures. In the issue sufficiently large number of compounds with antiviral action in a varying degree has been prepared. Hydroxy and nitrogen containing derivatives of the adamantane which have no other substituents in the cage unit show maximal activity against influenza viruses. The ability to suppress reproduction of pox viruses mostly belongs to cage compounds with high Log *P* values and derivatives of the heterocyclic system of the 4-azahomoadamantane.

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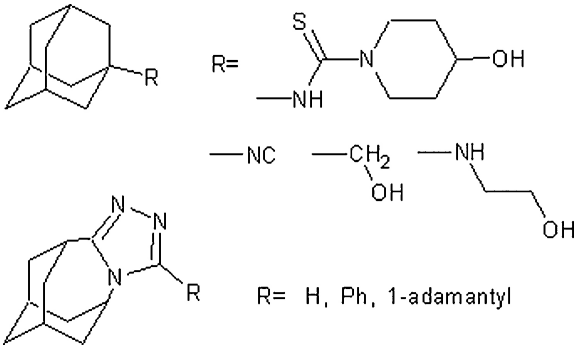

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Indolylarylsulfones as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors: New Cyclic Substituents at the Indole-2-carboxamide

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New indolylarylsulfone derivatives bearing cyclic substituents at the indole-2-carboxamide linked through a methylene/ethylene spacer were potent inhibitors of the WT HIV-1 replication in CEM and PBMC cells with inhibitory concentrations in the low nanomolar range. Against the mutant L100I and K103N RT HIV-1 strains in MT-4 cells, several compounds showed antiviral potency superior to NVP and EFV. Against these mutant strains, the derivatives were equipotent to ETV. Molecular docking experiments on this novel series of IAS analogues have also suggested that the H-bond interaction between the nitrogen atom in the carboxamide chain of IAS and Glu138:B is important in the binding of these compounds. These results are in accordance with the experimental data obtained on the WT and on the mutant HIV-1 strains tested.