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Properties of Aminoacid Esters Linked to Cyclo Sal-Pronucleotides

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Cyclo Sal-pronucleotides are used as prodrugs, delivering nucleotides into cells. The transport of these compounds across cellular membranes is basically achieved by passive diffusion, which is due to the high lipophilicity of the prodrug. As the release of the nucleotides is triggered by a pH dependent hydrolysis cascade, cleavage may occur inside as well as outside cells. This unselective process may be disturbed by attaching a trigger sensible to esterases to the pronucleotide. The activated trigger is supposed to keep the prodrug inside the cell, leading to enrichment of the cyclo Sal-pronucleotide (trapping concept). To achieve this goal, different aminoacid esters were linked to the aromatic ring of the cyclo Sal-masking unit via a C-3 carbonic acid linker. In the presence of, e.g. (carboxy)esterases, the aminoacyl ester is digested to the carbonic acid, resulting in higher polarity, and thus decreasing ability of the prodrug to diffuse passively across membranes. The compounds were examined concerning their pH stability, cell extract stability, cytotoxicity and antiviral activity in CEM/0 and TK-deficient cell lines.

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Discovery of Cage Antiviral Agents

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One of the perspective classes of organic compounds for searching antiviral agents the functional derivatives of “cage” compounds. To continue our research a serious of novel cage compounds containing different lipophilic polycyclic fragments (adamantane, bornane, etc.) and different functional groups have been synthesized. Their antiviral activity against viruses such as herpes simplex virus (HSV-I, C 1), vaccinia virus (VV, B-51), influenza virus (A/FPV/Rostock/34 (H7N1)), respiratory synthicial virus (RSV, Long), vesicular stomatitis virus (VSV, Indiana), venesuel equine encephalitis virus (VEEV-230), picornavirus ECHO-6 and rotavirus SA-11 have been investigated in cell culture experiments. It was found the active adamantane and bornane derivatives contain hydrazine fragment, amino or amide groups. Some compounds are active against several viruses. Structure–activity relationship for tested compounds has been investigated.

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Pyrimidine Nucleosides Containing 5-Substituent: Synthesis and Antiviral Activity

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Recently, we have discovered an unusual anti-HSV activity of 5-arylethynylated deoxyuridines (**1**, $\mathbf{R^1}$ = OH, $\mathbf{R^2}$ = H) containing bulky aryl groups. It was shown that the activity observed could not be attributed to the well-known mechanism of action of common nucleoside antivirals.

In order to reveal the mechanism of action, we have synthesized a series of compounds **1** featuring further variation of nucleoside moiety (Fig. 1). Several compounds of type **2** containing a triazolyl linker were prepared as well. Noteworthily, a cycloaddition reaction leading to **2** is a simple and high-yielding process allowing for production of combinatorial libraries.

We have also prepared dimeric structures consisting of two nucleoside moieties joined with a linker attached to 5-position of pyrimidine.

The antiviral data for the compounds is either reported or under evaluation.

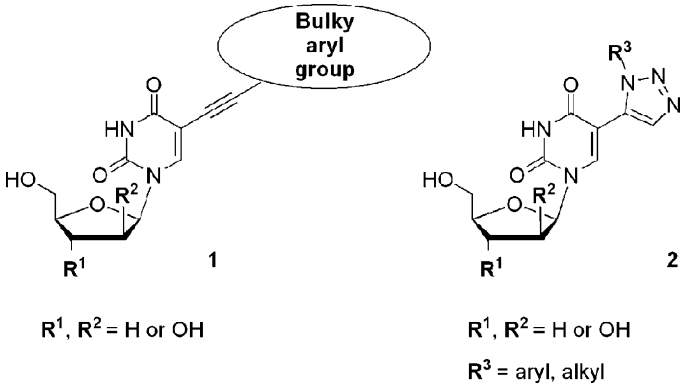

Fig. 1.

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