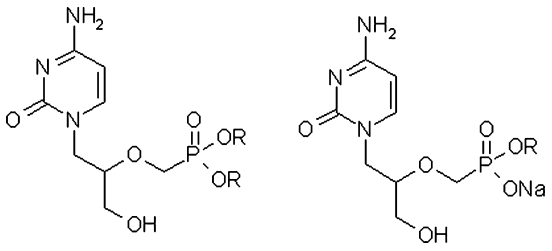

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137

The Activity of the New Adamantane Derivatives Against the Orthopoxviruses

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At present time the problem of development of drugs for prevention and treatment of orthopoxviral diseases becomes actual because the vaccination does not take place for a long time and there is a probability of arising of new centers of these infections, such as monkeypox in humans. Functional derivatives of cage compounds are as is known one of perspective substances for search of antiviral agents. During our investigation we have synthesized series of functional derivatives of adamantane: amides, hydrazones, hydroxy derivatives and wide range of adamantlyl substituted nitrogen containing heterocycles. Antiviral potency of synthesized compounds was evaluated against following orthopoxviruses: vaccinia, cowpox and mousepox in cell cultures (Vero, MK-2). More than 20 of synthesized compounds have showed very good antiviral action. Meanwhile, these substances have very low acute toxicity. Among them it is necessary to note adamantyl amides of p-bromobenzoic acid, which inhibits reproduction of orthopoxvirus in 2 mM concentration and adamantlyl disubstituted butanediol shows good potency against orthopoxvirus (IC_{50} = 2 mM). The presence of great number of high active compounds indicates some common principles of antiviral action of compounds, containing saturated cage moiety. Structures of compounds having activity against poxviruses allow supposing that their action occurs at the later stages of viral reproduction.

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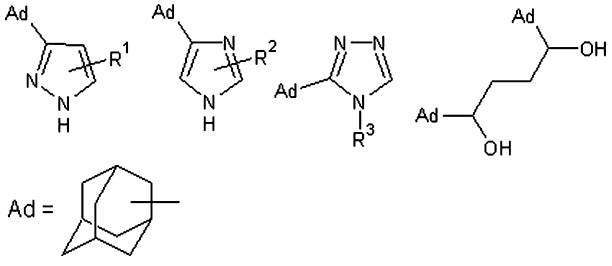

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138

The Influence of Combined Application of Interferon Inducers with Proteolysis Inhibitor on the Endogenic Interferon Level

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Increase of interferon formation intensity is the important problem for using its inducers as antivirals. We have supposed that one of the ways for the enhancement of antiviral efficacy of interferon inducers may be the prevention of hydrolysis of synthesized endogenic interferon by using proteolysis inhibitors. In our studies we used E-aminocaproic acid as a proteolysis inhibitor and amixin (tilorone) or SK-19 (which is a new phytoextract that we obtained) as interferon inducers. A noticeable increase of interferon level and prolongation of its circulation in the blood of experimental mice were established after the various schemes of combined application of interferon inducers and proteolysis inhibitors. E-aminocaproic acid has antiviral properties but it does not demonstrate interferon inducing activity. E-aminocaproic acid promoted the increase of interferon level in the blood of animals when used in 12 h after intraperitoneal injection of interferon inducer SK-19 in a dose of 40 mg/kg – in 16 times (from 80 to 1280 un/ml) and in 4 times (from 1280–2560 to 5120–10240 un/ml) when SK-19 was used in a dose of 60 mg/kg. A pique of interferon production in 24 h after per oral use of amixin in a dose of 200 mg/kg was from 640 to1280 un/ml. Combined application of this interferon inducer with E-aminocaproic acid (in 0.5–2 h after the use of amixin) stimulated interferon system more effectively and titers of serous interferon grew up to 2560–5120 un/ml. Also joint use of amixin and E-aminocaproic acid prolonged of interferon circulation: interferon was not detected in 48 h after amixin alone application and in case of its combination with E-ACA titers of serous interferon reached 20–40 un/ml. Higher antiviral efficacy of these schemes of combined application of SK-19 and amixin (tilorone) with proteolysis inhibitor E-aminocaproic acid than use of interferon inducers alone has been shown in the subsequent on experimental models of arboviral infections.

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139

Synthesis of Ester Prodrugs of 9-(S)-[3-Hydroxy-2-(phosphonomethoxy)propyl]-2,6-diaminopurine (HPMPDAP) as Anti-Poxvirus Agents

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Based on their in vitro activity and toxicity profile, (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]-2,6-diaminopurine (HPMPDAP) and its cyclic form (cHPMPDAP) were selected for further evaluation as potential drug candidates against poxviruses. To optimize potency and bioavailability of these compounds for therapeutic applications, synthesis of structurally