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N^6-benzyladenosine derivatives as inhibitors of human enterovirus replication EV-71

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Abstract

N^6-Substituted adenosine derivatives (cytokinin nucleosides) are an important class of biologically active compounds exhibiting a wide range of biological activity. It was found that a number of N^6-substituted adenosine derivatives exhibit antitumor, cytokinin, antiviral activities, activity against some protozoa that cause various infections. Also compounds with different physiological effects have been found. Recently, natural cytokinin nucleosides N^6-benzyladenosine (BAPR) and N^6-isopentenyl adenosine (IPR) were shown to be highly active against human enterovirus EV-71, but were quite cytotoxic. Based on these data, we have chosen BAPR as a lead compound for further optimization in order to find new nucleoside derivatives with high activity and low cell toxicity. We have obtained a series of new BAPR derivatives containing various substituents in the aromatic ring, and derivatives with different structure of the linker between the phenyl residue and the N^6-amino group of adenine. As a result of the optimization a number of synthesized compounds inhibit the replication of EV-71 in submicromolar concentrations and showed low cytotoxicity. It was shown that incorporation of fluorine and trifluoromethyl groups into aromatic residue significantly enhances antiviral activity. Monofluoro-substituted derivatives, despite the high activity, turned out to be cytotoxic, while the incorporation of the second fluorine atom led to significant improvement in selectivity. On the other hand, the presence of trifluoromethyl groups significantly increases activity and reduces cytotoxicity. As a result of the optimization, it was possible to increase the selectivity index by more than 250 times compared with BAPR.

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