Viroporins as a potential target of antiviral drugs based on pyrazine derivatives of amino acid esters

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Some highly pathogenic human viruses, such as influenza A virus, human immunodeficiency virus type 1, hepatitis C virus, modern coronaviruses, etc. produce proteins capable of forming ion-conducting pores in the membrane, namely, viroporins. They disrupt the ionic homeostasis of the target cell in favor of the virus to ensure proper replication and assembly of viral particles.

Pyrazine-2-carboxylic acid derivatives have found use as pharmaceutical molecules for the treatment of various diseases. The idea of the proposed work is to study antiviral compounds of pyrazine-2-carboxylic acid with amino acid esters similar to those that we obtained by condensation of aminoadamantane with amino acid and peptide residues. It is important to note that viroporins are an attractive and reliable target for the treatment of viral infections because ion channel activity is highly conserved and the virus is unlikely to become stable through mutational variability.

Derivatives of pyrazine-2-carboxylic acid with amino acid esters containing an aromatic and aliphatic side group were successfully synthesized (Ser-OMe, Thr-OMe, His-OMe, Trp-OMe). In biological experiments in vitro, the target compounds were used as complexes with iron(II) chloride formed in situ at the Fe : L = 1 : 2 ratio to give transparent colorless water solutions. Their antiviral activity against influenza A/H1N1 and SARS-CoV-2 viruses in vitro was studied. Using the MDCK cell culture, it was shown that only one of the presented amino acid derivatives with 2-pyrazinecarboxylic acid (namely, Trp-OMe) has the ability to suppress the replication of the pandemic strain of influenza A virus.

The cytotoxicity of the compounds was found to be about 190 mmol for a monolayer of Vero-E6 cells, and about 247 mmol for MDCK cells, i.e. these compounds are moderately toxic. The proposed method of attaching functional groups to molecules of heterocyclic carboxylic acids and creating chelated compounds based on these ligands makes it possible to obtain bioavailable forms of antiviral drugs. The proposed compounds of amino acids with heterocyclic carboxylic acids, due to their significant activity and low toxicity, can be considered a model for the creation of new antiviral drugs based on them. On the other hand, these compounds were found to have no antiviral properties against the modern strain of coronavirus SARS-CoV-2 in in vitro experiments.

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