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BIOTECHNOLOGICAL SYNTHESIS THE ANTIVIRAL DRUG RIBAVIRIN ANALOGUES MODIFIED ON THE AMIDE GROUP

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Abstract

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a well-known antiviral nucleoside. It has attracted interest for more than 40 years due to its unique spectrum of activity and still unclear mechanism of action. However, ribavirin has a high systemic toxicity and teratogenicity. Therefore, the search for new analogs of ribavirin with lower toxicity and high antiviral activity is still relevant.

Ribavirin analogs substituted at the C3 position of the heterocyclic in the carboxamide group were synthesized by the transglycosylation reaction with E. coli PNP.

The antiviral activity of nucleosides has been tested against herpes simplex virus type 1 (HSV-1) and influenza virus H5N1.

Ribavirin (1-β-Dribofuranosyl1,2,4-triazole-33-carboxamid, Virasole) is a modified nucleoside effective against a wide spectrum of DNA and RNA viruses. It demonstrates pronounced efficiency in treatment of hepatitis C and Lassa fever, as well as influenza of A and B types. Ribavirin, however, has serious side effects in the blood forming organs of patients: it causes hemolytic anemia. This fact motivates researchers to search for safer therapeutic drugs with less systemic toxicity. The chemo enzymatic (biotechnological) approach to the synthesis of ribavirin and its new analogues displaces the classic multistage chemical processes and allows carrying out the key reaction (transglycosylation) with high efficiency, region- and stereo-selectivity. Moreover, testing novel derivatives of 1,2,4-trizole as substrates of *E. coli* purine nucleoside phosphorylase (PNP) can reveal structural features of heterocyclic bases defining the potential for performing the reaction of the synthesis of modified nucleosides on their bases in the active site of the enzyme. This widens our view of the mechanism of the function and synthetic abilities of the enzyme.

N-cyclic aliphatic and aromatic 1,2,4-trizole carboxamides were found to be good substrates with the extent of conversion to the respective nucleosides up to 99 %. Ten ribavirin analogues were prepared after optimization of the conditions of enzymatic reactions (the most effective ribose donor was identified, the nucleoside/base ratio and the optimal amount of enzyme were determinate). A ribo- and 2-desoxyribo-nucleosides of N-substituted 1,2,4-triazole carboxamides were synthesized with a 30–90 % yield.

Unfortunately, this approach to the synthesis of nucleosides cannot be used in the synthesis of arabino- and 2-fluoroarabino- nucleosides of 1,2,4-trizole.

Investigation of antiviral activity of the synthesized compounds in the models of hepatitis C, herpes simplex virus type 2, type A and b flu viruses is currently being conducted in the National Research Centre for Epidemiology and Microbiology Named After the Honorary Academician N. F. Gamaleya.