Секция «Тезисы на английском языке»

Modeling of sulfonamide-based linkers for the design of bifunctional inhibitors of influenza virus neuraminidase

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Influenza is a serious problem, because it is associated with severe complications that are particularly dangerous for high-risk people groups [4]. Inhibitors of neuraminidase (zanamivir, oseltamivir), an important enzyme in the life cycle of the virus, are drugs with approved efficacy [2]. However, the high frequency of mutations leads to the influenza virus resistance, which creates demand for a search for new inhibitor classes. Detection of so-called 430-cavity in the neuraminidase structure [1] established the possibility of developing bifunctional inhibitors which simultaneously interact with the active site and above-mentioned cavity.

A crucial factor for the inhibitor binding in the neuraminidase active site is a carboxyl group and its interaction with the Arg371 amino acid residue. Required linker connecting structural fragments of a bifunctional inhibitor should provide the interaction with Arg371 and stable chemical bond between the fragments. In this work, the possibility of using a sulfonamide-based linkage between functional fragments has been studied by molecular modeling.

Using a molecular docking implementation in the Lead Finder software [3], virtual screening of sulfonamides was performed. Then, compounds were selected based on the ability of -SO_2-N= functional group to form hydrogen bonds with the Arg371 residue at the neuraminidase active site boundary, in the same manner as the carboxyl group. It was shown that the sulfonamide-based linker allows various functional fragments of diverse structure to bind to the neuraminidase active site and 430-cavity. These results demonstrate that proposed linker may be a universal component in the construction of bifunctional inhibitors out of various structural fragments.

As an example of bifunctional inhibitors, we obtained models of zanamivir derivatives containing -SO_2-NH-$(CH_2)_n$- linker, in which zanamivir (first functional fragment) is localized in the neuraminidase active site while the second, hydrophobic, fragment is localized in the 430-cavity.

Our study has demonstrated advantages of the use of sulfonamide-based linkers for the design of bifunctional neuraminidase inhibitors.

Источники и литература

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