Abstract

Computational methods are increasingly used in biomedical research, including toxicological research. They are used to search for new molecules for a particular pharmacological target or to optimize the properties of known active molecules. The main methods used in these areas are molecular docking and molecular dynamics.

New reactivators of butyrylcholinesterase inhibited by nerve agents were sought by methods of virtual screening. This reactivators would be applicable in prophylaxis and therapy of nerve agents poisonings. By combining the techniques of semi-flexible and flexible docking, two new structures were proposed that should specifically reactivate the inhibited butyrylcholinesterase.

In addition, a virtual screening of cyclophilin D inhibitors was performed. These compounds could be used as drugs for Alzheimer's disease. Based on the availability of a huge number of crystallographic data, we decided to use a pharmacophore for the primary screening of a large database of small molecules. Molecular docking was employed in the second search phase. At the same time, we focused on the physicochemical properties of molecules. Four ligands have been found that should be inhibitors of cyclophilin D bioavailable in the central nervous system.

Flexible molecular docking was used to optimize the properties of known molecules and describe their binding to enzyme targets. The binding of small molecules to acetylcholinesterase and butyrylcholinesterase, which are very important pharmacological and toxicological targets, was investigated. Mainly, ligands with inhibitory effect on these enzymes, which could become drugs of Alzheimer's disease, were studied. Molecular docking results described the binding poses of individual compounds. This information allows further modifications of the structures related to increasing the affinity to target proteins.

Relatively new use of computational methods is searching of biological targets for a given small molecule, respectively for a serie of small molecules. A methodology for reverse screening based on semi-flexible molecular docking was designed and implemented. With this methodology, we can test given series of molecules against a library of about 9,000 protein targets within a short time. Human monoaminooxidase B, tyrosine-protein kinase and prokaryotic nicotinate-nucleotide adenylyltransferase

were predicted as targets of the selected frentizole derivates. For the quinazolin-4-one derivates group, targeting of poly(ADP-ribose) polymerase 1 was predicted, thereby plausibly explaining their anti-tumor activity.

Molecular dynamics methods were used to study nerve agents, where the main goal of the project was focused on the parameterization of these molecules and their anchoring to serine.

Key words: computational chemistry, molecular modelling, molecular docking, molecular dynamics, protein, ligand, toxin