ABSTRACT

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Title of Doctoral Thesis: *In silico* studies of cholinesterases interactions with their modulators and design of new compounds of this type

Computer modeling is an important tool of contemporary scientific research. It allows to study the structure, conformation, dynamics and mutual interaction of nonbinding interactions of a biological system. The main objective is to find the best energy conformations by minimizing the energy of the system. On the base of these calculated values, one can predict the loss of activity for certain analogous compounds, thus reducing the number of materials that would be needed to subsequently synthesize. A molecular modeling contributes to describe the interactions of ligands with larger systems and improves the orientation in millions of active substances that could be used as potential drug. It becomes an important part of the pharmaceutical industry.

The aim of this study was to verify the selected methodology of computer prediction of protein-ligand complexes, to obtain a description of the basic interactions of the modulators of cholinesterase enzymes by molecular modeling, and on the basis of this knowledge to design the structure of a new potent inhibitor of acetylcholinesterase. For the *in silico* testing, the modulators synthesized in the present thesis and in the previous diploma thesis, compounds prepared by students in collaboration with the Department of Pharmaceutical Chemistry Pharmaceutical and Pharmaceutical analysis, Faculty of Charles University and the Department of Toxicology, Faculty of Military Health Sciences, University of Defence, and also widely used acetylcholinesterase modulators were used.

The method validation was performed at several crystal structures. The obtained results were used to describe the relationships between the basic structure and a manner of interaction and the affinity for the enzyme. According to endpoints some several potential inhibitors of acetylcholinesterase were obtained. Their interaction with the enzyme was described and their physical characteristics were calculated, too. These substances can be used in the prophylaxis of nerve agent poisoning or treating Alzheimer's disease or myasthenia gravis. The results were published in scientific journals and presented as posters at scientific conferences in Czech Republic and abroad.