ABSTRACT

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Title of Doctoral Thesis **The relationship between structure and activity of potential modulators of acetylcholinesterase**

The Ph. D. thesis is focused on finding structure activity relationships for the acetylcholinesterase activity modulating compounds. Standard in vitro test using rat brain homogenate as the source of acetylcholinesterase was chosen for enzyme activity assay. Later, the procedure employing the colorimetric approach according to Ellman was developed. New procedure for inhibitory efficacy assessment based on Ellman's method was designed as well.

Aldoxime reactivators are mainly used as the causal antidotes of organophosphorus compounds intoxications. Organophosphorus compounds are widely used for agricultural purposes as pesticides, and in the industry as a plasticizers or flame retardants. Beside the peaceful purposes, they were also developed as nerve agents applicable for chemical warfare. Toxic mechanism of the compounds is formation of covalent bond with serine (Ser203) hydroxyl in active site of acetylcholinesterase. Unfortunately, none of the currently used reactivators is able to reactivate acetylcholinesterase inhibited by variety of organophosphorus compounds.

Screening of several series of bisquaternary reactivators was performed, and the results were compared to the known reactivators. SAR of the tested reactivators against various inhibitors were proposed.

Reversible AChE inhibitors are known as a treatment of several disorders such as mysthenia gravis and Alzheimer disease.

Several series of bisquaternary inhibitors and tetrahydroacridine based inhibitors were assessed. The IC50 results for human acetylcholinesterase and butyrylcholinesterase were compared to the known inhibitors, and the SAR studies were performed accordingly.