ABSTRACT

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Title of diploma thesis: Assessment of pharmacological properties of new potencial drugs for Alzheimer's disease treatment

Alzheimer's disease is a neurodegenerative disease with a progressive and irreversible course. The cause of AD is still not exactly known. There are currently four drugs available that have been approved by the State Institute for Drug Control. Three of them act as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the fourth one as a N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). Unfortunately, these drugs do not affect the course of the disease and provide only temporary symptomatic relief. An important area of current research is MTDLs (Multi-Target Directed Ligands), which act on multiple target structures related to the pathophysiology of the disease. These agents represent a promising therapeutic strategy.

The aim of the study was to measure the ability to inhibit human acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of 58 new potential MTDLs derived from biphenyl and benzhydryl using Ellman´s method, as well as spectrophotometric determination of pK_a as an important property of drugs for selected compounds. The results of all measurements were evaluated in the statistical program GraphPad Prism6.

None of the tested compounds in concentration 10^{-6} M was able to inhibit human AChE and BuChE more than 20 %. The pKa values ranged from 7.41 to more than 12. Thus, pK_a of several compounds is suitable for distribution to the central nervous system and action on cholinesterases and NMDA receptors. Even though the tested substances had very low inhibitory abilities for AChE and BuChE activity, they should not be discarded from further testing. The second target of their action is NMDA receptors, where their antagonistic effect has been confirmed.

Key words: acetylcholinesterase, butyrcholinesterase, pKa, inhibition, Alzheimer´s disease