ABSTRACT

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Title of thesis: Determination of pharmacokinetic properties of potential drugs for the treatment of Alzheimer´s disease

Alzheimer´s disease (AD) is an illness caused by neurodegenerative changes in the brain tissue. It belongs to the diseases that lead to the origin of dementia. The occurrence of this illness has been rising over past years. Unfortunately, the causative treatment has not been found yet and the only available treatment is the symptomatic one. Therefore, it is necessary strive towards the discovery new and more efficient drugs.

The aim of this thesis is to determinate the inhibiting concentrations and to measure the antioxidative activity of the new synthetic potential anti-Alzheimer drugs. Seven hybrids of 6 – chlorotacrine – tryptophan (6-Cl-THA-Trp), 7 – methoxytacrine – tryptophan (7-MEOTA-Trp) and tacrine – tryptophan (THA-Trp) were tested. The *in vitro* inhibiting potentials of the tested compounds against human acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) were evaluated. Spectrophotometer was used for the measurements by Ellman´s method. The antioxidative activity was evaluated via DPPH assay. Based on the results obtained, it was analyzed if designed compounds are more effective than the standard ones and if the compounds were the proper multitarget-directed ligands (MTDL).

The results showed that the inhibiting activity is influenced by the substitution of the chlorine atom at the tacrine (THA) in the 6^{th} position. It has led to the better inhibition and selectivity to AChE. The substitution by methoxy group of THA at the 7^{th} position has lowered the inhibiting activity against cholinesterases. The tether length between the two

pharmacophores has influenced the inhibiting activity. The optimal tether length for the BChE inhibition has been six methylene groups, while for the AChE inhibition the tether length from five to eight methylene groups was optimal. Non of the tested compounds has shown higher antioxidative activity than standards N-acetylcysteine (NAC) and trolox. Only one of the compounds, the K1024, has shown the antioxidative activity at hundreds micromolar range.

The best candidate for the further testing and the potential AD drug was K1035. It exhibited the highest AChE inhibiting activity (IC_{50}= 11,28 nM), inhibited BChE (IC_{50}= 36,06 nM) and showed measurable antioxidative activity (EC_{50}= 2277 μM).

Key words: acetylcholinesterase, butyrylcholinesterase, acetycholinesterase inhibitors, multitarget-directed ligands