ABSTRACT

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Title of diploma thesis: A comparison of tacrine – phenothiazine derivatives in the efficacy of cholinesterase inhibition

Alzheimer's disease (AD) is a progressive fatal neurodegenerative disorder and the most common type of dementia. It is manifested by a variety of neuropsychiatric symptoms such as memory loss, social skills etc. Ethiology and pathogenesis of the disease has a multifactorial character and is not well known. Among the major pathological features belong: presence of neuronal loss, especially loss of cholinergic neurons, extracellular amyloid plaques, intracellular aggregates of hyperphosphorylated tau protein, oxidative stress etc. As AD is influenced by multiple factors, the main strategy in treatment is intervention multiple targets in the brain as well. Such drugs are denoted as multi-target-directed ligands (MTDLs) and they affect different molecular abnormalities of AD.

The aim of this diploma thesis was the evaluation of the ability of tacrine-phenothiazine derivatives to inhibit cholinesterases (AChE, BChE). Derivatives with two to five carbons linking chains between tacrine and phenothiazine moiety, which containing various substituents were tested.

The 36 structurally different derivatives of acetylcholinesterase and butyrylcholinesterase inhibitors were used for this study. The inhibitory activity of the compounds was determined *in vitro* by the Ellman's method. A concentration range of all inhibitors was established. The concentration of inhibitors solution started at a concentration 10^{-3} and finished at a concentration of $10^{-8.5}$ mol/l. The

all necessary components of the reaction were mixed and resulting yellow coloration of the solution was measured spectrophotometrically. The inhibitory concentrations were calculated from the obtained values.

The structural dependencies were confirmed comparing inhibitory concentrations. The compounds containing the chlorine atom at position 6 showed the best inhibitory activity of all tested compounds. The influence of the length of the linker chain was insignificant.

Keywords: acetylcholinesterase, butyrylcholinesterase, Alzheimer´s disease, inhibitor, tacrine, phenothiazine