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Title of Diploma Thesis: Tacrine-Benzothiazole Derivatives in Alzheimer's Disease Therapy

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, visuospatial deficits etc. Ethiology of the disease has a multifactorial character and is not well known. Among the major pathological features belong: presence of extracellular amyloid plaques, intracellular aggregates of hyperphosphorylated tau protein and neuronal loss, especially loss of cholinergic neurons. Also the oxidative stress of the neuronal cells contributes to the pathophysiology of the disease. As AD is influenced by multiple factors, the main strategy in treatment is hitting 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. Within this work, we would like to bring out new tacrine - benzothiazole hybrids combining tacrine with the amino benzothiazole moiety. Linkers of different lenghts were used to connect these two scaffolds. Tacrine was the first drug approved for AD treatment by FDA. Its mechanism of action is based on inhibition of cholinesterases and thereby increasing the level of synaptic acetylcholine. On the other hand, benzothiazole, as a planar molecule, could prevent the protein-protein interactions and thus it could exhibit potential anti-amyloid effect. Moreover, benzothiazole moiety represents a core scaffold of inhibitors of amyloid-binding alcohol dehydrogenase (ABAD). ABAD is a mitochondrial enzyme that contributes to oxidative stress in AD progression. Therefore, its inhibition could avoid ROS production and act neuroprotectively. Based on the above-mentioned facts, molecules bearing tacrine and benzothiazole skeleton could become promising drug candidates in AD therapy. Nevertheless, just *in vitro* and *in vivo* evaluation of biological activity will reveal their real value in the field of Alzheimer's disease. This work

includes synthesis of new compounds and their *in vitro* evaluation of acetylcholinesterase and butyrylcholinesterase inhibition. They exerted bio-activity in micromolar and nanomolar concentration.