ABSTRACT

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Title of Thesis: Propargyltacrines – acetylcholinesterase inhibitors with anti-MAO activity

Alzheimer´s disease (AD) is a serious neurodegenerative disorder that affects mainly aged people. Neurodegenerative disorders lead to dementia. However, dementia is not a part of normal aging. It is the result of pathologigal process. Alois Alzheimer was the first who described AD. The causes of this disease are not clear, however partial pathological mechanisms and the risk factors are known. There is no drug for casual treatment of AD. Nowadays, we can only slow down the symptoms or development of dementia by combining pharmacological and non-pharmacological techniques. Such approach could improve the quality of life of affected people.

The treatment of AD involves acetylcholinesterase (AChE) inhibitors and *N*-methyl-D-aspartate receptor antagonist (NMDA). Donepezil, rivastigmine and galantamine belong to AChE inhibitors. Decrease in AChE activity leads to balance in acetylcholine transmission, which is disturbed in early stages of the disease. Tacrine was the first drug launched on the market for the treatment of Alzheimer´s disease. However, a few years later it was withdrawn due to the side effects, especially hepatotoxicity. Tacrine is easily available, so it has become a key scaffold used in anti-AD drugs development, especially in the form of hybrids or multi-target-directed ligands (MTDLs).

An oxidative stress can evolve from various pathological processes and can damage the neurons. The change of mood and depression also belong to the symptoms of the AD in later stages. It is believed, that the products of amine oxidation (aldehydes, hydrogen peroxide etc.) are the causes of oxidative stress. So, the inhibition of monoamine oxidase (MAO) that catalyzes amine oxidation could relieve from the symptoms like depression and overall oxidative damage of nerve cells.

By using MTDLs design strategy with-in my work, I have focused on the synthesis of new molecules combining the tacrine moiety and propargylamine scaffold of selegiline (commercially available MAO inhibitor). Potentially, these compounds should inhibit both enzymes, AChE and MAO, ensuring thus sufficient concentration of neuromediators (acetylcholine and catecholamines) for proper cholinergic and monoaminergic neuro-transmission.