To the diseases of civilization next to cardiovascular diseases, cancer, and neurodegenerative diseases belongs dementia, which is characterized by a general cognitive impairment. One of the most common form of dementia is Alzheimer's disease (AD), resulting in degenerative changes in the brain. AD often occurs in the elderly people over 65 years of age and is one of the biggest burdens for both a patient and a society. It is estimated that currently AD affects more than 35 million people worldwide, and the frequency of the disease is increasing. Although AD has been known for over 100 years, it is still an incurable disease, as currently used drugs only slow a progression of the disease, but do not cause a withdrawal or stop of its development. Etiology of this disease is complex and many factors can influence its course and development. In a microscopic image of the brain of patients characteristic is the presence of extracellular amyloid plaques, composed of beta-amyloid aggregates and the intracellular neurofibrillary tangles, resulting from hyperphosphorylated forms of tau protein. It is known that AD is accompanied by changes in many neurotransmitter systems, however, the loss of cognitive function in patients with AD is mainly related to the constant and progressive damage of cholinergic transduction in the brain and lowering the levels of acetylcholine. Therefore, drugs restoring the cholinergic functions are beneficial for the slowing of the disease.

Purpose of this study is to design and synthesize novel compounds which, acting simultaneously on different biological targets will lead to increased acetylcholine levels in the brain. Selected biological targets are histamine H_3 receptors (H_3Rs), acetyl- and/or butyrylcholinesterase (AChE/BuChE) and monoamine oxidase B (MAO B). While in the literature there are known examples of double ligands, i.e. active histamine H_3Rs ligands and at the same time potent inhibitors of cholinesterases, compounds having concurrent activity of histamine H_3Rs and inhibiting MAO B have not yet been described.

Histamine H_3Rs are predominantly found in the central nervous system, where they inhibit release of certain neurotransmitters including acetylcholine. Moreover, the preclinical and clinical studies confirm the efficacy of certain ligands of these receptors in the treatment of cognitive dysfunction associated with neurodegenerative disorders. Acetyl- (AChE) and butyrylcholinesterase (BuChE) are enzymes which hydrolyze acetylcholine. In the brain of healthy humans dominates AChE and BuChE activity is small, but with the development of AD, and with age, the level of AChE in the various regions of the brain decreases and BuChE levels increase gradually. Three of the four drugs currently used in the treatment of AD are AChE inhibitors. Another enzyme, which enhanced activity has been observed in patients with AD, is MAO-B. This enzyme, in the central nervous system, is involved not only in regulating the level of neurotransmitters (such as dopamine, serotonine), but also in the processes leading to damage of nerve cells in the cholinergic neurons. Studies have also shown that both the cholinesterase and MAO have an effect on the formation of amyloid plaques and neurofibrillary tangles characteristic of AD.

The innovative nature of the project is to try to develop multifunctional compounds that acting on several targets simultaneously might affect several factors causing the disease, and increase the chance of a cure. The proposed strategy implies that a significant improvement of cholinergic transmission in the brain of AD patients will be possible through the use of one drug instead of a few, what undoubtedly reduces the number of side effects or interactions between different used drugs.

In the project it is planned: computer-aided design of new compounds, synthesis of designed compounds and biological studies with obtained derivatives. Performed the analysis of interactions of the planned compounds with the selected biological targets (H_3R, AChE, BuChE and MAO-B) and estimation in silico of their physicochemical properties will allow to select potential multifunctional compounds, which then will be obtained by methods of organic synthesis. The activity of the newly synthesized compounds will be determined *in vitro* (histamine H_3R affinity, inhibition of AChE, BuChE and MAO-B) and for the most active compounds (3-5) also in *in vivo* studies.

The expected result of this project will be new triple-ligands, which acting on the different molecular targets will improve the cholinergic cognitive function in animals. We hope that our findings will contribute to the search for new and effective methods of treating, inhibiting or even preventing Alzheimer's disease.