New multifunctional drug-like ligands focusing on molecular targets associated with the symptoms and causes of Alzheimer's disease

Everybody has ever forgotten something. For some of us, forgetting is something more. It becomes an everyday life, a disease you have to deal with each day. The Alzheimer's disease is just such a disorder. It is a progressive and chronic neurodegenerative disease in which nerve cells are dying and unable to function properly. It is the most common type of dementia that currently affects approximately 34 million people. Mainly they are people over 65 years of age. Unfortunately, due to the population ageing, this number is constantly growing. It is estimated that in every 3 seconds one patient is diagnosed with dementia and 2/3 of cases are patients with Alzheimer's disease. The global worldwide cost of dementia in 2018 was about was US$ 1 trillion. All these figures show that Alzheimer's disease can be considered as one of the main health, social and economic problems that we have to face nowadays. Although more than 100 years have passed since Alois Alzheimer described the first case of this disease, we still do not know what the exact causes and pathomechanism are. This disorder remains incurable and moreover, the available pharmacotherapy with 4 drugs can only temporarily alleviate the symptoms of the disease. There are some theories that scientists try to explain the complex nature of the disease. At the moment, many biological targets associated with it have been identified, but we do not know which ones are primary. There are also ongoing researches for an effective drug. Unfortunately, since 2003 no substance has managed to pass through the third phase of clinical trials and has been marketed. Finding a drug that can not only alleviate symptoms but modify the course of the disease thus becomes one of the crucial challenges of medical chemistry, which I decided to face.

Looking for new bioactive compounds I decided to rely on the strategy of multi-target-directed ligands (MTDL). The MTDL is a compound acting on more than one biological target. This approach seems to be a rational solution in a disease with such a complex and multifactorial pathomechanism as Alzheimer's disease. Previously promising preliminary results have encouraged me to design a series of new multifunctional inhibitors targeting butyrylcholinesterase (BuChE) and aggregation of tau protein and β-amyloid (Aβ) peptide. The first selected target is BuChE - an enzyme that degrades the neurotransmitter acetylcholine, responsible for memory processes. The activity of this enzyme increases during the disease’s progression, and its inhibition will help to impair the symptoms. The second one is tau protein. This protein is present mostly in nerve cells and is associated with microtubules. Its normal function is a stabilization of the microtubules. Under pathological condition it undergoes the phosphorylation and aggregation, creating neurofibrillary tangles. The last one is Aβ peptide which during AD progression aggregate and form extracellular deposits. These, together with neurofibrillary tangles, are the two main hallmarks in the brain of person with Alzheimer’s disease. Their formation is considered as primary causes of the disorder’s development. The synergistic effect of their inhibition can be beneficial and increase the effectiveness of the therapy. Moreover, the basic physicochemical properties for all designed derivatives were estimated using computer programs. I selected for synthesis only these compounds which fulfill well-known drug-like rules. This is an innovative approach providing that the obtained compounds will have a chance to get to preclinical studies and in the long term may be a drug candidate. The first step of my research project is the synthesis of designed derivatives using traditional and modern methods of organic synthesis. Then, I will examine the biological activity against selected biological targets *in vitro* (using biochemical tests). Finally, I will analyze all obtained results. I will try to find the relationship between the structure and activity of the synthetized compounds and select the most promising compound for further extended pharmacological research.