Synthesis and biological evaluation of novel, drug-like multifunctional ligands, as potential anti-Alzheimer's agents targeting cholinesterases and beta-secretase.

In 1906 Dr. Alois Alzheimer first described "disease of forgetting", studying a case of Auguste Dieter, 56 year old patient. This disorder refers especially to elderly patients and is primarily an important problem for developed countries in Europe and North America. The number of patients is estimated at about 36 million worldwide and continues to grow vigorously. The most pessimistic forecasts estimate that in the absence of significant progress in the treatment of Alzheimer's disease this number may even increase tripled by 2050. People with Alzheimer's disease are primarily the elderly, 84% of them are patients aged over 74 years old. Alzheimer's disease is becoming one of the most serious social and economic problems especially for developed countries. Currently, there are only four drugs which act symptomatic and possess limited effectiveness. These drugs don't cure the disease but only delay the progression of symptoms. In spite of many efforts Alzheimer's disease treatment remains one of the biggest gaps in current pharmacotherapy. An effective treatment for fighting the cause of the disease could give a chance to reverse the pessimistic, epidemiological forecasts. In this context, Alzheimer's disease is becoming one of the most important challenges of modern pharmacotherapy and science. Such a challenge we have taken, and this project is an important part of this.

The problem of Alzheimer's disease is extremely complex, and not only metaphorically but also literally, and in addition, there are still many unknowns. The state of art about the disease resembles stacking multipart jigsaw puzzle, when we have a lot of individual fragments and we still have to connect them. The similar to this is state of art in case of Alzheimer's disease: we know a lot of mechanisms, but we don't know for sure how they are connected and what is the relationship between them. For this reason since the beginning of recognition of Alzheimer's disease, a number of hypotheses and theories trying to explain the causes of this disease were created. Currently, the most recognized among them, with solid evidence is the theory of the creation of senile plaques consisting on β-amyloid peptide. It says, that between neurons of patient's brain deposits of β-amyloid occur, which is formed from amyloid precursor protein. The presence of such structures also known as senile plaques is a negative phenomenon. Deposits of β-amyloid in themselves are neurotoxic and also activate another, additional adverse mechanisms. The first effect of β-amyloid accumulation is an activation of immune cells (astrocytes, macrophages) and associated with it production of free radicals (oxidations stress). β-amyloid protein can also initiate mitochondrial dysfunction, apoptosis and calcium imbalance. The key enzyme for pathological amyloidogenic transformation of amyloid precursor protein is enzyme β-secretase. Proteolysis of β-amyloid precursor protein catalysed by β-secretase initiates further abnormal processes and pathomechanisms leading to the disease. Overarching objective for a modern pharmacotherapy of Alzheimer's disease, seems to be an inhibition of β-amyloid formation and accumulation. On the other hand we know, that before the first symptoms appear, a lot of neurons have been destroyed. Due to this fact even effective casual treatment doesn't guarantee a rapid and efficient removal of symptoms. Faced with such a dilemma, fortunately we do not have to choose, we can create a compound, that will treat simultaneously the causes and symptoms of the disease. Such compounds, which act at least two, independent biological targets, we called multitarget directed ligands and they are particularly useful for diseases with complex etiopathogenesis. Such is precisely the Alzheimer's disease. As the second biological target I chose cholinesterases. Currently used drugs act as inhibitors of acetyl- and/or butyrylcholinesterase, so their role is quiet well known and understood. By combining two activities: inhibition of cholinesterases and β-secreatase I would like to create a compound, that will have a chance to get to pre-clinical studies and in the long term may be a drug candidate.

Design of new compounds was based on previously obtained compounds. Among them I chose one, which possess the ability to inhibit butyrylcholinesterase and β-secretase. Additionally I estimated the basic physicochemical parameters, characteristic for drug-like compounds using suitable computer programs. I used the results of these studies to select the best compounds for synthesis. The first step of project will be chemical synthesis of designed compounds by using both traditional organic synthetic methods as well as unconventional such as microwave assistant organic chemistry. The obtained compounds will be tested in vitro to evaluate abilities to inhibit enzymes: β-secretase, cholinesterases and aggregation of β-amyloid. Collected data will be analyzed to find structure-activity relationship. When all the data will be known, the most active compounds, with drug-like properties will be selected for further studies.