The civilization progress in the developed countries lead to the increase of life expectancy in these countries. However, as the population ages, new problems arise, especially these related to the number of people affected by age-related diseases, like various forms of dementia. The most common form of dementia is Alzheimer's disease, in which the death of brain cells causes memory loss and impairment of other important cognitive functions. Although the disease was first described more than a century ago by Dr. Alois Alzheimer, from whom it takes its name, many aspects of its formation and development remain unsolved. The exact cause of Alzheimer's is unknown and the disease is still incurable.

Research planned in this project is related to the search for new, original compounds with biological properties useful in treatment of memory loss and disturbance of cognitive functions. It is known that changes observed in Alzheimer's disease are a progressive and complex process, which impairs proper functioning of neurons in the brain regions related to cognitive functions and results in dementia.

Two major pathological changes observed in the brain of patients with Alzheimer's disease are tiny inclusions (aggregates) in the nervous tissue, called plaques and tangles. Plaques, often called senile plaques, are found between dying nerve cells in the brain and are deposits of β-amyloid peptide. The tangles lie within the nerve cells and are the result of disintegration of another protein, called tau. The formation of both aggregates is a complex process which leads to the damage of nerve cells. In the brain, β-amyloid peptide is formed from its precursor, through cutting of larger protein by a group of enzymes called secretases. The function of secretases resembles the function of scissors. Under pathological conditions, β-amyloid is formed by the enzyme called β-secretase. Inhibition of activity of this enzyme could therefore reduce Aβ production. Due to the causative role of β-amyloid and tau protein aggregates in the Alzheimer's disease, inhibition of their aggregation could stop a development of the disease.

The general aim of the project is to design and obtain novel, original, organic compounds that lower the production of β-amyloid by inhibiting β-secretase as well as inhibit the aggregation of neurotoxic β-amyloid peptide and tau protein, and therefore ameliorate memory and cognitive processes.

Since Alzheimer's disease is a complex, multifactorial disorder, we decided to apply multi-target approach to design new compounds. This approach assumes that instead of using cocktail drugs, composed of two or more drugs, one can create a single, new chemical molecule which structure will be able to interact /interfere simultaneously with several impaired mechanisms associated with disease.

Our research proposal represents an interdisciplinary project including: computer methods, chemical synthesis and biochemical and pharmacological tests. With the use of special computer programs and known crystal structures of the enzyme we will design structures of new potential β-secretase inhibitors. Computer-aided simulations called molecular modelling will be also used for studies of interactions between β-amyloid and selected inhibitors, for design potential tau protein inhibitors as well as for estimation of physicochemical properties of designed molecules.

New designed compounds will be obtained with the use of general methods of organic synthesis and then will be tested by applying appropriate biological assays. Their inhibitory activity against enzyme β-secretase and anti-aggregating properties against β-amyloid and tau protein will be determined. As a result of these studies, several compounds will be selected for further studies. These include testing the ability of compounds to protect neurons (neuroprotective activity), estimation of possible toxicity on cells and the prediction of blood-brain barrier penetration. Subsequently, for two selected, most potent compounds pharmacological evaluation in mice will be performed including learning and memory tests and general behavior studies.

As the outcome of the project, we are expecting to obtain novel, original, multifunctional molecules that are able to inhibit β-amyloid production and are endowed with anti-aggregating properties against β-amyloid peptide and tau protein, and with potential beneficial effects on memory in mice.

The studies focused on a search for new compounds addressing Alzheimer's disease pathomechanisms has been initiated in our research group a few years ago. At the beginning our research focused on creating compounds for symptomatic therapies. The presented project proposes obtaining of new multifunctional molecules with biological properties essential for the causal treatment of Alzheimer's disease.

Creation of structures of new molecules from small fragments responsible for an appropriate property is like connecting three-dimensional puzzles into a proper figure. The design of multifunctional drug is a new, exciting area for medicinal chemists, particularly for those searching for drugs against complex diseases. In our opinion it is a fascinating research topic and results of these studies can be useful for further development of anti-Alzheimer's therapy, which is among the most urgent medical needs.