Despite significant advances in medicine in recent decades, both in the field of diagnosis and pharmacotherapy, many diseases remain incurable. One of such diseases is Alzheimer's disease (AD), in which irreversible changes in the brain lead to a progressive loss of memory, cognition and behavioural changes. Currently about 36 million people worldwide suffer from AD, and due to the aging of the population this number is growing and it is estimated that over the next thirty years it will triple. Therefore, intensive search for new effective therapies for this disease is needed.

Drug discovery is a long process that begins with a selection of a biological target for a drug. In case of Alzheimer's disease the choice is not that simple, because there are a number of its possible causes, and therefore many potential biological targets, and it is hard to say, which one is the most important. The complex nature of Alzheimer's disease has inspired many researchers to look for new drugs that improve cognition and memory (i.e. procognitive drugs) among the so-called multi-target-directed ligands (MTDLs). MTDLs are compounds designed to interact simultaneously with several biological targets and produce multidirectional therapeutic effect. The way to obtain such a multifunctional drug is particularly challenging, but its use is much more convenient and safer than taking several drugs at the same time.

**The aim of this project is the synthesis and pharmacological evaluation of new multi-target-directed ligands with potential procognitive activity.**

The MTDLs proposed in this project combine the activity of conventional drugs used in Alzheimer's disease - cholinesterase inhibition - with a new mechanism, which is blockade of serotonin 5-HT6 receptors. The cooperation of these two mechanisms can result in a positive influence on memory and cognitive functions, while the blockade of the 5-HT6 receptor may also alleviate some of the psychological symptoms associated with Alzheimer's disease.

The specific structures of the compounds will be designed based on the results of our previous studies. This process will be supported by computer modelling, which with a certain probability can predict various properties of compounds, including biological activity and toxicity. The designed structures will be obtained by chemical synthesis in our laboratory. The next step will be the evaluation of the obtained compounds in various laboratory (*in vitro*) tests in order to assess how the compounds interact with various biological targets, their physicochemical properties and toxicity, as well as whether they are able to cross the blood-brain barrier and reach their site of action. The next stage will be the *in vivo* evaluation. Animal testing is a necessary step in search for new drugs, but we make every effort to minimize the number of animals used in these studies and only the most promising compounds are admitted to this stage. Three most active compounds will be selected and their procognitive and antidepressant activity will be evaluated in specific tests in rodents.

Although the direct objective of this project is development of science, its results may help in determining new directions in the search for compounds with procognitive activity, and in the long term may contribute to finding effective treatment of Alzheimer's disease.