Towards innovative strategy for treatment of Alzheimer's Disease *via* dual inhibition of receptor 5-HT_6 and kinase CDK5.

Central nervous system (CNS) disorders, such as dementia and Alzheimer's disease (AD), occupy a significant place among civilization diseases. They are becoming a growing problem in our society due to the ever-increasing frequency of occurrence and the lack of access to effective therapies. A neurodegenerative disease with a complex etiology, which is Alzheimer's disease, is the most common memory dysfunction that particularly affects the elderly. These disorders are caused by the malfunctioning of proteins responsible for signal transmission in the body, mainly within the brain. So far, various protein targets have been classified that may be involved in AD therapy. These include serotonin receptors, consisting of 7 main classes. Among them is the 5-HT_6 receptor, which as one of the latest proteins discovered in this group, is a challenge for medicinal science. So far, its significant role in civilization diseases, i.e. depression, dementia, schizophrenia, or obesity has been confirmed. The 5-HT_6 receptor is a very important research goal in the future therapy of the above-mentioned diseases. It is worth adding that among the various chemical compounds acting on the 5-HT_6 receptor, none have yet been approved as a medicine, and most failed in clinical trials as being effective in laboratory rats, but not in people.

The second very important aspect in the treatment of AD is the inhibition of an enzyme, named CDK5 (cyclin-dependent kinase 5), which is involved in the neuroprotection, thus playing a very important role in the processes of the nervous system. Many examples of compounds that inhibit CDK5 are known in the literature, but also none of them has become a drug yet.

An invention of a molecule that simultaneously inhibits the action of CDK5 and the receptor 5-HT_6R, and also is well absorbed, stable and safe for the human body, is a great hope for finding a new effective medicine against AD disease.

Our previous research has led to the identification of a completely new structurally chemical group of triazines, interacting with the 5-HT_6 receptor. Other research teams described chemical molecules containing the triazine or triazine-like fragments that were act as the inhibitors of CDK5. Therefore, the goal of this project is to design and synthesize new molecules containing triazine fragments, which act on both, serotonin receptor 5-HT_6 and CDK5, thus being promising in search for new therapy of AD. Molecular modeling techniques will be applied to design the new molecules, followed by chemical synthesis to obtain them in laboratory. Biological tests *in vitro* will allow to assess their pharmacological action on the both targets (5-HT_6, CDK5) as well as the initial ability to be safe, absorbed and stable in the human body, so called „drug-likeness". Results of the studies will allow to select the most active and „drug-like" molecules for further studies in animals in the close future.

This project is important for the development of global AD's therapy due to its innovative approach, combining two key-points for AD therapy, which so far have been considered separately but not together. We believe that the planned research will significantly contribute to the discovery of an innovative drug that will go to the pharmaceutical market, improving the quality of life of people affected by Alzheimer's disease.