New multiple target-directed ligands - A_1/A_{2A} adenosine receptors antagonists and monoamine oxidase B inhibitors - searching for innovative therapeutic approaches for the neurodegenerative diseases.

The global phenomenon of human population aging and extending life expectancy are observed for many years. As a consequence, the proportion of older people grows significantly and thus - incidence of neurodegenerative disorders. Parkinson's disease is second common neurodegenerative disorder after Alzheimer disease and usually relates to patients after 50 years of age. The main symptoms of Parkinson's disease are associated with movement impairment such as bradykinesia, resting tremor and muscular rigidity. The increasing intensity of symptoms accompanies the chronic progression of the disease, leading to a significant reduction of quality of life. Unfortunately, the current therapy of neurodegenerative diseases often proves to be insufficient for the full control of symptoms. Furthermore, polypharmacotherapy is necessary in the advanced stages of the disease, what results in increased risk of serious side effects. Therefore, the adequate treatment of patient with Parkinson's disease is an important challenge for pharmaceutical science. The new compounds in the treatment of neurodegenerative diseases should present different mechanism of action from current drugs and therefore higher therapeutic efficacy with less expressed side effects. One of the new extensively explored areas on the field for Parkinson's disease treatment is the antagonism of A_{2A} adenosine receptors (ARs), which improves motor impairment and shows neuroprotective effect leading to the slowdown in the disease progression. The protective and motor effect of A_{2A} ARs blockade leads to the exploration for new selective and potent antagonist. Studies performed on A_{2A} receptor antagonists resulted in the approval letter of istradefylline (Nouriast®) for the treatment of Parkinson's disease in Japan in 2013. The search for new, selective and potent adenosine receptors ligands is one of the interest of scientists at the Department of Technology and Biotechnology of Drugs UJCM. As the result the xanthine derivatives has been synthesised with a special pharmacological profile. The *in vitro* studies confirmed A_{2A} and A_1 ARs antagonism and inhibition of the enzyme involved in the metabolism of dopamine - monoamine oxidase B (MAO-B) at the same time. A_1 adenosine receptors antagonists posses beneficial influence on cognition, which co-occurs with Parkinson's disease progression. „Multi-Target-Directed Ligands (MTDLs)" seem to be particularly beneficial in relieving symptoms of diseases with complex pathophysiology, including neurodegenerative disorders. The proposed studies allow to obtain the innovative compounds with multiple targets pharmacological profile - antagonism to A_1/A_{2A} receptors and inhibition of MAO-B.

The work plan of the project included:

1. Structures design.
2. Synthesis of designed compounds.
3. *In vitro* pharmacological studies.

The ultimate goal of this work, which is the obtainment and pharmacological evaluation of new compounds with the potential multi-target activity will be completed. This innovative combination of several activities in a single structure presented higher therapeutic effect in Parkinson's disease and potential application in Alzheimer's disease in animal models. Moreover, the results of this project will allow to find the structure ready for testing on animals, as well as to analyze carefully the structure-activity relationship for all biological targets.