Neuroprotective properties of 5-HT$_6$ receptor ligands in the group of 2-arylpyrrole derivatives – a new insight into neurodegenerative diseases treatment strategy

The importance of the project

Neurodegenerative disorders are one of the major global health problem and the number of patients is expected to rise significantly in the coming decades due to increasing of life expectancy of the worldwide population. According to data published by World Health Organization in 2018, dementia symptoms affected 50 million people around the world, and the number of patients will increase three-fold till 2050. Many neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), occur as a result of the progressive loss of structure and function of neurons. In the absence of disease-modifying therapies, existing symptomatic treatments only slightly alleviate a cognitive impairment associated with neurodegeneration. However, due to the complexity and progressive nature of diseases, current therapies are unsatisfactory and there is a paramount need to accelerate the development of new effective approaches.

The research objectives

Among many concepts regarding potential therapeutic targets for cognitive declines associated with neurodegenerative diseases, serotonin receptors type 6 (5-HT$_6$Rs) have garnered significant interest. 5-HT6Rs belong to G-protein coupled receptors and are localized almost exclusively in the central nervous system areas involving in learning and memory functions. Importantly, 5-HT$_6$Rs stand out substantial level of constitutive activity, i.e. activity independent of the presence of an agonist. Stabilization or inhibition of 5-HT$_6$R constitutive activity may lead to various biological effects. Our preliminary results obtained using *in vitro* assays, suggest glio- and neuro-protective effect of selected 5-HT$_6$R neutral antagonist. In contrast, such properties were not observed for 5-HT$_6$R inverse agonists (e.g., intepirdine, lead compound evaluated in clinical trials).

The major objective of the project concerns obtaining of new series of 2-arylpyrrole derivatives, which stabilize 5-HT$_6$R constitutive activity, to verify their impact on neuroprotective properties in *in vitro* cells-damage models characterized for neurodegenerative disorders. The obtained molecular probes – 5-HT$_6$R neutral antagonists – would allow to analyse of the relationship between the chemical structure and biological activity to explain the engagement of 5-HT$_6$R constitutive activity in neuroprotective processes.

The scope of the research

Novel compounds will be designed using computer tools and classical medicinal chemistry methods. The synthesis of selected compounds will be carried out using conventional methods of organic chemistry as well as advanced high-throughput methods, in particular flow chemistry, under the “green chemistry” concept. Then, the obtained compounds will be subjected to *in vitro* biological evaluation in order to determine the affinity for 5-HT$_6$R and their selectivity over structurally-related receptors, assess the activity relative 5-HT$_6$R constitutive activity and evaluate the metabolic stability. The most promising derivatives will be selected for neuroprotective studies. The latter will be performed by evaluation of cellular viability in *in vitro* models expressing neurons damage characteristic for neurodegenerative diseases. Since the project has the basic research character so far, identification of molecules with neuroprotective properties might initiate more advanced studies to develop potential approach for the treatment of neurodegenerative diseases.

The project will be conducted in interdisciplinary research groups, involving young scientists from Poland (Faculty of Pharmacy JUMC, Faculty of Biochemistry, Biophysics and Biotechnology JU and Institute of Pharmacology PAS) and France (Institute of Biomolecules Max Mousseron, Institute of Functional Genomics).