Dual-acting 5-HT$_6$/5-HT$_7$ receptor antagonists: exploring beneficial effects for the treatment of neurodegenerative disorders

The importance of the project

Neurodegenerative disorders (e.g. Alzheimer's disease) are a group of progressive and debilitating disorders of the central nervous system characterized by a gradual loss of neuronal structure or function, leading to cognitive, motor and behavioral impairment. According to the World Health Organization reports, neurodegenerative diseases are one of the leading causes of health disability, and premature death worldwide, and their prevalence is expected to increase significantly due to the aging of the global population. It is estimated that more than 55 million people are affected by Alzheimer's disease and related dementias, with numbers expected to double every 20 years. Despite significant efforts to develop drugs for complex neurodegenerative diseases, current treatment options remain largely symptomatic and do not halt disease progression. Thus, there is a critical need for the development of novel therapeutic approaches which might modify the course of the disease.

The research objectives

Among many concepts regarding potential therapeutic targets for cognitive declines associated with neurodegenerative diseases, serotonin type 6 (5-HT$_6$) receptor and type 7 (5-HT$_7$) receptor have attracted considerable interest. These receptors are widely expressed in brain regions implicated in cognition and neurodegeneration, modulating the neurotransmitter release, neuroplasticity and neuroprotection processes. Preclinical evidence demonstrates that selective 5-HT$_6$ and 5-HT$_7$ receptor antagonists reverse pharmacological-induced cognitive deficits in rodents and improved cognitive performance in genetic models of Alzheimer disease. Moreover, recent findings indicate that blockade of specifically activated states of these receptors differently impact the signaling cascades responsible for cytoprotective effects.

For instance, blockade of 5-HT$_6$ receptor-elicited Gs signaling confers glioprotective properties in cellular settings while inhibition of constitutive activity of 5-HT$_7$ receptor prevents Tau-related neurotoxicity in both *in vitro* and *in vivo* models. Therefore, a combined approach involving neutral antagonism at 5-HT$_6$ receptor and inverse agonism at 5-HT$_7$ receptor may more effectively address multiple pathological features of neurodegeneration than targeting a single receptor-based approach.

Scope of the research objectives

The major objective of this project is to obtain original dual-acting 5-HT$_6$ and 5-HT$_7$ receptor ligands which specifically behave as 5-HT$_6$ receptor neutral antagonists and 5-HT$_7$ receptor inverse agonists, to verify their impact on cytoprotective properties against β-amyloid and Tau protein toxicity in *in vitro* cell-damage models. Exploring beneficial effects of dual antagonism aligns with current strategy of developing multitarget-directed ligands to enhance treatment of complex neurodegenerative conditions with multifactorial pathology.

The application of *in silico* methods and structure-activity relationship studies will support the identification of structural features required for the dual targeting of 5-HT$_6$ and 5-HT$_7$ receptors, whereas elaboration of new sustainable synthesis protocols, would decrease the use of toxic reagents and organic solvents. The multidisciplinary nature of the project will contribute to a deeper understanding of the impact of simultaneous blockade of 5-HT$_6$ and 5-HT$_7$ receptors in *in vitro* models of neurodegenerative diseases.