DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Therapeutic potential of biased 5-HT_7 receptor ligands in the treatment of depression

Major depression is a recurrent and debilitating mental disorder characterized by behavioral, affective and cognitive symptoms. It has been estimated by the World Health Organization (WHO) that in 2020 depression will be the foremost contributor of severe disabilities, psychological and physical distress as well as of premature death. Currently, at least one millions Polish people suffer from depression, and while considering a worsening trends, this number may rise up to 1.5 mln. Despite advancements in the development of pharmacotherapy, currently used antidepressant agents have not reached optimal efficacy. In a view of these findings, an alternative therapeutic strategy for the treatment of depression is still required.

5-HT_7 receptor (5-HT_7R) represents the latest addition to a subfamily of serotonin receptors. Apart from the canonical coupling to G-protein, 5-HT_7R engages G-protein-independent signaling pathways (e.g., β-arrestin). In recent years 5-HT_7R has been considered as novel therapeutic target for the treatment of depression. This finding was confirmed by the fact that genetic and pharmacological blockade of 5-HT_7R produced antidepressant-like effect in animal models of depression. Recent data describing a link between 5-HT_7R and matrix metalloproteinase 9 (MMP-9), a biomarker of depression, have been reported suggesting a potential biochemical mechanism related to antidepressant properties. Additionally, 5-HT_7R antagonists display pro-cognitive properties in episodic memory task in rats.

Recent advances in GPCR biology has led to discovery of the functional selectivity (bias signaling) phenomenon. According to this paradigm, a biased ligand may specifically activate/inhibit either canonical or non-canonical signaling events**,** producing different overall physiological responses**.** This opens up the opportunity to design biased ligands at G-protein or β-arrestin pathway which might provide a new generation drugs with enhanced therapeutic efficacy.

The novelty of the project consists in proposing structural modifications allowing to elaborate compounds, which may selectively modulate 5-HT_7R-operated signaling pathways (G protein or β-arrestin). Such strategy shall provide molecular probes to explore their therapeutic potentials in the treatment of depression and co-morbid cognitive dysfunctions.

The proposed project aimed at the design (also using *in-silico* methods), and synthesis of two series of structurally diversified compounds, followed by determination of their *in vitro* pharmacological properties, and assessment of pharmacokinetic parameters. The project would determine the activity of new 5-HT7R biased ligands at the biochemical level and *in vivo* pharmacological level, determining the antidepressant and pro-cognitive properties in screening models and also confirmation their antidepressant potential in stress model of depression.

The outcomes of the project would verify the hypothesis that recruitment of G-biased and/or β-arrestin-biased signaling may show differences regarding antidepressant and pro-cognitive efficacy in animal models. Such as approach would indicate future directions for research in the field of 5-HT_7R biased ligands.