Design and Pharmacological Evaluation of Marine Alkaloid-Inspired Serotonin 5-HT_{2A} Receptors Ligands

Hallucinations, delusions, and cognitive impairments are hallmark symptoms of many psychiatric and neurological disorders, including schizophrenia, bipolar disorder, Parkinson's disease, and Alzheimer's disease. While current treatments – primarily antipsychotics – have helped many patients, they often rely on blocking dopamine D_2 receptors (D_2R). This strategy, although effective, is frequently accompanied by unwanted side effects and limited efficacy for certain symptoms. A newer generation of antipsychotics, such as risperidone and clozapine, combine D_2R blockade with serotonin 5-HT_{2A} receptor (5-$HT_{2A}R$) antagonism, offering better pharmacological profile.

But what if we could go even further – developing antipsychotic drugs that do not rely on dopamine receptor antagonism at all? Emerging evidence suggests that such an approach is not only plausible but also promising in terms of minimizing side effects. For example, pimavanserin, a selective serotonin 5-HT_{2A}Rs inverse agonist, demonstrates that targeting non-dopaminergic pathways can yield clinically effective antipsychotic effects. These findings open the door to a new class of therapeutics with potentially fewer motor side effects and improved tolerability profiles compared to traditional dopamine-targeting agents.

Nature has long served as a wellspring for drug discovery. In fact, nearly 60% of all FDA-approved drugs are either natural products, derivatives thereof, or synthetic molecules inspired by nature's chemical structures. Marine ecosystems, in particular, are home to an enormous variety of chemically rich organisms, including sponges that produce biologically active compounds with unique structures.

This project aims to harness the potential of such marine-derived chemistry. Specifically, our goal is to develop a new class of selective 5-HT_{2A} receptor antagonists inspired by alkaloids from marine sponges that share a common structural feature: the 2-aminoimidazole (2-AMI) scaffold. We believe that these natural molecules – carefully redesigned and optimized – could offer a novel pathway toward effective and better-tolerated treatments for psychiatric disorders.

To explore this promising avenue, our multidisciplinary research plan focuses on four major objectives:

- Design of virtual library of marine sponge alkaloids and its *in silico* assessment resulting in the selection of compounds for synthesis
- Synthesizing a targeted library of 2-AI derivatives based on marine sponge alkaloids, allowing us to identify the most active compound among those previously studied;
- Characterizing these compounds *in vitro*, particularly for their effects on the 5-$HT_{2A}R$ and D_2;
- Analyzing structure–activity relationships (SAR) through computational modeling, helping us understand how structural changes influence receptor binding;
- Developing a predictive design framework to support the creation of next-generation 2-AI-based compounds with enhanced selectivity for 5-$HT_{2A}R$ over dopamine D_2R.

Ultimately, this project aims not only to deliver novel bioactive compounds but also to establish a robust, knowledge-driven framework for the future development of 5-$HT_{2A}R$ agents. By defining the structural and pharmacophoric elements critical for receptor binding and selectivity, we will lay the groundwork for a new generation of ligands with improved therapeutic profiles. The findings are expected to advance both the scientific understanding of serotonergic signaling and the broader field of neuropsychopharmacology. In doing so, the project will underscore the enduring relevance of natural product scaffolds – particularly those of marine origin – as invaluable starting points in the search for innovative treatments for complex psychiatric diseases.