UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

In vitro pharmacological studies on novel ligands for the neuropeptide s receptor

2)Abstract (max 500 words)

G protein-coupled receptors (GPCRs) are the largest class of membrane proteins and the target of roughly 25% of approved drugs. Among them, Class A GPCRs are involved in the treatment of various conditions including central nervous system (CNS) disorders. About one-third of Class A GPCRs are activated by endogenous peptides, such as Neuropeptide S (NPS)—a 20-amino acid peptide that activates the formerly orphan receptor GPCR154, now known as NPSR.
NPSR activation, mediated via Gq and Gs proteins, enhances neuronal excitability and impacts brain regions involved in stress, memory, and arousal. Preclinical and clinical studies suggest that NPSR antagonists may reduce drug-seeking behaviours, while NPSR agonists could serve as non-sedating anxiolytics with memory-enhancing effects. Importantly, these anxiolytic actions appear to rely specifically on Gq signalling, pointing to Gq-biased agonists as an innovative therapeutic avenue.
Despite two decades of research, no high-affinity, drug-like NPSR ligands have reached clinical development. This highlights a critical need for new molecules to better explore and validate NPSR as a CNS drug target.
This PhD project will contribute to unlocking NPSR's therapeutic potential by characterizing its activation mechanisms and developing novel ligands. The candidate will perform in vitro pharmacological studies in collaboration with experts in molecular modelling, synthetic chemistry, and biochemistry. Key tasks will include:

- Developing and applying cAMP and calcium assays to evaluate newly designed peptide and non-peptide NPSR ligands.
- Screening commercial chemical libraries to discover new chemotypes.
- Synthesizing fluorescent NPS analogues for receptor-binding studies using confocal microscopy.
- Validating an active NPSR model through site-directed mutagenesis.

Together, these multidisciplinary approaches will provide a strong foundation for the structure-based design of selective NPSR modulators. The project will also offer the candidate advanced training in pharmacological profiling, receptor modelling, and assay development—key skills for a career in neuropsychopharmacology and CNS drug discovery.