University of Naples Federico II
Department of Pharmacy
Doctoral Course in Pharmaceutical Sciences XL Cycle

DISCOVERY OF NEW AGONISTS OF BILE ACID RECEPTORS FOR THE TREATMENT OF ENTEROHEPATIC AND METABOLIC DISEASES

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In the last two decades bile acids have been identified as important nutrient and metabolic sensors, playing a critical role in maintaining metabolic homeostasis. In addition to their primary functions in absorption of lipids and fat-soluble vitamins from the gastrointestinal tract, bile acids also act as signal molecules and endogenous ligands of various receptors and channels, above all the nuclear farnesoid X receptor (FXR) and membrane G protein-coupled bile acid receptor-1 (GPBAR1, also known as Takeda G protein-coupled receptor 5, TGR5). The exogenous regulation of these targets represents an attractive strategy for the treatment of enterohepatic and metabolic disorders. The present PhD project involves the development of new agonists of these receptors, with a particular focus on compounds confined to the gastrointestinal tract minimizing systemic exposure.

The PhD activity will be dedicated to the optimization of previously developed compounds and to the identification of new molecules able to modulate FXR and/or GPBAR1 receptors. The synthesis will be carried out using optimized synthetic procedures, taking in account the innovative and leading-edge technologies and, when possible, fast, sustainable and eco-friendly synthesis methodologies.

The proposed PhD project has a multidisciplinary structure including all the steps of drug discovery: design, synthesis, SAR studies, investigation of ligand/receptor molecular interaction, and pharmacological in vitro evaluation in the aim to develop derivatives with optimized potency/selectivity towards the two receptors involved in intestinal and metabolic disorders. As a matter of example, starting from BAR501 and BAR502, two semisynthetic bile acids previously synthesized in our research group and already involved in clinical trials, new synthetic derivatives will be developed to obtain gut-restricted compounds, focusing on the evaluation of ADME properties. The most promising synthetized compounds will be further subjected to deeper pharmacological investigation.

The research group's background in the design and synthesis of both steroidal and non-steroidal compounds and the active pharmacological collaborations, will ensure the PhD student a complete training path.

The objectives of this project, in line with those of Cluster 1 Health of PNRR, which aim to improve and protect health and well-being of people, are focused on the development of new drugs for the treatment of disorders for which there is still no effective therapies.