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PROJECT TITLE

Development of Nuclear Receptor Modulators for the Treatment of Metabolic Diseases: An Integrated Approach Based on Artificial Intelligence and Molecular Modeling

Project description (max 300 words)

Nuclear receptors (NRs) are ligand-dependent transcription factors that regulate gene expression involved in numerous pathophysiological processes, including lipid and glucose metabolism, inflammatory response, and cell proliferation.[1] Given their central role in regulating metabolic homeostasis, selective NR modulators represent a promising therapeutic strategy for complex diseases such as type 2 diabetes, NAFLD/NASH, and metabolic syndrome. Receptors of major interest for these applications include PPARs (α, β/δ, γ), FXR, RXR, and LXR.[2-4]
This project aims to identify and optimize novel modulators of these receptors using an integrated computational approach. We will employ state-of-the-art generative models, including chemical language models (CLMs),[5-8] which can learn complex chemical representations and generate bioactive molecular structures with high efficiency. These models will be used to specifically explore chemical space and propose innovative compounds with potential activity on one or more receptor subtypes. In parallel, the project also involves the development of new computational frameworks for drug design to: i) generate compound libraries using the aforementioned CLMs; ii) predict biological activity by means of QSAR; iii) simulate ligand-receptor interaction via docking and molecular dynamics.
These platforms will be designed to be adaptable not only to NRs but also to different targets and therapeutic contexts. The activities will take place at the Laboratorio di Eccellenza in Modellistica Molecolare (LMM), which provides the computational infrastructure and the know-how for developing advanced computational methodologies. The most promising compounds will be selected for in vitro assays to validate their biological activity on the receptors of interest (gene transcription, lipid, and glucose metabolism). Active molecules will be further optimized through iterative cycles of design and synthesis. This project aims to provide innovative tools for precision medicine in the metabolic field, accelerating the development of more selective, effective, and personalized therapies.

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