**Integrating Artificial Intelligence and Molecular Modeling: A Synergistic Approach to Nuclear Receptor Modulators Design**

Computational approaches have emerged as important tools in the field of pharmaceutical research, often representing the driving force behind the discovery of novel small molecule therapeutics. By leveraging computing capacity, these techniques can model, simulate, and evaluate molecular interactions and processes.1 *De novo* drug design, a computational approach for generating new potential drug molecules from scratch, is being revolutionized by generative models, which learn underlying data distributions to create novel and optimized molecular structures with desired properties.2 This project aims to leverage cutting-edge generative models, including chemical language models (CLMs), to efficiently explore chemical space and propose innovative compounds.3 CLMs are capable of learning intricate chemical representations and generating bioactive molecular structures with high precision.4 CLMs will be integrated into computational frameworks for drug design, in combination with QSAR (Quantitative Structure-Activity Relationship) for predicting biological activity, docking and molecular dynamics simulations for understanding ligand-receptor interactions. This pipeline will be employed to identify new bioactive compounds, with particular emphasis on novel modulators of nuclear receptors (NRs) involved in metabolic disfunctions, such as type 2 diabetes, NAFLD/NASH. Receptors of major interest for these applications include PPARs (α, β/δ, γ), FXR, RXR, and LXR.5-8

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). Ultimately, this project aims to provide innovative tools for precision medicine, accelerating the development of more selective, effective, and personalized therapies.

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