Computationally-Guided discovery and optimization of small molecule HNE enzyme inhibitors

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Our research activities focus on the application of computer-aided approaches like homology modelling, molecular docking, virtual screening, pharmacophoric models, *de novo* design, molecular dynamics and quantum mechanics to discover, develop and optimise new chemical entities for sustained drug discovery. Our group works with a significant portfolio of biological targets in the areas of inflammatory and metabolic diseases, cancer, and malaria.

Recently, our group has been engaged with the computational discovery, development and optimization of potent Human Neutrophil Elastase (HNE) inhibitors as drug candidates for the treatment of Chronic Obstructive Pulmonary Disease (COPD) inflammatory process. Over the last decades HNE inhibitors have been evaluated as potential drug candidates, nevertheless their development was discontinued for various reasons and only sivelestat has been approved for clinical use in Acute Respiratory Distress Syndrome (ARDS). Hence, there is an urgent need for new chemotypes that allow efficient and selective HNE enzyme inhibition. Recently, we developed a virtual screening protocol (docking based) that led to the discovery of the kojic acid hit compound **1** (Figure 1), which is a 18 μM acyl-enzyme inhibitor that showed to be selective for HNE when compared with parent proteases. However, this compound presented poor stability toward hydrolytic plasma and microsomal enzymes, a result consistent with that reported in the late 80's for closely related long chain bis-ester HNE inhibitors. We thus envisaged a hit-to-lead optimization campaign, where the computationally identified kojic acid scaffold was modified and the new compounds were redocked on the HNE active site. The most promising compounds were synthesized and tested. With this approach we were able to improve inhibitory activity (80 nM) as well as compounds stability. In addition, a pharmacophoric model for HNE inhibition was computationally built based on the oxo-β-lactam scaffold and a new library of oxo-β-lactams was generated by *de novo* design. This library were filtered with our 3D-pharmacoric model. Compounds that showed more potential were synthesised and tested in vitro. The established protocol led us to the development of a novel low nanomolar (7 nm) HNE inhibitor. Our findings validate the use of computational methodologies as a premier strategy for rapid lead-structure prototyping in drug discovery. An overview of the computational methodology, protocol and results involved in this study will be presented.

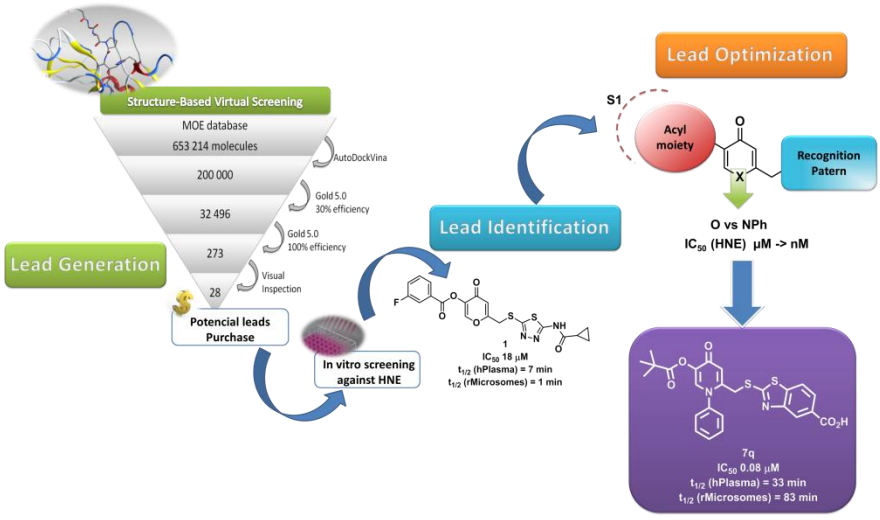

Figure 1. Partial hit-to-lead optimization scheme.