A Novel Approach to Target a Previously Unexplored Pocket in PI3Kγ

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Protein kinases play a key role in the development of numerous diseases, which makes this large enzyme family one of the most relevant targets in modern drug discovery.[1] [2]

This research focuses on PI3Kγ, an isoform of the phosphoinositide 3-kinase family, implicated in a range of pathological conditions, including cancer, autoimmune diseases and chronic inflammatory disorders. This isoform is predominantly expressed in cells of the myeloid lineage as well as in lymphoid cells. As a result, PI3Kγ is essential for proper immune system function and has become a highly investigated target in the field of immuno-oncology.[4]

The PI3K ATP-binding site is highly conserved among the different isoforms: this represents a significant challenge for designing selective inhibitors targeting PI3Kγ.[5] The presence of a less conserved accessory pocket in the vicinity of the ATP-binding site represents an additional potential target to design selective ligands. Indeed, the aim of the project is to design selective ligands for this isoform targeting the unexplored additional binding site and starting from the scaffold of a previously reported PI3Kγ inhibitor (NVS-PI3-4, Figure 1).[6]

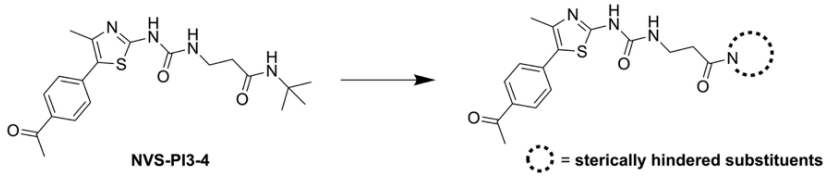

Figure 1: General structure of NVS-PI3-4 derivatives

The design was performed by exploiting Computer-Aided Drug Design (CAAD) techniques. Firstly, the Schrödinger's graphical interface Maestro was used to study the crystallographic structure of the target PI3Kγ in complex with NVS-PI3-4 that induce a conformational change in the protein structure. This allowed to analyze in detail the novel pocket near the ATP-binding site. Then, a ligand-based approach will be performed to design new ligands introducing sterically hindered functional groups on the reported scaffold, aiming to maximize the ligand-induced conformational rearrangement (Figure 1). The ligands were evaluated using docking scores and the most promising candidates were further evaluated using molecular dynamics (MD) simulations, to monitor the conformational changes induced over time. MD simulations were carried out using the pmemd.cuda module in Amber24 and, to ensure robustness, 1 microsecond-long MD simulations were performed in triplicate for each ligand. The analysis of these simulations has provided valuable insights for the future development of novel selective PI3Kγ inhibitors.

Bibliography :

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