Design of Beta Sliding Clamp inhibitors using fragment-based method

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Antimicrobial resistance (AMR) has become a worldwide issue over the past decades. It is estimated that AMR could be associated with around 8 million deaths annually by 2050 [1]. Therefore, it is now urgent to develop new antibacterial drugs to address this issue. Herein, we aim to design new inhibitors targeting the Beta Sliding Clamp, which is a promising antibacterial target. Indeed, this homodimer protein is key to the DNA replication of prokaryotic cells [2]. Consequently, inhibiting its activity would disrupt the replication process and ultimately lead to the bacterial cell death.

In collaboration with medicinal chemists, we designed a series of small molecules derived from a reference ligand [3] and developed a computational pipeline to prioritize these compounds for synthesis and in vitro testing. Particular efforts were made to efficiently filter the molecules before experimental evaluation. Since scoring docking poses remains a challenging and often unreliable task, we instead used a frequency-based ranking approach to prioritize the compounds. More specifically, the pipeline combined molecular dynamics simulations, used to account for the conformational flexibility of the reference ligand and the binding pocket of the protein, with molecular docking performed on multiple relevant molecular dynamics snapshots. The underlying assumption was that a compound producing a high number of favorable docking poses across different protein conformations should be prioritized over compounds producing fewer favorable poses. However, although the selected compounds did not show sufficient binding affinity, these results provided valuable insights into the binding modes of small molecules within the Beta Sliding Clamp binding site, thereby contributing to a better understanding of the challenges associated with the design of potent inhibitors targeting this protein. [4].

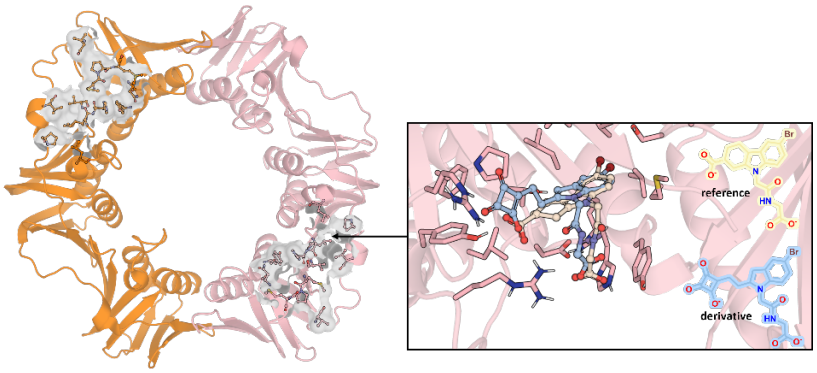

Figure 1 Structure of the Beta Sliding Clamp (left) and cristal structure of the reference ligand alongside a docked pose of one derivative in the binding site (right)

Bibliography:

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