Squashing the Superbug: Discovery of Irreversible SrtA Inhibitors as Potential Antibacterial Drugs using a Novel Computational Drug Design Workflow

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Each year in the United States, at least 23,000 people die each year as a direct result of antibiotic-resistant infections with 80% of these deaths from gram-positive bacteria. One promising approach for treating bacterial infections is to strip the bacteria of their surface proteins such as Sortase A (srtA), which frequently function as virulence factors and facilitate bacterial adhesion during infection. Virtual screening is a computational technique used in drug discovery to dock libraries of small molecules into the active site of the drug target in order to identify compounds which are most likely to inhibit an enzyme's activity. There has been a growing interest in the design of irreversible inhibitors which form a covalent bond with the target protein, however no free and customizable covalent virtual screening workflow has ever been created. The purpose of this experiment was to formulate covalent drug discovery workflow to identify potent irreversible small-molecule inhibitors for Sortase A. A combination of a non-covalent multi-phase virtual screening approach followed by covalent docking validation could form the basis of the workflow. Through a FRET-based assay, two fragment-compounds identified through the covalent virtual screening workflow displayed potent Sortase A inhibitory activity in vitro. Through kinetic studies, one of the compounds was found to irreversibly and covalently bind to Sortase A's active site. Utilizing further computational methods, the identified fragment was further grown into an even more potent molecule. The results validate the covalent drug discovery workflow. Additionally, the compound forms the basis for drug development which could potentially lead to a new therapy against multi-drug resistant bacteria infections.

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