Computational Design of Novel Small-Molecule Activators Targeting the AtlA Autolysin in Multi Drug-Resistant Staphylococcus aureus to Combat Antibiotic Resistance Through Internal Cell Death Mechanisms

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Antibiotic resistance is a major global health threat projected by the World Health Organization to cause 10 million deaths annually by 2050. Autolysins like AtlA, essential for bacterial cell wall remodeling, offer a novel therapeutic target. While typically studied as virulence factors, activating these enzymes could induce bacterial self-destruction, bypassing resistance mechanisms. This study employs computational approaches to design and optimize small-molecule activators that enhance AtlA activity in methicillin-resistant Staphylococcus aureus (MRSA). Structural characterization was performed using Protein Data Bank structures and homology modeling via SwissModel, with binding site identification through ProFunc and InterProScan, revealing four key targets on Atla: ALA 302, ASN 316, SER 373 and the center of a regulatory pocket. De novo drug design with LEA3D generated activator candidates for these targets based on drug-likeness criteria (Lipinski's Rule of Five, Pfizer's MPO Algorithm). Molecular dynamics (MD) simulations in GROMACS assessed binding stability, with energy minimization and equilibration under NVT/NPT ensembles before a 1 ns production run. Root Mean Square Deviation (RMSD) and Fluctuation (RMSF) tracked protein-ligand stability over time in a water solution. MM/PBSA calculations determined an average binding energy of -80 kcal/mol for the designed activators, and SwissADMET analysis identified promising drug-like candidates by evaluating the activators on drug parameters like absorption, metabolism and toxicity. This study presents autolysin activation as a groundbreaking strategy for combating MRSA, leveraging bacterial self-destruction to bypass conventional resistance mechanisms and introduce a novel class of antibiotic alternatives.

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