LasRuptide: Design of a Host-Mimic Peptide Inhibitor to Disrupt Pseudomonas aeruginosa Quorum Sensing and Biofilm Formation via Targeted Dimer Interface Perturbation

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Pseudomonas aeruginosa is prevalent in hospital-acquired pneumonia, with mortality reaching 70%, and chronic cystic fibrosis infections. The reason the anitbiotics don't work is the LasR quorum-sensing system, which creates virulence and biofilms. By mimicking host-defense interactions, this study aimed to silence pathogenic communication via mechanical destabilization of the LasR receptor, bypassing the selective pressure for antimicrobial resistance, a growing issue. A library of 3,306 sequences from the Antimicrobial Peptide Database was initially screened for length, stability, and toxicity. Top candidates were modeled and docked to the LasR ligand-binding domain found in PDB. The lead complex underwent 300-ns molecular dynamics (MD) simulations in GROMACS. After analyzing potential stability with RMSF, RMSD, and H-Bond Analysis, the peptide was redesigned to enhance affinity with the binding site. MD simulations revealed LasRuptide achieved a binding affinity of -9.8 kcal/mol. Unlike competitive inhibitors, it functions as a de-oligomerizing ligand that inserts into the dimer interface. Data showed a 15% reduction in inter-chain hydrogen bond stability, proving persistent interfacial disturbance. This mechanical disruption prevents the protein from maintaining its functional dimer shape, blocking the activation of genes required for biofilm architecture. LasRuptide works by physically compromising the dimer interface. This approach forces a structural collapse of the active protein assembly, reversing the ability to coordinate group-based virulence. This mechanism provides a high-impact strategy to restore antibiotic efficacy and reduce mortality by permanently disabling the pathogen's communication architecture.

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