Computational Identification of Novel Therapeutics for the PBP3 F533L Mutant of *Pseudomonas aeruginosa* Using Machine Learning Techniques

Srujal Kacha[1,2], Tushar Joshi[1], Santhiya Vijaykumar[1,3], Soumyadip Ghosh[1,3], Shalini Mathpal[1], Sudha Ramaiah[1,3], Anand Anbarasu[1,2*]

[1]*Medical and Biological Computing Laboratory, School of Bioscience and Technology (SBST), Vellore Institute of Technology (VIT), Vellore, 632014, Tamil Nadu State, India.*

[2]*Department of Biotechnology, School of Bioscience and Technology (SBST), Vellore Institute of Technology (VIT), Vellore, 632014, Tamil Nadu State, India*

[3]*Department of Biosciences, School of Bioscience and Technology (SBST), Vellore Institute of Technology (VIT), Vellore, 632014, Tamil Nadu State, India*

Email – srujal.kacha2023@vitstudent.ac.in

Abstract

Pseudomonas aeruginosa (*P. aeruginosa*) is a highly infectious and antibiotic-resistant bacterium that causes severe acute and chronic hospital-acquired infections. Its ability to develop resistant mutants and utilize multiple resistance mechanisms allows it to withstand almost all available antibiotics. To address this growing challenge, the present study focused on identifying potential therapeutic compounds targeting the antibiotic-resistant mutants of *P. aeruginosa*. The F533L mutation in penicillin-binding protein 3 (PBP3), an enzyme crucial for β-lactam antibiotic recognition, was selected as the target. A total of 147 antibacterial compounds from PubChem were screened using a machine learning model based on the Decision Stump algorithm, which achieved an accuracy of 75.75%. From this screening, 55 compounds were shortlisted, and 47 were further filtered based on their drug-like properties. Virtual screening of these compounds revealed binding affinities ranging from −11.3 to −4.6 kcal mol^{-1}, with the top 10 compounds showing favorable interactions at the mutation site. Molecular dynamics simulations were then performed for the top eight compounds to assess the stability of their complexes with the mutated PBP3. Among them, three compounds—Macozinone, Antibacterial Agent 71, and Antibacterial Agent 123—exhibited strong binding stability, supported by RMSD, RMSF, and binding free energy analyses. These findings suggest that the identified compounds hold promise as potential inhibitors against the F533L

mutant of PBP3 and may contribute to the development of new therapeutic strategies to combat resistant *P. aeruginosa* infections.

Keywords: *Pseudomonas aeruginosa,* Machine Learning, PBP3, Molecular dynamics simulations, Virtual screening