Beyond the Mutation: Evolution-Aware Antibiotic Discovery Through a Novel Resistance-Robust Computational Framework

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Declared a global crisis by the World Health Organization, antibacterial resistance causes over 5 million deaths annually. Existing models optimize binding affinity at a single evolutionary point, ignoring dynamic selective pressures that drive resistance emergence. Furthermore, current approaches focus exclusively on target-level interactions while neglecting critical multi-scale constraints—cellular penetration, efflux evasion, and human safety—that determine clinical efficacy and safety. This project introduces a paradigm shift in fluoroquinolone antibiotic design for Staphylococcus aureus through three integrated innovations. First, we incorporate evolutionary robustness by modeling resistance mutations and optimizing molecules that maintain binding affinity under mutational pressure. Second, we develop a multi-scale phenotypic integration framework that encompasses R-score, molecular binding, cellular permeability, efflux resistance, and human safety. Third, we employ mechanistic interpretability analysis to extract causal design rules, transforming black-box molecular generation into actionable chemical principles that can guide drug design. Our research generated top 99 evolutionary-robust candidates, with an average binding retention of 96% for the top 5 candidates and an average resistance score of 0.943/1.000. We maximized phenotypes of membrane permeability, resistance robustness, Gyrase A binding, efflux evasion, and human safety. Chemical analysis of drugs demonstrated the evolutionary application of a lactam carbonyl in the aromatic ring structure of fluorquinolones. This work demonstrates a computational framework that generates antibiotic candidates resilient to both biochemical constraints, evolutionary trajectories, and optimized for future fitness.

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