Optimizing Drug Design for Mycobacterium tuberculosis Focus on inhA and DprE1

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Abstract:

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health challenge, exacerbated by the rapid emergence of multidrug-resistant and extensively drug-resistant strains. The limitations of existing anti-tubercular drugs, including prolonged treatment duration, host toxicity, and reduced efficacy due to resistance, necessitate the development of novel and more targeted therapeutic strategies. In this study, a structure-based computational drug design approach was employed to identify potential inhibitors against essential molecular targets of *M. tuberculosis*.

The enzyme decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1), a key contributor to mycobacterial cell wall biosynthesis, was selected as the target due to its essentiality and druggability. Binding cavity analysis was performed to characterize accessible active sites suitable for ligand interaction. A library of designed ligands was prepared and optimized, followed by molecular docking to evaluate binding affinity, interaction stability, and orientation within the catalytic pocket. Docking validation was conducted using market anti-TB drugs as reference compounds.

Among the designed molecules, Ligand 5 demonstrated the most favorable docking score, stable protein– ligand interactions, and optimal positioning within the active site of DprE1. To assess translational feasibility, drug-likeness and ADMET profiling were performed using ADMETlab 2.0. The selected lead compound exhibited compliance with Lipinski's Rule of Five, acceptable pharmacokinetic properties, and low predicted toxicity.

Overall, this study highlights the effectiveness of integrating structure-based molecular docking with ADMETguided screening to prioritize promising anti-tubercular drug candidates. The findings provide a scalable computational framework to accelerate early-stage TB drug discovery, while emphasizing the need for subsequent experimental validation.