Structure-Based Identification of Novel Zinc-Binding Inhibitors Against the Essential Metalloprotein DapE in *Klebsiella pneumoniae*

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Abstract

Klebsiella pneumoniae (*K. pneumoniae*) has emerged as a major multidrug-resistant pathogen and is currently listed among the World Health Organization's top three critical priority organisms. The rapid rise of antibiotic resistance and associated treatment failures highlights the urgent need for novel therapeutic strategies. One promising target is N-succinyl-L, L-diaminopimelic acid desuccinylase (DapE), a key metalloenzyme in the lysine biosynthesis pathway. DapE plays an essential role in protein synthesis and peptidoglycan cross-linking, and its remarkable conservation across diverse bacterial species supports its potential as a broad-spectrum antimicrobial target. In this study, a library of 400 structural analogs was subjected to comprehensive virtual screening to evaluate their pharmacokinetic, toxicological, and bioactivity profiles. From this set, 52 compounds that met stringent drug-likeness and safety criteria were shortlisted for molecular docking. Five top candidates were identified based on docking affinities and interaction characteristics, and two compounds, ZINC262925003 (-7.1 kcal/mol) and ZINC237355153 (-7.0 kcal/mol), showed robust coordination with the catalytic zinc ion and critical active-site residues of DapE. To further validate their inhibitory potential, 250 ns molecular dynamics simulations were performed of the DapE-ligand complexes, followed by Molecular Mechanics Poisson-Boltzmann Surface Area (MM/PBSA) binding free-energy calculations. The simulations revealed high structural stability, persistent zinc coordination, and consistent retention of essential hydrogen-bonding and hydrophobic interactions. MM/PBSA results corroborated the strong binding affinities observed in docking. Overall, this integrative computational analysis identifies ZINC262925003 and ZINC237355153 as promising DapE-targeting lead molecules. These findings support their potential as novel antimicrobial candidates against multidrug-resistant *K. pneumoniae* and warrant further experimental validation through in vitro enzymatic assays and *in vivo* efficacy investigations.

Keywords: *Klebsiella pneumoniae*, antibiotic resistance, DapE, zinc, virtual screening