Identification of Berberine Analogues as Promising *Escherichia coli* FtsZ Inhibitors Through Machine Learning, Molecular Docking, and Molecular Dynamics Approaches

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Abstract

The bacterial cell-division protein FtsZ, a key GTPase, is essential for assembling the contractile Z-ring, a structure crucial for cytokinesis. Inhibiting FtsZ prevents protofilament formation and disrupts the cell-division process. Because of its high conservation across various bacterial species, FtsZ is a promising target for developing new antimicrobial agents. In this study, a library of 1,072 berberine analogues was screened for favorable pharmacokinetic properties. Sixty compounds that met drug-likeness criteria and showed non-toxic profiles were selected for virtual screening against Escherichia coli FtsZ (PDB ID: 8GZY). Molecular docking identified ZINC000524729297 (−8.73 kcal/mol) and ZINC000604405393 (−8.55 kcal/mol) as the top candidates, showing strong binding affinities supported by robust hydrogen bonding and hydrophobic interactions. To validate these results, 500-ns molecular dynamics simulations combined with MM/PBSA analyses were performed. The FtsZ–ZINC000524729297 and FtsZ–ZINC000604405393 complexes displayed minimal root-mean-square deviation, lower binding free energies, and increased conformational stability throughout the simulations. Overall, these findings suggest that ZINC000524729297 and ZINC000604405393 are promising lead compounds targeting FtsZ and deserve further experimental validation.

Keywords: Antimicrobial resistance, Binding free energy, Cell division, Pharmacokinetic, Z-ring