An Integrative Structure-Based *In Silico* and Quantum Simulation Approaches Uncover a Promising Quinoline Scaffold as GyrA Inhibitor against Fluoroquinolone-Resistant in *Pseudomonas aeruginosa*

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Abstract

Fluoroquinolone-resistant *Pseudomonas aeruginosa* poses a significant global health threat, exacerbated by the widespread emergence of mutations in the DNA gyrase subunit A (*gyrA*). This study integrates molecular modelling, molecular docking, quantum simulations, molecular dynamics (MD) simulations, and free energy analyses to identify novel quinoline analogues capable of overcoming resistance. Among 264 screened compounds, N-benzylquinoline-8-sulfonamide (M2) emerged as the most promising inhibitor of both wild-type and mutant *gyrA* forms (single mutants T83I, D87G, D87N, D87Y, and double mutant T83I_D87N). M2 demonstrated an average binding energy of -8.14 kcal/mol, outperforming control antibiotics like ciprofloxacin (-7.13 kcal/mol) and levofloxacin (-6.58 kcal/mol). It also exhibited a robust inhibition constant (Ki = 1.09 µM), markedly superior to ciprofloxacin (6.11 µM) and levofloxacin (15.34 µM). MD simulations confirmed the high structural stability of M2-*gyrA* complexes, with minimal RMSD fluctuations and consistent hydrogen bonding across all variants. MM/GBSA and MM/PBSA binding free-energy analyses supported these results, revealing favourable ΔG_bind values. Principal Component Analysis (PCA) identified a narrow global energy minimum, signifying stable conformational states induced by M2 binding. Furthermore, ADMET predictions indicated excellent pharmacokinetic attributes and low toxicity (Class 5; non-carcinogenic, non-mutagenic). Overall, these findings highlight M2's potential to counteract resistance mechanisms by stabilising the *gyrA* active site and reducing conformational entropy, effectively impairing enzymatic DNA supercoiling. This comprehensive *in silico* analysis establishes M2 as a next-generation lead molecule for combating multidrug-resistant *P. aeruginosa*, warranting further *in vitro* and *in vivo* validation.

Keywords: AMR, DFT, CADD, Quinoline, Ciprofloxacin, Levofloxacin