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In Silico Exploration of Quinoline Derivatives as Novel Antimicrobial Agents Targeting Resistance Mechanisms

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INTRODUCTION

The alarming rise in antibiotic resistance has intensified the global search for novel antimicrobial agents. Quinoline derivatives, known for their structural flexibility and broad pharmacological activity, present a promising scaffold for antimicrobial drug development. This study explores the in-silico potential of 22 quinoline-based compounds to inhibit DNA Gyrase (PDB: 2XCT) and Dihydropteroate Synthase (PDB: 5U10), two critical bacterial enzymes, through molecular docking and ADMET profiling.

AIMS AND OBJECTIVES

- Evaluate binding affinity of quinoline derivatives against DNA gyrase and DHPS.
- Analyze ligand-receptor interactions at the molecular level.
- Predict ADMET and drug-likeness profiles of the top-performing compounds.

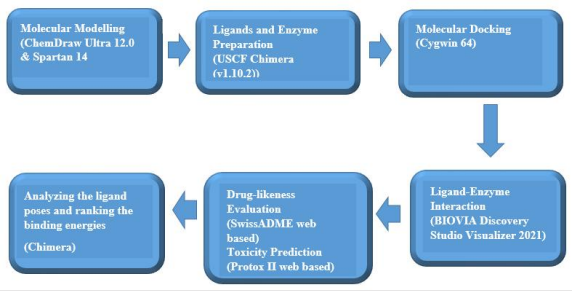
METHODOLOGY

Software and Tools:

- Ligand Preparation: ChemDraw, Chimera, Autodock tools
- Docking and Visualization Tools: Autodock Vina via Cygwin, Discovery Studio
- Targets**:** DNA Gyrase (2XCT), DHPS (5U10)
- ADMET Prediction: SwissADME, ProTox III

Docking Workflow:

- Ligand library optimization
- Receptor cleaning and grid generation
- Docking and scoring
- Visualization/ Interaction analysis
- ADMET screening



RESULT

Top Ligands Based on Binding Affinity

Compound	DNA Gyrase (2XCT)	DHPS (5U10)
CMPD1	-9.2 Kcal/mol	-7.4 Kcal/mol
CMPD2	–8.7 kcal/mol	–7.9 kcal/mol

Key Interactions

- CMPD 1 formed H-bonds with ARG98, ASP85 and π-π stacking with PHE104 in DNA gyrase.
- CMPD 2 interacted with ARG254 and GLY221 in DHPS.

ADMET Highlights

- High GI absorption
- No PAINS alerts
- Low predicted toxicity
- CMPD1 passed all Lipinski's Rule of Five parameters

DISCUSSION

- CMPD 1 and CMPD 2 showed binding affinities comparable to or better than known antibiotics like ciprofloxacin.
- The interaction patterns indicate strong target inhibition potential.
- Favorable ADMET predictions suggest the compounds are druggable and orally bioavailable.

CONCLUSION

The study validates quinoline derivatives as promising antibacterial agents, demonstrating potent inhibition of DNA gyrase and DHPS, along with favorable drug-likeness and safety profiles. These findings warrant further in vitro and in vivo evaluation to confirm their therapeutic potential.

REFERENCES

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