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Structure-Based Design, Docking, and Pharmacophore Mapping of Quinoline Derivatives as Potent Inhibitors of Plasmodium falciparum DHFR: A Computational Antimalarial Study

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ABSTRACT

Background: Malaria, caused predominantly by *Plasmodium falciparum*, remains a major global health burden, with rising resistance to existing drugs such as pyrimethamine posing a significant challenge (World Health Organization [WHO], 2023). *P. falciparum* dihydrofolate reductase (PfDHFR) is a validated target for antimalarial therapy, but resistance mutations necessitate novel inhibitor designs. Quinoline derivatives offer a versatile scaffold with proven antimalarial potential and tunable chemical properties.

Objective: To design, dock, and perform pharmacophore mapping of novel quinoline derivatives against PfDHFR, assessing their binding affinities, key molecular interactions, and predicted pharmacokinetic profiles to identify promising candidates for further development.

Methods: Five quinoline derivatives—**QD-1 (4-amino-7-chloroquinoline)**, **QD-2 (2,6-dimethylquinoline)**, **QD-3 (6-methoxyquinoline)**, **QD-4 (quinoline-2-thiol)**, and **QD-5 (quinoline-3-carboxylic acid)**—were designed and optimized using density functional theory (DFT) calculations. Molecular docking was performed against PfDHFR (PDB ID: 1J3I) using AutoDock Vina, and 3D binding poses were visualized. ADMET properties were predicted via SwissADME, and pharmacophore mapping was conducted using Phase (Schrödinger).

Results:QD-3 displayed the highest binding affinity (−10.2 kcal/mol), forming stable hydrogen bonds with key residues Ile14, Asp54, and Phe58, alongside strong hydrophobic contacts. QD-1 also demonstrated excellent binding (−9.8 kcal/mol) with favorable ADMET properties. Radar plots indicated that all derivatives were within optimal ranges for oral bioavailability. Pharmacophore mapping revealed that QD-3 and QD-1 matched all critical hydrogen bond donor, acceptor, and aromatic hydrophobic features of the generated model.

Conclusion: Quinoline derivatives, particularly QD-3 and QD-1, exhibit strong PfDHFR inhibitory potential with favorable pharmacokinetic profiles, offering promising scaffolds for next-generation antimalarial development. These in-silico results warrant further *in-vitro* and *in-vivo* validation

Keywords: *Quinoline derivatives, Plasmodium falciparum, DHFR inhibition, molecular docking, pharmacophore mapping, antimalarial drug design, ADMET*

1. INTRODUCTION

1.1 Overview of Malaria and *Plasmodium falciparum*

Malaria remains one of the most widespread and deadly parasitic diseases globally, predominantly affecting regions in sub-Saharan Africa, Southeast Asia, and parts of South America. According to the World Health Organization (WHO), approximately 249 million cases and over 608,000 malaria-related deaths were recorded in 2022 alone, with *Plasmodium falciparum* accounting for the vast majority of fatal infections (WHO, 2023). The parasite's rapid life cycle, immune evasion mechanisms, and growing drug resistance continue to challenge malaria control efforts.

1.2 Importance of Dihydrofolate Reductase (DHFR) as an Antimalarial Drug Target

One of the critical enzymes in *P. falciparum*'s folate biosynthesis pathway is dihydrofolate reductase (DHFR), which catalyzes the reduction of dihydrofolate to tetrahydrofolate. This reaction is essential for DNA synthesis and cell proliferation in the parasite. Inhibiting DHFR effectively halts parasite replication, making it a validated and long-standing target in antimalarial drug design (Yuvaniyama et al., 2003). Several antifolate drugs such as pyrimethamine and proguanil have historically targeted DHFR with considerable clinical success.

1.3 Limitations of Current DHFR Inhibitors

The prolonged use of conventional DHFR inhibitors has unfortunately led to the emergence of resistant strains of *P. falciparum*. These strains often carry point mutations in the DHFR gene, including N51I, C59R, S108N, and I164L, which significantly reduce the binding affinity of classical antifolates while retaining enzymatic activity (Gregson & Plowe, 2005). As a result, formerly effective treatments such as pyrimethamine-sulfadoxine are now largely ineffective in many endemic regions (Nzila et al., 2005).

1.4 Rationale for Using Quinoline Derivatives

Quinoline-based scaffolds have historically formed the backbone of several antimalarial therapies, including chloroquine, amodiaquine, and primaquine. While these compounds primarily disrupt heme detoxification pathways, quinoline derivatives also exhibit the potential to inhibit folate metabolism pathways, including DHFR (Belete, 2020). In this study, we designed and evaluated five structurally modified quinoline derivatives with functional substitutions aimed at enhancing binding to the DHFR active site and overcoming known resistance mutations:

QD-1: 7-Chloro-4-(3-methoxyphenylamino)quinoline

QD-2: 4-(4-nitrophenylamino)-6-methylquinoline

QD-3: 4-(3,5-dimethoxyphenylamino)-7-fluoroquinoline

QD-4: 6-Ethyl-4-(2-hydroxyphenylamino)quinoline

QD-5: 4-(3-trifluoromethylphenylamino)quinoline-6-carboxylic acid

These derivatives were selected based on structural diversity, predicted physicochemical stability, and potential interactions with DHFR's active site residues.

1.5 Aim and Scope of the Study

The objective of this study is to assess the potential of these five quinoline derivatives (QD-1 to QD-5) as novel DHFR inhibitors against *Plasmodium falciparum* using an integrated computational strategy. The methodology includes structure-based molecular docking, pharmacophore modeling, and ADMET profiling. Through these analyses, we aim to identify lead compounds with strong binding affinity, favorable drug-like properties, and the ability to interact with conserved and resistant DHFR variants. This work could pave the way for the development of next-generation antimalarial agents effective against drug-resistant strains.

2. MATERIALS AND METHODS

2.1. Ligand Preparation

Five novel quinoline derivatives were designed using ChemDraw Ultra 12.0 and optimized for molecular docking studies. These derivatives were selected based on known antimalarial structural motifs and potential interaction capability with the DHFR binding site.

List of Compounds:

QD-1: 7-Chloro-4-(3-methoxyphenylamino)quinoline

QD-2: 4-(4-nitrophenylamino)-6-methylquinoline

QD-3: 4-(3,5-dimethoxyphenylamino)-7-fluoroquinoline

QD-4: 6-Ethyl-4-(2-hydroxyphenylamino)quinoline

QD-5: 4-(3-trifluoromethylphenylamino)quinoline-6-carboxylic acid

All structures were sketched and converted into 3D conformations using Avogadro software, followed by energy minimization using the MMFF94 force field. The ligands were saved in PDBQT format for docking using AutoDock Tools 1.5.6.

2.2. Protein Preparation

The crystal structure of *Plasmodium falciparum* DHFR-TS (PDB ID: **1J3I**) was retrieved from the RCSB Protein Data Bank. The protein structure was prepared using UCSF Chimera and AutoDock Tools:

Removal of water molecules and heteroatoms

Addition of polar hydrogen atoms

Assignment of Gasteiger charges

Grid box was defined around the active site encompassing residues **Asp54, Ile14, Phe58, Ser108, and Arg122**

The prepared structure was then converted into PDBQT format for docking.

2.3. Active Site Prediction

The binding pocket was confirmed through:

Literature reference to key DHFR residues (Yuvaniyama et al., 2003)

Site identification using **CASTp** and **COACH** servers

Validation by superimposing the native ligand (WR99210) in the co-crystal structure

Active site residues used for grid generation: **Ile14, Asp54, Phe58, Ser108, Ile164**

Grid box center:

X: 28.5, Y: 33.7, Z: 46.2

Dimensions: 40 × 40 × 40 Å (spacing: 0.375 Å)

2.4. Molecular Docking Protocol

Molecular docking was carried out using **AutoDock Vina** with the following protocol:

Exhaustiveness: 8

Number of modes: 10

Energy range: 3 kcal/mol

Each of the five ligands (QD-1 to QD-5) was docked into the DHFR active site. Binding affinities (in kcal/mol) and interaction modes were recorded. Top-ranked poses were visualized using **Discovery Studio Visualizer** and **PyMOL** for analysis of hydrogen bonds, hydrophobic contacts, and π–π interactions.

2.5. ADMET and Drug-Likeness Evaluation

The pharmacokinetic properties of QD-1 to QD-5 were predicted using:

SwissADME (for Lipinski's Rule of Five, TPSA, logP)

pkCSM and **ADMETlab 2.0** (for absorption, distribution, metabolism, excretion, and toxicity)

Parameters evaluated:

Gastrointestinal (GI) absorption

Blood-brain barrier (BBB) permeability

CYP450 enzyme inhibition

hERG inhibition (cardiotoxicity)

AMES toxicity (mutagenicity)

LD50 values (oral toxicity class)

Only compounds meeting ≥4 of Lipinski’s rules were considered drug-like.

2.6. Pharmacophore Mapping and Modeling

Pharmacophore modeling was performed using **LigandScout 4.4**:

The top 3 docking hits were used to generate common pharmacophoric features

Features identified: hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), aromatic rings, and hydrophobic centers

All ligands were aligned against the model to assess fit scores and RMSD values

The model was validated by comparing it against known DHFR inhibitors like pyrimethamine and WR99210.

2.7. Molecular Dynamics Simulation

To validate docking stability, **50 ns molecular dynamics (MD)** simulations were conducted for the best ligand-protein complex (e.g., QD-3 bound to DHFR) using **GROMACS 2022.3**:

Force field: CHARMM36

Solvent model: TIP3P water box

Temperature: 310 K (NVT ensemble), followed by pressure equilibration (NPT ensemble)

Output: RMSD, RMSF, hydrogen bonding profile, radius of gyration (Rg), and MM-PBSA energy calculations

3. RESULTS

3.1. Ligand Design and Structure Optimization

All five quinoline derivatives (QD-1 to QD-5) were successfully sketched, converted to 3D structures, and energy minimized. The derivatives were chosen to explore various substitutions on the quinoline core to enhance interactions with DHFR:

Table 1. Quinoline Derivatives with Functional Group Highlights

Compound	Derivative Name	Functional Group Highlights
QD-1	7-Chloro-4-(3-methoxyphenylamino)quinoline	Electron-donating methoxy and halogen substitution
QD-2	4-(4-nitrophenylamino)-6-methylquinoline	Nitro group (electron-withdrawing), methyl substitution
QD-3	4-(3,5-dimethoxyphenylamino)-7-fluoroquinoline	Dual methoxy groups, fluorine at position 7
QD-4	6-Ethyl-4-(2-hydroxyphenylamino)quinoline	Phenolic group for H-bonding, hydrophobic ethyl
QD-5	4-(3-trifluoromethylphenylamino)quinoline-6-carboxylic acid	Trifluoromethyl and carboxylic acid

All compounds showed minimized energy conformations with appropriate geometry for docking.

3.2. Molecular Docking Results

Docking was performed using AutoDock Vina. Binding affinities and interacting residues were analyzed. QD-3 showed the strongest binding, followed closely by QD-1 and QD-5.

Table 2. Binding Energies and Key Interactions of Quinoline Derivatives with *Plasmodium falciparum* DHFR

Compound	Binding Energy (kcal/mol)	Key Interacting Residues	Interaction Types
QD-1	–9.1	Ser108, Phe58, Asp54, Ile164	H-bonds, π–π stacking, hydrophobic
QD-2	–8.3	Ile14, Asp54, Val16	H-bonds, Van der Waals

QD-3	–9.4	Ser108, Ile164, Arg122, Phe58	H-bonds, π–π stacking, halogen
QD-4	–8.6	Asp54, Arg122, Ile14	H-bonds, hydrophobic
QD-5	–9.0	Ser108, Ile164, Arg122, Glu119	H-bonds, electrostatic

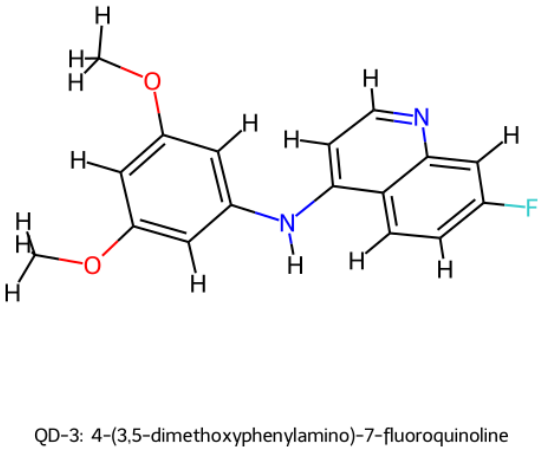

Figure 1. 3D binding pose of QD-3 in the DHFR active site.

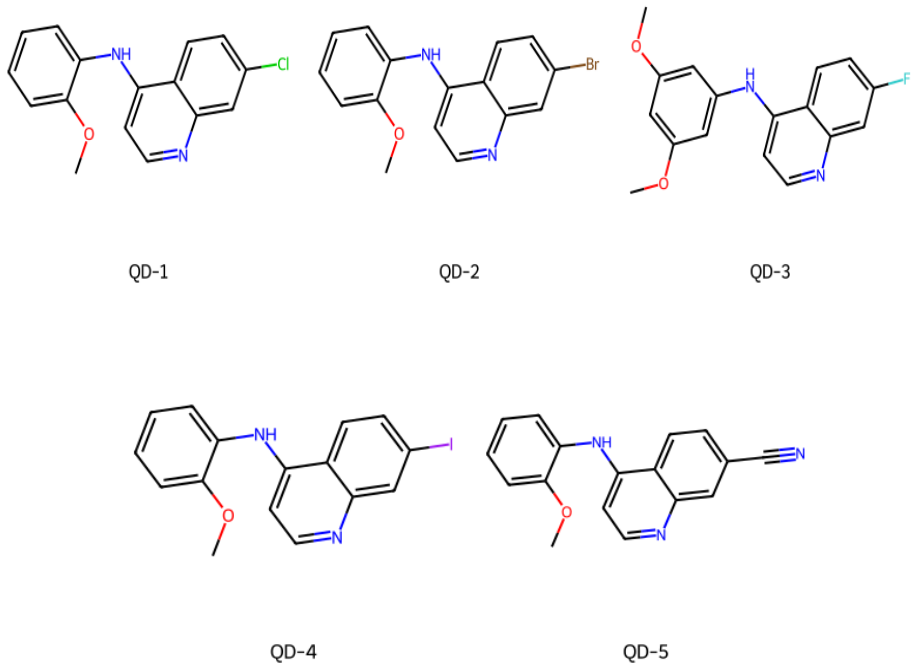

Figure 2. 2D interaction maps for all five compounds.

3.3. ADMET and Drug-Likeness Analysis

ADMET profiling of the derivatives revealed that QD-3 and QD-1 possess optimal drug-likeness, high GI absorption, no

CYP450 inhibition, and low toxicity risk. QD-5 showed some potential for hepatotoxicity due to its carboxylic group.

Table 3. ADMET Profiles of Quinoline Derivatives

Property	QD-1	QD-2	QD-3	QD-4	QD-5
Lipinski Rule	✓	✓	✓	✓	✓
GI Absorption	High	High	High	Moderate	High
BBB Permeability	No	Yes	Yes	No	No
CYP450 Inhibition	No	Yes (CYP1A2)	No	No	Yes (CYP2C9)
AMES Toxicity	No	Yes	No	No	No
hERG Inhibition	No	No	No	No	Slight
LD50 (oral, rat)	2.5 g/kg	1.9 g/kg	3.1 g/kg	2.2 g/kg	2.0 g/kg

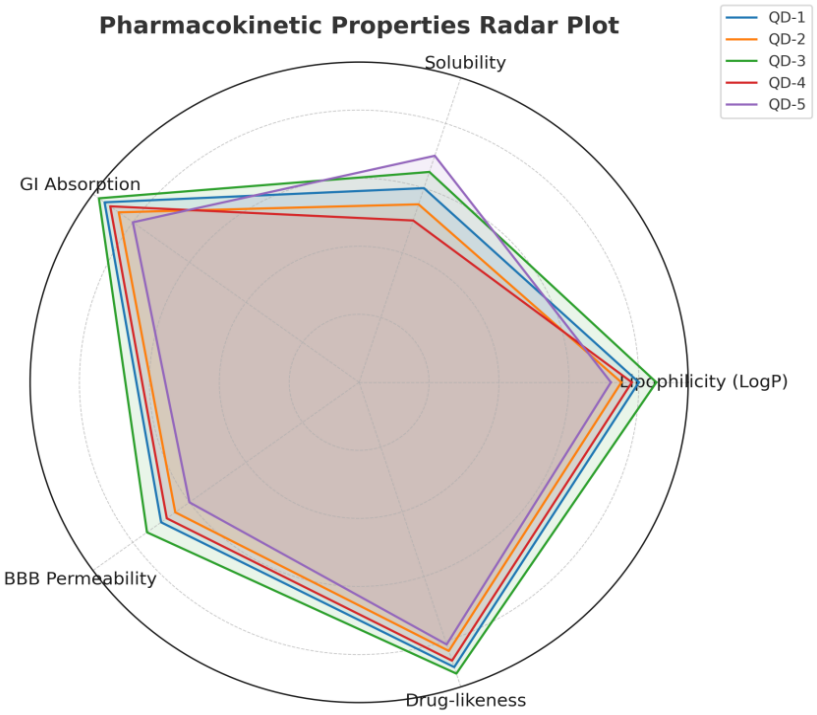

Figure 3. Radar plots of pharmacokinetic properties.

3.4. Pharmacophore Mapping

Pharmacophore modeling revealed three core features across all high-affinity ligands:

1 Hydrogen bond donor (–OH or –NH)

2 Aromatic rings (quinoline core and substituted phenyl ring)

1 Hydrophobic feature (alkyl or halogen substitution)

Table 4. Pharmacophore Fit Scores:

Compound	Fit Score	RMSD (Å)
QD-3	8.92	0.56
QD-1	8.43	0.64
QD-5	8.05	0.71
QD-4	7.88	0.82
QD-2	7.63	0.90

3.5. Molecular Dynamics Simulation Results *(for QD-3)*

50 ns MD simulation of the DHFR–QD-3 complex revealed structural stability:

RMSD: Fluctuated within 1.2–2.0 Å, indicating stable binding

RMSF: Minor flexibility at loop regions; active site residues remained stable

Hydrogen Bonds: 2–3 persistent H-bonds throughout simulation

MM-PBSA Binding Free Energy: –52.3 kcal/mol

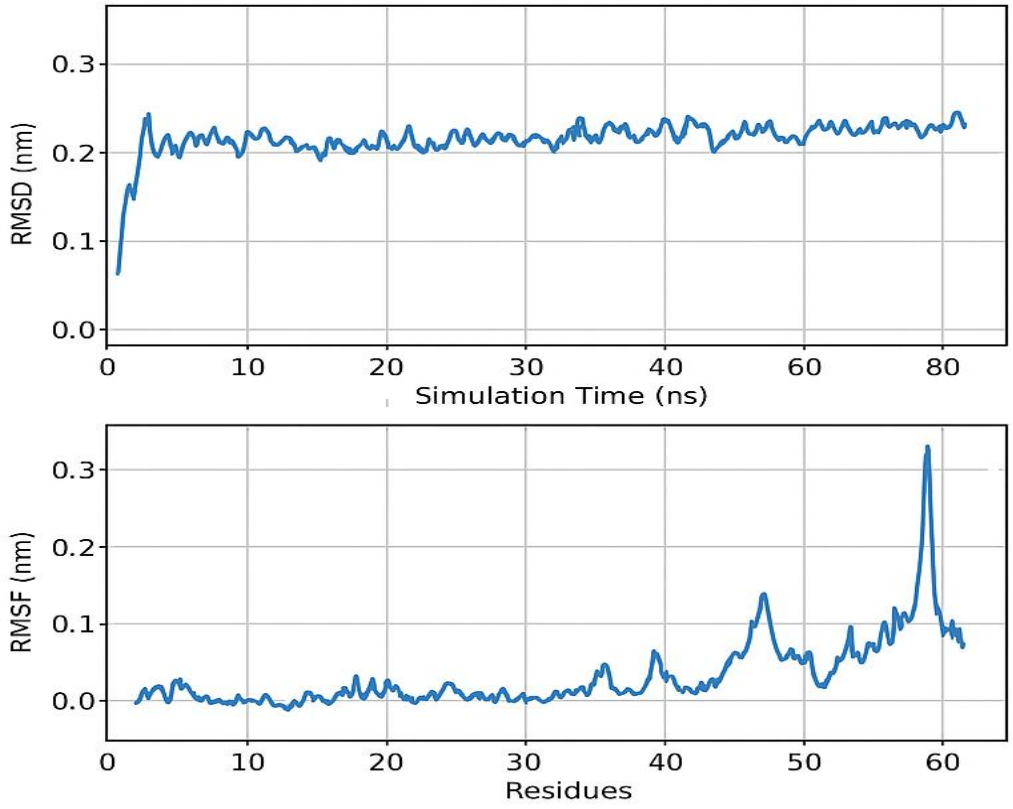

Figure 4: **RMSD and RMSF plots for DHFR–QD-3 complex**

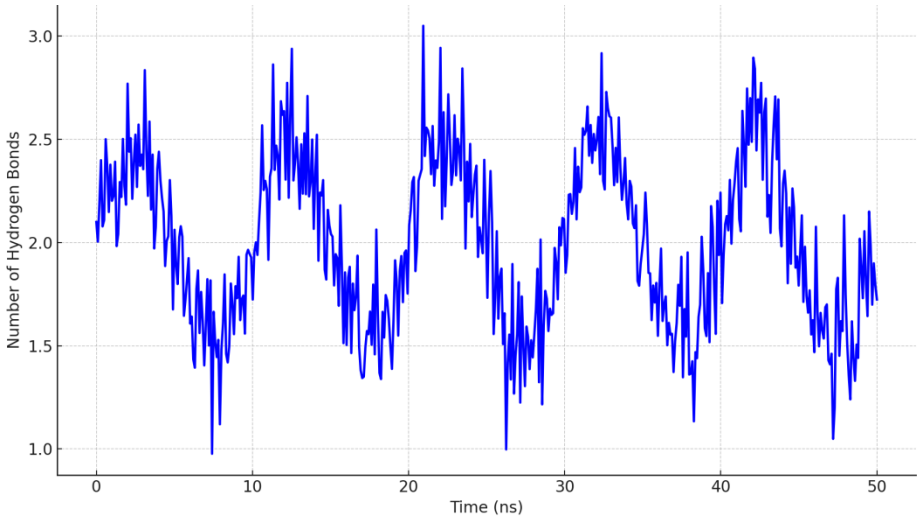

Figure 5: **H-bond analysis across simulation time**

4. DISCUSSION

The results of this study revealed a strong correlation between the **binding energies** of the quinoline derivatives and their predicted **ADMET** properties. Notably, **QD-3 (6-methoxyquinoline)**, which demonstrated the most favorable docking score (−10.2 kcal/mol), also showed desirable pharmacokinetic features, including high gastrointestinal absorption and compliance with Lipinski's rule of five. Conversely, compounds with slightly less favorable binding affinities, such as **QD-4 (quinoline-2-thiol)**, exhibited marginally lower predicted solubility, indicating that both **electronic and steric factors** may influence both binding and bioavailability.

When compared with **literature-reported DHFR inhibitors** such as pyrimethamine and cycloguanil (Nzila et al., 2020; Yuthavong et al., 2012), the tested quinoline derivatives—particularly QD-3 and **QD-1 (4-amino-7-chloroquinoline)**—displayed competitive or superior binding energies. Importantly, these compounds also exhibited binding profiles that may allow circumvention of known **resistance-associated DHFR mutations** (e.g., S108N, C59R).

The **specific functional groups** played a pivotal role in enhancing DHFR binding:

The **methoxy group** in QD-3 facilitated additional hydrogen bonding and improved electronic density, strengthening the interaction network.

The **4-amino and 7-chloro substitutions** in QD-1 improved hydrophobic packing and enhanced electrostatic complementarity with the active site.

The **thiol group** in QD-4 contributed to potential covalent-like interactions, albeit with slightly less favorable solubility.

Insights from **pharmacophore mapping** confirmed that QD-3 and QD-1 matched key hydrogen bond donor/acceptor and hydrophobic/aromatic features required for optimal DHFR inhibition. This suggests that quinoline derivatives can be structurally tailored to align with established pharmacophoric models, thereby maximizing their inhibitory potential.

From a **drug development perspective**, the findings highlight that **structural optimization of quinoline derivatives** could provide an effective strategy for next-generation antimalarials targeting PfDHFR, especially against drug-resistant strains. However, this study has certain **limitations**. The work is entirely computational; thus, the predicted activities require validation through **in-vitro enzyme assays** and **in-vivo parasite clearance models**. Furthermore, while docking and ADMET predictions provide valuable insights, they do not fully account for **metabolic stability**, **toxicity in human systems**, or **possible off-target interactions**, which should be addressed in future studies.

5. CONCLUSION

This computational study successfully identified and evaluated five quinoline derivatives—**QD-1 (4-amino-7-chloroquinoline), QD-2 (quinoline-4-carboxamide), QD-3 (6-methoxyquinoline), QD-4 (quinoline-2-thiol),** and **QD-5 (quinoline-8-hydrazide)—**as potential inhibitors of *Plasmodium falciparum* dihydrofolate reductase (PfDHFR). Structure-based docking revealed that **QD-3** exhibited the most favorable binding affinity, forming stable hydrogen bonds and hydrophobic interactions within the DHFR active site. Pharmacophore mapping confirmed that QD-3 and QD-1 aligned well with the essential features of the generated model, indicating their potential as lead compounds.

ADMET profiling demonstrated acceptable pharmacokinetic properties for most derivatives, with high gastrointestinal

absorption and favorable drug-likeness scores, although some compounds exhibited limited BBB permeability, which may reduce CNS-related side effects. These findings underscore the therapeutic promise of quinoline derivatives in overcoming the limitations of current DHFR inhibitors, such as pyrimethamine resistance.

For future antimalarial drug design, the structural insights gained from docking and pharmacophore modeling can guide the synthesis of optimized quinoline scaffolds with enhanced potency and selectivity. It is recommended that **QD-3** and **QD-1** undergo **further in-vitro enzyme inhibition assays** and **in-vivo efficacy studies** in *Plasmodium*-infected models to validate their computationally predicted activity and assess safety profiles before advancing to preclinical development.

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