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In silico Anti-malaria Activity of Quinolone Compounds against *Plasmodium falciparum* Dihydrofolate Reductase (pfDHFR)

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Authors' contributions

This work was carried out in collaboration among all authors. Author TAB designed the study, carried out the molecular docking. Authors DAO and OAS interpreted the docking results and manage the analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

Chemotherapy remains the kernel of malaria control and the available antimalarial drugs are not only expensive but also parade heterogeneous levels of toxicity and may invoke poor compliance in patients. The present study focuses on the screening of quinolone compounds against *Plasmodium falciparum* dihydrofolate reductase (pfDHFR) for anti-malarial potential using Glide (Schrodinger maestro 2017-1). Computational tool using Glide was employed to investigate the therapeutic relevance of six (6) quinolone derivatives retrieved from PUBCHEM via molecular docking against pfDHFR retrieved from protein data base. The results showed that, Lascufloxacin and moxifloxacin bind with higher affinity and lower free energy with catalytic domain of pfDHFR with glide score of -6.597 and -5.653 respectively compared to standard ligand (quinine) with glide score of -3.728. Lascufloxacin interacted with amino acid residue of the catalytic domain (SER 511, ARG 510, GLU 382) as evaluated by energy decomposition per residue lascufloxacin-pfDHFRcomplex. The results from this investigation, thus proposed quinolone derivatives as hit lead drug candidates which may be consider as potential inhibitor of pfDHFR.

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Keywords: Quinolone; dihydrofolatereductase; molecular docking; lascufloxacine; Malaria.

1. INTRODUCTION

Malarial has remained one of the devastating diseases in the tropic and sub-tropic regions of the world despite the global fight against this life threatening disease [1]. Plasmodium genus is the major cause of the disease and it remains the major causes of mortality [2]. Chemotherapy remains the major chemotherapeutic approach to the treatment of malaria and several anti-malarial drugs have been produced such as quinines, quinolones, artemether, antifolates etc.

Quinine, first isolated from the bark of the cinchona tree in 1820, quinine has been used as one of the most effective treatments for malaria to date [3]. Resistance was first reported in the 1980s [4]. Antifolate drugs for malaria treatment inhibit folate metabolic pathway which is crucial to plasmodium survival. The drugs tend to inhibit dihydrofolatereductase or dihydropteroate synthase, these enzymes are important in the de novo synthesis of folate resulting in inhibition of pyrimidines, purines, and some amino acids biosynthesis [5]. Antifolate drugs have been used as effective treatment regime with their efficacy compromised as a result of resistance at the binding site of dihydrofolatereductase [2].

Quinolones are often synthesized via a chemical method as reported by [6]. Quinolones are synthetic compounds containing the 4-oxo-1,4-dihydroquinoline skeleton. The quinolone nucleus is a chemotype, common to classes of chemotherapeutic agents such as antibiotics, anti-viral and cancer drugs [7]. Therefore, quinolones are mostly use as antibiotics with the discovery of nalidixic acid possessing antibacterial property against gram-negative bacteria [5]. Quinolone derivatives have been involved in the structures of certain anti-cancer and anti-viral drugs and also anti-oxidants [7]. Reports on the anti-malarial efficacy of quinolones are relatively limited. However, study involving anti-malarial potential of quinolones indicates that, these compounds possess promising potential showing several potency and target in several stages of malarial parasite life cycle. Thus, the present study aimed to assess the inhibitory potential of quinolone derivatives against plasmodium falciparum dihydrofolatereductase (pfDHFR) using computational approach.

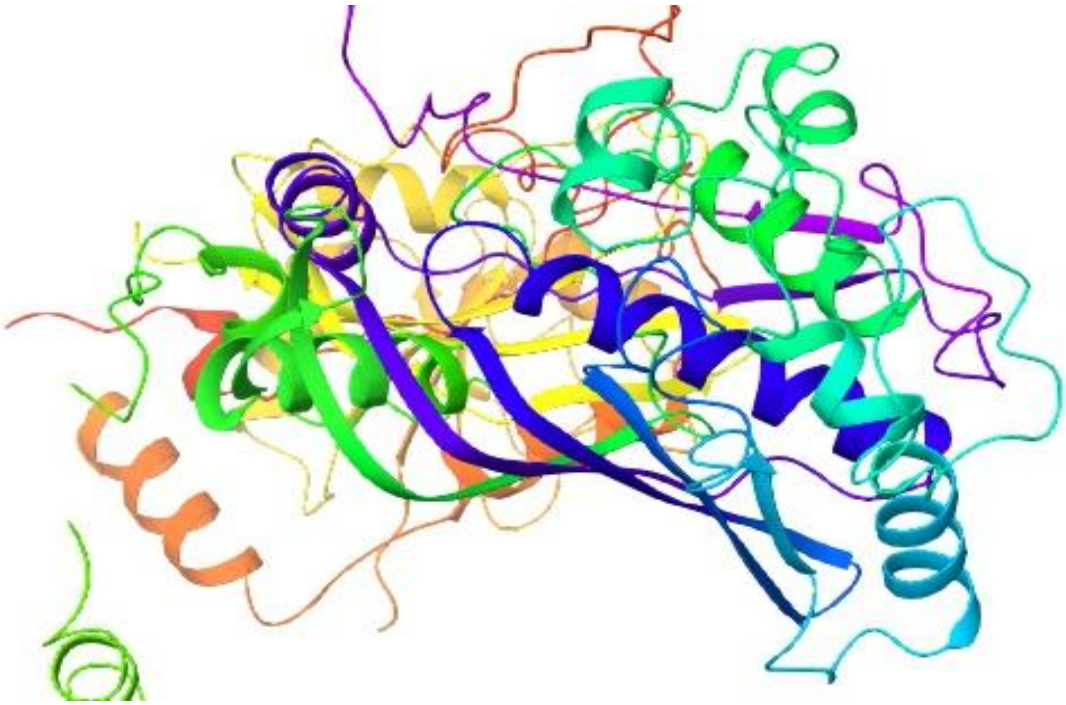

Fig. 1. 3D Structure of the protein (*Plasmodium falciparum* Dihydrofolate Reductase)

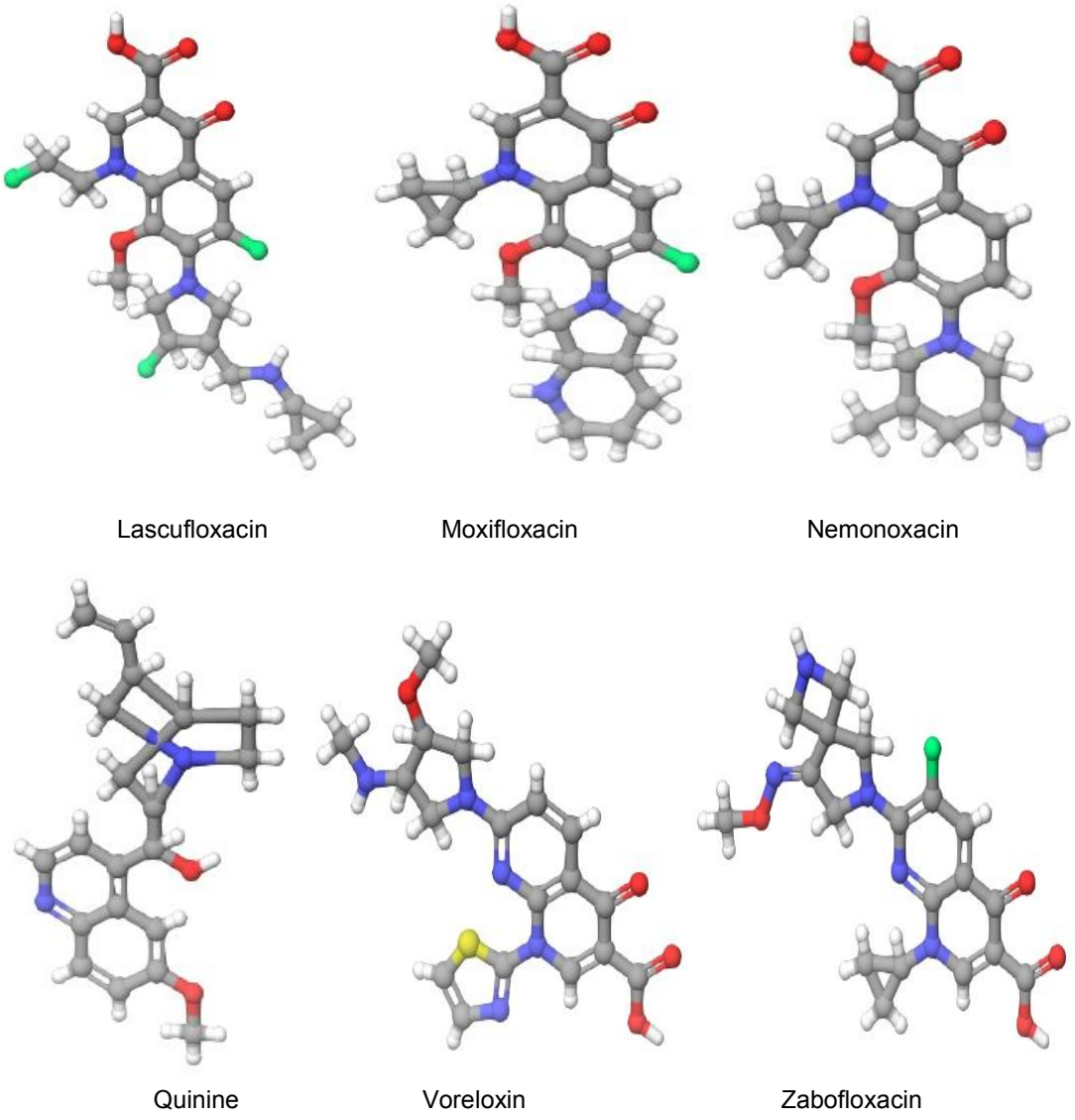

Fig. 2. 3D Structure of Ligands

2. MATERIALS AND METHODS

2.1 Methodology

Glide tool from Schrodinger molecular drug discovery suite (version 2017-1) was used in this research.

2.2 Ligands Preparation

Six (6) phyto-compounds of quinolone derivatives used in this research were obtained from published literatures and they were used to prepare the library for this research. The compounds were retrieved from NCBI PubChem database(https://www.ncbi.nlm.nih.gov/pccompound) in 2D (sdf) format. The ligands were prepared by LigPrep module of Maestro 11.5 interfaces in the Schrodinger suite 2017-1. They were converted from 2D to 3D structures by including stereo chemical, ionization, tautomeric variations, as well as energy minimization and optimized for their geometry, desalted and corrected for their chiralities and missing hydrogen atoms. The bonds orders of these ligands were fixed andthe charged groups were neutralized. The ionization and tautomeric states were generated between pH of 7.0 +_ 2.0 using Epik module. In the LigPrep module, the compounds were minimized by Optimized

Potentials for Liquid Simulations (OPLS3) force field. A single low energy ring confirmation per ligand was generated and the optimized ligands were used for docking analysis [6].

2.3 Protein Preparation

The crystal structure of protein *plasmodium falciparum* Dihydrofolate Reductase was retrieved from Protein Data Bank (http://www.rcsb.org/pdb/home.do) with PDB ID: 6A2K. The 3D structured was viewed with maestro 11.5 interface. In general, the protein structures are refined for their bond orders, formal charges and missing hydrogen atoms, topologies, incomplete and terminal amide groups as well as missing side chains. The water molecules beyond $5A^{o}$ were removed. The possible ionization states were generated in the protein structure and the most stable state was chosen. The hydrogen bonds were assigned and orientations of the retained water molecules were corrected. Finally, a minimization of the protein structure was carried out using OPLS3 force field to reorient side-chain hydroxyl groups and potential steric clashes. The minimization is restrained to the input protein coordinates by a predefined Root Mean Square Deviation (RMSD) tolerance of $0.3A^{o}$.

2.4 Receptor Grid Generation

The area of interaction between the proteins and ligands were generated with receptor grid generation module of maestro 11.5. The binding boxdimensions (within which the centroid of a docked pose is confined)of the protein in terms of coordinates is x, y, z.

2.5 Molecular Docking Using Glide

Molecular docking of the designed molecules was carried out usingthe receptor grid and the ligand molecules on maestro 11.5. The favorable interactions between ligand molecules and the receptor were scored using Glidemodule of ligand docking program. All the docking calculations were performed using extra precision (XP) mode with ligand sampling as none refine only. The docking process was run in a flexible docking mode which automatically generates conformations for each input ligand. The ligand poses generated were passed through a series of hierarchal filters that evaluate the ligand's interaction with the receptor. The spatial fit of the ligand to the defined active site, and examines the complementarity of the ligand receptorinteractions using grid-based method by the empirical Chem Score function. This algorithm recognizes favourable hydrogen bonding, hydrophobic, metal-ligation interactions, and penalizes steric clashes. Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization ofgrid approximation OPLS non bonded ligand-receptor interaction energy. Finally, the minimized poses were re-scored using Glide Score scoring function.

2.6 ADME Toxicity Screening

The in-silico ADME (Absorption, Distribution, Metabolism and Excretion) properties of the proposed compounds were determined by qikprop module of Schrodinger software 2017-1, maestro 11.5 version.

3. RESULTS AND DISCUSSION

The current study utilize computational techniques to study the molecular interaction, toxicity screening and inhibitory potential of quinolone derivatives against pfDHFR. The docking poses were ranked according to their docking scores, together with the ranked list of docked ligands and their corresponding binding poses [8].

Table 1. Docking results of phyto-compounds from quinine derivatives against *Plasmodium falciparum* Dihydrofolatereductase

S/N	Entry Name	Dock score	Glide score	Glide model
1.	Lascufloxacin	-5.404	-6.597	-45.860
2.	Moxifloxacin	-4.555	-5.653	-57.097
3.	Zabofloxacin	-3.896	-3.941	-35.484
4.	Quinine(standard ligand)	-3.713	-3.728	-43.258
5.	Voreloxin	-3.636	-3.679	-40.038
6.	Nemonoxacin	-3.506	-4.423	-50.862

Table 2. Insilico ADME Toxicity Screening

S/N	Entry Name	ROF	HOA	MW	Qlogkhsa	Pubchem Comp ID	Pubchem Molecular Formula
1.	lascufloxacin	0	2 (Medium)	439.434	0.396	71528768	$C_{21}H_{24}F_3N_3O_4$
2.	moxifloxacin	0	2 (Medium)	401.437	0.278	152946	$C_{21}H_{24}FN_3O_4$
3.	nemonoxacin	0	2 (Medium)	371.435	0.215	11993740	$C_{20}H_{25}N_3O_4$
4.	quinine(standard ligand)	0	2 (Medium)	324.422	0.260	3034034	$C_{20}H_{24}N_2O_2$
5.	voreloxin	0	2 (Medium)	401.439	-0.402	9952884	$C_{18}H_{19}N_5O_4S$
6.	zabofloxacin	0	2 (Medium)	401.396	0.134	10388396	$C_{19}H_{20}FN_5O_4$

ROF Viol: Rule of Five Violations. HOA: human Oral Absorption. M.W: Molecular Weight of compounds. Normal range is between 130.0 and 735.0. M.F: Molecular Formula. QlogKhsa: Prediction of binding to human serum albumin. Normal range between -1.5 to 1.5

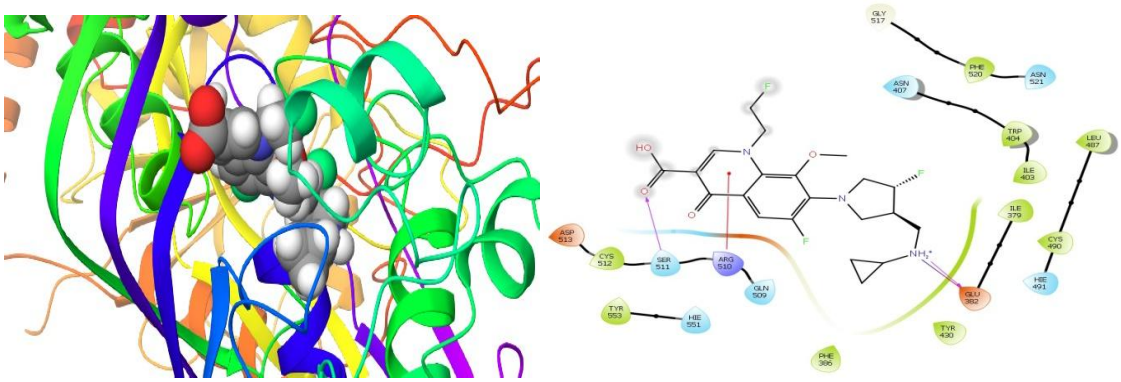

Fig. 3. Protein-ligand interaction of Lascufloxacin against pfDHFR

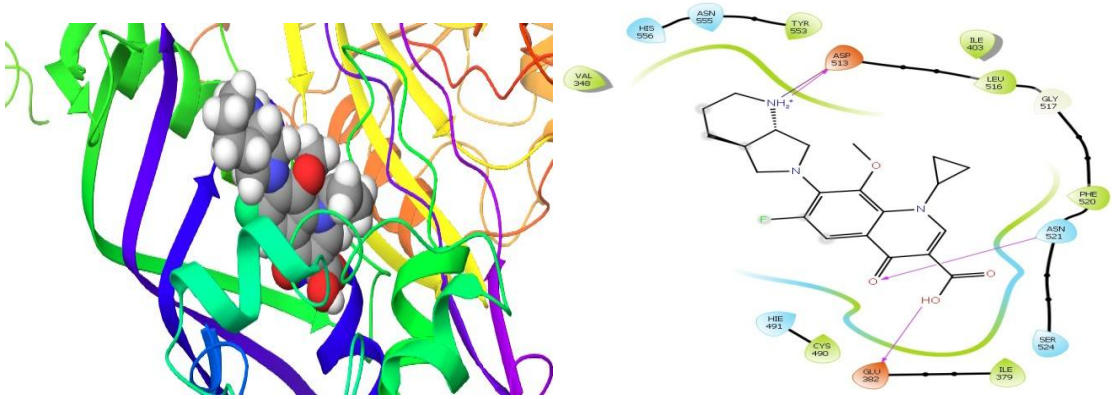

Fig. 4. Protein-ligand interaction of Moxifloxacin against pfDHFR

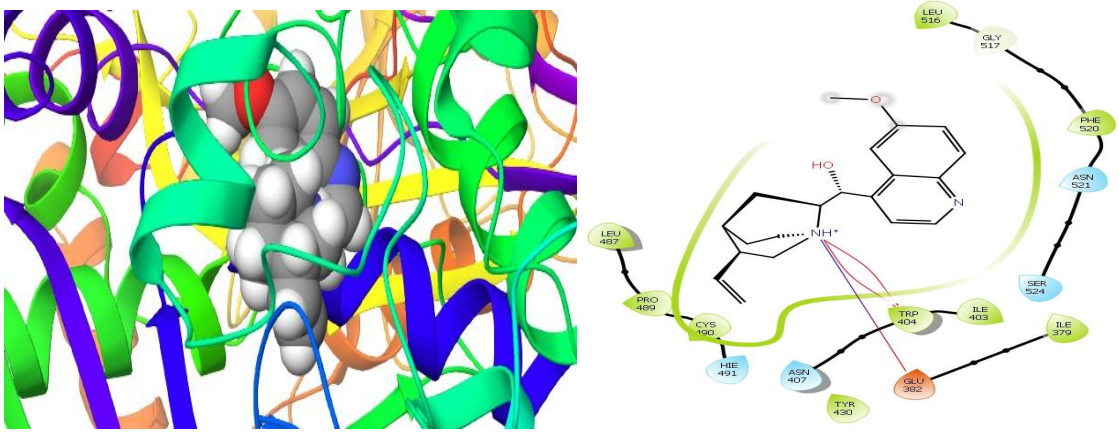

Fig. 5. Protein-ligand interaction of Quinine against pfDHFR

Molecular Docking is one of the most frequently used methods in structure-based-drug-design (SBDD) because of its ability to predict, with a substantial degree of accuracy, the conformation of small-molecule ligands within the appropriate target binding site [9]. The docking results from this research which investigate the crucial molecular events, including ligand binding modes and corresponding intermolecular interaction that stabilize the ligand receptor complex of six (6) compounds of quinine compounds downloaded from NCBI database against pfDHFR. The

docking results and ADME toxicity screening of the compounds and standard ligands (quinine) were showed in Tables 1-2.

Molecular docking programs use scoring functions for energy calculation of the predicted ligand-receptor complexes. The difference in energy is due to the binding of the ligand to the active site of the protein, is given by the binding constant and the Gibbs free energy [10]. Prediction of the binding energy is performed by evaluating the most important physical-chemical phenomena involved in ligand-receptor binding, including intermolecular interaction such as hydrogen bond interraction, desolvation and entropic effects [11].

The docking score of the compounds shows that three phyto-constituents namely lascufloxacin, moxifloxacin and zabofloxacin have a high binding affinity of -5.404, -4.555, -3.896 respectively at the active site of the protein (pfDHFR) as compared to the standard ligand with the docking score of -3.713.However, the following ligands, voreloxin and nemonoxacin demonstrated a lower binding score of -3.636 and -3.506 respectively than the standard ligand.

Thus, The ligand (lascufloxacin) with highest docking score shows the binding affinity with the amino acid residues at SER 511, ARG 510,GLU 382. The above residues are acting as a binding pocket for the ligand. Thus, it can be validated that the quinine derivatives will be more effective against pfDHFR compared to the standard drug quinine.

The ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of the phyto-compounds depicts the efficiency and abilty of the ligand to reach its target protein and rate of excretion from the body [2]. The pharmacokinetics of the ADMET screening obeys the lipinski's rule of five (ROF) which shows the pharmacological properties of the compounds. This attributes includes a molecular weight that is less than 500Da(<500Da), hydrogen bond donors that is less or equal to 5(≤5),hydrogen bond acceptors that is less or equal to (≤10) and octanol water partition coefficient (logP) that is less than 5(<5) [2]. Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution of the compounds is in the range of 1-2 [12].Therefore, table 2 show that the ADMET properties of this compounds agrees with these rules most especially the Rule of Five violations (ROF).In addition, the Qlogkhsa shows that the compounds will bind effectively to human serum albumin. Therefore, they exhibit drug-like character. In addition, the molecular docking and ADMET screening of phyto-compounds of quinine derivatives shows that lascufloxacin, moxifloxacin, zabofloxacin, voreloxin, and nemonoxacin might be of therapeutic purpose for the treatment of the resistant malaria parasite. Thus, we conclude that further studies should be employed to explore the pharmacological properties of quinine derivatives.

4. CONCLUSION

The computational study of the quinolone derivatives shows that, they might be a potent inhibitor of the *plasmodium falciparum* dihydrofolatereductase. The quinolone derivatives such as lascufloxacin, moxifloxacin and nemonoxacin showed better molecular interaction than the standard ligand (quinine) via hydrogen bonding and pi-stacking.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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