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Molecular docking screening, in silico drug design and ADME prediction of 10-amidinobenzonaphthyridines as potent inhibitors of Plasmodium falciparum Lactate Dehydrogenase

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Abstract: Management and control of malaria remain challenging due to the continuous emergence of drug resistance and the adaptive nature of the mosquito vector. This necessitates the constant discovery of potent antimalaria drugs. Lactate dehydrogenase from *Plasmodium falciparum* (*Pf*LDH) is an essential catalyst for the parasite's energy production. *Pf*LDH is a significant target in the design and discovery of antimalarial drugs because its inhibition leads to the parasite' death. In this work, fifteen 10-amidinobenzonaphthyridine molecules active against Chloroquine-sensitive and Chloroquine-resistant strains of *P. falciparum* were screened through molecular docking to find lead inhibitor of *Pf*LDH. The binding affinities of the compounds ranged from -5.5 to -7.8kcal/mol. The compound with the highest binding affinity was modified and nine novel 10-amidinobenzonaphthyridines were designed. The designed compounds have better binding affinity toward the target ranging from -7.8 to -8.8kcal/mol and four of which have better binding affinities than Pyronaridine, a 10-amidinobenzonaphthyridine antimalaria drug. Furthermore, ADME properties of the designed compounds were predicted *in silico* and their drug-likeness investigated using Lipinski's rule of five and Veber's rule of two. Based on these rules, compounds D1, D2, D3, D4, D5 and D8 are potential oral drug candidates. Compounds D2, D3 and D8 have good binding affinities and ADME properties therefore, can be developed into potent antimalaria targeting *Pf*LDH. The results of this work can be used to develop an active antimalaria drug capable of inhibiting *Pf*LDH.

Keywords: Molecular docking, 10-amidinobenzonaphthyridine, Plasmodium falciparum lactate dehydrogenase, ADME properties, in silico drug design

1. Introduction

Malaria is an infection common in the tropical and subtropical regions of the world, prevalent in Africa with 94% of the global cases in 2022 [1]. The heaviest malaria burden in the region can be attributed to poor hygiene that encourages the breeding of the vector (female Anopheles mosquitoes) transmitting the parasites (Plasmodium) from human to human. According to WHO's 2023 world malaria report, Nigeria is responsible for 27% and 31% global malaria cases and deaths respectively making it the most endemic country in the world [1]. Plasmodium falciparum malaria is the commonest in Africa and the most threatening which can cause dysfunction of the kidneys, lungs, liver, and the brain in case of cerebral malaria [2]. Chemotherapies used in the treatment of malaria are drugs from quinoline derivatives, artemisinin derivatives, antifolates and some antibiotics [3-6]. The greatest challenge in treating malaria is the parasite's resistance to any developed drugs. A fast-acting and a long-acting antimalarial are used together as combination therapy to reduce the development of resistance and have improved efficacy than monotherapy. World Health Organization recommended the use of

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artemisinin-based combination therapy to treat uncomplicated falciparum malaria [7]. These therapies such as artesunate/amodiaquine and artemether/lumefantrine are fundamental to the control of malaria in Africa. However, the emergence of artemisinin resistance is broadening across Africa and other part of the world, and high level of treatment failure in the use of artemisinin-based combination therapy was detected [1]. These pose a serious threat to the fight against malaria. Therefore, there is need for continuous exploration of therapeutic agents that can fight Plasmodium parasites.

The traditional approach to drugs discovery is an iterative process involving lots of chemical synthesis and testing for potential therapeutic activities. This makes the drugs discovery process costly, time-consuming and prone to failure. Rational drug design and discovery which relies on computational methods and technologies is a helpful approach in this direction. It deals with selection of only potent lead molecules, thereby preventing the late stage clinical failures, thus a major reduction in cost and time [8]. It involves the screening of test compounds by application of molecular docking technique to design target-specific compounds that bind strongly to the active site of the molecular target of interest [9]. Plasmodium falciparum lactate dehydrogenase (PfLDH) is an important enzyme for the survival of malaria parasites. It controls the production of adenosine triphosphate by catalyzing the interconversion of lactate and pyruvate in the final step of the glycolytic pathway during the anaerobic erythrocytic stages of the parasite's life cycle [10,11]. Inhibition of PfLDH leads to the parasite's death; therefore it is a significant target in the design and discovery of antimalarial drugs [12]. Chloroquine exerts its antimalarial activity by inhibition of PfLDH [13]. Pyronaridine, a 10-amidinobenzonaphthyridine shares similar mechanism of action with Chloroquine in fighting P. falciparum, therefore can be an inhibitor of PfLDH [14].

10-amidinobenzonaphthyridines such as Azacrin, Mepacrine and Pyronaridine have clinical use for the treatment of malaria. Pyronaridine is the most potent and has been used in Africa for the treatment of Chloroquine-resistant P. falciparum malaria [15]. However, Pyronaridine is a Mannich base and the use of Mannich base antimalarials has been strictly restricted because of hepatoxicity and agranulocytosis side effects linked to their long term use [16]. Ai and co-workers designed, synthesized and assessed the antimalarial activities of fifteen 10-amidinobenzonaphthyridine derivatives which are not Mannich base and may not likely have hepatotoxicity side effects like Pyronaridine [17]. Herein we investigated the interactions of these 10-amidinobenzonaphthyridines with the crystal structure of PfLDH as the potential target using a molecular docking study with to find a lead molecule and use it to design better inhibitors of the target as active antiplasmodial agents. Furthermore, ADME (absorption, distribution, metabolism, and elimination) properties of the designed molecules were predicted in silico to evaluate their drug-likeness.

2. Computational Method

2.1. Data collection

The 10-amidinobenzonaphthyridine derivatives used in this work were obtained from the article of Ai and co-workers where they were synthesized and tested to have potent activities against Chloroquine-sensitive D6 and Chloroquine-resistant W2 strain of *P. falciparum* (Table 1) [17]. Furthermore, the crystal structure of *Pf*LDH co-crystalized with chloroquine was downloaded in PDB format from the protein data bank (PDB ID: 1CET) [18].

2.2. Data preparation

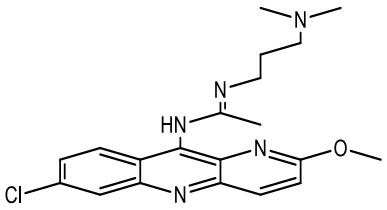
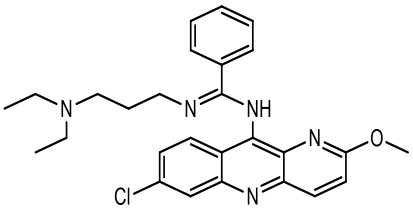
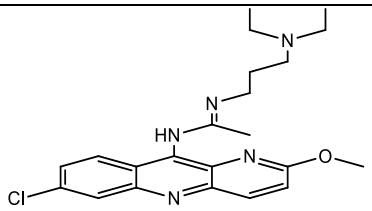
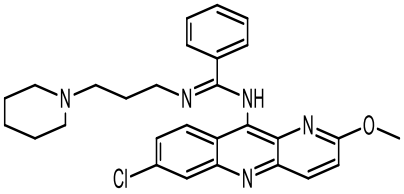
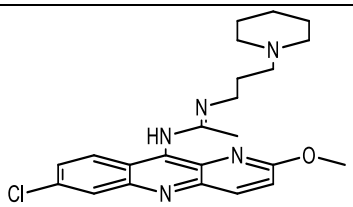
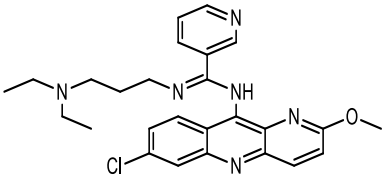
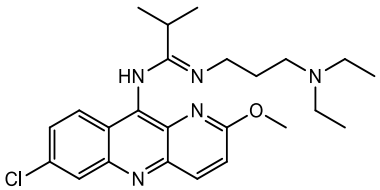
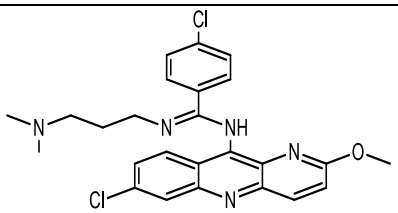
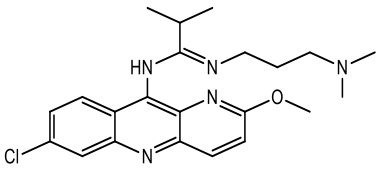
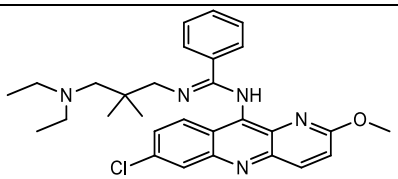
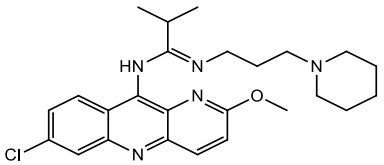
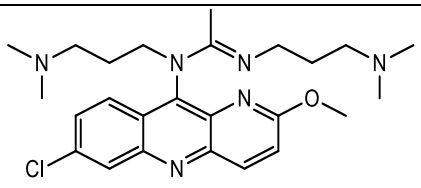
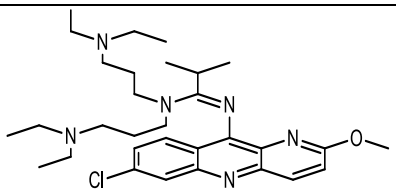
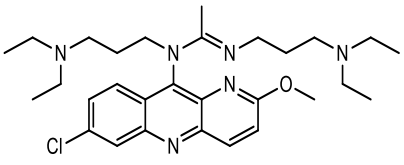
The structures of the 10-amidinobenzonaphthyridines as shown in Table 1 were drawn using Chemdraw, then exported to Spartan 14 software where they were optimized using B3LYP functional with 6-31G basis set and saved in PDB format [19, 20]. The downloaded *Pf*LDH was imported to Discovery Studio software its co-crystallized ligand, water molecules and hetero-atoms were removed, then Hydrogen atoms were added to supplement broken bonds and saved in PDB format. Figure 1 shows the crystal structure of the prepared receptor.

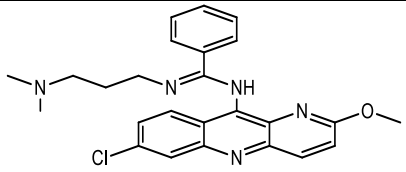
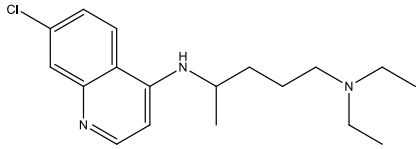
2.3. Molecular docking study

The prepared 10-amidinobenzonaphthyridines and the prepared *Pf*LDH were exported to pyrex

software where they were made ligands and the former was made macromolecule (receptor) all in PDBQT format. Autodock Vina in Pyrx software was used to dock the ligands and the receptor with grid box dimensions of 85.60Å x 44.25Å x 55.56Å and center of 25.80 x 26.87 x 9.39 (X x Y x Z) [21]. The receptor was re-docked with Chloroquine to assess the reliability of the protocol and docked with Pyronaridine for comparison.

Table 1. 10-amidinobenzonaphthyridine derivatives with their *in vitro* antiplasmodial activities

C/N	Structure	IC_{50} (nM)		C/N	Structure	IC_{50} (nM)	
		D6	D6			D6	
1		26	100	9		1.7	5.6
2		17.6	41	10		5.1	3.3
3		8.0	24.9	11		7.2	20.6
4		2.0	8.8	12		2.8	6.6
5		2.2	9.7	13		21.8	61
6		1.1	3.96	14		11.7	80.8
7		1.1	6.1	15		1.3	9.5

8		1.8	1.98	CLQ		15	525

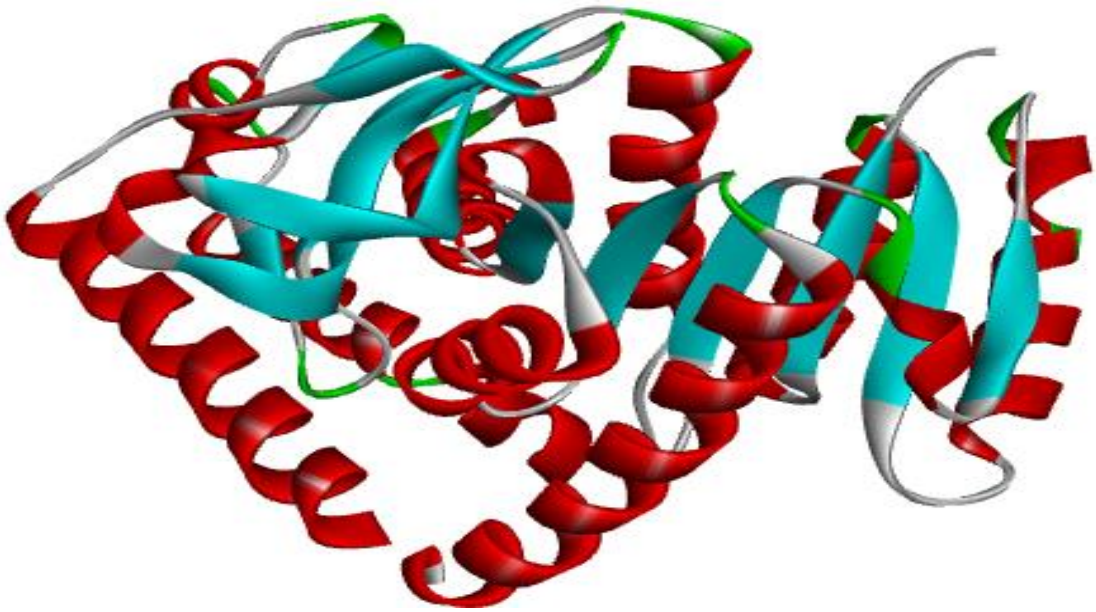


Figure 1. Crystal structure of *Plasmodium falciparum* lactate dehydrogenase (*pf*LDH)

2.4. Molecular design and ADME prediction

A lead compound was identified based on the docking result and used as a template in designing novel 10-amidinobenzonaphthyridines. This was achieved by substitution and adding of atoms at some strategic positions on the structure of the template to improve its interaction with the target, PfLDH. ADME property predictions were carried out using SwissADME free online software (http://www.swissadme.ch/) [22]. The physicochemical properties considered were molecular weights, partition coefficients, cLogP, topological polar surface areas (TPSA), number of hydrogen bond acceptors and donors, number of rotatable bonds and percentage absorption (ABS) determined as; % ABS = 109 – (0.345 × TPSA) [23]. Lipinski's rule of five and Veber's rule of two were the guides used to assess the drug-likeness of the designed compounds [24, 25].

3. Results and discussion

Table 2 shows the result of docking of the 10-amidinobenzonaphthyridines with pfLDH. The compounds bind to the target protein through different amino acids indicating different modes of action. All the compounds interacted strongly with the active sites of the target through significant hydrogen bonding and hydrophobic interactions with the amino acids of the protein. The binding affinities of the compounds ranged from -5.5 to -7.8kcal/mol are mostly better than that of Chloroquine, a well known inhibitor of pfLDH. However, the binding affinity of Pyronaridine is better than that of all the compounds (Table 2).

Table 2. Molecular docking result between *pf*LDH and 10-amidinobenzonaphthyridines

Ligand-Receptor	Binding affinity (kcal/mol)	Hydrogen bonding Amino acid(Bond length Å)	Hydrophobic interaction Amino acid[bond type]

1-*pf*LDH	-6.9	GLY99(1.96)[a], GLY99(1.96)[a], GLY99(2.26)[a], ASN140(3.47)[b], PRO246(3.47)[b]	MET30[c], TYR247[d]
2-*pf*LDH	-6.6	ASP230(2.89)[a], LEU201(3.019)[a], LEU201(2.67)[a]	VAL233[f], PHE229[e], VAL233[c]
3-*pf*LDH	-7.5	LEU201(2.22)[a], LEU201(2.14)[a], GLU311(3.63)[b] LEU201(2.62)[a],	PHE229[e], PHE229[e], LYS203[c], ARG204[c], LEU201[d], LYS203[d]
4-*pf*LDH	-6.4	LEU201(1.97)[a], LEU201(2.44)[a]	PHE229[e], PHE229[e], LEU201[d], LYS203[d]
5-*pf*LDH	-6.6	ASN197(2.67)[a], ASP230(2.57)[a], ASP230(2.73)[a]	VAL233[f], VAL200[c], LYS314[c], VAL233[d], LYS314[d]
6-*pf*LDH	-7.2	LEU201(1.98)[a], LEU201(2.44)[a]	PHE229[e], PHE229[e], LYS203[c], ARG204[c], LEU201[d], LYS203[d]
7-*pf*LDH	-5.5	LEU201(2.29)[a], LEU201(3.10)[a], LEU201(2.32)[a], MET199(3.58)[b]	PHE229[e], PHE229[e], LEU201[d], LYS203[d]
8-*pf*LDH	-7.4	LEU201(2.08)[a], LEU201(2.11)[a], LEU201(2.53)[a]	PHE229[e], PHE229[e], LEU201[d], LYS203[d], LYS314[d]
9-*pf*LDH	-6.9	LEU201(2.18)[a], LEU201(2.13)[a], LEU201(2.46)[a]	PHE229[e], PHE229[e], LEU201[d], LYS203[d], LYS314[d]
10-*pf*LDH	-7.8	MET199(2.66)[a], MET199(2.33)[a], LEU201(3.46)[b] MET199(3.38)[b],	LYS203[c], PHE229[d], VAL233[d], LYS198[d], VAL233[d]
11-*pf*LDH	-6.5	LEU201(2.74)[a], LEU201(2.45)[a], ASP230(2.29)[a], MET199(3.53)[b], LYS198(3.72)[b], MET199(3.51)[b]	LEU201[c], VAL233[c], PHE229[d], LYS203[d], LYS203[d], LYS203[d]
12-*pf*LDH	-7.4	LEU201(1.91)[a], LEU201(2.10)[a], LEU201(2.29)[a], GLU311(3.59)[b]	PHE229[e], PHE229[e], LYS314[c], LEU201[d], LYS203[d], LYS314[d],
13-*pf*LDH	-7.1	LEU201(2.20)[a], LEU201(2.62)[a], LEU201(2.10)[a], MET199(3.46)[b], GLU311(3.53)[b]	PHE229[e], PHE229[e], LEU201[d], LYS203[d], LYS314[d]
14-*pf*LDH	-5.8	LYS173(2.61)[a], LYS173(2.68)[a], ALA252(3.47)[b], GLU256(3.64)[b], GLU256(3.53)[b], GLU256(3.56)[b] VAL166(3.67)[b],	PRO184[d], LYS173[d], ARG185[d], PRO184[d]
15-*pf*LDH	-6.1	ASN197(2.31)[a], GLY196(3.56)[b]	GLY196[f], HIS195[e], HIS195[e], HIS195[e], LEU167[c], PRO250[c], ALA236[d], ALA236[d], ALA236[d]
CLQ-*pf*LDH	-6.1	ASP230(2.58)[a], LEU201(2.80)[a], MET199(3.45)[b]	PHE229[e]
PNR-*pf*LDH	-8.2	LEU201(1.88)[a], ASN308(2.76)[a], LEU201(2.28)[a], LEU201(2.13)[a], GLU310(3.50)[b], GLU311(3.51)[b]	PHE229[e], PHE229[e], LYS203[c], ARG204[c], LEU201[d], LYS203[d]

CLQ = Chloroquine, PNR = Pyronaridine, a = Conventional Hydrogen Bond, b = Carbon Hydrogen Bond, c = Alkyl-Alkyl interaction, d = Pi-Alkyl interaction, e = Pi-Pi interaction, f = Pi-Sigma interaction

Figure 2 shows the 2D and 3D interaction of compound 10 with the pfLDH. This interaction has the best binding affinity among the 10-amidinobenzonaphthyridines. Therein are two

conventional hydrogen bonds between the C=O of MET199 and one of the NH of the benzonaphthyridine moiety, and one of the NH of the extended 10-amidino carbon chain. The interaction contained two Carbon hydrogen bonds; one between the C=O of MET199 and Carbon of the methoxyl group on the benzonaphthyridine moiety, and the other between the C=O of LEU201 and one of the Carbon of the extended 10-amidino Carbon chain. Compound 10 also formed hydrophobic interactions with the receptor via Alkyl-Alkyl interaction with LYS203, and Pi-Alkyl interaction with PHE229, LYS198 and VAL233 (twice). The binding affinities of the docked compounds did not correlate well with their antiplasmodium activities. This suggests that pfLDH may not be their only target enzyme. However, the results can be used to develop novel 10-amidinobenzonaphthyridine molecules with high potency toward inhibition of pfLDH.

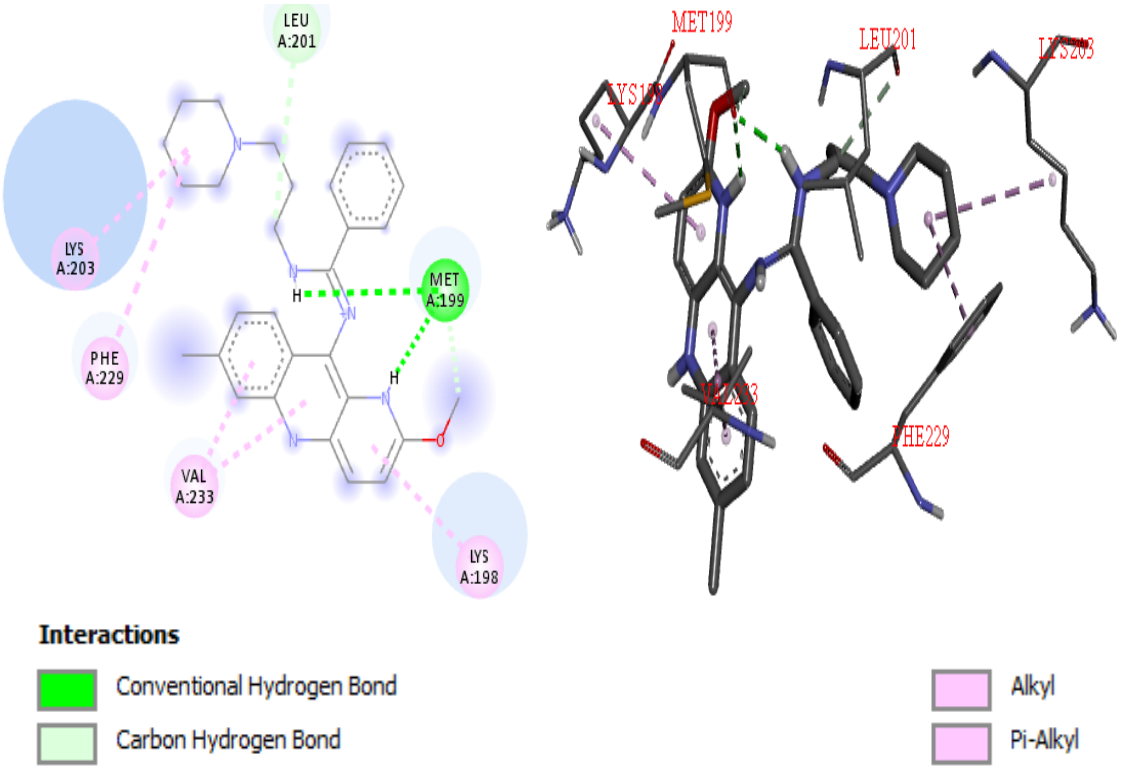
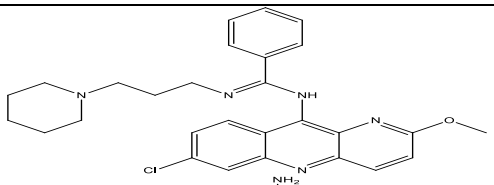
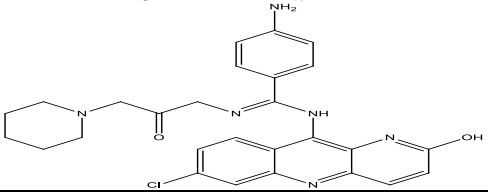
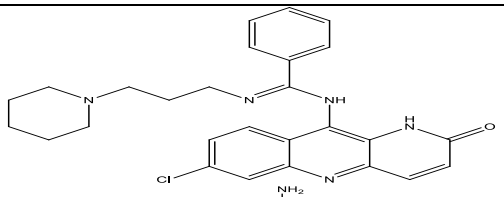
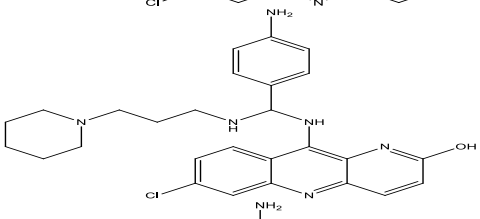
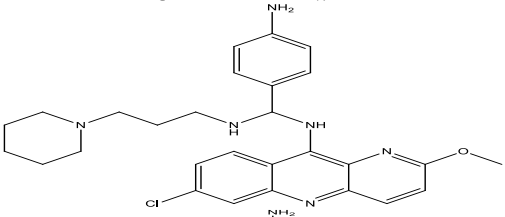
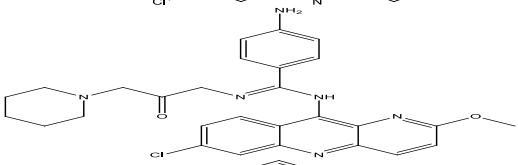
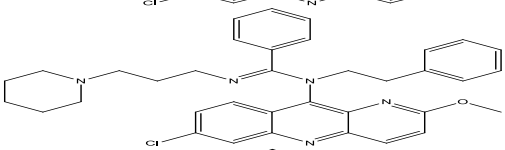
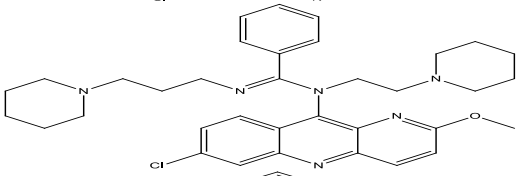
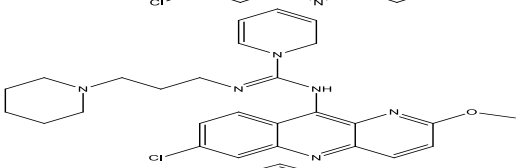
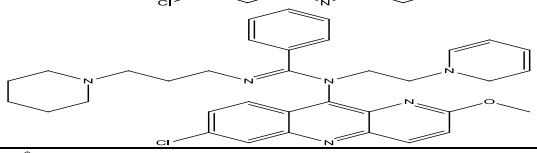


Figure 2. 2D and 3D structure of 10-*pf*LDH interactions.

Table 3. Structures of the designed 10-amidinobenzonaphthyridines

C/N	Structure	Binding affinity (kcal/mol)
10*		-7.8
D1		-8.8

D2		-8.7
D3		-8.6
D4		-8.4
D5		-8.1
D6		-8.1
D7		-7.9
D8		-7.9
D9		-7.8

C/N = compound number, 10* = Lead compound

Compound 10 was considered the lead compound (template) in designing novel 10-amidinobenzonaphthyridines because of its high binding affinity toward the target, *pf*LDH. Examining the interaction of compound 10 with the target gave information of active sites composition and the orientation of various amino acids at the binding sites of *pf*LDH. Based on this information, nine novel 10-amidinobenzonaphthyridines (Table 3) were designed by addition, substitution and elimination of some atoms on some strategic positions on the structure of compound 10. The designed compounds were docked with *pf*LDH and have better interactions and binding affinities than the template, hence can be better inhibitors of *pf*LDH. Furthermore, the designed compounds D1, D2, D3 and D4 have better binding affinities than Pyronaridine. Figure 3 shows the 2D and 3D structural interactions of the best designed compound (D1) with pfLDH.

Poor ADME properties of drug candidates are the major cause of the failure in the late phases of drug

development, raising the financial burden of research and development in the pharmaceutical industry [26]. Prediction of ADME properties in the early stage of drug discovery reduces significantly the amount of failed clinical trials related to pharmacokinetics [27]. Lipinski's rule of five and Veber's rule of two describe physicochemical properties significant for drug's pharmacokinetics in the human body. Lipinski's rule of five describes likely orally active drug to have a molecular weight below 500g/mol, not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors and a partition coefficient cLogP less than 5 [24]. Veber's rule of two proposed less than 10 number of rotatable bonds and Polar surface area less than 140Å^2 for oral bioavailability of drugs candidates [25].

Table 4 shows the ADME properties of the designed compounds. Compounds D1, D4, D5, D6, D7 and D9 like Pyronaridine have molecular weight greater than 500g/mol while D2, D3 and D8 like Chloroquine have less than that. There the latter are within the Lipinski's rule while the former are not. High molecular weight compound tends to have low concentration at the surface of the intestinal epithelium, hence low absorption, diffusion and transportation as compared to low molecular weight compound [28]. All the designed compounds as well as Chloroquine and Pyronaridine have hydrogen bond donors less than 5 and hydrogen bond acceptors less than 10 which are within the limit of Lipinski's rule of five. Lipophilicity described by LogP (partition coefficient between *n*-octanol and water) is a fundamental parameter for drug design and development. Compounds having high lipophilicity (LogP) tend to have high rapid metabolism, low solubility, poor absorption and high probability of binding to hydrophobic proteins other than the desired target therefore, more potential toxicity [29].

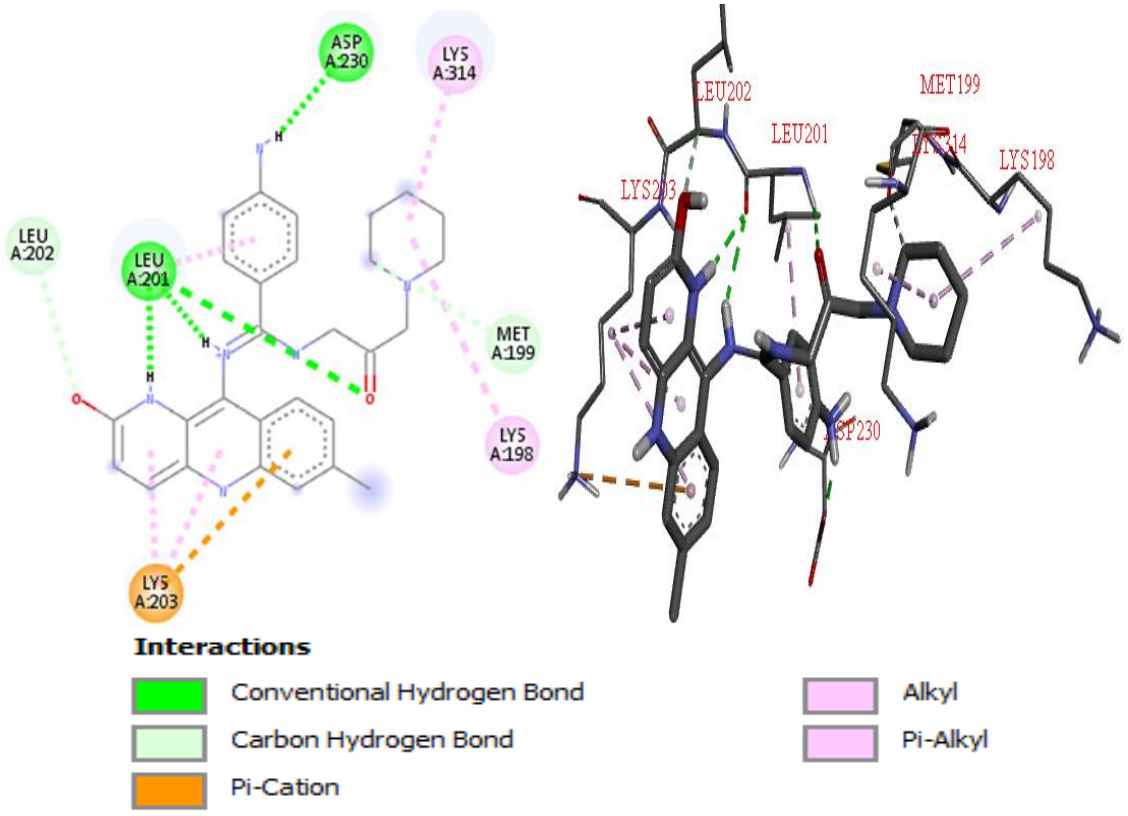


Figure 3: 2D and 3D structure of the designed 1-*pf*LDH interactions

SwissADME computes cLogP as the average of LogP obtained from five methods [30]. The cLogP of compounds D1, D2, D3, D4, D5, D8 as well as that of Chloroquine and Pyronaridine are within the limit of Lipinski's rule (less than 5) while that of D6, D7 and D9 are not (greater than 4), therefore, they are likely to have toxicity and poor absorption. Similarly, the latter compounds have number of

rotatable bonds greater than 10 (violation of veber's rule) while the former have less than 10 (no violation of veber's rule) (table 4). Topological Polar Surface Area (TPSA) evaluates drug transport properties of molecules. TPSA value less than 140Å^2 signifies good cell permeability and transport properties. The TPSA values of the designed compounds range from 53.85 to 116.73Å^2 (no violation of veber's rule) and that of Chloroquine and Pyronaridine are 28.16Å^2 and 73.75Å^2 respectively. Therefore, all the compounds have oral bioavailability. This is further confirmed by their percentage absorption (%ABS) ranging from of 68.73% to 90.42%. Chloroquine has excellent %ABS of 99.28% but Pyronaridine hass %ABS value within the range of that of the designed compounds.

Table 4. ADME properties and drug-likeness of the designed compounds

	MW							Number of violation	
C/N	(g/mol)	cLogP	TPSA(Å^2)	nHbd	nHba	nRb	%ABS	Lipinski	Veber
D1	503.00	3.78	116.73	3	6	7	68.73	1	0
D2	474.00	4.79	73.38	2	4	7	83.68	0	0
D3	491.03	4.04	99.33	4	5	8	74.73	0	0
D4	505.05	4.41	88.33	3	5	9	78.53	1	0
D5	517.02	4.02	105.73	2	6	8	72.52	1	0
D6	592.17	6.84	53.85	0	5	11	90.42	2	1
D7	599.21	6.11	57.09	0	6	11	89.30	2	1
D8	491.03	4.36	65.88	1	5	8	86.27	0	0
D9	595.18	5.93	57.09	0	5	11	89.30	2	1
CLQ	319.87	4.15	28.16	1	2	8	99.28	0	0
PNR	518.05	4.65	73.75	2	6	7	83.56	1	0

C/N = Compound number, CLQ = Chloroquine, PNR = Pyronaridine, MW = Molecular weight, cLogP = Consensus lipophilicity, TPSA = topological polar surface area, nHbd = number of Hydrogen bond donor, nHba = number of Hydrogen bond acceptor, nRb = Number of rotatable bonds, %ABS = Percentage absorption.

Compounds D2, D3, D8 and Chloroquine have no single violation of Lipinski's rule of five and Veber's rule of two while D1, D4, D5 and Pyronaridine have only one violation of Lipinski's rule of five, therefore, all of these compounds can be developed into oral drug. Compounds D6, D7 and D9 have two violations of Lipinski's rule of five and one violation of Veber's rule of two, therefore, are likely to fail clinical trials. It is observed that all compounds that failed Veber's rule of two also failed Lipinski's rule of five and vice versa, therefore, Lipinski's rule of five is enough to establish the drug-likeness of molecules. Compounds D2, D3 and D8 have good binding affinities and ADME properties therefore, can be developed into potent antimalaria targeting PfLDH. However, in vivo and in vitro studies of the designed compounds are necessary to ascertain their antiplasmodial acivity.

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