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Molecular Docking, Drug-likeness Studies and ADMET Prediction of Quinoline Imines for Antimalarial Activity

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Abstract

Objectives: Our objective was to develop quinoline imines as potent antimalarial molecules with plasmepsin 2 inhibitory activity effective against resistant strains of *Plasmodium falciparum* parasite.

Materials and Methods: A novel series of quinoline imines were designed by molecular manipulation approach using the principle of rational drug design. Newly designed quinoline imines were screened virtually for antimalarial effectiveness and also for drug-likeness using various *in silico* tools of drug design. The molecular docking was performed against *Plasmodium falciparum* parasite targeting specific *cysteine protease plasmepsin 2 enzyme*. In addition, drug-likeness and ADMET prediction studies were carried out using *in silico* tools.

Results: Our study reports the antimalarial potential of novel quinoline imines as drug-like molecules with plasmepsin 2 inhibitory activity in *Plasmodium falciparum* malaria.

Conclusion: Quinoline imines with 2-hydroxy and 4-nitro substituent's are reported to be the most potent antimalarial molecules in the series.

Keywords: *Plasmodium falciparum*; Drug resistance; Plasmepsin 2; Quinoline imines; Docking; Drug-likeness; Antimalarial drug

Introduction

Malaria is a growing infectious disease burden around the world. According to WHO, about 200-300 million people are afflicted by malaria with approximately 430,000 of deaths every year globally [1]. *Plasmodium falciparum* causes dreadful malaria infections such as cerebral malaria in children as well as in adults. *Plasmodium falciparum* is mainly responsible for most of the malaria-related mortality cases in humans [2,3]. Over the past several years, the spread and emergence of drug-resistant strains of *Plasmodium falciparum* parasite has been increasing at an alarming rate, particularly in malaria-endemic territories of the world. This has limited the clinical utility of currently available antimalarial drugs and/or antimalarial drug therapy. Today, the increasing incidence of resistant parasite has thus become a serious concern to public health in the prevention of malaria worldwide [4-6]. The above challenging issue has stimulated medicinal chemists and scientists to search for novel antimalarial lead molecules/drug candidates as alternative therapeutic options for curing dreadful resistant malaria. In this study, some novel quinoline imines were designed, modeled and screened for antimalarial effectiveness and drug-likeness assessment using various *in silico* tools of drug design. The molecular docking of designed quinoline imines was virtually performed against *Plasmodium falciparum* targeting specific *cysteine protease plasmepsin 2 enzyme*. In addition, drug-likeness screening and ADMET prediction studies were also carried out using *in silico* tools. Our objective was to develop quinoline imines as potent antimalarial molecules with plasmepsin 2 inhibitory activity effective against resistant strains of *P. falciparum* parasite.

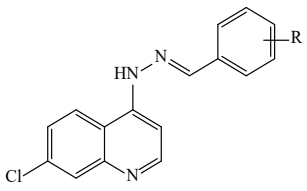
Experimental

Design strategy

In continuation of our previous research program [4] with an aim to develop novel and potent antimalarial molecules, a novel series of quinoline imines were designed by molecular manipulation approach. Fifteen molecules, QI-1 to QI-15 (Figure 1) were designed with a diverse range of structural substitutions (o/m/p- substituted aryl moiety) at the basic framework of the quinoline-imine scaffold, considering the pharmacodynamic potential of the quinoline imine component and other structural features and property parameters important for biological activity.

Docking study

Modelling studies were performed at Dell Precision work station T3400 running Intel Core 2 Duo Processor, 4 GB RAM and 250 GB hard disk with NVidia Quodro FX 4500 graphics card. Two-



R = H	(QI-1)
2-OH	(QI-2)
3-OH	(QI-3)
4-OH	(QI-4)
4-OCH_3	(QI-5)
4-OCH_3	(QI-6)
4-Cl	(QI-7)
4-NO_2	(QI-8)
4-OH, 3-OCH_3	(QI-9)
3,4-Di-OCH_3	(QI-10)
4-CH_3	(QI-11)
4-N$(CH_3)_2$	(QI-12)
1-naphthyl	(QI-13)
3,5-Di-CHO	(QI-14)
1-cinnamyl	(QI-15)

Figure 1: Designed quinoline imines

dimensional (2D) structures of compounds were sketched using ChemDraw Ultra 10.0 (Cambridge Soft Co., USA, 2010) and Marvin Sketch (ChemAxon LLC, Cambridge, USA, 2015) software. Protein-ligand docking was performed on Biovia Discovery Studio (DS) *vs* 4.5 (2015) software. Docking was performed for designed molecules (QI-1 to QI-15) using the plasmepsin 2 enzyme of *Plasmodium falciparum*. The x-ray crystal structure of plasmepsin 2/EH-58 (PDB id: 1lf3) was retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/). The protein molecule of plasmepsin 2 was obtained at a resolution of about 2.9 Å [4]. The protein molecule of plasmepsin 2 was energetically minimized and defined as a receptor molecule. The binding cavity (binding site sphere) was selected based upon the ligand (EH-58) binding location in the receptor molecule. Using the binding cavity of the protein molecule, a receptor grid was thereby generated by specifying the key amino acid residues (Phe 16, Leu 33, Val 78, Ser 79, Ser 215, Gly 216 and Asp 303) [1,7]. For the receptor grid box, binding site sphere was set with a radius of 20 Å and x, y, z dimensions of -52.25, -4.46, -19.25, respectively. Flexible docking was performed using the 'Dock Ligands' module of LibDock genetic algorithm program. During docking, the complex of plasmepsin 2/EH-58 was imported and the co-crystal ligand, E-58 molecule was removed from the binding pocket, and experimental ligands were placed in the predicted binding site. Parameters used for docking and consequent scoring function were kept the default. LibDock scores for all docked ligands were calculated. Different dock poses were studied to identify the best binding mode/ binding orientation of the receptor-ligand complex in terms of the scoring function. All docked poses were scored, ranked and the best pose (having the highest dock score) for each ligand molecule was selected. To study receptor-ligand interaction, binding modes of the best pose was also analyzed for each molecule with the help of 3D receptor-ligand complex. Different non-bonding interactions (hydrogen bonding and hydrophobic) were also analyzed with the help of 2D diagram of receptor-ligand complexes.

Drug-likeness studies

Molecular properties and drug-likeness parameters were calculated *in silico* for all the designed molecules (QI-1 to QI-15). It was performed based upon theoretical approaches with an aim to identify the molecules which satisfy the optimum requirements to exhibit as drug-like molecules. Molecular properties indicated in Lipinski's rule of five [8] and other physicochemical parameters were calculated using the 'Calculation of Molecular Properties' module of Biovia DS *vs* 4.5 software. Some other properties were also predicted using open web-based tools like Molsoft (http://www.molsoft.com/, 2016) and Molinspiration online software (http://www.molinspiration.com/, 2016) [1, 9-11].

ADMET prediction

ADME-Toxicity (ADMET) was calculated using the ADMET 'Descriptor' module of Biovia DS *vs* 4.5 software. The following six mathematical models such as aqueous solubility, blood-brain barrier penetration (BBB), cytochrome P450 2D6 (CYP2D6) inhibition, hepatotoxicity, human intestinal absorption and plasma protein binding were used to predict ADMET properties [12]. The study of ADMET properties is important because they determine oral bioavailability, cell permeation, metabolism and elimination (Pharmacokinetic characteristics) of drug molecules.

Results and Discussion

Designing quinoline imines

The 4-aminoquinoline scaffold is considered to be the prerequisite or the key pharmacophoric requirement for antimalarial activity for quinoline-based antimalarial drug molecules. The importance of 4-aminoquinoline scaffold incorporated with hydrazyl moiety as the antimalarial component has been reported. Substitution of quinoline hydrazine moiety with aryl/substituted aryl group could lead to our target quinoline-imine conjugate with diverse substitutions.

Docking

The protein model of plasmepsin 2/EH-58 co-crystal structure was validated and used for the docking simulation study. Prior to docking, the receptor grid model was generated and optimized in terms of binding site sphere for predictive interaction between a receptor molecule and ligands (Figure 2). The co-crystallized ligand, EH-58 (a selective plasmepsin 2 inhibitor) was re-docked using flexible docking simulations into the original structure of the receptor molecule using all docking parameters to the software's default values. The reference ligand, EH-58 was successfully re-docked to the predicted active site of plasmepsin 2 molecules with an acceptable RMSD value of 1.190 Å. This study was performed in order to reproduce the results of experimentally observed ligand binding modes in protein-ligand docking. Results confirmed experimental binding modes/ conformations of EH-58 in the binding pocket of the receptor molecule with well defined protein-ligand interactions (Figure 3).

The docking simulation study was performed to predict the efficacy of newly designed quinoline imines as possible novel plasmepsin 2 inhibitors. Molecular docking is a virtual tool intended to find the

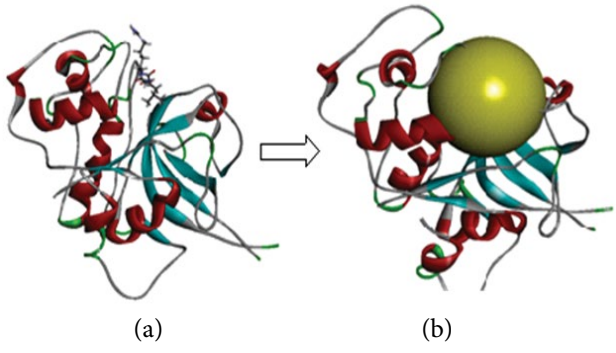


Figure 2: (a): Optimized co-crystal structure of plasmepsin 2 (Chain A)-E-64, (b): Receptor grid for docking

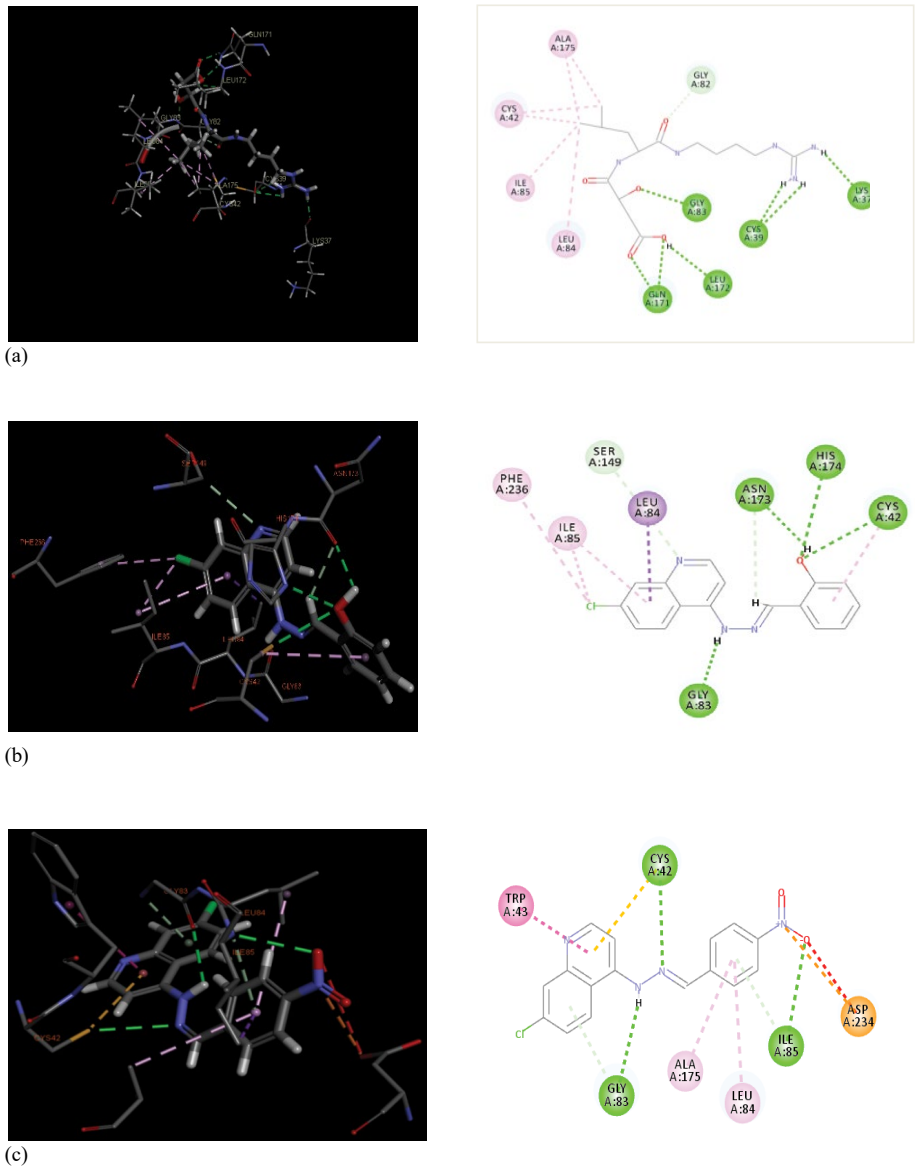


Figure 3: (a): Redocked conformer of EH-58 in the active site of the protein plasmepsin 2 (left) and 2D representation of the binding interaction (right); (b)&(c): Binding mode (left) and 2D receptor-ligand interaction diagram (right) of compounds, QI-2&QI-8 at binding pocket of plasmepsin 2 (left), respectively.

best binding orientation of small molecules bound to their target protein molecules. It is used to predict the binding affinity as well as the biological efficacy of small molecules [8]. Thus, docking thus plays an important role in the identification of bioactive molecules based on the target protein structure in rational drug discovery programme. In protein-ligand docking, LibDock program successfully docked all the compounds into the binding pocket of plasmepsin 2 molecule. Compounds could bind well with the predefined active site residues of the receptor sphere. High binding affinity was observed with LibDock scores ranging from 90.287 to 112.34. The LibDock scores of compounds, QI-1 to QI-15 are summarized in table 1. Results indicate that dock scores of designed quinoline imines are consistent in terms of their high binding affinity. Docking study may, therefore, serve as an important tool for assessing the antimalarial efficacy of newer quinoline imines as *Plasmodium falciparum* plasmepsin 2 inhibitors.

Docking searches for finding new lead molecules and also gives an understanding of structure-activity relationships and mode(s) of action of drug molecules based on scoring function and subsequent interaction analysis of ligand-protein complexes. The three-dimensional poses of bound ligand molecules reveal the best molecular orientation relative to the structure/orientation of the receptor molecule. Analysis of 2D diagram indicates that various non-bonded interactions including polar hydrogen bonding interactions were primarily involved between receptor and ligand molecule. Molecular interaction reveals well-defined binding between binding site residues of plasmepsin 2 molecule and complementary moieties/

Table 1: LibDock scores and no. of H-bonds.

Comp. code	Substituent	Libdock score	No. of H-bond(s)
QI-1	H	90.287	3
QI-2	2-OH	112.34	4
QI-3	3-OH	94.276	3
QI-4	4-OH	90.87	2
QI-5	3-OCH_3	95.614	2
QI-6	4-OCH_3	91.749	3
QI-7	4-Cl	90.992	1
QI-8	4-NO_2	95.65	3
QI-9	4-OH, 3-OCH_3	97.658	3
QI-10	3,4-$(OCH_3)_2$	95.881	5
QI-11	4-CH_3	90.989	3
QI-12	4-$N(CH_3)_2$	105.96	4
QI-13	1-Naphthyl	108.08	4
QI-14	3,4-$(CHO)_2$	97.704	2
QI-15	1-Cinnamyl	98.182	1
EH-58	-	114.45	6

Table 2: Details of hydrogen bonding for most active ligands.

Comp. code	H-bond(s)	H-binding ligand		H-binding receptor			H-bond distance (Å)
		Element	Type	Residue	Element	Type	
QI-2	4	O	A	Cys 42	S	D	3.411
		O	A	His 174	N	D	3.399
		H	A	Asn 173	O	D	2.43
		H	A	Gly 83	O	D	2.142
QI-8	3	O	A	Cis 42	H	D	2.925
		H	A	Gly 83	N	D	2.674
		O	A	Ile 85	H	D	3.128
QI-10	5	O	A	Cys 42	S	D	2.632
		O	A	Ile 85	N	D	2.84
		H	A	Gly 83	O	D	2.22
		H	A	Asp 234	O	D	3.009
		H	A	Gly40	O	D	2.53
QI-12	4	O	A	Glu 36	N	D	3.208
		N	D	Cys 42	O	A	3.266
		H	A	Asn 173	O	D	2.175
		H	A	Cys 42	S	D	3.543
QI-13	4	H	A	His 174	N	D	4.084
		H	A	Cys 42	S	D	3.381
		H	A	Leu 172	O	D	2.523
		H	A	Asn 173	O	D	2.546

Table 3: Drug-likeness properties.

Comp. code	Lipinski's parameters						MS	MV (A^3)	nRotB
	MW	LogP	nHBA	nHBD	TPSA (A^2)	N Violations			
QI-1	281.74	4.299	3	1	37.28	0	-6.07	252.27	3
QI-2	297.74	4.005	4	2	57.51	0	-5.52	262.8	3
QI-3	297.74	4.057	4	2	57.51	0	-5.58	262.89	3
QI-4	297.74	4.057	4	2	46.51	0	-5.62	262.82	3
QI-5	311.77	4.283	4	1	46.51	0	-6.21	284.19	4
QI-6	311.77	4.283	4	1	37.28	0	-6.23	284.12	4
QI-7	316.19	4.963	3	1	83.1	0	-6.85	269.46	3
QI-8	326.74	4.193	5	1	66.74	0	-6.46	290.45	4
QI-9	327.77	4.041	5	2	55.74	0	-5.69	295.54	4
QI-10	341.8	4.266	5	1	37.28	0	-6.31	315.54	5
QI-11	281.74	4.785	3	1	37.28	0	-6.6	273.21	3
QI-12	307.78	4.659	3	1	40.52	0	-7.03	293.58	4
QI-13	324.81	4.461	4	1	37.28	0	-6.04	301.82	4
QI-14	331.8	5.207	3	1	49.78	1	-7.91	301.09	3
QI-15	309.75	4.058	4	1	54.35	0	-6.26	280.53	4

MW-Molecular weight, LogP-Log of octanol/water partition coefficient, nHBA-No. of hydrogen bond acceptor(s), nHBD-No. of hydrogen bond donor(s), TPSA- Total polar surface area, nViolations- No. of rule of five violations, MS-Molar aqueous solubility, MR-Molar refractivity, MV-Molar volume, nRotB-No. of rotable bonds.

atoms of ligands. Higher the number of hydrogen bonds, higher is the binding affinity. Other non-bonded interactions like hydrophobic bonding were also observed but to a lesser extent. Table 2 shows details of hydrogen bonding interactions for the five best compounds (QI-2, QI-8, QI-10, QI-12 and QI-13). The following active site residues, Glu 36, Gly 40, Cys 42, Gly 83, Ile 85, Ser 149, Leu 172, Asn 173, His 174 and Asp 234 were involved in hydrogen bonding interactions. Compound QI-2 showed the highest degree of binding with LibDock score of 112.34. It could bind strongly with the active site residues of falcipain-2 predominantly through hydrogen bonding interactions. The binding modes (3D and 2D interaction diagrams) for the best two compounds, QI-2 and QI-8 are given in figure 3. Compound QI-2 formed four strong H-bonds with residues like Cys 42 (OHS), His 174 (OHN), Asn 173 (OHO) and Gly 83 (OHO). Three bonds were observed with residues like His 174 (OHO), Gly 83 (O·H·N) and Ser 149 (OHO) for compound QI-8. Analysis of best docking poses showed in 3D diagram revealed binding orientation of the quinoline scaffold into the binding cavity of plasmepsin 2 receptor molecule. The 2D diagram also exhibited the occupancy of quinoline imine moiety in the active sites of plasmepsin 2 through H-bonding interactions along with some hydrophobic interactions. Such interactions brought about good stability of the complex formed between the receptor and ligand molecule. Upon critial analysis of docking interactions, it was assumed that quinoline ring played a crucial role in protein-ligand interaction. Substituents increased the strength of intercation by forming additional H-bonds. It facilitated to afford even stronger interaction of ligands with the plasmepsin 2 molecule achieving the desired antimalarial activity. The imino component present as a bridge moiety attributed to contributing significantly in docking interaction of quinoline imines.

Drug-likeness

Results depicted in table 3 reveal that all designed molecules (**QI-1** to **QI-15)** possess acceptable drug-like properties based on Lipinski's rule of five [13,14] with some additional drug-likeness parameters. All the molecules obeyed Lipinski's rule of five and also Veber rule. Lipinski's rule of five is used to evaluate the drug-likeness of a pharmacologically active compound, whether the compound is orally active or not as a drug molecule [4]. Poor oral absorption of a drug molecule is observed if the drug molecule violates more than one of five rules. Values of Log P, MW and TPSA indicate good membrane permeability and oral bioavailability of compounds. Infact, hydrophobicity, membrane permeability and bioavailability of drug molecules are dependent on these parameters including HBA and HBD. Permissible values of nRotB and MR also reflects good intestinal absorption and oral bioavailability of compounds. It is therefore stated that molecules that violate above rules fail to exhibit the optimum property of membrane permeability, absorption and oral bioavailability. Moreover, it is also an important requirement that conformation (i.e., stereospecificity) of the drug molecule should be such that it must bring about optimal drug-receptor interaction. It depends on the property of nRotB. Further, TPSA and MR are very much useful to define the drug's transport and bio-distribution behaviour [8,9]. All parameters of drug-likeness discussed above and the risk of toxicity can be combined into a single numerical value called the drug-like score. It is predicted to be used as a global value for a compound to be potential as a new drug candidate [6]. After all, it can be suggested that newly designed quinoline imines have good drug-likeness behaviour favourable for optimal membrane permeability and oral bioavailability (pharmacokinetics) with desired drug-receptor interaction (pharmacodynamics).

Table 4: Theoretical ADMET parameters.

Comp. code	Aqueous solubility	BBB penetration	CYP P450 2D6 inhibition	Hepatotoxicity	Intestinal absorption	PP binding
QI-1	2	1	TRUE	TRUE	0	TRUE
QI-2	2	1	TRUE	TRUE	0	TRUE
QI-3	2	1	TRUE	TRUE	0	TRUE
QI-4	2	1	TRUE	TRUE	0	TRUE
QI-5	2	1	TRUE	TRUE	0	TRUE
QI-6	2	1	TRUE	TRUE	0	TRUE
QI-7	1	0	TRUE	TRUE	0	TRUE
QI-8	2	2	TRUE	TRUE	0	TRUE
QI-9	2	1	TRUE	TRUE	0	TRUE
QI-10	2	1	TRUE	TRUE	0	TRUE
QI-11	2	0	TRUE	TRUE	0	TRUE
QI-12	2	0	TRUE	TRUE	0	TRUE
QI-13	2	1	TRUE	TRUE	0	TRUE
QI-14	1	0	TRUE	TRUE	0	TRUE
QI-15	2	1	TRUE	TRUE	0	TRUE

Aqueous solubility: 3-Good, 2-Low; BBB (Blood brain barrier) penetration: 3-Low, 2-Medium, 1-Moderate; Cytochrome (CYP) P450 2D6 inhibition: False-Non-inhibitor; Hepatotoxicity: True-Toxic, False-Non-toxic; Intestinal absorption: 0-Good; Plasma protein (PP) binding: True-Highly bounded, False-Poorly bounded.

ADMET prediction

The predicted values of ADME-Tox studies are presented in table 4. All ADMET values were found within an acceptable range. ADMET properties affect pharmacokinetic (absorption, distribution, metabolism, excretion) and pharmacodynamic (drug efficacy and toxicity) properties of drug substances. The calculation of such properties is therefore, inevitable towards optimizing drug leads or new drug molecules. These properties are said to have influence bio-membrane absorption, oral bioavailability, and metabolism of drug molecules [15]. In our study, all designed compounds exhibited good intestinal absorption. They were non-inhibitors of cytochrome CYP2D6 with medium to moderate BBB penetration. The penetration across BBB is mandatory for a drug molecule to be used in the treatment of cerebral malaria. The CYP2D6 enzyme is believed to one of the important drug metabolizing enzymes. From the prediction of aqueous solubility (defined in water at 25°C), most of the compounds were soluble in water. Hepatotoxicity was observed for a few molecules. Some of the compounds were found to be highly protein bound, while some molecules were poorly bound with plasma protein [14-16].

Conclusion

Newly designed quinoline imines have been reported to be potent antimalarial molecules as possible *P. falciparum* plasmepsin 2 inhibitors. Docking, drug-likeness and ADMET studies confirmed the potential and drug-likeness of newer quinoline imines as antimalarial molecules. Quinoline imines with 2-hydroxy and 4-nitro substituents are reported to be the most potent antimalarial molecules in the series. Our present work may be a basis towards further molecular optimization of quinoline imines to establish quinoline antimalarials as still more potent and novel plasmepsin 2 inhibitors.

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