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Research article

DESIGN AND DOCKING STUDY OF NOVEL HETEROCYCLIC QUINOLINE IMINES AS ANTIMALARIALS

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Abstract

Background*:The discovery of new antianalrial drugs is stll a releavent field of drug discovery as the amalrial parasite Plasmodium falciparum has developmed resistance against the available drugs.*
Objective:*In this study, some new heterocyclic quinoline imines were designed and virtually screened against the plasmepsin 2 and facipain-2 proteins of P. falciparum by in silico technique.*
Methods:*The compounds were designed considering the 7-chloroquinoline pharmacophore of chloroquine using Marvinsketch. Then compounds were screened against the selected targetsby molecular docking study using Discovery Studio 2020. Finally, the best compounds were further analyzed for their toxicity and different in silico pharmacokinetic properties.*
Results and Discussion*:A total of 100 compounds were designed and analysed through in-silico method. 11 compounds are found to be more active than the standard drug Chloroquine againstPlasmepsin 2 and 12 compounds against falcipain 2. The ADMET properties of the designed drugs are found to be in acceptable range with moderate blood brain penetration and distribution properties.*
Conclusion:*Based on current findings and literature results, effective antimalarials may be developed and produced from the main 7-Chloroquinoline pharmacophore by structural and molecular alteration using heteroclic substitute, as well as the use of molecular modelling techniques and computer assisted QSAR studies.*

Keywords: Malaria,antimalarial, drug resistance, *in silico* study.

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Introduction

Malaria is a blood-borne parasitic disease that is spread through the bite of female mosquito (anopheles sp.). Malaria affects 36 percent of the world's population, or 2020 million people, in 107 tropical and subtropical countries and territories. Malaria case occurrence (cases per 1000 people at risk) has decreased globally from 80 in 2000 to 58 in 2015 and 57 in 2019. Global malaria case incidence fell by 27% between 2000 and 2015, and by less than 2% between 2015 and 2019, suggesting a slowdown of the rate of decline. Since 2015, there has been a fall.India was responsible for the greatest absolute decreases, from around 20 million cases in 2000 to approximately 5.6 million in 2019. In the period 2000–2019, the number of cases of malaria fell by 78 percent, from roughly 18 to 4 per 1000 people at risk. Malaria fatalities have decreased by 74%, from over 35 000 in 2000 to around 9 000 in 2019. In this region, India was responsible for 88 percent of malaria cases and 86 percent of malaria fatalities in the year 2019 (1). The National Vector Borne Disease Control Program (NVBDCP) in India has significantly increased malaria elimination efforts. In 2018, India recorded 0.39 million malaria cases and 85 deaths. In terms of malaria case distribution, India is very diverse. Odisha, a state in eastern India, has a high incidence of malaria infection, accounting for 16.6% of malaria infections and 4.7 percent of malaria deaths in India [2] (Kumari et al. 2020). The rise of malaria has been attributed in part to the development of resistance. Drug resistance makes the use of quinoline-based compounds for the treatment of malaria infections difficult. Due to medication resistance, quinolines have been paired with other antimalarial classes, resulting in better clinical results [3](Nqoro, Tobeka, and Aderibigbe 2017). Drug-drug reactions, however, restrict the number of antimalarials that can be used together. To address the aforementioned issues, a number of researchers have documented hybrid compounds made by combining quinoline-based compounds with other compounds through specific functionalities [3] (Nqoro, Tobeka, and Aderibigbe 2017).

The current study is to evaluate the antimalarial activity of novel series of heterocyclic imines of 4-Substituted-7-chloroquinoline on the Malaria parasite Plasmodium falciparum.

In-silico Design and Docking Methods

Design and preparation of compounds

Hundred compounds were designed usingMarvinSketch v20.4 and saved as a.sdf file format for future use. The SMILES of the compounds were loaded to Discovery Studio 2020 (DS 2020) molecular modeling software (DassaultSystèmes BIOVIA, San Diego, USA) and three-dimensional structures were generated using the 'Small Molecule' tool of the DS 2020 software. Then energy minimizations of the compounds were carried out usingCHARMM-based (Chemistry at Harvard Macromolecular Mechanics) smart minimizer, which performs 2000 steps of Steepest Descent followed by Conjugate Gradient algorithm with an energy RMSD gradient of 0.01 kcal/mol[4].

Preparation of the target protein and selection of binding site

X-ray crystal structure of the target proteins, Plasmepsin 2(PDB ID: 1LF3) and Falcipain 2 (PDB ID: 3BPF) were obtained from the Protein Data Bank websites (www.rcsb.org) [5]. Before the docking study, the target protein was prepared using DS 2020 software. After loading the target, it was cleaned and prepared by the 'Prepare Protein' protocol of DS 2020. During cleaning, alternate conformations were deleted, terminal residues were adjusted and bond orders were corrected. In addition, water molecules were removed from the structure, and co-crystal ligands were kept with the proteins in the preparation process. Finally,energy minimization of the target protein was performed using the CHARMM-based smart minimizer method at maximum steps of 200 and an energy RMSD gradient of 0.1 kcal/mol [6].

The predefined active site as reported in the PDB format was selected using the 'Edit and Define Binding Site' method under the 'Receptor-Ligand Interactions' tools of the DS 2020. The active binding site sphere of Plasmepsin 2 had the coordinates ofX: 16.064069,Y: 5.961775 Z: 27.851527 and radius12.413900Å The active binding site sphere of Falcipain 2 had the coordinates of X: -57.253734,Y: -0.877123,Z: -15.038906 and radius 8.526446Å. The validation of the binding sites and docking study was done by redocking the co-crystal ligand present in the selected active binding site [7].

Molecular docking and scoring study

The compounds library was docked with the target using simulation-based docking protocol 'CDocker' of the DS 2020. CDocker uses a CHARMm-based molecular dynamics (MD) algorithm to dock compounds into the active binding site of a receptor [8]. In the docking study, CQ was taken as reference drugs to evaluate the designed compound's results.

Determination of binding energies of the best protein-ligand complexes

The MM-PBSA based calculation of binding energy provides the stability of the formed protein-ligand complex in the docking study. The protein-ligand complexes obtained from the preliminary docking and scoring studies were further taken to calculate binding energies using the 'Calculate Binding Energy' protocol of DS 2020 with the MM-PBSA method [9, 10].

Determination ofmolecular properties

The best compounds obtained from the binding energy calculation study were further analysed for different molecular properties using molinspiration online tool[11].

Determination of pharmacokinetic parameters

The selected compounds were analyzed for ADMET (absorption, distribution, metabolism, elimination, and toxicology) and toxicity parameters using PreADMET online server [12].

Results and Discussion

Basis of the designed compounds

a) Quinine (active constituent of Cinchona Sp.) was the first effective treatment for malaria caused by P. falciparum and remained the drug of choice until the late 1940s, when other quinoline based drugs such as chloroquine and later on mefloquine etc. replaced it [13].

b) Sharma et al. found out Chloroquine analogues with a hydrazone or hydrazine moiety in the side chain had mild antimalarial activity [14].

c) According to the work of Singh et al. (2014), increase in the connecting chain between the quinoline and substituent ,increases the anti-plasmodial activity upto 4-carbon ;further increase leads to decrease in activity [15].

Based on these observations the following work was performed and a number compounds with different heterocyclic substitutes and varying chain length from hydrazine(no carbon) to 1,4-diaminobutane(4-carbon), have been designed and evaluated through in-silico method.

Molecular docking study

For the docking simulation two proteins, Plasmepsin2 and Falcipain2and have been used. Plasmepsin is a common enzyme in the *Plasmodium* sp. and falcipain is found mainly in *P. falciparum*. Both of these proteins are responsible to breakdown toxic (for parasite) host-Hemoglobin to non-toxic smaller peptides. So, the following study is performed by using these two proteins as receptor molecule. Out of the 100 designedcompounds c7, c9, c10, c11, c12, c13, c23, c30, c46, c65 and c75 showed better results than the choroquine in the case of Plasmepsin 2. Whereas in the case of Falcipain 2; c10, c11, c12, c23, c30, c40, c45, c46, c56, c78, c84 and c89 showed better results than chloroquine. These compounds are found to be better than standard drug chloroquin in terms of Cdocker energy (kcal/mol). In table 1 and table 2,Cdocker energies of those compounds against 1LF3 and 3BPF are summerized respectively.

Table 1: Docking results of the compounds and reference drugagaint 1LF3.

Name	Cdocker energy (kcal/mol)
c7	-23.3833
c9	-20.5091
c10	-20.9606
c11	-22.4651
c12	-21.4589
c13	-20.2913
c23	-21.6699
c30	-20.2693
c46	-20.814
c65	-21.3043
c75	-20.6377
Chloroquine	-20.1463

Table 2: Docking results of the compounds and reference drugagaint 3BPF.

Name	Cdocker energy (kcal/mol)
c10	-15.2369
c11	-17.8319
c12	-18.7146
c23	-15.0732
c30	-15.5143
c40	-17.3209
c45	-16.1063
c46	-16.9904
c56	-15.2429
c78	-15.3139
c84	-15.2634
c89	-15.0427
Chloroquine	-14.778

Determination of binding energies

From the calculation of binding energies, in the case of 1LF3 c7, c11, c13, c30, c46, c65 and c75 were found to have lower binding energies (kcal/mol) than the chloroquine. Wherease in the case of 3BPF, c10, c12, c23, c30, c40, c45, c56 and c89 showed lower binding energies (kcal/mol) than chloroquine.

Table 3: Binding energies of the best docking poses with 1LF3.

Name	Binding energy (kcal/mol)
c7	-57.5093
c11	-47.4485
c13	-53.557
c30	-69.7612
c46	-66.4391
c65	-60.3448
c75	-62.6956
Chloroquine	-46.7317

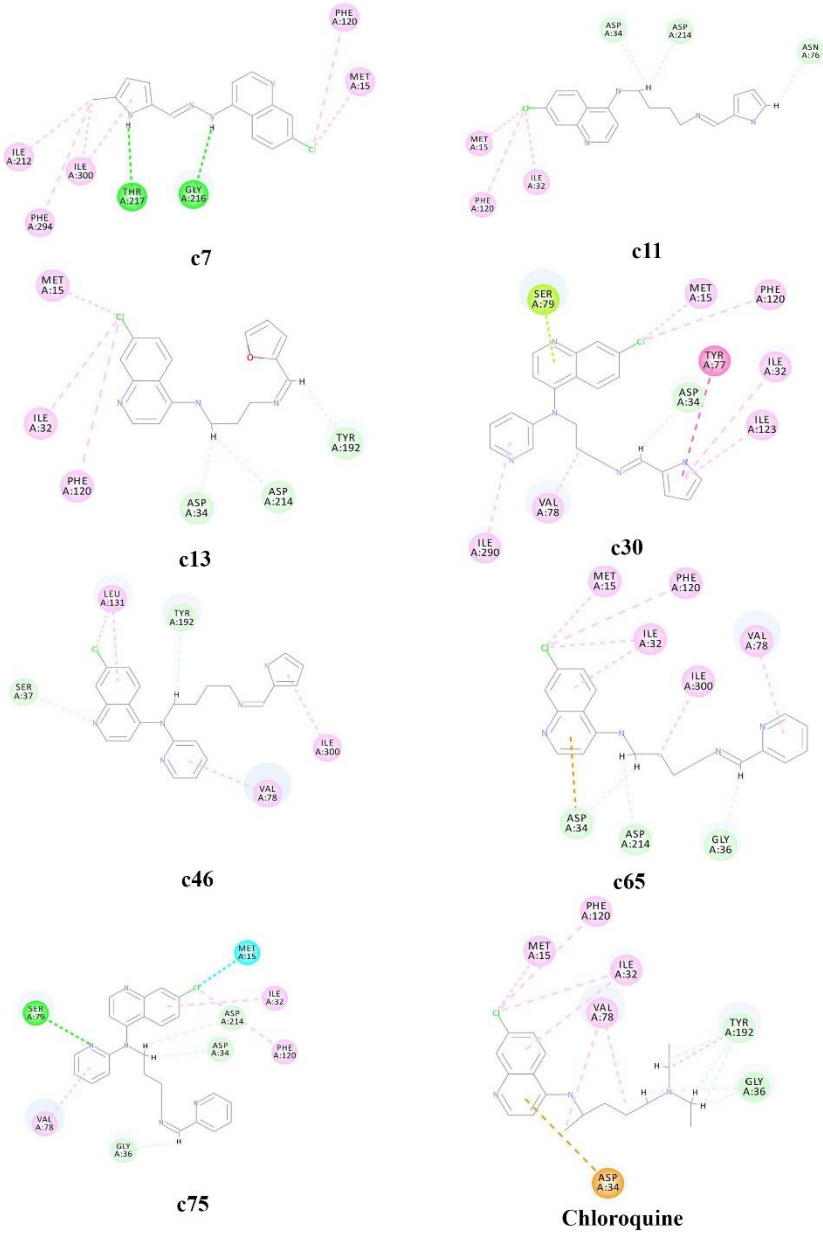

Figure 1: Interactions of the best compounds with 1LF3.

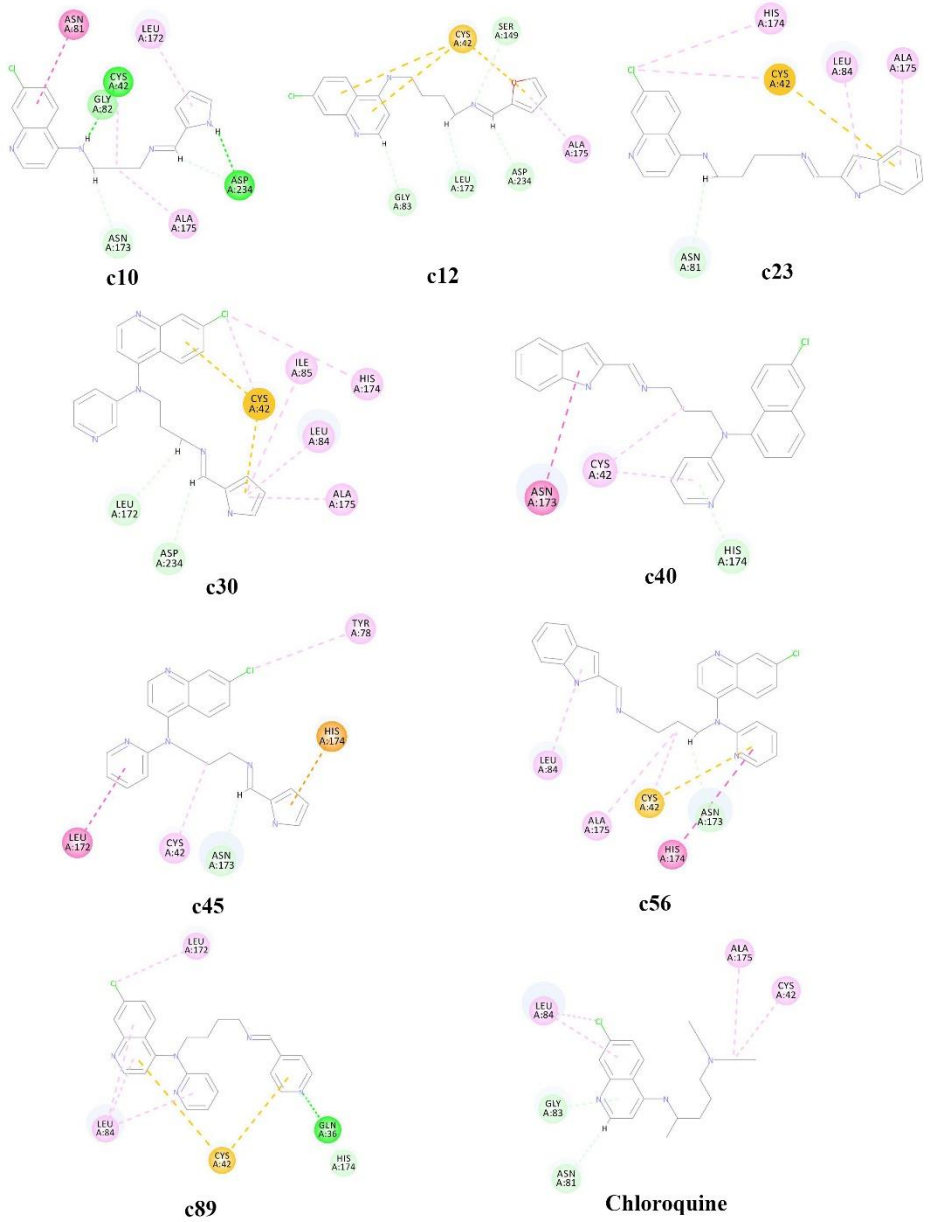

Figure 2: Interactions of the best compounds with 3BPF.

Table 4: Binding energies of the best docking poses with 3BPF.

Name	Binding energy (kcal/mol)
c10	-45.9322
c12	-63.2397
c23	-72.4151
c30	-91.9044
c40	-110.847
c45	-50.7277
c56	-49.2393
c89	-89.2493
Chloroquine	-31.2602

Determination of molecular properties

The proposed compounds results of predicted Lipinski's paramaters and other drug-likeness properties are shown in Table 5 Based on the Lipinski's rule of five and additional parameters such as ADMET solubility and number of rotable bonds, we can conclude that c10, c11, c12, c30, c45, c46, c65, c78, c84 and c89 possessed good drug-like properties. Good oral bioavailability and membrane permeability are possessed by the compounds, indicated by the values of Molecular Weight (MW), LogP and total polar surface area (TPSA). Good intestinal availability of the compounds is suggested by the number of rotable bonds. Molecular properties such as molecular weight (MW), LogP, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) clearly determines bioavailability, membrane permeability and hydrophobicity of molecules .

From the overall drug-likeness studies analysis a conclusion can be drawn which stronglyindicates that good drug-likeness behaviour favourable for optimal membrane permeability, bioavailability and transport, and eventual interaction with

the receptor molecule is possessed by the newly designed Heterocyclic Quinoline Imines.

Table 5: Molecular properties of the compounds

Name	Rotatable bonds	H-bond doner	H-bond acceptor	TPSA	LogP	Molecular wieght	nViolations
C7	3	2	4	53.07	5.03	284.75	1
C10	6	2	4	53.07	3.57	312.8	0
C11	7	2	4	53.07	3.84	326.83	0
C12	7	1	4	50.42	3.94	327.81	0
C23	7	2	4	53.07	5.15	376.89	1
C30	7	1	5	57.18	4.44	389.89	0
C40	7	1	4	44.28	6.67	438.96	1
C45	7	1	5	57.18	4.61	389.89	0
C46	8	1	5	57.18	4.88	403.92	0
C56	8	1	5	57.18	6.19	453.98	1
C65	7	1	4	50.17	3.52	338.84	0
C78	6	1	4	50.17	3.13	324.81	0
C84	8	0	5	54.28	4.27	415.93	0
C89	8	0	5	54.28	4.44	415.93	0

Pharmacokinetic parameters

Table 6 depicts the ADMET (Absorption Distribution Metabolism Elimination Toxicity) properties of the proposed Heterocyclic Quinoline Imines, which were found to be favourable and within the acceptable range. These results have been calculated by using Pre ADMET online software. Compounds C7, C9, C10, C11, C12, C23, C30, C40, C45, C46, C56, C65, C78, C84 and C89 were predicted to be the non-inhibitors of CYP2D6, with moderate blood brain barrier (BBB) penetration. For treating cerebral malaria BBB penetration is very much mandatory, so these compounds are predicted not to be very good for cerebral malaria. One of the important enzymes used in drug metabolism is CYP2D6. Most of the compounds are moderately soluble in water which can be predicted from the ADMET solubility data. High binding with plasma protein is observed in case of some compounds.

Table 6: ADMET parameters of the test compounds.

Name	Buffer solubility (mg/L)	Blood Brain Barrier permeability	CYP2D6 prediction	PPB Prediction
C7	9.39766e-006	4.08949	FALSE	83.343523
C9	1.27205	4.06247	FALSE	89.573192
C10	2.25854	3.4313	FALSE	87.533824
C11	0.434589	5.17218	FALSE	86.958494
C12	0.506402	0.355789	FALSE	91.365078
C23	0.0252698	9.13837	FALSE	87.649825
C30	0.848786	3.47321	FALSE	93.972957
C40	0.0136629	13.3455	FALSE	91.175055
C45	0.340587	4.95578	FALSE	95.513161
C46	0.0649798	6.92252	FALSE	92.596313
C56	0.00368256	10.7355	FALSE	90.105099
C65	0.270143	0.246181	FALSE	90.238990
C78	2.12688	0.0835191	FALSE	91.790004
C84	0.151225	1.10477	FALSE	96.242380
C89	0.0606812	0.720394	FALSE	95.715646

Table 7 depicts the mutagenicity of the designed compounds. These results are calculated by Pre ADMET online software. As evident from the result all the compounds are predicted to be mutagenic i. e. carcinogenic. These results are predicted, not experimentally proven so it cannot be said these compounds are going to be carcinogenic for real unless wet lab experiments are carried out.

Table 7: Toxicity study of the compounds.

Name	Carcino mouse	Carcino rat	Mutagenicity
C7	TRUE	FALSE	TRUE
C10	TRUE	FALSE	TRUE
C11	TRUE	FALSE	TRUE
C12	TRUE	TRUE	TRUE
C23	TRUE	FALSE	TRUE
C30	FLASE	FALSE	TRUE
C40	TRUE	FALSE	TRUE
C45	FALSE	FALSE	TRUE
C46	FALSE	FALSE	TRUE
C56	FALSE	FALSE	TRUE
C65	FALSE	FALSE	TRUE
C78	TRUE	FALSE	TRUE
C84	FALSE	FALSE	TRUE
C89	FALSE	FALSE	TRUE

C*onclu*sion

Derivatives of Heterocyclic quinolone imines were designed on the basis key 7-Chloroquinline pharmacophore of chloroquine. Designing of all the derivatives involve hydrazine hydrate and various diamino alkanes as linking chain and heterocyclic aldehydes. For the proposed derivatives, in-silico investigations were conducted. Among all the hundred developed compounds, docking experiments revealed that, eleven compounds (C7, C9, C10, C11, C12, C13, C23,C30, C46, C65 and C75) had favourable receptor molecule interactions with the targeted protein plasmepsin 2 (Pdb id: 1LF3), eleven compounds (C10, C11, C12, c30, C40, C45, C46, C56, C78, C84 and C89) had favourable receptor molecules interactions with falcipain 2. Different physicochemical parameters such as LogP value, molecular weight, polar surface area, number of hydrogen bond donor, number of hydrogen bond acceptor for the designed compounds was determined on the basis of Lipinski's rule of five, which resulted in better bioavailability when administered by oral route, membrane permeability, along with plasma protein binding was found to be in acceptable range for some of the compounds. Blood brain barrier permeability is found to be moderate. Due to unforeseen circumstances, the majority of the

synthesis effort, as well as the wet-lab antimalarial activity evaluation and screening, could not be completed.

Based on current findings and literature results, effective antimalarials may be developed and produced from the main 7-Chloroquinoline pharmacophore by structural and molecular alteration using heteroclic substitute, as well as the use of molecular modelling techniques and computer assisted QSAR studies.

Conflict of Interest

The authors declare that they haveno conflicts of interest.

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