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Research Article

Design, Synthesis, Molecular Docking and *In-vitro* Antimalarial Activity of 7-chloro-4-aminoquinoline Substituted Analogues

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ABSTRACT

In present work new series of 7-chloro-4-aminoquinoline analogs were designed to discover chemically diverse antimalarial leads. The widely used computational tool molecular docking is applied to study molecular recognition, which aims to predict analogs' binding mode and binding affinity to the active site. The potential binding of the selected analogs to the *Plasmodium falciparum* lactate dehydrogenase enzyme (PfLDH) active site was analyzed using SYBYL X2.0 software running on a core-2 duo Intel processor workstation. Compounds F5, F9 and F1 showed highest binding affinity in term of total scores 9.50, 7.86 and 7.01, respectively. Analogs with the best dock score were synthesized and evaluated for antimalarial potential against chloroquine sensitive RKL-2 strain. Compounds F5, F28 and F9 showed good antimalarial activity in term of MIC_{50} value 0.35, 0.45 and 0.56 µg/mL, respectively. Further optimization and exploration of 7-chloro-4-aminoquinoline lead could be useful to identify novel, antimalarial molecules.

Introduction

Malaria has been haunting mankind since evolution. It is a mosquito-borne parasitological disease occurs mostly in poor tropical and subtropical areas of the world. There are five species of malaria parasites that are responsible for infection in humans, namely *Plasmodium falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi.* Among these *P. falciparum* is the most prevalent and deadliest.[1,2]

According to the latest WHO estimates released in 2021, there were an estimated 1.7 billion cases of malaria occurred worldwide and 10.6 million deaths from malaria globally compared with 227 million cases in 2019. Every 2 minutes, a child dies of malaria.[3] The percentage of total malaria deaths among children aged under 5 years was 84% in 2000 and 67% in 2019. In the WHO South-East Asia Region, malaria deaths reduced during the early months of by 74%, from about 35000 in 2000 to 9000 in 2019. India accounted for about 86% of all malaria deaths in the WHO South-East Asia Region. In April 2020, the coronavirus disease (COVID-19) pandemic, analysis by the World Health Organization (WHO) and partners had projected a doubling of malaria deaths if the worst-case scenario of service disruptions occurred.[4,5]

P. falciparum strains have already generated severe resistance against quinoline based molecules (Fig. 1). In particular, point mutations in *P. falciparum* chloroquine resistance transporter (PfCRT) protein is a transmembrane protein that localizes to the parasite digestive vacuole, the site of CQ action, are regarded as the major machinery behind the inefficacy of CQ against drug resistant *P. falciparum*. The rapid emergence or spread of resistance in most of the available antimalarial drugs, including primaquine, pyrimethamine and mefloquine and the latest marketed combinations, the artemisinin-based combination therapies (ACTs), recurring problem in malaria prevention and cure, has increased the burden of

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mortality rate quite abnormally in the last few years.[6,7] So, there is an urgent need of new chemical entities that could be active against drug resistant parasites. However, despite emergence of drug resistance CQ scaffold still could be a choice for further chemical modifications due to its excellent efficacy, low toxicity and affordability.[8]

A literature survey of 4-aminoquinoline cleared that this class of compounds is useful in developing new therapies for malaria and cancer treatment.[9] The antimalarial mechanism shown by entering the parasite's food vacuole and inhibiting the parasite growth by inhibiting β-hematin formation and accumulation of the drug at the target site, resides in 4-aminoquinoline core.[10] However, various strategies have been introduced against the drug resistant. The 4-aminoquinoline hybridization emerged as promising strategies to construct the molecules with enhanced activity against drug-resistant *P. falciparum* and also with improved metabolic stability.[11]

Kondaparla *et al.*[10] synthesized short chain 4-aminoquinoline-imidazole derivatives in which diethylamine function of chloroquine is replaced by substituted imidazole derivatives containing tertiary terminal nitrogen and reported promising antimalarial activity against both chloroquine sensitive (3D7) and chloroquine resistant (K1) strains of *P. falciparum*.

Previously in our literature[11] we performed molecular modeling on a series of one hundred and twelve 7-substituted 4-aminoquinoline derivatives using software Sybyl X2.0 in search of new 4-amino quinoline derivatives as antimalarial. The CoMFA and CoMSIA studies gave an insight into the quantitative role of chemical features in fluctuating in terms of favorable and unfavorable contours. HQSAR uses counters of key molecular substructures and PLS to generate fragment-based structure-activity relationships identify the sub-structure requirement of antimalarial activity. We also performed molecular docking to explore the drug-receptor interaction. On the findings of previous results we designed a Pharmacophore based on 7-chloro-4-aminoquinoline nucleus.

In the present study, we designed a pharmacophore of 7-chloro-4-aminoquinoline and performed the molecular docking to explore the drug-receptor interaction. In our docking study, we used *P. falciparum* lactate dehydrogenase (PfLDH), a tetrameric enzyme that contains 316 amino acids and is found in *P. vivax, P. malariae* and *P. ovale* all exhibit ~90% identity to LDH. It is an important enzyme of glycolysis and necessary for energy production in *Plasmodium*, besides *Plasmodium* lack functional kreb cycle during some erythrocytic stage. As an essential enzyme, it catalyzes the interconversion of pyruvate and lactate with concurrent conversion of NADH and NAD.[12] On the basis of docking result we synthesized 7-chloro-4-aminoquinoline derivatives and evaluated the synthesized hybrids against chloroquine sensitive RKL2 strain of *P. falciparum* and characterized them.

Materials and Methods

Chemistry

All reagents and solvents used in this work were of synthetic grade obtained from Sigma Aldrich, Merk, Alfa Aesar, s-d fine, and Loba –chem. Open glass capillaries melting point (M.P.) apparatus was used for the measurement of M.P. of all synthesized compounds (˚C) and are uncorrected. Progress of the reactions was monitored by TLC (silica gel G plates), using different solvent system to ascertain the purity of the synthesized compound. Spot on TLC were observed under UV light and/or by exposing iodine vapours. IR spectrum was recorded on FTIR-8400S (Shimadzu, DAVV Indore). ^{1}H-NMR spectrums were measured on Avance II-400 (Bruker, SAIF Punjab University Chandigarh), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an waters, Q-TOF Micromass (LC-MS) (SAIF/CIL, Panjab university, Chandigarh).

Designing

A Pharmacophore which consists of two aromatic hydrophobic sites and a hydrogen bond acceptor site, preferably at a side chain nitrogen atom, appear to be necessary for potent resistance reversal activity professed by Bhattacharjee *et al.*[13] On the basis of reported literature review, selectively modifying the pendent amino group with a small heterocyclic system could modulate the antimalarial activity. Stocks *et al.* have reported a series of short-chain CQ derivatives, on the replacement of the diethyl amino function with the more metabolically stable side chain.[14] Peyton D. H. and Burgess S. J. designed reversal analog antimalarial derivatives which consist chloroquine like portion merged with the RA (Reversal agent) liken portion (Fig. 2 a and b) suggested that 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity and RA is generally worked as an efflux mechanism inhibitor.[15,16]

Encouraged by these results and findings of our previous molecular modeling study, we envisaged that substituting benzimidazole derivatives which consists two aromatic hydrophobic groups and a hydrogen bond acceptor site at a side chain and merging them with chloroquine would lead to develop the new antimalarial agents active against CQ-R strain of *P. falciparum*.

On the basis of above facts we have designed a Pharmacophore (Fig. 2 c) consists chloroquine like nucleus and a substituted benzimidazole side chain. On the basis of reported structure activity relationship, 33 compounds were designed using ChemDraw ultra 8.0 as potential antimalarial agents with different substitutions shown in Table 1.

Molecular Docking

Docking studies yielded crucial information about the orientation of the inhibitors in the binding pocket of the

enzyme and the interaction between the target (enzyme) and the small molecules (ligands) at the molecular level. Molecular docking studies were carried out using the Surflex Dock in SYBYL X2.0 to explore possible binding affinity conformations and offer more insight into the understanding of the relations of lactate dehydrogenase receptor with inhibitors. The protein structure of *PfLDH* and its inhibitor were retrieved from RCSB protein data bank (PDB entry code: 1LDG). The protein structures were subjected to energy minimization and charge calculation (AMBER7FF99). All ligands and water molecules were removed. The bloat value was set as 1 and the threshold value as 0.5 for generation of protomol and position was considered to be the active sites for potential receptor's binding sites.[17]

Table 1: Designed 7-Chloro-4-aminoquinoline substituted analogues.

S. No.	*Compound ID*	*R*
1.	F 1	H
2.	F 2	3-Amine
3.	F 3	4-Amine
4.	F 4	5-Amino-2-Hydroxy
5.	F 5	3-methoxy
6.	F 6	4-methoxy
7.	F 7	4-phenyl
8.	F 8	2-bromo
9.	F 9	2-Chloro
10.	F 10	3-Chloro
11.	F 11	4-Chloro
12.	F 12	2-Chloro-4-Nitro
13.	F 13	2-Chloro-5-Nitro
14.	F 14	3-Chloro peroxy
15.	F 15	2,4-Dichloro
16.	F 16	2,4-Dihydroxy
17.	F 17	3,5-Dihydroxy
18.	F 18	3,4-Dimethoxy
19.	F 19	3,5-Dinitro
20.	F 20	2-Hydroxy-3,5-Dinitro
21.	F 21	3-Hydroxy
22.	F 22	4-Hydroxy
23.	F 23	4-Hydroxy-3,5-Dimethoxy
24.	F 24	3-Methoxy
25.	F 25	4-Methoxy
26.	F 26	2-Methyl
27.	F 27	3-Methyl
28.	F 28	4-Methyl
29.	F 29	3-Nitro
30.	F 30	4-Nitro
31.	F 31	4-Hydroxy-3,4-Dimethoxy
32.	F 32	3,4,5-Trihydroxy
33.	F 33	2,3,5-Triiodo

Synthesis of the Compounds

On the basis of docking result, compounds F5, F9, F1, F2, F26 and F28 were synthesized using synthetic Scheme 1.

General Procedure for the Synthesis of 2-(7-Chloroqinoline-4-ylamino) ethanol (C)

A mixture of 4,7-dichloroquinoline (2.0 g, 10.1 mmol), ethanolamine (12.1 mL, 20.2 mmol), and triethyl amine (21.0 mL, 15 mmol) was stirred under nitrogen at 120°C for 2 hours. After cooling to room temperature, crushed ice was added and the resulting mixture stored in the refrigerator for 1 hour. The precipitate was filtered and the residue washed with cold water (2×5 mL) and then with cold ethyl ether (2×5 mL). Resulting 5-(7-Chloroqinoline-4-ylamino) ethanol was further used for synthesis of second intermediate product (D)

General Procedure for the Synthesis of 2-(7-Chloroqinoline-4-ylamino)ethyl Methane Sulfonate (D)

To a suspension of 5-(7-Chloroqinoline-4-ylamino) (1.5 g, 6.7 mmol) in anhydrous dichloromethane (25 mL) under nitrogen atmosphere was added triethylamine (2 mL, 14.3 mmol). The mixture was cooled to below 0°C.

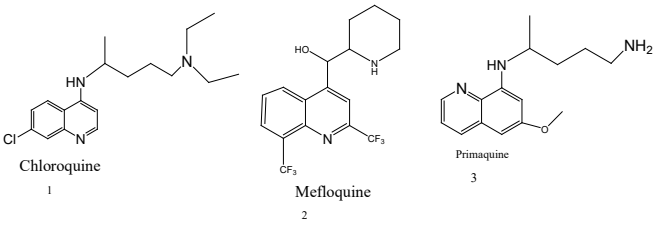


Fig.1: Structures of some molecules having antimalarial activity.

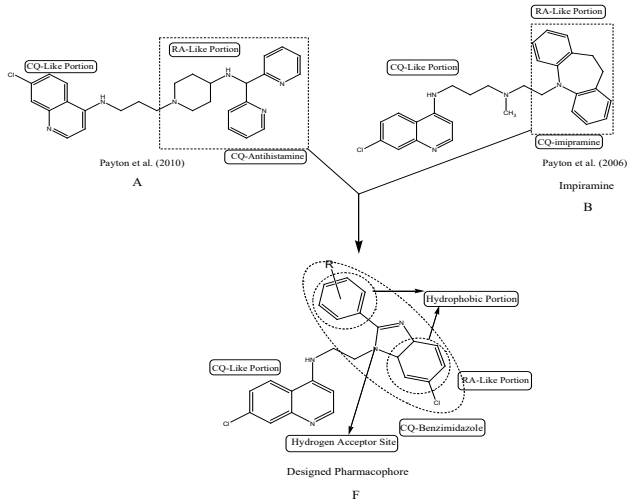


Fig. 2: (a) and (b) Reversal chloroquine molecules suggested by Peyton, (c) Designed Pharmacophore.

Methanesulfonyl chloride (0.57 mL, 7.41 mmol) was added slowly, keeping the temperature below 5°C, and the mixture was stirred in an ice bath for 2 hours. The mixture was added to a saturated $NaHCO_3$ solution (100 mL), and the organic layer was separated and washed with saturated $NaHCO_3$ solution (25 mL). The combined aqueous layers were extracted with dichloromethane (2 × 20 mL). The combined organic extracts evaporated to leave 2-(7-chloroqinoline-4-ylamino)ethyl methane sulfonate as off-white solid.

Table 2: Biological data of the synthesized compounds

S. No.	*Compound ID*	*In-vitro Antimalarial screening MIC50 (µg/mL)*[a]
1.	F1	1.25
2.	F2	1.35
3.	F5	0.35
4.	F9	0.56
5.	F26	2.36
6.	F28	0.45
7.	Chloroquine	0.020
8.	Quinine	0.268

[a]MIC 50: represents the MIC value at which 50% of the isolates in a test population are inhibited.

General Procedure for the Synthesis of 6-chloro-3a,7a-dihydro-2-phenyl-1H-benzo[d]imidazole derivatives (E 1-33)

The mixture of acetic acid (15 mmol) and 4-chloro-o-phenylenediamine (10 mmol) was stirred in the presence of the poly-phosphoric acid (5 mL), and irradiated in a household microwave oven three times at 18% full output power (162 W) for 6 minutes with 2 minutes cooling period after the 1st and 2nd irradiation cycle. After cooling, the reaction mixture was poured into cold water (50 mL) and neutralized with aq. $NaHCO_3$, and the solid products were filtered off, dried and recrystallized from hexane to get pure crystal. The resulting 6-chloro-3a,7a-dihydro-2-phenyl-1H-benzo[d]imidazole derivatives were further used to synthesize different derivatives.

Table 3: Results of docking analysis of designed compounds:

S. No.	*Compound ID*	*Total Score*	*Crash*	*Polar*	*Interaction*
1	F5	9.90	-1.64	1.29	MET30,SER245,GLY99
2	F9	7.86	-1.57	2.81	ASN140
3	F1	7.61	-2.81	1.67	ASN140
4	F2	6.54	-2.26	0.49	THR97,GLY32,ILE31,GLY29
5	F26	6.22	-3.07	0.13	ASN140
6	F28	6.20	-2.21	1.87	ASP53,GLY99

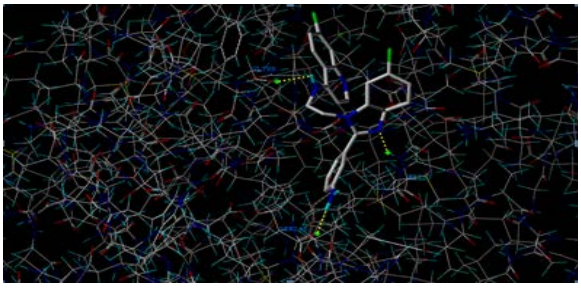


Fig. 3a: Interaction with hydrogen.

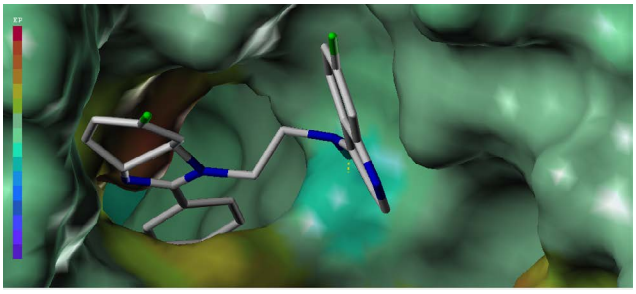


Fig. 3C: Electrophilic potential.

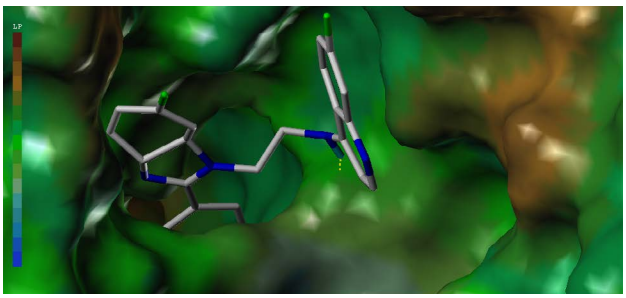


Fig. 3B: Lipophilic potential.

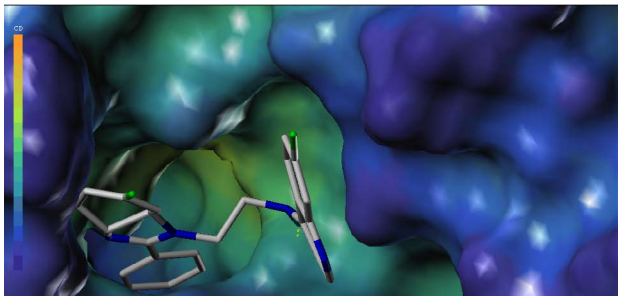
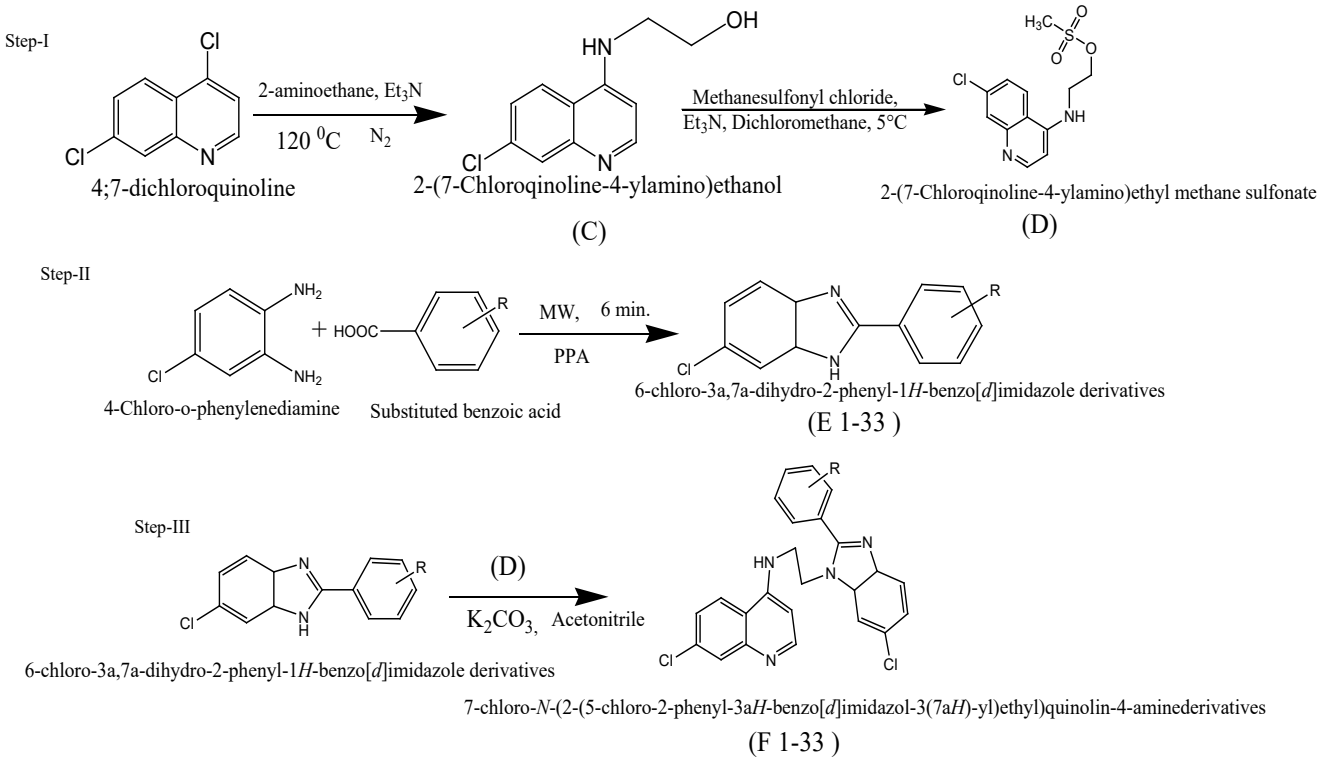


Fig. 3D: Cavity depth.

Fig. 3: Docking pose visualization of compound F5; A: Interaction with hydrogen, B: Lipophilic potential, C: Electrophilic potential, D: Cavity Depth.



Scheme 1: Synthesis of 7-Chloro-4-aminoquinoline substituted analogues.

General Procedure for the Synthesis of 7-chloro-N-(2-(5-chloro-2-phenyl-3aH-benzo[d]imidazol-3(7aH)-yl)ethyl) quinolin-4-amine derivatives (F 1-33)

6-chloro-3a,7a-dihydro-2-phenyl-1H-benzo[d]imidazole (E) (0.0065 mol) was dissolved in Acetonitrile (40 mL), then the 2-(7-Chloroqinoline-4-ylamino)ethyl methane sulfonate (D) (0.0043 mol) and potassium carbonate (2 g) was added. The mixture was stirred at 70°C for 2 days. After completion the mixture was cooled to room temperature, water (100 mL) was added to the mixture and stirred for 30 minutes. Thus the solid was separate out, filtered off, washed with water, dried and recrystallized from hexane to get crystals of 7-chloro-N-(2-(5-chloro-2-phenyl-3aH-benzo[d]imidazol-3(7aH)-yl)ethyl)quinolin-4-amine.

Structural Analysis of Compounds

7-chloro-N-(2-(5-chloro-2-(3-methoxyphenyl)-3aH-benzo[d]imidazol-3(7aH)-yl) ethyl)quinolin-4-amine (F5)

Yield 56%, mp 90–950°C, Rf = 0.84. FTIR (cm^{-1}): 3037 (Ar-H), 2988 (C-H, stretch), 867 (C-H, bend, ring), 1479 (C=N, stretch, ring), 1303 (C-N, stretch), 1697 (C=C stretch, ring str.), 3380 (N-H, Stretch), 1479 (C-H, bend, aliphatic), 702 (C-Cl, stretch), 2709 (C-H, stretch, OMe), 1216 (C-O, stretch, OMe). ^{1}H-NMR ($CHCl_3$-d): δ ppm, 7.5966 (7H, Ar), 7.2697 (3H, O-CH_3), 1.2498 (2H, N-CH), 1.2498(4H, CH_2-CH_2), 1.2498 (1H, NH), 8.7697 (5H, CQ). ESI Mass (m/z, %): 465 (M^+, 1).

7-chloro-N-(2-(6-chloro-2-(2-chlorophenyl)-1H-benzo[d] imidazole-1-yl)ethyl) quinoline-4-amine. (F9)

Yield 70%, mp 100–110°C, Rf = 0.52. FTIR (cm^{-1}): 3026 (Ar-H), 2879 (C-H, stretch), 814 (C-H, bend, ring), 1589 (C=N, stretch, ring), 3498 (N-H, Stretch), 1407(C-H, bend, aliphatic), 746 (C-Cl, stretch). ^{1}H NMR ($CHCl_3$-d): δ ppm, 7.4967 (7H, Ar), 1.9339 (2H, N-CH), 1.9339 (4H, CH2-CH2), 1.2504 (1H, NH), 8.7791 (5H, CQ). ESI Mass (m/z, %): 474 (M^+, 1).

7-chloro-N-(2-(6-chloro-2-phenyl-1H-benzo[d]imidazol-1-yl)ethyl)quinoline-4-amine (F1)

Yield 52%, mp 145–150°C, Rf = 0.83. FTIR (cm^{-1}): 3113 (Ar-H), 2887 (C-H, stretch), 845 (C-H, bend), 1564 (C=N, stretch, ring), 1268 (C-N, stretch), 1551 (C=C stretch, ring str.), 3481 (N-H, Stretch), 792 (C-Cl stretch). ^{1}H NMR ($CHCl_3$-d): δ ppm, 7.6011 (8H, Ar), 2.3841 (2H, N-CH), 1.2518 (4H, CH_2-CH_2), 1.2518 (1H, NH), 8.0682 (5H, CQ). ESI Mass (m/z, %): 435 (M^+, 1).

N-(2-(2-(3-aminophenyl)-5-chloro-3aH-benzo[d]imidazol-3(7aH)-yl)ethyl)-7-chloroquinolin-4-amine (F2)

Yield 65%, mp 90–95°C, Rf = 0.64. FTIR (cm^{-1}): 3027 (Ar-H), 2866 (C-H, stretch), 866 (C-H, bend, ring), 1489 (C=N, stretch, ring), 1327 (C-N, stretch), 1471 (C=C stretch, ring str.), 3438 (N-H, symmetric, Stretch), 3489 (N-H, asymmetric, Stretch), 1471 (C-H, bend, aliphatic), 746 (C-Cl, stretch). ^{1}H NMR ($CHCl_3$-d): δ ppm, 7.5984 (7H, Ar), 2.4023 (2H, NH2), 2.3728 (2H, N-CH), 1.9401 (4H, CH2-

CH2), 1.2501, (1H, NH), 8.7815 (5H, CQ). ESI Mass (m/z, %): 447 (M^+, 1).

7-chloro-N- (2- (5-chloro-2-o-tolyl-3aH-benzo [d] imidazol-3 (7aH)-yl) ethyl) quinolin-4-amine (F26)

Yield 60%, mp 85–90°C, Rf = 0.87. FTIR (cm^{-1}): 3076 (C-H, stretch), 809 (C-H, bend, ring), 1570 (C=N, stretch, ring), 1337 (C-N, stretch), 1560 (C=C stretch, ring str.), 3409 (N-H, Stretch), 1406 (C-H, bend, aliphatic), 809 (C-Cl, stretch), 3076 (C-H, stretch, Me), 1406 (C-H, end, Me). ^1H NMR ($CHCl_3$-d): δ ppm, 7.6008 (7H, Ar), 2.5925 (3H, CH3), 2.6063 (2H, N-CH), 1.2513(4H, CH2-CH2), 1.2513 (1H, NH), 8.7678 (5H, CQ). ESI Mass (m/z, %): 435 (M^+, 1).

7-chloro-N-(2-(5-chloro-2-p-tolyl-3aH-benzo[d]imidazol-3(7aH)-yl)ethyl) quinolin-4-amine (F28)

Yield 62%, mp 110–115°C, Rf = 0.77. FTIR (cm^{-1}): 3046 (Ar-H), 2916 (C-H, stretch), 735 (C-H, bend, ring), 1562 (C=N, stretch, ring), 1298 (C-N, stretch), 1562 (C=C stretch, ring str.), 3470 (N-H, Stretch), 1516 (C-H, bend, aliphatic), 675 (C-Cl, stretch), 2930 (C-H, stretch, Me). ^1H NMR ($CHCl_3$-d): δ ppm, 7.5980 (7H, Ar), 1.8943 (3H, CH3) 1.8943 (2H, N-CH), 1.8943 (1H, NH), 8.7706 (5H, CQ). ESI Mass (m/z, %): 444 (M^+, 1).

In-vitro Antimalarial Screening

All the synthesized compounds were evaluated for antimalarial activity. The *in-vitro* antimalarial assay was carried out in 96 well mL plates according to the microassay protocol of Rieckmann *et al.* with minor modifications. The culture of chloroquine sensitive *P. falciparum* RKL-2 strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasite of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain the only ring stage parasitemia of 0.8 to 1.5 at 3% haematocrit in a total volume of 200 µL of medium RPMI-1640 was determined and uniformly maintained with 50% RBC (O^+). A stock solution of 5 mg/mL of each of the test samples was prepared in DMSO and subsequently, dilutions were prepared with culture medium. The diluted sample in 20 µL volume was added to the test wells so as to obtain final concentration (at five fold dilutions) ranging between 0.4 to 100 µL/mL in deplicate well containing parasitized cell preparation. The culture plates were incubated at 37°C in a candle jar. After 36–40 hours incubation, thin blood smears from each well were prepared and stained with JSB (Jaswant singh Bhattacherji) stain. The sides were microscopically observed to record maturation of ring stage parasite into trophozoites and schizonts in presence of different concentration of test agents. The test concentration which inhibited complete maturation into schizonts was recorded as MIC shown in Table 2. Chloroquine and quinine was used as reference drug.

Observation of the *in-vitro* Antimalarial Drug

The mean number of rings, trophozoites and schizonts were recorded per 100 parasites from duplicate wells after incubation of 378 hours, and percent maturation inhibition with respect to control group. The minimum inhibitory concentration were determined and recorded.

Result And Discussion

Molecular Docking

For Docking analysis all designed compounds were docked at active site of the crystal structure of PDB code 1LDG to evaluate antimalarial activity using software Sybyl-X-2.0. Compounds with the highest total score showed interaction with the lactate dehydrogenase enzyme listed in Table 3.

Docking Analysis

Designed derivatives were docked at the active site of crystal structure of 1ldg.pdb. The docking result shows that six molecules F1, F2, F5, F9, F26 and F28 were found to exhibit good interaction with P*f*LDH in which compound no. F5 has the highest total score 9.90, crash-1.64 and polar 1.29. This structure's ligand-receptor interaction analysis (Fig. 3 (A)) revealed the hydrogen bond interaction with the amino acids of active side residue. Nitrogen atom of imidazole ring is interacting with MET30, hydrogen of -NH2 group at benzimidazole ring established interaction with SER245 and –NH showed interacting with GLY99. In the lipophilic potential pose view (Fig. 3 (B)) hydrophobic portion of the substituted CQ benzimidazole are situated in depth of cavity, and the benzimidazole ring showing slightly higher lipophilicity while aminoquinoline rings situated near medium lipophilic region. In electrophilic potential pose view (Fig. 3 (C)) hydrophobic portion of substituted benzimidazole situated in high electrostatic region, required for better activity. Analysis of cavity depth (Fig. 3 (D)) revealed that the compound situated in higher cavity depth region which is necessary for its activity.

Antimalarial Activity

The antimalarial potentials of all the synthesized hybrids against chloroquine sensitive RKL2 strain of *P. falciparum* were assessed according to micro assay of Rieckmann *et al.* (1978) in 96 well-microtitre plates, with minor modifications. All of the six compounds showed potent antimalarial activity Table 2.

Compound F5, exhibited comparable activity (MIC_{50} = 0.35 µg/mL) to quinine against chloroquine sensitive RKL2 strain, whereas derivative F28, F9 shows good antimalarial activity with the MIC values 0.45 and 0.56 µg/mL, respectively.

Conclusion

In present work we substituted benzimidazole and merged it with 4-amino-7-chloroquine ring to design new potent antimalarial hybrids. Molecular docking studies were performed to characterize a set of 7-substituted-4-aminoquinoline based derivatives which displayed strong interaction between the ligand and the binding site residue. The best-docked hybrids were synthesized and evaluated for antimalarial potential against chloroquine sensitive RKL-2 strain. The result revealed that current designed and synthesized hybrids were less active than the standard drug. However, it consists 4-aminoquinoline and benzimidazole ring which present in most of already proved effective pharmacophore and chloroquine like portion and reversal analogue portion similar to pharmacophore suggested by Peyton *et al.* 2006 and 2010. However, further studies are needed to optimize for building potent and chemically diversified antimalarial drug.

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