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Original Article

SYNTHESIS AND MOLECULAR DOCKING STUDY OF 2-ARYL/HETEROARYL-6-CHLOROQUINOLINE-4-CARBOXYLIC ACIDS WITH PLASMODIUM LDH RECEPTOR PROTEIN

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ABSTRACT

Objective: Synthesis and *in silico* molecular docking studies of 2-aryl/heteroaryl-quinoline-4-carboxylic acid derivatives **(3a-j)** with plasmodium LDH receptor protein.

Methods: The 2-aryl/heteroaryl-quinoline-4-carboxylic acids **(3a-j)** were obtained by Pfitzinger reaction. Ligands **(3a-j)** interaction with plasmodium LDH receptor protein was studied through molecular docking method.

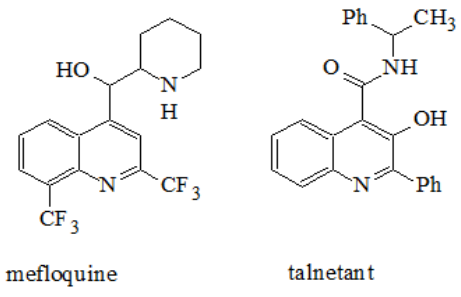
Results: Good yields of 2-aryl/heteroaryl-quinoline-4-carboxylic acid derivatives **(3a-j)** were obtained by convenient and economical procedure. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectral analysis. The binding site analysis of the synthesized compounds (**3a-j)** with plasmodium LDH receptor that are responsible for malaria parasite response was evaluated through molecular docking study. The results reveal that the ligand **3d** shows maximum of five hydrogen bonding interactions with binding energy -9.05 kcal/mol, shown to be a promising lead molecule to inhibit Plasmodium LDH receptor.

Conclusion: The docking studies of newly synthesized 2-aryl/heteroaryl-quinoline-4-carboxylic acids were found to be very useful ligands for antimalarial therapy particularly on Plasmodium LDH protein. However the installation of still many appropriate substitutions on quinoline moiety would lead to identification of novel antimalarial compounds that ascertained *via* molecular docking is underway in our lab.

Keywords: Pfitzinger synthesis, 2-aryl/heteroaryl-quinoline-4-carboxylic acids, Molecular docking, Lactate dehydrogenase (LDH), Antimalarial.

INTRODUCTION

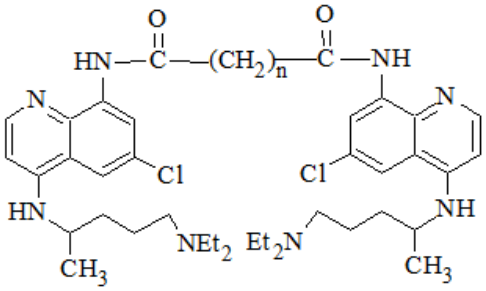
Diversely substituted quinolines are found to be valuable compounds and find wider applications in pharmaceutical field [1]. Most important use of the quinoline ring is its antimalarial potential. For example, the mefloquine and talnetant [2] are some important substituted quinoline nucleuses (**Fig. 1**) as antimalarial drugs. There are many 7-chloroquinolines [3, 4], and analogues of ferrochloroquine [5] are also exhibited good degree of antimalarial activity against both chloroquine-resistant and chloroquine-sensitive parasites. Certain, 7-chloroquinolinyl thioureas [6] are also reported as potential antimalarial agents.



mefloquine talnetant

Fig. 1

Hence, due to their importance a number of methods for the synthesis of quinolines have been developed [7-10]. The syntheses of 2-aryl/heteroaryl-quinoline-4-carboxylic acids are normally obtained by Pfitzinger synthesis. Besides, there are some classic condensation-type approaches, includes Skraup, Doebner-von Miller, Friedlander, and Combes reactions [11,12] are also known. Although, 6-chloroquinolines are also potential lead compounds for antimalarial property (**Fig. 2**) [13] there are no much reports on such molecules. Hence, in this report we studied the possibility for their synthesis to generate structurally distinct 6-chloroquinolines by very simple and convenient method and studied their binding interaction with malaria parasite as preliminary study.



n = 4,6,8

Fig. 2

Hence, keeping in view of biological activities exhibited by chloroquinolines and in continuation of our effort to identify new quinoline based therapeutic agents[14-25], in the present investigation we report one pot Pfitzinger synthesis of some novel 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids **(3a-j)** by using 5-chloroisatin and various substituted acetophenones and acetyl heterocyclic compounds with 33% potassium hydroxide solution.

We also performed molecular docking studies in order to understand how various 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids interact with Lactate dehydrogenase and to explain the differences in their activity. The characterization data of various

2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids are presented in the experimental section.

MATERIALS AND METHODS

Chemistry

The TLC was performed on alumina silica gel 60 F254 (Merck). The mobile phase was hexane and ethyl acetate (7:3 v/v) and detection was made using UV light (254 nm). Melting points of the synthesized compounds were determined by electrothermal apparatus in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra recorded on Brucker (Bangalore, India) AM 400 (at 400 and 100 MHz, respectively) model spectrophotometer in $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are expressed as δ values relative to TMS as internal standard. Mass spectra were recorded on a Jeol SX 102=DA-6000(10 kV) FAB mass spectrometer.

Typical procedure for the synthesis of 6-chloro-2-(furan-2-yl) quinoline-4-carboxylic acid (3a)

To a solution of 5-chloroisatin 1.0 g (0.006 mol) in 33% aqueous potassium hydroxide solution (15 mL) the 1-(furan-2-yl) ethanone 0.6 g (0.006 mol) was added, and the mixture was heated under reflux for 14-16 hr. The completion of the reaction was monitored by thin layer chromatography [hexane and ethyl acetate (7:3 v/v)]. The reaction mixture was poured into a crushed ice (100 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried under vacuum to afford crude product.

The crude product was purified by column chromatography with silica gel (60-120 mesh, petroleum ether: ethyl acetate, 7:3 v/v) furnished analytically pure compound **3a,** yield 80%**.** Similarly, all other derivatives (**3b-j)** were obtained.

Spectral data

6-chloro-2-(furan-2-yl) quinoline-4-carboxylic acid (3a)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=13.16 (s, 1H), 8.98 (s, 1H), 8.59 (s, 1H), 8.23 (d, *J*=2.40 Hz, 1H), 7.87 (d, *J*=2.40 Hz, 1H), 7.45 (d, *J*=3.20 Hz,1H), 6.75-6.76 (m, 1H),6.35-6.36 (m, 1H)ppm.^{13}C-NMR (100 MHz, DMSO-d_6) *δ*=10.23, 13.78, 91.85, 97.95, 112.53, 113.04, 113.47, 117.68, 120.58, 125.08, 127.06, 135.95, 141.59, 144.17, 145.90, 159.43 ppm. MS. *m/z* =273.95 (M^+).

6-chloro-2-(5-methylfuran-2-yl) quinoline-4-carboxylic acid (3b)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.01(s, 1H), 9.05 (s, 1H), 8.59 (s, 1H), 8.25 (d, *J*=2.40 Hz, 1H), 7.87 (d, *J*=2.40 Hz, 1H), 6.2 (*J*=3.20 Hz, 1H), 5.8-5.9 (m, 1H), 1.45 (s, 3H)ppm.^{13}C-NMR (100 MHz, DMSO-d_6) *δ*=13.58, 109.29, 113.16, 119.16, 123.87, 124.40, 130.66, 131.16, 131.75, 135.73, 146.95, 148.42, 150.57, 155.10, 159.76 ppm. MS. *m/z* =287.88 (M^+).

6-chloro-2-(1-methyl-1*H*-pyrrol-2-yl)quinoline-4-carboxylic acid (3c)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a brown solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=13.79 (s, 1H), 9.87 (s, 1H), 8.54 (s, 1H), 8.25 (d, *J*=7.60 Hz, 1H), 7.49 (dd, *J*=1.60, 8.60 Hz, 1H), 5.23 (d, *J*=8.40 Hz, 1H), 5.09-5.11 (m, 1H), 3.53 (s, 3H), 2.45 (s, 3H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6) *δ*=11.63, 13.75, 16.64, 97.18, 100.72, 100.75, 112.54, 113.06, 113.49, 117.65, 118.08, 120.58, 125.08, 127.03, 135.97, 136.56, 159.47 ppm. MS. *m/z* =300.03 (M^+).

2-(4-bromophenyl)-6-chloroquinoline-4-carboxylic acid (3d)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.17 (s, 1H), 9.77 (s, 1H), 8.59 (s, 1H), 8.21 (d, *J*=2.40 Hz, 2H), 8.18 (d, *J*=8.80 Hz, 1H), 7.88 (d, *J*=2.40 Hz, 1H), 7.77 (d, *J*=2.80 Hz, 2H) ppm.^{13}C-NMR (100 MHz, DMSO-d_6) *δ*=13.78, 120.24, 123.98, 129.19, 130.73, 131.75, 132.57, 136.56, 146.82, 150.10, 159.90 ppm. MS. *m/z* =361.80 (M^+).

6-chloro-2-[(*E*)-2-phenylethenyl]quinoline-4-carboxylic acid (3e)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.58 (s, 1H), 9.43 (s, 1H), 8.52 (s, 1H), 8.17 (d, *J*=9.20 Hz, 1H), 7.81 (d, *J*=2.40 Hz, 1H), 7.75-7.77 (m, 3H), 7.55 (d, *J*=16.40 Hz, 1H), 7.43 (t, *J*=7.60 Hz, 2H), 7.34-7.35 (m, 1H) ppm.^{13}C-NMR (100 MHz, DMSO-d_6): *δ*=13.59, 122.10, 124.28, 124.37, 125.98, 127.45, 127.60, 128.34, 128.84, 128.99, 130.49, 131.33, 135.30, 135.50, 135.92, 147.01, 150.89, 159.03 ppm. MS. *m/z* =309.90 (M^+).

6-chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinoline-4-carboxylic acid (3f)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.27 (s, 1H), 9.38 (s, 1H), 8.48 (s, 1H), 8.27 (d, *J*=9.20 Hz, 1H), 7.87 (d, *J*=2.40 Hz, 1H), 7.75-7.77 (m, 1H), 7.35-7.36 (m, 2H), 7.23-7.26 (m, 2H)7.20-7.21 (m,1H) ppm.^{13}C-NMR (100 MHz, DMSO-d_6) *δ*=13.87, 104.98, 113.04, 115.03, 117.14, 117.65, 117.83, 117.85, 118.84, 118.89, 120.78, 123.34, 123.38, 123.53, 126.87, 123.96, 135.58, 143.13, 159.48, ppm. MS. *m/z* =345.95 (M^+).

6-chloro-2-(2,4,5-trimethoxyphenyl)quinoline-4-carboxylic acid (3g)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=13.89 (s, 1H), 9.75 (s, 1H), 8.55 (s, 1H), 8.03 (d, *J*=9.20 Hz, 1H), 7.70 (d, *J*=2.00 Hz, 1H), 7.57 (s, 1H), 6.77 (s, 1H), 3.79-3.87 (m, 9H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): *δ*=13.23, 55.77, 56.10, 56.50, 98.28, 114.11, 118.20, 128.87, 123.73, 124.22, 125.24, 129.87, 131.48, 133.74, 143.15, 146.86, 151.50, 152.48, 150.84, 159.25 ppm. MS. *m/z* =373.91 (M^+).

6-chloro-2-(naphthalen-2-yl)quinoline-4-carboxylic acid (3h)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.05 (s, 1H), 9.80 (s, 1H), 8.35 (s, 1H), 8.16 (d, *J*=9.20 Hz, 1H), 7.83 (d, *J*=2.00 Hz, 1H), 7.87-7.88 (m, 3H), 7.43 (dd, *J*=3.20, 6.60 Hz, 1H), 7.30-7.31 (m, 3H) ppm.^{13}C-NMR (100 MHz, DMSO-d_6): *δ*=13.85, 106.75, 108.89, 112.56, 113.02, 113.47, 113.98, 116.65, 116.87, 117.65, 118.05, 118.76, 119.54, 120.34, 123.71, 125.04, 135.98, 142.98, 148.10, 159.47 ppm. MS. *m/z* =333.99 (M^+).

6-chloro-2-(1-hydroxynaphthalen-2-yl)quinoline-4-carboxylic acid (3i)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow solid.^{1}H-NMR (400 MHz, DMSO-d_6): δ=14.02 (s, 1H), 10.06 (s, 1H), 8.91 (s, 1H), 8.14 (t, *J*=8.40 Hz, 2H), 7.87-7.87 (m, 3H), 7.46 (d, *J*=7.60 Hz, 1H), 7.31-7.32 (m, 3H) ppm.^{13}C-NMR (100 MHz, DMSO-d_6): *δ*=13.98, 118.29, 118.95, 122.87, 123.59, 124.02, 124.36, 126.77, 126.97, 127.85, 128.04, 130.21, 130.57, 131.63, 132.49, 132.62, 134.54, 146.94, 152.82, 157.25, 159.01 ppm. MS. *m/z* =349.90 (M^+).

2-(anthracen-9-yl)-6-chloroquinoline-4-carboxylic acid (3j)

Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale brown solid.^{13}C-NMR (100 MHz, DMSO-d_6): *δ*=13.72, 112.57, 113.45,113.01, 116.32, 116.31, 117.64, 117.61, 117.34, 117.36, 117.67, 118.98, 118.91, 118.31, 118.32, 120.52, 120.31, 125.01, 127.01, 129.22, 135.96, 142.97, 159.48 ppm. MS. *m/z* =383.60 (M^+).

In silico molecular docking studies

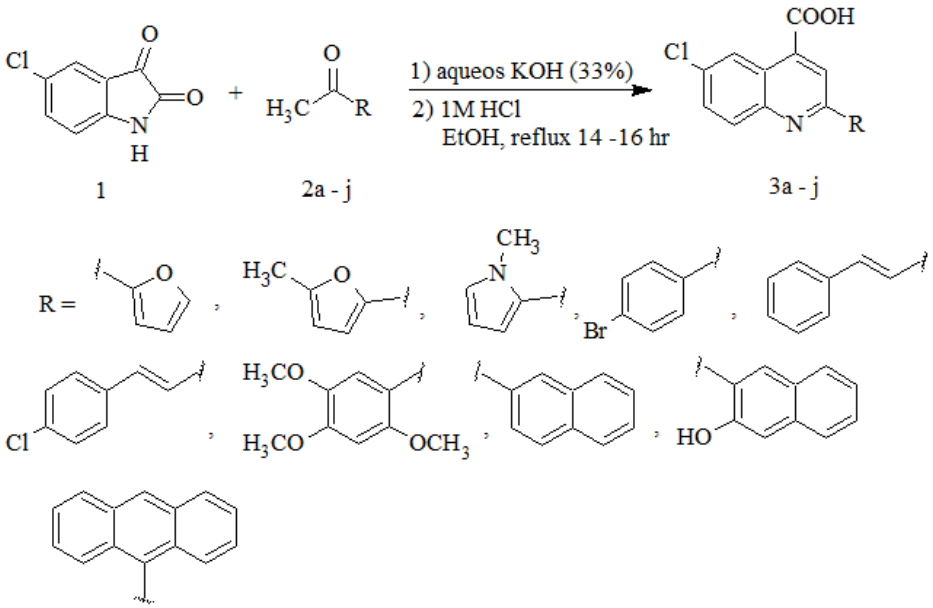
The three dimensional structure of target protein Lactate dehydrogenase (PDB ID: 1CET) was downloaded from PDB [26] structural database. This file was then opened in SPDB viewer edited by removing the heteroatoms, adding C terminal oxygen. The active pockets on target protein molecule were found out using CAST pserver [27]. The ligands were drawn using Chem Draw Ultra 6.0

and assigned with proper 2D orientation (Chem Office package). 3D coordinates were prepared using PRODRG server [28]. Auto dock V3.0 was used to perform Automated Molecular Docking in AMD Athlon (TM)2x2 215 at 2.70 GHz, with 1.75 GB of RAM. Auto Dock 3.0 was compiled and run under Microsoft Windows XP service pack 3. For docking, grid map is required in Auto Dock, the size of the grid box was set at 72, 106 and 82 Å (R, G, and B), and grid center 25.714, 26.958, 9.32 for x, y, and z-coordinates. All torsions were allowed to rotate during docking. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters [29].

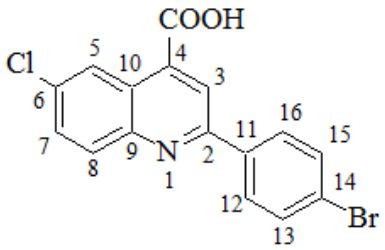
RESULT AND DISCUSSION

Chemistry

The syntheses of the desired products are outlined in **scheme-1** by following standard literature procedures [30]. Thus, the 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids were prepared in which the condensation of 5-chloroisatin and acetophenones/acetylheterocyclic compounds in aqueous potassium hydroxide (33%) solution with EtOH solvent *via* Pfitzinger synthesis. Since our interest was to generate some biologically more important 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids, we employed normal Pfitzinger synthesis methodology with slight modification in their reaction, such that we could get good to excellent yield of the products (**3a-j**). Initially, we have reported the synthesis of 2-furyl-6-chloroquinoline-4-carboxylic acid **3a** by condensation of 5-chloroisatin and 2-acetylfuran in aqueous potassium hydroxide (33%) solution with EtOH solvent *via* Pfitzinger synthesis. Finally, by adopting optimized condition various 2-aryl/heteroaryl-quinoline-4-carboxylic acids were synthesized. By this reaction we could easily incorporated different aryl/heteroaryl rings at 2-position and a chloro at 6thposition and carboxylic group at 4th position simultaneously in one pot reaction. Thus antimalarial property through molecular docking studies with Lactate dehydrogenase (LDH) protein was assessed for all new ten ligands (**3a-j**).



Scheme 1: Pfitzinger synthesis of 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acid derivatives (3a–j)



3d

The structure of 3d was elucidated as below

In ^{1}H-NMR spectrum four doublets at δ=8.25, 8.18, 7.77 and 7.88 ppm correspond to C_{12}-H, C_{8}-H, C_{7}-H and C_{13}-H protons. Singlet at δ=14.17 ppm corresponding to the acidic -COOH proton of quinoline, in addition two singlets at δ=8.77 and 8.54 ppm corresponds to C_{5}-H and C_{3}-H proton respectively. The other peaks have appeared in the expected region and the number of protons is in accordance with the expected structure. Additional support to elucidate the structure is obtained from ^{13}C-NMR spectra of this compound. The appearance of peak at δ=166.90 ppm corresponds to the acidic –COOH carbon atom. The peaks at δ=120.24, 123.98, 124.3, 129.18, 129.19, 129.19, 130.73, 131.75, 131.90, 132.57, 136.56, 136.56, 146.82, 155.10 ppm corresponds to C_{14}, C_{10}, C_{3}, C_{12}, C_{16}, C_{8}, C_{7}, C_{13}, C_{15}, C_{6}, C_{11}, C_{4}, C_{9} and C_{2}. The mass spectrum of **3d** was recorded as additional evidence to the proposed structure and it exhibited M+1 peak at m/z 363.6. From all these spectral evidences the structure of **3d** has been confirmed. Similarly, structures of all other derivatives were established and presented in experimental section.

Table 1: Physical data of 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acid derivatives (3a–j)

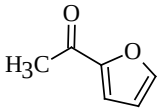
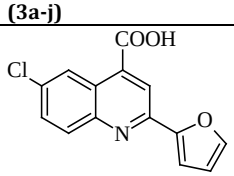
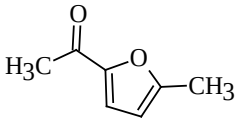
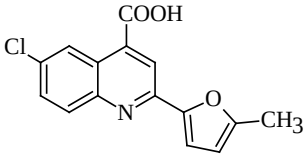
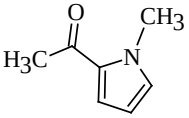
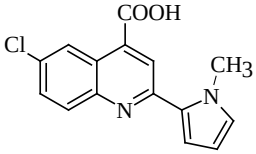
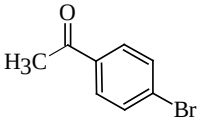
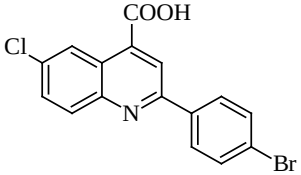
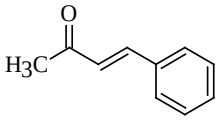
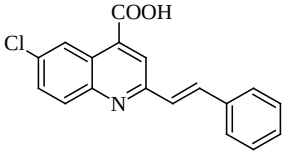
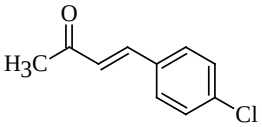
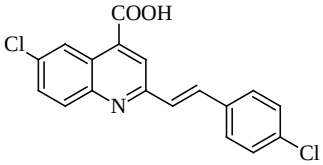
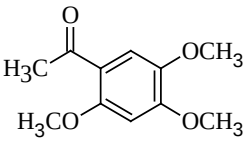
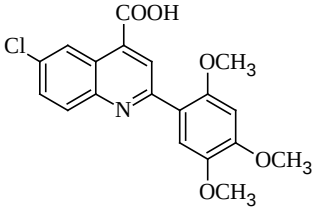
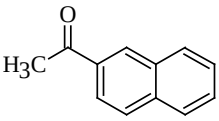
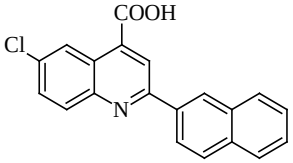
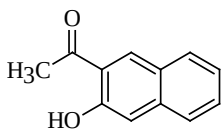
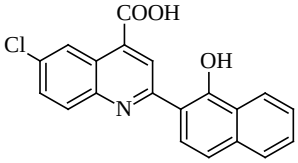
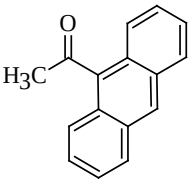
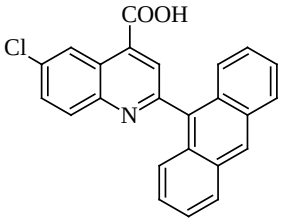
Entry	Acetophenones (2a-j)	Products (3a-j)	Yield (%)	M. P °C
3a			80	290-295
3b			78	285-290
3c			80	235-240
3d			75	270-275
3e			80	280-285
3f			78	300-305
3g			75	220-225
3h			80	310-315
3i			75	250-255
3j			75	315-320

Fig. 3: Three dimensional structure of LDH protein PDBID: 1CET)

Molecular docking studies

The synthesized 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acid derivatives (**3a–j)** were tested *in silico* to get the greatest conformer for their inhibitory properties against plasmodium LDH receptor protein (**Fig. 3**)**.** The different bonds i. e. hydrogen bonds, van der Waals forces and hydrophobic behavior with amino acids were in good agreement with the predicted binding affinities obtained by molecular docking studies as verified by antimalarial studies where ligand 2-(4-bromophenyl)-6-chloroquinoline-4-carboxylic acid (**3d)** was the most active compared with standard drug Chloroquine (Table 2). Based on the molecular docking studies, the Plasmodium LDH protein is interacts with Chloroquine drug has two hydrogen bonds within active site amino acids HIS195 and ALA236 having binding energy -6.74 kcal/mol (**Fig.4)**. The ligand 2-(4-bromophenyl)-6-chloroquinoline-4-carboxylic acid (**3d)** has five hydrogen bonds with strong interactions within active site amino acids GLY29, GLY32, THR97, ILE31 and THR97 with binding energy of -9.05 kcal/mol. In the same way ligands **3b**, **3c**, **3g** and **3j** forms four hydrogen bonding interaction with amino acids THR97, ILE31, GLY32, GLY29, ARG171, VAL138, ARG171 and ASN140 having binding energy -8.73, -8.75, -9.88 and-7.98 kcal/mol respectively, indicates more potent inhibitors of Plasmodium LDH. However, the ligands **3e**, **3h**, **3i** shows three hydrogen bonding interaction with binding energy of -8.0, -9.02, and -8.44 kcal/mol respectively implies that these ligands have moderate interaction. Surprisingly, the ligand **3f** has shown no interaction with target protein and hence can't be considered as an inhibitor of Plasmodium LDH. Overall the docking of ligands **3a-j** except **3f** with LDH domain revealed that, our synthesized molecules which are having inhibitory capability are exhibiting interactions with one or the other amino acids in the active pockets as shown in (**Fig. 5)**.

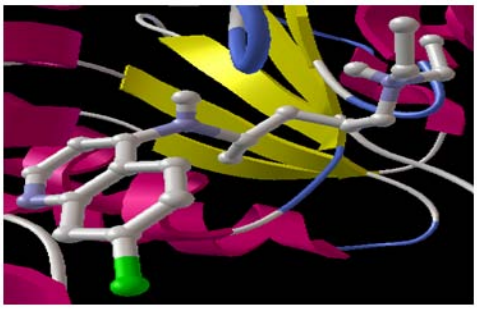
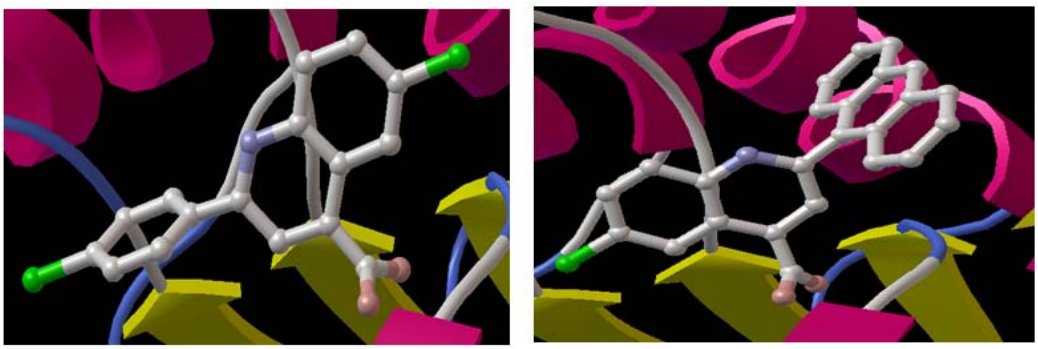


Fig. 4: Docking image of chloroquine interact with LDH protein

Table 2: Molecular docking results of chloroquine and synthesized ligands 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acid derivatives (3a–j) with plasmodium LDH receptor protein

Ligands	**Binding Energy** (kcal/mol)	**Docking energy**	**Inhibitory Constant** (μM**)**	**Intermol Energy** (kcal/mol)	**H- bonds**	**Bonding**
3a	-7.81	-9.3	1.89e-006	-9.05	2	3a: :DRG: OAM: LD: A: ASN140:HD22 3a: :DRG: OAR: LD: A: VAL142:HN
3b	-8.73	-9.32	3.99e-007	-9.35	4	3b: :DRG: OAS: LD: A: THR97:HG1 3b: :DRG: OAT: LD: A: ILE31:HN 3b: :DRG: OAS: LD: A: GLY32:HN 3b: :DRG: OAS: LD: A: GLY29:HN
3c	-8.75	-9.32	3.85e-007	-9.37	4	3c: :DRG: OAU: LD: A: GLY29:HN 3c: :DRG: OAT: LD: A: GLY32:HN 3c: :DRG: OAU: LD: A: THR97:HG1 3c: :DRG: OAT: LD: A: ILE31:HN
3d	**-9.05**	-9.7	2.33 e-007	-9.67	**5**	3d: :DRG: OAU: LD: A: GLY29:HN 3d: :DRG: OAT: LD: A: GLY32:HN 3d: :DRG: OAU: LD: A: THR97:HG1 3d: :DRG: OAT: LD: A: ILE31:HN 3d: :DRG: NAI: LD: A: THR97:O
3e	-8.44	-9.56	6.46e-007	-9.38	3	3e: :DRG: OAU: LD: A: GLY32:HN 3e: :DRG: OAV: LD: A: ILE31:HN 3e: :DRG: NAJ: LD: A: THR97:O
3f	112	111.18	-----	111.09	_	
3g	-7.98	-9.68	1.42 e-006	-9.54	4	3g: :DRG: OAZ: LD: A: RG171:HH11 3g: :DRG: OAQ: LD: A: VAL138:O 3g: :DRG: OAY: LD: A: RG171:HH21 3g: :DRG: OAR: LD: A: ASN140:OD1
3h	-8.0	-8.72	1.37e-006	-8.62	3	3h: :DRG: OAX: LD: A: ARG171:HH11 3h: :DRG: OAX: LD: A: ARG171:HH21 3h: :DRG: OAW: LD: A: HIS195:HE2
3i	-9.02	-9.66	2.44e-007	-9.64	3	3i: :DRG: OAX: LD: A: ARG171:HH21 3i: :DRG: OAY: LD: A: ARG171:HH11 3i: :DRG: HAW: LD: A: VAL138:O
3j	-9.88	-10.85	5.76e-008	-10.5	4	3j: :DRG: OBA: LD: A: THR97:HG1 3j: :DRG: OBB: LD: A: GLY32:HN 3j: :DRG: OAT: LD: A: ILE31:HN 3j: :DRG: OBA: LD: A: GLY29:HN
Chloroquine	-6.74	-8.43	1.15e-005	-9.23	2	STD: :DRG: HA5:LD: A: HIS195:O STD: :DRG: NAG: LD: A: ALA236:HN



3d **3j**

Fig. 5: Docking images of compound 3d and 3j interaction with LDH protein shows five and four hydrogen bonds with binding energy -9.05 kcal/mol & -9.88 kcal/mol

CONCLUSION

The convenient syntheses of new 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acid derivatives (**3a–j)** were described via Pfitzinger reaction. The i*n silico* molecular docking studies reveals that derivatives **3a-j** except **3f** were shown interaction with plasmodium LDH. In that the compound **3d** shows maximum of five hydrogen bonding interaction with binding energy -9.05 kcal/mol. Thus, this basic result would certainly draw attention from researcher to identify lead inhibitor of plasmodium LDH receptor protein.

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CONFLICT OF INTERESTS

Declared None

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