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In silico study of 4-amino substituted-7-chloroquinoline derivatives as *Plasmodium falciparum* lactate dehydrogenase inhibitors

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The docking between 4-amino substituted-7-chloroquinoline derivatives and *Plasmodium falciparum* lactate dehydrogenase were carried out. The designed 4-aminosubstitued-7-chloroquinoline derivatives show comparable dock score with chloroquine. The docking study reveals that the binding of 4-amino substituted-7-chloroquinoline derivatives and amino acids in the binding pocket of *Plasmodium falciparum* lactate dehydrogenase is observed. Predicted ADME properties of designed compounds are in range.

Keywords: 1LDG, 4-amino substituted-7-chloroquinolines, Docking and ADME, Malaria, *Plasmodium falciparum* lactate dehydrogenase

Malaria is caused due to the bite of female anopheles mosquitoes[1]. A protozoan parasite plasmodium when enters into the bloodstream of humans it will destroy red blood cells which subsequently causes malaria which is a fatal disease. Worldwide many people suffer through malaria and death occurs in severe cases[2]. The two species namely *Plasmodium falciparum* and Plasmodium vivax parasites cause malaria[3].

Malarial fever can be treated by using Olive leaf as a part of natural remedy[4]. Many researchers worldwide work to combat malaria and different therapies[5] used which includes drugs[6] *viz*., chloroquine, primaquine, amodiaquine and artesunate. Most recently malaria parasites have been developed resistant[7] to most drugs and hence the need of new drugs is utmost important.

Literature review reveals the quinoline class has potential antimalarial characteristics *in vivo* and *in vitro*[8]. Moreover substituted quinoline derivatives are known to exhibit antidengue[9], antituberculosis[10], anti HIV[11] and no doubt antimalarial[12] activities.

Docking[13-16] is important to screen compounds virtually to identify the lead. Multi-drug resistance[17] underscores the urgent need for research and development of new antimalarial drugs with novel mechanisms of action to combat resistant strains.

This prompt our research for searching alternative molecules as potential antimalarials lead compounds. Thus we revisited the quinoline class for designing new potential antimalarial derivatives. In current work, we studied the docking between designed 4-aminosubstitued-7-chloroquinoline derivatives as potential *Plasmodium falciparum* lactate dehydrogenase inhibitors using CB dock, a web based server[18].

Materials and Methods

Hardware

Molecular docking studies were performed on Dell Inspiron 15R Laptop (Intel® Core™ i3-processor) running Windows 7 Home Basic Operating System.

Docking studies

The various docking software's are available with their pros and cons. Some software's need certain commands which make docking cosy, while some softwares are time consuming and computer system gets hang or freeze and docking stops suddenly. But we found that CB dock software is fast, easy and can work on regular computer systems easily. The main CB dock web server is easy to operate and ease of generation of results which helps in quick interpretation of docking results.

Docking between protein and ligands was performed on CB Dock web server[18]. https://cadd.labshare.cn/cb-dock2/php/index.php. *Plasmodium falciparum* lactate dehydrogenase proteins[19,20] were downloaded from

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Suppl. Data available on respective page of NOPR

www.rcsb.org website in .pdb format. PDB ID used is 1LDG. PDB ID: 1LDG in .pdb format can only be uploaded on CB dock web server[18].

Ligands Preparation

Designed compounds means ligands were drawn on *Marvin sketch* or *Chem draw* software. Ligands file saved in.*sdf* file format. These files will be used for uploading on CB dock web server[18].

ADME Prediction

For studying ADME one can draw ligands structure on SWISS ADME website. Then after careful drawing we have to click on run to get ADME properties of ligands. ADME of molecules is studied by using SWISS ADME Software http://www.swissadme.ch/index.php#

Results and Discussion

The docking scores of Chloroquine[21], artesunate[21] and designed 4-amino substituted-7-chloroquioline compounds are comparable with each other. The docking score of designed compounds are summarized in (Table 1). Chloroquine show -4.8 dock score which is comparable with designed compounds. The good docking score of compounds no 2, 3, 7, 13 and 24 reveals strong binding with receptor. The 7th position of chlorine in designed quinoline nucleus is kept constant while only other fragments changed to check binding characteristics with *plasmodium falciparum* lactate dehydrogenase.

Although it was anticipated that increasing the methylene chain (represented by X) in the designed 4-aminosubstituted-7-chloroquinoline derivatives would elevate the docking score, the outcome has been a moderate score or even a slight decrease despite the addition of the methylene chain to the core structure. This observation contrasts with the initial expectation. The rationale behind incorporating the methylene chain was to capture a crucial fragment from the carbon chain of the chloroquine nucleus, which is believed to play a pivotal role in conferring antimalarial properties *in silico*.

The substitution of the phenyl Y-group with a heterocyclic moiety like furan or thiophene results in an improvement in the docking score.

Antimalarial approved drug Chloroquine show hydrogen bonding with Gly99 and hydrophobic interaction with Val26, Ile31, Phe52, Thr101, Ile119[17]. NADH binding pocket contains the amino acid residues[22] *viz*, Val26, Ile31, Gly27, Ser28, Phe52, Asp53, Ile54, Tyr85, Gly99, Ala98, Lys118, Ile119, Glu122 and Ile123 at site 1.

Table 1 — Dock score of designed 4-amino substituted-7-chloroquinoline derivatives

Comp. No	X	Y	Dock score
1	$-CH_2-CO-$	Phenyl	-5.8
2	$-(CH_2)_2-CO-$	Phenyl	-6.9
3	$-(CH_2)_3-CO-$	Phenyl	-6.4
4	$-(CH_2)_4-CO-$	Phenyl	-5.5
5	$-(CH_2)_5-CO-$	Phenyl	-5.2
6	$-(CH_2)_6-CO-$	Phenyl	-6.2
7	$-CH_2-CO-$	2-Furyl	-7.3
8	$-(CH_2)_2-CO-$	2-Furyl	-5.6
9	$-(CH_2)_3-CO-$	2-Furyl	-5.6
10	$-(CH_2)_4-CO-$	2-Furyl	-5.2
11	$-(CH_2)_5-CO-$	2-Furyl	-5.3
12	$-(CH_2)_6-CO-$	2-Furyl	-6.0
13	$-CH_2-CO-$	2-Thiophene	-7.6
14	$-(CH_2)_2-CO-$	2-Thiophene	-5.5
15	$-(CH_2)_3-CO-$	2-Thiophene	-4.6
16	$-(CH_2)_4-CO-$	2-Thiophene	-5.0
17	$-(CH_2)_5-CO-$	2-Thiophene	-4.7
18	$-(CH_2)_6-CO-$	2-Thiophene	-5.2
19	$-CH_2-CO-$	2-Azole	-6.2
20	$-(CH_2)_2-CO-$	2-Azole	-4.9
21	$-(CH_2)_3-CO-$	2-Azole	-5.2
22	$-(CH_2)_4-CO-$	2-Azole	-4.9
23	$-(CH_2)_5-CO-$	2-Azole	-5.4
24	$-(CH_2)_6-CO-$	2-Azole	-6.4
25	$-(CH)-CH_3-$	3-NH_2Phenyl	-5.6
26	Chloroquine	-	-4.8

Table 2 — ADME Properties

Sr. No	Compound		H-bond acceptor	H-bond donor	Log P	Log S	GI absorption	BBB	Log Kp	Lipinski
	X	Y								
1.	$-CH_2-CO-$	Phenyl	2	1	3.62	-5.02	High	Yes	-4.69	0
2.	$-(CH_2)_2-CO-$	Phenyl	2	1	4	-5.3	High	Yes	-4.45	0
3.	$-(CH_2)_3-CO-$	Phenyl	2	1	4.11	-5.17	High	Yes	-4.67	0
4.	$-(CH_2)_4-CO-$	Phenyl	2	1	4.5	-5.4	High	Yes	-4.5	0
5.	$-(CH_2)_5-CO-$	Phenyl	2	1	4.81	-5.63	High	Yes	-4.33	0
6.	$-(CH_2)_6-CO-$	Phenyl	2	1	5.15	-5.97	High	No	-4.04	0
7.	$-CH_2-CO-$	2-Furyl	3	1	2.89	-4.18	High	Yes	-5.49	0
8.	$-(CH_2)_2-CO-$	2-Furyl	3	1	3.18	-4.47	High	Yes	-5.24	0
9.	$-(CH_2)_3-CO-$	2-Furyl	3	1	3.48	-4.34	High	Yes	-5.47	0
10.	$-(CH_2)_4-CO-$	2-Furyl	3	1	3.73	-4.56	High	Yes	-5.3	0
11.	$-(CH_2)_5-CO-$	2-Furyl	3	1	4.1	-4.79	High	Yes	-5.13	0
12.	$-(CH_2)_6-CO-$	2-Furyl	3	1	4.42	-5.13	High	Yes	-4.83	0
13.	$-CH_2-CO-$	2-Thiophenyl	2	1	3.54	-4.67	High	Yes	-5.14	0
14.	$-(CH_2)_2-CO-$	2-Thiophenyl	2	1	3.9	-4.95	High	Yes	-4.91	0
15.	$-(CH_2)_3-CO-$	2-Thiophenyl	2	1	4.1	-4.83	High	No	-5.13	0
16.	$-(CH_2)_4-CO-$	2-Thiophenyl	2	1	4.41	-5.05	High	No	-4.97	0
17.	$-(CH_2)_5-CO-$	2-Thiophenyl	2	1	4.72	-5.28	High	No	-4.8	0
18.	$-(CH_2)_6-CO-$	2-Thiophenyl	2	1	5.1	-5.62	High	No	-4.5	0
19.	$-CH_2-CO-$	2-Azole	2	2	2.67	-4	High	Yes	-5.68	0
20.	$-(CH_2)_2-CO-$	2-Azole	2	2	3.09	-4.28	High	Yes	-5.44	0
21.	$-(CH_2)_3-CO-$	2-Azole	2	2	3.27	-4.16	High	Yes	-5.67	0
22.	$-(CH_2)_4-CO-$	2-Azole	2	2	3.63	-4.38	High	Yes	-5.5	0
23.	$-(CH_2)_5-CO-$	2-Azole	2	2	3.89	-4.61	High	Yes	-5.33	0
24.	$-(CH_2)_6-CO-$	2-Azole	2	2	4.32	-4.95	High	Yes	-5.03	0
25.	$-(CH)-CH_3-$	3-NH_2-phenyl	1	2	3.65	-4.97	High	Yes	-4.83	0
26	Chloroquine		2	1	3.95	-4.95	High	Yes	-4.96	0

In present work, the interaction of chloroquine with Val26, Ile31, Gly27,Ser28, Phe52, Asp53, Ile54, Tyr85,Gly99, Ala98, Lys118, Ile119, Glu122, Ile123 amino acids[22] is observed using CB dock that is at binding pocket[22].

Moreover Artesunate is found to interact at binding pocket[22] with Gly27, Ser28, Gly29, Asp53, Ile54, Val55, Tyr85, Thr97, Ala98, Gly99, Phe100, Ile119, and Glu122 either by hydrogen bonding, hydrophilic interaction or Van der Waals forces. The designed 4-amino substituted-7-chloroquinoline derivatives shows similar binding interactions including hydrogen bonding, hydrophobic interaction and van der waals forces with Val26, Gly27, Ser28, Phe52, Asp53, Ile54, Tyr85, Ala98, Gly99, Lys118, Ile119, Glu122 and Ile123 at binding pocket[22]. The designed compounds binds similarly like chloroquine at binding site of *Plasmodium falciparum* lactate dehydrogenase *in silico*. From above results it is clear that 4-amino substituted-7-chloroquinolines have potential *Plasmodium falciparum* lactate dehydrogenase inhibitor characteristics.

ADME profile of chloroquine contributes to its therapeutic efficacy as an antimalarial agent. Chloroquine and the designed 4-aminosubstituted-7-chloroquinoline derivatives demonstrate robust gastrointestinal (GI) absorption, ensuring efficient uptake from the gastrointestinal tract into the bloodstream upon oral administration. This heightened absorption capability plays a pivotal role in their efficacy when orally administered to treat malaria and various other ailments. The log Kp values of the designed compounds, resembling chloroquine, are within a desirable range. This indicates their ability to traverse biological membranes efficiently, aligning with chloroquine's absorption profile and suggesting promising pharmacokinetic properties. Top of form the docking images are available in (Suppl. Table 1). ADME results are presented in (Table 2)

Conclusion

The docking scores of Chloroquine, artesunate, and the designed 4-aminosubstituted-7-chloroquinoline compounds are quite similar, suggesting they could all bind effectively to the target enzyme, *plasmodium falciparum* lactate dehydrogenase. Notably, the designed compounds, especially numbers 2, 3, 7, 13, and 24, show particularly strong binding to the

receptor. Surprisingly, adding methylene chains to the 4-aminosubstituted-7-chloroquinoline derivatives didn't improve scores as expected, but substituting the phenyl Y-group with heterocyclic moieties like furan or thiophene did. The way Chloroquine and the designed compounds interact with amino acid residues in the binding pocket of the enzyme is similar, suggesting they could work as inhibitors. Moreover, their ADME profiles, especially their robust gastrointestinal absorption and favorable log Kp values, are in line with Chloroquine's effectiveness as an antimalarial drug, hinting at promising pharmacokinetic properties for the designed derivatives. In conclusion, the newly designed 4-aminosubstituted-7-chloroquinoline compounds show characteristics similar to Chloroquine, indicating potential as effective antimalarial agents.

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Conflict of interest

All authors declare no conflict of interest.

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