ORIGINAL ARTICLE

Designing of Ligand-107 an Effective Variant of Antimalarial Drug Lumefantrine through Structure-Based Computer-Aided Drug Development Approach

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Abstract

Background: Lumefantrine is a well-known antimalarial drug that has proven to be effective even against the multidrug-resistant *Plasmodium* sp. Although it is very effective, the shelf life of the drug is very short and is highly hydrophobic, hence, the drug has to be administered along with fat. Lumefantrine is also known for its undesired side effects that are overlooked in case of untreatable (drug resistant) malarial infections. **Methodology:** In this study, structure-based computational drug development approach was performed on lumefantrine structure to improve the biological properties using OSIRIS property explorer software. A total of 25 ligand molecules were designed that exhibited better Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) properties. **Results:** A total of 20 drug targets were chosen and docked with lumefantrine to identify its potential target. Lumefantrine demonstrated significant affinity toward falcipain-3 protein with a free binding energy of −10.92 Kcal/mol and inhibition constant of 9.94 nM, suggesting that falcipain-3 is the potential drug target of lumefantrine. Among the 25 designed ligands with improved ADMET properties, ligand-107 demonstrated 100-fold higher affinity toward falcipain-3 with a free binding energy of −14.26 Kcal/mol and inhibition constant of 35.11 pM. Based on this improved affinity to inhibit falcipain-3 and based on improved ADMET properties of ligand-107, it was concluded to be the most effective variant of lumefantrine in this study. **Conclusion:** The result of the study could be greatly useful to pharmaceutical industries to develop an efficient antimalarial drug.

Key words: ADMET properties, Antimalarial drug, AutoDock 4, Ligand-107, Lumefantrine, OSIRIS property explorer, Structure-Based Computational Drug Development

INTRODUCTION

Malaria is an epidemic prevalent in most of the tropics, which affects billions of people worldwide. According to the WHO statistics of 2019, about 228 million cases occurred worldwide in 2018 and an estimated 405,000 deaths resulted from this disease which included approximately 67% of children below the age of 5 years. It also stated that sub-Saharan Africa and India carried almost 85% of the global burden with approximately 213 million cases in the African region itself. This recent statistic shows the gravity of this epidemic.[1]

Plasmodium falciparum, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae,* and *Plasmodium knowlesi* are the known pathogens that cause this disease, with *P. falciparum* and *P. vivax* being the major ones. Transmission of the disease mainly occurs through the female *Anopheles* sp. mosquito, mainly between dusk and dawn.[2] Other comparatively rare mechanisms of transmission include congenitally acquired disease, blood transfusion, sharing of contaminated needles, and organ transplantation. The disease lifecycle can be studied in two major phases; exoerythrocytic phase and erythrocytic phase which translate to prior involvement of red blood cells (RBCs) and involvement of RBCs, respectively.[3,4] *P. knowlesi*

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can also cause life-threatening illness which includes severe respiratory diseases and anemia. In some severe cases, death also reported due to infection by *P. vivax*.[3]

P. falciparum has been reported to have major resistance to chloroquine, the most recommended treatment option for malaria. It first emerged in Southeast Asia in the late 1950s and spread to other countries in Asia and then to Africa over the next 30 years with devastating consequences.[5] Research evidence has also shown that the resistance to sulfadoxine-pyrimethamine (SP), another leading therapy for malaria, also originated in the same region of Southeast Asia and spread even more rapidly into the sub-Saharan Africa. It was also reported to have developed resistance to mefloquine in countries such as Thailand, Cambodia, and Vietnam soon after its introduction in the 1990s. *P. vivax*, by-far the most common causal organism of malaria, has also developed resistance to the frontline antimalarial drug chloroquine treatment. Development of the chloroquine-resistant strain *P. vivax* was first observed at the Papua New Guinea in 1989, but now, it is evident in most other endemic locations such as Brazil, Columbia, Peru, Myanmar, and Thailand.[6,7]

Artemisinin-based combination therapies (ACTs) are recommended by the WHO as the first line of treatment for malaria in many countries where the pathogen *Plasmodium* sp. are reported to be drug resistant for common antimalarial drugs such as chloroquine, SP, and amodiaquine. ACTs ensure the highest cure rates and also reduced the chance of developing drug-resistant strains.[8] Artemether and lumefantrine are used in combination and are administered to patients so that the resistance to the treatment of malaria is reduced. The first active component of the treatment artemether acts very rapidly but lumefantrine is present in the body for a comparatively longer period to clear out the residual pathogens present in the body, thereby reduces the reoccurrence of the disease.[8]

Lumefantrine is an antimalarial drug which was introduced in the 1990s and is used in combination with artemether for the treatment of malaria caused by multidrug-resistant *P. falciparum*. Lumefantine is known to be 97% effective against malaria, which is comparable to that of traditional malarial drugs such as chloroquine. After approval by the WHO in 1999, it is sold in the market as Coartem and is widely used worldwide.[9,10] Lumefantrine is known to cause a lot of adverse effects during the course of treatment in children and adults. It is also known to be tolerated by the body.[8-11] This drug is also not recommended for pregnant women in the first trimester as it has positive reproductive effect and also to prevent any undesirable side effects.[8] Lumefantrine is a non-polar compound and is highly insoluble in water. It has a high affinity to lipids and its bioavailability is increased when administered with fats. It has many adverse effects listed during the course of treatment which include headache, dizziness, weakness, muscle or joint pain, tiredness, difficulty of falling asleep, vomiting, loss of appetite, fever, and chills. Some serious side effects are also listed which include abnormal or fast heartbeat, fainting, rash, hives, difficulty breathing or swallowing, swelling of lips/tongue/face/throat, hoarseness, and difficulty in speaking.[12,13] Due to these adverse effects, there is a requirement for the development of a drug which is as effective but less toxic than lumefantrine.

Drug discovery and development are a time-consuming process and traditional *in vivo* and *in vitro* experimentation only tends to add on to its complexity. Sophisticated *in silico* approaches have given the pharmaceutical companies a much easier and efficient way of identifying potential drug targets helping them boost their speed in developing new drugs and molecules.[14] Low availability of antimalarial drugs and comparatively higher rates of infection, deaths, and resistance has led to a great demand for new and effective antimalarial drugs. In this study, computer-aided drug development approach has been used to modify the existing drug lumefantrine to create a better drug candidate which is much more effective, less toxic (side effects) and has a greater bioavailability than the lead molecule.

MATERIALS AND METHODS

Drug targets

Three-dimensional structures of known protein drug targets of *P. falciparum* and *P. vivax* were retrieved from RCSB-Protein Data Bank (www.rcsb.org). The lists of selected drug targets are tabulated in Table 1. The retrieved structure files were processed by removal of non-amino acid residues (HETATOMS) from the structures, removal of homologous dimmers or trimers so that the final monomer protein chain, with the reported ligand binding site is available for docking studies.

Lead development

The lead molecule was modified using the OSIRIS property explorer tool (https://www.organic-chemistry.org/prog/peo/). The molecular structure of lumefantrine was drawn in the stand alone Java Runtime Environment and was modified by substitution of carbon atom with oxygen (O) or nitrogen (N) such that to retain the skeleton structure but to increase the polarity and solubility and reduce the undesired side effects. The modifications were done with a condition to remove one of the three undesired side effects that were observed with the lead molecule. The physicochemical parameters such as LogP, solubility, Topological polar surface area (TPSA), molecular weight, druglikeness, and drug score were also noted for ADMET analysis using Lipinski's rule of five. The color code indicates the severity of the undesired side

Table 1: Antimalarial drug target proteins selected from Protein Data Bank (PDB) database

PDB ID	Name	Classification	Organism
3AUA	1-deoxy-d-xylulose 5-phosphate reductoisomerase	Isomerase	*P. falciparum*
2Q8B	Apical membrane antigen 1	Immune system	*P. falciparum*
1TV5	Dihydroorotate dehydrogenase homolog, mitochondrial	Oxidoreductase	*P. falciparum*
3LSY	Enoyl-ACP reductase	Oxidoreductase	*P. falciparum*
2NQ8	Enoyl-acyl carrier reductase	Oxidoreductase	*P. falciparum*
1ZRO	Erythrocyte-binding antigen region II	Cell invasion	*P. falciparum*
1YVB	Falcipain-2	Hydrolase	*P. falciparum*
2GHU	Falcipain-2	Hydrolase	*P. falciparum*
3BWK	Falcipain-3	Hydrolase	*P. falciparum*
1Q4J	Glutathione S-transferase	Transferase	*P. falciparum*
1Z1Y	Ookinete surface protein pvs25	Cell adhesion	*P. vivax*
1QNH	Peptidyl-prolyl cis-trans isomerase	Isomerase	*P. falciparum*
1QNG	Peptidyl-prolyl cis-trans isomerase	Isomerase	*P. falciparum*
3NI6	Peptidyl-prolyl isomerase	Isomerase	*P. vivax*
3PA7	Peptidyl-prolyl isomerase, putative	Isomerase	*P. vivax*
1MIQ	Proplasmepsin	Hydrolase	*P. vivax*
3QRV	Plasmepsin-1	Hydrolase	*P. falciparum*
2ANL	Plasmepsin-4	Hydrolase	*P. malariae*
4UOR	Reticulocyte binding protein 5	Immune system	*P. falciparum*
4LVO	Subtilisin-like serine protease	Hydrolase	*P. falciparum*

P. falciparum: Plasmodium falciparum, P. vivax: Plasmodium vivax, P. malariae: Plasmodium malariae

effects, that is, green indicates no undesired effects, whereas red indicates high risk of undesired effects, while yellow and orange indicate low and medium risk of undesired effects.[15] The conformers that yielded a better predicted properties were then drawn in ChemSketch tool and were saved as .pdb format for further docking analysis.

Protein-ligand docking

AutoDock4 software was used to study the protein-ligand interaction between the selected 20 protein drug targets and 25 ligand molecules, including the lead molecule lumefantrine and modified ligand molecules. The binding site/active site of the protein targets was identified based on the position of the cocrystallized ligand molecules and substrates along with the protein molecule in the rcsb website. The AutoGrid was set to enclose the binding site of cocrystallized ligand molecules and AutoDock was executed individually with all protein and ligand combinations (520 combinations of protein-ligand).[15-17] Results of the protein-ligand interactions were visualized using PyMOL software.[18] To validate the docking procedure, the cocrystallized ligands found in the protein structures (RCSB website) were subjected for protein-ligand docking and the docking conformation results were cross-verified with the conformation of the cocrystallized structure.[19] This validated the reproducibility and quality of the protein-ligand docking procedure.

RESULTS

Virtual screening of drug targets

The mechanism of the action of lumefantrine is yet a mystery and hence virtual screening of malarial protein drug targets was performed to identify its potential drug target. Twenty known drug target proteins [Table 1] belonging to *P. falciparum* and *P. vivax* were retrieved from RCSB website (Protein Data Bank [www.rcsb.org]) and were subjected for protein-ligand docking analysis using AutoDock4. Among the screened drug target proteins, highest significance was observed against falcipain-3 protein with a binding energy of −10.92Kcal/mol and formation of 1 hydrogen bond (Asp-44) and an inhibition constant of 9.94 nM. Based on this significant interaction between the lead molecule lumefantrine and falcipain-3 protein, it was identified that falcipain-3 is the potential drug target of the lumefantrine drug. Falcipain-3 is a cysteine protease enzyme that is vital for survival/virulence of the malarial parasite *Plasmodium*. Hence, lumefantrine could exert its well-known antimalarial activity by means of inhibition of falcipain-3.

Lead development

The key objective of this study is to develop a ligand molecule that is better efficient than the chosen lead molecule

(lumefantrine). The primary disadvantage/drawback of the lead molecule is its ADMET properties, where it is known to cause several side effects. Hence, the lead development was carried out to design/modify the lumefantrine chemical structure toward obtaining better ADMET properties. OSIRIS molecular property explorer tool was used to predict the properties of lead molecule lumefantrine. Lead modification/development was done using ChemSketch software, such that, each modification/alteration to the lead molecule structure would yield a better biological property in the OSIRIS molecular property explorer tool.

The lead molecule lumefantrine demonstrated harmful biological properties such as mutagenicity, tumorigenicity, and reproductive effect. Modifications to the lumefantrine structure were done to improve these predicted properties, to improve one of the three biological properties to yield a better drug-like molecule. A total of 25-lead developments were drawn using ChemSketch software which yielded a better biocompatibility in comparison to the lead molecule lumefantrine. The modified ligand molecules were labeled as ligand-101 to ligand-125, respectively. The structures of the modified ligands, along with the lead molecule lumefantrine, are graphically represented in Figure 1. The results of OSIRIS property explorer for all the 25-lead development ligands and the lead molecule lumefantrine are tabulated in Table 2. In addition to the OSIRIS property explorer, further ADMET properties of the ligands were analyzed based on Lipinski's rule of five, for further validation of the lead development. The lead molecule lumefantrine showed three violations of the rule of five. However, the designed ligand molecules demonstrated no violations to maximum two violations, suggesting that the lead development yielded ligand molecules with better ADMET values. The ADMET values of the lead molecule and developed ligand molecules are tabulated in Table 3. These designed 25 ligand molecules were further investigated using protein-ligand docking analysis.

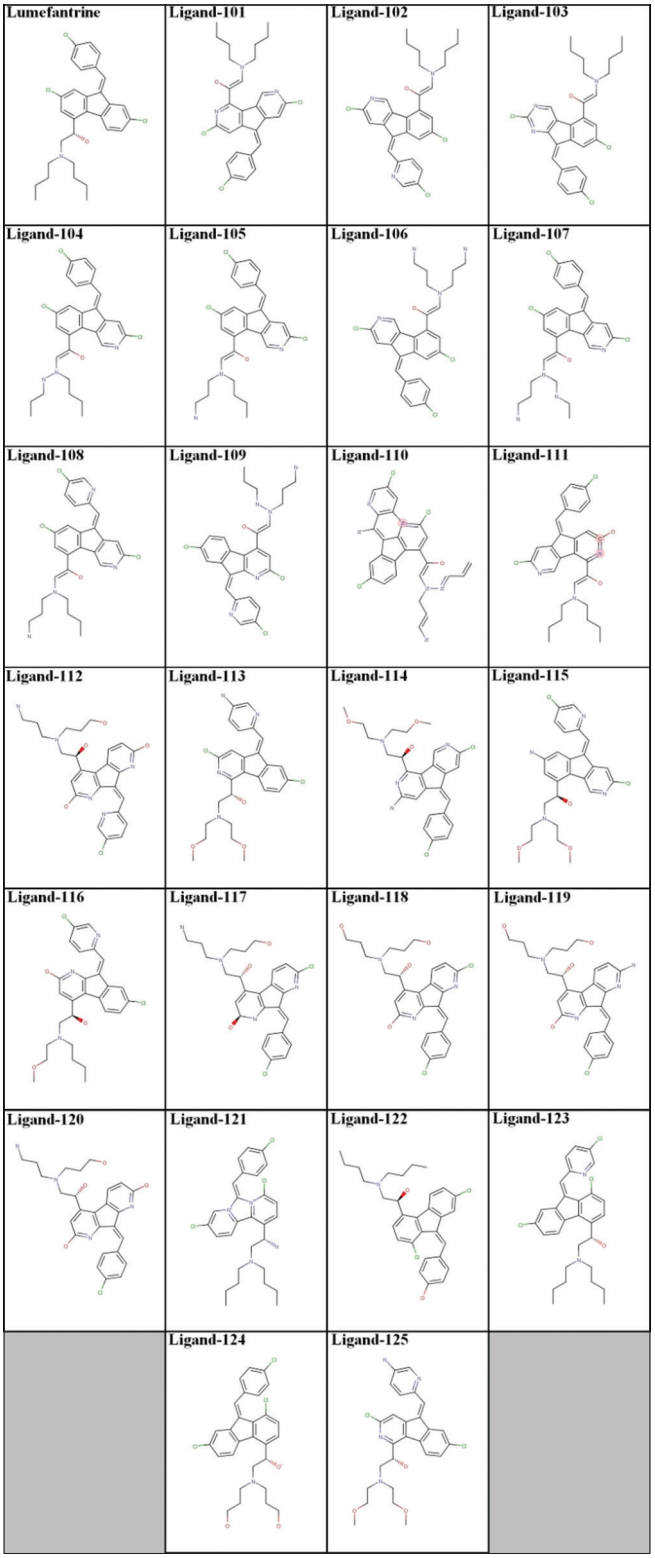

Figure 1: Chemical structure of lumefantrine and modified ligands

Efficiency of lead development ligand

The designed ligand molecules were subjected for protein-ligand docking analysis against all the 20 drug target proteins, similar to that of the lead molecule, lumefantrine. The individual results of all interactions between all 25 ligands with all 20 protein targets are not given in this section (a total of 520 combinations of protein and ligands were docked). A summarized table, with the docking values of the best significant interaction of each ligand molecule with the respective protein target, is tabulated in Table 4. This was performed to test the efficiency of the modified ligands to inhibit falcipain-3 with a better efficiency than that of the lead molecule lumefantrine, which demonstrated a binding free energy of −10.92 Kcal/mol and an inhibition constant of 9.94 nM. The most significant binding efficiency of all the modified ligands and lumefantrine with target proteins are summarized in Table 5. Among the 25 ligands that were screened, ligand-107 showed a high significant interaction with falcipain-3 with a free binding energy of −14.26 Kcal/mol and inhibition constant of 35.11 pM with the formation of five hydrogen bonds (two bonds with Asp-44; three

Table 2: Results of OSIRIS molecular property explorer for lumefantrine and modified ligands

Ligand	Mutagenic	Tumorigenic	Irritant	Reproductive effective
Lumefantrine	R	R	G	R
101	G	G	G	G
102	G	G	G	G
103	G	G	G	R
104	G	G	G	R
105	G	G	G	R
106	G	G	G	R
107	G	G	G	R
108	G	G	G	G
109	G	G	G	G
110	G	G	G	G
111	G	G	G	G
112	G	G	G	G
113	G	G	G	G
114	G	G	G	G
115	G	G	G	G
116	G	G	G	G
117	G	G	G	G
118	G	G	G	G
119	G	G	G	G
120	G	G	G	G
121	G	G	G	G
122	G	G	G	G
123	G	G	G	G
124	G	G	G	R
125	G	G	G	G

Green (G): No risk; red (R): High risk

bonds with Asp-218 of Chain-A). The interaction between ligand-107 and falcipain-3 was 100-fold more significant than the interaction between lumefantrine and falcipain-3. Ligand-107 has two nitrogen atoms (N) substituted instead of carbon (C) groups. The first nitrogen substituted in one of the three aromatic rings, and the other two substituted at the terminal branches of the molecule. The comparison of conformational positioning of lumefantrine and ligand-107 is shown in Figure 2 with the residue level interactions with the falcipain-3. Lumefantrine demonstrated polar interaction with Chain-D (Asp-44 residue) and non-polar interactions with Chain-D (Pro-41; Vl-42; Lys-43; Gln-45; Ala-46; Leu-47; Phe-54; Tyr-115; Gly-216; and Ser-217); Chain-A (Ser-217; Asp-218; Trp-219; Gly-220; Glu-221; Gly-222; and Gly-223); and Chain-C (Leu-119). However, the ligand-107 demonstrated significantly higher polar interactions of five hydrogen bonds with Chain-A (two bonds with Asp-44; three bonds with Asp-218) and non-polar interactions with Chain-A (Asp-44; Gln-45; Ala-46; Leu-47; Cys-48; Trp-215; Gly-216; Ser-217; Asp-218; and Trp-219); Chain-B (Asp-218) and with Chain-C (Asp-44; Alap-46; Leu-47; Asn-118; Trp-215; and Asp-218). The interactions of ligand-107 are concluded to be significantly stronger than the lead molecule lumefantrine and hence predicted to exert better antimalarial activity, with less or no side effects in comparison to lumefantrine.

Other than ligand-107, other modified ligands such as ligand-106 and ligand-117 also showed significant inhibition potential with pM inhibition constant against falcipain-3. These evidences suggest that modification of lumefantrine

Table 3: Lipinski's rule of five analysis of lumefantrine and modified ligand for ADMET properties

Ligands	ClogP	Solubility	Mol. wgt	TPSA	Druglikeness	Drug score
Lumefantrine	8.79	−9.34	528.0	26.71	2.57	0.04
101	7.23	−7.55	527.0	49.25	2.02	0.20
102	7.13	−7.79	527.0	49.25	1.24	0.18
103	7.71	−8.38	527.0	49.25	2.07	0.11
104	6.14	−8.38	527.0	48.39	2.12	0.13
105	6.3	7.86	527.0	62.38	0.31	0.11
106	4.52	−7.13	528.0	88.4	1.86	0.18
107	4.84	−7.63	528.0	74.41	2.4	0.17
108	5.35	−7.09	528.0	75.27	−0.55	0.19
109	5.52	−7.64	528.28	61.28	1.8	0.24
110	4.41	−7.24	543.0	87.3	1.57	0.28
111	5.55	−7.19	511.0	78.71	0.05	0.21
112	1.78	−4.79	495	148.8	−0.97	0.37
113	3.08	−5.31	512	93.73	2.94	0.47
114	3.38	−5.81	512	93.73	3.35	0.47
115	3.03	5.29	512	93.73	2.52	0.47
116	5.08	−6.62	511	78.71	1.62	0.29
117	3.42	−5.83	512	115.7	−0.07	0.32
118	3.83	−5.75	513	109.9	−1.65	0.39
119	2.79	−5.85	494	135.9	−1.63	0.43
120	2.3	−5.56	494	135.9	−0.07	0.37
121	4.53	−5.45	473.0	109.9	1.18	0.39
122	2.06	−4.4	477.0	150.4	0.78	0.53
123	1.47	−4.14	478.0	163.2	0.74	0.55
124	2.17	−4.67	476.0	137.5	1.01	0.31
125	3.3	−5.26	504.0	142.2	1.34	0.44

Green: No risk; Yellow: Low risk; Orange: Medium risk; Red: High risk

Table 4: Docking results of lumefantrine with protein drug targets

Protein name	Binding energy	Inhibition constant (units)	Hydrogen bonds	Ligand efficiency
Plasmepsin-1MIQ	−9.07	224.94 nM	2	−0.26
Glutathione s-transferase-1Q4J	−7.28	4.64 uM	1	−0.21
Cyclosporina-1QNG	−6.93	8.39 uM	1	−0.2
Cyclophilin-1QNH	−7.76	2.03 uM	1	−0.22
Dihydroototate-1TV5	−6.96	7.85 uM	0	−0.2
Cysteinprotease-1YVB	−6.71	12.03 uM	0	−0.19
Ookinete- 1Z1Y	−8.77	371.9 nM	1	−0.25
Erythrocyte-binding antigen region II-1ZRO	−7.23	4.97 uM	1	−0.21
Allophenylnorstatine-2ANL	−9.16	191.44 nM	1	−0.26
Falcipain-2-2GHU	−9.02	224.68 nM	3	−0.26
ACP reductase- 2NQ8	−7.88	1.68 uM	1	−0.23
Apical membrane antigen 1-2Q8B	−8.94	280.05 nM	0	−0.26
Quaternary complex-2-3AUA	−6.64	13.69 uM	2	−0.19
Falcipain-3 3BWK	−10.92	9.94 nM	1	−0.31
Enoyl-ACP reductase-3LSY	−10.24	31.4 nM	2	−0.29
PvFKBP35-3NI6	−9.8	65.81 nM	1	−0.28
Peptidyl-prolyl isomerase-3PA7	−8.17	1.03 uM	1	−0.23
Plasmepsin-1-3QRV	−9.17	188.4 nM	1	−0.26
Subtilisin-like serine protease-4LVO	−8.53	560.79 nM	2	−0.24
Reticulocyte-binding protein 5-4U0R	−7.35	4.09 uM	2	−0.21

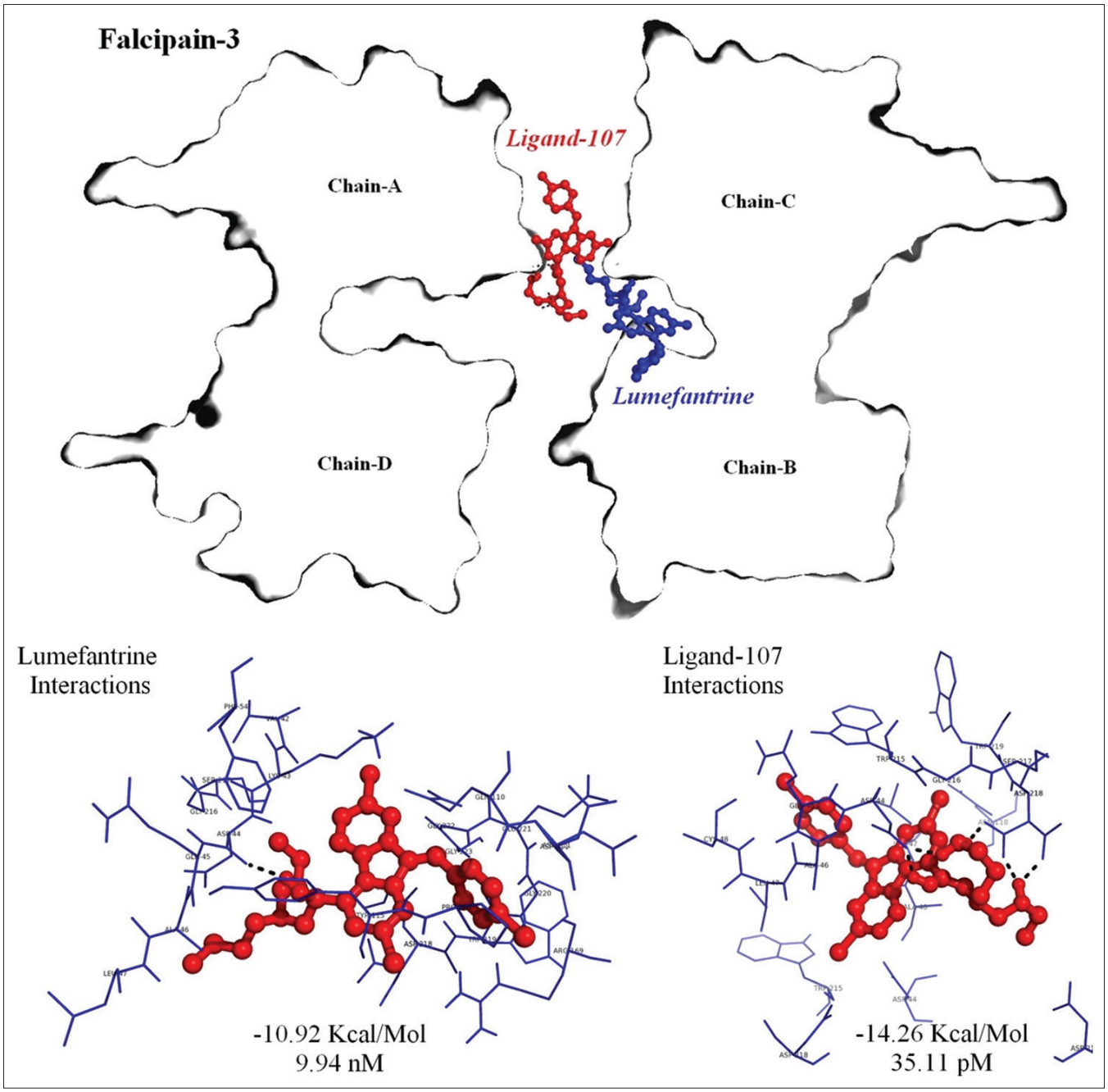

Figure 2: Interactions of lumefantrine and ligand-107 with falcipain-3

with polar atoms such as oxygen and nitrogen could significantly improve the antimalarial activity and also reduce the observed side effects. Hence, this study provides possibility for medicinal chemists and organic chemists to synthesize a better effective antimalarial drug.

DISCUSSION AND CONCLUSION

Malaria being rampant throughout the world and has become non-responsive to drugs due to drug resistance malarial parasites. Hence, it is the need of the hour to design a drug which is safe and effective. Artemether-lumefantrine combination treatment which is the best existing treatment for multidrug-resistant malaria is known to have several adverse side effects but still it is in use because of its effectiveness.

In silico drug design approach using molecular docking is employed in this study to obtain a drug molecule which is more effective, stable, safer, and more bioavailable than the existing drug lumefantrine as this approach has gained a lot of momentum because of its known benefits which includes

Table 5: Docking results of lumefantrine and modified ligands with protein drug targets

S. No.	Protein name	Binding energy (Kcal/mol)	Ki value	H bonds	Ligand efficiency
Lumefantrine	Falcipain-3 3BWK	−10.13	37.32 nM	1	−0.29
101	PvFKBP35-3NI6	−10.13	37.32 nM	1	−0.29
102	Erythrocyte-binding antigen region II-1ZRO	−11.62	3.04 nM	1	−0.33
103	Falcipain-3 3BWK	−10.21	32.73 nM	1	−0.29
104	Falcipain-3 3BWK	−10.44	22.25 nM	2	−0.3
105	Falcipain-3 3BWK	−11.71	2.61 nM	2	−0.33
106	Falcipain-3 3BWK	−13.8	76.36 pM	5	−0.39
107	Falcipain-3 3BWK	−14.26	35.11 pM	5	−0.41
108	Falcipain-3 3BWK	−11.44	4.14 nM	3	−0.33
109	Falcipain-3 3BWK	−12.26	1.04 nM	2	−0.35
110	Erythrocyte binding antigen region II-1ZRO	−10.69	14.61 nM	3	−0.3
111	Erythrocyte-binding antigen region II-1ZRO	−12.52	667.89 pM	2	−0.36
112	Falcipain-3 3BWK	−11.77	2.35 nM	5	−0.34
113	Falcipain-3 3BWK	−9.13	202.62 nM	4	−0.26
114	Falcipain-3 3BWK	−10.11	39.05 nM	5	−0.29
115	Falcipain-3 3BWK	−9.07	224.61 nM	5	−0.26
116	Falcipain-3 3BWK	−9.38	132.94 nM	3	−0.27
117	Falcipain-3 3BWK	−12.95	321.79 pM	8	−0.37
118	Falcipain-3 3BWK	−9.64	86.27 nM	7	−0.28
119	Plasmepsin-1MIQ	−8.63	472.28 nM	5	−0.25
120	Falcipain-3 3BWK	−12.19	1.17 nM	5	−0.35
121	Erythrocyte-binding antigen region II-1ZRO	−12.16	1.21 nM	6	−0.35
122	Erythrocyte-binding antigen region II-1ZRO	−9.72	74.83 nM	12	−0.28
123	Falcipain-3 3BWK	−8.42	675.48 nM	4	−0.24
124	Erythrocyte-binding antigen region II-1ZRO	−10.97	9.61 nM	8	−0.31
125	Erythrocyte-binding antigen region II-1ZRO	−8.54	548.81 nM	9	−0.23

cost-effectiveness, less time requirement, and wide range software availability.[20]

A similar study by Singh *et al*. (2013)[21] supports the idea of docking study and ADMET property analysis for *in silico* drug development. Docking study was carried out to design an inhibitor for *P. falciparum* S-adenosyl-L-homocysteine hydrolase enzyme. Results portrayed the better binding capacities of curcumin and its derivatives which could be used as lead molecules for further drug development.[21] The predicted ADMET properties of low solubility and high lipophilicity are supported by the study conducted by Govender (2012) in which a pharmacokinetic and efficacy study was done on lumefantrine in mice. This signifies the importance of ADMET property prediction in designing drug molecules.[22]

The successful prediction of drug target for the molecule lumefantrine in this study would further help in enhancing the current research being done in this field. Furthermore, molecules with greater inhibition capacities can also be designed based on the protein structure of falcipain-3 to curtail the havoc being caused by the rampant malaria in most of the affected countries. This study provides a lead for the pharmaceutical companies to further develop the existing antimalarial drug lumefantrine.

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CONFLICTS OF INTEREST

No known conflicts of interest.

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