Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Research Article

DOCKING STUDIES ON QUININE ANALOGS FOR PLASMEPSIN-II OF MALARIA PARASITE USING BIOINFORMATICS TOOLS

RUPANJALI BHATTACHARJYA SHARMA*, DIPAK CHETIA

Women Scientists Scheme-A (WOS-A) of Department of Science and Technology, Govt. of India, Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, Assam. Email: rupanjali_bhatta@yahoo.com

Received: 21 Jun 2013, Revised and Accepted: 15 July 2013

ABSTRACT

Objective:Malaria has been a perennial problem for people in developing countries and some other areas of India. Plasmepsins are aspartic acid proteases which are the probable target for quinine analogs as anti-malarial drugs. The objective of this study was to find out an inhibitor of such a protein. This will minimize the side effects and will increase therapeutic efficacy, which can also be enhanced by designing a suitable pharmaceutical dosage form for targeted delivery.

Method: The quinine based analogs were docked to the receptor plasmepsin II (1lee) using the docking software HEX. In docking calculations, all molecules were modelled using 3D expansions of real orthogonal spherical polar basis functions to encode both surface shape and electrostatic charge and potential distributions.

Result: Altogether 14 compounds were docked and the energy values obtained were ranged from -178.25 to -206.28 Kcal.mol^{-1}. The coded compounds, Comp-8, Comp-11 and Comp-13 exhibited better affinity and the energy values were -204.84, -205.73 and 206.28 Kcal.mol^{-1} respectively.

Conclusion: From the Docking study of 14 compounds, three compounds exhibited better affinity towards the receptor and may therefore, be considered for further studies.

Keywords: Malaria, Plasmepsins, Docking, *Plasmodium falciparum*, Aspartic acid protease.

INTRODUCTION

Malaria, a disease of antiquity, which affects a large population, has proved to be a hindrance in the cultural and socio-economic progress of society in the tropical, sub-tropical world. Malaria is prevalent in all the parts of the country except in areas which are not favourable for transmission and multiplication of malaria parasites. In India, some of the states like Madhya Pradesh, Orissa, Andhra Pradesh, West Bengal, Gujarat, N.E. States, Bihar, Maharashtra, etc. are highly endemic for *Plasmodium falciparum* (*P. falciparum*) and these states contribute around 97% of the total *P. Falciparum* affected cases in the country [1-3]. The malaria affected population, in Northeast region, is predominantly due to *P. falciparum* with widespread distribution of Chloroquine resistant strains. The situation is grave as the number of *P falciparum* resistant cases to the currently available drugs is increasing [4-6].

The parasite undergoes strain changes producing resistant strains to the exposed antimalarial drugs and export remodeling and virulent proteins into the erythrocyte during the infection. In the process of infection, the parasites express proteins on the red blood cell surface. The binding of these protein molecules to human cell surface receptors mediates the adherence of infected red blood cells to human tissues. The emergence and spread of strains resistant to currently available drugs highlight the need based priority for development of novel antimalarial drugs. To discover new drug leads to fight against resistant strains of the parasite, structure based design methods with focus on validated macromolecular targets are required [7-8].

The aspartic acid proteases of *Plasmodium* species known as plasmepsins are involved in the haemoglobin degradation inside the food vacuole. There are ten different isoforms of these target protein. These are the group of key enzymes in the life cycle of malarial parasites and inhibition of plasmepsins leads to the parasite's death [9-10].

An attempt was made to develop few quinine derivatives and to study the inhibitory effect of the molecules in order to find out possible inhibitors of plasmepsin II (1lee). The results of the study are reported here.

MATERIALS AND METHODS

Materials

In present study, various biological databases, bioinformatics tools and software were used. The software used with the sources and their utilities are presented in Table 1.

Table 1: **It Shows Software used in this study, source and their utilities**

Software	Source	Utility
ISIS draw	Open source for limited period	Drawing of 2D structure of ligands.
Chem office	Paid software from Cambridge soft	Chem3D generates 3D models. ChemFinder is a chemically-intelligent personal database system used to organize the compounds and to search and correlate structures with properties.
Ligandscout (2.0)	License was provided by the developer on request	Software tool that allows to rapidly and transparently derive 3D pharmacophores from structural data of macromolecule. It was been used to identify inhibitors of other drug targets.
ArgusLab (4.0.1)	Open source	The Argus Lab contains tools for building and visualising molecules as well as looking at the output from calculations.
SPDBV	Open source	Swiss-Pdb Viewer is an application that provides a user friendly interface allowing analyzing several proteins at the same time.
Hex (version 6.3)	Free for academic use	Docking software.

Method

Structural assessment of the protein

The Ramchandran Plot was generated using Pdbsum database. Ramachandran plots for all residue types, Chi1-Chi2 plots, Main-chain parameters, Side-chain parameters, Residue properties, Main-chain bond length, Main-chain bond angles, RMS distances from planarity and distorted geometry were analyzed for input atom only.

Docking studies

Docking allows screening a database of compounds and calculating the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme, fit together and dock to each other well. The molecule may bind to receptor and modify their function. The interaction of drug and receptor complex was identified via docking and their relative stabilities were evaluated using molecular dynamics and also evaluated their binding affinities using free energy simulations [11-15].

In this study, Plasmepsin II (1lee) as receptor and analogs of quinine were taken as ligands. Docking study was performed between receptor and ligands by using Hex. The structure of 1lee (Fig 1), an essential target for novel quinine based antimalarial drug design, was retrieved from protein data bank. All water molecules and ligands were removed from the protein for docking studies. The structures of the molecules under investigation were sketched using ChemOffice. The energy of PDB structures were minimized using ArgusLab.

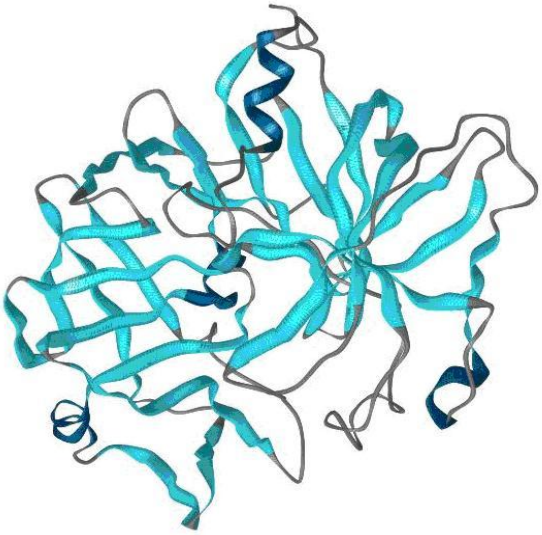

Fig. 1: It shows three dimensional structure of Plasmepsin II (1lee)

Then visualization and analysis of the protein structure was made and the docking analysis of the proposed compounds with 1lee was carried by using docking software Hex (version 6.3) and subsequent computation of the Lipinski's properties were carried out with Ligand Scout.

RESULTS AND DISCUSSION

Structural assessment of the protein

The Ramachandran plot analysis is presented in Fig 2.The Ramachandran Plot statistics and G-factors are presented in Table 2 and Table 3. The G factor provides a measure of how unusual, or out-of-the-ordinary, a property is. The values of G factor below -0.5 indicates, unusual; and values below -1.0 indicate highly unusual. In this study, the value of G factor was found to be -0.08.

Docking studies

The various quinine and their modified structures were docked to the receptor 1lee and the energy values were computed using Hex. The results of docking study and Lipinski's properties are presented in Table 4. The energy values of the 14 compounds were found within the range of -178.25 to -206.28 Kcal.mol^{-1}. The receptor ligand interaction of Comp 8, Comp 11 and Comp 13 are presented in Fig 3, Fig 4 and Fig 5 respectively. The enlarged images of the location of the interaction for these three compounds are presented as Fig 3a, Fig 4a and Fig 5a for Comp 8, Comp 11 and Comp 13 respectively. The results indicated that Comp 8, Comp 11 and Comp 13 exhibited promising inhibitory activity in comparison to the other compounds. Hence, may prove to be potential antimalarial drug candidate provided they satisfy other sequential phases of study.

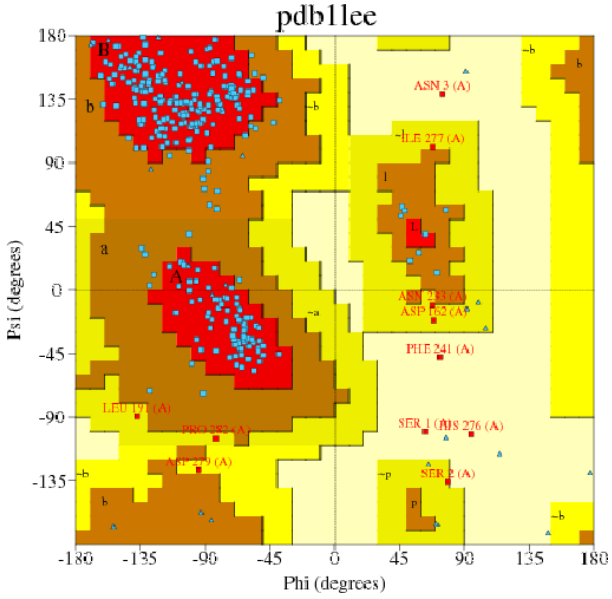

Fig. 2: It Shows Ramchandran Plot of 1lee receptor

Table 2: It shows the Ramachandran Plot statistics

	No. of residues	Percentage
Most favoured regions[A,B,L]	246	85.7%*
Additional allowed regions[a,b,l,p]	31	10.8%
Generously allowed regions[~a,~b,~l,~p]	6	2.1%
Disallowed regions [XX]	4	1.4%*
Non-glycine and non-proline residues	287	100.0%
End-residues (excl. Gly and Pro)	2	
Glycine residues	26	
Proline residues	16	
Total number of residues	331	

Table 3: It shows the G-Factors

Parameter	Score	Average Score
Dihedral angles:-		
Phi-psi distribution	-0.49	
Chi1-chi2 distribution	-0.37	
Chi1 only	-0.02	
Chi3 & chi4	0.13	
Omega	0.21	
		-0.16
Main-chain covalent forces:-		
Main-chain bond lengths	0.20	
Main-chain bond angles	-0.11	
		0.02
Overall Average		-0.08

Table 4: It shows chemical features and binding energy values

Compound	Molecular weight	-E value (Kcal.mol^{-1})	C Log P	H bond donor	H Bond acceptor
Comp-1	327.448	178.25	1.694	2	3
Comp-2	327.448	187..80	1.694	2	3
Comp-3	329.464	191.55	1.940	2	3
Comp-4	327.448	191.55	1.694	2	3
Comp-5	327.448	196.37	1.694	2	3
Comp-6	399.511	193.13	2.875	1	3
Comp-7	327.448	195.96	1.694	2	3
Comp-8	343.491	**204.84**	2.330	2	3
Comp-9	327.448	179.90	1.694	2	3
Comp-10	329.464	183.65	1.940	2	3
Comp-11	343.513	**205.73**	2.407	2	3
Comp-12	345.529	191.04	2.653	2	3
Comp-13	343.513	**206.28**	2.407	2	3
Comp-14	343.513	185.96	2.407	2	3

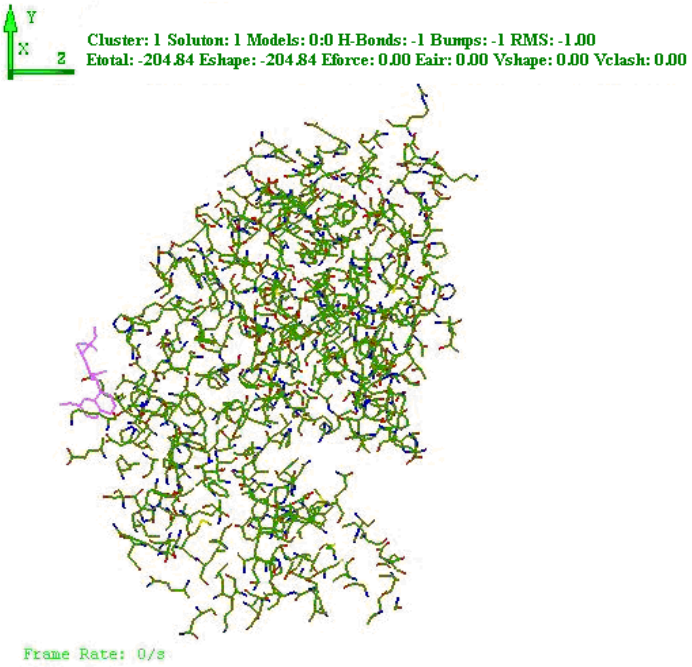

Fig. 3: It Shows Interaction and binding energy (compound 8)

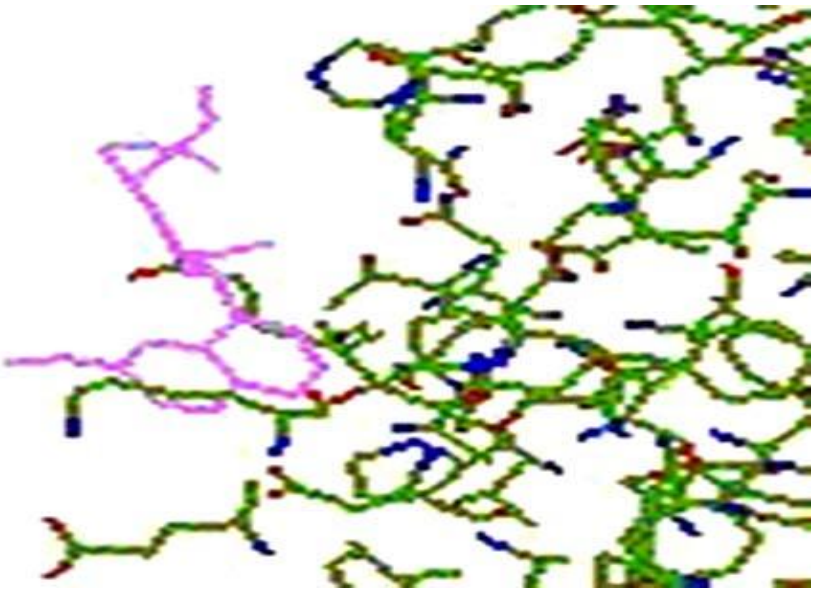

Fig. 3a:It shows the enlarged location of interaction of Comp 8 with the receptor

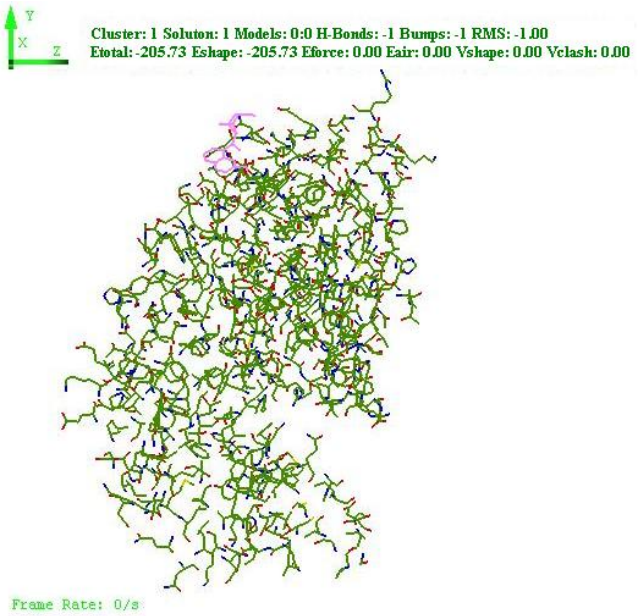

Fig. 4: It Shows Interaction and binding energy (compound 11)

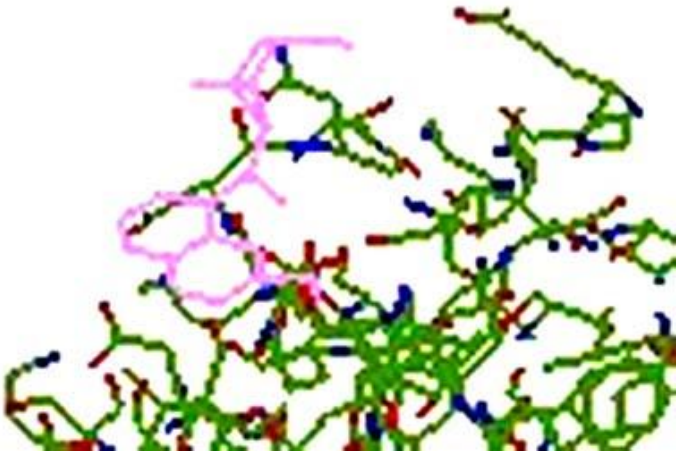

Fig. 4a: It shows the enlarged location of interaction of Comp 11 with the receptor

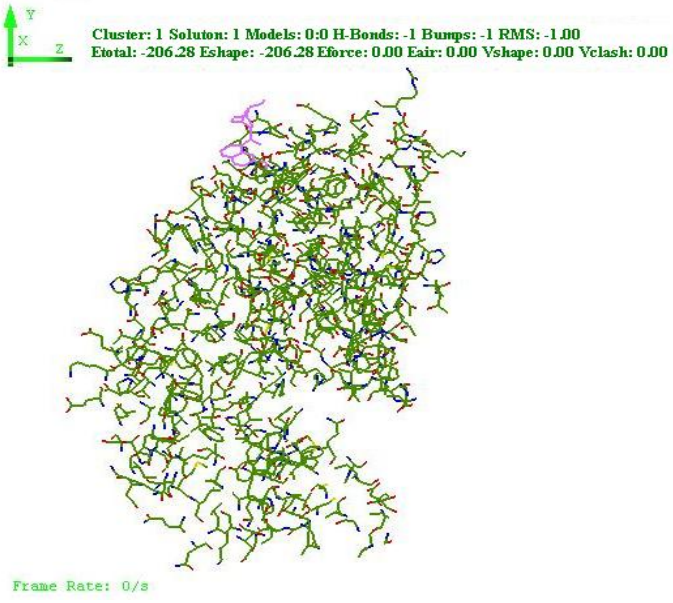

Fig. 5: It Shows Interaction and binding energy (compound 13)

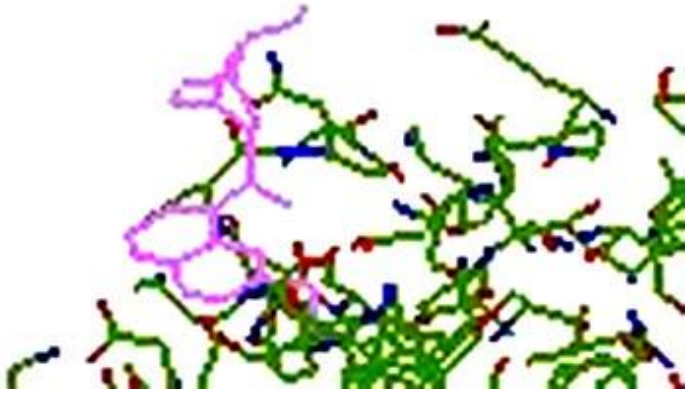

Fig. 5a: It shows the enlarged location of interaction of Comp 13 with the receptor

CONCLUSION

In this study, docking of 14 quinine analogs was carried out and three compounds namely, Comp 8, Comp 11 and Comp 13 exhibited minimum energy values. The energy values obtained were -204.84, -205.73 and -206.28 respectively. Computation of Lipinski's properties for the most part of the compounds followed all criteria. The anti-malarial activity of these three potential candidates may be ascertained by *in vitro* anti-malarial activity study.

ACKNOWLEDGEMENT

The authors thank Department of Science and Technology, Govt. of India for the financial support. Authors also extend their thanks to Inteligand for providing the evaluation license of Ligandscout 2.0, which was used as a supporting tool.

REFERENCES

1. Ahmed A, Lumb V, Das MK, Dev V, Wajihullah, Sharma YD. Prevalence of mutations associated with higher levels of sulfadoxinepyrimethamine resistance in *Plasmodium falciparum* isolates from Car Nicobar Island and Assam, India; Antimicrob Agents Chemother 2006; 50: 3934-3938.
2. Mittra P, Vinayak S, Chandawat H, Das MK, Singh N, Biswas S et al. Progressive increase in point mutations associated with chloroquine resistance in *Plasmodium falciparum* isolates from India; J Infect Dis 2006; 193: 1304-1312.
3. Ahmed A, Bararia D, Vinayak S, Yameen M, Biswas S, Dev V et al. *Plasmodium falciparum* isolates in India exhibit a progressive increase in mutations associated with sulfadoxine-pyrimethamine resistance; Antimicrob Agents Chemother 2004; 48: 879-889.
4. Mohapatra PK, Prakash A, Bhattacharyya DR, Mahanta J. Malaria situation in North-Eastern region of India; ICMR Bull 1998; 28: 21-30.
5. Sharma SK, Mahanta J. Prevalence of Haemoglobin variants in Malaria endemic northeast India; J Biological Sciences 2009; 9 (3): 288-291.
6. Dev V, Bhattacharyya PC, Talukdar R. Transmission of malaria and its control in the north eastern region of India; J Assoc Physicians India 2003; 51:1073-1076.
7. Dollery C. Chloroquin. In: Therapeutic Drugs. 2nd ed. Churchill Livingstone, New York; 1999. p. 177–182.
8. Panisko DM, Keystone JS. Treatment of malaria; Drugs 1990; 39(2):160–189.
9. Gowthaman R, Duraisamy S, Kalita MK, Gupta D. A database for *Plasmodium falciparum* protein models; Bioinformation. 2005; 1: 50-51.
10. Nagarajaram HA, Iengar P, Ghosh I. In silico approach to antimalarial drug discovery: Design of selective inhibitor to *Plasmodium falciparum* aspartic proteases; Frontiers in Biophysics; 2005:168-181.
11. Goodford PJ. A computational procedure for determining energetically favorable binding sites on biologically important macromolecules; J Med Chem 1985; 28: 849–857
12. Foloppe N, Hubbard R. Towards predictive ligand design with free-energy based computational methods; Curr. Med. Chem 2006; 13 (29): 3583–608.
13. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings; Adv Drug Del Rev 2001; 46: 3-26.
14. Parida P, Yadav R N S. Comparative docking study of M1 protein (influenza virus) to check drug efficacy; Int J Pharm Pharm Sci 2012; 4(3):243-246.
15. Kumari B, Chetia D. In-silico docking studies of selected n-glycoside bearing tetrazole ring in the treatment of hyperglycemia showing inhibitory activity on SGLT; Int J Pharm Pharm Sci 2013; 5(2):633-638.