ISSN No:-2456-2165

Molecular Docking Studies of some New Neocryptolepine Analogs as Antimalarial Agents

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Abstract- Malaria is a life threatening infectious disease that is widespread in tropical and subtropical regions. The increasing resistance of the parasites to antimalarial agents is responsible for some of the worst cases in the tropical world. In view of past history our effort is to develop some new anti-malarial agents. The objective of this study was to elucidate the binding mode analysis of new neocrytolepine analogs in the *P. falciparum* NF54. Molecular docking studies of 51 new neocrytolepine analogs were performed by Glide program using 4PD4 ligand in malaria. The novel neocrytolepine analogs bearing different substituted aryl groups were designed. The following 6 compounds with aryl substituents like R_1& R_3 =H, R_2=-NH$(CH_2)_3NH_2$, highest docking score in the 4PD4 of NF54 strain . Thus, it is evident that this kind of scaffold with hydrophobic in nature, having contribution of donating or withdrawing electrons substituted in the six member rings can be exploited for the development of new malarial inhibitors which can facilitate better patient adherence and also inhibit the resistant strains of malaria.

Keywords:- *Malaria, Molecular modelling Neocryptolepine, docking***.**

I. INTRODUCTION

Malaria kills over 1,500,000 people a year and it is responsible for human misery in tropical countries. Malaria is caused by a protozoal parasite of the genus Plasmodium and remains worldwide problem and there is an urgent need to identifying new class of antimalarials.[1] Emergence of resistance to antimalarial drugs has become a major hurdle in the successful treatment of the infection, and has contributed significantly to global malaria-related mortality.[2] Among the various mechanisms identified, basics that govern parasite invasion, remodeling, growth, and reinvasion of erythrocytes and the complex events leading to tissue pathology may yield new diagnostics criteria for treatments of malaria. This approach might be revealing a more useful scinerio to understand drugs action. From past few decades evidence shows that drug resistant towards malarial parasites are continuing explored. Due to the wide spreadibility of malarial infection and owing to the increased resistance of the parasite towards major drugs, it is necessary to identify some new effective lead to fight against malaria. [3-5]

II. MATERIALS AND METHODS

A. Molecular Modeling Studies

Molecular docking studies were performed on workstation running Red Hat enterprise and Linux 4.0 and selection of the compounds should be based on the activities of compounds,which obeying Lipinsky rule of five and used an automated docking software Glide 5.0 (Schrodinger-Maestro) that applies a two stage scoring process to sort out the best conformations and orientations of the ligand (defined as pose) based on its interaction pattern with the receptor.

B. Protein Preparation

The starting point of the docking simulation was the X ray structure of the protein, (4PD4) these are obtained through the protein data bank library (PDB. Chain C was retained, chain A B, D,E,F were removed from the complex. The protein was prepared using the protein preparation wizard. Partial atomic charges are assigned according to the OPLS_AA force field.

C. Ligand Preparation

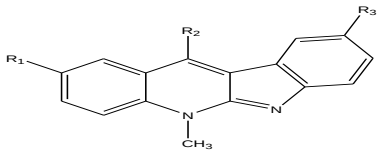
3D coordinates of the ligands, their isomeric forms, ionization states and tautomeric states generated using Ligprep. Partial atomic charges were assigned according to the OPLS-2005force field.3

III. RESULTS AND DISCUSSION

In the present study, efforts have been made to design the structural requirements to enhance inhibitory activity of neocryptolepine derivatives analogs against *P. falciparum* strain. Molecular modeling tools were used by means of taking care of structural contribution considering greater interaction between ligand and protein. Series of neocryptolepine analogs (51 compounds) were designed and selected for docking studies .Protein 4PD4 were taken from protein data bank and run on Glide 5. The compounds showing maximum docking score are summarized in Table 1. Only highest scoring poses of compounds was selected for further analysis.

ISSN No:-2456-2165

IV. TABLE



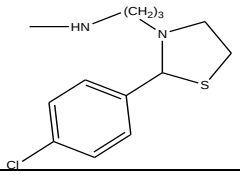
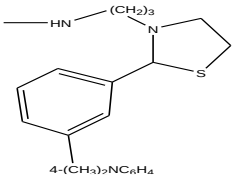
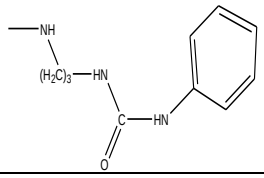
Compound Code	R_1	R_2	R_3	4PD4
1	H	H	H	-7.236
3	H	$-NH(CH_2)_3NH_2$	H	-7.111
4	Br	$-NH(CH_2)_3NH_2$	H	-7.139
9	H		H	-7.442
10	H		H	-7.040
18	H		H	-7.024

Table 1:- Structure and activities of Neocryptolepine derivatives

V. CONCLUSION

Molecular docking studies of 51 Neocryptolepine analogs were performed on NF54 strain of malaria by using Glide-5 and six compounds with substituents like R_1 & R_3=H , R_2= $NH(CH_2)_3NH_2$,-$NH(CH_2)_3NC_3H_3S$-C_6H_4-$4(CH_2)_3NC_6H_4$, $NH(CH_2)_3NHCO$-NHC_6H_6 exhibited highest docking score The compounds having highest docking score have been discussed in the present communication. Among these, is pose view analysis has been performed for compound 9 which exhibited highest docking score of -7.442. Thus, from the binding mode analysis as well as docking studies, it is concluded that the newly Designed compounds with a Neocrptolepine moiety flanked with phenyl rings which have been substituted with electron donating and electron withdrawing groups showed significant affinity towards the NF54 strain .Thus, this type of scaffold can be exploited for the development of novel antimalarial inhibitors which can facilitate better patient adherence and also inhibit resistant strains of malaria.

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