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DOCKING STUDIES OF AMINOHYDANTOIN DERIVATIVES AS ANTIMALARIAL AGENTS

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ABSTRACT

Objective: Docking studies of aminohydantoin derivatives as antimalarial agents. A novel derivative of aminohydantoins was selected from the literature. **Method:** *in-silco* studies using docking methodology. The compounds were sketched and energy minimized using Chem draw ultra and Chem 3D ultra respectively. Further, the compounds were docked into *Plasmodium falciparum* transferase inhibitor (3L7) using Molegro Virtual Platform. Twenty eight compounds were docked into the active site of Pf-lactate dehydrogenase cavity and all of them found to have similar binding interactions of a co-crystalized ligand. **Result:** The compounds were showed good docking score like moldock score and re-rank score. The finding of docking studies shows a typical molecular interaction pattern with lactate dehydrogenase. The binding interaction information derived from these molecules will be useful in future antimalarial agent design. **Conclusion:** From the docking study, it was observed that ligands bind to the electrostatic, hydrophobic clamp formed by the residues Asp 76(B), Tyr 190(B), Tyr 80(B) and Lys 72(B) which play an important role for *Plasmodium falciparum* inhibition. The binding affinity, grid calculation and RMSD percentage lower and upper parameters were calculated. Hence, the observable data indicated that, above compounds can serve as good leads for further modification and optimization in the of treatment malaria.

Keywords: Molegro, Chemdraw, aminohydantoins and docking, studies as *Plasmodium falciparum*, 4RAO, moldock score.

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INTRODUCTION

Malarial is a tropical parasitic disease caused by protozoa belonging to the genus *Plasmodium falciparum*. It occurs majorly in temperate regions and it also present globally due to climate change. Sub-Saharan Africa carries a disproportionately high share of the global malaria burden. In 2016, the region was home to 89% of malaria cases and 91% of malaria deaths. *P. falciparum* is the most prevalent malaria parasite on the African continent.[1-10] According to the latest WHO estimates, released in 2015, there were 216 million cases of malaria in 2016 and 445000 deaths. Some countries – mainly in sub-Saharan Africa – account for 90% of malaria cases and 78% deaths globally. In earlier 2000, the decrease in malaria prevalence in these 15 countries (32%) has straggle back that of other countries worldwide (54%). In areas with giant transferral of malaria, juvenile beneath 5 are extremely vulnerable to inflammation, sickness and demise; additional than two thirds (70%) of all malaria demises occur in this age group. Between 2000 and 2015, the under-5 malaria death rate fell by 65% globally, translating into an estimated 5.9 million child lives saved.[11] Molecular Docking is well established computational technique which predicts the interaction energy between two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy.[12] The small molecule, known as ligand normally lay within protein's cavity which is anticipate by the explore algorithm. These protein cavities overtake vital when they come in exposure with any external compounds and are consequently called as energetic sites. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which permit us to distinguish the behaviour of small molecules in the

binding site of desire proteins as well as to illuminate basic biochemical processes.[13] The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as *poses*) and assessment of the binding affinity.[14] These two steps are related to sampling methods and scoring schemes, respectively, which will be discussed in the theory section. The docking studies are normally employed to augur the binding direction of molecule to resident protein targets in concatenation to envisage the affinity and action of the molecule. Therefore docking plays a dominant key position in the rational drug design. Molegro virtual docker is an discriminatory programme for predicting- ligand interactions. MVD requires a 3d structures of both protein and ligand routinely acquire from x-ray /NMR demonstration or homology modelling. MVD execute flexible ligand docking, so the optimal calculation of the ligand will be purposive through the docking. MVD supervise all appearance of the docking procedure from construction of the molecules to determine of the probable binding sites, of the target protein and projection of the binding modes of the ligand. MVD suggest high quality docking based bases on a moves optimization techniques combined with a user interface experience focusing on usability and productivity.[15-17]

MATERIALS & METHODS

The software **Chemdraw Ultra ver. 8.0** and **Molegro virtual Docker ver. 6.0** were used for docking studies.

Protein primary sequence and structure retrieval

The three-dimensional x-ray crystallography structures of aminohydantoins, (PDB ID: **4RAO**) were obtained from Protein Data Bank (www. rcsb.org), which is a single worldwide archive of structural data of biological macromolecules.[18-19]

Ligand construction

All the ligands are reported in the research of M. J. Marvin *et al.,* on aminohydantion derivatives are sketch in chemdraw ultra 2d 8.0 and these structure are converted into the 3d using chemdraw ultra 8.0 now these structures are energy minimize to 0.01 iteration using Mopac grid now these structures are saved in the format of dot mol.[20-21] Docking studies is a type of computational approach used to study the Ligand-Enzyme interactions which are crucial for activity. The study would help to observe the binding fashion of compounds with enzyme's amino acids. Docking analysis of all 28 compounds were performed to explore the binging of compounds to the important amino acids responsible for antimalarial activity. In accordance with the targeted enzyme Pdb code- 4RAO was selected for antimalarial docking studies of the compounds. Validation of Molegro virtual Docker 6.0 is important because it is a computational approach, the result may be deviate on changing the software.[22]

As we know that each PDB has its own co-crystalize ligand on its active site. In the process of software validation we just re-docked that co-crystalize ligand with its PDB and observe the orientation and conformational changes on it. This will help to stabilize the software's repeatability and validate it.

Antimalarial docking

Molecular docking study showed the interaction between aminohydantion derivatives and active site of protein taken from transferase enzyme (Pdb code-4RAO). MolDock Score and MolDock Rerank Score of most active compound to that of reference ligand reveals the efficient docking interactions of the compound. Asp-76(B), Try-190(B), Leu-77(B), Thr-45(B), His-38(B), Gly-39(B), Asp-43(A), Tyr-80(B) and Met-42(B) are the major amino acid bindings responsible for biological activity. Among the reference ligand and compounds 1,9,18,19,26,27 and 28 of these amino acids bindings are in common which proves that the binding of the compounds takes place with the desired amino acids in the protein. Molecular docking scores and data also correlate and reconfirm the assumption regarding the design and development of new molecules.[23-24]

RESULT AND DISCUSSION

Docking analysis is important to study the ligand-enzyme interaction. For the docking analysis, the compounds were chosen based on their previously evaluated for antimalarial activity. Docking was carried out using PDB code 4RAO, using Molegro Virtual Docker 6.0.

PDB Description:

Name: 4RAO

Classification: Transferase/ Transferase Inhibitor.

Organism: Homo sapiens

Expression System: Escherichia coli

PDB Ligand: 3L7

IUPAC:(2-{[2-(6-oxo-1,6-dihydro-9H-purin-9-yl)ethyl](2{[(E)2 phosphonoethenyl] oxy} ethyl) amino}ethyl) phosphonic acid.

Molecular Formula: $C_{13}H_{21}N_5O_8P_2$

Pose analysis of docking of standard drug chloroquine and co-crystallized ligand (**3L7**) explore the common amino acid interaction like: Met-42(B), Leu-77(B), Thr-45(B), Asp-76(B), Tyr-190(B), His-38(B), Gly-39(B), Asp-43(A) and Tyr-80(B) which are considered to be the active amino acids important for binding of ligand on active site. Compound-**1** exhibit common binding interaction like: Met-42(B), Asp-76(B), Try-190(B), Leu-77(B), Thr-45(B), Gly-39(B), His-38(B), Asp-43(A) and Tyr-80(B) to that of standard active amino acids.Compound-**9** exhibit common binding interaction Met-42(B), Asp-76(B), His-38(B), Try-190(B), Leu-77(B), Thr-45(B) and Tyr-80(B) with amino acids responsible for activity. Compound-**18** has common binding interactions Met-42(B), Asp-76(B), Try-190(B), Asp-79(D), His-38(B) and Asp-43(A) with amino acids. Compound-**19** exhibit binding with essential amino acids like: Met-42(B), Asp-76(B), Try-190(B), Thr-45(B), Asp-76(B), Gly-39(B), His-38(B) and Asp-43(A).Compound-**26** exhibit binding with Asp-76(B), Try-190(B), Leu-77(B), Thr-45(B), Gly-39(B), His-

38(B), Tyr-80(B) and Asp-43(A).Compound-**27** exhibit common amino acid bindings with Asp-76(B), Try-190(B), Leu-77(B), Thr-45(B), Gly-39(B), His-38(B) and Asp-43(A). Compound-**28** exhibit common amino acid bindings with Asp-76(B), Try-190(B), Leu-77(B), Thr-45(B), Gly-39(B), His-38(B) and Asp-43(A).

Computer aided drug designing (CADD) helps the researcher to decrease the time and money for drug designing projects Molecular docking is very helpful in studying the interactions of ligand molecules with the target protein before its in vitro synthesis. Docking is performed through computer programs like Autodock , arguslab and discovery studio3.1.[25-26] All these molecules were taken from ligand database or draw with help of chemical organizer(draw) software like chemdraw ultra 2d & 3d in mol or pdb format and were stored in a database of MOE in mdb format or Pubchem database. All these molecules were docked against the same pocket where reference drug bound. Molecules were selected from a library of molecules and were further assessed by the interaction analysis. Finalized molecules showed the interactions with the active residue and with other residues.[27]

Table 1: Docking Scores of reported compounds (Pdb-4RAO)

Compound No.	Mol Dock Score	Re-rank Score	H-Bond
01	-131.531	-78.5204	-3.10212
02	-103.249	-75.8402	-0.384916
03	-101.301	-68.5639	-0.752536
04	-113.662	-87.5361	-2.37363
05	-113.777	-90.9875	-1.40004
06	-115.143	-94.3147	-
07	-110.555	-85.7039	-0.00511253
08	-102.064	-65.8804	-1.97476
09	-219.323	-161.412	-0.159418
10	-100.391	-58.364	0.199877
11	-97.2375	-57.0105	-0.383658
12	-102.768	-81.1365	-
13	-100.765	-58.0613	-0.516466
14	-98.8683	-72.2189	-
15	-100.875	-61.7457	0.351308
16	-100.477	-59.5785	-1.33243
17	-97.9958	-74.6467	-1.65333
18	-133.322	-60.3441	-0.914538
19	-131.747	-96.0003	-0.258545
20	-105.738	-25.2223	-0.0212229
21	-116.014	-80.3198	-0.244676
22	-140.886	-106.217	-1.56805
23	-118.095	-80.9378	-0.452932
24	-119.617	-78.4913	-2.5
25	-175.065	-121.149	-1.37088
26	-178.584	-121.801	-2.41728
27	-169.936	-133.218	-
28	-152.656	-94.752	-4.26752

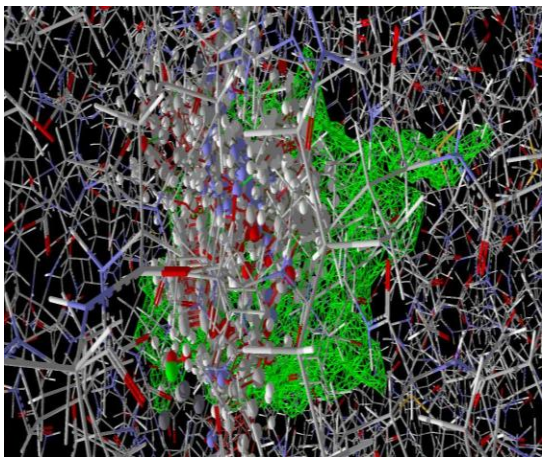

Figure 1: Docking view of all compounds

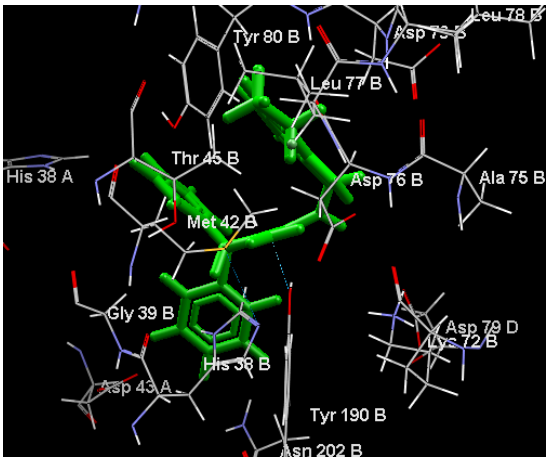

Figure 2: Docking pose of compound 1

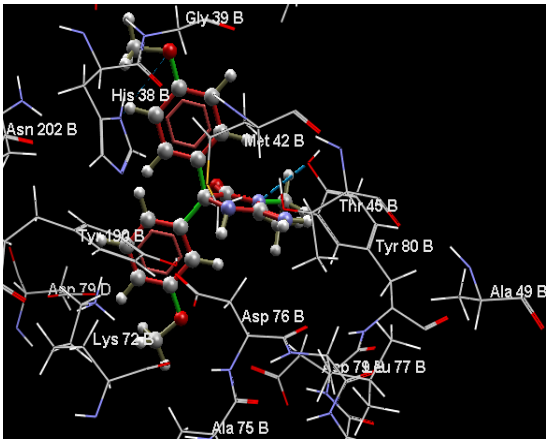

Figure 3: Docking pose of compound 9

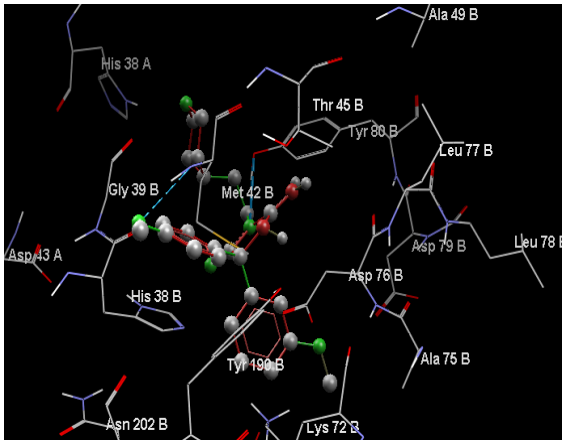

Figure 4: Docking pose of compound 18

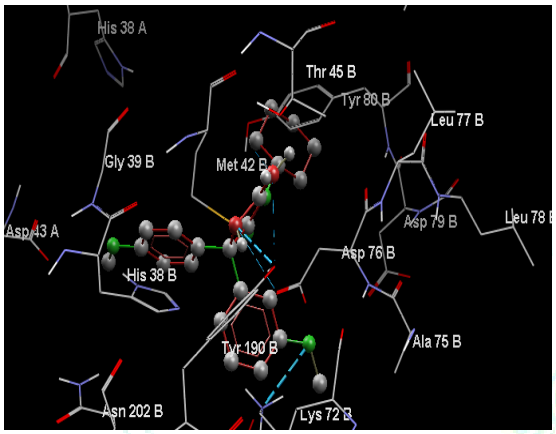

Figure 5: Docking pose of compound 19

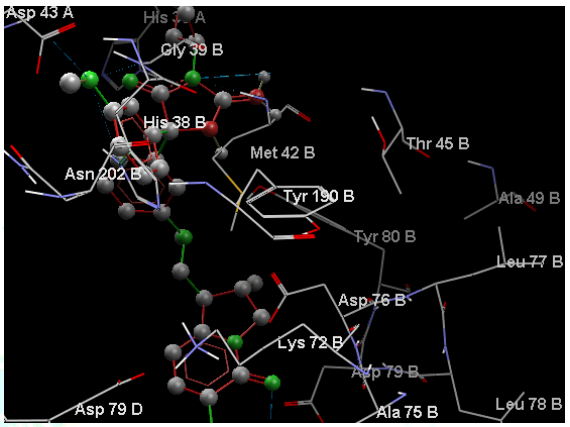

Figure 6: Docking pose of compound 26

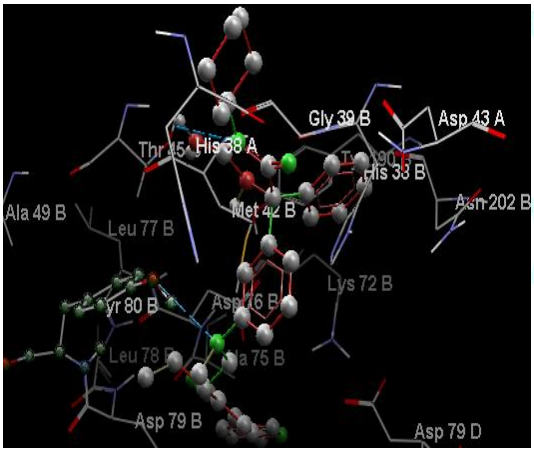

Figure 7: Docking pose of compound 27

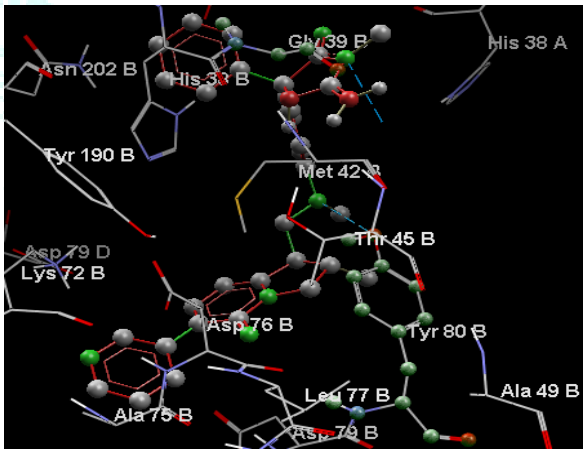

Figure 8: Docking pose of compound 28

CONCLUSION

From the present study concluded that the synthesize derivatives of aminohydantoin, showed the good docking score and more stable bonding with the *Plasmodium falciparum* so it can be said that, these derivatives may be significant against *Plasmodium falciparum* inhibitor. Further study will need to be conducted for other properties of drug like, absorption metabolism and excretion in human body. On the basis of comparison with standard drugs like chloroquine and other derivatives selected in this study, which have less docking score as compared to the standard. It can be concluded that these seven derivatives have good RMSD limit so it was made virtual derivatives in these molecules could be used as promising inhibitor of *Plasmodium falciparum* to therapeutic value for various types of malaria in future.

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