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MOLECUAR DOCKING ANALYSIS OF THIAZOLIDINEDIONE DERIVATIVES AGAINST ENOYL-ACYL CARRIER PROTEIN REDUCTASE

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ABSTRACT

Malaria is a life-threatening disease spread to humans caused by single-celled microorganisms of the Plasmodium group. The disease is widespread in the tropical and subtropical regions that exist in a broad band around the equator. In this paper we report the molecular docking studies of 9 thiazolidinedione derivatives having antimalarial activity. The derived compounds were analyzed for drug likeness based on the Lipinski's rule of five and protein-ligand docking studies by Autodockvina with PyRx and visualized by Biovia Discovery studio 2021 Client. Docking studies have shown that the thiazolidinedione derivatives interacts and bind efficiently with protein (1P44 (enoyl-acyl carrier protein reductase (InhA)) enzyme which resulted in antimalarial activity.

Keywords: Malaria, Drugs, Thiazolidinedione, Antimalarial activity, Molecular docking, Enoyl-acyl carrier protein.

INTRODUCTION

Malaria is a mosquito-borne infectious disease that affects human and other animals. It is spread exclusively through bites of infected Anopheles mosquitoes. It is preventable as well as curable. There are 5 parasite species that cause malaria in humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae [1]. Malaria causes symptoms that typically include fever, vomiting, headache tiredness and yellow skin. In severe cases it can cause jaundice, seizures, coma, or death. Symptoms usually begin ten to fifteen days after being bitten by an infected mosquito. If not properly treated, people may have recurrences of the disease months later. Although malaria can be a deadly disease, illness and death from malaria can usually be prevented [2].

According to the latest World malaria report, there were 247 million cases of malaria in 2021 compared to 245 million cases in 2020 and 232 million in 2019.Malaria case incidence (i.e., cases per 1000 population at risk) reduced from 82 in 2000 to 57 in 2019.Globally,the mortality rate halved from about 30 in 2000 to 15 in 2015; it then continued to decrease but at a slower rate, falling to 14 in 2019.In India, as per the provisional data until 2021, around 1.07 lakh cases of malaria were reported. While the number of cases of reduced significantly in 2020. There were over 45 thousand reported cases of malaria in 2022 [3].

The development of effective treatment for malaria has been one of the most significant advances during this century. The incomplete treatment of malaria causes, the infection can become severe and may cause kidney failure, seizures, mental confusion, coma and death.

The biological activities exhibited by thiazolidinedione derivatives, mostly the antimalarial activities of 2,4-substituted thiazolidinedione derivatives are interesting. The substituted thiazolidinedione possess wide range of bioactivities as antimicrobial, anti-mycobacterium, anticonvulsant, anti-tubercular, anti-diabetic, anti-inflammatory, anti-malarial and anti-cancer [4].

In this paper we are reporting the docking analysis of thiazolidinedione derivatives against enoyl-acyl carrier protein reductase (InhA) enzyme. The docking was performed to predict the binding affinity of the synthesized thiazolidinedione derivatives against this enzyme.

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The docking can also generate useful information for further studies on the structure-based drug design of thiazolidinedione based anti-malarial drugs. The reference drug used in this study is chloroquine.

MATERIALS AND METHODS

Materials

In present study, many software's and bioinformatics tools were used. The uses of software's are presented in the Table 1.

Methods

Protein preparation

Protein (pdb) ID, 1P44 was downloaded in the PDB format from protein data bank available at www.pdb.org . 1P44 protein is Enoyl-[acyl-carrier-protein] reductase [NADH] with 6 chains having 268 residues. Its synonym is NADH-dependent enoyl-acylreductase. Protein was then energy minimized by using MOE software.

Preparation of ligands

About 9 thiazolidine-2,4-dione derivatives were derived and docked with a protein PDB ID 1P44. Chemdraw Ultra 8.0 software used to draw the 2D structure of ligands, then converted to 3D structure and also the energy minimization done by using Chem3D Pro 8.0 and save in PDB format.

Lipinski's rule of five

Lipinski's rules of 5 mainly distinguish between drug like and non-drug like molecules. It calculates the Log P, molar refractivity, number of hydrogen bond acceptor, hydrogen bond donor and molecular weight. Based on these properties compounds adhere to Lipinski's rule were selected for the study.

Docking studies

Docking studies yielded the information regarding the orientation of inhibitors in the binding pocket of the enzyme and the interaction between the enzyme and the ligands. The two molecules, such as drugs and enzyme attach together and docked it. These docking process can also be evaluate molecular dynamics and binding affinities using free energy simulations [5-9].

In this study, Enoyl-[acyl-carrier-protein] reductase [NADH] (1P44) as receptor and thiazolidine-2,4-dione derivatives were taken as ligands. These docking studies of ligand and protein were performed by using Autodockvina PyRx. The structure of protein 1P44 (Fig.1), as the target for novel thiazolidine-2,4-dione based on antimalarial activity. The removal of water molecules and ligands from protein and the visualization of the proposed compounds with the protein was carried by using Biovia Discovery Studio 2021 client.

Table 1. List of software's and their utilities

S. No.	Softwares	Utilities
1.	ChemDraw Ultra 8.0	Software to draw the 2D structure of ligands.
2.	Chem3D Pro 8.0	Software to generate 3D model and energy minimization of ligands
3.	MOE (Molecular Operating Environment)	Software for energy minimization of protein by selecting active chain
4.	PyRx-Virtual screening tool	Autodockvina software
5.	Biovia Discovery Studio	Finding active site of protein and Docking result analysis

Table 2. Lipinski's properties of the compound.

SL.No.	Compound code	Mol.wt(g/mol) <500	H-Donor <5	H-Acceptor <10	LogP <5	No.of violation
1	A1a	443	2	6	3.312	0
2	A1b	443	2	6	3.312	0
3	A1c	443	2	6	3.721	0
4	A1d	399.50	2	6	2.431	0
5	A1e	399.50	2	6	2.840	0
6	B1a	399.50	2	6	2.840	0
7	B1b	410	2	8	0.476	0
8	B1c	410	2	8	0.476	0
9	B1d	410	2	7	1.102	0

Table 3. Interaction and binding affinities of designed thiazolidinedione derivatives.

Compound code	Binding energy	H- Bond residues	Vander waals forces residues	Pi-Pi stacked residues	Alkyl residues	Pi-alkyl residues	Pi-sigma residues	Halogen residues	RMSD Residues
A1a	-8.6	LYS	PRO A:156,		ILE	MET			0.0

		A:165	PRO A:193,ILE A:194,ASP A:148,MET A:147,ALA A:191,ILE A:21,GLY A:192,VAL A:238,PHE A:149		A:215,LEU A:218,ALA A:157	A:155, TYR A:158			
A1b	-8.3	ILE A:21,GLY A:96	SER A:94, SER A:20,LEU A:63,GLY A:14,THR A:196,ILE A:194	PHE A:41	PHE A:97,ILE A:122	VAL A:65,ILE A:95			0.0
A1c.	-8.4	LYS A:165,ASP A:148	VAL A:189,MET A:147,ILE A:21,ALA A:191,ILE A:194,GLY A:192,TYR A:158,GLY A:104,LEU A:207		ALA A:157	PRO A:193,MET A:199,ILE A:202	ILE A:215		0.0
A1d	-8.4	ILE A:21, SER A:94,SER A:20,ILE A:194	ALA A:22, MET A:147, LEU A:218, MET A:155, TYR A:158, GLY A:192, THR A:196			PRO A:193, ILEA 215		GLU A:219	0.0
A1e	-8.4	LYS A:165, PRO A:156			PHE A:149	ILE A:215, PRO A:193, LEU A:218			0.0
A1f	-8.5	LYS A:165	GLU A:219, TYR A:158, ILE A:194, GLY A:192, ILE A:21, SER A:94, MET A:147, ILE A:95, GLY A:96	PHE A:149	PRO A:193, LEU A:218, TRP A:222	ILE A:215			0.0
A1g	-8.4	GLY A:14	ASP A:64, LEU A:63, GLY A:96, ILE A:16, SER A:20, ALA A:21, SER A:94	PHE A:41	ILE A:122, VAL A:65	ILE A:95			0.0
A1h	-8.4	LYS A:165	LEU A:218, GLU A:219, PRO A:193, GLY A:192, ILE A:194, ILE A:21, TYR A:158, GLY A:96, ILE	PHE A:149		PHE A:149			0.0

			A:94, MET A:147, SER A:94						
A1i	-8.2	LUE A:63, THR A:39	ILE A:122, ASP A:64, SER A:13, GLY A:40, GLY A:14	PHE A:41		VAL A:65, ILE A:95			0.0
Standard	-8.2		GLN A:66, PHE A:97, ILE A:16, THR A:196, SER A:20, ILE A:21, SER A:94, GLY A:96, GLY A:14, GLY A:40LEU A:63, ASP A:64	PHE A:41	ILE A:122, ILE A:95, VAL A:65	ILE A:95, VAL A:65			0.0

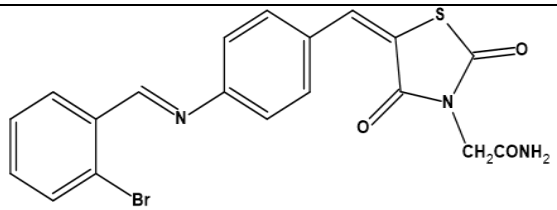
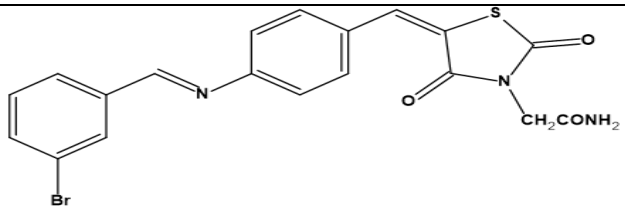
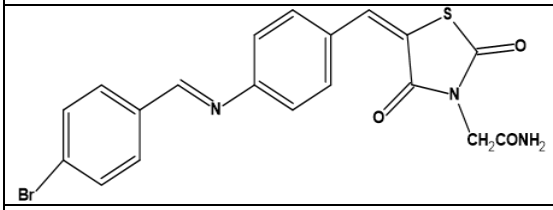
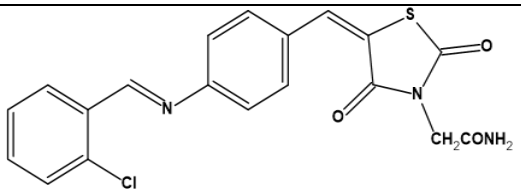
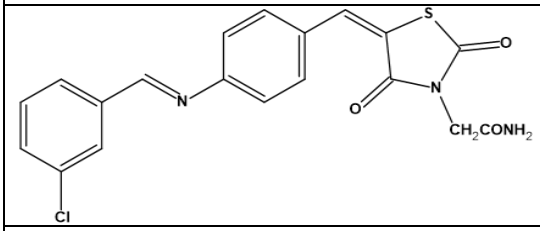
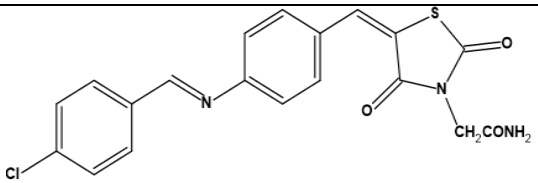
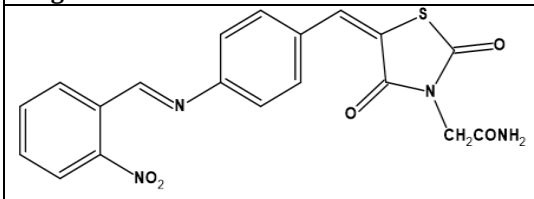
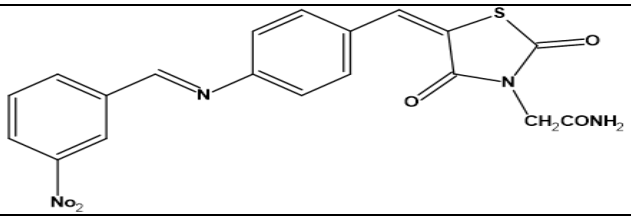
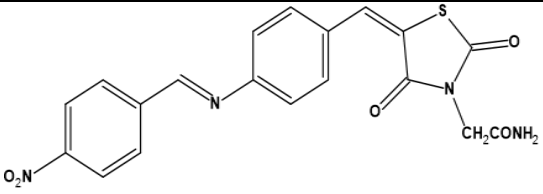
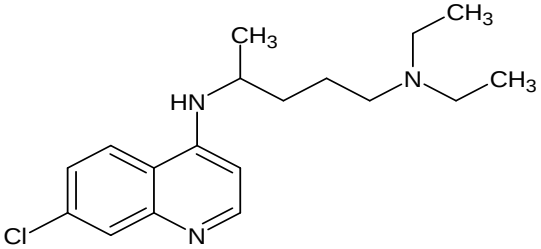
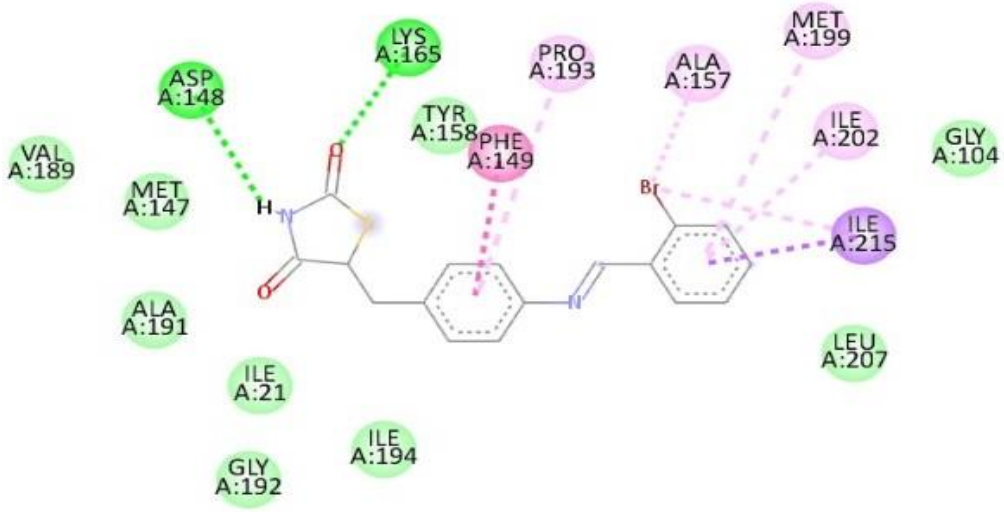
A1a	**A1b**
	
A1c	**A1d**
	
A1e	**A1f**
	
A1g	**A1h**
	
A1i	Chloroquine
	

Figure 1. 3D structure of protein (PDB ID: 1P44)

Figure 2. Binding interaction of ligand and aminoacids at the binding sites.

(a) 2D structure of ligand A1a interaction with binding site of protein 1P44



(b) 3D structure of ligand A1a interaction with binding site of protein 1P44.

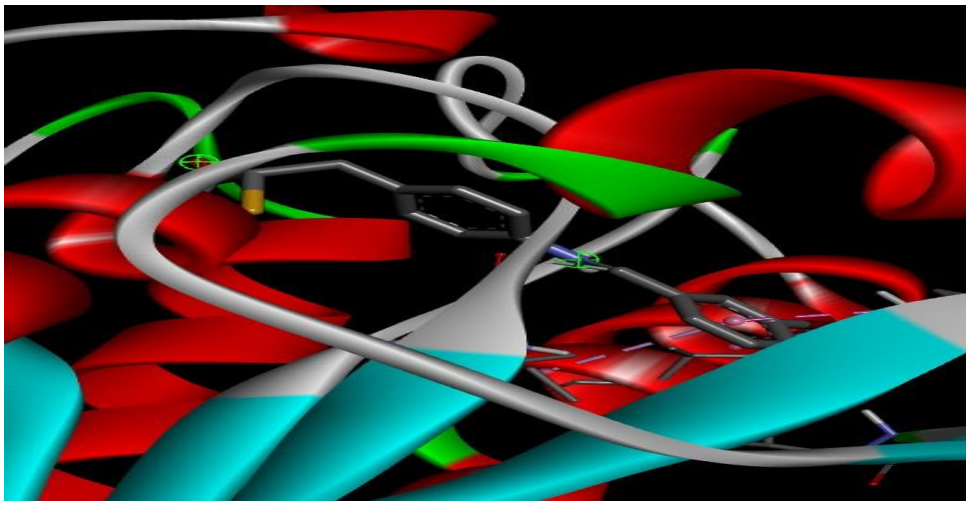
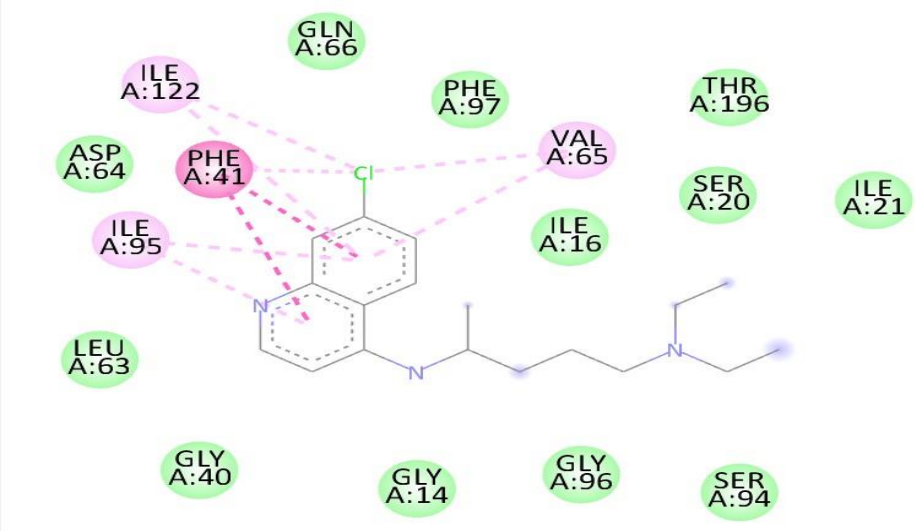
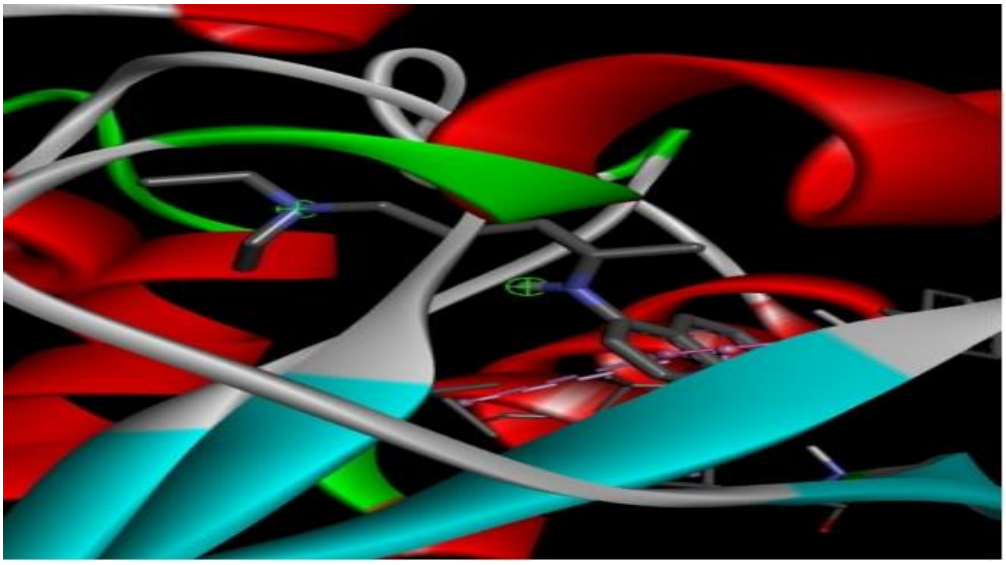


Figure 3. Binding interaction of standard drug chloroquine and aminoacids at the binding sites.

(c) 2D structure of chloroquine interaction with binding site of protein 1P44



(d) 3D structure of chloroquine interaction with binding site of protein 1P44



RESULTS AND DISCUSSION

Lipinski's rule of five

The designed thiazolidinedione derivatives were passed in Lipinski's rule of 5. It states that, in general, an orally active drug has no more than one violation of the following criteria: No more than 5 hydrogen bond donors (the total number of nitrogen-hydrogen and oxygen-hydrogen bonds), no more than 10 hydrogen bond acceptors(all nitrogen or oxygen atoms),molecular mass less than 500 Dalton, LogP less than 5 and molar refractivity should be between 40-130 when compared to the reference drug Chloroquine (Table.2).

Docking

The scoring function for the docking run is the binding energy, E_{bind} between the ligands and the protein. Molecular interaction studies were performed by Autodockvina with PyRx using bioactive compounds. The interaction of the compound with the target protein is important in the drug development process. The most common way to evaluate the correctness of the docking

geometry is to measure the Root Mean Square Deviation (RMSD) of the ligand from its from its reference position in the answer complex after the optimal superimposition of the receptor molecules [10].

By docking of 9 compounds, the binding energy values ranges from -8.2 to -8.6 kcal/mol^{-1}. Out of the 9 compounds the receptor-ligand interaction of 9 derivatives with name of aminoacids interacts with the ligands were given in Table 3.

By comparing the docking results of 9 derivatives the compounds A1a shows highest binding energy as compared to standard drug Chloroquine.A1a having binding affinity -8.6 kcal/mol^{-1}.The amino acid residues interact with the ligand A1a are LYS A:165 BY conventional H-bond, PRO A:156,PRO A:193, ILE A:194, ASP A:148, MET A:147, ALA A:191, ILE A:21, GLY A:192, VAL A:238, PHE A:149 by vander waals forces, ILE A:215,LEU A:218,ALA A:157 by alkyl bonds and MET A:155,TYR A:158 by Pi-alkyl bonds underlining the competitive inhibitory characteristics of compounds.

CONCLUSION

Malaria is a serious illness that caused by Plasmodium parasites. Over the past two decades, efforts to control malaria have met with less and less success. The threat of resistance of Plasmodium to some drugs is growing. In this study, docking of 9 thiazolidine-2,4-dione derivatives was carried out and two compounds such as A1a and A1f displayed minimum energy values with highest binding affinity. The energy values contain -8.6 and -8.5kcal/mol respectively obtained from Autodockvina PyRx when compared with standard chloroquine with binding affinity -8.2 kcal/mol^{-1}.A1i has least binding affinity (-8.2 kcal/mol^{-1}. We conclude that these thiazolidine-2,4-dione derivatives contain either halogen group or electron withdrawing and electron donating groups that showed higher resistance against the Plasmodium parasites. So it shows that it has maximum antimalarial activity.

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