Molecular Modeling and Docking Studies of Some Benzodiazole Derivatives on the Protein of *Staphylococcus aureus*

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Authors' contributions

This work was carried out in collaboration between both authors. Author ASS designed the study, performed the analysis, wrote the protocol and wrote the first draft of the manuscript. Author XS managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

Article Information

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ABSTRACT

In this work, molecular modeling and docking studies of antimicrobial heterocyclic compounds were carried out using Auto Dock. Docking studies were carried out for Benzodiazole derivatives to study their affinity to Cell wall anchored (CWA) protein of *Staphylococcus aureus*. The docking studies of the compounds showed binding energies ranging from -7 to -5 kcal/mol against clumping factor A (ClfA), a CWA protein of *Staphylococcus aureus*, [PDB file:1N67]. Molecular modeling and docking studies of Benzodiazole derivatives show that the main action of the compounds is inhibition of cell wall adhesion.

Keywords: Antimicrobial; docking; Staphylococcus aureus; heterocyclic.

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1. INTRODUCTION

Staphylococcus aureus is a commensal bacterium that causes infections such as sepsis, endocarditis, and pneumonia. *S. aureus* can express a variety of virulence factors, including surface proteins. The *Staphylococcus aureus* is a gram-positive bacteria that colonizes the nasal cavity of 20–30% of the human population without causing any apparent disease [1]. The surface proteins of *S. aureus* are covalently attached to the peptidoglycan, and for that reason, they are named as cell wall-anchored [2]. Based on its molecular structure and arrangement, the CWA proteins of *S. aureus* have been classified into four families: the MSCRAMM family, the NEAT motif family, the three-helical bundle family, and the G5-E repeat family. Compounds having benzodiazole as a structural motif have been widely used in medicinal chemistry and drug development, and researchers are actively seeking new uses and applications of this heterocycle [3]. In the medicinal field, the utility of heterocyclic entities has been raising each day because of structural similarities with biological molecules like nutrients, antibiotics. Although it including almost one-fourth of the best hundred offering drugs yet because of issues like obstruction, poisonous quality, there is a requirement for a minor change in existing drug molecules and to structure novel molecules which fuse benzodiazole as pharmacophore which are active against new targets [4]. The present study explores the uses of benzodiazole derivatives as a potential antibacterial antibacterial agent against S.aureus with the help of QSAR and molecular modeling using docking studies.

The benzodiazole moiety itself is an important pharmacophore in the present-day and has been used as privileged scaffolds to synthesize selective drugs of interest in numerous therapeutic areas. The bacterial pathogen *Staphylococcus aureus* binds to host extracellular matrix proteins using a variety of cell-wall–anchored proteins [5]. Among these, the fibrinogen binding microbial surface component recognizing the adhesive matrix molecule (MSCRAMM) protein clumping factor A (ClfA) is an important virulence factor of *S. aureus* involved in various infections. The present study uses molecular modeling and docking studies on ClfA protein of *S. aureus* it hbenzadiazole derivatives.

2. EXPERIMENTAL

The affinity of the drug to drug target is an important factor in drug discovery. This can be assed by predicting the binding energy of the ligand to the target site of the protein using molecular docking studies. Mathematical algorithms are used to predict the binding affinity of the docked molecules. A set of compounds were taken from literature [3]. While none of the compounds were novel, 47 of them were tested against a panel of strains of bacteria and fungi for the first time. Molecules were benzodiazole derivatives with substituents at the 1-, 2- and 5-positions. The molecules selected were drawn using the Marwin tool and uploaded to a web-based database of Docking server [6]. ClfA protein of S.aureus IN67 was downloaded from Protein data bank [7]. The crystal structure of ClfA protein 1N67 is given in Fig. 1. Details of the ligands used for the docking study are given in Table 1.

3. RESULTS AND DISCUSSIONS

Docking simulation was carried out using a molecular docking webserver which used Auto Auto Dock4.2®. Polar hydrogens were added using Autodock tools [8]. The Lamarckian Genetic Algorithm (LGA) [9] was used for conformational search. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied. The results of the docking studies are given in Fig 2 to 6.

Non-covalent interactions, such as hydrogen bonds, between ligands and protein forming a complex, provide important clues in the understanding of biological processes and the design of compounds with suitable properties. Schematic 2D diagrams are widely used to visualize the binding interactions of ligands. This will provide important information about their role and function. A lot of software packages are available for visualizing structure in 3D, but only a handful exists for generating 2D protein/ligand interaction diagrams. LIGPLOT [10] is the most commonly used software for the purpose.

The analysis of intermolecular interactions including hydrophobic and hydrogen-bonding interactions on the most representative structure was obtained using a 2D ligplot. The residue decomposition of ΔGbinding provides an avenue

for better understanding and more in-depth information for the interactions between molecule formed two hydrogen bonds with residues Tyr399 and Tyr488. The bond lengths of hydrogen bonding were 2.58 and 3.15A° respectively. Hydrophobic interactions were predominant. Decomposed interaction energies of the best-fitted ligand, 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole are given in Table 2. The 2D plot of the Protein-ligand interactions[10] of 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole is given in Fig 8.
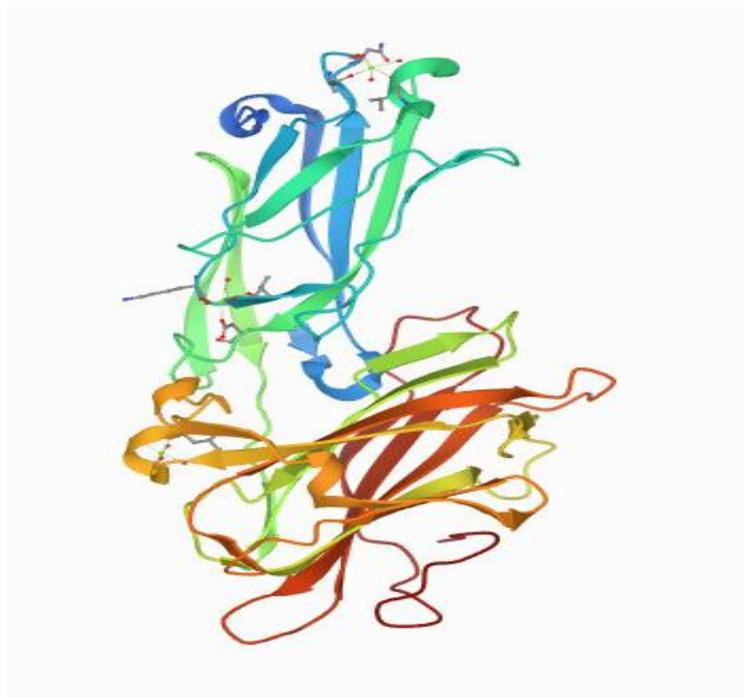

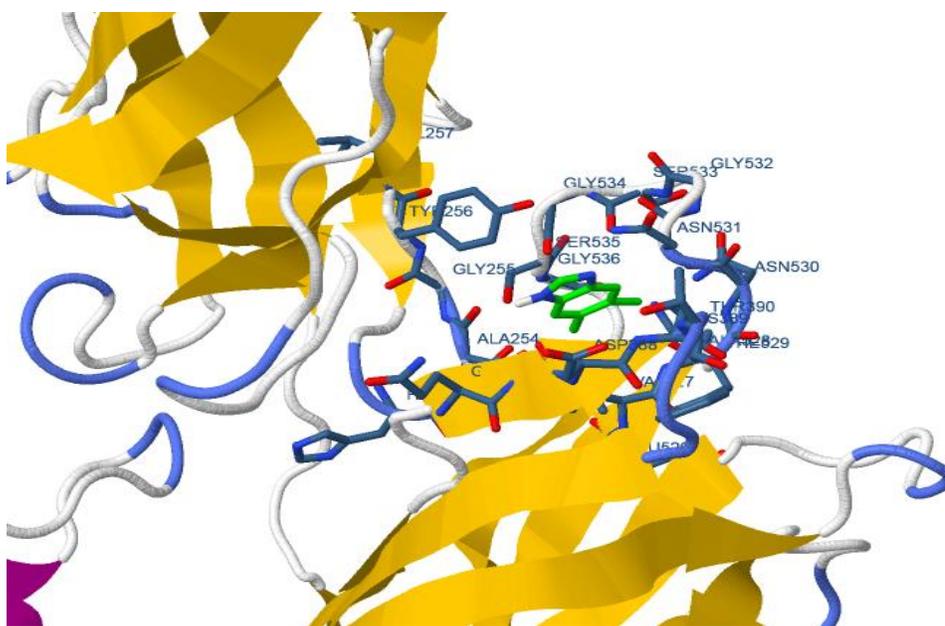**Fig. 1. Structure of CLFA protein 1N67**

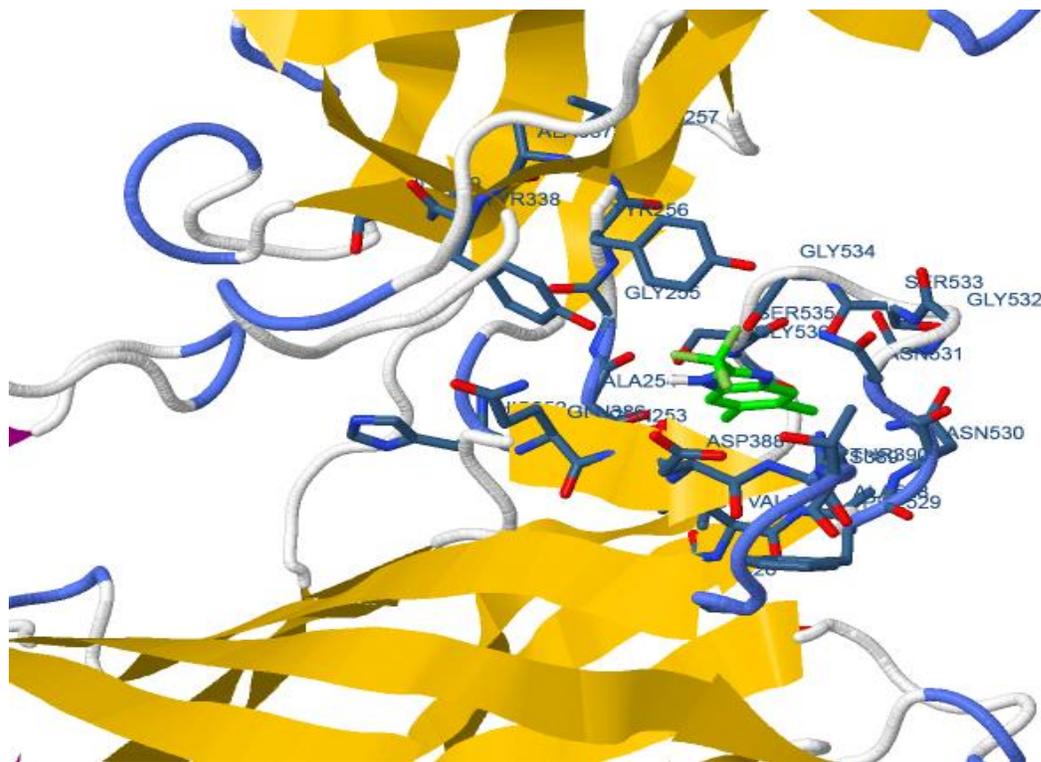**Fig. 2. Docking of 5,6-dimethyl-1H-1,3-benzodiazole**

Fig. 3. Docking of 4,6-dichloro-2-(trifluoromethyl)-1H-1,3-benzodiazole
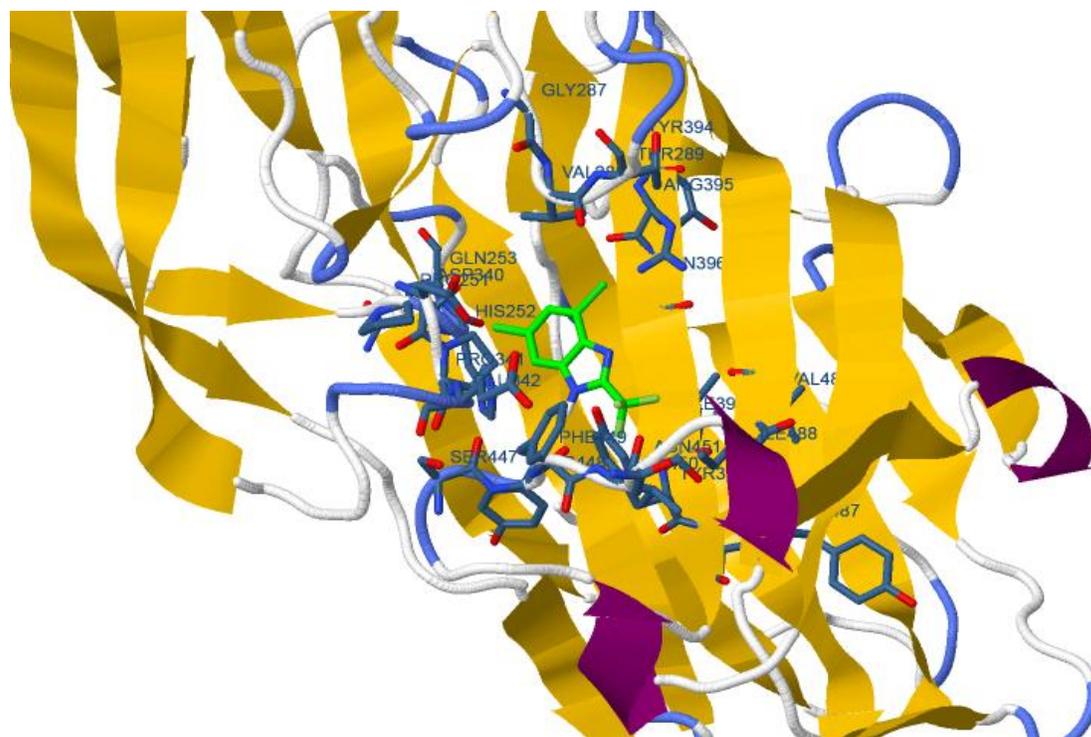
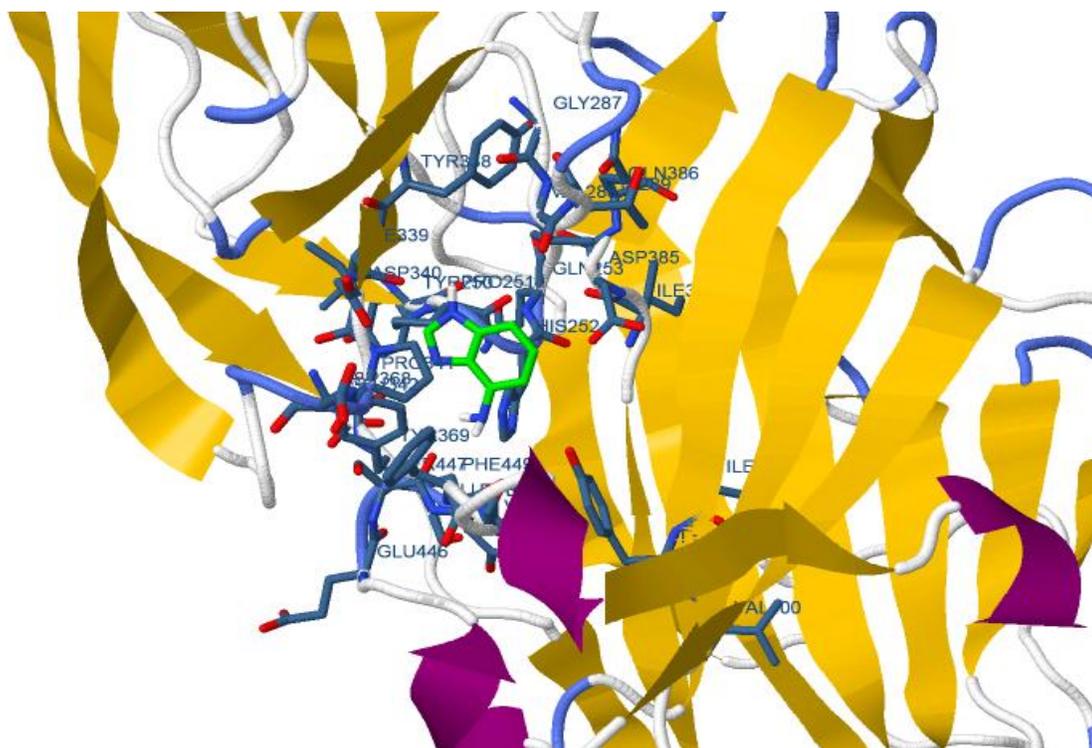**Fig. 4. Docking of 1H-1,3-benzodiazol-4-amine**

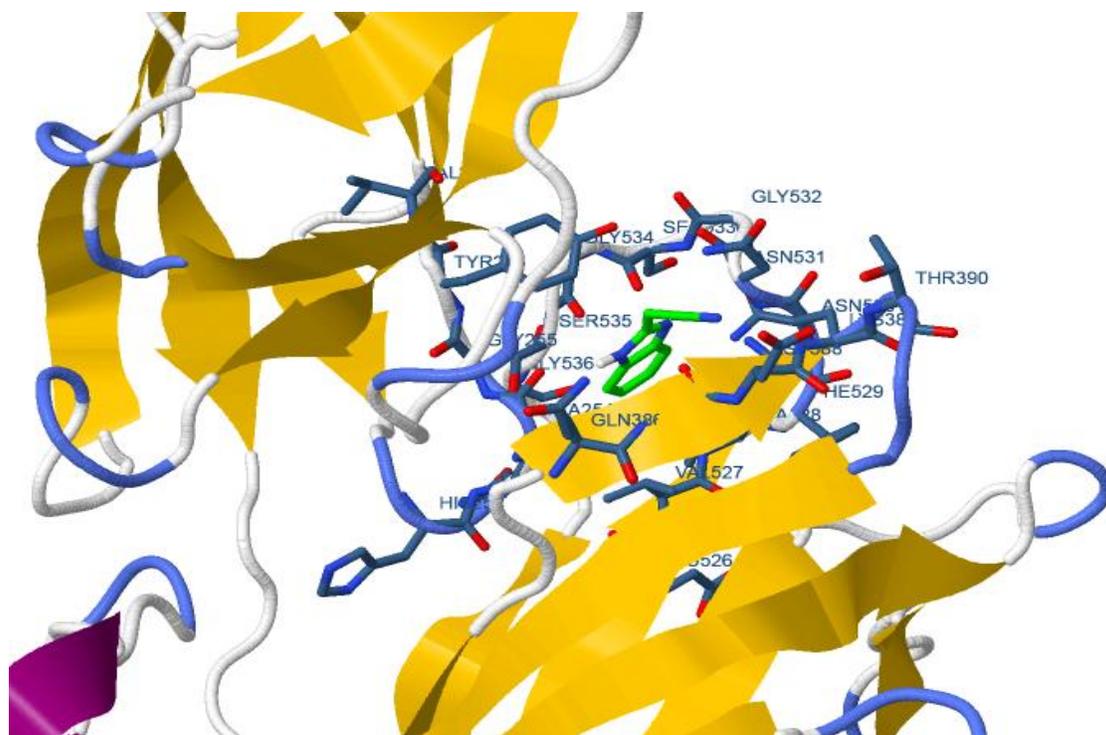**Fig. 5. Docking of 2-(1H-1,3-benzodiazol-2-yl)acetonitrile**
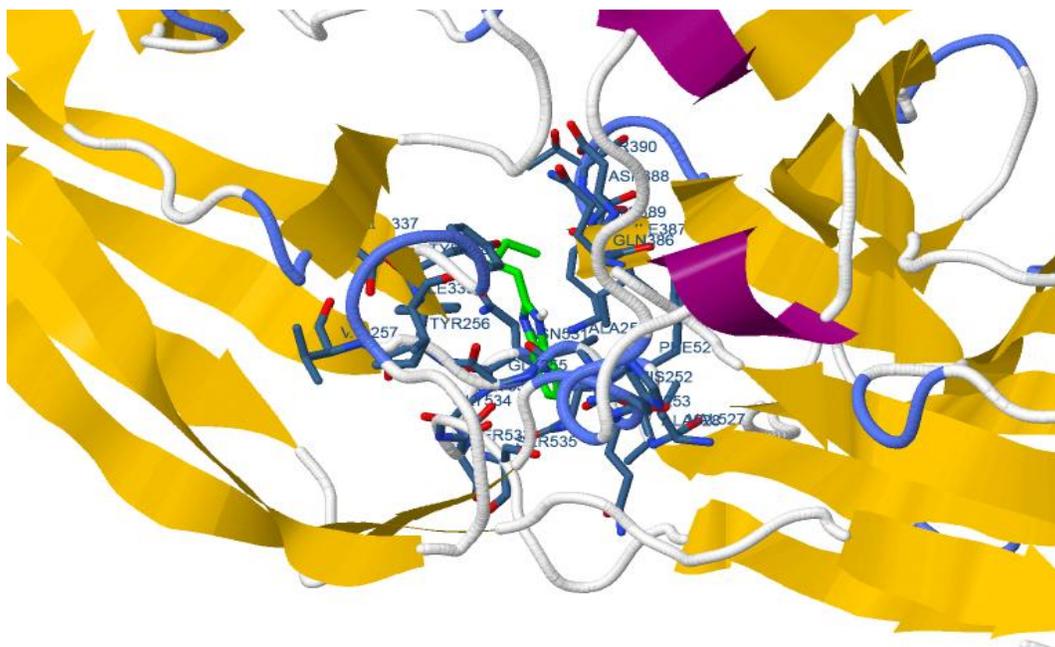

Fig. 6. Docking of 2-butyl-1H-1,3-benzodiazole

Fig. 7. Docking of 4,6-dibromo-2-(trifluoromethyl)-1H-1,3-benzodiazole

Table 1. Ligands used for docking study

No.	Ligands	Smiles	Molecular structure
1	5,6-dimethyl-1H-1,3-benzodiazole	CC1=CC2=C(C=C1C)N=CN2	
2	5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole	CC1=CC2=C(C=C1C)N=C(N2)C(F)(F)F	
3	4,6-dichloro-2-(trifluoromethyl)-1H-1,3-benzodiazole	C1=C(C=C(C2=C1NC(=N2)C(F)(F)F)Cl)Cl	
4	1H-1,3-benzodiazol-4-amine	C1=CC(=C2C(=C1)NC=N2)N	
5	2-(1H-1,3-benzodiazol-2-yl)acetonitrile	C1=CC=C2C(=C1)NC(=N2)CC#N	
6	2-butyl-1H-1,3-benzodiazole	CCCCC1=NC2=CC=CC=C2N1	

Table 2. Binding energy and Inhibition coefficients

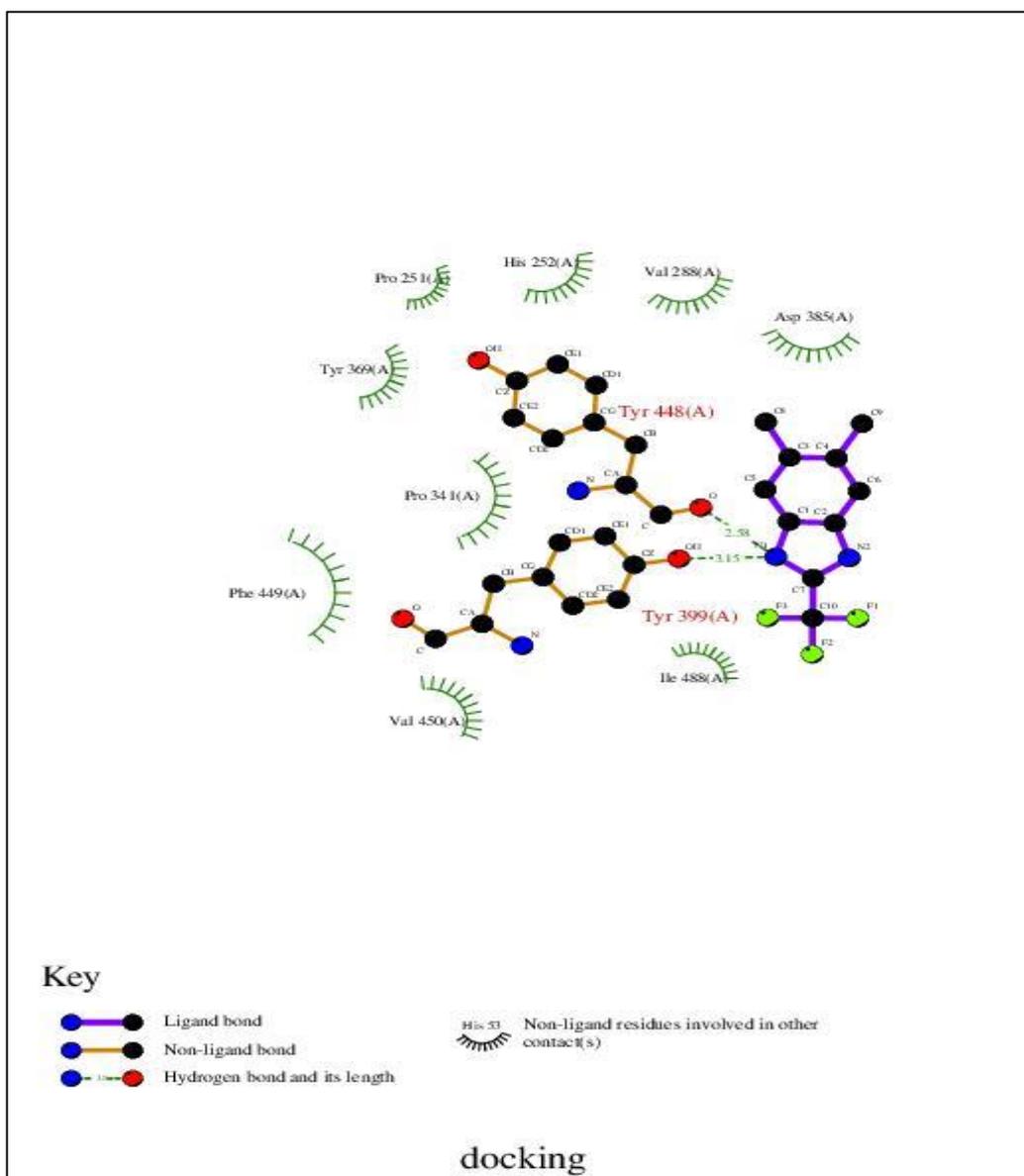| Compound	Binding Energy (kcal/mol)	Inhibition coefficient (Ki)
5,6-dimethyl-1H-1,3-benzodiazole	-6.21	28.03uM
5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole	-7.0	-7.40uM
4,6-dichloro-2-(trifluoromethyl)-1H-1,3-benzodiazole	-6.68	12.8uM
1H-1,3-benzodiazol-4-amine	-5.26	139.94uM
2-(1H-1,3-benzodiazol-2-yl)acetonitrile	-6.04	37.50uM
2-butyl-1H-1,3-benzodiazole	-5.58	81.76uM

Fig. 8. 2D interaction plot of protein and ligand molecule of 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole

Table 3. Decomposed interaction energies(in kcal/mol) of ligand molecule of 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole at the active site of protein 1N67

Hydrogen bonds	Halogen bonds	Cation-pi	hydrophobic	other
TYR399(-0.448)	VAL450	PHE449(-1.3292)	PRO341(-0.9721)	ASP385(-0.5968)
TYR448(1.573			HIS252(0.4917)	ILE488(-0.3323)
			VAL228(-0.4783)	
			TYR369(-0.4615	
			PRO251(-0.2264)	

The results of the docking studies of Benzodiazolederivatives against ClfA protein IN67 are tabulated in Table 2. Binding energies and inhibition coefficients of the ligands used in the docking study are given.The docking studies revealed that all the compounds studied showed a good docking score. The docking score is a measure of the antibacterial activity of the compounds studied. The binding energy of the molecules studied was ranging from -7.0 to -5.28 kcal/mol. The inhibition coefficient of the molecules studied shaved values from -7.4uM to 139uM. The second analog which is having dimethyl groups in 5,6 positions showed an increase in energy values (-7.0) was more compatible with the receptor than the rest of the molecules. Decomposed interaction energies of ligand molecule of 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole at the active site of protein 1N67 is given in Table 3. The hydrophobic pocket formed between the two DEv-IgG domains of the clumping factor act as the ligand-binding site. However, the binding site of the analog was similar to that of the rest of the molecules, which means that the functional group was responsible for the binding behavior. The most active compound attached more tightly in the active site of receptor due to interactions, which resulted in higher binding affinities than other compounds.

4. CONCLUSION

In conclusion, molecular modeling and docking studies of benzodiazole derivatives showed good binding towards CWA proteins of S.Aures. Studied molecules showed the best binding energies against ClfA protein receptors binding sites. Benzodiazole derivative 5,6-dimethyl-2-(trifluoromethyl)-1H-1,3-benzodiazole exhibited the lowest binding energy of -7 kcal/mol at the active site of ClfA (PDB code: IN67) consistent with its least inhibition coefficient (Ki = -7.4uM). Molecular modeling and docking studies demonstrated that benzodiazole derivatives studied are potential antibacterial drug candidates.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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