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DESIGN AND DOCKING STUDY OF SOME NEW CHALCONE DERIVATIVES FOR ANTI-MICROBIAL ACTIVITY

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ABSTRACT: In this work, we collected the three dimensional structure of Enterotoxin A from *Staphylococcus aureus* which plays an important role in staphylococcus pathway. The protein structures were collected from PDB data bank. From the 3D structures of the proteins, the targeted derivatives were designed. Docking studies was performed with designed ligands from the drug. The drug derivatives docked to the protein by hydrogen boding interactions and these interactions play an important role in the binding studies. Docking results showed the best compounds among the derivatives.

Key words: Antibacterial activity, docking studies, Enterotoxin A**,** *Staphylococcus aureus*

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INTRODUCTION

Staphylococcal Enterotoxins (SEs) are a family of structurally related basic secretory proteins that are important virulence factors for the pathogen. By mediating massive cellular proliferation and cytokine secretion at extremely low concentrations, these SAgs can cause systemic pathology in the host, ranging from nausea and fever up to toxic shock and death (Le Loir Y et al, 2003, Iandolo JJ 1989, Marrack P, Kappler J 1990). SEs can bind relatively non-polymorphic regions outside the peptide binding groove of MHC class II molecules on Antigen Presenting Cells (APCs) as well as conserved Vβ regions of TCR molecules leading various groups to hypothesize that these SAgs may act as a binding "bridge" between MHC class II and TCR, resulting in downstream signaling events and immune activation (Papageorgiou AC et al, 1998, Kluytmans J et al 1997, Bergdoll M.S et al 1981).

One of the most potent SEs is Staphylococcal Enterotoxin A (SEA), with an exceedingly low half-maximum stimulating dose of 0.1 pg/mL. SEA is somewhat atypical in that it has two binding sites for two corresponding sites on MHC class II, a high affinity Zinc coordinating site on the β chain of MHC class II and a second weaker (>1 μM affinity) binding site on the α chain that has been shown to play an important role in the complete functional activity of SEA. Studies have suggested a cooperative model where the binding of one SEA to MHC class II favors the binding of the second SEA molecule and MHC class II - (SEA)2 trimers have been isolated in solution (Ikeda T et al, 2005). These results have led to the speculation that SEA could crosslink multiple MHC class II molecules on the surface of APCs. Indeed, when MHC class II expressing cell lines were treated with SEA, but not with mutants missing either binding site or toxins with one MHC class II binding site, downstream signaling inflammatory cytokine gene upregulation and homotypic aggregation was observed, even in the absence of T cells (Al-Daccak R et al 1998).

These results hint a role for a multivalent binding mode between SEA and MHC class II, and indeed, many subsequent studies on super antigens have assumed this multivalency of SEA as part of its functionality (Li H et al 1998). However, the actual membrane reorganization of MHC class II on the surface of a cell in response to SEA treatment has not been directly probed, and as such, remains unknown.

METHODOLOGY

The structures of the compounds (Figure 1) were constructed and optimized using chemsketch software.

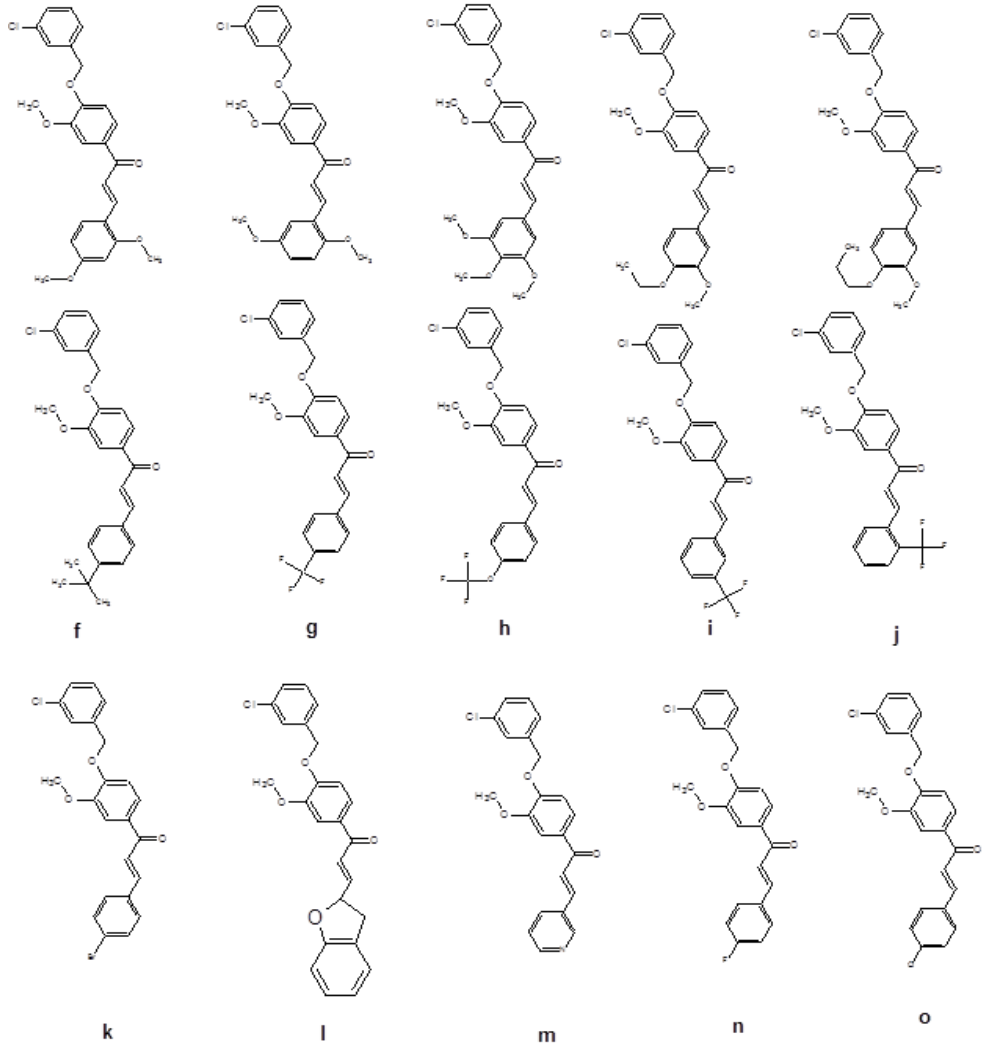


Fig 1: compounds used for docking studies

To prepare the Enterotoxin A from Staphylococcus, the crystal structure was taken from the Protein Data Bank (PDB_ID: 3NB6) (Figure 2).

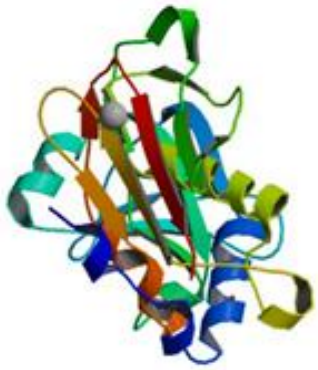


Fig 2: of Enterotoxin A

Hetero atoms were removed from the binding site and the chain A was selected for docking studies. Hydrogen atoms were added to the enzyme. The molecular docking method was performed using the Gold version 3.0.1 program to study the binding orientation of compounds into the Enterotoxin A structure. The docking experiments were performed using the binding site of Enterotoxin A. The binding site identification was carried out using CastP server. A new program, CAST, for automatically locating and measuring protein pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory. CAST identifies and measures pockets and pocket mouth openings, as well as cavities. The program specifies the atoms lining pockets, pocket openings, and buried cavities; the volume and area of pockets and cavities; and the area and circumference of mouth openings.

Docking method

Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software which is based on genetic algorithm (GA). This method allows as partial flexibility of protein and full flexibility of ligand. The compounds are docked to the active site of the protein. The interaction of these compounds with the active site residues are thoroughly studied using molecular mechanics calculations. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0 A° (dH-X) for hydrogen bonds and 6.0 A° for vanderwaals were employed. During docking, the default algorithm speed was selected and the ligand binding site in the of Enterotoxin A was defined within a 10 A° radius with the centroid as CE atom of ASP175. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a ligand were within 1.5A° RMSD. After docking, the individual binding poses of each ligand were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of each ligand was selected.

Gold Score fitness function:

Gold Score performs a force field based scoring function and is made up of four components: 1. Protein-ligand hydrogen bond energy (external H-bond); 2. Protein-ligand vander Waals energy (external vdw); 3.Ligand internal vander Waals energy (internal vdw); 4.Ligand intramolecular hydrogen bond energy (internal- H-bond). The external vdw score is multiplied by a factor of 1.375 when the total fitness score is computed. This is an empirical correction to encourage protein-ligand hydrophobic contact. The fitness function has been optimized for the prediction of ligand binding positions.

GoldScore = S (hb_ext) + S (vdw_ext) + S (hb_int) + S (vdw_int)

Where S (hb_ext) is the protein-ligand hydrogen bond score, S (vdw_ext) is the protein-ligand van der Waals score, S (hb_int) is the score from intramolecular hydrogen bond in the ligand and S (vdw_int) is the score from intramolecular strain in the ligand.

RESULTS AND DISCUSSION

After collecting the crystal structures, the possible binding sites of Enterotoxin A was searched with CASTP server as shown in Figure 3. The residues included in active site were ILE 110, ASP 111, SER 112, PRO 113, THR 115, TYR 116, GLY 121, TYR 122, LYS 123, ALA 137, LEU 138, PRO 139, PRO 140, VAL 141, ALA 142, CYS 145, GLY 150, LEU 352, GLN 355, GLN 356, PHE 357, GLN 358, and LYS 518.

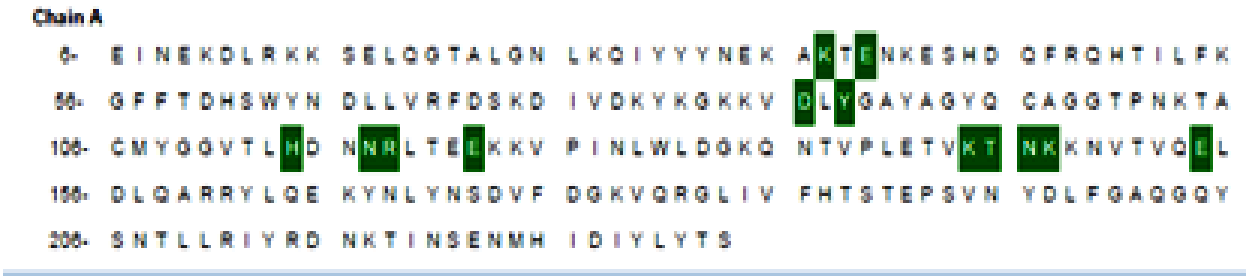
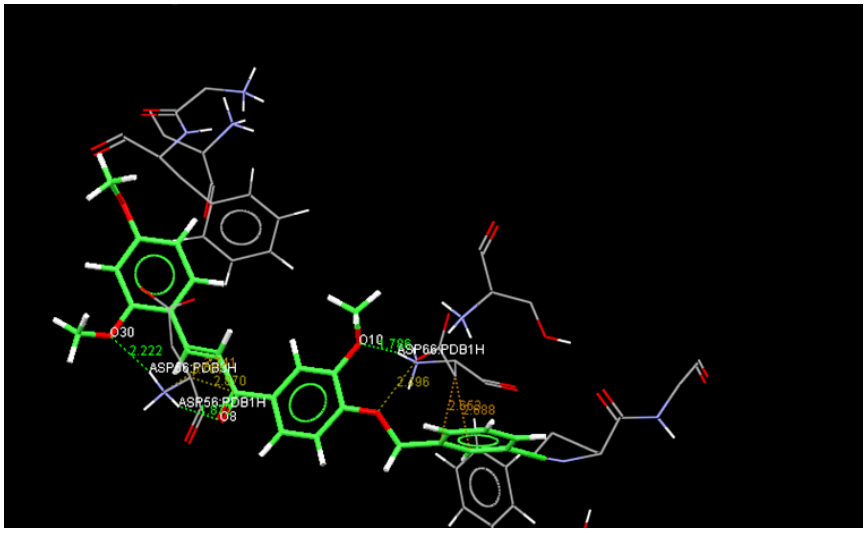


Fig 3: Active site

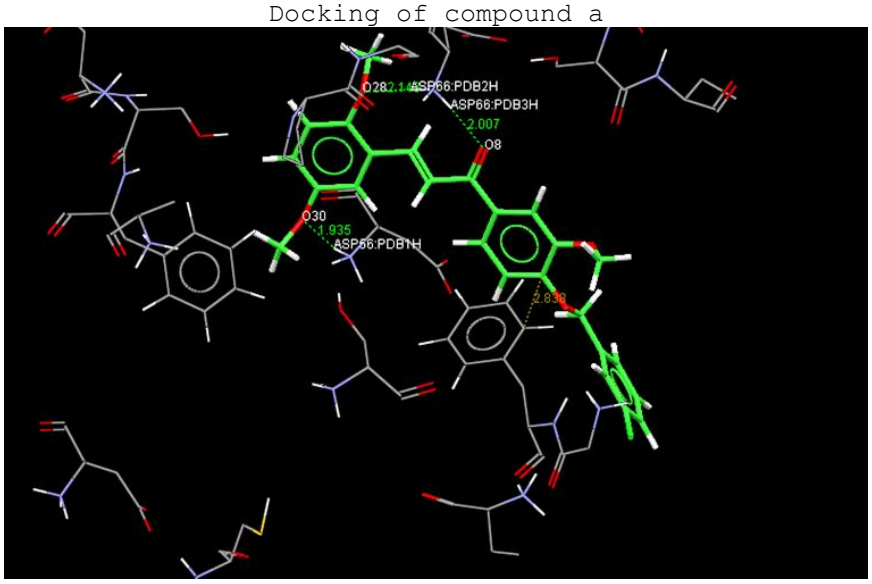
From the binding site analysis of Enterotoxin A we identified that, the binding pockets are identical in all chains and the largest binding pocket was taken for further docking studies. The crystal structure of of Enterotoxin A was similar hence we have taken as representative structure for docking studies. The docking of drugs into the active site of Enterotoxin A was performed using the GOLD software and the docking evaluations were made on the basis of Gold Score fitness functions. We preferred Gold fitness score than Chemscore fitness as Gold fitness score is marginally better than Chemscore fitness function. (Jayasimha Rayalu et al, 2010, 2014,2015, Sreenath Konanki et al, 2013)

Molecular docking study

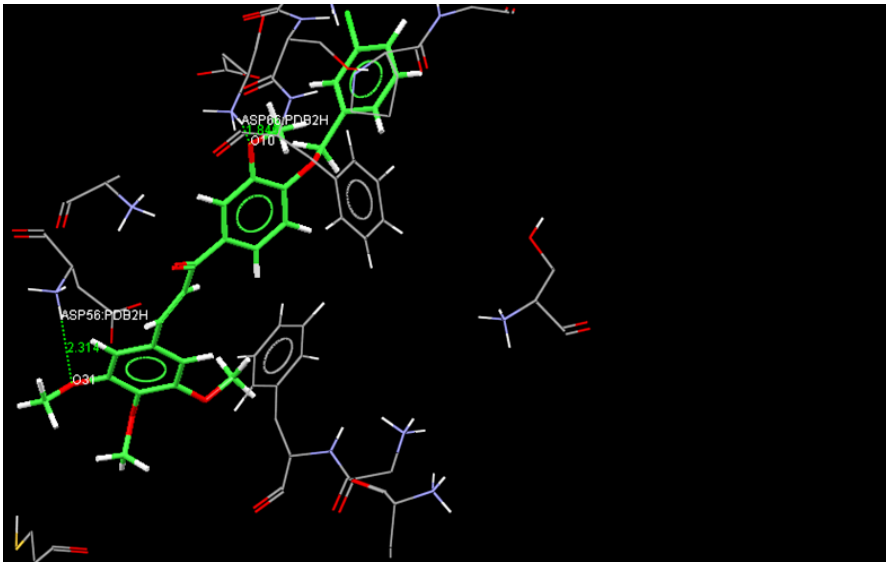
Structure-based drug design begins with the identification of a molecular target such as a protein such as of Enterotoxin A in this study. This structure is then used as a blueprint for the drug design of a lead compound. The compounds are modelled for their fit in the active site of the target, considering both steric aspects (*i.e.*, geometric shape) and functional group interactions, such as hydrogen bonding and hydrophobic interactions. The selected docked conformations of analogues into the 3NB6 binding site are shown in Figure 4.



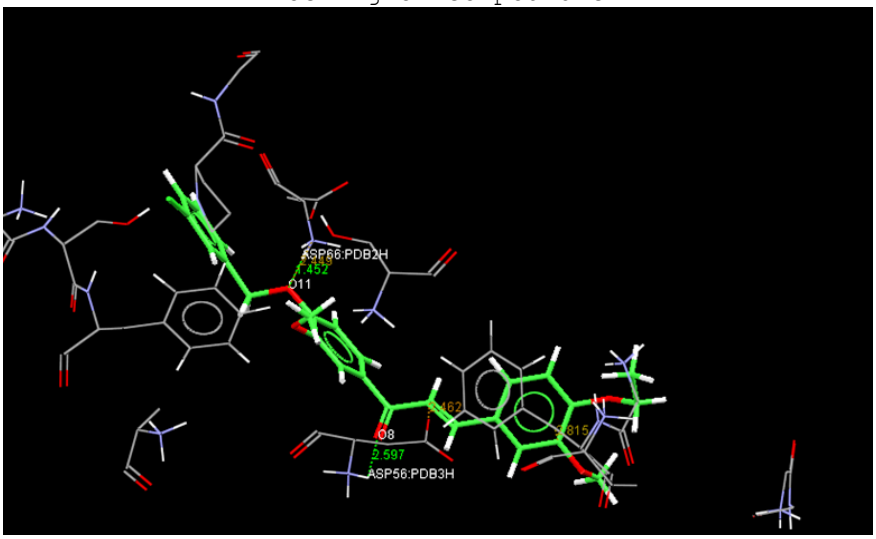
Docking of compound a



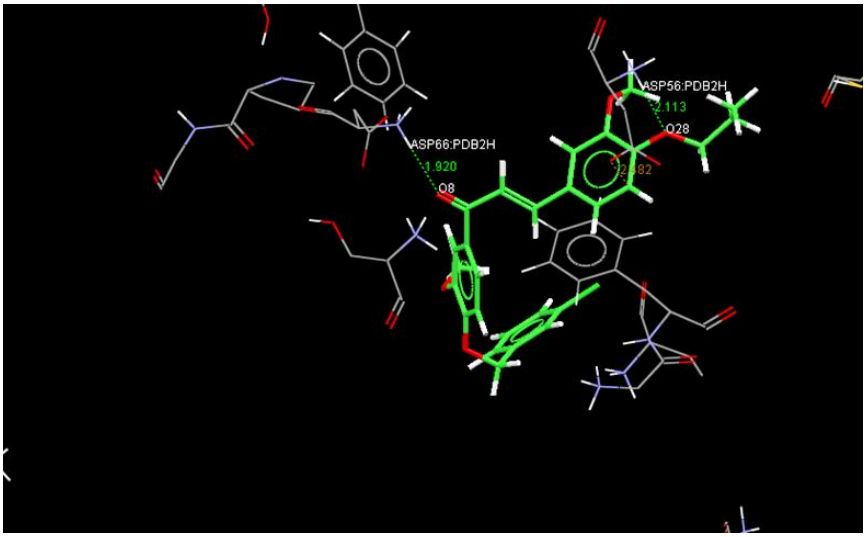
Docking of compound b



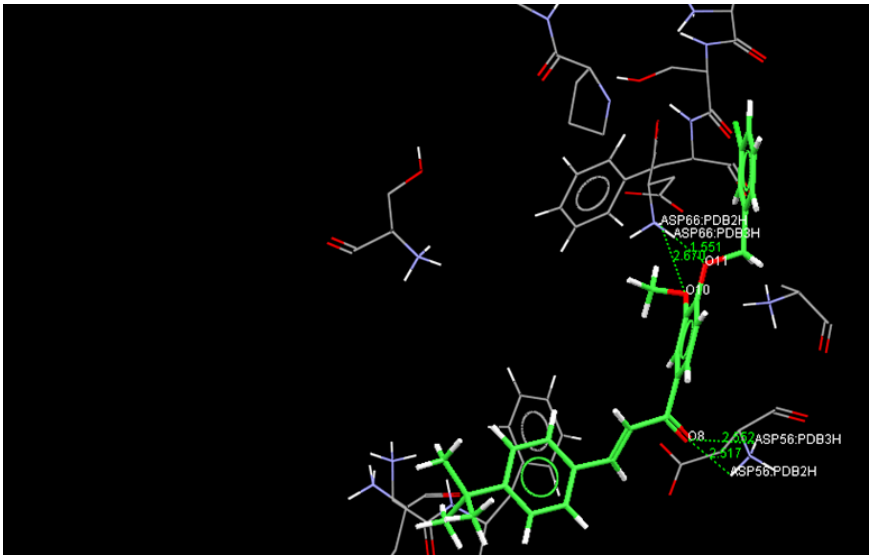
Docking of compound c



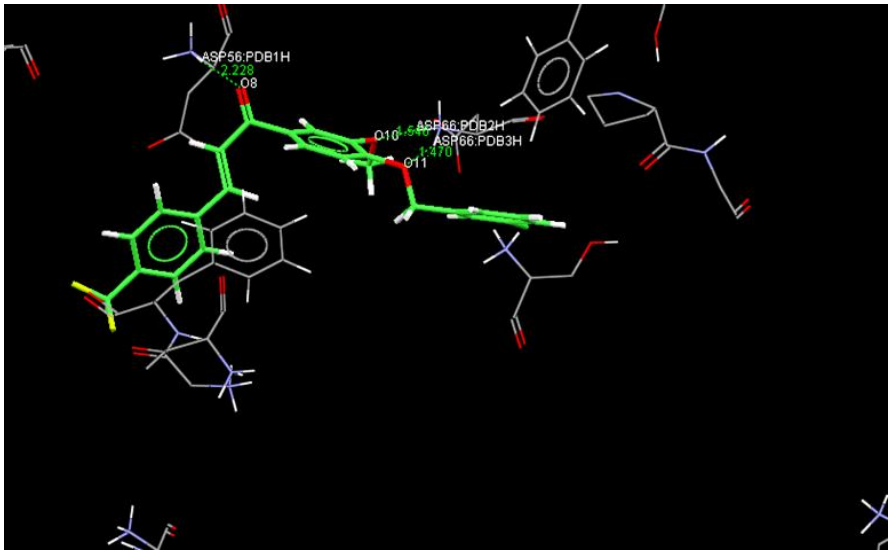
Docking of compound d



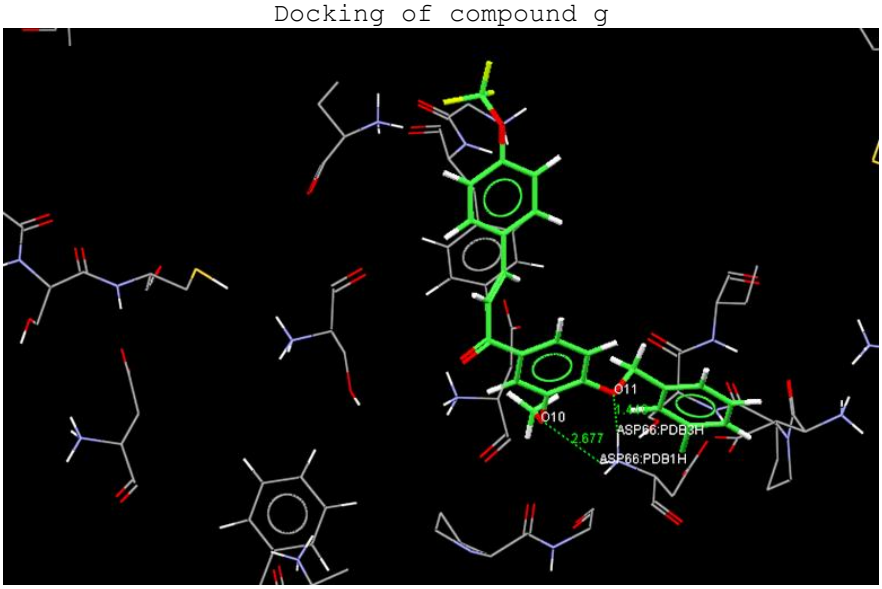
Docking of compound e



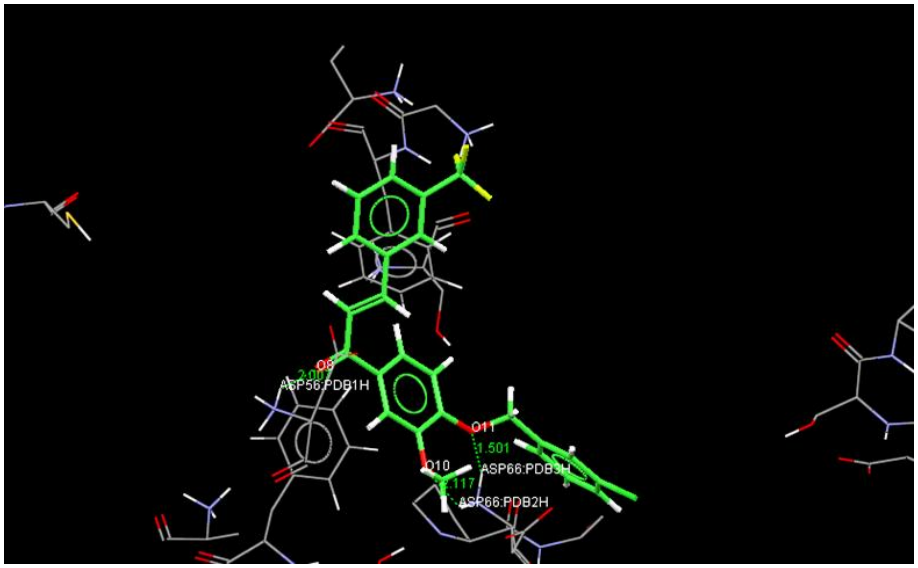
Docking of compound f



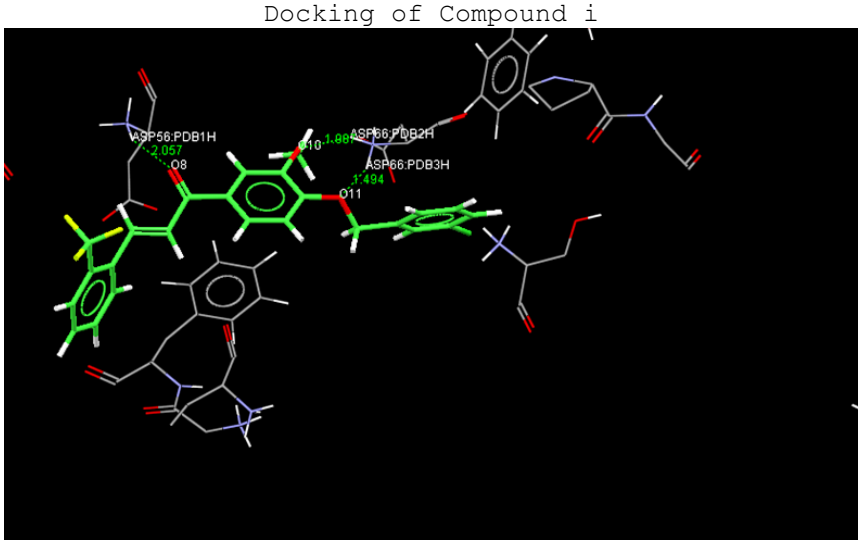
Docking of compound g



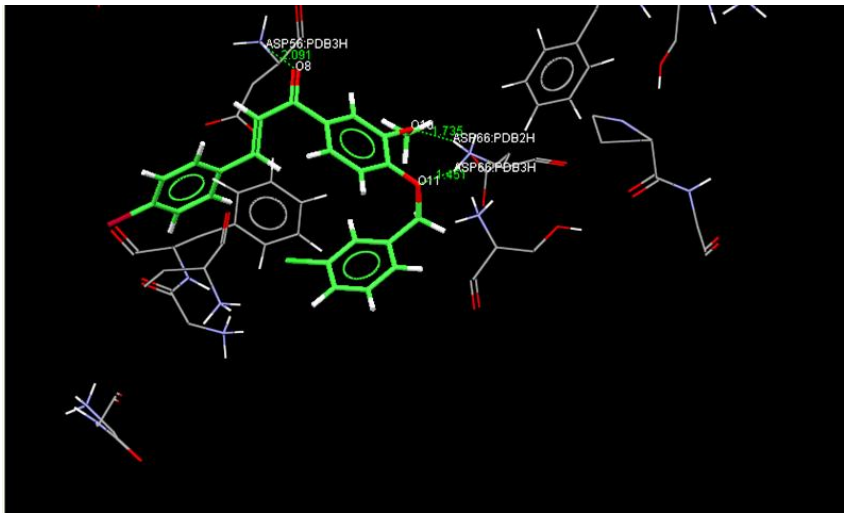
Docking of compound h



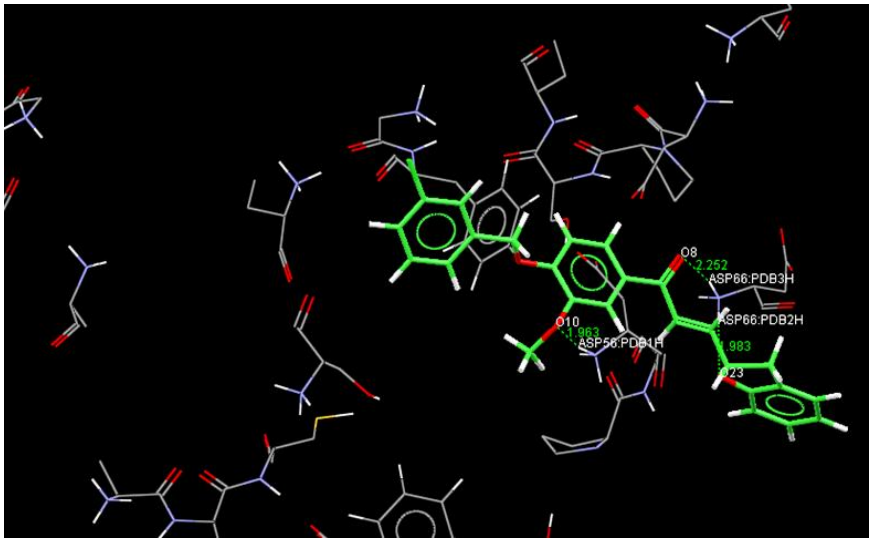
Docking of Compound i



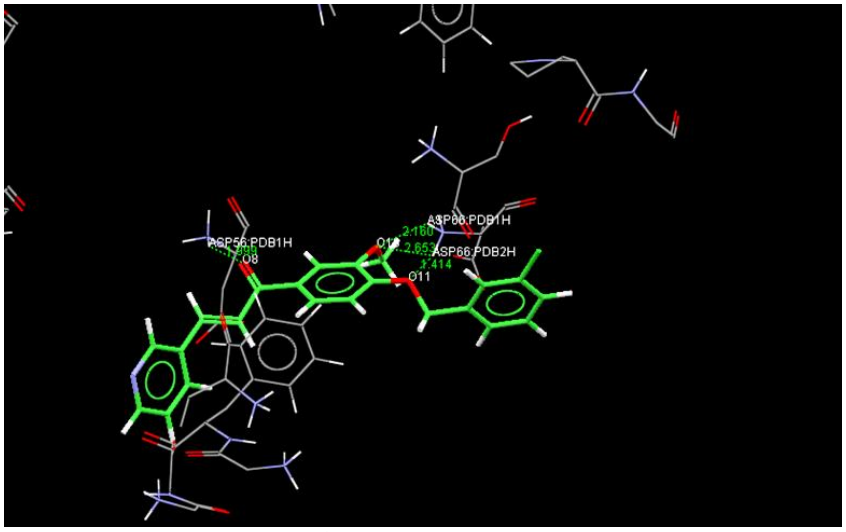
Docking of compound j



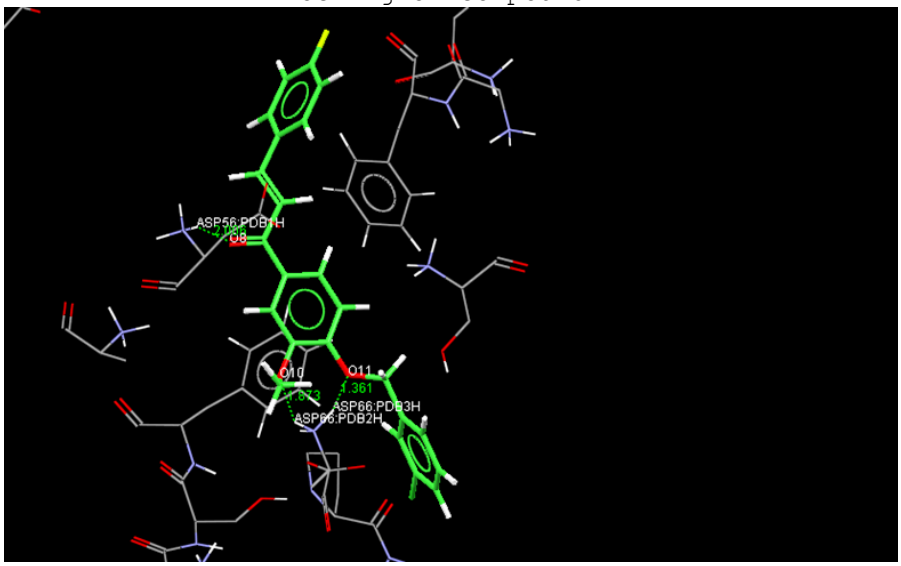
Docking of compound k



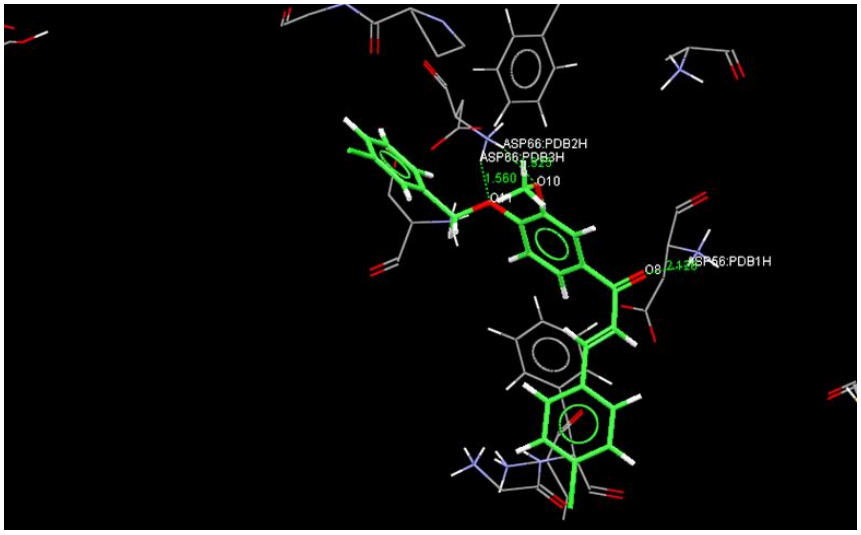
Docking of compound l



Docking of compound m



Docking of compound n



Docking of compound o

Fig 4a-40: Docking of compounds

The docked conformations revealed that all molecules were located in the hydrophobic binding pocket. In this study, all docked drugs were found to have some interactions between an oxygen atom of the drugs and target proteins. Moreover, these docked conformations also formed an H-bonding interaction within the active site (Table 1).

Table-1: Fitness score

Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)	Ligand name
29.94	13.48	22.20	0.00	-14.07	compound a
31.85	17.93	19.65	0.00	-13.10	compound b
26.48	11.92	21.82	0.00	-15.45	compound c
26.74	6.00	25.79	0.00	-14.72	compound d
31.84	12.00	24.44	0.00	-13.77	compound e
18.83	6.00	25.77	0.00	-22.61	compound f
26.17	6.60	23.57	0.00	-12.84	compound g
25.46	5.94	22.39	0.00	-11.27	compound h
28.81	5.19	25.22	0.00	-11.07	compound i
27.32	5.44	23.43	0.00	-10.33	compound j
26.47	5.29	21.80	0.00	-8.80	compound k
37.94	16.11	21.94	0.00	-8.33	compound l
26.27	4.80	22.72	0.00	-9.77	compound m
26.43	6.50	21.75	0.00	-9.98	compound n
27.56	5.46	24.21	0.00	-11.18	compound o

In the binding pocket, common H-bonding interactions were formed between all docked drugs and GLY 121, TYR 122, LYS 123, ALA 137. In order to explain the binding of these compounds, the H-bonding interactions with the other surrounding residues in the hydrophobic binding pocket were also investigated. In Figure 4, strong H-bonding interactions between the hydroxyl group (H12) of analogue and an oxygen atom of SER25 and another hydrogen bond between hydroxyl group (H11) and oxygen atom of ASP66. Two H-bonding interactions were also formed between Oxygen atom (O4) of analogues, ASP56 and CYS 44 of Enterotoxin A.

CONCLUSION

The docking results agreed well with the observed *in vitro* data, in which the anti-microbial activity of the analogues was higher than other drugs and formed five hydrogen bonds. The docking study revealed the binding orientation of compounds in the Enterotoxin A binding pocket surrounding the active site, which resulted in inhibition of enzyme activity. From these results we can conclude that compound e is one of the good inhibitory compounds of Enterotoxin A. The application of computational sciences to pharmaceutical research is a discipline, which is phenomenal.

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