DOI:10.7598/cst2018.1518
ISSN:2278-3458

Chemical Science Transactions
2018, **7(4),** 576-587

RESEARCH ARTICLE

Molecular Docking Study of Novel Aryl Imine Derivatives for Anti *Staphylococcus Aureus*

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Received 19 March 2018 / Accepted 10 April 2018

Abstract: In this work, we collected three dimensional structure of Sortase A from *Staphylococcus aureus* which plays an important role in structural stability of *staphylococcus aureus*. The protein structure was collected from PDB data bank. From the 3D structure of the protein, the targeted structure was developed. Docking studies was performed with designed compounds. The 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.

Keywords: Antibacterial activity, Docking studies, Sortase A**,** *Staphylococcus aureus*

Introduction

Sortase enzyme catalyzes transpeptidation reactions on the bacterial surface, utilizing protein precursors with *C*-terminal sorting signals as substrates[1]. *Staphylococcus aureus* Sortase A (SrtA), the prototypic transpeptidase of this class of enzyme[2,3], cleaves LPXTG motif-type sorting signals between the threonine (T) and the glycine (G) residues to generate an acyl enzyme intermediate[4]. Nucleophilic attack of the amino group of cell wall cross bridges resolves the acyl enzyme, forming an amide bond between the carboxyl group of the *C*-terminal threonine of surface proteins and the cell wall cross bridge of lipid II precursor molecules. The product of this reaction, surface protein linked to lipid II, is then incorporated into the cell wall envelope via the transpeptidation and transglycosylation reactions of peptidoglycan biosynthesis[5]. Twenty different surface proteins with LPXTG motif-type sorting signals have been identified in the staphylococcal genome sequence and deletion of the SrtA gene abolishes the cell wall anchoring and surface display of all sortase A substrates. As a result, staphylococcal SrtA mutants display significant defects in the pathogenesis of murine organ abscesses, infectious arthritis, or endocarditis. The genomes of most gram-positive bacteria encode two or more sortase enzymes, which fulfill different functions. For example, *S. aureus* Sortase B is involved in anchoring IsdC (iron-regulated

surface determinant C), a polypeptide with an NPQTN motif sorting signal, to the cell wall envelope[6]. Streptococcus pyogenes Sortases A and B both anchor surface proteins with LPXTG motif sequences to the envelope. These two Sortases appear to recognize unique surface protein substrates using the LPXTG motif as well as other features of cell wall sorting signals. Streptococcal SrtC2 recognizes surface protein substrates with QVPTGV motif sorting signals, consistent with the view that different Sortases recognize unique sets of substrates. Perhaps the most astonishing sortase-catalyzed reaction is the assembly of pili on the surface of corynebacteria, actinomycetales, enterococci, group B streptococci and pneumococci. For example, corynebacterial Sortases cleave precursor proteins in a manner that leads to the assembly of pili, high-molecular-weight polymerization products several microns long on the bacterial surface. Two domains of pilus surface proteins, the sorting signal and the pilin motif, are required for this reaction, which occurs in a Sortase-specific manner. This results in the assembly of different types of pili by dedicated pairs of Sortase enzymes and pilin subunit proteins.

Methodology

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

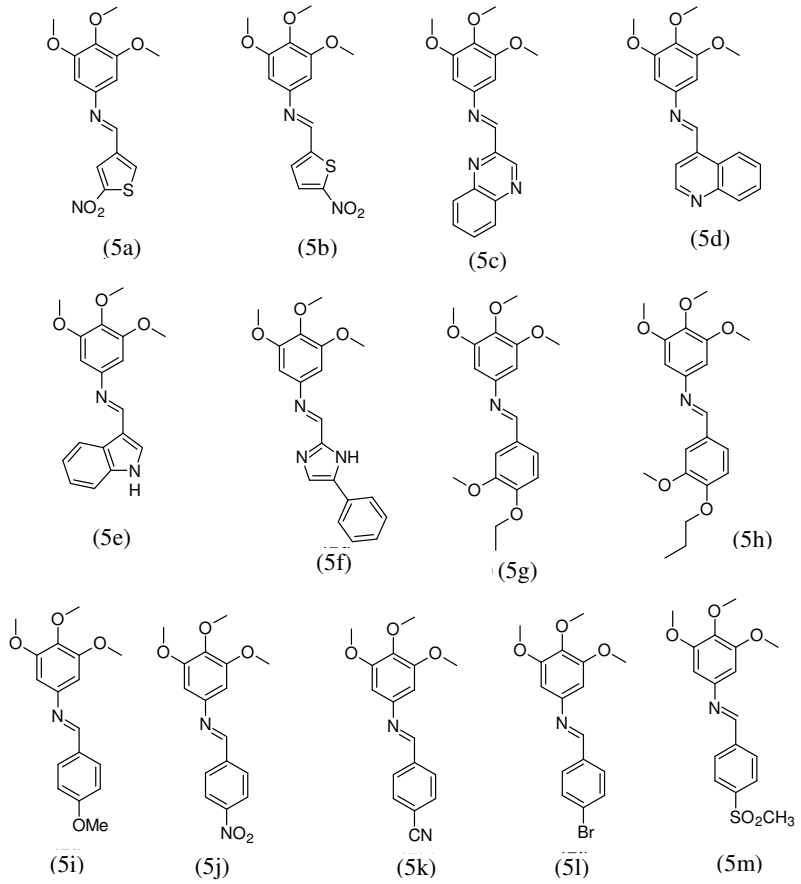


Figure 1. Compounds used for docking studies

To prepare the Sortase A from *staphylococcus*, the crystal structure was taken from the protein data bank (PDB_ID: 1IJA) (Figure 2).

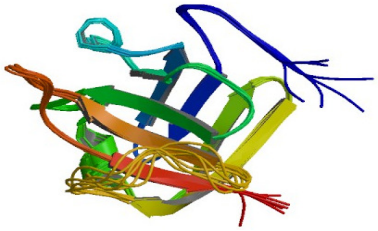


Figure 2. Structure of of Sortase A

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 Sortase A structure. The docking experiments were performed using the binding site of Sortase 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 Van der waals were employed. During docking, the default algorithm speed was selected and the ligand binding site in the of Sortase A was defined within a 10 A° radius with the centroid as CE atom of LYS356. 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[7-10].

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 Van der Waals energy (external vdw); 3.Ligand internal Van der 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.

Gold Score = 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 Sortase A was searched with CASTP server as shown in Figure 3. The residues included in active site were shown.

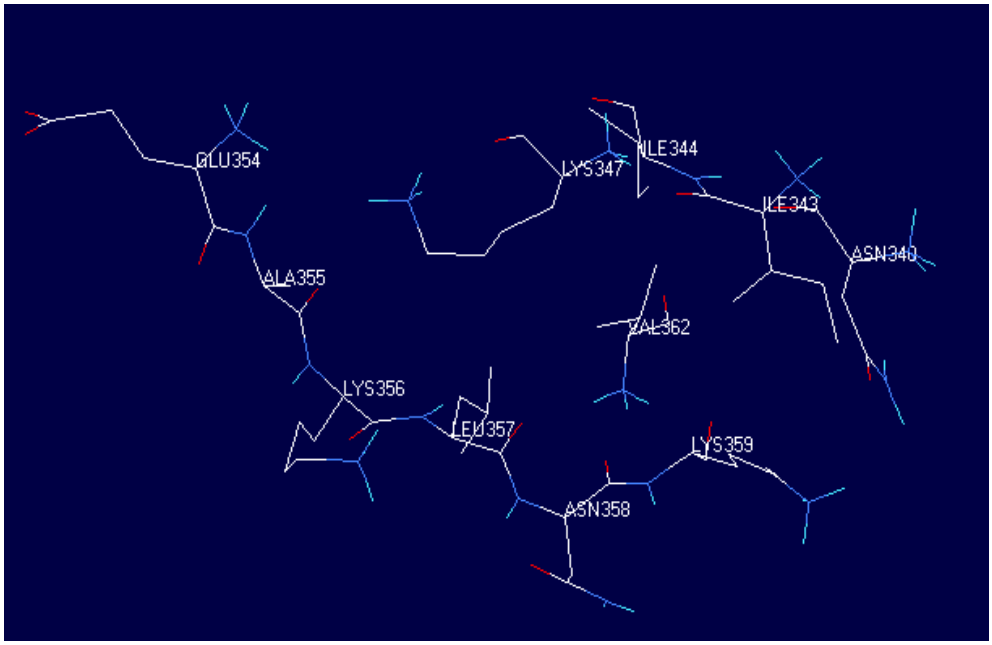
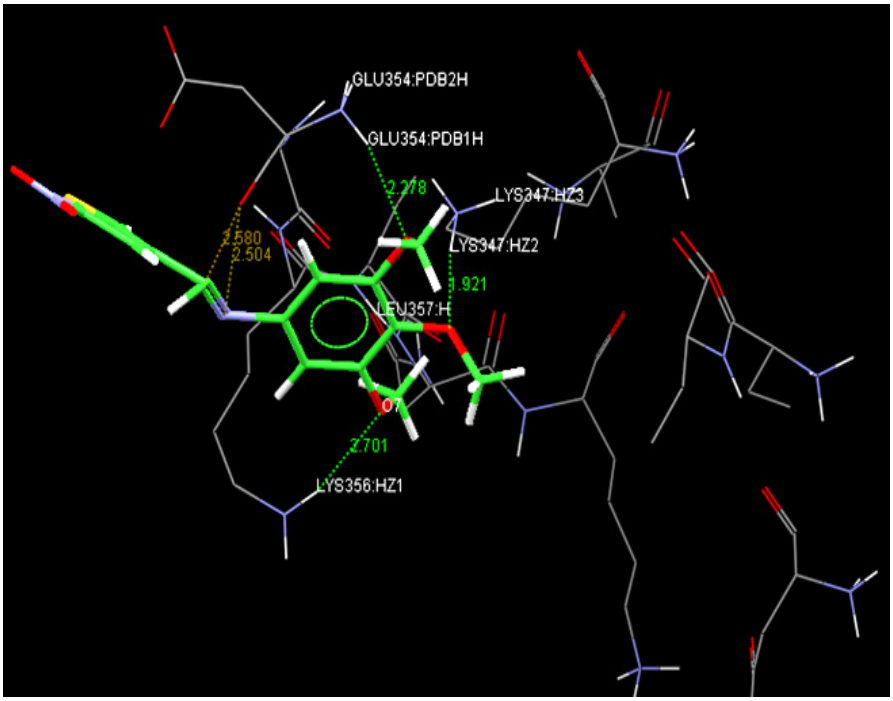


Figure 3. Active site of Sortase A

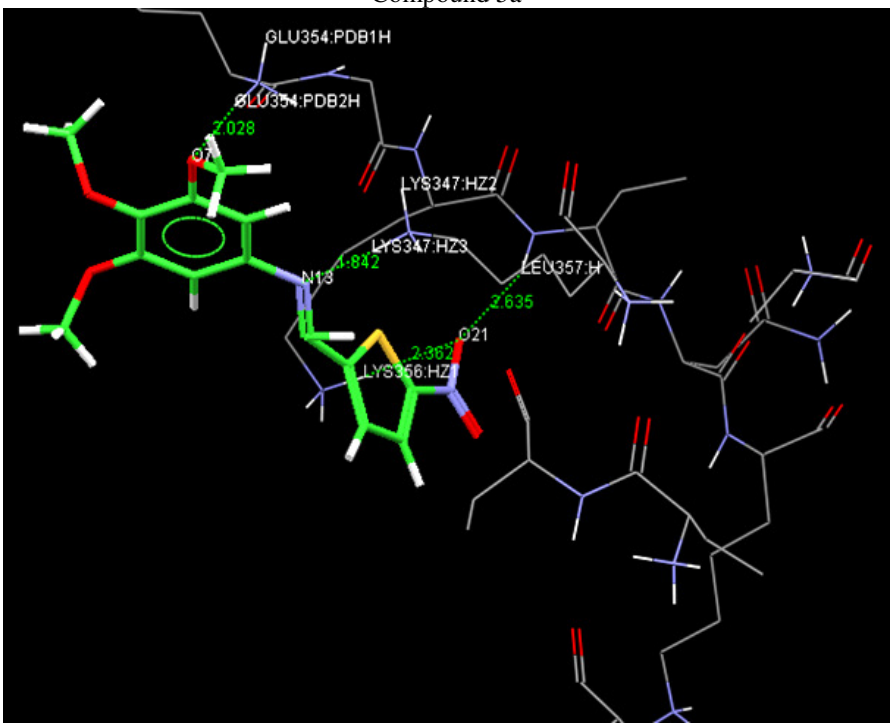
From the binding site analysis of Sortase A we identified that, the binding pockets are identical in all chains and the largest binding pocket was taken for further docking studies. The crystal structure of of Sortase A was similar hence we have taken as representative structure for docking studies. The docking of drugs into the active site of Sortase 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.

Molecular docking study

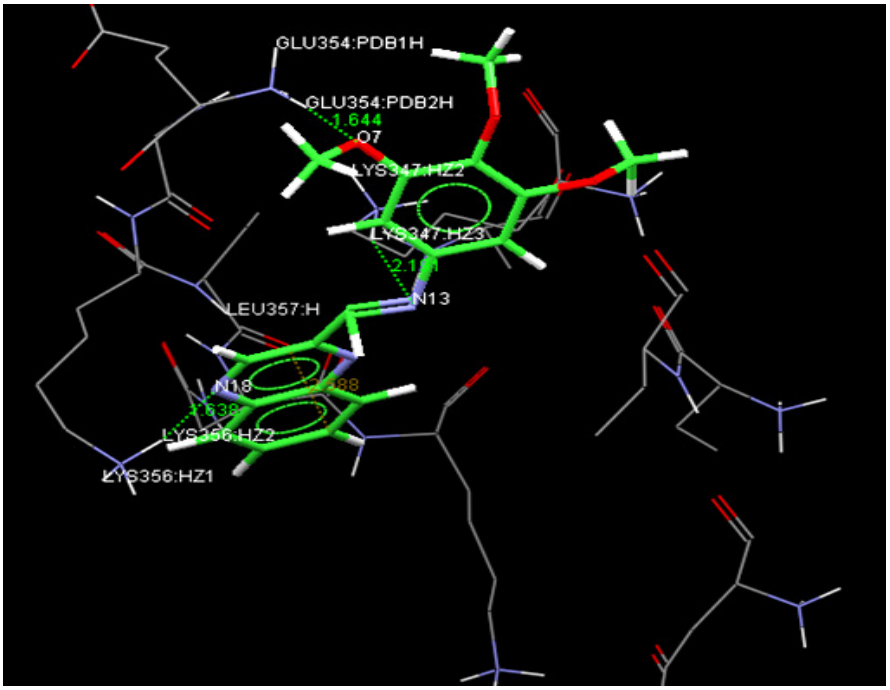
Structure-based drug design begins with the identification of a molecular target such as a protein such as of Sortase A in this study. This structure is then used as a blueprint for the drug design of a lead compound. The compounds are modelled for their fit in the active site of the target, considering 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 1IJA binding site are shown in Figure 4.



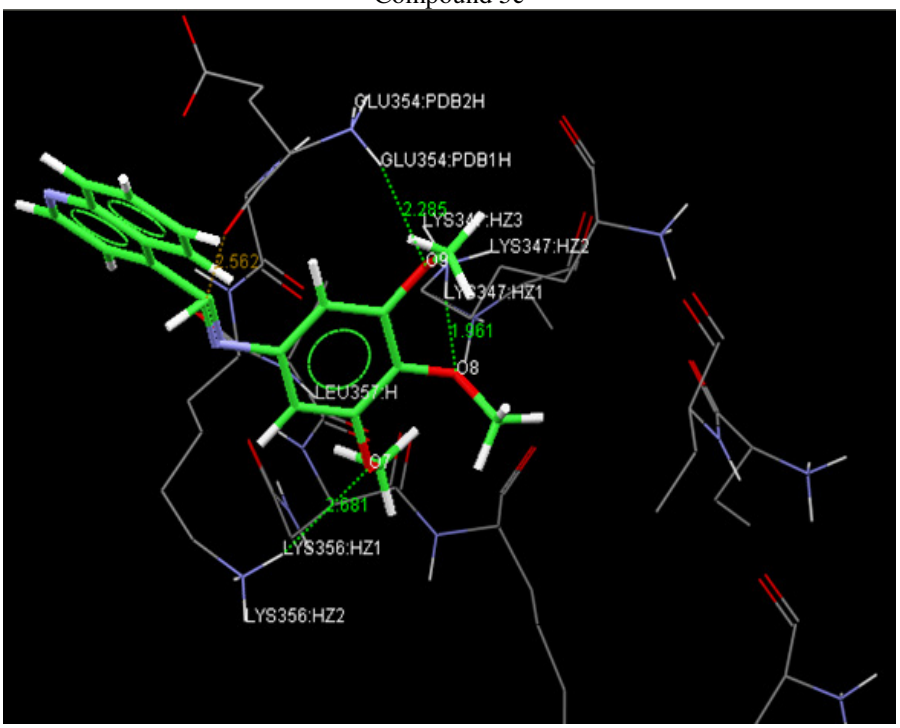
Compound 5a



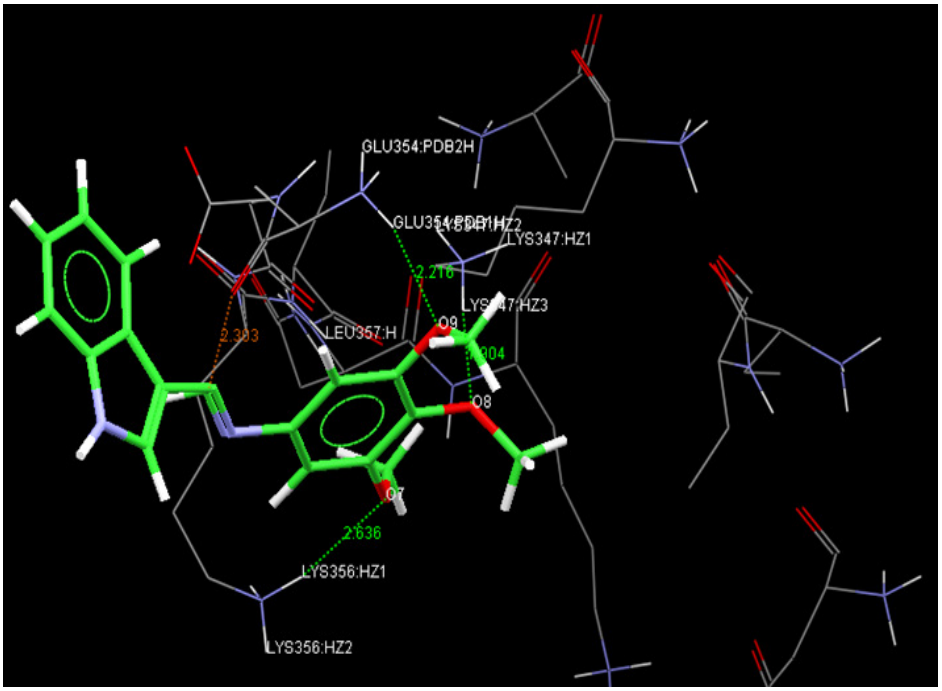
Compound 5b



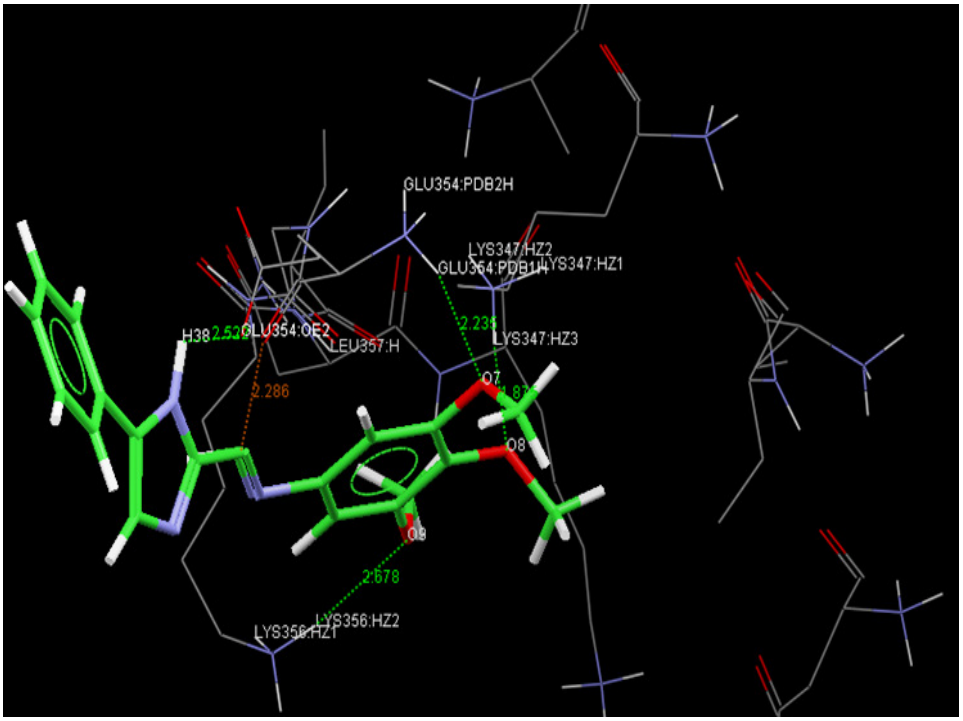
Compound 5c



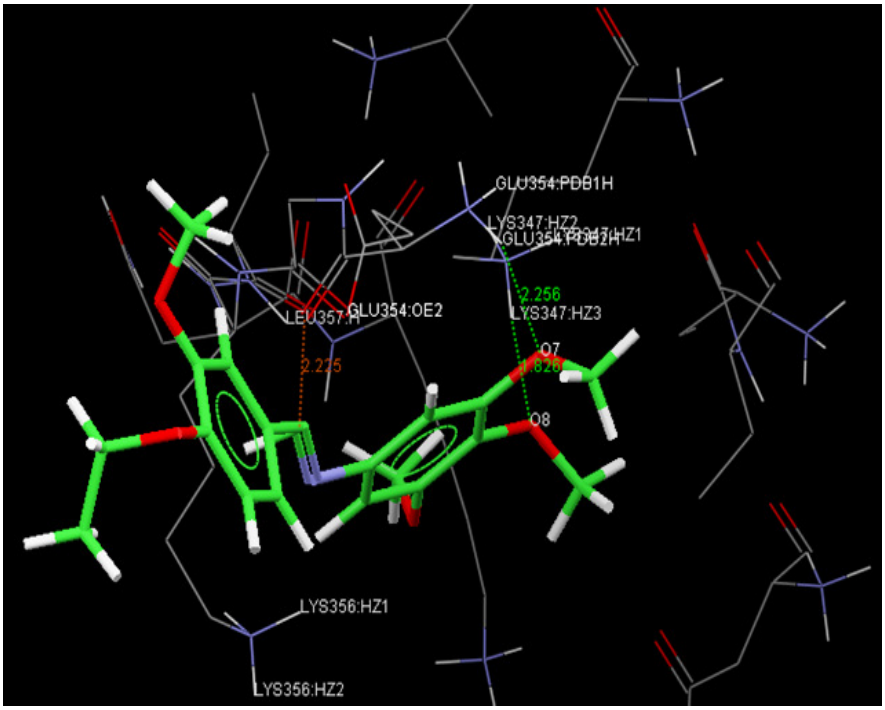
Compound 5d



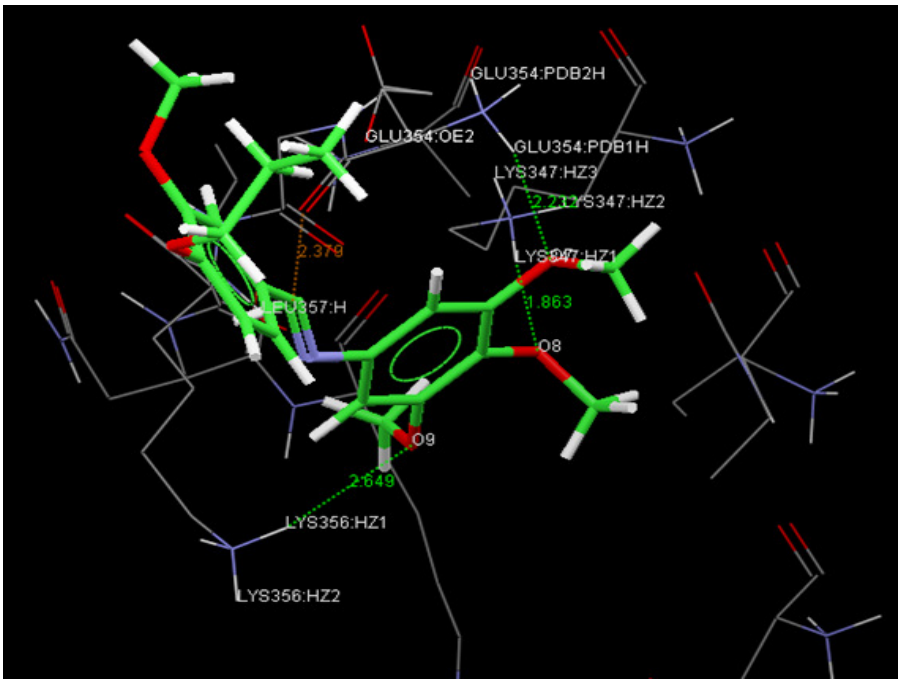
Compound 5e



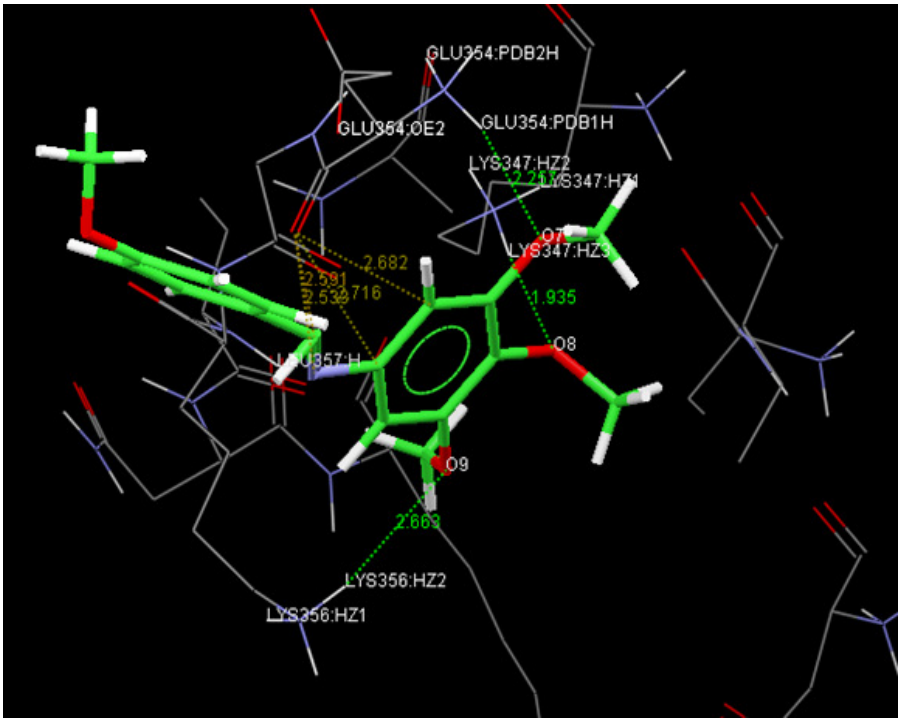
Compound 5f



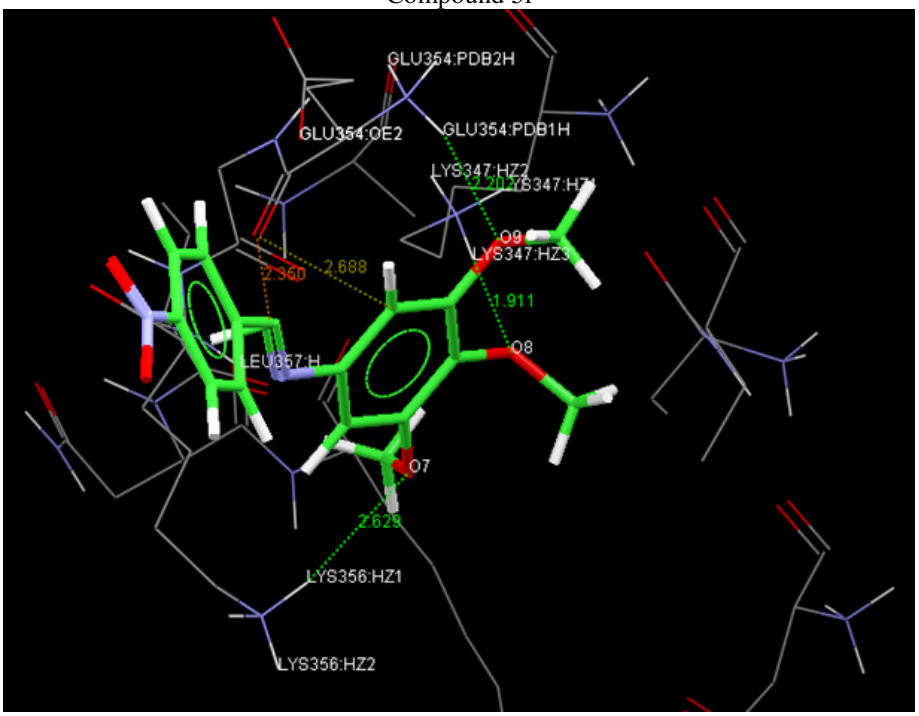
Compound 5g



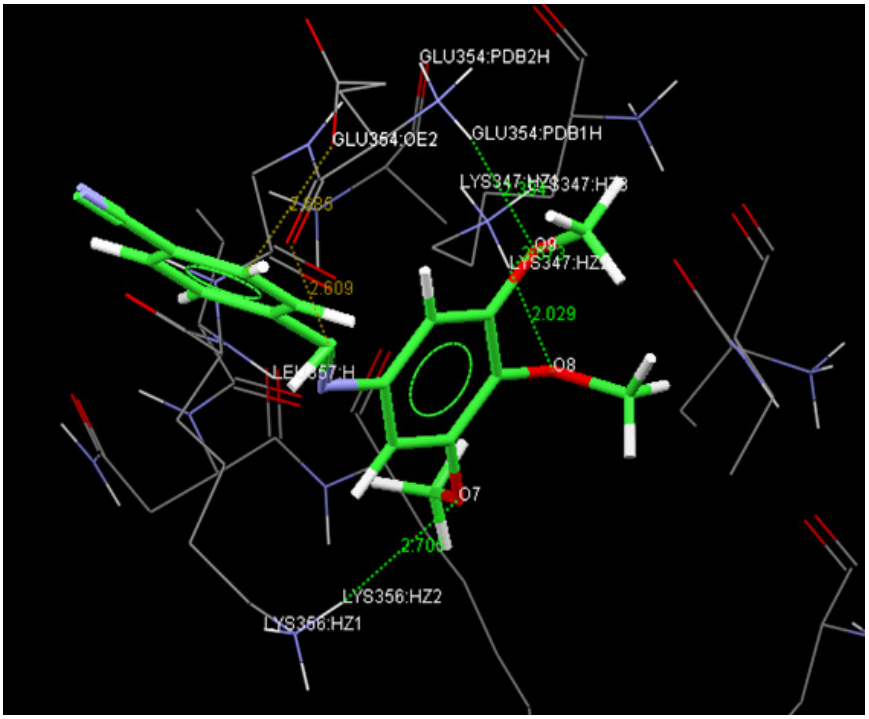
Compound 5h



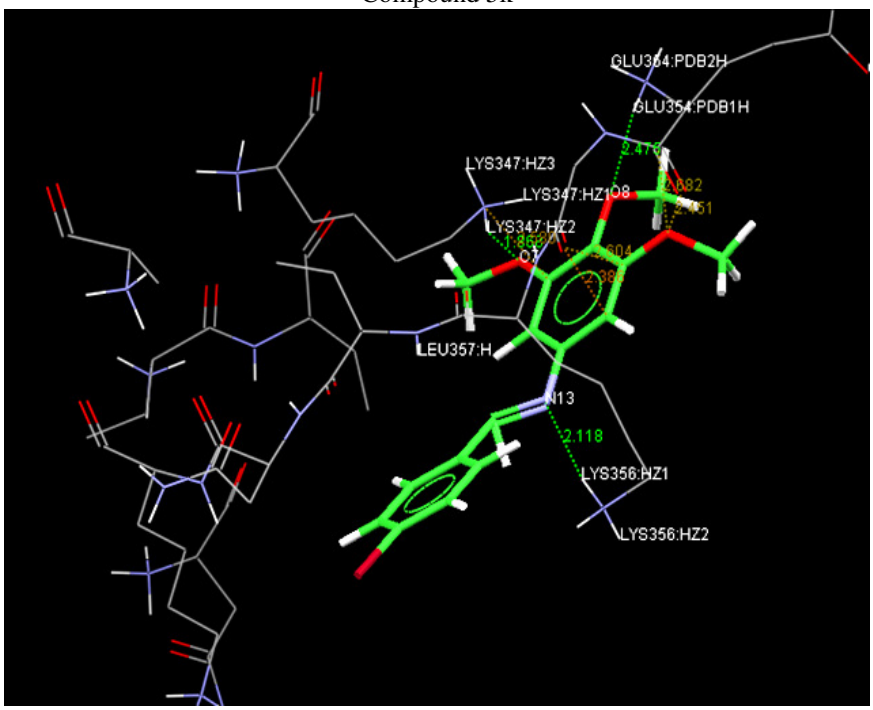
Compound 5i



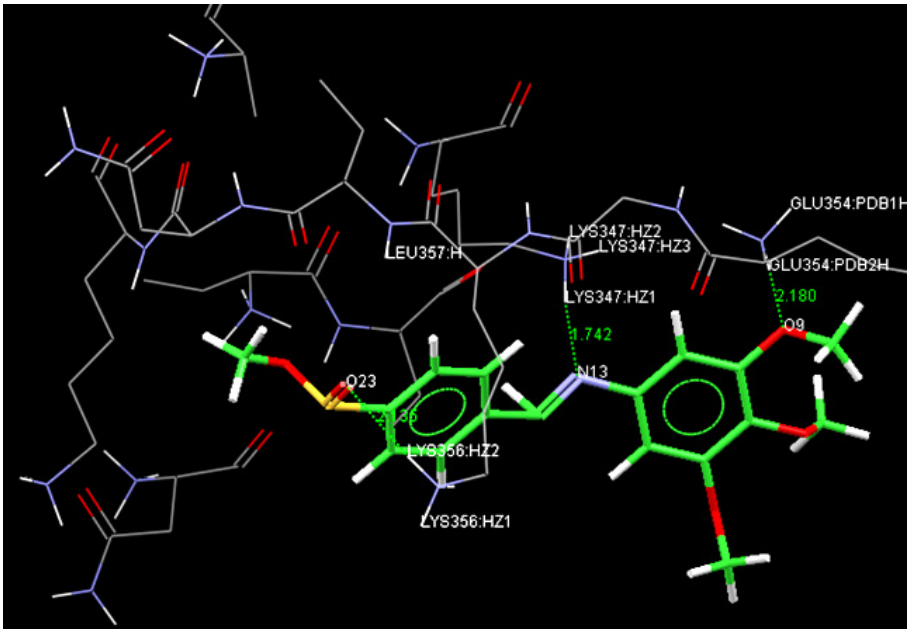
Compound 5j



Compound 5k



Compound 5l



Compound 5m

Figure 4. Docking of compounds (**5a-5m)**

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
27.00	12.72	19.01	0.00	-11.87	5a
28.73	18.00	16.53	0.00	-12.00	5b
26.96	12.04	19.05	0.00	-11.27	5c
26.52	13.22	19.19	0.00	-13.09	5d
29.10	12.97	19.99	0.00	-11.35	5e
26.11	12.44	18.55	0.00	-11.83	5f
20.30	11.19	18.66	0.00	-16.54	5g
21.59	12.60	18.91	0.00	-17.02	5h
22.74	13.01	17.55	0.00	-14.41	5i
23.13	13.05	17.34	0.00	-13.76	5j
24.39	13.75	17.38	0.00	-13.26	5k
26.32	14.02	19.83	0.00	-14.96	5l
21.69	18.00	17.37	0.00	-20.19	5m

In the binding pocket, common *H*-bonding interactions were formed between all docked drugs and LYS347, GLU 354, LYS356 and LEU357. 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**, compound **5e** showed highest docking score (Table 1) than other compounds. Strong *H*-bonding interactions

between the O7, O8 and O9 of compound **5e** with LYS347, GLU 354 and LYS356 amino acids of Sortase A. *H*-bonding interactions were also formed between oxygen atom of analogues and LYS347, GLU 354 and LYS356, of Sortase 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 three hydrogen bonds. The docking study revealed the binding orientation of compounds in the Sortase. A binding pocket surrounding the active site, which resulted in inhibition of enzyme activity. From these results we can conclude that compound **5e** is one of the good inhibitory compounds docked to Sortase A. The application of computational sciences to pharmaceutical research is a discipline, which is phenomenal.

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