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DESIGN AND SYNTHESIS OF PEPATALINE DERIVATIVES FOR ANTI-MRSA ACTIVITY

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ABSTRACT: A variety of highly efficient methodologies for the synthesis of aromatic heterocycles and their derivatives have been reported in the past, the development of novel methodologies is in continuous demand. Particularly, development of new synthetic approaches toward heterocycles, aiming at achieving greater levels of molecular complexity and better functional group compatibilities in a convergent and atom economical fashions from readily accessible starting materials and under mild reaction conditions, is one of the major research endeavors in modern synthetic organic chemistry. Transition metal-catalyzed transformations, which often help to meet the above criteria, are among the most attractive synthetic tools. In the present research a series of 20 pepataline Derivatives were designed and evaluated docking studies were performed using Open eye software against antibacterial and antifungal proteins. The docking results showed that highest value (-200.59K.cal/mol) for the compound 3 in antibacterial activity. The top six compounds which showed highest docking scores were synthesized. The compounds were isolated with TLC, purified with column chromatography and evaluated by spectroscopic method.

KEYWORDS: Pepataline Derivatives, Docking, anti bacterial activity, anti fungal activity.

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1.INTRODUCTION

Staphylococcus aureus is a Gram-positive coccal bacterium that is a member of the Firmicutes, and is frequently found in the human respiratory tract and on the skin. It is positive for catalase and nitrate reduction [1-3]. Although *S. aureus* is not always pathogenic, it is a common cause of skin

infections (e.g. boils), respiratory disease (e.g. sinusitis), and food poisoning. Disease-associated strains often promote infections by producing potent protein toxins, and expressing cell-surface proteins that bind and inactivate antibodies [4, 5]. The emergence of antibiotic-resistant forms of pathogenic *S. aureus* (e.g. MRSA) is a worldwide problem in clinical medicine. *S. aureus* is responsible for many infections but it may also occur as a commensal [6]. The presence of *S. aureus* does not always indicate infection. *S. aureus* can survive from hours to weeks, or even months, on dry environmental surfaces, depending on strain. *S. aureus* can infect tissues when the skin or mucosal barriers have been breached [7-9]. This can lead to many different types of infections including furuncles and carbuncles (a collection of furuncles). *S. aureus* infections can spread through contact with pus from an infected wound, skin-to-skin contact with an infected person by producing hyaluronidase that destroys tissues, and contact with objects such as towels, sheets, clothing, or athletic equipment used by an infected person [10]. Deeply penetrating *S. aureus* infections can be severe[11-15]. Prosthetic joints put a person at particular risk of septic arthritis, and staphylococcal endocarditis (infection of the heart valves) and pneumonia. Strains of *S. aureus* can host phages, such as Φ-PVL (produces Panton-Valentine leukocidin), that increase virulence [16-20]. *S. aureus* is extremely prevalent in persons with atopic dermatitis. It is mostly found in fertile, active places, including the armpits, hair, and scalp. Large pimples that appear in those areas may exacerbate the infection if lacerated.

2. MATERIALS AND METHODS

Docking studies

The initial model of Bacterial membrane receptor was built by using homology-modeling methods and the MODELLER software. The sequence of Bacterial membrane receptor was obtained from Uniprot. The query sequence from *Staphylococcus aureuss* was submitted to domain fishing server for Bacterial membrane receptor domain prediction. The predicted domain *was* searched to find out the related protein structure to be used as a template by the BLAST (Basic Local Alignment Search Tool) program against PDB (Protein Data bank). Sequence that showed maximum identity with high score and less e-value was aligned and was used as a reference structure to build a 3D model for Bacterial membrane receptor. The co-ordinates for the structurally conserved regions (SCRs) for Sortase A were assigned from the template using multiple sequence alignment, based on the Needleman-Wunsch algorithm. Finally, the structure having the least energy with low RMSD (Root Mean Square Deviation) was used for further studies. In this step, the quality of the initial model was improved. The final structure obtained was analyzed by Ramachandran's map using PROCHECK (Programs to check the Stereo chemical Quality of Protein Structures) and environment profile using ERRAT graph (Structure Evaluation server). This model was used for the identification of active site and for docking of the substrate with the enzyme.

Active site Identification

Active site of Bacterial membrane receptor was identified using CASTp server. A new program, CASTp, for automatically locating and measuring protein pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory. CASTp 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

MVD (Molgrow Virtual Docker) a genetic algorithm (GA) based software, mainly utilizes an evolutionary strategy involving 3 genetic operators; cross overs, mutations and migrations. MVD imports the partial flexibility to proteins and full flexibility to inhibitors. The compounds are docked into the active site and the interaction of these ligands with the active site residues are thoroughly studied using calculations of molecular mechanics. 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. Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0A° (dH-X) for hydrogen bonds and 6.0A° for vanderwaals were employed. The default algorithm speed was selected and the inhibitor binding site in Bacterial membrane receptor was defined within a 10A° radius with the centroid as HH atom of TYR75, HIS89 and GLN120 respectively. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of inhibitors were within 1.5A° RMSD. After docking, the individual binding poses of each inhibitor were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of each inhibitor was selected.

Fitness function

The four components vig, Protein-ligand hydrogen bond energy (external H-bond); Protein-ligand vanderwaals energy (external vdw); Ligand internal vanderwaals energy (internal vdw); and Ligand intramolecular hydrogen bond energy (internal- H- bond) were considered for calculating the fitness function of GOLD score. The protein-ligand hydrophobic contact was encouraged by making an empirical correction by multiplying external vdw score with 1.375. The fitness function has been optimized for the prediction of ligand binding positions.

AntiBacterial and Anti fungal Activity

Determination of zone of inhibition method

Preparation of Discs

Whatman No: 1 filter paper discs of 6mm diameter are prepared and autoclaved by keeping in a clean and dry Petri plate. The filter paper discs were soaked in plant extracts for 6 hours are taken as test material. After 6 hours the discs were shade dried. The concentrations of plant extracts per

disc are accounted for 0.1 grams/1ml. Subsequently they are carefully transferred to spread on cultured Petri plates. Filter paper discs immersed in ethanol, benzene, distilled water are prepared and used as control. The medium was steamed for 30 min neutralized at 37°c and steamed for half an hour and filtered. The medium was sterilized at 15 lbs for 20 min at 121ºc.

Testing of antimicrobial and anti fungal activity

To test the antimicrobial activity on agar plates, LB agar medium was prepared using the ingredients mentioned above. The medium was sterilized at 121°c for 30 min's. The agar test plates were prepared by pouring about 15ml of the medium into 10cm Petri dishes under aseptic condition and left undisturbed for 2hrs to solidify the medium [21-24]. 1ml of inocculum (containing suspension) of P.aeruginosa and Sta.aureus was poured to the respective plates separately containing solidified agar media. Six replicates were maintained. The prepared sterile whatman no :1 filter paper discs of 6mm diameter were impregnated with the extracts and shaken thoroughly and this test plates incubated for a period of 48 hrs in BOD at 37ºc for the development of inhibitory zones and the average of 2 independent readings for each organism in different extracts were recorded. The control Petri plates and also maintained above respective cultures

Measuring the diameter of inhibition zone

The inhibition zones were lead after 1 day at 37ºc for bacteria. The diameter of the inhibition zone was measured and recorded with the aid of plastic ruler. 7 paper discs placed in 1 Petri plate.

3. RESULTS AND DISCUSSION

The first step in this synthesis involve crossed aldol condensation between the acetophenone or its derivatives (I a-c) with the isatin in basic medium to give the aldol products, 3-hydroxy- 3-phenacyloxindoles (IIa-c) which then dehydrated easily by using dilute alcoholic hydrochloric acid, to yield the expected α, β-unsaturated carbonyl compounds, 3- phenacylidene-2-indolinones (IIIa-c). Nucleophilic Michael addition of hydrazine or phenyl hydrazine or phenylthiourea to the above compounds leads to the formation of spiro-5-(-3- indolyl-2-one)-3-phenylpyrazoline, spiro-5-(-3-indolyl-2-one)-2, 3-diphenylpyrazolin-3-ene, and spiro-6-(-3-indolyl-2-one)-3, 4-diphenylpyrimidinethione,(IVa-c;Va-c;VIa-c) respectively. The structures of these products were established by physical and spectral methods.

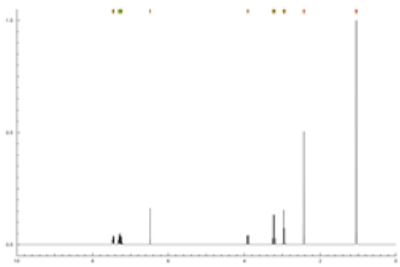

Fig 1: 1H-NMR (SOLUTION-CDCl3, 250 MHz)

δ 1.45 (s, 3H, CH3), 1.48 (s, 3H,CH3), 2.13 (s, 3H, CH3), 3.58 (s, 2H, CH2-N=), 4.32 (t, 1H, J = 9

Hz, CH-Ar), 4.75 (dd, 2H, J = 9,2 Hz, CH2-CH), 5.85 (s, 1H, =CH), 7.16-7.37 (m, 5H, H-Ar), 7.52 (s, 1H, NH), 13.80 (s, 1H, OH) (Fig 1).

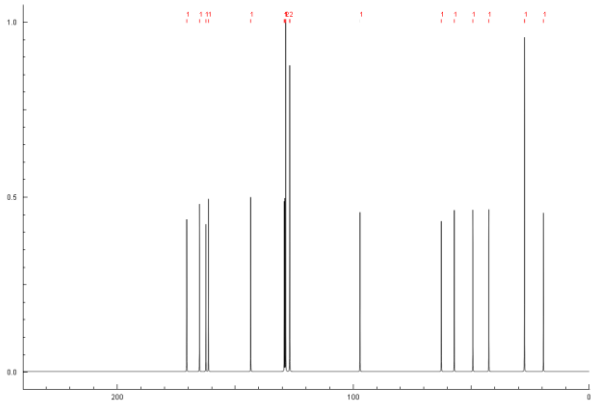

Fig 2: 13C-NMR (SOLUTION-CDCl3):

δ 20, 22, 30, 52, 53, 55, 62, 96, 108, 128, 129, 132, 143, 163, 164, 179, 184; MSm/z (%): 326 ([M·]+, 6), 235 (19) , 181 (60), 151 (27), 136 (14), 43 (37) (Fig 2).

19) 3-[2,2-Dimethyl-7-(4-methylphenyl)-3,6-dihydro-2H-1,4-diazepin-5-yl]-4-hydroxy-6-methyl-2Hpyran-2-one

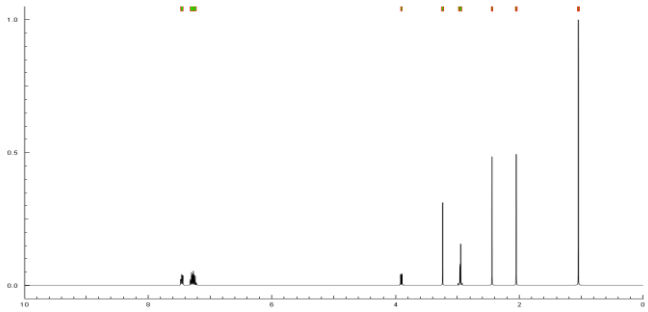

Fig 3: 1H-NMR (SOLUTION-CDCl3, 250 MHz)

δ 1.37 (s, 3H, CH3), 1.38 (s,3H, CH3), 2.14 (s, 3H, CH3), 2.24 (s, 3H, CH3), 3.54 (s, 2H, CH2-N=), 4.17 (t, 1H, J = 9 Hz, CH-Ar),4.70 (dd, 2H, J = 9, 2 Hz, CH2-CH), 5.75 (s, 1H, =CH), 7.00-7.10 (d, 2H, J = 8.3 Hz, H-Ar), 7.10-7.20(d, 2H, J = 8.1 Hz, H-Ar), 7.80 (s, 1H, NH), 14.03 (s, 1H, OH) (Fig 3).

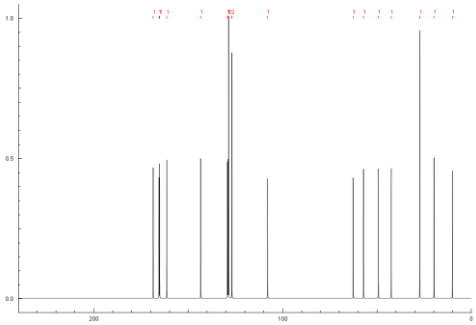

Fig 4: 13C-NMR (CDCl3):

δ 20, 21, 32, 51,53, 55, 61, 95, 108, 128 - 129, 134, 146, 163, 164, 178, 18; MS m/z (%): 340 ([M·]+, 2), 235 (16), 181(40), 151 (4), 136 (1), 43 (70).

8)-[7-(4-bromophenyl)-2,2-dimethyl-2,3,6,7-tetrahydro-1H-1,4-diazepin-5-yl]-4-hydroxy-6-methyl-2Hpyran-2-one

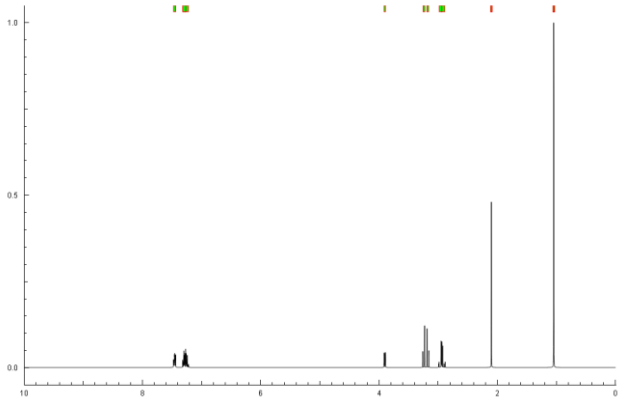

Fig 5: 1H-NMR (SOLUTION-CDCl3, 250 MHz)

δ 1.44 (s, 3H, CH3), 1.47(s, 3H, CH3), 2.15 (s, 3H, CH3), 3.62 (s, 2H, CH2-N=), 4.36 (t, 1H, J = 9 Hz, CH-Ar), 4.70 (dd, 2H,J = 9, 2 Hz, CH2-CH), 5.90 (s, 1H, =CH), 7.10-7.20 (m, 2H, H-Ar), 7.35-7.45 (m, 2H, H-Ar), 7.99 (s,1H, NH), 13.79 (s, 1H, OH) (Fig 6).

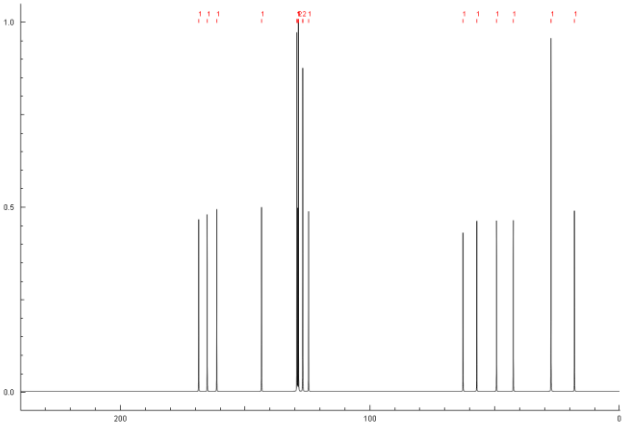

Fig 6: 13C-NMR (SOLUTION-CDCl3)

δ 19, 20, 34, 53, 54, 56, 60, 95, 107, 130, 131, 135,145, 163, 165, 178, 181; MS m/z (%): 371 ([M·]+, 0.5), 235 (18), 181 (20), 151 (3), 136 (5), 43 (66).

The Drug molecules Docking with the active site of bacterial membrane receptor used for Docking (Open Eye)

Docking of the inhibitors Drug molecules with 1VQQ receptor was performed using FRED v 2.1, which is based on Rigid Body Shape-Fitting (Open Eye Scientific Software, Santa Fe, NM). This program generates an ensemble of different rigid body orientations (poses) for each compound conformer within the binding pocket and then passes each molecule against a negative image of the

binding site. Poses clashing with this 'bump map' are eliminated. Poses surviving the bump test are then scored and ranked with a Gaussian shape function (Fig 7). We defined the binding pocket using the ligand-free protein structure and a box enclosing the binding site. This box was defined by extending the size of a cocrystalized ligand by 4 Å (add box parameter of FRED). This dimension was considered here appropriate to allow, for instance, compounds larger than the co crystallized ones to fit into the binding site. One unique pose for each of the best-scored compounds was saved for the subsequent steps (Fig 8-10). The compounds used for docking was converted in 3D with OMEGA (same protocol as above) (Open Eye Scientific Software, Santa Fe, NM). To this set, the substrate (generation of multiconformer with Omega) corresponding to the modeled protein were added [25-32].

Protein structures

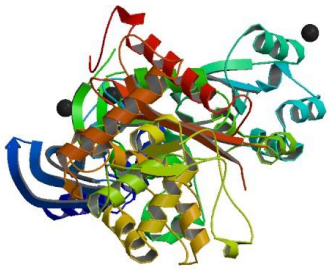

Fig 7: PBP2A [*Staphylococcus aureus*]

Active site Identification of Penicillin Binding Protein 2a prediction by CASTp

After selecting receptor from PDB and isolated the A-chain in SPDBV, the possible binding sites of Penicillin Binding Protein 2a receptor was searched based on the structural comparison of template and the model build and also with CASTp server and was shown in Figure-5.2.1 ,the residues are TYR18, TYR21, LYS22, GLN25, ARG26, ARG98, GLY101, ASP102, PHE104, SER105, ARG106, TYR108, ARG109, ASP111, PHE112, ALA113, MET115, SER116, GLN118, LEU119, ARG129, THR132, VAL133, GLU136, LEU137, ARG146, VAL148, ALA149, GLU152, PHE153, GLY155, VAL156, MET157, VAL159, GLU160 (Fig 8).

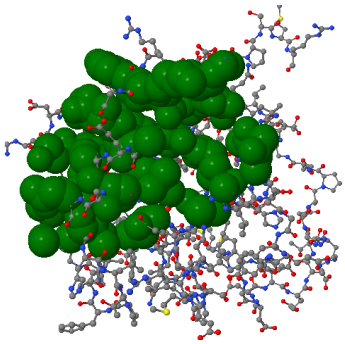

Fig 8: Representing active site Pockets of the Penicillin Binding Protein 2a shows highest area and volume

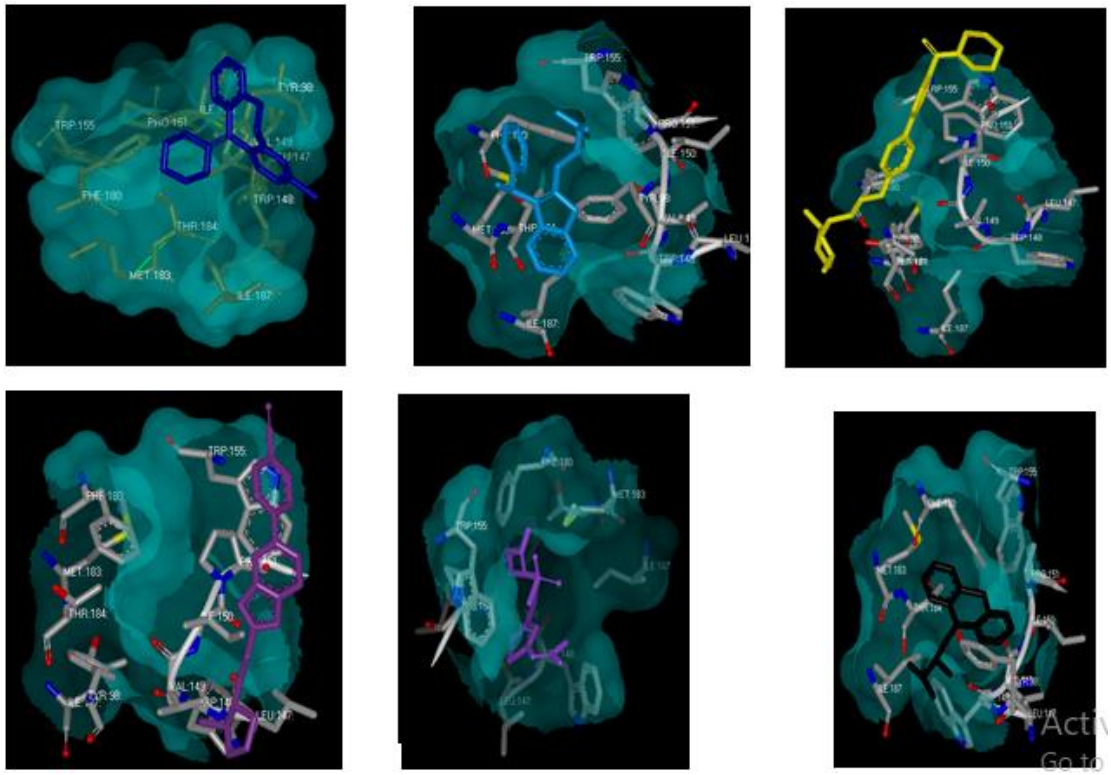

Fig 9: Docking studies of derivatives with receptor

Table 1: Docking scores of receptor

S. No	Derivatives of Primaquine	Chem scores	Chemgauss2 scores	Plp scores	Screen scores	Shapeguass Scores	Total Scores
1	**Derivative-1**	0.86	-51.47	-33.20	-73.25	-376.31	-157.06
2	**Derivative-2**	4.12	-49.99	-28.96	-79.33	-395.59	-154.16
3	**Derivative-3**	**-12.42**	**-50.39**	**-42.20**	**-95.45**	**-383.54**	**-200.46**
4	**Derivative-5**	-0.92	-53.79	-12.32	-61.16	-405.89	-128.19
5	**Derivative-9**	1.17	-51.51	-31.35	-76.79	-387.49	-158.48
6	**Derivative-12**	3.44	-51.07	-32.35	-80.99	-390.00	-160.97
7	**Derivative-13**	-0.86	-60.45	-32.09	-64.39	-435.50	-157.79
8	Derivative-14	2.55	-45.55	-15.63	-56.70	-380.78	-115.33
9	**Derivative-17**	2.29	-43.69	-24.54	-66.09	-392.23	-132.03
10	**Derivative-18**	0.38	-48.92	-21.45	-84.08	-398.94	-154.07
11	**Derivative-19**	3.47	-57.09	-29.39	-62.92	-402.50	-145.93

The total energies of Chem scores, Chemguass scores, Plp scores and shapeguass scores of the best-docked conformations of 1VQQ receptor.

Antimicrobial activity

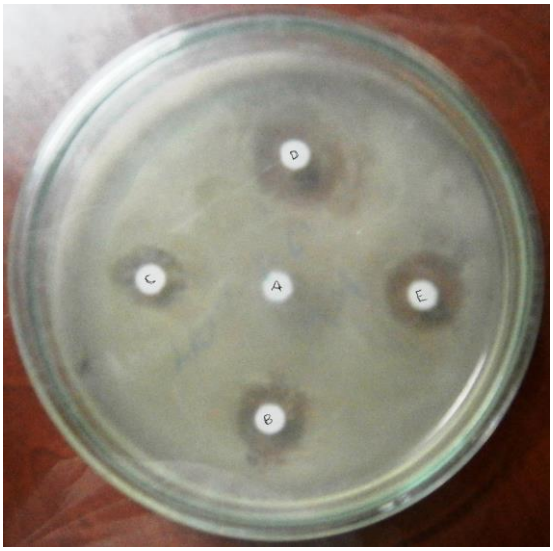

Fig 10: anti bacterial studies of derivatives

A: METHICILLIN

B: SYNTHESIZED COMPOUND1

C: SYNTHESIZED COMPOUND2

D: SYNTHESIZED COMPOUND3

E: SYNTHESIZED COMPOUND4

4. CONCLUSION

In this work we have synthesised pepataline Derivatives and all the compounds synthesized were characterized by spectral means and are evaluated for their antibacterial and antifungal. Bacterial membrane receptor (*Staphylococcus aureus*) involved in a variety of physiological actions of bacteria and fungi. In this work, we have constructed a 3D model of domain, using the SWISS-Model method and obtained a refined model after energy minimization. The final refined model was further assessed by Prosite and PROCHECK program, and the results show that this model is reliable. The stable structure is further used for docking with the 20 pepataline Derivatives. Docking results indicate that conserved amino-acid residues bacterial membrane receptor main play an important role in maintaining a functional conformation and are directly involved in donor substrate binding. The interaction between the domain and the inhibitors proposed in this study are useful for understanding the potential mechanism of domain and the inhibitor binding. As is well known, hydrogen bonds play important role for the structure and function of biological molecules. In this study it was found that, TYR 130, LEU 146, ILE 197 are conserved in this domain and may be important for structural integrity or maintaining the hydrophobicity of the inhibitor-binding pocket. The molecule 3 showed best docking results with target protein. The possible experimental values were identified from the docking results.

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CONFLICT OF INTEREST

Authors declare that they don't have any conflict of Interest

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