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Exploring the ability of *Streptomyces* antibiotics to combat Methicillin resistant *Staphylococcus aureus* using insilico studies

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ABSTRACT

Human Pathogens such as Methicillin resistant Staphylococcus aureus [MRSA] are becoming notorious as they confound the tools that are used to treat them. This owes to the enormous potential of these dreadful pathogens to combat against most of the available antibiotics. This raises the need for the discovery and development of novel antimicrobials that have the ability to demolish MRSA. The present study focuses on the exploration of antimicrobial activity of Streptomyces antibiotics to combat MRSA using docking studies. The Streptomyces antibiotic, Polymyxin B is found to have the potency of inhibiting the pathogen on acting upon a particular drug target. Thus the findings from the study can pave a novel way to treat the fatal pathogen.

Keywords: MRSA, Docking, Antimicrobials

INTRODUCTION

Antibiotics are the low molecular mass microbial metabolites which at low concentrations inhibit other microorganism and act as first line of defense against many diseases. These are endowed in many of the biological activities such as that of antibiotics, toxins, bioregulators and signaling agents **[16]**. The discovery, development and clinical exploitation of these antibiotics have revolutionized the field of medicine, industry and farming to a greater extent **[20]**. In recent trends, the resistance of pathogenic microorganism to common antibiotics has assumed a worrisome dimension. This drastic increment in antibiotic resistance is mainly due to the abuse of common antibiotics by the users and uncomplimentary fake drugs in circulation **[1].**

Consequently, diseases caused by the opportunistic pathogens such as *Staphylococcus aureus* are becoming increasingly difficult to treat as the resistant determinant genes they possess are notorious because they confound the tools that are used to treat the disease **[2].** *Staphylococcus aureus, a* non-motile, non-spore forming facultative anaerobe is a major pathogen of increasing importance due to their ability to resist against antibiotics **[11].** Particularly, Methicillin resistant *Staphylococcus aureus* is found to be the major cause of health- care associated and community- associated infections **[15].**

Actinomycetes are found to produce about half of the discovered bioactive secondary metabolites, notably antibiotics, anti-tumor agents, immunosuppressive agents and enzymes. They are the most economically and biotechnologically valuable prokaryote and are exploited for the production of novel secondary metabolites **[13]**.

Among 43,000 bioactive natural products, approximately 23,000 are bioactive metabolites produced by microorganism and over 10,000 of them are produced by Actinomycetes. About 74% of all actinomycetales products and over 80% of the rare actino products exhibit antibacterial or antifungal activity **[5].**

Streptomyces belonging to the bacterial order Actinomycetales is a soil inhabiting filamentous bacterial genus capable of producing a variety of secondary metabolites namely antibiotics. It is proclaimed as a model prokaryote for the study of multicellular differentiation and secondary metabolism **[17]**. Among 8,700 antibiotics produced by Actinomycetales, it was reported that 6,550 are produced by *Streptomyces* species representing 73% of all antibiotics produced **[5]**.

As antibiotic resistance is a serious and growing public health concern, it becomes inevitable to design new antibacterial to overcome the problem caused by these dreadful pathogens. Hence, antibacterial drugs must be designed such that it targets the essential bacterial pathways with novel mode of action or interfere with the identified bacterial targets **[3]**.

Molecular docking, a main tool for virtual screening of several compounds is used for reproducing experimental data through docking validation algorithms where the structural conformations are obtained *in silico* and compared to the experimental structures **[9]**.

Search for newer antibiotics effective against multi drug resistant pathogens become an important area of antibiotic research. Nature is serving as an excellent source of novel structures that possess useful biological activities. In search of newer antibiotics, several experiments are oriented towards isolation of *Streptomyces* from different habitats **[8]**.

Thus the present study focuses on exploiting the ability of antibiotics produced by *Streptomyces* species in fighting against the dangerous pathogen, methicillin resistant *Staphylococcus aureus* through docking procedures.

MATERIALS AND METHODS

5.1. Identification of drug target protein

Based on the comparison of metabolic pathways of MRSA and human, Proteins that are inadequate for the survival of pathogen but are not found in human are identified and has been listed as possible drug targets.

5.2. Retrieval of target protein sequence:

UniProtKB/Swiss-Prot, a manually annotated component of UniProtKB possess manually-annotated records with information extracted from the literature and curator- evaluated computational analysis providing an overview of relevant information by bringing together experimental results, computed features and even contradictory conclusions **[7]**. Sequences of the identified target proteins were thus retrieved using UniProtKB/Swiss-Prot.

5.3. Retrieval of *Streptomyces* antibiotics:

DrugBank is a richly annotated database of drug and drug target information pertaining data on the nomenclature, ontology, chemistry, structure, function, action, pharmacology, pharmacokinetics, metabolism and pharmacokinetic properties of drugs **[12]**. The antibiotics produced by *Streptomyces* were thus retrieved from DrugBank.

5.4. Literature search for finding drugs against Methicillin resistant *Staphylococcus aureus:*

An extensive literature search reveals the drugs that are available to treat methicillin resistant *Staphylococcus aureus.* In addition, the drugs were also retrieved from DrugBank and PubChem databases.

5.5. Structure retrieval:

RCSB PDB is a worldwide archive of the structural data of biological macromolecules, including proteins and nucleic acids **[6]**. The structure of the target proteins which has been proposed earlier were obtained from RCSB PDB..

5.6. Modeling the target protein:

The determined target proteins which were void of 3D structures in PDB were subjected for homology modeling through Swiss-Model, which is a fully automated, web based integrative protein structure homology-modeling

server, accessible via the Expasy web server, or from the program Deep-View. The program Deep-View or Swiss-PdbViewer can be efficiently used to generate, display, analyze and manipulate modeling project files for Swiss-Model workspace **[4]**.

5.7. Validation of the modeled protein:
The modeled proteins are validated with the help of various programs such as Procheck, Whatif check, Verify_3D and Errat. The covalent bond distances and angles, stereochemical properties and atom nomenclature were validated using PROCHECK. The statistics of non-bonded interactions between different atom types were detected and values of the error function were analyzed by ERRAT.

5.8. Determining the active site of the target protein:
WHAT IF, a versatile molecular modeling package that is specialized on working with proteins and molecules in the environment like water, ligand, nucleic acids etc. can be used to predict the active site of the target protein. It provides as intelligent and flexible environment for displaying, manipulating and analyzing small molecules, proteins, nucleic acids and their interactions. WHAT IF web interface provides large number of tools for examining PDB files **[18 & 21].**

5.9. Passing through Lipinski filter:
The drugs and the antibiotics that can pass through the Lipinski rule of 5 were considered for docking. Schrödinger's QikProp, a rapid ADME predictor of drug candidates is used for filtering purpose. The 'rule of 5' pertaining to the drug likeness states that the poor absorption is more likely when:

- There are more than 5 hydrogen bond donars.
- The molecular weight is over 500.
- The Logp is over 5.
- There are more than 10 hydrogen bond acceptors **[14]**.

5.10. Docking:
The docking of each of the drug and the antibiotics with that of the proposed target was performed using Schrödinger Glide module, which provides a complete systematic search of the conformational, orientational and positional space of the docked ligand **[10]**. SP and XP Glide score are the two different scoring functions used in Glide to rank-order compounds.

Docking with glide posses the following steps:

- Protein preparation and refinement
- Receptor grid generation
- Ligand preparation
- Ligand docking

RESULTS AND DISCUSSION

Based on the metabolic pathway comparison results along with choke point analysis result of our previous study **[19]**, the UDP-N-Acetyl glucosamine 1- carboxy vinyl transferase [murA1] involved in peptidoglycan biosynthesis pathway and signal transduction histidine-protein kinase involved in two-component system were found to be the most promisable drug targets. It is found that the identified target proteins do not have a proposed structure data available in PDB and hence is subjected to homology modeling through Swiss-Model server. Validation of predicted models is performed using a series of programs like Procheck, Whatif check, Verify_3D and Errat and the results are tabulated in Table 19 and Table 20. Figure 8 shows the Ramachandran plot generated by PROCHECK for Signal transduction histidine kinase and UDP-N-acetylglucosamine 1-carboxyvinyltransferase. Procheck 's Ramachandran plot shows 185[87.3%] residues out of 232 in Signal transduction histidine kinase and 322[88%] out of 421 in UDP-N-acetylglucosamine-1-carboxyvinyltransferase are found to be in the most favored region making these models more acceptable. The selected models passed the validation step of Verify_3D program having 57.33% and 98.34% residues with averaged 3D-1D score>0.2 respectively. The Errat's overall quality factor and Whatif check results also proved that the models are best.

Fig.1 Homology Modeled Structure of Signal transduction histidine kinase

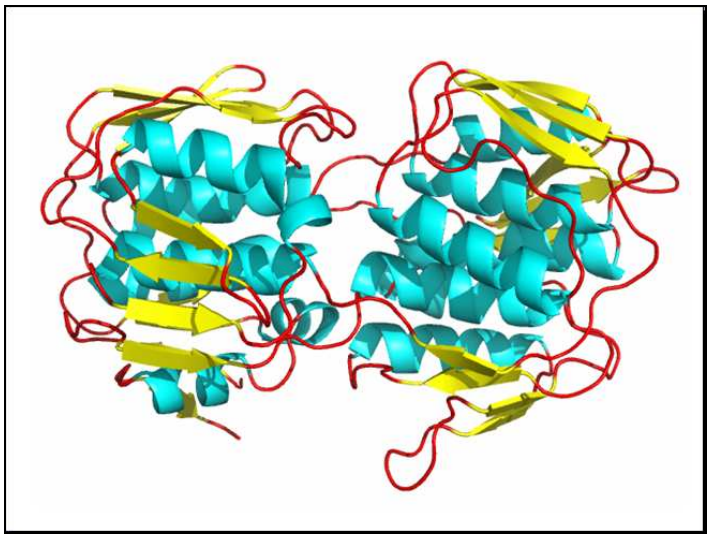


Fig.2 Homology Modeled Structure of UDP-N-acetylglucosamine 1-carboxyvinyltransferase

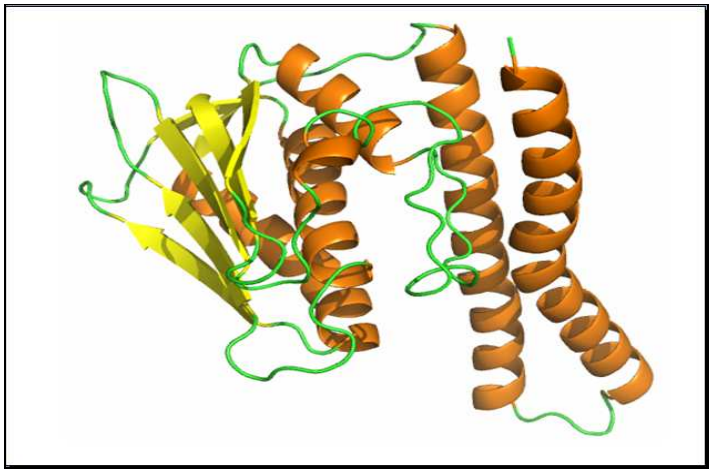


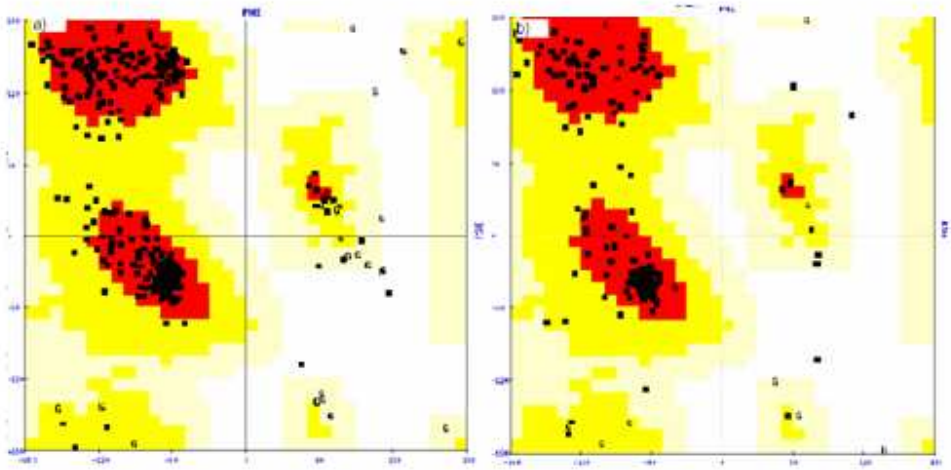
Table.1 Errat and Whatif check results of the modeled target proteins

Predicted structure	Ramachandran Z-score	Bond angle Z-Score	Bond length Z-Score	Errat overall quality factor
Signal transduction histidine kinase	-1.038	1.221	0.813	71.041
UDP-N-acetylglucosamine 1-carboxyvinyltransferase	-1.213	1.015	0.682	90.511

Table.2 Ramachandran statistics of the modeled target proteins

Predicted structure	No. of residues in				% in most favored region
	Most favored region	Additional allowed region	Generously allowed region	Disallowed region	
Signal transduction histidine kinase	185	21	3	3	87.3
UDP-N acetyl glucoseamine 1-carboxyl transferase	322	42	1	1	88

Fig.3 Ramachandran plot of modeled targets



6.1. Determining the active site of the target protein:
The modeled protein structure is used for further analysis. As the *in silico* modeled structures does not possess any ligands as of those seen in experimental structures, the active site of the target protein is determined and utilized during docking process. WHAT IF web interface is used to determine the active site of the target protein.

6.2. Retrieval of ligands:
A list of 103 antibiotics produced by *Streptomyces sp*. was collected from DrugBank along with their molecular formula, molecular weight, chemical structure and the target on which they act upon. Their corresponding structures are retrieved form PubChem database. In addition to the *Streptomyces* antibiotics, the drugs used against Methicillin resistant S*taphylococcus aureus* which are under clinical trials are also collected through comprehensive literature search.

6.3. Drug likeness of ligands:
The pharmacokinetic properties of the drug molecules are analyzed using the QikProp module of the Schrödinger 2009 software. Out of the 103 collected antibiotics, only 92 antibiotics can pass through QikProp module. The properties of 92 antibiotics under clinical trials against Methicillin resistant *Staphylococcus aureus* are found to be well within the acceptable range of Lipinski rule for drug like molecules with very few exceptions and are tabulated in Table.3. Hence these 92 antibiotics are chosen for docking studies against therapeutic targets.

6.4. Docking studies:
The collected antibiotics and drugs were subjected to molecular docking with the each of the target protein structures using the Glide module [version 9.0] of Schrödinger which predict protein ligand-binding modes and rank ligands via high-throughput virtual screening. The steps undertaken in the docking study includes:

- Protein preparation
- Ligand preparation
- Receptor grid generation
- Ligand docking
- Viewing docking results

Table.3 QikProp results of antibiotics

S.No.	Antibiotic	Lipinski rule of 5			
		Mol. Wt.	donarHB	acceptHB	QlogPo/w
1	Amikacin	585.607	17	26	-8.352
2	Amoxicillin	365.403	4	8	-2.621
3	Ampicillin	349.404	3	7	-1.986
4	Azlocillin	461.492	1	8	1.023
5	Aztreonam	435.426	3	12	0.358
6	Cefaclor	367.806	3	7	-1.344
7	Cefadroxil	363.387	4	8	-1.951
8	Cefamandole	462.497	2	10	0.904
9	Cefazolin	454.496	1	11	-0.342
10	Cefepime	480.561	2	6	-0.123
11	Cefoxitin	427.446	3	9	0.468
12	Cefprozil	389.425	4	8	-1.355
13	Carbenicillin	378.399	3	6	1.145
14	Ceftriaxone	554.57	4	1	-0.62
15	Cefuroxime	424.384	3	11	0.099
16	Cephalexin	347.388	3	7	-1.373
17	Cephalothin	396.432	1	8	1.923
18	Cilastatin	358.452	4	7	0.186
19	Ciprofloxacin	331.346	1	6	0.28
20	Clavulanic acid	199.163	2	6	-0.881
21	Clindamycin	424.928	4	11	2.115
22	Cloxacillin	435.881	1	7	2.475
23	Dicloxacillin	470.326	1	7	2.529
24	Enoxacin	320.323	1	6	-0.2
25	Ertapenem	475.515	4	11	-0.506
26	Floxacillin	453.872	1	7	2.474
27	Forazolidone	225.16	0	5	-0.178
28	Gatifloxacin	375.399	1	6	0.609
29	Gentamicin	477.6	11	16	-3.629
30	Grepafloxacin	359.399	1	6	0.726
31	Kanamycin	484.503	15	22	-6.7
32	Lincomycin	406.536	5	13	0.185
33	Lomefloxacin	351.352	1	6	-0.384
34	Loracarbef	349.773	3	6	-1.327
35	Meropenem	383.462	2	9	-1.39
36	Methicillin	380.415	1	7	2.088
37	Mezlocillin	539.577	1	11	0.333
38	Moxifloxacin	401.437	1	6	0.899
39	Nafcillin	414.475	1	7	3.184
40	Nalidixic acid	232.238	0	4	1.59
41	Neomycin	614.649	19	28	-9.156
42	Netilmicin	475.584	11	16	-3.364
43	Nitrofurantoine	238.159	1	5	-0.388
44	Norfloxacin	319.335	1	6	-1.026
45	Ofloxacin	361.372	0	7	-0.37
46	Oxacillin	401.436	1	7	2.305
47	Paramomicin	615.634	18	28	-8.558
48	Penicillin G	334.389	1	6	1.821
49	Penicillin V	350.389	1	7	2.069
50	Piperacillin	517.556	1	11	0.636
51	Polymyxin B	1203.47	18	18	-2.568
52	Roxithromycin	837.046	5	17	0.314
53	Spectinomycin	332.353	5	13	-2.239
54	Tazobactam	300.289	1	10	-1.426
55	Teichomycin	1879.65	24	34	0.005
56	Telithromycin	812.003	1	12	0.425
57	Ticarcillin	384.421	1	7	1.348
58	Tobramycin	467.518	15	20	-6.643
59	Trofloxacin	416.359	2	6	1.163
60	Troleandomycin	813.968	0	16	0.439
61	Vancomycin	1449.25	19	26	-2.689
62	Rifaximin	785.878	5	11	0.698

63	Sparfloxacin	392.405	2	6	0.641
64	Streptomycin	581.579	16	25	-5.722
65	Sulfacetamide	214.239	2	6	-0.091
66	Sulfadiazine	250.275	2	7	-0.089
67	Sulfamethiozole	270.324	2	7	0.445
68	Sulfamethaxazole	253.275	2	7	0.473
69	Sulfanilamide	172.201	3	5	-0.811
70	Sulfasalazine	398.392	2	10	1.043
71	Sulfizoxazole	267.302	2	7	1.004
72	Temafloxacin	417.387	1	6	1.865
73	Tetracycline	444.44	4	8	0.454
74	Tinidazole	247.268	0	6	0.048
75	Trimethoprim	290.321	4	5	0.927
76	Capreomycin	540.533	12	10	-8.853
77	Chloramphenicol	323.132	3	6	1.131
78	Clofazimine	473.404	1	3	7.818
79	Cycloserine	102.093	3	5	-1.946
80	Dalfopristin	690.85	1	18	2.293
81	Dapsone	248.299	3	6	0.968
82	Demeclocycline	464.858	4	9	0.413
83	Doxycycline	444.44	4	9	0.294
84	Ethambutol	204.312	4	6	-0.399
85	Ethinamide	166.24	2	3	1.241
86	Fosfomycin	138.06	0	5	-0.297
87	Isoniazid	137.141	3	4	-0.649
88	Linezolid	337.35	1	8	0.481
89	Metranidazole	171.155	1	4	-0.02
90	Minocycline	457.482	3	8	0.935
91	Oxytetracycline	460.44	5	10	-0.05
92	Pyrazinamide	123.114	2	5	-0.645

Table.4 Docking results of the antibiotics with Signal transduction histidine kinase

S.No.	Antibiotic	Signal transduction histidine kinase		
		Glide score	Glide energy	No. of Hbond
1	Amikacin	-5.963915	-49.488255	6
2	Amoxicillin	-5.047219	-45.047219	2
3	Ampicillin	-6.139355	-38.836755	1
4	Azlocillin	-4.842106	-39.858612	2
5	Aztreonam	-4.911422	-45.164839	2
6	Cefaclor	-6.596441	-43.228815	2
7	Cefadroxil	-5.083862	-38.536992	2
8	Cefamandole	-4.293714	-42.237476	1
9	Cefazolin	-4.062042	-4.062042	0
10	Cefepime	-1.161856	-31.90552	1
11	Cefoxitin	-5.199723	-41.213283	3
12	Cefprozil	-4.968858	-39.026623	2
13	Carbenicillin	-4.237736	-29.200067	1
14	Ceftriaxone	-3.314145	-39.266008	1
15	Cefuroxime	-4.603379	-38.636288	3
16	Cephalexin	-5.695295	-36.747687	3
17	Cephalothin	-4.851799	-36.056226	1
18	Cilastatin	-4.122521	-29.155355	1
19	Ciprofloxacin	-5.92897	-33.22925	1
20	Clavulanic acid	-4.840161	-23.141672	1
21	Clindamycin	-5.645425	-41.997544	1
22	Cloxacillin	-4.200104	-34.223579	1
23	Dicloxacillin	-3.707875	-35.885173	1
24	Enoxacin	-6.719258	-32.366089	1
25	Ertapenem	-7.361221	-49.099569	3
26	Floxacillin	-3.519336	-35.073486	0
27	Forazolidone	-4.335878	-26.036123	0
28	Gatifloxacin	-7.14647	-37.371185	0
29	Gentamicin	-6.658922	-48.864925	4
30	Grepafloxacin	-5.915732	-30.971919	1
31	Kanamycin	-5.548351	-48.574887	3

32	Lincomycin	-5.51957	-40.718368	4
33	Lomefloxacin	-7.48927	-37.665545	0
34	Loracarbef	-5.508527	-36.672809	3
35	Meropenem	-5.18276	-38.633547	2
36	Methicillin	-2.882894	-25.173291	0
37	Mezlocillin	-6.319618	-49.784771	2
38	Moxifloxacin	-6.573817	-37.514756	1
39	Nafcillin	-5.680063	-27.011697	1
40	Nalidixic acid	-5.937456	-28.797071	1
41	Neomycin	-7.231334	-55.351969	5
42	Netilmicin	-6.385082	-47.500982	2
43	Nitrofurantoine	-4.905816	-33.687984	0
44	Norfloxacin	-7.255382	-36.758269	1
45	Ofloxacin	-5.358554	-34.200959	0
46	Oxacillin	-5.016	-30.747852	1
47	Paramomicin	-7.057142	-49.163065	4
48	Penicillin G	-4.922586	-32.753307	1
49	Penicillin V	-5.492665	-34.971945	1
50	Piperacillin	-6.194488	-45.480116	2
51	Polymyxin B	-8.999599	-74.009994	6
52	Roxithromycin	-3.664126	-38.718263	2
53	Spectinomycin	-6.455969	-39.34963	1
54	Tazobactam	-5.843489	-32.70079	1
55	Teichomycin	-7.433641	-61.178209	3
56	Telithromycin	-8.090955	-62.846844	3
57	Ticarcillin	-3.957275	-26.965023	1
58	Tobramycin	-6.105467	-50.090883	4
59	Trofloxacin	-5.415769	-37.412266	2
60	Troleandomycin	Failed		
61	Vancomycin	Failed		
62	Rifaximin	-3.206241	-39.269129	2
63	Sparfloxacin	-5.746448	-38.620639	1
64	Streptomycin	-4.752883	-40.154353	4
65	Sulfacetamide	-4.578835	-28.107307	0
66	Sulfadiazine	-5.280542	-35.048971	1
67	Sulfamethiozole	-5.358662	-36.652934	1
68	Sulfamethaxazole	-5.272835	-35.4203	1
69	Sulfanilamide	-6.262461	-29.189479	3
70	Sulfasalazine	-7.103586	-49.445599	2
71	Sulfizoxazole	-4.55251	-34.199508	1
72	Temafloxacin	-5.183559	-39.238235	0
73	Tetracycline	-4.852401	-36.899154	2
74	Tinidazole	-6.051622	-31.265526	1
75	Trimethoprim	-5.607364	-36.199393	2
76	Capreomycin	-7.291654	-53.843841	3
77	Chloramphenicol	-5.356675	-43.829053	1
78	Clofazimine	-4.017757	-33.563412	0
79	Cycloserine	-5.168286	-19.842134	1
80	Dalfopristin	-3.50662	-40.027618	1
81	Dapsone	-4.952018	-31.860499	1
82	Demeclocycline	-5.001335	-41.463449	1
83	Doxycycline	-4.499394	-33.202524	3
84	Ethambutol	-4.061517	-37.077039	2
85	Ethinamide	-6.80489	-28.734784	1
86	Fosfomycin	-5.258105	-21.788044	2
87	Isoniazid	-6.248149	-30.7257	2
88	Linezolid	-5.402291	-40.663209	2
89	Metranidazole	-5.336861	-29.448679	2
90	Minocycline	-5.658992	-42.536031	3
91	Oxytetracycline	-3.951683	-34.91854	4
92	Pyrazinamide	-4.55505	-23.378358	1

Table.5 Docking results of antibiotics with UDP-N-acetylglucosamine 1-carboxyvinyltransferase

S.No.	Antibiotic	UDP-N-acetylglucosamine 1-carboxyvinyltransferase		
		Glide score	Glide energy	No. of Hbond
1	Amikacin	-6.190465	-55.608508	8
2	Amoxicillin	-4.514792	-40.262774	4
3	Ampicillin	-4.723156	-40.982079	4
4	Azlocillin	-5.054778	-51.053364	4
5	Aztreonam	-5.36855	-51.22529	5
6	Cefaclor	-4.998149	-37.078238	2
7	Cefadroxil	-6.184848	-42.017017	5
8	Cefamandole	-4.785432	-53.895739	3
9	Cefazolin	-5.231389	-56.468981	5
10	Cefepime	-5.185576	-48.615633	3
11	Cefoxitin	-5.657729	-51.272993	5
12	Cefprozil	-4.123615	-40.171737	3
13	Carbenicillin	-6.255848	-43.792142	4
14	Ceftriaxone	-5.259534	-57.764402	5
15	Cefuroxime	-5.461283	-52.465937	6
16	Cephalexin	-6.208355	-41.58745	5
17	Cephalothin	-4.98006	-46.704795	4
18	Cilastatin	-4.619047	-41.096142	6
19	Ciprofloxacin	-5.274097	-43.548751	2
20	Clavulanic acid	-6.413347	-31.622385	6
21	Clindamycin	-5.494687	-45.404879	5
22	Cloxacillin	-4.680084	-45.723715	6
23	Dicloxacillin	-3.602958	-48.836805	0
24	Enoxacin	-5.348712	-37.590003	2
25	Ertapenem	-5.733071	-60.949377	4
26	Floxacillin	-3.715438	-46.627725	1
27	Forazolidone	-4.746378	-34.6804	4
28	Gatifloxacin	-5.06648	-43.504352	2
29	Gentamicin	-3.904692	-36.64165	2
30	Grepafloxacin	-5.469958	-43.247984	2
31	Kanamycin	-4.192045	-45.007324	4
32	Lincomycin	-4.167623	-44.11634	2
33	Lomefloxacin	-5.220129	-39.95018	5
34	Loracarbef	-5.428503	-46.633195	2
35	Meropenem	-5.304961	-43.296161	2
36	Methicillin	-4.38133	-41.676946	3
37	Mezlocillin	-6.323451	-56.497585	3
38	Moxifloxacin	-5.234113	-44.661833	2
39	Nafcillin	-5.21252	-46.325047	4
40	Nalidixic acid	-5.319801	-31.168076	3
41	Neomycin	-6.114495	-48.249551	3
42	Netilmicin	-3.905728	-36.575344	6
43	Nitrofurantoine	-4.670676	-34.257437	2
44	Norfloxacin	-5.414824	-40.908931	2
45	Ofloxacin	-5.258129	-39.224676	2
46	Oxacillin	-5.290559	-44.580259	4
47	Paramomicin	-6.393108	-46.899035	6
48	Penicillin G	-5.818716	-42.694896	3
49	Penicillin V	-4.847737	-41.423557	3
50	Piperacillin	-5.340259	-60.590688	2
51	Polymyxin B	-5.341583	-28.785643	3
52	Roxithromycin	Failed		
53	Spectinomycin	-4.838595	-29.842576	2
54	Tazobactam	-5.798412	-37.190894	3
55	Teichomycin	Failed		
56	Telithromycin	-6.298756	-40.178832	4
57	Ticarcillin	-5.676225	-37.358934	7
58	Tobramycin	-4.706257	-40.185631	3
59	Trofloxacin	-5.505738	-44.874205	1
60	Troleandomycin	Failed		
61	Vancomycin	Failed		

62	Rifaximin	Failed		
63	Sparfloxacin	-4.681374	-43.401971	3
64	Streptomycin	-5.746348	-47.456988	5
65	Sulfacetamide	-4.483222	-30.687705	3
66	Sulfadiazine	-5.093215	-41.68084	2
67	Sulfamethiozole	-4.76578	-37.271829	0
68	Sulfamethaxazole	-4.625728	-33.415187	4
69	Sulfanilamide	-6.551196	-32.27604	2
70	Sulfasalazine	-6.619527	-55.680533	5
71	Sulfizoxazole	-5.006959	-36.506366	2
72	Temafloxacin	-5.404951	-47.228608	2
73	Tetracycline	-5.646273	-49.403932	3
74	Tinidazole	-4.188451	-32.981667	2
75	Trimethoprim	-4.851887	-40.469005	2
76	Capreomycin	-5.354167	-46.989171	6
77	Chloramphenicol	-5.693615	-45.0771	5
78	Clofazimine	-5.719602	-55.68617	1
79	Cycloserine	-5.003515	-18.055278	3
80	Dalfopristin	Failed		
81	Dapsone	-4.568869	-37.080097	2
82	Demeclocycline	-5.616442	-51.957949	3
83	Doxycycline	-5.608868	-52.789396	2
84	Ethambutol	-2.580204	-30.633731	5
85	Ethinamide	-5.376175	-27.135145	3
86	Fosfomycin	-6.482135	-25.493976	4
87	Isoniazid	-5.271126	-24.394219	3
88	Linezolid	-5.381416	-42.24154	2
89	Metranidazole	-4.181316	-26.681958	2
90	Minocycline	-5.092422	-48.233927	1
91	Oxytetracycline	-4.644681	-46.666714	4
92	Pyrazinamide	-4.964885	-23.481404	3

6.4. Interpretation of docking results:

The docking scores of each of the target proteins Signal transduction histidine kinase and UDP-N-acetyl glucosamine 1- carboxyvinyltransferase with that of the antibiotics are tabulated in the Tables 3 and 4 respectively.

About 60% of the antibiotics docking score ranges between - 4 kcal/mol to - 6 kcal/mol incase of signal transduction histidine kinase and 74% incase of UDP-N-acetyl glucosamine 1- carboxyvinyl transferase.

8 of the antibiotic structures failed to dock with the target protein UDP-N-acetylglucosamine 1-carboxyvinyltransferase and 2 failed to dock with the Signal transduction histidine kinase target structure. Except few, most of all the hits showed good dock score and formed similar type of interactions with the active site of the target structures.

Polymyxin B and telithromycin are found to be the best docked antibiotics with the target protein, Signal transduction histidine kinase having Glide score of -8.999599 kcal/mol, -8.090955 kcal/mol and energy values -74.00994,

-62.846844 respectively. They make about 6 and 3 hydrogen bond contacts respectively with that of target protein structure. In the same way, sulfasalazine and sulfanilamide are found to be best docked ligand with Glide Score of -6.619527 and -6.551196 respectively incase of the target protein, UDP-N-acetyl glucosamine 1- carboxyvinyl transferase.

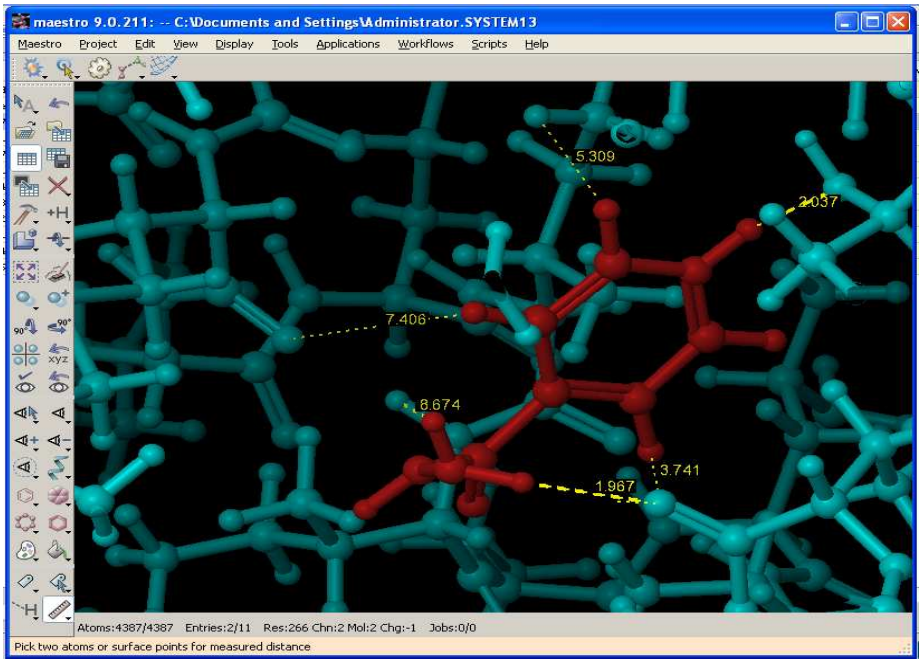


Fig.4 Docked structure of top scoring antibiotic with Signal transduction histidine kinase

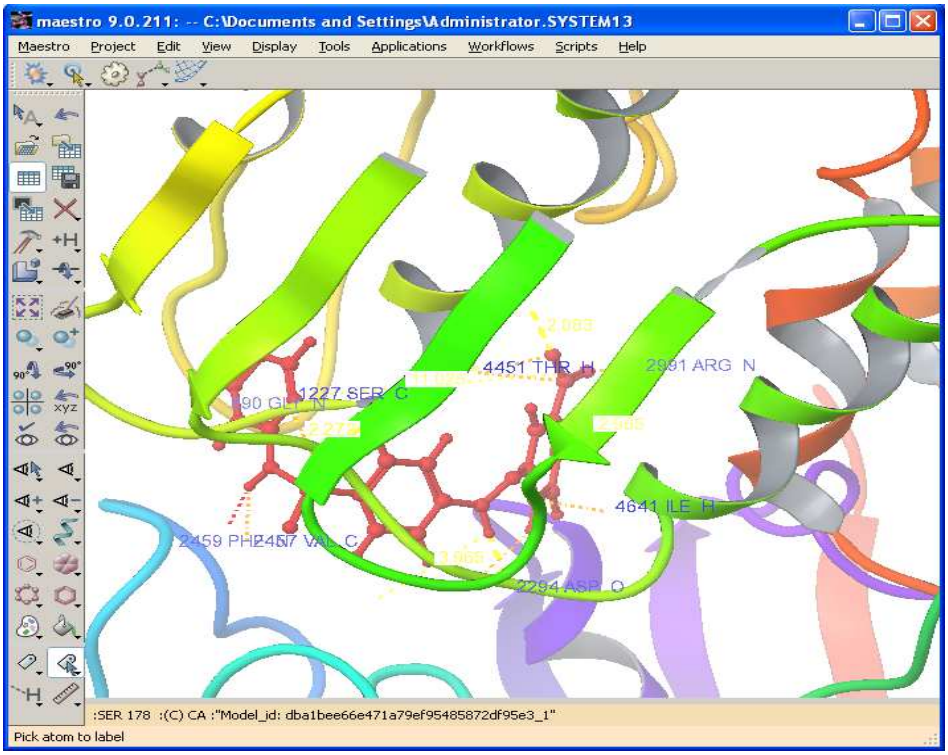


Fig.5 Docked structure of top scoring antibiotic with UDP-N-acetylglucosamine 1-carboxyvinyltransferase

It is noteworthy to identify the antibiotic which docked efficiently with both of the potential drug targets. Among the antibiotics, Polymyxin B is ranked one with the best docking score followed by telithromycin. Based on the docking analysis, Signal transduction histidine kinase is found to be efficient in docking with most of the antibiotics. Hence,

it can be used as a promisable drug target, for designing potential drugs which have the ability to protect against methicillin resistant S*taphylococcus aureus*.

Thus the present study suggests that the compounds with further *in vitro* and *in vivo* testing can be introduced as an effective inhibitor against the particular target to combat methicillin resistant S*taphylococcus aureus*.

CONCLUSION

Being in the era of rapidly growing, emerging and reemerging infectious diseases, it becomes indispensable to formulate new strategies for the prevention and control of dreadful pathogens like methicillin resistant *Staphylococcus aureus* [MRSA] which develops resistance among most of the antimicrobials. The discovery and development of novel antimicrobials against multi-drug resistant MRSA becomes the primary goal of many researchers. Thus the findings of the present study can be utilized in the development of novel antimicrobials which are efficient to overcome the problems brought about by methicillin resistant *Staphylococcus aureus*. It also aids in the proper usage of existing antibiotics to be prescribed against the infections caused by the dreadful MRSA.

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