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# Molecular Docking Studies of Nitrocefin and It's Analogs with PBP2A of *S. aureus*

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**In the Present study, Docking analysis was performed with Nitrocefin and it's analogs to determine their binding efficiency at the binding pocket of Pencillin binding protein 2a of *S.aureus*. As a result, based on the docking scores generated by the Software Glide, Two of the Nitrocefin analogs have scores nearer to that of nitrocefin. This indicates that this class of analogous compounds can be generated as new set of anti bacterial drugs against *S. aureus*.**

**Key words:** Nitrocefin, *S. aureus*, Glide, Schrodinger.

The β-lactam antibiotics perhaps form the best studied and most used antibiotics in the world today. The extensive and uncontrolled use of the ß-lactam antibiotics, particularly in developing countries has resulted in the evolution of resistance in many strains of bacteria. One common mechanism of resistance with ß-lactam antibiotics is the expression of a specific class of enzymes called β-lactamases by the bacteria. These enzymes destroy the antibiotic; before they exert their desired effect. Many distinct β-lactamases have been isolated and identified so far. Synthetically produced penicillin such as methicillin and oxacillin have been developed that are not degraded by the penicillinase enzyme, but these new penicillin have no effect on bacteria that have developed resistance by other means, e.g., by altered cell wall structure.

*Staphylococcus aureus* is a gram-positive coccus and is one of the leading causes of high morbidity and mortality associated with both community- and hospital-associated infections (Schleifer, 1986 and Walsh, and Howe 2002). This coccus shows extensive genomic variation, with over 22% of the genome dedicated to dispensable regions. A genome- scale analysis of a clinical strain of *S. aureus* is of particular interest in this context, wherein the conversion of a susceptible strain of *S. aureus* to a multidrug-resistant phenotype was shown to involve just 35 mutations in 13 loci, achieved within 3 months (Mwangi *et al*, 2007).

PBPs are membrane-bound proteins that catalyze carboxypeptidase and transpeptidase reactions of bacterial cell wall synthesis (Waxman and Strominger, 1983). PBPs are targets of beta-lactam antibiotics. These antibiotics are structural analogs of the natural PBP substrate and inhibit cell wall synthesis by covalently binding to PBP enzymatic sites (Park and Strominger 1957, and

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Waxman and Strominger, 1957). Of the five PBPs in *S. aureus*, an acquired PBP, PBP2a, is the most extensively examined, as it was noted to be a specific marker for methicillin-resistant *S. aureus* (MRSA) strains. PBP2 is a dual-function enzyme with both transglycosylase and transpeptidase activities, and inhibition of this protein leads to restrained peptidoglycan elongation and subsequent leakage of cytoplasmic contents due to cell lysis (Murakami *et al* 1994, Pinho *et al* 1998).

In bacteria susceptible to β-lactam antibiotics, the transpeptidase activity of their penicillin binding proteins (PBPs) is lost as a result of irreversible acylation of an active site serine by the β-lactam antibiotics. In contrast, the PBP2a of MRSA is resistant to β-lactam acylation and successfully catalyzes the DD-transpeptidation reaction necessary to complete the cell wall. The inability to contain MRSA infection with β-lactam antibiotics is a continuing public health concern. Insilico screening could be used as a viable alternative for well established targets. This will serve as a starting point for Structure-Based Drug Design based on molecular recognition between active site groups and interacting molecules. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. Thus, our work aims to derive the best conformation of the protein with most active ligand from a vast pool of Nitrocefin analogs obtained from Pubchem.

**Methodology**

1. The first step is to retrieve the NMR structure of the receptor from PDB. The PDB provides a variety of tools and resources for studying the structures of biological macromolecules and their relationships to sequence, function, and disease. From this database, the 3D structure of Penicillin binding protein 2a of Methicillin Resistant *Staphylococcus aureus* (Pdb id: 1mws) has been retrieved [Lim *et al*, www.rcsb.org.].
2. The various analogs of Nirocefin (ligand) were retrieved from Pubchem database [Bolton *et al*, https://pubchem.ncbi.nlm.nih.gov/].
3. Using Schrodinger software ligprep was done for nitrocefin analogs to convert the structures from .sd format to maestro format [Friesner *et al*].
4. The protein refinement is an essential step for docking which is performed using Proteinprep wizard of the maestro workspace.
5. Finally, both the refined protein and ligands were submitted for molecular docking process using Glide.

## RESULTS AND DISCUSSION

The target protein PBP2B was retrieved from PDB and the target ligands retrieved from Pubchem were subjected to docking process to find the efficiency of binding of various ligands to the active site of the target protein. Since, Nitrocefin binds to chain A, the other chain is deleted to carry out the protein refinement stage [Figure 1]. The total of 20 ligands which includes nitrocefin and its analogues were taken from pubchem [Table 1].

Ligprep was carried out to transfer the ligands structures to maestro format. It was done using OPLS2005 force field and other default parameters of the ligprep to generate only two isomers per ligand. Under such conditions ligprep generated ligand molecules that can be utilized for docking. With the given ligands to dock with the target protein, the glide docking process is set in such a way that it generates nearly 10000 ligand poses per run but it will return only one pose per ligand which has greatest binding efficiency to bind with the active site of the target protein.

As a result, the process gives us a maximum of 12 different poses of four different ligands which has the best binding mode. These poses can be viewed using the pose viewer panel. The total number of hydrogen bonds between the ligand and the protein in different poses can also be visualized. All the Four ligands each in it's own best pose is shown [Figure 2]. The ligand with best binding efficiency can be determined from the glide score, the ligand which has low value of glide score in its best pose will fit with maximum affinity or efficiency to the target protein. Ultimately, the table shows that the compound nitrocefin has the best score of -4.094, followed by its Analogues 8, 3, 4 and 9 [Table 2].

**Table 1.** Nitrocefin and its Analogues were taken from Pubchem

| S. No. | Compound | Pubchem Id | Hydrogen donor | Hydrogen acceptor | No.of rotatable bonds |
|---|---|---|---|---|---|
| 1 | Nitrocefin | 6436140 | 8 | 2 | 6 |
| 2 | Analog 1 | 9958170 | 8 | 2 | 6 |
| 3 | Analog 2 | 23082450 | 8 | 2 | 6 |
| 4 | Analog 3 | 6296955 | 13 | 5 | 12 |
| 5 | Analog 4 | 5192840 | 13 | 5 | 12 |
| 6 | Analog 5 | 18690358 | 8 | 2 | 6 |
| 7 | Analog 6 | 11005727 | 8 | 2 | 6 |
| 8 | Analog 7 | 9957982 | 8 | 2 | 6 |
| 9 | Analog 8 | 6296954 | 13 | 3 | 10 |
| 10 | Analog 9 | 5192839 | 13 | 3 | 10 |
| 11 | Analog 10 | 5288990 | 5 | 2 | 6 |
| 12 | Analog 11 | 5287907 | 5 | 2 | 6 |
| 13 | Analog 12 | 4473867 | 5 | 2 | 6 |
| 14 | Analog 13 | 19027584 | 6 | 3 | 6 |
| 15 | Analog 14 | 4369487 | 6 | 3 | 6 |
| 16 | Analog 15 | 21158886 | 6 | 3 | 6 |
| 17 | Analog 16 | 11987702 | 6 | 3 | 6 |
| 18 | Analog 17 | 4369222 | 7 | 4 | 7 |
| 19 | Analog 18 | 446820 | 6 | 3 | 6 |
| 20 | Analog 19 | 445836 | 6 | 3 | 6 |

**Table 2.** Four different ligands which has the best binding mode

| S. No. | Compound | Pose | Glide score | Energy | Hydrogen bond | VanderWaals interaction | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Good | Bad | Ugly |
| 1 | 6296954 | 3 | -4.09 | -41.2 | 5 | 169 | 9 | 0 |
| 2 | 6296955 | 10 | -4.02 | -40.6 | 4 | 196 | 5 | 0 |
| 3 | 5192840 | 4 | -3.85 | -39.7 | 5 | 183 | 9 | 0 |
| 4 | 5192839 | 12 | -3.81 | -36.4 | 3 | 64 | 7 | 0 |

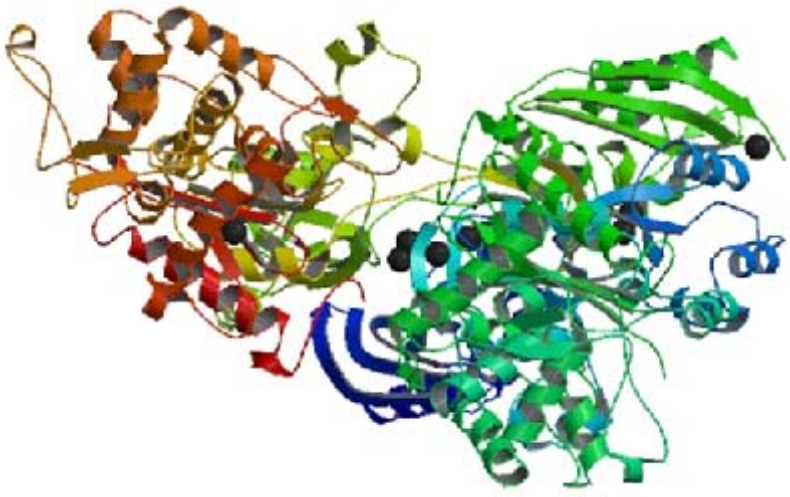

**Fig. 1.** Crystal structure of PBP2A [1MWS]

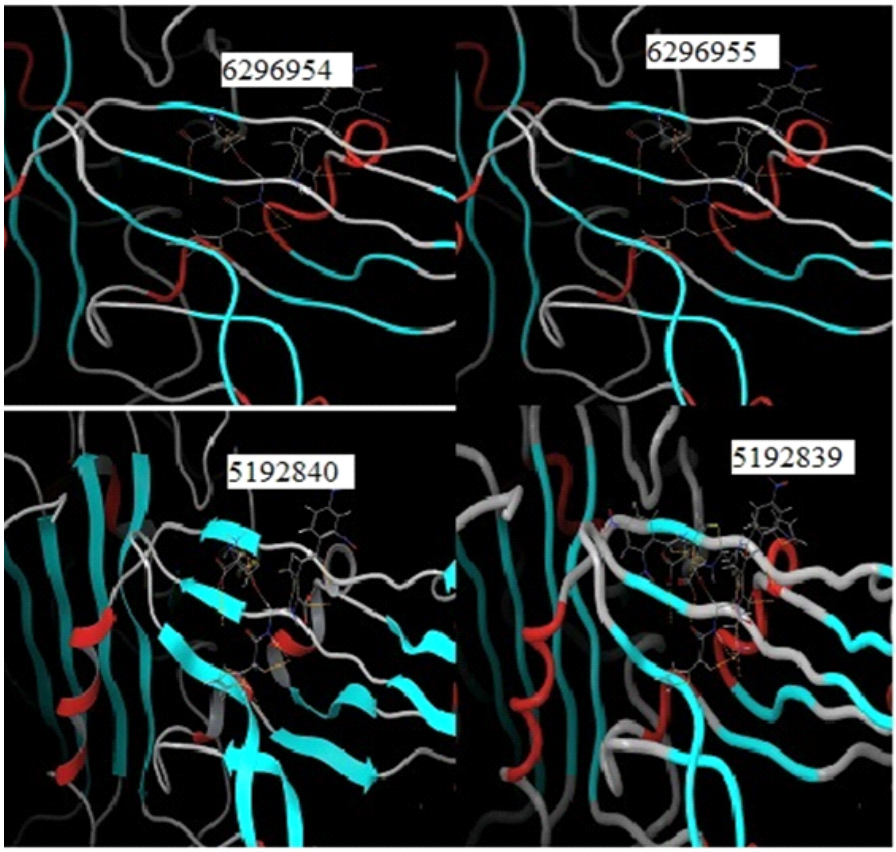


**Fig. 2.** The four best ligands in its best pose

## CONCLUSION

Molecular docking analysis has generated probable bioactive conformations of Nitrocefin analogs. The glide score for the analogs also falls nearer to the value of Nitrocefin. Since the analogues shows nearer score to nitrocefin they can also be targeted as new class of antibiotics against *Staphylococcus aureus* infection. Since, the software has generated only four ligands in different poses as best binding conformations from a set of 22 ligands, again this set of ligands can be further studied for molecular dynamics and QSAR analysis. There are various tools, which can be used for Computer aided drug design such as QSAR, Docking, Homology modeling, ADMET prediction etc. QikProp pharmacokinetic prediction provides us physicochemical properties with it BBB and % oral absorption predictions. These all parameters are helpful to find out bioavailability and toxicity prediction in human body.

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