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SCREENING AND DOCCKING STUDY OF *INSILICO* DESIGNED ANTIBIOTICS FOR THE TREATMENT OF METHICILLIN RESISTANCE *STAPHYLOCOCCOUS AUREUS*

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ABSTRACT

Molecular docking is a method to predict the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Computer programs (software) are used to predict or simulate the possible reaction (interactions) between two molecules based on their 3 dimensional structure information. The ability in predicting binding interactions and orientation, it was being widely used in rational drug design and structure based drug design processes. This process was sometimes called virtual screening or *In silico* drug screening (designing), where thousands of drug candidates are being screened rapidly using high speed or high performance computing facilities. In our current research PBP2a Protein is our target molecule and altered methicillin antibiotic/ analogs are taken as lead molecules for docking study. The analogs 17 with addition of methylbenzene at carboxylic group of β-lactam ring side chain have shown minimum energy value (-229.18 kcal/mol). The analog 17 showing the higest negative E-value (-229.18) compared with the original methicillin antibiotic which was showing (-173.45 K.cal/mole). The analog number 17 may be considered as a lead molecule/ligand to treat *Staphylococcus aureus* infections.

Key words: *In silico, β-lactam, Energy value ,HEX software S.aureus Analogs.*

[1] INTRODUCTION:

Drug design, sometimes referred to as rational drug design or more simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a bio molecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the bio molecular target with which they interact and therefore will bind to it. There are two major types of *in silico* drug design. The first is referred

to as ligand-based drug design: and the second, structure-based drug design. The ligand-based drug design relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target [1]. Structure-based drug design relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy[2] .

[II] MATERIALS AND METHODS:

2.1 Protein docking program:

Hex is an interactive protein docking and molecular superposition program, written by Dave Ritchie. Hex understands protein and DNA structures in PDB format, and it can also read small-molecule SDF files. For the current study Hex 6.3 advance version was used.

2.2 Docking of PBP2a structure with Methicillin antibiotic:

After finding the active site in PBP2a protein, which can interact with β-lactams antibiotics including methicillin [3]. The PDB ID 1VQQ PBP2a protein structure was downloaded from PDB structure database in PDB file format. The 1VQQ PBP2a protein consists of two Chains, Chain A and Chain B respectively. The Chain B was removed because it was replica of the Chain A. The Chain A consists of hetero atoms, replace all hetero atoms into atoms because the docking software will read only atoms and finally save PBP2a protein file into PDB file format containing only Chain A. The methicillin structure was downloaded from NCBI-PubChem Compound with PubChem ID CID_ 6087 in.sdf file format. Replace all the hetero atoms into atoms and again re-save sdf file format into PDB file format. The software version Hex 6.3 was used for the docking of the protein structure with CID_ 6087 (ligand) and the software Marvin Sketch was used for the sketching of the antibiotic structure. Docking studies were done initially by taking original structures of PBP2a protein and methicillin. Both structures were loaded on to the Hex 6.3 software and by using the option file-load receptor-ligand and the option controls-docking have to be clicked. The methicillin antibiotic finds the binding cavity in the PBP2a protein and automatically binds (docks) with the receptor molecule (PBP2a). The window will show docking energy. If the docking energy is in negative form, the efficiency to binding of methicillin antibiotic to the protein (PBP2a) was high [4].

2.3 Docking of Model structure with Methicillin antibiotic:

The modeled structure of the PBP2a was docked with methicillin antibiotic which was downloaded from NCBI-PubChem database (Ligand). The antibiotic finds the binding cavity in the model (PBP2a) protein structure and binds (docks) with the receptor/PBP2a molecule. The binding energy of the receptor and antibiotic was recorded. The software displays binding energy in the form of E-total (Energy total) and calculates in terms of K.cal/mole.

2.4 Docking of analogs with Model structure:

After preparing 25 methicillin antibiotic analogs, all the analogs were docked with modeled (PBP2a) structure. Software version Hex6.3 was used for docking of analogs with model (PBP2a) protein. The docking/binding energy was recorded for all 25 analogs. The binding energy will be in the form of E-total (Energy total) and measured in terms of K.cal/mole [5].

[III] RESULTS:

3.1 Docking of PBP2a and model PBP2a structure with methicillin antibiotic:

Both PBP2a structure and model PBP2a structures/receptors were docked with methicillin antibiotic which was downloaded from NCBI-

PubChem database and the energy value (E-total) showed after docking was -209.61 K.cal/mole for PBP2a and -173.45 K.cal/mole for model PBP2a structure respectively. (Table-1 and Figs: 1 and 2).

Sl. No	Compound	E-value (K.cal/mole)
1	With Methicillin PBP2a	-209.61
2	With Methicillin Model PBP2a	-173.45
3	Analog-02	-169.46
4	Analog-05	-191.46
5	Analog-06	-169.41
6	Analog-09	-223.16
7	Analog-12	-176.41
8	Analog-15	-163.78
9	**Analog-17**	**-229.18**
10	Analog-20	-149.22
11	Analog-21	-214.37
12	Analog-24	-204.91
13	Analog-25	-197.09

Table: 1 Results of docking studies of PBP2a protein and Model PBP2a protein with Methicillin antibiotics and analogs of Methicillin antibiotic.

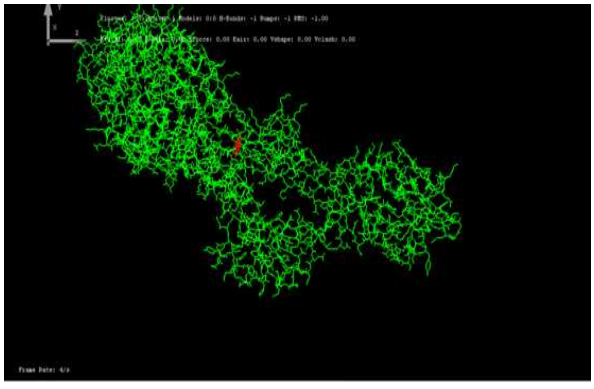

Fig: 1 Docking of PBP2a (PDB ID 1VQQ) receptor with Methicillin antibiotic

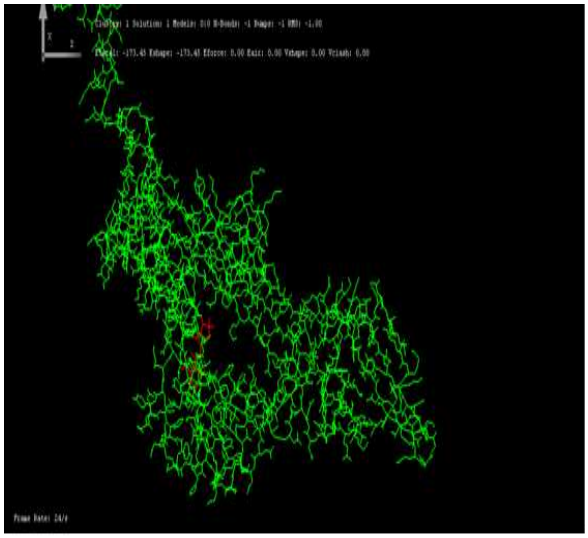

Fig: 2 Docking of PBP2a (model) receptor With Methicillin antibiotic.

3.2 Docking of model PBP2a structure with analogs:

The 25 different combination of lead structures/analogs were designed by using Marvin Sketch software and all the lead structures were docked with model PBP2a structure. The (Table-1) shows analogs with respective E-value. Among 25 designed lead/analog molecules, 11 analogs were shown above -150 E-vale in K.cal/mole. The analogs 17 with addition of methylbenzene at carboxylic group of β-lactam ring side chain have shown minimum energy value (-229.18 kcal/mol). The analog 17 showing the higest negative E-value (-229.18) compared with the original methicillin antibiotic which was showing (-173.45 K.cal/mole) (Fig: 3). the analog number 17 may be considered as a lead molecule/ligand to treat *Staphylococcus aureus* infections. To consider any molecule as a lead molecule/drug candidate it has to evaluate by *In silico* approaches as well as invitro pharmacokenetics studies which include drug adminstration, distribution, metabolism, excretion and toxicity (ADMET) by conducting the animal studies for the feasibility of the drug action.

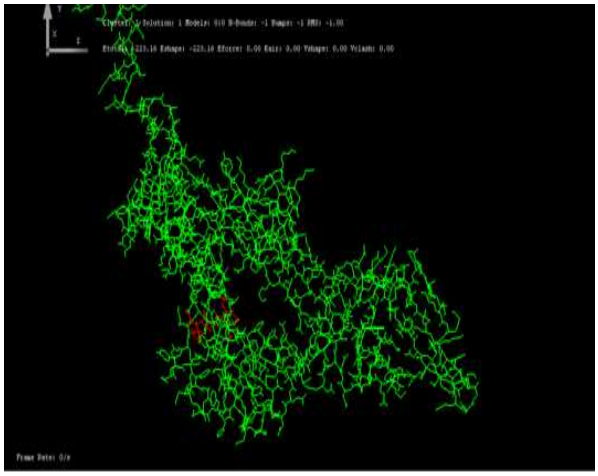

Fig: 3 Docking of PBP2a (model) receptor with Methicillin antibiotic analog-17

[IV] DISCUSSION:

In silico docking studies were performed for both original PBP2a structure and model PBP2a structure, the energy value (E-Total) after docking PBP2a original structure with methicillin antibiotic was -209 k.cal/mol and for model PBP2a structure with methicillin antibiotic was -173 k.cal/mol respectively. The 25 different methicillin analogs were docked with the model PBP2a protein, each analog were shown different energy values (E-Total). The energy value shown by the analog ranges between -54.23 k.cal/mol to -229.18 k.cal/mol. Out of 25 analogs 11 analogs have shown above -150 k.cal/mol the energy value (Table-1). The analogs 17 with addition of methylbenzene at carboxylic group of β-lactam ring side chain have shown minimum energy value (-229.18 k.cal/mol) and it was considered as a possible analog for the treatment of *S. aureus* infections. To support or study, the receptor (1MVT) was docked with the drug Proguanil the energy value obtained was (-6.59) using Argus Lab and (-174.54) using Hex. Similar report on docking study of *rPo* protein with rifampicin antibiotic in *Mycobacterium tuberculosis* was studied by [6 & 7]. Our own previous report supports for the molecular docking studies on antiviral drugs for SARS (Sever Acquired Respiratory Syndrome) for inhibition ACE-2 (Angieotensin converting enzyme-2) enzyme, we have docked modified drug of Lopinavir and Ritonavir. The docking energy range between two drugs namely Lopinavir -292.3 K. cal/mol to -332.73 K. cal/mol and Ritonavir -325.6 to -330.8 respectively, when docked with ACE-2 receptor of SARS [8]

[V] CUNCLUSION:

Docking studies were performed by taking first with original PBP2a (1VQQ) structure and latter with model PBP2a structure without doing any alteration in the methicillin antibiotics using Hex 6.3 version software. The results of docking studies were shown for original PBP2a structure was -209.61 K. cal/mole energy value (E-value) and model PBP2a structure was shown -173.45 K. cal/ mole energy value (E-value) respectively.

The results of docking studies with model PBP2a using different analogs were shown. Out of 25 analogs/lead molecules, 11 analogs have shown Energy value (E-value) between -150 K. cal/mole to -229.18 K. cal/mole.

The analog 17 was modified with addition of methylbenzene at carboxyl group of β-lactam ring. In our observation analog/lead molecule with No. CID_6087 (17) shown the highest negative E-value (Energy minimization value) is -229.18 K. cal/mole, which was higher than the original methecillin structure docked with original PBP2a protein (-209.61 K. cal/ mole) and model PBP2a protein (-173.45 K. cal/ mole) respectively.

The results of our docking studies shows that analog 17 may be the choice of drug to treat MRSA infections provided further clinical studies. In clinical studies to confirm a synthesized molecule as a drug candidate and the feasibility of the drug action, one has to address Administration, Distribution, Metabolism, Excretion and Toxicity (ADMET) by conducting animal studies.

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