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INSILICO DESIGNING OF METHICILLIN ANTIBIOTIC ANALOGS FOR THE TREATMENT OF *STAPHYLOCOCCUS AUREUS*

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ABSTARCT

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. In our current study we have designed alternative methicillin antibiotic/ligands/analogs. To design lead/ligand molecule methicillin structure was downloaded with ID number CID_6087. Using marvin sketch, by altering the side chain groups of methicillin antibiotic without altering the beta-lactam ring designed altered methicillin for docking studies.

Key words: *Ligand, PubChem, Marvin Sketch, Methicillin CD_6087, S. aureus*

[I] INTODUCTION

Drug discovery has evolved through various stages into more rational and evidence-based drug designing. Compared to conventional methods which were time consuming and less logical, new drug designing based on structure is rational, evidence based, faster and more scientific in nature. In the era of modern medicine, where newer insights into molecular level of disease processes are available, it is very essential that drug designing be based on molecular mechanism of pathologic processes. Structure-based drug designing has made tremendous contributions in the field of cancer chemotherapy, drug resistant infections, and neurological diseases [1]. The Remarkable progress has been made during the past five years in almost all the areas concerned with drug design and discovery. An improved generation of software with easy operation and superior computational tools to generate chemically stable and worthy compounds with refinement capability has been developed. These tools can tap into cheminformation to shorten the cycle of drug discovery, and thus make drug discovery more cost-effective [2]. The current study was taken up to synthesize the alternative drugs by

taking existing drugs. Using marvin sketch we made an effort to change the side chain group of the methicillin antibiotic for docking purpose in our further research.

[II] MATERIALS AND METHODS:

2.1 Methicillin Structure Retrieval from PubChem Compound database:

The PubChem Compound is the chemical compound database at NCBI (National centre for biotechnology information). The database is large collection of chemical structures. The PubChem compound database contains validated chemical depiction information provided to describe substances in PubChem Compounds are pre-clustered and cross- referenced by identity and similarity groups. The methicillin structure with ID number (CID_6087) was retrieved from the database.

2.2 Marvin Sketch (Chemical drawing tool):

Marvin Sketch is a chemical structure drawing tool designed by ChemAxon, chemical software developed for the biotechnology and pharmaceutical industries. Marvin Sketch allows to quickly drawing of molecules through basic functions on advanced functionalities such as sprout drawing, customizable shortcuts, abbreviated groups, default and user defined templates and context sensitive popup menus. Marvin Sketch allows creating and editing molecules in various file formats.

2.3 Designing of lead molecule (Methicillin Analogs):

Marvin Sketch was widely used for the design of lead molecule/drug analogs (Ligand) in docking studies. Analogs/ligands are the modified structure forms of the original structure. The modification was done by changing the functional group or atoms in the original structure. To modify, original methicillin antibiotic structure was downloaded from the NCBI-PubChem Compound with PubChem ID, CID_6087. The downloaded structure was loaded on to the soft ware Marvin Sketch. The CID_6087 (methicillin antibiotic) structure consists of following functional groups like, methoxy group (-OCH_3), methyl group (-CH_3), carboxylic group (-COOH) and carbonyl group (>C=O). The analogs were prepared by deletion or replacing with certain organic side chain groups with original methicillin structure [3]. The prepared analogs were docked with PBP2a (model) structure

[III] RESULTS

3.1 In silico designing of lead/ligand molecule:

The original structure of methicillin antibiotic was downloaded from NCBI PubChem database (Fig: 1). By using the original structure of methicillin antibiotic, a lead molecule were designed using the software MarvinSketch changing functional groups (addition/deletion of organic molecule). The functional groups were shown in (Fig: 2). The 25 analogs/lead molecules were designed and the important analogs/lead molecule/ligand was (Fig: 3). The Methicillin antibiotic can be modified by addition of Methylbenzene (aromatic) ring at carboxylic acid functional group of the antibiotic because, crystal structures of the PBP2 complexes show the carboxylate of the antibiotic moiety making a hydrogen bond with a serine or threonine residue. Modifed side chains with addition of Methylbenzene (aromatic) ring, which blocks β-lactamases enzymes and allow to binding of antibiotic to the receptor PBP2a protein.

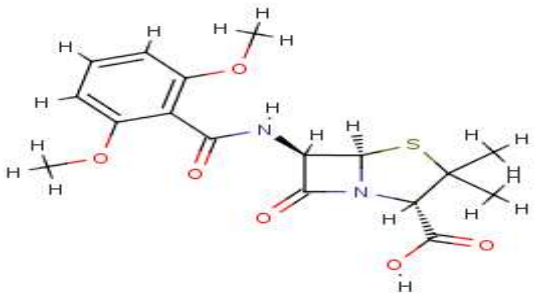

Fig: 1 Methicillin antibiotic structure from NCBI-PubChem compound database with ID Number CID_6087

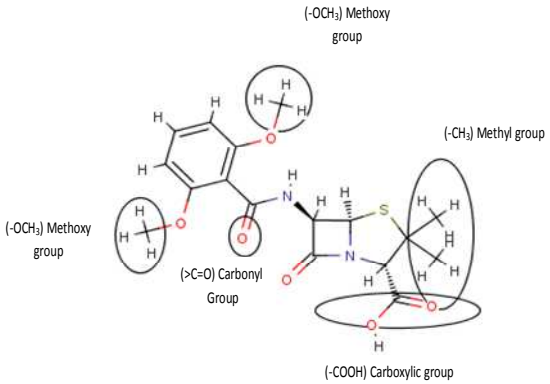

Fig: 2 Methicillin Antibiotic (CID_6087) structure with functional groups.

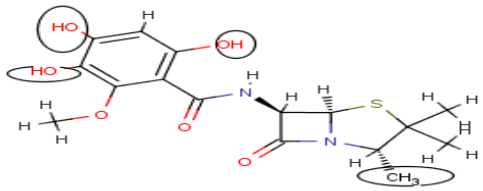

Fig: 3a

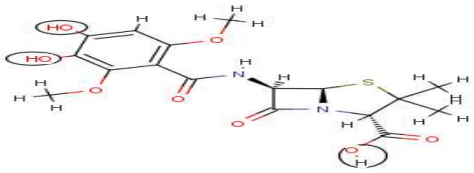

Fig: 3b

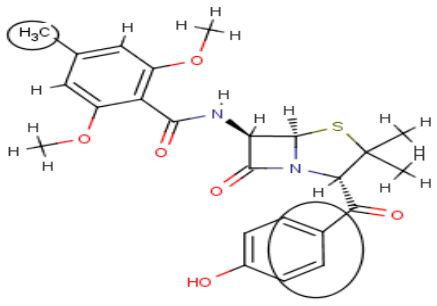

Fig: 3c

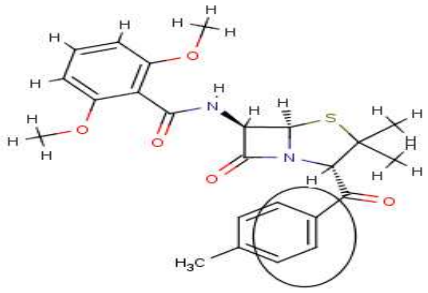

Fig: d

Fig: 3a, b, c, and d Analogs of Methicillin antibiotic

[IV] DISCUSSION:

After identifying β-lactam binding domain in PBP2a, the alternative antibiotics/lead molecules were prepared by taking methicillin antibiotic, the process is called *In silco* designing of lead molecule using the software Marvin Sketch [4 and 5]. The methicillin antibiotic structure was downloaded from NCBI–PubChem Compound database with PubChem ID Number CID_6087. The methicillin structure was modified at functional groups as well as non-functional groups to generate lead molecules/analogs. The methicillin antibiotic having methyl group, carboxylic groups and methoxy group, modification of these groups were done by adding sum of the organic molecules like addition of CH_3, Cl, Mg, and OH groups. Interestingly, analogues with substituent of Benzene, Methylbenzene, CH_3, C_2H_5, Cl, I and Mg in the position to the phenolic hydroxyl, retain substantial biological activity [6 and 7]. The 25 altered methicillin analogs/lead molecules were prepared and 11 analogs were shown with good results. Some of the important analogs were shown in fig: 3a, 3b, 3c and 3d.

[V] CONCLUSION:

To design lead molecule we have used Marvin Sketch software. Using Marvin Sketch we have designed 25 lead molecules/analogs by altering

original structure of methicillin antibiotic [8]. To modify methicillin antibiotic, the original structure was downloaded from NCBI-PubChem compound database with PubChem ID CID_6087.

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