Computer Aided drug studies of Methicillin containing Isoxazole derivatives as targeted antibiotics

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Abstract

Molecular docking techniques have become one of the most popular and successful approaches in drug discovery. This paper describes the comprehensive evaluation docking of Methicillin containing isoxazole derivatives as inhibitors to staphylococcus aureus .The inhibitory activities against S. aureus β-ketoacyl-acyl carrier protein (ACP) synthesis III (FabH) were enquired by molecular docking using the HEX docking software (v 6.1). Results confirm all the designed compounds were good binding

energy when compared with the binging energies of standard drugs such as Vancomycin (-179.66), Ciprofloxacin (-147.11) and Gentamcin (-234.45). Among all the designed compounds, the compound 4 indicate more binding energy value (-327.48). The present study therefore we designed to synthesis these Methicillin derivatives and screen for in-vitro antibacterial effect on S. aureus and other microorganisms.

Keywords: Docking energy, Drug design, FabH, isoxazole, Methicillin, S. aureus,

Introduction

Computer-aided analyses of protein ligand interactions have become significant in view of the difficulties in experimentally characterizing them. Automated prediction of molecular interactions is now an important step in rational drug design. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. This is otherwise called molecular docking and may be described as a method of obtaining the low- energy binding modes of a ligand inside the active site of a receptor, usually a protein or other biological macromolecule [1-3]. Staphylococcus aureus (S. aureus) is a gram-positive coccus that can motive very different types of diseases, about 20% of the human crowd carries this commensal bacterium without any clinical symptoms and respiratory infections to life-threatening pneumonia, endocarditis, sepsis, and toxic shock syndrome [4-5]. Briefly since the initial successful benefit of penicillin for treatment of S. aureus infection, penicillin-resistant strains began to emerge. Methicillin and other semisynthetic penicillins were operative against penicillin G-resistant S. aureus, when methicillin-resistant S. aureus (MRSA) became endemic in far hospitals [6]. The increasing accession of multidrug-resistant S. aureus strains and the appearance of

vancomycin resistance have heightened the importance of the increase of antibacterials with previously unexploited mechanisms of antibiotic action. Saturated fatty acid biosynthesis has lately issued as a prime volunteer for increase of such significant and novel antibacterials [7]. The omnipresent class II fatty acid synthase (FAS) in bacteria is not only urgent to cell survival but also demonstrates structural and organizational differences from that in higher organisms, such as humans. It is generally accepted that highly stout and broad-spectrum antibiotics which selectively aim components of this class II FAS can be obtained [8]. Compounds developed against again essential details of the class II FAS would potentially be sensational against multidrug-resistant bacteria, including MRSA and VRSA. In the analyzed class II FAS, each of the reactions is accomplished by particular enzymes and an ACP [9], The process initiates with a β-ketoacyl-ACP synthase III (KASIII, or FabH)-catalyzed condensation among acyl coenzyme A (CoA) (typically acetyl-CoA) and malonyl-ACP (MACP) to form a 3-ketoacyl-ACP product [6, 10, 11]. Every later extension steps utilize acyl-ACP derivatives and are catalyzed by β-ketoacyl synthase I and II (FabB and FabF) The up of multidrug-resistant strains of S. aureus requires the outspread of new antibiotics with previously unexploited mechanisms of action, such as inhibition of the β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH) [12, 13].

As Methicillin derivatives indicated strong antimicrobial activity, in the work presented here, we focus on the some Methicillin containing isoxazole derivative as targeted antibiotics agents, based on molecular docking among designed new inhibitors and FabH using HEX docking software.

Material and methods

In this study, we used bioinformatics from the RCSB PDB, Drug Bank databases. The PDB (Protein Data Bank) is the lone universal archive

of structural data of biological macromolecules, established in Brookhaven National Laboratories (BNL). The three-dimensional structure of the ligand was generated from the argus lab softwar, and its rotatable torsion angles were identified. The docking analysis was carried by HEX docking software. Hex is calculated protein-ligand docking, and it can superpose pairs of molecules using only witting of their 3D shapes. Docking permits the scientist to virtually screen a database of compounds and bode the strongest binders based on variant scoring functions. It explores ways in which two molecules, such as drugs and an enzyme β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH) (Fig.1) receptor fit together and dock to each other well. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of drug and receptor complex was discovered via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. The parameters applied for the docking process via HEX docking were:

• Correlation type – Shape only

• FFT Mode – 3D fast life

• Grid Dimension – 0.6

• Receptor range – 180

• Ligand Range – 180

• Twist range – 360

• Distance Range – 40

Result and discussion

To evaluate several biological assays and investigation the binding energy between β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH) receptor and designed Methicillin derivatives containing isoxazole performed, and listed in Table 1.

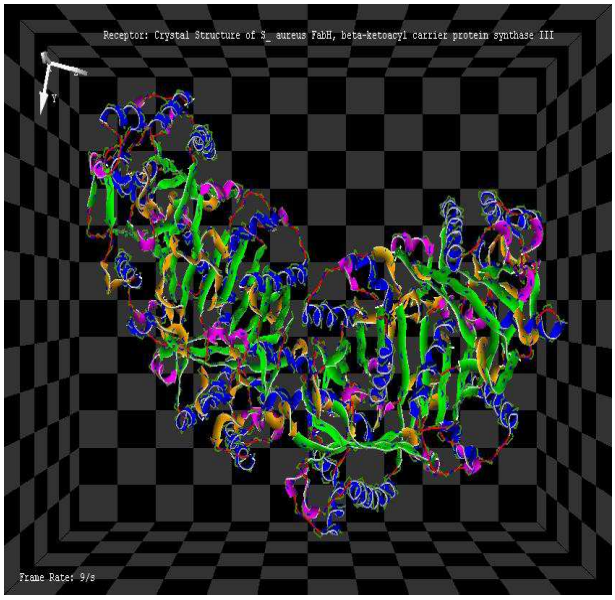

Fig 1. Structure of β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH).

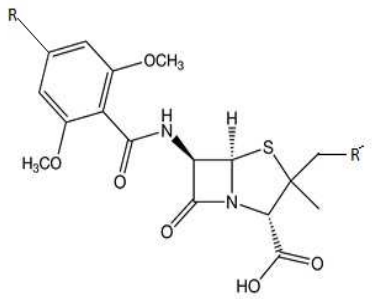

Fig 2. Basic structure of Methicillin derivatives containing isoxazole moiety.

Table 1: Docking Results of FabH enzyme with Methicillin derivatives containing Isoxazole moiety

Compound docked	**R**	**R'**	**E-value**
1	H	H	-289.04
2	CH3	H	-262.45
3	-CH2C6H5	H	-283
4	**-CH(OH)CH(OH)-COOH**	**H**	**-327.48**
5	-CH=CH-C6H5	H	-283.92

6	-C6H4(o-NH2)	H	-277.08
7	H	-NO2	-295.68
8	CH3	-NO2	-286.96
Vancomycin	-	-	-179.66
Ciprofloxacin	-	-	-147.11
Gentamcin	-	-	-214.55

Based on the literature it has been demonstrated clearly that Methicillin containing isoxazole derivatives which can be a potent antibacterial agent have been used to target β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH). The standard antimicrobial agents Vancomycin, Ciprofloxacin and Gentamcin on docking with FabH produce energy values of (-179.66), (-147.55) and (-234.45) (Fig. 3), respectively. Result show that among all the designed compounds, the compound 4 containing Methicillin group (similar position Figure2) position of Methicillin is showing better binding nature, which resulted in a decrease in the energy value. This particular compound showed a decreased in energy values (-327.48) (Fig. 4) which means it was more compatible with the receptor than the standard and other designed Methicillin derivatives. We calculated all five parameters for all the designed compounds. Result showed that satisfy the 'rule-of-5' and it was found that all the ligand molecules satisfied the rule for potent inhibitors. To evaluated relative binding/inhibition activities, this studied provide predicted protein–ligand interactions [14]. An analysis of predicted protein–ligand interactions from the docked poses was performed in order to understand the structural origins of these trends. For purposes of illustration, compound 4 having an H in the R′ position and a long chain (-CH (OH) CH (OH)-COOH) in the R position were used. The long

chain in the R position of compound 4 appears to increase favorable interactions with FabH.

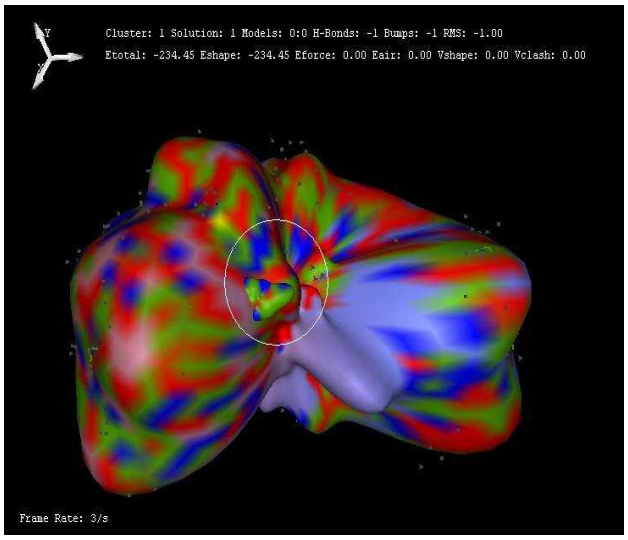

Fig.3: Interaction and binding energy of Gentamcin with β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH)

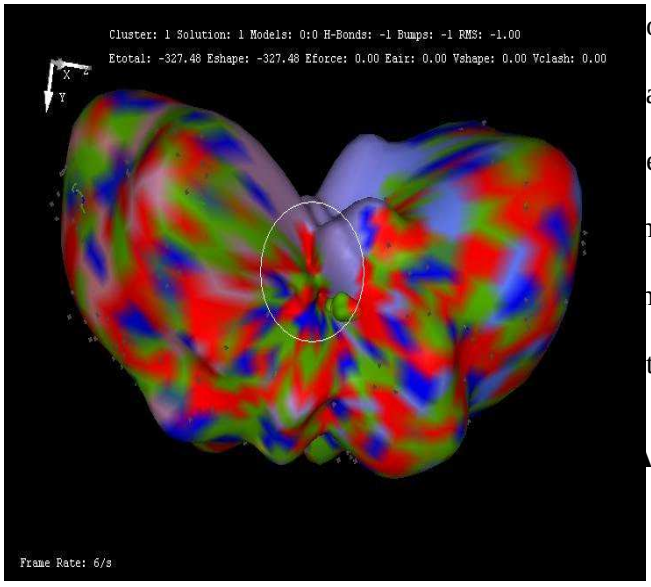

Fig. 4: Interaction and binding energy of compound 4 with β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH)

Conclusion:

The Protein-Ligand interaction plays a main role in structural based drug charting. Present work we have taken β-ketoacyl-acyl carrier protein (ACP) synthase III (FabH) which is a necessary goal for novel antibacterial drug design. When the receptor (FabH) was docked with Vancomycin, Ciprofloxacin, and Gentamcin and the energy values obtained. When the designed Methicillin containing isoxazole derivatives were ocked against the same receptor the energy alues are greater than the standards for some erivatives. Further we designed to synthesis hese Methicillin derivatives and screen for their n-vitro antibacterial effect on S. aureus and ther microorganisms.

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