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Computer Aided Drug Studies of Benzimidazole Containing Isoxazole Derivatives as Targeted Antibiotics

Siva Kumar R[1*], Kumarnallasivan. P[1], Vijai Anand P.R[1], Pradeepchandran. R[2], Jayaveera K.N[3] and Venkatnarayanan. R[1]

[1]*Department of Pharmacy, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore- 641 402, Tamilnadu. India.*
[2]*Department of Pharmacy, Narayana College of Pharmacy, Nellore, Andrapradesh. India.*
[3]*Jawaharalal Nehru Technological University of college of Engineering, Anantapur-515 002, Andrapradesh. India.*

Abstract

Molecular docking is routinely used for understanding drug-receptor interaction in modern drug design. Here we described the docking of benzimidazole containing isoxazole derivatives as inhibitors to Escherichia coli. The inhibitory activities against Escherichia coli β-ketoacyl-acyl carrier protein synthase III (ecKAS III) were investigated by molecular docking using the HEX docking software. All the designed compounds were showed good binding energy when compared with the binging energies of standard drugs such as Ciprofloxacin (-211.04), Amoxilin (-182.23) and cefotaxime (-207.62). Among all the designed compounds, the compound 3 shows more binding energy values (-298.32). Further we planned to synthesis these benzimidazole derivatives and screen for in-vitro anti bacterial effect on Escherichia coli and other micro organisms.

Key words: Benzimidazole, isoxazole, antibacterial activity, ecKAS III.

INTRODUCTION

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which

involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target).

Type II fatty acid synthesis (FAS II) pathway has been recently reported as a attractive targeting for their efficacy against infections caused by multi resistant Gram-positive bacteria [1,2]. FAS II it's proven to be a good target for Gram-negative bacteria [3]. Among the related FAS II enzymes, the condensing protein, β-ketoacyl-acyl carrier protein synthase (KAS), is an essential target for novel antibacterial drug design [4]. KAS III, regulates the fatty acid biosynthesis rate via an initiation pathway and its substrate specificity is a key factor in membrane fatty acid composition and this protein represents a promising target for the antimicrobial drugs design [5]. Moreover, the three-dimensional structure of the protein is highly conserved in various bacteria [6] and its inhibitors may thus act as potent antibiotics with broad-spectrum activity.

The emergence of resistance to the major classes of antibacterial agent is recognized as a serious health concern. Particularly, the emergence of multi drug-resistance strains of Gram-positive bacterial pathogens is a problem of ever increasing significance. The search for antibacterial agents with always remains an important and challenging task. A great number of heterocyclic compounds display interesting antimicrobial activity, especially benzimidazole derivatives having important role in this concern. Some benzimidazole derivatives showed potent antimicrobial activity against pathogenic organisms [7-9].

As benzimidazole derivatives showed potent antimicrobial activity, in this study, we designed some benzimidazole containing isoxazole derivative as targeted antibiotics agents, based on molecular docking between designed new inhibitors and ecKAS III using HEX docking software.

MATERIALS AND METHODS

For our present study we used bioinformatics tools, biological databases like PDB (Protein Data Bank) and software's like Hex, ACD ChemSketch. Hex is an Interactive Molecular Graphics Program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate Protein-Ligand Docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes [10]. It uses Spherical Polar Fourier (SPF) correlations to accelerate the calculations and its one of the few docking programs which has built in graphics to view the result [11].

The PDB (Protein Data Bank) is the single world wide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) [12]. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes.

Methodology

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [13]. The structure of β-ketoacyl-acyl carrier protein synthase (KAS) (Figure 1) which is an essential target for novel antibacterial drug design was retrieved from PDB (1HNJ).

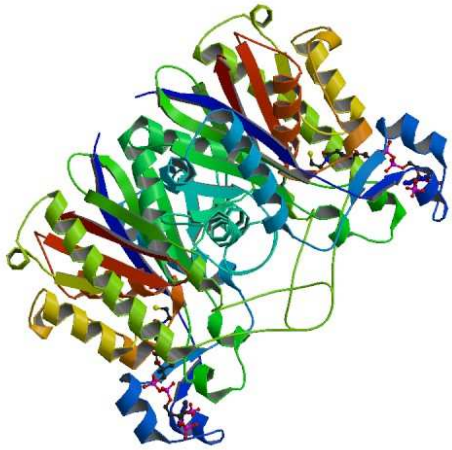


Figure 1: Structure of β-ketoacyl-acyl carrier protein synthase (KAS) 1HNJ

Using Chemsketch the structures of these drugs were sketched. The docking analysis of these compounds with 1HNJ was carried by using HEX docking software.

Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme β-ketoacyl-acyl carrier protein synthase (KAS) 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 identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The parameters used in HEX for the docking process were
• Correlation type – Shape only
• FFT Mode – 3D fast lite
• Grid Dimension – 0.6
• Receptor range – 180
• Ligand Range – 180
• Twist range – 360
• Distance Range – 40
The drug and its analogues were docked with the receptor using the above parameters.

Lipinski Rule of Five

Lipinski rule of 5 helps in distinguishing between drug like and non drug like molecules [14]. It predicts high probability of success or failure due to drug likeness for molecules complying with 3 or more of the following rules

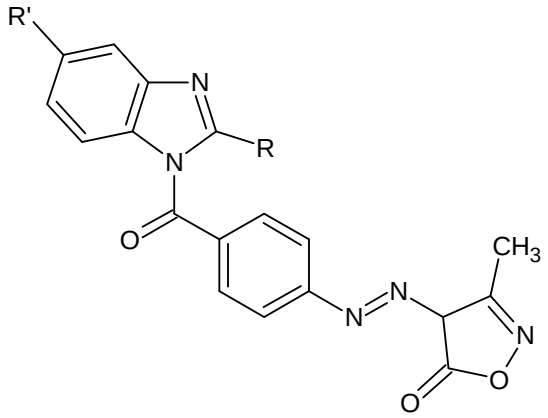
- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

These filters help in early preclinical development and could help avoid costly late-stage preclinical and clinical failures. In this study, we also calculated all five parameters for all the designed compounds.

RESULTS AND DISCUSSION

Docking results between β-ketoacyl-acyl carrier protein synthase (KAS) 1HNJ receptor and designed benzimidazole derivatives containing isoxazole moiety are reported in Table 1.

TABLE 1: Docking Results of 1HNJ enzyme with Benzimidazole derivatives containing Isoxazole moiety



Compound docked	R	R'	E-value
1	H	H	-213.29
2	CH_3	H	-213.49
3	**$-CH_2C_6H_5$**	**H**	**-298.32**
4	-CH(OH)CH(OH)-COOH	H	-173.34
5	$-CH=CH-C_6H_5$	H	-204.60
6	$-C_6H_4(o-NH_2)$	H	-230.45
7	$-C_6H_4(o-COOH)$	H	-242.69
8	$-C_6H_4(o-OH)$	H	-170.34

9	$-CH_2CH_2-COOH$	H	-195.02
10	$-C_6H_4(p-NH_2)$	H	-221.73
11	H	$-NO_2$	-233.83
12	CH_3	$-NO_2$	-222.45
13	$-CH_2C_6H_5$	$-NO_2$	-256.09
14	-CH(OH)CH(OH)-COOH	$-NO_2$	-236.79
15	$-CH=CH-C_6H_5$	$-NO_2$	-264.73
16	$-C_6H_4(o-NH_2)$	$-NO_2$	-231.88
17	$-C_6H_4(o-COOH)$	$-NO_2$	-271.59
18	$-C_6H_4(o-OH)$	$-NO_2$	-230.46
19	$-CH_2CH_2-COOH$	$-NO_2$	-230.85
20	$-C_6H_4(p-NH_2)$	$-NO_2$	-240.88
Ciprofloxacin	-	-	-211.10
Amoxicillin	-	-	-182.23
Cefotaxime	-	-	-207.62

Based on the literature it has been shown clearly that benzimidazole containing isoxazole derivatives which can be a potent antibacterial agent have been used to target β-ketoacyl-acyl carrier protein synthase (KAS). The standard antimicrobial agents Cefotaxime, Amoxicillin and Ciprofloxacin on docking with 1HNJ produce energy values of -207.62 (Figure 2), -182.23 (Figure 3) and -211.10 (Figure 4), respectively. The energy values were calculated using Hex. It was observed using RasMol that among all the designed compounds, the compound 3 containing benzyl group at 2nd position of benzimidazole is showing better binding nature, which resulted in a decrease in the energy value.

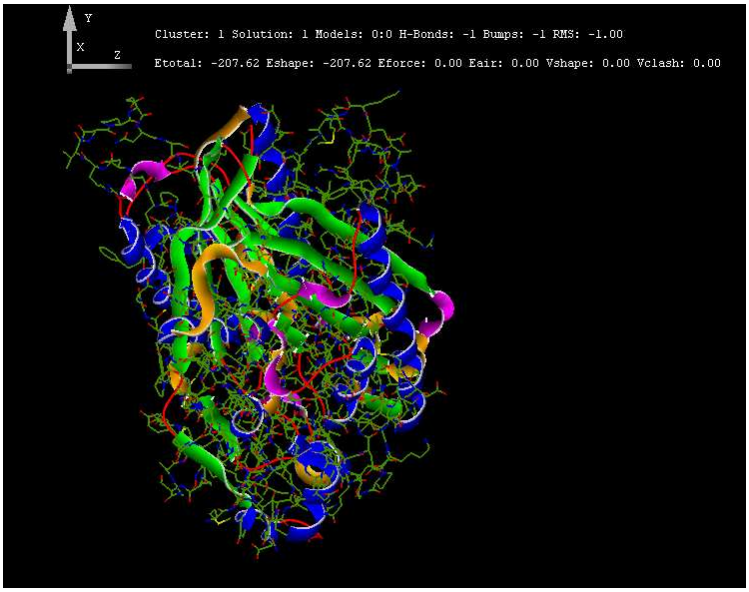


Figure 2: Interaction and binding energy of Cefotaxime with β-ketoacyl-acyl carrier protein synthase (KAS) (1HNJ)

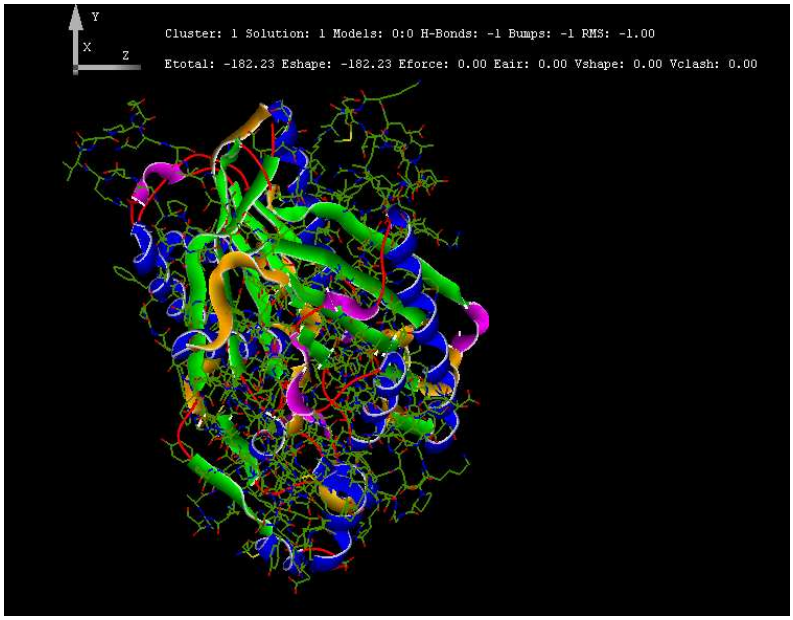


Figure 3: Interaction and binding energy of Amoxicillin with β-ketoacyl-acyl carrier protein synthase (KAS) (1HNJ)

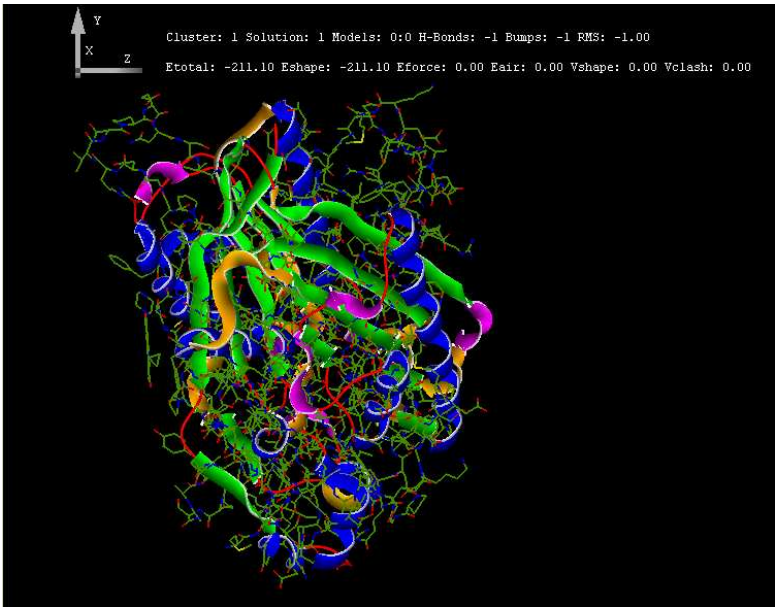


Figure 4: Interaction and binding energy of Ciprofloxacin with β-ketoacyl-acyl carrier protein synthase (KAS) (1HNJ)

This particular compound showed a decreased in energy values (-298.32) which means it was more compatible with the receptor than the standard and other designed benzimidazole derivatives (Figure 5).

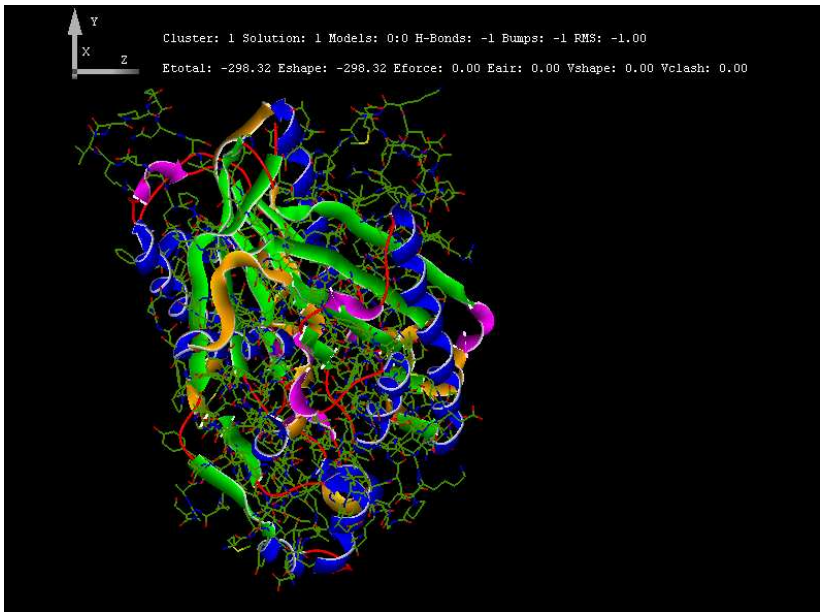


Figure 5: Interaction and binding energy of compound 3 with β-ketoacyl-acyl carrier protein synthase (KAS) (1HNJ)

Lipinski's rule of five was calculated for all the twenty ligand molecules that satisfy the 'rule-of-5' and it was found that all the ligand molecules satisfied the rule for potent inhibitors (Table 2).

Table 2: Lipinski properties of the docked ligands

Compound	Molecular weight	Log P	H bond donor	H bond acceptor	Molar refractivity	Number of criteria met [15]
rule	< 500	<5	<5	<10	40-130	At least 3
1	347	3.115	0	8	93.431	All
2	361	3.423	0	8	98.788	All
3	**437**	**4.706**	**0**	**8**	**122.679**	**All**
4	451	-1.511	3	9	31.793	4
5	449	5.285	0	8	128.801	All
6	438	3.984	2	7	121.958	All
7	467	3.063	1	9	124.367	All
8	439	4.107	1	8	119.209	All
9	419	2.095	1	9	109.250	All
10	438	3.984	2	7	121.958	All
11	393	3.506	1	10	100.684	4
12	407	3.815	1	10	105.421	4
13	483	5.097	1	10	129.932	3

14	497	-1.120	4	11	31.848	3
15	495	4.977	1	10	136.054	3
16	484	4.376	3	9	129.211	All
17	513	3.455	2	11	129.620	3
18	485	4.499	2	10	126.462	4
19	465	2.487	2	11	116.503	4
20	484	4.376	3	9	129.277	All

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken β-ketoacyl-acyl carrier protein synthase (KAS) which is an essential target for novel antibacterial drug design. When the receptor (1HNJ) was docked with Ciprofloxacin, Amoxicillin and Cefotaxime and the energy values obtained were -211.10, -182.23 and -207.62 respectively. When the designed benzimidazole containing isoxazole derivatives were docked against the same receptor the energy values are grater than the standards for some derivatives. So it can be concluded that the designed compounds can be potent antibacterial agent. In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion / Toxicity) properties of these compounds can be calculated using the commercial ADME/T tools available thus reducing the time and cost in drug discovery process. Further we planned to synthesis these benzimidazole derivatives and screen for their *in-vitro* anti bacterial effect on *E.coli* and other micro organisms.

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