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# Antibacterial property of marine *Streptomyces* derived 2-hydroxy benzoic acid screening through *In-Silico* molecular docking studies with bacterial drug target proteins

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**ABSTRACT**

*The development of antimicrobial resistance has increased worldwide and there is urgent need for developing new antimicrobial drugs which will be safe, more potent and less toxic when compared to the existing antibiotics currently available in the market. Molecular Docking is an effective and competent tool for in Silico screening of bioactive compounds derived from natural sources. In this study the interaction of 2-hydroxy benzoic acid (2HBA) with the group of 7 bacterial drug target proteins was studied using AutoDock 4.2.1. The binding energy of the ligand (2HBA) with the receptor proteins selected was found to be between -3.95 Kcal/Mol to -5.96 Kcal/Mol. It showed the least binding energy of -5.96 Kcal/mol, inhibition constant of (Ki) 42.77 μM and formed 4 hydrogen bonds with the penicillin binding protein 1 (PBP1). The results of the docking study suggest that the antibacterial activity of 2HBA was due to its interaction with PBP1, a key protein involved in bacterial cell wall synthesis.*

**Key words** 2-hydroxy benzoic acid; bacterial proteins; AutoDock; antibacterial activity

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## INTRODUCTION

Molecular docking is widely used for understanding drug-receptor interaction and plays a major role in drug designing. Currently, it is one of the well-established computational technique to determine the interaction of two molecules, predict the interaction energy between two molecules and to find the best orientation of ligand with receptor molecule. It also provides very useful information about the affinity and activity of the small molecule on the target proteins. Molecular docking is also used to predict the active site of the intermolecular complex formed between two or more molecules. The application of computational methods to study the formation of intermolecular complexes has been the subject of intensive research focus during the last decade. Docking of lead compounds with bacterial protein targets is currently a viable and cost effective approach before proceeding with experimental studies. In order to have a better understanding of the antibacterial activity of 2HBA against human bacterial pathogens (unpublished data), we have performed the molecular docking studies of the biologically active 2HBA with 7 bacterial drug target proteins.

## MATERIALS AND METHODS

### Ligands

To predict the mode of action of 2HBA on microbial drug target proteins, protein- ligand docking analysis was performed using AutoDock 4.2.1 with Lamarckian genetic algorithm parameters. The 3D structure of 2HBA was obtained from ZINC data base (Figure 1). The ligand structure was downloaded in MOL2 format and the files were downloaded in pdb format for docking studies using PyMOL software.

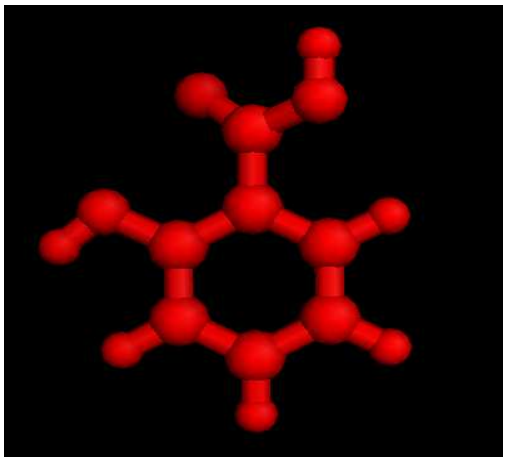

**Figure 1. 3D structure of the compound HBA from ZINC database**

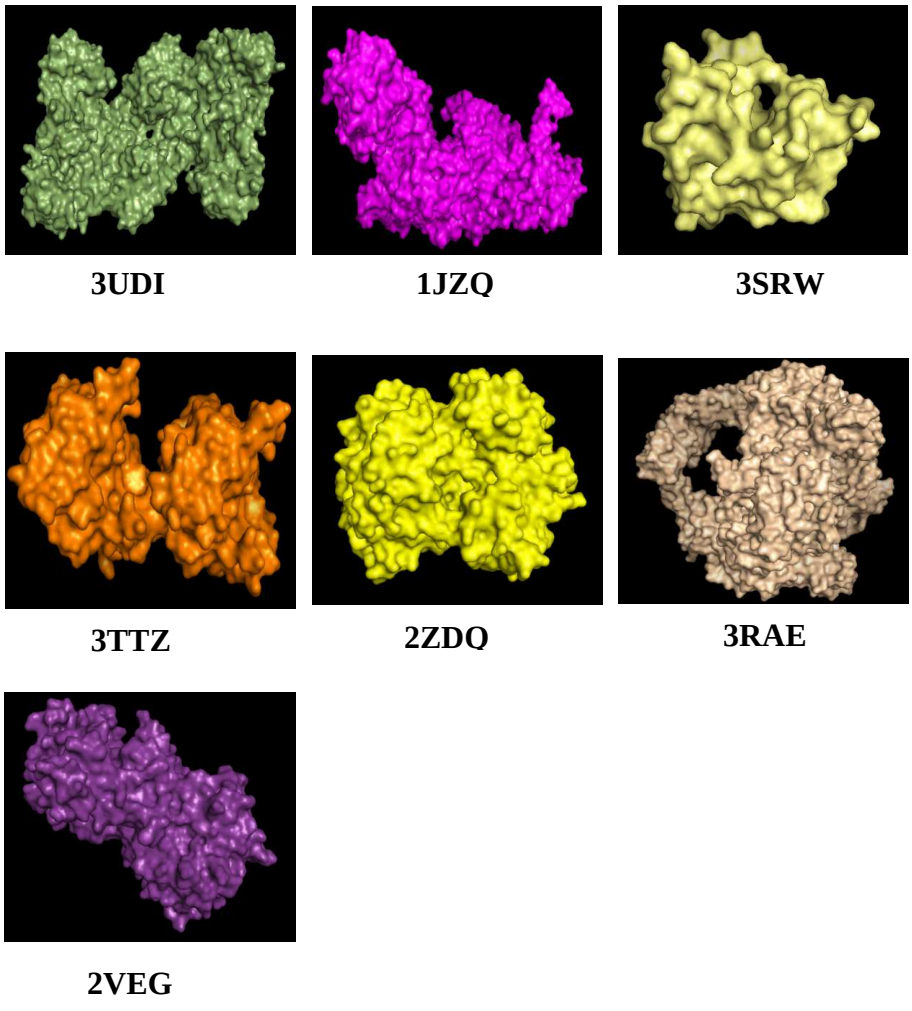


**Figure 2. 3D structures of bacterial target proteins with their respective PDB IDs**

**Bacterial target proteins**

Common anti-bacterial drug targets selected for this study and their respective PDB IDs are given in (Figure 2). They are penicillin binding protein 1 (3UDI), tRNA synthase (1JZQ), dihydrofolate reductase (3SRW), D-alanine ligase (3TTZ), dihydropteroate synthase (2ZDQ), Topoisomerase IV (3RAE) and DNA gyrase (2VEG).

The drug target proteins were downloaded from RCSB protein data bank website at http://www.rcsb.org/pdb/home/home.do, an online database of crystallographic structures of macromolecule with

their respective PDB IDs. All the protein structures downloaded were edited to remove water molecules and default ligand molecules present in the file by using PyMOL tool. Hydrogen atoms were added to the protein molecule as part of the docking procedure in AutoDock. The active sites / pockets present in proteins were identified using MetaPocket 2.0 online server. The Grid Box in AutoDock was set to cover these binding pockets.

AutoDock tools displayed 10 best active sites for all the chosen bacterial proteins and viewed based on ranking of their binding energy. The best ligand-protein confirmations with lowest binding energy requirement for every combination of ligand and receptors were saved as pdb files and were analysed using PyMol and LigPlot+ tools. The lowest binding energy exhibited by the ligand with the target proteins was considered as significant and the number of hydrogen bonds formed was also noted.

## RESULTS AND DISCUSSION

**Table 1. AutoDock results of 2HBA interaction with selected bacterial proteins**

| Protein | PDB ID | BindingEnergy(Kcal/Mol) | KiValue(μM) | No. ofH Bonds |
|---|---|---|---|---|
| Penicillin Binding Protein 1 | 3UDI | -5.96 | 42.77 | 4 |
| TRNA Synthase | 1JZQ | -5.62 | 75.98 | 6 |
| Dihydrofolate Reductase | 3SRW | -4.79 | 309.24 | 4 |
| D-Alanine Ligase | 2ZDQ | -4.38 | 614.28 | 4 |
| Dihydropteroate Synthase | 2VEG | -4.18 | 858.99 | 5 |
| Topoisomerase IV | 3RAE | -3.92 | 1340 | 3 |
| Topoisomerase | 3TTZ | -3.75 | 1790 | 4 |

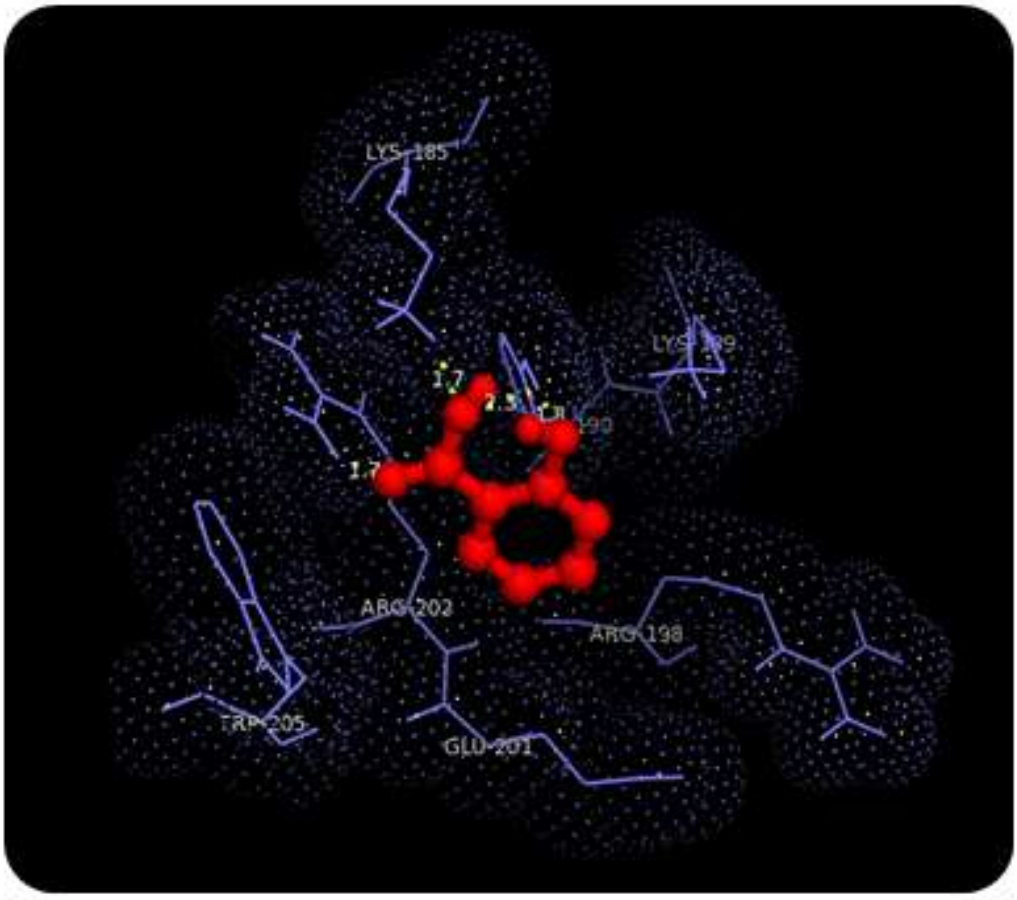


**Figure 3. Interaction of the ligand (HBA) with Penicillin Binding Protein 1 (PBP1)**

### Interaction of HBA with bacterial drug target proteins

Among the chosen anti-bacterial protein targets, 2HBA showed significant interaction with penicillin binding protein 1 (Table 1). It showed the least binding energy of -5.96 Kcal/mol, inhibition constant of (Ki) 42.77 μM and formed 4 hydrogen bonds i.e., Lys-185 (1.7Å), Arg-202 (1.7Å) and Tyr-190 (1.8Å & 2.3Å) (Figure 3). 2HBA showed the binding energy of -5.62Kcal/mol with tRNA synthase (1JZQ) (Figure 4), -4.79 Kcal/mol with dihydrofolate reductase (3SRW) (Figure5), -4.38 Kcal/mol with D-alanine ligase (3TTZ), -4.18 Kcal/mol with

dihydropteroate synthase (2ZDQ), -3.92 Kcal/mol with topoisomerase IV (3RAE) and -3.75 Kcal/mol with DNA gyrase (2VEG).

**Proposed mechanism of action of HBA with drug target proteins**

Molecular docking has been proved very efficient tool for novel drug discovery for targeting protein. Among different types of docking, protein-ligand docking is of special interest, because of its application in pharmaceutical industry (Syed and Sumra, 2013). Protein-ligand docking refers to search for the accurate ligand conformations within a targeted protein when the structure of proteins is known (Adhithya and Lokesh, 2015).Drug interaction with proteins involve hydrogen bonding and the stability of the hydrogen bond hardly permit the formation of an easily reversible drug receptor complex. H-bond is an important type of bonding between drug and receptor and it is a weak and can be easily broken. Since many drugs (ligand) contain hydroxyl, amino, carboxyl and carbonyl groups, they can form hydrogen bonds with the receptor (target proteins) complex. Hydrogen bond is unique to hydrogen because it is the only atom that can carry a positive at physiological pH while remaining covalently bonded in molecules(Godwin and Alvin, 2014).

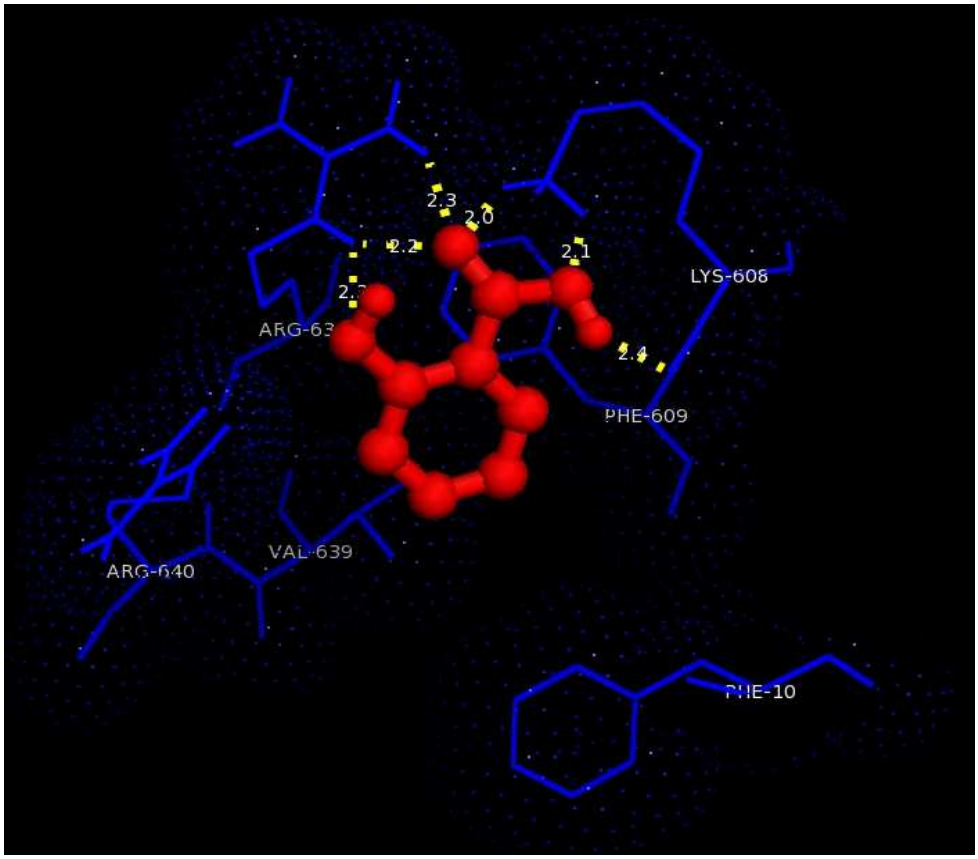


**Figure 4. Interaction of the ligand (HBA) with tRNA synthase**

The interaction of the ligand (HBA) with various bacterial drug target proteins by *in Silico* molecular docking approach predict the mechanism behind the antibacterial activity exhibited by HBA. Similarly, the existing antibacterial drugs such as penicillin, vancomycin, β-lactum drugs, cephalosporins and carbapenems inhibit bacterial growth by inhibiting cell wall synthesis (Harold and Thomas, 1996). These antibiotics inhibit bacterial cell synthesis by inhibiting the enzyme penicillin binding protein. The function of this enzyme is to form the peptidoglycan cross links in the cell wall. Thus, the formation of new cell wall is prevented and eventually leads to cell death. 2HBA (2.5Mm) has been reported to inhibit completely the growth of *Penicilliumexpansam* after 30 min of incubation and it inhibited the growth of *P. expansam* by causing damage to the plasma membrane of conidia (Ting and Xiao, 2006).

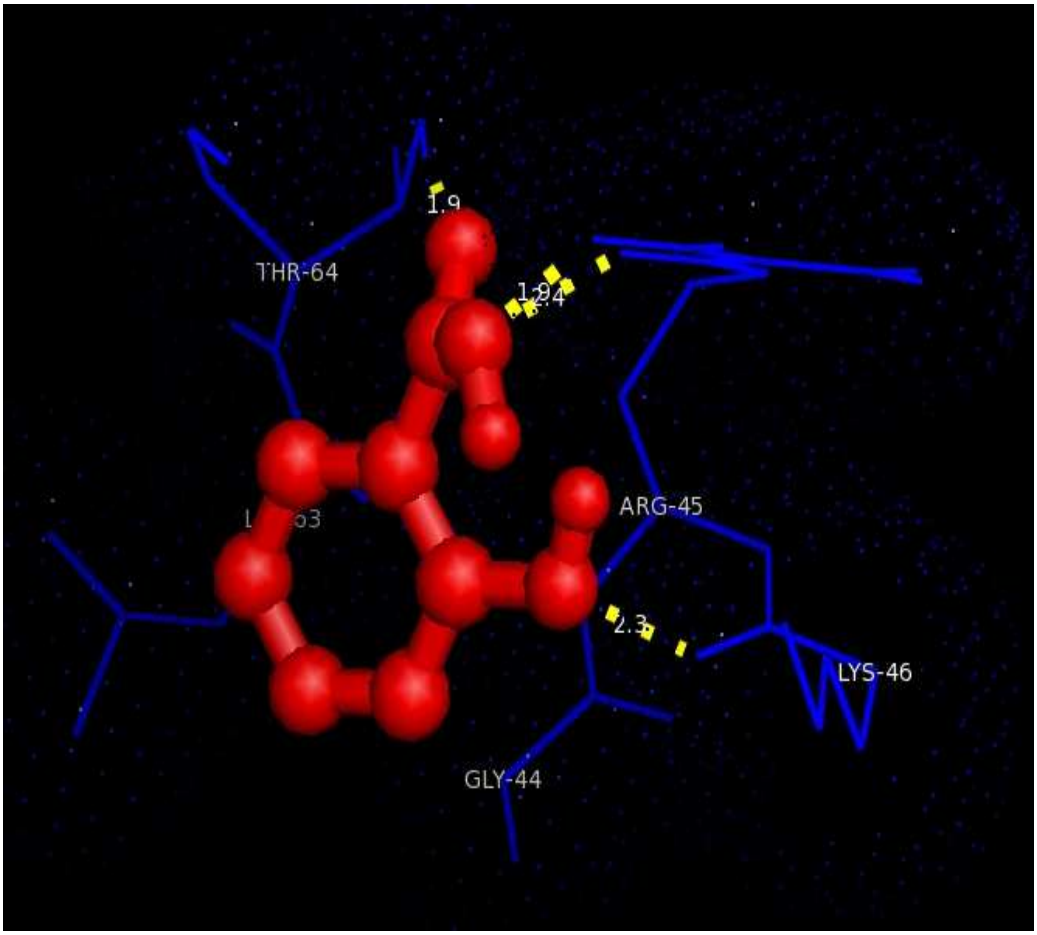


**Figure 5. Interaction of the ligand (HBA) with dihydrofolate reductase**

PBP involved in the synthesis of peptidoglycan, a major bacterial cell wall component. B-lactum antibiotics such as penicillin, cephalosporin, carbapenems, and monobactams target these enzymes to inhibit cell wall synthesis by binding with PBP.It was reported that ceftobiprole inhibits PBP1 with the least binding energy of -5.1Kcal/Mol. It formed more than five hydrogen bonds with PBP1. Amino acid residues Gln 582 (2.3 Å), Gln 582 (2.0 Å), Gln 582 (2.1), Gln 540 (2.5 Å), Lys 603 (2.3 Å)and Lys 603 (2.3 Å) (Kumar et al., 2014). Penicillin showed least binding energy of -84.3 Kcal/Mol with PBP1, ampicillin (-89.3 Kcal/Mol), cefadroxil (107.5 Kcal/Mol),methicillin (88.6 Kcal/Mol), oxacillin (-101.6 Kcal/Mol). Azlocillin showed least binding energy with PBP1 (-122.1 Kcal/Mol). Ervaticine, ibogamine, methylvoaphylline and coronaridine and hydroxyindolenine isolated from *Tabernaemontanadivaricata*, exhibited least binding energy with PBS and the binding energy was -5.14, -4.78, -4.7, -4.44, -4.72 Kcal/Mol respectively.

## CONCLUSION

*In-Silico* screening of 2HBA helped to identify its antibacterial property and based on the results of molecular docking studies, it can be concluded that HBA inhibit cell wall synthesis of bacteria thereby inhibiting the growth of the bacteria.

## REFERENCES

[1] R. Adhithya;RLokesh. *Journal of Chemical and Pharmaceutical Research*, **2015**,7, 352-357.
[2] SE Godwin JM Alvin. *International Journal of Drug Development and Research*, **2013**, 6, 248-258.
[3] CN Harold; DG Thomas. *Antimicrobial Chemotherapy*, University of Texas Medical Branch at Galveston, 4th ed., University of Texas Medical Branch at Galveston, **1996**.
[4] KM Kumar; PAnitha.*3 Biotechnology*,**2014**, 4, 241–251.
[5] XD Shao;XL Wen;HL Gong; F Jing. *PeerJournal*,**2016**, 4, e1791.
[6] SA Syed; WASumra. *Theoretical Biology and Medical Modelling*, **2013**,10, 63-79.
[7] Y Ting; DZ Xiao. *Journal of Plant Growth Regulator*, **2006**, 25, 166–174.