EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 Special Issue-3 (August-2016) pp. 96-108

Journal home page: http://www.ijcrar.com

In-Silico Approach to Predict the Antifungal Activity of Compounds from *Moringa concanesis* Nimmo against Flavohemoprotein (YHB1)

B. Brindha Banu[1,2]*, R. Tobika[1] and S. Santhi[1]

[1]Department of Biochemistry and Bioinformatics & Clinical Trial Management, Dr. MGR Janaki College of Arts and Science, Chennai, Tamil Nadu, India
[2]Department of Biochemistry, Kongunadu College of Arts and Science, Coimbatore, Tamil Nadu, India

Corresponding author

KEYWORDS

Moringa concanesis Nimmo,
antifungal activity,
Candida albicans,
YHB1,
nitrosative stress,
Modeller,
docking

A B S T R A C T

The plant *Moringa concanesis* Nimmo is one of the important medicinal tree belongs to family *Moringaceae* locally known as Kattu murungai by tribal people in Tamil Nadu. Hexanedioic acid, bis (2-ethylhexyl), 2-ethyl-2-propylhexan-1-ol was identified from ethanolic extracts of *Moringa concanesis* Nimmo which contains antifungal activity. *Candida albicans* is a form of yeast which cause Candidiasis in human. YHB1 is a gene present in *Candida albicans* which detoxifies NO and protects the fungus from various noxious nitrogen compound. Since nitric oxide is generated by macrophages of the host immune system. This plays a role in the inducible response to nitrosative stress and also virulence. There is no separate 3D Structure for YHB1 in PDB. Homology modelling were done to predict the 3D structure of the protein using Modeller. Molecular docking were studied using Auto dock and analyze the interaction of the above compounds with YHB1. The 3D structure of protein was predicted .The scores obtained from the docking study shows good interactions with Hexanedioic acid, bis (2-ethylhexyl), 2-ethyl-2-propylhexan-1-ol against YHB1. From the molecular docking analysis, these compounds showing least binding energy and good hydrogen bond interaction with YHB1.We conclude that these compounds may act as potent antifungal agent against YHB1.

Introduction

The use of medicinal plants has been used to treat human diseases since prehistorical times. It is not surprising that interest has increased in plant based natural products to combat infectious diseases (Cowan, 1999) (Liu *et al*., 2001) (Oumzil *et al*., 2002).

Moringa concanensis Nimmo is such plant that is popular in folk medicine and has been used for the management of various disease

conditions. *Moringa concanensis* Nimmo belongs to the family *Moringaceae* (Paliwal, 2011) Various parts of the plant have been used in traditional medicine to manage conditions like diabetes, inflammation, pain, fever, sore eyes, high blood pressure, jaundice, skin tumor, thyroid problems (Anbazhakan *et al*.,2007; Khare, 2007).

The macroscopical characters of the bark of *Moringa concanensis* Nimmo are described as externally grey or brownish white rough bark deep and irregularly fissured. Internally yellowish white or sandal colored. Externally and internally are granular in texture6.3 mm. thick, bitter, odorless, curved and quill bark, short in outer bark and fibrous in inner bark (Sandeep Singh *et al*., 2013)

Moringa concanesis Nimmo is one such genus whose various species have not been explored fully despite the enormous reports concerning the various parts of a few species' potentials such as: cardiac and circulatory stimulants; antitumor; antipyretic; antiepileptic; anti-inflammatory; antiulcer; antispasmodic; diuretic antihypertensive; cholesterol lowering; antioxidant; antidiabetic; hepato- protective; antibacterial and antifungal activities (Arora *et al*., 2013).

Anti-fungi activity of the *Moringa concanensis* plant bark of ethanolic extracts was determined against selected fungi showing activities (Balamurugan and Balakrishnan, 2013).

Sixteen components were identified by GC-MS analysis from bark of ethanolic extracts of *Moringa Concanensis* Nimmo (Balamurugan *et al*., 2015). Among them 2-ethyl-2-propylhexan-1-ol (11.04%) and Hexanedioicacid, bis (2-ethylhexyl) (6.36%) have antifungal activity (Xue-na *et al*.,)

Of all fungi, only around 600 species are human pathogens (Brown *et al*., 2012).This relatively small group encompasses fungi that cause relatively mild infections of the skin (e.g., dermatophytes and Malassezia species), fungi that cause severe cutaneous infections (e.g., Sporotrixschenkii) and fungi that have the potential to cause life-threatening systemic infections (e.g., *Aspergillus fumigatus, Cryptococcus neoformans, Histoplasmacapsulatum*, and *Candida albicans*). Indeed, *Candida spp* are the fourth most common cause of hospital-acquired systemic infections in the United States with crude mortality rates of up to 50% (Pfaller and Diekema, 2010, 2007). *C. albicans* can cause two major types of infections in humans: superficial infections, such as oral or vaginal candidiasis, and life-threatening systemic infections (Calderone and Clancy, 2012).

Candida albicans, the most prevalent human fungal pathogen. YHB1, a flavohemoglobin that detoxifies *NO (nitric oxide) by converting it to nitrate (Calderone and Clancy. 2012) in *C. albicans* and other microbes (Bethann *et al*., 2005). YHB1 inactivation renders *Candida albicans* cells sensitive to nitric acid (Calderone and Clancy, 2012).

In homology modeling, the higher the sequence identity between the protein sequence to be modeled (the target), and the protein template, the higher the quality of the model (Baker and Sali, 2001). In the absence of an experimentally determined structure, comparative or homology modeling often provides a useful 3-D model for a protein that is related to at least one known protein structure (Marti-Renom *et al*., 2000; Fiser, 2004; Misura and Baker, 2005; Petrey and Honig, 2005; Misura *et al*., 2006). Comparative modeling predicts the 3-D structure of a given protein sequence (target) based primarily on its alignment to

one or more proteins of known structure (templates).

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterization of the binding behavior plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes (Kitchen *et al*., 2004).

Materials and Methods

Uniprot

UniProt is a freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature.

UNIPROTKB

UniProt Knowledgebase (UniProtKB) is a protein database partially curated by experts, consisting of two sections: UniProtKB/ Swiss-Prot (containing reviewed, manually annotated entries) and UniProtKB/TrEMBL (containing unreviewed, automatically annotated entries). As of 19 March 2014, release "2014_03" of UniProtKB/Swiss-Prot contains 542,782 sequence entries (comprising 193,019,802 amino acids abstracted from 226,896 references) and release "2014_03" of UniProtKB/TrEMBL contains 54,247,468 sequence entries (comprising 17,207,833,179 amino acids)

Blast

The Basic Local Alignment Search Tool (BLAST) is one of the most well-known and widely used bioinformatics tools available. BLASTp is used to compare two gene or two protein sequences and find regions of local similarity between those sequences (Casey, 2005).

PDB-Protein Data Bank

The Protein Data Bank (PDB; http://www.rcsb.org/pdb/) is the single worldwide archive of structural data of biological macromolecules (Berman *et al*., 1999). Today depositors to the PDB have varying expertise in the techniques of X-ray crystal structure determination, NMR, cryoelectron microscopy and theoretical modeling.

Modeller

MODELLER uses Python as its control language. MODELLER is a computer program for comparative protein structure modeling (Fiser, 2000). In the simplest case, the input is an alignment of a sequence to be modeled with the template structure(s), the atomic coordinates of the template(s), and a simple script file (Marti-Renom, 2004) Using the structure template, the structure of YHB1 can be generated using MODELLER.

PDBsum

PDBsum is a validation program validates the predicted structure by checking various parameters. PDBsum is a database that provides an overview of the contents of each 3D macromolecular structure deposited in the Protein Data Bank (Laskowski, 1997). PDBsum contains a number of protein structures which may be of interest in structure-based drug design.

Chemsketch

ACD/ChemSketch, freeware from ACD Labs, is a chemical structure drawing program. Two-dimensional chemical

structures are the common representation in textbooks and other print materials in chemistry, biology, and the health sciences. They display the interconnectivity of atoms in the structure (Sinex and Gage, 2004).

Pubchem

PubChem (http://pubchem.ncbi.nlm.nih.gov) is an open repository for chemical structures and their biological test results (Bolton *et al*., 2008). PubChem Compound is a searchable database of chemical structures with validated chemical depiction information provided to describe substances in PubChem Substance. Structures stored within PubChem Compounds are pre-clustered and cross-referenced by identity and similarity groups. PubChem Compound includes over 5M compounds.

Autodock

Molecular docking studies were carried out using Autodock 4.2software (Gunda *et al*., 2015) which uses Genetic algorithm (GA). For inhibitory site direction, grid encompassing was used. The Autodock program went through pre calculated grids of affinity potentials with a variety of search algorithms and combined a rapid energy evaluation to find suitable binding positions (Morris *et al*., 2008). The search results were on the basis of the Lamarckian genetic algorithm and for analysis, binding energy was used. Then each ligand was processed in docking experiment with 10 simulations using Autodock and ranked according to increasing binding energy. All ligands were compared with each other on the basis of binding energy and other factors. (Ranjithreddy *et al*., 2015)

AutoDock was run several times to get various docked conformations, and used to analyze the predicted docking energy. The binding sites for these molecules were selected based on the ligand-binding pocket of the templates (Chang *et al*., 2010).

Pymol

Visualization of the docked structure was performed on PyMol molecular graphics program, a comprehensive software package for rendering and animating 3D-structures. This software produced high quality three dimensional images of small molecules, proteins and nucleic acids.

Open Babel

Open Babel is a chemical toolbox designed to speak the many languages of chemical data. It's an open, collaborative project allowing anyone to search, convert, analyze, or store data from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas. Open Babel is a project to facilitate the interconversion of chemical data from one format to another – including file formats of various types (Noel M O'Boyle, 2011).

Results and Discussion

Protein Structure Prediction

Retrieval of Protein Sequence

The protein sequence of YHB1 from Candida albicans organism is obtained from UniProt database (http://www.uniprot.org/) and its UniProtid is Q59MV9 .The FASTA sequence of the protein is used for our studies and the total number of amino acid is 398.

Protein Structure Retrieval

The target protein sequence was blasted using BLASTP (Mark Johnson, 2008) across Protein Data Bank to obtain the most identical structures based on the percentage

of identity, similarity, expectation values and alignment scores which could be considered as templates in the modeling procedure. From the, sequence we can identify the homologous structure for YHB1, which can be used as the template for Homology modelling. The structure of homologous template is used for homology modelling were downloaded as PDB format from PDB and its id 4zj1 from Escherichia coli organism.

Homology Modelling

Using the downloaded structure as a template, the structure of YHB1 can be generated using MODELLER. From the scores obtained target.BL00010001.pdb 33.73194 is the best model which is having least score.

target.BL00010001.pdb	33.73194
target.BL00020001.pdb	36.27905
target.BL00030001.pdb	36.29542

Validation of generated model

Structure verification programs such as PROCHECK and SAVES (http://nihserver.mbi.ucla.edu/SAVES/) were used to evaluate the 3D-model of YHB1.

The above mentioned validation programs validate the predicted structure by checking various parameters. While PROCHECK, a structure verification program relies on Ramachandran plot, determines the quality of the predicted structure by assessing various parameters such as lengths, angles and planarity of the peptide bonds, geometry of the hydrogen bonds, and side chain conformations of protein structures as a function of atomic resolution. The plot value was found to be 89.4% with 313 residues in the favored region. 8.6% of the residues lie in additional allowed region and 2.0% in the generously allowed region. Only about 1.5% of the residues were located in the disallowed region. The number of glycine residues is 21 and proline residues are 26.

In the structure of YHB1, red colour represents alpha helix, yellow colour represents beta sheets and green colour represents loops.

Ligand Preparation

The selected 2 ligands were then analyzed for drug- relevant properties by Molinspiration tool (http://www.molinspiration.com/cgibin/properties) .The 2D structure of hexanedioic acid, bis 2(ethylhexyl) and 1-Hexanol, 2-ethyl-2-propyl are drawn in ACD/chemsketch and then converted to 3D structure and saved as Mdl mol format. Then it is converted to pdb format for further docking process using Open Babel.

Docking Studies

Molecular docking may be defined as an optimization problem, which would describe the “best-fit” orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most interesting case is the protein -ligand interaction, because of its applications in medicines.

Table.1 Molecular properties of ligand molecules

S.no	Compound name	Molecular weight	No. of hydrogen bond donor	No. of hydrogen bond acceptor
1.	Hexanedioic acid,bis 2(ethylhexyl)	370.57	0	4
2.	2-ethyl-2-propylhexan-1-ol	172.31	1	1

Table.2 Docking scores and distance between YHB1 and Hexanedioic acid, bis 2(ethylhexyl)

YHB1		**Hexanedioic acid, bis2(ethylhexyl)**	**Distance (Å)**	**Binding energy (kcal/mol)**
Residues	**Atom**			
HIS93	**NE2**	**O**	**3.0**	**-4.28**
ASP55	**OD2**	**O**	**2.9**	
GLN61	**OE1**	**O**	**3.4**	

Table.3 Docking scores and distance between YHB1 and 2-ethyl-2-propylhexan-1-ol

YHB1		**2-ethyl-2-propylhexan-1-ol**	**Distance (Å)**	**Binding energy (kcal/mol)**
Residues	**Atom**			
PRO204	**O**	**H**	**2.0**	**-5.08**
GLU207	**N**	**O**	**3.0**	

Fig.1 (a) *Moringa concanesis* Nimmo plant; (b) bark of Moringa

(a) **(b)**

Fig.2 Alignment and description of sequence using BLAST

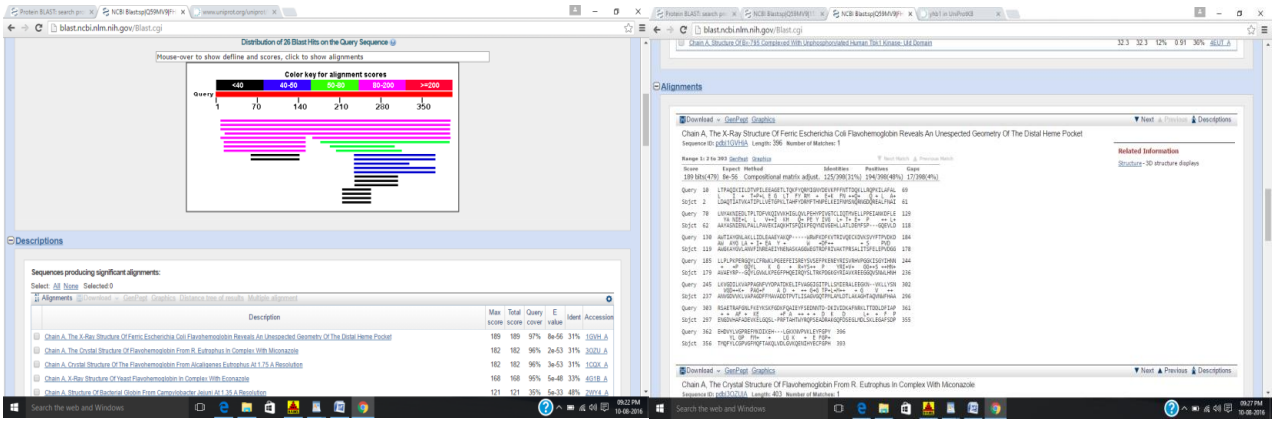
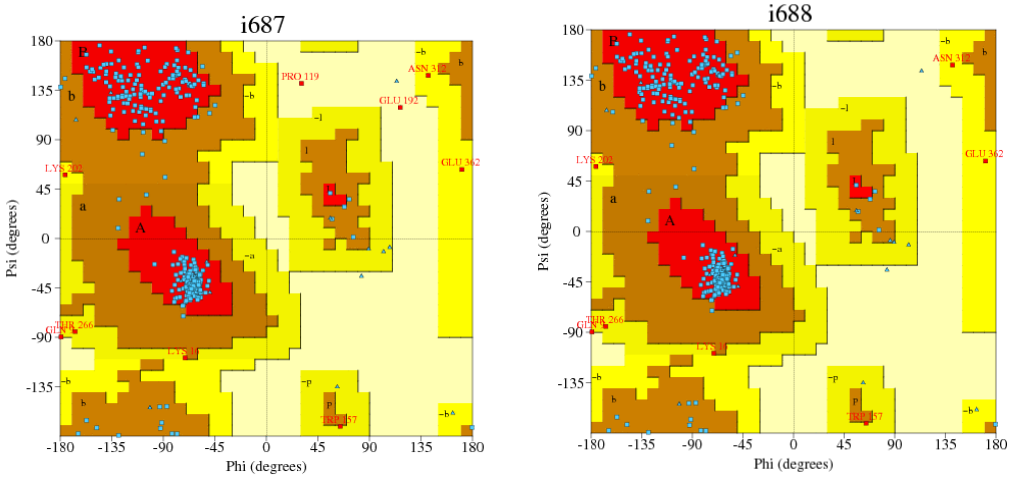


Table.4 Key residues of YHB1, hydrogen bonds and docking scores

S.No	Compounds	Key residues of YHB1	Docking scores Kcal/mol	H-Bond
1.	Hexanedioic acid,bis 2(ethylhexyl)	GLN61, ASP55, HIS93	-4.28	1
2.	2-ethyl-2-propylhexan-1-ol	PRO204, GLU207	-5.08	2

Fig.3 (a) Ramachandran Plot before loop refinement; (b) Ramachandran Plot after loop refinement.



(a) **(b)**

Fig.4 Verification of generated model of YHB1 using PROCHECK

PROCHECK statistics

1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	313	89.4%*
Additional allowed regions	[a,b,l,p]	30	8.6%
Generously allowed regions	[~a,~b,~l,~p]	7	2.0%
Disallowed regions	[XX]	0	0.0%
Non-glycine and non-proline residues		350	100.0%
End-residues (excl. Gly and Pro)		1	
Glycine residues		21	
Proline residues		26	
Total number of residues		398	

Based on an analysis of **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good qu
favoured regions [A,B,L].

2. G-Factors

Parameter	Score	Average Score
Dihedral angles:-		
Phi-psi distribution	0.02	
Chi1-chi2 distribution	-0.15	
Chi1 only	0.08	
Chi3 & chi4	0.39	
Omega	-0.25	
		-0.05

Fig.5 Structure of YHB1

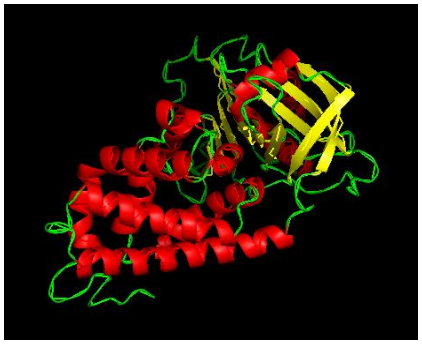
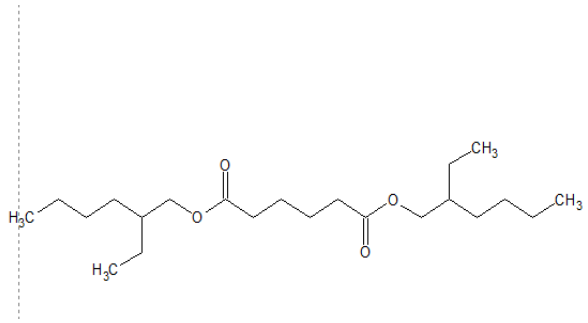
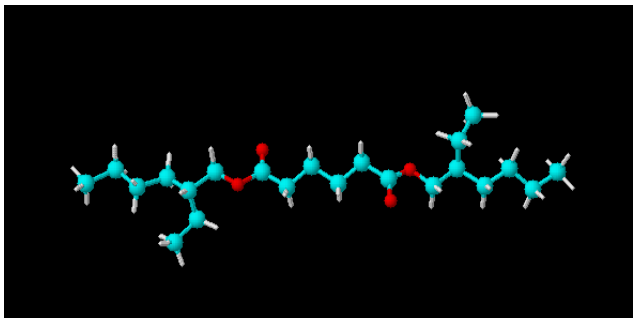


Fig.6 (a) Schematic representation drawn from ACD/chemsketch; (b) 3D structure of hexanedioic acid, bis 2(ethylhexyl)

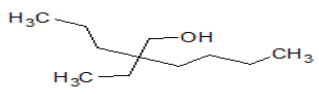


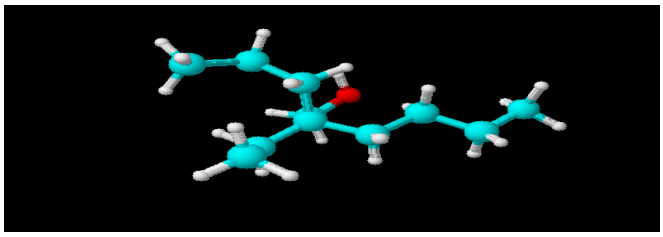
(a)



(b)

Fig.7 (a) Schematic representation drawn fromACD/chemsketch; (b) 3D structure of 2-ethyl-2-propylhexan-1-ol

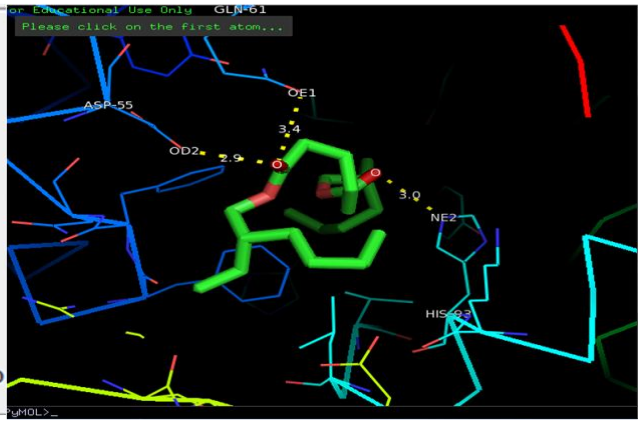




(a) **(b)**

Fig.8 (a) Docking properties of Hexanedioic acid, bis 2(ethylhexyl) and YHB1 ; (b) interactions are viewed in Pymol. green colour represents ligand, blue colour represents protein, yellow dotted lines represents hydrogen bond.

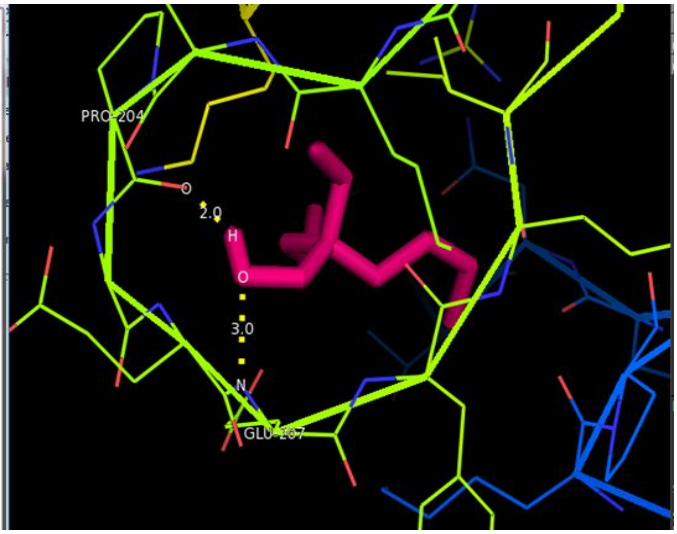
binding_energy=-4.28
ligand_efficiency=-0.16
inhib_constant=725.04
inhib_constant_units=uM
intermol_energy=-9.95
vdw_hb_desolv_energy=-10.01
electrostatic_energy=0.06
total_internal=-0.83
torsional_energy=5.67
unbound_energy=-0.83
filename=best.dlg
cIRMS=0.0
refRMS=51.04
rseed1=None
rseed2=None
1 hydrogen bonds formed:
yhb1_2: :HIS93:HE2 : hexa-3:A:MOL0:O



(a) **(b)**

Fig.9 (a) Docking properties of YHB1 and 2-ethyl-2-propylhexan-1-ol ; (b) interactions are viewed in Pymol. pink represents ligand, yellow represents YHB1, yellow dotted lines represents hydrogen bond

binding_energy=-5.08
ligand_efficiency=-0.42
inhib_constant=187.75
inhib_constant_units=uM
intermol_energy=-7.47
vdw_hb_desolv_energy=-7.44
electrostatic_energy=-0.03
total_internal=-0.53
torsional_energy=2.39
unbound_energy=-0.53
filename=best.dlg
cIRMS=0.0
refRMS=61.11
rseed1=None
rseed2=None
2 hydrogen bonds formed:
ethyl-3:A:MOL0:H : yhb1_2: :PRO204:O
yhb1_2: :GLU207:HN : ethyl-3:A:MOL0:O



(a) **(b)**

Ligand is a small molecule, which interacts with protein's binding sites. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes (Sharma *et al*., 2010). AutoDock Tools (ADT) assigned polar hydrogen's, united atom Kollman charges, solvation parameters and fragmental volumes to the protein. AutoDock saved the prepared file in PDBQT format. AutoGrid was used for the preparation of the grid map using a grid box. The docking poses were ranked according to their docking scores and both the ranked list of docked ligands and their corresponding binding pose (Zhang *et al*., 2008). The docking results show best interaction withYHB1 and the ligands.

After docking study, the interaction and distance between the YHB1 and ligand was viewed in Pymol, before that the file format should be changed using Open Babel.

Docking Studies between Yhb1 and Hexanedioic acid, bis 2(ethylhexyl)

The docking scores were obtained between the generated model of YHB1 and hexanedioic acid, bis 2(ethylhexyl) is -4.28 kcal/mol. This docking between YHB1 and hexanedioic acid, bis 2(ethylhexyl) shows 3 interactions and the distance between HIS93 residue's NE2 atom with O atom of ligand is 3.0 Å, ASP55 residue's OD2 atom with O atom of ligand is 2.9 Å and GLN61 residue's OE1 atom with O atom of ligand is 3.4 Å.

Docking studies between YHB1 and 2-ethyl-2-propylhexan-1-ol

The docking scores were obtained between the generated model of YHB1 and -Hexanol, 2-ethyl-2-propyl is -5.08 kcal/mol. The docking shows interaction and distance between PRO204 residue's O atom and H atom of ligand is 2.0 Å, GLU207 residue's N atom and the O atom of ligand is 3.0 Å.

Based on the docking studies, YHB1 inhibitory activity of compounds was to be decreased in the order of 2-ethyl-2-propylhexan-1-ol and Hexanedioic acid, bis 2 (ethylhexyl). On the basis of the above study, 2-ethyl-2-propylhexan-1-ol and Hexanedioic acid, bis 2(ethylhexyl) possess potential YHB1 inhibitory binding sites. This may be attributed due to the differences in the position of the functional groups in the compounds (Arumugam *et al*., 2013).

In Conclusion, the present study clearly demonstrated the *insilco* molecular docking studies of hexanedioic acid, bis2 (ethylhexyl) and 2-ethyl-2-propylhexan-1-ol with the generated model of YHB1 which detoxifies .NO (nitric acid) in *Candida albicans*. When the docking scores of the above compounds were compared, hexanedioic acid, bis2 (ethylhexyl) is having least score (-4.28kcal/mol) than the 2-ethyl-2-propylhexan-1-ol. So, docking studies with hexanedioic acid, bis2 (ethylhexyl) shows good inhibition of YHB1. Hence this compound is a potent antifungal agent against YHB1.

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How to cite this article:

Brindha Banu, B., R. Tobika and Santhi, S. 2016. In-Silico Approach to Predict the Antifungal Activity of Compounds from Moringa concanesis Nimmo against Flavohemoprotein (YHB1). *Int.J.Curr.Res.Aca.Rev.* Special Issue-3: 96-108.