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Insilico Docking Analysis of Bioactive Compounds from *Moringa concanesis* Nimmo against MabA (FabG1) Protein to Predict it Antibacterial Activity

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KEYWORDS

Moringa concanesis Nimmo, MabA, antibacterial, *Mycobacterium tuberculosis*, hexanedioic acid, bis (2ethyl hexyl).

A B S T R A C T

The traditional medicine plants contain more phytochemical and bioactive constituent and are the best source to obtain a variety of drugs to cure ailments. *Moringa Concanesis* Nimmo is a medicinal plant, which possesses anticancer, antibacterial, antifungal, analgesic and anti-inflammatory properties. In the present study Molecular docking studies were carried out on hexanedioic acid, bis (2ethyl hexyl) from *Moringa Concanesis* Nimmo ethanolic bark extract against enzyme involved in *Mycobacterium tuberculosis* cell wall biogenesis namely beta-keto acyl ACP reductase (MabA) which is essential for biosynthesis of coenzyme A, is important for the growth of Mycobacterium tuberculosis. The crystal structure of MabA was retrieved from the PDB. Molecular docking experiments were performed using AutoDock4.2. Hexanedioic acid bis (2ethyl hexyl) showed high docking score estimated binding free energy of-1.66 was estimated. Molecular interactions of Hexanedioic acid, bis (2-ethylhexyl) and MabA suggested that this compound may act as potent antibacterial agent.

Introduction

Moringa concanesis Nimmo is a tree belongs to the family moringaceae. The plant locally called as kattumurungai by tribal peoples of the Nilgiris hills in the region of Tamilnadu state. The leaves are highly nutritious rich in vitamins A, C and E act as a good source of natural anti-oxidant inflammation, hematological and hepatorenal renal (Anbazhakan, 2007).

The family moringaceae as single genus Moringa with species of which only to species have been recorded in India, *Moringa concanesis* Nimmo and *Moringa oleifera*. *Moringa* tree commonly known as horseradish tree. The horseradish odour of *Moringa concanesis* Nimmo is more intense than *Moringa oleifera* (Ashish Chauhan *et al*., 2014).

Moringa concanesis Nimmo is a medium sized deciduous tree with thick bark. Bark is a fissured to 10cm deep, and is corky grey.The tree is hairless except younger parts and inflorescence. *Moringa concanesis* is widely distributed on dry lands. (Awad *et al*., 2001; Fahey, 2005; Velayati, 2009).

Tuberculosis (TB) remains the leading cause of mortality due to bacterial pathogen, *Mycobacterium tuberculosis*. In 2008, there were an estimated 8.9-9.9 million incident cases of TB, killing 2 million people annually (Oliveira Jose, 1999). In the addition, there were an estimated 0.5 million cases of multi-drug resistant TB (MDR-TB), which is defined as strains resistant to at least ionized and rifampicin (Kirtikar, 1993).

The emergence of extensively drug-resistant to a fluoroquinolone and atleast one second-line injectable agent, its widespread distribution and unprecedented fatality rate raise the prospect of virtually incurable and deadly TB world wide.Recently,a total new strain was identified as resistant to all first and second line of anti-TB drug tested. (Ankita Dey; Bhattacharyya Sauryya and Pal Tapan Kumar, 2014)

The type II fatty acid bio synthesis system (FAS II) is present in bacteria, plants and organisms of the phylum apicomplexa, but generally considered to be absent from mammals (Dorman 2007).

Mycobacterium tuberculosis MabA (fabG1) encoded beta-keto acyl Acp reductase (MabA) is a member of FAS II system, which elongates acyl fatty acid precursors yielding the long carbon chain of the meromycolate.it as been shown that MabA is essential for *Mycobacterium tuberculosis* survival (Singh *et al*., 2007; Banerjee, 1998; Parish, 2007; Veyron-Churle, 2010; Robertson, 2007; Oppermann, 2003).

Materials and Methods

Uniprot

Uniprot is a comprehensive, high-quality and free online database of protein sequence and functional information, mainly derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature. The Uniprot/Swissprot knowledgebase UniProtKB is the central access point for extensive curated protein information, including function, classification, and cross-reference http://www.uniprot.org/

PDB

The Protein Data Bank PDB is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists are freely accessible. The PDB is a key resource in areas of structural biology, such as structural genomics.
http://www.rcsb.org/pdb/home/home.do

PubChem

PubChem is designed to provide information on biological activities of small molecules, generally those with molecular weight less than 500 Daltons. PubChem's integration with NCBI's Entrez information retrieval system provides sub/structure, similarity structure, bioactivity data as well as links to biological property information in PubMed and NCBI's Protein 3D Structure Resource http://pubchem.ncbi.nlm.nih.gov/

ACD Chem Sketch

ACD/Chemsketch is the powerful chemical drawing and graphics package from

ACD/Labs software, which will draw molecular structures, reactions and calculate chemical properties very quickly and easily. The three dimensional structures of Carbazole alkaloids were drawn by Chemsketch.

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.

Auto dock

Auto Dock is a suite of automated docking tools. The software is used for modelling flexible small molecules such as drug molecules and its binding to receptor proteins of known three dimensional structures. It uses Genetic Algorithms for the conformational search and is a suitable method for the docking studies. The technique combines simulated annealing for conformation searching with a rapid grid based method of energy evaluation. Auto Dock tools are used to prepare, run and analyze the docking simulations, in addition to modeling studies http://autodock.scripps.edu/resources/tools

PyMOL

PyMOL is an open-source tool to visualize molecules available from (www.pymol.org). It runs on Windows, Linux and MacOS equally well. PyMOL has excellent capabilities in creating high-quality images from 3D structures; it has well developed functions for manipulating structures and some basic functions to analyze their chemical properties. The possibilities to write scripts and plugins as well as to incorporate PyMOL in custom software are fast and superior to most other programs.

Results and Discussion

Sequence Retrivel

The sequence of MabA is retrived from Uniprot database and sequence accession number is P9WGT3, organism is *Mycobacterium tuberculosis.*

Structure retrieval

The three dimensional structure (crystal structure) of MabA is derived from PDB database and its PDB ID is 2NTN. Three dimensional is visualized using RASMOL. Pink color showing alpha helix, yellow color showing beta sheets and white color showing turns

Preparation of ligand

For further docking analysis of the compounds hexanedioic acid, bis (2ethylhexyl) from *Moringa concanesis* Nimmo bark are taken. The two-dimensional structures of the ligand were generated using the ACD/Chemsketch tool. This software contains tools for 2D cleaning, 3D optimization, and viewing. These data are saved as a molecular format file (MDL MOL format). The molecular format converter tool (Open Babel) is used to convert this file into the PDB format and is used during docking analysis. The structure and molecular formula of hexanedioic acid, bis (2ethylhexyl) compounds was shown in Table.1.

Table.1 Showing the compounds extracted from *Moringa concanesis* Nimmo bark

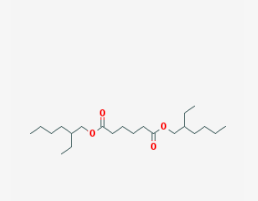
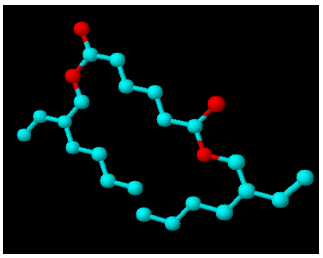
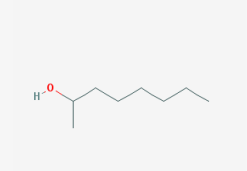
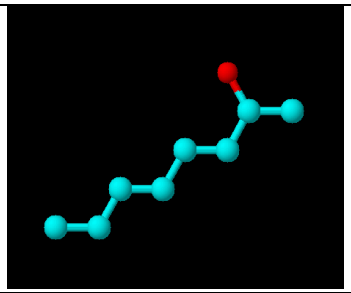
S.No	Compound	Molecular Formula	2D Structure	3D Structure
1	hexanedioic acid,bis (2ethylhexyl)	$C_{22}H_{42}O_4$		
2	isooctanol	$C_8H_{18}O$		

Table.2 Lipinski's rule of compounds:

Compounds	Molecular weight	No.of hydrogen accepter	No.of hydrogen donor
hexanedioic acid, bis (2ethylexyl)	198	4	0
Isooctanol	130	1	1

Table.3 Shows the docking interaction between MabA and hexanedioic acid, bis (2ethylexyl)

MabA		Hexanedioic acid bis(2ethlhexyl)	Distance	Binding score
Residue	Atom	Atom	3.2	-1.81
THR-188	OG1	O		

Table.4 Shows the docking interaction between MabA and isooctanol

MabA		**Isooctanol**	**Distance**	**Binding score**
Residue	Atom	Atom	1.9	-4.02
ILE-138	O	H		
ALA-139	N	O	3.1	

Table.5 Overall docking results between MabA and compounds

Compounds	**Key residue**	**Docking energy (Kcal/Mol)**	**No.of Hydrogen bonds**
Hexadenoic acid bis (2etylhexyl)	THR-188	-1.88	0
Isooctanol	ILE-138, ALA-139	-4.02	1

Fig.1 & 2

Fig.3

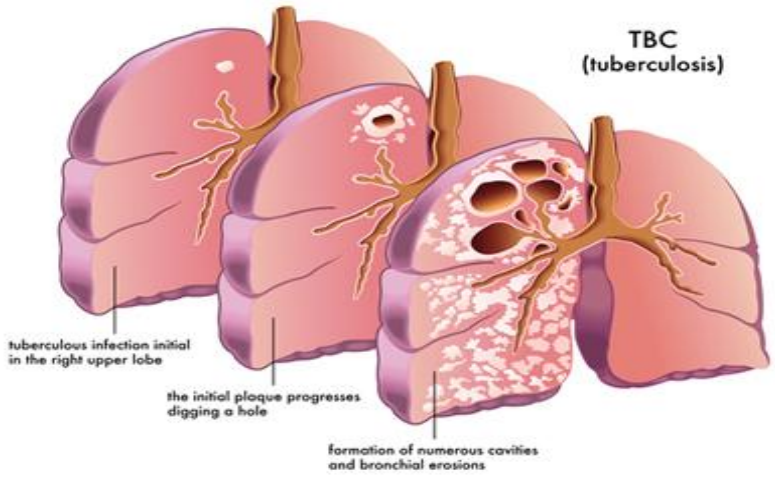
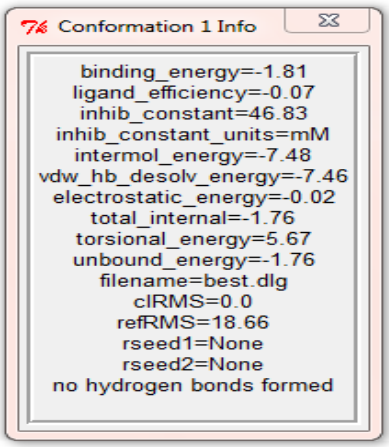
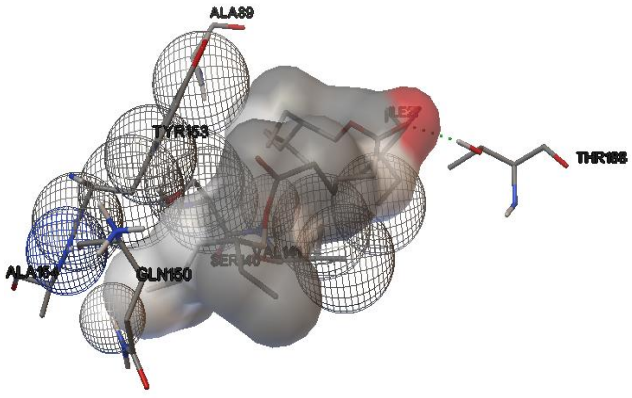


Fig.4 Crystal structure of the MabA visualized using Rasmol

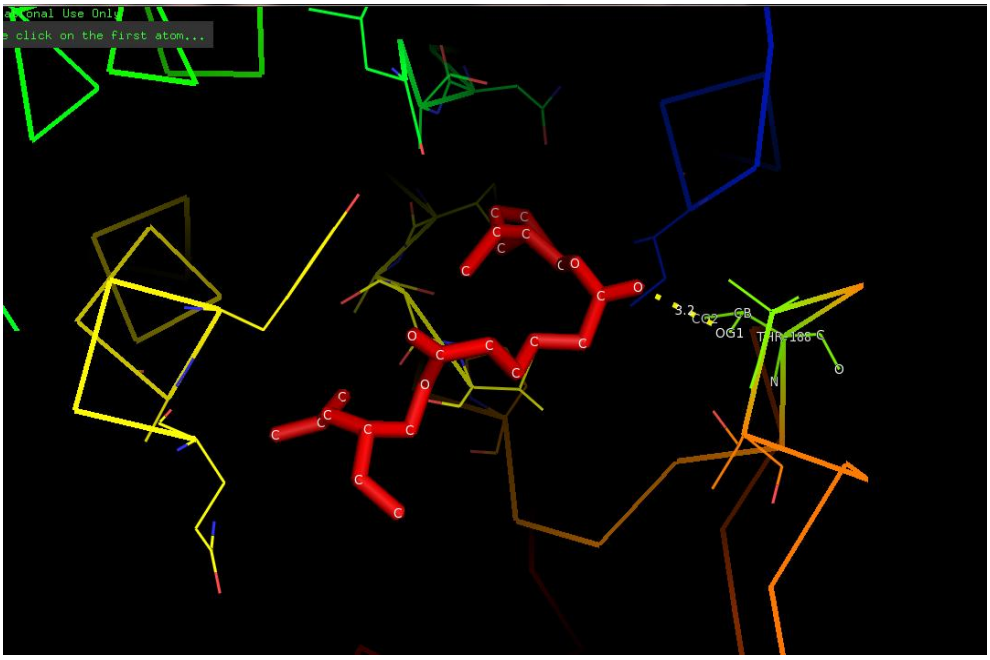
Fig.5 Docking of MabA and hexanedioic acid, bis (2ethylexyl): (a)Binding scoring (b) Interaction between MabA and hexanedioic acid, bis (2ethylexyl) is visualized using Autodock (c) Hydrogen bond forms between MabA and hexanedioic acid, bis (2ethylexyl) is visualized using Pymol



(a)

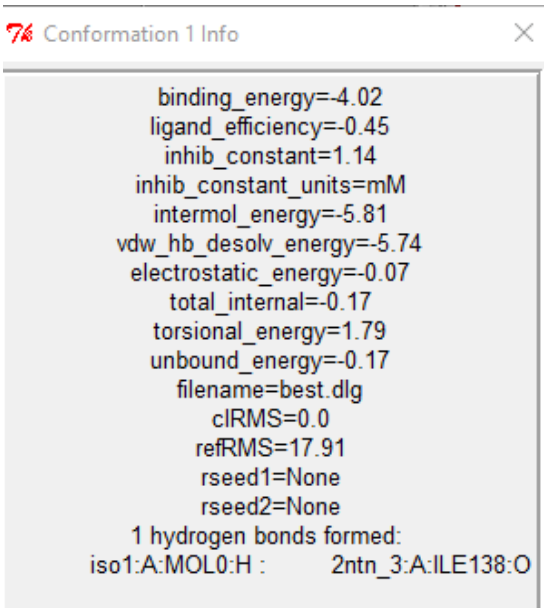


(b)

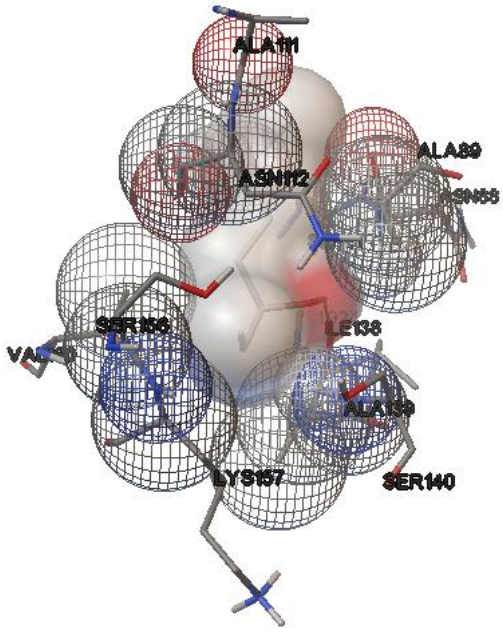


(c)

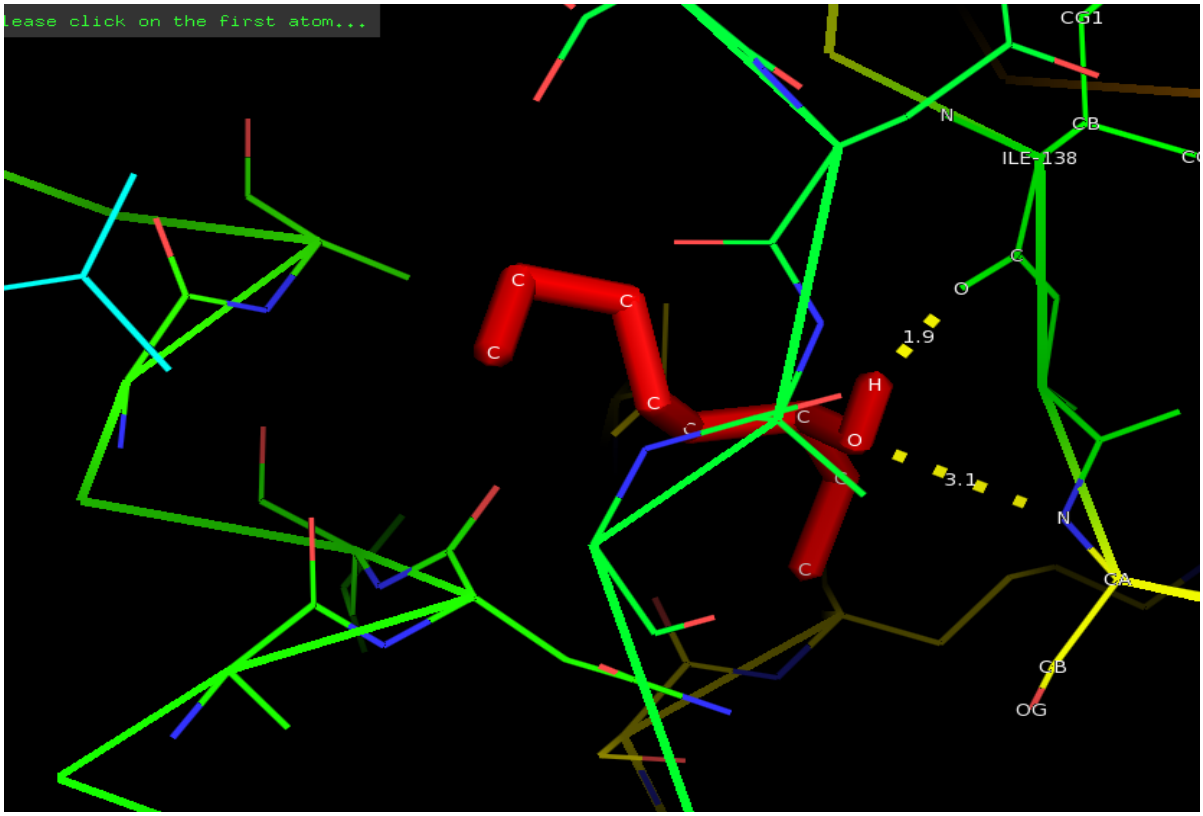
Fig.6 Docking of MabA and isooctanol: (a)Binding scoring (b) Interaction between MabA and acid, isooctanol is visualized using Auto dock (c) Hydrogen bond forms between MabA and isooctanol is visualized using Pymol



(a)



(b)



(c)

Molecular docking study of the hexanedioic acid, bis (2ethylexyl) against MabA

The alkaloid compound (hexanedioic acid, bis (2ethylexyl), isooctane) are docked against MabA. The Graphical User Interface program "Auto-Dock Tools" was used to prepare, run, and analyze the docking simulations. Koll man united atom charges, solvation parameters and polar hydrogens were added into the receptor PDB file for the preparation of protein in docking simulation. (Good sell, 1999; Jones, 1997; Rarey, 1996) requires precalculated grid maps, one for each atom type present in the flexible molecules being docked and its stores the potential energy arising from the interaction with rigid macromolecules. This grid must surround the region of interest in the rigid macromolecule. The grid box size was set at 126, 126 and 126 A° (*x*, *y*, and *z*) to include all the amino acid residues that present in rigid macromolecules. Auto Grid 4.2 Program, supplied with Auto Dock 4.2 was used to produce grid maps. The spacing between grid points was 0.375 angstroms. The Lamarckian Genetic Algorithm (LGA) (Morris, 1998) was chosen search for the best conformers.

The best ligand-receptor structure from the docked structures was chosen based on the lowest energy and minimal solvent accessibility of the ligand. The alkaloid compound (hexanedioic acid, bis(2ethylexyl), isooctanol) and MabA binding energy are shown in figure 2a-3a and the interactions visualization using the pymol Visualizer.

The docking study between hexadenoic acid bis (2ethylhexyl), Isooctanol compounds from *Moringa concanesis* Nimmo against MabA in receptor and ligand complex. The docked structures were analyzed and the

interactions were seen. Hydrogen bond interactions and the binding distance between the donors and acceptors were measured for the best conformers. From the binding energy values, the antibacterial activity of a ligand to the corresponding receptor was predicted. Hexanedioic acid, bis (2ethylhexyl) is having least binding score (-1.88 Kcal/mol) than the isooctanol. Therefore, this compound shows good inhibition against MabA and act as antibacterial agent.

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