R. Balajee et al /J. Pharm. Sci. & Res. Vol.3(6), 2011,1276-1279

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Molecular docking studies of Pantothenate synthase bound with novel molecules for *Mycobacterium Tuberculosis*.

R. Balajee[1], Dr. M. S. Dhana Rajan [2]*

[1] *Research Scholar, Department of Bioinformatics, Sathyabama University, Chennai- 119.*

[2] *Principal, Jaya College of Arts and Science, Thiruninravur.*

Abstract

The physiology of *M. tuberculosis* is highly aerobic and requires high levels of oxygen. Primarily a pathogen of the mammalian respiratory system, *Mycobacterium Tuberculosis* infects the lungs, causing tuberculosis. The Novel molecule which is linked by the unsaturated fatty acid compound and it is more abundant in nature sources. It possesses a broad spectrum of biological activities including antioxidative, antibacterial, antiviral, and anti-ulcer. This work represents the structure relationships of pantothenate synthase with the novel molecule and analyzing the properties for anti-tubercular activity.

Keywords: Argus Lab, asparatate-1-decarboxylase, Chimera, Genetic Algorithm, : Mycobacterium Tuberculosis, Pantothenate Synthase

INTRODUCTION

Mycobacterium tuberculosis (MTB) is a pathogenic bacterial species in the genus Mycobacterium and the causative agent of most cases of tuberculosis (Ryan *et al.,* 2004). First discovered in 1882 by Robert Koch, *M. tuberculosis* has an unusual, waxy coating on the cell surface.

A global spreading of *Mycobacterium Tuberculosis* is a catastrophe which demands an urgent need to design or develop novel Anti-TB drugs. We have presented docking studies of novel molecule using Argus Lab 4.0 in the active site of the X-ray crystal structure of Pantothenate synthase.

Pantothenate synthase and MTB pathology

M. tuberculosis divides every 15–20 hours, which is extremely slow compared to other bacteria, which tend to have division times measured in minutes (Escherichia coli can divide roughly every 20 minutes). It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks. Its unusual cell wall, rich in lipids (mycolic acid), is likely responsible for this resistance and is a key virulence factor (Murray ,2002).

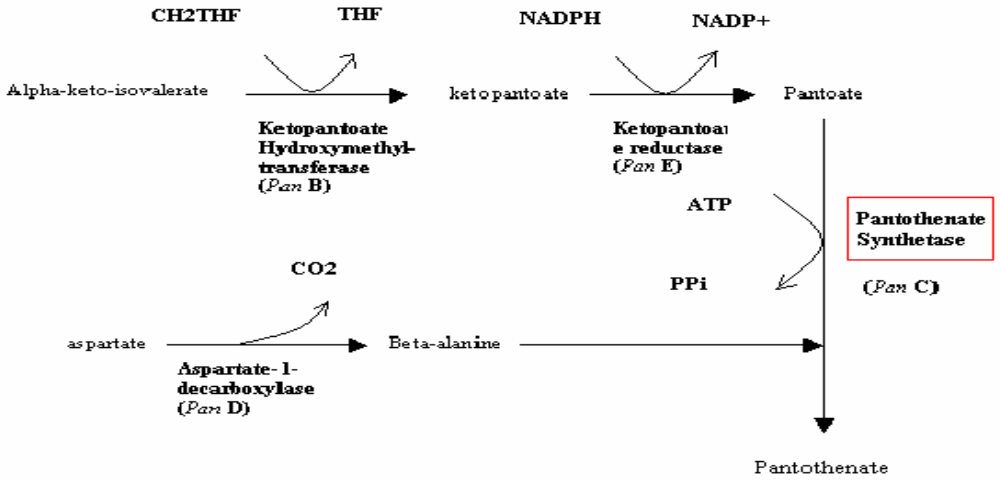
When in the lungs, *M. tuberculosis* is taken up by alveolar macrophages, but they are unable to digest the bacterium. Its cell wall prevents the fusion of the phagosome with a lysosome. Specifically, *M. tuberculosis* blocks the bridging molecule, early endosomal autoantigen 1 (EEA1); however, this blockade does not prevent fusion of vesicles filled with nutrients. Consequently, the bacteria multiply unchecked within the macrophage. The bacteria also carried the UreC gene, which prevents acidification of the phagosome. The bacteria also evade macrophage-killing by neutralizing reactive nitrogen intermediates (Bell, 2005).

Pantothenate Synthetase

The pantothenate synthase catalyzes the last step of condensation of ATP dependant to the reaction between pantoate and beta-alanine to form pantothenate. It too identified as an autotrophic mutants (Raman and Rathinasabapathi, 2004).

Pantothenate synthase is known to function within the cytoplasm and joins a series of reactions that transport proteins to the non-photosynthetic organelle. The target based on terminating the production of pantothenate and coA.

Figure-1: Synthesis of pantothenate from β-alanine and pantoate catalysed by pantothenate synthetase (re-drawn from www.taacf.org/SRI-HTS.htm)



The investigation demonstrates that identifying the potential inhibitors for *Mycobacterium tuberculosis* through expression level. Pantothenate also known as Vitamin B5, have a particular property of dietary requirement. It is a necessary precursor to coA and the prosthetic group of the acyl carrier protein (ACP), both of which are vital to a multitude of metabolic process.

The reaction begins with alpha-keto isovaleric acid, the reaction which followed by an enzyme catalyzed by ketopantoate hydroxymethyl transferase and keto pantoate reductase to form pantoate. The single reaction converts between aspartate and beta-alanine which is catalyzed by an enzyme catalyzed by asparatate-1-decarboxylase and enzyme encoded by *panD*. The pantothenate is formed by the precessor reaction catalysis to ATP dependant and it produces beta alanine and pantoate which is a condensation reaction (Cronan, 1980 and Cronan, et al 1982).

MATERIALS AND METHODS

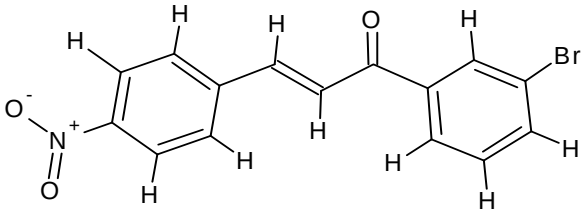
Preparation of Target Protein Structure

PDB is a repository of 3D structural data of bio macromolecules (http:/www.rcsb.org/pdb). In the present study, the atomic coordinates of the Pantothenate synthase was retrieved from pdb. The atomic coordinates were processed using Swiss PDB viewer to analyze protein structures (http://spdbv.vital-it.ch/)

Ligand Preparation

The ligand (Abdur *et al*., 2007) was taken from the online source and geometrically optimized. The docking procedure done by using Argus Lab 4.0, torsions in the ligands were set as flexible. RBMS-01 bound with the crystal structure of A chain (PDB code: 3LE8 Eisenberg and Wang, 2003) was used. All the hetero atoms including water molecules and bound ligands in PDB crystal structures were removed from the receptors.

Figure 2. Structure of Ligand Molecule (RBMS-01)



Binding Affinity

Using Ligand based drug designing approach, a Argus Lab 4.0 (www.arguslab.com), a grid spacing of 129 x 128 x 135 points was prepared. The docking performed using Lamarackian Genetic Algorithm. The grid was centered on the catalytic cleft of the enzyme for docking. Docking performed after the energy minimization of 0.30Å units. The top ranked model with the lowest energy cluster and maximum cluster size was considered for all further interaction studies.

RESULTS AND DISCUSSIONS

Protein-ligand Interaction

Docking of the receptor was performed using Argus Lab 4.0. The whole molecule selected for the docking purpose. Both the receptor and ligand were optimized for proper geometry using Argus Lab 4.0, prior to docking. Finally, the best ligand pose was found to be with lowest binding energy score -12.22 kcal/mol was identified. The obtained complex showed six hydrogen bonds within the range of 3 Angstrom distance.

Figure 3. Structure of ligand (RBMS-01) interaction with macromolecule (3LE8.pdb) represented in the ribbon form and the distance is calculated. The Hydrogen bond is clearly indicated and is mentioned in Table 3 also.

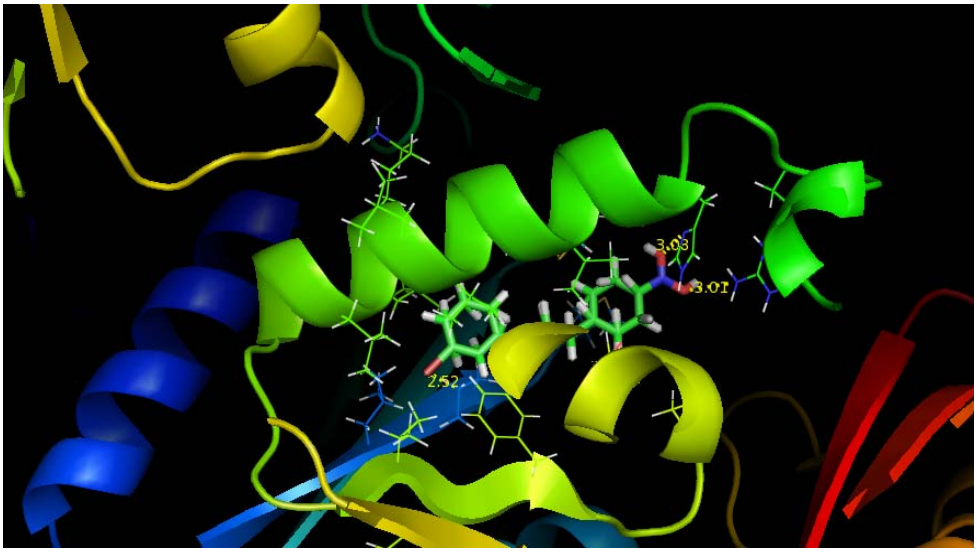
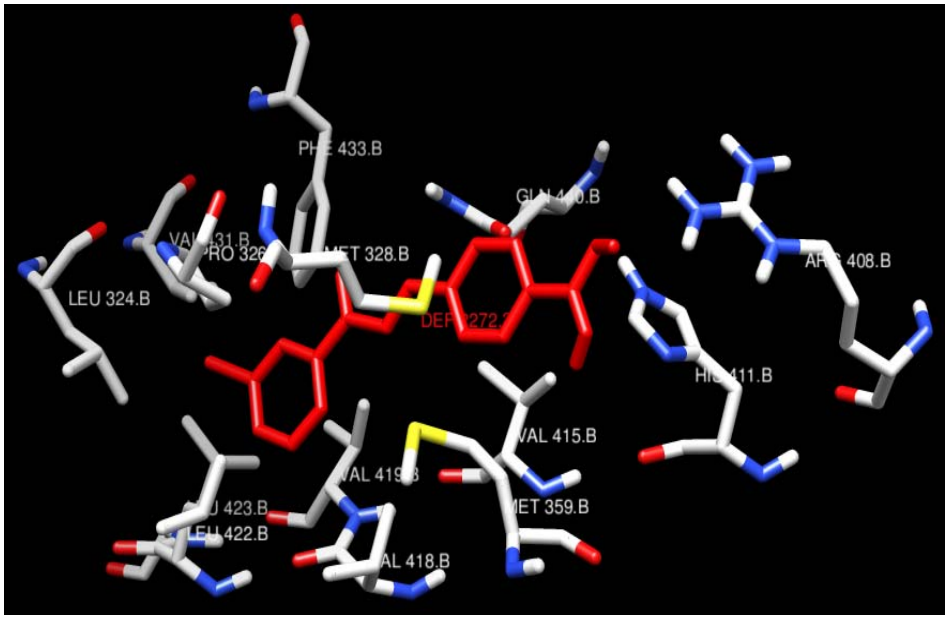
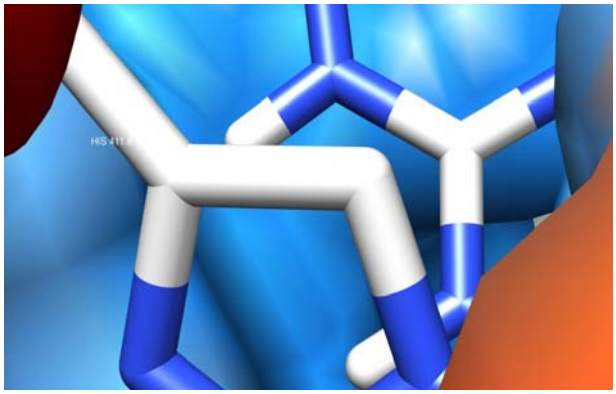


Figure 4. Representation indicates that the residues involved during interaction with ligand by using UCSF chimera tool.



The other Drug molecule is taken under the similarity of the main drug molecule (RBMS-01) from chemspider. Each docking run was repeated five times to get best results. The docking results are described in Table. The resulting docking molecules were saved as pdb files and best scored results were displayed**.**

Figure. 5. Representation of Ligand molecules which directly interacts with Hydrophobic pocket of Histidine 411 of B chain using UCSF Chimera Tool.



The other Drug molecule is taken under the similarity of the main drug molecule (RBMS-01) from chemspider. Each docking run was repeated five times to get best results. The docking results are described in Table. The resulting docking molecules were saved as pdb files and best scored results were displayed. The six molecules were compared with RBMS-01, were other molecule not fitted in the active site and other was not compact with physicochemical properties.

Table 1. Docked results compared with RBMS-01

Chemical Molecule ID *(taken from chemspider)*	***Energy Kcal/mol***
221004	-8.75
143817	-9.85
115605	-9.99
133537	-11.02
161087	-11.67

Lipinski's Rule of 5

This screening methodology was implemented to analyze the Drug likeness of the proposed ligand. Lipinski's rule of 5 is an essential screening methodology for rational drug design (Ekins and Rose, 2002; Miteva et al., 2006; Smith et al., 2004). It states that poor absorption or permeation are more likely when a ligand molecule violates Lipinski's rule of five i.e., has more than 5 hydrogen bond donors, the molecular weight is over 500, the log P is over 5 and the sum of N and O is over 10. The Ligand of the present study has well qualified in Lipinski's filter (http://www.scfbioiitd.res.in/utility/LipinskiFilters .jsp) (Table 1) (Umashankar et al., 2009)

Table 2: Lipinski Rule of 5

Lipinski Rule of 5	
Molecular Weight	332.15
Hydrogen Acceptors	3
Hydrogen Donors	0
No. of Rotatable Bonds	4
LogP	4.89

Pharmacophore analysis:

The pharmacophore properties of Pantothenate synthase with the RBMS-01 show the better conformations of hydrogen bonds and in physicochemical properties. It displays hydrogen bonds like N..H..O, O..H..O, N..H..H properties are more, this results in binding affinity. So, it has a better pharmacophoric activity of binding towards the ligands. Interaction between the macromolecule and ligand molecule shown below

Table 3: Interaction of macromolecule with ligand

Pantothenate synthase		*Distance (Å)*
Residue	***Atom***	
Arg 408	N – H – O	3.01
His 411	N – H – O	3.08
Gln 440	N – H – H	2.89
Pro 326	C – H – Br	2.52

CONCLUSION

Here, we focused that the binding of naturally occuring molecules were seated properly on the particular position and the hydrogen and hydrophobic interactions involves in the position of Arg, His, Gln and Pro residues, where the Pro residue of 326 is directly contacts with Br inorganic compound to have a better binding towards the ligand. Here, we suggests that the Mycobacterium tuberclosis structure of Pantothenate synthase having the same property of binding with novel ligand, as it also forms significant hydrogen bonds and qualifies the Lipinski's filter. Hence, the proposed drug is presented to the scientific community for further investigational confirmation.

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