ISSN 2664-4142 (Print) & ISSN 2664-6749 (Online)
South Asian Research Journal of Pharmaceutical Sciences
Abbreviated Key Title: South Asian Res J Pharm Sci

| Volume-4 | Issue-5 | Nov-Dec- 2022 | **DOI: 10.36346/sarjps.2022.v04i05.001**

Original Research Article

Molecular Docking Interaction of Mycobacterium Tuberculosis Enoyl-Acp-Reductase Enzyme with Delamaind

Kumari Neha[1*], Jitender K Malik[1]

[1]Institutes of Pharmacy, P.K. University, Shivpuri (M.P.), India

***Corresponding Author:** Kumari Neha
Institutes of Pharmacy, P.K. University, Shivpuri (M.P.), India

Article History
Received: 02.10.2022
Accepted: 15.11.2022
Published: 20.11.2022

Abstract: One of the eldest human diseases is tuberculosis (TB), for which there is molecular evidence dating back more than 17,000 years. Unfortunately, TB is still one of the top 10 infectious diseases that kill people worldwide, second only to HIV, despite advances in detection and treatment. The World Health Organization (WHO) claims that TB is an international pandemic. It is the main cause of death for those with HIV. In India, the fight against TB has largely been divided into three eras throughout its history: the early era, before the development of x-ray and chemotherapy; the post- independence era, when national TB control programmes were started and put into place; and the current era, when an ongoing WHO-assisted TB control programme is in place. Today's DOTS in India. A new anti-tuberculosis (TB) medication called delamanid, a nitroimidazo-oxazole derivative, has strong *in-vitro* and *in- vivo* antitubercular action against drug-susceptible and -resistant strains of Mycobacterium tuberculosis. With intention to propose the most probable mechanism of action of delamanid the docking based computational analysis has been performed against enyl ACP reductase (InhA) as targeted protein. The molecular docking of delamanid with enyl ACP reductase (InhA) showed binding energy (Kcal/mol) -10.86 having molecular interaction Lys165, Ala198, Phe149, Pro193, Met199, Glu219, Pro156, Met103 & Gly96. The concluding consequences of the existing research found out that the chosen molecule highly bounded with InhA thereby inhibiting the mycobacterial cell wall synthesis.

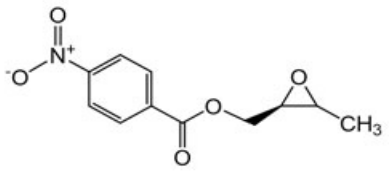
Keywords: Mycobacterium tuberculosis, delamanid, Enyl ACP reductase (InhA) & molecular docking.

INTRODUCTION

One of the primogenital diseases known to man, tuberculosis (TB) co-evolved with humans for at least several million years before that. The oldest known DNA evidence of tuberculosis was found in 9000-year-old human bones that were discovered in a neolithic town in the Eastern Mediterranean and in a fossil of an extinct bison (Pleistocene bison) that was radiocarbon dated at 17,870230 years [1]. The pulmonary form of TB was linked to "tubercles" by Dr. Richard Morton as early as 1689, but due to the disease's wide range of symptoms, TB was not recognised as a single illness until the 1820s. It was finally given the term "tuberculosis" by J. L. Schönlein in 1839. Robert Koch discovered Mycobacterium tuberculosis, the bacillus that causes tuberculosis, in 1882. In 1905, he was given the Nobel Prize in physiology or medicine for this discovery. The Mycobacterium tuberculosis complex is a collection of bacterial species that cause tuberculosis. Mycobacterium tuberculosis is currently the main cause of human tuberculosis. *M. bovis*, *M. microti*, and *M. africanum* are additional M. tuberculosis complex members that have been linked to tuberculosis. While M. africanum infections are extremely uncommon and M. microti is not known to cause TB in people, *M. bovis* has a wider host range and is the principal cause of tuberculosis in other animal species. *M. bovis* typically infects humans through milk, milk products, or meat from infected animals [2]. Millions of people are still afflicted with and dying from TB despite advancements in diagnostic and therapeutic methods. TB is one of the top three infectious diseases that claim lives worldwide, along with HIV/AIDS and malaria, which each claim the lives of 3 million people annually [3]. Delamanid, a nitroimidazooxazole derivative, is a novel anti- tuberculous (TB) drug that exhibits potent anti-tuberculous activity in vitro and in vivo against drug-sensitive and resistant strains of Mycobacterium tuberculosis. In several countries, including Japan and the EU, for use as part of appropriate combination regimens for adult multidrug-resistant

tuberculosis (MDR-TB) who cannot assemble an effective regimen due to resistance or tolerability approved. In a robust phase II study in adult patients with MDR-TB, delamanid 100 mg orally twice daily for 2 months, plus optimized background therapy, improved sputum culture conversion rates significant improvement over placebo [4].

Monographic Description [5]
Structure

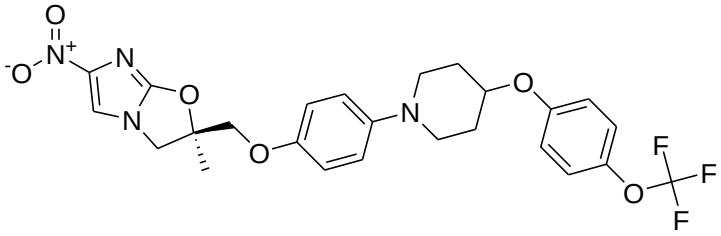


- **IUPAC Name:** (2R)-2-methyl-6-nitro-2-[[4-[4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl]phenoxy]methyl]-3H-imidazo[2,1-b][1,3]oxazole
- **Molecular Formula:** $C_{25}H_{25}F_3N_4O_6$
- **Molecular Weight:** 534.5
- **Therapeutic Category:** Antibacterial.
- **Physical Characteristics:** White to Light Yellow Solid.
- **Solubility:** Freely soluble in acetone, methanol, soluble in ethanol and very slightly soluble in water.
- **Melting Point:** >189°C
- **Half-life:** 38 Hrs.

EXPERIMENTAL WORK

Ligand Preparation:

2D Structure of ligand delamanid was drawn by using ChemDraw [K.R. Cousins; *et al.*, 2005]. The two-dimensional structure of ligand was converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for Auto Dock compatibility [6].



Preparation of the Grid File

The regions of interest used by Auto dock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grids points can be adjusted with another thumbwheel, the value in the study taken is given in table 1.[7].

Table 1: The grid-coordinates of the grid-box used in the current study

Proteins	x-D	y-D	z-D	Spacing (Å)	x center	y center	z center
5ugu	40	40	40	0.481	-16.903	5.179	-13.481

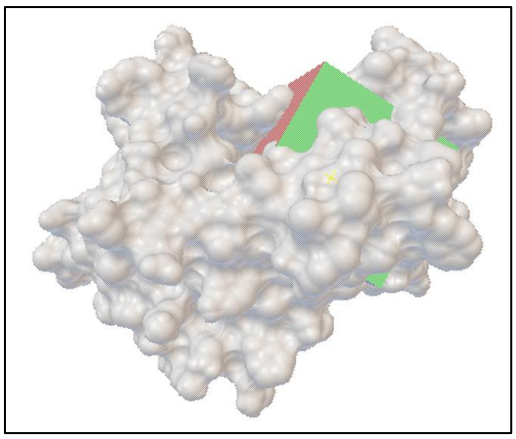


Figure 1: Grid box covering all active sites in enoyl ACP reductase enzyme (5ugu) of Mycobacterium tuberculosis

Preparation of the Docking File

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [8].

Macromolecular Structure

Enoyl ACP Reductase Enzyme of Mycobacterium Tuberculosis

The crystal structure of the Enoyl ACP reductase enzyme consisting of macromolecular receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (5ugu.pdb) registered in the Protein data bank was used [9].

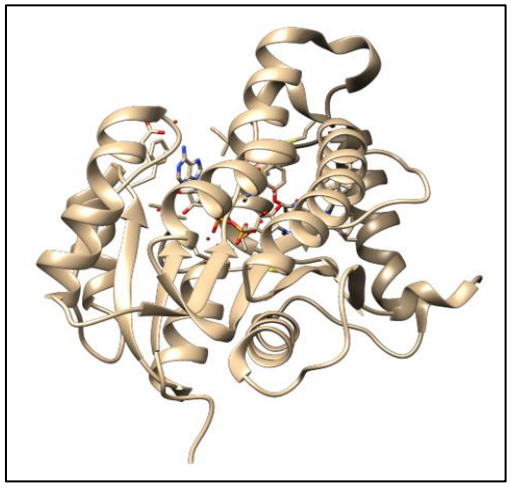


Figure 2: Crystal structure of Enoyl ACP reductase enzyme. (PDB ID-5ugu)

Molecular Docking Simulation Studies

Docking of ligand delamanid was performed against Enoyl ACP reductase enzyme was performed by Autodock to establish its probable mechanism of action for their antibacterial effect. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [10].

Toxicity & ADME-T Studies

The pharmacokinetics of delamanid ligand molecules was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME-T properties [11].

RESULT AND DISCUSSION

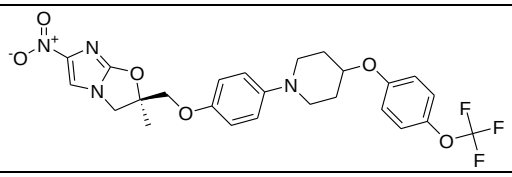
Over the past two decades, most antimycobacterial drug discovery efforts have focused on screening biochemically targeted inhibitors, and unfortunately have not led to new TB drugs. Recent anti-tuberculosis efforts have therefore shifted to the development of whole-cell screening assays, but due to the complex nature of the microenvironment encountered by the human host Mycobacterium tuberculosis, the causative agent of tuberculosis, this approach is not feasible. It's still very difficult. Therefore, various screening methods have been developed to better mimic the in vivo state of her MTB in a tuberculosis patient. Even when using whole-cell screening approaches, once a

promising hit or lead compound has been identified, its specific mycobacterial drug target can be identified to guide a potential optimization process and lead to drug-like compounds must be designed. In general, an ideal drug target that can be used to develop clinically useful antibiotics should be essential, drug sensitive and in vivo druggable. With the approval of his three new compounds, bedaquiline, delamanid and pretomanid, the landscape of tuberculosis treatment has changed significantly over the past decade. Delamanid and pretomanid are thought to have two mechanisms of action: (i) inhibition of mycolic acid synthesis and (ii) respiratory toxicity. In our current study, the antituberculous activity of delamanid was evaluated using *in silico* molecular docking. To this end, we reviewed the literature to identify various mycobacterial drug targets known to be essential for bacterial growth and survival. We then explored his PDB for available solved crystal structures for each of these primary targets. Our investigation revealed that there are many reports of essential targets for mycobacterial drugs. In this study, we selected enyl ACP reductase (InhA) to serve as structural models for molecular docking studies. Selection criteria for putative targets were based on the availability of a resolved 3D crystal structure of the H37Rv-MTB strain and the essentiality of the target for mycobacterial growth and survival. Selection of individual 3D crystal structures was guided by consideration of crystal resolution, non-mutability (wild-type), overall quality of the crystal structure, and absence of missing loops.

With intention to propose the most probable mechanism of action of delamanid the docking based computational analysis has been performed against enyl ACP reductase (InhA) as targeted protein. The molecular docking of delamanid with enyl ACP reductase (InhA) showed binding energy (Kcal/mol) -10.86 having molecular interaction Lys165, Ala198, Phe149, Pro193, Met199, Glu219, Pro156, Met103, Gly96. The result was tabulated in table 2 and fig.1-6. The outcome of investigation showed that delamanid binding effectively with InhA thereby inhibiting the mycobacterial cell wall synthesis.

The pharmacokinetic profiling of the delamanid ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of delamanid was shown in figure 7.

Table 2: Results of docking of Enoyl ACP reductase enzyme

S.No	Compound Name	Structure	Binding Energy (kcal/mol)	Interacting Residues
1	Delamanid		-10.86	Lys165, Ala198, Phe149, Pro193, Met199, Glu219, Pro156, Met103, Gly96, and Met161

Interactions

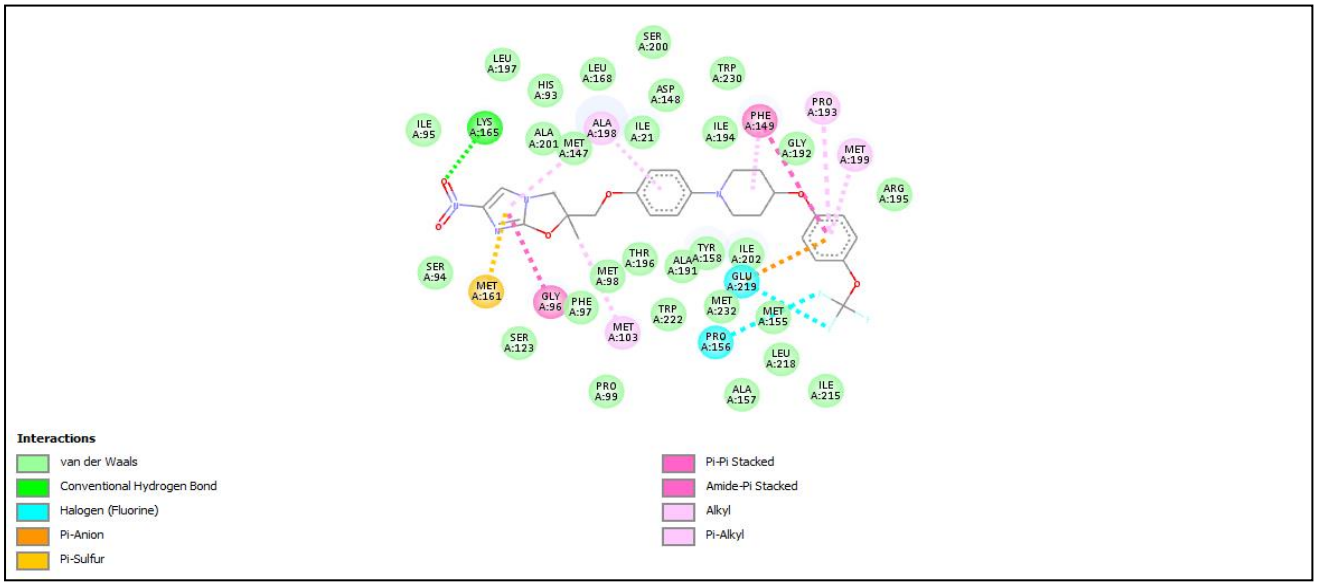


Figure 3: Two-dimensional binding interaction of delamanid with Enoyl ACP reductase enzyme

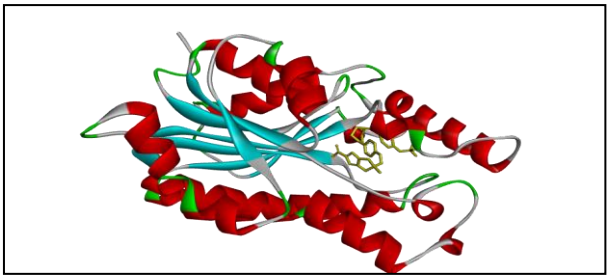


Figure 4: Three-dimensional binding interaction of Delamanidwith Enoyl ACP reductase enzyme

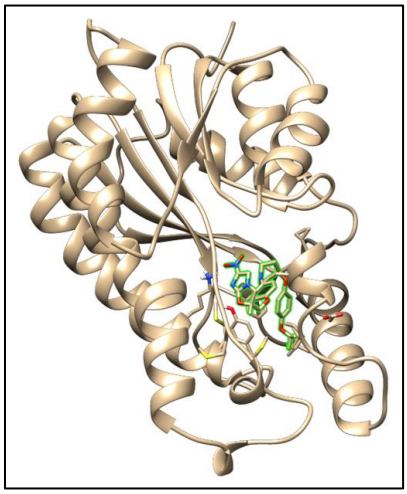


Figure 5: Binding conformation of ligand delamanid with Enoyl ACP reductase enzyme

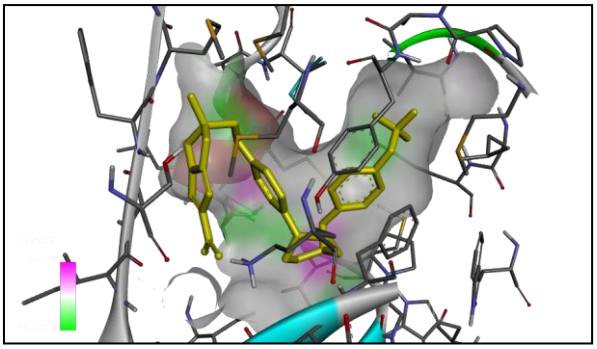


Figure 6: Binding conformation of ligand delamanid with Enoyl ACP reductase enzyme

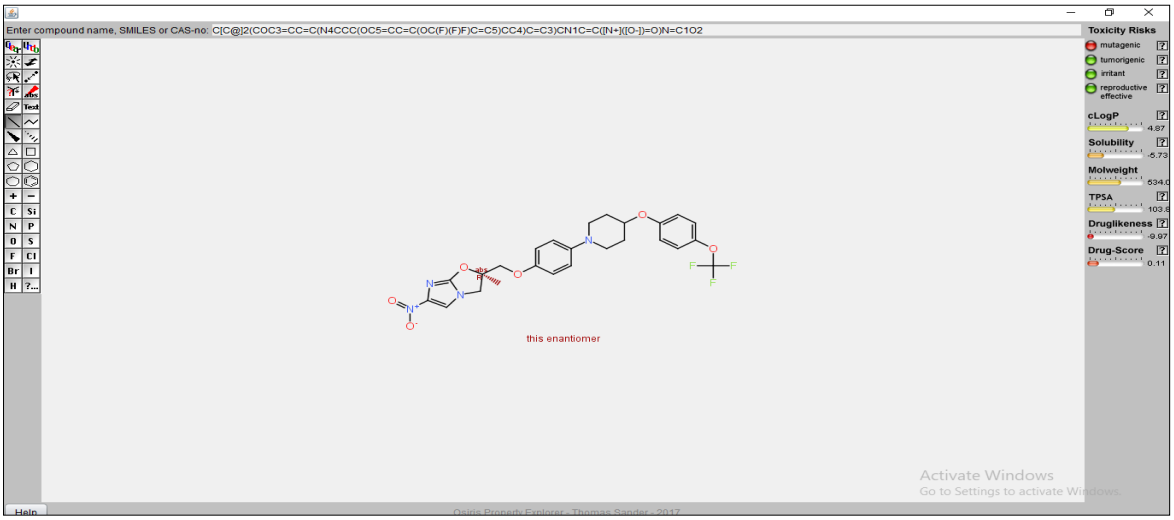


Figure 7: Pharmacokinetic and toxicity profiling of delamanid

CONCLUSION

Tuberculosis (TB) is a prime global hazard, often because of the improvement of antibiotic resistant types of Mycobacterium tuberculosis, the causal agent of the disease. Mycobacterium tuberculosis (Mtb) contamination is speedy countered with the aid of using the host immune system; but, the pathogen is in no way eradicated. In this contamination, 10% of infections are taken into consideration as open tuberculosis, at the same time as the last 90% are getting latent; a nation that could persist withinside the host for many years till immune manage is lost. Drug resistance in tuberculosis is important hazard to human population. Delamanid a new armor in fighting drug-resistant tuberculosis. The discovery of more modern anti-TB pills to address the problems which include drug resistance, HIV co-contamination and danger of drug-drug interactions with inside the control of TB. Delamanid, a more current mycobacterial cell wall synthesis inhibitor. In the existing research, we aimed to discover novel and powerful inhibitor molecules to conquer the resistance control. Selective antitubercular molecule delamanid turned into molecular docked with Enoyl ACP reductase (InhA). InhA catalyzes the discount of long-chain trans-2-enoyl-ACP with inside the type II fatty acid biosynthesis pathway of M. tuberculosis. Inhibition of InhA disrupts the biosynthesis of the mycolic acids which might be critical components of the mycobacterial cell wall. The final results of the existing research found out that the chosen molecule highly bounded with InhA thereby inhibiting the mycobacterial cell wall synthesis.

REFERENCES

1. Priyanka, S., Katoch, V. M., Himesh, S., Singhai, A. K., Nayak, G., & Mishra, K. (2010). Spoligotyping of Mycobacterium tuberculosis strains from Ziehl-Neelsen stained sputum slides from DTC, Satna (MP). *International Journal of Research in Pharmaceutical and Biomedical Sciences*, *1*(2), 97-101.
2. Himesh, S. (2020). A Brief Review on Extra-pulmonary Tuberculosis. *Sch Acad J Pharm*, 9(11), 290-295.
3. Hershkovitz, I., Donoghue, H. D., Minnikin, D. E., Besra, G. S., Lee, O. Y., Gernaey, A. M., ... & Spigelman, M. (2008). Detection and molecular characterization of 9000-year-old Mycobacterium tuberculosis from a Neolithic settlement in the Eastern Mediterranean. *PloS one*, *3*(10), e3426.
4. Blair, H. A., & Scott, L. J. (2015). Delamanid: a review of its use in patients with multidrug-resistant tuberculosis. *Drugs*, *75*(1), 91-100.
5. https://pubmed.ncbi.nlm.nih.gov/24923253/
6. Soni, H., Mishra, S., Mishra, R. K., & Mishra, S. R. (2022). Silibin as Potent Inhibitor of COVID-19 Main Protease: In-Silico Docking Approach. *Journal of Molecular Pharmaceuticals and Regulatory Affairs*, 1-7.
7. Malik, J. K., Soni, H., Sharma, S., & Sarankar, S. (2020). Hydroxychloroquine as potent inhibitor of COVID-19 main protease: Grid based docking approach. *Eurasian Journal of Medicine and Oncology*, *4*(3), 219-226.
8. Soni, H., Gautam, D., Sharma, S., & Malik, J. (2020). Rifampicin as potent inhibitor of COVID-19 main protease: In-silico docking approach. *Saudi J. Med. Pharm. Sci*, *6(9)*, 588-593.
9. Sander, T., Freyss, J., von Korff, M., Reich, J. R., & Rufener, C. (2009). OSIRIS, an entirely in-house developed drug discovery informatics system. *Journal of chemical information and modeling*, *49*(2), 232-246.
10. Kciuk, M., Mujwar, S., Szymanowska, A., Marciniak, B., Bukowski, K., Mojzych, M., & Kontek, R. (2022). Preparation of Novel Pyrazolo [4, 3-e] tetrazolo [1, 5-b][1, 2, 4] triazine Sulfonamides and Their Experimental and Computational Biological Studies. *International Journal of Molecular Sciences*, *23*(11), 5892.
11. Kciuk, M., Gielecińska, A., Mujwar, S., Mojzych, M., Marciniak, B., Drozda, R., & Kontek, R. (2022). Targeting carbonic anhydrase IX and XII isoforms with small molecule inhibitors and monoclonal antibodies. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *37*(1), 1278-1298.