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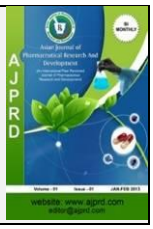

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Research Article

In Silico Study of Pretomanid: ADME Evaluation and Molecular Docking for Anti-Tubercular Activity

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ABSTRACT

One of the deadliest infectious diseases globally is tuberculosis (TB) due to the appearance of drug-resistant strains of the disease, such as multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB). Pretomaind is a new drug that has become increasingly vital in treating resistant TB and it successfully fights against the deadly bacteria known as 'Mycobacterium tuberculosis'. This essay covers its features, mechanism of action, efficiency, safety and overall importance in the fight against TB. Pretomaind works against the tuberculosis bacteria by inhibiting the building up of its cell walls, as well as releasing toxic compounds to kill all bacteria including those not in their active form. Patients on bedaquiline, linezolid and pretomaind (BPaL) treatment were seen to recover quicker and take less time in studies and have certain limitations such as the tendency to cause liver toxicity, stomach irritation, nerve damage and others that need close monitoring. Overall, pretomaind seems to be a vital addition to combat drug-resistant TB, which will in time further reduce tuberculosis around the world.

Keywords: Molecular Docking, Binding affinity, ADMET Analysis, Active sites, In Silico study.

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INTRODUCTION

In order to cure tuberculosis (TB), particularly the deadly types known as multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, the development of Pretomanid and related medications is crucial. Pretomanid, sometimes referred to as PA-824, is a member of the nitroimidazooxazines class of medications. In 2019, the US Food and Drug Administration authorized its usage in the conjunction with other medications totreat resistant tuberculosis.Pretomanid operates in a distinct manner. The medication is activated inside the TB bacteria, where it creates toxic compounds that disrupt the organism's vital metabolic functions. This aids in efficiently eliminating the bacteria and managing the infection. (1)

Researchers have developed a greater understanding of how pretomanid fights the TB bacteria due to recent research that made use of advanced metabolomic approaches. Pretomanid perturbs key bacterial metabolomic pathways such as the pentose phosphate pathway. Pretomanid causes the dangerous intermediate methylglyoxal and other harmful substances to accumulate within the bacterium. Accumulation of the harmful substances results in destruction and death of the bacterium and makes pretomanid a much more potent drug. Such findings may assist researchers in designing new and more effective pretomanid derivatives. (2)

Apart from laboratory procedures, computational methods are also employed to develop new pretomanid analogs. The interactions of these new molecules with the established tuberculosis target such as InhA are examined using computational tools such as molecular docking and molecular dynamics simulations. These computer-based methods are able to suggest how tightly a potential drug may be able to bind to its target and for how long, and also whether it might possess favourable drug-like characteristics, prior to it even being made in the laboratory. (3,4).

In this regard, some derivatives of hydantoin and isatin were analysed using docking and ADMET studies. From this results it is suggested that few of the derivatives exhibit better binding affinity and better pharmacokinetics

properties compared to presently known drugs used for TB such as isoniazid.

In addition to being modified by scientists to have better activity and reduce drug resistance, scientists are making changes to Pretomanid's chemical structure to make it more effective and to reduce drug resistance. A good example of change made to the chemical structure is the development of spirocyclic phenyl oxazole methyl (POM) analogues. These new drugs show very good pharmacokinetics and low toxicity toward host cells, while inhibiting normal and drug resistant TB bacteria effectively. (5)

Other researchers, on the other hand, used a combination of thiazole and benzothiazole moieties (both known to have antibacterial activity) together with pretomanid in hybrid molecules. The compounds obtained were synthesized quickly and efficiently with the help of present day approaches such as the multi-component reaction and microwave-assisted synthesis. Modification of SAR and molecular docking provided researchers with an idea of mechanism. (6)

Perhaps more usefully, by combining DFT calculations with ADMET analysis, which studies how a drug is absorbed by the body, how it is distributed throughout it, how it is metabolized, the speed with which it leaves the body and any potential toxicity, the researchers are able to chose better drug candidates to synthesize during drug design. These methods of analyzing the chemical properties of molecules allow scientists to predict if the compound would be safe, active against the disease and possess the right pharmacokinetic properties and allow them to design better derivatives with the correct properties and fewer side effects. (7)

Pretomanid is a newer drug that is being used for some very severe forms of TB, including multi-drug resistant TB and extensively resistant TB (MDR-TB and XDR-TB) that no longer respond to many common TB drugs. The drug was developed by the TB Alliance and was referred to by the code PA-824 during its development. In 2019, the US Food and Drug Administration (FDA) approved Pretomanid as part of a treatment regimen with Bedaquiline and Linezolid for drug-resistant pulmonary tuberculosis. Pretomanid is the first in a new group of drugs known as nitroimidazooxazines. In the TB bacteria it is activated by a unique bacterial enzyme to become active and toxic compounds which kill dormant, actively growing TB bacteria and stops them from producing certain key elements of their cell wall needed for their protection. These unique two actions help to combat forms of TB which are resistant to many drugs and are currently only commonly being used in combination with Bedaquiline and Linezolid to form the new shorter BPaL treatment regimens. (8)

Overview of Tuberculosis

Mycobacterium tuberculosis is the main cause of tuberculosis (TB), a chronic infectious disease that mainly affects the lungs, but may also involve extrapulmonary sites such as lymph nodes, bones, kidneys and the central nervous system. When a person with tuberculosis coughs or sneezes, droplets are released into the air. It remains one of the world's leading causes of sickness and mortality especially in lower and middle-income countries. Every year, the World Health Organization reports, there are millions of new cases of the disease, and drug-resistant strains of tuberculosis are a major threat to health around the globe. The disease causes a chronic cough, fever, night sweats, weight loss, chest pain and fatigue. Molecular, radiological, microbiological, culture, chest X-ray, nucleic acid amplification tests, sputum smear microscopy. Treatment is usually with a long-term multidrug regimen including first-line antibiotics such as isoniazid, rifampicin, pyrazinamide and ethambutol. Prevention measures include early detection, BCG vaccination, techniques of infection management and public health awareness campaigns. Tuberculosis remains a problem despite advances in diagnosis and treatment. (9,10)

Pretomanid

Pretomanid is a synthetic drug of the class of nitroimidazooxazine of antitubercular drugs and is one of the most crucial and new drugs introduced into chemotherapy of tuberculosis, especially the treatment of extensively drug resistant tuberculosis (XDR-TB) and multidrug resistant tuberculosis (MDR-TB). The burden posed by tuberculosis is a threat to public health globally today owing to the emergence of the resistant strains of bacteria that cannot be successfully treated by first line antitubercular drugs, such as isoniazid and rifampicin, to combat the increasing problem and improve treatment of the patients with drug-resistant TB, pretomanid has been developed. (11)

Pretomanid (previously identified by its research code, PA-824) was originally identified and developed by the TB Alliance. The drug was licensed by the FDA in 2019 as part of a combination therapy: BPaL, which includes linezolid, bedaquiline and pretomanid. This combination demonstrated promising rates of treatment success and greatly reduced treatment times compared to traditional MDR-TB drugs (which have durations of treatment from 18-24 months) (12). Combining pretomanid with an existing regimen reduces treatment duration to about six months, which offers increased potential for patient compliance and lower risk of failure.

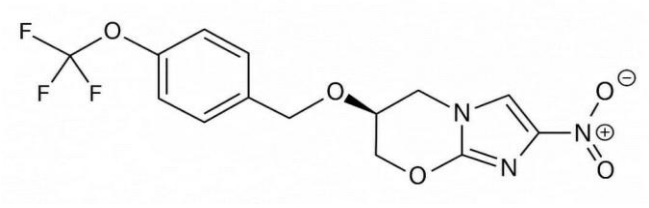
Chemical Classification and Structure

Chemical name (IUPAC name): (6S)-2-nitro-6-{4-(trifluoromethoxy)benzyl}-2,3-dihydroimidazo[2,1-b][1,3]oxazole

Molecular formula: $C_{14}H_{12}F_3N_3O_3$

Molecular weight: 359.26 g/mol

Chemical class: Nitroimidazooxazine derivative (antitubercular drug)



(IUPAC name**):** (6S)-2-nitro-6-{4-(trifluoromethoxy)benzyl}-2,3-dihydroimidazo[2,1-b][1,3]oxazole

Structural Features

The structure contains:

a) Nitro group (-NO_2) -Responsible for antimicrobial and antimycobacterial activity.
b) Imidazooxazine ring system -Core heterocyclic ring important for biological activity.
c) Trifluoromethoxy phenyl group (-OCF_3)- Increases lipophilicity and improves penetration into mycobacterial cells.
d) Benzyl side chain- Contributes to molecular stability and activity.
e) These structural features improve lipophilicity and penetration into mycobacterial cells.

Figure:1 Ddn (Deazaflavin-dependentnitroreductase)

Mechanism of Action

Mycolic acids Inhibition: Mycolic acids are long-chain fatty acids that form an essential component of the mycobacterial cell wall. They provide protection to bacteria against:

- Environmental stress
- Antimicrobial agents
- Host immune response

Pretomanid specifically inhibits:Ketomycolate synthesis and Methoxymycolate synthesis . As a result:Cell wall synthesis becomes defective and Bacterial growth is inhibitedDrug Activation: Pretomanid is a prodrug and requires intracellular activation inside Mycobacterium tuberculosis. Activation occurs through:

1. F420 cofactor system
2. Deazaflavin-dependent nitroreductase enzyme (Ddn)
3. After activation, Pretomanid generates: Reactive nitrogen species (RNS)
4. Nitric oxide (NO)

These reactive intermediates interfere with bacterial respiration and cellular metabolism, causing bacterial damage and death.

Pharmacokinetics of Pretomanid

Pharmacokinetics is one aspect of pharmacology which describes what a drug does in human body i.e., metabolization. The pharmacokinetics data is required in the determination of dosage, duration and efficacy of premanid in patients of XDR-TB and MDR-TB. Pretomanid is taken orally and its absorption is increased when taken with food particularly fatty food. Its oral administration must be taken with food to maximize the drug's bioavailability, which in turn boosts its antiproliferative effect against tubercle bacilli.

Pretomanid receives excellent absorption and tissue penetration, including into the lungs, where Mycobacterium tuberculosis prefers to replicate. The volume of distribution is very good and the drug fetched a low binding to plasma proteins; therefore, it can be effectively present at tissues as well cells. The metabolism of pretomanid occurs mostly in the liver by means of oxidation, reduction, and other chemical reactions. Liver enzymes (eg, Cytochrome P450 3A4) metabolise this drug metabolise this drug into inactive metabolites. With an elimination half-life of about 16 to 20 hours, the drug affords flexibility for once-daily dosing in combination therapy. (13)

Most of the radioactivity was recovered in the feces and very little was excreted in the urine following the administration of [14C]-pretomanid. Pretomanid is likely to be appropriate in those with mild renal impairment as only a small amount of the drug is eliminated by the kidneys. Its pharmacokinetic properties, as a rule, provide a strong antibacterial effect and contribute to maintaining effective

concentrations of the drug in the body during treatment of tuberculosis.

Adverse Effects of Pretomanid:

Pretomanid is an anti-tuberculosis drug indicated for the treatment of extensively drug-resistant tuberculosis (XDR-TB) and multidrug-resistant tuberculosis (MDR-TB). It works, but you have to watch it closely because of possible side effects . The most common side effects of Pretomanid are nausea, vomiting, headache, lightheadedness, tiredness, decreased appetite and gastrointestinal issues. Patients may also develop peripheral neuropathy, especially with the combination of Pretomanid and Linezolid, used in the BPaL regimen.(14,15)

Pretomanid therapy has a clinically significant side effect of hepatotoxicity (increased liver enzymes and possible liver damage). Patients under treatment should be regularly monitored for liver function. Pretomanid has also been associated with thrombocytopenia, myelosuppression and anaemia, especially when used in combination with other anti-TB drugs. Some cases have also been reported with electrolyte imbalance and increased blood creatinine levels. (15,16)

Rare side effects include skin rash, allergic reactions, chest pain and QT prolongation when used in combination with other QT prolonging medications such as bedaquiline. Patient safety during therapy is improved by routine clinical monitoring, dose adjustment as needed and evaluation of therapeutic response. (14,16)

Treatment of Tuberculosis

Pretomanid is primarily indicated for the treatment of extensively drug-resistant tuberculosis (XDR-TB), pulmonary multidrug-resistant tuberculosis (MDR-TB) and treatment-intolerant or non-responsive tuberculosis. Monotherapy can lead to resistance, so it is usually used as combinationtherapy.Pretomanid inhibits mycolic acid synthesis and upon activation by the deazaflavin-dependent nitroreductase (Ddn) enzyme in Mycobacterium TB generates reactive nitrogen species. This two-pronged process inhibits bacterial cell wall synthesis and leads to bacterial death. Pretomanid should be taken orally with food at a dose of 200 mg once daily to enhance absorption. When combined with the BPaL regimen, therapy usually lasts for six months.Pretomanid is commonly used in combination with:

a) Bedaquiline
b) Linezolid

a) Bedaquiline:

Bedaquiline is a diarylquinoline anti-tubercular drug used mainly for multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB). It acts by inhibiting mycobacterial ATP synthase enzyme, thereby blocking energy production and causing bacterial death. It is commonly used in the BPaL regimen with Pretomanid and Linezolid. Common adverse effects include nausea, QT prolongation, and liver toxicity.

b) Linezolid:

Linezolid is an oxazolidinone antibiotic used in drug-resistant tuberculosis treatment. It inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit and prevents bacterial growth. It is used as a part of the BPaL regimen and may cause adverse effects such as peripheral neuropathy, anemia, thrombocytopenia, and bone marrow suppression.

This regimen is known as the BPaL regimen (Bedaquiline + Pretomanid + Linezolid) and has shown improved treatment outcomes in resistant TB patients.During treatment, regular monitoring is essential. Patients should undergo:

1. Liver function tests
2. Complete blood count (CBC) monitoring
3. Clinical assessment of neuropathy symptoms
4. ECG monitoring when combined with QT-prolonging drugs
5. Evaluation of treatment response and adverse effects.

Pretomanid represents a significant improvement for the management of drug-resistant TB, because it provides an oral regimen and increases success rates, where options are already severely limited.

Material and Methods

Pretomanid research combines analytical, pharmacological, and computational approaches to determine the anti-tubercular activity of the drug against Mycobacterium tuberculosis. Such techniques are essential for understanding the mechanism of action of Pretomanid, predicting the pharmacokinetic properties, evaluating the toxicity and exploring the potential of Pretomanid in the treatment of extensively drug-resistant tuberculosis (XDR-TB) and multidrug-resistant tuberculosis (MDR-TB). Computational approaches are extensively used to cut down laboratory studies, reduce experimental costs and to predict the behavior of the drug quickly before the in vitro and in vivo studies. (17,18)

Pretomanid gets picked as the ligand because of its activity against tuberculosis. The structure can be pulled from online databases, and it comes in sdf or mol format to start with conversion to pdb happens through tools like Open Babel or PyRx. Preparation then includes energy minimization and adding hydrogens, plus fixing bond angles and errors to keep the conformation stable in three dimensions. It seems like some of the details around optimization get mixed up sometimes and I think that part might be easy to miss if you rush. The whole thing feels kind of connected to later steps but not everything lines up perfectly yet. (19,20)

The Ddn enzyme from Mycobacterium tuberculosis gets picked often as the target since it activates Pretomanid inside the cell. Protein structures are pulled from the Protein Data Bank and then waters along with any bound ligands get removed. Hydrogens are added next and missing residues are fixed before the geometry is optimized. It seems finding the active site through papers or some prediction tools matters for docking to work right. This part can get overlooked if the site is not obvious from the start. (17,21)

After preparing the ligand and the protein molecule, molecular docking studies are performed in order to estimate the interaction of Pretomanid to the protein target. In practice, AutoDock Vina, PyRx, and AutoDock Tools are frequently used docking software. It estimates the conformation of Pretomanid into the active site and provides with binding affinity values (in kcal/mol), which the lower is the energy, the stronger and more stable is the ligand-protein complex. (19,21)

A number of interactions between molecules, including Van der Waals forces, hydrogen bonding, hydrophobic and electrostatic interactions have been analyzed by docking studies. Pretomanid uses these interactions to stabilize it within the active site of Ddn enzyme, thus displaying an antimycobacterial effect. Such interactions allow the understanding of mechanism of action and optimizing the drug. Once docking is done, programs of molecular visualization are required to study the interactions, which is made by PyMOL, Discovery Studio Visualizer. From the two-dimensional and three-dimensional structures formed between ligand-protein, hydrogen bonds are detected, with bond distances to different residues and binding site; also it shows ligand orientation within the pocket. (20,21)

The application of ADMET prediction is significant in the study of Pretomanid. The name of absorption, distribution, metabolism, excretion and toxicity is referred as ADMET. Pretomanid's pharmacokinetic and toxicity behaviors are studied by computation methods, such as SwissADME, pkCSM and ADMETlab. The investigations include prediction of hepatotoxicity, cardiotoxicity, metabolic stability, excretion route, gastrointestinal absorption, plasma protein binding and drug likeness properties. Post the docking studies, detailed analyses on the stability of the protein-ligand complex on an extended timescale is performed using MD simulation. The analyzed features include radius of gyration, stability of hydrogen bond, RMSD and RMSF values. The stable value of RMSD suggests that Pretomanid forms a stable complex with Ddn enzyme and maintains interaction stability over time. (18,21,22)

Software and Tools Used:

Table No. 1

Software/Tools	Purpose
ChemDraw	Ligand structure retrieval
PyRx	Molecular docking
PyMOL	Visualization
SwissADME	ADMET prediction
pkCSM	Toxicity prediction

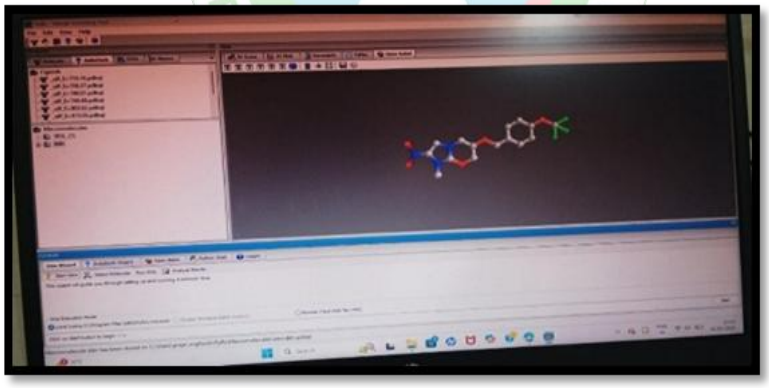


Figure 2: Docking of Pretomanid

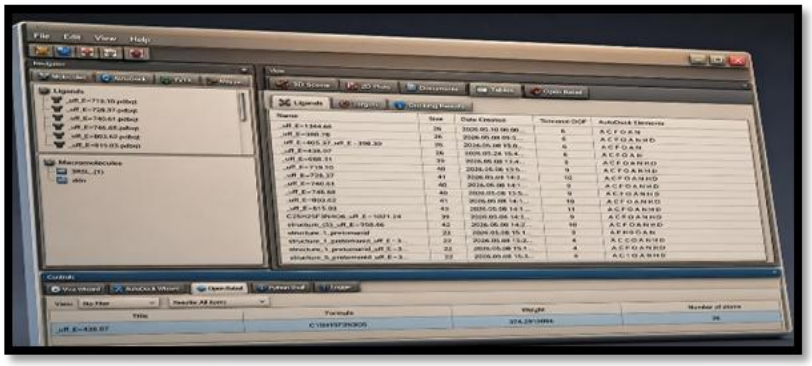


Figure 3: Graphical User Interface

Results and Discussion

ADMET Study :

1. Absorption

Systemic absorption occurs after the oral administration of Pretomanid. The drug is given orally in tablet form and absorption of Pretomanid into the systemic circulation occurs via the GI tract. The lipophilic nature of the drug is believed to enhance the oral absorption of Pretomanid when taken with food, especially a high fat diet which elevates and enhances the bioavailability and plasma concentration of the drug. Pretomanid exhibits good membrane permeability, enabling it to cross biological membranes and into the systemic circulation. It is predicted that through in silico ADMET tools (i.e., pkCSM and SwissADME) that Pretomanid would have high GI absorption and fair membrane permeability.

2. Distribution

Pretomanid's distribution involves movement from the plasma into tissues and organs following absorption. Pretomanid is distributed extensively into various parts of the body, but in particularly into the target of Mycobacterium tuberculosis i.e. Tissues of the lung and macrophages. There is a moderate to high level of plasma protein binding for Pretomanid which ensures a high sustained concentration of Pretomanid in the plasma prolonging its therapeutic effects. It is lipophilic, allowing cellular membrane penetration to occur and accumulate in infected macrophages thereby providing good antibacterial effects on both dormant and actively growing bacteria. Tissue penetration is vital in the treatment of tuberculosis as it will reside inside granulomas/macrophages. Predictions of ADMET showed good distribution into tissues with moderate penetration characteristics.

Importance of Distribution: Ensures delivery of drug to infected tissues. Enhances antimycobacterial activity. Supports intracellular penetration into macrophages.

3. Metabolism

Metabolism describes the biochemical changes of Pretomanid to its metabolites inside the body. It is predominantly metabolized in the liver through reductases and enzymatically into various metabolites, some of which could enhance the efficacy and excretion of the drug.Cytochrome P450 enzymes participate insignificantly in Pretomanid metabolism, so interactions mediated by significant CYP effects is reduced. The metabolic characteristics of Pretomanid therefore seems to result in beneficial interactions with frequently co-prescribed anti-tubercular agents. Pretomanid is well metabolically stable as observed in a number of studies indicating that it can be maintained at therapeutically effective levels for TB treatment.

4. Excretion

Excretion is the means of disposal of Pretomanid and its metabolites from the body. They are eliminated predominantly via metabolism then excretion via faeces and urine. It has an average excretion profile which is conducive to providing sufficient drug exposure to sustain antimicrobial action and achieve the right dosing intervals for multi-drug resistant TB.

Importance of Excretion: Maintains optimal drug concentration.Prevents drug accumulation.Supports safe therapeutic use.

5. Toxicity

Toxicity prediction models suggest that Pretomanid has a reasonable safety profile at therapeutic doses. But some adverse effects may be observed, they may include: Nausea and vomiting, Headache, Peripheral neuropathy, elevated liver enzymes (hepatotoxicity), QT interval prolongation (when used with combination therapy)

ADMET prediction tools such as pkCSM suggest manageable toxicity risks with appropriate clinical monitoring. Regular assessment of liver function and patient response is recommended during therapy.

Molecular Docking of Pretomanid

Molecular docking is a vital computational approach utilized in drug discovery and in silico studies and it predicts the possible binding interactions between the drug molecule (ligand) and the target protein (receptor). In the context of Pretomanid research, docking studies were performed to predict the binding of Pretomanid to Mycobacterium tuberculosis proteins. The interaction energy, binding affinity, interaction of ligand within the active site and the stability of protein-ligand complex were studied in detail during these studies. They have widespread applications since it helps to reduce the laboratory expenditure, the initial estimations and predictions can be made fast for possible drug activity. Pretomanid and target protein were considered as ligand and receptor respectively. The targets used in docking studies with Pretomanid include, Deazaflavin-dependent nitroreductase (Ddn), F420-dependent enzymes and other Mycobacterium tuberculosis proteins. The Ddn protein has great relevance, as it activates Pretomanid within the cell, through the F420 co-enzyme system. On activation by this system, Pretomanid produces harmful reactive nitrogen species and inhibits the mycolic acid synthesis. This in turn compromises the bacterial cell wall and causes its death.

Preparing ligand: Firstly the ligand Pretomanid's chemical structure was procured from sources like PubChem or ChemDraw and then converted to docking required format and energy minimized in order to stabilize the molecular geometry. Then hydrogenation and structural optimization were performed in order to increase the accuracy of docking. Preparing target protein: Secondly the 3D structures of the protein were retrieved from Protein Data Bank (PDB). The proteins need to be prepared by removal of water molecules, ions and any co-crystallized ligand present that might interfere with docking. Then the structure was hydrogenated, any missing residues were filled and the active binding site identified. Docking: After preparation the ligands were docked to their respective targets with software such as AutoDock Vina, PyRx, AutoDock Tools and Discovery Studio. Software calculated

the most favorable binding conformation and binding energy values which were presented in kcal/mol.

During docking studies, a number of interactions are investigated; these include hydrogen bonding, hydrophobic interactions, electrostatic forces and Van der Waals forces. Hydrogen bonds play a critical role in the stability of the protein-ligand complex. When Pretomanid docked with target proteins, the residues on the target protein had hydrogen bonds with Pretomanid which contributed to increased stability within the receptor cavity thus binding to the target protein strongly. Interacting residues, bond distances, ligand orientation and so on are visualized using Molecular visualization software such as PyMOL and Discovery Studio Visualizer to obtain 2D and 3D images of protein-ligand complex. Most studies show that Pretomanid has strong binding affinity and stable interaction with the targets of TB and such studies validate the mode of action of Pretomanid and the efficacy against the drug resistant strains of TB (MDR-TB and XDR-TB). Docking analysis also facilitates the designing of analogues with improved activities and reduced toxicity.

The major advantages of molecular docking studies include:

a) Prediction of protein–ligand interaction
b) Identification of active binding residues
c) Evaluation of binding affinity
d) Reduction in experimental cost and time
e) Support for drug design and optimisation
f) Early prediction of therapeutic effectiveness
g) Development of improved anti-tubercular agents.

Table 2: Derivative Design

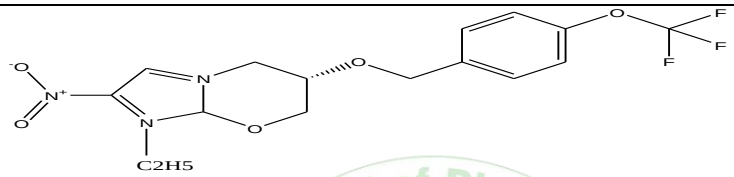
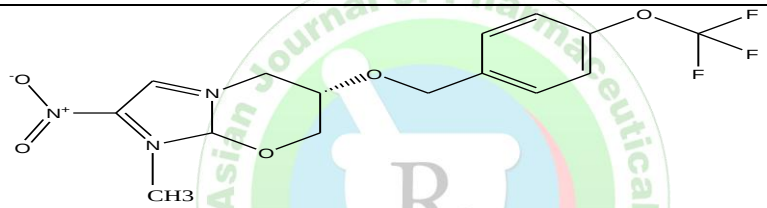
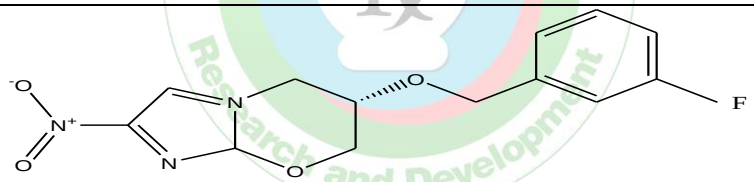
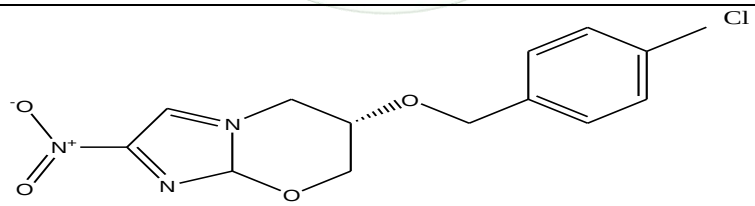
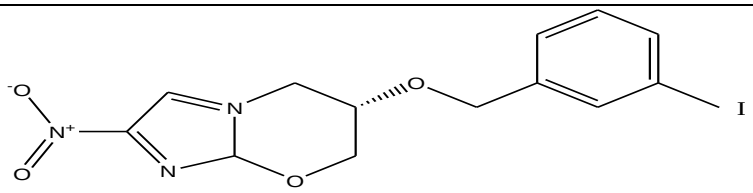
PA 1	
PA 2	
PA 3	
PA4	
PA5	

Table 3: Comparative ADME and Drug-Likeness Profile of Designed Compounds

Physicochemical Properties	PA -1	PA- 2	PA -3	PA- 4	PA- 5
Molecular formula	C16H19F3N3O5	C15H15F3N3O5	C13H12FN3O4	C13H13ClN3O4	C13H12IN3O4
Molecular Weight	390.33 g/mol	374.29 g/mol	293.25 g/mol	310.71 g/mol	401.16 g/mol
Num. heavy atoms	27	26	21	21	21
Num. arom. heavy atoms	11	11	11	6	11
Fraction Csp3	0.44	0.40	0.31	0.38	0.31
Num. rotatable bonds	6	6	4	4	4
Num. H-bond acceptors	8	8	6	5	5
Num. H-bond donors	0	0	0	0	0
Molar Refractivity	91.34	84.42	71.83	86.39	84.59

	PA -1	PA- 2	PA -3	PA- 4	PA- 5
TPSA	83.37 Å²		82.10 Å²	89.00 Å²	82.10 Å²
Lipophilicity					
Log $P_{o/w}$ (iLOGP)	0.00	0.00	1.82	89.00 Å²	2.20
Log $P_{o/w}$ (XLOGP3)	3.56	2.91	1.70	89.00 Å²	2.25
Log $P_{o/w}$ (WLOGP)	4.64	4.00	2.18	89.00 Å²	2.22
Log $P_{o/w}$ (MLOGP)	2.41	2.17	2.20	89.00 Å²	2.59
Log $P_{o/w}$ (SILICOS-IT)	-0.73	-0.73	-0.10	89.00 Å²	0.45
Consensus Log $P_{o/w}$	1.98	1.67	1.56	89.00 Å²	1.94

	PA -1	PA- 2	PA -3	PA- 4	PA- 5
Water Solubility					
Log *S* (ESOL)	-4.41	-3.91	-2.85	-2.58	-3.87
Solubility	1.52e-02 mg/ml ; 3.91e-05 mol/l	4.59e-02 mg/ml ; 1.23e-04 mol/l	4.12e-01 mg/ml ; 1.40e-03 mol/l	8.23e-01 mg/ml ; 2.65e-03 mol/l	5.43e-02 mg/ml ; 1.35e-04 mol/l
Class	Moderately soluble	Soluble	Soluble	Soluble	Soluble
Log *S* (Ali)	-5.00	-4.32	-3.04	-2.84	-3.61
Solubility	3.94e-03 mg/ml ; 1.01e-05 mol/l	1.78e-02 mg/ml ; 4.77e-05 mol/l	2.68e-01 mg/ml ; 9.13e-04 mol/l	4.47e-01 mg/ml ; 1.44e-03 mol/l	9.84e-02 mg/ml ; 2.45e-04 mol/l
Class	Moderately soluble	Moderately soluble	Soluble	Soluble	Soluble
Log *S* (SILICOS-IT)	-3.69	-3.69	-3.06	-3.31	-3.66
Solubility	7.88e-02 mg/ml ; 2.02e-04 mol/l	7.55e-02 mg/ml ; 2.02e-04 mol/l	2.68e-01 mg/ml ; 9.13e-04 mol/l	1.51e-01 mg/ml ; 4.86e-04 mol/l	8.72e-02 mg/ml ; 2.17e-04 mol/l
Class	Soluble	Soluble	Soluble	Soluble	Soluble

	PA -1	PA- 2	PA -3	PA- 4	PA- 5
Pharmacokinetics					
GI absorption	High	High	High	High	High
BBB permeant	No	No	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes	No
CYP1A2 inhibitor	No	No	No	No	No
CYP2C19 inhibitor	Yes	Yes	Yes	No	Yes
CYP2C9 inhibitor	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	No	No
Log K_p (skin permeation)	-6.15 cm/s	-6.52 cm/s	-6.88 cm/s	-7.22 cm/s	-7.15 cm/s

	PA -1	PA- 2	PA -3	PA- 4	PA- 5
Druglikeness					
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55

	PA -1	PA- 2	PA -3	PA- 4	PA- 5
Medicinal Chemistry					
PAINS	0 alert	0 alert	0 alert	0 alert	0 alert
Brenk	2 alerts: nitro_ group, oxygen nitrogen single_ bond	2 alerts: nitro_ group, oxygen nitrogen_ single _bond	2 alerts: nitro _group, oxygen-nitrogen_single_bond	2 alerts: nitro _ group, oxygen-nitrogen_ single _bond	3 alerts: iodine, nitro_ group, oxygen-nitrogen _single_ bond
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 1 violation: MW>350	Yes	Yes	No;1 violation: MW>350
Synthetic accessibility	4.00	3.82	3.60	4.38	3.68

Table 4: Molecular docking Table

Derivative No.	Binding Affinity
PA1	-8.4
PA2	-8.4
PA3	-10.7
PA4	-7.5
PA5	-8.1

CONCLUSION

The present in silico study of Pretomanid demonstrated its promising pharmaceutical and therapeutic potential in the treatment of drug-resistant tuberculosis. Molecular docking analysis indicated favourable interaction of Pretomanid with the selected target protein, suggesting good binding affinity and possible biological activity. ADME evaluation showed acceptable pharmacokinetic properties, supporting its drug-likeness, absorption, distribution, metabolism, and excretion profile. Overall, the study highlights the significance of Pretomanid as an effective anti-tubercular agent and supports its further research and clinical application. Overall, it appears that Pretomanid is an efficient and safe drug for the treatment of resistance TB and the in silico analysis plays an essential part to study its pharmacological and therapeutic potential.

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