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IN SILICO STUDY OF DELAMANID AGAINST MULTIDRUG-RESISTANT TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) is a leading infectious disease caused by Mycobacterium tuberculosis and is a serious global health threat due to rising multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). Delamanid is a novel anti-tubercular nitroimidazole drug developed for the treatment of resistant tuberculosis infections. The present study is aimed at in silico assessment of Delamanid through molecular docking and ADMET analysis to investigate its interaction with the target proteins of Mycobacterium tuberculosis and to predict its pharmacokinetic and toxicity profile. The interaction and binding affinity of Delamanid with Deazaflavin-dependent nitroreductase (DDN) enzyme were determined by carrying out molecular docking studies using computational tools such as PyRx and AutoDock Vina. The docking study revealed a good binding affinity and stable protein-ligand interaction through hydrogen bonding, hydrophobic interactions and van der Waals forces with key amino acid residues present in the active site of the target protein. The various properties of Delamanid were analysed using computational tools such as SwissADME and pkCSM to perform absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis. The results indicated favourable pharmacokinetic properties such as good oral absorption, effective tissue distribution, stable

metabolism, prolonged elimination half-life, and acceptable drug-likeness properties. The study also found that QT interval prolongation was the main toxicity concern with Delamanid therapy. Overall, the results indicate that delamanid has potent antimycobacterial activity, good pharmacokinetics, and high therapeutic potential for multidrug-resistant tuberculosis. The study underlines the importance of in silico approaches in the current anti-tubercular drug research and supports the continuous development of Delamanid based therapies for management of resistant tuberculosis.

KEYWORDS: Molecular docking, Binding affinity, ADMET analysis, Active sites, In silico study.

INTRODUCTION

Delamanid is a drug that was developed to treat multidrug-resistant tuberculosis (MDR-TB). The bioavailability of this prodrug was determined as 50 %.[1] The drug also blocks the bacteria from producing a cell wall and interferes with the bacterial respiratory system.[2] Researchers used molecular docking and quantitative structure activity relationship (QSAR) prediction for drug efficacy improvement and binding. Then structures of the obtained derivatives are used to design better and improved Delamanid derivatives with stronger and stable binding using different computer-aided methods.[3] These new derivatives of Delamanid are synthesised and evaluated in laboratory and animal experiments to assess their efficacy. The new derivatives of Delamanid are more effective than the drug Delamanid. The novel compounds were also evaluated for ADMET properties, toxicity and drug-likeness by the instruments such as ProTox-II.[4] Changing the lipophilicity or hydrophilicity can improve the drug binding and potency. However, if the toxicity is not properly considered, some modified molecules can also cause serious side effects. The exact mechanism by which delamanid acts is unknown, but it has been approved by the European Medicines Agency in 2014 and is considered a promising treatment for MDR-TB and XDRTB. Tuberculosis remains a major health problem worldwide, with millions of cases and deaths each year. Rising incidence of drug resistant TB has driven researchers to increasing use of in silico methods to accelerate the development and optimisation of new anti-TB drugs such as Delamanid.

Backgrounds

Multidrug-resistant tuberculosis (MDR-TB) is a persistent disease killing thousands of people every year and has affected millions of people globally. The causative agent Mycobacterium

tuberculosis has developed resistance to its main medicines, the anti-TTB medication class. Thus, there is an urgent need to identify new therapies for the treatment of MDR-TB. Recently described benzimidazole derivatives are promising drug family which demonstrated strong anti-tuberculosis activity.[5]

OBJECTIVE

* The goal is to find out how Delamanid interacts with the target protein of Mycobacterium tuberculosis at a level.
* We will use docking to see how well Delamanid binds to the target protein.[6]
* Delamanid will be analyzed to predict how it is absorbed. If it is toxic, through something called ADMET analysis.
* We need to check if Delamanid has the properties that make a drug, which is what we call drug-likeness properties of Delamanid.[7]

Overview of Tuberculosis

Tuberculosis is a problem. It happens when the body gets infected with the Mycobacterium tuberculosis bacterium.[8] When this bacterium gets inside the body it can really hurt the lungs. The lungs can get these bumps called nodules and little holes called tubercles. This can make it very hard to breathe. One thing that people with tuberculosis might do is cough up blood. Scientists have been trying to figure out how the tuberculosis bacteria hurt the cells in our body. It is still very hard to make people better. Scientists are now looking at the tuberculosis bacteria closely. They want to know more about the things that help the bacteria stay alive like how they make their cell walls and get energy.[9] They are hoping to find a way to kill the tuberculosis bacteria without hurting the cells, in our body. Tuberculosis is still a problem and scientists are working hard to find new ways to treat tuberculosis and make people with tuberculosis better.

Delamanid

Otsuka Pharmaceutical, a company from Japan made a medicine called Delamanid also known as Deltyba. The World Health Organization or WHO approved Delamanid to treat people with multidrug- tuberculosis, which is a kind of tuberculosis that does not respond to many medicines.[10] Delamanid works by stopping the bacteria that cause tuberculosis from making something called acids, which are important for the bacteria to survive.[11] Without these acids the bacteria get weak Die. A study was done with people who had multidrug-tuberculosis and were not responding to two common medicines called rifampicin and

isoniazid. The people in the study were divided into two groups. One group got Delamanid along with standard medicines for tuberculosis. The other group only got the medicines. After one year the people who got Delamanid did better than the others. Their bodies got rid of the tuberculosis bacteria effectively.[11] However Delamanid can cause some problems. It can make people feel sick, to their stomach, dizzy. It can affect their heart. This can lead to heart problems. So people who take Delamanid need to get their heart checked regularly with a test called an ECG while they are taking the medicine.[12]

Discovery and Development of Delamanid

- Multi-drug resistant tuberculosis treatment has made progress.
- There is now hope with Delamanid also known as OPC-67683.[13]
- Otsuka Pharmaceutical sells Delamanid as a treatment option.
- Delamanid is part of the World Health Organization recommended treatment plan for -drug resistant tuberculosis.[14]
- The European Medicines Agency approved Delamanid in 2014.
- This approval was due to Delamanids ability to fight tuberculosis bacteria.[15]
- Delamanid has shown toxicity compared to similar drugs
- Multi-drug resistant tuberculosis patients now have a chance of recovery with Delamanid.[16]
- Delamanid is helping to improve treatment outcomes for those, with this form of tuberculosis.[16]

Important Milestones

- Discovery of the Nitro-dihydro-imidazooxazole class
- Approved for treatment of MDR-TB
- Administered as an oral anti-TB drug Became part of WHO MDR-TB treatment guidelines.[17]

Chemical Classification and Structure

Delamanid is an antimycobacterial medication in the nitroimidazole class.

Molecular Information

- **Chemical name:** (2R)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy] piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole

- **Molecular formula:** $C_{25}H_{25}F_3N_4O_6$
- **Molecular weight:** Approximately 534.48 g/mol

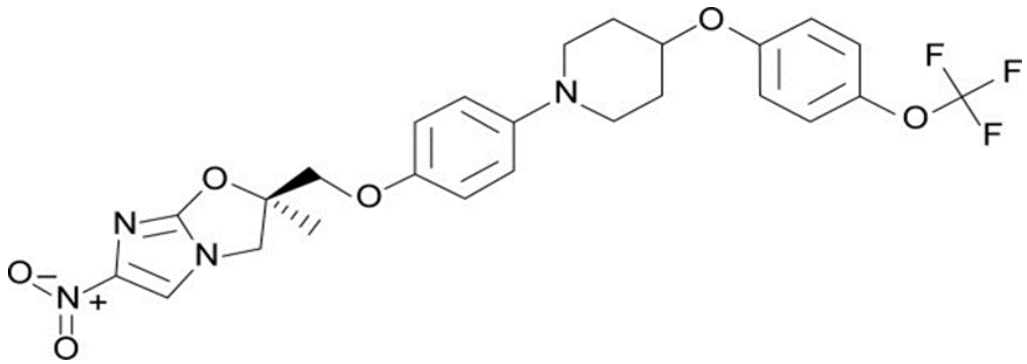


Fig : Structure of Delamanid.

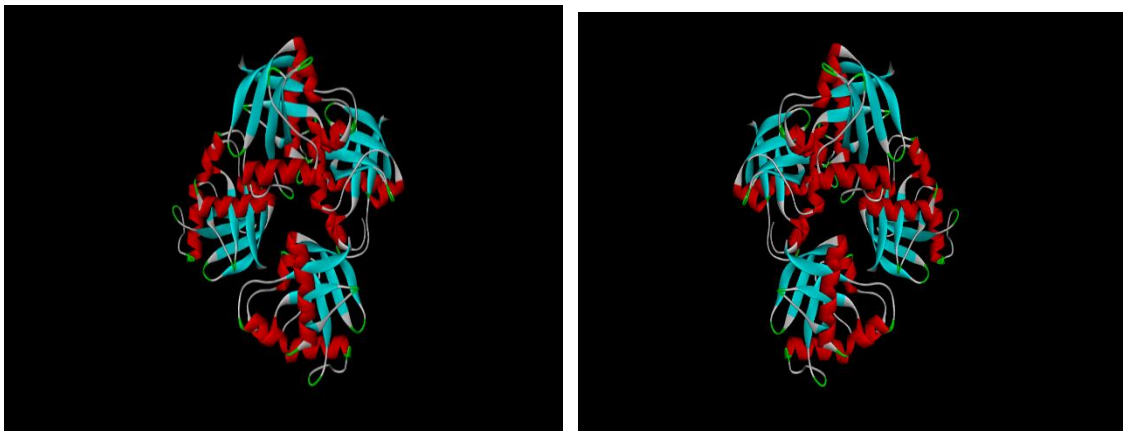
Iupac name: (2R)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole

Structural Features

The structure contains.

- Nitro group (important for antimicrobial activity)
- Imidazooxazole ring
- Piperidine ring
- Trifluoromethoxy phenoxy group

These structural features improve lipophilicity and penetration into mycobacterial cells.



Delamanid selectively inhibits the synthesis of methoxy mycolic acid and the production of keto mycolic acid in the cell wall of mycobacterium tuberculosis.

Mechanism of Action

Delamanid does its job by stopping the production of mycolic acid and keto-mycolic acid. These are parts of the mycobacterial cell wall. Mycolic acids are like chains of fatty acids. They help protect Mycobacterium tuberculosis from the system of the person it is in from stress in the environment and from antibiotics.[18] When Delamanid stops the production of acids it makes the bacterial cell wall weaker. This makes it easier for things to get into the cell. In the end this causes the bacteria to die. Delamanid is really good at doing this because it targets the acids that are so important, for Mycobacterium tuberculosis.[19]

Drug Activation

- Delamanid is a prodrug. It needs to be activated inside the cell. This happens in two ways:
- It uses the F420 coenzyme.
- It uses the Deazaflavin- nitroreductase enzyme. This enzyme damages parts.
- The activated drug makes nitrogen. This includes oxide.
- The drug gets activated by
- The F420 coenzyme
- The Deazaflavin-dependent nitroreductase enzyme
- The activated drug makes oxide. It makes reactive nitrogen. These harm parts.

Simplified Mechanism

1. The drug enters the cell.
2. The Deazaflavin-dependent nitroreductase enzyme gets activated.
3. It stops acid production.[20]
4. The cell wall gets weak.
5. The bacteria get killed.[20]

Pharmacokinetics of Delamanid

Delamanid is a medicine taken by mouth to treat tuberculosis that does not respond to treatment. It works better when you eat food with it food that has a lot of fat. This helps the medicine get into your body better and work effectively. When Delamanid gets into your body it goes to different parts, especially your lungs and the cells that fight infection. Most of the Delamanid binds to proteins in your blood, which helps keep the amount of medicine in your blood.[21] Delamanid is broken down by a protein in your blood called albumin. It does not use the liver enzymes that break down many other medicines. This means it is less likely

to interact with medicines you might be taking. One of the broken-down parts of Delamanid called DM-6705 can affect your hearts rhythm. Delamanid stays in your body for a time. About 30 to 38 hours. This is why you only need to take it twice a day. Most of Delamanid is removed from your body through your bowel movements. Very little is removed through your urine.[22] Delamanid Delamanid has an effect, on MDR-TB treatment because of these properties.

Adverse Effects of Delamanid

Delamanid is a medicine for treating MDR-TB. It can cause some problems that doctors need to keep a close eye on. The biggest problem is something called QT interval prolongation. This is a heart problem that can make your heartbeat irregular and cause heart issues. So patients usually need to get heart tests. This is especially true if they are taking medicines that can affect the heart.[23] Delamanid can also cause some problems. These include feeling sick throwing up headaches feeling dizzy feeling tired having trouble sleeping, stomach problems and not feeling like eating. Some people might also get liver problems or have low potassium levels. So doctors often check to make sure the liver is working okay. That potassium levels are good.[24] Sometimes people can have bad reactions to Delamanid. This can include being allergic, to it getting a skin rash having chest pain or having a heartbeat. Overall Delamanid is considered safe when doctors are watching closely and making sure everything is okay. Delamanid is a medicine that needs to be taken with care and regular check ups. Doctors need to monitor people taking Delamanid to make sure they are doing okay. Delamanid is used to treat MDR-TB. It is important to take it as directed.[24]

Treatment

Delamanid is a medicine that is used to treat tuberculosis that's hard to cure with regular medicines. This type of tuberculosis is called multidrug- tuberculosis or MDR-TB and extensively drug-resistant tuberculosis or XDR-TB. Delamanid is used with medicines to make the treatment work better and to prevent the tuberculosis from becoming even harder to cure. Delamanid works by stopping the tuberculosis bacteria from making things they need to survive. It does this by blocking the formation of substances in the bacterial cell wall, which weakens and kills the tuberculosis bacteria. Delamanid is usually taken as 100 mg twice a day with food because food helps the body absorb Delamanid better. The treatment can last for six months or longer depending on how the patient's doing. Delamanid is often used with medicines like Bedaquiline, Linezolid, Clofazimine and fluoroquinolones. When Delamanid

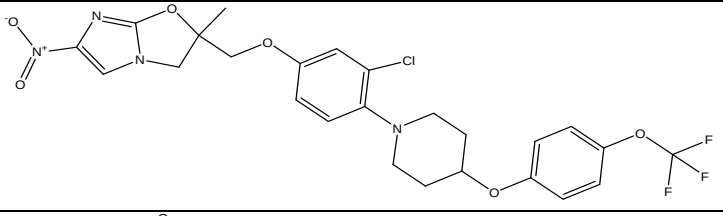
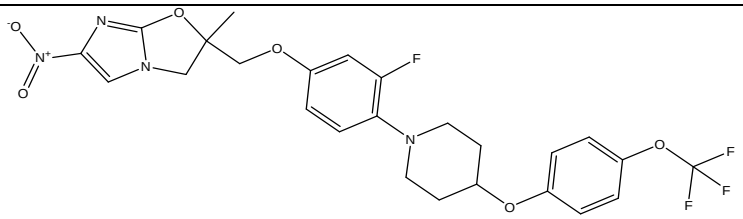
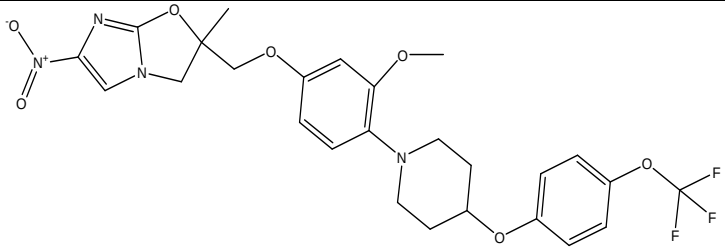
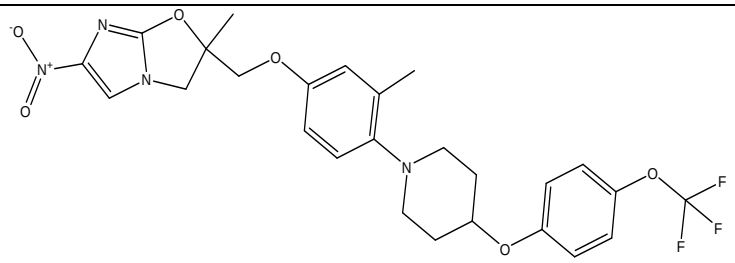
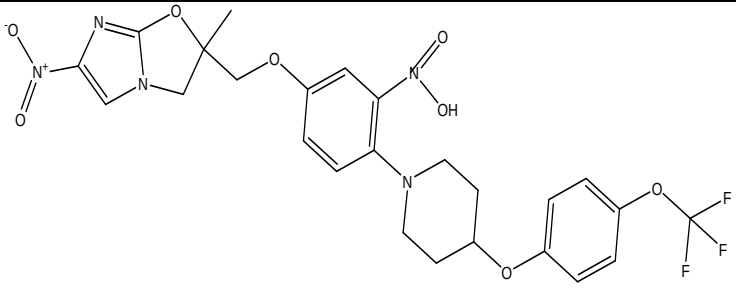
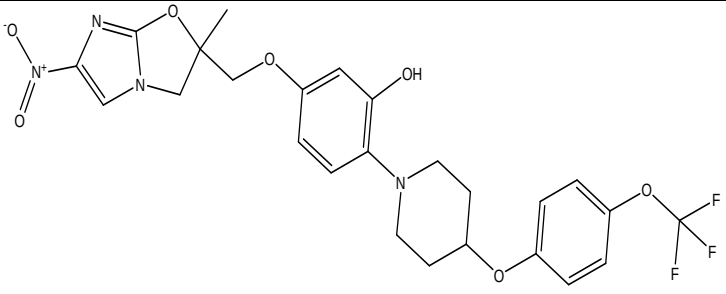
is used with these medicines it helps patients with MDR-TB get better and live longer. While the patient is taking Delamanid the doctor will check their heart, liver and blood to make sure Delamanid is working and is safe to take. Delamanid is a medicine for treating tuberculosis that is hard to cure because it is a medicine that can be taken by mouth and it works well.[25]

MATERIAL METHOD

To study Delamanid researchers use computers and science to see how Delamanid works against tuberculosis bacteria. They start by making a model of Delamanid and the part of the tuberculosis bacteria that Delamanid attacks. They use computer programs to make these models and to see how well Delamanid fits into the tuberculosis bacteria.[26] Next the researchers use a computer program to see how strongly Delamanid sticks to the tuberculosis bacteria. This helps them understand how well Delamanid will work against the tuberculosis bacteria. They also use tools to see what Delamanid looks like when it is stuck to the tuberculosis bacteria. This helps them understand how Delamanid works and which parts of the tuberculosis bacteria are important for Delamanid to work.[27] The researchers also do tests to see if Delamanid is safe and if it will work well in the body. They use computer programs to predict how Delamanid will be absorbed, distributed and removed from the body. If it will be toxic. They also do tests to see if Delamanid will stay stuck to the tuberculosis bacteria over time.[28] Other tests, such as Lipinski's Rule of Five are used to see if Delamanid is a medicine and to design new medicines that are similar, to Delamanid but work even better. All of these tests help the researchers understand how well Delamanid works if it is safe and if it can be used to treat tuberculosis that's hard to cure.[28]

Software/Tool	Purpose
ChemDraw	Ligand structure retrieval
Protein Data Bank	Protein structure retrieval
PyRx	Molecular docking
PyMOL	Visualization
SwissADME	ADMET prediction
pkCSM	Toxicity prediction

Table No. 1: Derivative Design.

 Dlm 1
 Dlm 2
 Dlm 3
 Dlm 4
 Dlm 5
 Dlm 6

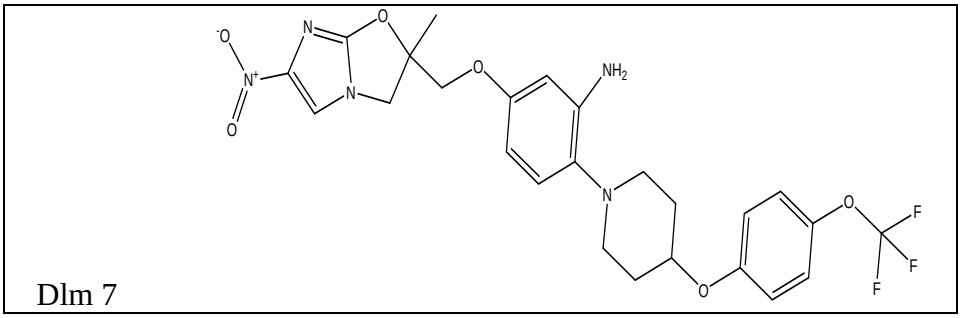


Table No. 2: Absorption Study.

Property	1	2	3	4	5	6	7
Absorption Water solubility	-3.334	-3.317	-3.31	-3.337	-3.290	-3.258	-3.251
Absorption Caco2 permeability	0.89	0.91	0.877	0.898	0.865	0.812	0.782
Absorption Intestinal absorption (human)	100	100	100	100	100	100	100
Absorption Skin Permeability	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735
Absorption P-glycoprotein substrate	No	No	No	No	No	Yes	Yes
Absorption P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Absorption P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table No. 3: Distribution study.

Property	1	2	3	4	5	6	7
Distribution VDss (human)	-0.097	-0.172	-0.153	-0.083	-0.118	-0.153	-0.123
Distribution Fraction unbound (human)	0.057	0.065	0.068	0.056	0.061	0.067	0.062
Distribution BBB permeability	-2.268	-2.301	-2.328	-2.093	-2.210	-2.304	-2.256
Distribution CNS permeability	-2.203	-2.916	-2.978	-2.244	-2.650	-3.031	-2.493

Table NO. 4: Metabolism study.

Property	1	2	3	4	5	6	7
Metabolism CYP2D6 substrate	No	No	No	No	No	No	No
Metabolism CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metabolism CYP1A2 inhibitor	No	No	No	No	No	No	No
Metabolism CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metabolism CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metabolism CYP2D6 inhibitor	No	No	No	No	No	No	No
Metabolism CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table No. 5: Excretion study.

Property	1	2	3	4	5	6	7
Excretion Total Clearance	-0.119	-0.153	-0.091	-0.094	-0.101	-0.105	0.048
Excretion Renal OCT2 substrate	No	No	No	No	No	No	No

Table No. 6: Toxicity Study.

Property	1	2	3	4	5	6	7
Toxicity AMES toxicity	No	No	No	No	No	No	No
Toxicity Max. tolerated dose (human)	0.743	0.74	0.739	0.74	0.67	0.679	0.674
Toxicity hERG I inhibitor	No	No	No	No	No	No	No
Toxicity hERG II inhibitor	Yes	Yes	Yes	Yes	No	Yes	Yes
Toxicity Oral Rat Acute Toxicity (LD50)	2.302	2.277	2.272	2.277	2.760	2.098	2.215
Toxicity Oral Rat Chronic Toxicity (LOAEL)	0.392	0.426	0.472	0.619	0.120	0.52	0.533
Toxicity Hepatotoxicity	No	No	Yes	No	Yes	No	No
Toxicity Skin Sensitisation	No	No	No	No	No	No	No
Toxicity T. Pyriformis toxicity	0.285	0.285	0.285	0.285	0.285	0.285	0.285
Toxicity Minnow toxicity	-1.616	-1.086	-1.152	-1.398	-0.240	-0.761	-0.944

Molecular docking Table No.7.

Derivative No.	Binding Affinity
Dlm 1	-9.6
Dlm 2	-10
Dlm 3	-9.4
Dlm 4	-9.9
Dlm 5	-9.7
Dlm 6	-10
Dlm 7	-9.1

RESULT AND DISCUSSION

ADMET Study

1. Absorption

Delamanid enters the bloodstream after you take it by mouth. Delamanid comes in a tablet. It goes into your body through your stomach and intestines. When you take Delamanid with food fatty food it works better because Delamanid likes fat. This helps Delamanid get into your blood and fight multidrug- tuberculosis also known as MDR-TB more effectively. Delamanid moves from your stomach into your bloodstream after you take it. You take Delamanid by mouth. It goes into your body through your stomach and intestines. Delamanid works better when you take it with food, fatty food because it likes fat. Food helps Delamanid get into your blood better and fight MDR-TB effectively. When you take Delamanid with food it gets into your blood faster. That helps it fight the bad bacteria in your body. Studies have shown that when you take Delamanid with food it gets into your blood two to three times faster. Delamanid can get into your bloodstream easily because it can cross the walls of

your stomach and intestines. This is important when you have MDR-TB because you need Delamanid to get into your blood to stop the bacteria from growing. Some computer programs, like SwissADME and pkCSM can predict how Delamanid will work in your body. They say that Delamanid is good, at getting into your bloodstream and crossing the walls of your stomach and intestines.[29]

2. Distribution

Delamanid moves from the blood to the tissues and organs in the body. After Delamanid is absorbed it goes to all parts of the body. Gets to the lung tissues where the bacteria that cause tuberculosis are. Delamanid is mostly bound to a protein in the blood which helps it work for a time and keeps the amount of Delamanid in the blood stable. Delamanid is also distributed to the lung tissues, macrophages and parts of the body where the tuberculosis bacteria're. The drug binds well to the protein in the blood and most of it stays bound when it is in the blood. This helps Delamanid work for a time and keeps the amount of Delamanid in the blood stable. Delamanid can also get into the tissues well which is important for treating tuberculosis because the bacteria that cause tuberculosis live in the lung tissues and macrophages where many drugs cannot get to.[30]

3. Metabolism

Delamanid is broken down in the body. This is different from other drugs that are broken down in the liver. Delamanid is mostly broken down by a protein in the blood. The enzymes in the liver play a role in breaking down Delamanid. When Delamanid is broken down it makes other substances that can affect how the drug works and its safety.[31]

4. Excretion

Delamanid is removed from the body. Delamanid is mostly removed from the body through the feces and a small amount is removed through the urine. The drug takes a long time to be removed from the body, which helps keep the amount of Delamanid in the blood stable for a longer time. Delamanid is removed from the body through the feces and only a small amount is removed through the urine. The main way Delamanid is removed is through the bile. Then the feces. The kidneys play a role in removing Delamanid from the body.[32]

5. Toxicity

Delamanid can cause effects. Although Delamanid is effective against tuberculosis it can cause side effects on the heart. One of the important harmful effects of Delamanid is that it can affect the heart.[33]

Molecular Docking Study of Delamanid

Molecular docking is a way to use computers to predict how a drug like Delamanid interacts with a protein. In the study of Delamanid molecular docking is used to see how well Delamanid binds to the proteins of the bacteria that cause tuberculosis. The first step in docking is to get the structure of Delamanid. The structure of Delamanid is obtained from a database. Prepared for docking. The next step is to get the structure of the protein that Delamanid binds to. The structure of the protein is obtained from a database. Prepared for docking.[34] The docking simulation is then done using software. The software predicts how well Delamanid binds to the protein and calculates the energy of the binding. The results of the docking study can be visualized using software. The advantages of docking include predicting how well a drug binds to a protein identifying the parts of the protein that the drug binds to and predicting the energy of the binding. Molecular docking can also reduce the cost and time of doing experiments.[35]

CONCLUSION

In conclusion Delamanid is a drug for treating tuberculosis. The study showed that Delamanid binds well to the proteins of the bacteria that cause tuberculosis. The drug has properties that help it work well in the body and it is effective, against tuberculosis. However Delamanid can cause side effects on the heart and this needs to be monitored when it is used.

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