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Pretomanid - A Novel Antibacterial Agent for The Treatment of Tuberculosis

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A B S T R A C T

Pretomanid is a novel nitroimidazole antibiotic approved for use in the treatment of drug-resistant tuberculosis (TB). It is particularly indicated for multidrug-resistant (MDR) and extensively drug resistant (XDR) TB, in combination with bedaquiline and linezolid (BPaL regimen). Pretomanid exerts its antibacterial activity through mechanisms involving inhibition of mycobacterial cell wall synthesis and the generation of reactive nitrogen species under anaerobic conditions. These mechanisms are effective against actively replicating and non-replicating Mycobacterium tuberculosis.

Keywords - Pretomanid, Tuberculosis, Antibacterial, Mycobacterium.

1. Introduction -

1.1 Tuberculosis -

Tuberculosis (TB) is an ancient disease caused by bacteria called Mycobacterium tuberculosis, and it remains one of the leading causes of death worldwide. According to the World Health Organization (WHO), it is a major killer after HIV/AIDS, especially affecting people from poorer and marginalized communities. In India, the National Strategic Plan (2017-2025) aims to eliminate TB by 2025, but this requires greater awareness and understanding of the disease.(1)

Tuberculosis (TB) is a contagious disease that affects over 1 million people in India each year. It is caused by the bacteria Mycobacterium tuberculosis, which usually affects the lungs but can spread to other parts of the body if left untreated. According to the World Health Organization (WHO), TB was the seventh deadliest disease in the world in 1990. In 2001, WHO estimated that about 32% of the world's population had been infected with TB. Each year, around 8 million people get the disease, and 2 million die due to not receiving proper treatment. TB spreads through tiny droplets in the air when someone with the infection coughs or sneezes.(2)

Tuberculosis (TB) spreads through the air when people with active TB cough or sneeze, releasing droplets. While some people get sick right after being infected, most don't show symptoms because the infection stays inactive, or "latent." This latent TB can become active later in about 5-10% of cases, especially in people with weak immune systems. Around 2 billion people worldwide have latent TB, creating a huge potential for more active cases. This makes controlling TB difficult, as the latent infection is a major challenge to eliminating the disease. In wealthier countries, the focus is on identifying and treating both active TB cases and people with latent infections to stop the spread.(3)

Tuberculosis (TB) is a widespread disease, affecting about 25% of the global population, and remains the deadliest infectious disease worldwide. While most people with TB can be cured, around 85%, a growing number of cases are becoming resistant to standard treatments. This is mainly due to the rise of drug-resistant TB strains, which are harder to treat because they don't respond to several commonly used medicines. Developing new drugs to fight TB is essential to address this growing problem of drug resistance.(4)

1.2 Sign and Symptoms of Tuberculosis –

General Symptoms:

1. Loss of weight.
2. Fever and sweating.
3. Loss of appetite.

4. Breathlessness.

Respiratory Symptoms:

1. Cough.
2. Sputum.
3. Blood-spitting.
4. Tiredness.
5. Amenorrhea.
6. Arrhythmia.(5,6)

1.3 Pathophysiology of Tuberculosis –

The story of how tuberculosis (TB) spreads starts and ends with the transmission of the bacteria. The process has several key steps. First, there must be a person with the bacteriacalled the "index case." This person must have active TB, which means they are contagious and can produce infectious particles. TB bacteria, M. tuberculosis, can spread through the

respiratory system (the most common route), as well as through damaged skin, mucous membranes, or the digestive system. The person with active TB in the lungs or throat can release the bacteria into the air through actions like coughing, sneezing, shouting, or singing. The bacteria then remain suspended in the air. Other people can inhale the bacteria when they breathe in these tiny droplets. If the droplets are very small (less than 5 microns), they can reach the tiny air sacs (alveoli) deep in the lungs and start an infection.(7)

When someone inhales droplets containing tuberculosis bacteria, most of the bacteria get stuck in the upper airways. Here, special cells called goblet cells produce mucus, which traps the bacteria. Tiny hair-like structures called cilia move the mucus, along with the trapped bacteria, upwards so it can be cleared out of the body. This process acts as the body's first defense against tuberculosis infection in most people.

If tuberculosis bacteria manage to get past the mucus and cilia system and reach the tiny air sacs in the lungs (alveoli), they are quickly surrounded and swallowed by immune cells called alveolar macrophages. These macrophages are the next defense of the body and belong to the immune system's first line of protection. Their job is to destroy the tuberculosis bacteria and prevent infection. Macrophages are always ready to fight off many harmful germs, even without having encountered them before. They use different methods and special receptors to capture and destroy the bacteria.

After the macrophages swallow the tuberculosis bacteria, the bacteria start to multiply slowly, dividing every 25 to 32 hours. Whether the infection is controlled or gets worse, the macrophages initially release special enzymes and signaling molecules (called cytokines) to try to break down the bacteria. These cytokines also attract T lymphocytes (T cells), which are important for the immune response. The macrophages display parts of the bacteria to the T cells to trigger a stronger immune response. This whole process can last for 2 to 12 weeks, during which time the bacteria continue to grow until there are enough of them to activate a full immune response. At this point, the infection can often be detected by a skin test.

For people with a strong immune system, the next defense against tuberculosis is the formation of granulomas. These are small, lump-like structures that form around the tuberculosis bacteria. The granulomas are made up of T cells and macrophages, creating an environment that slows down the growth and spread of the bacteria. This process can destroy some of the macrophages and cause early tissue damage at the center of the granuloma. However, the tuberculosis bacteria are able to adapt and survive by changing how they function, like adjusting their protein production to stay alive.

For people with weaker immune systems, the body tries to form granulomas around the tuberculosis bacteria but fails to contain them. The tissue in the granuloma breaks down into a semi-liquid state, and the protective wall around it weakens. This liquid can drain into the airways (bronchus) or nearby blood vessels, leaving an empty space in the lung. If the liquid drains into the bronchus, the person can cough up droplets that spread the infection to others. If it enters a blood vessel, the bacteria can spread to other parts of the body, causing extrapulmonary tuberculosis. The bacteria can also spread by the lymphatic system and form new granulomas in the lymph nodes near the lungs.

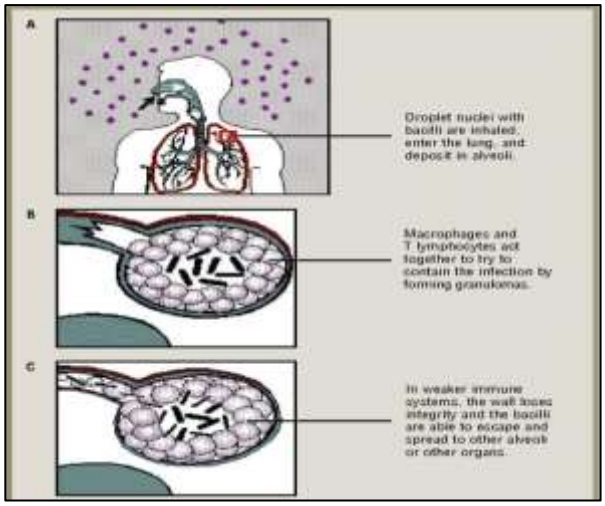

Fig 2 - Pathophysiology of Tuberculosis (8)

2. Pretomanid –

Pretomanid is a type of antibiotic used to treat tuberculosis (TB). It belongs to a group of drugs that work by stopping the production of the bacteria's protective cell wall, making it easier to kill the TB bacteria. When combined with two other medicines, bedaquiline and linezolid, it is used as part of a treatment known as the BPaL regimen. This combination is taken for six months and has been approved by the FDA in 2019 and the EMA in 2020 for treating adults with drug-resistant TB.(9)

Pretomanid is a drug used to treat certain severe forms of tuberculosis (TB), a serious lung infection. It is part of a three-drug combination that includes bedaquiline, pretomanid, and linezolid (known as the BPaL regimen). This treatment is taken by mouth for six months and is used to help adults with difficult-to-treat TB cases, such as extensively drug-resistant TB (XDRTB) or complicated cases of multidrug-resistant TB (MDR-TB). It has been approved for use in over 10 countries.(10)

2.1 Structure and Physical Properties of Pretomanid:

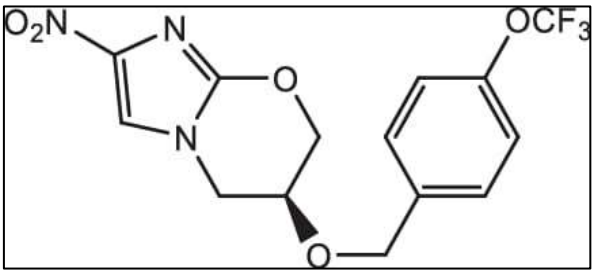

Fig 4 - Chemical Structure of Pretomanid

- Molecular formula –C14H12F3N3O5
- **IUPAC Name** –(6S)-2-nitro-6-[[4-(trifluoromethoxy)phenyl]methoxy]-6,7-dihydro-5H- [2,1b]oxazine
- **Synonyms –** PA-824
- **Molecular weight –** 359.26 uma
- **Solubility –** Insoluble in water and its solubility in buffers
- **Melting point –** 181-185°C
- **Boiling point –** 230-240°C
- **Uses-** Treatment of tuberculosis
- **Half life -** An FDA briefing document reports a half-life of 18 hours.

- **Indication –** Pretomanid is used together with two other drugs, bedaquiline and linezolid, to treat adults with certain severe forms of lung tuberculosis (TB). This combination is prescribed for people whose TB is either very resistant to other treatments, difficult to tolerate, or not responding well to standard treatments.(11,12)

3. Mechanism of Action –

Pretomanid is a drug that works specifically against Mycobacterium tuberculosis, the bacteria that cause tuberculosis (TB). It can kill the bacteria whether they are actively growing or dormant.

1.InOxygen-RichEnvironments (where the bacteria are growing):

Pretomanid stops the bacteria from making an essential part of their cell wall, called mycolic acid. Without this, the bacteria die.

2.Low-OxygenEnvironments (where the bacteria are not growing):

Pretomanid releases a harmful substance called nitric oxide (NO) inside the bacteria. This damages their respiratory system and kills them, though this method doesn't work well in oxygen-rich environments

To work, pretomanid needs to be activated by an enzyme Called dezaflavin- dependent

Nitroreductase (Ddn) which requires a molecule called F420. Which is produced by the F420Dependent glucose -6-phosphate dehydrogenase fgd1. F420 is synthesized by enzymes encoded by the genes fbiA, fbiB,, fbiC & fbiD.(13,14)

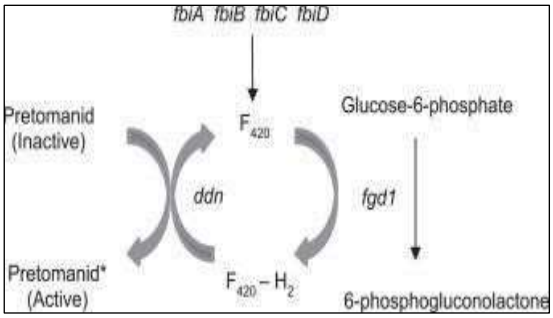

Fig 5 – Mechanism of Action of Pretomanid

4.Methods of Synthesis –

4.1Read and Fairlamb -

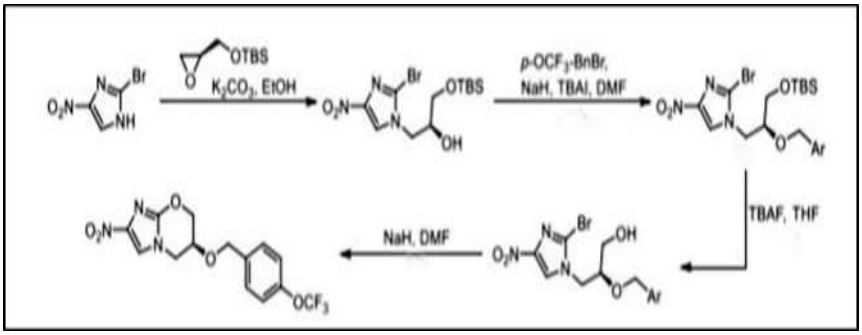

Fig 6 – Synthesis of Pretomanid by Read and Fairlamb.

The synthesis begins with 2-bromo-4 -nitroimidazol, a readily available starting material.

The key steps in the process are:

1.Nucleophilic Substitution:

The synthesis begins with a nucleophilic substitution reaction, where the bromo group on 2bromo4-nitroimidazole is replaced by TBS-protected glycidol.

In this step, the nucleophilic oxygen from the glycidol attacks the electrophilic carbon attached to the bromine in the imidazole ring, leading to substitution of the bromine atom.

2.Aryl Moiety Installation:

With the glycidol attached to the imidazole ring, the next step is the installation of an aryl group. This step introduces an aryl moiety (aromatic ring) onto the molecule, which is critical for the biological activity and stability of the final compound.

3.Protecting Group Cleavage: Once the aryl group is in place, the TBS protecting group on the glycidol moiety is removed. This deprotection step is essential, as it exposes the hydroxyl group, making it available for the subsequent cyclization reaction.

4.Final Cyclization:

In the final step, the molecule undergoes a cyclization reaction to form pretomanid.

This cyclization involves the reaction of the free hydroxyl group with another part of the molecule, creating a new ring structure.

4.2 Zhai etal-

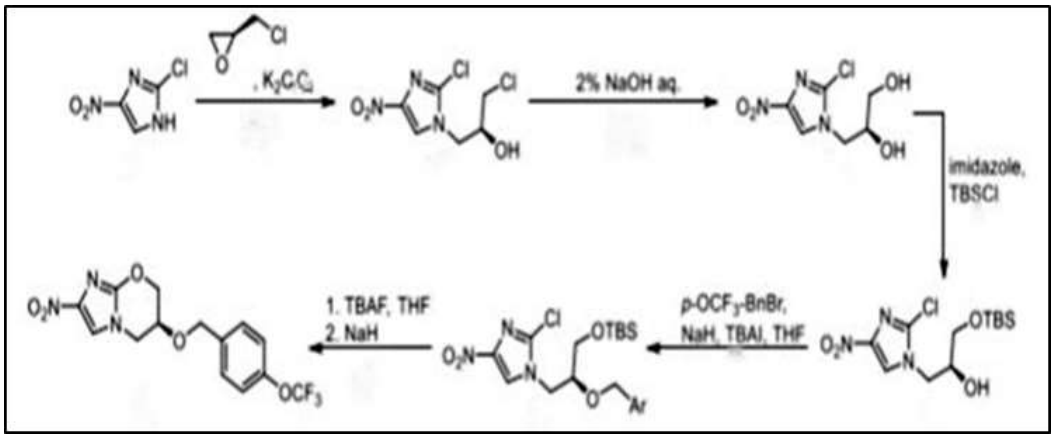

Fig 7 – Synthesis of Pretomanid by zhai et al.

The synthesis begins with 2-chloro-4-nitroimidazole and (S)-epichlorohydrin are used as starting materials to prepare pretomanid. The steps are as follows.

1.N-Alkylation:

The synthesis begins with an N-alkylation reaction, where 2-chloro-4-nitroimidazole is reacted with (S)-epichlorohydrin.

In this step, the nitrogen in the imidazole ring acts as a nucleophile, attacking the epoxide ring of (S)-epichlorohydrin. This results in the opening of the epoxide and the formation of an N-alkylated intermediate.

This reaction attaches the epichlorohydrin moiety to the nitrogen of the imidazole ring, creating a new chiral center in the molecule and setting up a precursor structure for further functionalization.

2.Hydrolysis; The next step is hydrolysis, which converts the newly attached epichlorohydrin moiety into a diol. In this process, the epoxide ring is opened under acidic or basic conditions,

resulting in the formation of diol, which contains both primary and secondary hydroxyl groups.

3. TBS Protection:

The primary hydroxyl group of diol is selectively protected with a TBS (tert-butyldimethylsilyl) group.

The TBS group acts as a protective group for the primary alcohol, rendering it inert and leaving the secondary alcohol free for subsequent reactions.

This step is crucial to control the reactivity of the hydroxyl groups, ensuring that only the secondary hydroxyl group is available for further functionalization in the next step.

4.Benzylation:

The secondary hydroxyl group, now exposed after TBS protection of the primary alcohol, is benzylated.

In this reaction, the secondary hydroxyl reacts with a benzylating agent, attaching a benzyl group to form benzyl ether, resulting in alcohol.

Benzylation of the secondary hydroxyl provides additional stability and sets up the molecule for the one-pot deprotection and cyclization step that follows.

5.One-Pot Deprotection and Cyclization:

In the final step, a one-pot reaction is performed to remove the TBS protecting group from the primary hydroxyl group and initiate cyclization to form pretomanid.

Upon deprotection, the free primary hydroxyl group participates in a cyclization reaction, which closes the ring structure and completes the formation of pretomanid.(15)

5. Evaluation Parameters of Pretomanid –

1.Solubility –

Water Solubility:

The compound is poorly soluble in water, with solubility decreasing at higher pH (from 0.17 mg/mL at pH 6.5 to 0.12 mg/mL at pH 7.4).

Temperature affects solubility; higher temperatures (e.g., 37°C) slightly decrease solubility.

Organic Solvent Solubility:

Highly soluble in methanol (10.4 mg/mL), moderately soluble in ethanol (4.8 mg/mL), and less soluble in acetonitrile (2.5 mg/mL).

Buffer Solubility:

Solubility is slightly higher at acidic pH (e.g., 0.25 mg/mL in pH 4.5 acetate buffer) compared to neutral/alkaline buffers.(16,17,18)

2.Stability –

Physical Stability -

5.1 Melting Point: 181-185°C

Indicates the temperature range at which Pretomanid changes from a solid to a liquid state.

5.2 Solubility: Water, methanol, ethanol

Pretomanid is soluble in various organic and aqueous solvents, making it suitable for various pharmaceutical formulations.

Polymorphism: No polymorphic changes observed

Polymorphism refers to the ability of a compound to exist in multiple crystalline forms. The absence of polymorphism suggests that Pretomanid's physical properties are consistent and predictable.

Chemical Stability -

1. **Acidic Conditions** (pH 1.2): Stable

Pretomanid remains stable in acidic environments, which is essential for its stability in the gastrointestinal tract.

2. **Basic Conditions** (pH 9.4): Moderate Degradation

Pretomanid undergoes moderate degradation in basic conditions, which may affect its stabilityin certain pharmaceutical formulations.

3. **Oxidizing Agents:** Stable

Pretomanid is resistant to oxidation, which is essential for its stability in the presence of oxidizing agents.

4. **Reducing Agents:** Significant Degradation

Pretomanid undergoes significant degradation in the presence of reducing agents, which may affect its stability in certain pharmaceutical formulations.

5. **Hydrolysis:** Slow Degradation at pH 7.4 and 37°C

Pretomanid undergoes slow hydrolysis at physiological pH and temperature, which may affect its stability in certain pharmaceutical formulations.(19,20)

Photostability -

400-800 nm Light Exposure for 12 Hours: Stable

Pretomanid remains stable when exposed to light in the visible spectrum, which is essential for its stability during handling and storage.

Solvent Stability –

Pretomanid's stability was evaluated in various solvents to assess its compatibility with different pharmaceutical formulations. Stability in Various Solvents

1.Water: Stable

Pretomanid remains stable in aqueous solutions, indicating its suitability for aqueous-based pharmaceutical formulations.

2.Methanol: Stable

Pretomanid is stable in methanol, which is commonly used as a solvent in pharmaceutical formulations.

3.Ethanol: Stable

Pretomanid remains stable in ethanol, which is often used as a solvent in pharmaceutical formulations.

4Acetonitrile: Moderate Degradation

Pretomanid undergoes moderate degradation in acetonitrile, which may affect its stability in certain pharmaceutical formulations.(21,22)

5.3.Melting point –

The melting point of Pretomanid is 181-185°C .

This indicates the temperature range at which Pretomanid changes from a solid to a liquid state.

Importance of Melting Point for Pretomanid:

The melting point of a compound is an important physical property that can affect its stability,

solubility, and bioavailability. In the case of Pretomanid, its melting point can impact its:

1.**Stability:**Pretomanid melting point can affect its stability in various environments, such as temperature and humidity.

2.**Solubility:** The melting point of Pretomanid can influence its solubility in various solvents, which can impact its formulation and bioavailability.

3.**Bioavailability:** Pretomanid's melting point can affect its bioavailability, as changes in its physical state can impact its absorption and distribution in the body.(23)

5.4.Boiling Point –

The boiling point of Pretomanid is: 230-240°C .

Importance of Boiling Point for Pretomanid:

1.**Pharmaceutical Formulation:** Boiling point data helps in selecting suitable solvents and designing stable formulations.

2. **Manufacturing Processes:** Boiling point information is essential for manufacturing processes,

such as crystallization and distillation.

3.**Stability Studies:** Boiling point data helps in predicting the stability of Pretomanid under various conditions.

Methods for Determining Boiling Point:

Several methods can be used to determine the boiling point of Pretomanid, including:

1.Distillation: A traditional method involving the distillation of the compound and measurement of the temperature at which it boils.

2.Thermogravimetry (TGA): A thermal analysis technique measuring the mass change of a sample as it is heated, providing information on the boiling point.

5.5.pKa (acid -base properties)–

The pKa values of Pretomanid are:

pKa1: 4.65 (acidic group)

pKa2: 7.31 (basic group)

Methods to Determine pKa Values –

Several methods can be used to determine the pKa values of Pretomanid, including:

1. **Potentiometric Titration:** Measures the pH of a solution as a strong acid or base is added.
2. **Spectrophotometric Titration:** Measures the absorbance of a solution as a strong acid or base is added.
3. **Nuclear Magnetic Resonance (NMR):** Measures the nuclear magnetic resonance signals of a solution as a strong acid or base is added.
4. **High-Performance Liquid Chromatography (HPLC):** Measures the retention time of a solution as a strong acid or base is added.(24)

6.Brand Product of Pretomanid –

6.1 Dovprela

- **Medicine Name** – Dovprela
- **Active substance -** pretomanid
- **Dosage form & Strength –** Tablet 200 mg
- **Pharmacotherapeutic group –** Antimycobacterials
- **Manufactured By** - Mylan Laboratories Limited.(25)

6.2.Pretomanid Oral Pill –

- **Medicine Name -**Pretomanid Oral Pill
- **Active substance –** pretomanid
- **Pharmacotherapeutic group –** Antimycobacterials
- **Manufactured By-** Mylan.(26)

7.Conclusion –

Pretomanid, a novel nitroimidazole antibiotic, represents a significant advancement in the treatment of tuberculosis (TB), particularly for multidrug-resistant (MDR) and extensively drugresistant (XDR) TB.Its use as part of the BPaL regimen (bedaquiline, pretomanid, and linezolid) has demonstrated high cure rates, reduced treatment durations, and better patient outcomes compared to traditional, prolonged therapies. While it marks a significant step forward in TB management, its successful implementation is contingent on addressing challenges such as side effects , accessibility in low-resource settings, and affordability. Pretomanid represents a vital advancement in global health efforts, offering new hope in the fight against one of the world's most persistent infectious diseases.

Reference –

1. Arvind Natrajan, P.M Beena, A systemic review on tuberculosis, Indian Journal of Tuberculosis Volume 67, Page 295 -311, Year 2020.
2. Dheeraj Bisht, Kumud Upadhyaya, A recent review on tuberculosis and its treatment, Journal of Research in Pharmacy & Chemistry, Volume 9, Page 200-210, Year 2019
3. Daniel Brodie, Neil W, The diagnosis of tuberculosis, Clinics in Chest Medicine, Volume 26, Page 247-27, Year 2005
4. Stephanil L Stancil, M Abdel- Rahman, Profiling pretomanid as a therapeutic option for a TB infection, Drug Design, Development & Therapy, Volume 15, Page 2815-2830, Year 2021.
5. Devender Sharma, Deepika Sarkar, Pathophysiology of tuberculosis, Magazine, Pharmatutor, volume 6, Page 15-21, Year 2018.
6. https://images.app.goo.gl/431AHJn7VkCP2Tp79
7. David P.. Maison, Tuberculosis pathophysiology and anti-VEGF intervention, Journal of Clinical Tuberculosis & other mycobacterial diseases, Volume 27, Page 1-6, Year 2022.
8. Nancy A. Knechel, RN, MSN, Tuberculosis pathophysiology, Clinical features & Diagnosis Critical Care Nurses, Volume 29, Page 34 -43, Year 2009.
9. Yuanxi Zou, Jerry Nedelman , Antonio Lombardi, Characterizing absorption properties of dispersible pretomanid tablet, Clinical Pharmacokinetics, Volume 61, Page 1585-1593, Year 2022.
10. Rebecca Bruning- Barry, Jeffrey L. Ambroso, John Dillberger, Toxicity & toxicokinetic assessment of an anti-tubercular drug pretomanid, Toxicology Reports, Volume 9, Page 927936, Year 2022.
11. Sara Occhineri, Tommaso Matucci, Laura Rindi, Pretomanid for tuberculosis treatment, Current Research in Pharmacology & Drug Discovery, Volume 3, Page 1-8, Year 2022.
12. https://go.drugbank.com/drugs/DB05154
13. Thi Van Anh Nguyen, Dinh Hoa Vu, Pretomanid resistance, International Journal of Antimicrobial Agents, Volume 62, Page 1-11, Year 2023.
14. Ginenus Fekadu, Tadesse Tolossa, Pretomanid development and its clinical roles in treating tuberculosis, Journal of Global Antimicrobial Resistance, Volume 31, Page 175-184, Year2022.
15. Tobias Lucas, Jule- Philipp Dietz, Short and Efficient synthesis of the Antituberculosis Agent Pretomanid, Organic Process Research & Development, Volume 27, Page 16411651, Year 2022.
16. Varun Raj vemula, Srikanth lingala. Solubility Enhancement Techniques ,International Journal of Pharmaceutical Sciences, Volume 5, Page 41-51, Year 2010.
17. Michael A. Lyons, Modeling and simulation of pretomanid, Antimicrobial Agents and Chemotherapy, Volume 63, Page 1-24, year 2018.
18. Singh S, Kumar A, solubility and dissolution rate of pretomanid, Journal of Pharmaceutical Sciences, Volume 109, Page 2841-2848, Year 2020.
19. francesca conradie, M.B, B. Ch, Treatment of Highly Drug – Resistant, The New England Journal of Medicine, Volume 382, Page 1-8, Year 2020.
20. Elisa H Ignatius, Nikhil Gupte, Pretomanid Pharmacokinetics in the presence of Rifamycins, Antimicrobial Agent and chemotherapy, Volume 65, Page 1-11 , Year 2021.
21. Oelofse S., Esmail A, Pretomanid with be bedaquiline and linezolid, The International Journal of Tuberculosis, Volume 25, Page 453-460, Year 2011.
22. Vaishali Pardeshi, Tushar Lokhande, Development & Validation of Stability Indicating HPTIC Method , International Journal of Pharmaceutical Sciences and Research, Volume 14, Page 4899-4906, Year 2023.
23. Peddi Srinivasa Rao, Tirukkovalluri Siva Rao, Stability Indicating RP-HPLC Method Development and validation, Research J. Pharm Tech., Volume 16, Page 2385-2392 Year 2023.
24. Sandra Babic, Alka J.M. Horvat, Determination of pKa values, Trends in Analytical chemistry, Volume 26, Page 1043-1061, Year 2007.
25. https://www.pharmasolutions-int.com/product/dovprela-pretomanid/
26. https://images.app.goo.gl/ehYnensRsqzkKA6A7