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A REVIEW ON CHEMISTRY, BIOLOGICAL PROPERTIES, ANALYTICAL METHODS, CLINICAL TRIALS OF BEDAQUILINE

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ABSTRACT

Bedaquiline, a diarylquinoline class medicine, delivers its bactericidal action by specifically blocking the adenosine triphosphate (ATP) synthase enzyme of Mycobacterium TB, therefore interrupting its energy metabolism. Tuberculosis (TB) remains an ongoing globally issue, with almost one-third of the world's population carrying latent TB infections. Due to the lipid-rich polysaccharide nature of the M. tuberculosis cell wall, which limits drugs penetration and increases antibiotic efflux, therapy for multidrug-resistant tuberculosis (MDR-TB) has become even more challenging. Bedaquiline has emerged as a crucial component of MDR-TB treatment plans, showing strong effectiveness when used in combination therapy for adults. With a focus on its therapeutic value in the management of MDR-TB, this study examines its chemical characteristics, structure-activity correlations, pharmacokinetics, and pharmacodynamics. Along with discussing the various analytical techniques created for its quantification in various biological and pharmaceutical matrices, it also looks at important clinical trials that demonstrate its therapeutic efficacy and safety profile, ensuring precise monitoring, quality control, and therapeutic use optimization.

KEYWORDS: Bedaquiline, Tuberculosis (TB), Mycobacterium tuberculosis, Synthesis, chemistry, Clinical trial, Analytical methods.

1. INTRODUCTION

About 10 million humans worldwide have been diagnosed with tuberculosis (TB), a long-term infectious disease that is a major source of morbidity and mortality.[1,2] According to the 2022 World Health Organization's (WHO's) Global TB Report, around 1.7 billion individuals, representing 23% of the world's population, are predicted to have latent tuberculosis. People who suffer from HIV disease have been confirmed to be at a higher risk of acquiring active tuberculosis (TB) during their life span, with certain proportions of this population carrying a Mycobacterium

tuberculosis infection. The risk of acquiring active tuberculosis is further exacerbated by a number of other factors that include diabetes, addiction to alcohol, smoking, and undernutrition.[3] A slow-growing Mycobacterium tuberculosis is the primary cause of tuberculosis (TB), although the bacterium M. bovis or M. africanum may have a part in it. *M. caprae, M. canettii, M. microti, and M. pinnipedii* are among the other species. If left untreated, these pathogenic microbes may also harm the kidney, spine, and brain in along with the lungs that is pulmonary tuberculosis (TB).

People with tuberculosis when they cough, sneeze, or speak, they release microbes into the air that may infect others.

The bacteria proliferate inside the lungs region then spread across different areas of one's body via the system of lymphatics, the blood, and airway. Even with the accessibility of the vaccine Bacillus Calmette-Guerin (BCG) and the successful DOTS (Directly Observed Therapy Shortcourse) treatment such as chemotherapy, the occurrence of tuberculosis remain more as compared to that of any other disease organism. It has influenced over one-third of the world's population and is predicted to account for approximately 2 million fatalities yearly.[4] The prevalence of resistant to medication forms of this illness is an important contributing factor. When an individual stops receiving first-line therapy for tuberculosis, the tuberculosis bacteria develops multidrug resistance (MDR) to the medication because the virus mutates or because the medication is given incorrectly.[5] Patients with tuberculosis who are resistant to both of the most significant first-line drugs—isoniazid and rifampicin—are considered to have multidrug-resistant strain of the disease. Numerous issues with the MDR regimen have been documented, including an expensive course of action, lower efficiency, more drug interactions, and an extended period to initiate effects. Also, with second-line anti-TB medications, fluoroquinolones, common drug resistance (XDR-TB) was seen. Between mid-2009 and mid-2016, MDR-TB infections emerged in a large number of people worldwide, primarily from eastern Europe to Asia. Drug intolerance and toxicities are additional issues regarding contemporary TB treatments that occasionally necessitate discontinuing treating and altering the dosage.[6] Therefore, when trying to meet the worldwide tuberculosis ambitions outlined in the Sustainable Development Goals and the End TB Approach, fresh findings in the area of tuberculosis study and advancement become crucial. As an outcome, a brand-new, unique substance known as bedaquiline was created to address the MDR problem with existing medications.[7,8] Andries and colleagues published the first medicine for multidrug-resistant tuberculosis in 2005. It was once known as TMC 207 but is currently sold under the brand name Sirturo and is known as bedaquiline (BDQ) fumarate. Strong and effective, bedaquiline works by a novel mechanism that involves inhibiting the proton pump of the mycobacterium-specific ATP synthase, an enzyme that the mycobacteria need for transforming energy for reproduction.[9,10]

2. Chemistry

The compound bedaquiline is based on diarylquinolines and has an antimycobacterial activity due to its quinolinic core heterocyclic nucleus with side chains of amines and alcohols. Its molecular weight is 555.50 g/ml and its formula is C32H31BrN2O2.[11] Bedaquiline's chemical name is (1R, 2S).1-(6-bromo-2-methoxy-3-quinolinyl)-4-dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol. Bedaquiline fumarate is created by combining bedaquiline and fumaric acid (1:1).[12]

Figure 1 depicts the chemical structure of bedaquiline.

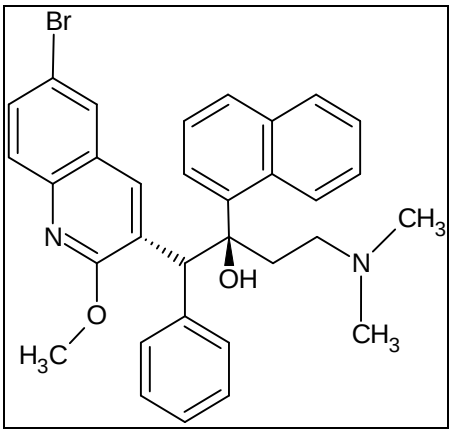
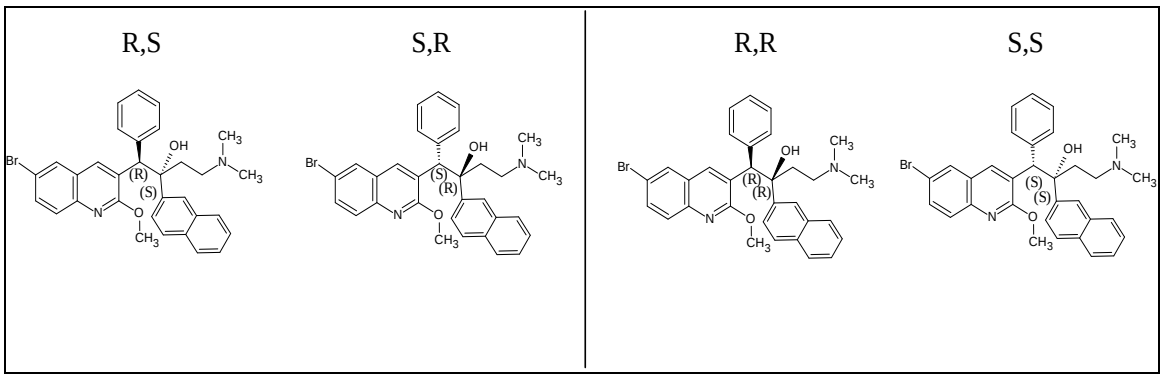


Figure 1: Chemical structure of bedaquiline.

Further, the dimethyl group binds to the amino acid residues at the A and C subunits Arg-186 and Glu-61, the H-Bonding stabilizes the structure of Bedaquiline. The hydroxy group, the naphthalene moiety, and the diarylquinoline ring are all essential for bedaquiline's anti-TB action. It works in concert with both first- and second-line medications to treat tuberculosis.[13] Because of its hydrophilic side chain (OHgroup) and hydrophobic ring structure, bedaquiline is classified as a cationic amphiphilic drug (CAD). Its cationic amine group (NMe2) can become protonated at physiological pH ranges. Having 2 chiral centers, bedaquiline is an enantiopure chemical (1R,2S isomer). BDQ, which is made from a combination of four distinct isomers, is a very effective stereoisomer against diverse strains of mycobacteria. In the absence of an external chiral media, the chemical synthesis of BDQ (Figure 2) yields four isomers due to its two stereogenic centers at the molecular level. The two pairs of diastereoisomers that these isomers belong to are RR, SS and RS, SR. The (1R, 2S) stereoisomer, commonly referred to as BDQ, is the isomer that is most efficient against tuberculosis.[14]



3. Synthesis

The most important medication in the world for treating multidrug-resistant Mycobacterium tuberculosis is bedaquiline (BDQ). Researchers are still faced with difficulties when it comes to the asymmetric synthesis of BDQ. Lithium diisopropylamide (LDA) is used as a base in the synthesis of bedaquiline, as shown in Scheme 1. This procedure uses n-BuLi and diisopropylamine in tetrahydrofuran (THF) at an equivalent ratio of 5:5. The electrophile reaction takes place at -78 °C for three hours after the deprotonation stage, which lasts for 30 minutes.

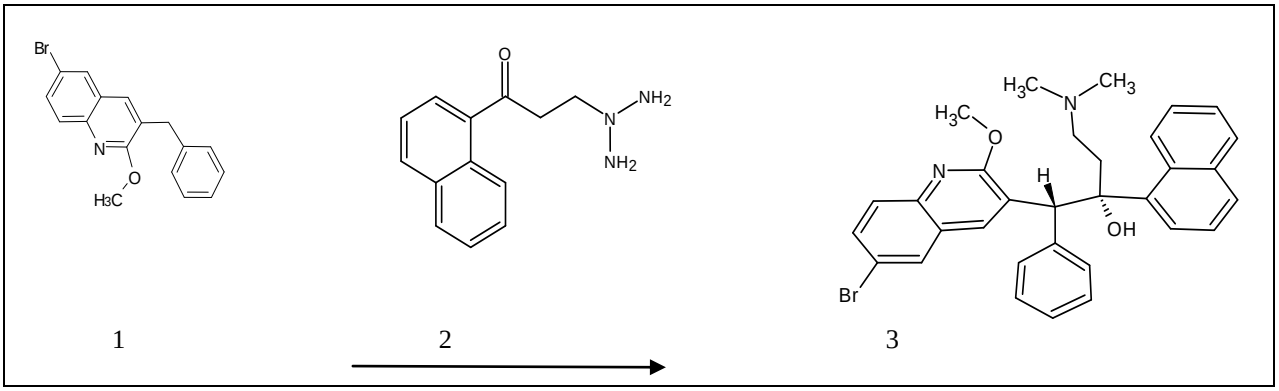


Figure 2: Scheme 1: Lithiation Reaction between the Appropriate 1) 3-Benzylquinoline and 2) 3-(Dimethylamino) phenylpropan-1-one (3) Product of BDQ

In the literature, there are a few synthetic routes published for the preparation of BDQ.[15] The work of Saga and associates, who developed a convergent asymmetric synthesis for BDQ, is one of the asymmetric approaches. With an overall yield of 5%, their synthesis required 12 linear steps, beginning with commercially available chemicals, despite the complex nature of their reaction procedure and the need for expensive reagents.[16] After then, the target BDQ isomer's asymmetric synthesis was reported by Chandrasekhar and colleagues. They achieved an overall yield of 12% by using a linear strategy spread across 10 phases.[17] Janssen Pharmaceutical most likely uses an industrial procedure that entails a one-step lithiation reaction with LDA as the base, followed by large-scale chiral resolution using binaphthol phosphate to isolate the desired isomer. Nevertheless, there are drawbacks to this approach, such as low overall yields caused by the loss of the intended diastereomer in the first step because there is no chiral environment. Recrystallization is used to extract the (RS, SR) diastereomer from a 50:50 crude diastereomer mixture. Next, a chiral resolution agent is used to transform the (RS, SR) diastereomer into a diastereomeric salt. After recrystallization and salt neutralization, the chosen stereoisomer (R, S) is separated, yielding the free medication as a single enantiomer. [18]

The most significant BDQ synthetic method, as well as the compounded BDQ Fumarate, were provided by Sebastian and associates.[19] which is shown in Figure 3

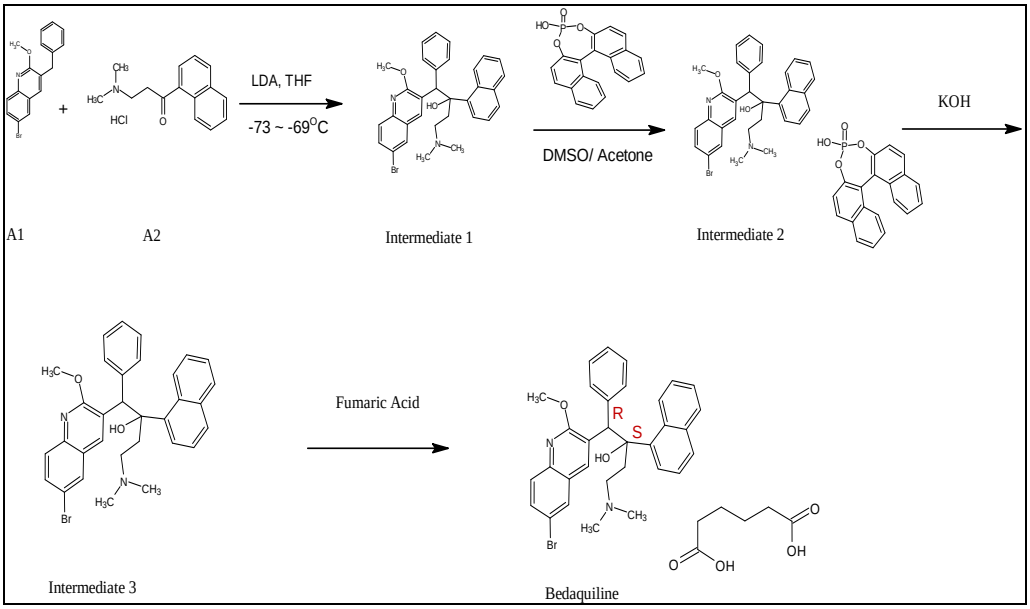


Figure 3: Synthesis route of Bedaquiline and BDQ Fumarate.

4. Pharmacology

MDR-anti-TB therapy, bedaquiline is given by oral route and acts by selectively blocking the enzyme mycobacterial ATP synthase produces. Significantly, compared to eukaryotic mitochondrial ATP synthase, bedaquiline has a selectivity index of twenty thousand for mycobacterial ATP synthase. As such, interaction with human ATP synthase is not predicted. Through blocking adenosine triphosphate (ATP) synthase, it has bactericidal as well as sterilizing actions for M tuberculosis and certain nontuberculous mycobacteria.[20] The quinolinic core heterocyclic nucleus and side chains of tertiary alcohol and tertiary amine groups constitute bedaquiline's pharmacologically active site, which provides its antitubercular properties.[21]

4.1 Mechanism of Action

The merely approved by the Food and Drug Administration anti-TB medication, Bedaquiline, is based on diarylquinoline compounds and suppresses the proton pump mechanism targeting adenosine triphosphate (ATP), which is necessary for mycobacterial energy synthesis.[22] By blocking the synthesis of ATP, it exerts bactericidal and sterilizing effects on M. tuberculosis. It specifically targets the core portion of the ATP synthase enzyme's c subunit.

Every biological cells, especially mycobacteria, require adenosine triphosphate (ATP) in order to survive. Mycobacteria that endure in lung cavities that are well-encapsulated and in macrophage endosomes, where they can thrive even in low oxygen environments and develop resistance to common TB medications.

The extensive metabolic path known as oxidative phosphorylation is usually responsible for ATP generation, and it is this process that Bedaquiline targets in its anti-TB effect. When electrons are transferred from NADH or succinate groups to membrane-bound protein complexes, this activity initiated by electron transport chain (ETC). These complexes then use menaquinone, an electron transporter, to transfer the electrons to terminal oxidases or reductases.

Together with the electron transport, some of the ETC complexes also pump protons from the cytoplasm to the periplasm throughout this process.

Proton pumping produces the transmembrane pH gradient and adds to the membrane potential, which are two aspects of the proton motive force.[23] In the laboratory, bedaquiline exhibits bactericidal action towards numerous mycobacterial organisms, including M. tuberculosis. It suppresses mycobacteria that are actively replicating as well as those that are not; one research found that at low levels, it can inhibit dormant cells in latent tuberculosis infection. The presence of resistance to other anti-TB medications, such as isoniazid, rifampicin, ethambutol, streptomycin, ethambutol, and moxifloxacin, does not affect mycobacterial sensitivity to the medication.[24] Resistant to drug tuberculosis patients now have access to a quicker and more bearable treatment regimen through the introduction of Bedaquiline

4.2 Absorption

When administered orally along with meals, bedaquiline is readily absorbed by the human body. Management for tuberculosis has included the use of this oral delivery technique. Bedaquiline has an efficient half-life of 24 hours on average and a linear connection among doses and maximum plasma concentration (Cmax). Peak level occurs an average of five to six hours after therapy. The relationship between cumulative weekly doses and drug efficacy suggests intermittent delivery is preferable.[25]

4.3 Distribution

Bedaquiline binds to protein in human plasma samples 99.9% at concentration of 5 mg/L and greater. At dosages of 10 and 30 mg/L, 99.7% of bedaquiline main metabolite, M2, is bound to human plasma proteins.[10] Human sputum has also been found to contain bedaquiline. Bedaquiline was identified in the sputum at a maximum concentration (Cmax) of 5 mg/L in a Phase II investigation of treatment-naive patients with drug-susceptible TB, when it was administered at a dose of 400 mg once daily for seven days.[26]

4.4 Metabolism

Human bedaquiline metabolism has only been detected in phase I. In all examined species, cytochrome P450 (CYP) isoenzyme 3A4 predominantly metabolizes bedaquiline in the liver to produce the N-monodesmethyl metabolite, M2.[20]

Apart from CYP3A4, bedaquiline metabolism in vitro is influenced by CYP isoforms 1A1, 2C8, and 2C18 (characterized by a metabolic rate more than 10% of that of CYP3A4). However, due to their much lower liver prevalence than CYP3A4, these isoenzymes are not likely to be relevant in vivo.[27]

4.5 Excretion

The primary mechanism of bedaquiline elimination is through feces. According to clinical trials, the unmodified drug accounted for 7.5%–85% of the drug-related material identified in 24-hour feces samples, while the metabolite M2 made about 3.7%–7.2%. Urine excretes very little M2 and bedaquiline. The amount of unaltered medication excreted in urine over a 24-hour period when 400 mg of bedaquiline was taken once daily was ≤0.001% of the oral dose.[20]

Bedaquiline and M2 are removed from plasma after lengthy half-lives. The average half-life of bedaquiline was 164 days (range from 62 to 408) and that of M2 was 159 days (ranging from 69 to 407) following 8 weeks of bedaquiline treatment for MDR-TB (2 weeks at 400 mg once daily and 6 weeks at 200 mg three times a week).[28]

Consequently, almost all patients' plasma still contained bedaquiline and M2 96 weeks after the conclusion of treatment. In that instance, the median concentration of M2 was 0.00258 mg/L (ranging from 0.00164 to 0.0116 mg/L), while the median concentration of bedaquiline was 0.010 mg/L (with a range of 0.00224 to 0.0436 mg/L). Because of their cationic amphiphilic characteristics, bedaquiline and M2 have lengthy half-lives, which are related to their slow release from peripheral tissues. During treatment, these medications build up in different tissues in non-human animals. Catalytic amphiphilic drugs (CADs), such as bedaquiline and M2, bind to intracellular phospholipids and cause the drug to accumulate in tissues.[29-31]

5. Analytical and Bio-analytical methods of Bedaquiline

Validation of a developed technique

A tried-and-true quantitative analytical approach for identifying changes over time in the chemical, biological, or physical characteristics of a drug substance or drug product is method validation. in a way that makes it possible to accurately measure the amount of active ingredient and distinguish each active component from its breakdown products.[32]

Important stages in validation

The first stage, known as pre-validation qualification, covers all work pertaining to the creation and enhancement of the product. This step includes overseeing pharmaceutical formulations both in-process and finished, qualifying equipment, validating master documents, defining process limits, sharing innovations with business scale groups, scaling up research, and pilot batch testing of formulations.[33]

Process validation is the main focus of this stage's second phase. The objective is to confirm that every installed constraint of the crucial process parameters is successful in guaranteeing the production of consistently high-quality products, even under difficult circumstances.

Phase Three, also referred to as the validation maintenance stage, entails a continuous review of all procedure-related documents, including validation review reports, to make sure that the manufacturing process has not been altered and that all standard operating procedures (SOPs), including change control processes, are being followed. At this point, the approval team—which consists of members from all pertinent departments—verifies that there haven't been any modifications or deviations that call for revalidation or requalification.[34]

5.1 Spectrophotometric techniques

The initial technique, which reports the UV-Spectrophotometric approaches, was created by Pooja et al. . This technique suggests that the UV-Spectrophotometric methods used for the estimation of Bedaquiline have been developed on the basis of the area under the curve, derivative, and calibration curve methods.[35]

5.2 Chromatographic Analysis of Bedaquiline

Table 1: Table showing various chromatographic methods for estimation of bedaquiline from different metrics.

S.N	Technique	Matrix	Mobile Phase	Flow rate	Column	Wavelength	Ref.
1	RP-HPLC	**API**	Methanol and triethyl amine phosphate buffer	1.2 mL/min	Luna C18, 5 µm, 150 × 4.6 mm	**225**	**[36]**
2	LC–MS/MS	**Rat Plasma**	Formic acid-water (0.1%v/v) and acetonitrile in the ratio of (10:90 v/v)	0.5 mL/min	Chromolith High-Resolution RP-18e column, 100 × 4.6 mm	-	**[37]**
3	LC–MS/MS	**Rodents**	0.1% v/v formic acid (mobile phase A) and 100% acetonitrile (mobile phase B)	0.4 mL/min	YMC Triart C18 column, 3 µm, 150 mm × 3.0 mm	-	**[38]**
4	RP-HPLC	**API**	10 mM buffer of triethylamine/ phosphoric acid pH 7 and acetonitrile at 40:60 ratio	0.1 to 1.4 mL/min	Chiralcel OJ-3R,3µm, 150×4.6 mm	**227**	**[39]**
5.	RP-HPLC	**API**	methanol and 10 mM ammonium acetate buffer in the ratio of 85:15 v/v	1.2 mL/min	Sunfire C18, 5µm, 250×4.6 mm, 5µm	**266**	**[40]**

Momin et al. developed a reverse phase HPLC method for simultaneously estimating bedaquiline, pyrazinamide, and moxifloxacin in a pharmaceutical powder dosage form. The analytes were separated using a Luna C18 column with dimensions of 150 × 4.6 mm and a particle size of 5 µm. The mobile phase comprised methanol and a triethylamine

phosphate buffer at pH 2.5. The method utilized gradient elution with a flow rate of 1.2 mL/min and a run time of 20 minutes. Detection wavelengths were 269 nm for pyrazinamide, 296 nm for moxifloxacin, and 225 nm for bedaquiline, with retention times of 2.9 minutes, 7.0 minutes, and 16.3 minutes, respectively. The method was validated according to ICH guidelines, showing linearity for all analytes in the concentration range of 1–100 µg/mL with correlation coefficients greater than 0.998. The limits of quantitation (LOQ) were 0.56 µg/mL for bedaquiline, 0.43 µg/mL for moxifloxacin, and 0.24 µg/mL for pyrazinamide. The method demonstrated precision and accuracy within the range of 100.0–104.7%.[36]

A bioanalytical LC-MS/MS method for determining bedaquiline in rat plasma was reported by Kotwal et al. The method was used to evaluate preclinical drug interactions between bedaquiline and cytochrome P3A4 inhibitors (isoniazid/ciprofloxacin/fluconazole/verapamil) or inducers (carbamazepine). The multiple reactions monitoring mode (MRM) and ESI source were employed with a triple quadrupole mass spectrometer. Rat plasma was used as the source of the samples using protein precipitation. The choice for an internal standard was diclofenac.

Analytes were successfully separated using an RP-18e column (100 × 4.6 mm). 0.1% (v/v) formic acid in water and acetonitrile in isocratic mode (10:90, v/v) at a flow rate of 0.5 mL/min was the ideal composition for the mobile phase. The methodology's accuracy, linearity, specificity, recovery, precision, stability, and matrix effect were all verified in accordance with FDA criteria.[37]

To ascertain the degree of bedaquiline's medication transport to the brain. The penetration of bedaquiline in the brains of healthy rodents was examined by Pamreddy et al. They used the LC-MS/MS method to quantify bedaquiline from the prepared sample. An electrospray ionization mass spectrometer and quadrupole time-of-flight mass analyzer were attached to the HPLC system. A YMC Triart C18 column (150 mm × 3.0 mm; particle size 3 mm) was used for the separation process. Water containing 0.1% v/v formic acid (mobile phase A) and 100% acetonitrile (mobile phase B) was the mobile phase utilized in gradient elution at a flow rate of 0.4 mL/min. The technique shows compliance to EMA regulations.[38]

Douša et al. reported the separation of bedaquiline stereoisomers using chiral columns and reversed phase HPLC.

Out of the a possible ten chiral columns that were tested, the Chiralcel OJ-3R Column with dimensions of 150 × 4.6 mm and a particle size of 3 µm was found to be more suitable because it was able to resolve all of the bedaquiline's enantiomers and all of the stereoisomers with a resolution of >2.0. As the mobile phase, a combination of acetonitrile in a 40:60 v/v ratio and a 10 mM triethylamine/phosphoric acid (pH 7.0) buffer was used. For the analysis, a wavelength of 227 nm was chosen. It was discovered that the technique used was sensitive and specific, making it useful for routine examination of the chiral purity of Bedaquiline. The technique was validated according to ICHQ2(R1) guidelines.[39]

A stability indicating verified RP-HPLC technique for bedaquiline fumarate was published by Pardhi et al. As a stationary phase, a Sunfire C18 column measuring 250 mm by 4.6 mm and containing particles as small as 5 µm was employed. The ideal mobile phase for elution consisted of methanol in an isocratic mode at a ratio of 15:85 v/v and 10 mM ammonium acetate buffer (pH 4.5). Using a PDA detector, the analysis was carried out at a wave length of 266 nm while maintaining the column temperature at 40°C. A study on the forced degradation of bedaquiline fumarate was conducted utilizing UV, thermal, and acid-alkali hydrolysis techniques.[40]

6. Clinical Trials of Bedaquiline

The following (Table 2) table offers a concise overview of key information from various clinical trials that investigated the use of bedaquiline. It details the number of participants involved (No. of Volunteers), the age range of those who could participate (Age of Participation), the specific research method employed (Study Design), and the stage of development the trial reached (Phase). Additionally, the table provides the unique identifier assigned by the National Clinical Trials registry (NCT No.), the date the trial information was first made public (First Post Date), a brief explanation of the study's goals (Purpose of Study), and its current status (Status), such as actively recruiting participants, completed, or terminated. It's important to note that this table offers a general summary. For more in-depth information, you can access the individual trial records on ClinicalTrials.gov or consult the provided references.

Table 2: Clinical trial overview of Bedaquiline.

SR NO	Title	No of volunteers	Age of participation	Study Design	Phase	NCT No.	First post date	Purpose of study	Status	References
1.	**Bedaquiline Enhanced Post Exposure Prophylaxis for Leprosy**	124000	2 Years and older (Child, Adult, Older Adult)	Interventional (Clinical Trial)	Phase 3	NCT05597280	28-October-2022	The study aims to compare leprosy risk in individuals receiving BE-PEP versus WHO SDR-PEP. The intervention arm will provide BE-PEP to all persons within 100 meters of an index case, followed by four weeks for household contacts. The comparator arm will provide the WHO recommended standard PEP. The study will continue until 2026.	Recruiting	[41]
2.	**A Study of TMC207 in Patients With Moderately Impaired Hepatic Function**	16	18 Years to 65 Years	Interventional (Clinical Trial)	Phase 1	NCT01012284	13-November-2009	The purpose of study to assess the pharmacokinetics, safety, and tolerability of Bedaquiline and its N-monodesmethyl metabolite in healthy and moderately impaired patients following a single 400 mg dose.	Completed	[42]
3.	Evaluation of Early Bactericidal Activity in Pulmonary Tuberculosis Bedaquiline	68	18 Years to 65 Years	Interventional (Clinical Trial)	Phase 2	NCT01215110	6-october-2010	The purpose of this study is to evaluate the extended bactericidal activity of oral Bedaquiline in smear-positive pilmonary tuberculosis patients over a period of 14 consecutive days,	Completed	[43]

								with a control group undergoing normal treatment.		
4.	**Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis**	84	18 Years and Older	Interventional (Clinical Trial)	Phase 2	NCT02583048	21-october-2015	The study evaluated the safety, tolerability, and pharmacokinetics of delamanid and bedaquiline, anti-TB medications, in individuals with or without HIV co-infection receiving multidrug treatment for rifampin-monoresistant TB or multidrug-resistant TB.	Completed	[44]
5.	**A Study to Evaluate the Efficacy and Safety of Bedaquiline (TMC207) in Participants With Multibacillary Leprosy**	11	18 Years to 65 Years	Interventional (Clinical Trial)	Phase 2	NCT03384641	27-December-2017	The purpose of this study is to evaluate the efficacy of bedaquiline monotherapy in 8-week regimen in participants with treatment-naive, multibacillary leprosy.	Completed	[45]
6.	**A Study to Assess the Drug-Drug Interaction Between Bedaquiline and Clarithromycin in Healthy Adult Participants**	16	18 Years to 55 Years	Interventional (Clinical Trial)	Phase 1	NCT03800550	11-January-2019	The Purpose of this work is to evaluate the impact of a single dose of bedaquiline on the pharmacokinetic parameters of bedaquiline and its active metabolite M2 when clarithromycin is administered in once every 12 hours in steady- state	Completed	[46]
7.	**Safety, Tolerability, and Effect of TMC207 and**	37	18 Years to 65 Years	Interventional (Clinical	Phase 1	NCT00992069	8-October-2009	The purpose of this study is to test the safety	Completed	[47]

	Efavirenz in Healthy Volunteers			Trial)				of combining a new TB medication with an approved HIV medication in healthy adults, as common TB treatments can interfere with ARV medications.		
8.	**An Exploratory Study of TMC207 in Japanese Participants With Pulmonary Multi-Drug Resistant Tuberculosis (MDR-TB)**	6	20 Years and older	Interventional (Clinical Trial)	Phase 2	NCT02365623	19-February-2015	The purpose of this study is to evaluate safety and efficacy of Bedaquiline, a multi-drug regimen to evaluate pharmacokinetics and primary metabolite M2 in Japanese MDR-TB patients.	Completed	[48]
9.	**Evaluating the EBA of Meropenem With Amoxicillin/Clavulanate and Pyrazinamide or Bedaquiline in Adults With PTB (TB_COMBO_01)**	22	18 Years to 65 Years	Interventional (Clinical Trial)	Phase 2	NCT04629378	16-November-2020	The purpose of this study is to compare meropenem and amoxicillin/clavulanate plus pyrazinamide vs. bedaquiline for early bactericidal activity and safety was conducted in a single-center setting, part of a series of 2-week EBA studies.	Completed	[49]
10.	**A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis**	109	14 Years and older	Interventional (Clinical Trial	Phase 3	NCT02333799	7-January-2015	The purpose of study to evaluate efficacy, safety, tolerability, and pharmacokinetics of bedaquiline plus PA-824 plus linezolid after 6 months of treatment in patients with XDR-TB, treatment intolerant, or non-responsive MDR-TB.	Completed	[50]

7. CONCLUSIONS

One major obstacle to the treatment of tuberculosis (TB) is the emergence of multi-drug resistant tuberculosis (MDRTB). In response, pulmonary MDR-TB in adults has been approved for treatment with bedaquiline, a groundbreaking oral diarylquinoline molecule. Bedaquiline boosts cure rates, lowers death rates, and improves culture conversion rates in tuberculosis treatment, according to systematic reviews. This review attempts to give a thorough and comprehensive appraisal of bedaquiline's position as an anti-TB medicine, emphasizing the need for additional efficacious and safe evidence from ongoing Phase III trials, even if its approval represents a substantial advancement in treating drug-resistant tuberculosis. It comes to the conclusion that using bedaquiline sparingly could minimize the negative effects of the medication while increasing the efficacy of MDRTB treatment.

Declaration of Interest Statement

The authors affirm the absence of any conflicting interests or pertinent associations with any organization or entity related to the topic or materials deliberated in the manuscript. This encompasses employment, consultancies, ownership of stocks or options, and expert testimonies.

Financial disclosure

The authors hereby declare their lack of financial engagement with any organization or entity possessing a financial stake in or financial discordance with the topic or materials deliberated in the manuscript. This encompasses employment, consultancies, honoraria, ownership of stocks or options, expert testimonies, grants or patents received or awaiting approval, and royalties.

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