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REVIEW ARTICLE

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An overview of new antitubercular drugs, drug candidates, and their targets

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Abstract

The causative agent of tuberculosis (TB), *Mycobacterium tuberculosis* and more recently totally drug-resistant strains of *M. tuberculosis*, display unique mechanisms to survive in the host. A four-drug treatment regimen was introduced 40 years ago but the emergence of multidrug-resistance and more recently TDR necessitates the identification of new targets and drugs for the cure of *M. tuberculosis* infection. The current efforts in the drug development process are insufficient to completely eradicate the TB epidemic. For almost five decades the TB drug development process remained stagnant. The last 10 years have made sudden progress giving some new and highly promising drugs including bedaquiline, delamanid, and pretomanid. Many of the candidates are repurposed compounds, which were developed to treat other infections but later, exhibited anti-TB properties also. Each class of drug has a specific target and a definite mode of action. These targets are either involved in cell wall biosynthesis, protein synthesis, DNA/RNA synthesis, or metabolism. This review discusses recent progress in the discovery of newly developed and Food and Drug Administration approved drugs as well as repurposed drugs, their targets, mode of action, drug-target interactions, and their structure-activity relationship.

KEYWORDS

bedaquiline, clofazimine, delamanid, delpazolid, levofloxacin, linezolid, moxifloxacin, PBTZ169, pretomanid, SQ109, structure-activity relationship, sutezolid

1 | INTRODUCTION

The causative agent of tuberculosis (TB), *Mycobacterium tuberculosis* complex, is capable of causing disease in any part of the body (extra-pulmonary TB) but it is primarily a pulmonary pathogen (pulmonary TB). A substantial part of human population remains infected with latent TB infection (LTBI). LTBI is asymptomatic and nontransmissible and remains controlled in most of the individuals; however, some individuals develop active TB disease.[1,2] Poverty and coinfection with HIV have made it difficult to combat the disease.[3,4] The major problem with HIV-TB coinfection is that HIV disrupts the immune system which activates the LTBI and also accelerates disease progression. In turn, TB also enhances the progression as well as the effects of HIV.[5,6] In 2017 an estimated 10 million people developed TB of which 1.3 million died. Approximately 300 000 more HIV-positive deaths were reported due to TB.[7] Another serious problem associated with the treatment of TB is the widespread emergence of resistance. The exact cause of resistance is not well understood but it is believed that genetic mutation is one of the major causes of resistance. The standard TB treatment regimen for drug-susceptible TB includes four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol for at least 6 months through directly observed therapy (DOT) and follow-up support. *M. tuberculosis* strains can be multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), or totally drug-resistant TB (TDR-TB).[2] MDR-TB is the infection caused by *M. tuberculosis* which is resistant to at least isoniazid and rifampicin, the two key anti-TB drugs. In 2006, a more resistant strain of *M. tuberculosis*, XDR-TB emerged which is resistant not only to isoniazid and rifampicin but also to fluoroquinolones and second-line aminoglycosides. XDR-TB may be defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the three second-line injectable drugs. Treatment of XDR-TB requires the use of third-line anti-TB drugs but these drugs have more side-effects than first- or second-line TB drugs.[2] First cases of TDR-TB were found in Italy in 2003, almost 15 years ago but were reported in 2007 due to lack of drug susceptibility testing techniques.[8] Later Iran, India, and South Africa also reported TDR-TB cases.[9] TDR-TB infection, which is the most severe of all, is caused by *M. tuberculosis* strains which are resistant to all the first- and second-line drugs. First-line TB drugs form the standard four-drug treatment regimen for drug-susceptible TB whereas the second-line drugs are used for the treatment of drug-resistant TB.[10] In 2016, 490 000 people were infected with MDR-TB of which 6% had XDR-TB.[11] Some DR-TB patients suffer from treatment failure either because of doubtful efficacy of the recommended drug regimen or high toxicity or both. To overcome this issue of treatment failure, World Health Organization (WHO) included Group 5 antibiotics. Group 5 antibiotics include repurposed drugs and drugs with unclear efficacy or an unclear role in the treatment of DR-TB, such as thiacetazone, high-dose isoniazid, clofazimine, linezolid, amoxicillin plus clavulanate, macrolides, carbapenem, and thioridazine.[12] Group 5 drugs also suffer from drawbacks like incomplete information regarding their efficacies, mechanism, and safety profiles.[13]

A new antitubercular drug should fulfill the following criteria: (a) should have a validated safety profile; (b) should result in shorter, safer, cheaper, and more effective treatment alternatives for MDR-TB; (c) should be effective on newer targets so as to circumvent MDR-TB and XDR-TB; (d) must be compatible with antiretroviral therapy, for the treatment of a large population of HIV-TB coinfected patients; (d) should not result in drug interactions with other anti-TB drugs or drug candidates.[14–16] Besides this, accurate diagnosis and proper screening for drug-resistance are also important factors in combating TB.

Several reviews have been published recently that focus on the current regimens and emerging drugs to combat XDR-TB, MDR-TB, and HIV-TB coinfected patients, major drug targets exploited and the role of emerging targets in TB drug discovery process while some articles analyze the effect of clinically approved antimycobacterial drugs on pathogens of the WHO priority pathogen list.[17–20] Some other reviews focus on strategies to prevent the development of resistance and reduce transmission instead of finding their treatment and how to strategically invest to have a tuberculosis-free world.[21,22] A recent review discusses fragment-based approach where fragments forming high-quality interactions with target molecules are identified and used to generate more potent lead compounds.[23]

This review overviews the discovery, development, structure-activity relationship, mechanism of action, and pharmacokinetics of recently developed drugs and candidates in the final stages of drug development process. In an attempt to bridge the gap that exists between drug and its relationship with target we tried to condense information regarding mechanism of action of drug, its interaction with target, and also the nature of target.

Bedaquiline and delamanid are the recently approved two new anti-TB drugs (Table 1). Pretomanid, delpazolid, sutezolid, SQ109, PBTZ169 are in phase II and phase III trials for TB (Table 2). Another category includes repurposed drugs like clofazimine, levofloxacin, moxifloxacin, and linezolid, which are also in phase II and phase III trials for TB (Table 3).[11] A diagrammatic representation of anti-TB agents and their mode of action is shown in Figure 1.

2 | BEDAQUILINE

Bedaquiline (Figure 2A) was approved in 2012 for use in treatment of MDR-TB by the Food and Drug Administration (FDA). It is marketed under the name Sirturo.[24] Bedaquiline belongs to diarylquinolines class of compounds which is a recently emerged class of antitubercular drugs.[25] In addition to this, including bedaquiline to current MDR-TB standard treatment regimen has proven to be cost-effective as well as cost-saving.[26] Unlike other drugs, bedaquiline targets the energy metabolism of mycobacteria. Though mycobacteria can survive under conditions of stress like hypoxia, nevertheless the production of energy molecule ATP by ATP synthase is essential for the survival of all sorts of mycobacteria whether active or dormant, replicating or nonreplicating, extracellular or intracellular, and fermenting or nonfermenting.[27–29] The ability of bedaquiline to be bactericidal for both replicating as well as dormant bacteria could also shorten the prolonged TB treatment.

2.1 | Mechanism of action of bedaquiline

Bedaquiline inhibits the membrane-bound ATP synthase enzyme of *M. tuberculosis*. ATP synthase converts ADP to ATP by utilizing the transmembrane electrochemical ion (H^+ or Na^+) gradient. The c subunit of ATP synthase has ion-binding sites which transport ions across the membrane and generate power for ATP synthesis. Bedaquiline blocks these ion-binding sites thereby interfering with the proton pump which results in decreased intracellular ATP levels.[25,30] A recent study suggested that in addition to the c subunit, bedaquiline also targets the ε subunit of F-ATP synthase by interacting with Trp16 residue.[31]

ATP synthase produces ATP through oxidative phosphorylation and is highly conserved in both prokaryotes and eukaryotes.[32,33] Bedaquiline is highly selective for mycobacterial ATP synthase as compared with human ATP synthase where it is 20 000 times less effective. Thus it is less likely to produce target-based toxicity in humans.[34] The difference in structure and mechanism of action of bedaquiline alleviates the chances of cross-resistance with other anti-TB drugs. Studies suggest that bedaquiline is an uncoupler of the proton motive force and is therefore capable of disturbing the proton gradient across the mycobacterial cell membrane.[35]

TABLE 1 Recently approved drugs

Drug	Chemical class	Target	Effect	Clinical status
Bedaquiline	Diarylquinoline	ATP synthase	Inhibits energy metabolism of cell	Phase III
Delamanid	Nitroimidazole	Exact target not yet known	Inhibits mycolic acid synthesis (keto and methoxy mycolic acids) and cell respiration	Phase III

TABLE 2 Drugs in phase II and phase III clinical trials

Drug	Chemical class	Target	Effect	Clinical status
Pretomanid	Nitroimidazole	Exact target not yet known	Inhibition of cell wall synthesis and respiratory poisoning	Phase III
Delpazolid	Oxazolidinone	50S subunit of ribosome	Inhibits protein synthesis	Phase II
Sutezolid	Oxazolidinone	50S subunit of ribosome	Inhibits protein synthesis	Phase II
SQ109	Diamine	MmpL3	Inhibits cell wall synthesis	Phase II
PBTZ169	Benzothiazinone	DprE1	Inhibits cell wall synthesis	Phase II
Q203	Imidazopyridine	Cytochrome *bc1* complex	Inhibits ATP synthesis	Phase II

TABLE 3 Repurposed drugs

Drug	Chemical class	Target	Effect
Clofazimine	Riminophenazine	Exact target not yet known	Transmembrane penetration and intracellular redox cycling
Levofloxacin	Fluoroquinolone	DNA gyrase	Inhibits DNA replication
Moxifloxacin	Fluoroquinolone	DNA gyrase	Inhibits DNA replication
Linezolid	Oxazolidinone	50S subunit of ribosome	Inhibits protein synthesis

2.2 | Interaction of bedaquiline and ATP synthase

Mycobacterium ATP synthase is a macromolecular protein complex responsible for ATP production. It is composed of two motor like domains, the F_1 motor and the F_o motor. The F_1 domain is ATP-driven, hydrophilic and is located in cytoplasm whereas the F_o domain is proton-driven and remains embedded in membrane. Both the domains are

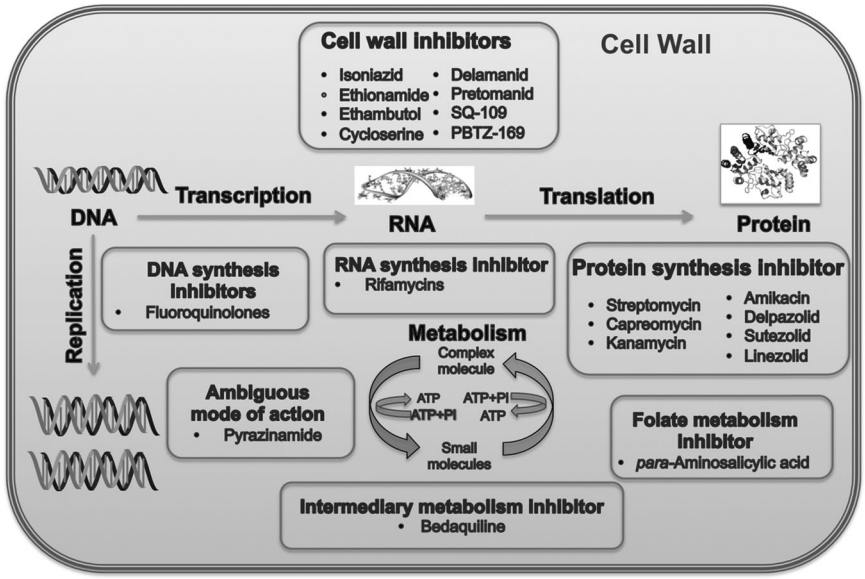

FIGURE 1 Antituberculosis agents and their targets

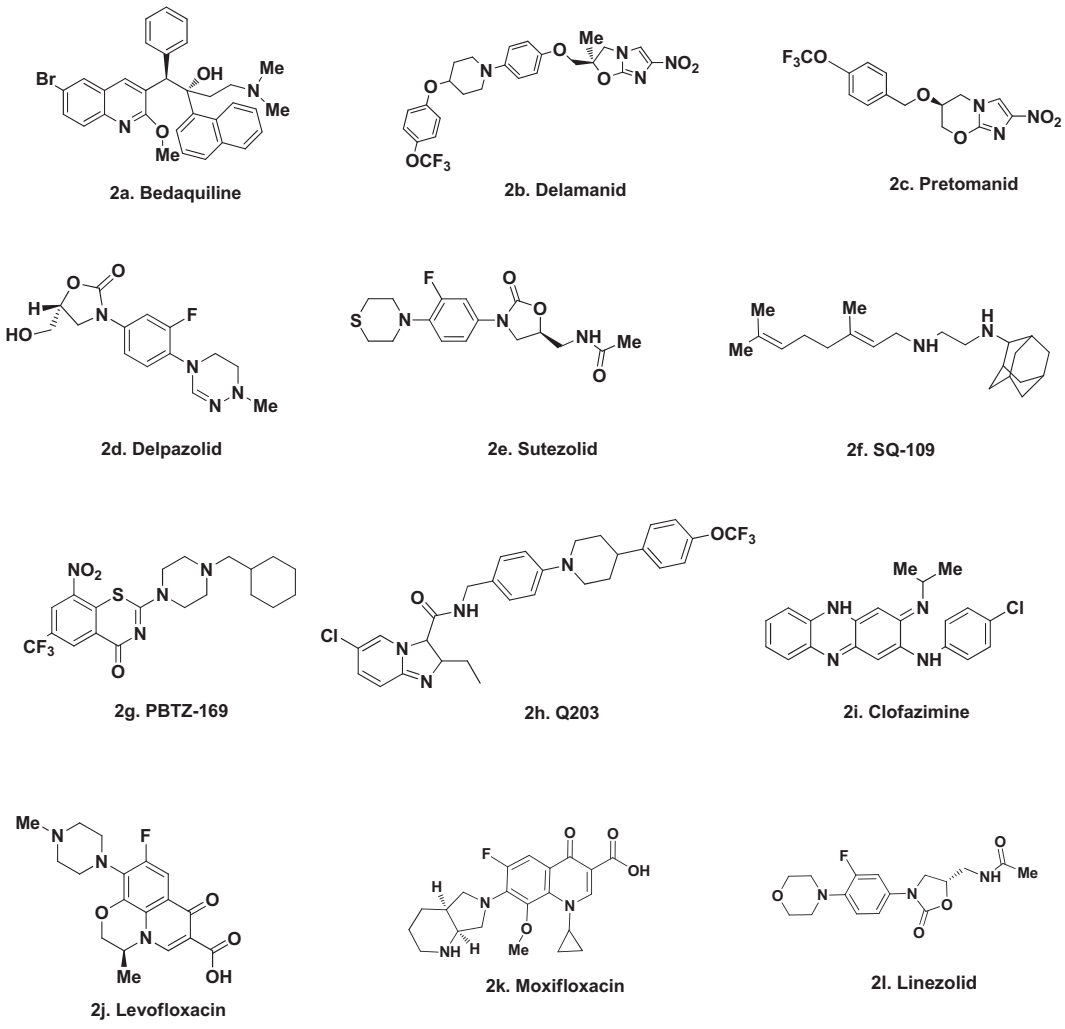

FIGURE 2 Molecular structure of newly approved drugs

capable of rotating in opposite directions.[36] The F_o domain is composed of three subunits $a_1b_2c_{10\text{-}15}$ and the F_1 domain, consists of five subunits $\alpha_3\beta_3\gamma\delta\varepsilon$ (Figure 3).[37] The "c" subunits of F_o motor are arranged as discs forming a cylinder with a central pore called as the c-ring which is the ion-binding site as it helps in transport of ions across the membrane.[38–40] The catalytic site is present in the F_1 part which produces ATP by combining ADP and Pi.[41] Bedaquiline molecules approach membrane-exposed ion-binding sites present in the c-ring. Residue Phe69 undergoes a conformational change to avoid any steric clashes with the hydroxyl group of bedaquiline and also to provide a hydrophobic environment for the quinolone moiety of the drug. A water molecule acts as a bridge by forming two hydrogen bonds simultaneously with the backbone carbonyl of residue Glu65 and the hydroxyl group of bedaquiline. Various van der Waals interactions are also observed between the drug and the ion-binding site of ATP synthase. The dimethylamino group of bedaquiline also forms hydrogen bond with the same Glu65 residue.[40]

The side chain of residue Arg-186 in the a-subunit adopts an extended conformation and interacts with Glu-61 of the c subunit to transfer a proton. As a result of this, a conformational change occurs in the c subunit, which converts the extended side chain of Arg-186 to a compact conformation and also rotates the c subunit to 30°. It is likely that bedaquiline mimics this role of side chain of Arg-186. In solution, the unbound bedaquiline remains in a

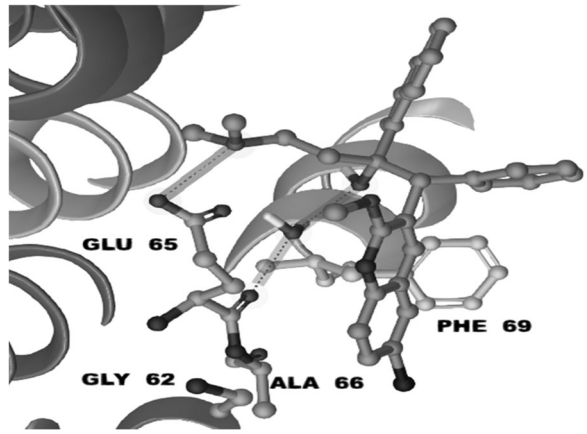

FIGURE 3 Interaction of bedaquiline (shown in green) with the ATP synthase c-ring of *Mycobacterium phlei* (PDB ID: 4v1f)

folded conformation because of intramolecular hydrogen bonding. This folded conformation is lost once bedaquiline enters the active site and forms new hydrogen bonds with Glu-61, as shown in Figure 3.[42–44] It is believed that the basic dimethylamino group of bedaquiline gets protonated and likely interacts with the carboxyl group of Glu-61 in subunit c of ATP synthase thereby blocking the rotation of discs.[45]

2.3 | Structure-activity relationship of bedaquiline

Bedaquiline has two chiral carbons. Structure-activity relationship studies showed that the (RS,SR) configuration of the two stereocentres displayed better antimicrobial activity than the (RR,SS) configuration because of the formation of an additional hydrogen bond between the hydroxyl moiety of the (R,S) stereoisomer and residue Glu-61 of the c subunit.[46] The dimethyl tertiary amine group of bedaquiline is essential for activity as it acts as an arginine mimic and interferes with the proton pump of ATP synthase.[42] Replacement of amino groups, less basic than dimethylamino group decreased the activity. Bringing the dimethylamine moiety near to the hydroxyl group by changing the chain length did not improve the antimycobacterial activity. Attaching halogen atoms to the phenyl ring significantly increased the activity. The bulky naphthyl group is necessary because of the lipophilic nature of binding site and its replacement with heteroaromatic substituents leads to cytotoxicity. Analogs with disubstituted phenyl ring in place of naphthyl group were also very potent. Removing the bromine atom at 6-position and methoxy group at 2-position of the quinolone ring adversely affected the potency of these compounds.[46] Figure 4 shows the structure-activity relationship of bedaquiline.

2.4 | Pharmacokinetics/toxicity of bedaquiline

Bedaquiline is metabolized in liver by cytochrome P450 isoenzyme to a fivefold less potent derivative, *N*-desmethyl TMC207.[47] The terminal elimination half-life of bedaquiline is very high, approximately 4 to 5 months.[48] It is highly lipophilic (logP 7.25) and has cationic amphiphilic properties due to which it interacts with intracellular phospholipids and this ultimately leads to its accumulation in tissues. This results in slow release of bedaquiline from peripheral tissues and leads to a long terminal elimination half-life. The high lipophilicity may also induce phospholipidosis.[48] It is given orally and its bioavailability increases if administered with food.[49]

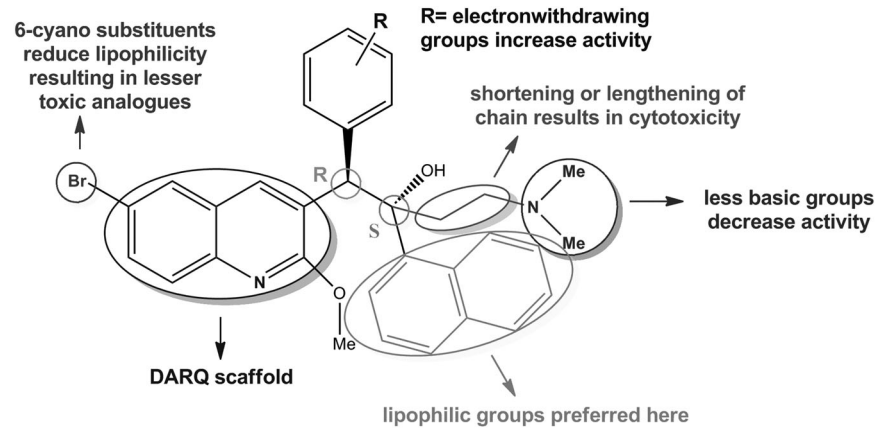

FIGURE 4 Structure-activity relationship of bedaquiline

3 | DELAMANID

Delamanid (Figure 2B previously known as OPC67683) is a drug of the nitroimidazole class approved by European Medicines agency for the treatment of MDR-TB infection.[50] Amongst other clinically approved TB drugs, delamanid exhibits the lowest minimum inhibitory concentration and is found to be active against both drug-sensitive and drug-resistant *M. tuberculosis* strains. The drug also inhibits replicating and dormant as well as extracellular and intracellular isolates.[50,51] However delamanid is not recommended for use in combination with bedaquiline by WHO as both are cardiotoxic. They cause QT prolongation, which is an alteration of the electrical activity of the heart.[52]

3.1 | Mechanism of action of delamanid

Delamanid is known to inhibit the synthesis of two key components of mycolic acids, keto mycolic acid, and methoxy mycolic acid. Mycolic acids are found only in mycobacterium cell wall and are absent in other Gram-positive or Gram-negative bacteria, therefore, the inhibitory action of delamanid is specific against mycobacteria.[50,53] These acids make the cell wall of mycobacterium difficult for drug penetration, therefore, disrupting the cell wall facilitates better drug penetration hence shortening the treatment regimen.[54,55]

Delamanid is a prodrug that requires activation through reduction of the nitro group present by deazaflavin (F420)-dependent nitroreductase (Ddn) enzyme.[56] This enzyme converts delamanid into an inactive desnitro derivative. But this conversion generates a number of intermediates which are considered to be responsible for the efficacy of delamanid.[57] The inhibitory action of delamanid probably involves the release of reactive radicals like NO which are crucial in mammalian defense mechanism against mycobacterial infections.[2,58,59] The exact target of delamanid is yet to be explored. Target identification of delamanid by studying mutation is difficult as the mutants showing resistance had mutations in genes responsible for activation of delamanid, not in genes responsible for the synthesis of mycolic acid.[57] Mutations in these five different genes (ddn, fgd1, fbiA, fbiB, and fbiC) have been found to be closely related to resistance to delamanid. These genes are either involved in prodrug activation or associated with the cofactor F420 biosynthetic pathway.[60,61]

3.2 | Structure-activity relationship of delamanid

The nitroimidazole class of antibiotics has yielded many drugs for the treatment of anaerobic bacterial and protozoan infections, but they are ineffective against *M. tuberculosis*.[62] In 1989, a bicyclic nitroimidazooxazole, CGI-17341 was discovered by researchers at Ciba-Geigy laboratories, potent against *M. tuberculosis* both in vitro and in

vivo.[63] However, further development of CGI-17341 was terminated as it was found to be mutagenic.[64] Later, another bicyclic compound, nitroimidazopyran, PA-824 (Figure 2C) was developed by the research group at PathoGenesis Corporation and found to be active against MDR *M. tuberculosis.* This led researchers to conclude that varying the substituents at 2-position of 6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles (Figure 5), which are structurally similar to CGI-17341, improves the quality by increasing antituberculosis activity and eliminating mutagenicity.[65] Structure-activity relationship of delamanid is summarized in Figure 5.[66]

3.3 | Pharmacokinetics/toxicity of delamanid

Delamanid has low water solubility consequently it is formulated in 5% gum Arabic.[67] The high binding tendency of delamanid to plasma proteins (≥99.5%), especially albumin increases its volume of distribution.[68] A large part of delamanid is metabolized by plasma albumin and only a small amount is degraded by cytochrome P450 enzymes. The electron-withdrawing nitro group of delamanid makes the neighboring C-5 carbon of delamanid electron-deficient. The amino acid residues of albumin act as nucleophiles and attack this carbon forming an albumin-delamanid adduct which is later hydrolyzed and degraded.[68,69] The oral bioavailability of delamanid is 35%–60% in animals and it increases with food particularly high fat containing food.[70] Delamanid does not interact with the CYP enzymes.[57] Moreover delamanid has little potential for interaction with antiretroviral drugs. This property makes it suitable for coadministration with antiretroviral drugs without any fear of drug interactions.[71]

4 | PRETOMANID

Pretomanid (Figure 2C, previously known as PA-824) like delamanid (Figure 2B) belongs to the nitroimidazole class of drugs. Like delamanid, pretomanid is also effective against both replicating and hypoxic nonreplicating strains of *M. tuberculosis.*[72,73]

Both these new TB drugs require activation since they are prodrugs and also exhibit a similar mechanism of action. Pretomanid undergoes bioreductive activation by Ddn enzyme, forming various metabolites by the

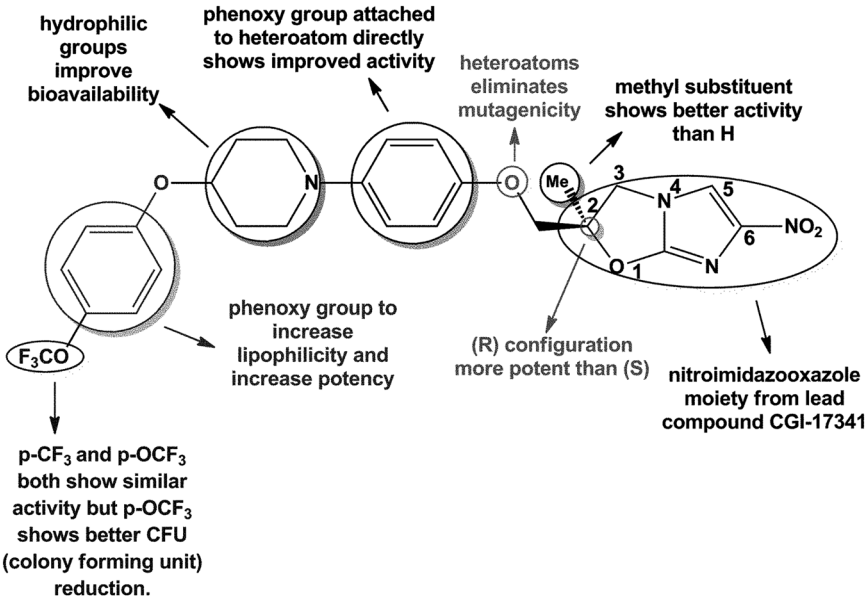

FIGURE 5 Structure-activity relationship of delamanid

reduction of the imidazole ring. One of the metabolites is a des-nitro derivative that releases nitric oxide which damages intracellular proteins, cell wall lipids, and various other macromolecules and turns out to be bactericidal for anaerobic bacteria. This des-nitro derivative is considered to be responsible for the antimycobacterial activity of pretomanid. However, studies suggest that aerobic bacteria are killed by pretomanid through the disruption of cell wall mycolic acid synthesis pathway, which in turn depletes ketomycolates and accumulates hydroxymycolates.[74–76] Thus pretomanid shows a dual mode of action, inhibition of cell wall biosynthesis and respiratory poisoning. Although these mechanisms explain how pretomanid acts on replicating bacteria, it does not reveal the mechanism of action of pretomanid on latent cells.

The pharmacokinetic profile of pretomanid is better than delamanid. It is readily absorbed, well tolerated, and shows a good bioavailability as well. Pretomanid has a long half-life (16-20 hours) and therefore requires a single daily dosage.[77] Currently pretomanid is under phase III clinical trial.[78]

5 | LINEZOLID

Linezolid (Figure 2L) belongs to oxazolidinone class and was initially approved for the treatment of infections caused by Gram-positive bacteria such as methicillin-resistant Staphylococcus and Vancomycin-resistant enterococcus, in the year 2000. It is sold under the brand name Zyvox.[79,80] The first candidate of the oxazolidinone class was identified at E. I. du Pont de Nemours & Company in 1978. However, further development of this class of antibacterials was terminated as clinical trials showed safety concerns specially hepatotoxicity. Later in 1990s, the development of resistance in Gram-positive bacteria led to reconsideration of the development of oxazolidinones with favorable safety profiles. Almost two decades after the discovery of oxazolidinones, the FDA approved the first oxazolidinone drug linezolid for clinical use in 2000.[81] Later it was discovered that this drug is active not only against Gram-positive bacteria but also shows promising antimycobacterial activity.[82]

All drugs belonging to the oxazolidinone class are synthetic antibiotics which act on the 50S ribosomal subunit of bacteria inhibiting the protein synthesis.[83,84] Some peculiar features of linezolid like, no cross-resistance with other clinically approved anti-TB agents and excellent oral bioavailability make it a drug of choice for the treatment of TB.[82] Two newer candidates of the oxazolidinone class, delpazolid (Figure 2D) and sutezolid (Figure 2E) are in early clinical trials. Both delpazolid and sutezolid are less toxic and almost equally effective as linezolid.[85]

5.1 | Mechanism of action of linezolid

Linezolid is known to inhibit the process of protein synthesis occurring in ribosomes.[86] Bacterial ribosome is a large nucleoprotein complex of a small (30S) and a large (50S) subunit. Each subunit is made up of ribosomal RNA (rRNA) and many proteins (rproteins) that work together to synthesize proteins for the cell.[87,88] At present streptomycin, pyrazinamide, kanamycin, capreomycin, and amikacin are the clinical drugs that target various components of ribosomes.[2]

The process of protein synthesis occurs in four main steps: initiation, elongation, termination, and recycling. There are three characteristic regions of ribosomes involved in protein synthesis, the A, P, and E sites. During initiation, the small (30S) and large (50S) subunits of ribosome combine to form a 70S ribosome and messenger RNA (mRNA) is aligned with transfer RNA (tRNA) at the ribosomal P-site for the peptide-bond formation.[88] In the elongation phase, the aminoacylated tRNA (aa-tRNA) is transferred to the A-site of the ribosome. This results in a peptide-bond formation between the amino acids attached to the A- and P-sites tRNAs. Amino acids are continuously transported from the P-site to the A-site leading to the elongation of peptide chain which later exits through the E-site to cytoplasm. The components are then recycled and the same cycle is repeated again.[82]

Linezolid binds at the A-site of 50S peptidyl-transferase center (PTC) occupying the space of aminoacyl residue of aa-tRNA. This interferes with the peptide-bond formation between the A- and P-site tRNAs. This prevents the formation of the large 70S ribosomal complex, as a result, protein synthesis is hindered.[86]

5.2 | Interaction of linezolid with 50S ribosomal subunit

Ribosomes are the site of protein biosynthesis in all living beings. In bacteria, ribosomes are composed of a small subunit (30S) and a large subunit (50S) that associate to form a 21-nm complex, the 70S ribosome. There are three essential components of ribosomes, the rRNA, ribosomal proteins and accessory factors.[89] In *M. tuberculosis* the 50S subunit is up made of rRNA 23S, rRNA 5S, and about 30 rProteins, while the 30S subunit is composed of rRNA 16S and about 20 rProteins.[90] rRNA is the major functional core of RNA since it carries out three major functions, catalysis of peptide-bond formation, decoding of mRNA, and translocation of mRNA and tRNA after completion of peptide-bond formation.[90]

During initiation of translation, tRNA carrying formylmethionine binds to the P-site of 50S subunit. The P-site is the binding site for peptidyl-tRNA and an adjacent A-site is the binding site for incoming aa-tRNA.[91] Linezolid binds to this A-site and interferes with the aminoacyl moiety of the A-site bound aminoacyl-tRNA. This binding inhibits the peptide-bond formation between the A- and P-site tRNAs. Drugs of the oxazolidinones class are also thought to influence P-site tRNA positioning during initiation step.[82]

A recently available crystal structure of LZD-114 (PDB ID: 4wfa), 20 times more potent analog of linezolid with *M. tuberculosis* ribosome gives useful insights about the exact site of action of linezolid. LZD-114 occupies the PTC of the 50S subunit (Figure 6).[91]

5.3 | Structure-activity relationship of linezolid

Structure-activity relationship studies suggest that the (S)-configuration at position 5 of the oxazolidinone ring is essential for activity. An acylaminomethyl moiety linked to the same C-5 with (S)-configuration is essential for activity but can be replaced with bioisosteres. The *N*-aryl ring is also required for activity and functionalization of this aryl ring results in improved activity or expanded antibacterial spectrum.[92] Substitution with fluorine atom further enhances antibacterial activity whereas incorporating azole moiety makes the drug more effective against

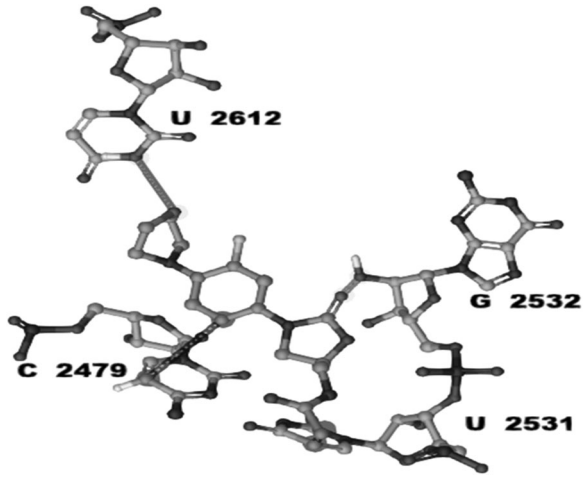

FIGURE 6 The linezolid-binding site as identified in the large ribosomal subunit of *Staphylococcus aureus* with hydrogen bonds and hydrophobic interactions between the bound drugs and 23S ribosomal RNA (PDB ID: 4wfa)

Gram-negative pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*.[93] Substitution with thiomorpholine results in activity toward mycobacteria.[94] The structure-activity relationship of linezolid has been reviewed in detail (Figure 7).[95]

5.4 | Pharmacokinetics/toxicology of linezolid

Since linezolid was already successfully implemented in the clinic for the treatment of Gram-positive infections and was repurposed for the treatment of TB, its pharmacokinetics was already well studied. Linezolid shows a very high oral bioavailability of approximately 100% and therefore its oral and injectable dosage is same. So, a patient getting intravenous therapy can be instantly converted to oral therapy once the condition becomes stable.[96] This gives linezolid an edge over other drugs that are administered only parenterally. After administration, linezolid maintains appreciable level in blood serum, which means less frequent dosage requirement in larger intervals of time. Another key characteristic of linezolid is its excellent penetration into the cerebrospinal fluid (CSF) which makes it appropriate for the treatment of MDR-TB meningitis.[97] The presence of food does not have much effect on the absorption of linezolid, so this antibiotic could be taken both with or without meals. Metabolism of linezolid occurs through nonenzymatic oxidation and the metabolites do not show any antibacterial activity. Linezolid is neither metabolized by cytochrome P450 nor does it inhibit any of the important P450 isoforms. Excretion of linezolid occurs majorly through urine and gut.[98,99]

However the toxicity profile of linezolid limits the wider use of drug. The drug showed a number of clinically significant adverse side-effects some of which include peripheral neuropathy, myelosuppression, gastrointestinal disorders, thrombocytopenia, and optic neuritis.[2] Myelosuppression is observed in patients on long-term linezolid therapy. Other common adverse effects include diarrhea, nausea, and headache.[100]

6 | SUTEZOLID

Sutezolid (Figure 2E, also known as PNU-100480) was developed alongside linezolid in 1996. After lying undeveloped for several years sutezolid became the second most promising candidate of the oxazolidinone class

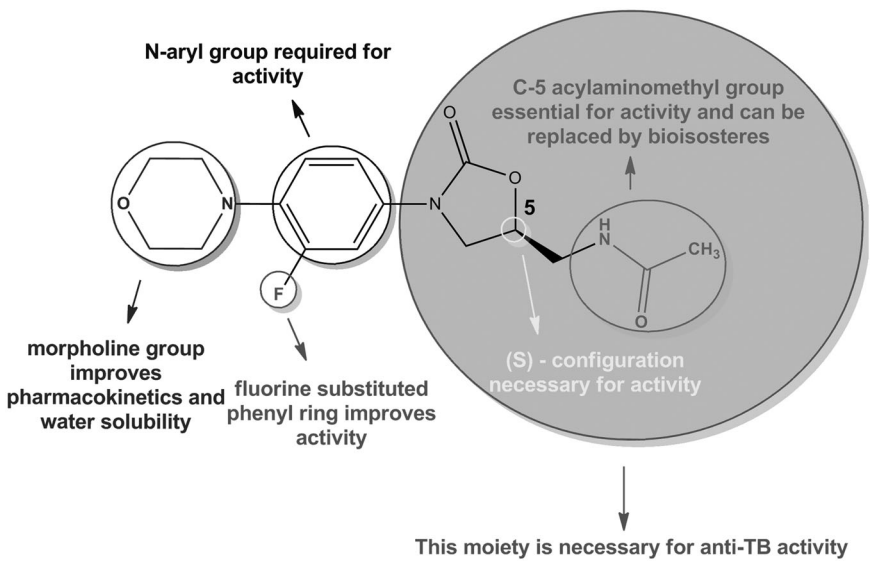

FIGURE 7 Structure-activity relationship of linezolid on the basis of antibacterial activity of linezolid

after linezolid, active against *M. tuberculosis*. This drug was active against drug-resistant strains of *M. tuberculosis* and also showed favorable pharmacokinetics and low toxicity in rat models. After showing promising results in murine models it was studied on humans, and appeared to be safe and well tolerated.[101,102]

Sutezolid shows superior efficacy in comparison to linezolid against *M. tuberculosis*.[103] The use of linezolid is limited to the treatment of drug-resistant TB because of its poor toxicity profile.[104] Sutezolid, on the other hand, has a better safety profile and is also 1 to 2 orders of magnitude more effective than linezolid in antimycobacterial activity.[1,80,100,102] These studies conclude that sutezolid may be a better candidate than linezolid for the treatment of TB. Currently sutezolid has successfully completed phase II trials but some stage 1 studies are being performed again because of the licensing issues.[85,105]

Sutezolid is a thiomorpholine analogue of linezolid and its mechanism of action is similar to linezolid. It inhibits protein biosynthesis by binding to the 23S rRNA of the large 50S subunit of ribosome. Sutezolid is converted to an active sulfoxide metabolite, which is more potent than sutezolid against extracellular TB. However, for the treatment of intracellular TB in pulmonary TB infection, the parent molecule, sutezolid was found to be 17 times more effective than its metabolite.[106] In addition, sutezolid is effective against both the drug-susceptible as well as the drug-resistant TB.[107] The drug and its metabolite both show a relatively short plasma half-life (approximately 4 hours) which favors a divided dosage rather than a single dose.[108] Sutezolid shows additive effects with SQ109 and is also efficacious in combination with other new TB drugs.[109] Combination studies, performed in whole-blood assays have shown that sutezolid paired with SQ109 and bedaquiline have additive effects and can be used for the treatment of both drug-susceptible and drug-resistant TB.[110]

7 | FLUOROQUINOLONES

Fluoroquinolones are a class of very potent, broad-spectrum synthetic antimicrobial agents that are currently being explored for the treatment of TB.[111,112] A survey on the antibiotic expenditure in the United States revealed that fluoroquinolones rank the highest, accounting for approximately one-fourth of the $10 billion antibiotic market.[113] Fluoroquinolones are fluorine derivatives of quinolones. Quinolones are bicyclic ring compounds, categorized into 2- and 4-quinolones. The most common clinically used quinolones are the 4-quinolones. Nalidixic acid was the first quinolone, clinically approved in 1962 for human urinary tract infection treatment.[114,115] Addition of fluorine to quinolones generated a new class of drugs, the fluoroquinolones exhibiting a broader antimicrobial spectrum and better pharmacokinetic profile. The major candidates of fluoroquinolone class are ciprofloxacin and ofloxacin (second generation drugs), levofloxacin (third generation), and moxifloxacin and gatifloxacin (fourth generation).[116] Fluoroquinolones are generally used for the treatment of respiratory tract infections, gastrointestinal and gynecological infections, sexually transmitted diseases, and so forth.[117] Introduced in the late 1980s, fluoroquinolones are characterized by a carboxyl group at C-3, a keto group at C-4, a fluorine atom at C-6, and a nitrogen-containing heterocyclic moiety at the C-7 position.[118,119] All fluoroquinolones generally have a similar mechanism of action that targets DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria.[120]

Currently, fluoroquinolones like ciprofloxacin, ofloxacin, and levofloxacin (Figure 2J) are recommended as second-line drugs for the treatment of TB whereas two candidates of the fluoroquinolone class, moxifloxacin (Figure 2K) and gatifloxacin are currently being evaluated for their promising anti-TB activity.[112,117] Besides their efficacy, there are side-effects also associated with the use of both these compounds like gatifloxacin causes hyperglycemia/hypoglycemia whereas moxifloxacin shows cardiovascular risks.[15,121,122]

Moxifloxacin holds the potential of becoming first-line anti-TB agent and is under phase III clinical trial.[123,124] However, the broad-spectrum activity of this drug class and good oral bioavailability may lead to overuse.

7.1 | Moxifloxacin

Moxifloxacin (Figure 2K) is a fluoroquinolone antibiotic used for the treatment of MDR-TB.[125] Presently the drug is being investigated in regimens combining bedaquiline, pretomanid, and pyrazinamide, or rifapentine. Current evidence suggest the use of moxifloxacin for patients intolerant to any of the first-line TB drug or resistant to isoniazid, however, it does not show potency in shortening treatment regimens. Pharmacokinetics of moxifloxacin varies from individual to individual. Moxifloxacin shows bactericidal activity against both the Gram-positive and the Gram-negative bacteria.[126,127]

7.1.1 | Mechanism of action of moxifloxacin

In mycobacteria, the bactericidal effect of moxifloxacin occurs by the inhibition of DNA gyrase, which in turn prevents bacterial DNA from replication.[123,128] DNA gyrase breaks the DNA strand forming an enzyme-DNA complex. Moxifloxacin, like other fluoroquinolones binds to this enzyme-DNA complex and stabilizes it forming a drug-enzyme-DNA complex. This blocks progress of the replication fork and cause chromosome fragmentation.[129,130] Another fluoroquinolone, gatifloxacin also works in a similar way.[129]

7.1.2 | Interaction of moxifloxacin and DNA gyrase

DNA gyrase, a member of topoisomerases class of enzymes, introduces supercoils into DNA.[131] The topoisomerases enzymes are involved in maintaining the DNA topology during DNA replication, transcription, translation, and recombination in prokaryotic and eukaryotic cells. Therefore the inhibition of DNA gyrase results in cell death.[132] DNA gyrase is a heterotetramer containing two A and B subunits each.[133] Amongst the many types of topoisomerases known, only topoisomerase II enzyme is present in *M. tuberculosis*. Topoisomerase II mainly consists of GyrA and GyrB subunits.[134] The GyrA subunit is responsible for DNA cleavage and reunion. The enzyme possesses a tyrosine moiety in the active site (Figure 8). The phenolic OH group of this tyrosine moiety acts as a nucleophile that cleaves the phosphodiester bonds of DNA.[135] The GyrB subunit contains an ATP-binding pocket which helps in the ATP hydrolysis.[132] The absence of this enzyme in eukaryotes, makes it an attractive target for developing novel TB drugs.[134]

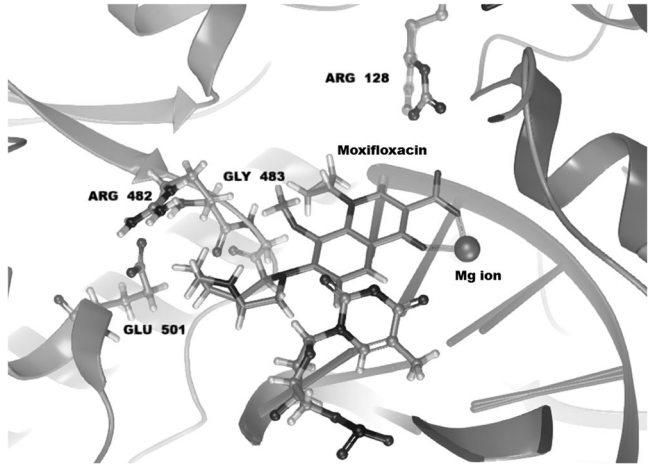

FIGURE 8 *Mycobacterium tuberculosis* GyrB active site bound with moxifloxacin (green sticks) in association with magnesium ion (PDB ID: 5bs8)

All fluoroquinolone class of antibiotics, including moxifloxacin, target the GyrA subunit whereas the natural product novobiocin belonging to aminocoumarin class of antibiotic targets GyrB. Ofloxacin, the fluoroquinolone antibiotic in clinical use for the treatment of TB also targets GyrA.[134] The emergence of resistance to fluoroquinolones and the toxicity of novobiocin have developed interest in targeting the GyrB subunit. The aminobenzimidazole class of antibiotics have been found to be targeting the ATP-binding site of GyrB.[134]

7.1.3 | Structure-activity relationship of moxifloxacin

Chemical variations have mainly been studied at positions N-1, C-5, C-6, C-7, and C-8 of moxifloxacin (Figure 9).[118,136] The 3-oxo-4-carboxylic acid group is essential as it forms hydrogen bonding interactions with bases of single-stranded regions of DNA produced as a result of DNA gyrase activity.[137] Amino and fluorine substituents at C-5 and C-6 position are the most favorable for Gram-positive bacteria. Varying substituents at C-7 site significantly alters potency, spectrum and pharmacokinetic profile.[137] The C-7 position is the most adaptable as substitutions at this position significantly affect the overall biological profile of molecule and is therefore exploited the most to develop several fluoroquinolone hybrids using various biologically active moieties. Incorporation of isatin using linkers at C-7 increases lipophilicity and hence anti-TB activity.[138,139] Introduction of azole variants at the same C-7 site shows significant antimycobacterial activity.[140,141] Complexing fluoroquinolones with hydrazone and hydrazide substituents not only show potent anti-TB activity but also improves toxicity profile. On the

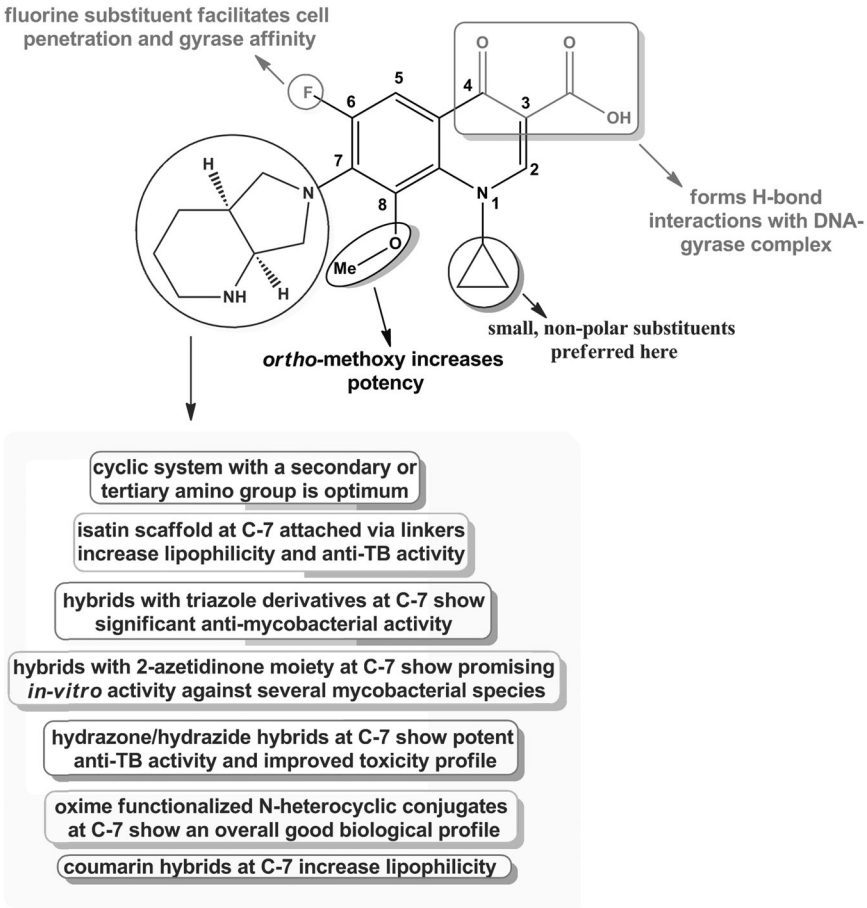

FIGURE 9 Structure-activity relationship of moxifloxacin. TB, tuberculosis

contrary, dimeric fluoroquinolones showed insignificant activity against TB.[142] Oxime-functionalized *N*-heterocyclic conjugates at C-7 show considerable biological profile.[143–145] Coumarin hybrids show better lipophilicity.[142] A semisynthetic derivative of artemisinin, dihydroartemisinin contains a hemiacetal OH group which when complexed with fluoroquinolones via a suitable linker produces potent anti-TB agents. Incorporating tetracycline at C-7 site produces hybrids showing promising anti-TB as well as anti-HIV activity that could assist HIV-TB coinfected patients.[142]

7.1.4 | Pharmacokinetics/toxicity of moxifloxacin

Moxifloxacin is orally administered and has a bioavailability of more than 90%.[146] It is widely distributed and shows good penetration into the CSF and is therefore used in combination with rifampicin for the treatment of TB meningitis.[147,148] Cytochrome P450 enzymes remain unaffected of moxifloxacin or any of its metabolites.[149] Instead the drug is metabolized in liver and excreted in urine.[150] Moxifloxacin also acts as a substrate of p-glycoprotein and this protein is associated with absorption, distribution, and elimination of this drug.[151,152] Coadministration of this drug with food causes insignificant effects and therefore the drug can be taken with or without food.[153] QT prolongation was observed as a result of interaction of moxifloxacin with other TB drugs including bedaquiline, delamanid, and clofazimine.[154] Fluoroquinolones have the tendency to bind to multivalent cations which results in decreased absorption. Therefore, moxifloxacin cannot be taken with multivitamin supplements having iron or zinc.[155,156] This poses a problem in HIV-TB coinfected patients as they are given multivitamin supplements.[157]

8 | CLOFAZIMINE

Clofazimine (Figure 2I), a member of riminophenazine class of antibiotics, is an established antileprosy drug which is repurposed for the treatment of MDR-TB.[158,159] The drug is sold under the brand name lamprene and was initially developed for the treatment of TB. Clofazimine exhibited significant antimycobacterial activity in vitro but further development of this drug was terminated as it was found to be therapeutically inefficient in humans showing side-effects like skin discoloration and mental disturbances.[160] The simultaneous discovery of better agents for the treatment of TB resulted in loss of interest in antimycobacterial efficiency of clofazimine. However, in 1981 WHO recommended clofazimine for the treatment of multidrug-resistant leprosy.[161] Later the growing DR-TB epidemic again developed interest in clofazimine which is presently a key constituent of newer TB regimens.[154,162] Besides possessing antimicrobial properties, clofazimine also shows anti-inflammatory properties which can be of therapeutic use in nonmicrobial and inflammatory disorders of cutaneous origin.[163]

8.1 | Mechanism of action of clofazimine

Clofazimine is a prodrug and the exact mechanism of action of clofazimine is not well understood. Studies suggest a redox cycling mechanism according to which clofazimine first undergoes reduction by type 2 NADH-quinone oxidoreductase (NDH-2) and then reoxidized to generate reactive oxygen species (ROS).[164] NDH-2 is an oxidoreductase enzyme involved in mycobacterial respiratory chain. This enzyme uses menaquinone as the substrate to initiate respiration. Clofazimine competes with this menaquinone for electrons and gets reduced.164 This reduced clofazimine then undergoes oxidation and generate ROS such as superoxide and hydrogen peroxide.[165]

ROS play an important role in control of *M. tuberculosis*. Normal respiration generates ROS as a by-product, which are neutralized by antioxidants, but excessive production of ROS causes an imbalance between ROS and

antioxidants which develops a condition called as the oxidative stress. The accumulation of these ROS radicals kills cells by breakage of nucleic acids, proteins, lipids, and other biomolecules.[166]

Although this redox cycling mechanism explains the contribution of antimycobacterial activity of clofazimine, it does not explain why under anaerobic or low oxygen conditions clofazimine does not show significant loss in antimycobacterial activity.[167] This led researchers to conclude that clofazimine shows different mechanisms of action in different environment conditions. Moreover, menaquinone is capable of stabilizing secondary membrane which may overcome the disruptive effect of the drug on bacterial membrane.[168] It is also not clear why the Gram-negative bacteria which are prone to antimicrobial effects of ROS are not susceptible to clofazimine.[169] These findings suggest alternate or multifaceted mechanisms of clofazimine activity. Clofazimine also shows cross-resistance with bedaquiline because of overexpression of the MmpL5 efflux pump. Recently mutations in *pepQ* gene were also proposed to be responsible for cross-resistance between bedaquiline and clofazimine.[170,171]

8.2 | Interaction of clofazimine with type 2 NADH-quinone oxidoreductase

Although the exact target of clofazimine is not well understood, the enzyme NDH-2 is considered to be the putative target of clofazimine. NDH-2 is a membrane-bound protein containing an FAD moiety.[172,173] It is a key enzyme of mycobacterial respiratory chain. It catalyzes electron transfer from NADH to menaquinone converting it to menaquinol. Menaquinol further supplies electrons to oxidoreductase enzymes of respiratory chain. The FAD moiety of menaquinone carries electrons for which clofazimine and menaquinone compete.[164,174]

8.3 | Structure-activity relationship of clofazimine

Structure-activity relationship (Figure 10) studies reveal that the central tricyclic phenazine system containing two aromatic rings at C-2 and C-5 positions are necessary for the anti-TB activity of clofazimine. Replacing the phenyl groups at C-2 and C-5 by a pyridyl group decreases lipophilicity significantly and anti-TB activity of clofazimine. However, if phenyl ring at C-2 position is substituted by a pyridyl group lipophilicity decreases and potency increases. The decrease in lipophilicity reduces the pigmentation potential.[175] Substituting the same C-2 position

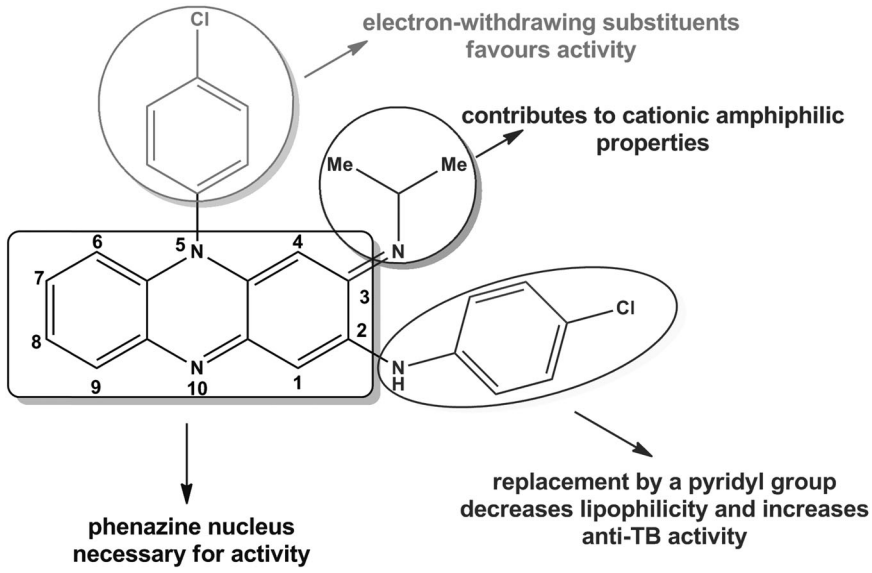

FIGURE 10 Structure-activity relationship of clofazimine. TB, tuberculosis

with a methoxypyridylamino group improves pharmacokinetics with retention of potency. Such compounds also reduce the skin discoloration side-effect.[176] The 2-methoxy group attached to the pyridyl moiety forms unique intramolecular H-bonds and reduces intermolecular π-π stacking interactions.[177] The isopropylimino group at C-3 position is responsible for the cationic amphiphilic character of the molecule. Cationic amphiphilic drugs are characterized by a hydrophobic aromatic ring and a hydrophilic side chain carrying an ionizable amine group.[170,178]

8.4 | Pharmacokinetics/toxicity of clofazimine

Clofazimine is a poorly soluble drug yet it is orally bioavailable.[179] There are three ionizable amine groups that in acidic medium get protonated and positively charged. Thus the solubility of this otherwise highly lipophilic drug increases in acidic medium.[180] The volume of distribution of clofazimine is very large with an extremely long half-life of upto 70 days. As mentioned above the major problem associated with clofazimine is its lipophilic nature. Clofazimine has to be administered as microcrystalline suspension in an oil-wax base for better absorption.[181] The high lipophilicity of clofazimine also leads to accumulation in fat tissue rich organs like lungs, liver, brain, spleen, and bone-marrow. As the level of accumulation of clofazimine increases in tissues, skin discoloration starts which is the most common side-effect of clofazimine.[182] Clofazimine also forms crystal-like drug inclusions in macrophages which is associated with various side-effects. But clofazimine is well tolerated and the associated side-effects disappear, as the drug is discontinued.[183]

9 | SQ109

SQ109 (Sequella, Figure 2F) is a 1,2-ethylenediamine currently in phase II clinical trial for DS-TB.[184] This drug candidate targets MmpL3 protein of *M. tuberculosis* involved in cell wall synthesis.[185,186] The structural design of SQ109 originated from ethambutol, an established first-line drug for the treatment of TB. Ethambutol was selected for the reason that when it was discovered in 1961 it could not be properly evaluated due to lack of combinatorial chemistry techniques during those times. Sequella, Inc. (Rockville, MD) and the Laboratory of Host Defenses, NIAID/NIH, synthesized a diverse chemical library of ethambutol analogs containing 1,2-ethylenediamine as pharmacophore and evaluated their activity against *M. tuberculosis*. This led to the discovery of SQ109. However, SQ109 is active against ethambutol-resistant strains which indicates that the mode of action of SQ109 is different from ethambutol.[184]

SQ109 is bactericidal against both MDR-TB and XDR-TB causing *M. tuberculosis* strains.[187] In vitro studies show that SQ109 shows synergistic effects with isoniazid and rifampicin and additive effects with ethambutol and streptomycin.[187,188] SQ109 also increases in vitro activity of bedaquiline by four- to eightfold.[189]

9.1 | Mode of action of SQ109

Mycolic acids synthesized in cytoplasm are transported to periplasm from where they are further transferred and incorporated to cell wall. This export of mycolic acids requires trehalose. Studies suggest that both trehalose and mycolic acids form conjugates inside cytoplasm from where they are transported to mycobacterium cell wall. MmpL3 protein is involved in this export process.[190]

9.2 | Interaction of SQ109 with MmpL3

Mycobacterial membranes protein large (MmpL) are a family of proteins that plays critical roles in substrate transport across the inner membrane of mycobacteria for building the unique mycobacterial cell wall.[191] These proteins export mycolic acids bound to arabinogalactan and trehalose monomycolate for the synthesis of trehalose

dimycolate.[192] The necessity of MmpL3 for the viability of *M. tuberculosis* has made it a successful target in the last decade.[193] There are 13 MmpL proteins encoded in *M. tuberculosis*. These proteins are known to transport lipophilic molecules and show little substrate specificity. MmpL proteins are also not known to cause any drug resistance except for MmpL5 which is involved in the active efflux of clofazimine, bedaquiline and azole drugs.[186]

There are two phylogenetic clusters into which MmpL proteins are divided. Cluster II contains MmpL3, MmpL11, and MmpL13 whereas the rest fall in cluster I. Proteins comprising cluster I contain two soluble domains whereas proteins of cluster II contain three soluble domains. Owing to the large size of MmpL proteins, containing approximately 1000 amino acid residues, the full-length structural and biochemical analysis of members of this family is not properly known.[187]

9.3 | Structure-activity relationship

The ethylenediamine scaffold of SQ109 is essential for antitubercular activity.[194] When this ethylenediamine scaffold was replaced with other long chain diamines or cyclohexane diamine or by phenylenediamine, a reduction in activity of SQ109 was observed. A variation in the basicity of any of the nitrogen present decreases the potency of SQ109. Presence of either a fluorine atom or a methoxy group on the carbon adjacent to ethylenediamine group enhances activity. Introducing saturation in the unsaturated aliphatic chain decreases activity. Incorporating more isoprene units at the terminal of the unsaturated aliphatic chain enhances the activity of SQ109 (Figure 11).[195]

9.4 | Pharmacokinetics

SQ109 can penetrate into macrophages where *M. tuberculosis* replicates. It is superior to ethambutol and equivalent to isoniazid in killing *M. tuberculosis* inside macrophages. SQ109 is rapidly transferred from circulation to vascularized tissue of lung probably because of the adamantane moiety present. Adamantane fragment is present in most of the drugs used for the treatment of viral lung pathogens. These drugs act by distributing specifically to lungs. The volume of distribution of SQ109 is high which could be attributed to the hydrophobic nature of compound and the diamine groups present which help in rapid penetration to lung and spleen. This is beneficial as SQ109 has the tendency to get concentrated in lungs and spleen where *M. tuberculosis* replicates. However, the bioavailability of SQ109 is low.[187]

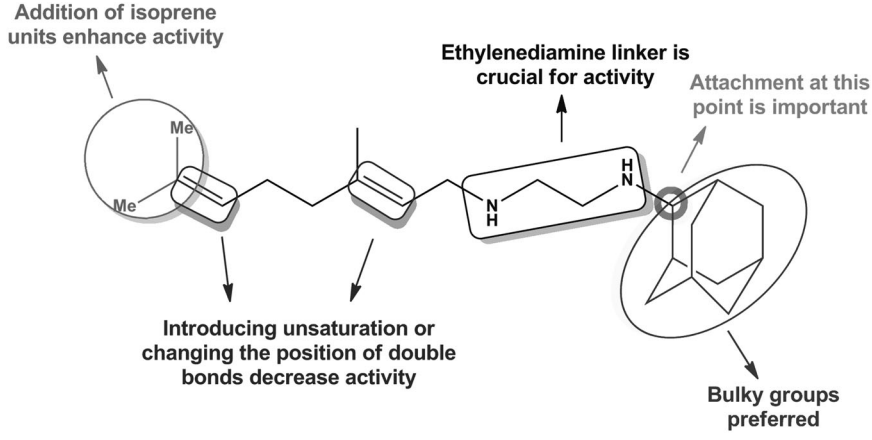

FIGURE 11 Structure-activity relationship of SQ109

10 | PBTZ169

PBTZ169 (Figure 2G) belongs to benzothiazinone (BTZ) class of drugs and is currently in phase II early bactericidal activity trials.[196] PBTZ169 is a piperazinobenzothiazinone developed by optimizing the lead compound of benzothiazinone class, BTZ043. BTZ043 was identified from an in vitro screening of compounds against antibacterial and antifungal activities.[197,198] PBTZ169 has various advantages over BTZ043, including easier synthesis due to lack of chiral centers and better pharmacodynamics. Compared with other BTZs, PBTZ169 is stable against nitroreductase attack probably because of the presence of cyclohexyl group.[199]

PBTZ169 and BTZ043 show promising bactericidal activity against MDR-TB strains. Both the drug candidates are very potent against replicating bacilli but show low activity against nonreplicating bacilli.[200] PBTZ169 shows synergistic effects with bedaquiline.[199] PBTZ169 is in phase II of drug development process while BTZ043 is in preclinical development.[196]

10.1 | Mode of action of PBTZ169

Like other BTZs, PBTZ169 also targets DprE1 enzyme. PBTZ169 forms covalent adducts irreversibly with DprE1.[200] It is proposed that the nitro group of PBTZ169 undergoes reduction to form a nitroso derivative, which then covalently reacts with a cysteine residue of active site of DprE1 and forms an irreversible adduct which inhibits DprE1.[201] Inhibition of DprE1 interferes with the production of decaprenylphosphoryl arabinose, which is a key component for the synthesis of the mycobacterium cell wall arabinans. This results in cell lysis and ultimately leads to cell death.[196]

10.2 | Interaction of PBTZ169 with DprE1

The decaprenylphosphoryl-β-D-ribose oxidase, DprE1 is an enzyme which works together with DprE2 to catalyze the epimerisation of decaprenyl-phospho-ribose (DPR) to decaprenyl-phospho-arabinose (DPA). DPA is the sole donor of D-arabinose in mycobacteria.[202,203] Arabinose polymers form the arabinogalactan component of the cell wall of mycobacteria. DprE1 oxidizes the 2′ hydroxyl group of DPR to ketone using FAD as the oxidant.[204] The epimerisation process occurs in the periplasmic space which makes DprE1 a vulnerable target.[205] The enzyme DprE1 is FAD dependent while DprE2 is NADH-dependent and are encoded by dprE1 and dprE2 genes, respectively.[206]

DprE1 is a dimer characterized by an FAD-binding domain and the substrate-binding domain, situated face to face to facilitate the interaction between the substrate and FAD.[207] The active site of DprE1 is bordered by the isoalloxazine ring of FAD.[208] The active site of DprE1 is surrounded by positively charged residues to interact with the negatively charged residues of cell membrane where DPR, the natural substrate of this enzyme remains embedded.[209]

Crystal structure of DprE1-PBTZ169 adduct shows a covalent bond between the Cys387 residue of DprE1 and PBTZ169 (Figure 12). The cyclohexylmethyl-piperazine moiety occupies the space between the flavin ring of FAD and residues Gly117, Trp230, and Leu363. A hydrogen bond interaction is observed between the carbonyl oxygen of benzothiazinone ring of PBTZ169 and the backbone carbonyl of Leu115 bridged by a water molecule.[199]

10.3 | Structure-activity relationship of PBTZ169

Structure-activity relationship analysis reveals a correlation between lipophilicity (logP) and antimycobacterial activity. An oxygen atom in the thiazine ring and strong electron-withdrawing groups (CF_3, CN, NO_2) at position 6 are essential.[199] A nitro group at position 8 is also necessary for antimycobacterial activity.[198] Hydrophilic groups

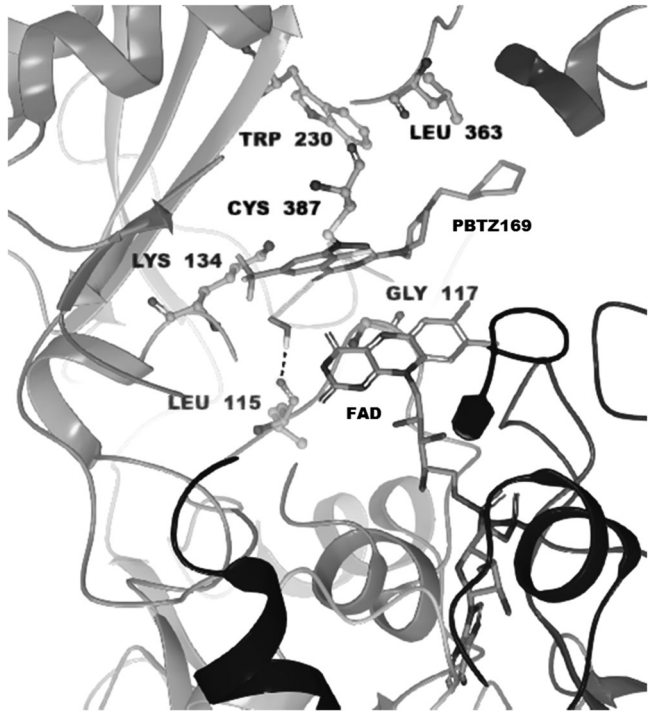

FIGURE 12 Interaction of PBTZ169 (shown in green) with DprE1 of *Mycobacterium tuberculosis* (PDB ID: 4ncr)

at N-4 of piperazine moiety, including hydroxyl, carboxylic acids and secondary or tertiary amine decreases antimycobacterial activity (Figure 13). Hydrophobic substituents at N-4 also result in loss of activity. Substitution of alkyl groups at N-4 result in better solubility and helps regulate hydrophobicity of molecule. The cyclohexyl group of PBTZ169 protects against attack by the nitroreductase enzyme.[199]

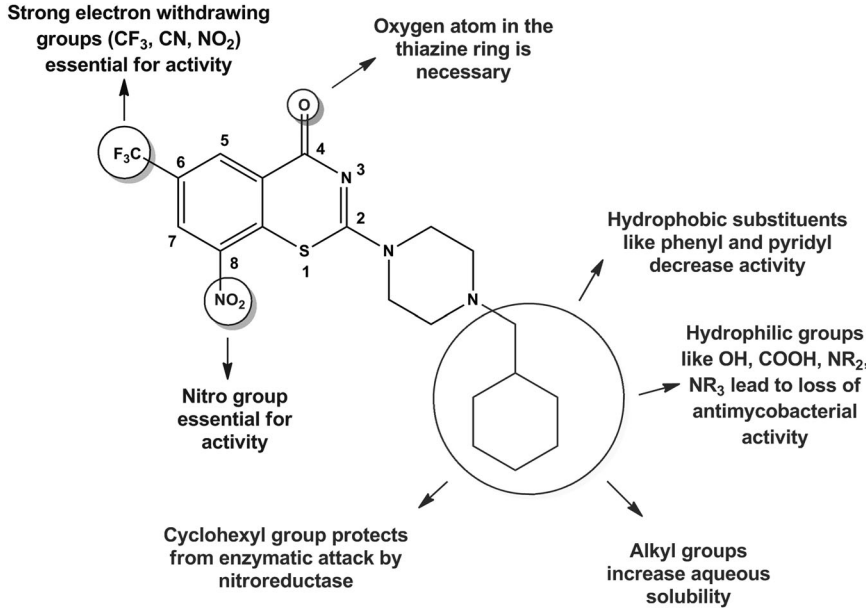

FIGURE 13 Structure-activity relationship of PBTZ169

11 | Q203

Q203 (Figure 2H) is an imidazopyridine amide identified through phenotype high-content throughput screening and is currently in phase II clinical trial. The compound was found to be active against MDR and XDR strains of *M. tuberculosis*.[210] Q203 showed promising action against tuberculosis in mice. Besides Q203 has no chiral center which aids in the large-scale synthesis of the compound.[210] The reasonable cost of goods required for large-scale production of Q203 gives the compound another edge as tuberculosis largely affects low-income group countries.[210]

11.1 | Mechanism of action of Q203

The electron transport chain of *M. tuberculosis* produces energy via oxidative phosphorylation.[211] The cytochrome *bcc* complex (also referred to as cytochrome bc_1 complex) is a component of electron transport chain of *M. tuberculosis* which catalyzes electron transfer from ubiquinol to cytochrome *c*.[210] Q203 interferes with the energy metabolism of *M. tuberculosis* by targeting the b subunit of the respiratory cytochrome *bcc* complex (also called as QcrB) encoded by *qcrB*.[210,212] This compels *M. tuberculosis* to utilize the less energetically efficient cytochrome *bd*, which is known to defend bacteria in conditions of stress. Hence Q203 exhibits a bacteriostatic effect.[213] A recent study suggested that the inhibitory action of Q203 can be enhanced by simultaneously targeting both cytochrome *bcc* and cytochrome *bd*.[214,215] Significant differences exist between the cytochrome *bcc* of *M. tuberculosis* and human mitochondrial cytochrome bc_1. These differences combined with the fact that cytochrome *bcc* is essential for *M. tuberculosis*, make it a suitable target for antitubercular drugs.[215]

11.2 | Interaction of Q203 and cytochrome bc_1 complex

Cytochrome *bcc* complex of *M. tuberculosis* is encoded by QcrCAB operon and is considered a homolog of mitochondrial cytochrome bc_1 complex and chloroplast b_6f complex.[215] The cytochrome *b* subunit contains two ubiquinol binding sites, the oxidation site (QP) and the reduction site (QN).[210] The crystal structure of *M. tuberculosis* QcrB is not yet elucidated. An alignment of cytochrome *b* subunit sequence with bc_1 and b_6f sequences suggests that mutations resulting in resistance are at the QP site which infers that Q203 must be interacting with the QP site.[215] Cytochrome *bcc* complex is a dimeric protein complex, consisting of three subunits: Rieske iron-sulfur protein (QcrA), cytochrome *b* subunit (QcrB), cytochrome *c* subunit (QcrC).[216]

11.3 | Structure-activity relationship of Q203

Structure-activity relationship studies show that carboxamide linker with *N*-benzyl is crucial for antimycobacterial activity (Figure 14). Smaller groups like methyl and ethyl at position 3 of Q203 show better activity.[212] Lipophilicity of the linker joining benzyl group and the para-substituted phenyl group shows a positive effect on antimycobacterial activity.[217]

11.4 | Pharmacokinetics/toxicity of Q203

The bioavailability of Q203 is 90% with a moderate volume of distribution. The terminal half-life of Q203 is 23.4 hours with a low systemic clearance. Q203 shows better concentration in lungs than serum, which indicates that this compound can penetrate the difficult to access thick-walled lung cavities and lesions where *M. tuberculosis* normally resides. Q203 shows no interference with the hERG potassium channel and therefore offers low-risk for cardiotoxicity. The compound also displayed no cytotoxicity or genetic toxicity.[210]

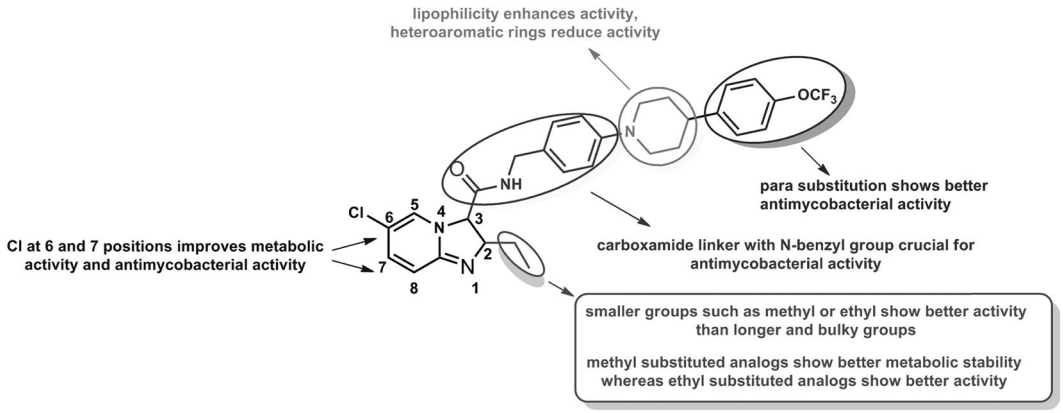

FIGURE 14 Structure-activity relationship of Q203

11.5 | Figures and molecular structures preparation

The two-dimensional (2D) structures of all the compounds were drawn using ChemBioDraw Ultra 12.0 (www.cambridgesoft.com). The images of protein-drug interaction were drawn using Maestro version 11.1.012 (2012; Schrödinger, LLC, New York, NY). The 3D crystal structures were retrieved from RCSB PDB (www.rcsb.org).

12 | CONCLUSION

The last decade experienced a surge in the development of new drugs, repurposed drugs and various treatment regimens for TB. Studies have shown that drugs with poor in vitro efficacy like ethambutol and pyrazinamide are efficient in vivo owing to their excellent biodistribution. Drugs like bedaquiline and delamanid contain two or more aromatic moieties, which makes them highly lipophilic (cLogP values of 7.3 and 5.6, respectively). High lipophilicity makes the formulation difficult and leads to unnecessary drug-drug interactions but on the other hand high lipophilicity helps in limiting drug distribution to specific microenvironments. So it is anticipated that careful designing of new molecules will lead to the development of new compounds that can solve all the problems which society is facing.

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