A Review on Novel Antituberculosis Agent

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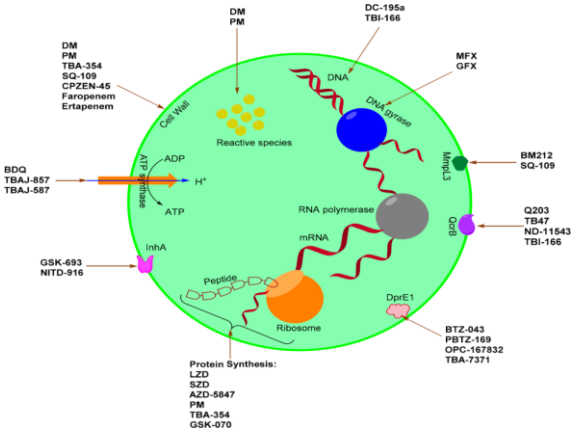
Abstract- *Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis (TB), an airborne infectious disease that is curable when treated with a four-drug regimen. A chronic problem to global tuberculosis control for many years has been the establishment of drug-resistant Mtb strains. The primary causes of treatment failures in tuberculosis are the length and intricacy of the treatment. Drug-drug interactions, mismatched pharmacokinetics characteristics of medications in a regimen, and lack of effectiveness against slow replicating subpopulation are further issues facing currently used TB regimens. These difficulties support the ongoing hunt for cutting-edge TB medications and therapy plans. Drug-drug interactions are a serious concern because effective TB therapy necessitates a mix of medications.*

Keywords- Tuberculosis; Drug development; Pharmacokinetics; Fluoroquinolones; Diarylquinolines; Nitroimidazoles.

I. INTRODUCTION

Antimicrobial resistance (AMR), primarily the multidrug-resistant Mtb (MDR-Mtb), extensively drug-resistant Mtb (XDRMtb), and totally drug-resistant Mtb strains (TDR-Mtb), is also partially responsible for the rising TB prevalence in addition to the risk factors already discussed. Due to patient monitoring, availability of anti-TB medications, errors in following chemotherapy instructions, and improper administration of anti-TB drugs, the global problem of MDR-TB and XDR-TB has reached extremely concerning levels . Increased immigration from TB-endemic nations to nations with low TB prevalence and the rising rate of homelessness combined with drug usage are Drug-sensitive (DS) tuberculosis is currently treated with two months of intense treatment with first-line medications such as rifampicin, isoniazid, pyrazinamide, and ethambutol. The remaining four months of treatment are spent using isoniazid and rifampicin. Various factors contribute to the failure of first-line medications, such as patient non-compliance, which can impact both clinical and microbiological cures and prescription drug adverse effects. MDR-TB, which is characterized as resistance to isoniazid and rifampicin, the two most effective first-line medications in the TB treatment regimen, frequently arises as a result of this failure . As a result, second-line medications that are more toxic and comparatively costlier must be used to treat MDR-TB. Furthermore, treating MDR-TB frequently necessitates a longer course of treatment—a minimum of up to 18 months.The ongoing search for novel compounds with antitubercular activity is crucial due to the toxicity and compliance issues with first-line drugs, the emergence and global spread of Mtb, which is resistant to drugs, the high failure rate of drug candidates



Scheme 1. TB drugs and drug candidates and their associated targets.

New Anti-Mtb Substances:

Mtb possesses a well developed cell wall that offers an exceptional lipid barrier.This barrier makes it easier for intrinsic or acquired antibiotic resistance to manifest. The inhibition of the cell wall, cell wall acids, peptidoglycan (WecA) synthesis, DNA gyrase and topoisomerases, DNA replication, protein synthesis, ATP synthase, Lipid synthesis, DprE1, InhA, QcrB, LeuRS, MmpL3 protein, and L,D-transpeptidase is the mode of action of both established and newly developed drugs against Mtb.

2.1. Derivatives of Quinolone:

Fluoroquinolones:

The DNA gyrase enzyme in Mtb, which is encoded by the gyrA and gyrB genes, is the usual target of fluoroquinolones. Effective DNA replication, transcription, and recombination depend on DNA gyrase, a tetrameric A2B2 enzyme that is unique in that it catalyzes the relaxing of negative supercoiling of DNA . The breakage-reunion active site is carried by the A subunit (90–100 kDa), while the B

subunit (70–90 kDa) facilitates ATP hydrolysis, an essential process for energy transmission. The genomic study revealed that the Mtb genes for DNA gyrase are located in a gyrB-gyrA contig, wherein gyrA and gyrB encode the A and B subunits, respectively. Fluoroquinolone is frequently caused by mutations .

(i) Amoxicillin:

When compared to other fluoroquinolones like ofloxacin and ciprofloxacin, moxifloxacin (MFX), an 8-methoxy fluoroquinolone, exhibits greater efficacy against wild-type Mtb. As a replacement for levofloxacin in the MDR-TB regimen, it is presently recognized as the best medication for MDR-TB. Additionally, MFX is a substitute medication for those who cannot handle the typical DS-TB medication schedule and for patients with XDR-TB as long as it has a minimum inhibitory concentration (MIC) of less than 2 mg/L against the isolate. The structural variations between other fluoroquinolones and MFX.

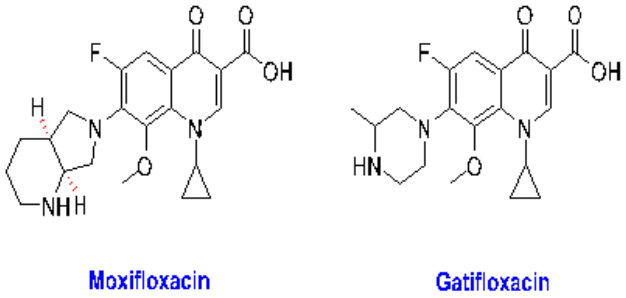


Figure 1. The chemical structures of potential anti-TB fluoroquinolones.

When MFX is taken orally, the gastrointestinal tract absorbs it quickly. Following the 400 mg oral dose that is advised, a mean maximum plasma concentration

This drug is anticipated to have a high safety profile in the treatment of tuberculosis as well because it is a repurposed medication with significant safety studies that show good druglike qualities. Nevertheless, it has been established that the use of MFX has a risk of QT prolongation, which is exacerbated when MFX is taken with medications like delamanid and bedaquiline. For this reason, cautious safety monitoring is needed in these situations.

Nitroimidazoles :

Related to metronidazole, nitroimidazoles show great promise as antimycobacterial drugs. They can be utilized to treat latent tuberculosis infection since they are known to decrease anaerobic bacterial action. The FDA has currently approved two nitroimidazole-based medications for the treatment of tuberculosis (TB): delamanid (DM) and pretomanid (PD). TBA-354 is also undergoing clinical studies for the treatment of tuberculosis.

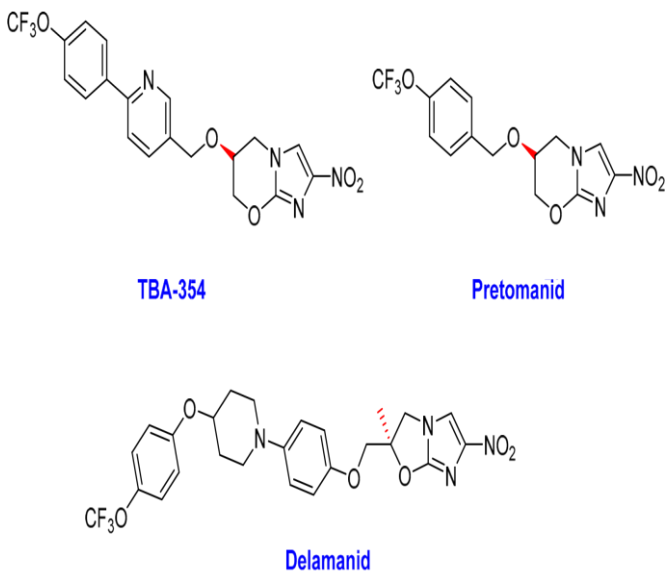


Figure 3. The chemical structure of nitroimidazoles undergoing clinical development as TB drugs.

I)Delamanid:

A novel anti-Mtb medication called delamanid (DM) is a member of the nitroimidazole (nitrodihydro-imidazooxazole) class of substances. Similar to BDQ, this medication was given provisional approval by the European Medicines Agency (EMA) in 2014 to treat adult MDR-TB. Reactive nitrogen species are produced when the Mtb enzyme deazaflavin-dependent nitroreductase (Rv3547) bioreduces the nitro group in DM, activating its pharmacological activity as a prodrug. The suppression of methoxy mycolic and keto mycolic acid production is linked to these reactive intermediates, which include nitrogen oxides and derivatives of desnitro-imidazooxazole. Because of this inhibition, which breaks down the Mtb cell wall and increases drug penetration, treatment can be effective faster .

`2.6. Amides of imidazopyridines:

(i)Telacebec:

Q203 is a new imidazopyridine that was found by SAR optimization after phenotypic high-throughput screening against human macrophages that were infected. It has been the subject of parallel investigations in phase II (EBA treatment-naïve, sputum smear-positive individuals with DS pulmonary TB) and phase Ib (evaluating safety, tolerability, and pharmacokinetics in healthy persons) research. Q203 has anti-

intracellular and anti-MDR-Mtb activity. Hoagland et al. (2016) state that the bc1 complex is a crucial part of ETC, which causes aerobic conditions for the production of ATP. Consequently, Q203 disrupts ATP homeostasis in aerobic settings and rapidly depletes intracellular ATP at an IC50 of 1.1 nM. All of these activities outperformed those found using BDQ. SEAR for a leadtically. Furthermore, SQ-109 with rifampicin demonstrated synergy at 300 mg or 0.5 MIC. Additionally, SQ-109's in vivo experiments demonstrated that this substance could treat TB in mice when administered at a concentration that SQ-109 appears to be safe and well-tolerated in human trials, with mild to moderate gastrointestinal discomfort being the most commonly reported adverse event.

(ii) TB47:

The identification of Q203, exhibiting favorable action against Mtb, has stimulated the hunt for several analogs that are similar (Figure 6). This ultimately resulted in the identification of TB47, a scaffold hopping-discovered pyrazolo[1,5-a]pyridine analog of Q203. Similar to Q203, TB47 functions by aiming at the QcrB subunit; hence, the class of pyrazolopyridine carboxyamides is recognized as an innovative framework for QcrB inhibitors. By preventing the cytochrome bc1 complex from functioning, TB47 lowers intracellular ATP levels and ultimately stops Mtb development. TB47 was docked into the quinol oxidation site (Qp) of the QcrB in order to better understand its mechanism of action. This allowed for possible hydrogen bonding interactions between the amide of TB47 and the glutamate residue (Glu314) of the Qp binding site.

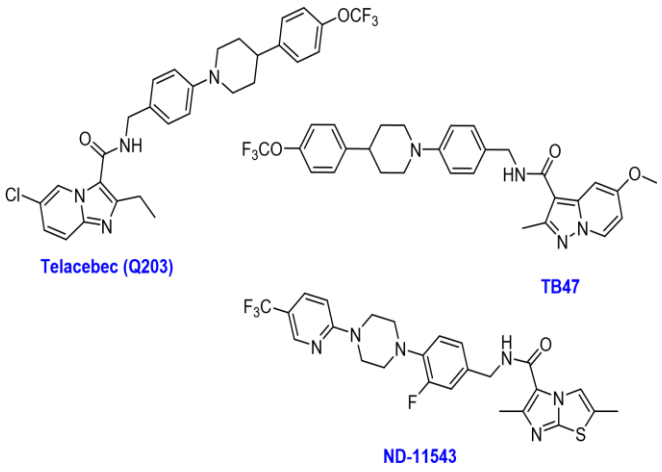


Figure 6. The structures of Q203 and its analogs (TB47 and ND-11543) that show potential as novel TB agents.

2.8. Antimicrobial agents:

Members of the class of naturally occurring liponucleoside antibiotics 60-N-alkyl-50-βO-aminoribosyl-glycyluridine (CPZs) were identified from Streptomyces spp. MK730-62F2. The phosphoMurNAc-pentapeptide translocase (MraY, translocase I), which catalyzes the attack of UDPN-acetylmuramoyl (UDP-MurNAc) pentapeptide by the undecaprenol monophosphate in the bacterial cell membrane supply the lipid I (undecaprenyl-pyrophosphoryl-MurNAcpentapeptide), is the target of the liponucleoside mechanism of action [202]. The (+)-caprazol makes up their core skeleton, which is made up of a N-alkylated α-5'-(ß-1-O-aminoribosyl)-uridinyl-glycine that cyclizes into a uridine, a fatty acid side chain, an amino ribose, and a seven-membered diazepanone ring.In contrast to the other caprazamycins, CPZEN-45 has an α,β-unsaturated amide instead of a fatty-acid side chain.

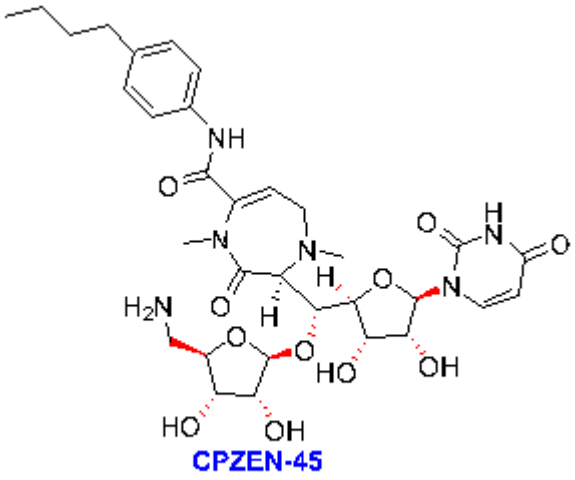


Figure8. Thechem(i) CPZEN-45, caprezene-4-butylanilide

CPZEN-45:

Pre-clinical research of CPZEN-45, a new semi-synthetic derivative of naturally occurring caprazamycin generated by Streptomyces spp., is now underway. Through SAR research intended to improve the limited hydrophilicity and poor oral bioavailability often associated with caprazamycins, the novel liponucleoside antibiotic was found, suggesting the possibility of distinct mechanisms of action amongst these inhibitors. The effectiveness of CPZEN-45 against WecA (Rv1302) of Mtb, an ortholog of TagO involved in the biosynthesis of the mycolylarabinogalactan of the Mtb cell wall, was confirmed by an extensive target identification research conducted by Ishizaki and colleagues. Membrane protein TagO facilitates the transfer of GlcNAc-1-phosphate from UDP-GlcNAc to undecaprenyl phosphate, the initial step in the production of teichoic acid.

2.10 Carbohydrates:

One of the most common heterocycles, pyrroles can be found in a wide variety of natural goods. For instance, it is a structural element of bile pigments (biliverdin and bilirubin), vitamin B12, chlorins, heme, and chlorophyll—pigments necessary for life. Furthermore, a broad range of actions, including antibacterial, antifungal, antitubercular, anti-inflammatory, analgesic, anticancer, anti-epileptic, antiviral, anti-hypertensive, and anti-diabetic properties, have been discovered in pyrrole derivatives. The pharmaceutical industry's need for novel pyrrole derivatives with enhanced biological activity and a multitude of applications was spurred by the multiplicity of therapeutic options available. The two members of this class that have recently been shown to show promising antimycobacterial action are BM-212 and LL-3858.

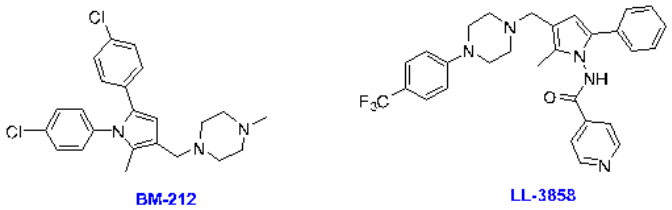


Figure10. The chemical structures of pyrrole drug candidates being investigated for TB treatment.

(i) LL-3858:

The researchers at Lupin, India, were motivated by the strong activity of BM212 to synthesis a number of pyrrole derivatives, which ultimately resulted in the identification of LL-3858. A substituted pyrrole derivative called LL3858 has undergone phase II clinical trials and finished phase I clinical research for the treatment of tuberculosis. Although LL3858's therapeutic target against Mtb is unknown, the compound's structure includes an isonicotinyl hydrazine moiety, and it exhibits activity against strains of the parasite that are resistant to isoniazid, indicating that it may have a distinct mode of action from isoniazid. Additionally, SAR analysis of LL-3858 analogs showed that while the phenyl ring at N-4 piperazine, the CF3, and electron-withdrawing groups had favorable effects on activity, the isonicotinyl hydrazine ring is not essential.

2.11. Inhibitors of InhA:

An essential component of the type II fatty acid biosynthesis pathway (FASII) in Mtb is enoyl-acyl carrier protein reductase (InhA). Because isoniazid has therapeutic potential in the treatment of tuberculosis, InhA was initially considered as a clinical target. Long-chain trans-2-enoyl-acyl carrier proteins (ACPs) undergo a reduction that is catalyzed by NADH and is dependent on InhA. Isoniazid is a prodrug that targets the Mtb's InhA and is activated by the mycobacterial catalase-peroxidase enzyme KatG. It is a crucial part of TB treatment regimens. Due to katG mutations, the primary clinical weakness (especially drug resistance) associated with isoniazid use is its dependence on KatG activation. Finding inhibitors that bind to InhA directly without needing to be activated by KatG (direct InhA inhibitors) may therefore.

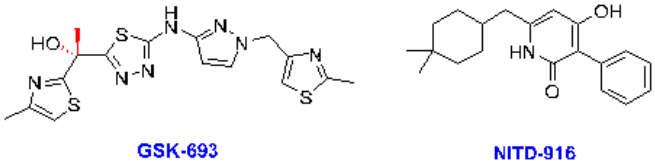


Figure 11. The chemical structures of GSK-693 and NITD-916; novel direct Mtb InhA

GSK-693:

Lead optimization studies by GlaxoSmithKline (GSK) led to the identification of the thiadiazole chiralcompound GSK-693 as a novel, selective, and promising lead compound with attractive antitubercular properties that overcome isoniazid resistance. GSK and other research units have carried out high-throughput screening against InhA using a collection of GSK compounds and identified the thiadiazole series to be the most promising compound class. Despite the interesting in vitro antitubercular profile obtained from the initial SAR studies, hits were affected by a number of compound development requirements such as physicochemical properties, drug metabolism, and pharmacokinetics (DMPK) profiles.

GSK-693 demonstrated a strong CYP 3A4 inhibition profile and equivalent potency (MICs of 0.2 µg/mL) against the Mtb H37Rv both inside and outside of macrophages. In acute and chronic mouse models, the chemical exhibits decreased lipophilicity, increased solubility, and reduced metabolic liabilities in addition to concurrently having good oral bioavailability at varying doses. Finally, early safety evaluations using a variety of enzymatic assays revealed that GSK-693 exhibited no cytotoxicity and no blockage of the hERG potassium channel, indicating a low risk of overall toxicity and cardiotoxicity associated with isoniazid.

2.12. β-Lactams:

The most common class of antibiotics, β-lactams, form the basis of most antibacterial medication therapy regimens; yet, their effectiveness against Mtb has never been fully realized. However, in comparison to other second-line options, β-lactams often provide a clearly defined safety

profile. As a result, phase II clinical trials are currently investigating two β-lactams: faropenem and ertapenem, which are briefly addressed below.

(i) Faropenem:

Compared to cephalosporins and carbapenems, faropenem is an oral bioavailable (72–84%) penem antibiotic that is more resistant to hydrolysis by β-lactamases. Although this penem ring structure is slightly less strained and thus has improved chemical stability, it is structurally comparable to carbapenems. It has also been changed to faropenem medoxomil, a prodrug ester, which allows for oral administration—both beneficial changes for the treatment of multidrug-resistant tuberculosis. In addition to its established use in treating human respiratory infections, the medication also shown encouraging bactericidal action in both replicating and non-replicating Mtb cells, on par with meropenem.

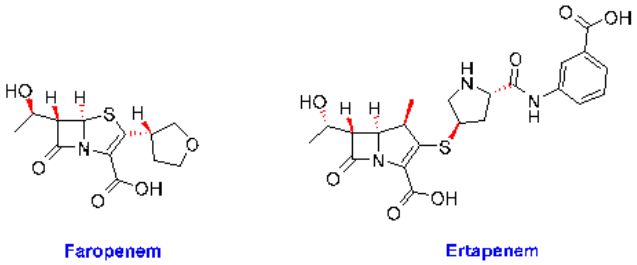


Figure 12. The chemical structures of faropenem and ertapenem.

The medication thereby prevents the L,D-transpeptidases from carrying out the final cross-linking stage of peptidoglycan production. Whether clavulanate is present or not, faropenem's minimum inhibitory concentration (MIC) against Mtb is 1.3 μg/mL. In contrast, meropenem's MIC increases eightfold and that of other β-lactams tested without clavulanate increases many times. Dhar and colleagues used the dehydropeptidase inhibitor probenecid to show that after 9 days of treatment with a combination of faropenem/clavulanate/probenecid, Mtb-infected mice showed a small but significant reduction in lung burden (7.7 and 7.5 log10 CFU/mouse at the beginning and end of treatment, respectively).

II. CONCLUSION

Thanks to the hard efforts of the drug development industry, effective antibiotics for the treatment of tuberculosis have been found to date. Nevertheless, in order to have a successful cure, the current therapy regimens call for an extremely lengthy course of treatment and involve multiple medications, some of which may not be well tolerated. Patients stop taking their medications because of the lengthy course of therapy and the negative effects of the medication, which increases the selection of resistant mutants. As a result, tuberculosis (TB) continues to be a major global health issue that affects over ten million people and claims at least a million lives annually. In particular, the worrying rise in MDR- and XDR-TB cases highlights the necessity of ongoing efforts to find novel treatment regimens to combat tuberculosis.

To enable the selection of optimum combination therapies free of drug-drug interactions, the effect of new TB drug candidates on cytochrome P450 isoenzymes should be identified and tested against other TB medications (candidates) as well as drugs used against common co-morbidities.

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