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Drug development pipeline for the treatment of tuberculosis: Needs, challenges, success and opportunities for the future

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Abstract: Tuberculosis (TB), a leading cause of mortality and morbidity with more than one-third of the world population infected with latent TB and the worldwide dissemination of multidrug (MDR) and extensively drug resistant (XDR) *Mycobacterium tuberculosis* poses a serious threat to human health. Due to inadequacy of long and cumbersome tuberculosis (TB) therapy. Several new molecules in clinical development encourage the scientific community to find new drug targets and new drug leads. In this perspective we present herein an overview of the new anti-TB agents with different molecular structures that are either being clinically used or in advanced stages clinical stages as well as of preclinical development. Here we have tried to provide snapshots of the efforts that are being made in the development of new drug molecules as lead anti-TB agents.

Keywords: Tuberculosis (TB), *Mycobacterium tuberculosis*, Multidrug resistance (MDR), Extensively drug resistance (XDR), Directly Observed Treatment, Minimum Inhibitory Concentration (MIC), Short-course (DOTs)

Tuberculosis, commonly known as TB, is an often severe and contagious airborne disease caused *Mycobacterium tuberculosis* and typically affects the lungs but can affect the other parts of the body called extrapulmonary tuberculosis.

M. tuberculosis is acid-fast, gram positive bacteria, grows slowly under aerobic conditions.

Multidrug-Resistant TB (MDR-TB) is defined by resistance to the two most commonly used drugs in the current four-drug (or first-line) regimen, isoniazid and rifampin.

Extensively drug resistance TB (XDR-TB) is caused by *M. tuberculosis* resistant to isoniazid, rifampin, at least one fluoro-quinolone, and one of the injectable antitubercular drugs such as amikacin, kanamycin, or capreomycin.

Minimum Inhibitory Concentration (MIC) is the concentration of antibacterial that will inhibit the growth of bacteria.

DOTs (Directly Observed Treatment, Short-course) is a strategy that framework for the tuberculosis control programme.

1. Introduction

Mycobacterium tuberculosis (*Mtb*), the causative agents of tuberculosis is one of humanity's oldest and most resilient plagues, despite the availability of four drug regimen to treat the disease [1]. The current first line anti-tuberculosis regimens require a minimum 6 months of DOTs therapy. Adherence to the long and complicated treatment course is challenging and is a major obstacle to the effective use of existing drugs [2]. As a result of treatment failure and poor adherence, epidemic with MDR-TB or XDR- TB is being more common [3]. In 2011, the number of MDR-TB infections was estimated at 60,000 cases (19 % of the global infected population) [4]. Recommended regimens for the treatment of MDR-TB require at least 20 months of treatment with drugs that are toxic, poorly tolerated, and limited efficacy of cure rate. The recent emergence of highly lethal, extremely expensive and virtually untreatable XDR-TB poses a new threat to TB control worldwide. The control of TB is also complicated due to latent TB where the infected persons are asymptomatic, and serve as the reservoir for the pathogen, making control of this disease a difficult and challenging task [5]. Recent advances in the knowledge of molecular biology and *Mtb* genome sequences has enabled the essentiality of genes for the rapid target identification for the new antiTB

compounds via identification of mutated genes of compound-resistant mutants [6-8].

In 2013, 6.1 million TB cases were reported out of these, 5.7 million were newly diagnosed. Number of MDR-TB infections was estimated at 23% of notified TB patients. 1.1 millions (13%) of the 9 million people who developed TB in 2013 were HIV-positive. About 60% of TB cases and deaths occur among men and 510 000 women died as a result of TB, more than one third of whom were HIV-positive. There were 80 000 deaths from TB among HIV-negative children in the same year [4]. Effective treatment of TB patients co-infected with HIV is complicated due to drug-drug interactions between anti-retrovirals (ARVs) and anti-tuberculosis drugs and increased the risk of adverse effects. There is urgent need for more effective and tolerable anti-tuberculosis therapy for the treatment of drug-susceptible, drug-resistant disease and latent-TB infection [9]. Regimens that can be safely co-administered with antiretroviral therapy are urgently needed for the growing number of patients co-infected with both HIV and TB.

2. Diagnosis of TB disease

Out of the major hurdles to control the tuberculosis different diagnostic techniques have been used to identify the bacterium as discussed below with gradual advancement.

- 2.1. Tuberculin skin test (Mantoux tuberculin skin test)
- 2.2. Interferon-gamma release assays (IGRA)
- 2.3. Rapid sputum tests for tuberculosis (TB)
- 2.4. New diagnostic technologies and tools

The major drawback of sputum smear microscopy is its poor sensitivity. There is a urgent need for development, introduction, and effective implementation of cost-effective new tools that contribute to improvement in patient-centered outcomes and public health

and effective in HIV-infected individuals also. technologies and tests currently in demonstration or late-stage evaluation phase [6, 10, 11].

Table 1 lists some of the more promising new

Table 1: Tuberculosis Diagnostic Tests in Use, Recently Endorsed by the WHO, and in Later Stages of Development

Methods	Intended or/and typical use	Main strengths	Main weaknesses
In Use			
Smear microscopy for acid-fast bacilli (light microscopy)	Rapid, point-of-care test for TB case detection	Requires moderate training; minimal infrastructure; minimal equipment	Low sensitivity
Culture on solid media	TB case detection and as prerequisite to drug-susceptibility testing	Good sensitivity	Slow time to growth
Chest radiograph	TB case detection (pulmonary TB)	Indications and use not restricted to TB	Low specificity; low sensitivity; requires equipment, trained Interpreter
Tuberculin skin test	Detection of <i>M. tuberculosis</i> infection	Extensive practical and published Experience	Sensitivity decreases with increasing immune compromise; cross reaction with BCG vaccine
Interferon-gama release assays	Detection of <i>M. tuberculosis</i> infection	Highly specific for <i>M. tuberculosis</i>	Requires moderate training and equipment; imperfect sensitivity, especially for immune compromised persons
Trial of antibiotics directed against routine bacterial pneumonia pathogens	TB case detection for persons with suspected pulmonary TB whose sputum smear results are negative	May be clinically beneficial to patients with bacterial pneumonia	Poor discriminatory power; engenders time delay in further evaluation and care for patients with TB
Automated, non-integrated NAAT	TB case detection (pulmonary TB)	Sensitivity between that of smear and culture; highly specific for TB	Requires moderate training and equipment; labor intensive, potential for cross-contamination among specimens
Endorsed by the WHO			
Culture in liquid media	TB case detection and as prerequisite to drug-susceptibility testing	High sensitivity (higher than culture on solid media)	Slow time to detection (although faster than culture on solid media); high contamination rates in some settings
Strip-based species identification (detects TB-specific antigen in positive cultures)	Species identification (TB versus not TB) in cultures positive for mycobacterial growth	Accurate; requires minimal training; minimal equipment; minimal consumables	
Line probe manual amplification and hybridization	TB case detection and as prerequisite to drug-susceptibility testing	Poor sensitivity in smear-negative specimens; relatively short time to result	Labor intensive; potential for cross-contamination; requires extensive training

3. First-line treatment

Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (ETH) are collectively called the first line of drugs (Fig 1.1) and were introduced around 1950,s. In fact until now INH and RIF are the two most effective and less toxic.

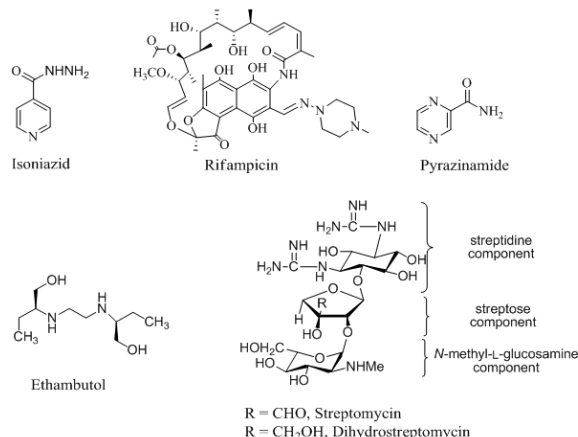


Figure 1: Structure of first-line drugs used for the treatment of tuberculosis.

3.1. Isoniazid(INH)

It was discovered in 1951 by Domagk as effective against *M. tuberculosis* [12] and requires activation by the mycobacterial catalase peroxidase enzyme (*kat G*), to exert a lethal effect on intracellular targets [13, 14]. INH is orally active and exhibits very low MICs (0.02-0.06 $\mu\text{g/mL}$) against the *M. tuberculosis* species [15, 16] and inhibits the mycolic acid biosynthesis in *M. tuberculosis* via mycolate synthetase, unique to *Mycobacteria* [17, 18] only.

3.2. Ethambutol (EMB)

It is ethylene diamino-di-*l*-butanol chemically and was synthesised by Wilkinson in 1961 [19, 20]. It inhibits the bacterial cell wall by specifically targeting the biosynthesis of arabinogalactane and liparabinomannane

[21]. Activity of EMB is stereospecific, the dextro isomer exhibits maximum anti-tubercular activity (*S,S* form is 600 times more active than *R,R*) [22]. The MIC of ethambutol is 0.5 $\mu\text{g/mL}$ against *M. tuberculosis* (H37Rv) *in vitro* [23].

3.3. Pyrazinamide (PZA)

It is a structural analogue of nicotinamide [24-26] and its antiTB activity depends on the presence of bacterial amidase which converts PZA to pyrazinoic acid, the active anti-tubercular entity and this activity is highly specific to *M. tuberculosis*. Pyrazinoic acid results into intake of proton and dysfunction of the pH balance of mycobacteria [27]. Mutation in the *pncA* gene produces pyrazinamidase responsible for resistance against this drug [28, 29].

3.4. Streptomycin

In 1944, streptomycin was the first compound used to treat TB discovered by Waksman. It is derived from the actinobacterium *Streptomyces griseus* and consists of three structural components, streptidine, streptose and *N*-methyl-*L*-glucosamine (Fig. 1). It has MIC value of 1 $\mu\text{g/mL}$ with 50-60 % plasma protein bound and a half-life 5-7 hours [30]. Due to exfoliative dermatitis, toxic manifestation on peripheral, central nervous system and hypersensitive reactions it is not a drug of popular choice [31].

4. Second-line treatment

These drugs are least tolerable and more toxic than the first-line treatment structure are given in Fig 2.

4.1. Amikacin and Kanamycin

These are an aminoglycoside antibiotic used for the treatment of different types of bacterial infections including *M. tuberculosis* [32] and they act by binding to the bacterial 30S ribosomal

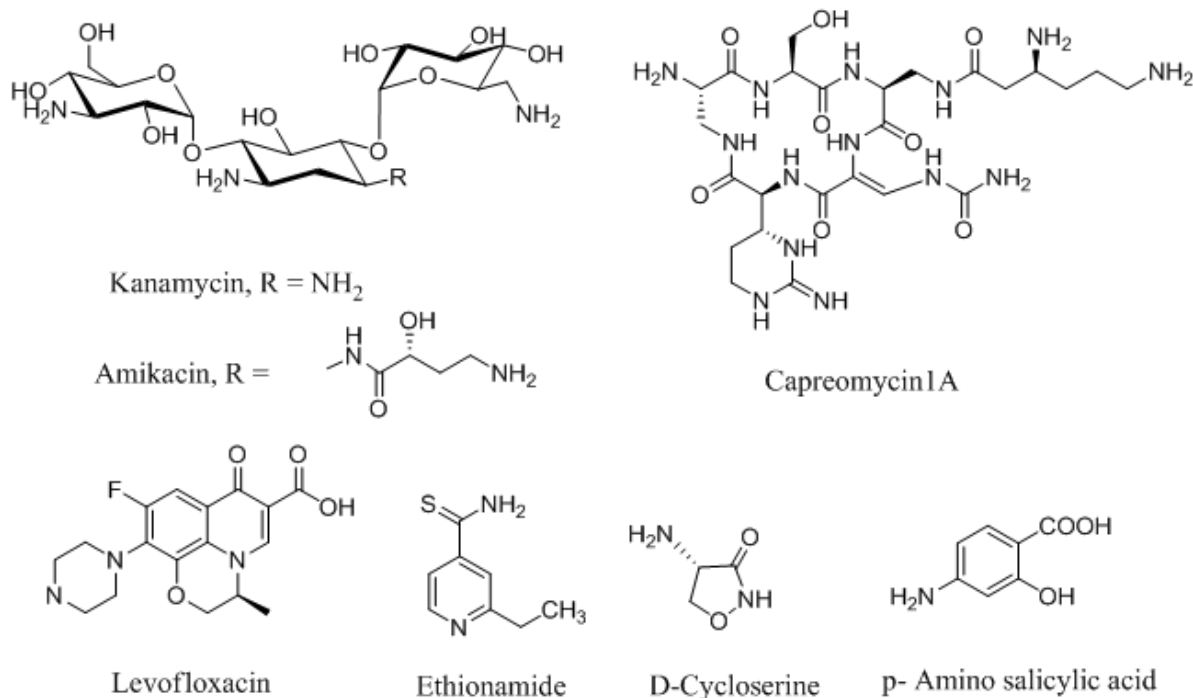


Figure 2: Structure of second line drug used for the treatment of tuberculosis

subunit [33-35] resulting in inhibition of protein synthesis.

4.2. Capreomycin A

Capreomycin is a polypeptide antibiotic and is given in combination with other antibiotics for treating tuberculosis. It acts by inhibiting the prokaryotic protein synthesis [36, 37].

4.3. *p*-Amino salicylic acid (PAS)

It was reported as antimycobacterial in 1946 [38] and is highly specific and effective against *M. tuberculosis* [39, 40]. It is thought to act via NF- κ B (nuclear factor-kappa B) inhibition and free radical scavenging mechanism. *In-vitro* potency against *M. tuberculosis* H37Rv is MIC₉₀ 0.3-1 μ g/mL [41].

4.4. Cycloserine

D-Cycloserine, a structural analogue of amino

acid D-alanine, inhibits *M. tuberculosis* at concentrations of 5-20 μ g/mL [42]. It blocks peptidoglycan biosynthesis by inhibiting the enzyme D-alanine racemase and D-alanyl alanine synthetase [43, 44].

4.5. Ethionamide(ETA)

Ethionamide, 2-ethyl thioisonicotinamide is structural analogue of isoniazid (Fig 2) [45] and it targets *InhA*, an enzyme involved in mycolic acid biosynthesis [46]. ETA induces expression of *EthA*, a NAD derivative which is toxic to the bacteria. MICs of ethionamide for *M. tuberculosis* were from 0.3 to 1.25 μ g/mL [47].

5. Standard therapy/DOTs

Directly Observed Treatment, Short-course (DOTs) strategy is the framework for tuberculosis control programme. The DOTs regimen lasts a minimum of 6 months for treating smear-positive, newly diagnosed pulmonary

disease and consists of a multidrug combination of four first-line TB drugs (isoniazid, rifampin, pyrazinamide and ethambutol), administered for an initial intensive period of 2 months. This is followed by a continuation phase of an additional 4 months of isoniazid and rifampin. It is effective, but it is very labor-intensive and requires a strong health infrastructure. Treatment failure is common problem and leads to drug resistance [48, 49]. MDR-TB is a major concern due to the associated high risk of death and requires treatment with second-line drugs under DOTsPlus [50]. XDR-TB raises concerns of a future TB epidemic with restricted treatment options and till now XDR-TB is almost untreatable [51].

Unfortunately, totally-drug resistant tuberculosis (TDR-TB) or extremely-drug resistant tuberculosis (XXDR-TB) a superbug has resulted from further mutations within the bacterial genome to confer resistance, beyond those seen in XDR-TB and MDR-TB. Development of resistance is associated with poor management of cases. TDR-TB is a deadlier iteration of the highly resistant forms of TB that have been increasingly reported over the past decade. "Totally resistant TB is not new at all [52]. India the third country in which a TDR-TB has emerged (in 2012), after Italy (in 2007) and Iran (in 2009) [53, 54].

6. Treatment of tuberculosis in HIV patients

M. tuberculosis and HIV co-infection, often called the 'dual epidemic', and each makes the other more severe. DOTS and antiretroviral drugs when administered together to infected individuals, the *M. tuberculosis* increases the replication of HIV in cell [55, 56]. Efavirenz-based HIV regimens are compatible with the DOTS for tuberculosis; and in patients with contraindications to efavirenz, standard twice-daily doses of nevirapine provide acceptable efficacy and safety [57-60]. According to the latest WHO recommendation, anti-retroviral

treatment (ART) should be initiated as soon as possible during the first 2-8 weeks of tuberculosis treatment in all patients with HIV-associated tuberculosis, regardless of CD41 cell count [55]. Recent studies support initiating ART for those with very low CD4 counts soon after starting tuberculosis therapy [61-63].

7. New application of existing drugs

A number of known drugs are being currently investigated for their contribution in simplification or improvement of the current TB drug regimen.

7.1. Rifamycins (Rifampin and Rifapentine)

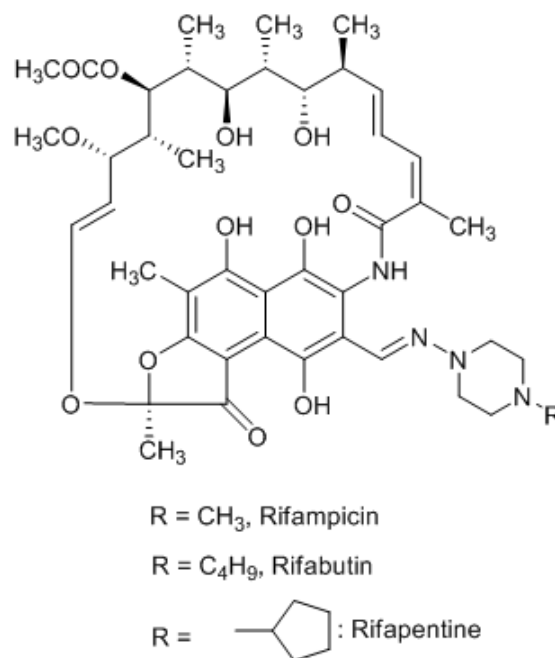


Figure 3: Structure of Rifamycins

The rifamycins belong to the family of ansamycin antibiotics and were first isolated by Sensi and co-workers at Lepetit SA in 1959 (fig 3). Rifamycin B, the product of the fermentation, has only modest activity, but it converted into rifamycin SV which has much more potent activity and was the first rifamycin

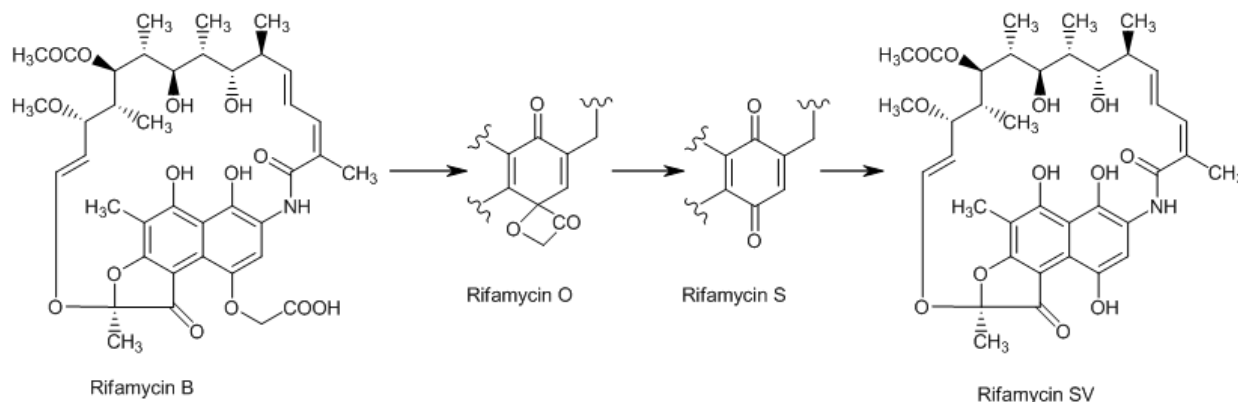


Figure 4: Conversion of Rifamycin B into Rifamycin SV

used clinically (Fig 4) [64].

Three semisynthetic rifamycins, therifampicin, rifapentine and rifabutin have been introduced for the treatment of various microbial infections. Rifampicin (INN) is a bactericidal antibiotic drug isolated from *Streptomyces mediterranei* considered to be the cornerstone in the current treatment of TB with MIC value ranging from 0.1-0.2 $\mu\text{g/mL}$. Its standard dose in TB treatment is 10 mg/kg of body weight, corresponding to 600 mg in most populations.

Rifampin inhibits the β -subunit of the RNA polymerase, a multi-subunit enzyme that transcribes bacterial RNA. Mycobacterial resistance to the rifamycins results from mutations in the *rpoB* gene those codes for the β -subunit of the RNA polymerase. About 95% of mutations occur in a region of less than 100 bp of the *rpoB* gene [65]. To avoid rapid development of bacterial resistance rifampicin is recommended in combination with other first line agents either INH or Etmb. However, combination of rifampicin and INH may increase the risk of hepatotoxicity. Drawbacks of rifampin are its inductive effect on the CYP450 enzyme system, which is involved in the metabolism of many other drugs, and the increasing rate of mycobacterial resistance to rifampin [66].

Rifabutin or mycobutin is used as a replacement for rifampicin, one of the strongest first-line drugs for the treatment of TB. The MIC of rifabutin against rifampin-susceptible *Mtb* strains is ≤ 0.08 mg/liter, 8 times less than the MIC of rifampin against the same strains [67, 68]. It is well tolerated by patients who develop rifamycin-related adverse effects and both have similar potency in treating TB [69]. It has much longer half-life than rifamycin (35 h vs 3.5 h). This difference in pharmacokinetics is responsible for acquired rifamycin resistance in HIV-positive individuals [70]. Rifabutin is the only rifamycin that does not appear to have a significant impact on the Cyp450 exzyme, which is involved in the metabolism of some antiretrovirals. It is therefore recommended for use with antiretrovirals but further studies are wanted.

RIFAQUIN a phase III clinical trial molecule is reported recently. Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by four months of once weekly moxifloxacin (500 mg) and rifapentine (1200 mg) in the continuation phase was non-inferior to control, even at the 95 % level, safe and well tolerated. Moreover, in the continuation phase, moxifloxacin and rifapentine were taken once weekly compared to the daily dosing of the standard regimen [71].

7.2. Fluoroquinolones

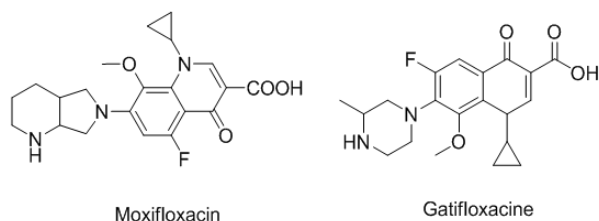


Figure 5: Structure of fluoroquinolones

Fluoroquinolones are broad-spectrum antimicrobial agents that have shown potent activity against *M. tuberculosis* *in vitro* and *in vivo*, used as second-line drugs in MDR-TB treatment [72]. The new C-8-methoxy-FQ moxifloxacin (MXF) and gatifloxacin (GATI) have a longer half life and are more active against *M. tuberculosis* than ofloxacin and ciprofloxacin, the older fluoroquinolones (Fig 5) [73].

Fluoroquinolones target gyrase and topoisomerase IV in most bacteria but in *Mtb* it is assumed they target mycobacterial topoisomerase II (DNA gyrase) since there is no evidence of topoisomerase IV present in *Mtb* [73]. MIC against *M. tuberculosis* H37Rv is 0.12-0.25 mg/mL for gatifloxacin and 0.18-0.5 mg/mL for moxifloxacin [74]. Gatifloxacin has a slightly better activity against *M. tuberculosis* clinical isolates (23 strains) than moxifloxacin. Indeed, the range of MIC₉₀ is 0.007-0.12 mg/mL for gatifloxacin and 0.031-0.12 mg/mL for moxifloxacin [75, 76].

Moxifloxacin has a mechanism that is distinct from isoniazid in that it affects bacteria by binding to the DNA gyrase and topoisomerase IV, which are involved in bacterial replication. Unlike some other effective fluoroquinolones, moxifloxacin is not phototoxic [73, 77].

REMoxTB was designed to test whether a moxifloxacin containing regimen of four

months can cure drug sensitive TB patients at rates those achieved with the standard six months TB regimen. The standard regimen is compared to (i) a regimen of 2RHZM/2RHM and (ii) a regimen of 2RMZE/2RM has recently started. Moxifloxacin is repurposed drug not approved for the treatment of tuberculosis [78].

8. New drugs in clinical trial:

8.1. Diarylquinolines: TMC207 (Bedaquiline)

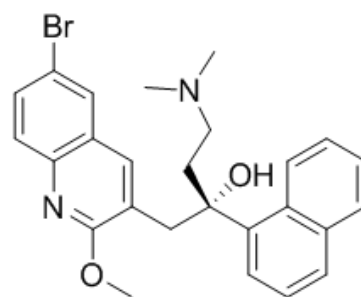


Figure 6: Structure of TMC 207

TMC207 (R207910, Bedaquiline, and compound J) is a lead compound in the diarylquinoline series (Figure 6) originally discovered by Koen Andries at Janssen Pharmaceutica through a whole cell-screening on *Mycobacterium smegmatis* [79]. A recently completed phase II trial found that it reduces the time, takes for sputum to become negative in patients, meaning that it has the potential to shorten the duration of TB treatment. In December 2012, The U.S. Food and Drug Administration (FDA) granted bedaquiline accelerated approval for the treatment of adults with multidrug-resistant tuberculosis (MDR-TB). Bedaquiline (trade name, Sirturo) is the first truly novel drug to be approved to fight TB in more than four decades. TMC207 is being developed in partnership between the developer, Tibotec, and the Global Alliance for TB Drug Development.

TMC207 mechanism of action is unique among anti-TB agents, inhibits the proton transfer

chain of the mycobacterial ATP synthase [80, 81]. The initial identification of the target of TMC207 relied on sequence analysis of a single mutant of *M. tuberculosis* and two mutants of *M. smegmatis* that were resistant to the drug [82]. Binding of TMC207 to the oligomeric and proteolipic subunit c of mycobacterial ATP synthase leads to inhibition of ATP synthesis, which subsequently results in bacterial death [83, 84]. TMC207 is not active on human mitochondrial ATP synthase [85]. TMC207 is a potent against *M. tuberculosis* H37Rv with a MIC₉₉ 0.030 mg/mL, also has similar efficiency against sensitive and resistant *M. tuberculosis* strain with MIC 0.030-0.120 mg/mL [84]. The *in vitro* activity of TMC207 did not increase with increasing drug concentration, suggesting time-dependent rather than concentration-dependent killing.

Co-administration with protease inhibitor lopinavir/ritonavir increased exposure to bedaquiline by approximately 20 %, and a trial with nevirapine indicated that steady-state NVP did not influence exposure to bedaquiline or its metabolite, and single-dose bedaquiline did not influence pre-dose nevirapine concentrations [86].

8.2. Nitroimidazole

The nitroimidazopyrans have been derived from the bicyclic nitroimidazofurans that were originally developed for cancer chemotherapy but also exhibited activity against actively growing and dormant *M. tuberculosis* OPC-67683 (dihydroimidazo-oxazole, Phase III)

and PA-824 (nitroimidazo-oxazine, Phase II) and are currently being investigated in clinical trials.

8.2.1. Delamanid (OPC-67683)

OPC-67683 is a member of the nitroimidazo-oxazole family, is a novel compound being studied for the treatment of MDR-TB. Delamanid is analogue of CGI-17431 (Fig 7), discovered and currently under development by Otsuka Pharmaceutical Company [87].

OPC-67683 is a methoxy-mycolic and keto-mycolic acid biosynthesis inhibitor with specificity to *M. tuberculosis* with IC₅₀ values 0.036 and 0.021 mg/mL respectively. OPC-67683 has to be activated by *M. tuberculosis* to exert its activity. Mutations in the mycobacterial Rv3547 gene found in OPC-67683 resistant *M. tuberculosis* strains suggest that this gene codes for the key enzyme in activating OPC-67683 [87].

Delamanid possesses highly potent activity against TB including drug susceptible and drug resistant strain as MIC ranging from 0.006 to 0.024 µg/ml *in-vitro*. Its activity at a concentration 0.1 µg/mL was reported to be similar to that of the first-line drug rifampicin at a concentration 3 µg/mL. The *in vitro* intracellular activity of OPC-67683 was also better than that of isoniazid and PA-824 at concentration 3 µg/mL. Besides, delamanid shows no cross-resistance with any of the currently used anti-TB drugs [88].

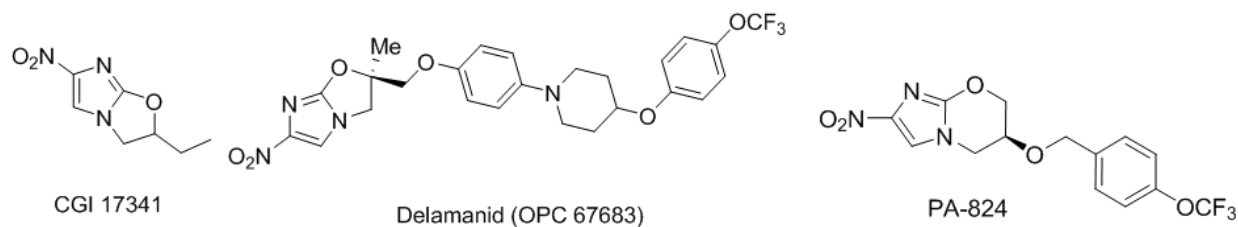


Figure 7: Structure of nitroimidazole

Delamanid neither induces nor suppresses the cytochrome P450 (CYP P450) enzymatic pathways at concentration up to 100 µg/mL. Therefore, additional drug-drug interaction studies are planned in phase III study.

8.2.2. PA-824

PA-824 is a member of the nitroimidazo-oxazine family (Fig 7), which has demonstrated bactericidal and sterilizing activity against drug-resistant and non drug-resistant TB. PA-824 has also shown activity against both active and latent TB. It is currently in Phase II clinical trials conducted by the TB Alliance.

PA-824 is a prodrug and is activated by a bacterial coenzyme F420 (deazaflavin) dependent glucose-6-phosphate dehydrogenase (FdG). Activated PA-824 inhibits the synthesis of protein and cell wall lipids. Mutation in mycobacterial gene *fbiA*, *fbiB* and *fbiC* leads to impaired coenzyme F420 synthesis and therefore resistance to PA-824 [89].

PA-824 is also active against latent TB bacteria. In a latent state, bacteria are anaerobic and either non-replicating or replicating very slowly. PA-824 kills latent bacteria by releasing nitric oxide (NO), which poisons the bacteria. NO gas is produced by two-electron reduction at the imidazole ring but not at the nitro group and it has been hypothesized that the resulting intermediates generate reactive nitrogen species, including nitric oxide [90] (Fig. 8) after immune cell engulf TB bacteria; this is one way the body fights TB infection. But this immune response is sometimes not sufficient to eliminate an infection. PA-824 mimics the body's natural immune response, but it is more specific and only releases the gas upon entering the TB bacteria [91]. However, under aerobic conditions the exact mechanism of action is not known although inhibition of mycolic acid biosynthesis may be involved. PA-824 is active in susceptible and resistant *M. tuberculosis*

strains. No cross-resistance with standard anti-TB drugs has been observed [92]. The *in-vitro* activity of PA-824 was found to be between MIC 0.015 and 0.25 µg/mL for drug-sensitive strains and between 0.03 and 0.53 µg/mL for drug-resistant strains [93].

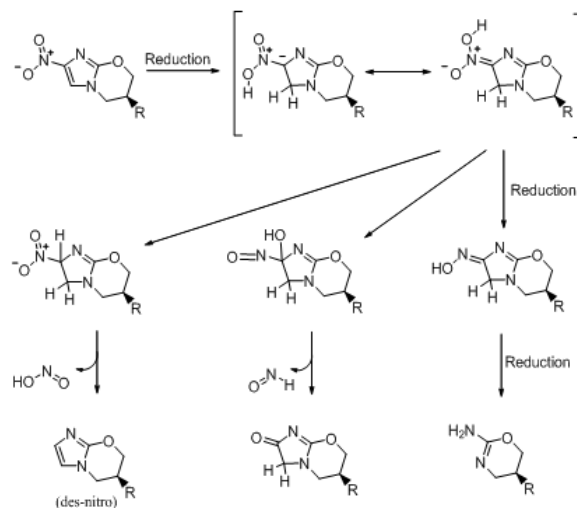


Figure 8: Mode of action of PA-824

The ACTG (The clinical trial group)'s drug-drug interaction study of PA-824 and two common antiretrovirals (ARVs), PA-824 is safe to use with lopinavir/ritonavir (a boosted protease inhibitor) and efavirenz (a non nucleoside reverse transcriptase inhibitor) as well as with rifampicin [94].

8.3. SQ-109

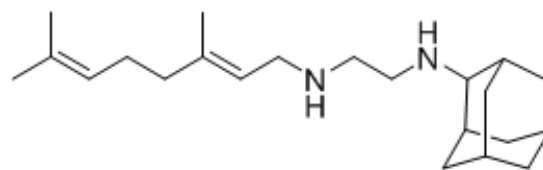


Figure 9: Structure of SQ-109

SQ109, a second-generation ethylene diamine antibiotic, is the lead compound from Sequella.

It is an analogue of ethambutol, but ten times more active in preclinical studies (Fig 9). SQ109 completed three phase I studies and being evaluated in a phase IIA trial in adults with smear positive pulmonary TB [95].

SQ109 inhibits mycobacterial cell wall synthesis; the exact target is unclear. In 2012 Tahlan *et al* demonstrated that SQ109 disrupts cell wall assembly of mycolic acids into the cell wall core of *Mtb*, as bacilli exposed to SQ109 show immediate inhibition of trehalose dimycolate (TDM) production and fail to attach mycolates to the cell wall arabinogalactan. SQ109 targets MmpL3, a transmembrane transporter of TMM involved in mycolic acid donation to the cell wall core of *Mtb* [96]. Interestingly, SQ109 is still active against EMB resistant strains, and therefore SQ109 is believed to act in a different manner than ethambutol [97].

The *in-vitro* activity of SQ109 ranging from MIC 0.16-0.64 $\mu\text{g/mL}$ in drug susceptible and drug resistant strain of *Mtb*. Its MIC is equal to 0.9 μM on EMB-resistant strain, 1.4 μM on INH-resistant strain and 0.7 μM on RIF-resistant strain. It interacts synergistically with isoniazid and rifampicin and reduced by 30 % the time required to cure mice of experimental TB [98]. The oral bioavailability of SQ-109 in mice, rats, and dogs is low (3.8 %, 12.0 %, and 2.4–5.0 %, respectively), and it is metabolised rapidly by mouse, rat, dog, and human liver microsomes [99].

8.4. Oxazolidinones

Oxazolidinones are protein synthesis inhibitors with a unique mechanism of action against TB. These compounds have a broad spectrum of activity against anaerobic and gram-positive aerobic bacteria, and mycobacteria [100]. It includes linezolid (Phase II), PNU100480 (Phase II) and AZD5847 (phase II).

8.4.1. Linezolid

Linezolid (Zyvox, Pfizer), a class of oxazolidinones (Fig. 10) possess a broad spectrum of antibiotic activity, encompassing anaerobic and Gram positive aerobic bacteria, as well as mycobacteria [101].

Linezolid presents a unique mechanism of action which was supported by the lack of cross-resistance between oxazolidinones and other antibiotics. Oxazolidinones stop the growth and reproduction of bacteria by disrupting translation of mRNA into protein in the ribosome. Linezolid appears to work on the initiation step by preventing the formation of initiation complex (composed of 30S, 50S subunit of ribosome, tRNA, and mRNA). Linezolid binds to the 23S portion of 50S subunit. In this way linezolid limits the growth of bacteria by disrupting the production of protein [102].

Linezolid exhibits *in vitro* bacteriostatic activity against *Mtb*, including multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains, with a minimum inhibitory concentration of less than 1 $\mu\text{g/mL}$ whose MIC_{50} is 0.5 $\mu\text{g/mL}$ and

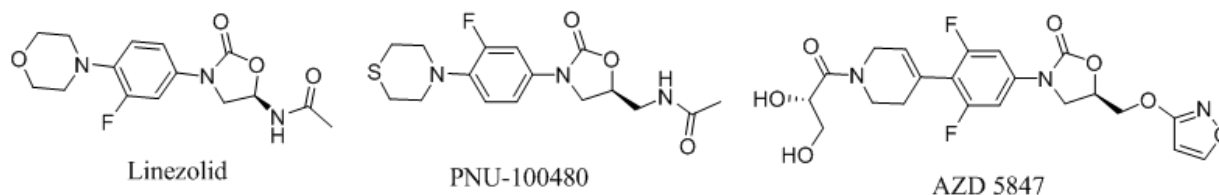


Figure 10: Structure of Oxazolidinones

MIC₉₀ is 1 µg/mL [103]. Modest EBA against *M. tuberculosis* was reported in patients with cavitary pulmonary TB during the first 2 days of administration, but the effect waned thereafter [104]. Its development was discontinued in Phase 1 due to toxicity issues such as peripheral and optic neuropathy, black hairy tongue, [105] pneumonia etc were common. Linezolid has already been approved in a non-tuberculosis indication [106].

8.4.2. PNU-100480 (Sutezolid)

PNU-100480 is a close analogue of linezolid developed by Pfizer, New York, USA, a close structural analogue of linezolid (Fig 10). Therefore, new analogues showing identical or better *in-vivo* activities and a better therapeutic index would be useful. A combination regimen of PNU-100480, moxifloxacin, and pyrazinamide was more active than was the standard regimen of rifampicin, isoniazid, and pyrazinamide. PNU-100480 has the potential to significantly shorten therapy for both drug-susceptible and drug-resistant TB [107].

PNU-100480 exhibits a MIC range of 0.03-0.50 mg/mL against drug-sensitive and drug-resistant strains of *Mtb* which is 3.2 times more efficient than linezolid [108].

Sutezolid not interact with cytp450 enzymes, it is not likely to interact with most antiretrovirals and may therefore be a good option for HIV-positive patients with TB [109].

8.4.3. AZD 5847

AstraZeneca's AZD5847 (formally known as AZD 2563) was originally intended as a broad-spectrum antibiotic, but has now been repurposed as an anti-TB agent (Fig 10). AZD 5847, an oxazolidinones work by stopping the creation of proteins that are essential to bacteria's survival. AZD 5847 is active in culture against a broad array of drug-sensitive and drug-resistant

strains of *Mtb*, which causes TB.

In-vitro, two studies (phase I), a single ascending dose and a multiple ascending dose over 14 days, have now been completed for AZD 5847 where the drug was administered up to 1,200 mg twice a day for a period of 14 consecutive days. Bioavailability in fasted volunteers was reported to decrease with increasing dose, declining from 100 % at 50 mg to less than 30 % at 1,200 mg. However, this tendency was corrected by food intake. AZD 5847 was tolerated over 14 days in healthy volunteers. In the multiple ascending-dose study, the most common adverse effects were nonserious gastrointestinal disorders, reversible and dose-related changes in white blood cells, and mildly increased reticulocyte counts at follow-up. Changes in reticulocyte counts were not accompanied by changes in hemoglobin measurements [110, 111].

9. Drugs in pri-clinical trial

9.1. DC 159a

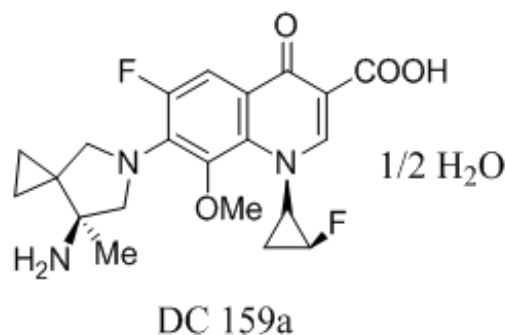


Figure 11: Structure of DC 159a

DC-159a is a newly synthesized broad-spectrum 8-methoxy fluoroquinolone (fig 11) was demonstrated to have potent *in vitro* and *in vivo* activity against quinolone-resistant *M. tuberculosis* (QR-TB) as well as MDR-TB. This compound has been shown previously to have potent activities against various respiratory pathogens, including quinolone-resistant strains

[112].

The mechanism of action of DC-159a is under investigation, DC-159a exhibits considerably high inhibitory activity against altered DNA gyrases with substitutions Ala90Val and/or Asp94Gly in *GyrA* as well as wild-type enzyme of *Mtb* which plays a role in DNA replication. A G88C mutation in *GyrA* is one of the key alterations to acquire DC-159a resistance in *Mtb* mutants *in vitro*. A novel double mutation, G88C+D94H, in *GyrA* conferred high DC-159a resistance. DC-159a showed better *in vitro* and *in vivo* activities against quinolone resistant multidrug resistant tuberculosis strains (QR-MDR-TB) than some other fluoroquinolones [112, 113].

DC-159a has MIC₉₀ 0.06 µg/mL against *M. tuberculosis*, which is 4 and 8 times lower than that of moxifloxacin and levofloxacin respectively. MIC₉₀ of DC-159a was 0.5 µg/mL against clinical MDR-TB isolates which are resistant to other fluoroquinolones (MXF and LVFX MIC₉₀ is 4 and 16 µg/mL respectively) [114, 115].

9.2. SQL-641

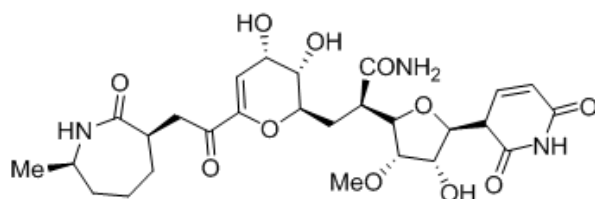


Figure 12: Structure of SQL-641

SQ641 is an analogue of capuramycin (CM), a naturally occurring nucleoside-based compound produced by *Streptomyces griseus* (Fig 12). It was derived from a library of over 7,000 CM analogues created by Daiichi-Sankyo (Japan) and was identified as anti-tubercular agent [116, 117].

SQ641 target the bacterial enzyme phospho-*N*-acetylmuramyl-pentapeptide-translocase (translocase-1, TL-1 or MraY), an essential enzyme in peptidoglycan (cell wall) biosynthesis lead to cell death and enzyme is unique in bacteria [118,119]. Since the TL-I enzyme is absent in eukaryotic cells, it is an attractive target for antibiotic development. Despite the ubiquity of TL-1 in all bacteria, SQ641, is remarkably specific for *Mycobacteria* and certain gram positive bacteria. SQ641 shows *in-vitro* activity against both *Mtb* (MIC 1.0 µg/ml) and *M.avium* complex (MIC 0.016-16 µg/ml) bacteria and more active than other anti-TB drugs, including isoniazid (INH) and rifampicin against *Mtb*. The SQ641 compound has an extraordinary postantibiotic effect of 55 h against *Mtb* and is active against MDR-TB. SQ641 is strongly synergistic with ethambutol, streptomycin, and SQ109, Sequella's lead anti-tubercular drug in clinical trials, and is effective in preventing the development of drug-resistant mutants of *Mtb* [119, 120].

9.3. BTZ 043

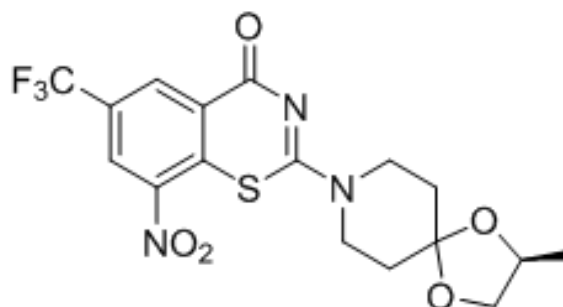


Figure 13: Structure of BTZ043

Nitro-benzothiazinones (BTZs) have emerged the current lead compound BTZ043 (Fig. 13), displays similar activity against all clinical isolates of *Mtb* yet tested, including MDR and XDR strains. The nanomolar activity and the strong bactericidal effect of BTZ043 make it a promising drug candidate against TB [121]. The structure activity relationships study showed

that sulphur atom and one or two nitro groups on the aromatic structure was required to inhibit bacterial growth *in vitro* [122].

BTZ inhibit the conversion of decaprenylphosphoryl- β -D-ribose (DPR) to decaprenylphosphoryl- β -D-arabinofuranose (DPA), a precursor of mycobacterial cell wall arabinan. This two-step epimerization reaction is catalyzed by the joint or successive action of the FAD-containing decaprenylphosphoryl- β -D-ribose 2'-epimerase (DprE1 or, Rv3790) and the NADH-dependent reductase DprE2 (Rv3791). BTZ 043 inhibits the DprE1, thus provoking cell lysis and bacterial death [123].

BTZ043 displays significant activity against *M. tuberculosis* H37Rv and *Mycobacterium smegmatis* with MIC of 1 ng/mL (2.3 nM) and 4 ng/mL (9.2 nM), respectively, which is more potent than those of the existing tuberculosis (TB) drugs. BTZ 043 has MIC, 20 folds less than that of isoniazid [124]. BTZ043 acts synergistically with TMC207. TMC207 at one-quarter the MIC (20 ng/mL) used in combination with BTZ043 (1/4 MIC 0.375 ng/mL) had a stronger bactericidal effect on *M. tuberculosis* than TMC207 at a concentration of 80 ng/mL [121].

9.4. DNB1

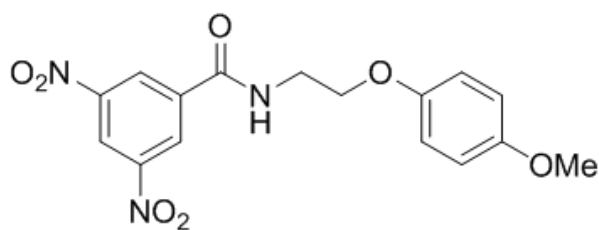


Figure 14: Structure of DNB1

Dinitrobenzamide analogues as DNB were recently identified from a phenotypic cell-based assay that uses automated confocal fluorescence microscopy [125]. They showed

high activity against sensitive and XDR *Mtb* strains. These derivatives were also shown to inhibit decaprenylphospho-arabinose synthesis by targeting decaprenylphospho-ribose 2'-epimerase DprE1 and are currently under development. BTZ and DNB class inhibitors both contain a central benzene ring carrying a nitro group at position 3 (Fig 13 and Fig 14). Inhibition of DprE1 by BTZ/DNB inhibitors has been shown to require conversion of the nitro to a nitroso group, proposed to form a semi-mercaptal linkage with a conserved cysteine in the active site of DprE1 (Cys387 in *M. tuberculosis*) [126].

9.5. BDM 31343

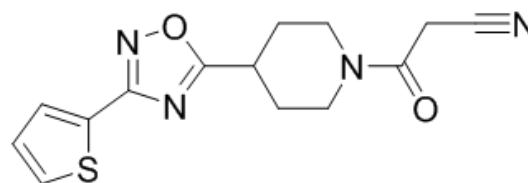


Figure 15: Structure of BDM 31343

BDM 31343 (Fig 15) inhibit the DNA-binding function of *EthR* and used them to boost the anti-mycobacterial efficacy of ethionamide both *in vitro* and *in vivo*, providing an antibacterial synergism which might permit the reconsideration of the use of ethionamide as a first-line therapy [127, 128]. *In vitro* overproduction of *EthR* was shown to confer resistance to ethionamide whereas *EthA* overproduction via *ethR* KO conferred at least a 25-fold increase of ethionamide potency [129].

9.6. CPZEN 45

CPZEN-45 is a nucleoside antibiotic (Fig 16) produced by *Streptomyces* sp, and was first described in 2003 by researchers at the Microbial Chemistry Research Foundation and Meiji Seika Kaisa Ltd in Japan. It has MIC 1.56 μ g/mL against *Mtb* H₃₇Rv and 6.25 μ g/mL against a MDR strain of *Mtb*. This compound

is active against both replicating and non replicating *Mtb* *in vitro*, suggesting it could be efficacious against latent organisms *in vivo*. Improved efficacy against drug-sensitive *Mtb* was shown when CPZEN-45 was administered in combination with other anti-TB drugs [130].

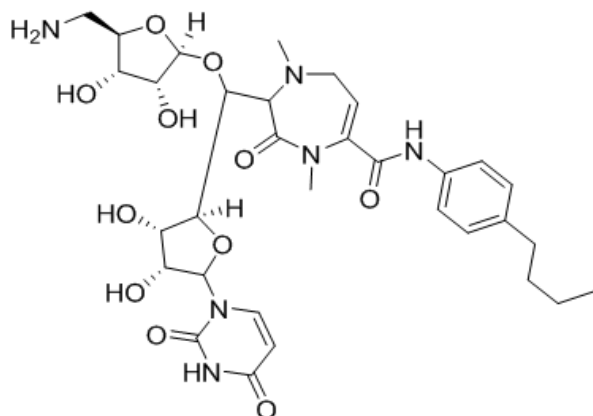


Figure 16: Structure of CPZEN 45

9.7. SQ-609

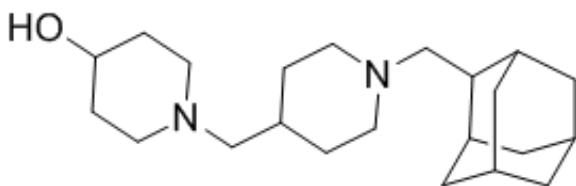


Figure 17: Structure of SQ-609

It is adamantane containing hydroxydipiperidine (Fig 17) with potent and specific activity against both drug-sensitive and drug-resistant forms of *Mtb*, low toxicity, activity in *in-vivo* models of *Mtb* infection, and a favourable safety and pharmacology profile. It acts by interrupting the biosynthesis of cell wall, but its specific mechanism is unknown [131].

9.8. LL-3858

LL-3858, a pyrrole was discovered in 2004 (Fig 18). The mechanism of action is unknown, early reports described a minimum inhibitory

concentration range of 0.06–0.5 mg/mL that was not affected by resistance to isoniazid and rifampicin. Additive activity in combination with first line drugs in the murine model was also described. LL3858 is being developed by Lupin and has been evaluated in a multi-dose Phase I trial involving healthy volunteers in India [132-135].

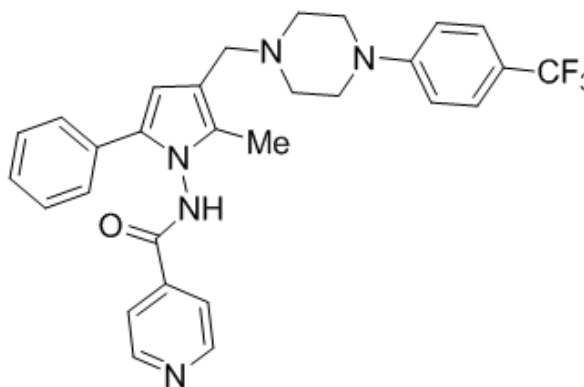


Figure 18: Structure of LL-3858

10. New chemical entities (discovery phase molecules)

10.1. Thiolactomycin and analogues

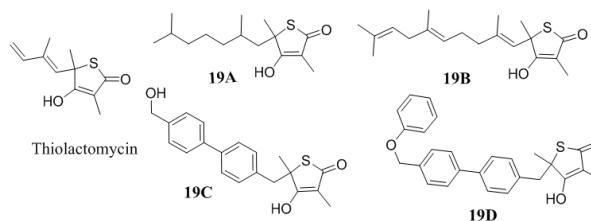


Figure 19: Structure of thiolactomycin and analogues

Thiolactomycin (isolated from *Nocardia* spp) is a thiolactone antibiotic [136] of considerable interest because of its selective activity in disrupting essential fatty acid synthesis in bacteria, plants and some protozoa, but not in eukaryotes. Thiolactomycin selectively inhibits the mycobacterial acyl carrier protein-

dependent type II fatty acid synthase *mtFabH* in FAS-II and the elongation step involved in the synthesis of α -mycolates and oxygenated mycolates [137-141].

Thiolactomycin is active *in vitro* against a wide range of strains of *Mtb*, including those resistant to isoniazid. It has MIC of 5 $\mu\text{g/mL}$. Several others analogues **19A-19D**, (Fig. 19) were also reported to have greater activity than parent in inhibiting *Mtb in vitro* [142, 143].

10.2. Riminophenazine (Isocitrate lyase inhibitors)

Isocitrate lyase plays a key role for survival of *Mtb* in the latent form during a chronic stage of infection. This enzyme is important for *Mtb* during steady stage growth when it converts isocitrate to succinate and glyoxylate. Then, the glyoxylate is condensed with acetyl-CoA to form malate by malate synthase. The carbon conserving glyoxylate pathway has not

been observed in mammals therefore, it has been determined as a potential drug target for discovery of a new antituberculosis agent [144, 145].

Riminophenazines have been effective in treating mycobacterial infections like leprosy, though existing compounds have poor solubility and can cause skin discoloration in patients. Riminophenazines show no cross-resistance with any other class of TB-drugs and are therefore potential agents for treating drug-resistant TB [146] their lack of intrinsic P450 interactions means that they should be safe to co-administer with antiretrovirals (ARVs) in patients who are co-infected with TB and HIV.

The clofazimine and several clofazimine analogs i.e. B4121, B4125, B4128, B4169 (Fig. 20) are active *in vivo* against *M. tuberculosis*, *M. bovis*, *M. leprae* and *M. avium* having MIC value of 0.01 to 3.3 $\mu\text{g/mL}$ [147-149]. Replacement of the phenyl group attached to the C2 position of

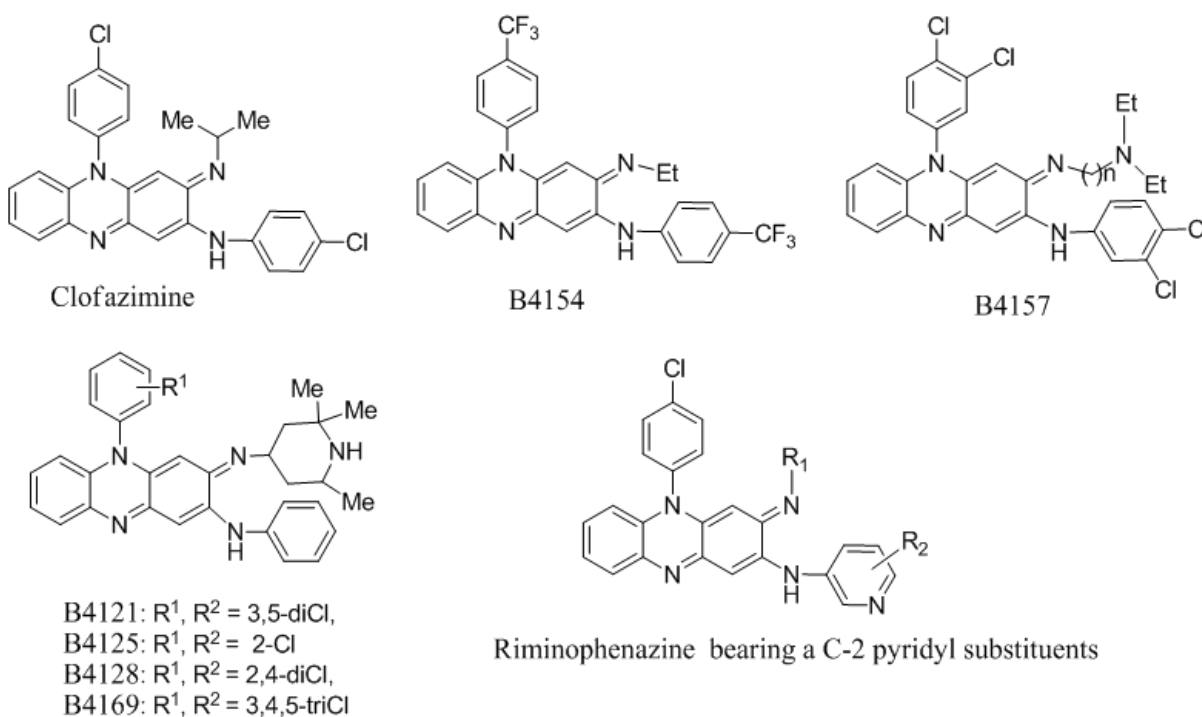


Figure 20: Structure of riminophenazine

clofazimine, by a pyridyl group has improved the anti-tuberculosis potency, and reduced pigmentation potential [150].

Riminophenazines B4154 and B4157 are more active against *Mtb* than clofazimine. MIC of B4154, B4157 and CFZ are 0.25, 0.12 and 1 $\mu\text{g/mL}$ respectively, both the agents cause less skin pigmentation, which is the main drawback of this group of compounds [146]. The mechanism of action of riminophenazine has not been clearly established. It has been suggested that generation of H_2O_2 may contribute to antimicrobial activity [151]. It has been also reported that clofazimine inhibits multiplication of organism by binding to guanine base of DNA [152]. Recently Huang *et al* have synthesized a series of novel riminophenazine analogues bearing a C-2 pyridyl substituent. All compounds were evaluated for their *in vitro* activity against *Mtb* and cytotoxicity. Many new compounds had potent activity with MICs of less than 0.03 $\mu\text{g/mL}$ and low cytotoxicity with IC_{50} values > 64 $\mu\text{g/mL}$. Some compounds were tested for *in vivo* efficacy against MDR-TB in an experimental mouse infection model [153].

10.3. Ethambutol analogues

A library of 67,238 compounds was generated

based on an ethylenediamine pharmacophore of ethambutol. Several ethambutol analogues **21A-21C** (Fig 21) displayed *in vitro* activities against *Mtb* [154]. Recently ferrocenyl diamines **21D**, **21E** were reported as anti-tubercular agent with MIC 8 $\mu\text{g/mL}$ [155]. The ethylenediamine analogs with diazepane ring **21F**, **21G** exhibited good *in vitro* efficacies against *Mtb* including MDR-TB clinical isolates (MIC 0.78-3.13 $\mu\text{g/mL}$) [156]. A series of polycyclic ‘cage’ derivatives of *N*-geranyl-1,2 diamines are reported with anti-mycobacterial activity against, H37Rv (MIC at 0.5 -1 $\mu\text{g/mL}$), multidrug resistant (MDR)-TB (1-4 $\mu\text{g/mL}$) and extensively drug-resistant (XDR)-TB (4-8 $\mu\text{g/mL}$) strains of tuberculosis. Compound **21H** and **21I** showed MIC 0.5 $\mu\text{g/mL}$ against H37Rv strain of *M. tuberculosis*. [157]

10.4. Thioacetazone

Thioacetazone (TAC) is an antitubercular, bacteriostatic drug having MIC value 0.1 $\mu\text{g/mL}$ against *M. tuberculosis* H37Rv. TAC has been widely used in combination with isoniazid in Africa and South America [158]. Chemical analogues of TAC, SRI-224 and SRI-286 (Fig 22) have MIC < 0.05 $\mu\text{g/mL}$ and 3.1 $\mu\text{g/mL}$ respectively against *M. tuberculosis* H37Rv. These were found to be more effective than TAC

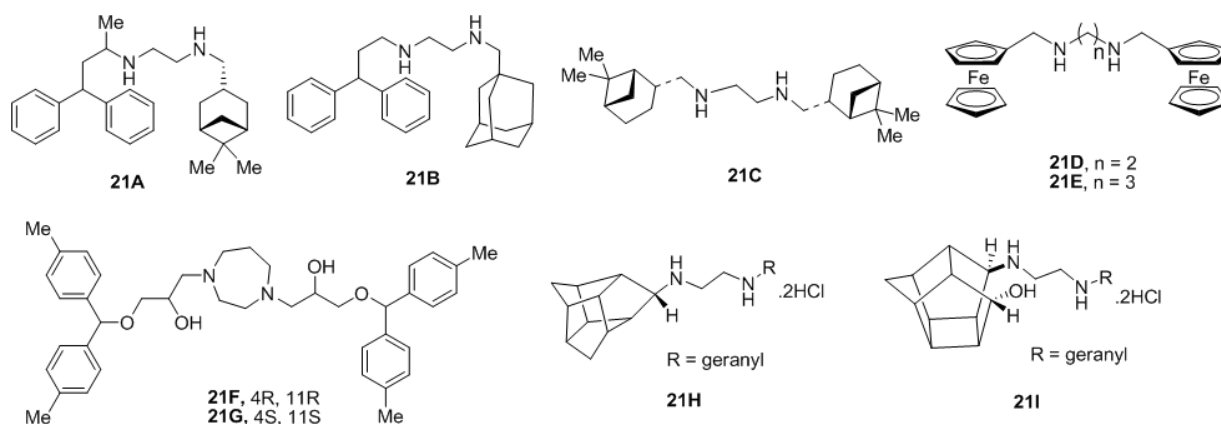
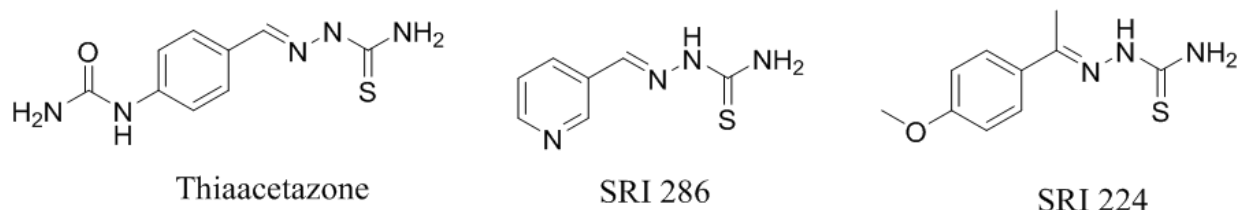
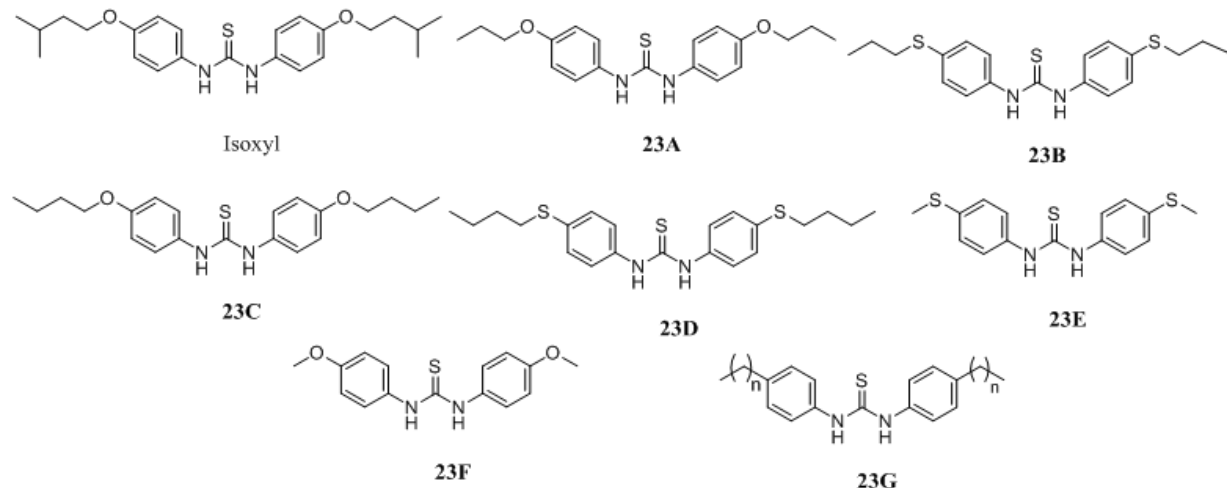


Figure 21: Structure of ethambutol analogues

**Figure 22:** Structure of thioacetazone analogues**Figure 23:** Structure of isoxyl derivatives

against *Mycobacterium avium* in mice [159].

10.5. Isoxyl and Urea derivatives

Isoxyl (ISO), thiourea (thiocarlide, 4,4'-diisoamyloxythiocarbanilide, Fig. 23), displayed potent activity against *Mtb* H37Rv (MIC, 2.5 mg/mL), *M. bovis* BCG (MIC, 0.5 mg/mL), *M. avium* (MIC, 2.0 mg/mL), and *M. aurum* A+ (MIC, 2.0 mg/mL), by inhibiting the mycolic acid synthesis. A comparison with isoniazid (INH) and ethionamide (ETH) demonstrated marked similarity in action. Isoxyl derivatives (23A-23G) also exhibited MIC value in the range of 0.1-0.5 µg/mL [160]. The Fas II synthesis are involved in ISO resistance [161].

potent anti-tuberculosis activity with MIC values 0.01, 0.4, 0.02, 0.4, .01, and 0.4 µg/mL. But they had undesirable pharmaceutical properties, particularly high lipophilicity and poor solubility [162]. Again they synthesized a new series of 1-adamantyl-3-heteroaryl ureas **24G-24K** by replacing the phenyl substituent of the original series with pyridines, pyrimidines, triazines, oxazoles, isoxazoles, oxadiazoles and pyrazoles. This study produced lead isoxazole (**24G**, MIC 0.10 µg/mL), thiazole (**24H**, MIC, 1.56 µg/mL), oxadiazole (**24I** and **24J**, MIC 1.56 and 0.78 µg/mL) and pyrazole (**24K**, MIC 1.56 µg/mL) substituted adamantyl ureas with improved *in vitro* PK profiles, increased selectivity and good anti-TB potencies [163].

10.6. Isoniazid analogues

Lee *et al* developed a series of 1-adamantyl-3-phenyl ureas **24A-24F** (fig 24) that had

Fatty acid hydrazide derivatives of isoniazid

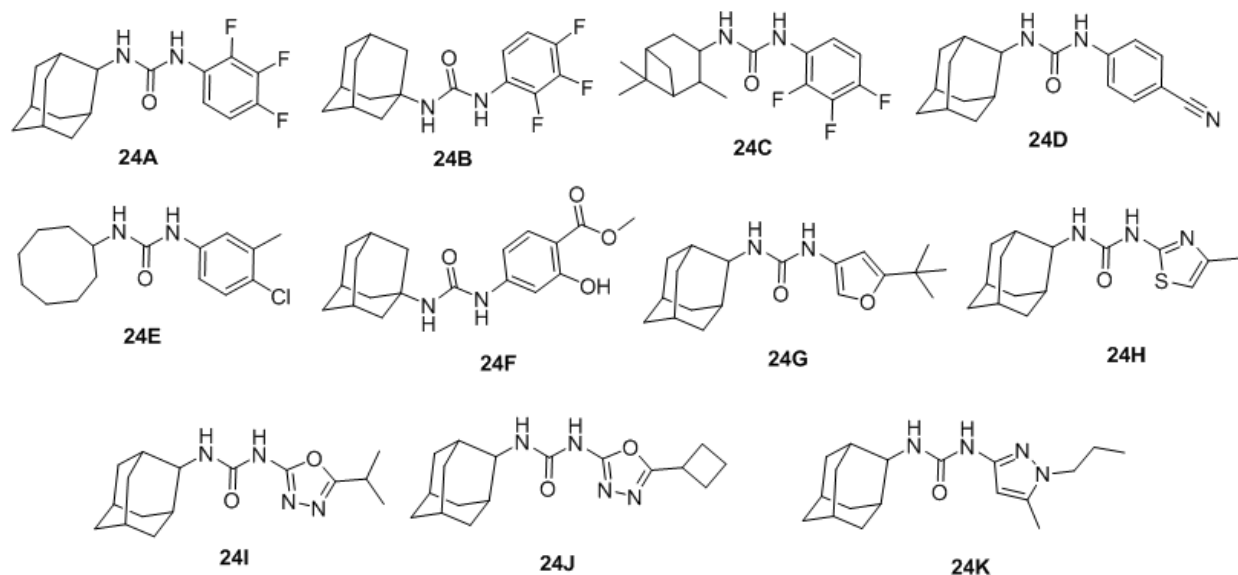


Figure 24: Structure of urea derivatives

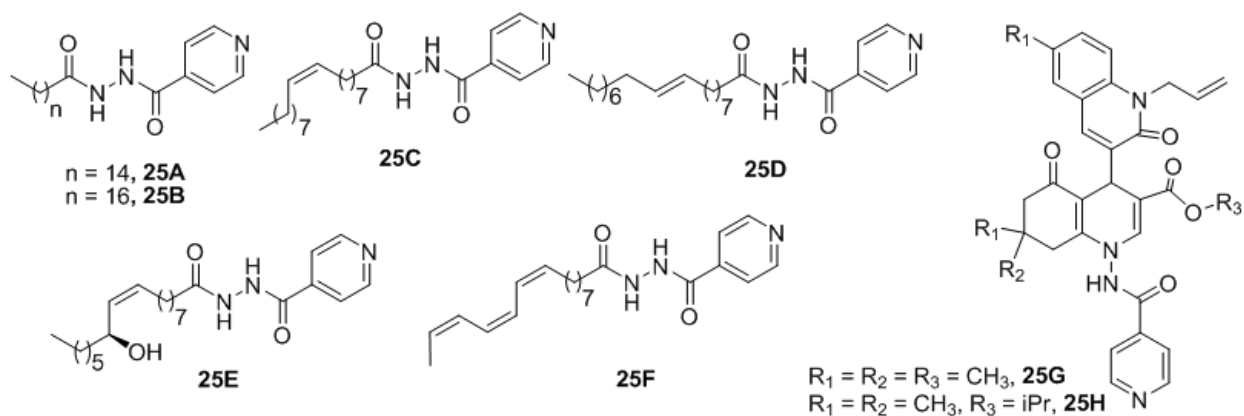


Figure 25: Structure of Isoniazid analogues

(INH) were tested against *M. tuberculosis* H37Rv (ATCC 27294) as well as INH-resistant (ATCC 35822 and 1896 HF) and rifampicin-resistant (ATCC 35338) *M. tuberculosis* strains. INH derivatives (**25A-25F**, Figure 25) showed high anti-mycobacterial potency with MIC value 0.015, 0.03, 0.015, 0.03, 0.03 and 0.06 $\mu\text{g/mL}$ respectively against H37Rv strain of *Mtb*, suggesting that the increased lipophilicity of isoniazid plays an important role in its antimycobacterial activity. [164] Biquinolone-isoniazid hybrids **25G** and **25H** displayed 99 % inhibition against *Mycobacterium tuberculosis*

with LC50 values 35.39 and 34.59 mg/mL, respectively [165].

10.7. Hydrazines, thiosemicarbazone and hydrazones, thiocyanate derivatives

Hydrazine carbothioamides **26A**, **26B** and **26C** were recently reported to have MIC 0.4 $\mu\text{g/mL}$ against *M. tuberculosis* [166]. Fluorine-containing hydrazones **26D** and **26E** (Fig. 26) have shown a remarkable activity against MDR-TB strain with MIC 0.5 mg/mL and high value

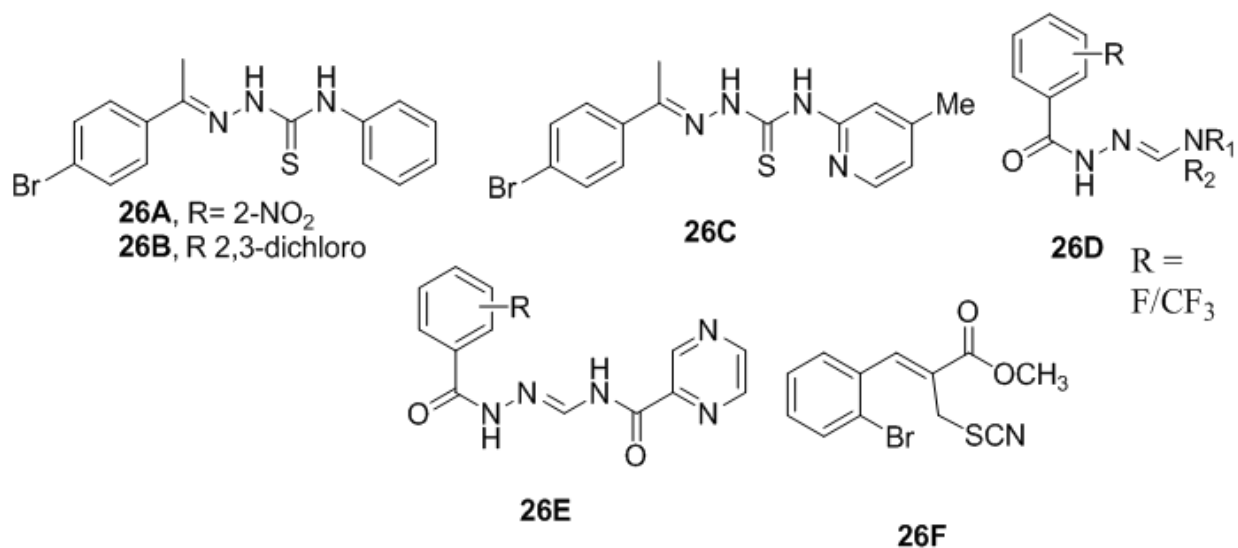


Figure 26: Structure of hydrazines, hydrazones, thiosemicarbazone and thiocyanate

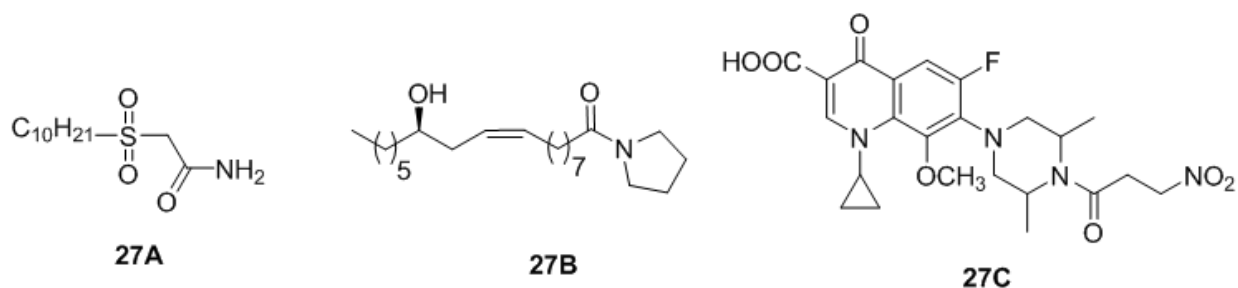


Figure 27: Structure of different amides

of selectivity index [167]. 2-Bromophenyl substituted thiocyanate **26F** showed MIC (0.25 μ M against replicating *Mtb* and 8.0 μ M against non-replicating *Mtb*) and IC₅₀ 32 μ M in the VERO cellular toxicity assay [168]. Several other hydrazones possessed anti-TB activity [169-171]. 5-nitrothiazolylthiosemicarbazones, *N*-(5-nitro-1,3-thiazol-2-yl)-2-((*Z*)-4-[(phenylmethyl)oxy] phenylmethylidene) hydrazine-1-carbothio-amide was found to be active with a MIC of 0.23 μ M against *Mtb* H37 Rv, and was three times more potent than isoniazid and equally active as rifampicin [172].

10.8. Alkyl-sulfinyl amides, fatty acid amides and nitro propionamides

Alkyl sulfinyl amides inhibit β -ketoacyl synthase (KAS), one of the accessory fatty acid synthases peculiar to mycobacteria. The compound **27A** showed good MIC at 0.75 μ g/mL, but its selectivity toward mycobacterium is still unknown [173]. The fatty acid amide derived from ricinoleic acid **27B** (Fig 27) is the potent one among a series of tested compounds, with MIC 6.25 μ g/mL for resistance strains of *Mtb* [174]. 1-cyclopropyl-7-(3,5-dimethyl-4-(3-nitropropanoyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **27C** was found to inhibit the *Mtb* isocitrate lyase (ICL) enzyme with *in vitro* MICs 0.16 and 0.04 μ M against log- and starved-phase culture of *Mtb* and also showed good enzyme inhibition of *Mtb* ICL with IC₅₀ of

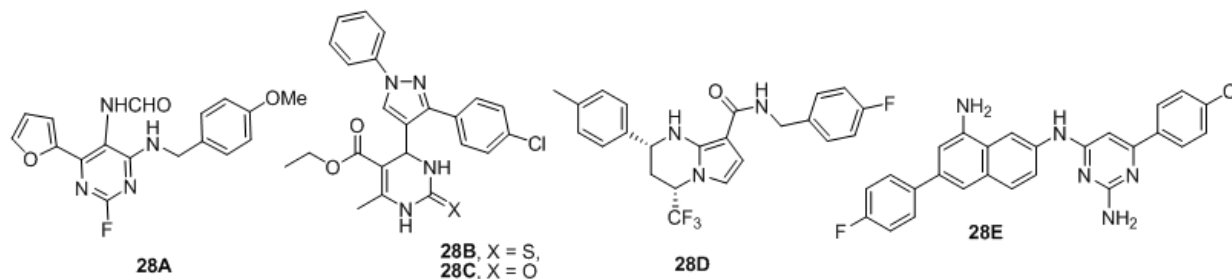


Figure 28: Structure of pyrimidine derivatives

$0.10 \pm 0.01 \mu\text{M}$ [175].

10.9. Pyrimidines, dihydropyrimidines, tetrahydropyrimidines

Several pyrimidine derivatives (Figure 28) were synthesized and evaluated against *Mtb* [176-180]. Compound **28A** (5-formamidopyrimidines) displayed IC_{90} values $\leq 1 \mu\text{g/mL}$, and exhibited low toxicity towards mammalian cells. A series of dihydropyrimidines also exhibited *in vitro* anti-tubercular activity against *Mtb* H37Rv. Compounds **28B**, **28C** were found to be the most potent against *Mtb* with MIC value 0.125 and 0.25 $\mu\text{g/mL}$ respectively [181].

Tetrahydropyrazolopyrimidine, **28D** exhibited *in vitro* MIC value $0.15 \pm 0.04 \mu\text{M}$ and potent *in vivo* activity in a mouse efficacy model, achieving a reduction of 3.5 log CFU of *Mtb* after oral administration to infected mice once a day at 100 mg/kg for 28 days [182]. One of the quinolinyl pyrimidines **28E** showed MIC 0.87 $\mu\text{g/mL}$ and enzyme inhibition ($\text{IC}_{50} = 0.043 \mu\text{M}$) against the NDH-2 target, which in turn translated into cellular activity against *Mtb* [183].

10.10. Piperidine-4-ones

Piperidinone derivatives were reported as potent antitubercular agents [184-187]. 4-(4-Fluorophenyl)-5-phenylpyrrolo(spiro[2.3']oxindole)spiro[3.3']-1'-methyl-5'-(4-fluorophenyl methylidene)

piperidin-4'-one **29A** was found to be active *in vitro* with a MIC value of 0.07 μM against *Mtb*. *In vivo*, compound **29A** decreased the bacterial load in lung and spleen tissues with 1.30 and 3.73-log₁₀ protections respectively and was considered to be promising in reducing bacterial count in lung and spleen tissues.

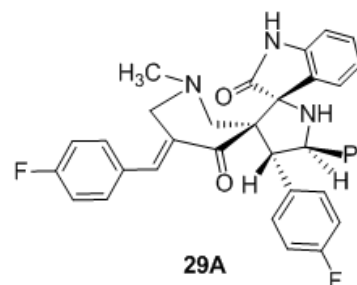


Figure 29: Structure of piperidinone

10.11. Quinoxaline 1,4-dioxides

The leading compound LVTZ **30A** (Fig. 30) belongs to quinoxaline 1,4-dioxides class of compounds showed very good selectivity and activity against *Mtb* with MIC 0.1 $\mu\text{g/mL}$ [188]. Antitubercular screening of 3-methyl-2-phenylthioquinoxaline 1,4-dioxides (**30B-30F**) exhibited MIC between 0.39 and 0.78 $\mu\text{g/mL}$ against *Mtb*. Amide of quinoxaline 1,4-di-N-oxides **30G** were active against *Mtb* as same as rifampin (RIF) [189].

A series of quinoxaline derivatives exhibited promising antitubercular activity compound **30H** of them emerged as a lead compound

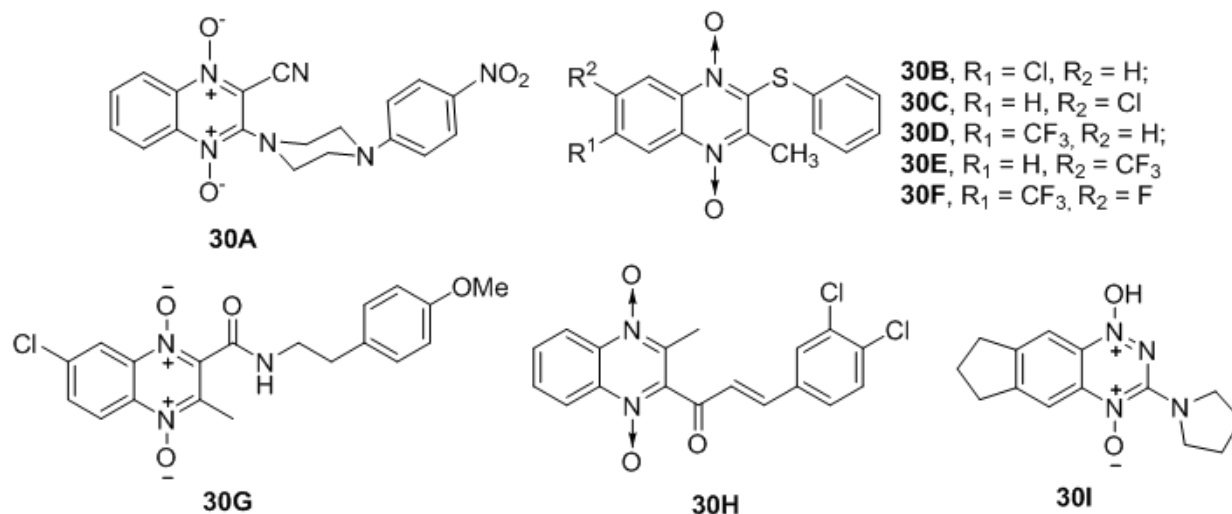


Figure 30: Structure of quinoxaline 1,4-dioxides

having IC_{50} and IC_{90} figures of 1.03 mM and 1.53 mM, respectively by affecting the respiration in rat liver mitochondria [190].

New lead compound **30I** from Benzotriazine Di-*N*-Oxides series has MIC 0.31 $\mu\text{g/mL}$ against H37Rv and cytotoxicity (CC_{50}) against Vero cells of 25 $\mu\text{g/mL}$. This was also negative in a L5178Y MOLY assay, indicating low potential for genetic toxicity [191].

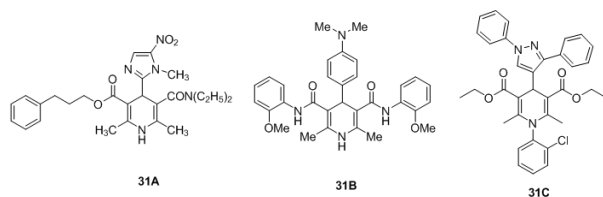


Figure 31: Structure of dihydropyridines

1,4-Dihydropyridines are the emerging class of antitubercular agent [192, 193]. Compound **31A** (fig 31) exhibits anti-tubercular activity with MIC 1 μM , *in vitro* screening. However no *in vivo* data is available [194]. 3D-QSAR study reveals new derivative of 1,4-dihydropyridines compound **31B** with antitubercular activity [195]. Recently compound **31C** was evaluated as potent antitubercular compound having MIC

0.02 $\mu\text{g/mL}$ and low toxicity [196].

10.13. Imidazopyridines and pyrazolo-tetraydropyridine

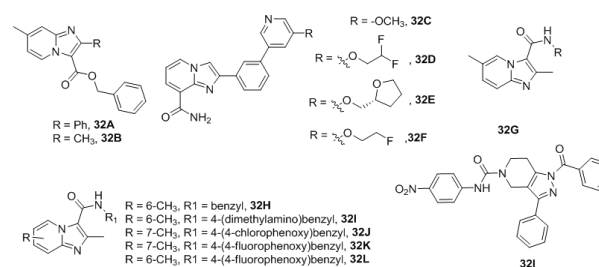


Figure 32: Structure of heterocyclic conjugated pyridines

Imidazopyridines were determined to have promising antitubercular activity against replicating *Mtb* H37Rv, compound **32A** and **32B** (fig 32) exhibited MIC value $<0.195 \mu\text{M}$ [197]. Antitubercular activity of imidazo-pyridine-8-carboxamides (figure 32) were evaluated by S. Ramachandran *et al.*, compounds **32C-32F** exhibited MIC value 0.5, 0.5, 0.25, and 0.25 $\mu\text{g/mL}$ respectively against *Mycobacterium tuberculosis* [198].

A series of 2,7-dimethylimidazo[1,2-a]

pyridine-3-carboxamides **32G** were evaluated for their *in vitro* anti-tuberculosis activity versus replicating, nonreplicating, multi- and extensive drug resistant *Mtb* strains. The MIC90 values of these compounds were $<1 \mu\text{M}$ against the various tuberculosis strains tested [199]. The minimum inhibitory concentrations of compounds (**32H-32L**) against replicating bacteria had MIC values $\leq 0.006 \mu\text{M}$. These results indicate that readily synthesized imidazo[1,2-a]pyridine-3-carboxamides (fig 32) are an exciting new class of potent anti-TB agents that merit additional development opportunities [200].

1-benzoyl-*N*-(4-nitrophenyl)-3-phenyl-6,7-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine-5(4*H*)-carboxamide (**32M**) was found to be active with IC50 of $21.8 \pm 0.8 \mu\text{M}$ against *Mtb* PS [201].

10.14. Galactopyranosyl amino alcohols

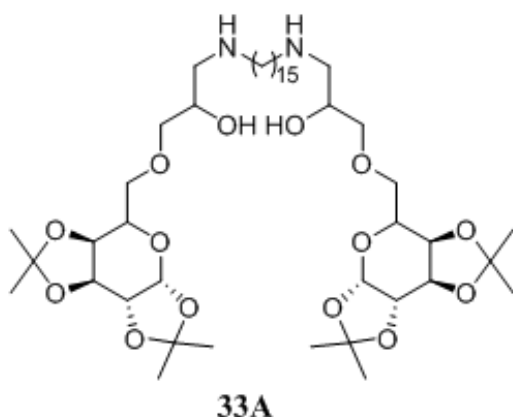


Figure 33: Structure of galactopyranosyl amino alcohol

A dimeric hybrid of a galactopyranosyl amino alcohol **33A** (Fig. 33) displayed potent *in vitro* activity with MIC $1.56 \mu\text{g/mL}$ against *Mtb*. However, on progression into a murine model, toxicity was observed at dosage levels (50 mg/kg per day) that offered no significant protection against *Mtb* infection. The target of this compound is mycobacterial cell wall biosynthesis [202].

10.15. Cyclopropylphenyl derivatives

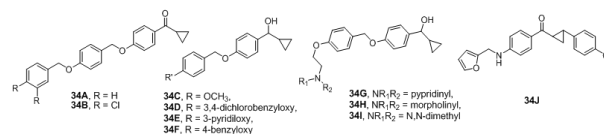


Figure 34: Structure of cyclopropylphenyl derivatives

In our group a series of cyclopropylphenylmethanone and cyclopropylphenylmethanol (Fig. 34) were synthesized and most of them possessed very good *in vitro* activity against both drug sensitive and drug resistant *M. tuberculosis* [203]. Compounds **34C**, **34E**, **34F**, **34H** and **34I** have shown minimum inhibitory concentration (MIC) $3.12 \mu\text{g/mL}$, while compounds **34A**, **34D** and **34B** exhibited MIC of 1.56, 1.56 and $0.78 \mu\text{g/mL}$ respectively. Compound **35G** showed 98 % killing of intracellular bacilli in mouse bone marrow derived macrophages and were active against MDR, XDR and rifampicin clinical isolates resistant strains with MIC $12.5 \mu\text{g/mL}$. Compound **34G** was orally active *in vivo* in mice against *M. tuberculosis* H37Rv with an increase in MST by 6 days with 1 log reduction in the bacillary density in lungs as compared to control on 30th day after infection [204]. A series of 4-alkylaminoaryl phenyl cyclopropyl methanones were also screened for their antitubercular activities against *Mtb* H37Rv. Compound **34J** exhibited *in vitro* antitubercular activities with MIC values $3.12 \mu\text{g/mL}$ [205].

10.16. Chromene, chromone, chroman and coumarin derivatives

The chromene, chromane and its analogue are reported to have antimycobacterial activity [206-207]. Oxadiazole-chromenes **35A**, **35B** (Fig. 35) exhibited *in vitro* activity with MIC $0.31 \mu\text{g/mL}$ and $0.73 \mu\text{g/mL}$ against *Mtb* H37Rv [208]. Recently 2,10-dihydro-4*aH*-chromeno[3,2-*c*]

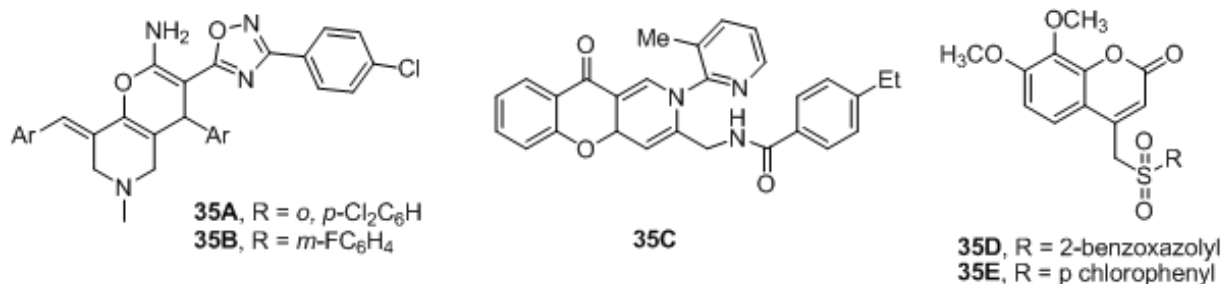


Figure 35: Structure of Chromene, chromone, chroman and coumarin derivatives

pyridin-3-yl derivatives were evaluated for their *in vitro* and *in vivo* activity against *Mtb* H37Rv and MDR-TB. Among them compound **35C** was found to be active *in vitro* with MIC's of 0.22 and 0.07 µg/mL against *Mtb* and MDR-TB respectively. During the *in vivo* study in animal model compound **35C** decreased the bacterial load in lung and spleen tissues with 1.11 and 2.94 log₁₀ protections at 25 mg/kg body wt. dose [209]. Arylsulfonylmethylcoumarin screened for *in vitro* anti-tubercular activity against *Mtb* H37Rv, compounds **35D** and **35E** showed MIC 0.78 µg/mL and 1.56 µg/mL respectively [210]. Phenyl substituted coumarins [211], and spirochromone conjugates [212] also displayed potent activity against tuberculosis.

10.17. Thiazoline, thiazole, benzothiazinone and dithiazolone analogues

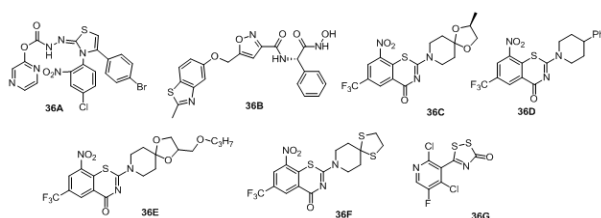


Figure 36: Structure of thiazolines, thiazoles and benzothiazinones

The antitubercular activity in thiazoline class of compounds (Fig 36) has been reported recently [213]. The most potent compound **36A** of this series showed MIC 0.3 µg/mL. A series of

potent 5-(2 methylbenzothiazol-5-yloxymethyl) isoxazole-3-carboxamide derivative **36B**, led to potent anti-TB activity with MIC value 1.4 µM against replicating *Mtb* H37Rv [214]. Several other thiazoles and benzothiazoles are reported as potent inhibitor of *M. tuberculosis* [215-217]. A. Cooper *et al* synthesized a series of benzothiazinones, **36C-36E** of this series showed MIC ≤ 0.015 µg/mL activities against MDR-TB with low toxicity [218]. Heterocycle substituted 1,3-benzothiazin-4-one derivative **36F** showed MIC of 0.0001 µM against *M. tuberculosis* H37Rv, 20-fold more potent than BTZ043 racemate [219, 220].

Compound **36G** dithiazol-3-one derivative was found to be active with a lowest MIC₉₀ value of 1 µg/mL [221].

10.18. Pyrrole and pyrrolotiazole

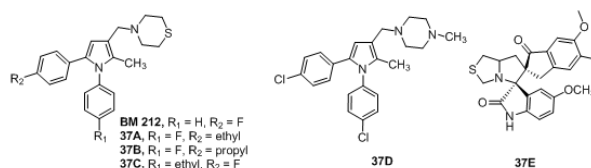


Figure 37: Structure of substituted pyrroles

Pyrrole derivative BM 212 is moderately active against *Mtb* (MIC = 0.7 to 6.2 µg/mL) and *M. avium* (MIC 0.4 to 3.1 µg/mL) [222]. It has recently been found that the thiomorpholine introduction in BM 212 molecule improved its antimycobacterial activity. Four compounds

37A, **37B**, **37C** and **37D** (Fig. 37) had MIC between 1 and 2 $\mu\text{g/mL}$ [223, 224]. Several derivatives have shown significant activities against drug-resistant tuberculosis *in vitro* and offer considerable protection in a rigorous mouse model of the disease [225]. Dispiropyrrrolothiazoles derivative **37E** showed antimycobacterial activity against *Mtb* H37Rv and INH resistant *Mtb* strains with MIC of 0.210 and 8.312 μM respectively [226].

10.19. Oxazole, Oxadiazole and Isoxazoline derivatives

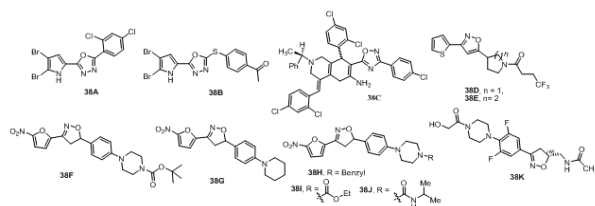


Figure 38: Structure of oxazole, oxadiazole and isoxazoline derivatives.

Several 2-(biphenyl-4-yl)oxazole-4-carboxylates possess good activity against *Mtb* with extremely low toxicity toward VERO cells and high therapeutic indexes [227]. Oxadiazoles **38A** and **38B** (fig 38) indicate inhibition of *Mtb* at concentrations 1.6 and 1.5 $\mu\text{g/mL}$ [228]. Compound **38C** showed *in vitro* anti-TB activity with MIC value 0.07 and 0.14 mM against *Mtb* and MDR-TB respectively [229]. Several oxazoles [230] and oxadiazoles are identified as potential candidate for the treatment of MDR and XDR tuberculosis [231, 232].

Nicolas Willand repoted thiophen-2-yl-1,2,4-oxadiazoles **38D**, **38E** as *EthR* inhibitors that boost antibacterial activity of ethionamide with nanomolar potency [233]. The anti-TB activity of isoxazoline linked nitrofurans compounds **38F-38J** was reported by Tangallapally *et al* [234]. Further Barbachyn *et al* have described very good *in vivo* efficacy in analogue of phenylisoxazoline **38K** with MIC as low as 0.5

$\mu\text{g/mL}$ [235].

10.20. Triazoles

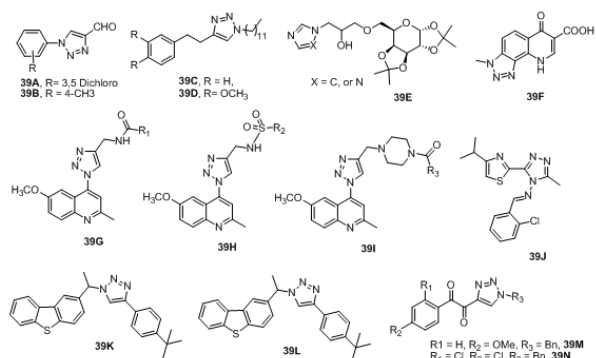


Figure 39: Structure of triazole derivatives

In our group several triazoles were synthesized and evaluated for their anti-tubercular activity against *Mtb* H37Rv (MIC 3.12 - 12.5 $\mu\text{g/mL}$) [236, 237]. *N*-substituted-phenyl-1,2,3-triazole-4-carbaldehydes **39A** and **39B** (Fig. 39) showed inhibition at MIC 2.50 $\mu\text{g/mL}$ [238]. M. Baltas *et al* evaluated triazoles as inhibitors of *InhA* as well as inhibitors of *Mtb* H37Rv. Compound **39C** and **39D** (Fig 39), were good inhibitors against *Mtb* with MIC 0.50 and 0.25 mg/mL, respectively [239]. Preliminary results of galactose-linked triazoles, exhibited MIC values in the range of 1.56-12.5 $\mu\text{g/mL}$ against *Mtb* H37Rv. Compound **39E** inhibited bacterial growth at MIC 1.56 $\mu\text{g/mL}$ [240]. A number of triazole and quinolone hybrids have been reported to possess anti-mycobacterial activity, compound **39F** showed MIC 0.5 $\mu\text{g/mL}$ against *Mtb* [241]. Three new series of quinoline-4-yl-1,2,3-triazoles carrying amides **39G**, sulphonamides **39H** and amidopiperazines **39I** possess MIC 1 $\mu\text{g/mL}$ against *Mtb* H37Rv [242]. 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole **39J**, exhibited promising activities against *Mtb* H37Rv strain [231]. 1,2,3-triazole-based *Mtb* inhibitors and tricyclic (carbazole, dibenzo[*b,d*]furan, and dibenzo[*b,d*]thiophene) were integrated in one molecular platform to prepare various novel clubbed 1,2,3-triazole

hybrids as potential inhibitors of *Mtb* H37Rv. Two of them **39K** and **39L** inhibit the *Mtb* at MIC 0.78 $\mu\text{g/mL}$ [243].

α -ketotriazole and α,β -diketotriazole derivatives were evaluated for antitubercular and cytotoxic activities. Among them, two α,β -diketotriazole compounds, **39M** and **39N**, exhibited good activities (MIC = 2.5 $\mu\text{g/mL}$) against *M. tuberculosis* and MDR-TB strains and presented no cytotoxicity (IC₅₀ > 50 mM) on colorectal cancer HCT116 and normal fibroblast GM637H cell lines [244].

10.21. Imizazoles, pyrazoles and pyrazolones

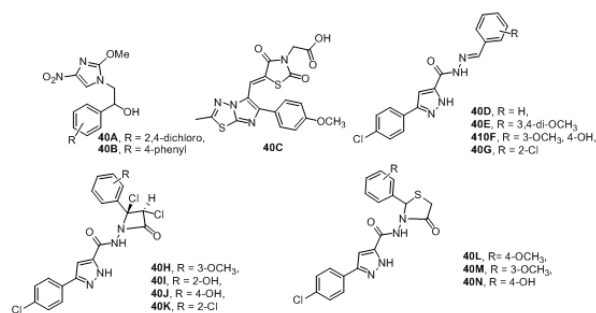


Figure 40: Structure of imidazole and pyrazole derivatives

Several nitroimidazoles were reported as potent antitubercular agents [245]. MIC of **40A** turned out to be 0.5 $\mu\text{g/mL}$ and compound **40B** showed activity as good as PA-824 against non-replicating *Mtb* [246]. New class of 2-(trifluoromethyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole derivative **40C** has MIC 1.56 $\mu\text{g/mL}$ against *Mtb* H37Rv. Most compounds from the series exhibited activity within range of MIC 3.12-1.56 $\mu\text{g/mL}$ [247]. Ring substituted imidazoles are the emerging class of antitubercular agents [248-251].

A series of 3-(4-chlorophenyl)-4-substituted pyrazoles were tested for antitubercular activity *in vitro* against *Mtb* H37Rv strain using the BACTEC460 radiometric system, 2-azetidinones

and 4-thiazolidinones bearing a core pyrazole scaffold, **40D-40N** (Figure 40) exhibited MIC 0.85, 0.37, 0.55, 0.36, 0.6, 0.5, 0.36, 0.55, 0.65, 0.65 and 0.39 $\mu\text{g/mL}$ respectively against *Mtb* [252]. Different analogues of 1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl] methylamino)-1,2-dihydro-3H-pyrazol-3-one was also found active against *M.tb* H37Rv and isoniazid resistant *Mtb* [253]. 4-[(2,4-dichlorophenyl)(2-hydroxy-1-naphthyl) methyl]-2-(4-fluorophenyl)-5-methyl-2,3-dihydro-1H-3-pyrazolone displayed the maximum potency with a minimum inhibitory concentration of 1.6 μM against *Mtb* [254].

10.22. Dihydroimidazo-oxazines analogues

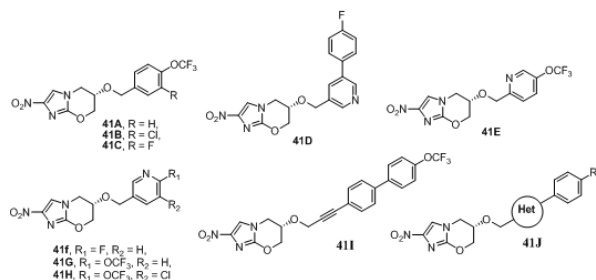


Figure 41: Structure of dihydroimidazo-oxazines analogues

Biphenyl analogues of PA-824 were evaluated for their efficacy in a mouse model of acute *Mtb* infection. Three compounds **41A**, **41B**, **41C** (Fig 41) bearing combinations of lipophilic, electron-withdrawing groups achieved >200-fold higher efficacies than the parent drug [255]. Heterocyclic analogues of PA-824 compounds **41D**, **41E**, **41F**, **41G**, **41H** (MIC 0.31, 0.065, 0.06, 0.05, 0.017 $\mu\text{g/mL}$ respectively) were >100-fold better than PA-824 in a mouse model of acute *Mtb* infection, and two orally bioavailable were superior to anti-TB drug OPC-67683 in a chronic infection model [256]. Different analogues of PA-824 were prepared by replacing OCH_2 with amine, [257] amide, carbamates and urea functionality and investigated their improved efficacy

against *Mtb* [258]. Extension of OCH_2 linkers (propenyloxy, propynyloxy, and pentynyloxy) provided greater potencies against replicating *Mtb*. One propynyloxy-linked compound **41I** displayed 89-fold higher efficacy than PA-824 in the acute model [259]. 1-Methylpyrazole, 1,3-linked-pyrazole, 2,4-linked-triazole, and tetrazole bearing compound **41J**, analogues of PA-824 had 3- to 7-fold higher MIC potencies than parent molecule against replicating *Mtb* [260].

10.23. Phenyl butenyl and phenyl cyclopropyl methyl azoles

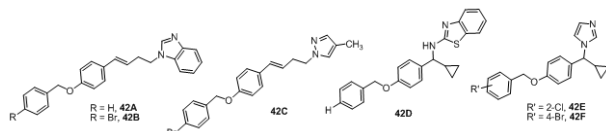


Figure 42: Structure of phenyl butenyl and phenyl cyclopropyl methyl azoles

In our group a series of 1-[(4-benzyloxyphenyl)-but-3-enyl]-1*H*-azoles has been identified as potent antitubercular agents against *M. tuberculosis*. Compounds **42A**, **42B**, and **42C** (fig 42) exhibited significant antitubercular activities with MIC value as low as 1.56, 1.56, and 0.61 $\mu\text{g/mL}$, respectively. Cyclopropyl methyl azoles, **42D-42F** inhibited the bacterial growth at MIC 2.41, 3.12 and 3.12 $\mu\text{g/mL}$ respectively [261].

10.24. Quinolines

Several quinoline derivatives were reported with significant antitubercular activity [262-269]. 4-Quinolylhydrazone **43A** the structural hybrids of isoniazid and quinolones (Fig. 43) showed antitubercular activity with MIC 0.78 $\mu\text{g/mL}$ but poor selectivity for mycobacteria. Several quinolinequinone, 6-amino-7-chloro-5,8-quinolinequinone **43B** and 6-amino-7-methane sulfinyl-5,8-quinolinequinone **43C**

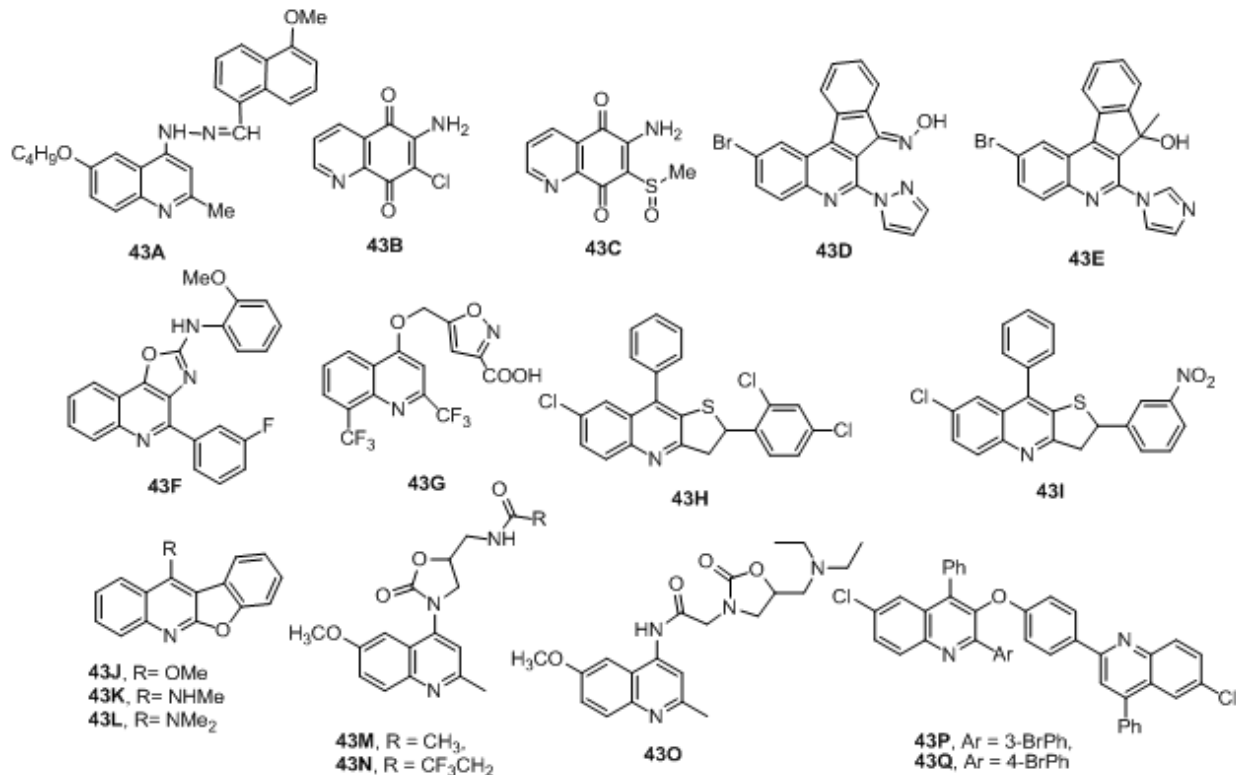


Figure 43: Structure of quinoline derivatives

exhibited MIC's (1.56 and 3.13 $\mu\text{g/mL}$) for the 100 % growth inhibition of *M. bovis* BCG [270]. The efficacies of indeno [2,1-*c*] quinolines were evaluated *in vitro* using the BACTEC radiometric assay and compounds shows 85-99 % growth inhibition of *Mtb*. Compounds **43D** and **43E** (fig 43) showed MIC, 0.39 and 0.78 $\mu\text{g/mL}$ respectively [271]. Fused oxazoloquinoline **43F** exhibited 99 % bacterial growth inhibition and MIC, 1 $\mu\text{g/mL}$ against *Mtb* H37Rv [272]. Another hybrid of isooxazole and quinoline **43G** is reported to have excellent anti-TB activity against both replicating and non-replicating *Mtb*, with MIC 0.9 μM [273]. A series of quinoline derivatives *viz.* hydrazones, ureas, thioureas and pyrazoles were evaluated for their *Mtb* H37Rv and MDR-TB [274, 275].

The lead compound 2,9-diaryl-2,3-dihydrothieno[3,2-*b*]quinolines (**43H** and **43I**) displayed MIC 0.90 and 0.95 μM against *Mtb* and MDR-TB [276]. A series of 11-alkoxylated and 11-aminated benzofuro[2,3-*b*]quinoline derivatives **43J**, **43K** and **43L** (Fig. 43) exhibited significant activities against the growth of *Mtb* (MIC values of <0.20 $\mu\text{g/mL}$) and low cytotoxicities against VERO cell with IC₅₀ values of 11.77, 5.55, and >30.00 $\mu\text{g/mL}$ respectively [277]. Compounds **43M**, **43N** and **43O** have MIC 0.65 $\mu\text{g/mL}$ against *M. tuberculosis* H37Rv strain [278]. Phenoxy linked bisquinoline derivatives **43P** and **43Q** have MIC 1.1 and 2.2 μM respectively against *Mtb* and no *in vivo* cytotoxic effects against mouse fibroblasts (NIH 3T3) [279].

10.25. Tetrahydroindazole, Indolecarboxamide and indenone derivatives

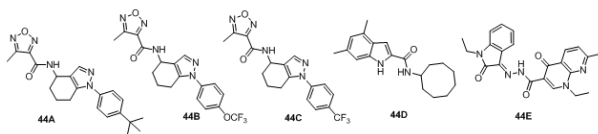


Figure 44: Structure of tetrahydroindazole, indolecarboxamide and indenone
A class of tetrahydroindazole (Fig. 44) based

compounds are reported as potent and unique inhibitors of *Mtb*. Compounds **44A**, **44B** and **44C** exhibited MICs of 1.7, 1.9, and 1.9 μM respectively against *Mtb* [280]. Indole-2-carboxamide analogue, **44D** showed potent antitubercular activities against actively replicating *M. tuberculosis*, with MIC values 0.013 μM . Compound **44E** was found to be active against the tested XDR-TB strains and orally active in the serum inhibition titration assay [281]. A series of 2-(arylmethylene)-2,3-dihydro-1*H*-inden-1-ones were screened for their *in vitro* activity against *Mtb* H37Rv, Compound **44F** displayed MIC at 2.8 μM against *Mtb* [282]. A library of trans 6-methoxy-1,1-dimethyl-2-phenyl-3-aryl-2,3-dihydro-1*H*-inden-4-yloxy alkyl amines exhibited MIC between 1.56 and 6.25 $\mu\text{g/mL}$ against drug sensitive and multidrug resistant strains of *Mtb* [283].

10.26. Benzimidazoles

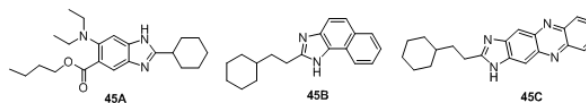


Figure 45: Structure of benzimidazole derivatives

Libraries of trisubstituted benzimidazoles were created through rational drug design. A number of benzimidazoles exhibited promising MIC values in the range of 0.5-6 $\mu\text{g/mL}$, against *Mtb* H37Rv strain (one of them compound **45A**, has MIC 0.5 μM , figure 46) [284]. Compounds **45B** and **45C** bearing benzimidazole ring showed the potent tuberculostatic activity against *Mtb* with MIC of 1.56 and 3.1 $\mu\text{g/mL}$ [285].

10.27. Nitrofuran and benzofuran

Several 4-(5-nitro furan-2-yl) prop-2-en-1-one derivatives, exhibited antitubercular activity against *Mtb* H37Rv with MIC < 5 $\mu\text{g/mL}$ and low toxicity. Compound **46A** (fig 46) was

evaluated as potent anti-TB with MIC 0.19 $\mu\text{g/mL}$ and selective index $\text{MIC}_{99}/\text{CC}_{55} > 1800$ [286].

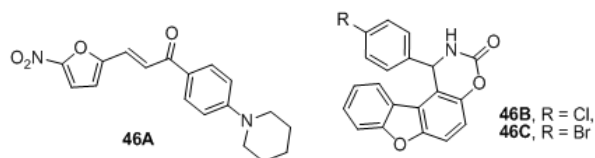


Figure 46: Structure of furan and benzofuran derivatives

A new class of benzofuro-oxazines, 1-(4-chlorophenyl)-1*H*-benzo[2,3]benzofuro[4,5-*e*][1,3]oxazin-3(2*H*)-one **46B** and 1-(4-bromophenyl)-1*H*-benzo[2,3]benzofuro[4,5-*e*][1,3]oxazin-3(2*H*)-one **46C** (Fig 46) displayed same MIC 1.56 $\mu\text{g/mL}$ against *Mtb* [287].

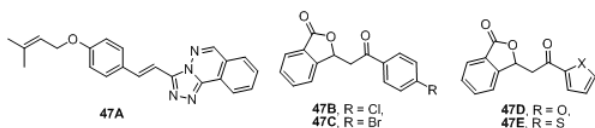


Figure 47: Structure of triazolophthalazine and 3-aracylphthalide derivatives

Compound **47A**, 4-isopentenylloxycinnamyl triazolophthalazine derivative, was found to be 100-1800 times more active than isoniazid (INH) when tested for its ability to inhibit the growth of INH-resistant *Mtb* strains. It does not interfere with mycolic acid biosynthesis, thereby pointing to a different mode of action and representing an attractive lead compound for the development of new anti-TB agents [288].

3-Aracylphthalides (Fig. 47) were synthesized and were subjected to *in vitro* anti-TB screening against *Mtb* H37Ra. Among the phthalides **47B**, **47C**, **47D** and **47E** exhibited half maximal inhibitory concentration (IC_{50}) in the range of 0.97, 0.93, 0.81 and 1.24 $\mu\text{g/mL}$ respectively [289].

10.29. Tryptanthrin

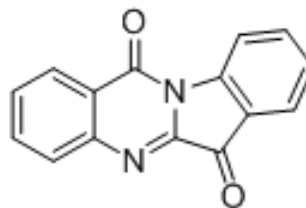


Figure 48: Structure of tryptanthrin

Tryptanthrin is indolo-quinazolinone alkaloid (Fig. 48) and active against MDR-TB with MIC 0.5-1.0 $\mu\text{g/mL}$. *In vitro* toxicity and *in vivo* studies are needed before this structural prototype is applied as antitubercular [290].

10.30. 13-*n*-Octylberberine derivatives

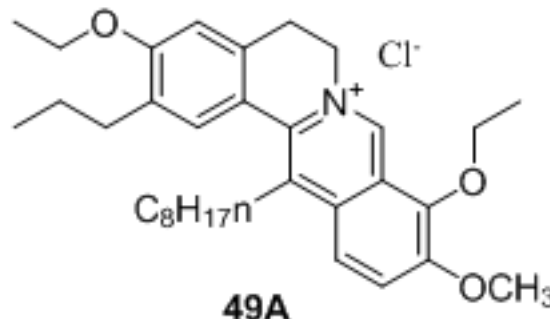


Figure 49: Structure of 13-*n*-octylberberine

A series of 13-*n*-octylberberine derivatives were synthesized and evaluated for their anti-TB activity. Among these, compound **49A** (Fig. 49) was the most effective anti-TB with a MIC value of 0.125 $\mu\text{g/mL}$, and also exhibited more potent effect against rifampicin (RIF)- and isoniazid (INH)-resistant *Mtb* strains than both RIF and INH, suggesting a new mechanism of action [291].

In our group a series of 9-substituted tetrahydroacridines were synthesized and evaluated against *Mtb* H37Rv and H37Ra strains, which exhibited potent activities with MIC 6.25-0.78 $\mu\text{g/mL}$. Comp **50** (Fig 50) was

found to be most active (MIC 0.78 $\mu\text{g/mL}$ against *Mtb* H37 Rv) [292].

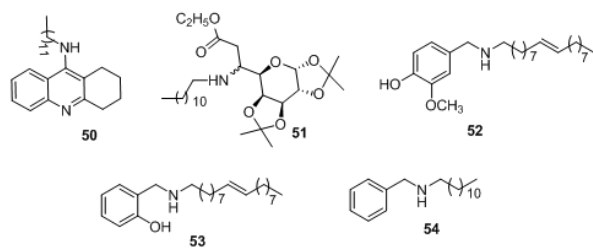


Figure 50: Structure of antitubercular agent

Glycosyl β -amino esters [293] and glysylated amino-alcohols [294] were evaluated for their antitubercular activity against *Mtb* H37Ra and H37Rv. Compound **52** showed MIC 3.12 $\mu\text{g/mL}$ against both *Mtb* H37 Rv and H37Ra strains [293].

Benzyl- and pyridylmethyl amines, compound **53**, **54** and **55** exhibited MIC 1.56 $\mu\text{g/mL}$ against *Mtb*. Some of them were also evaluated against clinical isolates of MDR-TB and found to be active with MIC 3.12 $\mu\text{g/mL}$ (Fig 1.51) [295]. α, α' -(*EE*)-bis(benzylidene)-cycloalkanones displayed moderate antitubercular activity with MIC 12.5-1.56 $\mu\text{g/mL}$ [296].

The potent *in vitro* and moderate *in vivo* antitubercular activities thiadiazine thiones have been reported against *M. tuberculosis* H37Rv even in resistant strains and also protected mice marginally in experimental TB [297].

6-Oxo and 6-thio analogue of purin [298] and carboxylic uracil derivatives [299] showed good inhibitory activity against *Mtb*.

4-Oxo-4-chlorophenylbutenoyl methyl ester has MIC of 0.6 and 1.5 $\mu\text{g/mL}$ against replicating and non-replicating *M. tuberculosis*, respectively, it penetrates the cell where it is hydrolyzed and reacts with CoA to generate the active antibacterial [300]. Recently piperazine derivatives [301a], Pyrrolodiquinolines and vermehotin [301b], 1*H*-benzo[*d*]imidazole

derivatives [301c], Bi(III), Fe(III) and Ga(III) complexes of pyridine-2-thiolato-1-oxide [301d], asymmetrical *N,N*-bis(alkanol)amine aryl esters [301e], benzonitrile/nicotinonitrile based s-triazines [301f], substitutedpiperazinyl phenanthridine [301g], acridine and fused-quinoline derivatives [301h], quinoline-aminopiperidine hybrid [301i], and benzo[*d*]oxazol-2(3*H*)-ones derivatives [301j] are reported with potent antitubercular activity.

11. Novel drug delivery approach

To optimize the delivery system for drug administration, various techniques are under investigation. Two new methods are being used simultaneously.

One of the most promising approaches is the use of nanoparticles [302, 303]. Nanoparticles in particular have emerged as a remarkably useful tool for this purpose due to their high stability, feasibility of incorporation of both hydrophilic and hydrophobic substances, and ease of oral and inhalational administration in addition to parenteral administration. Treatment of *M. tuberculosis* infected mice with the nanoparticles bound drugs resulted in complete bacterial clearance from the organs. Free drugs produce bacterial clearance only after daily administration of 46 doses [304]. Nanoparticles may also be useful for targeted therapies aiming to deliver drugs selectively to intracellular sites, such as those within monocytes, macrophages or the reticuloendothelial system, where dormant persistent organisms responsible for lengthy treatment periods may be lodging [305-309]. Although liposomal formulations have also been considered for similarly novel delivery systems of TB drugs, the potential flexibility with nanoparticles appears much greater than for liposome-encapsulated drugs.

Dry powder inhalers and nebulizers are another approach being tested [310, 311]. Dry porous particle aerosols of PA-824 have been tested

in low and high (eight-fold higher than the oral dose) dosages and compared with oral administration of PA-824 for treatment of tuberculosis in guinea pigs. The results show a lower degree of inflammation and tissue damage, suggesting a potential role for these inhalational agents in the treatment of tuberculosis [312].

Capreomycin, second line drug is being tested in human volunteers in a Phase I study as an inhalational product. The formulation being used with capreomycin is large porous particles [313]. Many of the other commonly used first-line drugs, as well as some investigational agents, have also been formulated and tested in an inhalational delivery system. Inhalational approaches deliver much higher doses of drug to the lung, but the exact histological localization of increased delivery is not clear.

Conclusions:

In recent years, the R&D programs to control TB, an extensive studies are made to enhance the anti- TB activity of new drugs particularly against resistant mycobacterium strains. These advances in TB drug research and development are encouraging, but new drugs are needed that have strong, synergistic and complementary activities against various M. tuberculosis subpopulations in order to shorten TB treatment, be effective against MDRTB/XDR-TB, and be easily administered in conjunction with HIV.

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