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Chapter

Study of Various Chemically and Structurally Diverse Currently Clinically Used and Recently Developed Antimycobacterial Drugs

Saad Alghamdi and Mohammad Asif

Abstract

Infectious diseases originate from pathogens and increased severely in current years. Despite numerous important advances in antimicrobial therapy, the extensive use and misuse of these antimicrobial drugs have caused the emergence of microbial resistance, which is a serious risk to public health. In particular, the emergence of multidrug-resistant pathogens has become a serious difficulty in the therapy of pathogenic diseases. Therefore, the progress of novel drugs to deal with resistant pathogens has become one of the most essential areas of antimicrobial research today. In addition to the development of novel and efficient antimicrobial agents against multidrug-resistant pathogens, recent attention has focused on the treatment of tuberculosis. Therefore, recent developments have been directed towards examining currently used and newly developed antimycobacterial drugs and their toxicities and mechanism of action.

Keywords: Chemotherapy, epidemiology, tuberculosis, multidrug-resistant, Mycobacterium

1. Introduction

Tuberculosis (TB) is a chronic infectious and zoonotic disease caused by the *Mycobacterium tuberculosis* (*Mtb*) complex. It is responsible for a lung infection (pulmonary TB) and other body parts (extrapulmonary TB) [1, 2]. TB is the second cause of death next to human immunodeficiency virus (HIV) infection. TB is a global public health disaster since 1993 at a time of expected 7–8 million cases and 1.3–1.6 million deaths occurred yearly. In 2010, 8.8 million new cases of TB and 1.1 million deaths from TB, and 0.35 million deaths from that HIV-allied TB and worsen due to the maturity of anti-TB drug resistance (DR) [3]. The emergence of resistance against anti-TB drugs is a barrier to the success of TB treatment. Inadequate TB treatment is responsible for the incident of DR-TB [4]. According to the World health organization (WHO) report, TB has spread to every area of the world. As much as one-third of the world's population is presently infected, more than any other infectious microbial disease [5]. These numbers however are only a partial

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representation of the world TB threat. It was predictable that nearly 1 billion more people will be infected with TB in the coming 20 years. However, the number of new TB cases is still growing slowly, 95% occur in developing nations every year, and about one million young women per year are offended with this infectious disease in the developing world. The occurrence of TB is associated with a dense population, deprived sanitation, and, poor diet [6]. Directly observed treatment, short-course (DOTS), is the effective way of the control of TB. The three main anti-TB drugs, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) are used. These drugs are hepatotoxic and may cause drug-related hepatitis. Despite the success of the DOTS therapy, the appearance of MDR-TB strains, persistently isolated from the sputum of pateints, darkens the future [7]. The expansion in TB incidence during current years is primarily due to the incidence of TB in synergy with the HIV pandemic, which increases the risk of growing the new TB cases were attributable to HIV co-infection, and as well as the emergence of MDR-TB strains [8, 9]. Therefore, the objective of this paper is to review the current status of antimycobacterial drugs.

2. Etiology and routes of transmission

Tuberculosis (TB) is caused by the *Mtb* complex. The mycobacterium is non-motile, Gram-positive, rod-shaped, obligate aerobic bacteria that belong to the order Actinomycetales and family Mycobacteriaceae. This *Mtb* complex includes (subspecies *M. canetti*), *M. bovis*, *M. microti, M. africanum*, *M. caprae*, *M. bovis* BCG, and *M. pinnipedii* [10]. The cough in a TB patient is caused by the infection of *Mtb* and distributed to air during coughing. The healthy persons who inhaled air droplets of TB infected person and make contact become infected [11].

Tuberculosis-HIV Combination:

The current opinion disclosed that one-third of the 42 million people living with HIV/AIDS all around the world are co-infected with TB. As per the WHO report, about 90% of the patients containing both TB and HIV died within only some months after clinical indications have arisen. Thus, WHO warned the world of the "even bigger TB-HIV crisis" and explained for extensive accessibility of free anti-TB drugs to individuals living with HIV. The HIV cases are spreading quickly in India with the biggest number of TB cases all around the world [12–15].

3. Chemotherapy of tuberculosis

First-line anti-TB drugs:

Treatment of TB is mainly dependent on first-line anti-TB drugs (**Figure 1**), which comprises SM, INH, RMP, EMB, and PZA, these are more effective and less toxic effects as compare to second-line anti-TB drugs [15].

Second-line anti-TB drugs:

According to the WHO, there are six drugs of second-line anti-TB drugs. These drugs are categorized as second-line anti-TB drugs due to one of two potential reasons: 1) they are less active than the first-line anti-TB drugs or more toxic side-effects or 2). These drugs involve different classes namely, aminoglycosides (**Figure 1**): (kanamycin, amikacin), polypeptide analogs (**Figure 2**): (viomycin, capreomycin), FQs (**Figure 3**): (CPX, MXF, OFX, etc), thioamides: (prothioamide, ethionamides), cycloserine and para-aminosalicylic acid (**Figure 4**) [2–4].

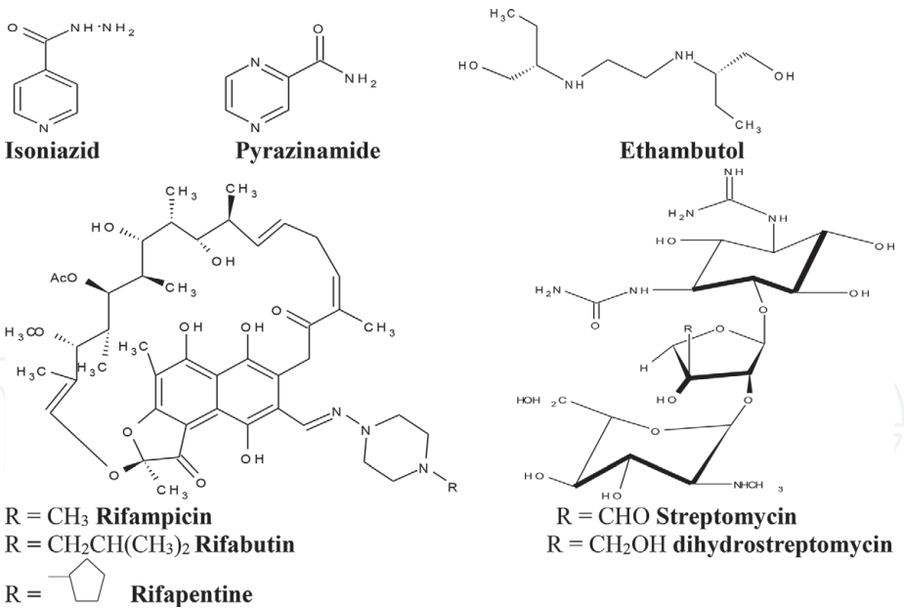


Figure 1.
Structures of first-line anti-TB drugs.

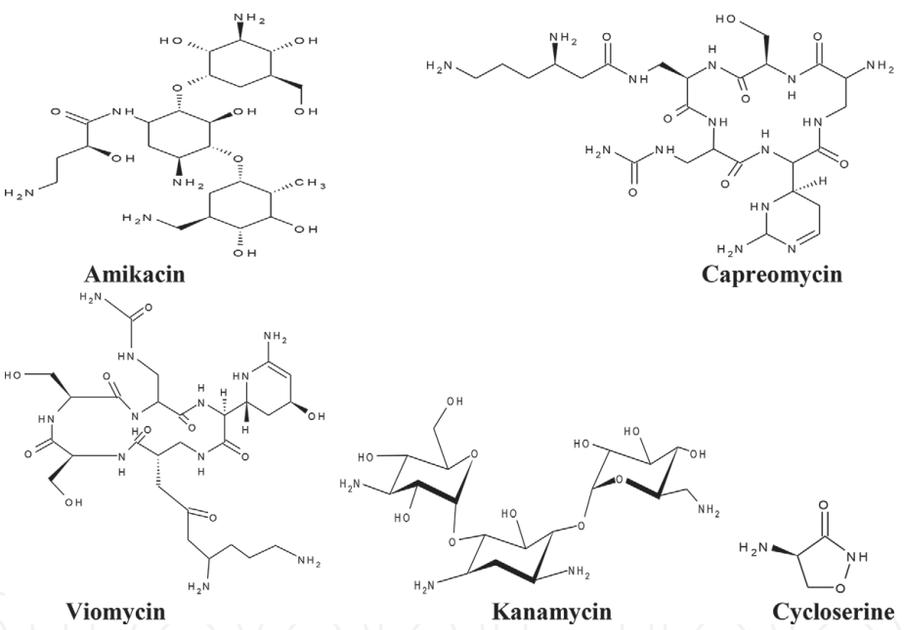


Figure 2.
Structures of different antibiotics (second-line drugs).

Drugs for HIV/TB

Clarithromycin (**Figure 5**) is a macrolide antibiotic drug used in HIV infected TB patients to cure the *M. avium* complex (MAC). It has an analogous of erythromycin but is more efficient against certain Gram-negative bacteria, mainly *Legionella pneumophila*. Thioacetazone (**Figure 5**) is valuable in stopping resistance to more influential drugs like INH and RIF. It is not at all used on its own to treat TB. It uses is declining because it can originate severe skin reactions in HIV positive patients. It is also identified to kill MDR-TB. It is no longer suggested for treatment due to its adverse effects like urination-difficulties, dry mouth, glaucoma, and postural hypotension. The circumstances are further complex by the emergence of MDR-TB and XDR-TB by infections with lethal synergy with HIV/AIDS [4, 15].

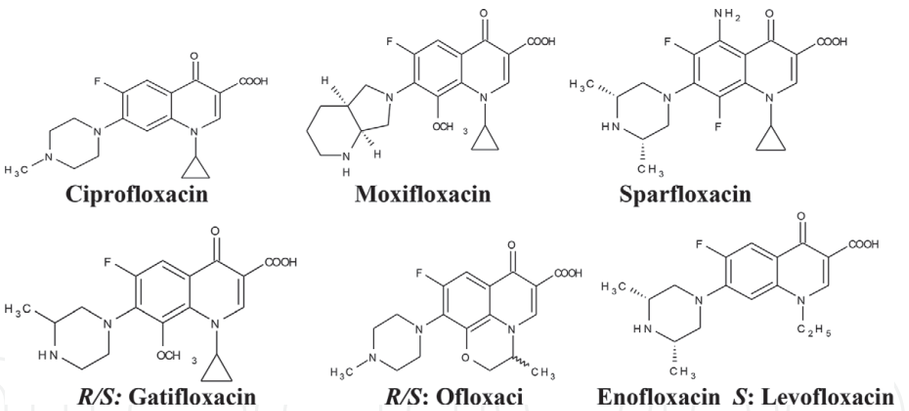


Figure 3.
Structures of different fluoroquinolones (second-line anti-TB drugs).

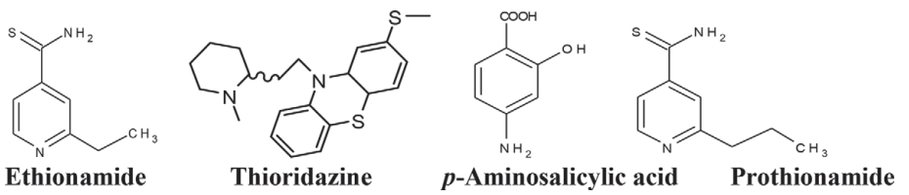


Figure 4.
Structures of different second-line anti-TB drugs.

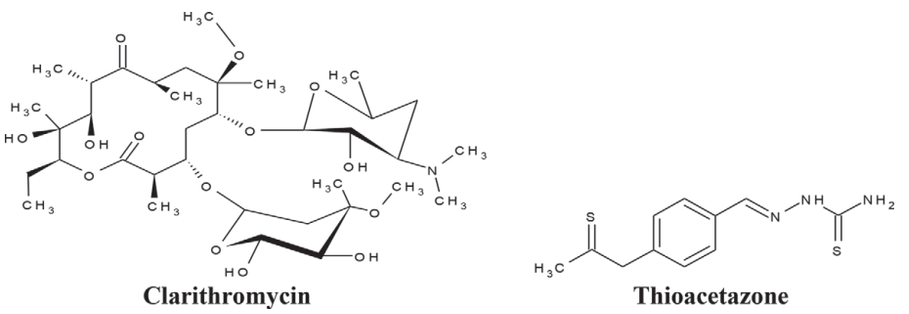


Figure 5.
Structures of drugs for HIV/TB.

4. Properties and mechanism of currently used common anti-TB drugs

4.1 Primary agents

Isoniazid (Nydrazid, Laniazid)

It is a bacteriostatic drug against resting cells and bactericidal against dividing microorganisms. Isoniazid (INH) is an anti-TB drug since 1952 and acts as a bactericidal and bacteriostatic for rapidly and slowly growing bacilli. It diffuses across the *Mtb* cell membrane [16]. The INH targets KatG and inhA gene. KatG gene encodes catalase/peroxidase enzyme that activates prodrug and peroxynitrite that are involved in pathways of reactive nitrogen and oxygen intermediates [17, 18]. InhA gene encodes NADH dependent enoyl-Acyl Carrier Protein (ACP)-reductase that causes inhibition of mycolic acid synthesis [19, 20]. The INH is a close to ideal antibiotic and very selective (MIC value ~0.025–0.05 μg/mL and other bacteria MIC vale >500 μg/mL). The INH has good oral availability and low toxicity. It Inhibits mycolic acid biosynthesis and targets the enoyl-acyl carrier protein reductase enzyme (InhA) engaged in mycolic acid synthesis. The INH inactivation of

IhhA needs metabolic activation. It is also utilized in combinations, INH and RIF and INH, RIF, and PZA.

Rifampicin

Rifampicin (RIF) was isolated from *Streptomyces mediterranei* from the soil sample and used as an anti-TB since 1972 [21]. It is still utilized as the best choice of anti-TB drugs. RIF diffuses across *Mtb* cell membrane due its lipophilic nature. RIF inhibits the mycobacterial transcription by binds to the β-subunit of DNA-dependent-RNA polymerase [22–24].

Rifamycins

Rifamycins are natural products from *Amicolaptosis mediterranei* belong ansamycin family and are. These are active towards various bacteria but used almost exclusively against TB [2–4].

Rifampin (Rifadin)

Rifampin is a semisynthetic analog of rifamycin and the most effective anti-TB agent with MIC values as low as 0.005 μg/mL. It is used as an oral or parenteral formulation, it can access CNS and it is sensitive to moisture [2–4].

Rifapentine (Priftin)

Rifapentine is a cyclopentyl analog of RIF. The benefit over rifampin is less repeated dosing. It inhibits bacterial DNA-dependent RNA polymerase and binds to the β subunit. The RIFs blocks the elongation of the RNA transcript and inhibits gene expression. It also acts as a CYP450 inducer. One remarkable side effect is the discoloration of body fluids. The RIFs are not suggested for use in HIV infected patients. Two RIF analogs are existing for indications other than TB [2–4].

a. **Rifabutin** (Mycobutin): It is used mostly in MAC infections [2–4].

b. **Rifaximin** (Xifaxan): Indicated for the treatment of traveler's diarrhea [2–4].

Ethambutol (Myambutol):

Ethambutol (EMB) is a bacteriostatic, active against growing bacilli, and used as an anti-TB drug in 1966. It obstructs polymerization of cell wall component lipoarabinomannan and arabinogalactan that interrupted biosynthesis of darabinofuranosyl-P-decaprenol and produced bacteriostatic effect [25, 26]. EMB (+) isomer is orally active, 16 times more potent than meso isomer, and 200 times more potent than (−) isomer. The EMB inhibits the polymerization of cell wall arabinan and results in the addition of the lipid carrier deca-prenol phosphoarabinose. The EMB interferes with the transfer of arabinose to the cell wall acceptors. EMB is effective only towards energetically dividing cells and its action is synergistic with RIF. Arabinosyl transferase enzyme is a target for the action of EMB in both *Mtbs* and *M. avium*. The enzyme is encoded by the embCAB gene organized as an operon and engaged in the arabinogalactan synthesis [27, 28].

Pyrazinamide (Aldinamide)

Pyrazinamide (PZA) is a pyrazine derivative of nicotinamide and its mechanism is assumed to be analogous to INH. It has to be metabolically activated and PZA-resistant strains of *Mtb* contain a mutation in the hydrolase gene. PZA activity against *Mtb* depends on the anaerobic and acidic conditions. PZA is activated to pyrazine acid by the pyrazinamide/nicotinamidase that encoded by gene pncA [29]. Acidic condition favors the production of protonated pyrazinoic acid that collected in the *Mtb* cell membrane which interrupts cell membrane potential and altered membrane transport [30]. The new target of PZA', clpC1 (Rv3596c) that encodes an ATP-dependent ATPase is liable for protein degradation by the complex structure with protease clpP1 and clpP2 [31, 32].

Streptomycin

Streptomycin (STR) is the first antibiotic cure for TB and it is isolated from the soil microbe *Streptomyces griseus* in 1943 [1]. It is active against growing bacilli, but not active against intracellular and non-growing bacilli. STR is still considered a first-line anti-TB drug but is used less frequently than the other drugs. It has no action against *M. avium*. Resistance is frequently due to phosphorylation. It targets both rpsl and rrs genes that encode 30S ribosomal protein S12 and 16S rRNA, respectively, and finally inhibit the instigation of the translation in the protein synthesis [33, 34].

Secondary/Retreatment Agents:

Aminosalicylic Acid (P.A.S. Parasal):

Para-aminosalicylic acid (PAS) is an oral drug that fell out of use because of adverse effects and frequent resistance. Related to sulfonamides, it is bacteriostatic and acts as a competitive inhibitor of mycobacterial dihydropteroate synthase. There are two mechanisms to produce the desired effect. First, it inhibited folic acid synthesis by the inhibiton of dihydrofolate synthase and dihydropteroate synthase that produces hydroxyl dihydrofolate antimetabolite responsible for the folic acid synthesis [35]. Secondly, it reduced the uptake of iron, that is essential for cell wall component mycobactin synthesis [15].

Ethionamide (Trecator SC):

Ethionamide (ETH) is developed as a derivative of INH but less potent than INH. Two genes play a role in the mechanism of actions ETH is ethA and inhA. EthA is regulated by the transcriptional repressor ETH [36]. The mechanism of action is like INH. The oxidative activation comes into sight it is by an enzyme other than KatG projected to form a covalent connection with InhA. The mechanism of action of the ETH is a disruption of mycolic acid synthesis by which monooxygenase enzyme activated ETH that binds to NAD+ and forms an adduct which inhibits enoyl acyl-ACP reductase enzyme [37–39] (**Figure 6**).

Cycloserine (Seromycin):

Cycloserine (CYS) is a natural compound and restricted to being retreatment because of CNS toxicity. CYS is a cyclic derivative of serine hydroxamic acid and terizidone. It is isolated from *Streptomyces orchidaceous* in the 1950s. Its acts by interrupting mycobacterial cell wall synthesis by inhibition of L-alanine racemase encoded by alrA that forms D-alanine from L-alanine and D-phenylalanine synthetase crucial for the production of peptidoglycan and cell wall synthesis by the inclusion of Dalanine into pentapeptide [40, 41]. It inhibits peptidoglycan formation, particularly-blocks the alteration of L-Ala to D-Ala.

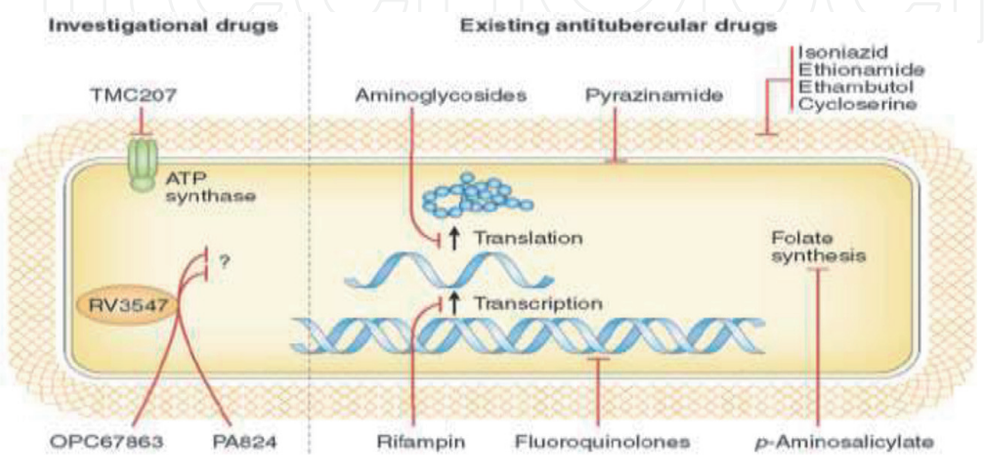


Figure 6.
Presently used anti-TB drugs and sites of action.

Fluoroquinolones (FQs) are the derivative of chloroquine in the 1960s and were used as bactericidal in human and veterinary medicines [42]. The FQs are acted by blocking of mycobacterial DNA replication by binding to α and β subunits of DNA gyrase (gyrA and gyrB), which catalyze the supercoiling of DNA and finally, inhibits DNA synthesis [43].

Aminoglycosides and polypeptides

The aminoglycosides (amikacin, kanamycin) and polypeptides (capreomycin, viomyocin) act by inhibiting protein synthesis. Kanamycin and amikacin alter 16S rRNA and capreomycin and viomycin interfere with small and large subunits of the 70S ribosome [44, 45].

Capreomycin (Capastat)

Capreomycin belongs to the tuberactinomycin family, a highly basic cyclic pentapeptide with a sixth amino acid side chain. It is the most active compound of this family and blocks protein synthesis and interferes with initiation tRNA selection and chain elongation. It binds to a site on 16S rRNA and the 23S rRNA. Some mycobacterium resistant to capreomycin is also resistant to kanamycin [2–4].

Kanamycin

The most commonly used second-line aminoglycoside and only given by intramuscular (IM) administration [14, 15].

Linezolid

Linezolid is an oxazolidinone derivative that interrupts the early stage in protein synthesis by binding to the 23S rRNA of the 50S subunit. The gene rplC and rrl are concerned in the action of Linezolid. The rplC gene that encodes 50S ribosomal L3 protein to involve in the synthesis of the ribosomal peptidyl-transferase. Hence, rrl gene has 3138 bp length that encodes 23S ribosomal RNA [46].

5. Compounds originating from existing families of drugs

Fluoroquinolones

Fluoroquinolones (FQs) were established into clinical applications in the 1980s and extensively used for the treatment of various bacterial infections [47]. The FQs have been also originated to have anti-TB activity [48] and are presently used as second-line anti-TB drugs. Cross-resistance has been accounted for within the FQs class such that reduced vulnerability to one FQ possibly presented reduced vulnerability to all FQ derivatives [49–51]. With the extensive use of FQSs for the therapy of common microbial infection, resistance to FQs remains uncommon and occurs mostly in MDR strains. The cross-resistance was observed among the various FQ compounds tested (OFX, LVX, GAT, MXF, and CPX) [52]. The rapid progress of resistance is mostly when FQs are used as the only active drugs in a failing multi-drug therapy [53–55]. These new agents are currently taken in concern as anti-TB drugs.

Gatifloxacin

Gatifloxacin (GAT) has bactericidal activity against *Mtb* [56]. It revealed the highest bactericidal effect during the first 2 days. GAT was used in combination with the first-line anti-TB drug INH or RIF: GAT was able to somewhat enhance the bactericidal activity of INH or RIF only for the first 2 days [57]. One study reported that when evaluated in mice in combination with ethionamide and PZA (high doses: 450 mg/kg, 5 days per week). The GAT was capable to clear the lungs of infected animals after 2 months of therapy [58].

Moxifloxacin

*In-vitro m*oxifloxacin (MXF) show to kill a subpopulation of tubercle bacilli that not killed by RIF, while the older FQs, (ciprofloxacin) CPX, and (ofloxacin) OFX did not have any major bactericidal effect. The MXF obstructs protein synthesis in gradually metabolizing bacteria through a mechanism that varies from that used by RIF. In mice models, the effect of MXF against tubercle bacilli was comparable to that of INH [59]. In combination with MXF and PZA has been killing the bacilli more successfully than the INH + RIF + PZA combination [60]. The substitution of MXF with INH in the standard drug therapy could relieve a probable antagonism among the presently used drugs [61]. The MXF might be a promising candidate drug to shorten TB treatment [62, 63].

Non-fluorinated quinolones

A series of 8-methoxy non-fluorinated quinolone analogs (NFQs) lack a 6-fluorine atom in their quinolone ring distinguishing them from fluorinated quinolone compounds such as GAT and MXF. The NFQs target a broad range of bacteria and they appear to operate preferentially through inhibition of DNA gyrase. The NFQs are presently being tested against *Mtb* [4].

Macrolides

The anti-TB effect of the macrolide antibiotics through the synthesis of additional chemically modified analog of erythromycin. Some analog were recognized as anti-TB agent superior to the clarithromycin [4, 15].

New rifamycin derivatives

Rifalazil, a semisynthetic RIF, is described by a long half-life and is more effective than RIF and rifabutin against *Mtb* strains [64]. However, high-intensity RIF–resistant strains present cross-resistance to all rifamycin drugs [65].

Bedaquiline or TMC207

Bedaquiline is a diarylquinoline and used bactericidal. Bedaquiniline involves blocking the proton pump of ATP synthase of *Mtb* then depletes the energy demand of both replicating and nonreplicating (dormant) mycobacteria and at the result in cell death [66, 67].

Delamanid or OPC 67683

Delamanid is a dihydro-nitroimidazooxazole derivative and activated by deazaflavin-dependent nitroreductase enzyme (Rv3547). It acts by interrupting the mycobacterial cell wall component synthesis. Delamanid inhibits the methoxy- and keto-mycolic acid synthesis which is a vital component of the *Mtb* cell wall. It is active against both growing and nongrowing mycobacteria [68, 69].

PA-824

PA-824 is a nitroimidazole derivative and it activated by deazaflavin-dependent nitroreductase like delamanid. Mechanism of action is not clearly konown but it could be described as its activity in replicating and non-replicating mycobacteria. In aerobically replicating cell PA-824 interrupts mycolic acid synthesis by the collecting of hydroxymycolates instead of ketomycolates [70, 71]. In hypoxic non replicating mycobacteria, PA-824 release nitric oxide (NO) that interferes with cytochrome oxidase to disrupt the energy metabolism of the cell wall [72].

SQ-109

SQ-109 is an ethambutol analog and its mechanism of action is not known. It has no inhibitory activition against the secreted Ag85 mycolyltransferase. Rather SQ-109 causes collection of trehalose monomycolate a precursor of trehalose dimycolate by obstructing accumulates of mycolic acids into the *Mtb* cell wall core [73].

Antitubercular drugs with the new and different moiety

To investigating useful drug candidate's currently in two major categories: Novel chemical entity and compounds instigating from existing relatives of currently used drugs, where novel chemistry is used to optimize the new compounds.

Nitroimidazopyrans and Nitroimidaoxazoles derivatives

In this series, the lead molecules are CGI 17341 and PA824/PA1343 and inhibit the cell wall synthesis. However, two key areas of concern also require to attend-possible mutagenicity resulting from the presence of a nitro group, and the chance for the development of drug resistance. The latter is encouraged by the reality that the nitroimidazoles induce a high rate of mutation [2–4], leading to uncertainties that this might cause the appearance of MDR bacteria. Since the drugs will certainly be used in combination therapy [74].

Nitroimidazole PA-824

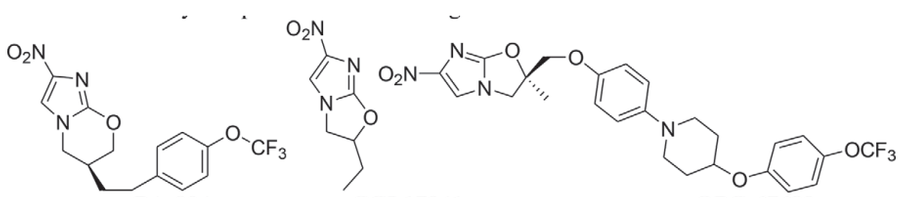
The PA-824 is a nitroimidazole derivative and used as anti-TB agent. PA-824 acts mainly as synthesis of cell wall components inhibitor. *In vitro*, PA-824 showed high activity against drug-sensitive and MDR-TB strains, there is no cross-resistance with currently used anti-TB drugs. Moreover, PA-824 has shown *in-vitro* bactericidal activity against both replicating and static bacteria [4]. The PA-824 bactericidal effect against nonreplicating bacteria was equivalent to the RIF. Use of PA-824 as monotherapy in mice and cause reduced bacterial counts in the lungs is better than RIF or INH monotherapy. After 12 weeks of treatment with PA-824, RIF, or INH, complete removal of the bacterial load was not getting in any of the treated mice [2–4].

Nitroimidazoles CGI 17341

The CGI 17341 has substantial potential as anti-TB agent in a preclinical study. *In-vitro* at 0.04 to 0.3 μg/ml, it inhibited both drug-susceptible and MDR-TB strains and exhibited no cross-resistance with INH, RIF, SM, or EBM. *In-vitro* against *Mtb*, its action was similar to that of INH and RIF and higher to SM, norfloxacin, ciprofloxacin, and the oxazolidinone DuP 721. In *Mtb*-infected mice, oral treatment with CGI 17341 on days 11 and 12 after infection resulted in an ED_{50} of 7.7 mg/kg and showed a significant dose-dependent progress in survival time [75]. These drugs were not mutagenic and showed potent activity against replicating and static *Mtb*, including MDR strains.

Nitroimidazole OPC-67683

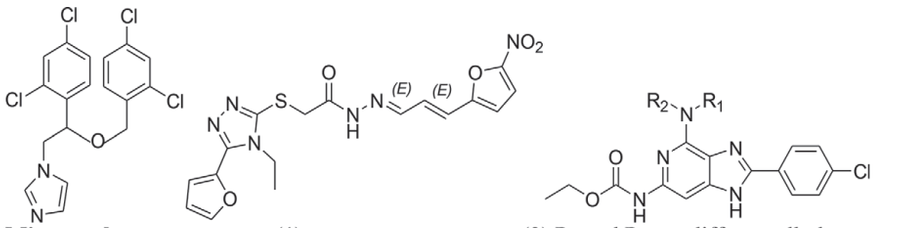
It is mycolic acid inhibitors and interferes with the biosynthesis of the mycobacterial cell wall. *In vitro*, OPC-67683 was exhibited high activity against drug-sensitive as well as DR strains with MICs varying 6–24 ng/mL. There is no cross-resistance with any of the current first-line anti-TB drugs. Moreover, OPC-67683 exhibited strong intracellular activity against the *Mtb*H37Rv residing within human macrophages and type II pneumocytes. The OPC-67683 is active against *Mtb*H37v and MDR-TB strains *in-vivo* starting from a concentration of 0.03125 mg/body [2–4]. The OPC-67683 exhibited 6–7 fold elevated activity compared to first-line drugs INH and RIF.



PA-824 **CGI 17341** **OPC-67683**

Imidazole Analogues

Miconazole is a well-known antifungal drug that has been accounted for to have anti-TB activity *in vitro* against *Mtb*H37Ra (MIC 2 μg/ml). It inhibiting replicating bacteria and also has some effect on stationary phase bacilli [88]. Unfortunately, miconazole is not active orally and therefore is little additional interest in progressing TB indication [76].



1,2,4-Triazoles

Various 1,2,4-triazoles have been estimated against *Mtb* H37Rv. Compound (**1**) gave 61% inhibition at 6.25 μg/ml. Other triazole analogs were inactive [2–4].

Imidazo(4,5-c)pyridine compounds

A series of imidazo(4,5-c)pyridines, one compound (**2**) for common formula (R_1, R_2 unrevealed)-inhibited *Mtb*H37Rv and other strains with MICs range 0.256–2.56 μg/ml. Imidazo(4,5-c)pyridines were initially prepared as anti-mitotic agents but in the present work, fewer cytotoxic agents were chosen and found to have anti-TB activity [4].

Diarylquinoline compounds

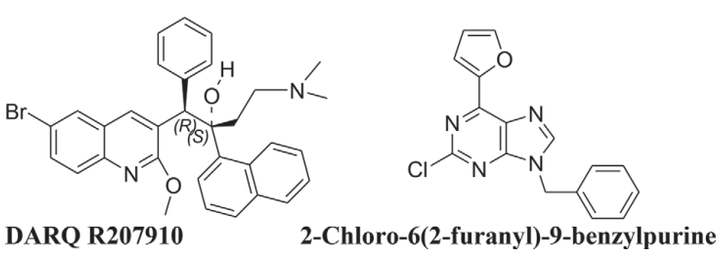
Diarylquinolines (DARQs) is structurally unlike both FQs and other quinolines derivatives. The DARQ R207910 is a new class of anti-TB drugs. It has specificity towards mycobacteria as well as atypical species, important in humans such as MAC, *M. kansai,* and the fast-growing *M. fortium* and *M. abscessus* [77]. The anti-TB specific spectrum differs from that of INH, which has very poor activity against MAC. It will be extremely targeted to the treatment of TB infections, mainly targeting the proton pump of ATP synthase [78].

Diarylquinoline TMC207

Diarylquinoline (DRQ) TMC207 is an exceptionally promising class of anti-TB drugs. About, 20 compounds of the DRQ series have been exhibited a MIC value below 0.5 μg/ml against *Mtb* H37Rv [78]. The most active compound of this class is TMC207 against *Mtb*. The mechanism of action of DRQ TMC207 is different from those of other anti-TB drugs involving a low probability of cross-resistance with accessible anti-TB drugs. The DRQ TMC207 is capable to inhibit bacterial growth against MDR-TB isolates and appears to act by inhibiting the ATP synthase [79], most important to ATP depletion and pH imbalance. Substitutions of RIF, INH, or PZA with DRQ TMC207 hasten activity [80].

Purine Analogs

The 9-Benzylpurines, with a variety of substituents on 2, 6, and/or 8 positions, have high inhibitory activities against *Mtb*. One compound, carrying trans-styryl or aryl substituents at 6 positions and generally chlorine in 2 positions tends to increase the *in vitro* activity and has MIC of 0.78 mg/mL [81]. The anti-TB activity of 6-arylpurines [82] and 9-sulphonylated or sulphenylated-6-mercaptopurines are also known [83].



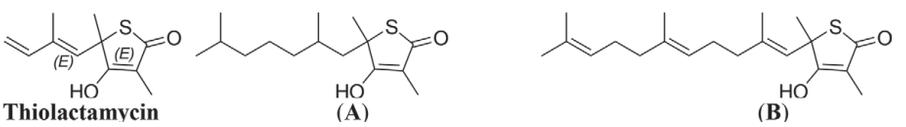
Benzylpurines

The 9-benzylpurines, 2-chloro-4(2-furanyl)-9-benzylpurine was potently inhibited *Mtb* H37Rv *in-vitro* with a MIC value of 0.78 μg/ml with low cytotoxicity towards VERO cells (IC_{50} value-8.1 μg/ml) selectivity index (MIC/IC_{50}) of 10.4 [4].

Thiolactomycin Analogues

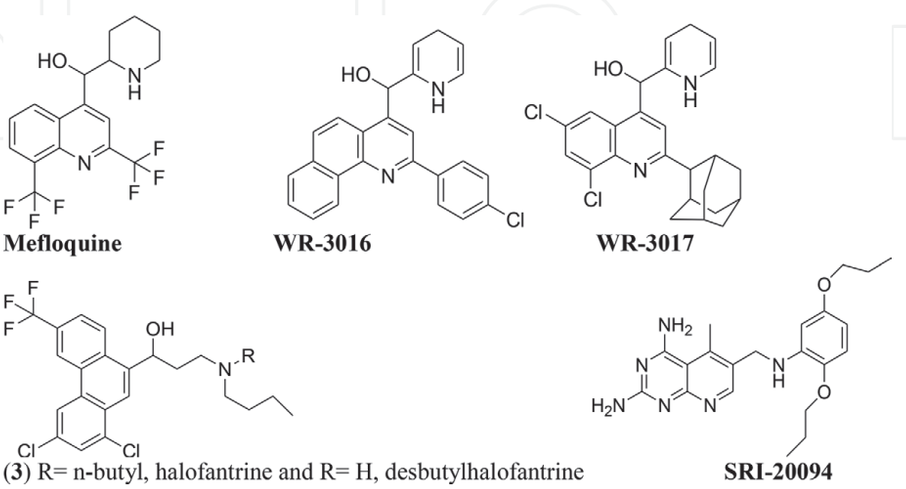
Naturally occurring (5*R*)-thiolactomycin (TLM) exhibits potent *in vivo* activity against many pathogenic bacteria, and *Mtb* [84]. TLM inhibited bacterial and plant type II fatty acid synthases (FAS-II) but not inhibited mammalian or yeast type I fatty acid synthases (FAS-I) [85]. In *E. coli*, it inhibited both β-ketoacyl-ACP synthase I to III and acetyl coenzyme A (CoA): ACP transacylase activities [86, 87]. The TLM was the first example of naturally occurring thiolactone to displayed antibiotic action. The TLM analogs have improved activity against whole cells of pathogenic *Mtb* strains [88]. The TLM analogs act by the inhibition of the mycolate synthase, an enzyme involves in the biosynthesis of the *Mtb* cell wall.

This has led to the hope that inhibitors of the TLM target enzyme, FAS-II, are potentially important in the treatment of malaria [89], trypanosomiasis, or sleeping sickness [90], and a range of bacterial indications including TB. It also blocks long-chain mycolate synthesis in a dose-dependent mode [91]. The TLM is active *in vitro* against an extensive range of strains of *Mtb*, including INH- resistant, although at somewhat high concentrations. For example, complete inhibition of growth on solid media of the strain *Mtb* Erdman is seen at 25 μg/ml. The TLM itself as an anti-TB agent [92] and racemic mixtures, e.g. compounds (**A**) and (**B**), which are accounted to have superior activity than the parent in inhibiting *Mtb* H37Rv *in-vitro*.



Mefloquine Analogues

The antimalarial agent mefloquine and its analogs have activity against a range of bacteria including *Mtb* [93]. A series of quinolinemethanol analogs, two compounds, WR-3016, and WR-3017, exhibited potent inhibitory effects in vitro in the *M. avium* complex-1 (MAC) assay with MIC_{50} values of 1 and 2 μg/ml respectively, compared to 16 μg/ml for mefloquine. Other mefloquine analogs, two enantiomers of mefloquine and might be valuable to test some representative 4-aminoquinoline antimalarials such as chloroquine [94]. Another compound desbutylhalofantrine (**3**) is in progress for its antimalarial activities with an advantage over the parent drug halofantrine of lesser cardiotoxicity.



(**3**) R= n-butyl, halofantrine and R= H, desbutylhalofantrine

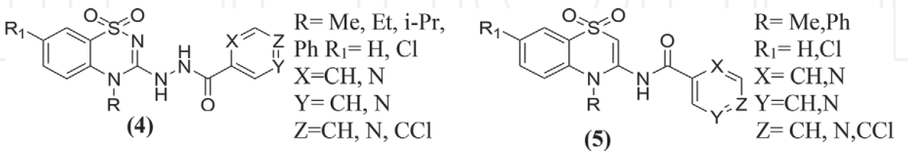
Deazapteridines

Some 2,4-diamino-5-deazapteridine derivatives, SRI-20094 has potent inhibition of MM6 cells infected with MAC strain NJ3440 with a MIC value 0.13 μg/ml. SRI-20094 inhibits the dihydrofolate reductase (DHFR) of the MAC, with an IC_{50} value 1.0 nM as compared to 4100, 1.4 and 1.0, nM for the trimethoprim,

piritrexim, and trimetrexate,. It confirmed limited inhibition for human DHFR having an IC_{50} value 7300 nM. SRI-20094 is a value for the *M. avium* infection and in particular for HIV co-infected persons. Other close analogs were highly active against *Mtb* with MICs of ~0.1 mg/l [95].

1,2,4-Benzothiadiazines

The 1,2,4-benzothiadiazine dioxides have a close relation to sulfonamide and could be considered as cyclic sulfonamides. These compounds exhibited antimicrobial activity [96]. The 1,2,4-benzothiadiazines were explored by incorporating other heterocyclic rings like pyridine and pyrazine moieties (**4** and **5**) and these compounds were exhibited interesting anti-TB activity [97].

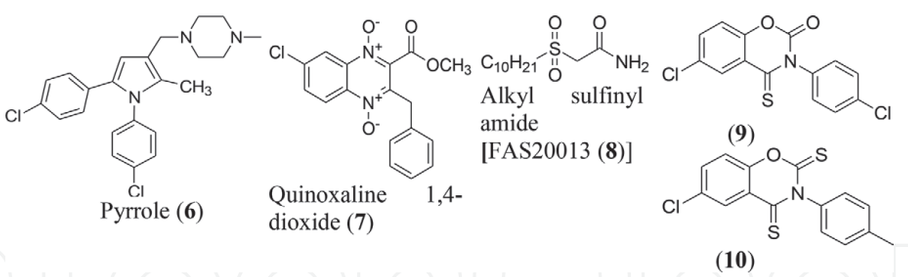


Other Molecules

Several other molecules like pyrroles (**6**) [98], quinoxaline-1,4-dioxides (**7**) [99], and alkylsulfinyl amides (**8**) [100] have been tested for their anti-TB activity. In the analysis of the constant MDR-TB problem, new drugs should concentrate on different targets, including the reduction of TB therapy [101], with negligible toxicity and thus structures based on this lead could provide a novel class of anti-TB drugs.

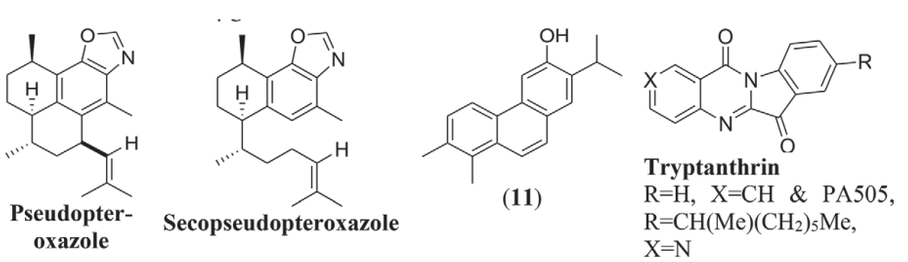
Benzoxazine derivatives

Some 6-chloro-3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(*3H*)-ones (**9**) and 6-chloro-3-phenyl-2H-1,3-benzoxazine-2,4(*3H*)-dithiones (**10**) have potent anti-TB activity against *Mtb* (MIC values 0.5 mcmol/l), *M. avium* (16 and 16 μmol/l), *M. kansasii* (2 and 2 μmol/l), and *M. kansaii* (1 and 0.5 μmol/l), compared with MIC values of 4, 8, 500 and 500 μmol/l for INH after 14 days [4].



Diterpenoids

Marine products gorgonian coral *Pseudopterogorgia elisabethae* from the West Indian have the anti-TB activity of two active diterpenoid alkaloidal compounds, secopseudopteroxazole and pseudo-pteroxazole [4, 71]. The pseudopteroxazole against *Mtb* H37Rv was claimed to be a powerful inhibitor giving 97% growth inhibition at 12.5 μg/ml even as seco-pseudopteroxazole was rather less active. Some of these derivatives are significantly more active than the marine diterpenoids (11) with the MIC value of *Mtb* H37Rv = 0.46 μg/ml.

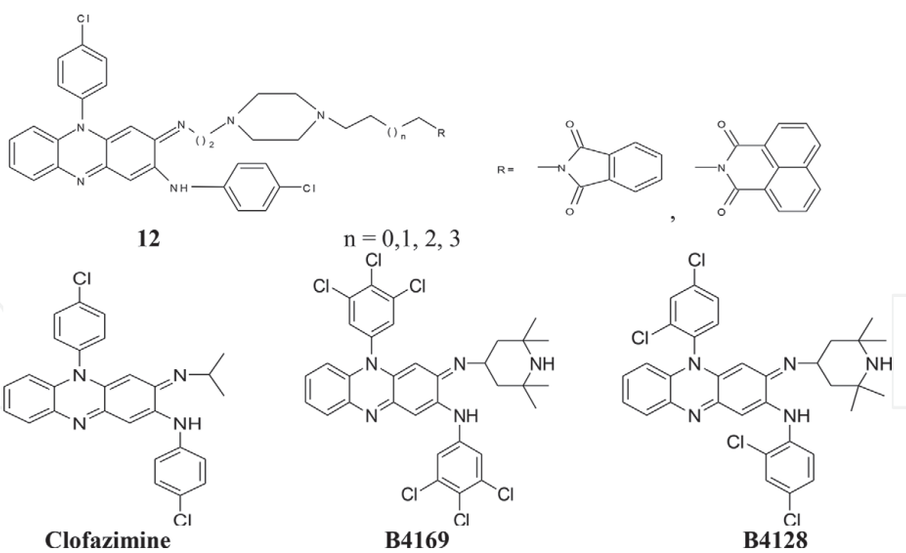


Tryptanthrin derivatives

Tryptanthrin is an indoloquinazolinone containing alkaloid and evaluated against different strains of *Mtb* including the drug-sensitive *Mtb* H37Rv strain. The MIC value of tryptanthrin was 1.0 μg/ml compared to the MIC value of INH was 0.03 μg/ml. When evaluated against a section of MDR-TB strains, even as tryptanthrin sustain its effectiveness (MIC = 0.5-1 μg/ml), INH had declined activity with MIC value 4-16 μg/ml. Many derivatives have been tested for their potential in TB treatment like PA-505 having powerful *in vitro* activity towards *Mtb* H37Rv-MIC 0.015 μg/ml and had only modest actions in reducing *Mtb* in the spleen of infected mice when given orally at 50 mg/kg/day for ten days [102].

Clofazimine or Tetramethylpiperidino (TMP) Phenazines Analogues

The tetramethyl piperidine substituted phenazines B4169 and B4128 (TMP phenazines) have possessed significantly activity against *Mtb*, including MDR clinical strains than clofazimines [103]. Recently, new conjugates of phenazine with phthalimido and naphthalimido moieties (**12**) have anti-TB activity [33]. Some phenazine hybrids have shown potential inhibition of *Mtb* ATCC 27294 as well as their clinical isolates (both sensitive and resistant). There is a potential to design new phenazine hybrids for the research and development of new anti-TB agents [14]. The anti-TB effects of tetramethyl piperidinophenazine derivatives are closely related to the clofazimine. The intra- and extracellular effects of these drugs were compared to clofazimine and RIF against *Mtb* H37Rv. The B4169 has effectively inhibited the bacterium with a MIC value of 0.015 μg/ml; the equivalent value for clofazimine was 0.06 μg/ml. These compounds were more active than clofazimine against a series of *Mtb* isolates plus MDR-TB strains. Besides, some derivatives, B4128, exhibited significant intracellular activity (~60% inhibition of growth) at 0.001 μg/ml against *Mtb* infected monocyte-derived macrophages and were better to both clofazimine and RIF drug [14, 15].



Phenazine B4157

The B4157 is a phenazinamine derivative, closely related to clofazimine, has a potential action for TB. *In vitro*, clofazimine and B4157 were screened against various *Mtb* strains, most of resistance strains, and all were vulnerable to B4157 including which were resistance to clofazimine. The MICs value of B4157 and clofazimine at which 90% of strains inhibited were 0.12 and 1.0 μg/ml. However, C57BL against *Mtb* at 20 mg/kg, clofazimine was slightly better to B4157 [4, 15].

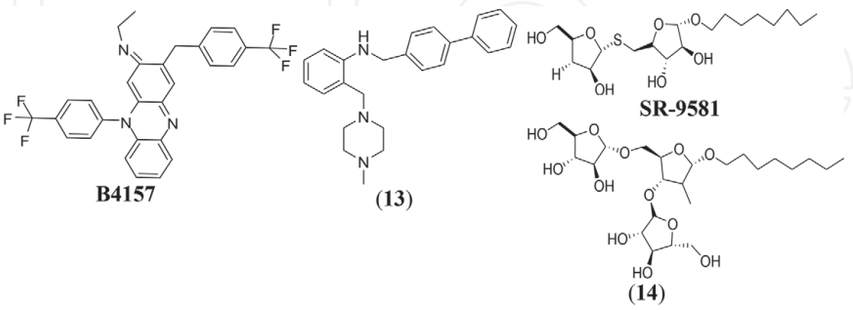
Toluidine Derivatives

Some analogs of toluidines have attractive *in vitro* activity against *Mtb* 103471, the best compound (**14**), having MICs values 4 μg/ml-cf MICs of INH, 0.25 μg/ml,

and SM, 0.5 μg/ml. However, these amines will undergo rapid metabolic degradation, possibly toxic metabolites [4, 15].

Saccharides

The arabinose disaccharide SR-9581 is *in vitro* effective against *Mtb*, with a MIC value 4 μg/ml. It reduced the viability of *Mtb* 76.1%, 97.8%, and 99.9% at 8, 16, and 32 μg/ml in 3 days. Another saccharide, an arabinofuranoside oligosaccharide (**14**), substrate for mycobacterial arabinosyltransferases, both compounds can disrupt biosynthesis of *Mtb* cell wall [104, 105].

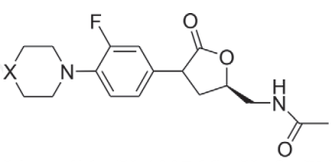


Oxazolidinones (Linezolid)

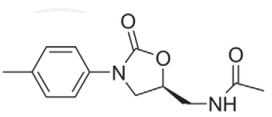
The Oxazolidinones are a class of broad-spectrum antibiotic compounds. They inhibit protein synthesis through binding to the 50S subunit of ribosomes. Oxazolidinones had considerable activities against *Mtb in-vitro* in mice [106]. Oxazolidinones are less promising due to their toxicities and high-cost value [107, 108].

Oxazolidinones PNU 100480 and AZD 2563

They have bacteriostatic activity against various human pathogens together with drug-resistant microorganisms [109, 110]. The oxazolidinones have activity against *Mtb* and linezolid (U-100766) inhibiting MDR isolates *in vitro* at 2 μg/ml [111]. Oxazolidinones having a thiomorpholine group in place of the morpholine group present in linezolid has mainly active against *Mtb* with MICs value 0.125 μg/ml [112]. PNU-100480 was also tested in a murine model against ten strains of *Mtb* in comparison to linezolid and INH. PNU-100480 was found equivalent to INH and more active than linezolid [106].



Linezolid (**U-100766**) X=O PNU & **100480** X=S,



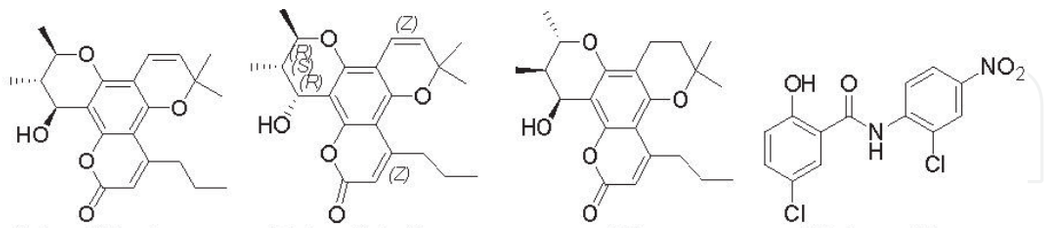
DuP 721 R=MeCO and **DuP 105** R=MeSO

Calanolides

Calanolide A is a naturally pyranocoumarin that has double action against TB and HIV infections. This compound is an inhibitor of the HIV-1 reverse transcriptase enzyme. It also exhibits good in vitro effects towards *Mtb*. In a beginning test of its activity, calanolide A was analogous to the positive control INH and staying effective against RIF and SM resistant TB strains. Calanolide A decreasing the dependency upon acquiring the material from limited natural resources [4, 27] and some compounds, e.g. (**15**), have patented for their anti-TB activities. Calanolide B, which distinct calanolide A, is existing in considerable quantities from renewable natural sources, e.g. from Calophyllum seed oil, [113] has a similar range of activity to calanolide A against *Mtb* and may be an additional cost-effective treatment.

Poloxamer 315 (CRL-1072)

Poloxamer 315 is a methyl oxirane surfactant polymer that shows to disrupt the cell membranes of microorganisms or their intracellular components. The purified polymer is effective against *Mtb* and *M. avium*. *In vitro* effect against *Mtb* showed MIC values 3.1–6.2 μg/ml even as, in a macrophage assay, these go down to 0.92 to 1.25 μg/ml. This compound was effective against strains of *Mtb* resistant to INH, SM, and RIF [114].



Niclosamide

The anthelmintic drug niclosamide was found to have anti-TB activity *in vitro* (MIC 0.5-1 μg/ml) against *Mtb* H37Ra. However, niclosamide is useful for the treatment of human tapeworm infections; it is not absorbed to any significant extent from the intestine [115].

Mikasome

The liposome-encapsulated drug for the anti-TB activity, Mikasome, is useful against *M. avium* infections *in vitro* and *in vivo*. In animals, Mikasome formed 7-fold higher peak plasma levels compared to free drug amikacin (i.v.). The AUC was 150-fold higher with the liposomal substance and a single dose of liposomal amikacin formed therapeutic levels of antibiotics for more than 72 hr. The pilot Phase II studies showed that MiKasome was capable to resolve *Mtb* infections who had failed conventional therapies [4, 14].

Fulleropyrrolidines

A series of fullerene analogs, compound (**2.158**) exhibited anti-TB activity. It inhibited the growth of a human clinical isolate, *Mtb* H6/99, MIC value of 5 μg/ml, and *Mtb* H37Rv MIC value of 50 μg/ml. Some fullerene derivatives have also exhibited *in-vitro* activity against the HIV protease contributing to the tantalizing option of combined actions towards both AIDS and TB [2–4].

Pyrrole LL- 3858

Some pyrroles analogs were effective *in-vitro* against the standard and drug-sensitive *Mtb* strains [116]. Compounds LL-3858 was exhibited a higher bactericidal effect than INH when given as monotherapy to infected mice.

Dipiperidine SQ-609

Dipiperidine SQ-609 is structurally dissimilar to the existing anti-TB drug. It destroyed *Mtb* by interfering with cell wall biosynthesis. The antimicrobial effect has been established *in vivo* in mice models [117–119].

Pleuromutilins

The pleuromutilins is a novel natural antibiotic. They interfere with protein synthesis by binding to the 23S rRNA and consequently inhibiting the formation of a peptide bond [118]. The cross-resistance might happen between pleromutilins and oxazolidinones [119]. Pleuromutilins have been revealed to in-vitro inhibition of the *Mtb* growth. The pleuromutilin compound is active against MDR-TB and permitted shortening of the treatment time.

ATP Synthase inhibitor FAS20013

The FAS20013 belongs to the β-sulphonylcarboxamide analogs. FAS20013 destroys more organisms in a 4-hour exposure than INH or RIF can throughout a

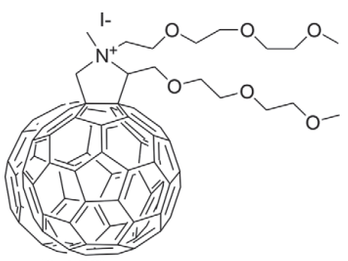
12- to 14-day exposure. This compound is especially effective in killing MDR-TB strains that are resistant to currently used multiple drugs. The greater effect of FAS20013 compared to current anti-TB drugs in terms of its ability to sterilize TB injuries and kill latent TB strains. The FAS20013 has its efficiency in mice with no serious adverse effects and it is up to 100% bioavailable when orally used. The compound is acted by inhibition of ATP synthase [120].

Diamine SQ-109

Diamine SQ-109 was developed as a second-generation drug from the first-line drug ethambutol (EMB). When examined in a low-dose infection model of TB in mice, SQ-109 at 1 mg/kg was as efficient as EMB at 100 mg/kg. However, SQ-109 did not prove improved efficacy at higher doses (10 mg/kg; 25 mg/kg) and was less efficient than INH [121]. The SQ-109 is effictive against MDR-TB, together with those that are EMB-resistant.

Nitrofuranylamides

The *Mtb* is relatively vulnerable to Nitro-containing compounds [122]. Nitrofuranylamide (**16**) was accepted in testing for UDP-Gal mutase inhibition. A prolonged set of nitrofuranylamides was tested for anti-microbial activity. This led to the recognition of several nitrofuranylamides with activity effective against *Mtb* [123].



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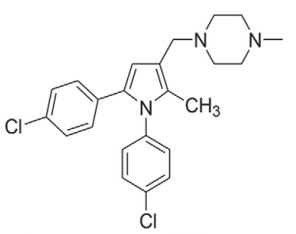
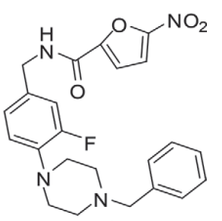


Pyrrole LL- 3858



(16)

6. Conclusion

Tuberculosis (TB) is a chronic infectious disease caused by *M. tuberculosis*. Anti-TB drugs developed since the 1940s and their discovery resistance also developed against them. Acquired and primary drug resistances are the common pathways for the development of anti-TB drug resistance. Anti-TB drugs mainly act on protein synthesis, folic acid synthesis, mycolic acid synthesis, DNA synthesis, and ATP synthase. These anti-drugs cause bacteriostatic and/or bactericidal effects on the mycobacterium. The major resistance mechanism is the mutation of the target gene responsible for the action of anti-TB drugs. Anti-TB drug resistance produces a destructive effect on public health. Therefore, the advance study should be conducted in the areas of finding new targets for the development of novel anti-TB drugs.

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