

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Chemotherapeutic Strategies and Targets Against Resistant TB

Neeraj Shakya¹, Babita Agrawal² and Rakesh Kumar¹

¹Department of Laboratory Medicine and Pathology,

²Department of Surgery, 728-Heritage Medical Research Center,
Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB,
Canada

1. Introduction

Chemotherapeutic cure for about 40,000 years old lethal disease - TB (Callaway, 2008), was started mere ~65 years ago, with the discovery of antibiotic- streptomycin. A few effective drugs against TB have been developed since then and have been classified mainly as first-line (viz. rifampicin, isoniazid, pyrazinamide and ethambutol) and second-line drugs (e.g. ciprofloxacin, levofloxacin, cycloserine, clofazimine etc.). Drugs like rifambutin, clarithromycin and linezolid may be considered as "third line" drugs. The current course of therapy with the first-line TB drugs is more than 40 years old and is slowly becoming outdated due to emergence of multidrug-resistant tuberculosis (MDR-TB, resistant to the two first line drugs) and extensively drug-resistant tuberculosis (XDR-TB, an MDR-TB that is resistant to fluoroquinolones and also to any one of the three injectable second-line drugs: amikacin, capreomycin or kanamycin) (World Health Organisation, [WHO], 2011). Treatment with the second line drugs is limited due to the associated toxicity which halts therapy prior to cure in more than half of the patients suffering from serious side effects. The "third line" drugs have issues of proven efficacy/effectiveness and impractical cost. Longer duration of treatment, usually for six months, with complex regimens leads to poor compliance. Although poor compliance can be managed to great extent by Directly Observed Treatment, Short course (DOTS) launched by World Health Organization (WHO); but that is possible practically in developed countries only where manpower along with financial needs are met adequately. Apart from these problems, during this long treatment period, the patient and one's family suffer from socioeconomic problems, whereby psychological issues such as risk of depression come in picture. Side effect(s) of drugs, due to long treatment, is another major concern.

Researchers have been trying to find out the answer for why the TB treatment is so long and complex. McCune et al found considerable difference in the efficacy of drugs against *Mycobacterium tuberculosis* (*Mtb*) *in vitro* and *in vivo* (McCune & Tompsett, 1956; McCune et al 1956). However, other researchers (Barclay et al. 1953; Clark, 1985) showed that bioavailability is not a concern. It was proposed that this persistence of *Mtb* might be due to physiologic heterogeneity of bacteria in the tissues (Mitchison, 1979; Handwerker & Tomasz, 1985).

Mitchison found that the lesions have at least four different populations of *Mtb*:

- a. Actively growing bacilli: can be killed by isoniazid
- b. Bacilli with spurts of metabolism: can be killed by rifampicin
- c. Bacilli with low metabolic activity (reside in acidic pH environment): can be killed by pyrazinamide
- d. Dormant bacilli: not killed by any existing drug/regimen.

The actively multiplying bacilli are killed in the first 2 days, the remaining are dormant, which are sterilized very slowly by the existing drugs and thus the treatment period is stretched so long (Jindani et al., 2003).

Bacillus Calmette Guerin (BCG), the only approved vaccine for TB in humans, contains attenuated strain of *M. bovis*. It is generally considered safe; however this vaccination may lead to TB infection in immunocompromised individuals. Moreover, BCG only reliably protects against tuberculosis in newborns and fails in adult pulmonary tuberculosis, the most prevalent form (Kaufmann, 2011).

Due to the associated global health and socioeconomic concerns, the increasing rates of MDR-, XDR-TB, and TB-HIV coinfection, the discovery and development of potent new anti-TB agent(s), without cross-resistance with current antimycobacterial drugs, is urgently needed.

This chapter includes brief discussion on existing TB drugs and covers a comprehensive picture of the anti-TB drug discovery status heading to achieve a goal of better drugs/regimen in terms of the desired properties stated above.

2. Existing TB drugs

After the discovery of Streptomycin in 1944, 15-20 antimycobacterial drugs have been approved and used for TB therapy according to the need, availability, cost and safety profile. These existing TB drugs can be classified into first line, second line and third line drugs (also summarized in Tables 1-3).

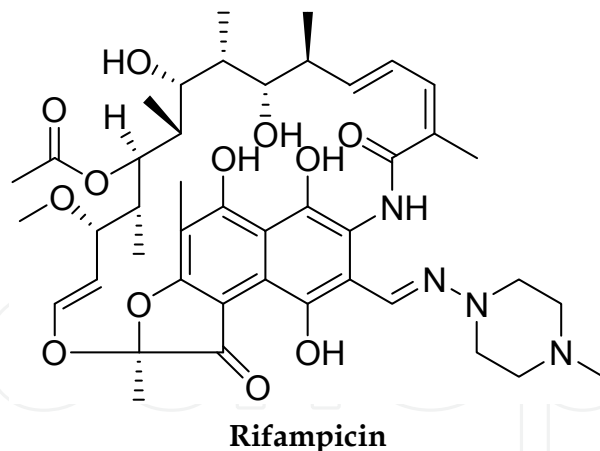
2.1 First line drugs

2.1.1 Rifampicin, RMP or R

Rifampicin was discovered in 1966. It is a semisynthetic, intensely red coloured bactericidal antibiotic (MIC 0.05-0.5 µg/mL) derived from *Amycolatopsis rifamycinica*. Its penetration to cerebrospinal fluid makes it useful to treat tuberculosis meningitis (Nan et al, 1992). RMP, should be used in combination with other antibiotics as resistance develops quickly during monotherapy. RMP may be excreted in breast milk, therefore breast feeding may be avoided during treatment. However no serious side effects have been observed in breastfed infants during RMP therapy (Peters & Nienhaus, 2008; Drobac et al 2005).

2.1.1.1 Mode of action

RMP inhibits DNA-dependent RNA polymerase in bacterial cells by binding its β -subunit, thus preventing transcription to RNA and subsequent translation to proteins (Aristoff et al, 2010; Tomioka, 2006). RMP-resistant bacteria produce RNA polymerases with subtly different β subunits which resists drug-inhibition (O'Sullivan et al, 2005)



2.1.1.2 Dosing

Daily regimen 10 mg/kg (up to 600 mg/day) orally or intermittent regimen 10 mg/kg (up to 600 mg/day) orally, are prescribed. (The American Thoracic Society [ATS], 2006).

2.1.1.3 Adverse effects

The main target organs for side effects of RMP are the liver and the gastrointestinal system. Adverse effects include hepatitis with elevation of bile and bilirubin concentrations, anaemia, leucopenia, thrombocytopenia, bleeding, febrile reaction, eosinophilia, leucopenia, thrombocytopenia, purpura, haemolysis and shock, and nephrotoxicity (International Programme on Chemical Safety [INCHEM] a).

2.1.1.4 Pharmacokinetics

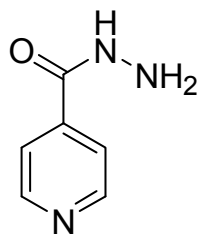
The half-life of RMP is generally 2 h (Acocella, 1978). Its absorption is not affected by antacids (Peloquin et al., 1999 a). RMP ester function is hydrolyzed in the bile by esterase catalyzed high pH. The deacetylated form of RMP can not be absorbed by the intestine and thus eliminated from the body.

2.1.1.5 Interactions

Absorption of RMP is considerably hindered when it is combined with another anti-TB drug, 4-aminosalicylic acid (PAS). Therefore, these two anti-TB drugs must be administered separately (8 to 12 hours interval). RMP affects metabolism of several known drugs, viz. warfarin, oral contraceptives, cyclosporine, itraconazole, digoxin, verapamil, nifedipine, simvastatin, midazolam and HIV protease inhibitors. Other drugs for possible interactions include clarithromycin, lorazepam atorvastatin, antiretroviral agents, rosiglitazone/pioglitazone, celecoxib, caspofungin (Baciewicz et al., 2008).

2.1.2 Isoniazid, INH or H

INH (isonicotinylhydrazine) was discovered in 1952. It is bactericidal (MIC 0.01-0.2 µg/mL) to fast replicating mycobacteria (Singh & Mitchison, 1954) but is bacteriostatic to slow-growing mycobacteria. Since the bacteria may exist in a non growing state (latent) for long periods, therapy for latent tuberculosis with INH is continued for a longer duration (6-12 months). However, INH monotherapy is never recommended to treat active tuberculosis due to the development of resistance.

**Isoniazid**

2.1.2.1 Mode of action

INH itself is a prodrug and is activated by mycobacterial catalase-peroxidase enzyme KatG which catalyzes the formation of isonicotinic acyl-NADH complex from isonicotinic acyl and NADH. This complex then binds to the enoyl-acyl carrier protein reductase known as InhA, consequently blocking the natural substrate enoyl-AcpM and fatty acid synthase. This results in inhibition of mycolic acid synthesis which is essential for the mycobacterial cell wall formation. A direct role for some INH-derived reactive species, such as nitric oxide, in inhibiting mycobacterial metabolic enzymes has also been shown (Timmins & Deretic, 2006; Suarez et al., 2009).

2.1.2.2 Metabolism

INH is metabolized in liver and its metabolites are excreted in the urine with 75 to 95% of the dose excreted in 24 hours (Ellard & Gammon, 1976).

2.1.2.3 Dosing

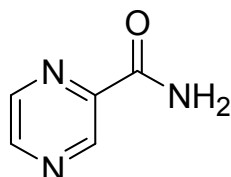
In adults, the recommended dose is 5 mg/kg/day (max 300 mg daily). For intermittent dosing (twice or thrice/week), 19-15 mg/kg/day (max 900 mg/day) is a standard dose. For patients with slow clearance of INH are put on reduced dosages. The recommended dose for children is 8 to 12 mg/kg/day (McIlleron et al., 2009; [ATS], 2006).

2.1.2.4 Adverse effects

INH causes acute toxicity in the CNS. It induces generalized convulsions, coma and metabolic acidosis. Death may occur from acute respiratory failure or hypotension. Liver, peripheral nervous and haematologic systems are the main target organs of INH chronic toxicity resulting in acute hepatitis, peripheral neuropathy, haemolytic anaemia (INCHEM, b). Vitamin B₆ (10-50 mg/day) supplements are suggested to compensate its (Vitamin B₆) depletion during treatment which may lead to peripheral neuropathy and CNS related side effects (Yamamoto et al., 2011).

2.1.3 Pyrazinamide, PZA or Z

PZA was discovered in 1952. It acts mainly as bacteriostatic agent but can be bactericidal for replicating *Mtb*. Its MIC is 20-100 µg/mL at pH 5.5 or 6.0. This drug is used in the first two months of treatment to shorten the duration of treatment, since regimens not containing PZA must be taken for nine months or more (Hong Kong Chest Service [HKCS]/ British Medical Research Council [BMRC], 1981). PZA crosses meninges and thus is effective for the treatment of tuberculous meningitis (Donald & Seifart, 1988).



Pyrazinamide

2.1.3.1 Dosing

20–25 mg/kg daily or 30–40 mg/kg thrice a week is a recommended dose. ([ATS], 2006).

2.1.3.2 Pharmacokinetics

PZA is well absorbed orally. It is metabolised by liver and the metabolic products are excreted by kidneys (Lacroix et al, 1989). The overall pharmacokinetics may differ in childrens (Arya et al., 2008).

2.1.3.3 Mode of action

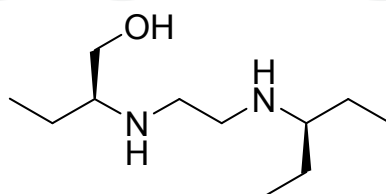
PZA is actually a prodrug. In acidic conditions, the enzyme pyrazinamidase (present in *Mtb*), converts it to the active form, pyrazinoic acid which consequently inhibits the enzyme fatty acid synthase (FAS) I, required by the bacterium to synthesise fatty acids (Zhang & Mitchison, 2003; Zimhony et al., 2007). Mutations of the pyrazinamidase gene (*pncA*) are responsible for PZA resistance in *Mtb* (Scorpio & Zhang, 1996)

2.1.3.4 Adverse effects

Some common adverse effects of PZA treatment include hepatotoxicity, joint pains (arthralgia), nausea, vomiting, anorexia, sideroblastic anemia, skin rash, hyperuricemia, dysuria, urticaria, pruritus, interstitial nephritis, malaise, porphyria and fever (rare) (Forget & Menzies, 2006).

2.1.4 Ethambutol, EMB or E

EMB was discovered in 1961 by Lederle Laboratories. It is a bacteriostatic drug. In spite of a relatively modest MIC of 10 μ M like PZA, it is a useful drug for tuberculosis chemotherapy, partly because of very low toxicity and relatively few side-effects (Wilkinson et al., 1961; Thomas et al., 1961).



Ethambutol

2.1.4.1 Adverse effects

Adverse effects may include peripheral neuropathy, red-green color blindness, arthralgia, hyperuricaemia, vertical nystagmus and optic neuritis (Lim, 2006).

2.1.4.2 Mode of action

It blocks formation of *Mtb* cell wall by interfering in the synthesis of arabinogalactan (an essential component for the formation of mycolyl-arabinogalactan-peptidoglycan complex of the *Mtb* cell wall) via inhibiting the enzyme arabinosyl transferase (Belanger et al., 1996; Wiles & Jacobs Jr, 1997).

2.1.4.3 Pharmacokinetics

It is well absorbed in the gastrointestinal tract, and well distributed in body tissues and fluids. 50% of the given dose is excreted unchanged in urine (Peloquin et al., 1999 b).

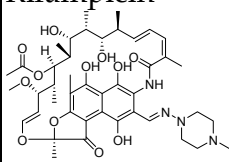
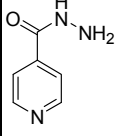
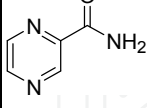
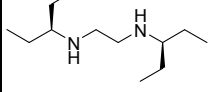
| Drug | Mode of Action | Target | Daily Dose (Max. Dose) | Possible adverse reactions |
|---|---|--------------------------------|------------------------------|--|
| Rifampicin  | Inhibits RNA synthesis | RNA polymerase beta subunit | 10mg/kg (600 mg/day) | Pruritus, rash, flushing, redness and watering of eyes, breathlessness, nausea, vomiting, abdominal cramps, diarrhea, jaundice, hepatitis, liver failure (rare and in severe cases), chills, fever, headache, arthralgia, and malaise |
| Isoniazid  | Inhibition of cell wall formation | Acyl carrier protein reductase | 5 mg/kg/day (300 mg daily) | Rash, hepatitis, sideroblastic anemia, metabolic acidosis, peripheral neuropathy, mild central nervous system (CNS) effects, intractable seizures (status epilepticus), headache, poor concentration, weight-gain, poor memory, and depression |
| Pyrazinamide  | Disruption of membrane transport and energy depletion | Membrane energy metabolism | 20–25 mg/kg daily (30 mg/kg) | Hepatotoxicity, joint pains (arthralgia), nausea, vomiting, anorexia, sideroblastic anemia, skin rash, hyperuricemia, dysuria, urticaria, pruritus, interstitial nephritis, malaise; porphyria |
| Ethambutol  | Inhibition of cell wall formation | Arabinosyl transferase | 15 mg/kg daily (25 mg/kg) | Peripheral neuropathy, color blindness, arthralgia, hyperuricaemia, vertical nystagmus and optic neuritis. |

Table 1. First Line Drugs

2.2 Second Line Drugs (SLDs)

A drug may be categorized as second (or as third) line if it includes one or more of the following: i. it has side-effects beyond a tolerance threshold (e.g., cycloserine), ii. its

administration is not oral and at the same time (sub)equivalent/better affordable oral medications are available, iii. it is less effective than the first-line drugs (e.g., *p*-aminosalicylic acid); iv. its cost is impractical for routine treatment.

2.2.1 Classification of SLDs

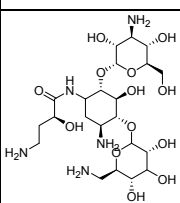
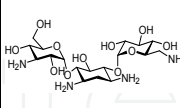
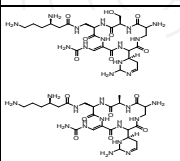
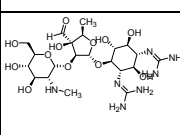
The available second-line TB drugs (SLDs) can be classified as:

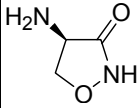
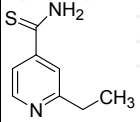
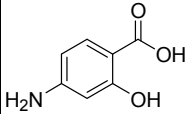
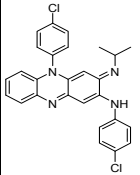
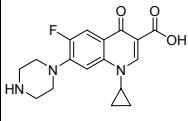
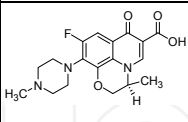
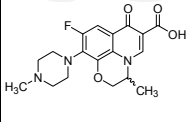
1. Aminoglycosides: e.g. amikacin (AMK), kanamycin (KM), gentamicin etc;
2. Polypeptides: e.g., capreomycin, viomycin, enviomycin;
3. Fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF);
4. Thioamides: e.g. ethionamide, prothionamide
5. Oxazolidinone: (Cycloserine, the only antibiotic in its class);
6. *p*-Aminosalicylic acid (PAS or P).

Details of some of these SLDs are provided in the table 2.

2.3 Third line drugs

Apart from the reasons listed under second line drugs, a drug may be considered as a third line if it is useful but lacks sufficient efficacy proofs. Rifabutin, macrolides: (e.g., clarithromycin), linezolid, thioacetazone, thioridazine, arginine, vitamin D may be considered as third line antituberculosis drugs.

| Drug (Discovery) Route | Structure | Mode of Action | Daily Dose (Max. Dose) | Adverse effects |
|--------------------------------|---|---|---|---|
| Amikacin (1972) IM or IV |  | Inhibits protein synthesis by (binds to the bacterial 30S ribosome) | 15 - 30 mg/kg (1 g) MIC 4-8 µg/mL (CDC, 1994) ^a | Auditory, vestibular, and renal toxicity, dizziness |
| Kanamycin (1957) IM or IV |  | Inhibitions protein synthesis via S12 ribosomal protein & 16 S RNA. | 15 - 30 mg/kg (1 g) MIC 1-8 µg/mL | Auditory, vestibular, and renal toxicity |
| Capreomycin (1963) IM or IV |  | Inhibits protein synthesis (binds to ribosomal subunit 16S and 23S rRNA (Johansen et al., 2006) | 15 - 30 mg/kg (1 g) MIC 1.25-2.5 µg/mL (Heifets, 1988; Heifets & Lindholm-Levy 1989) | Auditory, vestibular, and renal toxicity |
| Streptomycin (1944) IM |  | Same as Kanamycin | 15-40 mg/kg (1 g) MIC 2-8 µg/mL | Renal, ophthalmic and respiratory toxicity |

| Drug (Discovery) Route | Structure | Mode of Action | Daily Dose (Max. Dose) | Adverse effects |
|----------------------------|---|---|---|--|
| Cycloserine (1952) Oral |  | Inhibition of peptidoglycan synthesis (D-alanine racemase) | 15 - 20 mg/kg (1 g) MIC 5-20 µg/mL | Psychosis, Rashes, Convulsions Depression |
| Ethionamide (1956) Oral |  | Inhibition of mycolic acid synthesis | 15 - 20 mg/kg (1 g) MIC 0.6-2.5 µg/mL | GI upset Hepatotoxicity Hypersensitivity Metallic taste |
| PAS (1946) Oral |  | Inhibition of folic acid and iron metabolism (unknown target) | 150 mg/kg (16 g) MIC 1-8 µg/mL | GI upset Hypersensitivity Hepatotoxicity Sodium load |
| Clofazimine (1954) Oral |  | Inhibits bacterial proliferation by binding to the guanine bases of bacterial DNA | 100 - 300 mg/day MIC 0.12 - 0.24 µg/mL (Lu et al. 2008) | Eosinophilic enteritis, GI irritation, discoloration of the skin (upon sun exposure) |
| Ciprofloxacin (1960s) Oral |  | Inhibition of DNA replication and transcription by inhibiting DNA gyrase | 750 - 1500 mg/day MIC 0.4 to 6.2 µg/mL (Trimble et al., 1987) | GI upset Dizziness Headache Hypersensitivity Restlessness |
| Levofloxacin (1992) Oral |  | Same to Ciprofloxacin | 500 mg/day MIC 0.50 to 0.75 µg/mL (Rastogi et al., 1996) | Same as for Ciprofloxacin |
| Ofloxacin (1980) Oral |  | Same to Levofloxacin | 600 - 800 mg/day MIC 0.12-2 µg/mL (Vacher et al, 1999) | Same as for Ciprofloxacin |

MIC (wherever not referenced) is based on Inderlied & Salfinger, 1999.

IM - intramuscular, IV - intravenous

^aCentre for Disease Control and Prevention

Table 2. Some Second Line Drugs (Source partly from North Dakota Department of Health, 2011).

3. Drug discovery programme

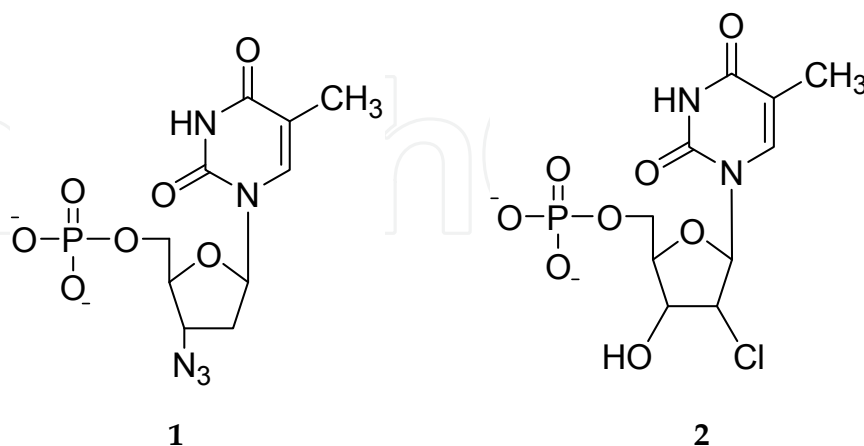
3.1 Early stage drug discovery

Tuberculosis is not only a health threat in Asian or European countries, but a serious problem globally. There is an ever increasing threat of drug-resistant TB appearing as an epidemic in many countries, particularly because no new classes of drugs have been specifically developed for the treatment of tuberculosis since the introduction of RMP in 1967. To tackle this devastating disease, continued high priority research and great efforts are being made to investigate new classes of drugs all over the world. Bill and Melinda Gates foundation has made a major financial philanthropic contribution in this regard worldwide. Governments and private sectors are also opening new avenues with significant funds to fight this disease. Apart from big industries, great roles are being played behind the curtains by basic and semi-applied researchers who start from scratch and work within financial constraints. Following are such examples of different classes of compounds from early stage screening studies.

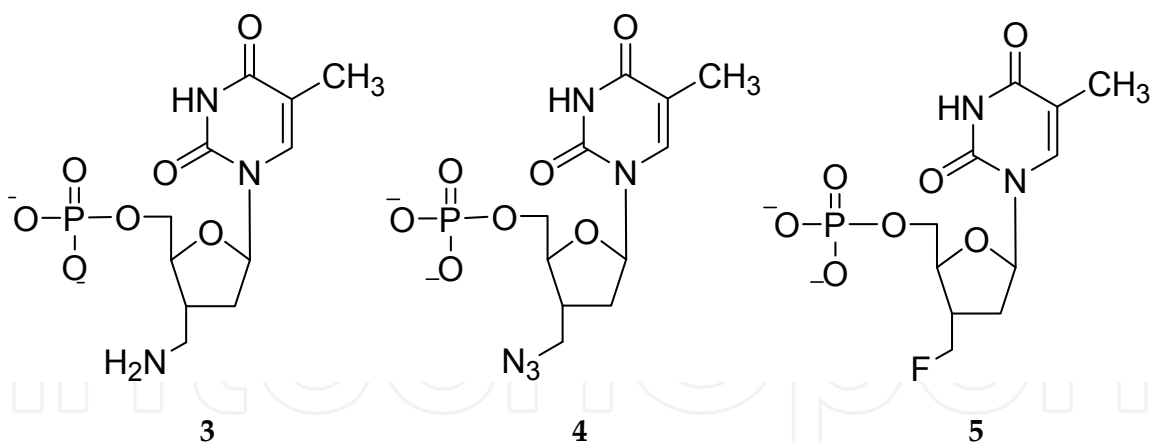
Since research in this field gained momentum after the year 2000, selected reports published from the year 2000 onwards are included here. In view of the scope and timelines of this chapter, the focus of the literature cited is medicinal chemistry.

3.1.1 Nucleosides

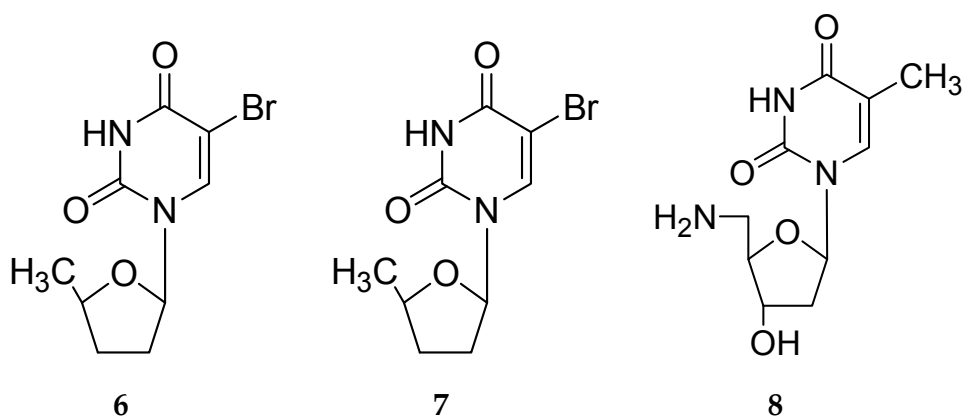
Nucleosides have been of great interest as antiviral agents since decades back. Soon after the emergence of *Mtb* thymidine monophosphate kinase (TMPKmt) as a potentially attractive target for the design of a novel class of antituberculosis agents in year 2001 (Munier-Lehmann et al., 2001), several series of 2'-, 3'-, and 5'-modified nucleosides and nucleotides were synthesized and evaluated for their affinities with respect to TMPKmt. Vanheusden et al, in 2002, reported monophosphates of AZT (**1**) and 2'-chloro-2'-deoxythymidine (**2**), as potent inhibitors of TMPKmt with K_i values of 10 and 19 μM , respectively.



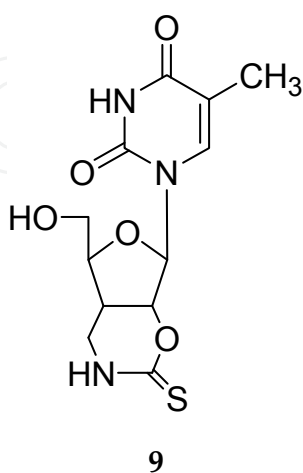
These authors in the following year (Vanheusden et al, 2003) further reported a series of 3'-C-branched-chain-substituted nucleosides and nucleotides for the same target. The compounds **3**, **4**, and **5** were reported to exhibit K_i values of 10.5, 12, and 15 μM , respectively, for TMPKmt.



In the year 2003, another series was reported by the same authors (Vanheusden et al., 2003) where 5-substituted-2',3',5'-trideoxyuridines (6-8) exhibited K_i values of 5, 7 and 12 μM , respectively, for TMPKmt.

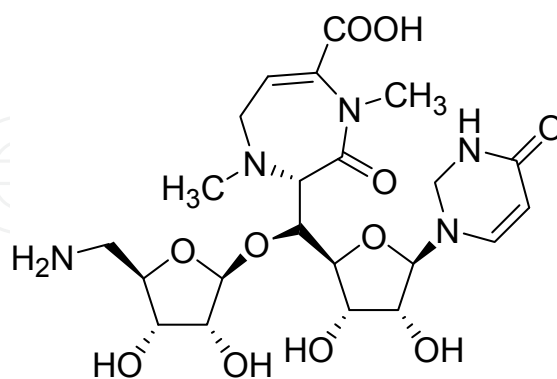


Vanheusden et al. (Vanheusden et al., 2004) also reported a series of bicyclic analogues of thymidine where compound 9 demonstrated K_i of 3.5 μM for TMPKmt with good selectivity index (SI 200) over TMPKh.



In all these reports, however, only enzyme inhibition was described and inhibition of mycobacterial replication was not demonstrated.

A nucleoside antibiotic (CPZEN-45) produced by *Streptomyces* sp., first described in 2003 by the Microbial Chemistry Research Foundation (MCRF) and Meiji Seika Kaisa Ltd. of Japan, is now undergoing preclinical studies as an anti-TB agent. Details of CPZEN-45 are provided in the preclinical section.

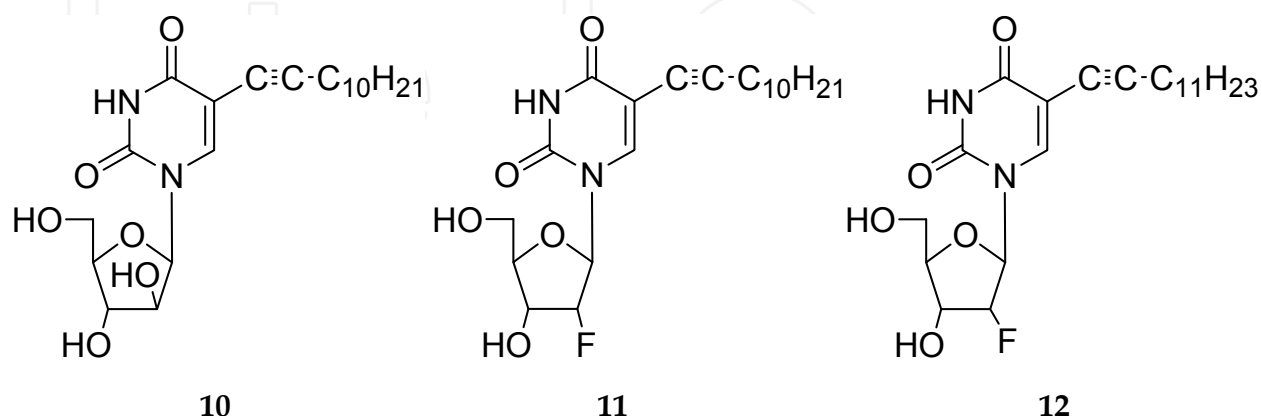


CPZEN-45

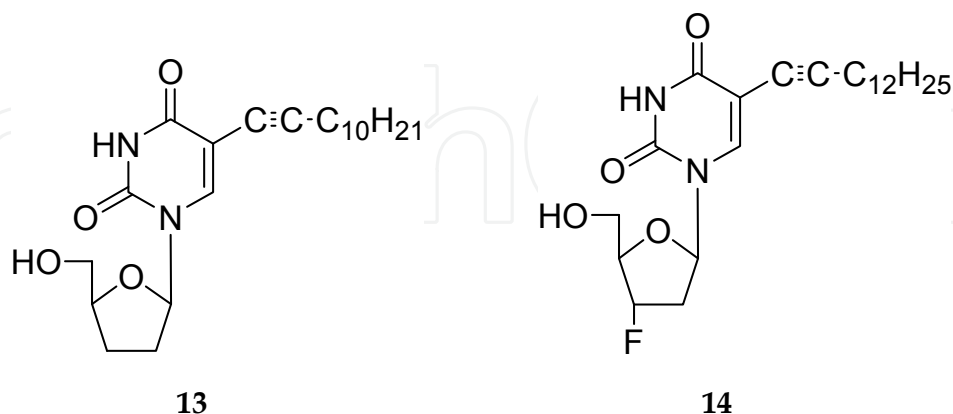
The complete genome sequence of *Mtb* has been deciphered (Cole et al., 1998). It encodes many of the enzymes required for DNA and RNA synthesis, and pyrimidine and purine biosynthesis. Our group (Johar et al., 2005) therefore hypothesized that modified nucleoside analogs could target several enzymes involved in nucleic acid metabolism. We were first to investigate and demonstrate potent antimycobacterial activity of 5-substituted pyrimidine nucleoside analogs (Johar et al., 2005). The antimycobacterial activity of test nucleosides was examined by mycobacterial growth inhibition using microplate alamar blue assay (MABA) (Franzblau et al., 1998). We observed that the most potent TMPK_{mt} inhibitors reported earlier (Pochet et al., 2003; Vanheusden et al., 2002; Vanheusden et al., 2003) did not show antituberculosis activity in whole cell based assays. Thus the ability of a compound to function as a selective inhibitor of TMPK_{mt} may not correlate well with its antimycobacterial activity. A cell based assay includes the steps of entry into bacterial cells and metabolism which could otherwise limit the efficacy of test molecules (Johar et al., 2005).

Since the initial report in 2005, our group (Kumar, R. and colleagues) has made a significant contribution in the evaluation of pyrimidine nucleosides as anti-tuberculosis agents. During our studies, we initially investigated the effect of a number of known antiviral and anticancer nucleosides modified in the base and/or sugar moiety against *Mtb*, *M. bovis* and *M. avium*. At concentrations upto 100 µg/ml, none of these agents showed potent inhibition of mycobacterial growth. In our subsequent studies, we designed, synthesized and examined a variety of 2-, 4-, 5- and/or 6-substituted/unsubstituted pyrimidine nucleosides containing various deoxyribose, ribose, arabinose, dideoxyribose and acyclic moieties. During our continued search of novel anti-TB agents, we found that 5-alkynyl substituted pyrimidine nucleosides were very potent inhibitors of mycobacteria (Rai et al., 2005). We (Johar et al., 2007), reported that pyrimidine nucleoside analogs 1-β-D-2'-arabinofuranosyl-5-dodecynyluracil (**10**), 1-(2'-deoxy-2'-fluoro-β-D-ribofuranosyl)-5-dodecynyluracil (**11**), and 1-(2'-deoxy-2'-fluoro-β-D-ribofuranosyl)-5-tetradecynyluracil (**12**) exhibited potent antimycobacterial potency in the series against *M. bovis* and *Mtb*. The MIC₉₀ exhibited by compounds **10**, **11**,

and **12** (1-5 $\mu\text{g}/\text{mL}$) against *Mtb* H37Ra was close to that of the reference drug RMP (0.5-1 $\mu\text{g}/\text{mL}$). These compounds were also found to retain sensitivity against a RMP-resistant strain of *Mtb* H37Rv (American Type Culture Collection [ATCC] 35838, resistant to RMP at 2 $\mu\text{g}/\text{mL}$) at similar concentrations. No significant toxicity for these compounds was observed in MTT test *in vitro* against Vero cells and human foreskin fibroblast (HFF cells) up to a concentration of 100 $\mu\text{g}/\text{mL}$ ($\text{CC}_{50} > 100 \mu\text{g}/\text{mL}$).

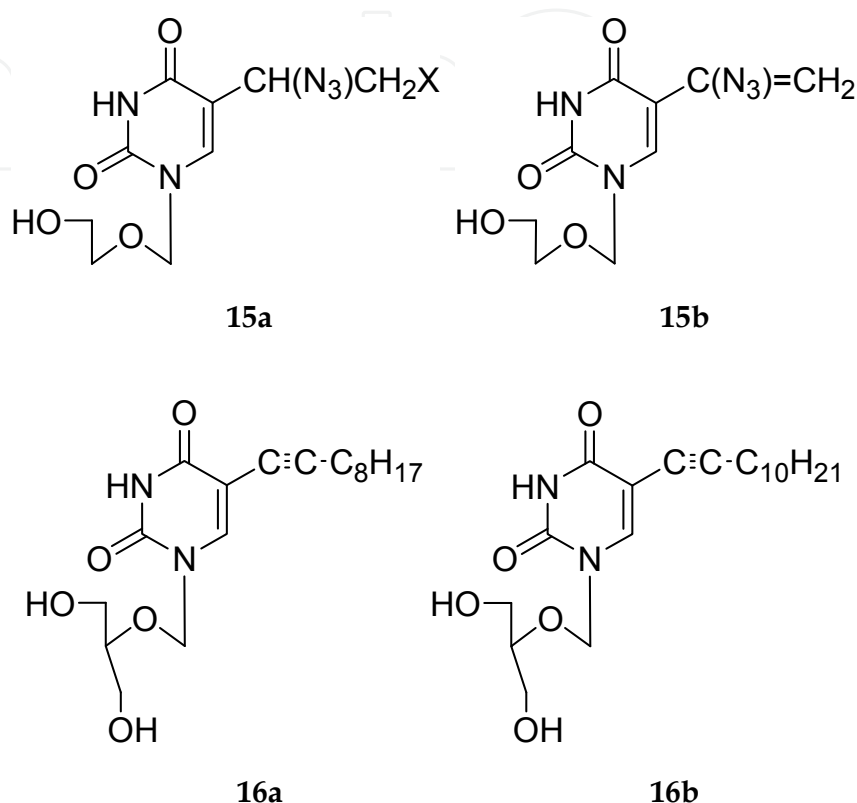


In the same year, we (Rai et al, 2007) further reported syntheses and evaluation of a series of 5-acetylenic derivatives of 2',3'-dideoxyuridine, and 3'-fluoro-2',3'-dideoxyuridine for their antimycobacterial activity against *M. bovis*, *Mtb*, and *M. avium*. Compound **13** (among 2',3'-dideoxyuridine series) and compound **14** (among 3'-fluoro-2',3'-dideoxyuridine series) demonstrated excellent antimycobacterial activity (MIC 1-2 $\mu\text{g}/\text{mL}$) against *Mtb* H₃₇Ra. The compounds **13** and **14**, were also subjected to determine their antimycobacterial activity against a RMP-resistant H37Rv strain (ATCC 35838, resistant to RMP at 2 $\mu\text{g}/\text{mL}$) of *Mtb* using the radiometric-BACTEC assay. The drug-resistant *Mtb* strain was susceptible to the compounds **13** and **14** (MIC_{90} 1-2 $\mu\text{g}/\text{mL}$). No toxicity was observed *in vitro* against Vero cells (MTT test) up to the highest concentrations tested ($\text{CC}_{50} > 100 \mu\text{g}/\text{mL}$).

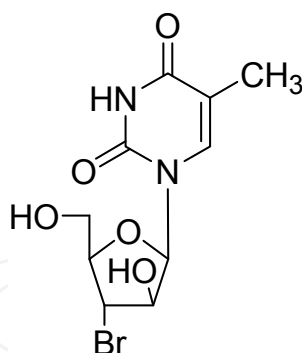


In a subsequent article in the same year by our group (Srivastav et al, 2007), *in vitro* antimycobacterial activities of several 5-substituted acyclic pyrimidine nucleosides containing 1-(2-hydroxyethoxy)methyl and 1-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl] acyclic moieties were investigated against *Mtb* H37Ra, *M. bovis*, and *M. avium*. In this study, 1-(2-hydroxyethoxy)methyl-5-(1-azido-2-haloethyl) (**15a**), 1-azidovinyl) analog (**15b**), 1-[(2-

hydroxy-1-(hydroxymethyl)ethoxy)methyl]-5-decynyluracil (**16a**), and 1-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]-5-dodecynyluracil (**16b**) exhibited moderate *in vitro* anti-tubercular activity (100% inhibition @ 50 $\mu\text{g}/\text{mL}$) against these mycobacteria. These compounds did not show any toxicity *in vitro* against Vero cells and HepG2 cells up to a concentration of 100 $\mu\text{g}/\text{mL}$.

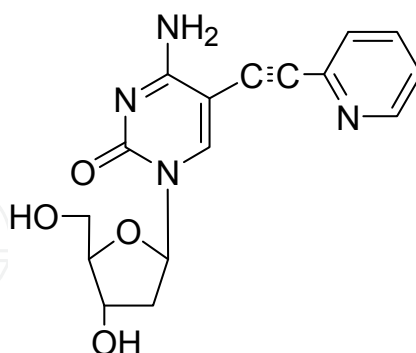


In continued efforts in drug design and discovery for anti-tuberculosis agents, our group (Shakya et al, 2010) investigated various 2'- or 3'-halogeno derivatives of pyrimidine nucleosides containing uracil, 5-fluorouracil, and thymine bases. Among the compounds tested, 3'-bromo-3'-deoxy-arabinofuranosylthymine (**17**) was the most effective antituberculosis agent in the *in vitro* assays against wild-type *Mtb* strain (H37Ra) which displayed $\text{MIC}_{50} = 1 \mu\text{g}/\text{mL}$ by the MABA assay. Further, it displayed $\text{MIC}_{50} = 1\text{-}2 \mu\text{g}/\text{mL}$ against drug-resistant (H37Rv) (RMP-resistant and INH-resistant) strains of *Mtb* using BACTEC assay (Collins & Franzblau, 1997). The antimycobacterial effect of potent compounds was also determined against intracellular mycobacteria in a human monocytic cell-line (THP-1) infected with *Mtb* H37Ra strain using the colony-forming units (CFU) assay (Bermudez et al., 2001). Interestingly, the compound **17** demonstrated slightly better activity against intramacrophagic mycobacteria (80% reduction at 10 $\mu\text{g}/\text{mL}$ concentration) than extracellular mycobacteria (75% reduction at 10 $\mu\text{g}/\text{mL}$ concentration). In contrast, pyrimidine nucleosides possessing 5-fluorouracil base were weak inhibitors of *Mtb* H37Ra. The XTT and ^3H incorporation assays were performed to evaluate the toxicity of the investigated compounds *in vitro* against a human hepatoma cell line (Huh7). No cytotoxicity was found up to the highest concentration of compounds tested ($\text{CC}_{50} > 100\text{-}200 \mu\text{g}/\text{mL}$).



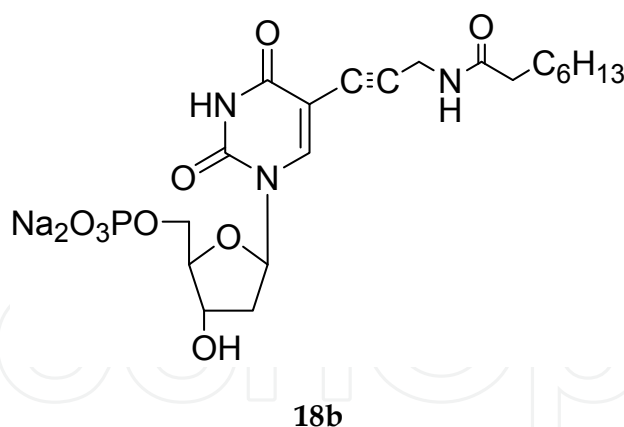
17

Our group in the same year (Srivastav et al., 2010) reported investigation of antimycobacterial activities of several 5-alkyl, 5-alkynyl, furanopyrimidines and related 2'-deoxynucleosides against *Mtb*. Compounds with 5-arylalkynyl substituents displayed potent *in vitro* antitubercular activity against *M. bovis* and *Mtb* (MIC 0.5-5 $\mu\text{g/mL}$). We found that 5-(2-pyridynylehynyl)-2'-deoxycytidine (18) exhibited potent activity against *Mtb* and showed no cytotoxicity Huh-7 cells up to a concentration of >200 $\mu\text{g/mL}$ using XTT and ^3H -thymidine uptake assays. Therefore it was selected to test its potency in a mouse model (BALB/c) of *Mtb* (H37Ra) infection. At a dose of 50 mg/kg for 5 weeks, compound 18 showed promising *in vivo* efficacy in this mouse model. Statistically significant reduction in mycobacterial load was observed in lungs, livers and spleens of the treated mice. Our work provides first evidence of antimycobacterial potential of 5-substituted pyrimidine nucleosides in an animal model as a potential new class of antituberculosis agents.

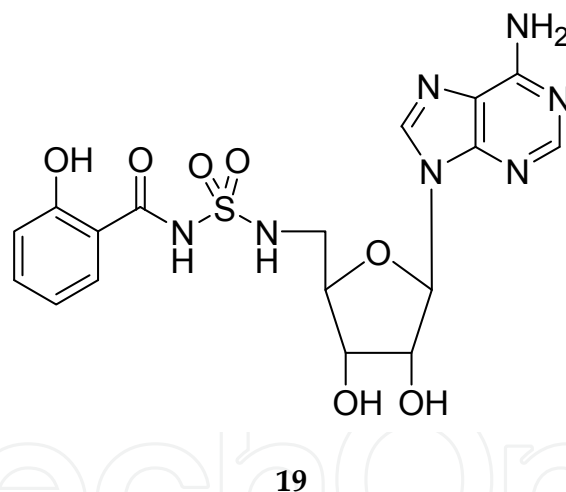


18a

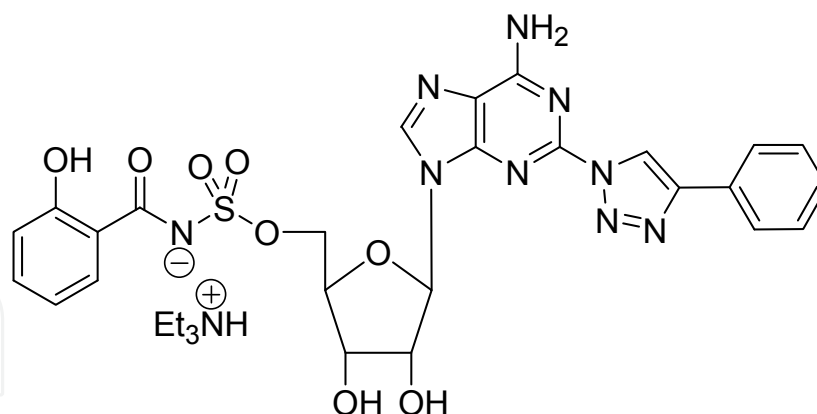
Recently, Kogler et al (Kogler et al., 2011) reported a series of 5-substituted -2'-deoxyuridine monophosphate analogs as potential inhibitors of mycobacterial flavin-dependent thymidylate synthase (ThyX). Compound N-(3-(5-(2'-deoxyuridine-5'-monophosphate)) prop-2-ynyl)-octanamide displayed selective potent inhibition of ThyX with an IC_{50} value of 0.91 μM . This derivative was found to lack activity against the classical mycobacterial thymidylate synthase (ThyA, IC_{50} >50 μM).



Somu et al (Somu et al., 2006) reported a purine nucleoside compound **19** ($\text{MIC}_{99} = 0.19 \mu\text{M}$) inhibiting siderophore biosynthesis of *Mtb* in H37Rv strain under iron-limiting conditions (Domenech et al., 2005, as cited in Somu et al., 2006). The activity of **19**, according to the authors, was due to inhibition of the adenylate-forming enzyme MbtA, which is involved in biosynthesis of the mycobactins. The cytotoxicity of the potent compounds in the series was evaluated against the P388 murine leukemia cell line. None of the inhibitors displayed any toxicity up to the maximum concentration tested ($\text{ED}_{50} > 100 \mu\text{g/mL}$).

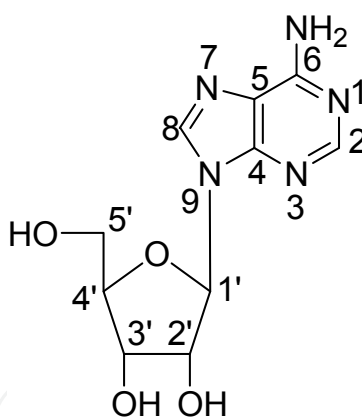


Gupte et al (Gupte et al., 2008) demonstrated 2-triazole derivatives of 5'-O-[N-(salicyl)sulfamoyl]adenosine as inhibitors of aryl acid adenylating enzymes (AAAE) involved in siderophore biosynthesis by *Mtb* H37Rv. Enzyme assays were performed at 37 °C with recombinant MbtA expressed in *E. coli*. On the basis of observed potency ($\text{MIC} 3.13 \mu\text{M}$), selectivity, lack of cytotoxicity, and enhanced lipophilicity, compound **20** was reported as the best candidate. No inhibition of cell growth was observed upto 100 μM when this class of compounds were evaluated for inhibition of cell viability against Vero cells using the MTT assay. The compound **20** was also evaluated against MEL, OCL-3, and REH human cancer cell lines. Cell proliferation of OCL-3 and REH lines were not affected at 100 μM , while in the MEL line approximately 25% inhibition was shown at 100 μM .



20a

Adenosine (Ado) kinase is a purine salvage enzyme that phosphorylates adenosine to adenosine-monophosphate. A large number of adenine modified nucleosides were evaluated as substrates and inhibitors of Ado kinase from *Mtb* (Long & Parker, 2006) The best substrates were 2-aza-adenosine, 8-aza-9-deazaadenosine and 2-fluoroadenosine and the most potent inhibitors were N-1-benzyladenosine ($K_i = 0.19 \mu\text{M}$), 2-fluoroadenosine ($K_i = 0.5 \mu\text{M}$), 6-cyclopentylloxy purine riboside ($K_i = 0.15 \mu\text{M}$) and 7-iodo-7-deazaadenosine ($K_i = 0.21 \mu\text{M}$). Several of these adenosine analogs showed promising antitubercular activity when MIC studies were performed.



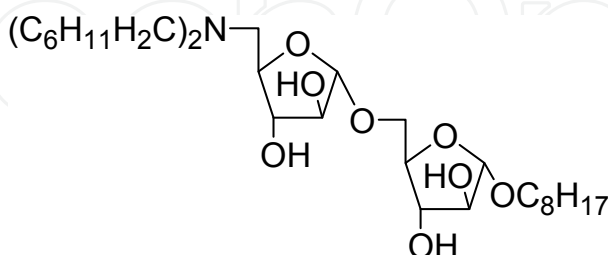
20b

In an extension of their work (Long et al, 2008) modifications to the base and ribofuranosyl moiety or modifications to the glycosidic bond positions of adenosine were analyzed against *Mtb* Ado kinase. In this study, the best substrates identified were carbocyclic adenosine, 8-aza-carbocyclic adenosine and 9-[α -L-lyxofuranosyl]-adenine.

3.1.2 Carbohydrates

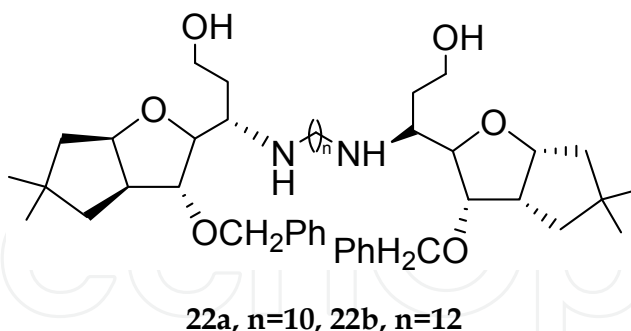
Sugar derivatives have also been examined as antimycobacterial agents. Although many reports have been published, most of them did not include toxicity data. Some representative examples of this class are summarized here.

Pathak et al (Pathak et al, 2003) synthesized several octyl 5-O-(α -D-arabinofuranosyl)- α -D-arabinofuranoside disaccharide analogs substituted at the 5-position of the non-reducing end of sugar and tested *in vitro* (Suling et al., 1998, as cited in Pathak et al, 2003) against *Mtb* (H37Ra, ATCC 25177), *M. avium* complex (MAC) as well as in a cell free assay system for arabinosyltransferase acceptor/inhibitor activity (Lee et al., 1997, as cited in Pathak et al, 2003). Compound **21** displayed IC₅₀ of 1.56 mM in cell free assay and MIC 8 μ g/mL against *Mtb*. No toxicity data was reported.

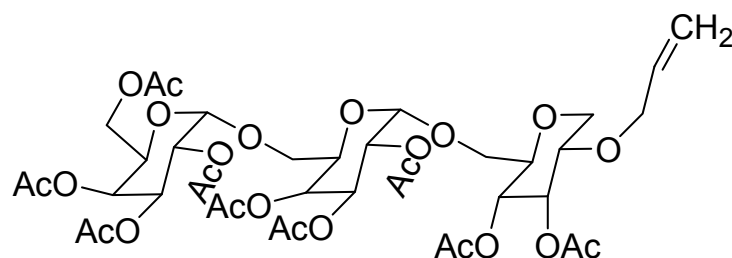


21

Tripathi et al (Tripathi et al., 2005) reported bis-glycosylated diamino alcohols with the most active compound **22a** showing MIC of 3.12 μ g/mL against *Mtb* H37Ra as determined by MABA assay. But this compound displayed MIC > 50 μ g/mL against *Mtb* H37Rv by Agar microdilution method (Saito et al., 1991, as cited in Tripathi et al., 2005). In this series, they discovered the next active compound **22**, exhibiting activity against *Mtb* H37Ra (MIC 12.5 μ g/mL by MABA assay) and against *Mtb* H37Rv (MIC 6.25 μ g/mL by Agar microdilution method) that was considered to test further. The compound **22** was also found to be active against MDR strain and showed mild protection in mice. According to the report, this compound seems to possess efficacy against *Mtb* infection in mice at non-toxic concentration (25 mg/Kg). However, at higher doses it caused toxicity.

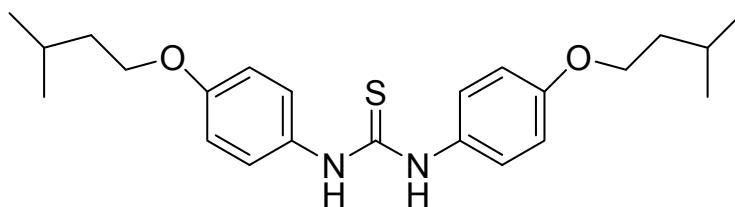


Chiba et al (Chiba et al., 2007) synthesized sugar derivatives of stachyose, and evaluated them for antibacterial activity against *Mtb*, *M. avium*, and *S. aureus* using broth dilution methods (Takii et al., 2002, as cited in Chiba et al., 2007) in MiddleBrook 7H9 broth. The compound **23** (OCT359) was identified as the most active compound in the series with MIC 3.13 μ g/mL against *Mtb* H37Rv. OCT359 was also tested against various drug-sensitive and -resistant clinical isolates of *Mtb*. Among them 25 clinical isolates of drug-resistant *Mtb* and 19 drug-sensitive *Mtb* were sensitive to OCT359. The MICs of OCT359 for these clinical isolates ranged from 3.13 to 25 μ g/mL. No toxicity data was reported on any host cell lines.

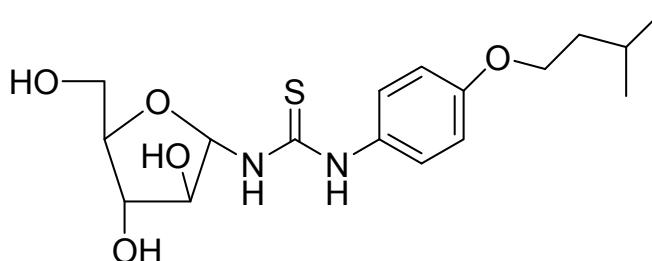


23

Liav et al (Liav et al., 2008) prepared derivatives of thiocarlide (THC), a previously known antitubercular drug, for their evaluation against *Mtb* H37Rv using MABA assay. The most active compound reported was **24** having MIC in the range of 1.56-3.12 $\mu\text{g}/\text{mL}$. No toxicity data for this compound was presented on any host cell line.

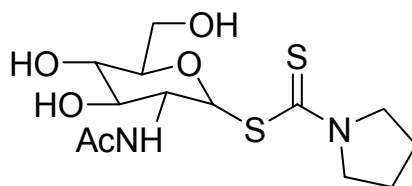


THC



24

In a recent report, Horita (Horita et al, 2011) described modification of their previously reported lead compound OCT313 (Glc-N-Ac -DMDTCB) (MIC 25 $\mu\text{g}/\text{mL}$ against *Mtb* H37Rv by Broth dilution method). The resultant compound Glc-N-Ac-pyrrolidine dithiocarbamate (**25**, OCT313HK, Glc-N-Ac-PDTC) exhibited potent anti-tubercular activity with MIC of 6.25 $\mu\text{g}/\text{mL}$. OCT313HK was also effective against *Mtb* clinical isolates, including MDR and XDR strains at similar concentrations (MIC 6.25-12.5 $\mu\text{g}/\text{mL}$). No toxicity data was reported on mammalian cell lines.



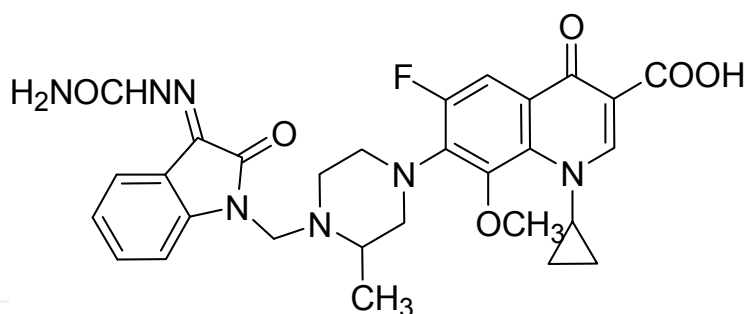
25

3.1.3 Heterocyclic compounds

3.1.3.1 Quinolines and quinoxalines

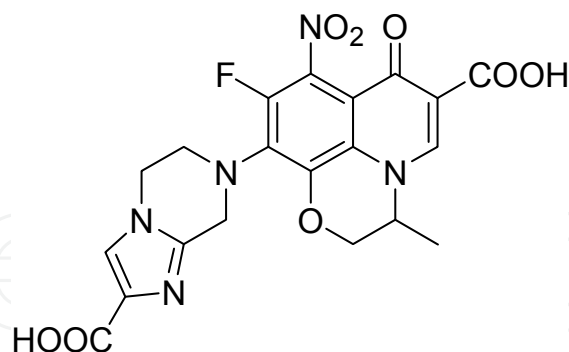
Quinolines have also been of interest for evaluation as antibacterial agents since fluoroquinolones are already used as antibiotics (e.g. ciprofloxacin, levofloxacin, ofloxacin). Moxifloxacin and Gatifloxacin from this class are in Phase III clinical trial for tuberculosis treatment (see details in the section describing drugs in Phase III). Many research articles are available in literature on quinoline as anti-TB agents.

Sriram (Sriram et al, 2006) reported a series of 7-substituted derivatives of gatifloxacin and evaluated them for antimycobacterial activity *in vitro* and *in vivo* against *Mtb* H37Rv and MDR-TB. The compounds were also tested for their ability to inhibit the supercoiling activity of DNA gyrase from *Mtb*. Among this series, compound **26** was found to be equally active (IC_{50} of 3.0 $\mu\text{g}/\text{mL}$) as gatifloxacin in the inhibition of the supercoiling activity of wild-type *Mtb* DNA gyrase. The compound **26** was also found to be the most active *in vitro* with an MIC of 0.0125 $\mu\text{g}/\text{mL}$ against *Mtb* and MDR-TB. Activity evaluation *in* animal model showed that this compound decreased the bacterial loads in lung and spleen tissues by 3.62- and 3.76- \log_{10} , respectively. After 72 h exposure with the test compounds, viability of Vero cells was assessed using MTT assay to determine their cytotoxicity. The compounds were found to be non-toxic up to a concentration of 62.5 $\mu\text{g}/\text{mL}$. The compound **26** showed selectivity index (IC_{50}/MIC) of >1250.



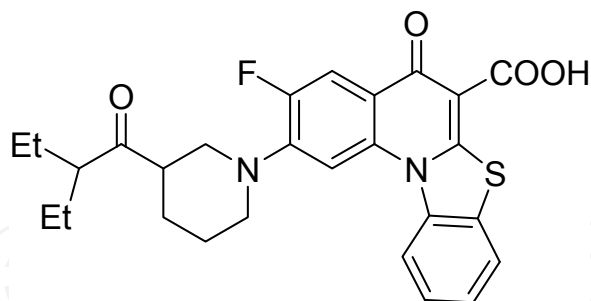
26

Sriram and coworkers (Dinakaran et al, 2008 a) also synthesized novel ofloxacin (OFX) derivatives and evaluated them for *in vitro* and *in vivo* antimycobacterial activities against *Mtb* H37Rv, MDR-TB, and *M. smegmatis* using agar dilution method. These compounds were also tested for their ability to inhibit the supercoiling activity of DNA gyrase from mycobacteria. Among the synthesized compounds, **27** exhibited most potent activity (MIC_{99} of 0.19 μM and 0.09 μM against *Mtb* and MDR-TB, respectively). The compound **27** decreased bacterial loads (strain ATCC 35801) in lung and spleen tissues by 1.91 and 2.91 - \log_{10} , respectively, at 50 mg/kg dose when evaluated in a mouse model. This compound was reported to possess a selectivity index (IC_{50}/MIC) of >1467.



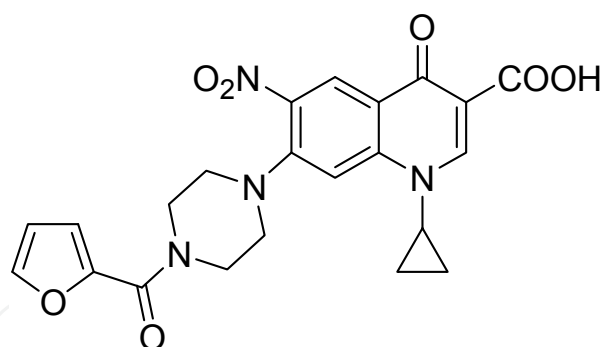
27

Another publication by the same group (Dinakaran et al, 2008 b) described various 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid derivatives. Among the reported compounds, **28** displayed the most potent activity *in vitro* with MICs of 0.18 and 0.08 μM against *Mtb* and MDR-TB, respectively. In a mouse model of *Mtb* infection, **28** decreased bacterial loads in lung and spleen tissues with 2.78 and 3.12 \log_{10} , respectively, at the dose of 50 mg/kg. The selectivity indices ($\text{IC}_{50}/\text{MIC}$) of the compound **28** were reported to be 1576 against MDR-TB and 700 against *Mtb*. Phototoxicity evaluation was also performed (Mayne et al., 1997, as cited in Dinakaran et al, 2008 b) and no significant phototoxicity was recorded.



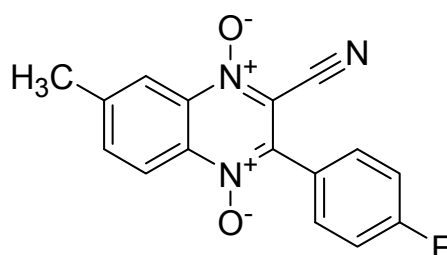
28

Senthilkumar et al, 2009, published synthesis of various 1-(substituted)-1,4-dihydro-6-nitro-4-oxo-7-(sub-secondary amino)-quinoline-3-carboxylic acids. Among the compounds investigated, **29** was found to be the most potent compound *in vitro* with MIC values of 0.08 and 0.16 μM against *Mtb* and MDR-TB, respectively. In the *in vivo* studies, **29** significantly decreased bacterial load in lung and spleen tissues, at 50 mg/kg dose. The SI ($\text{IC}_{50}/\text{MIC}$) of **29** was stated to be 793 against MDR-TB and 1586 against *Mtb*. No significant phototoxicity was described for **29**.



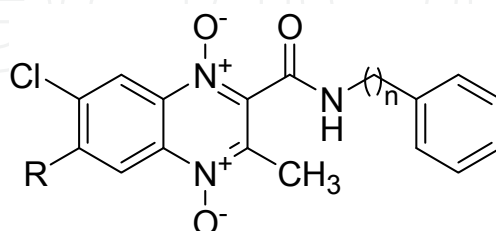
29

Other groups have also been exploring quinoline derivatives as anti-TB agents. Vicente et al (Vicente et al., 2009) published a series of 3-phenylquinoxaline 1,4-di-N-oxide against *Mtb* H37Rv using MABA assay. The compounds exhibiting fluorescence were tested in the BACTEC 460-radiometric system. The compounds affecting <90% inhibition in the primary screen (MIC >6.25 $\mu\text{g}/\text{mL}$) were not evaluated further. Thirty-four of the seventy tested compounds showed MIC values less than 0.2 $\mu\text{g}/\text{mL}$. The most active compound reported was **30** (MIC <0.2 $\mu\text{g}/\text{mL}$) with an IC_{50} >100 (SI >500).



30

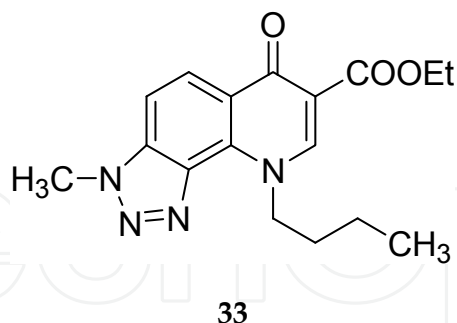
Ancizu et al (Ancizu et al., 2010) described a series of 3-methylquinoxaline-2-carboxamide 1,4-di-N-oxide derivatives. Many of the tested compounds showed MIC values less than 1 $\mu\text{g}/\text{mL}$. In this report, compounds **31** and **32** displayed most significant inhibition of *Mtb* H37Rv (MIC <0.2 $\mu\text{g}/\text{mL}$). Cytotoxicity evaluation indicated that **31** and **32** were non-toxic with IC_{50} value of >100 and SI >500.



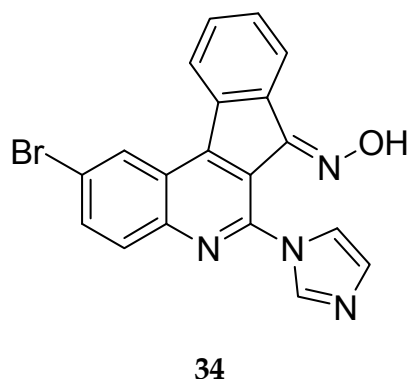
31, R=Cl, n=1; 32, R=H, n=2

Carta et al (Carta et al., 2007) reported antimycobacterial evaluation of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3H-[1,2,3]-triazolo [4,5-h]quinolone-carboxylic acids and their esters against wild-type H37Rv and 11 clinically isolated strains of *Mtb*. Several derivatives inhibited mycobacterial replication with MIC_{90} in the range of 0.5–3.2 $\mu\text{g}/\text{mL}$. The most

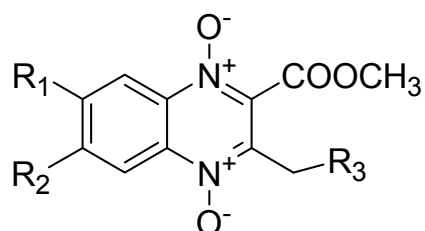
potent compound **33** ($MIC_{90} = 0.5 \mu\text{g/mL}$) showed no cytotoxicity ($CC_{50} > 50 \mu\text{g/mL}$), when tested against human macrophages and Hep-2 cells.



Upadhayaya et al (Upadhayaya et al., 2011) identified indeno[2,1-c]quinoline derivatives which were considerably active (MIC 0.39-0.78 $\mu\text{g/mL}$) but had solubility problems. Ester derivatives of the lead compound indeno[2,1-c]quinolines were synthesized, which showed 2- to 4-fold improved anti-TB activities, with increased solubility and superior selectivity index (SI) over their respective parent compounds. In this study, compound **34** was described to be the most potent agent with MIC of $<0.39 \mu\text{g/mL}$. In general, no cytotoxicity was observed in Vero cells.



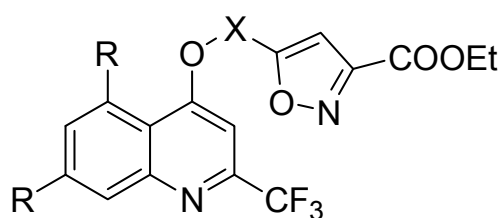
Jaso et al (Jaso et al., 2005) evaluated a series of 6(7)-substituted quinoxaline-2-carboxylate 1,4-dioxide derivatives against *Mtb* H37Rv. Fourteen compounds were selected to test for their activity against intramacrophagic mycobacteria. It was found that ethyl and benzyl 3-methylquinoxaline-2-carboxylate 1,4-dioxide derivatives with a chlorine group at position 7 of the benzene moiety (compound **35**, MIC 0.1 $\mu\text{g/mL}$, SI 470) and the unsubstituted derivative (**36**, MIC 0.1 $\mu\text{g/mL}$, SI 76) have good antitubercular activity, including activity in macrophages (EC_{90} 0.15 $\mu\text{g/mL}$ and 0.0005 $\mu\text{g/mL}$, respectively). The compounds **37** and **38** of the series were also active against drug-resistant strains of *Mtb* H37Rv with MIC 0.39-1.56 and 3.13-12.5, respectively.



35, $R_1 = \text{H}$, $R_2 = \text{H}$, $R_3 = \text{Ph}$; **36**, $R_1 = \text{Cl}$, $R_2 = \text{H}$, $R_3 = \text{Ph}$;

37, R₁ = R₂ = R₃ = CH₃; **38**, R₁ = Cl, R₂ = Cl, R₃ = Ph

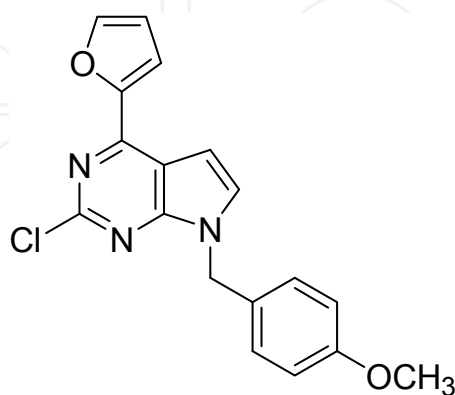
Lilienkampf et al (Lilienkampf et al., 2009) revealed several potent quinolines bearing an isoxazole containing side-chain as anti-TB compounds. These compounds were first tested for their activity against the *Mtb* strain H37Rv using MABA assay. The compounds showing good anti-TB activity were further evaluated for their potency against non replicating persistent TB (NRPTB) in a low oxygen recovery assay (LORA). The most active compounds, **39** and **40**, exhibited MICs of 0.77 μ M and 0.95 μ M, respectively against the replicating bacteria. These compounds, in general, also had good potency against the nonreplicating persistent bacteria without toxicity on Vero cells up to 128 μ M. The compounds **39** and **40** also retained anti-TB activity against RMP-, INH-, and streptomycin resistant *Mtb* strains.



39, R = CF₃, X = CH₂; **40**, R = H, X = m-Ph

3.1.3.2 Pyrimidine and purines

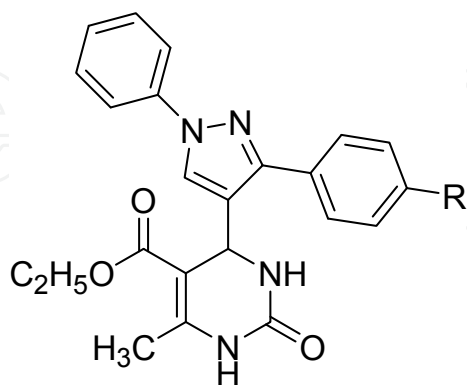
Khoje et al (Khoje et al, 2010) synthesized various purine analogs and evaluated them *in vitro* against *Mtb* H37Rv using MABA assay. The 8-aza-, 7-deaza- and 8-aza-7-deazapurine analogs displayed good antimycobacterial activities. The 7-deazapurine analogs exhibited MIC values between 0.08 and 0.35 μ M; comparable or better than the reference drugs (RMP, MIC 0.09 μ M; INH, MIC 0.28 μ M and PA-824, MIC 0.44 μ M). The most active compound among 7-deaza purines was **41** with MIC 0.11 μ M and SI 1063. The 7-deazapurines were slightly more toxic towards mammalian cells, but still had good selectivity indices. In this study, five most active compounds were also evaluated against a panel of drug-resistant *Mtb* strains, where they all were found to retain activity. However, these compounds were significantly less active when tested against non-replicating persistent *Mtb*.



41

Trivedi et al (Trivedi et al., 2010) examined a series of dihydropyrimidines for their *in vitro* activity against *Mtb* H37Rv. All compounds were initially screened for their *in vitro* activity

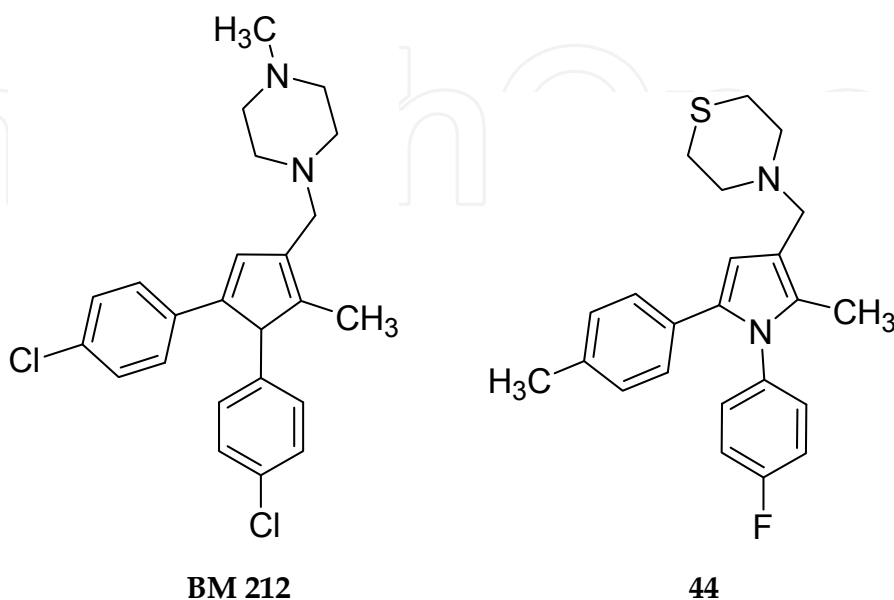
at 6.25 $\mu\text{g}/\text{mL}$. The compounds exhibiting 90% inhibition in the initial screen were re-examined at and below 6.25 $\mu\text{g}/\text{mL}$ using two-fold dilutions to determine the actual MIC. Two compounds, **42** and **43** were found to be the most active agents with MIC of 0.02 $\mu\text{g}/\text{mL}$. These compounds were more potent than the reference drug INH. In Vero cells, they exhibited $\text{IC}_{50} > 10 \mu\text{g}/\text{mL}$ (SI >500).



42, R=F, **43**, R=NO₂

3.1.3.3 Pyrrole derivatives

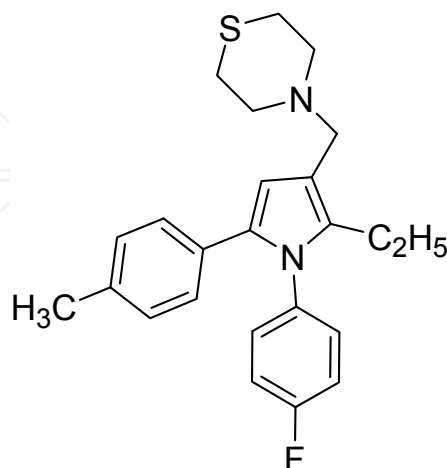
Biava et al (Biava et al., 2006) reported design and synthesis of pyrrole analogues of BM212. The compounds were preliminarily screened for their activity toward *Mtb B814* and *M. fortuitum CA10*. Compounds showing MIC values of 16 $\mu\text{g}/\text{mL}$ or lower were further tested against *Mtb CIP 103471* and a panel of atypical mycobacteria, such as *M. marinum CIP 6423*, *M. avium CIP 103317*, and *M. smegmatis CIP 10359*. Cytotoxicity was examined in Vero cells to determine the maximum nontoxic dose (MNTD₅₀) defined as the drug concentration that decreased cell multiplication to less than 50% of the control. The best compound reported in this series was **44** with MIC of 0.4 $\mu\text{g}/\text{mL}$, MNTD₅₀ of 64 $\mu\text{g}/\text{mL}$ and a high protection index (MNTD/MIC, 160) that was better than BM212, INH, and streptomycin (6, 128, and 128, respectively).



BM 212

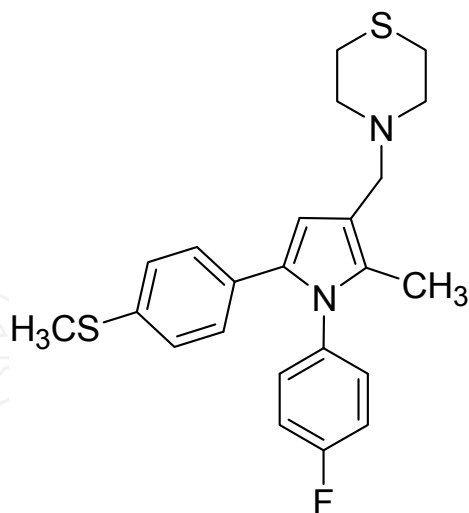
44

In the year 2009, the same group (Biava et al., 2009) further investigated new diarylpyrroles on the basis of SAR analysis of pyrroles, reported by them previously. The compound **45** emerged as the most potent agent (MIC 0.25 $\mu\text{g}/\text{mL}$) with protective index (maximum non toxic dose in Vero cells/ MIC) > 512.



45

Biava et al (Biava et al., 2010) also identified 4-((1-(4-fluorophenyl)-2-methyl-5-(4-(methylthio)phenyl)-1H-pyrrol-3-yl)methyl)thiomorpholine (**46**) as a potent antimycobacterial agent against *Mtb* 103471 and H37Rv strains (MIC values of 0.125 $\mu\text{g}/\text{mL}$ comparable to streptomycin and RMP), with a cytotoxicity (CC_{50}) value of >128 $\mu\text{g}/\text{mL}$ and protection index of >1000.

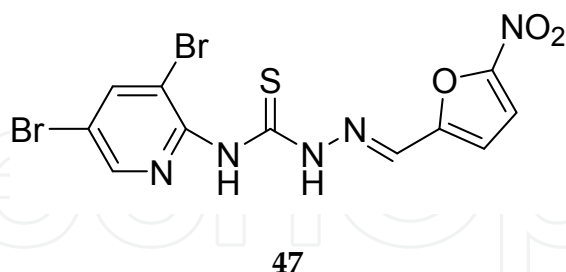


46

3.1.3.4 Furan

5-Nitrofuran-2-yl derivatives (Sriram et al. 2009) were investigated against tubercular (H37Rv) and various non-tubercular mycobacterial species in log-phase and 6-week-starved cultures. The compound **47** exhibited MIC of 0.22 μM . This compound showed 3 times more activity than INH and equal activity as RMP in log-phase culture of *Mtb*

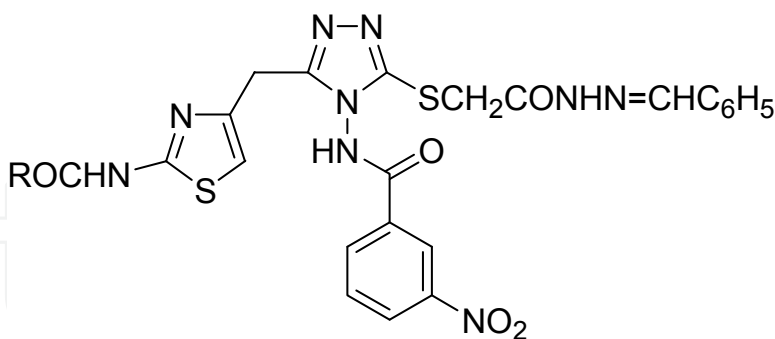
H37Rv. It inhibited starved *Mtb* H37Rv with MIC of 13.9 μM and was 50 times more active than INH and slightly more active than RMP. It displayed an IC_{50} of 139 μM in Vero cells.



3.1.3.5 Azoles

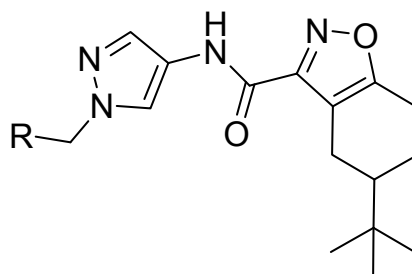
Azoles are one of the major classes of compounds which have been probed for anti-TB activity, but unfortunately, many of the publications emerging on azoles did not provide toxicity data, making it difficult to analyze their potential. Following are some of the representatives studies found worthy to summarize here.

Shiradkar et al (Shiradkar et al, 2007) published synthesis and antituberculosis activity of a series of N-{4-[(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)methyl]-1,3-thiazol-2-yl}-2-substituted amide derivatives against *Mtb* H37Rv (ATCC 27294) using MABA and BACTEC 460 assays where compounds **48** and **49** demonstrated MICs of 0.78 and 0.39 μM , respectively. The cytotoxicity analysis by neutral red uptake assay in Vero-C-1008 cell line showed that none of this class of compounds was toxic up to a concentration of 50 $\mu\text{g}/\text{mL}$.



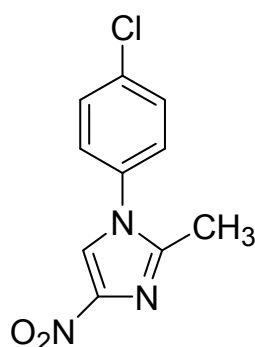
48, R = CH₃; 49, R = Ph

Velaparathi et al (Velaparathi et al., 2008) reported 5-*tert*-butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide derivatives as novel and potent inhibitors of *Mtb* pantothenate synthetase (PS). Pantothenate is a key precursor of coenzyme A and acyl carrier protein, essential for many intracellular processes including fatty acid metabolism, cell signaling, and synthesis of polyketides and nonribosomal peptides. The PS pathway is not present in humans. Compounds **50** and **51** displayed the best inhibition in terms of IC_{50} of < 100 nM.



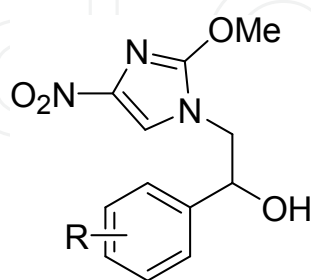
50, R = Ph; 51, R = 2-naphthyl

N-Aryl-*C*-nitroazoles were investigated by Walczak et al (Walczak et al., 2004) against H37Rv (ATCC 27294) using MABA assay. Compound **52** exhibited MIC 0.39 $\mu\text{g}/\text{mL}$ with SI >160.



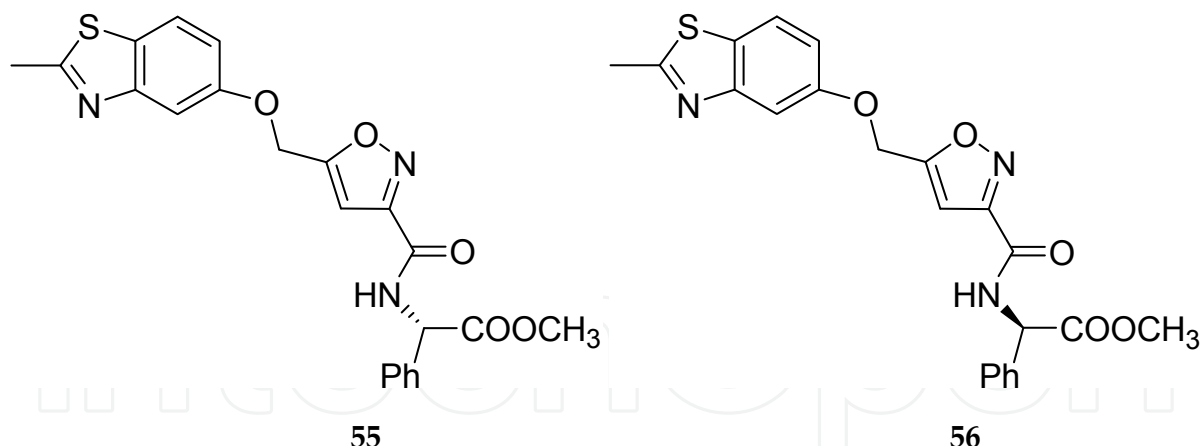
52

Lee et al (Lee et al., 2011) synthesized econazole-derived nitroimidazoles and reported their antitubercular activity against H37Rv by MABA assay. The MIC against non-replicating *Mtb* was determined by using the green fluorescent protein (GFP) expressing *Mtb* strain in the Wayne hypoxia model (anaerobic conditions) (Wayne et al. 1996, as cited in Lee et al., 2011). The MICs of the most active azoles **53** and **54** was found to be 0.5 $\mu\text{g}/\text{mL}$ under aerobic conditions and 4 and 1 $\mu\text{g}/\text{mL}$, respectively, under anaerobic conditions against H37Rv. The $\text{IC}_{50\text{s}}$ in Vero cell noted for **53** and **54** were 100 and >100, respectively.



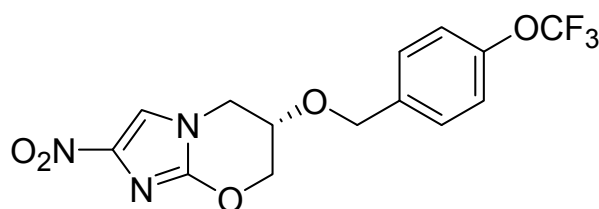
53, R=2,4-dichloro; 54, R= 4-Ph

In the year 2009, a series of 2-methylbenzothiazole derivatives was described by Huang et al (Huang et al, 2009). The most potent compounds found in this series were **55** and **56** with MIC values of 1.4 and 1.9 μM , respectively, against replicating *Mtb* H37Rv. All the active compounds in this series were nontoxic toward Vero cells ($\text{IC}_{50} > 128 \mu\text{M}$).

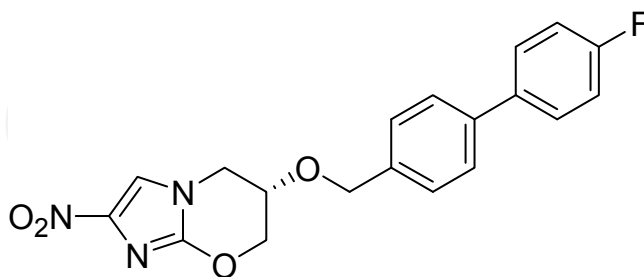


3.1.3.6 Azines

Palmer et al (Palmer et al., 2010) reported antitubercular activity of biphenyl analogs of PA-824, which is currently under phase II clinical trial (pl. see Phase II section), using MABA and LORA assays. Among these, several of the compounds showed potent *in vitro* activity with MIC values of $<1 \mu\text{M}$. The most active compound **57** had MICs of 0.015 and $1.4 \mu\text{M}$ in MABA and LORA assays, respectively. All the compounds investigated were relatively nontoxic to mammalian Vero cells, with $\text{IC}_{50} >125 \mu\text{M}$. In a mouse model of acute *Mtb* infection, seven of the compounds showed substantially (>10 -fold) improved efficacies over PA-824, while three of them were >200 -fold more effective than PA-824.



PA-824

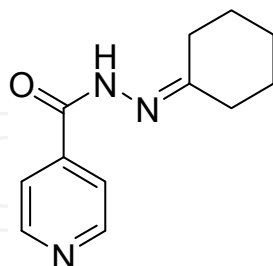


57

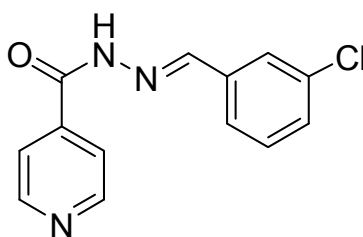
3.1.3.7 Pyridine hydrazides (INH analogs)

Several INH derived Schiff bases were investigated by Hearn et al (Hearn et al, 2009). These compounds showed high *in vitro* activity against *Mtb* and mycobacteria-infected macrophages. They provided strong protection in tuberculosis-infected mice with low toxicity. The mean of the MIC values determined against *Mtb* H37Rv strain Erdman for

the forty-four compounds tested was 1 $\mu\text{g}/\text{mL}$. A representative cyclohexanone derivative **58** displayed MIC of 0.03 $\mu\text{g}/\text{mL}$ (SI >40,000) and exhibited log CFU reduction/lung of 4.65.

**58**

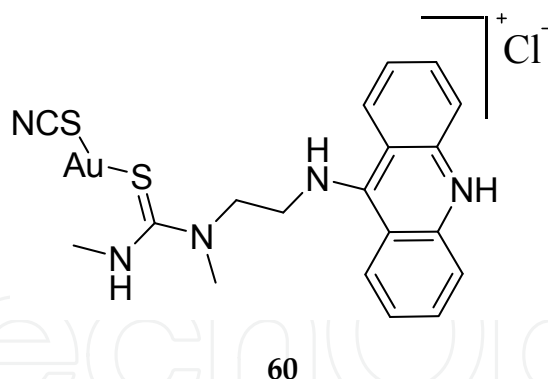
Lourenco et al (Lourenco et al., 2008) prepared a series of (E)-N'-(monosubstituted-benzylidene) isonicotinohydrazide derivatives and evaluated their antibacterial activity against *Mtb* H37Rv (ATCC 27294, susceptible both to rifampin and INH) *in vitro* using Alamar Blue assay. Compound **59** exhibited significant activity (MIC 0.31 $\mu\text{g}/\text{mL}$). Cellular viability of murine macrophage cells in the presence and absence of test compounds was determined by Mosmann's MTT(3-(4,5-dimethylthylthiazol-2yl)-2,5-dimethyl tetrazolium bromide; Merck) microculture tetrazolium assay (Souza et al., 2003, as cited in Lourenco et al., 2008) and 100% cell viability was found for the compound **59** @ 100 $\mu\text{g}/\text{mL}$.

**59**

3.1.4 Metal complexes

Not very many reports are available on metal complexes since metal complexes are generally found to be toxic. A few representatives are summarized here.

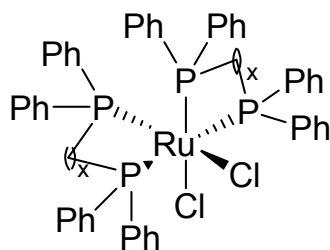
Eiter et al (Eiter et al, 2009) described Gold(I) analogues of a platinum-acridine. Compound **60** exhibited an IC_{50} of 0.652 μM and IC_{90} of 1.141 μM against *Mtb* H37Rv in a high-throughput screen. It also demonstrated inhibition of non-small-cell lung cancer cell line (IC_{50} of 3.940 ± 0.38) with a selectivity index of 23.66. The compound **60** was selected to test its efficacy *in vivo* but serum samples collected from mice treated at a maximum tolerated dose (MTD) of 300 mg/kg orally did not inhibit *Mtb*. This indicated limited oral bioavailability of the complex.



60

Melnic et al (Melnic et al., 2010) investigated new hetero(Mn, Co, Ni)trinuclear iron(III) furoates where compound **61** $[\text{Fe}_2\text{CoO}(\alpha\text{-fur})_6(\text{THF})(\text{H}_2\text{O})_2]\cdot\text{H}_2\text{O}$ displayed potent in vitro inhibition (MIC = 0.827 $\mu\text{g}/\text{mL}$) of *Mtb* H37Rv (ATCC 27294) with an SI of >36.2 (cytotoxicity assay was performed using Vero cell lines).

In a series of Ruthenium (II) phosphine/picolinate complexes, Pavan et al (Pavan et al, 2010) reported MIC values of 0.78 and 0.26 $\mu\text{g}/\text{mL}$ for compounds **62** and **63**, respectively, against H37Rv ATCC 27294 using REMA (Resazurin Microtiter Assay) method (Palomino et al., as cited in Pavan et al., 2010). No toxicity data, however, was reported in the article.

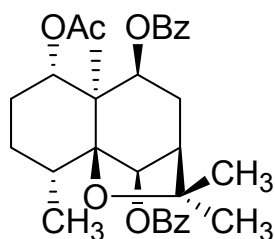


62, x=1; 63, x=2.

3.1.5 Natural products

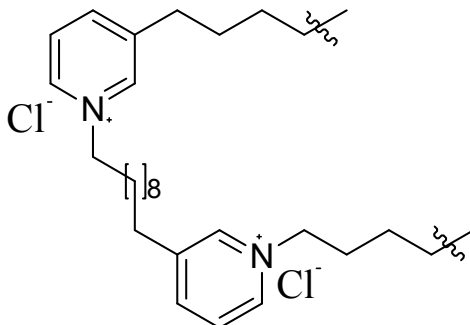
Natural product research is a tedious, labour-intensive and difficult process. Only a few publications have emerged describing significant anti-mycobacterial activity in this field. Selected reports are presented here.

Torres-Romero et al (Torres-Romero et al., 2011) evaluated new dihydro- β -agarofuran sesquiterpenes, isolated from the leaves of *Celastrus vulcanicola*, and their derivatives against H37Rv ATCC 27294 and multidrug-resistant (clinical isolate, strain 02TBDM039EP097) using the tetrazolium microplate assay (TEMA) method. (Rojas et al., 2006, as cited in Torres-Romero et al., 2011). All of the 25 compounds reported showed MIC values of >25 $\mu\text{g}/\text{mL}$ against the sensitive H37Rv strain whereas 1a-acetoxy-6b,9b-dibenzoyloxy-dihydro- β -agarofuran (**64**) had MIC value of 11.9 μM against MDR TB strain, which was comparable to or better than INH or RMP. No toxicity data was included in this article.



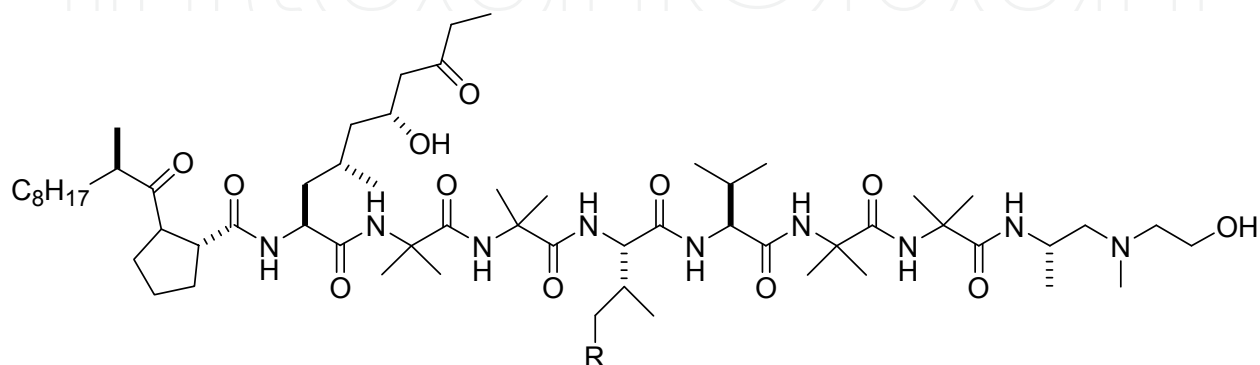
64

Nicholas et al (Nicholas et al., 2003) screened 1500 extracts derived from marine plants, invertebrates and terrestrial fungi for their ability to inhibit a newly described mycobacterial detoxification enzyme mycothiol-S-conjugate amidase (MCA) using a fluorescence-based assay that measures the extent of cleavage of the substrate mycothiol bimane by MCA (Newton et al., 2000, as cited in Nicholas et al., 2003). Only compound **65** showed inhibition of MCA (IC_{50} 0.1 μ M).

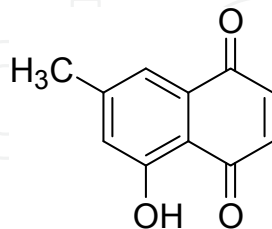


65

Three new aminolipopeptide, trichoderins were isolated by Pruksakorn et al (Pruksakorn et al., 2010) from a culture of marine sponge-derived fungus of *Trichoderma* sp. as anti-mycobacterial substances. Trichoderins showed potent activity against *M. smegmatis*, *M. bovis* BCG, and *Mtb* H37Rv under standard aerobic growth conditions as well as dormancy-inducing hypoxic conditions using the established methods, (Sobou et al., 2008; Arai et al., 2009, as cited in Pruksakorn et al., 2010) with MIC values in the range of 0.02–2.0 μ g/mL. The best compounds **66** and **67** displayed MICs of 0.12 and 0.13 μ g/mL, respectively, for aerobic and hypoxic *Mtb*. No toxicity data was included in this report.

66, R=CH₃; 67, R=H

Mahapatra et al (Mahapatra et al., 2007) reported a series of synthetic and plant-derived naphthoquinone derivatives of the 7-methyljuglone scaffold and their evaluation against *Mtb* H37Rv (ATCC 27294). Several of these compounds have been shown to operate as subversive substrates with mycothiol disulfide reductase. The synthesized compound **68** exhibited MIC of 0.5 µg/mL as determined by radiometric respiratory technique using the BACTEC system. The SI obtained for **68** was 30.22 (cytotoxicity evaluation was done using Vero cells).

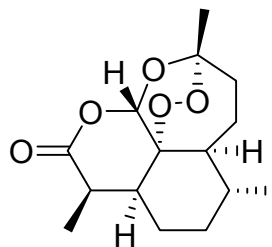


68

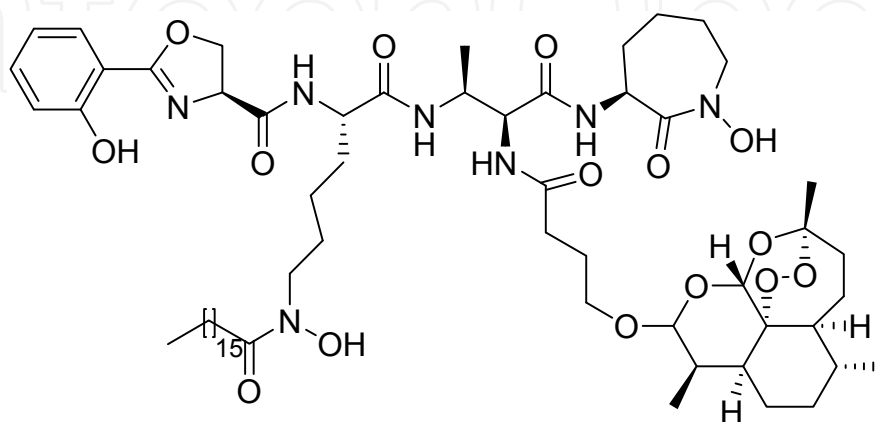
3.1.6 Miscellaneous

3.1.6.1 Artemisinin analog

Artemisinin also called qinghaosu, is a natural peroxide containing sesquiterpene based on 1,2,4-trioxane, and is a highly active and relatively nontoxic antimalarial agent (Devdutt, C. et al., 2010, as reported by Miller et al., 2011). Miller et al (Miller et al., 2011) reported Mycobactin-Artemisinin Conjugate **69** that had submicromolar activity against different clinical strains of tuberculosis. In H37Rv, it displayed MIC 0.338 µM, and in one XDR strain (HREPKOTh) it exhibited MIC of 0.078 µg/mL. No toxicity data was mentioned, however.



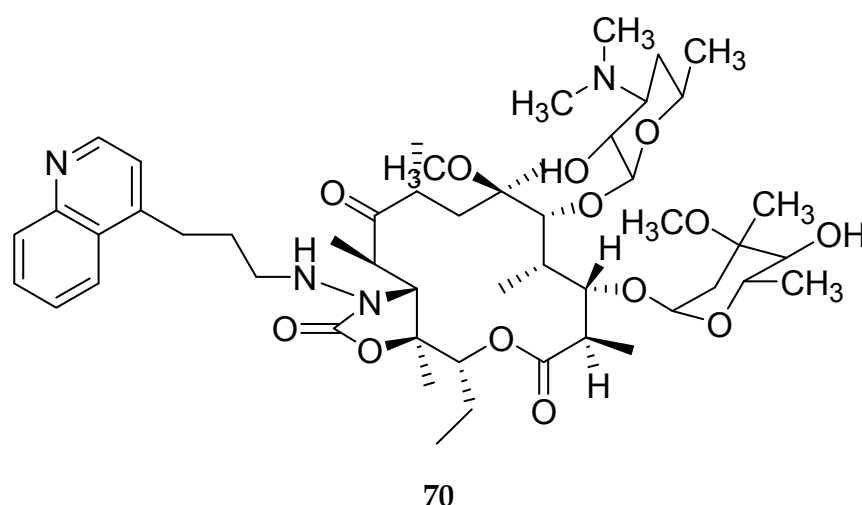
Artemisinin



69

3.1.6.2 Macrolides

Falzari et al (Falzari et al., 2005) reported macrolides and ketolides (descladinose) with substitutions at positions 9, 11, 12, and 6, which were assessed for activity against *Mtb*. Several compounds with 9-oxime substitutions or aryl substitutions at position 6 or on 11, 12 carbamates or carbazates demonstrated submicromolar MICs. Four compounds possessing low MICs also effected significant reductions in CFU in infected macrophages. The active compounds were assessed for tolerance and the ability to reduce CFU in the lungs of BALB/c mice in an aerosol infection model. A substituted 11,12 carbazate macrolide demonstrated significant dose-dependent inhibition of *Mtb* growth in mice, with a 10- to 20-fold reduction of CFU in lung tissue. The compound **70** (RU66252) was found to be a promising compound having MIC of 0.25 μ M with SI 99.52.



3.1.6.3 Peptides

Jiang et al (Jiang et al, 2011) reported evaluation of a series of α -helical peptides consisting of all D-amino acid residues and synthetic human L-LL37 (L-enantiomer) and D-LL37 (D-enantiomer), against *Mtb* H37Rv and a clinical MDR strain. Not very good activity was observed. The most active analog had MIC of 11.2 and 15.6 μ M, against H37Rv and MDR strains, respectively.

3.2 Molecules in pipeline

(Source: Working Group on New Drugs [WGND] and TB Alliance, and Tuberculosis Trial Consortium [TBTC])

After years of vacuum, TB drug development pipeline has begun to enrich during the past decade. The major credit goes to the Global Alliance for TB Drug Development (TB Alliance) which is largely funded by Bill & Melinda Gates Foundation as a philanthropic effort and Working Group on New Drugs (WGND). It is also to be noted in regard of this pipeline that many of the compounds here are either derivatives of existing drugs or are working on the same target as existing drugs. This is obviously a shorter and a quicker method for new drug development, however, this approach may pose a risk of cross-resistance in these future drugs. This risk may be neglected, however, in view of urgent need of effective drugs

to halt TB associated mortalities. Following are the compounds that are at various stages of preclinical and clinical development (summarized in tables 3-5).

3.2.1 Hit to lead

| Sponsor/Developer | Compounds | Target | Remarks |
|--|--|--------------------------------------|---|
| The Lilly TB Drug Discovery | Novel synthetic compounds | Unknown | Not much information is available |
| FAPESP/Brazil | Ruthenium(II)phosphine/picolinate complexes, synthetic (>100). | Unknown | MIC less than 1 μ M against H37Rv and resistant strains. <i>In vivo</i> assays are underway |
| AstraZeneca R & D Bangalore | 200,000 Synthetic, novel compounds | Not mentioned | Target against H37Rv strain |
| GlaxoSmithKline, TB Alliance: | Synthetic compounds | Not mentioned | Whole cell microorganism screen |
| University of Illinois, TB Alliance | Total 1,21,0000 compounds. 66,000 synthetic and semisynthetic | Whole cell | Approximately 1500 hits have been identified and confirmed |
| Shaw Environmental and University of Illinois at Chicago | 30 Indole-based combinatorial biosynthetic compounds (Several compounds showed activity comparable to first line drugs). | Under investigation | Whole cell microorganism screening against replicating and nonreplicating <i>Mtb</i> . |
| Mycosynthetix, University of Illinois at Chicago | 15,000 Natural product extracts as fungal metabolites | Not mentioned | Not much information is available |
| University of Illinois at Chicago, Myongji University | Actinomycete metabolites purified and derived from 70,000 natural products extract | Not mentioned | Several samples showing MIC of less than 0.5 μ g/mL. |
| Vertex Pharmaceuticals, Incorporated | 315,000+ Compounds | <i>Mtb</i> Protein Kinase Inhibitors | The screening assay uses a basic protein kinase assay. |

| Sponsor/Developer | Compounds | Target | Remarks |
|--|--|--|--|
| AstraZeneca R & D Bangalore, India | 500,000 Synthetic compounds. | Enzyme(s) involved in DNA synthesis | Not much information is available |
| AstraZeneca, TB Alliance | Synthetic compounds are under screening via high throughput assay | Folate Biosynthesis Inhibitors | Not much information is available |
| GlaxoSmithKline, Texas A & M University, TB Alliance | Library of 1.4 million synthetic compounds has been screened via High throughput screening | Malate Synthase Inhibitors | Hits have been identified. |
| Colorado State University, TB Alliance | Synthetic, known already and evaluated as cholesterol synthesis inhibitors. | Menaquinone Synthase (MenA) Inhibitors | Project aims to "retro-design" and evaluate derivatives of the known compounds |
| UPenn and TB Alliance | 110,000 Synthetic compounds derived from natural products | Inhibitors of <i>Mtb</i> energy metabolism, electron transport chain | About 100 hits have been identified |

Table 3. Various Compounds at Lead Identification stage

3.2.2 Lead optimization

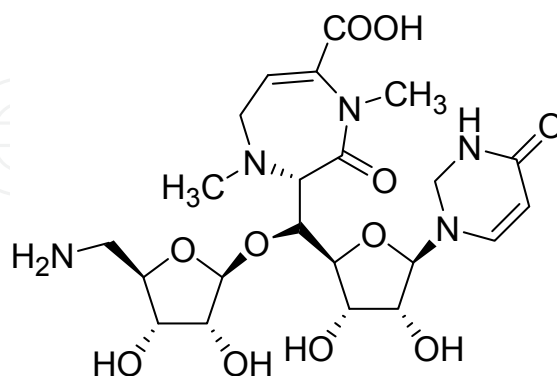
| Sponsor/Developer | Compounds | Target | Remarks |
|--|--|--|---|
| TB Alliance, Institute of Materia Medica, The Beijing Tuberculosis and Thoracic Tumor Research Institute and University of Illinois. | Riminophenazine (clofazimine) derivatives >500 synthetic compounds | Considered to inhibit energy metabolism in <i>Mtb</i> (<i>Mtb</i>) | Riminophenazines (clofazimine) have been employed to treat leprosy. <i>In vivo</i> studies are underway |
| GlaxoSmithKline, TB Alliance | >2 Million synthetic compounds. | InhA Inhibitors | ----- |
| Anacor Pharmaceuticals | >1000 Synthetic boron-containing compounds | LeuRS inhibitors, Protein synthesis | ----- |
| TB Alliance, GlaxoSmithKline | >1 Million synthetic compounds | Mycobacterial Gyrase Inhibitors | Several lead compounds have been identified and are being evaluated further. |
| AstraZeneca, TB Alliance | Synthetic | Mycobacterial Gyrase Inhibitors | ----- |

Table 4. Various Compounds at Lead Optimization stage

3.2.3 Pre clinical

3.2.3.1 CPZEN-45

Sponsor/developer: Microbial Chemistry Research Foundation, Tokyo, Japan Lilly TB Drug Discovery Initiative NIAID, IDRI, Lilly, YourEncore.



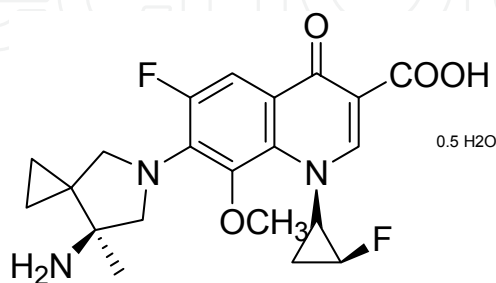
CPZEN-45

Synonyms: Caprazene, caprazamycin, nucleoside antibiotic

Summary: CPZEN-45 is a nucleoside antibiotic produced by *Streptomyces* sp. first described in 2003 by investigators at the Microbial Chemistry Research Foundation (MCRF) and Meiji Seika Kaisha, Ltd of Japan. CPZEN-45 possesses MIC of 1.56 µg/mL against *Mtb* H37Rv and 6.25 µg/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*. CPZEN-45 has shown efficacy against both drug sensitive and XDR *Mtb* in a mouse model of acute tuberculosis (TB). Recent data by NIAID using the gamma interferon gene-disrupted (GKO) mouse model of acute tuberculosis in which infection was achieved by aerosol exposure to *Mtb* (Erdman) also demonstrated efficacy of CPZEN-45 with 1-1.5 log CFU reduction in lungs of infected mice. Its mode of action is not specified (Hirano et al., 2008; WGND)

3.2.3.2 Quinolone DC-159a

Sponsor or developer: Japan Anti-Tuberculosis Association, JATA Daiichi-Sankyo Pharmaceutical Co.



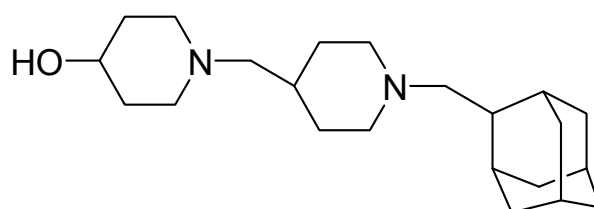
DC-159a

Summary: DC-159a exhibited the highest activity against drug-susceptible (MIC = 0.03 µg/mL), quinolone-resistant (QR) MDR-TB and non-tuberculous mycobacteria isolates

compared to that of moxifloxacin, gatifloxacin, levofloxacin and RMP. The potent activity of DC-159a is ascribed to the inhibition of DNA gyrase from wild-type and MDR-*Mtb*. In the drug-susceptible-*Mtb* infection model, it exhibited better early bactericidal activity (EBA) and higher log reduction of CFU in lungs, compared to moxifloxacin, levofloxacin, INH and RMP. In the QR MDR-TB infection model, it showed 2~3 times longer “mean survival days” which was superior to moxifloxacin, levofloxacin, INH and RMP. Pharmacokinetic study of DC-159a in a monkey model after an oral dose of 5 mg/kg of body weight, showed that it achieved a higher peak concentration (C_{max} ; 2.20 $\mu\text{g}/\text{ml}$) and area under the concentration-time curve from 0 to 24 h (AUC 0-24; 16.9 $\mu\text{g}\cdot\text{h}/\text{ml}$) than the MIC against *Mtb*, and showed better pharmacokinetic properties than levofloxacin (C_{max} , 1.68 $\mu\text{g}/\text{ml}$; AUC 0-24, 15.3 $\mu\text{g}\cdot\text{h}/\text{ml}$). DC159a lacked interaction with cytochrome P450 3A4 (WGND; Disratthakit, & Doi, 2010; Sekiguchi et al., 2011), suggesting a better safety profile.

3.2.3.3 SQ-609

Sponsor/developer: Sequella



SQ-609

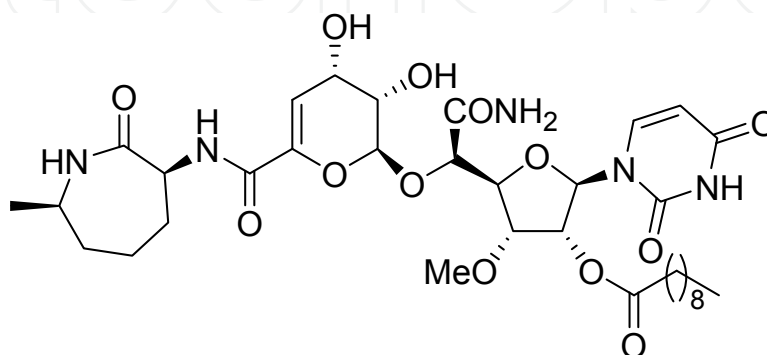
Summary: Sequella screened >100,000 molecules for anti-mycobacterial activity and identified SQ609 as the most potent (MIC = 4 $\mu\text{g}/\text{mL}$) and promising candidate among a new series of potential cell-wall inhibiting dipiperidines that are structurally different than any existing antitubercular drugs/candidates. Precise mode of action of SQ 609 is unknown (WGND; Bogatcheva et al., 2011).

3.2.3.4 SQ-641

Sponsor/developer: Sequella

Target: Translocase 1 (TL1) enzyme Inhibitors

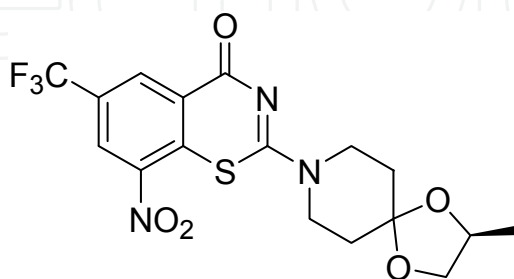
Compounds: >7000 compounds synthetic compounds derived from natural products



SQ-641

Summary: Translocase 1 (TL1) enzyme, which is absent in eukaryotic cells, is an essential enzyme in bacteria for the biosynthesis of the peptidoglycan layer of the cell wall. The semi-synthetic nucleoside Capuramycin has been studied as inhibitor of TL1 enzyme. The lead candidate SQ-641 (MIC = 0.5 µg/mL) is under preclinical development for the treatment of TB. Its mycobactericidal rate is faster than any existing TB drugs. SQ-641 possesses activity against MDR clinical strains of *Mtb*. It has shown efficacy in a mouse model of chronic TB by reducing CFU in lungs of infected mice by 1.0 to 1.5 log (WGND; Bogatcheva et al., 2011).

3.2.3.5 Benzothiazinone (BTZ-043)



BTZ-043

Summary: BTZ-043 belongs to a new class of antimycobacterial agents. It is highly active against *Mtb* (MIC = 1-10 ng/mL) and other actinobacteria. It also possesses activity against MDR- and XDR-TB strains. It showed *in vitro* bactericidal activity comparable to INH. It is non-mutagenic and has good oral bioavailability. BTZ-043 inhibits cell wall biosynthesis, and targets the DprE1 (Rv3790) subunit of the enzyme decaprenylphosphoryl-beta-D-ribose 2'-epimerase.

3.2.3.6 Q-201

Sponsor/developer: Quro Science, Inc.

It is an imidazopyridine compound. Not much detail is available about this compound.

| Phase | Compound | Sponsor/developer | Mode of action |
|--------|-------------|---|--|
| I | AZD5847 | Astrazeneca | Protein synthesis inhibitor |
| II | PNU-100480 | Pfizer | Protein synthesis inhibitor |
| | LL3858 | Lupin Pharmaceuticals Inc. | Not yet known |
| | SQ-109 | Sequella, NIH | Not yet known |
| | PA-824 | TB Alliance | Protein synthesis and cell wall lipids inhibitor |
| | OPC67683 | Otsuka Pharmaceutical Co. Ltd. | Protein synthesis and cell wall lipids inhibitor |
| | TMC 207 | Tibotec | Affects proton pump of ATP synthase |
| | Linezolid | Tuberculosis Trials Consortium (TBTC), Pfizer | Protein synthesis inhibitor Novel unique |
| II/III | Rifapentine | CDC, Sanofi-aventis | Inhibits DNA dependent RNA polymerase |

| Phase | Compound | Sponsor/developer | Mode of action |
|-------|--------------|--|--------------------------------|
| III | Moxifloxacin | University College London | Inhibits bacterial replication |
| | Gatifloxacin | Institut de Recherche pour le Développement, WHO, European Commission (primary developers) | Inhibits bacterial replication |

Table 5. Compounds in phase I-III clinical trials

3.2.4 Phase I

3.2.4.1 AZD-5847

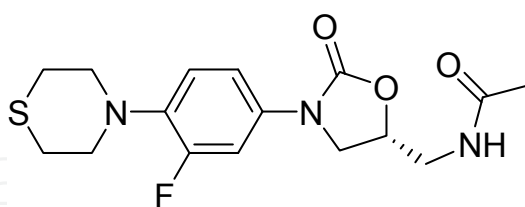
Sponsor/developer: Astrazeneca

Summary: AZD-5847, an oxazolidinone antibiotic (structure is not disclosed), originally developed for staphylococcal infections, is currently in Phase 1 clinical trials. It possesses MIC₉₀ of 1 µg/mL against laboratory *Mtb* strains and clinical isolates resistant to INH, RMP, streptomycin, EMB or OFX (Abstract Balasubramanian et al., 2011). Studies to examine safety, tolerability and blood levels of AZD-5847 in healthy volunteers are underway.

3.2.5 Phase II

3.2.5.1 PNU-100480

Sponsor/developer: Pfizer

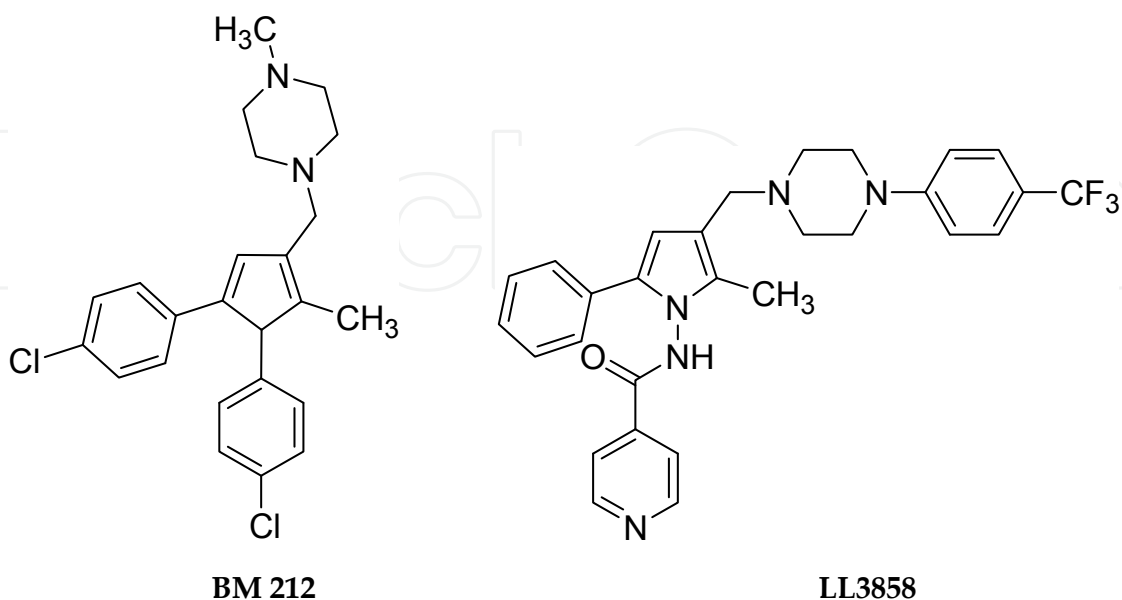


PNU-100480

Summary: PNU-100480 is a structural analogue of linezolid (see details in Phase II section). It is more active than linezolid against TB (Williams, et al., 2009 as cited in Alffenaar et al., 2011) and possesses similar efficacy to that of INH and RMP (Cynamon et al., 1999, as cited in Alffenaar et al., 2011). Its MIC was found in the range of .0625-0.5 µg/mL in drug-susceptible and drug-resistant clinical strains of *Mtb* (Alffenaar et al., 2011). When added to a first-line regimen in a murine model, PNU-100480 had a synergistic bactericidal effect, while linezolid had an antagonistic effect (Williams, et al., 2009 as cited in Alffenaar et al., 2011). 14 day dose-escalation and 28 day dose study in healthy volunteers have been completed (WGND, 2011).

3.2.5.2 Pyrrole (LL-3858) or Sudoterb.

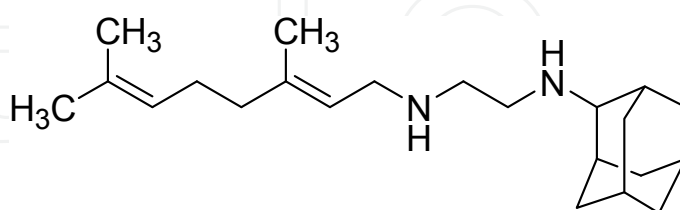
Sponsor/developer: Lupin Pharmaceutical Inc.



Summary: Deidda et al. (Deidda et al., 1998) first reported the activity of the pyrroles against *Mtb*. The most potent compound identified was BM212 (MICs = 0.7 to 1.5 $\mu\text{g}/\text{mL}$ against several strains of *Mtb*). This work by Deidda et al. later on inspired Lupin to synthesize a series of pyrroles and one of their leads LL3858 is currently in clinical development for the treatment of TB (Arora et al., 2004). The MIC₉₀ of LL3858 for *Mtb* is reported to be 0.25 $\mu\text{g}/\text{mL}$ (Tuberculosis. 2008. Ll-3858, as cited in van den Boogaard et al., 2009). LL3858, in combination with current anti-TB drugs, is reported to sterilize the lungs and spleens in lesser time than the conventional therapy (Sinha et al., 2004). The mechanism of action for this class of compounds has not yet been established.

3.2.5.3 Diamine (SQ-109)

Sponsor/developer: Sequella, NIH



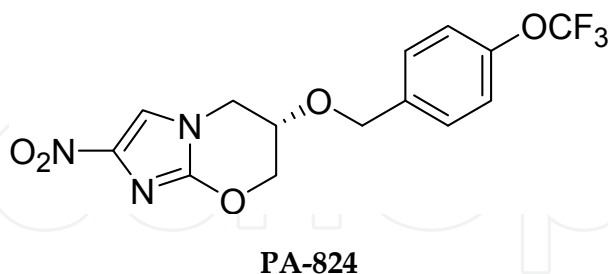
SQ-109

Summary: SQ109, or N-adamantan-2-yl-N'-(3,7-dimethylocta-2,6-dienyl)-ethane-1,2-diamine, is being developed by Sequella. It was the most potent compound (MIC = 0.1-0.63 $\mu\text{g}/\text{mL}$) in the series (Lee et al., 2003). *In vivo* studies showed 1 to 2.0-log reduction in CFU counts in the lung and spleen at 25 mg/kg. Its oral bioavailability is only 4% (Jia et al., 2005). Preclinical toxicology studies have been completed and further phase 2 clinical studies are underway.

3.2.5.4 Nitroimidazoles (PA824 AND OPC67683)

3.2.5.4.1 PA-824

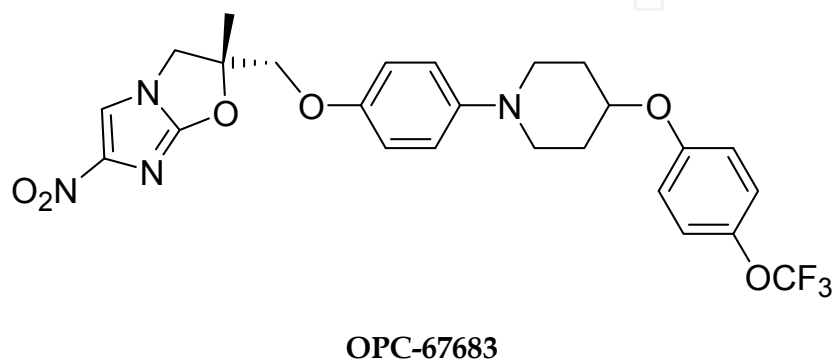
Sponsor/developer: TB Alliance



In 1970s Ciba-Geigy in India screened a series of nitroimidazoles as radiosensitizers. Many of them were later found to possess antimicrobial activity, (including anti-*Mtb* activity). However, further development was discontinued after the lead molecule CGI-17341 was found to be mutagenic. In 1995 a pharmaceutical company, PathoGenesis, modified Ciba-Geigy's molecules and screened around 700 compounds against *Mtb* and found PA824 as the most active (Stover et al., 2000) and non mutagenic (Ginsberg & Spigelman, 2006). After PathoGenesis, Chiron Corporation obtained the rights and finally the Global Alliance for TB Drug Development acquired its rights for its clinical development. It has potent *in vitro* activity against *Mtb*, as evidenced by an MIC range of 0.015 to 0.25 mg/ml, and retains this activity against isolates resistant to a variety of commonly used anti-TB drugs. PA-824 kills *Mtb* bacilli by inhibiting the synthesis of protein and cell wall lipids (Stover et al., 2000). In mouse model it was highly active for latent TB in combination with moxifloxacin (Nuermberger et al.; 2005). It is suggested, however, that PA-824 is a prodrug and requires reductive activation of the aromatic nitro group (Manjunatha et al., 2006). PA-824 showed good tissue permeability in rat studies. Its minimum bactericidal dose (to reduce the lung CFU count by 99%) was found to be 100 mg/kg/day in murine studies. PA-824 in combination with INH prevents selection of TB mutants resistant to INH. It is effective against replicating and persistent TB bacilli. It is also effective against MDR strains and *Mtb* grown under oxygen depletion (Tyagi et al., 2005; Lenaerts et al., 2005). It has completed phase 1 studies in healthy volunteers (Spigelman, 2005).

3.2.5.4.2 OPC-67683 (Delamanid)

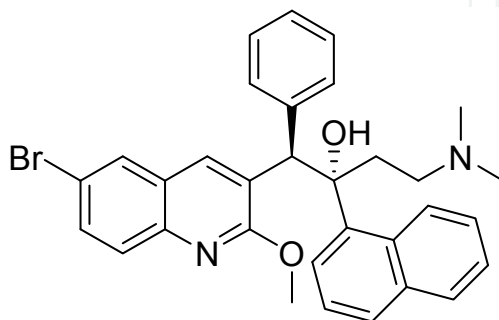
Sponsor/developer: Otsuka Pharmaceutical Co. Ltd.



Another nitroimidazole compound, OPC-67683 (MICs 0.006 $\mu\text{g}/\text{mL}$) is being developed by Otsuka Pharmaceutical. It was found to be potent against *Mtb* *in vitro* and *in vivo* (Matsumoto et al., 2005). In a mouse model, its efficacy was reported to be superior to that of currently used TB drugs. The effective plasma concentration of OPC-67683 was 0.100 $\mu\text{g}/\text{mL}$ (achieved with an oral dose of 0.625 mg/kg). It showed no cross-resistance with the current anti-TB drugs. The mechanism of action of OPC-67683 is suggested to be similar to PA-824 (Kawasaki et al., 2005).

3.2.5.5 Diarylquinoline (TMC-207 or R-207910 or Bedaquiline)

Sponsor/developer: Tibotec

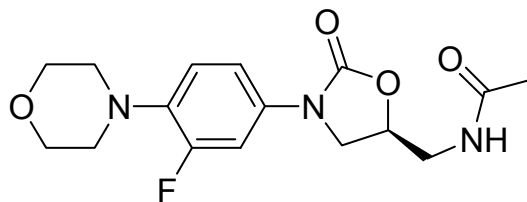


TMC-207

TMC-207 is owned by Johnson & Johnson (J&J) and is being developed at its research subsidiary Tibotec. TMC-207 not only showed very potent *in vitro* activity against both MDR and drug-susceptible strains of *Mtb* but also has potent activity against other Mycobacterial species (*M. avium*, *M. marinum*, *M. fortuitum*, and *M. abscessus* *M. smegmatis*). Its MIC ranges from 0.002 to 0.06 $\mu\text{g}/\text{mL}$ for drug susceptible and drug resistant strains (Andries et al., 2005; Huitric et al., 2007). It is active *in vitro* against TB organisms resistant to INH, RMP, streptomycin, EMB, PZA, and moxifloxacin. It has no cross-resistance with current anti-TB medications (Andries 2004). In mice, a single dose had bactericidal potency for about eight days. When used as monotherapy, a single dose of TMC-207 was as potent as the triple combination of RMP, INH, and PZA and was more active than RMP alone. It works on the proton pump of ATP synthase (Andries et al., 2005). The effective half-life was found was ~ 24 h. Single ascending dose and 14-day multiple ascending dose studies in healthy human males showed no severe adverse effects. Further clinical trials are underway.

3.2.5.6 Linezolid for the Treatment of Multi-Drug Resistant Tuberculosis

Sponsor/developer: Tuberculosis Trials Consortium (TBTC), Pfizer

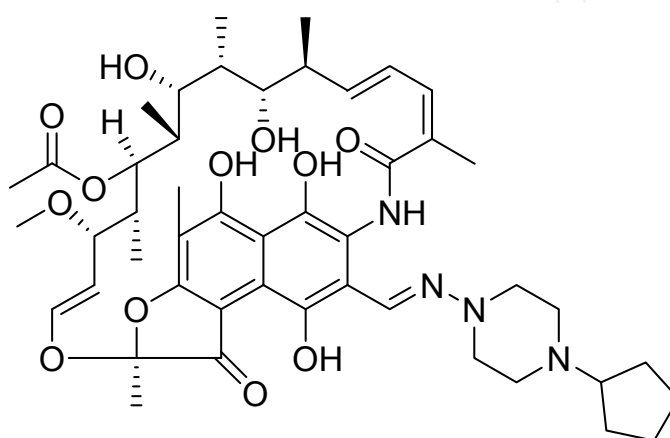


Linezolid

Linezolid is an approved antibacterial drug without a TB indication. It was discovered in 1990s and approved in 2000 for the treatment of Gram positive bacterial infections. It is active against most Gram-positive bacteria with MIC₉₀ 1-2 µg/mL (Alcalá et al., 2003). It works as a protein synthesis inhibitor. Lack of information on its efficacy is one of the major concerns for its use as anti-TB agents (Migliori et al., 2009). Long-term use has been associated with thrombocytopenia, neuropathy and haematopoietic suppression (Gerson et al., 2009).

3.2.5.7 Rifapentine (TBTC study)

Sponsor/developer: CDC, Sanofi-aventis



Rifapentine

Rifapentine is a cyclopentyl derivative of the first-line TB drug RMP. Its MIC was found to be 0.03 µg/mL by 7H12 broth radiometric assay (Heifets et al., 1999). Its mechanism of action is the same as of RMP (Williams et al., 1998). It induces the CY450 system to a lesser extent than RMP (Weiner et al., 2004). It can also be used for latent TB as a part of regimen with either moxifloxacin or INH (Nuermberger et al., 2005). The aim of the clinical trial is to examine antimycobacterial activity and safety of an experimental intensive phase (first 8 weeks of treatment) tuberculosis treatment regimen in which RMP is substituted by rifapentine.

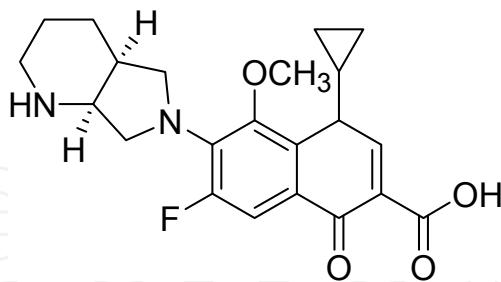
3.2.6 Phase III

3.2.6.1 Fluoroquinolones

In the past few years, attention has been focused on the use of fluoroquinolones for shortening the treatment duration of *Mtb*. Most of the credit for the use of fluoroquinolones goes to a clinical trial by the Tuberculosis Research Centre, Chennai, India (Tuberculosis Research Centre [TRC], 2002). In this trial, newly diagnosed pulmonary TB patients were randomly divided to receive one of four regimens containing a fluoroquinolone – ofloxacin (OFX). The rates of sputum conversion by this treatment at 2 months ranged from 92%-98% (superior to ~80% conversion rate by conventional therapy) (Tuberculosis Trials Consortium [TBTC], 2002).

3.2.6.1.1 Moxifloxacin

Sponsor/developer: University College London

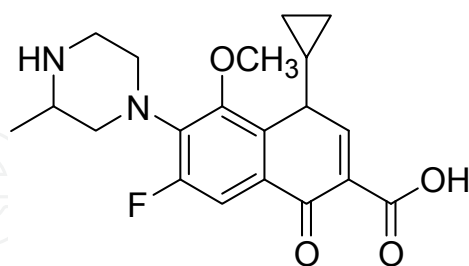


Moxifloxacin

Moxifloxacin (“Avelox” by Bayer) is a broad-spectrum antibiotic (400 mg/day dose) and is active against both gram positive and gram negative bacteria. It exhibits MIC of 0.5 µg/mL against *Mtb* (Shandil et al., 2007). It displayed early bactericidal activity comparable to INH and rifampin in humans (Pletz 2004; Gosling 2003). It affects bacteria by binding to the DNA gyrase and topoisomerase IV, which are involved in bacterial replication. It has no cross-resistance to other antituberculosis drug classes; therefore, it might be useful against MDR-TB and XDR-TB. Further, it has been shown to display good activity profile against MDR strains (Tortoli et al., 2004). However, it has CNS side effects and drug interactions with other fluoroquinolones. Moxifloxacin has not been reported to be safe or effective in children younger than 18 or in pregnant or lactating women (Bayer, n.d.). Nuermberger et al. (2004) found that substituting moxifloxacin for INH shortens the duration of therapy for active disease much better than does substituting moxifloxacin for EMB.

3.2.6.1.2 Gatifloxacin

Sponsor/developer: Institut de Recherche pour le Developpement, WHO, European Commission (primary developers)



Gatifloxacin

Gatifloxacin (“Tequin” by Bristol-Myers Squibb) is also a broad-spectrum antibiotic (dosage of 400 mg/day). It works by the same mechanism as moxifloxacin. It is active against occasionally dividing *Mtb*, but not for dormant bacteria (Paramasivan et al., 2005). Gatifloxacin in combination with ethionamide and PZA was most effective to sterilize the lungs and prevent relapse (Cynamon & Sklaney, 2003). Gatifloxacin can cause CNS toxicity and has been associated with increases in insulin levels among diabetics. It has not been shown to be safe or effective in children younger than 18 or in pregnant or lactating women. Gatifloxacin has completed a phase 2 study on randomized patients receiving 8 weeks of

therapy with either conventional treatment or the combination of INH, PZA, and RMP with either OFX or moxifloxacin, or gatifloxacin. In this study, serial sputum colony count measurements indicated that the patients in the moxifloxacin and gatifloxacin arms cleared their sputum more quickly than the patients receiving conventional therapy or the regimen containing OFX (Lienhardt et al., 2005).

3.2.7 Experimental compounds

The following experimental compounds are not commercially available. Their efficacy and safety are unknown.

3.2.7.1 A herbal product from Ukraine has been subjected to many open label clinical trials, with promising results in TB and TB/HIV coinfecting patients (Zaitzeva et al., 2009; Nikolaeva et al., 2008a, 2008b). Open label trials with adjuvant Dzherelo (Immunoxel) have also been positive in MDR-TB and XDR-TB patients (Prihoda et al., 2007).

3.2.7.2 V-5 Immunitor or "V5", is an oral vaccine available in tablets for hepatitis B and hepatitis C treatment. TB sputum clearance was unexpectedly noted within a month, in hepatitis C-TB co-infected patients. Blinded studies suggest that V5 is also effective against MDR-TB (Olga et al., 2010; Butov et al., 2011).

4. Conclusion

After decades of reluctance in the TB drug discovery, several groups/institutions such as TB Alliance, Working Group on New Drugs (WGND) and New Medicines for Tuberculosis (NM4TB) have rekindled hope for new anti-tuberculosis drug(s) which may offer promise against MDR- and XDR-TB, and HIV-TB co-infection. The new drugs may also have capability of shortening the treatment duration of drug susceptible TB. Apart from the above big organizations, smaller research teams worldwide including our laboratory are actively involved in the search of new classes of potent and safe anti-tuberculosis drug(s).

The current TB drug pipeline (Table 6), no doubt, is the richest we have ever seen, but still it will take a long before any new drug hits market with approval. There are hurdles on the way ahead. Fund constraints, slow pace trial designs, insufficient infrastructure to validate the drug(s), validation and approval mechanism of Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA), and most importantly, the strong political will power, are the crucial issues ahead. The TB Trials Consortium (TBTC) (funded by The Centers for Disease Control and Prevention), National Institutes of Health (NIH) and European and Developing Country Clinical Trials Program (EDCTP) have to play better and expanded roles along with the ongoing efforts to accelerate the drug development. Governments, regulatory agencies, pharmaceutical and biotechnology companies, involved international agencies and communities, and basic and applied researchers worldwide all have to work together to achieve the goal of eradicating TB, like other big burden disease such as HIV.

It is worth to mention here lastly, that not only cure by drugs, but prevention measures and awareness steps by Governments and social bodies are also crucial and play very important role to stop any such infectious devil. Particular area on alert which need drastic improvements are imprisonment, health care systems, sex workers, travel and transportations,

and mass gathering activities such as festivals and events. The most important but neglected part of prevention program, which might be addressed and implemented urgently and effectively, is a separate and intense educational program designed for families having a member with diagnosed active TB. Together with a successful drug hunt and preventive measures, we can soon hope of the world without fear of millions of yearly deaths from tuberculosis.

| Discovery Classes, (Sponsor/developer) | | | Preclinical | Clinical | | | Existing Drugs |
|---|---|---|---|----------|--------------------|----------------------|--|
| Screening | Lead Identification | Lead Optimization | | Phase I | Phase II | Phase III | |
| Natural Products (IMCAS) | Whole-Cell Hit to Lead Program (GSK) | Mycobacterial Gyrase Inhibitors (GSK) | Nitroimidazoles (U. of Auckland/ U. Ill Chicago) | AZD5847 | PNU-100480 | Moxifloxacin (Bayer) | First Line Rifampicin Isoniazid Pyrazinamide Ethambutol |
| Topoisomerase I Inhibitors (AZ/NYMC) | Folate Biosynthesis Inhibitors (AZ) | | | | | | |
| | RNA Polymerase Inhibitors (AZ) | InhA Inhibitors | CPZEN-45 | | PA-824 (Novartis) | | |
| Nucleosides | Ruthenium(II)phosphine/picolinate complexes | Pyrazinamide Analogs (Yonsei) | Preclinical TB Regimen Development (JHU/U. Ill Chicago) | | Lnezolid; low dose | Gatifloxacin | Second Line Amikacin Kanamycin Capreomycin Streptomycin Cycloserine Ethionamide, PAS Clofazimine Ciprofloxacin Levofloxacin Ofloxacin |
| Carbohydrates | Whole-Cell Hit to Lead Program (AZ) | | | | | | |
| Metal Complexes | Folate Biosynthesis Inhibitors | Diarylquinolines Tibotec/U. of Auckland | DC-159a | | TMC 207 (Tibotec) | | |
| Hydrazides and hydrazones | Menaquinone Synthase (MenA) Inhibitors | | | | | | |
| Hetero-cyclics Quinolines, Quinoxalines, Pyrimidines, Purines, Pyrroles, Azines | Protein Kinase Inhibitors | Riminophenazines (IMM/BTTTRI) | SQ-641 | | LL3858 | Rifapentine | "Third Line" Rifabutin, Macrolides: (e.g., clarithromycin); Linezolid, R207910, Thioacetazone; Thioridazine; Arginine; vitamin D; |
| | Enzyme(s) involved in DNA synthesis | | SQ-609 | | SQ-109 OPC67683 | | |
| Chalcones | Malate Synthase Inhibitors | | BTZ-043 | | | | |
| Artemisinin derivatives | Actinomycete metabolites | | | | Rifapentine | | |
| | Fungal metabolites | | | | | | |
| Macrolids | | | Q-201 (Quro Science Inc.) | | | | |
| Peptides | | | | | | | |

Table 6. Drug discovery: Screening to Existing Drugs.

5. References

- Acocella G. (1978). Clinical Pharmacokinetics of Rifampicin. *Clinical Pharmacokinetics*, Vol. 3, pp. 108-127.
- Ahmad, Z.; Peloquin, C. A.; Singh, R. P.; Derendorf, H.; Tyagi, S.; Ginsberg, A.; Grosset, J. H. & Nuermberger, E. L. (2005). PA-824 Exhibits Time-Dependent Activity in a Murine Model of Tuberculosis. *Antimicrobial Agents and Chemotherapy*, Vol. 55, pp. 239-224.
- Alcalá, L.; Ruiz-Serrano, M. J.; Turégano, C. P. F.; de Viedma, D. G.; Díaz-Infantes, M.; Marín-Arriaza, M. & Bouza, E. (2003). In vitro activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* that are susceptible or resistant to first-line antituberculous drugs. *Antimicrobial Agents and Chemotherapy*, Vol. 47, pp. 416-417.
- Alffenaar, J. W. C.; van der Laan, T.; Simons, S.; van der Werf, T. S.; van de Kastelee, P. J.; de Neeling, H. & van Soolingen, D. (2011). Susceptibility of Clinical *Mycobacterium tuberculosis* Isolates to a Potentially Less Toxic Derivate of Linezolid, PNU-100480. *Antimicrobial Agents and Chemotherapy*, Vol. 55, pp. 1287-1289.
- Ancizu, S.; Moreno, E.; Solano, B.; Burguete, A.; Torres, E.; Pérez-Silanes, S.; Aldana, I. & Monge, A. (2010). New 3-methylquinoxaline-2-carboxamide 1,4-di-N-oxide derivatives as anti-*Mycobacterium tuberculosis* agents. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 2713-2719.
- Andries, K.; Verhasselt, P.; Guillemont, J.; Göhlmann, H. W. H.; Neefs, J. M.; Winkler, H.; Gestel, J. V.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N. & Jarlier, V. (2005). A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*. *Science*, Vol. 307, pp. 223-227.
- Aristoff, P. A.; Garcia, G. A.; Kirshhoff, P. D. & Hollis Showalter, H. D. (2010). Rifamycins-obstacles and opportunities. *Tuberculosis*, Vol. 90, pp. 94-118.
- Arjanova, O. V.; Prihoda, A. D.; Yurchenko, L. V.; Sokolenko, N. I.; Frolov, V. M.; Tarakanovskaya, M. G.; Jirathitikal, V. & Bourinbaiar, A. S. (2010). Phase 2 Trial of V-5 Immunitor (V5) in Patients with Chronic Hepatitis C Co-infected with HIV and *Mycobacterium tuberculosis*. *Journal of Vaccines and Vaccination* Vol. 1, 103. doi:10.4172/2157-7560.1000103
- Arora, S. K.; Sinha, N.; Sinha, R. K.; Uppadhyaya, R. S.; Modak, V. M. & Tilekar, A. (2004) Synthesis and *in vitro* anti-mycobacterial activity of a novel anti-TB composition LL4858 [abstract F-1115]. In: *Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology.
- Arya, D. S.; Ojha, S. K.; Semwal, O. P. & Nandave, M. (2008). Pharmacokinetics of Pyrazinamide in Children with Primary Progressive Disease of Lungs *Indian Journal of Medical Research*, Vol. 128, pp. 611-615.
- Baciewicz, A. M.; Chrisman, C. R.; Finch, C. K. & Self, T. H. (2008) Update on Rifampin and Rifabutin Drug Interactions. *American Journal of Medical Sciences*, Vol. 335, pp. 126-136.
- Balasubramanian, V.; Gaonkar, S.; Solapure, S.; Sambandamurthy, V.; Shandil, R.; Mahesh, K. N.; Sharma, S.; Kaur, P. Deepthi, R.; Subbulakshmi, V.; Ramya, V.; Ramachandran, V.; Reddy, J.; Giridhar, J.; Deshpande, A.; Bharath, S.; Kumar, N.; Balganes, M.; Nandi, V.; Wright, L.; Melnick, D.; (Scheduled Presentation on

- Monday, Sep 19, 2011) AZD5847, an Oxazolidinone for the Treatment of Tuberculosis: Pre-clinical Studies. [Presentation no. F1-1364]. American Society for Microbiology, 1752 N Street NW Washington, DC. USA. Available from <http://www.abstractsonline.com/plan/ViewAbstract.aspx?mID=2789&sKey=5f3fa01a-9c86-4ebd-8cab-50756d6faa6f&cKey=c393491b-4fdf-42a8-8857-3756dce2a517&mKey={0C918954-D607-46A7-8073-44F4B537A439}>
- Barclay, W. R.; Ebert, R. H.; Le Roy, G. V.; Manthei, R. W.; & Roth, L. J. (1953). Distribution and Excretion of Radioactive Isoniazid in Tuberculous Patients. *Journal of the American Medical Association*, Vol. 151, pp. 1384-1388.
- Bayer. Avelox® (moxifloxacin hydrochloride) Product Safety. 12.08.2001, Available from http://www.avelox.com/en/physician/product_information/avelox_safety/index.php
- Belanger, A. E.; Besra, G. S.; Ford, M. E.; Mikusova, K.; Belisle, J. T.; Brennan, P. J. & Inamine, J. M. (1996). The *Embab* Genes of *Mycobacterium avium* Encode an Arabinosyl Transferase Involved in Cell Wall Arabinan Biosynthesis that is The Target for the Antimycobacterial Drug Ethambutol. *Proceedings of the National Academy of Sciences*, Vol. 93, pp. 11919-11924.
- Bermudez, L. E.; Inderlied, C. B.; Kolonoski, P.; Wu, M.; Aralar, P. & Young, L. S. (2001) Telithromycin is Active against *Mycobacterium avium* in Mice Despite Lacking Significant Activity in Standard *In vitro* and Macrophage Assays and is Associated With Low Frequency of Resistance During Treatment. *Antimicrobial Agents and Chemotherapy*, Vol. 45, pp. 2210-2214.
- Biava, M.; Porretta, G. C.; Poce, G.; Supino, S.; Deidda, D.; Pompei, R.; Molicotti, P.; Manetti, F. & Botta, M. (2006). Antimycobacterial Agents. Novel Diarylpyrrole Derivatives of BM212 Endowed with High Activity toward *Mycobacterium tuberculosis* and Low Cytotoxicity. *Journal of Medicinal Chemistry*, Vol. 49, pp. 4946-4952.
- Biava, M.; Porretta, G. C.; Poce, G.; Logu, A. D.; Meleddu, R.; Rossi, E. D.; Manetti, F & Botta, M. (2009). 1,5-Diaryl-2-ethyl pyrrole derivatives as antimycobacterial agents: Design, synthesis, and microbiological evaluation. *European Journal of Medicinal Chemistry*, Vol. 44, pp. 4734-4738.
- Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, c.; Alfonso, S.; Logu, A. D.; Serra, N.; Manetti, F & Botta, M. (2010). Identification of a Novel Pyrrole Derivative Endowed With Antimycobacterial Activity and Protection Index Comparable to that of the Current Antitubercular Drugs Streptomycin and Rifampin. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 8076-8084.
- Bogatcheva, E.; Hanrahan, C.; Nikonenko, B.; de los Santos, G.; Reddy, V.; Chen, C.; Barbosa, F.; Einck, L.; Nacy, C. & Protopopova, M. (2011). Identification of SQ609 as a Lead Compound from A Library Of Dipiperidines. *Bioorganic & Medicinal Chemistry Letters*, Vol. 21, pp. 5353-5357.
- Bogatcheva, E.; Dubuisson, T.; Protopopova, M.; Einck, L.; Nacy, C. A. & Reddy, V. M. (2011). Chemical Modification Of Capuramycins To Enhance Antibacterial Activity. *Journal of Antimicrobial Chemotherapy*, Vol. 66, pp. 578-587.
- Butov, D. A.; Pashkov, Y. N.; Stepanenko, A. L.; Choporova, A. I.; Butova, T. S.; Batdelger, D.; Jirathitikal, V.; Bourinbaiar, A. S. & Zaitzeva, S. I. (2011). Phase IIb Randomized Trial of Adjunct Immunotherapy In Patients With First-Diagnosed Tuberculosis,

- Relapsed and Multi-Drug-Resistant (MDR) TB. *J Immune Based Ther Vaccines*, Vol. 9:3. Available from <http://www.jibtherapies.com/content/pdf/1476-8518-9-3.pdf>
- Callaway E. (October 15, 2008). Oldest cases of human TB found beneath the sea. In: *New Scientist*, 12.08.2011, Available from [www.newscientist.com /article/dn14941-oldest-cases-of-human-tb-foundbeneath-the-sea.html](http://www.newscientist.com/article/dn14941-oldest-cases-of-human-tb-foundbeneath-the-sea.html)
- Carta, A.; Palomba, M.; Paglietti, G.; Molicotti, P.; Paglietti, B.; Cannas, S. & Zanetti, S. (2007). [1,2,3]Triazolo[4,5-h]quinolones. A New Class of Potent Antitubercular Agents against Multidrug Resistant *Mycobacterium tuberculosis* Strains. *Bioorganic & Medicinal Chemistry Letters*. Vol. 17, pp. 4791–4794.
- Centre for Disease Control and Prevention [CDC] (1994) 12.08.2011, Available from <http://wonder.cdc.gov/wonder/prevguid/p0000413/p0000413.asp#head00600100000000>
- Chiba. T.; Takii, T.; Nishimura, K.; Yamamoto, Y.; Morikawa, H.; Abec, C. & Onozaki, K. (2007). Synthesis of New Sugar Derivatives from *Stachys sieboldi* Miq and Antibacterial Evaluation against *Mycobacterium tuberculosis*, *Mycobacterium avium*, and *Staphylococcus aureus*. *Bioorganic & Medicinal Chemistry Letters*. Vol. 17, pp. 2487–2491.
- Clark, D. W. (1985). Genetically determined variability in acetylation and oxidation. Therapeutic implications. *Drugs*, Vol. 29, 342-375.
- Cole S. T.; Brosch, R.; Parkhill, J.; Garnier, T.; Churcher, C.; Harris, D.; Gordon, S. V.; Eiglmeier, K.; Gas, S.; Barry, C. E. 3rd; Tekaia, F.; Badcock, K.; Basham, D.; Brown, D.; Chillingworth, T.; Connor, R.; Davies, R.; Devlin, K.; Feltwell, T.; Gentles, S.; Hamlin, N.; Holroyd, S.; Hornsby, T.; Jagels, K.; Krogh, A.; McLean, J.; Moule, S.; Murphy, L.; Oliver, K.; Osborne, J.; Quail, M. A.; Rajandream, M. A.; Rogers, J.; Rutter, S.; Seeger, K.; Skelton, J.; Squares, R.; Squares, S.; Sulston, J. E.; Taylor, K.; Whitehead, S. & Barrell, B. G. (1998). Deciphering the Biology of *Mycobacterium tuberculosis* from the Complete Genome Sequence. *Nature*, Vol. 393, pp. 537-544.
- Collins, L. & Franzblau, S .G. (1997) Microplate Alamar Blue Assay versus BACTEC 460 System for High-throughput Screening of Compounds against *Mycobacterium tuberculosis* and *Mycobacterium avium*. *Antimicrobial Agents and Chemotherapy*, Vol. 41, pp. 1004–1009.
- Deidda D.; Lampis G.; Fioravanti R.; Biava, M.; Porretta, G. C.; Zanetti, S. & Pompei, R. (1998). Bactericidal Activities o The Pyrrole Derivative BM212 against Multidrug-Resistant and Intramacrophagic *Mycobacterium tuberculosis* Strains. *Antimicrobial Agents and Chemotherapy*, Vol. 42, 3035-3037.
- Dinakaran, M.; Senthilkumar, P.; Yogeewari, P.; China, A.; Nagaraja, V. & Sriram, D. (2008 a). Novel Ofloxacin Derivatives: Synthesis, Antimycobacterial and Toxicological Evaluation. *Bioorganic & Medicinal Chemistry Letters*, Vol. 18, pp. 1229–1236.
- Dinakaran, M.; Senthilkumar, P.; Yogeewari, P.; China, A.; Nagaraja, V. & Sriram, D. (2008 b). Antimycobacterial activities of novel 2-(sub)-3-fluoro/nitro-5, 12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid. *Bioorganic & Medicinal Chemistry*, Vol. 16, pp. 3408–3418.
- Domenech, P.; Reed, M. B. & Barry, C. E. (2005) Contribution of the *Mycobacterium tuberculosis* MmpL protein family to virulence and drug resistance. *Infection and Immunity*, Vol. 73, pp. 3492-3501.

- Donald PR. & Seifart H. (1988). Cerebrospinal Fluid Pyrazinamide Concentrations in Children with Tuberculous Meningitis. *Pediatric Infectious Disease Journal*, Vol 7. pp. 469-471.
- Drobac P. C.; del Castillo H.; Sweetland A.; Anca G.; Joseph J. K.; Furin J. & Shin S. (2005). Treatment of Multidrug-Resistant Tuberculosis During Pregnancy: Long-Term Follow-Up of 6 Children With Intrauterine Exposure to Second-Line Agents. *Clinical Infectious Diseases*, Vol. 40, pp. 1689-1692.
- Disratthakit, A. & Doi, N. (2010). *In vitro* Activities of DC-159a, a Novel Fluoroquinolone, against *Mycobacterium* Species, *Antimicrobial Agents and Chemotherapy*, Vol. 54, pp. 2684-2686.
- Eiter, L. C.; Hall, N. W.; Day, C. S.; Saluta, G.; Kucera, G. L. & Bierbach, U. (2009). Gold(I) Analogues of a Platinum-Acridine Antitumor Agent are Only Moderately Cytotoxic but Show Potent Activity against *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, 52, 6519-6522.
- Ellard, G. A. & Gammon, P. T. (1976). Pharmacokinetics of Isoniazid Metabolism in Man. *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 4, pp. 83-113.
- Falzari, K.; Zhu, Z.; Pan, D.; Liu, H.; Hongmanee, P. & Franzblau, S. G. (2005). *In vitro* and *In vivo* Activities of Macrolide Derivatives against *Mycobacterium tuberculosis* *Antimicrobial Agents and Chemotherapy* Vol. 49, pp. 1447-1454.
- Forget, E. J. & Menzies, D. (2006) Adverse Reactions to First-Line Antituberculosis Drugs. *Expert Opinion on Drug Safety*, Vol. 5, pp. 231-249.
- Franzblau, S. G.; Witzig, R. S.; McLaughlin, J. C.; Torres, P.; Madico, G.; Hernandez, A.; Degnan, M. T.; Cook, M. B.; Quenzer, V. K.; Ferguson, R. M.; Gilman, R. H. (1998). Rapid, Low-technology MIC Determination with Clinical *Mycobacterium tuberculosis* Isolates by Using the Microplate Alamar Blue Assay. *Journal of Clinical Microbiology*, Vol. 36, pp. 362-366.
- Fung-Tomc, J.; Minassian, B.; Kolek, B.; Washo, T.; Huczko, E. & Bonner, D. (2000). *In vitro* antibacterial spectrum of a new broad-spectrum 8-methoxy fluoroquinolone, gatifloxacin. *J Antimicrob Chemother.* Vol. 45, pp. 437-446.
- Gerson, S. L.; Kaplan, S. L.; Bruss, J. B.; Le, V.; Arellano, F. M.; Hafkin, B. & Kuter, D. J. (2002). Hematologic Effects Of Linezolid: Summary Of Clinical Experience. *Antimicrobial Agents and Chemotherapy*, Vol. 46, pp. 2723-2726.
- Ginsberg A & Spigelman M. (2006). New drugs for tuberculosis, In: *Tuberculosis: a comprehensive international approach*, Reichman L, Hershfield E, pp. 1135-1151. 3rd ed. New York and London: Informa Healthcare.
- Gosling, R. D.; Uiso, L. O.; Sam, N. E.; Bongard, E.; Kanduma, E. G.; Nyindo, M.; Morris, R. W. & Gillespie, S. H. (2003). The Bactericidal Activity of Moxifloxacin In Patients With Pulmonary Tuberculosis. *Am J Respir Crit Care Med.*, Vol. 168, pp. 1342-1345.
- Gupte, A.; Boshoff, H. I.; Wilson, D. J.; Neres, J.; Labello, N. P.; Somu, R.; Xing, C.; Barry, C. E.; Aldrich, C. C.; (2008). Inhibition of Siderophore Biosynthesis by 2-Triazole Substituted Analogues of 5'-O-[N-(Salicyl)sulfamoyl]adenosine: Antibacterial Nucleosides Effective against *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, Vol. 51, pp. 7495-7507.
- Handwerker, S., & Tomasz, A. (1985). Antibiotic Tolerance Among Clinical Isolates of Bacteria. *Reviews of Infectious Diseases*, Vol. 7, pp. 368-386.

- Hearn, M. J.; Cynamon, M. H.; Chen, M. F.; Coppins, R.; Davis, J.; Joo-On Kang, H.; Noble, A.; Tu-Sekine, B.; Terrot, M. S.; Trombino, D.; Thai, M.; Webster, E. R. & Wilson R. (2009). Preparation and Antitubercular Activities *In vitro* and *In vivo* of Novel Schiff Bases of Isoniazid. *European Journal of Medicinal Chemistry*. Vol. 44,, pp. 4169–4178.
- Heifets L. (1988). MIC as a Quantitative Measurement of Susceptibility of *M. Avium* to Seven Antituberculosis Drugs. *Antimicrobial Agents and Chemotherapy*, Vol. 32, pp. 1131–1136.
- Heifets L. & Lindholm-Levy P. A. (1989). Comparison of Bactericidal Activities of Streptomycin, Amikacin, Kanamycin, and Capreomycin against *M. Avium* and *M. tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 33, pp. 1298–1303.
- Heifets, L.; Sanchez, T.; Vanderkolk, J. & Pham, V. (1999). Development of Rifapentine Susceptibility Tests for *Mycobacterium tuberculosis*. *Antimicrobial Agents And Chemotherapy*, Vol. 43, pp. 25–28.
- Hirano, S.; Ichikawa, S. & Matsuda, A. (2008). Structure–activity relationship of truncated analogs of caprazamycins as potential anti-tuberculosis agents. *Bioorganic & Medicinal Chemistry*, Vol 16, pp. 5123–5133.
- Hong Kong Chest Service, Medical Research Council. (1981). Controlled Trial of Four Thrice Weekly Regimens and a Daily Regimen Given for 6 Months for Pulmonary Tuberculosis. *Lancet*, Vol 1, pp. 171–174.
- Horita, Y.; Takii, T.; Kuroishi, R.; Chiba, T.; Ogawa, K.; Kremer, L.; Sato, Y.; Lee, Y.; Hasegawa, T. & Onozaki, K. (2011). Synthesis and Evaluation of Anti-Tubercular Activity of New Dithiocarbamate Sugar Derivatives. *Bioorganic & Medicinal Chemistry Letter* Vol. 21 pp. 899–903.
- Hu, Y.; Coates, A. R. & Mitchison, D.A. (2003). Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 47, pp. 653–657.
- Huang, Q.; Mao, J.; Wan, B.; Wang, Y.; Brun, R.; Franzblau, S. G. & Kozikowski, A. P. (2009). Searching for New Cures for Tuberculosis: Design, Synthesis, and Biological Evaluation of 2-Methylbenzothiazoles. *Journal of Medicinal Chemistry*, Vol. 52, 6757–6767.
- Huitric, E.; Verhasselt, P.; Andries, K. & Hoffner, S. E. (2007). *In vitro* antimycobacterial spectrum of a diarylquinoline ATP-synthase inhibitor. *Antimicrobial Agents and Chemotherapy* Vol. 51, pp. 4202–4204.
- Inderlied, C. B. & Salfinger, M. (1999). Antimycobacterial Agents and Susceptibility Tests. In: *Manual of Clinical Microbiology*, ed. PR Murray, EJ Baron, MA Pfaller, FC Tenover, RH Tenover, pp1601–1623. Washington DC: ASM Press/ III ed.
- International Programme on Chemical Safety [INCHEM], a) n.d. and reference therein. 12.08.2011 Available from <http://www.inchem.org/documents/pims/pharm/rifam.htm#SectionTitle:2.1%20Main%20--risks%20and%20target%20organs> b) Available from <http://www.inchem.org/documents/pims/pharm/pim288.htm#SectionTitle:2.1%20%20Main%20risks%20and%20target%20organs>
- Jaso, A.; Zarranz, B.; Aldana, I. & Monge, A. (2005). Synthesis of New Quinoxaline-2-carboxylate 1,4-Dioxide Derivatives as Anti-*Mycobacterium tuberculosis* Agents. *J. Med. Chem.* Vol. 48, pp. 2019–2025.

- Jia, L.; Tomaszewski, J. E.; Hanrahan, C.; Coward, L.; Noker, P.; Gorman, G.; Nikonenko, B. & Protopopova, M. (2005) Pharmacodynamics and Pharmacokinetics of SQ109, A New Diamine-Based Antitubercular Drug. *British Journal of Pharmacol*, Vol. 144, pp. 80–87.
- Jiang, Z.; Higgins, M. P.; Whitehurst, J.; Kisich, K. O.; Voskuil, M. I. & Hodges, R. S. (2011). Anti-tuberculosis Activity of A-Helical Antimicrobial Peptides: De Novo Designed L- and D-Enantiomers versus L- and D-LL-37. *Protein and Peptide Letters*, Vol. 18, pp. 241–252.
- Jindani, A.; Dore, C. J. & Mitchison, D. A. (2003). Bactericidal and Sterilizing Activities Of Antituberculosis Drugs During The First 14 Days. *Am. J. Respir. Crit. Care Med.*, 167, 1348–1354.
- Johansen, S. K.; Maus, C. E.; Plikaytis, B. B. & Douthwaite S. (2006). Capreomycin Binds Across The Ribosomal Subunit Interface Using TlyA-Encoded 2'-O-Methylations in 16S and 23S rRNAs. *Molecular Cell*, Vol. 23, pp. 173–182.
- Johar, M.; Manning, T.; Kunimoto, D. Y. & Kumar, R. (2005). Synthesis and In Vitro Anti-Mycobacterial Activity of 5-Substituted Pyrimidine Nucleosides. *Bioorganic & Medicinal Chemistry*, Vol. 13, pp. 6663–6671.
- Johar, M.; Manning, T.; Tse, C.; Desroches, N.; Agrawal, B.; Kunimoto, Y. & Kumar, R. (2007). Growth Inhibition of *Mycobacterium bovis*, *Mycobacterium tuberculosis* and *Mycobacterium avium* In vitro: Effect of 1-*b*-D-2'-*b*-D-Arabinofuranosyl and 1-(2-Deoxy-2-fluoro-*b*-D-2'-ribofuranosyl) Pyrimidine Nucleoside. *Journal of Medicinal Chemistry*, Vol. 50, pp. 3696–3705.
- Kaufmann, S. H. E. (2011). Tuberculosis Vaccines – A New Kid on the Block. *Nature Medicine*, Vol. 17, pp. 159–160.
- Kawasaki, M.; Yamamoto, K. & Matusmoto M. (2005) Mechanism of action of OPC-67683 against *Mycobacterium tuberculosis* [abstract F-1463]. In: *Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology.
- Khoje, A. D.; Kulendrn, A.; Charnock, C.; Wan, B.; Franzblau, S. & Gundersen, L. L. (2010). Synthesis of Non-Purine Analogs of 6-Aryl-9-Benzylpurines, and Their Antimycobacterial Activities. Compounds Modified in the Imidazole Ring. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 7274–7282.
- Kogler, M.; Vanderhoydonck, B.; De Jonghe, S.; Rozenski, J.; Van Belle, K.; Herman, J.; Louat, T.; Parchina, A.; Sibley, C.; Lescrinier, E. & Herdewijn, P. (2011). Synthesis and Evaluation of 5-Substituted 2'-deoxyuridine Monophosphate Analogues As Inhibitors of Flavin-Dependent Thymidylate Synthase in *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, Vol. 54, pp. 4847–4862.
- Lacroix, C.; Phan Hoang, T.; Nouveau, J.; Guyonnaud, C.; Laine, G.; Duwoos, H. & Lafont, O. (1989). Pharmacokinetics of Pyrazinamide and Its Metabolites in Healthy Subjects. *European Journal of Clinical Pharmacology*, Vol. 36, pp. 395–400.
- Lee, R. E.; Brennan, P. J. & Besra, G. S. (1997) Mycobacterial Arabinan Biosynthesis: The Use of Synthetic Arabinoside Acceptors in The Development of An Arabinosyl Transfer Assay. *Glycobiology*, Vol. 7, pp. 1121–1128.
- Lee R.; Protopopova, M.; Crooks, E.; Slayden, R. A.; Terrot, M.; Barry, CE. (2003). Combinatorial Lead Optimization of [1,2]-Diamines Based On Ethambutol As

- Potential Antituberculosis Preclinical Candidates. *Journal of Combinatorial Chemistry*, Vol. 5, pp. 172–187.
- Lee, S. H.; Kim, S.; Yun, M. H.; Lee, Y. S.; Cho, S. N.; Oh, T. & Kim, P. (2011) Synthesis and Antitubercular Activity of Monocyclic Nitroimidazoles: Insights From Econazole. *Bioorganic & Medicinal Chemistry Letter*, Vol. 21, pp. 1515–1518.
- Lenaerts, A.; J.; Gruppo, V.; Marietta, K. S.; Johnson, C. M.; Driscoll, D. K.; Tompkins, N. M.; Rose, J. D.; Reynolds, R. C. & Orme I. M. (2005) Preclinical testing of the nitroimidazopyran PA-824 for activity against *Mycobacterium tuberculosis* in a series of *in vitro* and *in vivo* models. *Antimicrobial Agents and Chemotherapy*, Vol 49, pp. 2294–301.
- Liav, A.; Angala, S. K.; Brennan, P. J. & Jackson, M. (2008). N-D-Aldopentofuranosyl-N0-[p-(isoamyloxy)phenyl]-thiourea derivatives: Potential anti-TB therapeutic agents *Bioorganic & Medicinal Chemistry Letter*, Vol. 18, pp. 2649–2651.
- Lienhardt, C.; Rustomjee, R.; Mthigane, T.; Levin, J.; Fourie, B.; Horton, J.; Kanyok, T. & Mitchison, D. (2005) Comparison of 2-months sterilizing activities of several quinolone-containing regimens: preliminary results of a phase II trial in South Africa [abstract LB2-13]. In: *Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology.
- Lilienkampf, A.; Mao, J.; Wan, B.; Wang, Y.; Franzblau, S. G. & Kozikowski, A. (2009). Structure-Activity Relationships for a Series of Quinoline-Based Compounds Active against Replicating and Nonreplicating *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, Vol. 52, pp. 2109–2118.
- Lim, S. A. (2006). Ethambutol-Associated Optic Neuropathy. *Annals Academy of Medicine Singapore*. Vol 35, pp. 274–278.
- Long, M. C. & Parker, W. B. (2006). Structure-Activity Relationship For Nucleoside Analogs as Inhibitors or Substrates of Adenosine Kinase from *Mycobacterium tuberculosis* I. Modifications to the Adenine Moiety. *Biochemical Pharmacology*, Vol. 71, pp. 1671–1682.
- Long, M. C.; Shaddix, S. C.; Moukha-Chafiq, O.; Maddry, J. A.; Nagy, L. & Parker, W. B. (2008) Structure-activity relationship for adenosine kinase from *Mycobacterium tuberculosis* II. Modifications to the ribofuranosyl moiety. *Biochemical Pharmacology*, Vol. 75, pp. 1588–1600.
- Lounis N.; Bentoucha A.; Truffot-Pernot C.; Ji, B.; O'brien, R. J.; Vernon, A.; Roscigno, G. & Grosset1, J. (2001). Effectiveness of once-weekly rifapentine and moxifloxacin regimens against *Mycobacterium tuberculosis* in mice. *Antimicrob Agents Chemother*, Vol. 45, pp. 3482–3486.
- Lourenço, M. C.; Ferreira, M. de L.; de Souza, M. V. N.; Peralta, M. A.; Vasconcelos, T. R. A. & Henriques M. G. M. O. (2008). Synthesis and Anti-Mycobacterial Activity of (E)-N'-(Monosubstituted-Benzylidene)Isonicotinohydrazide Derivatives. *European Journal of Medicinal Chemistry*, Vol. 43, 1344–1347.
- Lu Y.; Zheng, M. Q.; Wang, B.; Zhao, W. J.; Li, P.; Chu, N. H. & Liang B. W. (2008). Activities of Clofazimine against *Mycobacterium tuberculosis* *In vitro* and *In vivo*. *Zhonghua Jie He He Hu Xi Za Zhi*. Vol. 31, pp. 752–755.
- Mahapatra, A.; Mativandlela, S. P. N.; Binneman, B.; Fourie, P. B.; Hamilton, C. J.; Meyer, J. J. M.; van der Kooy, F.; Houghton, P. & Lall, N. (2007). Activity of 7-methyljuglone

- derivatives against *Mycobacterium tuberculosis* and as Subversive Substrates For Mycothiol Disulfide Reductase. *Bioorganic & Medicinal Chemistry*, Vol. 15, pp. 7638–7646.
- Manjunatha, U. H.; Boshoff, H.; Dowd, C. S.; Zhang, L.; Albert, T. J.; Norton, J. E.; Daniels, L.; Dick, T.; Pang, S. S. & Barry, C. E. (2005). Identification of a nitroimidazo-oxazine-specific protein involved in PA-824 resistance in *Mycobacterium tuberculosis*. *Proc Nat Acad Sci USA*, Vol. 103, pp. 431–436.
- Matsumoto, M.; Hshizume, H.; Tomishige, T. & Kawasaki M. (2005). *In vitro* and *in vivo* efficacy of novel antituberculous candidate OPC-67683 [abstract F-1462]. In: *Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology.
- McCune, R. M., Jr.; & Tompsett, R. (1956 a). Fate of *Mycobacterium tuberculosis* In Mouse Tissues as Determined by the Microbial Enumeration Technique. I. The Persistence of Drug-Susceptible Tubercle Bacilli In The Tissues Despite Prolonged Antimicrobial Therapy. *Journal of Experimental Medicine*. Vol. 104, pp. 737-762.
- McCune, R. M., Jr.; McDermott, W., & Tompsett, R. (1956 b). Fate of *Mycobacterium tuberculosis* In Mouse Tissues as Determined by the Microbial Enumeration Technique. II. The conversion of Tuberculous Infection to the Latent State By The Administration of Pyrazinamide and a Companion Drug. *Journal of Experimental Medicine*. Vol. 104, 763-802.
- McIlleron, H.; Willemse M.; Werely, C. J.; Hussey, G. D.; Schaaf, H. S.; Smith, P. J. & Donald, P. R. (2009). Isoniazid Plasma Concentrations in a Cohort of South African Children with Tuberculosis: Implications for International Pediatric Dosing Guidelines. *Clinical Infectious Diseases*, Vol. 48, pp. 1547–1553.
- Melnic, S.; Prodius, D.; Stoeckli-Evans, H.; Shova, S. & Turta, C. (2010). Synthesis and Anti-Tuberculosis Activity of New Hetero(Mn, Co, Ni)Trinuclear Iron(III) Furoates. *European Journal of Medicinal Chemistry*, Vol. 45, pp. 1465–1469.
- Migliori, G. B.; Eker, B.; Richardson, M. D.; Sotgiu, G.; Zellweger, J. P.; Skrahina, A.; Ortmann, J.; Girardi, E.; Hoffmann, H.; Besozzi, G.; Bevilacqua, N.; Kirsten, D.; Centis, R. & Lange, C. TBNET Study Group. A Retrospective TBNET Assessment Of Linezolid, Safety, Tolerability and Efficacy In Multidrug Resistant Tuberculosis. *European Respiratory Journal*, Vol. 34, pp. 387-393.
- Miller, M. J.; Walz, A. J.; Zhu, H.; Wu, C.; Moraski, G.; M€ollmann, U.; Tristani, E. M.; Crumbliss, A. L.; Ferdig, M. T.; Checkley, L.; Edwards, R. L. & Boshoff, H. (2011). Design, Synthesis, and Study of a Mycobactin-Artemisinin Conjugat That Has Selective and Potent Activity against Tuberculosis and Malaria. *Journal of American Chemical Society*, Vol. 133, pp. 2076–2079.
- Mitchison, D. A. (1979). Basic Mechanisms of Chemotherapy. *Chest*, Vol. 76, pp. 771-781.
- Munier-Lehmann, H.; Chafotte, A.; Pochet, S.; Labesse, G. (2001) Thymidylate kinase of *Mycobacterium tuberculosis*: a chimera sharing properties common to eukaryotic and bacterial enzymes. *Protein Science*, Vol. 10, 1195-1205.
- Nau, R.; Prange, H. W.; Menck, S.; Kolenda, H.; Visser, K.; & Seydel, J. K. (1992). Penetration of Rifampicin into the Cerebrospinal Fluid of Adults with Uninflamed Meninges. *Journal of Antimicrobial Chemotherapy*, Vol. 29, pp. 719-724

- Nicholas, G. M.; Eckman, L. L.; Newton, G. L.; Fahey, R. C.; Ray, S. & Bewley, C. A. (2003). Inhibition and Kinetics of *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* Mycothiol-S-conjugate Amidase by Natural Product Inhibitors. *Bioorganic & Medicinal Chemistry*, Vol. 11, pp. 601–608.
- Nikolaeva, L. G.; Maystat, T. V.; Pylypchuk, V. S.; Volyanskii, Y. L.; Masyuk, L. A. & Kutsyna, G. A.; (2008 a). Effect of Oral Immunomodulator Dzherelo In TB/HIV Co-Infected Patients Receiving Anti-Tuberculosis Therapy Under DOTS. *International Immunopharmacology*, Vol. 8, pp. 845–851.
- Nikolaeva, L. G.; Maystat, T. V.; Pylypchuk, V. S.; Volyanskii, Y. L.; Frolov, V. M. & Kutsyna, G. A. (2008 b). Cytokine Profiles of HIV Patients With Pulmonary Tuberculosis Resulting From Adjunct Immunotherapy With Herbal Phytoconcentrates Dzherelo and Anemin. *Cytokine*, Vol. 44, pp. 392–396.
- North Dakota Department of Health, 2011, 28.07.2011. Available from [http://www.ndhealth.gov/disease/tb/Documents/Second line TB drugs.pdf](http://www.ndhealth.gov/disease/tb/Documents/Second%20line%20TB%20drugs.pdf)
- Nuermberger E. L.; Yoshimatsu, T.; Tyagi, S.; Williams, K.; Rosenthal, I.; O'Brien, R. J.; Vernon, A. A.; Chaisson, R. E.; Bishai, W. R. & Grosset, J. H. (2004). Moxifloxacin-Containing Regimens of Reduced Duration Produce A Stable Cure In Murine Tuberculosis. *Am J Respir Crit Care Med*, Vol. 170, pp. 1131–1134.
- Nuermberger, E.; Tyagi, S.; Williams, K. N.; Rosenthal, I.; Bishai, W. R.; Grosset, J. H. (2005). Rifapentine, Moxifloxacin, or DNA Vaccine Improves Treatment of Latent Tuberculosis In A Mouse Model. *Am J Respir Crit Care Med*. Vol. 172, pp. 1452–1456.
- O'Sullivan D. M.; McHugh, T. D & Gillespie S. H. (2005). Analysis of rpoB and pncA Mutations In The Published Literature: An Insight Into The Role of Oxidative Stress in *Mycobacterium tuberculosis* Evolution?. *Journal of Antimicrobial Chemotherapy*, Vol. 55, pp. 674–679.
- Palmer, B. D.; Thompson, A. M.; Sutherland, H. S.; Blaser, A.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z. & Denny, W. A. (2010). Synthesis and Structure-Activity Studies of Biphenyl Analogues of the Tuberculosis Drug (6S)-2-Nitro-6-[[4-(trifluoromethoxy)benzyl]oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (PA-824). *Journal of Medicinal Chemistry*, Vol. 53, pp. 282–294.
- Palomino, J. C.; Martin, A.; Camacho, M.; Guerra, H.; Swings, J.; & Portaella, F. (2002). Resazurin Microtiter Assay Plate: Simple and Inexpensive Method for Detection of Drug Resistance in *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 46. p. 2720–2722.
- Paramasivan, C. N.; Sulochana, S.; Kubendiran, G.; Venkatesan, P. & Mitchison, D. (2005). A. Bactericidal action of gatifloxacin, rifampin, and isoniazid on logarithmic- and stationary-phase cultures of *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 49, pp. 627–631.
- Pathak, A. K.; Pathak, V.; Kulshrestha, M.; Kinnaird, D.; Suling, W. J.; Gurcha, S. S.; Besra, G. S. & Reynolds, R. C. (2003). Arabinofuranose disaccharide analogs as inhibitors of *Mycobacterium tuberculosis* *Tetrahedron*, Vol. 59, pp. 10239–10248.
- Pavan, F.R.; Poelhsitz, V. G.; do Nascimento, F.; Leite, S. R. A.; Batista, A. A.; Deflon, V. M.; Sato, D. N.; Franzblau, S. G. & Leite, C. Q. F. (2010) Ruthenium (II) phosphine/picolinate complexes as antimycobacterial agents. *European Journal of Medicinal Chemistry*, Vol. 45, pp. 598–601

- Peloquin, C. A.; Namdar, R.; Singleton, M. D. & Nix, D. E. (1999 a) Pharmacokinetics of Rifampin under Fasting Conditions, with Food, and with Antacids. *Chest*, Vol. 115, pp. 12-18.
- Peloquin, C. A.; Bulpitt, A. E.; Jaresko, G. S.; Jelliffe, R. W.; Childs, J. M. & Nix, D. E. (1999 b). Pharmacokinetics of Ethambutol under Fasting Conditions, with Food, and with Antacids. *Antimicrobial Agents and Chemotherapy*, Vol. 43, pp. 568-572.
- Peters, C. & Nienhaus, A. (2008). Case report-tuberculosis in a health care worker during pregnancy. *Pneumologie*, Vol. 62, pp. 695-698.
- Pletz, M. W. R.; De Roux, A.; Roth, A.; Neumann, K. H.; Mauch, H. & Lode, H. (2004) Early Bactericidal Activity of Moxifloxacin In Treatment of Pulmonary Tuberculosis: A Prospective, Randomized Study. *Antimicrobial Agents and Chemotherapy*, Vol. 48, pp. 780-782.
- Pochet, S.; Dugue', L.; Douguet, D.; Labesse, G.; Munier-Lehmann, H. (2002). Nucleoside Analogues as Inhibitors of Thymidylate Kinases: Possible Therapeutic Applications. *ChemBioChem.*, Vol. 3, pp. 108-110.
- Pochet, S.; Dugue', L.; Labesse, G.; Delepierre, M.; Munier-Lehmann, H. (2003). Comparative Study of Purine and Pyrimidine Nucleoside Analogues Acting on the Thymidylate Kinases of *Mycobacterium tuberculosis* and of Humans. *ChemBioChem.*, Vol. 4, pp. 742-747.
- Prihoda1, N. D.; Arjanova1, O. V.; Yurchenko, L. V.; Sokolenko, N. I.; Vihrova, L. A.; Pylypchuk, V. S. & Kutsyna, G. A. (2007). Open Label Trial of Adjuvant Immunotherapy with Dzherelo, Svitanok and Lizorm, in MDR-TB, XDR-TB and TB/HIV Co-Infected Patients Receiving Anti-Tuberculosis Therapy under DOT. *Journal of Medicinal Plants Research*, Vol. 1, pp. 117-122.
- Pruksakorn, P.; Arai, M.; Kotoku, N.; Vilchèze, C.; Baughn, A. D.; Moodley, P.; Jacobs, W. R., Jr. & Kobayashi, M. (2010). Trichodermins, Novel Aminolipopeptides From A Marine Sponge-Derived Trichoderma Sp., are Active against Dormant Mycobacteria. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, pp. 3658-3663.
- Rai, D.; Johar, M.; Manning, T.; Agrawal, B.; Kunimoto, D. Y. & Kumar R. (2005). Design and Studies of Novel 5-Substituted Alkynylpyrimidine Nucleosides as Potent Inhibitors of Mycobacteria. *Journal of Medicinal Chemistry*, Vol. 48, pp. 7012-7017.
- Rai, D.; Johar, M.; Srivastav, N. C.; Manning, T.; Agrawal, B.; Kunimoto, D. Y. & Kumar, R. (2007). Inhibition of *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium avium* by Novel Dideoxy Nucleosides. *Journal of Medicinal Chemistry*, Vol. 50, pp. 4766-4774.
- Rastogi, N.; Goh, K. S.; Bryskier, A. & Devallois, A. (1996). *In vitro* Activities of Levofloxacin Used Alone and in Combination with First- and Second-Line Antituberculous Drugs against *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 40, p.p. 1610-1616
- Saito H.; Tomioka H.; Sato K.; Emori M.; Yamane T.; Yamashita K.; Hosoe K. & Hidaka T. (1991) *In vitro* Antimycobacterial Activities of Newly Synthesized Benzoxazinorifamycins. *Antimicrobial Agents and Chemotherapy*, Vol. 35, pp. 542-547.
- Scorpio, A. & Zhang Y. (1996). Mutations In PncA, A Gene Encoding Pyrazinamidase/Nicotinamidase, Cause Resistance To The Antituberculous Drug Pyrazinamide In Tubercle Bacillus. *Nature Medicine*, Vol. 2, pp. 662-667.

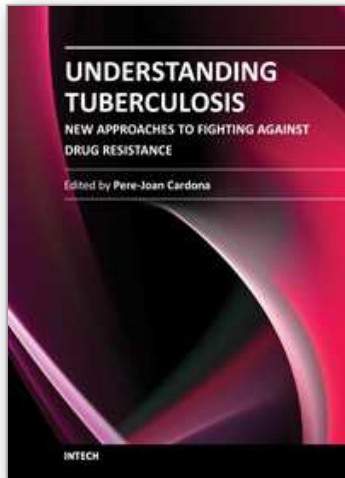
- Sekiguchi, J.; Disratthakit, A.; Maeda, S. & Doi, N. (2011). Characteristic Resistance Mechanism of *Mycobacterium tuberculosis* to DC-159a, a New Respiratory Quinolone. *Antimicrobial Agents and Chemotherapy*, Aug. 2011, Vol. 55, pp. 3958–3960.
- Senthilkumar, P.; Dinakaran, M.; Yogeewari, P.; Sriram, D.; China, A. & Nagaraja, V. (2009). Synthesis and antimycobacterial activities of novel 6-nitroquinolone-3-carboxylic acids. *European Journal of Medicinal Chemistry*. Vol. 44, pp. 345–358.
- Shakya, N.; Srivastav, N. C.; Desroches, N.; Agrawal, B.; Kunimoto, D. Y. & Kumar, R. (2010). 3-Bromo Analogues of Pyrimidine Nucleosides as a New Class of Potent Inhibitors of *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, 2010, Vol. 53, pp. 4130–4140.
- Shandil, R. K.; Jayaram, R.; Kaur, P.; Gaonkar, S.; Suresh, B. L.; Mahesh, B. N.; Jayashree, R.; Nandi, V.; Bharath, S. & Balasubramanian, V. (2007). Sowmya, and V. Moxifloxacin, Ofloxacin, Sparfloxacin, and Ciprofloxacin against *Mycobacterium tuberculosis*: Evaluation of In Vitro and Pharmacodynamic Indices That Best Predict In Vivo Efficacy. *Antimicrobial Agents and Chemotherapy*, Vol. 51, pp. 576–582
- Shiradkar, M. R.; Murahari, K. K.; Gangadasu, H. R.; Suresh, T.; Kalyan, C. A.; Panchal, D. & Kaur, R. (2007). Synthesis of New S-Derivatives of Clubbed Triazolyl Thiazole As Anti-*Mycobacterium tuberculosis* Agents. *Bioorganic & Medicinal Chemistry*. Vol. 15, pp. 3997–4008.
- Singh, B. & Mitchison, D. A. (1954). Bactericidal Activity of Streptomycin and Isoniazid against Tubercle Bacilli. *British Medical Journal*, Vol. 130, pp. 130–132.
- Sinha, R. K.; Arora, S. K.; Sinha, N.; Modak, V. M.; *In vivo* activity of LL4858 against *Mycobacterium tuberculosis* (2004) [abstract F-1116]. In: *Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology, 212.
- Somu, R. V.; Boshoff, H.; Qiao, C.; Bennett, E.; Barry, C. E. & Aldrich, C. C. (2006). Rationally Designed Nucleoside Antibiotics That Inhibit Siderophore Biosynthesis of *Mycobacterium tuberculosis*. *Journal of Medicinal Chemistry*, Vol. 49, pp. 31–34.
- Spigelman, M. K. (2005) Current and future therapeutic options for tuberculosis [presentation 2190 in symposium 220{F}]. In: *Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC)*. Washington, DC: American Society for Microbiology.
- Sriram, D.; Aubry, A.; Yogeewari, P. & Fisher, L. M. (2006). Gatifloxacin derivatives: Synthesis, Antimycobacterial Activities, and Inhibition of *Mycobacterium tuberculosis* DNA gyrase. *Bioorganic & Medicinal Chemistry Letters* Vol. 16, pp. 2982–2985
- Sriram, D.; Aubry, A.; Yogeewari, P.; Dhakla, P.; Senthilkumar, P.; Banerjee, D. & Manjashetty, T. H. (2009). 5-Nitrofuran-2-yl derivatives: Synthesis and Inhibitory Activities against Growing and Dormant *Mycobacterium* Species. *Bioorganic & Medicinal Chemistry Letters*, Vol. 19, pp. 1152–1154.
- Srivastav, N. C.; Manning, T.; Kunimoto, D. Y. & Kumar, R. (2007). Studies on Acyclic Pyrimidines as Inhibitors of *Mycobacteria*. *Bioorganic & Medicinal Chemistry*, Vol. 15, pp. 2045–2053.
- Srivastav, N. C.; Rai, D.; Tse, C.; Agrawal, B.; Kunimoto, D. Y. & Kumar, R. (2010). Inhibition of *Mycobacterial* Replication by Pyrimidines Possessing Various C-5 Functionalities

- and Related 20 -Deoxynucleoside Analogues Using *in vitro* and *in vivo* Models. *Journal of Medicinal Chemistry*, Vol. 53, 6180–6187.
- Stover, C. K.; Warrenner, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barry, C. E. & Baker, W. R. (2000). A Small-Molecule Nitroimidazopyran Drug Candidate for The Treatment of Tuberculosis. *Nature*, Vol. 405, pp. 962–966.
- Suarez J, Ranguelova K, Jarzecki AA, , Manzerova, J.; Krymov, V.; Zhao, X; Yu, S; Metlitsky, L.; Gerfen, G. J. & Magliozzo, R. S. (2009). An Oxyferrous Heme/Protein-based Radical Intermediate is Catalytically Competent in the Catalase Reaction of *Mycobacterium tuberculosis* Catalase-Peroxidase (KatG), *Journal of Biological Chemistry*, Vol. 284, pp. 7017–7029.
- Suling, W. J.; Reynolds, R. C.; Barrow, E. W.; Wilson, L. N.; Piper, J. R.; Barrow, W. W. *Journal of Antimicrobial Chemotherapy*, 1998, 42, 811–815.
- Takii, T.; Yamamoto, Y.; Chiba, T.; Abe, C.; Belisle, J. T.; Brennan, P. J. & Onozaki, K. (2002). Simple fibroblast-based assay for screening of new antimicrobial drugs against *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, Vol. 46, pp. 2533–2539.
- The American Thoracic Society [ATS]. (2006) 09.08.2011. Available from <http://www.thoracic.org/assemblies/mtpi/resources/istc-report.pdf>
- Thomas, J. P.; Baughn, C. O.; Wilkinson, R. G. & Shepherd, R. G. (1961). A new synthetic compound with antituberculous activity in mice: ethambutol (dextro-2,2'-(ethylenediimino)-di-1-butanol). *American Review of Respiratory Disease*, Vol. 83, pp. 891-893.
- Timmins, G. S. & Deretic, V. (2006) Mechanisms of Action of Isoniazid. *Molecular Microbiology*, Vol 62, pp. 1220–1227.
- Tomioka, H. (2006). Current Status of Some Antituberculosis Drugs and the Development of New Antituberculous Agents with Special Reference to their *In vitro* and *In vivo* Antimicrobial Activities. *Current Pharmaceutical Design*, Vol. 12, No. 31, pp. 4047–4070.
- Torres-Romero, D.; Jiménez, I. A.; Rojas, R.; Gilman, R. H.; López, M. & Bazzocchi, I. L. (2011). Dihydro-b-Agarofuran Sesquiterpenes Isolated From *Celastrus Vulcanicola* As Potential Anti-*Mycobacterium tuberculosis* Multidrug-Resistant Agents. *Bioorganic & Medicinal Chemistry*, Vol. 19, pp. 2182–2189.
- Tortoli, E.; Dionisio, D. & Fabbri, C. Evaluation of Moxifloxacin Activity *In vitro* against *Mycobacterium tuberculosis*, Including Resistant and Multidrug-Resistant Strains. (2004). *Journal of Chemotherapy*, Vol. 16, pp. 334-336.
- Trimble, K. A.; Clark, R. B.; Sanders, W. E., Jr.; Frankel, J. W.; Cacciatore, R. & Valdez, H. (1987) Activity of Ciprofloxacin against *Mycobacteria In vitro*: Comparison of BACTEC and Macrobroth Dilution Methods. *Journal of Antimicrobial Chemotherapy*. Vol. 19, pp. 617-622.
- Tripathi, R. P.; Tiwari, V. K.; Tewari, N.; Katiyar, D.; Saxena, N.; Sinha, S.; Gaikwad, A.; Srivastava, A.; Chaturvedi, V.; Manju, Y. K.; Srivastava, R. & Srivastava B. S. (2005), Synthesis and antitubercular activities of bis-glycosylated diamino alcohols. *Bioorganic & Medicinal Chemistry*, Vol. 13, pp. 5668–5679.

- Trivedi, A. R.; Bhuva, V. R.; Dholariya, B. P.; Dodiya, D. K.; Kataria, V. B. & Shah, V. H. (2010). Novel Dihydropyrimidines as a Potential New Class of Antitubercular Agents. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, pp. 6100–6102.
- Tuberculosis Research Centre (Indian Council of Medical Research), Chennai (2002). Shortening Short Course Chemotherapy: A Randomized Clinical Trial for the Treatment of Smear Positive Pulmonary Tuberculosis With Regimens Using Ofloxacin In The Intensive Phase. *Indian Journal of Tuberculosis*, Vol. 49, pp. 27–38.
- Tuberculosis Trials Consortium (2002). Rifapentine and Isoniazid Once A Week Versus Rifampicin and Isoniazid Twice A Week For Treatment of Drug-Susceptible Pulmonary Tuberculosis In HIV-Negative Patients: A Randomized Clinical Trial. *Lancet*, Vol. 360, pp. 528–534
- Tyagi, S.; Nuermberger, E.; Yoshimatsu, T.; Williams, K.; Rosenthal, I.; Bishai, W. & Grosset, J. (2005). Bactericidal Activity of The Nitroimidazopyran PA-824 In The Murine Model of Tuberculosis. *Antimicrobial Agents and Chemotherapy*, Vol. 49, pp. 2289–2293.
- Upadhayaya, R. S.; Shinde, P.; Kadam, S. A.; Bawane, A.N.; Sayyed, A. Y.; Kardile, R. A.; Gitay, P. N.; Lahore, S. V.; Dixit, S. S.; Földesi, A. & Chattopadhyaya, J. (2011). Synthesis and Antimycobacterial Activity of Prodrugs of Indeno[2,1-C]Quinoline Derivatives. *European Journal of Medicinal Chemistry*, Vol. 46, pp. 1306–1324.
- Vacher, S; Pellegrin, J. L.; Leblanc, F.; Fourche, J. & Maugein J. (1999). Comparative Antimycobacterial Activities of Ofloxacin, Ciprofloxacin and Grepafloxacin. *Journal of Antimicrobial Chemotherapy*, Vol. 44, pp. 647–652.
- van den Boogaard. J.; Kibiki, G. S.; Kisanga, E. R.; Boeree, M. J. & Aarnoutse, R. E. (2009). New Drugs against Tuberculosis: Problems, Progress, and Evaluation of Agents in Clinical Development. *Antimicrobial Agents and Chemotherapy*, Vol. 53, pp. 849–862
- Vanheusden, V.; Munier-Lehmann, H.; Pochet, S.; Herdewijn, P. & Van Calenbergh, S. (2002). Synthesis and evaluation of thymidine-5'-O-monophosphate analogues as inhibitors of *Mycobacterium tuberculosis* thymidylate kinase. *Bioorganic & Medicinal Chemistry Letter*, Vol. 12, pp. 2695–2698.
- Vanheusden, V.; Van Rompaey, P.; Munier-Lehmann, H.; Pochet, S.; Herdewijn, P.; Van Calenbergh, S. (2003). Thymidine and Thymidine-5'-O-Monophosphate Analogues as Inhibitors of *Mycobacterium tuberculosis* Thymidylate Kinase. *Bioorganic & Medicinal Chemistry Letter*, Vol. 13, pp. 3045–3048.
- Vanheusden, V.; Munier-Lehmann, Froeyen, M.; Busson, R.; Rozenski, J.; Herdewijn, P. & Van Calenbergh, S. (2004). Discovery of Bicyclic Thymidine Analogues as Selective and High-Affinity Inhibitors of *Mycobacterium tuberculosis* Thymidine Monophosphate Kinase. *Journal of Medicinal Chemistry*, Vol. 47, pp. 6187–6194
- Velaparthi, S.; Brunsteiner, R. & Petukhov, P. A. (2008) 5-*tert*-Butyl-*N*-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide Derivatives as Novel Potent Inhibitors of *Mycobacterium tuberculosis* Pantothenate Synthetase: Initiating a Quest for New Antitubercular Drugs. *Journal of Medicinal Chemistry*, Vol. 51, pp. 1999–2002.
- Vicente, E.; Pérez-Silanes, S.; Lima, L. M.; Ancizu, S.; Burguete, A.; Solano, B.; Villar, R.; Aldana, I. & Monge, A. (2009). Selective activity against *Mycobacterium tuberculosis* of new quinoxaline 1,4-di-*N*-oxides. *Bioorganic & Medicinal Chemistry*, Vol. 17, pp. 385–389.

- Walczak, K.; Gondela, A. & Suwin´ski, J. (2004). Synthesis and Anti-Tuberculosis Activity of N-Aryl-C-Nitroazoles. *European Journal of Medicinal Chemistry*, Vol. 39, pp. 849-853.
- Weiner, M.; Bock, N.; Peloquin, C. A.; Burman, W. J.; Khan, A.; Vernon, A. ; Zhao, Z.; Weis, S.; Sterling, T. R.; Hayden, K.; Goldberg, S. & the Tuberculosis Trials Consortium. (2004). Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med*. Vol. 169, pp. 1191-1197.
- Wieles, J. M.; Musser, & W. R. Jacobs, Jr. (1997). The *Emb* Operon, a Gene Cluster of *Mycobacterium tuberculosis* Involved In Resistance to Ethambutol. *Nature Medicine*, Vol. 3, pp. 567-570.
- Wilkinson, R. G.; Shepherd, R. G.; Thomas, J. P. & Baughn, C. (1961). Stereospecificity in a New Type of. Synthetic Antituberculous Agent. *Journal of American chemical Society*, Vol. 83, pp. 2212-2213.
- Williams, D. L.; Spring, L.; Collins, L.; Miller, L. P.; Heifets, L. B.; Gangadharam, P. R. J. & Gillis, T. P. (1998). Contribution of *rpoB* mutations to development of rifamycin cross-resistance in *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*. Vol. 42, pp. 1853-1857.
- Working Group on New Drugs. (WGND) (2011). 12.08.2011, Available from <http://www.newtbdrugs.org/>
- World Health Organisation (WHO). (17 October 2006). WHO Global Task Force outlines measures to combat XDR-TB worldwide. 12.08.2011, Available from <http://www.who.int/mediacentre/news/notes/2006/np29/en/index.html>
- Yamamoto Y.; Hasegawa Y. & Ogawa K. (2011). Retrospective Cohort Study of Risk Factors for Adverse Effects of Antituberculous Therapy. *Kekkaku*, Vol. 86, pp. 499-507.
- Zaitzeva, S. I.; Matveeva, S. L.; Gerasimova, T. G.; Pashkov, Y. N.; Butov, D. A.; Pylypchuk, V. S.; Frolov, V. M. & Kutsyna, G. A. (2009). Treatment of Cavitory and Infiltrating Pulmonary Tuberculosis With and Without The Immunomodulator Dzherelo. *Clinical Microbiology and Infection*, Vol. 15, pp. 1154-1162.
- Zhang Y. & Mitchison D (2003). The Curious Characteristics of Pyrazinamide: A Review. *Int. J. Tuberc. Lung Dis.*, Vol. 7, (1), pp. 6-21.
- Zimhony, O.; Vilcheze, C.; Arai, M.; Welch, J. & Jacobs, W. R. (2007). Pyrazinoic acid and its n'Propyl Ester Inhibit Fatty Acid Synthase I in Replicating Tubercle Bacilli. *Antimicrobial Agents and Chemotherapy*, Vol. 51, pp. 752-754.

IntechOpen



Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance

Edited by Dr. Pere-Joan Cardona

ISBN 978-953-307-948-6

Hard cover, 376 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

In 1957, a Streptomyces strain, the ME/83 (*S.mediterranei*), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomycin. The euphoria generated by the success of this regimen led to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in *Mycobacterium tuberculosis*. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Neeraj Shakya, Babita Agrawal and Rakesh Kumar (2012). Chemotherapeutic Strategies and Targets Against Resistant TB, *Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance*, Dr. Pere-Joan Cardona (Ed.), ISBN: 978-953-307-948-6, InTech, Available from:

<http://www.intechopen.com/books/understanding-tuberculosis-new-approaches-to-fighting-against-drug-resistance/chemotherapeutic-strategies-for-management-of-tb>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen