Antituberculosis Drug Research: A Critical Overview†

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Abstract: The increasing drug resistance of *Mycobacterium tuberculosis* to the currently used drugs and HIV coinfection has caused alarm in the international scientific community. Subsequently, there is an urgent need for the development of new drug molecules with newer targets and with an alternative mechanism of action. Since the last 50 years, the same long-duration, multidrug treatment plan is being followed for the treatment of tuberculosis. The objective of this review article is to critically analyze the antitubercular potential of various classes of compounds (quinoline, diamine, quinolone, fluoroquinolone, quinone, nitroimidazole, terpenoid, isonicotinyl, oxazolidinone, pyrimidine, and purine), their possibility to be a future drug candidate, and latest information on the clinical status of some novel antitubercular compounds. Compounds such as moxifloxacin, PA824, and TMC207 are well tolerated and there is no adverse effect shown by them. Moxifloxacin and gatifloxacin shows cross-resistance to the currently used drugs while no cross-resistance observed in case of TMC207 and PA824. Some compounds like OPC67683 and PA824 are bactericidal in nature. Med Res Rev, 33, No. 4, 693–764, 2013

Key words: *Mycobacterium tuberculosis*; H37Rv; multidrug resistant; ethambutol; isoniazid; PA824; SQ109; TMC207

1. INTRODUCTION

Tuberculosis (TB) is a chronic disease that gets transmitted through air. It is caused predominantly by *Mycobacterium tuberculosis,* while other strains of mycobacteria that can cause this disease includes *M. avium* and *M. africanum*.[1–11] Robert Koch was the first scientist who isolated the bacteria, *M. tuberculosis* in 1882 and got Nobel Prize for this discovery. Blood-stained cough, chest pain, loss of weight, perspiration during night, and feeling cold are the main identifiable symptoms in a person infected with TB.[12] Three-fourths of the active TB cases are pulmonary while in 1/4th of the cases meninges, lymphatic system, bones, pleura, joints, and so on are affected by the bacteria.[13] The gravity of the situation can be understood from the report published in 2010 by World Health Organization (WHO) according to which, 9.4 million new

†Dedicated to Late Dr. Vinod Bhakuni

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TB cases occurred in 2009. In the same year, 1.7 million deaths were reported due to TB, out of which 0.38 million people were infected with both human immunodeficiency virus (HIV) and TB.[14] The situation is even more deplorable than it appears as 0.5 million new cases were due to multidrug-resistant (MDR) TB.[15] The alarming estimates exposes that 0.22 billion people may acquire TB and 79 million could die due to TB by the year 2030. TB is predominant in many Asian and African countries with 80% of the population infected, while only 5–10% population affected in the Unites States.[16] In terms of absolute number of TB cases, 22 countries of the world have the highest TB burden, among them the top five ranking countries are India, China, Indonesia, South Africa, and Nigeria.[17,18] About 0.23 million cases of MDR-TB occur per year in India only.[19] TB is also responsible for deaths in HIV-infected people due to infection by both HIV/AIDS and TB.[20,21] The determination of *M. tuberculosis* (*M. tb*) H37Rv genome sequence in 1998 was a breakthrough for scientists throughout the world. It facilitated the discovery of novel drug targets, assisted the understanding of the biological phenomenon of *M. tb*, and in the inquiry of the cause of resistance developed by this micro-organism.[22]

A number of other approaches such as target-based drug design, combinatorial synthesis, high-throughput screening, etc., have been explored but chemical modification of a known anti-TB drug has been a successful approach in the development of anti-TB agent.[23] In the last decade, several review articles have been published on the subject matter ranging from target identification, validation, individual class of compounds, and clinical status of various anti-TB agents.[1,24–27] To the best of our knowledge, there is no review article published on TB that covers all major classes of anti-TB agents and clinical status of anti-TB agents. Herein, we made an attempt to present a critical overview of various classes of anti-TB agents and also present an up to date literature review on clinical status of various molecules in clinical trials.

2. DRUGS IN USE FOR TUBERCULOSIS TREATMENT

Bacille Calmette-Guerin popularly known as BCG is the main vaccine used for eradication of TB. This vaccine was first tried in human subjects in France in the year 1921 and later on it was subcultured to get some new strains of BCG vaccine.[28] The "BCG World Atlas" is an online resource that was launched in 2008 so that information regarding BCG immunization can be gathered and updated.[29] The current vaccine BCG provides some degree of protection against the most severe manifestations of childhood TB. However, this vaccine does not reduce TB rates in adults.[25] BCG is a live vaccine that can cause serious infections in immune-compromised patients, and cannot be safely given to persons with HIV infection, who are at greatest risk for TB.[30]

The antitubercular drugs are categorized as first line, second line, and third line. The first-line anti-TB drugs are streptomycin (STM/S, 1944),[31] isoniazid (INH/H, 1952),[32,33] pyrazinamide (PZA/Z, 1952),[34–37] rifampicin (RIF/R, 1957),[38,39] and ethambutol (EMB/E, 1961)[40] (Fig. 1). Second-line drugs (SLDs) are those that are less effective than the first line or have some side effects. The unavailability of a drug in many developing countries also makes it SLD. Further, the SLDs are divided into six classes; these are (i) aminoglycosides (amikacin/AMK, kanamycin/KM), (ii) polypeptides (capreomycin, viomycin, enviomycin), (iii) fluoroquinolones (ciprofloxacin/CIP, moxifloxacin/MXF, levofloxacin), (iv) thioamides (prothionamide, ethionamide), (v) cycloserine, and (vi) *p*-aminosalicylic acid/PAS/P. Drugs that are practiced and not included as SLDs are called third-line drugs. The third-line drugs are either not very efficient or their effectiveness is not yet established. This includes linezolid (LZD), rifabutin, macrolides (clarithromycin /CLR), vitamin D, thioacetazone (T), thioridazine, and arginine.[41] Despite the effectiveness of rifabutin, WHO does not consider it as a SLD as yet because of its unaffordability in developing nations. The standard Directly Observed Treatment Short (DOTS)

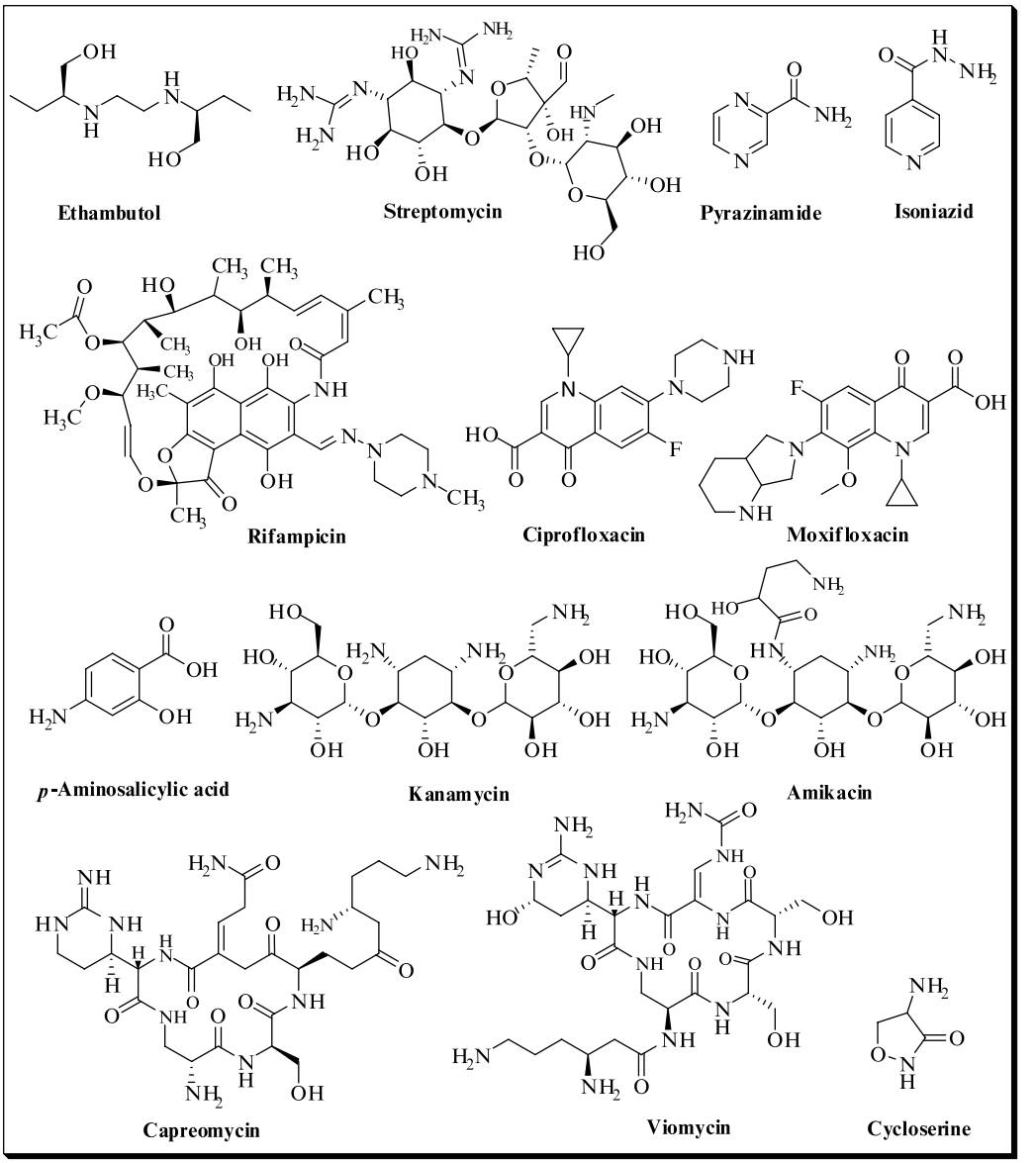


Figure 1. First-line and second-line antituberculosis drugs.

course for TB is a 6 months treatment. This includes the first 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol in the intensive phase and after isoniazid and rifampicin in the continuous phase.[42,43] India has a major contribution in the discovery of DOTS programme.[44,45]

The rise in number of people affected by drug-resistant TB (multidrug resistant/MDR-TB, extensive-drug resistant/XDR-TB) and latent TB is alarming. This has already had several fatal consequences. The resistance to first-line antitubercular drugs (INH and RIF) is known as MDR-TB, while resistance to INH, RIF, fluoroquinolones, and to at least one of the SLDs capable of being injected is called XDR-TB.[46–48] Though many countries do not have sufficient facilities to diagnose XDR-TB, still in 2010 about 58 countries reported XDR-TB cases. There are limited drugs used for the treatment of XDR-TB and they may also cause serious side effects.

The treatment of this form of TB fails in many cases and the failure is more where HIV/AIDS is more prevalent. The transmission and control of drug-resistant TB (mainly XDR-TB) is not yet completely known as yet and the real magnitude of the problem is quite underestimated.

According to Denholm et al., about 33% of the population in the world is at risk of reactivation by latent TB infection (LTBI) in the future.[49] In the case of latent TB, only INH is prescribed for 6–9 months. The present-day treatment of TB involves a longer duration of time (6–12 months) and a combination of various drugs.[50] In the absence of proper medication, the person with active form of TB would potentially transfer this disease to dozens of others irrespective of age, gender, or other social factors. In 1993, the WHO declared TB as a global emergency.[51] Thus, it is high time that a highly effective drug is discovered for the complete eradication of TB.

3. ANTI-TB COMPOUNDS IN CLINICAL TRIALS

Despite the severe outbreak of TB and the rise of MDR strains, progress to find a new vaccine or improvement of the BCG vaccine has been very slow.[52] However, in recent years there are some new drug candidates developed, which have reached early stages of clinical trials (Table I).[20] Out of the numerous anti-TB compounds, only a couple of the compounds are in phase I or II clinical trials and three of the compounds have entered phase III clinical trials. The seven new antitubercular drugs, namely moxifloxacin, gatifloxacin, TMC207, or R207910 (Tibotec and Johnson & Johnson), PA824 (Global Alliance for Tuberculosis Drug Development), OPC67683 (Otsuka), LL3858 (Lupin), and SQ109 (Sequella Incorporated) are at different stages of clinical development (Fig. 2). The compound SQ109 completed its phase

Table I. Compounds Undergoing Clinical Trials for Tuberculosis Treatment

Drug name	Class	Licensor/Sponsor	Mode of action	Phase
Moxifloxacin	Fluoroquinolone	Bayer/Global TB Alliance	Inhibition of *M. tb* DNA topoisomerase II	III
Gatifloxacin	Fluoroquinolone	EU/TDR	Inhibition of *M. tb* DNA topoisomerase II	III
PA824	Nitroimidazole	Global TB Alliance	Inhibition of lipid and protein synthesis, *M. tb* activated prodrug	II
TMC207	Diarylquinoline	Tibotec/ J&J	Target ATP synthase subunit c proton pump	II
SQ109	Ethylene diamine	Sequella	Thought to be cell wall synthesis but different to EMB	II
OPC67683	Nitroimidazole	Otsuka	Inhibits mycolic acid synthesis, prodrug, and requires activation	III
LL3858	Pyrrole	Lupin	N/A	I

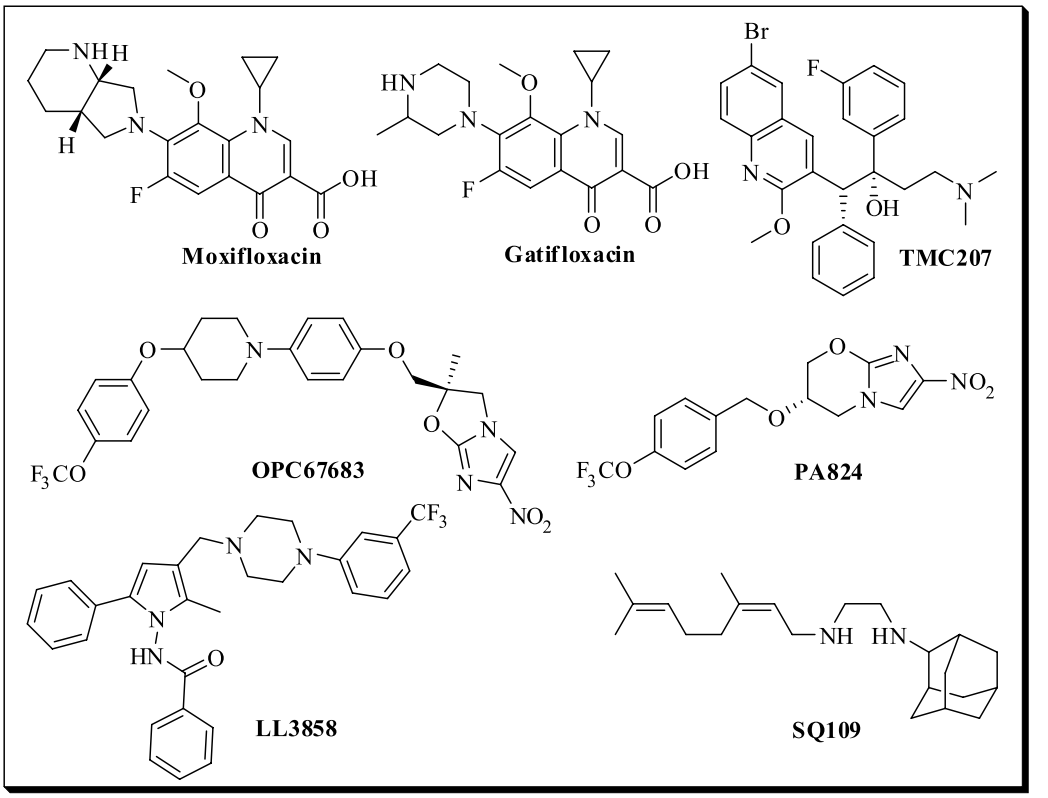


Figure 2. Antituberculosis drugs under clinical trials.

I clinical evaluations in 2009 and currently this compound is in phase II clinical trials and LL3858 is currently in phase I.[53–57] The nitroimidazole-based compound PA824 has completed its phase I clinical studies.[58] These studies show that PA824 is well tolerated and it has no side effects at the prescribed dosage. PA824 (currently in phase II clinical trials) shows MIC in the range 0.015–0.25 μg/mL in vitro against *M. tb.*[59] TMC207 is bactericidal and it is tolerated very well during its initial clinical studies.[60] Based on the promising phase I clinical trials, the compound TMC207 has entered into the phase II clinical trials.[61] Another compound OPC67683 (Delamanid) has completed its phase II clinical studies successfully and it exhibits excellent in vitro activity against resistant and nonresistant drug strains of *M. tb* and there is no cross-resistance to the first-line antitubercular drugs, thus occasional and low dosing may be effective.[62,63] It has completed a placebo-controlled phase II trial and the safety and pharmacokinetics properties in MDR refractive TB have also been accomplished.[64,65] The phase II clinical results of two fluoroquinolones GFX and MFX were compared to check their sterilizing activity in human subjects affected with pulmonary TB. In a study with INH, RIF, and PZA together, in combination with GFX, MFX, EMB, or ofloxacin done in 217 patients who were smear-positive, it was found that MFX is better in the initial stages but in the later stage GFX and MFX removed *Mycobacterium* with equal competency.[66] Both GFX and MFX have entered phase III trials but GFX has been withdrawn from the US and Canadian markets due to side effects such as dysglycemia.[67]

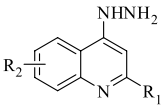
4. VARIOUS CLASSES OF COMPOUNDS AS ANTITUBERCULOSIS AGENT

Microbial infections, like that as TB have always been a threat to the human civilization but the development of resistance strain has further magnified the problem manifold. To overcome this challenge, development of a new class of compound with new drug target seems to be the only solution.[68,69] Resultantly, much effort is being directed in the development of a new structural class as anti-TB drug with altered mode of action. This requires a target-directed screening of new molecules against the various strains of *M. tuberculosis*. In order to address drug resistance, classes of compounds such as quinoline, diamine, quinolone, fluoroquinolone, quinone, nitroimidazole, terpenoid, isonicotine, oxazolidinone, pyrimidine, and purine have been explored as an alternative to the existing drugs. The anti-TB activity of these classes of compounds along with the structural requirements for their biological activity is summarized below.

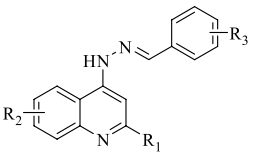
A. Quinoline Derivatives as Anti-TB Agent

The quinoline nucleus has been recognized as a medicinally privileged nucleus because it shows a wide range of biological activities such as antibacterial,[70] anti-TB,[71] anticancer,[72] antimalarial,[73] antiproliferative, anti-inflammatory,[74] antihypertensive,[75] tyrokinase PDGF-RTK inhibiting agent,[76] and anti-HIV.[77,78] Structural optimization of quinoline class of compounds by various groups across the globe has led to the identification of several potent anti-TB compounds exhibiting significant activity against drug-sensitive strains of *M. tb*. Tibotec Medicinal Compound 207 (TMC207) has emerged as a lead molecule out of this work and currently this compound is under phase II clinical assessment (Fig. 2). Detailed mechanistic study revealed that oligomeric (F ATPase) and proteolipic (V ATPase) subunit c of ATP synthase of mycobacteria is the target of this compound.[79,80] TMC207 is effective for resistant and nonresistant strains of *M. tb* at MIC 0.03 μg/mL.[79] The results of its clinical trials show that TMC207 may shorten the treatment of TB and be effective in its treatment.[60]

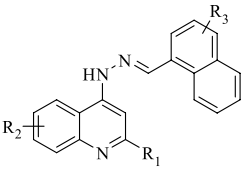
In 2002, Savini et al. reported the synthesis of 4-quinolylhydrazines (**1a-1q**) and a series of 4-quinolylhydrazones (**2a-2m** and **3a-3w**), with various substituents on quinoline nucleus and with aryl- or heteroaryl-hydrazonic moiety.[81] All the compounds were evaluated against *M. tb* H37Rv and majority of the tested compounds showed 95–100% inhibitory activity with MIC values between 0.78 and 12.5 μg/mL against *M. tb* H37Rv. The reported in vitro anti-TB data conclude that the activity of these compounds depends on the substitutions present in the quinoline ring and as well as in the hydrazonic moiety. The MIC values ranging from 0.78 to 3.13 μg/mL (**2c**, **2j**, **3a**, **3c**, **3f**, **3h**, **3j**, **3l**, **3m**, **3n**, **3r**, **3s**, and **3u**) were obtained when 6-cyclohexyl, 7-methoxy, 7-ethoxy, and 7-chloro substituents were present on the quinoline nucleus and *para*- or *ortho*-methoxynaphtyl substituents on hydrazonic moiety. The chloro group at 5 and 7 positions of quinoline nucleus has negative effect on the antibacterial activity (**2d**, **2l**, **3k**, and **3v**). Though quinolylhydrazines **1a-1d**, **1h-1l**, **1q** possess considerable inhibitory activity with selective index (SI) < 4, with the exception of **1f** and **1n** (SI $= 4.28$ and 6.16), while some quinolylhydrazones (**2i**, **2j**, **3b**, **3c**, **3h**, **3l**, and **3r**) showed significantly higher SI. Three compounds (**2i**, **3b**, and **3c**) that had high SI values (10.24, 11.68, and 9.23, respectively) were also tested for their effectiveness in vitro in TB-infected macrophage model with significant EC_{90} and EC_{99} values. These three compounds were also evaluated for their inhibitory activity against a single strain of *M. avium* and compounds **2i** and **3b** were found to be the most active with MIC 3.13 μg/mL and SI value of 20.45 and 23.32, respectively. Quinolylhydrazones **2i** and **3b** that were active against *M. tb* H37Rv and *M. avium* were also found to be the least toxic among all these synthesized compounds.



1a, R_1 = H, R_2 = 7-OCH_3
1b, R_1 = H, R_2 = 7-OC_2H_5
1c, R_1 = H, R_2 = 6-nC_4H_9
1d, R_1 = H, R_2 = 6-nOC_4H_9
1e, R_1 = H, R_2 = 6-cyclohexyl
1f, R_1 = H, R_2 = 7-Cl
1g, R_1 = H, R_2 = 5,7-Cl
1h, R_1 = CH_3, R_2 = 7-OCH_3
1i, R_1 = CH_3, R_2 = 8-OCH_3
1j, R_1 = CH_3, R_2 = 7-OC_2H_5
1k, R_1 = CH_3, R_2 = 6-nC_4H_9
1l, R_1 = CH_3, R_2 = 6-nOC_4H_9
1m, R_1 = CH_3, R_2 = 6-cyclohexyl
1n, R_1 = CH_3, R_2 = 7-Cl
1o, R_1 = CH_3, R_2 = 5,7-Cl
1p, R_1 = CH_3, R_2 = 6-F
1q, R_1 = C_6H_5, R_2 = 6-OCH_3



2a, R_1 = H, R_2 = 7-OCH_3, R_3 = 4-$N(C_2H_5)_2$
2b, R_1 = H, R_2 = 7-OC_2H_5, R_3 = 4-$N(C_2H_5)_2$
2c, R_1 = H, R_2 = 7-Cl, R_3 = 4-$N(C_2H_5)_2$
2d, R_1 = H, R_2 = 5,7-Cl, R_3 = 3,4-(OCH_2O)
2e, R_1 = CH_3, R_2 = 7-OCH_3, R_3 = 4-$N(C_2H_5)_2$
2f, R_1 = CH_3, R_2 = 7-OCH_3, R_3 = 3,4-(OCH_2O)
2g, R_1 = CH_3, R_2 =7-OC_2H_5, R_3 = 4-$N(C_2H_5)_2$
2h, R_1 = CH_3, R_2 = 6-nOC_4H_9, R_3 = 3,4-(OCH_2O)
2i, R_1 = CH_3, R_2 = 6-cyclohexyl, R_3 = H
2j, R_1 = CH_3, R_2 = 6-cyclohexyl, R_3 = 4-$N(C_2H_5)_2$
2k,R_1 = CH_3, R_2 = 7-Cl, R_3 = 4-$N(C_2H_5)_2$
2l, R_1 = CH_3, R_2 = 5,7-Cl, R_3 = 3,4-(OCH_2O)
2m, R_1 = C_6H_5, R_2 = 6-OCH_3, R_3 = 4-$NHCOCH_3$



3a, R_1 = H, R_2 = H, R_3 = 4-OCH_3
3b, R_1 = H, R_2 = 7-OCH_3,R_3 = 2-OCH_3
3c, R_1 = H, R_2 = 7-OCH_3, R_3 = 4-OCH_3
3d, R_1 = H, R_2 = 7-OC_2H_5, R_3 = 2-OCH_3
3e, R_1 = H, R_2 = 7-OC_2H_5, R_3 = 4-OCH_3
3f, R_1 = H, R_2 = 6-n-C_4H_9, R_3= 4-OCH_3
3g, R_1 = H, R_2 = 6-n-OC_4H_9, R_3 = 4-OCH_3
3h, R_1 = H, R_2 = 6-cyclohexyl, R_3 = 4-OCH_3
3i, R_1 = H, R_2 = 7-Cl, R_3 = 2-OCH_3
3j, R_1 = H, R_2 = 7-Cl, R_3 = 4-OCH_3
3k, R_1 = H, R_2 = 5,7-Cl, R_3 = 4-OCH_3
3l, R_1 = CH_3, R_2 = 7-OCH_3, R_3 = 2-OCH_3
3m, R_1 = CH_3 R_2 = 7-OCH_3, R_3 = 4-OCH_3
3n, R_1 = CH_3, R_2 = 8-OCH_3, R_3 = 4-OCH_3
3o, R_1 = CH_3, R_2 =7-OC_2H_5, R_3 = 2-OCH_3
3p, R_1 = CH_3, R_2= 7-OC_2H_5, R_3 = 4- OCH_3
3q, R_1 = CH_3, R_2 = 6-n-C_4H_9, R_3 = 4-OCH_3
3r, R_1 = CH_3, R_2 = 6-n-OC_4H_9, R_3 = 4-OCH_3
3s, R_1 = CH_3, R_2 = 6-cyclohexyl, R_3 = 4-OCH_3
3t, R_1 = CH_3, R_2 = 7-Cl, R_3 = 2-OCH_3
3u, R_1 = CH_3, R_2 = 7-Cl, R_3 = 4-OCH_3
3v, R_1 = CH_3, R_2 = 5,7-Cl, R_3 = 4-OCH_3
3w, R_1 = CH_3, R_2 = F, R_3 = 4-OCH_3

The quinolyl hydrazones (**3c**, **3l**, and **3m**) having C-7 alkoxy substituent on quinoline ring showed impressive anti-TB activity and in order to explore the structure–activity relationship study, the same authors reported the synthesis and anti-TB activity of some new compounds (**4–11**) in 2009.[82] Among the 7-methoxyquinolines (**4a-4l**), compound **4a** with unsubstituted phenyl ring had a low MIC value (16.4 μM) but when the phenyl ring was substituted with OMe (**4d**), OH (**4c** and **4b**), $N(Me)_2$ (**4e**) groups, the activity of these compounds increased, with MIC = 9.8, 5.3, 2.7, and 4.9 μM, respectively. The compound **4b** with a hydroxyl group at *meta* position was twofold active than **4c** in which hydroxyl group was at *para* position. Replacement of phenyl ring by 2-napthyl group leads to the compound **4h** (MIC = 0.6 μM) with enhanced anti-TB activity (Table II). The compounds **4j** and **4k** (MIC = 9.5 μM) having quinolyl system had lower activity than **4h** but the presence of 7-OMe group makes the compound **4l** (MIC = 2.2 μM) highly active.

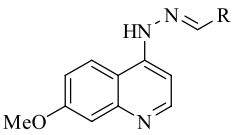
There was a slight difference in the activity when methyl group was introduced at position 2 of the quinoline nucleus (**6a** vs. **4d**, **6b** vs. **4j**, and **7b** vs. **5b**). When OMe group at C-7 of quinoline nucleus was moved to 6 or 8 position (**8a-8g** and **9a-9i**) similar SAR was observed

Table II. Antimycobacterial Activity of a Few Selected Quinolyl Hydrazine and Hydrazone Derivatives Against *M. tb* H37Rv

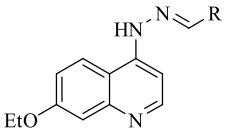
Comp no.	MIC (μM)	Comp no.	MIC (μM)
2j	1.56	**3u**	0.78
3c	0.78	**4h**	0.6
3f	0.78	**4i**	0.6
3m	1.56	**4l**	2.2
3n	1.56	**8d**	2.4
3p	1.56	RIF	0.031
3s	1.56	INH	0.36

with very few exceptions. The position of alkoxy group in the quinoline ring had an important role in the anti-TB activity, which could be explained from the activity pattern of compounds **4g**, **8d**, and **9c**. The compound **8d** (Table II) having methoxy group at 6 position in quinoline ring (MIC = 2.4 μM) was found to be four times more potent when compared to the corresponding 7-methoxy quinoline analog **4g** (MIC = 9.7 μM), whereas its 8-methoxy (**9c**) and 8-ethoxy analogue **5c** found to be inactive at the tested concentration.

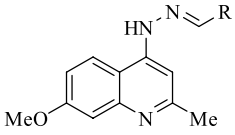
The anti-TB activity of compounds **5c** and **9c** was retained when 2-methyl group was introduced in the quinoline nucleus (**7c** and **9f**). After observing the promising effect of methoxy group at C6 or C7 of the quinoline ring, a 6,7-methylendioxy substituent (**10a**, **10b**, **11a-11s**) was introduced in order to study the effect of both alkoxy groups. These compounds showed 100% inhibition at a concentration of 6.25 μg/mL. From the activity data it was concluded that the unsubstituted phenyl ring (**11b**) in the hydrazone center had the best activity (MIC = 2.6 μM) and introduction of electron-donating groups such as 4-OMe (**11f**, MIC = 9.3 μM), 3-OMe (**11e**, MIC = 9.3 μM), 3,4-methylenedioxy (**11j**, MIC = 4.5 μM) diethylamino (**11h**, MIC = 8.3 μM) resulted in a decreased potency compared to the compound **11b**. The electron-withdrawing group such as a 4-F (**11i**, MIC = 19.3 μM) lead to decrease in activity. The 2- and 4-pyridyl substituents (**11o** and **11p**) at the hydrazone center caused total loss of activity. Introduction of a pyrrole (**11n**, MIC = 10.6 μM) or a 2-imidazole (**11r**, MIC = 5.3 μM) resulted in active analogues but they were less potent than the compound **11b**. Among the cyclohexyl derivatives **8a**, **10a**, and **11a**, the 6,7-methylendioxy derivatives (**10a** and **11a**) were found to be inactive but the 6-methoxyquinoline **8a** (MIC = 11.1μM) was similar to the corresponding aryl-derivatives (**8b**) in its activity.



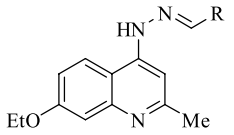
4a, R = Ph
4b, R = 3-OHPh
4c, R = 4-OHPh
4d, R = 4-OMePh
4e, R = 4-N(Me)$_2$Ph
4f, R = 2-pyrrolyl
4g, R = 3,4-methylendioxyPh
4h, R = 2-napthyl
4i, R = 6-OMe-2-napthyl
4j, R = 2-quinolyl
4k, R = 4-quinolyl
4l, R = 7-OMe-4-quinolyl



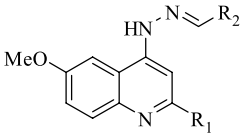
5a, R = 4-OMePh
5b, R = 4-pyridyl
5c, R = 3,4-methylenedioxyPh



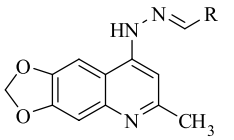
6a, R = 4-OMePh
6b, R = 2-quinolyl
6c, R = 4-quinolyl



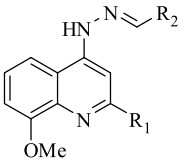
7a, R = 4-OMePh
7b, R = 4-pyridyl
7c, R = 3,4-methylemnedioxyPh



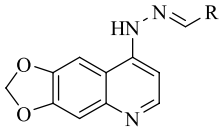
8a, R$_1$ = H, R$_2$ = cyclohexyl
8b, R$_1$ = H, R$_2$ = 4-OMePh
8c, R$_1$ = H, R$_2$ = 4- N(Me)$_2$Ph
8d, R$_1$ = H, R$_2$ = 3,4-methylenedioxyPh
8e, R$_1$ = Me, R$_2$ = 4-OMePh
8f, R$_1$ = Me, R$_2$ = 4-N(Me)$_2$Ph
8g, R$_1$ = Me, R$_2$ = 3,4-methylenedioxyPh



11a, R = cyclohexyl
11b, R = Ph
11c, R = 3-OHPh
11d, R = 4-OHPh
11e, R = 3-OMePh
11f, R = 4-OMePh
11g, R = 3,4-OMePh
11h, R = 4-N(Me)$_2$Ph
11i, R = 4-FPh
11j, R = 3,4-methylendioxyPh
11k, R = 2-OMe-1-napthyl
11l, R = 4-OMe-1-napthyl
11m, R = 6-OMe-2-napthyl
11n, R = 2-pyrrolyl
11o, R = 2-pyridyl
11p, R = 4-pyridyl
11q, R = 4-quinolyl
11r, R = 2-imidazolyl
11s, R = 2-napthyl



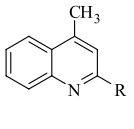
9a, R$_1$ = H, R$_2$ = Ph
9b, R$_1$ = H, R$_2$ = 4-N(Me)$_2$Ph
9c, R$_1$ = H, R$_2$ = 3,4-methylenedioxyPh
9d, R$_1$ = H, R$_2$ = 1-napthyl
9e, R$_1$ = H, R$_2$ = 2-quinolyl
9f, R$_1$ = Me, R$_2$ = 3,4-methylenedioxyPh
9g, R$_1$ = Me, R$_2$ = 1-napthyl
9h, R$_1$ = Me, R$_2$ = 2-quinolyl
9i, R$_1$ = Me, R$_2$ = 4-quinolyl



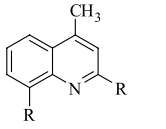
10a, R = cyclohexyl
10b, R = 4-OMePh

Jain et al. synthesized 4-methylquinoline derivatives (**12a-12k** and **13a-13k**) and evaluated them against *M. tb* H37Rv strain (ATCC 27294) using microplate alamar blue assay (MABA).[83] Among the synthesized compounds, only three compounds (**13c**, **13d**, and **13i**) showed moderate to good activity, while rest of the compounds showed poor activity with MIC values >6.25 μg/mL. The compound **13d** with two cyclopentyl groups at C-2 and C-8 position of the quinoline ring showed 100% inhibition at a dose level of 6.25 μg/mL. Replacing cyclopentyl group with cyclobutyl group (**13c**) resulted in decrease in activity with MIC 12.5 μg/mL. The monosubstituted analogs of **12c** and **12d** were less potent (67% and 74% inhibition) than **13c** and **13d**, which showed 100% inhibition. Analysis of anti-TB activity data clearly indicates that the compounds with four or five membered cyclic ring showed better activity than their acyclic counterparts.

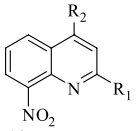
The most active compound 2,8-dicyclopentyl-4-methylquinoline (**13d**, DCMQ) when tested against *M. avium* (ATCC25291) at 6.25 μg/mL was not active. This compound showed significant activity against the *M. tb* resistant strains of RIF, INH, EMB, and CIP (MIC = 12.5 μg/mL) and low activity against *M. tb* strain resistant to kanamycin (MIC = 25 μg/mL). Also, the minimum bactericidal concentration of compound **13d** was found against *M. tb* H37Rv, INH resistant, and RIF resistant strains, using middlebrook 7H9 media. The bacteriostatic nature of the compound **13d** is indicated by the minimum bactericidal concentration (50 μg/mL), which was higher than the MIC value (25 μg/mL) against H37Rv.



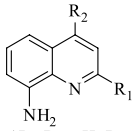
12a, R = $CH(CH_3)_2$
12b, R = $C(CH_3)_3$
12c, R = *c*-C_4H_7
12d, R = *c*-C_5H_9
12e, R = *c*-C_6H_{11}
12f, R = *c*-C_3H_3
12g, R = 1-adamantyl
12h, R = $(CH_2)_2CH_3$
12i, R = $(CH_2)_3CH_3$
12j, R = $(CH_2)_4CH_3$
12k, R = $(CH_2)_5CH_3$



13a, R = $CH(CH_3)_2$
13b, R = $C(CH_3)_3$
13c, R = *c*-C_4H_7
13d, R = *c*-C_5H_9
13e, R = *c*-C_6H_{11}
13h, R = $(CH_2)_2CH_3$
13i, R = $(CH_2)_3CH_3$
13j, R = $(CH_2)_4CH_3$
13k, R = $(CH_2)_5CH_3$

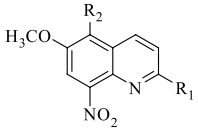


14a, R_1 = H, R_2 = H
14b, R_1 = $CH(CH_3)_2$, R_2 = H
14c, R_1 = $C(CH_3)_3$, R_2 = H
14d, R_1 = *c*-C_5H_9, R_2 = H
14e, R_1 = *c*-C_6H_{11}, R_2 = H
14f, R_1 = $CH(CH_3)_2$, R_2 = $CH(CH_3)_2$
14g, R_1 = $C(CH_3)_3$, R_2 = $C(CH_3)_3$
14h, R_1 = *c*-C_5H_9, R_2 = *c*-C_5H_9
14i, R_1 = *c*-C_6H_{11}, R_2 = *c*-C_6H_{11}

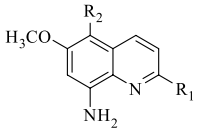


15a, R_1 = H, R_2 = H
15b, R_1 = *c*-C_6H_{11}, R_2 = H
15c, R_1 = *c*-C_6H_{11}, R_2 = c-C_6H_{11}

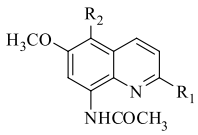
16a, R_1 = H, R_2 = H
16b, R_1 = H, R_2 = H
16c, R_1 = *c*-C_6H_{11}, R_2 = H
16d, R_1 = *c*-C_6H_{11}, R_2 = H
16e, R_1 = *c*-C_6H_{11}, R_2 = *c*-C_6H_{11}



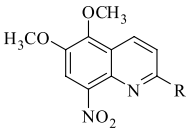
17a, R_1 = H, R_2 = H
17b, R_1 = H, R_2 = $CH(CH_3)_2$
17c, R_1 = $CH(CH_3)_2$, R_2 = $CH(CH_3)_2$
17d, R_1 = $C(CH_3)_2$, R_2 = H
17e, R_1 = $C(CH_3)_2$, R_2 = $C(CH_3)_2$
17f, R_1 = 1-adamantyl, R_2 = H
17g, R_1 = H, R_2 = *c*-C_5H_9
17h, R_1 = *c*-C_5H_9, R_2 = *c*-C_5H_9
17i, R_1 = H, R_2 = *c*-C_6H_{11}
17j, R_1 = *c*-C_6H_{11}, R_2 = *c*-C_6H_{11}



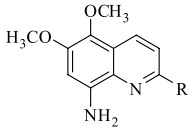
18a, R_1 = H, R_2 = H
18b, R_1 = $C(CH_3)_3$, R_2 = H
18c, R_1 = H, R_2 = *c*-C_5H_9
18d, R_1 = H, R_2 = *c*-C_6H_{11}
18e, R_1 = 1-adamantyl, R_2 = H



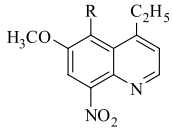
19a, R_1 = H, R_2 = H
19b, R_1 = H, R_2 = H



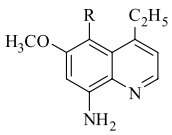
20a, R = H
20b, R = $CH(CH_3)_2$
20c, R = $C(CH_3)_3$



21a, R = H
21b, R = $CH(CH_3)_2$
21c, R = $C(CH_3)_3$



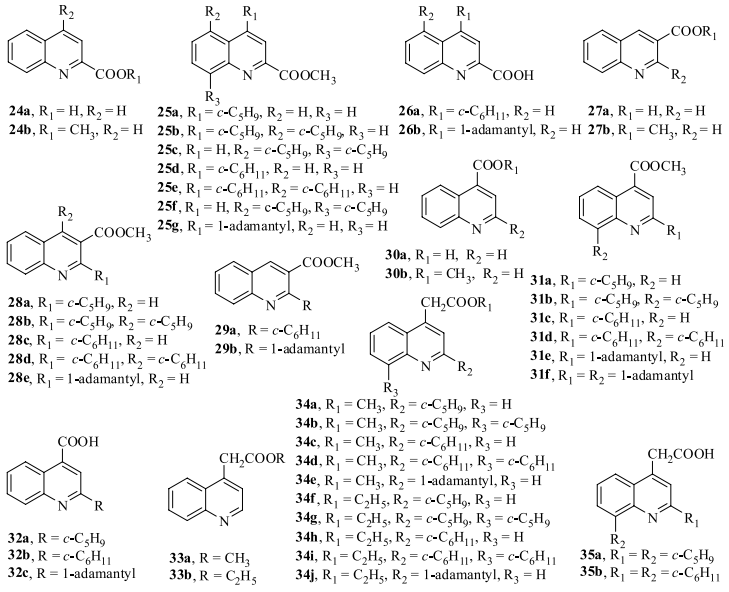
22a, R = OC_3H_7
22b, R = $OCH(CH_3)_2$
22c, R = OC_4H_9
22d, R = OC_5H_9
22e, R = OC_5H_{11}
22f, R = OC_6H_{13}
22g, R = OC_7H_{15}
22h, R = OC_8H_{17}



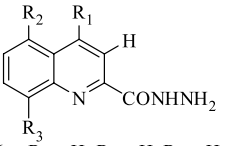
23a, R = OC_3H_7
23b, R = $OCH(CH_3)_2$
23c, R = OC_4H_9
23d, R = OC_5H_9
23e, R = OC_5H_{11}
23f, R = OC_6H_{13}
23g, R = OC_7H_{15}
23h, R = OC_8H_{17}

Encouraged by the activity shown by compound **13d** (DCMQ), Jain et al. further synthesized 56 new compounds with different substitutions at various positions of the quinoline nucleus.[84] Anti-TB activity of these compounds (**14–23**) was determined against drug-sensitive and drug-resistant strains of *M. tb* H37Rv. The 8-nitroquinoline analogue (**14i)** with cyclohexyl group at 2 and 4 positions was found to have excellent activity equivalent to isoniazid with MIC value of 1.0 μg/mL. The presence of cyclopentyl and cyclohexyl group has a crucial role in determining the activity of these compounds. This can be seen from activity data of compounds **14e**, **14h**, and **16e**, which exhibited 95% inhibition at 6.25 μg/mL concentration. When NO_2 group of compound **14i** was replaced by NH_2 group (**15c**), complete loss in activity with no inhibition was observed. But when the amino group was blocked with $NHCOCH_3$ group (**16e**) the activity was enhanced with MIC 6.25 μg/mL. Compound **17c** with *iso*-propyl group at 2 and 5 positions also showed promising activity. Among the 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines compound **22g** having a seven carbon linear chain at fifth and NO_2 group at eighth position showed excellent activity (MIC = 1 μg/mL) with 99% inhibition, while other two compounds **22b** and **23e** also exhibit significant activity with 97% and 99% inhibition, respectively (MIC = 6.25 μg/mL). Eight most active compounds (**14e**, **14h**, **14i**, **16e**, **17c**, **22b**, **22g**, and **23e**) were also screened against single drug-resistant (SDR) *M. tb* strains. Out of these eight compounds, three of them (**14i**, **22g**, and **23e**) were active against *M. tb* strains resistant to INH, RIF, and EMB with MIC value 6.25 μg/mL each, while remaining five compounds were found to be moderately active.

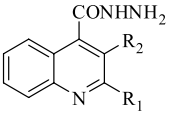
In the same year 2004, Jain et al. also reported the synthesis and activity of 45 analogues (**24–35**) of quinolinecarboxylic acids or esters against *M. tb* H37Rv with a core structure **13d** (2,8-dicyclopentyl-4-methylquinoline or DCMQ).[85] Most of the derivatives exhibited mild activity $\geq$ 6.25 μg/mL. Some compounds (**25e**, **28b**, **28d**, and **34i**) showed better activity with MIC of 6.25 μg/mL and > 95% inhibition compared to DCMQ. Two compounds **25b** and **25c** were also tested against isoniazid resistant strain of *M. tb* H37Rv and compound **25c** showed good activity with MIC 6.25 μg/mL and 92% inhibition. Activity of three compounds **25b**, **25c**, and **34g** was found to be better than DCMQ with MIC of 1, 2, and 4 μg/mL, respectively. Interestingly, these most active compounds also contain two cyclopentyl groups in the quinoline ring. It is evident that the cyclopentyl group has prominent role in determining the activity of these compounds.



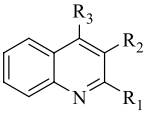
In continuation with these reports, Jain et al. also synthesized 22 quinolinecarbohydrazides (**36**, **37**, **38**, and **39**) and 13 quinoline carboxamide (**40**) analogues and evaluated them against *M. tuberculosis* H37Rv.[86] Out of the 22 quinoline carbohydrazides only four compounds (**36d**, **36e**, **36f**, and **36g**) showed good activity against *M. tb* H37Rv (MIC = 6.25 μg/mL), rest of the compounds were moderately active. Compound **36d**, the most active compound (MIC = 6.25 μg/mL and 99% inhibition) of the series was further evaluated and 13 new analogues of **36d** were prepared. Among these compounds, **40h** and **40m** (3.125 μg/mL, 99% inhibition) showed very good activity even better than the compound **36d**. The compound **40h** also showed good activity against *M. tb* strains resistant to INH and pronounced inhibition (99%) at 6.25 μg/mL.



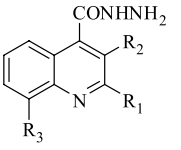
36a, R_1 = H, R_2 = H, R_3 = H
36b, R_1 = *c*-C_5H_9, R_2 = H, R_3 = H
36c, R_1 = *c*-C_6H_{11}, R_2 = H, R_3 = H
36d, R_1 = 1-adamantyl, R_2 = H, R_3 = H
36e, R_1 = *c*-C_5H_9, R_2 = *c*-C_5H_9, R_3 = H
36f, R_1 = *c*-C_5H_9, R_2 = H, R_3 = *c*-C_5H_9
36g, R_1 = *c*-C_6H_{11}, R_2 = *c*-C_6H_{11}, R_3 = H
36h, R_1 = *c*-C_6H_{11}, R_2 = H, R_3 = *c*-C_6H_{11}



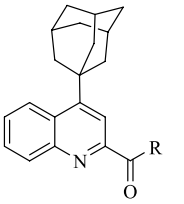
38a, R_1 = H, R_2 = H
38b, R_1 = *c*-C_5H_9, R_2 = H
38c, R_1 = *c*-C_6H_{11}, R_2 = H
38d, R_1 = 1-adamantyl, R_2 = H



37a, R_1 = H, R_2 = $CONHNH_2$, R_3 = H
37b, R_1 = 1-adamantyl, R_2 = $CONHNH_2$, R_3 = H
37c, R_1 = *c*-C_5H_9, R_2 = $CONHNH_2$, R_3 = *c*-C_5H_9
37d, R_1 = *c*-C_6H_{11}, R_2 = $CONHNH_2$, R_3 = *c*-C_6H_{11}

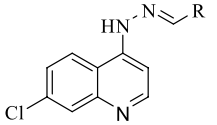


39a, R_1 = H, R_2 = H, R_3 = H
39b, R_1 = *c*-C_5H_9, R_2 = H, R_3 = H
39c, R_1 = c-C_6H_{11}, R_2 = H, R_3 = H
39d, R_1 = 1-adamantyl, R_2 = H, R_3 = H
39e, R_1 = *c*-C_5H_9, R_2 = H, R_3 = *c*-C_5H_9
39f, R_1 = *c*-C_6H_{11}, R_2 = H, R_3 = *c*-C_6H_{11}

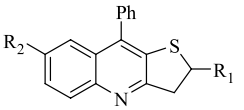


40a, R = NH_2
40b, R = $NH(CH_2)_2CH_3$
40c, R = $NH(CH_2)_3CH_3$
40d, R = $NH(CH_2)_4CH_3$
40e, R = $NH(CH_2)_5CH_3$
40f, R = $NH(CH_2)_6CH_3$
40g, R = $NH(CH_2CH_3)_2$
40h, R = Ph
40i, R = 4-OCH_3Ph
40j, R = 3-Cl,4-OCH_3Ph
40k, R = 4-NO_2Ph
40l, R = 3-quinolyl
40m, R = benzyl

Recently in 2009, Candea et al. reported the synthesis and anti-TB activity of some 7-chloro-4-quinolyl hydrazone derivatives (**41a–41u**).[87] The activity of these derivatives was screened against *M. tb* ATCC 27294 using MABA. When compared to ethambutol (MIC = 3.12 μg/mL) these compounds showed significantly good activity (MIC = 3.12–12.5 μg/mL) with few exceptions **41d**, **41h**, **41k**, **41p-41r, 41s**, and **41t**, which were not active even at MIC >100 μg/mL. Nine compounds **41b**, **41e**, **41f**, **41g**, **41i**, **41j**, **41m**, **41n**, and **41o** showed activity better than or comparable to EMB (MIC = 2.5–3.25 μg/mL, respectively). Derivatives with bromo (**41f**), fluoro (**41i**), and methoxy (**41o**) substituent at *para* position of the phenyl ring were the most active (MIC = 2.5 μg/mL). Compounds **41c**, **41f**, **41i**, and **41o** were nontoxic to host cells.



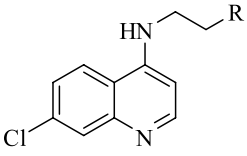
41a, R = 2-ClPh; **41b**, R = 3-ClPh;
41c, R = 4-ClPh; **41d**, R = 2-BrPh;
41e, R = 3-BrPh; **41f**, R = 4-BrPh
41g, R = 2-FPh; **41h**, R = 3-FPh;
41i, R = 4-FPh; **41j**, R = 2-OHPh;
41k, R = 3-OHPh; **41l**, R = 4-OHPh;
41m, R = 2-OMePh; **41n**, R = 3-OMePh;
41o, R = 4-OMePh; **41p**, R = 2-NO_2Ph;
41q, R = 3-NO_2Ph; **41r**, R = 4-NO_2Ph;
41s, R = 3-CNPh; **41t**, R = 4-CNPh;
41u, R = Ph



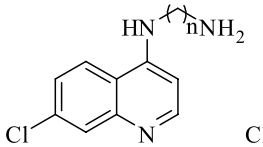
42a, R_1 = C_6H_5, R_2 = H; **42b**, R_1 = 4-MeC_6H_4, R_2 = H;
42c, R_1 = 4-*i*PrC_6H_4, R_2 = H; **42d**, R_1 = 2-ClC_6H_4, R_2 = H;
42e, R_1 = 4-ClC_6H_4, R_2 = H; **42f**, R_1 = 2,4-ClC_6H_3, R_2 = H;
42g, R_1 = 4-FC_6H_4, R_2 = H; **42h**, R_1 = 3-$NO_2C_6H_4$, R_2 = H;
42i, R_1 = 1-napthyl, R_2 = H; **42j**, R_1 = H, R_2 = Cl;
42k, R_1 = C_6H_5, R_2 = Cl; **42l**, R_1 = 4-MeC_6H_4, R_2 = Cl;
42m, R_1 = 2-ClC_6H_4, R_2 = Cl; **42n**, R_1 = 4-ClC_6H_4, R_2 = Cl;
42o, R_1 = 2,4-ClC_6H_3, R_2 = Cl; **42p**, R_1 = 4-FC_6H_4, R_2 = Cl;
42q, R_1 = 3-$NO_2C_6H_4$, R_2 = Cl; **42r**, R_1 = 1-napthyl, R_2 = Cl

A series of 2,9-diaryl-2,3-dihydrothieno[3,2-*b*]quinolines (**42a-42r**) were synthesized by Balamurugan et al. and anti-TB activity of these compounds was tested against *M. tb* H37Rv and MDR *M. tb* (MDR-TB) by agar dilution method.[88] All the compounds were found to be active against *M. tb* with MIC values ranging from 0.90 to 36.82 μM. Seven compounds (**42f**, **42h**, **42m-42q**) exhibited better activity than EMB (MIC = 7.64 μM) with MIC values of 3.82, 4.06, 3.82, 3.82, 0.90, 3.98, and 1.86 μM, respectively. The compound **42o** showed excellent activity against *M. tb* with MIC = 0.90 μM and it was manifold active than CIP and EMB but it exhibited lesser activity than INH and RIF. These seven most active compounds (**42f**, **42h**, **42m-42q**) when tested against MDR-TB possessed MIC in the range of 0.95–15.30 μM. All the compounds (**42f**, **42h**, **42m-42q**) were more potent than EMB (MIC = 61.18 μM) with MIC of 15.30, 8.14, 1.91, 3.82, 1.76, 3.9, and 0.95 μM, respectively. From the activity pattern it is clear that compounds with a chloro group at 7 position of thienoquinolines (**42m-42q**) have better activity as compared to the unsubstituted compounds. Compound **42q** was found to be most active against MDR-TB and displayed several times better activity than EMB, RIF, INH, and CIP. The structure–activity relationship study clearly demonstrate that Cl at 7 position of the quinoline ring is essential for better activity. Compounds with electron-withdrawing groups (NO_2 or halogen) in the phenyl ring of the thiophene displayed greater activity than the compound possessing electron-donating groups.

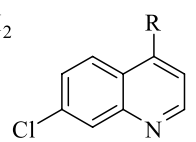
4-amino-7-chloroquinoline derivatives (**43a-43k**, **44a-44f**, **45a-45j**, and **46a-46b**) were synthesized and evaluated for their in vitro anti-TB activity against *M. tb* H37Rv (ATCC27294) by De Souza et al. using the MABA method.[89] In the 7-chloro-4-amino-quinolines (**43a-43k**), compound **43c** having chlorine atom at terminal of amino alkyl chain was the most active with MIC value of 12.5 μg/mL. On replacement of chlorine atom by other groups such as azide (**43b**) or other amino groups (**43e-43k**), the activity gets reduced that indicates the importance of chlorine atom. In the same series (**44a-44f**), the activity of the compound increases on increasing the chain length, which is evident from the MIC values of compounds **44d** (MIC = 25 μg/mL), **44e** (MIC = 6.25 μg/mL), and **44f** (MIC = 3.12 μg/mL). The most active derivative **44f** also showed the highest *c*log*P* value (5.55), which indicates the role of lipophilicity in the observed activity. Same trend was also observed among the compounds **45a-45j** and the anti-TB activity of quinoline derivatives (**45c-45f**) increases, as MIC decreases from >100 to 12.5 μg/mL due to increase in length of the alkyl chain. Compounds **45g-45j** with a hydroxyl group at the terminal were devoid of anti-TB activity. Replacement of hydroxyl group by Cl atom in compounds **45g** and **45j** (MIC > 100 μg/mL) leads to more active compounds **46a** and **46b** (MIC = 50 μg/mL).



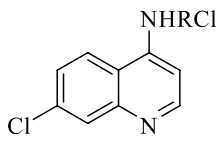
43a, R = OH
43b, R = N_3
43c, R = Cl
43d, R = CN
43e, R = NHMe
43f, R = NHPr
43g, R = NH*i*-Pr
43h, R = NHBu
43i, R = NHBn
43j, R = NHcyclohexyl
43k, R = $NHCH_2CH_2OH$



44a, n = 2
44b, n = 3
44c, n = 4
44d, n = 6
44e, n = 8
44f, n = 10



45a, R = N_3
45b, R = NH_2
45c, R = NHMe
45d, R = NHPr
45e, R = NH*i*-Pr
45f, R = NHBu
45g, R = NHPrOH
45h, R = NH(*R*)CH(Et)CH_2OH
45i, R = NH(*S*)CH(Et)CH_2OH
45j, R = NH(*R,S*)CH(Et)CH_2OH



46a, R = Pr
46b, R = (*R,S*)CH(Et)CH_2

Table III. Antituberculosis Activity of Compounds **47–51** Against *M. tb* H37Rv

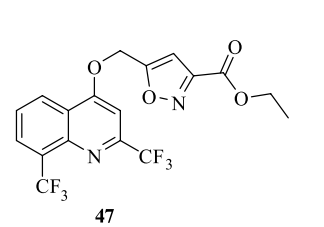
Comp no.	LORA (MIC, μM)	MABA (MIC, μM)	Comp no.	LORA (MIC, μM)	MABA (MIC, μM)
47	12.2	0.9–1.9	**51j**	7.0	2.6
48	9.9	3.4	**51k**	49.3	62.9
49	3.7	0.95	**51l**	39.0	11.3
51a	13.2	25.1	**51m**	nd	14.6
51b	56.6	10.6	**51n**	nd	66.1
51c	99.7	3.8	**51o**	10.0	0.77
51d	81.9	3.3	**51p**	3.7	1.9
51e	25.1	3.2	**51q**	52.8	41.2
51f	nd	3.8	**51r**	15.7	7.9
51g	7.6	3.7	RIF	1.9	0.1
51h	nd	1.3	INH	>128	0.5
51i	10.4	1.8			

*nd, not determined.

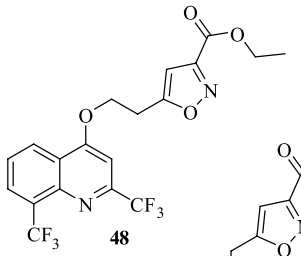
Kozikowski and Franzblau et al. reported the synthesis of a series of quinoline-based compounds (**47–52**) and compound **47** (MABA MIC = 0.9–1.9 μM and low-oxygen recovery assay [LORA] MIC = 12.2 μM) was found to be most active (Table III) and structural modifications of lead compound **47** resulted in very interesting observations.[71] Some of the derivatives with CF_3 group at various positions of quinoline nucleus (**51b, 51d-51h**, and **51o**) were synthesized and the methylene ether linker was fixed at C4 position. Without the CF_3 substituent (**51a**, MIC = 25.1 μM), the activity gets reduced by 20-fold as compared to the lead compound **47**. Compound **51e** (MIC = 3.2 μM) with -CF_3 group at C2 position was more active than **51b** (MIC = 10.6 μM) in which -CF_3 substituent was present at C8 position. Compound **51c** (MIC = 3.8 μM) and **51d** (MIC = 3.3 μM) containing Cl and CF_3, respectively, at C7 also showed good activity. The C2, C7-disubstituted compound **51h** (MIC = 1.3 μM) was found to be equally potent to **47** and C2, C5-disubstituted compound **51f** (MIC = 3.8 μM) also displayed significant activity. Replacing C2-CF_3 substituent of **51e** (MIC = 3.2 μM) by an ethyl ester resulted into less active compound **51r** (MIC = 7.9 μM). Among the various trisubstituted compounds (**51m-51q**), two compounds **51o** and **51p** exhibited excellent activity with MIC values of 0.77 and 1.9 μM, respectively (Table III). On introducing another methylene group into the linker moiety at C4 of compound **47** the activity gets reduced (**48**, MIC = 3.4 μM) whereas an aryl ether linker (**49**, MIC = 0.95 μM) exhibited much better activity. The quinol-4-one derivative **50** having isoxazole side chain at the ring nitrogen was found to be inactive.

Modifications in the isoxazole ring or introduction of other nitrogen and oxygen containing heterocycles (**52a-52j**) lead to reduced or a complete loss of activity. Compound **52d** (MIC = 27.4 μM), having ethyl ketone instead of ethyl ester group was 20-fold less active as compared to the lead compound **47**. The compounds that were found to be active in MABA assay were also tested against NRP-TB in LORA. This is a luminescence-based high-throughput assay for evaluating activity in low-oxygen conditions.[90] Most of the compounds retained their activity in LORA as well; however, the SAR obtained against NRP-TB was different when compared to SAR against R-TB. In LORA assay compound **51p** (MIC = 3.7 μM) displayed pronounced activity than **51o** (MIC = 10.0 μM). Compounds **51c** and **51d**, which showed very good activity in MABA (3.8 μM and 3.3 μM), were found 25 times less active in LORA (Table III). Monosubstituted compounds **51b** and **51e** exhibited mild activity (56.6 and 25.1 μM) in LORA whereas they showed good activity against MABA (10.6 and 3.2 μM). Furthermore, all the

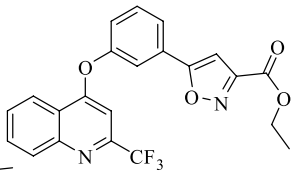
compounds were tested for their cytotoxicity against Vero cell lines and all of the compounds were found to be nontoxic at 128 μM concentration. The two most active compounds, **49** and **51o** were also found to be active against mycobacterial strains resistant to INH, RIF, and STM.



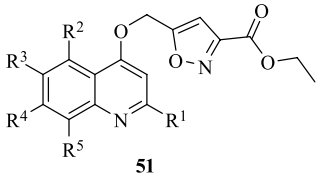
47



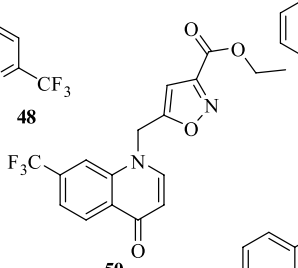
48



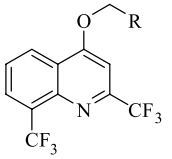
49



51

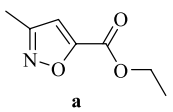


50

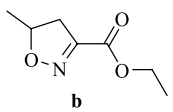


52a-52j

51a, R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = H
51b, R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = CF_3
51c, R_1 = H, R_2 = H, R_3 = H, R_4 = Cl, R_5 = H
51d, R_1 = H, R_2 = H, R_3 = H, R_4 = CF_3, R_5 = H
51e, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = H, R_5 = H
51f, R_1 = CF_3, R_2 = CF_3, R_3 = H, R_4 = H, R_5 = H
51g, R_1 = CF_3, R_2 = H, R_3 = CF_3, R_4 = H, R_5 = H
51h, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = CF_3, R_5 = H
51i, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = H, R_5 = CH_3
51j, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = H, R_5 = OCF_3
51k, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = H, R_5 = Cl
51l, R_1 = CF_3, R_2 = H, R_3 = H, R_4 = H, R_5 = F
51m, R_1 = CF_3, R_2 = H, R_3 = F, R_4 = H, R_5 = F
51n, R_1 = CF_3, R_2 = H, R_3 = OCH_3, R_4 = H, R_5 = CF_3
51o, R_1 = CF_3, R_2 = CF_3, R_3 = H, R_4 = CF_3, R_5 = H
51p, R_1 = CF_3, R_2 = Cl, R_3 = H, R_4 = Cl, R_5 = H
51q, R_1 = CF_3, R_2 = F, R_3 = H, R_4 = H, R_5 = F
51r, R_1 = COOEt, R_2 = H, R_3 = H, R_4 = H, R_5 = H



a



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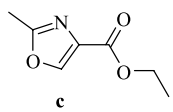

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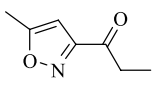

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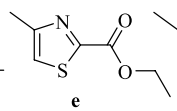

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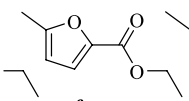

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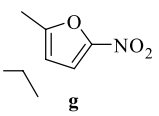

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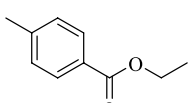

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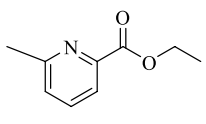


j

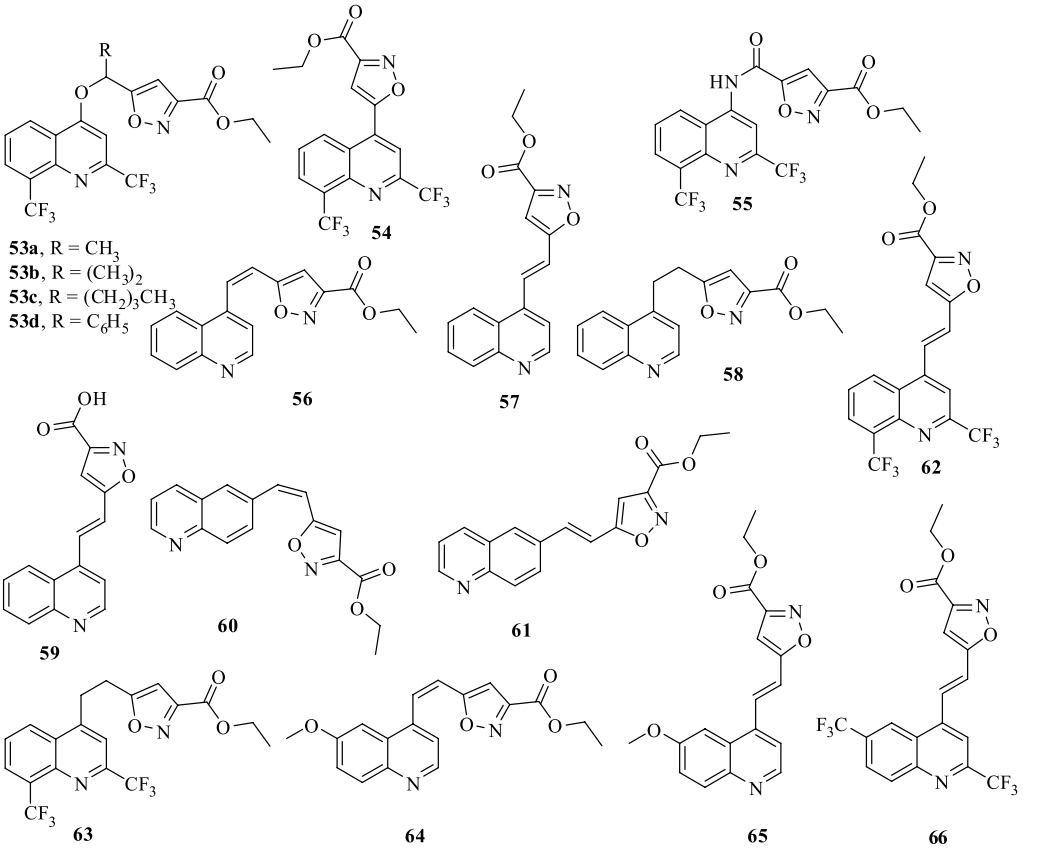
The in vitro and in vivo metabolic studies reveal that compound **47** gets metabolized to its acid and phenolic components and none of these metabolites showed any anti-TB activity. So, in order to get metabolically stable and potent anti-TB agent, modifications on the oxymethylene linker of compound **47** were carried out and the study resulted in many potent anti-TB agents (**53–66,** Table IV).[91] These compounds were proved to be neurotoxic at high dose but with increased anti-TB activity in vitro. Two isomeric compounds **56** and **57** with an alkene linker exhibited good activity as compared to compound **47** with the *trans* isomer **57** (MIC = 0.2 μM) being more active than the *cis* isomer **56** (MIC = 0.6 μM).

On moving the alkene linker from 4 position to 6 position the resulting *cis* isomer **60** (MABA MIC = 1.3 μM) was slightly less active than the *trans* isomer **61** (MABA MIC = 0.9 μM) however, both were about 4–sixfold less active than their corresponding 4-substituted counterparts **56** (MABA MIC = 0.6 μM) and **57** (MABA MIC = 0.2 μM), respectively (Table IV). Compound **62** with two CF_3 groups at the 2 and 8 positions and the linker attached to the 4 position of the quinoline ring was quite active (MABA MIC = 2.7 μM) but it was 13-fold less active than the unsubstituted compound **57** (MIC = 0.2 μM). Similarly, the compound with saturated linker and 2,8-CF_3 group (**63)** was less active (MIC = 5.7 μM) than the unsubstituted compound **58** (MIC = 2.7 μM). The MIC values of compounds **65** and **66** (0.4 μM) were of the same order as the derivative **57**, which were sevenfold more potent than the 2,8-CF_3 compound

Table IV. Antimycobacterial Activity of Compounds **53–66** Against *M. tb* H37Rv

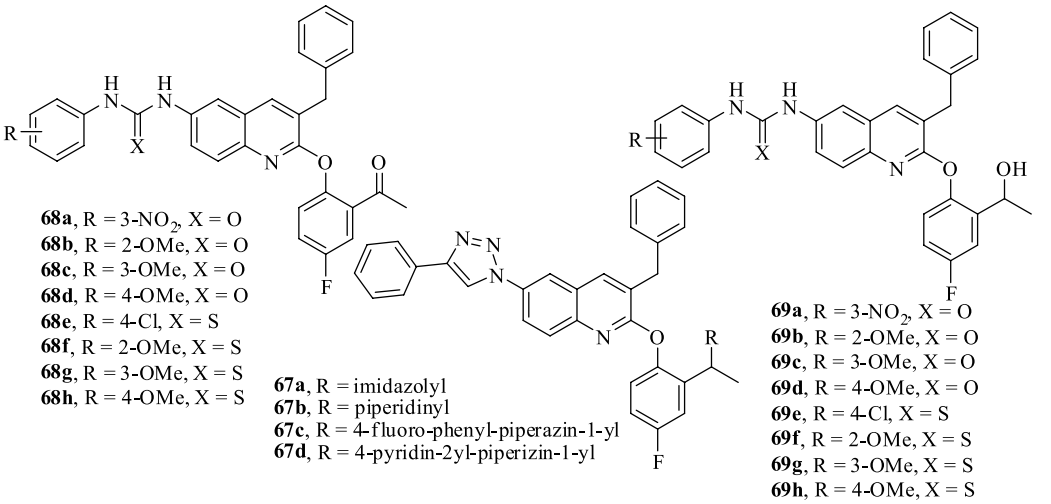
Comp no.	LORA (MIC, μM)	MABA (MIC, μM)	Comp no.	LORA (MIC, μM)	MABA (MIC, μM)
53a	20.7	4.2	**59**	-	12.5
53b	22.1	6.8	**60**	12.4	1.3
53c	11.9	115.8	**61**	9.3	0.9
53d	>128	>128	**62**	38.9	2.7
54	48.1	16.5	**63**	12.6	5.7
55	>128	29.5	**64**	2.0	1.6
56	3.0	0.6	**65**	1.1	0.4
57	2.6	0.2	**66**	8.4	0.4
58	22.5	2.7	RIF	2	0.1

62 (MIC = 2.7 μM) and compound **65** was very potent in the LORA assay (MIC = 1.1 μM). Activity results of these compounds **56–66** suggest that an alkene linker is essential for activity, and a *trans* alkene is more favorable. Based on the reported data, peptide deformylase and ATPase have been considered as possible promising targets of these compounds.

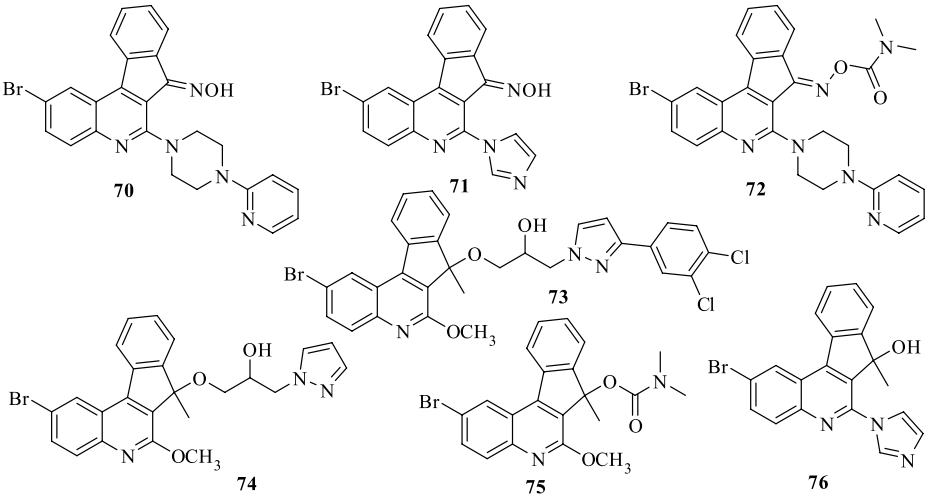


Upadhayaya et al. reported the synthesis and antimycobacterial activity of some quinoline-based compounds. The compounds **67a-67d** contain a triazole linkage and compounds **68a-68d** and **69a-69d** contain ureido linkage. They also synthesized some compounds with thioureido (**68e-68h** and **69e-69h**) substituent.[92] Among the derivatives **67a-67d** the activity decreases with

increase in stearic bulk (96%, 81%, 20%, and 29%, respectively). The activity of **67a** and **67b** could be due to their small size and better interaction to the binding site. In general, the urea derivatives (**69a-69d**) showed better activity than the thiourea derivatives (**69e-69h**). Compounds with NO_2 (**69a**) or OMe (**69c**) groups at *meta* position exhibit good inhibitory activity. But placing OMe group at *ortho* (**69b**) or *para* (**69d**) position leads to decrease in activity. At 6.25 μg/mL concentration compounds **67a**, **69a**, and **69c** inhibited *M. tb* H37Rv up to 96%, 98%, and 94%, respectively (INH 99% inhibition). The MIC of 3.125 μg/mL was obtained for compounds **67a** and **69c** while for compound **69a** it was 6.25 μg/mL. For compounds **67a** and **69a** up to 9 days no growth in mycobacteria was observed. At a concentration 6.25 μg/mL, activity of compounds **67a**, **69a**, and **69c** was similar to the standard drug (INH) used.

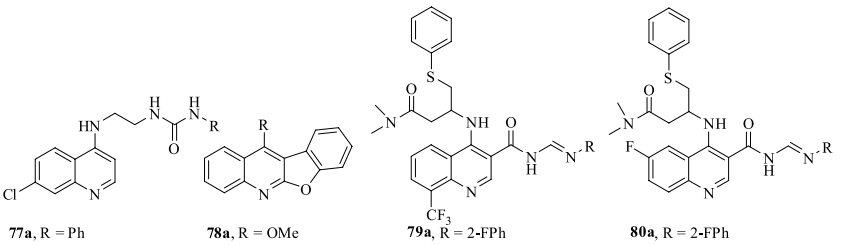


Recently, Upadhayaya et al. synthesized conformationally constrained indeno[2,1-*c*]quinolines (analogs of TMC207) and tested their antimycobacterial activities against *M. tb* H37Rv.[93] Among all the synthesized compounds, seven compounds (**70–76**) were found to possess interesting anti-TB activity and the main structural feature present in these compounds was either an oxime group (**70** and **71**) or 2-pyridyl-piperizine groups (**70** and **72**) or an imidazole (**71** and **76**) or methoxy group (**73**, **74** and **75**) or pyrazole (**74**) or a tertiary hydroxyl group (**76**). Compound **71** has imidazole ring at C2, which can be protonated at physiological pH, and could also act as a binding region and this may enhance the membrane permeability. The binding of compound **71** to the protein can be through the polar oxime group. From the docking studies it was clear that due to small size compound **71** fits in the binding site. Compound **71** showed 99% TB inhibition and excellent activity (MIC <0.39 μg/mL) among all the compounds tested, which was comparable to the standard drug INH (99% inhibition and MIC = 0.256 μg/mL). Whereas compound **70** with 2-pyridylpiperazine group instead of imidazole group was found to be less active (GI inhibition = 90% and MIC = 6.25 μg/mL). Compound **76** (GI inhibition = 91% and MIC = 0.78 μg/mL) with a less polar hydroxyl group was slightly less active than the corresponding oxime analogue **71**. Both the compounds **71** and **76** contain an imidazole moiety at C2 position, which emphasizes the importance of imidazole group in the anti-TB activity of these of compounds. The anti-TB activity of compound **72** (85% GI, MIC = 1.56 μg/mL) and compound **70** (90% GI, MIC = 6.25 μg/mL) was due to the 2-pyridyl-piperizine moiety at the C2 position. The 2-pyridyl-piperizine group makes the molecule bulky but at the same time it increases the proton affinity or hydrogen bonding.



Nava-Zuazo et al. also reported synthesis of novel quinoline-based compounds and all the reported compounds (**77a-77h)** were evaluated against *M. tb* H37Rv (ATCC 27294) using MABA method.[94] Compounds **77d** and **77f** exhibited very good activity with MIC values of 2 and 4 μg/mL, respectively, and rest of the compounds showed identical activity pattern with MIC = 8 μg/mL. Compound **77d** was twice as active as the reference drugs ethambutol and isoxyl (MIC = 4 μg/mL each), whereas compound **77f** was equally potent to these drugs. The most active compound **77d** was further tested for cytotoxicity against mammalian Vero cells and shows CC_{50} value of 5 μM with SI 625, which indicates the nontoxic nature of the molecule.

Tzeng et al. reported the synthesis of some benzofuro[2,3-*b*]quinoline derivatives (**78a-78k**) and their anti-TB activity using rifampicin as reference drug.[95] Compounds **78a**, **78f**, and **78k** exhibited pronounced activity against *M. tb* with MIC < 0.20 μg/mL, comparable to rifampin (MIC = 0.125–0.25 μg/mL). In alkoxy-substituted derivatives, methoxy derivative (**78a**) was found to be more potent than ethoxy derivative (**78b)** followed by phenoxy derivative (**78c**) indicating that with the increase in size of the alkoxy group activity decreases. The same SAR was also observed in case of aminated derivatives. The primary amine derivative **78e** was found to be totally inactive with MIC > 100 μg/mL, whereas its methyl and dimethyl derivatives **78f** and **78k** showed very promising activity (MIC < 0.20 μg/mL, 99% inhibition). Compounds with other substitutions on nitrogen atom (**78g-78j**) showed mild activity (5.35, 14.57, 2.63, and 17.83 μg/mL, respectively).



77a, R = Ph
77b, R = 4-OMePh
77c, R = 4-OEtPh
77d, R = 4-OBuPh
77e, R = 4-FPh
77f, R = 4-ClPh
77g, R = 4-NO_2Ph
77h, R = cyclohexyl

78a, R = OMe
78b, R = OEt
78c, R = OPh
78d, R = OPh-4-COMe
78e, R = NH_2
78f, R = NHMe
78g, R = NHPh
78h, R = NHPh-4-COMe
78i, R = NHPh-4-OMe
78j, R = NHPh-3-OMe
78k, R = $N(Me)_2$

79a, R = 2-FPh
79b, R = 4-FPh
79c, R = 4-OCF_3Ph
79d, R = 4-OMePh
79e, R = 3-OH, 4-OMePh
79f, R = 5-F, 2-OHPh
79g, R = 3-OC_2F_4HPh
79h, R = 2-F,4-OMePh
79i, R = 2-SCH_3Ph
79j, R = 3-(methylthio)propyl
79k, R = 3-pyridyl
79l, R = 5-bromo thiophene
79m, R = octyl

80a, R = 2-FPh
80b, R = 4-FPh
80c, R = 4-OCF_3Ph
80d, R = 4-OMePh
80e, R = 3-OH, 4-OMePh
80f, R = 5-F, 2-OHPh
80g, R = 3-OC_2F_4HPh
80h, R = 2- F, 4-OMePh
80i, R = 2-SCH_3Ph
80j, R = 3-(methylthio)propyl
80k, R = 3-pyridyl
80l, R = 5-bromo thiophene
80m, R = octyl

In 2010, the synthesis and anti-TB activity of about 26 derivatives of quinoline (**79a-79m** and **80a-80m**) was reported by Eswaran et al.[96] The in vitro anti-mycobacterial activity was carried out against *M. tb* H37Rv (ATCC 27294) and nontubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420 and *M. fortuitum* ATCC 19542 taking INH and RIF as reference by resazurin assay method. The compounds **79g**, **79k**, **79m**, **80a**, **80b**, **80g**, and **80m** exhibited moderate to good activity at 1.0 and 10 μg/mL against all tested *Mycobacterium* strains. Derivatives with F and OCH_3 groups (**79a-79e**, **79l**, **80a**, **80b**, **80c**, **80e**, and **80g**) exhibited good activity in comparison to INH and RIF. The derivatives that were substituted with thiophene and OH groups (**79f**, **79i**, **79j**, **79l**, **80f**, **80i**, **80j**, and **80l**) were less active. Eight compounds (**79a**, **79g**, **79k**, **79m**, **80a**, **80b**, **80g**, and **80m)** showed better activity than INH (MIC = 50 μg/mL) against *M. smegmatis* strain. Thirteen compounds (**79b**, **79c**, **79e**, **79k**, **79g**, **79m**, **80a**, **80b**, **80c**, **80e**, **80k**, **80g**, and **80m)** were more active than INH (MIC = 12.5 μg/mL) against *M. fortuitum.* Two compounds **79k** and **80g** exhibited excellent activity (MIC = 1.0 μg/mL) against *M. fortuitum* and *M. tb* H37Rv. Some of the compounds were tested for the toxicity against mammalian Vero cell line up to 62.5 μg/mL concentrations and were found to be nontoxic.

B. Diamine Derivatives as Anti-TB Agent

Diamine compounds have been used as therapeutic agents or as biological tools and these compounds have received considerable amount of interest from medicinal chemists across the globe due to their significant role in the process of development of some drugs, essentially the synthesis of intermediate molecules. The medicinal potential of diamine-based compounds has been reported in the beginning of medicinal history. Some of the most interesting diamine-based drugs (Fig. 3) are oseltamivir or tamiflu (antiviral), zanamivir or relenza (antiviral), ethambutol (anti-TB), lorabid (antibacterial), eloxatin (anticancer), and nutlin-3 (anticancer).[97–103] Ethambutol is one of these diamine-based anti-TB drug, which was developed by Lederle Laboratories in 1950s. The alkyl groups attached to nitrogen of the ethylene diamine linkage plays a crucial role in determining the activity of EMB analogs. The introduction of even a single methylene group or heteroatom into the chain of EMB results in total loss of activity, while some aromatic and heteroaromatic amines have shown very good antitubercular activities.[104] According to Kilburn et al., the primary mode of action of EMB was the inhibition of arabinan

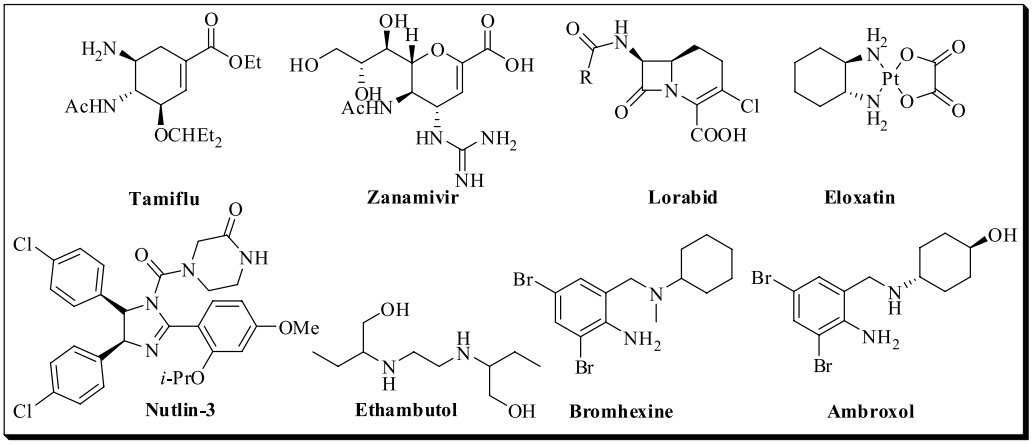
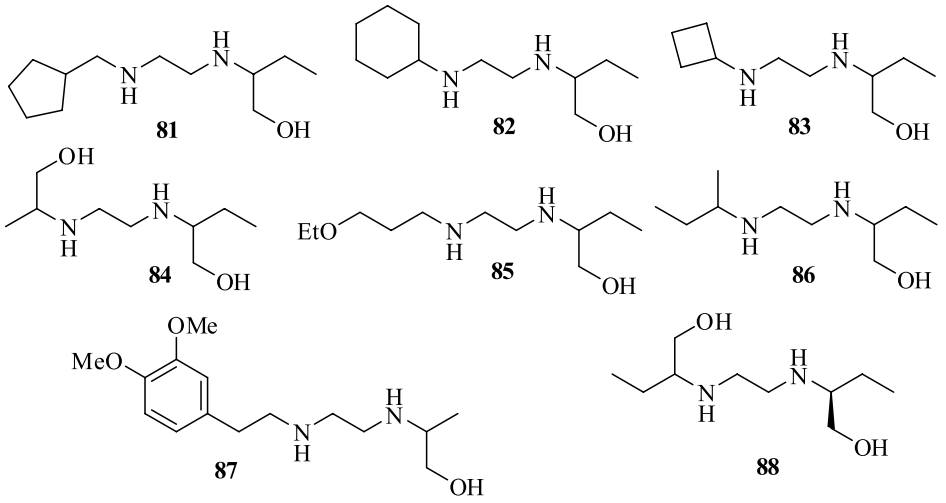


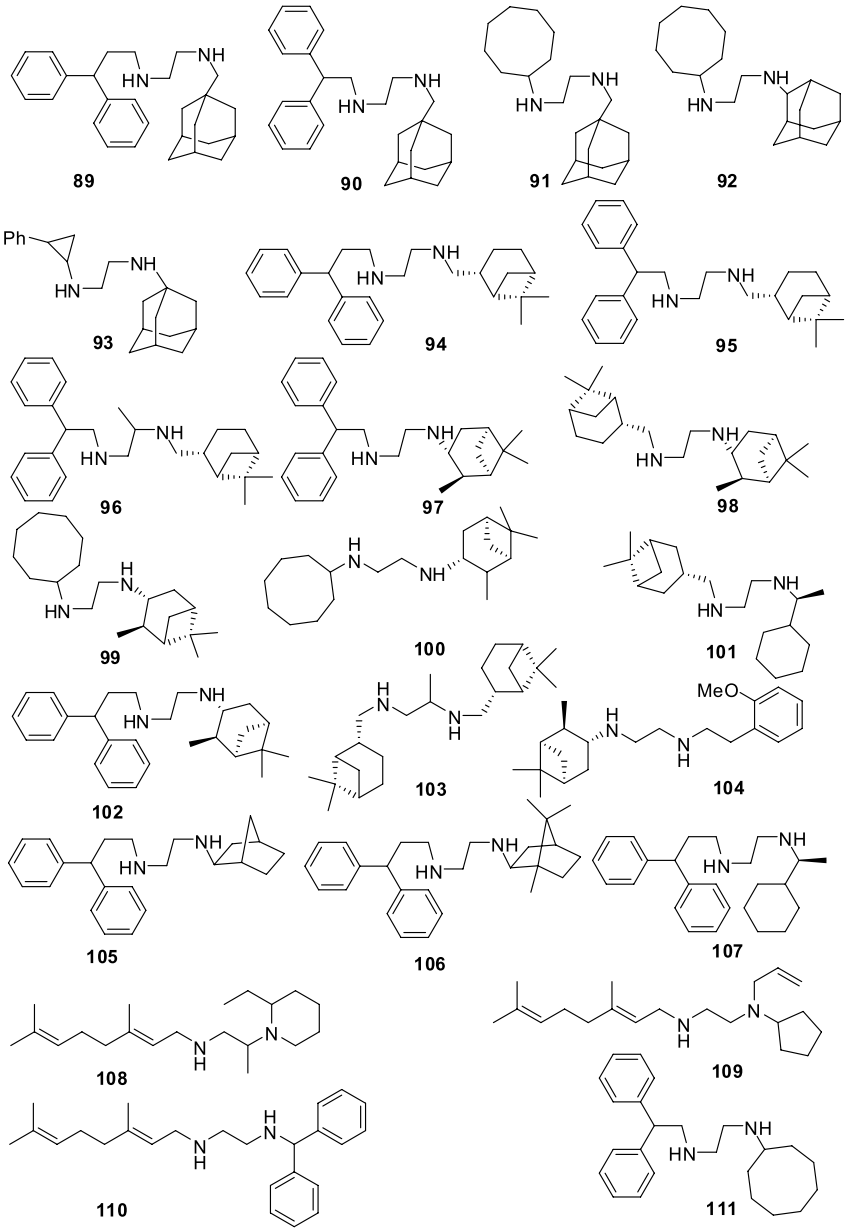
Figure 3. Some diamine-based biologically active compounds.

biosynthesis in the cell wall.[105–108] Amines and polyamines based on spermine and spermidine display very good antiparasitic and antitubercular activity.[109] The anti-TB activity of these compounds gets enhanced by increasing the hydrophobic character. The *N*-alkyl benzylamines bromohexine and ambroxol (Fig. 3) isolated from *Adhatoda vasica* are used as mucolytic agents and they inhibit the growth of *M. tuberculosis* with different rates at different pH values.[110]

Screening of 63,238 compounds having 1,2-ethylenediamine pharmacophore[111,112] led to the development of *N*-geranyl-*N*′-(2-adamantyl)ethane-1,2-diamine (SQ109) from the first-line anti-TB drug ethambutol and it is giving very assuring results during its clinical studies.[55,113] The SQ109 is highly potent against the H37Rv strain and MDR strains of *M. tb*[111,112] and showed relatively potent activity against *M. tb*, *M. bovis*, *M. marinum* and less active against *M. avium* and *M. smegmatis*.[114] The SQ109 when used with INH and RIF showed synergistic effect while with STM the effect was additive.[54] SQ109 interferes with the cell wall synthesis in *M. tb* though the exact mechanism of action on the cell wall is not well understood.



In 2003, Barry et al. from Sequella Inc. reported anti-TB activity of eight EMB analogues **81–88** by broth microdilution in middlebrook 7H9 media against *M. tb* H37Rv.[111] These derivatives were found to possess MIC_{99} between 37.5 μM and 300 μM, which is higher than EMB (MIC_{99} = 6.25 μM). Some branching in the ethylene linker was permissible with lower activity, branched alkyl compound **86** has MIC = 150 μM, aryl substituted compound **87** has MIC = 300 μM, and cycloalkyl substituted compounds **81**, **82**, and **83** have MIC values 150, 300, and 150 μM, respectively.



In the same paper, Barry et al. have also reported the synthesis and anti-TB activity of compounds **89–111** and SQ109 having MICs in the range 0.2–6 μM (Table V). The two most active molecules with MICs of 0.2 μM contain either 2-adamantanamine (**SQ109**) or (*1R*,*2R*,*3R*,*5S*)-(-)-isopinocamphylamine (**103**). The compounds **108**, **109**, and **110** containing an isoprenylamine unit in one of the two positions of the diamine showed potent activity with 1.0 μM MIC.[115] Wilkinson and colleagues at Lederle had also reported the occurrence of highly R-branched aliphatic moieties in the active compounds.[116] MIC values of 0.5 μM were calculated for compounds **89** and **96**. Compounds **90**, **91**, **94**, **95**, **97**, **98**, **99**, **100**, **101**, and **105** were also found to be highly active with MIC value 1.0 μM.

In 2006, Bogatcheva et al. from Sequella Inc. reported the activity of eight symmetrically substituted homopiperazines (**112a-112h)** and seven piperazine derivatives (**113a-113g)** against

Table V. Antimycobacterial Activity of Some Ethylene Diamine Analogues (**89–111**)

Comp no.	MIC (μM)	Comp no.	MIC (μM)	Comp no.	MIC (μM)
89	0.5	**97**	1	**105**	1
90	1	**98**	1	**106**	6
91	1	**99**	1	**107**	3
92	6	**100**	1	**108**	1
93	5	**101**	1	**109**	1
94	1	**102**	3	**110**	1
95	1	**103**	0.2	**111**	3
96	0.5	**104**	5	SQ109	0.2

M. tb in both broth microdilution and Luc assays.[117] The MIC values of the compounds were found to be within 1.56–12.5 μM range. Interestingly, compounds **112d** and **112f** were found to be the most active with MIC value of 1.56 μM while three compounds **112e**, **113e**, and **113g** have MIC of 3.13 μM. These synthesized compounds were also evaluated[112] for predicted membrane permeability based on log*P* values, in vitro cytoxicity in HepG2 cells to determine IC_{50} and SI.[55] Compounds **112a** (MIC = 6.25 μM) and **112g** (MIC = 1.56 μM) were selected for in vivo efficacy evaluation in murine models of TB. The compound **113e** displayed MIC value 6.25 μM on *M. tb* with low cytotoxicty (IC_{50} = 54 μM) and with log*P* value of 4.02. Moreover, mechanistic studies conducted on this series of compounds revealed that cell wall was not a target of these compounds. The in vivo activity of compounds **112a**, **112f**, and **113e** were conducted on C3H mice, which were inoculated intravenously with 10^6 colony forming unit (CFU) of virulent *M. tb* H37Rv and the chemotherapy was done from the seventh to tenth day of inoculation. The mice treated with compounds **112a** and **113e** lost only 12% of their initial body weight after 21 days. Compound **112f** induced 21% weight loss and was thus found to be ineffective in this model. The in vivo testing results of **112a** and **113e** in a low-dose mouse model of chronic TB infection[118] shows that these compounds could be important for developing new anti-TB agents.

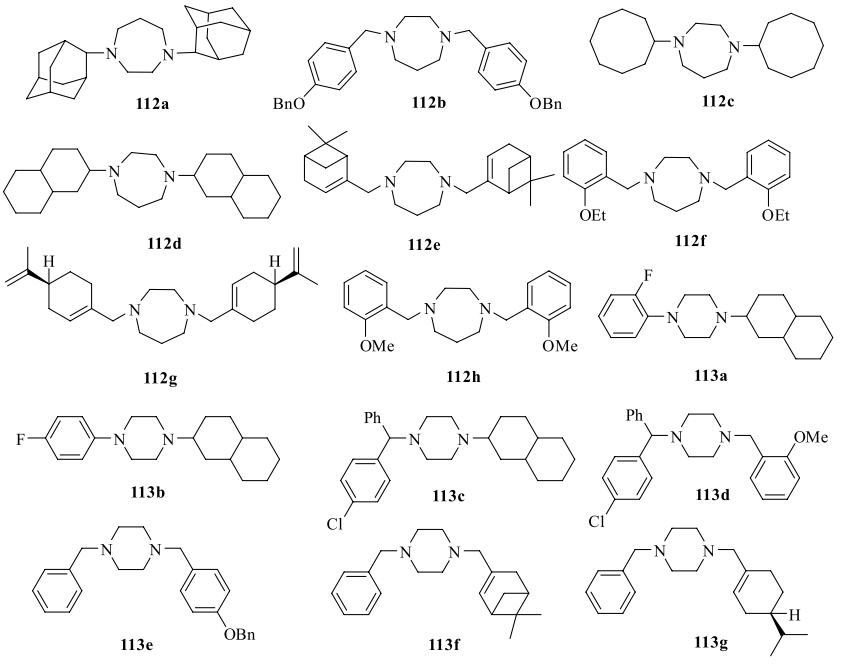
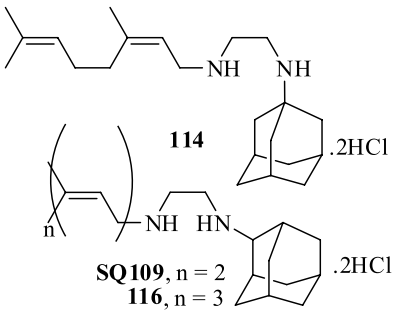
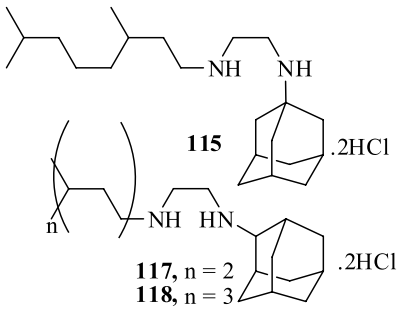


Table VI. Antimycobacterial Activity of SQ109 Analogues (**114–118**)

	MIC (μM)	
Comp no.	H37Rv	XDR173
114	1–10	-
115	0.5–1	0.5–1
116	0.25–0.5	0.25–0.5
117	1–2	-
118	0.5–1	1–2
SQ109	0.5–1	0.5–1

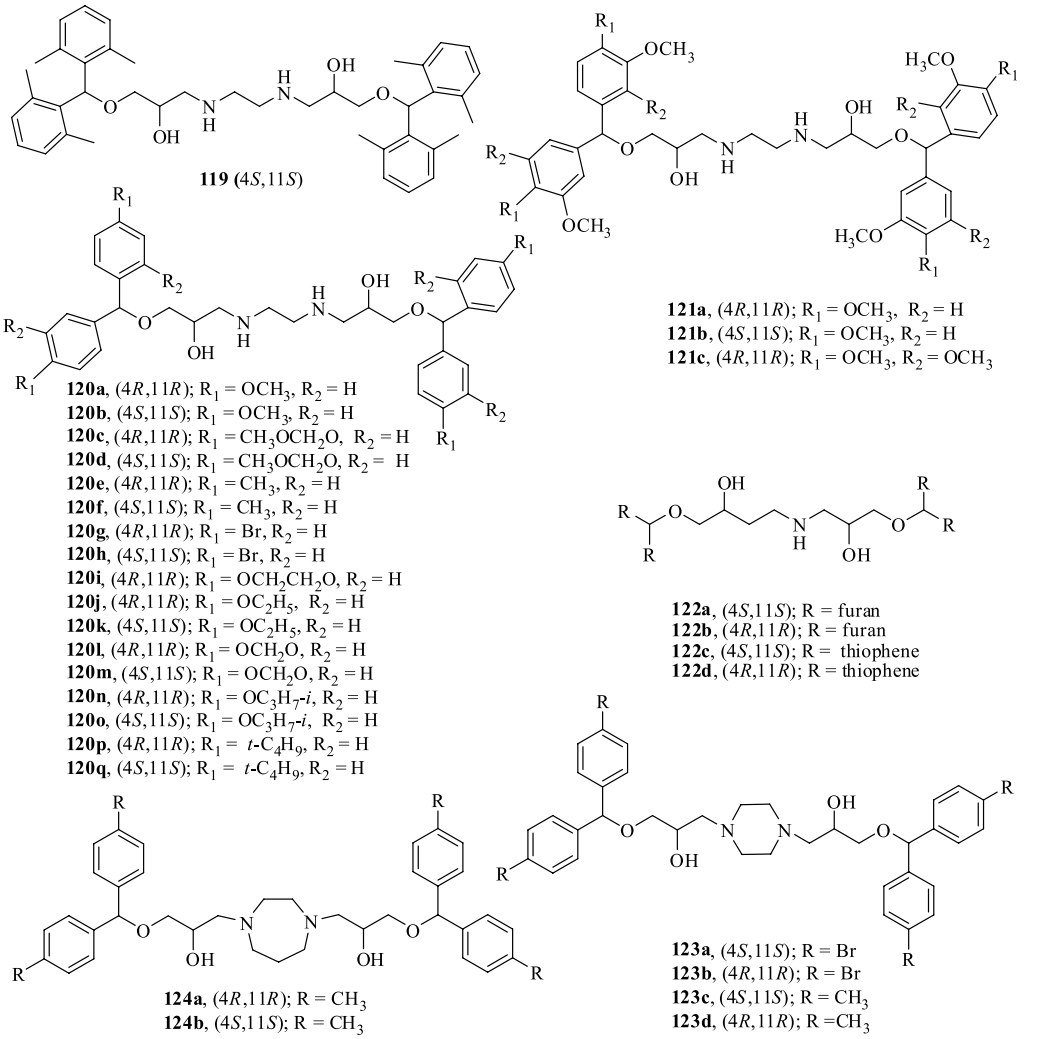
A series of six SQ109 derivatives were synthesized and screened for their anti-TB activity against the H37Rv ATCC in vitro (Table VI) by Onajole et al.[119] The compound SQ109 was fantastic with MIC range 0.5–1.0μM while the corresponding reduced compound **117** showed less activity (MIC = 1–2 μM), which indicates the importance of alkene part of the compound for activity, but activity difference between compound **114** (1–10 μM) and **115** (0.5–1 μM) contradicts this observation. The 2-adamantyl moiety was found to show better activity over 1-adamantyl as in compound **114** but **115** was equally potent to SQ109 with MIC 1–0.5 μM. The three most active compounds were also tested against XDR 173 clinical isolate strain. Among these, compound **116** was found to be most active and displayed MIC value 0.25–0.5 μM while SQ109 has MIC of 0.5–1 μM. The compound **115** was equally potent to SQ109 but **116** was found to be fourfold more active than the reduced compound **118**.





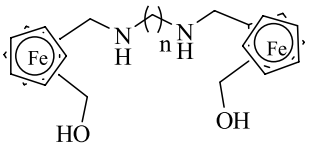
Zhang et al. reported the synthesis of 30 analogs of ethambutol, which are modifications of (*S*,*S*)-*N*,*N*′-bis-[3-(2,2′,6,6′-tetramethylbenzhydryloxy)-2-hydroxy-propyl]-ethylenediamine (**119**, MIC = 6.25 μg/mL)[120] from diaryl methanol with 2-(chloromethyl)oxirane followed by ring opening of intermediate by ethylene diamine, piperazine, or homopiperazines.[56,121] All the compounds **120–124** were found to be active against H37Ra with MIC range 0.78–25 μg/mL. The compounds **124a** and **124b** with homopiperazine ring showed excellent activity with MIC value of 0.78 μg/mL each. It is clear from the activity data that compounds with bromo (**120g** and **120h**) and methyl (**120e** and **120f**) substituents were more active having MIC in the range 3.13–6.25 μg/mL, whereas substituents like tertiary butyl (**120p** and **120q**) or oxy*iso*-propyl (**120n** and **120o**) led to decrease in activity (MIC range 6.25–25 μg/mL) of these compounds. The activity also depends on the relative configuration at 4 and 11 position as evident by the MIC difference between **123c** (MIC = 25 μg/mL) and **123d** with (MIC = 1.56 μg/mL). Other compounds **120b**, **120e**, **120f**, and **120h** have also shown good activity. Seven active compounds (**120b**, **120e**, **120f**, **120h**, **123d**, **124a**, and **124b**) were also screened against H37Rv strain and for except **120b** and **120h** the ratio of MIC to MBCs was found to be $\leq$ 4. Compounds **120e**, **120f**, and **124b** could be considered as bactericidal due to

low value of MBC/MIC whereas compounds **120b** and **120h** were primarily bacteriostatic in nature (MBC/MIC = 8). Three most potent compounds (**123d**, **124a**, and **124b**) were evaluated against drug-sensitive and MDR clinical isolates of *M. tb* by BACTEC 460 assay. The compounds **124a** and **124b** were found to be strongly active against the strains used with MIC values ranging from 0.78 to 3.13 μg/mL and both of these compounds have shown better activity than ethambutol against the strains used. However, compound **123d** showed mild activity against drug-resistant strains when compared to ethambutol.

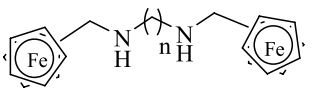


Razafimahefa et al. have synthesized a series of ferrocenyl diamino alcohols and diamine derivatives and evaluated them against *M. tb*.[122] Mycobacteria growth indicator tube system (MGIT) was used to study in vitro antimycobacterial activity of ferrocenyl compounds **125a-125c**, **126a-126d**, and **127a-127b.** These compounds showed inhibition against *M. tb* H37Rv strain at a concentration of 2 μg/mL. In particular, diamines **126a** and **126b** showed promising activity against *M. tb* H37Rv strain with MIC value of 8 μg/mL whereas compounds **126c** and **126d** showed MIC of 32 μg/mL each. Incorporation of hydroxyl group in the ferrocenyl moiety (**125b** and **125c)** causes decrease in activity (MIC > 64 μg/mL) whereas replacement of ferrocenyl moiety with phenyl ring results in complete loss in antitubercular activity in **127a** and **127b** (MIC > 64 μg/mL). From the activity data it was observed that the activity drops when

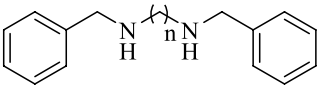
the number of carbon atoms increases between the amino groups of the diamines (**126a-126d)**. In 2003, Barry III et al. have also shown that [1,2]-diamines gives better activity results,[111] hence the activity obtained on introducing a ferrocene group in the diamine frame will be interesting.



125a, n = 2
125b, n = 4
125c, n = 6



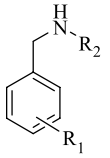
126a, n = 2
126b, n = 3
126c, n = 4
126d, n = 6



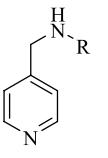
127a, n = 2
127b, n = 6

Tripathi et al. synthesized 42 benzyl- and pyridylmethyl amine derivatives (**128–134**)[123] and evaluated them for their anti-TB activity. The compounds were tested against the avirulent and the virulent strains. Moderate to potent activity was observed for nearly all the compounds against H37Ra and H37Rv strains. The compounds **128c**, **128h**, and **131** were active with very low MIC value (1.56 μg/mL). Some of the compounds, which showed very good anti-TB activity against H37Rv (MIC < 6.25 μg/mL) were screened for their activity against the clinical isolates of MDR-TB and they exhibited potent activity. In terms of potency, the compounds **128h**, **129b**, and **130a** were found to be the most active against MDR-TB with MIC value 3.12 μg/mL. Most of the compounds were active at 12.5–1.56 μg/mL concentration except compounds **128k**, **129a**, **132a-132c**, **133a**, **133c**, **133f**, **133g**, **133i**, and **133k-133o**. Functional groups such as F, Cl, NO_2, OH, and OMe on the phenyl ring have noticeable effects on the activity of these compounds, which is observed in the activity trends of the fluoro-containing compounds as compared to the chloro group. Those compounds in which benzylic carbon is substituted with carbethoxy or hydroxyl ethyl groups were found to be inactive. The compound **128g** with 12-carbon chain substituent exhibited moderate activity (MIC = 6.25 μg/mL). The compound **132d** containing 2-hydroxy phenylmethyl amine side chain showed potent activity against *M. tb* (MIC = 3.12 μg/mL). The presence of OH group at 2 position of the phenyl ring causes an increase in the activity than OH group at any other positions. The compound **128c** with OH at 4 and OMe at 3 positions of aromatic ring showed good activity (MIC = 1.56 μg/mL) but compound **128f** with substituted 4-OH group was less active (MIC = 3.12 μg/mL). The pyridyl methyl amine substituted compounds showed activity at concentration ranging from 1.56 to 25 μg/mL with activity following the sequence 2-pyridyl > 3-pyridyl > 4-pyridyl.

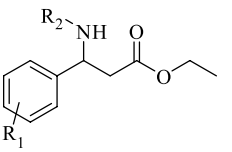
De Souza et al. screened 11 α,ω-diaminoalkanes (**135**), with the structure $H_2N(CH_2)_nNH_2$, where n varies from 2 to 12, in vitro against *M. tb* H37Rv.[124] Four compounds with longer aliphatic chain ($n = 9$–12) showed good anti-TB activity. Among these 11 reported compounds, the 12-carbon chain diamine was found to have the highest activity with MIC = 2.50 μg/mL, while other three compounds have activities comparable to ethambutol (MIC = 3.12 μg/mL). Compounds with shorter chains (n = 2–8) were found to be inactive. These results clearly indicate that the lipophilicity of the compounds has a significant role for the compounds to show activity. QSAR studies also indicates that both primary amine groups free are essential for the activity, as mono or disubstitution with acetyl, Boc, benzyl, butyl, Cbz, methyl made the compounds inactive.



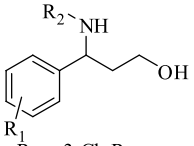
128a, R_1 = 4-OH, 3-OMe, R_2 = cyclopropyl
128b, R_1 = 4-OH, 3-OMe, R_2 = *n*-hexadecyl
128c, R_1 = 4-OH, 3-OMe, R_2 = *n*-octadec-9-enyl
128d, R_1 = 4-F, R_2 = *n*-hexadecyl
128e, R_1 = 4-F, R_2 = *n*-octadec-9-enyl
128f, R_1 = 3,4-OMe, R_2 = *n*-octadec-9-enyl
128g, R_1 = 2-OH, R_2 = *n*-dodecyl
128h, R_1 = 2-OH, R_2 = *n*-octadec-9-enyl
128i, R_1 = 4-Cl, R_2 = *n*-octyl
128j, R_1 = 4-Cl, R_2 = *n*-dodecyl
128k, R_1 = 4-Cl,R_2 = *n*-hexadecyl
128l, R_1 = 4-Cl, R_2 = *n*-octadec-9-enyl
128m, R_1 = 2-NO_2, R_2 = *n*-octyl



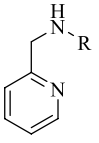
129a, R = *n*-octyl
129b, R = *n*-hexadecyl
129c, R = *n*-octadec-9-enyl



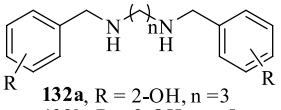
133a, R_1 = 3-Cl, R_2 = *n*-butyl
133b, R_1 = 3-Cl, R_2 = *n*-octyl
133c, R_1 = 3-Cl, R_2 = *n*-dodecyl
133d, R_1 = 3-Cl, R_2 = pyrrolididene
133e, R_1 = 3-Cl, R_2 = phenylmethyl
133f, R_1 = 3-NO_2, R_2 = *n*-butyl
133g, R_1 = 3-NO_2, R_2 = *n*-octyl
133h, R_1 = 3-NO_2, R_2 = *n*-dodecyl
133i, R_1 = 3-NO_2, R_2 = pyrrolididene
133j, R_1 = 3-NO_2, R_2 = phenylmethyl
133k, R_1 = 4-NO_2, R_2 = *n*-octyl
133l, R_1 = 4-NO_2, R_2 = *n*-dodecyl
133m, R_1 = 2-NO_2, R_2 = *n*-dodecyl
133n, R_1 = 4-F, R_2 = *n*-octyl
133o, R_1 = H, R_2 = *n*-octyl



130a, R = *n*-hexadecyl
130b, R = *n*-octadec-9-enyl

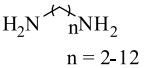


131, R = *n*-Dodecyl



132a, R = 2-OH, n =3
132b, R = 2-OH, n = 5
132c, R = 2-OH, n = 7
132d, R = 2-OH, n = 12
132e, R = 3-OH, n = 5

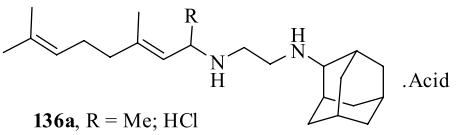
134a, R_1 = 3-Cl, R_2 = *n*-octyl
134b, R_1 = 3-NO_2, R_2 = *n*-octyl
134c, R_1 = 3-NO_2, R_2 = *n*-dodecyl



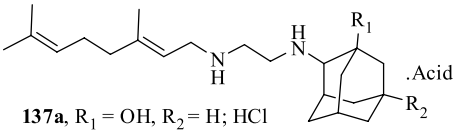
n = 2-12

135

Meng et al. synthesized SQ109 derivatives with different substitutions such as F, OH, OMe in the adamantane ring or methyl, ethyl in the geranylamine part and the 11 compounds (**136a-136e** and **137a-137f**) were evaluated for their activity against *M. tb* H37Rv strain (ATCC 27294, susceptible both to RIF and INH) using microbroth dilution assay.[125] Compounds **136a** and **136b** with methyl and ethyl substitution in the geranyl moiety had same activity (MIC = 1.2 μM) in comparison to SQ109 (MIC = 0.6 μM) and benzyl-substituted compound **136c** was equally potent (MIC = 1.0 μM). The compounds with fluoro (**136d**) and OCF_3 (**136e**) groups at the *para* position of aromatic ring lead to drastic decrease in the activity. In order to study the effect of substitution in adamantly ring, the functional groups such as OH, OMe, F at 1 or 5 positions were introduced. Out of this study, two compounds **137b** (MIC = 0.5 μM) and **137c** (MIC = 0.3 μM) were found to be more active than SQ109. There was a slight decrease in activity when these two groups were present at position 5, but in the case of OH substituent there was more difference in activity due to positioning of the OH group in the adamantane ring, the activity gets decreased drastically when OH was at position 5 (**137d**, MIC = 8.6 μM) than the same group at position 1 (**137a**, MIC = 0.6 μM).



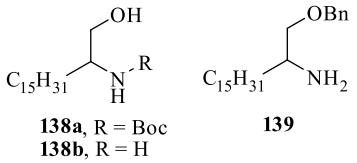
136a, R = Me; HCl
136b, R = Et; HCl
136c, R = CH_2Ph;HCl
136d, R = CH_2Ph4-F; maleic acid
136e, R = CH_2Ph-4-OCF_3; maleic acid



137a, R_1 = OH, R_2 = H; HCl
137b, R_1 = OMe, R_2 = H; maleic acid
137c, R_1 = F, R_2 = H; maleic acid
137d, R_1 = H, R_2 = OH; maleic acid
137e, R_1 = H, R_2 = OMe; maleic acid
137f, R_1 = H, R_2 = F; HCl

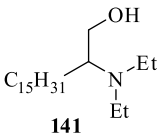
Considering that sphingolipids, ceramide, and their basic component sphingosine (SPH) have a vital role on *M. tb* containing endosomes, del Olmo et al. synthesized 18 aminoalcohols and diamines and evaluated them in vitro against *M. tb* H37Rv.[126] Two aminoalcohols **139**

(MIC = 3.6 μM) and **140b** (MIC = 3.1 μM) as well as a diamine **144** (MIC = 4 μM) were found more potent than EMB (MIC = 39.9 μM). The 1,2-diamine **142b** (12.6 μM) was more potent than the free 2-aminopalmitol **138b** (24 μM). Comparison of the activity shown by compounds with Boc group **138a**, **142a**, and **143b** (MIC = 84, 30, and 15.2 μM, respectively) and those without Boc **138b**, **142b**, and **144** (MIC = 24, 12.6, and 4 μM, respectively) clearly indicates that this group leads to decrease in activity and compounds with free amine exhibit better activity. Compounds with benzyl ether moiety **139** and **140b** (MIC = 3.6 and 3.1 μM, respectively) were more active than their alcohol derivatives **138b** and **141** (MIC = 24 and 20 μM, respectively). The negative influence due to *N*-Boc protection can also be seen in hemisuccinyl (**140c**, MIC = 140 μM) and hemiglutaryl amides (**140d**, MIC = 68 μM) in comparison with compounds **139**, **140a**, and **140b** (3.6, 16.6, and 3.1 μM, respectively). Also the potency of amide **143c** (133 μM) was less than compounds **142b**, **143a**, and **143b** (12.6, 32, and 15.2 μM, respectively). The results also demonstrated that in comparison to the monosubstituted derivatives, the unsubstituted and dialkylated amines were more active. Anti-*M. tb* potencies of ethyl (**140a** and **143b**, MIC = 16 and 15.2 μM) or methoxycarbonylmethyl (**140e** and **143d**, MIC = 72 and 59 μM) alkylated amines show that diamines were more active than aminoethers. Three compounds **139**, **140b**, and **144** were also tested against 11 MDR strains, namely strain no. 160, 331, 332, 363, 366, 401, 411, 494, 429, 528, and 535. The compound **144** was very less active against these strains with MIC >20 μM, but it showed considerable activity against CIB99 strain. The other two compounds showed significantly good activity against most of the MDR strains used. The compound **139** exhibited similar potency (MIC = 4.5 μM) toward strain numbers 366, 401, and 411. Compound **140b** exhibited MIC value of 3.91 against strain numbers 363, 366, and 535 and it showed excellent activity (MIC = 1.9 μM) against strain no. 332.

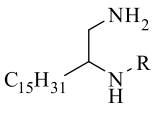


138a, R = Boc
138b, R = H

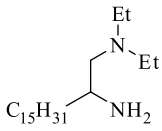
139



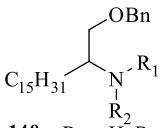
141



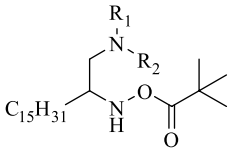
142a, R = Boc
142b, R = H



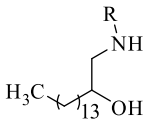
144



140a, R_1 = H, R_2 = Et
140b, R_1 = Et, R_2 = Et
140c, R_1 = H, R_2 = $CO(CH_2)_2COOH$
140d, R_1 = H, R_2 = $CO(CH_2)_3COOH$
140e, R_1 = H, R_2 = CH_2COOEt

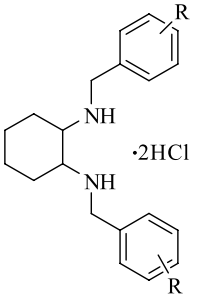


143a, R_1 = H, R_2 = Et
143b, R_1 = Et, R_2 = Et
143c, R_1 = H, R_2 = $CO(CH_2)_3COOH$
143d, R_1 = CH_2COOEt, R_2 = CH_2COOEt

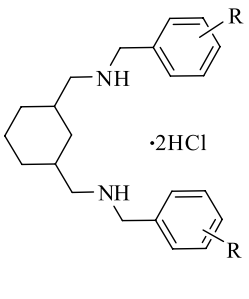


145a, R = cyclohexyl
145b, R = Bn

Recently, we have initiated a program toward the development of novel antimicrobial agents,[127–132] among these cyclohexane-1,2-diamine (**146a-146t**)[133] and cyclohexane-1,3-diyldimethanamine based compounds (**147a-147l**)[134] have shown potent antibacterial and antifungal activities with low nano molar MIC values.[135] Interestingly, all these compounds did not show any toxicity even at very high concentration. In order to study their anti-TB potential few compounds (**147a-147l**) were tested against H37Rv and have shown very promising activity. These compounds can be considered as ethambutol (EMB) analogues.



146a, R = 2-Me; **146b**, R = 3-Me; **146c**, R = 4-Me; **146d**, R = 4-Et; **146e**, R = 4-*i*-Pr; **146f**, R = 4-*n*-Bu; **146g**, R = 4-*t*-Bu; **146h**, R = 2-Cl; **146i**, R = 3-Cl; **146j**, R = 4-Cl; **146k**, R = 2-Br; **146l**, R = 3-Br; **146m**, R = 4-Br; **146n**, R = 2-NO_2; **146o**, R = 3-NO_2; **146p**, R = 4-NO_2; **146q**, R = 2-CF_3; **146r**, R = 3-CF_3; **146s**, R = 4-CF_3; **146t**, R = 3-F



147a, R = 3-Cl; **147b**, R = 4-Cl; **147c**, R = 3-Br; **147d**, R = 4-Br; **147e**, R = 4-Me; **147f**, R = 4-Et; **147g**, R = 4-*n*-Pr; **147h**, R = 4-*i*-Pr; **147i**, R = 4-*n*-Bu; **147j**, R = 4-*t*-Bu; **147k**,R = 3-Me; **147l**, R = 3,5-Me

C. Quinolone and Fluoroquinolone Derivatives as Anti-TB Agent

Quinolones are synthetic antimicrobials, which possess potent bactericidal activity against *M. tb*. These compounds have excellent oral bioavailability and ability to penetrate macrophages, which are the essential features for a compound to be a good therapeutic agent against TB. There are many drugs in the market such as ciprofloxacin, levofloxacin, sparfloxacin, gatifloxacin, and moxifloxacin, which contain quinoline nucleus.[136–138] Fluoroquinolones are used for the treatment of community and nosocomial infections of the respiratory, gastrointestinal and urinary tracts, skin and soft tissue infections, chronic osteomyelitis, and sexually transmitted diseases.[139–142] Fluoroquinolones are also active against INH and RIF resistant mycobacteria. Ciprofloxacin, moxifloxacin, levofloxacin, and oxfloxacin (Fig. 4) are some of the most important fluoroquinolones that are used for the treatment of various diseases. This class of compounds act by inhibiting the topoisomerases II and IV enzymes. Nalidixic acid, the first narrow-spectrum agent was discovered in 1962 by Lesher and his co-workers is used for the treatment of infections of the urinary tract.[143,144] Since the discovery of nalidixic acid, several structural modifications have been carried out in the quinolone structure to synthesize new antimicrobials with better pharmacokinetic parameters, enhanced in vivo efficacy, and negligible side effects.[145–149]

Quinolones have been classified as first generation (nalidixic acid, oxolinic acid, and cinoxacin), second generation (ciprofloxacin, ofloxacin, enoxacin, lomefloxacin, and norfloxacin), third generation (gatifloxacin, sparfloxacin, and levofloxacin), and fourth generation (moxifloxacin and trovafloxacin) (Fig. 4).[150] Norfloxacin was introduced in the 1980s and showed preferentially better activity against Gram-negative bacteria as compared to Gram-positive bacteria.[151,152] Subsequent developments produced quinolones with improved solubility (e.g., ofloxacin), antimicrobial activity (e.g., ciprofloxacin), or prolonged serum half-life (e.g., pefloxacin).[153] The modifications in the quinoline nucleus have been done to achieve favorable properties and less side effects.[154,155] The efficacy, pharmacology, pharmacokinetic parameters, activity spectrum, and adverse effects of the next generation of fluoroquinolones was already approved by FDA.[156] TBK613 is a lead compound of the quinolone backup project at the TB Alliance. Both TB Alliance and Bayer are currently involved in the moxifloxacin clinical trials.

Zhao et al. reported the synthesis and antimycobacterial activity of various fluoroquinolone derivatives having different substituents at N-1 and C-7 positions in the basic fluoroquinolone

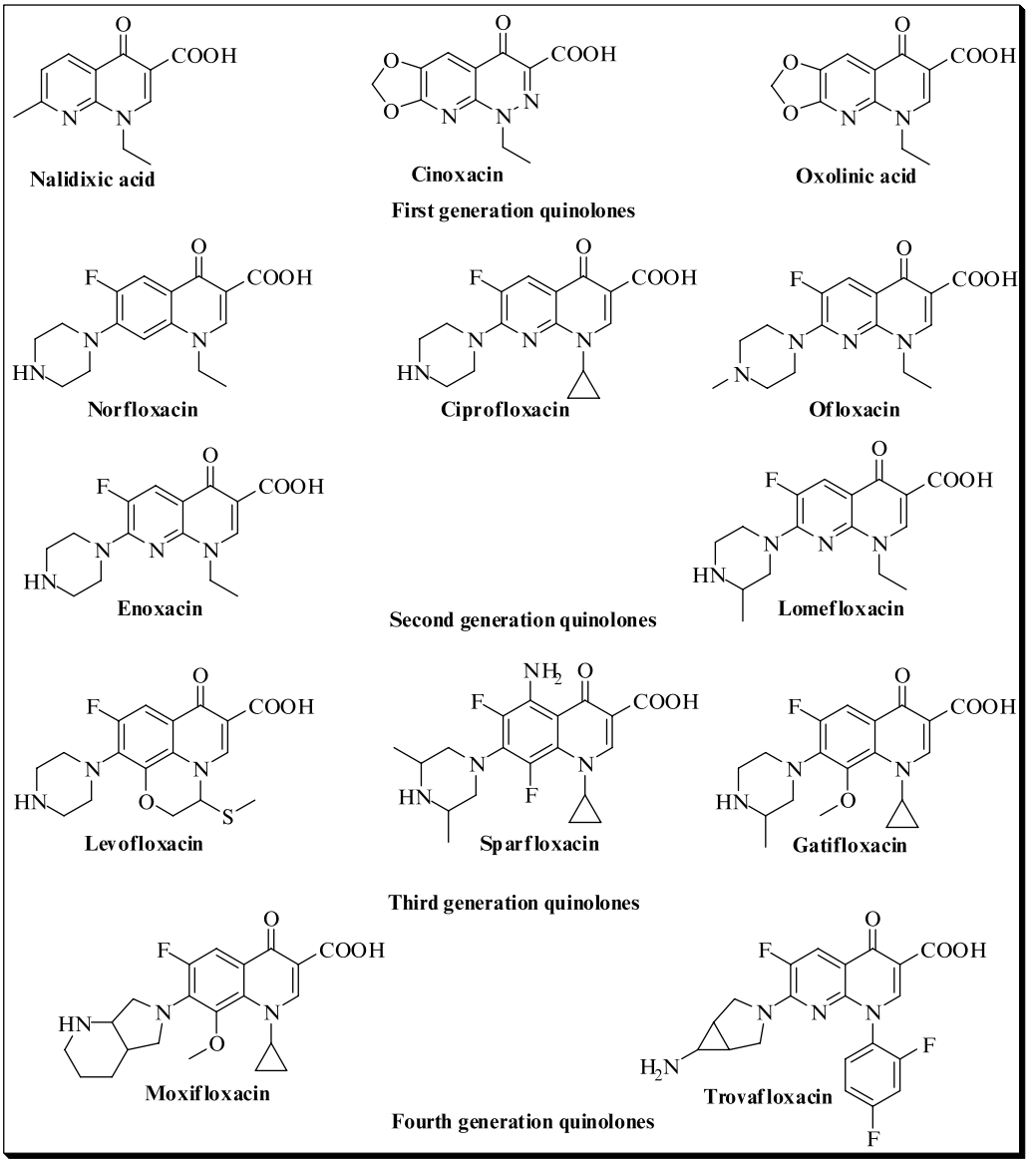
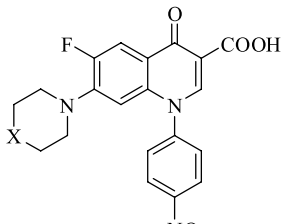


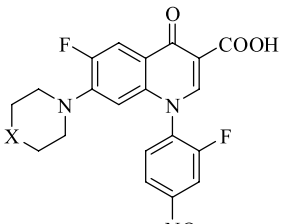
Figure 4. Quinolones of various generations.

ring.[157] The antimycobacterial activity was performed against *M. tb* (ATCC 27294) in BACTEC 12B and MABA. From the activity profile it was found that in case of 1-arylfluoroquinolones most of the 1-(4-nitrophenyl) derivatives (**148a** and **148b)** were totally inactive whereas their fluoro counterparts, that is, 1-(2-fluoro-4-nitrophenyl) derivatives (**149a** and **149b**) showed good activity indicating that the fluoro group at 2 position in the phenyl ring is crucial for the activity. The same pattern was also indicated in derivatives with 1-(4-aminophenyl) linkage (**151–152**). The 1-(4-aminophenyl) compounds were found to be totally inactive, while 1-(2-fluoro-4-aminophenyl) compounds exhibited potent activity (**152a-152c**). Among 1-(4-amino-2-fluorophenyl)quinolones, the 7-piperazinyl (**152c**) and 7-piperidinyl derivative **152a** inhibited 100% and 95% growth of *M. tb*, respectively, while its 7-morpholinyl counterpart **152b** showed

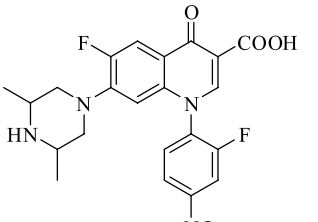
very less inhibition (48%). Among the bifunctional fluoroquinolone-hydroxy quinoline conjugates, most of the compounds showed promising activity but ciprofloxacin and ofloxacin derivatives (**153b** and **154**) were found to be most potent compounds with 98% inhibition followed by the norfloxacin derivative (**153a**) that showed 86% inhibition. The compound **148c** was found to have no activity, while due to the chelating capability of 8-hydroxyquinoline moiety 44% inhibition was observed by compound **155a** on the growth of *M. tb.* It was also observed that compound **155b** causes 47% inhibition of *M. tb* growth but compound **149c** showed no activity.



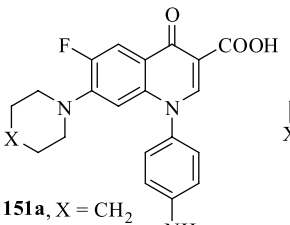
148a, X = CH_2
148b, X = O
148c, X = NCH_3



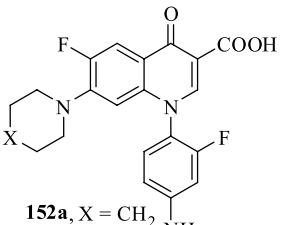
149a, X = CH_2
149b, X = O
149c, X = NCH_3
149d, X = NH



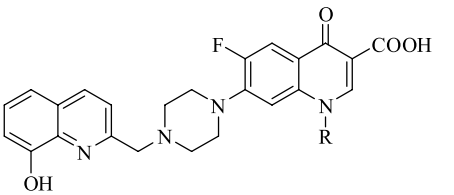
150



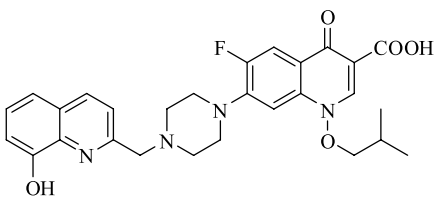
151a, X = CH_2
151b, X = O



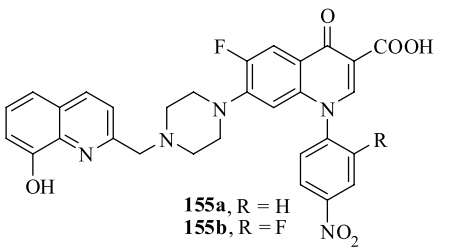
152a, X = CH_2
152b, X = O
152c, X = NH



153a, R = CH_2CH_3
153b, R = cyclopropyl



154



155a, R = H
155b, R = F

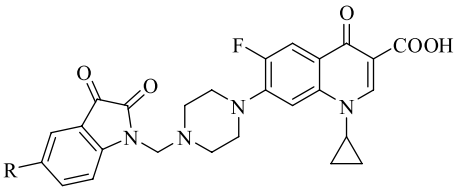
Sriram et al. reported the synthesis of various 7-substituted ciprofloxacin-isatin conjugates (**156–158**) in which isatin derivatives were linked by a methylene linker to ciprofloxacin molecule and studied the variation in antitubercular activity due to lipophilicity of various groups at 7 position of ciprofloxacin at a dose level of 6.25 μg/mL (Table VII).[158] Compounds that showed >90% inhibition when tested at <6.25 μg/mL concentration retained their inhibitory effect. The secondary screening results showed that except **158d** all the compounds exhibited better activity than ciprofloxacin (MIC = 6.04 nM) and five compounds (**156a**, **157c**, **157d**, **158a**, and **158c**) showed activity less than 2 nM. Among all the tested compounds **158c** (MIC = 1.21 nM) displayed the maximum activity.

Further, all the compounds were tested for toxicity toward Vero cells. Compounds having MIC less than 2 nM were found nontoxic up to 100 nM and their SI were greater than 100. Compound **157d** was tested for in vivo activity on 8–10 week old female mice at dose level of 300 mg/kg body weight. The animal was treated with the compound 20 days after the inoculation of *M. tb* into the animal. After 28 days bacterial counts of lung and spleen tissues were calculated against the untreated controls (for lung tissues mean CFU = 8.78, for spleen

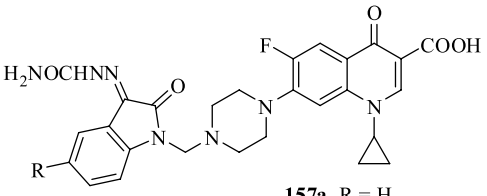
Table VII. Antimycobacterial Activity of 7-Substituted Ciprofloxacin Derivatives (**156–158**) Against *M. tb* H37Rv

Comp no.	% inhibition at 6.25 μg/mL	MIC (nM)	Comp no.	% inhibition at 6.25 μg/mL	MIC (nM)
156a	99	1.59	**157d**	100	1.39
156b	100	2.97	**158a**	100	1.38
156c	100	2.74	**158b**	95	2.61
156d	100	3.09	**158c**	100	1.21
157a	100	2.85	**158d**	100	10.82
157b	100	2.68	CIP	98	6.04
157c	99	1.24	MXF	100	1.94

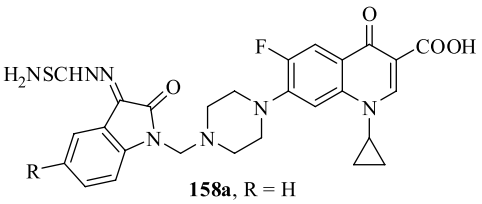
tissues mean CFU = 6.84). The compound **157d** led to decreased bacterial count in spleen tissues (mean CFU = 6.08) and was considered to be moderately active whereas in lung tissue, it showed no activity (mean CFU = 9.26). Some of the compounds were evaluated for DNA gyrase inhibitory activity. All the tested compounds were found to show mild to good activity with IC_{50} value ~10 μg/mL. From the activity data it is clear that lipophilic fluoroquinolones retained their inhibitory activity even after the modification on the basic moiety.



156a, R = H
156b, R = Cl
156c, R = Br
156d, R = CH_3



157a, R = H
157b, R = Cl
157c, R = Br
157d, R = CH_3

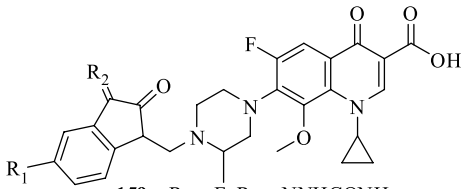


158a, R = H
158b, R = Cl
158c, R = Br
158d, R = CH_3

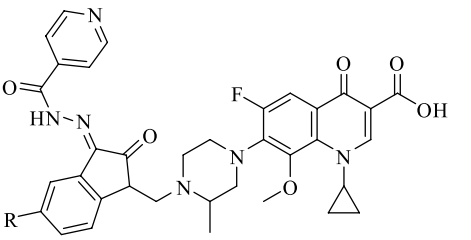
Same group also reported the synthesis of 16, 7-substituted gatifloxacin derivatives (**159–161**) and carried out the screening of these compounds against *M. tb* H37Rv and MDR *M. tb* (MDR-TB) for the anti-TB activity. These compounds were checked for inhibition of supercoiling activity of DNA gyrase of *M. tb*.[159] All the synthesized compounds were found to be equally or even more potent than the reference compound gatifloxacin (Table VIII). Four compounds **159d**, **159e**, **161a**, and **161d** showed better activity (MIC < 0.2 μg/mL) than gatifloxacin (MIC = 0.2 μg/mL). In case of MDR-TB all the compounds were found to be more potent (MIC ≤ 0.78 μg/mL) than gatifloxacin (MIC = 3.12 μg/mL). Among the series compound **159d** was the most active compound against MDR-TB (MIC = 0.05 μg/mL). Compound **159d** was further evaluated for in vivo *M. tb* activity in mice at a dose level of 50 mg/kg body weight and decrease in the bacterial count in lungs and spleen tissues with mean CFU values of 4.26 and 5.08, respectively, was observed. All the synthesized compounds also inhibited DNA gyrase activity.

Table VIII. In Vitro Antimycobacterial Activity of Gatifloxacin Derivatives (**159–161**)

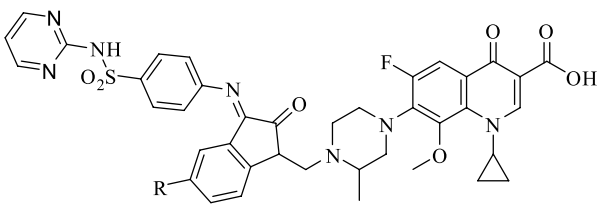
Comp no.	MIC-MTB (μg/mL)	MIC-MDR-TB (μg/mL)	Comp no.	MIC-MTB (μg/mL)	MIC-MDR-TB (μg/mL)
159a	0.2	0.2	**160b**	0.78	0.78
159b	0.39	0.78	**160c**	0.39	0.78
159c	0.39	0.78	**160d**	0.2	0.78
159d	0.0125	0.05	**161a**	0.1	0.1
159e	0.1	0.1	**161b**	0.2	0.1
159f	0.78	0.78	**161c**	0.2	0.1
159g	0.39	0.78	**161d**	0.1	0.78
159h	0.2	0.2	Gatifloxacin	0.2	3.12
160a	0.78	0.78			



159a, R_1 = F, R_2 = $NNHCONH_2$
159b, R_1 = CH_3, R_2 = $NNHCONH_2$
159c, R_1 = Cl, R_2 = $NNHCONH_2$
159d, R_1 = H, R_2 = $NNHCONH_2$
159e, R_1 = F, R_2 = $NNHCSNH_2$
159f, R_1 = CH_3, R_2 = $NNHCSNH_2$
159g, R_1 = Cl, R_2 = $NNHCSNH_2$
159h, R_1 = H, R_2 = $NNHCSNH_2$

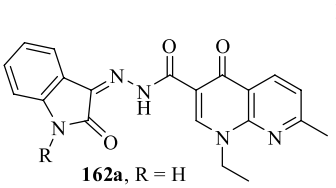


160a, R = F
160b, R = CH_3
160c, R = Cl
160d, R = H

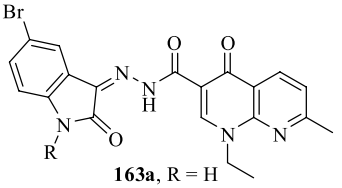


161a, R = Cl
161b, R = F
161c, R = H
161d, R = CH_3

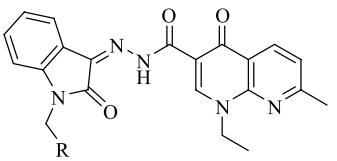
In 2010, Aboul-Fadl et al. reported the synthesis and anti-TB activity of imine-based derivatives of isatin (**162–165**).[160] These derivatives were screened against four *Mycobacterium* strains, namely *M. smegmatis* (ATCC 35797), *M. intercellulari* (ATCC 35743), *M. cheleneo* (ATCC 35751), and *M. xenopi* (ATCC 14470) by agar dilution method using isoniazid (INH) as a reference drug. Most of the compounds showed modest anti-TB activity, whereas compound **162f** with a benzylic substituent in the isatin moiety exhibited pronounced anti-TB activity. The compound **162f** possessed MIC value of 0.625 μg/mL, which was manifold better than isoniazid (MIC = 12.5 μg/mL). A hypothetical pharmacophore model revealed that aromaticity and hydrogen-bonding parameters are necessary for anti-TB activity of these compounds.



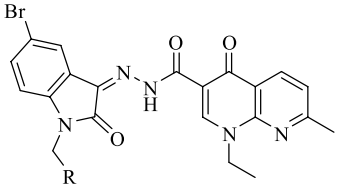
162a, R = H
162b, R = CH_3
162c, R = C_2H_5
162d, R = C_3H_7
162e, R = $CH_2CH{=}CH_2$
162f, R = $CH_2C_6H_5$
162g, R = OH



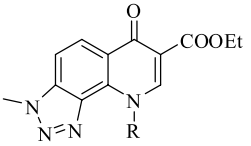
163a, R = H
163b, R = CH_3
163c, R = C_2H_5
163d, R = C_3H_7
163e, R = $CH_2CH{=}CH_2$
163f, R = $CH_2C_6H_5$
163g, R = OH



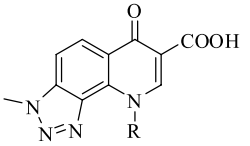
164a, R = $N(C_2H_5)_2$
164b, R = piperidyl
164c, R = *N*-methylpiperazine



165a, R = $N(C_2H_5)_2$
165b, R = piperidyl
165c, R = *N*-methylpiperazine



166a, R = H
166b, R = CH_3
166c, R = $CH_2CH_2CH_3$
166d, R = $CH_2CH_2CH_2CH_3$
166e, R = $CH_2CH{=}CH_2$
166f, R = benzyl
166g, R = 4-Me-benzyl
166h, R = 4-Br-benzyl
166i, R = CH_2CH_2-phenyl



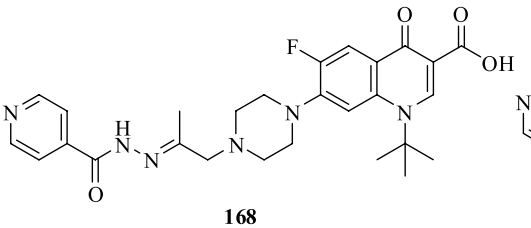
167a, R = CH_3
167b, R = $CH_2CH_2CH_3$
167c, R = $CH_2CH_2CH_2CH_3$
167d, R = $CH_2CH{=}CH_2$
167e, R = benzyl
167f, R = 4-Me-benzyl
167g, R = 4-Br-benzyl
167h, R = CH_2CH_2-phenyl

Carta et al. reported the synthesis and antitubercular activity of some quinolone-carboxylic acids (**167a-167h**) and their esters (**166a-166i**) against MDR *M. tb*.[161,162] These compounds were tested against H37Rv and 11 clinically isolated strains of *M. tb* that are sensitive to one or more of the standard antitubercular drugs (STM, INH, RIF, and EMB). Six compounds (**166a**, **166b**, **166d**, **167a**, **167b**, **167h**) exhibited MIC_{90} in the range 0.5–1.6 μg/mL (Table IX). Compound **166d** was the most potent derivative among the series with $MIC_{90} = 0.5$ μg/mL against all *M. tb* strains. Compounds **166c**, **166e-166i**, **167c-167g** were inactive ($MIC_{90} > 32$ μg/mL). Human macrophages J774-A1 infected with H37Rv strain were grown without any anti-TB compound and also with **166d** at 0.5 and 0.25 μg/mL concentrations. The growth of mycobacterial culture after 7 days was found to be 5000 and 8000 CFU/mL, respectively, with a normal growth of culture treated with no compound. CC_{50} value of compound **166d** against human macrophages and Hep-2 cells was found to be >50 μg/mL. From the structure–activity relationship it was found that alkyl substituent at *N*-9 position (**166a**, **166b**, **166d**, **167a**, and **167b**) gives better activity results than other groups.

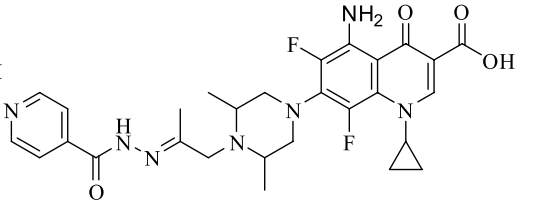
Table IX. Antimycobacterial Activity (MIC, μg/mL) of [1,2,3]triazolo[4,5-*h*]quinolones Against H37Rv and SS1–SS11 Strains of *M. tb*

Comp no.	H37Rv	SS1	SS2	SS3	SS4	SS5	SS6	SS7	SS8	SS9	SS10	SS11
166a	1.6	1.6	0.8	3.2	3.2	1.6	1.6	3.2	1.6	1.6	1.6	1.6
166b	0.5	0.5	0.5	0.5	2	0.5	0.5	0.5	0.5	0.5	0.5	0.5
166d	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
167a	0.5	0.5	0.5	0.5	2	0.5	0.5	0.5	0.5	0.5	0.5	0.5
167b	1.6	1.6	1.6	1.6	3.2	3.2	1.6	3.2	1.6	1.6	1.6	0.5
167h	0.8	0.8	0.8	3.2	3.2	3.2	3.2	3.2	0.8	0.8	3.2	1.6
RIF	0.7	>4	>4	0.5	0.7	0.5	>4	0.8	0.5	0.5	0.8	0.8

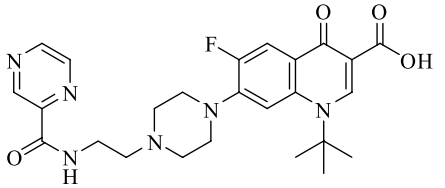
Shindikar et al. in 2005 reported the synthesis of compounds **168–171** and evaluated them in vivo against *M. tb* H37Rv in Swiss albino mice using sparfloxacin as a standard drug.[163] Test compounds exhibited activity comparable to that of sparfloxacin at a dose of 200 mg/kg. Each compound was tested in a group of five mice. Total four parameters such as spleen weight, rate of survival, lung lesions, and CFUs were studied in this study. Compound **170** and sparfloxacin exhibited 100% survival rate, whereas compounds **168**, **169**, and **171** showed 80% survival. Compounds **170**, **171**, and sparfloxacin showed no lung lesions, whereas compounds **168** and **169** showed some lung lesions. At a dose level of 200 mg/kg, the groups treated with compound **169** and sparfloxacin caused same inhibition of CFUs (55–56%). While compound **170** leads to greater inhibition at the same dose level. Among the four compounds, **170** was found to be the most potent with 100% survival rate, no lung lesions, and 75% inhibition of CFUs at a dose level of 200 mg/kg body weight.



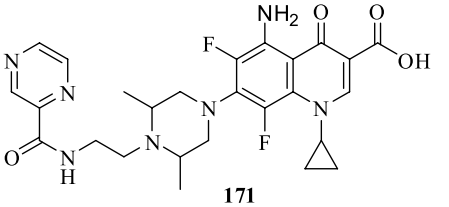
168



169

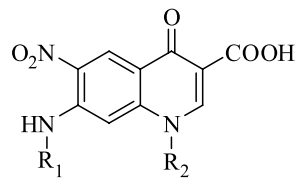


170

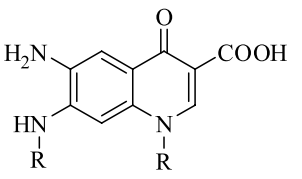


171

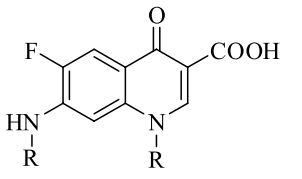
Quinolone carboxylic acid derivatives (**172–174**) bearing alkylamino substituents at C-7 position and fluoro or nitro group at the C-6 positions have been synthesized by Artico et al. and all compounds were screened against various bacterial and mycobacterial strains.[164] Some compounds (**172b-172d**) exhibited good activity against *M. tb* and various atypical mycobacteria, while the 6-fluoro and 6-amino derivatives were less active, which suggest that the presence of electron withdrawing groups such as NO_2 is essential for activity. Compound **172b**, a di-*t*-butyl derivative was found to be the most active with $MIC_{50} = 0.5–1.5\ \mu M$, which was comparable to ciprofloxacin and ofloxacin ($MIC_{50} = 1–2\ \mu M$ and $MIC_{50} = 1.5–3\ \mu M$, respectively). Compounds **172c** and **172d** exhibited mild activity (MIC_{50} range $2 \geq 125\ \mu M$), followed by **172a** (MIC_{50} range $3.2 \geq 200\ \mu M$).



172a, R_1 = cyclopropyl, R_2 = cyclopropyl
172b, R_1 = *t*-butyl, R_2 = *t*- butyl
172c, R_1 = cyclopropyl, R_2 = *t*-butyl
172d, R_1 = *t*-butyl, R_2 = cyclopropyl



173a, R = cyclopropyl
173b, R = *t*-butyl

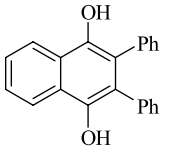


174a, R = cyclopropyl
174b, R = *t*-butyl

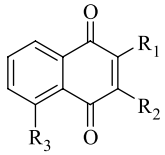
D. Quinone Derivatives as Anti-TB Agent

Quinones are found in eukaryotes and bacteria.[165] Benzoquinones, naphthoquinones, and anthraquinones are present as pigments in flora and fauna and as intermediates in cellular processes.[166] Quinones also act as antifungal agents, broad-spectrum antibacterials, anticancer agents, and protects plants.

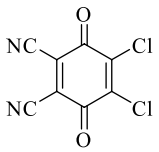
Some quinone-based compounds **175–178** were screened for their anti-TB activity against *M. tb* by Tran et al.[167] From the activity results it was clear that compounds with a 1,4-diketone quinone exhibit greater inhibition (**176a**) as compared to hydroquinol counterparts (**175**). Plumbagin (**176g**) with a hydroxyl group at position R3 found in some plants of the genus *Plumbago*[168,169] shows very good activity against rapidly growing nontuberculous mycobacteria (RGM) and minimum anaerobicidal concentration (MAC) (MIC = 66 μM). Juglone (**176b**) had an MIC of 72 μM against MAC. The other quinone compounds (**176a**, **176c**, **176h**, **176i**, **176j**) were bacteriostatic against *M. avium*, **176g** and **176a** are bacteriocidal. The growth of *M. avium* was affected by compounds **176g** and **176b** while other quinone derivatives showed no activity. *M. tb* showed resistance to compound **176g** while *M. avium* and *M. smegmatis* were sensitive toward it.



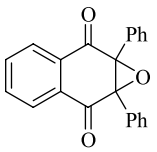
175



176a, R_1 = H, R_2 = H, R_3 = H
176b, R_1 = H, R_2 = H, R_3 = OH
176c, R_1 = CH_3, R_2 = CH_3, R_3 = H
176d, R_1 = Ph, R_2 = Ph, R_3 = H
176e, R_1 = CH_2CH_3, R_2 = CH_3, R_3 = H
176f, R_1 = $CH_2CH_2CH_3$, R_2 = H, R_3 = H
176g, R_1 = CH_3, R_2 = H, R_3 = OH
176h, R_1 = CH_2CH_3, R_2 = CH_2CH_3, R_3 = H
176i, R_1 = $CH_2CH{=}C(CH_3)_2$, R_2 = OH, R_3 = H
176j, R_1 = $CH_2CH_2CH_3$, R_2 = $CH_2CH_2CH_3$, R_3 = H
176k, R_1 = CH_3, R_2 = $(CH_2CH{=}CCH_3CH_2)_3CH_2CH{=}CCH_3$, R_3 = H

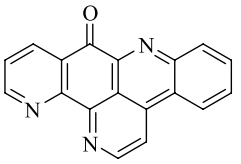


177



178

Copp et al. prepared several analogues of natural marine alkaloid *Ascididemin* containing quinone and enamine motif (**179–188**)[170] and evaluated them against *M. tb* H37Rv in BACTEC 12B media using the MABA. All the compounds showed good to mild inhibitory activity. Compounds **180** and **182** showed equal activity which indicates that the unsaturation in the side chain (**180**) hardly matters for determining the activity, whereas compound **181** exhibited poor activity when compared with **180** and **182**, which indicates the importance of side chain containing enamine moiety for the activity. Compound **183** exhibited better activity than the compound **184**, which indicates that the quinone moiety is important (**183**) for the activity. In compounds **185**, **186**, and **188** when one of the pyridine ring was replaced by benzene ring the activity increased. Furthermore, toxicity of these compounds was tested against Vero cell lines and compound **185** showed less cytotoxicity. This compound was further evaluated against SDR strains of *M. tb* but no cross-resistance was observed indicating that it acts differently. The compound **185** tested against clinical isolates of *M. avium* showed MIC value of 1–2 μg/mL. Subsequently, **185** was evaluated for in vivo activity in tested C57BL/6 interferon-γ gene depleted mice at a dose level of 300 mg/kg. It reduced bacterial load in the spleen by 0.5 log CFU, which was very poor when compared to the control (INH).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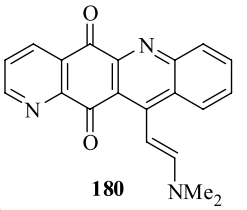
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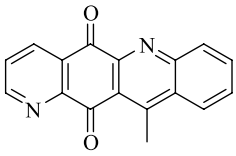
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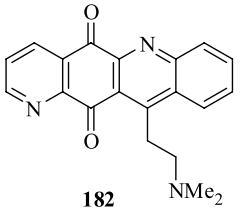
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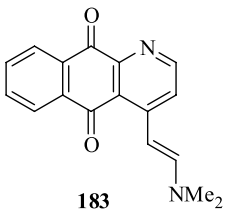
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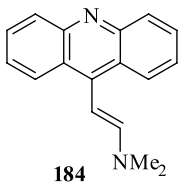
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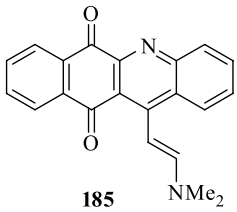
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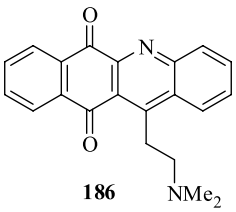
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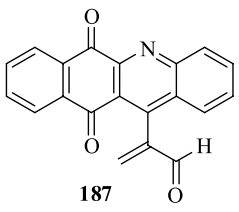
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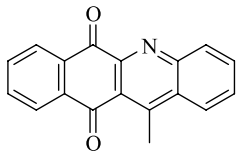
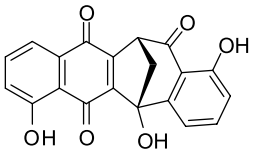

188

Wu et al. isolated engelharquinone (**189**), engelharquinone epoxide (**190**), engelharolide (**191**), and engelhardic acid (**192**) from *Engelhardia roxburghiana* in 2007.[171] Engelharquinone (**189**) exhibited moderate antitubercular activity (MIC $\leq$ 20 μg/mL) against *M. tb* 90–221387.

A series of synthetic and plant-derived naphthoquinone derivatives of the 7-methyljuglone have been synthesized and evaluated them for activity against *M. tb.*[172] The MIC of compounds **193a-193g**, **194a-194c**, **195a-195c**, **196a-196c**, **197a-197c**, and **198** against *M. tb* H37Rv were determined in liquid media. Among all the tested naphthoquinones, compounds **193b-193d**,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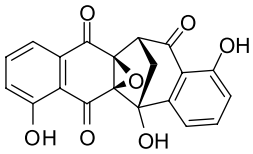
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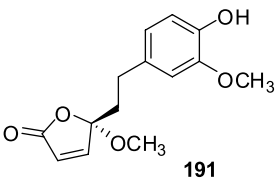
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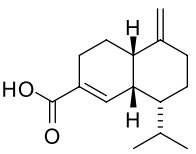
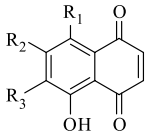
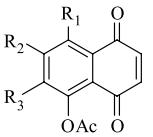

192

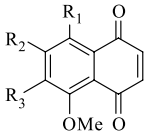
193g, **194a**, and **198** exhibited good activity out of which **193c** was found to be the most potent with MIC value of 0.5 μg/mL followed by its 5-acetoxy derivative **194a** (MIC = 2.5 μg/mL). In halogen-containing compounds it was observed that the activity increases with the bulkiness of the halogen atom and decreases with the increase in electronegativity. Interestingly the methyl group at 7 position (**193c**) has pronounced effect on activity rather than at 6 position. But the opposite SAR was observed in the case of 8-chloro derivatives (**193e** and **193g**). The methoxy and ethoxy derivatives (**195a-195c** and **196a-196c**) were found to be less active than their hydroxyl precursors (**193c**, **193e**, and **193g**). The tetraacetate derivatives (**197a-197c**) showed mild activity with MIC > 20 μg/mL, which was supposed be due to the lack of quinone moiety. Compounds with MIC < 20 μg/mL were also evaluated for their bactericidal activity. Out of 14 compounds **193a** and **194a** showed the highest bactericidal activity.



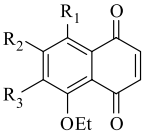
193a, R_1 = H, R_2 = H, R_3 = H
193b, R_1 = H, R_2 = H, R_3 = Me
193c, R_1 = H, R_2 = Me, R_3 = H
193d, R_1 = Br, R_2 = Me, R_3 = H
193e, R_1 = Cl, R_2 = Me , R_3 = H
193f, R_1 = F, R_2 = Me, R_3 = H
193g, R_1 = Cl, R_2 = H, R_3 = Me



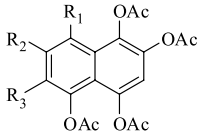
194a, R_1 = H, R_2 = Me, R_3 = H
194b, R_1 = Cl, R_2 = Me, R_3 = H
194c, R_1 = Cl, R_2 = H, R_3 = Me



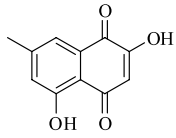
195a, R_1 = H, R_2 = Me, R_3 = H
195b, R_1 = Cl, R_2 = Me, R_3 = H
195c, R_1 = Cl, R_2 = H, R_3 = Me



196a, R_1 = H, R_2 = Me, R_3 = H
196b, R_1 = Cl, R_2 = Me, R_3 = H
196c, R_1 = Cl, R_2 = H, R_3 = Me



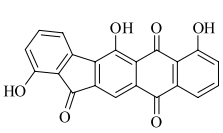
197a, R_1 = H, R_2 = Me, R_3 = H
197b, R_1 = Cl, R_2 = Me, R_3 = H
197c, R_1 = Cl, R_2 = H, R_3 = Me



198

Sturdy et al. isolated eucapsitrione (**199**), an anthraquinone derivative with an indeno-anthracene-trione skeleton, from the cyanobacterium *Eucapsis* sp. by bioassay-guided fractionation.[173] Eucapsitrione (**199**) showed anti-*M. tuberculosis* activity in the LORA and MABA with MIC values of 6.4 and 3.1 μM, respectively.[90,174] Virulent H37Rv strain was used in both assays. The MIC value was determined as the least drug concentration showing $\geq$ 90% inhibition.

Five new metabolites, fusaranthraquinone (**200a**), fusarnaphthoquinones A-C (**201–203**), and fusarone (**204**), were isolated by Rukachaisirikul et al. from the sea fan-derived fungi *Fusarium* spp. PSU-F14 and PSU-F135 along with some known compounds.[175] The structures were determined using spectroscopic techniques. The known octahydroanthraquinone **200c** exhibit antimycobacterial[176] activities against *M. tb* H37Ra with MIC value 38.57 μM. Compounds **205c** and **209c** exhibited milder activity than **200c** against *M. tb*.



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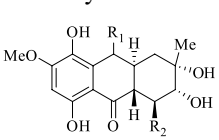
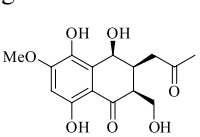


200a, R_1 = β-OH, R_2 = H
200b, R_1 = α-OH, R_2 = H
200c, R_1 = α-OH, R_2 = OH



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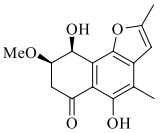

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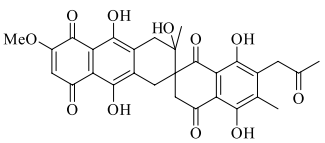

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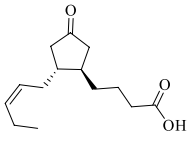

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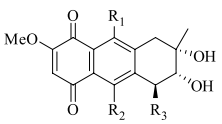
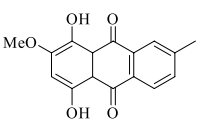


205a, R_1 = OH, R_2 = R_3 = H
205b, R_1 = R_2 = R_3 = OH
205c, R_1 = R_3, R_2 = OH



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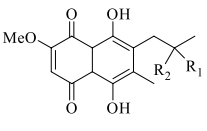
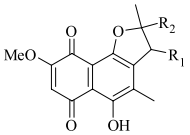
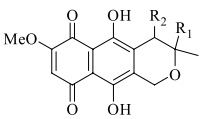


207a, R_1 = H, R_2 = OH
207b, R_1+R_2 = O



208a, R_1+R_2 = double bond
208b, R_1 = R_2 =H



209a, R_1 = OH, R_2 = H
209b, R_1 = OMe, R_2 = H
209c, R_1+R_2 = double bond

E. Nitroimidazole Derivatives as Anti-TB Agent

The compounds belonging to nitroimidazole class are primarily used for the treatment of infections caused by anaerobic bacteria. Nitroimidazoles are very important class of therapeutics, which have shown anti-TB effects and two compounds PA824 and OPC6768 (Fig. 5) are currently in the clinical trials.[177] Though the pO_2 of TB lesions is less than 10 mmHg and they are hypoxic in nature,[178] most of the antitubercular drugs interferes with aerobic growth and are less effective for hypoxia so they are taken for longer duration of time.[179] Metronidazole (MTZ), a 5-nitroimidazole (Fig. 5), is widely used against anaerobic bacterial diseases.[180] It has been known for almost 15 years that under low-oxygen conditions *M. tb* cultures become sensitive on treatment with MTZ.[181,182] However, MTZ has no activity against aerobic populations of *M. tb* and is not used in the treatment of human TB. The 4-nitroimidazoles based on MTZ originally synthesized as radiosensitizing agents[183] were later found to have significant activity against *M. tb*.[184,185] From a large number of 2,3-dihydro-6-nitroimidazo[2,1-*b*]oxazole derivatives, compound 2-ethyl-6-nitro-2,3-dihydroimidazo[2,1-*b*]oxazole (CGI-17341) (Fig. 5) emerged as an interesting compound with potent in vitro and in vivo activity against *M. tb* strains. The nitroimidazole (*S*)-2-nitro-6-(4-(trifluoromethoxy)-benzyloxy)-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (PA824)[186] is a promising new class of compound, which shows antitubercular activity under hypoxic conditions, no cross-resistance to current TB drugs and efficacy in the mouse model of TB infection. PA824 is currently being developed as a drug molecule by the Global Alliance for TB Drug Development.[187] PA824 has an aerobic MIC of 0.4 μM, anaerobic activity at 8–16 μM and efficacy in the mouse model of TB infection. PA824 is a prodrug and needs bioreductive activation to show its anti-TB activity. Both PA824 and OPC67683 are sparingly soluble in water. Due to low water solubility, PA824 is administered orally as complex formulation in MC or CM2 while OPC67683 requires formulation in 5% gum arabic.[188]

The synthesis and anti-TB activity of two diastereomers of the 7-methyl-nitroimidazo-oxazine (**210** and **211**) were reported by Li et al. in 2008,[188] and these compounds exhibited antitubercular activities similar to PA-824 under aerobic conditions. The MIC values for compound **210**, **211**, and PA824 were 0.2–0.4 μM. Both the methyl-oxazines require reduced coenzyme F420. Some of the mutated H37Rv strains (T3 and 5A1) showed cross-resistance because either they could not reduce this cofactor or they are deficient in its biosynthesis. The nitroreductase Rv3547 also reduces these nitroimidazoles.[189] The MAC for compounds **210** and **211**

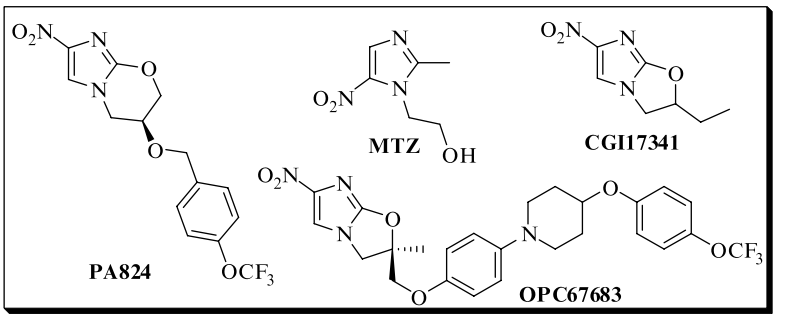
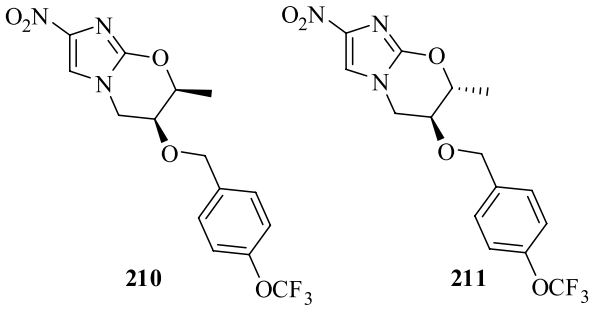


Figure 5. Antitubercular nitroimidazoles.

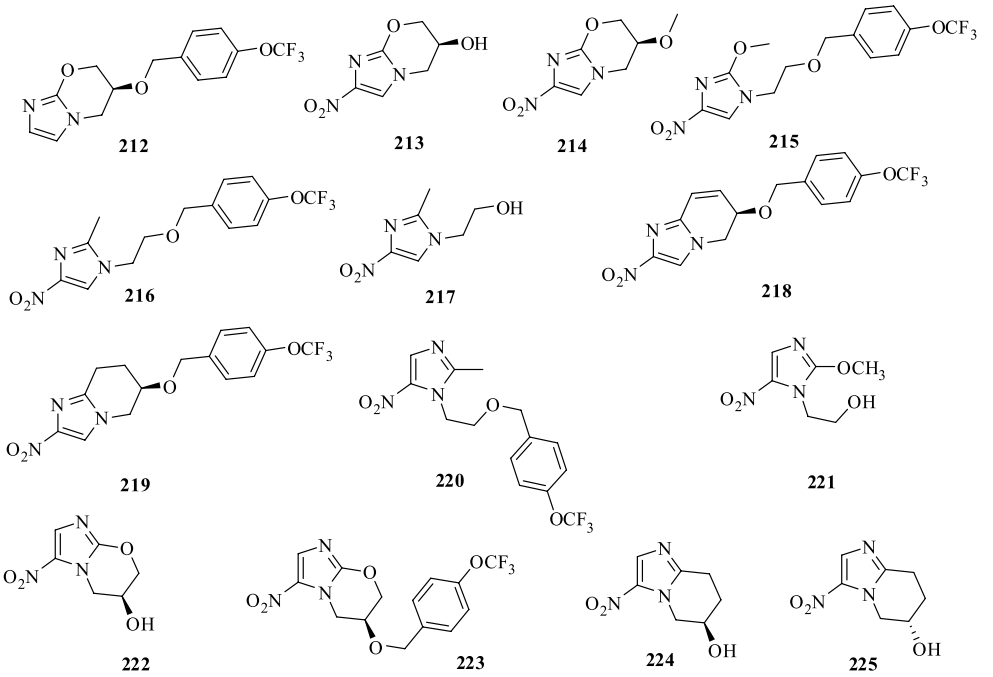
were equivalent to PA824. Both the compounds were evaluated against wild-type H37Rv and three different mutants resistant to PA824.



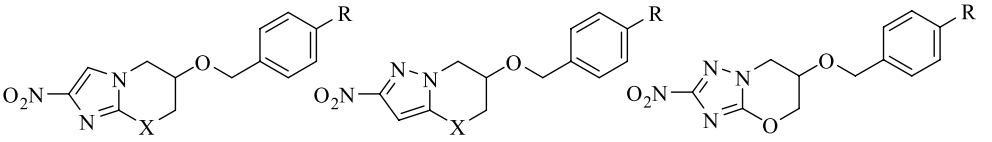
210 **211**

In 2009, Kim et al. synthesized a large number of derivatives of 4- and 5-nitroimidazoles (**212–225**) and evaluated their antitubercular activity.[190] In order to understand the importance of trifluoromethyl benzyl ether side chain on activity of 4-nitroimidazoles they prepared compounds **213** and **214** without side chain containing benzyl group. Compounds **213** and **214** resulted in complete loss of activity when compared to PA824. Compound **215**, which is an open chain analogue of PA824 showed considerable aerobic activity with MIC 6.25 μg/mL, whereas anaerobic activity was more significantly decreased. Compound **216** having methyl group at 2 position instead of OCH_3 group exhibited very less activity against aerobic bacteria than compound **215**, which suggest the importance of oxygen atom at 2 position of 4-nitroimidazoles. The compound **217**, which looks like MTZ (5-nitro), showed no activity against both aerobic and anaerobic bacteria and from the activity profile of **217** and **216** it can be concluded that not only the side chain but the position of NO_2 group is significant for anaerobic activity of these compounds.

The compound **219** in which the oxygen atom of oxazine ring was replaced by methylene unit displayed significant aerobic activity (30 times less than PA824) with negligible anaerobic activity. Interestingly, compound **218** with double bond, showed equal activity to **219** whereas the anaerobic activity was ~4 times better than its saturated analogues. On the other hand, 5-nitro imidazole with lipophilic side chain (**220**), having the benzyl ether and MTZ core structure, failed to show any aerobic activity but exhibited a significant decrease in anaerobic activity relative to MTZ. This observation clearly indicates that the lipophilic side chain is important for both aerobic and anaerobic activity in case of 4-nitroimidazole, but in 5-nitroimidazoles lipophilic side chain does not confer aerobic activity while anaerobic activity decreases to some extent. Compound **221** having OCH_3 group at 2 position instead of CH_3 as in MTZ was found inactive against anaerobic bacteria relative to the parent MTZ, but this feature is essential in 4-nitroimidazole for aerobic and anaerobic activities. Compound **222** showed aerobic activity and weak anaerobic activity. This rigid bicyclic structure showed both aerobic and anaerobic activity compared to compound **221**. Compound **223**, a 5-NO_2 isomer of PA824 displayed good activity, but slightly less than PA824 against both aerobic (4–8 μM) and anaerobic (31.25 μM) bacteria.



In 2009, Thompson et al. synthesized a series of bicyclic nitroheterocycles (**226–228**) and evaluated them for their ability to inhibit *M. tb* in two assays (MABA and LORA).[191] When compared to the parent molecule PA824, compound **226b** an imidazothiazine derivative showed almost same activity in terms of potency against MABA and slightly less activity against LORA assay. In imidazooxazine series, the benzyloxybenzyl ether side chain containing compound **226a** displayed a marginal increase in the potency, against both the assay studied in comparison to PA824. However, in the case of imidazothiazine the activity of compound **226c** was not significantly enhanced when compared to **226b**. Compounds **226d-226g** displayed markedly reduced activity in which S atom is oxidized to SO or SO_2. The imidazopyridine **226i** exhibited very weak activity (MIC for MABA 126 μM and for LORA > 128 μM) while the benzyloxybenzylether analogue was even less active. Replacement of imidazole ring of PA824 by pyrazole (**227a**) or triazole ring (**228a**) also lead to compounds with weak activity (MIC = 128 μM). Pyrazolopyrimidine analogue (**227c-227f**) also showed marginal activity (MIC = 128 μM). From the activity profile it can be concluded that lipophilic side chain and nitroheterocyclic core are important for activity.



226a, X = O, R = OCH_2Ph
226b, X = S, R = OCF_3
226c, X = S, R = OCH_2Ph
226d, X = SO, R = OCF_3
226e X = SO, R = OCH_2Ph
226f, X = SO_2, R = OCF_3
226g, X = SO_2, R = OCH_2Ph
226h, X = CH_2, R = OCF_3
226i, X = CH_2, R = OCH_2Ph
226j, X = NH, R = OCF_3

227a, X = O, R = OCF_3
227b, X = O, R = OCH_2Ph
227c, X = NH, R = OCF_3
227d, X = NH, R = OCH_2Ph
227e, X = NMe, R = OCF_3
227f, X = NMe, R = OCH_2Ph

228a, R = (S)-OCF_3
228b, R = (R)-OCF_3
228c, R = OCH_2Ph

Table X. Antimycobacterial Activity of *Ortho*-Linked Biphenyl Analogues (**229a-229m**) of PA824

	MIC (μM)			MIC (μM)	
Comp no.	LORA	MABA	Comp no.	LORA	MABA
229a	2.5 ± 0.5	0.64 ± 0.32	**229h**	19 ± 5	8.4 ± 1.4
229b	6.2 ± 0.3	1.2 ± 0.4	**229i**	4.3 ± 0.7	2.3 ± 0.4
229c	3.0 ± 0.6	0.62 ± 0.17	**229j**	36 ± 13	17 ± 1
229d	8.2 ± 2.9	0.80 ± 0.31	**229k**	3.4 ± 0.2	1.3 ± 0.4
229e	6.3 ± 0.7	1.9 ± 0.7	**229l**	3.8 ± 0.2	1.8 ± 0.3
229f	3.2 ± 0.3	0.81 ± 0.07	**229m**	3.1 ± 0.8	1.6 ± 0.4
229g	3.4 ± 0.2	1.2 ± 0.3	PA824	2.6 ± 1.4	0.50 ± 0.30

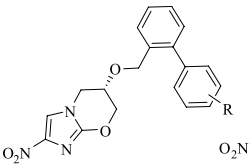
Table XI. Antimycobacterial Activity of Selected *Meta*-Linked Biphenyl Analogues (**230**) of PA824

	MIC (μM)			MIC (μM)	
Comp no.	LORA	MABA	Comp no.	LORA	MABA
230a	2.1 ± 0.8	0.095 ± 0.015	**230o**	2.2 ± 0.5	0.11 ± 0.05
230c	2.7 ± 0.8	0.18 ± 0.03	**230p**	2.8 ± 1.0	0.06 ± 0.01
230e	3.7 ± 2.1	0.17 ± 0.01	**230q**	1.9 ± 0.4	0.30 ± 0.19
230f	3.7 ± 0.22	0.30 ± 0.16	**230r**	1.5 ± 0.2	0.36 ± 0.12
230j	1.4 ± 0.1	0.070 ± 0.037	**230t**	0.93 ± 0.08	0.095 ± 0.025
230k	3.8 ± 0.7	0.077 ± 0.034	**230u**	2.2 ± 0.5	0.19 ± 0.10
230l	2.9 ± 1.4	0.12 ± 0.01	**230v**	3.2 ± 0.4	0.12 ± 0.01

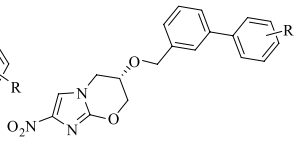
In 2010, Palmer et al. synthesized a series of biphenyl analogues of PA824 and evaluated them for their antitubercular activity against both replicating (MABA) and nonreplicating (LORA) cultures of *M. tb* (**229–235**).[192] The MIC values for the selected *ortho*-, *meta*- and *para*-linked biphenyl analogues are shown in table X, XI, and XII, respectively. The SAR revealed that *para*-linked biphenyl analogues (Table XII) were more active then the *meta*- and *ortho*-linked derivatives (Tables XI and X). Most of the *para*-linked and some *meta*-linked biphenyl analogues were found to exhibit improved activity than the reference compound PA824 in both LORA and MABA assays. Among the *para*-linked analogues compounds **234a** and **234b** were found to be the most active against MABA with MIC values of 0.015 μM, whereas compound **235o** was the most active against LORA. Some of the *para*-linked biphenyl analogues were also evaluated for in vivo activity taking PA824 as a reference compound. Compounds **234e**, **234o**, **235g**, **235e**, **235j**, **235o**, and **235q**, having lipophilic and electron withdrawing groups, were found to be more potent than the reference compound. Compounds **234o**, **235j**, and **235o** were the best compounds among these with >200 times potency in comparison to the reference compound.

Table XII. Antimycobacterial Activity of Selected *Para*-Linked Biphenyl Analogues (**231–235**) of PA824

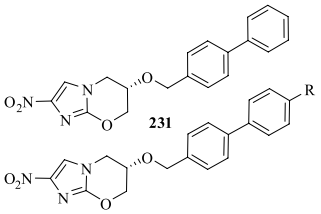
	MIC (μM)			MIC (μM)	
Comp no.	LORA	MABA	Comp no.	LORA	MABA
231	3.9 ± 2.0	0.045 ± 0.005	**234y**	0.77 ± 0.24	0.05 ± 0.01
232d	1.4 ± 0.3	0.065 ± 0.005	**235e**	0.72 ± 0.29	0.045 ± 0.015
232e	0.82 ± 0.19	0.03 ± 0	**235f**	0.74 ± 0.04	0.055 ± 0.005
232g	0.78 ± 0.16	0.08 ± 0.02	**235g**	0.78 ± 0.03	0.04 ± 0.01
232h	0.97 ± 0.08	0.035 ± 0.005	**235h**	1.4 ± 0.1	0.03 ± 0
232i	1.8 ± 0.1	0.06 ± 0	**235i**	0.97 ± 0.44	0.06 ± 0.03
233a	2.2 ± 0.7	0.045 ± 0.005	**235j**	0.90 ± 0.12	0.03 ± 0
233b	1.6 ± 0.5	0.06 ± 0.01	**235k**	0.95 ± 0.15	0.040 ± 0.014
233j	1.4 ± 0.6	0.077 ± 0.026	**235l**	1.9 ± 0.2	0.035 ± 0.005
233n	0.95 ± 0.04	0.077 ± 0.026	**235m**	1.6 ± 0.1	0.045 ± 0.015
234a	1.4 ± 0.5	0.015 ± 0.005	**235n**	1.9 ± 0.8	0.040 ± 0.014
234b	2.7 ± 0.6	0.015 ± 0.005	**235o**	0.34 ± 0.16	0.03 ± 0
234e	1.4 ± 0.5	0.03 ± 0.01	**235p**	1.5 ± 0.1	0.045 ± 0.015
234f	0.58 ± 0.33	0.025 ± 0.005	**235q**	1.1 ± 0.4	0.03 ± 0
234l	0.73 ± 0.22	0.04 ± 0.01	**235t**	0.86 ± 0.22	0.04 ± 0.01
234n	2.7 ± 1.2	0.04 ± 0.01	**235v**	0.76 ± 0.26	0.04 ± 0.01
234o	1.3 ± 0.1	0.035 ± 0.015	**235x**	1.3 ± 0.4	0.045 ± 0.015
234u	0.63 ± 0.30	0.060 ± 0.016	**235y**	0.87 ± 0.13	0.045 ± 0.025



229a, R = H
229b, R = 2-OCF_3
229c, R = 3-F
229d, R = 3-CN
229e, R = 3-OCF_3
229f, R = 3-SMe
229g, R = 4-F
229h, R = 4-CN
229i, R = 4-OCF_3
229j, R = 4-COMe
229k, R = 4-SMe
229l, R = 3-F, 4-OMe
229m, R = 3,4-benzo

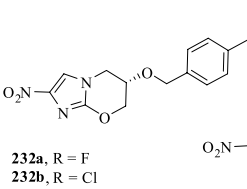


230a, R = H; **230b**, R = 2-OCF_3;
230c, R = 3-F; **230d**, R = 3-CF_3;
230e, R = 3-CN; **230f**, R = 3-OH;
230g, R = 3-OCF_3; **230h**, R = 3-$O(CH_2)_3OH$;
230i, R = 3-$O(CH_2)_3$Nmorph; **230j**, R = 3-SMe;
230k, R = 4-F; **230l**, R = 4-CF_3;
230m, R = 4-CN; **230n**, R = 4-OH;
230o, R = 4-OCF_3; **230p**, R = 4-OCF_2H;
230q, R = 4-COMe; **230r**, R = 4-$O(CH_2)_3OH$;
230s, R = 4-$O(CH_2)_3$Nmorph; **230t**, R = 4-SMe;
230u, R = 3-F, 4-OMe; **230v**, R = 3,4-benzo

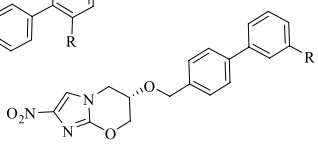


231

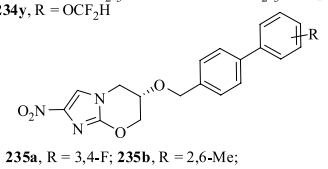
234a, R = F; **234b**, R = Cl;
234c, R = OH; **234d**, R = OMe;
234e, R = CF_3; **234f**, R = CN;
234g, R = *i*-Pr; **234h**, R = *t*-Bu;
234i, R = CHO; **234j**, R = Ph;
234k, R = $CONH_2$; **234l**, R = COMe;
234m, R = O*i*Pr; **234n**, R = OPh;
234o, R = OCF_3; **234p**, R = SMe;
234q, R = SO_2Me; **234r**, R = NH_2;
234s, R = CH_2OH; **234t**, R = CH_2OtBu;
234u, R = CH_2NHPh; **234v**, R = $O(CH_2)_2OH$;
234w, R = $O(CH_2)_3OH$; **234x**, R = $O(CH_2)_3$Nmorph;
234y, R = OCF_2H



232a, R = F
232b, R = Cl
232c, R = OH
232d, R = OMe
232e, R = OEt
232f, R = CF_3
232g, R = CHO
232h, R = OCF_3
232i, R = OPh
232j, R = $O(CH_2)_3OH$
232k, R = SMe



233a, R = F; **233b**, R = Cl;
233c, R = OH; **233d**, R = OMe;
233e, R = CN; **233f**, R = CHO;
233g, R = CF_3; **233h**, R = Ph;
233i, R = *i*Pr; **233j**, R = OCF_3;
233k, R = OCH_2Ph; **233l**, R = NH_2;
233m, R = NO_2; **233n**, R = SMe;
233o, R = $O(CH_2)_2OH$; **233p**, R = $O(CH_2)_3OH$;
233q, R = $O(CH_2)_2NMe_2$; **233r**, R = $CONH_2$



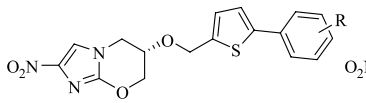
235a, R = 3,4-F; **235b**, R = 2,6-Me;
235c, R = 2,6-OMe; **235d**, R = 2-F, 6-OMe;
235e, R = 2-F, 4-OCF_3; **235f**, R = 2-Cl, 6-OMe;
235g, R = 2-Cl, 4-OCF_3; **235h**, R = 2-Cl, 4-CF_3;
235i, R = 3-Cl, 4-CF_3; **235j**, R = 3-Cl, 4-CF_3;
235k, R = 3-OCF_3, 4-Cl; **235l**, R = 3-CF_3, 4-Cl;
235m, R = 3-NO_2, 4-OCF_3; **235n**, R = 3-F, 4-OMe;
235o, R = 3-F, 4-OCF_3; **235p**, R = 3-OMe, 4-F;
235q, R = 3-OCF_2H, 4-Cl; **235r**, R = 3-OH, 4-Cl;
235s, R = 3,5-OMe; **235t**, R = 2-OMe, 3,5-F;
235u, R = 2,6-Me, 4-OMe; **235v**, R = 3,4,5-F;
235w, R = 3,5-Me, 4-OH; **235x**, R = 3,5-F, 4-OMe;
235y, R = 3,4-benzo

Table XIII. Antimycobacterial Activity of Selected Arylheterocyclic Analogues (**236–247**) of PA824

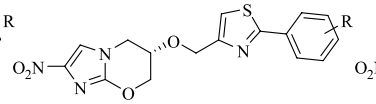
	MIC (μM)			MIC (μM)	
Comp no.	LORA	MABA	Comp no.	LORA	MABA
236a	1.9 ± 0.5	0.05 ± 0.01	**242d**	1.2 ± 0.5	0.55 ± 0.19
236b	1.0 ± 0.4	0.16 ± 0	**244b**	3.4 ± 0.2	0.11 ± 0.02
236c	1.7 ± 0.6	0.055 ± 0.005	**244d**	3.3 ± 0.2	0.075 ± 0.015
236e	1.0 ± 0.3	0.06 ± 0	**244e**	8.7 ± 1.2	0.86 ± 0.13
236g	4.5 ± 0.7	0.22 ± 0.02	**245a**	2.2 ± 0.9	0.25 ± 0.04
236h	1.7 ± 0.2	0.28 ± 0.16	**245b**	1.4 ± 0.2	0.17 ± 0.06
236i	4.4 ± 2.3	0.05 ± 0	**245c**	2.1 ± 1.2	0.05 ± 0.01
237a	2.8 ± 1.0	0.35 ± 0.13	**245d**	1.6 ± 0.2	0.03 ± 0
237b	3.2 ± 0.3	0.67 ± 0.31	**246b**	3.4 ± 0.1	0.29 ± 0.17
237e	1.7 ± 0.3	0.20 ± 0.04	**246c**	1.4 ± 0.6	0.20 ± 0.03
238c	9.7 ± 4.0	0.65 ± 0.16	**246d**	1.3 ± 0.4	0.035 ± 0.005
239c	0.58 ± 0.20	0.06 ± 0	**247a**	3.8 ± 0.7	0.077 ± 0.034
240c	1.8 ± 0.2	0.15 ± 0.03	**247b**	2.9 ± 1.4	0.12 ± 0.01
241a	7.2 ± 2.4	0.11 ± 0.02	**247c**	4.8 ± 1.1	0.23 ± 0.01
241b	1.0 ± 0.1	0.045 ± 0.005	**247d**	2.2 ± 0.5	0.11 ± 0.05
241c	0.61 ± 0.41	0.05 ± 0.01	**247e**	2.2 ± 0.5	0.19 ± 0.10

Encouraged by the activity of biaryl analogues of PA824, Thompson et al. synthesized heterobiaryl analogues (**236–247**), in which the proximal phenyl ring was replaced by various 5-membered heterocycles and evaluated them for antitubercular activity (Table XIII).[193] The 5-aryl thiophene derivatives (**236a-236k**) were found to be almost equally active to their corresponding biaryls (**247a-247e**). The mean MIC values for compounds **236a-236e** were 0.24 and 1.6 μM against MABA and LORA, respectively similar to biaryl compounds **247a-247e** that showed MIC values of 0.15 μM and 3.2 μM, respectively. The aza-containing compounds **236g-236k** were also synthesized to understand the effect of N atom on the anti-TB activity. These compounds displayed low MIC values of 0.46 μM and 3 μM against MABA and LORA, respectively (Table XIII). Out of these, compound **236i** showed exceptionally high MIC value of 0.05 μM toward MABA. On the other hand, the MIC values of 2-aryl thiazoles derivatives (**237a-237f**) were comparable to the corresponding biaryl analogues (**247a-247e**) against LORA, whereas ~5 times less potent against MABA assay. The 2-aryl-1-methyl imidazole derivatives (**238a-238e**) were hydrophilic but they showed poor activity than their corresponding biaryl analogues.

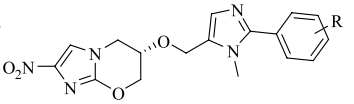
The other pyrazoles (**239b**, **239c**, **240b**, **240c**, **241b**, **241c**), which were slightly less hydrophilic showed varied activity patterns. Compounds **239a-239c** showed MIC identical to their biaryl analogues, compound **239c** being highly potent in both the assays with MIC values of 0.06 and 0.58 μM in MABA and LORA, respectively. The 1-aryl-4-linked pyrazole analogues **240a-240c** were also equally potent toward LORA but were ~3 times less potent in MABA assay. The 1-aryl-3-linked pyrazole derivatives (**241a-241c)** showed very potent activity with compound **241c** being the most active in both the assays.



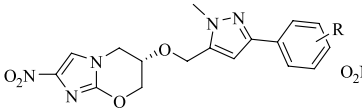
236a, R = 4-F
236b, R = 4-CF_3
236c, R = 4-CN
236d, R = 4-OCF_3
236e, R = 3-F, 4-OCF_3
236f, R = 4-OCF_2H
236g, R = 3-aza, 4-OCH_3
236h, R = 2-aza, 5-CF_3
236i, R = 3-aza, 4-CF_3
236j, R = 3-aza, 4-F
236k, R = 3-aza, 5-F



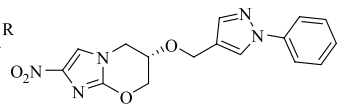
237a, R = 4-F
237b, R = 4-CN
237c, R = 4-CF_3
237d, R = 4-OCF_3
237e, R = 3-F, 4-OCF_3
237f, R = 3-aza, 4-OCH_3



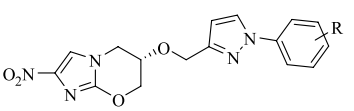
238a, R = 4-F
238b, R = 4-CN
238c, R = 4-CF_3
238d, R = 4-OCF_3
238e, R = 3-F, 4-OCH_3



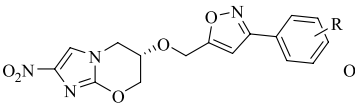
239a, R = 4-F
239b, R = 4-CF_3
239c, R = 4-OCF_3



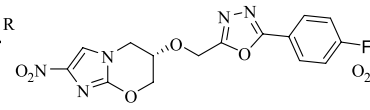
240a, R = 4-F
240b, R = 4-CF_3
240c, R = 4-OCF_3



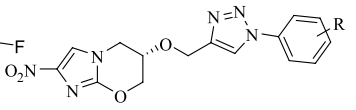
241a, R = 4-F
241b, R = 4-CF_3
241c, R = 4-OCF_3



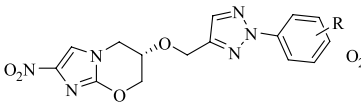
242a, R = 4-F
242b, R = 4-CN
242c, R = 4-CF_3
242d, R = 4-OCF_3
242e, R = 3-F, 4-OCF_3
242f, R = 3-aza, 4-OCF_3



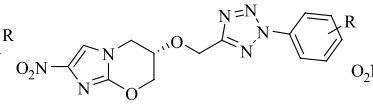
243



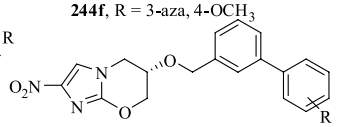
244a, R = 4-F
244b, R = 4-CF_3
244c, R = 4-CN
244d, R = 4-OCF_3
244e, R = 3-F, 4-OCH_3
244f, R = 3-aza, 4-OCH_3



245a, R = H
245b, R = 4-F
245c, R = 4-CF_3
245d, R = 4-OCF_3



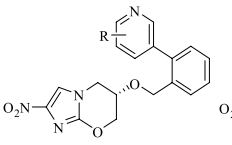
246a, R = H
246b, R = 4-F
246c, R = 4-CF_3
246d, R = 4-OCF_3



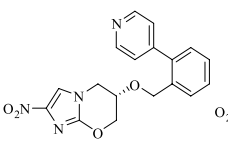
247a, R =4-F
247b, R = 4-CF_3
247c, R = 4-CN
247d, R = 4-OCF_3
247e, R = 3-F, 4-OCF_3

The 3-aryl-isooxazole derivatives (**242a-242f)** were found to be more hydrophilic than pyrazole class of compounds but showed less potency in MABA, whereas considerably good activity in LORA assay. The 5-aryl-1,3,4-oxadiazole (**243**) being the most hydrophilic but yet displayed the weakest activity among all the compounds tested. Two different series based on 1,2,3-triazole moiety (**244a-244f** and **245a-245d**) were evaluated. Compounds **245a-245d** were found more active than **244a-244f** and exhibited ~2 times better activity in both the assays and compound **245d** was found to be highly active in the series in MABA assay (MIC = 0.03 μM). The two aryl tetrazole analogues (**246a-246d)** also showed comparable activity to triazole and biaryl analogues with compound **246d** being most active out of the four tetrazoles with MIC values of 0.035 and 1.3 μM in MABA and LORA assays, respectively.

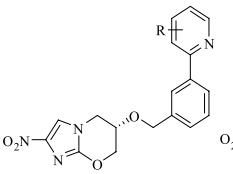
Encouraged by the activity of the biphenyl class (**229–235**), Thompson et al. also synthesized a series of heterocyclic analogues of the biphenyl class to improve the aqueous solubility and metabolic stability and efficacy.[194] The phenyl group of the biaryl were replaced by pyridine, pyridazine, pyrazine, or pyrimidine (**248–265**). Most of the compounds having pyridine ring instead of phenyl showed better activity and aqueous solubility. Two compounds **253b** and **254b** showed better efficacy than PA824 in mouse models.



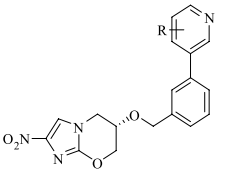
248a, R = H
248b, R = 4-F
248c, R = 4-OCH_3
248d, R = 4-OCH_2Ph



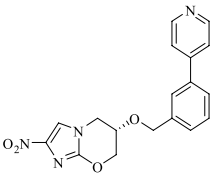
249



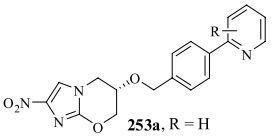
250a, R = H
250b, R = 4-CF_3
250c, R = 4-OCF_2H



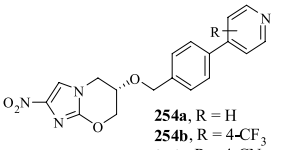
251a, R = H
251b, R = 4-CF_3
251c, R = 4-F
251d, R = 4-OCH_3
251e, R = 4-OCH_2Ph



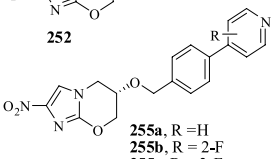
252



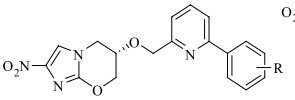
253a, R = H
253b, R = 4-CF_3
253c, R = 4-CF_3, 6-Cl
253d, R = 4-CN
253e, R = 3-F
253f, R = 4-F
253g, R = 4-OCF_2H
253h, R = 4-OCH_3



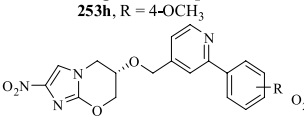
254a, R = H
254b, R = 4-CF_3
254c, R = 4-CN
254d, R = 4-F
254e, R = 5-F
254f, R = 4-NH_2
254g, R = 4-OCF_2H
254h, R = 4-OCH_3
254i, R = 4- OCH_2Ph



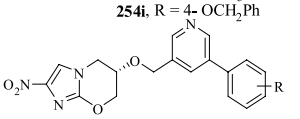
255a, R =H
255b, R = 2-F
255c, R = 3-F



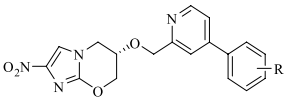
256a, R = 4-CF_3
256b, R = 4-CN
256c, R = 4-F
256d, R = 4-OCF_3
256e, R = 4-OCF_2H
256f, R = 3-F, 4-OCH_3
256g, R = 3-aza, 3-OCH_3



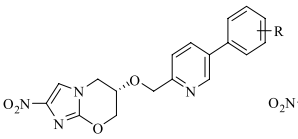
257a, R = 4-CF_3
257b, R = 4-CN
257c, R = 4-F
257d, R = 4-OCF_3
257e, R = 4-OCF_2H
257f, R = 3-F, 4-OCH_3
257g, R = 3-aza, 4-OCH_3



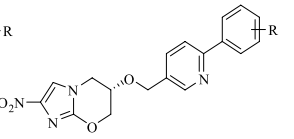
258a, R = 4-CF_3
258b, R = 4-CN
258c, R = 4-F
258d, R = 4-OCF_3
258e, R = 4-OCF_2H
258f, R = 3-F, 4-OCH_3
258g, R = 3-aza, 4-OCH_3



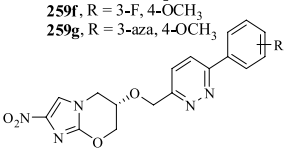
259a, R = 4-CF_3
259b, R = 4-CN
259c, R = 4-F
259d, R = 4-OCF_3
259e, R = 4-OCF_2H
259f, R = 3-F, 4-OCH_3
259g, R = 3-aza, 4-OCH_3



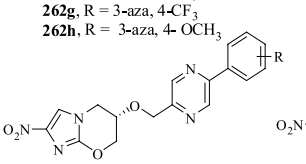
260a, R = 4-CF_3
260b, R = 4-CN
260c, R = 4-F
260d, R = 4-OCF_3
260e, R = 4-OCF_2H
260f, R = 3-F, 4-OCH_3
260g, R = 2-Cl, 4-OCF_3
260h, R = 3-Cl, 4-OCF_3
260i, R = 2-F, 4-OCF_3
260j, R = 3-F, 4-OCF_3
260k, R =3-OCF_3, 4-Cl
260l, R = 2-aza, 3-F
260m, R =2-aza, 4-CF_3
260n, R = 3-aza, 4-CF_3
260o, R = 3-aza, 4-F
260p, R =3-aza, 5-F
260q, R = 3-aza, 4-OCH_3
260r, R = 4-aza, 2-F
260s, R = 4-aza, 3-F



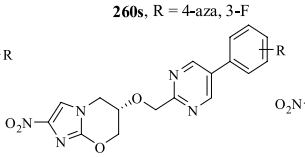
261a, R = 4-CF_3
261b, R = 4-CN
261c, R = 4-F
261d, R = 4-OCF_3
261e, R = 4-OCF_2H
261f, R = 3-F, 4-OCH_3
261g, R = 2-Cl, 4-OCF_3
261h, R = 3-Cl, 4-OCF_3
261i, R = 2-F, 4-OCF_3
261j, R = 3-F, 4-OCF_3
261k, R = 3-OCF_3, 4-Cl
261l, R = 3-aza, 4-CF_3
261m, R = 3-aza, 4-F
261n, R = 3-aza, 4-OCH_3



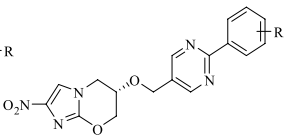
262a, R = 4-CF_3
262b, R = 4-CN
262c, R = 4-F
262d, R = 4-OCF_3
262e, R = 4-OCF_2H
262f, R = 3-F, 4-OCH_3
262g, R = 3-aza, 4-CF_3
262h, R = 3-aza, 4- OCH_3



263a, R = 4-CF_3
263b, R = 4-F
263c, R = 4-OCF_3
263d, R = 4-OCF_2H
263e, R = 3-aza, 4-CF_3



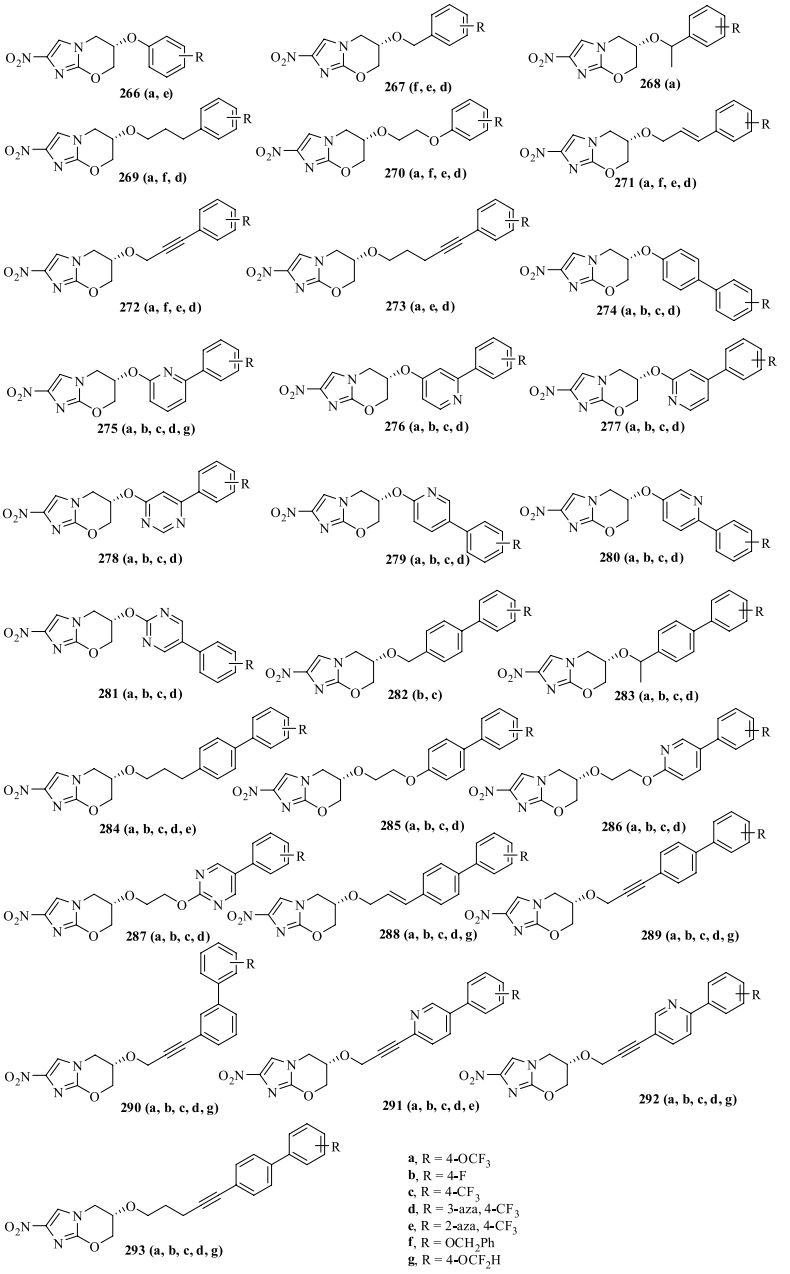
264a, R = 4-CF_3
264b, R = 4-F
264c, R = 4-OCF_3
264d, R = 4-OCF_2H
264e, R = 3-aza, 4-CF_3



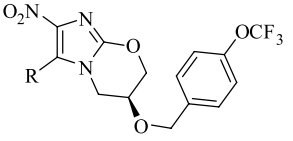
265a, R = 4-CF_3
265b, R = 4-F
265c, R = 4-OCF_3
265d, R = 4-OCF_2H
265e, R = 3-aza, 4-CF_3

Very recently, Thompson et al. have also reported the synthesis and anti-TB activity of ether analogues of PA824 under MABA and LORA conditions (**266–293**) against *M. tb*.[195] The two lead compounds PA824 (MIC = 0.50 μM) and **234o** (MIC = 0.035 μM) discussed above on modification at the benzylic position resulted into compounds **268a** (MIC = 0.60 μM) and **283a** (MIC = 0.19 μM) showed no significant improvement in aqueous solubility.

The *para*-linked biaryls showed better activity than the *meta*-linked analogues. The biphenyls (**274a-274d**) and 5-phenyl-2-pyridyls (**279a-279d**) showed slightly better activity in MABA. The 6-phenyl-3-pyridyl (**280a-280d**) analogues were found to have very good LORA activity. Compounds **274a** (MIC = 0.09) and **280a** (MIC = 0.14 μM, respectively) showed very good activity among the aryl ethers synthesized.



Bollo et al. synthesized novel analogues of PA824 with Cl, Br, NH_2, and CN substituents at the 5 position of the imidazole ring (**294a-294e**) and evaluated them for antitubercular activity using PA824 as reference compound.[196] Compounds **294b** and **294c** exhibited 30 times lower activity against wild type *M. tb* as compared to PA824. Whereas, cyano and amino derivatives were found to be inactive. Compounds **294b** and **294c** have also shown activity against class B1 (can not produce coenzyme F420) and C (can not produce Ddn enzyme) mutant *M. tb* strains while PA824 was found to be inactive against these strains. The activity of compounds **294b** and **294c** was found to be independent of the biosynthesis of F420.

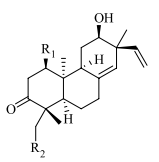


294a, R = H; **294b**, R = Cl;
294c, R = Br; **294d**, R = NH_2;
294e, R = CN

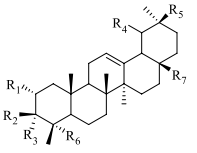
F. Terpenoids as Anti-TB Agent

Terpenoids are the largest class of natural products. These are the main constituent of many spices, cosmetics, food additives, flavoring agents, and perfumes. This class of compounds also possess a wide range of biological activities such as antimalarial (artemisinin) and anticancer (taxol).

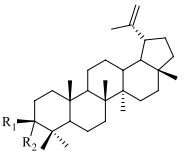
Woldemichael et al. reported the isolation of four new compounds **295a**, **295b**, **298b**, and **300a** in the 1:1 mixture of methanol and dichloromethane fraction, from the extract of the parts of plant *Sapium haematospermum*.[197] This fraction showed activity against *M. tb*. They also isolated some known compounds as well, which includes some flavonol glucosides and triterpene derivatives from this fraction. The four compounds **295a**, **296a**, **297b**, and **298a** exhibited very good activity and their MICs were 4, 12.2, 13.4, and 8 μg/mL, respectively. These compounds were also found to be slightly cytotoxic. The IC_{50} in Vero cells of compounds **295a**, **296a**, **297b**, and **298a** were 104.8, 127.2, 127.2, and 102.4 μg/mL, respectively. Other compounds **296c**, **296d**, **297a**, **298b**, **300a**, and **300b** were found to be inactive having MIC > 128 μg/mL.



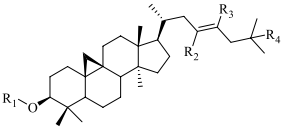
295a, R_1 = OH, R_2 = H
295b, R_1 = H, R_2 = OH



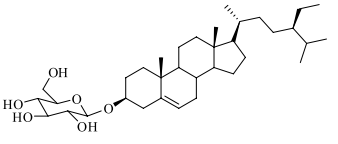
296a, R_3 = OH, R_1 = R_2 = R_4 = H, R_5 = R_6 = R_7 = CH_3
296b, R_2 = OH, R_1 = R_3 = R_4 = H, R_5 = R_6 = R_7 = CH_3
296c, R_3 = OH, R_1 = R_2 = R_5 = H, R_4 = R_6 = R_7 = CH_3
296d, R_1 = R_2 = OH, R_3 = R_4 = H, R_5 = H, R_6 = CH_2OH, R_7 = COOH



297a, R_1 = OH, R_2 = H
297b, R_1 = H, R_2 = OH



298a, R_1 = H, R_2 = H, R_3 = H, R_4 = H
298b, R_1 = $CO(CH_2)_{10}CH_3$, R_2 = H, R_3 = H, R_4 = OH



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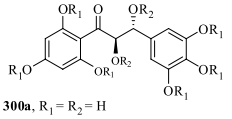
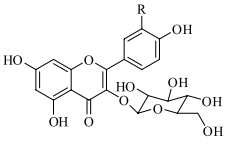
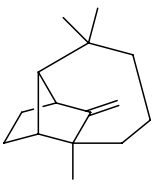


300a, R_1 = R_2 = H
300b, R_1 = CH_3, R_2 = H
300c, R_1 = CH_3, R_2 = (*R*)-MTPA
300d, R_1 = CH_3, R_2 = (*S*)-MTPA

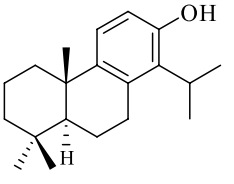


301a, R = H
301b, R = OH

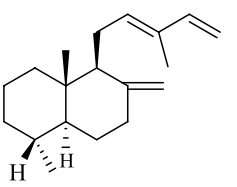
The isolation and antimycobacterial activity of longifolene (**302**) and totarol (**303**) from *Juniperus communis* roots, and of *trans*-communic acid (**304**) from the aerial parts was first reported by Gordien et al. in 2009.[198] Compound **303** with an MIC of 21.1 μg/mL was most active among these three compounds against *M. tb* H37Rv, while compound **304** was not active against *M. tb* H37Rv (MIC > 100μg/mL). The compounds **302** and **303** also showed activity against the resistant strains of rifampicin and the MIC values of compounds **302** and **303** were found to be of 4.9 and 5.8 μg/mL, respectively. The compound **303** also exhibited activity against the resistant strains of streptomycin (MIC = 23.9 μg/mL), isoniazid (MIC = 11.0 μg/mL), and moxifloxacin (MIC = 17.2 μg/mL).



302

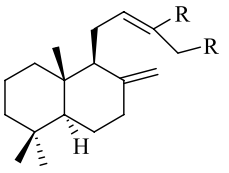


303

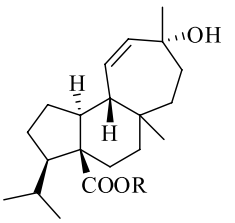


304

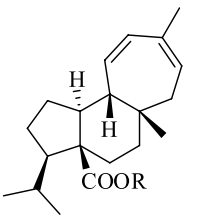
The rhizomes of *Curcuma amada* when extracted with chloroform were found to contain a labdane diterpene dialdehyde (**305a**), which was first time isolated by Singh et al.[199] The activity of compound **305a** and its semisynthetic derivatives (**305b-305d**) were found by BACTEC-460 assay. The compound **305a** was found to possess MIC 500 μg/mL against *M. tb* H37Rv strain. Two of the derivatives **305b** and **305d** had MIC of 250 μg/mL and 500 μg/mL, respectively. The third derivative **305c** was inactive at even higher concentrations. Thus, the compound **305b** was more active than the natural analogue **305a**.



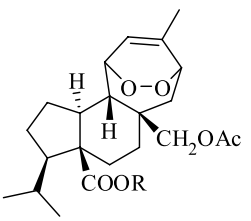
305a, R = CHO
305b, R = CH_2OH
305c, R = CH_2OAc
305d, R = CH=NOH



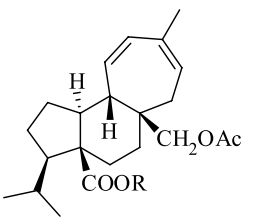
306a, R = H
306b, R = CH_2CH_3
306c, R = $CH_2CH_2CH_3$



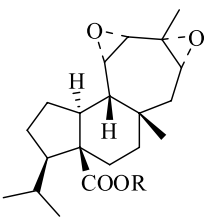
307a, R = H
307b, R = CH_2CH_3
307c, R = $CH_2CH_2CH_3$
307d, R = $CH_2(CH_2)_2CH_3$
307e, R = $CH(CH_3)_2$
307f, R = $CH_2CH(CH_3)_2$
307g, R = $CH(CH_3)CH_2CH_3$



308a, R = H
308b, R = $CH_2CH_2CH_3$
308c, R = $CH_2CH(CH_3)_2$



309a, R = H
309b, R = $CH_2CH_2CH_3$
309c, R = $CH(CH_3)_2$
309d, R = $CH(CH_3)CH_2CH_3$



310a, R = H
310b, R = $CH_2CH_2CH_3$
310c, R = $CH_2(CH_2)_2CH_3$
310d, R = $CH(CH_3)_2$
310e, R = $CH_2CH(CH_3)_2$
310f, R = $CH(CH_3)CH_2CH_3$

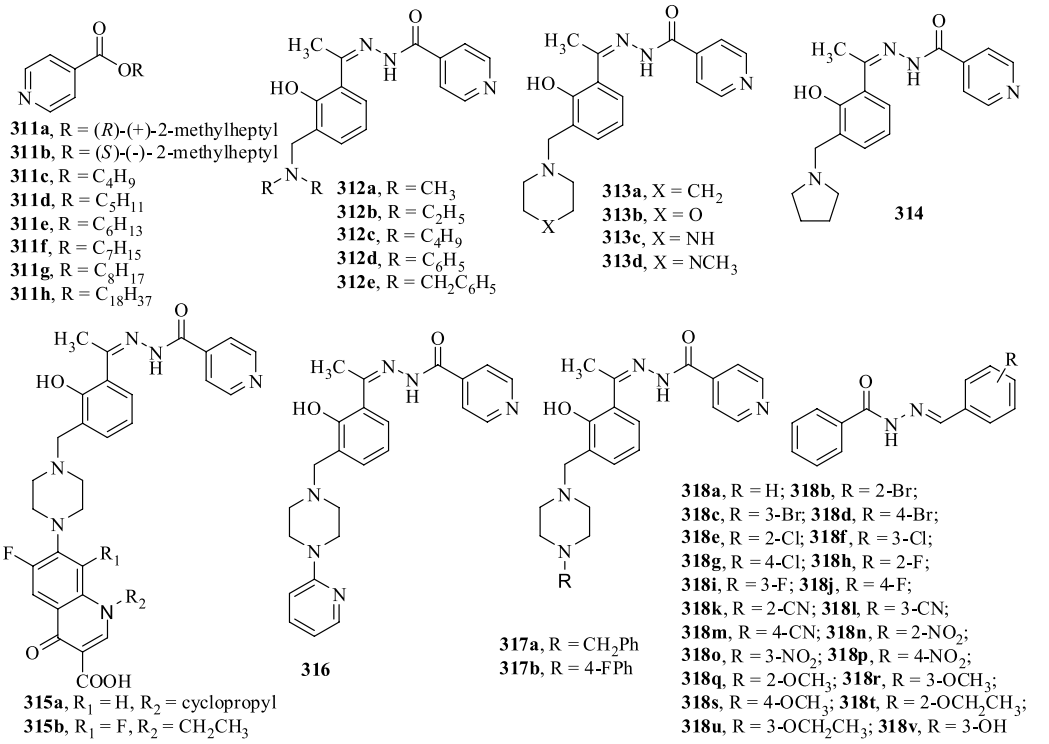
Three semisynthetic diterpenoids, 13 hydroxy-mulin-11-en-20-oic acid *n*-propyl ester (**306c**), and the *n*-propyl (**310b**) and *n*-butyl (**310c**) esters of isomulinic acid, were found to be antitubercular with MIC = 6.25 μg/mL against drug-resistant strain of *M. tb*.[200] The ethyl ester of 13-hydroxy-mulin-11-en-20-oic acid (**306b**) and the three alkyl derivatives of mulin-11,13-dien-20-oic acid (**307b–307d**) also showed some level of activity. The *n*-propyl ester of 17-acetoxy-mulinic acid (**308b**), and the *iso*-propyl (**310d**) and *iso*-butyl (**310c**) esters of isomulinic acid showed some activity, against resistant strain of *M. tb*. The C-20 alkyl derivatives were active against the resistant strain of *M. tb*, and compounds **306c**, **310b**, and **310c** showed more activity against the same strain with MIC = 6.25 μg/mL, as compared to the known drugs. A linear C-20 alkyl ester group was important for the activity in the majority of the derivatives. The *n*-propyl and *n*-butyl esters of isomulinic acid **310b** and **310c** were more active than the branched ones (**310d-310f**), and the activity of the linear mulin-11,13-dien-20-oic acid alky-esters (**307b-307d**) was found to be two times than the branched ones (**307e-307g**), or the parent metabolite **307a**.[201]

G. Isonicotinyl Derivatives as Anti-TB Agent

Isonicotinic acid hydrazide (Isoniazid/INH) is a first-line anti-TB drug. The prodrug isoniazid is activated by mycobacterial catalase peroxidase and then affects fatty acid synthetase II to prevent synthesis of mycolic acid synthesis.[202–205] Many isoniazid derivatives possess very good antitubercular properties.

Boruwa et al.[206] synthesized the analogues of 2-methylheptylisonicotinate (a natural analogue of INH), an antifungal and antibacterial antibiotic compound produced by *Streptomyces* sp. 201. Among them, compound **311g** possessed maximum activity (MIC = 8 μg/mL) against *M. tb*. This was followed by compound **311d** with MIC 10 μg/mL and compound **311f** with MIC 16 μg/mL, whereas compound **311c** and **311h** were found to be completely inactive. Compound **311e** showed antimycobacterial activity in the range of 24 μg/mL. The R isomer **311a** (MIC = 10 μg/mL) was slightly more active than the corresponding S isomer (**311b**, MIC = 14 μg/mL).

Sriram et al. prepared some isoniazid derivatives (**312a-312e**, **313a-313d**, **314**, **315a**, **315b**, **316**, **317a**, and **317b**) and screened them for antimycobacterial activity using the MABA method.[207] Six compounds **313c**, **315a**, **315b**, **316**, **317a**, and **317b** (MIC = 0.56–1.30 μM) showed better activity than INH (MIC = 2.04 μM). The activity of compound **313c** with piperazinyl group was very good and gave elating MIC value of 0.56 μM. But the *N*-methyl piperazine group (**313d**, MIC = 8.61 μM) leads to drastic decrease in activity. It was observed that on increasing the chain length in case of compounds **312a, 312b**, and **312c** there was decrease in activity (MIC = 2.49, 2.75, and 5.29 μM, respectively). Compounds **317a** and **317b** have similar activity (MIC = 0.88 μM and 0.87 μM), hence presence of fluoro group in the benzene ring has no effect on activity. All the compounds were further tested for their toxicity toward Vero cell lines and they were found to be nontoxic. Compound **313c** was also tested for efficacy against *M. tb* at a 25 mg/kg in mouse model and it was found that the potency of this compound was almost similar to INH.



Lourenco et al. reported the synthesis of some isonicotinohydrazide derivatives (**318a-318v**) and their antimycobacterial activity against *M. tb* H37Rv (ATTC 27294) by using alamar blue susceptibility test (Table XIV).[208] Compounds **318f**, **318g**, **318j**, and **318q** were most potent (MIC = 0.31 μg/mL) and their activity was comparable to INH (0.2 μg/mL) and better than RIF (1.0 μg/mL). Presence of F or Cl groups at the *para* position of benzene ring leads to derivatives with excellent activity but a dramatic loss in activity was observed when Br was at *para* position. Six other compounds (**318e**, **318l**, **318p**, **318t**, **318u**, and **318v**) exhibited same activity with MIC 1.25 μg/mL.

H. Oxazolidinones as Anti-TB Agent

The oxazolidinones class of antimicrobial agents target Gram-positive and anaerobic bacteria.[209–213] In the late 1970s, the scientists from E. I. du Pont de Nemours & Company uncovered the antimicrobial properties of oxazolidinones, a totally synthetic antibacterial class of compounds. DuP105 and DuP721 (Fig. 6) were the first clinical candidates of the oxazolidinone

Table XIV. In Vitro Antituberculosis Activity of Compounds **318a-318v** Against *M. tb* H37Rv Strain (ATCC 27294), MIC (μg/mL)

Comp no.	MIC	Comp no.	MIC	Comp no.	MIC	Comp no.	MIC
318a	3.12	**318g**	0.31	**318m**	5.0	**318s**	5.0
318b	5.0	**318h**	3.12	**318n**	5.0	**318t**	1.25
318c	2.5	**318i**	3.12	**318o**	5.0	**318u**	1.25
318d	5.0	**318j**	0.31	**318p**	1.25	**318v**	1.25
318e	1.25	**318k**	0.62	**318q**	0.31	INH	0.2
318f	0.31	**318l**	1.25	**318r**	5.0	RIF	1.0

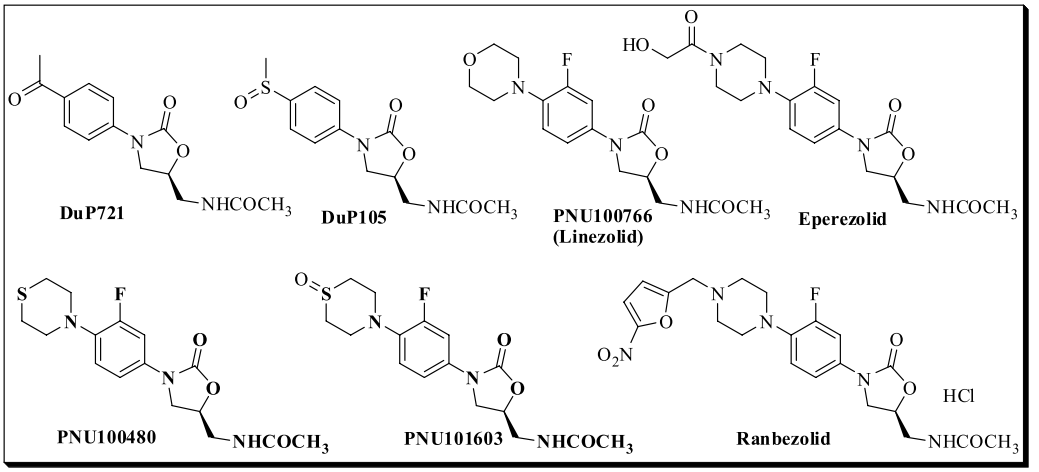
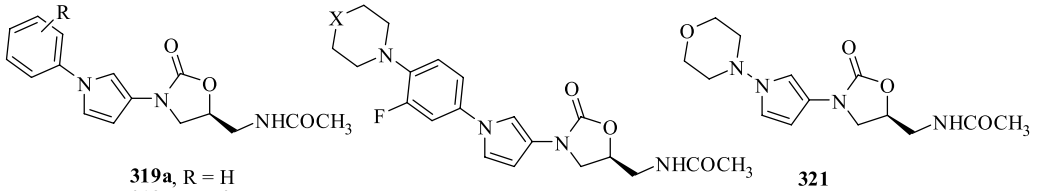


Figure 6. Oxazolidinone-based clinical candidates.

class of compounds.[209] They developed the antibacterial properties of DL-*S*-*n*-[3-(4-acetyl phenyl)-2-oxo-5-oxazolidynylmethyl] acetamide (DuP721), which exhibited fairly good antimycobacterial activity.[214] The Upjohn Company Laboratories in Kalamazoo, Michigan did SAR studies on DuP721 and discovered a new anti-TB drug named linezolid.[215–218] Eperezolid and linezolid (PNU100766) were the two clinical candidates of Amersham Pharmacia (Pfizer) and the later was introduced into the market, which was found to inhibit the binding of fMet-tRNA to 70S ribosomes.[219,220] Barbachyn et al. from Upjohn Laboratories reported that oxazolidinones PNU100480 and PNU101603 (Fig. 6) exhibit potent activity against *M. tb* with MIC $\leq$ 0.125 μg/mL.[221] The safety profile observed was good when 50 mg/kg b.i.d of PNU100480 was administered to rats for 29 days. Ranbaxy developed an oxazolidinone-based compound RBx7644 (Ranbezolid) as a clinical candidate.[222]

Sbardella et al. synthesized 3-(1*H*-pyrrol-1-yl)-2-oxazolidinone analogues (**319a-319d**, **320a**, **320b**, and **321)** of PNU100480 and evaluated them in vitro against atypical *M. tb* strain ATCC 27294.[223] All the compounds were found to be active against *M. tb* but less active than the reference compounds (INH and PNU100480). Compound **319d** with a fluoro group at *para* position was the most active with MIC_{50} = 1.9 μM. Compound with a morpholine (**320a**) and thiomorpholine (**320b**) have MIC_{50} values of 12.9 μM and 9.8 μM, respectively, while compound **321** with a morpholine directly attached to pyrrole was inactive.



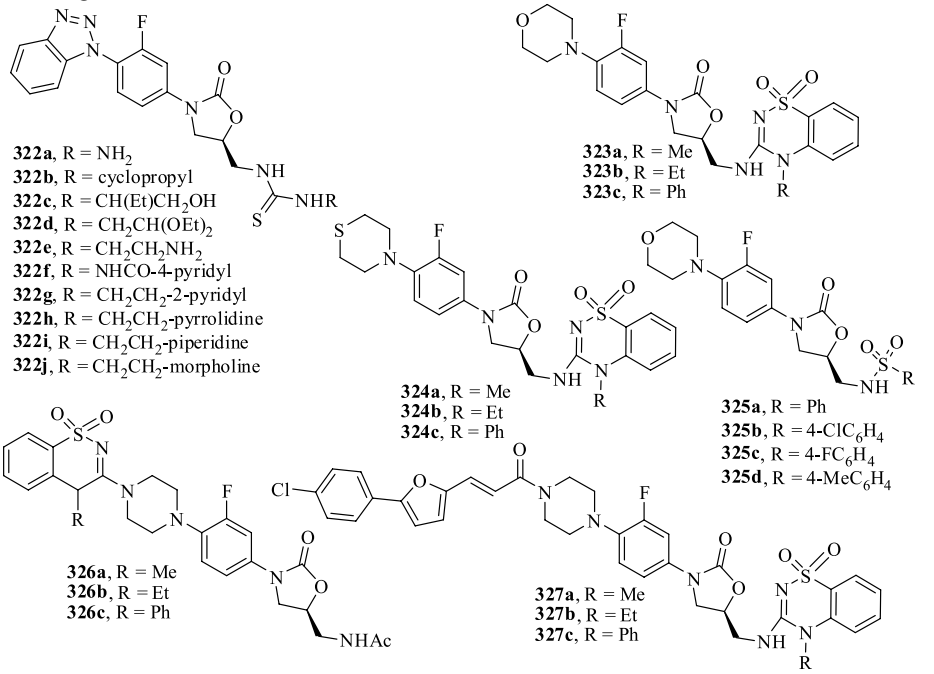
319a, R = H
319b, R = 2-F
319c, R = 3-F
319d, R = 4-F

320a, X = O
320b, X = S

321

Dixit et al. synthesized substituted thiourea derivatives of oxazolidinones (**322a-322j**) and screened them against *M. tb* ATCC27294 strain using isoniazid (MIC = 0.25 μg/mL) and linezolid (MIC = 0.5 μg/mL) as reference drugs.[224] Compounds with amino (**322e**), 2-pyridyl (**322g**), 1-pyrrolidinyl (**322h**), and 1-piperidinyl (**322i**) groups exhibited potent activity with MIC value in the range 0.5–1.0 μg/mL. Compound **322b** (MIC = 0.06 μg/mL) with a

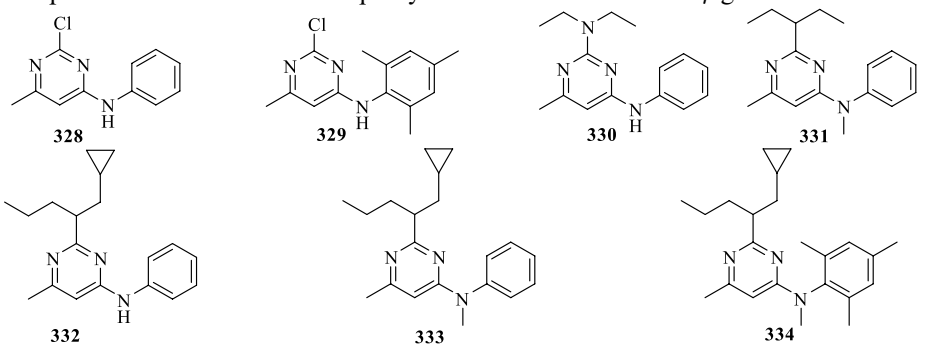
cyclopropyl group was found to be more active in vitro than the standard drugs. Compounds **322c** and **322j** were completely inactive whereas compounds **322d** and **322f** have similar MIC values of 8 μg/mL.



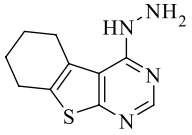
Kamal et al. synthesized arylsulfonamido conjugated oxazolidinones (**323–327**) and tested them against *M. tb* H37Rv using MABA and rifampicin (MIC = 0.12 μg/mL) as well as linezolid (MIC = 2 μg/mL) were used as reference compounds.[225] Three compounds (**325c**, **326a**, and **326b**) showed good activity with MIC 1.0 μg/mL while for rest of the compounds MIC was $\geq$ 6.25 μg/mL.

I. Pyrimidine Derivatives as Anti-TB Agent

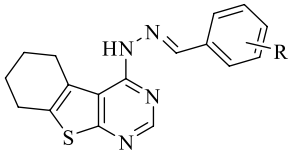
Pyrimidine moiety is present in DNA and RNA and thus it is associated with various biological activities. The pyrimidine derivatives act as antibacterial, antitumor, antilukemic, and antifungal agents.[226,227] Morgan et al. have reported the synthesis and anti-TB activity of some anilinopyrimidine analogues (**328–334**) against *M. tb* H37Ra in MABA and kanamycin sulfate and isoniazid (MIC = 2.0–5.0 and 0.040–0.090 μg/mL) were used as the reference drugs.[228] Except **329** all other compounds were found to be active against *M. tb* and compound **334** showed maximum activity among the seven compounds with MIC value of 3.12 μg/mL. Two other compounds **332** and **333** were equally active with MIC of 12.5 μg/mL.



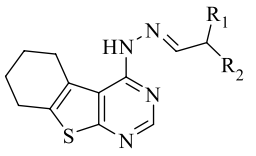
Aponte et al. reported the synthesis of 2-(5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-yl)hydrazone derivatives (BTPs, **335**, **336a-336y**, **337a-337l**) and evaluated them against *M. tb* using the H37Rv virulent strain in a MABA anti-TB assay.[229] Compound **336q** and **336r** showed highest anti-TB activity among the tested compounds with MIC value 15.7 and 16.2 μM, respectively. On the other hand, compounds **336g** (MIC = 26.9 μM), **336d** (MIC = 9.7 μM), and **336j** (MIC = 8.7 μM) showed higher anti-TB activity in nonreplicating TB model under low-oxygen conditions. It was found that the compounds **336q** and **336r** possessed similar inhibition in both assays (MABA and LORA).



335



336a, R = H; **336b**, R = 4-CH_3;
336c, R = 4-CH_2CH_3; **336d**, R = 4-$CH(C_2H_6)$;
336e, R = $CH(C_3H_9)$; **336f**, R = 4-OH;
336g, R = 4-OCH_3; **336h**, R = 3-OCH_3;
336i, R = 3,4-O-CH_2-O; **336j**, R = 2,4-OCH_3;
336k, R = 3,4,5-OCH_3; **336l**, R = 3-OCH_3, 4-OH;
336m, R = 3,5-OCH_3, 4-OH; **336n**, R = 3,5-allyloxy, 4-Br;
336o, R = 4-NO_2; **336p**, R = 2-NO_2; **336q**, R = 4-CF_3;
336r, R = 2-CF_3; **336s**, R = 4-F; **336t**, R = 2-F;
336u, R = 4-Cl; **336v**, R = 2-Cl; **336w**, R = 4-Br;
336x, R = 2-Br; **336y**, R = 4-CN

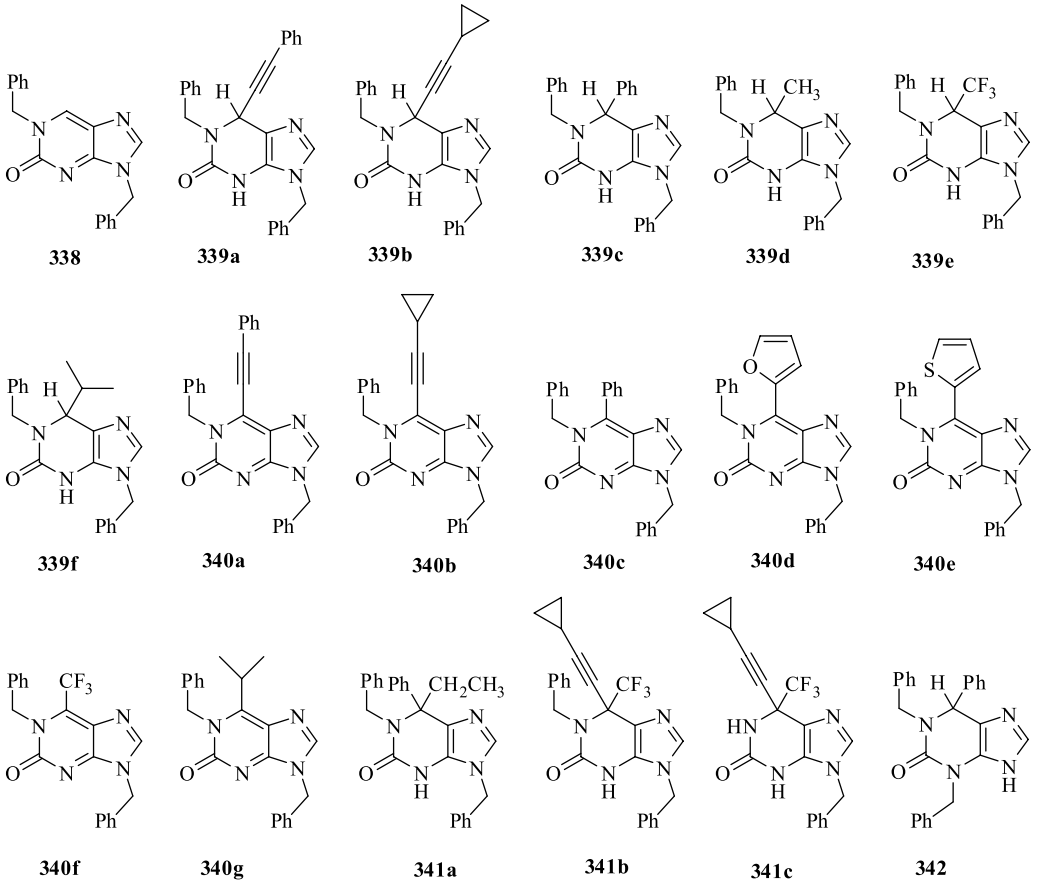


337a, R_1 = H R_2 = 1-napthalenyl
337b, R_1 = H, R_2 = 2-napthalenyl
337c, R_1 = H, R_2 = cinnamyl
337d, R_1 = H, R_2 = 2-furyl
337e, R_1 = H, R_2 = 2-pyrrolyl
337f, R_1 = R_2 = 4-pyridinyl
337g, R_1 = H, R_2 = 2-pyridinyl
337h, R_1 = H, R_2 = $C(CH_3)_3$
337i, R_1 = CH_3, R_2 = CH_3
337j, R_1 = CH_3, R_2 = C_6H_5
337k, R_1 = CH_2CH_3, R_2 = CH_2CH_3
337l, R_1 = C_6H_5, R_2 = C_6H_5

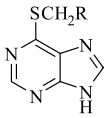
J. Purine Derivatives as Anti-TB Agent

The purine derivatives exhibit various biological activities as they are found in a large number of naturally occurring compounds and also in many medicinally important compounds.[230,231] Purine and pyrimidines are important constituents of various biomolecules (RNA, DNA, ATP, dATP, CTP, UTP, GTP, etc.) and their analogues are also used as anticancer and antiviral agent.[232]

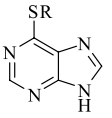
Andresen et al. tested 2-oxopurines (**338**, **393a-339f**, **340a-340g**, **341a-341c**, and **342**) for inhibitory effect on *M. tb* H37Rv (ATCC 27294) in BACTEC 12B medium using MABA.[233] Compounds **339a-339f**, **340b-340g**, and **341a-341c** were found to be completely inactive. Only the phenylethynylpurine **340a** showed some activity with MIC = 12.5 μg/mL.



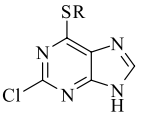
Pathak et al. reported the synthesis of thio analogues of purine (**343a-343b**, **344a-344e**, **345a-345d**, **346a-346d**, **347a-347h**, and **348a-348j**) and evaluated their antimycobacterial activity against H37Rv and H37Ra strains of *M. tb*.[234] Two purine analogues **348a** and **348b** exhibited MIC values 1.56 and 0.78 μg/mL, respectively against the *M. tb* H37Rv strain. *N*9-substitution was found to increases the antimycobacterial activity of these purine derivatives. The compound **343b** exhibited significant activity against H37Rv with MIC_{90} of 3.13 μg/mL and its N9-alkylated analogue **348a** displayed two times better activity ($MIC_{90} = 1.56$ μg/mL). Among the other N9-alkylated purine analogues (**348b-348j**), compound **348b** showed maximum activity with MIC_{90} value of 0.78 μg/mL against *M. tb* H37Rv. Compounds **346a-346d** were found to be less active than **348a** with MIC_{90} greater than 3.13–6.25 μg/mL. Only compound **346c** exhibited some activity with MIC_{90} value of 3.13 μg/mL. In case of H37Ra strain of *M. tb*, most of the analogues were found to be inactive or very less active ($MIC_{90} \geq 12.8$ μg/mL). However, some N9-alkylated analogues showed improved activity. Compounds **348g**, **348h**, and **348i** showed significant activity against H37Ra strain with MIC_{90} of 4.0 μg/mL. Compounds **343b** and **348a** were also tested against *M. tb* Erdman in monolayers of a mouse bone marrow macrophages model.[235] After 7 days, at concentrations 2.53 and 1.65 μg/mL, these two compounds caused about 90% decrease in the viable cell count.



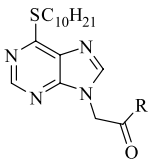
343a, R = C_6H_5
343b, R = C_9H_{21}



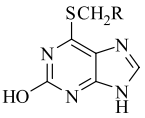
344a, R = 2-quinolyl
344b, R = 2-napthyl
344c, R = C_6H_4-4-Cl
344d, R = C_6H_4-3-Me
344e, R = C_6H_4-4-Me



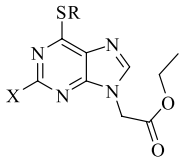
345a, R = C_6H_4-2-Me
345b, R = 1-napthyl
345c, R = $C_{10}H_{21}$
345d, R = 2-pyrimidyl



346a, R = $OCH_2C_6H_5$
346b, R = OC_6H_5
346c, R = $OC(CH_3)_3$
346d, R = NH_2



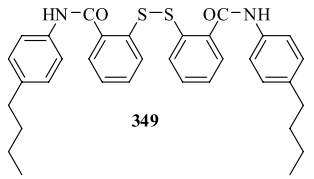
347a, R = C_6H_5
347b, R = C_6H_4-3-OMe
347c, R = C_6H_4-2-Cl
347d, R = C_6H_4-4-Cl
347e, R = C_6H_4-2-F
347f, R = C_6H_4-4-F
347g, R = C_6H_4-2-NO_2
347h, R = C_6H_3-4-F-2-CF_3



348a, X = H, R= $C_{10}H_{21}$; **348b**, X = H, R= $C_{12}H_{25}$;
348c, X = H, R= C_6H_4-4-Cl; **348d**, X = H, R= C_6H_4-3-Me;
348e, X = H, R= C_6H_4-4-Me; **348f**, X = H, R= 2-napthyl;
348g, X = OH, R= $CH_2C_6H_5$; **348h**, X = OH, R= $CH_2C_6H_4$-2-F;
348i, X = OH, R= $CH_2C_6H_3$-3-Cl-6-F;
348j, X = OH, R= $CH_2C_6H_3$-2-Me-3-NO_2

K. Miscellaneous Anti-TB Compounds

Okachi et al. synthesized a series of 2,2′-dithiobis(benzamide) analogues and evaluated them for their activity against *M. tb* by agar dilution technique.[236] Out of the number of compounds synthesized five compounds (**349**, **350a**-**350d**) showed excellent activity with MIC either 0.39 or 0.78 μg/mL, which is equivalent to standard drugs STM and EMB.



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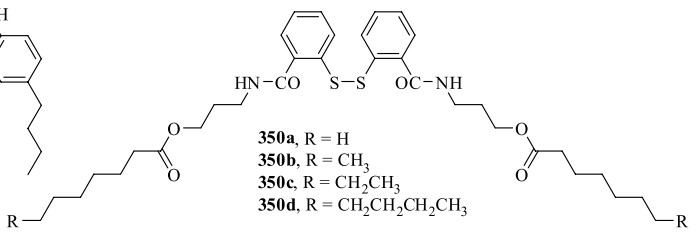
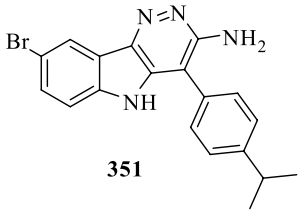


350a, R = H
350b, R = CH_3
350c, R = CH_2CH_3
350d, R = $CH_2CH_2CH_2CH_3$

A series of 3-amino-4-arylpyridazino[4,3-*b*]indoles (pyridazinoindoles) were screened for their antimycobacterial activity by Velezheva et al.[237] Only two compounds (**351** and **352**) were found to have significantly good activity with MIC 1.77 and 1.42 μg/mL, respectively, other compounds were found to be less active.



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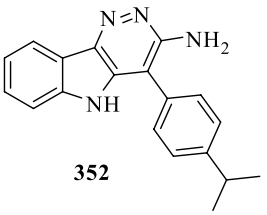

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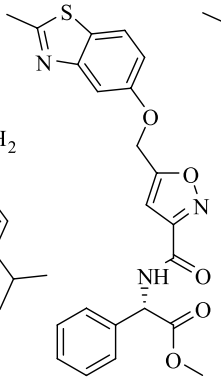

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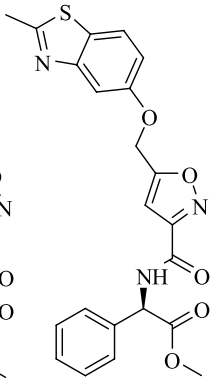
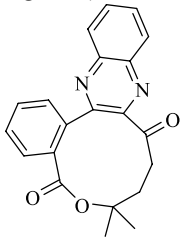


354

A series of 5-(2-methylbenzothiazol-5-yloxymethyl)isoxazole-3-carboxamide derivatives were screened against *M. tb* by Huang et al. RMP (MIC = 0.1 μM) and INH (MIC = 0.5 μM) were used as reference drugs.[238] Two compounds **353** and **354** showed MIC of 1.4 and 1.9 μM, respectively. Silva et al. reported the *M. tb* activity of macrolide **355** (MIC = 0.62 μg/mL), which was found to be more active than the reference compound rifampicin (MIC = 1μg/mL).[239]



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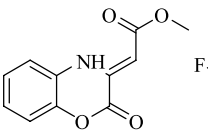

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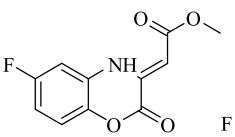

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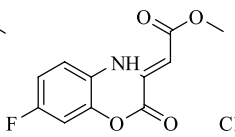

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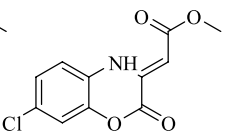
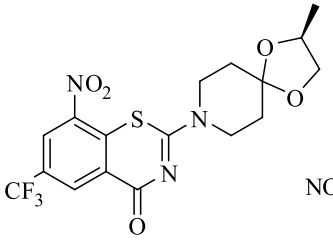


359

X. Li et al. synthesized several (*Z*)-methyl-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)ylidene)acetates.[240] Among the synthesized compounds four compounds (**356–359**) showed very good activity with MIC 0.63 μg/mL.

Benzothiazinones (BTZs) show potent activity against *M. tb*. Compounds **360** (BTZ043), **361** (MTX), and **362** (CT319) were found to possess MIC values 0.001, 0.125, and 0.31 μg/mL, respectively.[241] Thus, compound **360** with nanogram activity could be an excellent candidate for further exploration and we can expect a good lead from this for clinical trials. The target of BTZs is decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1, Rv3790).[242,243]



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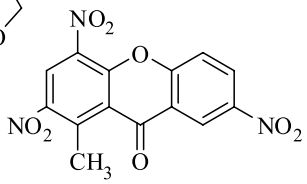

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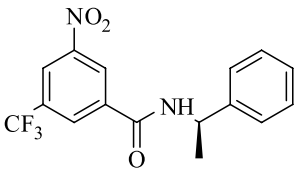
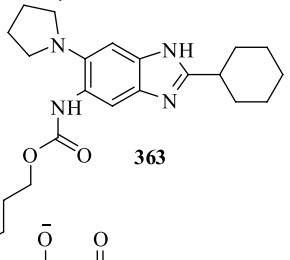


362

From a series of benzimidazoles synthesized by Kumar et al., a 2,5,6-trisubstituted compound (**363**) was found to exhibit excellent activity against *M. tb* H37Rv (MIC = 1 μM).[244] This compound has a cyclohexyl moiety at position 2 and a pyrrolidine at position 5.

Dighe et al. synthesized isatinyl thiazole-azetidinone **(364)** derivative, which possessed MIC = 0.39 μM.[245]



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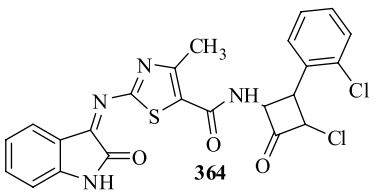

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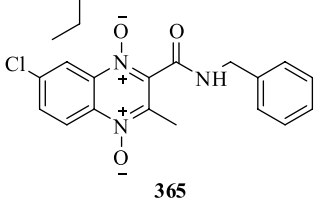

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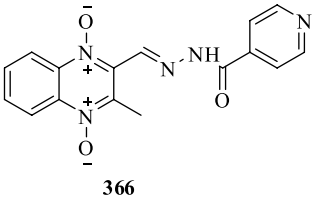

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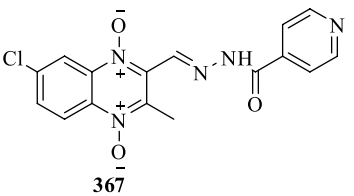
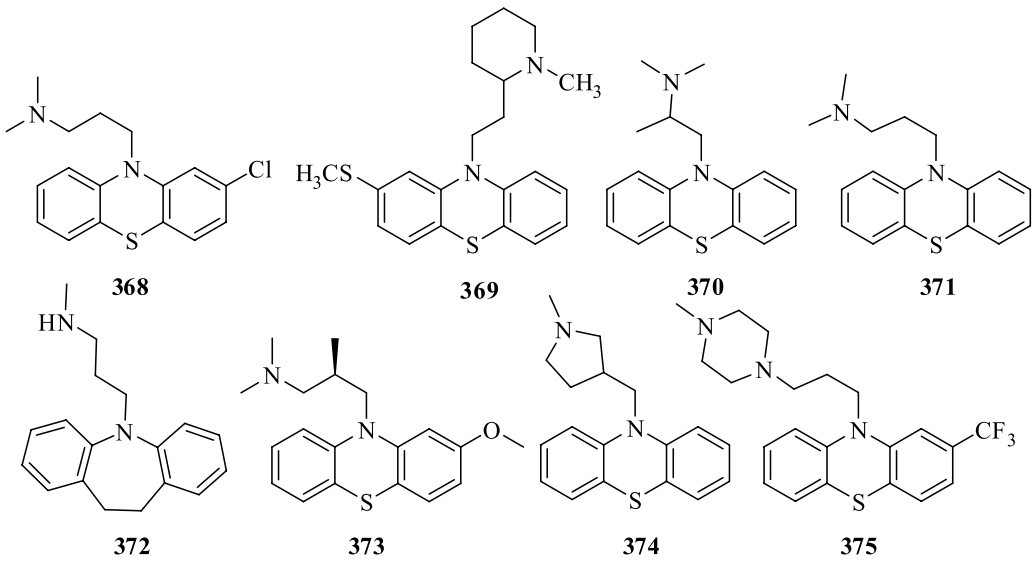


367

Torres et al. reported that the 1,4-di-*N*-oxide-quinoxaline-2-ylmethylene isonicotinic acid hydrazide derivatives **365**, **366**, and **367** showed potent activity against *M. tb* H37RV with IC_{90} values 1.25, 1.32, and 1.16 μM, respectively.[246] The reference drug INH showed IC_{90} of 0.21 μM under similar conditions.

Phenothiazines are mainly antipsychotic drugs but some of these compounds have also shown activity against *M. tb*.[247,248] The chloropromazine (CPZ) was the first molecule that belonged to phenothiazine class of compounds, reported for its in vitro and in vivo activity against mycobacteria.[249–251] Bettencourt et al. screened five phenothiazines (**368–372**) against MDR-TB strains using BACTEC 460 system[252] and CPZ (**368**) was found to be equally potent to thioridazine (**369**) while promethazine (**370**) and promazine (**371**) were less active and desipramine (**372**) was found to be least active. The in vitro MIC value of thioridazine or THZ (**369**) and chlorpromazine (**368**) against *M. tb* ATCC 27294 were found to be 10 μg/mL and 15 μg/mL, respectively.[253] THZ (**369**) exhibits activity against susceptible and MDR or XDR *M. tb* in vitro.[254–258] The anti-TB potential of phenothiazines particularly THZ (**369**) has been attributed to inhibition of NADH2-menaquinone oxidoreductase (Ndh2) or calmodulin.[259–262] A pioneering research in this field was done by the groups of Crowle and Amaral,[249] according to them the killing activity of macrophages against intracellular mycobacteria is due to intracellular concentration of the these compounds. According to Ordway et al., *M. tb* bacteria that reside in macrophages are susceptible to thioridazine (**369**) at 0.1 μg/mL concentration.[253] Phenothiazines can inhibit MDR-TB strains in vitro.[258,263] Moreover, both ex vivo[264–266] and in vivo[267] studies also support the use of phenothiazines for the treatment of MDRTB. The CFU MIC of levopromazine (**373**),[247] trifluoperazine (**375**),[260,268] methdilazine (**374**)[269] were found to be 10, 8–32, and 5–15 μg/mL, respectively. According to van Soolingen et al., compound **369** (THZ) when given at a dose of 70 mg/kg to mice infected with drug susceptible *M. tb* (H37Rv) resulted in killing of the bacilli.[254] A daily administration of the same dose to mice infected with MDR-TB strain reduced the CFU at 30 and 60 days (5.1×10, SD 6×10^4). Compound **369** is now out of patent and treatment of some XDR-TB patients with this compound has shown good results.[270]



368 **369** **370** **371**

372 **373** **374** **375**

5. CONCLUSION

TB is a challenging health problem mainly in the developing countries. The increase in the number of MDR strains and TB-HIV coinfection has been a matter of concern for the scientific community. With the increase in the number of new compounds screened against mycobacteria, the opportunity exists to develop a novel drug for the cure and complete eradication of TB. The identification of small molecule for the treatment of many infectious diseases including TB remains one of the most attractive areas of research. A large number of compounds are showing promising activity in vitro to name a few of them are **4h**, **14i**, **42o**, **47**, **56**, **57**, **77d**, **78a**, **78f**, **78k**, **116**, **137b**, **137c**, **156a**, **157c**, **157d**, **158d**, **158c**, **234a**, **234b**, **236i**, **245d**, **234o**, etc. A large number of other compounds not included in this review, also shows promising anti-TB activity. This opens a door for new opportunities for the development of new anti-TB agents. It is anticipated that some of the compounds will reach the clinical market for the treatment of the deadly disease.

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