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.

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

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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. The situation is even more deplorable than it appears as 0.5 million new cases were due to multidrug-resistant (MDR) TB. The alarming estimates expose 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. 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. About 0.23 million cases of MDR-TB occur per year in India only. TB is also responsible for deaths in HIV-infected people due to infection by both HIV/AIDS and TB. 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.

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. 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. 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. The “BCG World Atlas” is an online resource that was launched in 2008 so that information regarding BCG immunization can be gathered and updated. 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. 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.

The antitubercular drugs are categorized as first line, second line, and third line. The first-line anti-TB drugs are streptomycin (STM/S, 1944), isoniazid (INH/H, 1952), pyrazinamide (PZA/Z, 1952), rifampicin (RIF/R, 1957), and ethambutol (EMB/E, 1961) (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. 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.\textsuperscript{42, 43} India has a major contribution in the discovery of DOTS programme.\textsuperscript{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.\textsuperscript{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>
<thead>
<tr>
<th>Drug name</th>
<th>Class</th>
<th>Licensor/Sponsor</th>
<th>Mode of action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td>Bayer/Global TB Alliance</td>
<td>Inhibition of M. tb DNA topoiso merase II</td>
<td>III</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Fluoroquinolone</td>
<td>EU/TDR</td>
<td>Inhibition of M. tb DNA topoiso merase II</td>
<td>III</td>
</tr>
<tr>
<td>PA824</td>
<td>Nitroimidazole</td>
<td>Global TB Alliance</td>
<td>Inhibition of lipid and protein synthesis, M. tb activated prodrug</td>
<td>II</td>
</tr>
<tr>
<td>TMC207</td>
<td>Diaryquinoline</td>
<td>Tibotec/ J&amp;J</td>
<td>Target ATP synthase subunit c proton pump</td>
<td>II</td>
</tr>
<tr>
<td>SQ109</td>
<td>Ethylene diamine</td>
<td>Sequella</td>
<td>Thought to be cell wall synthesis but different to EMB</td>
<td>II</td>
</tr>
<tr>
<td>OPC67683</td>
<td>Nitroimidazole</td>
<td>Otsuka</td>
<td>Inhibits mycolic acid synthesis, prodrug, and requires activation</td>
<td>III</td>
</tr>
<tr>
<td>LL3858</td>
<td>Pyrrole</td>
<td>Lupin</td>
<td>N/A</td>
<td>I</td>
</tr>
</tbody>
</table>

\(\text{Medicinal Research Reviews DOI 10.1002/med}\)
I clinical evaluations in 2009 and currently this compound is in phase II clinical trials and LL3858 is currently in phase I.\textsuperscript{53–57} The nitroimidazole-based compound PA824 has completed its phase I clinical studies.\textsuperscript{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 $\mu$g/mL in vitro against \textit{M. tb}.\textsuperscript{59} TMC207 is bactericidal and it is tolerated very well during its initial clinical studies.\textsuperscript{60} Based on the promising phase I clinical trials, the compound TMC207 has entered into the phase II clinical trials.\textsuperscript{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 \textit{M. tb} and there is no cross-resistance to the first-line antitubercular drugs, thus occasional and low dosing may be effective.\textsuperscript{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.\textsuperscript{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 \textit{Mycobacterium} with equal competency.\textsuperscript{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.\textsuperscript{67}
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.\textsuperscript{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 \textit{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,\textsuperscript{70} anti-TB,\textsuperscript{71} anticancer,\textsuperscript{72} antimalarial,\textsuperscript{73} antiproliferative, anti-inflammatory,\textsuperscript{74} antihypertensive,\textsuperscript{75} tyrokinase PDGF-RTK inhibiting agent,\textsuperscript{76} and anti-HIV.\textsuperscript{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 \textit{M. tb}. 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.\textsuperscript{79, 80} TMC207 is effective for resistant and nonresistant strains of \textit{M. tb} at MIC 0.03 \(\mu\)g/mL.\textsuperscript{79} The results of its clinical trials show that TMC207 may shorten the treatment of TB and be effective in its treatment.\textsuperscript{60}

In 2002, Savini et al. reported the synthesis of 4-quinolylhydrazines (\textit{1a-1q}) and a series of 4-quinolylhydrazones (\textit{2a-2m} and \textit{3a-3w}), with various substituents on quinoline nucleus and with aryl- or heteroaryl-hydrazonic moiety.\textsuperscript{81} All the compounds were evaluated against \textit{M. tb} H37Rv and majority of the tested compounds showed 95–100% inhibitory activity with MIC values between 0.78 and 12.5 \(\mu\)g/mL against \textit{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 \(\mu\)g/mL (\textit{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-methoxy naphtyl substituents on hydrazonic moiety. The chloro group at 5 and 7 positions of quinoline nucleus has negative effect on the antibacterial activity (\textit{2d, 2l, 3k, and 3v}). Though quinolylhydrazines \textit{1a-1d, 1h-1l, 1q} possess considerable inhibitory activity with selective index (SI) < 4, with the exception of \textit{1f} and \textit{1n} (SI = 4.28 and 6.16), while some quinolylhydrazones (\textit{2i, 2j, 3b, 3c, 3h, 3l, and 3r}) showed significantly higher SI. Three compounds (\textit{2i, 3b}, and \textit{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\textsubscript{90} and EC\textsubscript{99} values. These three compounds were also evaluated for their inhibitory activity against a single strain of \textit{M. avium} and compounds \textit{2i} and \textit{3b} were found to be the most active with MIC 3.13 \(\mu\)g/mL and SI value of 20.45 and 23.32, respectively. Quinolylhydrazones \textit{2i} and \textit{3b} that were active against \textit{M. tb} H37Rv and \textit{M. avium} were also found to be the least toxic among all these synthesized compounds.
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.\(^2\) Among the 7-methoxyquinolines (4a–4l), compound 4a with unsubstituted phenyl ring had a low MIC value (16.4 \(\mu\)M) 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 \(\mu\)M, 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 \(\mu\)M) with enhanced anti-TB activity (Table II). The compounds 4j and 4k (MIC = 9.5 \(\mu\)M) having quinolyl system had lower activity than 4h but the presence of 7-OMe group makes the compound 4l (MIC = 2.2 \(\mu\)M) 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>
<thead>
<tr>
<th>Comp no.</th>
<th>MIC ((\mu)M)</th>
<th>Comp no.</th>
<th>MIC ((\mu)M)</th>
</tr>
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<tbody>
<tr>
<td>2j</td>
<td>1.56</td>
<td>3u</td>
<td>0.78</td>
</tr>
<tr>
<td>3c</td>
<td>0.78</td>
<td>4h</td>
<td>0.6</td>
</tr>
<tr>
<td>3f</td>
<td>0.78</td>
<td>4i</td>
<td>0.6</td>
</tr>
<tr>
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<td>4l</td>
<td>2.2</td>
</tr>
<tr>
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<td>1.56</td>
<td>8d</td>
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</tr>
<tr>
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<td>1.56</td>
<td>RIF</td>
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</tr>
<tr>
<td>3s</td>
<td>1.56</td>
<td>INH</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Table II. Antimycobacterial Activity of a Few Selected Quinolyl Hydrazine and Hydrazone Derivatives Against \(M. \) \(t b\) \(H37Rv\)
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 5e 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-methylenedioxy 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) diethyramino (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-methylenedioxy derivatives (10a and 11a) were found to be inactive but the 6-methoxyquinoline 8a (MIC = 11.1 μM) was similar to the corresponding aryl-derivatives (8b) in its activity.
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). 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.
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. 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 NO₂ group of compound 14i was replaced by NH₂ group (15c), complete loss in activity with no inhibition was observed. But when the amino group was blocked with NHCOCH₃ 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 NO₂ 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). Most of the derivatives exhibited mild activity ≥ 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 \((36, 37, 38, 39)\) and 13 quinoline carboxamide \((40)\) analogues and evaluated them against \(M.\) \(tuberculosis\) H37Rv.\(^86\) Out of the 22 quinoline carbohydrazides only four compounds \((36d, 36e, 36f, 36g)\) showed good activity against \(M.\) \(tb\) H37Rv \((\text{MIC} = 6.25 \mu\text{g/mL} \text{ and } 99\% \text{ inhibition})\) of the series was further evaluated and 13 new analogues of \(36d\) were prepared. Among these compounds, \(40h\) and \(40m\) \((3.125 \mu\text{g/mL}, 99\% \text{ inhibition})\) 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 \(\mu\text{g/mL}\).

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 \((\text{MIC} = 3.12 \mu\text{g/mL})\) these compounds showed significantly good activity \((\text{MIC} = 3.12–12.5 \mu\text{g/mL})\) with few exceptions \(41d, 41h, 41k, 41p–41r, 41s, 41t\), which were not active even at \(\text{MIC} > 100 \mu\text{g/mL}\). Nine compounds \(41b, 41c, 41f, 41g, 41i, 41j, 41m, 41n,\) and \(41o\) showed activity better than or comparable to EMB \((\text{MIC} = 2.5–3.25 \mu\text{g/mL}, \text{respectively})\). Derivatives with bromo \((41f)\), fluoro \((41i)\), and methoxy \((41o)\) substituent at para position of the phenyl ring were the most active \((\text{MIC} = 2.5 \mu\text{g/mL})\). Compounds \(41c, 41f, 41i,\) and \(41o\) were nontoxic to host cells.
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. 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. 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 clogP 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).
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. 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) whereas another 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. 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.

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). 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 CF₃ 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-CF₃ 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-CF₃ compound.
Table IV. Antimycobacterial Activity of Compounds 53–66 Against *M. tb* H37Rv

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

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.

Upadhyay 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. 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 NO₂ (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 69c 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. 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-piperazine moiety at the C2 position. The 2-pyridyl-piperazine 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. 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<sub>50</sub> 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. 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).
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.

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 OCH₃ 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 relena (antiviral), ethambutol (anti-TB), lorabid (antibacterial), eloxatin (anticancer), and nutlin-3 (anticancer).

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. 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.](Medicinal Research Reviews DOI 10.1002/med)
biosynthesis in the cell wall.\textsuperscript{105–108} Amines and polyamines based on spermine and spermidine display very good antiparasitic and antitubercular activity.\textsuperscript{109} The anti-TB activity of these compounds gets enhanced by increasing the hydrophobic character. The \(N\)-alkyl benzylamines bromhexine and ambroxol (Fig. 3) isolated from \textit{Adhatoda vasica} are used as mucolytic agents and they inhibit the growth of \textit{M. tuberculosis} with different rates at different pH values.\textsuperscript{110}

Screening of 63,238 compounds having 1,2-ethylenediamine pharmacophore\textsuperscript{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.\textsuperscript{55,113} The SQ109 is highly potent against the H37Rv strain and MDR strains of \textit{M. tb}\textsuperscript{111,112} and showed relatively potent activity against \textit{M. tb}, \textit{M. bovis}, \textit{M. marinum} and less active against \textit{M. avium} and \textit{M. smegmatis}.\textsuperscript{114} The SQ109 when used with INH and RIF showed synergistic effect while with STM the effect was additive.\textsuperscript{54} SQ109 interferes with the cell wall synthesis in \textit{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\textsuperscript{81–88} by broth microdilution in middlebrook 7H9 media against \textit{M. tb} H37Rv.\textsuperscript{111} These derivatives were found to possess MIC\textsubscript{99} between 37.5 \(\mu\)M and 300 \(\mu\)M, which is higher than EMB (MIC\textsubscript{99} = 6.25 \(\mu\)M). Some branching in the ethylene linker was permissible with lower activity, branched alkyl compound \textsuperscript{86} has MIC = 150 \(\mu\)M, aryl substituted compound \textsuperscript{87} has MIC = 300 \(\mu\)M, and cycloalkyl substituted compounds \textsuperscript{81}, \textsuperscript{82}, and \textsuperscript{83} have MIC values 150, 300, and 150 \(\mu\)M, 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. Wilkinson and colleagues at Lederle had also reported the occurrence of highly R-branched aliphatic moieties in the active compounds. 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)

<table>
<thead>
<tr>
<th>Comp no.</th>
<th>MIC (μM)</th>
<th>Comp no.</th>
<th>MIC (μM)</th>
<th>Comp no.</th>
<th>MIC (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>0.5</td>
<td>97</td>
<td>1</td>
<td>105</td>
<td>1</td>
</tr>
<tr>
<td>90</td>
<td>1</td>
<td>98</td>
<td>1</td>
<td>106</td>
<td>6</td>
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<td>91</td>
<td>1</td>
<td>99</td>
<td>1</td>
<td>107</td>
<td>3</td>
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<td>92</td>
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<td>109</td>
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<td>102</td>
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<tr>
<td>95</td>
<td>1</td>
<td>103</td>
<td>0.2</td>
<td>111</td>
<td>3</td>
</tr>
<tr>
<td>96</td>
<td>0.5</td>
<td>104</td>
<td>5</td>
<td>SQ109</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*M. tb* in both broth microdilution and Luc assays. 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 for predicted membrane permeability based on logP values, in vitro cytotoxicity in HepG2 cells to determine IC₅₀ and SI. 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 cytotoxicity (IC₅₀ = 54 μM) and with logP 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 10⁶ 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 shows that these compounds could be important for developing new anti-TB agents.
Table VI. Antimycobacterial Activity of SQ109 Analogues (114–118)

<table>
<thead>
<tr>
<th>Comp no.</th>
<th>H37Rv</th>
<th>XDR173</th>
</tr>
</thead>
<tbody>
<tr>
<td>114</td>
<td>1–10</td>
<td>-</td>
</tr>
<tr>
<td>115</td>
<td>0.5–1</td>
<td>0.5–1</td>
</tr>
<tr>
<td>116</td>
<td>0.25–0.5</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>117</td>
<td>1–2</td>
<td>-</td>
</tr>
<tr>
<td>118</td>
<td>0.5–1</td>
<td>1–2</td>
</tr>
<tr>
<td>SQ109</td>
<td>0.5–1</td>
<td>0.5–1</td>
</tr>
</tbody>
</table>

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. The compound SQ109 was fantastic with MIC range 0.5–1.0 μM 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 oxyiso-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*. 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.

Tripathi et al. synthesized 42 benzyl- and pyridymethyl 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, NO₂, 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$_2$N(CH$_2$)$_n$NH$_2$, 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.
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 \textit{M. tb} H37Rv strain (ATCC 27294, susceptible both to RIF and INH) using microbroth dilution assay.\textsuperscript{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 \textit{para} position of aromatic ring lead to drastic decrease in the activity. In order to study the effect of substitution in adamantane 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).

Considering that sphingolipids, ceramide, and their basic component sphingosine (SPH) have a vital role on \textit{M. tb} containing endosomes, del Olmo et al. synthesized 18 aminoalcohols and diamines and evaluated them in vitro against \textit{M. tb} H37Rv.\textsuperscript{126} Two aminoalcohols 139...
Compounds with benzyl ether moiety $139$ and $140b$ (MIC = 3.6 and 3.1 $\mu$M, respectively) were more active than their alcohol derivatives $138b$ and $141$ (MIC = 24 and 20 $\mu$M, respectively). The negative influence due to $N$-Boc protection can also be seen in hemisuccinyl ($140c$, MIC = 140 $\mu$M) and hemiglutaryl amides ($140d$, MIC = 68 $\mu$M) in comparison with compounds $139$, $140a$, and $140b$ (3.6, 16.6, and 3.1 $\mu$M, respectively). Also the potency of amide $143c$ (133 $\mu$M) was less than compounds $142b$, $143a$, and $143b$ (12.6, 32, and 15.2 $\mu$M, 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 $\mu$M) or methoxycarbonylmethyl ($140e$ and $143d$, MIC = 72 and 59 $\mu$M) alkylated amines show that diamines were more active than aminethers. 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 $>20$ $\mu$M, 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 $\mu$M) 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 $\mu$M) against strain no. 332.

Recently, we have initiated a program toward the development of novel antimicrobial agents, among these cyclohexane-1,2-diamine ($146a$-$146t$) and cyclohexane-1,3-diyl(dimethanamine based compounds ($147a$-$147l$) have shown potent antibacterial and antifungal activities with low nmoIal MIC values. 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.
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. 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. Fluoroquinolones are also active against INH and RIF resistant mycobacteria. Ciprofloxacin, moxifloxacin, levofloxacin, and oxofloxacin (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. 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.

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). Norfloxacin was introduced in the 1980s and showed preferentially better activity against Gram-negative bacteria as compared to Gram-positive bacteria. Subsequent developments produced quinolones with improved solubility (e.g., ofloxacin), antimicrobial activity (e.g., ciprofloxacin), of prolonged serum half-life (e.g., pefloxacin). The modifications in the quinoline nucleus have been done to achieve favorable properties and less side effects. The efficacy, pharmacology, pharmacokinetic parameters, activity spectrum, and adverse effects of the next generation of fluoroquinolones was already approved by FDA. 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.
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-aminomethyl-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.

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). 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

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

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 IC₅₀ 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.

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. 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.

Medicinal Research Reviews DOI 10.1002/med
Table VIII. In Vitro Antimycobacterial Activity of Gatifloxacin Derivatives (159–161)

<table>
<thead>
<tr>
<th>Comp no.</th>
<th>MIC-MTB (μg/mL)</th>
<th>MIC-MDR-TB (μg/mL)</th>
<th>Comp no.</th>
<th>MIC-MTB (μg/mL)</th>
<th>MIC-MDR-TB (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>159a</td>
<td>0.2</td>
<td>0.2</td>
<td>160b</td>
<td>0.78</td>
<td>0.78</td>
</tr>
<tr>
<td>159b</td>
<td>0.39</td>
<td>0.78</td>
<td>160c</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>159c</td>
<td>0.39</td>
<td>0.78</td>
<td>160d</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>159d</td>
<td>0.0125</td>
<td>0.05</td>
<td>161a</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td>159e</td>
<td>0.78</td>
<td>0.78</td>
<td>161b</td>
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<td>0.1</td>
</tr>
<tr>
<td>159f</td>
<td>0.78</td>
<td>0.78</td>
<td>161c</td>
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<td>0.1</td>
</tr>
<tr>
<td>159g</td>
<td>0.39</td>
<td>0.78</td>
<td>161d</td>
<td>0.2</td>
<td>0.78</td>
</tr>
<tr>
<td>159h</td>
<td>0.2</td>
<td>0.2</td>
<td>Gatifloxacin</td>
<td>0.2</td>
<td>3.12</td>
</tr>
<tr>
<td>160a</td>
<td>0.78</td>
<td>0.78</td>
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</tbody>
</table>

In 2010, Aboul-Fadl et al. reported the synthesis and anti-TB activity of imine-based derivatives of isatin (162–165). 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.

*Medicinal Research Reviews* DOI 10.1002/med
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. 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<sub>90</sub> in the range 0.5–1.6 μg/mL (Table IX). Compound 166d was the most potent derivative among the series with MIC<sub>90</sub> = 0.5 μg/mL against all M. tb strains. Compounds 166c, 166e-166i, 167c-167g were inactive (MIC<sub>90</sub> > 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<sub>50</sub> 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

<table>
<thead>
<tr>
<th>Comp no.</th>
<th>H37Rv</th>
<th>SS1</th>
<th>SS2</th>
<th>SS3</th>
<th>SS4</th>
<th>SS5</th>
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<tbody>
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<td>1.6</td>
<td>0.8</td>
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<td>1.6</td>
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<td>1.6</td>
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</tr>
<tr>
<td>166b</td>
<td>0.5</td>
<td>0.5</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<td>0.5</td>
<td>0.5</td>
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<td>0.5</td>
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<tr>
<td>167a</td>
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<td>0.5</td>
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<tr>
<td>167b</td>
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<td>1.6</td>
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<td>3.2</td>
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<tr>
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<td>&gt;4</td>
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<td>0.5</td>
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</table>

Medicinal Research Reviews DOI 10.1002/med
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. 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.

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. 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 NO₂ is essential for activity. Compound 172b, a di-t-butyl derivative was found to be the most active with MIC₅₀ = 0.5–1.5 μM, which was comparable to ciprofloxacin and ofloxacin (MIC₅₀ = 1–2 μM and MIC₅₀ = 1.5–3 μM, respectively). Compounds 172c and 172d exhibited mild activity (MIC₅₀ range 2 ≥ 125 μM), followed by 172a (MIC₅₀ range 3.2 ≥ 200 μM).
D. Quinone Derivatives as Anti-TB Agent

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

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

Copp et al. prepared several analogues of natural marine alkaloid *Ascididemin* containing quinone and enamine motif and evaluated them against *M. tb* H37Rv in BACTEC 12B media using the MABA. All the compounds showed good to mild inhibitory activity. Compounds and showed equal activity which indicates that the unsaturation in the side chain (hardly matters for determining the activity, whereas compound exhibited poor activity when compared with and, which indicates the importance of side chain containing enamine moiety for the activity. Compound exhibited better activity than the compound, which indicates that the quinone moiety is important for the activity. In compounds, 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 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 tested against clinical isolates of *M. avium* showed MIC value of 1–2 μg/mL. Subsequently, 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).
Wu et al. isolated engelharquinone (189), engelharquinone epoxide (190), engelharolide (191), and engelhardic acid (192) from Engelhardia roxburghiana in 2007. Englarharquinone (189) exhibited moderate antitubercular activity (MIC ≤ 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*. 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, 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.
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Sturdy et al. isolated eucapsitrone (199), an anthraquinone derivative with an indenoanthracene-trione skeleton, from the cyanobacterium Eucapsis sp. by bioassay-guided fractionation. Eucapsitrone (199) showed anti-M. tuberculosis activity in the LORA and MABA with MIC values of 6.4 and 3.1 μM, respectively. Virulent H37Rv strain was used in both assays. The MIC value was determined as the least drug concentration showing ≥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. The structures were determined using spectroscopic techniques. The known octahydroanthraquinone 200c exhibit antimycobacterial activities against M. tb H37Ra with MIC value 38.57 μM. Compounds 205c and 209c exhibited milder activity than 200c against M. tb.
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.\textsuperscript{177} Though the pO\textsubscript{2} of TB lesions is less than 10 mmHg and they are hypoxic in nature,\textsuperscript{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.\textsuperscript{179} Metronidazole (MTZ), a 5-nitroimidazole (Fig. 5), is widely used against anaerobic bacterial diseases.\textsuperscript{180} It has been known for almost 15 years that under low-oxygen conditions \textit{M. tb} cultures become sensitive on treatment with MTZ.\textsuperscript{181,182} However, MTZ has no activity against aerobic populations of \textit{M. tb} and is not used in the treatment of human TB. The 4-nitroimidazoles based on MTZ originally synthesized as radiosensitizing agents\textsuperscript{183} were later found to have significant activity against \textit{M. tb},\textsuperscript{184,185} From a large number of 2,3-dihydro-6-nitroimidazo[2,1-\textit{b}]oxazole derivatives, compound 2-ethyl-6-nitro-2,3-dihydropyrimido[2,1-\textit{b}]oxazole (CGI-17341) (Fig. 5) emerged as an interesting compound with potent in vitro and in vivo activity against \textit{M. tb} strains. The nitroimidazole (5)-2-nitro-6-(4-(trifluoromethoxy)-benzyl oxy)-6,7-dihydro-5\textit{H}-imidazo[2,1-\textit{b}][1,3]oxazine (PA824)\textsuperscript{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.\textsuperscript{187} PA824 has an aerobic MIC of 0.4 $\mu$M, anaerobic activity at 8–16 $\mu$M 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.\textsuperscript{188} The synthesis and anti-TB activity of two diastereomers of the 7-methyl-nitroimidazooxazine (210 and 211) were reported by Li et al. in 2008,\textsuperscript{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 $\mu$M. 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.\textsuperscript{189} The MAC for compounds 210 and 211

\textbf{Figure 5.} Antitubercular nitroimidazoles.

\textbf{Medicinal Research Reviews DOI 10.1002/med}
were equivalent to PA824. Both the compounds were evaluated against wild-type H37Rv and three different mutants resistant to PA824.

In 2009, Kim et al. synthesized a large number of derivatives of 4- and 5-nitroimidazoles (212–225) and evaluated their antitubercular activity. 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). 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 imidazopyrimidine 226i exhibited very weak activity (MIC for MABA 126 \( \mu \)M and for LORA > 128 \( \mu \)M) 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 \( \mu \)M). Pyrazolopyrimidine analogue (227c-227f) also showed marginal activity (MIC = 128 \( \mu \)M). From the activity profile it can be concluded that lipophilic side chain and nitroheterocyclic core are important for activity.
Table X. Antimycobacterial Activity of Ortho-Linked Biphenyl Analogues (229a-229m) of PA824

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

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

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

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). 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 Analouges (231–235) of PA824

<table>
<thead>
<tr>
<th>Comp no.</th>
<th>LORA (μM)</th>
<th>MABA (μM)</th>
<th>Comp no.</th>
<th>LORA (μM)</th>
<th>MABA (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>231</td>
<td>3.9 ± 2.0</td>
<td>0.045 ± 0.005</td>
<td>231</td>
<td>3.9 ± 2.0</td>
<td>0.045 ± 0.005</td>
</tr>
<tr>
<td>232d</td>
<td>1.4 ± 0.3</td>
<td>0.065 ± 0.005</td>
<td>232d</td>
<td>1.4 ± 0.3</td>
<td>0.065 ± 0.005</td>
</tr>
<tr>
<td>232e</td>
<td>0.82 ± 0.19</td>
<td>0.03 ± 0</td>
<td>232e</td>
<td>0.82 ± 0.19</td>
<td>0.03 ± 0</td>
</tr>
<tr>
<td>232g</td>
<td>0.78 ± 0.16</td>
<td>0.08 ± 0.02</td>
<td>232g</td>
<td>0.78 ± 0.16</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>232h</td>
<td>0.97 ± 0.08</td>
<td>0.035 ± 0.005</td>
<td>232h</td>
<td>0.97 ± 0.08</td>
<td>0.035 ± 0.005</td>
</tr>
<tr>
<td>232i</td>
<td>1.8 ± 0.1</td>
<td>0.06 ± 0</td>
<td>232i</td>
<td>1.8 ± 0.1</td>
<td>0.06 ± 0</td>
</tr>
<tr>
<td>233a</td>
<td>2.2 ± 0.7</td>
<td>0.045 ± 0.005</td>
<td>233a</td>
<td>2.2 ± 0.7</td>
<td>0.045 ± 0.005</td>
</tr>
<tr>
<td>233b</td>
<td>1.6 ± 0.5</td>
<td>0.06 ± 0.01</td>
<td>233b</td>
<td>1.6 ± 0.5</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>233j</td>
<td>1.4 ± 0.6</td>
<td>0.077 ± 0.026</td>
<td>233j</td>
<td>1.4 ± 0.6</td>
<td>0.077 ± 0.026</td>
</tr>
<tr>
<td>233n</td>
<td>0.95 ± 0.04</td>
<td>0.077 ± 0.026</td>
<td>233n</td>
<td>0.95 ± 0.04</td>
<td>0.077 ± 0.026</td>
</tr>
<tr>
<td>234a</td>
<td>1.4 ± 0.5</td>
<td>0.015 ± 0.005</td>
<td>234a</td>
<td>1.4 ± 0.5</td>
<td>0.015 ± 0.005</td>
</tr>
<tr>
<td>234b</td>
<td>2.7 ± 0.6</td>
<td>0.015 ± 0.005</td>
<td>234b</td>
<td>2.7 ± 0.6</td>
<td>0.015 ± 0.005</td>
</tr>
<tr>
<td>234e</td>
<td>1.4 ± 0.5</td>
<td>0.03 ± 0.01</td>
<td>234e</td>
<td>1.4 ± 0.5</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>234f</td>
<td>0.58 ± 0.33</td>
<td>0.025 ± 0.005</td>
<td>234f</td>
<td>0.58 ± 0.33</td>
<td>0.025 ± 0.005</td>
</tr>
<tr>
<td>234l</td>
<td>0.73 ± 0.22</td>
<td>0.04 ± 0.01</td>
<td>234l</td>
<td>0.73 ± 0.22</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>234n</td>
<td>2.7 ± 1.2</td>
<td>0.04 ± 0.01</td>
<td>234n</td>
<td>2.7 ± 1.2</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>234o</td>
<td>1.3 ± 0.1</td>
<td>0.035 ± 0.015</td>
<td>234o</td>
<td>1.3 ± 0.1</td>
<td>0.035 ± 0.015</td>
</tr>
<tr>
<td>234u</td>
<td>0.63 ± 0.30</td>
<td>0.060 ± 0.016</td>
<td>234u</td>
<td>0.63 ± 0.30</td>
<td>0.060 ± 0.016</td>
</tr>
</tbody>
</table>

![Diagram of para-linked biphenyl analogues]
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). 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.

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

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

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. 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.
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. 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. 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.

![Chemical structures](image)

**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*. 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.
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. 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 > 100 μg/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).

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. 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.
Three semisynthetic diterpenoids, 13 hydroxy-mulin-11-en-20-oic acid \( n \)-propyl ester (306c), and the \( n \)-propyl (310b) and \( n \)-butyl (310e) esters of isomulinic acid, were found to be antitubercular with MIC = 6.25 \( \mu \)g/mL against drug-resistant strain of \( M. \) \( \text{tb} \). 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 \( \text{iso} \)-propyl (310d) and \( \text{iso} \)-butyl (310e) esters of isomulinic acid showed some activity, against resistant strain of \( M. \) \( \text{tb} \). The C-20 alkyl derivatives were active against the resistant strain of \( M. \) \( \text{tb} \), and compounds 306c, 310b, and 310e showed more activity against the same strain with MIC = 6.25 \( \mu \)g/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 310e 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.

**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 \( \text{Streptomyces} \) sp. 201. Among them, compound 311g possessed maximum activity (MIC = 8 \( \mu \)g/mL) against \( M. \) \( \text{tb} \). This was followed by compound 311d with MIC 10 \( \mu \)g/mL and compound 311f with MIC 16 \( \mu \)g/mL, whereas compound 311c and 311h were found to be completely inactive. Compound 311e showed antimycobacterial activity in the range of 24 \( \mu \)g/mL. The R isomer 311a (MIC = 10 \( \mu \)g/mL) was slightly more active than the corresponding S isomer (311b, MIC = 14 \( \mu \)g/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 \( \mu \)M) showed better activity than INH (MIC = 2.04 \( \mu \)M). The activity of compound 313c with piperazinyl group was very good and gave elating MIC value of 0.56 \( \mu \)M. But the \( N \)-methyl piperazine group (313d, MIC = 8.61 \( \mu \)M) 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 \( \mu \)M, respectively). Compounds 317a and 317b have similar activity (MIC = 0.88 \( \mu \)M and 0.87 \( \mu \)M), 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 \( M. \) \( \text{tb} \) 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 (ATCC 27294) by using alamar blue susceptibility test (Table XIV). 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, 318i, 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. 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>
<thead>
<tr>
<th>Comp no.</th>
<th>MIC</th>
<th>Comp no.</th>
<th>MIC</th>
<th>Comp no.</th>
<th>MIC</th>
<th>Comp no.</th>
<th>MIC</th>
</tr>
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<td>318a</td>
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<td>318g</td>
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<td>318m</td>
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<td>318t</td>
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<td>2.5</td>
<td>318i</td>
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<td>318o</td>
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<td>318u</td>
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<td>318d</td>
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<td>318j</td>
<td>0.31</td>
<td>318p</td>
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<td>318v</td>
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<tr>
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<td>318l</td>
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<td>318r</td>
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</tr>
</tbody>
</table>

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

*Medicinal Research Reviews* DOI 10.1002/med
class of compounds.\textsuperscript{209} They developed the antibacterial properties of DL-$S$-$n$-[3-(4-acetyl phenyl)-2-oxo-5-oxazolidinylmethyl] acetamide (DuP721), which exhibited fairly good antitubercular activity.\textsuperscript{214} The Upjohn Company Laboratories in Kalamazoo, Michigan did SAR studies on DuP721 and discovered a new anti-TB drug named linezolid.\textsuperscript{215-218} Eperzolid 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.\textsuperscript{219, 220} Barbachyn et al. from Upjohn Laboratories reported that oxazolidinones PNU100480 and PNU101603 (Fig. 6) exhibit potent activity against \textit{M. tb} with MIC \textlesssim 0.125 $\mu$g/mL.\textsuperscript{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.\textsuperscript{222}

Sbardella et al. synthesized 3-([1H]-pyrrol-1-yl)-2-oxazolidinone analogues (319a-319d, 320a, 320b, and 321) of PNU100480 and evaluated them in vitro against atypical \textit{M. tb} strain ATCC 27294.\textsuperscript{223} All the compounds were found to be active against \textit{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\textsubscript{50} = 1.9 $\mu$M. Compound with a morpholine (320a) and thiomorpholine (320b) have MIC\textsubscript{50} values of 12.9 $\mu$M and 9.8 $\mu$M, respectively, while compound 321 with a morpholine directly attached to pyrrole was inactive.

Dixit et al. synthesized substituted thiourea derivatives of oxazolidinones (322a-322j) and screened them against \textit{M. tb} ATCC27294 strain using isoniazid (MIC = 0.25 $\mu$g/mL) and linezolid (MIC = 0.5 $\mu$g/mL) as reference drugs.\textsuperscript{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 $\mu$g/mL. Compound 322b (MIC = 0.06 $\mu$g/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. Three compounds (325c, 326a, and 326b) showed good activity with MIC 1.0 μg/mL while for rest of the compounds MIC was ≥ 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. 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. 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).

**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 \textit{M. tb}. Two purine analogues 348a and 348b exhibited MIC values 1.56 and 0.78 $\mu$g/mL, respectively against the \textit{M. tb} H37Rv strain. N9-substitution was found to increase the antimycobacterial activity of these purine derivatives. The compound 343b exhibited significant activity against H37Rv with MIC$_{90}$ of 3.13 $\mu$g/mL and its N9-alkylated analogue 348a displayed two times better activity (MIC$_{90}$ = 1.56 $\mu$g/mL). Among the other N9-alkylated purine analogues (348b-348j), compound 348b showed maximum activity with MIC$_{90}$ value of 0.78 $\mu$g/mL against \textit{M. tb} H37Rv. Compounds 346a-346d were found to be less active than 348a with MIC$_{90}$ greater than 3.13–6.25 $\mu$g/mL. Only compound 346c exhibited some activity with MIC$_{90}$ value of 3.13 $\mu$g/mL. In case of H37Ra strain of \textit{M. tb}, most of the analogues were found to be inactive or very less active (MIC$_{90}$ $\geq$ 12.8 $\mu$g/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 $\mu$g/mL. Compounds 343b and 348a were also tested against \textit{M. tb} Erdman in monolayers of a mouse bone marrow macrophages model. After 7 days, at concentrations 2.53 and 1.65 $\mu$g/mL, these two compounds caused about 90% decrease in the viable cell count.
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. 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.

A series of 3-amino-4-arylpuridazino[4,3-b]indoles (puridazinoindoles) were screened for their antimycobacterial activity by Velezheva et al. 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.
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. 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 = 1 μg/mL).

X. Li et al. synthesized several (Z)-methyl-2-(2-oxo-2*H*-benzo[b][1,4]oxazin-3(4H)ylidene)acetates. 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. 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).

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). 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.
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 $\mu$M, respectively.$^{246}$ The reference drug INH showed IC$_{90}$ of 0.21 $\mu$M under similar conditions.

Phenothiazines are mainly antipsychotic drugs but some of these compounds have also shown activity against *M. tb*.$^{247,248}$ The chlorpromazine (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 $\mu$g/mL and 15 $\mu$g/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 $\mu$g/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 MDR-TB. The CFU MIC of levopromazine (373),$^{247}$ trifluoperazine (375),$^{260,268}$ methdilazine (374)$^{269}$ were found to be 10, 8–32, and 5–15 $\mu$g/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 ($5.1 \times 10^4$, SD $6 \times 10^4$). Compound 369 is now out of patent and treatment of some XDR-TB patients with this compound has shown good results.$^{270}$

![Chemical structures](image_url)
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.

ACKNOWLEDGMENTS

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