Review Article

Mini review on diarylquinolone compound Bedaquiline and some other quinolone derivatives and their antitubercular activity

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Abstract
The strategies design for new anti-tuberculosis (anti-TB) compounds is based on the development of analogs of currently used drugs and novel compounds. The strategies employed and analyze structural features which have led to the development of new anti-TB agents. It is important to determine if compounds have potential activity against these bacteria at the onset of design. The physicochemical properties that directly affect the pharmacokinetics and pharmacodynamics of drugs influence of stereoisomers on biological activity, because individual enantiomers have significant differences in activity, although sometimes the activity of some enantiomers cannot be explained. In this article, detailed study of diarylquinoline and some other quinolone compounds have been reported.

1. Introduction
Mycobacterium tuberculosis (Mtb) is a causative agent of tuberculosis (TB). It is a pathogen that has latently infected about one third of the world population. Infection occurs via aerosol, and inhalation of a few droplets containing Mtb bacilli is enough for lung infection. After infection, Mtb pathogenesis occurs in two stages. The first is an asymptomatic state that can persist for many years in the host, called latent TB. The second stage requires only a weakened immune response to become activated, then the bacteria begins replicating and causing characteristic symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death. The emergence of Human Immunodeficiency Virus (HIV) and the resultant Acquired Immune Deficiency Syndrome (AIDS) pandemic underlined the importance of reactivation of the disease and its potentially catastrophic outcome since over 50% of deaths among HIV infected patients results from co-infection with Mtb with the two pathogens inducing each other’s replication, thus accelerating the collapse of the immune system.[1-6] The World Health Organization (WHO) survey estimated that close to 2 million deaths occur every year, that there are approximately 8 million new cases annually, and that every third individual on the planet has been exposed to or infected by Mtb. Although TB can be treated and even cured with chemotherapy, treatment is exceedingly lengthy and takes 6-9 months. In addition to significant toxicity, lengthy therapy also causes poor patient compliance, which is a frequent cause for selection of drug resistant and often deadly multidrug resistant TB (MDR-TB) bacteria.[7-10] Currently, TB therapy is made up of a cocktail of first-line drugs, Isoniazid (INH), Rifampicin (RIF), pyrazamide (PZA) and ethambutol, which are given for six months. If this treatment fails as a result of bacterial drug resistance or intolerance to one or more drugs, second-line drugs are used, such as para-aminosalicylate, kanamycin, fluorquinolones, capreomycin, ethionamide and cycloserine. These are generally less effective or more toxic with serious side effects. This second-line treatment can also result ineffective since MDR-strains that exhibit resistance to these second-line drugs are currently on the rise. Treatment is also made quite difficult by the presence of metabolically silent, persistent or dormant bacteria within host lesions. These are not susceptible to the anti-TB drugs that usually kill growing but not persistent bacteria. While there are many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, and ineffective drugs, duration of lengthy treatments is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid health improvement, thereby favoring the emergence of drug-resistant strains.[11-15]

2. Diarylquinolines
The diarylquinoline compound Bedaquiline (TMC207 or R207910), first reported in 2005, is the first known anti-TB agent in the diarylquinoline class.[16-18] The vast research and development on TMC207, have contributed new related compounds.[19,20] TMC207 was one of the lead compounds discovered in a high-throughput screen for compounds with activity against Mycobacterium smegmatis (nonpathogenic fast-growing mycobacterium), which were subsequently evaluated against Mtb.

Bedaquiline is formerly known as TMC207 or R207910, bedaquiline is a new antibiotic belonging to the class of diarylquinolines with specific activity against Mtb, which has also shown in vitro activity against other non-tuberculous mycobacteria.[21,22] Bedaquiline was discovered after a high-throughput evaluation of thousands of compounds using M. smegmatis in a whole-cell assay.[16] The drug showed activity against Mtb and then entered into clinical evaluation for drug susceptible and MDR-TB. Based on the results of two phase II clinical trials, bedaquiline has recently received conditional approval for the treatment of MDR-TB under the trade name Sirutro. A black box warning is, however, accompanying this authorization due to the reported unexplained deaths and QT interval prolongation.[23,24] Bedaquiline is also being evaluated in new combination regimens with the purpose of reducing the length of treatment. The mode of action of bedaquiline is by inhibiting the ATP synthase of Mtb, which was a completely new target of action for an anti-TB drug. This mode of action was discovered by analyzing Mtb and M. smegmatis mutants resistant to bedaquiline. By sequencing the genome of these mutants and comparing to that of the susceptible strains, the only mutation found was in the atpE gene, which encodes the F0 part of the F0-F1 subunit of the ATP synthase.[25] This is a complex structure that
generates the ATP needed by the mycobacterial cell for which bedaquiline has a favored specificity compared to mitochondrial ATP synthase.[26-28]

![Structure of bedaquiline](image)

**Figure 1: Structure of bedaquiline**

The most prevalent mutation in the *atpE* gene found in bedaquiline resistant mutants is A63P but also I66M has been found. The latter introduces a modification that interferes with the proper binding of bedaquiline to its target.[29,30] Nevertheless, in a study to further assess the mechanisms of resistance to bedaquiline in *Mtb*, it was found that only 15 out of 53 resistant mutants had mutations in *atpE*. The other 38 strains lacked mutations in *atpE* or even in the F0 or F1 operons, which suggests that other mechanisms of resistance are still possible.[22]

Relative configuration of the two stereocenters of TMC207,[31,32], are required for activity.[16,33] Sterically undemanding functional groups can be substituted for the bromine on the quinoline ring without significant loss of activity, although a bromine atom appears to be preferred. The naphthyl substituent can be replaced with other electron-poor aryl groups and still maintain good activity against *Mtb*. Based on initial reports, the dimethyl substituted tertiary amine appears to be required for activity, with the replacement of one methyl substituent with a proton or ethyl substituent resulting in a decrease in activity.[16,24] However, more recent reports suggest that the N-monodesmethyl metabolite of TMC207 produced by oxidation by CYP3A4, a cytochrome P450 that is potently induced by RIF, maintains significant antitubercular activity.[34,35]

The TMC207 is highly specific for mycobacteria. Both H37Rv and clinical isolates show MICs in the range of 54–217 nM. TMC207 targets the c subunit of ATP synthase (*atpE* gene), a mechanism of action distinct from fluoroquinolones and other quinoline derivatives.[29] The tertiary amine of TMC207 serves as an arginine mimic, allowing the compound to disrupt the proton transport chain of ATP synthase.[36] Point mutations in *atpE* confer resistance; these mutations occur at a rate of one in 10⁷ to 10⁸, similar to the bacterial mutant frequency of rifampin resistance. Treatment of *Mtbc* infected mice with TMC207 at 25 mg/kg was as effective as triple combination therapy of RIF/INH/PZA in mice.[37] In guinea pigs, treatment with TMC207 for 6 weeks resulted in almost complete eradication of *Mtbc* bacilli from lesions.[38] Furthermore, TMC207 has also been shown to be bactericidal in vitro against non-replicating *Mtbc*, suggesting that TMC207 might prove therapeutically effective against latent TB. Also, a once-weekly schedule of administration of TMC207/rifapentine/PZA tested in mice was more active than the standard regimen of RIF/INH/PZA given daily.[39] Because TMC207 has a long half-life in humans [44–64 h in plasma], once-weekly TB treatments might one day be possible. However, metabolism of TMC207 is enhanced by the presence of RIF, suggesting that coadministration of these drugs might not be straightforward.[33,34]

In humans, Cmax is reached in 4–5 h, and a daily dose of 400 mg administered daily for 7 days results in a Cmax of 10 nM. A steady-state concentration of 1 nM, which appears to be required for bactericidal activity, can be maintained with a dosing schedule of 400 mg daily for 2 weeks followed by reduced doses of 200 mg three times weekly. Adverse events occurred at a low rate and side effects were considered mild to moderate.[24,25] The TMC207 showed significant bactericidal activity after 4 days of a 7-day trial treating previously untreated TB patients, although onset of bactericidal activity was delayed in comparison to RIF and INH. The TMC207 in combination with a standard, five-drug, second-line anti-TB regimen in MDR patients showed that after 8 weeks of treatment, 49% of study participants receiving the TMC207 regimen converted to negative sputum culture, compared with 9% of those on the standard regimen.[40] Additional trials are ongoing in MDR patients,[40], and TMC207 is undergoing further development for drug-resistant TB.[41]

3. Other quinoline derivatives

A quinoline ring is one of the moieties frequently used in new drug design. It has been considered a pharmacophore for the design of anti-TB agents. Dihaloquinone, denominated TMC207, is an adenosine ATP synthase inhibitor that is one of the most important quinoline derivatives with anti-TB activity. TMC207 is currently in Phase II clinical trials. Also, butanamide has been established as an important pharmacophore with good antibacterial activity and the carbahdyrazine moiety is also known as a pharmacophore group. Based on the above, the design of new quinoline derivatives with active carboxylic acid and butanamide moieties has been actively pursued.[42-48] The study of these compounds shows that the presence of a trifluoromethyl group at 8-position increases activity; however, the introduction of a fluoroo group in 6-position partially decreases activity (1) considering these type of compounds nontoxic.[49] Following the development of mefloquine analogs (2) in a series of compounds (3), good anti-TB activity has been attributed to the presence of pharmacologically active heterocyclic groups such as pyrazole, imidazole, and indole rings on the quinoline ring. Compounds with a heteroaromatic pyrazole ring have activity against resistant strains, which can be attributed to the presence of substituents (electron donating groups) that stabilize the pyrazole ring, making the quinoline ring a more active entity.[50] The conformational restriction-like strategy in flexible drugs is extensively used in medicinal chemistry. This helped determine steric requirements of receptor–drug interaction and identification of new structures with high efficiency and selectivity. Based on this, Goncalves et al studied the conformational restriction of the piperidinyl ring of mefloquine through the construction of an oxazolidine ring and different substituents on the phenyl ring (4). Conformational restriction showed that the introduction of an oxazolidine core in the mefloquine structure enhances anti-TB activity. The activity of these compounds is affected by substituents on the aromatic ring bound to C-17 of the oxazolidinyl nucleus. Compounds that show hydroxyl or methoxyl groups, which are both electron donors and capable of forming strong hydrogen bonds, in general are active. In contrast, with one exception, compounds with nitro or halogenated groups (electron withdrawing groups and capable of forming only weak hydrogen bonds), are inactive.[51] Thus, mefloquine has been used to design anti-TB agents, introduction of a hydrazine linker into mefloquine at 4-position, substitution of a piperidine with a piperazine ring and extension of
the basic terminus of the piperazine ring at 4-position. Additionally, isoxazole is emerging as one of the most powerful hits in high-throughput screening (HTS) against M.tb. Both types of compounds show an aromatic ring, a two-atom linker and a five or six member ring. Hybridization strategies have been the basis for the design of new chemical entities (5). One problem that has been detected in this type of compounds is poor penetration of acid derivatives through the M.tb cell wall. It is suggested that these compounds may act as produgs when ester derivatives generate acid derivatives (5). SAR studies of these compounds show that when a methyl group replaces a trifluoromethyl group, it is 10 times less active, suggesting that electronic effects may play an important role in anti-TB activity. Moreover, steric effects can affect anti-TB activity. Subsequently, making use of drug design strategies, the authors included ester biososters, such as amides and oxadiazole, although none of these biososters showed better activity than ester derivatives. It was determined that 2 and 3-trifluoromethyl groups on quinoline ring (5) are essential for anti-TB activity against replicative bacteria.[52] The quinoline and oxazole ring hybridization has been used to develop a series of new anti-TB agents (6) which have good activity due to the presence of aryl substituents at 2-position on quinoline ring. The studies show that the introduction of a 1,3- oxazole ring significantly increases activity, obtaining compounds that are more potent than INH.[49] In search of a new moiety that confers anti-TB activity with low cytotoxicity, Yang and colleagues reported methoxybenzofuro[2,3-b]quinoline derivatives (7), compounds that have a potent Mtb growth inhibition of 99% at low concentrations (0.20 µg/mL) and very low cytotoxicity against VERO cells with an Inhibitor Concentration 50 (IC50) value of > 30.00 µg/mL.[53] Several studies have analyzed alterations in the quinoline ring, mainly at 3,6 and 7- position. A new strategy for anti-TB agent development, they made a modification in the 2-position, including an aliphatic side chain with various degrees of unsaturation, lengths chains, and double bond positions (8). Their results showed that increasing the chain length enhances anti-TB activity, showing optimal activity with 14 C atoms. If there is an increase of more carbon atoms in the chain, activity decreases dramatically. This behavior has also been described for ciproflaxacin derivatives where lipophilicity could play an important role in anti-TB activity. The saturated aliphatic chain has less activity than unsaturated analogues. This means that unsaturation of an aliphatic chain is an essential structure for in vitro anti-TB activity.[54]

The 5-[(E)-2-arylethenyl]-3-isoxazolcarboxylic acid alkyl ester derivatives and found them as a promising anti-TB agents. Among all compound 5-(E)-2-(6-methoxy-4-quinolyl) ethenyl]-3- isoxazolcarboxylic acid butyl ester (9) showed the best activity against Mtb H37Rv with a MIC1.8 µM. This compound showed almost equal potency with standard drugs (INH, RMP) in terms of activity and cytotoxicity.[55] A series of 3H-1,3,4-Oxadiazole-2-thione and 3H-1,3,4-oxadiazol-2-one derivatives and tested for their in vitro anti-TB activity against Mtb H37Rv. Among both the series, oxadiazolone derivatives 10 showed an interesting anti-TB activity of MIC 1.25 µg/mL while the corresponding thione derivatives showed poor activity.[56]

The quinoline derivatives to be evaluated against TB were quinoline based antimalaria drugs, such as quinine, chloroquine, mefloquine, primaquine, and amodiaquine which possessed moderate biological activity against TB. In addition, identification of new promising quinoline based anti-TB agents, 2,8-dicyclopropyl-4-methylquinoline (DCMQ, 11)[44] and Diarylquinoline (TMC207)[31] have definitively initiated the optimization of quinoline for antitubercular drugs. In this concern, 1-(5-isouquinoline sulfonf)-2-methylpiperazine (12), a protein kinase inhibitor for its anti-TB profile and found to inhibit the growth of two different mycobacterial strains, the slow-growing M. bovis Bacille Calmette Guerin (BCG) and the fast-growing sarcophyre M. smegmatis mc2 155, in a dose-dependent manner. While screening for the effect of kinase inhibitors on mycobacterial growth, millimolar concentrations of 12 induced a 40% decrease in the growth of M. bovis BCG when measured as a function of oxidative phosphorylation. Compound 12 induced decreases in growth was shown to involve a 2-log fold decrease in the viable counts of M. smegmatis within a 48h period and a 50% reduction in the number of BCG viable counts within a 10-day period. Micromolar concentrations of 12 induced a significant decrease in the activity of the Mtb protein serine/threonine kinase (PSTK) PknB. The inhibition of mycobacterial growth as well as the inhibition of a representative Mtb protein serine/threonine kinase PknB suggests that conventional PSTK inhibitors can be used to study the role that the mycobacterial PSTK family plays in controlling bacterial growth.[57] A series of quinolinyl hydrazones and majority of the tested compounds showed an inhibitory activity between 95 and 100%. The most potent compounds of the series (13a-c) were having a MIC of 0.78µg/mL. These results indicated that the activity was significantly affected by substituents both on the quinoline nucleus and hydrazinoic moiety. On quinoline nucleus the most effective substituents resulted were 6-cyclohexyl, 7-methoxy or ethoxy and 7-chloro groups. Similarly, for the hydrazinoic moiety greater effectiveness resulted for para and ortho-methoxyanphthyl substituents whereas substitution with chloride resulted in inactive compounds.[48]

Inspired with the activity profile of DCMQ (11) four new series of the ring-substituted quinoline carboxyhydrazides. Of these 3-quinolinelhdydrazides and N2-alkyl/N2,N2-dialkyl/N2-aryl-4-(1-adamantyl)-2-quinolinecarboxamides showed moderate activity of MIC in the range of 6.25-3.125 µg/mL against Mtb H37Rv. The most
active compounds were adamantyl derivatives (14a and 14b) exhibited MIC of 3.125 μg/mL. Whereas, a number of thirty-three quinoline derivatives based on TMC207 and found a molecule (15) active with a MIC=3.12 μg/mL.[58,59] With the same interest, 3-benzyl-6-bromo-2-methoxy-quinolines and amidoxies of 2-{[6-bromo-2-methoxy-quinolin-3-yl]-phenylmethyl]-malonic acid monomethyl ester. Four compounds (16a-d) showed moderate activity of MIC 6.25 μg/mL against Mtb H37Rv.[19,20] A series of substituted quinolinyl chalcones and substituted quinolinyl pyrimidines and evaluated for their in vitro anti-TB activity against Mtb H37Rv. Among both the series, chalcone derivatives 17a and 17b have shown anti-TB activity of MIC 3.12 μg/mL and were nontoxic against VERO, MBMDM cell lines.[60]

![Chemical structures](image)

The anti-TB potential of NAS-91 (18) and found that NAS-91 has multiple targets, which is particularly desirable for avoiding the emergence of resistant strains of Mtb. Therefore, NAS-91 represents a potent pharmacophore and appears to be a promising lead compound for future inhibitor development against TB.[61] Quinoline-3-carboxyhydrazone derivatives and screened for their antitubercular activity. Among all, two compounds (19a and 19b) have shown promising activity with a MIC 0.625, 2.5 and 1.25 μg/mL against Mtb H37Rv, *M. smegmatis* and *M. fortuitum* respectively. These compounds have shown almost equal potency similar to that of standard rifampicin.[43] Whereas in the series of 4-quinolylhydrazones, the most active compound (20) displayed an anti-TB activity of MIC 0.6 μg/mL and selectivity index 2.27.[62]

The 7-chloro-4-quinolylhydrazone derivatives and found three molecules (21a-c) with a moderate anti-TB activity with a MIC 2.5 μg/mL. These compounds were found to be nontoxic against J774 cell line up to the concentration 100 μg/mL.[63] In search of new potent quinoline derivatives consisting of triazolo, ureido and thioureido substituents at C-6 position. Of these, ureido derivative (22a) and triazolo derivative (22b) have shown moderate activity of MIC 3.125 μg/mL against Mtb H37Rv.[20] With the same motivation, a novel series of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines. The most active nontoxic compound (23) of the series exhibited increased potency of 1 μg/mL against Mtb H37Rv and 3.125 μg/mL against drug-resistant strain, in comparison to molecules (22a and 22b).[64] The quinoline-based derivatives were evaluated for their anti-TB efficiency. Among all, compound 24 has shown remarkable activity of MIC 0.77 μM against Mtb H37Rv and 0.99-1.55 μM against drug-resistant strains.[65] The isoxazole based quinoline derivatives and found a lead molecule 25, which showed MIC of 0.2 μM and 2.6 μM against Mtb H37Rv.[66] Thus, optimization of quinolines for the development of anti-TB agents is a fruitful approach.

![Chemical structures](image)

4. Conclusion

Tuberculosis remains the leading infectious disease worldwide, despite the availability of TB chemotherapy. Structure-based drug design strategies have allowed the discovery of new anti-TB drugs. These are increasingly receiving more attention, and a large number of new compounds or derivatives from existing drugs are under investigation. With this and a better understanding of the unique biology of TB, more targets will be validated, and hopefully a pattern will emerge that will help us reach the goals of more potent compounds that allow multiple stages and drug targets to be addressed.

References


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