Quinoline: A promising antitubercular target

ARTICLE *in* BIOMEDECINE [?] PHARMACOTHERAPY · OCTOBER 2014

Impact Factor: 2.02 · DOI: 10.1016/j.biopha.2014.10.007

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Review

Quinoline: A promising antitubercular target

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ARTICLE INFO

Article history:
Received 13 September 2014
Accepted 16 October 2014

Keywords:
Quinoline
Synthesis
Anti-tubercular
Tubercle Bacillus
Mycobacterium tuberculosis
Medicinal chemistry

ABSTRACT

Tuberculosis (TB) remains a global public health problem in recent years. TB originated mainly from various strains of *Mycobacterium tuberculosis*, is a highly infectious and chronic disease with high infection rate since ancient times. Since the last 50 years, the same long-duration, multidrug treatment plan is being followed for the treatment of tuberculosis. Due to the development of resistance to conventional antibiotics there is a need for new therapeutic strategies to combat *M. tuberculosis*. Subsequently, there is an urgent need for the development of new drug molecules with newer targets and with an alternative mechanism of action. Among hetrocyclic compounds, quinoline compounds are important privileged structure in medicinal chemistry, are widely used as "parental" compounds to synthesize molecules with medical benefits, especially with anti-malarial and anti-microbial activities. Certain, quinoline-based compounds, also show effective anti-TB activity. This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows the generation of a large number of structurally diverse derivatives. To pave the way for future research, there is a need to collect the latest information in this promising area. In the present review, we have collated published reports on this versatile core to provide an insight so that its full therapeutic potential can be utilized for the treatment tuberculosis. It is hoped that, this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic quinoline-based anti-TB drugs.

1. Introduction

Tuberculosis (TB) is a lung infection caused mainly by *Mycobacterium tuberculosis* (*M. tuberculosis* [MTB]). It is considered to be one of the most contagious and deadly diseases and is a major threat for public health. In combination with the HIV-1 infection TB is today amongst the biggest threat to the mankind. A large proportion of these new cases and deaths occur mostly in developing countries and the number of HIV-positive patients coinfected with *MTB* is constantly rising [1]. As a result, the TB situation may become even worse with the spread of HIV-1 worldwide, emergence of multi-drug (isoniazid and rifampin) resistant (MDR-TB) and the extensively drug resistant (XDR-TB) strains. Tuberculosis, also known as TB and 'white plaque', is caused by infection with members of the *MTB* complex, which includes *Mycobacterium tuberculosis* itself, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canettii* [2,3]. Robert Koch was the first scientist who isolatedthe bacteria, MTB in 1882 and got Nobel Prize for this discovery [4].

Abbreviations: AIDS, acquired immunodeficiency syndrome; CQ, 7-chloroquinoline; DOS, directly observed therapy short-course; DNA, deoxyribonucleic acid; EMB, ethambuthol; ETH, ethylenediamine spacer; GI, growth inhibition; HIV, human immunodeficiency virus; HTS, high throughput screening; INH, isoniazid; LORA, low-oxygen-recovery assay; LRP, luciferase reporter phage; LTBI, latent tuberculosis infection; MABA, Micro plate Alamar Blue Assay; *M. africanum*, *Mycobacterium africanum*; *M. smegmatis (MS)*, *Mycobacterium smegmatis*; *M. bovis (MB)*, *Mycobacterium bovis*; *M. caprae*, *Mycobacterium caprae*; *M. fortuitum (MF)*, *Mycobacterium fortuitum*; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MDR-TB, multi-drug resistant tuberculosis; NTM, non-tubercular mycobacterial; MTB, *Mycobacterium tuberculosis (M. tuberculosis)*; *NR-MTB*, non-replicating *Mycobacterium tuberculosis*; PZA, prazinamide; R-Mtb, replicating *Mycobacterium tuberculosis*; RIF, rifampicin; RTK, receptor tyrosine kinases; SAR, structure activity relationship; SI, Selectivity index; TB, Tubercle Bacillus; TMC, Tibotec Medicinal Compound; WHO, World Health Organization; XDR-TB, Extensively drug-resistant tuberculosis.

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http://dx.doi.org/10.1016/j.biopha.2014.10.007
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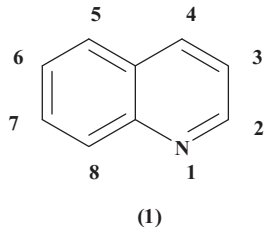
TB has been one of the deadliest diseases over the past few decades affecting nearly one-third of the world's population [5] with new infection occurring at 1% of population each year [6]. According to WHO studies, in 2011, there were 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB including one million HIV negative people [7]. The estimated 8.8 million new cases every year correspond to 52,000 deaths per week or more than 7000 each day [8,9]. These number shows ever, are only a partial depiction of the global TB threat. More than 80% of TB patients are in the economically productive age of 15–49 years, which results in tremendous economic and social problems. It was estimated that nearly 1 billion more people will be infected with TB in the next 20 years. About 15% of that group (150 million) will exhibit symptoms of the disease, and about 3.6% (36 million) will die from TB if new disease prevention and treatment measures are not developed [10]. In 2012, nearly nine million people around the world became sick with TB disease. There were around 1.3 million TB-related deaths worldwide. Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44. In 2012, an estimated 530,000 children became ill with TB and 74,000 HIV-negative children died of TB [11]. These data facilitated chemists and biologist to discovery of novel drug targets, assisted the understanding of the biological phenomenon of *MTB*. Currently, the six to nine month multidrug protocol used in the treatment of TB is highly effective with drug-susceptible TB, but poor patient compliance promotes development of drug resistance [12]. Although the existing method of curing is very effective against TB, the length of treatment, the toxicity and the potential for drug-drug interactions are factors that highlight the need for new anti-TB drugs [13,14]. In addition, *MTB* is resistant to some of the first and second line drugs [15]. Therefore, effective new drugs [16] and strategies [17] are essential to treat the TB bacilli.

It has been established that heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Among pharmacologically important heterocyclic compounds, quinoline and its derivatives are significant because of their wide spectrum of biological activities and



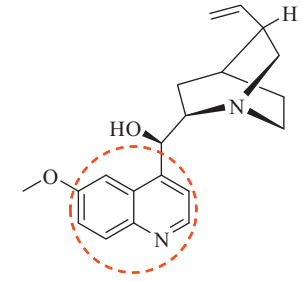
(1)

Fig. 1. Chemical structure and numbering of quinoline.

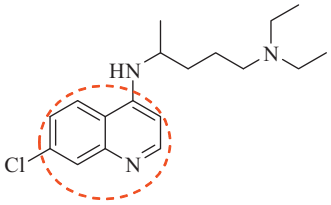
their presence in naturally occurring compounds. Quinoline is a heterocyclic aromatic nitrogen compound characterized by a double-ring structure that contains a benzene ring fused to pyridine at two adjacent carbon atoms (Fig. 1) [18,19]. It can also be named as, benzopyridine, benzo[b]pyridine, 1-azanaphthalene, 1-benzazine and benzazine.

In the recent time, quinoline nucleus has gathered an immense attention among chemists as well as biologists as it is one of the key building elements for many naturally occurring compounds. In particular, quinoline alkaloids are found in many different plants including Berberidaceae, Fumariaceae, Papavaraceae and Rutaceae [20–24]. Quinoline and its derivatives are important class of bioactive molecules in the field of drugs and pharmaceuticals. They exhibit significant activity against several viruses including antimalarial [25–27], antibiotic [28,29], anticancer [30], anti-inflammatory [31], antihypertensive [32], tyrokinase PDGF-RTK inhibition [33] and anti-HIV [34,35] properties. To list a few quinoline derivatives quinine (antipyretic, antimalarial, analgesic, and anti-inflammatory properties), chloroquine (antimalarial), amidiaquine (antimalarial and anti-inflammatory agent), camptothecin (DNA enzyme topoisomerase I), and saquinavir (anti-retroviral drug), which are actively used in pharmacological field are given below (Fig. 2).

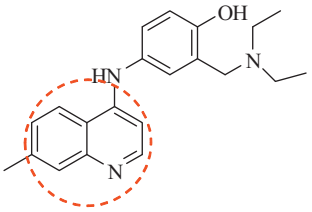
This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinoline, which allows creating a large number of structurally diverse derivatives. Quinoline has been considered a pharmacophore for



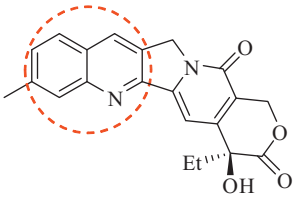
Quinine



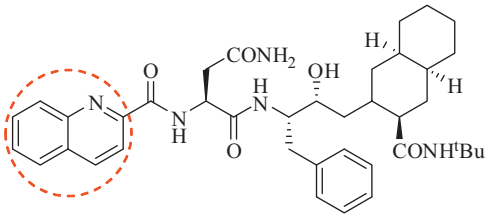
Chloroquine



Amidiaquine



Camptothecin



Saquinavir

Fig. 2. A few quinoline derivatives in clinical use.

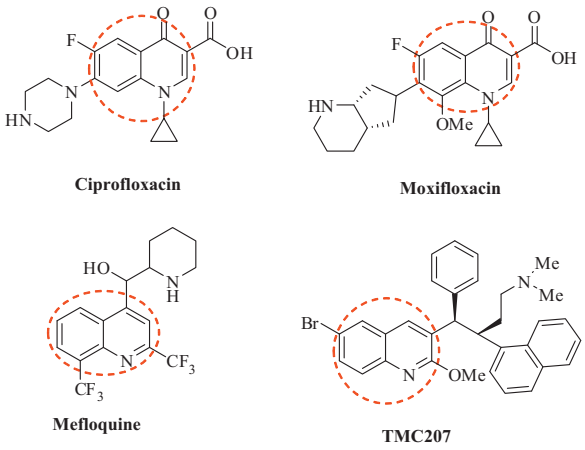


Fig. 3. Chemical structures of quinoline derivatives as anti-TB drugs.

the design of anti-TB agents. Ciprofloxacin and moxifloxacin (Fig. 3) are promising agents for the treatment of TB [36] having quinoline moiety. Quinoline based mefloquine (Fig. 3) is known for anti-tubercular activity [37–40] and its analogs have displayed moderate [41] to submicromolar [42] anti-TB activity. Tibotec Medicinal Compound 207 (TMC207) has emerged as a lead molecule out of this work and currently this compound is under phase II clinical assessment (Fig. 3). Detailed mechanistic study revealed that oligomeric (F ATPase) and proteolipic (V ATPase) subunit of ATP synthase of mycobacteria is the target of this compound. TMC207 is effective for resistant and nonresistant strains of *MTB* at MIC 0.03 μg/mL. The results of its clinical trials show that TMC207 may shorten the treatment of TB and be effective in its treatment [43–45].

Therefore, the syntheses of quinoline and its derivatives have received an increasing attention to synthetic organic chemists and biologists. It is still a challenge for the pharmaceutical chemist to develop more effective and less toxic agents to treat signs and symptoms of TB disorders. A large amount of effort has been invested in the past decade to develop quinoline-based compounds as modulator of anti-TB, which is active on different clinically approved therapeutic targets showing excellent therapeutic potency. By looking into the importance of this therapeutic area we decided to collect the published anti-TB data on quinoline (from 2010 to date), the indispensable anchor in medicinal chemistry. In this review, we have attempted to shed light and compile published reports on quinoline derivatives along with some opinion on different approaches to help the medicinal chemists in designing future generation potent yet safer anti-TB agents.

2. Quinoline: structural requirements for anti-TB activity

From collected published data, it is found that the quinoline nucleus substituted at all position with varied substituent's has produced potent anti-TB activity. However the 5-position of the nucleus is unsubstituted. The 1-position of quinoline may be unsubstituted or substituent's may vary from alkyl and aryl groups. Among them, quinoline with ethyl substituent's, showed excellent anti-TB activity. Similarly the 2-position may be substituted with alkyl or bulky lipophilic aryl/heteroaryl groups and shows a good activity. The 3 or 4-position of the nucleus may be substituent's are more because of the conjugation and substituent's may range from functional groups like halogens, alkene linker, hydrozones, butanamide derivatives heteroaryl groups. The 6 or 7-position of the nucleus may be unsubstituted or substituent's may range from functional groups like halogens, nitro, amino, 5-nitrofuran, dialkylamino, 4-fluorophenoxy, dimethylamino groups and quinoline with at-CF_3 at 8th position, shows good anti-TB activity (Fig. 4).

3. Quinoline derivatives for treatment of tuberculosis

A spectrum of pharmacological activities exhibited by quinoline and its derivatives has been reviewed by several authors [18,46]. But, no one review published on quinoline as anti-TB agents.

In 2010, Eswaran et al., reported the synthesis of quinoline-3-carbohydrazone derivatives and evaluated for their in vitro anti-TB activity against *MTB $H_{37}Rv$, Mycobacterium smegmatis (MC2)*, and *Mycobacterium fortuitum* by broth micro dilution assay method. The presence of substituted hydrazones and *(3R)*-3-amino-*N,N*-dimethyl-4-(phenylthio)butanamide respectively, at positions 3 and 4 of quinoline skeleton has tremendously enhanced the TB activity. Compounds **(2)** and **(3)** showed good activity against both *M. fortuitum* and *MTB $H_{37}Rv$* and they are more potent than isoniazid (INH) and rifampin (RIF). SAR study revealed that, the presence of -CF_3 group at position-8 enhanced the activity, while the introduction of -F at position-6 partially lowered the activity [47]. Same research group synthesized quinoline derivatives carrying oxazolidinone ring and tested for their both preliminary and second level *in vitro* antimycobacterial activity against *MTB $H_{37}Rv$, M. smegmatis* and *M. fortuitum*, results were compared with standard anti-TB drugs INH and RIF. Compounds **(4-6)** were active

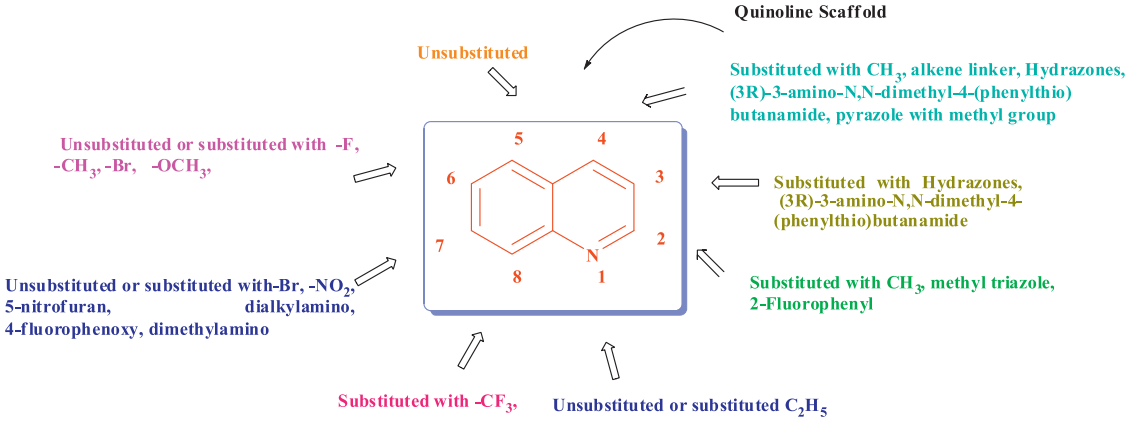
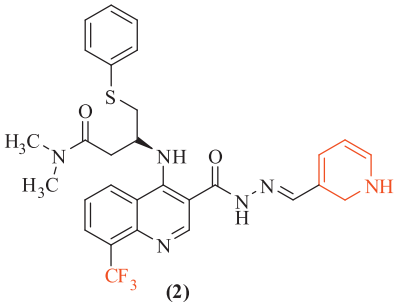


Fig. 4. Structural requirement around quinoline nucleus for an anti-TB activity.

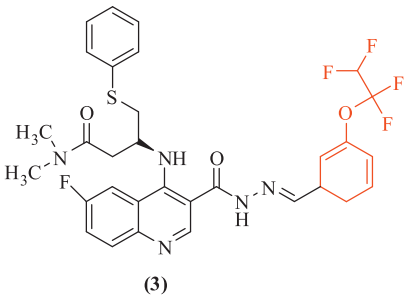
at 0.625 μg/mL against *MTB H37Rv* strains. These compounds are more potent than the reference compound INH (MIC = 0.7 μg/mL) against *MTB H37Rv*, 50 μg/mL against *M. smegmatis* and 12.5 μg/mL against *M. fortuitum*. Also, the compounds **(4)** and **(6)** exhibited promising activity against *M. smegmatis* strain at 2.5 μg/mL concentration whereas compound **(5)** displayed activity at 2.5 μg/mL against *M. fortuitum* strain. The promising activities of these compounds are mainly due to the presence of alkylamines, methyl, ethyl and acetyl substituted piperazines are responsible for their improved activity [48].

showed very good anti-TB activity against both the TB strains. It may be attributed to the presence of electron donating -CH_3 group, which is responsible for stabilizing the pyrazole ring, thereby making the quinoline ring more active species [49]. Trifluoromethyl-quinoline derivatives synthesized and screened for their in vitro antimycobacterial activity against *MTB H37Rv*, and non-tubercular mycobacterial (NTM) species like *M. smegmatis*, and *M. fortuitum* by Resazurin assay method. The standard drugs, *viz*. INH and RIF were used for comparison. Compounds **(8–12)** displayed significant activity against *MTB H37Rv* strain and **(9)** and **(10)** displayed significant activity at 1.25 mg/mL against *M. smegmatis*, Compounds **(8–11)** showed substantial activity against the MDR-TB strain at 6.25 mg/mL. The activities of these compounds could be attributed to the incorporation of heterocyclic compounds *viz*., substituted indoles, pyrrole, imidazole, benzotriazole and aromatic compounds with methoxy and fluoro substituents to active 4-hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide [50].



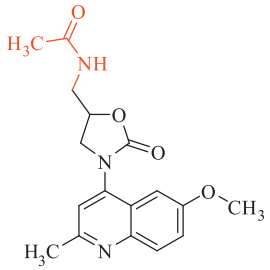
(2)

MIC(*MTB*) =1 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =1 μg/mL
% GI > 95 %
IC_{50} > 62.5 μg/mL



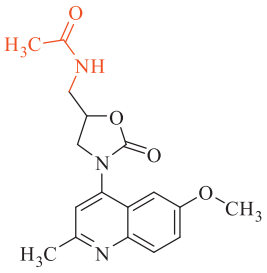
(3)

MIC(*MTB*) =1 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =1 μg/mL
% GI > 95 %
IC_{50} > 62.5 μg/mL



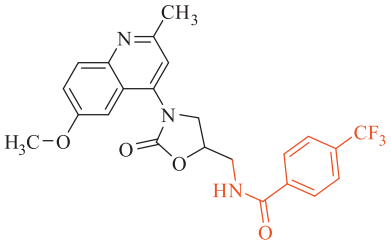
(4)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =2.5 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 95%



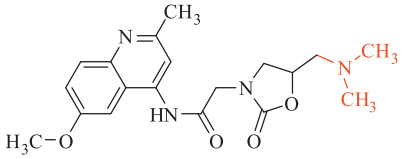
(4)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =2.5 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 95%



(5)

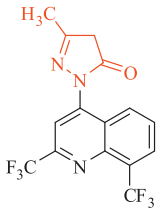
MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =2.5μg/mL
% GI = 90 %



(6)

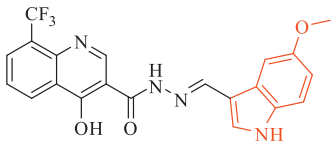
MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =2.5 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 95 %

Same researcher reported, the synthesis of quinoline derivatives carrying biologically active entities *viz*., hydrazones, ureas, thioureas and pyrazoles and evaluated anti-TB activity against *MTB H37Rv* and *MDR-TB*. Most of synthesized compounds showed good activity against MDR-TB strain with MIC ranging from 6.25–25 μg/mL and were found more active than INH and RIF. The good anti-TB activity is attributed to the presence of pharmacologically active hetero-aryl groups attached to the quinoline ring. Compound **(7)**



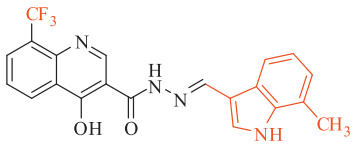
(7)

MIC(*MTB*) = 3.12μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 99 %



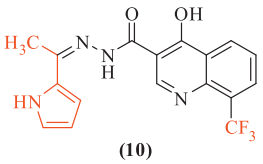
(8)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =10 μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 95 %



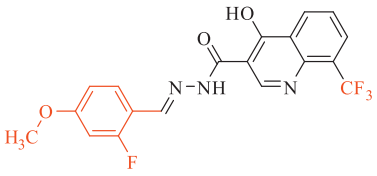
(9)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =1.25 μg/mL
MIC(*MF*) =10 μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 95 %



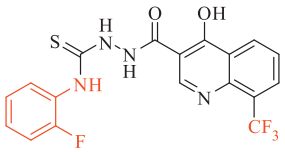
(10)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =1.25 μg/mL
MIC(*MF*) =10 μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 95 %



(11)

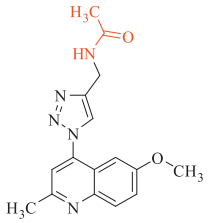
MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =10 μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 95 %



(12)

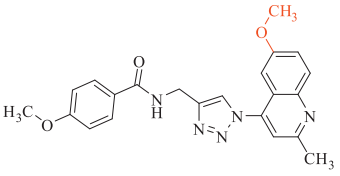
MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =10 μg/mL
MIC(*MDR-TB*) =6.25 μg/mL
% GI = 95 %

Quinoline-triazoles carrying amides, sulphonamides and amidopiperazine derivatives reported as antimycobacterial agents. Compounds **(13-15)** showed promising activity against *MTB H$_{37}$Rv* at 0.625 μg/mL. Compound **(16)** displayed promising activity at 0.625 μg/mL against *MTB H$_{37}$Rv* and active at 10 μg/mL against *M. smegmatis (MS)* and *M. fortuitum(MF)*. Compound **(17)** showed substantial activity at 0.625 μg/mL against *MTB* and more potent than INH against *M. smegmatis*. Overall, compounds **(13–17)** were active against *MTB*, *MS* and *MF* mycobacterial strains. The substantial activity of these compounds may be attributed to the important pharmacophoric groups present in the molecule, viz., acetyl, methoxy, trifluoromethyl and fluoro group [51]. Fused oxazoloquinoline derivatives showed good anti-TB activity against *MTB H$_{37}$Rv* and compounds **(18a-b)**, **(19a-b)**, and **(20a-c)** showed very good anti-TB activity. The activity is attributed to the presence of substituted aryl group at position-2 of quinoline ring. SAR study reveals that with the introduction of 1,3-oxazole ring has tremendously increased the activity of the molecules [52].



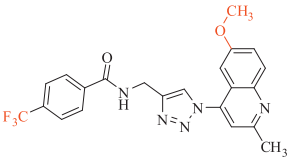
(13)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 95 %



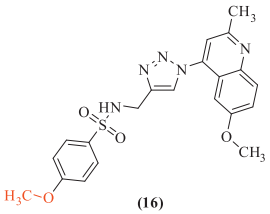
(14)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =5 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 95 %



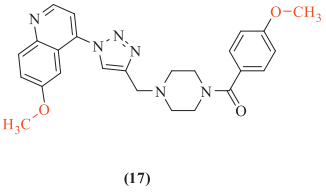
(15)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =5 μg/mL
% GI = 95 %



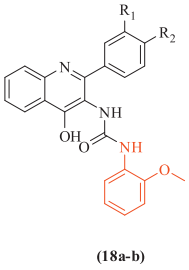
(16)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =10 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 90 %



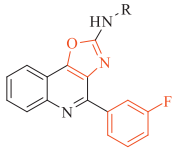
(17)

MIC(*MTB*) =0.625 μg/mL
MIC(*MS*) =5 μg/mL
MIC(*MF*) =10 μg/mL
% GI = 90 %



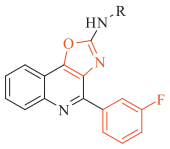
(18a-b)

a) R_1= F, R_2=H; MIC(*MTB*) =1 μg/mL
% GI = 99 %
b) R_1= H, R_2=F; MIC(*MTB*) =1 μg/mL
% GI = 99 %



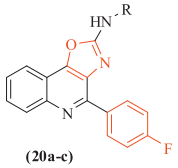
(19a-b)

a) R= 2-methoxy phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
b) R= Benzyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %



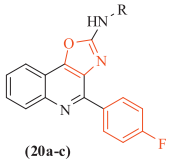
(19a-b)

a) R= 2-methoxy phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
b) R= Benzyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %



(20a-c)

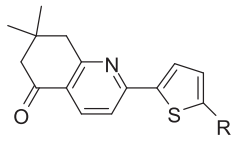
a) R= 4-flouro phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
b) R= 2-methoxy phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
c) R= 3-chloro phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %



(20a-c)

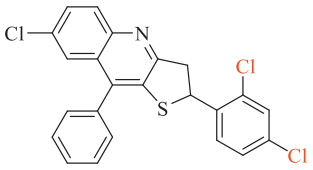
a) R= 4-flouro phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
b) R= 2-methoxy phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %
c) R= 3-chloro phenyl; MIC(*MTB*) =1 μg/mL
% GI = 99 %

Aryl and thiophenyl-quinolinones derivative reported as antimycobacterial agents against *MTB* $H_{37}Rv$. Compounds **(21a-b)** inhibited *MTB* with MIC of 3.13 μg/mL, compared to one of the first line anti-TB drug ethambutol (MIC 3.13 μg/mL), are found equally active. SAR study revealed that, introduction lipophobic hydroxymethyl groups profoundly decreased their MIC values (>25 μ/mL). In comparison with aryl tethered dihydro-6H-quinolin-5-ones, thiophenyl tethered dihydro-6H-quinolin-5-ones are better placed to show potent anti-TB activity. Dihydro-6H-quinolin-5-ones derived from dimedone are structurally better correlates and showed potent activity against *MTB* [53]. Thienoquinolines derivatives were synthesized using by the Friedlander annulations and screened for their in vitro antimycobacterial activity against *MTB* and *MDR-TB*. All the synthesized compounds showed promising *in vitro* activity against *MTB* with MIC in the range of 0.90–36.82 μM and against MDR-TB with MIC ranging from 0.95 to >15.30 μM. Compound **(22)** is the most active compound with MIC of 0.90 μM against *MTB*. This compound is five and eight times more active than ciprofloxacin and ethambutol respectively, while three and eight times less active than INH and RIF respectively. Compounds **(23)** displayed maximum activity in vitro with MIC of 0.95 μM against *MDR-TB*, being 40, 12 and four times more potent than ciprofloxacin, INH and RIF respectively. The thienoquinolines with chlorine at the 7-position displayed significantly greater activity than the corresponding unsubstituted compounds. It is found that the thienoquinolines with electron withdrawing groups like halogen or nitro group in the phenyl ring of the thiophene ring of 3 showed better activity than that with electron donating groups like alkyl. Disubstitution in the phenyl ring enhances the activity many-fold relative to monosubstitution [54].



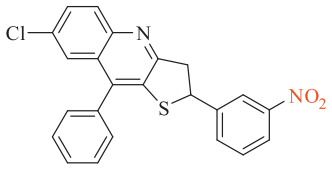
(21a-b)

a) R = Cl; MIC(*Mtb* $H_{37}Rv$) =3.13 μg/mL
b) R = Br; MIC(*Mtb* $H_{37}Rv$) =3.13 μg/mL



(22)

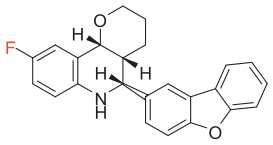
MIC(*MTB*) = 0.90 μg/mL
MIC(*MDR-TB*) =1.76 μg/mL



(23)

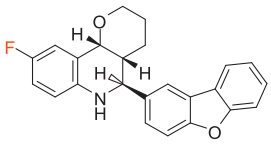
MIC(*MTB*) = 1.86 μg/mL
MIC(*MDR-TB*) =0.95 μg/mL

Pyranoquinoline analogues synthesized using $SnCl_2.2H_2O$ as a catalyst by one-pot Povarov reaction and evaluated for their in vitro antimycobacterial activity against *MTB*, they show activity MIC ranging from 3.13–25.0 μg/mL. Among them, compounds **(24–26)** inhibited *MTB* with MIC 3.13 μg/mL. When compared to one of the first line anti-TB drug ethambutol (MIC 3.13 μg/mL), these three compounds are found equally active as ethambutol. From SAR, halo substituent's is needed for hexahydro-2*H*-pyrano[3,2-c]quinolines to be active against *MTB* and among them fluoro analogues with trans geometry are structurally better correlates and showed better activity [55].



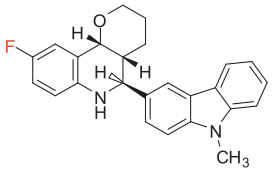
(24)

MIC(*MTB*) =3.13 μg/mL



(25)

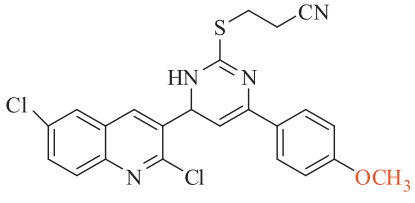
MIC(*MTB*) =3.13 μg/mL



(26)

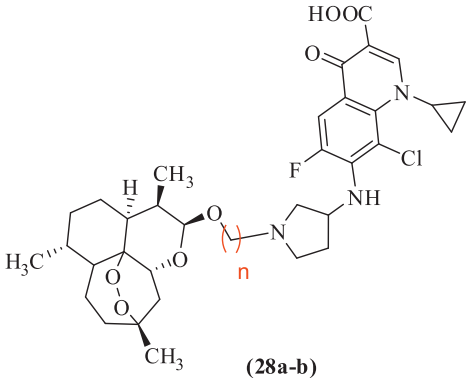
MIC(*MTB*) =3.13 μg/mL

Quinoline bearing pyrimidine motifs synthesized by Desai et al., and evaluated for their in vitro antimycobacterial activity against *MTB* strain by using Lowenstein-Jensen slope method. Compound **(27)** having methoxy at 4th position, at the phenyl ring of pyrimidine substitution showed most promising anti-TB activity with MIC of 0.20 μg/mL. SAR study revels, substituent's with electron donating groups such as methoxy, methyl and hydroxy at *para* position of phenyl ring demonstrated high inhibitory activity against *MTB* as compared *meta* substituted derivatives, indicating that the electronic properties of the substituents have major influence on the antimycobacterial activity [56]. Zhou et al. reported the synthesis of dihydroartemisinin-fluoroquinolone conjugates as potential anti-TB agents. Compound **(28a)** exhibited the good inhibitory activity (MIC = 0.0625 μg/mL), which was comparable to the positive control moxifloxacin and even stronger than ofloxacin. Conjugates **(28a, b)** also displayed comparable activities against various clinically isolated sensitive and resistant *MTB* strains (MIC = 0.125–16 μg/mL) to Moxifloxacin. SAR study reveals that, short linker between dihydroartemisinin and fluoroquinolone was favorable for strong anti-TB activity [57].



(27)

MIC(*MTB*) =0.20 μg/mL
% GI = 99 %

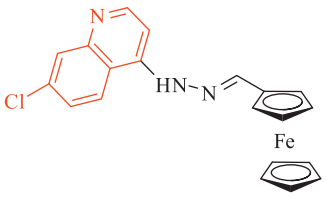


(28a-b)

a) n=2; MIC(*MTB*) =0.0625 μg/mL
b) n=3; MIC(*MTB*) =0.125 μg/mL

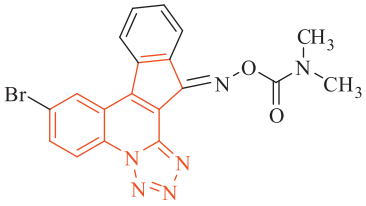
The ferrocene-based hydrazones showed better antimycobacterial activity against *MTB*. Especially, quinoline-ferrocene hybrid **(29)** exhibited significant activity (MIC = 2.5–5 μg/mL) against *Mtb*, it is comparable to the one of EMB (MIC = 2.5 μg/mL). The good anti-TB activity of **(29)** may be attributed to the presence of the quinoline ring [58]. Azole-fused indeno[2,1-*c*]quinolines synthesized and tested against *MTB* $H_{37}Rv$. Compound **(30)** and **(31)** inhibited growth of *MTB* very effectively at MIC) < 0.39 μg mL^{-1} (0.89 μM and 1 μM respectively, which is comparable to that of the existing front-line drug INH (MIC 0.25 μg/mL) [59].

Mefloquine-isoxazole carboxylic acid esters synthesized and screened for anti-TB activity against *MTB* $H_{37}Rv$ using the microplate MABA and low oxygen recovery assay (LORA). Compound with an alkene linker between the 4-position of the quinoline ring and the 5-position of the isoxazole, had markedly improved anti-TB activity and the trans isomer **(35)** (MABA MIC = 0.2 μM) was found to have a MIC only 2-fold higher than RIF, the most active anti-TB drug used today. SAR study revels, an alkene linker is important for activity, and a transalkene is more favored. The position(s) of the substitution(s) on the quinoline ring



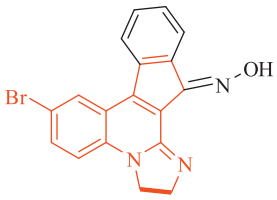
(29)

MIC(*MTB*) =2.5-5 μg/mL



(30)

MIC(*MTB*) < 0.39 μg/mL
% GI = 97 %

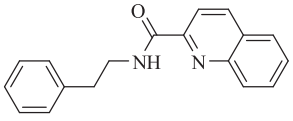


(31)

MIC(*MTB*) < 0.39 μg/mL
% GI = 97 %

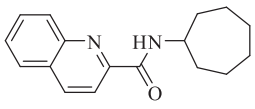
Gonec et al. have reported quinoline-2-carboxamides as anti-TB agnets. *N*-(2-Phenylethyl) quinoline-2-carboxamide (**32a**), *N*-cycloheptylquinoline-2-carboxamide (**32b**) and *N*-cyclohexylquinoline-2-carboxamide (**32c**) showed high activity against *MTB* and 2-(pyrrolidin-1-ylcarbonyl)quinoline (**32d**) showed high activity against *M. kansasii* and *M. avium paratuberculosis* and these are comparable with or higher than the standards INH or pyrazinamide [60]. Quinoline-based azetidinone and thiazolidinone analogues were synthesized and screened against mycobacteria. Compound **(33)** with 2-amino 5-methyl thaizole moiety to the azetidinone class as well as **(34)** with electron-withdrawing and strong electronegative fluoro substituent within the thiazolidinone class exhibited good inhibitory potential at 12.5 μg/mL of MIC against *MTB* $H_{37}Rv$ strain. The inhibitory potential of the said derivatives was half-fold as compared to standard drugs. Azetidinones and thiazolidinones bearing various amines containing halogen(s) such as chloro or fluoro and nitro functional groups have showed high potency [61,62].

may also affect the activity to some extent, while the electron effect of the substitution(s) is less important [63]. Quinoline with different heterocyclic compounds like oxadiazoles, pyrazolines, and pyrazoles moieties and screened for antimycobacterial activity performed with *M. smegmatis* strain using growth inhibition assay by turbidimetry. Heteroaryl substitutions at 5th position of oxadiazole ring, in compounds **(36)**, and **(37)** led to better antimycobacterial activity and the free pyrazole with quinolinyl **(38)** have shows the good anti-TB activity. The aryl ring substitutions, with flouro, methyl, methoxy have showed good activity [64]. Tukulula et al. reported synthesis of quinoline-tetrazole derivatives and evaluated *in vitro* antimycobacterial activities using *MTB* $H_{37}Rv$ strain in MABA and LORA assays. Compound **(39)**, inhibited 94% (MIC_{90} = 123.2 μM) of non-replicating bacteria and **(40)**, which showed 98% inhibition (MIC_{90} = 92.5 μM) of replicating bacteria. SAR study revels; the replacement of the hydroxyl group of 4-quinoline was accompanied by complete loss of activity [65].



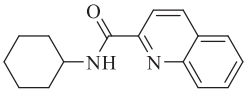
(32a)

MIC(*MTB*) =109 μmol/L



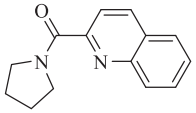
(32b)

MIC(*MTB*) =111 μmol/L



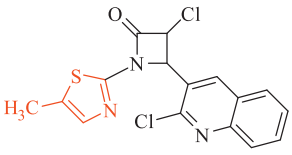
(32c)

MIC(*MTB*) =125 μmol/L



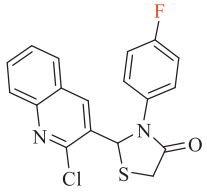
(32d)

MIC(*MK*) =111 μmol/L
MIC(*MAP*) =111 μmol/L



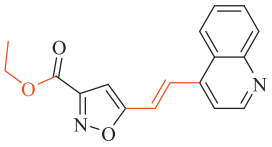
(33)

MIC(*MTB*) = 12.5 μg/mL
% GI = 99 %



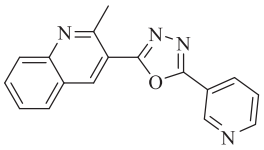
(34)

MIC(*MTB*) = 12.5 μg/mL
% GI = 99 %



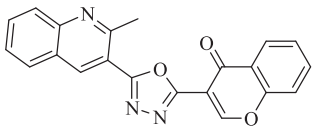
(35)

MIC(*MTB*) = 0.2 μM (MABA)
= 2.6 μM (LORA)



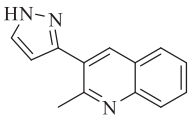
(36)

MIC(*MS*) =22.71 μg/mL



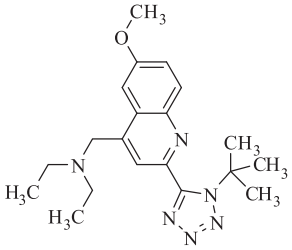
(37)

MIC(*MS*) =16.83 μg/mL



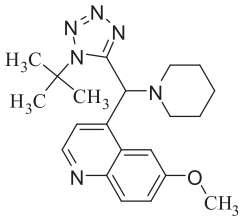
(38)

MIC(*MS*) =14.66 μg/mL



(39)

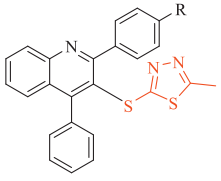
MIC$_{90}$(*MTB*) =123.2 μM (LORA)
% GI = 94 %



(40)

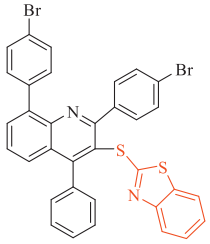
MIC$_{90}$(*MTB*) =92.5 μM (MABA)
% GI = 98 %

3-Heteroarylthioquinolines derivatives were synthesized and screened for their *in vitro* antimycobacterial activity against *MTB*, some of the compounds showed good in vitro activity against *MTB* with MIC ranging from 3.2- 55.9 μM. Compounds (**41(a-c)** and **42**) inhibited *MTB* with MIC less than 6.5 μM and were more potent than the first line anti-TB drug, ethambutol (MIC = 7.6 μM). When compared to ciprofloxacin (MIC = 4.7 μM), two compounds (**41a)** (MIC = 3.5 μM) and (**41b)** (MIC = 3.2 μM) were found to be more potent against *MTB*. Quinolines with sulfur heterocyclic unit at position 3 are found to be more active than quinolines having a heterocycle with four nitrogen atoms at this position. The presence of halogens in the aryl ring enhances the antimycobacterial activity as seen from the MIC values of compound (**41a)** and compound (**41b)** [66]. Quinoline with piperazinyl/piperidinyl)-s-triazines derivatives reported as anti-TB agents by Patel and co-workers against *MTB H$_{37}$Rv*. Compound **(43)** with substitution of two methyl groups at the 3rd and 5th position of the piperidine ring, **(44)** and **(45)** bearing trifluoromethylation and trimethoxy substitution to the phenyl ring of piperazine base coupled to the nucleus exhibited highest inhibition (99%) at a constant concentration level (6.25 μg/mL) against *MTB*. In Lowensteine Jensen MIC method, **(43)** was displayed inhibition of *MTB* completely (99%) at the MIC of 3.12 μg/mL and this compound better efficacy, than the standard drug, pyrazinamide [67].



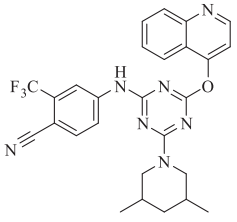
(41a-c)

a) R= Cl; MIC(*MTB*) =3.5 μM
b) R= Br; MIC(*MTB*) =3.2 μM
c) R= Ph; MIC(*MTB*) =6.4μM



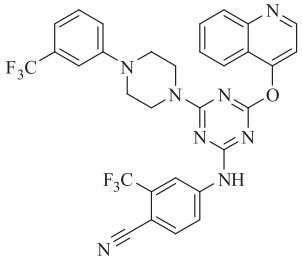
(42)

MIC(*MTB*) =5.9 μM



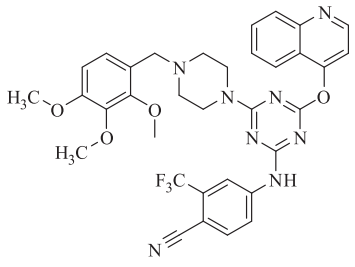
(43)

% inhibition (*MTB*) = 99 %
(6.25 μg/mL)



(44)

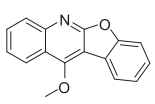
% inhibition (*MTB*) = 99 % (6.25 μg/mL)



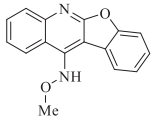
(45)

% inhibition (*MTB*) = 99 % (6.25 μg/mL)

Benzofuro[2,3-b]quinoline derivatives synthesized for evaluated for their anti-TB against *MTB*. The less bulky methoxy derivative **(46)**, 11-aminated derivatives in which the less bulky methylamino derivative **(47)**, and a tertiary amine derivative **(48)** exhibited significant activities against the growth of *MT* (MIC values of < 0.20 μg/mL) [68]. Tetrazolo[1,5-a]quinoline based tetrasubstituted imidazole derivatives synthesized and evaluated for their activity against *MTB* $H_{37}Rv$ strain. Compounds **(49a)** and **(49b)** showed best activity against *MTB*. The SAR study revels, change in the substituent might also affect the anti-TB activity, compounds **(49a)** and **(49b)** carrying electron negative groups on quinoline ring displayed excellent anti-TB activity against tubercular strains [69].

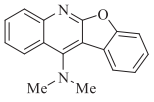


(46)



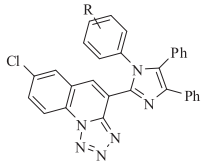
(47)

MIC(*MTB*) < 0.20 μg/mL



(48)

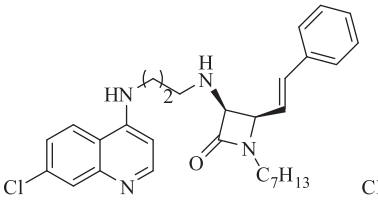
MIC(*MTB*) < 0.20 μg/mL



(49a-b)

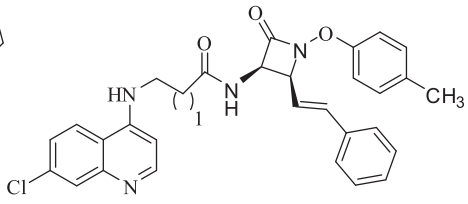
a) R= CH_3; % inhibition (*MTB*) = 99 % (25 μg/mL)
b) R= OCH_3; % inhibition (*MTB*) = 98 % (62.5 μg/mL)

Raj et al. reported synthesis of quinoline-β-lactam hybrids and tested for their anti-TB activities. Most of the compounds exhibited better anti-TB activity than standard srugs ethionamide (up to three times) and cephalexin (up to five times). Compounds **(50–52)** showed good anti-TB activity at MIC 5 μg/mL [70]. Quinoline coupled 1,2,3-triazoles compounds synthesized by 'click chemistry' and screened for anti-TB activity against *MTB* by luciferase reporter phage (LRP) assay. Quinoline coupled triazole sugar hybrid, **(53)** is the exhibit potent anti-TB activity against *MTB* strain with 76.41% and 78.37% reduction calculated based on percentage reduction in relative light units at 5 and 25 μg/mL, respectively. SAR study revels, introduction of the phenyl ring at the C-4 position of triazole induced reasonable inhibition against *MTB*. It was apparent that the introduction of bulky and lipophilic substituent such as benzene exhibits potent inhibition against *MTB*. However, introduction of small hydrophilic substituent such as hydroxyl linked to the C-4 of triazole via methylene showed dramatic loss in potent inhibition against *MTB*. Pentoses or hexoses in the chair conformation with 3,4-trans diacetyl orientation such as quinoline glycoconjugate of D-galactose **(53)** (3S,4R), were generally more potent inhibitor than those with corresponding 3,4-cis-diacetyl orientation (3S,4S) among the saccharide coupled compounds [71].



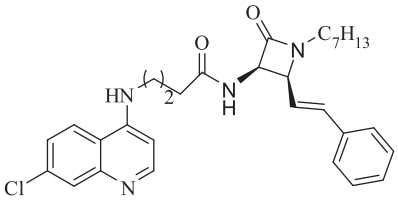
(50)

MIC(*MTB*) = 5 μg/mL



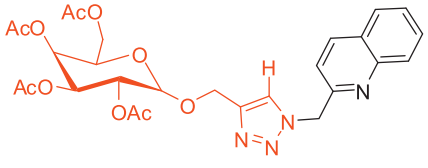
(51)

MIC(*MTB*) = 5 μg/mL



(52)

MIC(*MTB*) = 5 μg/mL

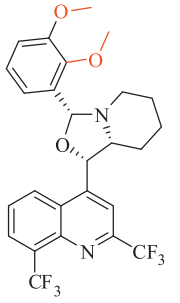


(53)

MIC(*MTB*) = 5 μg/mL

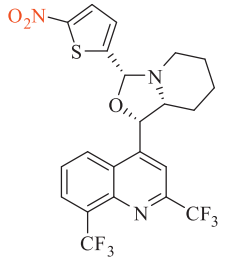
Gonçalves et al. reported synthesis of mefloquine-oxazolidine derivatives as anti-TB agents against *MTB H$_{37}$Rv*. The most active of the compounds was the dimethoxy derivative **(54)** and nitro derivative **(55)** with a MIC value of 11.9 μM and 12.1 μM respectively, showed 2.7 times more active than mefloquine (MIC = 33 μM), with a better tuberculostatic activity than the first line tuberculostatic agent ethambutol (MIC = 15.9). SAR study revels, the longer alkyl chain length scarcely affected the biological activity [72]. Tripartite hybrids from pharmacophores 7-chloroquinoline (CQ), ethylenediamine spacer (ETH) and phenylurea as thiourea bioisostere (ISO) synthesized and tested in vitro for their antimycobacterial activity against *MTB H$_{37}$Rv*. Compounds **(56)** and **(57)** exhibited high mycobactericidal activity, these structures were found to be the most potent compounds with MIC's of 4 and 2 μg/mL, respectively. Compound **(57)** was two fold more potent than reference drugs EMB and isoxyl (MIC 4 μg/mL), whereas compound **(56)** was as active as these two antimycobacterial drugs [73].

Aldehyde-arylhydrazone-oxoquinoline derivatives were synthesized and evaluated for their anti-TB activity against *MTB H$_{37}$Rv* strain. The 1-ethyl-N'-[(1E)-(5-nitro-2-furyl)methylene]-4-oxo-1,4-dihydroquinoline-3-carbohydrazide **(58)** was effective against *MTB*. The determination of the MIC of **(58)** showed a value (6.25 μg/mL) better than current drugs in the market. The insertion of the ethyl substituent in the nitrogen atom of quinoline nucleus as possibly involved in the lack of anti-TB activity of most compounds probably due to steric hindrance effects. The ethyl-quinoline ring without any substitution and the 5-nitro-2-furyl group at Ar in the active compound **(58)** seem to be important for the anti-TB activity [74]. Substituted quinolinyl chalcones, quinolinyl pyrimidines, and pyridines were synthesized and evaluated for their anti-TB activity in vitro against *MTB H$_{37}$RV*. The analogs **(59–61)** exhibit promising activity and inhibit the growth of mycobacterium to 99%, 97%, and 99%, respectively, at a concentration of 6.25 μg/mL. Analogs **(62,63)** were most active of the series inhibiting the growth of drug-sensitive bacteria to 99% at 4.25 and 6.25 μg/mL concentration, respectively. Compound with fluorine substituent's in the phenyl ring enhances the anti-TB activity against *MTB H$_{37}$RV* in case of chalcone and cyanopyridine derivatives [75].



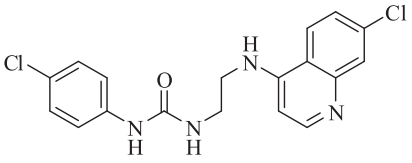
(54)

MIC(*MTB*) = 11.9 μg/mL
MIC(*MDR-TB*) = 11.9 μg/mL



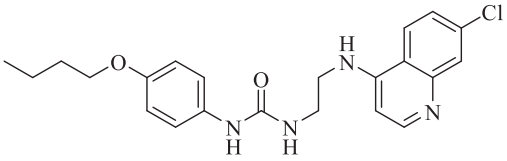
(55)

MIC(*MTB*) = 12.1 μg/mL
MIC(*MDR-TB*) = 12.1 μg/mL



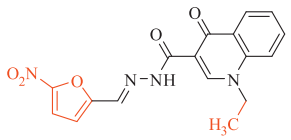
(56)

MIC(*MTB*) = 4 μg/mL



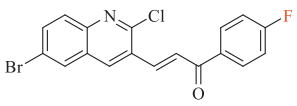
(57)

MIC(*MTB*) = 2 μg/mL



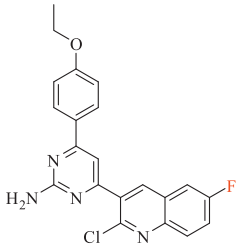
(58)

MIC(*MTB*) = 6.25 μg/mL



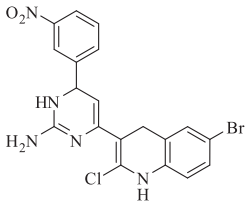
(59)

% inhibition (*MTB*) = 99 % (6.25 μg/mL)



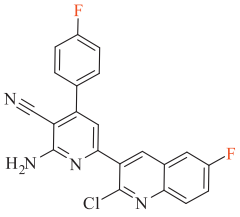
(60)

% inhibition (*MTB*) = 97 % (5 μg/mL)



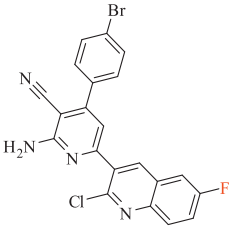
(61)

% inhibition (*MTB*) = 99 % (6.25 μg/mL)



(62)

% inhibition (*MTB*) = 99 % (4.5 μg/mL)

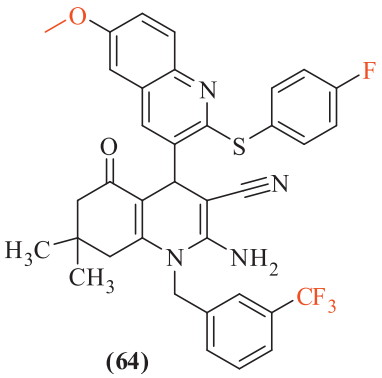


(63)

% inhibition (*MTB*) = 99 % (6.25 μg/mL)

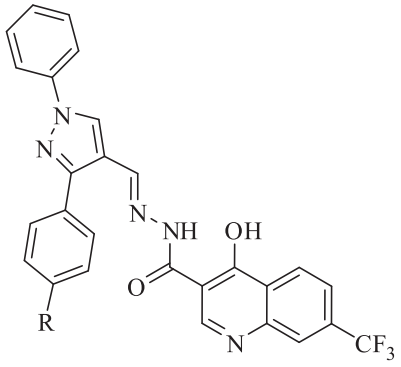
Flourine substituted biquinoline derivatives synthesized and screened for their in vitro anti-TB activity against *MTB H37Rv* strain was determined using Lowenstein-Jensen medium. Compound **(64)** with 91% inhibition displayed excellent activity against *MTB H37Rv*. Authors reported, activity because of the combination effect of electron releasing -OCH_3 and, electron withdrawing -F and -CF_3 groups [76]. Quinoline-3-carbohydrazide derivatives synthesized by Garudachari et al., screened against *M. smegmatis*. Compounds, **(65a-b)** showed the lowest MIC value of 6.25 μg/mL against *M. smegmatis* indicating these compounds can be possible future anti-TB agents. The activity increases with increase of electron withdrawing group on pyrazole carbohydrazide and electron donating groups on phenyl carbohydrazide at third position of quinoline [77].

Carmo et al. reported the synthesis of 4-aminoquinoline analogues and their platinum(II) complexes as new antileishmanial and antitubercular agents. Compounds (**66**), and (**67**) inhibit promising activity against *MTB*, with MIC values ranging from 15.6–12.5 μg/mL, comparable to the "first and second line" drugs used to treat tuberculosis. The platinum complexes not show good activity, when compared without metal. SAR study revels; the addition of certain mono- and di-alkynes to the intermediate amino compounds increases their antitubercular activity [78]. Recently, Nazarenko et al. patented some chloroquinoline derivatives as anti-TB agents. The compound 5,6,7-substituted 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ols **(68)** showed excellent anti-TB activity, when compared with standard anti-TB drugs [79].



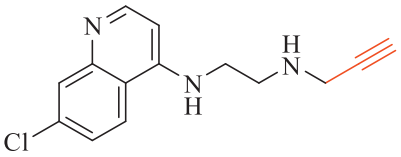
(64)

% inhibition (*MTB*) = 91 % (25 μg/mL)



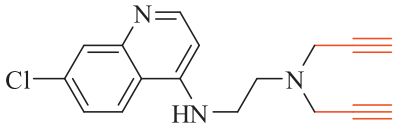
(65a-b)

a) R= NO_2; MIC (*MS*) = 6.25 μg/mL
b) R= CH_3; MIC (*MS*) = 6.25 μg/mL



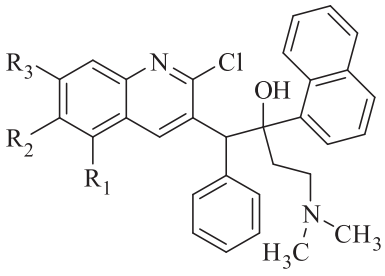
(66)

MIC(*MTB*) =15.6 μg/mL



(67)

MIC(*MTB*) =12.5 μg/mL



(68)

R_1 = H, MeO; R_2, R_3 = H, MeO,$O(CH_2)_nO$

4. Conclusions and future aspects

Tubercular infections pose a continuous and serious threat to human health and life in recent years. There has been an increased use of antibuercular agents and has resulted in the development of resistance. This has given rise to search for molecules acting on a novel target or a multi targeted combination therapy. 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. Numerous outstanding achievements revealed that quinoline-based compounds possess extensively potential anti-TB agents. To further optimize the full potential of quinoline compounds, the SAR-based study will likely continue to play an important role. It is highly likely that optimized quinoline compounds with excellent potency and little side effects will continue to be created. Some of these quinoline compounds will undoubtedly be used as first and second line anti-TB therapeutic agents in the near future. Further research in this field will bring innovative pharmaceutical developments with a considerable spectrum of use.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

Authors acknowledge Jain University, Bangalore for the financial support.

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