


Cite this: *RSC Adv.*, 2025, 15, 3646

# Quinoline analogs: multifaceted heterocyclic compounds with varied synthetic strategies and potent antitubercular properties

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Tuberculosis cases have continuously increased by 64% over the last nine years, from 2014 to 2023. Approximately 33% of the global population is affected by TB. It is a bacterial disease, and *Mycobacterium tuberculosis* is the most common bacteria that affects the lungs of human beings during the infection. Other hazardous bacterial species causing tuberculosis are *M. pinnipedii*, *M. canettii*, *M. caprae*, *M. bovis*, *M. africanum*, and *M. microti*. TB symptoms in TB-infected patients include fever, chest pain, weight loss, and fatigue. Depending on the stage of infection, the treatment for TB can take approximately six months to two years. Quinoline comprises a pyridine ring fused with a benzene ring, and both these rings share two adjacent carbon atoms and can take part in electrophilic substitution reactions. Quinoline-based heterocyclic compounds are attracting substantial interest owing to their vital role as a class of synthetic and natural molecules. Quinoline and its derivatives display various biological activities, including anti-TB, anticonvulsant, antibiotic, antifungal, antimalarial, antipsychotic, antihypertensive, antileishmanial, antioxidant, tyrosine kinase inhibitory, anti-inflammatory, anticancer, anti-asthmatic, cardiogenic, anthelmintic, antiprotozoal, anti-HIV, and anti-Alzheimer effects. Some fused analogs of quinoline, such as graveolinine, ciprofloxacin, kokusaginine, bedaquiline, levofloxacin, moxifloxacin, and mefloquine, are commercially available as antitubercular drugs. There are various methods available to synthesize quinoline-containing antitubercular drugs. In this review paper, we present three types of synthetic methods in which substituted quinolines, substituted anilines, and miscellaneous starting materials are used and outline MIC values for all the synthesized compounds to signify their anti-TB activity.

Received 26th November 2024  
Accepted 20th January 2025

DOI: 10.1039/d4ra08362h

rsc.li/rsc-advances

## 1 Introduction

Tuberculosis (TB) is a disease involving lung infection<sup>1</sup> and is one of the top ten causes of death globally.<sup>2</sup> It can particularly

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arise in HIV patients, in whom the pathogenic alliance between HIV and TB can have severe consequences.<sup>3</sup> *Mycobacterium tuberculosis* (MTB) is the main cause of TB, while some other hazardous species of bacteria that can also cause TB are *M. caprae*, *M. pinnipedii*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*.<sup>4</sup> In 2023, India recorded a total of 2.31 lakh deaths due to TB. The country saw 2.43 million TB cases reported in 2022, while 2.23 million TB patients were documented by the end of November 2023. Over the past nine years, from 2014 to 2023, TB cases have steadily increased by 64% worldwide, with the maximum number of cases reported in China, Russia, and India.<sup>5</sup> Around one-third of the global population is estimated to be infected with TB.<sup>6</sup> The WHO is dedicated to eradicating TB worldwide and has included this aim as part of the SDGs, with a target to reduce TB mortality by 90% and its incidence by 80% by 2035.<sup>7</sup>

The TB infection process begins when an infected individual expels MTB-laden aerosols into the air, which are then inhaled by a new host, leading to bacterial deposition in their lungs. Upon entry, the innate immune system responds by recruiting macrophages to engulf the bacteria. The bacteria then multiply within the macrophages, prompting an inflammatory response that attracts immune cells, such as lymphocytes and neutrophils, to form an early-stage granuloma.<sup>8</sup> As the granuloma matures, immune cells such as T cells, natural killer cells, dendritic cells, and fibroblasts contribute to its structure, surrounding the bacteria and containing the infection in a latent state, termed the “solid granuloma”. In some cases, when the immune system is weakened due to factors like HIV, malnutrition, or chronic stress, the granuloma breaks down, releasing bacteria into the surrounding tissues.<sup>9</sup> This disintegration of the granuloma leads to caseous necrosis, resulting in the formation of a “caseous granuloma”, characterized by a cheese-like center. If left unchecked, the breakdown continues, causing further bacterial spread and

symptomatic TB. Here, the immune system plays a balancing role; whereby a strong immune response keeps the bacteria contained within the granuloma, whereas a compromised immune system allows the granuloma to rupture, leading to active disease and dissemination of the bacteria throughout the body (Fig. 1).<sup>10</sup>

Quinolines are bicyclic N-containing heterocyclic naturally occurring organic compounds, which serve as important segments of both synthetic and pharmacologically active compounds.<sup>11</sup> Quinoline's ability to form salts with acids makes it a weak tertiary base, displaying electrophilic substitution reactions similar to pyridine and benzene.<sup>12</sup> The logical design of small compounds that can target crucial MTB enzymes and pathways has attracted much attention due to the urgent need for new therapeutic medicines. Because of their wide range of biological actions and proven effectiveness in blocking important MTB targets, quinoline derivatives have become one of the most promising classes of such chemicals.<sup>13</sup> These include enzymes that are essential for cell wall production, fatty acid metabolism, and DNA replication, such as decaprenylphosphoryl-beta-D-ribose 2'-epimerase (DprE1), enoyl-acyl carrier protein reductase (InhA), and DNA gyrase. By directly targeting the MTB ATP synthase, such as diarylquinoline, bedaquiline has demonstrated extraordinary efficacy and has been approved for treating multi-drug-resistant (MDR) TB. Molecular docking, structure-based drug design, and computer methods like QSAR modeling have all sped up the creation of new quinoline derivatives with enhanced pharmacokinetic, selectivity, and effectiveness profiles. Utilizing these developments, it is considered that quinoline-based drug discovery has enormous potential to provide safer and more efficient treatment choices while also addressing the problems caused by drug-resistant TB.<sup>14</sup> An effective foundation for comprehending and maximizing the antitubercular potential of quinoline derivatives can be provided by the utilization of computational approaches. Through these, researchers can precisely understand the binding mechanisms of such drugs by modeling their interactions with important MTB targets, including DprE1, InhA, and DNA gyrase. Meanwhile, molecular dynamics simulations can allow evaluating the stability of ligand-protein complexes over time, guaranteeing their applicability in physiological settings, while molecular docking can assist in identifying crucial binding residues and quantifying interaction energies.<sup>15</sup> Furthermore, *in silico* toxicity and ADMET predictions can expedite lead selection by guaranteeing that the drugs have advantageous pharmacokinetic characteristics. In addition to confirming the biological activity of quinoline derivatives, these computational approaches can also speed up the search for new candidates that are more effective against strains of MTB that are resistant to drugs.<sup>16</sup> Several important proteins linked to TB have also been found through computational research, and these could be research targets for future medication development. Such enzymes include DNA gyrase, QcrB T313I, InhA, DprE1, the mycobacterial membrane protein large 3 (MmpL3), and the gyrase enzyme. Numerous quinoline derivatives have been demonstrated to bind to these



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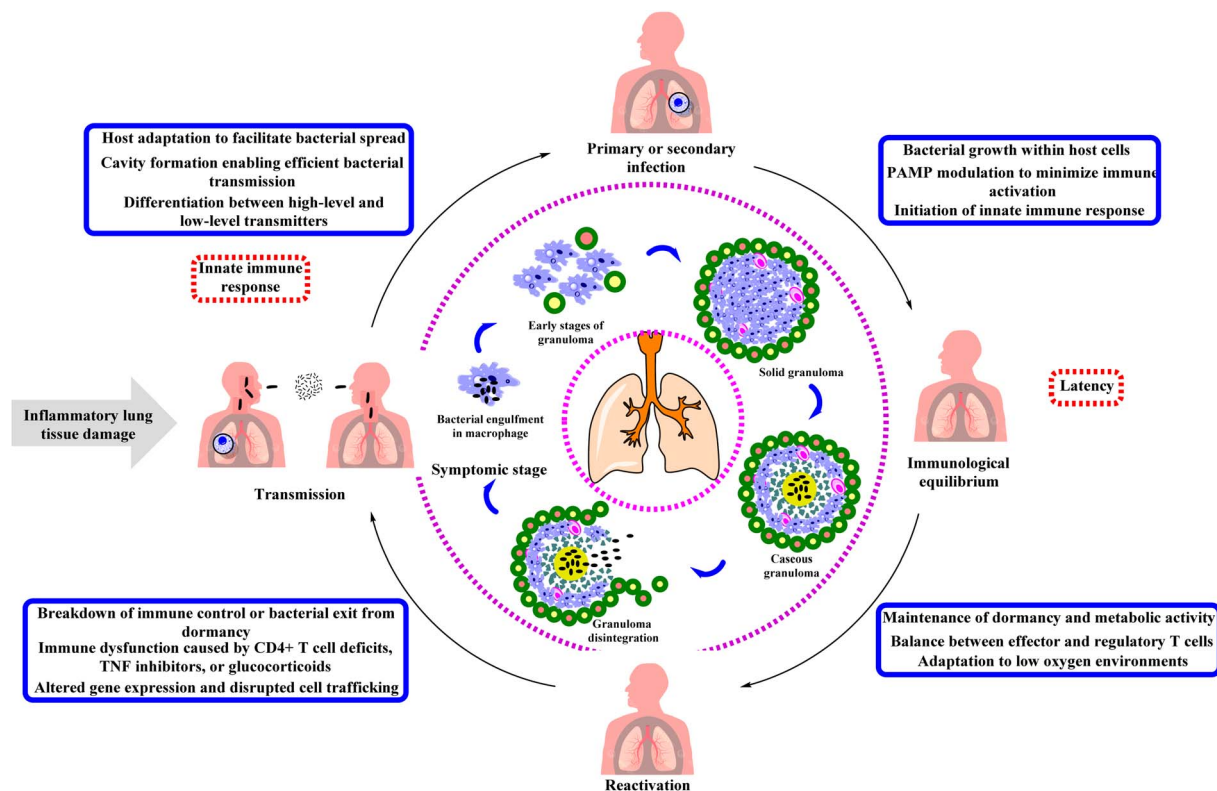


Fig. 1 Diagrammatic representation of the mechanism of tubercular activity.

proteins with differing affinities, offering important information about their possible medical uses.<sup>16</sup> These interactions demonstrate the vital role that quinoline derivatives can play in developing TB treatment plans, especially when it comes to combating MDR bacteria.

Quinoline derivatives exhibit several biological activities and uses, including anti-bacterial,<sup>17</sup> histamine H3 receptor antagonist,<sup>18,19</sup> antibiotic,<sup>20</sup> anti-inflammatory,<sup>21,22</sup> antihypertensive,<sup>21</sup> antileishmanial,<sup>23</sup> anti-oxidant,<sup>24</sup> tyrosine kinase inhibitors,<sup>25</sup> antimalarial,<sup>26</sup> anticancer,<sup>27</sup> anti-HIV,<sup>28</sup> anti-asthmatic,<sup>29</sup> cardio-tonic,<sup>30</sup> anticonvulsant,<sup>31</sup> anthelmintic,<sup>32</sup> antifungal,<sup>33</sup> anti-protozoals,<sup>34</sup> anti-alzheimer,<sup>35</sup> tyro kinase PDGF-RTK-inhibitor, agents for the treatment of lupus, antipsychotics,<sup>36</sup> anti-glaucoma, and local anesthetic.<sup>12</sup> The structures of some important biologically active quinoline-containing drugs are presented in Fig. 2. TB is a highly challenging task in the medicinal field for human beings. Presently, various anti-TB new medicines are required that are more cost-effective, less toxic, affordable, simpler, and more potent than current anti-TB drugs, which are typically costly, toxic, and complex. Anti-TB drugs are generally classified into two categories: first-line drugs (*i.e.* rifampicin, pyrazinamide, and isoniazid) and second-line anti-TB drugs (*i.e.* gatifloxacin, levofloxacin, moxifloxacin, ciprofloxacin, ofloxacin, and trovafloxacin).<sup>37</sup> Quinoline-based anti-TB drugs have both nonpolar and polar properties, which allow them to permeate bacterial cells.<sup>2</sup> Bedaquiline is a vital anti-TB drug based on diarylquinoline. It is typically used in combination with rifampicin, pyrazinamide, and isoniazid as a highly

effective therapy for the treatment of MDR-TB.<sup>7</sup> It was first prepared by Janssen in 2005 (ref. 38) and later permitted by the US FDA and WHO in 2012. Some other important marketed anti-TB drugs bearing quinoline nucleus are gatifloxacin,<sup>39</sup> ciprofloxacin,<sup>40</sup> moxifloxacin,<sup>39,41</sup> sparfloxacin, ofloxacin, enrofloxacin, levofloxacin,<sup>37</sup> kokusaginine,<sup>42</sup> lomefloxacin,<sup>43</sup> mefloquine, and norfloxacin<sup>44</sup> (Fig. 3).

The use of minimum inhibitory concentration (MIC) values has significantly enhanced the understanding of how to develop quinoline derivatives for more effective TB treatment. Modifications to the structure, such as the incorporation of alkene linkers and specific substituents, have proven crucial to enhancing the efficacy of synthesized compounds against TB. Research has indicated that the strategic placement of functional groups, like -F, -CF<sub>3</sub>,<sup>45</sup> and azomethine (-C=N-)<sup>3</sup> linkages, at a particular position on the quinoline nucleus can lead to varied inhibitor effects on MMTB. Furthermore, investigations into various quinoline hybrids, including quinoline-triazole,<sup>45</sup> quinoline-tetrazole,<sup>3</sup> oxazoloquinoline,<sup>45</sup> quinoline-pyrazole,<sup>46</sup> and trifluoromethyl-fused quinoline combinations, have yielded promising results.<sup>45</sup> Quinoline hydrazones as well as fluorine-substituted hydrazones have been reported to have anti-TB activity with high potency compared to rifampicin and isoniazid.<sup>5</sup> The pharmacological effectiveness and safety of quinoline derivatives in the treatment of TB are largely determined by their metabolic metabolism. The liver's cytochrome *P*<sub>450</sub> enzymes are the main catalysts for the several biotransformation processes that these substances go through. Typical metabolic processes





Fig. 2 Biologically active agents bearing a quinoline nucleus.

that increase their solubility and ease of excretion include hydroxylation, N-oxidation, and conjugation reactions, including glucuronidation and sulfation.<sup>47</sup> The bioactivity of quinoline scaffolds is frequently influenced by the site-specific metabolism of their functional groups; metabolites may show more potency or less toxicity than the parent molecule. The addition of fluorine atoms or sterically hindered groups are examples of structural changes that can increase metabolic stability, delay fast degradation, and increase the drug's half-life.<sup>48</sup> It was reported that expanding the ring size and incorporating a dimethylamine group within the quinoline ring could maintain strong potency. However, the introduction of highly polar substituents, such as *N*-methyl piperazine, and secondary amines, resulted in

a significant reduction in anti-TB activity.<sup>49</sup> Furthermore, the ADMET properties of quinoline derivatives can be studied *in vitro* and computationally, which offers important insights into their metabolic fate and aids in optimizing their pharmacokinetic profiles. Researchers can increase the therapeutic potential of these derivatives while reducing side effects by comprehending and modifying their metabolic activity.<sup>13</sup> Quinoline Schiff base-derived metal complexes find diverse applications, including as an anti-TB antioxidant, catalyst for olefin polymerization, corrosion inhibitor in acidic conditions, anticancer and antimicrobial applications, and as a dye in solar cells. Lugosi *et al.* reported on BCG, which was derived from a virulent strain of *M. Bovis* and utilized as a vaccine for totally drug-resistant TB and MTB.<sup>3</sup>



Fig. 3 Quinoline-containing marketed anti-TB drugs.

## 2 Synthesis of quinoline-based anti-TB drugs

There are several classical named reactions for synthesizing quinoline derivatives, often using simple arylamines as starting materials. Here are few notable methods that involve arylamines: Reihm synthesis, Gould-Jacob reaction, Skraup synthesis, combes quinoline synthesis, Conrad-Limpach synthesis, and Doebner synthesis. In this review paper, we have classified the synthesis of quinoline derivatives into three categories based on their starting materials.

### 2.1. From substituted quinolines

Leveraging the inherent reactivity of quinoline derivatives to create novel compounds, this method often involves strategic modifications to the existing quinoline framework, allowing the introduction of various functional groups that can enhance biological activity. Through techniques such as cyclization, oxidation, or rearrangement, substituted quinolines can be transformed into more complex structures with diverse

pharmacological properties. This synthetic strategy not only facilitates the exploration of structure–activity relationships but also contributes to an expansion of the range of novel therapeutic agents available, particularly for use in the fight against diseases like TB. The flexibility in substituent placement offers chemists the opportunity to tailor quinoline derivatives for specific applications, thus enlarging their utility in medicinal chemistry. Alegaon's team reported obtaining the target semicarbazones **4a–b** in good yields from the reaction of 4,7-dichloroquinoline **1a** with 4-amino acetophenone **2** in dry methanol to form the corresponding amino derivative, which was then treated with various aromatic aldehydes **3a–b** in the presence of NaOH to get the relative chalcones through the Claisen–Schmidt mechanism. Compounds **4a–b** were prepared by the reaction of these chalcones and semicarbazide hydrochloride in glacial acetic acid. Likewise, another semicarbazone **7** was synthesized by the reaction of **1a** and 3-amino acetophenone **5** to produce the relative amino derivative. This derivative reacted with 4-methyl benzaldehyde **6** in the presence of NaOH to obtain the corresponding chalcone, which was treated with



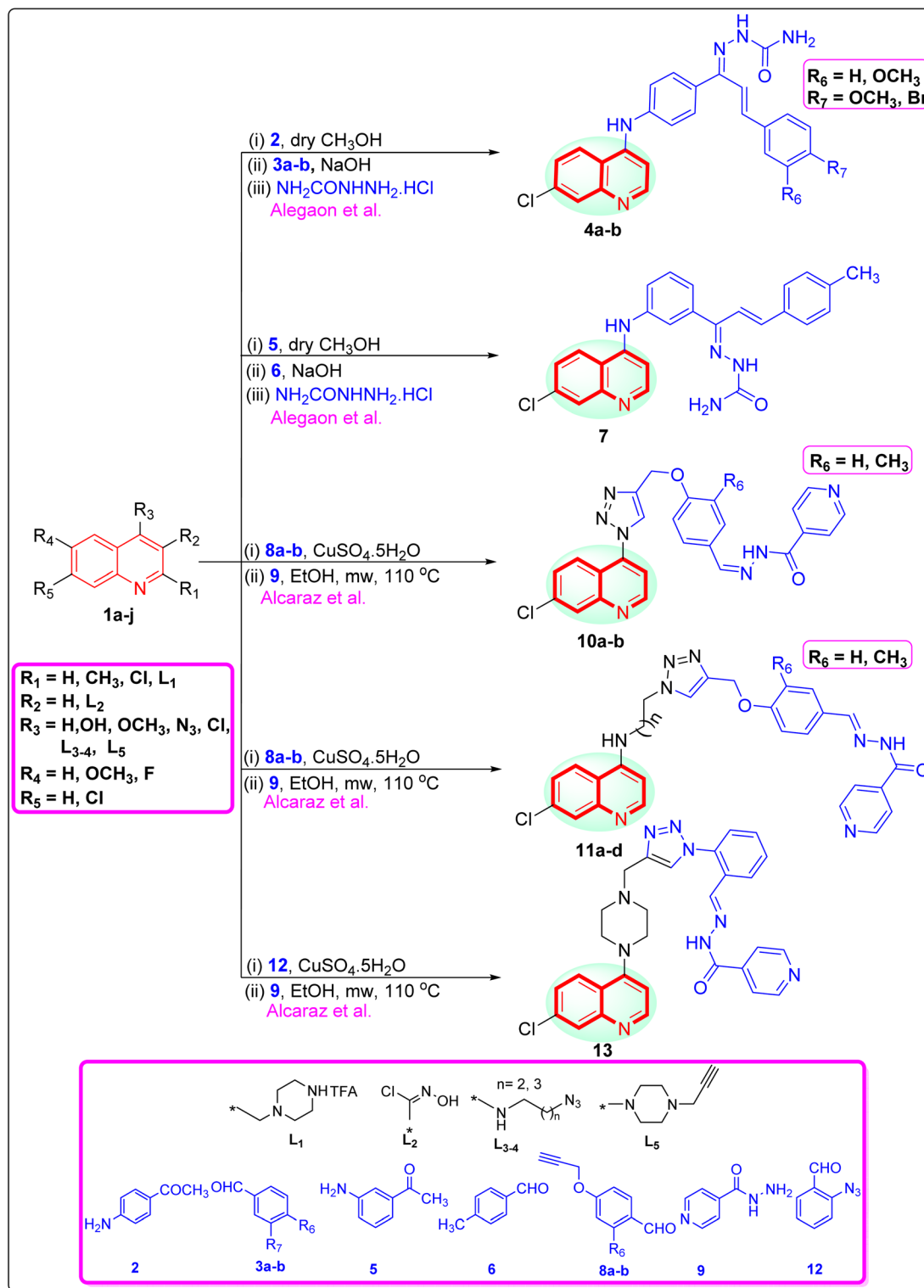


Fig. 4 Synthesis of anti-TB quinoline analogs from substituted quinolines.

semicarbazide hydrochloride to produce compound **7** (Fig. 4). Excellent activity against MTB was exhibited by **4a**, **4b**, and **7** with MIC values of 1.56, 1.56, and 6.25  $\mu\text{M}$ , respectively<sup>50</sup> (Table 1). Similarly, Alcaraz and colleagues prepared Schiff bases of the 7-chloroquinoline-isoniazid hybrids **10a-b** and

**11a-d** from 4-azido-7-chloroquinoline **1b** and the *N*-(2-azidoalkyl)-7-chloroquinolin-4-amines **1c-d**, respectively. Compounds **1b** and **1c-d** were treated with alkynes **8a-b** in the presence of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and sodium ascorbate, at room temperature for 3 h to produce the relative triazolyl quinolines,

Table 1 MIC values and yields of quinoline derivatives for anti-TB activity

| S. No. | Compound   | MIC value                  | Yield (%) | S. No. | Compound   | MIC value                  | Yield (%) |
|--------|------------|----------------------------|-----------|--------|------------|----------------------------|-----------|
| 1      | <b>4a</b>  | 1.56 $\mu\text{M}$         | 56        | 28     | <b>38a</b> | 16 $\mu\text{g mL}^{-1}$   | 33.3      |
| 2      | <b>4b</b>  | 1.56 $\mu\text{M}$         | 51        | 29     | <b>38b</b> | 16 $\mu\text{g mL}^{-1}$   | 50        |
| 3      | <b>7</b>   | 6.25 $\mu\text{M}$         | 55        | 30     | <b>41a</b> | 31.5 $\mu\text{M}$         | 85        |
| 4      | <b>10a</b> | 0.25 $\mu\text{g mL}^{-1}$ | 74        | 31     | <b>41b</b> | 34.8 $\mu\text{M}$         | 88        |
| 5      | <b>10b</b> | 0.5 $\mu\text{g mL}^{-1}$  | 74        | 32     | <b>43a</b> | 12.5 $\mu\text{g mL}^{-1}$ | 93        |
| 6      | <b>11a</b> | 0.5 $\mu\text{g mL}^{-1}$  | 72        | 33     | <b>43b</b> | 12.5 $\mu\text{g mL}^{-1}$ | 80        |
| 7      | <b>11b</b> | 0.5 $\mu\text{g mL}^{-1}$  | 75        | 34     | <b>47a</b> | 4 $\mu\text{g mL}^{-1}$    | 54        |
| 8      | <b>11c</b> | 0.5 $\mu\text{g mL}^{-1}$  | 73        | 35     | <b>47b</b> | 4 $\mu\text{g mL}^{-1}$    | 56        |
| 9      | <b>11d</b> | 0.25 $\mu\text{g mL}^{-1}$ | 71        | 36     | <b>47c</b> | 4 $\mu\text{g mL}^{-1}$    | 51.4      |
| 10     | <b>13</b>  | 0.25 $\mu\text{g mL}^{-1}$ | 76        | 37     | <b>49</b>  | 4.7 $\mu\text{g mL}^{-1}$  | 90.14     |
| 11     | <b>15</b>  | 0.3 $\mu\text{M}$          | 63        | 38     | <b>53a</b> | 1.6 $\mu\text{g mL}^{-1}$  | 67        |
| 12     | <b>16</b>  | 1.3 $\mu\text{M}$          | 38        | 39     | <b>53b</b> | 1.6 $\mu\text{g mL}^{-1}$  | 70        |
| 13     | <b>18</b>  | 0.07 $\mu\text{M}$         | 69.8      | 40     | <b>53c</b> | 1.6 $\mu\text{g mL}^{-1}$  | 63        |
| 14     | <b>19</b>  | 1.1 $\mu\text{M}$          | 68        | 41     | <b>53d</b> | 1.6 $\mu\text{g mL}^{-1}$  | 61        |
| 15     | <b>21</b>  | 0.90 $\mu\text{M}$         | 84.81     | 42     | <b>53e</b> | 1.6 $\mu\text{g mL}^{-1}$  | 64        |
| 16     | <b>23</b>  | 6.25 $\mu\text{g mL}^{-1}$ | 84        | 43     | <b>53f</b> | 1.6 $\mu\text{g mL}^{-1}$  | 71        |
| 17     | <b>25</b>  | 18.27 $\mu\text{M}$        | 85        | 44     | <b>56a</b> | 62.5 $\mu\text{g mL}^{-1}$ | 78        |
| 18     | <b>27</b>  | 15 $\mu\text{M}$           | 91        | 45     | <b>56b</b> | 62.5 $\mu\text{g mL}^{-1}$ | 70        |
| 19     | <b>29</b>  | 0.26 $\mu\text{g mL}^{-1}$ | 84        | 46     | <b>56c</b> | 25 $\mu\text{g mL}^{-1}$   | 78        |
| 20     | <b>32</b>  | 9.97 $\mu\text{M}$         | 25        | 47     | <b>56d</b> | 62.5 $\mu\text{g mL}^{-1}$ | 75        |
| 21     | <b>35</b>  | 0.24 $\mu\text{g mL}^{-1}$ | 84        | 48     | <b>56e</b> | 12.5 $\mu\text{g mL}^{-1}$ | 48        |
| 22     | <b>37a</b> | 3.12 $\mu\text{g mL}^{-1}$ | 89        | 49     | <b>56f</b> | 50 $\mu\text{g mL}^{-1}$   | 80        |
| 23     | <b>37b</b> | 1.60 $\mu\text{g mL}^{-1}$ | 90        | 50     | <b>56g</b> | 62.5 $\mu\text{g mL}^{-1}$ | 78        |
| 24     | <b>37c</b> | 1.60 $\mu\text{g mL}^{-1}$ | 88        | 51     | <b>59a</b> | 14.4 $\mu\text{g mL}^{-1}$ | 68        |
| 25     | <b>37d</b> | 3.12 $\mu\text{g mL}^{-1}$ | 78        | 52     | <b>59b</b> | 9.2 $\mu\text{g mL}^{-1}$  | 65        |
| 26     | <b>37e</b> | 1.60 $\mu\text{g mL}^{-1}$ | 90        | 53     | <b>63</b>  | 3.1 $\mu\text{g mL}^{-1}$  | 83        |
| 27     | <b>37f</b> | 1.60 $\mu\text{g mL}^{-1}$ | 90        |        |            |                            |           |

which were treated with isoniazid **9** in a microwave synthesizer at 110 °C in the presence of ethanol through a condensation reaction to form the corresponding compounds **10a–b** and **11a–d**. Additionally, the target compound **13** was prepared by substituted piperazin-1-yl-quinoline **1e**, which was reacted with 2-azidobenzaldehyde **12** according to the above-mentioned process to produce the relative triazolyl quinoline, which was then treated with **9** in the microwave synthesizer in ethanol at 110 °C to form the desired compound **13** (Fig. 4). These compounds **10a–b**, **11a–d**, and **13** all showed excellent activity against MTB, with MIC values in the range of 0.25–0.50  $\mu\text{g mL}^{-1}$  (ref. 51) (Table 1). In another investigation, Borsoi and team-mates prepared 2,4,6-trisubstituted quinolines **15** and **16** with good yields by the nucleophilic substitution reaction of 6-methoxy-2-methylquinolin-4-ol **1f** with 3,4-dichloro benzyl bromide **14** and 2-bromo-1-arylethanone, respectively, in  $\text{K}_2\text{CO}_3$  as a base in DMF solvent at 25 °C (Fig. 5). These compounds were most potent against MTB, with MIC values of 0.3 and 1.3  $\mu\text{M}$  (Table 1). The excellent activity of compound **15** was due to the existence of chloro groups at the 3 and 4 positions.<sup>52</sup>

In another research effort, Gnanavelu *et al.* synthesized quinoline-piperazine hybrids of sulfonamides **18** and **19** in excellent amounts by the reaction of 4,6-dimethoxy- and 6-fluoro-4-methoxy-2-(piperazin-1-ylmethyl)quinolines **1g–h** as a TFA salt with 2-fluorobenzenesulfonyl chloride **17** in DCM solvent, at 0 °C, in the presence of Hünig's base (Fig. 5). These compounds presented good activity against MTB, with MIC values of 0.07 and 1.1  $\mu\text{M}$ , respectively<sup>53</sup> (Table 1).

Likewise, Moodley and associates prepared **21** as a main product with a good yield from 4,7-dichloroquinoline **1a**, which reacted with propane-1,2-diamine by a nucleophilic substitution reaction to form  $N^1$ -(7-chloroquinolin-4-yl)propane-1,2-diamine, which was then treated with **20** in dry ACN and set to reflux at 85 °C for 24 h to obtain compound **21** (Fig. 5). This showed good activity against MTB, with an MIC value 0.90  $\mu\text{M}$ .<sup>6</sup> Kanchrana's group developed the targeted compound **23** in an 84% yield by the reaction of (*Z*)-2-chloro-*N*-hydroxyquinoline-3-carbimidoyl chloride **1i** and **22** in the presence of  $\text{Et}_3\text{N}$  base through ultrasonication in DCM solvent at room temperature for 15 min, while in MeOH solvent, when using the conventional method at room temperature for 12 h without any base, they found only a trace amount of the targeted compound **23** (Fig. 5). This showed significant resistance activity against MTB, with an MIC value of 6.25  $\mu\text{g mL}^{-1}$ <sup>54</sup> (Table 1).

## 2.2. From substituted anilines

The synthesis of quinoline from substituted aniline represents a valuable strategy in organic chemistry, facilitating the production of these important heterocyclic compounds. This method typically involves the cyclization of substituted anilines, utilizing various reagents and catalysts to promote the formation of the quinoline ring. By altering the substituents on the aniline, chemists can fine-tune the properties of the resulting quinoline derivatives, thereby enhancing their biological activity and pharmacological potential. Different synthetic routes, such as the Skraup and Friedländer methods, allow for





Fig. 5 Synthesis of anti-TB quinoline hybrids from substituted quinolines.

the introduction of diverse functional groups, contributing to the versatility of quinoline compounds. This approach not only streamlines the synthesis process but also allows expanding the repertoire of quinoline derivatives available for therapeutic applications, particularly in treating TB and other diseases. In a similar vein, Zaheer *et al.* prepared the novel compounds *N'*-((2-chloro-6-methoxyquinolin-3-yl)methyl)isonicotinohydrazide **25** and *N*-((2-chloro-6-methoxyquinolin-3-yl)methyl)-3-fluoro-4-morpholinoaniline **27** by 4-methoxy acetanilide **24a**, which

was reacted with  $POCl_3$ /DMF at 80 °C to give 6-methoxy 2-chloroquinoline-3-carbaldehyde through the Vilsmeier–Haack reaction, which was then treated with **9** and 3-fluoro-4-morpholinoaniline **26** to form the corresponding Schiff bases. These Schiff bases were reduced by  $NaBH_4$  in methanol solvent to produce the corresponding compounds **25** and **27**, respectively (Fig. 6). These compounds exhibited exceptional activity against MTB, with MIC values of 15.00 and 18.27  $\mu$ M, respectively<sup>55</sup> (Table 1). Similarly, Baliram's team synthesized Schiff

base **29** by 4-methylaniline **24b**, which reacted with acetic anhydride to form *N*-(*p*-tolyl)acetamide, which was then treated with POCl<sub>3</sub>/DMF and water in acetic acid to obtain 2-hydroxy-6-methylquinoline-3-carbaldehyde in two steps, which was then

combined with 4-methylbenzenesulfonylhydrazide **28** and acetic acid in ethanol at 70 °C to synthesize the desired compound **29** (Fig. 6). This showed good activity with an MIC value of 0.26 µg mL<sup>-1</sup> against MTB<sup>3</sup> (Table 1). By comparison, Alsayed and



Fig. 6 Synthesis of anti-TB quinoline derivatives from substituted anilines.



colleagues synthesized arylamide *N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)-5-bromo-4-hydroxyquinoline-2-carboxamide **32** from 3-bromo aniline **24c**, which was treated with dimethyl acetylenedicarboxylate **30** to prepare the substituted 1,4-dihydroquinoline-2-carboxylate through an intramolecular Friedel–Crafts reaction. This was then hydrolyzed by 10% basic NaOH to form the corresponding carboxylic acid, which reacted with (3*s*,5*s*,7*s*)-adamantan-1-amine **31** in the presence of DIPEA as a base, and HOBt hydrate and EDC-HCl as coupling agents to produce compound **32** (Fig. 6). This exhibited excellent activity against MTB with an MIC value of 9.97  $\mu\text{M}$ <sup>56</sup> (Table 1). The novel product (Z)-*N'*-(1-benzyl-2-oxoindolin-3-ylidene)-7-chloro-4-hydroxyquinoline-3-carbohydrazide **35** was synthesized by Abdelrahman *et al.* through 3-chloro aniline **24d**, which was treated with diethyl 2-(ethoxymethylene)malonate **33** and phenyl ether under reflux conditions in two steps to give ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate, which was reacted with hydrazine and 1-benzylindoline-2,3-dione **34** to produce compound **35** in two steps (Fig. 6). This compound showed excellent activity with an MIC value of 0.24  $\mu\text{m mL}^{-1}$  against MTB<sup>57</sup> (Table 1).

Quinoliny-1,2,3-triazoly-1,2,4-triazol-3(4*H*)-ones **37a–f** were prepared by Nesaragi and associates in a very short time with good yields through 2/3/4-substituted *N*-phenylacetamides **24e–h**, which were reacted with POCl<sub>3</sub> and DMF under reflux conditions to produce 2-chloro-6/7/8-substituted quinoline-3-carbaldehydes through a Vilsmeier–Haack reaction, which were then treated with NaBH<sub>4</sub>, PBr<sub>3</sub>, and NaN<sub>3</sub> in three steps to form 6/7/8-substituted 3-(azidomethyl)-2-bromoquinolines, which were reacted with acetylenic dipolarophiles **36a–b** to prepare compounds **37a–f**, respectively, through a cycloaddition reaction in the presence of CuSO<sub>4</sub> and sodium ascorbate under microwave conditions at 100 °C (Fig. 6). These showed an anti-TB activity with MIC values ranging from 1.60–3.25  $\mu\text{g mL}^{-1}$  (ref. 58) (Table 1). Likewise, Quimque's team developed quinoline derivatives **38a–b** from 4-butylaniline **24i** and 4-isopropylaniline **24j**, respectively. These were then reacted with hydroxylamine hydrochloride and chloral hydrate in aqueous Na<sub>2</sub>SO<sub>4</sub> to produce the corresponding 2-(hydroxyamino)-*N*-phenylacetamide intermediates, which reacted with H<sub>2</sub>SO<sub>4</sub> to form 5-substituted isatins, respectively. These diones were treated with substituted ketones in the presence of 33% KOH in ethanol solvent at 120 °C under microwave conditions for 90 min to obtain compounds **38a–b** (Fig. 7). These showed highly effective resistance against MTB with MIC values of more than 16  $\mu\text{g mL}^{-1}$  (Table 1). Their activity varied due to the effect of the aryl group at the C-2 position and the expansion of the alkyl chain at the C-6 position.<sup>59</sup> In a similar fashion, Ramprasad *et al.* developed a synthetic protocol for obtaining 6-bromo-3-((4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)(phenyl)methyl)-2-methoxyquinoline **41a** and 6-bromo-2-methoxy-3-((4-octyl-1*H*-1,2,3-triazol-1-yl)(phenyl)methyl)quinoline **41b** using 4-bromo aniline **24k**, which was reacted with 3-phenylpropanoyl chloride **39**, POCl<sub>3</sub>/DMF, NaOMe/MeOH, respectively, in three steps to form 3-benzyl-6-bromo-2-methoxyquinoline. This was then treated with *N*-bromosuccinamide and NaN<sub>3</sub>/DMF in two

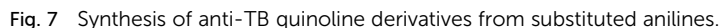
steps to prepare 3-(azido(phenyl)methyl)-6-bromo-2-methoxyquinoline, which was reacted with 1-ethynyl-3-fluorobenzene **40a** and dec-1-yne **40b** in the presence of CuI and ACN at 80 °C for 3 h to obtain **41a–b**, respectively, through a click reaction (Fig. 7). These showed excellent resistance against the growth of *M. bovis* with MIC values of 31.5 and 34.8  $\mu\text{M}$ , respectively<sup>60</sup> (Table 1). Sahana and researchers synthesized 2,4,5-trisubstituted imidazole-quinolines **43a–b** from *N*-phenylacetamide **24l** with POCl<sub>3</sub>/DMF under reflux conditions to form 2-chloroquinoline-3-carbaldehyde, which was refluxed with 70% acetic acid for 4 h to give 2-hydroxyquinoline-3-carbaldehyde, which was further reacted with **42a–b** in the presence of NH<sub>4</sub>OAc and acetic acid under reflux conditions to synthesize compounds **43a–b** (Fig. 7). These demonstrated good resistance activity against MTB with MIC value of 12.5  $\mu\text{g mL}^{-1}$  (Table 1). Due to the presence of halogen substituents on the aryl ring, the activity was increased.<sup>2</sup>

Quinoline derivatives with a hydrazone moiety **47a–c** were prepared with excellent yields by Shruthi *et al.* from 3-chloro aniline **24m**. Specifically, this was treated with diethyl ethoxymethylenemalonate **44** and then heated at 240 °C in DOW-THERM medium in two steps to produce 7-chloroquinolin-4-ol, which then reacted with POCl<sub>3</sub> and piperazine in two steps to prepare 7-chloro-4-(piperazin-1-yl)quinoline, which was coupled with 4-chloromethyl-benzaldehyde **45** to obtain the substituted benzaldehyde intermediate. This intermediate combined with hydrazine hydrochloride **46** in ethanol to give the targeted compounds **47a–c** (Fig. 7). These showed moderate inhibitory activity against MTB with MIC values of 4  $\mu\text{g mL}^{-1}$ . Due to the occupancy of the chloro group at the 7-position of the quinoline nucleus and hydrazones with 4-tolyl-4-fluoro- and 4-isopropyl-phenyl groups, these showed elevated activity.<sup>5</sup> Murnane and teammates synthesized the quinoline hybrid **49** by the reaction of 4-methoxyaniline **24n** with ethyl acetoacetate to form 6-methoxy-2-methylquinolin-4-ol, which was then treated with 2-(bromomethyl)quinoline **48** in K<sub>2</sub>CO<sub>3</sub> and anhydrous DMF at RT to obtain compound **49** (Fig. 7). This exhibited high resistance against QcrB T313I with MIC value of 4.7  $\mu\text{g mL}^{-1}$ .<sup>61</sup>

### 2.3. From miscellaneous starting materials

These methods typically involve non-traditional reactants, thereby expanding the scope of possible structural modifications. The flexibility in choosing the starting materials enables the introduction of unique functional groups into the quinoline ring, enhancing properties like anti-TB activity. Some examples include cyclization reactions, multi-component reactions, and the use of heterocyclic intermediates. This approach not only broadens the range of synthesized quinolines but also contributes to the discovery of novel therapeutic agents targeting TB and other diseases. For instance, Babu *et al.* prepared **53a–f** from the reaction of **50** and **51** in the presence of DMF under reflux conditions to form 5,5-dimethyl-3-((3-methyl-1*H*-pyrazol-5-yl)amino)cyclohex-2-en-1-one, which was reacted with substituted aromatic aldehydes





acetyl)-1*H*-quinoline-2-one, which was treated with various aromatic thioamides **55a–g** under reflux conditions in ethanol reaction medium to give the final compounds **56a–g** (Fig. 8). These displayed potential activity against MTB with MIC values of 62.5, 62.5, 25, 62.5, 12.5, 50, and 62.5  $\mu\text{g mL}^{-1}$  respectively<sup>62</sup> (Table 1). Shinde and colleagues designed **59a–b** from the 5-substituted isatins **57a–b** and **58** to get the corresponding 6-substituted quinoline-2,4-dicarboxylic acids through a Pfitzinger reaction, which were then selectively decarboxylated in nitrobenzene at 210 °C to give the 6-

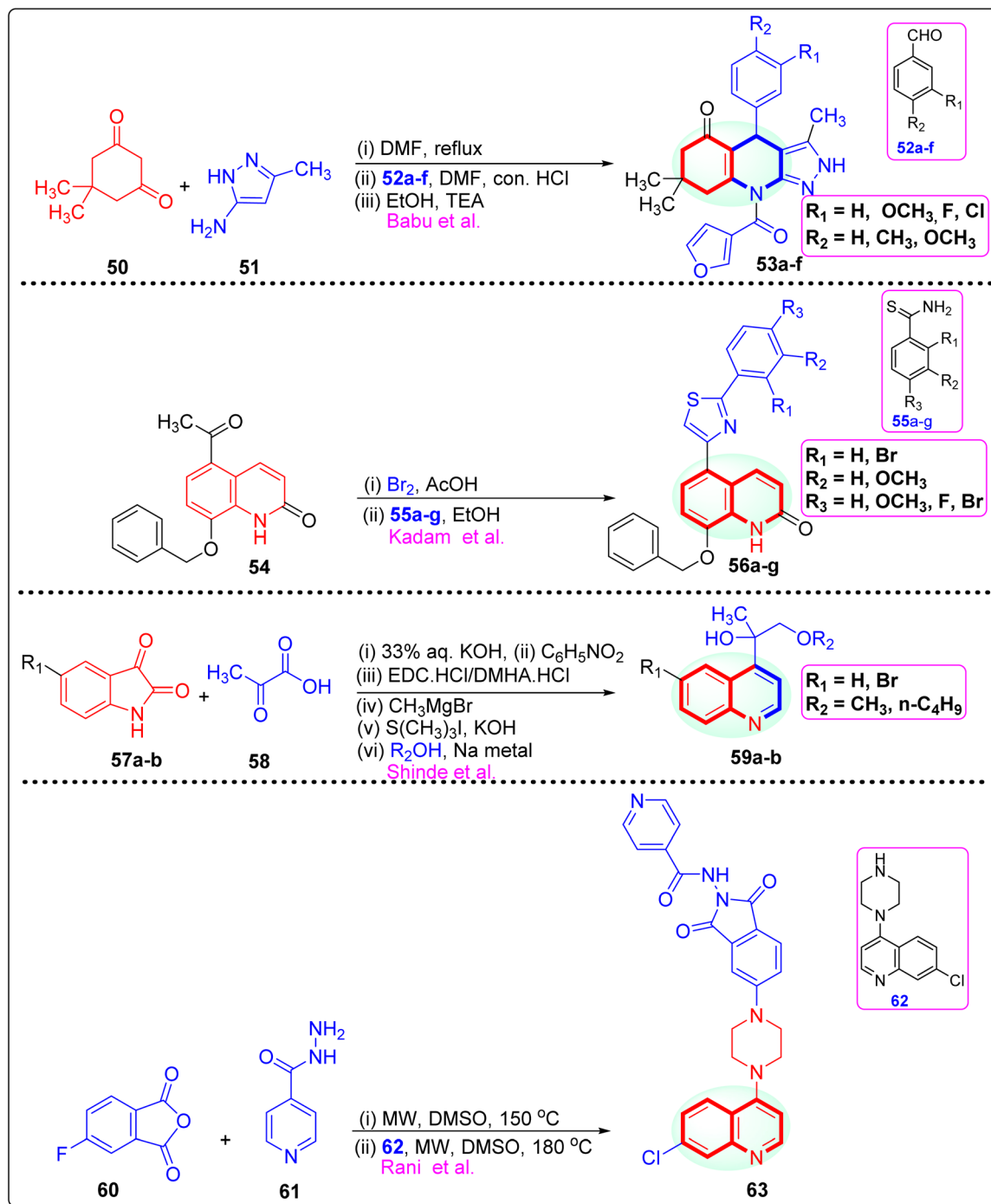


Fig. 8 Synthesis of anti-TB quinolines from miscellaneous reactants.

substituted-4-quinoline carboxylic acids and then coupled with *N,O*-dimethylhydroxamine hydrochloride, in the presence of the coupling agent EDC, and HCl and DMAP as a base to synthesize the corresponding carboxamides at 0 °C. These carboxamides reacted with  $\text{CH}_3\text{MgBr}$  and the epoxidizing agent  $\text{S}(\text{CH}_3)_3\text{I}$  in two steps to obtain the relative 6-substituted-4-(2-methyloxiran-2-yl)quinolines, which were finally combined with alcohols to synthesize compounds **59a-b** (Fig. 8). These displayed good activity against MTB with MIC

values of 14.4 and 9.2  $\mu\text{g mL}^{-1}$ , respectively<sup>63</sup> (Table 1). Similarly, Rani *et al.* prepared **63** in a good yield from **60**, which was reacted with **61** under microwave heating at 150 °C to obtain *N*-(5-fluoro-1,3-dioxoisindolin-2-yl)isonicotinamide. This was then treated with 7-chloro-4-(piperazin-1-yl)quinoline **62** under microwave heating at 180 °C for 15 min to synthesize compound **63** (Fig. 8). This compound displayed potential activity against MTB with an  $\text{MIC}_{50}$  value of 3.1  $\mu\text{g mL}^{-1}$ <sup>64</sup> (Table 1).

### 3 Study compendium

Quinoline and its derivatives exhibit a broad spectrum of pharmacological activities. The consideration of MIC values has significantly helped advance our understanding of how to develop more effective quinoline-based drugs for combating TB. Structural modifications, such as incorporating specific substituents, as well as adding alkene, tetrazole, hydrazone, and pyrazole groups to the quinoline ring, have been shown to enhance anti-TB activity. In this review, we compiled 53 commonly synthesized quinoline-containing anti-TB agents. Of these, 17 compounds were synthesized *via* substituted quinolines, 20 compounds were derived from substituted anilines, and the remaining 16 compounds were formed using miscellaneous reactant molecules, all with good yields (Fig. 9).

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Fig. 9 Quinoline analogues as anti-TB agents.



The synthesized compounds exhibited strong efficacy against MTB, with varying MIC values. In summary, reviews of this nature are crucial in the current landscape, as there is a crucial requirement to develop anti-TB drugs that are less toxic, more cost-effective, simpler to produce, and highly potent. This is especially true as the current tuberculosis treatments are typically costly, have high toxicity, and are complex, driving the search for molecules that can interact with novel targets or support multi-target combination therapies. As the number of newly tested compounds against mycobacteria continues to rise, there is significant potential to develop innovative drugs aimed at fully eradicating TB. We also highlighted the latest advancements in the synthesis of quinoline compounds. Several traditional methods have been refined and improved over the years, while new synthetic techniques have been developed. There is a pressing need for new anti-TB drug regimens that can reduce treatment duration and effectively combat the rising threat of drug-resistant and MDR-TB strains.

One of the main variables affecting quinoline derivatives' MIC values against MTB is their substitution patterns. By increasing the electron density on the quinoline ring, electron-donating groups, like  $-OH$  or  $-NH_2$ , can improve the binding affinity with bacterial enzymes and thereby reduce the MIC.<sup>65</sup> By lowering the electron density, electron-withdrawing groups, such as  $-NO_2$  or  $-CN$ , on the other hand, impair the compound's interaction with the target and raise the MIC values. Heterocyclic or aryl substitutions can decrease the MIC by increasing the affinity for particular MTB targets, such as enzymes involved in cell wall formation.<sup>66</sup> Additionally, by increasing the stability and bioavailability, these changes may maximize effectiveness. Bulkier groups, on the other hand, may make it more difficult to bind or penetrate cell walls, which would raise the MIC values. Thus, improving quinoline compounds for the successful treatment of drug-resistant TB requires strategic replacements of the groups.<sup>67</sup> The use of MIC values has significantly helped the understanding of how to make quinoline derivatives for more effective TB treatment. The MIC values for all the quinoline derivatives mentioned in this paper are summarized in the table given below.

## 4 Future challenges

There are several current and likely upcoming obstacles to the development and commercialization of target-based quinoline core designs for the treatment of MDR MTB. The development of drug resistance as a result of mutations in important therapeutic targets is one significant barrier and would make it challenging for quinoline derivatives to remain effective.<sup>8</sup> Furthermore, it is still very difficult to optimize these drugs' pharmacokinetics for increased bioavailability, tissue penetration, and low toxicity. Targeting certain MTB processes, including resistance-related enzymes or efflux pumps, necessitates a thorough comprehension of the bacterium's adaptive mechanisms. The development process is further complicated by the requirement for

quinoline derivatives to work in synergistic combinations with other anti-TB medicines. Another layer of difficulty is the possibility of cytotoxicity and off-target effects brought on by the highly reactive nature of quinoline derivatives, particularly when heterocyclic groups are added. Overcoming the adaptation mechanisms of resistant MTB strains, the development of creative design approaches, and thorough pharmacological profiling will be necessary to meet these obstacles.<sup>68</sup>

## 5 Conclusion

Quinoline and its derivatives have attracted significant attention for their potential in anti-TB drug development. The structural versatility of the molecule allows for modifications that can enhance its antibacterial efficacy, particularly against MTB, the causative agent of TB. These compounds have demonstrated promising activity by targeting various bacterial enzymes and processes, including DNA gyrase, cell wall synthesis, and energy metabolism. Additionally, quinoline derivatives have shown the ability to act synergistically with existing TB treatments, which is a potential avenue for improving therapeutic outcomes. The ability to design derivatives with improved pharmacokinetic properties would further enhance their therapeutic potential. The pharmacokinetic properties of quinoline derivatives, including ADME, are crucial in determining their efficacy and toxicity. Factors like lipophilicity, molecular size, and stability influence bioavailability and tissue penetration, while metabolism *via* cytochrome P450 enzymes can affect their half-life and active forms. Quinoline derivatives with favorable pharmacokinetics often exhibit lower  $IC_{50}$  values, indicating their higher potency against MTB. Various enhancements have been investigated and reported, such as an aryl core, triazole ring, and heterocyclic analogs like nicotinic acid hydrazide, that can improve their anti-TB activity. However, challenges remain, including the excessive accumulation of reactive nitrogen species, which can cause cytotoxicity, damaging essential macromolecules, and affecting efficacy. Other challenges remain in overcoming resistance mechanisms, optimizing selectivity for the TB pathogen, and ensuring low toxicity profiles to minimize adverse effects. Continued research and development in this area could lead to novel quinoline-based therapies that could address the urgent necessity for new and effective anti-TB drugs, especially in the face of rising drug resistance and the limited efficacy of current treatments against MDR and widely drug-resistant TB strains. The initial transformation of quinoline by *D. indolicum* proceeded *via* hydroxylation at the 2-position. This mechanism has been reported several times under various redox conditions; however, other degradation pathways have also been identified for the metabolism of quinoline under sulfate-reducing conditions. In earlier studies of the anaerobic degradation of quinoline, the successive transformation of 2-OH-quinoline was only described under methanogenic conditions, leading to the formation of methylated and hydroxylated intermediates.



Another new pathway leading to hydroxylated and hydrogenated intermediates was thus observed.

## Abbreviations

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| TB              | Tuberculosis                                                  |
| HIV             | Human immunodeficiency virus                                  |
| MTB             | Mycobacterium tuberculosis                                    |
| DprE1           | Decaprenylphosphoryl- $\beta$ -D-ribose 2'-epimerase          |
| InhA            | Enoyl-acyl carrier protein reductase                          |
| MmpL3           | Mycobacterial membrane protein large 3                        |
| ATP             | Adenosine triphosphate                                        |
| QSAR            | Quantitative structure-activity relationships                 |
| ADMET           | Absorption, distribution, metabolism, excretion, and toxicity |
| QcrB            | A subunit of cytochrome bcc, working as                       |
| T313I           | a component of the electron-transport chain of MTB            |
| MDR             | Multidrug resistance                                          |
| WHO             | World Health Organization                                     |
| US-FDA          | US Food and Drug Administration                               |
| BCG             | Bacillus Calmette-Guerin                                      |
| <i>M. Bovis</i> | <i>Mycobacterium bovis</i>                                    |
| HOBt            | Hydroxybenzotriazole hydrate                                  |
| DIPEA           | Diisopropylethylamine                                         |
| EDC-HCl         | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride   |
| DMHA-HCl        | Dimethylhydroxyamine hydrochloride                            |
| DMAp            | Dimethyl amino pyridine                                       |
| MIC             | Minimum inhibitory concentration                              |
| SDGs            | Sustainable development goals                                 |
| PDGF            | Platelet-derived growth factor                                |
| RTK             | Receptor tyrosine kinase                                      |
| DMF             | Dimethylformamide                                             |
| TFA             | Trifluoroacetic acid                                          |
| DCM             | Dichloromethane                                               |
| TFA             | Trifluoroacetic acid                                          |
| DNA             | Deoxyribonucleic acid                                         |
| RT              | Room temperature                                              |

## Data availability

No primary results, software, or code has been included and no new data were generated or analyzed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors are thankful to the University College of Science, MLSU, Udaipur, Rajasthan, India for providing essential research and library facilities and also grateful to the University Grant Commission (UGC), New Delhi, India for financial support.

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