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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, cardiotonic, 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.

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1 Introduction

Tuberculosis (TB) is a disease involving lung infection¹ and is one of the top ten causes of death globally.² It can particularly

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arise in HIV patients, in whom the pathogenic alliance between HIV and TB can have severe consequences.3 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.4 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.5 Around one-third of the global population is estimated to be infected with TB.6 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 2035.7

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.8 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.9 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



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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).10

Quinolines are bicyclic N-containing heterocyclic naturally occurring organic compounds, which serve as important segments of both synthetic and pharmacologically active compounds.11 Quinoline's ability to form salts with acids makes it a weak tertiary base, displaying electrophilic substitution reactions similar to pyridine and benzene.12 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.¹³ 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 quinolinebased drug discovery has enormous potential to provide safer and more efficient treatment choices while also addressing the problems caused by drug-resistant TB.14 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.15 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. 16 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

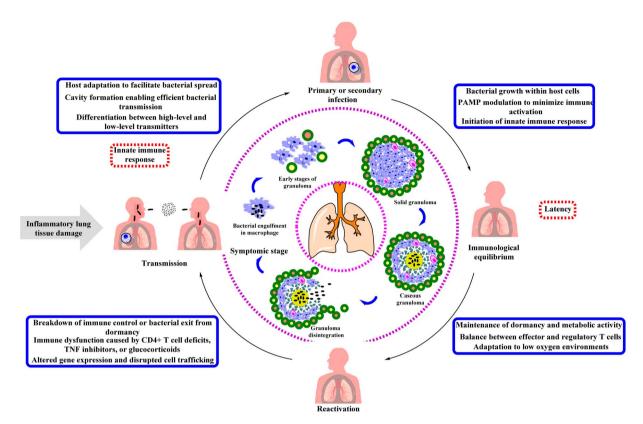


Fig. 1 Diagrammatic representation of the mechanism of tubercular activity.

proteins with differing affinities, offering important information about their possible medical uses. ¹⁶ 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,17 histamine H3 receptor antagonist, 18,19 antibiotic, 20 anti-inflammatory, 21,22 antihypertensive, 21 antileishmanial,23 anti-oxidant,24 tyrosine kinase inhibitors,25 antimalarial,26 anticancer,27 anti-HIV,28 anti-asthmatic,29 cardiotonic,30 anticonvulsant,31 anthelmintic,32 antifungal,33 antiprotozoals,34 anti-alzheimer,35 tyro kinase PDGF-RTK-inhibitor, agents for the treatment of lupus, antipsychotics,36 antiglaucoma, and local anesthetic.12 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).37 Quinoline-based anti-TB drugs have both nonpolar and polar properties, which allow them to permeate bacterial cells.² 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.⁷ 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,³⁹ ciprofloxacin,⁴⁰ moxifloxacin,^{39,41} sparfloxacin, ofloxacin, enrofloxacin, levofloxacin,³⁷ kokusaginine,⁴² lomefloxacin,⁴³ mefloquine, and norfloxacin⁴⁴ (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, -CF₃,45 and azomethine (-C=N-)3 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,45 quinolineoxazoloquinoline,45 tetrazole,3 quinoline-pyrazole,46 trifluoromethyl-fused quinoline combinations, have yielded promising results.45 Quinoline hydrazones as well as fluorinesubstituted hydrazones have been reported to have anti-TB activity with high potency compared to rifampicin and isoniazid.5 The pharmacological effectiveness and safety of quinoline derivatives in the treatment of TB are largely determined by their metabolic metabolism. The liver's cytochrome P450 enzymes are the main catalysts for the several biotransformation processes that these substances go through. Typical metabolic processes

Antibacterial

Fig. 2 Biologically active agents bearing a quinoline nucleus.

Antiprotozoal

that increase their solubility and ease of excretion include hydroxylation, N-oxidation, and conjugation reactions, including glucuronidation and sulfation.47 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.48 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.49 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.13 Quinoline Schiff basederived 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.3

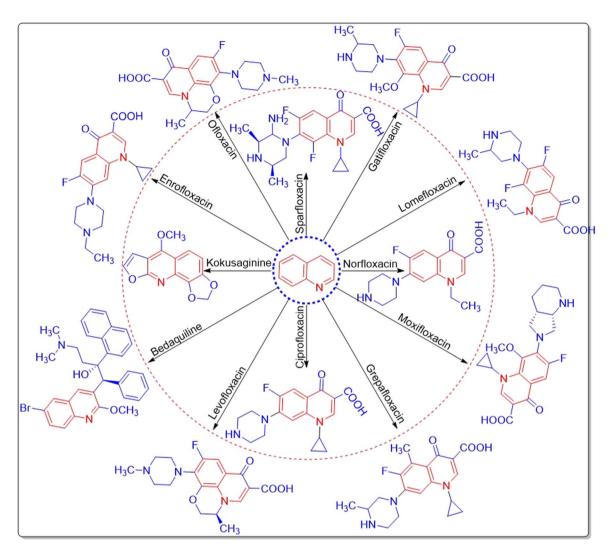


Fig. 3 Quinoline-containing marketed anti-TB drugs

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 4,7dichloroquinoline 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 μ M, respectively⁵⁰ (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 $CuSO_4 \cdot 5H_2O$ 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	4a	1.56 μΜ	56	28	38a	$16~\mu \mathrm{g~mL^{-1}}$	33.3
2	4b	1.56 μΜ	51	29	38b	$16 \mu \mathrm{g \ mL}^{-1}$	50
3	7	6.25 μM	55	30	41a	31.5 μM	85
4	10a	$0.25~\mu \mathrm{g~mL}^{-1}$	74	31	41b	34.8 μM	88
5	10b	$0.5~\mu\mathrm{g~mL}^{-1}$	74	32	43a	12.5 $\mu g \; m L^{-1}$	93
6	11a	$0.5~\mu\mathrm{g~mL}^{-1}$	72	33	43b	12.5 $\mu g \; m L^{-1}$	80
7	11b	$0.5~\mu\mathrm{g~mL}^{-1}$	75	34	47a	$4 \mu \mathrm{g \ mL}^{-1}$	54
8	11c	$0.5~\mu\mathrm{g~mL}^{-1}$	73	35	47b	$4~\mu \mathrm{g}~\mathrm{mL}^{-1}$	56
9	11d	$0.25~\mu g~mL^{-1}$	71	36	47c	$4 \mu \text{g mL}^{-1}$	51.4
10	13	$0.25~\mu {\rm g}~{\rm mL}^{-1}$	76	37	49	$4.7~\mu\mathrm{g~mL^{-1}}$	90.14
11	15	0.3 μΜ	63	38	53a	$1.6~\mu\mathrm{g~mL}^{-1}$	67
12	16	1.3 μΜ	38	39	53b	$1.6~\mu \mathrm{g~mL^{-1}}$	70
13	18	0.07 μΜ	69.8	40	53c	$1.6~\mu\mathrm{g~mL}^{-1}$	63
14	19	1.1 μΜ	68	41	53 d	$1.6~\mu\mathrm{g~mL}^{-1}$	61
15	21	0.90 μΜ	84.81	42	53e	$1.6~\mu \mathrm{g~mL^{-1}}$	64
16	23	$6.25~\mu\mathrm{g~mL}^{-1}$	84	43	53f	$1.6~\mu\mathrm{g~mL}^{-1}$	71
17	25	18.27 μM	85	44	56a	$62.5~\mu\mathrm{g~mL}^{-1}$	78
18	27	15 μM	91	45	56b	$62.5~\mu\mathrm{g~mL}^{-1}$	70
19	29	$0.26~\mu g~mL^{-1}$	84	46	56c	$25~\mu g~mL^{-1}$	78
20	32	9.97 μΜ	25	47	56 d	62.5 $\mu g \text{ mL}^{-1}$	75
21	35	$0.24~\mu \mathrm{g~mL}^{-1}$	84	48	56e	$12.5~\mu\mathrm{g~mL}^{-1}$	48
22	37a	$3.12~\mu\mathrm{g~mL}^{-1}$	89	49	56f	$50~\mu \mathrm{g~mL^{-1}}$	80
23	37 b	$1.60~\mu { m g}~{ m mL}^{-1}$	90	50	56g	62.5 $\mu g \text{ mL}^{-1}$	78
24	37 c	$1.60~\mu {\rm g}~{\rm mL}^{-1}$	88	51	59a	$14.4~\mu \mathrm{g~mL^{-1}}$	68
25	37 d	$3.12~\mu\mathrm{g~mL}^{-1}$	78	52	59 b	$9.2~\mu\mathrm{g~mL}^{-1}$	65
26	37 e	$1.60~\mu {\rm g}~{\rm mL}^{-1}$	90	53	63	$3.1~\mu\mathrm{g~mL}^{-1}$	83
27	37f	$1.60~\mu {\rm g}~{\rm mL}^{-1}$	90			10	

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 11ad. 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 $0.25-0.50 \,\mu\mathrm{g}\,\mathrm{mL}^{-1}$ (ref. 51) (Table 1). In another investigation, Borsoi and teammates prepared 2,4,6-trisubstituted quinolines 15 and 16 with good yields by the nucleophilic substitution reaction of 6methoxy-2-methylquinolin-4-ol 1f with 3,4-dichloro benzyl bromide 14 and 2-bromo-1-arylethanone, respectively, in K₂CO₃ 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 μM (Table 1). The excellent activity of compound 15 was due to the existence of chloro groups at the 3 and 4 positions.⁵²

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 $^{\circ}$ 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 μ M, respectively⁵³ (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 N¹-(7-chloroquinolin-4-yl)propane-1,2diamine, 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 µM.6 Kanchrana's group developed the targeted compound 23 in an 84% yield by the reaction of (Z)-2-chloro-N-hydroxyquinoline-3carbimidoyl chloride 1i and 22 in the presence of Et3N 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 μ g mL⁻¹⁵⁴ (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

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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-methoxyquinoilin-3-yl)methyl)-3-fluoro-4morpholinoaniline 27 by 4-methoxy acetanilide 24a, which

was reacted with POCl₃/DMF at 80 °C to give 6-methoxy 2chloroquinoline-3-carbaldehyde through the Vilsmeier-Haack reaction, which was then treated with 9 and 3-fluoro-4morpholinoaniline 26 to form the corresponding Schiff bases. These Schiff bases were reduced by NaBH₄ 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 μM, respectively⁵⁵ (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 POCl₃/DMF and water in acetic acid to obtain 2-hydroxy-6-methylquinoline-3-carbaldehyde in two steps, which was then

combined with 4-methylbenzenesulfonohydrazide **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⁻¹ against MTB³ (Table 1). By comparison, Alsayed and

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

MTB⁵⁷ (Table 1).

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colleagues synthesized arylamide N-((3s,5s,7s)-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 (3s,5s,7s)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 µM56 (Table 1). The novel (Z)-N'-(1-benzyl-2-oxoindolin-3-ylidene)-7-chloro-4hydroxyquinoline-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 7chloro-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 µm mL⁻¹ against

Quinolinyl-1,2,3-triazoly-1,2,4-triazol-3(4H)-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 POCl₃ 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 NaBH₄, PBr₃, and NaN₃ in three steps to form 6/7/8-substituted 3-(azidomethyl)-2bromoquinolines, which were reacted with acetylenic dipolarophiles 36a-b to prepare compounds 37a-f, respectively, through a cycloaddition reaction in the presence of CuSO₄ 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 μg 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 Na2SO4 to produce the corresponding 2-(hydroxyamino)-N-phenylacetamide intermediates, which reacted with H₂SO₄ 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 µg 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.⁵⁹ In a similar fashion, Ramprasad et al. developed a syntheticsic protocol for obtaining 6-bromo-3-((4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)(phenyl)methyl)-2methoxyquinoline 41a and 6-bromo-2-methoxy-3-((4-octyl-1H-1,2,3-triazol-1-yl)(phenyl)methyl)quinoline 41b using 4bromo aniline 24k, which was reacted with 3-phenylpropanoyl chloride 39, POCl₃/DMF, NaOMe/MeOH, respectively, in three steps to form 3-benzyl-6-bromo-2-methoxyquinoline. This was then treated with N-bromosuccinamide and NaN₃/DMF in two

3-(azido(phenyl)methyl)-6-bromo-2steps prepare methoxyquinoline, which was reacted with 1-ethynyl-3fluorobenzene 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 μM, respectively (Table 1). Sahana and researchers synthesized 2,4,5-trisubstituted imidazole-quinolines 43ab from N-phenylacetamide 24l with POCl₃/DMF under reflux conditions to form 2-chloroquinoline-3-carbaldehyde, which was refluxed with 70% acetic acid for 4 h to give 2hydroxyquinoline-3-carbaldehyde, which was further reacted with 42a-b in the presence of NH4OAc 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 μ g mL⁻¹ (Table 1). Due to the presence of halogen substituents on the aryl ring, the activity was increased.2

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-4ol, which then reacted with POCl3 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 $\mu g \text{ mL}^{-1}$. Due to the occupancy of the chloro group at the 7position of the quinoline nucleus and hydrazones with 4-tolyl-4-flouro- and 4-isopropyl-phenyl groups, these showed elevated activity.5 Murnane and teammates synthesized the quinoline hybrid 49 by the reaction of 4-methoxyaniline 24n with ethyl acetoacetate to form 6-methoxy-2-methylquinolin-4ol, which was then treated with 2-(bromomethyl)quinoline 48 in K2CO3 and anhydrous DMF at RT to obtain compound 49 (Fig. 7). This exhibited high resistance against QcrB T313I with MIC value of 4.7 μ m mL⁻¹.61

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

Fig. 7 Synthesis of anti-TB quinoline derivatives from substituted anilines

52a-f in DMF under reflux conditions to prepare the corresponding intermediates. These intermediates were then treated with furoyl chloride to synthesize compounds 53a-f under reflux conditions for 5-6 h (Fig. 8). All six compounds 53a-f showed MIC values of 1.6 μ g mL⁻¹ (Table 1) and had exceptional resistance against MTB. An excellent anti-TB activity was also reported due to the presence of the heteroaryl group pyrazole linked to the quinoline ring. ⁴⁶ In the same way, Kadam and colleagues synthesized 56a-g from 54 and bromine in acetic acid to obtain 8-benzyloxy-5-(2-bromo-

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 μg mL⁻¹ respectively⁶² (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-

 R_2 CH₃ (i) DMF, reflux 52a-f (ii) **52a-f**, DMF, con. HCI (iii) EtOH, TEA $R_1 = H$, OCH₃, F, CI H_2N $R_2 = H, CH_3, OCH_3$ 53a-f 50 51 **55**a-d R₁ = H, Br $R_2 = H, OCH_3$ (i) Br₂, AcOH $R_3 = H, OCH_3, F, Br$ (ii) 55a-g, EtOH Kadam et al 56a-g ΗÖ OR₂ (i) 33% aq. KOH, (ii) C₆H₅NO₂ (iii) EDC.HCI/DMHA.HCI $R_1 = H, Br$ (iv) CH₃MgBr $R_2 = CH_3, n-C_4H_9$ (v) S(CH₃)₃I, KOH (vi) R₂OH, Na metal 59a-b 57a-b 58 NH_2 (i) MW, DMSO, 150 °C (ii) 62, MW, DMSO, 180 °C

Synthesis of anti-TB quinolines from miscellaneous reactants.

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substituted-4-quinoline carboxylic acids and then coupled with N,O-dimethylhydroxyamine 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 CH3MgBr and the epoxidizing agent S(CH₃)₃I in two steps to obtain the relative 6substituted-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 μg mL⁻¹, respectively⁶³ (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-dioxoisoindolin-2-yl)isonicotinamide. 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 MIC₅₀ value of 3.1 $\mu g \ mL^{-164}$ (Table 1).

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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).

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 -NH2, can improve the binding affinity with bacterial enzymes and thereby reduce the MIC.65 By lowering the electron density, electronwithdrawing groups, such as -NO2 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.66 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.67 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.

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.8 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.68

Conclusion 5

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 IC₅₀ 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 2position. 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.

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

Abbreviations

ТВ **Tuberculosis**

HIV Human immunodeficiency virus MTB Mycobacterium tuberculosis

DprE1 Decaprenylphosphoryl-β-D-ribose 2'-epimerase

Enoyl-acyl carrier protein reductase InhA Mycobacterial membrane protein large 3 MmpL3

ATP Adenosine triphosphate

QSAR Quantitative structure-activity relationships ADMET Absorption, distribution, metabolism, excretion,

and toxicity

A subunit of cytochrome bcc, working as QcrB

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** M. Bovis Mycobacterium bovis

HOBt Hydroxybenzotriazole hydrate

DIPEA Diisopropylethylamine

EDC-HCl 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride

DMHA-Dimethylhydroxyamine hydrochloride

HCl **DMAP**

Dimethyl amino pyridine

MIC Minimum inhibitory concentration Sustainable development goals **SDGs 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.

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