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Review

Quinoline Scaffold in Drug Discovery: Synthetic Strategies, Therapeutic Applications, and Emerging Drug Candidates

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Abstract

Quinoline is a bicyclic aromatic heterocycle composed of a fused benzene and pyridine ring, and it has held an important place in medicinal chemistry for nearly two centuries. F. Runge first isolated it from coal tar in 1834, and it was later found to form the structural core of well-known natural products such as quinine, camptothecin, and γ-fagarine. Its asymmetric electron distribution, amphoteric character, and ability to undergo both electrophilic and nucleophilic substitution confer considerable pharmacophoric versatility on the quinoline scaffold. This review covers the chemistry and therapeutic relevance of quinoline derivatives, with an emphasis on their pharmacological significance rather than on their synthesis alone. It begins with a brief account of the scaffold's structural features and main synthetic routes, then examines the biological activities reported for quinoline-based compounds, including antibacterial, anticancer, anti-inflammatory, antimalarial, antiparasitic, antitubercular, antioxidant, and antiviral activities, together with structure–activity relationships discussed at the level of specific ligand–target interactions where data allow. The last section covers more recent directions in quinoline-based drug discovery, including PROTAC degraders, kinase inhibitors, and multitarget-directed ligands, an area not extensively addressed in earlier reviews of this scaffold. The literature surveyed here shows that quinoline derivatives continue to serve as a versatile scaffold for generating new leads, linking established synthetic chemistry with current mechanistic and computational approaches. The continued diversification of quinoline-based chemotypes and their biological mechanisms reinforces the importance of this scaffold as a versatile platform for medicinal chemistry and drug discovery.

Keywords: quinoline; heterocyclic compounds; medicinal chemistry; antibacterial; anticancer; antimalarial; drug discovery

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1. Introduction

Quinoline, also known as leucoline, 1-azanaphthalene, 1-benzazine, or benzo[b]pyridine, is one of the most studied members of the aromatic heterocyclic compounds. Its chemical formula, C_9H_7N, reflects the fusion of a benzene ring with a pyridine ring, and it behaves as a

weak base (pKa = 4.85) [1]. It can act as either a nucleophile or an electrophile, and the uneven electron density between the pyridine and benzene rings gives it a distinctive reactivity profile. Quinoline forms salt complexes with acids and undergoes electrophilic and nucleophilic substitution in patterns comparable to those of pyridine and benzene (Figure 1) [2].

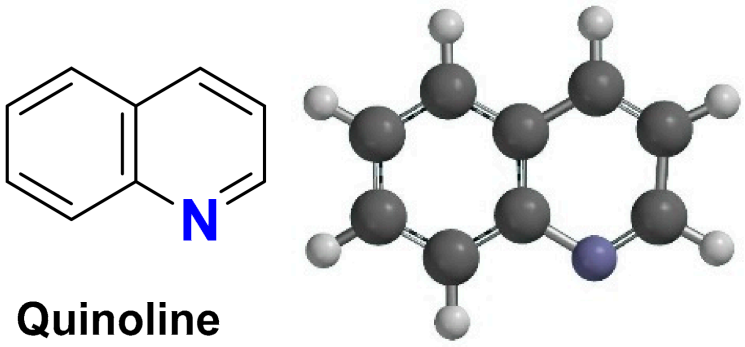


Figure 1. Chemical Structure of Quinoline.

F. Runge first isolated quinoline from coal tar in 1834, and this discovery led to the later recognition of the quinoline core in a number of well-known natural alkaloids, including quinine [3], camptothecin [4], and γ-fagarine [5], all valued for their therapeutic properties. Beyond these natural sources, the quinoline core has also been deliberately incorporated into fully synthetic derivatives, including fluoroquinolone antibiotics and, more recently, kinase inhibitors developed for targeted cancer therapy, discussed further in Section 11 (Figure 2).

Because extracting naturally occurring quinoline compounds directly from their sources is costly and technically demanding, laboratory synthesis became the preferred alternative, making it possible not only to reproduce these molecules but also to design improved variants with better efficacy and fewer side effects. This effort led, among other things, to quinoline-based fluoroquinolones, which remain effective against a wide range of bacterial infections. Building on this interest, our laboratory has focused on a series of quinoline-based compounds, in particular 2-oxo-1,2-dihydroquinoline-4-carboxylic acid derivatives synthesized from isatin [6,7].

The literature search for this review was identified through systematic searches of major scientific databases, combining the terms quinoline with each therapeutic domain discussed below (e.g., “antibacterial,” “anticancer,” “antimalarial,” “kinase inhibitor,” “PROTAC”), as well as with structural and mechanistic descriptors (“structure-activity relationship,” “molecular docking,” “binding mode”) to capture studies addressing target-level interactions rather than phenotypic activity alone.

The review is organized in two parts: the first covers the main synthetic methodologies for quinoline derivatives, from classical routes to more recent, sustainable approaches, and the second covers their therapeutic applications, antibacterial [8,9], anticancer [10], anti-inflammatory [11], antimalarial [12], antiparasitic [13], antitubercular [14], antiviral [15], and antioxidant [16] activities, along with emerging directions such as PROTACs, kinase inhibitors, and multitarget-directed ligands. Throughout, we use selected examples to illustrate structure-activity relationships and to discuss why particular quinoline-based scaffolds have proven pharmacologically relevant, not just how they are made.

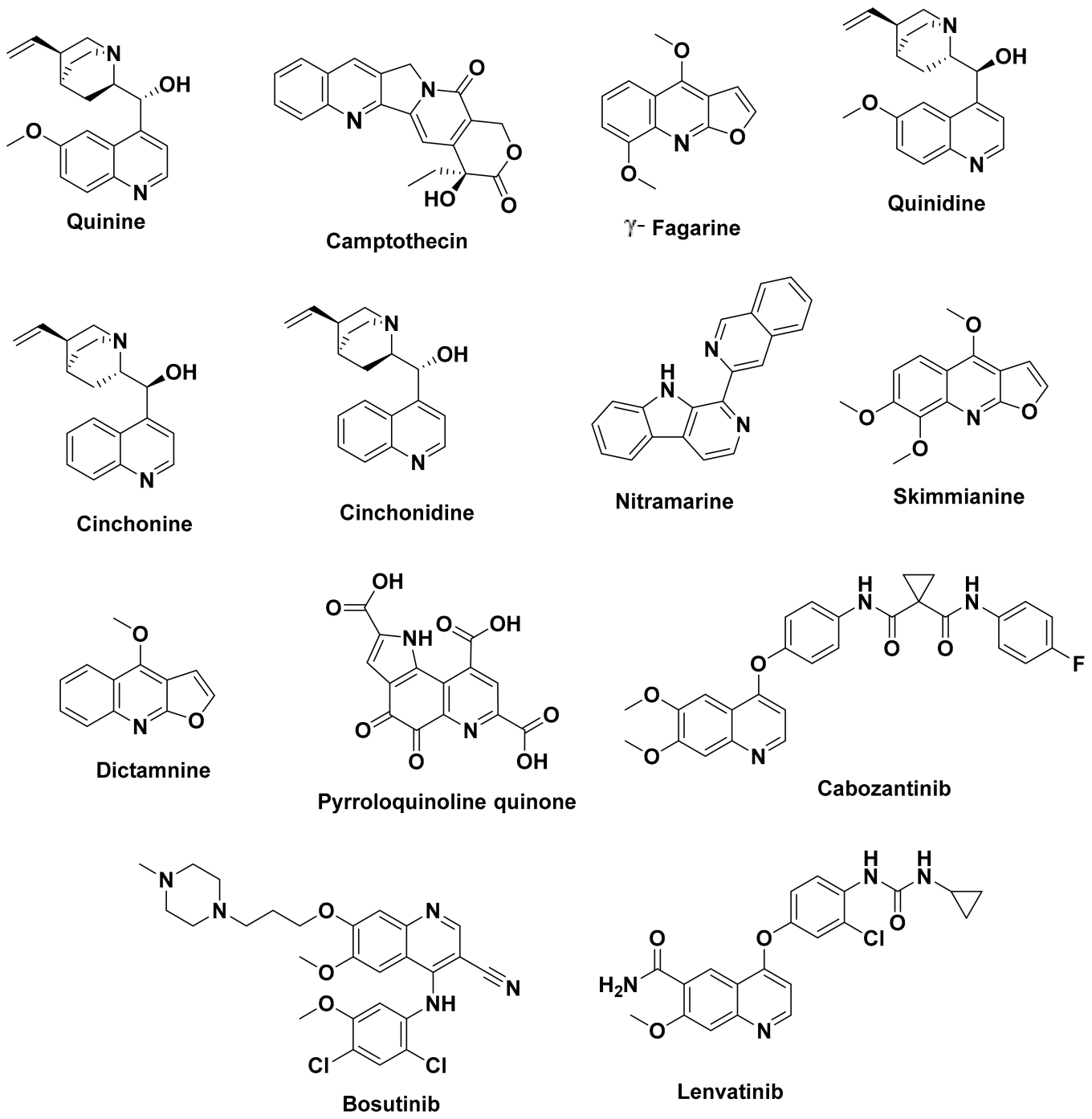


Figure 2. Natural and synthetic quinoline derivatives.

2. Methods of Synthesis of Quinoline Derivatives

2.1. Conventional Methods

A number of classical methods have been used over the years to build the quinoline ring, each starting from different reagents and proceeding through a distinct mechanism [17]. In the Skraup synthesis [18], aniline is condensed with glycerol in the presence of a strong acid (H_2SO_4) and an oxidizing agent ($PhNO_2$), and the quinoline ring forms through subsequent cyclization and aromatization. The Doebner synthesis [19] combines aniline with an aldehyde and pyruvic acid in a condensation-cyclization sequence to give quinoline-4-carboxylic acid derivatives. The Conrad-Limpach reaction [20] proceeds by condensing aniline with a β-ketoester, followed by acid-catalyzed intramolecular

cyclization, giving access to 4-hydroxyquinolines. The Combes synthesis [21] works in a related way, using aniline and a β-dicarbonyl compound under acid catalysis (H_2SO_4) to form substituted quinolines. The Povarov reaction [22], an aza-Diels–Alder-type process, involves cycloaddition between an imine (formed from aniline and an aldehyde) and an alkene, giving highly substituted tetrahydroquinolines that can then be oxidized to the aromatic quinoline. Finally, the Riehm synthesis [23] builds functionalized quinoline frameworks from aniline derivatives and carbonyl compounds under acidic conditions ($AlCl_3$). Taken together, these six reactions form the classical foundation of quinoline chemistry and continue to inform the design of newer synthetic methods (Figure 3).

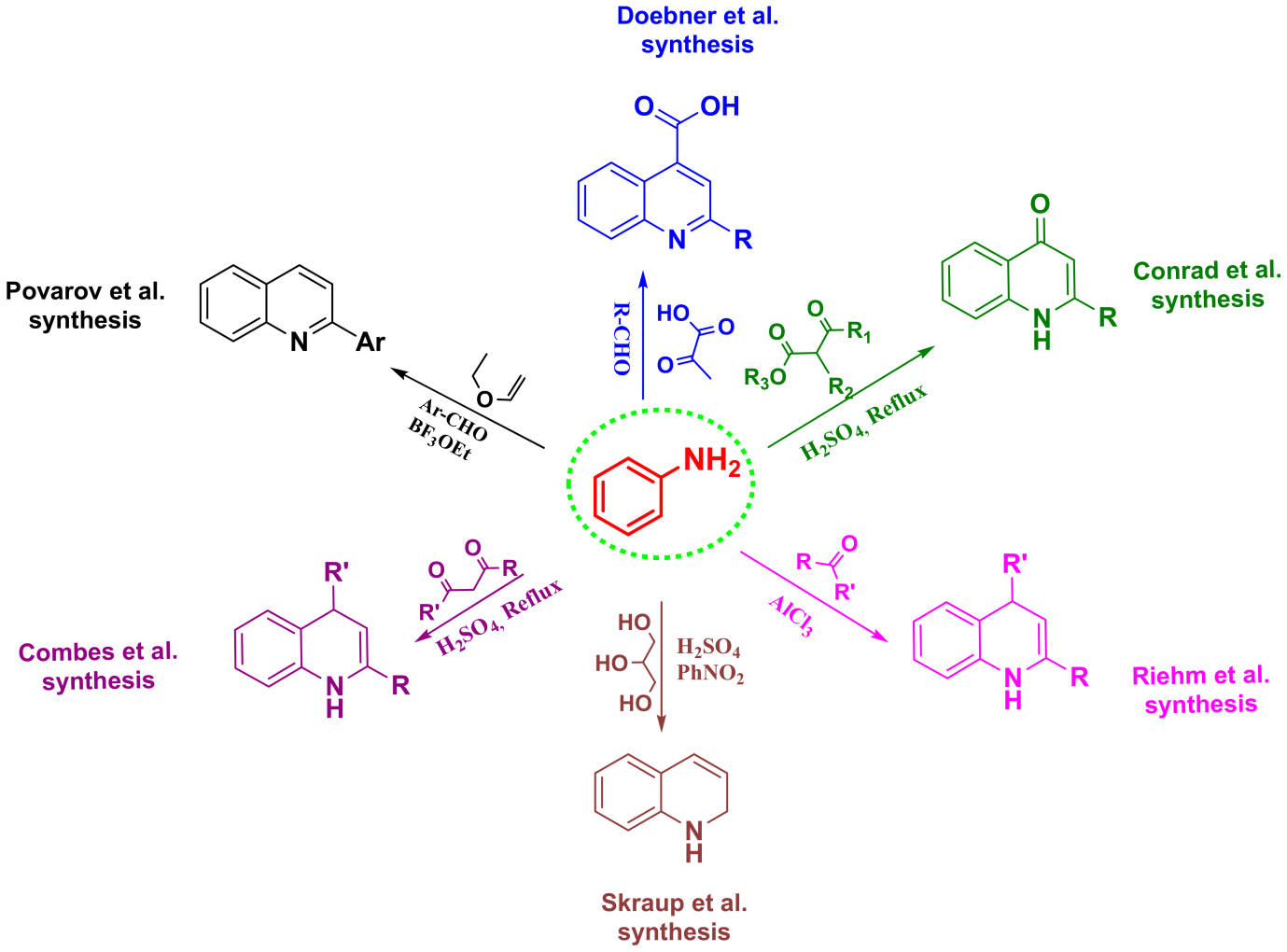


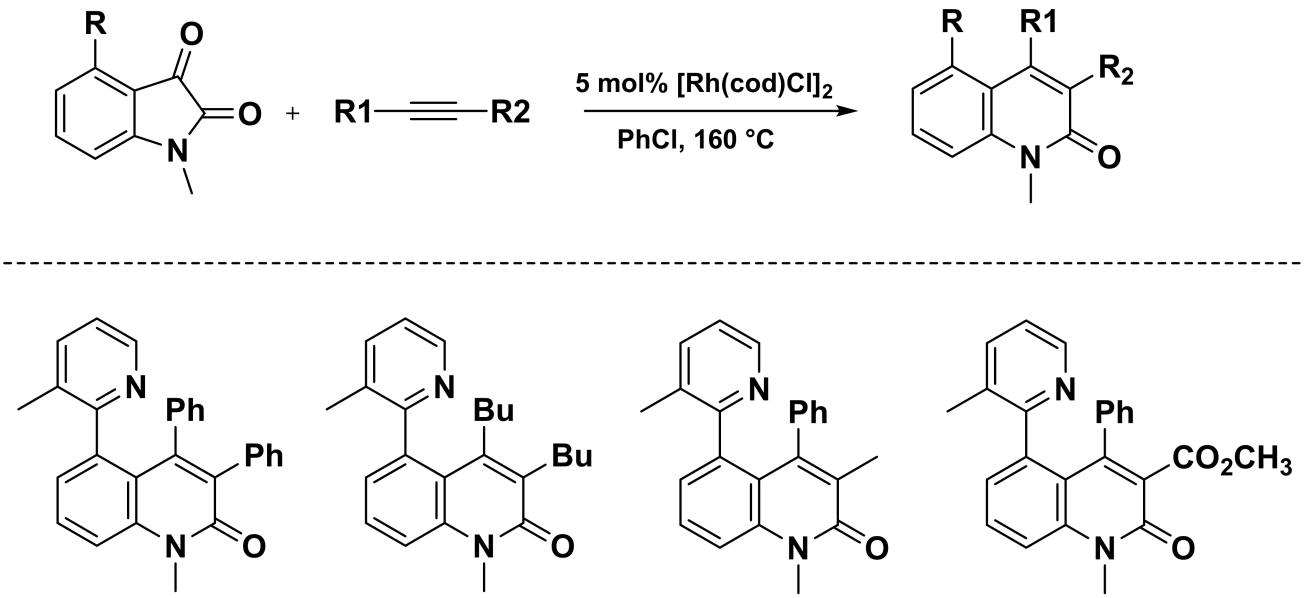
Figure 3. Overview of conventional synthetic approaches to quinoline derivatives [18–23].

2.2. Recent Synthetic Methodologies

2.2.1. Synthesis from Indoles

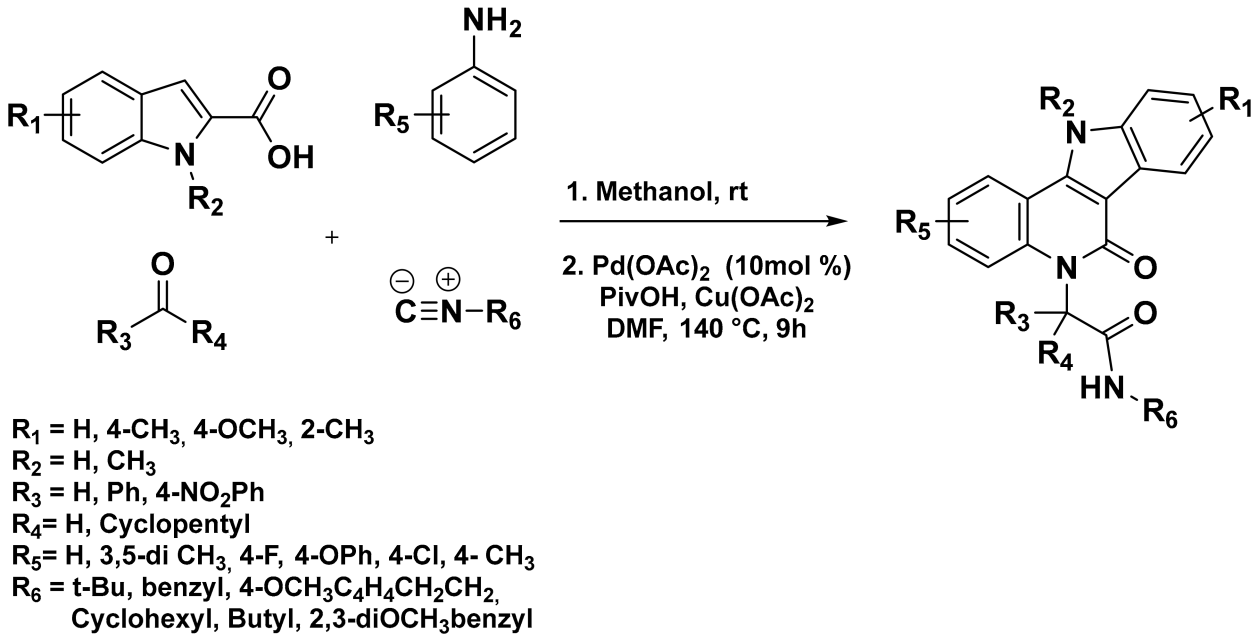
Zeng and Dong developed a rhodium-catalyzed reaction between isatins and alkynes that proceeds through an unusual decarbonylative coupling pathway [24]. A notable feature of this method is that it activates a C–C bond selectively, rather than the arene C–H bond activation more commonly seen in this type of synthesis, achieved by controlling the orientation of the directing group. Here, the methyl substituent at the 3-position of the pyridine ring directs the rhodium catalyst toward the carbonyl group of the isatin substrate. Mechanistic work allowed the authors to isolate a rhodium intermediate, complex II (L = pyridine), which forms even at room temperature, though alkyne insertion into this intermediate only proceeds above 130 °C [24]. This temperature dependence indicates that

the alkyne insertion step, rather than formation of the rhodium intermediate, is what limits the overall catalytic cycle (Scheme 1).



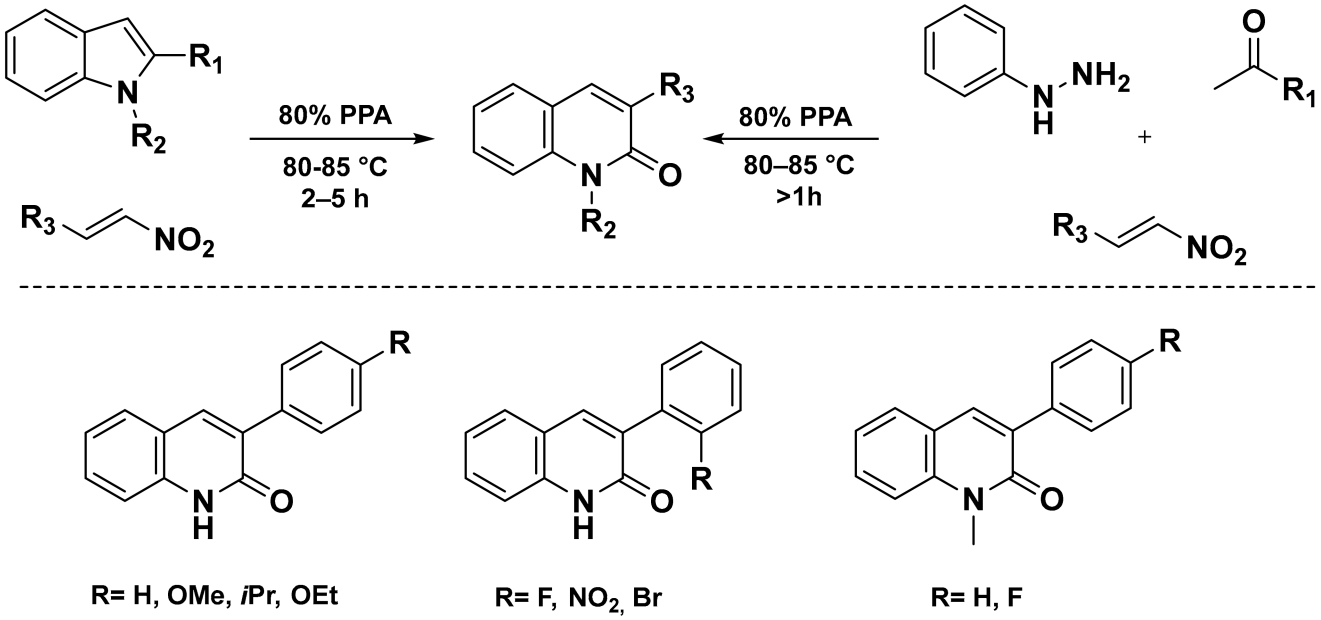
Scheme 1. Rh-catalyzed decarbonylative coupling reaction.

Dömling and co-workers applied the Ugi multicomponent reaction to the synthesis of fused indoloquinolone derivatives [25]. Indole-2-carboxylic acids served as the starting point for the synthesis of the tetracyclic framework, and the resulting intermediates were then subjected to palladium-catalyzed dual C–H functionalization, giving the tetracyclic indoloquinolones in moderate yields (Scheme 2). One advantage of this route is that it relies on readily available building blocks, which makes the overall strategy flexible and easy to adapt. The authors also evaluated the synthesized compounds by in silico molecular docking, pointing to their potential as kinase inhibitors (Scheme 2) [25].



Scheme 2. Preparation of indoloquinolones using four-component reaction and C–H activation.

In 2015, the Aksenov research group developed an efficient method for the synthesis of 3-substituted 2-quinolones [26]. The reaction proceeded through the formation of hydroxamic acid intermediates generated by the electrophilic alkylation of indoles in the presence of polyphosphoric acid (PPA). These intermediates subsequently underwent a ring-opening/ring-closing cascade process to afford the desired 2-quinolinones. The reaction outcome was strongly influenced by the steric properties of the nitrostyrene substrates, with ortho-substituted derivatives providing lower yields. Furthermore, the methodology was extended to a one-pot three-component process, where the indole intermediate was generated in situ through a Fischer indole synthesis before cyclization (Scheme 3).

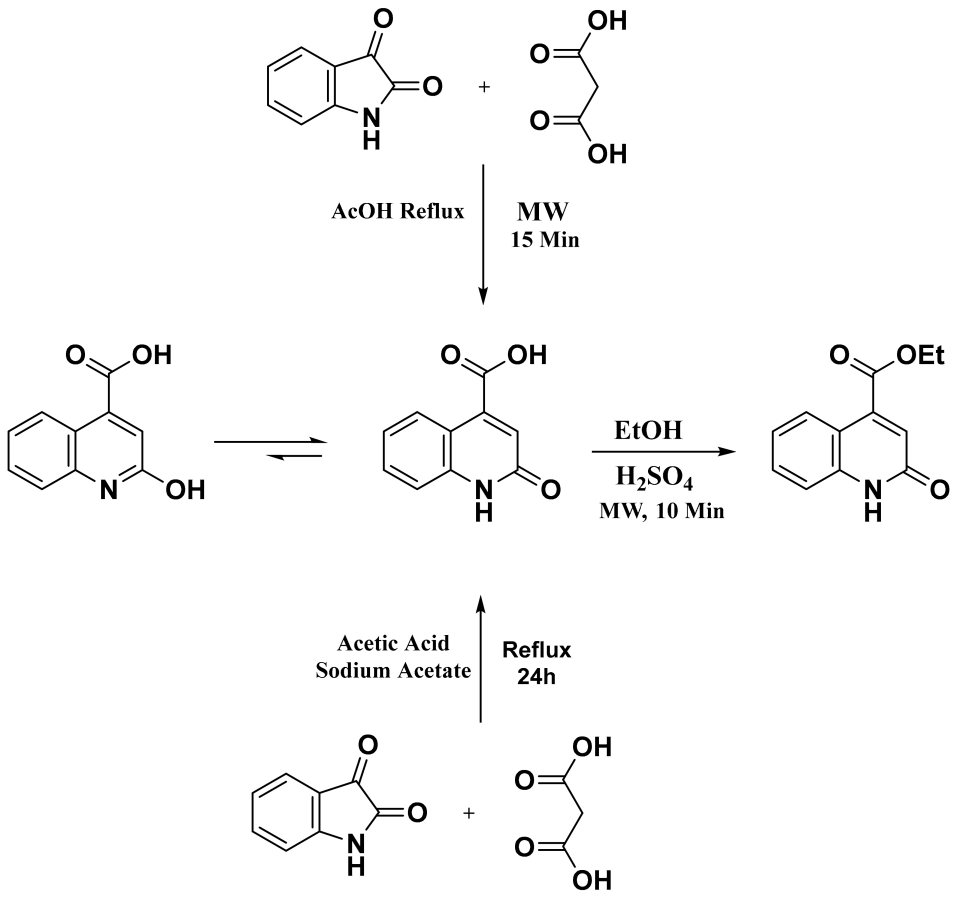


Scheme 3. Synthesis of quinolones by reaction of 2-substituted indoles with 2-nitroalkenes under PPA.

El Ashry et al. [27] developed a microwave-assisted route to 2-quinolone-4-carboxylic acid derivatives as a faster alternative to conventional reflux. Under microwave irradiation, the target compound was obtained in 78% yield after only 15 min, and the resulting acid was then converted into ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylate by microwave-promoted esterification, illustrating how microwave heating can shorten reaction times without sacrificing yield (Scheme 4).

In our own work [28–30], 2-quinolone-4-carboxylic acid derivatives were obtained by condensing isatin with malonic acid under reflux in acetic acid. This route is straightforward, gives the target compounds in excellent yields, and does not require specialized equipment or harsh reaction conditions, making it a convenient way to access the quinolone scaffold (Scheme 4).

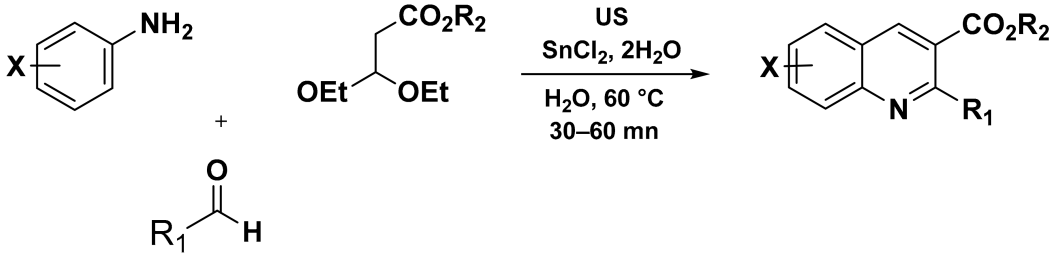
Given the wide range of biological activities associated with quinoline derivatives, finding efficient ways to synthesize these heterocycles remains an active research area [31]. Notable progress has been made in recent years, largely through methods that are both more environmentally friendly and more cost-effective: microwave-assisted synthesis, multicomponent reactions, solvent-free transformations, ultrasound-assisted protocols, phase-transfer catalysis, and photocatalysis [31]. Compared with traditional procedures, these approaches generally offer higher reaction efficiency and product yields, lower energy consumption, and better alignment with green chemistry principles.



Scheme 4. Synthesis of 2-quinolone-4-carboxylic acid derivatives.

2.2.2. Ultrasound-Assisted Synthesis

Prasad et al. reported a one-pot method for the rapid synthesis of 2-substituted quinolines using ultrasound irradiation (US) in aqueous medium [32]. The reaction uses $CuCl_2 \cdot 2H_2O$ as a precatalyst and atmospheric oxygen as the terminal oxidant, and proceeds through a three-component condensation of aniline, an aldehyde, and ethyl 3,3-diethoxypropionate under ultrasonic activation, giving the target quinolines in satisfactory yields within relatively short reaction times. Carrying out the reaction in water under ultrasonic irradiation makes this protocol simpler to run and more environmentally friendly than conventional synthetic routes to quinolines (Scheme 5) [32].

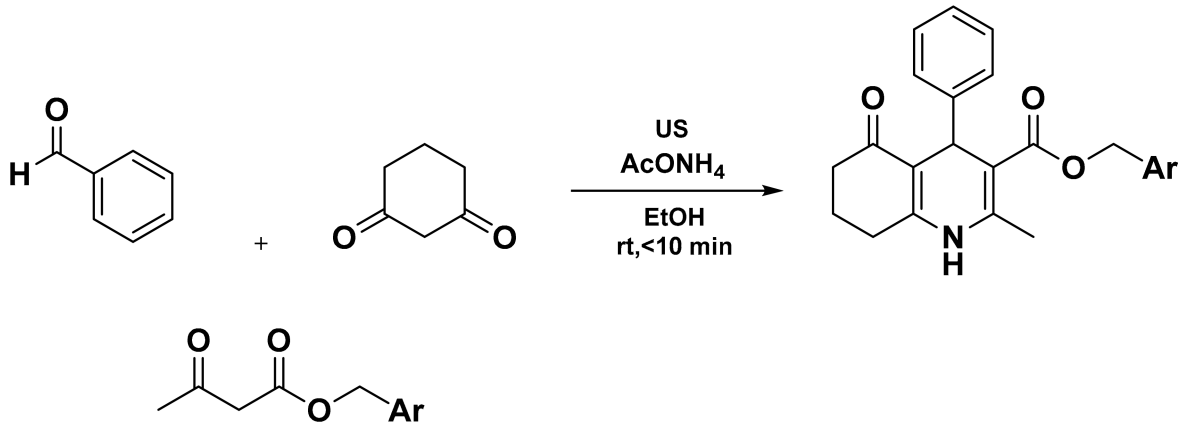


R_1= 3,4-diFC_6H_3; 4-FC_6H_4; 4-ClC_6H_4; 2-BrC_6H_4; 4-BrC_6H_4; 3,4-diMeC_6H_3; 4-$MeOC_6H_4$; 4-$NO_2C_6H_4$; Ph; 4-$CF_3C_6H_4$

X= H; 4-F; 4-Br; 3,4-diMe

Scheme 5. Prasad's Method.

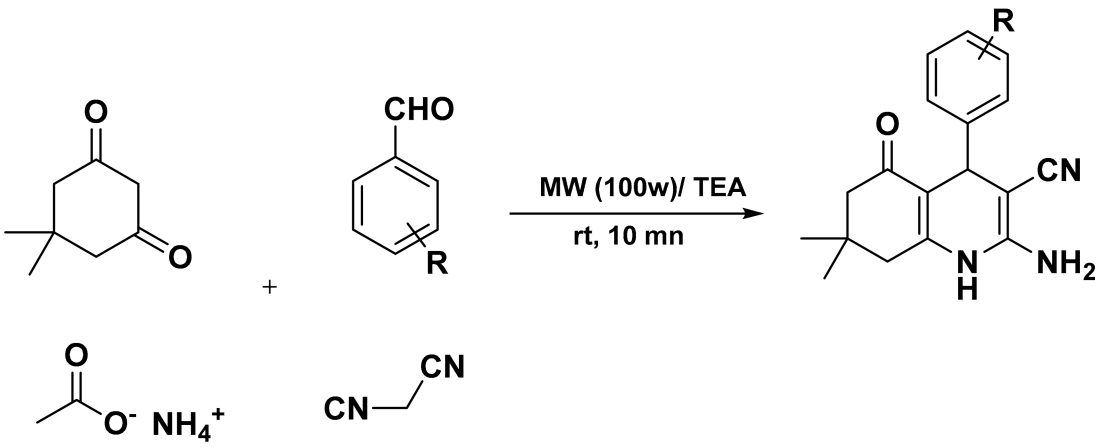
In 2020, Devi et al. [33] reported a low-cost, environmentally friendly protocol for synthesizing 2-methyl-5-oxo-hexahydroquinoline-3-carboxylate derivatives through a one-pot multicomponent reaction of substituted benzaldehydes, 1,3-cyclohexanedione, benzyl acetoacetate, and ammonium acetate in ethanol, carried out under ultrasound irradiation at room temperature. Ultrasonic activation markedly increased the reaction rate, giving the products in excellent yields (92–98%) in under 10 min. With its operational simplicity, short reaction times, and mild, environmentally benign conditions, this method offers a practical and sustainable route to hexahydroquinoline derivatives (Scheme 6).



Scheme 6. Devi's Method.

2.2.3. Microwave-Assisted Synthesis

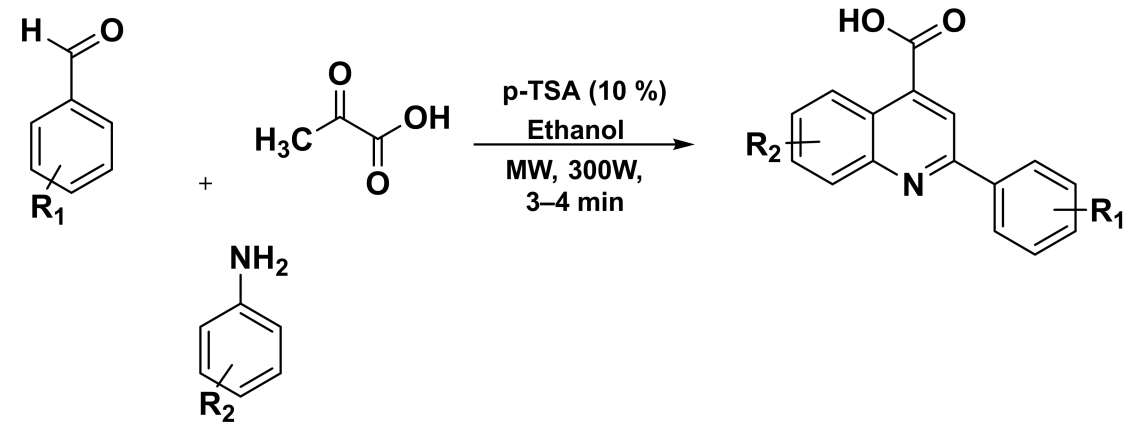
In 2017, Moloi et al. [34] reported a microwave-assisted, four-component synthesis of novel quinolone derivatives from aromatic aldehydes, malononitrile, 5,5-dimethylcyclohexane-1,3-dione, and ammonium acetate. The reaction was run in ethanol with triethylamine (Et_3N) as catalyst under microwave irradiation and gave rapid access to the target quinolones in excellent yields, an example of how microwave-assisted multicomponent reactions can be a useful strategy for building biologically relevant heterocycles (Scheme 7).



Scheme 7. TEA-Catalyzed Reaction.

In 2019, Patel and co-workers [35] used p-toluenesulfonic acid (p-TSA) as an organocatalyst for the synthesis of quinoline-4-carboxylic acid derivatives, prepared through a one-pot, three-component reaction of an aromatic benzaldehyde, a substituted aniline, and pyruvic acid under microwave irradiation. The reaction reached completion in only 3–4 min and gave the target quinolines in moderate to good yields (50–80%), underlining

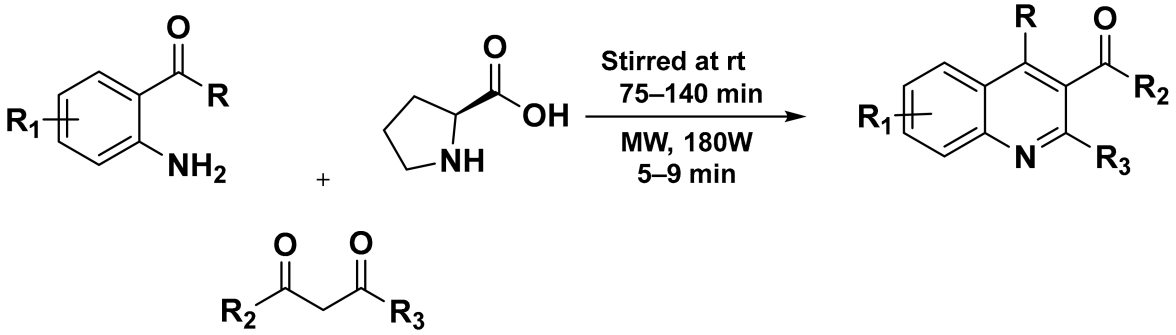
how fast and practical microwave-assisted synthesis can be for this class of compounds (Scheme 8).



R_1 = H, Cl
R_2 = H, CH_3, OCH_3, NO_2, Cl, F, OH

Scheme 8. Dhaval's Method.

In 2020, Tasqeeruddin et al. [36] reported an environmentally friendly synthesis of quinoline derivatives using L-proline as an organocatalyst in a Knoevenagel condensation, in which substituted 2-aminoaryl ketones were reacted with active methylene compounds in the presence of L-proline. Carried out under microwave irradiation, the reaction was complete within 5–10 min, showing how microwave heating can speed up the cyclization step and shorten overall reaction time. This methodology combines the advantages of green chemistry with operational simplicity, providing an efficient route to quinoline-based heterocyclic frameworks (Scheme 9).



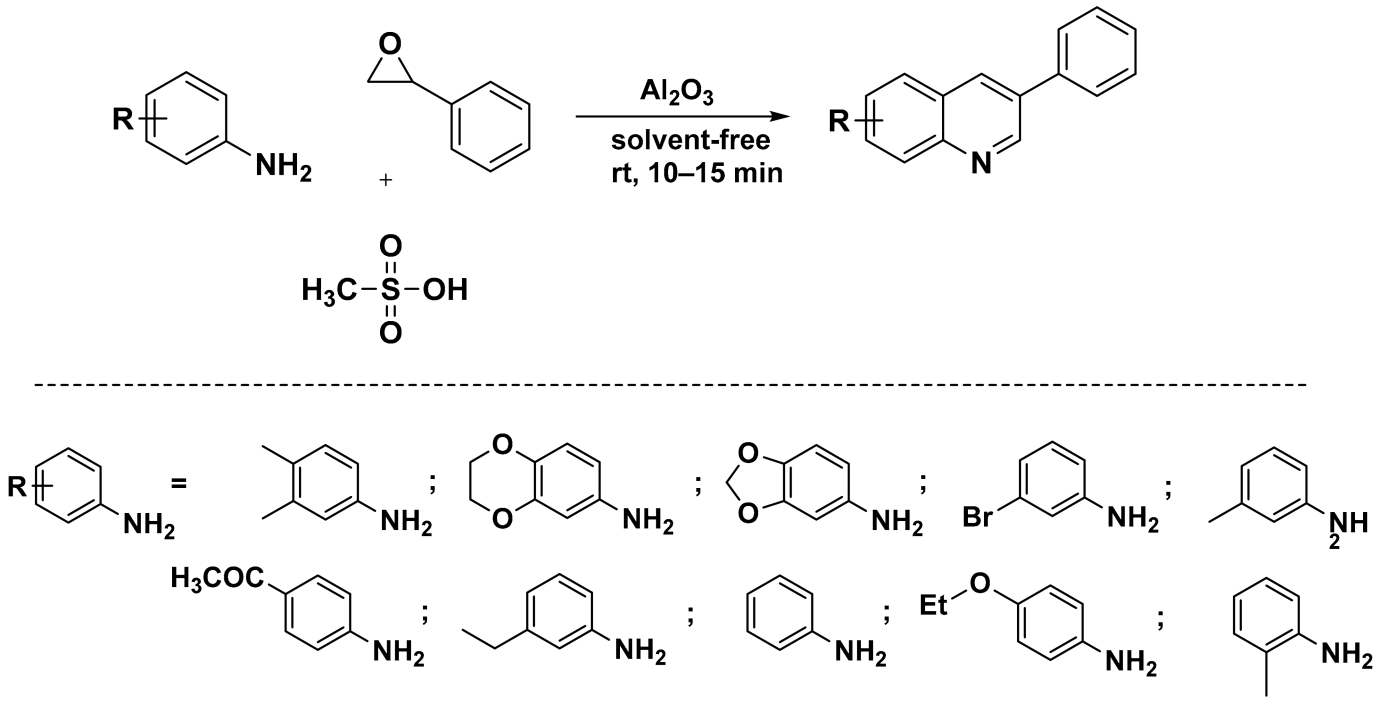
R= Ph, C_6H_4Cl, CH_3, C_6H_4F
R_1 = H, C_6H_4Cl, NO_2
R_2 = CH_3, OC_2H_5, OCH_3
R_3 = CH_3

Scheme 9. L-Proline-Catalyzed Knoevenagel Condensation.

2.2.4. Solvent-Free Reactions

In 2017, Sharghi and colleagues [37] developed a simple, efficient, and environmentally benign protocol for the synthesis of 3-arylquinolines. The methodology involves a one-pot reaction between anilines and styrene oxide catalyzed by activated alumina (Al_2O_3) in the presence of methanesulfonic acid ($MeSO_3H$). The reaction proceeds under solvent-free conditions at room temperature, providing rapid access to the desired 3-arylquinoline derivatives within 10–15 min. The method produced the target compounds in good yields

and provides a practical and sustainable alternative to conventional synthetic methods, highlighting the advantages of solvent-free organic synthesis in the synthesis of quinoline-based heterocycles (Scheme 10).

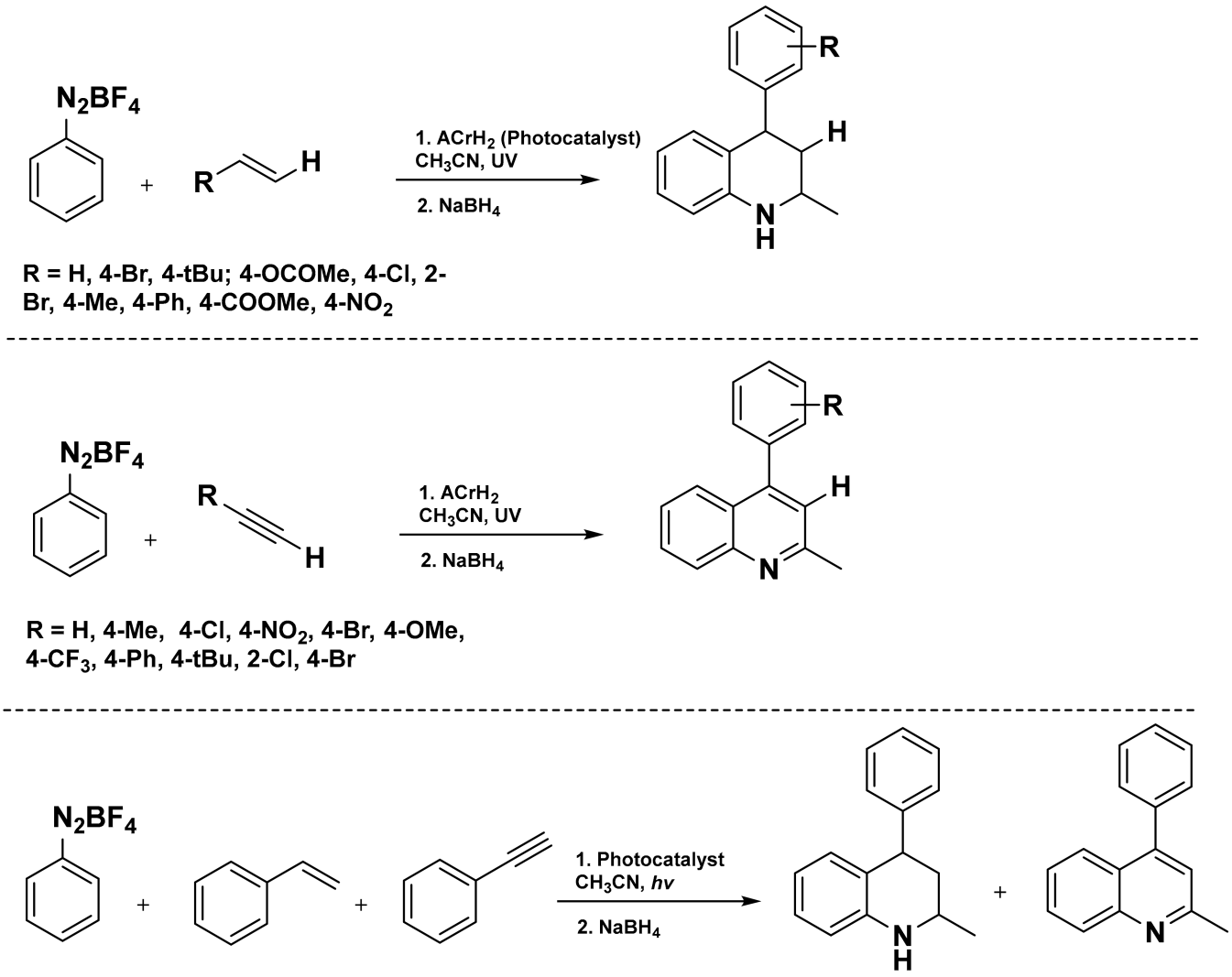


Scheme 10. Sharghi's Method.

In 2018, Zhou and co-workers developed new UV light-induced synthetic methodologies for the synthesis of disubstituted quinoline derivatives [38]. They identified 10-methyl-9,10-dihydroacridine ($AcrH_2$) as a highly efficient metal-free photoredox catalyst for the synthesis of quinoline derivatives through a cascade annulation process. The reaction proceeds under mild conditions at room temperature via a single-electron transfer (SET) mechanism followed by intramolecular cyclization. This photocatalytic strategy enabled the efficient synthesis of a wide range of quinoline and tetrahydroquinoline derivatives, demonstrating the potential of visible-light-driven photoredox catalysis as a sustainable and versatile approach for the preparation of nitrogen-containing heterocyclic frameworks [38]. In conclusion, a UV light-driven and transition metal-free methodology was developed for the synthesis of quinoline and tetrahydroquinoline derivatives under mild conditions at room temperature using simple and readily accessible starting materials (Scheme 11).

Khakyzadeh et al. [39] reported the use of magnetite nanoparticles (Fe_3O_4) as a green, efficient, heterogeneous, and recyclable nanocatalyst for the atom-economical synthesis of hexahydroquinoline derivatives. The target compounds were prepared through a one-pot multicomponent reaction involving aryl aldehydes, dimedone, β-ketoesters, and ammonium acetate under solvent-free conditions at 50 °C.

This method gave the hexahydroquinoline derivatives in excellent yields (85–92%) within short reaction times, and worked well with both electron-donating and electron-withdrawing substituents on the aromatic aldehydes. Reaction conditions were further optimized using Response Surface Methodology, specifically a Central Composite Design, to identify the conditions giving the highest yields. Between the high catalytic efficiency, the recyclable catalyst, and the solvent-free conditions, this approach offers a sustainable route to quinoline-based heterocycles [39].



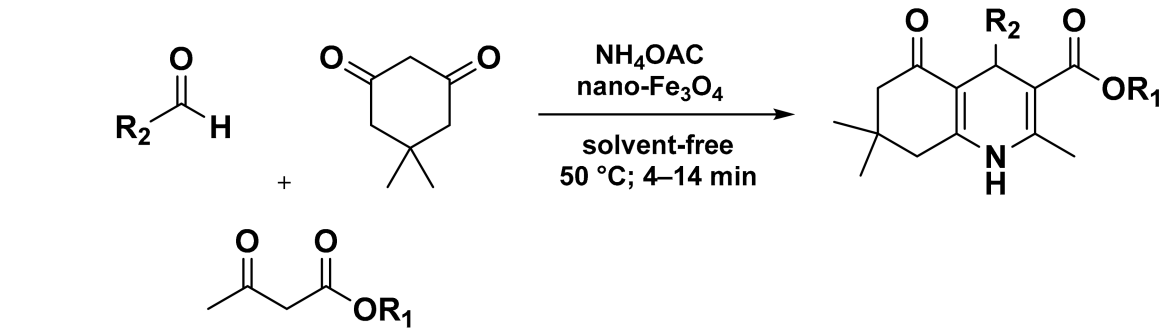
Scheme 11. Zhou's Method.

In 2014, Farhang et al. reported an environmentally friendly synthesis of quinoline derivatives using $CuFe_2O_4$ nanoparticles as a heterogeneous nanocatalyst in aqueous medium [40]. The reaction proceeds by condensing substituted anilines with ketones in water, giving the corresponding quinolines in excellent yields (84–95%) under mild conditions and with broad substrate compatibility. The $CuFe_2O_4$ nanoparticles were prepared through the thermal decomposition of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in an aqueous sodium hydroxide solution. Notably, the catalyst could be recovered and reused for up to five consecutive cycles without a significant decrease in catalytic activity or product yield. These findings demonstrate the potential of $CuFe_2O_4$ nanoparticles as a sustainable and recyclable catalyst for the green synthesis of quinoline derivatives (Scheme 12) [40].

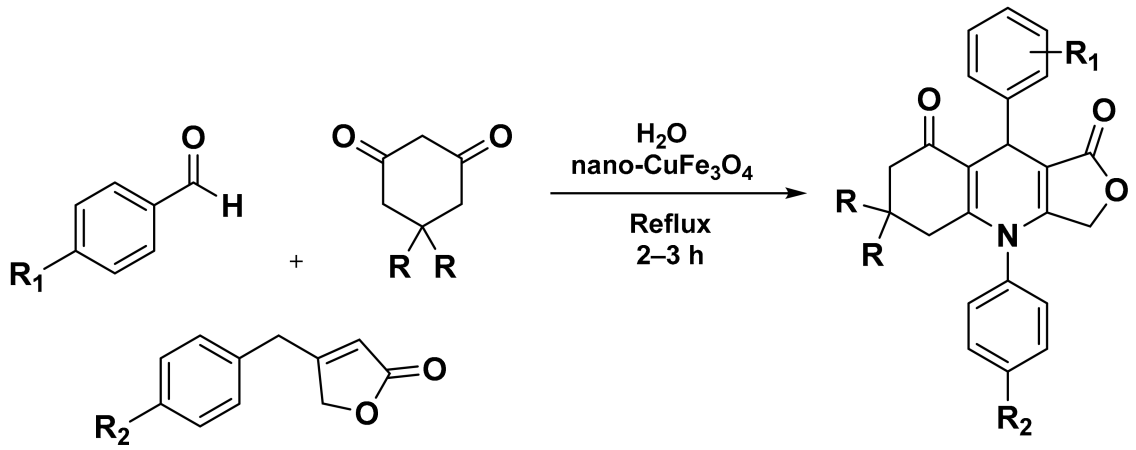
Firouzi-Haji and co-workers [41] developed a novel hybrid magnetic organometallic nanocatalyst by immobilizing *o*-phenylenediamine onto silica-coated Fe_3O_4 magnetic nanoparticles. Characterization by scanning electron microscopy (SEM) revealed a core–shell spherical morphology with a uniform particle size distribution and an average diameter of approximately 40 nm.

The catalytic performance of this nanomaterial was evaluated in the selective synthesis of 7-aryl-8H-benzo[h]indeno [1,2-b]quinoline-8-one derivatives. The target compounds were obtained in good to excellent yields ranging from 86% to 98% under solvent-free conditions and ultrasonic irradiation at room temperature. The combination of a recyclable

magnetic nanocatalyst, mild reaction conditions, and high product yields highlights the efficiency and sustainability of this approach for the construction of complex quinoline-fused heterocyclic frameworks (Scheme 13) [41].



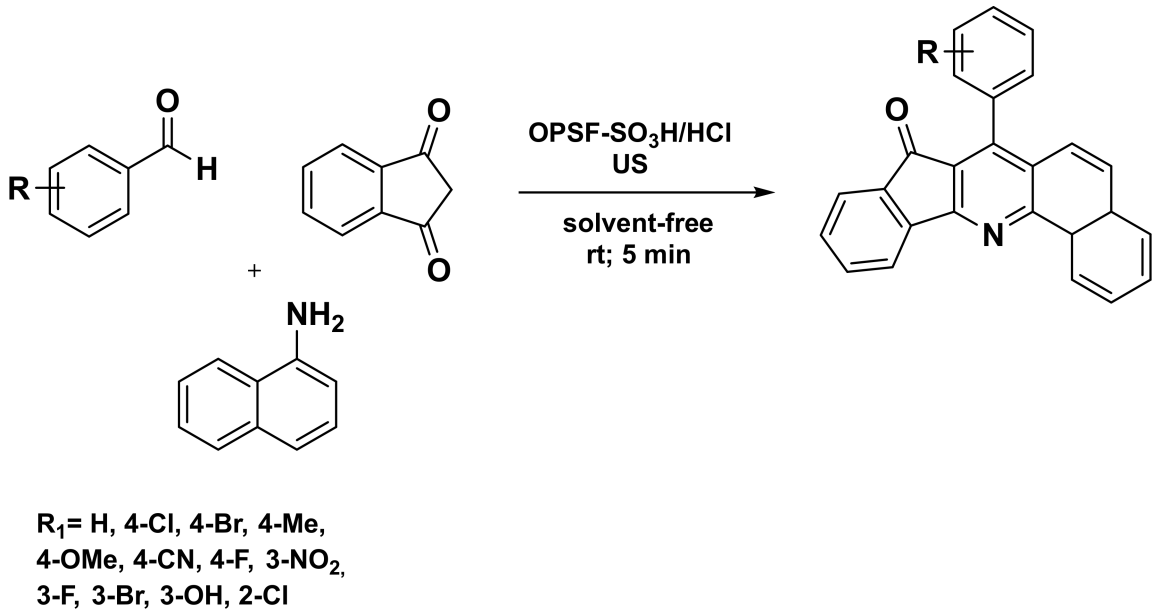
R_1= C_6H_5, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-OHC_6H_4, 4-BrC_6H_4, $OMeC_6H_4$, 2,4-$Cl_2C_6H_3$, 3-OHC_6H_4, 3-$NO_2C_6H_4$, furyl, 1-napthyl, 3-NO_2-4-ClC_6H_3
R_2 = Me, Et



R = H, Me
R_1 = H, 4-Cl, 4-OMe, 4-Br, 4-Me, 3-NO_2, 4-NO_2
R_2 = H, Me, Cl, F, Br

Scheme 12. Role of Pure Nanoparticles in the Synthesis of Quinoline Derivatives.

Having covered the main classical and recent synthetic approaches to quinoline derivatives, microwave- and ultrasound-assisted protocols, solvent-free reactions, photocatalytic methods, and nanocatalyst-mediated transformations, we now turn to their biological and therapeutic significance. The sections below discuss the medicinal potential of these molecules and the relationship between structural modification and pharmacological activity, supported by tables and figures summarizing target, mechanism of action, and reported potency for each activity.



Scheme 13. Firouzi-Haji's Method.

3. Antibacterial Activity

Quinoline derivatives have drawn considerable interest as antibacterial agents for their ability to interfere with essential cellular processes, including DNA replication, enzyme activity, and membrane integrity. Among the classical quinoline-based drugs, mepacrine (quinacrine) [42] has shown inhibitory activity against several Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

Its antimicrobial effect is generally attributed to its capacity to intercalate into DNA and alter membrane-associated functions. Chloroquine [43], although primarily developed as an antimalarial drug, has demonstrated moderate antibacterial activity against intracellular pathogens and has been reported to enhance the susceptibility of resistant bacterial strains when used in combination therapies [44]. Mefloquine [45] has exhibited significant activity against Gram-positive bacteria, particularly *S. aureus*, including methicillin-resistant strains (MRSA), with minimum inhibitory concentration (MIC) values of 16 μg/mL. Moreover, mefloquine has been reported to inhibit the growth of *Enterococcus faecalis* and *Streptococcus pneumoniae* at low micromolar concentrations [46]. Primaquine generally displays weaker antibacterial activity; however, its quinoline remains an attractive scaffold for structural optimization. Recent studies have demonstrated that hybrid quinoline derivatives containing indole, pyrrolidinedione, thiazolidinone, or other heterocyclic fragments exhibit enhanced antibacterial potency against clinically relevant pathogens such as *S. aureus*, *Bacillus subtilis*, *E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*. Several of these compounds showed good MIC values, highlighting the potential of quinoline-based molecules as promising candidates for the development of new antibacterial agents capable of addressing the growing challenge of antimicrobial resistance (Figure 4 and Table 1) [46].

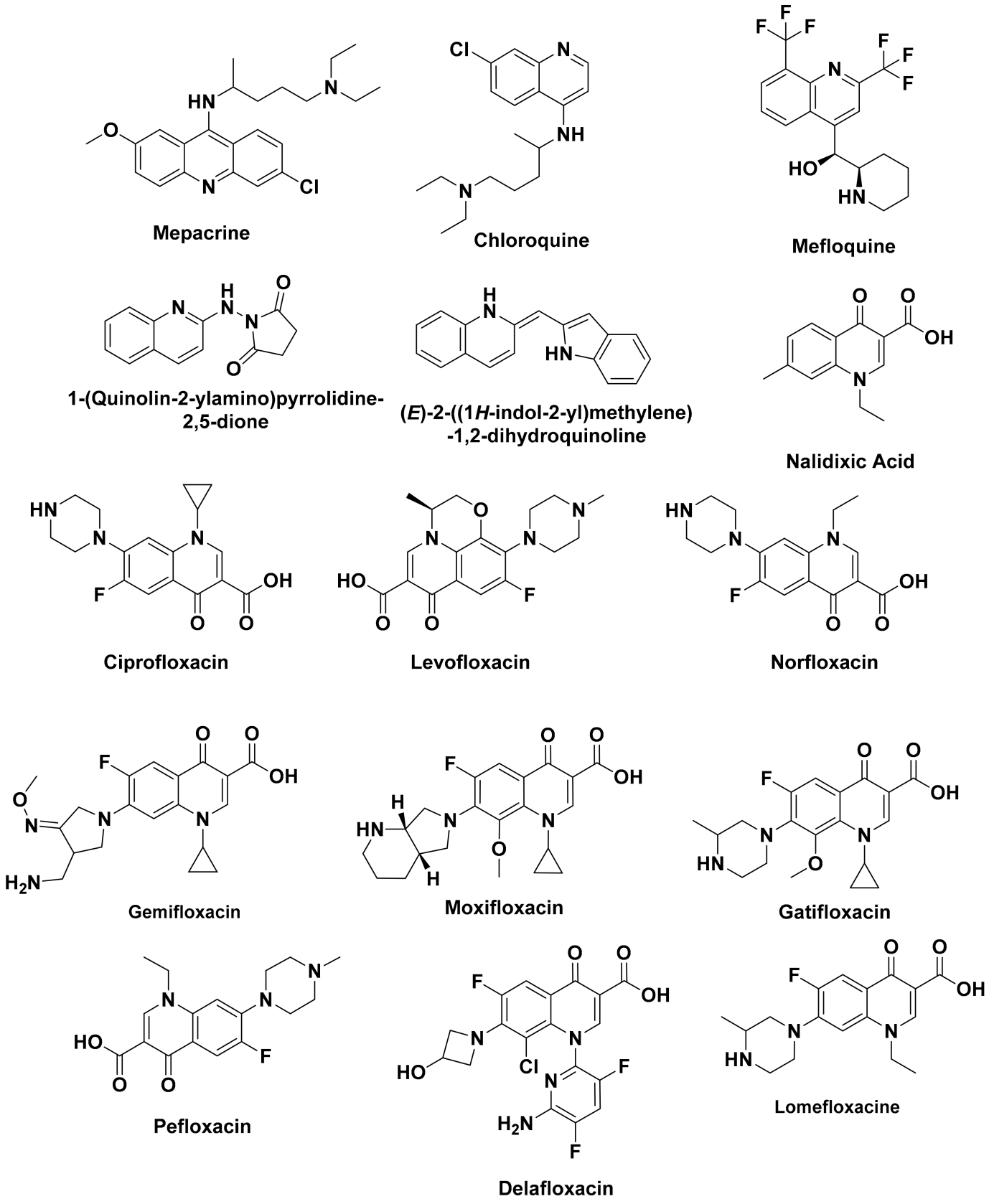


Figure 4. Quinoline-Based Antibacterial Derivatives.

Table 1. Quinoline-based antibacterial derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency	Ref.
Mepacrine	*S. aureus*, *E. coli*, *P. aeruginosa*	DNA intercalation, topoisomerase inhibition and membrane perturbation	MIC = 2–64 μg/mL	[42]
Chloroquine	Intracellular bacteria (*Mycobacterium* spp.)	Lysosomal alkalinization, efflux pump inhibition and antibiotic potentiation	Weak direct activity (MIC > 128 μg/mL); synergistic in combination therapy	[43,44]
Mefloquine	*S. aureus* (including MRSA), *E. faecalis*, *S. pneumoniae*	Membrane perturbation and inhibition of bacterial energy metabolism	MIC = 0.2–16 μg/mL	[45,46]
Hybrid quinoline derivatives (indole, pyrrolidinedione, thiazolidinone)	*S. aureus*, *B. subtilis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*	Structure-dependent; likely DNA gyrase inhibition and membrane interaction	MIC = 0.5–16 μg/mL	[46]
Nalidixic acid	*E. coli*, *P. mirabilis*, *K. pneumoniae*, *Enterobacter* spp.	DNA gyrase (GyrA) inhibition	MIC = 1–16 μg/mL	[47]
Norfloxacin	*E. coli*, *Proteus* spp., *Klebsiella* spp., *P. aeruginosa*	DNA gyrase and topoisomerase IV inhibition	MIC = 0.03–0.5 μg/mL	[48]
Moxifloxacin	*S. pneumoniae*, *S. aureus*	DNA gyrase and topoisomerase IV inhibition	MIC_{90} = 0.06–0.25 μg/mL	[49,50]
Gemifloxacin	Respiratory pathogens (*S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*)	DNA gyrase and topoisomerase IV inhibition	MIC = 0.008–0.12 μg/mL	[49,50]

Quinolone antibiotics make up one of the most successful families of synthetic antibacterial agents derived from the quinoline scaffold. This class began with the discovery of nalidixic acid in 1958, which proved effective against Gram-negative pathogens such as *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, and *Enterobacter* spp., with MIC values typically between 1 and 16 μg/mL. Its narrow antibacterial spectrum and poor tissue distribution, despite its clinical usefulness in urinary tract infections, prompted the search for more potent derivatives [47].

The introduction of a fluorine atom at the C-6 position marked a major step forward, giving rise to the fluoroquinolones. SAR studies showed that C-6 fluorination substantially increases lipophilicity, bacterial cell penetration, and affinity for DNA gyrase and topoisomerase IV, while adding a piperazinyl or related heterocyclic group at C-7 broadens the spectrum of activity, particularly against Gram-negative organisms such as *P. aeruginosa*. Together, these changes produced compounds up to 100-fold more active than the parent quinolones [48].

Norfloxacin, among the earliest fluoroquinolones, showed strong activity against *E. coli*, *Proteus* spp., *Klebsiella* spp., and *P. aeruginosa*, with MIC values generally under 1 μg/mL. Later optimization produced moxifloxacin and gemifloxacin, both markedly more potent against Gram-positive pathogens such as *S. pneumoniae* and *S. aureus*. Moxifloxacin reaches MIC_{90} values of about 0.06–0.25 μg/mL against *S. pneumoniae*, while gemifloxacin is active at MICs as low as 0.008–0.12 μg/mL against susceptible strains, and both retain activity against atypical respiratory pathogens including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* [49,50].

From a SAR standpoint, the 3-carboxylic acid and 4-keto groups are what make quinolones effective antibacterials, since they are required for magnesium-mediated binding to the target enzyme, while substitutions at C-6, C-7, and C-8 shape pharmacokinetics, spectrum, and resistance behavior [51]. These structural principles still guide the design of new agents active against multidrug-resistant bacteria, including MRSA and resistant *P. aeruginosa* [52–54].

At the molecular level, fluoroquinolones work by trapping the cleavable complex that forms between DNA and type II topoisomerases, DNA gyrase in Gram-negative bacteria, topoisomerase IV in Gram-positive bacteria, once DNA strand cleavage has occurred,

preventing religation and causing lethal double-strand breaks. Structural and modeling data show that the C-3 carboxylic acid and C-4 keto group chelate a Mg^{2+} ion, which bridges the drug to a conserved serine and acidic residue (Ser83 and Asp87 in *E. coli* GyrA numbering) through a water-mediated network [55]. This water–metal bridge holds the quinolone within the DNA–enzyme complex, and mutations at these residues, a frequent clinical resistance mechanism, disrupt the bridge and reduce drug binding accordingly. The C-7 piperazinyl or pyrrolidinyl group points toward the GyrB/ParE subunit, and its basicity and size affect both potency against Gram-negative efflux pumps/porins and affinity for topoisomerase IV, which is part of why later agents like moxifloxacin and gemifloxacin cover Gram-positive organisms so well. The C-8 fluorine or methoxy substituent also improves anaerobic activity and lowers phototoxicity by shifting the electron density of the quinolone core [56].

Quinoline antibiotics remain essential against resistant pathogens, and hybrid designs, such as coupling quinolines to amino acids or peptides, are currently being explored. Resistance, driven mainly by mutations in gyrase and topoisomerase IV and by efflux pump overexpression, remains the main obstacle facing this drug class. Two strategies proposed to work around this are combining quinolones with efflux pump inhibitors, and shifting the target from direct bactericidal action toward quorum-sensing disruption. On the structural side, future design will need to balance lipophilicity carefully, enough for good cell penetration, but not so much that it invites efflux recognition, while also steering clear of the cardiotoxicity linked to certain substitution patterns in this class [57].

4. Anticancer Activity

Quinoline-based compounds received significant attention in anticancer drug discovery for their ability to interact with key molecular targets involved in cell proliferation, DNA replication, and signal transduction. Several naturally occurring and synthetic quinoline derivatives have shown potent antitumor activity and have gone on to serve as lead structures for clinically relevant anticancer agents [58,59].

One of the earliest examples is streptonigrin, a naturally occurring aminoquinoline antibiotic isolated from *Streptomyces flocculus* in 1959 [58]. This compound exhibits potent cytotoxic activity against a broad spectrum of tumor cell lines, including murine leukemia and melanoma models, with IC_{50} values typically ranging from 1 to 50 nM [4]. Its antitumor activity is primarily attributed to DNA strand cleavage and inhibition of topoisomerase II, together with redox cycling that promotes the generation of reactive oxygen species. However, its clinical development has been severely limited by dose-limiting systemic toxicity. SAR studies have demonstrated that the quinoline-5,8-dione core is indispensable for its redox-mediated cytotoxic activity, highlighting this pharmacophore as the key structural determinant of its biological effects (Figure 5 and Table 2) [59].

Table 2. Quinoline-based anticancer derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency	Refs.
Streptonigrin	Topoisomerase II/DNA	DNA strand cleavage; redox-mediated cytotoxicity via quinoline quinone moiety	IC_{50} = 1–50 nM (murine leukemia, melanoma)	[4,56,57]
Camptothecin	Topoisomerase I	Stabilizes cleavable complex via α-hydroxylactone E-ring	IC_{50} = 5–100 nM (HCT-116, MCF-7, A549)	[58]
Topotecan	Topoisomerase I	Semi-synthetic analogue; improved solubility	IC_{50} = 10–100 nM (ovarian, SCLC)	[58]
Irinotecan	Topoisomerase I	Prodrug metabolized to active SN-38	Subnanomolar–low nM (colorectal cancer cell lines)	[58]
Lavendamycin	Topoisomerase I	Bioreductive activation; DNA damage/apoptosis	Low μM (leukemia, breast, colon)	[59]

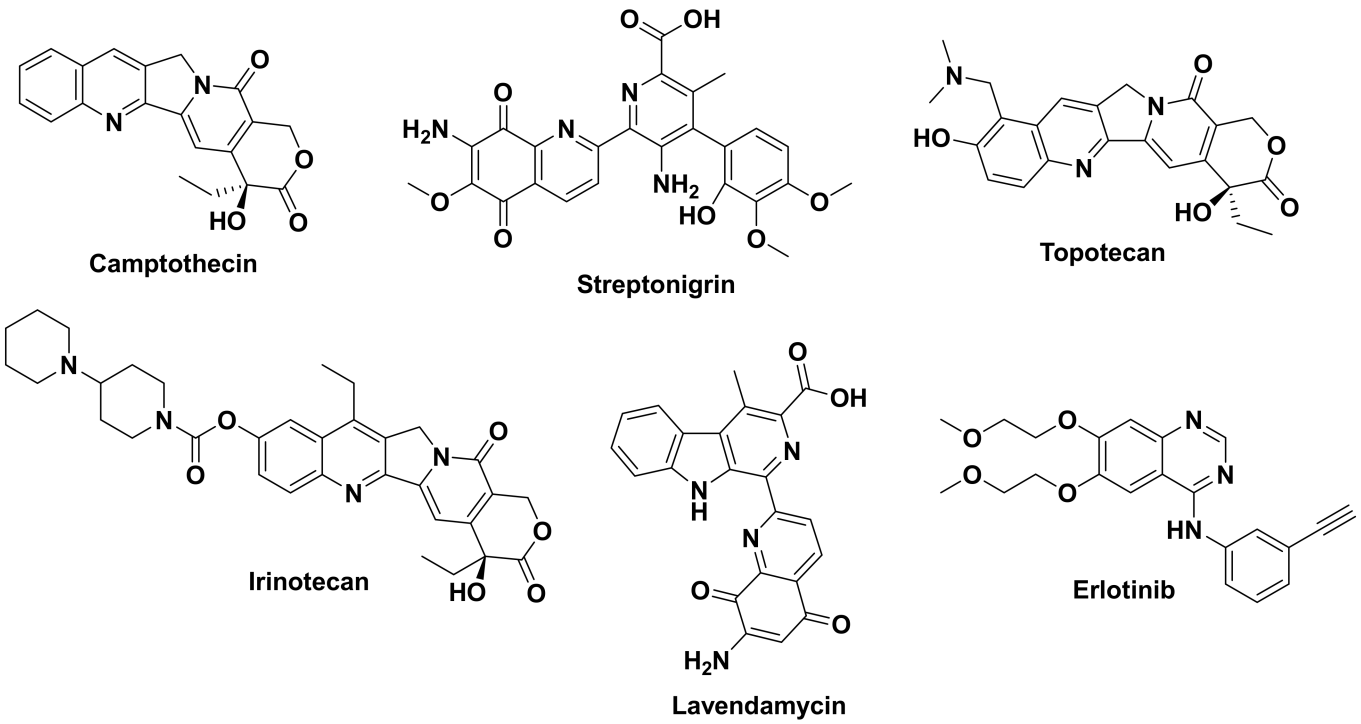


Figure 5. Quinoline-Based Anticancer Derivatives.

Camptothecin, a quinoline alkaloid isolated from *Camptotheca acuminata*, inhibits DNA topoisomerase I by stabilizing the DNA–topoisomerase I cleavage complex, thereby blocking DNA religation during replication. This mechanism results in irreversible DNA damage and subsequent cell death. Camptothecin has demonstrated potent cytotoxic activity against several human cancer cell lines, including colon (HCT-116), breast (MCF-7), and lung (A549), with IC_{50} values generally ranging from 5 to 100 nM. SAR studies established that the intact α-hydroxylactone E-ring is essential for activity, while modifications elsewhere on the quinoline nucleus have given derivatives with improved pharmacological profiles [60].

Mechanistically, camptothecin stabilizes the covalent DNA–topoisomerase I cleavage complex by binding at the DNA–enzyme interface rather than directly inhibiting the catalytic activity of the enzyme. Its α-hydroxylactone E-ring forms key hydrogen-bonding interactions with active-site residues, whereas the planar pentacyclic scaffold intercalates between the DNA base pairs flanking the cleavage site. This interaction prevents DNA religation, converting transient single-strand breaks into persistent lesions that are transformed into irreversible double-strand breaks during DNA replication, ultimately triggering cell death. Hydrolysis of the α-hydroxylactone ring to the inactive carboxylate form at physiological pH destroys this hydrogen-bonding network, which is why the semi-synthetic derivatives topotecan and irinotecan were designed specifically to improve lactone stability and aqueous solubility while keeping the E-ring intact.

The poor aqueous solubility and dose-limiting toxicity of camptothecin prompted the development of semisynthetic derivatives, notably topotecan and irinotecan. Topotecan exhibits potent activity against ovarian and small-cell lung cancer, with reported IC_{50} values of 10–100 nM. Irinotecan is a prodrug that is converted by carboxylesterases into SN-38, a highly potent topoisomerase I inhibitor displaying subnanomolar to low-nanomolar activity against colorectal cancer cell lines. Structural modifications at positions 9 and 10 of the quinoline scaffold improve aqueous solubility, lactone stability, and pharmacokinetic properties while preserving topoisomerase I inhibition.

Another representative quinoline-containing natural product is lavendamycin, isolated from *Streptomyces lavendulae* [61]. Lavendamycin exhibits cytotoxic activity against leukemia, breast, and colon cancer cell lines, with IC_{50} values generally in the low micromolar range. Its antitumor activity has been attributed to topoisomerase I inhibition together with bioreductive activation, leading to DNA damage and apoptosis.

Furthermore, gefitinib and erlotinib have revolutionized targeted cancer therapy through selective inhibition of the epidermal growth factor receptor (EGFR) tyrosine kinase. Structurally, both compounds are 4-anilinoquinazolines rather than quinolines, bearing an additional ring nitrogen relative to the quinoline core; they are discussed here because of their close structural relationship to the quinoline scaffold and because the underlying hinge-binding SAR principles apply equally to both ring systems. Erlotinib displays potency with IC_{50} values close to 2 nM against EGFR kinase. SAR studies have established that the 4-anilinoquinazoline pharmacophore is crucial for ATP-binding site recognition and kinase inhibition, making it one of the most successful quinazoline-based motifs in modern oncology.

The 4-anilinoquinazoline pharmacophore of gefitinib and erlotinib occupies the ATP-binding cleft of the EGFR tyrosine kinase domain, forming a key hydrogen bond between the ring nitrogen and the backbone NH of Met793 in the hinge region. The aniline substituent at C-4 extends into a hydrophobic back pocket lined by Thr790, the gatekeeper residue, and its steric and electronic complementarity to this pocket determines both potency and susceptibility to the T790M gatekeeper mutation, which sterically hinders drug binding and is the principal mechanism of acquired resistance. The solubilizing substituents at positions 6 and 7 are oriented toward solvent-exposed regions, where they mainly improve physicochemical and pharmacokinetic properties without significantly affecting target binding. This structural insight has guided the rational design of third-generation EGFR inhibitors capable of overcoming T790M-mediated resistance.

5. Anti-Inflammatory Activity

Quinoline derivatives have attracted considerable interest as anti-inflammatory agents because of their ability to modulate multiple signaling pathways involved in the inflammatory response. Numerous quinoline-based compounds have demonstrated significant anti-inflammatory activity through diverse mechanisms, including inhibition of cyclooxygenase (COX) and lipoxygenase (LOX), suppression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as attenuation of oxidative stress [11].

SAR studies indicate that electron-donating substituents, particularly hydroxyl and amino groups, generally strengthen anti-inflammatory activity by improving interactions with inflammatory targets, while bulky aromatic substituents tend to favor COX-2 selectivity (Figure 6 and Table 3) [62].

Table 3. Quinoline-based anti-inflammatory derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency	Ref.
Chloroquine/ Hydroxychloroquine	Lysosomes; endosomal TLR7/TLR9; antigen presentation	Inhibits lysosomal acidification, suppresses TLR signaling, and decreases TNF-α, IL-1β and IL-6 production	IC_{50} = 1–10 μM (cytokine production)	[61]
Montelukast	$CysLT_1$ receptor	Selective cysteinyl leukotriene receptor antagonist	IC_{50} = 0.5–5 nM	[62]
Nicafenine	Cyclooxygenase (COX)	Non-selective NSAID; inhibits prostaglandin biosynthesis	Moderate anti-inflammatory activity	[63]
Glafenine	Cyclooxygenase (COX)	Non-selective NSAID; inhibits prostaglandin biosynthesis	Moderate anti-inflammatory activity	[64]
Floctafenine	Cyclooxygenase (COX)	Non-selective NSAID; inhibits prostaglandin biosynthesis	Moderate anti-inflammatory activity	[65]

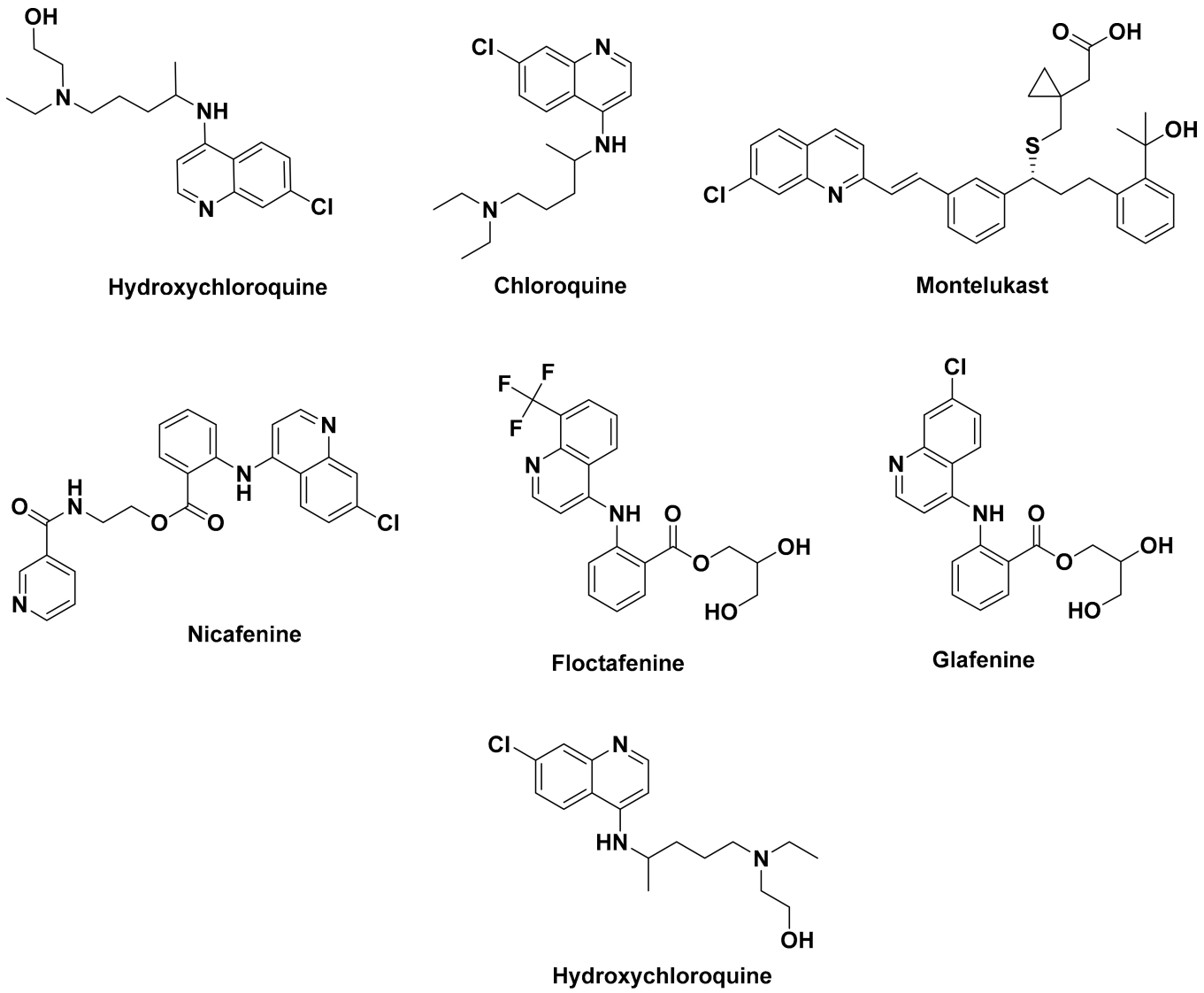


Figure 6. Quinoline-Based Anti-inflammatory Derivatives.

Among clinically relevant quinoline derivatives, chloroquine and hydroxychloroquine remain the most studied [61]. Beyond their antimalarial use, both compounds exert immunomodulatory effects by inhibiting lysosomal acidification, antigen presentation, and cytokine production. Hydroxychloroquine is widely used in rheumatoid arthritis and systemic lupus erythematosus, where it markedly lowers serum TNF-α and IL-6, and in cellular assays it inhibits inflammatory mediator production with IC_{50} values in the low micromolar range (roughly 2–10 μM), consistent with its clinical efficacy in these conditions [61].

Chloroquine and hydroxychloroquine accumulate preferentially in acidic intracellular compartments such as lysosomes and endosomes, a consequence of their weakly basic, diprotic amine side chain, and this raises the intraluminal pH enough to impair lysosomal enzyme activity, antigen processing, and TLR9 signaling triggered by nucleic acid-containing immune complexes, a pathway particularly relevant in lupus [61]. This mechanism differs fundamentally from the direct cyclooxygenase inhibition produced by conventional nonsteroidal anti-inflammatory drugs (NSAIDs) and accounts for the delayed onset of clinical response typically observed in autoimmune diseases.

Montelukast [62], a quinoline-containing leukotriene receptor antagonist, represents another important anti-inflammatory agent. It selectively antagonizes the cysteinyl leukotriene

receptor 1 (CysLT1), thereby suppressing leukotriene-mediated bronchoconstriction and inflammatory cell recruitment. Its high affinity for CysLT1 ($IC_{50} \approx 0.5–5$ nM) underlies its established efficacy in the long-term management of asthma and allergic rhinitis [62].

Other quinoline derivatives, including nicafenine [63], glafenine [64], and floctafenine [65], exhibit both analgesic and anti-inflammatory properties. Their pharmacological activity has been associated with modulation of prostaglandin biosynthesis and related inflammatory pathways. SAR studies indicate that aromatic amino substituents and appropriate substitution patterns on the quinoline nucleus play important roles in optimizing anti-inflammatory activity.

In general, these examples illustrate the remarkable versatility of the quinoline scaffold in anti-inflammatory drug discovery. Quinoline derivatives exert their therapeutic effects through distinct mechanisms, including modulation of lysosomal function, inhibition of inflammatory mediator production, antagonism of leukotriene receptors, and regulation of prostaglandin biosynthesis, highlighting the scaffold as a valuable platform for the development of anti-inflammatory agents.

6. Antimalarial Activity

Quinoline derivatives have been the cornerstone of antimalarial chemotherapy for over a century and continue to represent one of the most important classes of antiplasmodial agents [66]. Their mechanism of action is primarily associated with the inhibition of heme detoxification within the digestive vacuole of *Plasmodium* parasites, leading to the accumulation of toxic free heme and subsequent parasite death. The effectiveness of quinoline-based compounds against both chloroquine-sensitive and resistant strains has stimulated continuous efforts to develop new derivatives with improved efficacy and safety profiles (Figure 7 and Table 4) [67].

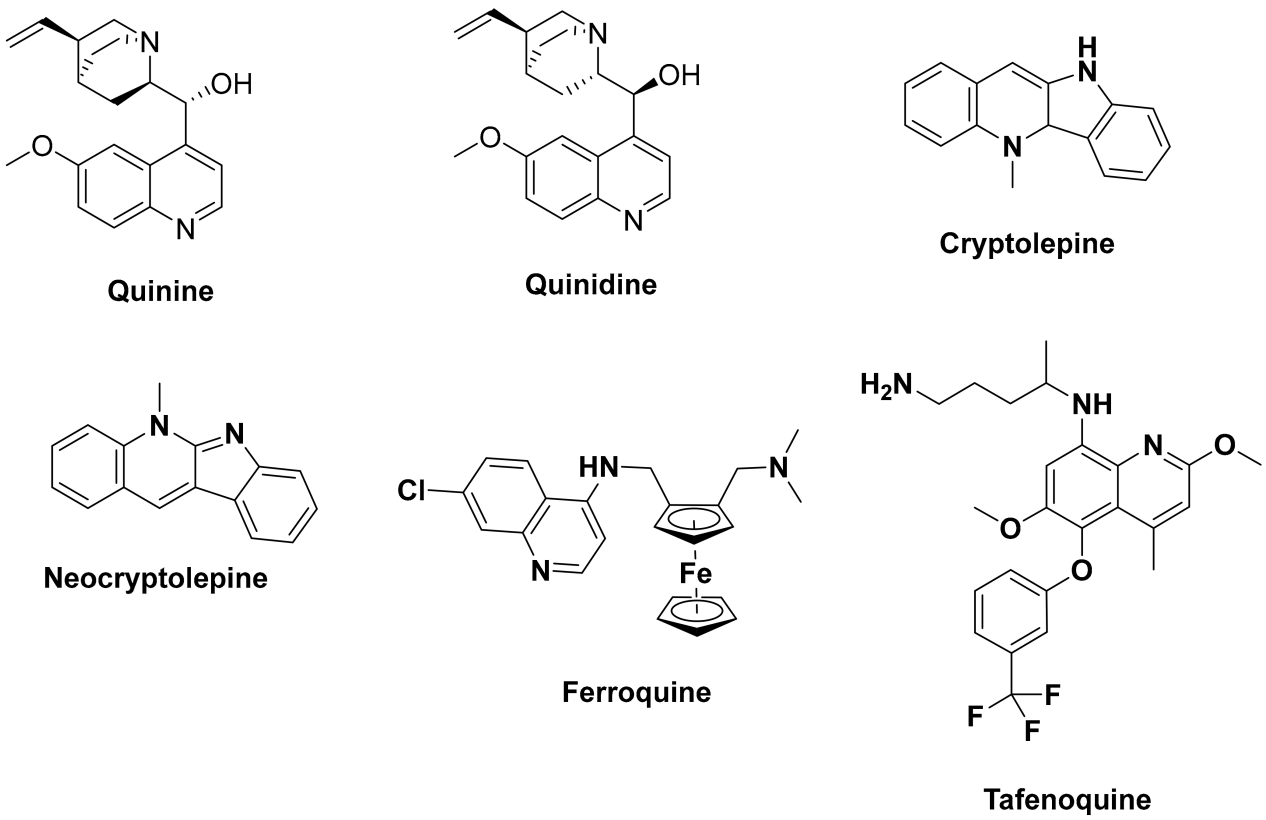


Figure 7. Quinoline-Based Antimalarial Derivatives.

Table 4. Quinoline-based antimalarial derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency (Against *P. falciparum*)	Refs.
Quinine	Hemozoin formation (food vacuole)	Inhibits heme detoxification; the quinuclidine ring and secondary alcohol are essential for activity	IC_{50} = 100–500 nM	[68]
Quinidine	Hemozoin formation (food vacuole)	Diastereomer of quinine with similar mechanism; higher cardiotoxicity limits clinical use	IC_{50} = 50–300 nM	[69]
Cryptolepine	Hemozoin formation/DNA	Inhibits hemozoin formation and intercalates into DNA; indoloquinoline scaffold	IC_{50} = 20–200 nM (CQ-sensitive and CQ-resistant strains)	[70]
Chloroquine	Hemozoin formation (food vacuole)	4-Aminoquinoline that accumulates in the digestive vacuole and inhibits heme polymerization	IC_{50} = 10–50 nM (CQ-sensitive); IC_{50} > 100 nM (CQ-resistant)	[66,67]
Tafenoquine	Liver-stage and blood-stage parasites	8-Aminoquinoline causing oxidative stress after metabolic activation; active against hypnozoites	IC_{50} = 50–200 nM	[66,67]
Ferroquine	Hemozoin formation (food vacuole)	Ferrocenyl 4-aminoquinoline active against chloroquine-resistant parasites	IC_{50} = 5–30 nM	[66,67]

Quinine, the first clinically used antimalarial alkaloid isolated from the bark of Cinchona species, exhibits potent activity against Plasmodium falciparum, with reported IC_{50} values generally ranging from 100 to 500 nM depending on the parasite strain. Its antimalarial activity is mainly attributed to inhibition of heme detoxification within the parasite digestive vacuole, resulting in the accumulation of toxic free heme. Although quinine remains an effective treatment for severe malaria, its long-term use is limited by adverse effects, including cinchonism and neurotoxicity. SAR studies have shown that both the quinuclidine ring and the secondary alcohol group are essential for antiplasmodial activity [68].

Quinidine, the stereoisomer of quinine, exhibits comparable antiplasmodial potency, with IC_{50} values generally ranging from 50 to 300 nM against *P. falciparum*. However, its clinical use as an antimalarial has been largely restricted because of its pronounced cardiotoxic and proarrhythmic effects. Despite these limitations, quinine and quinidine have served as important lead compounds for the development of modern quinoline-based antimalarial agents [69].

Among naturally occurring quinoline alkaloids, cryptolepine, neocryptolepine, and isocryptolepine, isolated from *Cryptolepis sanguinolenta*, show strong activity against *P. falciparum*. Cryptolepine in particular has IC_{50} values of 20–200 nM against both chloroquine-sensitive and chloroquine-resistant strains [70].

Its antiplasmodial activity is attributed to DNA intercalation, inhibition of hemozoin formation, and interference with nucleic acid synthesis. SAR investigations have demonstrated that substitutions on the indoloquinoline nucleus strongly influence potency and selectivity, with appropriate modifications at the nitrogen atom and aromatic ring system leading to improved antimalarial activity and reduced cytotoxicity [70].

4-Aminoquinolines such as chloroquine accumulate within the acidic digestive vacuole of the parasite, where they bind free heme released during hemoglobin digestion and prevent its polymerization into inert hemozoin crystals [66].

The quinoline ring stacks with the porphyrin macrocycle, while the protonated side chain at C-4 stabilizes the drug-heme complex, and the resulting adduct becomes toxic to the parasite. Mutations in the *P. falciparum* chloroquine resistance transporter (PfCRT) reduce vacuolar drug accumulation through increased chloroquine efflux and represent

the main resistance mechanism, which is consistent with the retained activity of ferroquine against chloroquine-resistant strains, since its ferrocenyl side chain is less readily recognized by mutant PfCRT [67].

The remarkable efficacy of these quinoline alkaloids has established the quinoline scaffold as a privileged structure in antimalarial drug discovery. This has ultimately led to the development of clinically important agents such as chloroquine, mefloquine, and more recently tafenoquine and ferroquine, which continue to play a significant role in the fight against malaria, particularly in regions affected by drug-resistant *Plasmodium* strains.

7. Antiparasitic Activity

Quinoline derivatives constitute an important class of antiparasitic agents and have demonstrated efficacy against a wide variety of protozoan and helminth infections [71]. Their antiparasitic activity is generally associated with disruption of mitochondrial function, interference with nucleic acid synthesis, inhibition of haem detoxification, and induction of oxidative stress [13]. Owing to these diverse mechanisms of action, quinoline-based compounds continue to serve as valuable therapeutic agents and lead structures for the development of novel antiparasitic drugs (Figure 8 and Table 5).

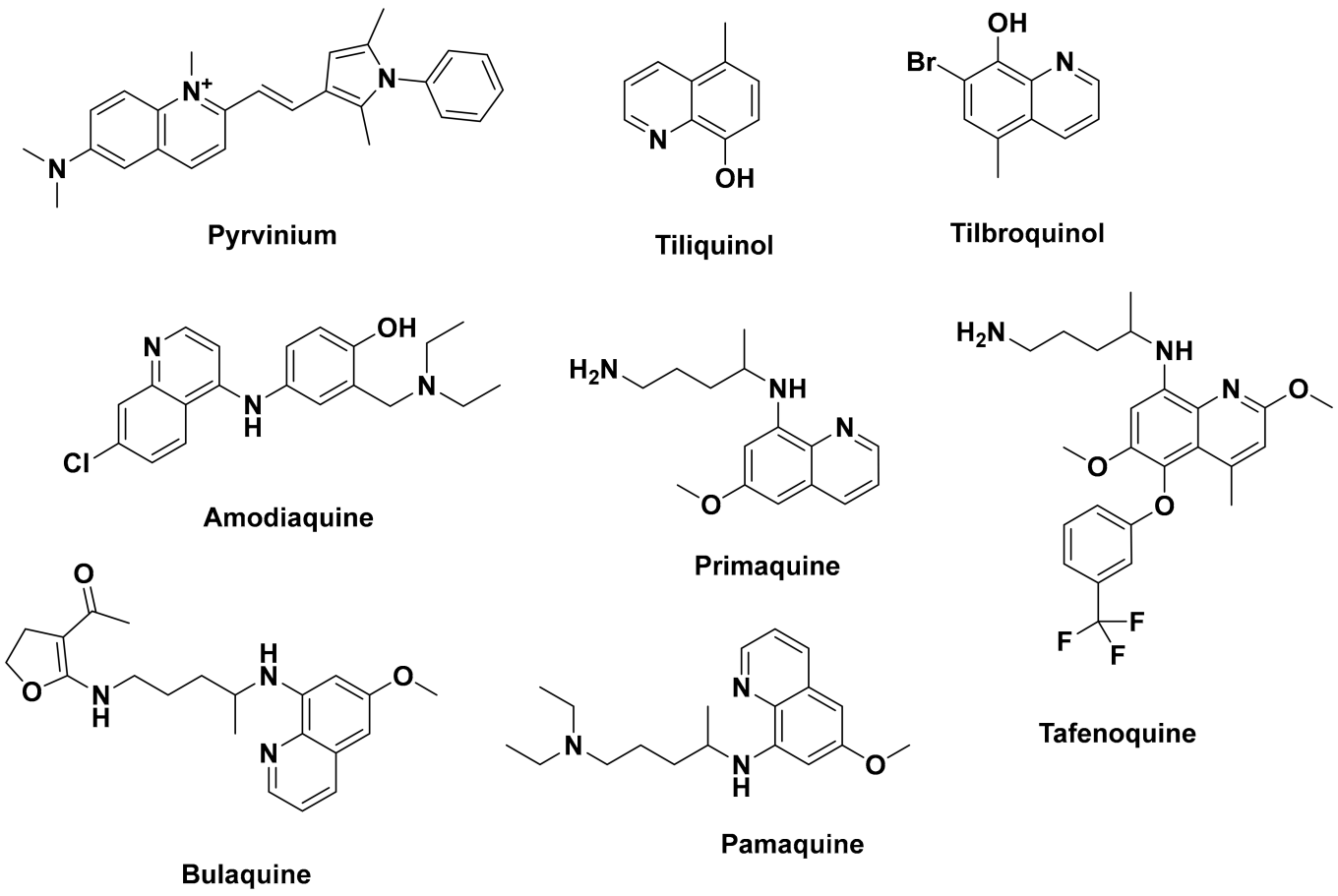


Figure 8. Quinoline-Based Antiparasitic Derivatives.

Among the earliest examples, pyrvinium has been widely used for the treatment of enterobiasis caused by *Enterobius vermicularis*. The compound acts by inhibiting parasite mitochondrial respiration and ATP production, ultimately leading to parasite death [72]. Tiliquinol and tilbroquinol, commonly administered in combination, exhibit potent amoebicidal activity against *Entamoeba histolytica* and remain effective treatments for intestinal amoebiasis. SAR studies have shown that halogen substitution on the quinoline nucleus,

particularly the bromine atom present in tilbroquinol, contributes significantly to enhanced antiparasitic activity by increasing lipophilicity and membrane permeability [73].

Table 5. Quinoline-based antiparasitic derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency	Ref.
Pyrvinium	*Enterobius vermicularis*	Inhibits mitochondrial oxidative phosphorylation and ATP production	EC_{50} = 20–100 nM (helminths, in vitro)	[72]
Tiliquinol/ Tilbroquinol	*Entamoeba histolytica*	Amoebicidal; membrane disruption and inhibition of protozoal metabolism	MIC = 0.5–2 μg/mL	[73]
Primaquine	*Plasmodium* spp. (liver stages, gametocytes)	8-Aminoquinoline; oxidative stress following CYP2D6-dependent bioactivation	IC_{50} = 100–500 nM	[31]
Tafenoquine	*Plasmodium falciparum*, *P. vivax*	Long-acting 8-aminoquinoline causing oxidative stress after metabolic activation	IC_{50} < 100 nM	[31]
Amodiaquine	*P. falciparum* (CQ-sensitive and resistant isolates)	4-Aminoquinoline; inhibits hemozoin formation after accumulation in the digestive vacuole	IC_{50} = 10–50 nM	[74]

The 8-aminoquinoline class, represented by primaquine, pamaquine, tafenoquine, and bulaquine, plays a pivotal role in the radical cure of malaria caused by *Plasmodium vivax* and *P. ovale* by eliminating dormant hepatic hypnozoites [31]. Primaquine exhibits antiplasmodial activity with reported IC_{50} values generally ranging from 100 to 500 nM, whereas tafenoquine displays greater potency, with IC_{50} values frequently below 100 nM against several *P. falciparum* strains. Structure–activity relationship (SAR) studies have identified the 8-aminoquinoline nucleus and its aminoalkyl side chain as key structural features required for antiplasmodial activity [31].

In contrast to 4-aminoquinolines, which inhibit heme detoxification within the parasite digestive vacuole, 8-aminoquinolines require metabolic activation to exert their antiparasitic effects. Primaquine and tafenoquine are metabolized primarily by cytochrome P450 2D6 (CYP2D6) to reactive intermediates that induce oxidative stress through the generation of reactive oxygen species [31]. This mechanism enables effective elimination of hepatic hypnozoites but also accounts for the risk of hemolytic anemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, limiting the use of these agents in susceptible patients.

Amodiaquine, a 4-aminoquinoline related to chloroquine, is potent against both chloroquine-sensitive and resistant strains of *Plasmodium falciparum*, with IC_{50} values typically between 10 and 50 nM. SAR studies show that substituting the C-4 position with aminoalkyl groups increases accumulation within the parasite's digestive vacuole and strengthens inhibition of haem polymerization [74]. More recently, quinoline derivatives bearing nitroaromatic and chalcone pharmacophores have shown promising activity against *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei*, with IC_{50} values in the low micromolar range (0.5–5 μM) [74]. These findings highlight the importance of electron-withdrawing substituents in improving antiparasitic potency and support the continued development of quinoline-based molecular architectures as broad-spectrum antiparasitic agents.

What stands out in this class is how well the same scaffold performs across parasites that have little in common biologically: protozoa such as *Plasmodium*, *Entamoeba*, *Trypanosoma*, and *Leishmania*, and helminths such as *Enterobius*. This is mostly because these organisms all rely heavily on mitochondrial function and redox balance, which quinoline derivatives disrupt through fairly general mechanisms, membrane permeabilization and ROS induction, rather than by binding tightly to one specific target. That broad activity is useful in settings where precise diagnosis is not always possible, but it also means selectiv-

ity toward host mitochondria is not guaranteed and deserves more attention in future SAR work on this class.

8. Antitubercular Activity

Quinoline derivatives have emerged as valuable scaffolds in the search for new antitubercular agents, particularly in response to the growing prevalence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of *Mycobacterium tuberculosis*. Their biological activity is associated with the inhibition of essential mycobacterial processes, including energy metabolism, redox homeostasis, and metal-dependent enzymatic pathways. The structural versatility of the quinoline nucleus has enabled the development of several compounds with significant activity against both replicating and dormant mycobacterial populations (Figure 9 and Table 6) [75,76].

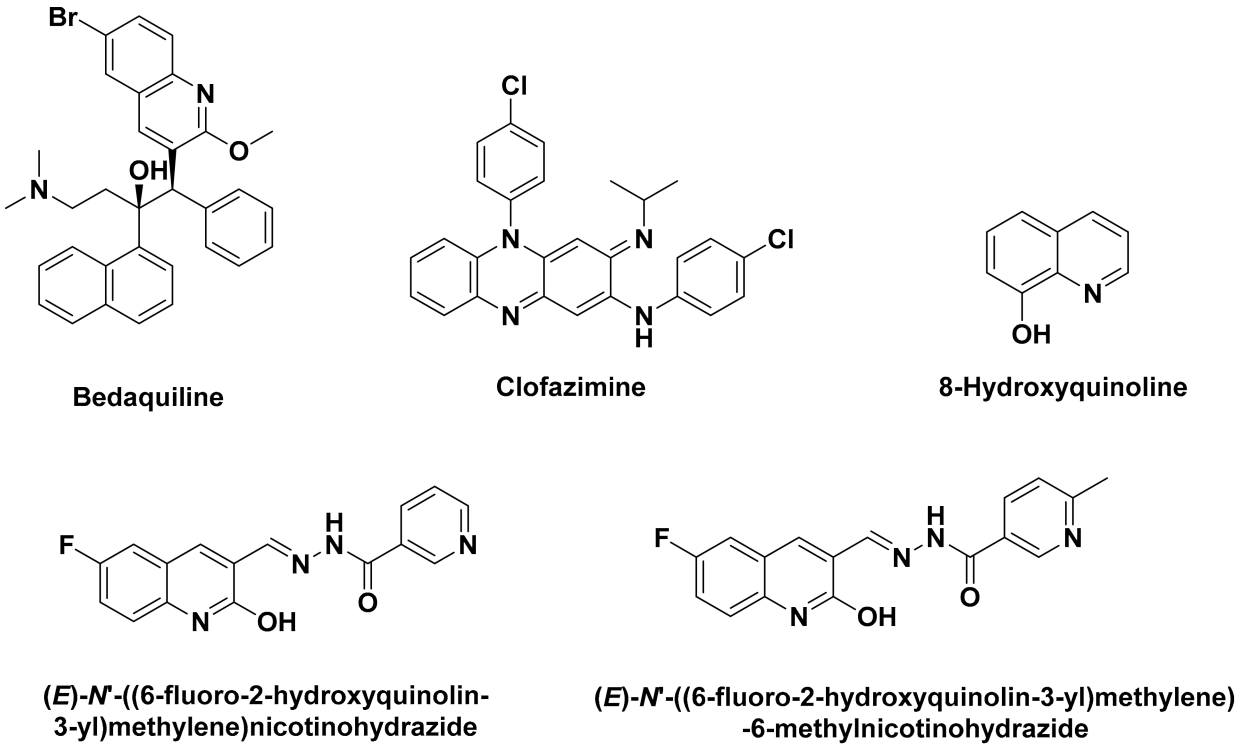


Figure 9. Quinoline-Based Antitubercular Derivatives.

Table 6. Quinoline-based antitubercular derivatives: targets, mechanisms, and potency.

Compound	Target	Mechanism	Reported Potency	Ref.
Bedaquiline	Mycobacterial ATP synthase (c subunit, F0 proton rotor)	Diarylquinoline; inhibits ATP synthase by blocking proton translocation and ATP production	MIC = 0.015–0.12 μg/mL (including MDR-*M. tuberculosis*)	[75]
Clofazimine	Membrane respiratory chain (NDH-2)	Riminophenazine; redox cycling, ROS generation, and disruption of membrane electron transport	MIC = 0.06–0.5 μg/mL	[76]
8-Hydroxyquinoline derivatives	Metal-dependent metalloenzymes	Metal chelation, disrupting essential metalloprotein functions	MIC = 0.5–4 μg/mL (replicating and non-replicating *M. tuberculosis*)	[77]
Fluorinated 2-hydroxyquinoline hydrazones	Metal-dependent enzymes/redox pathways	C-6 fluorine, C-2 hydroxyl and pyridine-hydrazone linker enhance antimycobacterial activity	MIC = 6.25 μg/mL	[78]

Among clinically approved drugs, bedaquiline stands out as a major breakthrough in tuberculosis therapy. This diarylquinoline derivative selectively inhibits the proton pump of mycobacterial ATP synthase, leading to depletion of intracellular ATP and bacterial

death, and shows remarkable potency against *M. tuberculosis*, with MIC values typically between 0.015 and 0.12 μg/mL, including activity against MDR-TB strains [75]. SAR studies show that the diaryl and aminoalcohol substituents are essential for interaction with the ATP synthase complex and account for much of its exceptional antimycobacterial activity.

Bedaquiline, the first approved diarylquinoline for the treatment of multidrug-resistant tuberculosis, selectively inhibits mycobacterial ATP synthase by binding to the c-subunit of the Fo proton channel, thereby blocking proton translocation and ATP synthesis. This unique mechanism results in rapid depletion of intracellular ATP and potent bactericidal activity against *Mycobacterium tuberculosis*. The structural differences between mycobacterial and human ATP synthase largely account for its selectivity, whereas resistance is primarily associated with mutations in the atpE gene encoding the ATP synthase c-subunit [75].

Clofazimine, another clinically important quinoline-containing antimycobacterial agent, exhibits potent activity against *M. tuberculosis*, with MIC values generally ranging from 0.06 to 0.5 μg/mL against susceptible strains. Its antimicrobial activity is mainly attributed to disruption of the mycobacterial electron transport chain and the generation of reactive oxygen species. Owing to its highly lipophilic phenazine framework, clofazimine accumulates efficiently within macrophages, contributing to its activity against persistent mycobacterial infections [76].

8-Hydroxyquinoline and its derivatives have also attracted considerable interest because of their ability to chelate metal ions essential for mycobacterial growth, displaying MIC values of 0.5–4 μg/mL against both replicating and dormant *M. tuberculosis*. In addition, Mandewale and co-workers synthesized a series of fluorinated 2-hydroxyquinoline hydrazone derivatives that completely inhibited *M. tuberculosis* growth at 6.25 μg/mL. Structure–activity relationship (SAR) studies demonstrated that the combined presence of a fluorine atom at C-6, a hydroxyl group at C-2, and a pyridyl hydrazone moiety significantly enhances antimycobacterial activity [78].

Collectively, these findings highlight the versatility of the quinoline scaffold in antitubercular drug discovery. Quinoline derivatives exert antimycobacterial activity through diverse mechanisms, including inhibition of ATP synthesis, disruption of respiratory electron transport, and metal-ion chelation, providing multiple opportunities for the development of agents active against drug-resistant and persistent *M. tuberculosis* strains.

9. Antioxidant Activity

Oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and cellular antioxidant defenses, plays a key role in the pathogenesis of numerous chronic disorders, including cancer, cardiovascular diseases, neurodegenerative disorders, and inflammatory conditions. Consequently, the development of effective antioxidant agents has attracted considerable attention, with quinoline derivatives emerging as promising candidates because of their ability to scavenge free radicals, attenuate oxidative stress, and protect cells from oxidative damage (Figure 10 and Table 7) [79].

Table 7. Quinoline-based antioxidant derivatives: targets, mechanisms, and potency.

Compound	Antioxidant Mechanism	Reported Potency	Ref.
Clioquinol	Fe^{2+}/Cu^{2+} chelation through the 8-hydroxyquinoline pharmacophore; inhibition of Fenton-type ROS generation	Active in DPPH and H_2O_2 scavenging assays	[80]
6-Chloro-3-(1,3-dioxolan-2-yl)quinoline	Electron-withdrawing Cl substituent enhances radical-scavenging efficiency	84.6–85.8% DPPH radical scavenging	[80]
3-Quinolinecarboxaldehyde	Direct radical scavenging through the quinoline aromatic system	92.96% DPPH radical scavenging (most active derivative)	[80]
2-Chloro-3-quinolinecarboxaldehyde	Chlorine substitution improves antioxidant activity through electronic effects	84.6–85.8% DPPH radical scavenging	[80]

Table 7. *Cont.*

Compound	Antioxidant Mechanism	Reported Potency	Ref.
Bromoquinoline derivative	Bromine substitution enhances electron delocalization and radical stabilization	Moderate-to-good antioxidant activity (DPPH assay)	[80]
Thiophene-based quinoline derivative	Phenolic OH-mediated hydrogen atom transfer (HAT) combined with quinoline–thiophene conjugation	EC_{50} = 12.03 ± 1.45 µg/mL	[81]

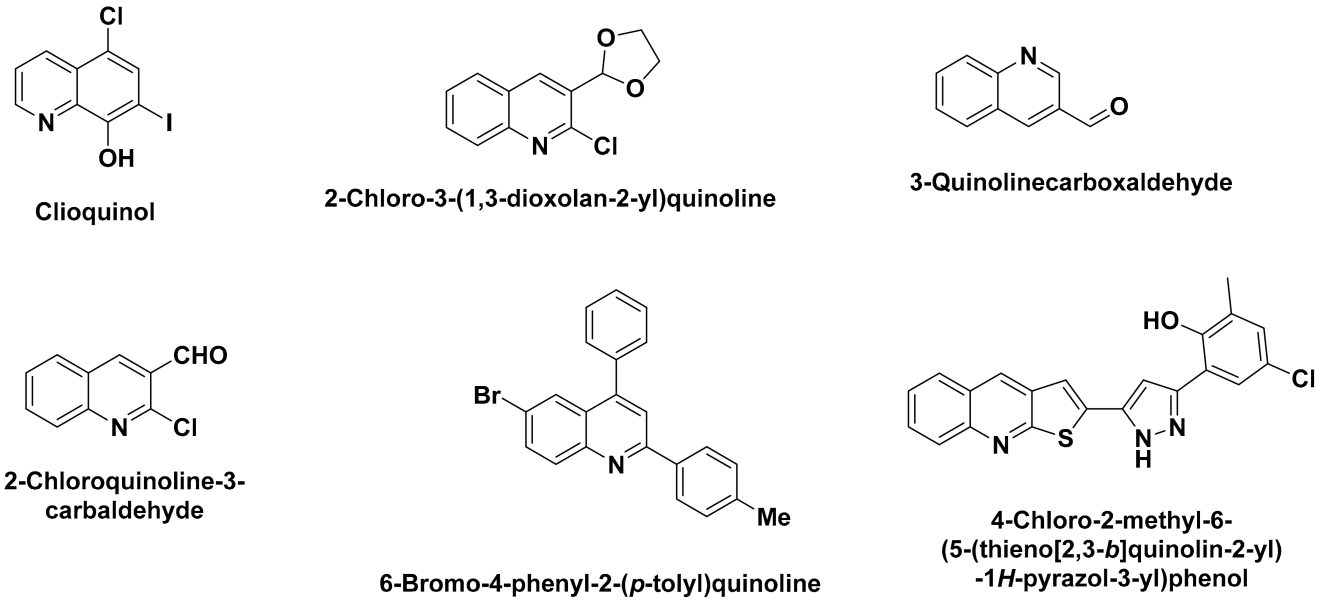


Figure 10. Quinoline-Based Antioxidant Derivatives.

Several quinoline derivatives have demonstrated significant antioxidant activity in both chemical and cell-based assays. Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is a representative example, exerting its antioxidant activity primarily through chelation of redox-active metal ions, thereby reducing metal-catalyzed reactive oxygen species (ROS) formation. SAR studies have identified the C-8 hydroxyl group as a key structural feature required for efficient metal coordination and antioxidant activity [80]. In addition, 3-(1,3-dioxolan-2-yl)quinoline and chlorine-substituted 3-quinolinecarboxaldehyde derivatives have shown promising antioxidant activity in DPPH and hydrogen peroxide scavenging assays, suggesting that appropriate electron-withdrawing substituents can enhance antioxidant performance [80].

The antioxidant properties of clioquinol arise primarily from the formation of a stable metal-chelating complex involving the C-8 hydroxyl group and the adjacent quinoline nitrogen, enabling efficient coordination of transition metal ions such as Fe^{2+} and Cu^{2+}. By limiting the availability of these redox-active metals, clioquinol suppresses Fenton-type reactions and the subsequent generation of highly reactive hydroxyl radicals [80].

Furthermore, Liberto and co-workers reported that appropriately substituted quinoline derivatives effectively reduce intracellular ROS levels, highlighting the importance of substitution patterns on the quinoline scaffold in optimizing antioxidant activity [10].

Mahajan et al., in a separate study, reported a series of thiophene-based quinoline derivatives, the most active of which had an EC_{50} of 12.03 ± 1.45 µg/mL in radical scavenging assays [81]. SAR analysis suggested that the combination of a quinoline nucleus with a thiophene ring and phenolic hydroxyl substituents enhances electron-donating capacity and stabilizes radical intermediates, thereby improving antioxidant efficiency. These findings demonstrate that both the nature and position of substituents on the quinoline

scaffold play a decisive role in determining antioxidant potential and support the continued development of quinoline-based antioxidants for biomedical applications [81].

Taken as a whole, the antioxidant quinoline derivatives discussed here work through two distinct routes, metal chelation (clioquinol-type) and direct radical scavenging (thiophene/phenolic-substituted derivatives), and it is not yet clear from the current literature which of these contributes more to the biological benefit seen in cellular and animal models, an open question that future mechanistic studies on this class should address directly rather than relying solely on chemical DPPH-type assays.

10. Antiviral Activity

Beyond their well-established roles in antibacterial, antimalarial, and antiparasitic chemotherapy, quinoline derivatives have emerged as a promising class of antiviral agents with activity against coronaviruses, flaviviruses, and other RNA viruses [82]. Their antiviral effects are mediated through multiple mechanisms, including inhibition of viral proteases, interference with viral entry and endosomal trafficking, modulation of host–cell pathways, and disruption of viral replication, highlighting the remarkable versatility of the quinoline scaffold in antiviral drug discovery [82,83].

a. Coronavirus inhibitors

Among quinoline-based antivirals, chloroquine and hydroxychloroquine have been the most extensively investigated against human coronaviruses [82]. In a comparative evaluation of ten antimalarial quinoline derivatives against a panel of α- and β-coronaviruses, including SARS-CoV, SARS-CoV-2, HCoV-229E, and HCoV-OC43, both compounds exhibited broad-spectrum antiviral activity, with EC_{50} values ranging from 0.12 to 12 μM. Chloroquine displayed the highest selectivity, achieving a selectivity index (SI) of 165 against HCoV-OC43 in HEL cells, indicating a favorable balance between antiviral potency and cytotoxicity [82].

Amodiaquine, ferroquine, and mefloquine also displayed potent anti-coronavirus activity, although mefloquine's activity was accompanied by substantial cytotoxicity, whereas primaquine, quinidine, quinine, and tafenoquine were only active at higher concentrations, and piperaquine lacked both antiviral and cytotoxic effects. Mechanistic studies indicated that chloroquine interferes with viral entry at a post-attachment stage and inhibits SARS-CoV-2 RNA synthesis, an effect coinciding with impaired autophagic flux, pointing to a host-directed rather than a purely virus-targeted mode of action [82].

More recently, structure-based design has been applied to develop quinoline inhibitors of the SARS-CoV-2 papain-like protease (PLpro), an enzyme required for polyprotein processing and suppression of host innate immune responses [15]. By exploiting the Val70Ub binding site on PLpro, a series of quinoline analogues was designed showing potent PLpro inhibition and antiviral activity, with X-ray structures of six lead compounds revealing that the 2-aryl substituent can occupy either the Val70Ub site or, in a flipped binding mode, the BL2 groove. The optimized lead compound, Jun13296, displayed favorable pharmacokinetic properties and potent inhibition of SARS-CoV-2 variants and nirmatrelvir-resistant mutants, and improved survival, reduced lung viral titers, and prevented lung damage in a mouse model of SARS-CoV-2 infection following oral administration. This SAR clearly identifies the Val70Ub/BL2 dual-binding capacity of the 2-aryl-quinoline substituent as a key structural determinant of potency and oral efficacy (Figure 11) [15].

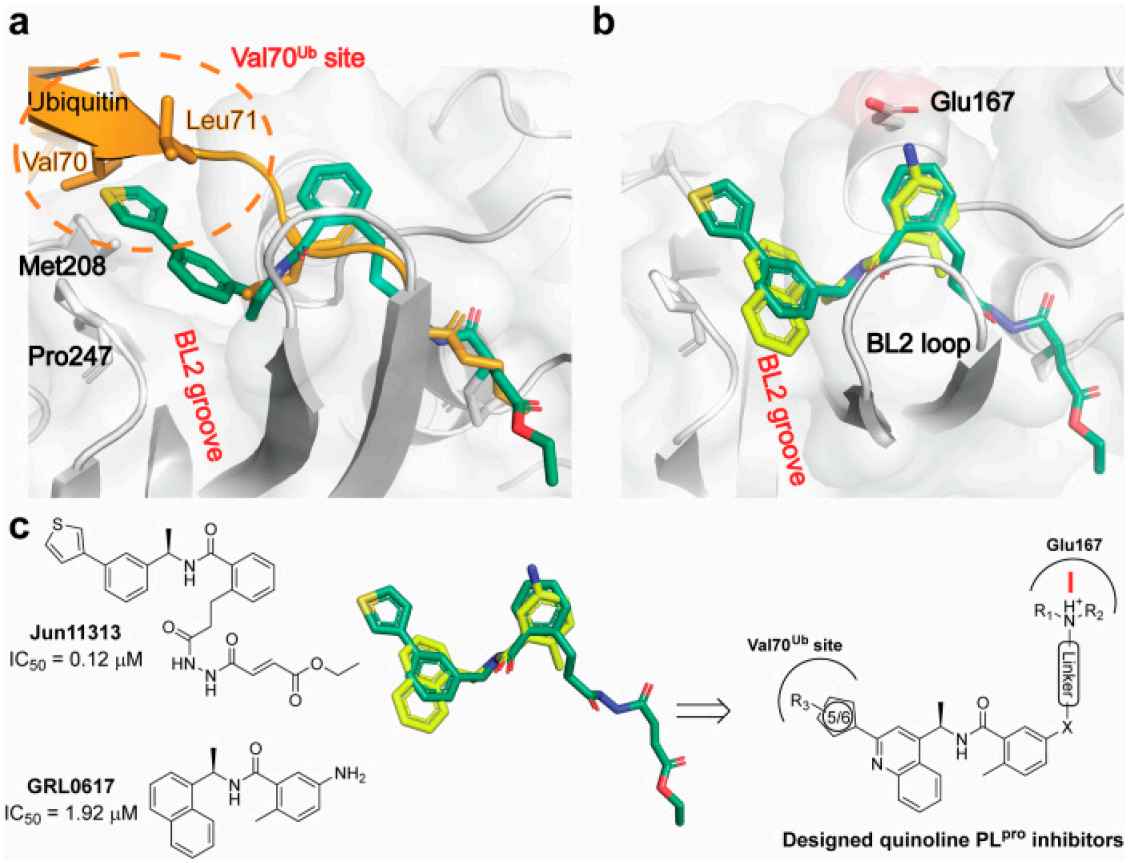
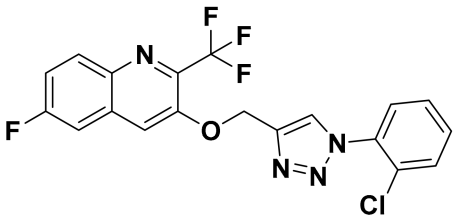


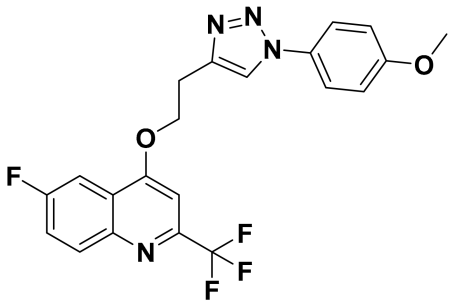
Figure 11. Design of quinoline-based SARS-CoV-2 PLpro inhibitors. (**a**) Superposition of the X-ray crystal structures of SARS-CoV-2 PLpro bound to Jun11313 (green; PDB: 8UVM) and ubiquitin (orange; PDB: 6XAA). (**b**) Superposition of the X-ray crystal structures of SARS-CoV-2 PLpro complexed with Jun11313 (green; PDB: 8UVM) and GRL0617 (yellow; PDB: 7JRN). (**c**) Structure-based design strategy of quinoline-derived PLpro inhibitors inspired by Jun11313 and GRL0617.

Hybridization strategies combining the quinoline core with a 1,2,3-triazole pharmacophore have also yielded promising anti-SARS-CoV-2 candidates. A series of quinoline-triazole conjugates was designed and synthesized via microwave-assisted click chemistry, among which 3-((1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2-(trifluoromethyl)quinoline (**S1**) and 6-fluoro-4-(2-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)ethoxy)-2-(trifluoromethyl)quinoline (**S2**) showed high antiviral potency together with a favorable selectivity index relative to the chloroquine/hydroxychloroquine reference standards [82]. SAR analysis of this series indicates that the nature of the triazole N1-aryl substituent (halogen vs. methoxy) and the length of the linker connecting it to the C-4 position of the trifluoromethylquinoline core are key modulators of both potency and selectivity (Figure 12 and Table 8) [83,84].

These findings show that the antiviral relevance of the quinoline scaffold spans several mechanistic classes, host-directed entry/autophagy modulation (chloroquine-type), direct viral protease inhibition (PLpro inhibitors), and allosteric polymerase inhibition (diaminopurine-quinoline hybrids), reinforcing its status as a versatile platform for antiviral hit-to-lead development, even though this application remains comparatively less mature than the antibacterial or antimalarial uses of the scaffold [85].



3-((1-(2-Chlorophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-6-fluoro-2-(trifluoromethyl)quinoline (S1)



6-Fluoro-4-(2-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)ethoxy)-2-(trifluoromethyl)quinoline (S2)

Figure 12. Promising anti-SARS-CoV-2 candidates.

Table 8. Representative quinoline derivatives with antiviral activity.

Compound	Viral Target	Mechanism	Reported Potency	Ref.
Chloroquine/ hydroxychloroquine	SARS-CoV-1, SARS-CoV-2, HCoV-229E, HCoV-OC43	Blocks post-attachment viral entry; impairs autophagic flux	EC_{50} 0.12–12 μM (panel-wide); SI = 165 vs. HCoV-OC43 in HEL cells (most favorable of the series)	Persoons et al. [82]
Amodiaquine, ferroquine, mefloquine	Alpha-/beta-coronaviruses	Antimalarial quinoline analogues repurposed; entry-stage interference	Potent anti-coronavirus activity (mefloquine cytotoxic)	Persoons et al. [82]
Jun13296 (2-aryl-quinoline)	SARS-CoV-2 papain-like protease (PLpro)	Occupies Val70Ub site/BL2 groove of PLpro	IC_{50} = 0.13 μM (enzymatic), Ki = 8.8 nM, antiviral EC_{50} = 0.1 μM	Jadhav et al. [15]
Quinoline-triazole S1/S2	SARS-CoV-2 (cytopathic effect assay)	Click-chemistry hybrid; mechanism under investigation	S1: IC_{50} = 0.060 mM (60 μM); most potent and selective conjugate of the series S2: IC_{50} = 0.204 mM (204 μM), CC_{50} = 3.493 mM, SI = 17.12	Seliem et al. [82]
Quinoline–2,6-diaminopurine hybrids	Dengue virus (DENV), Zika virus	Allosteric inhibition of NS5 polymerase thumb domain	DENV-2 (EC50 = 2.8 ± 1.0 μm; CC50 = 14.6 ± 7.7 μm) ZIKVE (EC50 = 12.2 ± 6.4 μm; CC50= >122 μm)	Kaptein et al. [85]

(SI = selectivity index, CC_{50}/EC_{50} or IC_{50} ratio).

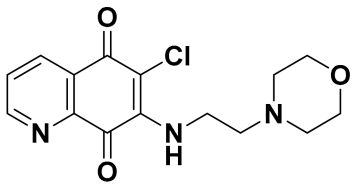
11. Emerging Directions: PROTACs, Kinase Inhibitors, and Multitarget-Directed Ligands

Beyond the well-established therapeutic areas discussed above, the quinoline scaffold has recently been incorporated into several emerging drug-design paradigms that extend its pharmacological relevance beyond classical occupancy-based inhibition: targeted protein degradation, next-generation kinase inhibition, and multitarget-directed ligand (MTDL) design [86–88].

11.1. PROTAC-Based Quinoline Degraders

Proteolysis-targeting chimeras (PROTACs) exploit a bifunctional architecture in which a target-binding warhead is linked, via a chemical linker, to an E3 ubiquitin ligase recruiter, inducing degradation rather than mere inhibition of the target protein [86]. A recent first-in-class example directly employs a quinoline-dione core as the warhead: Dong et al. [87] reported quinoline-dione-derived PROTACs as potent degraders of Cdc25 phosphatases for antitumor therapy, representing one of the first demonstrations that the quinoline

scaffold itself, rather than only quinazoline-based kinase warheads, can serve as an effective degrader component (Figure 13) [88].



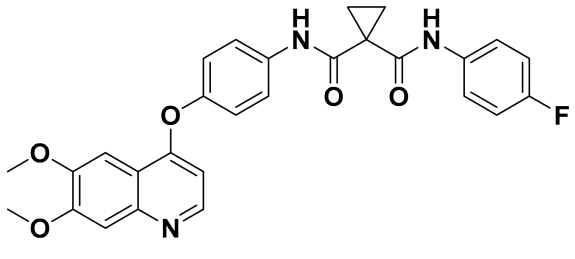
6-Chloro-7-(2-morpholin-4-ylethylamino)quinoline-5,8-dione

Figure 13. Quinoline-dione-derived PROTACs.

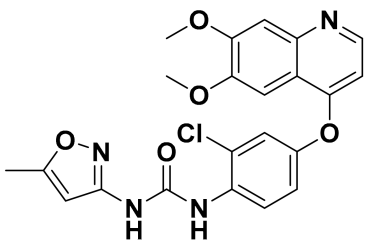
SAR consideration: unlike classical inhibitors, PROTAC potency depends not only on warhead affinity but on ternary complex formation and linker geometry; for quinoline -based warheads derived from established kinase pharmacophores, the hinge-binding nitrogen interaction identified in Section 3 (Table 2) is generally preserved, while the exit vector for linker attachment must avoid disrupting this key hydrogen bond, an emerging structural constraint specific to degrader design that classical SAR optimization does not need to consider.

11.2. Modern Quinoline-Containing Kinase Inhibitors

Building on the EGFR-inhibitor paradigm discussed before, several additional multi-kinase inhibitors bearing a genuine quinoline core have reached clinical use over the past decade. Cabozantinib, an oral inhibitor of VEGFR-2 and c-Met with IC_{50} values of 0.035 nM and 1.3 nM, respectively, is approved for medullary thyroid carcinoma and renal cell carcinoma [89]. Tivozanib, a quinoline-urea derivative and potent VEGFR2 inhibitor, is FDA-approved for third-line treatment of renal cell carcinoma, with its crystal structure showing that the quinoline nitrogen hydrogen-bonds with the hinge residue, while the urea moiety engages the αC-helix glutamate and the DFG-Asp motif characteristic of type-II inhibitor binding (Figure 14) [90].



Cabozantinib



Tivozanib

Figure 14. Structure of Tivozanib and Cabozantinib.

SAR consideration: across this class, the quinoline nitrogen consistently acts as the hinge-binding hydrogen-bond acceptor (as established for fluoroquinolones and EGFR inhibitors in earlier sections), while peripheral substituents and, critically, the choice between a type-I (ATP-pocket-only, e.g., cabozantinib) or type-II (DFG-out-extending, e.g., tivozanib) binding mode determine kinase selectivity across the VEGFR/MET/RET/BTK panel.

11.3. Multitarget-Directed Ligands (MTDLs)

In place of the traditional one-drug-one-target paradigm, quinoline-based MTDLs have been designed to simultaneously engage multiple pathological targets [91]. In neurodegenerative disease, this strategy typically combines acetylcholinesterase inhibition with metal chelation and antioxidant activity, drawing on the same C-8 hydroxyquinoline chelating motif discussed (clioquinol), reflecting the mechanistic overlap between metal dyshomeostasis, oxidative stress, and cholinergic dysfunction in Alzheimer's disease pathology [92]. In oncology, dual kinase/topoisomerase-directed hybrids extend the DNA-intercalating quinoline pharmacophores discussed (camptothecin-type agents) with kinase-inhibitory anilinoquinoline fragments (Figure 15 and Table 9).

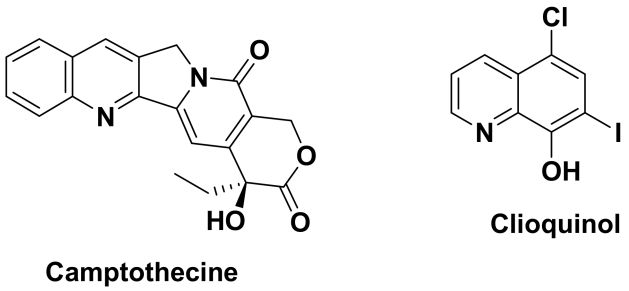


Figure 15. Structure of clioquinol and camptothecin.

Table 9. Emerging quinoline-based therapeutic strategies.

Compound	Target	Mechanism	Reported Potency	Ref.
Cabozantinib (XL184, Cometriq®/Cabometyx®)	VEGFR-2/c-Met/RET/KIT	Type-I ATP-competitive; quinoline N binds hinge region	IC_{50} = 0.035 nM (VEGFR-2); 1.3 nM (c-Met)	[89]
Tivozanib (AV-951, Fotivda®)	VEGFR-2	Type-II (DFG-out) binding; quinoline-urea engages αC-helix Glu and DFG-Asp	Potent VEGFR-2 inhibition; approved 3rd-line RCC	[89]
8-Hydroxyquinoline-based MTDLs	AChE, Cu^{2+}/Zn^{2+}, ROS	Simultaneous acetylcholinesterase inhibition, metal chelation, antioxidant activity, and inhibition of Aβ aggregation	Multi-target activity in the low-micromolar range	[92]
6-chloro-7-(2-morpholin-4-ylethylamino)quinoline-5,8-dione	Cdc25A/Cdc25B2/Cdc25C phosphatases	Mixed competitive inhibition; quinoline-dione core; precursor/warhead structure for later PROTAC degraders	Ki = 29 nM (Cdc25A), 95 nM (Cdc25B2), 89 nM (Cdc25C); 20-fold selective vs. VHR, 450-fold vs. PTP1B	[93]
Camptothecin	DNA Topoisomerase I	Stabilizes the topoisomerase I–DNA cleavable complex via α-hydroxylactone E-ring H-bonding	IC_{50} = 5–100 nM (HCT-116, MCF-7, A549 cell lines)	[94]
Clioquinol	Zn^{2+}/Cu^{2+} chelation; Aβ oligomer assembly	C-8 OH metal-protein-attenuating compound (MPAC); reduces metal-catalyzed ROS and Aβ aggregation	IC_{50} < 10 μM for inhibition of Aβ(1-42) oligomer assembly	[95]

SAR consideration: MTDL design imposes an additional constraint beyond single-target SAR, each pharmacophoric fragment must retain sufficient target engagement while the hybrid molecule remains within acceptable physicochemical (Lipinski-type) space, which in practice limits the size of the linker and often favors fusing rather than merely tethering the two pharmacophores, as is achieved when the quinoline nitrogen itself is shared between the metal-chelating and radical-scavenging functions rather than added as a separate appendage [96,97].

These three emerging directions indicate that the pharmacological relevance of the quinoline scaffold continues to evolve well beyond its classical applications [98,99]. PROTAC-based degradation offers a route to durably overcome the point-mutation resistance mechanisms that recur throughout this review; quinoline-core multi-kinase inhibitors demonstrate that the same hinge-binding chemistry validated for antibacterial

and first-generation anticancer agents can be systematically re-purposed across the kinome through peripheral SAR alone; and MTDL design leverages the scaffold's dual metal-chelating/antioxidant capacity toward multifactorial diseases where single-target inhibition has historically underperformed [100]. Continued innovation in quinoline-based drug discovery is therefore likely to proceed along these three complementary axes, degradation, kinome-wide re-optimization, and polypharmacology, rather than through the discovery of entirely new binding mechanisms.

12. Conclusions

Quinoline derivatives are nitrogen-containing heterocycles valued for their broad range of medicinal applications and their role in treating various diseases. Their structural diversity, along with favorable chemical and physicochemical properties, has made them a scaffold of choice for developing new therapeutic agents.

This review has covered the evolution of synthetic strategies toward quinoline derivatives, from classical condensation-based routes, the Skraup, Doebner, Conrad–Limpach, Combes, Povarov, and Riehm syntheses, to more sustainable modern approaches such as microwave and ultrasound-assisted protocols, solvent-free reactions, photocatalytic methods, and nanocatalyst-mediated transformations. These methods have improved reaction efficiency and yields, reduced environmental impact, and given access to a wider range of quinoline scaffolds for biological testing.

From malaria to cancer and beyond, quinoline derivatives remain an active area of drug discovery, involving both the optimization of known scaffolds and the design of new hybrids acting through different mechanisms. We have grounded this discussion in the primary literature, covering bioactivity data, mechanistic detail, and structure-activity relationships across the antibacterial, anticancer, anti-inflammatory, antimalarial, antiparasitic, antitubercular, antioxidant, and antiviral domains, as well as the more recent directions discussed in Section (PROTACs, kinase inhibitors, and multitarget-directed ligands).

Progress in synthetic methodology, together with a clearer picture of how quinoline derivatives interact with their biological targets, keeps this scaffold relevant to drug discovery. Its continued use alongside computational design tools suggests it will remain part of therapeutic development for some time to come.

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