

Fig. 3 Chemical structure of biologically active compounds containing 4-quinolone scaffold.

infections such as hepatitis, HIV, and herpes.⁵ Quinolone and its derivatives exhibit a potential antimicrobial agent that acts as therapy for many infections with broad-spectrum properties.

The comment examples with the quinolone scaffold are as follows (Fig. 3).



Fig. 4 Chemical structure of 7-chloro-1,4-dihydro-1-ethyl-4-oxoquinolone-3-carboxylic acid and nalidixic acid.

2. Structural and historical background of 4-quinolone

In 1962, Lesher and coworkers showed that 7-chloro-1,4-dihydro-1-ethyl-4-oxoquinolone-3-carboxylic acid **2a**, obtained as an impurity during the synthesis of chloroquine, possessed antibacterial activity (Fig. 4).¹⁰

Consequently, various derivatives of the title compound were synthesized and evaluated owing to their antibacterial activities. For instance, nalidixic acid **2b** is one of the oldest quinolone



Fig. 5 Structural-activity relationship (SAR) of 4-quinolone derivatives.



derivatives used as an antibiotic to treat urinary tract infections.⁴ Currently, 4-quinolone derivatives used as antibacterial agents are halogenated at the 6-position, and some are halogenated at position 8. Thus, by modifying the chemical structure of the 4-quinolone scaffold, the action or potency of the compound can be altered. The quinolone scaffold can be structurally modified using various substituents by introducing it at various sites of the skeleton. The chemical modifications on the quinolone scaffold at the N-1, C-2, C-3, C-5, C-6, C-7, and C-8 positions have resulted in molecules that boost the physical, chemical, pharmacokinetic, and pharmacological properties.⁹ The substituents and their positions improve the properties of the biological activities of 4-quinolone and its derivatives (Fig. 5).

In the past few years, efficient, various new, convenient with broad scope synthetic approaches towards the title compound and its derivatives have been designed and developed to prepare diverse quinolone-based scaffolds. In this review, we summarize recent advancements in the synthesis of 4-quinolones and their derivatives as well as the pharmacological potential properties of the drug with the scaffold of the title compound. The reactions discussed in this review were selected owing to their high yield, relative simplicity to conduct and highly selective catalytic processes under mild reaction conditions. This review is divided into two sections: general catalytic synthesis and post modification of the scaffold.

3. Development of the syntheses of 4-quinolone and its derivatives

Because of their broad spectrum of antibacterial, antimalarial, antiviral, antifungal, and anti-cancer activities, quinolones and their derivatives are an omnipotent class of drugs. An update in the syntheses of 4-quinolone and its derivatives *via* selectivity of functionalization at a specified position on the scaffold is an interesting field of research planned to enhance their bioactivities. Generally, there are various methods for synthesizing title scaffolds. Herein, metal-free or green synthesis, metal-catalyzed synthesis, and post-functionalization at various positions of the skeleton are discussed briefly.

3.1 Metal-free 4-quinolone synthesis

To date, various synthesis protocols have been reported in the literature for preparing 4-quinolone and its derivatives. Among them, the metal free synthesis method has attracted the interest

of various researchers owing to its simplicity, low cost, and non-hazardous materials.

3.1.1 Synthesis of *N*-substituted 4-quinolone. Fu and coworkers reported a convenient and efficient method through the selective cleavage of aromatic carbon–oxygen (C–O) bonds under metal free and in the presence of a base to afford 4-quinolone derivatives in moderate yield (Scheme 1).¹¹ However, the cleavage of aromatic C–O bonds is extremely difficult because of their energy requirements. The synthesis of *N*-substituted-4-quinolone **4** was accomplished *via* the cleavage of aromatic C–O from the O-methoxy group, followed by condensation of aldehyde derivatives **3** with a primary amine in the presence of K₂CO₃ base and DMSO solvent under inert conditions to generate an imine intermediate, which is subjected to intramolecular aromatic nucleophilic substitution to afford the *N*-substituted-4-quinolone derivatives **4**.¹¹

Through a tandem fashion amination followed by conjugated Michael addition reaction under a free catalyst, Zhao and coworkers reported functionalized *N*-substituted-4-quinolone derivatives **6** (Scheme 2) under high temperature and an inert atmosphere.¹² Aliphatic amines afford the target product a good to excellent yield. The electron-withdrawing group substituents, such as –NO₂ or –F, at the ynone **5** moiety participated in the reaction smoothly.¹²

Janni and coworkers disclosed a new metal-free protocol to prepare fused heterocycle quinolone derivatives **8** from single *S,N*-acetal precursors **7** through double hetero-annulation under basic conditions (Scheme 3).¹³ Furthermore, the resulting quinolones **8** are transformed into fused heterocycles upon C–S and C–O coupling reactions under radical and metal-mediated conditions, respectively. It has been observed that the corresponding products from the substituted aniline nitrogen atom of *S,N*-acetals bear both electron-withdrawing and electron releasing groups synthesized in moderate to excellent yields. Unfortunately, aliphatic amino *S,N*-acetals exhibited poor yield.

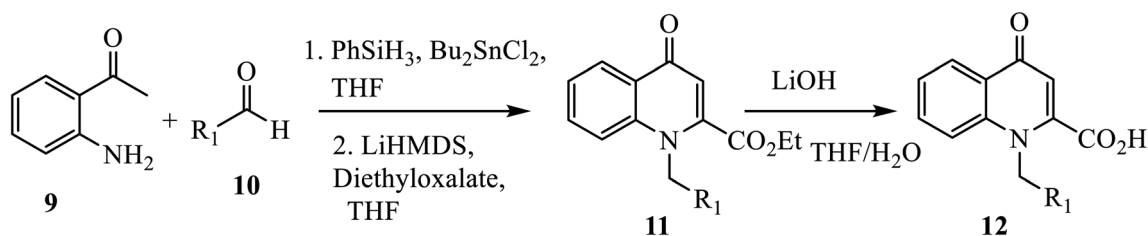


Scheme 2 Synthesis of functionalized *N*-substituted-4-quinolone derivatives.



Scheme 1 Synthesis of *N*-substituted-4-quinolone derivatives *via* cleavage of aromatic C–O bonds.



Scheme 3 Synthesis of 4-quinolone derivative **8** using KO^tBu.Scheme 4 Synthesis of 4-quinolone derivative **12** using LiHMDS-induced cyclo-condensation.

An efficient strategy based on direct reductive amination, followed by LiHMDS-induced *in situ* cyclo-condensation of aminoacetophenone **9** and aldehyde derivative **10**, was reported for the synthesis of *N*-substituted 2-carboxy-4-quinolones **12** (Scheme 4).¹⁴ Treatment of 2'-aminoacetophenone **9** and aldehyde **10** with phenyl silane (PhSiH₃)/dibutyltin dichloride (Bu₂SnCl₂), followed by *in situ* cyclo-condensation in the presence of LiHMDS, affords ester **11** in a very good yield under reflux. Further, the hydrolysis of ester **11** gave the corresponding acid **12** in moderate to good yield with a broad scope.

3.1.2 Synthesis of 2-substituted 4-quinolone. Zewge and coworkers reported a very mild, efficient and scalable method for the synthesis of 4-quinolone derivative **15** from aniline **13** using an inexpensive and commercially available Eaton's reagent under mild conditions (Scheme 5).¹⁵ Broad scopes of functionalized anilines participate and afford the target product in very good to excellent yields.

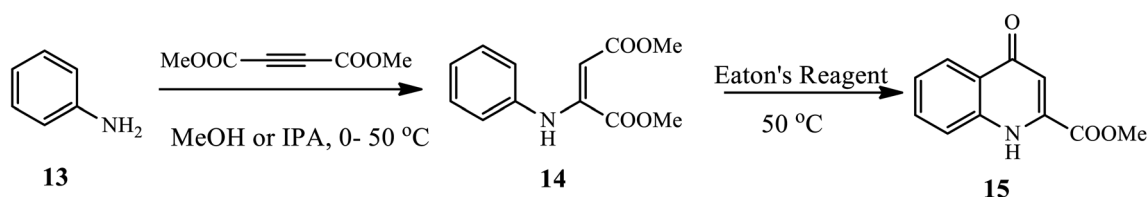
Duarte's group reported a microwave-assisted synthesis of various substituted 2-methyl-4-quinolone derivatives **18** in a one-step reaction procedure. Here, using electron-rich aniline **16** and ethyl acetoacetate **17** in the presence of diphenyl ether as a solvent under reflux at very high temperatures afforded the target compound in good yields. Anilines substituted with electron-donating groups afforded the required 4-quinolones **18** in a good yield. However, using the same procedure with

electron withdrawing substituents *N,N'*-diarylureas was afforded in moderate to good yields.¹⁶ Similarly, an efficient microwave-assisted procedure for the synthesis of ethyl-quinolone-4-one-3-carboxylates **21** from *p*-substituted aniline **19** and diethyl-ethoxymethylenemalonate **20** in the presence of diphenyl ether at 80 °C under MW irradiation was reported by Malvacio and coworkers (Scheme 6).¹⁷ Further, the quinolone obtained after hydrolysis under MW irradiation furnished the corresponding quinolone-4-one-3-carboxylic acids **22** in very good to excellent yields. The advantage of this procedure is that it works for a wide substrate scope, and this route offers the benefits of a very short reaction time and relatively good yield.

In 2015, Hu *et al.* designed a straight forward method for the synthesis of numerous 2-aryl-4-quinolone derivatives **23** from *N*-aryl methyl-2-aminophenyl ketones **23a** through a metal-free oxidative intramolecular oxidative Mannich reaction, followed by C(sp³)-H/C(sp³)-H coupling and aromatization using TEMPO as an oxidant and KO^tBu as the base (Scheme 7).¹⁸

The above reaction between secondary amine and ketone derivatives was developed simply and directly to afford the title compound and its derivatives with a broad scope. This reaction is further described using a plausible mechanism (Scheme 8).

In 2016, Wright *et al.* established the insertion of arynes **24** into acyclic imides and anhydrides **25** to afford aryl ketoamides **26** under mild conditions in the presence of TBAT, which was

Scheme 5 Synthesis of 4-quinolone-2-carboxylic acid **15** using Eaton's reagent.



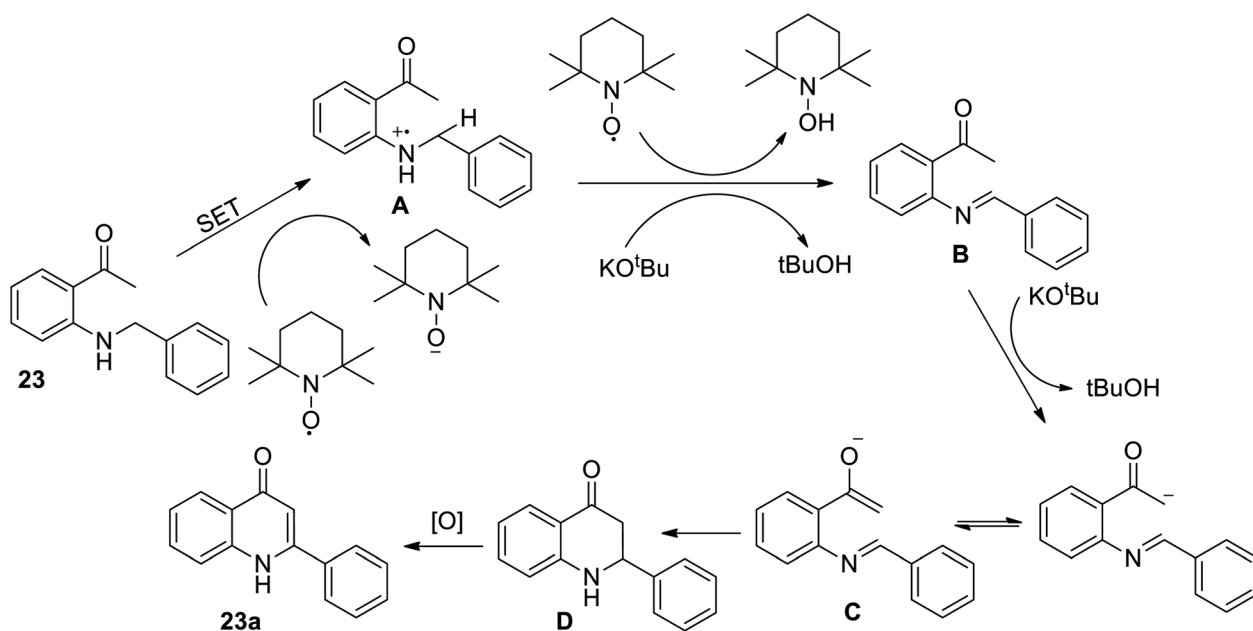
Scheme 6 Microwave-assisted synthesis of 4-quinolone derivatives.

Scheme 7 TEMPO catalyzed intramolecular tandem oxidative C(sp³)-H/C(sp³)-H coupling.

then cyclized through base-initiated camp cyclization to provide quinolones 27 in a moderate to good yield (Scheme 9).¹⁹ However, electron withdrawing substituents, such as F, failed to afford aryl ketoamide.

Later on, in 2018, Xu and coworkers presented the synthesis of 2-methyl-thioquinolin-4(1*H*)-ones as an antibacterial agent

via free radical reaction. The nucleophilic reaction of acetoacetanilide 28 with carbon bisulfide in the presence of K₂CO₃ following methylation with dimethyl sulfate forms the intermediate (bis(methylthio)methylene)-3-oxo-*N*-phenylbutanamide 29, which was then cyclized thermally to yield compound 30 in the presence of *o*-dichlorobenzene. Further,



Scheme 8 Proposed mechanism for metal free promoted oxidative annulation.





Scheme 9 Camp cyclization of ketoamide insertion products to provide quinolones.



Scheme 10 Synthesis of sulfur-containing 4-quinolone by free-radical reaction.

upon hydrolysis in 50% sulfuric acid and oxidation using hydrogen peroxide in AcOH, the 2-methylthio of quinolone **30** was converted to compounds **31** and **32** (Scheme 10).²⁰

3.1.3 Synthesis of 3-substituted 4-quinolone. A phosphino-catalysis approach toward the synthesis of several 3-aryl-4-quinolones **35** and methyl-4-quinolone-3-carboxylate esters **36** from *S*-phenyl-2-(*N*-tosylamido) benzothioates **33** and activated alkynes **34** under microwave irradiation at 82 °C for 2 h was reported by Khong and Kwon (Scheme 11).²¹ The method provides moderate to very good yields for both electron rich and electron withdrawing substituents containing starting materials. However, the electron deficient aromatic ring resulted in a lower yield compared to the electron-rich aromatic rings.

In 2016, Zhou and coworkers reported a novel one-pot metal free protocol for the synthesis of sulfone-containing 4-quinolones upon radical oxidative cyclization of *o*-azidoaryl acetylenic

ketones **37** and sulfinic acids **38** in the presence of radical initiators (TBHP) at 80 °C under Ar for 0.5 h affording phenyl-3-(phenylsulfonyl) quinolin-4(1*H*)-one **39** (Scheme 12).²² Both electron-donating and electron-withdrawing groups on the aromatic ring produced the corresponding phenyl-3-(phenylsulfonyl) quinolin-4(1*H*)-one **39** in good to excellent yields. However, the reaction was influenced by the steric effect, and aliphatic sulfinic acid, such as methanesulfinic acid, failed to produce the desired 4-quinolone.

Novel water-soluble antiproliferative agents, 4-quinolones **42**, were synthesized by Zhang's group (Scheme 13).²³ Heating aniline **13** with ethoxy methylene malonic ester **40** at 100 °C afforded Schiff bases **41**, which was then cyclized to ethyl 4(1*H*)-quinolone-3-carboxylates **42** using diphenyl ether under reflux conditions.



Scheme 11 Triphenylphosphine-catalyzed synthesis of 4-quinolone derivatives.

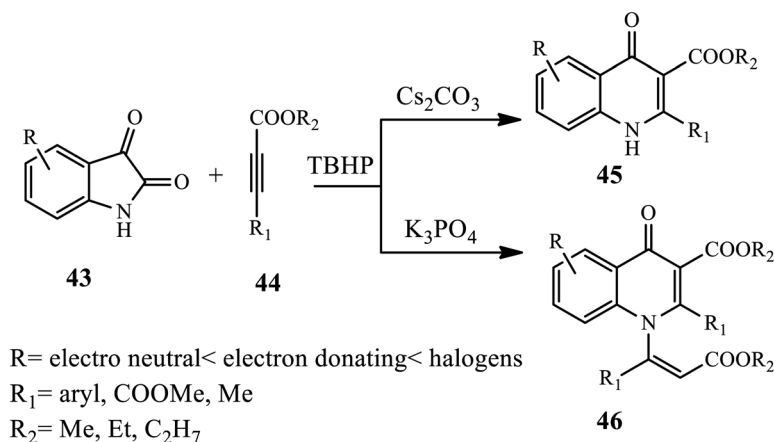




Scheme 12 Metal-free synthesis of sulfone containing 4-quinolones.



Scheme 13 Synthesis of 4-quinolone using diphenyl ether.



Scheme 14 Synthesis of 4-quinolones through transition-metal-free oxidative cyclization.

In 2018, Jiang and coworkers developed an efficient transition-metal-free oxidative cyclization reaction for the synthesis of 3-carboxylate-4-quinolones **45** and 1-vinyl-3-carboxylate-4-quinolone **46** using isatins **43** and alkynes **44** in the presence of DMSO solvent, Cs_2CO_3 base, and TBHP as an oxidant, while in the case of 1-vinyl-3-carboxylate-4-quinolones,

K_3PO_4 was used as a base. The authors examined various substrate effects, including electron-neutral, electron-donating and electron withdrawing substituted isatins, which provided excellent yields of the desired product (Scheme 14).²⁴

Recently, 3-cyano 4-quinolone derivatives **49** were synthesized in good to excellent yields upon DABCO-mediated



Scheme 15 Synthesis of 4-quinolone via one-pot DABCO-mediated decarboxylative cyclization.



decarboxylative cyclization of isatoic anhydrides **47** with active methylene groups **48**, such as aroyl/heteroaryl/alkoylacetonitriles, in CH₃CN under microwave irradiation at 80 °C for 30 min. Further, this method provides mild reaction conditions and a short reaction time compatible with a wide substrate scope (Scheme 15).²⁵

3.1.4 Synthesis of di-substituted 4-quinolone. In 2017, Chen's group successfully synthesized 4-quinolone derivatives **51** in one pot using a tandem procedure in good to excellent yields (Scheme 16).²⁶ An intermolecular nucleophilic addition of various amines to (*Z*)-β-chlorovinyl ketones **50** followed by elimination of chlorine anion gives *Z*-enamine intermediates, which can be transformed to 4-quinolones **51** through intramolecular S_NAr reaction in the presence of a base (Cs₂CO₃) in DMSO at 140 °C. Various substitution patterns and functionalities (such as Me, *t*-Bu, MeO, F, and Cl) are applicable and tolerated in this protocol. Interestingly, the dihalo-substituted ketone substrates converted to the corresponding quinolones in very good yields.

In 2018, Bandatmakuru and Arava reported a direct procedure for the synthesis of *N*-functionalized 4-quinolones **54** and

1,2-substituted 4-quinolones **53** from 2-aminoacetophenones **52**. Various 2-aminoacetophenone derivatives **52** were transformed into the corresponding 4-quinolones **54** and 1,2-substituted 4-quinolones **53** upon refluxing with benzoyl chloride in TEA and with PTSA in DMFDMA, respectively. The authors examined various substrate effects, including electron-donating/electron-withdrawing groups on the phenyl ring, *ortho*-, *meta*- and *para*-substituted aminoacetophenones, along with *N*-alkyl and *N*-aryl aminoacetophenones that can be successfully transformed into the corresponding 4-quinolones in good yields (Scheme 17).²⁷

3.1.5 Synthesis of tri-substituted 4-quinolone. Dave and Joshipura reported a microwave-assisted protocol for the synthesis of 4-quinolone by the condensation of aromatic amines **55** with diethyl ethoxy methylene malonates **56**, giving an intermediate **57** cyclized to 4-quinolones **58** at 2–14 min in good to excellent yield (Scheme 18).²⁸ Recently, Liu and co-worker developed a one-step tandem Michael addition/Smiles rearrangement/*N*-arylation reaction for the synthesis of 1,2,3-trisubstituted 4-quinolones **61** between ynone **59** and sulfonamide **60** under transition-metal free conditions.²⁹ The author



Scheme 16 Synthesis of 4-quinolone through nucleophilic addition–elimination–S_NA reaction.



Scheme 17 Synthesis of *N*-functionalized 4-quinolone and 1,2-substituted 4-quinolones.



Scheme 18 Synthesis of tri-substituted 4-quinolone under microwave assistance.





Scheme 19 Synthesis of 1,2,3-trisubstituted 4-quinolone derivatives.

examined various substrate scopes and functional groups tolerated to give good to excellent yields.

Similarly, Xie *et al.* recently synthesized tri-substituted 4-quinolone derivatives **64** *via* a cascade reaction of Michael addition and Truce–Smiles rearrangement between benzene-sulfonamide derivatives **62** and 1-(2-bromophenyl)-3-phenyl prop-2-yn-1-ones **63** in the presence of K_2CO_3 in DMF at 100°C in excellent yield (Scheme 19).³⁰

3.2 Transition metal-catalyzed synthesis of 4-quinolone

Over the last decade, the metal-catalyzed synthesis of 4-quinolones has become increasingly relevant in organic processes. As catalysts, various transition-metal complexes, including those of Pd, Cu, Co, Au, Ni, and Rh, have been utilized. Transition-metal-based catalysts are essential for achieving a wide range of beneficial chemical transformations that would otherwise be difficult or impossible to achieve.³¹

3.2.1 Palladium-catalyzed synthesis. In 2010, Zhao and coworkers reported the palladium-catalyzed synthesis of *N*-aryl-4-quinolones **67** from *o*-haloaryl acetylenic ketones **65** and primary amines **66** in PPh_3 as a ligand, K_2CO_3 as a base and dioxane as a solvent. Numerous electronically and structurally varied aromatic amines participated well under the optimized conditions to provide the desired product in moderate to good yields. Similarly, Shao's group developed a palladium-catalyzed synthesis of *N*-alkyl-substituted 4-quinolones **68** using *o*-

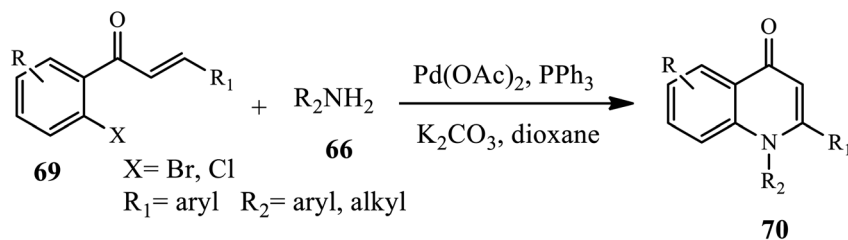
chloroaryl acetylenic ketones **65** and various alkyl amines **66** in the presence of K_3PO_4 in DMSO at 140°C in good to excellent yields (Scheme 20).^{12a,b}

An efficient palladium-catalyzed one-pot synthesis of 1,2-disubstituted 4-quinolones **70** was developed by Fei and coworkers through Buchwald–Hartwig coupling, followed by Michael addition reaction of chalcone **69** and primary amines **66** under PPh_3 as a ligand in anhydrous dioxane with K_2CO_3 as the base. Both aromatic and aliphatic amines gave rise to 4-quinolones in moderate to high yields except for a chloro-substituted substrate that gives low yields of product because of the poor reactivity of the C–Cl bond during the oxidative addition step. Further, arylamines containing electron-donating groups gave higher yields than those with electron-withdrawing groups (Scheme 21).³²

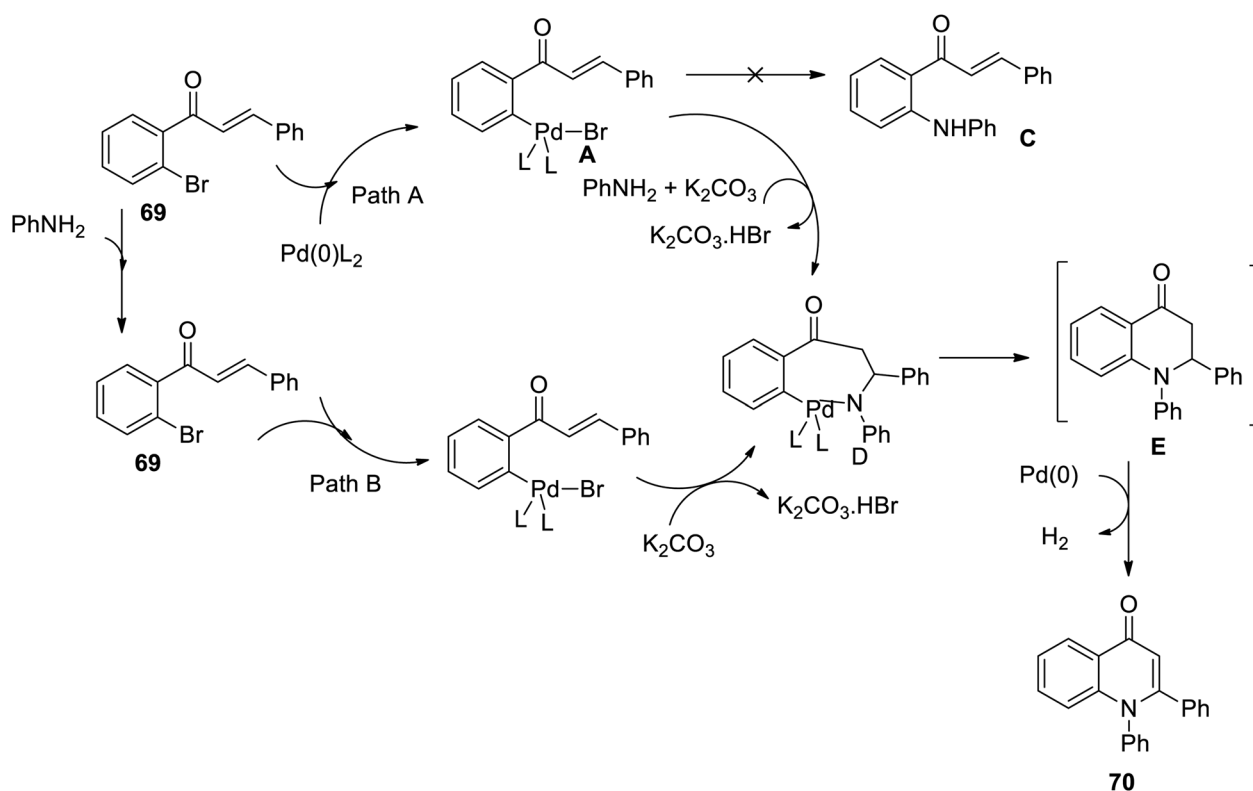
The Buchwald–Hartwig coupling followed by the Michael addition reaction has been successfully applied and reported for the synthesis of functionalized 1,2-disubstituted 4-quinolone derivatives using $\text{Pd}(\text{OAc})_2$ as a catalyst and PPh_3 as a ligand. Under these conditions, the intermediate products first formed from chalcones and primary amines underwent catalytic dehydrogenation to afford the 1,2-disubstituted 4-quinolone derivative.

A plausible reaction mechanism for the one-pot synthesis of 1,2-disubstituted 4-quinolones is outlined in Scheme 22 (Paths A and B).³² In Path A, the oxidative addition of **69a** to the palladium zero catalyst leads to palladium complex **A**. The

Scheme 20 Synthesis of *N*-functionalized 4-quinolones *via* palladium-catalyzed synthesis.



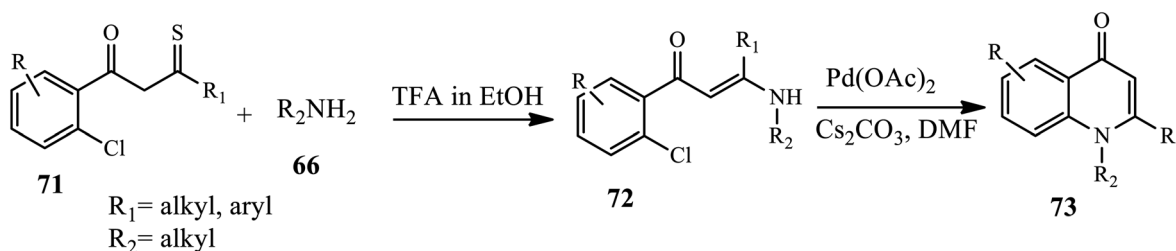
Scheme 21 Synthesis of 1,2-disubstituted 4-quinolones through Buchwald–Hartwig Coupling.



Scheme 22 Plausible mechanism for the synthesis of 4-quinolone derivative 70.

carbon–carbon double bond in **A** can be activated through coordination to Pd(II) and attacked by aniline to form intermediate **D**. In the course of the reaction, intermediate **C** was not formed from complex **A** under these reaction conditions. Path **B** involves the Michael addition of aniline to **69a** and oxidative addition, and then intermediate **D** is formed by eliminating HBr.³²

Vinayaka groups synthesized 1,2-disubstituted 4-quinolone derivative **73** starting from monothiodiketone substrate **71** and arylamine **66** in the presence of TFA in ethanol through the formation of an intermediate **72**, which is further subjected to Pd(OAc)₂ catalyst in the presence of Cs₂CO₃ as a base cyclized to afford **73** (Scheme 23).³³



Scheme 23 Synthesis of 1,2-disubstituted 4-quinolones via Pd-catalyzed.



Scheme 24 Synthesis of 4-quinolone *via* carbonylative Sonogashira coupling/cyclization.

Scheme 25 Synthesis of 1,2-disubstituted 4-quinolone derivative through palladium-catalyzed.

3.2.2 Sonogashira coupling. 4-Quinolone derivative **76**, which is the key substructure of protease inhibitor BILN 2061, was synthesized and reported through carbonylative Sonogashira coupling, followed by cyclization of 2-iodo-5-methoxyaniline derivative **74** with thiazolylacetylene **75** in the presence of $\text{PdCl}_2(\text{dppf})$ as the catalyst in a good yield (Scheme 24).³⁴

In 2017, 1,2 di-substituted 4-quinolone derivatives **79** were synthesized *via* palladium-catalyzed oxidative carbonylation by Wu and coworkers. In this reaction, various amines **77** and ketones **78** were reacted using carbon monoxide as a carbonyl source at atmospheric pressure in the presence of $\text{Pd}(\text{dba})_2$ and $\text{CuBr}(\text{Me}_2\text{S})$. Substituted ketones with electron-rich groups afford the corresponding 4-quinolone derivative in good yields. Interestingly, halogen substituents participated smoothly, affording the desired products in moderate to good yields (Scheme 25).³⁵

A CO gas free synthesis of 4-quinolone **82** *via* carbonylative Sonogashira annulation sequence in the presence of a Pd-NHC catalyst was reported by Ghosh and coworkers (Scheme 26).³⁶ The reaction occurred between substituted 2-iodoanilines **80** and various acetylenes **81** using Pd-NHC as a catalyst and $\text{Mo}(\text{CO})_6$ as a source of CO at 95 °C under N_2 . The authors observed a slight decrease in the yield of the final products

when an electron-withdrawing group is present in the phenylacetylene moiety, whereas, in the presence of electron-donating groups, the products were obtained in good to excellent yields. The absence of toxic CO gas, lower catalyst loading and use of inexpensive salt are the advantages of this approach over others.

3.2.3 Copper-catalyzed synthesis. Jones and coworkers established a two-step method, Cu-catalyzed amidation followed by base-promoted camp cyclization for the synthesis of 2,3-substituted 4-quinolones **86** (Scheme 27).³⁷ Cu-catalyzed amidation of 2-halophenones **83** with amide derivatives **84** afforded *N*-(2-ketoaryl) amides intermediate **85**, which then underwent base-catalyzed Camps cyclization at 110 °C to form the desired product in good to excellent yields. The 2-halophenones bearing both electron-withdrawing and electron-donating groups, both aryl and alkyl vinyl amides, were well tolerated in good yields. Unfortunately, acyclic secondary amides were ineffective coupling partners.

The Cu-catalyzed intermolecular cyclization protocol for the synthesis of 4-quinolones **91** was investigated by Zhang and Xu (Scheme 28).³⁸ Heating secondary anilines **89** with alkynes **90** using CuI as a catalyst, HOTf and Ti_2O as additives and DCE as solvent at 120 °C for 12 h formed the target compound in good yields. Similarly, under the same conditions, this group reported the construction of 4-quinolone **89** from primary



Scheme 26 Synthesis of 4-quinolone by palladium-catalyzed carbonylative Sonogashira.





Scheme 30 Synthesis of thiochromenoquinolinone through Cu-catalyzed.



Scheme 31 Cobalt-catalyzed C–H amidation for the synthesis of 4-quinolone derivatives.

(30a). The authors used Co(III)-catalyzed C–H bond functionalization of enaminones as a coordinating directing group to promote the C–H amidation of a series of arenes in the presence of $\text{CpCo}(\text{CO})\text{I}_2$, KOAc and AgSbF_6 in 1,4-dioxane solvent (Scheme 31).⁴¹ This procedure was found to be suitable for enaminones bearing electron donating, withdrawing or halogen groups generally coupled under cobalt-catalyzed conditions in excellent yields.

Similarly, Shi *et al.* synthesized 7-substituted 4-quinolones **103** from (*E*)-3-dimethylamino-1-phenyl prop-2-en-1-one **100** and 3-ethyl-1,4,2-oxazole-5-one **102** using $[\text{CpCo}(\text{CO})_2]$ as a catalyst, AgBF_4 as an additive, and DCE as a reaction medium, which was then deacetylated by refluxing in HCl or by treating with trimethylsilyl trifluoromethane sulfonate (TMSOTf), thereby generating a free amino group, which in turn undergoes nucleophilic attack at the alkene moiety of enaminone to afford a diverse range of quinolone derivatives (30b). The authors claim that substituent effects, such as *para*-, *meta*-, and *ortho*-substituted enaminone carrying both electron donating and electron withdrawing groups at different positions of the phenyl ring, also reacted smoothly under the procedural reaction conditions.⁴²

3.2.5 Gold catalyst. Gold-catalyzed cyclization of alkyl- or aryl-substituted 1-(aminophenyl)-2-propyn-1-ones **104** towards the synthesis of the corresponding 2-substituted 4-quinolones **105** was reported by Helaja and coworkers (Scheme 32).⁴³ Various substrates, including both electron-withdrawing and

donating substituents and straight chain alkyl substrates, were cyclized in good to excellent yields. However, TMS-protected substrates failed to be cyclized.

Wu *et al.* reported the synthesis of 1,2-disubstituted-4-quinolone **107** via gold-catalyzed cyclization of 1-(2'-azidoaryl) propynols **106** in the presence of John Phos AuNTf_2 and DCE at 65 °C under N_2 (Scheme 33).⁴⁴ The authors found that the yield

Scheme 32 Gold-catalyzed synthesis of 4-quinolone **105**.Scheme 33 Gold-catalyzed synthesis of 1,2-disubstituted 4-quinolone derivative **107**.



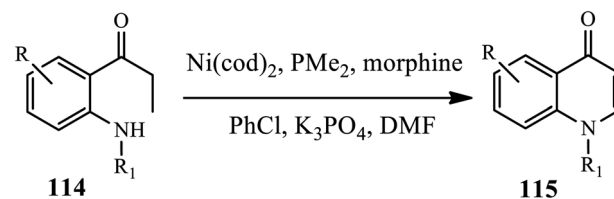
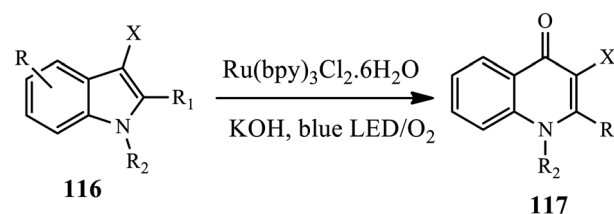
Scheme 34 Gold(III)-catalyzed synthesis of 3-alkoxy-4-quinolone.

of the product increased when different aryl or alkyl substituents were adjacent to the carbon-carbon triple bond. Additionally, the presence of electron-donating or electron-withdrawing groups on the azido-substituted phenyl ring led to the generation of the desired products in good yields except for benzo^{1,3} dioxolyl-substituted propynol, which gave a relatively lower yield.

A straightforward method for the synthesis of 3-alkoxy-4-quinolone **110** derivatives *via* a gold-catalyzed 6-*endo-dig* azide-yne cyclization, followed by an intermolecular O-H insertion cascade reaction of *o*-azidoacetylenic ketones **108** with alcohols **109** at room temperature under an argon atmosphere, was described by Huang's group (Scheme 34).⁴⁵ In this method, both electron-donating and electroneutral halides were cyclized in good yields, whereas 8-methyl substituted substrate and alkyne tethered with electron-deficient aryl group gave the cyclized product in lower yields.

3.2.6 Nickel catalyst. Yoshino and coworkers disclosed a Ni-catalyzed protocol for the synthesis of polysubstituted 4-quinolones **113** (Scheme 35).⁴⁶ The reaction occurred between alkynes **111** and isotonic anhydrides **112** in the presence of Ni(cod)₂, PCy₃, and toluene at 80 °C for 24 h in excellent yields. Decarboxylative carboamination was proposed to be initiated by the oxidative addition of an anhydride O-CO bond to Ni. Then, a Ni(II) intermediate was formed *via* subsequent decarboxylation and coordination by the alkyne. After insertion by an alkyne into the acyl Ni bond, a nickel cycle species was obtained. The nickel cycle intermediate then underwent reductive elimination to form the desired product along with the formation of Ni(0). Various alkyl- and aryl-substituted alkynes are well tolerated in this protocol.

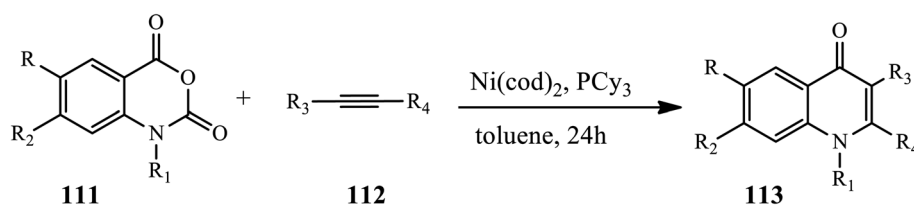
Another (Ni)-catalyzed synthesis of 4-quinolones **115** through the intramolecular amination of *o*-(*N*-alkylamino) propiophenones **114** was developed by Ueno and coworkers (Scheme 36).⁴⁷ The Ni(0) catalyst reacts with propiophenones to form a C-bound Ni enolate, yielding a β-unsaturated ketone

Scheme 36 Nickel(0) catalyzed synthesis of 4-quinolones from *o*-(*N*-alkylamino) propiophenones.Scheme 37 Synthesis of 4-quinolones *via* photocatalysis using ruthenium catalysis.

through β-hydride elimination. This is followed by a 1,4-addition of the morpholine catalyst to give a β-aminoketone intermediate. Then, the β-aminoketone is transformed into β-enaminone through the formation of Ni enolate and ensuing elimination. Subsequently, the addition of an intramolecular conjugate followed by β-elimination of morpholine reaction yields the 4-quinolone derivatives in good yields.

3.2.7 Other metal-catalyzed synthesis of 4-quinolone. A one-pot method for the synthesis of 4-quinolones **117** from indoles (*N*-methylindole) **116** in the presence of a Ru catalyst was developed by Ji group in 2018 (Scheme 37).⁴⁸ This method involves the photocatalytically aerobic oxidation of indoles with a blue LED light and subsequent base-promoted Camps cyclization in the presence of Ru(bpy)₃Cl₂·6H₂O catalyst at room temperature, affording the desired product in moderate to high yield. In this reaction, various *N*-substituted-3-methylindoles bearing *N*-ethyl, *N*-benzyl, and *N*-allyl provide corresponding 4-quinolone products in moderate to good yields. Unfortunately, *N*-H indole and *N*-Ts indole were found to be ineffective substrates for this reaction.

In 2020, Shi and coworkers reported a condition-controlled divergent synthesis strategy for constructing 1,2,3 trisubstituted 4-quinolones **120** (Scheme 38).⁴⁹ A C-H activation of *N*-nitrosoaniline **118** and diphenylcyclopropenone **119** in the presence of AgNTf₂ and [RhCp(OAc)₂]₂ catalysts in 4 AMS at



Scheme 35 Nickel-catalyzed 4-quinolone synthesis.





Scheme 38 Synthesis of 1,2,3 tri-substituted 4-quinolones by C–H activation.



Scheme 39 Synthesis of 4-quinolone derivatives using iron(III) catalyzed reactions.

120 °C afforded the corresponding quinolones after 24 h in good yields. Broad substrate scope, mild reaction conditions, high functional group tolerance and amenability to gram-scale synthesis are the characteristics of this protocol.

The synthesis of 4-quinolone derivative **122** from arylaminoacrylate **121** through a Conrad–Limpach reaction in the presence of a catalytic amount of iron(III) phosphate under refluxing conditions was reported by Samadi *et al.* (Scheme 39a).⁷⁹ The reaction was carried out in toluene, ethanol, chloroform and acetonitrile solvents; with the standard reaction protocol, no product was observed. However, when the reaction was carried out in diphenyl ether solvent at room and high temperature, a high yield of product was observed. The reaction affords a good-to-excellent yield.

Similarly, Lee and coworkers demonstrated the synthesis of 4-quinolones *via* the iron(III)-catalyzed oxidative coupling of alcohol/methyl arene **124** with 2-amino phenyl ketone **123**. Initially, alcohols and methyl arenes are oxidized to aldehyde in the presence of an iron catalyst and di-*tert*-butyl peroxide, followed by a tandem process condensed with amine/Mannich-type cyclization/oxidation, to complete the 4-quinolone ring **125** (Scheme 39b).⁸⁰ This method tolerates various functional groups and provides a direct approach for synthesizing 4-quinolones from less functionalized substrates.

In 2016, Jousset and coworkers described a one-pot synthesis of 3-substituted-4-quinolones **127** *via* a silver catalyst. In this transformation, the desired 3-substituted-4-quinolones were prepared by reacting enaminones **126** and electrophiles in the

presence of silver (Ag(I)) catalyst (Scheme 40).⁵⁰ The authors suggested a mechanism for this reaction in which they expected the reaction to follow two different routes. Initially, in path 1, the alkylation of enaminones **126** led to the formation of iminium salt, which was then cyclized to a new ammonium salt. In pathway 2, cyclization precedes alkylation, resulting in identical iminium salt. Finally, with the removal of dimethylamine, 3-substituted quinolone **129** was produced in low to moderate yields.

3.3 Functionalization of 4-quinolone and its derivatives

The addition of new functional groups and the fusing of a polycyclic ring to a quinolone core could result in a novel class of chemicals with biological and material science uses. Various ways to functionalize the 4-quinolone scaffold have been



Scheme 40 Silver(I) mediated cyclization of enaminone to 4-quinolone derivative.





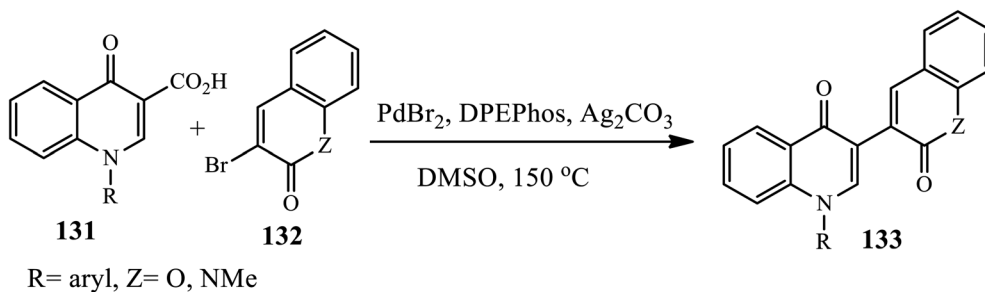
Scheme 41 Heck cross-coupling reaction through ohmic heating induced.

reported in the literature, such as C–C cross-coupling, C–hetero cross-coupling, C–H bond activation, decarboxylative cross-coupling, and regioselective electrophilic insertion.

3.3.1 C–C cross-coupling reactions. Silva *et al.* reported the synthesis of (*E*)-3-styrylquinolin-4(1*H*)-ones **130** via the Heck coupling reaction of 3-iodo substituted 4-quinolones **128** and styrene derivatives **129** under heating in the presence of Pd(OAc)₂ catalyst in TBAB as a phase transfer catalyst in aqueous media (Scheme 41).⁵¹ Using water as a solvent instead of other toxic solvents, avoiding toxic phosphine ligands, and using ohmic heating instead of conventional and microwave heating are the main advantages of this method. Styrenes that contain electron-withdrawing and electron-donating substituents participate to give the desired product in moderate to good yields.

Reddy's group reported a novel palladium-catalyzed synthesis of a series of bis-heterocycle derivatives **133** through the direct decarboxylative coupling of quinolin-4-ones 3-carboxylic acids **131** with 3-bromo-coumarins or quinolin-2(1*H*)-one **132** in the presence of PdBr₂, DPEphos, Ag₂CO₃ and DMSO in a sealed tube at 150 °C for 10 min (Scheme 42).⁵² The authors examined the effect of substrates as all the couplings proceeded cleanly and selectively in good to excellent yields regardless of the nature of the substituents on the aromatic ring of the quinolin-4-one 3-carboxylic acid or coumarin/quinolin-2-one moieties.

Recently, a novel, simple and efficient protocol for Pd–NHC-catalyzed the etherification and selenylation of 3-iodo-4-quinolones **134** under aerobic conditions was developed by Ghosh and Das. The target products **136** and **137** were



Scheme 42 Pd-catalyzed decarboxylative cross-coupling of 4-quinolone with heterocyclic halides.



Scheme 43 Synthesis of ipso-C–S and C–Se-substituted 4-quinolone derivatives through Pd–NHC-catalyzed cross-coupling.



synthesized *via* Pd–NHC catalyzed cross-coupling reactions of 3-iodo-2-phenyl-4-quinolone **136** and thiophenol/diphenyl diselenide **135** in the presence of DBU as a base in DMF at 80 °C (Scheme 43).⁵³ A broad range of thiophenols was coupled with various 3-iodo-2-phenylquinolin-4-(1*H*)ones, affording the corresponding 3-aryl sulfide-4-quinolones in good to excellent yields. Both thiophenols possessing electron-donating and electron-withdrawing groups performed well in this transformation. Interestingly, the electron-withdrawing groups at C-2 increased the yield, whereas the steric bulk groups lowered the yield. The highest yield was obtained when 2-(4-fluorophenyl)-3-iodo-4-quinolone was coupled with 4-fluorothiophenol; however, 2-(2-methylphenyl)-3-iodo-4-quinolone did not afford the corresponding product. In the case of **134**, 4-quinolones possessing 2-cyclohexyl and 2-cyclopropyl substituents gave the highest yields, whereas 2-aryl substituents possessing electron-withdrawing groups, such as 4-chloro and 4-fluoro, resulted in low yields.

3.3.2 C-hetero cross-coupling. Xia and coworkers established a highly efficient and practical procedure for palladium-catalyzed direct thioetherification of quinolinone-3-carboxylic acids **138** with diaryl disulfides **139** through decarboxylative C–S coupling under an air atmosphere in the presence of Pd(OAc)₂ and Ag₂CO₃ in DMSO at 130 °C to prepare derivative **140**. The authors claim that the effect of substrates such as diaryl disulfides bearing an electron-donating group, such as diphenyl disulfide, *p*-tolyl disulfide, and bis(4-methoxyphenyl)disulfide, increase the yield, whereas bis(4-chlorophenyl)disulfide substituted with an electron-withdrawing group coupled decrease the yield (Scheme 44).⁵⁴

A ligand free copper(II) mediated selective C–NH₂ arylation of both unprotected and protected 4-quinolones under ambient conditions was reported by Ghosh and Das in 2018 (Scheme 45).⁵⁵ The coupling of substituted amino 4-quinolone **141** obtained through the reduction of the corresponding nitro 4-quinolone with phenylboronic acid **142** in the presence of Cu(OAc)₂·H₂O and K₂CO₃ in EtOH at room temperature

afforded the corresponding *N*-arylated derivatives **143** in good to excellent yields. Functional groups, such as –Br, –Cl and –NO₂, were well compatible in this reaction, whereas thiopheneboronic acid did not participate in the reaction at all. Additionally, sterically hindered 2-bromophenylboronic acid gave the highest yield product, but 2-naphthylboronic acid resulted in a slight decrease in yield.

3.3.3 C–H bond activation. Li *et al.* demonstrated a cascade two-step one-pot synthesis of quinolinone-fused isoquinolines **146**. In this method, the desired *N*-fused polyheterocycles were synthesized by regio- and stereo-selective nucleophilic addition of 4-quinolinones **144** to alkynyl bromides **145**, which provided (*Z*)-*N*-alkenylated bromides, followed by ligand-free Pd-catalyzed intramolecular C–H alkenylation in the presence of PdCl₂ and K₃PO₄/K₂CO₃. The authors examined the substrate effects, including both electron withdrawing and electron releasing groups bearing 4-quinolone at the C-2 position, which gave the desired product in moderate to excellent yields. Additionally, *para*- and *meta*-substituted arylbromo acetylenes participated smoothly in this reaction. However, ortho substituents decrease the yield of the desired product (Scheme 46).⁵⁶

3.3.4 Nitration. In 2013, Azad and coworkers developed a decarboxylative nitration method for the conversion of 3-carboxy-4-quinolones **147** to 3-nitro-4-quinolones **148** *via ipso* nitration using polysaccharide-supported Cu nano-particles in the presence of Chit-Cu-NP and NO₂BF₄ in DMF at 100 °C. The bi-functional groups, such as hydroxyl and amine, in chitosan were found to be responsible for providing the excellent stability of the metal nanoparticles (Scheme 47).⁵⁷

3.3.5 Regioselective electrophilic insertion. A Lewis acid-catalyzed Diels–Alder reaction for the synthesis of new 2-(3-arylnaphthalen-2-yl)-1-methylquinolin-4(1*H*)-ones **151** was disclosed by Silva's group in 2016. Cycloaddition reaction of (*E*)-1-methyl-2-styrylquinolin-4(1*H*)-ones **149** with *ortho*-benzoquinodimethane afforded *trans*-2-(3-aryl-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-4(1*H*)-ones **150** in the presence of Lewis acid (AlCl₃) by refluxing 1,2,4-TCB, which further



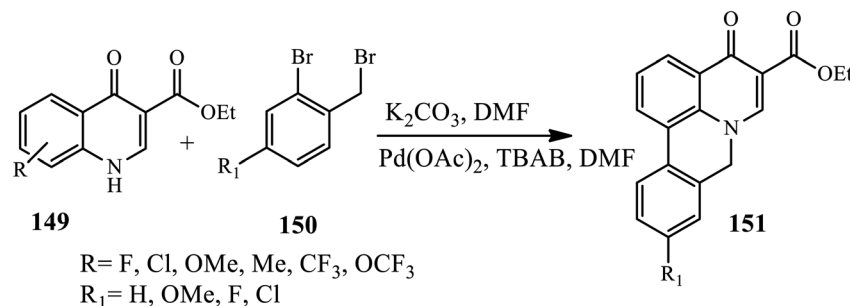
Scheme 44 Palladium-catalyzed thioetherification of quinolones through C–S cross coupling.



Scheme 45 Copper(II) catalyzed selective C–NH₂ arylation of 4-quinolones.



Scheme 46 Synthesis of quinolone-fused isoquinolines via intramolecular C–H alkenylation.

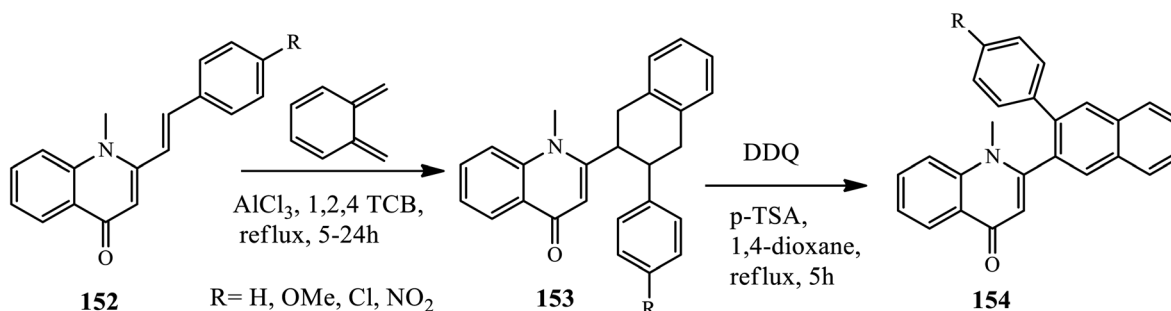
Scheme 47 Chitosan Cu-NP catalyzed *ipso*-nitration of 4-quinolones.

Scheme 48 Synthesis of phenanthridone fused 4-quinolone derivative.

converted to a **150** dehydrogenation reaction using DDQ and the catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in dry 1,4-dioxane. The authors claimed that the effect of substitutes as an electron donating group (–OMe) decreases the reactivity towards cycloaddition reaction, whereas the electron withdrawing group showed higher reactivity to afford an excellent yield of the desired product (Scheme 48).⁵⁸

Similarly, Arasakumar and coworkers reported a direct protocol towards the formation of phenanthridone fused

heterocycles **151** by the intramolecular C–H arylation of *N*-benzylquinolone **149** with 2-bromobenzyl bromide **155** mediated by Pd(OAc)₂ in the presence of K₂CO₃ as a base and tetrabutylammonium bromide (TBAB) as an additive in DMF at 80 °C for 3 h under an argon atmosphere (Scheme 48). Electron-withdrawing groups (F, Cl, or CF₃) or electron-donating groups (Me, OMe, OEt, or OCF₃) on the phenyl ring of 4-quinolones gave moderate to excellent yields (Scheme 49).⁵⁹



Scheme 49 Synthesis of 4-quinolone via acid-catalyzed Diels–Alder Reactions.



4. Bioactivities of 4-quinolones scaffolds and their derivatives

4-Quinolones possess diverse pharmacological properties, such as anticancer, anti-HIV, antibacterial, antifungal, antimalarial, anti-tubercular, anti-Alzheimer's disease activities, playing an intriguing role in the development of new drugs. Some of them are discussed below.

4.1 Anti-cancer activity

In an organism, cancer is defined as aberrant cell division, proliferation, and accumulation. It is one of the leading causes of death in the world. It might affect just one organ and spread to other parts of the body.⁶⁰ DNA topoisomerases play a key role in cancer because they regulate cell division through the modulation of the DNA supercoiling process during replication. Quinolone can inhibit DNA topoisomerase, leading to its potential for the treatment and control of solid tumors.⁶¹ Vorloxin **155** was the first quinolone derivative approved by the FDA as a therapy for acute myeloid leukemia.⁶ In 2017, Zhang and coworkers reported the synthesis of a series of novel water-soluble 4-quinolone-3-carboxamide derivatives **156** for anti-cancer activity against seven human tumor cell lines. The authors revealed that compound **156** showed reasonable anti-cancer activities against tested tumor cell lines (laryngeal carcinoma (Hep-2), breast carcinoma (MCF-7), gastric carcinoma (BGC-823), liver carcinoma (HepG2), cervical carcinoma (HeLa), prostate carcinoma (PC-3) and colorectal carcinoma (HCT-8, HCT-116 and RKO)) with IC_{50} values lower than 10.0 μ M.⁶²

Li and coworkers also demonstrated the synthesis of anti-cancer active compounds. Among synthesized compounds, compound **157** showed excellent topoisomerase inhibitory

activity against human cancer cell lines (A549, HL-60 and HeLa cell line). The authors revealed that the compound was found to be 5 times more potent in cell-killing activity for cell lines A549, HL-60, and HeLa than the positive control irinotecan or cisplatin, with IC_{50} of 0.009, 0.008 and 0.010 μ M, respectively. Docking studies of compound **157** showed that it was actively bound to the active site of the Top I-DNA complex *via* a hydrogen bond, cation- π interaction, and π - π interaction.⁶³

Ciprofloxacin has been reported to be a Topo-II inhibitor and antitumor active against various human cancer cell lines, such as colorectal, leukemia, and osteosarcoma cell lines. Thus, ciprofloxacin derivatives also showed potent activities. Hydrazone derivatives attached to ciprofloxacin **158a** and **158b** showed significant antitumor activities against the UO-31 cancer cell line with IC_{50} values of 0.75 μ M and 0.72 μ M, respectively. Additionally, compound **158b** displayed cytotoxicity against NCI-H226 and IGROV1 cancer cell lines with IC_{50} of 1.02 and 0.75 μ M, respectively. Moreover, they revealed a potent pro-apoptotic effect through the induction of apoptosis and an increase in the level of active caspase-3 compared to control and cell cycle arrest at the G2/M phase.⁶ Generally, SAR studies revealed that Azoles connecting to the C-8 and N-1 positions, small ring at the C-2 position, amide, ester, and heterocycles, such as azoles at the C-3 position, -H, -F, -Me, and -OMe substitutes at the C-5 position, and N, C-H, C-F substituted at the C-8 position, can improve anticancer activity (Fig. 6).²

4.2 Antiviral activity

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), which is one of the world's deadliest and most deadly public health pandemics. In the recent decade, several quinolone compounds have been studied for anti-HIV activity, and some of them have shown

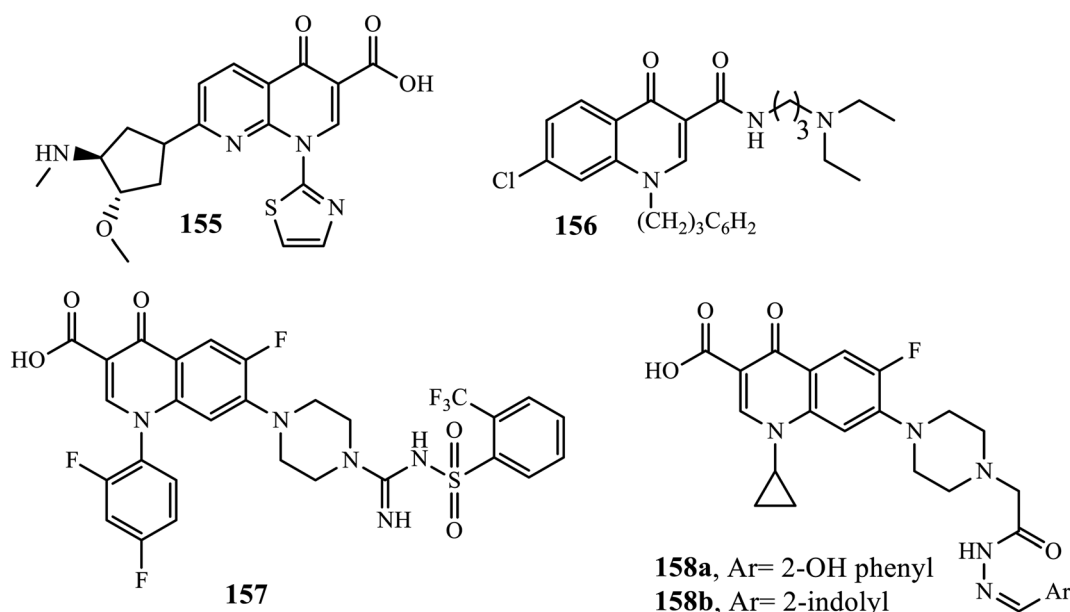


Fig. 6 Chemical structures of some anticancer containing 4-quinolone derivatives.

compounds, compound **166a** exhibited high antibacterial activities against *E. coli* *P. aeruginosa* species with MIC values of 0.036 and 0.043 $\mu\text{g mL}^{-1}$, respectively. Compound **167b** showed potent activities against *S. aureus* and MRSA with MIC values of 0.061 and 0.066 $\mu\text{g mL}^{-1}$, respectively, which is higher than the reference drug, ciprofloxacin, with MIC values of 1.6 and 1.5 $\mu\text{g mL}^{-1}$, respectively.^{71,72}

Asadipour and coworkers reported the synthesis and *in vitro* antibacterial evaluations of *N*-substituted piperazinyl sarafloxacin derivatives. Among them, compound **168** exhibited comparable activity as sarafloxacin (positive control) against *S. aureus*, *S. epidermidis* and *B. subtilis* ($\text{MIC} \leq 0.125 \mu\text{g mL}^{-1}$) and Gram-negative bacteria *E. Coli* ($\text{MIC} = 0.2\text{--}2 \mu\text{g mL}^{-1}$) compared to the standard drug sarafloxacin ($\text{MIC} \leq 0.125 \mu\text{g mL}^{-1}$). It was revealed that the antibacterial activities against both Gram-negative and Gram-positive bacteria were reduced upon the introduction of bulky substituents on the piperazine ring at the C-7 position of fluoroquinolones.⁷³

Novel 7-(3-alkylaminoazetididin-1-yl)fluoroquinolones were designed, synthesized and evaluated owing to their antibacterial activities by Itoh's group. Interestingly, all compounds **169a-f** exhibited strong inhibition of *E. coli* DNA gyrase with IC_{50} values ranging from 0.078 to 0.33 mg L^{-1} . Furthermore, the compounds showed better antibacterial activity against *E. coli* (MIC of 0.004 to 0.012 mg L^{-1} for **169a-e** and 0.038 mg L^{-1} for **169f**) and Gram-negative bacteria (11 species, 15 strains, 0.061

to 0.21 mg L^{-1} for **169a-e** and 0.57 mg L^{-1} for **169f**). Additionally, the oral absorption rates (in rats) of various analogs (**169a-e**) were determined, and the results indicated that oral absorption rates (%) increased as the chain length increased, which in turn may be due to the increased lipophilicities of the compounds, thereby resulting in enhancing membrane permeability. From the series of fluoroquinolone synthesized, WQ-3810 (**169e**) was identified as an orally active antibacterial agent with potent *in vitro* activity along with better oral bioavailability. Thus, compound **169e** (WQ-3810) is considered a promising lead molecule for further exploration (Fig. 8).⁷⁴

4.4 Anti-malarial activity

Quinolones have been known as potential anti-malarial agents starting from endochin **170** since the 1940s. *In vitro*, quinolones showed potential anti-malarial activities against the erythrocytic and hepatic stages of CQ-sensitive (CQS) and CQ-resistant (CQR) *P. falciparum* as well as exhibited excellent activities *in vivo* potency.⁷⁵

Awasthi *et al.* synthesized several fluoroquinolone analogs **171** and **172**. All derivatives (IC_{50} : 1.33–15.20 μM) showed promising malarial activities and negligible or very low toxicity profiles, and the majority of them were more potent than ciprofloxacin (IC_{50} : 8.82 μM).⁷⁶ Among quinolone synthesized by Dixit *et al.*, **173a** was the most potent with ED_{50} ranging from



Fig. 8 Chemical structure of some antibacterial containing 4-quinolone derivatives.





Fig. 9 Chemical structures of some anti-malaria containing 4-quinolone derivatives.

<1 to 20 nM against CQS D10, MDR K1, and TM90-C2B strains, and it was more active than atovaquone. Additionally, derivatives **173b, c** exhibited excellent anti-plasmodia activities *in vitro* (ED₅₀: 80–200 nM), and showed the highest hepatic metabolic stability in the *in vitro* mouse liver microsome assay, demonstrating 38 and 31 μM maximum concentrations in plasma (C_{max} at a 50 mg kg⁻¹ dose, while C_{max} was 66 and 39 μM, respectively, at 200 mg kg⁻¹). Both of them also displayed significant AUC values at both dosages (>125 μM h for **173b** and >70 μM h for **173c**), suggesting significant systemic exposure for those two derivatives relative to their potency. *In vivo* antimalarial potency was evaluated in a *P. berghei* infected mouse model; the results indicated that both compounds **173b, c** displayed *in vivo* activity. Ester **173b** exhibited suppression activity comparable to that of amodiaquine but was not curative, while **173c** showed high *in vivo* toxicity with no survival after day 14. In general, compound **173b** exhibited the best balance between potency, physicochemical properties, *in vitro* mouse liver microsome stability, *in vivo* pharmacokinetic profile, and the best efficacy, which was equivalent to that of amodiaquine, so **173b** is promising for further development as antimalarials.⁷⁷

Winter *et al.* synthesized endochin-like quinolones **174**, and half of the derivatives exhibited promising antiplasmodial activities with IC₅₀ values ranging from 0.02 to around 30 nM against CQS D6, MDR Dd2, and TM90-C2B *P. falciparum* strains. Compound **174a** (IC₅₀: 0.02 nM) was found to be most active against CQSD6 and MDRDd2, which was 15–320 fold more potent than the references, chloroquine, artemisinin, and

atovaquone (IC₅₀: 6.4, 0.81 and 0.3 nM, respectively) against CQS 3D7, and 25–5650 times more active than the three references (IC₅₀: 113, 0.6 and 0.5 nM, respectively) against MDR Dd2. Compound **174b** (IC₅₀: 5 nM) was the most potent against TM90-C2B, which was comparable to artemisinin (IC₅₀: 2.1 nM), 28- and 1083-fold more potent than chloroquine and atovaquone (IC₅₀: 134 and 5090 nM, respectively). Moreover, both derivatives displayed non-cytotoxicity in murine splenic lymphocytes even at a concentration of >25 μM. Combined with excellent antiplasmodial activity with low cytotoxicity, these novel quinolones suggest a favorable therapeutic index *in vivo* and emphasize the developmental potential of this structural class for clinical use.⁷⁸ Generally, the SAR study showed that the electro-donating group at the C-2 position, ester at the C-3 position, hydrophobic, electronegative, and large volume atom at the C-7 position, a small hydrophobic electron donating group at the C-6 position is preferred, whereas dimethoxy, dihalogen substituted at the C-5, C-7, and C-6 positions is disfavored (Fig. 9).⁷⁵

5. Conclusion

To date, various studies have been carried out based on the synthesis procedure and pharmaceutical potential for various diseases of 4-quinolone and its derivatives. Regarding synthetic methods, researchers have focused on using classical routes to obtain simpler, cheaper, cleaner, and faster methods with the highest yield. Recently, researchers have synthesized hybrid 4-



quinolone and its derivatives scaffolds with compounds containing other heterocyclic compounds using various synthetic procedures, such as metal-free or green synthesis, metal-catalyzed synthesis, microwave irradiation or multicomponent one-pot synthesis methodologies and further post modification techniques. 4-Quinolone and its derivatives are found in a broad spectrum range of physiologically and therapeutically active compounds. They play an important role in drug development and discovery. Researchers pay attention not only to the synthesis of 4-quinolone and its derivatives but also to the development and design of eco-friendly reaction processes towards the title compound. Reactions catalyzed by typical metal-free, solvent-free, aqueous media, and ionic liquids are environmentally friendly protocols and are discussed well in this review. Furthermore, quinolone and its derivatives exhibit a broad spectrum of bioactivities and have been applied in the treatment of various types of human infections.

Conflicts of interest

There are no conflicts to declare.

References

- 1 Y. Hu, S. Zhang, Z. Xu, Z. Lv and M. Liu, 4-Quinolone hybrids and their antibacterial activities, *Eur. J. Med. Chem.*, 2017, **335**–345.
- 2 F. Gao, J. Xiao and G. Huang, Current scenario of tetrazole hybrids for antibacterial activity, *Eur. J. Med. Chem.*, 2019, **184**, 111744–111785.
- 3 P. Lucia, *Quinolone: Synthesis and Antibacterial Activity*, National Institute for Chemical-Pharmaceutical Research and Development, Bucharest, 2012, pp. 255–272.
- 4 C. Shen, A. Wang, J. Xu, Z. An, K. Y. Loh, P. Zhang and X. Liu, Recent Advances in the Catalytic Synthesis of 4-Quinolones, *Chem*, 2019, 1059–1107.
- 5 V. L. M. Silva and A. M. S. Silva, Palladium-Catalysed Synthesis and Transformation of quinolones, *MDPI, Molecules*, 2019, 1–74.
- 6 M. Samir, M. Ramadan, M. H. Abdelrahman, M. Abdel-Aziz and G. E.-D. A. Abuo-Rahma, Recent Strategies in Design of Antitumor and Antibacterial Fluoroquinolones, *J. Adv. Biomed. Pharm. Sci.*, 2021, 134–151.
- 7 R. I. Al-Bayati, M. R. Ahamad and L. S. Ahamed, Synthesis and Biological Activity Investigation of Some Quinoline-2-One Derivatives, *Am. J. Org. Chem.*, 2015, **5**(4), 125–135.
- 8 P. Dhiman, N. Arora, P. V. Thanikachalam and V. Monga, Recent advances in the synthetic and medicinal perspective of quinolones: A review, *Bioorg. Chem.*, 2019, **92**, 1–45.
- 9 P. Dhiman, N. Arora, P. V. Thanikachalam and V. Monga, Recent advances in the synthetic and medicinal perspective of quinolones: A review, *Bioorg. Chem.*, 2019, **92**, 1–45.
- 10 G. Y. Leshner, E. J. Froelich, M. D. Gurett, J. H. Baily and R. P. Brundage, 1,8-Naphthyridine derivatives. A new class of chemotherapeutic agents, *J. Med. Pharm. Chem.*, 1962, **91**, 1063–1065.
- 11 J. Zhao, Y. Zhao and H. Fu, K_2CO_3 -Catalyzed Synthesis of Chromones and 4-Quinolones through the Cleavage of Aromatic C-O Bonds, *Org. Lett.*, 2012, **14**, 2710–2713.
- 12 (a) T. Zhao and B. Xu, Palladium-Catalyzed Tandem Amination Reaction for the Synthesis of 4-Quinolones, *Org. Lett.*, 2010, **12**, 212–215; (b) J. Shao, X. Huang, X. Hong, B. Liu and B. Xua, Synthesis of N-Alkyl-Substituted 4-Quinolones via Tandem Alkenyl and Aryl C-N Bond Formation, *Synthesis*, 2012, **44**, 1798–1808.
- 13 M. Janni, S. Aroraa and S. Peruncheralathan, Double heteroannulation of S,N-acetals: a facile access to quinolone derivatives, *Org. Biomol. Chem.*, 2016, **14**, 8781–8788.
- 14 P. Hasan, B. Aneja, M. Masood, B. Ahmad, U. Yadava, C. Daniliuc and M. Abid, Efficient synthesis of novel N-substituted 2-carboxy-4-quinolones via lithium bis(trimethylsilyl)amide (LiHMDS)-induced in situ cyclocondensation reaction, *RSC Adv.*, 2017, **7**, 11367–11372.
- 15 D. Zewge, C.-y. Chen, C. Deer, P. G. Dormer and D. L. Hughes, A Mild and Efficient Synthesis of 4-Quinolones and Quinolone Heterocycles, *J. Org. Chem.*, 2007, **72**, 4276–4279.
- 16 P. D. Duarte, M. W. Paixão and A. G. Corrêa, Microwave assisted synthesis of 4-quinolones and N,N'-diarylureas, *Green Process. Synth.*, 2013, **2**, 19–24.
- 17 I. Malvacio, D. Vera and E. Moyano, Microwave assisted synthesis of ethyl-quinolon-4-one-3-carboxylates and hydrolysis to quinolon-4-one-3-carboxylic acids, *Curr. Microwave Chem.*, 2014, **1**, 52–58.
- 18 W. Hu, J.-P. Lin, L.-R. Song and Y.-Q. Lon, Direct Synthesis of 2-Aryl-4-quinolones via Transition-Metal-Free Intramolecular Oxidative C(sp³)-H/C(sp³)-H Coupling, *Org. Lett.*, 2015, **5**(17), 1268.
- 19 A. C. Wright, C. K. Haley, G. Lapointe and B. M. Stoltz, Synthesis of Aryl Ketoamides via Aryne Insertion into Imides, *Org. Lett.*, 2016, 1–3.
- 20 K. Xu, S. He, S. Chen, G. Qiu, J. Shi, X. Liu, X. Wu, J. Zhang and W. Tang, Free radical rearrangement synthesis and microbiological evaluation of novel 2-sulfoether-4-quinolone scaffolds as potential antibacterial agents, *Eur. J. Med. Chem.*, 2018, **154**, 144–154.
- 21 S. Khong and O. Kwon, Phosphine-Initiated General-Base-Catalyzed Quinolone Synthesis, *Asian J. Org. Chem.*, 2014, **3**, 453–457.
- 22 N. Zhou, Z. Yan, H. Zhang, Z. Wu and C. Zhu, Metal-free radical Oxidative Cyclization of o-Azidoaryl Acetylenic Ketones with Sulfinic acids to Access Sulfone-Containing 4-Quinolones, *J. Org. Chem.*, 2016, 1–19.
- 23 Z. Zhang, X. Xiao, T. Sun, J. Wub, J. Ren, J. Zhu, X. Zhanga, R. Cao and R. Du, Synthesis, structure-activity relationships and preliminary mechanism of action of novel water-soluble 4-quinolone-3-carboxamides as antiproliferative agents, *Eur. J. Med. Chem.*, 2017, 1–41.
- 24 S.-F. Jiang, C. Xu, Z.-W. Zhou, Q. Zhang, X.-H. Wen, F.-C. Jia and A.-X. Wu, Switchable Access to 3 - Carboxylate-4-quinolones and 1 - Vinyl-3-carboxylate-4-quinolones via



- Oxidative Cyclization of Isatins and Alkynes, *Org. Lett.*, 2018, 1–4.
- 25 M. S. Rao and S. Hussain, DABCO-mediated decarboxylative cyclization of isatoic anhydride with aroyl/heteroaroyl/alkoylacetoneitriles under microwave conditions: Strategy for the synthesis of substituted 4-quinolones, *Tetrahedron Lett.*, 2021, 1–8.
- 26 D. Wang, P. Sun, P. Jia, J. Peng, Y. Yue and C. Chen, Transition-Metal-Free One-Pot Tandem Synthesis of 4-Quinolone and 4-H-Thiochromen-4-one Derivatives Through Sequential Nucleophilic Addition–Elimination–SNAr Reaction, *Synthesis*, 2017, 49, 1–11.
- 27 S. Bandatmakuru and V. Arava, Novel Synthesis of 1,2-Substituted 4-Quinolones, *SynOpen*, 2018, 2, 285–292.
- 28 C. G. Dave and H. M. Joshipura, Microwave assisted Gould-Jacob reaction: Synthesis of 4-quinolones under solvent free conditions, *Indian J. Chem.*, 2002, 650–652.
- 29 J. Liu, D. Ba, W. Lv, Y. Chen, Z. Zhao and G. Cheng, Base-Promoted Michael Addition/Smiles Rearrangement/N Arylation Cascade: One-Step Synthesis of 1,2,3-Trisubstituted 4-Quinolones from Ynones and Sulfonamides, *Adv. Synth. Catal.*, 2019, 1–13.
- 30 C. Xie, D. Yang, X. Wang and C. Ma, A Cascade Reaction of Michael Addition and Truce-Smiles Rearrangement to Synthesize Trisubstituted 4-Quinolone Derivatives, *J. Org. Chem.*, 2020, 1–8.
- 31 B.-H. Zhu, Y.-Q. Zhang, H.-J. Xu, L. Li, G.-C. Deng, P.-C. Qian, C. Deng and L.-W. Ye, Regio- and Stereoselective Synthesis of Diverse 3,4-Dihydro-2-quinolones through Catalytic Hydrative Cyclization of Imine- and Carbonyl-Ynamides with Water, *ACS Catal.*, 2021, 11, 1706–1713.
- 32 X.-D. Fei, Z. Zhou, W. Li, Y.-M. Zhu and J.-K. Shen, Buchwald–Hartwig Coupling/Michael Addition Reactions: One-Pot Synthesis of 1,2-Disubstituted 4-Quinolones from Chalcones and Primary Amines, *Eur. J. Org. Chem.*, 2012, 3001–3008.
- 33 C. Shen, A. Wang, J. Xu, Z. An, K. Y. Loh, P. Zhang and X. Liu, Recent Advances in the Catalytic Synthesis of 4-Quinolones, *Chem*, 2019, 5, 1059–1107.
- 34 N. Haddad, J. Tan and V. Farina, Convergent synthesis of the quinolone substructure of BILN 2061 via carbonylative sonogashira coupling/cyclization, *J. Org. Chem.*, 2006, 71, 5031–5034.
- 35 J. Wu, Y. Zhou, T. Wu, Y. Zhou and A. Lei, From ketones, amines, and carbon monoxide to 4-quinolones: palladium-catalyzed oxidative carbonylation, *Org. Lett.*, 2017, 19, 6432–6435.
- 36 P. Ghosh, A. K. Nandi and S. Das, Carbonylative Sonogashira annulation sequence: One-pot synthesis of 4-quinolone and 4H-chromen-4-one derivatives, *Tetrahedron Lett.*, 2018, 1–4.
- 37 C. Jones, K. Anderson and S. L. Buchwald, Sequential Cu-catalyzed amidation-base-mediated camps cyclization: a two-step synthesis of 2-aryl-4-quinolones from o-halophenones, *J. Org. Chem.*, 2007, 72, 7968–7973.
- 38 X. Xu and X. Zhang, Direct synthesis of 4-quinolones via copper-catalyzed anilines and alkynes, *Org. Lett.*, 2017, 19, 4984–4987.
- 39 S. Kang, S. Park, K.-s. Kim, C. Song and Y. Lee, Copper-Catalyzed Aza-Michael Addition of 2-Aminobenzoate to β -Substituted α,β -Unsaturated Ketones: One-Pot Synthesis of 3-Carbonyl-2-Substituted Quinolin-4(1H)-ones, *J. Org. Chem.*, 2018, 83(5), 2694–2705.
- 40 N. Sundaravelu and G. Sekar, Cu-Catalyzed one-pot synthesis of thiochromeno quinolinone and thiochromeno-thioflavone via oxidative double hetero Michael addition using in situ generated nucleophiles, *Chem. Commun.*, 2020, 56, 8826–8829.
- 41 F. Wang, L. Jin, L. Kong and X. Li, Cobalt(III)- and rhodium(III)-catalyzed C-H amidation and synthesis of 4-quinolones: C-H activation assisted by weakly coordinating and functionalizable enaminone, *Org. Lett.*, 2017, 19, 1812–1815.
- 42 P. Shi, L. Wang, K. Chen, J. Wang and J. Zhu, Co(III)-catalyzed enaminone-directed C–H amidation for quinolone synthesis, *Org. Lett.*, 2017, 19, 2418–2421.
- 43 O. Seppänen, M. Muuronen and J. Helaja, Gold-Catalyzed Conversion of Aryl- and Alkyl-Substituted 1-(o-Aminophenyl)-2-propyn-1-ones to the Corresponding 2-Substituted 4-Quinolones, *Eur. J. Org. Chem.*, 2014, 4044–4052.
- 44 X. Wu, L.-L. Zheng, L.-P. Zhao, C.-F. Zhu and Y.-G. Li, Gold-catalyzed cyclization of 1-(2-azidoaryl) propynols: synthesis of polysubstituted 4-quinolones, *Chem. Commun.*, 2019, 55, 14769–14772.
- 45 J. Huang, H. Su, M. Bao, L. Qiu, Y. Zhang and X. Xu, Gold(III)-catalyzed azide-yne cyclization/O-H insertion cascade reaction for the expeditious construction of 3-alkoxy-4-quinolinone frameworks, *Org. Biomol. Chem.*, 2020, 18, 3888–3892.
- 46 Y. Yoshino, T. Kurahashi and S. Matsubara, Nickel-catalyzed decarboxylative carboamination of alkynes with isatoic anhydrides, *J. Am. Chem. Soc.*, 2009, 131, 7494–7495.
- 47 S. Ueno, R. Shimizu, R. Maeda and R. Kuwano, Synthesis of 4-quinolones through nickel-catalyzed intramolecular amination on the β -carbon of o-(N-alkylamino) propiophenones, *Synlett*, 2012, 23, 1639–1642.
- 48 X. Ji, D. Li, Z. Wang, M. Tan, H. Huang and G.-J. Deng, visible light-induced aerobic oxidation of indoles: one-pot formation of 4-quinolones at room temperature, *Asian J. Org. Chem.*, 2018, 7, 711–714.
- 49 Y. Shi, H. Xing, T. Huang, X. Liu, J. Chen, X. Guo, G.-B. Li and W. Yong, Divergent C-H Activation Synthesis of Chalcones, Quinolones and Indoles, *ChemComm*, 2020, 1–4.
- 50 J. Joussot, A. Schoenfelder, L. Larquetoux, M. Nicolas, J. Suffert and G. Blond, Synthesis of 3-Substituted Chromones and Quinolones from Enaminones, *Synthesis*, 2016, 48, 3364–3372.
- 51 J. Pinto, V. Silva, L. Santos and A. Silva, Synthesis of (E)-3-styrylquinolin 4(1H)-ones in water by ohmic heating: A comparison with other methodologies, *Eur. J. Org. Chem.*, 2016, 2888–2896.
- 52 K. H. V. Reddy, J.-D. Brion, S. Messaoudi and M. Alami, Synthesis of Biheterocycles based on Quinolinone,



- Chromone and Coumarin Scaffolds by Palladium-Catalyzed Decarboxylative Couplings, *J. Org. Chem.*, 2016, **81**, 424–432.
- 53 P. Ghosh and S. Das, Creation of 4-Quinolone Thioether and Selenoether Derivatives via Pd-NHC Catalysed Cross-Coupling Reaction, *SynOpen*, 2020, **4**, 33–37.
- 54 C. Xia, Z. Wei, Y. Yang, W. Yu, H. Liao, C. Shen and P. Zhang, Palladium-Catalyzed Thioetherification of Quinolone Derivatives via Decarboxylative C-S Cross-Couplings, *Chem.-Asian J.*, 2016, **11**, 360–366.
- 55 P. Ghosh and S. Das, Ligand Free Approach for the Copper(II)-Mediated C-NH₂ Arylation of 4-Quinolone Derivatives Under Ambient condition, *ChemistrySelect*, 2018, **3**, 8624–8627.
- 56 X. Li, Y. Bian, X. Chen, H. Zhang, W. Wang, S. Ren, X. Yang, C. Lu, C. Chen and J. Peng, Tunable synthesis of quinolinone-fused isoquinolines through sequential one-pot nucleophilic addition and palladium-catalyzed intramolecular C–H alkenylation, *Org. Biomol. Chem.*, 2019, **17**, 321–332.
- 57 C. S. Azad and K. A. Narula, An operational transformation of 3-carboxy-4-quinolones into 3-nitro-4-quinolones via ipso-nitration using polysaccharide supported copper nanoparticles: synthesis of 3-tetrazolyl bioisosteres of 3-carboxy-4-quinolones as antibacterial agents, *RSC Adv.*, 2016, **6**, 19052–19059.
- 58 G. D. Silva, L. M. V. Silva and M. S. A. Silva, Lewis Acid Catalyzed Diels–Alder Reactions of (E)-1-Methyl-2-styrylquinolin-4(1H)-ones with ortho-Benzoquinodimethane: Synthesis of New 2-(3-Arylnaphthalen-2-yl)-1-methylquinolin-4(1H)-ones, *Synthesis*, 2016, **48**, 4519–4524.
- 59 S. Arasakumar, S. Shyamsivappan, S. Gopalan, A. Ata and P. S. Mohan, One-Pot Approach to Pyrido-4-phenanthridinones by PalladiumCatalyzed Annulation of 4 Quinolones with 2-Bromobenzyl Bromides, *Synlett*, 2019, **30**, 63–68.
- 60 E. Akkol, Y. Genc, B. Karpuz, E. S. Sanchez and R. Capasso, Coumarins and Coumarin-Related Compounds in Pharmacotherapy of Cancer, *Cancers*, 2020, **12**, 1959–1984.
- 61 P. Horta, A. Secrieru, A. Coninckx and M. L. S. Cristiano, Quinolones for Applications in Medicinal Chemistry: Synthesis and Structure, *Med. Chem.*, 2019, 261–297.
- 62 Z. Zhang, X. Xiao, T. Su, J. Wu, J. Ren and J. Zhu, Synthesis, structure-activity relationships and preliminary mechanism of action of novel water-soluble 4-quinolone-3-carboxamides as antiproliferative agents, *Eur. J. Med. Chem.*, 2017, **140**, 239–251.
- 63 J. Li, T. Zheng, Y. Jin, J. Xu, J. Yu and Y. Lv, synthesis, molecular docking and biological evaluation of quinolone derivatives as novel anticancer agents, chemical and pharmaceutical bulletin, *Chem. Pharm. Bull.*, 2018, **66**, 55–60.
- 64 R. Wang, K. Xu and W. Shi, Quinolone derivatives: Potential anti-HIV agent development and application, *Arch. Pharm.*, 2019, 1–17.
- 65 X. Xu, Z. Luo, K. He and M. Zhan, Synthesis and Biological Evaluation of Quinolone Acid Derivatives Having Polyhydroxylated Aromatics as HIV-1 Integrase Inhibitions, *Adv. Mater. Res.*, 2013, **634–638**, 1116–1119.
- 66 H.-K. Wang, K. F. Bastow, L. M. Cosent and K.-H. Lee, Antitumor Agents. 166. Synthesis and Biological Evaluation of 5,6,7,8-Substituted-2-phenylthiochromen-4-ones, *J. Med. Chem.*, 1996, **39**, 1975–1980.
- 67 J. D. Yoneda, M. G. Albuquerque, K. Z. Leal, F. d. Costa Santos, P. N. Batalah, L. Brozeguinia, S. R. Peter, R. B. Alencastro, A. C. Cunha, M. C. de Souza, V. F. Ferreira, V. A. Giongo, C. C. Sanos and G. C. P. Paixãs, Docking of anti-HIV-1 oxoquinoline-acylhydrazone derivatives as potential HSV-1 DNA polymerase inhibitors, *J. Mol. Struct.*, 2014, **1074**, 263–270.
- 68 S. Massari, D. Daelemans, G. Manfroni, t. Sabatini, O. Tabarrini, C. Pannecouque and V. Cecchetti, Studies on anti-HIV quinolones: New insights on the C-6 position, *Bioorg. Med. Chem.*, 2009, **17**(2), 667–674.
- 69 D. Sriram, P. Yogeewari, N. Srichakravarthy and T. R. Bal, Synthesis of stavudine amino acid ester prodrugs with broad-spectrum chemotherapeutic properties for the effective treatment of HIV/AIDS, *Bioorg. Med. Chem. Lett.*, 2005, **14**(5), 1085–1087.
- 70 A. Chrzanowska, P. Roszkowski, A. Bielenica, W. Olejarz, K. Stepień and M. Struga, Anticancer and antimicrobial effects of novel ciprofloxacin fatty acids conjugates, *Eur. J. Med. Chem.*, 2020, **185**, 111810.
- 71 H. M. Faidallah, A. S. Girgis, A. D. Tiwari, H. H. Honkanadavar, S. J. Thomas, A. Samir, A. Kalmouch, K. A. Alamry, K. A. Khan and T. S. Ibrahim, Synthesis, antibacterial properties and 2D-QSAR studies of quinolone-triazole conjugates, *Eur. J. Med. Chem.*, 2018, **143**, 1524–1534.
- 72 I. M. Abdel-Rahman, M. Mustafa, S. A. Mohamed, R. Yahia, M. Abdel-Aziz, G. E.-D. A. Abu-Rahma and A. M. Hayallah, Novel Mannich bases of ciprofloxacin with improved physicochemical properties, antibacterial, anticancer activities and caspase-3 mediated apoptosis, *Bioorg. Chem.*, 2021, **107**, 104629.
- 73 A. Asadipour, M. H. Moshaf, L. Khosravani, S. Moghimi, E. Amou, L. Firoozpour, G. Ilbeigi, K. Beiki, E. Soleimani and A. Foroumadi, N-substituted piperazinyl sarafloxacin derivatives: synthesis and in vitro antibacterial evaluation, *DARU J. Pharm. Sci.*, 2018, **26**, 199–207.
- 74 K. Itoh, Y. Kuramoto, H. Amano, D. Kazamori and A. Yazaki, Discovery of WQ-3810: design, synthesis, and evaluation of 7-(3-alkylaminoazetid-1-yl)floro-quinolones as orally active antibacterial agents, *Eur. J. Med. Chem.*, 2015, **103**, 354–360.
- 75 Y.-L. Fan, X.-W. Cheng, J.-B. Wub, M. Liu, F.-Z. Zhanga, Z. Xuc and L.-S. Feng, Antiplasmodial and antimalarial activities of quinolone derivatives: An overview, *Eur. J. Med. Chem.*, 2018, 1–48.
- 76 S. K. Dixit, N. Mishra, M. Sharma, S. Singh, A. Agarwal, S. K. Awasthi and V. Bhasin, Synthesis and in vitro antiplasmodial activities of fluoroquinolone analogs, *Eur. J. Med. Chem.*, 2012, **51**, 52–59.
- 77 Y. Zhang, W. A. Guiguemde, M. Sigal, F. Zhu, M. C. Connelly, S. Nwaka and R. K. Guy, Synthesis and structure–activity



- relationships of antimalarial 4-oxo-3-carboxyl quinolones, *Bioorg. Med. Chem.*, 2010, **18**, 2756–2766.
- 78 W. Rolf, X. K. Jane, J. S. Martin, H. David, R. K. Dennis and K. R. Michael, Optimization of endochin-like quinolones for antimalarial activity, *Exp. Parasitol.*, 2011, **127**, 545–551.
- 79 S. Samadi and F. K. Behbahani, Iron (III) Phosphate Catalyzed the Synthesis of 4-quinolones, *Chem. Methodol.*, 2018, **2**, 181–185.
- 80 S. B. Lee, Y. Jang, J. Ahn, S. Chun, D.-C. Oh and S. Hong, One-Pot Synthesis of 4-Quinolone via Iron-Catalyzed Oxidative Coupling of Alcohol and Methyl Arene, *Org. Lett.*, 2020, **22**, 8382–8386.

