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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Current progress toward synthetic routes and medicinal significance of quinoline

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Abstract

Quinoline motifs are essential in several pharmacological active heterocyclic compounds due to their various applications in medicinal and industrial chemistry. Furthermore, there are greater societal expectations in the current scenario that synthetic and medicinal chemists should produce greener and more sustainable chemical processes. Therefore, this mini-review article highlights the traditional and green synthetic approaches of quinoline and its analogs, including multicomponent one-pot reactions and solvent-free reaction conditions utilizing microwave and ultraviolet irradiation-promoted synthesis using eco-friendly and safe reusable catalysts, in addition to discussing the medicinal importance of quinoline derivatives such as anticancer, antioxidant, anti-inflammatory, antimalarial, anti-SARS-CoV-2, and antituberculosis activities within the period from 2011 till 2021. Therefore, the quinoline scaffolds signify a unique class of pharmacophores present in various therapeutic agents.

Keywords Quinoline · Hydroxychloroquine · Multi-Component Reactions · Green chemistry

Introduction

Quinoline is a nitrogen-based heterocyclic aromatic compound with systematic IUPAC name as benzo[*b*]pyridine or 1-aza-naphthalene with the C_9H_7N chemical formula. It exhibits chemical reactivity similar to the benzene and pyridine ring system as it undergoes nucleophilic and electrophilic substitution reactions [1].

Quinoline and its derivatives are a vital nucleus in several natural products and FDA-approved drugs (Fig. 1) [2]; also, they are considered a privileged structure in drug discovery programs because of their broad spectrum of bio-responses, including anticancer [3], antioxidant [4], anti-COVID-19 [5], anti-inflammatory [6], anti-mycobacterial [7], antimicrobial [8], anticonvulsant [9], cardiovascular [10], antituberculosis [11], anti-plasmodial [12], anti-bacterial [13] activities. Additionally, quinoline systems are still being applied to create compounds with wide-ranging pharmacological activities [14].

Lately, authors have reviewed the access and applicability of quinoline frameworks. Abdanne and Endale [15], Ramandeep and Kapil [16], Tomoya et al. [17], and Shraddha et al. [18] reported classical methods for quinoline motifs synthesis. Jaideep et al. [19] and Ginelle and Bryan [20] revealed metal-free quinoline synthesis approaches. Ankit Kumar et al. [21] and Lalit et al. [22] briefly tackled green recipes for quinoline preparation. Furqan et al. [23] deliberated synthetic tactics for the tricyclic fused-quinoline derivatives. Shweta et al. [24] conveyed the anticancer activity of quinoline heterocycles. Rangappa and Siddappa [25] and Mustapha et al. [26] compiled the antituberculosis potential of quinoline derivatives—Atukuri [27] and Stéphanie and Matthias [28] overviewed hybrid-quinoline derivatives with antimalarial potencies. Finally, Soumita and Manojit [29] explored the anti-inflammatory activities of quinoline scaffolds.

Owing to this wide range of applications, quinoline chemistry has attained the synthetic and medicinal

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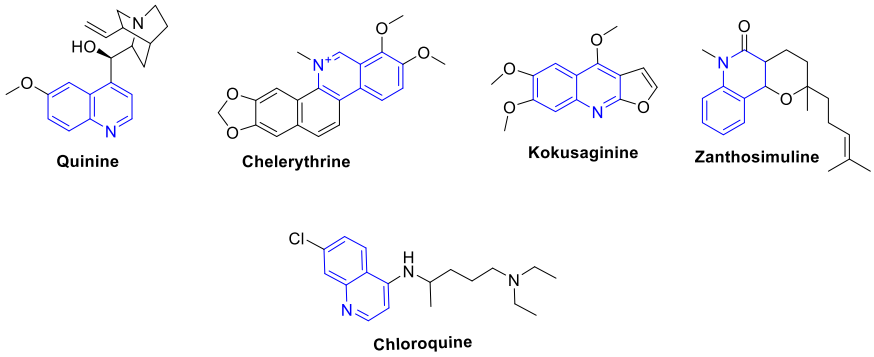


Fig. 1 Examples of natural products and approved drugs with a quinoline ring system

chemists' efforts; therefore, many studies discussed synthetic protocols succeeding quinoline and its analogs, such as conventional methods, but these pathways suffer from non-environmental reagents, generating a significant quantity of waste, long reaction times, and objectionable byproducts which lead to undesirable yields [30]; so, the scientific communities urgently needed to create green and more feasible chemical reactions utilizing unconventional reaction media, energy sources, and safe catalysts to synthesize quinoline derivatives [31].

Based on our interests and efforts in the green synthetic organic and medicinal chemistry research field [32–37], in the present mini-review, we exhibit an overview of the classical and novel strategies for various quinoline compounds production, including multicomponent one-pot reactions, electrophilic annulation, oxidative and radical-promoted cyclization, cascade reactions, solvent-free reaction conditions under microwave and ultraviolet irradiation-promoted synthesis using eco-friendly and safe reusable catalysts in addition to explaining their various pharmacological properties including anticancer, antioxidant, anti-inflammatory, antimalarial, anti-SARS-CoV-2, and antituberculosis activities within the period from 2011 till 2021.

Synthetic routes of quinolines

Traditional synthetic routes of quinolines

Traditional methods are summarized in Fig. 2. Ferdinand Runge was the first researcher to isolate quinoline from coal tar in 1834. Since then, the primary source of industrial quinoline remains coal tar. Up to this time, the preparation of quinoline and its derivatives has fascinated many researchers. Quinoline production has been described in numerous traditional reactions such as the Skraup method that involved the heating of aromatic amine with glycerol in sulfuric acid, which acted as a dehydrating agent that converted glycerol to acrolein, and $PhNO_2$ and oxidizing agent, which finally converted 1,2-dihydroquinoline into quinoline [38].

The Friedländer condensation of 2-aminoarylaldehyde with α-carbonyl molecule bearing a reactive a-methylene group in the presence of sodium ethoxide (10 mol%) as a catalyst has been developed to produce different polysubstituted quinolines. The tetrahydroacridine derivatives and *11H*-indeno[*1,2-b*]quinolines achieved good yields ranging from 51 to 93%. Friedländer reactions were performed in entirely anhydrous ethanol with sodium ethoxide under reflux for about 2–3 h [39]. 2-Aminoarylketones underwent condensation with α-methylene ketones in the presence of 10 mol% poly(ethylene glycol) (PEG)–supported sulfonic acid under moderate reaction conditions to generate good yields of polysubstituted quinolines. A catalytic amount of PEG-supported sulfonic acid was used to perform the Friedlaender condensation of 2-aminoacetophenone with ethyl acetoacetate to obtain ethyl 2,4-dimethylquinoline-3-carboxylate at room temperature in various solvents such as CH_3OH, Et_2O, CH_3CN, and CH_2Cl_2. It was reported that the best results were achieved when the reaction was carried out in CH_2Cl_2 at reflux room temperature for 40 min in the presence of 10 mol% PEG-supported sulfonic acids, resulting in a 96% yield [40]. Cu−mesoporous organic nanorod was employed to synthesize quinoline via the Frieldländer method. The catalyst successfully catalyzes the one-pot sequential multi-step oxidative dehydrogenative coupling of 2-aminobenzyl alcohol with various aromatic ketones to give high yields of quinolines up to 97% [41]. Doebner reaction produced quinoline derivatives through two mechanisms. The first was an aldol condensation between the aldehyde and pyruvic acid to give a β,γ-unsaturated α-keto acid, which subsequently underwent a Michael addition with aniline, and the second mechanism involved the formation of a Schiff's base from the 1,2-addition of the aniline to aromatic aldehyde which was subjected to Mannich reaction with pyruvic acid. Doebner-von Miller mechanism involved the condensation of aniline derivatives with an α,β-unsaturated ketones, and then, the fragmentation to the corresponding imine occurred. The fragments were recondensed to the conjugated imine followed by nucleophilic addition to another aniline molecule [42]; the Pfitzinger reaction, which entails condensation in an alkaline medium of an isatin and a ketone with the general

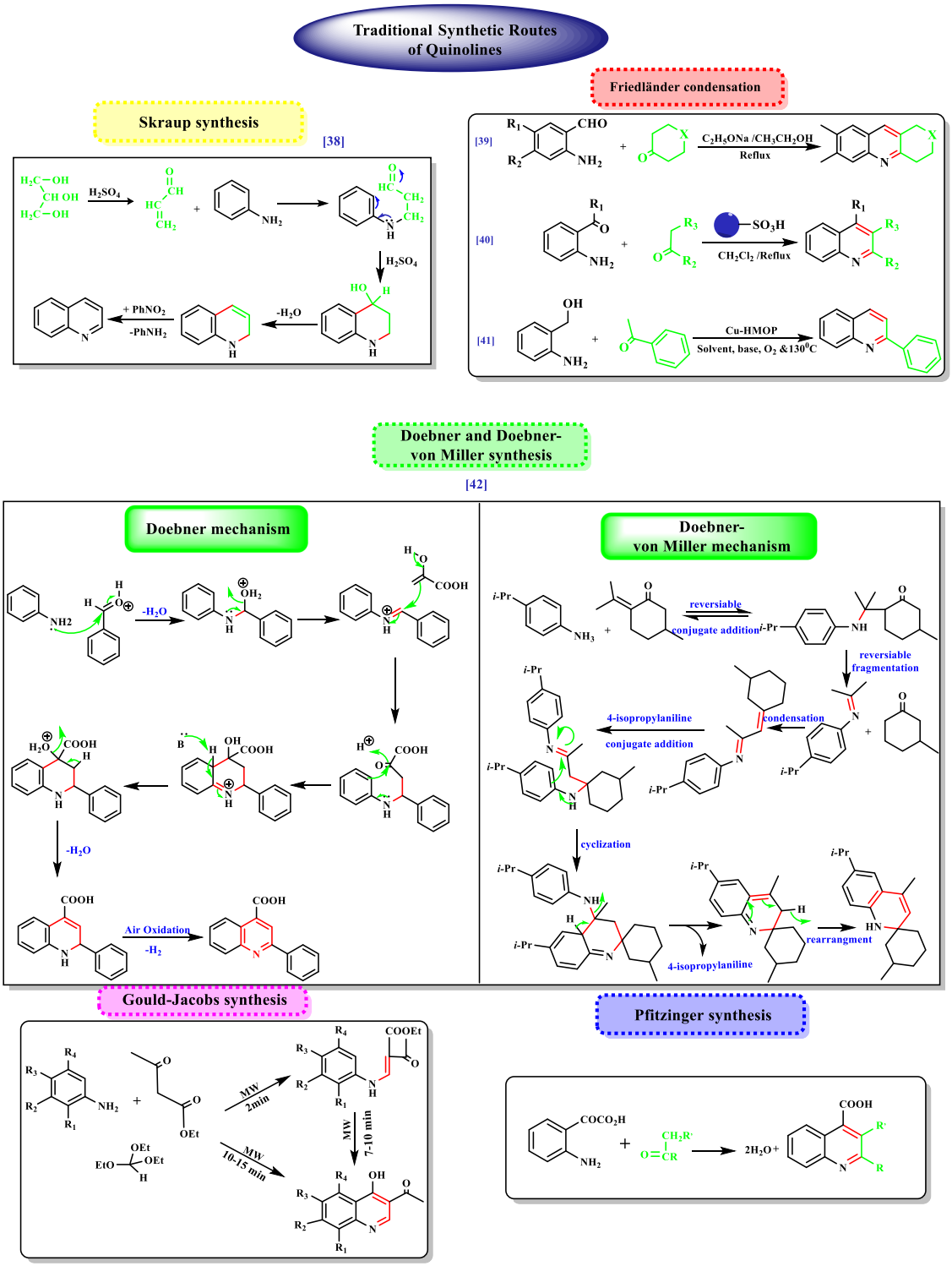


Fig. 2 Conventional methods of quinoline synthesis

formula $RCOCH_2R'$, was employed throughout to create these quinoline derivatives [43, 44]. Riehm, Combes, Povarov hour methods synthesized quinoline derivatives [45–48]. Gould-jacobs reaction, which is a method for the synthesis of 4-hydroxyquinolines via the condensation of aniline with alkoxy methylene malonic ester by cyclization and subsequent decarboxylation and this protocol was developed by using new techniques such as microwave [49] as indicated in (Fig. 2), There are many proven protocols for the production of the quinoline group, which can be widely

changed to prepare a series of quinolines that are replaced differently.

Lewis acids-catalyzed synthesis of quinoline

1-(2,4-Dimethylquinoline-3-yl) ethenone **1** was produced when 1-(2-aminophenyl) ethenone reacted with pentane-2,4-dione using 4-toluenesulfonic acid ($TsOH.H_2O$), magnesium chloride ($MgCl_2.6H_2O$), or cupric nitrate ($Cu(NO_3)_2.3H_2O$) as a catalyst at 80 °C (Scheme 1) [50] in fair yield. The treatment of anthranil with 1,3-diphenylpropane-1,3-dione resulted in quinoline cyclization producing 2-Phenyl-3-benzoylquinoline **2** (Scheme 2) [51]. The reaction of aniline and polyhydric alcohols or monohydric alcohols had quinoline **3–5** (Scheme 3) [52]. Quinoline **6** was created by Friedlander reaction in solvent-free conditions between 2-amino aryl ketones and ketones at 84–85 °C in good yield (Scheme 4) [53].

One-pot multicomponent synthesis of quinolines

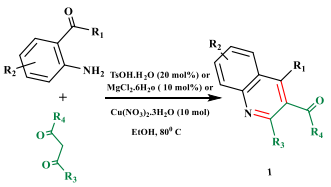
2,4-Diphenylquinolines **7** were produced by the reaction of anilines, benzaldehyde, and phenylacetylene (Scheme 5) [54]. Compound **8** was produced via treating aniline derivatives with phenylacetylene and benzaldehyde under reflux in anhydrous acetonitrile in the presence of niobium pentachloride as a catalyst (Scheme 6) [55].

The condensation of p-nitroaniline synthesized Nitroquinoline derivatives 9, benzaldehyde derivatives, and phenylacetylene under air atmosphere, room temperature, and constant stirring using anhydrous acetonitrile as solvent. $NbCl_5$ was used in the proportion of 50% for each mole of benzaldehyde derivative used. Reduction of the nitro group in the nitroquinoline derivatives was conducted with hydrazine monohydrate in the presence of 10% Pd/C (Scheme 7) [56].

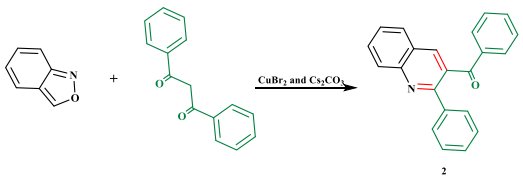
Synthesis of functionalized quinoline

The synthesis of quinoline by quinoline N-oxide

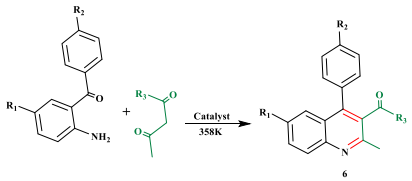
Consequently, there is a substantial supply of new methods to synthesize structurally and mechanically complex quinolines efficiently. In this context, the existing activities of organic production rely more on the direct functionalization of the quinoline scaffold than on the development of this center from the methods of cyclocondensation or cyclization. Easy quinoline *N*-oxides have populations more significant as an ideal substrate to change this *N*-heterocycle because of the capacity of the *N*-oxide moiety to act as a directing group to conduct and regulate the region-selectivity of the *C-H* functional groups, being widely available or readily manufactured at multi-gram scale in the lab. Use of reactions between quinoline *N*-oxides and various acrylates with *N*-oxide alkenylation, high quinoline production was developed **10** (Scheme 8) [57]. Over microwave irradiation at 120 °C,



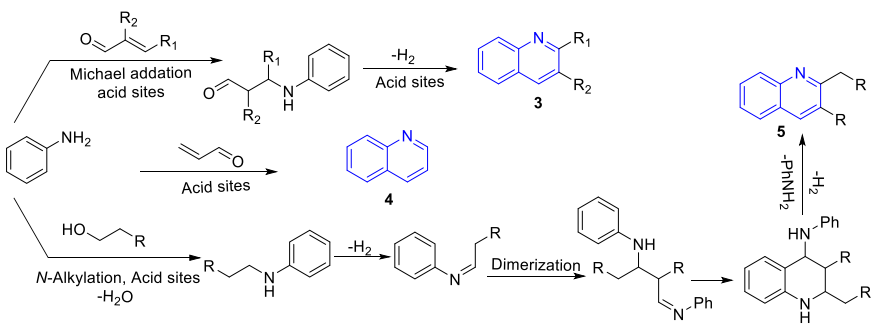
Scheme 1 Synthesis of 1-(2,4-dimethylquinoline-3-yl) ethenone 1



Scheme 2 Synthesis of 2-Phenyl-3-benzoylquinoline 2

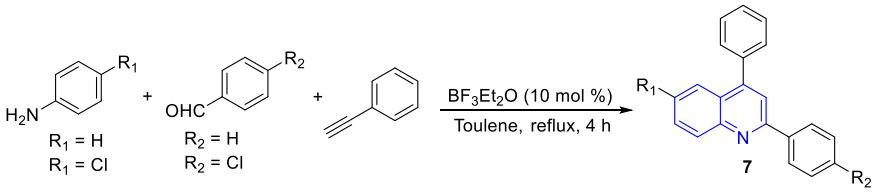


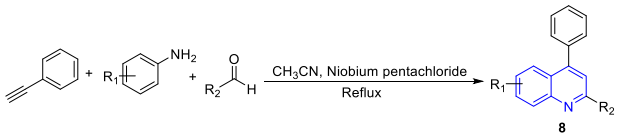
Scheme 4 The reaction between 2-amino aryl ketones and ketones to produce quinolines 6



Scheme 3 The reaction of aniline and polyhydric or monohydric alcohols produces quinolines **3–5**

Scheme 5 Synthesis of 2,4-diphenyl quinolines **7**





Scheme 6 The reaction of aniline with phenylacetylene and benzaldehyde produces quinolines **8**

quinoline *N*-oxide and *p*-methoxybenzene diazonium tetrafluoroborate in acetonitrile contribute to producing a C2-aminated quinoline **11** (Scheme 9) [58]. Olefination of 2-methyl substituted quinoline *N*-oxide with ethyl acrylate in the involvement of $Cu(OAc)_2$ at 90 °C generated high yielded quinoline derivatives (**12, 13**) (Scheme 10) [59].

Synthesis of quinoline via electrophile-driven cascade cyclization

The reaction of 2-tosyl aminophenyl prop-1-yn-3-ol with molecular iodine (I_2) leads to iodocyclization resulting in the good yield for the derivative of quinoline **14** synthesis (Scheme 11) [60].

Green synthetic approaches of quinolines

Synthesis of quinolines using a non-metal catalyst

Quinoline derivatives **15** were produced in the presence of iodine by the reaction of amino acids and aniline derivatives (Scheme 12) [61].

Muo et al. identified a three-component procedure for preparing 4-ferrocenyl quinoline derivatives **16** utilizing anilines and ferrocenyl acetylene with aldehydes such as isonicotinaldehyde, 2-furan carboxaldehyde and 2-thiophene carboxaldehyde catalyzed by *p*-toluene sulfonic acid using water as a solvent (Scheme 13) [62].

Synthesis of functionalized quinolines under solvent-free conditions

The cyclo condensation reaction between 2-aminoarylketones and α-aroyl ketene dithioacetals was performed under solvent-free conditions using indium chloride ($InCl_3$) as a catalyst to produce a decent yield of quinolines **17** (Scheme 14) [63].

Synthesis of quinoline using photocatalysis

The transformation of *m*-nitrotoluene soluble in ethanol was studied as a first-time model reaction to define the ability of newly synthesized molecules. Irradiation ($\lambda > 320$ nm) of the reaction mixture below 25 °C in the presence of acid-modified mesoporous TiO_2-SiO_2 molecules resulted in the creation of 2,7-dimethyl quinoline **18** (Scheme 15) [64].

N-aryl glycine, cinnamyl ester derivatives, undergoes intramolecular cyclization using tris(2,2′-(*p*-CF_3)bipyridine) ruthenium(II) tetrafluoroborate ($Ru(bpy)_3(PF_6)_2$) as a photocatalyst, boron trifluoride etherate, and acetonitrile as a solvent under irradiation with a 23 W fluorescent bulb at room temperature for 24 h to obtain substituted quinoline-fused lactones **19** (Scheme 16) [46].

The photocatalytic reaction between aniline, methyl propionate, and paraformaldehyde catalyzed by polythiophene encapsulated Au-Fe_3O_4 NPs (0.5 mol%) using water as a solvent under irradiation of 60 W tungsten filament bulb produced quinoline carboxylates **20** (Scheme 17) [65].

Photocatalytic radical transformation reaction toward the synthesis of quinoline

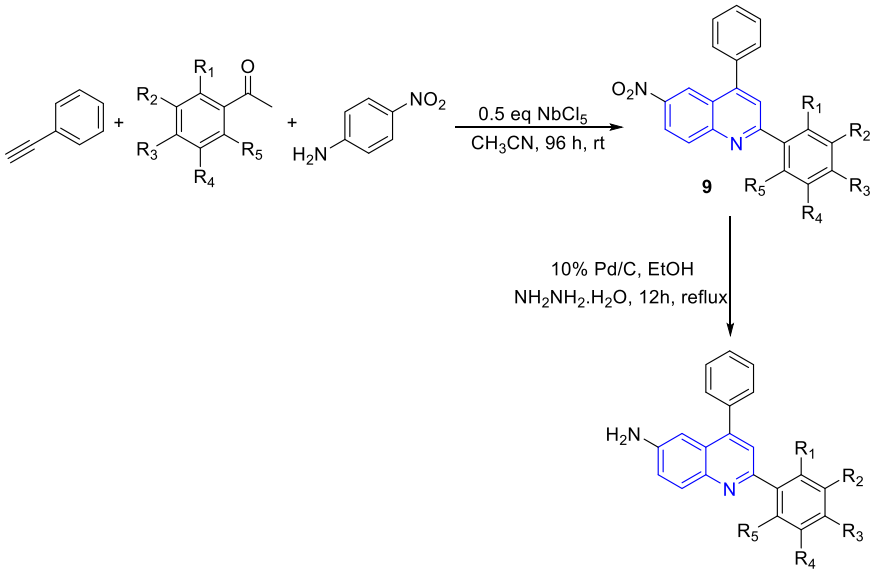
The reaction of β-aryl propionitrile derivatives with aryl lithiums and water produced 1,3-diphenylpropan-1-imines, which were treated with *N*-iodosuccinimide via iminyl radical-mediated cyclization under transition metal-free condition with a tungsten lamp irradiation to attain 2-aryl quinoline **21** in a good yield (Scheme 18) [66].

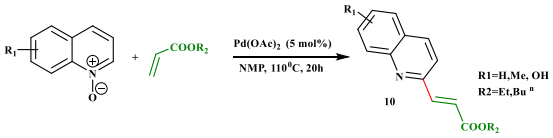
A mixture of biphenyl-4-isocyanide and diethyl 2-Bromo-2-(4-phenyl but-3-yn-1-yl)malonate in dimethylformamide as a solvent was reacted under irradiation with a blue LED strip for 24 h at room temperature using fac-Tris(2-phenyl pyridine)iridium(III) (fac $Ir(ppy)_3$) as a photocatalyst and Na_2HPO_4 produced two quinoline fused cyclopentane derivatives **22** and **23** with regioselectivity up to 29% (Scheme 19) [67].

2-isocyanobiphenyls and ethyl bromofluoroacetate were reacted with fac $Ir(ppy)_3$ and Na_2HPO_4 under 3 W blue LED irradiation followed by decarboxylation step to produce fused quinoline derivatives **24** and **25** (Scheme 20) [68].

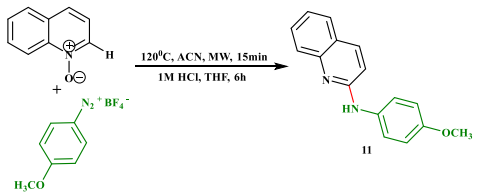
The treatment of *N*-tosylamide derivatives of (aza)-Morita–Baylis–Hillman adducts with the photocatalyst $Ru(bpy)_3Cl_2$ using blue light photoredox-catalyzed single

Scheme 7 Synthesis of nitroquinoline derivatives **9**

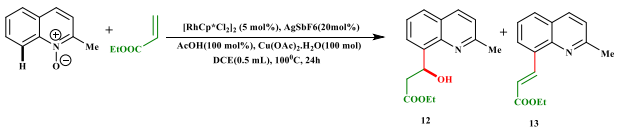




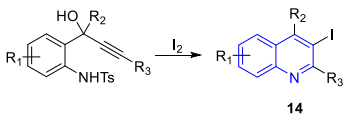
Scheme 8 Synthesis of C_2-alkenylated quinoline 10



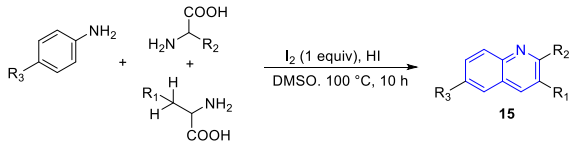
Scheme 9 Synthesis of C_2- aminated quinoline 11



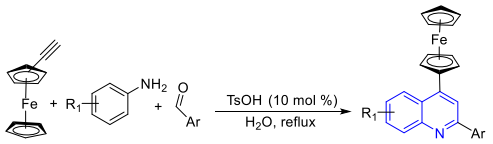
Scheme 10 Olefination of 2-methyl substituted quinoline N-oxide producing 12 and 13



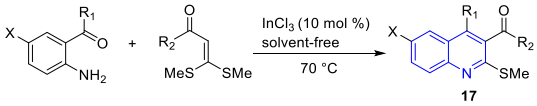
Scheme 11 Electrophile-driven cascade cyclization resulting in quinolines **14** synthesis



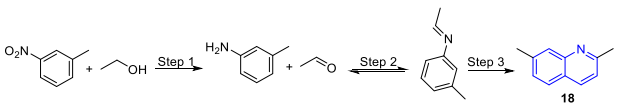
Scheme 12 Synthesis of quinoline derivatives **15** the reaction of amino acids and anilines



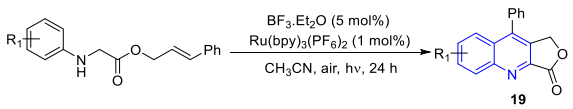
Scheme 13 Synthesis of 4-ferrocenyl quinoline derivatives **16**



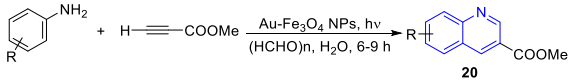
Scheme 14 Regio-selective synthesis of quinolines **17** under solvent-free conditions



Scheme 15 One-Pot Photocatalytic synthesis of 2,7-dimethyl quinoline **18** from *m*-nitrotoluene soluble in ethanol



Scheme 16 Photocatalytic intramolecular cyclization of *N*-aryl glycine cinnamyl ester derivatives to produce substituted quinoline-fused lactones **19**



Scheme 17 The photocatalytic reaction between aniline and methyl propiolate produces substituted quinoline carboxylate **20**

electron transfer conditions at room temperature resulted in the production of quinoline derivatives **26** and **27** (Scheme 21) [69].

Synthesis of quinoline by microwave irradiation

Microwave irradiation exhibits electric and magnetic fields, but the starting materials are controlled only by the electric field. As a result, [70].

Reactions under solvent conditions Zhang et al. established a new green method for the preparation of pyrroloquinolinediones **28** and quinolinedicarboxylates **29** by reacting 2-azido benzaldehydes with *N*-maleimide and dimethyl fumarate, respectively, via a one-pot synthesis reaction including denitrogenation of azide, benzisoxazole formation, aza-Diels–Alder cycloaddition, and dehydrative aromatization in acetonitrile as a solvent under microwave heating at 115 °C for 35 min (Scheme 22) [71].

The treatment of indolyl-ones with a specific Brønsted-acid (trifluoroacetic acid in chloroform) induced the production of 3,4-cyclopentane-quinoline-3-ones **30** utilizing the microwave effect (100 W) at 100 °C in around 30 min (Scheme 23) [72].

The domino reaction technique for the synthesis of spiropyrroloquinolines **31, 32**, and **33** was performed between anilinosuccinimide derivatives and α-dicarbonyl compounds such as 1*H*-indene-1,2,3-trione, acenaphthylene-1,2-dione, and 5-chloroindoline-2,3-dione derivatives utilizing acetic acid as a Brønsted-acid catalyst under microwave irradiation at 150 °C for 20 min in moderate yield (Scheme 24) [73].

Poly-functionalized dihydroquinoline derivatives **34** were synthesized through the reaction of aldehydes and aryl ethylidene malononitriles (2 equiv) via an intermolecular cyclization process under microwave irradiation in ethylene glycol and NaOH as a base (Scheme 25) [74].

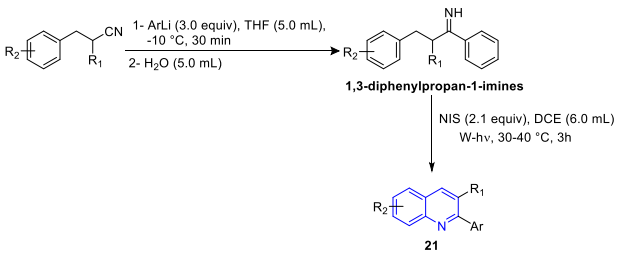
Furoindenoquinolin-1-one derivatives **35** were prepared when 9*H*-fluoren-2-amine was condensed with tetronic acid and benzaldehydes in acetic acid under microwave irradiation for **10** min (Scheme 26) [75].

Reactions under solvent-free conditions Microwave irradiation assisted the diastereoselective synthesis of quinoline-2,5-diones 36 and 37 in virtuous yield via reacting aryl aldehydes with N-aryl enaminones 4-hydroxy-6-methyl-2H-pyran-2-one in acetic acid at 100 °C (Scheme 27) [76].

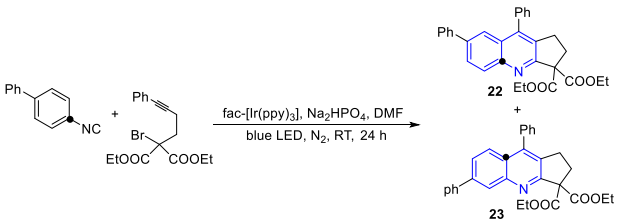
The treatment of anilines with benzaldehydes and phenylacetylene using catalytic amounts of reusable potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}{\cdot}3H_2O$) as a catalyst under 800 W microwave irradiation yields quinoline and bis-quinoline derivatives **38** and **39** (Scheme 28) [77].

The condensation reaction of 2-amino benzophenone with different heteroaromatic ketones under M.W. irradiation highly yielded quinoline derivatives **40** and 12-diphenyldibenzo[b,f][1,5]diazocine **41** as a byproduct (Scheme 29) [78].

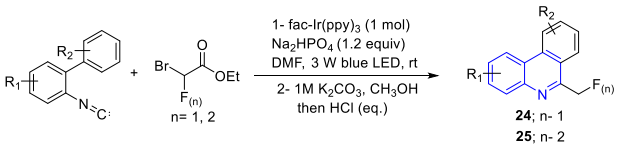
Under solvent-free conditions and using microwave irradiation at 80 °C, the condensation reaction between acyl anilines and pentane-2,4-dione (10 equiv) was achieved in the presence of barium or calcium imidazolium-dicarboxylate (10 mol%) as a heterogeneous catalyst to afford quinoline derivatives **42** with a decent yield (Scheme 30) [79].



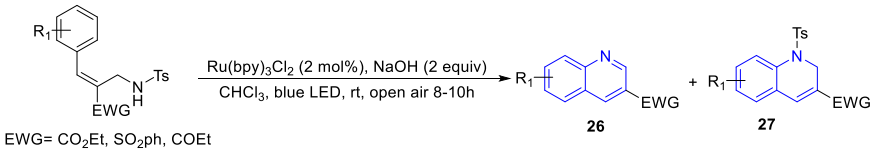
Scheme 18 Synthesis of 2-aryl quinolines **21** from β-arylpropionitriles with aryl lithiums and NIS



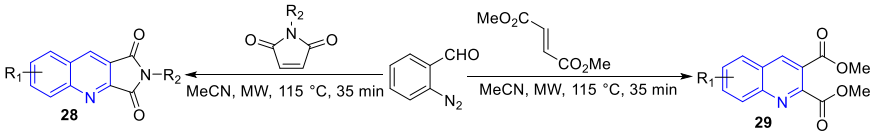
Scheme 19 Synthesis of quinoline fused cyclopentane **22** and **23** from biphenyl-4-isocyanide



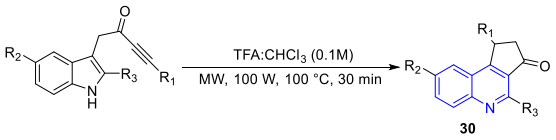
Scheme 20 Synthesis of fused quinoline derivatives **24** and **25** from 2-isocyanobiphenyls



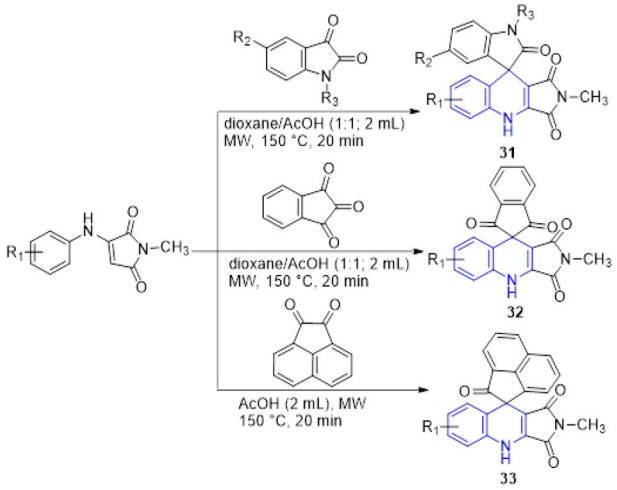
Scheme 21 Synthesis of quinolines derivatives **26** and **27** from (aza)-Morita–Baylis–Hillman adducts



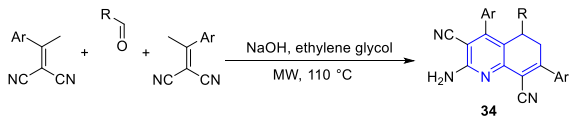
Scheme 22 Synthesis of pyrroloquinolinediones **28** and quinolinedicarboxylates **29**



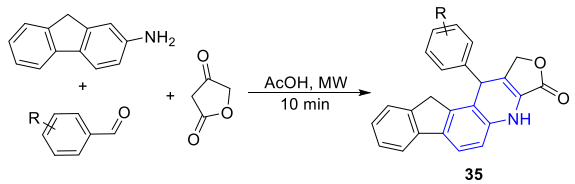
Scheme 23 Synthenderzsis of 3,4-cyclopentan-quinoline-3-ones **30**



Scheme 24 Synthesis of spiro pyrroloquinoline's **31, 32**, and **33** from anilinosuccinimide derivatives and α-dicarbonyl compounds



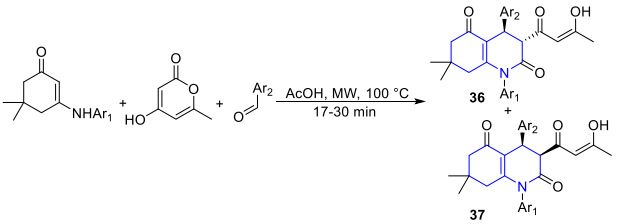
Scheme 25 Synthesis of Poly-functionalized dihydroquinoline derivatives **34** from aryl ethylidene malononitriles



Scheme 26 Synthesis of furoindeno[2,1-f]quinolin-1-one derivatives **35**

Computer prediction of biological activity of quinoline

A drug-like organic molecule, whose molecular mass ranges from 50 to 1250 Da, can have its likely biological activity profile estimated using computer tools like the PASS and Swiss ADME web resources based on its structural formula. The estimation is based on examining



Scheme 27 Diastereoselective synthesis of quinoline-2,5-diones **36** and **37**

the structure-activity relationships for a large training set that includes pharmaceutical agents, chemical probes, compounds for which specific toxicity data is known, drug substances, drug candidates in various clinical and pre-clinical research stages, and drug substances.

Drug-likeness and oral bioavailability analysis of quinoline nucleus using Swiss ADME web resources

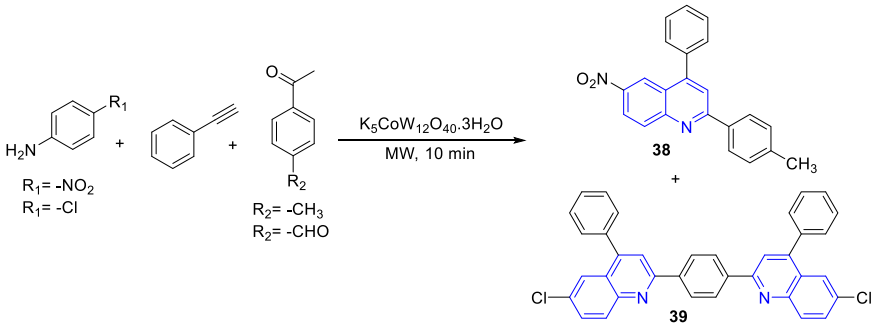
Analysis of the pharmacokinetic properties of the potential drug is essential in the early stage of drug discovery. According to Lipinski and his team (Lipinski CA. Lead, and drug-like compounds: the rule-of-five revolution. Drug Discov Today. 2004; 1:337–341), drug-like quinoline must obey the rule of five (RO5), i.e., molecular weight (M.W.) ≤ 500 Da, number of hydrogen bond donor ≤ 5, number of hydrogen bond acceptor ≤ 10, as shown in Fig. 3 [80].

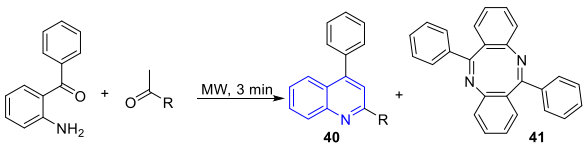
Using the Pass Web resource for prediction of biological activity of quinoline

PASS Online, a free online resource, is given. With an average accuracy above 95%, this resource (http://www.way2drug.com/passonline) is made to predict the biological activity spectra of organic compounds based on their structural formulas for more than 4000 categories of biological activity. A study of the structure-activity relationships in the training set, which contains data on the composition and biological function of more than 300,000 organic compounds, served as the foundation for the prediction [81].

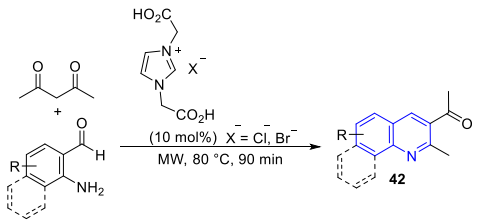
Table 1S shows biological activity spectrum predictions obtained using the Pass Program for the quinoline nucleus; it gives the prediction score for biological properties on the ratio of probability to be active (Pa)' and 'probability of being inactive (Pi).' A higher Pa means the biological

Scheme 28 Synthesis of quinoline and bis-quinoline derivatives **38** and **39**





Scheme 29 Synthesis of quinoline derivatives **40** and dibenzo[b,f][1,5]diazocines **41**



Scheme 30 Synthesis of quinoline derivatives **42** catalyzed by barium or calcium imidazolium-dicarboxylate

property has more probability for a compound.., while Table 2S shows possible adverse & toxic effects of quinoline nucleus calculated through the PASS webserver.

Biological activity of quinoline derivatives

Almost heterocyclic compounds such as coumarin, indole, pyridone, quinoline, tetrazole, pyrimidine, thiazole, purine, imidazole, flavones, and others have already been employed as a tool for drug discovery research and development. For example, the quinoline ring is an attractive scaffold with many essential properties, mainly anticancer, antioxidant, antimicrobial, anti-inflammatory, and antituberculosis.

Anticancer activity

Kamal et al. synthesized and screened a variety of quinoline-chalcone attached podophyllotoxin against different cancer cell lines such as lung (A549), melanoma (A375), breast (MCF-7), colon (HT29), and renal cancer ACHN in comparison with doxorubicin, etoposide, and podophyllotoxin as a reference using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. This study showed that quinoline-chalcone in compound **43** enhanced the anticancer activity of podophyllotoxin with IC_{50} ranging from 2.2 to 15.4 µM (Fig. 4) [82].

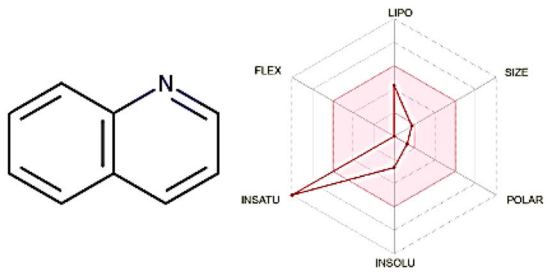
A series of cyano, Bromo, methoxy, and nitro groups-substituted quinoline were synthesized and evaluated for their anticancer activity against lung (A549), cervical (HeLa), colon (HT29), liver (Hep3B), and breast (MCF7) cancer cell lines using MTT cell proliferation assay and 5-fluorouracil and cisplatin as standard drugs. These efforts revealed that the newly synthesized compounds such as 6-Bromo tetrahydro quinoline **44**, 6,8-dibromo-tetrahydro quinoline **45**, 8-Bromo-6-cyanoquinoline **46**, 5-Bromo-6,8-dimethoxyquinoline **47**, 6,8-dimethoxy-1-nitroquinolin-1-ium **48**, and 5,7-dibromo-8-hydroxyquinoline **49** (Fig. 5) displayed a potential anticancer activity against the Hep3B, HeLa, A549, HT29, and MCF7 cancer cell lines with IC_{50} band from 2 to 50 µg/ml and low cytotoxicity equals a proximately 7–35% [83].

Özcan et al. [84] prepared quinoline derivatives (Fig. 6) and tested their anticancer potencies. The newly synthesized compounds' activities were determined in the cervical (HeLa), rat brain tumor (C6), and colon (HT29) cancer cell lines according to the MTT, sulforhodamine B, and bromodeoxyuridine cell proliferation ELISA assays using 5-fluoro uracil as a reference. This study's results show that the compound 5,7-dibromo-8-hydroxyquinoline 50 is the most hopeful anticancer against the HeLa, HT29, and C6 cell lines with IC_{50} ranging from 3.7 to 16.3 µM.

Antioxidant activity

Hegde et al. [85] synthesized and screened quinoline derivatives bearing carbothioamide and triazole moiety as antioxidant agents using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay under ascorbic acid control ($IC_{50} = 0.032 \pm 0.001$). Compounds **53, 54, 55**, and **56** showed potent antioxidant activity up to 92% inhibition.

Nagargoje et al. [86] formulated a set of quinoline-based aminocarbonyl curcumin analogs **57–61** and



SMILES c1ccc2c(c1)nccc2

Physicochemical Properties	
Formula	C9H7N
Molecular weight	129.16 g/mol
Num. heavy atoms	10
Num. arom. heavy atoms	10
Fraction Csp3	0.00
Num. rotatable bonds	0
Num. H-bond acceptors	1
Num. H-bond donors	0
Molar Refractivity	41.74
TPSA	12.89 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.73
Log $P_{o/w}$ (XLOGP3)	2.03
Log $P_{o/w}$ (WLOGP)	2.23
Log $P_{o/w}$ (MLOGP)	1.85
Log $P_{o/w}$ (SILICOS-IT)	2.57
Consensus Log $P_{o/w}$	2.08

Water Solubility	
Log *S* (ESOL)	-2.66
Solubility	2.83e-01 mg/ml ; 2.19e-03 mol/l
Class	Soluble
Log *S* (Ali)	-1.93
Solubility	1.52e+00 mg/ml ; 1.18e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-3.66
Solubility	2.82e-02 mg/ml ; 2.18e-04 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.65 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 2 violations: MW<160, #atoms<20
Veber	Yes
Egan	Yes
Muegge	No; 2 violations: MW<200, Heteroatoms<2
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW<250

Fig. 3 Computed values for prediction parameters of quinoline

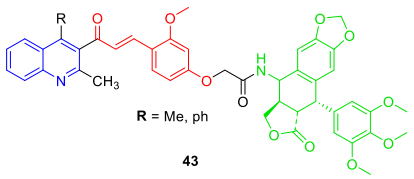


Fig. 4 Quinoline-chalcone attached podophyllotoxin **43** enhanced anticancer activity

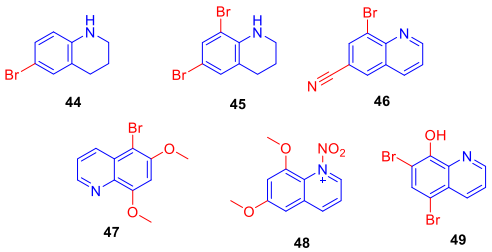


Fig. 5 Quinoline-chalcone attached podophyllotoxin **44–45** enhanced anticancer activity

assessed their in vitro antioxidant activity using DPPH radical scavenging assay butylated hydroxytoluene (BHT) regulation. Most newly synthesized compounds (Fig. 7) showed potent antioxidant activity compared to BHT ($IC_{50} = 16.47 \pm 0.18$ µg/mL).

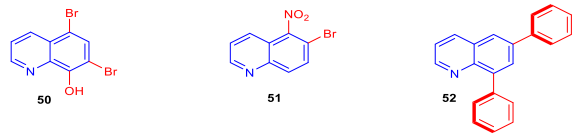


Fig. 6 Quinoline derivatives **50–52** as anticancer agents

Antimalarial and anti-SARS-CoV-2 activity

Chloroquine **62** contributes to chloroquine phosphate **63** (Fig. 8), a promising medication for malaria and SARS-CoV-2 diseases. In 1950, hydroxychloroquine **64** (Fig. 9) was derived from chloroquine **62** and gave better safety features besides a similar action mechanism to chloroquine [87]. In addition, chloroquine has a small molecular size and lipophilic properties, so chloroquine can diffuse through erythrocyte and parasite membranes and inhibit DNA and RNA synthesis. Furthermore, hydroxychloroquine can inhibit SARS-CoV-2 replication [88].

On February 17, 2020, the Chinese State Council announced chloroquine phosphate **63** as an effective SARS-CoV-2 treatment based on clinical trials at a different clinic center in China [89]. Chloroquine **62** prevents in vitro SARS-CoV-2 infection at low concentrations on micromolar scale with a maximum effective concentration (EC_{50})

of 1.13 µM, and a Cytotoxic (CC_{50}) concentration greater than 100 µM [90].

Anti-inflammatory activity

Ghodsia et al. [91] synthesized a class of quinoline derivatives **65–69** (Fig. 10) possessing imidazole and methylsulfonyl motifs and examined their in vitro COX-1 and COX-2 inhibition activities, which declared that almost new synthesized compounds were effective with IC_{50} in the full scope of 0.063–0.090 µM as compared to celecoxib (IC_{50} = 0.060–24.3 µM). Results showed increased lipophilic properties of substituents on the C-7 and C-8 quinoline ring increased COX-2 inhibitory potency and selectivity. The relative COX-2 potency and COX-2 selectivity profiles for the 4-imidazolyl methyl quinoline derivatives concerning the C-7 and C-8 substituents were 68 > 67 > 65 > 66 > 69. However, among the 4-imidazolyl methyl quinoline derivatives, compound 68, possessing an unsaturated cyclohexyl ring attached to C-7 and C-8 quinoline ring, exhibited the highest COX-2 inhibitor potency and selectivity (COX-2 IC_{50} = 0.063 µM; SI = 547.6) that was as potent as the reference drug celecoxib and more selective COX-2 inhibitor than celecoxib (COX-2IC_{50} = 0.060 µM; SI = 405).

Antituberculosis activity

Thakare et al. [92] prepared several quinoline-substituted benzyl groups **70–74** (Fig. 11) containing pyrazole and triazole moiety. They tested their in vitro activity as antituberculosis agents against *M. tuberculosis* H37Ra strains using rifampicin as a reference. The results revealed that most new compounds displayed excellently to moderate Activity against *M. tuberculosis* H37Ra with 34.10–54.60% inhibition. Based on the results outcomes from the study, it

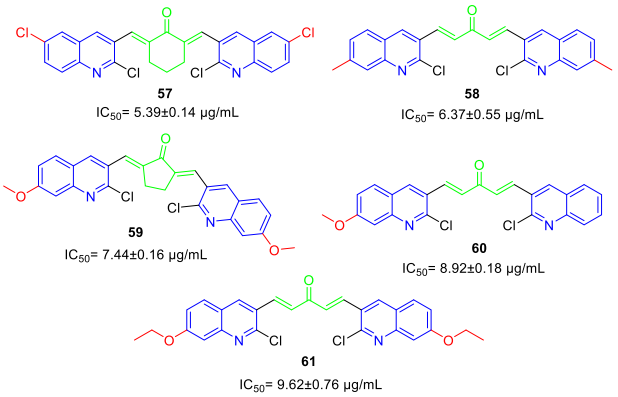


Fig. 7 Quinoline-based aminocarbonyl curcumin analogs **57–61** as anticancer agents

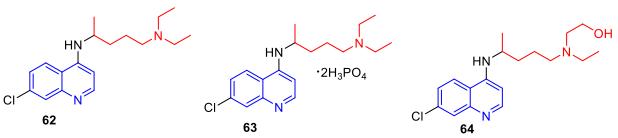


Fig. 8 Chloroquine **62**, chloroquine phosphate **63**, and hydroxychloroquine **64** as SAR-COV-2 medicine

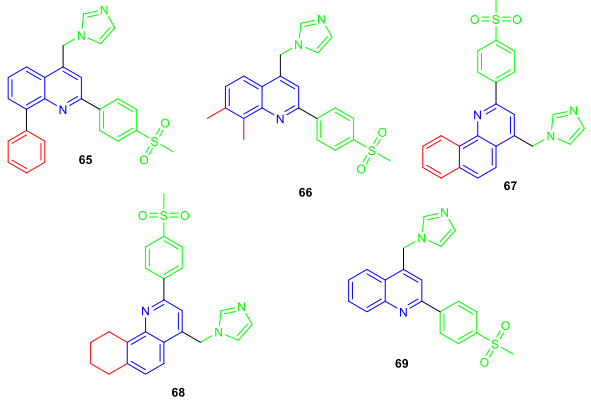
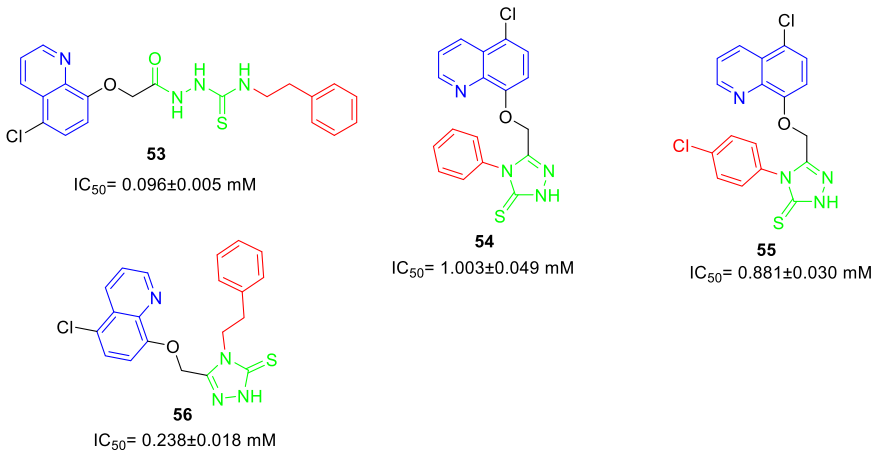


Fig. 10 Quinoline derivatives **65–69** possess imidazole and methylsulfonyl moiety

Fig. 9 Quinoline derivatives **53–56** bearing carbothioamide and triazole moiety as antioxidant agents



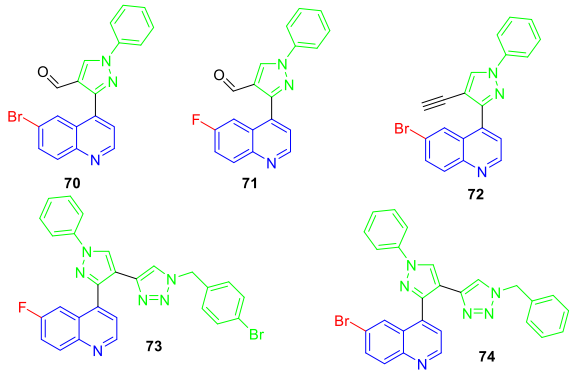


Fig. 11 Quinoline-substituted benzyl group, 70–74, containing pyrazole and triazole moiety as antituberculosis agents

was noticed that fluorine derivatives have stronger inhibitory ability than bromine derivatives.

Conclusion and future perspectives

Based on a great interest in quinoline compounds chemistry and its medicinal applications, it is clear that quinoline and its derivatives interact with diverse biological targets like proteins, receptors, and enzymes, which could pave the way for finding novel medication candidates to overcome recent world health problems such as the present COVID-19 crisis.

In this regard, we have briefed traditional and novel synthetic methods for accessing quinoline and its congeners, including green multicomponent one-pot synthesis, cascade reactions, and solvent-free reaction conditions besides a microwave ultraviolet irradiation-promoted synthesis using reusable and recyclable green catalysts. All these aspects are highly significant to the achievement of these pharmacologically active heterocycles; on these bases, we have summarized the current progress and recent studies of the biological importance of different quinoline derivatives, mainly anticancer, anti-inflammatory, antioxidant, antituberculosis, antimalarial, and anti-SARS-CoV-2.

The significant markers of advances in this sector are signs of quinoline core compounds entering the preclinical stages and clinical usages. Therefore, the researchers are still using synthetic approaches to prepare and improve bioactive quinoline derivatives utilizing classical methods and novel developed reaction procedures. These protocols will significantly impact the quick construction of molecular libraries and the cohort of structure-activity relationship studies. So we predict that more signs of progress will be made in the synthetic process with these findings.

Regarding the scope of topics covered in this mini-review, we expect that the combined approach of the conventional methods with green synthetic procedures will find widespread applications and continue to capture great interest and developments in the eco-friendly, fast, and economical synthetic methods of quinoline motifs. Finally, we hope the subjects mentioned above of quinoline scaffolds will lead the researchers to develop and find novel and efficient therapeutic products.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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