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Quinoline Heterocycles: Synthesis and Bioactivity

Yamajala B.R.D. Rajesh

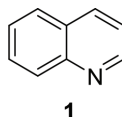
Abstract

Among heterocyclic compounds, quinoline is a privileged scaffold that appears as an important construction motif for the development of new drugs. Quinoline nucleus is endowed with a variety of therapeutic activities, and new quinolone derivatives are known to be biologically active compounds possessing several pharmacological activities. Many new therapeutic agents have been developed by using quinoline nucleus. Hence, quinoline and its derivatives form an important class of heterocyclic compounds for the new drug development. Numerous synthetic routes have been developed for the synthesis of quinoline and its derivatives due to its wide range of biological and pharmacological activities. The article covers the synthesis as well as biological activities of quinoline derivatives such as antimalarial, anticancer, antibacterial, anthelmintic, antiviral, antifungal, anti-inflammatory, analgesic, cardiovascular, central nervous system, hypoglycemic, and miscellaneous activities.

Keywords: quinoline, heterocyclic compound, quinoline derivatives, synthesis, biological activity

1. Introduction

Quinoline **1** or 1-azanaphthalene or benzo[*b*]pyridine is an aromatic nitrogen-containing heterocyclic compound having a molecular formula of C_9H_7N , and the molecular weight is 129.16. Being a weak tertiary base, it forms salts with acids and exhibits reactions similar to benzene and pyridine. It participates in both electrophilic and nucleophilic substitution reactions.



Quinoline moiety commonly exists in various natural compounds (*Cinchona* alkaloids), and pharmacological studies have shown that the quinolone ring system is present in many compounds exhibiting a broad range of biological activities. Quinoline has been found to have antibacterial, antifungal, antimalarial, anthelmintic, anticonvulsant, cardiotonic, anti-inflammatory, and analgesic activities.

2. Synthesis

In the literature, a number of established protocols have been reported for the synthesis of quinoline ring, which can be altered to produce a number of differently substituted quinolines. The quinoline ring has been generally synthesized by various conventional named reactions such as Skraup, Doebner-Von Miller, Pfitzinger, Friedlander, Conrad-Limpach, and Combes synthesis (**Figure 1**) [1].

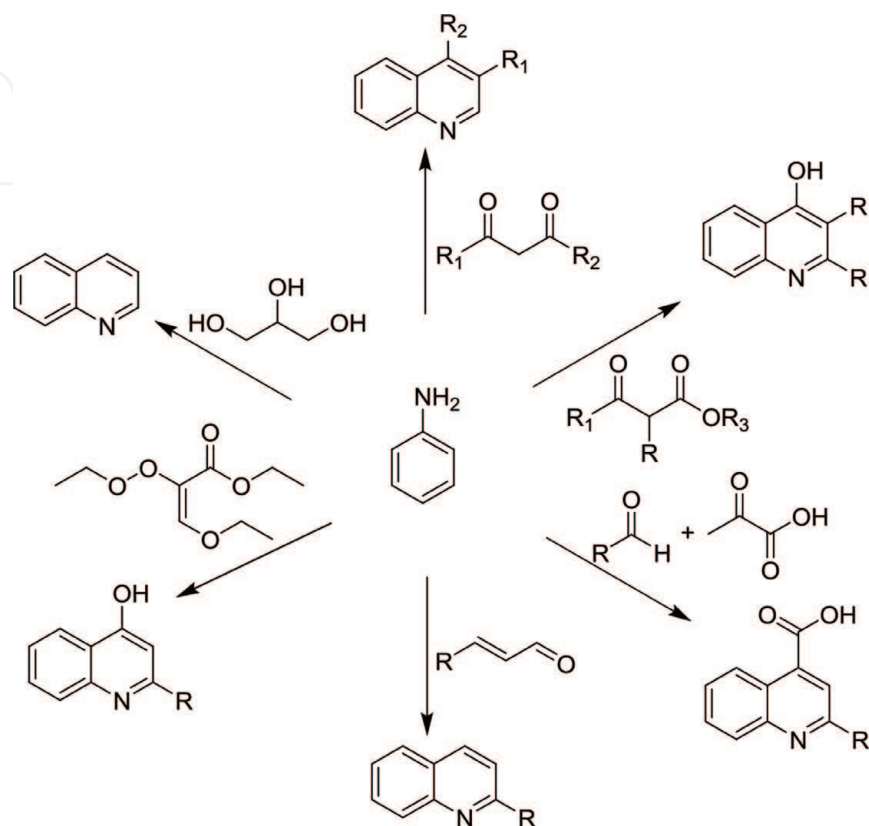
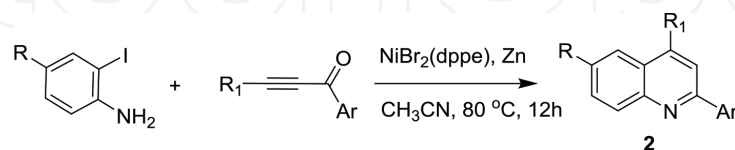
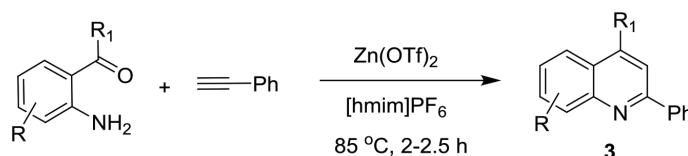


Figure 1.
Conventional methods of synthesis of various substituted quinolines.

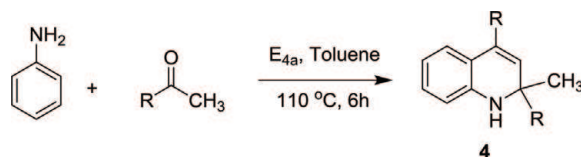
Apart from the conventional methods, a vast number of synthetic routes have been developed for the synthesis of quinoline and quinoline derivatives. Chen et al. reported the synthesis of 2,4-disubstituted quinolines, **2** by the condensation of 2-iodoanilines with alkynyl aryl ketones using nickel catalyst [2].



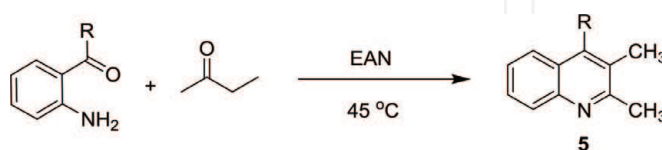
2,4-Disubstituted quinolones, **3** have been obtained by the cyclization of 2-aminoaryl ketones with phenylacetylenes. This reaction takes place in ionic liquid medium ([hmim]PF₆) in the presence of zinc trifluoromethanesulfonate catalyst [3]. Lekhok et al. synthesized the same product in the presence of catalytic amount of indium(III) trifluoromethanesulfonate (In(CF₃SO₃)₃) under microwave and solvent-free conditions [4].



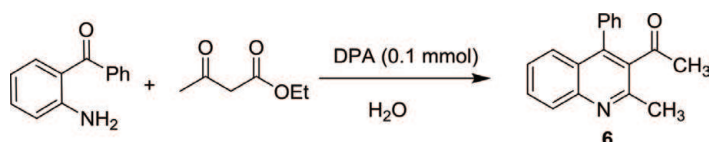
2,4-Diphenyl-2-methyl-1,2-dihydroquinoline, **4** has been prepared by the condensation followed by cyclization of aniline and acetophenone. The reaction proceeds with the help of a zeolite catalyst, E_{4a} [5].



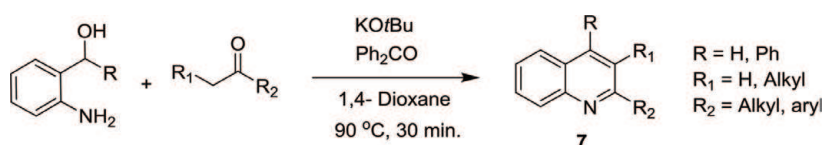
2,3,4-Trisubstituted quinolones, **5** have been synthesized by Friedlander annulation of 2-amino substituted aromatic ketones and reactive methylene group containing carbonyl compounds in the presence of ethyl ammonium nitrate (EAN) [6].



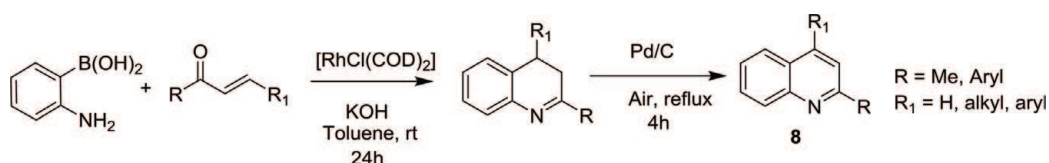
By stirring 2-aminoaryl ketones and various α -methylene ketones in the presence of dodecylphosphonic acid (DPA) catalyst in water or solvent-free conditions, poly-substituted quinolones, **6** have been synthesized [7].



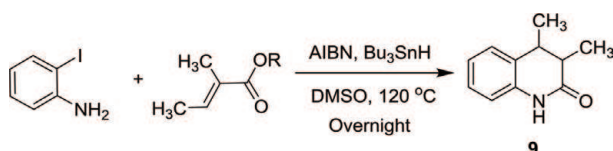
2-Aminobenzyl alcohol reacts with ketones or alcohols in the presence of a base, and benzophenone resulted in the formation of poly-substituted quinolones, **7** [8]. Here, benzophenone acts as a hydride scavenger.



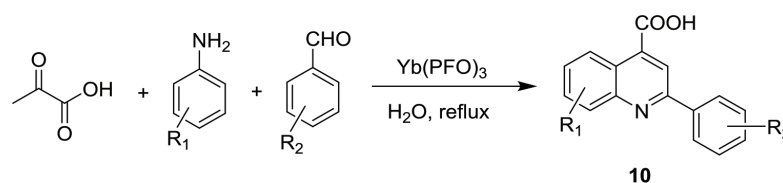
Horn et al. reported the synthesis of quinolines, **8** from α , β -unsaturated ketones and *o*-aminophenylboronic acid derivatives [9]. This method is the modification of the conventional Skraup-Doebner-Von Miller synthesis and that the reaction proceeded under basic conditions.



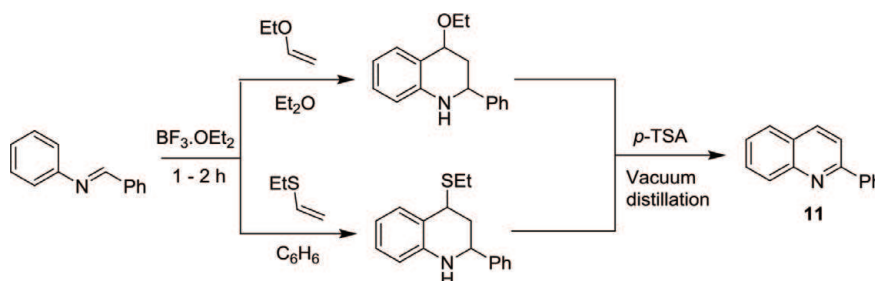
3,4-Dihydroquinolin-2-ones, **9** have been synthesized by treating 2-iodoanilines and various acrylates using azobisisobutyronitrile (AIBN) in the presence of tributyltin hydride [10].



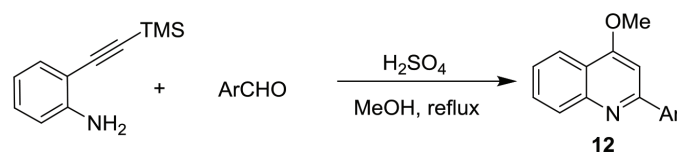
Wang et al. developed a method for the synthesis of 2-phenylquinoline-4-carboxylic acids, **10** by the treatment of pyruvic acid with substituted aniline and benzaldehyde in the presence of rare-earth metal catalysts in water under reflux condition [11].



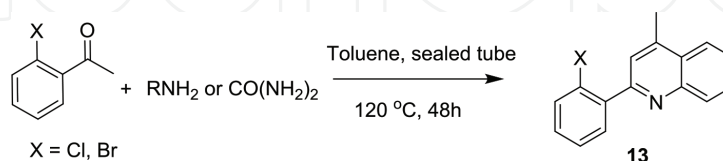
Kouznetsov et al. synthesized phenyl-substituted quinolones, **11** by reacting ethyl vinyl ether or ethyl vinyl sulfide with N-aryldimine in the presence of Lewis acidic catalysts such as boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$) to obtain 2,4-substituted tetrahydroquinolines. The tetrahydroquinolines were aromatized to 2-phenyl-substituted quinolines under vacuum distillation in the presence of *p*-TSA [12].



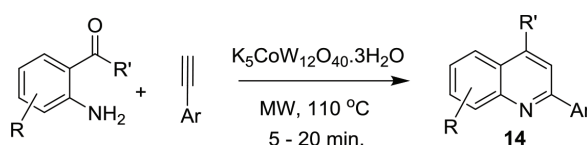
Wang et al. reported the synthesis of 2-phenyl-4-alkoxy quinolines, **12** by cyclocondensation of 2-(2-trimethylsilyl)ethynyl aniline with aromatic aldehydes in the presence of sulfuric acid as catalyst in methanol solvent [13].



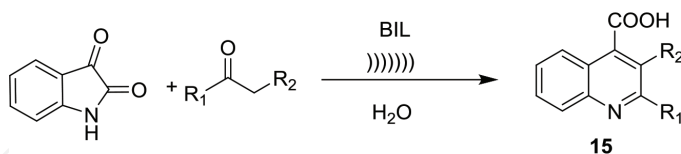
Two molecules of *o*-haloacetophenones condensed with urea or primary amines yielded certain halogen-substituted quinolones, **13**. The halogen-substituted quinolines were formed through the cleavage of $\text{C}(\text{sp}^2)$ -halogen and $\alpha\text{-C}(\text{sp}^3)\text{-H}$ bonds and the formation of new bonds in a selective manner [14].



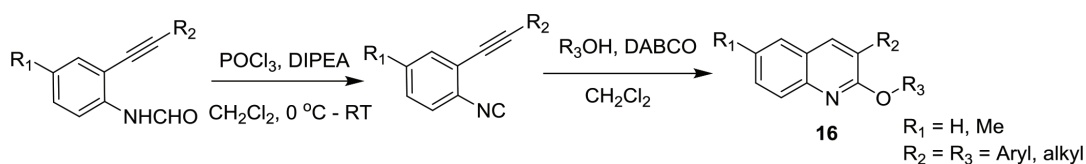
A one-pot reaction of 2-aminoaryl ketones with certain arylacetylenes results in the formation of 2,4-disubstituted quinolones, **14**. The reaction was performed in a green synthetic route using potassium dodecatungstocobaltate trihydrate ($\text{K}_5\text{CoW}_{12}\text{O}_{40} \cdot 3\text{H}_2\text{O}$) as a recyclable and eco-friendly catalyst under microwave and solvent-free conditions [15].



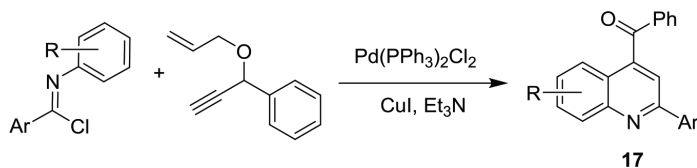
Kowsari et al. synthesized certain quinolones, **15** by reacting isatin with aryl methyl ketones in the presence of basic ionic liquids in water [16]. The reaction was conducted under ultrasound green synthetic conditions. The main advantages of this procedure are (i) a green method, (ii) milder and shorter reaction time, and (iii) higher yields and selectivity without a transition metal catalyst.



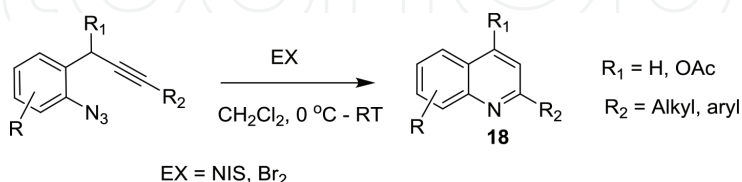
1,4-Diazabicyclo[2.2.2]octane (DABCO) promoted structurally diverse 2-alkoxy- and 2-aryloxy-3-substituted quinolones, **16** that have been synthesized by treating *o*-alkynylaryl isocyanides with alcohols and phenols [17]. DABCO initiates the reaction as a nucleophile and facilitates the formation of the product as a leaving group being replaced by oxygen nucleophiles.



Benzimidoyl chlorides when treated with 1-(1-(allyloxy)prop-2-ynyl)benzene (1,6-enynes) yielded diverse quinoline derivatives, **17** via a domino palladium-catalyzed Sonogashira coupling and followed by cyclization [18].



Diversified quinolones, **18** have been synthesized by the intramolecular cyclocondensation of 1-azido-2-(2-propynyl)benzenes using electrophilic reagents (I_2 , Br_2 , ICl , NBS, NIS, and $HNTf_2$) in nitromethane at 0°C to room temperature. The reaction also proceeds in the presence of $AuCl_3/AgNTf_2$ catalysts in THF at 100°C [19].

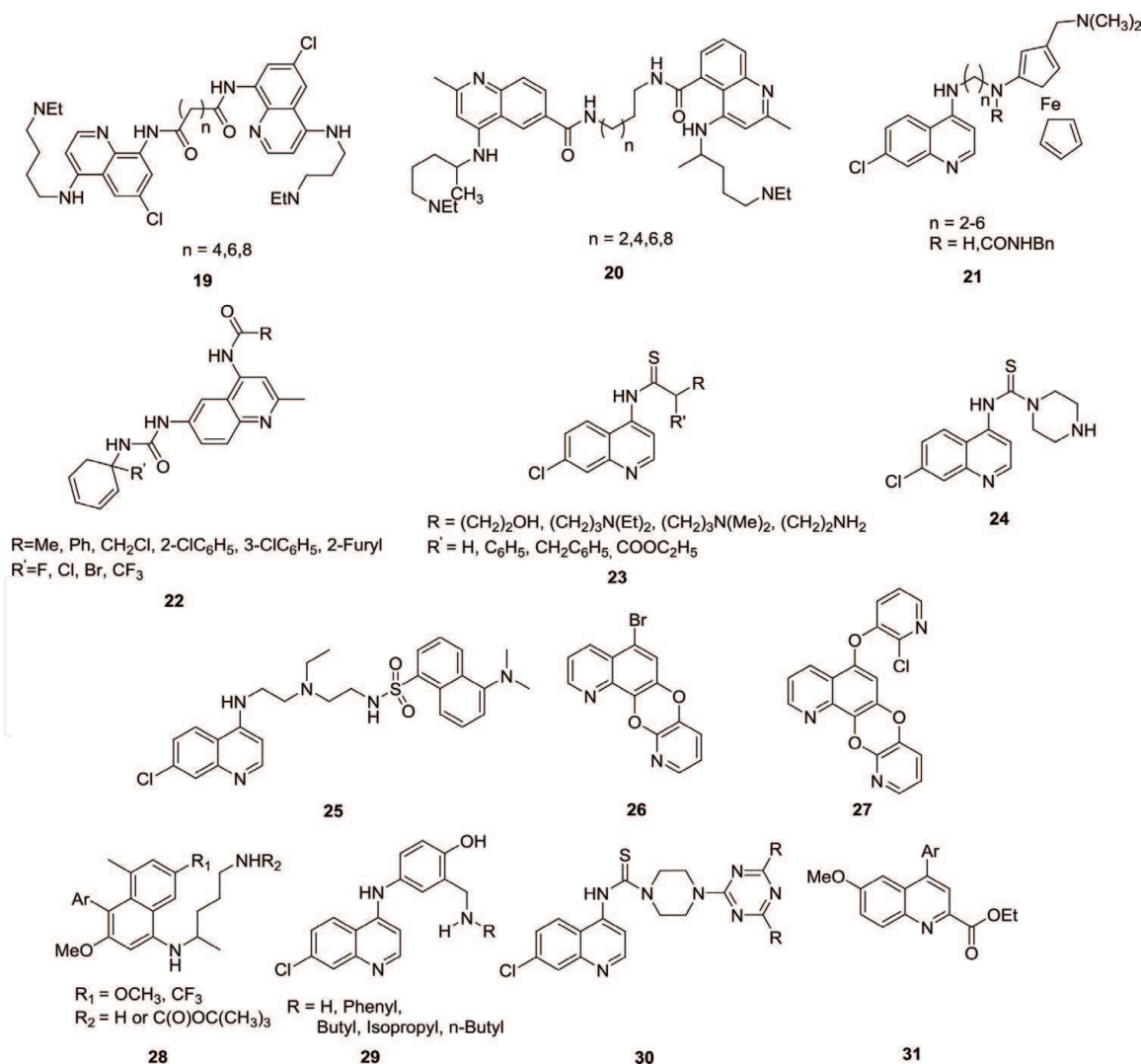


3. Biological activity

3.1 Antimalarial

Quinolines are known for their excellent antimalarial properties. Raynes et al. developed bisquinolines, **19**, **20** that exhibit antimalarial activity against chloroquine-resistant and chloroquine-sensitive parasites [20]. Derivatives of ferrochloroquine, **21** were also found to possess antimalarial activity [21]. In these derivatives, the carbon skeleton of chloroquine is replaced by ferrocene group. Modapa et al.

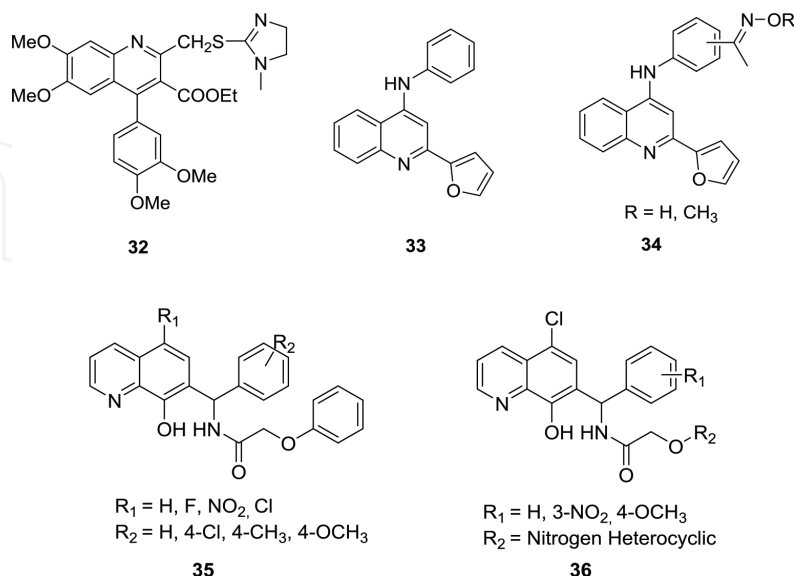
reported that the synthesis of ureido-4-quinolinamides, **22** showed antimalarial activity at MIC 0.25 mg/mL against chloroquine-sensitive *Plasmodium falciparum* strain [22]. Several 7-chloroquinolinyl thioureas, **23**, **24** have been synthesized by Mahajan et al. that possess excellent antimalarial properties [23]. Kovi et al. synthesized a chloroquinolyl derivative, **25** that has an excellent antimalarial activity even at very low concentrations [24]. Acharya et al. reported the synthesis and potent antimalarial activity of certain pyridine-quinoline hybrid conjugates, **26**, **27** against chloroquine susceptible *P. falciparum* strain [25]. Shiraki et al. produced some 5-aryl-8-aminoquinolines, **28** with good antimalarial activity and had mild hemolytic activity than tafenoquine [26]. Singh et al. developed several antimalarial 4-anilinoquinolines, **29** which showed good antimalarial activity against chloroquine-sensitive *P. falciparum* strains [27]. Novel hybrid conjugates of N-(7-chloroquinolin-4-yl) piperazine-1-carbothioamide and 1,3,5-triazine derivatives, **30** have been synthesized by Bhat et al. These hybrid conjugates possess considerable antimalarial activity against both wild and mutant parasites on changing the pattern of substitution [28]. McNulty et al. developed 4-arylquinoline-2-carboxylate derivatives, **31** which show antiprotozoal activity against the pathogenic parasite *Toxoplasma gondii* [29].



3.2 Anti-inflammatory activity

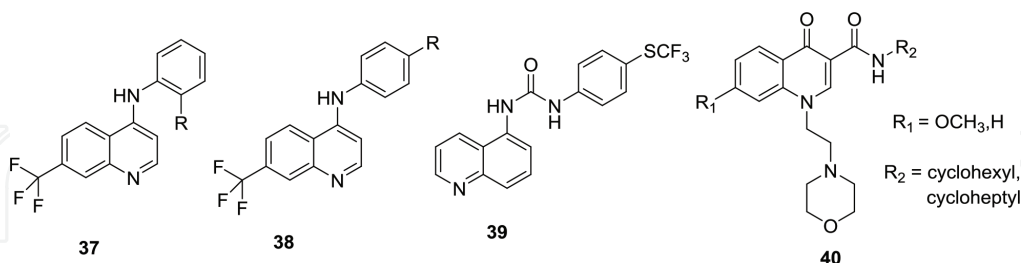
A quinoline derivative, **32** with strong anti-inflammatory activity was synthesized by Baba et al. in adjuvant arthritis rat model [30]. Chen et al. developed

2-(furan-2-yl)-4-phenoxy-quinoline derivatives, **33**, **34** that inhibit the lysozyme and β -glucuronidase release [2]. Few quinoline derivatives, **35**, **36** have been synthesized and evaluated by Gilbert et al. for treating osteoarthritis and that are amino-acetamide inhibitors of aggrecanase-2 [31].



3.3 Analgesic activity

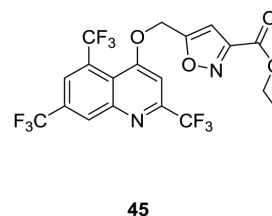
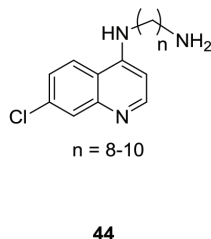
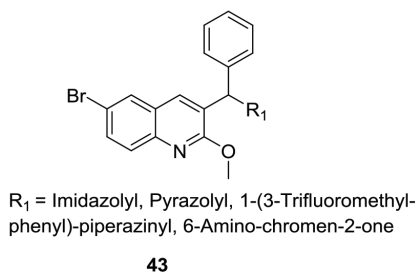
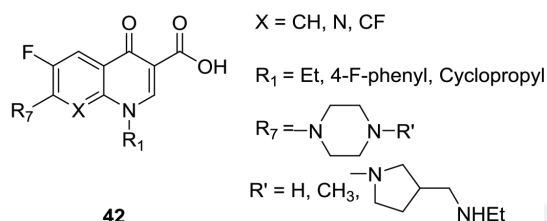
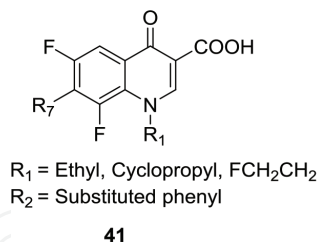
4-Substituted-7-trifluoromethylquinolines **37**, **38** have been developed by Abadi et al., and these derivatives were found to possess excellent analgesic activity with nitric oxide releasing characteristics [32]. Gomtsyan et al. synthesized an analgesic active derivative, **39**. The activity is due to its antagonism at vanilloid receptors [33]. Some quinoline derivatives, **40** were synthesized by Manera et al. that show analgesic activity and are selective agonists at cannabinoid CB₂ receptors [34].



3.4 Antibacterial

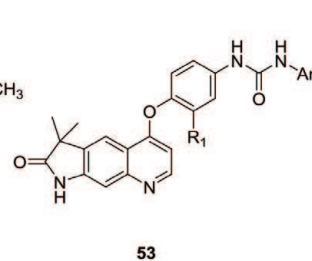
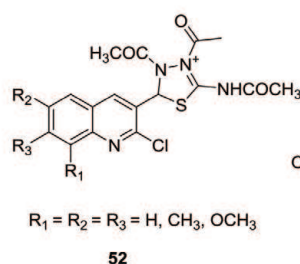
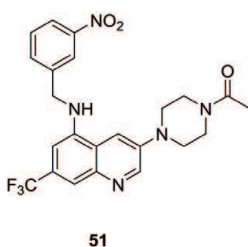
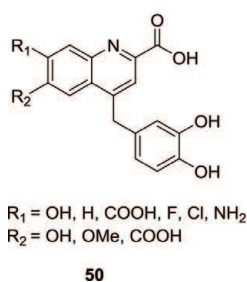
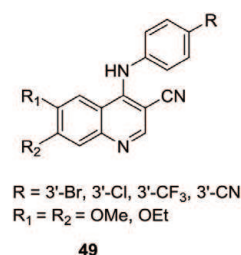
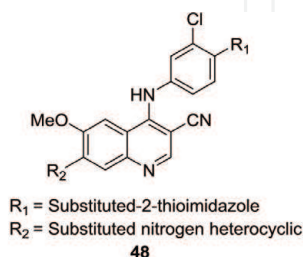
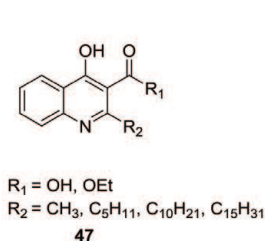
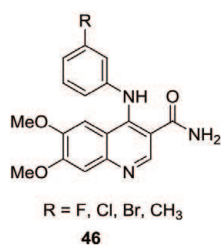
Ma et al. reported the synthesis and antibacterial evaluation of phenoxy-, phenylthio-, and benzyloxy-substituted quinolones, **41** [35]. A few 8-substituted quinoline carboxylic acids, **42** were synthesized by Sanchez et al. that showed antibacterial activity [36]. Upadhayaya et al. developed 3-benzyl-6-bromo-2-methoxy quinoline derivatives, **43**, and these derivatives are active against *Mycobacterium tuberculosis* H37Rv strain [37]. A few analogues of 7-chloro quinolones, **44** were synthesized by De Souza et al., and these derivatives were found to be effective against multidrug-resistant tuberculosis [38]. Lilienkamp et al. synthesized quinoline-based compounds containing an isoxazole unit and side chain, **45** that was active against *Mycobacterium tuberculosis* [39]. The novel hybrid

conjugates of N-(7-chloroquinolin-4-yl) piperazine-1-carbothioamide and 1,3,5-triazine derivatives, **30** synthesized by Bhat et al. also showed excellent antibacterial activity against several Gram-positive and Gram-negative microorganisms [40].



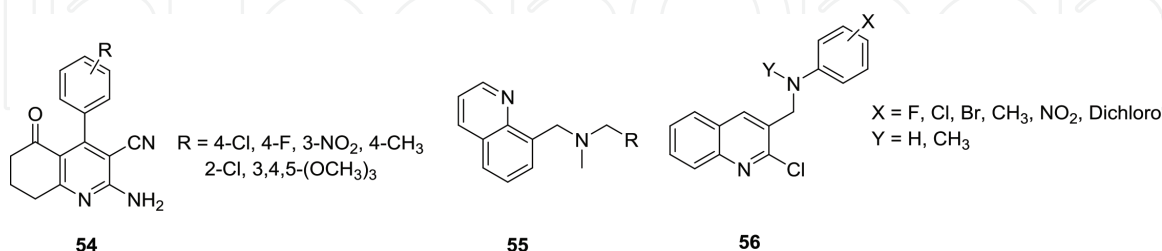
3.5 Antitumor

Some amido-anilinoquinolines, **46** were synthesized by Scott et al. that act as antitumor agents by inhibiting CSF-1R kinase [41]. Certain derivatives of 4-hydroxyquinolines, **47** were synthesized by Mai et al. that showed histone acetyltransferase (HAT) inhibitory activity [42]. A few 3-cyanoquinolines, **48** were developed by Miller et al. as inhibitors of growth factor receptors (IGF-1R) for treating cancer [43]. 4-Anilinoquinolines, **49** were synthesized by Assefa et al. which were found to contain tyrosine kinase inhibitors [44]. Quinoline carboxylic acids, **50** have been synthesized by Chen et al. that act as antitumor compounds by inhibiting insulin-like growth factors [45]. A few c-Met kinase inhibitory quinolones, **51** were developed by Wang et al. with $\text{IC}_{50} < 1 \text{ nM}$. These derivatives were found to show the inhibition of c-Met phosphorylation in c-Met-dependent cell lines [46]. Marganakop et al. developed few 6,7,8-substituted thiosemicarbazones of 2-chloro-3-formyl-quinoline derivatives, **52** which exhibit excellent anticancer activities [47]. Recently, some quinoline derivatives, **53** were synthesized as novel Raf kinase inhibitors with potent and selective antitumor activities. These derivatives were synthesized by modifying the structure of sorafenib [48].



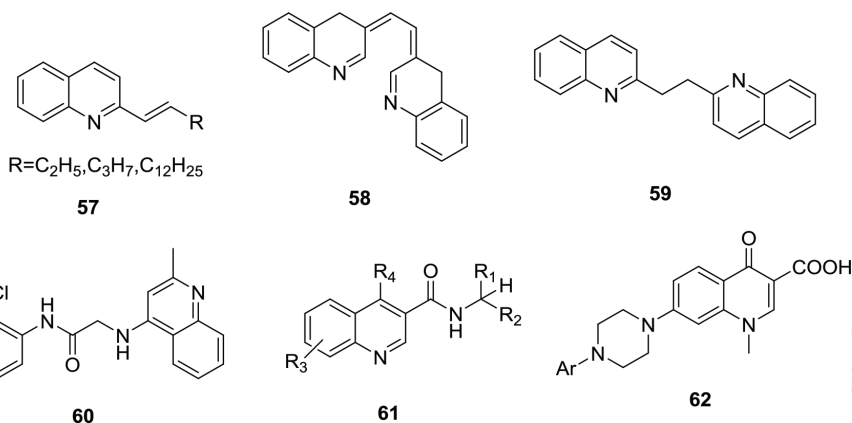
3.6 Antifungal

Certain tetrahydroquinolines, **54** were synthesized by Gholap et al. which were found to possess good antifungal activity against *Candida albicans*, *Fusarium oxysporum*, and *Mucor* fungi [49]. Kharkar et al. synthesized few quinoline derivatives, **55** that show good antifungal properties [50]. Kumar et al. developed few non-azole antimycotic agents having secondary amine attached 2-chloroquinolines, **56** and evaluated their antifungal activity against *Penicillium citrinum*, *Aspergillus niger*, *Monascus purpureus*, and *A. flavus* sp. [51].



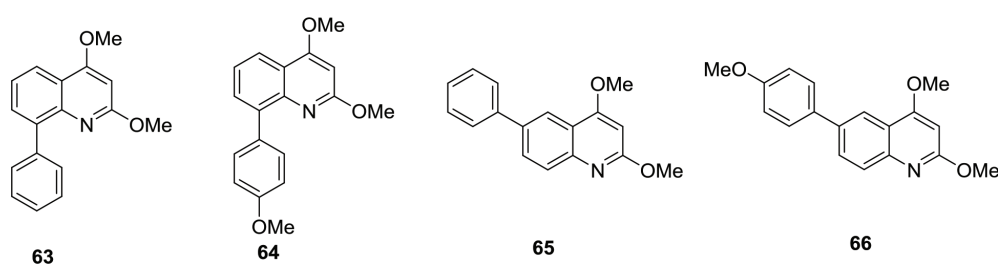
3.7 Antiviral

Several mono- and poly-substituted quinolones, **57–59** synthesized by Fakhfakh et al. were found to exhibit activity against HIV-1 [52]. Ghosh et al. synthesized anilidoquinoline derivatives, **60** which were found to possess an excellent antiviral activity against Japanese encephalitis virus [53]. A few quinoline derivatives, **61** possessing the behavior as HIV-1 Tat-TAR interaction inhibitors were synthesized by Chen et al. [45]. Massari et al. synthesized few desfluoroquinolones, **62** for treating HIV infection [54].



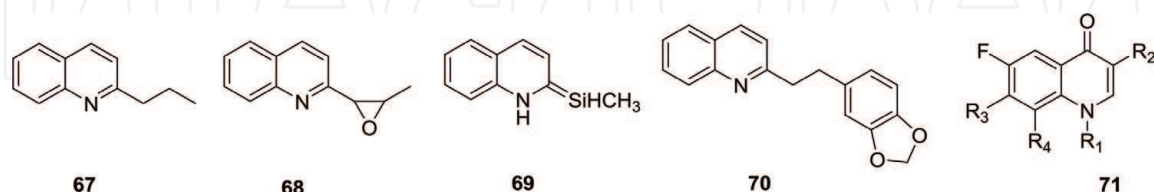
3.8 Anthelmintic

Substituted 2,4-arylquinolines, **63–66** have been synthesized by Rossiter et al. which possess good anthelmintic activity against levamisole-, ivermectin-, and thiabendazole-resistant strains of *H. contortus* [55].



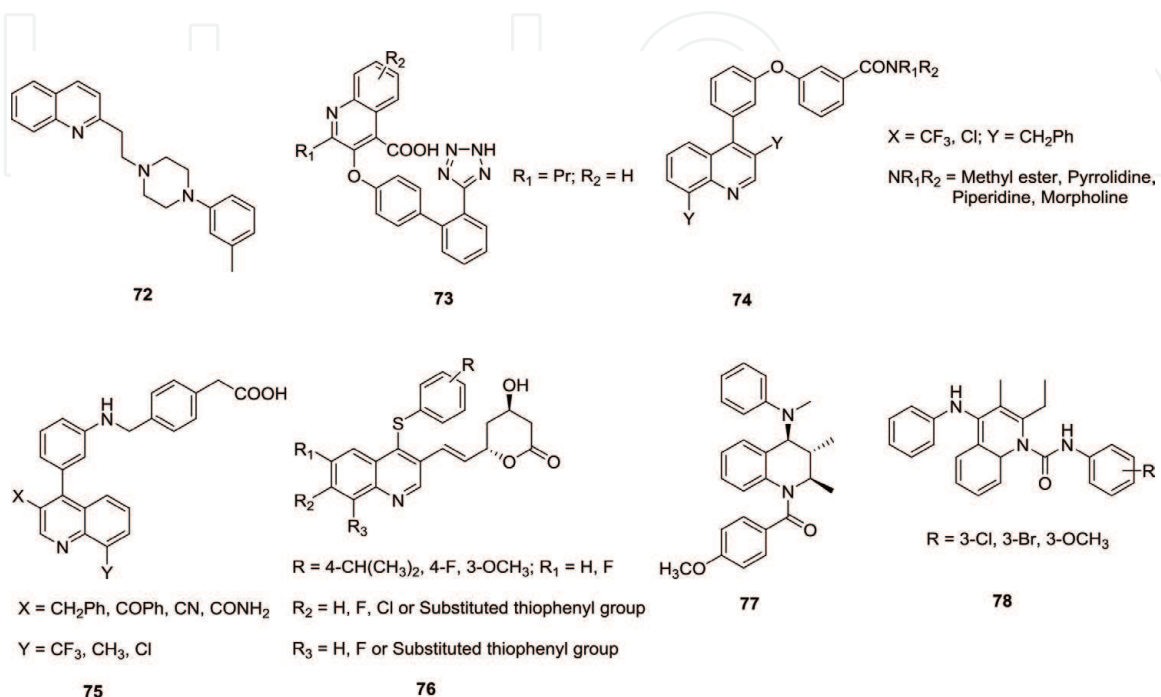
3.9 Antiprotozoal

2-Propyl quinoline and 2-(3-methyloxiran-2-yl)quinoline alkaloids **67**, **68** isolated from *G. longiflora* plant were found to show antileishmanial activity against *Leishmania* spp. [56]. Alkenyl and alkynyl quinolones, **69**, **70** reported by Fakhfakh et al. were found to have antiprotozoal activity against cutaneous leishmaniasis, African trypanosomiasis, Chagas disease, and visceral leishmaniasis [52]. Ma et al. developed a few quinolones, **71** that showed activity against *Trypanosoma cruzi* [35].



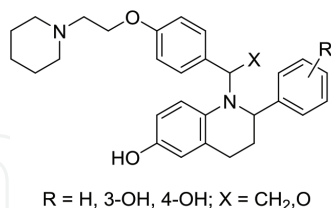
3.10 Cardiovascular activity

Strimal et al. demonstrated the hypotensive activity of centhaquin, **72**, and it was found to show the property of reducing the blood pressure in cat in a dose-dependent manner [57]. Quinoline-4-carboxylic acids, **73** have been synthesized by Lloyd et al. that are angiotensin II receptor antagonists and thereby act as hypotensive agents [58]. Certain biarylether amide quinolones, **74** have been developed by Bernotas et al. which act as liver X receptor agonists and are useful in the situation of dyslipidemia [59]. Phenyl acetic acid-based quinolones, **75** have been developed by Hu et al. which act as agonists at liver X receptors and found to have good binding affinity for LXRb and LXRa receptors [60]. A few 4-thiophenyl quinolones, **76** have been developed by Cai et al. that are HMG-CoA reductase inhibitors and useful as hypocholesterolemic agents [61]. Tetrahydroquinolines, **77** which inhibit the cholesteryl ester transfer protein have been synthesized by Rano et al. [62]. Certain tetrahydroquinolinamines, **78** have been developed by Ramos et al. which are found to inhibit platelet aggregation [63].

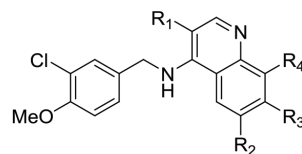


3.11 Reproductive system

Tetrahydroquinolines, **79** have been synthesized by Wallace et al. that are selective estrogen receptor modulators [64]. Bi et al. developed few quinolones, **80** which are potent PDE5 inhibitors thus are useful in the treating erectile dysfunction [65].



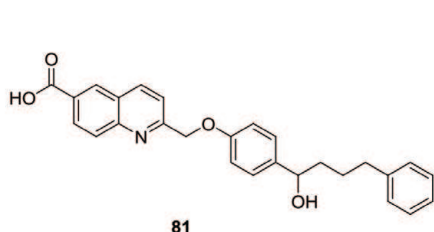
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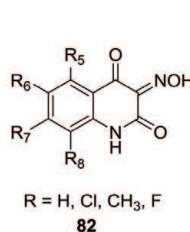
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3.12 Miscellaneous

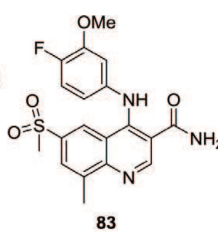
Quinolines and quinoline derivatives possess a number of miscellaneous biological activities also. Evans et al. synthesized few quinolones, **81** that are leukotriene synthesis inhibitors [66]. 1,2,3,4-Tetrahydroquinoline-2,2,4-trione oximes, **82** are developed by Cai et al. that act as antagonists of NDMA in glycine receptors and also found to be used as agents against neurodegenerative diseases (e.g., Alzheimer's disease) [61]. Lunniss et al. developed few selective PDE4 inhibitor quinolones **83**, **84** which are useful in chronic obstructive pulmonary disorder [67]. Bachiller et al. have developed few tacrine-8-hydroxyquinoline hybrids, **85** that show activity against Alzheimer's [68]. Tetrahydroquinoline-6-yloxy propanes, **86** have been developed by Shakya et al. which show the β -3 agonists [69]. Few aminoalkoxy-quinolines, **87** which act as somatostatin receptor subtype-2 agonists have been developed by Wolkenberg et al. which are useful in proliferative diabetic retinopathy and also found utility in exudative age-related macular degeneration [70].



81



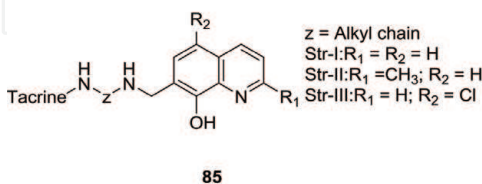
82



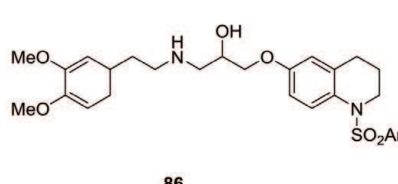
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4. Conclusion

Since quinoline and its derivatives are known for their wide spectrum of pharmacological activities, a number of synthetic methods have been developed from time to time for their synthesis by conventional, homogeneous, and heterogeneous acid-catalyzed methods; rare-earth-catalyzed, transition metal-catalyzed, radical-catalyzed, microwave-assisted, ultrasound-promoted, or solvent-free conditions, and many more. This book chapter will be very useful to the researcher working in

this field, and it would help them to develop new synthetic methods for the potent quinoline derivatives with good or enhanced biological activities for the future.

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Conflict of interest


The authors declare that there is no conflict of interest.

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