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Recent advances in chemistry and therapeutic potential of functionalized quinoline motifs – a review

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Quinoline, which consists of benzene fused with *N*-heterocyclic pyridine, has received considerable attention as a core template in drug design because of its broad spectrum of bioactivity. This review aims to present the recent advances in chemistry, medicinal potential and pharmacological applications of quinoline motifs to unveil their substantial efficacies for future drug development. Essential information in all the current and available literature used was accessed and retrieved using different search engines and databases, including Scopus, ISI Web of Knowledge, Google and PUBMED. Numerous derivatives of the bioactive quinolines have been harnessed *via* expeditious synthetic approaches, as highlighted herein. This review reveals that quinoline is an indisputable pharmacophore due to its tremendous benefits in medicinal chemistry research and other valuable areas of human endeavour. The recent *in vivo* and *in vitro* screening reported by scientists is highlighted herein, which may pave the way for novel drug development. Owing to the array of information available and highlighted herein on the medicinal potential of quinoline and its functionalized derivatives, a new window of opportunity may be opened to medicinal chemists to access more biomolecular quinolines for future drug development.

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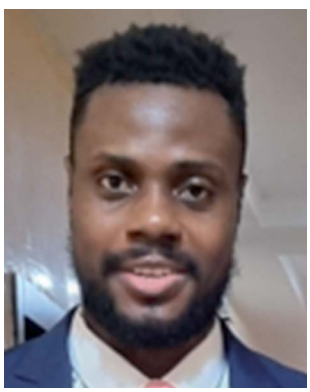
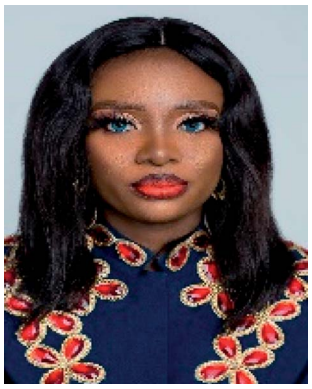


King Tamunodikibugerere IYAYE was born in Okrika and attained his elementary and secondary school education in Rivers State. He obtained his Bachelor's and Master's Degree in Industrial Chemistry from Covenant University, Ota, Ogun State. His BSc dissertation was entitled Synthesis, Characterization and Antibacterial Activity of Novel Hydrazide–Hydrazones of Quinoline. King is a first-class student who finished his BSc with a CGPA of 4.87 out of 5.00, which earned him a scholarship with Covenant University, Ota Ogun State with his research focused on functional and biologically active oxadiazole linked to quinoxaline. His carried out his project under the supervision of Prof. O. O. Ajani. King's Master's thesis was titled Synthesis and Antimicrobial Activity of 1,3,4-Oxadiazole-Linked 1,4-Dihydroquinoxaline Derivatives. He completed his Master's Degree with a CGPA of 5.0/5.0. Furthermore, King has been actively involved in research leading to publications in accredited/peer-reviewed scientific journals. He has, to his credit, publications in reputable journals, which are indexed in the Scopus database.

Introduction

Heterocyclic compounds are deemed to be found in the total structure of at least four out of the five US top-selling drugs, having pharmaceutical activities such as anticancer, antibacterial, anti-tumor and anti-inflammatory. In biological and pharmaceutical processes, heterocyclic compounds play a vital role in the core structures of many drugs.[1] A typical example of bicyclic heterocyclic compounds is quinoline **1**, which is the heterocycle of interest in this review. The quinoline core framework exists in many naturally occurring biologically active entities including quinine, chloroquine, bulaquine, primaquine and tafenoquine from *Cinchona* alkaloids.[2] Typical drug design formulations attempt to imitate naturally available heterocycles and exercise potency by disrupting and intercepting regular pathways essential for the growth of pathogenic organisms.[3] They have contributed significantly to society through their use as therapeutic agents,[4–6] application in human and veterinary medicine,[5] use in agriculture,[7,8] dyes,[9] polymers,[10] bioinformatics,[11] and molecular engineering[12] and they are of increasing importance in many other areas.

Furthermore, functionalized quinoline moieties are highly essential pharmacophoric motifs with undeniable therapeutic propensity owing to their numerous reported biological and pharmacological activities, which include anticancer,[13] antimicrobial,[14] anti-inflammatory,[15] antioxidant,[16] antitubercular,[17] antimalarial,[18] anti-leishmanial,[19] antiprotozoal,[20] anti-HIV,[21] and DNA binding[22] among others. However, the previous review by Sharma and coworkers only highlighted the anti-cancer activities of quinoline derivatives,[2] while the review by Martins and coworkers focused on the quinoline heterocycle as a tool box in nanomedicine.[3] Shiro and coworkers addressed the chemistry and biological activity of quinoline up to 2015,[1] while Dib and coworkers reviewed the recent works on the synthesis and biological potential of quinoline-based compound up to 2021.[23] Hence, there is a need to bridge the gap regarding these potent pharmacological compounds since then to date. Our present review also presents diverse methods for the synthesis of quinoline, which can pave the way for synthetic chemists to achieve various synthetic modifications to access a new series of quinoline motifs for novel drug design.



Mrs Olabisi Ademosun was born in Ota, Ogun State and attained her elementary and secondary school education in the same town, Ota. She obtained her Bachelor's Degree in Pure Chemistry from Olabisi Onabanjo University, Ago Iwoye, Ogun State, Nigeria and Master's Degree in Industrial Chemistry from Covenant University, Ota, Ogun-State, Nigeria, where she is currently a PhD student working on cancer nutrition. Mrs Ademosun has been actively involved in collaboration with other researchers, home and abroad, leading to publications in accredited/peer-reviewed scientific journals. Olabisi T. Ademosun is an Assistant Lecturer who is involved with teaching and projects and research supervision at the undergraduate level at Covenant University. She has served and still serving in various capacities in various committees at the Departmental, College and University levels. She is a member of The Royal Society of Chemistry (RSC). Mrs Ademosun is happily married and blessed with children to the glory of God.

Historical background of quinoline

Historically, cinchocaine was the first local anesthetic to be synthesized from the quinoline-based group.[24] In 1834, quinoline was first discovered and isolated by Friedlieb Ferdinard Runge from coal tar.[25,26] It belongs to the alkaloid family and is a secondary metabolite under the nitrogen-containing natural products. Quinoline and its derivatives are available as drugs, with the outstanding ones being anti-malarial (chloroquine **2**, quinine **3**, primaquine **4**, *etc.*), antibacterial (fluoroquinolones such as ciprofloxacin **5**), anticancer (topotecan **6** and camptothecin **7**), local anesthetic (dibucaine **8**) and anti-tubercular (bedaquiline **9**) drugs. Quinoline derivatives have been reported to be vital agents in the development of anticancer drugs, which induce apoptosis. This is successfully achieved through the elimination of cells that threaten the survival of animals and cell migration disruption, and they also act as angiogenesis inhibitors.[27]

Compounds that contain a quinoline core template show a wide range of therapeutic properties including anti-malarial, antitumor, and antimicrobial.[28] As a lead structure, quinoline is used in the synthesis of many anti-malarial drugs such as chloroquine, pyrimethamine, and mefloquine. Quinine is utilized for the treatment of severe *Plasmodium falciparum* infection (malaria parasite).[29] The quinoline motif can also be used to differentiate various species as quality control markers. Quinine was used in the treatment of the blood stages of *Plasmodium*, as the core structure for the production of many antimalarial drugs and to treat severe cases of *Plasmodium falciparum* infections.[29]

Since the 1980s, fluoroquinolones have been employed in pharmaceutical processes and the treatment of diverse bacterial infections.[30] The synthesis of quinoline and its derivatives can be performed using different methods due to the increasing interest in them. This is because of their array of documented applications in pharmaceutical processes. Some of these methods will be discussed further in this review (Fig. 1).

Natural occurrence of quinoline

Quinoline can be derived from different natural sources such as flowering plants, animals and microorganisms.[31] The primary source of quinoline is coal tar.[32] The bark of the *Cinchona* plant contains quinine, quinidine, cinchonine and cinchonidine, which are combined and administered as "Quinimax" in malarial therapy.[33] Nitidine, an anticancer agent, is a dimethoxylated-quinoline compound obtained from *Zanthoxylum nitidum*, which belongs to the citrus family. Reticuline, which is isoquinoline, occurs naturally in some notable medicinal plants

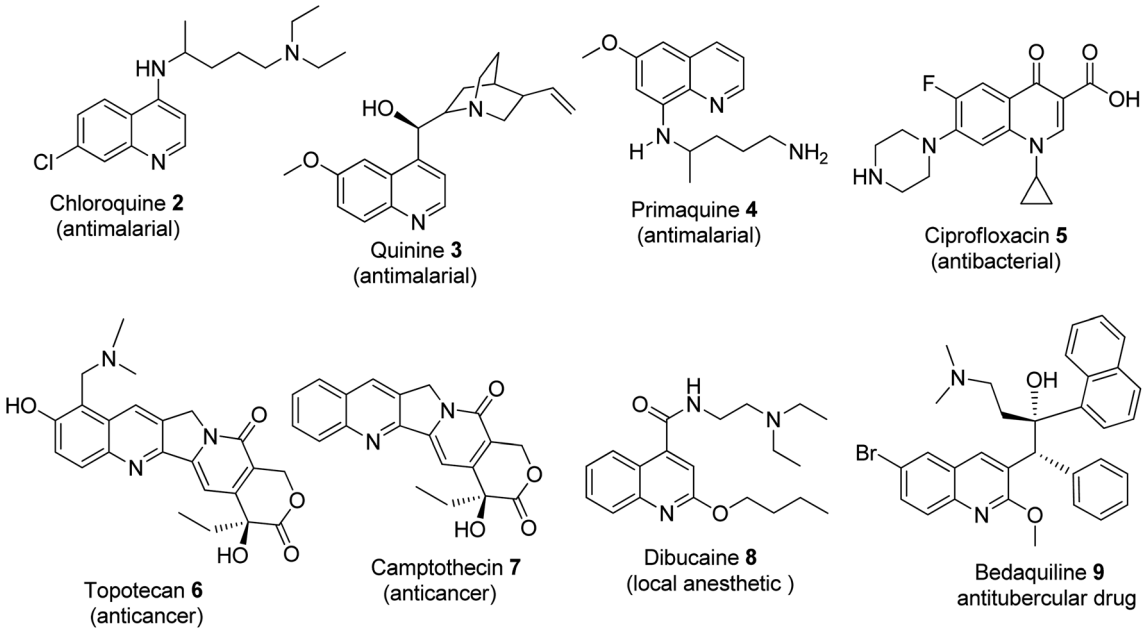


Fig. 1 Selected quinoline-based marketed drugs.

such as *Papaver somniferum*, *Asimina triloba* and *Ocotea fasciculata* and in opium species. Skimmianine (furoquinoline alkaloid) found in *Skimmia japonica* is used in sedative and anticonvulsant drugs. Sandramycin, which serves as an antitumor and antibiotic drug, can be found in *Nocardioides* sp. It is a biomolecule possessing two molecules of 2-amidoquinoline in its core structure.[34] Camptothecin (pentacyclic quinoline) can be derived and extracted from the tree bark and stem of *Camptotheca acuminata*.[27] Quinoline alkaloids can be isolated from the *Dictamnus* species. For instance, robustine is a quinoline alkaloid obtained from the *Dictamnus angustifolius* plant source, evolitrin, a tricyclic quinoline, which is isolable from *Dictamnus albus*, ribalinidine is from *Dictamnus hispanicus* and dictamnine from *Dictamnus dasycarpus* and *Dictamnus angustifolius*.[35]

Physical properties of quinoline

Quinoline is a liquid with a strong odour, which is sparingly miscible with cold water, but completely miscible with hot water. It is readily soluble in many organic solvents at ambient temperature. It possesses the ability to absorb water molecules from the environment.[31] It is a colorless hygroscopic liquid, which when aged and exposed to light, changes color to yellow, and then brown.[32] Quinoline exhibits a density of 1.093 g mol^{-1}, melting point of −15 °C and boiling point of 238 °C. Similar to monocyclic *N*-heterocycle (pyridine derivatives) derivative, quinoline congeners have been documented over the years to have ecological effects with buildings/structures related to production of the oil coal, and also water contamination given that aqueous quinoline can be transported in the environment easily.[26]

Chemical structures of quinoline and its analogs

Quinoline **1** can be identified by its double ring structure, consisting of a pyridine and benzene structure fused together by a change in the state of the benzene ring with pyridine. Pyridine has the chemical formula of C_5H_5N, similar to the benzene structure, wherein a methine group is replaced with a nitrogen atom.[28] Isoquinoline **10** is a unit of quinoline but differs in the position of the nitrogen, which is situated at position 2 in the structure of isoquinoline, whereas the heteroatomic nitrogen in quinoline is at position 1 of the heterocyclic ring portion, as shown in Fig. 2.[31]

The issue of drug resistance and the outbreak of new diverse life-threatening infectious diseases have increased recently and there are many more infectious diseases that are claiming lives in the 21st century than in the past centuries.[36] The pandemic nature of Covid 19 is quite sufficient evidence to prove that the scientific world should devote more effort to drug design. Considerable attention has been given to quinoline derivatives such as 8-aminoquinoline because of the potential role of metabolic transformation in its *in vivo* activation.[21] To protect life and make the world a better place to live, there is a need for continuous updates on various scientific research and attempts to use quinoline motifs in drug discovery and medicinal chemistry.

Fig. 2 Chemical structures of quinoline and isoquinoline heterocycles.

Synthesis of quinoline derivatives

The Skraup synthetic approach

This reaction is very valuable for synthesizing non-substituted quinoline **1**. It involves the heating and thermal cyclization of aniline on acrolein in the presence of concentrated sulfuric acid, a mild oxidizing agent, and glycerol at refluxing temperature to give unsubstituted quinoline **1** (Scheme 1). The acid used therein serves a double role because it acts as both a catalyst and dehydrating agent simultaneously.[26] The Skraup synthesis enabled the laboratory-scale synthesis of quinoline for the first time, and subsequently other methods were developed for the preparation of diverse substituted quinolines with great medicinal efficacy.

Friedlander synthetic approach

The Friedlander synthetic approach was described in 1882 by Friedlander, which is considered one of the most convenient procedures designed and executed for the preparation and synthesis of quinoline scaffolds. It proceeds *via* the condensation of 2-aminobenzaldehydes with ketones to form quinoline derivatives. This reaction has been catalyzed using agents such as trifluoroacetic acid (TFA), Lewis acids, iodine and *p*-toluenesulfonic acid. It has been greatly explored for the condensation and cyclodehydration in acidic or basic medium.[2,37] Wang and co-workers showed an eco-friendly and cost-effective method for the preparation of 2,3,7-trisubstituted quinoline derivatives **11** *via* the Friedlander reaction of 1-amino-4-bromo benzaldehyde with ethyl acetoacetate using HCl as the catalyst and H_2O as the solvent[38a] (Scheme 2). The Friedlander heteroannulation reaction was utilized for the synthesis of polysubstituted quinoline in 77–95% yield.[38b] Generally, the Friedlander technique involves a 2-in-1 step, *i.e.*, the base-catalyzed preparation of a Schiff base followed by intramolecular Claisen condensation. Although, this method has high versatility, its drawback is instability of its aminobenzaldehyde precursor, which can undergo unsolicited intramolecular cyclization of the its amino and aldehydic functional groups; thus, hindering the formation of quinoline.

Conrad–Limpach synthetic approach

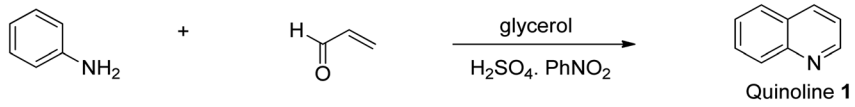
The Conrad–Limpach method employs aniline derivatives as a precursor, which are condensed with β-ketoesters under suitable reaction conditions to form 4-hydroxy quinolines **12** having a Schiff base as an intermediate.[39] 4-Oxyquinolines are synthesized by the change in the state of matter of β-keto acids esters, and then reacted with aromatic amines.[39,40] The overall reaction includes an addition reaction and condensation reaction. The rate-determining step is that involved in the thermal cyclization *via* molecular ring closure. The Schiff base is strongly heated 250 °C for this to occur and the nature of the solvent used is also crucial to achieve improved yields of the expected products.[39,41] This reaction is difficult to drive to completion at low temperature. However, the extremely high temperature required for product formation can lead to decomposition unless it is carried out in mineral oil (BP > 275 °C) (Scheme 3).

Doebner–Miller synthetic approach

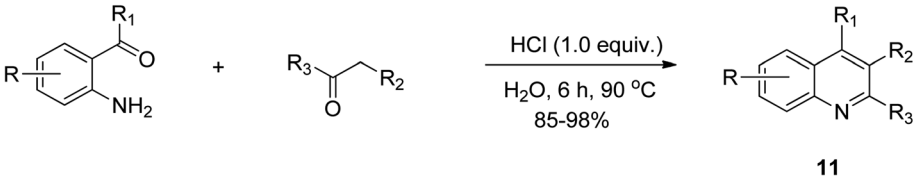
The Doebner–Miller synthesis involves the use of an aldehyde or α,β-unsaturated ketone with aniline.[40] This method comprises the condensation of aromatic amines with chalcones to afford quinolines.[42] Wu and co-workers reported that when aniline and its substituted derivatives were thermally treated with chalcones in the presence of trifluoroacetic acid solvent,[43] an intermediate was formed, which upon oxidative cyclization, afforded trisubstituted quinoline derivatives **13** effortlessly, as shown in Scheme 4. This approach is much simpler than the Skraup method because it is avoids harsh reaction conditions and use of an oxidizing agent.

Synthesis *via* intramolecular cyclization of acetanilides

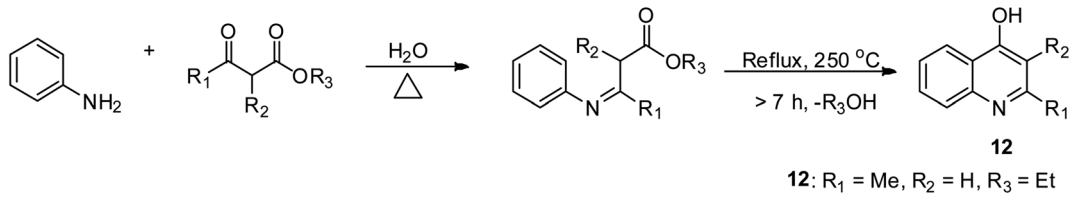
It has been reported that the intramolecular cyclization of acetanilide by phosphorus oxychloride in dimethylformamide at 80–90 °C for 5 h provided easy access to 2-chloroquinoline-3-



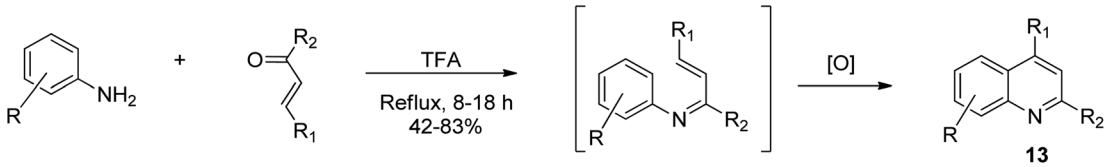
Scheme 1 Synthetic pathway to access unsubstituted quinoline.



Scheme 2 Friedlander synthetic route for the formation of substituted quinolines.



Scheme 3 Conrad–Limpach synthetic route for the formation of 4-hydroxyquinoline.



Scheme 4 Doebner–Miller synthetic route for the formation of substituted quinolines.

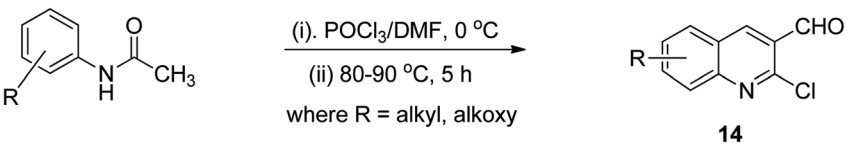
carboaldehydes **14** through a the Vilsmeier–Haack reaction (Scheme 5). This synthesis could be heat-driven *via* the conventional technique or new microwave-assisted methods.[44]

Synthesis *via* radical induced rearrangement

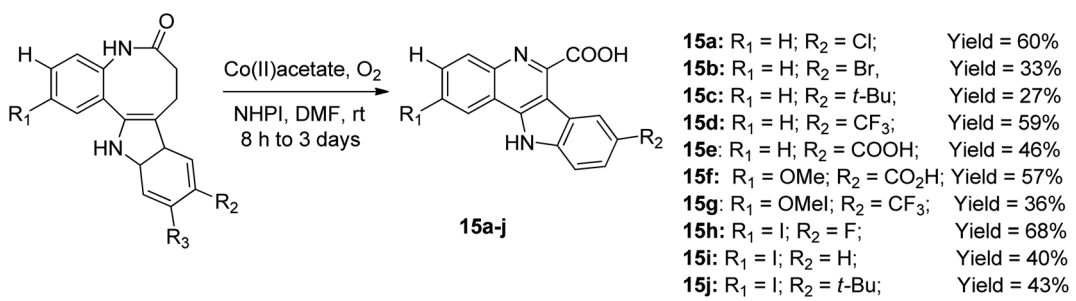
The cobalt-catalyzed radical-induced rearrangement of benzazepinone motifs in the presence of molecular oxygen and *N*-hydroxyphthalimide (NHPI) at a temperature ranging from ambient temperature to 70 °C afforded a series of ten tetracyclic quinoline derivatives **15a–j**, as shown in the Scheme 6.[45] The solvent for the optimum reaction yield and effective rearrangement was reported to be dimethylformamide (DMF), while the yields of the products varied from 27–68%. In a recent study, this was further developed by designing the new derivative of **15** with other substitution patterns to afford other products with yields ranging from 13% to 88%. These new compounds were synthesized and investigated for their protein kinase DYRK1A inhibitory properties.[46]

Pfitzinger synthetic approach

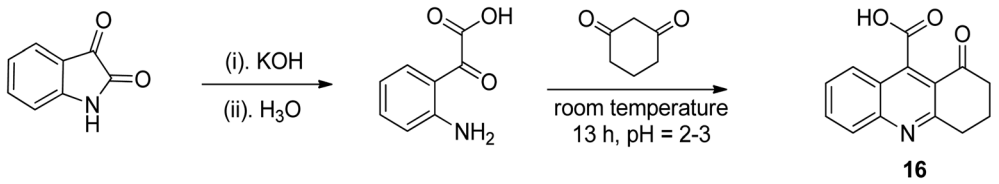
Hydrolysis was carried out on isatin in potassium hydroxide (aqueous), and subsequently the pH was carefully adjusted to 2–3, resulting in ring opening to access anilino-based acid as an intermediate. This intermediate was further reacted immediately with cyclic diketone to furnish the desired tricyclic quinoline **16** in encouraging yield.[42] In a condensation reaction under acidic conditions, the obtained keto-acid was reacted with 1,3-diketone to give tricyclic quinoline **16**, as shown in the Scheme 7.



Scheme 5 Synthetic pathway to quinoline derivative **14** *via* Vilsmeier–Haack reaction.



Scheme 6 Radical-induced rearrangement to afford tetracyclic quinolines.



Scheme 7 Synthetic pathway to access tricyclic quinolines *via* Pfitzinger method.

One-pot three-component synthetic approach

In the report by Jumade and co-workers, a newer Mannich base synthetic approach was utilized to access five different disubstituted quinolines to overcome the water insolubility problem associated with cinchophen-like molecules.[47] When a mixture of pyruvic acid, benzaldehyde and aniline was utilized in the presence of ethanol solvent at a refluxing temperature for 3 h, it afforded crystalline 2-phenyl quinoline-4-carboxylic acid **I**.[47] This was synthetically modified at the COOH moiety and allowed to undergo Mannich base reaction to afford five compounds **17a–e** in varying yields (53–72%)[47] (Scheme 8).

Povarov synthetic approach

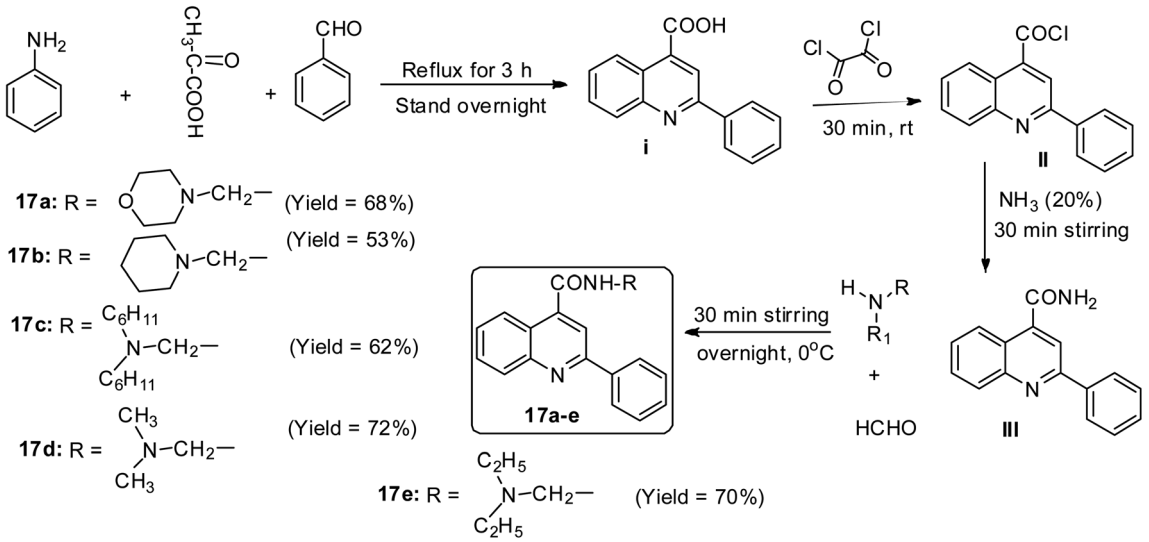
The Povarov route is an aza-Diels–Alder reaction, which was reported originally as a one-pot reaction of aryl aldimines derived from the reaction of benzaldehyde with aminobenzene bearing an electron-rich attachment, particularly ethyl vinyl ether **a** (where R = H and R′ = OC_2H_5) or ethyl vinyl sulfide **b** (where R = H and R′ = SC_2H_5) in BF_3/OEt_2 catalyst, resulting in the production of quinoline derivatives with a tetrahydro-hetero-ring, which were further oxidized to the corresponding quinolines **18a** and **18b**, respectively (Scheme 9a). To address the drawback in the previously reported work, another study showed the five-step transformation of phenylalanine to valuable intermediate **VI**, which was subsequently reacted with an aniline derivative *via* Povarov intramolecular reaction to give eight tetrahydropyrrolo-containing tricyclic quinolines **19a–h** in 92–97% yield,[48] as shown in Scheme 9b.

Aza-vinylogous Povarov stereoselective synthetic approach

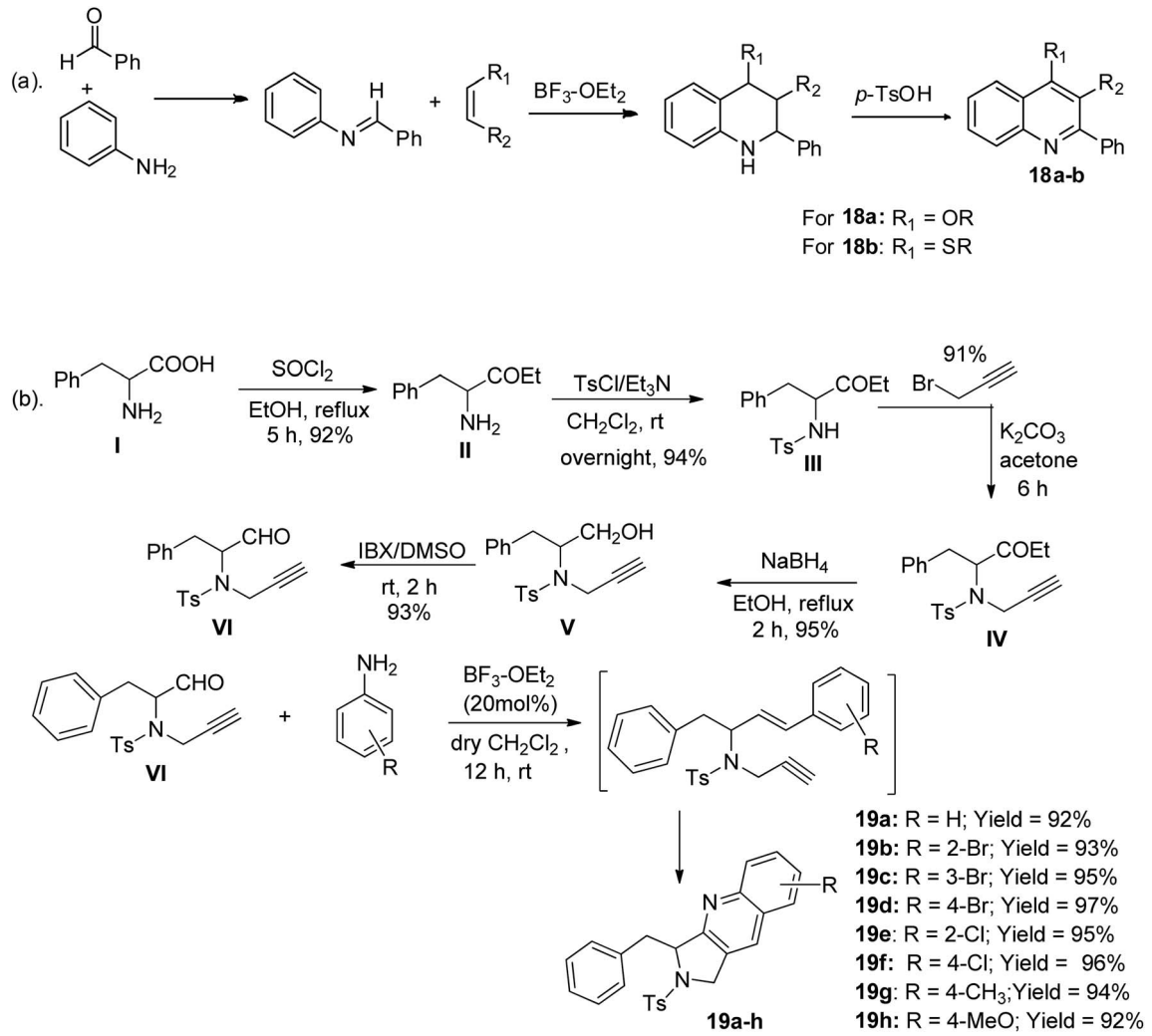
Sridharan and co-workers illustrated the aza-Diels Alder reactive condition for the first time, which involved the use of hydrazonized alkene *via* the cycloaddition strategy to access twelve final quinoline motifs **20a–l** *via* $InCl_3$-mediated catalysis.[49] This reaction protocol is termed the aza-vinylogous Povarov reaction and the route to this effective preparation is shown in Scheme 10. The reaction for the formation of all the products was executed within 2–3 h except that for **20k**, which lasted for 5 h according to the TLC analysis. The reaction was carried out at room temperature to achieve the products in good to excellent yields of 70–93%.

Chemical properties of quinoline

Quinoline is a heterocycle with its two six-membered rings fused. It is also called benzo[*b*]pyridine or 1-azanaphthalene. It contains a nitrogenous aromatic heterocyclic ring[50] with its common chemical reactions being nucleophilic and electrophilic substitution in nature.[51] In the presence of acids, it can form a salt and shows similar reactions to that of benzene and pyridine. As a tertiary base, it is weak.[50] Quinoline hydrazones (functional group containing $R_1R_2C{=}NNH_2$) have both polar and non-polar properties, which are beneficial for the penetration of bacterial cells.[52]



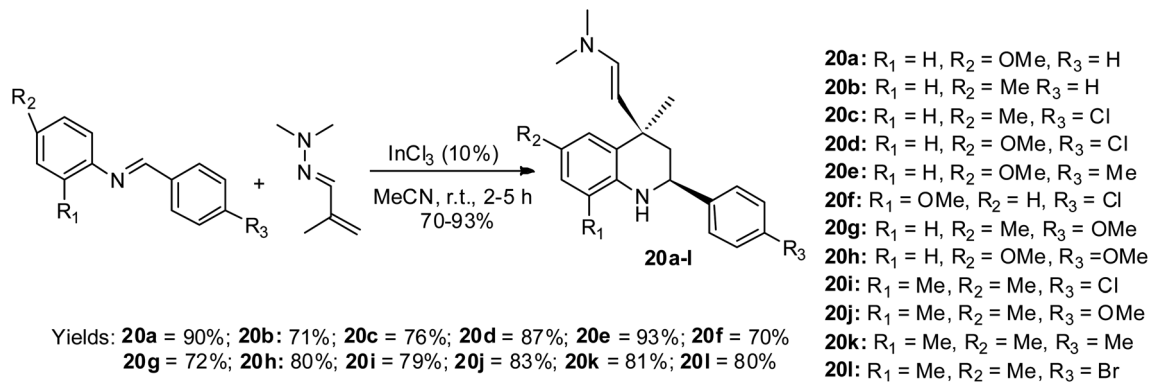
Scheme 8 One-pot synthetic route to access 2-phenylquinoline-4-carboxylic acid.



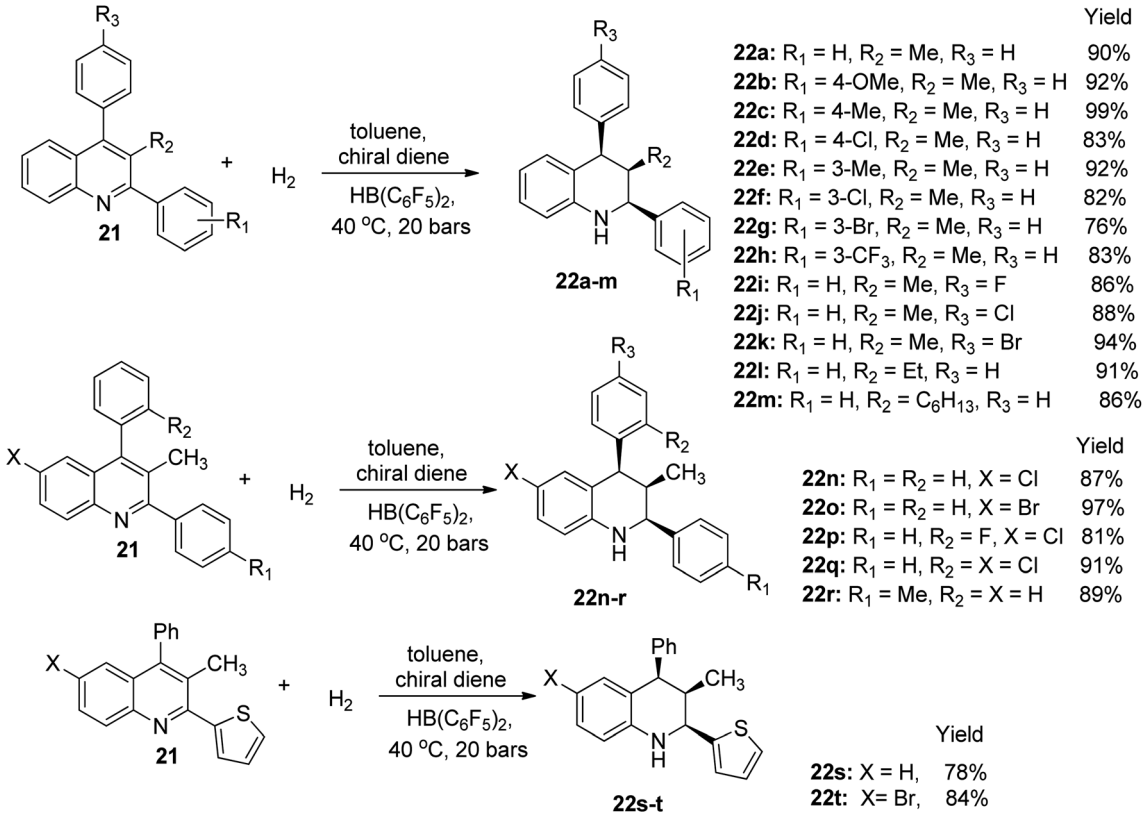
Scheme 9 (a) Povarov synthetic route for the formation of 2-aryl-substituted quinolines. (b) Povarov synthetic route for the formation of tricyclic quinolines.

Hydrogenation reaction of quinoline

The hydrogenation of 3-alkyl-2,4-*s*-diphenylquinoline **21** was achieved using $HB(C_6F_5)_2$ and bubbling about 20 bars of H_2 in the presence of toluene solvent and a chiral diene to afford twenty examples of 1,2,3,4-tetrahydroquinoline derivatives **22a–t.** The first eighteen derivatives **22a–r** (without substitution on the benzene portion of quinoline) were obtained under metal-free enantioselective conditions in yields ranging from 76% to



Scheme 10 Aza-vinylogous Povarov stereoselective synthesis of substituted quinolines.



Scheme 11 Hydrogenation reaction of trisubstituted quinoline derivatives.

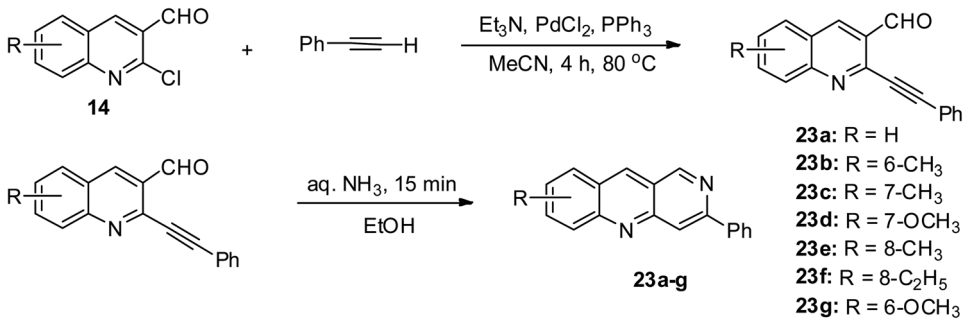
99%. However, when the 2-substituent was changed to heterocyclic thiophene, hydrogenation in molecular H_2 afforded the last two quinoline derivative **22s**, **22t** in 78% and 84% yield, respectively, as shown in Scheme 11.[53] This result was highly interesting because it was an improvement in previous report, and it also authenticated the possibility of realizing asymmetric reactions with the aid of a chiral borane catalyst.

Electrophilic substitution reaction

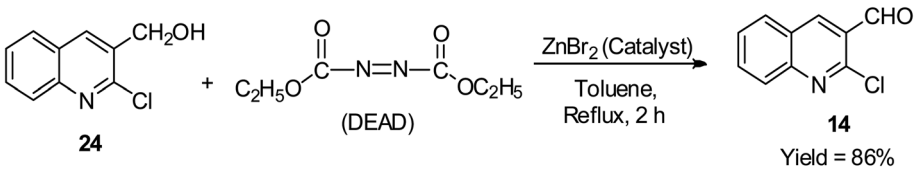
2-Chloroquinoline-3-carbaldehyde **14** conveniently undergo substitution reaction at its 2-chloro position by treating it with phenylacetylene *via* $PdCl_2$ mediation in CH_3CN, triethylamine and triphenylphosphine at 80 °C under an inert atmosphere, giving an 87% yield of 2-(phenylethynyl) quinoline-3-carbaldehydes, which were reacted with aqueous ammonia to give 88% yield of 3-phenylbenzo[*b*][1,6]naphthyridine **23**, as shown in Scheme 12.[44] The seven derivatives **23a–g** were obtained in varying yields with the highest yield being 88%.

Oxidation reaction of quinoline derivatives

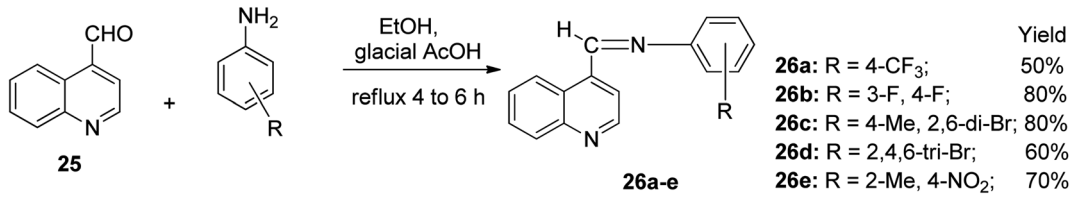
The mild oxidation of the alcoholic side chain of 2-chloroquinolin-3-yl methanol **24** was reported to proceed smoothly using both diethyl diazene-1,2-dicarboxylate (DEAD) and a catalytic amount of zinc bromide in Ph-CH_3 at refluxing temperature for 2 h to afford 2-chloroquinoline-3-carbaldehyde **14** in 86% yield, as shown in Scheme 13.[44]



Scheme 12 Electrophilic substitution reaction of disubstituted quinoline derivatives.



Scheme 13 Oxidation reaction of disubstituted quinoline derivatives.



Scheme 14 Condensation reaction of quinoline derivatives to afford imines.

Condensation reaction of quinoline derivatives

Quinoline-4-carboxaldehyde **25** conveniently underwent a condensation reaction when treated with 4-(trifluoromethyl) aniline and four other substituted anilines in the presence of ethanol solvent using heterogeneous catalysis in glacial CH_3-COOH to access five Schiff bases **26a–e**. The reaction was completed after refluxing for 4 to 6 h with an obvious color change. The reaction mixture was left to stand overnight to afford the imine products **26a–e** as colored crystals with yields ranging from 50% to 80%, as shown in Scheme 14.[32]

Pharmacological activities of quinoline derivatives

The quinoline motif was reported by Lv and co-workers to have various biological activities such as being an anticancer agent and involved in anti-inflammatory, anti-microbial, and anti-HIV activities and lots more.[35] There are new developments in quinoline-derived drugs due to the occurrence of drug resistance in bacteria, which is the cause of several diseases, and side effects over the years.[54]

Antibacterial activities of quinoline derivatives

It was reported by Kharb and Kaur that nine quinoline-based compounds were designed with that bearing a carbothioamide-based quinoline motif, **27**, exhibiting the most significant antibacterial activity with a zone of inhibition of 20 mm against *P. aeruginosa*.[55] The commercially available quinoline-based antimicrobial drugs include ciprofloxacin **5**, which acts synergistically with ZnO nanoparticles against biofilm cells[56] and ofloxacin **28** in s fixed-dose combination,[57] and their structures are shown in Fig. 3.

Anti-malarial activities of quinoline derivatives

Malaria is known to be among the deadliest pathogenic infections globally. It is a parasitic (hematoprotozoan) disease caused by a specific species of anopheline mosquitoes. The species that affects humans the most is *Plasmodium falciparum* among the four species causative agents of malaria.[58] To date, quinoline derivatives are considered to be the dominant class of heterocyclic compounds used as anti-malarial agents. In the pharmaceutical area, two subclasses of quinoline are used *i.e.*, 4-amino quinolines (chloroquine **2**, amodiaquine **29**, and piperaquine **30**) and aminoalcohols (quinine **3** and mefloquine **31**). These two subclasses having different mechanisms of action, depending on haemoglobin digestion inference with the endocytic process.[59] Their structures are shown in Fig. 4.

c-Met kinase inhibitory activities of quinoline derivatives

c-Met is a receptor tyrosine kinase, which drives the effective transformation of a pro-enzyme to an active enzyme. When fused with the scatter factor/hematopoietin A, it causes various composite signaling pathways, which show outcomes such as

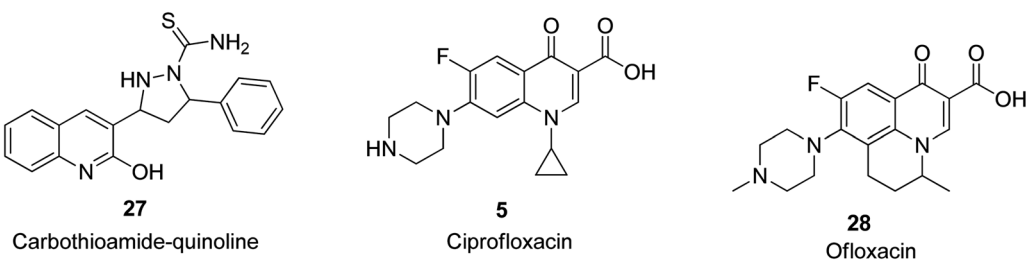


Fig. 3 Selected quinoline derivatives with antibacterial activity.

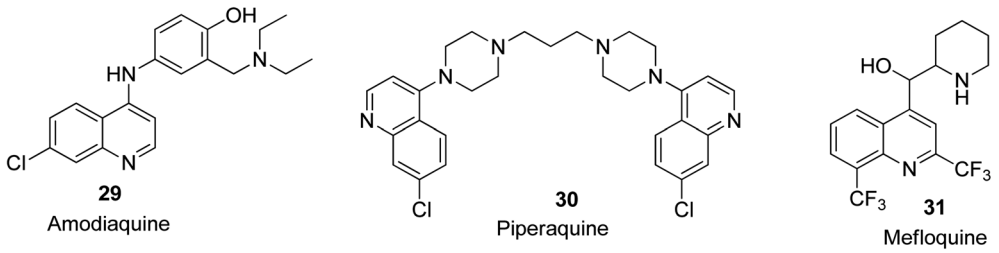


Fig. 4 Selected quinoline derivatives with anti-malarial activity.

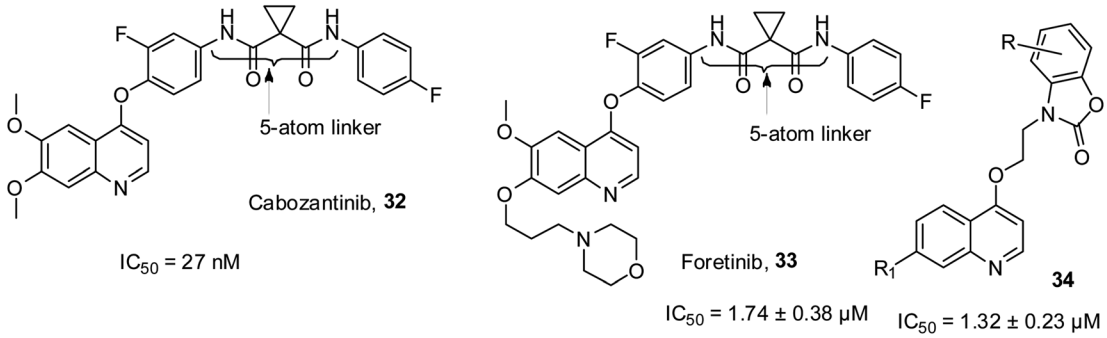


Fig. 5 Selected quinoline derivatives with c-Met kinase inhibitory activity.

cell migration, proliferation and invasion. Poor clinical results for cancer patients have been associated with an increase in c-Met and SF. Cabozantinib **32** was the first small molecular inhibitor of c-Met, which received approval in 2012. Later, foretinib **33** with a similar 5-atom linker as **32** was reported to have notable inhibitory efficacy on c-Met.[60] In recent years, benzo[*d*]oxazol-2(3*H*)-one-quinoline **34** has been reported to be a powerful c-Met inhibitor.[61] The structures of these kinase inhibitors are shown in Fig. 5.

Antileishmanial activities of quinoline derivatives

The occurrence of cutaneous leishmaniasis could be through different strains of *Leishmania*, some of which are the most prominent in Columbia and other regions of the world. It is a pathogenic disease. Accordingly, quinolinic core frameworks have been reported to exhibit leishmanicidal (killing the leishmania parasite) activities, and when coupled with hydrazone in a single molecule, they are said to become more potent. The leishmanicidal activity of a series of quinoline–hydrazone hybrids was investigated, among which compounds **35** and **36** were found to be potent with high efficacy.[62] Their structures are shown in Fig. 6.

Anti-cancer activities of quinoline derivatives

Quinoline-based compound **37** was designed and reported by Abdel-Wahab and co-workers to be a potent anti-cancer agent against breast, lung and CNS tumors.[44] Synthetic quinoline structures that possess 2,4-disubstitution such as *N*-2-diphenylquinol-4-carboxamide **38**, as well as naturally occurring quinoline-based alkaloids such as dictamine **39** and berberine **40** have been reported to play a vital function as new anti-cancer agents.[31] Their structures are shown in Fig. 7.

Antioxidant activities of quinoline derivatives

The antioxidant system and free radicals need to be in a state of equilibrium to maintain the health status of an organism. Many health issues over the years are related to oxidative stress. Quinoline motifs are known to be free radical scavengers.[63] It was reported by Subashini and co-workers that 3-(1,3-dioxolan-2-yl)quinoline **41** and 3-quinolinecarboxaldehyde **14**, which

Fig. 6 Selected quinoline derivatives with anti-leishmanial activity.

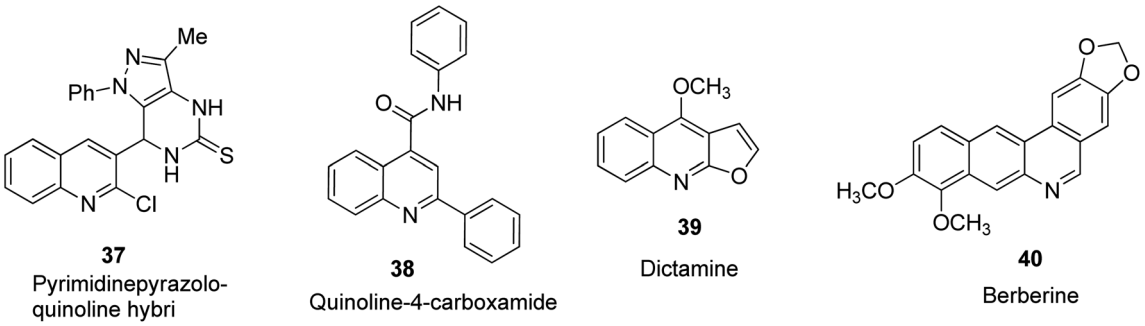


Fig. 7 Selected quinoline derivatives with anti-cancer activity.

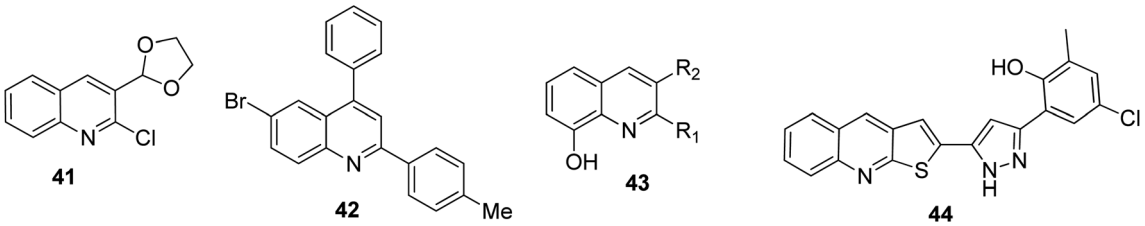


Fig. 8 Selected quinoline derivatives with anti-oxidant activity.

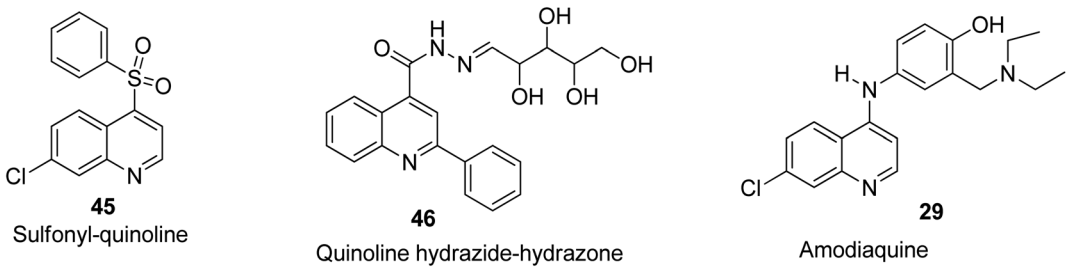


Fig. 9 Selected quinoline derivatives with anti-inflammatory activity.

both contain a chlorine substituent on their 2-positions, were potential antioxidants.[64] Liberto and co-workers synthesized a series of quinoline derivatives, among which compound **42** was found to be the most potent captor of reactive oxygen species.[65] Al-Busafi and co-workers stated that 8-hydroxyquinoline derivatives **43** showed antioxidant activities,[66] while according to the research by Mahajan and co-workers,[67] among the synthesized and screened thiophene-fused quinolines, **44** emerged as the best antioxidant with an EC_{50} of 12.03 ± 1.45 μg mL^{-1}. Their structures are shown in Fig. 8.

Anti-inflammatory activities of quinoline derivatives

The 7-chloro-4-phenylsulfonyl quinoline **45** bearing a chlorine substituent on the 7-position was screened against inflammation in mice with use of croton oil and was found to exhibit good anti-inflammatory potential.[68] Among the 2-phenylquinoline-based designed motifs by Khalifa and co-workers, compound **46** being a nucleoside-linked analogue possessed remarkable anti-inflammatory properties comparable to the standard drug (diclofenac sodium).[69] Also, amodiaquine **29** was reported by

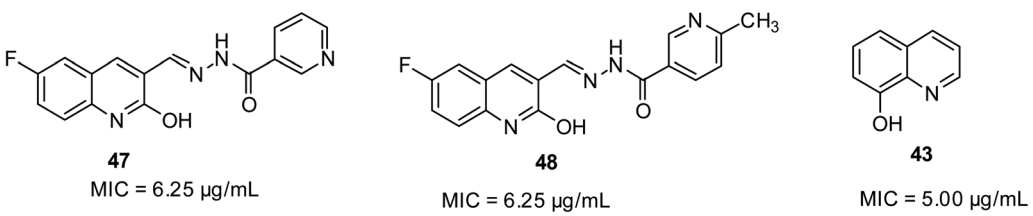


Fig. 10 Selected quinoline derivatives with anti-tubercular activity.

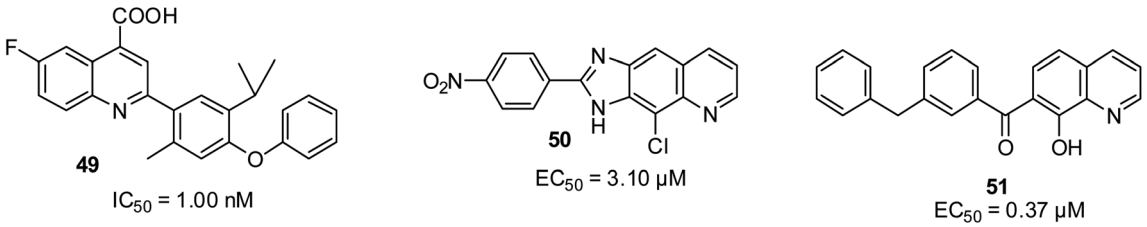


Fig. 11 Selected quinoline derivatives with antiviral activity.

Mandewale and co-workers to be an anti-inflammatory agent with high efficacy.[52] Their structures are shown in Fig. 9.

Anti-tubercular activities of quinoline derivatives

Mycobacterium tuberculosis is the cause of tuberculosis in humans. It is a type of respiratory disease affecting the lungs.[54] In the report by Mandewale and co-workers, some quinolone motifs were prepared to evaluate their anti-tubercular potential.[52] Their findings showed that quinoline-based compounds **47** and **48** displayed superior efficacy among the motifs, exhibiting 100% inhibition activity at 6.25 μg mL^{-1}. 8-Hydroxyquinoline **43** is well-known as a growth inhibitor for both replicating and non-replicating *M. tuberculosis.* Their structures are shown in Fig. 10.

Antiviral activities of quinoline derivatives

Resistance to drugs can occur due to the rapid mutation of viruses, which can become a problem especially for essential small RNA viruses such as HCV and HIV. In the report by Das and co-workers, compound **49** was found to be a potential drug candidate after showing a wide spectrum of antiviral efficacy.[70] It inhibited the growth of human dihydroorotate dehydrogenase (DHODH) at 1 nM. In addition, quinoline compound **50** emerged as the most promising anti-HCV motif with an EC_{50} of 3.1 μM against the entire tested HCV virus,[71] while Zhuang and co-workers reported that **51** possessed antiviral potential at IC_{50} of 0.37 μM due to the inhibition of HIV-1 integrase.[72] Their structures are shown in Fig. 11.

Antifungal activities of quinoline derivatives

According to Al-Busafi and co-workers, 5,7-dichloro- and 5,7-dibromo derivative **52** showed great fungicidal activities.[66] According to the report by Desai and co-workers, 2-chlorophenyl-substituted quinoline derivative **53** with an MIC of 12.5 μg mL^{-1} and 4-bromophenyl-substituted **54** with an MIC of 50 μg mL^{-1} were shown to possess outstanding growth inhibitory potential against *A. clavatus*.[73] They were more efficient than the standard antifungal drug Griseofulvin (MIC of 100 μg mL^{-1}). The previous review by Dorababu unveiled **55** as eminent antifungal pharmacophore against *Cochliobolus lunata* at MIC of 13.3 μg mL; **56** against *Pyricularia oryzae* at 50 mg L; and **57** against *C. albicans* MTCC 227 at MIC of 100 μg mL^{-1}.[74] Their structures are shown in Fig. 12.

Anti-HIV activities of quinoline derivatives

HIV-1 integrase is a crucial target for stopping the viral cycle replication. It is important for integrase inhibitors to show low toxicity but high selectivity given that integrase has no

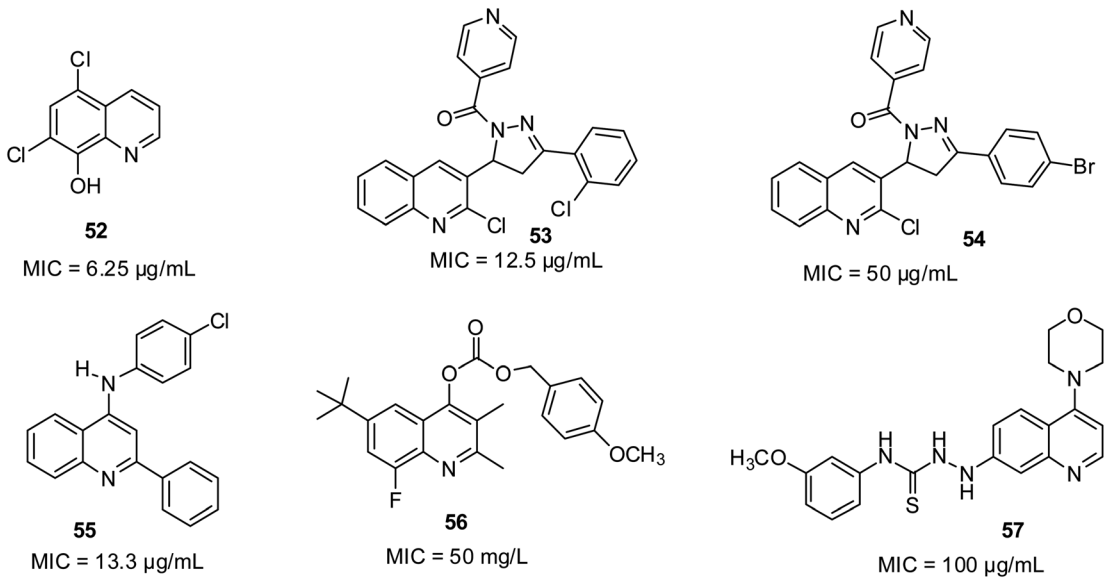


Fig. 12 Selected quinoline derivatives with antifungal activity.

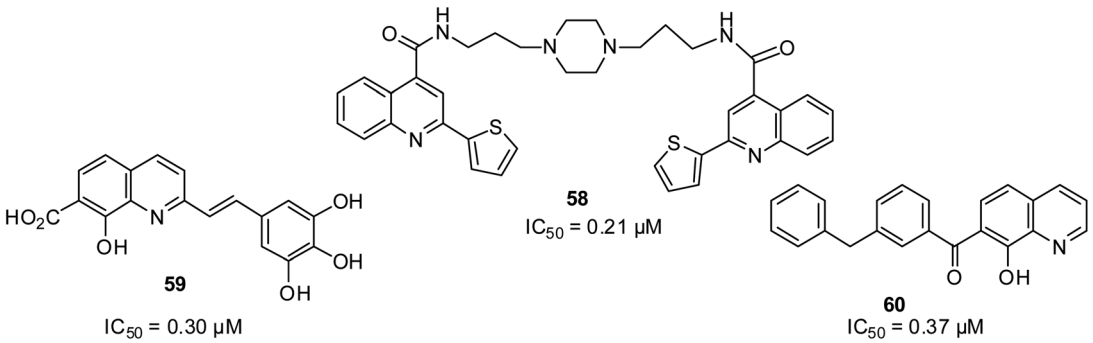


Fig. 13 Selected quinoline derivatives with anti-HIV activity.

counterpart in the cells of mammals. Luo and co-workers designed quinoline-based structures as HIV-1 inhibitors, and then screened eight quinoline derivatives.[75] Among the eight quinoline derivatives, compound **58** was found to be the most active. Among the quinoline motifs designed and screened by Mouscadet and Desmaële, the 3′,4′,5′-trihydroxyphenyl styrylquinolines **59** and **60** were found to be highly active with a strand transfer IC_{50} of 0.3 μM.[76] Their structures are shown in Fig. 13.

Antidepressant activities of quinoline derivatives

Depression is known globally to be the fourth cause of diseases. Affective disorders, schizophrenia and bipolar disorder are still very disturbing diseases in society, regardless of the development of novel therapy analysis.[77] However, the nature of treatment for these affective disorders is still found to be undesirable due to the side effects from anti-depressant drugs such as sexual dysfunction, weight gain and sometimes cardiovascular activities and failure of drugs to achieve remission in patients. Compounds **61** at the IC_{50} of 2.8 μM and **62** at the IC_{50} of 3.8 μM were documented to have appreciable antidepressant properties, which were established by their behavioral status as 5-HT_7 agonists.[77] It is worthy to note that the more active **61** possessed a short alkyl side chain on its amine linker than that of **62**. However, although they were the most potent among the ten motifs designed, they were less efficient compared to the standard drug methiothepin, which exhibited an IC_{50} as low as 2.2 nM. Their structures are shown in Fig. 14.

Anticonvulsant activities of quinoline derivatives

The result from the maxima electroshock (MES) test using intraperitoneally injected mice showed that quinoline-1-carboxamide **63** with an ED_{50} of 30.1 mg kg (ref. 78) and triazolo[4,3-*a*]quinoline **64** with an ED_{50} of 11.8 mg kg^{-1} were the most active anticonvulsants.[79] The careful incorporation of a halogen atom, particularly fluorine as a substituent on the benzene ring tremendously enhanced the anti-MES propensity,

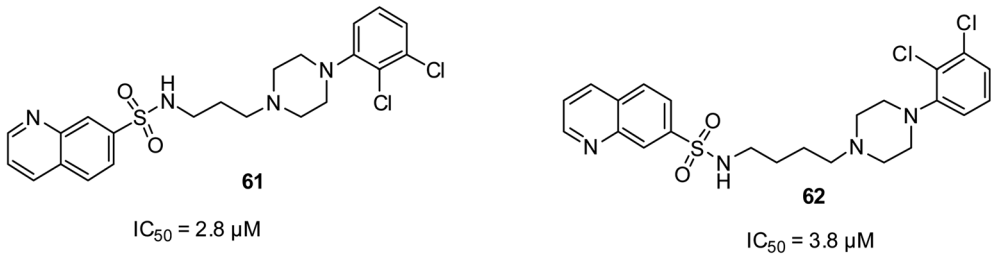


Fig. 14 Selected quinoline derivatives with anti-depressant activity.

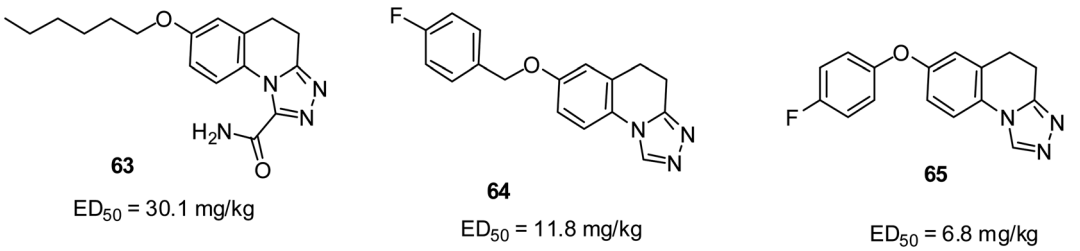


Fig. 15 Selected quinoline derivatives with anti-convulsant activity.

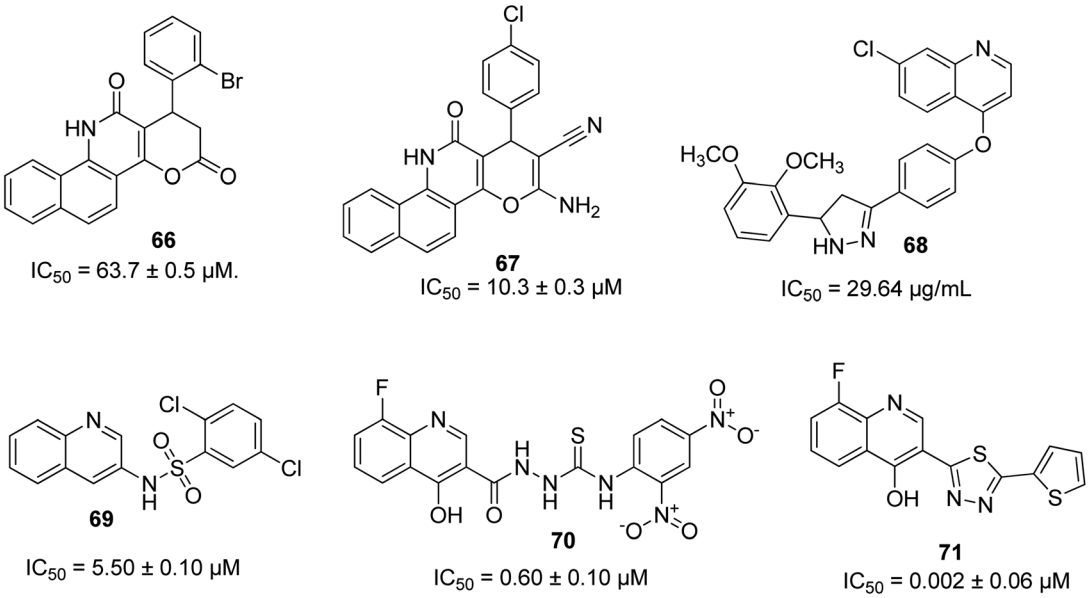


Fig. 16 Selected quinoline derivatives with anti-diabetic activity.

which led to the occurrence of **65** with an ED_{50} of 6.8 mg kg^{-1} as the most promising in another study.[80] Their structures are shown in Fig. 15.

Antidiabetic activities of quinoline derivatives

A series of pyrano-quinoline derivatives was synthesized *via* a two-step approach. The investigation of their α-glucosidase inhibitory potential was carried out using α-glucosidase from *Saccharomyces cerevisiae*, where **66** was the most active with an IC_{50} of 63.7 ± 0.5 μM.[81] Among the series of pyrano-quinolines designed and synthesized by Nikookar and coworkers, **67** possessed the best activity as an antidiabetic motif (IC_{50} of 10.3 ± 0.3 μM), which was shown to be 75-times more active than the standard drug acarbose.[82] Other outstanding quinoline-based antidiabetic molecules are **68** with an IC_{50} of 26.94 μg mL^{-1},[83] **69** with an IC_{50} of 5.50 ± 0.10 μM,[84] **70** with an IC_{50} of 0.60 ± 0.01 μM (ref. 85) and **71** with an IC_{50} of 0.002 ± 0.06 μM.[86] Their structures are shown in Fig. 16

Structure activity relationship (SAR) study

The quinoline template is a pharmacophore of tremendous biological potential for drug design. In addition, various substituents on different positions in the quinoline can enhance the pharmacological efficacy of the quinoline scaffold.[87] For instance, SAR studies of the antimalarial capability of quinoline-imidazole hybrid **72** against chloroquine-sensitive strain 3D7 (IC_{50} = 0.10 μM) showed that the presence of the electron-donating OCH_3 at position-2 enhanced its activity,

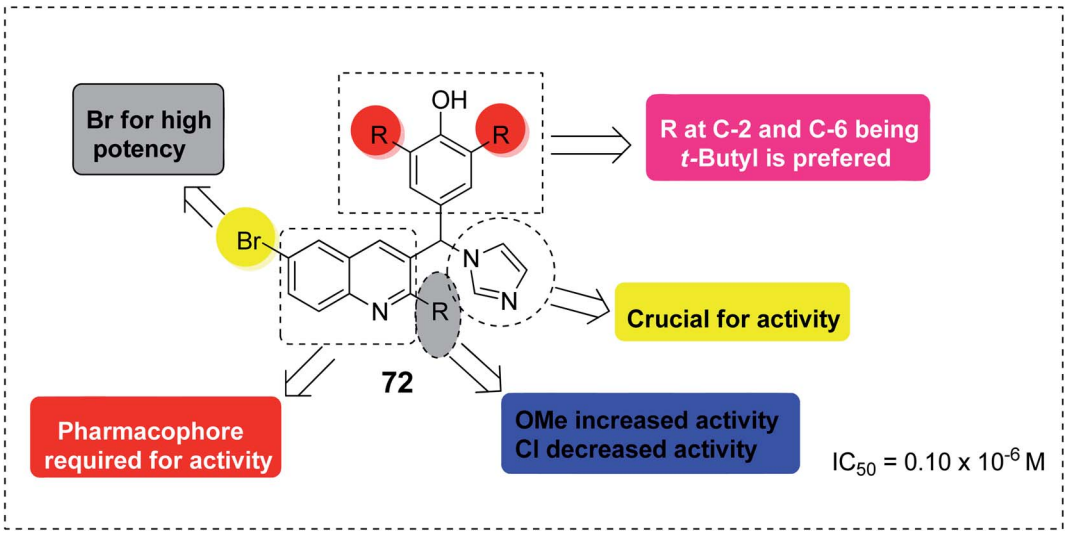


Fig. 17 SAR-identified moieties responsible for activity in quinoline-imidazole hybrid **72**.

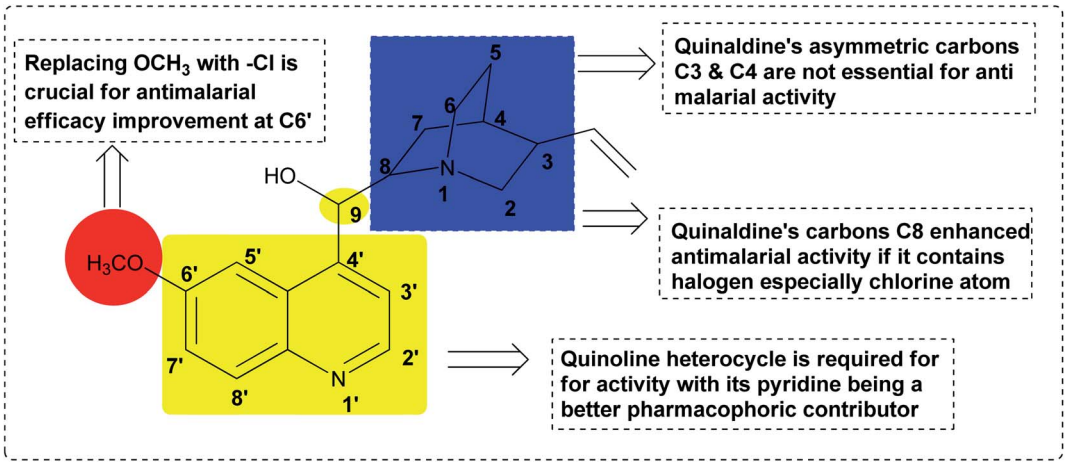


Fig. 18 SAR-identified moieties responsible for activity in quinine 3.

while the presence of the electron-withdrawing Cl at C-2 led to the loss of activity.[87] The presence of Br at C-6 is an essential moiety for activity improvement. However, although the presence of imidazole is crucial for activity, substitution on its nucleus was not preferred,[87] as shown in Fig. 17.

Quinine 3 is another strong antimalarial drug, which is present in nature in the bark of the *Cinchona* tree.[88] It has been an effective treatment of malaria for more than four centuries.[89] A summary of the pharmacophoric properties and SAR diversity of the quinaldine and quinoline portions of quinine antimalarial drugs is presented in Fig. 18. The detailed SAR study of quinine showed that at the C3 and C4 positions, asymmetry is not essential for antimalarial potential in quinine. Secondly, halogen substitution at the C8 position increases its antimalarial efficacy. In quinine, the presence of methoxy at the C6′ position is not essential for antimalarial activity. Replacing OCH_3 with a halogen such as chloro (Cl) enhances its activity. Placing a phenyl group at the C2 position increases the activity. Modification in the secondary alcohol at the C9 position through oxidation and esterification reduces the antimalarial activity of quinine.[90]

Combined signaling pathways in oncology

The aberrant signaling pathways of combined interest play a highly effective functional role in the survival, differentiation and proliferation of cancer cells.[91] These aberrant signals, which are competent in providing diagnostic tools and oncological therapeutic efficacy, are EGFR, VEGFR and c-Met.[92] This is because they are the three most crucial growth factor receptors with direct implication in cancerous cell lines.[93] Some

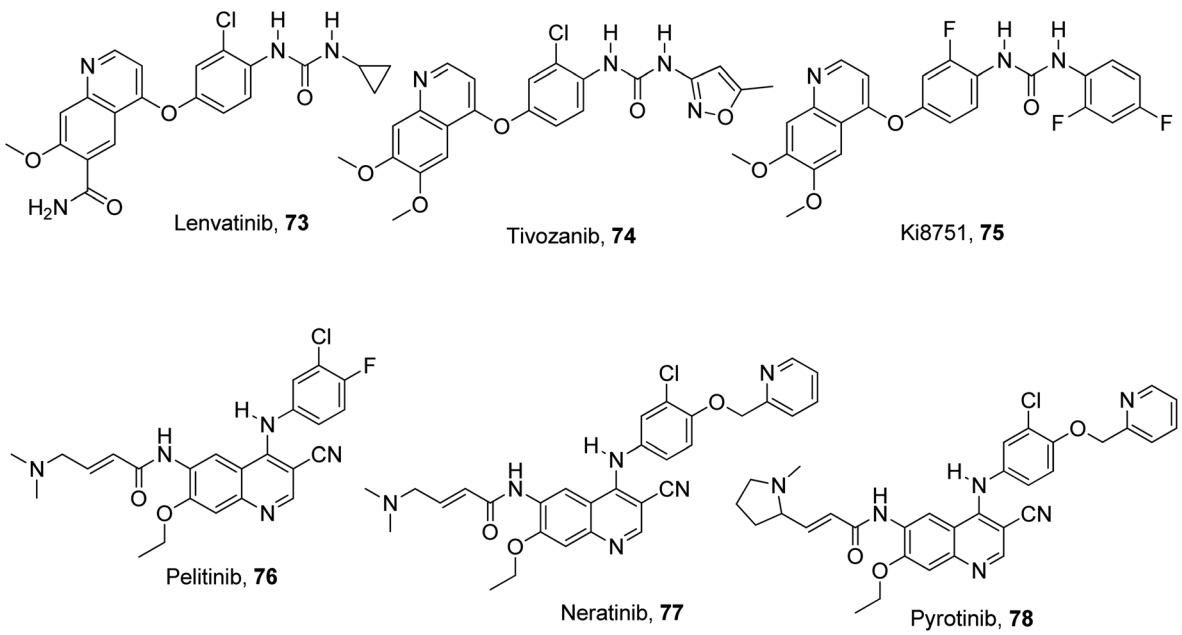


Fig. 19 Structures of quinoline-based inhibitors of the growth factor receptor.

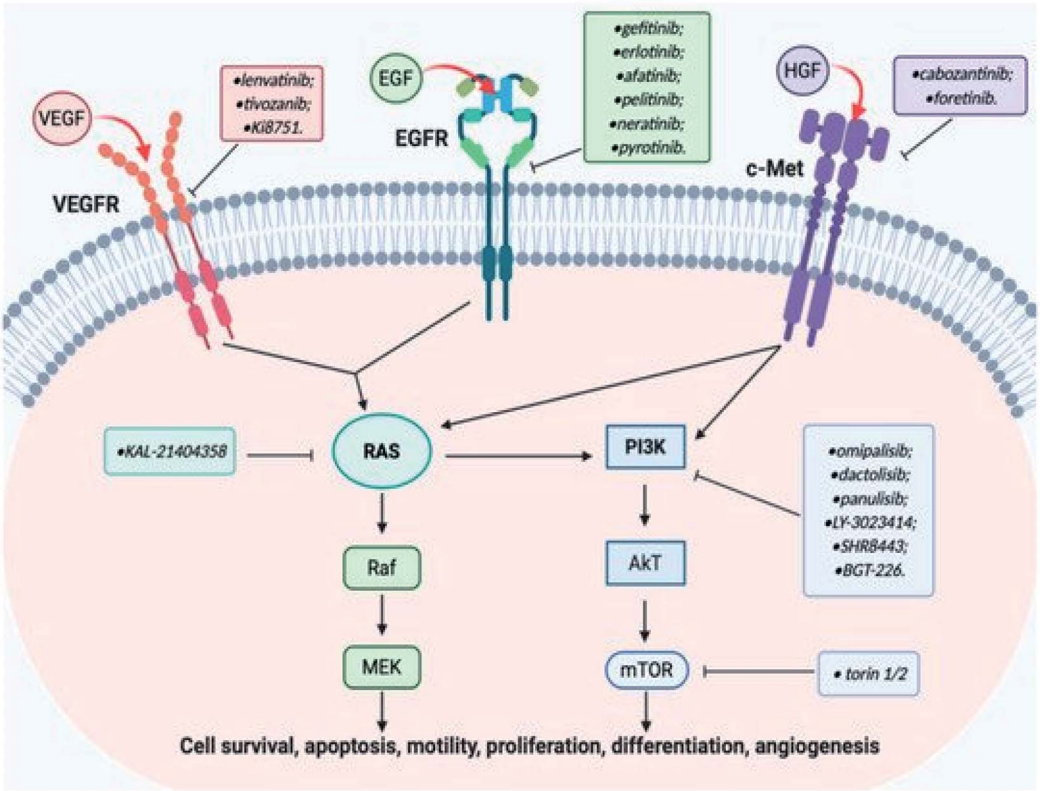


Fig. 20 Cross-talk among EGFR, VEGFR, and c-Met signaling pathways and quinoline-based ligands as their targeted inhibitors.[106]

designed quinoline-based inhibitors used in the treatment of different types of cancers are lenvatinib **73**,[94] tivozanib, **74**,[95] Ki8751 **75**,[96] pelitinib **76**,[97] neratinib **77**,[98] pyrotinib **78**,[99,100] cabozantinib **32**,[101,102] and foretinib **33**.[103] They are ligands with good binding affinity to these growth factor receptors, selectively or collectively. The structures of these quinoline-based inhibitors are presented in Fig. 19.

For instance, cabozantinib, **32** which was branded in the USA as Cometriq, is an anticancer drug approved as a selective inhibitor of non-specific tyrosine kinase.[104] Tivozanib **74** is a pan-inhibitor of VEGF receptors.[95] In addition, foretinib **33** exhibited dual inhibition of the c-Met/VEGFR2 signaling pathway for an improvement in antitumor effect in a gastric cancer model.[103] The reference to EGFR as a biomarker of new opportunity also qualified it to be effectively combined with c-Met in cancer therapy.[105] Recent work focused on compounds effective on the c-Met, VEGF and EGF receptors, pivotal targets for the activation of important carcinogenic pathways (Ras/Raf/MEK and PI3K/AkT/mTOR).[106] A pictorial representation of the cross talk among the EGFR, VEGFR, and c-Met signaling pathways is shown in Fig. 20.[106]

Conclusion

Quinoline derivatives are privileged heterocyclic nuclei with high bioactivities essential for medicinal chemistry research. The chemistry of quinoline elucidated herein from the effort of various synthetic chemists corroborated the diverse derivatives being used in medicinal chemistry. Based on the reviewed information highlighted herein on the medicinal potential of quinoline and its functionalized derivatives, a new window of opportunity may be opened to medicinal chemists to access more biomolecular quinolines for future drug development.

Conflicts of interest

The authors have declared no conflict of interest.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

Author contributions

Conceptualization and supervision of the write-up was done by OOA. Writing and Chemistry of Original draft was done by KTI. Writing and pharmacological portion of original draft was done OTA. The review was written through contributions of all authors. All authors have given approval to the final version of the review.

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