https://doi.org/10.48047/AFJBS.6.11.2024. 205-227

African Journal of Biological Sciences

EXPLORING QUINOLINE SCAFFOLDS: BIOLOGICAL ACTIONS AND ADVANCES IN CANCER TREATMENT

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Article History
Volume 6, Issue 11, 2024
Received: 02 Jun 2024
Accepted: 15 Jun 2024
doi: ***10.48047/AFJBS.6.11.2024.205-227***

Abstract

Among heterocyclic compounds, quinoline stands out as a highly advantageous scaffold and serves as a significant foundation for developing new drug entities. Quinoline and its derivatives, tested for various biological activities, represent an essential class of compounds in drug development. Consequently, numerous scientific communities have focused on creating these compounds as key structures and assessing their biological activities. This review offers an overview of the natural sources of quinoline, highlights marketed drugs based on quinoline, and examines the biological activities of quinoline derivatives. Quinoline compounds hold considerable medicinal value, particularly in cancer treatment. However, challenges such as drug resistance and potential toxicity can limit their effectiveness. There is a need for new derivatives that minimize harm to normal cells and reduce side effects, aiming for better treatment outcomes.

Key words

Benzo-pyridine, Aminoquinoline, Anti malarial, Antineoplastic

Introduction

An impure form of quinoline was initially extracted from coal tar by Runge in 1834. Subsequently, in 1842, Gerhardt produced quinoline through the degradation of quinine and cinchonine. It was later named quinoline.[1] Quinoline is also known by the chemical names benzo-pyridine or 1-aza-naphthalene. It is a weak tertiary base with an alkaloidal nature and features a nitrogen-containing heterocyclic aromatic ring. Quinoline has the molecular formula C9H7N and a molecular weight of 129.16. The quinoline nucleus undergoes similar reactions to those of pyridine and benzene. Its primary chemical reactions are nucleophilic and electrophilic substitution.[2] Quinoline is non-toxic to humans when ingested or inhaled. Several reduced forms of quinoline are known, including 1,2-dihydroquinolines, 1,2,3,4-tetrahydroquinolines, and decahydroquinoline (Fig. 1). Among these, 1,2,3,4-tetrahydroquinolines are particularly

significant and can often be synthesized by directly reducing the corresponding quinoline.[3-4] Quinoline is considered a heterocyclic molecule due to its double-ring structure, which features two adjacent carbon atoms fused to an arene. Quinoline compounds possess a diverse range of pharmacological activities, including antibacterial, antifungal, antimalarial, antileishmanial, and anticancer effects.[5-7]

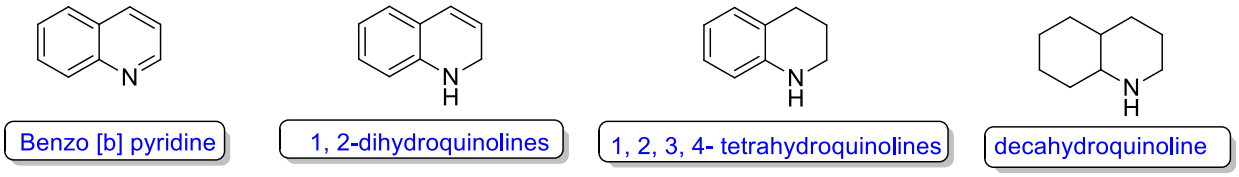
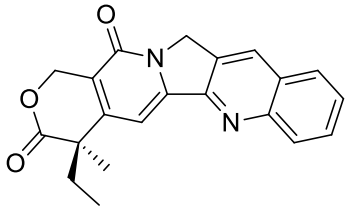
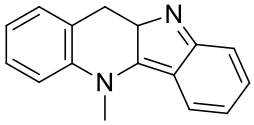
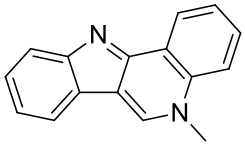
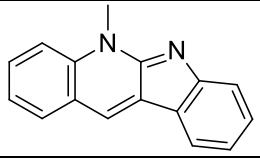
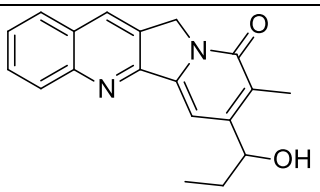
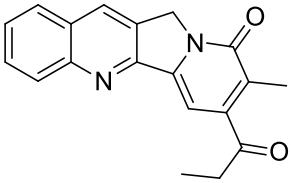
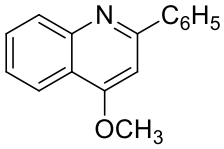
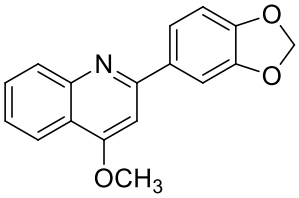
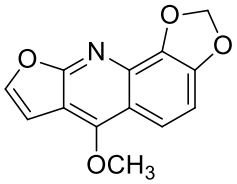
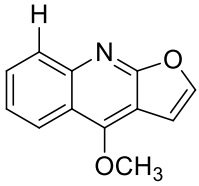
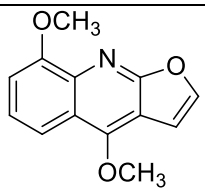
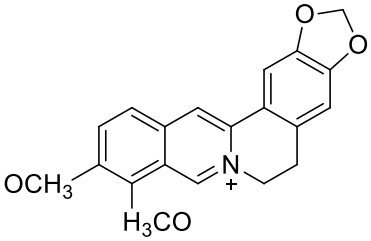
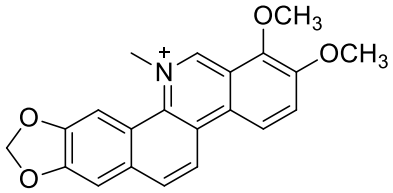


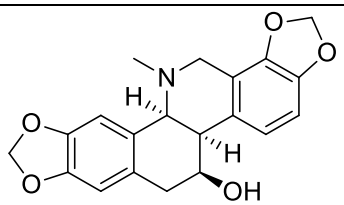
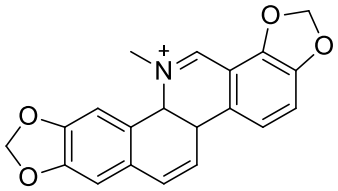
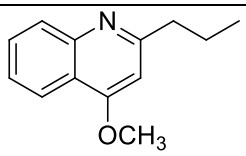
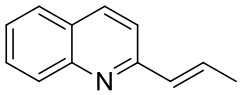
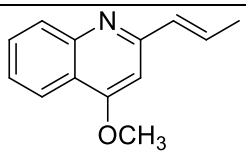
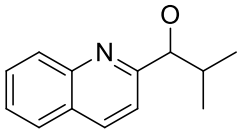
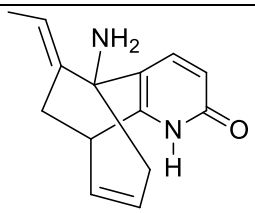
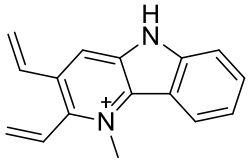
Fig.1 - Quinoline and its derivatives in reduced forms

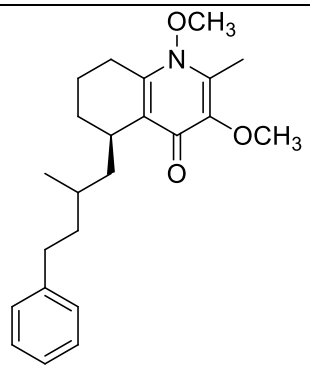
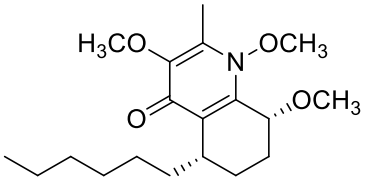
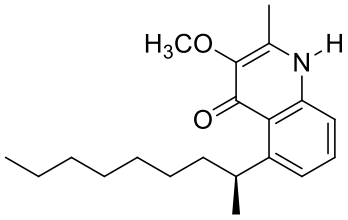
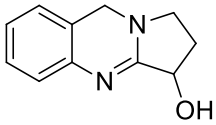
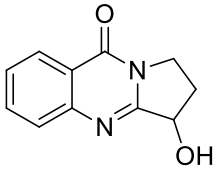
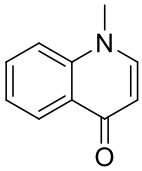
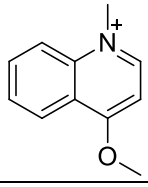
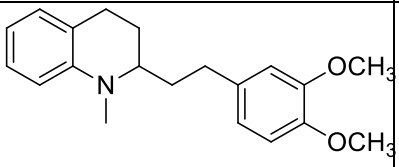
The quinoline ring system is found in various natural products, especially alkaloids, and is often incorporated into the design of numerous synthetic compounds with diverse pharmacological properties.[8] Table 1 below summarizes various natural sources of quinoline and their uses.[3]

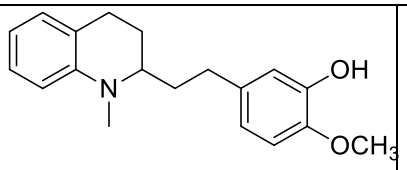
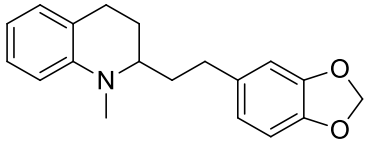
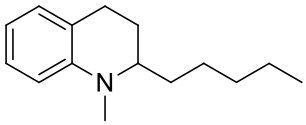
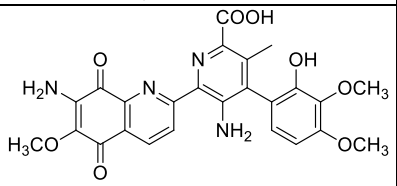
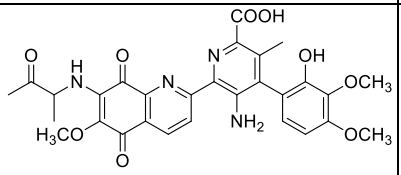
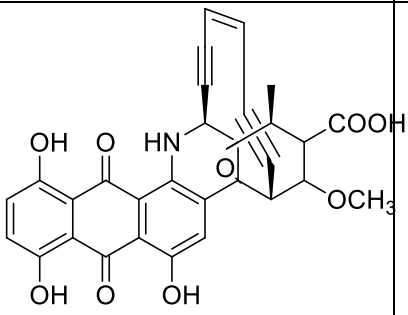
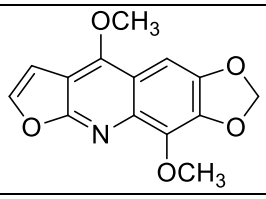
Table 1:- Quinoline: Structures and Applications from Natural Sources.

Sr. No.	Name	Structure	Source	Application
1.	Camptothecin		Bark and stem of Camptotheca acuminata	Anticancer drugs
2.	Cryptolepine		Cryptolepis sp.	Antiplasmodial activity, antimalarial
3.	Isocrytolepine		Cryptolepis sp.	Antimalarial activity
4.	Neocryptolepine		Cryptolepis sp.	Antimalarial activity

5.	Mappicine		Mapia foetida Miers	Activity against herpes viruses HSV-1 and HSV-2
6.	Mappicine ketone		Mapia foetida Miers	Activity against herpes viruses HSV-1 and HSV-2
7.	4-methoxy-2-phenylquinoline		Lunasiaamara	Activity towards m. Tuberculosis h37rv
8.	Graveolinine		Lunasiaamara	Activity towards m. Tuberculosis h37rv
9.	Kokusagine		Lunasiaamara	Activity towards m. Tuberculosis h37rv
10.	Dictamnine		Zanthoxylumwutaiense	Antitubercular activity (H37Rv strain)
11.	Γ-fagarine		Zanthoxylumwutaiense	Antitubercular activity (H37Rv strain)
12.	Berberine		Stem of Berberis aristata	Antimicrobial activity
13.	Chelerythrine		Argemone mexicana	Antifungal activity

14.	Chelidonine		Chelidonium majus	Antifungal activity
15.	Sanguinarine		Macleaya cordata	Antifungal activity
16.	Chimanines A		Galipea longiflora	Antileishmanial and antitrypanosomal agent
17.	Chimanines B		Galipea longiflora	Antileishmanial and antitrypanosomal agent
18.	Chimanines C		Galipea longiflora	Antileishmanial and antitrypanosomal agent
19.	Chimanines D		Galipea longiflora	Antileishmanial and antitrypanosomal agent
20.	Huperzine A		Huperzia serrata	Treatment Alzheimer's disease
21.	Cryptolepine		Cryptolepis sanguinolenta	Activity against adenocarcinoma

22.	Waltheriones G		Root extracts of Waltheria indica L.	Antichagasic agents
23.	Waltheriones H		Root extracts of Waltheria indica L.	Antichagasic agents
24.	Waltheriones F		Root extracts of Waltheria indica L.	Antichagasic agents
25.	Vasicine		Peganum harmala	Bronchodilatory, bronchoconstrictory and antianaphylactic action
26.	Vasicinone		Peganum harmala	Bronchodilatory, bronchoconstrictory and antianaphylactic action
27.	Echinopsine		Echinops albicaulis	Antioxidant activity
28.	Echinorine		Echinops albicaulis	Antioxidant activity
29.	Cuspareine		G. Officinalis	Antimalarial activity

30.	Galipeine		G. Officinalis	Antimalarial activity
31.	Galipinine		G. Officinalis	Antimalarial activity
32.	Angustureine		G. Officinalis	Antimalarial activity
33.	Streptonigrin		Micromonospora sp.	Induce apoptosis
34.	7-(1-methyl-2-oxopropyl)streptonigrin		Micromonospora sp.	Induce apoptosis
35.	Dynemicin A		Micromonospora chersina	Induce apoptosis
36.	Flindersiamine		E. Yaaxhokob	Antimicrobial activity

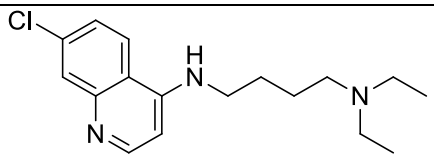
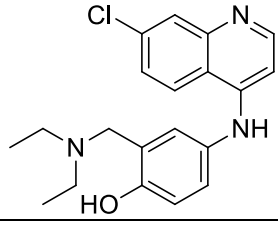
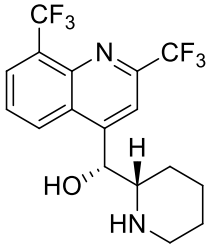
Approved Drugs Featuring the Quinoline Scaffold

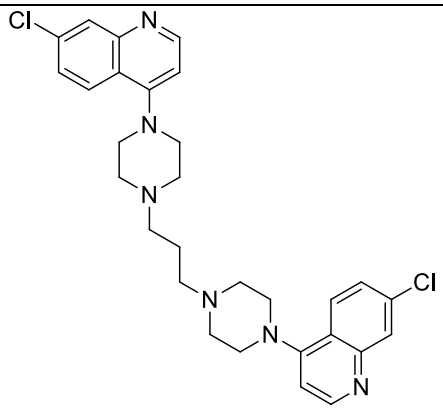
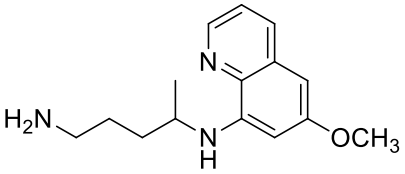
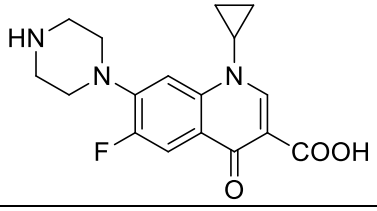
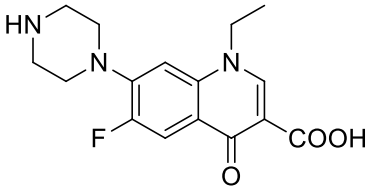
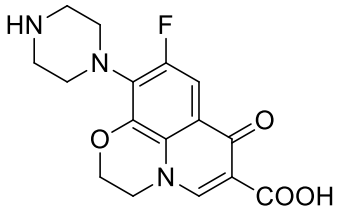
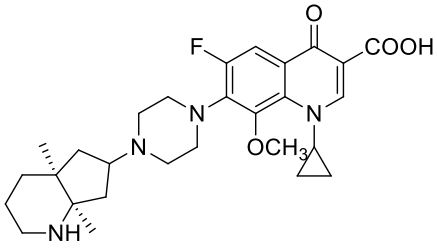
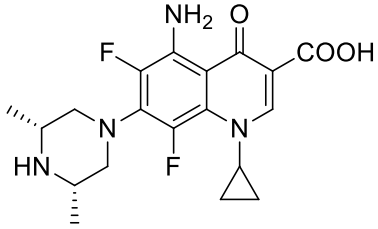
The substantial number of publications in the literature has consistently motivated researchers to investigate this structural class for therapeutic applications. Quinoline-containing systems are a common structural component of many drugs that are used clinically to treat various diseases.

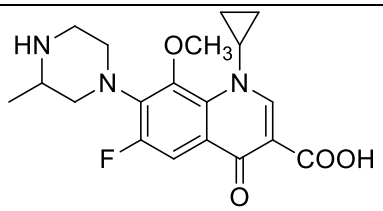
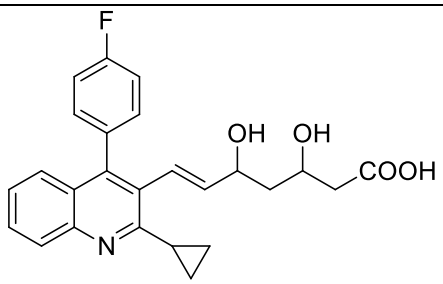
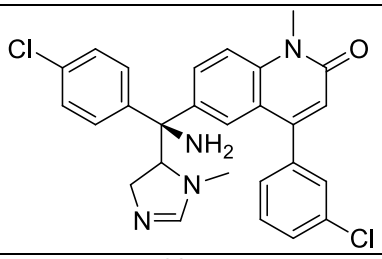
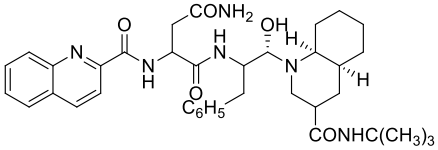
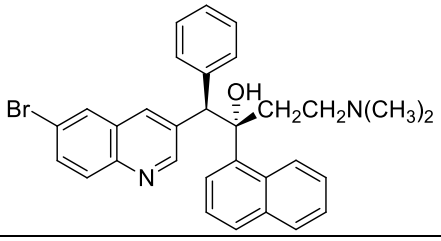
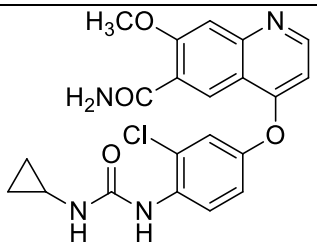
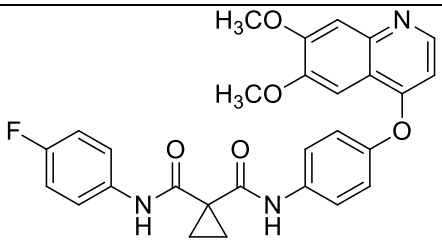
Quinoline is also found in several clinically used drugs, particularly among antimalarial medications.[9] The aminoquinoline scaffold has served as the foundation for antimalarial drugs since the 1940s. For example, chloroquine, discovered in 1934, led to the development of analogues such as amodiaquine, mefloquine, and piperaquine in response to chloroquine resistance. Quinoline is also part of drugs used for other diseases, including fluoroquinolone antibiotics like ciprofloxacin and its analogues norfloxacin and levofloxacin.[10] Quinolines are also used in drugs for various other conditions, including the cholesterol-lowering agent pitavastatin, the antiretroviral drug saquinavir, the anti-TB medication bedaquiline, the kinase inhibitor lenvatinib, the antineoplastic agent irinotecan, and the fluoroquinolone antibiotic finafloxacin etc.[11-12] A table 2 listing some approved drugs is provided below.

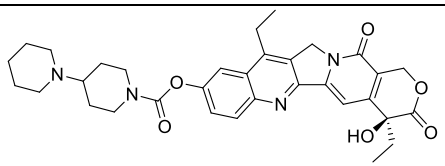
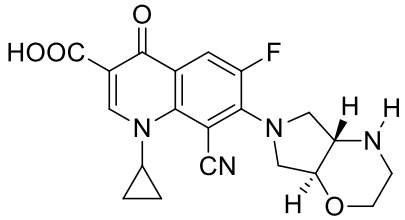
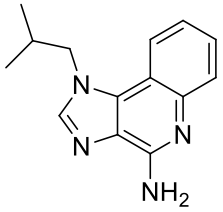
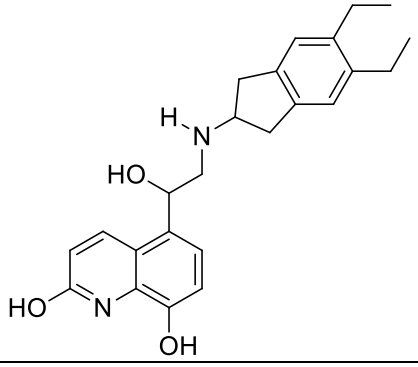
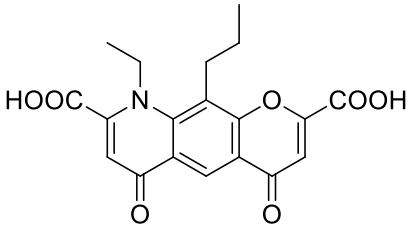
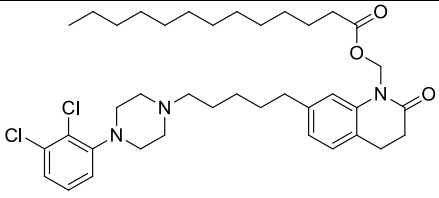
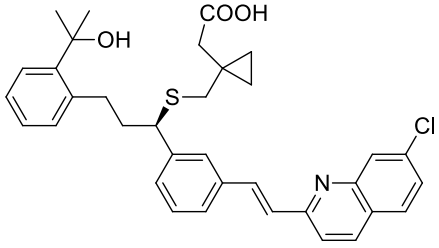
In addition to approved drugs, research efforts by scientists worldwide have led to the design and development of new quinoline derivatives, many of which are currently in various stages of clinical trials such as Dovitinib, Clinafloxacin, Mardepodect, Sitamaquine, Procaterol, Pelitinib, Foretinib and Garenoxacin etc.[13-17]

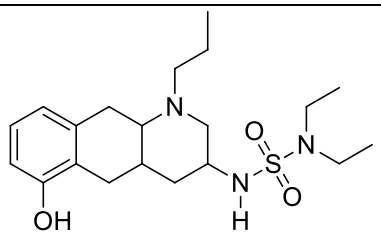
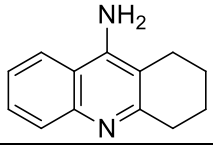
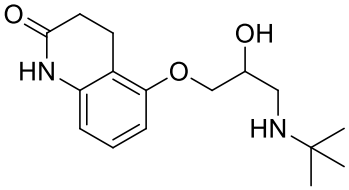
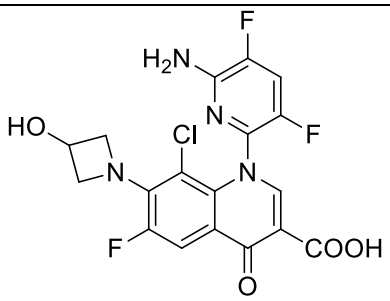
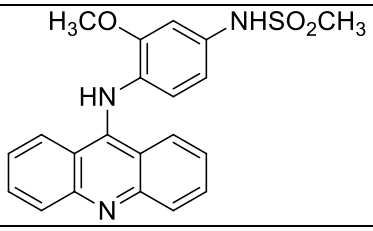
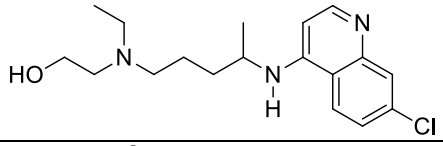
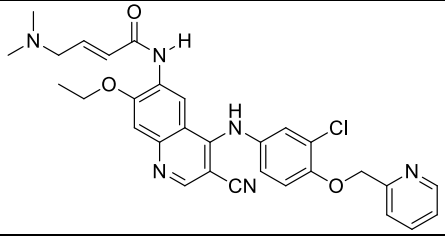
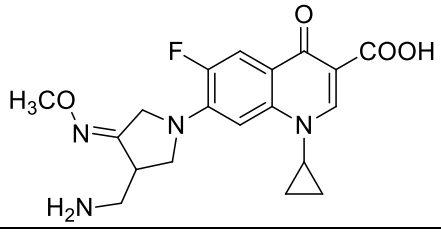
Table 2- List of approved drugs of quinoline and its derivatives

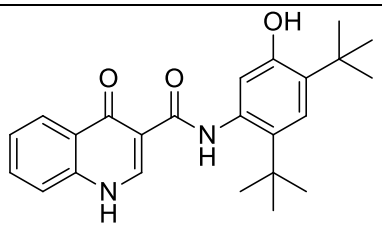
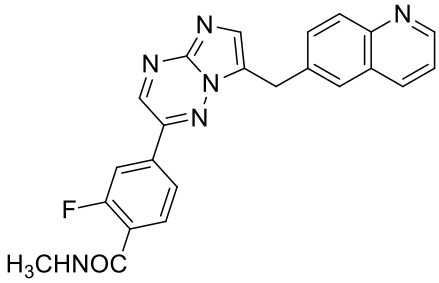
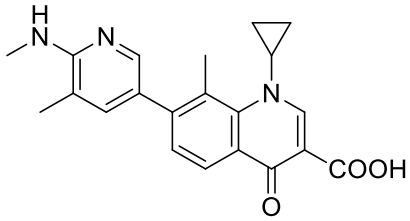
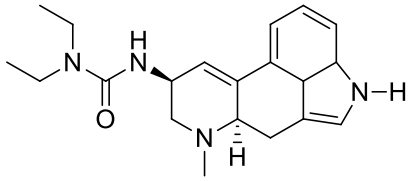
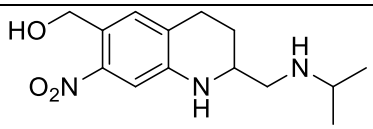
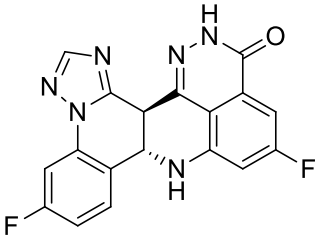
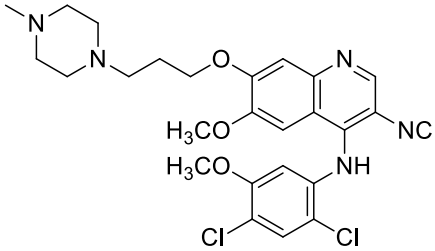
Sr. No.	Name	Structure	Application
1.	Chloroquine		Antimalarial drug
2.	Amodiaquine		Antimalarial drug
3.	Mefloquine		Antimalarial drug

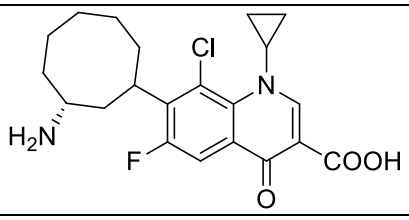
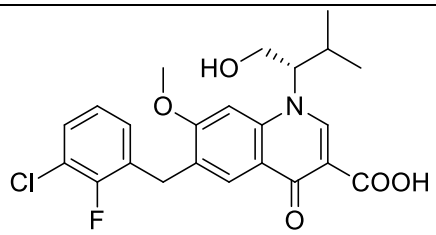
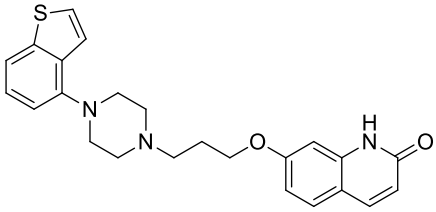
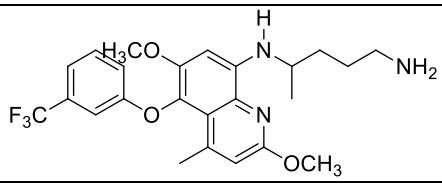
4.	Piperquine		Antimalarial drug
5.	Primaquine		Antimalarial drug
6.	Ciprofloxacin		Antibiotic
7.	Norfloxacin		Antibiotic
8.	Levofloxacin		Antibiotic
9.	Moxifloxacin		Antibiotic
10.	Sparfloxacin		Antibiotic

11.	Gatifloxacin		Antibiotic
12.	Pitavastatin		Cholesterol-lowering agent
13.	Tipifarnib		Farnesyl transferase inhibitor for leukemia
14.	Saquinavir		Antiretroviral
15.	Bedaquiline		Anti-TB
16.	Lenvatinib		Kinase inhibitor for cancer
17.	Cabozantinib		Non-specific tyrosine kinase inhibitor

18.	Irinotecan		Treatment of colorectal cancer
19.	Finafloxacin		Treatment of acute otitis externa (swimmer's ear)
20.	Imiquimod		Treat warts on the skin of the genital and anal areas
21.	Indacaterol		Management of asthma and chronic obstructive pulmonary disease
22.	Nedocromil		Inhibits activation of of inflammatory cells which are associated with asthma, including eosinophils, neutrophils, macrophages, mast cells.
23.	Aripiprazole lauroxil		Antipsychotic drug used in the treatment of schizophrenia in adult patients.
24.	Montelukast		Leukotriene receptor antagonist

25.	Quinagolide		Treatment of elevated levels of prolactin or hyperprolactinaemia
26.	Tacrine		Treatment of Alzheimer's disease and other CNS disorders
27.	Carteolol		Used as anti-arrhythmia agent, anti-angina agent, antihypertensive agent, and as an antiglaucoma agent
28.	Delafloxacin		Treatment of gonorrhea, hepatic impairment & bacterial skin diseases
29.	Amsacrin		Antineoplastic agent
30.	Hydroxy chloroquine		Treat malaria
31.	Neratinib		Breast cancer
32.	Gemifloxacin		Treatment of acute bacterial exacerbation of chronic bronchitis and mild-to-moderate pneumonia.

33.	Ivacaftor		Management of Cystic Fibrosis
34.	Capmatinib		Kinase inhibitor targeted against c-Met (HGF receptor)
35.	Ozenoxacin		Treatment of impetigo caused by S. Aureus or S. Pyogenes
36.	Lisuride		Agonist at dopamine D2 receptors
37.	Oxamniquine		Anthelmintic
38.	Talazoparib		Metastatic breast cancer
39.	Bosutinib		Src/Abl tyrosine kinase inhibitor

40.	Besifloxacin		Ophthalmic antibiotic for the treatment of bacterial conjunctivitis
41.	Elvitegravir		Treat HIV infection
42.	Brexpiprazole		Treatment of schizophrenia
43.	Tafenoquine		Antimalarial

Pharmacological actions of quinoline and its derivatives

Quinolines are among the most significant classes of heterocyclic alkaloids, known for their wide range of pharmaceutical activities. Heterocyclic molecules, such as quinoline, indole, coumarin, purine, pyrimidine, thiazole, imidazole, tetrazole, and flavones, have long been a rich source for drug discovery and development.[18] The quinoline ring, in particular, is recognized as a highly advantageous scaffold due to its extensive array of beneficial properties, including antibacterial, antifungal, antimycobacterial, antiviral, antiprotozoal, antimalarial, anticancer, cardiovascular, CNS effects, antioxidant, anticonvulsant, analgesic, anti-inflammatory, anthelmintic, and various other activities[19-22] (fig. 2).

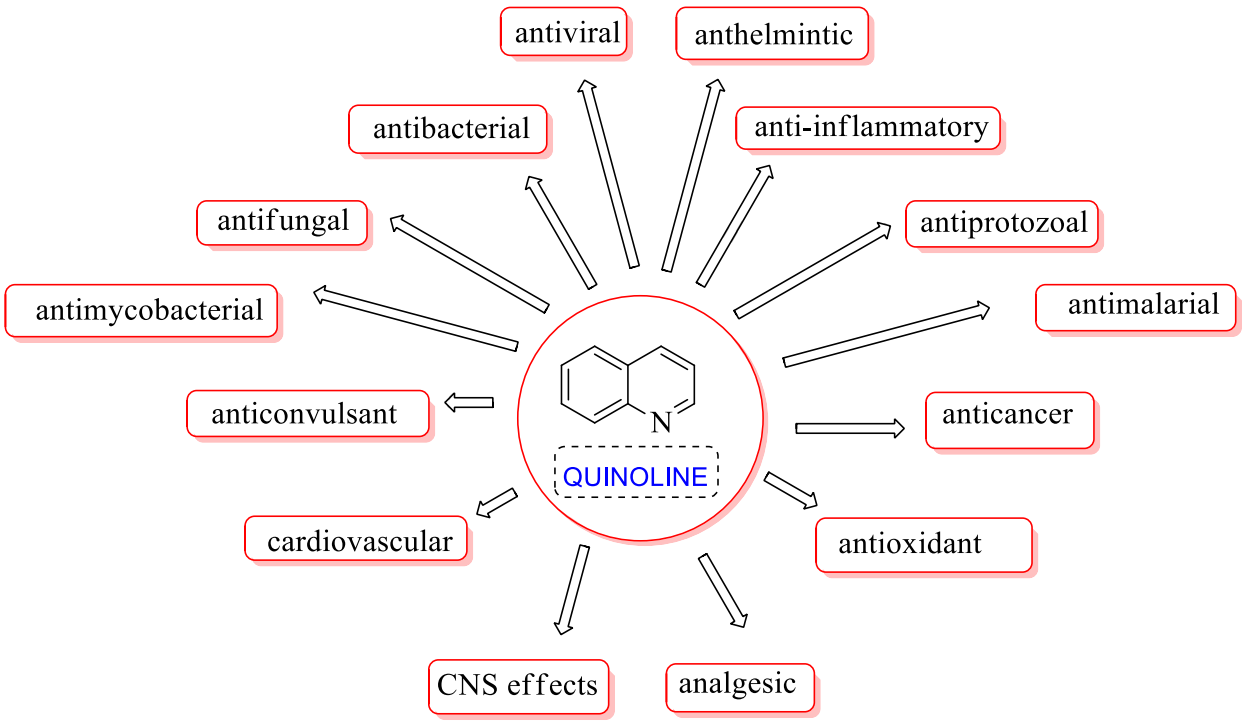


Fig. 2 Biological Activity of Quinoline Scaffold

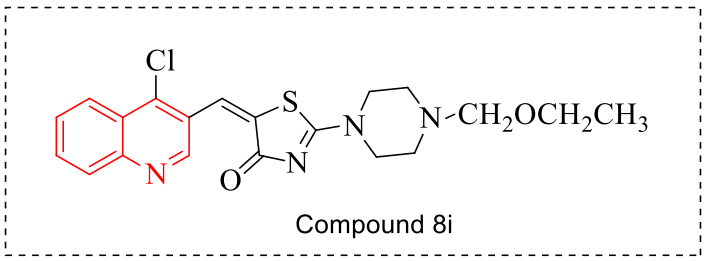
Advancement of Quinoline and its derivatives in Cancer Treatment

Quinoline is classified as a heterocyclic molecule due to its double-ring structure, which features two adjacent carbon atoms fused to an arene. It exhibits a wide range of pharmacological activities. Recent research has demonstrated that quinoline and its derivatives can inhibit tyrosine kinase, topoisomerase, and DHODH kinase.[23-24] Quinoline derivatives are increasingly used as anticancer drugs in pharmaceutical chemistry. They act as significant antiproliferative agents by intercalating with DNA and disrupting replication, thereby inducing cytotoxicity. The epidermal growth factor receptor (EGFR) belongs to the class of tyrosine kinase receptors. Upon ligand binding, major tyrosine groups within the receptor autophosphorylate, activating the PI3K/AKT pathways. These pathways synergistically promote cell vitality. EGFRs are abundant in cell membranes and frequently influence processes such as growth, apoptosis, and proliferation.[26]

With advances in cytobiology and molecular biology, the fundamental principles of tumorigenesis, invasion, migration, and metastasis induced by quinoline derivatives have been further elucidated. The antitumor mechanisms of quinoline derivatives include DNA alkylation,

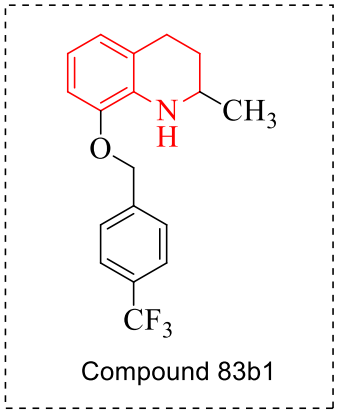
inhibition of c-Met kinase, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF).[27-28]

To overcome drug resistance and potential toxicity of existing quinoline derivatives, Priya MG et al. designed and synthesized novel quinoline derivatives with substituted piperazine moieties. These new compounds aim to enhance anticancer efficacy by inhibiting EGFR, a key therapeutic target for breast cancer. Their binding affinity was assessed through molecular docking studies, and their anticancer efficacy was evaluated against MCF-7 cell lines. Compound 8i demonstrated promising anti-breast cancer activity, confirmed by both in vitro and in vivo studies, warranting further investigation as a potential anticancer agent.[29]



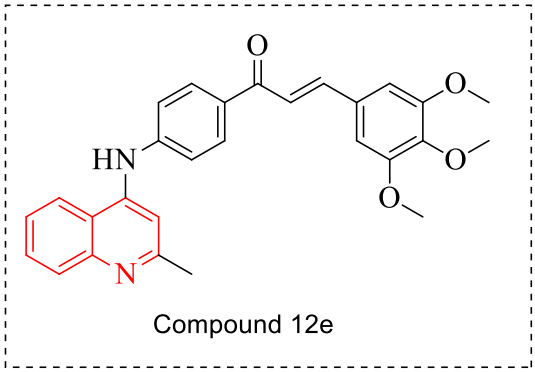
Compound 8i

Pun IH et al. reported that 83b1, a novel quinoline derivative, has been shown to inhibit cancer growth in human esophageal squamous cell carcinoma (ESCC). Various ESCC and non-tumor immortalized cell lines were treated with 83b1 and cisplatin (CDDP) in a dose-dependent manner, with cytotoxicity assessed using an MTS assay kit. The expression of cyclooxygenase 2 (COX-2) mRNA and COX-2–derived prostaglandin E2 (PGE2) was measured by quantitative real-time polymerase chain reaction and enzyme-linked immunosorbent assay, respectively. The in vivo anti-tumor effect was evaluated using a nude mice xenograft model with the ESCC cell line KYSE-450. The study suggests that the potential anti-cancer effects of 83b1 on human esophageal cancers may occur through the oncotarget PPARγ and the down-regulation of cancer-related genes and molecules.[30]



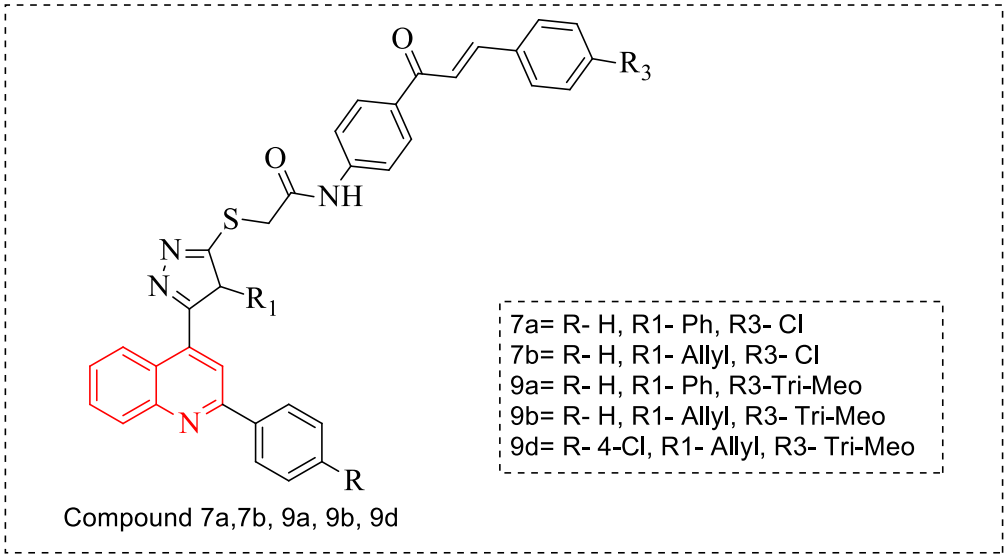
Compound 83b1

Guan YF et al. reported the design and synthesis of quinoline-chalcone derivatives and assessed their antiproliferative activity against MGC-803, HCT-116, and MCF-7 cells. Among these derivatives, compound 12e exhibited the strongest inhibitory effect, with IC50 values of 1.38, 5.34, and 5.21 μM against MGC-803, HCT-116, and MCF-7 cells, respectively. Mechanistic studies indicated that compound 12e inhibited MGC-803 cells in a dose-dependent manner, reduced cell colony formation, caused cell cycle arrest at the G2/M phase, and significantly increased the levels of apoptosis-related proteins (Caspase3/9 and cleaved-PARP) in MGC-803 cells.[31]



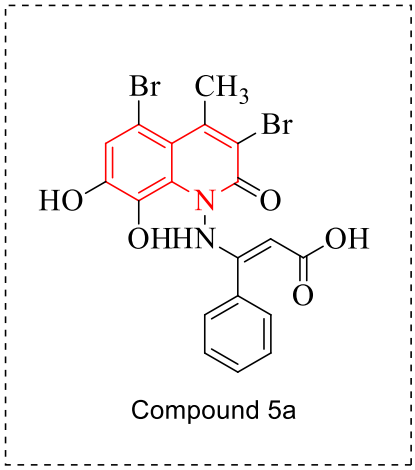
Compound 12e

Mohassab AM et al. designed and synthesized new quinoline/chalcone hybrids containing a 1,2,4-triazole moiety, with their structures confirmed by various spectroscopic techniques. Compounds 7b, 7d, 9b, and 9d exhibited the most significant activity against several cancer cell lines, showing growth inhibition percentages between 77% and 94% and demonstrating promising antiproliferative properties. Molecular docking studies of compounds 7a, 7b, 9a, 9b, and 9d revealed good binding into the active sites of EGFR and BRAFV600E kinase.[32]



Compound 7a,7b, 9a, 9b, 9d

Abu Almaaty AH et al. designed and synthesized a new series of hybrid molecules containing cinnamic acid and 2-quinolinone derivatives. Among these, compound 3-(3,5-dibromo-7,8-dihydroxy-4-methyl-2-oxoquinolin-1(2H)-ylamino)-3-phenylacrylic acid (5a) demonstrated the highest potency with an IC50 of 1.89 µM against HCT-116 cells, outperforming the standard drug staurosporine. A DNA flow cytometry assay of compound 5a showed G2/M phase arrest and pre-G1 apoptosis. Additionally, topoisomerase enzyme inhibition assays indicated that hybrid molecule 5a exhibits potent inhibitory activity compared to the control.[33]

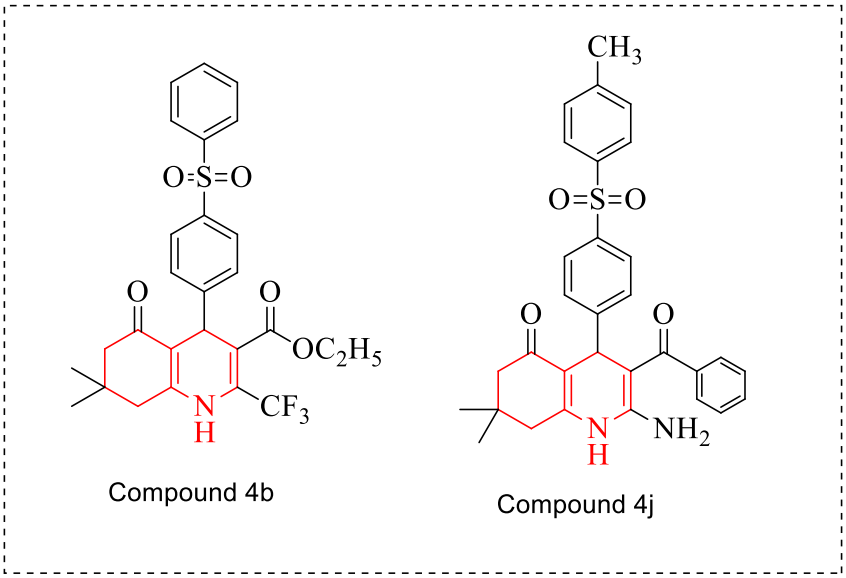


Compound 5a

Molecular hybridization is emerging as a promising strategy for drug design, particularly for discovering new anticancer drugs. This approach involves combining two or more pharmacophores within a single molecular structure, which can reduce the risk of drug-drug

interactions, overcome drug resistance, and enhance biological efficacy by binding to multiple targets simultaneously.[34]

Mokhtar M et al. demonstrated that a new series of 4,6,7,8-tetrahydroquinolin-5(1H)-ones were designed as cytotoxic agents against the breast cancer cell line (MCF-7) and synthesized using a chitosan-decorated copper nanoparticle (CS/CuNPs) catalyst under ultrasonic irradiation. The most promising cytotoxic compounds, 4b and 4j, were evaluated as multi-targeting agents against RTK protein kinases EGFR, HER-2, PDGFR-β, and VEGFR-2.[35]



Conclusion

Quinoline and its analogs are significant heterocyclic compounds in drug discovery and development. They represent a crucial class of scaffolds in medicinal chemistry and occur naturally with potent therapeutic properties. There has been growing interest in utilizing quinoline derivatives as drug molecules to combat pathogens and various disorders. Quinolines exhibit a wide range of therapeutic properties, making them valuable in numerous medical applications and underscoring their importance for human health. In cancer therapy, drug resistance poses a significant challenge. To address this, various strategies must be explored to enhance the efficacy of quinoline derivatives in delaying or overcoming resistance. The development of new quinoline compounds holds great promise and potential for drug development scientists.

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