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Annotated Review on Various Biological Activities of Quinoline Molecule

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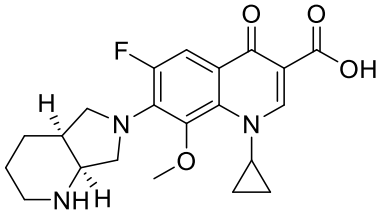
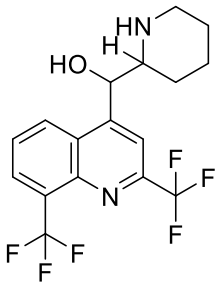
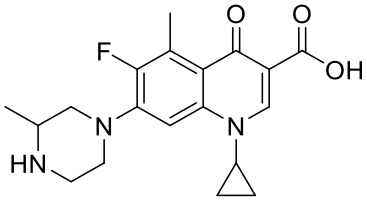
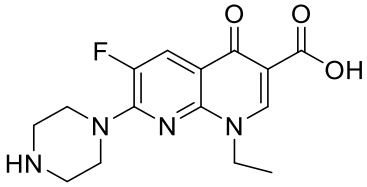
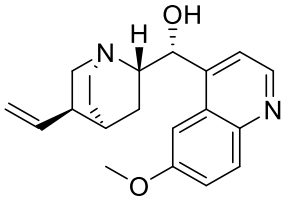
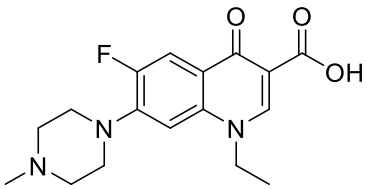
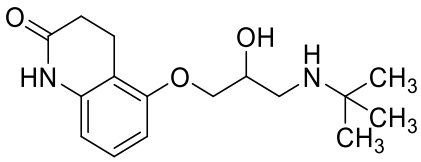
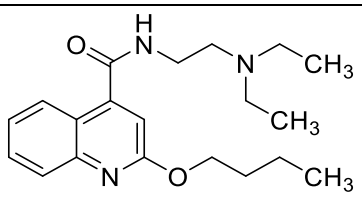
Abstract: Quinoline or Benzopyridine moiety remained an attraction among researchers in the 21st century. Quinoline is a heterocyclic aromatic organic compound with the chemical formula C9H7N. This moiety is considered a biologically important active source that possesses all types of medicinal potentials due to its simple chemistry, ease of synthesis, and a wide variety of numerous biological potentials in both natural and synthetic derivatives such as antimalarial, antibacterial, anti-inflammatory, anti-arrhythmic, anti-anginal, antihypertensive, anti-depressant, anti-convulsant. This pharmacological diversity of quinoline has attracted researchers to explore this moiety by making modifications at various possible positions. In the present review, we are outlining the potential of quinoline as an antimalarial, anticancer, anti-inflammatory, and antibacterial agent. Furthermore, by attaining the knowledge of molecular targets, structural insights, and SARs, this review may be supportive for medicinal chemists to design more potent, safe, selective, and cost-effective quinoline derivatives for various biological properties.

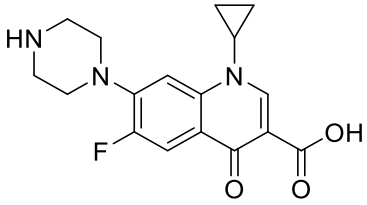
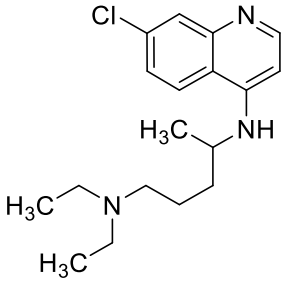
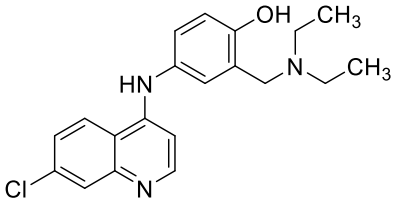
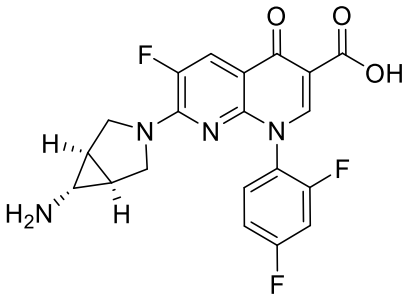
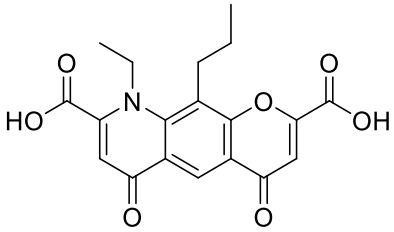
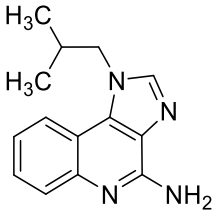
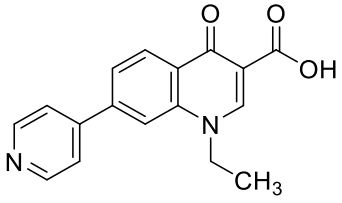
Keywords: Quinoline; antimalarial; chloroquine; anticancer; anti-inflammatory; quinoline-chalcone hybrids.

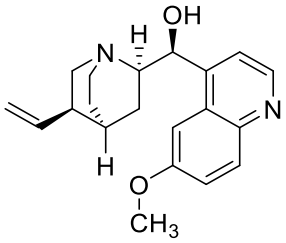
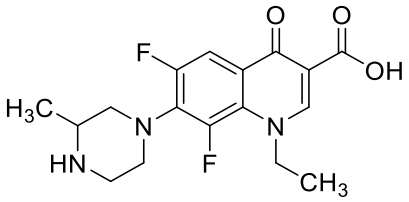
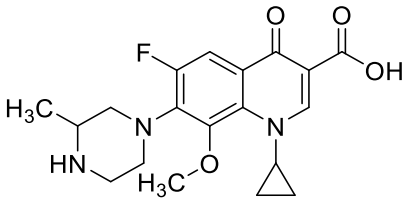
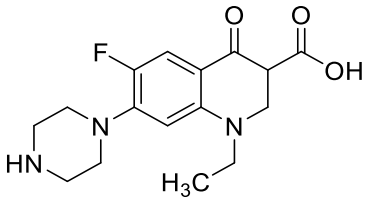
1. Introduction

Quinoline is considered an important biological active moiety with numerous biological properties such as antimalarial, antibacterial, anti-inflammatory, anti-arrhythmic, anti-anginal, antihypertensive, antituberculosis, anti-depressant, and anti-convulsant [1–10]. Successful introduction of quinine, mefloquine, and chloroquine as antimalarial, ofloxacin, and chloroxine as antibacterial, and various other activities proved the potential of the quinoline system. This variety in the biological response profile has delighted the attention of researchers to explore the quinoline skeleton to its multiple possibilities as an active moiety. In the present review, we are outlining the potential of quinoline as an antimalarial, anticancer, anti-inflammatory, and antibacterial agent. Chemically, Quinoline (Benzopyridine) is a heterocyclic aromatic organic compound (C_9H_7N) that possesses all types of medicinal potential, this diversity in the biological potential has attracted many researchers to explore the quinoline ring [11]. Some of the marketed drugs related to Quinoline moiety are shown in Table 1 [12-22].

Table 1. Marketed drugs based on quinoline moiety.

Comp No.	Drug name	Drug description	Structure
1.	Moxifloxacin	To treat various bacterial infections.	
2.	Mefloquine	Antimalarial, Anti-inflammatory activities.	
3.	Grepafloxacin	Effective against both gram-positive & negative bacterial infections.	
4.	Enoxacin	1,8-naphthyridine derivative with an antibacterial agent.	
5.	Quinine	Natural alkaloidal compounds for the treatment of malaria.	
5.	Pefloxacin	Used for gram-positive and negative bacterial causing g.i.t. and genitourinary tract infections.	
6.	Carteolol	β-adrenergic antagonist.	
7.	Cinchocaine	Local anesthetic.	

Comp No.	Drug name	Drug description	Structure
8.	Ciprofloxacin	2nd generation fluoroquinolone derivative for bacterial infection treatment.	
9.	Chloroquine	Antimalarial drug used to treat susceptible infections and is also effective for rheumatoid arthritis.	
10.	Amodiaquine	Effective in case of acute malarial attacks.	
11.	Trovafloxacin	Antibiotic for gonorrhoea and chlamydia.	
12.	Nedocromil	To treat allergic conjunctivitis.	
13.	Imiquimod	Used for basal cell carcinoma, genital or perianal warts.	
14.	Rosoxacin	Effective in various bacterial infections.	

Comp No.	Drug name	Drug description	Structure
15.	Quinidine	Most preferable to restore normal sinus rhythm, treat atrial fibrillation and flutter, and treat ventricular arrhythmias.	
17.	Lomefloxacin	Able to prevent and treat a wide variety of infections.	
18.	Gatifloxacin	4th generation fluoroquinolone used for a variety of infections.	
19.	Noefloxacin	A broad-spectrum fluoroquinolone antibiotic effective against bacterial infection of UTIs.	

2. Materials and Methods

2.1. Quinoline derivatives as antimalarial agents.

For controlling and eradicating malaria, the highly famous chloroquinoline as quinoline scaffold has been used for decades. Moxifloxacin, Mefloquine, Quinine, Amodiaquine, and piperaquine are other reported antimalarial agents of the quinoline family. Drugs from this class interfere with the parasite's life cycle or target tissue stages [23, 24]. Natural and synthetic derivatives of quinoline such as 4-aminoquinoline, 4-anilinoquinolines, isoquinoline, tetrahydroquinoline, and other miscellaneous quinolines have such properties for malarial parasites [25, 26].

2.1.1. Natural quinolines based quinoline derivatives.

N-methyl-4-hyrdoxy-3-(2',3'-epoxyisobutyl)-2-quinoline (20, 21) and candicine have been reported as active antimalarials and have also been active against *Mycobacterium tuberculosis*, and it has been isolated from the dry bark of *Galipea officinalis* (Rutaceae) [27]. Jacobs *et al*. reported benz[g]isoquinoline-5,10-dione (22) as an active chemical constituent, as antimalarial isolated from *Psychotria camponutans* [28]. *Aurachin E* has been isolated and reported as the most potent isoprenoid quinoline alkaloid derivative (23) derived from *Stigmatella aurantiaca* and *Stigmatella erecta* [29, 30] [Fig.1].

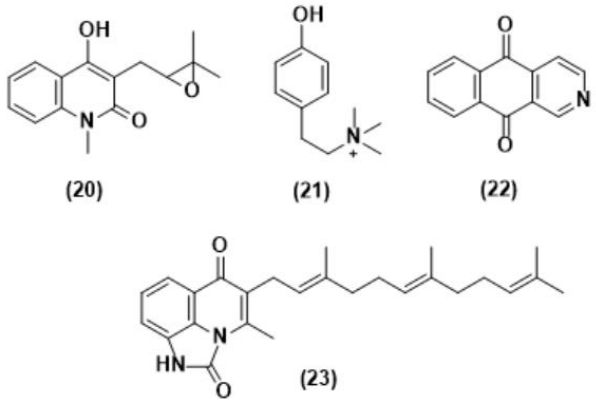


Figure 1. Few Natural quinolines-based quinoline derivatives**.**

2.1.2. 4-Anilinoquinoline derivatives.

Amodiaquine (AQ), is the most active 4-anilinoquinoline-based antimalarial but is not much recommended for the prevention of malaria as it is reported for agranulocytosis and hepatitis as side effects. The oxidation of 4-hydroxyanilino moiety of AQ forms reactive amido-quine quinonimine (AQQI), which further reacts to glutathione. Fluro group is placed in the place of the hydroxyl group in the aromatic ring of amodiaquine (24) oxidative bioactivation reduces. Emilia Păunescu *et al.* have reported a series of 4-aminoquinoloine by removing the hydroxyl group and retaining the aromatic ring of amodiaquine [31]. Carbamate and amide derivatives of amodiaquine have also been synthesized and examined for antimalarial activity. The compound (25) with IC50 = 9.7 nM was the most potent among the reported series [32] [Fig. 2]

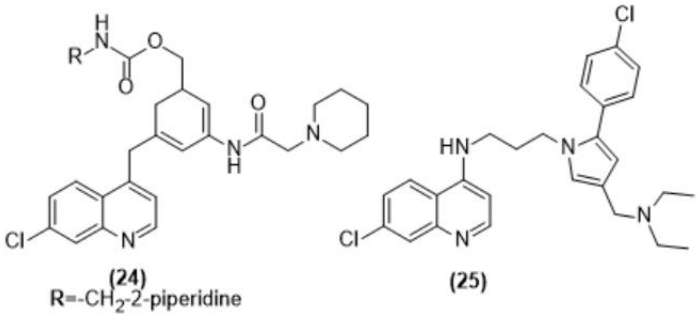


Figure 2. 4-Anilinoquinoline derivatives.

The carbamate and amide series presents interesting compounds in terms of in vitro antimalarial activity and cytotoxicity and contribute to completing the study of the structure-activity relationship on 4-anilinoquinoline derivatives. It has been proven that introducing the amide or carbamate linker improves the efficiency of those derivatives compared to the ester linker in selectivity index and *in vivo* activity. Compound (26) presents the best results in those two series with high *in vitro* activity whatever the strains used, a good selectivity index, and a reasonable activity *in vivo* [33] [Fig. 3]

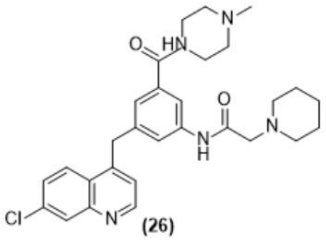


Figure 3. Compound 26**.**

2.1.3. 4-aminoquinoline derivatives.

Chloroquine (CQ) is the drug belonging to this class that acts as a substitute for quinine. In the early 1950's CQ was most frequently used for treating and preventing malaria. Due to the appearance of CQ-resistant parasites, chloroquine is not recommended in many parts of the world for malaria treatment. To overcome the resistance problem, worldwide researchers work on it and develop a number of 4-aminoquinoline-related compounds, such as bisquinoline, hybrid 4-aminoquinoline derivatives, and compounds with modifications in the side chain. Casagrande et al. synthesized and evaluated nine new aryl-pyrrolyl compounds of 7-chloro-4-aminoquinoline and evaluated them against two strains of P. falciparum (CQ-S and CQ-R). The compound with Thienyl (27), aryl imidazolyl (28), and N-methyl imidazolyl (29) was categorized as the most potent under this synthesized series [34] [Fig. 4]

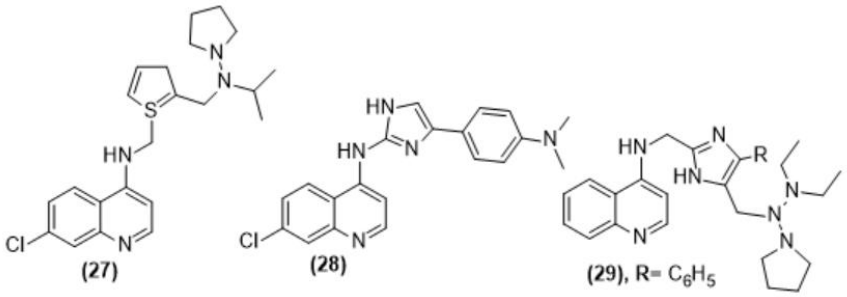


Figure 4. Compound with Thienyl, aryl imidazolyl, and ***N***-methyl imidazolyl moiety**.**

Equally potent against chloroquine-resistant and chloroquine-sensitive *P. falciparum*, Zishiri *et al.* intended a series of 4-amino-7-chloroquine derivatives with dibenzo methylamine as a side chain. The most potent compound (30) with IC_{50} values 26nM and 23nM for chloroquine-resistant and chloroquine-sensitive strains, respectively. Aminoquinoline hybrids with acridine and artemisinin also have been synthesized and detected by Ashok *et al.* and Lombard *et al.* respectively [35, 36]. Acridine-based derivatives (31) tested against NF 54 strain of *P. falciparum* and artemisinin-aminoquinolines (32) were screened against D10 and D2 strains of *P. falciparum* [37] [Fig 5].

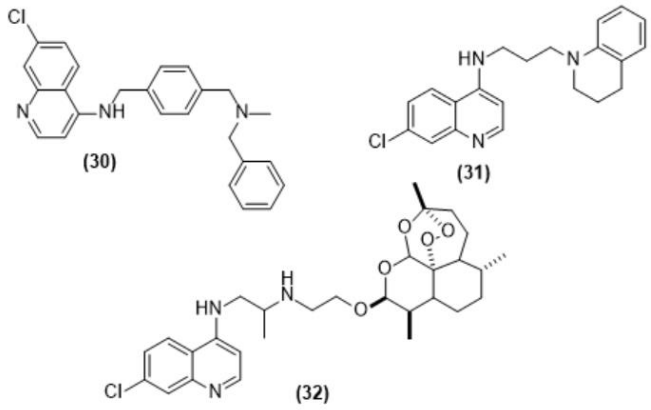


Figure 5. 4-Amino-7-chloroquine derivatives**.**

2.1.4. Bis(4-aminoquinoline) derivatives.

Piperaquine has been reported as Bis(4-aminoquinoline) derivative, in which CQ resistance is tried to overcome by attaching two molecules of 4-aminoquinoline structures by various linkers. This resistance is well explained by improper binding of substrate and PfCRT (*P. falciparum* chloroquine resistance transporter) due to bulkier structures of Bis(4-aminoquinoline). The linkers' chain length and attached position affect the activity. Bis, tris, and tetra quinoline have been reported for antiplasmodial activity with cyclic amino and linear linkages [38].

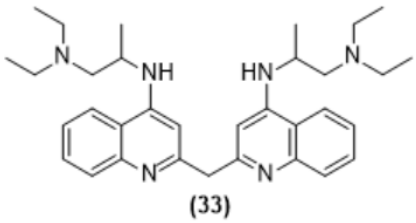


Figure 6. Alkylidene-linked Compound**.**

The compound with alkylidene-linked CQ dimers has been reported (33) as most potent with IC_{50}=17 nM with better potency than CQ (IC_{50}=540 nM). Other cinchonine, like bisquinoline has also been reported to overcome CQ resistance and toxicity in various animal studies [39] [Fig 6].

7-substituted 4-aminoquinoline derivatives with phenyl, di-aryl ethers, bi-aryls, and alkyl-aryls using different reactions such as Ullmann reaction, Suzuki reaction, and Negishi reaction had been synthesized and evaluated by Jong Yeon Hwang *et al.* for antimalarial activity, against CQ- Sensitive and CQ-Resistance strains. The study resulted in 4-aminoquinoline derivatives substituted with bi-aryl at 7-position were most potent compared to other substituents [40].

2.2. Quinoline derivatives as an anti-inflammatory.

Due to various infections and autoimmune diseases, a complicated response arises in body tissue, i.e., inflammation. The anti-inflammatory substance has the property to treat or reduce inflammation and also relieve pain related to it. A well-known strategy to treat

inflammation is to inhibit Cyclooxygenase (COX-1/COX-2). Celecoxib, valdecoxib, etc., are approved classical NSAIDs as inhibitors of COX's, but many of them are withdrawn from the market because of their cardiovascular-related side effects [41, 42].

Celecoxib is reported as a potent anti-inflammatory agent; Ibrahim *et al.* combined Celecoxib with quinoline moiety to detect its anti-inflammatory action. Synthesized compounds have been reported with similar or even higher inhibitory action on COX-1/COX-2, among which compounds (34, 35, 36) were found as a potent inhibitor of the COX-2 enzyme, having IC_{50} values ranging between 0.1- 0.11 µM, respectively [43, 44] [Fig 7].

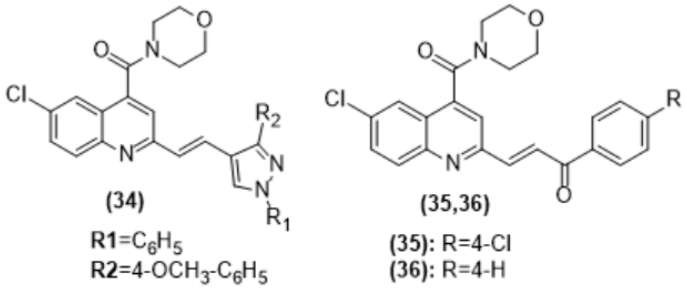


Figure 7. Celecoxib with quinoline moiety.

Abderlrahman *et al.* have synthesized and reported quinoline-2-carboxamides-based series for its dual inhibition towards COXs/LOX. Compound (37, 38) exhibits the highest potency towards COX-2 as compared to Celecoxib with IC_{50} 1.21 and 1.14 Mm, respectively [45, 46][Fig 8].

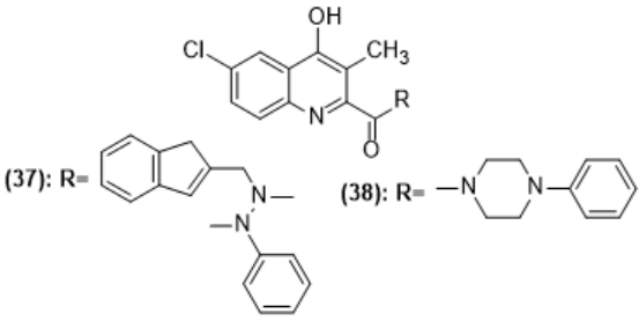


Figure 8. Carboxamides-based compound**.**

Cyclopenta [a] anthracene, quinolin-2-one, and 1-oxa-3,5-diaza-anthracen-6-one based quinoline derivatives were three series reported as potential anti-inflammatory agents using the ear-edema test, which is induced by xylene in mice by Xiang *et al.* [47]. The compound (39, 40) showed maximum anti-inflammatory potential with 63.19% and 68.28% after half an hour of intraperitoneal administration. The pharmacological capability was compared with ibuprofen as a standard drug [Fig 9].

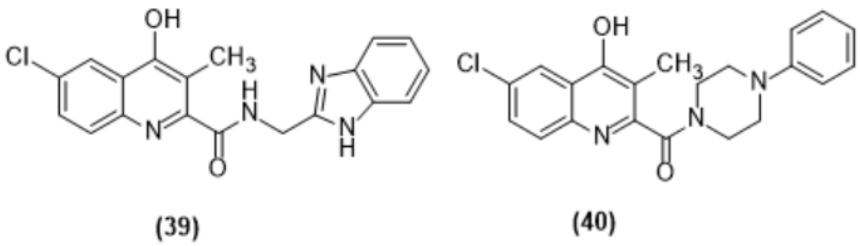


Figure 9. Anthracene-quioloine-based compound**.**

Gastric irritation and gastric ulceration are the two main problems associated with the existing anti-inflammatory agents. To overcome these drawbacks, Kumar *et al.* synthesized and evaluated the azetidine-2-one scaffold-based quinoline derivatives for anti-inflammatory and analgesic agents using two models named Rat paw and Eddy's hot plate model. Two compounds (41, 42) with halogen (chloro) at position 3 and methoxy substitution at 2,3-position of azetidine-2-one possess the maximum anti-inflammatory property [48] [Fig 10].

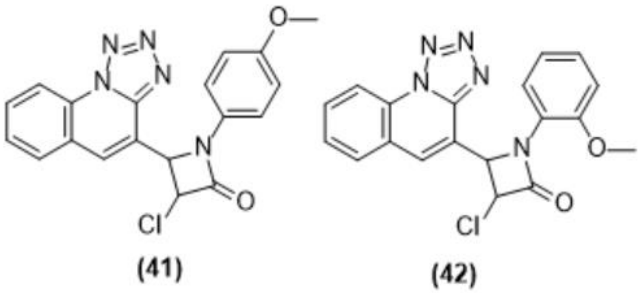


Figure 10. Azetidine-2-one scaffold-based quinoline derivatives**.**

Amany *et al.* evaluated the synthesized conjugates of ibuprofen and quinoline ring fused with alkyl linkage for its anti-inflammatory and ulcer-causing potential using a carrageenan-induced rat paw edema test. The ibuprofen and quinoline conjugates without substitution and halogen-containing derivatives are linked together by a propyl chain, showing maximized activity for inflammation and analgesic actions [49].

Three series have been made and evaluated for anti-inflammatory action by condensing substituted imidazole and substituted quinoline compounds with an ethylene bridge. QSAR and CADD studies also predict these compounds as a fit target for COX-1 and COX-2 enzymes compared with standard ibuprofen. 1-(2-((18*Z*)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-1,2-dihydro-4-methyl-2-oxoquinolin-7-yl were three series belonging to these series [50].

2.3. Quinoline derivatives as anticancer agents.

As a genetic disorder, cancer involves changes in genes that are able to control cell functions, such as cell growth and development. Cancer is a group of fatal diseases involving the unwanted growth of normal cells and spreading to all body parts. The death rate of cancer is gradually increasing, so cancer treatment and control have become the most important objective for researchers and the pharmaceutical industries to work on it. The development of therapeutic tools for cancer treatment has been advanced in the last few years. The approaches for cancer treatment have gradually moved towards specific targets. These cancer cure approaches include eradicating cancer cells without affecting normal cells. But currently, not even a single available agent meets this target. Compounds with heterocyclic cores play a significant role in designing and developing a new class of structural entities with anticancer potential [51, 52].

2.3.1. Quinoline-chalcone hybrids**.**

Mirzaei *et al.* synthesized and evaluated quinoline-chalcone hybrids for anticancer activities in resistant cancerous cells and parent cells. A2780 (ovarian carcinoma),

A2780/RCIS (Cisplatin resistant ovarian carcinoma), MCF-7 (breast cancer cells), and MCF-7/MX (Mitoxantrone resistant breast cancer cells) were the four selected human cancer cell lines against which anticancer activity of these compounds was evaluated. Compound (43, 44, 45) having benzoyl substituent has resulted in most antiproliferative probability with IC_{50} ranges from 2.32 to 22.4µM [53] [Fig 11].

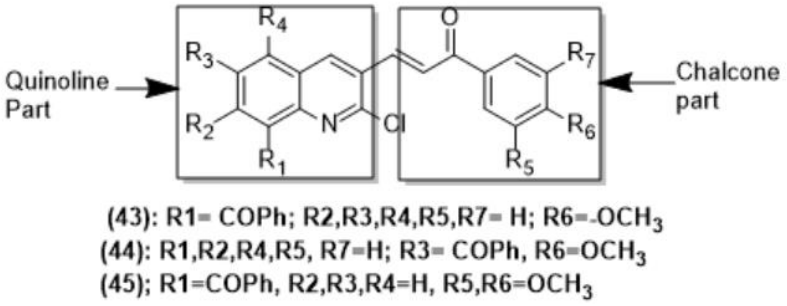


Figure 11. Quinoline-chalcone hybrids**.**

10 compounds of chalcones fused with quinoline have been synthesized and evaluated for the anticancer property by Veera *et al.*, out of which six compounds (46-51) exhibit more anticancer potency than positive control doxorubicin. Three cancer cell lines, MCF-7, A-549, and A375 belonging to breast, lungs, and melanoma, were selected for checking anticancer activity by employing the MTT assay [54] [Fig 12].

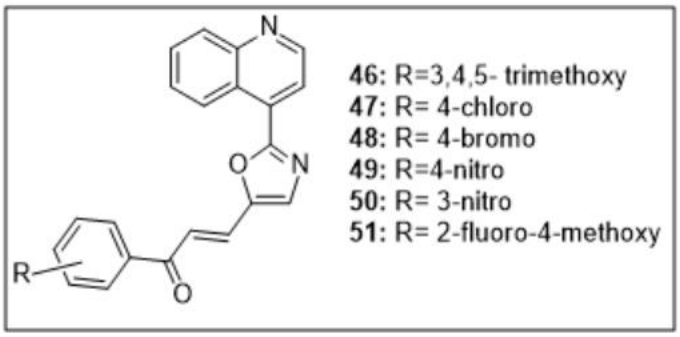


Figure 12. 2,3,4,5-Quinoline-Chalcone Hybrid**.**

Yong-Feng *et al.* designed, synthesized, and explored quinoline-chalcone derivatives substituted at all possible sites for their antiproliferative activity against various cell lines, such as MGC-803, HCT-116, and MCF-7 cells.

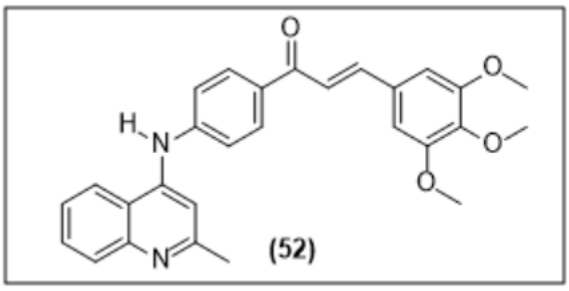


Figure 13. 3,4,5-Trisubsituted methoxy derivative**.**

Out of which compound (52) having 3,4,5-trisubsituted methoxy groups at chalcone exhibited a most excellent inhibitory potency against all selected lines with IC_{50} values ranging from 1.38- 5.21 µM [55, 56] [Fig 13].

The compounds quinoline-2-one-based chalcones derivatives have been synthesized and evaluated for anticancer potency by Rodrigo A *et al.* against 50 human cells of cancer. Compounds (53-56) showed the maximum potency against all the selected 50 human cell lines, whereas compound (56) exhibited more remarkable potency toward all cell lines [57] [Fig 14].

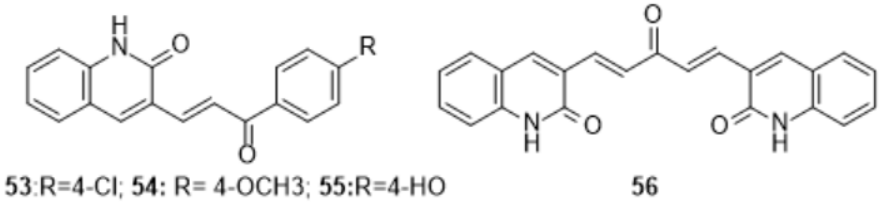


Figure 14. Quinoline-2-one-based chalcones derivatives**.**

2.3.2. 5-Methoxylquinoline derivatives.

Xiang *et al*. discovered a new class of 5-methoxylquinoline derivatives as potent EZH2 inhibitors. BIX-01294 (57), *i.e.* (2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-6,7-dimethoxy-*N*-[1-(phenylmethyl)4-piperidinyl]-4-quinolinamine is known to be a most potent inhibitor of G9a/GLP. The 2-bromo-5-methoxyaniline and malonic acid were cyclized by using $POCl_3$ as solvent and catalyst for preparing 5-methoxyquinoline derivatives [Fig 15].

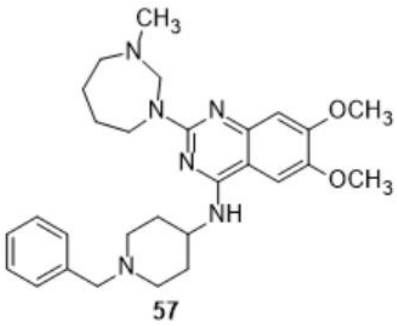


Figure 15. Structure of BIX-01294**.**

EZH2 has been over-expressed in various cancerous tissues of the colon, prostate gland, lungs, and breast.

2.3.3. N-mustard-quinoline conjugates.

Alkylation of DNA by chemotherapeutic agents is known to be the most widely used in cancer treatment. A huge number of nitrogen mustards are recognized as DNA-directed alkylating agents. Kakadiya *et al*. synthesized a sequence of *N*-mustard-quinoline conjugates with urea and hydrazine carboxamide (A) as linking moieties. The synthesized compounds (58-61) were evaluated for antitumor activity, and compounds with hydrazine carboxamide linker showed maximum cytotoxic activity as compared to compounds with urea linker [58] [Fig 16].

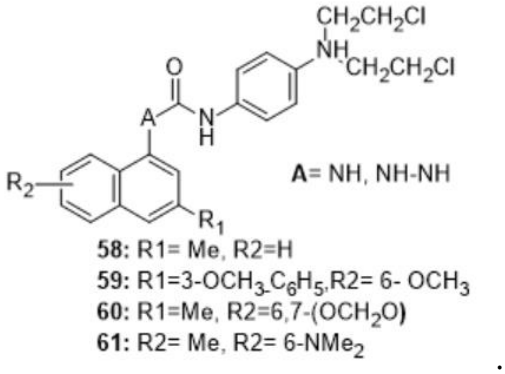


Figure 16. *N*-mustard-quinoline conjugates**.**

2.3.4. 2,4,8-trisubstituted quinoline.

The quinolines possess more substitution used as possible anticancer agents, whereas 2,4,8-trisubstituted quinoline aid as most known moieties for developing new anticancer agents. Heteroaryl substitution at C-2 of quinoline increases the lipophilicity and DNA binding properties which are required to enhance the anticancer property. Both five and six-membered heterocyclics are equally potent for anticancer capability. Compound series of quinoline derivatives with the heterocyclic structure were prepared and evaluated by Kouznetsov *et al.* against MCF-7, H-460, and SF-268 cell lines and Vero cell lines, and THP-1 monocyte macrophages.

The potential of all synthesized compounds was compared with Adriamycin and camptothecin as standard drugs. Thiophene and pyridine-based compounds (62-64) were found with positive activity against all selected human cancer cell lines [59] [Fig 17].

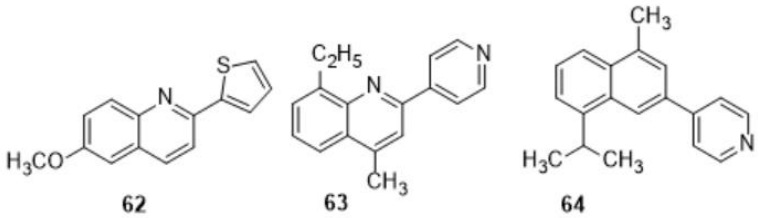


Figure 17. Thiophene and pyridine-based compounds**.**

2.3.5**.** 2,4,6-trisubstituted quinoline**.**

Amino substitution at position-4 in the quinazoline ring is the most frequently used arrangement for anticancer activity, such as gefitinib and pelitinib. Jiang *et al.* synthesized and evaluated the compounds with substitution at carbon-2,4, and 6.

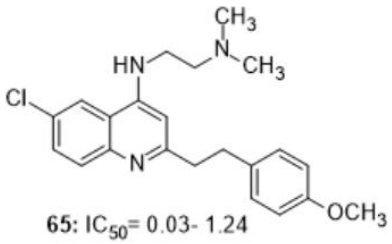


Figure 18. 2,4,6-Trisubstituted quinoline-based compound**.**

The compound 65 was reported to be active against cancerous cell lines of the lung, colon, liver, and stomach, with IC_{50} ranges between 0.03 µM to 1.24 µM [60] [Fig 18].

2.3.6. Heterocyclic-based quinoline derivatives.

The huge number of heterocyclic (piperidine, indole, pyrrole, pyridine, pyrimidine etc.) fused quinoline derivatives also have been stated with anticancer activity.

2.3.7. Piperidine-based compounds.

Da *et al.,* Solin *et al.,* and Thanh *et al*. reported that 1,2-Quinoline platinum complexes with pyridine cycle exhibit antitumor properties. The compound 66 shows cytotoxicity activity against various cancerous cell lines such as HepG2, RD, MCF7, and F1 [61].

2.3.8. Pyrroloquinoline derivatives.

The P-gp (P-glycoprotein) is inhibited by a series of substituted Pyrroloquinoline derivatives, as reported by Lee *et al.* The anticancer property was described by detecting it against various cancerous resistant cells such as MCF-7, T24, and NCI/ADR. The compound 67 P gp-4008 possesses is the most potent inhibitor of P-gp *in-vitro* [62].

2.3.9. Indole-quinoline derivatives.

By carrying out various reactions such as alkylation, chlorination, ring cyclization, and nucleophilic reaction, a series of indole-based quinoline derivatives have been detected by Chen *et al*. for their anticancer property. The derivative 68 possesses activity against HL-60, K-562, MOLT-4, RPMI-8226, and SR, with G_{50} values ranging from 0.09- 0.42 µM. The compounds with methyl-substituted at C-5 of quinoline show more potent activity against cancer cells than C-6 substituted derivatives [63].

2.3.10. Pyrimido-quinoline derivatives.

The free sulphonamide moiety containing quinoline and pyrimido-quinoline derivatives has been synthesized and investigated by Al-Said & co-workers for anticancer activity. The compound 69 with free amino, benzamide, and butanamide substitution showed maximum anticancer activity [64] [Fig 19].

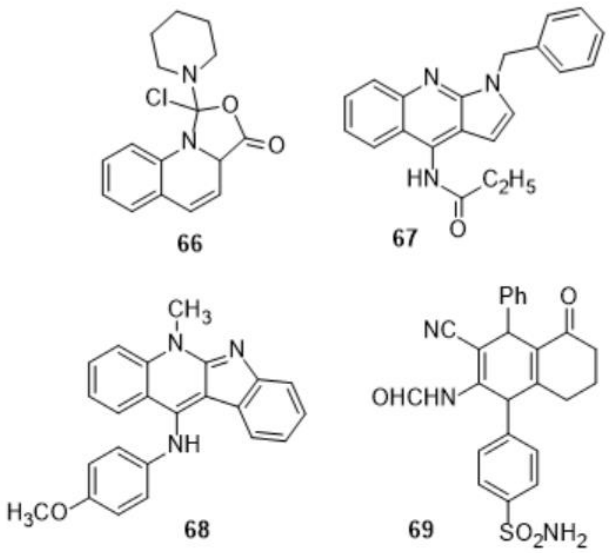


Figure 19. Heterocyclic based compounds.

The various pyrimido [4, 5-b] quinoline derivatives were synthesized, and *in vitro* antitumor activity of these compounds (70-76) against human breast cancer cells (MCF-7) with IC_{50} values ranges from 48.54-70.33 μM with doxorubicin as a standard drug [65-69] [Fig 20].

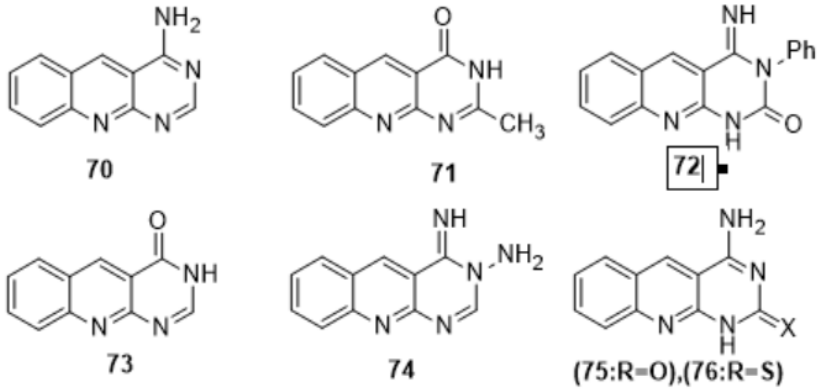


Figure 20. Pyrimido [4, 5-***b***] quinoline derivatives**.**

3. Conclusions

The potency of the quinoline nucleus is cleared from the various marketed used quinoline-based drugs. It possesses all the activities; many more potentials are still to be explored. As in this review, we explored only three major potentials of quinoline moiety, *i.e.*, antimalarial, anticancer, and anti-inflammatory agents. The activity of the compounds depends on the type, positions, and nature of substituents attached to the quinoline ring. So, further investigation of the quinoline ring may be fruitful and quite rewarding. From these observations, it has been concluded that quinoline has diverse biological potential, which has attracted researchers' attention.

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Conflicts of Interest

The authors declare no conflict of interest.

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