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THE THERAPEUTIC VERSATILITY OF QUINOLINES

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ABSTRACT

Quinoline or 1-aza-naphthalene or benzo[b]pyridine is an N-based heterocyclic compound which attracted tremendous attention from researchers worldwide since the 19th century. Quinoline is a weak tertiary base and exhibits similar reactions to pyridine and benzene. Quinoline is nontoxic to human. The present review provides an in depth view of work done so far on quinolines and its biological activities covering antimalarial, antibacterial, antiviral, anticancer, cardiovascular, anti-inflammatory, analgesic, antidiabetic, anticonvulsant, antifungal, antihelemintic, antiprotozoal, reproductive and miscellaneous activities.

Keywords: Quinoline derivatives, marketed quinolines, therapeutic versatility

INTRODUCTION

Quinoline **(Figure 1)** is nitrogen containing six membered aromatic heterocycle, where benzene ring fused to pyridine moiety and is known with alternative names such as 1-aza-napthalene or benzo[b]pyridine with molecular formula of C9H7N and molecular weight 129.16. The logP value of quinoline is 2.04 and has an acidic pKb of 4.85 and a basic pKa of 9.5 **[1]**. It is a weak tertiary base and can form salts with acids. It exhibits similar reactions to pyridine and benzene and can also participate in both electrophilic and nucleophilic substitution reactions. Generally, quinoline is an essential segment for many bioactive natural and synthetic compounds. It is nontoxic to human on oral absorption and inhalation **[2]**.

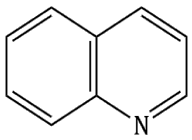


Figure 1: Quinoline

The quinoline ring system occurs in various natural products, especially in alkaloids **[3]** and is often used for the design of many synthetic compounds with diverse pharmacological properties. Quinoline has been found to possess antimalarial, antibacterial, antiviral, anticancer, cardiovascular, anti-inflammatory, analgesic, antidiabetic, anticonvulsant, antifungal, antihelemintic, antiprotozoal, reproductive and miscellaneous activities **[4]**. A few quinoline based marketed drugs are given in **Table 1**, and a few pharmacological agents bearing quinoline ring given in **Table 2**.

BIOLOGICAL ACTIVITIES:

Owing to the diverse pharmacological activities of this ring, a number of researchers across the globe are engaged in the development of pharmacologically active agents bearing it. Recent developments made by researchers in the filled are documented below:

1. Antimalarial activity:

Few 4-aminoquinoline triazines were synthesized by Kumar *et al*. which showed antimalarial activity against chloroquine (CQ) sensitive strain 3D7 of *P.falciparum* in an *in-vitro* model **[16]**. Compounds **I** and **II** exhibited more than 99% suppression on day 4 and on day 6 post treatment, where compound **II** showed impressive 99.11% suppression against CQ resistant strain N-67 of *P. yoelii* in an *in vivo* assay **[17]**. The mechanisms involved for this activity were rapid degradation of ribosomes and dissimilation of ribosomal RNA and finally inhibited biosynthesis of RNA and DNA. Sometimes, protein synthesis inhibition was also observed as a secondary effect of compound I and II **[18]**. Compound II accumulated in the food vacuoles of parasites **[19]**. It bound

to heme (or FP) and formed a complex known as FP-compound II complex. This complex is highly toxic for the parasite's cells and disrupts membrane function. Finally, cell lysis and auto digestion of the parasitic cell take place **[20]**.

2. Antibacterial activity:

The growing incidence of bacterial resistance with marketed antibiotics is a serious problem. So, there is an urgent need to develop new classes of drugs to treat bacterial infections **[21-25]**. A lot of quinoline derivatives have been reported against bacterial activity so far. Few 3-benzyl-6-bromo-2-methoxy quinoline derivatives were synthesized by Upadhayaya *et al*. in 2009 using molecular modeling techniques and were found to be active against *Mycobacterium tuberculosis* H37Rv strain **[26]**. These compounds shown antibacterial activity against two gram positive bacteria i.e. *Staphylococcus auerus* (NCDC 110), *Bacillus subtilis* (NCDC 71) and two gram negative bacteria i.e. *Escherichia coli* (NCDC 134), *Pseudomonas aeruginosa* (NCDC 105). Compound III and IV showed more potent inhibition than other compounds when compared with standard drug (Ciprofloxacin) [27]. These agents inhibited the DNA gyrase and topoisomerase IV and became covalently bound to the 5′ ends of the DNA **[28-29]**. Quinolones bound rapidly to enzyme-DNA complexes [30], probably before occuring DNA cleavage, drug bound with mutant gyrase (*gyrA*) or topoisomerase IV (*parC*) that failed to cleave DNA. Thus, gyrase-mediated inhibition of DNA synthesis appeared to arise from collision of replication forks with cleaved complexes, which explained correlations between inhibition of DNA synthesis and cleaved complex formation in drug-treated cells **[31]**.

3. Antiviral activity:

Novel anilidoquinoline derivatives were developed by Ghosh *et al.* in 2008, among which compound V showed good degree of *in vitro* antiviral activity against Japanese encephalitis virus **[32]**. Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Acidification at the surface of the cell membrane inhibiting fusion of the virus and immunomodulation of cytokine release **[33, 34]**. Hydroxychloroquine, an antimalarial drug, is now under clinical trials for coronavirus disease **[35-37]**.

4. Anticancer Activity:

Cancer is one of the leading causes of deaths worldwide **[38-41]**. Quinoline alkaloids obtained from natural sources showed remarkable anticancer activities and relatively simple structures have

attracted great interest in the scientific community, especially researchers involved in the chemistry of natural products **[42]**. The Bcl-2 protein had been studied as an anticancer drug target in recent years, due to its gatekeeper role in resisting programmed cancer cell death (apoptosis) to the identification of quinolin-4-yl based oxadiazole and triazole analogues **[43]**. Target compounds were readily synthesized via a common aryl-substitutedquinolin-4-carbonyl-N-arylhydrazine-1-carbothioamide (Compound VI and VII) Intermediate, through simple variation of the basic cyclisation conditions **[44]**.

5. Cardiovascular Activity

A series of phenyl acetic acid based derivatives of quinoline were synthesized by Hu *et al*. in 2007 as agonist liver X receptors, which is important regulators of cholesterol, fatty acid, and glucose homeostasis. These agents have good binding affinity for LXRb and LXRa receptors **[45]**. The five compounds were synthesized and evaluated against isolated perfused rat and guinea pig heart. Compound VIII exhibited potent cardiovascular activity, as well as potent inotropic effect in rat heart **[46]**. It inhibited fibrillation, where there was no coordinated contraction of muscle fibers in the heart **[47]**.

6. Anti-inflammatory Activity:

Inflammation is the response to body aggression by a pathogen agent, an allergen, a toxic compound, a tissue lesion, etc. It is generally a phenomenon with fever and tiredness, with local symptoms, pain, and edema. New anti-inflammatory substances are still vitally necessary due to intolerable side effects such as gastric ulceration, of the marketed anti-inflammatory drugs **[48-53]**. Inflammation has long been a well-known symptom of many diseases such as arthritis, diabetes, obesity, cancer, neurodegenerative diseases, autoimmune disorders, dementia, scleroderma, allergy, asthma, bronchitis, inflammatory bowel disease, and cardiovascular diseases, which have been increased dramatically over the last three decades **[54-59]**. A Novel series of 2-(furan-2-yl)-4-phenoxyquinoline derivatives were synthesized by Chen *et al.* in 2006 and found to be inhibited lysozyme and β-glucoronidase **[60-61]**. The novel series of 2-(furan-2-yl)-4-phenoxyquinoline derivatives were synthesized and evaluated for disease modifying anti-rheumatic drugs (DMARD) as a results significantly suppressed the swelling of adjunct arthritic rat paw at doses less than 25 mg/kg (acute/chronic) **[62]**. The Compound IX and X were most effective for the treatment of osteoarthritis **[63]**.

7. Analgesic Activity:

A series of quinoline derivatives were designed by Manera *et al*. in 2007 and were found to be active as analgesic via acting as selective agonist at cannaboid CB_2 receptors [64]. Compound XXII showed potency against inflammation **[65]**, via selective COX inhibition together and nitric oxide releasing function, as a result reduction in pain **[66]**.

8. Antidiabetic Activity:

A series of quinoline carboxyguanides were designed by Edmont *et al.* in 2000 as hypoglycemic agents **[67]**. The synthesis and *in vivo* activities of this series of substituted quinoline carboxyguanidines were found to be a novel class of antidiabetic agents. Compound XI and XII were shown good antidiabetic activities against alloxan induced diabetic rat **[68]**. Compound XI and XII were used to treatment of type-II diabetes mellitus. The mechanisms involved for this activity were found to lower the fasting levels of insulin in plasma then to reduce gluconeogenesis in liver, as a result reduced the level of glucose in the blood **[69]**.

9. Anticonvulsant Activity:

The neuronal and physiological convulsions are the disease state in which epileptic seizures and neuronal dysfunctions are observed. Anticonvulsant drugs do find the space in managing epileptic seizures by various mechanisms **[70].** Monoamine oxidase (MAO) plays an important role in regulating convulsion and MAO inhibitors might act as anticonvulsants **[71-72]**. A new series of substituted quinoline-2(1*H*)-one and 1, 2, 4-triazolo [4, 3-*a*]-quinoline derivatives were designed and synthesized to meet the structural requirements essential for anticonvulsant properties **[73]**. Their anticonvulsant activities were evaluated by the MES test and the *sc*-PTZ test, and their neurotoxicity was evaluated by the rotarod neurotoxicity test with a median toxic dose (TD_{50}) value of 54.5 mg/kg, MES and *sc*-PTZ tests showed that two compounds (Compound XIII and XIV) were the most potent of this series with an effective dose (ED_{50}) value of 11.8 and 6.7 mg/kg respectively **[74]**. The mechanisms involved for this activity are like antiepileptic drugs (AEDs) that act on diverse molecular targets to selectively modify the excitability of neurons so that seizures related firing can be blocked without disturbing non-epileptic activity which sub serves normal signal between neurons. At the cellular levels, three basic mechanisms are recognized, modulation of voltage-dependent ion channels (Na^+, Ca^{2+}, K^+), and enhancement of GABA mediated inhibitory neurotransmission and attenuation of excitatory transmission. Ion channels activity is important for

signaling. The inflow and out flow of ions is controlled by the differential permeability and gating of the ion channels. Na^+ and Ca^{2+}channels are important for mediating excitation whereas the opening of K^+ and Cl^- channel may promote inhibition **[75]**.

10. Antifungal Activity

Few derivatives of quinoline were designed using terbinafine as lead by Kharkar *et al.* in 2009 as antifungal agents **[76]**. The toxicity of unmodified quinolines was low while their activity against some fungal strains was relatively high. A number of quinoline alkaloids were found in plants from Rutaceae falmily e.g. *Haplophyllum sieversii*, originating in Kazakhstan, possessed an interesting activity against plant pathogens from the Colletotrichum genus (*C. fragariae*, *C. gloeosporioides* and *C. aculatum*). The extracts from *Haplophyllum sieversii* contain three active alkaloids such as compound XV (haplamine), compound XVI (flindersine) and compound XVII (anhydroevoxine) [77]. The mechanisms involved for this activity were inhibitory interaction between azoles and 14α-demethylase. It has a complex mode of action, inhibiting several membrane-bound enzymes as well as membrane lipid biosynthesis **[78]**.

11. Antihelemintic Activity:

A novel series of substituted 2, 4-arylquinolines were developed by Rossiter *et al.* in 2005 and found to have a good degree of activity against the nematode *Haemoncus contortus* **[79]**. Compound XVIII and XIX showed good activity against levamisole, ivermectin and thiabendazole resistance strains of *H. contortus* [80]. The mechanisms involved for this activity are the inhibitory effect on tubulin polymerization which results in the loss of cytoplasmic microtubules in the intestines of nematodes worms, ultimately causing energy depletion and death of the organism **[81]**.

12. Antiprotozoal Activity:

A new series of chloroquinoline based chalcones were synthesized and evaluated by Faisal *et al*. in 2011 for *in vitro* antiamoebic and antimalarial activities. The results showed that out of fifteen , compound XX was found to be most active against *Entamoeba histolytica* when compared to the standard drug metronidazole (IC_{50} = 1.46 μM). In contrast, *in vitro* antimalarial activity against the chloroquine-sensitive (3D7) strain of *P. falciparum* indicated relatively low activity when compared to controls such as chloroquine and quinine (IC_{50} = 0.0065 μM and 0.14 μM, respectively) **[82]**. The mechanisms involved for this activity are affects these

organisms by causing nicks in, or breakage of, strands of DNA or by preventing DNA replication as a results dead of protozoa **[83]**.

13. Reproductive system:

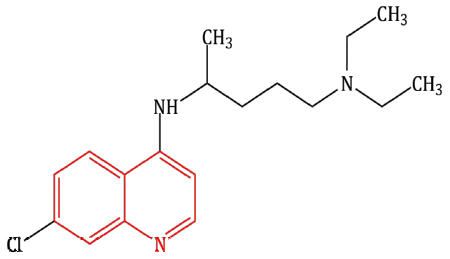
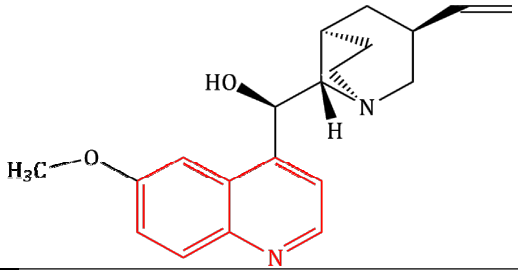
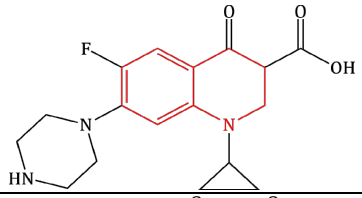
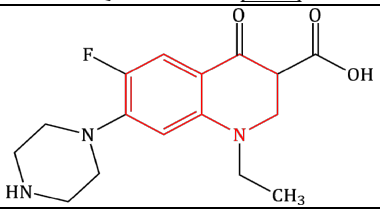
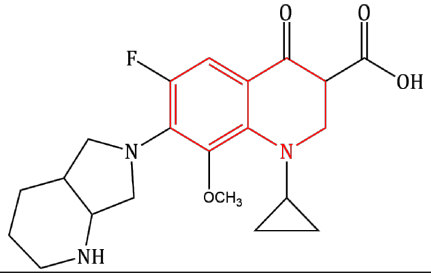
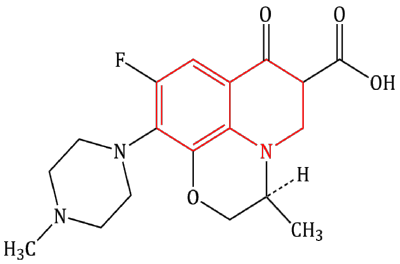
Sex hormones, synthesized from cholesterol **[84]**, help to develop and maintain our reproductive system. A series of tetrahydroquinolines derivatives were synthesized by Wallace *et al*. in 2003 as selective estrogen receptor modulator (SERMs). Compound XXI were shown to be high affinity ligands and antagonists in the MCF-7 proliferation assay **[85]**. Traditional approaches to discovery of selective estrogen receptor modulators have relied on ER binding and cell-based estrogen response element-driven assays to identify compounds that are osteoprotective but nonproliferative in breast and uterine tissues. To discover new classes of potential SERMs, workers have employed a cell-free microsphere-based binding assay to rapidly characterize ERα interactions with conformation-sensing cofactor or phage display peptides. Peptide profiles of constrained triarenes were compared to known proliferative and nonproliferative ER ligands to discover potent quinoline-based ligands with minimal Ishikawa cell stimulation **[86]**. Selective estrogen receptor modulators are now being used as a treatment for breast cancer, osteoporosis and postmenopausal symptoms, as these drugs have features that can act as an estrogen agonist and an antagonist, depending on the target tissue **[87]**.

14. Miscellaneous activity:

Quinolines have been found to posses other activities as well.

Some quinolines have been synthesized by Evans *et al.* in 2009 as PDE4 inhibitors. Compound XXIII was found to be most potent as PDE4 inhibitors for the treatment of chronic obstructive pulmonary disorder **[88]**. Some novel tetrahydroquinoline-6-yloxy propanes were designed by Shakya *et al*. in 2009, among which compound XXIV was found to be a good β-3 agonists **[89]**. Few aminoalkoxyquinolines were synthesized by Wolkenberg *et al*. in 2011, where compound XXV was found to be potent somatostantin receptor subtype-2 agonist which had utility in proliferative diabetic retinopathy and oxidative age related macular degeneration **[90]**.

Table 1: Quinoline based marketed drugs

S. No.	Name of the drug	Structure	Pharmacological class
1.	**Chloroquine (Marketed Drug)**		**Antimalarial [5, 6]**
2.	**Quinine (Withdrawn from US market on December 12, 2006)**		**Antimalarial [7]**
3.	**Ciprofloxacin (Marketed Drug)**		**Antibacterial [8]**
4.	**Norfloxacin (Marketed Drug)**		**Antibacterial [9]**
5.	**Moxifloxacin (Marketed Drug)**		**Antibacterial [10]**
6.	**Ofloxacin (Marketed Drug)**		**Antibacterial [11]**

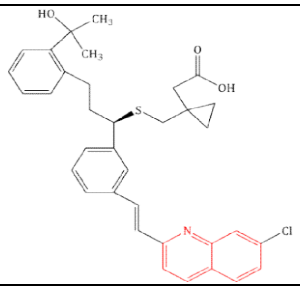
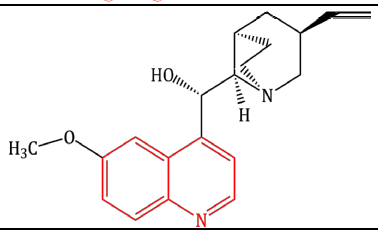
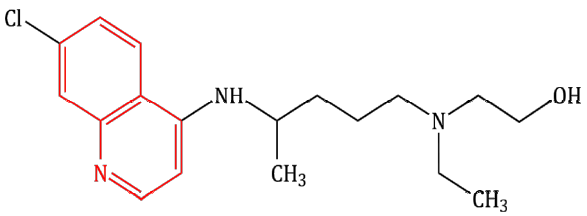
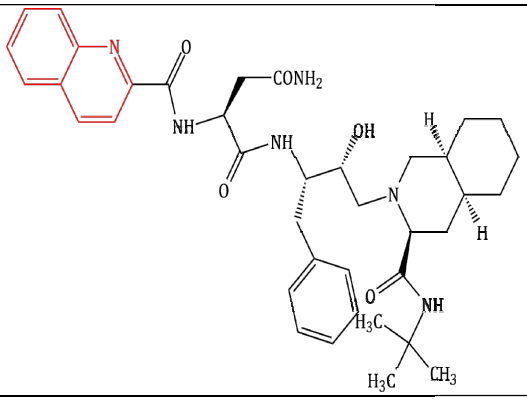
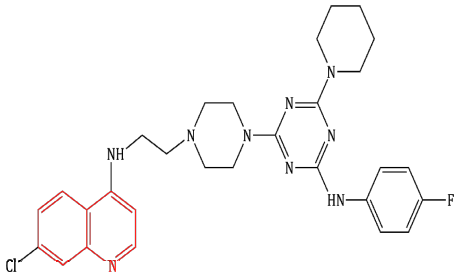
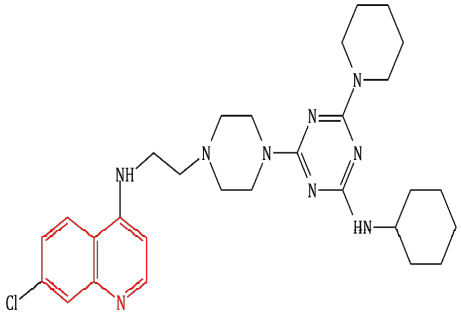
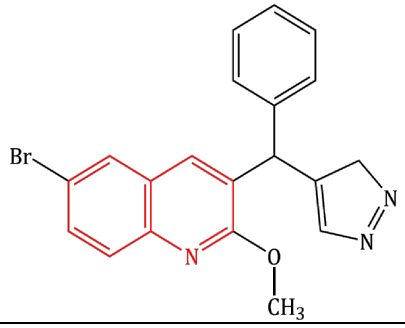
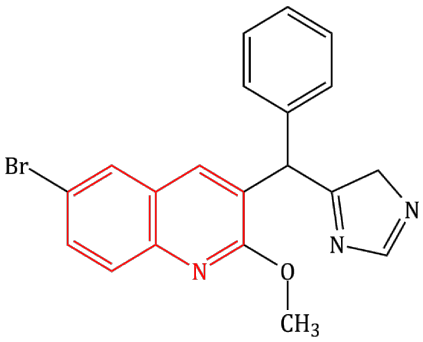
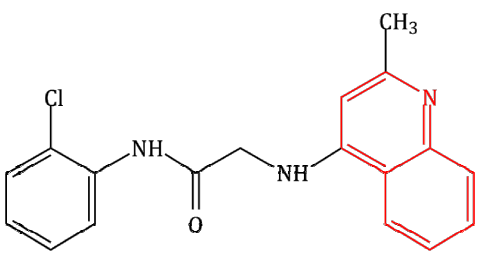
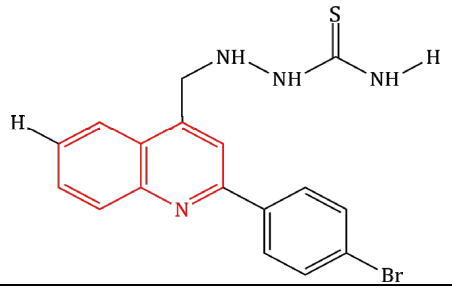
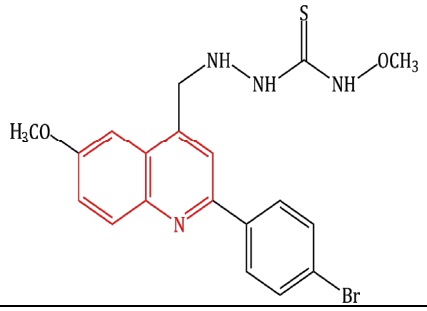
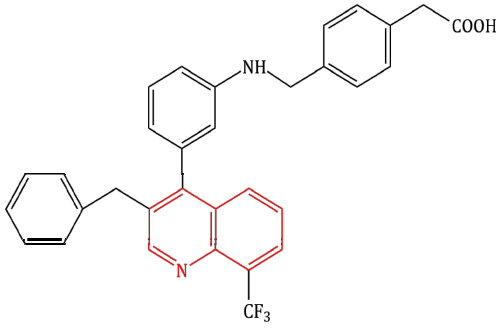
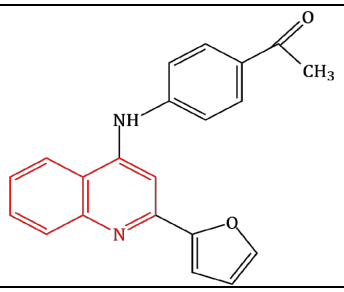
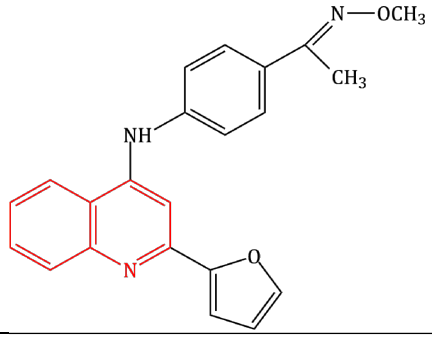
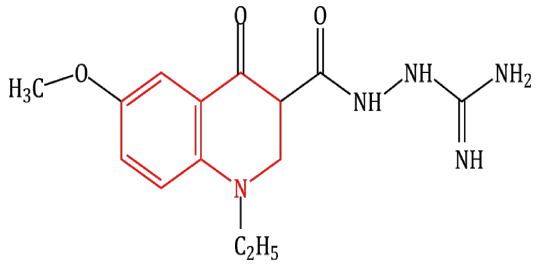
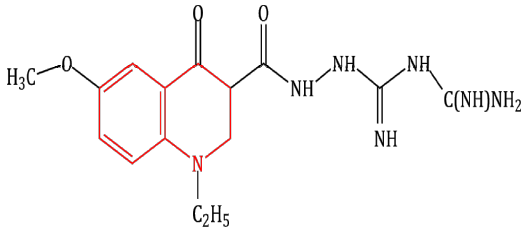
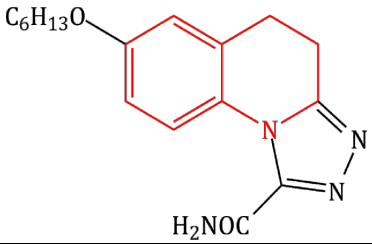
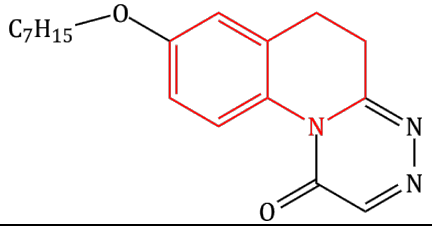
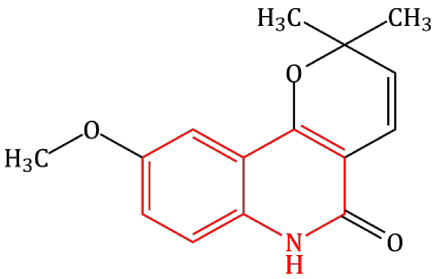
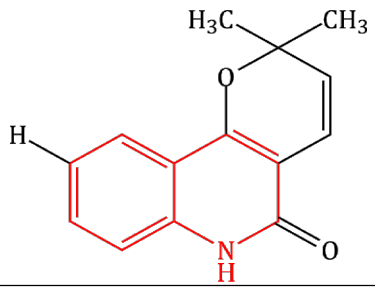
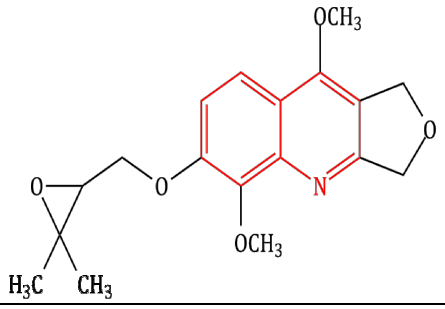
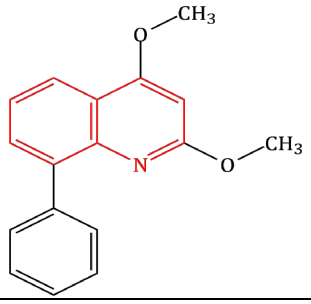
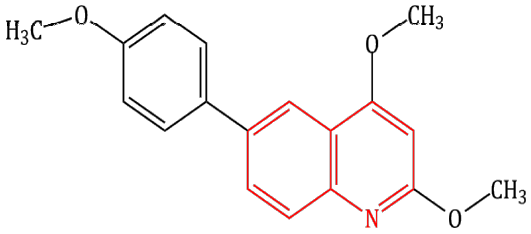
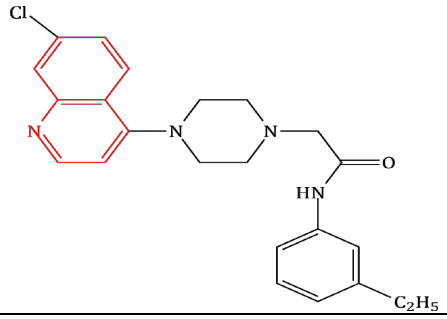
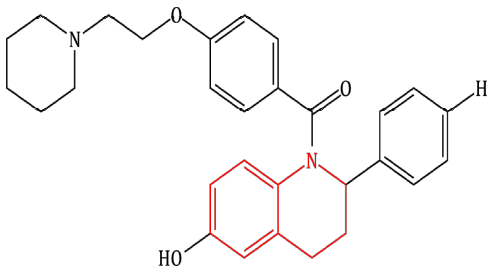
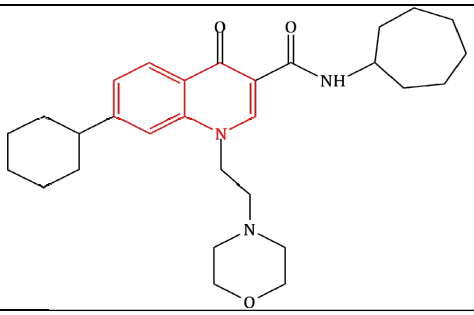
7.	**Montelukast (Marketed Drug)**		**Antidepressant [12]**
8.	**Quinidine (Withdrawn from US market on 2006)**		**Antiarrhythmic [13]**
9.	**Hydroxychloroquine (Marketed Drug)**		**Antimalarial (Under study for COVID-19) [1**
10.	**Saquinavir (Marketed Drug)**		**Antiviral [15]**

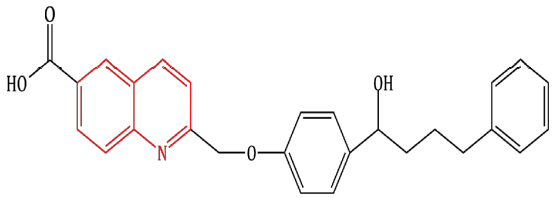
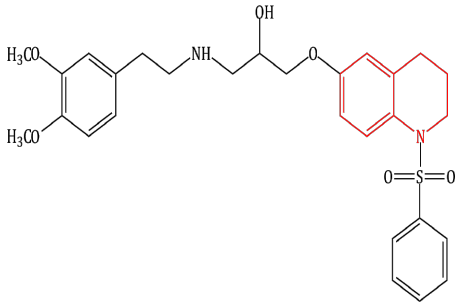
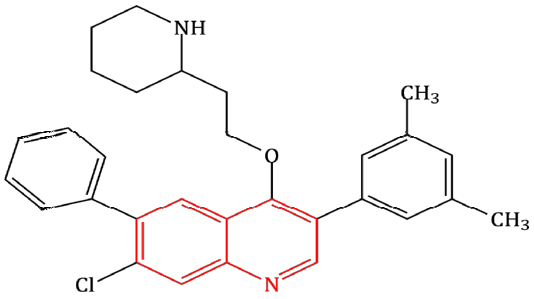
Table 2: Pharmacological agents bearing quinoline ring

S. No.	Name of the compound	Structure	Pharmacological class
1.	I		Antimalarial
2.	II		Antimalarial
3.	III		Antibacterial
4.	IV		Antibacterial
5.	V		Antiviral

6.	**VI**		**Anticancer**
7.	**VII**		**Anticancer**
8.	**VIII**		**Cardiovascular**
9.	**IX**		**Anti-inflammatory**
10.	**X**		**Anti-inflammatory**

11.	**XI**		**Antidiabetic**
12.	**XII**		**Antidiabetic**
13.	**XIII**		**Anticonvulsant**
14.	**XIV**		**Anticonvulsant**
15.	**XV**		**Antifungal**
16.	**XVI**		**Antifungal**

17.	**XVII**		**Antifungal**
18.	**XVIII**		**Antihelemintic**
19.	**XIX**		**Antihelemintic**
20.	**XX**		**Antiprotozoal**
21.	**XXI**		**Selective estrogen receptor modulator (SERMs)**
22.	**XXII**		**Analgesic**

23.	**XXIII**		**Anti-inflammatory**
24.	**XXIV**		**β-3 agoniststst**
25.	**XXV**		**Somatostatin receptor subtype-2 agonists**

CONCLUSION

In conclusion, numerous quinoline derivatives have big applications to medicinal chemistry. Quinoline is a six membered nitrogen containing heterocycle present in a number of commercially available therapeutic agents. Many researchers have synthesized quinoline and its fused heterocyclic derivatives. There has been a rising interest in the development of quinoline based compounds targeting different diseases and observations have been guiding for the development of new quinoline derivatives that possess varied biological activities i.e. antimalarial, antibacterial, antiviral, anticancer, cardiovascular, anti-inflammatory, analgesic, antidiabetic, anticonvulsant, antifungal, antihelemintic, antiprotozoal, reproductive and miscellaneous activities. Developments of newer quinolines have immense possibilities and scope for drug development scientist. This review highlights the status of quinoline in the development on novel quinoline based drug candidates work to aid in present knowledge and to help researchers to explore an interesting quinoline class.

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