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A Review On Substitution Quinoline Derivatives and its Biological Activity

Devyani Choudhary[1*], Rekha Birle[2], Nandu Kayande[3], Sanchita Patil[4]
[1,2,3,4]*Department of Pharmacy, Thakur Shiv Kumar Singh Memorial Instituted of Pharmacy, Burahanpur, India*

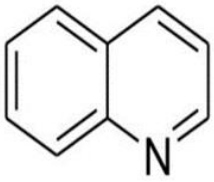
***Abstract*: Quinoline or 1-aza-naphtalene or benz[b]pyridine is nitrogen containing heterocyclic aromatic Compound. Quinoline ring having 2,4-disubstitution plays an important role in the search of new anti-cancer agents as these derivatives have shown excellent results through different mechanism of action such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis. Quinoline and its fused heterocyclic derivatives tested with diverse pharmacological activity functional groups constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. The present review provides an in depth view of work done so far on quinolines and its biological activities covering anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory and cardiovascular activities.**

***Keywords*: Anti-cancer, anti-convulsant, anti-inflametry, antimalarial, antimicrobial, quinolone.**

1. Introduction

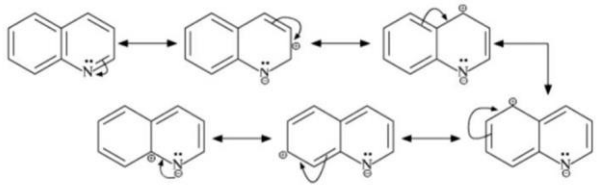
Quinoline or 1-aza-naphtalene or benz[b]pyridine is nitrogen containing heterocyclic aromatic Compound. It has a molecular formula of C_9H_7N and its molecular weight is 129.16. The log P value is 2.04 and has an acidic pKb of 4.85 and a basic pka of 9.5. Quinoline is a weak tertiary base. It can Form salt with acids and displays reactions similar to those of pyridine and benzene. It shows both Electrophilic and nucleophilic substitution reactions. It is non-toxic to humans on oral absorption and Inhalation. Quinoline nucleus occurs in several natural compounds (Cinchona Alkaloids) and Pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess an anti-malarial, antimicrobial, ant-inflammatory, anticonvulsant, anticancer and anti-mycobacterial activity [1].

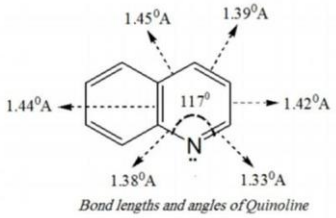
Quinolines and their derivatives are very important in medicinal chemistry because of their wide Occurrence in natural products and drugs. In addition to the medicinal applications, quinolones have been employed in the study of bioorganic and bio organometallic processes. Quinolones are also Known for their formation of conjugated molecules and polymers that combine enhanced electronic, Optoelectronic, or nonlinear optical properties with excellent mechanical properties [2].



2. Structure of Quinoline

- It has molecular formula C_6H_7N.
- All ring atoms in Quinoline are SP^2 Hybridize.
- The nitrogen lone pair electrons reside in an SP^2Orbital and not involved in the formation of the delocalized π molecular orbital.
- It shows aromatic properties because its π orbital contains ten electrons & satisfied the Huckel's rule (n = 2 is 4n+2).
- The resonance of Quinoline:





Bond lengths and angles of Quinoline

3. Properties of Quinoline

Table 1
Physical properties of quinoline

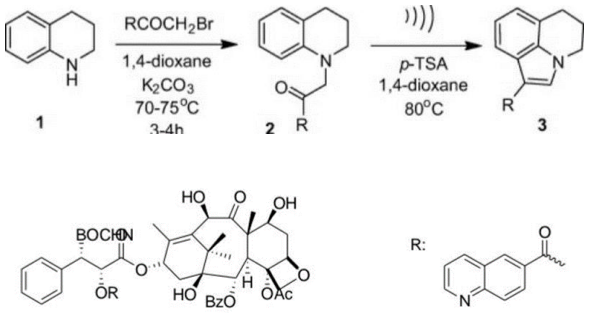
S. No.	Properties	Information
1	Molar mass	129.16 g/mol
2	Appearance	Colourless to brown liquid
3	Density	1.093 g/ml
4	Melting point	-15°C
5	Boiling point	283°C
6	Molecular weight	129.16
7	Odour	Unpleasant odour
8	Solubility in water	Slightly soluble
9	Solubility	Soluble in alcohol, ether

*Corresponding author: devyanichoudhary2018@gmail.com

4. Biological Activities

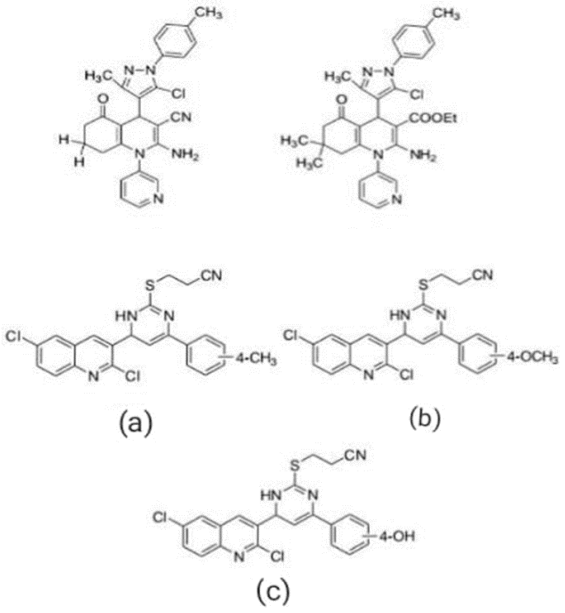
A. Anticancer activity

Manam srineevasa Rao has been reported as potential cytotoxic agents a series of 6-Substituted 2,3-dihydro-1Hpyrrolo[3,2,1-ij] quinoline derivatives were synthesized by using a Bischler type reaction tested for their in vitro anti-Proliferative properties against cancer (leukemia) and non-cancerous cell lines. Some of the Compounds showed promising and selective cytotoxic effects toward leukemia cell [3].



Chen have a report the designed and synthesized a series of novel quinoline-docetaxel analogues by introducing bioactive quinoline scaffold to C2'-OH of docetaxel. The anticancer activities of these novel analogues were investigated against different human cancer cell [4].

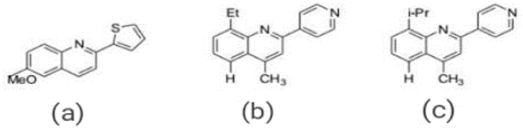
Sangani has been designed a new series of pyrazol-quinoline-pyridine hybrid based on molecular Hybridization technique and synthesized by a base-catalyzed cyclo-condensation reaction through one-pot multicomponent reaction and were tested for in vitro anti-cancer activities. Enzyme inhibitory activities of all compounds were carried out against FabH and EGFR [5].



Okten has-described a short and easy route for 6,8-disubstituted derivatives of quinoline & 1,2,3,4-Tetrahydroquinoline. Several 6,8-disubstituted quinolines were obtained by treatment of 6,8-Dibromoquinoline with n-BuLi followed by trapping with an electrophile. The anticancer activities give anticancer activities against the tumor cell lines [16].

Shi has been reported - anti-breast cancer agents from substituted quinolines. The quinolines were readily synthesized in a large scale from a sequence of reactions starting from 4-Acetamidoanisole. showed that synthesize new compound 6-methoxy-8-[(2-furanylmethyl)]-4-methyl-5-(3-trifluoromethylphenyloxy) [6].

Kouznetsov has been tested sixteen C-2-substituted quinolines in both human cancer cell lines and normal cell lines Preliminary results indicate that 2-α-Furyl- and 2-β-pyridinylquinoline derivatives are active against three human cancer cell [7].



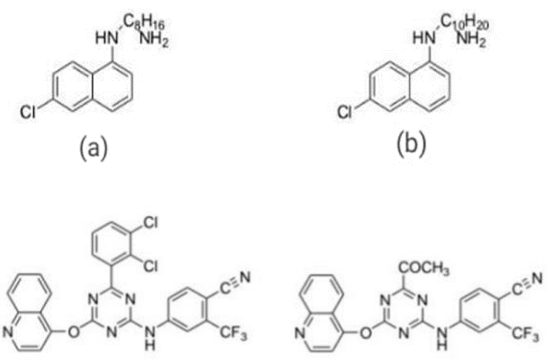
B. Antibacterial activity

N. C. Desai were synthesize a series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) thiazolidin-4-ones (V)1–12 give the abtibacterial and antifungal activity [8].

Eswaran has been reported- synthesized a new class of quinoline derivatives containing 1,2,4-triazole moiety from Derivatives of 4-hydroxy-8-(triflouromethyl) quinoline-3-carbohydrazide through multistep reaction. The newly synthesized compounds were evaluated for their in vitro antibacterial and antifungal [9].

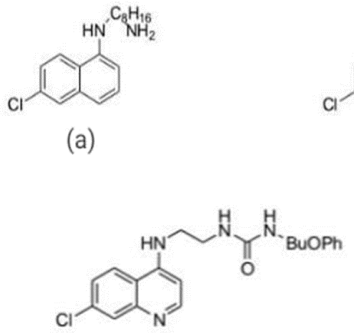
C. Anti-tuberculosis activity

Patel synthesized a series of novel s-triazineanalogs and characterized by IR, 1H NMR, 13C NMR, 19F NMR spectroscopy and elemental analysis. Preliminary screening of target compounds against Mycobacterium tuberculosis H37Rv indicated that a and b were the most active compounds among twenty one studied [10].



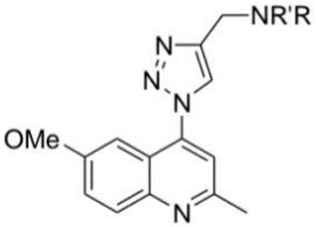
Souza has been reported-synthesized a series of quinoline derivatives and evaluated for their in vitro Antibacterial activity against Mycobacterium tuberculosis [11].

Nava-Zuazo has synthesized a new series of quinoline tripartite hybrids from chloroquine, Trichomonasvaginalis, Entamoebahistolytica, Leishmaniamexicana and Trypanosoma cruzi) and Mycobacterium tuberculosis. N-(4-Butoxyphenyl)-N′-{2-[(7-chloroquinolin-4yl) amino] ethylurea was the most active compound against all Parasites tested as compare to Metronidazole against G. intestinalis [12].



D. Anti-fungal activity

Thomas has been - synthesized a new series of [1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl] methanamine derivatives. All the new compounds were characterized by spectral and elemental analyses. The newly synthesized final compounds were evaluated for their in vitro antibacterial and antifungal activities against pathogenic strain antifungal activities, comparable to the first-line drugs [13].



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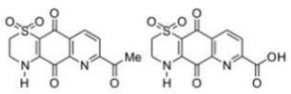
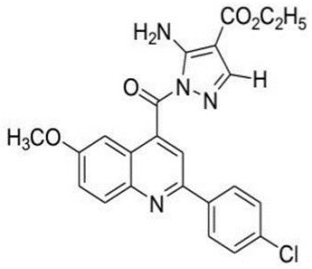
E. Anti-inflammatory activity

Chia has been synthesized sixteen new thiazine-quinoline-quinones, plus one bicyclic analogue. These Compounds inhibited neutrophil superoxide production in vitro with IC50s as low 60 nM. Compounds with high in vitro anti-inflammatory activity were also tested in a mouse model of acute Inflammation [14].

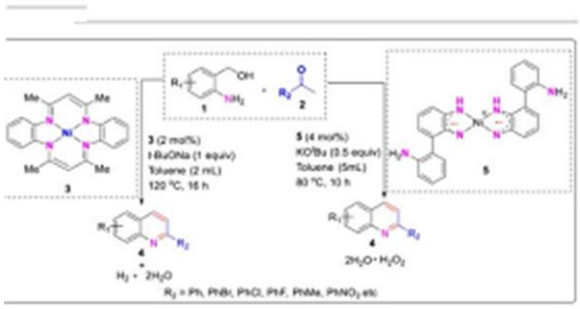


El-Feky has been -studied novel quinolines with anti-inflammatory activity and by using the Pfitzinger reaction, several new quinoline derivatives were synthesized and tested for their anti-inflammatory effect. A docking study on the COX-2 binding pocket was carried out for the target compounds to rationalize the possible selectivity of them against COX-2 enzyme. some Compound demonstrated the highest anti-inflammatory activity [15].

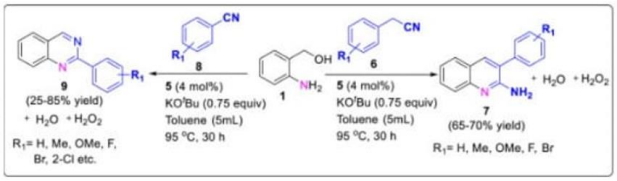


F. Anti-viral activity

Ramandeep Kaur and Kapil Kumar has been reported the Synthetic and medicinal perspective of quinolines as antiviral agents. Quinoline derivatives were found potent against various strains of viruses like zika virus, enterovirus, herpes virus, human immunodeficiency virus, ebola virus, hepatitis C virus, SARS virus and MERS virus etc. [16].

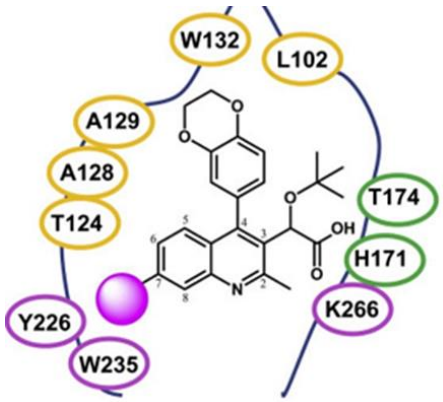


The nickel catalyzed synthesis of poly substituted quinoline from a-2-aminoaryl alcohol Biomimetic method for the construction of poly substituted quinolones.



Jian Sun et.al. have been saw the Optimized binding of substituted quinoline ALLINIs within the HIV-1 integrase oligomer. In this study, we tested the hypothesis that these dual properties of ALLINIs could be decoupled toward late stage

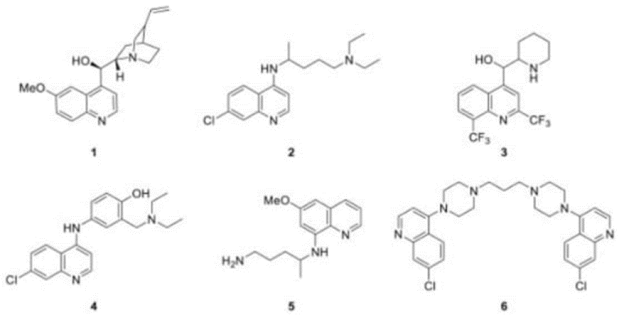
viral replication effects by generating additional contact points between the bound ALLINI and a third subunit of IN [17].



Binding pocket with compound NGJ9002 with positive number) with residues of the three HIV-1 in subunit) yellow, green and magenta). the megenta ball represent the position derivatives. ALLINI, allosteric in inhibitor; HIV-1 human immunodefiency virus type 1; IN. integrase.

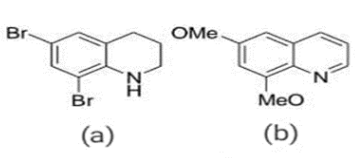
G. Anti-malarial activity

Tim Van de Walle has been develop a new series the Synthesis and biological evaluation of novel quinoline-piperidine scaffolds as anti-plasmodium agents. Anti-plasmodium agent is used in the treatment of malaria disease [18].

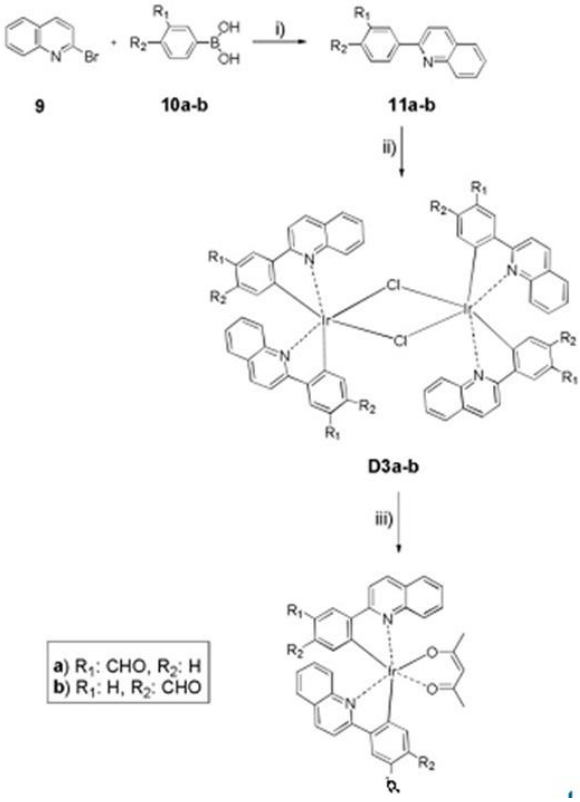


Example of clinically used antimalarials containing a quinoline scaffold: quinine 1, chloroquine 2, Mefloquine 3, amodiaquine 4, primaquine 5, and piperaquine 6

Pretorius has been synthesized a series of quinoline–pyrimidine hybrids and evaluated in vitro antimalarial activity. The hybrids were brought about in a two-step nucleophilic substitution process Involving quinolone moieties [19].



Nuray Altinolceka have been reported the Two novel heteroleptic iridium(III) acetylacetonate (acac) complexes K3a and K3b were synthesised from cyclometallating ligands of 2-(4′-formylphenyl) quinoline 11a and 2-(5′-formylphenyl) respectively and also reported the thrmal, optical and electrochemical properties and OLED application [20].



5. Conclusion

Since quinoline and its derivatives are known for their wide spectrum of biological activities, a number of synthetic methods have been developed from time to time for their synthesis by conventional, homogeneous, and heterogeneous acid-catalyzed methods; rare-earth-catalyzed, transition metal-catalyzed, radical-catalyzed, microwave-assisted, ultrasound-promoted, or solvent-free conditions, and many more. Quinoline derivatives have to be screened for their biological activities such anticancer, antimycobacterial, antimicrobial, anticonvulsant activity, antiinflammatory activity, antimalarial activity. This Review will be very useful to the researcher working in this field, and it would help them to develop new synthetic methods for the potent quinoline derivatives with good or enhanced biological activities for the future.

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