QUINOLINE: A PROMISING AND VERSATILE SCAFFOLD FOR FUTURE


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ABSTRACT

Quinoline is one of the condensed heterocyclic systems reported for its wide range of chemotherapeutic importance. Subsequently, quinolines have been highlighted as the important biologically active scaffold. Quinoline not only has a wide range of biological and pharmacological activities but there are several established protocols for the synthesis of this ring. This article aims to assess various routes for the synthesis of quinoline ring, pharmacological aspects and future aspects of quinoline scaffold.


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INTRODUCTION
Quinoline is a condensed heterocyclic system. Quinolines are also termed as Benzopyridines because they have fused benzene and pyridine rings. Quinoline has a molecular formula of C9H7N 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 and it is a weak tertiary base. The quinoline ring system occurs in various natural products, especially in alkaloids.

The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties and alteration in it shows numerous biological activities. Quinoline was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge. Various quinoline compounds can be prepared by Skraup synthesis using series of different oxidizing agents. Quinoline family compounds are widely used as a parent compound to make drugs (especially anti-malarial medicines), fungicides, alkaloids, dyes, rubber chemicals and flavouring agents. They have antiseptic and antipyretic properties. They are also used as catalyst, corrosion inhibitor, preservative, and as a solvent for resins and terpenes. They are used in transition-metal complex catalyst chemistry (for uniform polymerization) and luminescence chemistry. They are also used as antifoaming agent in refinery field [1].

METHODS OF SYNTHESIS
A number of recognized protocols are there for the synthesis of quinoline ring, which can be well tailored to prepare different substituted quinolines.

Friedlaender Synthesis
It involves in the condensation of aldehyde and ketone containing active methylene group in presence of alcoholic NaOH. The starting materials for this quinoline synthesis are o-aminobenzaldehyde or o-aminoacetophenone which is condensed with aldehydes or ketones containing an active methylene group in refluxing alcoholic sodium hydroxide solution to yield quinoline (2) [2].

Skraup synthesis
In the archetypal Skraup reaction, aniline is heated with sulfuric acid, glycerol and an oxidizing agent such as nitrobenzene to yield quinoline (4) [2, 5, 6].
The reaction has been shown to proceed by dehydration of glycerol to \( \alpha, \beta \)-unsaturated aldehyde, acrolein (produced in situ), aniline added to acrolein via the Michael addition across the vinyl group to give aniline propanal on the aromatic ring resulting in ring closure [7]. Dehydration leads to 1, 2-dihydroquinoline [8, 9] which on oxidation results in quinoline.

**Doebner reaction**

This is the chemical reaction of aniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids (5) [10, 11].

![Diagram of Doebner reaction](image)

**Conrad-Limpach synthesis**

The Conrad-Limpach synthesis involves the condensation of aniline with \( \beta \)-ketoesters to form 4-hydroxyquinolines (6) via a Schiff bases. The overall reaction type is a combination of both an addition as well as a rearrangement reaction. This reaction was discovered by Max Conrad (1848-1920) and Leonhard Limpach (1852-1933) in 1887 while they were studying the synthesis of quinoline derivatives.

![Diagram of Conrad-Limpach synthesis](image)

The mechanism begins with an attack of aniline on the keto group of the \( \beta \)-ketoester to form a tetrahedral intermediate. The newly formed oxide is then twice protonated to form the Schiff base, which then undergoes keto-enol tautomerization. The mechanism concludes with the removal of an alcohol, a series of proton transfers, and a keto/enol tautomerization to form a 4-hydroxyquinoline, which is final product of the Conrad-Limpach synthesis [12].

**Doebner-Miller reaction**

It is closely related to the Skraup synthesis as it also utilizes an aromatic amine and proceeds through the intermediate formation of a dihydroquinoline. The reagent which brings about dehydrogenation differs from the Skraup synthesis. In this synthesis an aromatic amine, aniline and two molecules of an aldehyde are heated in the presence of hydrochloric acid [13] to form Schiff’s base. Two molecules of this schiff’s base self-condense [14, 15] to form the quinoline nucleus (7).

![Diagram of Doebner-Miller reaction](image)

**Camps quinoline synthesis (also known as the Camps cyclization)**

It is a chemical reaction whereby an \( o \)-acylaminoacetophenone is transformed into two different hydroxyquinolines (products 8 and 9) using hydroxide ion [16-19]. The relative proportions of the hydroxyquinolines (8 and 9) produced are dependent upon the reaction conditions and structure of the starting material. Although the reaction product is commonly depicted as a quinoline (the enol form), it is believed that the keto form predominates in both the solid state and in solution, making the compound a quinolone [20].
Knorr Quinoline synthesis
It is an intramolecular organic reaction converting a β-ketoanilide to a 2-hydroxyquinoline (10) using sulphuric acid. This reaction was first described by Ludwig Knorr (1859-1921) in 1886 [21].

Niementowski Quinoline synthesis
It involves the reaction between anthranilic acid and ketone or aldehyde to form γ-hydroxyquinoline derivative (11) [22-25].

Pfitzinger synthesis
This is a modification of the Friedlander method. The required o-aminobenzaldehyde in the Friedlander synthesis is difficult to obtain and often unstable. The difficulty has been overcome in the Pfitzinger synthesis which insisted the use of Isatin. Isatin in the presence of alkali is converted to Isatoic acid which is condensed with a ketone to form quinoline (12).

Pictet Method
According to this procedure, N-ethylacetamide is heated with zinc chloride to yield 2-methylquinoline (13). Pictet found that N-ethylacetamide afforded a mixture of quinoline and toluidine.

Combes synthesis
In Combes synthesis, condensation of β-diketone with the unsubstituted arylamine yielded substituted quinoline (14) after an acid catalyzed ring closure of an intermediate Schiff base [26, 27].
CHEMICAL REACTIONS

Quinoline exhibits chemical properties associated with a tertiary amine. In addition because of the fusion of a benzene ring, properties of both benzenoid and pyridinoid compounds frequently manifest themselves.

Reaction with Acids

Quinoline is a weak base and is thus protonated on the ring nitrogen with mineral acids to form water soluble salts (15).

Electrophilic substitution

The electron-rich nitrogen atom of quinoline is the main centre for attack by electrophiles. The hetero atom has considerable deactivating effect on the ring towards electrophilic attack. In this respect the electrophilic reaction of quinoline may be compared with 1-nitronaphthalene just as that of pyridine with nitrobenzene. Therefore, electrophilic substitution on quinoline nucleus requires severe conditions through less than those in the case of pyridine. The attack in the protonated quinoline takes place in the carbocyclic ring at C-5 and C-8 position (16, 17) because the corresponding intermediates [28] can be represented by resonance structure in which the aromaticity of the heterocyclic ring is still preserved. As a π-electron deficient heterocycle, quinoline is less reactive than benzene particular in acid solutions.

Halogenation

Attack by a halogen depends on the nature of the reagent employed for halogenation. Chlorination (SO₂Cl₂) of quinoline for instance, yields 3-chloroquinoline while bromination (Br₂, CCl₄) yields 3-bromoquinoline (18). The product is obtained by the following addition–elimination mechanism. Orientation in the presence of strong acids (Br₂, Ag₂SO₄) proceeds to give a mixture of 5- and 8-bromoquinolines [29] the reacting species being Quinolinium cation.

Nitration

The nitration and sulfonation of quinoline can be carried out under conditions which are less strenuous than those in the case of pyridine. The pyridine ring is already π-electron deficient and becomes more so by protonation of the ring nitrogen atom. Acidic electrophilic reagents thus show a strong preference for attack on the benzene ring. Nitration (HNO₃, H₂SO₄) of quinoline gives a mixture of 5- and 8-nitroquinolines (19, 20) in equal amounts. In acetic anhydride as solvent or with dinitrogen tetroxide as nitrating agent, the nitration proceeds in a totally different manner and very inefficiency [30].

Sulfonation

The products of sulfonation vary with the experimental conditions. In conc. sulphuric acid quinoline almost entirely converted into quinolinium cation. Sulfonation at 220°C results in attack at the benzene ring to give largely quinoline 8-sulfonic acid. At a very high temperature (300°C), 6-quinolinesulfonic acid is obtained because the 5- and 8-isomers (21, 22) rearrange to the 6-isomer which is thermodynamically more stable.
Mercuration

With mercuric acetate, quinoline forms the quaternary N-mercuracetate at room temperature. At 160°C further substitution occurs and treatment with sodium chloride, gives a mixture of 3- and 8-mercuric chlorides (23, 24).

Friedel-Crafts Reaction

This reaction is rare in the quinoline series because of the deactivation of the ring by the nitrogen atom. However, the friedel-Crafts acylation of quinoline occurs at the 5th position (25) but not 7th position.

Reaction with Nucleophiles:

Attack by a nucleophile occurs on the pyridine ring of quinoline and 2nd position (26) is the preferred site for such an attack. If this position is occupied then attack may takes place at the 4th position. The Chichibabin reaction is an example of a normal attack at C2.

Quaternization at the nitrogen atom reinforces the ability to react with nucleophilic reagents [34] even weak nucleophiles attack readily on the 1-alkylquinolinium cations. This, behaviour is illustrated by the attack of a Grignard reagent and the resultant formulation of 1-methyl-2-phenyl-1, 2-dihydroquinoline (28) known as Reissert compounds [34, 35].

Halo derivative of quinoline on reaction with potassium amide in liquor ammonia give rise to product 2, 3-diamino quinoline (29) [36].
Besides halo derivative of quinoline, isoquinoline and naphthalene undergo rapid nucleophilic substitution with nucleophiles like alkoxides and thiolate ions [37]. The reaction is accomplished using microwave irradiation to form 2-methoxy quinoline (30).

Reaction with Reducing Agents
Quinoline is more readily reduced than naphthalene just as pyridine is easily reduced than benzene. Reduction of quinoline to 1,2,3,4-tetrahydroquinoline is best achieved with Raney nickel or PtO₂, H₂ [38], or ammonium carbonate [39]. Pd/C in acid media the benzo group can be selectively reduced [40]. Hydrogenation to decahydroquinoline is difficult.

Reaction with Oxidizing Agents
In the course of degradative oxidation of quinoline, pyridine ring remains intact while the benzene ring is destroyed on treatment with alkaline potassium permanganate this is because of pyridine ring is π-deficient and oxidation is independent of electron availability [41].

Oxidation of quinolines with peracids leads to quinoline N-oxides in excellent yields. In substituted quinolines the yield depends on the nature and location of the substituents [42]. The ring activation by N-oxide group of quinoline is analogous to that of

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pyridine N-oxide. The electrophilic attack in quinoline N-oxide takes place at C₄ to give 4-nitroquinoline N-oxide while at low temperature 5-and 8-isomers are also obtained [43, 44].

**PHARMACOLOGICAL ACTIVITY**

**Antioxidant activity**

Savegnago L., have reported 7-chloro, 4-(phenylselanyl) quinoline, derivative as new inhibitors of oxidation of levolicin acid. Among the synthesized compounds, compounds (42a) and (42b) have shown the potent antioxidant activity and also showed the inhibition of levolic acid values of 50 and 0.1 µM, respectively [45].

![Antioxidant activity](image)

**Antimicrobial activity**

Desai NC, have reported 3-chloro-4-methyl-1-phenyl-4-(5-(pyridin-4-yl)-2-(quinolin-3-yl)-1, 3, 4-oxadiazo1,3(2H)-yl)azetidin-2-one derivatives as new potent antibacterial agents against E. coli. Among the synthesized compounds (43a) and (43b) have showed the MIC of 62.5 µg/ml and 50 µg/ml respectively [46].

![Antimicrobial activity](image)

Miniyar PB, have reported N-((1Z, 3E)-1-(2-chloroquinolin-3-yl)-3-(methylmino)-3-phenylprop-1-enyl) acetamide derivatives as new potent antibacterial agents against B. subtilis. Among the synthesized compounds, (44a) and (44b) have showed the MIC of 54 µg/ml and 44 µg/ml respectively [47].

![Antimicrobial activity](image)
Antitumor activity
Bondok S., have reported 2-chloro-3-((E)-((Z)-(1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazono)methyl) quinoline derivatives as new antitumor agents [48].

Antibacterial activity
Desai NC, have reported (Z)-5-benzylidene-2-(3-chloro-6-methylquinolin-4-yl)-3-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)thiazolidine-4-one derivatives as antibacterial agents. Among all the derivatives 46a and 46b showed very good Antibacterial activity on E. Coli. MIC for that found to be 50 µg/ml and 25 µg/ml respectively [49].

Treatment of leukemia
Kumar S., have reported 2, 3-dihydro-2-(quinoline-5-yl) quinazolin-4(1H)-one as potent inhibitor of apoptotic cell death. MIC of 2, 3-dihydro-2-(quinoline-5-yl) quinazolin-4(1H)-one was found to be 2-15 µM for 24 hrs [50].
CONCLUSION
Since Quinoline and its derivatives possess wide spectrum of pharmacological activity, we have made here efforts to compiled most of the synthetic procedure for quinolines and their pharmacological activities that have been reported in the literature. This review will be very useful to the researchers working in this field, and it would help them to develop a new eco-friendly, efficient and economical method for the synthesis of quinolines. This is necessary from today’s point of view as we need an environmentally clean protocol for the large scale production of such an important biological moiety, which may be used further in many reactions to develop a potent pharmacophore for the future.

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