**Synthesis of Quinoline and its Derivatives Using Various Name Reactions: An Overview**

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**ABSTRACT**

Quinolines are a significant class of heterocyclic compounds and an essential component of natural alkaloids. They exhibit a broad range of biological and therapeutic actions. In order to efficiently synthesize quinoline and its derivatives, researchers and scientists have been paying close attention to the development of quinoline synthetic methods in recent years. This review summarizes the development of quinoline synthesis by numerous name reactions with reaction mechanisms and the application of synthesis techniques for quinolines and their derivatives, which develops innovative ideas and serves as a source of creative inspiration for researchers working in this area.

**GRAPHICAL ABSTRACT**



**Keyword**- Quinoline; Conventional synthesis; Synthesis of quinolines; Name reactions

**I. INTRODUCTION**

Quinoline was first time isolated by Runge in 1834 from coal tar [1]. Coal tar also contains isoquinoline, alkyl quinolines and alkyl isoquinoline.  Quinine, cinchonidine, and cinchonine from *Cinchona* alkaloids are just a few examples of naturally occurring physiologically active substances that have the quinoline scsffold [2]. Quinoline (Fig. 1) consists of a benzene ring fused to the α and β positions of a pyridine ring hence derives its other name is benzo[b]pyridine, Benzo[b]azine, Benzo[b]azabenzene [3]. The physical and chemical properties of quinoline are shown in Table 1 [4-5].



**Figure 1: Structure of quinoline.**

**Table 1: Physical and Chemical Properties of Quinoline**

|  |  |
| --- | --- |
| Physical Properties | Chemical Properties |
| * Color: Colorless hygroscopic liquid. * Odour: Characteristics odour. * Taste: Bitter * Solubility: sparingly miscible in cold water but completely miscible in hot water. * Melting point (MP): 15°C * Boiling point (BP): 238°C * Density: 1.093 gmol-1 * Molecular weight: 129.16. | * Basic or alkaline in nature and SP2 hybridized ring. * Electrophilic aromatic substitution reaction at 5th and 8th positions of quinoline ring. * Nucleophilic substitution reaction at 2nd and 4th positions of quinoline ring. * Oxidation and Reduction reaction occurs. * Reaction with alkyl halides. |

Quinolines have been made using a variety of conventional methods, including Skraup synthesis (6), Doebner von Miller (7), Conrad-Limpach-Knorr (8), and Combes (9), Friedlander (10), Pfitzinger (11), and Niementowski synthesis techniques [12]. This chapter discusses several naming reactions techniques involving quinoline ring that will be useful to chemists in the field of organic and medicinal chemistry in the future [13].

**II. NAME REACTIONS METHOD**

Since the late 1800s, a variety of synthetic techniques for quinoline and its derivatives are discovered such as Skraup, Doebner-von Miller, Friedlander, Pftzinger, Conrad-Limpach, Combes synthesis, Riehm synthesis, Gould-Jacob's synthesis, Povarov reaction, Knorr synthesis, and Niementowski [14-24].

**1. SKRAUP SYNTHESIS** (Zdenko Hans Skraup, 1880)

In this reaction quinoline is synthesized by the condensation of glycerine with aniline (aromatic amine) in presence of concentrated sulphuric acid and nitrobenzene (oxidizing agent) [25]. The synthetic reaction involved is shown in Fig. 2.



**Figure 2: General reaction of quinoline synthesis by Skraup Reaction.**

**1.1 Reaction Mechanism:**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** In this step, acrolein is formed from the reaction of sulfuric acid and glycerine, which results in the loss of two molecules of water by dehydration of glycerine [26].



**Step-II:** In second step acrolein react with aniline to form an intermediate product, (E)-3-phenylamino prop-1-en-1-ol.



**Step-III:** Ring closure and intramolecular electrophilic addition reaction take place in this step through protonation. Then quinoline is formed from dehydration and oxidation.



**1.2 Representative of Skraup reaction**

Some examples of Skraup synthesis are mentioned below-

A) The benzoquinoline can be synthesized from α-Naphthylamine with the help of Skraup synthesis [27].



B) The 1,10-Phenanthroline can be synthesized from 8-Aminoquinoline with the help of Skraup synthesis [27].



C) The 1,5-Naphthylidine can be synthesized from 3-Aminopyridine with the help of Skraup synthesis [27].



**1.3 Application of Skraup Reaction**

**A) Intermediate in drug synthesis-**

Synthesis of 7-methyl-8-nitroquinoline by two-step synthesis from *m*-toluidine using Skraup reaction as a starting material in the field of drug discovery and medicinal chemistry [28-30].



**B) Green chemistry-**

In green chemistry approach Skraup synthesis can be carried out from Solketal (a by-product of the biodiesel industry) which is derived by reaction of acetone with glycerol. Solketal is a potential replacement of glycerol in case of smaller scale reactions special in green Chemistry point of view for larger scale preparation [31].



**C) Other reactions-**

Skraup reaction is applied using ionic liquid medium under microwave irradiation condition for synthesis of quinoline derivatives [32].



**2. COMBES SYNTHESIS** (Combes, 1888)

2,4-disubstituted quinoline is formed by condensation of aniline with acetoacetone followed by cyclization in the presence of sulfuric acid or polyphosphoric acid [33]. The synthetic reaction involved is shown in Fig. 3.



**Figure 3: General reaction of quinoline preparation by Combes synthesis.**

**2.1 Reaction Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** In this step formation of enamine occurs by dehydration [34].



**Step-II:** In this stepprotonation of ketone and cyclisation followed by loss of water resulting in the end product of a substituted [quinoline](https://en.wikipedia.org/wiki/Quinoline).



**2.2 Representative of Combes reaction**

Some examples of Combes synthesis are mentioned below-

A) The 2,4-dimethyl-7-chloroquinoline can be synthesized from *m-*Chloroaniline with the help of Combes synthesis [35].



B) The 3,4-cyclohexano-6-methoxy quinoline can be synthesized from Cyclohexanone-2-aldehyde with the help of Combes synthesis [36].



C) The benzo[g] quinoline derivatives can be synthesized from β-Naphthylamine with the help of Combes synthesis [37].



**2.3 Application of Combes Synthesis**

**A) Intermediate in drug synthesis-** Synthesis of 2-Aryl-4-quinolones from o-Halophenones a base-promoted camps cyclization using as a key starting material in field of medicinal chemistry [38].



the construction of useful

**B) Use of gold metal catalyst-** Preparation of quinoline and quinolone scaffolds using gold catalyzed annulations of anthranils with aryloxyethynes or aryl propargyl ethers [39].



**3. DOEBNER REACTION** (Doebner,1887)

In this reaction, aniline and aldehyde mixed with pyruvic acid to synthesized derivatives of quinoline-4-carboxylic acid [40-41]. The synthetic reaction involved is shown in Fig. 4.



**Figure 4: General reaction of quinoline synthesis by Doebner reaction.**

**3.1 Mechanism**

The reaction mechanism for quinoline-4-carboxylic acid derivative is as follows.



**3.2 Representatives of** **Doebner reaction**

Some examples of Doebner reaction are mentioned below-

A) The benzocinchoninic acid (quinoline derivative) can be synthesized from Naphthylamine in the presence of pyruvic acid with help of Doebner synthesis [42].



B) synthesis of quinoline derivatives using aromatic amines and pyruvic acid [ 43].



**3.3 Application of Doebner reaction**

**a) Green Chemistry-** Quinoline derivatives can be synthesized by reaction of ethyl/methyl lactate, anilines and aldehydes through simple iron (III) chloride catalysis without using organic solvent or external oxidant [43].



**b) Synthesis of drug Intermediate-** Aniline reacts with an aldehyde and pyruvic acid to produce quinoline-4-carboxylic acid derivatives, which may be used as a step in the synthesis of drug [44].



**4. DOEBNER-MILLER REACTION** (Doebner and von Miller, 1881)

It is also known as Skraup-Doebner von miller synthesis. Aniline interacts with, α,β-unsaturated carbonyl compound in the presence of concentrated hydrochloric acid to produce 2,4-disubstituted quinoline derivatives [45-46]. The synthetic reaction involved is shown in Fig. 5.



**Figure 5: General reaction of quinoline synthesis by Doebner-miller reaction.**

**4.1 Mechanism**

The reaction mechanism for Skraup-Doebner von miller synthesis is as follows.



**Figure 9: General mechanism of quinoline synthesis by Doebner-miller reaction.**

**4.2 Representative of Doebner-miller reaction**

Some examples of Doebner-miller reaction are mentioned below-

A) The 2-methyl quinoline derivatives can be synthesized using water as a solvent with the aniline and crotonaldehyde by Doebner-miller reaction [47].



B) The quinoline can be synthesized using aniline and acrolein in the presence of HCl and toluene using Doebner-miller reaction [48].



**4.3 Application of Doebner-miller reaction**

**a) Cross-over reaction-** The rection for formation of substituted quinolines from anilines and unsaturated ketones have been studied by the use of 13C-labeled ketones in cross-over experiments [49].



**b) In green synthesis-** Synthesis of quinoline derivative was done using H2SO4 catalyst in water [50].



**5. RIEHM SYNTHESIS** (P. Riehm, 1885)

In this reaction, arylamine hydrochlorides and ketones are heated for an extended period of time either with or without the addition of aluminum chloride or phosphorus pentachloride to produce quinoline derivatives [51-52]. The synthetic reaction involved is shown in Fig. 6.



**Figure 6:** **General reaction of quinoline preparation by Riehm synthesis.**

**5.1 Mechanism**

The general mechanism of Riehm synthesis is as follows-



**5.2 Representative of Riehm synthesis**

Some examples of Riehm synthesis are mentioned below-

A) The 2-methyl-4-ethylquinoline derivatives can be synthesized with the help of aniline and 2-butanone in the presence of iodine using Riehm synthesis [53].



**5.3 Application of Riehm synthesis**

2,4-disubstituted quinolines derivatives can be synthesized from aniline and nitro benzaldehyde and ethynol using Riehm synthesis [54].



**6. FRIEDLANDER SYNTHESIS (**Paul Friedländer, 1882**)**

This is an aldol condensation type reaction. In the presence of potassium hydroxide, *o*-amino aryl aldehyde reacts with a ketone to produce a quinoline derivative [55]. The synthetic reaction involved is shown in Fig. 7.



**Figure 7:** **General reaction of quinoline synthesis by Friedlander synthesis.**

**6.1 Mechanism**

The reaction mechanism participating in the synthesis of quinoline is as follows.

**Step-I:** Quinoline synthesized from reaction between *o*-amino aryl aldehydes or ketones and a ketone possessing α-methylene group [56].



**Step-II:** This process involves amino-ketone condensation, in which the intermediate passes through cyclocondensation, similar to aldol condensation, which is catalyzed by a base or an acid, producing substituted quinoline derivatives.



**6.2 Representative of Friedlander synthesis**

Some examples of Friedlander synthesis are mentioned below-

A) The poly-substituted quinolines can be synthesized with the help of *ortho*-aminoaryl aldehydes or ketone with *p*-toluene sulphonic acid [57].



B) The functionalized quinolines can be synthesized with the help of *ortho*-amino aldehydes or ketone catalyzed by Neodymium (III) Nitrate Hexahydrate [58].



C) The synthesis of quinolines with the help of *ortho*-amino aldehydes or ketone and molecular iodine as a highly efficient catalyst [59].



**6.3 Application of Friedlander synthesis**

**a) Synthesis of metabolite drug-** SN38 (active metabolite of Irinotecan) is anticancer agents used in colon and lung cancers treatment was synthesized from Friedlander reaction [60].



**b) Synthesis of pentacyclic core**

Synthesis of pentacyclic core was obtained by authors using 2-aminoacetophenone and tert-butyl acetoacetate through quinoline [61].



**7. PFITZINGER REACTION (**Pfitzinger, 1886**)**

In this reaction the  [isatin](https://en.wikipedia.org/wiki/Isatin) react with [carbonyl](https://en.wikipedia.org/wiki/Carbonyl) compound (ketone or aldehyde) in the presence of strong basic media and produce 2,3-disubstituted [quinoline](https://en.wikipedia.org/wiki/Quinoline)-4-[carboxylic acids](https://en.wikipedia.org/wiki/Carboxylic_acid). This reaction is also known as Pfitzinger-Borsche reaction [62]. The synthetic reaction involved is shown in Fig. 8.



**Figure 8: General reaction of quinoline synthesis by Pfitzinger-Borsche reaction.**

**7.1 Mechanism**

The reaction mechanism involved in the synthesis of quinoline is as follows.

**Step-I:** The ring is opened in the presence of KOH [63].

**Step-II:** Condensation of -NH2 group with the carbonyl group (Schiff s base).

**Step-III:** In this step Claisen condensation occurs between benzylic carbonyl and active α-methylene group of the amine.

**Step-IV:** In this final step cyclization reaction occurs and substituted quinoline forms.



**7.2 Representative of Pfitzinger reaction**

Some examples of Pfitzinger reaction are mentioned below-

A) The 2,6-dimethyl-3-phenoxy-quinoline-4-carboxylic acid can be synthesized with the help of 5-Methylisatin with phenoxy acetone in the presence of potassium hydroxide using Pfitzinger reaction [64].



B) The quinoline derivative can be synthesized with the help of Isatin with large carbon ring ketones using Pfitzinger reaction [65].



C) The 5,6-dimethoxy indano [2,3-b]-6-chloro-4-quinolinic acid is synthesized with the help of 5-chloroisatin with 5,6-dimethoxy indanone in basic and acidic medium using Pfitzinger reaction [66].



**7.3 Application of Pfitzinger reaction**

**a) Microwave irradiation-** Zhu and coworkers’ synthesized quinoline-4-carboxylic acid, unsubstituted in the 2-position using microwave irradiation by Pfitzinger reaction [67].



**b) Green chemistry-** Through the use of green chemistry methods, authors have reported an enhanced Pfitzinger reaction for the synthesis of quinaldines from 1,3-dicarbonyl compounds, isatins, alcohol and Trimethylsilyl chloride (TMSCl) [68].



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**8. KNORR QUINOLINE SYNTHESIS** (Ludwig Knorr, 1886)

This reaction involves converting a β-ketoanilide to a 2-hydroxyquinoline using H2SO4, as shown in Fig. 9 [69-70].



**Figure 9: General reaction of quinoline synthesis by Knorr synthesis.**

**8.1 Mechanism**

The mechanism for synthesis of 2-hydroxyquinoline is as follows-



**8.2 Representative of Knorr Synthesis**

Some examples of Knorr synthesis are mentioned below-

A)Theamino tetrahydroquinoline can be synthesized with the help of 4-ethyl-1,2,3,4-tetrahydroquinoline and ethyl-4,4,4-trifluoroacetoacetate in presence of ZnCl2 using Knorr synthesis method [71].



B) The quinoline derivatives can be synthesized by 4-amino-6- Bromo veratrole and ethyl acetoacetate with sulfuric acid with the help of Knorr synthesis method [72].



**8.3 Application of Knorr Synthesis**

**a) Other molecule synthesis-** The Knorr synthesis offers a valuable and practical route to a number of [pyrrole carboxylates](https://www.sciencedirect.com/topics/chemistry/pyrrolecarboxylate) synthesis [73].



**9. CONRAD-LIMPACH QUINOLINE SYNTHESIS** (Max Conrad and Leonhard Limpach, 1887)

It is the condensation reaction in which [anilines](https://handwiki.org/wiki/Chemistry:Aniline) reacts with β-ketoesters to produce 4-hydroxy[quinolines](https://handwiki.org/wiki/Chemistry:Quinoline) by a [Schiff base](https://handwiki.org/wiki/Chemistry:Schiff_base) [74]. The synthetic reaction involved is shown in Fig. 10.



**Figure 10:** **General reaction of quinoline synthesis by Conrad-Limpach Quinoline Synthesis.**

**9.1 Mechanism**

The reaction mechanism for synthesis of quinoline is as follows [75].



**9.2 Representatives of Conrad-Limpach Synthesis**

Some examples of Conrad-Limpach synthesis are mentioned below-

A) The 4-hydroxy-2-methyl-6-nitroquinoline derivatives can be synthesized with the help of nitroaniline and vinyl ether with H2SO4 using Conrad-Limpach Quinoline Synthesis [76].



B) The methylquinoline derivatives can be synthesized with the help of *ortho*-nitroaniline and dimethyl acetylene dicarboxylate in the process of reflux using Conrad-Limpach Quinoline Synthesis [77].



**9.3 Application of Conrad-Limpach synthesis**

**a) Field of green chemistry-** TheConrad-Limpach reaction is useful for green synthesis [78].



**10. GOULD- JACOB’S SYNTHESIS** (Gould and Jacobs, 1939)

In this reaction preparation of 4‐hydroxyquinoline derivative from anilines and diethyl ethoxymethylenemalonate involving the condensation reaction [79]. The synthetic reaction involved is shown in Fig. 11.



**Figure 11:** **General reaction of quinoline synthesis by Gould- Jacob’s synthesis.**

**10.1 Mechanism**

The reaction mechanism for synthesis of quinoline is as follows [80].



**10.2 Representatives of Gould- Jacob’s synthesis**

A) The quinoline derivatives can be synthesized with the help of aniline and alkoxy methylenemalonic ester by cyclization and decarboxylation [81].



B) The different variety of quinoline derivatives can be synthesized with the help of amino aldehyde and formamide ester by Gould- Jacob’s synthesis [82].



**10.3 Application of Gould- Jacob’s synthesis**

a) In field of medicinal chemistry various antibiotics are synthesized by using gold Jacob’s reaction such as  [rosoxacin](https://en.wikipedia.org/wiki/Rosoxacin), [oxolinic acid](https://en.wikipedia.org/wiki/Oxolinic_acid) etc [83].



**11. POVAROV REACTION** (Povarov and Mikhailov, 1963)

[Aniline](https://en.wikipedia.org/wiki/Aniline) reacts with [benzaldehyde](https://en.wikipedia.org/wiki/Benzaldehyde) to forms Schiff base and subsequently involve [cycloaddition](https://en.wikipedia.org/wiki/Cycloaddition) between [aromatic](https://en.wikipedia.org/wiki/Aromatic) [imine](https://en.wikipedia.org/wiki/Imine) and [alkene](https://en.wikipedia.org/wiki/Alkene) [84]. The synthetic reaction involved is shown in Fig.12.



**Figure 12: General reaction of quinoline synthesis by Povarov reaction.**

**11.1 Mechanism**

The reaction mechanism involved in the synthesis of substituted quinoline is as follows [85].



**11.2 Representative of Povarov reaction**

A) The 2-methylquinoline derivatives can be synthesized from aniline and acetaldehyde using Povarov reaction [86].



B) The quinoline derivative can be synthesized by the three-com­ponent Povarov reaction [87].



**11.3 Application of Povarov reaction**

**a) Multicomponent reaction (MCR) -** The Povarov MCR is particularly productive for the synthesis of anti-infective hits molecules [88].



**b) Drug intermediate synthesis-** The Povarov reaction is useful in drug intermediate synthesis such as dienophile, indenonaphthyridine derivatives with antiproliferative activity [89].



**III. CONCLUSION**

In this chapter, the brief history, synthesis and related mechanisms of quinolines by various synthetic routes have been discussed. The multiple-name reaction has been chosen among the various suitable quinoline syntheses in this regard. A variety of quinolone derivatives are produced when aniline and various reagents i.e., glycerol combine in the presence of an acidic or other suitable medium. This book chapter provides creative inspiration and expands innovative ideas by summarizing the advancement of quinoline synthesis through various name reactions, reaction mechanisms, and applications of synthesis methods.

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**V. CONFLICT OF INTEREST**

The authors state that there are no known financial conflicts of interest.

**REFEENCES**

1. G.A. Ramann, and B.J. Cowen, “Recent advances in metal-free quinoline synthesis,”Molecules, vol. 21(8), pp. 986, 2016. doi:10.3390/molecules21080986.
2. O. Ajani, K.T. Iyaye, and O.T. Ademosun, “Recent advances in chemistry and therapeutic potential of functionalized quinoline motifs–a review” RSC advances, vol.12(29), pp.18594-18614, 2022. doi: 10.1039/d2ra02896d
3. A. Marella, O.P. anwar, R. Saha, M.R. Ali, S. Srivastava, M. Akhter and M. M. Alam,” Quinoline: A versatile heterocyclic”, Saudi Pharmaceutical Journal, vol. 21(1), pp.1-12, 2013. doi: 10.1016/j.jsps.2012.03.002
4. M. Matsumoto, H.O.T. Kano, T. Noguchi, Y. Umeda and S. Fukushima, “Carcinogenicity of quinoline by drinking-water administration in rats and mice” ,The Journal of Toxicological Sciences, vol. 43(2), pp. 113-127, 2018.
5. R. Tabassum, M. Ashfaq and H. Oku, “Current pharmaceutical aspects of synthetic quinoline derivatives”, Mini Reviews in Medicinal Chemistry, vol. 21(10), pp. 1152-1172, 2021. doi: https://doi.org/10.2174/1389557520999201214234735
6. A. Patel, S. Patel, M. Mehta, Y. Patel, R. Patel, D. Shah and P. Patel, “A review on synthetic investigation for quinoline-recent green approaches”, Green Chemistry Letters and Reviews, vol. 15(2), pp. 337-372, 2022. https://doi.org/10.1080/17518253.2022.2064194
7. G.A. Ramann and B.J. Cowen, “Quinoline synthesis by improved Skraup–Doebner–Von Miller reactions utilizing acrolein diethyl acetal”, Tetrahedron letters, vol. 56(46), pp. 6436-6439, 2015. https://doi.org/10.1016/j.tetlet.2015.09.145.
8. F. Misani and M.T. Bogert, “The search for superior drugs for tropical diseases. II. Synthetic studies in the quinoline and phenan-throline series. Skraup and Conrad-Limpach-Knorr reactions”, The Journal of Organic Chemistry, vol. 10(4), pp. 347-365, 1945. doi.org/10.1021/jo01180a014
9. S. Plaskon, Andrey, et al. "Synthesis of quinolines from 3-formylchromone", The Journal of Organic Chemistry, vol. 73.15 pp. 6010-6013, 2008.
10. Arcadi and Antonio, "A new green approach to the Friedländer synthesis of quinolines", Synlett 2003 vol. 02, pp. 0203-0206, 2003. doi: 10.1055/s-2003-36798
11. N.P. Buu-Hoi, R. Royer, N.D. Xuong and P. Jacquignon, “The Pfitzinger reaction in the synthesis of quinoline derivatives” The Journal of Organic Chemistry, vol. 18(9), pp. 1209-1224, 1953. https://doi.org/10.1016/j.tetlet.2015.11.070
12. C.C. Cheng and S.J. Yan, “The Friedländer Synthesis of Quinolines”, Organic Reactions, vol. 28, pp. 37-201, 2004. doi.org/10.1002/0471264180.or028.02
13. B.S. Matada, R. Pattanashettar, N.G. Yernale, “A comprehensive review on the biological interest of quinoline and its derivatives”, Bioorganic & Medicinal Chemistry, vol. 32, pp. 115973, 2021.
14. R.J. Man, N. Jeelani, C. Zhou and Y.S. Yang, “Recent progress in the development of quinoline derivatives for the exploitation of anti-cancer agents”, Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), vol. 21(7), pp. 825-838, 202.
15. J. Zhang, S. Wang, Y. Ba, Z. Xu, “1, 2, 4-Triazole-quinoline/quinolone hybrids as potential anti-bacterial agent”, European journal of medicinal chemistry, vol. 174, pp. 1-8, 2019.
16. X, Wen, S.B. Wang, D.C. Liu, G. Gong, and Z.S. Quan, “Synthesis and evaluation of the anti-inflammatory activity of quinoline derivatives”, Medicinal Chemistry Research, vol. 24, pp. 2591-2603, 2015.
17. L. Kumari, A. Mazumder, D. Pandey, M.S. Yar, R. Kumar, R. Mazumder, S. Gupta, “Synthesis and biological potentials of quinoline analogues: A review of literature”, Mini-Reviews in Organic Chemistry, vol.16(7), 653-688, 2019.
18. B. Sureshkumar, Y.S. Mary, C.Y. Panicker, S. Suma, S. Armaković, S.J. Armaković, B. Narayana, “Quinoline derivatives as possible lead compounds for anti-malarial drugs: Spectroscopic, DFT and MD study”, Arabian Journal of Chemistry, vol. 13(1), pp. 632-648, 2020.
19. N. Chokkar, S. Kalra, M. Chauhan, R. Kumar, “A review on quinoline derived scaffolds as anti-HIV agents”, Mini Reviews in Medicinal Chemistry, vol.19(6), pp.510-526, 2019.
20. J.J. Casals, S.E. Asís, “Natural and synthetic quinoline derivatives as anti-tuberculosis agents”, Austin Tuberc. Res. Treat, vol. 2(1), pp. 1007-1010, 2017.
21. K. Supong, C. Thawai, S. Supothina, P. Auncharoen, P. Pittayakhajonwut, “Antimicrobial and anti-oxidant activities of quinoline alkaloids from Pseudomonas aeruginosa BCC76810”, Phytochemistry Letters, vol. 17, pp. 100-106, 2016.
22. A. Patel, S. Patel, M. Mehta, Y. Patel, R. Patel, D. Shah and P. Patel, “A review on synthetic investigation for quinoline-recent green approaches”, Green Chemistry Letters and Reviews, vol. 15(2), pp. 337-372, 2022. doi.org/10.1080/17518253.2022.2064194
23. A. Danel, E. Gondek, M. Kucharek, P. Szlachcic and A. Gut, “1 H-Pyrazolo [3, 4-b] quinolines: Synthesis and Properties over 100 Years of Research” Molecules, vol. 27(9), pp. 2775, 2022. doi: 10.3390/molecules27092775
24. B. Bieszczad, L. A. Perego and P. Melchiorre, “Photochemical C− H hydroxy alkylation of quinolines and isoquinolines”, Angewandte Chemie, vol. 131(47), pp. 17034-17039, 2019. doi.org/10.1002/ange.201910641
25. S. Yamashkin and E. Oreshkina, “Traditional and modern approaches to the synthesis of quinoline systems by the Skraup and Doebner-Miller methods”, Chemistry of Heterocyclic Compounds, vol. 42(6), 2006.
26. S.E. Denmark and S. Venkatraman, “On the mechanism of the Skraup− Doebner− Von Miller quinoline synthesis”, The Journal of Organic Chemistry, vol. 71(4), pp. 1668-1676, 2006. doi.org/10.1021/jo052410h
27. R.H. Manske and M. Kulka, “The Skraup Synthesis of Quinolines”, Organic Reactions, vol. 7, pp. 59-98, 2004.
28. A. Weyesa and E. Mulugeta, “Recent advances in the synthesis of biologically and pharmaceutically active quinoline and its analogues: a review”, RSC advances, vol.10(35), pp. 20784-20793, 2020.
29. E.W. Cohn, “A modification of the Skraup synthesis of Quinoline” Journal of the American Chemical Society, vol. 52(9), pp. 3685-3688, 1930. doi.org/10.1021/ja01372a038
30. R. Zibaseresht, M.R. Amirlou, P. Karimi, “An Efficient Two-step Selective Synthesis of 7-Methyl-8-nitroquinoline From m-Toluidine as a Key Starting Material in Medicinal Chemistry”, Journal of Archives in Military Medicine, vol. 2(1), 2014.
31. J. Jin, S. Guidi, S. Abada, Z. Amara, M. Selva, M.W. George and M. Poliakoff, Continuous niobium phosphate catalysed Skraup reaction for quinoline synthesis from solketal. Green Chemistry, vol. 19(10), pp. 2439-2447, 2017. doi.org/10.1039/C6GC03140D
32. G.A. Ramann and B.J. Cowen, “Recent advances in metal-free quinoline synthesis”, Molecules, vol. 21(8), pp. 986, 2016. https://doi.org/10.3390/molecules21080986
33. A. Combes, Compt. Rend, vol. 106, pp. 142, 1888.
34. J.J. Li, and J. J. Li, “Combes quinoline synthesis. Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications”, pp. 131-132.
35. J. J. Hirner, and M. J. Zacuto, “7-Chloroquinoline: a versatile intermediate for the synthesis of 7-substituted quinolines” Tetrahedron Letters, vol. 50(35), pp. 4989-4993, 2009.
36. R. Sharma, P. Kour, and A. Kumar, “A review on transition-metal mediated synthesis of quinolines” Journal of Chemical Sciences, vol. 130, pp. 1-25, 2018.
37. J.B. Bharate, R.A. Vishwakarma, and S.B. Bharate, “Metal-free domino one-pot protocols for quinoline synthesis” RSC advances, vol. 5(52), pp. 42020-42053, 2015.
38. C. Shen, A. Wang, J. Xu, Z. An, K.Y. Loh, P. Zhang and X. Liu, “Recent advances in the catalytic synthesis of 4-quinolones” Chem, vol. 5(5), pp.1059-1107.
39. M.D. Patil and R.S. Liu, “Direct access to benzofuro [2, 3-b] quinoline and 6 H-chromeno [3, 4-b] quinoline cores through gold-catalyzed annulation of anthranils with arenoxyethynes and aryl propargyl ethers” Organic & Biomolecular Chemistry, vol. 17(18), pp. 4452-4455, 2019.
40. N. Omidkhah and R. Ghodsi, “Synthesis of novel 2-methyl-4-carboxyquinolines, the new by-products of the Doebner reaction” Synthetic Communications, vol. 51(13), pp. 1947-1955, 2021.
41. Y.Yang, L. Yu, T. Chu, H. Niu, J. Wang, Y. Cai, “Constructing chemical stable 4-carboxyl-quinoline linked covalent organic frameworks via Doebner reaction for nanofiltration” Nature communications, vol. 13(1), pp. 2615, 2022.
42. S.K. Ghosh and R. Nagarajan, “Total synthesis of actinophenanthroline A via double Doebner–Miller reaction” Tetrahedron Letters, vol. 57(36), pp. 4009-4011, 2016.
43. S.M. Prajapati, K.D. Patel, R.H. Vekariya, S.N. Panchal and H.D Patel, “Recent advances in the synthesis of quinolines: a review” Rsc Advances, vol. 4(47), pp. 24463-24476, 2014.
44. M.A. Shaban, “The chemistry of C-nucleosides and their analogs II: C-nucleosides of condensed heterocyclic bases”, Advances in heterocyclic chemistry, vol. 70, pp. 166-338, 1998.
45. O. Doebner, W.v. Miller, "Ueber eine dem Chinolin homologe Base", Ber. Vol. 14 (2), pp. 2812, 1881. doi:10.1002/cber.188101402258.
46. S. Yamashkin and E. Oreshkina, “Traditional and modern approaches to the synthesis of quinoline systems by the Skraup and Doebner-Miller methods” Chemistry of Heterocyclic Compounds, vol. 42(6), 2006.
47. L. Wu, R. Jiang, J.M Yang, S.Y. Wang and S.J. Ji. “Catalyst-free diastereoselective synthesis of 2-methyl-4-amino-1, 2, 3, 4-tetrahydro-quinoline derivatives in water” Tetrahedron Letters, vol. 54(22), pp. 2849-2852, 2013.
48. G.A. Ramann and B.J. Cowen, “Quinoline synthesis by improved Skraup–Doebner–Von Miller reactions utilizing acrolein diethyl acetal”, Tetrahedron letters, vol. 56(46), pp. 6436-6439, 2015.
49. S.E. Denmark and S. Venkatraman, “On the mechanism of the Skraup− Doebner− Von Miller quinoline synthesis” The Journal of Organic Chemistry, vol. 71(4), pp. 1668-1676, 2006.
50. H. Yalgin, D. Luart and C. Len, “First examples of Doebner-Miller reaction in flow: Efficient production of 2-methylquinoline derivatives in water” Journal of Flow Chemistry, vol. 6(2), pp. 80-85, 2016.
51. C. Engler, and P. Riehm, Ber, vol.18, pp. 2245, 1885.
52. R.H. Manske, “The Chemistry of Quinolines”, Chemical Reviews, vol. 30(1), pp. 113-144, 1942.
53. Y. Rong, N. Ji, Z. Yu, X. Diao, H. Li, Y. Lei and A. Fukuoka, “Lignin amination valorization: heterogeneous catalytic synthesis of aniline and benzylamine from lignin-derived chemicals” Green Chemistry, vol. 23(18), pp. 6761-6788, 2021.
54. A.S.G. Prasad, A.G., Reddy, V.N.B. Tokala, K. Deepthi, T.B. Rao and M. B. Rao, “Synthesis of novel 2, 4-disubstituted quinoline derivatives” Chemical Data Collections, vol. 28, pp. 100469, 2020.
55. S.N. Pandeya and A. Tyagi, “Synthetic approaches for quinoline and isoquinoline” ChemInform, vol. 43(3), 2012.
56. C.C. Cheng and S.J. Yan, “The F riedländer Synthesis of Quinolines” Organic Reactions, vol. 28, pp. 37-201, 2004.
57. M. Fallah-Mehrjardi, “Friedlander Synthesis of poly-substituted quinolines: a mini review” Mini-Reviews in Organic Chemistry, vol. 14(3), pp. 187-196, 2017.
58. R. Varala, R. Enugala and S.R. Adapa, “Efficient and rapid Friedlander synthesis of functionalized quinolines catalyzed by neodymium (III) nitrate hexahydrate” Synthesis, pp. 3825-3830, 2006.
59. U. Tekale, S.S. Kauthale, S.A. Dake, S.R. Sarda, “Molecular iodine: an efficient and versatile reagent for organic synthesis” Current Organic Chemistry, vol. 16(12), pp. 1485, 2006.
60. M. Ramesh, P. Ahlawat and N.R. Srinivas, “Irinotecan and its active metabolite, SN‐38: review of bioanalytical methods and recent update from clinical pharmacology perspectives” Biomedical chromatography, vol. 24(1), pp.104-123, 2010.
61. N. Ghobadi, N. Nazari and P. Gholamzadeh, “The Friedländer reaction: A powerful strategy for the synthesis of heterocycles”, In Advances in Heterocyclic Chemistry ,Vol. 132, pp. 85-134, 2020.
62. N.P. Buu-Hoi, R. Royer, N.D. Xuong and P. Jacquignon, “The Pfitzinger reaction in the synthesis of quinoline derivatives”, The Journal of Organic Chemistry, vol. 18(9), pp. 1209-1224, 1953.
63. M.G.A. Shvekhgeimer, “The Pfitzinger Reaction”, Chemistry of Heterocyclic Compounds, vol. 40, pp. 257-294, 2004.
64. I. Elghamry and Y. Al-Faiyz, “A simple one-pot synthesis of quinoline-4-carboxylic acids by the Pfitzinger reaction of isatin with enaminones in water” Tetrahedron Letters, vol. 57(1), pp. 110-112, 2016.
65. G.A. Ramann and B.J. Cowen, “Recent advances in metal-free quinoline synthesis” Molecules, vol. 21(8), pp. 986, 2016.
66. V.M. Patel, N.D. Bhatt, P.V. Bhatt and H.D. Joshi, “Novel derivatives of 5, 6-dimethoxy-1-indanone coupled with substituted pyridine as potential antimicrobial agents”, Arabian Journal of Chemistry, vol. 11(1), pp. 137-142, 2018.
67. S.M. Prajapati, K.D. Patel, R.H. Vekariya, S.N. Panchal and H.D. Patel, “Recent advances in the synthesis of quinolines: a review” Rsc Advances, vol. 4(47), pp. 24463-24476, 2014.
68. L. Lu, P. Zhou, B. Hu, X. Li, R. Huang and F. Yu, “An improved Pfitzinger reaction: Eco-efficient synthesis of quinaldine-4-carboxylates by TMSCl-mediated” Tetrahedron Letters, vol. 58(37), pp. 3658-3661, 2017.
69. L. Knorr, “Synthetische Versuche mit dem Acetessigester Justus Liebig's Annalen der Chemie”, vol. 236, 1–2, pp. 69–115, 1886. doi:10.1002/jlac.18862360105
70. K.D Sharma and Y.R. Sharma, Kalyani Publishers, UnitIII pp. 27.
71. U.N. Dash, K.K. Ojha, Himalaya, University Chemistry, Vol-IV, Publishing house, Unit IV, pp.380.
72. P. López-Alvarado, , C. Avendaño and J.C. Menéndez, “A general synthesis of quinoline-2, 5, 8 (1H)-triones via acylation of 2, 5-dimethoxyaniline with S-tert-butyl thioacetates by application of the Knorr cyclization”, Synthesis, vol. 1998(02), pp. 186-194, 1998.
73. R.J. Sundberg, “Pyrroles and their benzo derivatives:(iii) Synthesis and applications” Comprehensive heterocyclic chemistry, vol. 4, pp. 313-376, 1984.
74. J.C. Brouet, S. Gu, N.P. Peet and J.D. Williams, “Survey of solvents for the Conrad–Limpach synthesis of 4-hydroxyquinolones”, Synthetic Communications, vol. 39(9), pp. 1563-1569, 2009.
75. M. Conrad, and L. Limpach, Ber., vol. 20, pp. 944, 1887.
76. A.A. Aly, E.M. El-Sheref, A.F.E., Mourad, M.E. Bakheet and S. Bräse, “4-Hydroxy-2-quinolones: syntheses, reactions and fused heterocycles” Molecular Diversity, vol. 24, pp. 477-524, 2020.
77. Y.B. Rajesh, "Quinoline heterocycles: synthesis and bioactivity. In Heterocycles-Synthesis and Biological Activities” IntechOpen, 2018.
78. A. Weyesa and E. Mulugeta, “Recent advances in the synthesis of biologically and pharmaceutically active quinoline and its analogues: a review” RSC advances, vol. 10(35), pp. 20784-20793, 2020.
79. R.G. Gould and W A. Jacobs, J. Am. Chem. Soc., 61, 2890, 1939.
80. L. A. Mitscher, Chem. Rev., vol. 105, pp. 559, 2005.
81. H. Bai, F. Liu, X. Wang, P. Wang and C. Huang, “Three-Component one-pot approach to highly efficient and sustainable synthesis of the functionalized quinolones via linear/branched domino protocols, key synthetic methods for the Floxacin of Quinolone Drugs”, ACS omega, vol. 3(9), pp. 11233-11251, (2018.
82. S.M. Prajapati, K.D. Patel, R.H., Vekariya, S.N., Panchal and H.D. Patel, “Recent advances in the synthesis of quinolines: a review”, Rsc Advances, vol. 4(47), pp. 24463-24476, 2014.
83. S. Yang, C. Chen, J. Chen and C. Li, “Total synthesis of the potent and broad-spectrum antibiotics amycolamicin and kibdelomycin”, Journal of the American Chemical Society, vol. 143(50), pp. 21258-21263, 2021.
84. L.S. Povarov, B.M. Mikhailov,SSR. Akad Nauk*,* SSR khim, pp. 953, 1963.
85. L.L. Su, Y.W. Zheng, W.G. Wang, , B. Chen, X.Z. Wei, L.Z. Wu and C. H. Tung, “Photocatalytic Synthesis of Quinolines via Povarov Reaction under Oxidant-Free Conditions” Organic Letters, vol. 24(5), pp. 1180-1185, 2022.
86. D. Orozco, V.V. Kouznetsov, A. Bermúdez, L.Y.V. Méndez, A.R.M. Salgado and C.M.M. Gómez, “Recent synthetic efforts in the preparation of 2-(3, 4)-alkenyl (aryl) quinoline molecules towards anti-kinetoplastid agents”, Rsc Advances, 10(9), 4876-4898, (2020.
87. O. Ghashghaei, C. Masdeu, C. Alonso, F. Palacios and R. Lavilla, “Recent advances of the Povarov reaction in medicinal chemistry”, Drug Discovery Today: Technologies, vol. 29, pp. 71-79, 2018.
88. J.R. Duvall, L. Bedard, A.M. Naylor-Olsen, A.L. Manson, J.A. Bittker , W . Sun, et al, “Identification of highly specific diversity-oriented synthesis-derived inhibitors of Clostridium difficile” ACS Infect Dis, vol. 3, pp. 349–59, 2017.
89. C. Alonso, M. Fuertes, M. Gonza´lez Rubiales, C. Tesauro, B.R. Knudsen, et al. “Synthesis and biological evaluation of indeno[1,5]naphthyridines as topoisomerase I (TopI) inhibitors with antiproliferative activity”, Eur J Med Chem. Vol. 115, pp. 179–90, 2016.