Synthesis & Characterization of Biologically Important Quinoline & It's Derivatives

Mr. Ramling D. Mali[1], Shreya Shirdhone[2], Snehal Waingade[3], Akanksha Sajagane[4], Megha Koli[5]

[1]Guide, Dr. J.J. Magdum Pharmacy College, Jaysingpur, India
[2,3,4,5]B. Pharmacy Final Year Students, Dr. J.J. Magdum Pharmacy College, Jaysingpur, India

Abstract:
Quinoline is a heterocyclic aromatic compound and the essential platform in medicinal chemistry, from which several pharmaceutical drugs are synthesized, including Antimalarial drugs, Quinine and Chloroquine, Quinoline and its derivatives show diverse biological activities such as Antimalarial, Antifungal, Antibacterial and Anticancer properties, making them of high importance is drug design and development. Several synthetic methods including Skraup reactions, highlights its versatility in organic synthesis.

Index Terms: Quinoline, Quinoline derivatives, Heterocyclic compounds, Organic synthesis, Characterization techniques, Spectroscopic analysis, UV-Visible Spectroscopy, Pharmacological activity.

1. INTRODUCTION

Quinoline is an Aromatic heterocyclic organic compound with the chemical formula C9H7N; whose structure is formed by the fusion of Benzene ring with Pyridine at two neighboring carbon atoms that gives a double ring structure. Benzo pyridine, Benzazine and Ben-zazine are another name of Quinoline. It's hygroscopic, yellowish oily liquid soluble in alcohol, ether and a variety of other solvents.
It is an Indole alkaloid and classified mainly as Indolo- Quinoline alkaloid. They are a subtype of Heterocyclics that contain both an Indole ring and Quinoline ring. Both the rings have nitrogen atoms in them. Structural complexity usually gives Quinoline and such Derivatives quite significant biological activity and hence researchers have further investigated their medicinal worth, particularly Anticancer and Antimicrobial effects along with Antituberculosis activity. It also exhibit Antimalarial, Antiviral and Anti-Inflammatory properties.

Physical Properties of Quinoline:

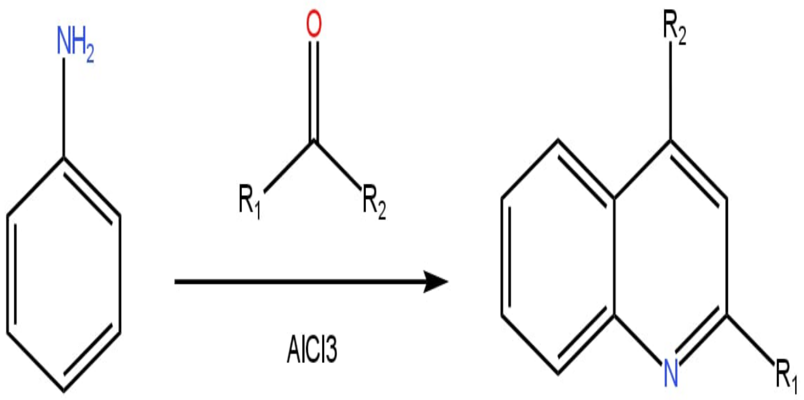
1) **Appearance:**
- **State:** Liquid at room temperature.
- **Colour:** Colourless to pale yellow (can darken with age due to oxidation).
- **Odour:** Pungent, Unpleasant, Tar-like odour.

2) **Molecular Characteristics:**
- **Molecular Formula:** C_9H_7N
- **Molecular Weight:** 129.16 g/mol.

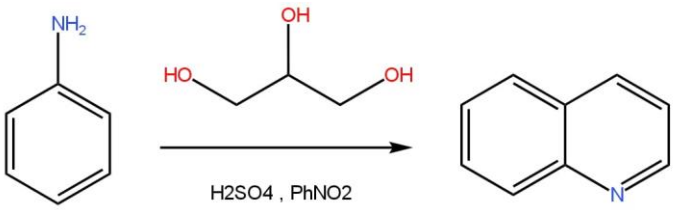
- **Melting & Boiling points:**
- **Melting Point: -**15ºCS
- **Boiling Point**: 237-239ºC
3) **Density:**
- **Density:** 1.093 g/cm^3 at 20ºC
4) **Solubility:**
- **Water:** Slightly soluble
- **Organic Solvents:** Soluble in alcohol, ether, and most organic solvents.
5) **Viscosity:**
- Low viscosity liquid.

Chemical Properties of Quinoline:
1) **Aromaticity:**
- Quinoline is aromatic, with 10 π-electrons, satisfying Huckel's rule.
- The aromaticity is Distributed, making the benzene ring more reactive toward electrophiles than the pyridine part.
2) **Basicity:**
- The nitrogen atom in the pyridine ring has a lone pair that does not participate in aromaticity
- Weak Base: Forms salts with strong acids like HCL- Quinoline Hydrochloride.
- pKa of conjugate acids: ~4.85 (weaker base than pyridine due to electron- withdrawing benzene ring).
3) **Electrophilic Substitution Reactions (EAS):**
- Quinoline undergoes electrophilic substitution primarily at the benzene ring (C_5, C_8).
- Reactions:
- Nitration – 5-nitroquinoline
- Sulfonation
- Halogenation
4) **Oxidation:**
- Quinoline is relatively stable to oxidation, but under strong oxidizing conditions (e.g., $KMnO_4$), it can degrade or for Quinolinic acid.

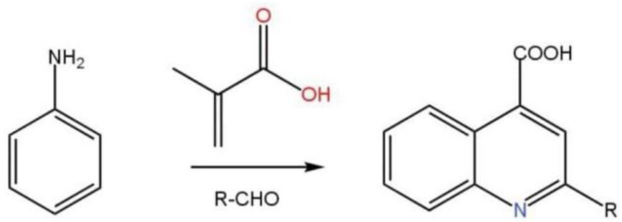
Traditional Methods of Making Quinoline Compounds:
Riehm Synthesis: Aniline reacts with acetone, in aluminium chloride as a catalyst, to form Quinoline compound.



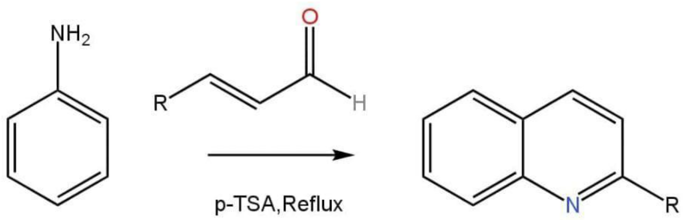
Skraup Synthesis: When aniline reacts with glycerol and nitrobenzene in the presence of sulfuric acid to produce a Quinoline compound.



Doebner reaction: Aniline reacts with aldehyde and pyruvic acid to form Quinoline compound.

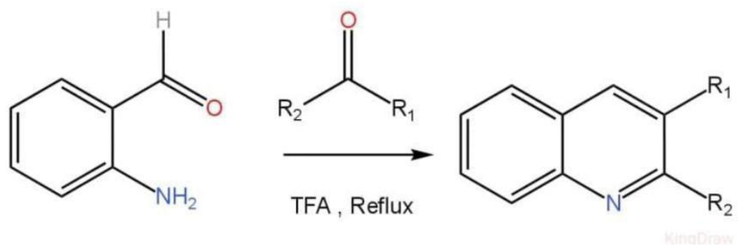


Doebner- Miller reaction: When aniline reacts with a b-unsaturated carbonyl compound in the presence of P-toluenesulfonic acid to form Quinoline compound.

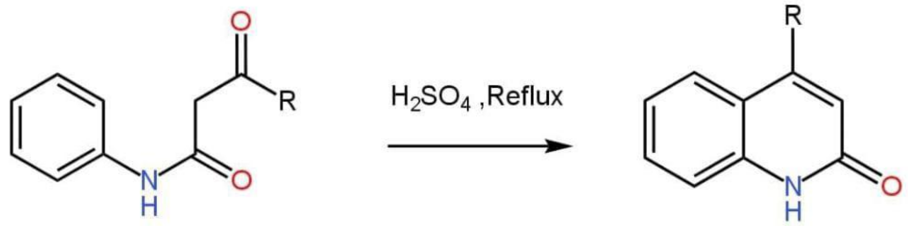


Modern Methos of Making Quinoline Compound:

Friedlander Synthesis: When two amino benzaldehyde reacts with carbonyl compounds in the presence of tri-fluroacetic acid to produce a Quinoline compound.



Knorr Quinoline Synthesis: When b-ketoanilide reacts with sulfuric acid to produce a Quinoline compound.



Advantages:

1) **Pharmacological Potential:**

Quinoline derivatives exhibit a wide range of biological activities including; Antimalarial, Antibacterial, Antiviral, Anticancer, Anti-Inflammatory, Antioxidant.

2) **Structural Versatility:**

Quinoline has a fused aromatic ring system, which allows for:

- Easy modification at a different positions.
- Enhancement of biological properties through substitution.

3) **Drug Development:**

Many FDA-approved drugs are based on Quinoline scaffolds.
Their derivatives serve as lead compounds in drug discovery and development.

4) **Synthetic Accessability:**

Quinoline can be synthesized by various simple and cost-effective methods such as,

- Skraup synthesis
- Friedlander synthesis

5) **Characterization ensures Purity and Identity:**

- Characterization techniques like TLC & UV-Visible spectroscopy.
- Confirms the structure.
- Ensure Purity and Reproducibility.
- Identify possible impurities.

Limitations & Challenges:

1) **Toxicity & Side effects:**

Many Quinoline derivatives can causes serious side effects like Retinopathy or Neurotoxicity.
Some may have poor selectivity affecting both healthy and diseased cells.

2) **Synthetic Challenges:**

Some synthetic routes involve harsh reaction conditions like high temperature and strong acids which can:

- Be hazardous
- Cause low yields or unwanted byproducts

3) **Purification Issues:**

Quinoline derivatives can be difficult to purify, particularly when forming complex mixtures or tautomers**.** Some compounds have low solubility, complicating isolation & analysis.

4) **Characterization Complexity:**

Structural similarity among derivatives may make spectroscopic interpretation (like UV) challenging. Need for multiple analytical techniques to confirm the structure, which can be time-consuming & costly.

5) **Environmental & Safety Concerns:**

Some reagents & solvents used in Quinoline synthesis are toxic or non-environmentally friendly. Waste disposal & handling of chemicals pose ecological & safety issues.

6) **Biological Evaluation:**

Extensive in-vitro & in-vivo testing is required to validate pharmacological activity, which:

- Takes time & resources
- May still fail in clinical trials

Applications of Quinoline:

1) **Pharmaceutical Applications:**

- **Antimalarial Agents:** Chloroquine, Amodiaquine and Mefloquine are Quinoline-based drugs used to treat malaria.
- **Antibacterial & Antiviral Agents:** Some derivatives show activity against bacterial infections & viral diseases, including tuberculosis & HIV.
- **Anticancer Agents:** Quinoline derivatives act as DNA intercalators or enzyme inhibitors, showing promise in cancer treatment.
- **Anti-inflammatory & Analgesic:** Used to reduce inflammation & pain in condition like Arthritis.
- **CNS-Active Agents**: Some derivatives have antidepressant, antipsychotic, or anticonvulsant properties.

2) **Industrial Applications:**

- **Dyes & Pigments**: Quinoline derivatives are precursors in the synthesis of Azo dyes & other industrial colorants.
- **Corrosion Inhibitors**: Used in metal industries to prevent corrosion by forming protective films.

3) **Agrochemical Applications:**

Serve as pesticides, herbicides, fungicides, helping protect crops from various threats.

4) **Synthetic Intermediates:**

Quinoline is a key intermediate of complex organic molecules, ligands, & coordination compounds in catalysis

5) **Antioxidant Activity:**

Some Quinoline derivatives have the ability to neutralize free radicals, thus showing protective effects against

Oxidative stress-related diseases like Alzheimer’s & Parkinson’s.

6) **Antifungal Agents:**

Effective against a variety of fungal strains, Quinoline derivatives are used in the treatment of dermatophytosis & systemic fungal infections.

7) **Antihypertensive & Cardiovascular Drugs:**
Certain Quinoline derivatives act as vasodilators or calcium channel blockers, useful in managing hypertension & heart disorders.
8) **Antidiabetic Potential:**
Some studies have shown that Quinoline derivatives can regulate blood glucose levels & act as enzyme inhibitors (e.g., DPP-4), aiding in diabetes treatment.
9) **Enzyme Inhibition:**
Used as enzyme inhibitors for various biological targets:
- Kinases
- Topoisomerases
- Carbonic anhydrase
- Acetylcholinesterase

Conclusion:
Synthesis of Quinoline was of great importance for the generation of the compound of heterocyclic material in Pharmaceutical, Material science application etc. Generally, the traditional Skraup methods, Doebner-Miller, & Friedlander synthesis, being based on the same principles, apply only to relatively high temperature, acidic or oxidative conditions. Which immediately limits the scope of the substrate & may result in small or worse.
Quinoline may therefore be synthesized using this method, which is efficient, but requires careful handling of the reagent in consideration of the exothermic nature of the reaction & corrosive property of sulphuric acid. Optimization of the reaction conditions are therefore required to be in order to achieve the desired purity & yield for this product.

Acknowledgment:
We would like to express our sincere gratitude to all who supported us throughout the completion of this review paper.
Our heartfelt thanks go to our guide for their continuous encouragement, valuable suggestions, & insightful feedback, which greatly improved the quality of our work. We also thanks Dr. J. J. Magdum Pharmacy College, Jaysingpur, for providing the necessary support & academic resources.
We appreciate the efforts & coordination of our team members & are truly grateful to our families & friends for their constant motivation & support.

Reference:
1. **Elebiju, O.F., et al. (2023).**
Recent advances in functionalized quinoline scaffolds and hybrids- Exceptional pharmacophore in therapeutic medicine. Frontiers in Chemistry,10, 1074331.
2. **Ajani, O. O., et al.(2022).**
Recent advances in chemistry & therapeutic potential of functionalized Quinoline motifs- a review. RSC Advances,12, 18594-18614.
3. **Batista, A. C., et al. (2025).**
A review on Quinolines: New green synthetic methods and bioactive derivatives. Bioorganic and Medicinal Chemistry, 85, 117132.

4. **Kumar, S., & Sharma, R. (2022).**
A review on synthetic investigation for Quinoline: Recent green approaches. Green Chemistry Letters & Reviews, 15(2), 123-135.
5. **Patel, D., & Mehta, P. (2023).**
A review on synthesis and biological applications of Quinoline derivatives. Synthetic Communications, 53 (15), 1234-1250.
6. **Kamble, R.R., & Dabhade, D. S. (2019).**
Quinoline-based materials for optoelectronic applications. Materials Chemistry & Physics, 237, 121619.
7. **Sahu, S., & Sahu, S. (2021).**
A review on Quinoline: Diverse pharmacological agent. Chemistry Research Journal,6(4), 81-96.
8. **Gupta, R., & Sharma, S. (2022).**
Quinoline- based materials for optoelectronic applications. Materials Chemistry & Physics, 275, 125-133.
9. **Bhattacharya, S., & Sinha, S. (2020).**
Quinoline: A versatile heterocyclic scaffold for Medicinal Chemistry. European Journal of Medicinal Chemistry, 207. 112728.

10. **Shrivastava, V. K., & Mishra, A. (2019).**
Quinoline & its Derivatives: A patent review (2014-2018). Expert Opinion on Therapeutic Patents, 29(6), 423-447.
11. **Sullivan, D. J., Gluzman, I. Y., & Goldberg, D. E. (1996).**
Plasmodium hemozoin formation mediated by histidine- rich proteins. Science 271 (5246), 219-222.
12. **Yadav, P., & Yadav, D. (2021).**
Quinoline- based Anticancer agents: A review. Bioorganic Chemistry, 111, 104781.
13. **Katritzky, A.R. (Ed.). (2008).**
The Chemistry of Heterocyclic Compounds: Quinoline & Isoquinoline Derivatives. Wiley- Interscience.
14. **Lemke, T. L., & Williams, D. A. (Eds). (2013).**
Foye's Principles of Medicinal Chemistry (7th ed.). Lippincott Williams & Wilkins.
15. **Block, J.H., & Beale, J. M. (2011).**
Wilson & Gisvold's Textbook of Organic Medicinal & Pharmaceutical Chemistry (12th ed.). Lippincott williams & Wikins.