GREEN SYNTHETIC APPROACHES TOWARDS QUINOLINE DERIVATIVES

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DECLARATION

We, **BABITA & KANIKA**, hereby declare that the work which is being submitted in this dissertation entitled "**GREEN SYNTHETIC APPROACHES TOWARS QUINOLINE DERIVATIVES**" in the partial fulfilment for the award of the degree of **Master of Science** in the **Department of Applied Chemistry**, Delhi Technological University is an authentic record of our own work carried out during the period from **August, 2024 to April, 2025** under the supervision of **Dr. Richa Srivastava (Associate Professor, Department of Applied Chemistry, Delhi Technological University)**.

We further declare that the dissertation has not been submitted by us for the award of any other degree of this or any other Institute.

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CERTIFICATE

This is to certify that the Project report entitled **"GREEN SYNTHETIC APPROACHES TOWARS QUINOLINE DERIVATIVES"** which is submitted by **Babita (2K23/MSCCHE/81)** and **Kanika (2K23/MSCCHE/64)**, Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of **Master of Science**, is a record of the project work carried out by the students under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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ABSTRACT

Quinoline derivatives are a well-established group of heterocyclic compounds that have gained considerable importance due to their wide-ranging biological properties and applications in medicinal, pharmaceutical, and materials science. Their synthesis has mostly depended on conventional methods over the years, which frequently use dangerous chemicals, produce toxic waste, and require a significant amount of energy. Such actions raise questions about long-term sustainability and economic viability in addition to posing significant risks to the environment and human health. The emphasis has steadily moved toward more sustainable and environmentally friendly methods of chemical synthesis in response to these difficulties. By using safer reagents, reusable catalysts, and energy-efficient techniques, green chemistry has created exciting opportunities for the environmentally friendly synthesis of quinoline-based compounds. These modern techniques include solvent-free conditions, biocatalysis, photocatalysis, nanocatalysis, ultrasound-assisted synthesis, microwave-assisted reactions, and even reactions that don't require a catalyst at all. These methods frequently produce higher yields, better selectivity, and quicker reaction times in addition to minimizing environmental harm. With a focus on advancements in energy-saving technologies, sustainable solvents, and catalytic systems, this thesis examines current trends in the environmentally friendly synthesis of quinoline derivatives. It also talks about how these developments lessen the environmental impact of the chemical industry without sacrificing scalability or efficiency, which helps to achieve larger sustainability goals. Even though great progress has already been made, issues like exorbitant prices, restricted scalability, and the requirement for standardized processes still exist. However, it is anticipated that continued study and development in this area will improve these techniques even more, opening the door to a more ethical and sustainable chemical manufacturing future.

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1.1Background of quinoline derivatives and their applications

1.1.1 Historical background of Quinoline

Friedlieb Ferdinand Runge first isolated quinoline from coal tar in 1834, which was the first time the compound was identified [1,2]. Quinoline is a heterocyclic nitrogen-containing compound that is a member of the larger alkaloids family, which is well-known for its wide range of biological functions. The creation of cinchocaine, one of the first local anesthetics made from this chemical class, was one of the first therapeutic applications of quinoline derivatives [3]. Quinoline-based structures have been essential to pharmaceutical chemistry over the years, acting as scaffolds for a variety of drug classes.
These include antimalarials like quinine, chloroquine, and primaquine; antibiotics like fluoroquinolones (e.g., ciprofloxacin); anticancer agents like topotecan and camptothecin; local anesthetics like dibucaine; and medications used to treat tuberculosis, like bedaquiline. The potential of a number of quinoline derivatives to cause programmed cell death (apoptosis), impede tumor cell motility, and prevent the development of new blood vessels (angiogenesis)—all crucial processes in cancer treatment is also being studied [4].

1.1.2 Natural occurrence of Quinoline

Animals, microbes, and flowering plants are among the many natural sources of quinoline [5]. However, coal tar continues to be its main industrial source [6]. The bark of the Cinchona tree contains a number of quinoline-derived alkaloids, including quinine, quinidine, cinchonine, and cinchonidine, which combine to form the compound mixture known as "Quinimax," which is frequently used to treat malaria [7]. The citrus plant Zanthoxylum nitidum yields nitidine, a dimethoxylated quinoline derivative with anticancer qualities. Numerous medicinal plants, including *Papaver somniferum*, *Asimina triloba*, *Ocotea fasciculata*, and *opium* species, naturally contain the isoquinoline alkaloid reticuline. The furoquinoline alkaloid skimmianine, which is present in *Skimmia japonica*, is used in anticonvulsant and narcotic drugs. Sandramycin is a bioactive molecule with two 2-amidoquinoline units at its core that is produced by *Nocardioides* species. It is known to have antitumor and antimicrobial properties [8]. The bark and stems of Camptotheca acuminata can be used to isolate camptothecin, a pentacyclic quinoline and another quinoline-based compound. Plants belonging to the genus *Dictamnus* also yield a variety of quinoline alkaloids. For example, *Dictamnus angustifolius* is the source of robustine, *Dictamnus albus* of evolitrine (a tricyclic quinoline), *Dictamnus hispanicus* of

ribalinidine, and *Dictamnus dasycarpus* and *Dictamnus angustifolius* of dictamnine [9].

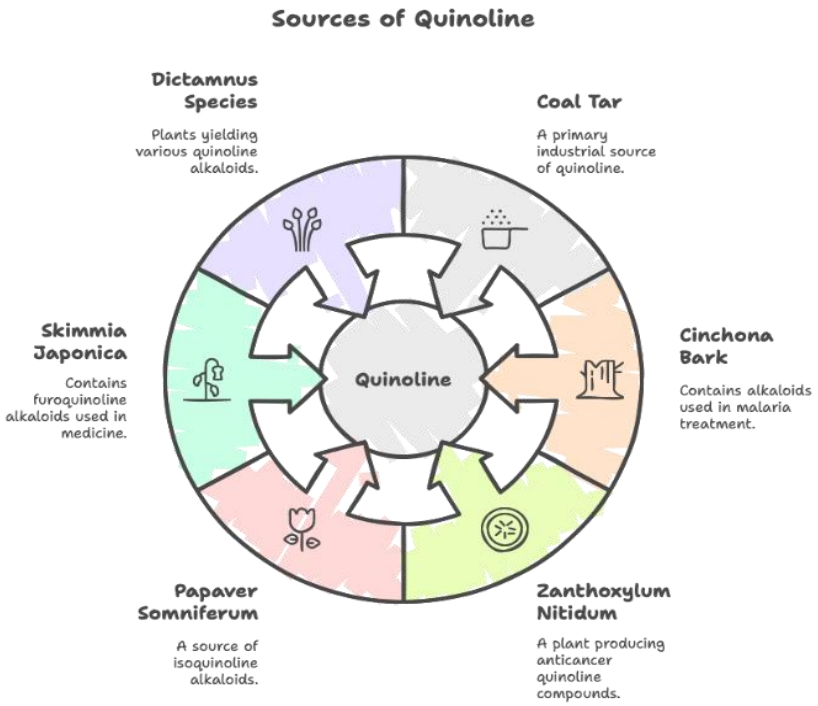


Figure 1: Different sources of Quinoline

1.1.3 Physical properties of Quinoline

Quinoline is a liquid with a potent smell. It dissolves fully in hot water but only slightly in cold water. Quinoline can also absorb moisture from the air and mixes easily with a variety of organic solvents at room temperature [5]. Fresh quinoline is a colorless, hygroscopic liquid, but as it ages and is exposed to light, it gradually turns yellow and then brown [6]. Quinoline's melting and boiling points are close to -15°C and 238°C, respectively, and its density is about 1.093 g/cm³. Quinoline and its related compounds have been identified for their biological activities in contrast to monocyclic nitrogen-containing heterocycles such as pyridine derivatives. Furthermore, because they are derived from coal tar and readily disperse in air and water, these compounds are important environmental contaminants [3].

1.1.4 Chemical structure of quinoline and its applications

Quinoline (C_9H_7N) is also known as benzazine, benzo[b]pyridine and ben-zazine [10]. It's an oily, hygroscopic liquid with a yellowish tint that dissolves in ether, alcohol, and several other solvents. It is a class of chemical compounds belonging to the aromatic heterocyclic series. It is distinguished by having a double-ring structure made up of two neighboring carbon atoms fused to form the pyridine and benzene

rings [11]. There are six carbon atoms in the benzene ring, five carbon atoms, and one nitrogen atom in the pyridine ring. Because it contains an atom of nitrogen, which attracts electrons through resonance, quinoline is an essential component of medicinal chemistry. This bicyclic aromatic molecule is an electron-deficient system and has poor tertiary base characteristics. It shows both nucleophilic and electrophilic substitutions. Its structural flexibility makes it an important scaffold to design many biologically active molecules such as pharmaceuticals, and dyes. Its derivatives are widely recognized for their diverse applications in medicinal [12], bioorganic, and industrial chemistry, as well as in synthetic organic chemistry [13], and represent a major structural core found in various natural products and FDA-approved small molecules. Literature survey revealed that these derivatives are considered privileged scaffolds in drug discovery because of their broad spectrum of biological properties such as exhibiting anticancer [14], antioxidant [15], anti-COVID-19 [16], anti-inflammatory [17], anti-mycobacterial [18], antimicrobial [19], anticonvulsant [20], cardiovascular [21], antituberculosis [22], antimalarial [23], anti-plasmodial [24], and antibacterial [25] activities. Consequently, their scaffolds are still paving the way for compounds exhibiting multiple pharmacological functions [26].

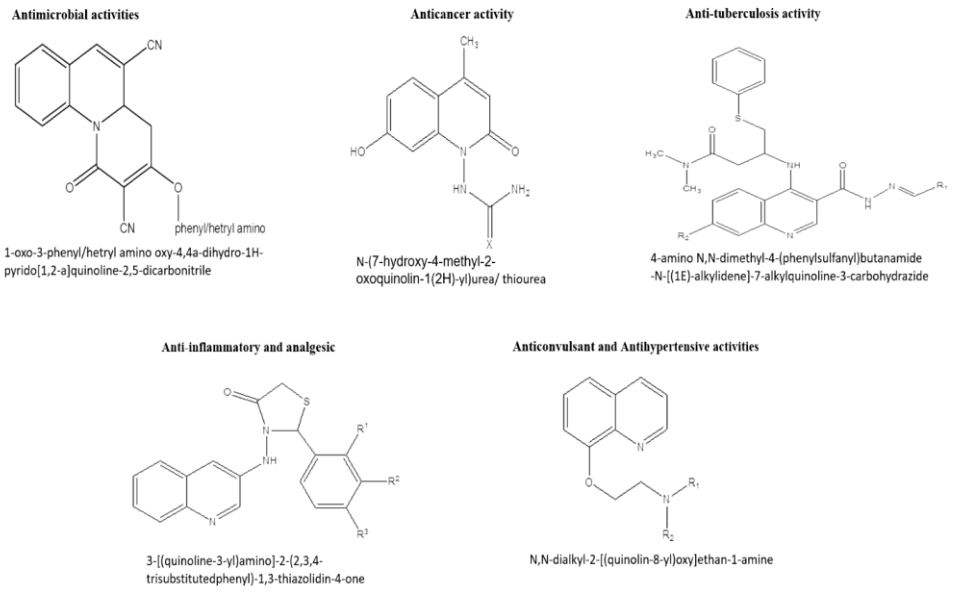


Figure 2: Pharmacologically Active Quinoline Derivatives: Structural Overview

1.2 Importance of sustainable chemistry in synthesis

Sustainable chemistry has become crucial in quinoline derivative synthesis, addressing environmental concerns while increasing efficiency and cost-effectiveness. Traditional approaches often need such toxic reagents as chlorinated or nitrosated catalysts, and need to take place at high temperature with the risk that ethanol may result in nearby explosion; nonetheless, even all the same methods,

finally cannot guarantee that the desired product is made. The green process emphasizes these ideas of atom economy, renewable raw materials, and preventing pollution. Here are some of the major breakthroughs and contending forces.

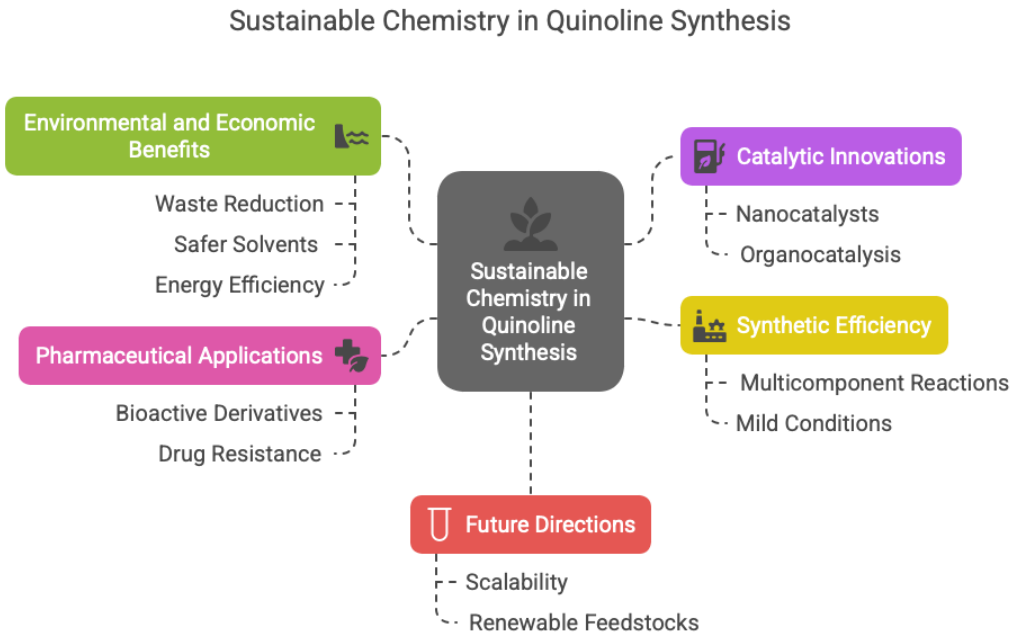


Figure 3: Key Domains Highlighting the Importance of Sustainable Chemistry in the Synthesis of Quinoline Derivatives.

1.2.1 Environmental and Economic Benefits

Waste minimization: Methods such as microwave-assisted synthesis and electrosynthesis for quinoline production reduce waste to almost nothing. For instance, in the case of electrosynthesis, quinolines can be produced from nitro compounds purely through the application of electricity [27].

Biomass-derived solvents such as ethyl lactate, clean organic solvents, and particulates from MCRs [28], are non-toxic solvents. The elimination of solvent frees up waste as well.

Energy efficiency: Using light-affiliated photocatalytic methods lowers energy requirement. Photocatalytic lowering of energy use was illustrated in the production of quinolin-2(1H)-one, which was synthesized using minimal catalyst, a complete sealed system, and no waste byproducts [29].

1.2.2 Catalytic Innovations

Nanocatalysts: The use of Fe_3O_4, Ni, and Co in the form of reusable nanoparticles leads to rapid reactions (5 to 15 minutes) and a high-end product (up to 95%). These

catalysts can be used many times, which saves on cost and has the added benefit of damage reduction to the earth.

Organocatalysis: Condoning heavy metals in the form of chlorite (III) iron) within MCRs is a green tactic which helps prevent environmental pollution. For example, quinolines in the neat state can be produced from aniline, aldehyde, and ethyl lactate [30].

1.2.3 Synthetic Efficiency

Multicomponent reactions: More efficient use of resources (Convergent MCRs) improve physical economy, as in Povarov and Gewald's one-pot synthesis of complex atom-economical quinoline containing methyl groups and necessitating less purification [28].

Gentle conditions: Friedlander annulations with nickel nanocatalysts are solvent-free, and electrosynthesis is performed at room temperature.

1.2.4 Pharmaceutical Applications

Green methods Pyrrolo[1,2- a]quinolines synthesized via ecologically benign routes, predicted to be anti-inflammatory and antihypertensive, show increased bioactivity. Hybrid quinoline scaffolds with dual action against drug resistance exhibit combined pharmacological effects [30].

1.3 Brief comparison of traditional and green synthesis methods

The green synthesis of quinoline derivatives offers a sustainable alternative to traditional methods based on toxic reagents, dangerous solvents and energy-intensive environments. While traditional approaches such as Skraup and Doebner-Miller reactions produce considerable waste and require high temperatures, while green methods prefer to be based on 95% on eco-friendly solvents (such as water, ethylates), recyclable nanocatalysts (Fe_3O_4, Ni), and energy efficient techniques like microwave assisted or electrosynthesis. In keeping with the ideas of the atom economy, green protocols also produce high yields (up to 95 percent) with few byproducts. Green synthesis is essential for the sustainable pharmaceutical and industrial uses of quinoline derivatives because of these developments, which also lessen the environmental impact while increasing cost-effectiveness and scalability.

Table 1 Comparative Overview of Traditional vs. Green Synthesis Methods for Quinoline Derivatives

Aspect	Traditional Methods	Green Methods
Catalysts	Strong acids (e.g., H_2SO_4, HCl) or toxic reagents [31].	Recyclable nanocatalysts (Fe_3O_4, Ni, Co NPs) or organocatalysts ($FeCl_3$) [32].
Solvent	Hazardous organic solvents (e.g., toluene, acetic acid) [31].	Water, biomass-derived solvents (e.g., ethyl lactate), or solvent-free [32].
Reaction conditions	High temperatures, energy-intensive (e.g., 50–90°C) [33].	Mild conditions (ambient temperature, microwave/light irradiation).
Yield	Moderate to high (55–65% in some cases), but variable with substituents [33].	High yields (up to 95%) with consistency across substrates [32].
Waste Generation	Significant hazardous byproducts and solvent waste [33].	Minimal waste due to atom economy and recyclable catalysts.
Energy Efficiency	Low (prolonged refluxing or high-pressure setups) [31].	High (fast reactions under microwave/electrochemical conditions).
Scalability	Established for industrial use but with environmental costs [31].	Emerging scalable protocols (e.g., flow reactors, nanocatalysts) [31].
Key examples	Skraup, Doebner–von Miller, Conrad–Limpach [31].	Multicomponent reactions (Povarov, Gewald), nanocatalyzed Friedländer [32].

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of traditional synthesis methods

Quinolines are a large and diverse class of heterocyclic molecules traditionally synthesised through classical organic reactions such as condensation, cyclization, or oxidation processes. These reactions are typically carried out under harsh conditions, requiring strong acids/oxidising agents and high temperatures. Although these approaches do offer historical significance and process utility, they often remain restricted by issues relating to low product yield as well as environmental effects and the production of unwanted side products. In this context, we have reviewed some of the most common classical methods for the synthesis of quinoline and its derivatives (Skraup, Doebner-Miller, Pfitzinger, Friedländer, Combes quinoline, and Conrad-Limpach syntheses [34]). The specific advantages and challenges of each method make them continue to be used in academic research and industrial applications [35].

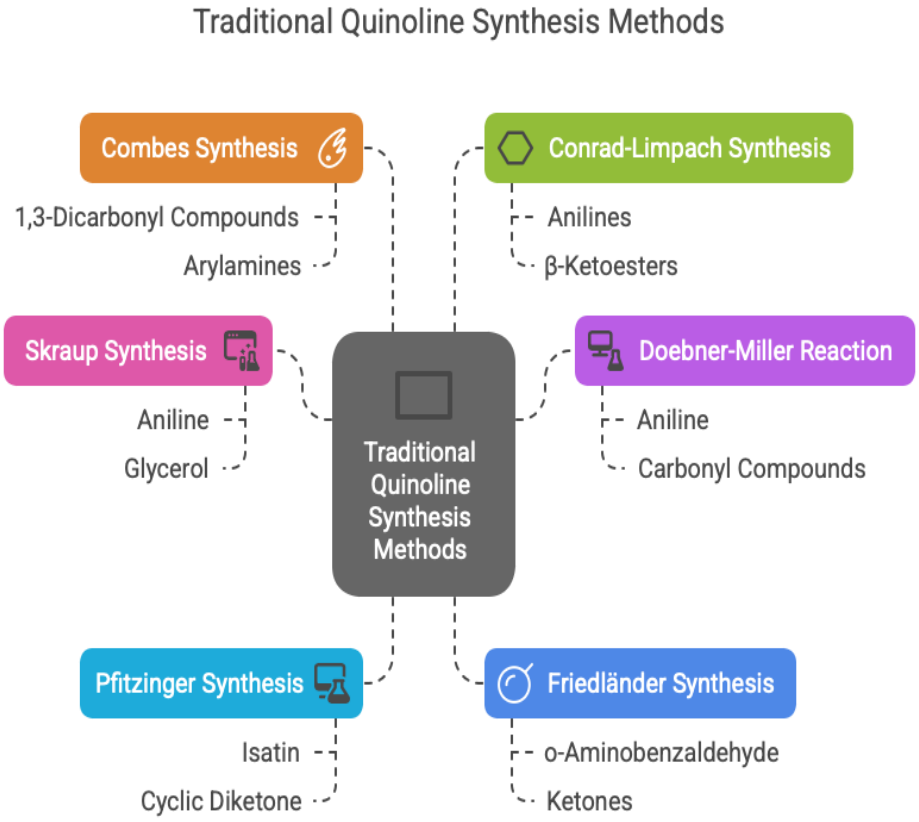
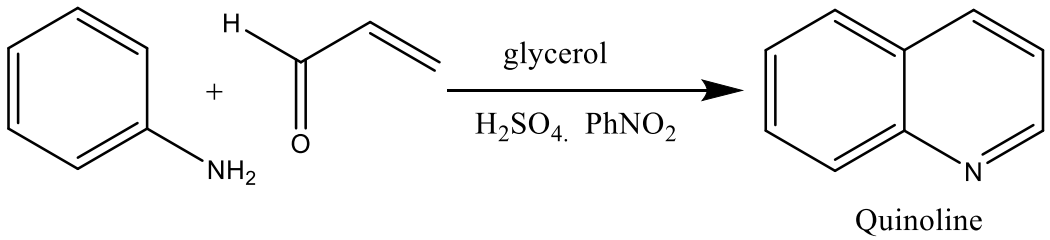


Figure 4: Traditional quinoline methods with respective key reactants

1. Skraup Synthesis

The Skraup synthesis is a traditional chemical process that is frequently used to create quinoline and its derivatives. This tried-and-true method usually uses concentrated sulfuric acid to react aniline with glycerol in highly acidic conditions. The acidic medium plays a vital dual role in the process by acting as a dehydrator in addition to starting the reaction. Glycerol undergoes a transformation into the extremely reactive intermediate acrolein during the reaction. The quinoline ring system is created by further oxidizing the compound that results from this acrolein's cyclization with aniline. An oxidizing agent, such as arsenic acid or nitrobenzene, is typically used to propel the oxidation step. Even though this technique works well, it is notorious for using harsh chemicals and raising safety and environmental issues. For these reasons, more environmentally friendly alternatives are currently being investigated. This reaction was noteworthy historically because it was the first synthetic pathway to quinoline in a lab environment.It established the foundation for the synthesis of numerous substituted quinolines, many of which have pharmacological significance. The Skraup synthesis has significant disadvantages despite its fundamental significance, such as comparatively low product yields, the requirement for strict conditions, and the generation of hazardous byproducts. Because of its hazardous and exothermic nature, nitrobenzene in particular presents serious safety risks, raising questions about reaction control and environmental impact [36,37].

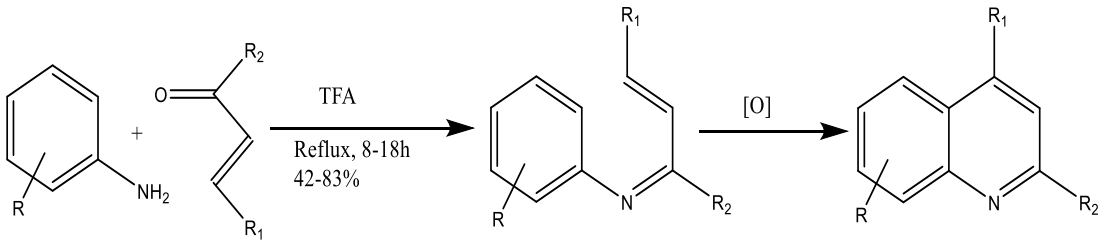


Scheme 1: Synthesis of the Quinoline Scaffold via the Skraup Method

2. Doebner-Miller Reaction

One well-known technique for creating compounds based on quinolines is the Doebner–Miller reaction. In this reaction, aniline or its derivatives are usually catalyzed by an acid to condense with α,β-unsaturated carbonyl compounds like crotonaldehyde.[38] By employing aldehydes or ketones as important reactants, the Doebner–Miller method provides more structural flexibility than the Skraup synthesis, which depends on glycerol and potent oxidizing agents. In a noteworthy study, Wu and colleagues showed that chalcones react with aniline derivatives in trifluoroacetic acid to form a reactive intermediate, which subsequently undergoes oxidative cyclization to produce trisubstituted quinolines. This method's comparatively mild reaction conditions are one of its key benefits. It is more user-

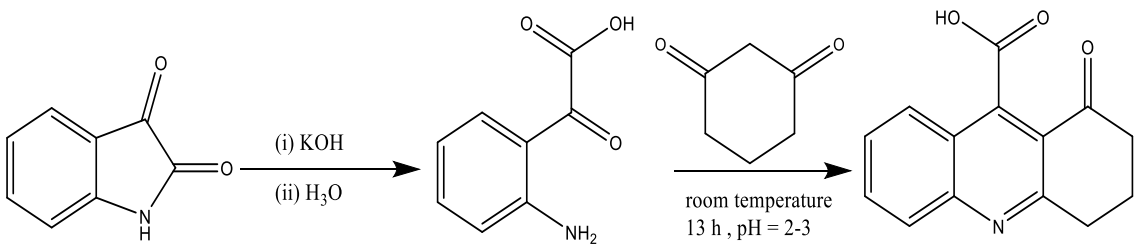
friendly and versatile for creating a wide variety of quinoline derivatives because it typically does not require harsh oxidants or high temperatures. The Doebner–Miller reaction does have certain drawbacks, though, despite its ease of use and adaptability. One of the main problems is that α,β-unsaturated aldehydes have a propensity to undergo acid-promoted polymerization, which can drastically lower yields and make it more difficult to isolate the desired product. Purification can occasionally be difficult because of these side reactions, which frequently result in the creation of complex mixtures.[39]



Scheme 2: Synthesis of the Quinoline Scaffold via the Doebner-Miller Method

3. Pfitzinger Synthesis

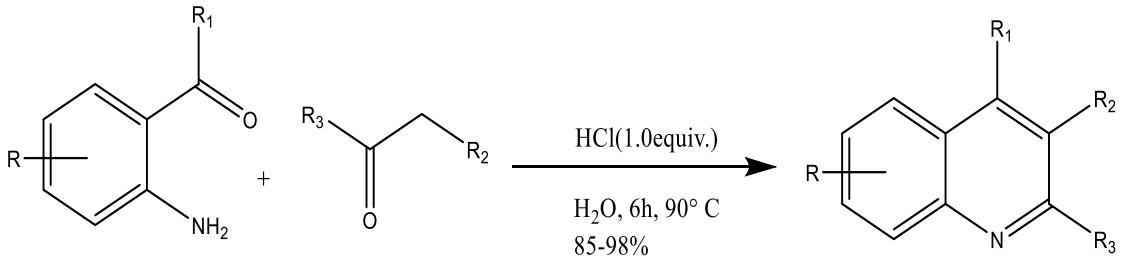
Using isatin as the starting material, the Pfitzinger synthesis provides a traditional pathway to quinoline derivatives. The ring structure of isatin opens as a result of alkaline hydrolysis caused by treatment with an aqueous potassium hydroxide solution. An anilino-substituted carboxylic acid is the intermediate that is produced by this reaction. The mixture must be carefully acidified, usually to a pH range of 2 to 3, in order to stabilize this intermediate and direct the reaction toward the intended pathway. Following this stabilization, a cyclic diketone reacts with the intermediate, starting a chain of changes that eventually forms a tricyclic quinoline framework. The tricyclic quinoline structure is then assembled through an acid-catalyzed condensation between the produced keto-acid and a 1,3-diketone. This approach is prized for its capacity to add structural complexity and typically produces respectable yields. Notwithstanding these benefits, the reaction's versatility may be limited to a smaller range of synthetic applications due to its dependence on particular starting materials, such as isatin. [40]



Scheme 3: Pfitzinger Reaction Pathway for Synthesizing Quinoline Derivatives

4. Friedländer Synthesis

One of the most well-known and adaptable techniques for creating quinoline derivatives, especially those with substitution at the 2-position, is the Friedländer synthesis, which was initially created in 1882. In this reaction, ortho-substituted aromatic amines like o-aminobenzaldehyde or o-aminoacetophenone condense with carbonyl-containing compounds like ketones or aldehydes. Usually, the process starts with the creation of an imine, also referred to as a Schiff base. The quinoline framework is the end result of intramolecular cyclization of this intermediate, which is frequently referred to as a Claisen-type condensation. Trifluoroacetic acid, iodine, different Lewis acids, and p-toluenesulfonic acid are just a few of the many catalysts that have been investigated to increase the efficiency of this reaction. The particular substrates and intended products play a major role in the selection of the catalyst and reaction conditions, which can range from basic to acidic. Notwithstanding the method's wide range of applications and flexibility, o-aminobenzaldehyde's high reactivity is a significant drawback. The molecule is susceptible to premature or side cyclizations because it contains both amino and aldehyde functional groups. Particularly in intricate synthetic schemes, this may complicate the reaction pathway and lower the total yield or purity of the desired quinoline derivative. [41]



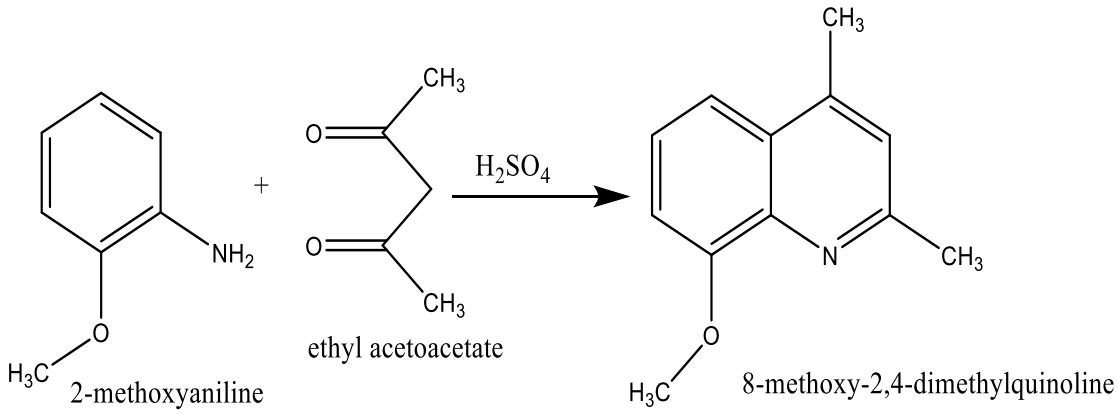
R= H, 2,4-$(Br)_2$: R_1 = H, Me, 4-F-C_6H_4:R_2 = CO_2Et, COMe
R_3 = Me , n-Pr ; R_2 & R_3 = -$(CH_2)_2$, -$(CH_2)_3$-, -$CO(CH_2)_2$-,-$COCH_2CMe_2CH_2$-

Scheme 4: Friedländer Reaction Pathway for Synthesizing Quinoline Derivatives

5. Combes Quinoline Synthesis

A well-known technique for creating quinoline frameworks is the Combes synthesis, which depends on arylamines condensing with 1,3-dicarbonyl compounds or keto-aldehydes while an acid catalyst is present. A β-amino enone intermediate is formed at the start of the reaction, which is followed by cyclization and water removal to produce a variety of quinoline derivatives. This method's capacity to effectively generate 2,4-disubstituted quinolines in comparatively large yields is one of its main advantages. Notwithstanding its dependability, the Combes synthesis's wider use

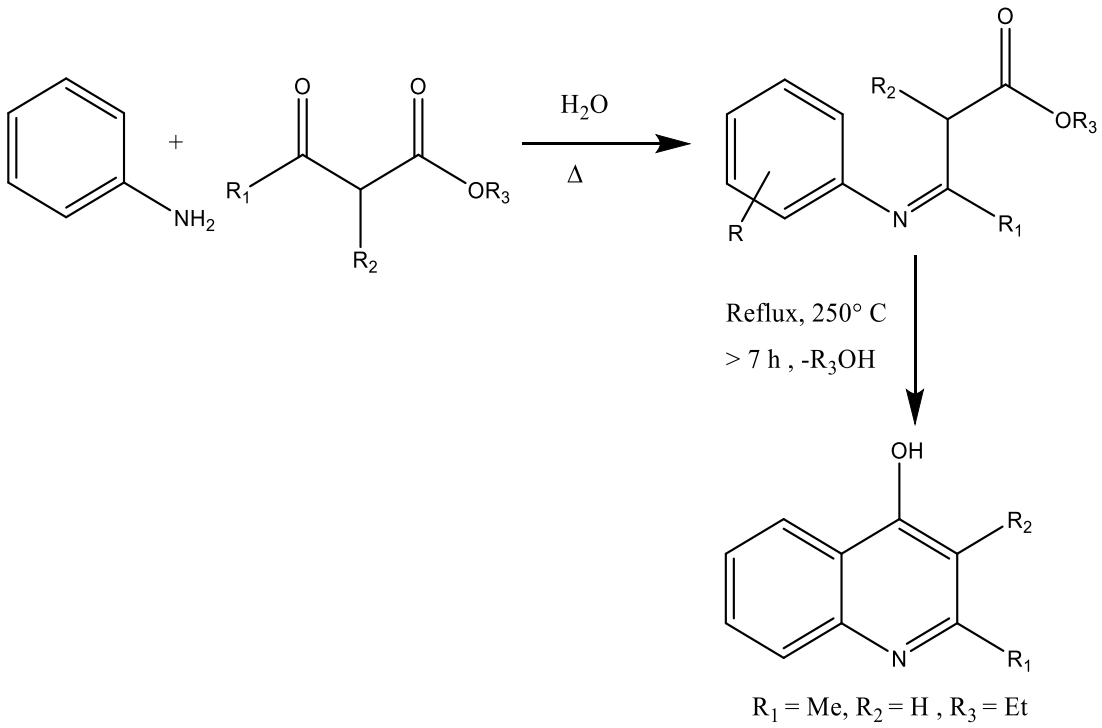
may be limited by the scarcity of appropriate β-diketones, which are necessary to start the reaction. [42]



Scheme 5: Combes Quinoline Synthesis

6. Conrad-Limpach Synthesis

One well-known technique for creating 4-hydroxyquinoline derivatives is the Conrad–Limpach reaction. It works by condensing aniline derivatives with β-keto esters to create an intermediate Schiff base. This change can be thought of as a mix of molecular rearrangement and addition processes. Thermal ring closure is a crucial, rate-limiting step that necessitates high temperatures (usually about 250 °C) for efficient cyclization. The success of the reaction heavily depends on solvent selection, as certain solvents can significantly influence product yield. Carrying out the reaction at lower temperatures tends to be inefficient or incomplete [43].
But there is also a chance of decomposition when working in such hot conditions. This can be lessened by using high-boiling solvents, such as mineral oil, which must frequently boil above 275 °C to preserve stability and encourage successful conversion [44].



Scheme 6: Conrad-Limpach quinoline synthesis

2.2 Green Synthesis Approaches

Green synthetic approaches for quinoline derivatives have increasingly become vital solutions to align with the twelve principles of green chemistry, addressing inefficacy and environmental damage innate in conventional methods like Skraup or Friedländer reactions. Modern approaches emphasize energy efficiency, renewable resources, and reduce waste. For instance, electrosynthesis allows reagent-free synthesis for quinoline from nitro compounds using electric current under mild conditions, accomplishing high productivity (up to 90%) and high atom economy [45]. Nanocatalysts like nickel oxide nanoparticles with sizes around 80–100 nm facilitate Friedländer annulations without solvents, allowing the process to be repeated five times while minimizing chemical waste [46]. Within minutes, microwave-assisted multicomponent reactions under solvent-free conditions can generate antiproliferative quinolinones, while ultrasound irradiation accelerates hybrid quinoline-imidazole derivatives without toxic solvents. Reagents (e.g., H_2SO_4, $POCl_3$), causing health hazards, replace volatile organic compounds with safer alternatives like water and ethyl lactate and simplify purification via precipitation or filtration [47]. By integrating scalable techniques such as flow reactors and renewable materials, green synthesis to improve cost effectiveness and reduce 30 to 40% of energy consumption, ensuring compliance with global goals for sustainability. Such advances not only minimize the environmental footprints but also expand pharmaceutical applications, including anti-cancer and anti-bacterial

drugs, emphasizing their role in transforming industrial environmental chemistry [48].

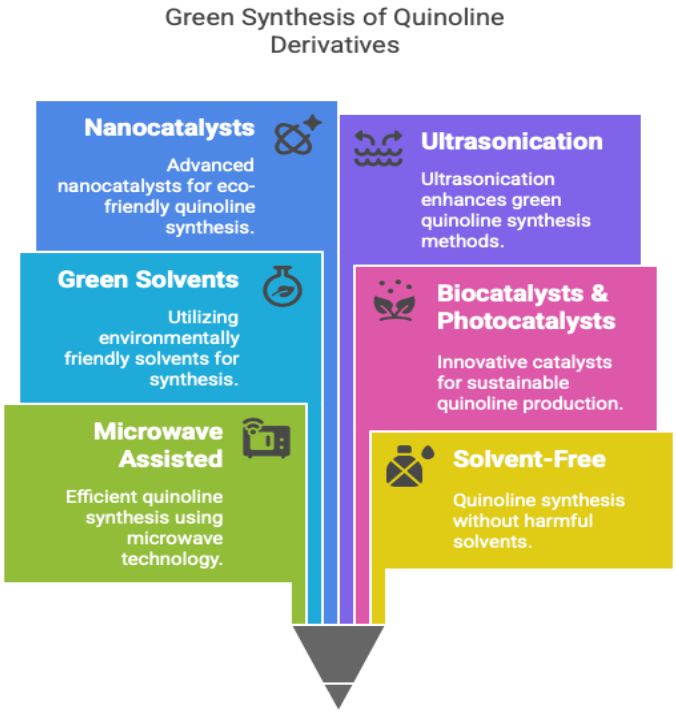


Figure 5: Green synthesis approaches for quinoline derivatives

1. Microwave-Assisted Synthesis

In contemporary synthetic chemistry, microwave-assisted synthesis (MWA) has grown in importance, particularly in the context of "green" or ecologically friendly techniques. Compared to conventional heating methods, this technique offers a quicker, cleaner, and more energy-efficient solution. Microwave heating introduces energy directly into the reaction mixture, producing a quick and consistent temperature rise, in contrast to conventional heating, which depends on external heat transfer through conduction and convection [33]. The reaction mixture heats up swiftly and evenly because of dielectric heating. This improves control over reaction kinetics and product distribution by accelerating the reaction and reducing temperature gradients[49]. MWA is very advantageous from the standpoint of green chemistry. It can lessen the environmental impact of the process by reducing or eliminating the need for solvents [50]. Reactions frequently take place in milder environments, producing cleaner products and fewer side effects . It is a more sustainable approach because the effective energy transfer also results in less energy being used overall.

2. Solvent-Free Reactions

The conventional wisdom that a successful chemical reaction always requires a liquid medium is called into question by the idea of solvent-free synthesis [51,52]. Many reactions can proceed effectively without the addition of external solvents, even though doing so might seem impossible. Either the reactants themselves serve as the medium in these systems (by melting or eutectic formation) or the reactants interact with one another through mechanical processes like milling, grinding, or solid-state heating [53,54].

There are many benefits to solvent-free conditions:

- Sustainability of the environment: The goal of lowering chemical hazards in the laboratory is aligned with the elimination of hazardous solvents, which also minimizes environmental pollution and chemical waste [55].
- Cost-effectiveness: Solvent-free reactions reduce operating costs by doing away with the need to buy, purify, and dispose of solvents [56].
- Higher conversion and cleaner product formation: In certain situations, the lack of solvents can change equilibrium or reaction pathways, leading to improved reaction rates and yields [57].
- Simplified work-up: By eliminating the solvent step, product isolation is made easier, frequently requiring fewer purification steps [58].

3. **Green solvents**

Green solvents are a class of solvents that are specifically chosen or designed to have minimal impacts on the environment and human health. As awareness of these issues has grown, there has been a conscious shift toward their adoption [68]. Green solvents are generally less toxic, biodegradable, and often made from renewable resources than their hazardous counterparts [69]. The use of several kinds of green solvents has increased recently:

- The most environmentally friendly choice is still water, which can support a wide range of organic transformations when used properly or with the right catalysts [59].
- Another promising substitute is supercritical carbon dioxide ($scCO_2$), which has special qualities that lessen the need for hazardous organic solvents in procedures like extractions and polymerizations [60,61].
- While ongoing research is still evaluating their long-term environmental behavior, ionic liquids (ILs) have the advantages of thermal stability and negligible vapor pressure [62].
- Deep eutectic solvents (DESs) are inexpensive, biodegradable alternatives that are created by combining organic acids or sugars with natural, non-toxic substances like choline chloride.
- Plant-based bio-based solvents, like ethanol, limonene, and ethyl lactate, are great alternatives in a variety of synthetic applications [63].

In addition to being environmentally friendly, the shift to green solvents supports the larger objectives of green chemistry, which promotes the development of procedures

that minimize waste, use less energy, and stay away from dangerous chemicals [64]. Additionally, post-reaction workups are frequently made simpler and workplace safety is enhanced by the use of safer solvents [65].

4. Biocatalyst and Photocatalyst-based green approach

Designing chemical processes that are more economical, ecologically friendly, and efficient is one of the main objectives of green chemistry. This entails making the most of starting materials, enhancing reaction selectivity, and substituting safer reagents for potentially harmful ones. Green catalysts, especially biocatalysts and photocatalysts, are important in this situation. Enzymes and other biocatalysts provide a sustainable substitute for traditional chemical catalysts. Under mild circumstances, these biological molecules can speed up a wide range of chemical reactions, frequently in aqueous media or at room temperature. Enzymes enable reactions to proceed effectively without the need for excessive heat or pressure by reducing the activation energy of a reaction [66]. High substrate specificity, which results in fewer adverse reactions and cleaner product formation, is a key benefit of biocatalysts. They are also non-toxic, biodegradable, and sourced from renewable resources, which makes them perfect for green synthesis [67].

5. Nano catalyst based green approach

With the creation of nanocatalysts- catalytic materials designed at the nanoscale- nanotechnology has emerged as a potent instrument for promoting green chemistry. Because of their high surface-area-to-volume ratio, which greatly increases catalytic activity when compared to their bulk counterparts, these nanoscale catalysts have garnered a lot of attention lately [68]. Reactions can therefore be driven more effectively with smaller amounts of nanocatalyst, which makes them appealing from an economic and environmental standpoint [69]. The reusability of nanocatalysts is one of their most advantageous characteristics. After a reaction, many of these materials can be readily recovered using straightforward methods like magnetic separation or filtration, and they can be used repeatedly without suffering appreciable performance degradation [70]. This directly contributes to lowering catalyst-related waste as well as the overall cost of chemical processes. Additionally, nanocatalysts are known to function well in mild environments, frequently requiring lower temperatures and quicker reaction times, which reduces energy consumption. These materials can also be made to be selective for particular substrates or reactions, increasing the yield and purity of the final product while lowering the production of undesirable byproducts [71].

Metal nanoparticles (like Au, Ag, Pt, and Pd), metal oxides (like TiO_2 and ZnO), magnetic nanoparticles, and carbon-based nanostructures like graphene and carbon nanotubes are among the many kinds of nanomaterials that have been investigated in green synthesis. These systems are frequently employed in catalytic processes like hydrogenation, oxidation, and C–C coupling reactions, many of which are critical to the pharmaceutical and fine chemical industries.[72] Crucially, when compared to conventional heavy-metal-based catalysts, the environmental profile of nanocatalysts is typically better [73]. In accordance with the ideas of green and sustainable

chemistry, many nanoparticle systems are made to be less hazardous, more biodegradable, or to minimize leaching into the environment.

6. Ultrasonication

In organic synthesis, ultrasonication—the application of high-frequency sound waves to chemical systems—has recently become a popular and sustainable method. Its capacity to increase reaction rates, boost yields, and permit reactions under milder conditions—all of which are consistent with the tenets of green chemistry—is the reason for its rising popularity. Faster and more effective chemical transformations are made possible by the mechanical effects of ultrasound, especially acoustic cavitation, which produce localized high temperatures and pressures within microenvironments.

The method has been particularly investigated in recent years for the synthesis of heterocyclic compounds, a class of molecules that contains a large number of compounds with biological and pharmacological activity. Because it provides a solvent-reducing, frequently catalyst-free method of assembling complex ring systems, ultrasonication is appealing from both an ecological and practical standpoint. Sonochemical techniques have been comparatively underutilized in the synthesis of quinoline derivatives, despite their expanding use in heterocyclic chemistry [26].

Ultrasonication has a great chance of becoming a standard component of green synthetic strategies as long as researchers continue to investigate this area, especially when preparing nitrogen-containing heterocycles, where selectivity and reaction control are frequently crucial. Ultrasonication helps achieve the main goal of green chemistry, which is to create safer, cleaner, and more energy-efficient chemical processes, by providing unconventional activation energy and lowering the need for hazardous reagents or solvents [50].

2.3 Deep Eutectic Solvent

Deep eutectic solvents (DESs) can be innovative, tunable solvents formed through mixing hydrogen bond acceptors (HBAs) as well as hydrogen bond donors (HBDs) in some specific ratios. These mixtures exhibit some depression in melting point compared to their separate components, usually remaining liquid at room temperature due to definite hydrogen bonding and other intermolecular interactions like van der Waals forces and ionic interactions [74]. DESs are known for sustainability and low toxicity. They also have biodegradability and cost-effectiveness, making them viable alternatives to customary organic solvents and ionic liquids [75].

Figure 6: Properties, Principles, and Applications of Deep Eutectic Solvents (DES)

Key mechanism:

- Hydrogen Bonding: Halide anions (X^-) from some ammonium salts form some hydrogen bonds to the HBD (e.g., -OH or -NH_2 groups). This action delocalizes that charge, further stabilizes each liquid phase, and nearly lowers all energy required to melt the mixture.
- Lattice Energy Reduction: The disruption of most ordered crystal structures of most of the individual components (e.g., choline chloride and $ZnCl_2$) results in one non-ideal eutectic mixture with one melting point far below that predicted by ideal solution behavior [76].

DESs can be described by that formula:

$$Cat^+X^-.zY$$

Cat^+: Some cation types (e.g., choline, ammonium, or imidazolium ions).
X^-: Each halide or each Lewis base anion.
Y: A Lewis or Bronsted acid (e.g., $ZnCl_2$, urea, or glycerol).
z: The count of the Y molecules interacting with an anion.

For instance, choline chloride ([ChCl]) combined with urea (HBD) in a one to two molar ratio is forming of the widely studied DES Reline, which then melts at 12°C due to strong Cl^-–urea hydrogen bonds [77].

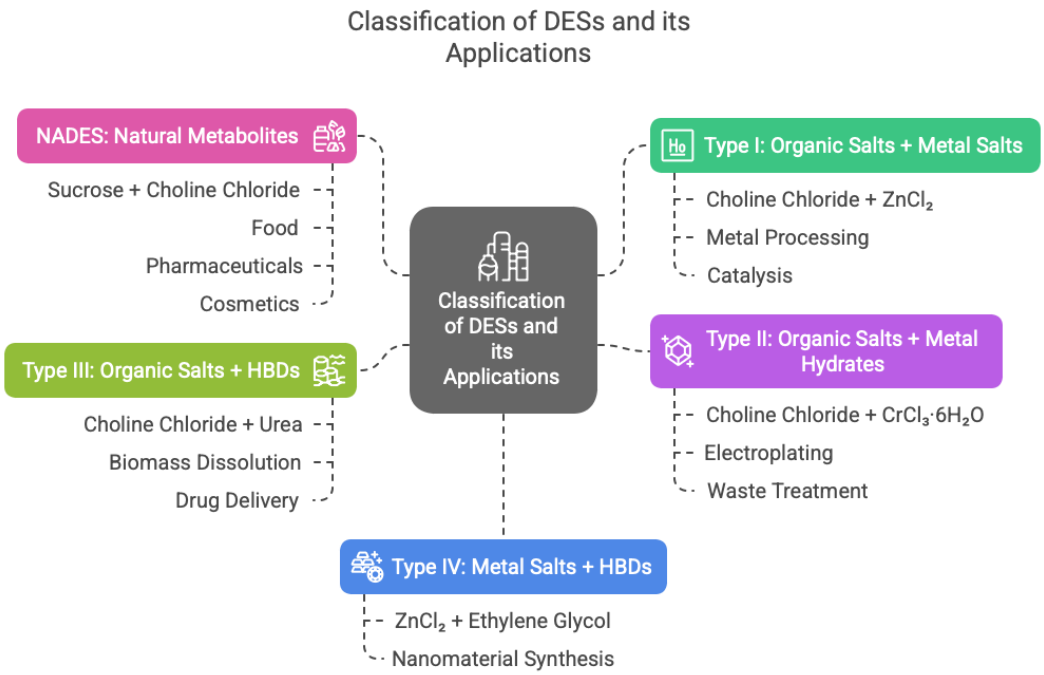


Figure 7: Classification of DESs and its Applications

2.4 Research Gap

The green synthesis of Quinoline derivatives has attracted significant attention due to their large applications in pharmaceutical products and chemicals. The recent process of green chemistry has launched sustainable approaches, such as using DESs, biological and microwave assisted synthesis. Out of these, DESs stands out with ecological nature, adjustable properties and their ability to improve their reaction dynamics. Despite their promises, the **DESs application in the green synthesis of Quinoline derivatives remains underexplored.**

This research gap highlights the ability to study the DESs as solvents to synthesize quinoline derivatives. Potential advantages include: -

- Enhanced reaction efficiency: can improve productivity and selection for difficult quinoline derivatives
- Environmental sustainability: reduces dependence on toxic solvents in accordance with the principles of green chemistry
- Cost efficiency: The use of ingredients of renewable energy or derivatives can reduce production costs

This project aims to address this gap and lead to more sustainable and effective methods to synthesize quinoline derivatives.

2.5 Objectives of the Study

To address these gaps, the following objectives are proposed in the present work:

1. To critically review and compare conventional synthetic routes for quinoline derivatives with contemporary green chemistry-based methods.
2. To synthesize selected deep eutectic solvents as potential alternative solvents for green synthesis of quinoline, focusing on their preparation and optimization.
3. To optimize the reaction conditions in the synthesis of deep eutectic solvents.
4. To potentially use the synthesized deep eutectic solvents in the synthesis of quinoline derivatives.

CHAPTER 3

EXPERIMENTAL WORK:

Green Synthesis of Quinoline Derivatives Using Deep Eutectic Solvents (Des)

DESs are prepared by mixing hydrogen bond acceptors and hydrogen bond donors (HBA and HBD). Common preparation methods include heating, evaporation, milling and freeze-drying.

3.1 Materials and Methods

The chemical structures of the HBAs and HBD used in this study are shown in Fig. 8. All the chemicals used in this study are purchased from local suppliers and were used as received without additional purifications.

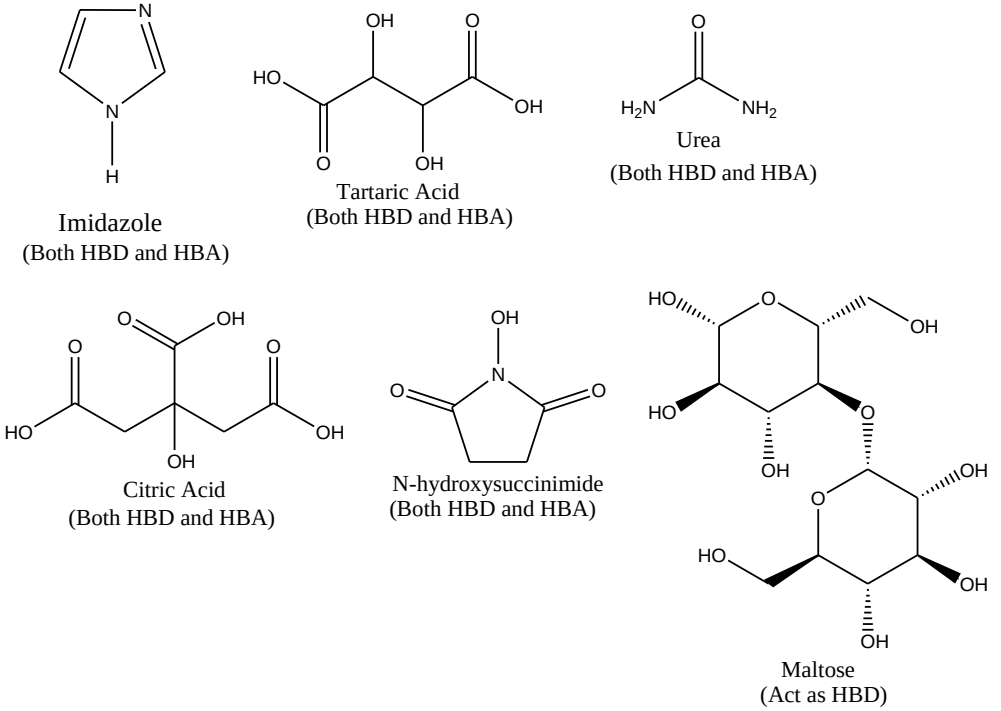


Figure 8: Structures of the HBAs and HBDs used for deep eutectic solvent formation

3.2 Preparation of DES

The method of preparation of the DESs used in this work is based on the earlier reported work. DESs were prepared by weighing the appropriate mass of each component in a vial, which was stirred and heated until a homogeneous liquid was obtained. The DESs were stored in the sealed vial, with parafilm used to help prevent the ingress of moisture. The details of various combinations of prepared DES are given below and summarized in the respective optimization table.

3.2.1 Synthesis of Tartaric acid-Imidazole DES

The Tartaric acid-Imidazole DES was synthesized by carefully weighing out tartaric acid and imidazole according to molar ratios of 1:2, 1:3, and 1:4. For the 1:2 ratio, tartaric acid was weighed 0.150g, and imidazole was weighed 0.136g. Similarly, for 1:3 and 1:4 ratios, the imidazole was weighed 0.204g and 0.272g, respectively. The weighed solid components were quantitatively transferred into separate clean, dry glass vials.

Figure 9: Tartaric acid–imidazole DES prepared via heating and mixing

A magnetic bead was added to each vial, and a magnetic stir bar was introduced. Each vial containing the solid mixture was securely positioned on a heating plate equipped with a temperature controller and a magnetic stirrer set to 500 rpm.

For the 1:2 molar ratio, is heated and stirred at 60°C for 30 minutes.

For the 1:3 molar ratio, is heated and stirred at 60°C for 40 minutes.

For the 1:4 molar ratio mixture was heated and stirred at three different temperatures: 60°C, 80°C and 100°C, each for 60 minutes.

After each heating cycle, the molten mixture was allowed to cool undisturbed to room temperature, forming a homogeneous liquid DES. The resulting cooled liquids were carefully evaluated for yield.

3.2.2 Synthesis of Maltose-Urea DES

The Maltose-Urea DES was synthesized by carefully weighing out maltose and urea according to molar ratios of 1:3, 1:4, and 1:5. For the 1:3 ratio, maltose was weighed 0.342g, and urea was weighed 0.180g. Similarly, for 1:4 and 1:5 ratios, the imidazole was weighed 0.240g and 0.3g, respectively. The weighed solid components were quantitatively transferred into separate clean, dry glass vials.

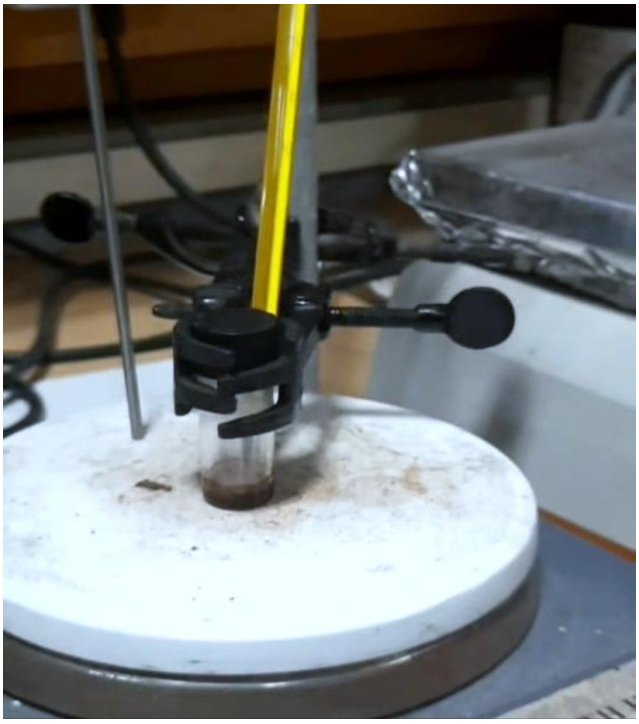


Figure 10: Maltose-urea DES preparation via heating and mixing

A magnetic bead was added to each vial, and a magnetic stir bar was introduced. Each vial containing the solid mixture was securely positioned on a heating plate equipped with a temperature controller and a magnetic stirrer set to 500 rpm.

For the 1:3 molar ratio, is heated and stirred at 60°C for 20 minutes.

For the 1:4 molar ratio, is heated and stirred at 60°C for 30 minutes.

For the 1:5 molar ratio, two syntheses were performed - one with heating and stirring at 90°C for 60 minutes, and the other at 100°C for 60 minutes.

The 1:5 molar ratio mixture was heated and stirred at three different temperatures: 75°C, 90°C, and 100°C, each for 60 minutes.

After each heating cycle, the molten mixture was allowed to cool undisturbed to room temperature, forming a homogeneous liquid DES. The resulting cooled liquids were carefully evaluated for yield.

3.2.3 Synthesis of N-Hydroxysuccinimide-Citric acid DES

The N-hydroxysuccinimide-citric acid was synthesized by carefully weighing out N-hydroxysuccinimide and citric acid according to molar ratios of 1:1 and 1:2. For the 1:1 ratio, citric acid was weighed 0.210g, and N-hydroxysuccinimide was weighed 0.115g. Similarly, for 1:2 ratio, the N-hydroxysuccinimide was weighed 0.230g. The weighed solid components were quantitatively transferred into separate clean, dry glass vials.

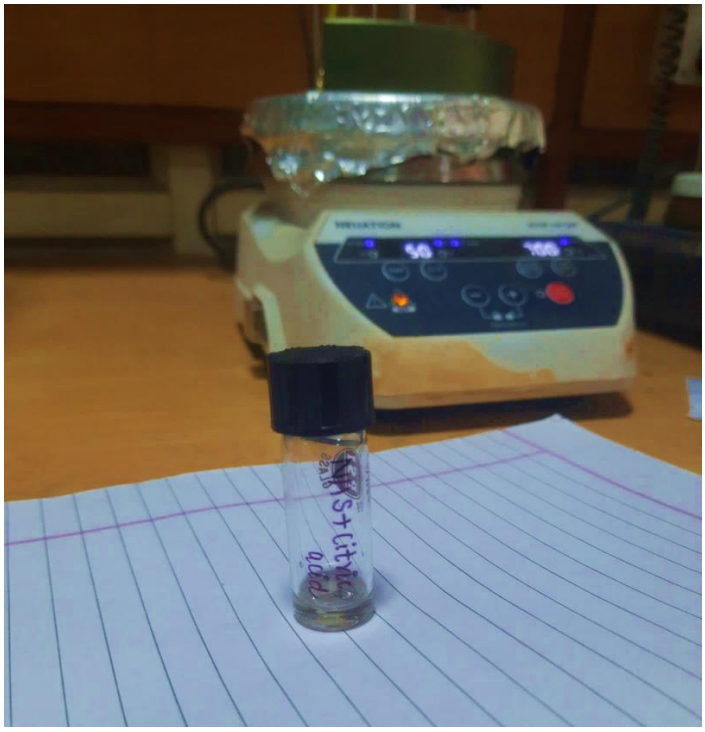


Figure 11: N-Hydroxysuccinimide-Citric acid DES prepared via heating and mixing

A magnetic bead was added to each vial and a magnetic stir bar was introduced. Each vial containing the solid mixture was securely positioned on a heating plate equipped with a temperature controller and a magnetic stirrer set to 500 rpm.

For the 1:1 molar ratio, is heated and stirred at 60°C for 30 minutes.

For the 1:2 molar ratio, two syntheses were performed - one with heating and stirring at 60°C for 60 minutes, and the other at 90°C for 60 minutes.

The 1:2 molar ratio mixture was heated and stirred at two different temperatures: 60°C and 90°C each for 60 minutes.

After each heating cycle, the molten mixture was allowed to cool undisturbed to room temperature, forming a homogeneous liquid DES. The resulting cooled liquids were carefully evaluated for yield.

3.2.4 Synthesis of N-Hydroxysuccinimide-Imidazole DES

The N-hydroxysuccinimide-imidazole was synthesized by carefully weighing out N-hydroxysuccinimide and imidazole according to molar ratios of 1:1 and 1:2. For the 1:1 ratio, N-hydroxysuccinimide was weighed 0.115g, and imidazole was weighed 0.068g. Similarly, for 1:2 ratio, the imidazole was weighed 0.136g. The weighed solid components were quantitatively transferred into separate clean, dry glass vials.

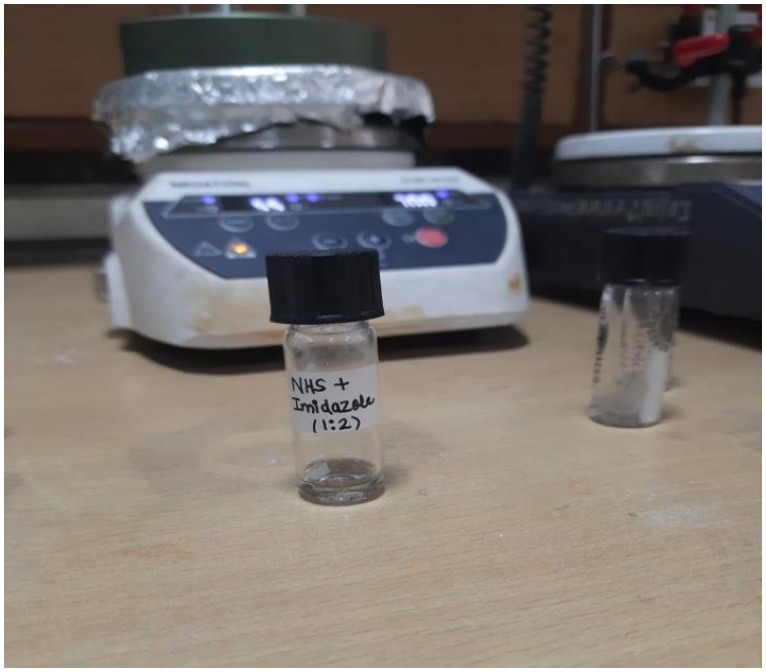


Figure 12: N-Hydroxysuccinimide-imidazole acid DES prepared via heating and mixing

A magnetic bead was added to each vial and a magnetic stir bar was introduced. Each vial containing the solid mixture was securely positioned on a heating plate equipped with a temperature controller and a magnetic stirrer set to 500 rpm.

For the 1:1 molar ratio, is heated and stirred at 60°C for 30 minutes.

For the 1:2 molar ratio, two syntheses were performed - one with heating and stirring at 80°C for 60 minutes, and the other at 120°C for 60 minutes.

After each heating cycle, the molten mixture was allowed to cool undisturbed to room temperature, forming a homogeneous liquid DES. The resulting cooled liquids were carefully evaluated for yield.

3.3 Optimization of DES

The synthesis conditions, including the molar ratio of tartaric acid to imidazole, reaction temperature, and time, were optimized. The investigated parameters are summarized in Table 2.

Table 3 Optimization studies for Tartaric Acid-Imidazole DES

S. No.	Tartaric Acid-Imidazole	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:2	30	300	60	58
2.	1:3	40	300	60	66
3.	1:4	60	300	60	80
4.	1:4	60	600	80	88
5.	1:4	60	700	100	85

The optimization of molar ratio, reaction temperature, and time was carried out for the synthesis of the maltose-urea DES system, as shown in Table 3.

Table 4 Optimization studies for Maltose-Urea DES

S. No.	*Maltose-Urea*	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:3	20	500	60	55
2.	1:4	30	500	60	72
3.	1:5	60	500	75	80
4.	1:5	60	500	90	86
5.	1:5	60	500	100	90

The optimization of molar ratio, reaction temperature, and time was carried out for the synthesis of the N-hydroxysuccinimide-citric acid DES system, as shown in Table 4.

Table 4 Optimization studies for N-hydroxysuccinimide-citric acid DES

S. No.	N-hydroxysuccinimide-citric acid	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:1	30	500	30	55
2.	1:2	60	500	60	72
3.	1:2	60	500	90	89

The optimization of molar ratio, reaction temperature, and time was carried out for the synthesis of the N-hydroxysuccinimide-imidazole DES system, as shown in Table 5.

Table 5 Optimization studies for N-hydroxysuccinimide-imidazole DES

S. No.	N-hydroxysuccinimide-imidazole	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:1	30	500	60	55
2.	1:2	60	500	60	72
3.	1:2	60	600	80	84
4.	1:2	60	600	120	91

3.4 Characterization:

FT-IR

A PerkinElmer FT-IR instrument was used in the ATR mode for FT-IR. The data was collected with a 4 cm 1 resolution with 8 scans per run. Neat samples were introduced on the scanning window at room temperature for scanning.

Thermogravimetric analysis

Thermogravimetric analysis of the DESs was done on the Perkin Elmer instrument. All measurements were carried out at atmospheric pressure. Approximately 10 mg of the sample was weighed in an open aluminum pan, and the temperature increased at 10 K/min. All the samples were analysed in triplicates to ascertain measurement reliability.

CHAPTER 4

RESULTS & DISCUSSION

The optimization table provides valuable insights into the synthesis conditions for four distinct deep eutectic solvents (DESs): Tartaric acid-Imidazole DES, Maltose-Urea DES, N-hydroxysuccinimide-citric acid, and N-hydroxysuccinimide-imidazole DES. The data presented in the table helps in the identification of the optimum conditions for achieving the highest yield of each DES.

Figure 13: Preparation of deep eutectic solvent (DES)

4.1 Tartaric acid-Imidazole DES

Using a molar ratio of 1:4 (tartaric acid to imidazole) and a reaction time of 60 minutes at 80°C, the Tartaric acid–Imidazole DES demonstrated its maximum yield of 88%, according to the experimental results. These circumstances seem to be ideal for maximizing the DES's formation. Interestingly, raising the temperature to 100°C caused the yield to slightly decrease to 85%, suggesting that too much heat may have a detrimental effect on the eutectic mixture's stability or formation process. The use of 1:2 and 1:3 molar ratios produced noticeably lower yields of 58% and 66%, respectively, at a lower temperature of 60°C. This pattern implies that increasing the relative concentration of imidazole is essential for improving the effectiveness of DES synthesis for this system.

4.2 Maltose-Urea DES

According to the results of the experiment, the best conditions for creating the Maltose–Urea DES were a molar ratio of 1:5 (Maltose: Urea), a reaction time of 60

minutes, and a temperature of 100°C. A maximum yield of 90% was obtained under these conditions. This suggests that the efficiency of DES formation is greatly increased by these parameters. Raising the temperature from 60°C to 100°C consistently increased yield, indicating that higher temperatures in this range promote the DES system's formation and stability. The role of urea concentration in promoting DES synthesis was also demonstrated by increasing the yield from 55% to 72% by increasing the urea content from a 1:3 to a 1:4 molar ratio at a fixed temperature of 60°C. The yield significantly improved at all tested temperatures, especially at 100°C, when the ratio was increased to 1:5 and the reaction time was extended. These results highlight how important temperature and molar ratio are for maximizing the production of maltose-urea DES.

4.3 N-Hydroxysuccinimide-Citric acid Deep Eutectic Solvent

At a molar ratio of 1:2 (N-hydroxysuccinimide:citric acid), a temperature of 90°C, and a reaction time of 60 minutes, the synthesis of the N-hydroxysuccinimide–citric acid DES achieved its maximum yield of 89%. These circumstances seem to be the most successful in promoting the best possible DES formation. There was a noticeable trend that the yield increased as the temperature rose, indicating that higher thermal energy improves component interaction and encourages more effective DES formation. For example, the yield at 60°C with the same 1:2 molar ratio was 72%, which was much higher than the 55% yield at 30°C with a 1:1 ratio. This comparison shows that a higher percentage of citric acid and higher temperatures both have a beneficial effect on the synthesis process. All of the data point to how crucial it is to adjust the molar ratio and reaction temperature in order to optimize the yield of the N-hydroxysuccinimide–citric acid DES system.

4.4 N-Hydroxysuccinimide-Imidazole Deep Eutectic Solvent

According to the data collected, the synthesis was carried out at a molar ratio of 1:2 (N-hydroxysuccinimide to imidazole), with a reaction time of 60 minutes and a temperature of 120°C. This resulted in the highest yield (91%) for the N-hydroxysuccinimide–imidazole deep eutectic solvent (DES). In this system, these specific circumstances turned out to be the most advantageous for effective DES formation. It was discovered that a slow increase in temperature greatly increased the yield, which increased from 72% at 60°C to 84% at 80°C and 91% at 120°C. This pattern implies that increased thermal input is essential for enhancing the stability of the DES and fortifying the component-to-component interaction. Additionally, yield increased significantly from 55% to 72% when the molar ratio was increased from 1:1 to 1:2 while maintaining the same temperature and stirring conditions. This indicates the benefit of using a larger percentage of imidazole to maximize DES formation. When combined, the results show that higher temperatures and a higher imidazole ratio are crucial factors for optimizing the yield of the N-hydroxysuccinimide–imidazole deep eutectic solvent.

CHAPTER 5

FUTURE PROSPECTS, CONCLUSION & SOCIAL IMPACT

5.1 Future Prospects

Quinoline derivatives remain an important class of compounds, and the work reported here shows that the derivatives can be accessed with equal or greater efficiency via a greener synthetic method. While substantial progress has been made in recent years, the field remains ripe for innovation, with numerous opportunities to refine existing methodologies and integrate emerging technologies.

The **enzymatic synthesis of quinolines** is a relatively new field, particularly when compared to the many decades of research devoted to non-enzymatic methods. Nonetheless, it offers several compelling advantages. First, quinolines and their derivatives are pharmacologically very important compounds. Second, enzymatic methods provide the selectivity necessary to access the wide variety of quinoline derivatives that might be useful in drug discovery. Finally, these enzymatic methods typically operate under mild conditions and are inherently green-since the enzymes are protein-based, reactions are often conducted in aqueous media, and harmful by-products are minimal. Thus, enzymatic synthesis seems a promising route to take if we wish to develop efficient and clean methods for the synthesis of quinoline derivatives.

Heterogeneous catalysis and nanocatalysis present viable avenues for more environmentally friendly quinoline synthesis. Nanostructured materials can greatly increase catalytic efficiency, selectivity, and reusability because of their large surface area and distinctive physicochemical characteristics. Although issues like waste generation and toxic metal leaching need to be addressed to ensure sustainability, these advantages are essential for large-scale applications. Cleaner, quicker quinoline synthesis is also supported by techniques that use ultrasound and microwaves. These energy-efficient methods improve product quality and reduce reaction times. Although encouraging, there is still a lack of integration with continuous-flow systems. In industrial settings, combining these technologies could improve process control, scalability, and safety.

Eco-friendly synthetic options are further expanded by green solvents such as supercritical fluids, ionic liquids, and deep eutectic mixtures. They are biodegradable and non-toxic, offer distinct solvation environments, and, when combined with green energy inputs like light or ultrasound, may uncover novel reaction pathways. Green chemistry metrics and life cycle assessments (LCA) are crucial for verifying the sustainability of these innovations. These resources aid in assessing the practical viability of scale-up as well as the environmental impact. In the end, creating effective,

scalable, and genuinely environmentally friendly synthetic processes will require interdisciplinary cooperation between chemists, engineers, and data scientists.

- Future directions include:

(i) Creating durable green reagents and recyclable catalysts
(ii) expanding using automated synthesis and continuous-flow systems.
(iii) Optimizing synthetic routes through the use of AI and computational models.
(iv) establishing partnerships between academia, industry, and regulators to ensure adherence to environmental standards.

5.2 Conclusion

- In medicinal and materials chemistry, quinoline-based compounds are essential because they are the building blocks of numerous medications (such as antimalarial, anticancer, antibacterial, and antiviral ones) and functional materials with sophisticated electronic and optical capabilities.
- With increasing industrial demand, traditional synthesis methods raise significant safety, environmental, and ethical concerns because they rely on toxic chemicals, harsh conditions, and solvents.
- This thesis highlights contemporary and environmentally friendly techniques for the synthesis of quinoline derivatives.
- Green chemistry promotes safer production methods and conscientious consumption patterns, which are essential to true sustainability, which calls for both scientific and societal changes.
- Despite advancements, difficulties still exist:

(i) Numerous techniques are still in the experimental stage and have not yet been refined for widespread use.
(ii) Although microwave and ultrasonic technologies work well in the lab, their safe and reliable industrial application necessitates creative setups.

5.3 Social Impact

There are significant social consequences towards exploring sustainable quinoline derivative synthesis techniques. Toxic reagents and dangerous byproducts are frequently used in conventional synthetic pathways, which can have adverse effects on ecological systems and human health. In order to make chemical processes safer and cleaner, this research promotes the use of greener methods like biological catalysts, nano-based systems, and non-toxic solvent substitutes. In addition to protecting employees from chemical exposure, these techniques also lessen pollution and the harm that industrial waste causes to the environment. Since many quinoline-based compounds are essential parts of therapeutic agents, making their production more sustainable helps achieve public health objectives by guaranteeing safer and more moral pharmaceutical production. Adopting green chemistry in industrial practice can, on a larger scale, inspire interdisciplinary efforts on environmental and social well-being, foster

innovation in line with global sustainability targets, and shape more responsible policies. The study's conclusions thus lend credence to the long-term goal of a healthier planet and a more responsible scientific community.

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