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ANALYSIS OF CONTEMPORARY METHODS FOR THE SYNTHESIS OF QUINOLINE DERIVATIVES

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ABSTRACT

Quinoline derivatives have attracted a lot of interest because of their numerous uses in agrochemicals, materials science, and medicines. Modern techniques for synthesising quinoline derivatives have developed recently, providing more effective, long-lasting, and focused pathways. These techniques provide excellent yields under softer circumstances by using contemporary catalytic procedures such microwave-assisted synthesis, metal-catalyzed cyclizations, and MCRs. To reduce harmful consequences, transition metal catalysts such as palladium, copper, and gold have been used in combination with green chemistry principles. Moreover, improved atom economy and functional group tolerance have been made possible by the invention of organ catalysts and photocatalysis. The conventional trial-and-error method of quinoline synthesis is being greatly reduced by the use of computational methods and machine learning models to forecast reaction paths and optimise settings. With an emphasis on their benefits over traditional methods in terms of sustainability, yield, and scope, this study seeks to give an overview of these modern approaches while highlighting the obstacles that still need to be overcome in order to increase substrate variety and scalability. Future developments in the large-scale synthesis of quinoline derivatives for industrial purposes are made possible by the investigation of these techniques.

INTRODUCTION

A key building block in organic chemistry is quinoline, a heterocyclic aromatic molecule with a fused double-ring structure made up of a pyridine and benzene ring. It is essential to the creation of a wide range of physiologically active molecules, which makes it a fundamental component of research in the fields of medicine, agriculture, and material science. Due to the pharmacological activity of quinoline derivatives, including their anti-viral, anti-inflammatory, anti-bacterial, anti-malarial, and anti-cancer effects, research on these compounds has increased dramatically. Moreover, quinoline derivatives are used as organic synthesis intermediates, ligands in coordination chemistry, and in the creation of colours.

The processes used to synthesise derivatives of quinolines have changed dramatically throughout the years. Even though they work well, traditional techniques like the Skraup, Doebner, and Friedländer syntheses have drawbacks such severe reaction conditions, poor selectivity, and hazardous byproducts that might harm the environment. Green chemistry ideas have been

included into modern synthetic methodologies due to the growing demand for more ecologically friendly, selective, and efficient synthetic procedures. These developments have made it easier to synthesise a variety of quinoline derivatives and have also improved control over functional group tolerance and regioselectivity.

It is impossible to exaggerate the importance of quinoline derivatives in medical chemistry. Because of their well-established range of medicinal uses, molecules containing quinolin are prime prospects for drug development and discovery. For example, quinine is a naturally occurring alkaloid that has been used for centuries as an anti-malarial drug. Chloroquine and hydroxychloroquine are two more noteworthy quinoline-based medications that are well-known for their anti-inflammatory and anti-malarial qualities. Within the field of oncology, quinoline derivatives, including camptothecin and its analogues, have demonstrated exceptional effectiveness as topoisomerase inhibitors, laying the groundwork for the creation of anti-cancer medications.

The capacity of quinoline derivatives to interact with a wide range of biological targets, such as enzymes, receptors, and DNA, is primarily responsible for their biological actions. Quinoline derivatives are extremely beneficial in the generation of medications that target numerous disease pathways due to their variety in target binding. Moreover, quinoline derivatives have proven to be effective against newly developing infectious illnesses, such as hepatitis, HIV, and, more recently, SARS-CoV-2, highlighting their significance in the creation of broad-spectrum antiviral drugs.

Even though they are fundamental, traditional synthesis approaches for quinoline derivatives sometimes call for unfavourable circumstances such high temperatures, strong acids, and extended reaction durations. The restricted spectrum of substrates exhibited by these techniques limits their usefulness in the synthesis of complex, functionalised derivatives of quinolines. One of the first techniques for synthesising quinoline, the Skraup synthesis, for instance, entails oxidising aniline derivatives with glycerol and sulphuric acid in the presence of a potent oxidising agent, such nitrobenzene. Despite being dependable, the process is infamous for producing ecologically dangerous byproducts and using poisonous chemicals.

Comparably, low yields and poor regioselectivity are frequently encountered in the Friedländer synthesis, which entails the condensation of 2-aminobenzaldehyde with a carbonyl molecule. Another conventional method, the Doebner synthesis, has limitations due to the need for activated methylene compounds, which limits the range of quinoline derivatives that may be obtained. The quest for substitute synthetic approaches that may meet these constraints while upholding the ideals of sustainable and green chemistry has been spurred by these limits.

Current quinoline synthesis techniques have been developed mostly because to the trend towards green chemistry. The use of renewable feedstocks, energy efficiency, and a decrease in harmful compounds are the main focusses of green chemistry. Organocatalysis has shown promise in this

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area as a method for synthesising derivatives of quinolines. Small organic compounds known as "organocatalysts" provide a number of benefits over transition metals in chemical processes. These advantages include low toxicity, simplicity of handling, and recyclability.

The production of quinoline derivatives has also made use of photocatalysis, another green technique. Light energy is used in photocatalytic processes to activate catalysts, which allows quinoline compounds to develop under moderate circumstances. Because it can function in ambient settings and has a high atom economy, this approach is especially appealing as a sustainable substitute for conventional thermal technologies.

The efficiency of quinoline synthesis has been significantly improved by the use of machine learning and computational approaches into synthetic chemistry. Chemists can reduce the requirement for trial-and-error experimentation by using predictive models to forecast reaction outcomes and optimise reaction conditions. This strategy minimises resource usage while simultaneously accelerating the development of novel quinoline compounds, in keeping with sustainability standards.

Aniline + Glycerol → Quinoline (via acid catalysis)

$$C_6H_5NH_2 + HOCH_2CHOHCHHOH_2 \rightarrow C_9H_7\ N + H_2O$$

Doebner-Miller Reaction
Aniline + Cinnamic Acid → 2-Substituted Quinoline

$$C_6H_5NH_2 + C_6H_5CH - CHCOOH \rightarrow C_9H_7\ N + H_2O$$

Friedländer Synthesis
2-Aminobenzaldehyde + Acetone → Quinoline Derivative

$$C_6H_4(NH_2)CHO + CH_3COCH_3 \rightarrow C_9H_7\ N + H_2O$$

Povarov Reaction
Aniline + Alkene + Aldehyde → Quinoline Derivative

$$C_6H_5NH_2 + RCH - CH_2 + R'CHO \rightarrow C_9H_7\ N + H_2O$$

Microwave-Assisted Quinoline Synthesis
Aromatic Amine + Ketone → Quinoline

$$C_6H_5NH_2 + R_2CO \rightarrow C_9H_7\ N + H_2O$$

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Skraup Synthesis with Substituents

Substituted Aniline + Glycerol - Substituted Quinoline

$$C_6H_4XNH_2 + HOCH_2CHOHCHHOH_2OH \rightarrow C_9H_6XN + H_2O$$

Owing to their wide biological activity and chemical characteristics, quinoline derivatives are important in a number of sectors, including materials science, agrochemicals, and medicines. Thus, organic chemistry has spent decades focussing on the synthesis of quinoline derivatives. While conventional techniques like Skraup, Doebner-Miller, and Friedländer syntheses are still often employed, more modern techniques have evolved to overcome their shortcomings, such as microwave-assisted reactions and green chemistry approaches. Four major components of the synthesis of quinoline derivatives will be examined in this analysis: catalysts, reaction conditions, yields, and the environmental effect of different techniques.

A comparison of several catalysts and reaction conditions is shown in Table 1, which highlights the significance of catalytic agents in influencing the yield and efficiency of quinoline synthesis. Utilising ferric sulphate (FeSO4) and concentrated sulphuric acid (H_2SO_4), the Skraup synthesis yields a high percentage (70–80%) but requires severe conditions, such as extreme temperatures (180°C) and prolonged reaction durations (up to 6 hours). Because of the caustic and dangerous character of the reagents, these extreme circumstances restrict their application in large-scale or environmentally aware enterprises.

Table 1: Catalysts and Reaction Conditions for Quinoline Synthesis

Method	**Catalyst**	**Reaction Conditions**	**Temperature (°C)**	**Time (h)**	**Yield (%)**
Skraup Synthesis	Conc. H_2SO_4, $FeSO_4$	Aromatic amines + glycerol	180	5	70-80
Doebner-Miller	Pyridine, AcOH	Aniline + α,β-unsat. acids	130	8	60-75
Friedländer	$ZnCl_2$, EtOH	2-aminobenzaldehyde + ketone	100	10	50-65
Povarov Reaction	$BF_3 \cdot OEt_2$	Aniline + alkene + aldehyde	RT	12	55-70
Microwave-Assisted	None	Aromatic amines + ketones	150	0.5	80-90

Table 2: Reagents Used in Various Quinoline Derivative Syntheses

Method	**Starting Material 1**	**Starting Material 2**	**Additional Reagents**
Skraup Synthesis	Aniline	Glycerol	H_2SO_4, $FeSO_4$
Doebner-Miller	Aniline	Cinnamic acid	Pyridine, AcOH
Friedländer	2-aminobenzaldehyde	Acetone	$ZnCl_2$, EtOH

Povarov Reaction	Aniline	Styrene	$BF_3 \cdot OEt_2$
Microwave-Assisted	2-aminobenzophenone	Cyclohexanone	None

Table 3: Quinoline Derivatives Synthesized Using Modern Methods

Derivative Name	Method Used	Reaction Time (h)	Yield (%)	Purity (%)
2-Methylquinoline	Skraup Synthesis	6	72	95
4-Hydroxyquinoline	Doebner-Miller	8	68	90
3-Benzoylquinoline	Friedländer	12	62	92
6-Chloroquinoline	Povarov Reaction	5	70	88
7-Methoxyquinoline	Microwave-Assisted	0.5	85	98

Table 4: Comparative Analysis of Quinoline Synthesis Methods

Method	Reaction Time (h)	Temperature (°C)	Yield (%)	Environmental Impact
Skraup Synthesis	6	180	70-80	High (use of strong acids)
Doebner-Miller	8	130	60-75	Moderate
Friedländer	10	100	50-65	Moderate
Povarov Reaction	12	RT	55-70	Low
Microwave-Assisted	0.5	150	80-90	Low

Lower temperatures (130°C) and a longer reaction time (8 hours) are necessary for the Doebner-Miller synthesis, which is more selective towards certain quinoline derivatives and uses pyridine and acetic acid (AcOH) as catalysts. However, the method's middling yields (60–75%) suggest a trade-off between efficiency and the mild reaction conditions. Under milder circumstances (100°C), the Friedländer technique, which uses zinc chloride ($ZnCl_2$) in ethanol, offers similar yields (50–65%). However, because of its lengthy reaction time (10 hours), it is not as ideal for industrial applications that demand quick throughput.

One notable feature of the Povarov reaction is that it may occur at room temperature and is catalysed by boron trifluoride etherate ($BF3_3 \cdot OEt_2$). Nevertheless, the yield (55-70%) is not much higher than with conventional procedures, and the reaction time is prolonged (12 hours). The gentler circumstances make this approach attractive for the synthesis of some quinoline derivatives, even with its moderate efficiency.

The yield and reaction time of the microwave-assisted synthesis, on the other hand, are significantly improved. This technology has a low environmental effect and delivers high yields (80-90%) when it operates at 150°C for only 30 minutes. One of the main benefits of microwave-assisted synthesis is that it doesn't require any extra catalysts, which makes it an effective method for producing quinoline derivatives quickly and sustainably.

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Table 2 offers information about the range of substrates that the different quinoline derivative synthesis techniques can employ. Aniline and glycerol are the initial ingredients used in the Skraup synthesis, and sulphuric acid serves as a catalyst and a dehydrator. Although this process works well for producing simple quinoline compounds, it cannot be used for more complicated or sensitive substrates due to its severe conditions.

Aniline and α,β-unsaturated acids (such cinnamic acid) are used as starting materials in the Doebner-Miller synthesis, which provides a greater range of substrates for the addition of functional groups to the quinoline ring. Although 2-substituted quinolines may be synthesised selectively using this approach, the purification procedure becomes more complicated due to the use of acetic acid and pyridine as reagents.

Friedländer synthesis provides a more flexible method for generating quinoline derivatives with different substitution patterns. It makes use of 2-aminobenzaldehyde and ketones. Because of its great adaptability to various aldehyde and ketone combinations, this approach may be used to produce a wide range of quinoline structures. However, its practical applicability is limited by the low yields and long response times.

Aniline, alkenes, and aldehydes are used in the Povarov reaction, which has the special benefit of enabling the simultaneous creation of two bonds in a single step. This one-pot approach is less effective than more recent techniques due to its low yields and lengthy reaction periods, but it is perfect for creating complicated quinoline derivatives with several substituents.

The most adaptable technique is microwave-assisted synthesis, which can handle a wide range of aromatic amines and ketones without the need for harsh chemicals or catalysts. Microwaves offer a quick and effective way to synthesise a variety of quinoline derivatives by drastically reducing reaction times and increasing yields.

The yields of several quinoline derivatives synthesised using the previously mentioned techniques are contrasted in Table 3. Quinoline compounds with moderate to high yields across many techniques include 2-methylquinoline, 4-hydroxyquinoline, and 3-benzoylquinoline. The yield of 2-methylquinoline from the Skraup synthesis is consistently 72%, which indicates that this method works well for basic quinoline derivatives. In a similar vein, the Doebner-Miller reaction yields a respectable amount of 4-hydroxyquinoline (68%) demonstrating its applicability to derivatives of hydroxylated quinoline.

Despite having a broad range of substrates, the Friedländer synthesis delivers smaller amounts of 3-benzoylquinoline (62%), which might be related to the prolonged reaction time and potential side reactions. However, the Povarov reaction shows promise for the selective synthesis of halogenated quinoline derivatives, with a respectable yield (70%) for 6-chloroquinoline.

Microwave-assisted synthesis is the most efficient approach; it produces high yields (85%) of 7-methoxyquinoline in a short reaction time. Because of its effectiveness and quick reaction time, this technology is a desirable choice for large-scale manufacturing, particularly in sectors where speed and sustainability are valued highly.

Each synthesis technique has a different environmental impact, as Table 4 illustrates. Because the reagents used in the Skraup synthesis are corrosive and produce hazardous waste, there is a significant environmental effect associated with the use of concentrated sulphuric acid and ferric sulphate. For this reason, this approach is less advantageous when considering the principles of green chemistry.

Even though they work in gentler environments, the Doebner-Miller and Friedländer procedures nevertheless need cautious handling and disposal of poisonous compounds like zinc chloride and pyridine. Though not as ecologically friendly as other approaches, these techniques are still not as good as more sustainable ones.

Although the Povarov reaction has a very small environmental effect when it uses $BF_3 \cdot OEt_2$ and operates at room temperature, its overall efficiency is decreased by the lengthy reaction time. However, this approach is attractive for some applications where minimising energy usage is important because of its moderate reaction conditions.

The most ecologically benign technique is microwave-assisted synthesis because of its quick reaction times, high yields, and lack of hazardous catalysts or reagents. Using microwaves minimises waste production and lowers energy consumption, which is in line with the green chemistry principles.

CONCLUSION

The analysis's findings show that, although more modern techniques like microwave-assisted synthesis have their benefits in terms of efficiency, yield, and sustainability, more conventional techniques like Skraup and Doebner-Miller syntheses are still useful for some applications. Microwave-assisted synthesis is a valuable tool for the large-scale manufacturing of quinoline derivatives, particularly in sectors focussing on sustainability and green chemistry, because of its quick reaction times, high yields, and minimal environmental effect.

Subsequent investigations in this domain need to concentrate on enhancing current techniques, specifically microwave-assisted synthesis, in order to broaden their suitability for handling more intricate quinoline derivatives and diminish any residual constraints concerning substrate range and scalability. In order to reduce the environmental impact of quinoline synthesis and maintain the viability of these techniques for large-scale commercial applications, it will also be imperative to create more environmentally friendly reagents and catalysts. With the development of modern techniques including multicomponent reactions, metal-catalyzed cyclizations, and microwave-assisted synthesis, the synthesis of quinoline derivatives has undergone substantial change. These technologies overcome the drawbacks of traditional techniques and provide notable benefits in terms of efficiency, selectivity, and sustainability. The field has been further refined by the use of computational methods and green chemistry principles, which present new opportunities for the large-scale synthesis of quinoline derivatives. These cutting-edge

techniques will be essential in helping to realise the full potential of quinoline-based compounds in a variety of sectors as research continues to progress.

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