Advances on Quinoline Derivatives: A Review of Synthesis and Biological Activities

Emmanuel Chinedu Nnadi[2,4], Vivian Ifeoma Okonkwo[2], Chidinma Eucharia Ikwelle[1*], Faith Temitope Elijah[1], Anulika Ruphina Phil-Mba[3], Vivian Chinenye Odo[1], Blessing Ginika Eke[1]

[1]Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Nigeria

[2]Department of Science Laboratory Technology, University of Nigeria, Nsukka, Nigeria

[3]Department of Pharmacy, University of Nigeria, Nsukka, Nigeria

[4]Department of Chemistry, University of Iowa, USA

DOI: https://doi.org/10.51244/IJRSI.2025.120800228

Received: 25 Aug 2025; Accepted: 01 Sep 2025; Published: 25 September 2025

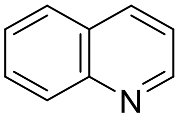
ABSTRACT

Quinoline compounds and their derivatives have a vast distribution in nature coupled with their immense therapeutic potential. Due to the unfading therapeutic benefits of these compounds over the years, a lot of researchers are exploring the synthesis of various derivatives of quinoline which are screened for different therapeutic activities including, anti-malarial, anti-microbial, anti-inflammatory, anti-convulsant, anti-cancer anti-mycobacterial, cardio-protective, neuroprotective activity etc. This review highlights various advances in the synthetic routes and methodology for some quinoline derivatives including Friedlander modified metal-catalyzed reactions, Photo-induced oxidative annulation reaction, Microwave-assisted doebner reaction and their biological properties.

Key Words: Quinolines, Derivatives, Synthetic routes, biological properties

INTRODUCTION

Quinolines are important class of organic compounds characterized with the basic skeleton C_9H_7N and belong to the class of Organic compounds of the hetero aromatic series which are characterized by a double-ring structure composed of compounds of benzene and a nucleus pyridine ring fused at two adjacent carbon atoms as seen in fig. (1) which makes it offer enough opportunities for substitution. Quinolines are also considered to be heterocyclic analogues of naphthalene (1-azanaphthalene) **[1-6].**



1

Fig 1: Structure of Quinoline

Quinolines can be derived from natural sources such as flowering plants, animals, microorganisms and coal tar which is the primary source of quinoline; they occur in different natural products (Cinchona Alkaloids) and pharmacological active substances displaying a broad range of biological activity **[7-8]**. The versatility of the quinoline derivatives has caught the attention of researchers for several decades, owing to their vast distribution in nature and immense therapeutic potential. The interest of this compound class does not appear to fade **[9-11].** Compounds containing quinoline and quinoxaline nucleus have been reported to have various pharmacological activities such as anti-malarial, anti-microbial, anti-inflammatory, anti-convulsant, anticancer, anti-mycobacterial, cardio-protective, neuroprotective activity, etc. **[12-15].** Due to their broad range of bioactivity, quinolines and their derivatives are known as privileged structures in drug discovery programs **[16-19].**

In addition to the medicinal applications, quinolines have been employed in the study of bio-organic and bio-organometallic processes, formation of conjugated molecules and polymers that can be combined to enhance electronic and opto-electronic or non-linear optical properties with excellent mechanical properties **[20-24].** In agriculture, quinolines and their derivatives have been largely beneficial in fighting pests and fungi that attack plants, farm produce and livestock **[25-27].**

The structure determination and structure activity relationship (SAR) studies of these compounds have also resulted in the discovery of newer antimalarial drugs like chloroquine, primaquine and mefloquine **[28-32].** Quinoline on its own has few applications but is considered a privileged molecule because its derivatives have a vast area of application in Medicinal chemistry **[33-35].** Due to their wide spectrum of bioactivities, the scientific communities are continuously looking for more efficient synthetic routes to form quinoline derivatives by improving on the existing routes through optimization of reactions **[36-40].**

A good number of synthetic processes have been developed for various quinoline derivatives including transition metal catalysts, Brønsted acid/base catalysts and non-catalyst synthesis. The well-known synthetic techniques include but are not limited to Friedländer, Pfitzinger, Povarov, Skraup, Doebner and Conrad–Limpach–Knorr synthesis **[41-44].**

Recently, synthesis of quinoline derivatives through multi-component reactions (MCRs) has emerged as an efficient and versatile strategy in organic synthesis giving room for synthesizing complex molecular structures in a single step **[45-49].**

This review focuses on Friedlander Modified Metal-Catalyzed Reactions, Photo-Induced Oxidative Annulation Reaction and Microwave-Assisted Doebner Reaction as these are environmentally friendly synthetic methods **[50].**

Synthetic Approaches Of Quinoline And Its Derivatives

Several approaches have been reported for quinoline synthesis. Some of the oldest and prevalent approaches are Skraup, Doebner-von Miller, Conrad-Limpach-Knorr, Povarov, Riehm, Gould-Jacobs and Combes reactions, which primarily employed aniline as a common reactant in the presence of strong acids, high temperatures, and organic solvents (Fig. 2). However, even though these techniques are quite successful, they are often criticized for their environmental impact since they produce a lot of waste that needs to be disposed of and require a lot of effort to separate the output. In recent years, significant advances have been made in the development of more efficient, environment-friendly, and sustainable methods of synthesizing quinoline. This section reviews recent advancements in quinoline synthesis, emphasizing its reaction pathways.

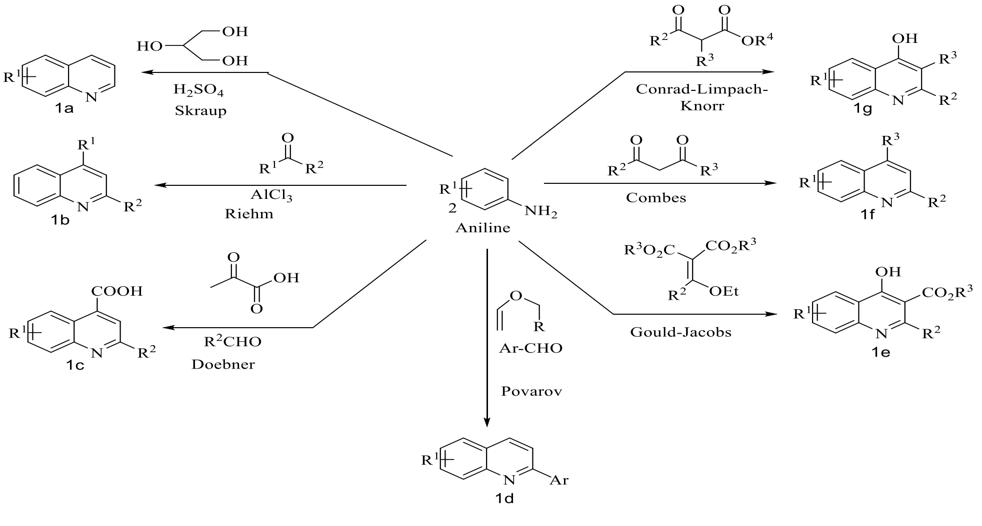
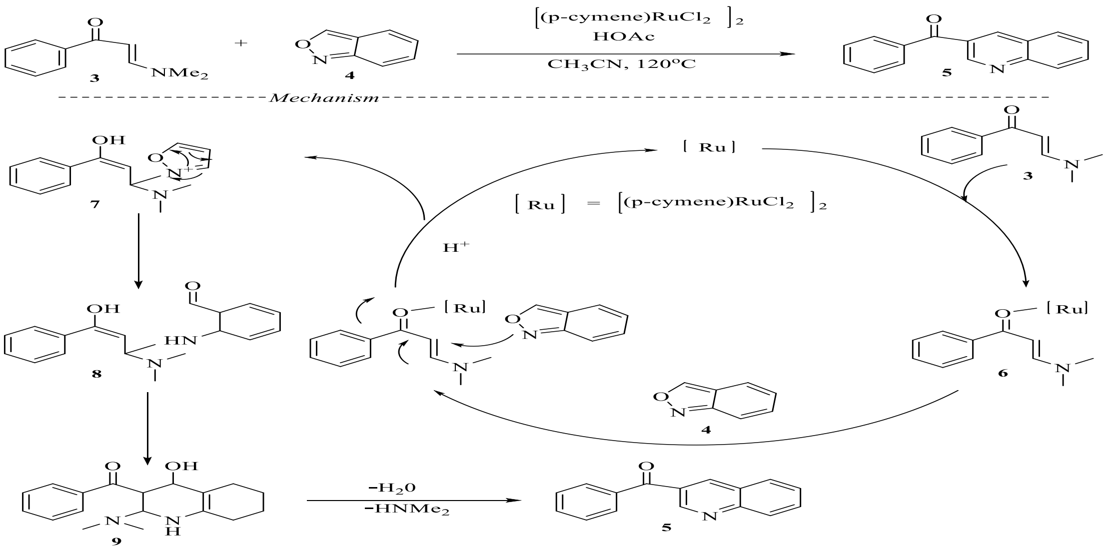


Fig. 2: Traditional methods of synthesizing Quinoline derivatives [51]

Friedlander Modified Metal-Catalyzed Reactions

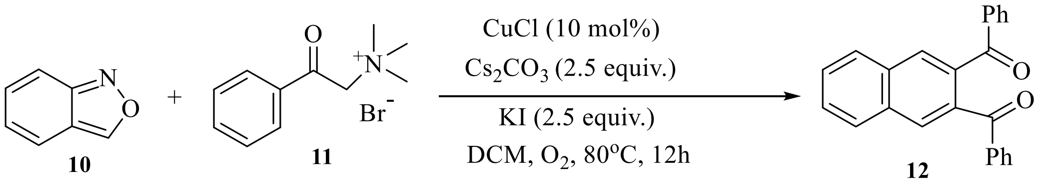
The Friedlander reaction has been one of the traditional methods with a larger number of modifications to cleaner versions because it is one of the most simple and practical ways to develop quinoline compounds **[52].**

In 2022, Xiu Wang *et al.*, reported a Ruthenium-catalyzed aza-Michael addition and intramolecular annulation of enaminones with anthranils to access substituted quinolines (Scheme 1) **[53].** The catalytic process began with the treatment of compound **3** with [(*p*-cymene)$RuCl_2$]$_2$, which resulted in the formation of intermediate **6**. Then, intermediate **6** passes through an aza-Micheal addition-type C-N coupling with anthranil to obtain intermediate **7** and the ruthenium catalyst was released to participate in the next cycle. An intermolecular cyclization process was carried out by intermediate **8** to give rise to intermediate **9**, which undergoes the process of dehydration and deamination to give the final product **5**.



Scheme 1: Synthesis of 3-substituted quinolines by ruthenium-catalyzed annulation of enaminones with anthranils

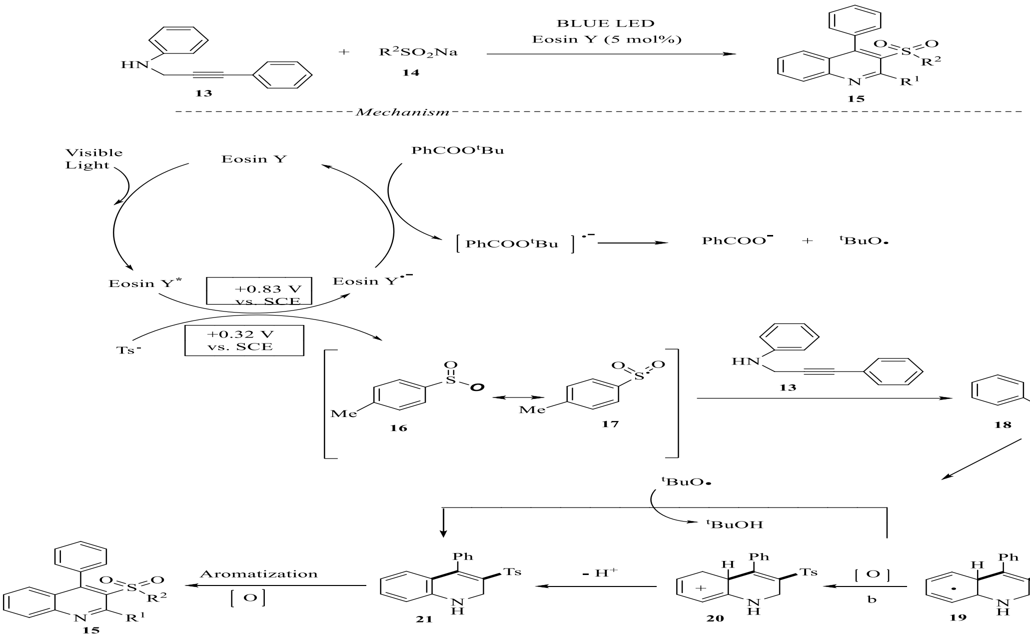
Zou *et al.*, in 2024, reported a copper(I)-catalyzed [4 + 1 + 1] annulation strategy using anthranils and ammonium salts to access 2,3-diaroylquinolines under mild condition (Scheme 2) **[54].** Using only CuCl as the catalyst and molecular oxygen as the terminal oxidant, this transformation showed some noteworthy benefits, such as excellent product yield, wide substrate compatibility, and easily accessible starting materials. An efficient and practical approach to constructing these valuable heterocyclic scaffolds was provided using this methodology, which were otherwise challenging to synthesize using other conventional pathways.



Scheme 2: copper(I)-catalyzed [4 + 1 + 1] annulation to synthesize 2,3-diaroylquinolines

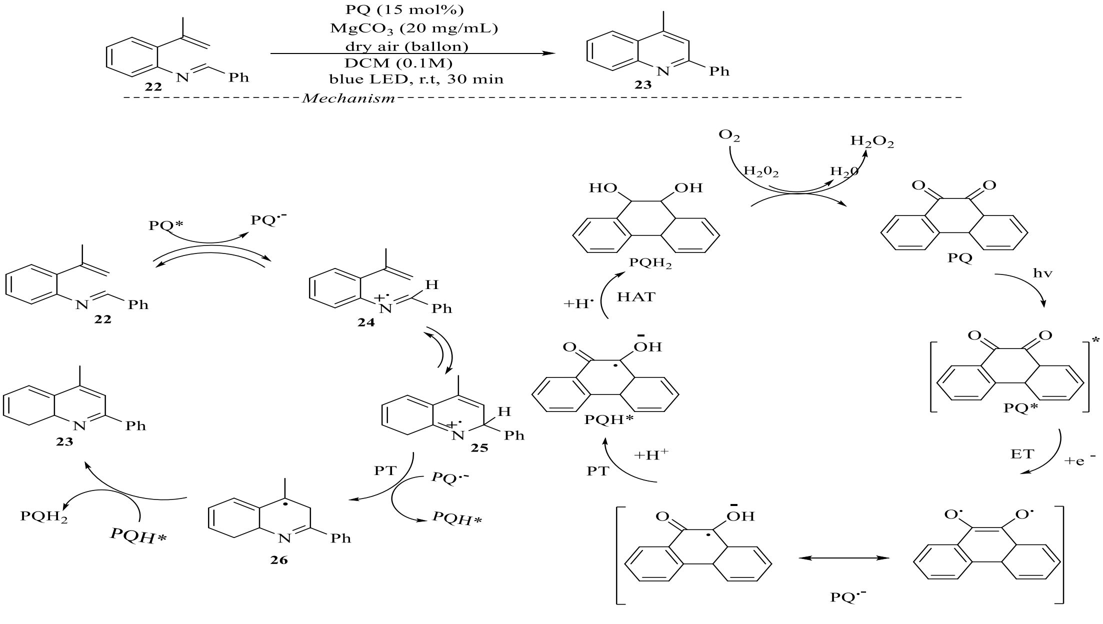
Photo-Induced Oxidative Annulation Reaction

Huang *et al.*, 2020 reported sodium sulfinates as a green inorganic sulfur source to synthesize quinoline derivatives **[55].** Scheme 3 outlines the plausible mechanism which led to the formation of 3-sulfonylquinolines involving N-propargylanilines and sodium sulfinates. Under blue LED irradiation, the photocatalyst, Eosin Y transits to its excited state, which was subsequently deductively quenched by the sulfinyl anion, yielding Eosin $Y^{\cdot -}$ and an oxygen-centered radical **16** that resonated with a sulfonyl radical **17**. The addition of **15** to **13** gave new radical intermediate **18**, followed by an intramolecular radical cyclization to form the cyclized radical intermediate **19**. The *t*-BuO· radical generated from the single electron transfer process between TBPB and Eosin Y$^{\cdot-}$ abstracted a hydrogen atom from **19** to afford the 1,2-dihydroquinoline **20** and *t*-BuOH. Intermediate **19** was oxidized to the corresponding cyclohexadienyl cation **20**, which was transferred to **21** after deprotonation. Finally, an aromatization process of **21** was executed smoothly to construct the target product **15**.



Scheme 3: Visible-light promoted metal-free synthesis of 3-sulfonylquinolines

An efficient and sustainable approach for the synthesis of polysubstituted quinolines through the electrocyclization of 2-vinylarylimines which was visible-light-excited to give 9,10-phenanthrenequinone (PQ*) was developed by Talvitie et al., in 2022 (Scheme 4) **[56].** The process involved the use of $MgCO_3$ as an additive in DCM and after being excited to its triple state, PQ* induced a single-electron transfer (SET) from 2-vinylarylimine **22**. This reaction generated a radical cation **24** that cyclized to a dihydroquinoline cation radical **25**. Then, the radical anion removed an acidic proton, providing an intermediate **26**. Finally, the process of hydrogen-atom (HAT) formed the quinoline product **23**, and 9,10-phenanthrenequinone was regenerated by molecular oxygen.

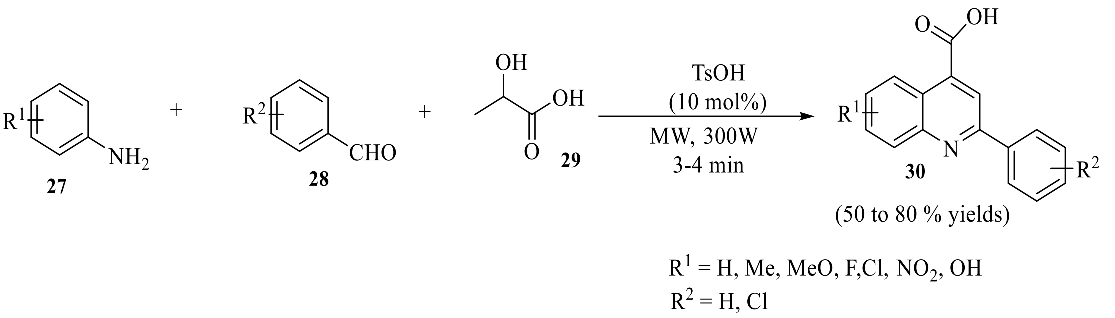


Scheme 4: Phenanthrenequinone-sensitized photocatalytic synthesis of polysubstituted quinolines from 2-vinylarylimines

Microwave-Assisted Doebner Reaction

Transition-metals are interesting catalysts in quinoline synthesis showing several advantages when compared with traditional non-catalytic methods **[57-58].** However, metal catalyzed reactions could be disadvantageous in the preparation of pharmaceutical products due to potential metal residues in the final products. Consequently, other approaches have been explored by researchers, one of them is the replacement of transition-metal catalysts with less toxic and more environmentally friendly organocatalysts **[59-60].**

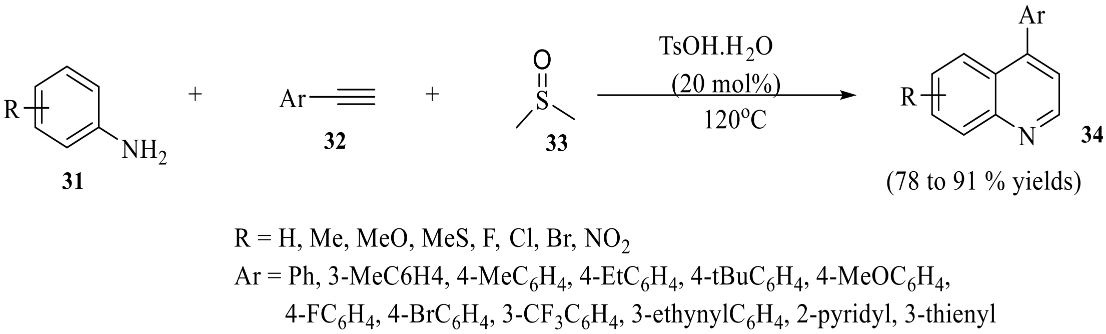
Patel *et al.*, 2020 reported a one-pot three component synthesis of 4-carboxyquinoline derivatives using *p*-toluensulfonic acid (TsOH) catalyst under MW irradiation **[61].** Optimal conditions were achieved with 10 mol% TsOH and 300W MW for 3–4 min. Mechanistically, the imine was formed between aniline and aldehyde and CSA acted as a promoter of the subsequent [4 + 2] cycloaddition with the alkyne. The results obtained in the work concluded that imines with electron donating groups and arylalkynes with electron withdrawing groups favored the synthesis of 4-arylated quinolines.



R^1 = H, Me, MeO, F,Cl, NO_2, OH
R^2 = H, Cl

Scheme 5: Doebner reaction catalyzed by TsOH under microwave irradiation [61]

The lack of sustainable and less toxic methods for the synthesis of quinolines encouraged Faraz et al. to develop a new eco-friendly and transition metal-free method by using TsOH.H$_2$O as catalyst **[62].** 4-Arylquinolines were obtained in a three-component one-pot synthesis using arylamines, arylacetylenes and dimethylsulfoxide (DMSO), in the presence of 20 mol% of TsOH.H$_2$O. A variety of differently substituted arylacetylenes were tested under the optimal conditions. It was observed that all reactions underwent well with good to high yields of the final products (78 - 91 %), independently of their substituent.



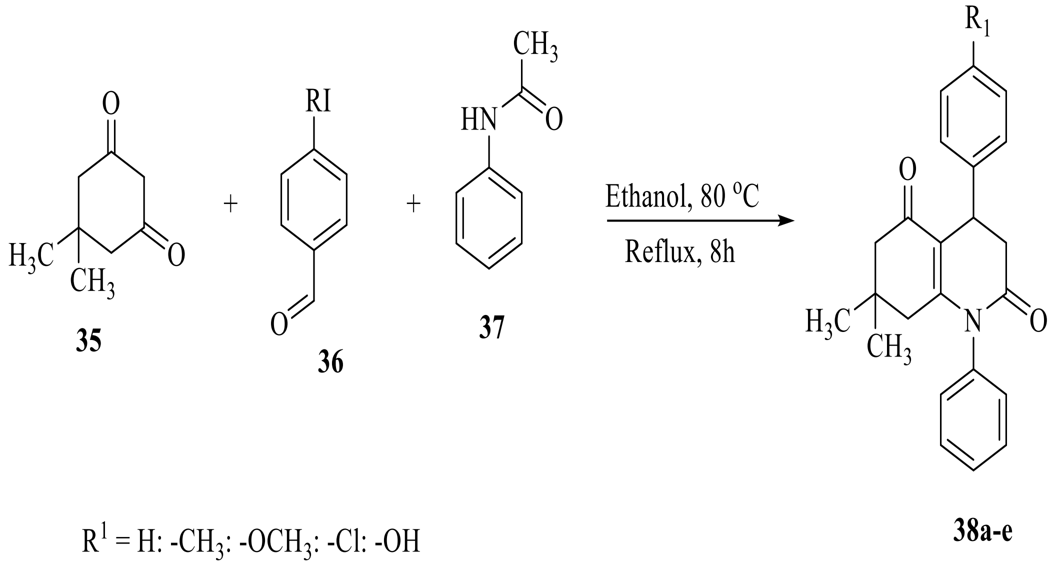
R = H, Me, MeO, MeS, F, Cl, Br, NO_2
Ar = Ph, 3-MeC6H4, 4-MeC_6H_4, 4-EtC_6H_4, 4-tBuC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 3-$CF_3C_6H_4$, 3-ethynylC_6H_4, 2-pyridyl, 3-thienyl

Scheme 6: Reaction of substituted anilines, arylacetylenes and DMSO catalyzed by TsOH

Biological Activities Of Quinoline

Antimicrobial Activity

Rao *et al.*, (2024) reported a one-pot synthesis, characterization, and antimicrobial activity of novel Quinolines. A reaction mixture of 5,5-dimethylcyclohexane-1,3-dione **35,** aromatic substituted benzaldehyde **36**, and *N*-phenylacetamide hydrate **37** was heated in 50mL of ethanol for 8 hours and monitored using TLC for completion. Upon completion, the crude products were recrystallized using ethanol to obtain the target product **38** (Scheme 7) **[63].**



Scheme 7: Synthetic route of quinoline derivatives.

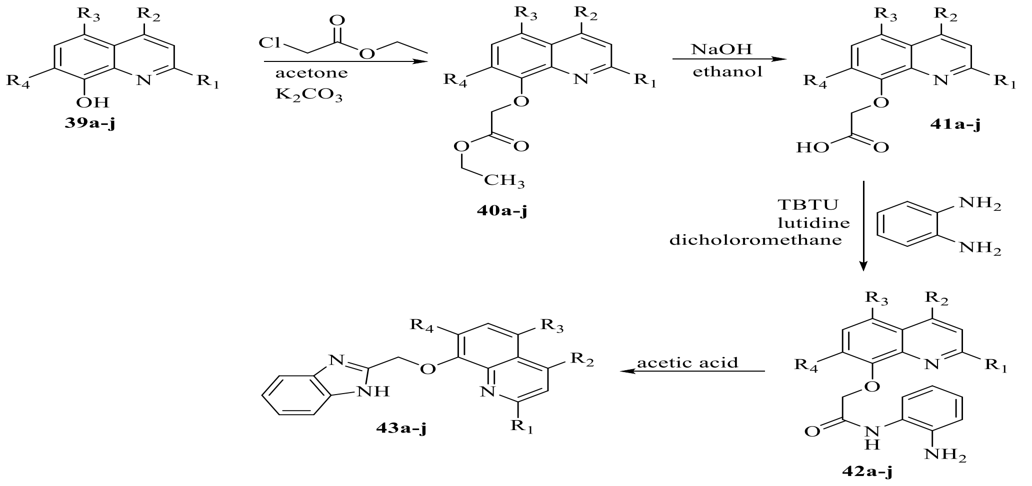
The synthesized compounds were screened against *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus fumigatus*, and *Candida albicans* as fungal strains and *Enterobacter cloacae*, *Staphylococcus haemolyticus*, *Bacillus cereus*, and *Staphylococcus aureus* as bacterial strains for their antimicrobial activity using the disc diffusion assay. The results showed that compound **38d** exhibited the lowest inhibition among all bacterial strains (Table 1), while compounds **38a, 38b, 38c,** and **38e** exhibited the highest inhibition for all strains when compared to the reference drug, ciprofloxacin. Against the fungal strains, compound **38a** exhibited the lowest activity, while compounds **38d** and **38e** exhibited the maximum antifungal activity against all strains when compared to fluconazole.

Table 1: Antibacterial activity of quinoline derivatives (38a-e)

S. No.	Bacterial	Zone of inhibition in mm					
		38a	38b	38c	38d	38e	Control (Dimethyl sulphoxide)
1	*Enterobacter cloacae*	13	12	11	10	12	16
2	*Staphylococus Haemolytics*	10	9	10	8	10	17
3	*Bacillus cereus*	11	10	11	9	11	16
4	*Staphylococcus aureus*	12	11	10	8	10	19

Ref: Ciprofloxacin

Recently, more quinoline derivatives were synthesized by Prashanth, *et al., in* 2025, they reported the multi-step synthesis of 2-(quinolin-8-yloxy) acetate analogs **(43a-j)** by the esterification of quinolin-8-ol derivatives **(39a-j)** with ethyl chloroacetate in the presence of potassium carbonate and dry acetone as solvent. This afforded 2-(quinolin-8-yloxy) acetic acid ethyl esters **(40a-j),** which on further refluxing with sodium hydroxide in ethanol yielded 2-(quinolin-8-yloxy) acetic acids **(41a–j) [64].** Subsequently, compounds **41a-j** were further coupled with 1,2-diaminobenzene using TBTU (o-(benzotriazol-1-yl)- *N,N,N',N'*-tetramethyl aminium tetrafluoroborate in the presence of dichloromethane as solvent and lutidine as base, to afford 2-[2-(quinolin-8-yloxy) aceto] amino anilines **(42a-j)**. On cyclization of compounds **42a-j** with acetic acid, the target products **(43a-j)** were obtained.

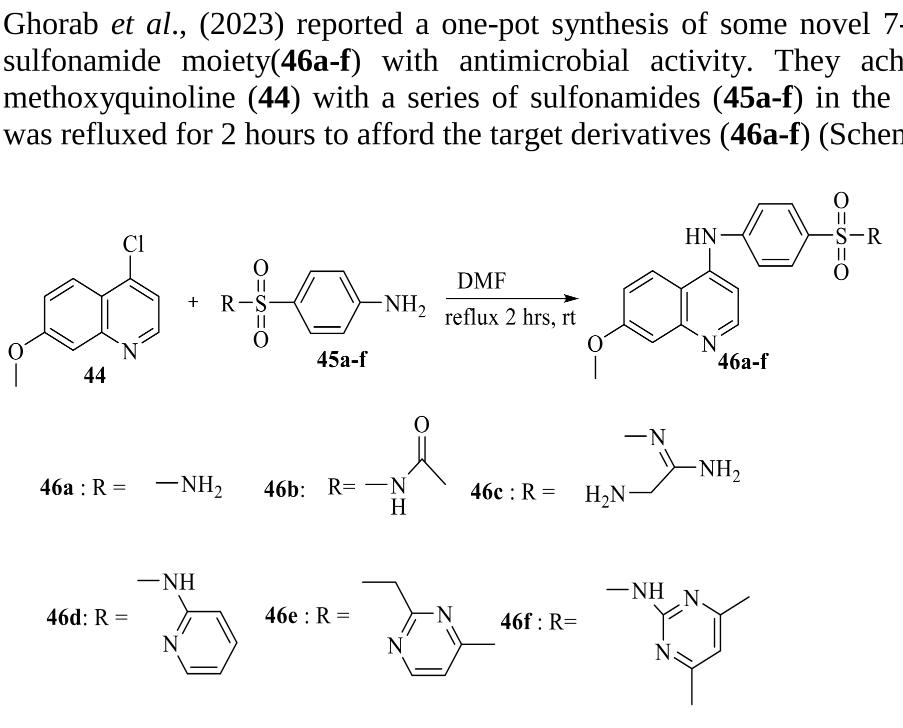


43a = R_1=R_2=R_3=R_4= H
43b = R_1=CH_3, R_2=R_3=R_4 = H
43c = R_2=CH_3, R_1=R_3=R_4 = H
43d = R_3=NO_2, R_1=R_2=R_4 = H
43e = R_3=Cl, R_1=R_2=R_4 = H
43f = R_4=Br, R_1=R_2=D_3 = H
43g = R_2=Br, R_1=R_3=R_4 = H
43h =R_3=Cl, R_4=I, R_1=R_2 =H
43i =R_3=R_4=Br, R_1=R_2 = H
43j = R_3=R_4=I, R_1=R_2 = H

Scheme 8: Synthesis of 8-((1*H*-benzo[*d*]imidazol-2-yl)methoxy) quinoline analogs (43a-j)

The synthesized compounds were subjected to antibacterial activity using five gram-positive bacterial strains *(Methicillin-resistant Staphylococcus aureus, Staphylococcus simulans, Staphylococcus epidermidis, Staphylococcus aureus, and Enterococcus faecalis)* and five gram-negative strains *(Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, and Salmonella typhi).* Results showed that eight of the derivatives are active with inhibition zones against both gram-positive and gram-negative bacteria (8-31 mm), comparable to those of vancomycin and ciprofloxacin which were positive controls and DMSO as negative control. Compound **43i** showed better activity against all gram-positive and four gram-negative bacteria. Compounds **43e, 43g, and 43i** inhibited gram-negative bacteria *E. coli* and *P. aeruginosa* better than others, while compounds **43f, 43d**, and **43j** showed good inhibition activity against *S. aureus* and *S. aureus* MRSA.

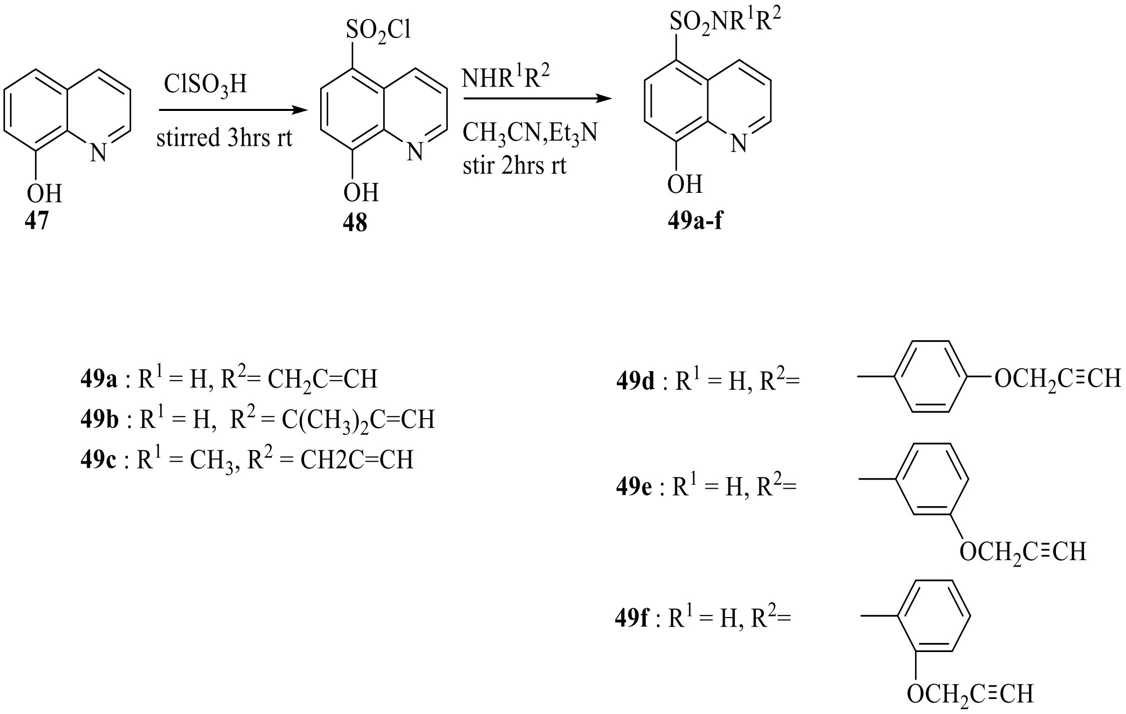
Ghorab *et al.*, (2023) reported a one-pot synthesis of some novel 7-methoxyquinoline derivatives bearing a sulfonamide moiety(**46a-f**) with antimicrobial activity. They achieved this by reacting to 4-chloro-7-methoxyquinoline (**44**) with a series of sulfonamides (**45a-f**) in the presence of DMF. The reaction mixture was refluxed for 2 hours to afford the target derivatives (**46a-f**) (Scheme 32) **[65].**



Scheme 9: Synthesis of novel 7-methoxyquinoline derivatives bearing sulfonamide moiety

The synthesized compounds (**46a-e**) were screened for their antimicrobial potential against *E. coli, P. aeruginosa, S. aureus, B. subtilis, C. albicans,* and *C. neoformans* and compared with a reference standard drug, amoxicillin/clavulanic acid. The results revealed that compound **46f,** bearing sulfamethazine, had the highest effect on most of the tested bacterial and fungal strains when compared to the other derivatives. Compounds **46c** and **46d** displayed moderate antimicrobial activity against the test bacteria and fungi.

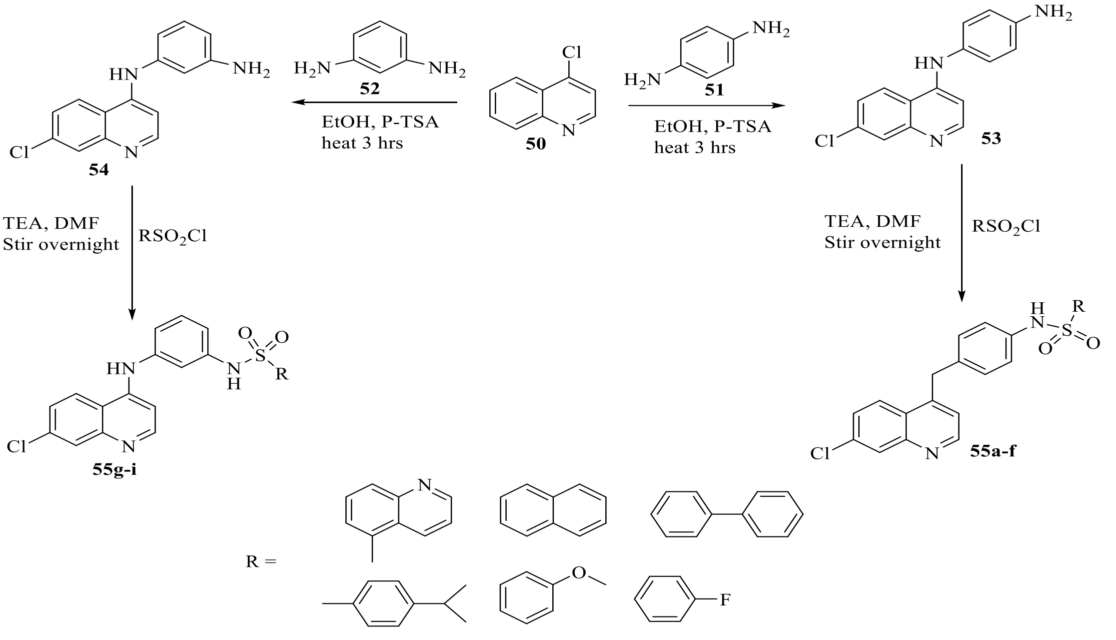
Zieba *et al.*, (2024) reported the synthesis, anticancer, and antimicrobial activities of quinoline-5-sulfonamide derivatives(**49a-f**). The synthesis began with the treatment of 8-hydroxyquinoline (**47**) with chlorosulfonic acid under stirring at room temperature for 3 hours to give 8-hydroxyquinoline-5-sulfonyl chloride (**48**). The compound was further reacted with different amines containing an acetylene moiety in the presence of acetonitrile, and the mixture was stirred for 2 hours at room temperature to afford the target products, 8-hydroxyquinoline-5-sulfonamides (**49a-f**) (Scheme 10) **[66].**



Scheme 10: Synthesis of 8-hydroxyquinoline-5-sulfonamide derivatives

The synthesized compounds (**49a-f**) were screened for their antimicrobial activity against *Staphylococcus aureus* and *Enterococcus faecalis* and for their anticancer activity against human amelanotic melanoma cells (C-32), human breast adenocarcinoma cells (MDA-MB-231), and human lung adenocarcinoma cells (A549). The results of the anticancer activity and the results showed that compound **49c** had the highest activity against human amelanotic melanoma cells (C-32), human breast adenocarcinoma cells (MDA-MB-231), and human lung adenocarcinoma cells (A549) when compared to the reference standard drugs cisplatin. Compound **49a**, **49b**, **49d**, **49**e**,** and **49f** displayed moderate anticancer activity against the three cancer cell lines. All the novel derivatives (**49a-f)** demonstrated good antimicrobial activities against the tested bacterial strain, *Staphylococcus aureus and Enterococcus faecalis* when compared to the reference standard drugs and doxorubicin.

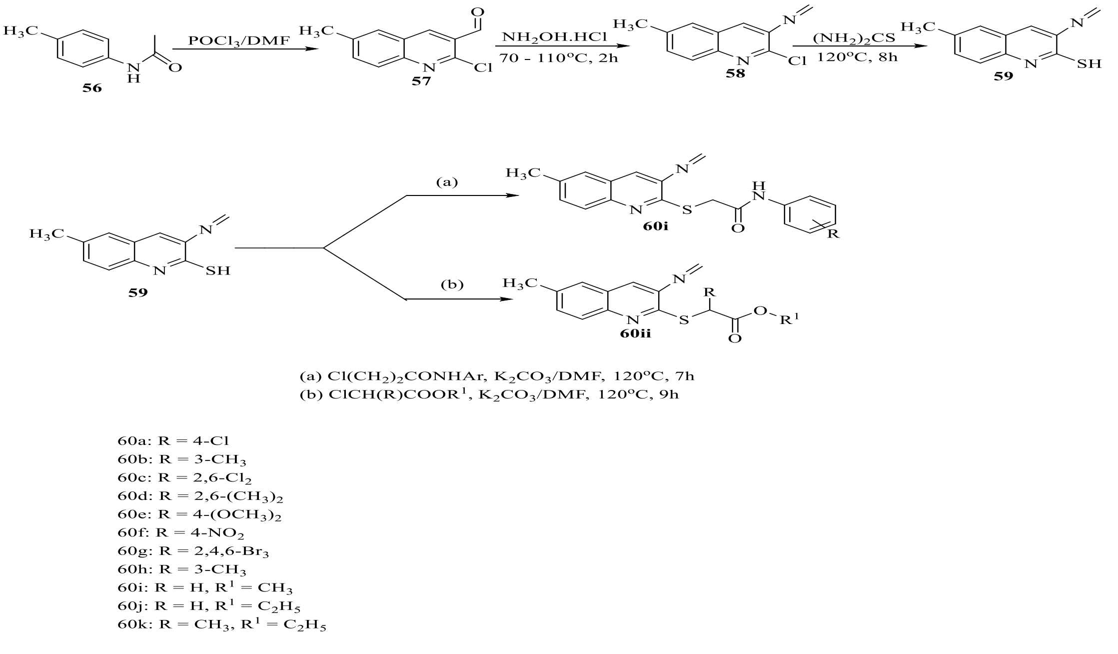
Saifi *et al*., (2025) reported the synthesis and antibacterial activities of novel quinoline-sulfonamide derivatives. In this synthesis, 4,7-dichloroquinoline (**50**) was condensed with p-phenylenediamine (**51**) and m-phenylenediamine (**52**) in the presence of the catalyst p-TSA and ethanol and heated for 3 hours to afford N-(7-chloroquinolin-4-yl)-benzene-1,4-diamine (**53**) and N-(7-chloroquinolin-4-yl)-benzene-1,3-diamine (**54**). Both compounds (**53** and **54**) were further reacted with different substituted benzenesulfonyl chlorides in the presence of DMF and TEA, and the reaction mixtures were stirred at room temperature to 60°C for 12-16 hours to yield the target derivatives (**55a-l**) (Scheme 11) **[67].**



Scheme 11: Synthesis of novel quinoline-sulfonamide derivatives

The synthesized compounds (**55a-i**) were evaluated for their antimicrobial activity against Gram-positive bacterial strains, specifically *E. faecalis*, and Gram-negative strains, *E. coli*, *P. aeruginosa*, and *S. typhi*, and compared with a reference standard drug, ciprofloxacin. The results revealed that compound **55c** had the highest inhibition property. The other compounds displayed moderate to low inhibition activity.

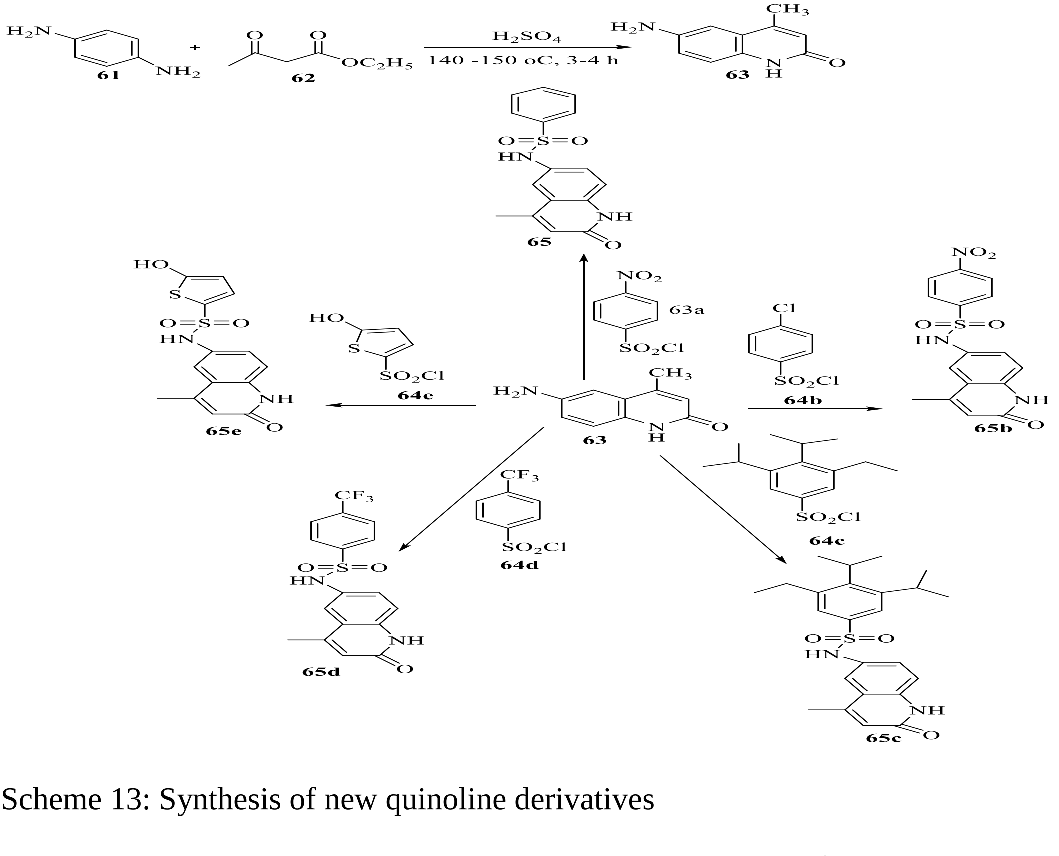
El-Shershaby *et al.*, (2020) reported the synthesis and in vitro antimicrobial evaluation of novel quinoline derivatives (**60a-k**). They began the synthesis with the treatment of p-methyacetanilide (**56**) with dimethylformamide (DMF) and phosphorus oxychloride. The reaction mixture was then stirred at 0°C for 2 hours to yield quinoline-3-carbaldehyde derivatives (**57**). The quinoline-3-carbaldehyde derivatives (**57**) were treated with hydroxylamine hydrochloride at 70°C for 2 hours to produce 2-chloro-6-methylquinoline-3-carbonitrile (**58**). The compound (**58**) was further reacted with thiourea to yield 6-methyl-2-mercaptoquinoline-3-carbonitrile (**59**). Finally, 6-methyl-2-mercaptoquinoline-3-carbonitrile (**59**) was treated with various ester derivatives in the presence of potassium carbonate to neutralize the effects of the HCl side product to yield the target products (**60a-k**) (Scheme 12) **[68].**



Scheme 12: Synthesis of new quinolines derivatives

The synthesized compounds (**60a-k**) were evaluated for their antimicrobial activity against a range of pathogenic microbes, including Gram-positive bacteria (*Streptococcus pneumoniae* and *Bacillus subtilis*), Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), and fungal strains (*Aspergillus fumigatus*, *Syncephalastrumracemosum*, *Geotrichumcandidum*, and *Candida albicans*). The compounds that demonstrated the best activity were subjected to further biological studies to determine their minimum inhibitory concentrations (MICs) against the selected pathogens. Additionally, the *in vitro* activity against E. coli DNA gyrase was assessed to determine whether their antimicrobial action is mediated through the inhibition of this enzyme. The result showed that **60c, 60f, 60g**, and **60i** exhibit relatively potent antimicrobial activity with MIC values ranging from 0.66 to 5.29 μg/mL. Compound **60c** showed broad-spectrum antimicrobial activity against most of the tested strains of bacteria and fungi, with MIC values between 0.66 and 3.98 μg/mL.

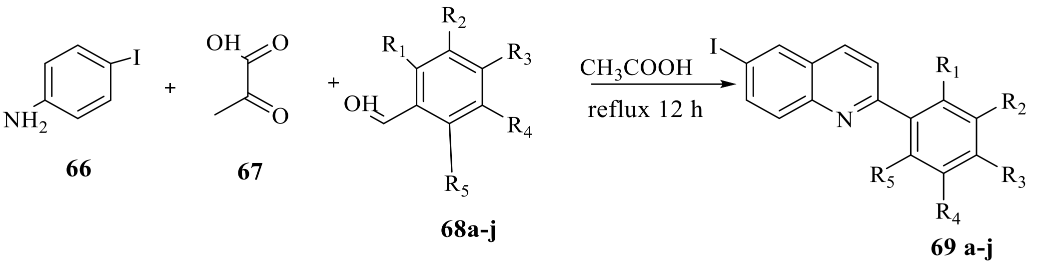
Singh *et al.*, (2024) reported the design, synthesis and antimicrobial activity of novel quinoline derivatives (**65a-e**). They achieve this by reacting to aromatic amine (**61**) with acetoacetate (**62**) in the presence of H_2SO_4 as a catalyst. The reaction mixture was stirred at 140-150°C for 3-4 hours to give 6-amino-4-methyl-1H-quinoline-2-one (**63**). The compound (**63**) was further reacted with benzenesulphonyl chloride/benzoyl chloride (**64a-e**) in the presence of DCM and stirred overnight at room temperature to afford the target products (**65a-e**) (Scheme 13) **[69].**



Scheme 13: Synthesis of new quinoline derivatives

These new synthesized compounds (**65a-e**) were evaluated for their *in vitro* antibacterial and antifungal activity. Antibacterial screening of all compounds showed excellent MIC value (MIC, 50 -3.12μg/mL) against bacteria strains such as B*acillus cerus*, *Staphylococcus, Psedomonas*and *Escherichia coli*. Compound **65b** and **65e** showed better activity. Furthermore, antifungal screening against fungal strains such as *A. flavus, A. niger, F. oxysporum,* and *C. albicans* also revealed that all compounds were potentially active, and compound **65e** being most potent.

Al-Matarneh *et al*., (2024) reported the synthesis of iodo-quinoline derivatives(**69a-j**) and their antimicrobial activity. In this reaction, iodo-aniline (**66**) and pyruvic acid (**67**) were reacted with various aldehydes (**68a-j**) in the presence of acetic acid and TFA under reflux for 12 hours. The crude products were then recrystallized using dichloromethane and ethanol to obtain the target products (**69a-j**) (Scheme 14) **[70].**



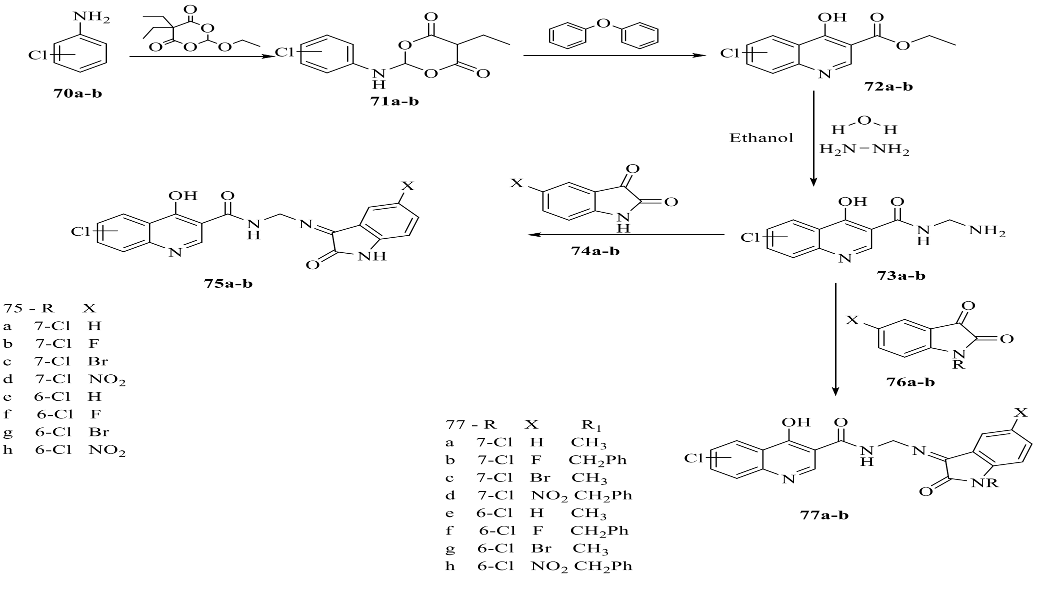
69a: $R_1 = R_2 = R_3 = R_4 = R5 = H$
69b: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = F$
69c: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Cl$
69d: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Br$
69e: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CF_3$
69f: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CN$
69g: $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = OH$
69h: $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OCH_3$
69i : $R_1 = R_4 = R_5 = H$, $R_2 = OH$, $R_3 = OH$
69j: benzo[d][1,3]dioxide

Scheme 14: Synthesis of Iodo-quinoline derivatives

The synthesized compounds (**69a-j**) were evaluated for their *in vitro* antimicrobial activity against *S. epidermidis, K. pneumonia* and *C. parapsilos* and the result suggested that the new derivatives are interesting scaffolds for the development of novel antimicrobial agents.

Antitubercular Activity

Abdelrahman *et al.*, in 2022 reported the multiple-step synthesis, characterization, and antitubercular activity of quinoline-isatin conjugates. The reaction began with the condensation of 3-chloroaniline **70a** and 4-chloroaniline **70b** with diethyl ethoxymethylene malonate to yield ethyl anilinomethylene malonate **71a-b**, and on cyclization with diphenyl ether, it yielded ethyl esters of 4-hydroxyquinoline-3-carboxylic acids **72a-b.** On further reaction with hydrazine hydrate in the presence of ethanol, acid hydrazides **73a-b** were obtained. To afford the target products **75a-b** and **77a-b**, the hydrazine derivatives (13a-b) were further condensed with various 5-substituted isatins (**74a-d**) or *N*-substituted isatins (**76a-d**) in glacial acetic acid **[71].**



75 - R	X
a 7-Cl	H
b 7-Cl	F
c 7-Cl	Br
d 7-Cl	NO_2
e 6-Cl	H
f 6-Cl	F
g 6-Cl	Br
h 6-Cl	NO_2

77 - R	X	R_1
a 7-Cl	H	CH_3
b 7-Cl	F	CH_2Ph
c 7-Cl	Br	CH_3
d 7-Cl	NO_2	CH_2Ph
e 6-Cl	H	CH_3
f 6-Cl	F	CH_2Ph
g 6-Cl	Br	CH_3
h 6-Cl	NO_2	CH_2Ph

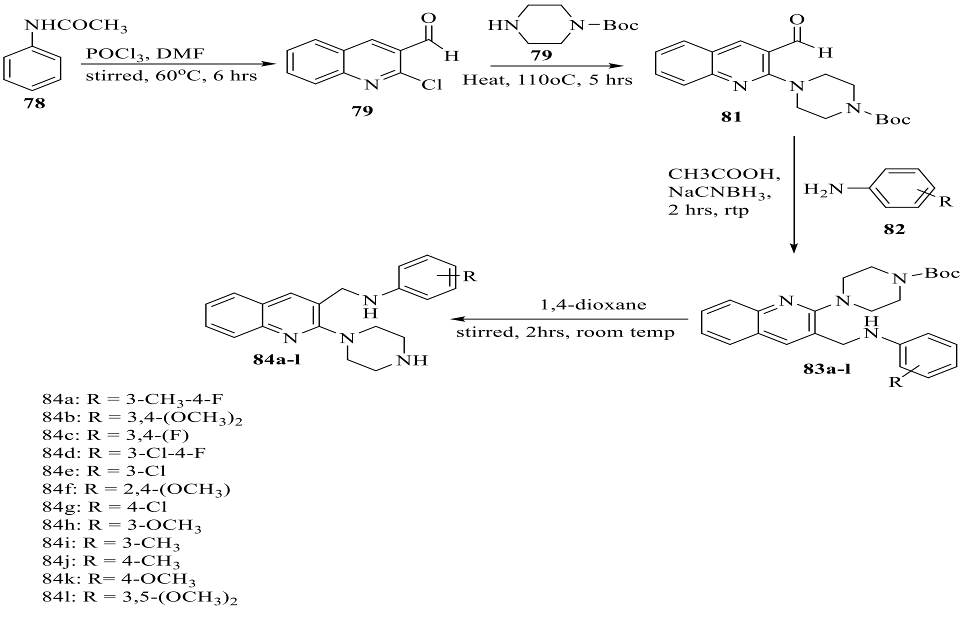
Scheme 15: Synthetic routes for Quinoline-isatin conjugates 74a-b and 76a-b

They further investigated the anti-tubercular activity of the novel target compounds against RCMB 010126 *M. tuberculosis, the MDR strain (FJ05120), and the XDR strain (FJ05195)* using isoniazid as a reference. The result showed that the derivatives have potent to moderate anti-*M. tuberculosis* activity, with the MICs ranging between 0.06 and 7.81 g/mL, except for **75c and 77d** with MICs of 31.25 and 15.63µg/mL, respectively. Compound **77b** showed a 100-fold increase in activity in terms of growth inhibition towards *M. tuberculosis* with a MIC of 0.06g/mL, and compound **77h** showed excellent anti-mycobacterial action with a MIC value of 0.12µg/mL that equals the MIC for the reference drug, isoniazid.

Against both MDR and XDR *M. tuberculosis* strains, derivatives **77b and 77h** showed excellent antitubercular activity with MIC values of 0.24µg/mL and 0.98µg/mL for MDR and 1.95µg/mL, 3.9µg/mL for XDR, respectively. Compounds **75a, 75b, 77a, 77c, 77e, and 77f** showed good activity against the MDR strain with MIC values of 3.9, 3.9, 7.81, 3.9, 7.81, and 7.81µg/mL while compounds **75a, 75b, 75c,** and **75f** showed moderate activity against the XDR strain with a MIC range from 7.81 to 15.63µg/mL.

Antimalarial Activity

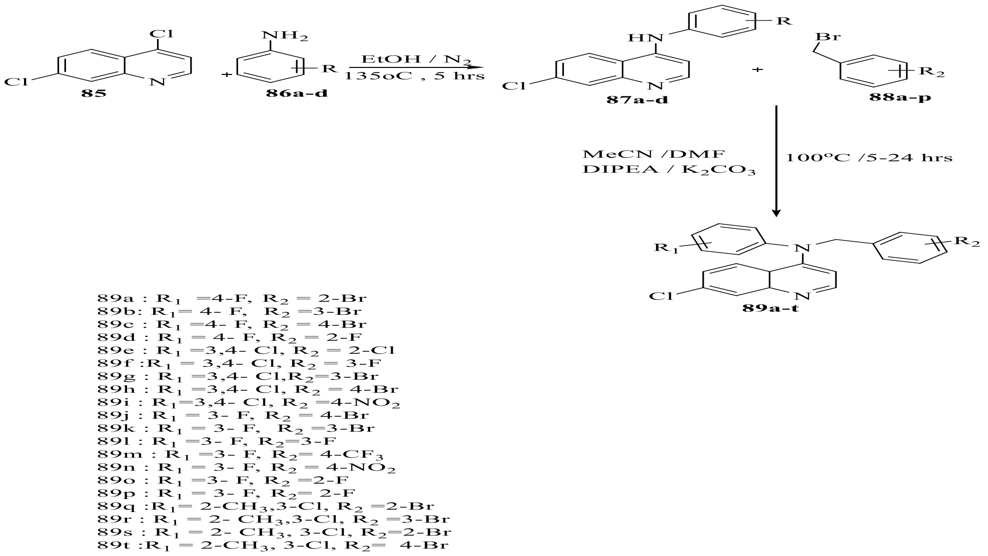
Lagdhir *et al*., (2021) reported the design and synthesis of new quinoline hybrid (**84a-l**) derivatives with antimalarial properties. The synthesis began with the treatment of acetanilide (**78**) with $POCl_3$ in the presence of DMF. The reaction mixture was stirred at 80°C for 6 hours to obtain 2-chloroquinoline-3-carbaldehyde **(79)**. This compound (**79**) was then reacted with tert-butyl piperazine-1-carboxylate (**80**) and heated at 110°C for 5 hours, resulting in tert-butyl 4-(3-formylquinolin-2-yl) piperazine-1-carboxylate **(81)**. This was followed by reacting compound (**81**) with amines (**82a-l**) in the presence of acetic acid and $NaCNBH_3$ and the mixture was stirred at room temperature for 2 hours, yielding tert-butyl 4-(3-phenylamino) methyl(quinoline-2-yl) piperazine-1-carboxylate derivatives (**83a-l**). Finally, the target products (**84a-l**) were obtained by treating these compounds (**83a-i**) with 1,4-dioxane and stirring at room temperature for 2 hours **[72].**



Scheme 16: Synthesis of new quinoline hybrid

All synthesized compounds (**84a-l**) were screened for in vitro antimalarial activity against the Plasmodium f*alciparum* 3D7 chloroquine-sensitive strain, and their activity was compared to that of a reference standard drug, Quinine/Chloroquine. The results indicatede that compounds (**84a-l**) exhibited moderate antimalarial activity.

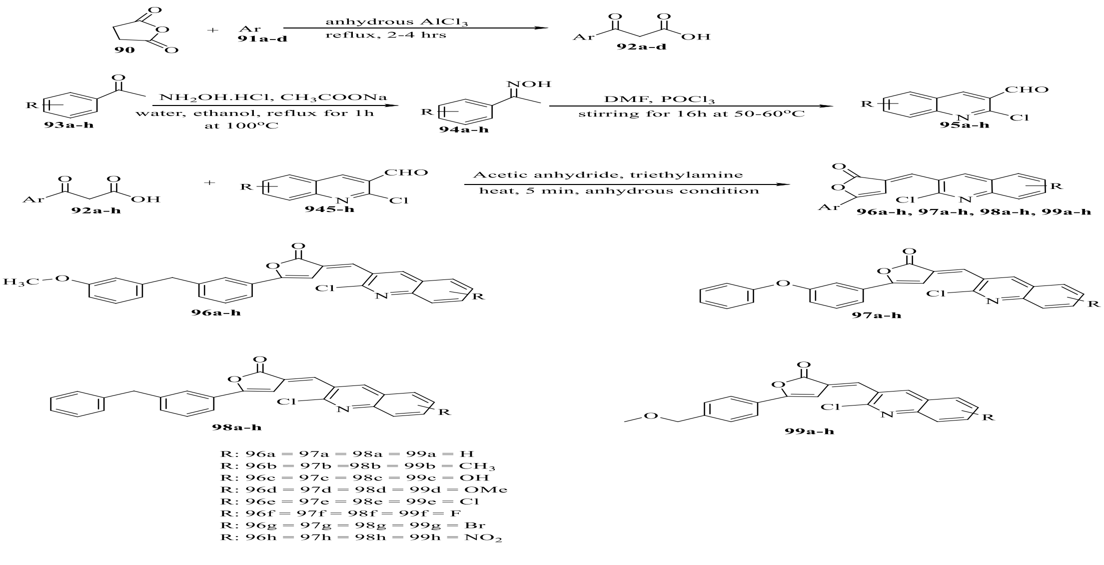
Touré *et al*., (2024) reported the synthesis and *in vitro*/*in silico* evaluation of the antimalarial activity of potential amino-quinoline derivatives. They achieve this by reacting to 4,7-dichloroquinoline (**85**) with various amines (**86a-d**) in the presence of absolute ethanol. The mixture was stirred under reflux at room temperature for 4 hours to obtain 4-arylamino-7-chloroquinoline (**87a-d**). The compounds (**87a-d**) were further reacted with substituted brominated benzyl derivatives (**88a-p**) in the presence of MeCN/DMF or DIPEA/K_2CO_3 and stirred for 5-24 hours at 100°C to afford the target products, *N*-aryl-*N*-benzylamino-7-chloroquinoline (**89a-t**) **[73].**



Scheme 17: Synthesis of *N*-aryl-*N*-benzylamino-7-chloroquinoline

The synthesized compounds (**89a-t**) were evaluated to have their antimalarial efficacy against chloroquine-sensitive (Pf3D7) and chloroquine-resistant (PfW2) Plasmodium falciparum strains. The result showed that compound **89i** and **89c** have promising efficacy against the Pf3D7 strain with IC_{50}values of 0.25 μM and 0.54 μM, respectively, while compound **89l** demonstrated significant activity against the PfW2 strain with an IC_{50} of 5.82 μM.

Choudhary *et al*., (2024) reported the synthesis of novel anti-plasmodial quinoline-furanone hybrids (**96a-h**, **97a-h**, **98a-h, 99a-h**) through a multi-step process. Initially, succinic anhydride (**90**) was reacted with various aromatic compounds (2-methoxy-naphthalene, diphenyl ether, diphenylmethane, and methoxy methyl benzene) (**91a-d**) in the presence of anhydrous aluminum chloride and dry nitrobenzene. The mixture was heated and stirred at room temperature for 2-3 hours to yield β-aryl propionic acid (**92a-d**). In a separate step, acetophenone (**93a-h**) was treated with hydroxylamine hydrochloride, sodium acetate, ethanol, and sufficient water. The reaction mixture was refluxed in a water bath for 3-6 hours at 100°C to obtain 4-substituted-1-phenylethanone oxime (**94a-h**). This intermediate was then treated with DMF and phosphorus oxychloride under stirring for 16 hours at 50-60°C to give substituted 2-chloroquinoline-3-carbaldehydes (**95a-h**). Finally, β-aryl propionic acid (**92a-d**) was reacted with aromatic aldehydes (**95a-h**) in the presence of acetic anhydride and triethylamine and the reaction mixture was heated for 5 minutes under anhydrous conditions to yield the target products 3-{(2-chloro-6-substituted-quinolin-3-yl)methylene}-5-(aryl-2-yl)-furan-2(3H)-one (**96a-h**, **97a-h**, **98a-h, 99a-h**) **[74].**

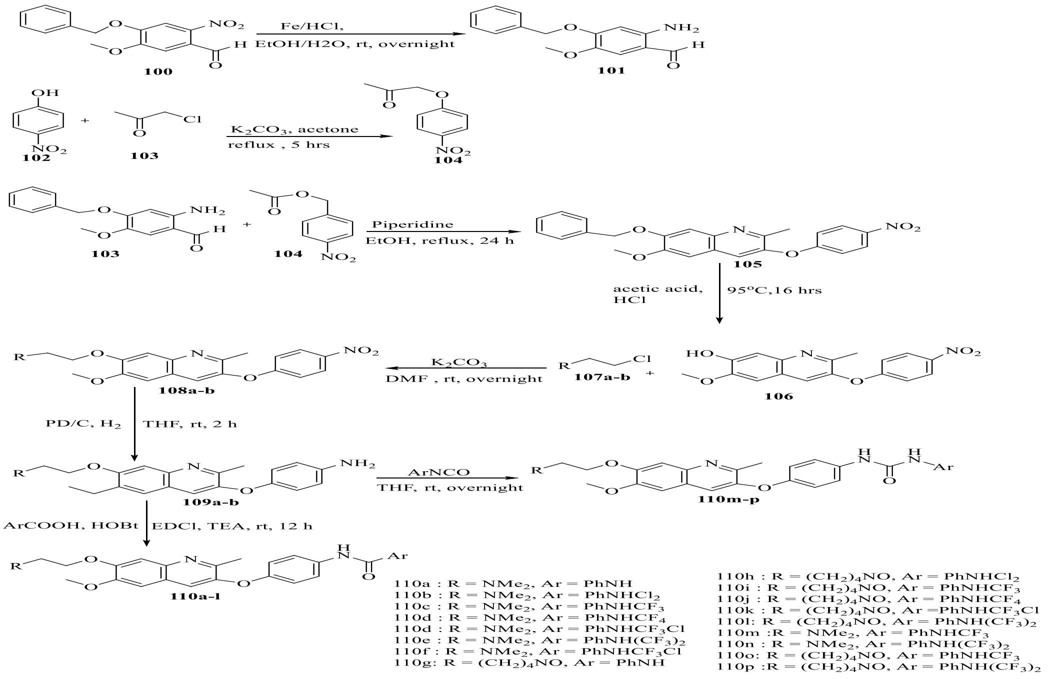


Scheme 18: Synthesis of quinoline-furanone hybrids

The synthesized compounds (**96a-h**, **97a-h**, **98a-h, 99a-h**) were studied for their antimalarial properties against the resistant strain of Plasmodium through Schizont Maturation Inhibition assays. Among the compounds tested, **96g** and **97e** demonstrated the best activity, with IC_{50} values like chloroquine (CQ), and **96g** exhibited superior LDH inhibition compared to CQ. Compounds **96f, 98a**, and **98f** showed IC_{50} values comparable to CQ and moderate LDH inhibition. Structure-activity relationship (SAR) analysis revealed that halogen substitutions, particularly Br and Cl, enhanced antimalarial activity, while strong electron-withdrawing ($–NO_2$) or -donating (–OH) groups led to diminished activity. Additionally, bulkier aromatic substitutions were favored for antimalarial activity and LDH inhibition. The investigation successfully found potent anti-plasmodial quinoline–furanone hybrids, demonstrating promising prospects for combating malaria.

Anticancer Activity

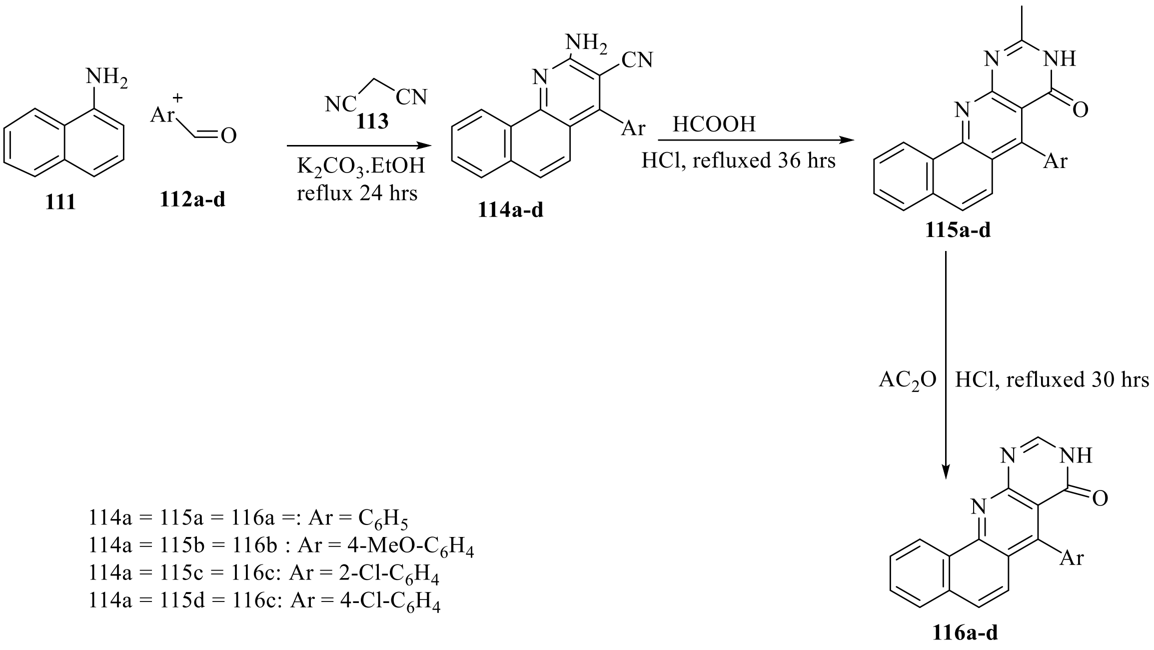
Zaraei *et al*., (2022) reported the design and synthesis of novel quinoline derivatives (**110m-P)** exhibiting potent anticancer activity. The synthesis began with the reduction of the nitro group in 4-(benzyloxy)-5-methoxy-2-nitrobenzaldehyde (**100**) to its corresponding amino derivative (**101**) using iron and hydrochloric acid. In a separate reaction, 4-nitrophenol (**102**) was reacted with chloroacetone (**103**) in the presence of potassium carbonate. The reaction mixture was refluxed for 5 hours to yield 1-(4-nitrophenoxy) propan-2-one (**104**). This was followed by a Friedländer cyclization reaction between the o-aminobenzaldehyde derivative (**101**) and 1-(4-nitrophenoxy) propan-2-one (**104**) in refluxing ethanol, using piperidine as a catalyst, to produce the 3-(4-nitrophenoxy) quinoline intermediate (**105**). The subsequent step involved acid-catalyzed benzyl ether deprotection using a hydrochloric acid and acetic acid, yielding the 7-quinolinol intermediate (**106**). The hydroxy group in the compound (**106**) was then reacted with (2-chloroethyl) dimethylamine or 4-(2-chloroethyl) morpholine (**107a-b**) in the presence of potassium carbonate. The reaction mixture was stirred overnight to obtain the nitro intermediate (**108a-b**), which was later converted to the corresponding aniline derivatives (**109a-b**) under a hydrogen atmosphere using Pd/C as a catalyst at room temperature. Finally, compounds (**109a-b)** were reacted with aryl isocyanate to produce the target diarylurea-containing compounds (**110a-l)**. Additionally, they reacted with appropriately substituted benzoic acid derivatives using 1-hydroxybenzotriazole (HOBt), EDCI, and TEA to yield the target diarylamide-containing compounds (**110m-P)** (Scheme 19) **[75].**



Scheme 19: Synthesis of new quinoline derivatives

The synthesized compounds (**110a-p**) were screened for their anticancer activities, and the results showed that compounds **110j-l** had the highest mean inhibition percentage values over the 60-cell line panel at 10 µM with broad-spectrum antiproliferative activity. Subsequently, compounds **110j-l** were subjected to a dose-response study to measure their GI50 and total growth inhibition (TGI) values against the cell lines. Three of the tested molecules exerted higher potency against most of the cell lines than the reference drug, sorafenib. Compound **110l** indicated higher potency than sorafenib against the tested cancer cell lines. Compounds **110j-l** demonstrated promising selectivity against cancer cells rather than normal cells. Moreover, compound **110l** induced apoptosis and necrosis in the RPMI-8226 cell line in a dose-dependent manner.

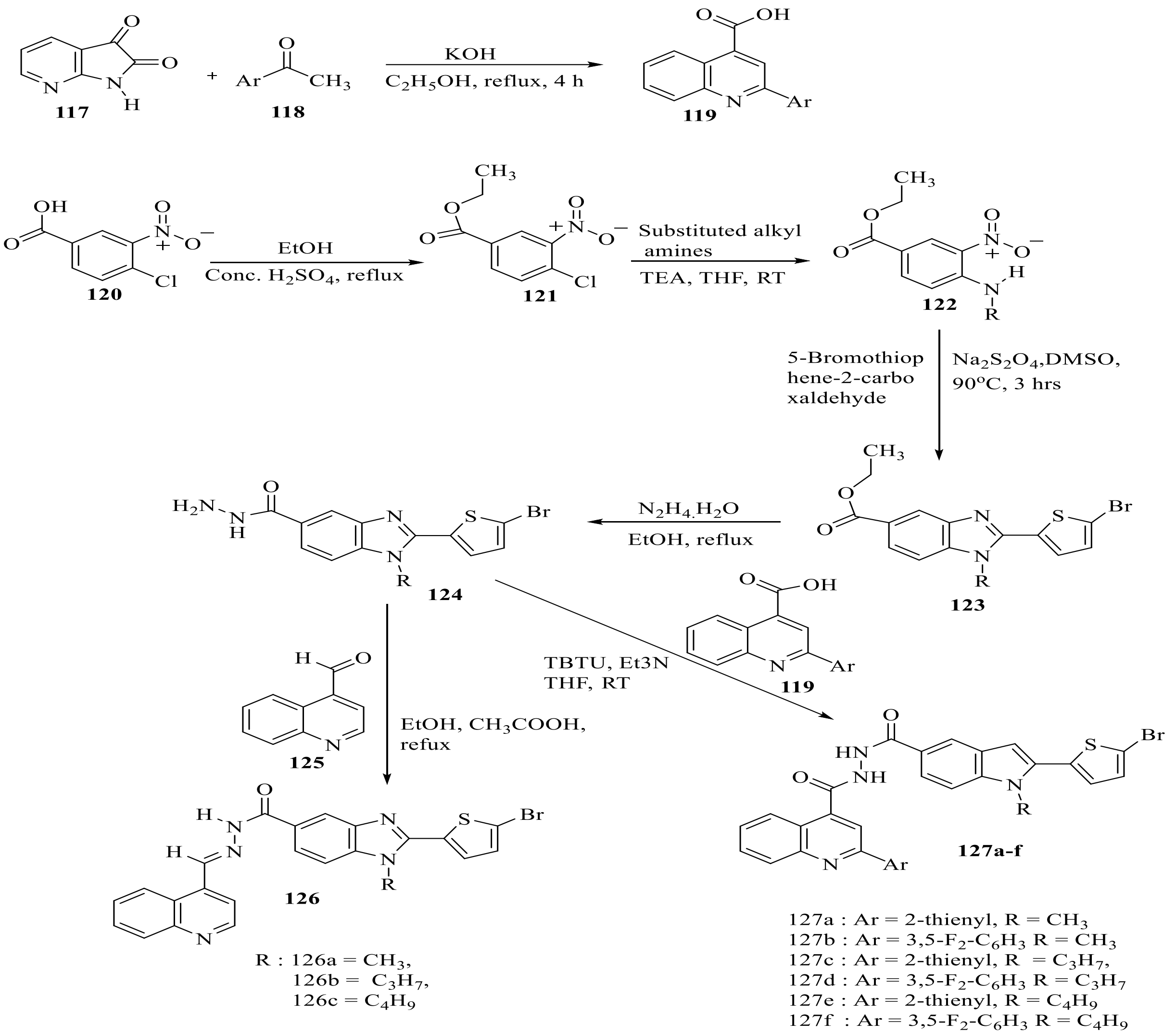
Khodair *et al.*, (2024) reported the synthesis and anticancer activity of novel benzo[h]quinoline derivatives(**116a-d**). The compounds were synthesized by reacting α-naphthylamine (**111**) with an appropriate aldehyde (**112a-d**) and malononitrile (**113**) in the presence ofethanol, and a catalytic amount of potassium trioxocarbonate (IV). The mixture was refluxed at room temperature for 24 hours to obtain amino-benzo[h]quinoline-3-carbonitriles (**114a-d**). The compounds (**114a-d**) were further treated with formic acid and a few drops of HCl, then refluxed for 30 minutes to yield compounds (**115a-d**). In a separation reaction, amino-benzo[h]quinoline-3-carbonitriles (**114a-d**) were treated with acetic anhydride and a few drops of HCl, then refluxed for 30 hours to yield the target compounds (**116a-d**) (Scheme 20) **[76].**



Scheme 20: Synthesis of novel Benzo [*h*] quinoline Derivatives

They evaluated the synthesized compounds (**114a-d, 115a-d & 116a-d)** for their anticancer activities. Among all tested compounds compound **114b** and compound **116c** exhibited the strongest activity, especially against melanoma compared to the standard imatinib.

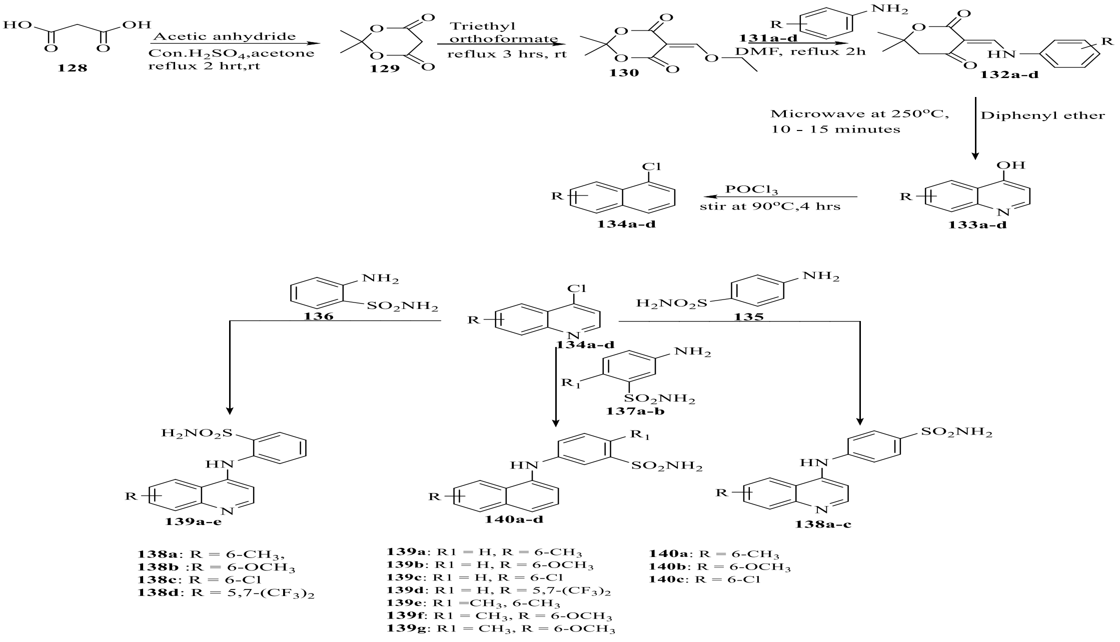
Srinivasa *et al.*, (2024) reported the synthesis and anticancer activity of novel benzimidazole containing quinoline hybrids (**127a-f)**. Isatin (**117**) was reacted with 3,5-difluoroacetophenone (**118**) in the presence of potassium hydroxide and ethanol. The reaction mixture was heated under reflux for 4 hours to obtain 2-aryl-quinoline-4-carboxylic acid (**119**). In a separate reaction, ethyl 4-chloro-3-nitrobenzoate (**120**) was reacted with a substituted amine (**121**) in the presence of THF and triethylamine, and the reaction mixture was stirred overnight at room temperature to afford ethyl 4-(alkylamino)-3-nitrobenzoate (**122**). This was followed by treating ethyl 4-(alkylamino)-3-nitrobenzoate (**122**) with 5-bromothiophene in the presence of sodium dithionite, DMSO, and the reaction mixture was stirred at 90°C for 3 hours to yield ethyl 2-(5-bromothiophen-2-yl)-1-alkyl-1*H*-benzo[d]imidazole-5-carboxylate (**123**). The compound (**123**) was then reacted with hydrazine hydrate in ethanol and refluxed on an oil bath for 10 hours to yield 2-(5-bromothiophen-2-yl)-1-alkyl-1*H*-benzo[*d*]imidazole-5-carbohydrazide (**124**). Finally, compound (**124**) was reacted with quinoline-4-carboxaldehyde (**125**) in the presence of glacial acetic acid, and the reaction mixture was stirred and refluxed for about 3 hours to afford 2-(5-bromothiophen-2-yl)-1-alkyl-*N*-[quinoline-4-ylmethylene]-1*H*-benzo[*d*]imidazole-5-carbohydrazide (**126a-c**).In a separate reaction, compound (**124**) was reacted with 2-aryl-quinoline-4-carboxylic acid (**119**) in the presence of THF, TBTU, and TEA, and stirred for about 30 minutes to afford 2- (5-bromothiophen-2-yl) -1-alkyl-1*H*-benzo [*d*] imidazole -5-carbohydrazide-2-(3,5-fluorophenyl) quinoline-4-carboxylate (**127a-f**) (Scheme 21) **[77].**



Scheme 21: Synthesis of benzimidazole-quinoline hybrids

The novel derivatives (**126a-c & 127a-f**) were screened (*in-silico* and *in-vitro*) for their anti-cancer activities (human melanoma cell line (A375) and human breast cancer cell line (MDA-MB-231) and compared with a reference standard drug, cisplatin. The result showed that compounds **126a**, **127a** and **127b** have significant cytotoxicity against these human cancer cell lines (melanoma and breast cancer) and can be potential anti-cancer molecules.

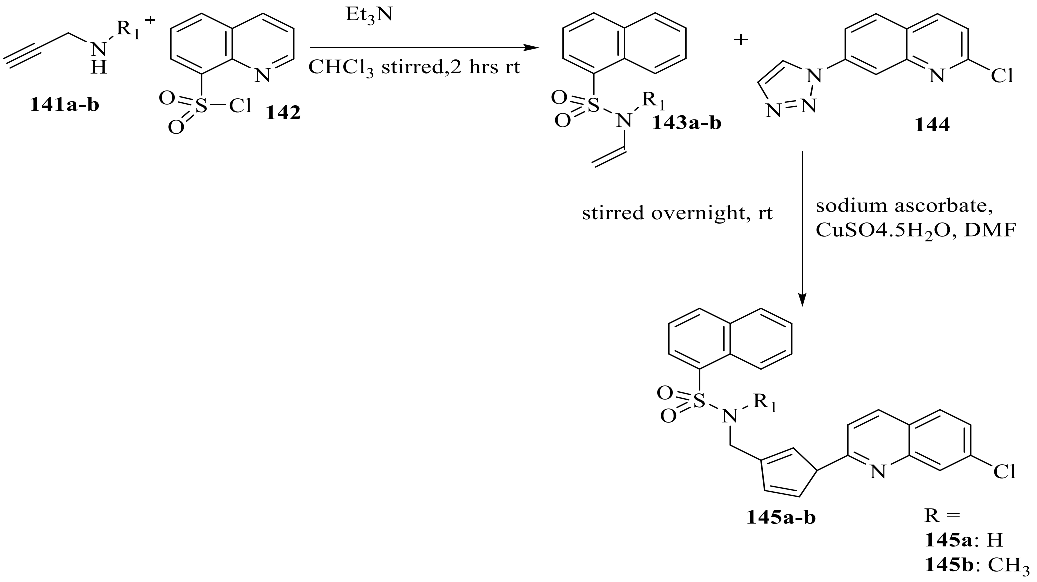
Shaldam *et al*., (2021) reported the synthesis of novel quinoline-based sulfonamides (**138a-d, 139a-d,** and **140a-e**) as anticancer agents. The synthesis began with the treatment of malonic acid (**128**) with acetic anhydride in the presence of acetone and concentrated H_2SO_4. The reaction mixture was stirred at room temperature to yield 2,2-dimethyl-1,3-dioxane-4,6-dione (**129**). The compound was then heated with triethyl orthoformate under reflux for 3 hours to give 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**130**). Compound (**130**) was further reacted with substituted anilines (**131a-d**) in the presence of DMF under reflux for 2 hours to afford 5-(phenylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**132a-d**). This was followed by cyclization of compounds (**132a-d**) via microwave irradiation at 250 ℃ for 10-15 minutes to produce 4-hydroxyquinolines (**133a-d**). Compounds (**133a-d**) were further converted to the corresponding 4-chloroquinoline derivatives (**134a-d**) by heating with excess phosphorus oxychloride for 4 hours. Finally, 4-chloroquinoline derivatives (**134a-d**) reacted with different aminobenzenesulfonamide derivatives (**135, 136,** and **137a-d**) in the presence of a catalytic amount of HCl under reflux to yield the corresponding target derivatives (**138a-d, 139a-d,** and **140a-e**) (Scheme 22) **[78].**



Scheme 22: Synthesis of novel quinoline-based sulfonamide

The synthesized compounds (**138a-d, 139a-e** and **140a-d**) were screened for their CA inhibitory action against *h*CA I, II, IX, and XII, and the results showed that 191a-c had the best inhibitory activity against both cancer-related isoforms *h*CA IX (Kis = 25.8, 5.5, and 18.6 nM) and hCA XII (Kis = 9.8, 13.2, and 8.7 nM), respectively.

Marciniec *et al.*, (2023) reported the design, synthesis, and anticancer activity of quinoline-8-sulphonamide derivatives (**145a-b**). They achieved this by the reaction of propargylamine or N-methylpropargylamine (**141a-b**) with 8-quinolinesulfonyl chloride (**142**) in the presence of triethylamine and chloroform. The reaction mixture was stirred at room temperature for 2 hours to give 8-N-substituted (prop-2-ynyl) quinoline sulfonamide (**143a-b**). The compound (**144a-b**) was further reacted with 4-azido-7-chloroquinoline (**145**) in the presence of sodium ascorbate, $CuSO_4·5H_2O$, and DMF, and the reaction mixture was stirred overnight at room temperature to afford the target derivatives (**146a-b**) (Scheme 23) **[79].**

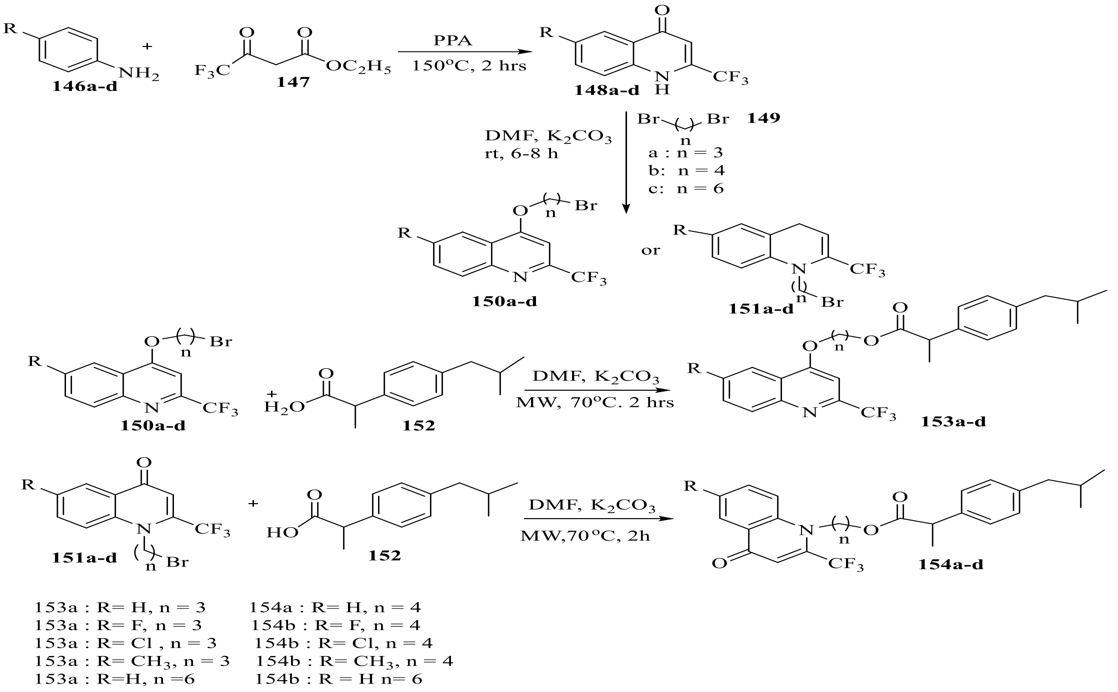


Scheme 23: Synthesis of quinoline-8-sulphonamide derivatives

The synthesized compounds (**145a-b**) were studied for their anticancer properties using *in silico* and *in vitro* assays. The results from the *in silico* studies revealed that compound **145a** is a potent modulator of muscle isoform 2 of pyruvate kinase. The in vitro experiment confirmed the ability of compound **145a** to reduce the intracellular pyruvate level in A549 lung cancer cells, with a simultaneous impact on cancer cell viability and cell-cycle phase distribution.

Anti-Inflammatory Activity

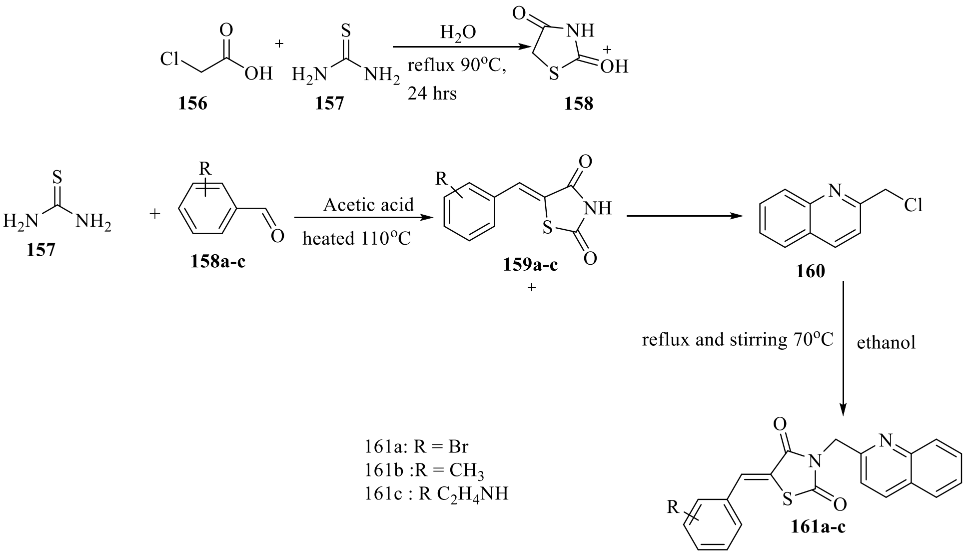
Ghanim *et al.*, (2022) reported the design and synthesis of an ibuprofen-quinoline conjugate (**153a-d and 154a-d**) with potential anti-inflammatory activity. They reacted substituted aniline (**146a-d**) with ethyl 4,4,4-trifluoro-3-oxobutanoate (**147**) in the presence of polyphosphoric acid. The reaction mixture was stirred at 150°C for 2 hours, forming 6-substituted-2-(trifluoromethyl)quinoline-4(1H)-ones (**148a-d**). These compounds (**148a-d**) were then treated with dibromoalkane (**149**) in the presence of anhydrous potassium trioxocarbonate (IV) and DMF and stirred for 6-8 hours at room temperature to yield 6-substituted-2-(trifluoromethyl)quinoline derivatives (**150a-d & 151a-d**). Subsequently, the bromo-derivatives (**150a-d & 151a-d**) reacted with ibuprofen (**152**), which was dissolved in DMF and anhydrous potassium trioxocarbonate (IV) and the reaction mixture was subjected to microwave irradiation (20 W) at 70°C for 2 hours to afford the target products (**153a-d and 154a-d**) (scheme 24) **[80].**



Scheme 24: Synthesis of ibuprofen-quinoline conjugate

The synthesized conjugates (**153a-d and 154a-d**) were screened for their anti-inflammatory and ulcerogenic properties. The results showed that several conjugates exhibited significant anti-inflammatory properties in the carrageenan-induced rat paw edema test without demonstrating any ulcerogenic liability. Compounds **153a**, **153b**, and **153c** displayed potent anti-inflammatory properties comparable to those of their precursor, ibuprofen. Moreover, conjugates **153b** and **153c** did not exhibit ulcerogenic liability. The most promising anti-inflammatory agents were evaluated in vitro as COX-1/COX-2 inhibitors, and the results revealed considerable selectivity toward COX-2 compared to ibuprofen.

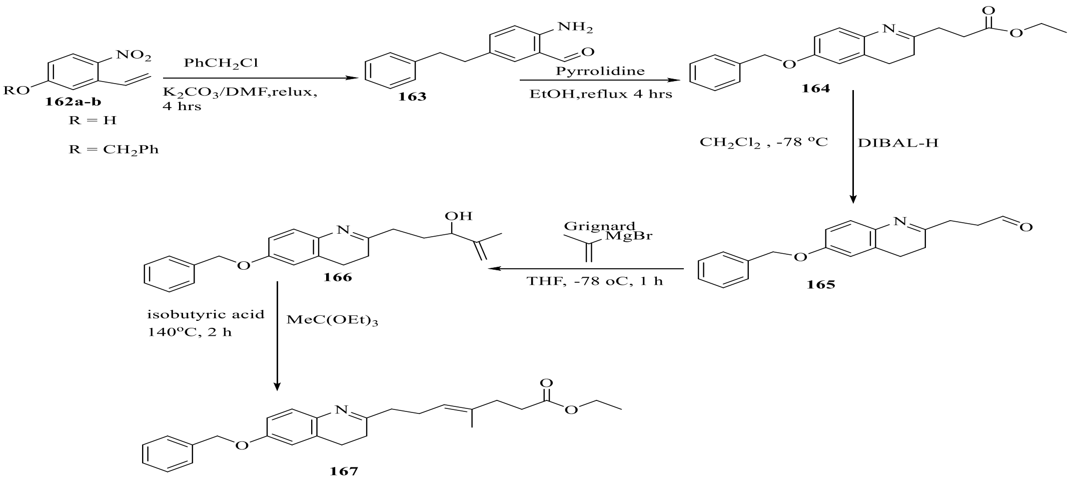
Silva *et al.*, (2024) reported the synthesis, *in vitro*, and *in silico* anti-inflammatory activity of new thiazolidinedione-quinoline derivatives (**161a-c**). They achieved this synthesis by reacting to 2-chloroacetic acid (**155**) with thiourea (**156**) in an aqueous medium under reflux and agitation at 90°C for 24 hours to yield thiazolidine-3,4-dione (**157**). The compound (**157**) was further reacted with substituted benzaldehyde (**158**) in the presence of acetic acid and ammonium acetate. The reaction mixture was heated at 110°C for 5-8 hours to obtain 5-aryl-2,4-thiazolidinedione (1**59**). Finally, the target products (**161a-c**) were obtained by reacting 5-aryl-2,4-thiazolidinedione (**159**) with 2-chloromethyl-quinoline (**160**) in the presence of sodium hydroxide and ethanol at 70°C under reflux and stirring (scheme 25) **[81].**



Scheme 25: Synthesis of new thiazolidinedione-quinoline derivatives

The synthesized compounds (**161a-c**) were screened for their anti-inflammatory activities using various assays, including cell viability testing (MTT), ELISA for IFN-γ and TNF-α, adipogenic differentiation, and molecular docking with PPARγ and COX-2 targets. The results showed that they exhibited a significant, dose-dependent decrease in IFN-γ and TNF-α concentrations. At a concentration of 50 µM, the compounds (**161a-c**) significantly reduced IL-6 expression. Furthermore, the compounds demonstrated lipid accumulation with significant differences between the untreated and negative control groups, indicating relevant agonist action on the PPARγ receptor. Molecular docking revealed that all synthesized compounds (**161a-c**) exhibited good affinity for PPARγ and COX-2, with binding energies approaching -10,000 kcal/mol.

Villarrel-Vicente *et al*., (2024) reported the synthesis of new 2-prenylated quinolines **(167)** as potential anti-inflammatory drugs. The synthesis began with the treatment of 5-hydroxy-2-nitrobenzaldehyde (**162a-b**) with benzyl chloride in a basic medium, followed by refluxing for 4 hours to yield 5-benzyloxy-2-nitrobenzaldehyde. Subsequent reduction of the ortho-nitrobenzaldehyde with iron powder in aqueous HCl and ethanol, refluxed for 30 minutes, gave the intermediate compound (**163**). The quinoline nucleus (**164**) was then formed through a Friedländer reaction, involving the condensation of the ortho-aminobenzaldehyde intermediate (**163**) with ethyl levulinate in the presence of pyrrolidine as catalyst under refluxed for 4 hours to give quinoline ester (**164**). The resulting quinoline ester (**164**) was further reduced using DIBAL-H in dichloromethane to obtain aldehyde (**165**). Finally, introduction of the prenylated hydrocarbon side chain (**166**) was achieved through an efficient Grignard reaction with isopropenylmagnesium bromide, and this reaction was followed by Johnson-Claisen rearrangement with triethyl orthoacetate and catalytic amounts of isobutyric acid, yielding the target product 2-prenylated quinoline **(167)** (scheme 26) **[82].**

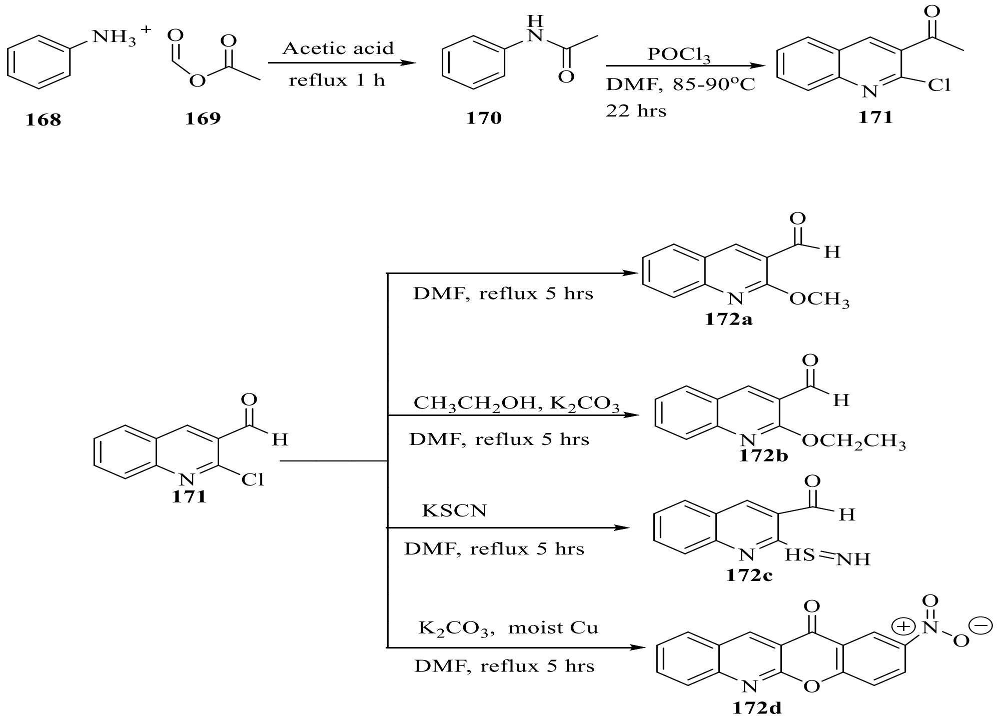


Scheme 26: Synthesis of 2-prenylated quinoline

They screened the synthesized compound **167** for its anti-inflammatory properties, and the result showed that compound **167** has anti-inflammatory effects on macrophages by reducing LPS-induced expression of both MCP-1 and IL-6.

Antioxidant Activity

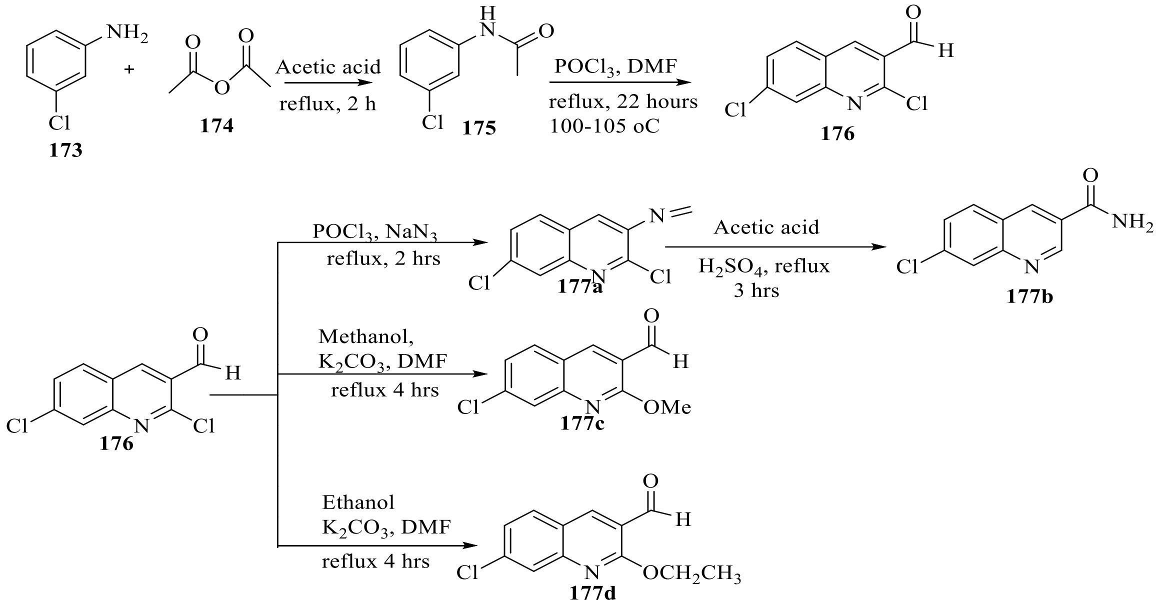
Zeleke *et al*., (2020) reported the synthesis and antioxidant activities of some novel quinoline derivatives (**172a-d**). They achieve this by the reaction of aniline (**168**) and acetic anhydride (**169**) in the presence of zinc powder and acetic acid under reflux for 1 hour to give acetanilide (**170**). The compound (**170**) was then treated by heating with N,N-dimethylformamide and phosphorus oxychloride at a temperature of 85-90 ℃ for 22 hours to give 2-chloroquinoline-3-carbaldehyde (**171**).The derivatives of 2-chloroquinoline-3-carbaldehydederivatives (**172a-d**) were obtained by reacting 2-chloroquinoline-3-carbaldehyde (**171**) with alcohol, potassium carbonate, N,N-dimethylformamide, and potassium thiocyanate under reflux for 5 hours (Scheme 27) **[83].**



Scheme 27: 2-chloroquinoline-3-carbaldehydederivatives

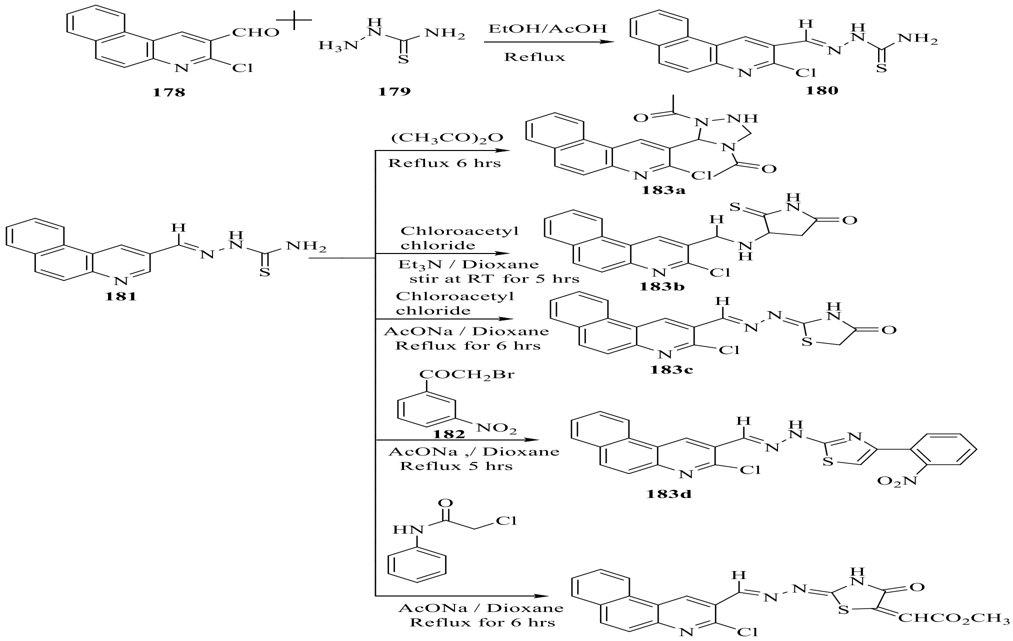
The radical scavenging activity of these compounds (**172a-d)** was evaluated using 1,1-diphenyl-2-picryl hydrazyl (DPPH), and all of them displayed moderate antioxidant activity,with compound **172c** exhibiting the strongest activity.

Abdi *et al*., (2021) reported the synthesis and evaluation of novel chloroquinoline analogs. 3-chloroaniline (**173**) was reacted with acetic anhydride (**174**) in the presence of zinc powder and acetic acid. The mixture was boiled under reflux using a water condenser for 2 hours to give 3-chloroacetanilide (**175**). The compound (**175**) was then treated by heating with N,N-dimethylformamide and phosphorus oxychloride at a temperature of 100-105 ℃ for 22 hours to give 2,7-dichloroquinoline-3-carbaldehyde **176**). Finally, the derivatives of 2,7-dichloroquinoline-3-carbaldehyde (**177a-d**) were obtained by treating 2,7-dichloroquinoline-3-carbaldehyde (**176**) with alcohol, potassium carbonate, and N,N-dimethylformamide under reflux for 4 hours to yield compound (**177c-d**), while compound **177a** was obtained by treating 2,7-dichloroquinoline-3-carbaldehyde with phosphorus oxychloride and sodium azide under reflux for 6 hours, and upon further treatment of compound **177a** with acetic acid and tetraoxosulfate (VI) acid under reflux for 3 hours, **177b** was formed (Scheme 28) **[84].**



The synthesis compounds **(177a-d)** were evaluated for their antioxidant activityusing 1,1-diphenyl-2-picrylhydrazyl (DPPH), and compounds **177a** and **177b** displayed the strongest antioxidant activity with IC_{50} of 2.17 and 0.31 µg/mL relative to ascorbic acid (2.41 µg/mL), respectively.

Asran *et al.,* (2023) reported the synthesis and antioxidant activity of some benzoquinoline-based heterocycles derived from 2-((3-chlorobenzo[f]quinoline-2-yl)methylene)hydrazine-1-carbothioamide **(183)**. The synthesis was achieved by reacting 3-chlorobenzo[f]quinoline-2-carbaldehyde (**178**) with thiosemicarbazide (**179**) in the presence of absolute ethanol and glacial acetic acid under reflux for 3 hours. The resulting solid crude compound was recrystallized from an ethanol/dioxane mixture (2:1) to yield 2-((3-chlorobenzo[f]quinolin-2-yl)methylene) hydrazine-1-carbothioamide (**180**). The new derivatives (**183a-d**) were subsequently obtained by treating the compound (**180**) with various reagents, including acetic anhydride under reflux for 6 hours, a mixture of chloroacetyl chloride, dioxane, and triethylamine at ambient temperature for 5 hours, a mixture of chloroacetyl chloride, dioxane, and anhydrous sodium acetate under reflux for 6 hours, a mixture of 2-bromo-1-(3-nitrophenyl)ethan-1-one (**181**), dioxane, and anhydrous sodium acetate under reflux for 5 hours, and a mixture of 2-chloro-N-phenylacetamide (**182**), dioxane, and sodium acetate under reflux for 6 hours, yielding compounds **183a, 183b, 183c, 183d,** and **183e**, respectively **[85].**



Scheme 19: Synthesis of Benzoquinoline-Based Heterocycles Derivatives

The synthesized compounds **183a-e** were examined for antioxidant activity according to phosphomolybdenum method using ascorbic acid as standard. The results showed that the compounds have good antioxidant activity. Compounds 1**83d** and **183e** displayed the highest potent levels of activity.

CONCLUSION

Over the years, many researchers have synthesized quinoline and its derivatives via various methodologies. This review focuses on the recent advancements in quinoline synthesis and their biological activities. Quinoline derivatives are versatile heterocyclic compounds that possess a wide range of biological activities, such as anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory, and cardiovascular activities. This work illustrates different synthetic methods of quinoline derivatives, such as Friedlander-modified metal-catalyzed reactions, photo-induced oxidative annulation reactions, and microwave-assisted Doebner reactions. The therapeutic potential of quinoline derivatives has drawn increasing attention from researchers in the fields of medicinal chemistry, pharmacy, and biochemistry. This review aims to provide useful insights for researchers seeking to advance the development of quinoline derivatives with enhanced biological activities via environmentally benign methods.

Conflicts of Interest: The Authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Authors Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting this paper is available in the cited references.

Ethical Approvals: Not applicable

REFERENCES

1. Tanaka, M.; Szatmári, I.; Vécsei, **L.** Quinoline Quest: Kynurenic Acid Strategies for Next-Generation Therapeutics via Rational Drug Design. Pharmaceuticals **2025**, 18 (5), 607. https://doi.org/10.3390/ph18050607.
2. Zhao Y.Q., Li X., Guo H.Y., Shen Q.K., Quan Z.S., Luan T. Application of Quinoline Ring in Structural Modification of Natural Products. Molecules **2023**, 28(18): 6478. https://doi.org/10.3390/molecules28186478.
3. Mittal R.K, Aggarwal M.,Khatana K.,Purohit P. Quinoline: Synthesis to application. Medicinal Chemistry **2023**, 19 (1),pp 31-46
4. Li, J.; Gu, A.; Nong, X.; Zhai, X.; Yue, Z.; Li, M.; Liu, Y. Six-Membered Aromatic Nitrogen Heterocyclic Anti-Tumor Agents: Synthesis and Applications. Chem. Rec. **2023**, 23 (12), e202300293. https://doi.org/10.1002/tcr.202300293.
5. Kumaraswamy, B.; Hemalatha, K.; Pal, R.; Matada, G. P.; Hosamani, K. R.; Aayishamma, I.; Aishwarya, N. S. An Insight into Sustainable and Green Chemistry Approaches for the Synthesis of Quinoline Derivatives as Anticancer Agents. Eur. J. Med. Chem. **2024**, 275, 116561. https://doi.org/10.1016/j.ejmech.2024.116561.
6. Gach-Janczak, K.; Piekielna-Ciesielska, J.; Waśkiewicz, J.; Krakowiak, K.; Wtorek, K.; Janecka, A. Quinolin-4-ones: Methods of Synthesis and Application in Medicine. Molecules **2025**, 30 (1), 163. https://doi.org/10.3390/molecules30010163.

7. Ajani, O. O.; Iyaye, K. T.; Ademosun, O. T. Recent Advances in Chemistry and Therapeutic Potential of Functionalized Quinoline Motifs—A Review. RSC Adv. **2022**, 12 (29), 18594–18614. https://doi.org/10.1039/d2ra02896d.
8. Bharti, A.; Bijauliya, R. K.; Yadav, A.; Suman. The Chemical and Pharmacological Advancements of Quinoline: A Mini Review. J. Drug Deliv. Ther. **2022**, 12 (4), 211–215.
9. Ferreira, L. M.; García-García, P.; García, P. A.; Castro, M. A. A Review on Quinolines: New Green Synthetic Methods and Bioactive Potential. Eur. J. Pharm. Sci. **2025**, 209, 107097. https://doi.org/10.1016/j.ejps.2025.107097.
10. Rao, I. R.; Punitha, P.; Premalatha, B.; Prasad, T. S.; Suresh, M. Synthesis, Structure Identification, Antioxidant and Antimicrobial Activities of Some Novel Quinoline Derivatives. Discov. Chem. **2024**, 1 (65), 1–13. https://doi.org/10.1007/s44371-024-00068-w.
11. Dine, I.; Mulugeta, E.; Melaku, Y.; Belete, M. Recent Advances in the Synthesis of Pharmaceutically Active 4-Quinolone and Its Analogues: A Review. RSC Adv. **2023**, 13, 8657–8682.
12. Jatolia, S. N.; Shubh, L.; Kanahiya, L.; Bhojak, N.; Regar, O. P. A Review of Quinoline and Its Derivatives. Int. J. Novel Res. Phys. Chem. Math. **2022**, 9 (2), 6–16.
13. Martin-Àcosta, P.; Cuadrado, I.; Gonzàles-Confrade, L.; Pestano, R.; Hortelano, S.; De-las Heras, B.; Esteves-Braun, A. Synthesis of Quinoline and Dihydroquinoline Embeline Derivatives as Cardio-Protectives. J. Nat. Prod. **2023**, 86, 317–329.
14. Ahmad, A.; Yarima, U.; Ibrahim, A. A.; Salihu, F. A.; Goni, I.; Yunusa, Z. Y. Plants That Have Quinoline Alkaloid and Their Biological Activity. J. Appl. Pharm. **2023**, 15 (6), 387.
15. Abdelgalil, M. M.; Ammar, Y. A.; Ali, A. M.; Ali, K. A.; Ragab, A. A Novel of Quinoxaline Derivatives Tagged with Pyrrolidinyl Scaffold as a New Class of Antimicrobial Agents: Design, Synthesis, Antimicrobial Activity, and Molecular Docking Simulation. J. Mol. Struct. **2023**, 1274 (2), 134443. https://doi.org/10.1016/j.molstruc.2022.134443.
16. Wesam, S. S.; Mostafa, M. K.; Doaa, A. E.; Krishna, K. Y.; Magda, H. A. Current Progress Toward Synthetic Routes and Medicinal Significance of Quinoline. Med. Chem. Res. **2023**, 32, 2443–2457.
17. Panchal, N. B.; Vaghela, V. M. From Molecules to Medicine: The Remarkable Pharmacological Odyssey of Quinoline and Its Derivatives. Orient. J. Chem. **2023**, 39 (3).
18. Kavalapure, R. S.; Alegaon, S. G.; Gharge, S.; Ranade, S. D.; Gudasi, S.; Venkatasubramanian, U.; Priya, S. A. Structure-Guided Development of Quinoline Derivatives Targeting Kinesin Spindle Protein. Bioorg. Med. Chem. Lett. **2025**, 125–126, 130278. https://doi.org/10.1016/j.bmcl.2025.130278.
19. Asokan, K.; Sivaraman, S.; Nallasamy, K.; Subbiah, J.; Paranthaman, S. Spectroscopic, DFT, In Silico, and Estimation of Biological Activity of 2,4-Dichloro-6,7-Dimethoxyquinazoline as a Potential Anti-Alzheimer's Disease Therapeutic Agent. Int. J. Quantum Chem. **2025**, 125 (1). https://doi.org/10.1002/qua.70006.
20. Lewinska, G.; Jerzy, S.; Marszalek, K. W. Application of Quinoline Derivatives in Third-Generation Photovoltaics. J. Mater. Sci.: Mater. Electron. **2021**, 32, 18451–18465.
21. Burlov, A. S.; Vlasenko, V. G.; Garnovskii, D. A.; Uraev, A. I.; Koshchienko, Y. V.; Mal'tsev, E. I.; Lypenko, D. A.; Dmitriev, A. V. Photoluminescence and Electroluminescence of Metal Complexes of Quinoline Derivatives. Russ. J. Coord. Chem. **2023**, 49 (1), S29–S37. https://doi.org/10.1134/S107032842360021.
22. Faydy, M. E.; Barrahi, A.; Timoudan, N.; Warad, I.; Safi, Z.; Wazzan, N.; Kaichouh, G.; Benhiba, F.; Dafali, A.; Lakhrissi, B.; Zarrouk, A. Corrosion Inhibition and Adsorption Behaviour of Two Novel Quinolin-8-ols on Carbon Steel Surface in HCl: Synthesis, Electrochemical, Surface Characterisation, and Quantum Chemical Approaches. Can. Metall. Q. **2025**, 1–23.
23. Bouassiria, M.; El Faydy, M.; Benhiba, F.; Laabaissi, T.; Fakhry, H.; Saoiabi, S.; Touir, R.; Warad, I.; Guenbour, A.; Lakhrissi, B.; Oudda, H.; Zarrouk, A**.** Corrosion Effectiveness of 5-(4-Phenylpiperazin-1-yl)methyl)quinolin-8-ol for Carbon Steel in 1.0 M HCl. J. Bio Tribo Corros. **2022**, 8 (43). https://doi.org/10.1007/s40735-022-00641-9.
24. Răuță, D.; Matei, E.; Avramescu, S. Recent Development of Corrosion Inhibitors: Types, Mechanisms, Electrochemical Behavior, Efficiency, and Environmental Impact. Technol. **2025**, 13 (3), 103. https://doi.org/10.3390/technologies13030103.
25. Cai, Q.; Song, H.; Zhang, Y.; Zhu, Z.; Zhang, J.; Chen, J. Quinoline Derivatives in Discovery and Development of Pesticides. J. Agric. Food Chem. **2024**, 72 (22), 12373–12386.

26. Zhang, Y.; Lu, S.; Zhu, Z.; Du, T.; Zhu, M.; Chen, J. Fungicidal and Nematicidal Activities of Pyrazolopyrimidine against 14 Pathogenic Fungi and 3 Plant Nematodes. Physiol. Mol. Plant Pathol. **2025**, 139, 102798. https://doi.org/10.1016/j.pmpp.2025.102798.
27. Elnaggar, N. N.; Hamama, W. S.; El Salam, M. A.; Ghaith, E. A. Chemoselective Synthesis of Tunable Poly-Functionalized Binary Pyrazolyl and Annulated Pyrazolo/Pyrido Anchored on Quinolinone: Insecticidal and Antioxidant Studies. RSC Adv. **2025**, 15 (8), 6050–6067. https://doi.org/10.1039/D4RA08834D.
28. Peron, C.; Gonçalves, R. S.; Moura, S. Advances in the Potential of Quinoline-Derived Metal Complexes as Antimalarial Agents: A Review. Appl. Organomet. Chem. **2025**, 39 (3), 70050.
29. Mishra, R.; Xavier, J.; Kumar, N.; Krishna, G.; Dhakad, P. K.; Silva dos Santos, H.; Bandeira, P. N.; Rodrigues, T. H.; Gondim, D. M.; Ribeiro, W. H.; Sales da Silva, D.; Teixeira, A. M.; Pereira, W. F.; Marinho, E. S.; Sucheta. Exploring Quinoline Derivatives: Their Antimalarial Efficacy and Structural Features. Med. Chem. **2025**, 21 (2), 96–121. https://doi.org/10.2174/0115734064318361240827072124.
30. Roy, D.; Anas, M.; Manhas, A.; Saha, S.; Kumar, N.; Panda, G. Synthesis, Biological Evaluation, Structure–Activity Relationship Studies of Quinoline-Imidazole Derivatives as Potent Antimalarial Agents. Bioorg. Chem. **2022**, 121, 105671. https://doi.org/10.1016/j.bioorg.2022.105671.
31. Srinivasa, B. J.; Ullal, S. N.; Kalal, B. S. Quinoline Conjugates for Enhanced Antimalarial Activity: A Review on Synthesis by Molecular Hybridization and Structure–Activity Relationship (SAR) Investigation. Am. J. Transl. Res. **2025**, 17 (2), 1335–1375. https://doi.org/10.62347/TTHX6526.
32. Kucharski, D. J.; Jaszczak, M. K.; Boratyński, P. J. A Review of Modifications of Quinoline Antimalarials: Mefloquine and (Hydroxy)Chloroquine. Molecules **2022**, 27 (3), 1003. https://doi.org/10.3390/molecules27031003.
33. Hernández-Ayala, L. F.; Guzmán-López, E. G.; Galano, A. Quinoline Derivatives: Promising Antioxidants with Neuroprotective Potential. Antioxidants **2023**, 12 (10), 1853. https://doi.org/10.3390/antiox12101853.
34. Mathada, B. S. The Versatile Quinoline and Its Derivatives as Anti-Cancer Agents: An Overview. Polycycl. Aromat. Compd. **2022**, 43 (5), 4333–4345. https://doi.org/10.1080/10406638.2022.2089177.
35. Zieba, A.; Pindjakova, D.; Latocha, M.; Plonka-Czerw, J.; Kusmierz, D.; Cizek, A.; Jampilek, J. Design, Synthesis, and Anticancer and Antibacterial Activities of Quinoline-5-Sulfonamides. Molecules **2024**, 29 (17), 4044. https://doi.org/10.3390/molecules29174044.
36. Kushwaha, P. Quinoline as a Privileged Structure: A Recent Update on Synthesis and Biological Activities. Curr. Top. Med. Chem. **2024**, 24 (27), 2377–2419. https://doi.org/10.2174/0115680266314303240830074056.
37. Elebiju, O. F.; Ajani, O. O.; Oduselu, G. O.; Ogunnupebi, T. A.; Adebiyi, E. Recent Advances in Functionalized Quinoline Scaffolds and Hybrids—Exceptional Pharmacophore in Therapeutic Medicine. Front. Chem. **2023**, 10, 1074331. https://doi.org/10.3389/fchem.2022.1074331.
38. Wang, X.; Yang, A.; Xiao, H.; Xiao, W.; Xu, L.; Wang, D. C3–H Trifluoroacetylation of Quinolines and Pyridines: Access to Heteroaryl Ketones, Carboxylic Acids, and Amides. Org. Lett. **2025**, 27 (22), 5625–5631. https://doi.org/10.1021/acs.orglett.5c01350.
39. Gao, M.; Ding, C.; Huang, P.; Xie, R.; Liu, Y. Photoredox Radical Cyclization of o-Vinylaryl Isocyanides and Aryldiazonium Tetrafluoroborates for the Synthesis of 2,4-Disubstituted Quinolines. J. Org. Chem. **2025**, 90 (13), 4571–4579. https://doi.org/10.1021/acs.joc.4c03121.
40. Suresh, S.; Keerthana, P.; Khan, F. N. Alkylated Quinolines through Benzylic sp^3 C−H Functionalization: Sequential Synthesis and Photophysical Studies. Asian J. Org. Chem. **2025**, 14 (2). https://doi.org/10.1002/ajoc.202400607.
41. Rao, L. B.; Sreenivasulu, C.; Kishore, D. R.; Satyanarayana, G. Trending Strategies for the Synthesis of Quinolinones and Isoquinolinones. Tetrahedron **2022**, 127, 133093. https://doi.org/10.1016/j.tet.2022.133093.
42. Mohasin, M.; Alam, M. Z.; Ullah, Q.; Ahmad, A.; Rahaman, P. F.; Khan, S. A. A Review on Synthesis and Biological Applications of Quinoline Derivatives as Fused Aromatic Compounds. Polycycl. Aromat. Compd. **2023**, 44 (9), 6369–6398. https://doi.org/10.1080/10406638.2023.2270118.
43. Shehab, W. S.; Amer, M. M. K.; Elsayed, D. A.; Yadav, K. K.; Abdellattif, M. H. Current Progress Toward Synthetic Routes and Medicinal Significance of Quinoline. Med. Chem. Res. **2023**, 32, 2443–2457. https://doi.org/10.1007/s00044-023-03121-y.

44. Darbandizadeh, S. A.; Balalaie, S. Recent Advances in the Synthesis of Fused-Cyclic Quinolines: Review. Asian J. Org. Chem. **2024**, 13 (5), e202400041. https://doi.org/10.1002/ajoc.202400041.
45. Mandal, A.; Khan, A. T. Recent Advancement in the Synthesis of Quinoline Derivatives via Multicomponent Reactions. Org. Biomol. Chem. **2024**, 22 (12), 2339–2358.
46. Hellel, D.; Chafaa, F.; Nacereddine, A. K. Synthesis of Tetrahydroquinolines and Quinoline Derivatives through the Lewis Acid Catalysed Povarov Reaction: A Comparative Study between Multi-Step and Multi-Component Methods. Sci. Radices **2023**, 2 (3), 295–308.
47. Mondal, A.; Pal, D.; Phukan, H. J.; Roy, M.; Kumar, S.; Purkayastha, S.; Guha, A. K.; Srimani, D. Manganese Complex Catalyzed Sequential Multi-Component Reaction: Enroute to a Quinoline-Derived Azafluorenes. ChemSusChem **2023**, 17 (7), e202301138. https://doi.org/10.1002/cssc.202301138.
48. Dhara, S.; Islam, S.; Das, A. R. One-Pot Three-Component Synthesis of Quinolines and Some Other Selective Six-Membered Heterocycles with Biological Importance. In Multicomponent Synthesis: Bioactive Heterocycles; **2023**; 5, 117.
49. Mohareb, R. M.; Zahran, M. K.; Maghraby, H. R.; Abdallah, A. E. Multicomponent Reactions of Cyanoacetanilide Derivatives: Synthesis of Coumarin and Quinoline Derivatives and Evaluations of Their Cytotoxicity. Bull. Chem. Soc. Ethiop. **2024**, 38 (3), 739–750.
50. Kumar, A.; Dhameliya, T. M.; Sharma, K.; Patel, K. A.; Hirani, R. V**.** Environmentally Benign Approaches Towards the Synthesis of Quinolines. ChemistrySelect **2022**, 7 (22), e202201059. https://doi.org/10.1002/slct.202201059.
51. Wang, Z.-H.; Shen, L.-W.; Yang, P.; You, Y.; Zhao, J.-Q.; Yuan, W.-C. Access to 4-Trifluoromethyl Quinolines via Cu-Catalyzed Annulation Reaction of Ketone Oxime Acetates with ortho-Trifluoroacetyl Anilines under Redox-Neutral Conditions. J. Org. Chem. **2022,** 87, 5804–5816.
52. Chen, B.W.J., Chang, L.L., Yang, J., Wei, Y., Yang, J., Ying, J.Y. Palladium-based nanocatalyst for one-pot synthesis of polysubstituted quinolines. Chem. Cat. Chem. **2013**, 5, 277–283
53. Wang, X.; Yan, K.; Liu, M.; Wen, J.; Liu, X.; Sui, X.; Shang, W.; and Xiaoyu, W. Synthesis of 3-substituted quinolines by ruthenium-catalyzed aza-Michael addition and intramolecular annulation of enaminones with anthranils. New Journal of Chemistry, **2022**, 16
54. Zou, L.-H.; Yang, J.-C.; Ma, C.-W.; Liao, M.-L.; Li, P.-G. Copper-Catalyzed [4+1+1] Annulation of Ammonium Salts and Anthranils: Synthesis of 2,3-Diaroylquinolines. J. Org. Chem. **2024**, 89, 7446–7454
55. Huang, G.; Yuan, J.-M.; Li, J.; Zhou, H.; Xu, J.; Zhu, F.; Liang, Q.; Liu, Z.; Huang, J. Synthesis of 3-Sulfonylquinolines by Visible-light Promoted Metal-free Cascade Cycloaddition Involving N-Propargylanilines and Sodium Sulfinates. New J. Chem. **2020**, 44, 3189–3193.
56. Talvite, J.; Alanko, I.; Bulatov, E.; Koivula, J.; Pollanen, T.; helaja, J.. Phenanthracenequinone-Sensitized Photocatalytic Synthesis of Polysubstituted Quinolines from 2-Vinylarylimines. Org. Lett. **2022**, 24, 274-278
57. Crabtree, R. H. An Organometallic Future in Green and Energy Chemistry. Organometallics. **2011**
58. Chen, P., Nan, J., Hu, Y., Ma, Q., Ma, Y. Ru(II)-catalyzed/NH2-assisted selective alkenyl C-H [5 + 1] annulation of alkenylanilines with sulfoxonium ylides to quinolines. Org. Lett. **2019**, 21, 4812–4815
59. Dunn, P.J. The Importance of Green Chemistry in Process Research and Development. Chem. Soc. Rev. **2012**, 41, 1452–1461
60. Ramann, G.A., Cowen, B.J. Recent Advances in Metal-free Quinoline synthesis. Molecules **2016**
61. Patel, D.B., Rajani, D.P., Rajani, S.D., Patel, H.D. A green synthesis of quinoline-4- carboxylic derivatives using p-toluenesulfonic acid as an efficient organocatalyst under microwave irradiation and their docking, molecular dynamics, ADME-tox and biological evaluation. J. Heterocycl. Chem. **2020**, 57, 1524–1544
62. Faraz, S., Khan, A.T. p-TSA.H2O catalyzed metal-free and environmentally benign synthesis of 4-aryl quinolines from arylamine, arylacetylene, and dimethyl sulfoxide. Org. Biomol. Chem. **2023**, 21, 7553–7560
63. Rao, I. R.; Punitha, P.; Premalatha, B.; et al. Synthesis, structure identification, antioxidant and antimicrobial activities of some novel quinoline derivatives. Discov. Chem. **2024**, 1, 65. https://doi.org/10.1007/s44371-024-00068-w

64. Prashanth, T.; Lakshmi Ranganatha, V.; Al-Ghorbani, M.; et al. Design, synthesis and characterization of 8-[(1H-benzo[d]imidazol-2-yl) methoxy] quinoline derivatives as antimicrobial agents. Discov. Chem. **2025**, 2, 19. https://doi.org/10.1007/s44371-025-00089-z.
65. Ghorab, M.M.; Soliman, A.M.; El-Sayyad, G.S.; Abdel-Kader, S.M.; and El-Batal, A.I. Synthesis, Antimicrobial and Antibiofilm Activities of some novel-7-Methoxyquinolines Derivatives Bearing Sulfonamide Moiety against urinary tract infection-causing pathogenic microbes, International Journal of Molecular Sciences, **2023,** 24, 8933
66. Zieba, A.; Pindjakova, D.; Latocha, M.; Plonka-Czerw, J.; Kusmierz, D.; Cizek. A.; and Jampilek, J. Design, Synthesis , and Anticancer and Antibacterial Activities of Quinoline-5-Sulfonamides, Molecules, **2024** 29,4044.
67. Saifi, Z.; Ali, A.; Inam, A.; Kamthan, M.; Abid, M.; and Ali, I. Synthesis and antibacterial evaluation of quinoline- sulfonamide hybrid compounds: a promising strategy against bacteria resistance, RSC Adv. **2025**, 15,1680-1689.
68. El-Shershaby, M.H.; El-Gamal, K.M.; Bayoumi, A.H.; El-Ad, K.; Ahmed, H.E.A.; and Abulkhair, S.H. Synthesis, antimicrobial evaluation, DNA gyrase inhibition, and in silico pharmacokinetic studies of novel quinoline derivatives, Arch pharm. **2020**, 20(2),810-824.
69. Singh, V.K.; Kumari, P.; Som, A.; Rai, S.; Mishra, R.; and Singh, R. Design, synthesis and antimicrobial activity of novel quinoline derivatives: an in silico and in vitro study, Journal of Biomolecular Structure and Dynamics, **2024**, 42(13): 6904-6924.
70. Al-Materneh, C.M.; Nicolescu, A.; Marinas, I.C.; Gaboreanu, D.M.; Shova, S.; Dascalu, A.; Silion, M.; and Pinteala, M. New Library of Iodo-quinoline derivatives obtained by analternative synthetic pathway and their antimicrobial activity, Molecule, **2024,** 29, 772
71. Abdelrahman, M. A.; Almahli, H.; Al-Warhi, T.; Majrashi, T. A.; Abdel-Aziz, M. M.; Eldehna, W. M.; Said, M. A. Development of novel isatin-tethered quinolines as anti-tubercular agents against multi- and extensively drug-resistant Mycobacterium tuberculosis. Molecules **2022**, 27(24), 8807. https://doi.org/10.3390/molecules27248807
72. Lagdhira, M.; Pandya, C.; Pandyab, A.; Vekariyac, H.R.; and Rajanid, D.P. Design and synthesis of new quinoline hybrid derivatives and their antimicrobial, antimalarial and antitubercular activities, Indian Journal of Chemistry, **2021**, 60, 986-998.
73. Touré, M.; Gassama, A.; Sambou, O.; Cavé, C.; and Cojean, S. Synthesis and in vitro/in silico evaluation of the antimalarial activity of potential amino-quinoline derivatives, European journal of Medicinal Chemistry, **2024**, 13,10024-10056.
74. Choudhary, D.; Rani, P.; Rangra, N.K.; Gupta, G.K.; Khokra, S.L.; Bhandare, R.R.; and Shaik, B.A. Designing novel anti-plasmodial quinoline–furanone hybrids: computational insights, synthesis, and biological evaluation targeting Plasmodium falciparum lactate dehydrogenase, Royal Society of Chemistry Advance, **2024**, 14, 18764-18776.
75. Zaraei, S.; Al-Ach, N.N.; Anbar,S.H.; El-Gamal, R.; Tarazi ,H.; Tokatly,T.S.; Kalla,R.R.; Munther,M.A.; Wahba,M.M.; Alshihabi,M.A.; Shehata, M.K.; Sbenati, R.M.; Shahin, I.A.; Awady,R.; Al-Tel, T.H.; and El-Gamal, M.I. Design and synthesis of new quinoline derivatives as selective C-RAF kinase inhibitors with potent anticancer activity, European Journal of Medicinal Chemistry, **2022**, 238, 114434-53.
76. Khodair, M.A.; Mohamed, M.S.; Awad, S.M.; and Abd El-Hameed, H.R. Synthesis, Anticancer Activity, and Docking Study of Novel Benzo[h]quinoline Derivatives, Trends in Advanced Science and Technology, **2024**, 1,159-176.
77. Srinivasa, B.S.; Poojary, B.; Kalal S.B.; Brahmavara, U.; Vaishali, D.; Das, J.A.; Kalenga, T.M.; Paidikondala, M.; and Shankar,K.M. Design, synthesis and anticancer activity of Novel benzimidazole containing quinoline hybrids, Results in Chemistry, **2024**, 9,101631.
78. Shaldam, M.; Nocentini, A.; Elsayed, Z.M.; Ibrahim, T.M.; Salem, R.; El-Domany, R.A.; Capasso, C.; Supuran, C.T.; and Eldehna W.M. Development of Novel Quinoline-Based Sulfonamides as Selective Cancer-Associated Carbonic Anhydrase Isoform IX Inhibitors, International Journal of Molecular Sciences, **2021**, 22, 11119.
79. Marciniec, K.; Rzepka, Z.; Chrobak, E.; Boryczka, S.; Latocha, M.; Wrzesniok, D.; and Bebetro. A. Design, Synthesis and Biological Evaluation of Quinoline-8-Sulfonamides as Inhibitors of the tumor Cell-SpecificM2Isoform of Pyruvate Kinase: Preliminary Study, Molecules, **2023**, 28**,** 2509.

80. Ghanim, A. M.; Girgis, A. S.; Kariuki, Benson M.; Samir, N.; Said, M. F.; Abdelnaser, A. N.; Bekheit, M. S.; Abdelhameed, M. F.; Almalki, A. J.; Ibrahim, T.S.; and Panda, S.S. Design and synthesis of ibuprofen-quinoline conjugates as potential anti-inflammatory and analgesic drug candidates. Bioorganic Chemistry, **2022**, ;, 105557.
81. Silva, S.E.B.; Moura, J.A.S.; Júnior, J.F.B.; Gomes, P.A.; Paula, S.K.S.; Carvalho, D.; Viana, F.; Ramalho, E.A.; Melo , J.V.; Pereira, M.C.; Pitta, M. G.; Pitta, I.R.; and Pitta, M.G. Synthesis and In vitro and In silico Anti-inflammatory Activity of New Thiazolidinedione-quinoline Derivatives, Current Topics in Medicinal Chemistry, **2024**, 24, 1264-1277.
82. Villarroel-Vicente, C.; García, C.; Zibar, K.; Schiel, M.A.; Ferri, J.; Hennuyer, N.; Enriz, D.R.; Staels, B.; Cortes, D.; and Cabedo, N. Synthesis of a new 2-prenylated quinoline as potential drug for metabolic syndrome with pan-PPAR activity and anti-inflammatory effects. Bioorganic & Medicinal Chemistry Letters, **2024,** 106(1): 129770.
83. Zeleke, D.; Eswaramoorthy, R.; Belay, Z.; and Melaku, Y. Synthesis and Antibacterial, Antioxidant, and Molecular Docking Analysis of Some Novel Quinoline Derivatives, Journal of Chemistry, **2020,** 24, 2962-2978.
84. Abdi, B.; Fekadu, M.; Zeleke, D.; Eswaramoorthy, R.; and Melaku, Y. Synthesis and Evaluation of the Antibacterial and Antioxidant Activities of Some Novel Chloroquinoline Analogs , Journal of Chemistry, **2021,** 36, 262-275.
85. Asran, M.; El-Helw, E.A.; Azab, M.E.; Ramadan, S.K.; and Helal, H.M. Synthesis and Antioxidant Activity of some Benzoquinoline-based Heterocycles from 2-((3-Chlorobenzo[f]quinoline-2-yl)methylene)hydrazine-1-carbothioamide, Journal of the Iranian Chemical Society, **2023,** 30: 3023-3032.