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REVIEW ARTICLE

A Review on Emerging Insights and Novel Innovations in Quinoline Derivatives

Sakshi Gupta[1,2,*], Shweta Verma[1] and Nalini Kanta Sahoo[2]

[1]*Faculty of Pharmacy, IFTM University, Lodhipur-Rajput, Moradabad-244102, India;* [2]*MIT College of Pharmacy, MIT Campus, Moradabad, Uttar Pradesh-244001 India*

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Sakshi Gupta

Abstract: Quinoline derivatives are considered highly promising for developing anticancer drugs due to their ability to disrupt essential cellular processes by inserting themselves between DNA base pairs. This interference inhibits crucial activities like DNA replication and transcription, making these compounds effective against cancer cells, thereby further boosting their potential to improve overall treatment outcomes. The synthesis of quinoline derivatives involves several named reactions such as the Riehm Quinoline Synthesis, Doebner reaction, Doebner Miller reaction, Gould-Jacobs reaction, Conrad-Limpach synthesis, Combes quinoline synthesis, Skraup reaction, and many others. Furthermore, the novel innovations by various researchers described in this article allow for the production of novel derivatives with specific substitution patterns and biological activities, enabling researchers to optimize pharmacological properties like bioavailability and target specificity. Recent studies have yielded quinoline derivatives that exhibit an increased ability to kill cancer cells and greater specificity for different types of cancer. Moreover, many researchers have demonstrated the strong effectiveness of quinoline derivatives against tumors in early-stage testing, setting the stage for continued research and clinical trials. Thus, quinoline derivatives show great potential in combating cancer, presenting new opportunities for developing innovative therapies for cancer treatment.

Keywords: Quinoline, anti-cancer, treatment, apoptosis.

1. INTRODUCTION

Cancer is a genetic disorder that originates from the genetic changes and epigenetic makeup of certain cells, leading them to undergo abnormal growth and potentially spread to other parts of the body [1]. Cells multiplying uncontrollably form a cluster known as a neoplasm or tumor, which manifests as a lump or mass and can spread throughout the body in a scattered manner [2].

It is marked by disruptions and changes, cellular conversion, faulty control of cell division, formation of new blood vessels, and heightened invasion, leading to the spread of cancer [3,4]. Cancer is a complex disease with various factors contributing to its development. Genetic mutations play a significant role, and while some mutations occur naturally during cell division, environmental factors like tobacco smoke and UV radiation can increase the likelihood of mutations that ultimately lead to cancer. Understanding these factors is essential to develop effective prevention and treatment strategies [5,6]. Currently, cancer ranks among the foremost causes of mortality globally [7]. While numerous anticancer treatments exist, the majority of them exhibit cytotoxic effects not only on cancer cells but also on healthy cells [8]. resulting in significant adverse effects such as vomiting, alopecia, reduced body weight, fatigue, dermatological reactions, and decreased appetite [9]. Given this reality, the quest for innovative chemotherapy drugs remains a dynamic and compelling area of cancer research. Nonetheless, there is a pressing need to create treatments that are both more potent against cancer and less harmful to the body, targeting specific molecular pathways for optimal anticancer effects [10].

In this view, Quinoline **(1)** stands out as the most prevalent heterocyclic aromatic compound, structurally a fusion of benzene and the *N*-heterocyclic pyridine, as shown in (Fig. **1**) [11]. Additionally referred to as 1-Azanapthalene and benzo[b].pyridine, it holds versatility in various applications, being used both for industrial and medicinal purposes, and is now considered a common pharmacophore for designing new drugs [12]. Friedlieb Runge discovered quinoline in 1834, obtaining it by coal-tar distillation, and it was identified as a colorless, hygroscopic liquid [13].

The quinoline motif and its derivatives have shown various pharmacological activities, as they are used in the treatment of inflammation [14], HIV [15], protozoal infections [16], tuberculosis [17], fungal infections [18], psychosis [19], cancer [20], lupus treatment [21], and neurodegenerative diseases [22]. The quinoline structure is crucial in the development of anticancer drugs because its variations have demonstrated promising outcomes through various mechanisms, including halting cell growth by arresting the cell cycle, inducing programmed cell death (apoptosis), stopping the formation of new blood vessels (angiogenesis), interfering with cell movement, and altering how nuclear receptors respond [23].

Looking at some approved, marketed drugs (depicted in Fig. **1**) like Quinine **(2)**, the primary antimalarial treatment historically, which shares a common structural foundation known as the quinoline scaffold with its derivatives, such as chloroquine **(3)** and mefloquine **(4)**, also widely utilized in combating malaria [24]. Moreo-

*Address correspondence to this author at the Faculty of Pharmacy, IFTM University, Lodhipur-Rajput, Moradabad-244102, India; MIT College of Pharmacy, MIT Campus, Moradabad, Uttar Pradesh-244001 India;
E-mail: sakshig1654@gmail.com

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ver, quinoline has found its way into numerous drugs designed to serve various medical conditions. These include ciprofloxacin **(5)**, a fluoroquinolone antibiotic and its variants, pitavastatin **(6)**, which helps lower cholesterol levels, and Lenvatinib **(7)**, a kinase inhibitor used in cancer treatment, along with structurally similar analogs like carbozantinib **(8)** and bosutinib **(9)** [25,26]. Additionally, medications like tipifarnib **(10)**, saquinavir **(11)**, and bedaquiline **(12)** utilize quinoline in their formulations to combat leukemia, HIV/AIDS, and tuberculosis, respectively [27,28]. For the prevention and treatment of COVID-19, hydroxychloroquine **(13)** is under investigation. However, clinical trials carried out in 2020 concluded that it is not effective and may lead to serious adverse effects [29].

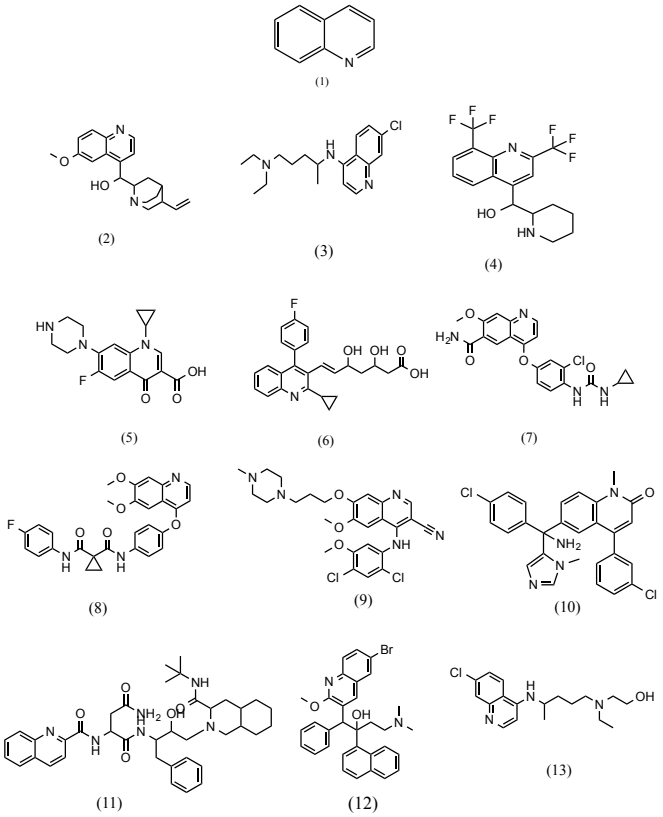


Fig. (1). Structure of quinoline and their various approved marketed drugs [11,24-29].

Furthermore, researchers worldwide have undertaken extensive exploration efforts, resulting in the creation and advancement of novel quinoline derivatives, many of which are currently undergoing various phases of clinical trials (depicted in Fig. **2**), among which a promising preclinical anticancer compound known as 2-(2-fluorophenyl)-6,7-methylenedioxyquinoline-4-one monosodium phosphate (CHM-1-P-Na) (14) has demonstrated impressive efficacy in inhibiting tumor growth in experimental models involving SKOV-3 xenograft nude mice [30]. Dovitinib (15) is a small molecule taken orally that effectively blocks several receptor tyrosine kinases (RTKs) crucial for tumor growth and new blood vessel formation. Research conducted prior to clinical trials demonstrates that dovitinib can effectively hinder various kinases linked to diverse cancer types, such as acute myeloid leukemia (AML) and multiple myeloma [31]. Procaterol (16) is a medication that activates the beta-2-adrenergic receptors for an extended period. It effectively widens the air passages in the lungs and can be taken either orally or as an aerosol inhalation [32]. Sitamaquine (17), also known as WR-6026, is a medication taken orally that belongs to the class of 8-aminoquinoline analogs. It is being investigated as a possible treatment for visceral leishmaniasis, a severe parasitic infection [33]. Pelitinib (EKB-569) (18) is a powerful medication specifically designed to block the epidermal growth factor receptor (EGFR) in a lasting and targeted manner. It is currently under development as a potential anticancer drug [34]. Laquinimod (19) is a medication that modulates the immune system and is now undergoing phase III clinical trials for the oral treatment of multiple sclerosis, similar to fingolimod. Research indicates that it diminishes disease activity observed on magnetic resonance imaging and is well-received when taken orally [35]. Foretinib (20) has been examined in clinical trials for treating different cancers such as breast cancer, renal cell carcinoma, recurrent breast cancer, head and neck neoplasms, and others. It specifically targets multiple receptor tyrosine kinases (RTKs) involved in the initiation, advancement, and dissemination of cancer [36]. Mardepodect (21), also known by the PF-2545920 code name, is a medication that works as a selective inhibitor of phosphodiesterase, particularly targeting the PDE10A subtype [37].

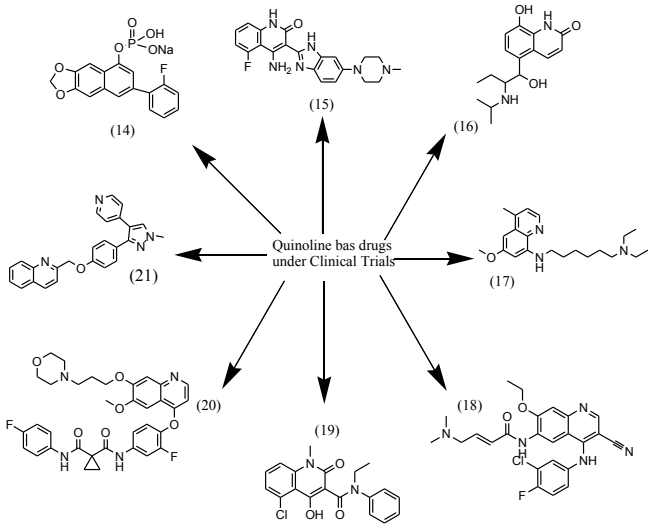


Fig. (2). Various quinoline based drugs under clinical trials [30-37].

2. METHODOLOGY

This review article was designed using a structured approach to collect, analyze, and summarize relevant scientific literature on quinoline and its pharmacological activities. A comprehensive literature search was carried out in databases such as PubMed, Scopus, Web of Science, and Google Scholar, covering articles published between 2006-2024. Keywords such as "quinoline," "quinoline derivatives," "pharmacological activity," "synthesis," and "biological evaluation" were used in various combinations to identify the relevant data. This review covers the various approved marketed drugs and quinoline-based drugs under clinical trials, as well as traditional methods for the synthesis of quinoline derivatives. Also, the article is based on the relevance of experimental work related to synthetic strategies and the pharmacological significance of the quinoline moiety. The gathered data were categorized into different sections, including synthetic schemes and pharmacological activities of the quinoline moiety. Moreover, the mechanism of action of quinoline derivatives against cancer is incorporated in the article. This method ensured the inclusion of high-quality studies that provide a comprehensive overview of the medicinal potential of quinoline-based compounds.

2.1. M.O.A of Quinolines

The latest research has shown that quinoline and its derivatives can hinder the activity of tyrosine kinases[38], topoisomerase[39], tubulin polymerization[40], and DHODH kinase[41]. In simpler terms, these compounds were found to interfere with various important enzymes and processes within cells. Additionally, DNA is essential for controlling cell function, making it a prime target for the initial wave of anticancer medications. Despite advancements in therapies, most effective treatments for cancer still revolve around compounds that directly affect DNA. The primary classes of these compounds are intercalating agents and topoisomerase inhibitors. With the various learning outcomes from genetics and molecular biology, our understanding of DNA and its role in cancer has grown immensely. We now know that various molecular mechanisms, such as G-quadruplex tetrad stabilization and epigenetic regulation of histones, play significant roles in the expression of oncogenes and cancer cell proliferation (as in Fig. **3**). These insights have led to the generation of novel therapeutic strategies which focus on disrupting proteins and enzyme expression that drive cancer cell growth [42,43].

Also, most of these medications focus on topoisomerase enzymes, particularly type II, which are crucial in treating cancers. These inhibitors are termed "poisons" because they form complexes with DNA that can be cleaved, causing significant damage to DNA. This damage triggers a series of biological reactions that ultimately result in either programmed cell death or cell death through various pathways. In simpler terms, these drugs interfere with key enzymes in cancer cells, causing irreparable damage to their DNA and leading to their destruction [44,45]. Topoisomerases are essential enzymes found in the cell nucleus, which aim to maintain the shape of DNA, either by relaxing positively or negatively supercoiled DNA. Apart from this, they are involved in various other functions, such as DNA replication and transcription. Most of the current anticancer drugs target a specific type of topoisomerase enzyme, called topoisomerase II. Additionally, many new drug combinations are being developed to specifically target these enzymes for treating different types of cancers in humans [46, 47].

3. TRADITIONAL METHODS FOR QUINOLINE DERIVATIVES SYNTHESIS

There are multiple ways to discover quinoline compounds. Most of these methods start with basic anilines and use well-known reactions to create quinolines (depicted in Fig. 4). These reactions often involve arylamines as starting materials.

3.1. Riehm Quinoline Synthesis

When aniline **(22)** and acetone **(23)** are mixed together in the presence of NH_4Cl, they combine to produce a quinoline compound **(24)** [48].

3.2. Doebner Reaction

When aldehyde **(25)** and pyruvic acid **(26)** react with an aniline **(22)**, it leads to the formation of a quinoline compound **(27)** [49].

3.3. Doebner Miller Reaction

In the presence of p-toluenesulfonic acid, when an alpha-beta unsaturated carbonyl compound **(28)** reacts with an aniline **(22)**, it forms a quinoline compound **(29)** [50].

3.4. Gould-Jacobs Reaction

When ethyl ethoxymethylenemalonate **(30)** undergoes a reaction with aniline **(22)** in the presence of conc. H_2SO_4, it forms a quinoline compound **(31)**[51].

3.5. Conrad-Limpach Synthesis

When beta-ketoester **(32)** undergoes a reaction with an aniline **(22)** the presence of H2SO4, it results in the formation of a quinoline compound **(33)** [52].

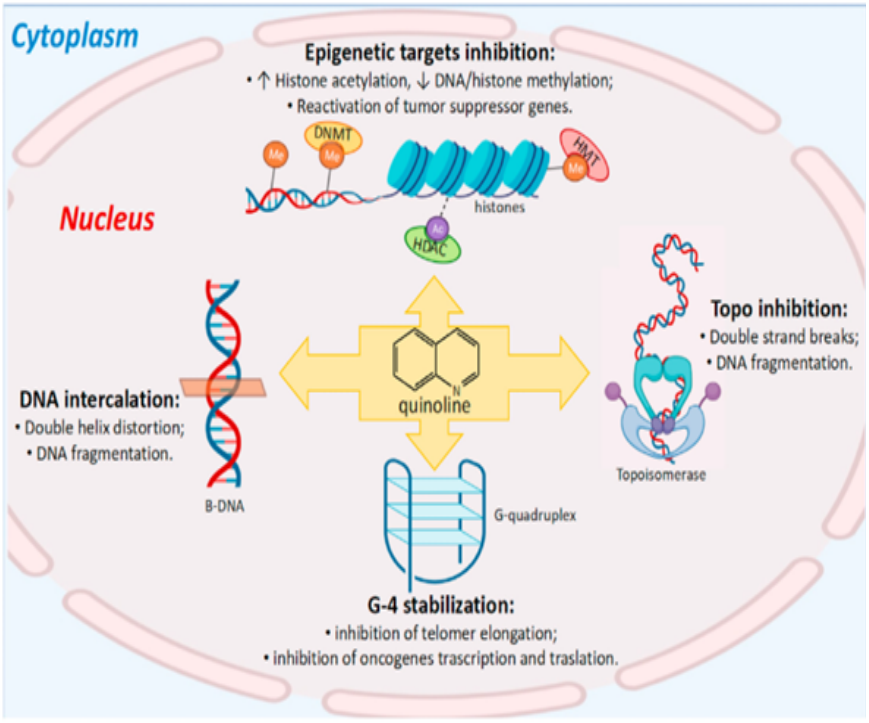


Fig. (3). Quinoline agents targeting active sites in the nucleus [44]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3.6. Combes Quinoline Synthesis

When beta-diketones **(34)** undergo a reaction with an aniline **(22)** in the presence of H_2SO_4, quinoline compounds are formed **(35)** [53].

3.7. Skraup Reaction

When glycerol **(36)** and nitrobenzene **(37)** combine with an aniline **(22)** in the presence of H_2SO_4, it results in the synthesis of a quinoline compound **(38)** [54].

3.8. Povarov Reaction

Quinoline compound can be prepared when benzaldehyde **(39)** undergoes a reaction with an aniline **(14)** in activated alkene presence. **(40)** [55].

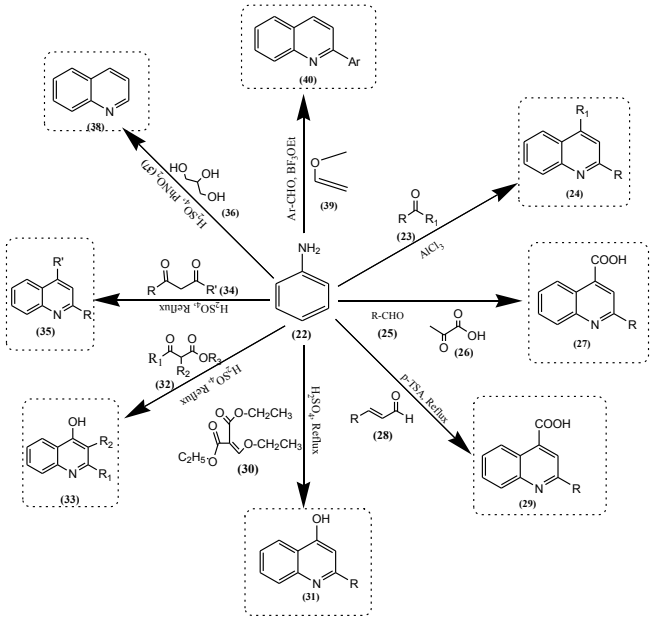


Fig. (4). Various named reaction for quinoline synthesis [48-55].

Additionally, the procedures mentioned above are commonly used to create quinoline compounds from substituted anilines or similar starting materials.

3.8.1. Friedlander Synthesis

Friedlander synthesis (Fig. **5**) involves the reaction of carbonyl compounds **(42)** with 2-amino benzaldehyde **(41)** in the presence of a trifluoroacetic acid catalyst, which forms a quinoline compound **(43) [**56].

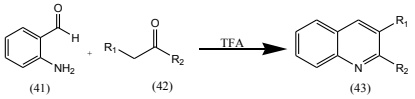


Fig. (5). Friedlander reaction [56].

3.8.2. Snieckus Synthesis

This reaction (Fig. **6**) occurs when ortho substituted aniline **(44)** condensed with acetone **(45)** in the presence of sulfuric acid. Further, upon deprotonation and intramolecular cyclization it forms quinoline **(46)** [57].

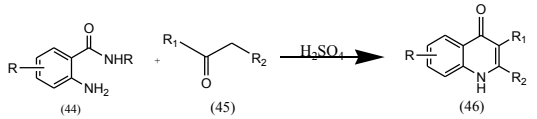


Fig. (6). Snieckus synthesis [57].

3.8.3. Knorr Quinoline Synthesis

This reaction (Fig. **7**) occurs when an aryl amine **(47)** is reacted with β-keto ester **(48)** in the presence of sulfuric acid, it undergoes a cyclization reaction to form a quinoline compound **(49)** [58].

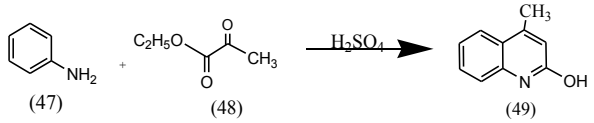


Fig. (7). Knorr quinoline reaction [58].

3.8.4. Niementowski Quinoline Synthesis

This reaction (Fig. **8**) occurs between anthranilic acid **(50)** with a carbonyl compound **(51)** in basic conditions, it transforms into a quinoline compound **(52)** [59].

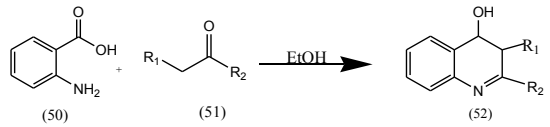


Fig. (8). Niementowski quinoline reaction [59].

3.8.5. Dieckman Synthesis

The Dieckmann cyclization (Fig. **9)** involves an intramolecular Claisen condensation between a dicarboxylic acid **(53)** with an α-hydrogen **(54)** in the presence of base will form an intermediate **(55)** and further it will form a cyclic compound **(56)**.Further, this reaction can yield two final products: a quinoline **(57)** and 2,3,4,5-tetrahydro-2,5-dioxo-1H-benzo[b].azepine-4-carboxylic acid **(58)** [60].

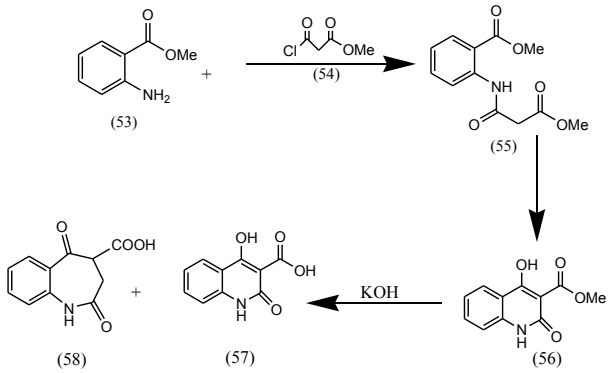


Fig. (9). Dieckman reaction [60].

3.8.6. Pfitzinger Reaction

This reaction (Fig. **10**) occurs when isatin **(59)** undergoes a reaction with a carbonyl compound **(60)** in the presence of KOH which acts as a base, it yields a quinoline compound **(61)** [61].

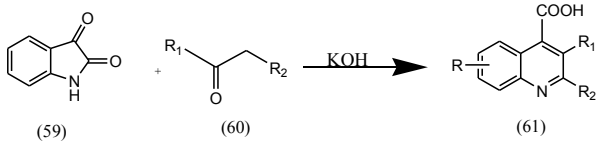


Fig. (10). Pfitzinger reaction [61].

3.8.7. Camps Quinoline Synthesis

This reaction (Fig. **11**) involves o-acylaminoacetophenone **(62)** which undergoes a reaction with sodium hydroxide **(63)**, it results in the formation of a quinoline compound **(64)** [62].

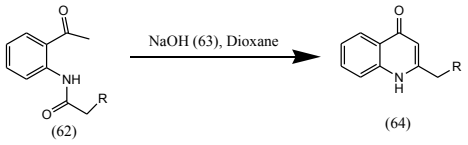


Fig. (11). Camps quinoline reaction [62].

3.8.8. Meth-Cohn Synthesis

When acylanilides **(65)** undergo a reaction (as in Fig. **12**) with dimethylformamide **(66)** in the presence of $POCl_3$, they give rise to quinoline compounds **(67)** [63].

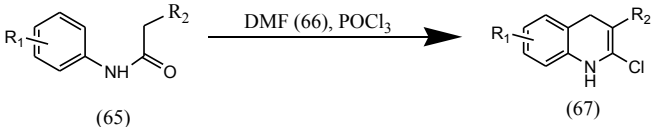


Fig. (12). Meth-Cohn reaction [63].

3.8.9. Biere-Seelen Synthesis

This reaction occurs (Fig. **13**) when the substituted ester enamine **(68)** is treated with dimethyl acetylenedicarboxylate **(69)** in the presence of a strong base, which is followed by hydrolysis to obtain first intermediate **(70)**, further intermediate of dicarboxylic acid **(71)** is obtained and then upon decarboxylation, quinoline compound **(72)** is formed [64].

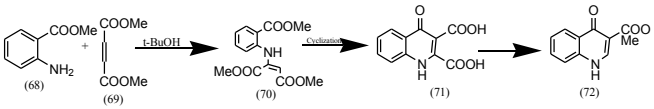


Fig. (13). Biere-Seelen reaction [64].

3.8.10. Vilsmeier-Haack Synthesis

The reaction (Fig. **15**) of acetanilide **(73)** with phosphorus oxychloride **(74)** in dimethylformamide resulted in an efficient synthesis of 2-chloroquinoline-3-carbaldehydes **(75)** through intramolecular cyclization [65].

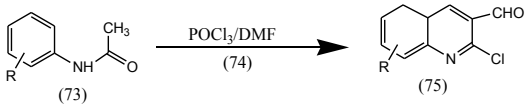


Fig. (14). Vilsmeier-Haack reaction [65].

4. SYNTHETIC SCHEME FOR VARIOUS QUINOLINE DERIVATIVES SYNTHESIS

Jamal A, *et al.* 2024, discovered a novel quinoline derivative (depicted in Fig. **15**), i.e, (E)-N-phenyl-4-((quinolin-4-ylmethylene)amino)aniline (PQYA), which was synthesized by reacting 4-quinolinecarboxaldehyde (76) with N-phenyl-p-phenylenediamine (77) in methanol (78) to form the final product PQYA (79) with an 80% yield using a reported method. Structural characterization *via* single-crystal X-ray diffraction (SC-XRD) revealed a monoclinic crystal structure with a P21/n space group. Spectral analysis using FT-IR, UV-Vis, ESI-MS, 1H NMR, and 13C NMR, supported by density functional theory (DFT), demonstrated excellent agreement between theoretical and experimental results. The DFT study included investigation of the energy gap, molecular electrostatic potential (MEP) map, nonlinear optical (NLO) response, and Hirshfeld surface (HS) analysis for molecular interactions. SwissADME confirmed drug-likeness, and AutoDock Vina was used to predict docking scores with the PDB ID: 2ZCQ receptor to reveal the promising interactions [66].

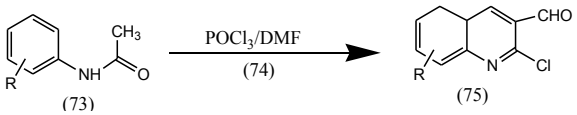


Fig. (15). Synthetic Scheme for formation of (E)-N-phenyl-4-((quinoli-4-ylmethylene)amino)aniline (PQYA) [66].

In their 2024 study, Ibrahim and colleagues worked on the development of newer therapeutic agents (as illustrated in Fig. **16**) targeting diseases caused by bacterial pathogens. In order to find possible drug candidates as antibacterial agents through inhibition of the DNA gyrase enzyme, the research emphasizes creating a novel pathway of compounds with multiple bioactive elements, such as quinazolin-2,4-dione, acylthiourea linkages, and five-membered nitrogen heterocycles (pyrazole and oxazole) (81, 84, 85, 88a-c). The precursor, N-[N'-(2-cyano-acetyl)-hydrazinocarbothioyl].-4-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-benzamide (81), was created by combining compound (80), cyanoacetic acid hydrazide, and ammonium thiocyanate in a multicomponent reaction (MCR). Additionally, compounds (84a-d) and (85a-b) were produced by using the Knoevenagel reaction to react (81) with aromatic aldehydes (82) or ketones (83) to produce high-purity products with acceptable efficiencies. Moreover, 84c was treated with nucleophilic reagents such as hydrazine, phenyl hydrazine (86), and hydroxylamine (87) to create heterocyclic derivatives that included pyrazole and oxazole groups connected to the quinazolin-2,4-dione core (88a-c). All synthesized compounds underwent structural characterization using techniques like IR, 1H-NMR, 13C-NMR, and MS analysis. The minimum inhibitory concentration (MIC) and antibacterial activity of two Gram-positive (B. subtilis and S. aureus) and two Gram-negative (E. coli and P. aeruginosa) bacterial strains were tested. Compound 84c exhibited the most potent antibacterial activity, outperforming the standard drug ciprofloxacin at lower concentrations. The study noted that electron-withdrawing groups such as -NO2 and -Cl enhanced antibacterial efficacy. To further explore the interaction mechanisms, the synthesized compounds underwent in-silico study to examine the binding interactions with the DNA gyrase enzyme (PDB: 2XCT). This data provides valuable insights into the antibacterial activity of the compounds [67].

Muthiah Gnana Ruba Priya, *et al.* 2024, explored quinoline derivatives, as illustrated in Fig. **17**, which are significant heterocyclic compounds with promising therapeutic applications, especially for cancer treatment, such as breast cancer. Although they have potential, problems such as toxicity and medication resistance may limit their efficacy. For improved therapeutic results, novel compounds that can precisely target cancer cells—particularly breast cancer—while minimizing adverse effects and causing less harm to healthy cells are required. This study centers on the development and synthesis of newer derivatives of quinoline featuring substituted piperazine groups to increase their anticancer properties by targeting EGFR, a critical protein in breast cancer treatment. Techniques like IR, MASS, and NMR spectroscopy were among the analytical methods used to confirm the structures of the synthesized compounds. Following their synthesis, the compounds underwent molecular docking studies to assess their binding affinity, and their anticancer efficacy was evaluated both *in vitro* against MCF-7 cell lines and *in vivo* using a DMBA-induced rat model. The synthesis began with 2-aminobenzaldehyde (89), which was reacted with phosphorus chloride to produce 4-chloro-3-quinoline carbaldehyde (90). This compound was then condensed with rhodanine in the presence of sodium acetate, yielding the key intermediate (E)-5-((4-

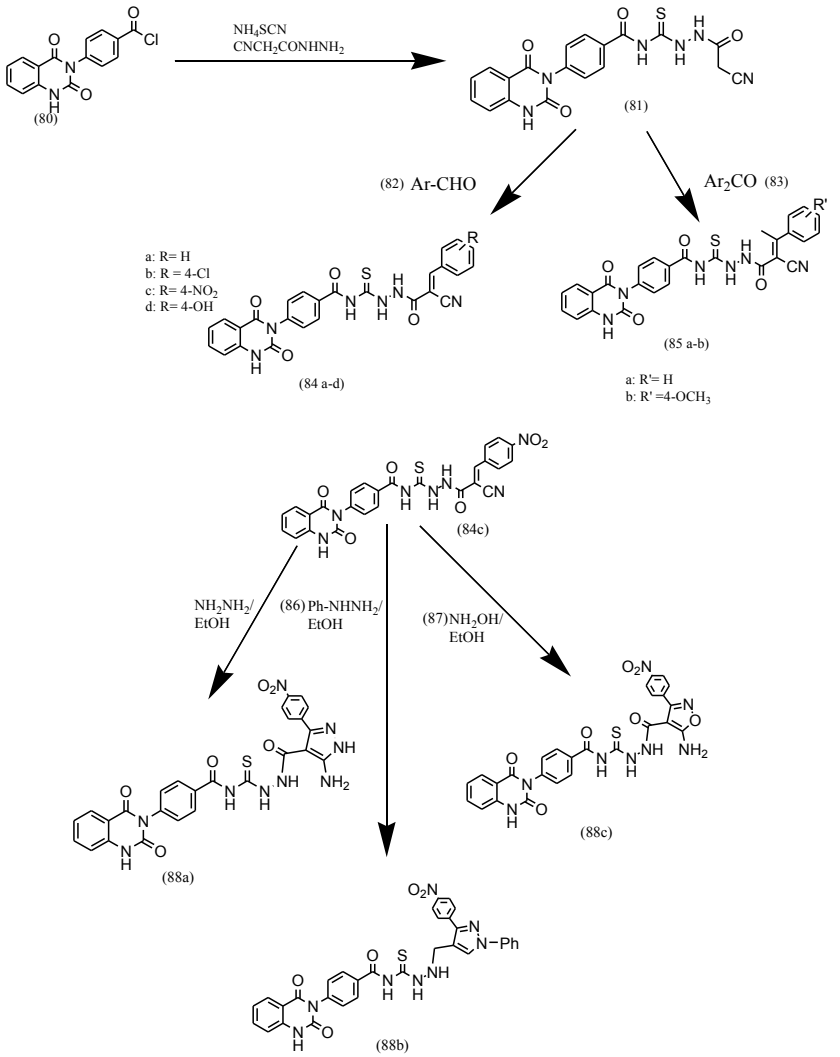


Fig. (16). Synthetic scheme for novel quinoline derivative [67].

chloroquinolin-3-yl)methylene)-2-(methylthio)thiazol-4(5H)-one (91). The intermediate (91) was further activated with triethylamine (TEA) under ice-cold conditions to form another intermediate (92), which was subsequently treated with methyl iodide. The reaction mixture was then refluxed in ethanol with substituted piperazines (93a-i) for 2 hours, resulting in the formation of 5-((4-chloroquinolin-3-yl)methylidene)-2-(piperazin-1-yl)-1,3-thiazol-4(5H)-ones (94a-i). Synthesized compounds (94a-i) underwent molecular docking at the ATP binding site of EGFR, which revealed enhanced docking scores and favorable MM/GBSA energy values, indicating strong binding affinities. In-vitro assays confirmed their effectiveness in inhibiting the EGFR-TK enzyme, with compound 94i displaying the highest inhibitory activity at 87.5%. The superior anticancer potency of 94i was attributed to electron-donating groups, which strengthened interactions with biological targets. Compound 94i demonstrated significant effects against breast cancer both *in vitro* and *in vivo*, highlighting its potential as a promising anticancer agent and supporting the need for further investigation [68].

Fikriya, S.H, *et al.* 2023 researched the Pfitzinger reaction for the synthesis of a quinoline-4-carboxylic acid derivative (Fig. **18**). Isatin (95) was treated with a base (96) to form intermediate (97), which underwent modification through reaction with a ketone (98), followed by refluxing for 24 hours to produce quinoline-4-carboxylic acid (99), which exhibited a higher inhibition percentage compared to isatin. The objective of modifying isatin was to enhance its antioxidant activity, which was tested using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant assay, and results demonstrated the better inhibitory effect of the quinoline-4-carboxylic acid derivative. This improvement is attributed to its increased ability to donate hydrogen radicals, highlighting its enhanced antioxidant properties over isatin [69].

Sun, X, *et al.* 2023, discovered new fluorinated quinoline analogs (Fig. **19**), which were synthesized by treating 2-fluoroaniline (100) and ethyl 2-methylacetoacetate (101) in the presence of PPA to form the 2,3-dimethyl-4-hydroxyquinoline intermediate (102), which was further treated with various substituted benzoic acids (103a-p) and underwent the esterification process to generate the final compounds (104a-p). Confirmation of their structures was done through 1H NMR, 13C NMR, and HRMS, with compound 104b further validated by X-ray single-crystal diffraction. Antifungal activity at 50 µg/mL revealed significant efficacy in these derivatives. Some of the compounds, i.e, 104b, 104e, 104f, 104k, and 104n, displayed strong activity (>80%) against S. sclerotiorum, while compound 104g exhibited notable activity (80.8%) against R. solani [70].

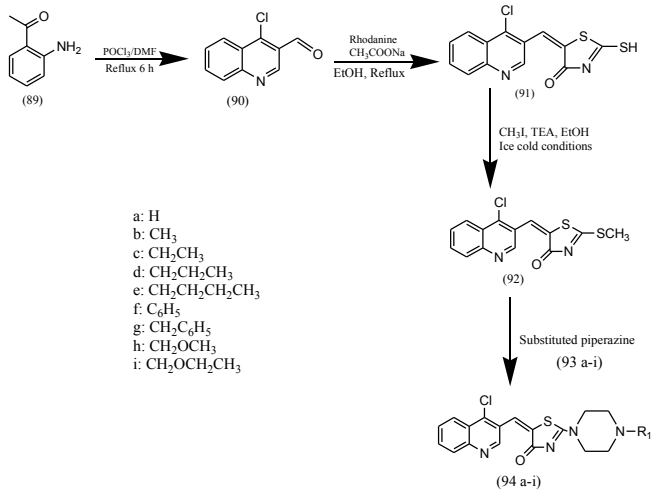
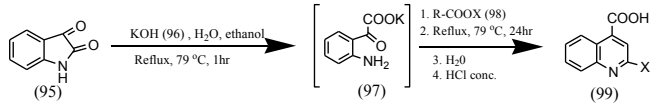
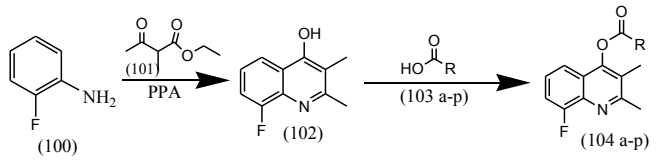


Fig. (17). Designed scheme for newer quinoline derivative [68].



Here, X= Methyl or 4-Methylphenyl
Fig. (18). Scheme for quinoline-4-carboxylic acid derivative [69].



Here, R).- a). Ph, b). t-BuPh, c). 2-FPh, d). 3-FPh, e). 4-FPh, f). 2-MeOPh, g). 4-MeOPh, h). 2-MePh, i). 3-MePh, j). 4-MePh, k). 2-ClPh, l). 3-ClPh, m). 4-ClPh, n). 4-i-PrPh, o). 2-NO2Ph, p). cyclopropyl
Fig. (19). Scheme for new fluorinated quinoline analogs [70].

Cahyana A. Herry, *et al.* 2022, aimed to create quinoline and its derivatives, known for various pharmacological benefits such as antibacterial and antioxidant activities. Quinoline was synthesized from isatin (105) and ethyl acetoacetate (106) in the presence of potassium hydroxide (107) using the Pfitzinger reaction to form the quinoline intermediate (108). This intermediate was further treated with hydrazine (109) to form the final quinoline hydrazide product (110) (Fig. **20**). From quinoline (108), a benzimidazole derivative (112) (Fig. **21**) was produced with o-phenylenediamine (111) through a solvent-free reaction. Another derivative (Fig. **22**), the hydrazone (115), was formed by reacting the quinoline hydrazide derivative (110) with 4-hydroxybenzaldehyde (113) in the presence of base (114). The synthesized compounds were analyzed using several methods, including TLC, melting point determination, FTIR, liquid chromatography-mass spectrometry, and UV-visible spectrophotometry. Their potency as antioxidants and antibacterials was tested. Although the antioxidant power of the compounds was weaker compared to ascorbic acid, the quinoline hydrazone derivative (115) showed the highest antioxidant activity with an IC50 of 843.52 ppm, while for quinoline benzimidazole (112), the IC50 value was found to be 4784.66 ppm. However, none of the compounds were effective against S. aureus and E. coli within the tested concentrations. In summary, the study effectively generated novel compounds based on benzimidazole and quinoline-derived hydrazone structures, which were then evaluated for their antibacterial and antioxidant properties [71].

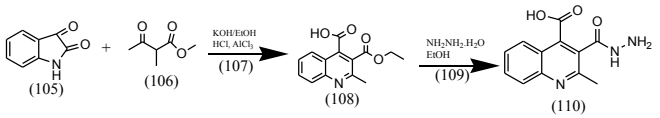


Fig. (20). Synthetic scheme for Quinoline hydrazide derivative [71].

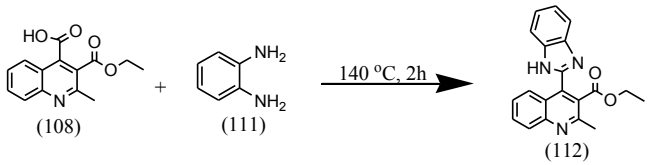


Fig. (21). Synthetic scheme for Quinoline -benzimidazole derivative [71].

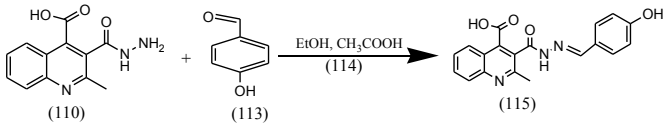


Fig. (22). Synthetic scheme for quinoline hydrazone derivative [71].

Kardile Ramakant A, *et al.* 2022. In this study, they designed and tested a new set of 24 chemical compounds similar to quinoline. These compounds, which are variations of amide and sulphonamide, were designed and synthesized for their potential to combat cancer. In Fig. **22**, the amine intermediate was synthesized, beginning with treating ethyl 6-bromo-4-chloro-2-(1H-imidazole-1-yl)quinoline-3-carboxylate (116) with Boc-protected piperazine (117), which is commercially available, in the presence of DIPEA (118), to form ethyl 6-bromo-4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(1H-imidazole-1-yl)quinoline-3-carboxylate (119). Upon further reaction with dioxane (120), it formed the salt of ethyl 6-bromo-2-(1H-imidazole-1-yl)-4-(piperazin-1-yl)quinoline-3-carboxylate (121). It was then treated with DMF (122), which gave rise to the nitro compound intermediate (123), and subsequent reaction with ammonium chloride (124) produced the final amine intermediate (125) (Fig. **23**). Further sulphonamide derivatives (Fig. **23**) were synthesized by reacting (125) with different sulphonyl chlorides (126) in the presence of pyridine to form the final derivatives (127-139) (Fig. **24**). Additionally, a series of amide derivatives (Fig. **24**) were formed by reacting compound (125) with different acids (140) in the presence of HATU and another catalyst (141) to form the final amide derivatives (142-148) (Fig. **25**). Moreover, in laboratory testing using various cancer cell lines, including HCC827, H1975 (with specific mutations), A549, and BEAS-2B, most of these synthesized compounds showed significant effectiveness in killing cancer cells. Among them, compound 139 stood out as the most potent, demonstrating strong anticancer effects compared to Osimertinib, a known cancer drug. Compound 139 also showed promising results in inhibiting specific enzymes related to cancer growth, comparable to Osimertinib's performance. The mechanisms of action of compounds 136 and 139 were investigated using laboratory experiments focusing on how they affect the signaling pathways in cancer cells. Additionally, computer simulations were used to examine how these compounds interact with different forms of the EGFR enzyme, a key player in cancer development. These simulations suggested that compound 139 maintains stability when bound to the enzyme, indicating its potential as a drug candidate. Furthermore, computational predictions regarding the compounds' absorption, distribution, metabolism, and excretion suggest they possess favorable properties for use as drugs [72].

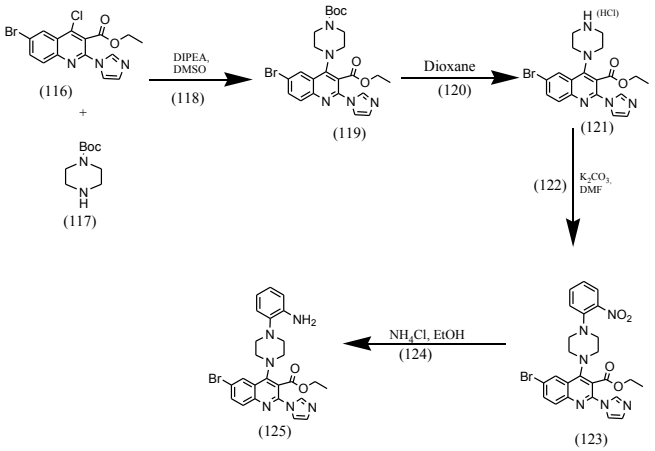
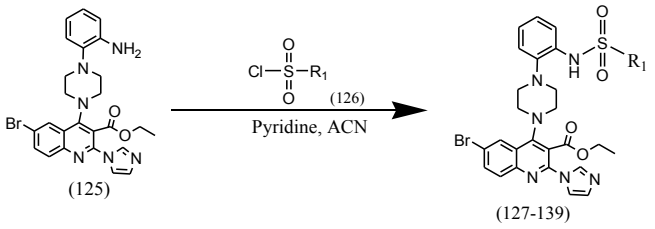
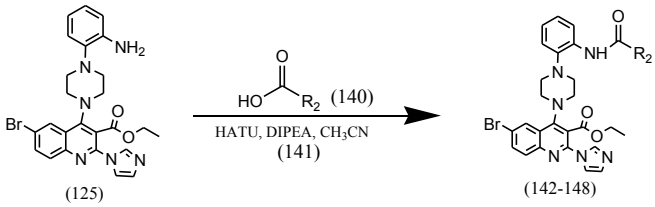


Fig. (23). Formation of amine intermediate [72].



Here, R_1).- 127). -4-F-C_6H_4, 128). -4-Br-C_6H_4, 129). -4-Cl-C_6H_4, 130). -4-I-C_6H_4, 131). -4-CN-C_6H_4, 132). -4-OMe-C_6H_4, 133). -4-$MeSO_2$-C_6H_4, 134). -3,4-F-C_6H_3, 135). -Cyclopropane, 136). -2-F-C_6H_4, 137). -5-CN-C_6H_4, 138). -4-tert-butyl-C_6H_4, 139). 4-CF_3-C_6H_4

Fig. (24). Synthetic scheme for sulphonamide derivatives [72].



Here, R_2).- 142). -2-I-5-F-C_6H_3, 143). -2-Br-5-F-C_6H_3, 144). -2,3-OMe-C_6H_3, 145). -2-methyl-3-propyl-1H-pyrazole, 146). -cyclobutan-3-one, 147). -2-F-C_6H_4, 148). -3-Br-C_6H_4

Fig. (25). Scheme for quinoline-amides derivatives [72].

In 2022, Govindarao and colleagues explored the potential candidates against EGFR tyrosine kinase, a key enzyme associated with breast carcinomas, through *in vitro* enzymatic assays. Their research involved designing two series, A and B, of quinoline derivatives conjugated with 2-azetidinone moieties (depicted in Fig. **26**). These compounds demonstrated greater activity against MCF-7 cancer cell lines compared to MDA-MB-231, with some exhibiting higher potency than the standard drug erlotinib. The estimation of anti-EGFR activity utilized the EGFR kinase enzyme (PDB ID: 6S9B). The synthesis process began with the preparation of substituted acetanilides (150) by reacting substituted anilines (149) with AcOH. These were then converted into substituted 2-chloro-3-formylquinolines (152) through a Vilsmeier-Haack reaction using dimethylformamide (151). The resulting compounds (152) were reacted with acetophenone (153) to form Schiff bases (154), which were subsequently cyclized with chloroacetyl chloride (155) to yield quinoline-conjugated 2-azetidinones (156a-p). The study emphasized that EGFR-targeted therapies are gaining attention as promising approaches for inducing cytotoxicity in breast cancer cells. A variety of tyrosine kinase inhibitors, including erlotinib, gefitinib, and lapatinib, are in different stages of development as EGFR inhibitors. These molecules are characterized by the quinazoline nucleus, a well-established pharmacophore. Additionally, the quinoline nucleus is highlighted for its ease of synthesis and favorable "drug-like" properties, emphasizing a pharmacophore for medicinal chemistry efforts [73].

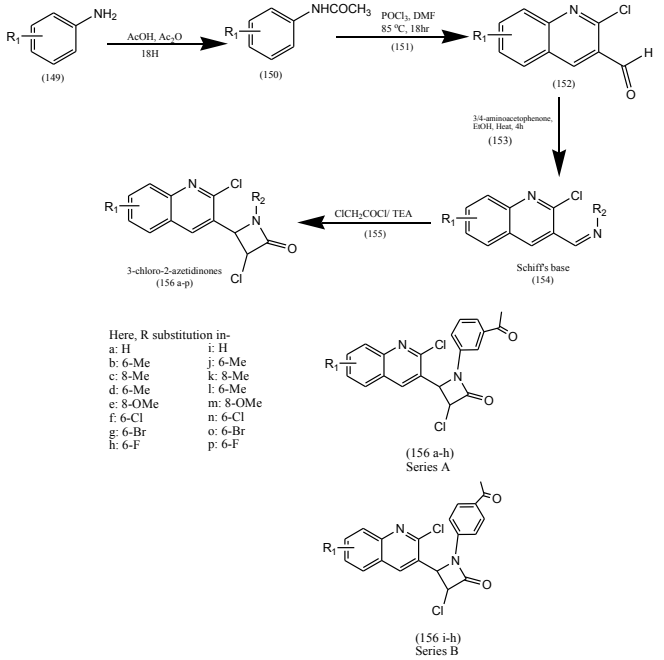


Fig. (26). Novel quinoline derivatives conjugated with 2-azetidinone moiety [73].

In 2022, Singh Vishal K. and collaborators developed a novel synthetic scheme for quinoline derivatives (depicted in Fig. **27**) as potential protease inhibitors (PIs) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In silico analysis, conducted using DS v20.1.0.19295 software, indicated that these compounds act as PIs by targeting the allosteric site of the main protease enzyme (Mpro, PDB ID: 6LU7). In this research, the synthesis began with the reaction of an aromatic amine (158) with ethyl acetoacetate (157) in the presence of a few drops of H2SO4, resulting in 8-amino-4-methyl-1H-quinoline-2-one (159). Compound (159) was then treated with substituted benzenesulfonyl chloride (160) or benzoyl chloride (161) to produce various sulfonamide and benzamide derivatives (162-169). These designed compounds showed promising docking results, forming hydrogen bonds with conserved amino acids such as His41, His164, Glu166, Tyr54, and Asp187, along with π-interactions with His41 within the target protein. Analysis using Toxicity Prediction by Komputer-Assisted Technology (TOPKAT) verified that these substances were less harmful than the reference medication. Compound 166 and Remdesivir in conjunction with the protease enzyme were subjected to molecular dynamics simulations. The simulations evaluated hydrogen bonding, solvent-accessible surface area (SASA), compactness, conformational stability, residue flexibility, and binding free energy. The protease:166 complex demonstrated stability similar to that of the protease:remdesivir complex, according to the data. The bonding in H-atom analysis revealed numerous intermolecular hydrogen bonds formed between ligand 166 and protein residues, specifically Glu166 and Gln189, demonstrating strong interactions that supported the docking results. Additionally, analysis studies

like SASA and other interactions confirmed the inhibitory potential of compound 166, which closely resembled the inhibitory properties of the standard drug. The proposed compound 166 may therefore act as a strong inhibitor of the protease enzyme [74].

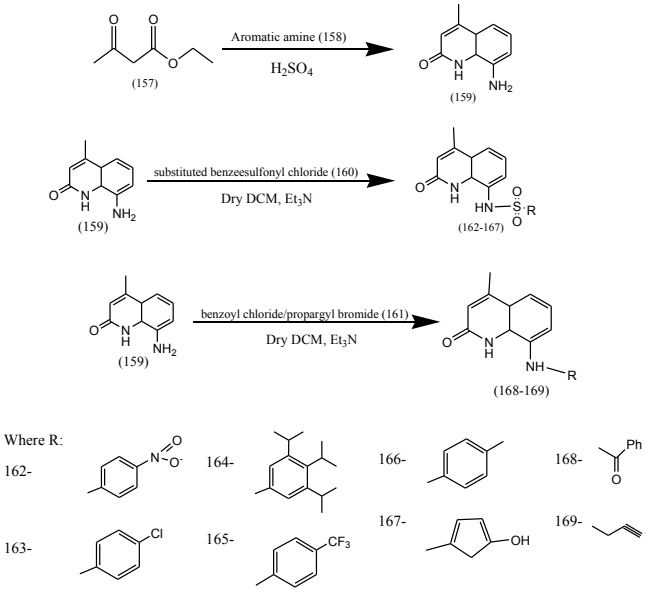


Fig. (27). Synthesis of novel series of quinoline derivatives [74].

Guan, Y.-F, *et al.* 2021, worked on chalcone and quinoline scaffolds (as in Fig. **28**), which were then utilized for the preparation of novel anticancer agents. As part of their ongoing research into effective anticancer compounds, the researchers hypothesized that hybridizing a chalcone fragment with a quinoline scaffold could yield novel molecules with potential anticancer properties. Researchers synthesized compounds by reacting 4-aminoacetophenone (170) with aromatic aldehydes (171a-j) in the presence of sodium hydroxide in ethanol to produce compounds (172a-j). Target compounds (174a-j) were produced by a substitution reaction between compounds (172a-j) and commercially available 4-chloro-2-methylquinoline (173) in EtOH at 80°C with HCl present. Furthermore, compounds 175a-f were produced by the reaction of compounds 174a, 174b, 174e, and 174f with iodomethane or iodoethane in acetonitrile at 80°C in the presence of KOH. Consequently, researchers explored a series of quinoline-chalcone derivatives by synthesizing and evaluating their antiproliferative effects on MGC-803, HCT-116, and MCF-7 cancer cell lines. Among the synthesized compounds, 172e demonstrated the most potent inhibitory effects, exhibiting IC50 values of 1.38 μM, 5.34 μM, and 5.21 μM against MGC-803, HCT-116, and MCF-7 cells, respectively. Additionally, this work examined the structure-activity relationship for these quinoline-chalcone derivatives. Mechanistic studies showed that compound 172e produced cell cycle arrest during the G2/M phase, decreased the ability of MGC-803 cells to form colonies, and inhibited them in a dose-dependent manner. In MGC-803 cells, it also markedly raised the amounts of apoptosis-related proteins (Caspase-3, Caspase-9, and cleaved-PARP). Additionally, it was discovered that compound 172e generated reactive oxygen species (ROS), and that the creation of ROS was necessary for the compound's inhibitory effects on gastric cancer cells. Overall, these findings indicate that the direct linkage of chalcone and quinoline fragments can lead to the creation of promising anticancer molecules, with compound 172e serving as a potentially valuable lead for future anticancer agent development [75].

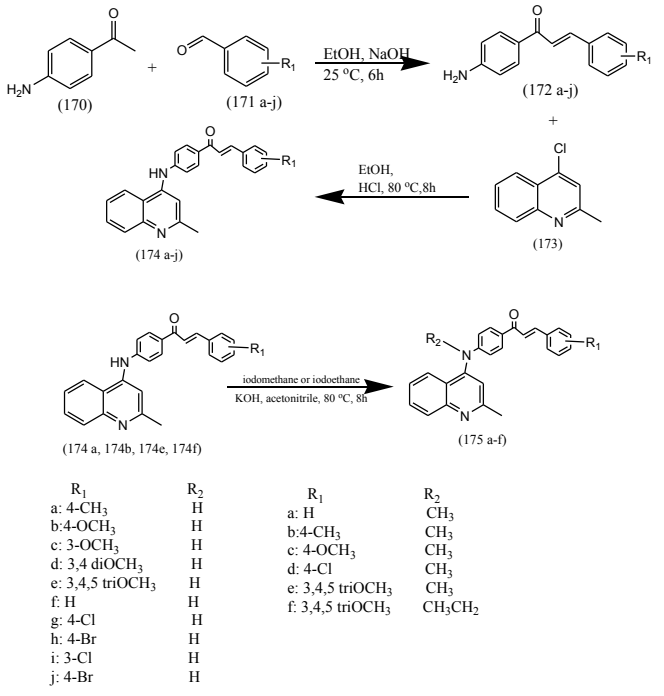


Fig. (28). Synthesis of novel series of chalcone-quinoline derivatives [75].

Matarneh M. C. Al, *et al.* 2021, explored novel cyano-substituted derivatives with pyrroloquinoline and pyrroloisoquinoline scaffolds (depicted in Fig. **29**), which were created by cycloaddition of (iso)quinolinium ylides to fumaronitrile [3 + 2]. Using p-substituted 2-bromoacetophenone (177a-c), salts (178a-c) and (180a-c) were first created by directly N-alkylating isoquinoline (176) and quinoline (179), respectively, in order to introduce a 4-substituted phenacyl substituent. Different compounds based on the (iso)quinolinium salt structure were generated *via* the in situ reaction of fumaronitrile with cycloimmonium ylides. Sixty human cancer cell lines were used to assess the antineoplastic activity of various compounds. Broad-spectrum antiproliferative action against multiple cancer types was demonstrated by the most active molecule. The compound's interaction with tubulin was discovered by molecular docking and *in vitro* tests [76].

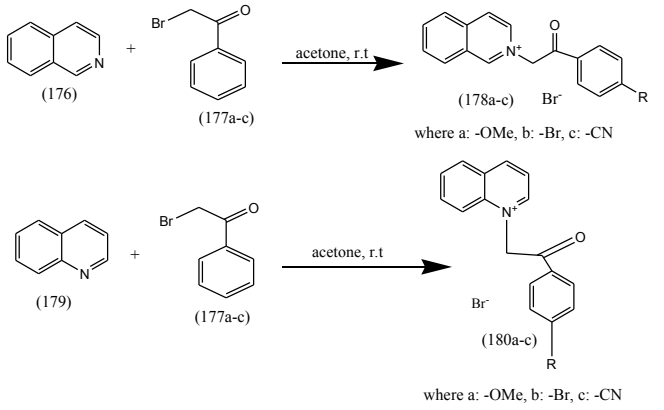


Fig. (29). Synthetic scheme for novel cyano-substituted derivatives [76].

Shah Kamal, *et al.* 2021, reviewed quinolines, which are multipurpose scaffolds in medicinal chemistry. Additionally, quinoline hybrids have shown remarkable potential by targeting novel pathways through diverse mechanisms of action. These include blocking cell migration, causing apoptosis, lowering angiogenesis, pre-

venting cell proliferation through cell cycle arrest, and altering important signalling pathways. These effects are attributed to the active pharmacophores present in quinoline hybrids, making them highly promising candidates for innovative anticancer therapies [77].

Bouzian Y, *et al.* 2020, synthesized two new quinolone derivatives (as in Fig. **30**). They were characterized using a variety of spectroscopic methods and examined using single-crystal X-ray diffraction. To investigate variations in their electrical characteristics, DFT-B3LYP investigations were carried out. The reactant, 2-oxo-1,2-dihydroquinoline-4-carboxylic acid (181), was treated with K2CO3, and two new compounds (182) and (183) were obtained by stirring n-dodecyl bromide with tetra-n-butylammonium bromide as a catalyst in DMF for 48 hours at room temperature. In comparison to the standard, compounds 182 and 183 demonstrated remarkable activity against the bacterial strains Escherichia coli ATCC 4157, Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus ATCC 25923, and Streptococcus faecalis ATCC 29212, with MIC values of 6.25 mg/mL. In order to rationalize the molecules' likely mode of action, binding affinity, and orientation at the receptor's active site, compounds 182 and 183 were positioned into the S. aureus 1JIJ active site using in-silico experiments [78].

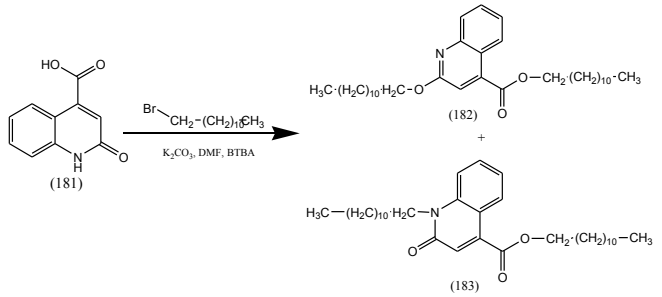
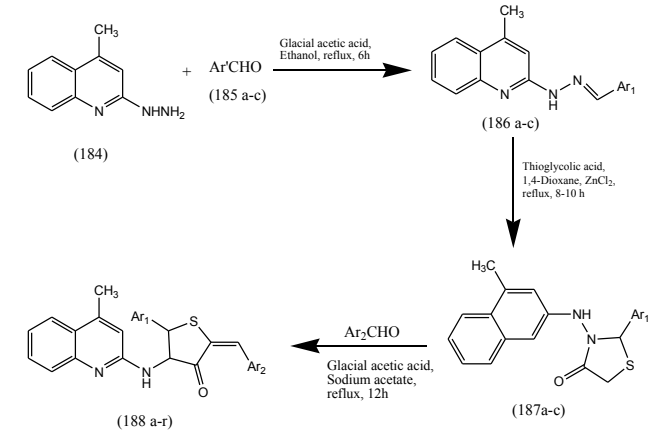


Fig. (30). Synthetic scheme for new quinoline derivative [78].

Jain S, *et al.* 2018, synthesized and characterized arylidene derivatives of thiazolidinones based on quinolines (depicted in Fig. **31**). Initially, 2-hydrazino-4-methylquinoline (184) and compound (185a-c) were reacted in EtOH to synthesize hydrazones (186a-c). Moreover, thiazolidinones (187a-c) were prepared by treating compounds (186a-c) with 1,4-dioxane and mercaptoacetic acid. Furthermore, compounds (187a-c) were treated with various aromatic aldehydes to synthesize (188a-r). Assessment of the *in vitro* antimalarial capability was performed against P. falciparum strains, both CQ-sensitive and CQ-resistant. The top five most active compounds were tested against P. berghei *in vivo*. The active site of P. falciparum lactate dehydrogenase was also examined through docking investigations. Overall, compound 188g was determined to be the most promising candidate for parasite suppression [79].

Iqbal J, *et al.* 2019, investigated quinolones and quinolines (Fig. **32**) for their anticancer activity against breast cancer cells (MCF-7) using the MTT assay. The derivatives were synthesized by mixing 5-chloro isatin (189) with aryl-substituted acetophenones (190a-j), producing derivatives of 4-quinoline carboxylic acid (191a-j). The most successful derivatives underwent flow cytometry analysis and fluorescence microscopic analysis utilizing propidium iodide (PI) staining and 4′,6-diamidino-2′-phenylindole (DAPI). All of the compounds examined in this investigation were found to be selective for cancer cells. Additionally, the compounds caused nuclear fragmentation, chromatin condensation, maximal contact with DNA, and either G2 or S-phase cell cycle arrest within the corresponding cancer cell line. The compounds (191a) from 4-quinolone and (191j) from quinoline-4-carboxylic acid, respectively, showed the highest apoptotic cell death in the G2 phase, at 19.7% and 22.5%, indicating that these derivatives have strong potential to inhibit the growth of breast cancer cells (MCF-7) [80].

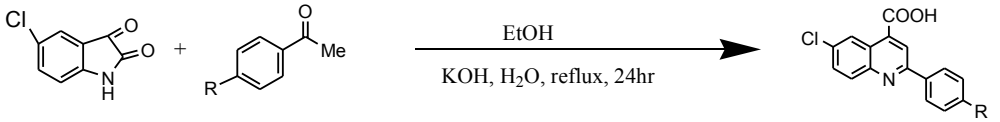


where substitutions in (188 a-r) are:.

Compound	Ar_1	Ar_2
a:	C6H5-	C6H5-
b:	C6H5-	p-ClC6H4-
c:	C6H5-	p-CH3C6H4-
d:	C6H5-	p-OCH3C6H4-
e:	p-ClC6H4-	C6H5-
f:	p-ClC6H4-	p-ClC6H4-
g:	p-ClC6H4	-p-CH3C6H4-
h:	p-ClC6H4-	p-OCH3C6H4-
i:	p-CH3C6H4-	C6H5-
j:	p-CH3C6H4-	p-ClC6H4-
k:	p-CH3C6H4-	p-CH3C6H4-
l:	p-CH3C6H4-	p-OCH3C6H4-
m:	p-OCH3C6H4-	C6H5-
n:	p-OCH3C6H4-	p-ClC6H4-
o:	p-OCH3C6H4-	p-CH3C6H4-
p:	p-OCH3C6H4-	p-OCH3C6H4-
q:	2-thienyl	C6H5-
r:	2-thienyl	p-CH3C6H4-

Fig. (31). Synthetic scheme for arylidene derivatives of quinoline based thiazolidinones [79].

In 2019, Khan Salman A. *et al.* synthesized and evaluated novel quinoline-3-carbonitrile derivatives (depicted in Fig. **33**) for their



5-chloro istatin (189) Aryl substituted acetophenones(190 a-j)

Derivatives of 4-quinoline carboxylic acid (191 a-j)

Where, a: 2-Br, b: 3-Br, c: 3-F, d: 3-Me, e: 4-OMe, f: 4-I, g: 3-F-4-OMe, 4
h: 3-I-4-OMe, i: 2,4-diOMe, j: 4-OH-3-OMe

Fig. (32). Scheme for quinolones and quinolines derivatives [80].

antibacterial properties. A one-pot multicomponent reaction involving 6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-one, ammonium acetate (192), the appropriate aldehyde (193), and ethyl cyanoacetate (194) produced compounds (195a-e). Various spectroscopic and physical methods were used to establish their structures. DFT investigations using the DFT/RB3LYP method evaluated these compounds' molecular geometry, vibration frequencies, HOMO-LUMO energy gap, molecular hardness (g), ionization energy (IE), electron affinity (EA), and total energy. Both Gram-positive and Gram-negative bacterial strains were used in preliminary antibacterial investigations, and cytotoxicity tests on mammalian cells demonstrated their promising antibacterial activity without posing a serious threat to the host. With log P values, every compound (195a-e) in this investigation complied with Lipinski's Rule of Five [81].

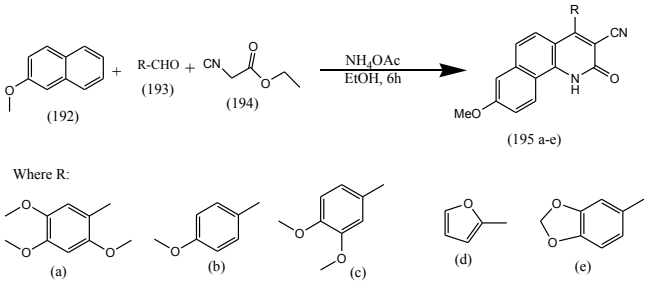


Fig. (33). Derived novel quinoline-3-carbonitrile derivatives [81].

Taha, M, *et al.* 2019 explored the quest for potent α-glucosidase inhibitors. As shown in Fig. **34**, researchers synthesized 25 analogues of quinoline-based Schiff bases and assessed their inhibitory potency against the enzyme by comparing them to the positive control, acarbose (IC50 = 38.45 ± 0.80 µM). Quinoline-6-carbohydrazide (197) was produced by combining methyl quinoline-6-carboxylate (196) with hydrazine hydrate. To obtain the pure product of quinoline-based Schiff bases (199a-y), the intermediate (197) was then reacted with several aromatic aldehydes (198) in ethanol. Several analogues 198a, 198b, 198c, 198d, 198k, 198l, and 198t exhibited notable inhibition with IC50 values of 12.40 ± 0.40, 9.40 ± 0.30, 14.10 ± 0.40, 6.20 ± 0.30, 14.40 ± 0.40, 7.40 ± 0.20, and 13.20 ± 0.40 µM, surpassing the standard acarbose. Particularly, the 198d analogue displayed significantly improved α-glucosidase inhibitory activity with an IC50 of 6.20 ± 0.30 µM compared to acarbose. Eight analogues also showed inhibition of less than 50%. A structure-activity relationship (SAR) investigation was used to investigate substituent effects on the phenyl ring. The analogues' binding interactions with the target enzyme's active site were validated by molecular docking experiments. Using spectroscopic methods including 1H-NMR, 13C-NMR, and ESI-MS, the analogues were characterized [82].

In 2018, Amer *et al.* worked in accordance with the interest in novel quinoline derivative synthesis with predicted biological activity. This began with quinoline hydrazone formylation using the Vilsmeier-Haack reaction, a popular approach for the synthesis of 4-formyl pyrazoles, to produce newer derivatives of quinoline with pyrazole and pyridine moieties (illustrated in Fig. **35**). When 2-hydrazinylquinoline (200) was treated with 4-substituted acetophenone, it yielded the corresponding 2-(2-(1-arylethylidene) hydrazinyl)quinoline derivatives (201a-c). Further, these derivatives were reacted with DMF, leading to the formation of 3-(4-aryl)-1-(quinolin-2-yl)-1H-pyrazole-4-carbaldehyde derivatives (202a-c). Compounds 202a-c were then treated with malononitrile and thiophenol or ethyl mercaptan (203) in a one-pot reaction to derive the novel derivatives 2-amino-4-(3-(4-aryl)-1-(quinolin-2-yl)-1H-pyrazol-4-yl)-6-(alkylthio)pyridine-3,5-dicarbonitriles (204a-f). Gram-positive and Gram-negative bacteria, as well as fungi, were used to assess the synthetic compounds' antibacterial effects. When compared to the reference medications, the majority of compounds exhibited superior antibacterial activity. IR, 1H NMR, MS, and elemental studies were used to characterize the newly synthesized compounds [83].

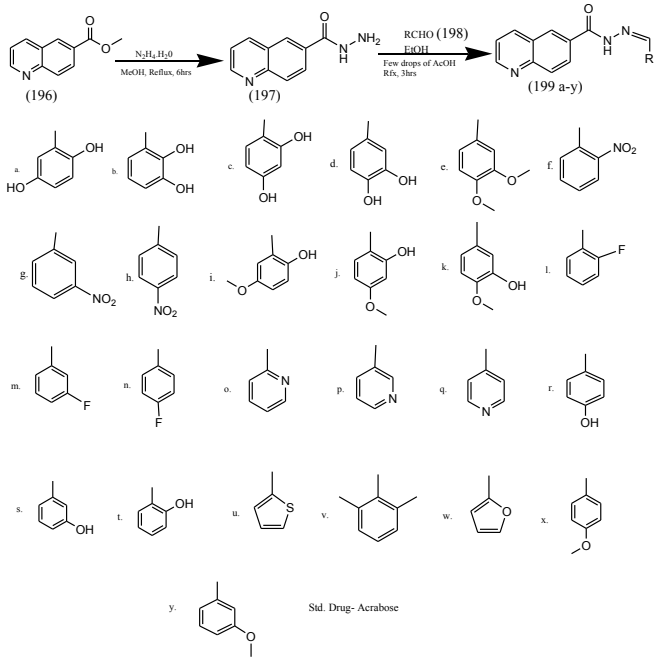


Fig. (34). Synthetic scheme for quinoline-based Schiff bases [82].

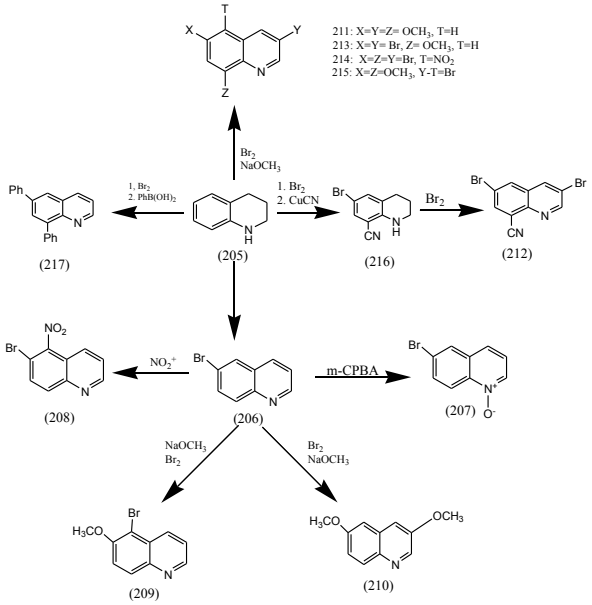


Fig. (35). Novel quinoline derivatives with pyrazole and pyridine moieties [83].

In 2018, Koprulu *et al.* worked on quinoline derivatives (illustrated in Fig. **36**), which have attracted attention for their synthesis and biological activities in the quest for new anticancer drug development because of their numerous biological properties. This study

examined the biological activity of many substituted (phenyl, nitro, cyano, N-oxide, and methoxy) quinoline derivatives (207-217) against cancer cell lines such as human cervical cancer cells (HeLa), human adenocarcinoma (HT29), and rat glioblastoma (C6). This synthesis produced 6-bromoquinoline (206) by brominating 1,2,3,4-tetrahydroquinoline (205). Moreover, 6-bromoquinoline-1-oxide (207) was obtained by N-oxidizing 206 with meta-chloroperbenzoic acid (m-CPBA). Additionally, nitration of the compounds produced 5-nitro-3,6,8-tribromoquinoline (214) and 6-bromo-5-nitroquinoline (208). Furthermore, 6,8-diphenylquinoline (217) was synthesized from 205 *via* Suzuki coupling. Starting with 6,8-dibromo-1,2,3,4-tetrahydroquinoline and 6,8-dibromoquinoline, treatment with NaOMe or CuCN yielded the brominated methoxy and cyano quinolines (209-213, 215-216). When compared to the reference drug, 5-fluorouracil (5-FU), compounds 208 and 217 showed the strongest antiproliferative effects, while the remaining compounds displayed weaker antiproliferative activity. In the HT29 cell line, compound 208 exhibited lower cytotoxic activity than 5-FU. Compound 208 demonstrated the capacity to destroy cancer cells through its apoptotic action [84].

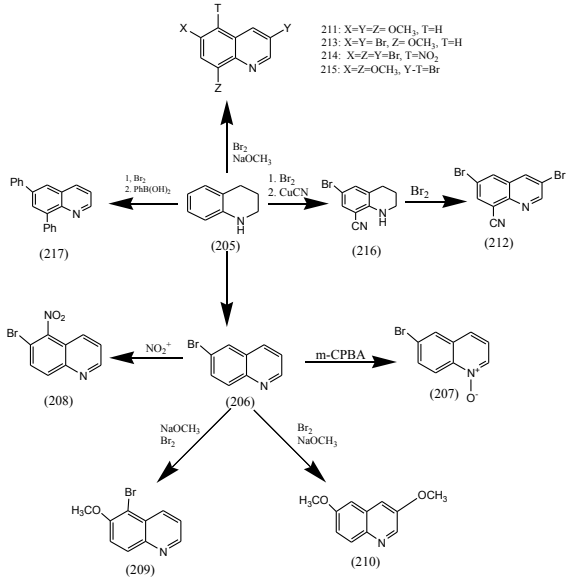


Fig. (36). Synthetic scheme for novel quinoline derivatives [84].

Shabeeb I. *et al.* 2018 described the synthesis of 3-quinolinecarboxylic acid hydrazide-hydrazones (depicted in Fig. **37**). In this reaction, when the corresponding ethyl ester (218) was refluxed with hydrazine hydrate in absolute ethanol, it yielded quinoline-3-carboxylic acid hydrazide (219). Subsequent treatment with phthalic anhydride produced 3-carboxamide (220). Further, treatment of compound 219 with substituted aldehydes afforded hydrazones (221-231). The new compounds were confirmed through elemental analysis, IR, and ^1H NMR, ^13C NMR spectroscopy. Moreover, properties such as structural features and Frontier Molecular Orbital (FMO) distributions were examined through Density Functional Theory (DFT) calculations. The hydrazide-hydrazones demonstrated low to moderate antibacterial activity against Staphylococcus aureus and Escherichia coli, with two compounds showing the highest efficacy, particularly the phthalimide derivative of 3-quinolinecarboxylic acid hydrazide, which exhibited remarkable antibacterial activity compared to gentamycin. Among all tested compounds, compounds 227 and 231 exhibited remarkable effects [85].

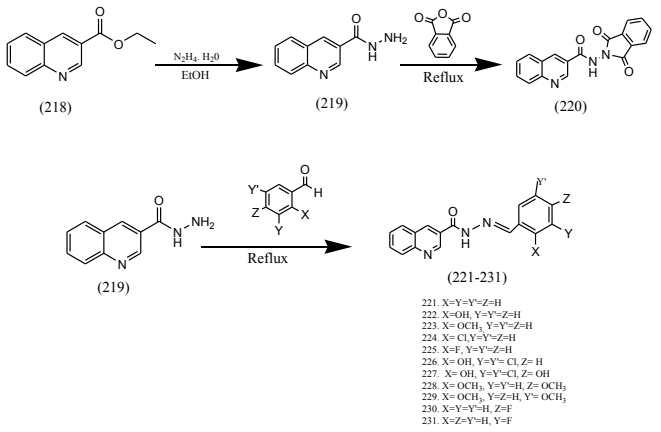


Fig. (37). Scheme for hydrazide-hydrazones derivatives of 3-quinoline carboxylic acid [85].

Saini D. *et al.* 2016 synthesized a series of 1-(4-methylquinolin-2-yl)-4,6-diaryl-1H-pyrazolo[3,4-b].pyridin-3-amine derivatives (236a-t) (as shown in Fig. **38**). In this reaction scheme, 2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonitrile derivatives (234a-t) were prepared using a mixture of ethyl cyanoacetate (232) and aromatic aldehydes or ketones (233). Subsequently, compounds 234a-t were treated with phosphorus pentachloride and phosphorus oxychloride to produce 2-chloro-4,6-diphenylnicotinonitrile derivatives (235a-t). Then, compounds 235a-t were treated with 2-hydrazino-4-methylquinoline to form compounds 236a-t. The newly synthesized compounds were characterized using mass spectrometry, ^1H NMR, and infrared spectroscopy. Five active analogues of the quinoline-pyrazolopyridine hybrids were further evaluated in an *in vivo* suppressive test in Swiss albino mice for 4 days after being screened for the chloroquine-sensitive 3D7 strain of Plasmodium falciparum in an *in vitro* schizont maturation assay. The 5-Cl substituent, which is linked to both aryl rings in series 5p, demonstrated significant antimalarial activity in both *in vitro* and *in vivo* studies [86].

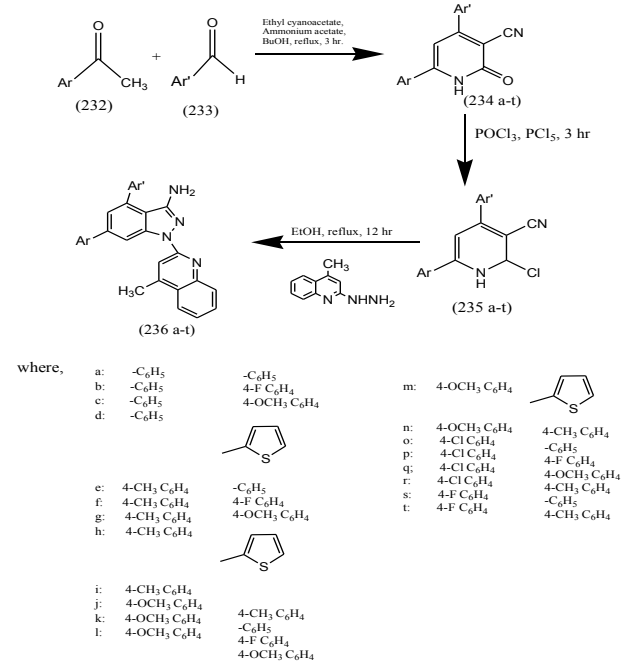


Fig. (38). Synthetic scheme for 1-(4-methylquinolin-2-yl)-4,6-diaryl-1H-pyrazolo[3,4-b].pyridin-3-amine derivatives [86].

According to Gamal *et al.* (2016), the synthesis began with 6-methoxy-1H-pyrazolo[3,4-b].quinolin-3-amine (239), which was treated with various acid anhydrides, such as succinic anhydride, maleic anhydride, and phthalic anhydride, to create a series of 3-substituted 6-methoxy-1H-pyrazolo[3,4-b].quinoline derivatives (243, 244, 245) (shown in Fig. **39**). Additionally, compound 237 was reacted with p-methoxyacetophenone in alcoholic NaOH to create the starting material (239). The 1,3-dipolar cycloaddition of several binucleophiles, such as hydrazine hydrate, hydroxylamine hydrochloride, thiourea, guanidine hydrochloride, urea, and metformin hydrochloride, to the chalcone derivative also produced a variety of 3-heteroaryl-2-chloro-6-methoxyquinolines (247-253) and 1-(4-methoxyphenyl)prop-2-en-1-one-3-(2-chloro-6-methoxyquinolin-3-yl) (246) (depicted in Fig. **40**). The *in vitro* antimicrobial activity of the novel compounds was evaluated against Gram-positive bacteria (Streptococcus pneumoniae and Bacillus subtilis), Gram-negative bacteria (Pseudomonas aeruginosa and Escherichia coli), and fungi (Aspergillus fumigatus, Syncephalastrum racemosum, Geotrichum candidum, and Candida albicans). The structural identities of all products were recorded. The majority of the evaluated compounds exhibited moderate activity against the selected species. Among the tested compounds, pyrimidine derivatives 252 and 253 showed the strongest antibacterial activity against Gram-positive pathogens, whereas 247 and 253 demonstrated the strongest activity against Gram-negative strains, such as E. coli. Three of the selected fungal strains were found to be highly susceptible to compounds 250 and 253 [87].

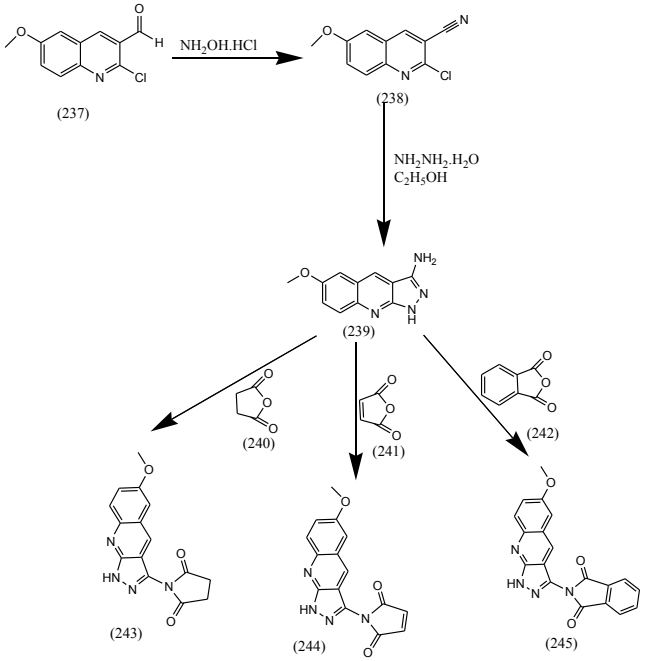


Fig. (39). Synthesis of 3-substituted 6-methoxy-1H-pyrazolo[3,4-b] quinoline derivatives [87].

Ahsan, M. J, *et al.* (2016) searched for newer antiproliferative agents. The researchers reported herein the synthesis of two series (258a-j and 264a-c) of heterocyclic compounds (depicted in Fig. **41**, 42). Moreover, IR, NMR, and mass spectrum data were used to characterize each of the novel compounds. The reaction was carried out by treating resorcinol (254) with ethyl acetoacetate (255) to form coumarin (256). Further treatment with various semicarbazides/thiosemicarbazides/substituted phenyl semicarbazides (257a-j) produced the final products 1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)urea/thiourea (258a-b) and 1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-3-substituted phenyl urea (258c-j). Moreover, another series of 2,5-disubstituted-1,3,4-oxadiazole analogues (264a-c) was formed by reacting 2-aminopyridine (259) with ethyl chloroacetate (260) to form the intermediate semisolid ethyl(pyridin-2-ylamino)acetate (261). Then, it was refluxed with hydrazine hydrate to obtain 2-(pyridin-2-ylamino)acetohydrazide, and was subsequently refluxed with various aromatic aldehydes to obtain N-{[5-aryl-1,3,4-oxadiazol-2-yl].methyl}pyridin-2-amine analogues (264a-c). Additionally, ten compounds (258a-j) were tested for their antiproliferative activity against the cervical cancer cell line HeLa and the melanoma cell line MDA-MB-435, and LC50, TGI, and GI50 values were determined. In compliance with the National Cancer Institute (NCI, US) protocol, three compounds (264a-c) were evaluated at 10 μM against nine different panels of approximately 60 cell lines (NCI-60). The compound 1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-3-(4-methoxyphenyl)urea (258j) exhibited antiproliferative activity, with GI50 values of 35.1 μM against the cervical cancer cell line HeLa and 60.4 μM against melanoma MDA-MB-435. The compounds 264a, 264b, and 264c showed antiproliferative activity with comparatively superior selectivity against HOP-92 (non-small cell lung cancer) at 34.14, 35.29, and 31.59 percent growth inhibition (GI), respectively [88].

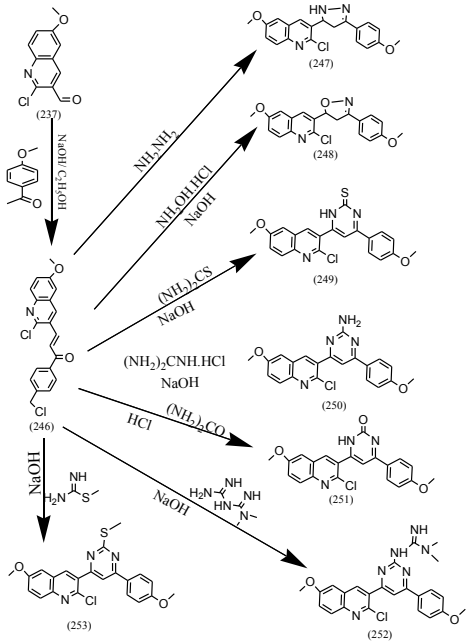


Fig. (40). Synthesis of 3-hetero aryl-2-chloro-6-methoxyquinolines [88].

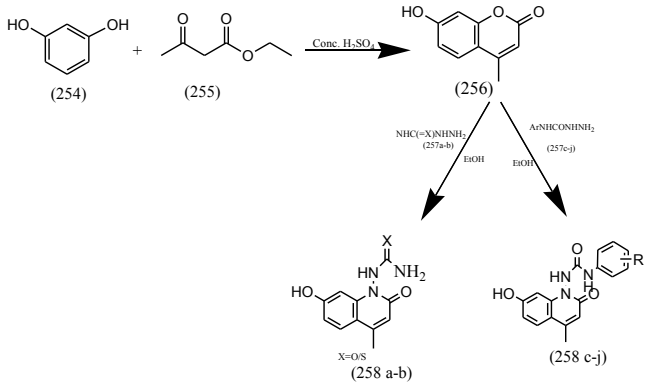


Fig. (41). Synthesis of urea/thiourea (258a-b) and substituted phenyl urea (258c-j) [88].

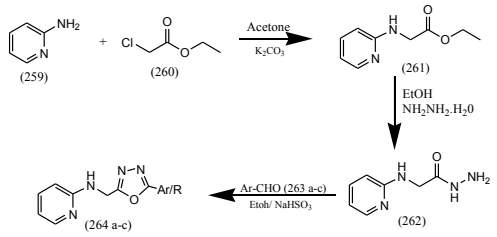


Fig. (42). Synthesis of N-{[5 aryl-1,3,4-oxadiazol-2-yl].methyl}pyridin-2-amine analogues [88].

Gopinath, V. S, *et al.* (2014) designed and synthesized novel quinoline analogues and their substituted derivatives (as in Fig. **43**). ADME characterization and antileishmanial evaluation were also performed. The reactions began with substituted anilines (265a-b), which were treated with ethyl acetoacetate to form 4-hydroxy-substituted quinoline compounds (266a-b and 267a-b). Then, upon treatment with phosphorus tribromide, 4-bromoquinoline derivatives (268a-b) were formed. Additionally, selenium dioxide was used to synthesize quinoline aldehydes (270a-d) from (269a-d). Subsequently, when these compounds (270a-d) were condensed with various substituted ketones (271), they produced chalcone derivatives (272a-g). With IC50 values of 0.84 μM and 0.17 μM, respectively, in comparison to the standard of 0.22 μM, compounds 272b and 272f were determined to be the most active at the end of *in vitro* testing. By contrast, compound 272d, with an IC50 of 6.42 μM, lost its effectiveness despite remaining stable in hamster, mouse, and human liver microsomes. Among all the analogues examined, compounds 272b and 272f appear to be the most promising candidates for further screening based on their DMPK profile and *in vitro* effectiveness [89].

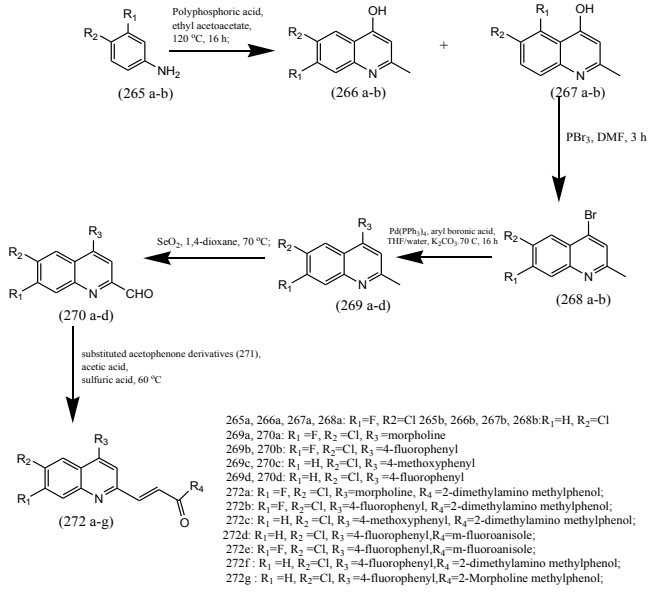


Fig. (43). Scheme for novel substituted quinoline analog [89].

Okten *et al.* (2013) described a new method for the synthesis of 6,8-disubstituted derivatives of quinoline and 1,2,3,4-tetrahydroquinoline substitution reactions (depicted in Fig. **44**). Dibromides (274) were prepared according to previous procedures, starting from 1,2,3,4-tetrahydroquinoline. Moreover, a combination of methoxyquinolines (275 and 276) was produced by treating compound 274 with MeONa in boiling DMF in the presence of CuI. Additionally, a 1:3 ratio of monomethoxide (277) to dimethoxide (278) was generated after longer reaction durations of up to 120 hours. HeLa, HT29, and C6 tumour cell lines were used to investigate the anticancer properties of these compounds. The compounds with the best anticancer activity against the tumour cell lines were 6,8-dibromo-1,2,3,4-tetrahydroquinoline (274) and 6,8-dimethoxyquinoline (278) [90].

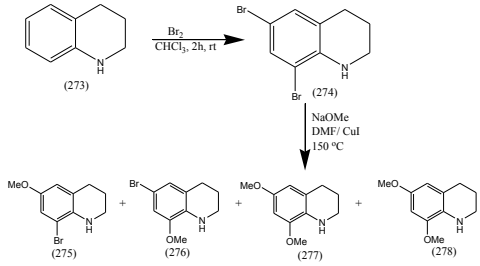


Fig. (44). Method for 6,8-disubstituted derivatives of quinoline and 1,2,3,4-tetrahydroquinoline substitution reactions [90].

Tiwari *et al.* (2013) discovered a novel series of Mannich bases (Fig. **45**), which were evaluated for their analgesic, antipyretic, and anti-inflammatory potential. In this study, the compounds were synthesized by reacting o-substituted aniline (279) with diethyl malonate (280) to produce 4-hydroxyquinolin-2(1H)-one (281), which was further reacted with $POCl_3$ and pyridine to give 4-chloroquinolin-2(1H)-one (282). Moreover, phenylhydrazine (283) was added to produce (284K-L), which was then treated with diethyl malonate to produce 1-(2-oxo-1,2-dihydroquinolin-4-yl)-2-phenylpyrazolidine-3,5-dione (285K-L). This was further reacted with substituted secondary amines (286) to produce 1-(1-((dimethylamino)methyl)-2-oxo-1,2-dihydroquinolin-4-yl)-2-phenylpyrazolidine-3,5-dione (287K-L). Further, the characterization of the synthesized compounds was performed using IR, ^{1}H NMR, and mass spectroscopy. The hot plate and acetic acid-induced writhing methods were used to assess analgesic potential, yeast-induced pyrexia was used to assess antipyretic potential, and the carrageenan-induced rat paw oedema method was used to assess anti-inflammatory potential. Furthermore, it was discovered that, in comparison to the control, compounds 287K, 287N, 287O, 287P, and 287S exhibited strong anti-inflammatory activity. Compound 287K showed effects similar to the standard drug. When compared to the control, compounds 287K, 287N, 287O, 287R, and 287S were shown to have statistically significant analgesic activity, comparable to the standard drug. In contrast, compounds 287N, 287O, 287P, and 287R were found to have significant antipyretic activity when compared to the control [91].

Desai *et al.* (2013) explored a new series of 2-(5-(2-chloroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-ones (292a-l) (depicted in Fig. **46**), which were prepared and characterized by IR, NMR, and mass spectroscopy. The reactions began with the condensation of chloroquinoline aldehyde (288) and acetophenone derivatives (289a-l) to give chalcone intermediates (290a-l), which were then treated with thiosemicarbazide to form 5-(2-chloroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamides (291a-l). Moreover, compounds (291a-l) were cyclized with ethyl bromoacetate to form (292a-l), and the synthesized compounds were screened for antimicrobial activity against microbial strains: Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Candida albicans, Aspergillus niger, and Aspergillus clavatus. Various degrees of antibacterial activity were identified in the compounds that were evaluated. Altogether, compounds 292e, 292g, 292h, 292i, and 292l may be promising agents with antibacterial properties [92].

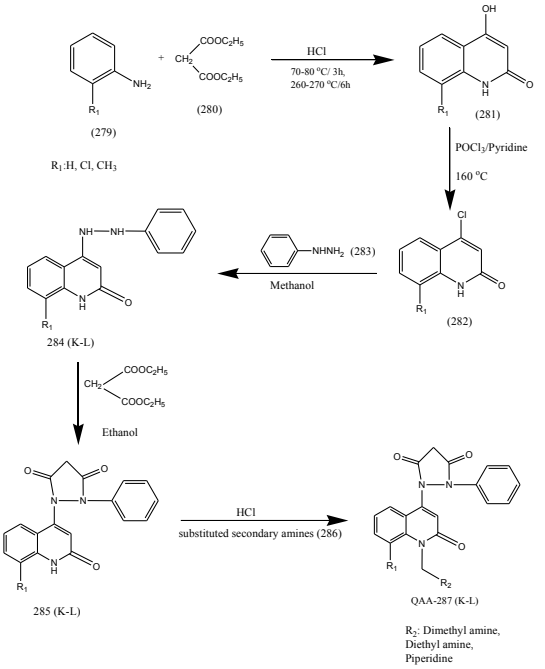


Fig. (45). Novel series of mannich bases [91].

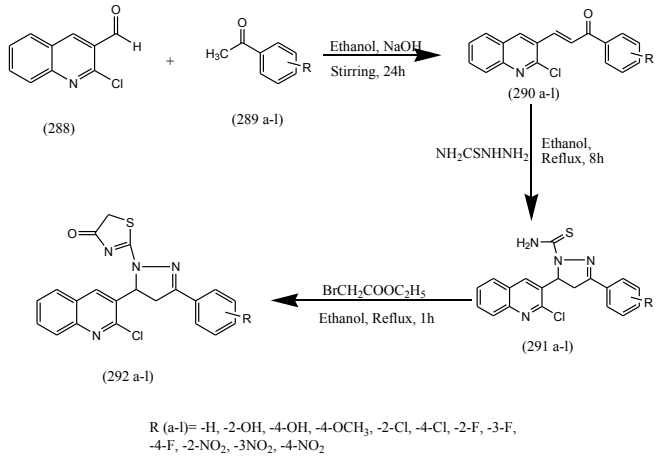


Fig. (46). Synthesis of new series of 2-(5-(2-chloroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)ones [92].

Amir *et al.* (2013) explored novel quinoline derivatives containing pyrazoline-5-one and pyrazole moieties (296a-j and 297a-j) (as in Fig. **47**). These compounds were synthesized by the condensation of various ethyl-2-(arylhydrazono)-3-oxobutyrates (294a-j) and 3-aryl diazenylpentane-2,4-dione (295a-j) derivatives with 8-quinolinoxyacetic acid hydrazide. Moreover, compounds 294a-j and 295a-j were synthesized by reacting aryldiazonium chlorides (293a-j) with ethyl acetoacetate and acetylacetone in the presence of sodium acetate. Additionally, the newly synthesized compounds were subjected to elemental analysis, and their structures were confirmed by IR, 1H NMR, and mass spectrometry data. The serial plate dilution method was then used to assess the antibacterial efficacy of the compounds against S. aureus, E. coli, A. niger, and C. albicans. Among these, 4-(2-(4-fluorophenyl)hydrazono)-2-(quinolin-8-yloxy)acetyl-3-methyl-1H-pyrazol-5(4H)-one (297f), with a log P value of 1.52, was found to be the most effective antibacterial agent of the series [93].

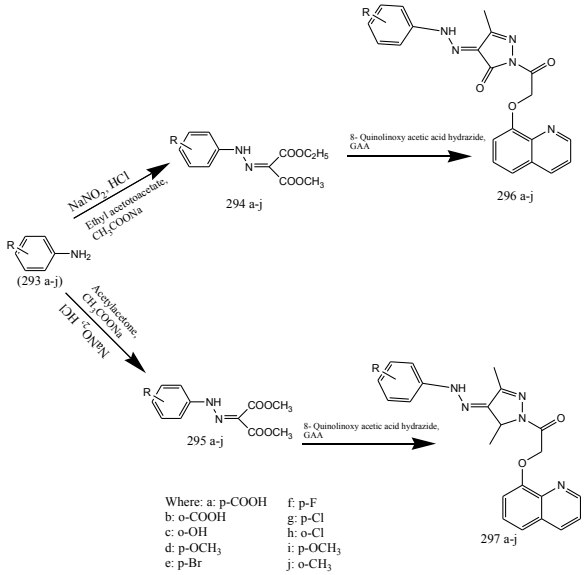


Fig. (47). Synthetic derivatives of quinoline derivatives containing pyrazoline-5-one and pyrazole moiety [93].

Garudachari *et al.* (2012) used a multi-step procedure to create two novel series of benzimidazole compounds containing a quinoline moiety (as in Fig. **48**). A series of 4-carboxyquinolines (304) was created by reacting isatin (302) with α-methylketone (303), while the first series of 6-substituted-4-carboxyquinolines (300a, b) was created by the Doebner reaction employing substituted aniline (298) and 4-fluorobenzaldehyde (299). Continuing with these procedures, six substituted-4-carboxyquinolines (300a, b, and 304) were reacted with different aromatic 1,2-diamines in polyphosphoric acid media to create the intended quinoline-integrated benzimidazole derivatives (301a-i and 305a-f). All of the newly synthesized compounds were examined using C, H, and N analysis, in addition to IR and NMR spectroscopy. The well plate method (zone of inhibition) was used to screen the resulting compounds for their *in vitro* antibacterial and antifungal activities. Compounds 301c, 301d, 305c, and 305d demonstrated strong antibacterial activity, according to the data. It was discovered that compound 305b was a strong antifungal agent. In comparison to conventional medications, compounds 301a, 305a, and 305f demonstrated moderate to good antibacterial activity against all examined microbial strains [94].

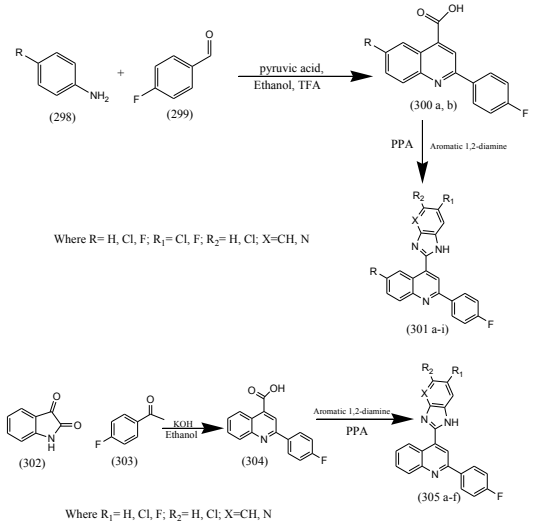


Fig. (48). Scheme for novel series of benzimidazole compounds [94].

Fiorito Jole *et al.* (2012) examined how phosphodiesterase type 5 (PDE5) breaks down cGMP and how this affects the nitric oxide/cGMP/cAMP-responsive element-binding protein (CREB) pathway, which is important for memory and learning in the brain and other tissues. As a result, PDE5 inhibitors (PDE5Is) are being researched as possible treatments for Alzheimer's disease (AD), a disorder characterized by memory loss. Using commercially available 4-amino-3-bromobenzonitrile (306), which was condensed with ethoxymethylenemalonate by refluxing in toluene to give compound (307), a series of quinoline derivatives 312a-f was synthesized in this study. Oxoquinoline (308) was produced after 307 was cyclized in refluxing diphenyl ether. 4-chloroquinoline (309) was produced in good yield by chlorinating 308 with POCl3. The quinoline ester 310 was produced when 309 reacted with (3-chloro-4-methoxyphenyl)methanamine hydrochloride in the presence of DIPEA. Quinolines 311a-f were obtained by organometallic reactions with palladium present. Furthermore, three hydroxymethyl derivatives, 312a-f (as in Fig. **49**), were produced by reducing quinoline esters 311a-f with lithium tri(tert-butoxy)aluminum hydride. With an IC50 of 0.27 nM, compound 312a was found to be a selective PDE5 inhibitor and showed blood-brain barrier crossing capabilities. The 312a molecule successfully restored synaptic and cognitive impairments in an AD mouse model. The development of these CNS-permeant quinoline-based PDE5Is as a treatment for AD appears promising [95].

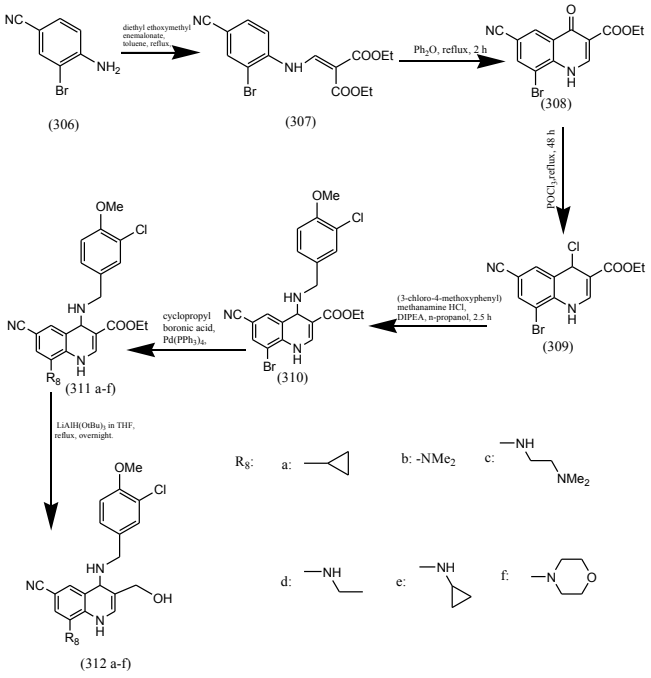


Fig. (49). Synthetic scheme for quinoline derivatives [95].

Tiwari *et al.* (2011) focused on quinolones (illustrated in Fig. **50**), which are broad-spectrum antibacterial drugs frequently used in veterinary and clinical settings. Bacterial resistance has developed as a result of their widespread use. A number of substituted quinolones (318A-D) were synthesized for the present investigation. In this study, the reaction begins with substituted anilines (313) treated with diethyl malonate (314). The reaction proceeds to produce N-methyl-4-hydroxy-2-quinolone (315), which is then further condensed with phosphoryl chloride to produce N-methyl-4-chloro-2-quinolone (316). Subsequently, compound 316 reacts with substituted phenylhydrazines (317A-D) to produce the corresponding final derivatives, phenylhydrazides (318A-D). IR and 1H NMR were used to characterize the synthesized compounds. Using norfloxacin and gatifloxacin as reference standards, all of the compounds were evaluated for their antibacterial activity against two Gram-positive (Staphylococcus aureus, Enterococcus species) and two Gram-negative (Escherichia coli, Shigella species) pathogens. Clotrimazole and amphotericin B were used as benchmarks to test the synthetic compounds' antifungal activity against Aspergillus niger and Aspergillus flavus. The results showed a notable antibacterial effect when the phenyl ring of the phenylhydrazine moiety was substituted. Comparable to the standards, compounds 318B and 318D demonstrated strong antibacterial and antifungal properties, respectively [96].

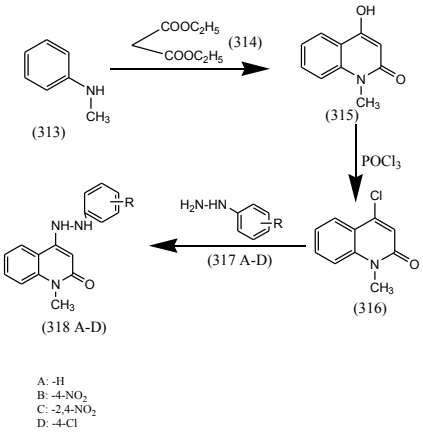


Fig. (50). Synthetic derivative of substituted quinolones [96].

Eswaran S. *et al.* (2010) synthesized four novel series of quinoline derivatives (as in Fig. **51**) *via* multi-step processes, beginning with 2-trifluoromethylaniline (319). Compound 319 was cyclized to 4-hydroxyquinoline (320) in the reaction sequence, which was subsequently converted into 4-chloro-2,8-bis(trifluoromethyl)quinoline (321). The final derivatives of quinoline, namely hydrazones (323a-t), ureas (324a-e), thioureas (325a-c), and pyrazoles (326a-d), were efficiently synthesized from the crucial scaffold 4-hydrazinyl-2,8-bis(trifluoromethyl)quinoline (322), which was derived from compound 321, in good yields. The newly synthesized compounds were evaluated for *in vitro* antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and recultured Klebsiella pneumoniae, as well as antituberculosis activity against Mycobacterium tuberculosis H37Rv and MDR-TB strains. Preliminary studies revealed that the majority of the hydrazone derivatives exhibited excellent antibacterial and antituberculosis properties, while other compounds demonstrated moderate activity [97].

Upadhayaya R. Shankar *et al.* (2009) synthesized and evaluated 27 novel derivatives (shown in Fig. **52**a & b) for antimycobacterial activity against Mycobacterium tuberculosis H37Rv. In this work, the synthesis began with 3-benzyl-6-bromo-2-methoxyquinoline (327), which was brominated to form the intermediate compound (328). Further, a series of 3-benzyl-6-bromo-2-methoxyquinoline derivatives (329-346) was obtained by nucleophilic displacement of bromine with a suitable amine (R-H). Moreover, another series was initiated from the intermediate compound (328) with dimethyl malonate in tetrahydrofuran using sodium hydride as a base, yielding malonic acid dimethyl ester (347). Selective hydrolysis of compound 329 with aqueous potassium hydroxide in methanol produced compound (348). Subsequently, the amide derivatives of 2-[(6-bromo-2-methoxyquinolin-3-yl)-phenylmethyl].-malonic acid

monomethyl ester (compounds 349-357) were formed upon treatment of compounds 328 and 348. *In vitro* testing over nine days revealed that several compounds showed 92-100% growth inhibition and a minimum inhibitory concentration (MIC) of 6.25 µg/mL. Molecular modeling and docking studies, inspired by the antitubercular drug R207910, highlighted the importance of phenyl, naphthyl, and halogen moieties. Electrostatic interactions were identified as crucial. These findings suggest promising avenues for developing new lead compounds with enhanced antimycobacterial activity [98].

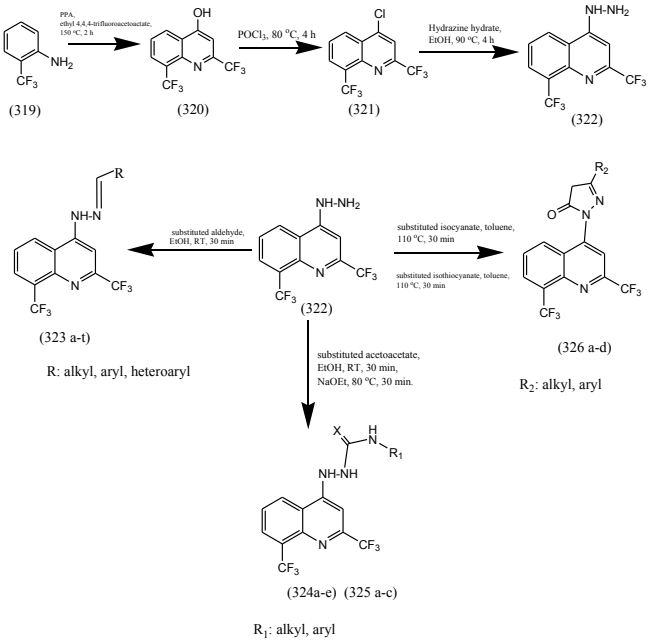
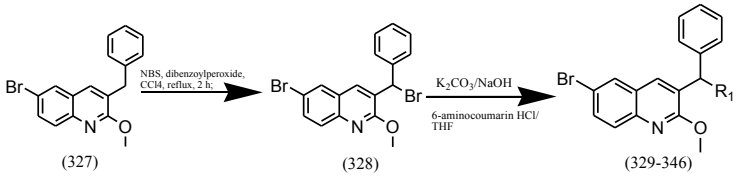


Fig. (51). Multi-step process for quinoline derivatives [97].

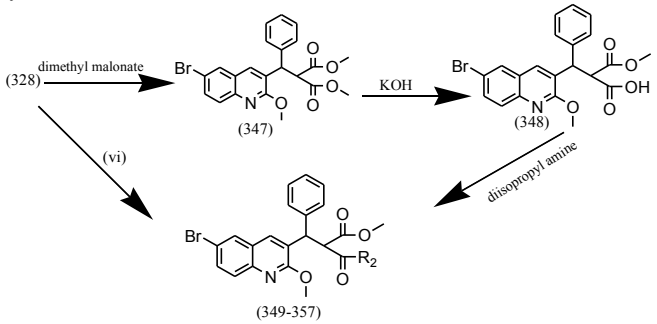
Metwally K.A. *et al.* (2006) explored a novel pathway for the synthesis of 2-arylquinoline-4-carboxylic acid hydrazide-hydrazones (as shown in Fig. **53**) using the versatile Pfitzinger reaction, which begins by treating isatin or substituted isatins (358) with α-methylketones (359) in ethanol to yield 2-arylquinoline-4-carboxylic acids (360). By reacting these acids with hydrazine hydrate in refluxing ethanol, and subsequently treating them with thionyl chloride (361) under reflux in benzene, the corresponding acid chlorides (362) were produced. These chlorides were then directly utilized to prepare the hydrazides (363). Under reflux conditions, the desired hydrazones (365-384) were synthesized by condensing the acid hydrazides (363) with the appropriate aldehydes (364) in glacial acetic acid. The *in vitro* antibacterial activity of each target compound was evaluated against the fungal species Candida albicans, the Gram-negative bacterium Escherichia coli, and the Gram-positive bacterium Staphylococcus aureus. The minimal inhibitory concentration (MIC) was determined for both the reference standards and the test compounds. When tested against E. coli, compounds with nitro substituents at the arylidene moiety exhibited the strongest antifungal and antibacterial properties. The antifungal activity of compound (384) was comparable to that of nystatin. However, against S. aureus, none of the compounds exhibited antibiotic activity. When tested for hemolytic toxicity, the most potent compounds—368, 379, 380, and 383-384—were found to be non-hemolytic up to a concentration of 100 µg/mL. Additionally, the cytotoxic efficacy of the most active compound (384) against different cancer cell lines was assessed *in vitro*. It was discovered that this compound increased the proliferation rate of Hep-G2 cells rather than exhibiting any toxic effects [99].

5. PHARMACOLOGICAL ACTIVITY

Mohareb R.F. *et al.* (2024) conducted a study to assess the anticancer potential of new 5,6,7,8-tetrahydro-4H-chromenes against the prostate cancer cell line PC-3, as well as six other cancer cell



329).R1 =Imidazolyl; 330).R1 = Pyridine 2-ylamine; 331).R1 =6-Methyl-pyridine-2-ylamine; 332).R1 =C-(Tetrahydro-furan-2-yl)-methylamine; 333).R1 = C-(Thiophen-2-yl) methylamine; 334).R1 =1-(3-Trifluoromethyl-phenyl)-piperazinyl; 335).R1 =Piperidinyl; 336).R1 = Morpholinyl; 337).R1 = 5-Methyl-tetrazol-1-yl; 338).R1 =Pyrrolidine 2-carboxylic acid ethyl ester ; 339).R1 = Piperidine-4-carboxylic acid ethyl ester; 340).R1 = C-Pyridin-4-yl-methylamine ; 341).R1 =Indolyl;342).R1 = 4-Nitro-imidazolyl; 343).R1 =Pyrazolyl; 344).R1 = 6-Amino-chromen-2-one; 345).R1 =Naphthalen1-yl-acetic acid ethyl ester; 346).R1 = Naphthalen-1-yl-acetic acid ethyl ester



349).R2 = Morpholinyl; 350).R2 = Morpholinyl;351).R2 =Pyrrolidinyl;
352).R2 =Pyrrolidinyl; 353).R2 =Piperidinyl; 354).R2 =Piperidinyl; 355).R2 =Pyrazolyl; 356).R2 = 1-(3-Trifluoromethyl-phenyl)-piperazinyl; 357).R2 = 1-(3-Trifluoromethyl-phenyl)-piperazinyl Where, (vi) R = 3-morpholin-4-yl-3-oxo-propionic acid methyl ester, 3-oxo-3-pyrrolidin-1-yl-propionic acid methyl ester, 3-oxo-3-piperidin-1-yl-propionic acid methyl ester(for 27 and 28); in dry THF, NaH, 1.5 h, dry THF

Fig. (52). (a, b). Synthesis of amide-quinoline derivatives [98].

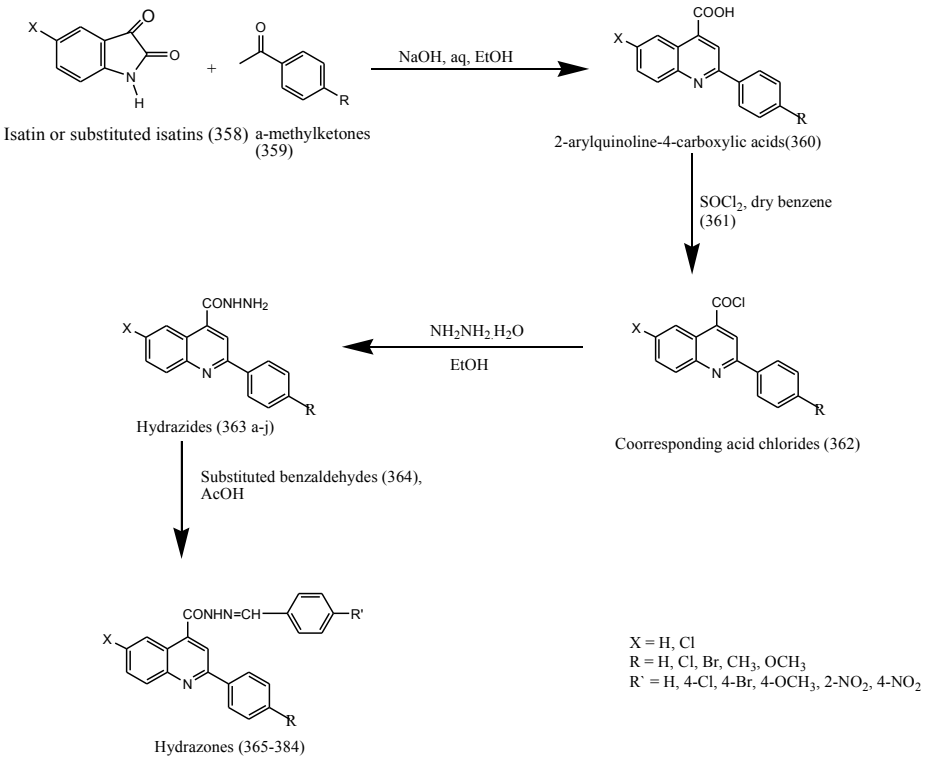
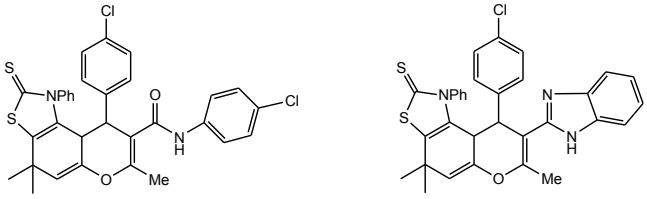


Fig. (53). Novel scheme for series of 2-arylquinoline-4-carboxylic acid hydrazide-hydrazones[99].

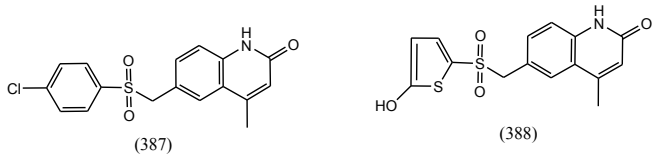
lines. Using a practical synthesis approach, a new series of substituted 5,6,7,8-tetrahydro-4H-chromenes was developed (as shown in Fig. **54**). In this work, 5,6,7,8-tetrahydro-4H-chromene derivatives were synthesized through multi-component reactions between dimedone, aromatic aldehydes, and ethyl acetoacetate as the first step in the synthetic procedure. Conversely, hexahydroquinoline compounds were obtained by carrying out the same reactions in the presence of NH4OAc. All the synthesized compounds were tested for their ability to inhibit specific cancer cell lines and to exhibit anti-proliferative properties. According to the findings, many of the compounds displayed strong inhibitory effects. The morphology of the A549 cell line was also examined in relation to the effects of compounds 385 and 386 [100].



(385) (386)

Fig. (54). Derivatives of 5,6,7,8-tetrahydro-4H-chromenes [100].

Singh *et al.* (2024) developed and synthesized novel derivatives of quinoline and, using computational and experimental approaches, evaluated them as antibacterial and antifungal agents that act as fungal cell wall disruptors and peptide deformylase enzyme (PDF) inhibitors. Molecular docking and ADMET evaluation facilitated the synthesis of quinoline derivatives, starting with 6-amino-4-methyl-1H-quinolin-2-one, which was modified with different sulfonyl/benzoyl/propargyl moieties. The antibacterial and antifungal properties of the newly synthesized compounds were evaluated using *in vitro* methods. Outstanding MIC values (MIC, 50–3.12 µg/mL) were obtained for all compounds screened against the bacterial strains Escherichia coli, Pseudomonas, Bacillus cereus, and Staphylococcus. Compounds 387 and 388 (as shown in Fig. **55**) demonstrated superior activity in this regard. Additionally, antifungal screening against the fungal strains A. flavus, A. niger, F. oxysporum, and C. albicans revealed that most derivatives exhibited promising activity, with compound 388 being the most effective. Moreover, cytotoxicity tests showed that compound 388 was the least toxic. Molecular dynamics (MD) simulations further clarified the conformational stability of the compound 388-PDF complex, highlighting flexible binding pocket residues [101].

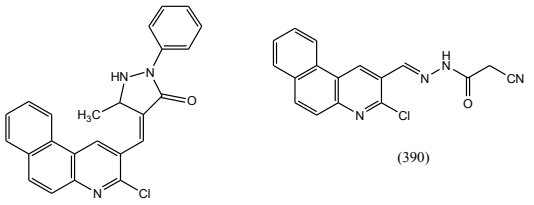


(387) (388)

Fig. (55). Newer quinoline derivative [101].

El-Helw, Eman A. E, *et al.* (2024) began the reaction with 3-chlorobenzo[f].quinoline-2-carbaldehyde, which was treated with N-phenyl-3-methylpyrazolone, 4-aminoacetophenone, 1,2-diaminoethane, and 2-cyanoethanohydrazide to create a sequence of benzoquinolines using heterocycles. Additionally, from the derived cyanoethanohydrazone, derivatives of pyridine, chromene, α,β-unsaturated nitrile, thiosemicarbazone, and 1,2-bis(aryl)hydrazine were synthesized. The experimental results and the DFT calculations were in agreement. Their antiproliferative effectiveness was tested *in vitro* against the MCF7 and HCT116 cancer cell lines. The docking study revealed binding affinity between the CDK5 enzyme and derivatives of pyrazolone 389 and cyanoethanohydrazone 390 (as shown in Fig. **56**), which were the most potent. Compounds 389

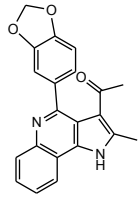
and 390 had binding energies comparable to those of the co-crystallized ligand (EFP): −6.6320 kcal/mol (with RMSD of 0.9477 Å) and −6.5696 kcal/mol (with RMSD of 1.4889 Å), respectively. This suggests a very high affinity for binding to the CDK5 enzyme. To create novel chemotherapeutic drugs, pyrazolone derivative 389 would be regarded as a strong candidate for further optimization. Additionally, its favorable drug-likeness and oral bioavailability properties were demonstrated by the ADME (absorption, distribution, metabolism, and excretion) tests [102].



(389) (390)

Fig. (56). Derivatives of pyrazolone and cyanoethanohydrazone based quinoline derivative [102].

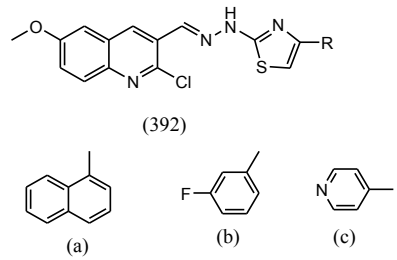
When Mingoia Francesco *et al.* (2023) screened around 60 tumor cell lines (NCI), they found a pathway of uniquely substituted 1,3,4-pyrrolo[3,2-c].quinoline derivatives (PQs) (as shown in Fig. **57**). After optimization, a promising compound (391) was synthesized, which, at low μM concentrations, showed improved activity against leukemia, CNS, melanoma, renal, and breast cancer cells. Initial studies were performed on MCF-7 and non-tumorigenic MCF-10 cells, including ROS content and cell cycle analyses. Anticancer targets HSP90 and ER receptors were the focus of computational research, which provided important insights into binding mechanisms and optimization possibilities [103].



(391)

Fig. (57). Substituted 1,3,4-substituted-pyrrolo[3,2-c]. quinoline derivative [103].

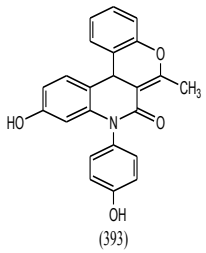
A.E. Evren *et al.* (2023) found that, globally, infectious diseases are a serious concern. New chemotherapeutics for infectious illnesses are desperately needed. As a result, their team created, produced, and examined 14 novel quinoline derivatives that possess the fluoroquinolone pharmacophore moiety, mainly for their antibacterial properties. The NIH/3T3 cell line and six bacterial and four fungal strains were used to investigate their cytotoxic effects. Furthermore, their modes of action were assessed against lanosterol 14α-demethylase (LMD) and DNA gyrase. In addition, the aromatase enzyme was used to analyze the active components in order to rule out any potential negative effects. Molecular docking and simulation studies were used to evaluate the experimental enzymatic data for the binding processes of the active compounds. The data were also used to clarify the structure-activity relationship (SAR). Compound 392a was found to be the most effective molecule for its antifungal activity, with low cytotoxicity against healthy cells and fewer potential side effects. However, compounds 392b and 392c (as shown in Fig. **58**) could be given individually to patients who have fungal infections in addition to the primary disease [104].



(392) (a) (b) (c)

Fig. (58). Synthesized newer derivatives [104].

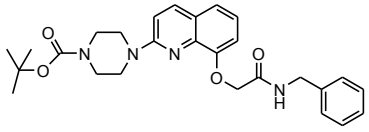
In 2021, El-Saghier A.M. *et al.* effectively synthesized a new series of quinoline derivatives using a solvent-free, one-pot multicomponent reaction (MCR) comprising resorcinol, aromatic aldehydes, β-ketoesters, and aliphatic/aromatic amines. All compounds were produced in a short time, with low processing costs, and in excellent yields. Spectral and elemental analyses were used to characterize the structures of all compounds. Additionally, the antioxidant and antibacterial properties of each synthesized molecule were examined *in vitro*. Furthermore, to confirm the binding affinities of the new quinoline derivatives and to understand potential ligand-enzyme intermolecular interactions, in silico molecular docking experiments were conducted with the target enzymes human NAD(P)H dehydrogenase (quinone 1) and DNA gyrase. In addition to having the highest negative binding energies for human NAD(P)H dehydrogenase (quinone 1) and DNA gyrase, respectively, at −9.1 and −9.3 kcal/mol, compound 393 demonstrated promising antioxidant and antibacterial activities. Moreover, it adhered to Veber's, Ghose's, and Lipinski's rules of five. Thus, the quinoline analogue (393) (as in Fig. **59**) may be a viable molecular framework for the development of antibacterial and antioxidant therapeutic candidates in the future [105].



(393)

Fig. (59). Quinoline analogue derivative [105].

Wang M. *et al.* (2021) described the synthesis of several new quinoline derivatives based on the lead compound identified using a high-throughput screening test for rRSV-mGFP. According to their findings, compound 394 (IC50: 1.87 ± 0.58 mM) was the most active molecule (shown in Fig. **60**). It was 8.2 times more effective than the reference drug and was able to suppress the viral transcription and replication cycle at an early stage [106].

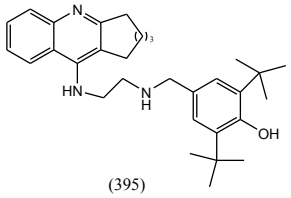


(394)

Fig. (60). Novel quinoline derivative [106].

According to Makhaeva *et al.* (2020), new 4-amino-2,3-polymethylenequinoline hybrids with varying aliphatic ring widths, connected to butylated hydroxytoluene (BHT) *via* enaminoalkyl or aminoalkyl spacers, were developed as potential multipurpose

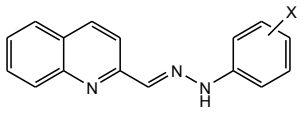
treatments for Alzheimer's disease (AD). All of the compounds were strong inhibitors of butyrylcholinesterase (BChE) and acetylcholinesterase (AChE), with selectivity for BChE. The lead compound 395, 2,6-di-tert-butyl-4-{[2-(7,8,9,10-tetrahydro-6H-cyclohepta[b].quinolin-11-ylamino)-ethylimino].-methyl}-phenol (depicted in Fig. **61**), demonstrated IC50 (AChE) = 1.90 ± 0.16 µM, IC50 (BChE) = 0.084 ± 0.008 µM, and 13.6 ± 1.2% propidium displacement at 20 µM. The low activity of the compounds against carboxylesterase suggests that clinically undesirable drug-drug interactions are unlikely [107].



(395)

Fig. (61). Structure of 2,6-di-tert-butyl-4-{[2-(7,8,9,10 tetrahydro-6H-cyclohepta[b].quinolin-11-ylamino)-ethylimino].-methyl}-phenol [107].

In 2020, Celik I. *et al.* synthesized a number of derivatives of quinoline-2-carbaldehyde hydrazone and assessed their antioxidant properties. The microdilution method was used in this investigation to assess the antibacterial activity of these quinoline-2-carbaldehyde hydrazone derivatives, and the MTT test was used to examine their cytotoxic effects in MCF-7 and A549 cells. Compounds 396a (2 mg/mL) and 396c (1 mg/mL) against E. faecalis, and 396b (8 mg/mL) against P. aeruginosa, were the most effective derivatives of the series, according to the activity results, even though the antimicrobial activity of quinoline derivatives was generally on par with or better than that of standard medications (as in Fig. **62**). When these three compounds were subjected to the disc diffusion test, a notable zone of inhibition was observed with 396c (7 mm) in contrast to vancomycin (9 mm). In A549 and MCF-7 cell lines, the compounds had no antiproliferative effects. Compounds 396a, 396b, and 396c, which exhibited the most antibacterial activity, were tested in healthy cells (Beas-2b) and showed no effect on cell viability. Molecular docking studies were conducted on 15 distinct proteins to determine the mechanism of action of these compounds against E. faecalis. The results showed that the compounds interacted with FabH but not sufficiently with other protein structures [108].

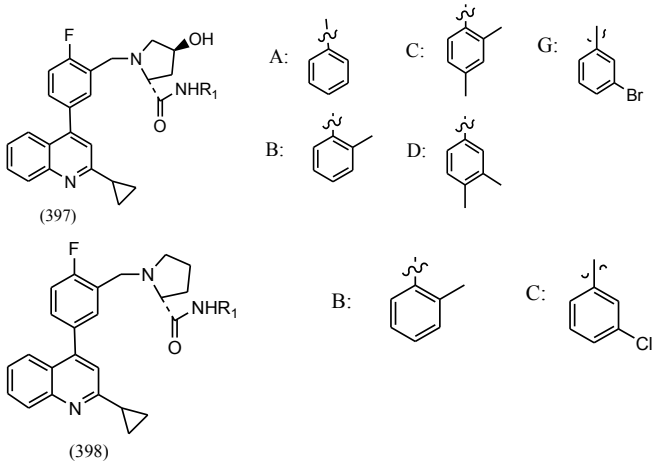


(396)

X: a: 2,5-difluoro
b: 2-chloro
c: 3,5-dichloro

Fig. (62). Derivatives of quinoline-2-carbaldehyde hydrazone [108].

Ganesan M.S. *et al.* (2020) discovered that a key molecular target for type 2 diabetes mellitus is the α-amylase enzyme, which hydrolyses carbohydrates into glucose. We created seventeen new quinoline-bearing proline analogues during the development of α-amylase enzyme inhibitors. The physicochemical characteristics of these analogues were then in silico predicted for their drug similarity assessment. Mass, IR, ^{1}H NMR, ^{13}C NMR, and other spectral analyses were used to characterize the compounds that were synthesized during the study. Acarbose, a typical medication, was then used to screen for α-amylase inhibitory action *in vitro*. The α-amylase inhibitory activity of seven analogues, 397a, 397b, 397c, 397d, 397g, 398b, and 398c (as in Fig. **63**), was found to be significant [109].

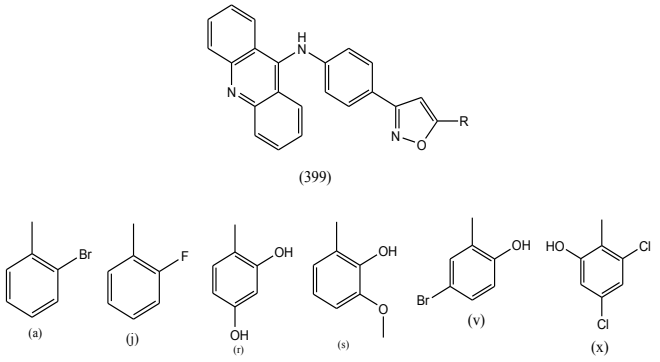


(397)

(398)

Fig. (63). Structure of newer quinoline-bearing proline analogues [109].

In 2019, Rajagopal Kalirajan R. *et al.* investigated human Epidermal Growth Factor Receptor-2 (HER2), a membrane tyrosine kinase that is overexpressed and has its gene amplified in human breast tumours. Twenty percent of breast cancer cases have been shown to involve significant tumour cell proliferation and survival pathways associated with HER2 amplification and overexpression. Due to their antiproliferative characteristics, 9-aminoacridines are important DNA-intercalating agents. The scientists used MM-GBSA binding free energy, ADMET screening, and in silico design of a few novel isoxazole-substituted 9-anilinoacridines as HER2 inhibitors targeting breast cancer. The Schrödinger Suite 2016-2 was used to choose PDB ID 3PP0, against which the developed derivatives were docked. Additionally, compounds 399s, 399x, 399v, 399a, 399j, and 399r (mentioned in Fig. **64**), out of 26 synthesized derivatives, exhibited substantial anti-breast cancer activity with a significant Glide score. Furthermore, based on *in vitro* and *in vivo* investigations, they have the potential to be highly effective against breast cancer [110].

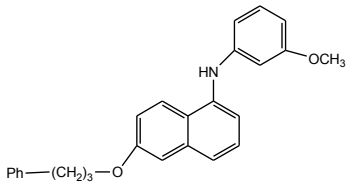


(399)

Fig. (64). Novel derivatives of quinoline pharmacophore [110].

In 2019, Cao Rihui and colleagues synthesized and evaluated new quinoline derivatives for their antiproliferative properties. When tested against seven human tumour cell lines, some compounds showed strong antiproliferative activity with IC50 values less than 10 µM. Notably, the most effective compound was N-(3-methoxyphenyl)-7-(3-phenylpropoxy)quinolin-4-amine (400), which showed IC50 values of 2.56, 3.67, 3.46, and 2.71 µM against the HeLa, RKO, A2780, and HCT-116 cell lines, respectively. Representative compound (400) (as in Fig. **65**) was shown in *in*

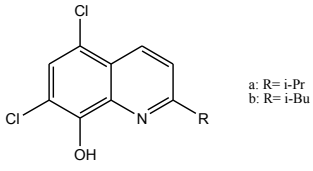
vivo experiments to effectively suppress tumour growth and reduce tumour weight in mice. Through the ATG5-dependent autophagy system, this compound reduced the growth of colorectal cancer, according to mechanistic research. These quinoline derivatives represent a promising class of compounds for possible development as anticancer medicines [111].



(400)

Fig. (65). Structure of N-(3-methoxyphenyl)-7-(3-phenylpropoxy)quinolin-4-amine [111].

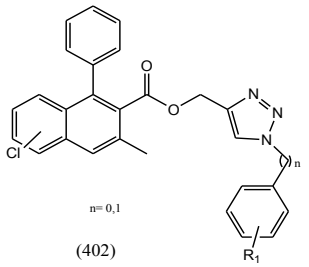
In 2018, Guardia D.L. and colleagues conducted a study on the dengue virus, which causes dengue fever, a debilitating illness that is becoming more common in many tropical and subtropical regions. Currently, this virus cannot be treated with any licensed antivirals. The pharmacophore "quinoline" has demonstrated promise for the development of molecules with a range of biological functions. Here, we report the synthesis and evaluation of the antiviral activity of two compounds. At low and submicromolar concentrations, two of the examined compounds demonstrated dose-dependent suppression of dengue virus serotype 2. Compounds 401a and 401b (Fig. **66**) also prevented the accumulation of the viral envelope glycoprotein in infected cells, possibly through an early infection-related mechanism, even though they did not directly exert a virucidal effect. These findings are consistent with earlier research demonstrating the potential of quinoline derivatives as a suitable scaffold for the development of novel antivirals to combat this significant virus [112].



(401)

Fig. (66). Newer quinoline scaffold derivative [112].

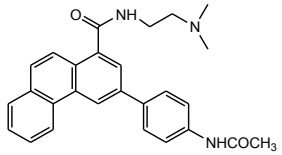
Upadhyay *et al.* (2018) investigated the great potential of natural products and their derived compounds that contain quinolines in chemistry. They identified a new series of 25 compounds that might be used to create new antileishmanial drugs. Using a molecular hybridisation technique inspired by click chemistry, several triazolyl 2-methyl-4-phenylquinoline-3-carboxylate derivatives were created and tested against Leishmania donovani. Most of the screened derivatives demonstrated significant *in vitro* antileishmanial activity against promastigotes (IC50 ranging from 2.43 to 45.75 μM) and intracellular amastigotes (IC50 ranging from 7.06 to 34.9 μM) in comparison to the control, miltefosine (IC50 = 8.4 μM), and showed less cytotoxicity than the standard medications. The prototype represents a novel structural lead for antileishmanial chemotherapy, according to the overall results. Interestingly, compound 402 (Fig. **67**) showed encouraging *in vivo* leishmanicidal activity in the L. donovani/golden hamster model, which is noteworthy because the hamster model of VL is quite similar to the human VL situation [113].



(402)

Fig. (67). Structure of triazolyl 2-methyl-4-phenylquinoline-3-carboxylate derivatives [113].

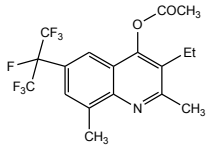
According to Jafari *et al.* (2018), a novel class of benzo- and tetrahydrobenzo[h].quinolines (Fig. **68**) with a flexible (dimethylamino)ethyl carboxamide side chain was designed and synthesized as anticancer drugs that intercalate DNA. The cytotoxic potential of the synthesized compounds was assessed using four human cancer cell lines: MCF-7, A2780, C26, and A549. Tetrahydrobenzo[h].quinolines, which are saturated quinolines, generally showed greater cytotoxicity than their unsaturated counterparts, benzo[h].quinolines. With IC50 values ranging from 1.86-3.91 μM, compound 403 showed lower cytotoxicity against all four human cancer cell lines. Additionally, compared to other compounds, this one demonstrated the strongest apoptotic induction activity and the greatest cytotoxic effect against A549 cancer cells. The purpose of the docking study was to investigate these compounds' DNA interaction characteristics. Based on the computational data, these substances have the capability to interact with DNA as DNA-intercalating agents [114].



(403)

Fig. (68). Structure of benzo- and tetrahydro benzo-[h]quinolines [114].

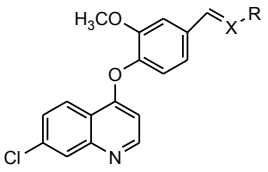
Fang and colleagues (2018) explored and synthesized several new quinoline derivatives (depicted in Fig. **69**) with a perfluoropropanyl moiety. Some of them showed good control efficacy against Pyricularia oryzae, according to the bioassay data. The substitution position of the molecule had an impact on the fungicidal activity. At varying concentrations, compound 404 was determined to have the strongest control effect against P. oryzae, and it was superior to Tebufloquin [115].



(404)

Fig. (69). Newer derivatives of quinoline with a perfluoropropanyl ring [115].

In 2018, Valdivieso *et al.* identified two compounds, 405A and 405B (depicted in Fig. **70**). The MTT assay against Leishmania donovani was used to assess these compounds for *in vitro* antileishmanial activity; no cytotoxic effect was observed in a macrophage cell line. These substances had a synergistic impact on promastigotes and amastigotes when combined with miltefosine and amphotericin B [116].

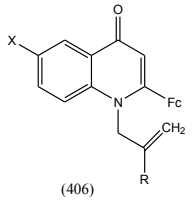


(405)

A. R=H, X=O
B. R= thiourea, X=N

Fig. (70). 7-chloro-4-aryloxyquinoline derivatives [116].

Pejović *et al.* synthesized and described new derivatives of substituted hexahydroquinolines. These compounds, like calcium channel blockers, were evaluated for pharmacological activity. IR, 1H NMR, X-ray crystallography, mass spectrometry, and elemental analysis were used to characterize each of the synthesized compounds. Compound 406a (Fig. **71**) exhibited the highest cytotoxic activity of all, but compound 406b had the most detrimental effect on K562 cells. Additionally, the SAR analysis showed that biological activity is influenced by the Cl, Br, H, and allyl substituents on the nitrogen atom in the quinoline ring [117].

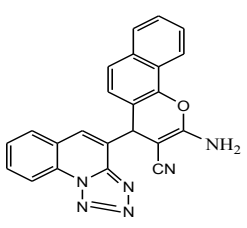


(406)

a. Fc= C_5H_4-Fe-C_5H_4, R=H, X=Cl
b. Fc= C_5H_4-Fe-C_5H_4, R= CH_3, X=Br

Fig. (71). Substituted hexohydroquinolines derivative [117].

Nasr Eman E. *et al.* (2018) worked to combine different heterocycles and chalcone moieties with the quinoline moiety as a primary scaffold to create new hybrid compounds (as in Fig. **72**), guided by various literature reviews to generate an efficacious antitumor agent. New quinoline-substituted compounds were created by the researchers and tested against 60 human cancer cell lines *in vitro*. With unique growth inhibition values (GI50) against most of the cell lines, including SR, HL-60 (TB) strains (leukaemia), and MDA-MB-435 strains (melanoma), compound 407 had the maximum cytotoxicity towards 58 cell lines. Its GI50 values were 0.232, 0.260, and 0.300 μM, respectively. With a reduced harmful effect on normal cells, such as skin fibroblasts (BJ) and breast epithelial cell lines (MCF-10F), it demonstrated high selectivity for cancer cell lines. Compound 407's enzyme inhibitory activity was assessed against vascular EGFR and topoisomerase I (Topo I). It demonstrated competent Topo I inhibition activity with an IC50 value of 0.278 μM in comparison to camptothecin, the reference medication (IC50 0.224 μM). To find out how well compound 407 recognized the Topo I enzyme binding site, docking tests were conducted [118].



(407)

Fig. (72). Derivative of quinoline heterocycles containing chalcone moieties [118].

Chanquia *et al.* 2018 derived a series of aryl derivatives of 2- and 3-aminoquinoline (depicted in Fig. **73**), some of which were novel compounds, which were designed, synthesized, and assessed as antiproliferative agents against Leishmania mexicana, the etiological agent of leishmaniasis, and Trypanosoma cruzi, the parasite that causes American trypanosomiasis (Chagas' disease), in an effort to develop new safe chemotherapeutic agents against tropical diseases. Several of them demonstrated exceptional efficacy as growth inhibitors for parasites. Fluorine-containing derivatives 408a and 408b showed more than double the potency of geneticin against the intracellular promastigote form of Leishmania mexicana, with both IC50 values of 41.9 μM. These compounds are intriguing examples of powerful antiparasitic substances with exceptional promise for use as lead compounds as well as in subsequent *in vivo* research. Furthermore, the compounds obtained did not exhibit any toxicity in Vero cells, making them promising candidates for the management of tropical disorders. Regarding the likely mechanism of action, the tested quinoline derivatives reacted with haemin, preventing its breakdown and producing oxidative stress that the parasite's antioxidant defense system was unable to combat [119].

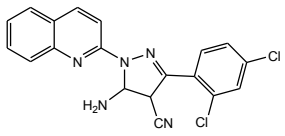
(408a) (408b)

Fig. (73). Derivative of 2- and 3-aminoquinoline [119].

In 2018, M.F. El Shehry *et al.* worked on three different series of quinoline derivatives with a pyrazole moiety in an effort to discover new antibacterial drugs. 4-(Quinolin-2-yloxy)benzaldehyde and 4-(quinolin-2-yloxy)acetophenone were synthesized to create the first series, which was further treated with ketone or aldehyde derivatives to produce the corresponding chalcones. By cyclizing these chalcones with hydrazine derivatives, new pyrazoline compounds were obtained. For the second series, 2-hydrazinylquinoline was synthesized first and then treated with formyl pyrazoles to yield the corresponding hydrazonyl pyrazole derivatives. 2-Hydrazinylquinoline was treated with ethoxyethylidene, dithioacetal, and arylidene derivatives to produce the third series, which comprised the appropriate pyrazole derivatives. The synthesized compounds' predicted antibacterial and antifungal properties were evaluated, and most of them demonstrated strong activity against the tested bacterial and fungal strains. As indicated by their MIC values (0.12-0.98 μg/mL), pyrazole derivative 409 (depicted in Fig. **74**) outperformed the reference drugs. The growth of S. flexneri was inhibited by pyrazole derivative 409 four times more effectively than gentamicin (MIC 0.12 μg/mL). Additionally, compound 409 demonstrated four times the potency of amphotericin B in preventing the growth of M. albicans (MIC 0.12 μg/mL) and A. clavatus (MIC 0.49 μg/mL), respectively. The compound exhibited the same potency as gentamicin in inhibiting P. vulgaris (MIC 0.98 μg/mL) and was equally effective as ampicillin and amphotericin B in inhibiting S. epidermidis (MIC 0.49 μg/mL) and A. fumigatus (MIC 0.98 μg/mL), respectively. Accordingly, our investigations suggest that pyrazole-containing quinoline derivatives are promising scaffolds for the development of new antibacterial and antifungal agents [120].

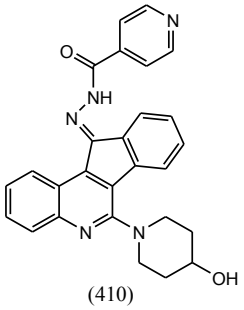
Tseng and colleagues investigated a series of indeno[1,2-c].quinoline derivatives that were synthesized, characterized, and evaluated for their anti-inflammatory and anti-tuberculosis (anti-TB) properties. Mycobacterium tuberculosis H37Rv was used to

determine the minimum inhibitory concentration (MIC) of the newly synthesized compounds. With a potency approximately equivalent to that of the anti-TB drug isoniazid (INH), (E)-N-[6-(4-hydroxypiperidin-1-yl)-11H-indeno[1,2-c].quinolin-11-ylidene] isonicotinohydrazide (410) (depicted in Fig. **75**) exhibited significant activity against the growth of M. tuberculosis (MIC 0.96 μg/mL) among the compounds tested. Key structural features were analyzed using quantitative structure-activity relationship (QSAR) methods to better understand the determinants of anti-TB activity. The anti-inflammatory effect in human neutrophils, stimulated with formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLF), was assessed *via* the inhibition of neutrophil elastase (NE) release and superoxide anion generation. Compound 410 exhibited potent dual inhibitory effects on superoxide anion production and NE release, with IC50 values of 1.76 and 1.72 μM, respectively. These results suggest that compound 410 may serve as a promising lead for the development of anti-inflammatory and anti-TB drugs [121].



(409)

Fig. (74). Pyrazole-Quinoline Derivative [120].

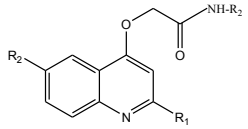


(410)

Fig. (75). Structure of indeno-quinoline derivatives [121].

Patel Dhawal B, *et al.* (2017) reviewed that quinoline-4-carboxylic acid holds significant importance in synthetic medicinal chemistry, serving as a key pharmacophore. Its incorporation into various compounds expands their biological activity, making it a central moiety in medicinal chemistry. Numerous synthetic methods have been developed for constructing the quinoline scaffold. Evaluations of quinoline-4-carboxylic acid derivatives have revealed diverse biological activities, including antimicrobial and antifungal properties, as well as efficacy against various enzyme inhibitors [122].

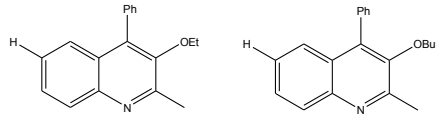
According to Pissinate K *et al.* (2016), they worked on 2-(quinolin-4-yloxy)acetamides, which are potent *in vitro* growth inhibitors of Mycobacterium tuberculosis. Chemical modifications of the lead compounds resulted in highly potent antitubercular agents with minimum inhibitory concentrations (MICs) of 0.05 μM. The synthesized compounds exhibited no significant toxicity to Vero and HaCat cells (IC50 ≥ 20 μM) and were effective against drug-resistant strains. Additionally, compound 411 (Fig. **76**) demonstrated minimal risk of drug-drug interactions, showed intracellular activity against bacilli in infected macrophages comparable to rifampin, and displayed negligible cardiac toxicity in zebrafish (Danio rerio) at 1 and 5 μM. These results suggest that this class of compounds could represent promising candidates for further investigation and development as potential drug alternatives for tuberculosis treatment [123].



(411)

Fig. (76). Structure of 2-(quinolin-4-yloxy)acetamides [123].

Tanwar *et al.* (2016) investigated two series of quinoline-based compounds that were synthesized, prepared, and evaluated for their ability to inhibit the growth of Mycobacterium tuberculosis H37Rv (ATCC 27294 strain). A novel Friedländer quinoline synthesis process in water, catalyzed by the Brønsted acid surfactant DBSA, was employed. Of the 42 compounds tested, 23 showed significant activity against M. tuberculosis, with MIC values ranging from 0.02 to 6.25 μg/mL. Compounds 412a and 412b (as in Fig. **77**), in particular, exhibited excellent anti-TB activity, with MIC values of 0.2 and 0.39 μg/mL, respectively, and were more effective than the conventional medications ethambutol (E), cefixime (Cfx), and pyrazinamide (Z) used clinically to treat TB. All active compounds were found to be nontoxic (<50% inhibition) when tested for cytotoxicity in Human Embryonic Kidney 293T cell lines at MIC ≤ 6.25 μg/mL. These findings suggest that the synthesized substituted quinolines represent promising candidates for the development of novel anti-tuberculosis agents [124].



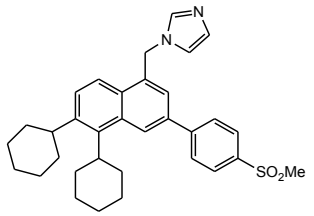
(412a) (412b)

Fig. (77). Quinoline substituted derivative [124].

Ghodsi *et al.* (2016) synthesized a novel class of 4-(imidazolylmethyl)quinoline compounds as potential *in vitro* anticancer agents and selective COX-2 inhibitors. These derivatives featured a methylsulfonyl COX-2 pharmacophore at the para position of the C-2 phenyl ring. *In vitro* COX-1 and COX-2 inhibition assays demonstrated that all compounds were potent and selective COX-2 inhibitors, with IC50 values ranging from 0.063 to 0.090 μM and COX-2 selectivity indexes between 179.9 and 547.6. Molecular modeling studies suggested that the methylsulfonyl substituent can occupy the COX-2 active site's secondary pocket, interacting with Arg513. The cytotoxicity of quinolines 9a-e was also evaluated against human breast cancer cell lines T47D and MCF-7. All compounds were more cytotoxic to MCF-7 cells than to T47D cells, which express lower aromatase mRNA levels than MCF-7 cells. The results indicated that increased lipophilicity of substituents on the C-7 and C-8 quinoline rings enhanced both cytotoxicity and COX-2 inhibitory activity. Among the quinoline derivatives, 4-((1H-imidazol-1-yl)methyl)-7,8,9,10-tetrahydro-2-(4-methylsulfonylphenyl)-benzo[h].quinoline (413) (depicted in Fig. **78**) was the most cytotoxic agent against MCF-7 cells and the most potent and selective COX-2 inhibitor [125].

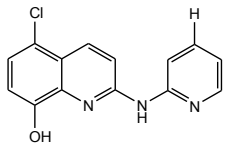
Li, K, *et al.* (2016) synthesized a series of quinoline-based derivatives as potential anticancer agents. Most of the quinolines exhibited strong antiproliferative effects against the PC-3 human prostate cancer cell line. Structure-activity relationship (SAR) analysis revealed that the secondary amine linking the pyridine and quino-

line rings is crucial for these antiproliferative effects. Mechanistic studies suggested that compound 414 (depicted in Fig. **79**) may act as a Pim-1 kinase inhibitor, inducing apoptosis and cell cycle arrest. Since Pim-1 is overactive in prostate cancer, these compounds have potential as anti-prostate cancer therapeutics [126].



(413)

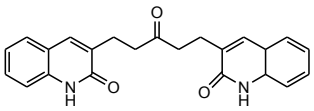
Fig. (78). 4-(Imidazolylmethyl)quinoline derivative[125].



(414)

Fig. (79). Quinoline derivative [126].

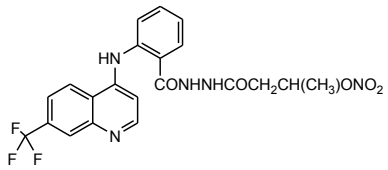
Abonia, *et al.* (2012) developed new chalcones based on quinoline-2-one, synthesized *via* a Claisen-Schmidt condensation in a KOH/1,4-dioxane reaction medium. The intermediate in the synthesis of the target chalcones was identified as a comparatively stable aldol. Nine of the compounds were evaluated *in vitro* by the US National Cancer Institute (NCI) for their ability to inhibit 60 human cancer cell lines. The most active compound in the study was 3,3′-((1E,4E)-3-oxopenta-1,4-diene-1,5-diyl)bis(quinolin-2(1H)-one) (415) (depicted in Fig. **80**), which showed exceptional activity against 50 human tumor cell lines, 13 of which had GI50 values of 1.0 μM. The most sensitive cell lines were LOX-IMVI (Melanoma, GI50 = 0.134 μM) and HCT-116 (Colon, GI50 = 0.131 μM). The NCI's Biological Evaluation Committee referred compound 415 for a hollow fiber assay and *in vivo* acute toxicity studies. According to the acute toxicity investigation, athymic nude mice tolerated compound 415 well when administered intraperitoneally at a dose of 150 mg/kg. This molecule may serve as a lead structure for the development of new anticancer medications [127].



(415)

Fig. (80). Chalcones based on quinoline-2-one derivative [127].

Adabi *et al.* (2006) focused on six new derivatives of hydrazides and oximes in combination with quinolines. These compounds were synthesized and evaluated for their ability to release nitric oxide *in vitro*, as well as for their anti-inflammatory, analgesic, and ulcerogenic properties *in vivo*. In the acetic acid-induced writhing model, 2-(7-trifluoromethylquinolin-4-ylamino)benzoic acid N'-(2-nitrooxypropionyl)hydrazide (416) (depicted in Fig. **81**) showed equipotency to glafenine at 100 mg/kg p.o, and in the carrageenan-induced rat paw oedema test, it exhibited anti-inflammatory activity comparable to indomethacin. None of the compounds induced stomach ulcers in rats; their remarkable safety profile appears to be partly due to nitric oxide [128].



(416)

Fig. (81). Structure of Quinoline hydrazide derivative[128].

CONCLUSION

Quinoline derivatives have been found to be a multi-purpose scaffold for various biological activities, including anticancer, antituberculosis, antifungal, antibacterial, and more. This review found that various synthetic schemes exist for the preparation of newer quinoline derivatives. Additionally, the designed derivatives were synthesized by the mentioned authors, and their structures were confirmed using spectral analyses. Moreover, the compounds have been tested against multiple targets using *in vitro* and *in vivo* methods, among which many derivatives showed promising effects, even surpassing some marketed preparations, indicating the potential of the quinoline scaffold for developing higher-potency compounds in future research.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Generation of idea- S. G., S.V., N.K.S.; writing—drafting manuscript- S. G., S.V.; writing—review S.G., S.V., N.K.S. The paper reading has been done by all the authors also being verified.All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

EGFR = Epidermal Growth Factor Receptor

DNA = Deoxyribonucleic Acid

U.V = Ultra-Violet

NE = Neutrophil Elastase

COX = Cyclooxygenase

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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