[Review Article] Green Strategies for the Synthesis of Quinolone Derivatives

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Abstract

Background: Green chemistry is currently one of the most explored areas and has been a desire since the 1990s. Green chemistry research is focused on reducing the energy required to develop desirable products and reducing or even stopping the synthesis of hazardous by-products from minimizing any environmental or health impact.

Objective: Nalidixic acid has been synthesized and developed into derivatives known as quinolones. The alteration of the elementary structure exhibits fascinating pharmacological activities in numerous fields, e.g., anticancer, antimicrobial, diuretics, anti-inflammatory, and so on.

Methods: Nearly all structural modifications to the quinolone moiety are possible. Chemical alteration at locations N-1, C-(5-8) can result in molecules with various pharmacological, physiological, biochemical, and pharmacokinetic properties. The quinolone moiety can be synthesized by multiple methods, including microwave-assisted, solvent-free, photocatalyst, biocatalyst, ultra-sonication-mediated, catalyst-free methods, and green solvent reactions (water, ethanol, supercritical CO_2, aq. H_2O_2, oxidation).

Results: Health and environmental risks are associated with synthetic chemicals, solvents, and catalysts. Scientists

are now minimizing the use of solvents, chemicals, and catalysts by developing novel approaches. Quinolone derivatives introduced various new pharmacologically active compounds to the market through novel drug development.

Conclusion: The main motive of this study is to summarise the recent advancements in green chemistry methods for establishing quinolone scaffolds from various scientific journals, online databases, and libraries, which will help scientists to develop non-toxic and eco-friendly techniques for the synthesis and development of novel drugs.

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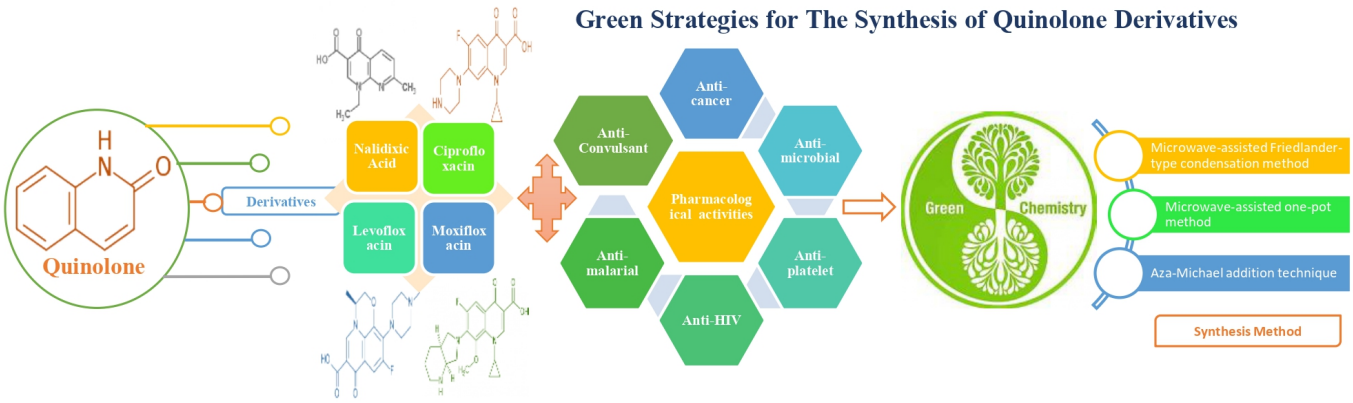
Graphical Abstract



Introduction

The quinolone family is one of the most important groups of heterocycles with nitrogen. They are widespread and rank among the most significant pharmacophores, essential to the new drug development process [1]. In a wide range of chemotherapeutic and antimicrobial medicines, the quinolone-based structural unit is prominent [2]. Nalidixic acid is a synthetic compound of quinolone antibiotics. Numerous therapeutically active molecules are developed by chemically modifying the basic nucleus of nalidixic acid [3][4][5]. The biggest concern of the 20th century was infectious diseases, responsible for at least one-third of human illness and mortality [6]. In the meantime, researchers did some of the most outstanding scientific achievements, including developing synthetic antibiotics like quinolones [7][8]. Among all the synthetic antibiotics, quinolones are a frequently employed subclass [9]. Our present study is based on quinolones, a crucial family of broad-spectrum antibacterial medicines. The production of nalidixic acid marked the beginning of the investigation into quinolones in 1962 [10][11]. Quinolone derivatives exhibit excellent antibacterial effects on gram-negative microbes. Various novel medications with antimicrobial properties were produced by changing the ring structure and substituting the ethyl group following the discovery of nalidixic acid. These novel substances were more powerful against most bacteria and highly potent, wide-ranging antibiotics [12][13].

Structure of Quinolone

After synthesizing nalidixic acid, several derivatives were produced, including ciprofloxacin, levofloxacin, and moxifloxacin [14]. Unfortunately, some quinolone derivatives (tosufloxacin, trovafloxacin, and grepafloxacin) have been pulled off the market due to significant side effects [15][16]. The development of quinolone derivatives is still the most concerning area of research due to their efficacy, distinct mode of action, and bactericidal qualities. Over the past 50 years, this class has been the focus of extensive research, leading to the publication of multiple studies on the topic. The quinolone heterocyclic group is influential as a scaffold in different therapeutic fields. It has shown effectiveness as an anticancer, anxiolytic, anti-ischemic, antiviral, and cannabinoid type-2 receptor agonist [17].

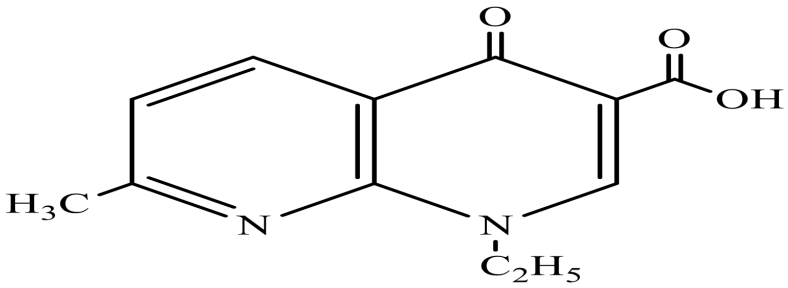


Fig. 1. Nalidixic acid (Quinolone) [17].

Antimicrobial Targets of Quinolone

Quinolones are frequently attached to the complex of enzymes and DNA to stop DNA synthesis[18]. Quinolones also stabilize topoisomerase IV, which is responsible for DNA gyrase-induced DNA strand breaks [19]. The replication fork is halted by medication, enzymes, and DNA ternary complexes [20]. The cytotoxicity of fluoroquinolones on cells can be attributed to the two-step procedure that generates a double-strand break by denaturing the topoisomerase. Uncertainty exists regarding the molecular prerequisites for the change from step I to step II [21]. Quinolones are the fundamental structural components of several medicinal agents [22][23]. Quinolones are bicyclic molecules that differ in where the carbonyl group is located. They may be broadly divided into two substantially different categories, namely, 2-quinolones and 4-quinolones [24][25]. The 2- and 4-hydroxyquinolines coexist harmoniously with their minor tautomeric counterparts, as seen in **Fig. (2)** [26].

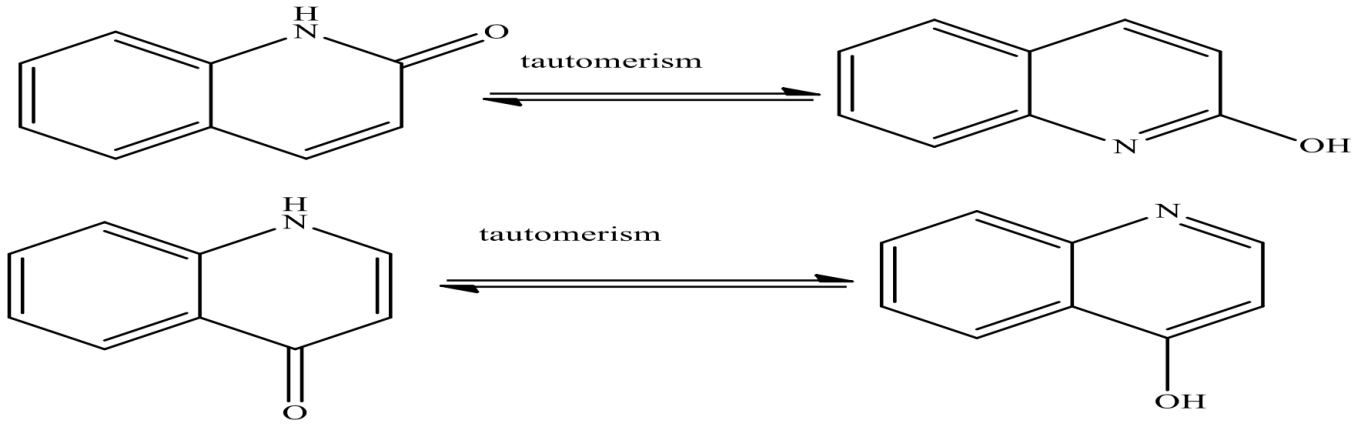


Fig. 2. Tautomerism of quinolones [26].

The N1 and C-(5-8) locations of the quinolone nucleus may be chemically modified using various molecules[27]. Consequently, multiple structural changes occur in these places, leading to molecules with varying physical, chemical, pharmacokinetic, and pharmacological characteristics [28]. Additionally, 4-quinolone is thought to be bio-isosteric for chromen-4-one. Some researchers have successfully used medicinal chemistry bio-isosteric replacement techniques to

design and produce molecules with the required therapeutic profile [29].

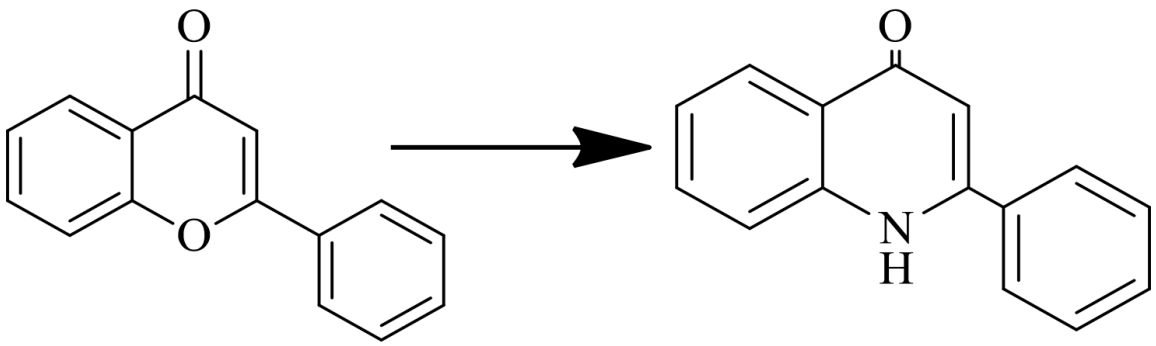


Fig. 3. Bio-isosteric replacement [29].

Many biological activities have been linked to quinolone derivatives, including antibacterial properties[30][31]. Quinolones can also be used to treat lung diseases like cystic fibrosis. The Federal Drug Administration (FDA) has also authorized the use of several quinolones, such as ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and gatifloxacin, in pediatric patients for a variety of conditions, including conjunctivitis, otitis, sinusitis, respiratory disease, asthma, UTI, and gastrointestinal disorders [32].

SAR of Quinolones

Fig. (4) illustrates the basic chemical compound and the positions where essential modifications are made. Some of these chemicals shouldn't be changed since they would interact with the primary mechanism of action of the drug or significantly lessen it. These are positions 2, 3, and 4. Position 2 is best served by a hydrogen moiety; any more considerable molecular additions may cause steric hindrances at positions 3 and 4, respectively [33]. This is because the bases of the DNA are bound at these locations. The enzyme DNA gyrase subsequently helps these sites to accept new hydrogen-bonding partners. A fluorine atom is the best choice for the tiny moiety at position 6 because it imparts between five and one hundred times more effectiveness than any other conceivable halogen moiety. Numerous possible substitutes are available for the four additional substituents [34][35].

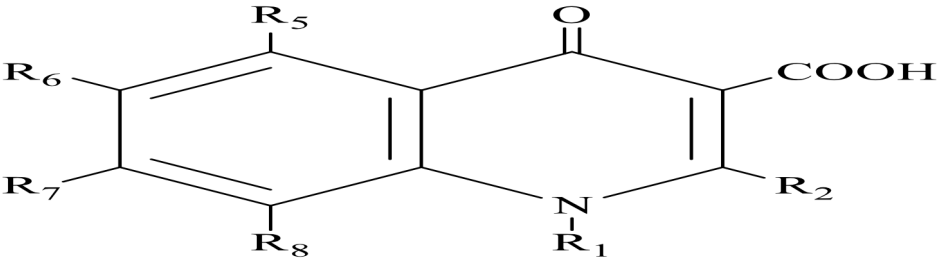


Fig. 4. The most renowned structure of a quinolone molecule [33].

The following list of characteristics that cause certain modifications is the result of SAR investigations[33][35]:

Position 1: influences an agent's pharmacokinetics and ultimate efficacy.

Position 5: Particular moieties replaced at this point have contributed to greater effectiveness against gram-positive microorganisms.

Position 7: 5 and 6 membrane rings with an "N" atom provide the highest activity at this stage, and both the range of activities and the pharmacokinetics are under control.

Position 8: It is now possible to modify the pharmacokinetics and the particular action towards anaerobes.

Green Chemistry

In the 1990s, twelve "Green Chemistry" tenets were developed to "fulfill the demands of the current generation without compromising the requirements of future generations." Industries and academia are currently attempting to improve conformity with these 12 principles of green chemistry [36]. To maximize yields, selectivity, and productivity and conserve the environment, time, energy, and life, we must now adapt innovative, environmentally friendly technologies into our everyday reaction practices [37]. The current study thoroughly compiles the used green chemistry methods to synthesize quinolones. The benefits and drawbacks of these methods are inadvertently emphasized. This study seeks to raise awareness of the newly developed greener protocol for manufacturing quinolones and to encourage researchers worldwide to adopt greener research methodology [36].

Fig. 5. Twelve principles of green chemistry [36].

Pharmacological Activities of Quinolone Derivatives

Anticonvulsant Activity

X. Sun *et al.* synthesized and observed in 7-benzyloxy-4, 5-dihydro[1][2][4] triazolo[4,3-a] that the anticonvulsant potency of these compounds was considerably improved by the addition of the triazole ring to the 1st and 2nd positions of the quinoline [38][39][40].

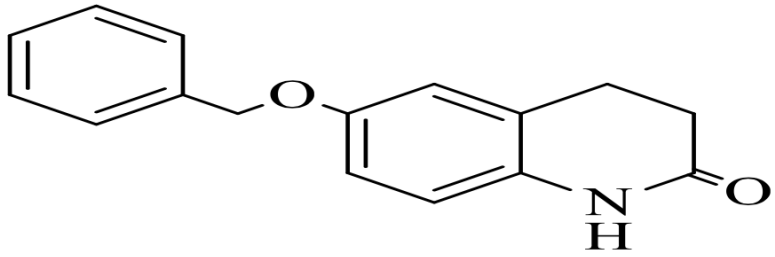


Fig. 6. Anticonvulsant activity of quinolone derivatives [38][39][40].

Antiplatelet Activity

L. Huang *et al.* synthesized several new antiplatelet drugs with seven positional phenyl quinolone isomers. Initial testing was supported because arachidonic acid inhibited platelet aggregation. The antiplatelet activity of these isomers significantly changes depending on the substitution position of the phenyl group. 3-phenyl-4-quinolone, the most potent compound, outperformed indomethacin [41].

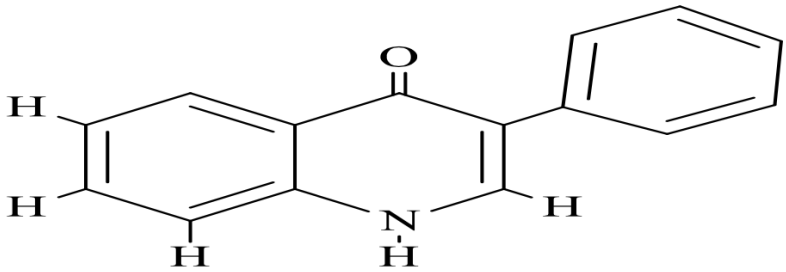


Fig. 7. Antiplatelet activity of quinolone derivatives [41].

Anti-HIV Activity

Souza *et al.* synthesized several variants of quinolones and tested them for effectiveness against HSV-1. The anti-HSV-1 variants were compounds (a) and (b), which showed increases in the antiviral activity of 1.5 and 1.3 times over acyclovir, respectively [42].

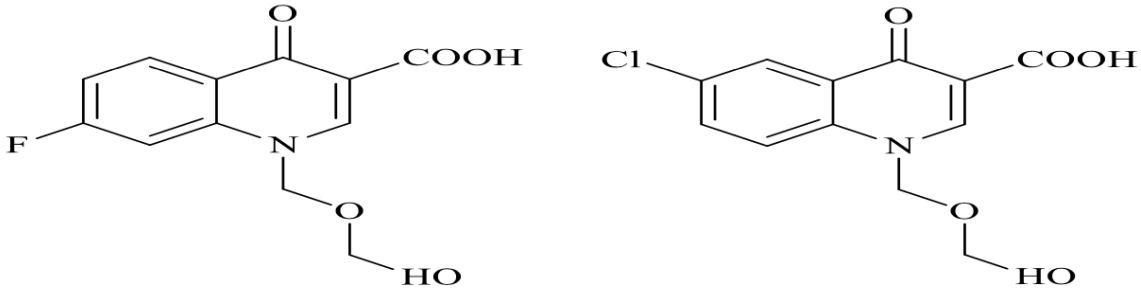


Fig. 8. The anti-HIV activity of quinolones derivatives [42]

Anticancer Activity

Several kinds of cancer medications focus primarily on topoisomerase-II[43]. These substances frequently treat human tumors [44][45]. Their ability to preserve covalently fragmented DNA molecules that are intermediates in the catalytic cycle of the enzyme is correlated with their clinical efficacy [46]. Research findings suggested that quinolones might have promise as antineoplastic medications. The effectiveness of quinolone-based medicines as antibacterial treatments has been well-proven [47][48][49] and a crucial prerequisite for effectiveness in antibacterial quinolones is the 3-COOH or its isosteric substitution. However, even hydrogen can also be used to substitute this functional group, maintaining the Topo-2 poisoning effect [50]. Coplanarity of the quinolone ring with the C-3 ligand is a fundamental need for inhibiting the eukaryotic enzyme. The carboxyl group will prevent the acidic moiety from orienting in a coplanar manner. The carboxylic acid group created additional synthesis possibilities [51].

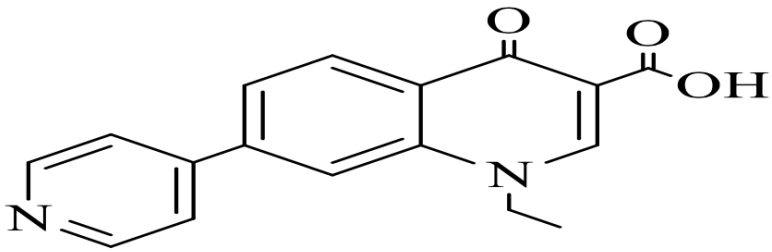


Fig. 9. Structure of rosoxacin [51].

At position C-7, several replacements were also made. Antibacterial activity strictly depends on an aliphatic cyclic substituent having a primary amino group at position C-7. Additionally, it has been demonstrated that changes made in this position are crucial in channeling the medication in a way that favors Gyrase or Topo-4 [52].

Anti-HCV Activity

Antiviral medications can be divided into direct and indirect antiviral treatments; the former targets the structural or encoding enzymes of the virus, while the latter targets the components of the host cell (immunomodulators, etc.). The most advanced research on HCV infection therapy focuses on NS3 protease inhibitors, RNA virus RNA inhibitors, and NS5B polymerase inhibitors. A combination of medications with various mechanisms will be used to treat HCV to prevent the development of resistance [53]. An overview of the most recent advances in developing quinoline-based treatments for HCV from the standpoint of medicinal chemistry is given, emphasizing natural small-molecule antiviral medicines. The development of anti-HCV drugs has centered chiefly on blocking necessary viral enzymes, similar to how HIV is treated. As protease inhibitors have proven successful in the treatment of HIV, many pharmaceutical companies have focused on the HCV NS3 proteolytic enzyme. HCV has both NS2/3 and NS3/NS4A, two proteolytic enzymes. Additionally, the host cell proteases largely control NS2/3 processing. It is a less desirable target for therapeutic development [54][55].

Antimalarial Activity

Winter *et al.* developed synthetic compounds derived from halogenated alkyl and alkoxy 4(1H)-quinolones that can treat and prevent malaria [56]. *In-vitro* studies have shown the effectiveness of quinolones in inhibiting parasite activity, making them an introductory class in treating malaria [57].

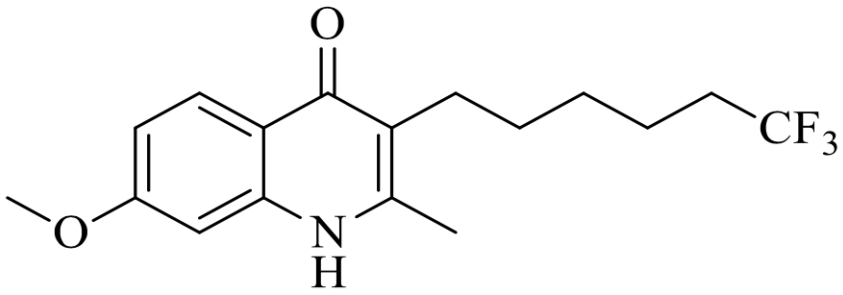


Fig. 10. Anti-malarial activity of quinolone derivatives [57].

Antitumor Activity

You *et al.* synthesized a few quinolone derivatives with benzimidazole, benzoxazole, or benzothiazole rings. Twelve new compounds were tested for their cytotoxicity in the KB, Bel7402, A2780, and HT-29 cell lines. Most synthetic drugs had a mild inhibitory effect on cancer cells. For example, Fig. 11 has similar inhibitory actions against K.B. and A2780 tumor cell lines [58].

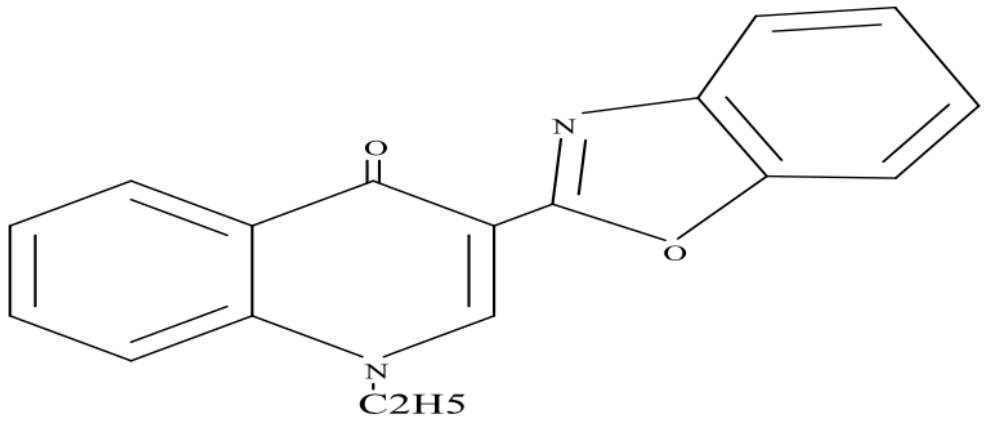


Fig. 11. Antitumor activity of quinolone derivatives [58].

Chemical Interactions

Amporndanai *et al.* explored the malarial cytochrome bc1 complex as a potential drug target and developed some 4(1H)-quinolone-based inhibitors as potential antimalarials by interacting with the ubiquinone-reduction (Qi) site. The malarial

bc1 complex was structurally compared with the human cytochrome bc1 to avoid the chances of cross-reactivity caused by the designed inhibitors. The bovine cytochrome bc1 complex was used because it has high structural selectivity with the human cytochrome bc1 complex, and the selectivity of inhibition was compared. The homology model of the cytochrome bc1 complex of *Plasmodium falciparum* (Pf) was prepared, and docking analysis was performed to reveal the selectivity of the concerned inhibitors for the Pf bc1 complex. The findings suggested that the residues His201, Asp228, Ser205, and Ser35 of the Qi site of the bc1 complex play an important role in interacting with the inhibitor molecules, while the residues Phe30, Phe37, and Thr16 are involved in the selectivity of the inhibitor molecule for the Pf bc1 complex [59].

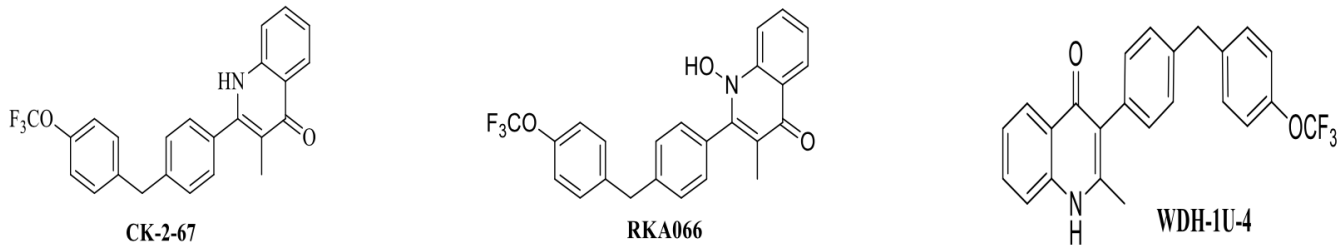


Fig. 12 (a). Chemical interactions of quinolone derivatives [59].

Sinha *et al.* have computationally designed a series of chloroquine and hydroxychloroquine analogs and evaluated them in contradiction of the viral spike protein of SARS-CoV-2 for their affinity in contrast to the macromolecular target and pharmacokinetic profiling by using molecular docking, dynamic simulation, and pharmacokinetic profiling. The compounds CQ1 and HCQ1 were found to interact with the macromolecular target in a similar manner to that of their parent compounds with sufficient stability. Compound CQ1 was found to be interacting with the macromolecular residues via Pi-alkyl, Pi-Pi, Pi-sigma & weak van der Waals interactions. At the same time, HCQ1 was found to be interacting with the macromolecular residues via Pi-alkyl, Pi-Pi interactions, and Pi-Donor Hydrogen bonding [60].

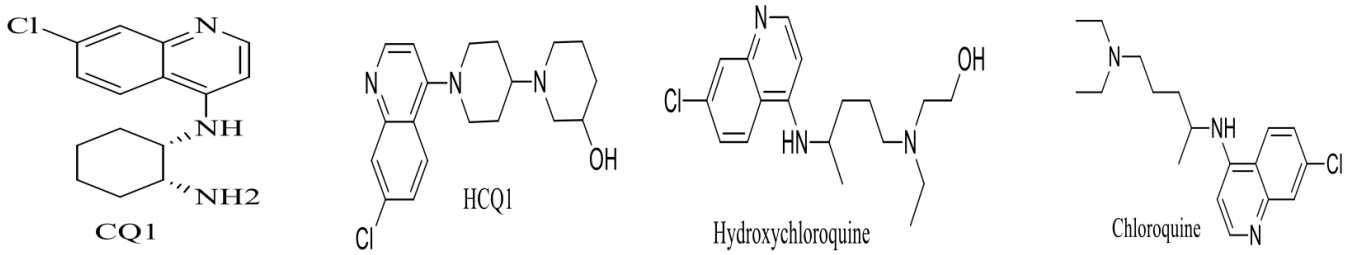


Fig. 12 (b). Chemical interactions of quinolone derivatives [60].

Sweidan *et al.* developed a variety of new variants of quinolones as possible PI3K inhibitors and tested them for anticancer activity using the CCK8 assay on MCF-7 and HCT-116 cell lines. Compound c in Fig. 12 was found to have the minimum IC_{50} at the maximal apoptotic level in all cell cultures[61]. Docking analysis has revealed that these compounds are found to have excellent affinity for both the wild-type (pdb: 2RD0) and the mutant-type (pdb: 3HHM) PI3Kα receptors.

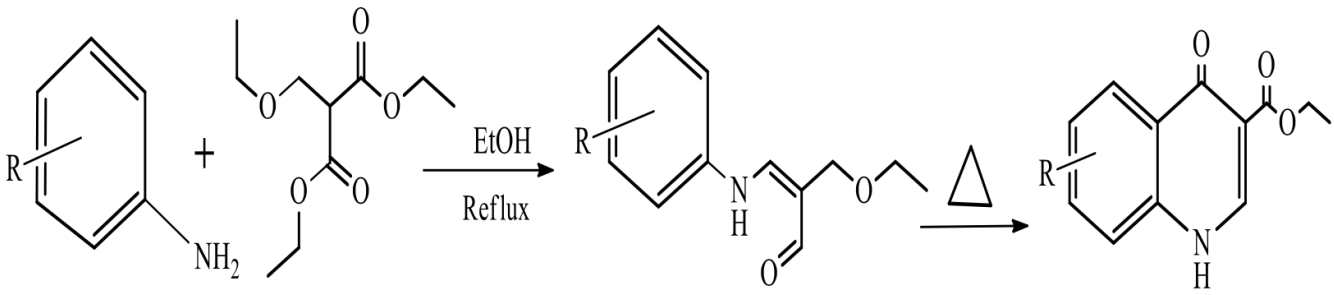
Compound 8b was found to be interacting with the residues Val851 and Gln859 of the wild-type receptor and Ser919, Asp933, and Phe1059 of the mutant-type PI3Kα receptor, whereas compound 8f was found to be interacting with the residues Lys802, Tyr836, Val851, and Asn920 of the wild-type receptor and residues Asp810, Tyr836, and Glu849 of the mutant-type PI3Kα receptor [61].

Fig. 12 (c). Chemical interactions of quinolone derivatives [61].

Methods of Synthesis of Quinolone Derivatives

Scheme: 1

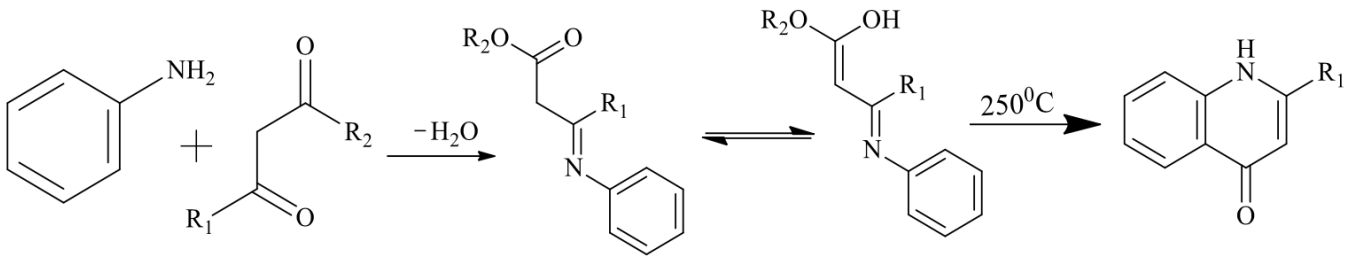
Gould Jacob *et al.* developed the most widely used technique for manufacturing quinolones in 1939. The quinolone derivatives were synthesized by the Michael addition reaction, eliminating substituted anilines using diethyl methoxy methylene malonate as a reagent in ethanol with agitation and reflux at high temperatures [62].



Scheme 1. The technique of Gould Jacob for assortment of quinolones [62].

Scheme: 2

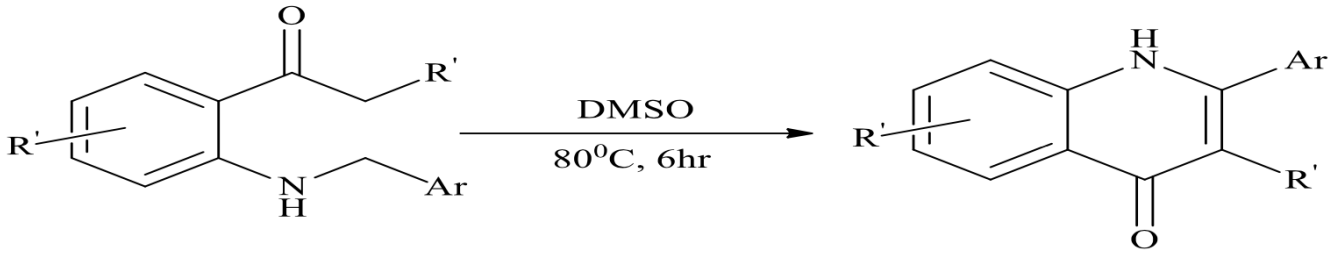
The Conard-Limpach method is used to condense a modified aniline to create a quinolone. Quinolones are made by performing this reaction at a high temperature [63].



Scheme 2. Conard-Limpach synthesis method of quinolones [63].

Scheme: 3

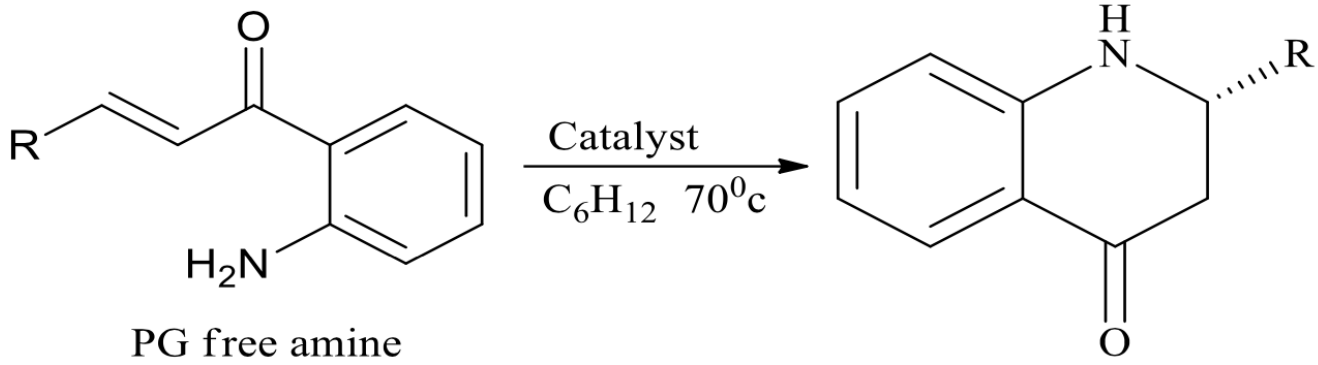
Hu *et al.* reported that secondary amines and unchanged ketones undergo an oxidative Mannich reaction without using metals. This brand-new technique allows the production of several 2-aryl quinoline-4 (1H)-ones. This procedure is carried out under eco-friendly circumstances that don't require a catalyst made of a transition metal [9].



Scheme 3. Mannich process for the production of quinolones [9].

Scheme: 4

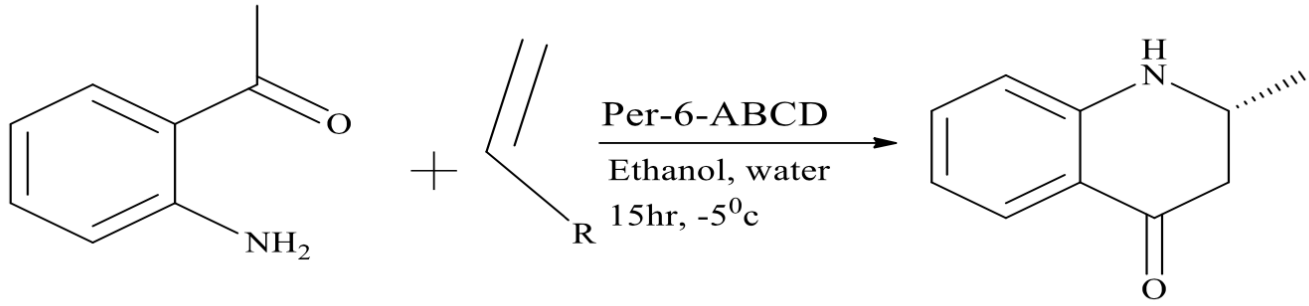
The Aza-Michael addition technique was used to produce significant amounts of chiral-modified 2,3-dihydro-4-quinolones. This method has the advantage of being enantioselective in chemical synthesis. It is possible to develop new useful quinolone analogues by combining the chiral 2,3-dihydro-4 quinolones. This anticancer drug may prevent mitosis [64].



Scheme 4. The Aza-Michael additive process for the production of quinolones [64].

Scheme: 5

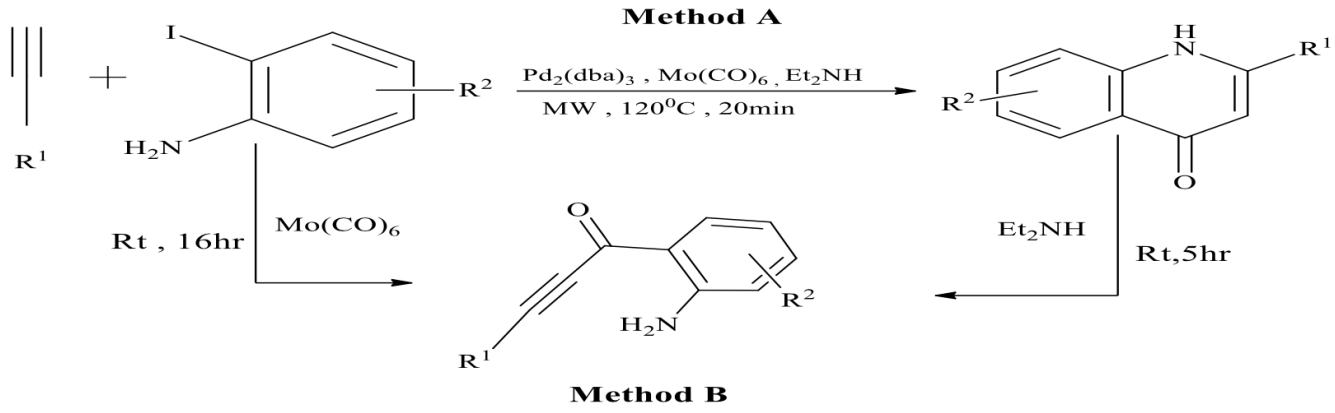
Kuppusamy and Kasi *et al.* developed the high-yielding, enantiomerically improved 2-aryl-2,3-dihydroquinoline-4(1H)-ones by using per-6-ABCD [up to 99%]. This technique is performed in a single step, in which the expensive metal is reused after separation from the product. However, a long reaction time is needed [65].



Scheme 5. Synthesis of quinolone derivatives via substituted aldehydes [65].

Scheme: 6

Akerbladh *et al.* used two distinct approaches to produce functionalized 4-quinolones. The first technique employed molybdenum hexacarbonyl as a dependable basis of C.O. The cyclized product was produced by microwave heating at 1200°C in 20 minutes. Sensitive substituents like nitro and Bromo groups are employed, and one-pot synthesis takes place in the second step at room temperature [66].

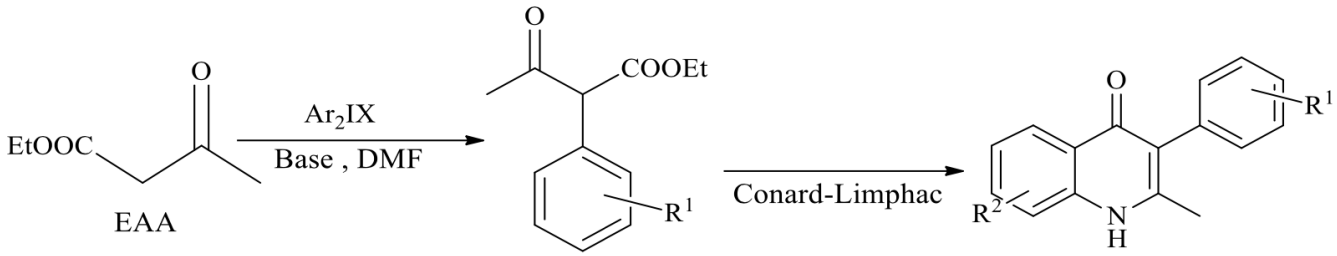


Scheme 6. Sonogashira cross-coupling process for the synthesis of 4-quinolones [66].

Scheme: 7

Monastyrskyi *et al.* developed a method for producing 3-aryl-4(1H)-quinolones from EAA. Hypervalent diaryliodonium salt

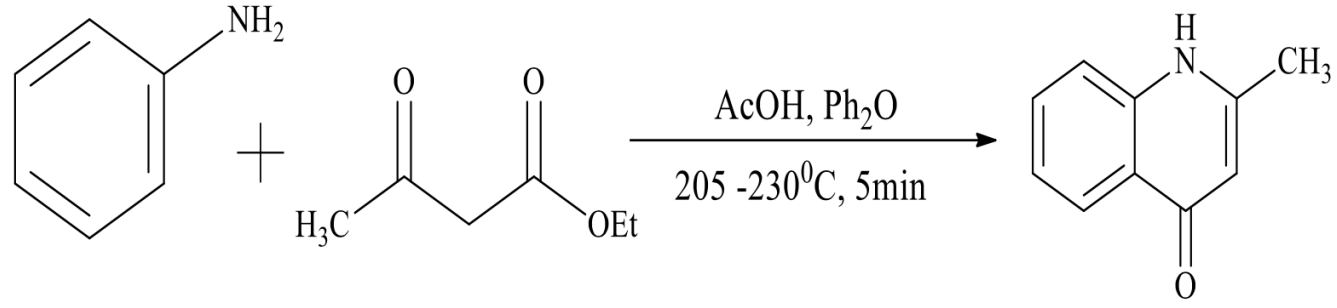
is used as a catalyst. The anti-malarial drug ELQ-300 was synthesized using this method. This molecule is active at all stages of the *Plasmodium falciparum* and *Plasmodium vivax* lifecycles and is currently undergoing preclinical testing. The toxicity of this substance has yet to be determined. However, preclinical studies have shown that it is safe. Finding data gives crucial information about the efficacy of the synthesized substance. The benefit of this synthetic approach is that it may be used in various situations. Malaria is the most deadly infection, killing millions of people yearly, and this synthetic approach is beneficial to treat various malarial ailments [67].



Scheme 7. Quinolone derivatives synthesis using arylation method [67].

Scheme: 8

Duarte *et al.* developed one-step microwave irradiation synthesis techniques for different substituted 2-methyl-4-quinolones. The reaction was placed at 205-230^{0}C for 5 min with irradiation at 300W. Furthermore, the substituents that donate electrons to aniline resulted in the required 4-quinolones. But anilines with electron-withdrawing substituents led to N, N′-di-aryl urease. The essential features of this procedure were the readily available starting ingredients, excellent yield, and decreased reaction durations [68].



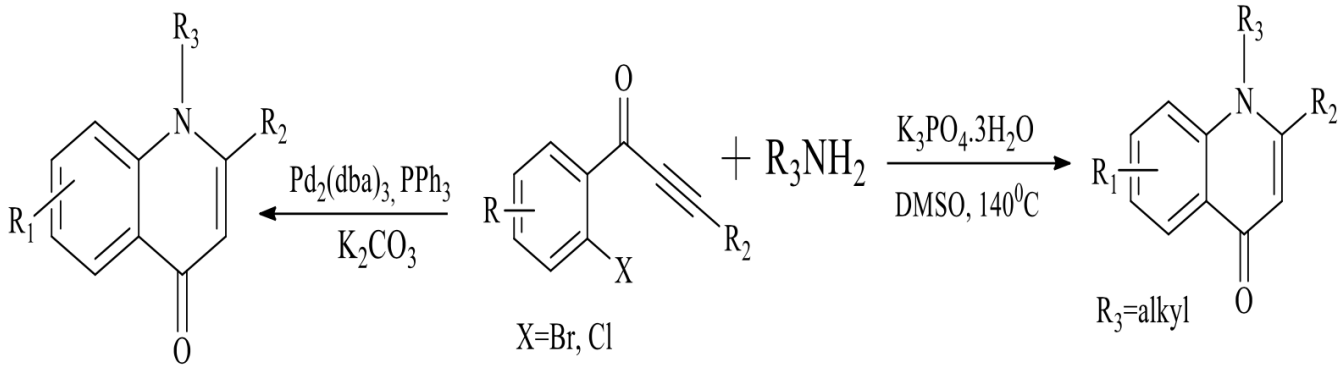
Scheme 8. Synthesis of 4-quinolones via MW-assisted methods [68].

Scheme: 9

Xiao *et al.* established an efficient palladium-catalyzed method for the functionalization of N-aryl-4-quinolones[24]. The reaction is carried out in the presence of K_2CO_3, $Pd_2(dba)_3$ as a catalyst, PPh3 as a ligand, and dioxane as a solvent, which achieved a high yield of 84%. High-yield substituted N-aryl-4-quinolones were synthesized under ideal

circumstances using a variety of aromatic amines. Alkyl amines produce noticeably fewer product yields when nitrogen is used as unit substrates [69].

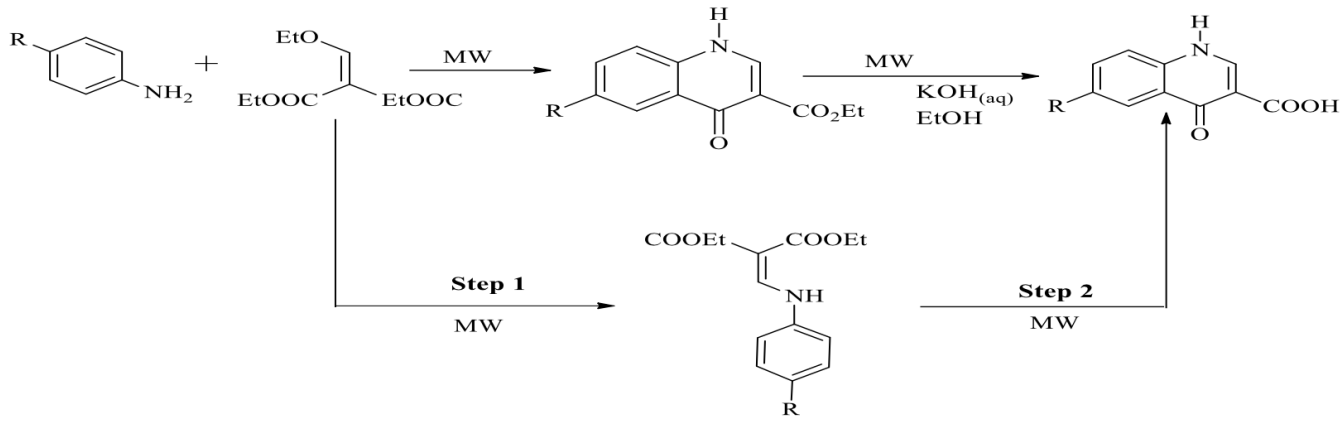
Shao *et al.* developed a more practical method for producing large yields of N-alkyl-substituted-4-quinolones by palladium catalysis to get over this restriction. According to optimization studies, Cs_2CO_3, K_2CO_3, and K_3PO_4 were the most efficient in DMSO at 140°C. The reaction is quicker in the presence of K_3PO_4. Moreover, several alkylamines with several allopathic chain lengths interacted efficiently to produce good yields of quinolones [70].



Scheme 9. Quinolone derivatives via tandem amination method [69][70].

Scheme: 10

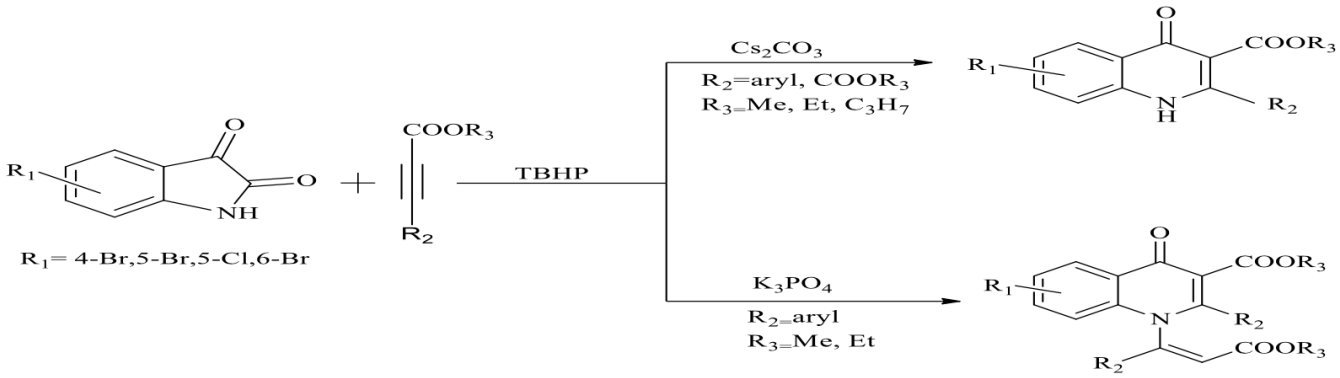
Malvacio *et al.* synthesized two quinolone derivatives by microwave-assisted one-pot techniques from various p-substituted anilines and diethyl ethoxy methylene malonate. Consistent carboxylic acids are then generated by irradiating quinolones under base hydrolysis conditions. Its defining characteristics are the large yields and short timeframes achieved in this reaction [71].



Scheme 10. Synthesis of quinolone derivatives by the microwave-assisted method [71].

Scheme: 11

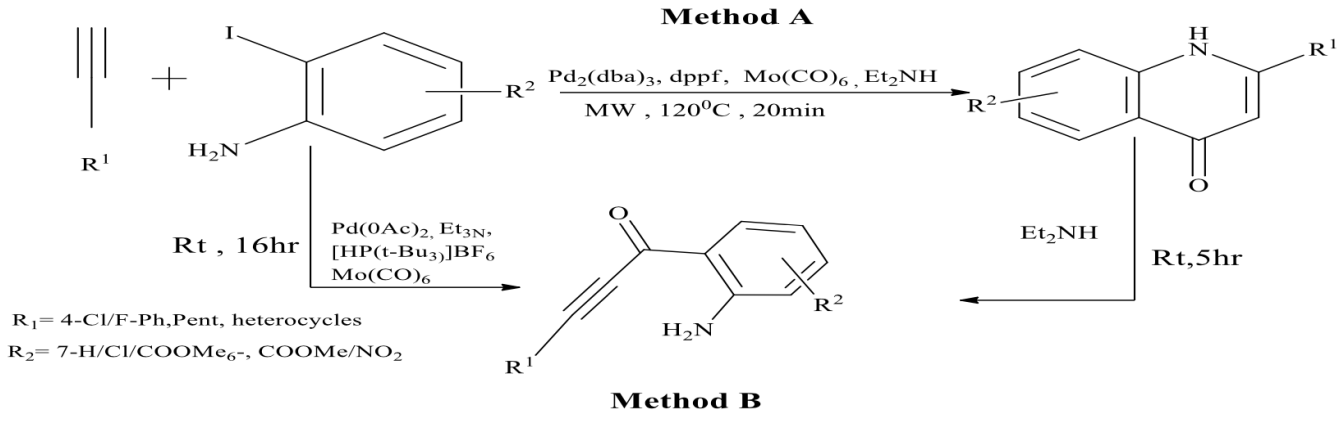
Jiang *et al.* demonstrated a method for synthesizing quinolone derivatives called 1-vinyl-3-carboxylate-4-quinolone by using isatins and alkynes as starting materials using a metal-free oxidative method [72]. DMSO, CS_2CO_3, and TBHP (tertiary butyl hydroperoxide) are used as the solvent, base, and oxidant, respectively. This reaction is carried out at 100^0C for 12 hours in a sealed jar[73][74].



Scheme 11. Synthesis of 4-quinolones using switchable oxidative cyclization method [72].

Scheme: 12

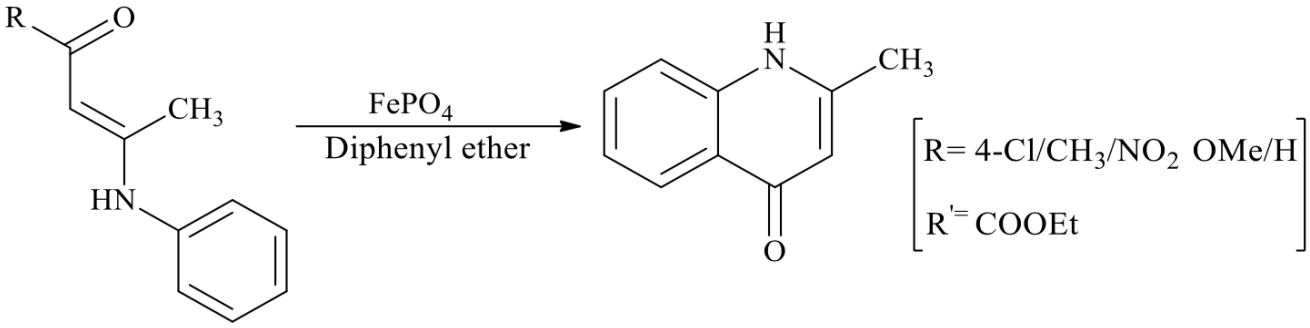
Åkerbladh *et al.* developed a method for synthesizing 4-quinolones using acetylenes and 2-iodoanilines as starting materials [75]. This reaction employs two distinct methods: non-gaseous $Mo(CO)_6$ as a base and M.W. heating for 20 minutes at 120°C with palladium catalysts [76]. The synthesis is carried out at 120^0C for 20 minutes using $Pd(dba)_2$, 1 mmol Mo $(CO)_6$, 12 mmol% DPPF (bis(diphenyl-phosphino) ferrocene), and EtOH. The second technique uses a one-pot, two-step procedure that is carried out at room temperature to provide an intermediate step without the need for M.W. heating and without using DPPF as a catalyst. The essential characteristics of this technique are ease of reaction time with decreasing by-product production and excellent tolerance towards delicate functional groups [66].



Scheme 12. Synthesis of 4-quinolones using microwave heating technique by Sonogashira CC [66].

Scheme: 13

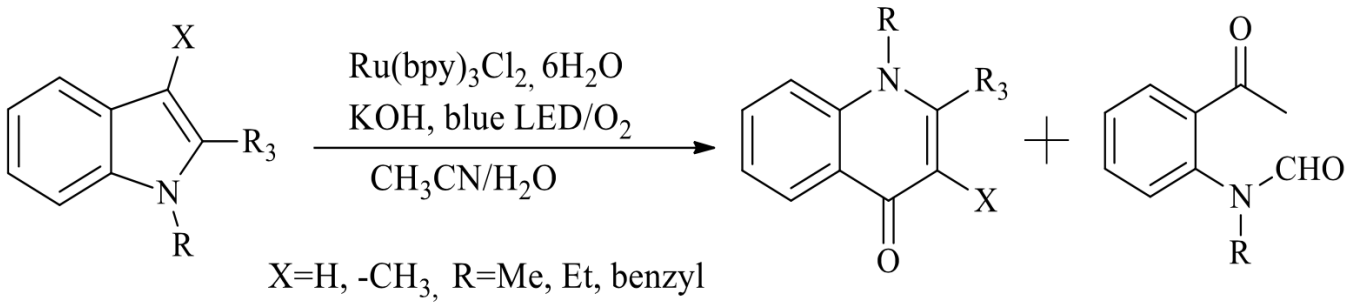
Samadi *et al.* developed the effective Conard-Limpach method for synthesizing 4-quinolones from beta-aryl amino crotonates and iron phosphate. However, when the reaction occurred at temperatures of 100, 150, and 200°C, large yields of the product were produced. This method is needed to eliminate the column and atom economies and uses catalysts that are good for the environment and can be changed [77].



Scheme 13. Synthesis of 4-quinolones using iron(iii) phosphate-catalyzed method [77].

Scheme: 14

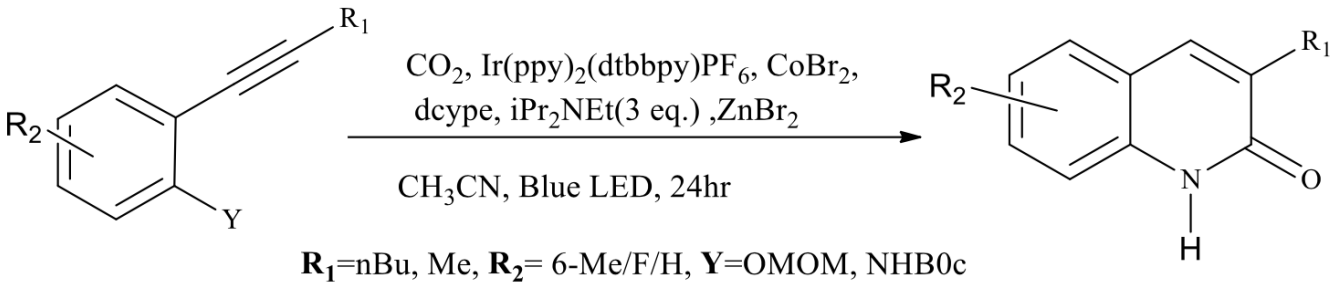
Ji *et al.* discovered a technique for producing 4-quinolones from indoles via one-pot synthesis. The substrate N-methyl indole was combined with the photocatalyst Ru(bpy)3Cl_2.6H_2O. The combination of 37 and 38 with a 20:1 ratio was created using KOH as a basis and the aforementioned ideal circumstances. The product yields are moderate to excellent when using different N-substituted 3-methyl indoles containing N-ethyl, N-benzyl, and N-allyl. The steps and atoms are economical and easy to handle at room temperature. The use of oxygen as the oxidant is the most important feature of this method [78][79].



Scheme 14. Photocatalytic ruthenium-mediated 4-quinolone synthesis [78][79]

Scheme: 15

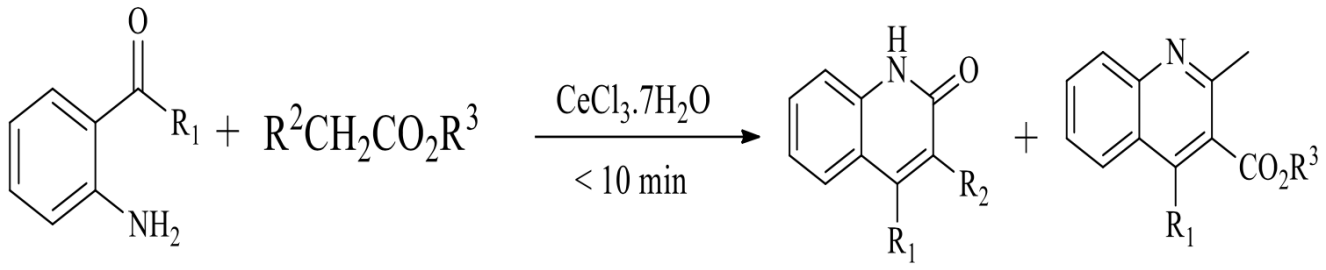
Hou *et al.* developed photocatalytic techniques for producing 2-quinolones by combining photoredox, cobalt or iridium catalysis, and hydrocarboxylation of alkynes in a single-pot synthesis with CO_2. This method produced the relevant 2-quinolones with high yields from various aryl-substituted alkynes [24]. In addition, a considerable yield of 2-quinolones was generated under photocarboxylation conditions by the reaction of alkynes with a free aniline molecule [80].



Scheme 15. Synthesis of 2-quinolones by photosynthesis techniques [80].

Scheme: 16

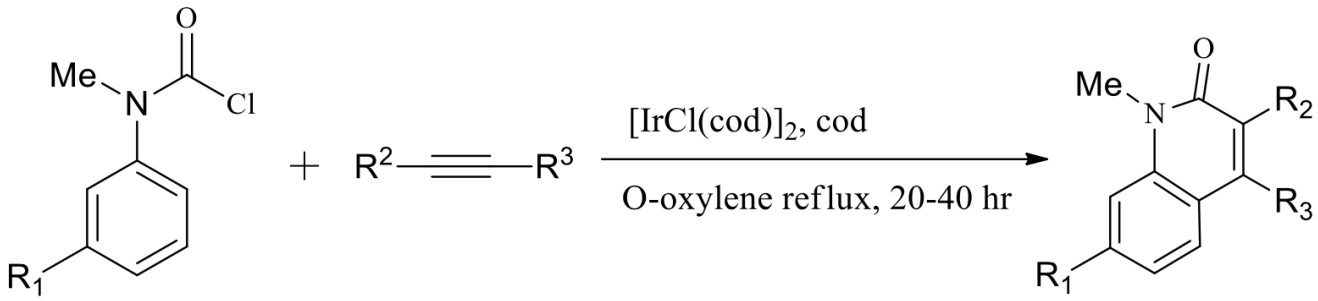
Wang *et al.* established a microwave-assisted Friedlander-type condensation method for making 2-quinolones by combining O-amino aryl ketones and esters with a reactive alpha-methylene moiety and using $CeCl_3.7H_2O$ as a catalyst. Lewis's acid resulted in high yields and selectivity for 2-quinolones in under 10 minutes [81][82].



Scheme 16. Synthesis of 2-quinolones by microwave-assisted reaction [81][82].

Scheme: 17

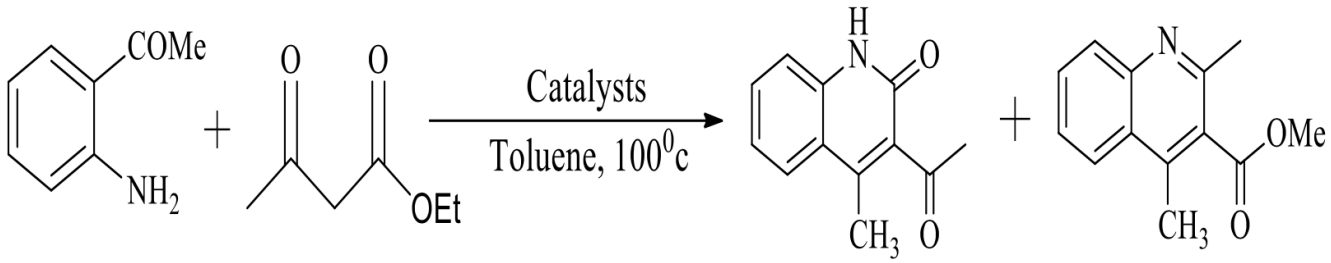
Tsuji *et al.* discovered a method for the synthesis of N-methyl-2-quinolones using iridium as a catalyst. This reaction contained N-methyl-2-quinolones from different methyl aryl carbamoyl chlorides and internal alkynes. The best results were obtained by using $[IrCl(cod)]_2$ under optimal conditions. Symmetrical alkynes provide higher yields of essential products than unsymmetrical alkynes, which only have a yield of 62-67% [83][84].



Scheme 17. Synthesis of quinolones by Cascade reaction [83][84].

Scheme: 18

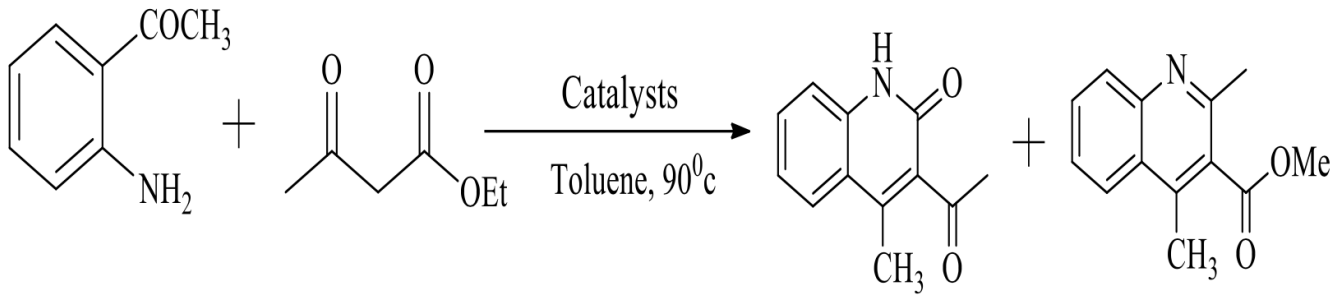
Simple mesoporous catalysts were effective in a traditional Friedlander method for synthesizing 3,4-disubstituted 2-quinolones. The basic heterogeneous catalysts dimethyl aminopropyl (DEAP), methyl aminopropyl (MAP), and aminopropyl are used in this method. Compared to the primary amine-supported (A.P.) catalyst, the yield was better with the secondary (MAP) or tertiary (DEAP) amino-supported (amine) catalyst. The maximum productivity was demonstrated with a MAP-based catalyst (20%) [85].



Scheme 18. Friedlander reaction by basic mesoporous catalysts [85].

Scheme: 19

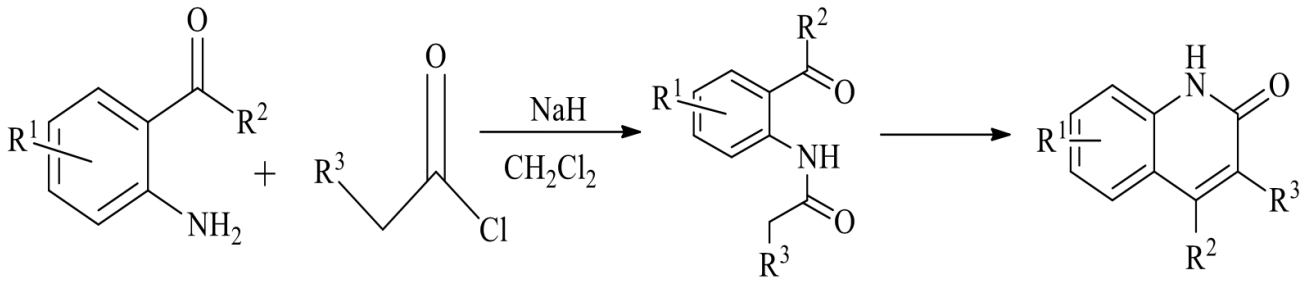
Lopez-Peinadi *et al.* investigated a Friedlander reaction induced by zeolites in 2010. Lewis and Bronsted acid catalyst sites are looked at in bifunctional zeolites. The best conditions for combining 2-amino aryl ketones and ethyl acetoacetate at an increased temperature were determined. Compared to 2-quinolone, H-MOR had a better yield. Khan *et al.* also performed the same method using amber light NaSr1L as a catalyst [86][87].



Scheme 19. Friedlander reaction for the synthesis of 2-quinolone [86][87].

Scheme: 20

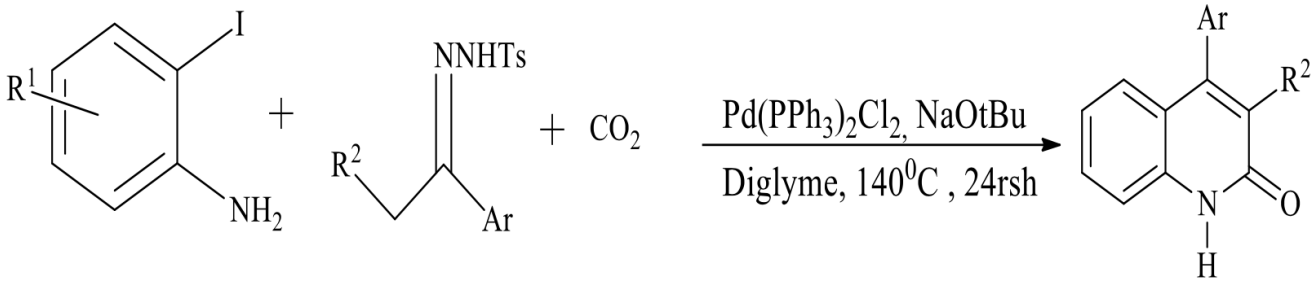
Bui *et al.* discovered a method to produce 2-quinolones using microwave radiation, starting with substituted 2-amino benzophenone and acid chlorides. The results demonstrated that M.W. irradiation produces high yields and reduces reaction time [88].



Scheme 20. Synthesis of 2-quinolones via M.W. assisted one-pot method [88].

Scheme: 21

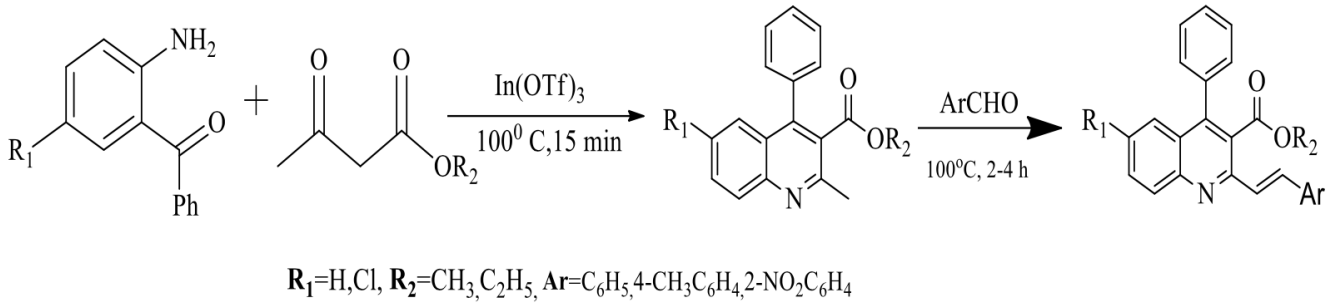
Cheng *et al.* synthesized 4-aryl-2-quinolones in the presence of a palladium catalyst. The existence of a base in the reactions yielded 2-quinolones with moderate to good yields. Palladium carbene intermediates are produced from N-tosyl hydrazones by converting them into diazo substrates [89].



Scheme 21. 4-aryl-2-quinolinone synthesis using CO_2 gas [89].

Scheme: 22

Kumar *et al.* developed a Friedlander annulation-Knoevenagel condensation [36] at 100ºC for 5 hours to synthesize 2-steryl quinolones from 2-amino benzophenone and ethyl acetoacetate using indium triflate as a substrate [90].

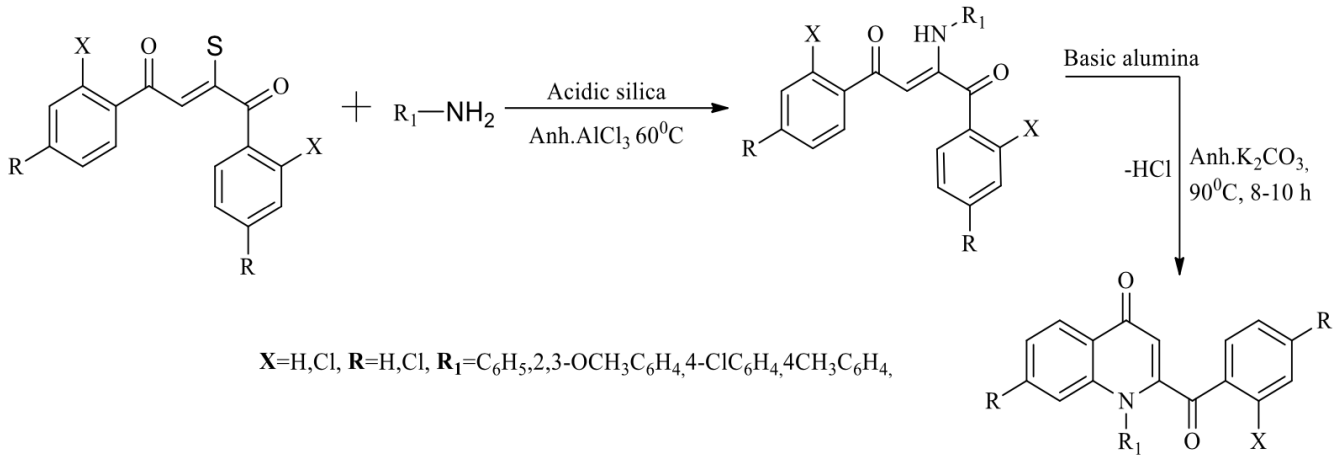


R1=H,Cl, **R2**=CH_3,C_2H_5, **Ar**=C_6H_5,4-$CH_3C_6H_4$,2-$NO_2C_6H_4$

Scheme 22. Quinolone derivatives synthesis via condensation method [90].

Scheme: 23

Vinayaka *et al.* reported a metal-free solid-phase conversion technique for synthesizing 4-quinolones using K_2CO_3 as a catalyst. Basic alumina and enaminones were used as substrates for structuring 4-quinolones [36][91].



X=H,Cl, **R**=H,Cl, **R1**=C_6H_5,2,3-$OCH_3C_6H_4$,4-ClC_6H_4,4$CH_3C_6H_4$,

Scheme 23. Synthesis of 4-quinolones by transition metal-free techniques [36][91].

Results and Discussions

Quinolones are a major characteristic of nitrogen-containing heterocycles. They exhibit potential antibacterial, anti-inflammatory, antimalarial, anticancer, antifungal, antitubercular, and other biological activities. Quinolone derivatives are

tremendously important in medicinal chemistry. The N-1 position of quinolones requires a basic cyclical system as a substituent, position 3 requires a carboxylic group, and position 4 requires a ketone. These requirements vary depending on the function of the quinolone. Different molecules with various pharmacological, physiological, and pharmacokinetic features resulted from chemical modifications at the N-1 and C-(5-8) positions. There are several methods for synthesizing quinolone derivatives, including microwave-assisted synthesis, solvent-free method, photocatalyst, biocatalyst, low-energy protocol, ultrasonication-mediated synthesis, catalyst-free approach, and green solvent reaction (water, ethanol, supercritical CO_2, aq. H_2O_2, oxidation).

Conclusions

Quinolone is a pharmacophore, an essential heterocyclic ring system in medicinal chemistry. As a result, there is never-ending research for an environmentally friendly way to synthesize it. The review summarized and categorized the majority of green approaches, including their benefits, implications, and substrate scope. Future researchers have a variety of scopes and opportunities to plan further studies on green chemistry approaches. The advantages of this review will assist in the further improvement of present studies.

Statements and Declarations

Authors Contribution

All authors have participated combinedly in the literature survey and completion of the document.

Ethical Approval and Consent to Participate

Not applicable.

Conflict of Interest

The authors declare no competing interests.

Availability of Data and Materials

All the data are available within the article, and the authors do not have permission to share data.

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