Review

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An Overview of Quinolones as Potential Drugs: Synthesis, Reactivity and Biological Activities

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Review

An Overview of Quinolones as Potential Drugs: Synthesis, Reactivity and Biological Activities

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Abstract: Quinolones represent one of the largest classes of synthetic antibiotics used in both human and veterinary medicine. Subsequent to the discovery of nalidixic acid, a substantial body of research has been carried out on quinolones, resulting in the synthesis of a number of quinolone derivatives with exceptional pharmacology. In addition to their antibacterial action, quinolones have a broad spectrum of diverse biological activities. In this regard, the present review examines the literature of recent years describing synthesis protocols, reactivity and biological properties, with particular emphasis on the antibacterial, antimalarial, antitrypanosomal, antileishmanial, antiviral and anticancer activities of these famous nuclei. Finally, this review highlights the potential of quinolones as preferred pharmacophores in medicinal chemistry. The aim is to highlight the innovative aspects of rationally designing new therapeutic agents with this structural motif, in the face of emerging antibiotic resistance and the urgent need for new active molecules.

Keywords: quinolones; antibiotics; one-pot reactions; metal-catalyzed couplings; drug candidates; biological activities

1. Introduction

The synthesis of organic molecules has gained so much intricacy over the years and applies to several areas such as pharmaceutical chemistry, agrochemicals, and cosmetics [1,2]. Contributing further is probably the fact that most of these molecules need to be synthesized in a multistep fashion a factor that results in increased complexity on how newly evolved reaction techniques can be ingeniously applied. In particular, recent advances in new pharmacophore design are being focused on addressing the ever-growing problem of antibacterial resistance, which has been created by bacteria, fungi, parasites, and viruses, represents a significant concern to human health and the safety of our food products [3]. Over the past seven decades, antibacterial compounds have played a very important role in preventing serious bacterial infections. However, in view of the emergence of resistant populations, there is an urgent need to develop newer and more potent antibacterial agents [4]. Quinolones represent a class of useful antibacterial agents that have been used in human medicine since they were first synthesized. This category ranges from the earliest agent, nalidixic acid, to the advanced fourth-generation fluoroquinolones. Quinolines **I-III** belong to the benzo-pyridine family and are naturally occurring compounds derived from plants. A wide range of derivatives can be synthesised from them (Scheme 1) [5,6].

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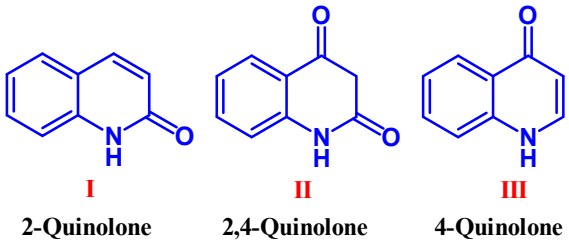

Scheme 1. Quinolones cores.

Quinolones, or oxo-quinolines, are among the most commonly encountered heterocycles in drug discovery. Their derivatives have found extensive use in medicinal chemistry due to their distinctive structure, which confers several remarkable pharmacological effects (Figure 1). These effects include activities such as antitubercular [7], antimalarial [8], antibacterial [9], anti-HIV [10], antitumor [11], anti-HCV [12], anticancer [13] and numerous other biological properties [14–17] (Figure 1).

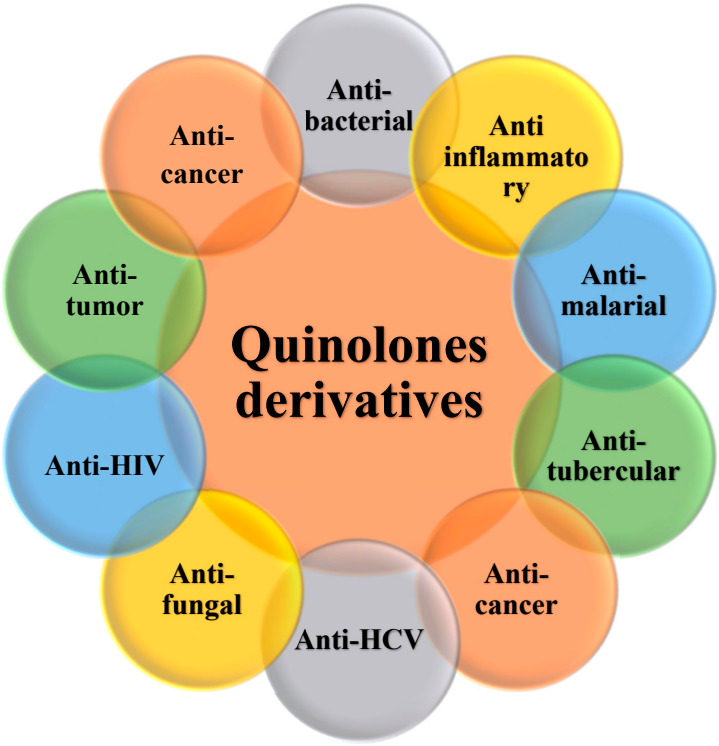

Figure 1. Biological activities quinolone derivatives.

Quinolones, a widely prescribed class of antibacterial agents worldwide, are used to treat a wide range of bacterial infections in humans [18,19]. However, the extensive utilization of these medications has resulted in a substantial surge in quinolone-resistant bacterial strains since the early 1990s [20], a trend that continues to escalate. With the emergence of bacterial and fungal resistance to established chemotherapeutic drugs [21], the search for new chemotherapeutic molecules has become an ongoing challenge. There is an urgent need for new, potent chemotherapeutic agents, ideally with novel mechanisms of action [22,23].

The medicinal chemistry of quinolones has been the subject of research studies, with a particular attention given to 4-quinolones. Liu et al. emphasized the medicinal potential of quinolones as putative antitubercular agents, while Jiang et al. focused on the potential therapeutic usage of 4-quinolones against gram-negative bacteria [23]. Another research group, Gao et al., examined the anticancer potentials of quinolone hybrids [24]. From a more general point of view, other researchers have investigated the antibacterial and antituberculosis activities of fluoroquinolone derivatives [25–29]. However, these works only cover certain aspects of the medicinal chemistry of these compounds,

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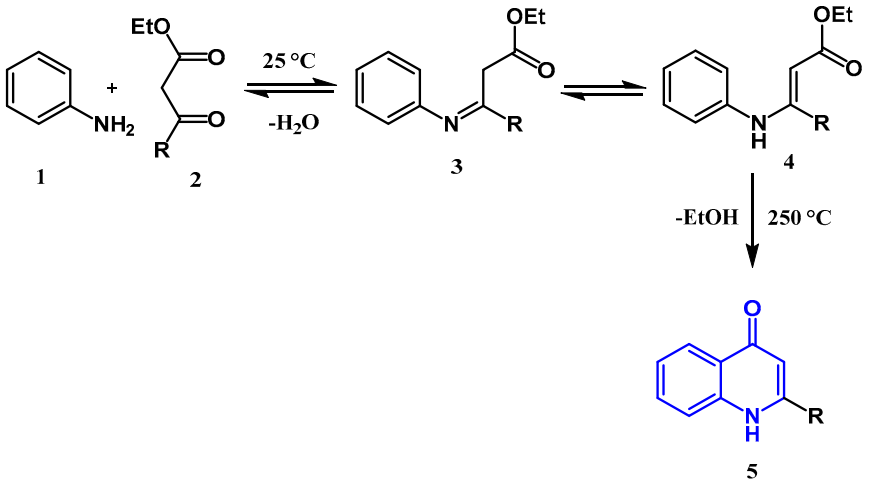
and recent developments in this field have not been included. Although the ring system is recognized as, having played a key role in the medicinal chemistry of quinolones, and considerable progress has been made in understanding their biological activities. The present review aims to fill this gap by highlighting important and recent advances in the synthesis of new quinolone derivatives, as well as various reactions carried out on the reactive sites of the molecules and these derivatives. This review will also highlight the potential activities of synthetic 2- and 4-quinolone derivatives. It aims to provide an overview of recent research studies carried out on these compounds with regard to their antibacterial, antiproliferative, antiviral, antitrypanosomal, and antimalarial activities. Through its objectives, this review will hopefully assist organic and medicinal chemists working in the field of drug discovery and development, as well as those interested in exploiting the rich chemistry of quinolone derivatives for chemical or biological purposes.

2. Methods of Synthesis of Quinolone Derivatives

2.1. Synthesis from Derivatives of Aniline and an Arylamine

2.1.1. Conrad Limpach Knorr's Reaction

Conrad's group [30] developed a synthesis method for quinolone derivatives **5** using β-ketoester **2** as a cyclization agent. Different products are formed depending on the reaction conditions. Heating to 250°C leads to the formation of p-arylaminoacrylate **3**, which then undergoes intramolecular cyclization to give 4-quinolones **5**. Conversely, at temperatures above 100°C and in the presence of a strong acid, a β-ketoanilide **4** is formed which undergoes cyclization to give a 2-quinolone **5** (Scheme 2).



Scheme 2. Conrad-Limpach-Knorr reaction.

Conrad et al. [30] proposed a reaction mechanism for this synthesis, described in (Scheme 3).

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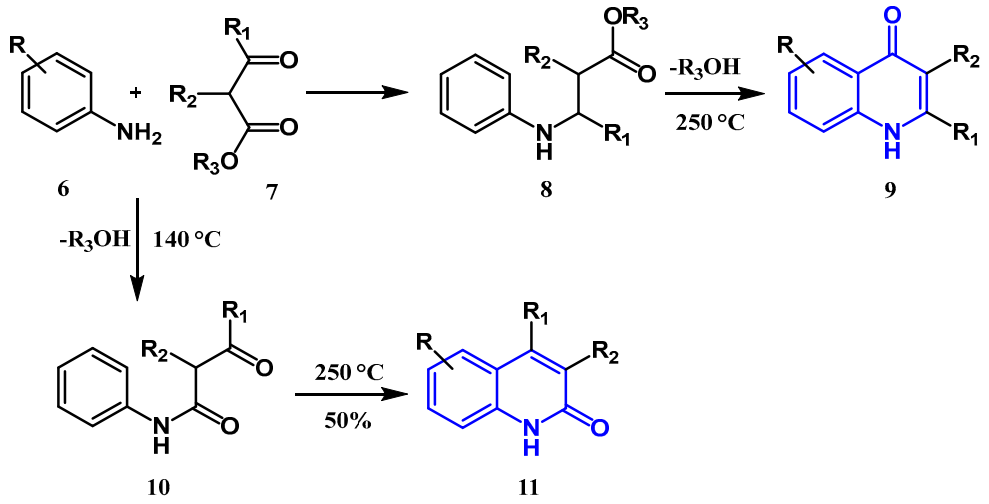
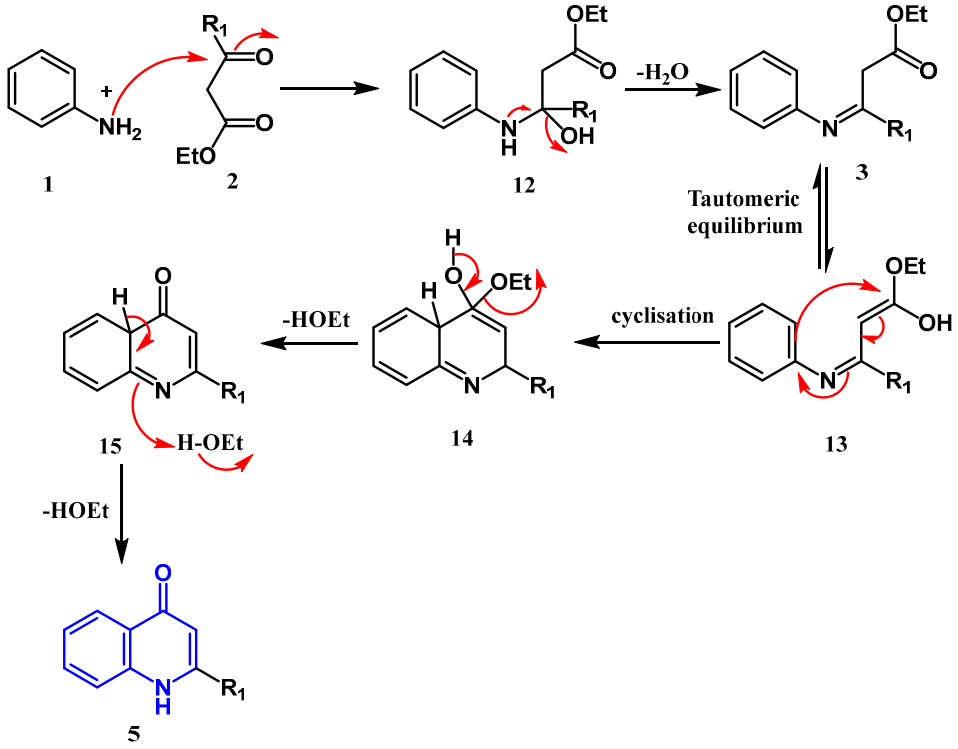


Scheme 3. Reaction mechanism of Conrad et al.

The same authors [30] showed that the synthesis of aminoacrylates required for the Conrad-Limpach synthesis could be achieved by the interaction of arylamines **1** with either β-ketoesters or ethyl ethoxymethylene malonate **2**. The proposed mechanism is shown in Scheme 4.



Scheme 4. Mechanism of formation of quinolone derivatives from dicarbonyl compounds.

An alternative and highly efficient method of synthesis, a modification of the Conrad-Limpach reaction, has been developed [31]. The mechanism of this method is shown in Scheme 5. It uses aniline 1, ethyl orthoformate and a compound with an activated methylene group (such as ethyl malonate or malononitrile) as starting materials.

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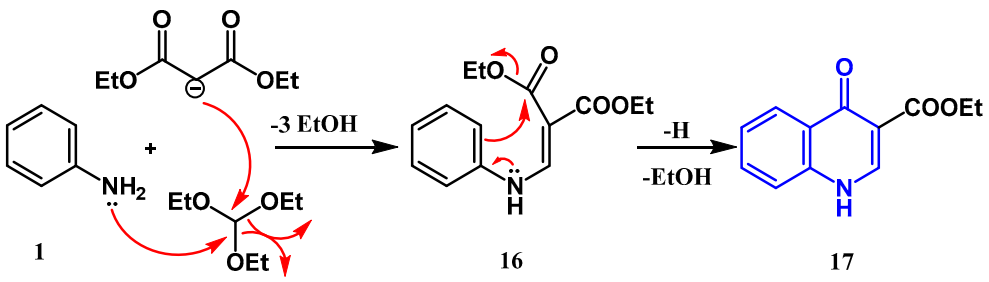
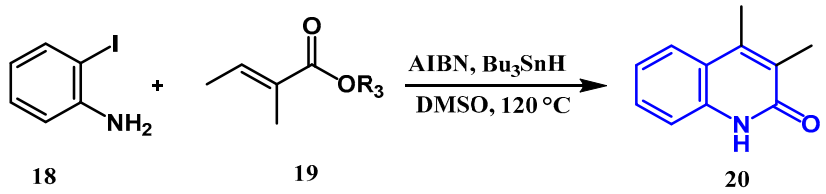


Scheme 5. Mechanism of formation of quinolone derivatives by a condensation reaction between three compounds.

The use of a basic medium promotes the condensation reaction between ethyl orthoformate, aniline, and ethyl malonate.

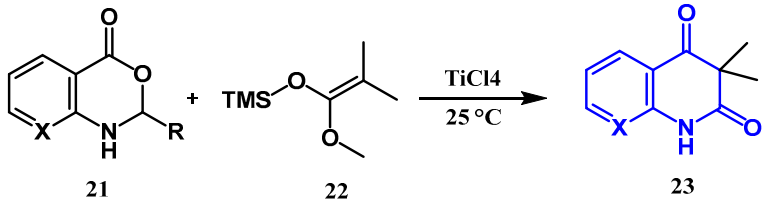
2.1.2. Doebner Multicomponent Reaction

Zhou et al. [32] synthesized 3,4-dimethylquinolin-2(1H)-one **20** by reacting 2- iodoaniline **18** with a derivative of an alkyl acrylate **19** in the presence of AIBN (azobisisobutyrononitrile) and n-Bu_3SnH (Scheme 6).



Scheme 6. 3,4-dimethylquinolin-2-one Synthesis.

In a single step, Zografos et al. [33] achieved the synthesis of alkaloid analogues of 2,4-quinolone **23**, using the Mukaiyama aldol **24** as a precursor and exploiting the enhanced reactivity of anhydrides (Scheme 7).



Scheme 7. 2,4-quinolone alkaloid analogues Synthesis**.**

2.1.3. Gould-Jacobs Reactions

The Gould-Jacobs synthesis is a widely used technique for the synthesis of quinolone derivatives [34]. By heating ethanol to reflux and stirring while reacting anilines **1** with an acyl malonic acid ester or an alkoxymethyl malonic acid ester 22, Michael products are formed. The corresponding quinolone derivatives **25** [35] are then prepared by condensation of the resulting condensed product 24 in an alkaline environment (Scheme 8).

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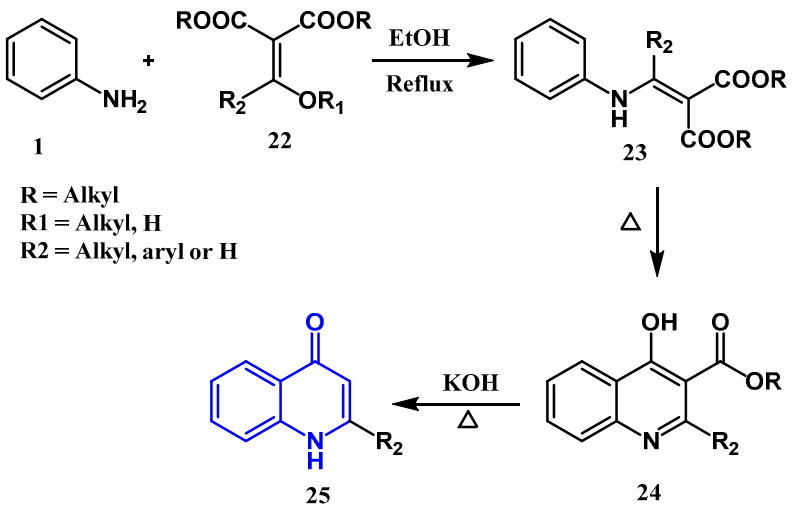
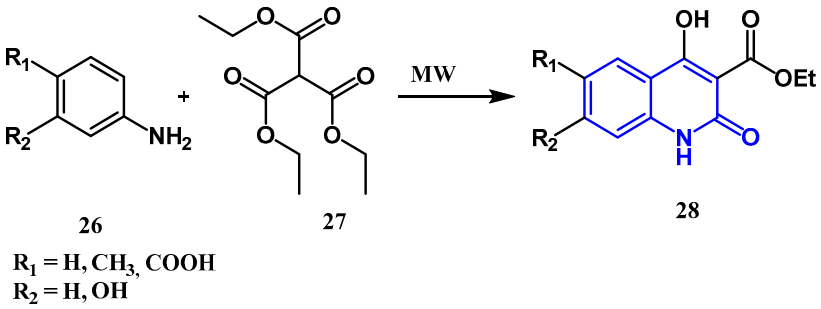


Scheme 8. Gould-Jacobs reactions.

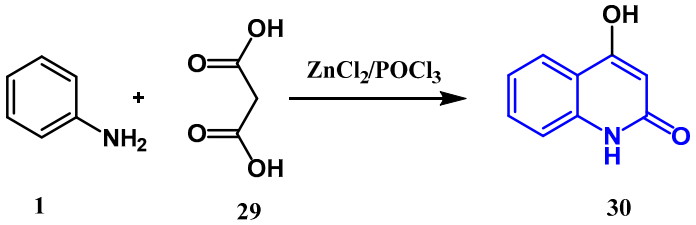
2.1.4. Jampilek Reaction:

In 2009, Jampilek et al. prepared ethyl 4-hydroxy-2-quinolone-3-carboxylate derivatives **28** in excellent yields using an aniline 26 and triethylmethanetricarboxylate 27 in a microwave-assisted process [36] (Scheme 9).



Scheme 9. Jampilek et al reactions.

As reported and shown in Scheme 10, 4-hydroxyquinolin-2-one **30** was prepared by combining anhydrous zinc chloride, phosphorus oxychloride, aniline **1**, and malonic acid **29** [37].



Scheme 10. 4-hydroxyquinolin-2-one synthesis.

2.1.5. Cheng Reaction

Long reaction times, the use of toxic phosphorus oxychloride, low yields and the use of dehydrating agents such as $ZnCl_2$ are disadvantages of this method [38]. However, it has been found that MW-assisted condensation can increase the yield in the presence of DMF (N,N-dimethylformamide) is present [39–41]. In the process described by Cheng et al. in Scheme 11, excess diethylmalonate **32** was reacted with anilines to give N,N-diarylmalonamide derivatives **31**, which

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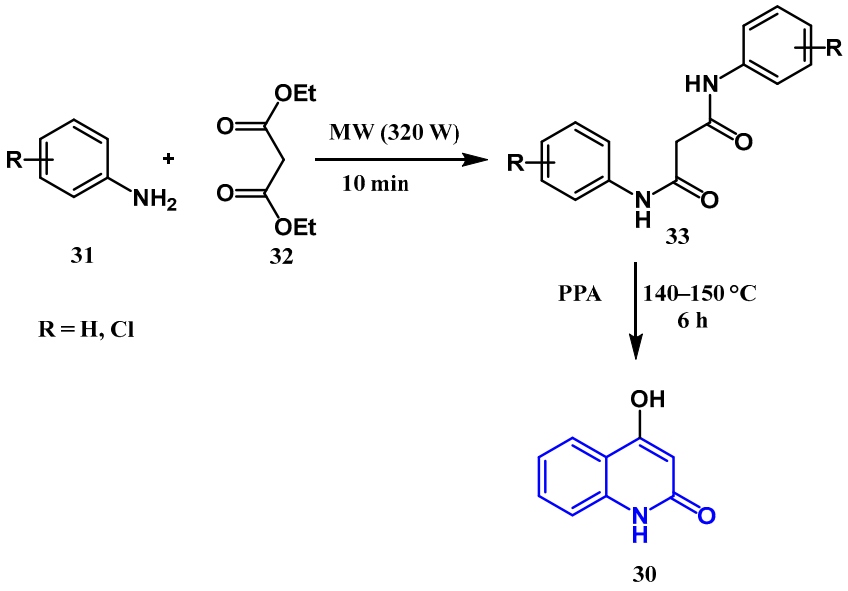
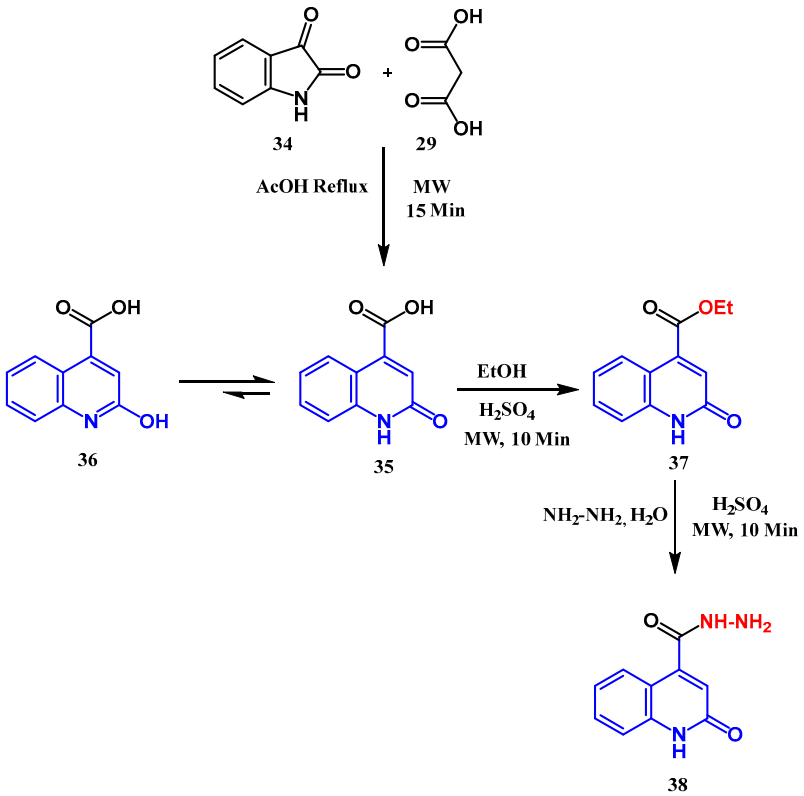
were then catalytically cyclized with polyphosphoric acid (PPA) to give 4-hydroxyquinolin-2(1H)-one **33** [42].



Scheme 11. 4-hydroxyquinolin-2-one synthesis under irradiation MW.

2.2. Syntheses from the Indole-2,3-Dione Ring

Instead of conventional techniques such as reflux, El Ashry et al [43] established a productive approach for the synthesis of 2-quinolone-4-carboxylic acid derivatives **35** using microwave irradiation. Surprisingly, 2-quinolone-4-carboxylic acid **35** was produced with a yield of 78% in only 15 minutes. An esterification reaction was also performed under microwave irradiation to produce ethyl 2-oxo-1,2-dihydroquinoline-4-carboxylate **37**. The equivalent of 2-quinolone-4-carbohydrazide **38** was obtained after further addition of hydrazine hydrate (Scheme 12).



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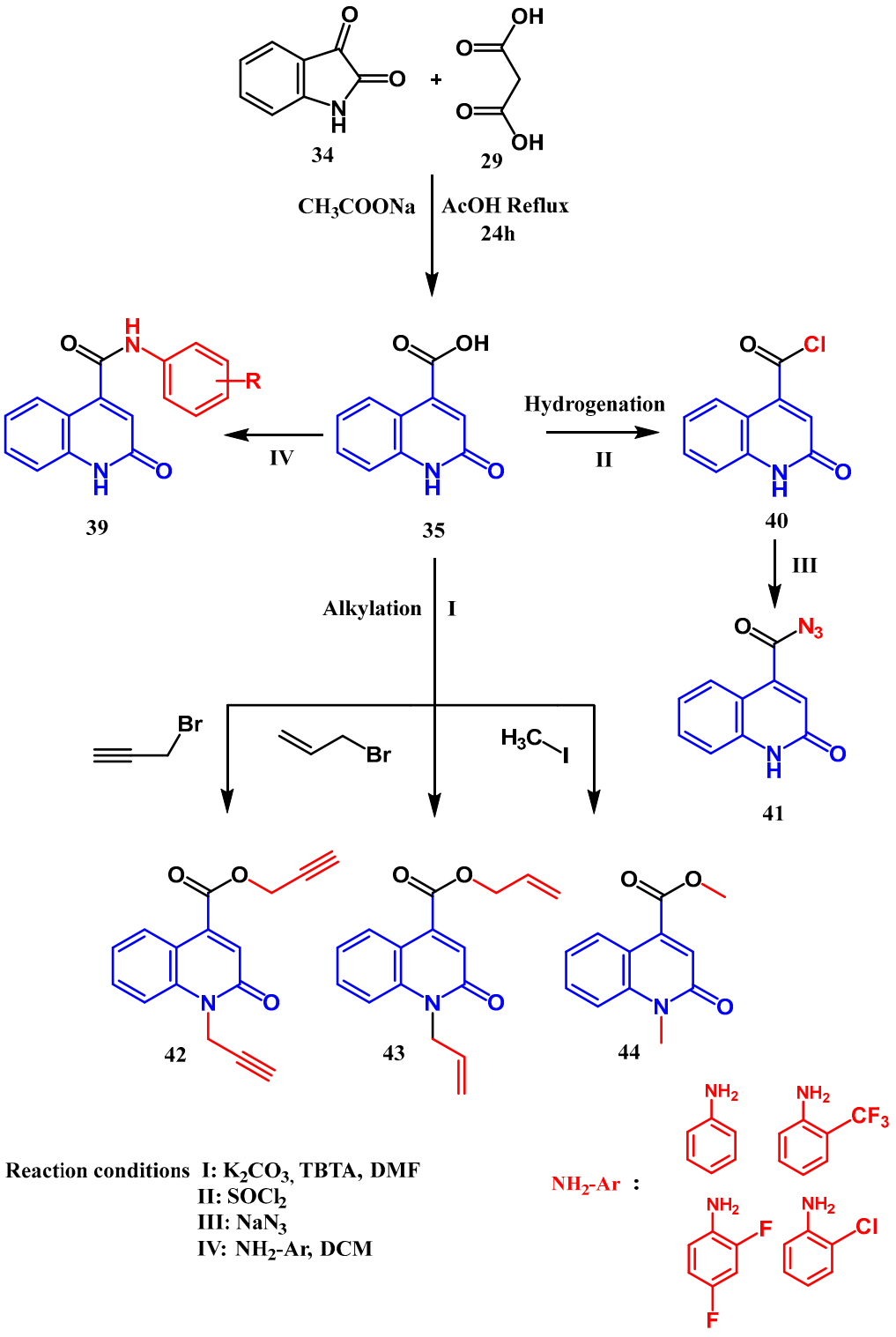
Scheme 12. 2-quinolone-4-carboxylic acid microwave-irradiated and its derivatives synthesized.

The same applies to the reaction pathway shown above, between 2014 and 2020, Filali Baba et al [44,45] carried out a series of investigations on the Pfitzinger reaction was used in conjunction with the N-alkylation method and the esterification reaction to prepare new derivatives of quinoline-4-carboxylic acid **35**. They then investigated several quinoline-4-carboxamide derivatives **39**, as a result of their research (Scheme 13).



Scheme 13. The synthetic pathway for new 2-quinolone-4-carboxylic acid derivatives.

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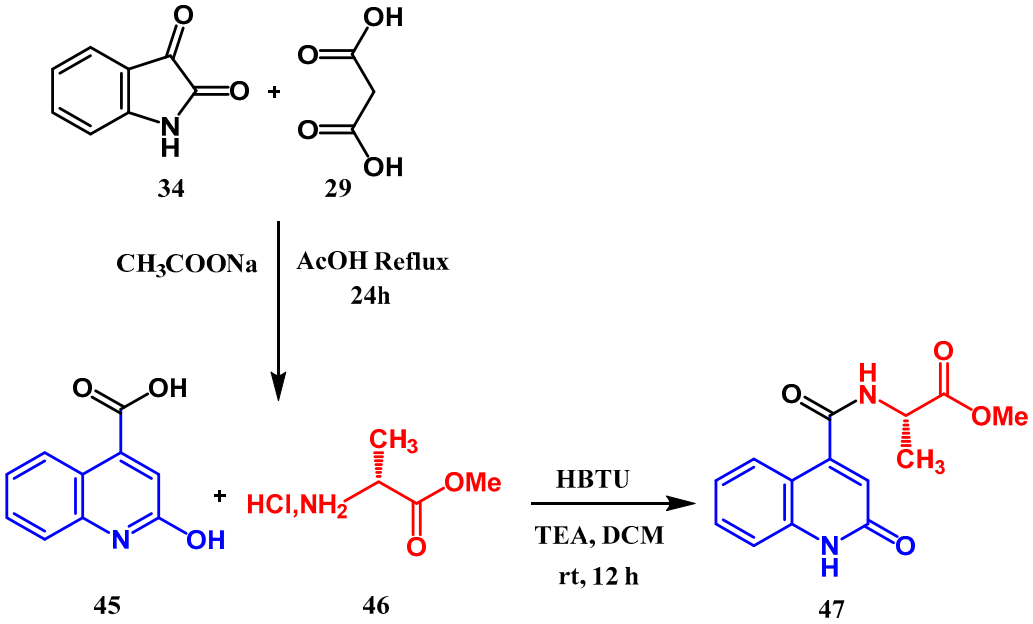
Under these aspects, Moussaoui et al. [46] realized an extended synthesis towards different 2-quinolone-4-carboxamide derivatives **47** with microbial inhibitory activity. Their synthesis approach consists of coupling protected L-alaninate with 2-oxo-quinoline-4-carboxylic acid **45** under controlled conditions (TEA/DCM), which is necessary to obtain analogs with strong antibacterial activity (Scheme 14).



Scheme 14. Synthesis of 2-quinolone-4-carboxamide derivatives.

Previous studies have highlighted the enormous role of various quinolones in a wide range of biological applications [47–50]**.** However, there is a need for newer strategies with an emphasis on simplifying the synthesis route and reducing the number of steps. Using the readily available starting materials, isatoic anhydride **48** and indoline-1,3-dione **34**, Ma et al. established an effective, green one-step method for the preparation of 4-quinolone derivatives **50**. The process involves the interaction of isatoic anhydride **48** with compounds having a carbonyl function in the presence of K_2CO_3 as a weak base and water as a solvent to give bioactive 4-quinolone derivatives **50**.

Similarly, indoline-1,3-dione **34** was reacted with alkyl/aryl substituted aldehydes in the presence of tert-butyl hydroperoxide (TBHP) and potassium carbonate (K_2CO_3) in DMSO solvent. This reaction led to the synthesis of a series of 4-quinolone derivatives **50** with yields varying between 87% and 95% [51]**,** these synthesized quinolone derivatives were further evaluated for their antimalarial activity (Scheme 15).

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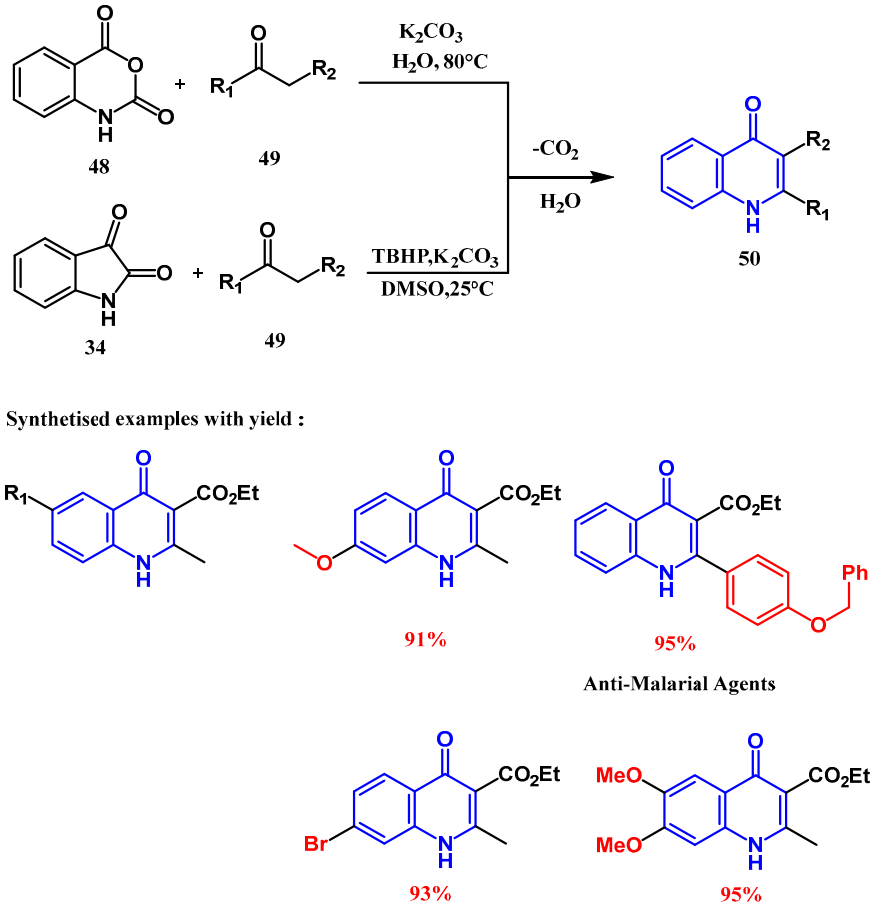

Scheme 15. 4-quinolone synthesis from indoline derivatives.

2.3. Reactions Catalyzed by Pd

The synthesis of 2-quinolones has been approached in a variety of ways in recent years, with palladium-catalyzed reactions involving two coupling components emerging as practical procedures for the preparation of 2-quinolone derivatives with a wide range of substituents.

O-iodoanilines **51** have often been used in the preparation of the 2-quinolone derivatives **54**. In addition, dimethyl maleate and readily available 2-iodoanilines can be used to prepare (Z)-acrylic esters **3**, from which methyl 2-oxo-1,2-dihydroquinoline-4-carboxylate **54** can be efficiently prepared with yields ranging from 30% to 73% (Scheme 16). The Heck reaction provides the essential intermediate. In addition, 4-phenyl-2-quinolone **57** can be prepared from 2-iodoaniline **55** and (Z)-N-phenylcinnamamide **56** with a yield of 66%, whereas the yield of the E-isomer is only 15%. This finding demonstrates that (Z)-isomers are preferred substrates for arylpalladium complexation [52,53].

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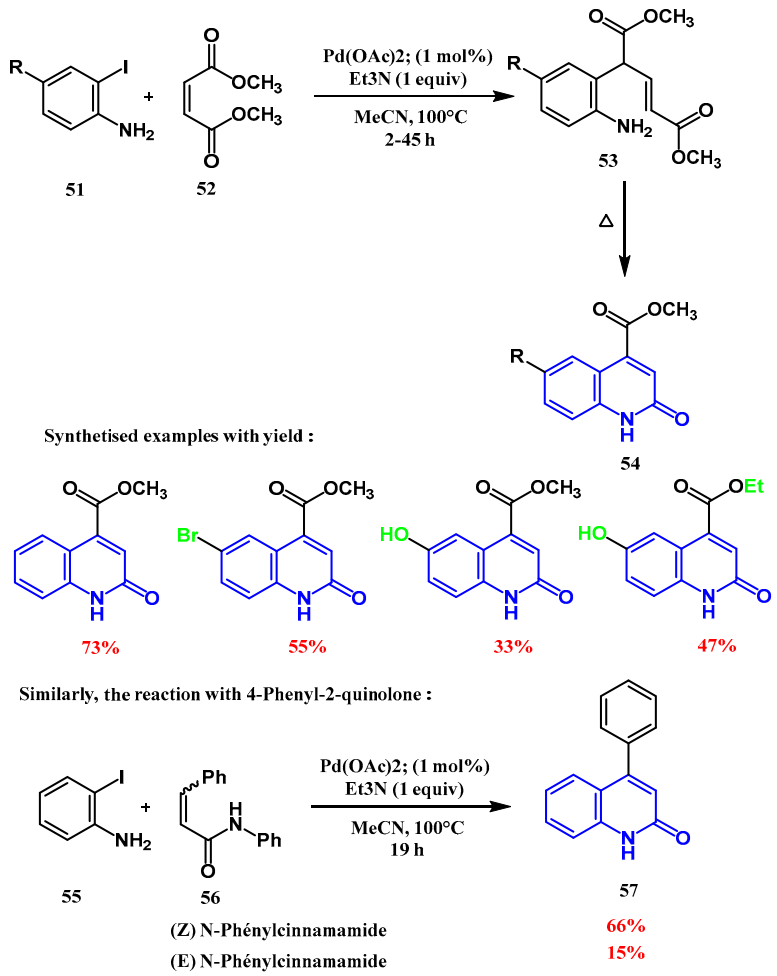

Scheme 16. 2-Iodoanilines undergo a Pd-catalyzed reaction to produce derivatives of 2-quinolones.

In their 2007 study, Cho and Kim described a reaction between dialkyl itaconates **58** and 2-iodoaniline **59** that produced 2-quinolones **61** with substituents at the C-3 position. And the conditions used to optimize the reactions: PPh_3, $Pd(OAc)_2$ as catalyst and NaOAc as base. The reactions were carried out at 100 °C for 20 hours. The desired products were obtained in yields ranging from 67% to 76% [54] after studying several dialkyl itaconates **58**. It's also important to note that 2,3-dialkyl-substituted quinoline, rather than quinolone, was produced when 2,3,-unsaturated ketones were used (Scheme 17).

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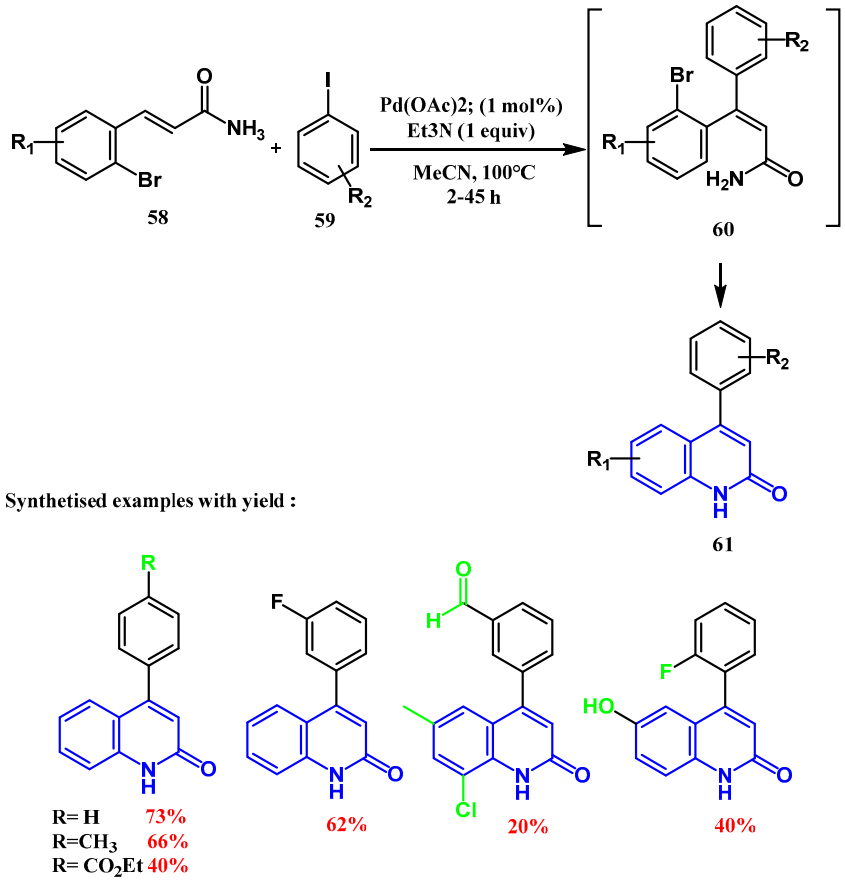

Scheme 17. 4-aryl-2-quinolones are produced by sequential Heck reaction/amination.

For the synthesis of 4-quinolone derivatives **65**, Linda et al. proposed a two-stage substituted 2-iodoaniline **63** and terminal alkyne carbonylation **62** cyclization approach in 2015.

The first phase produced the cyclized products **64** were obtained in less than 20 min at 120°C and MW heating.

For the second phase, the catalyst used was Palladium (II) (Acetate ($Pd(OAc)_2$) to produce the cyclized product at room temperature in equivalent yields. It was found that under ideal conditions, the $Pd(OAc)_2$ catalyst is required for aryl halogenide activation. As demonstrated in Scheme 18, $Mo(CO)_6$ was employed as a solid source of carbon monoxide in both processes, providing favorable environmental properties as well as tolerance to a variety of functional groups. This method of synthesis allowed the preparation of a variety of substituted quinolones **65** [55]**.**

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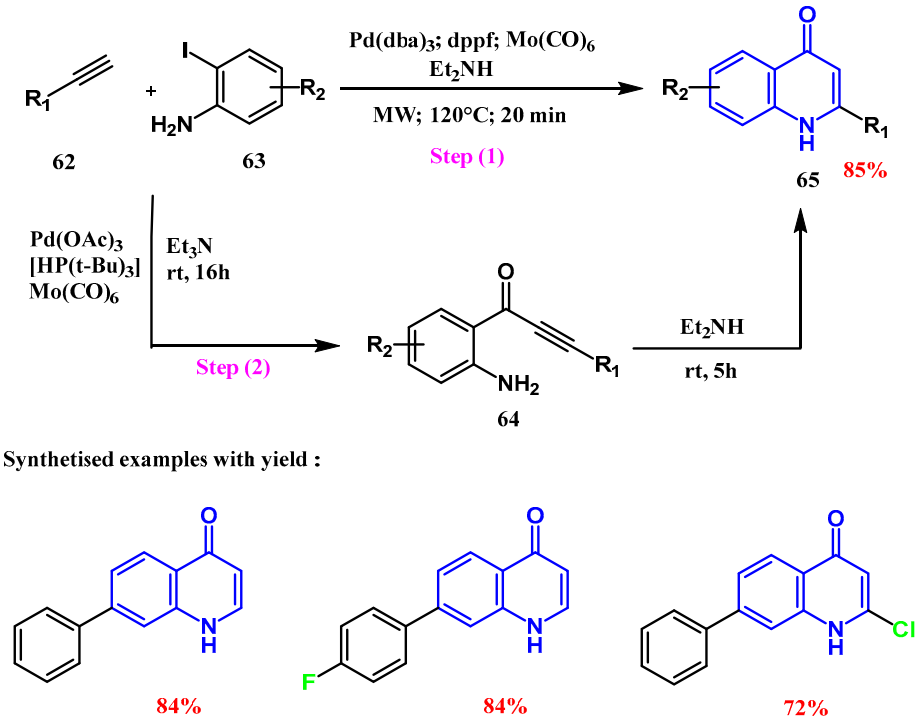
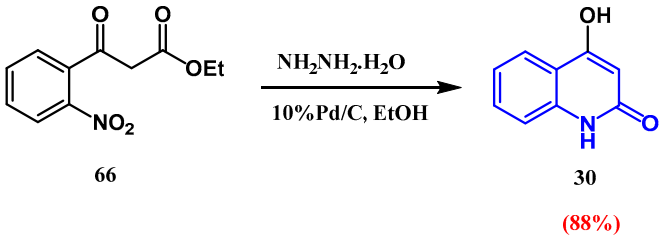


Scheme 18. Sonogashira reactions for the preparation of 4-quinolones and their derivatives.

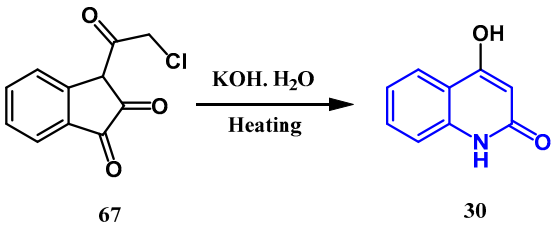
2.4. Catalytic Reduction:

In an excellent yield of 88%, the synthesis of 4-hydroxyquinolin-2-one **30** was achieved by the catalytic reduction of ethyl 2-nitrobenzoylacetate **66** with hydrazine NH_2NH_2, H_2O in the presence of Pd/C at 25°C. This was followed by an intramolecular cyclization step (Scheme 19) [56].



Scheme 19. synthesis of 4-hydroxyquinolin-2-one.

This reduction can be successfully accomplished with hydrogen and a platinum black catalyst [57]. Additionally, Huntress and Bornstein described a reaction in which N-chloroacetylisatin **67** generated 4-hydroxy-2(1H)-quinolone 30 when it was treated with alkali [58] (Scheme 20).



Scheme 20. Huntress and Bornstein reaction.

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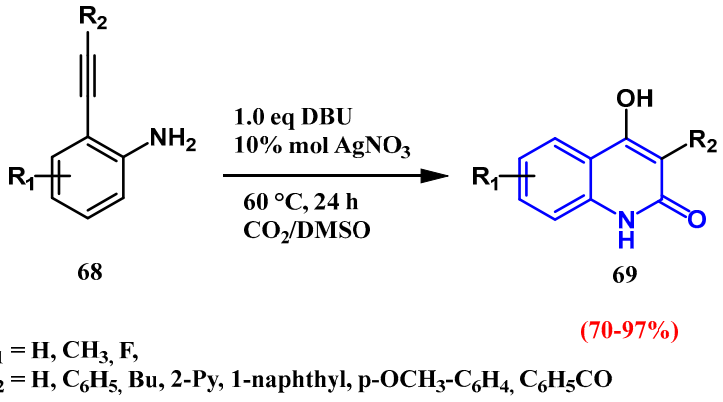
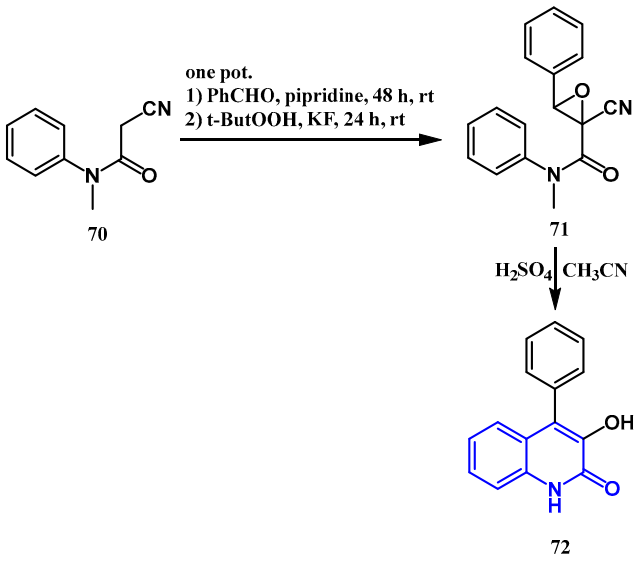
2.5. Silver-Catalyzed Carboxylation:

In 2014, Kikuchi and Yamada reported a high-yield reaction with o-alkynylaniline derivatives **68**. The reaction was carried out with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and $AgNO_3$. The reaction was performed under atmospheric pressure of CO_2 in dimethylsulfoxide. As a result, the C-C bond was formed. Moreover, the yield from 70% to 97% (Scheme 21) [59].



Scheme 21. Kikuchi and Yamada reactions.

Kobayashi and Harayama also described an efficient one-pot synthesis of 3-hydroxy-4-phenylquinolin-2(1H)-one **72**. A decyanative epoxide-arene cyclization is used to prepare the quinolinone **72**; this technique involved a Knoevenagel condensation/epoxidation of cyanoacetanilide **71**, (Scheme 22) [60].



Scheme 22. Kobayashi and Harayama reactions.

In addition, Ribeiro et al. described the synthesis of a compound derived from 2-quinolone **75** with a phenyl at C4 and a methoxy at C3. In this procedure, 2-aminobenzophenone **73** was acylated with methoxyacetyl chloride and then subjected to an alkaline cyclization step. The formation of an intermediate allowed the reaction to continue. Various substituents could be added at the 3-position by controlling the reaction between an aminobenzophenone and bromoacetyl bromide (Scheme 23) [61].

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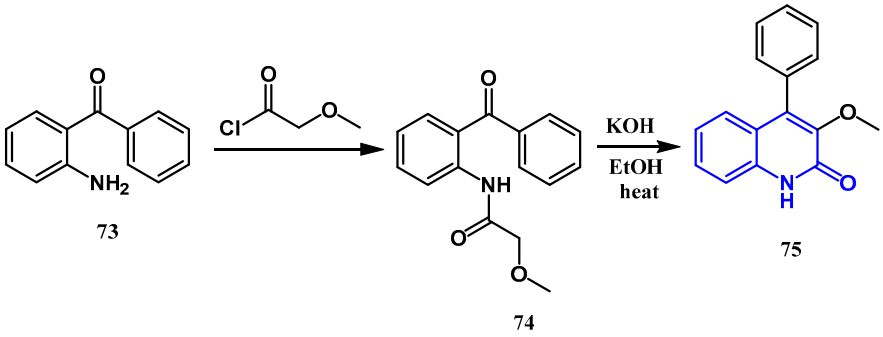
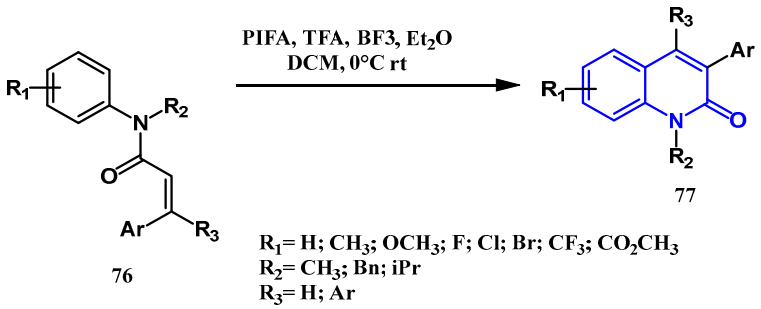


Scheme 23. synthesis of 3-methoxy-4-phenyl-2-quinolone.

In 2013, Liu et al. published a versatile and effective approach for the synthesis of different 3-arylquinolin-2-ones **77**. This included the preparation of substituted 3-arylquinolones by the reaction of N-alkyl-N-phenylcinnamides **76** with PIFA (phenyliodine bis(trifluoroacetate)) in the presence of BF_3, which is a Lewis acid (Scheme 24) [62].

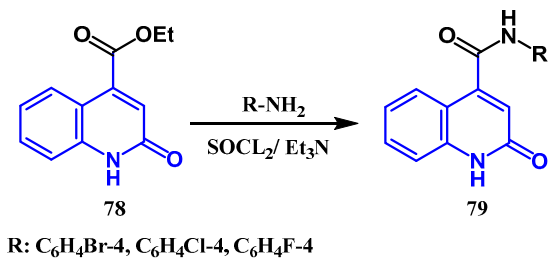


Scheme 24. The formation of various 3-arylquinolin-2-ones.

3. Reactivity of Quinolones Derivatives

3.1. Amidation and Amination

The large number of organic syntheses of amines holds an important position in the development of biologically active compounds. Their functions are quite versatile, and thus usually many chemical transformations are usually in the synthesis of pharmaceuticals, agrochemicals, and functional materials. Among them, the nucleophilic substitution of alkyl halides and the Buchwald-Hartwig reaction on aryl halides are among the most common ways to establish C-N bonds in modern organic chemistry. These reactions not only emphasize the growing importance of amines but also extend in their versatility to aid in the synthesis of complex organic compounds [63]. Mikhalev et al. reported the synthesis of 2-oxo-4-quinoline-carboxylic acid arylamides **79** in a two-step process. First, they carried out the esterification of 2-oxo-1,2-dihydro-quinoline carboxylic acid in ethanol using H_2SO_4 as a catalyst. This step facilitated the formation of the corresponding ester **78** (Scheme 25) [64].



Scheme 25. Synthesis of 1,2-dihydroquinolone-4-carboxamide derivatives.

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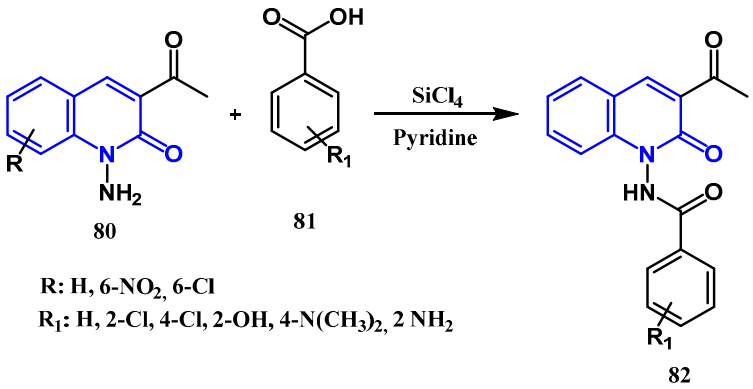
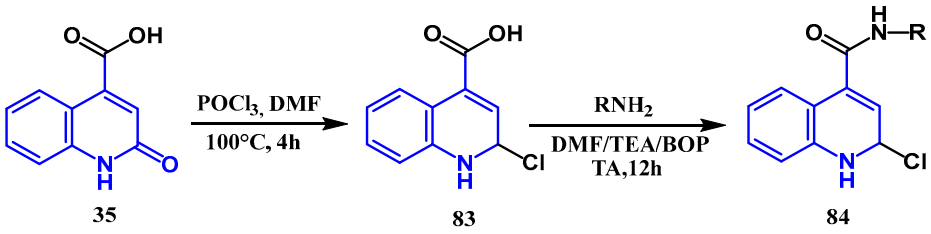
Otherwise, Kumar et al. reported an efficient synthetic route to access a library of substituted N-(3-acetyl-2-oxoquinoline-1(2H)-yl)benzamides **82** by coupling 3-acetyl-1-aminoquinoline-2-one **80** with various benzoic acids **81** under reflux conditions using pyridine and silicon tetrachloride. These compounds were prepared to investigate their therapeutic potential and structure-activity correlations (Scheme 26) [65] .



Scheme 26. Synthesis of N-(3-acetyl-2-oxoquinolin-1(2H)-yl)benzamide derivatives.

Shivaraj and colleagues [66] synthesized and evaluated the in vitro antibacterial activity of a series of 2-chloroquinolin-4-carboxamides **84** against Escherichia coli and Staphylococcus aureus (Scheme 27). The results indicate that the majority of the prepared compounds exhibited activity against the tested microorganisms when evaluated on a milligram scale.



Scheme 27. synthesis of 2-chloroquinolin-4-carboxamides and -6-carboxamides.

Kumar Suthar and his team [67] introduced additional substitutions to increase the biological activity of these backbones. They synthesized a library of thirty-one quinolone-thiazolidinone hybrids **86** and evaluated them for their ability to depict cancer and inflammation. The hybrids **86** were obtained through a one-pot reaction sequence involving the addition of dicyclohexylcarbodiimide in the presence of various aldehydes and thioglycolic acid (Scheme 28).

Scheme 28. Synthesis of hybrid compounds of quinolone and thiazolidinone.

In a recent publication, Ibrahim et al. [68] described the synthesis of a variety of bioactive molecules [69–73]. They attempted to prepare a series of methyl salts of dipeptides bearing amino acids conjugated to quinoline nucleosides at position 4. The reaction sequence depended on the regioselective silylation of quinolines **35** and **87** [74] with protected ribose tosylate **88** in dry DMF in the presence of NaH. Using a slightly modified technique, this resulted in the synthesis of methyl 5-

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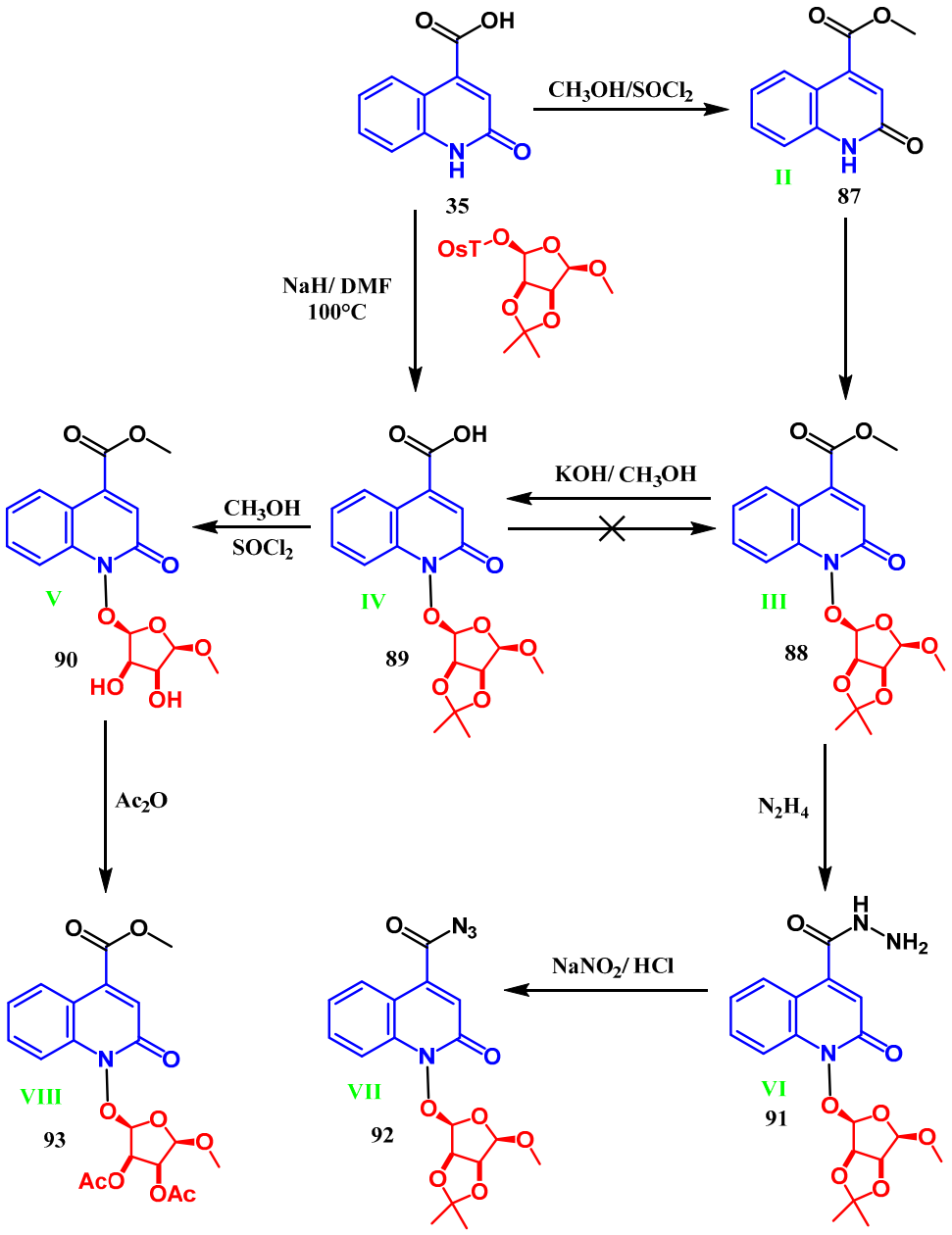
deoxy-2,3-O-isopropylidene-D-ribofuranosyl-5-yl)-2-oxo-1,2-dihydroquinoline-4-carboxylate **89** and acid **90** in 80-90% yields [75,76].The structure of the nucleoside was chemically validated by hydrolysis with alcoholic potash from ester **89**. Furthermore, ester **90** was esterified using thionyl chloride in 100% methanol to gave fully deprotected nucleoside **93** in a yield of 60%.

Furthermore, compound **92** was obtained by heating ester **89**, under the influence of hydrazine hydrate in ethyl alcohol; ester **89** was subjected to a reaction which resulted in the formation of hydrazide **91**. This hydrazide **91** was then converted to the azide **92** by treatment with $NaNO_2$ and HCl (Scheme 29).



Scheme 29. synthesis of various bioactive molecules.

3.2. Esterification

Esterification is one of the most important fundamental chemical reactions involving the formation of esters by the reaction of alcohol with a carboxylic acid. Thus, this process is very important in organic chemistry and applicable directly to food, cosmetic, and pharmaceutical industries. The esterification of quinolone derivatives, especially ciprofloxacin, is reported in the literature with different methods and biological activity relationships [77].

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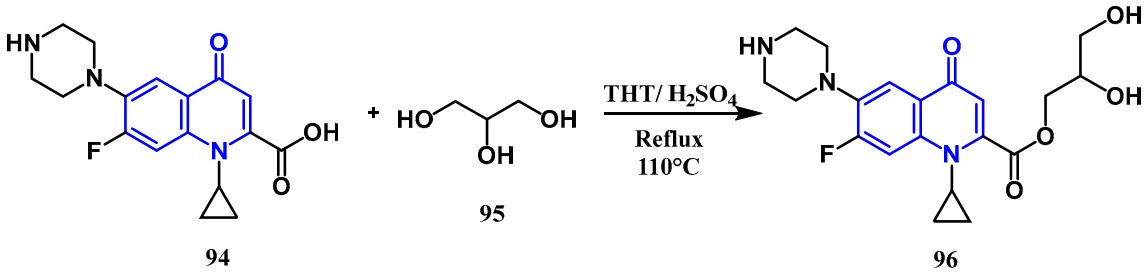
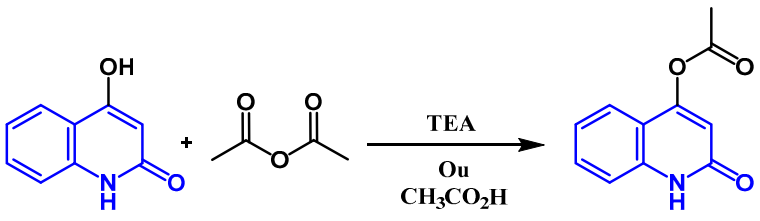
Among the factors influencing the increasing resistance of some microbes to antibiotics, their irrational use should be highlighted. Therefore, the design and study of heterocyclic compounds with various biological activities become highly important. The antimicrobial agent ciprofloxacin **94** was the subject of recent studies by Alasadi et al., who reported the preparation of novel esterification products of ciprofloxacin **96** by reacting ciprofloxacin **94** with glycerol **95** in the presence of sulfuric acid as a refluxing Brønsted-Lowry acid [78] (Scheme 30).



94 95 96

Scheme 30. esterification of ciprofloxacin.

Selig and Bach were the first to report that acetoxy-quinolones **98** have antiplatelet activity. This process is accomplished by the activation of platelet Nitric Oxide Synthase (NOS) through CRTAase, which results in acetylation. This acetylation then leads to the inhibition of platelet aggregation that is dependent on ADP/Arachidonic acid (AA). The researchers discovered that the selectivity of platelet CRTAase towards various acetoxy quinolone analogues **98**, as well as the resulting levels of intracellular NO, played a critical role in inhibiting platelet aggregation. Among the acetoxy-quinolones **98** studied, 2-oxo-1,2-dihydroquinolin-4-yl acetate was found to be the most efficient substance for platelet CRTAase. It exhibited the best antiplatelet activity in both in vitro and in vivo experiments. The target molecule was synthesized by the esterification reaction of 4-hydroxy-2(1H)-quinolone **30** with acetic anhydride **97** in a basic solution containing triethylamine. Under acidic conditions, the reaction with acetic acid produced 4-acetoxyquinolin-2-one **98** in a good yield (Scheme 31) [79,80].



30 97 98

Scheme 31. Synthesis of 2-oxo-1,2-dihydroquinolin-4-yl acetate.

The SARS CoV 3CL^{pro} is a very promising target for the development of therapeutic agents against SARS. In this direction, Y. Sun et al. reported the synthesis of the 2-oxo-1,2-dihydroquinolin-4-yl acetate derivatives **100** from the acyl chloride derivatives **99** reacting with 4-hydroxy- 2-quinolone **30** in the presence of pyridine as solvent at room temperture (Scheme 32) [79].

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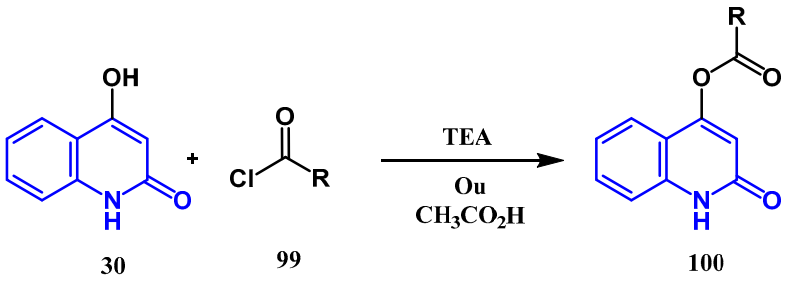
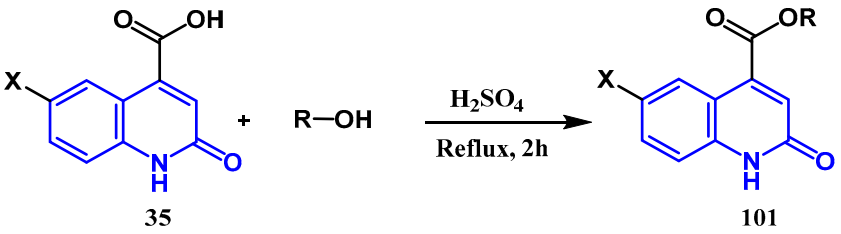


30 99 100

Scheme 32. Synthesis of 2-oxo-1,2-dihydroquinolin-4-yl acetate derivatives.

In the other, to protect the acid function and alkylate the NH site of 2-quinolone, A. El-mrabet et al. [81] esterified 2-oxo-1,2-dihydroquinoline carboxylic acid **35** in ethanol using sulfuric acid as a catalyst for 2h at reflux (Scheme 33).



35 101

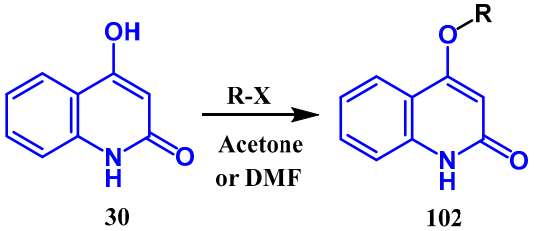
X= H; Br; Cl

Scheme 33. Esterification of 2-oxo-1,2-dihydroquinoline carboxylic acid derivatives.

3.3. N-, O- and C-Alkylation

Alkylation is one of the most important reactions in the synthesis of new quinolone derivatives. The substitutions at the N and O positions vary from substituent to substituent, but after optimization of the reaction conditions, i.e. temperature, base, and alkylating agent—selectivity and higher yields could be achieved. New methods, such as microwave irradiation, are far ahead of classical heating methods.

Xian-Qing Deng and his colleagues [82] have reported the synthesis of various 2-quinoline alkylation products. The starting product, 4-hydroxyquinoline-2(1H) **30,** was reacted with the appropriate alkyl halide or benzyl chloride to give 4-alkoxyquinolinones **102** in DMF or acetone, with stirring (Scheme 34).



30 102

R: -CH_3; -C_2H_5; n-C_3H_7; n-C_4H_9; n-C_5H_{11}; -$CH_2C_6H_5$;

Scheme 34. Alkylation of 4-hydroxyquinolin-2-one.

According to Morel et al. [83], the reaction of 4-hydroxy-2-quinolones **30** with alkyl iodides, benzyl bromides, and allyl bromides in benzene at room temperature, using Ag_2CO_3 as a catalyst, 2,4-dialkoxyquinolines **103** are produced with moderate to excellent yields. This method exhibits a

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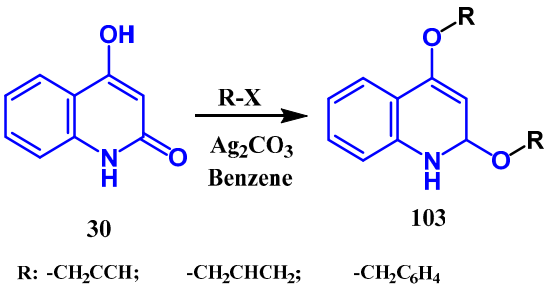
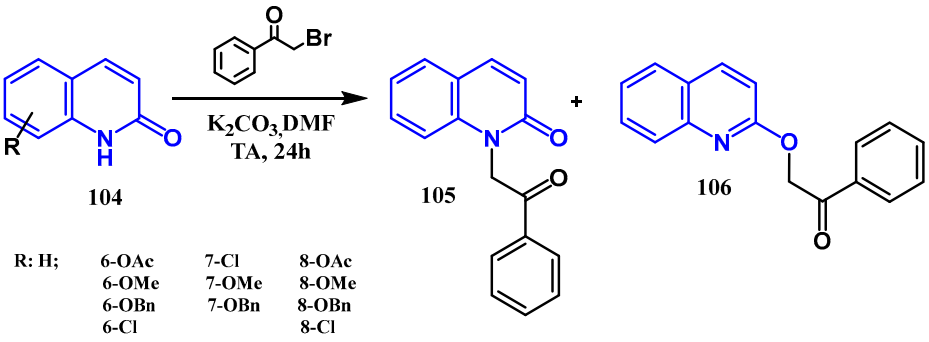
high degree of regioselectivity and provides a novel and gentle one-pot strategy for synthesizing this particular class of compounds (Scheme 35).



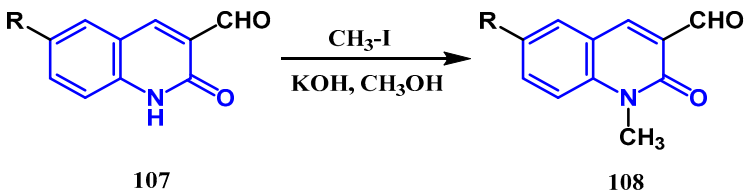
Scheme 35. 4-hydroxy-2-quinolone derivatives synthesis.

In addition, Chen et al. [84] successfully carried out the targeted alkylation of substituted quinoline-2(1H)-one derivatives **104**. They demonstrated the alkylation of relatively large 8-methoxy, 8-benzyloxy, and 8-chloroquinoline-2(1H)-ones **104** using 2-bromoacetophenone, DMF, and K_2CO_3 under standard conditions. The selectivity observed in this case does not apply to the substituted C(6) and C(7) homologues of quinoline-2(1H)-one. In these compounds, alkylation takes place at both the N1 and O2 positions, with the N1-alkylated product being the major one. Thus, the process of introducing alkyl groups into substituted quinoline-2(1H)-ones **104** was primarily affected by the size and shape of the substituents rather than their electronic properties (Scheme 36).



Scheme 36. O and N-Alkylation of quinolin-2(1H)-one.

Recently, Grzelakowska et al. [85] synthesized new compounds derived from 3-formyl-2(1H)-quinolones **107** and N-methyl-3-formyl-2-quinolones **108**, through attaching a methyl or methoxy group at the 6-position of both compound. The resulting compounds were evaluated for their activity as chemosensors for detecting thiol-containing amino acids. The spectroscopic properties of the samples were analyzed, which included studying their absorption and emission spectra, fluorescence quantum yields, and singlet lifetimes. The behavior of the compounds was studied at pH 7.4 in the presence of amino acids. The findings demonstrated that these compounds exhibited a notable decrease in fluorescence and a strong preference for L-cysteine over other amino acids, indicating their potential as L-cysteine sensors (Scheme 37).



Scheme 37. Synthesis of N-methyl-3-formyl-2-quinolones derivatives.

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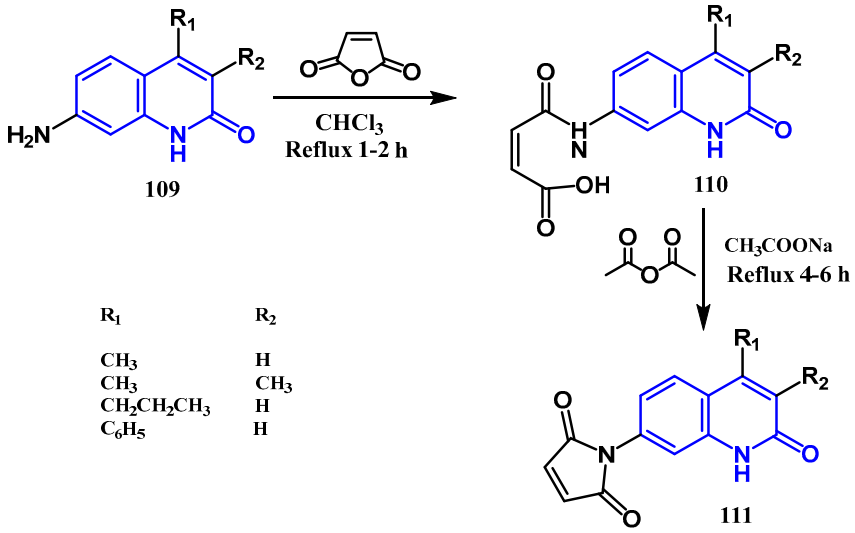
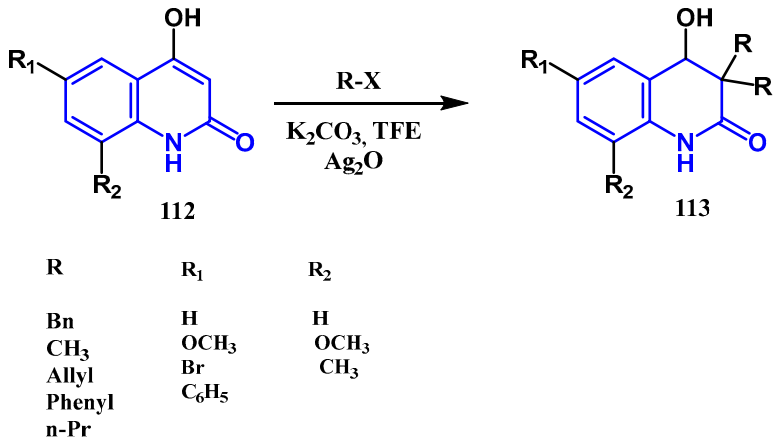
The same authors [86] synthesized and characterized new compounds derived from the 2(1H)-quinolone structure. The samples were subjected to studies of spectroscopic properties, including their absorption and emission spectra evaluation, as well as fluorescence quantum yield determination. The maleimide derivatives 7-maleimido-4-methyl-2(1H)-quinolone, 7-maleimido-3,4-dimethyl-2(1H)-quinolone, 7-maleimido-4-propyl-2(1H)-quinolone, and 7-maleimido-4-phenyl-2(1H)-quinolone **111** were investigated as potential sensors for the determination of sulfhydryl amino acid groups. Newly prepared compounds **111** showed a large fluorescence enhancement with prominent selectivity to L-cysteine over other amino acids and metal cations (Scheme 38).



Scheme 38. Synthesis of 1-(2-oxo-1,2-dihydroquinolin-7-yl)-1H-pyrrole-2,5-dione derivatives.

Selevero et al. [87] used 2,2,2-trifluoroethanol as a solvent for the highly effective and simple preparation of symmetrical 3,3-disubstituted quinoline-2,4-diones **113**. This method is based on the reaction of 4-hydroxy-2-quinolones **112** with electrophiles such as methyl iodide, benzyl bromides, allyl bromides, phenyl iodide, and isopropyl iodide in the presence of K_2CO_3. Ag_2O enhances the efficiency of the methylation reactions. The developed method proceeds with very good yields and excellent regioselectivity (Scheme 39).



Scheme 39. The alkylation at the C3 position of 4-hydroxyquinoline-2,4-diones derivatives.

Refouvelet et al. [88] prepared aromatic coumarins and aromatic α-quinolones **115** through the Knovenagel condensation of 2,4-quinolinediol **30** with benzaldehyde **114** in pyridine. The formed compounds were provided in only one diastereoisomeric (Z) form. These compounds **115** were

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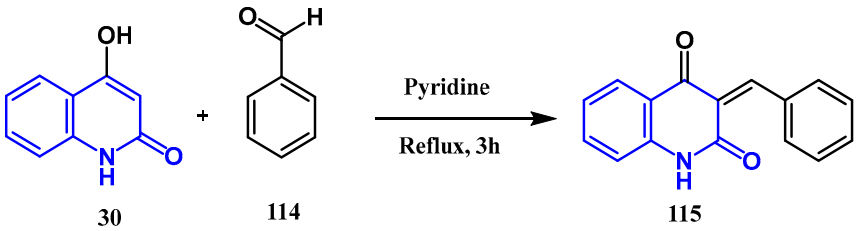
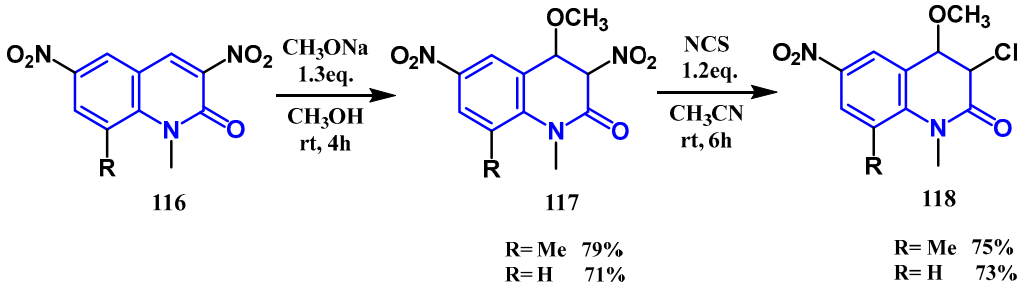
subsequently tested in vitro for their potential to protect human liver cells, represented by a human hepatoma cell line, HepG2, and primary human hepatocytes, against oxidative insults exerted by t-BHP. Their work demonstrated that the protective efficacy of such compounds against t-BHP-induced decrease in cell viability decline depended on the presence of a benzylidene group at the 3-position or a heterocycle containing nitrogen and sulfur atoms on the benzopyrone or quinolone system. Furthermore, it was found that the presence of a methoxy group on the aromatic ring systems reduced the protective ability (Scheme 40).



Scheme 40. Synthesis of aromatic coumarins and aromatic α-quinolones.

3.4. Halogenation

However, Hao et al. evaluated the potential for vicinal functionalization using 1-methyl-3,6-dinitroquinolin-2(1H)-one **116** as a model substrate. Upon treatment of 1-methyl-3,6-dinitroquinolin-2(1H)-one **116** with sodium methoxide in methanol at ambient temperature, the solution promptly exhibited a reddish-yellow color, and a yellow solid precipitated from the reaction mixture. Then chlorination of the product formed **117** by NCS in acetonitrile leads to the formation of 3-chloro-4-methoxy-1-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one **118** (Scheme 41) [89].



Scheme 41. Synthesis of 3-chloro-4-methoxy-1-methyl-6-nitro-3,4-dihydroquinolin-2(1H)-one derivatives.

3.5. Thionation

Tetraphosphorus decasulfide (P_4S_{10}) **120** is commonly used as a thionating agent in pyridine. The thionating capabilities of this reagent have been investigated and extended to include solvents such as acetonitrile and pyridine. In these solvents, the reagent has shown considerable utility in synthesis and remarkable selectivity. The properties of this substance have been compared to those of the well known Lawesson reagent (LR).

Bergman et al. [90] described the method of thionation of 3-hydroxy-2-quinolone **119** using tetraphosphorus decasulfide (P_4S_{10}) **120**. The compound 2-phenylquinoline-4(1H)-thione **121** was produced through the reaction of 2-phenylquinoline-4(1H)-one **119** with P_4S_{10} **120** in the presence of pyridine. The reaction was carried out under reflux conditions using dimethyl sulfone as the solvent for a duration of 2 hours. The reaction afforded 2-phenylquinoline-4(1H)-thione **121** in a favorable yield of 77%, exhibiting a melting point range of 192-194°C (Scheme 42).

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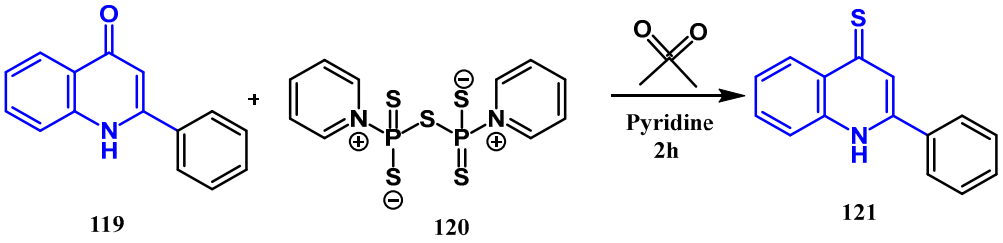
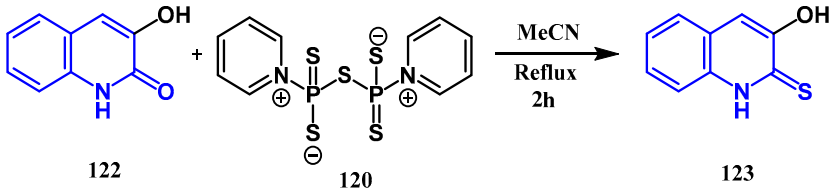


119 120 121

Scheme 42. Synthesis of 2-phenylquinoline-4(1H)-thione.

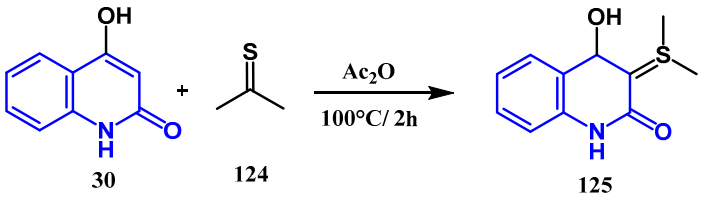
The same authors carried out the thionation reaction of 3-hydroxy-2-quinolone **122** using tetraphosphorus decasulfide (P_4S_{10}) **120** in acetonitrile. This reaction synthesized 3-hydroxyquinoline-2(1H)-thione **123** with a yield of 93%, which is higher than that of the previous reaction. The product had a melting temperature of 306-308°C (Scheme 43).



122 120 123

Scheme 43. Synthesis of 3-hydroxyquinoline-2(1H)-thione.

Researchers have been highly interested in derivatives of thioquinolines, which has resulted in the development of several methods for thionation of this compound class. An example of a method entails the synthesis of 3-(dimethylsulfaneylidenes)-4-hydroxy-3,4-dihydroquinolin-2(1H)-one **125**. The synthesis is accomplished by combining 4-hydroxy-2-quinolones **30** with dimethyl sulfoxide **124** and using acetic anhydride as the solvent at a temperature of 100°C for a duration of 2 hours (Scheme 44) [97].



30 124 125

Scheme 44. Synthesis of 3-(dimethyl-sulfaneylidene)-4-hydroxy-3,4-dihydroquinolin-2(1H)-one.

3.6. Hydrolyse and Decarboxylation

Furthermore, Ukrainets et al. (2006) reported that the ethyl esters of 4-halo-substituted 2-oxo-1,2-dihydroquinoline-3-carboxylic acids are formed when 3-ethoxycarbonyl-4-morpholino-2-oxo-1,2-dihydroquinoline **126** is treated with aqueous solutions of hydrohalogenic acids for a short time. Upon longer boiling, it was found that hydrolysis in HF leads exclusively to the formation of the 4-hydroxy2-quinolones **30** derivatives (Scheme 45) [92].

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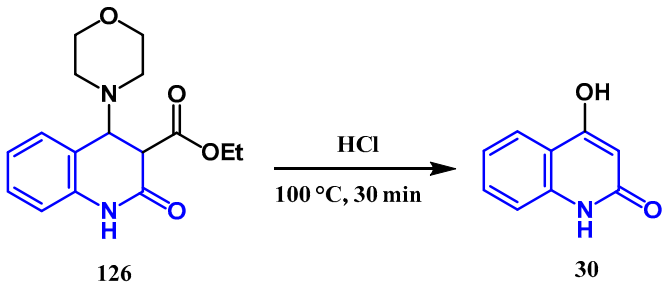
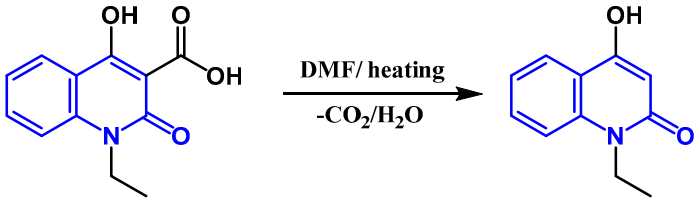


126 30

Scheme 45. Hydrolysis of ethyl 4-morpholino-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate.

In addition, the same authors studied the decarboxylation and hydration of 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **127** in DMF at high temperatures, resulting in the formation of N-ethyl 4-hydroxy-1H-quinoline-2-one **128**. The structures of these compounds, obtained in crystal form, were confirmed by X-ray analysis (Scheme 46) [93].

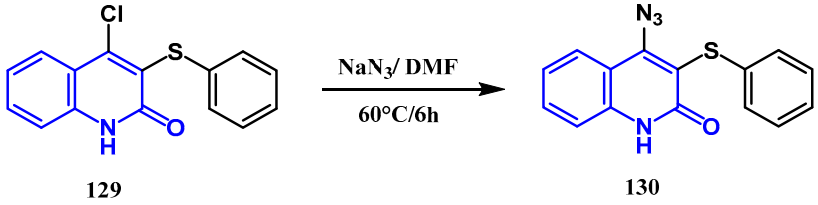


127 128

Scheme 46. Synthesis of 1-ethyl-4-hydroxyquinolin-2(1H)-one.

3.7. Azidation

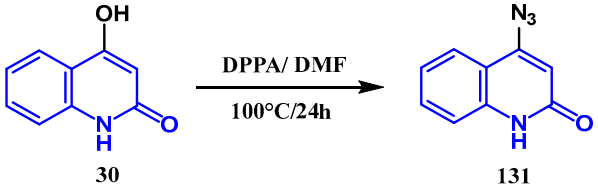
Täubl et al. have described the nucleophilic substitution of chlorine in 4-chloro-1-methyl-3-phenylsulfanyl-2-quinolone **129** using the azide anion. This was carried out with sodium azide in dimethylformamide at a temperature of 60°C, giving an almost quantitative yield of the product (Scheme 47) [94].



129 130

Scheme 47. Nucleophilic substitution of 4-chloro-1-methyl-3-phenylsulfanyl-2-quinolone.

Aizikovich et al. [95] describe the conversion of the hydroxy group in 2-quinolone **30** to a 4-azido-2-quinolone **131**, which is subsequently converted to 4-amino derivatives with moderate yields. This conversion is accomplished through a novel, concise, and convenient process employing diphenylphosphoryl azide (DPPA) as the reagent. A proposed mechanism for this innovative application of DPPA is derived from the identification of certain intermediates (Scheme 48).



30 131

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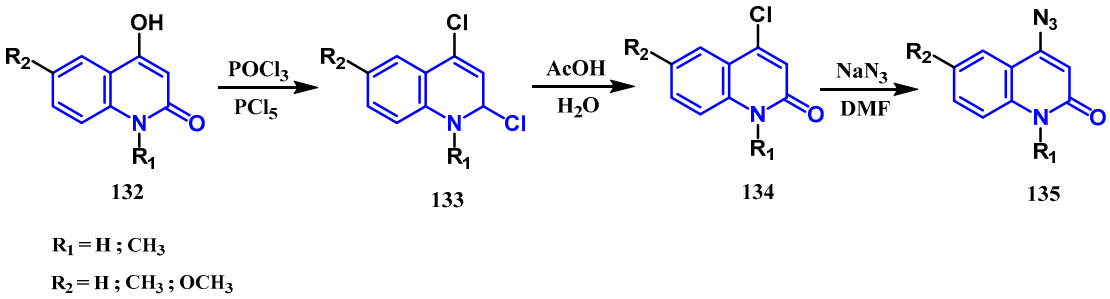
Scheme 48. Synthesis of 4-azidoquinolin-2(1H)-one.

4-Azido-2-quinolone derivatives **135** were synthesized in several steps from 4-hydroxy-2-quinolone **132** by Alshammari et al. [96]. First of all, 4-hydroxy-2-quinolone **132** was treated with phosphoryl chloride to form the corresponding intermediate compound. The hydrolysis of the latter gave 4-chloro-2-quinolone **134**, which was then treated with sodium azide in DMF. This afforded the desired 4-azido-2-quinolone derivatives **135** (Scheme 49).



132 **133** **134** **135**

$R_1 = H ; CH_3$

$R_2 = H ; CH_3 ; OCH_3$

Scheme 49. Synthesis of 4-azido-2-quinolone derivatives.

3.8. Cycloaddition

3.8.1. Preparation of Triazoles-Quinolone:

Quinoline molecules are frequently present in living organisms as important secondary metabolites [97], while 1,2,3-triazoles, which are chemically unreactive compounds, have not been observed in naturally occurring substances [98]. The combination of quinoline and 1,2,3-triazole skeletons through various methods can produce important biomolecules that are useful for the development of drugs. Moreover, 1,2,3-triazole has the ability to function as pharmacophores and linkers connecting quinoline with other pharmacophoric molecules, which makes them particularly interesting in molecular hybridization strategies [99].

Scientists are motivated to synthesize uniform and diverse ring compounds in order to develop treatments for a wide variety of diseases [100]. 2-quinolones represent an interesting class of compounds due to their greater pharmacological importance and diverse biological activity [101,102]. 1,2,3-triazoles are an important class of compounds containing a wide range of biological activities such as antibacterial, anti-tubercular, anticancer, antifungal, and anti-HIV activities [99,103]. The development of the copper-catalyzed [3 + 2] cycloaddition of organic azides with terminal alkynes under mild conditions has significantly increased the value and applications of 1,2,3-triazole compounds [104,105]. One of the most representative examples of click chemistry is the regioselective preparation of 1,2,3-triazoles, which has recently been used extensively in almost all fields of chemistry [106–108]. The Cu-catalyzed [3 + 2] cycloadditions of azides and alkynes, commonly referred to as the Meldal-Sharpless 'click' reaction, is one of the most widely used methods for the generation of 1,2,3-triazoles. Indeed, this reaction provides a wide functional range for biomolecules. Cycloaddition, which is used in molecular hybridization strategies for heterocyclic compounds, is a chemical cyclization reaction in which two or more unsaturated molecules or fragments of the same molecule join to form a cyclic structure. It reduces the number of bonds between atoms and therefore facilitates the formation of new heterocyclic compounds. Click chemistry is used in the synthesis of 8-((1-(anthracen-9-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-hydroxyquinoline-2-carbaldehyde **140**. The widely applied synthetic methodology in bioconjugation, drug design, and materials chemistry has been click chemistry through the coupling of terminal alkynes with organic azides via a 1,3-dipolar cycloaddition process, which afforded 1,2,3-triazoles.

Additionally, the 1,2,3-triazole linker has the potential to be utilized for the attachment of cations, which could be advantageous for the identification of metal ions. According to this method, the probe is 8-((1-(anthracen-9-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-hydroxyquinoline-2-

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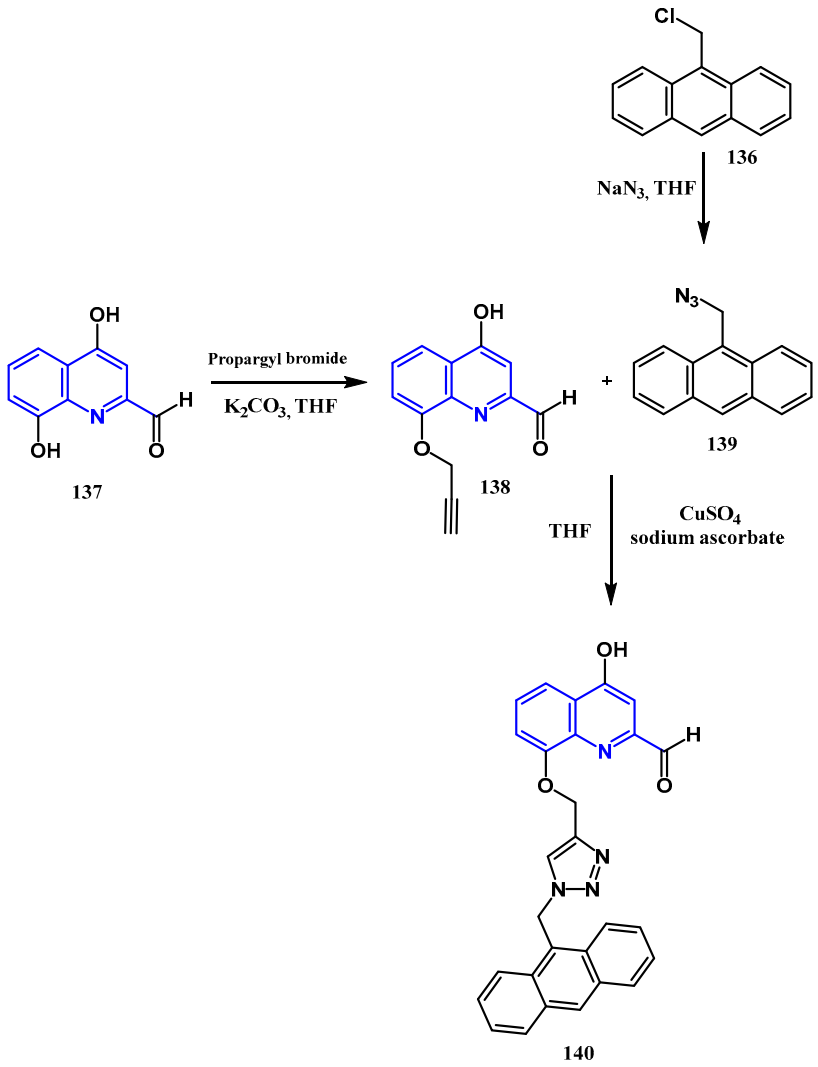
carbaldehyde **140** can be achieved by reacting anthracene azide **139** with the alkyne of 8-oxyquinoline **138** in the presence of CuSO4 as a catalyst (Scheme 50) [109].



Scheme 50. Synthesis of 8-((1-(anthracen-9-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)-4-hydroxyquinoline-2-carbaldehyde.

In this study, El-Sheref et al. described the synthesis of novel classes of 1,2,3-triazoles derived from 2-quinolone via Cu-catalyzed [3+2] cycloadditions (Meldal-Sharpless 'click' reactions). The reactions included the treatment of 4-azidoquinolin-2(1H)-ones **141** with various alkynes such as ethyl propiolate **142** and 1-(4-(prop-2-yn-1-yloxy)phenyl)ethan-1-one derivatives **144**. These reactions were performed in the presence of sodium ascorbate, which reduced Cu(II) to Cu(I), and DMF was used as the solvent. The reactions were carried out for a duration of 12 hours at temperatures that varying from 30 to 50°C (Scheme 51) [110].

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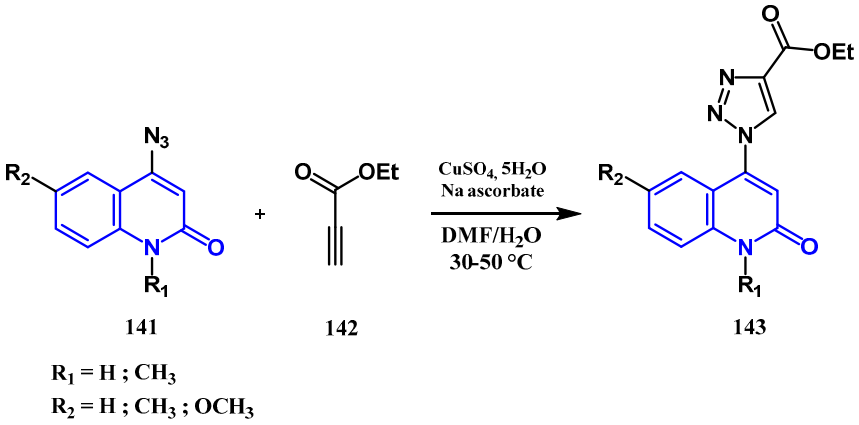
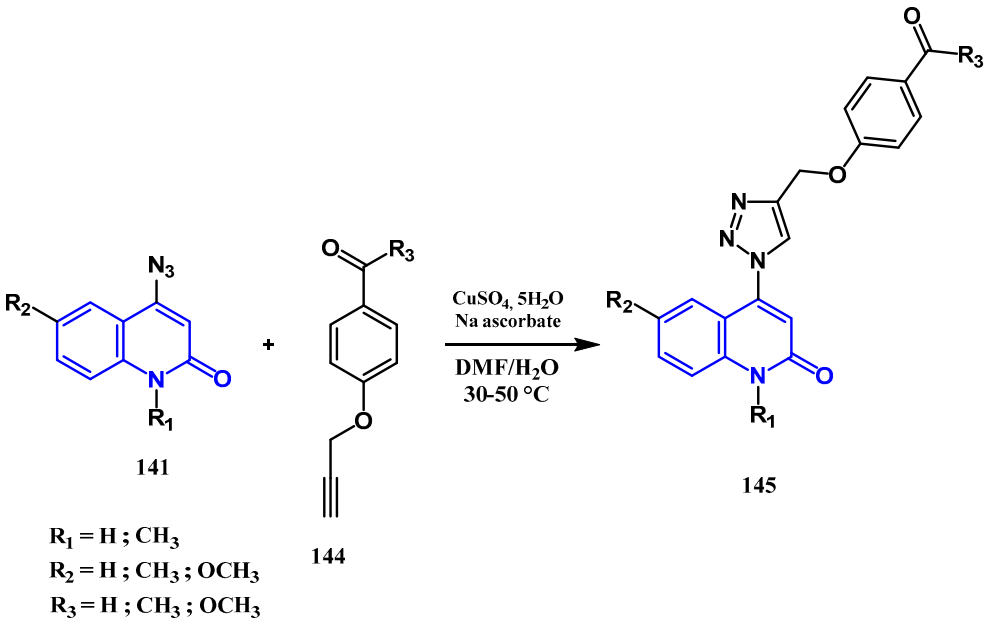


141 142 143

R_1 = H ; CH_3
R_2 = H ; CH_3 ; OCH_3

Scheme 51. Synthesis of ethyl 1-(2-oxo-1,2-dihydroquinolin-4-yl)-1H-1,2,3-triazole-4-carboxylate derivatives.



141 144 145

R_1 = H ; CH_3
R_2 = H ; CH_3 ; OCH_3
R_3 = H ; CH_3 ; OCH_3

Scheme 52. Synthesis of 4-(4-((4-acetylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one derivatives.

On the other hand, El-Sheref E. M. et al. [111] reported the synthesis of a new hybrid molecule from the previously synthesized triazole ring with 1,8-bis(prop-2-yn-1-yloxy)naphthalene **147** through Cu(I)-catalyzed [3+2] cycloadditions. The hybrid product produced **148** in the anti-form acts as a fascinating precursor for functionalized inhibitors of the epidermal growth factor receptor (EGFR) with the potential to inhibit cell proliferation and induce apoptosis. The synthesized compound demonstrated potent antiproliferative activity against four cancer cell lines, with average GI50 values ranging from 34 nM to 134 nM (Scheme 53).

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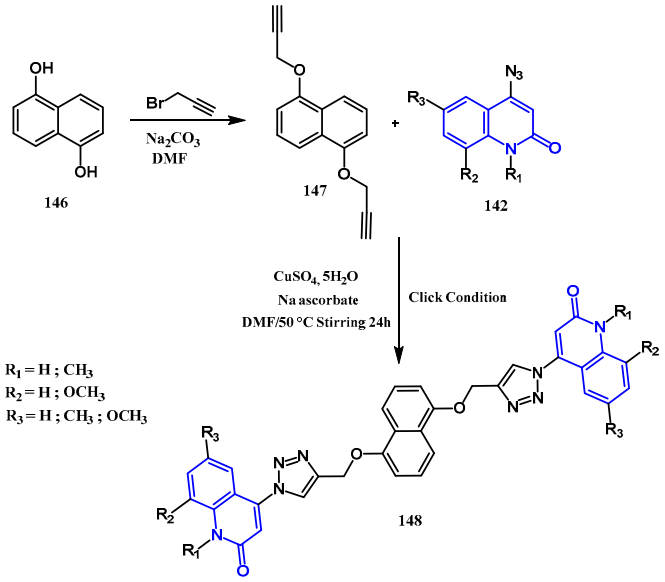
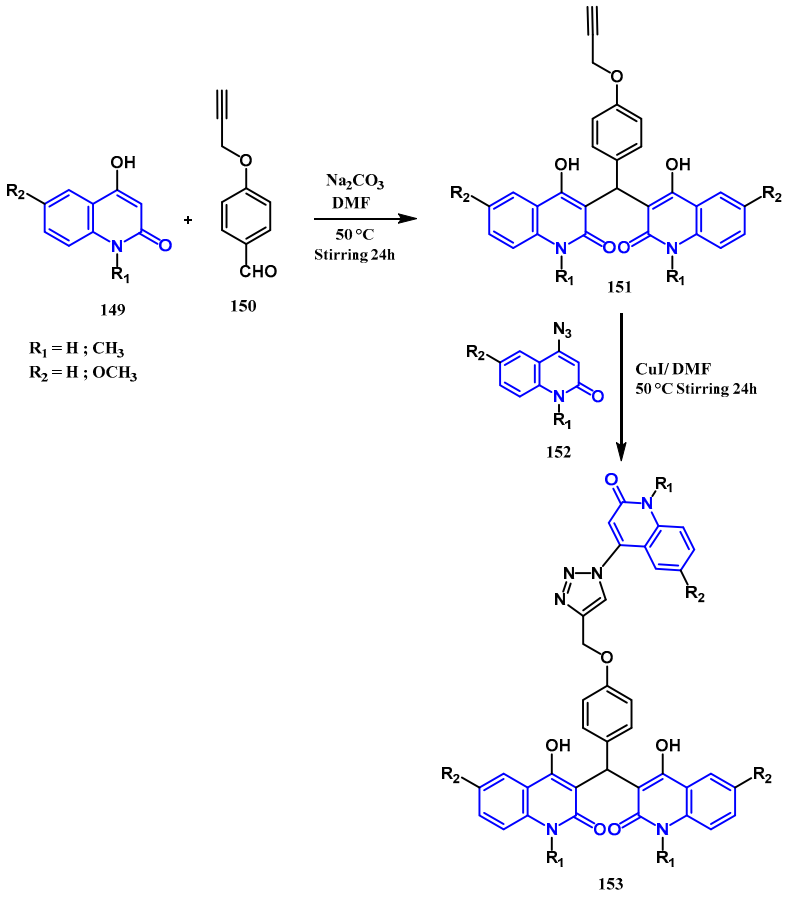


Scheme 53. Synthesis of a new hybrid molecule.

The same authors, M. El-Sheref et al. [112], developed an effective and adaptable technique that utilizes Cu-catalyzed [3+2] cycloaddition (Huisgen-Meldal-Sharpless reaction) for coupling 3,3'-((4-(prop-2-yn-1-yloxy)phenyl)methylene)bis(4-hydroxyquinoline-2(1H)-ones) **151** with 4-azido-2-quinolone derivatives **152**. This process produces products **153** with high yields. This approach facilitated the joining of three quinolone molecules using a triazole linker. The resulting products are valuable precursors because of their potential to inhibit cell proliferation (Scheme 54).



Scheme 54. Cu-catalyzed [3+2] cycloaddition.

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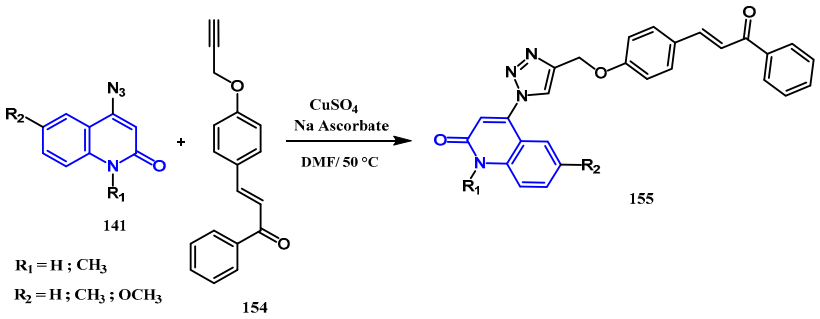
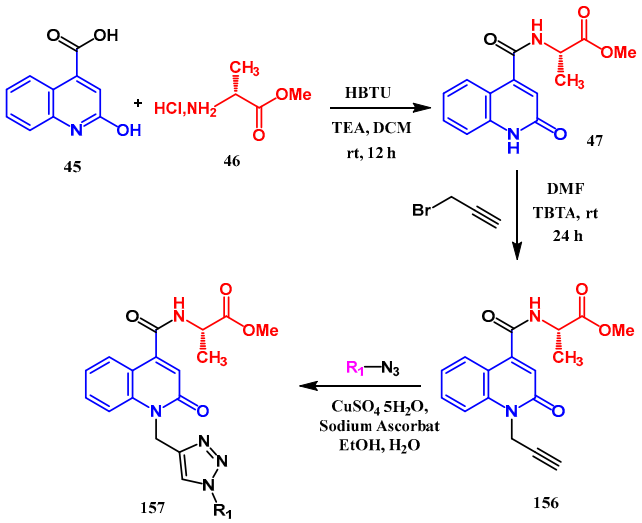
In a recent study, M. Alshammari et al. [96] synthesized (E)-4-(4-((4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one **155** through the reaction of 4-azido-2-quinolone derivatives 141 with 1-phenyl-3-(4-propargyloxyphenyl)prop-2-en-1-one **154** in the click condition. The desired hybrids were synthesized with excellent yields using a copper (I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC).

The synthetic sequence initiated with the preparation of 4-hydroxy-2-quinolone, which was subsequently treated with phosphoryl chloride to yield an intermediate compound. In the next step, the compound was subjected to hydrolysis. Finally, treatment of the 4-chloro-2-quinolone with sodium azide in DMF yielded the formation of 4-azido-2-quinolone derivatives **141** (Scheme 55).



Scheme 55. Synthesis of (E)-4-(4-((4-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one.

As microbial inhibitors, Moussaoui et al. **[8]** described in detail the synthesis of a variety of 2-quinolone-4-carboxamide derivatives **18**. Under appropriate conditions, protected L-alaninate **46** is coupled with 2-oxo-quinoline-4-carboxylic acid **45** using triethylamine (TEA) as the base and DCM as the solvent. The resulting chemical was then subjected to N-alkylation using propargyl bromide. The desired products, methyl (1-((1H-1,2,3-triazol-4-yl)methyl)-2-oxo-1,2-dihydroquinoline-4-carbonyl)-L-alaninate derivatives **157** (shown in Scheme 9), were then prepared by an azidation reaction using different azides (Scheme 56).



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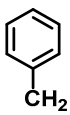
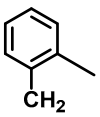
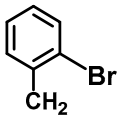
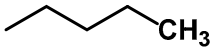
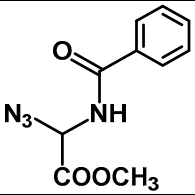
R1					

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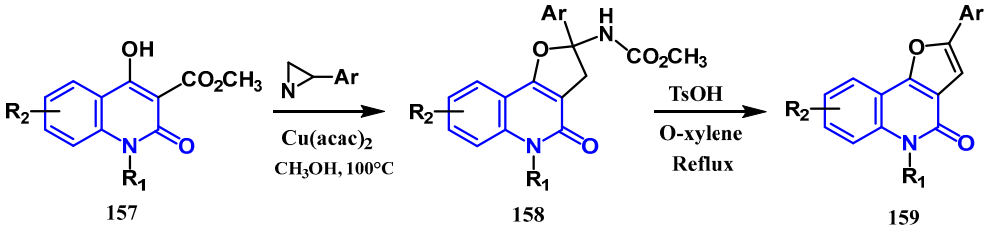
Scheme 56. Synthesis of 2-quinolone-4-carboxamide derivatives containing a triazole nucleus.

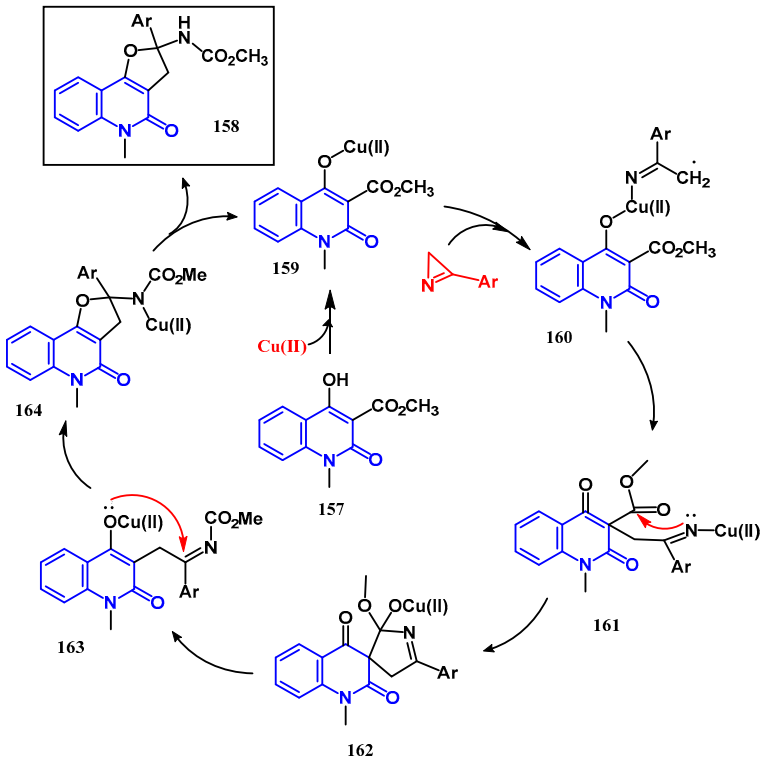
3.8.2. Preparation of Furanoquinolones and Pyranoquinolones

Furanoquinolones and pyranoquinolones are organic compounds that have a wide range of biological applications, making them of great interest. Sakharov et al. discovered a method for the furo-annulation of 4-hydroxy-2-oxoquinoline-3-carboxylates **158** using 3-arylazirines and Cu(acac)2 as a catalyst. This method combines various 2-phenylfuro[3,2-c]quinolin-4(5H)-one compounds. The reaction entails the cleavage of the azirine ring at the N–C2 bond, resulting in the formation of a dihydrofuran ring that includes two carbon atoms from the azirine. Additionally, the ester group undergoes a migration to the nitrogen atom. The efficacy of this approach ranges from 56% to 87% (Scheme 57) [113].



R_1 = H ; CH_3
R_2 = H ; 8-CH_3 ; 8-OCH_3 ; 7-Cl ; 8-Cl ; 7-NO_2
Ar = p-Tol ; Ph ; 4-$OCH_3C_4H_6$; 2-$OCH_3C_4H_6$; 4-ClC_4H_6 ; 4-$O_2NC_4H_6$; 3-BrC_4H_6

Scheme 57. Synthesis of 2-phenylfuro[3,2-c]quinolin-4(5H)-one derivatives.



Scheme 58. Plausible mechanism of Sakharov reaction.

Furthermore, Aly et al. reported a reaction in which 4-Hydroxy-quinoline-2-ones were combined with 2-[bis(methylthio)methylene]malononitrile **165** in the presence of DMF as a solvent and triethylamine (Et_3N). This reaction resulted in the formation of two distinct products. 3-

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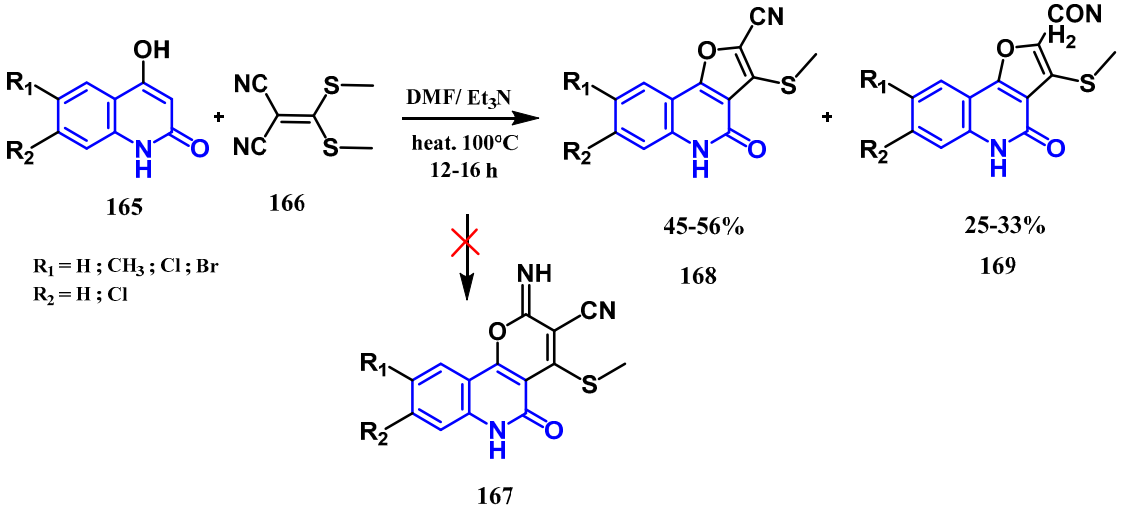
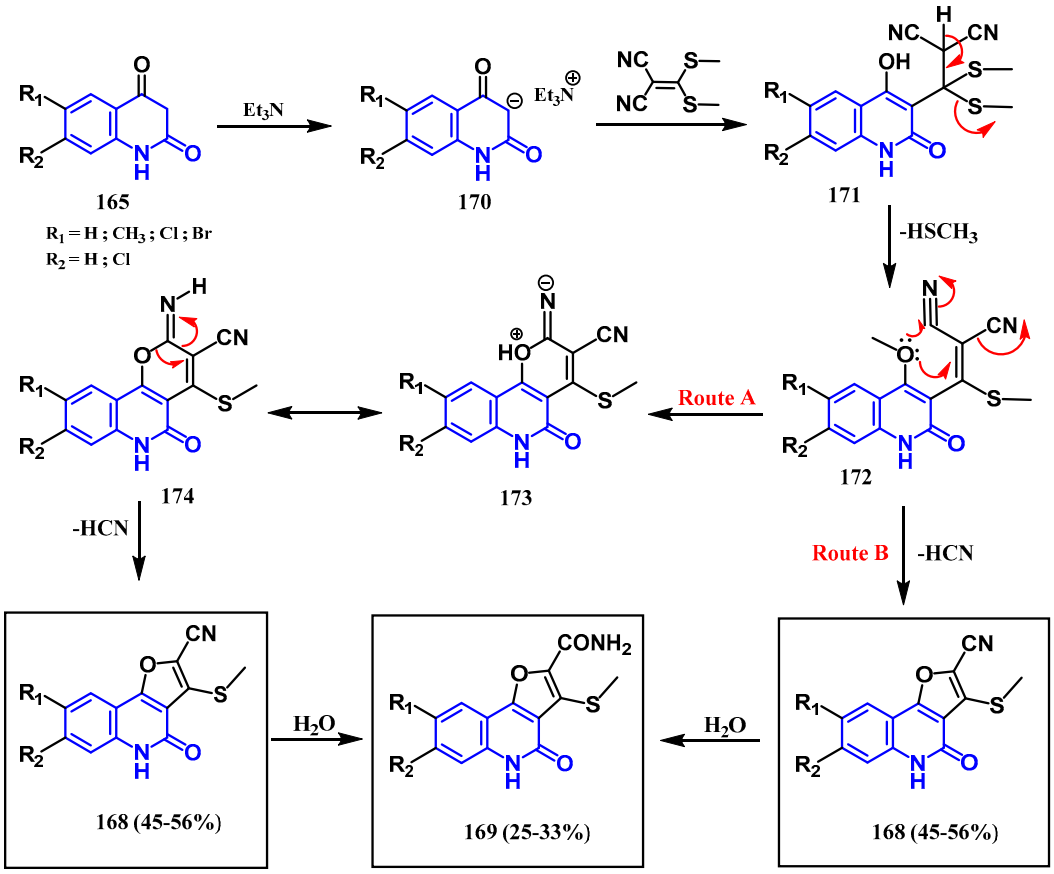
(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c] **168-169** . The predominant product obtained is quinolone-2-carbonitriles **168**, with yields ranging from 45% to 56%. Additionally, 3-(methylthio)-4-oxo-4,5-dihydrofuro[3,2-c] **169** was identified as a secondary product, albeit with lower yields ranging from 25% to 33% (Scheme 59) [114].



Scheme 59. Synthesis of furo[3,2-c]quinolin-4(5H)-one derivatives.

The mechanism proposed for the formation of the three compounds depicted in Scheme 60.



Scheme 60. Plausible mechanism of Aly reaction.

Pyrano[3,2-c]quinolone forms a class of scaffolds that present a wide range of important biological activities in nature. Haiting Y. et al. have reported the acid-catalyzed formal [3+3]/ [3+2]

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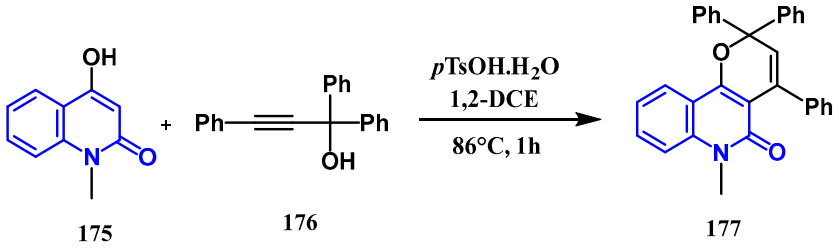
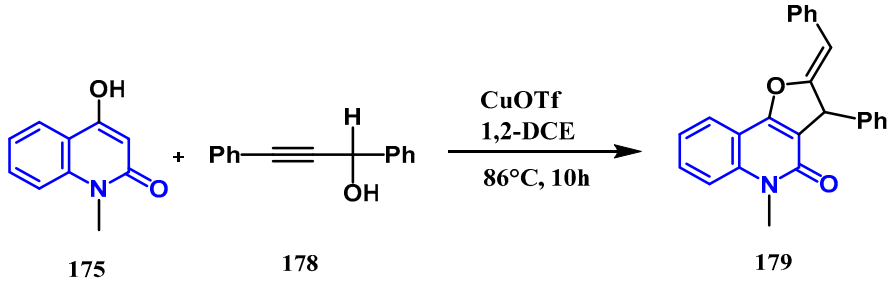
cascade annulation processes for the synthesis of pyrano[3,2-c]quinolone and furo[3,2-c]quinolone derivatives **177**. These processes utilize 4-hydroxy-1-methylquinoline-2(1H)-one **175** and propargylic alcohols **176** as starting materials [115,116].

In the initial reaction, 4-hydroxy-1-methyl-2-quinolone **175** was reacted with 1,1,3-triphenylprop-2-yn-1-ol in 1,2-dichlorethane (DCE) **176** with pTsOH·H_2O as a catalyst for 1 hour. This reaction yielded 6-methyl-2,2,4-triphenyl-2,6-dihydro-5H-pyrano[3,2-c]quinolin-5-one **177** with a 70% yield (Scheme 61).



Scheme 61. Synthesis of 6-methyl-2,2,4-triphenyl-2,6-dihydro-5H-pyrano[3,2-c]quinolin-5-one.

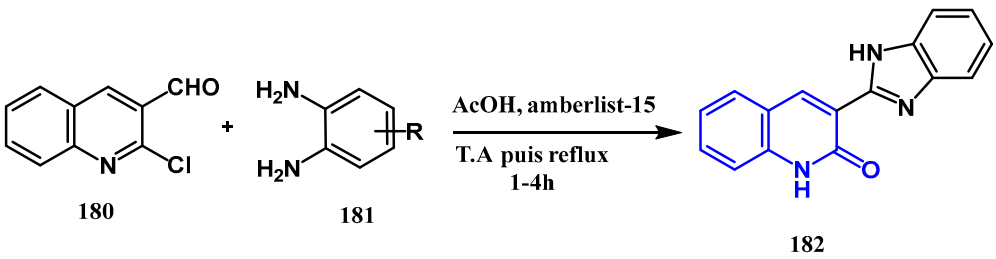
In the subsequent reaction, the same starting material **175** was reacted with 1,3-diphenylprop-2-yn-1-ol **178** and CuOTf, acting as a catalyst. The isolated product was identified as (Z)-2-benzylidene-5-methyl-3-phenyl-3,5-dihydrofuro[3,2-c]quinolin-4(2H)-one **179**, with a yield of 60% (Scheme 62) [117].



Scheme 62. Synthesis of (Z)-2-benzylidene-5-methyl-3-phenyl-3,5-dihydrofuro[3,2-c]quinolin-4(2H)-one.

3.8.3. Preparation of Imidazole Quinolones

Abonia and colleagues [118] presented a one-pot synthesis of hybrid compounds. The synthesis of 3-(1H-benzimidazol-2-yl)quinolin-2(1H)-ones **182** was achieved by the addition of variously substituted o-phenylenediamines **181** to 2-chloro-3-formylquinoline **180**. The reaction was carried out in a 70% aqueous acetic acid solution, with the use of Amberlyst-15 at a concentration of 20% w/w. The resulting hybrid compounds exhibited antitumor potential against various cancer cells (Scheme 63).



Scheme 63. Synthesis of a 2-quinolone with a benzimidazol ring.

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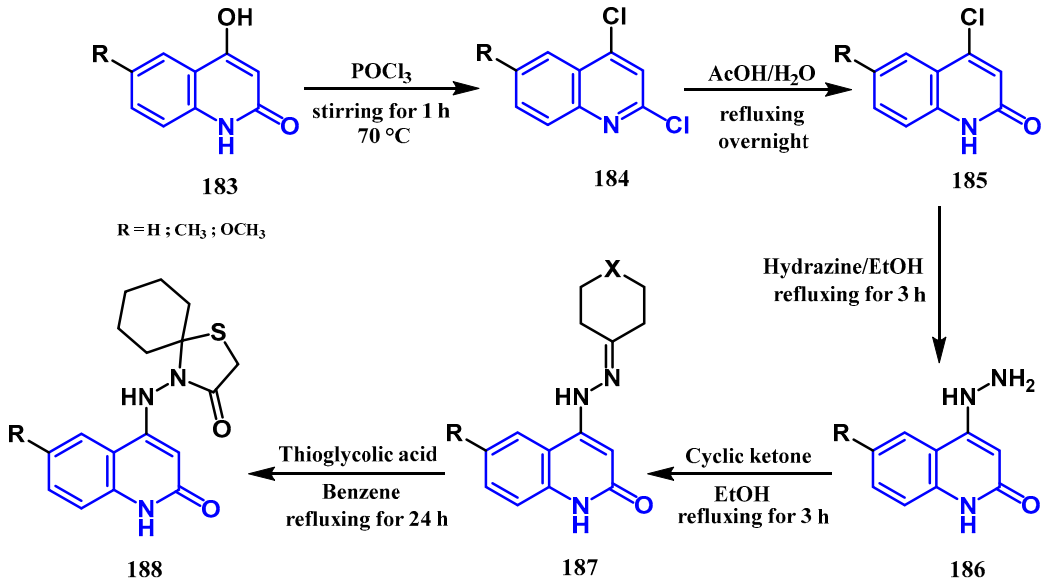
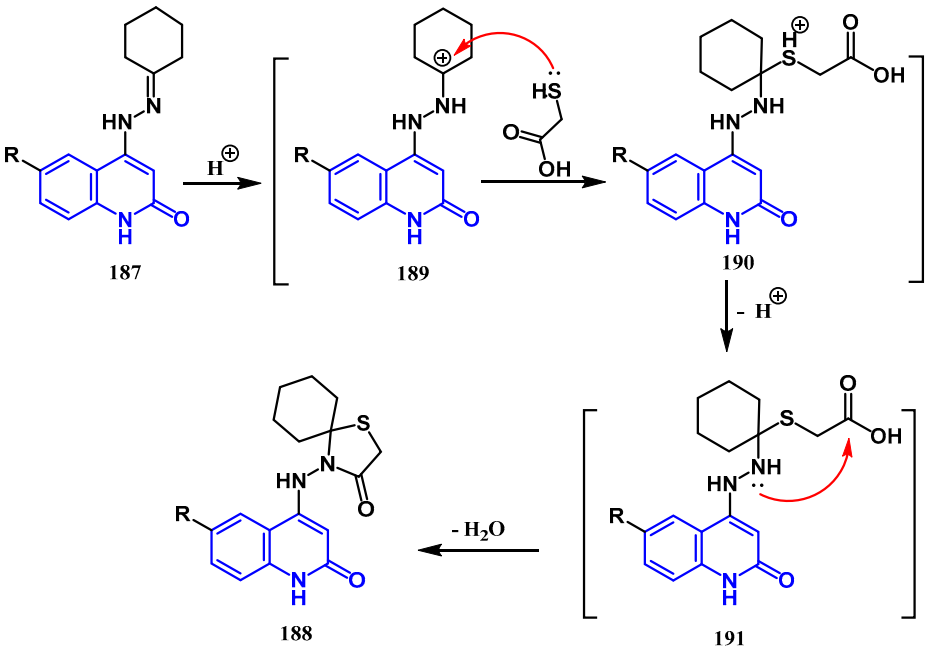
3.8.4. Preparation of Thiazolidin-4-One Quinolones:

H. Al-Wahaibi et al. described the synthesis of novel series of quinoline-2-one-based derivatives as potential apoptotic antiproliferative agents targeting the epidermal growth factor receptor (EGFR) inhibitory pathway. Specifically, 4-((quinolin-4-yl)amino)-thia-azaspiro[4.4/5]alkan-3-ones **188** were prepared via thioglycolic acid-catalyzed reactions between 4-(2-cyclodenehydrazinyl)quinolin-2(1H)-one **187** and thioglycolic acid. [119]. Compounds **187** and **188** exhibited potent EGFR inhibitory activity, with IC_{50} values of 0.18 and 0.09 µM, respectively. Additionally, these compounds markedly increased apoptotic markers (caspase-3, caspase-8, and Bax) while reducing anti-apoptotic BCl2 levels (Scheme 64).



Scheme 64. Synthesis of 4-((2-oxo-1,2-dihydroquinolin-4-yl)amino)-1-thia-4-azaspiro[4.5]decan-3-one.

The mechanism proposed for the formation of the compounds **188** depicted in Scheme 65.



Scheme 65. Proposed mechanism for the cyclization step.

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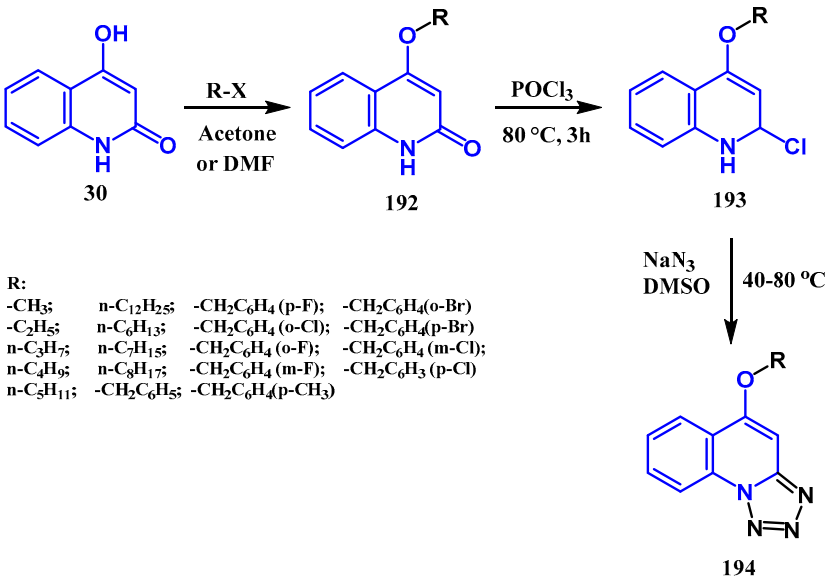
3.8.5. Preparation of Tetrazole Quinolones

Xian-Qing Deng et al. [82] reported the synthesis of a series of 5-alkoxy-tetrazolo[1,5-a]quinolines **194** and evaluated their anticonvulsant and antidepressant properties. The target compounds **194** were obtained through a multistep process. Initially, 4-hydroxyquinoline-2(1H) **30** was reacted with the appropriate alkyl halide or benzyl chloride in DMF, yielding 4-alkoxyquinolinones **192**. These intermediates **192** were subsequentlytreated with $POCl_3$ at 80°C to produce 2-chloro-4-alkoxyquinoline derivatives **193**. Finally, reaction of compounds 3a–3s with sodium azide in DMSO afforded the desired target compounds **194**. All the synthesized compounds exhibited potent anticonvulsant activity at a dose of 300 mg/kg (Scheme 66).



Scheme 66. Synthesis of a series of 5-alkoxy-tetrazolo[1,5-a]quinolones.

4. Biological Activities of Quinolone Derivatives

4.1. Antibacterial Activity

Such variations can be considered important in estimating the effect of esterification on the antibiotic activity and selectivity of fluoroquinolones, which are broad-spectrum antimicrobial agents. In this regard, Pais, J. P. [120] reported that the newly synthesized derivatives were tested against several clinically significant bacterial strains belonging to both Gram-positive (Gram+) and Gram-negative (Gram-) categories. As expected and consistent with previous studies, the minimum inhibitory concentration (MIC) values for the ester derivatives increased compared to the original compounds, levofloxacin and ciprofloxacin. Nevertheless, the data may provide additional valuable information [121–124]. The results show discernible patterns of bioactivity differences between Gram-negative and Gram-positive bacteria.

Similar to mycobacteria, MIC values for Gram-negative bacteria generally increase as a function of increasing ester chain length. For Gram-positive bacteria, there is no simple relationship between chain length and MIC; there is an optimal chain length. Typically, this level of efficacy is observed in compounds containing aliphatic chains of 9 and 10 carbons, reflecting an optimal chain length for the effectiveness of antibacterial activity (Figure 2).

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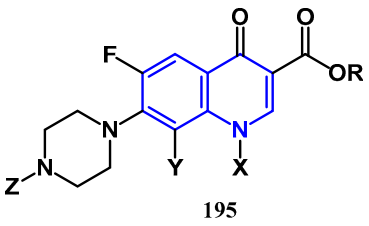


195

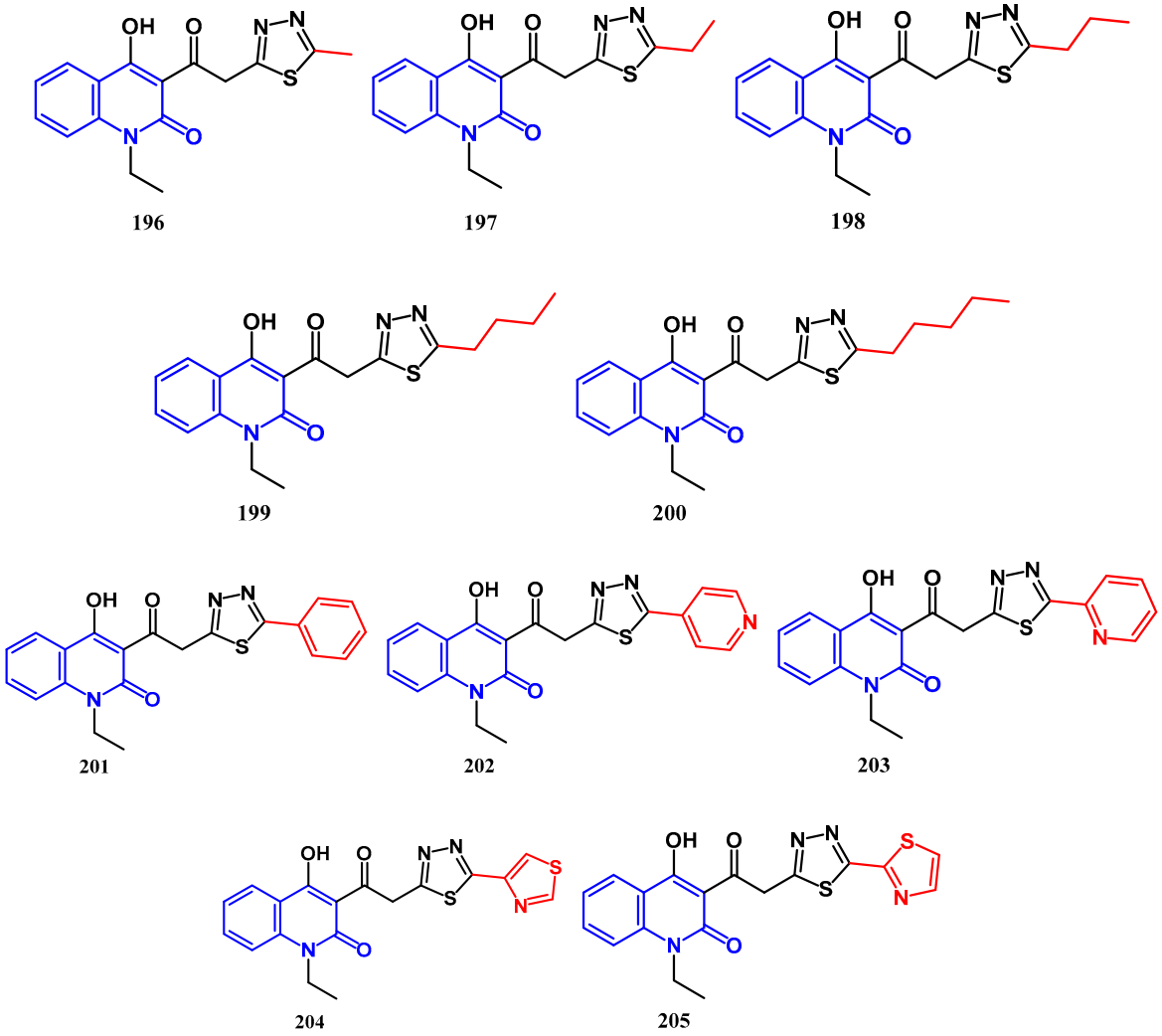
Lifloxacin: X= $-CH_2(CH_3)CH_2Y-$; Y= -O- ; Z= $-CH_3$

Ciprofloxacin: X= $-CH(CH_2)_2$; Y= Z= H

R= H; C_6H_{13}; C_7H_{15}; C_8H_{17}; C_9H_{19}; $C_{10}H_{21}$; $C_{11}H_{23}$; $C_{12}H_{25}$; $C_{13}H_{27}$; $C_{14}H_{29}$; $C_{16}H_{33}$

Figure 2. Antibacterial activity of fluoroquinolone esters.

Xue et al. [124] reported the activity of N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides against *Staphylococcus aureus* ATCC29213 through both in vitro and in vivo systems. Ten derivatives with better antibacterial activities than those previously reported were identified (**196, 197, 198, 199, 200, 201, 202, 203, 204**, and **205**); It was observed that all compounds demonstrated a minimum inhibitory concentration of less than 1 μg/mL. Of these, compound **205** was the most active in this chemical series; however, until now, its target has not been reported. Although promising activity can be observed from this compound, its high PPB may limit its wider use clinically (Figure 3).



196 197 198

199 200

201 202 203

204 205

Figure 3. Quinolones demonstrating antibacterial efficacy.

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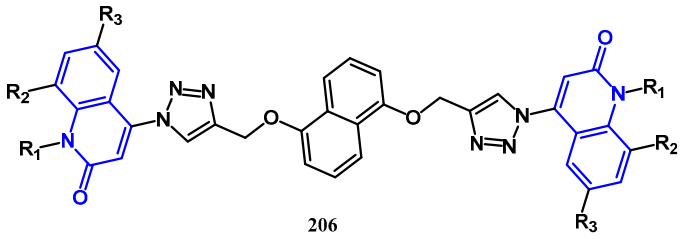
4.2. Antiproliferative Activity:

The compounds recently developed by El-Sheref, E.M. et al. in 2019, 2021, and 2022 were tested for their ability to inhibit the growth of four different types of cancer cells: A-549 (epithelial cancer), MCF-7 (breast cancer), Panc-1 (pancreatic cancer), and HT-29 (colon cancer) [111]. The mean GI50 value of the test compounds ranged from 34 to 134 nM, indicating their substantial antiproliferative activity. In contrast, the GI50 for the reference compound erlotinib was 33nM against the four tested cancer cell lines. The synthetic derivative with R1 = R2 = R3 = H exhibited an average GI50 of 34nM, which was nearly equivalent to the GI50 of erlotinib at 33nM, designating it as the most potent synthetic derivative.

The study also examined the properties and placement of substitutions on the quinoline structure. The derivative, 6-methylquinoline, compound 4b, which has $R_1 = R_2 = H$ and $R_3 = CH_3$ and is 1.8 times more potent than the derivative, 6-methoxyquinoline, compound 4c, that has $R_1 = R_2 = H$ and $R_3 = OCH_3$. This finding suggests that the methyl group is better tolerated than the methoxy group. Moreover, compound 4d ($R_1 = R_3 = H$, $R_2 = CH_3$) demonstrated that the compound 4b, being a derivative of 6-methylquinoline, possessed at least half the potency of compound 4c, a derivative of 8-methylquinoline. This observation suggests that 6-substituted quinoline structures are better tolerated than 8-substituted ones (Figure 4).



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$R_1 = H ; CH_3$
$R_2 = H ; OCH_3$
$R_3 = H ; CH_3 ; OCH_3$

Figure 4. Quinolones exhibiting efficacy against cancer cells.

The most potent activities against all four cell lines, with average IC50 values within 1.57 –3.85 μM, were recorded for those compounds bearing R2 and R4 groups as OCH_3. The highest antiproliferative activity was shown by the compound possessing $R_1 = R_3 = H$ and $R_2 = R4 = OCH_3$ with an average IC50 of 1.575 μM. In comparison, the reference doxorubicin had an average IC50 of 1.136 μM. Subsequently, compounds with the substituents $R_1 = R_3 = R_4 = H$ and $R_2 = OCH_3$ with an average IC50 of 1.875 μM and and compound 8c, with R1 = R2 = R3 = H and R4 = OCH3, demonstrating an average IC50 of 3.850 μM, exhibited higher IC50 values, indicative of diminished potency, in comparison to the aforementioned compound. Substitution of the OCH3 group with either H or CH3 resulted in a decrease in antiproliferative activity. The results clearly indicate that the electronic effect of substitutions (R_2 and R_4) on the phenyl groups of the quinoline moieties is crucial for the antiproliferative activity. It means that the position in the scaffold of the substituent determines significantly the activity of these compounds. In general, the triazoles substituted in positions (R_1 and R_3 = H) exhibited higher antiproliferative activity compared to N-methylated analogues with radicals (R_1 and $R_3 = CH_3$). To illustrate, the derivative lacking substitutions (R1 = R2 = R3 = R4 = H) exhibited an average IC50 of 5.575 μM against the four cell lines examined. Substitution of the NH group with N-CH3 resulted in a minimum 4-fold increase in the average IC50 value (average IC50 = 24.725 μM) [110,112] (Figure 5).

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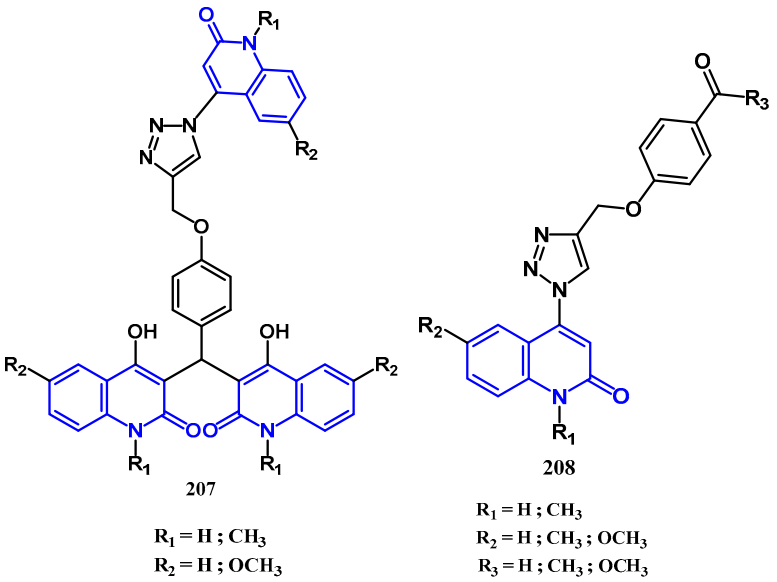

Figure 5. Antiproliferative activity of quinolones.

In addition, H. Al-Wahaibi et al. reported synthesizing two novel series of quinoline-2-one-based derivatives as potential apoptotic antiproliferative agents targeting the epidermal growth factor receptor (EGFR) inhibitory pathway [119]. The three Compounds **209**, **210** and **211** inhibited significant inhibitory effects on EGFR, with IC_{50} values of 0.18 and 0.09 µM, respectively. Furthermore, the two compounds significantly increased the apoptotic markers caspase-3, caspase-8, and the Bax levels while decreasing the antiapoptotic BCl_2 levels (Figure 6).

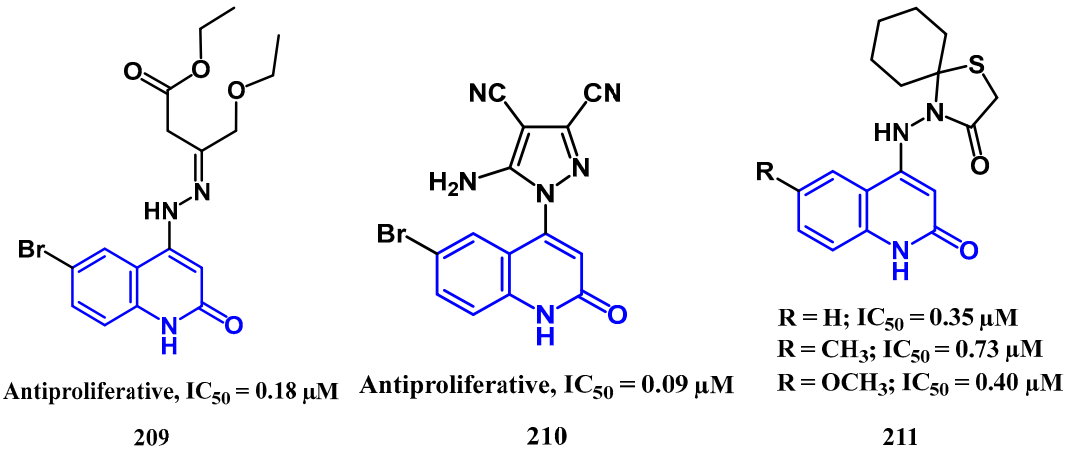

Figure 6. Quinolones derivatives as potential apoptotic antiproliferative.

4.3. Antiviral Activity:

Acquired immune deficiency syndrome (AIDS) represents the most advanced stage of infection caused by the human immunodeficiency virus (HIV) [126–128]. One of most effective classes of chemical agents reported to be useful against HIV is quinolone derivatives, among which are drugs like Elvitegravir (GS-9137). A representative compound showing the scope of quinolone derivatives in AIDS treatment, Elvitegravir is a member of the quinolone derivative class and was approved by the FDA in 2012 [129]. Recent studies have demonstrated that certain quinolone-3-carboxylic acid derivatives contain integrase enzyme, a key in the cycle of viral replication. This finding underscores the significant therapeutic value of these derivatives in combating drug-resistant strains of HIV [130]. For this reason, these structure-activity relationship (SAR) investigations for quinolone derivatives

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are directed toward increasing their ability to attack HIV. Substitutions at individual positions of the quinolone nucleus, such as C-7, C-8, and others, have been found to give an improved antiviral profile; however, the substitutions at the C-2 position of the quinolone ring have not yielded significant added advantages [130].

In a recent study, Xu et al. developed novel quinolone acid derivatives that may have the ability to inhibit HIV-1 integrase. Of these synthesized compounds, **160**, featuring 3,4,5-trihydroxylated aromatic substituents at the N-1 position of the quinolone ring, showed most effective inhibitory activity against the strand transfer process of HIV-1 integrase with an IC50 value of 2.6 μM. In contrast, its IC50 value in a control compound, S-1360, was lower at 0.50 μM. A new derivative, compound **163**, was synthesized and reported by Massari et al. This compound displayed significant antiviral activity on both HIV-1IIIB and HIV-2ROD in MT-4 cells, with effective concentration (EC50) values of 1.85 ± 0.76 mg/mL and 1.31 ± 0.89 mg/mL, respectively. The findings indicate that compound **163** exhibits higher potency compared to nevirapine, an antiretroviral agent currently in clinical use. The EC50 value of nevirapine for HIV-1 is 23nM, and it is more than 4000-fold higher (i.e., greater than 4000nM) for HIV-2.Sriram and colleagues have developed a novel series of prodrugs for the treatment of HIV/AIDS. Bioevaluation studies revealed that compound **164** exhibited the greatest activity against HIV-1 replication, with an EC50 value of 5.2 μM. The compound also demonstrated low toxicity against CEM cells, with a CC50 value of 200 μM. Additionally, compound 164 exhibited a MIC of 0.2 mg/mL against the Mycobacterium tuberculosis H37Rv strain (Figure 7).

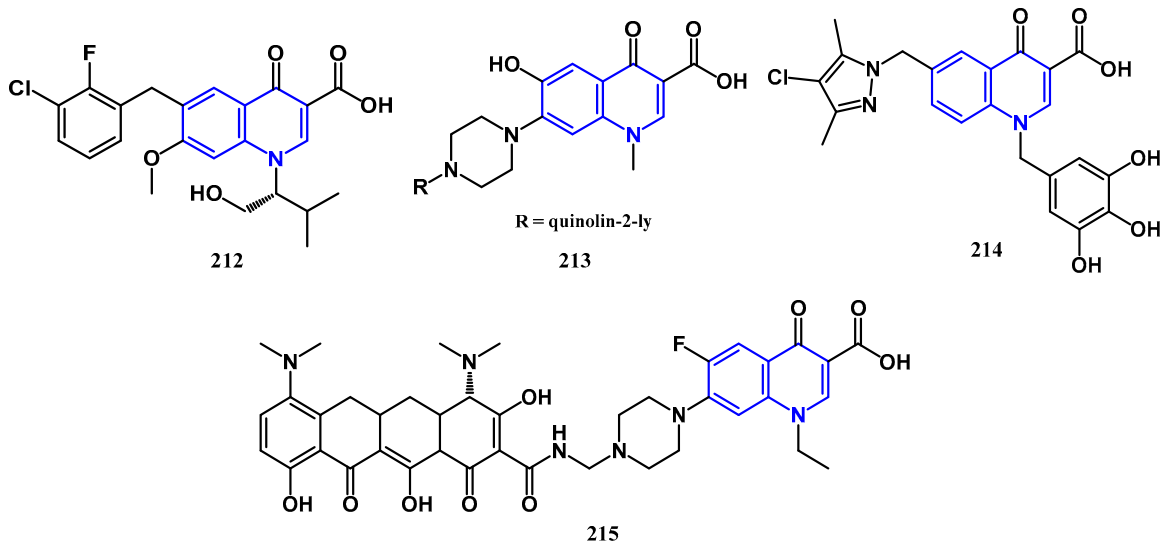

Figure 7. Quinolones exhibiting efficacy against HIV.

In their study, Naik et al. described a novel class of compounds, 4-aminoquinolone piperidine amides (AQs), which were identified in whole-cell screening. The estimation of minimum inhibitory concentrations (MICs) and whole-genome sequencing on mutants resistant to 4-aminoquinolone piperidine amides (AQs) indicated DprE1 as the main target for these compounds against M. tuberculosis. Results from mass spectrometry and enzyme kinetic experiments revealed that AQs function as slow-binding, reversible noncovalent inhibitors of DprE1, characterized by long residence times on the enzyme, around 100 minutes. Overall, AQs present promising hit-like properties and an interesting secondary pharmacological profile in vitro. Initially, the scaffold started with a single compound showing moderate potency in whole-cell screening. Through structure-activity relationship (SAR) optimization, the series produced compounds with potent DprE1 inhibition (IC50 < 10 nM) and strong cellular activity (MIC = 60 nM) against Mtb [131] (Figure 8).

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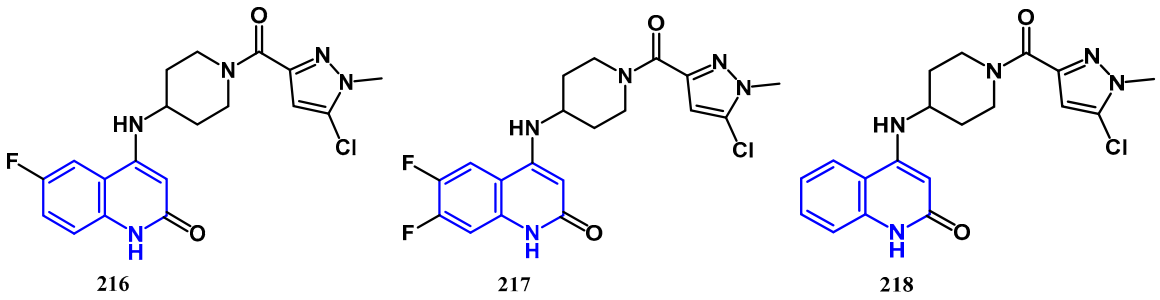

Figure 8. 2-Quinolones with activity against HIV.

4.4. Antitrypanosomal and Antileishmaniasis Activity:

The protozoan parasites *Trypanosoma brucei* are the causative agents of two distinct human diseases. The more prevalent of these is African trypanosomiasis, which is also referred to as sleeping sickness. Sleeping sickness is a severe, neglected tropical disease caused by protozoan parasites of the species *Trypanosoma brucei*. Humans contract the disease through the bite of an infected tsetse fly, primarily in regions south of the Sahara desert. An additional protozoan parasite, *Trypanosoma cruzi*, is the causative agent of chagas disease, which is more commonly referred to as American trypanosomiasis. The disease is transmitted to humans through bites from an infected Triatominae bugs, commonly known as the kissing bug. The disease is endemic in many regions in Central and South America; hence, about 6 million cases are estimated to occur among people globally [132–134].

In recent years, quinoline derivatives have been increasingly recognized in the treatment of various infectious diseases, especially those caused by species of *Leishmania* and *Trypanosoma*, leading to devastating diseases such as leishmaniasis and Chagas disease. More contemporary studies have focused on the preparation and evaluation of new quinolone derivatives and the pharmacological activity of potent antitrypanosomal agents. On that line, Pedron et al. reported a study of a series of new quinolone derivatives and their evaluation against *Leishmania infantum*, *Trypanosoma brucei brucei*, and *Trypanosoma cruzi*. Among these, Compound **219** emerged as the lead compound, potent with inhibitory effects showing EC50 values of 12 nM against *T. b. brucei* trypomastigotes and 500 nM against *T. cruzi* amastigotes. Furthermore, this compound was highly microsomal stable with a half-life of less than 40 min and displayed good pharmacokinetic properties in mice. Notably, bioactivation by the type 1 nitroreductase was also reported to occur within the *Leishmania* and *Trypanosoma* species, giving a probable mechanism of their antiprotozoal activity [135].

Moreover, quinolone derivatives have been reported to exhibit significant cytotoxic effects on the HepG2 cell line, underscoring the selective nature of Compound **219**, which was shown to target parasitic cells while sparing human cells. This property is crucial for the development of safe and effective therapeutic agents [135–137].

Hiltensperger et al. very recently presented a library of quinolone-based compounds exhibiting strong antitrypanosomal activity, with selective activity against *Trypanosoma brucei*. However, Compound **220**, the lead compound in the study, inherently suffers from problems associated with its poor aqueous solubility. This is a significant challenge in drug development: better solubility will enhance bioavailability and pharmacokinetics to effectively support therapeutic applications [138].

Beteck et al. also reported a library of nonfluoroquinolones, which revealed moderate to poor antitrypanosomal activity. Compound **221** was the most active compound obtained in the research of his group, showing an IC50 value of 7.14 μM against *Trypanosoma brucei*. Most importantly, the compounds tested within this study were not cytotoxic, which suggests that such nonfluoroquinolone derivatives may be safe [139]. Continuing with this work, Angula et al. studied new quinolone derivatives which had a heteroarylidene moiety at position 6 of the quinolone ring. This was followed by the discovery of compound **221**, which had relatively improved antitrypanosomal activity compared with the previously synthesized derivatives, showing an IC50 value of 80 nM against *T. b. brucei*. This enhancement in potency suggests the potential for structural

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modifications within the quinolone framework to provide effective treatment for Trypanosomiasis [140].

Both studies underline the importance of exploring various structural modifications to the quinolone framework in the quest for optimization of antitrypanosomal activity with low toxicity. Further relevance of the finding is that it can be valuable for emerging opportunities in the search for effective therapies for diseases caused by *Trypanosoma* spp.—which are a significant global health challenge (Figure 9).

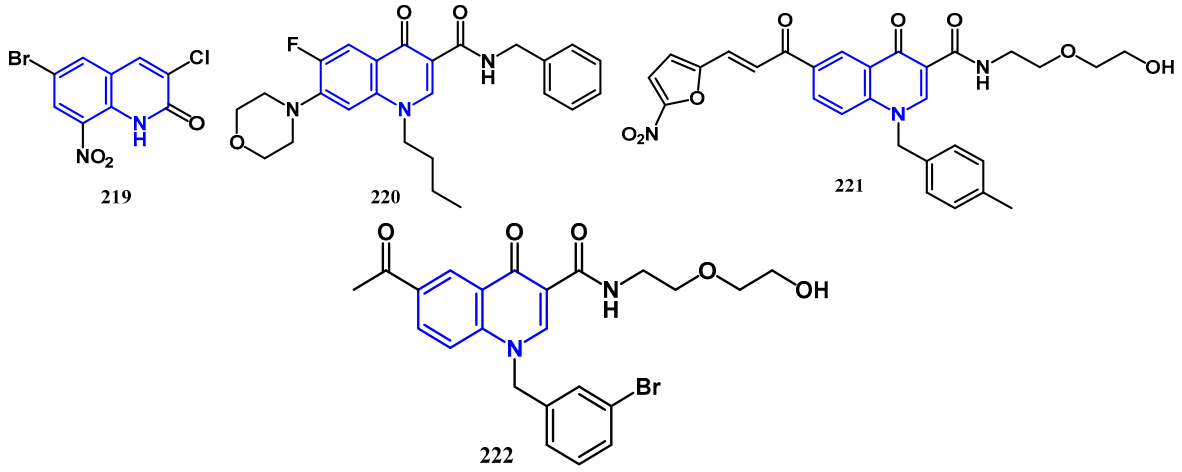

Figure 9. Quinolones exhibiting efficacy against the trypanosoma.

Another kind of neglected tropical disease is leishmaniasis, caused by protozoan parasites of the genus *Leishmania*. The major mode through which these protozoa are transmitted to humans is through bites from infected female phlebotomine sandflies. The disease manifests in various clinical forms, with cutaneous, mucocutaneous, and visceral leishmaniasis being the most common [141] (Figure 10).

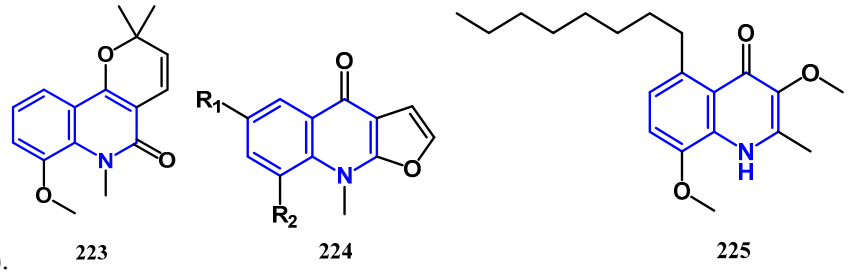

Figure 10. Quinolones exhibiting efficacy against Leishmania parasites.

4.5. Anti-Malaria Activity:

Malaria is an acute, life-threatening infectious disease caused by protozoan parasites of the Plasmodium type. These parasites are transmitted to humans through the bites of infected Anopheles mosquitoes. The parasites undergo multiplication in the liver cells prior to invading red blood cells, where they subsequently multiply and proliferate rapidly within the blood cells [142]. The disease is concentrated in 11 countries; 70% of the global burden rests there. In Africa, young children bear the brunt of the majority of cases, where under-fives account for 61% of all malaria deaths in the world [143].

Even though preventable and curable, artemisinin resistance developing, a drug widely used in the treatment of malaria, already poses a huge challenge in the control of malaria. Therefore, there is a need for urgency for new compounds that target the malarial parasite [3]. Quinolone-based derivatives have exhibited activity against all stages of the Plasmodium life cycle, including blood, liver, and gametocyte. Their multi-target effectiveness positions them as promising lead compounds

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in the development of novel antimalarial treatments, a critical endeavor to ensure the ongoing effectiveness of efforts to combat the emerging resistance [144,145].

Endochin-like quinolones (ELQs) are a promising class of antimalarial agents that have garnered attention due to their unique chemical structure and potent activity against various stages of the malaria parasite *Plasmodium falciparum*. These compounds are characterized by a quinolone nucleus that features a methyl group and a diphenyl ether substituent at positions 2 and 3, respectively. This distinctive configuration, along with various substituents in the benzenoid ring, enhances their pharmacological properties and efficacy [146]. ELQs, particularly ELQ-300, have been shown to inhibit the cytochrome bc1 complex of the malaria parasite, disrupting the mitochondrial electron transport chain. This mechanism is similar to that of atovaquone, a well-known antimalarial drug. By targeting the electron transport chain, ELQs effectively impair the parasite's ability to generate ATP, leading to reduced viability and replication of the parasite within the host [147,148].

Research has demonstrated that ELQ-300 and its prodrugs, ELQ-331 and ELQ-337, exhibit significant antimalarial activity. In preclinical studies, a single oral dose of ELQ-300 (0.03 mg/kg) effectively prevented malaria infections in mouse models. Furthermore, administering four daily doses of 1 mg/kg resulted in complete cures of established infections. These findings indicate that ELQ-300 possesses favorable pharmacokinetic properties that allow for effective oral administration and the ability to block transmission in rodent models of malaria [149]

Despite its promising efficacy, ELQ-300 faces challenges related to its physicochemical properties. Its relatively high degree of crystallinity limits its aqueous solubility and absorption, leading to low blood concentrations after oral dosing. This limitation can significantly affect the drug's overall efficacy, making it difficult to achieve therapeutic levels in the bloodstream.To address these challenges, researchers have turned to prodrug strategies, which involve modifying the chemical structure to enhance bioavailability and absorption [150].

One notable prodrug, ELQ-337, has been developed to overcome the limitations of ELQ-300. Studies have shown that ELQ-337, a bio-reversible prodrug, achieves a three- to fourfold increase in bioavailability compared to ELQ-300 when administered at a molar equivalent dose of 3 mg/kg body weight. This prodrug reaches a maximum serum concentration (Cmax) of 5.9 μM and has demonstrated the ability to cure malaria infections in mice with low doses. These results suggest that prodrug strategies can effectively enhance the delivery of the active drug to the bloodstream, improving therapeutic outcomes.In addition to ELQ-337, several bio-reversible ester prodrugs of ELQ-300 have been synthesized. These compounds are converted back to ELQ-300 by esterases present in the liver and bloodstream, further improving their pharmacokinetic profiles. For instance, ELQ-331 has shown the ability to cure *Plasmodium yoelii* infections in murine models at a single dose of 3 mg/kg, indicating its potential for clinical application [151,152].

ELQs are not limited to treating malaria; they also show promise against other apicomplexan pathogens. For example, ELQ-316 has been identified as a lead compound for treating toxoplasmosis, a disease caused by *Toxoplasma gondii*. This compound exhibits specificity for *T. gondii* cytochrome b over human cytochrome b, which is crucial for minimizing potential side effects.A carbonate ester prodrug of ELQ-316, known as ELQ-334, has been synthesized to improve its pharmacokinetic properties. Oral administration of ELQ-334 resulted in a sixfold increase in both maximum plasma concentration (Cmax) and area under the curve (AUC) of ELQ-316. This enhanced bioavailability has led to effective treatment against latent toxoplasmosis, demonstrating the versatility of ELQs in combating various parasitic infections [153] (Figure 11).

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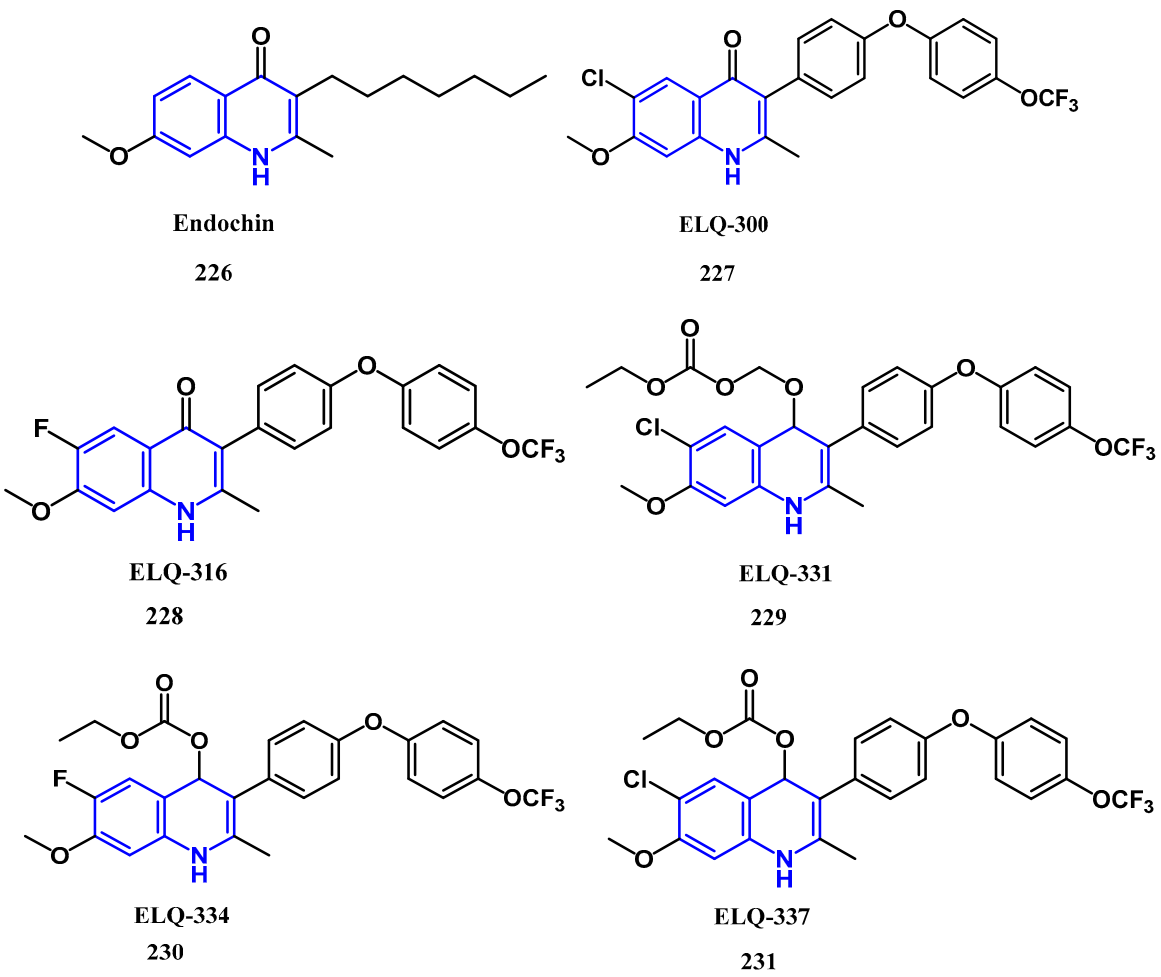

Figure 11. Quinolones with activities against malaria.

5. Conclusion and Perspectives

In conclusion, quinolones represent an important class of synthetic antibiotics with high therapeutic potential to treat a wide range of medical conditions. Due to their wide-ranging biological activities attained by the development of innovative approaches in organic synthesis, numerous derivatives have been prepared to respond critical demands in health, such as bacterial resistance and efficient anti-cancer agents.

Going forward, the sustained struggle against antimicrobial resistance demands a further deliberate attempt at designing and synthesizing novel quinolone derivatives with higher potency against resistant strains. Future research should be directed toward the pursuit of new synthetic strategies enabling structural diversification and functionalization of the quinolone scaffold. The reactivity study of quinolones will enhance the possibility of finding new derivatives with new mechanisms of action and wider scopes of therapeutic application beyond traditional antibacterial uses.

To further elucidate of the pharmacodynamics and pharmacokinetics of quinolones requires close interdisciplinary collaboration among medicinal chemists, biologists, and pharmacologists. This would encompass computational methodologies such as molecular docking and structure-based drug design. Keeping an eye on the rich chemistry of quinolone derivatives and with determination to solve the challenge of drug resistance, it would be a labor toward next-generation therapeutics that would answer emerging needs in modern medicine.

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