2022
2(1), 338

Journal of
Molecular Chemistry

Synthesis and medicinal applications of quinoline hybrid heterocycles: a comprehensive review

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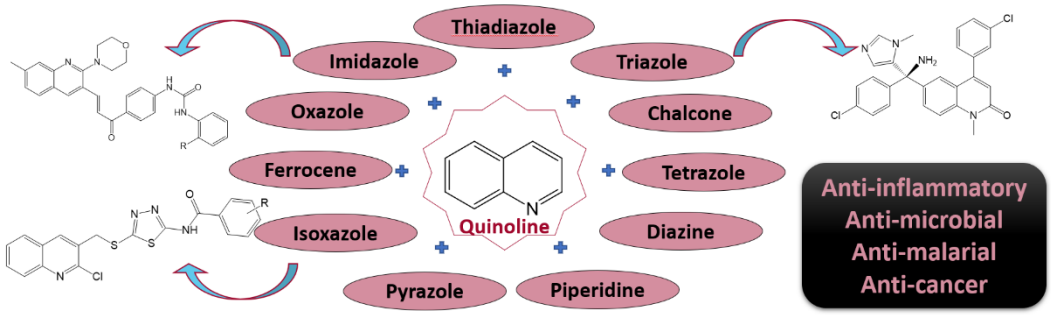
Submitted on: 14-Jan-2022, Accepted and Published on: 7-Apr-2022

Review Article

ABSTRACT



Quinoline is a privileged scaffold with immense studies carried out on its synthetic methods and wide range of biological properties. In order to intensify its properties and afford potent molecules, a variety of other heterocyclic units have been combined with quinoline in a single molecule. Since it was thought that these single, highly potent molecules can serve as replacements to combination therapies and overcome problems relating to drug-resistance, an array of various quinoline hybrids have been synthesized by different methods. In view of the growing use of quinoline moiety in drug design and development, this review focuses on the synthesis and biological applications of different quinoline hybrid scaffolds.

Keywords: Quinoline, Quinoline-azoles, Quinoline-azines, Quinoline-ferrocene, Quinoline-chalcone

INTRODUCTION

Back in 1834, a German chemist named Friedlieb Ferdinand Runge, was the first to extract quinoline. He termed it as a white oil. Ever since, quinoline and its derivatives have become an important class of aromatic, heterocyclic compounds.[1] The simplest of this class, is named quinoline itself and this ring system is observed in many natural products, especially alkaloids.[2] Quinoline and its derivatives possess antimalarial, antimicrobial, antiasthmatic, antiallergic and many such properties.[3] Given its wide range of pharmacological abilities, it has captured the interest of chemists ever since its discovery. In order to inspect its possible applications, many experiments were carried out to synthesize these compounds. With time, many modifications have been achieved in synthesizing a variety of quinoline hybrids to enhance its biological applications. This paper reviews in depth, the traditional, modern and more greener approaches in synthesizing quinolines and its hybrid derivatives along with their applications.

METHODS OF SYNTHESIS

Owing to the importance of quinoline and its derivatives, it gained the attention of researchers, that resulted in discovery of various modifications over the years through which these compounds can be synthesized. Detailed description of traditional and modern methods of synthesis is presented here in this review article.

1. TRADITIONAL METHODS OF SYNTHESIS

In 1880, Zdenko Hans Skraup successfully reported the synthesis of quinoline, which later brought forth numerous other methods of synthesis. This synthesis was named after him as Skraup synthesis.[4] In this, a mixture of aniline and glycerol was heated with sulphuric acid and an oxidizing agent, nitrobenzene to produce quinoline (Scheme 1). Quinoline was the first member of its class to be discovered, with the formula C_9H_7N. It is a colorless, hygroscopic liquid with a strong odd odor. In this reaction, nitrobenzene acts as a solvent and an oxidizing agent. This was a violent reaction and to avoid this, ferric oxide, arsenic

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URN:NBN:sciencein.jmc.2022.338

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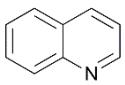
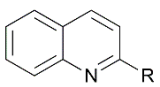
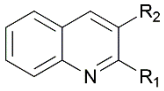
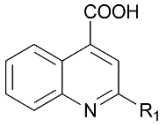
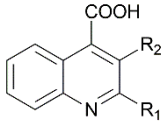
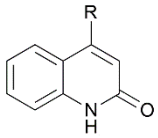
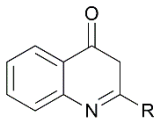
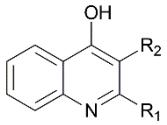
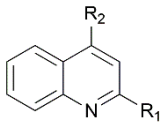
acid or picric acid could be substituted.[4] Similar to this, Doebner-Miller reaction[5] involved the formation of quinoline using the reactants, aniline and an α, β- unsaturated carbonyl compound. It is sometimes also referred to as Skraup-Doebner-Von Miller quinoline synthesis.[6] Subsequently, Friedländer synthesis[6] came out in 1882 which involved the reaction between amino-aldehyde or ketone with another aldehyde or ketone to produce a substituted quinoline. This reaction was catalyzed by acid, base or heat. This was a major reaction that has been modified repeatedly to produce modern methods of quinoline synthesis.[7]

Doebner reaction involves the formation of 4-carboxyquinoline. Reported in 1883, it was prepared by the reaction of aniline, aldehyde and pyruvic acid.[8] A substitute of this reaction is the Pfitzinger synthesis put forth in 1886.[9,10] Carboxyquinoline that was obtained here is the product of α-methylene and isatic acid along with a strong aqueous base. Desired quinoline derivatives are hence furnished by the decarboxylation of the above formed intermediate.

Yet another traditional reaction was given in 1886 named as Knorr Synthesis[11,12] by Ludwig Knorr. The general reaction involved reactants such as β-ketoester, aryl amine and sulphuric acid for the formation of 2-hydroxyquinolines at a temperature above 100°C. Theoretically, this reaction is similar to Gould Jacob synthesis and Dobner-Miller synthesis. Synthesis of 4-quinoline derivatives was given by Gould-Jacob synthesis[13] which was a reaction between aniline and ethyl ethoxymethylenemalonate. Conrad-Limpach synthesis [14] of 4-hydroxyquinolines was the result of condensation of primary amines and β-ketoesters. Similar to this reaction, Combes synthesis [15] was put forth in 1887. Condensation and cyclization of the intermediates formed by the reaction between anilines and β-diketones in the presence of sulphuric acid takes place to produce the quinolines. All these traditional methods are summarized in Table 1.

Table 1 Traditional methods of synthesis of quinoline and its derivatives

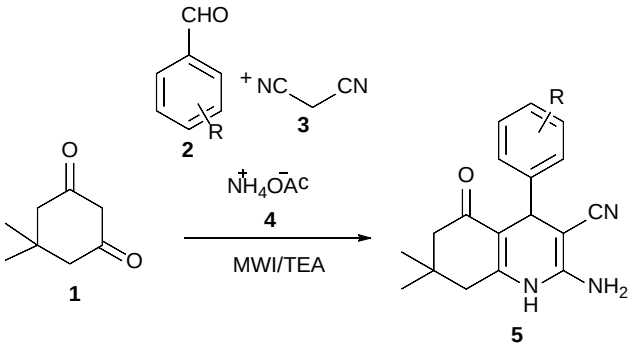
Method of synthesis	Reactants	Product
Skraup synthesis	Aniline and glycerol	
Doebner Miller reaction	Aniline and α, β-unsaturated carbonyl compound	
Friedlander synthesis	2-Aminobenzaldehyde and ketone	
Doebner synthesis	Aniline, pyruvic acid and aldehyde	
Pfizinger reaction	Isatin and carbonyl compound	
Knorr synthesis	β-Ketoester and arylamine	
Gould Jacob synthesis	Aniline and ethyl ethoxymethylenemalonate	
Conrad Limpach synthesis	Primary aromatic amine and β-ketoester	
Combes synthesis	Aniline and β-diketone	

2. Modern Methods of Synthesis

The necessity for newer procedures has grown immensely in the recent times. Traditional methods offered the production of desired products but at the cost of harsh conditions, toxic solvents and less yield. Thus, a need for newer methods arose keeping in mind the sustainability of the environment and efficiency of the reaction. The newer strategies included microwave irradiation to reduce reaction time, ionic liquid mediated synthesis to replace the use of toxic organic solvents, different catalytic substances to enhance the yield and also recycling of the catalyst without the loss of efficiency. Some of the modern methods have been discussed here.

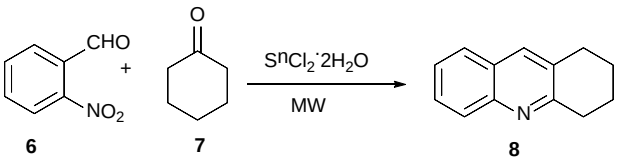
2.1 Microwave Irradiation

Microwave reactions diminishes the reaction time tremendously. Reactions that required hours for synthesis now has been reduced to minutes or even few seconds depending on the microwave conditions. High temperature requiring reactions were efficiently brought to low temperature along with solvent free conditions. Moloi *et al* [16] reported an easy, one pot method for the synthesis of 11 substituted quinoline derivatives using microwave irradiation. It involved the equimolar addition of 5,5-dimethylcyclohexan-1,3-dione (**1**), aromatic aldehyde (**2**), malononitrile (**3**) along with ammonium acetate (**4**) and triethylamine in ethanol taken in a shielded container with magnetic stirring, in a microwave of 100W for 12 minutes at room temperature. Some reactions were optimized with the use of different catalysts. The reaction furnished good yield of the product (**5**) and in some cases, purification was not necessary (Scheme 1).



Scheme 1 Substituted quinoline synthesis using microwave irradiation

Meanwhile, Chaudhuri and Hussain reported an efficient synthesis of quinolines (**8**) where the quinoline is fused to a cyclohexane ring, under solvent free conditions.[17] The overall procedure of this method involved irradiating 2-nitro aryl aldehyde (**6**), enolizable ketone (**7**) and $SnCl_2.2H_2O$ mixture at 1050 W in the ratio of 1:1:3 for 5 minutes (Scheme 2). Quinoline product was extracted with a yield of 85%. Nadaraj *et al.* reported the synthesis of 4-hydroxy-2-quinoline derivatives[18] where a paste of aniline, diethylmalonate and *p*-toluenesulfonic acid was made followed by irradiation in a 320W microwave oven for 3-6 min. Another efficient, modified synthesis of 2-methyl-4-quinolines was reported by Yuan *et al.* using an acidic resin.[19] A mixture of aromatic amines, ethyl acetoacetate and resin (NKC-9, 100mg) was subjected to room temperature homogenization followed by irradiation in a 400W microwave oven for 1.5 minutes with 10 seconds of interval.

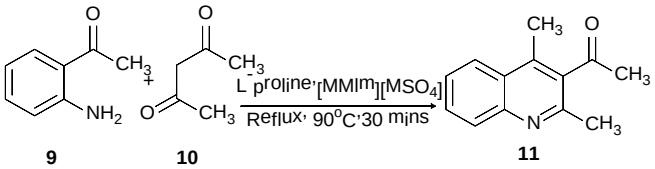


Scheme 2 Solvent free synthesis of quinoline under microwave irradiation

2.2 Ionic Liquids

One of the most popular methods of synthesis is the use of ionic liquids. Many reactions use ionic liquids (IL) both as catalyst and solvent, whereas it can be used as either catalyst or solvent depending on the required reaction conditions. Optimization of these methods yield nearly 98% product. One of the major advantages of this type of reactions is the reusability of ionic liquids. They can be obtained and reused up to 4-5 times with no loss in efficiency. Le *et al.* [20] performed an enzyme (α-chymotrypsin) catalyzed, modified Friedlander condensation in the presence of ionic liquids. 20% IL aqueous solution [EMIM][BF_4]/([EMIM][BF_4]) along with a mixture of 2-aminoaryl ketone and α-methylene ketone, in slight excess, in the presence of α-chymotrypsin was incubated at 55°C at 260 rpm. Once the product was synthesized, it was extracted with ethyl acetate. Under reduced pressure, the crude product was obtained and further purified via column chromatography. Similar to the above reaction, Zhao *et al.*[21] used ethyl ammonium nitrate and 2-aminobenzophenone or 2-aminoacetophenone with a range of methylene groups. The reactions also required ethyl ammonium nitrate, a temperature of 45°C, a reaction time of 24 hours[21] and the yield obtained was moderate to good.

Ionic liquids were used widely for the synthesis of quinolines also because they provided better efficiency and is a green method. The product yields were generally increased to 75-90% in most reactions. One such reaction was performed by Prola *et al.*[22] using the ionic liquid, [HMIM][TsOH] along with the reactants, 4-alkoxyvinyl ketone and 2-aminoacetophenone. They were taken in a microwave vessel and irradiated at 4-10 W, 150°C for certain substituted reactants, and at 10-13 W, 90°C and 15-51W, 80°C for a few others, for a time period of 10 to 20 minutes. The reaction was air compressed and the product was extracted. This reaction was tried with different catalysts to modify the yields of the products obtained. Another modification of a traditional reaction (Knoevenagel condensation) was given by Asiri and Tasqueerudin.[23] Using different molar concentration of the catalyst, L-proline, the yield was maximized in the ionic liquid, [MMIm][MSO_4]. In a Schlenk flask, reactants 2-aminoacetophenone (**9**) and acetylacetone (**10**), were taken along with the catalyst and ionic liquid. Stirring was done at 90°C for approximately 30 min. Once the reaction was complete, evaporating the solvent yielded the crude product which was then purified by column chromatography to give (**11**). Many substituted quinolines were prepared following the above procedure which was reported to have excellent yields (Scheme 3).



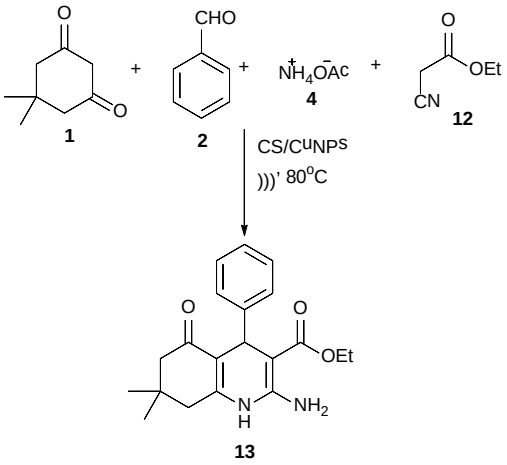
Scheme 3 Synthesis of quinoline derivative using ionic liquid and L-proline

2.3 Nanoparticles

With many green synthetic procedures, there has been a great necessity for good, efficient catalysts that can increase the rate of the reaction with trace amounts. One such kind of catalysts are nanoparticles. Due to their small size, they provide larger surface areas for the reaction to take place. They can also be reused after the completion of reaction. Use of nanosized particles for the synthesis of quinolines has shown excellent yields and faster reaction rates. H. R. Prakash Naik *et al.*[24] used titanium dioxide (TiO_2) in the one pot synthesis of the quinoline, benzo[h]quinoline-3-carbonitrile. A mixture of arylaldehyde, cyanoacetate, aniline and titanium dioxide was irradiated in a microwave at 300 W or 150 W for 60 seconds depending on the completion of the reaction. The obtained reaction mass was poured onto crushed ice after cooling it to room temperature. The

solid was filtered and recrystallized in DMF. Similar to this, SiO_2 was also used as catalyst in a reaction put forth by Hasaninejad *et al.*[25] A variety of derivatives of carbonyl compound and 2-aminoaryl ketone was irradiated with silica nanoparticles in a microwave oven at 600 W for 5-15 minutes and the yield varied between 81-92% respectively. Using ethyl acetate, the reaction mixture was centrifuged to reobtain the catalyst and evaporated to get the crude product, which was recrystallized using ethanol.

Aggregation of nanoparticles in the reaction using high temperature is unfavorable as the reaction loses its purpose. Hence, many polymer-supported catalysts were developed to minimize the aforesaid problem. An excellent material for a catalyst support, reported by Alghamdi *et al.*[26] was Chitosan. It is a biopolymer produced by the *N*-deacetylation of chitin which is the second most abundant natural polymer after cellulose.[26] In 10 ml of absolute ethanol, dimedone (**1**), aromatic aldehyde (**2**), ethyl cyanoacetoacetate (**12**), ammonium acetate (**4**) and Cu-chitosan nanoparticles were taken, and ultrasonic waves were irradiated at 80°C (Scheme 4). Filtration was then carried out to remove the catalyst and room temperature cooling gave a solid product of quinolone (**13**) which was recrystallized in ethanol. Another nanoparticle mediated synthesis, a two-component reaction, was put forth by Qandalee *et al.*[27] This was a simple reflux reaction which uses the catalyst SnO_2. In ethyl acetate, 2-aminobenzophenone, acetylenic ester and SnO_2 were added. Refluxing the mixture for 1 hour yielded the solid product which was filtered and purified by chloroform.[27] The catalyst was successfully reused without any decline in its activity. 4-arylquinolines derivatives were thus synthesized successfully with the yield ranging between 60-95% by optimizing the reaction conditions.

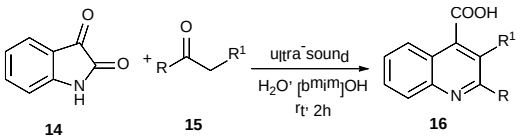


Scheme 4 Synthesis of quinoline derivative using copper nanoparticle

2.4 Ultrasound Method

Among the modern methods of synthesis, ultrasound method is another most important method as it makes use of sound waves for cavitation, which decreases the amount of time required for the reaction. Borsoi *et al.* synthesized 4-alkoxy-2-methylquinolines by a simple procedure involving the reactants alkyl (allyl) halides and 3-hydroxychromes in the presence of a base K_2CO_3 when sonicated for about 15 mins. The solvents used were dimethylformamide (DMF) and N-methyl pyrrolidinone and the temperature was maintained at about 115-120°C. The yield percentage ranged from 45-85%.[28] Refluxing whilst sonicating for the preparation of 1-(7-chloroquinolin-4-yl) derivatives was proposed by Aboelnaga and El-Sayed.[29] The general procedure followed included the introduction of an amine (*o*-phenylenediamine, thiosemicarbazide) with 4,7-dichloroquinoline, 3-amino-1,2,4-triazole and ethanol in a reaction vessel which was refluxed for 30 mins in an ultrasound bath at appropriate temperature.

Prasad *et al.* reported the synthesis of quinoline derivatives using $SnCl_2{\cdot}2H_2O$ using ultrasonication. The general procedure follows the introduction of 3,3-diethoxypropionate ester and aniline and aldehyde with $SnCl_2{\cdot}2H_2O$ in pure water. The reaction was stirred for 1-8 hours with an ultrasound irradiation of 35 kHz in the presence of air. The yield percent was about 80% when water was used as a solvent.[30] Ultrasound when used with ILs as solvent, enhanced the yield of the reactions. The same was reported by Gurpreet Kaur *et al*. The yield percent of the various derivatives made, ranged between 72-90%. 4-carboxyquinolines (**16**) were prepared using α-methylene ketones (**15**), isatin (**14**), 1-butylimidazolium tetrafluoroborate ([hbim]BF_4). This was irradiated with ultrasonic waves in methanol at room temperature (Scheme 5).[31]



Scheme 5 Synthesis of quinoline derivatives using combination of ultrasound and ionic liquid

Quinoline Hybrids

Quinoline hybrids refer to molecules consisting of quinoline and other heterocyclic moieties combined in a single molecule by a common bond or atom, by a single covalent bond, by an alkyl or aryl group, or fused to a common ring.

Quinoline-Azole Derivatives

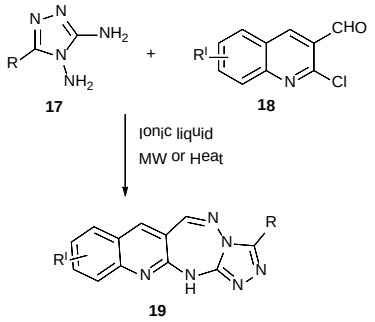
Quinoline-azole derivatives have been widely studied due to their potential applications in medicinal chemistry. Some of the important molecules are discussed below.

Quinoline-1,2,4-Triazole

1,2,4-Triazole has shown various desirable features in medicinal chemistry. 1,2,4-triazole nucleus possesses great applications in anti-inflammatory, anti-cancer, anti-depressant, anti-bacterial, anti-allergic[32] and anti-convulsant drugs.[33] These are also used in DNA cleaving agents and potassium channel activators[34] due to their moderate dipole character, rigidity, hydrogen bonding capability and stability.[35] These are

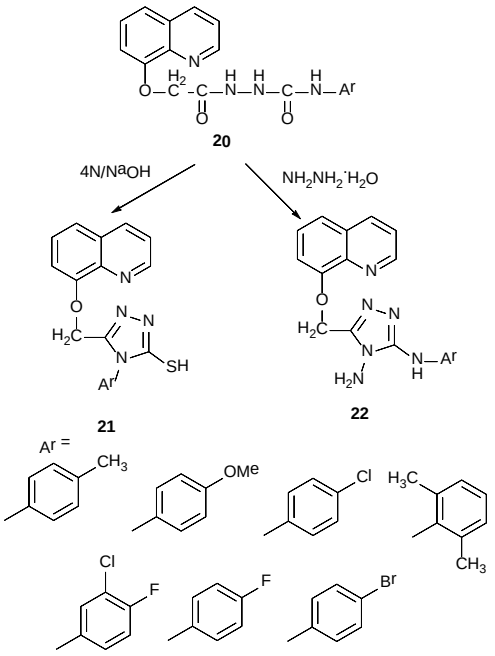
resistant to metabolic degradation, stable to reductive/oxidative and acidic/basic hydrolysis condition.[32]

Gupta *et al.* synthesized 9-substituted-3-aryl-5*H*,13a*H*-quinolino[3,2-f][1,2,4]-triazolo-[4,3-b][1,2,4]-triazepines (**19**) by condensation of 2-chloro-3-formylquinolines (**18**) and 5-aryl-3,4-diamino-1,2,4-triazoles (**17**) in ionic liquid as solvent. The reaction was accomplished both by conventional heating at 80^{0}C and by microwave irradiation (Scheme 6).[36] In (**19**) the quinoline and 1,3,5-triazole rings are both fused to a common 1,2,4-triazepine ring. Triazepine rings show fascinating biological properties and fusion with other heterocyclic rings has led them to exhibit a much wider range of biological properties.



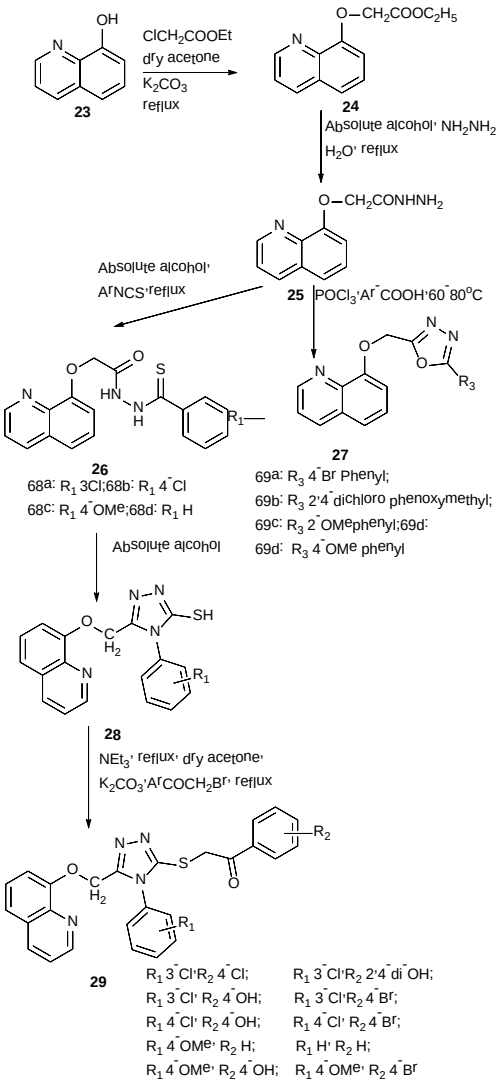
Scheme 6 Synthesis of quinoline derivative using ionic liquid

Hybrid molecules connecting quinoline at the 8th position and 1,2,4-triazole by the 3rd position via an alkyl chain (O-CH$_2$), were synthesized by using N-(4-methylphenyl)-2-[(quinolin-8-yloxy)acetyl]hydrazide (**20**). (**20**) when reacted with NaOH and hydrazine hydrate gave 4-(4-methylphenyl)-5-[(quinolin-8-yloxy)methyl]-4*H*-1,2,4-triazole-3-thiol (**21**) and N^{3}s-(methylphenyl)-5-[(quinolin-8-yloxy)methyl]-4*H*-1,2,4-triazole-3,4-diamine (**22**) respectively (Scheme 7).[37]



Scheme 7 Synthesis of quinolone derivatives using hydrazide

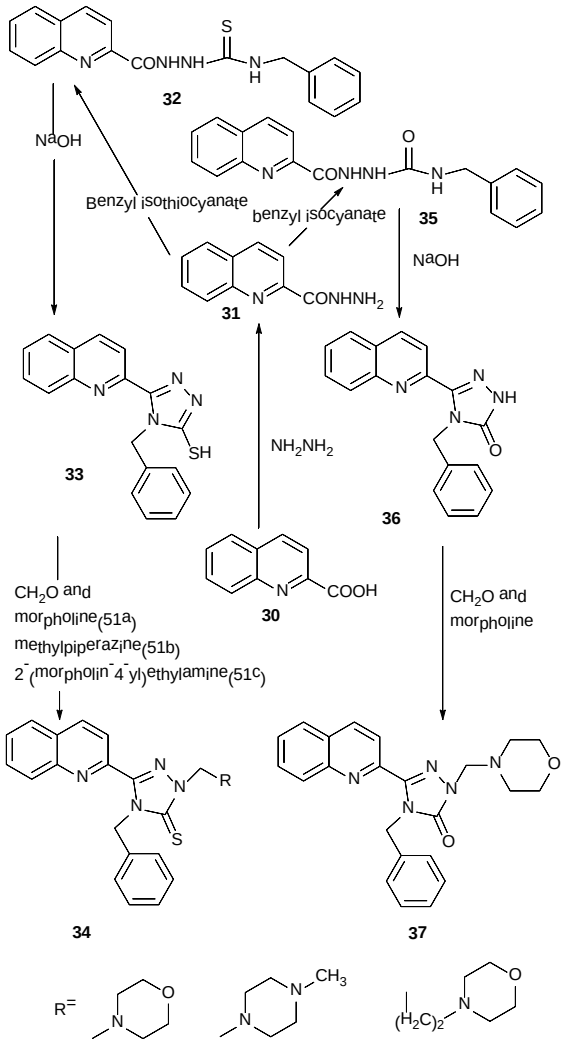
Mahboob Alam *et al.* synthesized novel 2-[4-aryl-5-{(quinolin-8-yloxy)methyl}-4H-1,2,4-triazole-3-ylthio]-1-arylethanones (**29**) which were similarly linked. Cyclization of 4-amyl-1-(2-quinolin-8-yloxy)acetyl)thiosemicarbazides (**26**) prepared from hydrazides (**25**),[37,38] using triethylamine gave 4-phenyl-5-{(quinolin-8-yloxy)methyl}-4*H*-1,2,4-triazole-3-thiol **(28)** which was further alkylated with substituted phenacyl bromides to obtain (**29**) (Scheme 8).[38]



Scheme 8 Synthesis of novel quinoline –triazole derivatives

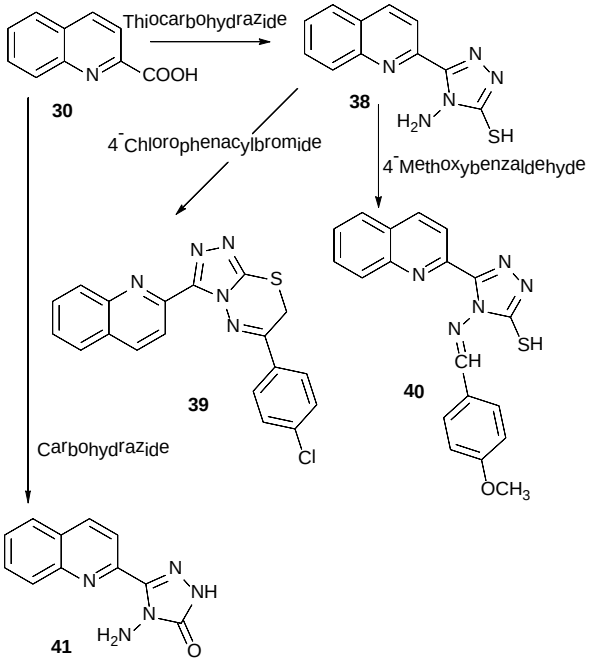
Ozyanik *et al.* synthesized 1,2,4-triazole-quinoline derivatives with various substituted 1,2,4-triazoles directly bonded to the quinoline at the second position. Quinoline-2-carbohydrazide (**31**) was treated with benzylisothiocyanate and benzylisocyanate to give carbothiamide (**32**) and carboxamide (**35**) respectively. Intramolecular cyclization of (**32**) & (35) gave the corresponding 1,2,4-triazole derivatives (**33**) & (**36**). The Mannich reaction of the triazole derivatives (**33**) & (**36**) led to the formation of amino-alkylated derivatives (**34**) & (**37**) (Scheme 9). The fusion between thiol, amino and acyl nucleus in the reaction between 4-amino-5-

(quinolin-2-yl)-4*H*-1,2,4-triazole-3-thiol (**38**) and 4-chlorophenacylbromide led to the formation of 2-[6-(4-chlorophenyl)-8*H*-[1,2,4]triazole[1,3,4]thiadiazine-3-yl]quinolone (**39**). The Schiff base 4-{[(4-methoxyphenyl)methylidene]amino}-5-(quinolin-2-yl)-4H-1,2,4-triazole-3-thiol (**40**) was obtained by condensation of (**38**) with 4-methoxybenzaldehyde in solvent free media at melting temperature (Scheme 10).[33]

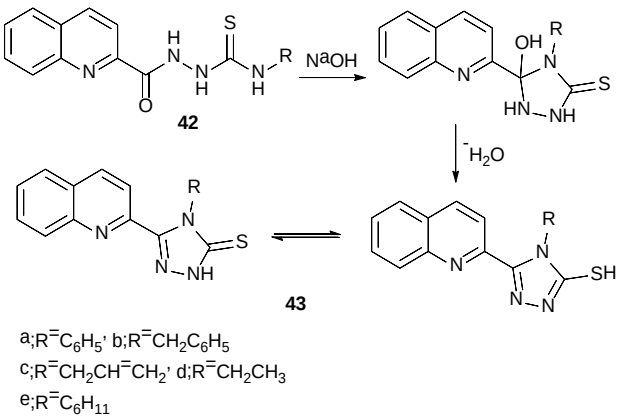


Scheme 9 Synthesis of amino-alkylated quinoline derivatives

Similar hybrid molecules were synthesized by Keshk *et al.*[37] using 4-substitued thiosemicarbazides **(42)** as starting material. (**42**) was prepared from the reaction of quinoline-2-carbohydrazide with aryl or alkyl isothiocyanates, which underwent cyclization to yield 4-substituted-5-(quinolin-2-yl)-2*H*-1,2,4-triazole-3(4*H*)thiones (**43**) (Scheme 11).[39]

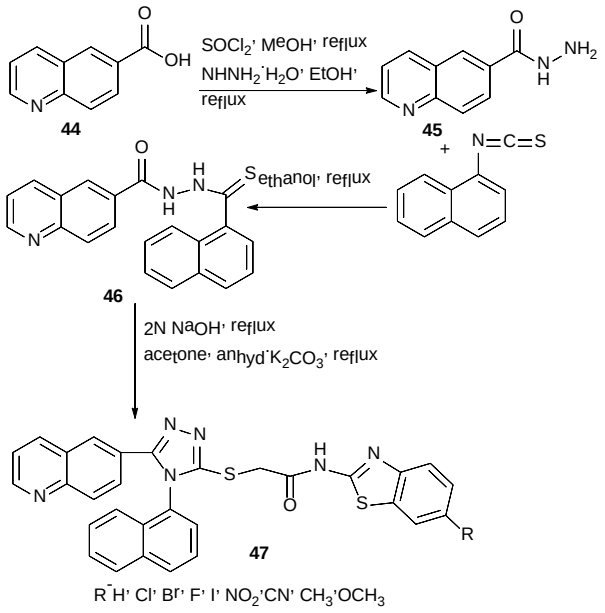


Scheme 10 Synthesis of quinoine-(1,2,4)triazole derivative



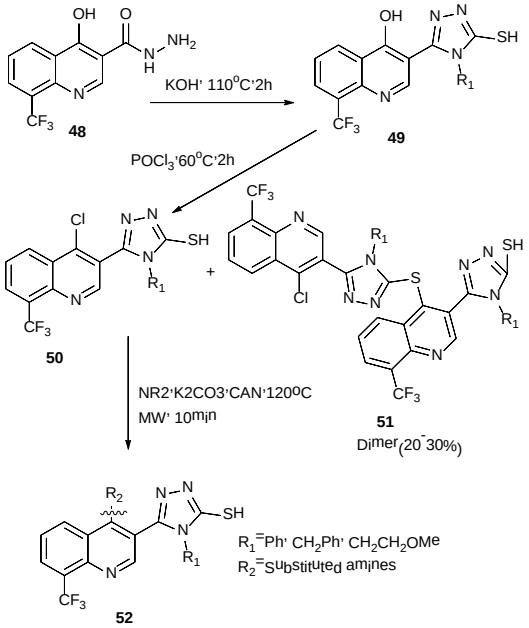
Scheme 11 Synthesis of quinolone derivative using thiosemicarbazides

Patel *et al.* synthesized hybrid molecules substituted with 1,2,4-triazoles at the 6th position of the quinoline. For this, carbohydrazide precursor (**45**) was reacted with α-naphthyl isothiocyanate to obtain N'-(naphthalene-1-carbonothioyl)quinoline-6-carbohydrazide (**46**), followed by 4-(naphthalen-1-yl)-5-(quinolin-6-yl)-4*H*-1,2,4-triazole-3-thiol moiety which was coupled with N-(benzo[d]thiazol-2-yl)-2-chloroacetamides to yield N-(benzo[d]thiazol-2-yl)-2-(4-(naphthalene-1-yl)-5-(quinolin-6-yl)-4*H*-1,2,4-triazol-3-ylthio)acetamides (**47**) (Scheme 12).[40]



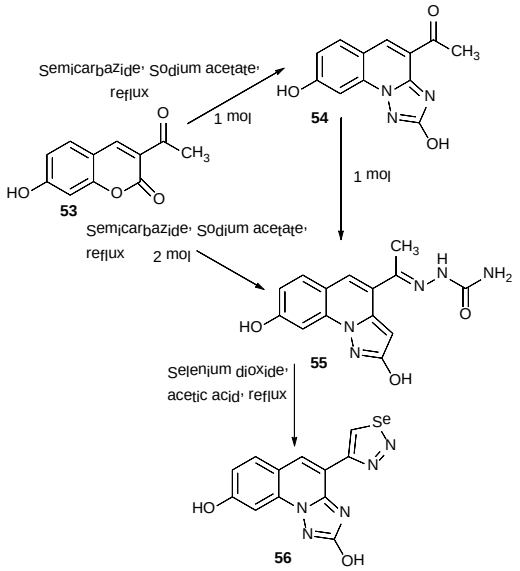
Scheme 12 Synthesis of quinoline derivatives using carbohydrazide

Eswaran *et al.* treated 4-Hydroxy-8-(trifluoromethyl)quinoline-3-carbohydrazide (**48**) to a multi-step reaction to form quinoline derivatives containing 1,2,4-triazole moiety bonded covalently to the 3rd atom of the quinoline ring. (**48**) was reacted with isothiocyanates substituents in alcoholic medium to yield 4-hydroxy-8-(trifluoromethyl)quinoline thiosemicarbazide (**49**), which cyclized to (5-mercapto-4H-triazol-3-yl)-8-(trifluoromethyl)quinolin-4-ol (**50**) in basic medium. These compounds were further derivatized as shown in Scheme 13. [41]



Scheme 13 Multistep synthesis of quinolone-triazole derivatives

Bassyouni *et al.* prepared quinoline-triazole derivatives sharing a common nitrogen atom with the two moieties fused at the 'a' bond or 1st and 2nd atoms of quinoline; and the 2nd and 3rd atoms of 1,2,4-triazole using 3-acetyl-7-hydroxy-2*H*-chromen-2-one (**53**) as starting material. Reaction of (**53**) with 1 mole and 2 moles of semicarbazide gave 1-(2,8-dihydroxy-[1,2,4]triazolo[1,5-a]quinolin-4-yl)ethenone (**54**) and 2-(1-2,8-dihydroxy-[1,2,4] triazolo[1,5-a]quinolin-4-yl)-ethylidene)hydrazinecarboxamide (**55**) respectively. (**55**) underwent oxidative cyclization with selenium dioxide in presence of acetic acid to give 4-(6*H*-1,2,3-selenadiazol-4-yl)-[1,2,4]triazolo[1,5-a]quinoline-2,8-diol (**56**) (Scheme 14).[42]



Scheme 14 Synthesis of quinolone derivatives using semicarbazide

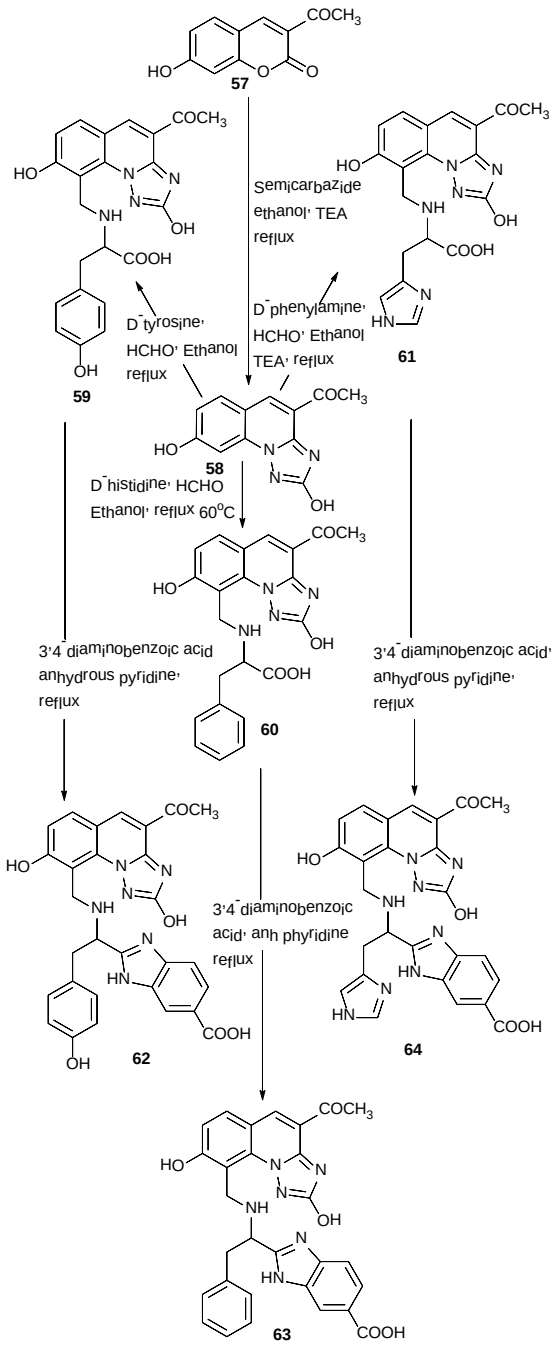
Sumangala *et al.* synthesized similar fused derivatives (**59-64**). 2-((2,8-dihydroxy-4-acetyl–[1,2,4]-triazolo[1,5-a]quinolin-9-yl)methylamino) carboxylic acid derivatives (**59-61**) were formed from the reaction of (**58**) with amino acids such as D-phenylamine, D-histidine, D-tyrosine and formaldehyde. Compounds (**59-61**) were condensed and cyclized to give 2-(2,8-dihydroxy-4-acetyl-[1,2,4]triazolo[1,5-a]quinolin-9-yl)methylamino-9-(benzimidazolecarboxylic acid) derivatives (**62-64**) (Scheme 15).[43]

1*Quinoline-1,2,3-triazole*

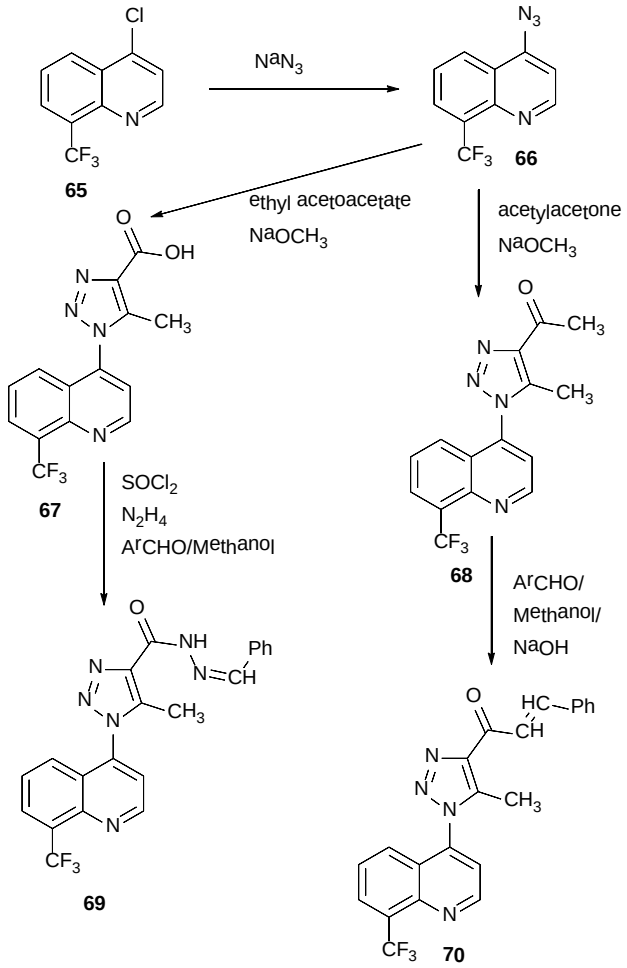
It is well established that attachment of 1,2,3-triazole moiety to the quinolines enhance its antimicrobial activity and other biological properties.[41]

Synthesis of quinoline derivatives directly bonded by its 4th atom to the 1st N atom of 1,2,3-triazoles was achieved by Holla *et al.* 1,3 dipolar cycloaddition reaction of 4-azido-8-(trifluoromethy)quinolone (**66**) with acetylacetone and ethyl acetoacetate to give the 1,2,3-triazoles 1-{1- [8-(trifluoromethyl)-quinolin-4-yl]-5-methyl-1*H*-1,2,3,triazol-4-yl}ethanone (**69**) and 1-[8-(trifluoromethyl)quinolin-4-yl]-5-

methyl-1*H*-1,2,3-triazole-4-carboxylicacid (**67**) respectively.[34] Conversion of (**67**) into acid hydrazide and condensation with various aromatic aldehydes yielded the Schiff base N-[1-arylmethylene]-1-[8-(trifluoromethyl)quinolin-4-yl]-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide (**69**) and condensation of (**68**) with different aldehydes gave 1-aryl-4-{1-[8-(trifluoromethyl)quinolin-4-yl]-5-methyl-1*H*-1,2,3-triazole-4-yl}prop-2-en-1-one (**70**) (Scheme 16).



Scheme 15 Synthesis of quinoline –triazole carboxylic acid derivatives

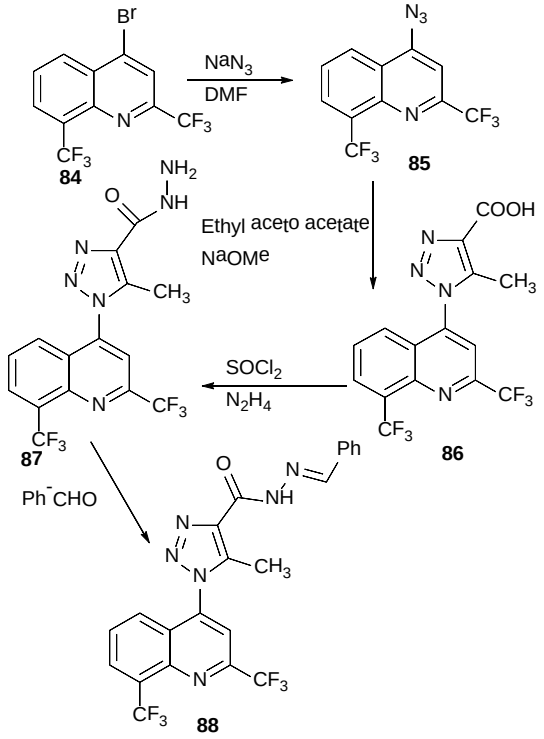


Scheme 16 Synthesis of quinoline-1,2,3-triazole derivatives

Thomas *et al.* synthesized similar but differently derivatized molecules: quinoline-4-yl-1,2,3-triazole carrying amides, sulphonamides, and amido piperazines from [1-(6-methoxy-2-methylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methylmethane-sulfonate (**73**) key intermediate (Scheme 17).[13]

An improvised synthesis of quinoline-4-yl-1,2,3-triazole derivatives, N-[1-(6-methyoxy-2-ethylquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methylamine by Thomas *et al.* involved three component one-pot reaction of propargyl bromide, azide intermediate (**82**) and different alkyl heterocyclic amines in the presence of triethylamine and copper iodide (Scheme 18).[35]

Sumangala *et al.* synthesized similar quinoline-4-yl-1,2,3-triazoles, N-[1-arylmethylene]-1-[2,8-bistrifluoro methylquinoline-4-yl]-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazides (**88**) from 1-(2,8-bistrifluoromethylquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylicacid (**87**). (**87**) was obtained from 1,3-dipolar cycloaddition reaction of 4-azido-2,8-bistrifluormethyl quinoline (**86**) with ethyl acetoacetate (Scheme 19).[43]



Scheme 19 Synthesis of quinoline-triazole carbohydrazide derivatives

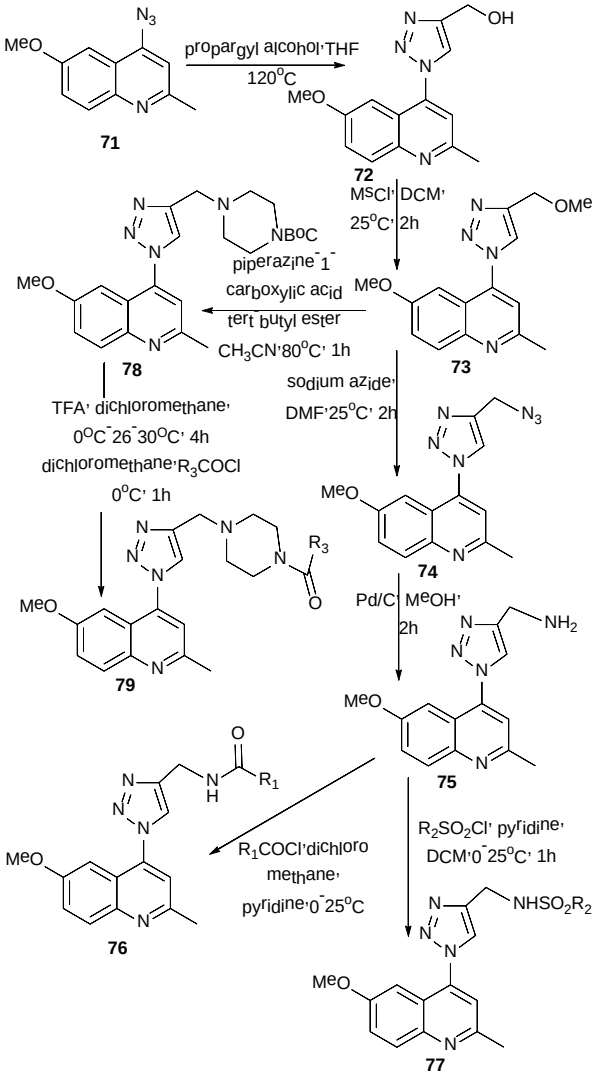
Synthesis of similar hybrids: 7-chloro-4-(1*H*-1,2,3-triazol-1-yl)quinoline (**91,92**) was achieved by Ghandi *et al.* Swern oxidation of alcohol derivative (**89**) yielded the aldehyde (**90**). Reaction of (**89**) with dimethylaminosulfur trifluoride in CH_2Cl_2 gave monofluorinated derivative (**91**). Di-fluorinated derivative (**92**) was obtained from reaction of aldehyde (**90**) with dimethylaminosulfur trifluoride (Scheme 20).[44]

Quinoline derivatives substituted with 1,2,3-triazoles at the 2nd position of quinoline were synthesized as stable intermediates by Peczynska-Czoch *et al.* for the preparation of 6*H*-Indolo[2,3-b]quinolines.[45] Quinoline (**93**) was reacted with benzotriazole (**94**) at 110-120^{0}C to obtain 2-(1-[Benzotriazolo]quinolones (**95**) (Scheme 21). Condensation of quinolone (**97**) with 4-methyl-3-nitroaniline (**98**) followed by the reduction of nitro group intermediate (**99**) and diazotization of the amine yielded 2-5(-methyl-1-benzotriazolo)quinoline triazole derivative (**100**) (Scheme 22).

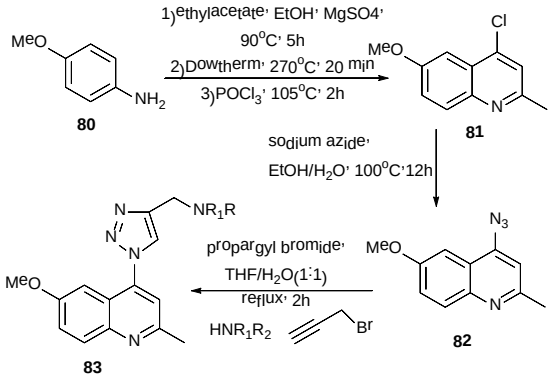
Quinoline-triazole derivatives connecting the 3rd atom of quinoline with the 1st N atom of 1,2,3-triazole via a methylene group was achieved by Kategaonkar *et al.* who synthesized 2-chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline (**105**) derivatives using Click reaction to connect phenyl acetylene and 2-chloroquinolyl moiety containing terminal azide compounds (**104**) in the presence of Cu(I)catalyst (Scheme 23).[32]

QUINOLINE-TETRAZOLE

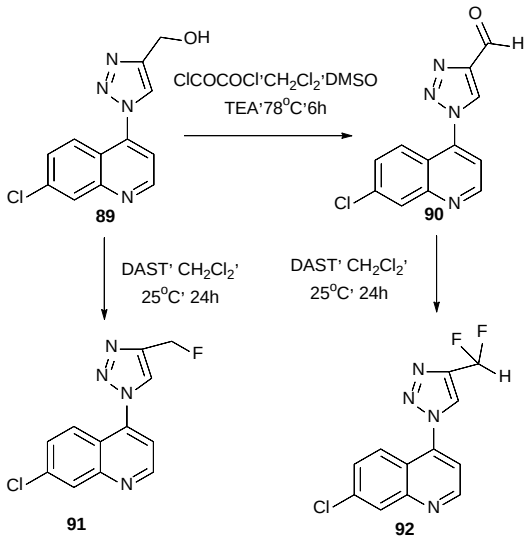
Ghandi *et al.* synthesized novel tetrazole-based quinoline compounds by one pot multi-component reaction that proceeded through Ugi-Azide and Pictet-Spengler processes.[46] Ugi-Azide reaction of 2-chloroquinoline-3-carbaldehydes (**107**), isocyanides and trimethylsilyl azide in MeOH yielded N-((2-chloroquinolin-3-yl)(1-cyclohexyl-1H-tetrazol-5-yl) (**111**). Addition of formaldehyde and trifluoroacetic acid to the combination of aldehyde (**107**), isocyanide (**109**), trimethylsilylazide (**108**) and tryptamine yielded novel quinoline based 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-Carbolines (Scheme 24).[46]



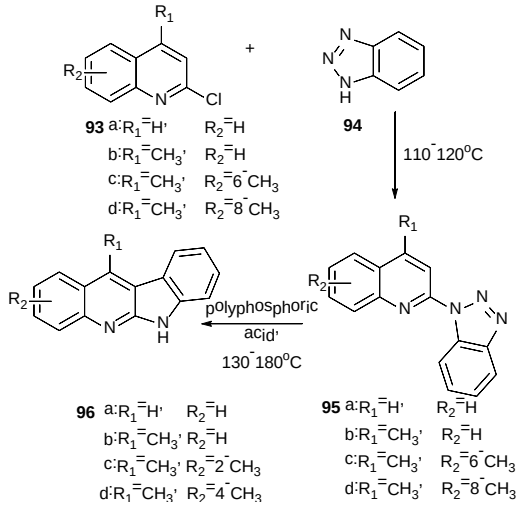
Scheme 17 Synthesis of quinoline-triazole derivatives having amides, sulfonamides, and amido piperazines



Scheme 18 Synthesis of quinoline-derivatives by one-pot reaction



Scheme 20 Synthesis of fluorinated quinoline-triazole derivatives

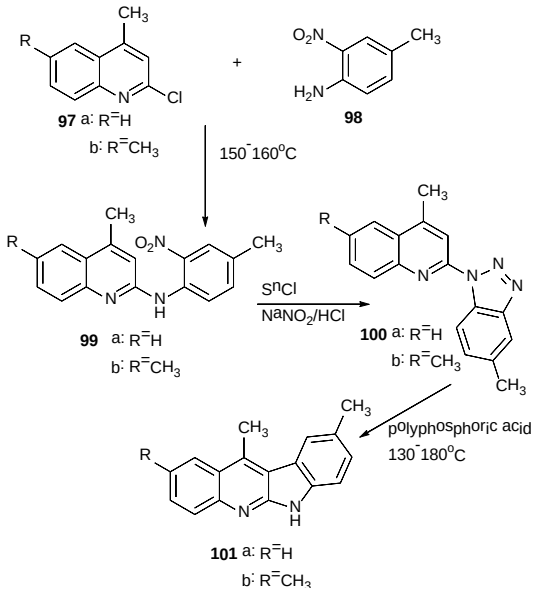


Scheme 31 Synthesis of quinoline-triazole derivative as intermediate

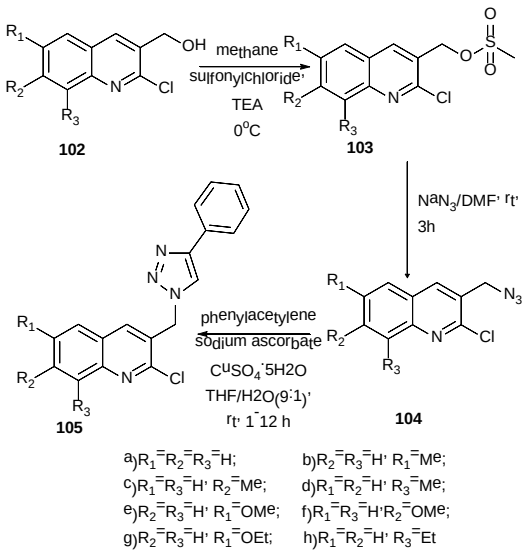
Tetrazole moiety attached to biphenyl ring which is linked to quinoline in the compounds (**114, 117**) was synthesized using starting materials (**112, 116**) by Nellisara *et al*. These (**114, 117**) were converted to Schiff base derivatives (**115, 118**) in K_2CO_3/DMF by condensation with different amines in ethanol, followed by deprotection of acid by acid-catalyzed hydrolysis (Scheme 25).[47]

8-[(2H-tetrazole-5-yl)methoxy]quinolone (**119**) sugar hydrazones and N-glycoside derivatives connecting the tetrazole to the 8th position of the quinoline via an alkyl chain (O-CH_2) were synthesized by Rashad *et al.* Compound (**119**) was reacted with acetobromo sugars (**120**) to yield glycosides (**121**), which on treatment with methanolic ammonia at 0^0C gave the corresponding de-acrylated N-glycosides(**122**) (Scheme 26). [48]

Adnan *et al.* synthesized similar hybrid ester, sugar, hydrazone and other derivatives wherein the quinoline and tetrazole were linked similarly as in Scheme 26. *N*-substituted ethyl ester was obtained by reaction of (**119**) with ethyl chloroacetate. (**123**) on hydrazinolysis in ethanol gave 2-{5-[(quinolin-8-yloxy)mrethyl]-2H-tetrazol-2-yl} acetohydrazide (**124**). Sugar-2-{5-[(quinolin-8-yloxy)methyl]-2H-tetrazol-2-yl}acetylhydrazones (**125**) were synthesized by reaction of hydrazide derivative (**124**) with D-galactose or D-arabinosein, in the presence of catalytic amount of glacial acetic acid in ethanol. Acetylation of sugar hydrazones (**125**) in pyridine with acetic anhydride at room temperature gave per-*O*-acetylated sugar hydrazone derivative (**126**) (Scheme 27).[49]

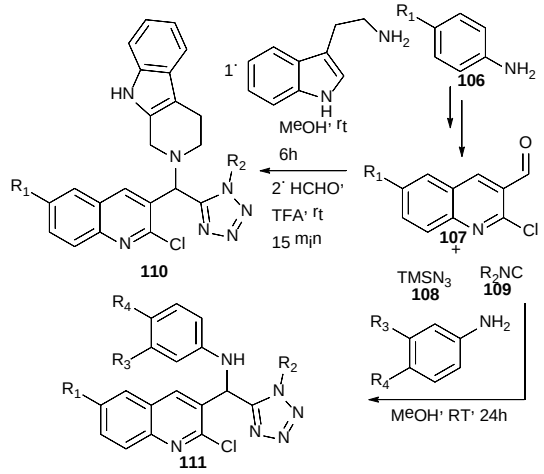


Scheme 22 Synthesis of quinoline derivatives by condensation reaction

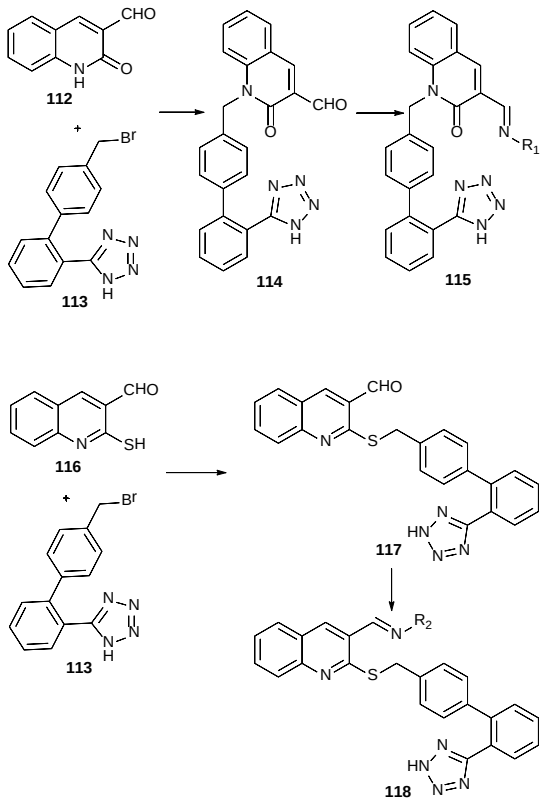


Scheme 23 Synthesis of quinoline derivatives by Click reaction

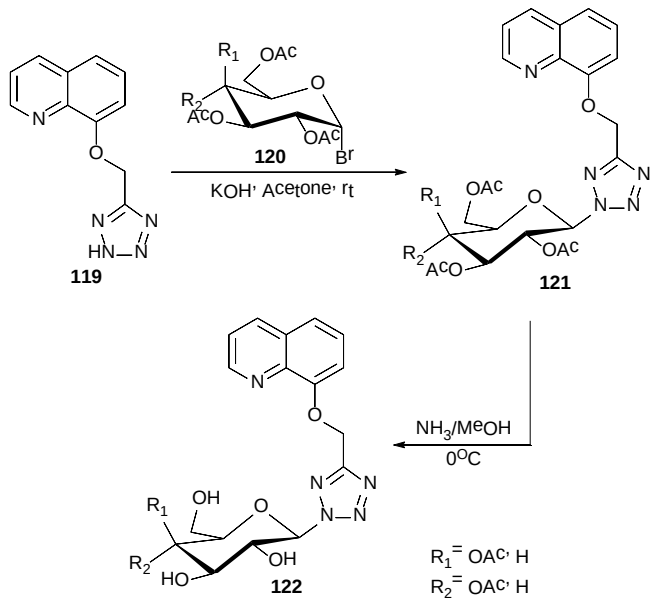
Adnan *et al.* also accomplished the synthesis of derivatives where the 'a' bond or 1st and 2nd atoms of the quinoline are fused to the 1st and 5th atoms of the tetrazole resulting in a shared nitrogen atom. 2-chloroquinoline-3-carboxaldehyde (**127**) was reacted with sodium azide which afforded Tetrazolo[1,5-a]quinoline-4-carboxyaldehyde (**128**).[49] This could be condensed with substituted thiosemicarbazides and ketones to yield 4-substituted thiocarbanoylhydrazonomethyltetrazolo[1,5-a]quinolines (**132**) and tetrazoloquinolinylchalcone derivatives 4-(3-aryl-3-oxopropenyl)-tetrazolo[1,5-a]quinolines (**130**). The products obtained were further derivatized to obtain (**131,133,134**) (Scheme 28).



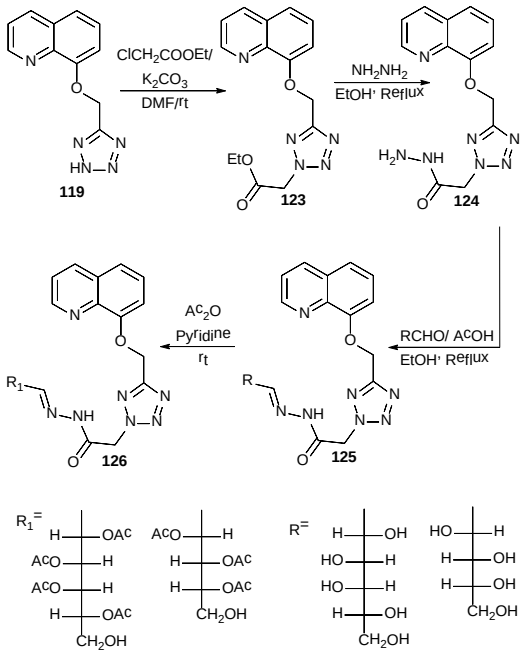
Scheme 24 Synthesis of quinoline-tetrazole carbolines derivatives



Scheme 25 Synthesis of quinolone-tetrazole derivatives having biphenyl moiety



Scheme 26 Synthesis of quinolone-tetrazole glycosides derivatives



Scheme 27 Synthesis of quinoline-tetrazole hydrazine derivatives

QUINOLINE-IMIDAZOLE-TETRAZOLE

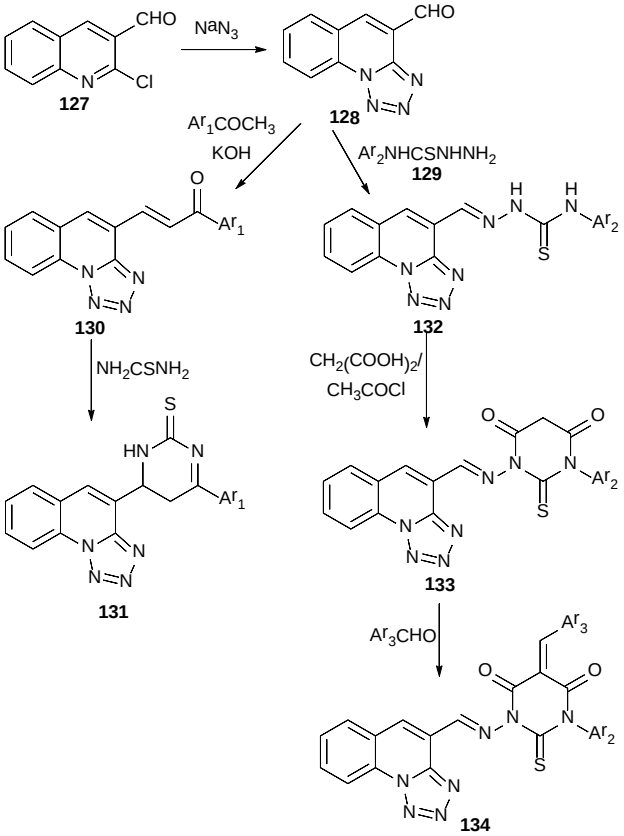
Rajashri *et al.* synthesized quinoline derivative containing both tetrazole (fused to a quinoline moiety as in Scheme 28) and benzimidazole moieties. Benzimidazolyl acetamide (**138)** was reacted with Vilsmeier-Haack reagent to give the cyclized product 2-chloroquinoline 3-carbaldehyde (**139**). Reaction of (**139**) with sodium azide gave quinoline ring fused with tetrazole **(140)**. Methanamine *N*-((7-(1H-benzo[d]imidazol-2-yl)tetrazole[1,5-a]quinolin-4-yl)methylene) (**141**) was obtained by reaction of (**140**) with substituted aniline (Scheme 29).[50]

Kateganokar *et al.* treated 2-chloroquinoline-3-carbaldehyde derivative (**142**) with sodium azide in DMSO/AcOH mixture to obtain tetrazolo[1,5-a]quinline-4-carbaldehyde (**143**). Treatment of (**143**) with Benzil (**144**) and ammonium acetate in the ratio of 1:2:4 in glacial acetic acid yielded 4,5-diphenyl-1H-imidazole (**145**) where a quinoline is fused to a tetrazole moiety and bonded directly by the 3rd atom of quinoline to the 2nd atom of an imidazole moiety (Scheme30).[51]

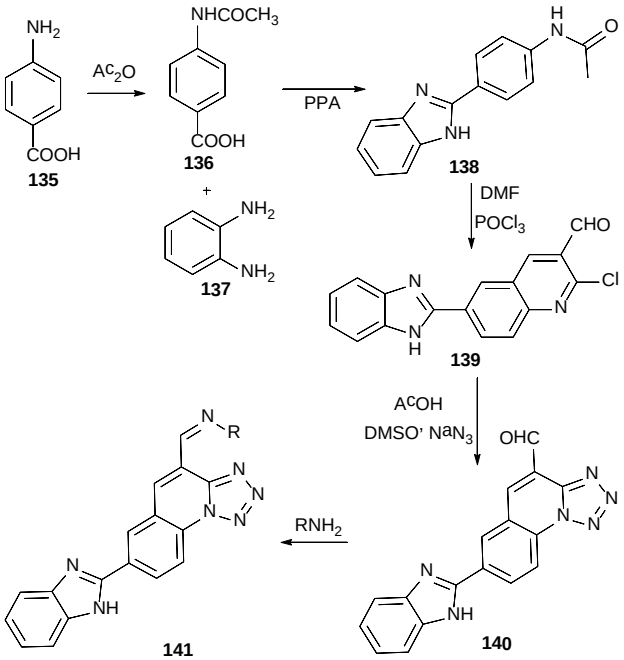
QUINOLINE-IMIDAZOLE

Imidazole and Benzimidazole are leading structures in the manufacture of anticancer and anti-tubercolosis drugs. They showed very good anti-infammatory, anti-malaraial, anti-microbial and anti-fungal activity.[33] Imidazole rings are structural motifs in pharmacologically important molecules and are well tolerated drugs.[37] Some of the methods of synthesis of these molecules are mentioned below:

Musonda *et al.* synthesized derivatives of Chloroquine-Astemizole (CQ-Astemizole) where the quinoline is connected to the benzimidazole moiety via a piperazine moeity. Coupling reaction of **(149)** with 4,7-dichloro quinoline **(150)** yielded CQ-

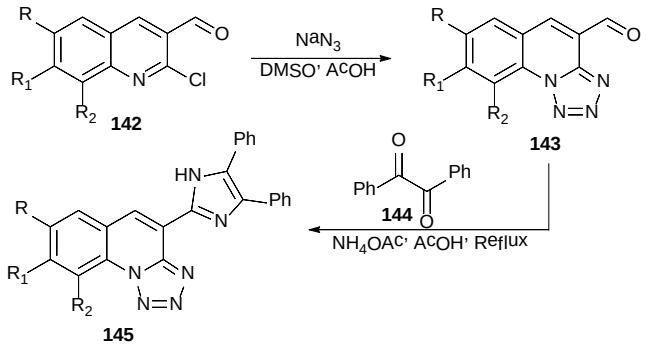


Scheme 28 Synthesis of quinoline-tetrazole derivatives with chalcone and hydrazine moiety



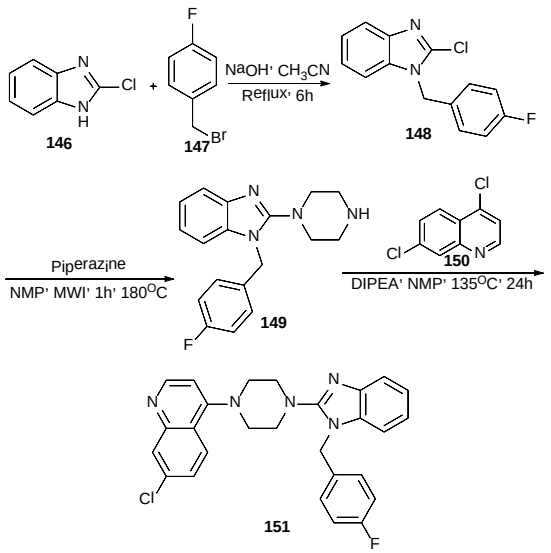
Scheme 29 Synthesis of quinolone-benzimidazole-tetrazole derivative

astemizole derivative (**151**) (Scheme 31). Another derivative of CQ-astemizole **(154)** was synthesized by nucleophilic substitution of triflate (**153**) with (**149**) (Scheme 32).[52]



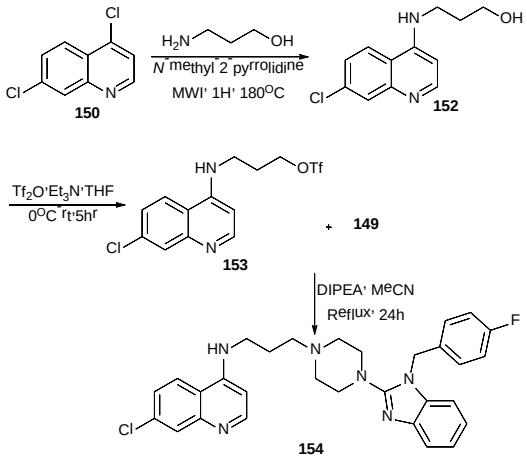
Scheme 30 Synthesis of quinoline-imidazole-tetrazole derivatives

Musonda *et al.* synthesized the similar derivatives as in Scheme 32 with varied chain length of the linker. Coupling of 4-aminopiperdine with (**150**) gave (**156**), which when reacted with (**148**) yielded the CQ-astemizole derivative (**157**) (Scheme 33).[53] Coupling reaction between (**158**) with (**150**) under microwave irradiation afforded the CQ-astemizolo derivative (**159**) (Scheme 34).[52]

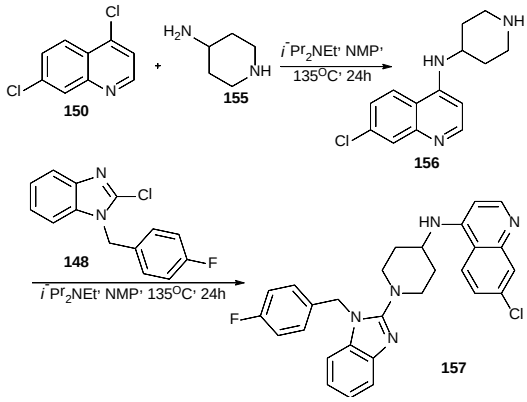


Scheme 31 Synthesis of quinoline-imidazole derivative by coupling reaction

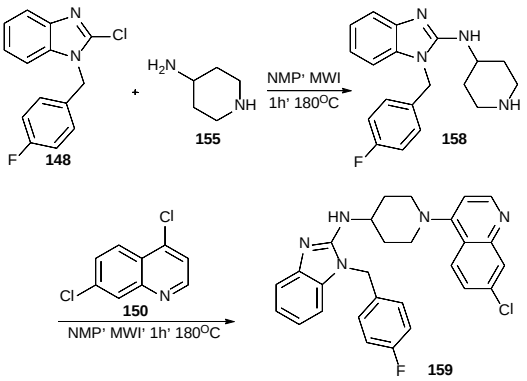
Bartzees *et al.* synthesized phenyl-benzimidazoles (**161**) & ferrocene-benzimidazole (**162**) through multistep reactions. 1,2-diamine amino quinoline (**160**) underwent condensation and cyclization with benzaldehyde or ferrocene carboxaldehyde in presence of catalytic amount of trifluoroacetic acid (TFA) and anhydrous magnesium sulphate to give (**161**) **&** (**162**) respectively (Scheme 35).[53]



Scheme 32 Synthesis of quinoline-imidazole derivative using triflate**4**

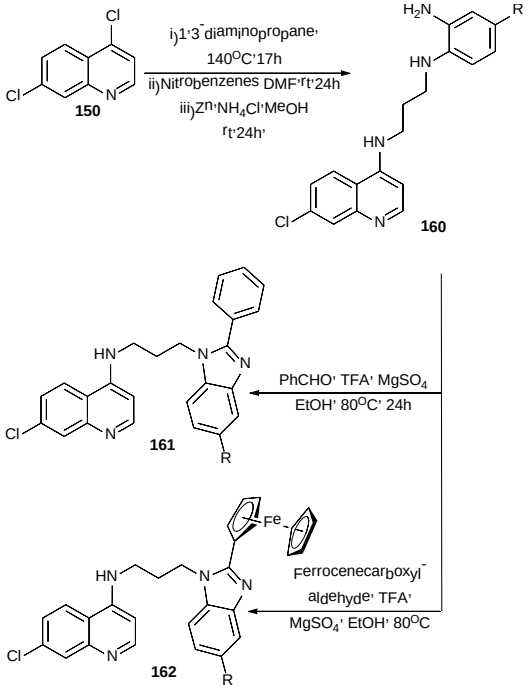


Scheme 33 Synthesis of CQ-Astemizole

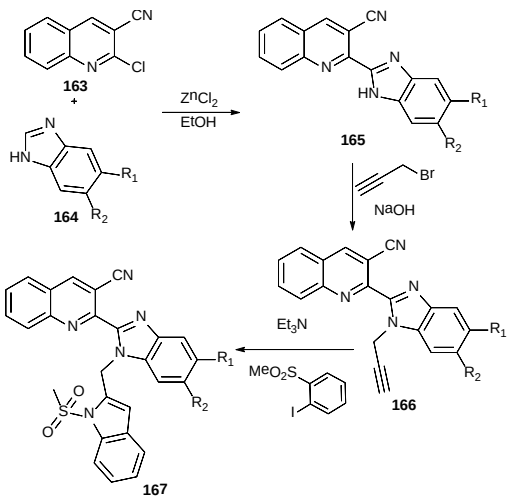


Scheme 34 Synthesis of quinoline-imidazole derivative by microwave irradiation

Quinoline derivatives directly bonded by its 2nd atom to the 2nd atom of benzimidazole were synthesized by Merugu *et al.* 2-(1-((1-(methylsulfonyl)-1H-indol-2-yl)methyl)-1H-benzo[d]imidazol-2-yl)quinoline-3-carbonitrile (**167**) was synthesized by cyclization of (**166**) with 1-iodo-2-(methyl sulfonyl)benzene. For the synthesis of (**166**), starting material 2-chloroquinoline-3-carbonitrile (**163**) was reacted with benzimidazole (**164**) to afford 2-(1H-benzo[d]imidazol-2-yl)quinoline-3-carbonitrile (**165**), which on treatment with propargyl bromide yielded 2-(1-(prop-2-ynyl)-1H-benzo[d] imidazole -2-yl)quinoline-3-carbonitrile (**166**) (Scheme 36).[54]

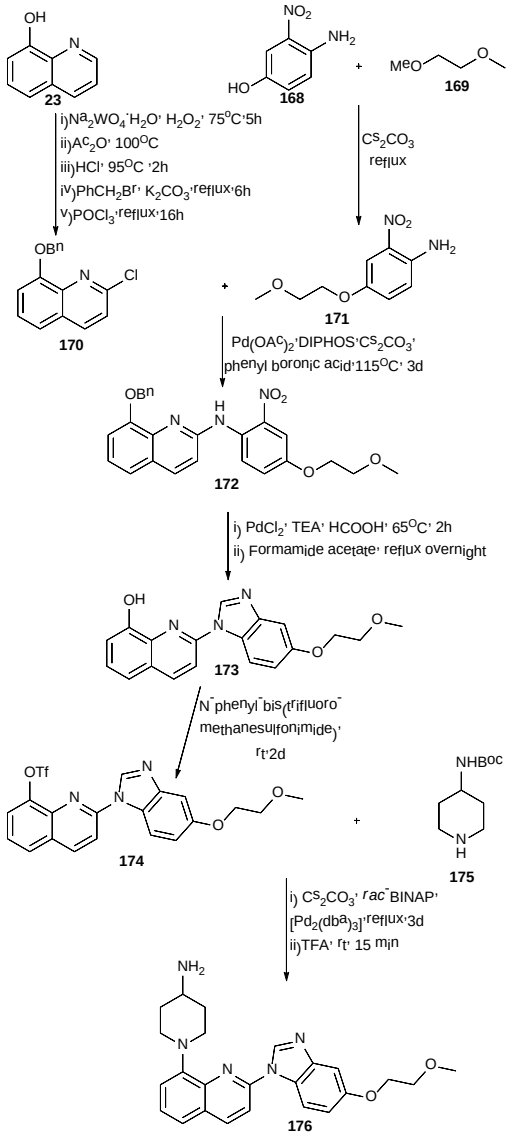


Scheme 35 Synthesis of quinoline-imidazole derivatives having phenyl and ferrocene moiety



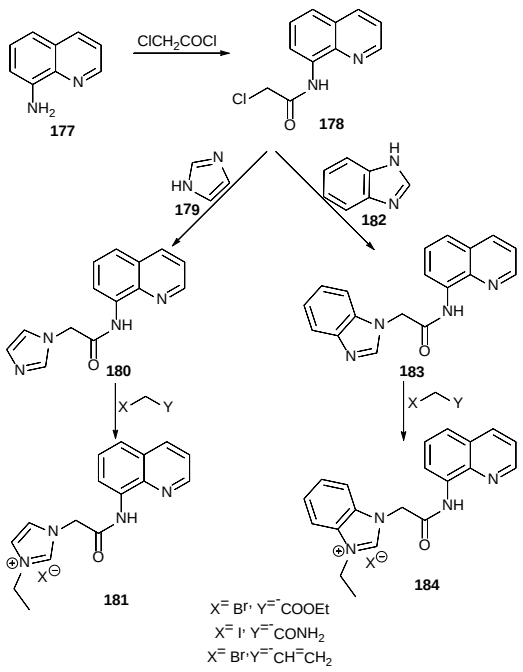
Scheme 36 Synthesis of quinoline imidazole derivatives having carbonitrile moiety

Effendi *et al.* synthesized similar hybrid derivatives (**173, 174, 176**) with different sustituents by a series of reactions using hydroxyl quinoline as starting material (Scheme 37).[55]



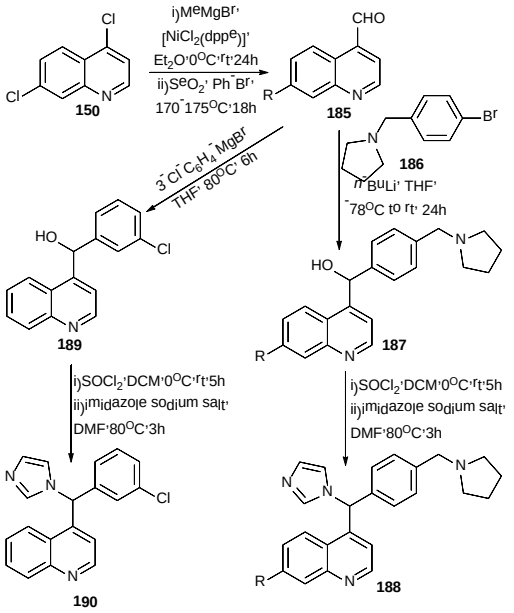
Scheme 37 Synthesis of quinoline –imidazole derivative using hydroxyl quinoline

Mantu *et al.* carried out *N*-acylation, *N*-alkylation and quaternization of N-heterocycles by a three-step procedure for the synthesis of quinolone-benzimidazole and quinoline-imidazole derivatives where the two moieties in each, are linked by a functionalized alkyl chain. *N*-acylation 7-aminoquinoline with 2-chloroacetylchloride yields the amide (**178**). Subsequent treatment of (**178**) with imidazole and benzimidazole gave 2-(1H-imidazol-1-yl)-N-(quinolin-8-yl)acetamide (**180**) and 2-(1H-benzo[d]imidazol-1-yl)-N-(quinolin-8-yl)acetamide (**183**) respectively. Quaternization reaction of (**180** & **183**) with various activated halogenated derivatives gave (**181** & **184**) respectively. (Scheme 38).[56]

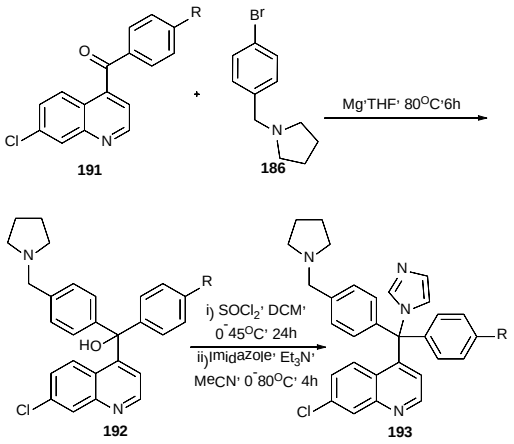


Scheme 38 Synthesis of quinoline derivatives by quaternization

Gemma *et al.* synthesized quinoline-imidazole derivatives consisting of quinoline and imidazole moieties linked to a common tertiary carbon, starting from 7-chloroquinoline-4-carbaldehyde (**185**). (**150**) was coupled with Grignard reagent, followed by oxidation to give (**185**) which on reaction with (**186**) under different conditions gave carbinols (**187) & (189).** These compounds were converted to corresponding chloride, followed by treatment with sodium salt of imidazole in DMF to yield **(188)**



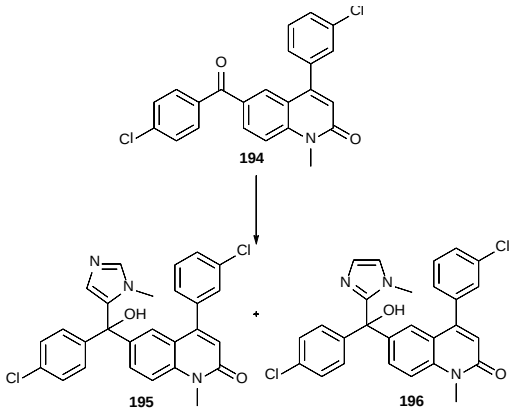
Scheme 39 Synthesis of quinoline derivatives using chloroquinoline



Scheme 40 Synthesis of quinoline-derivatives using carbinols

& **(190)** (Scheme 39).[54] Carbinols (**192**) which were prepared in a similar manner using **(191)** and Grignard reagents, underwent subsequent chlorination and on further treatment with imidazole and triethylamine yielded (**193**) where the quinoline and imidazole moieties are bonded to a common quaternary carbon (Scheme 40).[57]

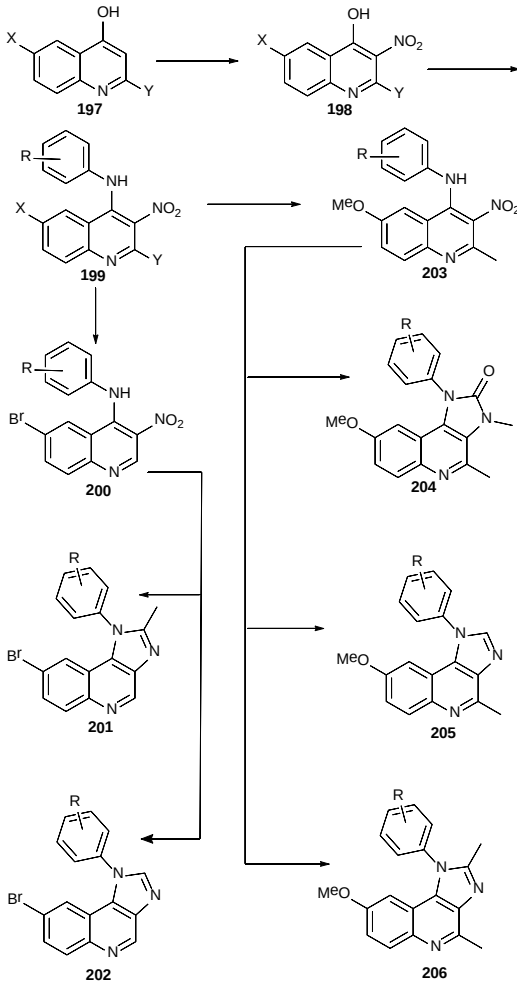
Angibaud *et al.* reacted 6-(4-chlorobenzoyl)-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone (**194**) with N-methylimidazole to give 4-(3-cholorophenyl)hydroxyl(1-methyl-1H-imidazol-5-yl)methyl]-1-methyl-2(1H)-quinolinone (**195**) and 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxyl(1-methyl-1H-imidazole-2-yl)methyl]-1-methyl-2(1H)-quinolinone (**196**) (Scheme 41).[58]



Scheme 41 Synthesis of quinoline derivatives using N-methylimidazole

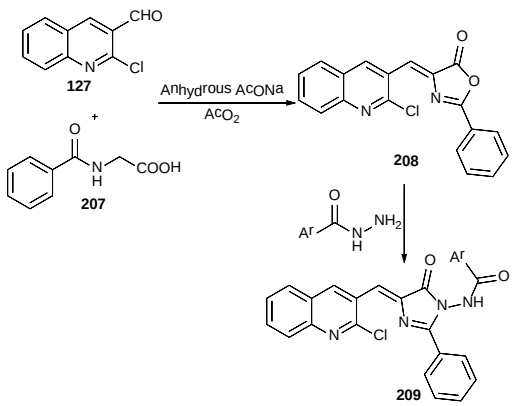
Xiao *et al.* synthesized compounds (**201, 202**, **204-206**) where the imidazole is fused by its 4th and 5th atoms to the 'c' bond or 3rd and 4th atoms of the quinoline moieties starting from (**199**). Methylation using methyliodide under the action of sodium hydride afforded compound (**204**). Compounds (**205**) **&** (**202**) were obtained after cyclization of (**200**) with triethylorthoformate. (**203**) when heated with triethylorthoacetate

and 1,4 dioxane as solvent gave (**206**). Similar method was used to obtain (**201** & **202**) from **(200)** (Scheme 42).[59]



Scheme 42 Synthesis of quinoline derivatives by multistep procedure

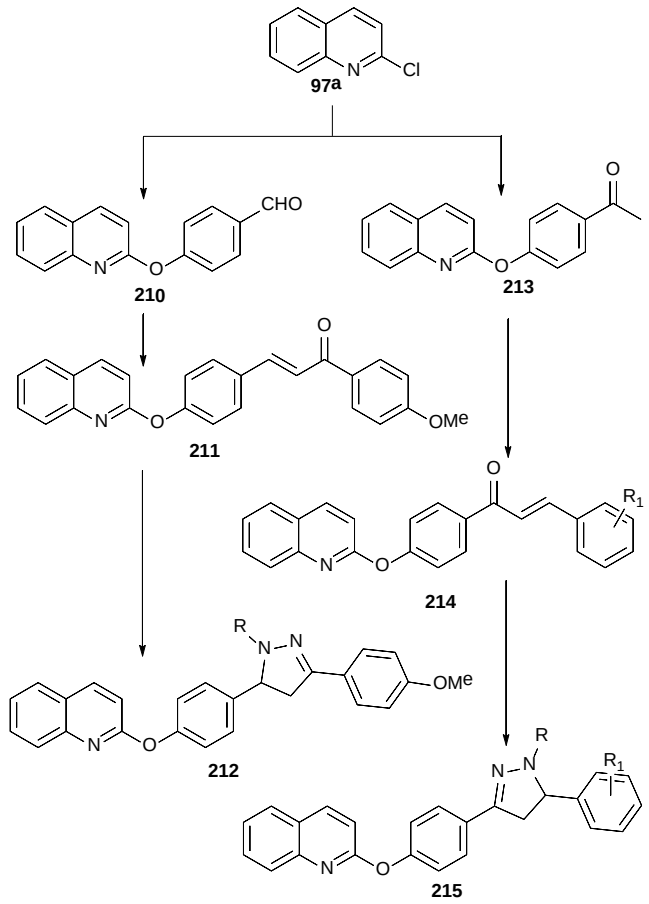
Desai *et al.* synthesized *N*-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1- yl) (aryl)amides (**209)** which consists of 2-Chloroquinoline linked by its 3rd position to the 4th position of a substituted imidazole moiety via an alkyl chain, by both conventional method and microwave method. Reaction of 2-chloroquinoline-3-carbaldehyde with hippuric acid, in presence of acetic anhydride and anhydrous sodium acetate yielded 4-((2-chloroquinolin-3-yl)methylene)-2-phenyloxazol-5(4H)-one (**208**). (**208**), on reaction with *N*-aminoarylcarboxamides in pyridine gave (**209**) (Scheme 43).[60]**6**



Scheme 53 Synthesis of quinoline derivatives using both convential and microwave methods

QUINOLINE-PYRAZOLE

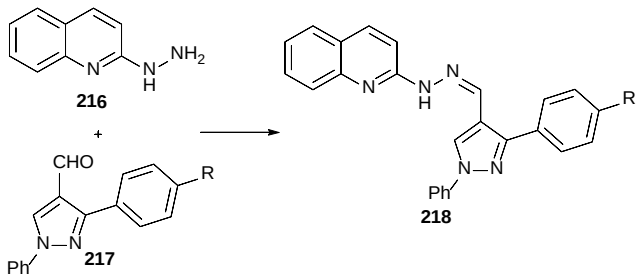
2-Chloroquinoline was used as the starting material to generate molecules containing quinoline linked by its 2nd atom to the 3rd (carbon) atom of pyrazole by an aryl linkage. 2-(4-(3-(4-methoxyphenyl-4,5-dihydro-1H-pyrazol-5-yl) phenoxy) quinoline (**212**) & 2-(4-(3-(4-methoxyphenyl)-1-phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy) quinoline (**212**) were synthesized by cyclocondensation of chalcone (**211**) with hydrazine hydrate and phenylhydrazine respectively by El. Sheshry *et al.*. Similarly, cyclocondensation of chalcone (**214**) with hydrazine hydrate and phenyl hydrazine yielded (**215)** respectively, Chalcone derivative (**214**) was obtained from Claisen-Schmidt condensation of (**213**) with aldehyde (Scheme 44).[61]



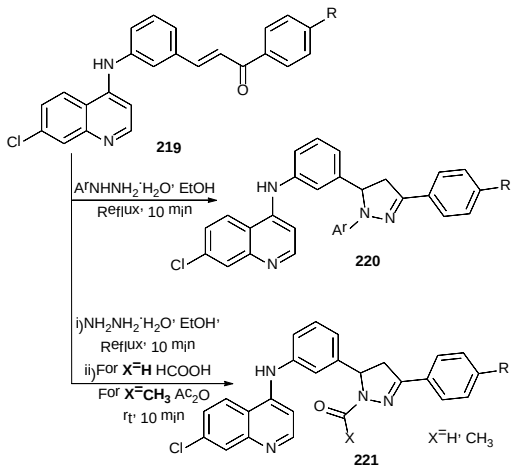
Scheme 44 Synthesis of quinoline-pyrazole derivatives using chalcone

Another set of derivatives synthesized involved quinoline linked by its 2nd atom to the 4th (carbon) atom of pyrazole by an alkyl chain. 2-hydrazinylquinoline (**216**) was synthesized from 2-chloroquinoline and condensed with formylpyrazoles (**217**) in ethanol to yield hydrazone derivative (**218**) (Scheme 45).[61]

Hybrid molecules linking the 4th atom of quinoline to carbon atom of pyrazole by aryl groups have been reported by different groups. Acetylated 1-(3-aryl-5-(3-((7-chloroquinolin-4-yl)amino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-ones (**221; X=H**) and formylated 3-aryl-5-(3-((7-chloroquinolin-4-yl)amino) phenyl) -4,5-dihydro-1H-pyrazole-1-carbaldehydes (**221; X=Me**) were synthesized by reacting [(7-chloroquinolin-4-yl)amino]chalcone (**219**) with hydrazine monohydrate and subsequent treatment with acetic anhydride (Scheme 46). The chalcone (**219**) reacted with phenylhydrazine, 4-chlorophenylhydrazine, and 3,5-dichlorophenylhydrazine to afford *N*-(3-(3-aryl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-7-chloroquinolin-4-amines, *N*-(3-(3-aryl-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-7-chloroquinolin-4-amines and N-(3-(3-aryl-1-(3,5-dichlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)phenyl)-7-chloro quinolin-4-amines (**220**) respectively(Scheme 46).[62,63]

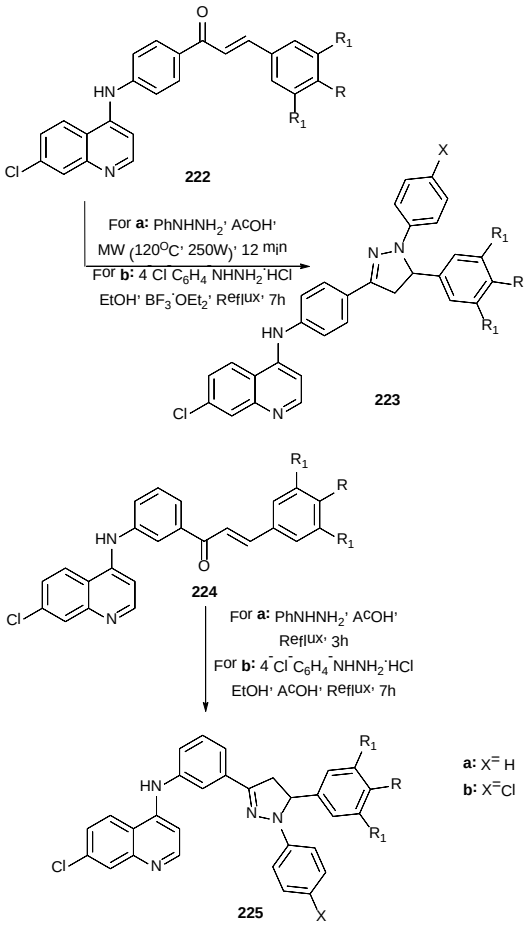


Scheme 45 Synthesis of quinoline-hydrazone derivatives from 2-hydrazinylquinoline



Scheme 46 Synthesis of quinoline-pyrazole derivatives from [(7-chloroquinolin-4-yl)amino]chalcone

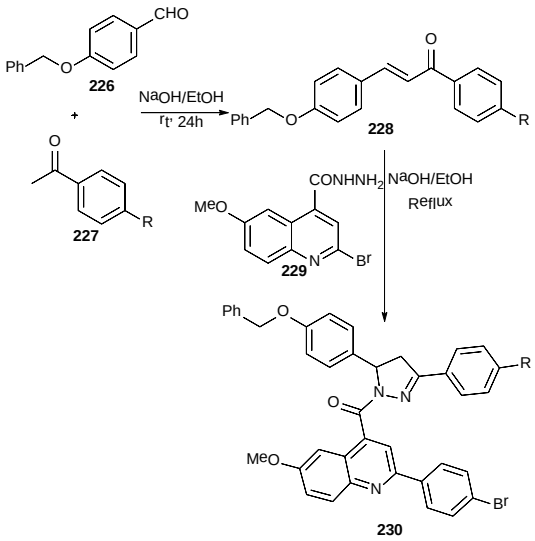
Compounds (**223a, 223b, 225a, 225b**) were synthesized using α,β unsaturated carbonyl compounds (**222, 224**) by Montoyo *et al.*. Reaction of 4-(7-chloroquinolin-4-yl)amino chalcone substituents (**222, 224**) with phenyl hydrazine in glacial actic acid under microwave irradiation yielded compounds (**223a, 225a**) and with 4-chlorophenylhydrazine hydrochloride yielded compounds (**223b, 228b**) (Scheme 47).[64]



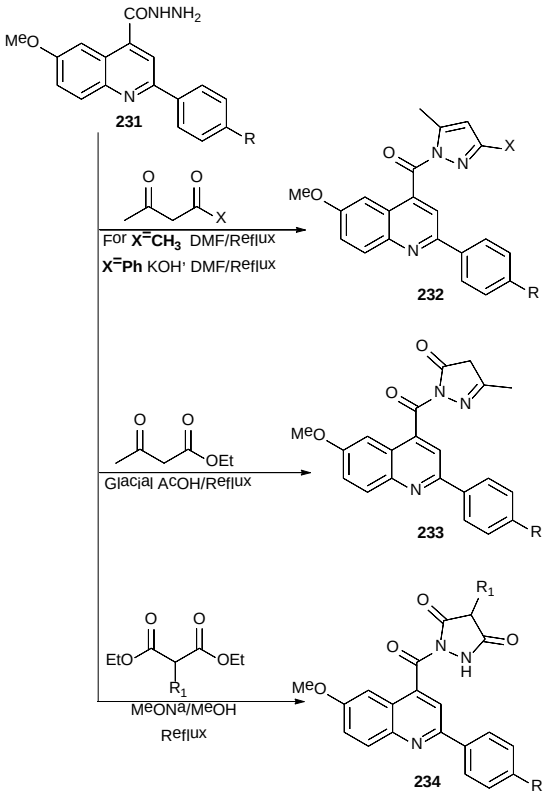
Scheme 47 Reaction of chalcones with hydrazine derivatives

The next set of hybrids have the quinoline moiety linked by its 4th atom to the Nitrogen atom of pyrazole via an acyl group. (**229**) was treated with an electrophile to synthesis pyrazole derivatives. Hydrazide derivative underwent cyclocondensation with chalcones (**228**) to yield (**230**) (Scheme 48). Further, derivatives (**233, 233, 234**) were also synthesized by cyclocondensation of hydrazide (**231**) with β-dicarbonyl compounds acetyl acetone, benzoylacetone, ethyl acetate, & diethyl malonates respectively (Scheme 49).[65]

Synthesis of hybrid molecules with the nitrogen atom of the pyrazoline moiety directly bonded to the 2nd atom of quinoline was done using 2-Hydrazinylquinoline (**216**) as starting material. Reaction of (**216**) with 2-(1-ethoxyethylidene)malonitrile and with ethyl 2-cyano-3-ethoxybut-2-enoate gave 5-amino-4-

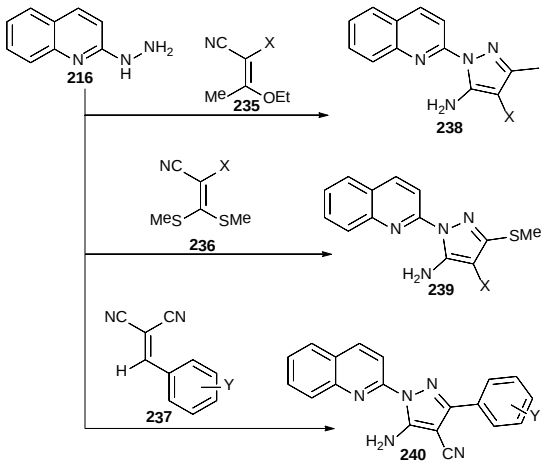


Scheme 487 Quinoline-pyrazole derivatives by cyclocondensation of hydrazide with β-dicarbonyl compounds



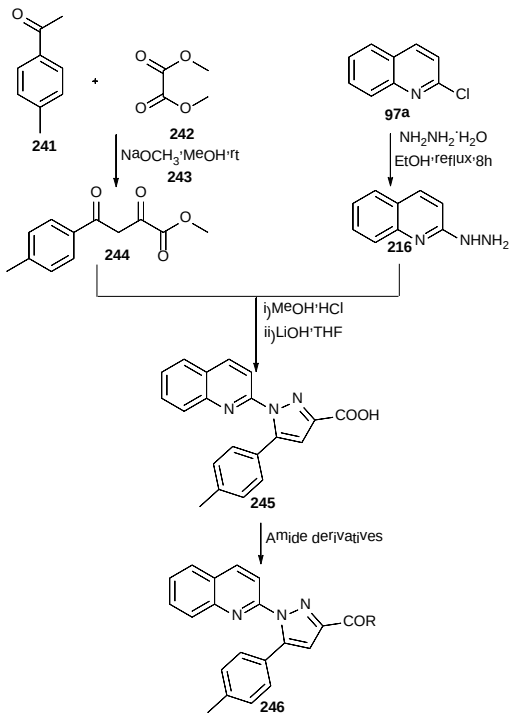
Scheme 49 Synthesis of quinoline-pyrazole derivatives

cyano-3-methyl-pyrazole derivative (**238**) and 5-amino-4-ethylcarboxylate-3-methylpyrazole derivative (**239**). Reaction of (**216**) with ketene dithioacetal [ethyl2-cyano-3,3-bis(methylthio)acrylate] and (2-(bis(methylthio)methylene) malononitrile gave 5-amino-4-ethyl-carboxylate-3-methylthio-pyrazole derivative (**239**). Arylidene malonitrile derivative reacted with (**216**) to yield 5-amino-4-cyano-3-aryl-pyrazole derivative (**240**) (Scheme 50).[61,66]



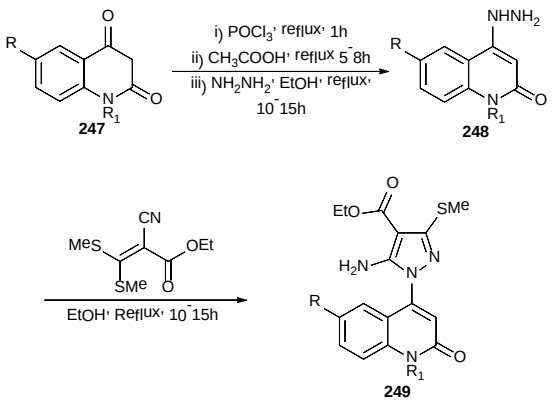
Scheme 50 Synthesis of quinoline- pyrazoline derivatives from 2-hydrazinylquinoline

Cankara *et al.* also successfully synthesized hybrid moleculs with the same type of linkage between the two heterocycles, and starting with the same reactant, (**216**). Methyl-4-(4-methylphenyl)-2,4-dioxobutanoate (**244**) was condensed with 2-hydrazinyl quinoline (**216**) to obtain the methyl ester of 1-(quinolin-2-yl)-5-(4-methylphenyl)pyrazole-3-carboxylic acid (**245**) which on reaction with amine gave (**246**) (Scheme 51).[67]



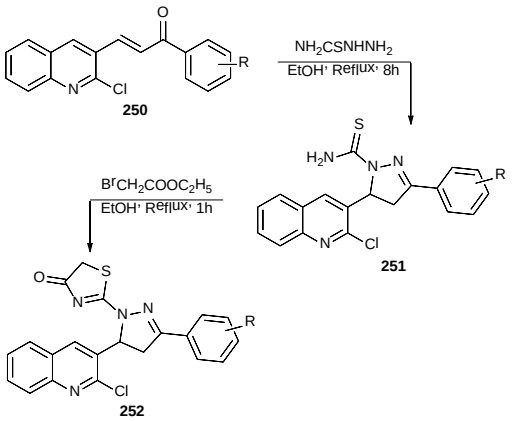
Scheme 51 Synthesis of quinoline-pyrazole esters

Aly *et al.* synthesized hybrid molcules with the pyrazole moiety directly bonded by its nitrogen atom to the 4th atom of quinoline. quinolines (**248**) by heating (**247**) with hydrazine hydrate. (**248**) on reaction with ethyl 2-cyano-3,3-bis(methylthio)propenoate yielded compound (**246**) (Scheme 52).[66]



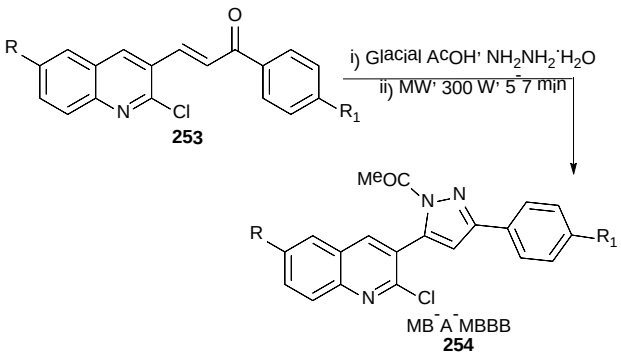
Scheme 52 Synthesis of quinoline derivatives by Aly et al.

Starting from chalcones, Desai *et al.* synthesized quinoline derivatives bonded by their 3rd atom to the carbon atom of pyrazole, and also containing the thiazole moiety directly bonded to the pyrazole. α,β-unsaturated ketones (**250**) were reacted with thiosemicarbazide to give 5-(2-chloro-quinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazole-1-carbothiomide (**251**) which underwent cyclization with ethylbromo acetate to give 2-(5-(2)-chloroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)ones (**252**) (Scheme 53).[68]

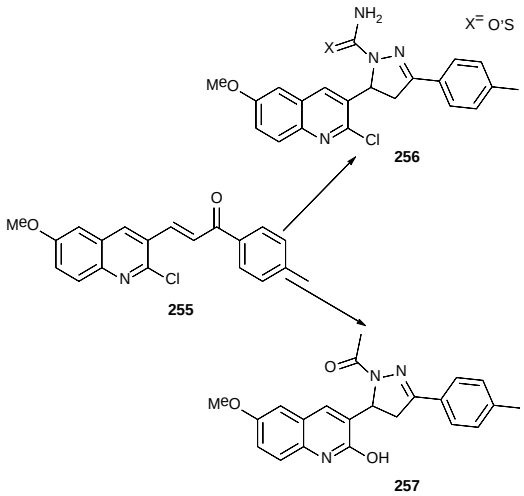


Scheme 53 Synthesis of quinoline derivatives with pyrazole and thiazole moieties

Molecules with similar linkage of quinoline and pyrazole was achieved in microwave conditions, using similar reactants. Chalcones (**253**) underwent cyclization with hydrate hydrazine under microwave irradiation to yield chloroquinoline substituted pyrazole (**254**) (Scheme 54).[69] Chalcone (**255**) underwent cyclization with semicarbazide or thiosemicarbazide to give pyrazole derivatives 1-carbamoyl-5-(2-chloro-6-methoxyquinolin-3-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole (**256; X=O**) and 5-(2-chloro-6-methoxyquinolin-3-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**256; X=S**). 1-acetyl-5-(2-hydroxy-6-methoxy-quinolin-3-yl)-3-p-tolyl-4,5-dihydro pyrazole (**257**) was synthesized by cyclocondensation of chalcone (**255**) with hydrazine hydrate (Scheme 55).[70]



Scheme 54 Synthesis of chloroquinoline substituted pyrazole derivative



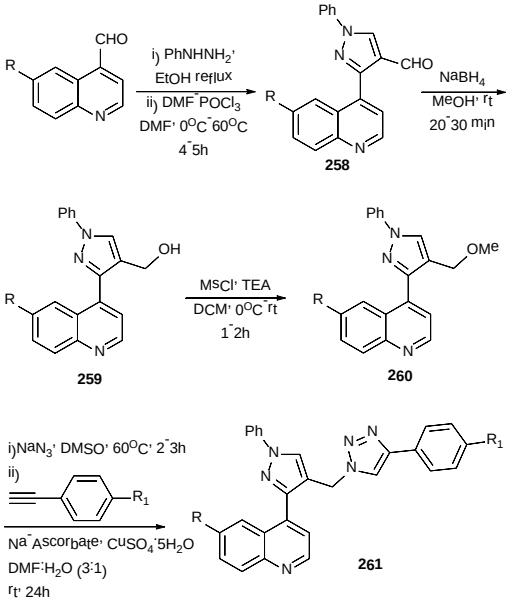
Scheme 55 Cyclisation of chalcones with semicarbazide derivatives and hydrazine hydrate

QUINOLINE-THIAZOLE DERIVATIVE

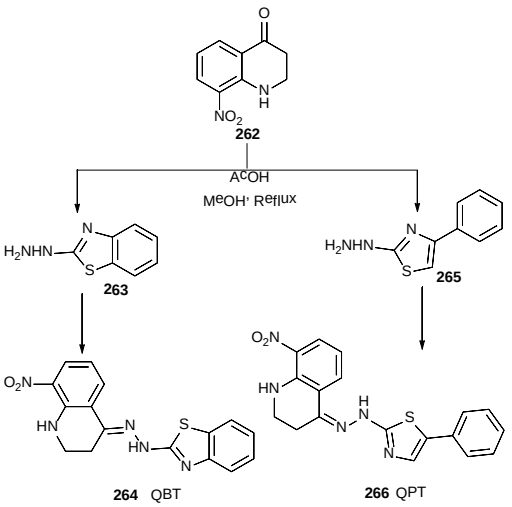
Selvaraj *et al.* synthesized Novel quinoline-based phenyl thiazole (QPT) (**266**) and benzothiazole (QBT) (**264**) using 2,3-dihydro-8-nitro-4-quinolone (**262**) as starting material (Scheme 57).[72] QBT and QPT are formed by the condensation of keto group of quinoline with benzothiazole hydrazine and phenylthiazole hydrazine, respectively.

Hybrids synthesized in Scheme 53, 54 and 55 contain thiazole fused by its 4th and 5th carbon atoms to the 2nd and 3rd atoms (or the 'b' bond) of quinoline. Derivatives of thiazolo[5,4-b]quinoline (**269**) and 9-chloro-2-(methylthio)thiazolo[5,4-b]

quinoline (**270**) and their derivatives were synthesized by Rodriguez-Loaiza *et al.* using starting material 4-(Ethoxycarbonyl)-2-(methythio)-5-(phenylamino) thiazole (**267**) (Scheme 58).[73]



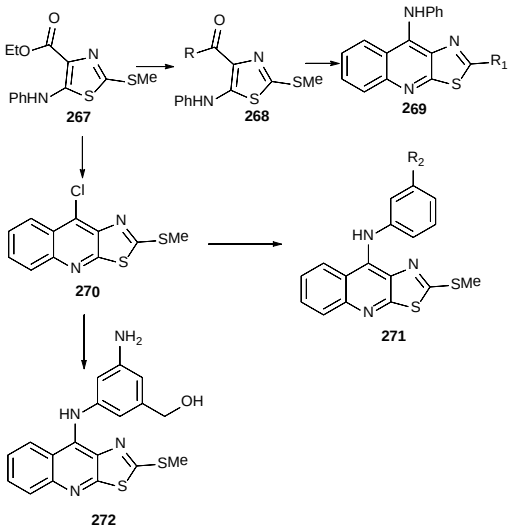
Scheme 56 Synthesis of quinoline derivatives with pyrazole and triazole



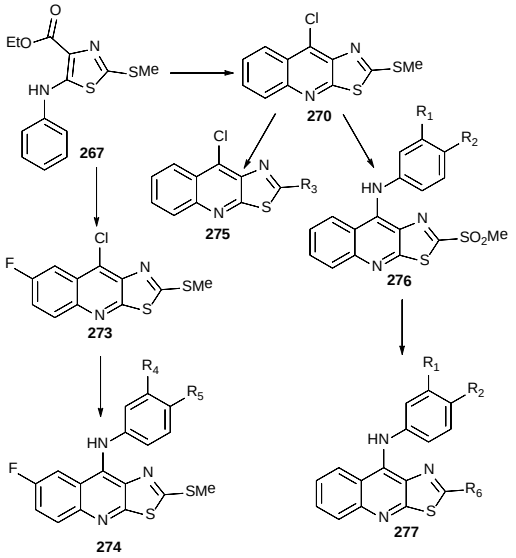
Scheme 57 Synthesis of novel QPT and QBT

Marco *et al.* synthesized quinoline-thiazolo derivatives by cyclization of (**267**) with $POCl_3$/PPA to obtain (**270**) and (**273**). These were further derivatized to obtain variously substituted quinoline-thiazolo derivatives (**274, 276, 277**) (Scheme 59).[74]

Marco *et al.* worked on direct condensation of compound (**270**) with 2-(N,-N-diethyl)ethylenediamine and N,N-diethyl ethylenediamine to obtain 9-[[2-(N,N-diethylamino)] ethyl]amino]-2-(methylthio)-thiazolo[5,4-b]quinoline **(280)** and



Scheme 58 Synthesis of fused quinoline-thiazole derivatives

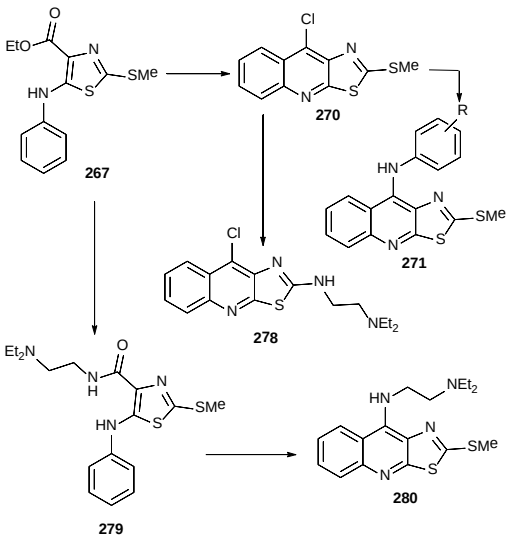


Scheme 59 Synthesis of fused quinoline-thiazole derivatives by cyclisation

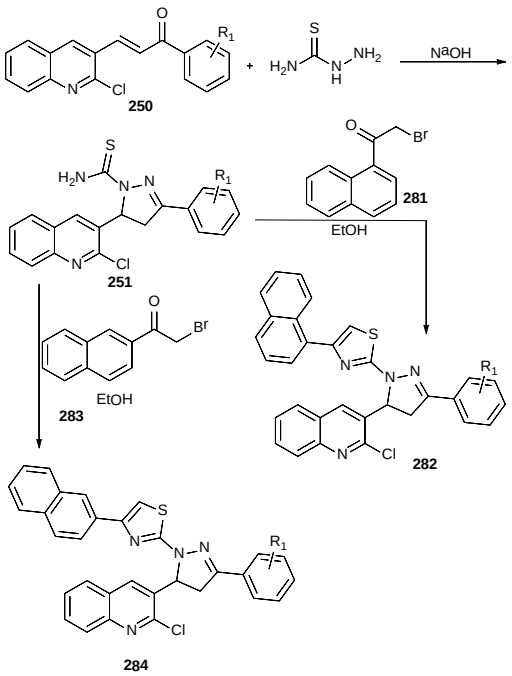
9-chloro-2-[[2-(N,N-diethylamino) ethylamino]-thiazolo[5,4-b]quinoline (**278**) respectively (Scheme 60).[75]

Mohd Imran *et al.* synthesized hybrid molecules consisting of multiple heterocyclic moieties including quinoline, thiazole, pyrazole and naphthalene. Compound (**251**) was treated with 2-bromo-1-(1-naphthyl) (**281**) and 2-bromo-1-(2-napthyl)ethanone (**283**) to obtain 2-(3-substitutedphenyl-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(naphthalene-1-yl)thiazole (**282**) and 2-(3-substituted phenyl-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(naphthalene-2-yl)thiazole (**284**) respectively (Scheme 61).[76]

George *et al.* synthesized the quinoline-thiazole derivative also containing pyrazole as the linking moiety between quinoline and



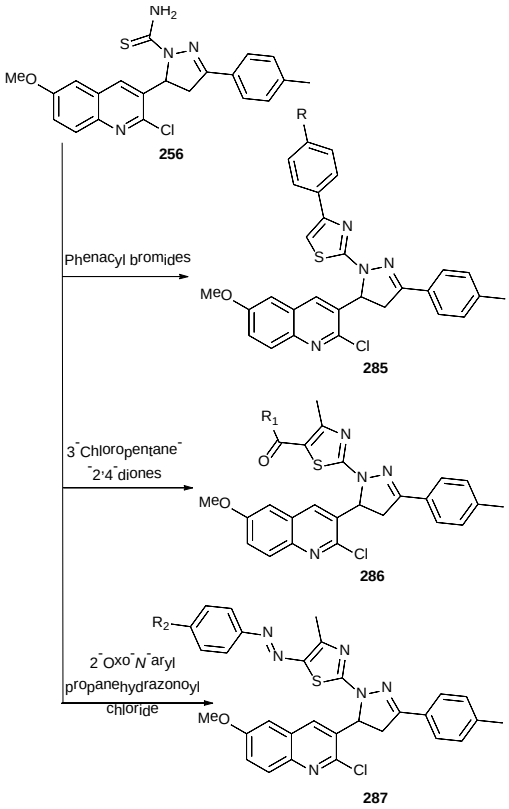
Scheme 60 Derivatisation of fused quinoline-thiazolo compounds



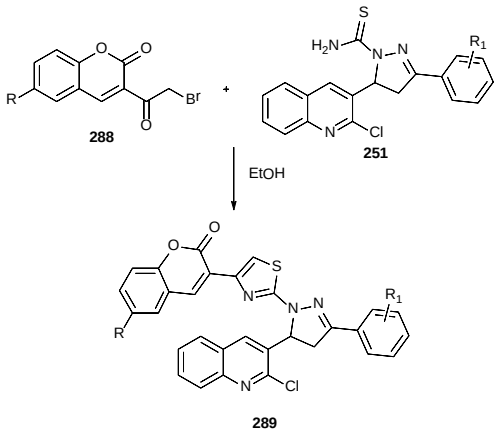
Scheme 61 Synthesis of quinoline-thiazole derivatives with naphthalene and pyrazole moieties

thiazole, starting from Carbothioamide (**256**). (**256**) was reacted with appropriate 1-aryl-2-bromoethananones, 3-chloropentane-2,4-diones,and with 2-oxo-N-arylpropanehydrazonoyl chlorides to give 4,5-dihydro-1-(4-phenylthiazol-2-yl)-1H-pyrazole derivatives (**285**), 2-chloro-3-[4,5-dihydro-1-(5-substituted-4-methylthiazole-2-yl)-3-p-toyl-1H-pyrazol-5-yl]-6-methoxy quinolines (**286**) and (e)-1-[2-(4,5-dihydropyrazol-1-yl)-4-methylthiazol-5-yl]-2-aryl diazene derivative (**287**) respectively, all having thiazole moiety (Scheme 62).[70]

(**251**) was synthesized starting from quinoline via quinolinyl chalcone (Refer Scheme 53) and was further derivatized to (**289**) (Scheme 63).[57] Mohd Imran Ansari *et al.* synthesized 3-(2-(5-(2-chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1H pyrazol-1-yl)-6-H/halo-2H-chromen-2-ones (**289**) from 3-(2-bromoacetyl)-6-H/halo-2H-chromen-2-one (**288**).[77]



Scheme 62 Synthesis of quinoline-thiazole derivatives from carbothioamide

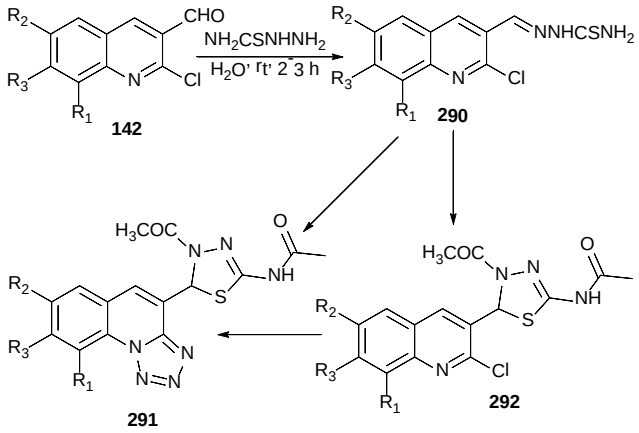


Scheme 63 Synthesis of derivatives with multiple heterocycles

QUINOLINE-THIADIAZOLE

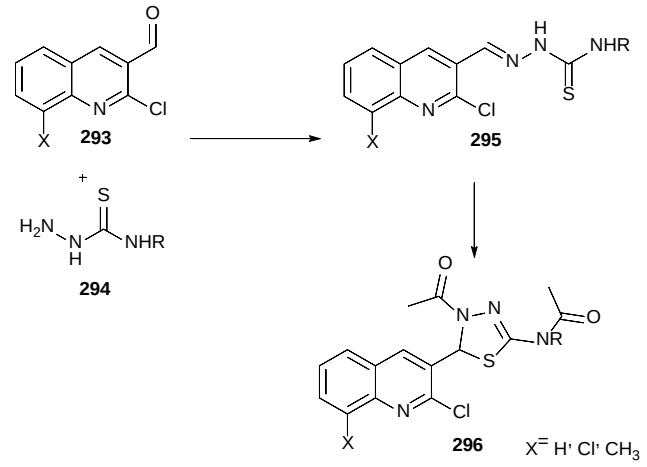
Novel quinoline-thiadiazole with thiadiazole directly bonded to the quinoline at the 3rd atom, N-(4-acetyl-4,5-dihydro-5-(7,8,9-substituted-tetrazolo[1,5-a] quinolin-4-yl)-1,3,4-thiadiazol-2-yl)acetamide (**291**) was synthesized by Babu *et al.* from N-[4-acetyl-5-(6,7,8-substituted-2-chloroquinolin-3-yl)-4,5-dihydro-1,3,4-thiadazol-2-yl]-aceatmides(**292**) by conventional two-step

method and from thiosemicarbazones (**290**) by a one pot reaction (Scheme 64).[78]



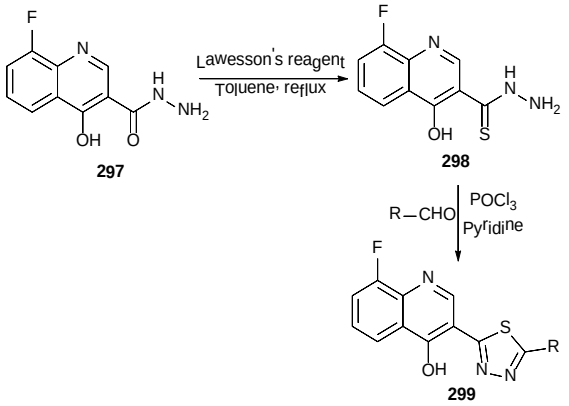
Scheme 64 Synthesis of N-(4-acetyl-4,5-dihydro-5-(7,8,9-substituted-tetrazolo[1,5-a] quinolin-4-yl)-1,3,4-thiadiazol-2-yl)acetamide

Bhat *et al.* also synthesized similar hybrid molecules: N-4-acetyl-5-(2,8-substituted quinolin-3-yl)-4,5-dihydro-1,3,4-thiadazole-2-yl)acetamide derivatives (**296**). 2,8-substituted-quinolin-3-carbaldehyde was reacted with thiosemicarbazide to obtain 4-substituted-1-((2,8-dichloroquinolin-3-yl)2,8-disubstituted quinoline-3-carboxyaldehyde (**295**), followed by reaction with excess of acetic anhydride to afford (**296**) (Scheme 65).[79]



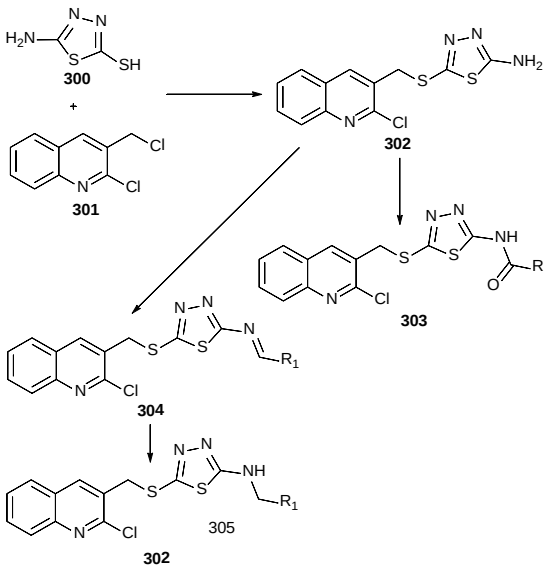
Scheme 65 Synthesis of N-4-acetyl-5-(2,8-substituted quinolin-3-yl)-4,5-dihydro-1,3,4-thiadazole-2-yl)acetamide derivatives

Similar compound (**299**) was synthesized using 8-fluoro-4-hydroxyquinoline-3-carbohydrazide (**297**) as starting material. The intermediate thiohydrazide formed cyclised adducts (**299**) in presence of $POCl_3$ when reacted with aryl aldehydes (Scheme 66).[80]



Scheme 66 Synthesis of quinoline-thiadiazole from 8-fluoro-4-hydroxyquinoline-3-carbohydrazide

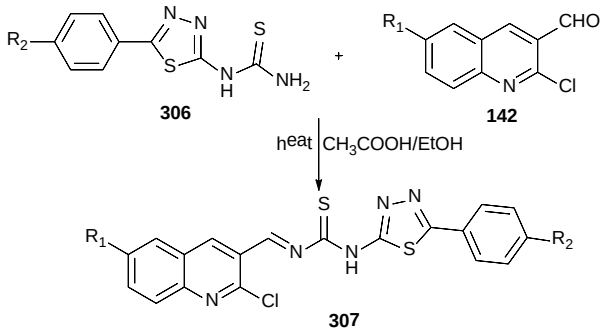
Kumar *et al.* synthesized molecules linking quinoline by the 3rd atom to a carbon atom on thiadiazole by an alkyl chain containing sulphur. The intermediate 5-{[(2-chloroquinoline-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine (**302**) obtained from a convergent synthesis, was used to synthesize compound (**303, 304 & 305**). (**302**) on acylation in presence of acid chloride yielded N-(5-{[(2-chloroquinoline-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-yl) derivatives (**303**). (**302**) also reacted with substituted carbaldehyde to give (**304**) which on addition of sodium borohydride yielded compound (**305**) (Scheme 67).[81]



Scheme 67 Synthesis of quinoline-thiadiazole from 5-{[(2-chloroquinoline-3-yl)methyl]sulfanyl}-1,3,4-thiadiazol-2-amine

Dayanand P *et al.* synthesized 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substituted-5-phenyl-1,3,4-thiadiazole-2-yl]thiourea (**307**) from reaction between 6-substituted-2-chloro-3-formyl quinolines(**142**) and 1-(5-

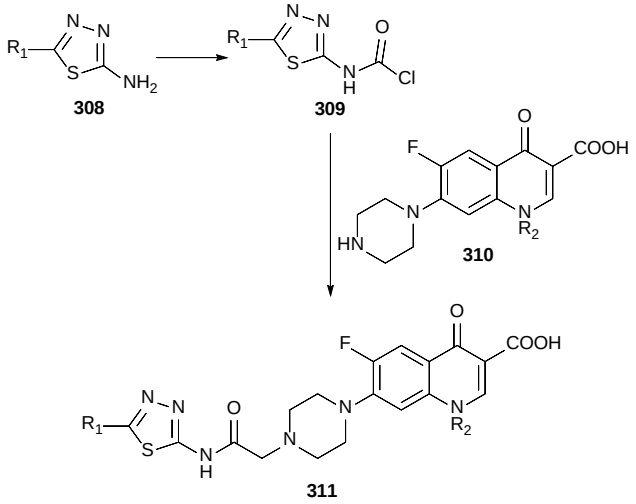
substituted phenyl-1,3,4-thiadiazole-2-yl)thiourea (**306**) (Scheme 68).



Scheme 68 Synthesis 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substituted-5-phenyl-1,3,4-thiadiazole-2-yl]thiourea

The chloroquinoline was linked to the thiadiazole by a longer alkyl chain containing sulphur and nitrogen atoms.[82]

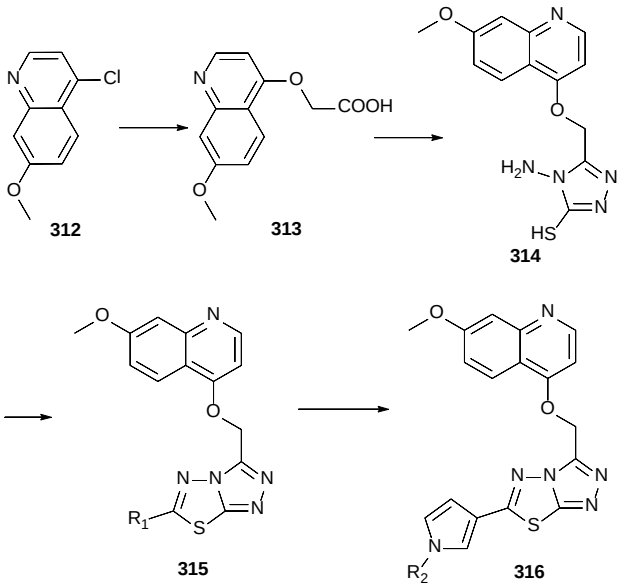
Fluoroquinolones derivatives (**311**) were synthesized by Li-Zuang *et al.* The fluroquinolone was linked to the thiadiazole by an alkyl chain containing piperazine. 2-chloro-N-(5-substituted-1,3,4-thiadiazole-2-yl)acetamide derivatives (**309**) were reacted with ciprooxacin /noroxacin to obtain (**311**) (Scheme 69).[83]



Scheme 69 Synthesis of fluoroquinolones

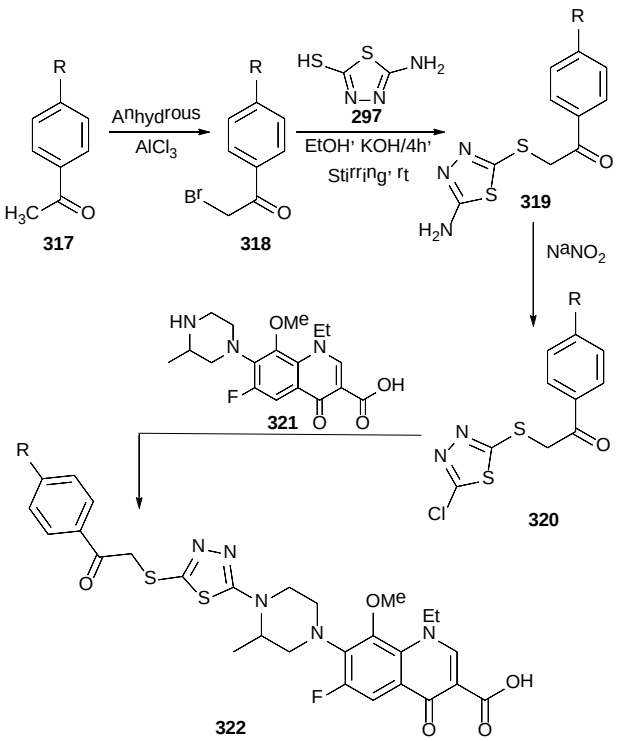
Derivatives containing quinoline, and thiadizole fused with a 1,3,5-triazole was synthesized in a multi-step synthesis. Acid (**313**) was used as a key intermediate for the synthesis of compound (**315**), which on treatment with appropriate bromide yielded compound (**316**) (Scheme 70).[84]

A flouroquinolone derivative containing piperazine, thiadiazole and benzene derivatives were synthesized by Agrawal *et al.* Benzoylmethylenethio-1,3,4-thiadiazole (**319**) underwent diazotization of amines and chlorination to give 2-chloro-5-benzoylmethylenethio-1,3,4-thiadiazole (**320**). They. carried out aromatic nucleophilic substitution of (**320**) with



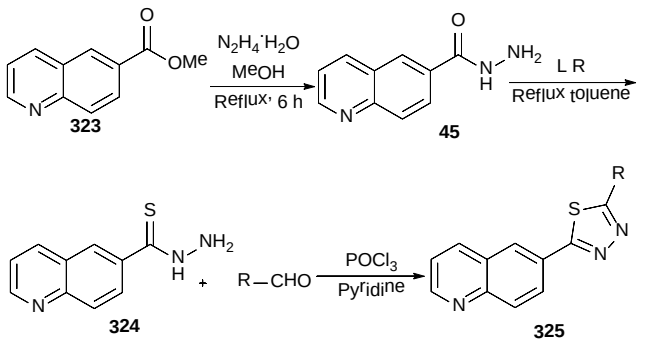
Scheme 70 Multi-step synthesis of quinoline-thiadiazole starting from 4-chloro-7-methoxy quinoline

fluoro-quinolone to afford 7-[4-{5-(2-oxo-2-p-substituted-phenylethylthio)-1,3,4-thiadiazol-2-yl}-3-methylpiperazine-1-yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydro quinoline-3-carboxylic acid (**322**) (Scheme 71).[85]



Scheme 71 Synthesis of 7-[4-{5-(2-oxo-2-p-substituted-phenylethylthio)-1,3,4-thiadiazol-2-yl}-3-methylpiperazine-1-yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

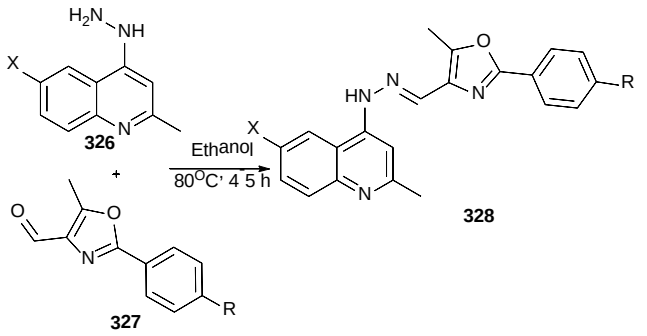
Almandil *et al.* synthesized compound (**325**), a molecule with thiadiazole directly bonded to the 6th position of quinoline, by the reaction of (**324**) with aryl aldehyde in presence of $POCl_3$ and pyridine (Scheme 72).[86]



Scheme 72 Synthesis of quinoline-thiadiazole from quinoline ester

QUINOLINE-OXAZOLE

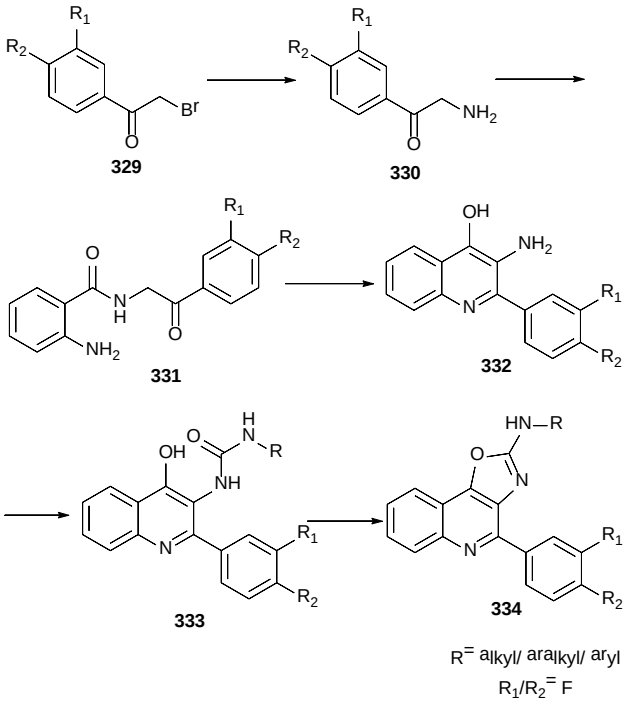
Shah *et al.* synthesized hybrid (**328**) linking the 4th atom of quinoline and a carbon atom of oxazole by a hydrazone linkage. (**328**) was synthesized by condensation reaction of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes (**327**) with 6-bromo/6-chloro-2-methyl-quinolin-4-yl-hydrazines (**326**) (Scheme 73).[87]



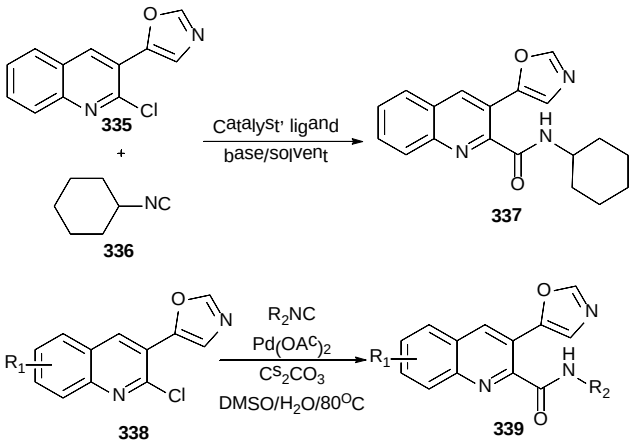
Scheme 73 Condensation reaction of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes

Eswaran synthesized (**334**) containing quinoline fused to oxazole by 2 common carbon atoms, by a multi-step synthesis. In the last step, compound (**333**) was reacted with $POCl_3$ to obtain 4-(3 & 4fluorophenyl)-N-substituted phenyl) [1,3]oxazolo[4,5-c]quinolin-2-amines (**334**) (Scheme 74).[88]

Derivatives (**337, 339**) containing oxazole substituted by its carbon at the 3rd position of quinoline were synthesized in a catalysed, one-step synthesis. Reaction of 5-(2-chloroquinolin-3-yl)oxazole (**335**) with cyclohexyl isocyanide resulted in N-cyclohexyl-3-(oxazol-5-yl)quinolin-2-carboxamide (**337**). Its derivatives (**339**) were also similarly synthesised (Scheme 75).[89]



Scheme 74 Synthesis of 4-(3 and 4 fluorophenyl)-N-substituted phenyl)[1,3]oxazolo[4,5-c]quinoline-2-amines

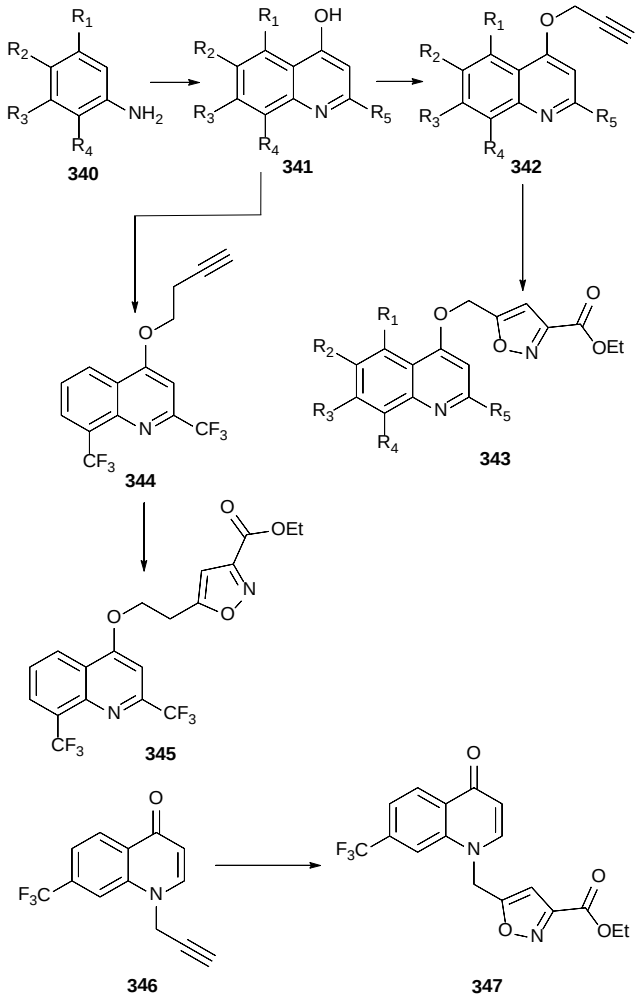


Scheme 75 Synthesis of N-cyclohexyl-3-(oxazol-5-yl)quinolin-2-carboxamide and its derivative

QUINOLINE-ISOXAZOLE

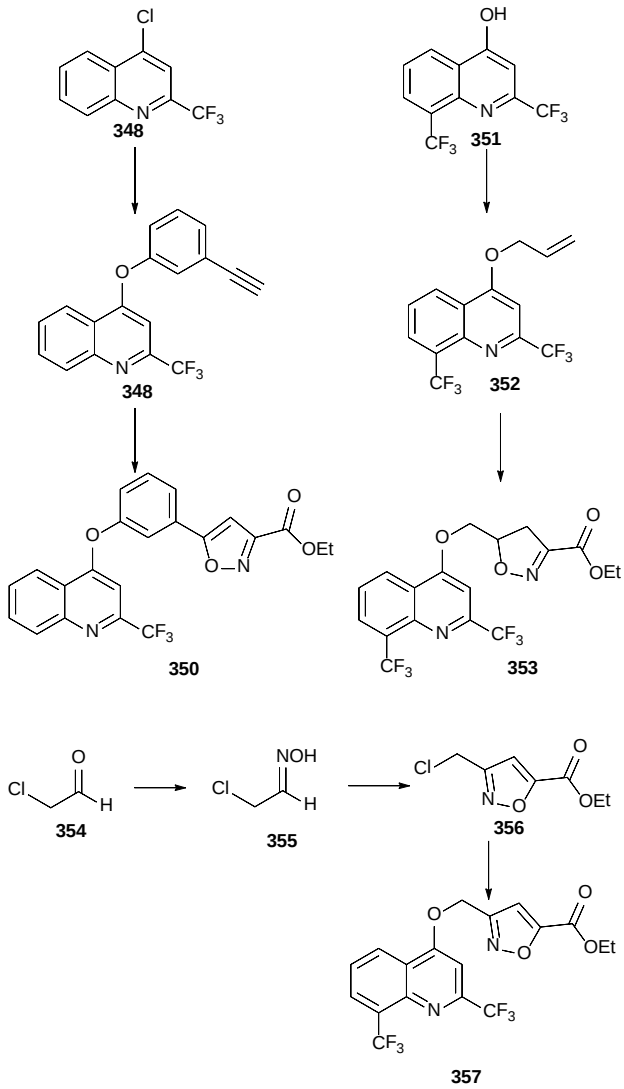
Lilienkampf *et al.* synthesized (**343, 345, 353, 357**) containing an alkyl chain linking quinoline by the 4th atom to isoxazole, (**350**) containing an aryl linkage and (**347**) containing the isoxazole directly bonded to the nitrogen of quinoline. 4-hydroxyquinoline was used as starting material for the synthesis of compound (**343**), (**345**) and (**347**). Acetylenic intermediates (**342**) was obtained from the reaction of (**341**) in presence of base with propargyl bromide. Both N-alkylated (**346**) and C-alkylated (**342**) products were obtained from Williamson reaction with 7-(trifluoromethyl)-4-quinolinol (**341**). Dipolar cycloaddition of

acetylene intermediates with nitrile oxides derived from ethyl-2chloro-2-(hydroxyimino)acetate introduced isoxazole moiety in (**343**) & 8,5-(bromomethyl) isoxazole-3-carboxylic acid ethyl ester was used for alkylation of 4-hydroxyquinolines to obtain (**343**). Mitsunobu coupling of 3-butyn-1-ol with 2,8-bis(trifluoromethyl)-4-quinolinol (**341**) gave acetylenic intermediates (**344**), which on further reaction cyclises to give oxyethylene link compound (**345**) (Scheme 76).[90]



Scheme 76 Synthesis of quinoline-isoxazole

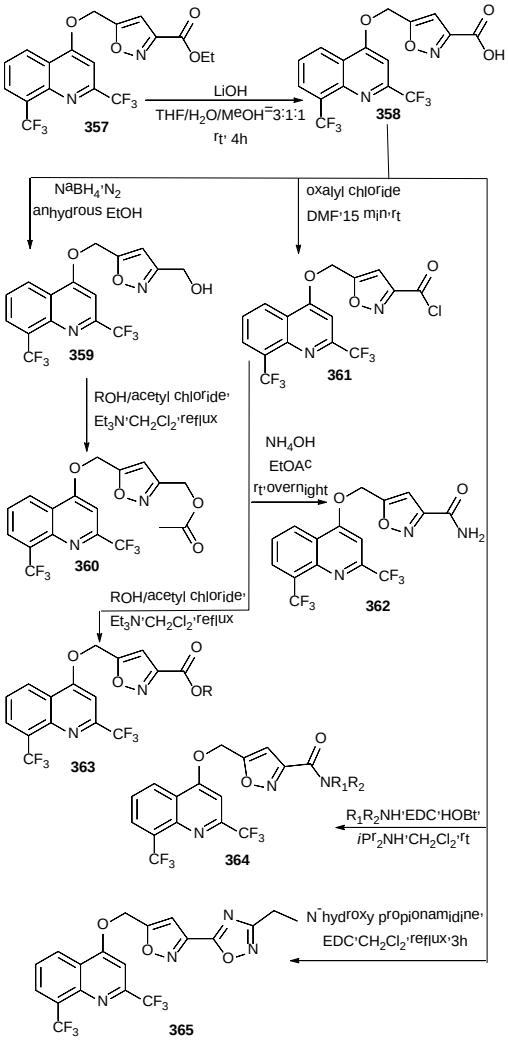
Cycloaddition reaction of 3-hydroxyphenylacetylene (**349**) with nitrile oxide obtained from ethyl-2-chloro-2-(hydroxyimino)acetate gave 5-[3-[[2-(trifluoromethyl)-4-quinolinyl]oxy] phenyl]-3-isoxazolecarboxylic acid ethyl ester (**350**) having aryl ether linker. Intermediate (**352**) reacted with ethyl-2-chloro-2-(hydroxyimino)acetate to yield 5-[3-[[2,8-bis(trifluoromethyl)-4-quinolinyl] oxy]phenyl]-4,5-dihydro-3-isoxazolecarboxylic acid ethyl ester (**353**). Chloroacetaldehyde (**354**) underwent a two-step reaction to give 3-(chloromethyl)isoxazole-5-carboxylic acid ethyl ester (**356**) which was used for alkylating (**351**) to yield 3,5,-substituted isoxazole regioisomer 3-[[[2,8-bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-5-isoxazole carboxylic acid ethyl ester (**357**)(Scheme 77).[90] Various other similarly linked derivatives of quinoline-isoxazole have also been synthesized (Scheme 78).[91]



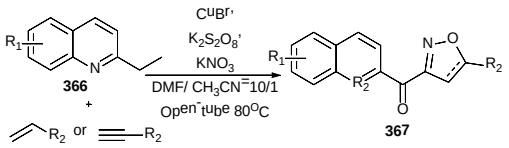
Scheme 77 Synthesis of3-[[[2,8-bis(trifluoromethyl)-4-quinolinyl]oxy]methyl]-5-isoxazole carboxylic acid ethyl ester

Series of isoxazoline derivatives (**367**) with an acyl linkage between quinoline and isoxazole were synthesized by one pot Cu-catalyzed selective cascade sp^3 C-H bonds oxidative functionalization of alkylazaarenes. Reaction of 2-ethylquinoline (**366**) with butyl acrylate in presence of catalyst, solvent, oxidant and nitro sources yielded isoxazoline derivative.[92] Different derivatives are synthesized using different substituents (Scheme 79).[93]

The rest of the schemes incorporate synthesis of quinoline-isoxazole derivatives with the two moieties directly bonded to each other. Reaction of 2-chloroquinolin-3-carbaldehyde (**142**) prepared by Vilsmeier reagent, reacted with hydroxylamine



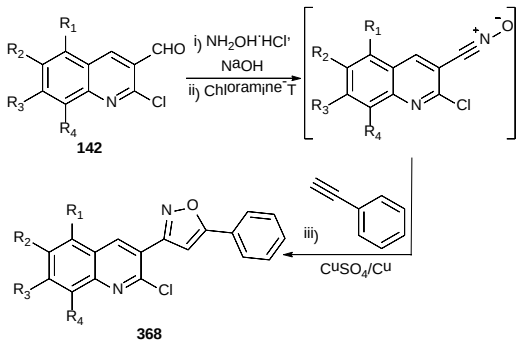
Scheme 78 Synthesis of derivatives of quinoline-isoxazole



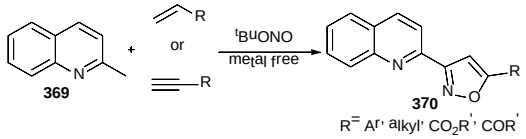
Scheme 79 Synthesis of isoxazoline derivative

hydrochloride to give aldoxime intermediate. Regioselective copper(I)-catalyzed cycloaddition reaction using Click chemistry approach yielded 3-(2-chloroquinolin-3-yl)-5-phenylisoxazoles (**368**) (Scheme 80).[92]

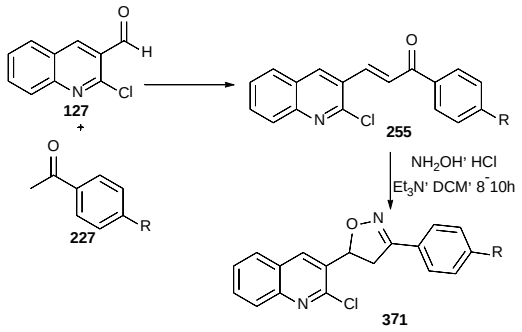
Wang *et al.* achieved metal free cascade access to 3-(quinolin-2-yl)isoxazoles. Quinoline-2-carbaldehyde oxime underwent 1,3-dipolar cycloaddition with alkynes or alkenes to form biheteroaryls (**370**) with tert-butyl nitrite acting as nitrogen source. Other derivatives were also synthesized using this method (Scheme 81).[94] Bindu *et al.* synthesized 4,5-dihydroisoxazoles(2-isaxazolines) (**371**) from quinolinyl chalcones (**255**) (Scheme 82).[95]



Scheme 80 Synthesis of 3-(2-chloroquinolin-3-yl)-5-phenylisoxazoles



Scheme 81 1,3-dipolar cycloaddition with alkyne or alkene to form biheteroaryls



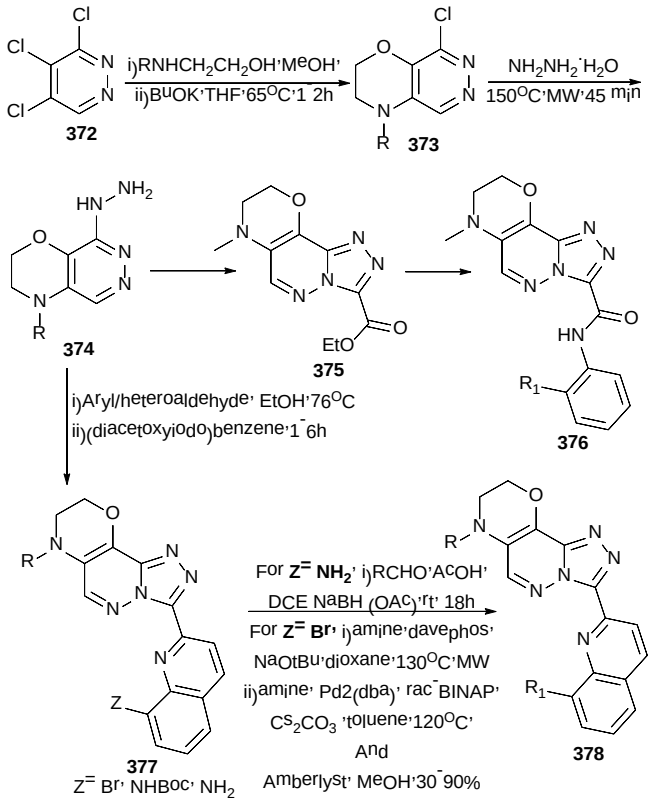
Scheme 82 Synthesis of 4,5-dihydroisoxazoles(2-isaxzolines) from quinolinyl chalcones

QUINOLINE-AZINE HYBRIDS

QUINOLINE-PYRIDAZINE

Martinez *et al.* synthesized many derivatives of quinoline-pyridazine hybrids. 3,4,5-Trichloropyridazine was treated with amino-alcohols to generate (8-chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazine) (**373**) which was treated with hydrazine hydrate at 150°C for 45 minutes under microwave irradiation to generate the hydrazine derivative (**374**) of (**343**). This was then treated with an aldehyde in ethanol at 76°C, followed by reaction with Quinoline-2-carboxaldehyde derivatives in presence of (diacetoxyiodo)benzene for 1-6 hours to obtain (**377**), which could be derivatized to (**378**). (**379**) on

similar treatment with aldehyde in ethanol at 76°C, followed by reaction with Quinoline-2-carboxaldehyde or Isoquinoline-7-carboxaldehyde derivatives in presence of (diacetoxyiodo)benzene for 1-3 hours at room temperature yielded derivatives (**380**) and (**382**) respectively, which was also similarly derivatized (Scheme 83,84).[96]



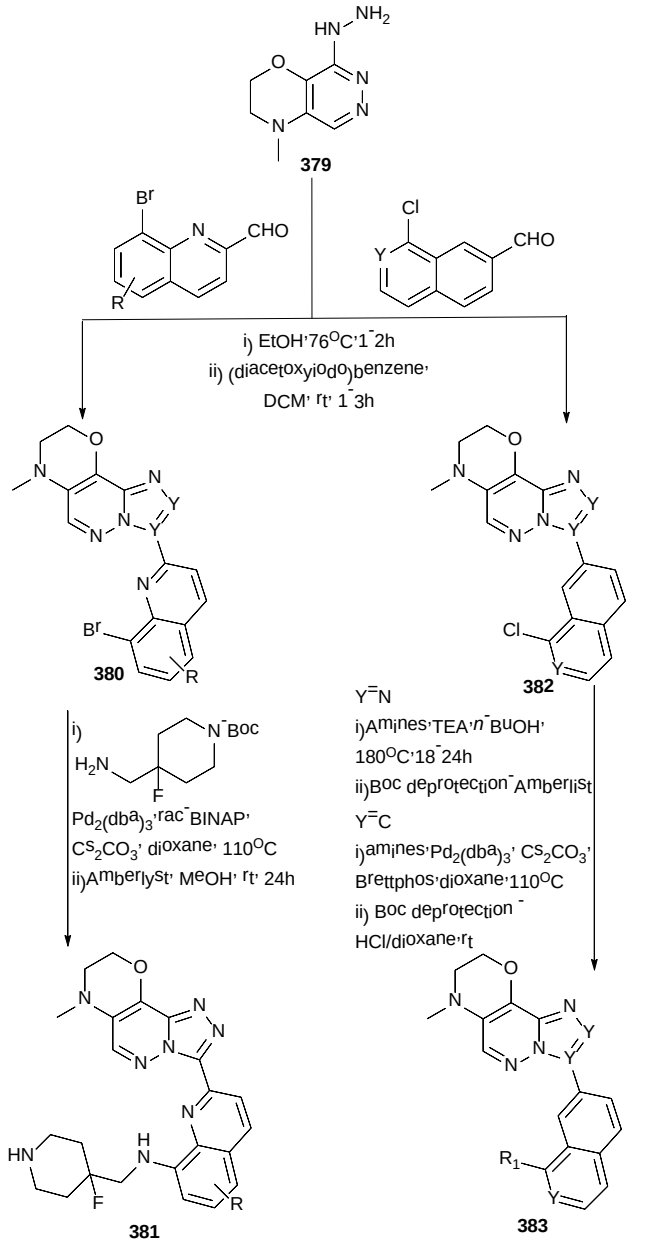
Scheme 83 Synthesis of quinoline pyridazine from (8-chloro-4-methyl-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazine

QUINOLINE-PYRAZINE

N-(2-((7-chloroquinolin-4-yl)amino)ethyl)pyrazine-2-carboxamide (L) (**387**) was synthesized by the reaction of N_1-(7-chloroquinolin-4-yl)ethylene diamine (**384**) with pyrazine carbonyl chloride (**386**) (Scheme 85).[97]

QUINOLINE-PIPERIDINE

Van de Walle *et al.* synthesized quinoline-piperidine derivative containing the two moieties linked by an alkyl chain. *N*-[(1-allyl-3,3-dimethylpiperidin-4-yl)methyl]quinolin-4-amines (**391, 392**) was synthesized from *cis*-1-allyl-5-benzyloxy-3,3-dimethyl piperidine-4-carbonitrile (**388**). Reduction of **(388)** with $LiAlH_4$ gave 4-(aminomethyl)piperidine (**389**) and small amount of (**390**). These primary amine compounds were then reacted with quinoline moiety (**158**) to obtain (**391, 392**) (Scheme 86).[98]

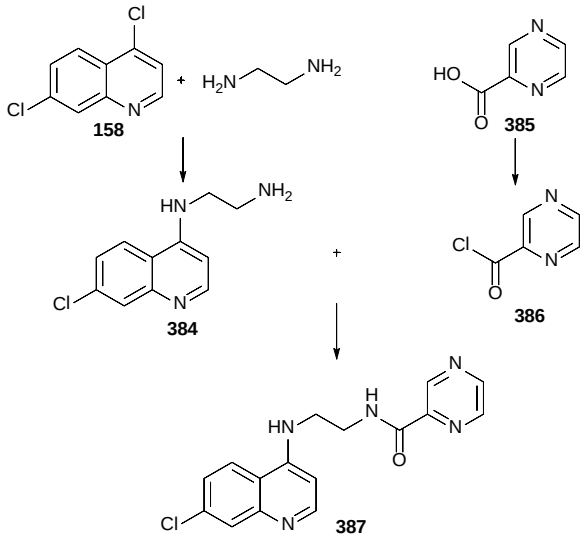


Scheme 84 Synthesis of quinoline pyridazine

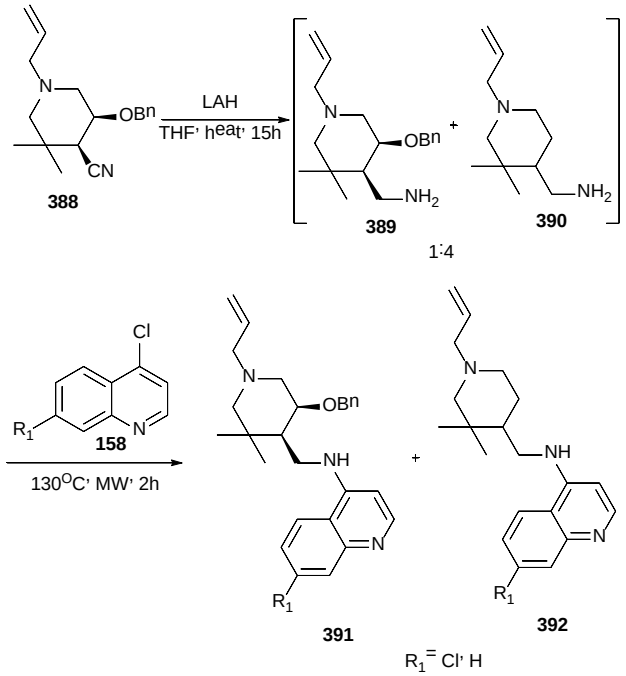
Mefloquine (**396**) also contains quinoline linked to piperidine by an alkyl chain. Quinolin-4-ol was obtained by condensation reaction of ethyl-4,4,4-trifluoroacetoacetate with *O*-trifluoromethylaniline and then converted into 4-bromoquinoline using $POBr_3$. Carboxylation of gave Cinclioninic acid (**394**), which when followed by reaction with 2-pyridyllithium afforded pyridyl ketone (**395**). Mefloquine (**396**) was synthesized by the hydrogenation of (**395**) with H_2-PtO_2 (Scheme 87).[99]

Ashok *et al.* synthesized hybrid molecules containing quinoline and piperidine directly bonded to each other, using 2-morpholine or 2-piperidine or 2-pyrrolidine substituted quinoline 3-carbaldehydes (**397**) as starting material. These underwent Claisen-Schmidt condensation with four different acetyl naphthalene and resulted in substituted quinoline based chalcone

in good yields both by conventional and microwave method (Scheme 88).[100]



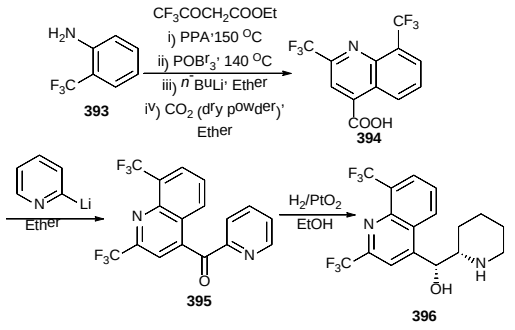
Scheme 85 Synthesis of *N*-(2-((7-chloroquinolin-4-yl)amino)ethyl)pyrazine-2-carboxamide (L)



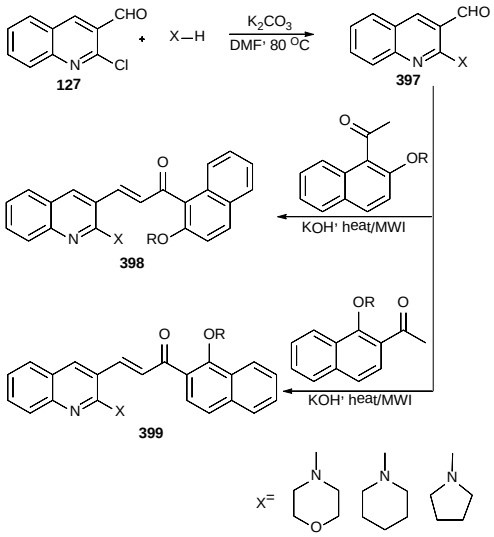
Scheme 86 Synthesis of *N*-[(1-allyl-3,3-dimethylpiperidin-4-yl)methyl]quinolin-4-amines

QUINOLINE-FERROCENE DERIVATIVES

Ferrocenes are an important group of organometallic compounds, with interesting biological properties.[101] Ferrocene moiety has greater stability and non-toxicity and hence competes with other drugs for most treatments. Some conjugates are specially designed for anti-malarial and anti-cancer therapies.[102] Promising cytostatic effects have been found in ferrocenes



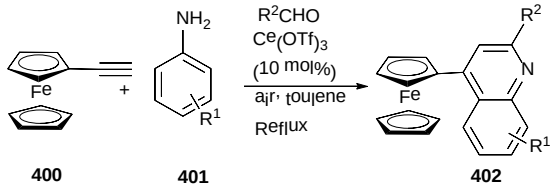
Scheme 87 Synthesis of Mefloquine



Scheme 88 Synthesis of substituted quinoline based chalcone by Claisen-Schmidt condensation from 2-piperidine substituted quinoline 3-carbaldehydes

conjugated with biologically active compounds.[103] New medicinal properties and enhancement of biological properties has been observed from the integration of ferrocenyl moiety into quinoline.[101] Synthesis of some of the quinoline–ferrocene compounds are mentioned below.

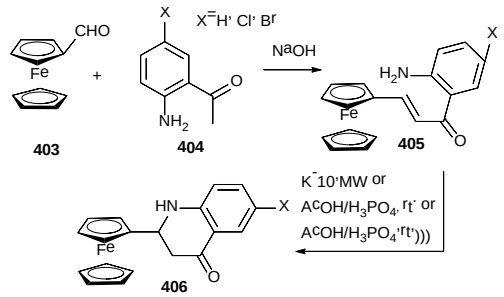
The molecules (**402**) and (**424**) contain quinoline directly bonded by a carbon atom at 4th and 2nd positions respectively, to a carbon of the ferrocene moiety. The synthesis to achieve these hybrids involve an intramolecular cyclization in their mechanism. Chen *et al.* achieved a one pot three component cyclization (aromatization) of ferrocenylacetylene (**400**), aldehydes, and amines (**401**) using $Ce(OTf)_3$ as catalyst in the presence of solvent (Scheme 89).[101] Xi *et al.* synthesised ferrocenylquinoline (**402**) by Povarov, one-pot three-component reaction of similar reactants: benzaldehyde, ferrocenylacetylene (**400**) and substituted anilines (**401**) in the absence of solvent, using $Ce(OTf)_3$ as catalyst[104] which possess Lewis acidic and oxidative properties. Reaction period was found to reduce from 6 hours [101] to 3 hours [104] (Scheme 89).



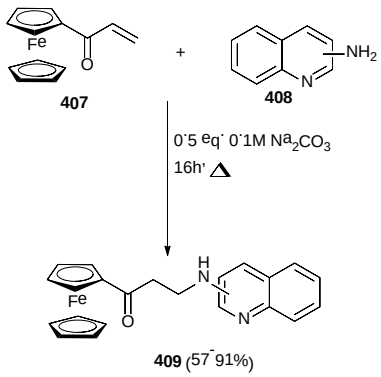
Scheme 89 Synthesis of quinolone derivative using $Ce(OTf)_3$ as catalyst

Pejovic *et al.* synthesized 2-ferrocenyl-2,3-dihydroquinolin-4(1*H*)-ones by intramolecular Aza-Michael addition. Mixed aldol condensation of *O*-aminoacetophenones (**404**) with ferrocenecarboxyaldehyde (**403**) gave chalcone analogues (**405**) which isomerize to quinolines (**406**). The reaction, when subjected to microwave irradiation on montmorillonite K-10 clay surface gave very poor yield (Scheme 90).[105]

The rest of the synthetic schemes discussed involve hybrid molecules containing ferrocene and quinoline linked by alkyl or aryl groups. Synthesis of 1-ferrocenyl-3-(quinoline-4-ylamino)propan-1-one (**409**) and other derivatives by Aza-Michael addition of 1-ferrocenylpropenone (**407**) and 4-aminoquinoline (**408**) was achieved by Minić *et al.* 2-Ferrocenoyl-3-ethyl aryl amines which are Mannich bases were proven to be good heterocyclic starting material for synthesis of ferrocene derivative (Scheme 91).[106]

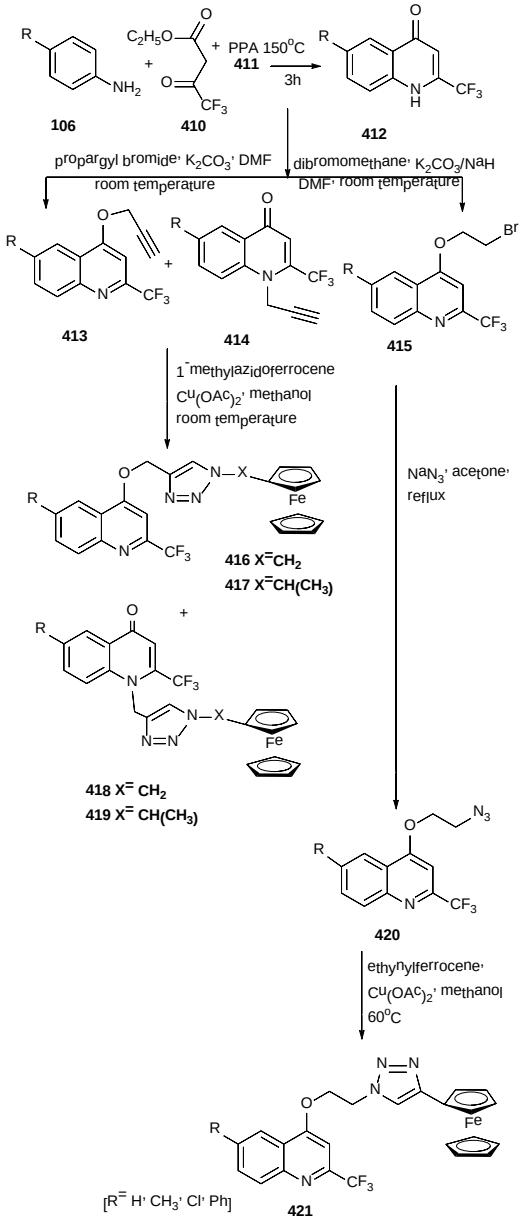


Scheme 90 Synthesis of quinolone derivative from chalcone analogue



Scheme 91 Synthesis of quinoline derivative by Aza-Michael addition

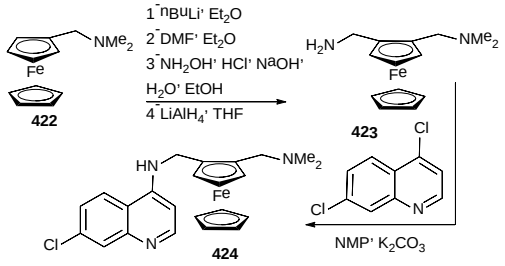
Maracic *et al.* synthesised novel *N*-alkylated 4-quinolone and *O*-alkylated quinoline derivatives attached to ferrocene moiety through 1,4-disubstituted (**418 & 419**) and 4,1- disubstituted (**416, 417 & 421**) 1,2,3, triazole moiety[103] (Scheme 92) in a multi-step synthesis starting from the Conard-Limpach cyclocondensation of β-ketoesters and aniline derivatives which yielded substituted quinolin-4(1*H*)ones.



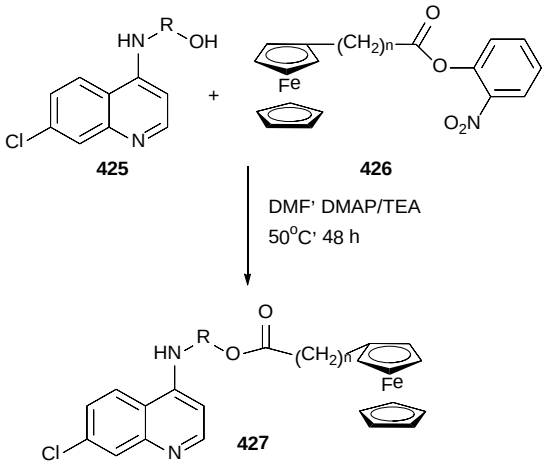
Scheme 92 Synthesis of N-alkylated and O-alkylated quinolone-ferrocene derivative

Ferroquine (FQ,(SSR97193)), a derivative of chloroquine with antimalarial property was designed by Biot *et al.* in 1994 using ((dimethylamino)methyl)ferrocene (**423**) as starting material in a multi-step process. Ferroquine (**424**) is the most successful among the chloroquine derivatives (Scheme 93).[107]

Quinoline-ferrocene esters (**427**) was synthesized by esterification of ferrocenyl-2-nitrophenolate (**426**) and hydroxyl functionalized quinoline (**425**) dissolved in DMF, using catalytic amount of DMAP by N-Da *et al.* (Scheme 94).[108]



Scheme 93 Synthesis of Ferroquine



Scheme 94 Synthesis of quinolone derivative by esterification

QUINOLINE-CHALCONE HYBRIDS

Chalcones or trans-1,3-diaryl-2-propen-1-ones refer to molecules consisting of two aromatic rings linked to each other through an α, β-unsaturated ketone system. While most synthesis mentioned here cover the synthesis of chalcones containing the aryl systems: quinoline and benzene derivatives linked by an α, β-unsaturated ketone system, the last scheme is the synthesis of a system of two benzene derivatives linked by an α, β-unsaturated ketone system with one of the benzene moieties forming a linkage to a quinoline moiety, in addition.

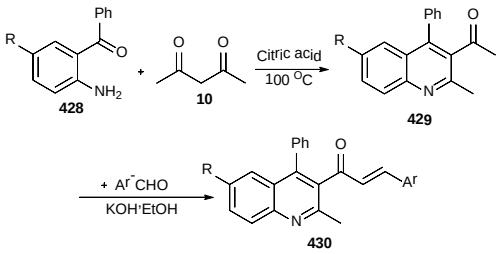
Quinolinyl chalcones have been synthesised by Claisen-Schmidt condensation by Kotra *et al.* by condensing an ethanolic solution of synthesised 3-acetyl quinoline derivatives with an alkaline solution of a substituted aromatic aldehyde. The 3-acetyl quinoline derivatives (**430**) were in turn synthesised by Friedlander synthesis by reacting *o*-amino-4-chlorobenzophenone or o-aminobenzophenone (**428**) with a ß-ketoester (**10**) in presence of an acid catalyst (Scheme 95).[109]

Shikha et al synthesised (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones by treating 2-chloro-3-formyl-quinoline (**127**) and an ethanolic solution of substituted 2-hydroxyacetophenones (**431**) with aqueous NaOH solution. It was treated with DMSO/I_2 to get the corresponding iodo-derivative (**433**) (Scheme 96).[110]

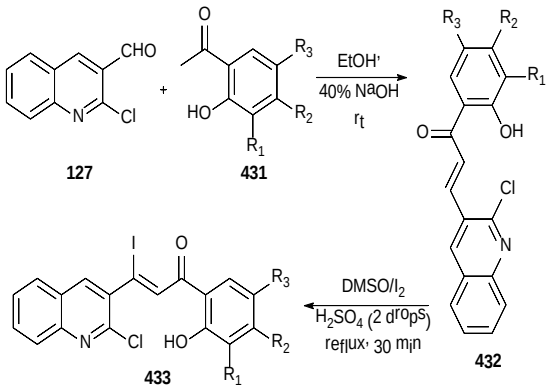
Sirsat *et al.* condensed an ethanolic solution of substituted quinoline carbaldehyde with an alkaline solution of substituted hydroxyl acetophenone via Claisen-Schmidt condensation to prepare general 1-[substituted aryl]-3-[substituted hetero aryl]-2-propen-1-ones (Scheme 97).[111]

Afron Patan *et al.* synthesised quinolinyl chalcones (**436**) by Claisen-Schmidt condensation using *o*-amino-5-chlorobenzophenone (**434**), acetyl acetone and aromatic aldehydes (Scheme 97).[112]

Ferr et al treated 4,7-Dichloroquinoline (**158**) with an ethanolic solution of 3- or 4-aminoacetophenone to obtain [(7-Chloroquinolin-4-yl)]acetophenone (**438**). A mixture of the prepared compound and benzaldehyde was treated with KOH in MeOH to obtain [(7-chloroquinolin-4-yl) amino]chalcone (**438**) (Scheme 98).[110]



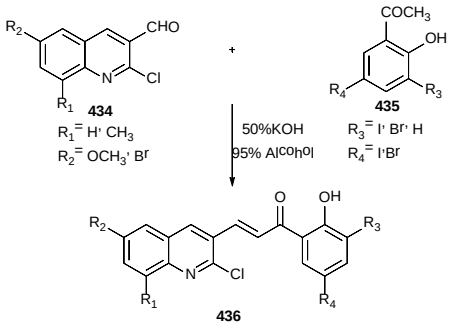
Scheme 95 Synthesis of 3-acetyl quinoline derivative from o-aminobenzophenone with β-ketoester



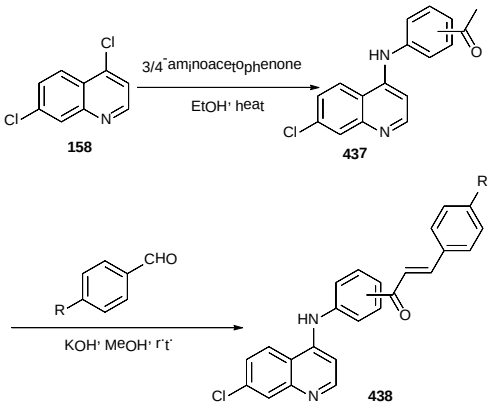
Scheme 96 Synthesis of (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones

QUINOLINE-HYBRID DERIVATIVES USING A SINGLE STARTING MATERIAL

Multiple hybrid molecules, each containing a different heterocycle either fused to or bonded to quinoline or anywhere



Scheme 97 Synthesis of quinolinyl chalcones by Claisen-Schmidt condensation

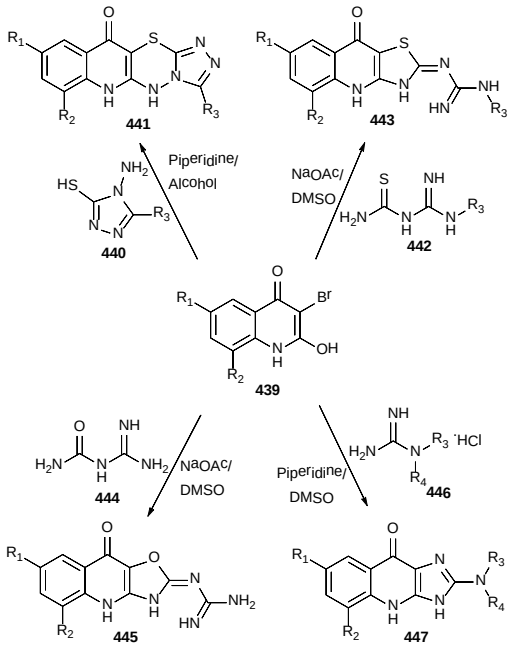


Scheme 98 Synthesis of [7-chloroquinolin-4-yl)amino]chalcone

else in the molecule, can be synthesized from the same quinoline derivative by treating it with different reactants under specific conditions. The use of reactant molecules containing different atoms and more than one atom of each kind along with unsaturation makes it possible to create these hybrid molecules, all starting with the same quinoline derivative.

Starting material, 3-bromo carbostyril **(439)** in presence of piperidine reacted with 4-amino-3-mercaptotriazole **(440)** to give 3,4,6-trisubstituted-9-10-dihydro-11-oxo-[quinolino[2,3-b]-1,3,4-thiadiazone[2,3-d]1,2,4-triazole **(441)**. In presence of base NaOAc, **(439)** fused with amidinothiocarbathiamides **(442)** to afford 2-guanidino/substituted guanidine 1,3-thiazolo [4,5-b]-1-H-6,8-disubstituted-4-oxo-quinoline **(443)**. **(439)** when reacted with amidinocarbamide **(444)** yielded 2-guanidino/substituted guanidine 1,3-oxazole[4,5-b]-1-H-6,8-disubstituted-4-oxo-quinoline **(445)**. Condensation of **(439)** in presence of piperidine with guanidine hydrochloride **(446)** gave 2-amino/substituted amino-3,8-dihydro-9-oxo-4,6-disubstituted quinolino [2,3-d]imidazole **(447)**. Synthesis of **(441, 443, 445 & 447)** was achieved using the said reagents by conventional method and by using microwave irradiation (Scheme 99).[113]

2-(4-phenylpiperazin-1-yl)quinolin-3-carbaldehyde **(448)** was used as starting material to synthesize other 2,3-disubstituted quinoline derivatives (Scheme 100).[114]

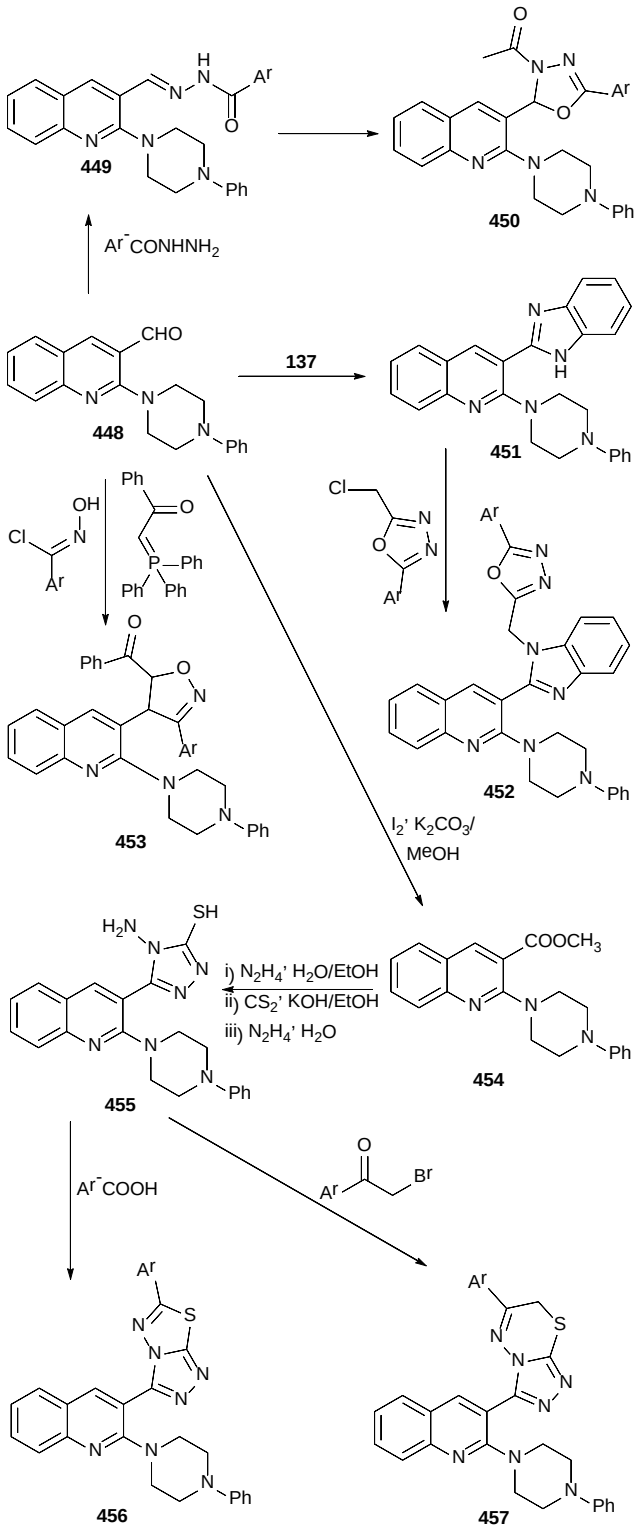


Scheme 99 Synthesis of different quinoline hybrids from 3-bromo carbostyril

MEDICINAL APPLICATIONS OF QUINOLINE AND ITS HYBRID DERIVATIVES

MEDICINAL APPLICATIONS OF QUINOLINE

With the development of quinoline, its action against many biological problems were observed and it came to notice that many of these drugs were shown to be effective. Quinoline and its derivatives hence became very vital in the treatment and prevention of tumors, fungal, and bacterial diseases. 4-carboxyquinoline derivatives proved to be effective against tumors which was shown by Daniel L. Dexter and group.[115] NSC 368390, in particular was efficient against leukemia in mice with drug administration for 9 days at optimal limits. They also showed good pursuit against CX-1 human colon carcinoma, MX-1 human mammary carcinoma, moderate activity against breast tumors and human lung tumor. The said molecule was compared to Adriamycin and verified to be effective against human stomach tumor. Not only was it effective against tumors but also showed good immunosuppressive activity. This type of suppressions is important in transplant recipients which allows the body to receive the organs transplanted. Brequinar sodium's structural changes were tested against cell activity reduction. Douglas G. Batt and his group,[116] reported that substitution at 6th, 7th and 8th positions with electron withdrawing groups showed good loss of cellular activities although it had little effect on the enzyme activity. In a report of 1998, Styrylquinoline derivatives were shown to have antiretroviral activity against HIV-1 Integrase. Mekouar and group reported that these derivates could be used to build new antiviral drugs as they were seen to have HIV-1 integrase inhibition marked against ex-vivo HIV replication and could be useful in co-crystallization studies with



Scheme 100 Synthesis of different quinoline hybrids from 2-(4-phenylpiperazin-1-yl)quinolin-3-carbaldehyde

this enzyme.[117] Antioxidant agents are those that are involved in the protection of a target against oxidative damage which can cause many diseases. Savegnago and group effectively synthesized 4-arylchalcogenyl-7-chloroquinolines and proposed its antioxidative activities. The protocol suggested by them was effective for the synthesis of selenium-nitrogen compounds showing antioxidative property.[118] 8-hydroxyquinoline also showed a wide range of activities as iron-chelators for neuroprotection, inhibitors of 2OG-dependent enzymes, chelators for metalloprotein, etc.

Some of the released quinoline drugs include pefloxacin, ciprofloxacin, levofloxacin and norfloxacin. Norfloxacin and silver norfloxacin are potential antimicrobial agents. In a report of Holder *et al.*, all the *Candida* organisms showed susceptibility towards silver norfloxacin and also has been more effective than norfloxacin.[119] Quinolines are potentially effective for not only life-threatening cancers and many such problems but they also have proven to be quite useful in our day-to-day problems which are less life threating. Same was reported for levofloxacin medicines by North and group. These drugs had a good efficacy for acute bacterial exacerbations of chronic bronchitis, skin structure infections, acute urinary tract infections, and acquired pneumonia.[120]

Having great potential in the field of pharmaceuticals and medicine, variety of quinoline hybrids have also been explored by scientists to enhance its biological applications. An overview of variety of quinoline hybrids is represented below.

MEDICINAL APPLICATIONS OF QUINOLINE-AZOLE DERIVATIVES

Depending on the substituent attached and type of linking, a wide variety of and different extent of biological importance is seen to be exhibited.

ANTI-MICROBIAL ACTIVITY

Quinoline-triazole moiety containing morpholine moiety showed good anti-bacterial property.[1] Compounds **(36, 37)** showed good activity against enteric bacteria, *Escherichia coli* and *Enterobacter aerogenes* when compared with standard ampicillin drug and moderate activity against *Yersinia pseudotuberculosiss.*[33] When compared to standard drug ampicillin, **(40)** showed equal activity against *Enterococcus faecalis* (Ef) and *Escherichia coli* (Ec). **(41)** showed moderate activity on *Bacilius cereus.*[33] Potent activity against Gram-positive bacteria *Staphylococcus aureus* was shown at 25mg/ml by compound **(47)** having electron withdrawing fluorine substituent and against *Bacillius cereus* by the bromine substituent halo-analogue of **(47)**. Nitro and cyano substituent of **(47)** shows greater inhibition for gram negative bacteria *Escherichia coli* and *K. pneumonia* at 50mg/ml.[40] **(115 & 118)** showed anti-bacterial property when screened using nutrient agar medium and DMSO as control by well diffusion method and chloramphenicol as standard bactericide.[47]

Compound **(261)** shows moderate to good activities against fungus *C. albicans* and *A. niger* and against bacterial strains *B. subtillis* and *P. mirabillis.*[66] Compound **(36)** showed antifungal property when screened using paper disc method against *Aspergillus niger*, *Rhizopus* species, *Pencilium notatum* and *Aspergilius flavus* for two concentrations- 500µg/ml and 1000µg/ml.[36] Compound **(88)** was screened for *Aspergilius*

fumigants, *Aspergilius flavus*, *Pencilium marneffei* using serial plate dilution method and was found to exhibit anti-fungal property.[43] Some other molecules also exhibited anti-fungal property against *Aspergilus niger* and *Pencillium notatum* species.[32,34-36,37,40] Most compounds showed a moderate to good anti-microbial property depending on the microbes and the methods used for evaluation.[32,34,37,39,41, 43 50]

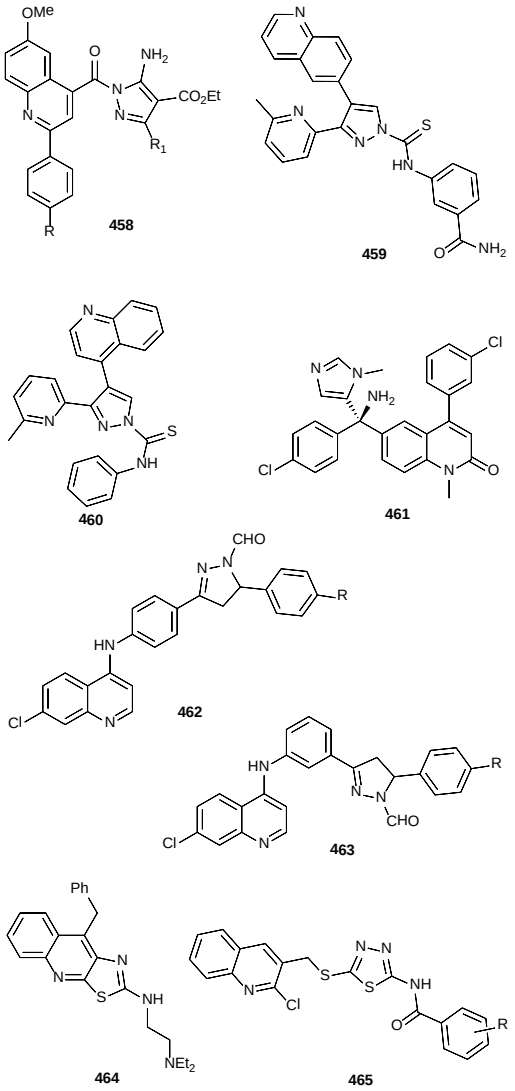
Anti-fungal property of **(246)** was tested against fungus *C. neoformans*, the opportunistic fungus which is the main cause of cryptococcal meningoencephalitis, and *C. albicans*. Compound **(105)** showed moderate antifungal and antibacterial property when screened with different concentrations and standard antibiotics like Griseofluvin and Streptomycin.[32] **(21),** having chloro group in phenyl ring at para position exhibited significant anti-microbial activity and compound **(201)** showed activity against *S.aureus* and *A.niger*.[37] **(201 & 202)** showed very good anti-bactrial[60] property, anti-fungal property. Derivatives of **(221)** showed inhibition for *N. gonorrhoeae* bacteria.[62] **(252)** showed good antimicrobial property.[68] Most compounds show anti-microbial[43,38,32] property and anti-fungal property.[66,67,69]

ANTI-INFLAMMATORY ACTIVITY

Quinoline-triazole derivative exhibited anti-inflammatory[49] property when evaluated using carrageenan induced hindpaw edema method and analgesic property when determined by tail-flick method[39]. Compound **(458)** (Scheme 101) with chlorine substituents showed COX-2 inhibition when evaluated using a COX-1/COX-2 assay kit and also best anti-inflammatory properties. Compound **(230)** having bromophenyl at position 3 (i.e. R=Br), showed good anti-inflammatory activity, due to the presence of bromo group which adds to the lipophilicity.[65] **(459 & 460)** are ALK5 inhibitors and showed very good anti-inflammatory activity.[67]

ANTI-CANCER ACTIVITY

Compound **(183)** showed good antitumor activity against leukaemia, breast cancer cells, renal cancer cells. The presence of benzimidazole was responsible for anti-cancer and good antimycobacterial property.[56] Tipifarnib **(461)** (Scheme 101) is a novel selective, nonpeptide farnesyl protein inhibitor exhibiting *in-vitro* activity in nanomolar range, currently undergoing human clinical trials for orally active antitumor agent.[58] **(201 & 202)** showed very good anti-tumour activity than a leading compound NVPBEZ235.[59] Compound **(221)** showed prominent GI_{50} value for anti-cancer activity for some cell lines.[62] **(462 & 463)** (Scheme 101) showed anti-cancer activity against 60 cancer cell lines and also showed higher activity than the standard, Asriamycin against several cell lines.[63] Derivatives of **(246)** was evaluated for cytotoxic activity on different cancer cell including breast (MCF7), colon (HCT116), liver (Huh7) carcinoma cells by SRB assay for determining IC_{50} values and it showed more potent activity against all cell lines.[67]



Scheme 101 Some biomedically significant quinoline hybrid molecules

ANTI-MALARIAL ACTIVITY

Compound **(151 & 154)** were chloroquine-astemizole derivatives that possessed good in vitro activity against a *Plasmodium falciparum* CQ-resistant strain. **(157 & 159)** were found to be active *in-vivo* in mouse models of malaria.[53] **(193)** showed activity against plasmodia.[57] **(220 & 221)** showed anti-malarial activity with EC_{50}=5.54 µg/mL and 0.70 µg/mL respectively.[62] Compound **(462)** (Scheme 101) also showed good anti-malarial activity.[63]

OTHER APPLICATIONS

Derivatives of **(76, 77, 79)** showed anti-tubercular activity.[121] **(115 & 118)** are good anti-oxidant agents. They showed anti-oxidant property when analyzed using DPPH free radical scavenging assay method. They also showed more anthelmintic activity than a standard, against earthworms, due to the presence the more potent quinoline, triazole and tetrazole rings in the compound.[86]

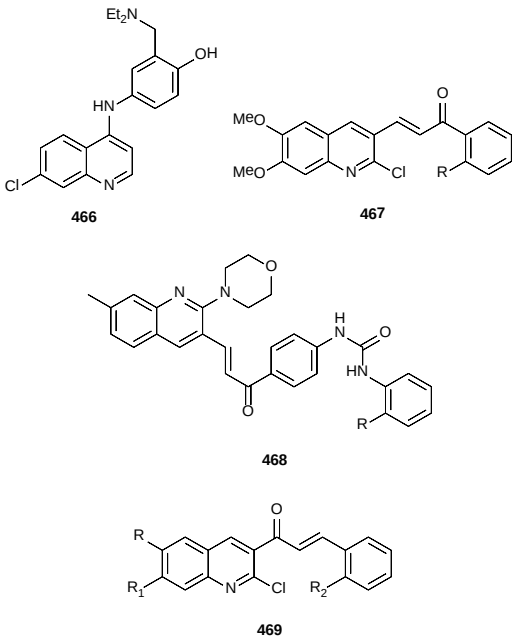
MEDICINAL APPLICATIONS OF QUINOLINE-DIAZINE, QUINOLINE-OXAZOLE, QUINOLINE-THIAZOLE HYBRIDS

ANTI-MICROBIAL ACTIVITY

(398, 399) showed anti-fungal property and anti-bacterial property.[100] Derivatives of **(284)** showed good activity against *S. aureus*, *E.faecalis*, *B.subtilis*, *B.cereus* and *S. epidermis*. **(282)** showed good activity against fungal *Candida albicans*, *A. niger*, *M. purpureous* and *A. flavus* when analysed using serial plate dilution technique with standard dug ketoconazole and ofloxacin.[76] **(289)** also showed anti-microbial activity using same technique.[87] Some of the thiadiazole derivatives shows anti-microbial property.[79] Compound **(307)** was analyzed for antibacterial and antifungal activity by serial dilution method using minimum inhibitory concentration, against bacteria *Staphycococcus aureus*, *Escherichia coli* and fungi *Aspergillus flavus*, *Candida albican.* Standard drug Nitrofurazone and Flucanazole were used for comparison. Derivatives having $–NO_2$ and –Cl as electron withdrawing groups showed highest activity.[82] Derivatives of **(311)** showed anti-bacterial activity when analysed using microwell dilution method, anti-tuberculosis activity against *M. tuberculosis* H_{37}Rv strain when compared with ciprooxacin and noroxacin.[83] **(322)** showed good anti-mycobacterial property when compared to standard drug rifampicin and moderate activity compared to gatifloxacin and moxioxacin.[85] **(334)** was analyzed for anti-bacterial activity using serial dilution method against *E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae* using ciprofloxacin as standard drug and it showed moderate to good activity. It also exhibited good anti-tuberculosis property.[88] **(357)** showed specific activity for organisms of *M. tuberculosis* complex and it acts as a prodrug[97]. **(350, 343 & 345)** showed anti-TB activity against both the replicating and non-replicating persistent forms of *Mycobacterium tuberculosis* (Mtb). These compounds had the ability to shorten the long treatment by targeting non-replicating persistent (Mtb) phenotype.[90]

ANTI-PROLIFERATIVE ACTIVITY

Thiazole derivatives **(285, 286 & 287)** showed antiproliferative activities against MCF-(breast), normal fibroblast cells(w1-38), Hela(cerivical) and DLD1(colon) human cancer cells when analyzed using sulforhodamine B method.[70] They showed more effective activity against colon cancer cell line[70] and were found to be safe to normal fibroblast cells. **(464)** showed best cytotoxicity for several cell lines, with broader specificity for binding DNA and inhibition of ^{14}C-thymidine incorporation into DNA.[75] Derivatives of **(291)** with Bromo and Chloro group at 7th position was found to exhibit good anticancer activity against HeLa human cervix cancer cell. Its derivatives showed DNA cleavage activity when analysed by gel electrophoresis method.[78] **(328)** showed good anti-cancer activity with good cytotoxic activity against several cell lines[17]. Derivatives of **(311)** showed cytotoxic property against A579 (lung cancer), PC3 (prostate cancer) and SKMEL1 (melanoma)[83] (Scheme 102).



Scheme 102 Quinolinyl chalcone derivatives

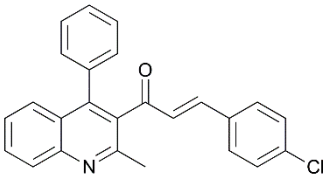
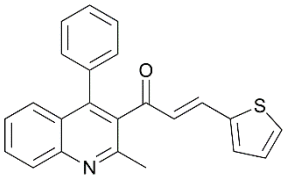
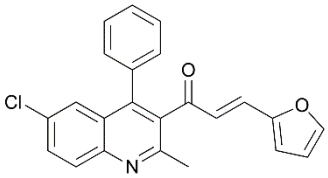
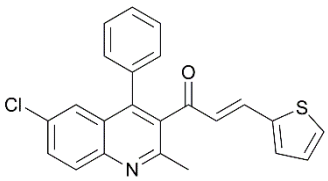
OTHER ACTIVITY

QPT **(266)** & QBT **(264)** showed chemosensor property for detection of Fe^{2+}, Fe^{3+}, and Cu^{2+} ions based on absorbance property.[72] Some of the compounds shows cytotoxicty, DNA

Table 1 Testing of anti-malarial activity of quinoline-chalcone derivatives **432**

R	R^1	R^2	R^3	Docking score (Kcal/mol)	MIC (µg/mL)	Remarks
H	Cl	H	Br	-10.8542	10	Highest binding score with pfLDH enzyme active site cavity and inhibited the maturation at MIC 10µg/mL and above.
OCH_3	Cl	H	Br	-8.8395	10	
H	CH_3	H	H	-10.4993	50	Inhibited 95% maturation of parasite at MIC 50µg/mL

Table 3 Anti-cancer study of quinoline-chalcone derivatives

Quinoline-chalcone Derivative	Colour	Yield (%)	Melting point(˚C)	Inhibition (%)
3-(4-chlorophenyl)-1-(3-methyl-1-phenyl-2-naphthyl)-2-propen-1-one	Orange	65	195-97	103
				
(3-Methyl-1-phenyl-2-naphthyl)-3-(2-thienyl)-2-propen-1-one	Brown	72	166-68	101.59
				
1-(7-Chloro-3-methyl-1-phenyl-2-naphthyl)-3-(2-furyl)-2-propen-1-one	Brown	67	154-58	100.20
				
1-(7-Chloro-3-methyl-1-phenyl-2-naphthyl)-3-(2-thienyl)-2-propen-1-one	Brown	70	152-54	100.14
				

binding[75] and DNA topoisomerase-II inhibition.[74] Some of the derivatives of fluoro-quinolone **(465)** that were synthesized, showed anti-convulsant activities.[80] Derivatives of compound **(299)** possess α-amylase inhibitory activity and the derivative having thiophene moiety attached to thiadiazole ring showed more activity.[80] Mefloquine **(396)** is a long-acting antimalarial drug known for its efficiency against SP-resistant *Plasmodium falciparum* and chloroquine.[99] Many synthesized compounds showed antiplasmodium activity.[91, 97]

MEDICINAL APPLICATIONS OF QUINOLINE-FERROCENE DERIVATIVES

Radical scavenging abilities of ferrocenylquinoline: Ferrocenylquinoline improves the anti-oxidative property, inhibits DNA oxidations and exhibits radical scavenging abilities.[104] Ferrocenyl group at position 4 in quinoline exhibits more radical scavenging ability than hydroxyl group at the same position. Ferrocenyl is an active group in **(402)** with various subtituents, to quench some of radicals that are stable at ambient temperature like $ABTS^{+\cdot}$, DPPH. 7-chloro-4-hydroxylquinoline, an anti-cancer drug cannot react with DPPH but the presence of ferrocenyl along with hydroxyl group improved the ability to reduce $ABTS^{+\cdot}$ and also to quench DPPH.[104] *O*-quinoline ferrocene with 4,1-disubstituted 1,2,3 triazole showed moderated radical scavenging activities.[103]

Cyclic voltametry studies revealed that some of the derivatives show single-electron reversible oxidation behaviour attributed to ferrocene nucleus, and some exhibited two well defined oxidation curve and one reduction curve.[106,105] A compound synthesized by Minić showed high selectivity, low micromolar antiplasmodium activity and low resistance, which led to a new hit in malarial research.[106] Another ferrocene-quinoline compound showed anti-proliferative effect[103] and cytostatic activity. Inhibitory effect on some tumour cell lines was exihbited by N-alkylated analogs, with selective activity on Raji cells.[103] Ferroquine and its derivatives have been used as anti-malarial agents.[102,105,107,108] Other compounds also showed anti-malarial activity and hence led to new research in the field.[108]

MEDICINAL APPLICATIONS OF QUINOLINE-CHALCONE DERIVATIVES

ANTI-MALARIAL ACTIVITY

Malaria is a life-threatening disease which is caused by Plasmodium parasites. It is spread from person to person through the bite of female Anopheles mosquitoes. Among the five parasite species that spreads this disease among humans, *P. falciparum* and *P.vivax* are the gratest threat. The best available treatment, especially for *P.falciparum* malaria is antimisinin-based combination therapy (ACT). Children below five-years are the most vulnerable group affected by malaria. From 2019 census, around 229 million cases and 409 deaths have been reported. Apart from vector control, usage of anti-malarial drugs is the only alternative to prevent malaria.

Quinolinyl chalcones have been reported to possess good anti-malarial properties. Amodiaquine (AQ) **(466)** (Scheme 102) is a Mannich base of 4-aminoquinoline that is highly effective against chloroquine resistant strains of P. Falciparum. The anti-malarial potentials of aminoquinolines prompted Ferrer et al. to synthesise [7-chloroquinolin-4-yl)amino]chalcones. Isoquine, an analogue of amodiaquine was found to possess high anti-malarial against *P. yoelli* than amodiaquine. Tebuquine, a biaryl analogue of amodiaquine was more significant and active than amodiaquine and chloroquine in both *in-vivo* and *in-vitro* tests. Both amodiaquine and tebuquine have *in-vivo* toxicity on prolonged usage due to production of active quinonamine metabolite.[121]

Differently substituted quinolinyl chalcone **(432)** (Scheme 96) was synthesised and tested for anti-malarial activity by binding in the pfLDH active sites (molecular docking) and results are tabulated as below.[109] Only atovaquone had better binding with pfLDH when compared to other lead anti-malarial drugs (Table 2).

Domynguez et al synthesised different derivatives of the quinolinyl chalcones **(467)** (Scheme 102) and evaluated their inhibition of Plasmodium falciparum cystein protease falcipain and their activity against cultured P.falciparum parasites. From the study, it was found that a substitution in the benzoyl ring plays a crucial role in their anti-malarial activities. Among the synthesised compounds, 1-(2,4-Dichlorophenyl)-3-(3-(2-chloro-6,7-dimethoxyquinolinyl)-2-propen-1-one showed highest anti-malarial activity with IC_{50} 19.0µM.[122]

ANTI-CANCER ACTIVITY

Cancer has emerged as a leading reason of deaths in the world. Healthy cells have a specific life cycle of division and decay which is determined by the cell-types and new cells follow the old or damaged cells as they die. Cancer that is caused due to the changes or mutations in DNA disrupts this routine and causes abnormal cell growth. There are several clinical terms used for

Table 4 Anti-inflammatory studies of quinoline-chalcone derivatives

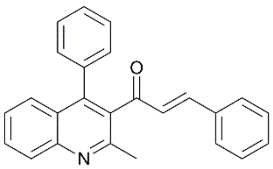
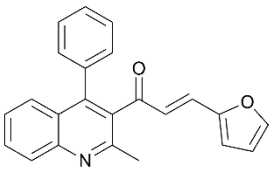
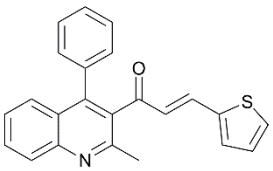
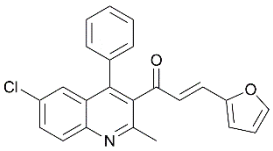
Quinoline-chalcone derivative	After 1hr	After 2hrs	After 5hrs	Protection (%)	Result
Standard-Indomethacin (10mg/mL)	0.26±0.01	0.52±0.02	0.15±0.02	82	
	0.28±0.01	0.54±0.03	0.21±0.01	72.18	
	0.28±0.03	0.52±0.04	0.17±0.04	80.36	
	0.24±0.02	0.52±0.04	0.18±0.02	79.48	
	0.27±0.04	0.52±0.04	0.16±0.03	81.78	Reduced paw oedema with highest protection percentage

Table 5 Study of anti-bacterial activity of quinoline-chalcones

Derivative	Gram-positive (µg/mL)				Gram-negative (µg/mL)				Observation
	B. subtilis		*B. pumillus*		*P. vulgaris*		*E. coli*		
	50	100	50	100	50	100	50	100	
1-(6-chloro-2-methyl-4-phenylquinoline-3-yl)-3-(2-hydroxy-5-nitrophenyl) prop-2-en-1-one	-	-	10	15	-	-	-	-	Active against only B. pumillus
1-(6-chloro-2-methyl-4-phenylquinoline-3-yl)-3-p-tolylprop-2-en-1-one	4	10	9	14	-	-	-	-	Inactive against Gram-negative strains
1-(6-Chloro-2-methyl-4-phenylquinoline-3-yl)-3-(4-flurophenyl)prop-2-en-1-one	15	19	17	22	13	19	10	15	Shown comparable activity to that of standard Ciprofloxacin
1-(6-Chloro-2-methyl-4-phenylquinoline-3-yl)-3-(4-chlorophenyl)prop-2-en-1-one	12	15	14	18	10	16	6	13	Fluro-substituted compound, high electronegativity showing high lipophilicity and penetrate effectively.
3(3-bromophenyl)-1-(6-chloro-2-methyl-4-phenylquinoline-3-yl)prop-2-en-1-one	-	-	-	-	-	-	-	-	Does not show any activity
1-(6-chloro-2-methyl-4-phenylquinoline-3-yl)-3-(2-chlorophenyl)prop-2-en-1-one	10	15	13	16	10	15	4	11	Shows activity against all strains
1-(6-chloro-2-methyl-4-phenylquinoline-3-yl)-3-(2-hydroxyphenyl)prop-2-en-1-one	-	-	-	-	-	-	-	-	Does not show any activity
1-(6-Chloro-2-methyl-4-phenylquinoline-3-yl)-3-(2-hydroxy-5-nitrophenyl)prop-2-en-1-one	18	23	20	25	15	23	14	19	Has nitro group as substituent in pharmacophore, shows excellent antibacterial activity at higher concentration
Ciprofloxacin(50µg/mL) (control standard)	28	32	30	24					

certain general types of cancer like Carcinoma - that starts in the skin or tissues that line other organs, Sarcoma - the cancer of connective tissues such as bones, muscles, cartilage and blood vessels, Leukemia or Blood cancer - the cancer of bone marrow that produces blood cells, Lymphoma and myeloma - cancers that affect the immune system.

The most common types of cancer treatments include surgery, chemotherapy, radiation therapy, stem cell (bone marrow) transplant, Immunotherapy (biological therapy), and targeted drug therapy. Modern anti-cancer drug discovery continues to search for improved cytotoxic agents and more advanced clinical therapies.

Quinoline-chalcone derivatives were found to possess effective anti-cancer properties. From the *in-vitro* anti-cancer study, inhibition percentage of different quinoline-chalcone derivatives were determined by subjecting them on RAW cell lines. The toxicity of different quinolinyl chalcone derivatives were evaluated by MTT assay that is based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly coloured blue for formazan product. All experiments were carried out in triplicate and toxicity of different quinolinyl chalcones were calculated from plot drawn with viability (% from control) versus concentration of compounds tested in medium. Results and corresponding data were as tabulated (Table 3).[123]

ANTI-INFLAMMATORY ACTIVITY

Inflammation refers to the body's process of resisting infections, injuries and toxins in an attempt to heal the damaged cells. In this process, the immune system releases anti-bodies and proteins. Inflammation can be caused due to pathogens such as bacteria, fungi or viruses, external skin injuries like scrapes or splinter because of some foreign bodies and from allergy towards chemicals. In situation of chronic inflammation, the person would experience fatigue, rashes, fever, mouth sores, body pain (abdominal and chest areas). Factors that cause chronic inflammation includes smoking, obesity, alcohol consumption

and even stress. Medical conditions that cause inflammation often have suffix “itis” such as Bronchitis (inflammation of bronchi), Cystitis (inflammation of bladder), Otitis media (inflammation of middle ear) and Dermatitis (inflammation of skin). Over time, chronic inflammations can lead to DNA damage, tissue death and internal scarring. Severe diseases associated with inflammation include heart disease, Rheumatoid arthritis, Type 2 diabetics, Obesity, Asthma and Alzheimer’s disease.

Quinoline-chalcone derivatives synthesised via Claisen-Schmidt condensation were subjected to anti-inflammatory activity in Albino rats. Indomethacin 20mg/kg was used as the standard. The protection (%) of different quinoline-chalcones was calculated (Table 4).[109]

ANTI-BACTERIAL ACTIVITY

Sirsat *et al*. (2012) tested 1-[substituted aryl]-3-[substituted hetero aryl]-2-propen-1-ones derivatives for their *in-vitro* anti-bacterial activity against Gram-positive and Gram-negative strains using micro-dilution procedure and found them to be active anti-bacterial agents.[112]

Chikhalia et al. synthesised substituted quinoline-chalcones **(468)** (Scheme 102) (where R=H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, 2,4-$(NO_2)_2$) that gave positive activity profile as anti-microbial agents.[111]

Afron Patan et al screened synthesised quinolinyl chalcones for their antibacterial activity using cup-plate method at a concentration of 50µg/mL against Escherichia Coli and Proteus vulgaris (Gram Negative strains), Bacillus substilis and Bacillus pumilus (Gram positive strains). Solvent DMSO was used as control. Standard drug Ciprofloxacin 50µg/mL was used for comparison purpose. After incubation at 30^{O}C in 24h, the zones of inhibition were measured (Table 5).[112]

ANTI-AMOEBIC ACTIVITY

Hayat et al. synthesized a series of chloroquinoline-based chalcones **(467)** (Scheme 102) and evaluated their anti-amoebic activity by screening *in-vitro* against HMI: IMSS strain of E. histolytica by micro-dilution method[122] where, R=H, CH_3, R_1=H, CH_3, R_2= 3-Br, 4-Br, 3-Cl, 4-Cl.

CONCLUSION

Quinoline scaffolds have played an important role in the field of medicinal chemistry as potent and effective drugs against various pathogens and infectious diseases. This sort of vast impact led to the discovery of different methods of synthesis for quinolines, which has improved over the years to achieve better yields and sustainability. But over the years, problems such as drug resistance and mutated strains of pathogens arose, rendering the existing quinoline-based drugs ineffective. The effective solution to this problem was the use of combination therapies in treatments and synthesis of new hybrid drugs. Hybrid drugs were found to be more advantageous as they were able to overcome the issues encountered in combination therapies due to lower occurrence of drug-to-drug interactions and better patient-compliance.

In this review, an effort has been made to compile the synthesis and medicinal applications of many such quinoline hybrids including quinoline-azole, quinoline-triazole, quinoline-tetrazole, quinoline-imidazole-tetrazole, quinoline-imidazole, quinoline-pyrazole, quinoline-thiazole, quinoline-thiadiazole, quinoline-oxazole, quinoline-isoxazole, quinoline-pyridazine, quinoline-pyrazine, quinoline-piperidine, quinoline-ferrocene and quinoline-chalcone derivatives. Their anti-microbial, anti-cancer, anti-malarial and anti-oxidant properties, among some others, have been discussed. There are molecules that have shown good activity against the tested pathogens. These synthesized molecules exhibit potential to be used as lead molecules in drug design, and hence, there exists scope for further *in-vivo* studies and evaluation of these molecules.

FURTHER SCOPE

Hybrid drugs are designed by fusing more than one bioactive component or pharmacophore into one single molecule which represents the desired features of the original drug, generally for a specific application. These molecules are expected to show greater therapeutic effect than the molecules from which they are derived either by amplification or via independent actions on multiple targets. These single molecules are advantageous in terms of pharmacokinetics and at times, bioavailability. They also exhibit lesser drug-drug interactions, enhanced patient compliance, have lesser adverse effects and lower toxicity. All of these make hybrid drugs the first in line to be considered as candidates for drugs, where drug resistance is a growing problem and combination therapies have more cons. That being said, obtaining an effective hybrid drug is still a complex multi-stage process. Once the bioactive pharmacophores and linkages have been identified and synthesised, as in the various molecules discussed here, ample research has to be carried out on their structure-activity relationship (SAR), followed by optimization of the structure resulting in identification of lead molecules. These molecules then have to undergo a series of further studies and modifications to optimize its drug-like properties. They have to be screened *in-vivo* for their ability to cross membranes, bioavailability, toxicity, etc. before passing off as effective drugs.

ACKNOWLEDGEMENTS

The authors acknowledge St. Joseph’s College (Autonomous), Bangalore for providing financial support to carry out this research work.

Conflict of Interest

On behalf of all the authors, the corresponding author states that there is no conflict of interest.

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