1. Introduction

1.1. Homocyclic compounds:

Homocyclic compounds are compounds in which a series of atoms are connected to form loop or ring, while the vast majority of cyclic compounds are organic, cyclic compounds may or may not be aromatic have an uninterrupted ring of π electrons, and according to Huckel' s rule the number of π electrons in an aromatic monocyclic compound must be equal to 4n+2 where n=1,2,3,.....etc.(March, 1985). Benzene Fig (1.1) is a well known example.

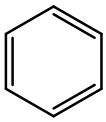


Figure (1.1): Chemical structure of benzene a homocyclic compound.

There is a class of aromatic cyclic compounds called poly cyclic benzenoid aromatic compounds, possess substantial resonance energies because each is a collection of benzene rings fused together, naphthalene, anthracene and phenanthrene are the three simplest members of this class Fig (1.2).

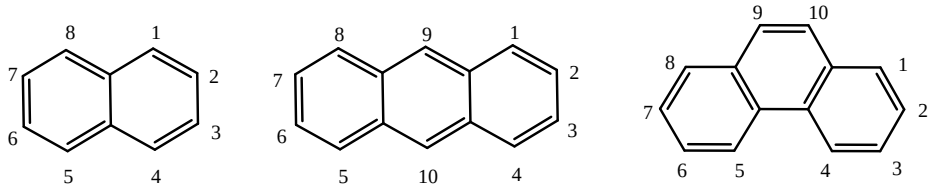


Figure (1.2): Poly cyclic benzenoid aromatic compounds.

1.2. Heterocyclic compounds:

Heterocyclic compounds are an extraordinarily important class of compounds, making up more than half of all known organic compounds, almost all the compounds known as drugs, most vitamins and many other natural products are heterocycles. (Bruice, 2003).

A definition of a heterocyclic compound is one which possess a cyclic structure with at least two different kinds of atoms in the ring, nitrogen, oxygen and sulphur are the most common heteroatom. Heterocyclic compounds may be classified into aliphatic

and aromatic, they usually possess a stable ring structure which does not readily hydrolyze or depolymerise (Rossmoore, 1979).

1.3. Classification of heterocyclic compounds:

Heterocyclic compounds can be usually classified based on their electronic structure, the saturated hetero cycles behave like cyclic derivatives, but most studies focus on unsaturated derivatives.

1.3.1. Three – membered rings:

Heterocycles with three atoms in the ring are more reactive because of ring strain, those containing one heteroatom are in general, stable like ethylene oxide, those with two heteroatom's are more likely to occur as reactive intermediates Fig (1.3).

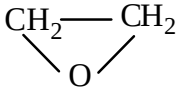


Figure (1.3): Ethylene oxide a three – membered rings.

1.3.2. Four – membered rings:

Heterocycles with four atoms in the ring are most unstable because of bond stretch, and therefore tend to be highly reactive like azete (Campaigne, 1986), some of them contain one heteroatom while others may contain more than two heteroatoms. Fig (1.4).

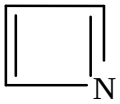


Figure (1.4): Azete a four – membered rings.

1.3.3. Five – membered rings:

Heterocycles with five atoms in the ring have three pairs of delocalized π electrons: two of the pairs are shown as π bonds, and one pair is shown as a lone pair on the heteroatom, pyrrole, furan and thiophene are well known examples.

Furan and thiophene have a second lone pair that is not part of the π cloud. These electrons are in a sp^2 orbital perpendicular to the P orbitals Fig (1.5).

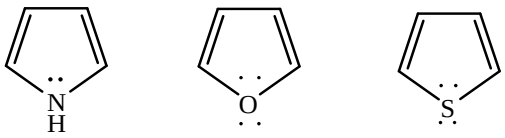


Figure (1.5): Five – membered rings.

Indole, benzofuran and benzothiophene contain a five – membered aromatic ring fused to a benzene ring Fig (1.6).

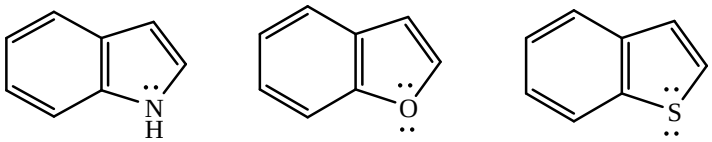


Figure (1.6): Fused five – membered rings.

A large group of heterocyclic aromatic compounds are related to pyrrole by replacement of one of the ring carbons β to nitrogen by second heteroatom, compounds of this type are called azoles Fig (1.7).

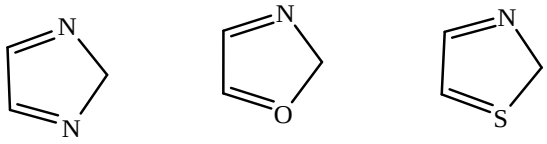


Figure (1.7): Azoles.

1.3.4. Six – membered rings:

When one of the carbons of benzene ring is replaced by nitrogen, the resulting compound is called pyridine Fig (1.8).

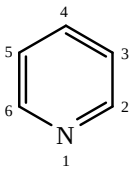


Figure (1.8): Chemical structure of pyridine.

1.3.5. Fused six – membered rings:

Quinoline and isoquinoline contain six – membered aromatic ring fused to a benzene ring they are also known as benzopyridine Fig (1.9).

Figure (1.9): Benzopyridine a fused six – membered rings.

1.4. Quinolines:

1.4.1. Definition and occurrence:

Quinoline and its derivatives are receiving increasing importance due to their wide range of biological and pharmacological activities. Quinoline Fig (1.9) ring characterized by a double ring structure composed of a benzene and a pyridine ring fused at two adjacent carbon atoms, it is also called 1- azanaphthalene or benzo [b] pyridine, it was isolated from coal tar bases and subsequently obtained it from the alkaline pyrolysis of cinchonine an alkaloid related to quinoline. The numbering in quinoline commences from the nitrogen atom which is assigned position – 1. (Revanasiddappa *et al*, 2009), the simplest member of the quinoline family is quinoline itself, a compound with molecular structure C_9H_7N.

Quinoline ring system is present both in the natural products and synthetic compounds, the world production of quinoline is over 2000 tons, and it is an intermediate in metallurgical processes and in dye, polymer and agrochemical production. In organic synthesis it is sometimes used as a high boiling basic solvent (Collin, 1993).

It has interesting biological activities such as antimalarial (Maqbool *et al*, 2006), anti-inflammatory agent, anti – asthmatic, antibacterial (Mohammed *et al*, 1992), antihypertensive, anti cancer (Balaji *et al*, 2010), tyrosine kinase inhibiting agent, and anti nuclear inhibitors of immune deficiency virus (Baba *et al*, 1997). In addition, quinoline has been used for the prepration of nanostructures and polymers that combine enhanced electronic, optoelectronic or non – linear optical properties with excellent mechanical properties. (Xiao *et al*, 2011).

1.4.2. Classical synthesis of quinolines:

As a result of their importance as substructures in a broad range of natural and designed products, the structural core of quinoline has been synthesized by various methods.

1.4.2.1. Skraup/ Doebner – Von miller:

Skraup discovered that quinoline could be synthesized by heating aniline with glycerol, sulphuric acid and an oxidizing agent, in this reaction glycerol is dehydrated to acrolein by sulphuric acid and then reacts with aniline by nucleophilic conjugate addition. This intermediate is then cyclised, oxidized and dehydrated to give the quinoline.(Li, 2006).

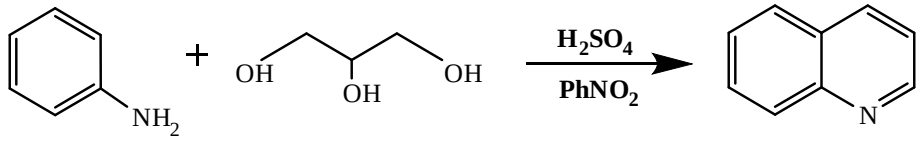
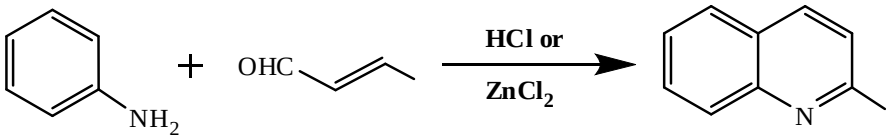


Figure (1.10): Skraup / Doebner – Von miller quinoline synthesis.

By substituting 1,2-glycols or an α , β unsaturated aldehyde for the glycerol, Doebner and Von miller were able to generalize Skraup's method for the synthesis of quinolines bearing substituents in pyridinoid ring.(Eisch and Dlzniewski, 1989).



This reaction can be violently exothermic a moderator such as iron (II) sulphate is usually added, to improve yields, the reaction is catalyzed by lewis acid such as tin tetrachloride, scandium (III) triflate and Bronsted acid such as p-toluene sulfonic acid, perchloric acid, amberlite and iodine.(Bergstrom, 1944).

1.4.2.2. Doebner reaction:

Is a three component coupling of aniline with an aldehyde and pyruvic acid to form quinoline 4-carboxylic acids. (Pflum, 2005).

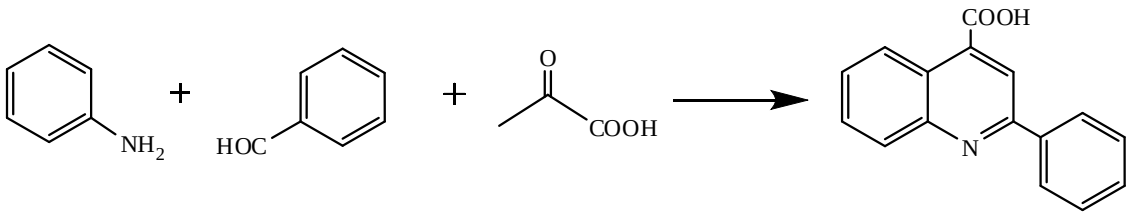


Figure (1.11): Doebner reaction.

1.4.2.3. Combes quinoline synthesis:

Is a formation of quinoline and benzoquinoline by the condensation of primary aryl amines with β- diketones followed by an acid catalyzed ring closure of the schiff base intermediate. (Johnson and Mathews, 1944).

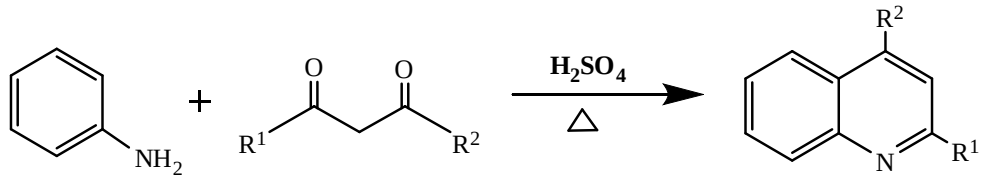


Figure (1.12): Combes quinoline synthesis.

1.4.2.4. Knorr quinoline synthesis:

The formation of α – hydroxyl quinolines (2-hydroxy quinoline) from β – ketoesters and arylamines requires heating above 100 ºC, the intermediate anilide undergoes cyclization by dehydration with concentrated sulphuric acid. (Staskun, 1964).

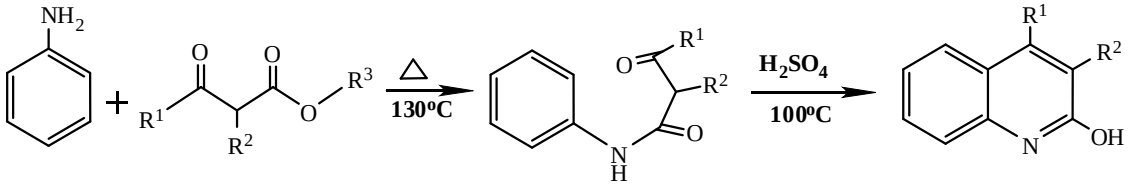


Figure (1.13): Knorr quinoline synthesis.

1.4.2.5. Conrad – Limpach cyclization:

The thermal condensation of primary aromatic amines with the carbonyl group of β – keto esters, followed by the cyclization of schiff base intermediate (alkyl β-arylaminocrotonates) to synthesize 4-quinolones, which often isomerize or aromatize to 4-hydroxy quinolines. (Brouet *et al*, 2009).

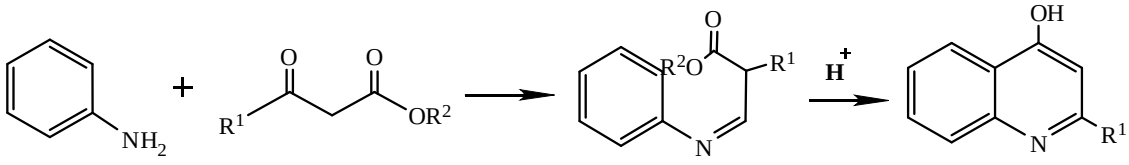


Figure (1.14): Conrad-Limpach cyclization.

1.4.2.6. Camps quinoline synthesis:

Base catalyzed intramolecular condensation of 2 – acetamidoacetophenone to 2 – substituted quinolin – 4 – ol, 4 – substituted quinolin – 2 – ol, using hydroxide ion. The relative proportions of the hydroxy quinolines are dependent upon the reaction conditions, and structure of the starting material. Although the reaction product is commonly depicted as a quinoline (the enol form), it is believed that the keto form predominates in both the solid state and in solution, making the compound a quinoline (Jone *et al*, 2007).

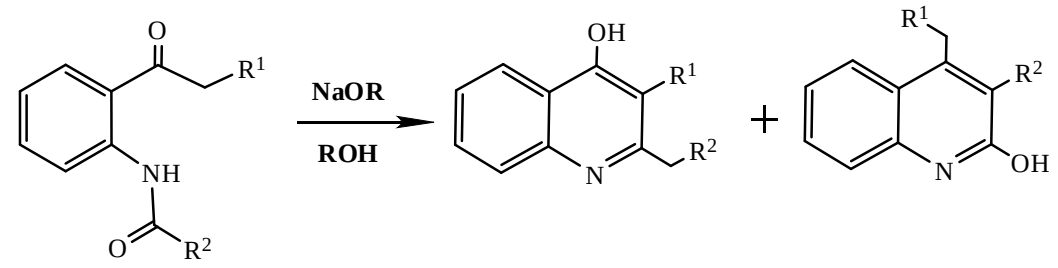


Figure (1.15): Camps quinoline synthesis.

1.4.2.7. Gould – Jacobs reaction:

In this reaction aniline or an aniline derivative first reacts with malonic acid derivative ethyl ethoxy methylene malonate with substitution of the ethoxy group by nitrogen, a benzannulation takes place by application of heat to quinoline, the ester group is hydrolysed by sodium hydroxide to the carboxylic acid and decarboxylation again by application of heat to 4 – hydroxy quinoline. (Gould and Jacobs, 1939).

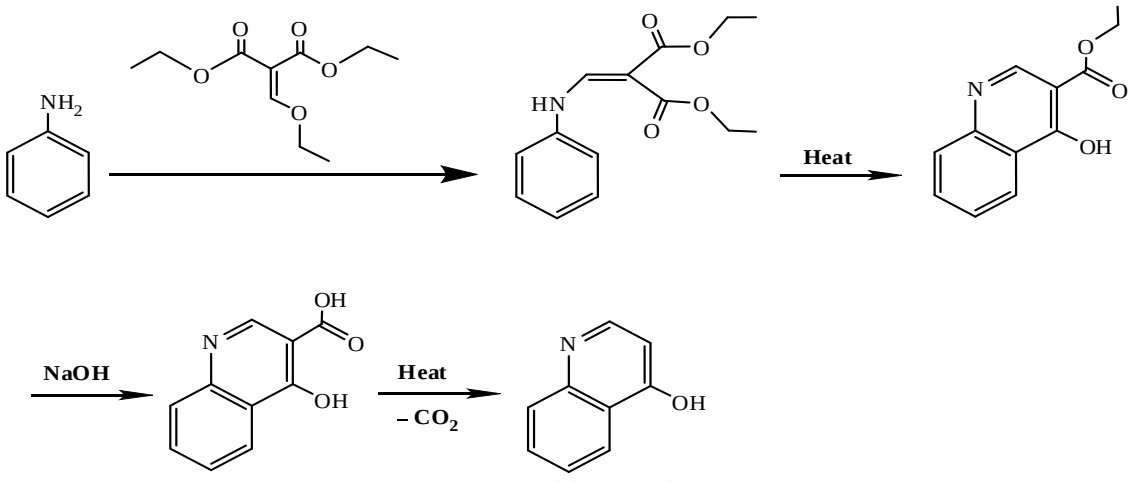


Figure (1.16): Gould – Jacobs reaction.

1.4.2.8. Friedlander synthesis:

It is a condensation of *o*-amino-benzaldehyde with ketones to form quinoline derivatives, this reaction has been catalyzed by trifluoroacetic acid (Shaabani *et al*, 2007), toluenesulfonic acid, and Lewis acids, some quinolines can also be prepared simply by heating a mixture of the reactants with or without solvent.

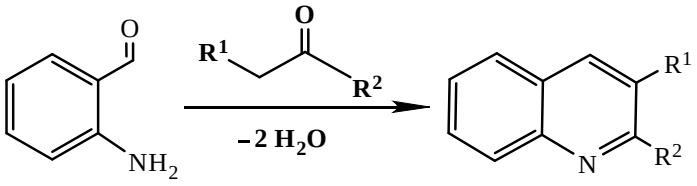


Figure (1.17): Friedlander synthesis.

1.4.2.9. Povarov reaction:

It is a cycloaddition reaction between an aromatic imine and an alkene, the imine in this organic reaction is a condensation reaction product from an aniline type compound and benzaldehyde type compound, the alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons, such as alkenes are enol ethers and enamines (Sun *et al*, 2012).

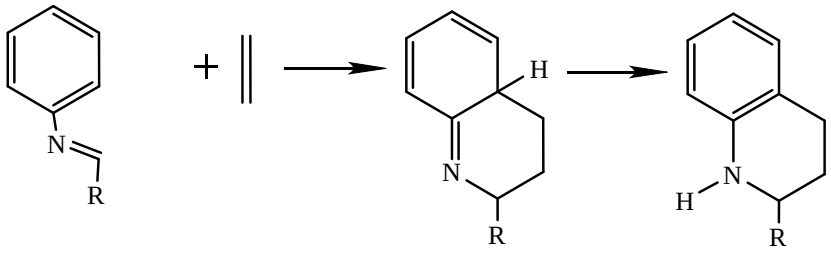


Figure (1.18): Povarov reaction.

1.4.2.10. Riehm quinoline synthesis:

The formation of quinolines via the reaction of an aniline hydrochloride salt and ketone. (Craig, 1938).

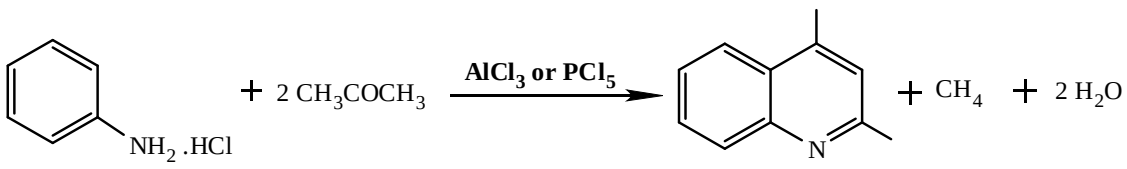


Figure (1.19): Riehm synthesis.

1.4.2.11. Niementowski quinoline synthesis:

The formation of γ – hydroxy quinoline derivatives via the reaction of an anthranilic acid and ketone or aldehyde.(Li, 2011).

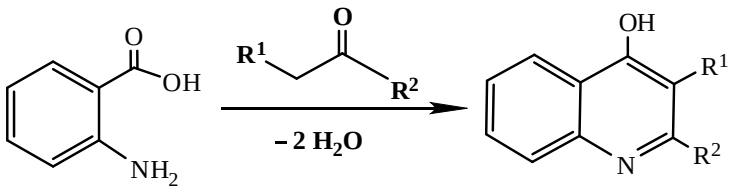


Figure (1.20): Niementowski synthesis.

1.4.2.12. Pfitzinger reaction:

It is a ring condensation reaction of isatin with base and a carbonyl compound to yield substituted quinoline 4 – carboxylic acids. (Shvekhgeimer, 2004).

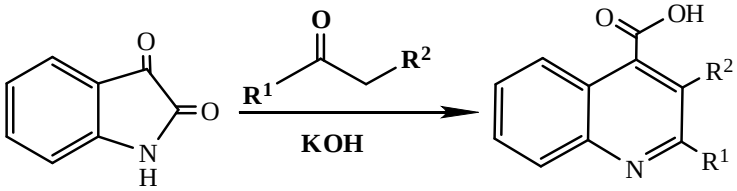


Figure (1.21): Pfitzinger reaction.

1.4.3. Modern methods for quinoline synthesis:

Quinoline ring is the subject of extensive research in organic chemistry, because it is present in many biologically active compounds, however, many classical methods that have been mentioned previously suffer from harsh conditions, multi step, low stereoselectivity, resulting in low overall yields and expensive or harmful metals.

Some studies suggest two approaches towards the synthesis of quinoline structure, the first one relates to the use of the aromatic primary amine as a nucleophilic component providing nitrogen as the C–C–N unit and electrophilic three carbon unit, whereas the second one employs the ortho substituted aniline as the C–C–C–N unit and two carbons unit usually carbonyl compounds containing a reactive α – methylene group (Denmark and Venkatraman, 2006).

1.4.3.1. Approach employing aromatic primary amines as the nucleophilic nitrogen donating component as C – C – N unit:

Microwave – assisted reactions between anilines and alkyl vinyl ketones or 1,3-diketones on the surface of diverse absorbents proceeded smoothly to give new substituted quinolines, a simple and efficient procedure consists of a one – pot reaction of anilines with methyl vinyl ketone or its analogs on the surface of silica gel impregnated with indium trichloride (III) under microwave irradiation without any solvent.(Ranu *et al*, 2003). This method was used in the synthesis of 6-aminoquinoline derivatives, antimalarial agents, (Jiranusornkul *et al*, 2002). Alumina supported synthesis of antibacterial quinolines using microwaves was also reported. (Kidwai *et al*, 2000). The reaction times in both methods have been shortening from hours to seconds with improved yield as compared to conventional heating. The salient feature of these approaches is coupling microwaves with solvent free technique keeping modernization and simplification of classical procedures, avoiding volatile and toxic organic solvents, corrosive mineral acids, which make them a clean, efficient and cheap technology to obtain various useful quinolines.

The utilization of organometallic reagents in the construction of quinolines continues to be an area of great interest. The formation of quinoline skeletons has been attempted by a remarkable catalytic action of transition metal catalysts such as palladium, rhodium, cobalt, ruthenium and iron complexes. It was suggested that this metal – catalyzed heteroannulation proceeds via amine exchange reaction between anilines and alkanoamines, amines, allyl alcohols or 1,3-diols. For instance, anilines react with 3-amino-1-propanol in dioxane at 180 $^{\circ}$C in the presence of a catalytic amount of $RuCl_3$ nH_2O / $3PPh_3$ and $SnCl_2 2H_2O$ together with hydrogen acceptor (acetone, nitrobenzene or hex-1-ene) to afford the corresponding quinolines in moderate yields (29-46%).

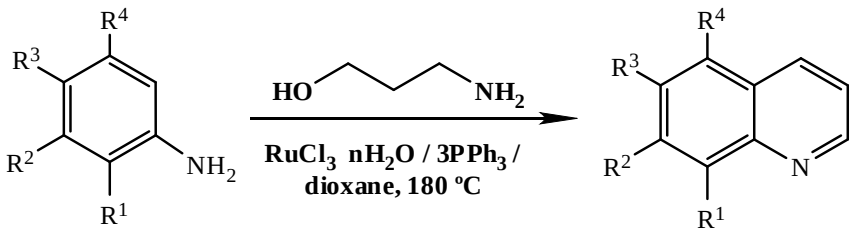


Figure (1.22): Organometallic reagents in synthesis of quinolines.

1.4.3.2. Approach employing ortho – substituted anilines C – C – C - N unit and two carbon unit:

Another way of preparing quinoline derivatives is to utilize ortho – substituted anilines (C-C-C-N unit) and two carbon unit, usually carbonyl compounds containing a reactive α – methylene group. Aniline derivatives substituted at the 2-position and *o* substituted nitrobenzenes are frequently employed as starting materials.

The Friedlander synthesis of quinolines from *o*-aminobenzaldehydes is a stable reaction of organic synthesis. Although it does not require catalyst, the Friedlander synthesis can be acid or base catalysed. Uncatalyzed Friedlander synthesis required more drastic reaction conditions with temperatures in the range 150 – 220 $^{\circ}$C, hydrochloric acid, sulfuric acid, polyphosphoric acid and *p*-toluenesulfonic acid were widely employed as catalysts.

Some of the restrictions of the former reactions involve the substitution pattern on the available starting materials and thus, limits the functional groups on the quinoline product, and high temperatures in some cases. *O*-aminophenylketones are used most often in the Friedlander quinoline synthesis because they are more stable, a green approach was developed to the Friedlander synthesis of quionlines that requires neither harsh conditions nor the use of hazardous acids or bases. Substituted 2-methylquinolines were readily prepared under mild conditions through a gold (III)-catalyzed sequential condensation /annulations reaction of *o*-amino aromatic carbonyls and ketones containing active methylene groups.(Wu *et al*, 2009).

The same quinolines can be prepared using a catalytic amount of bismuth triflate an easy and efficient synthesis of 3-nitroquinoline derivatives from *o*-aminobenzaldehyde and β-nirostyrenes in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) and silica gel, this one-pot reaction represents an interesting variation in the Friedlander-type quinoline synthesis.

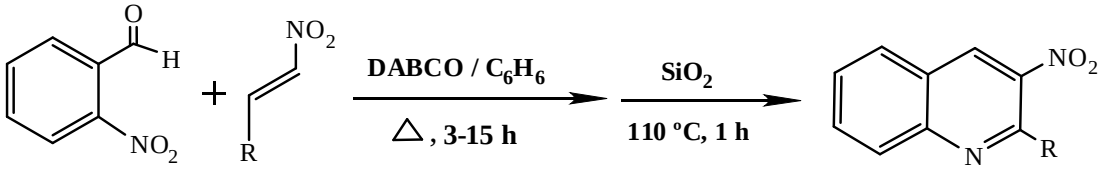


Figure (1.23): One-pot Friedlander reaction.

Cyclization of ortho-functionalized aryl isocyanides has been an attractive strategy for the synthesis of nitrogen-containing heterocyclic aromatic compounds. For instance, cyclization of *o*-alkynylisocyanobenzenes in methanol at 50 $^{\circ}$C afforded the corresponding 3-substituted 2-methoxyquinolines in good yields. Use of diethylamine as the nucleophile rather than methanol resulted in the formation of 2-(diethylamino) quinoline derivatives.(Vladimir *et al*, 2005).

1.5. Reactions of quinolines:

Quinoline displays chemical properties associated with a tertiary amine. In addition because of the fusion of a benzene ring, properties of both benzenoid and pyridinoid compounds frequently manifest themselves.

1.5.1. Reactions with electrophilic reagents:

1.5.1.1. Addition to nitrogen:

This reaction involves donation of the nitrogen lone pair to electrophiles.

1.5.1.1.1. Protonation of nitrogen:

Quinolines form crystalline salts with most protic acids. Quinoline itself, with pk_{aH} 4.94 in water, is a much weaker base than saturated aliphatic amines which have pk_{aH} values mostly between 9 and 11, electron – releasing substituents such as methyl generally increase the basic strength of the quinoline to which they are attached, but with other classes of substituent the situation becomes too complicated.

1.5.1.1.2. Nitration at nitrogen:

This occurs readily by interaction of quinolines with nitronium salts such as nitronium borofluoride. Protic nitrating agent such as nitric acid of course leads exclusively to N-protonation, 1-nitro-2-methylquinolinium borofluoride has been used as a non – acidic nitrating agent: the 2-methyl compound is used because in it the 2-methyl group sterically inhibits stabilizing resonance overlap between the nitro group and ring, and is in consequence a more reactive nitronium ion donor.

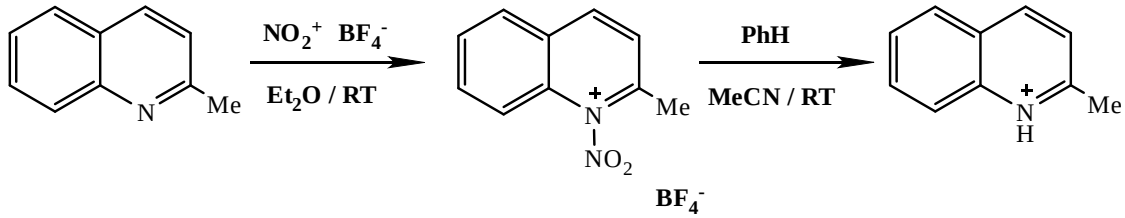


Figure (1.24): Nitration at quinoline nitrogen.

1.5.1.1.3. Sulfonation at nitrogen:

Quinoline reacts with sulfur trioxide to give the crystalline zwitterionic quinolinium – 1 – sulfonate, usually referred to as the quinoline – sulfur trioxide compound, this compound is quite reactive: it is hydrolysed in hot water to sulfuric acid and quinoline, and it has found much use as a mild sulfonating agent.(Sainsbury, 2001).

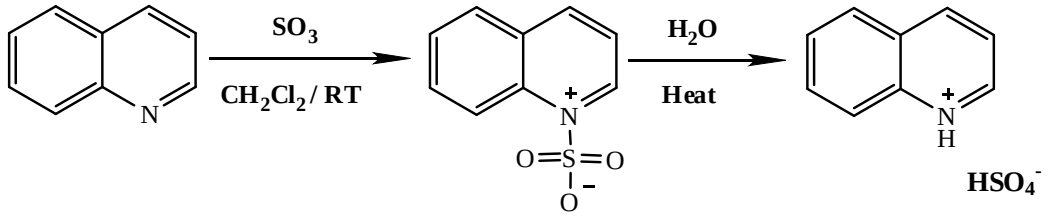


Figure (1.25): Sulfonation at quinoline nitrogen.

1.5.1.1.4. Halogenation at nitrogen:

Quinoline reacts easily with halogens and interhalogens to give crystalline compounds best formulated as resonance hybrids formally related to the tri-bromide and tri-iodide anions, they are largely undissociated in non polar solvents such as CCl_4.

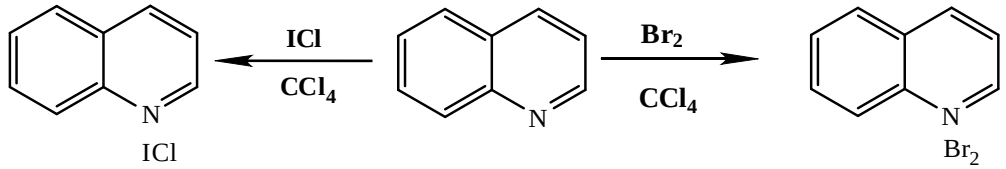


Figure (1.26): Halogenation at quinoline nitrogen.

1.5.1.1.5. Acylation at nitrogen:

Carbonyl halides react very rapidly to give 1-acyl quinolinium salts, which are themselves, very reactive and widely used acylating agents. The usual acylation procedure is to add the alcohol or amine to a solution prepared by the addition of the acyl halide to an excess of quinoline.

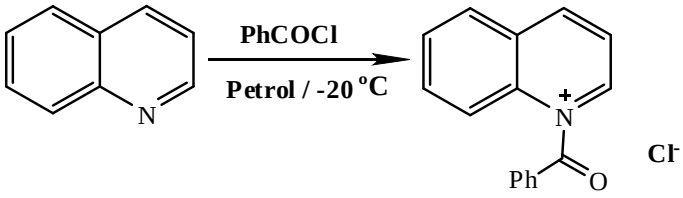


Figure (1.27): Acylation at quinoline nitrogen.

1.5.1.1.6. Alkylation at nitrogen:

Alkyl halides and sulphates react readily with quinolines to give quaternary quinolinium salts. As with aliphatic tertiary amines, increasing substitution around the nitrogen or around the halogen or sulphate-bearing carbon causes an increase in the alternative, competing, elimination reaction which gives olefin and tertiary salts: thus 2,4,6-tri methyl quinoline is often used in dehydrohalogenation reactions.(Joule and Smith, 1978).

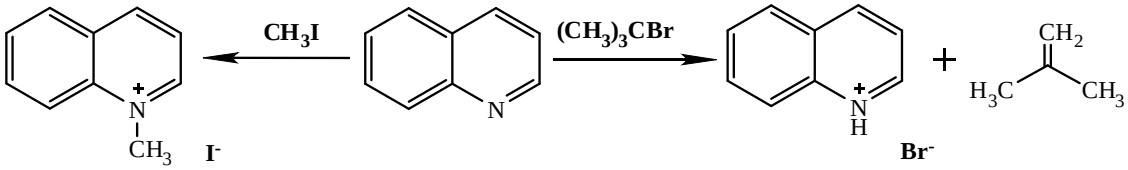


Figure (1.28): Alkylation at quinoline nitrogen.

1.5.1.2. Substitution at carbon:

1.5.1.2.1. Proton exchange:

Benzene ring C-protonation, and thence exchange, via N- protonated quinoline, requires strong sulfuric acid and occurs fastest at C-8, then at C-5 and C-6 (Bressel *et al*, 1971), at lower acid strengths system undergoes exchange α to nitrogen, at C-2, these processes involve a zwitterion produced by deprotonation of the N-protonated heterocycle.

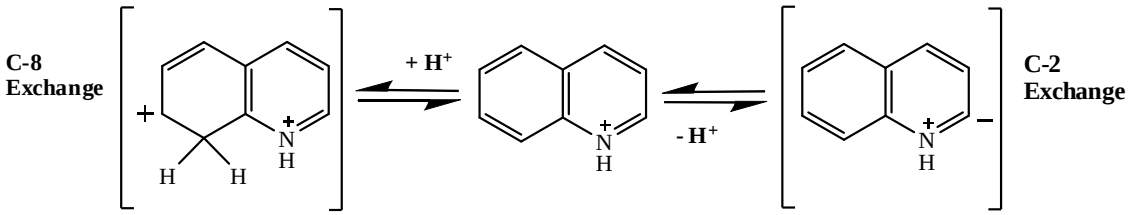


Figure (1.29): Proton exchange of quinoline.

1.5.1.2.2. Nitration:

Nitration in quinoline gives approximately equal amounts of 5-and 8-nitro-quinolines. (Austin and Ridd, 1963).

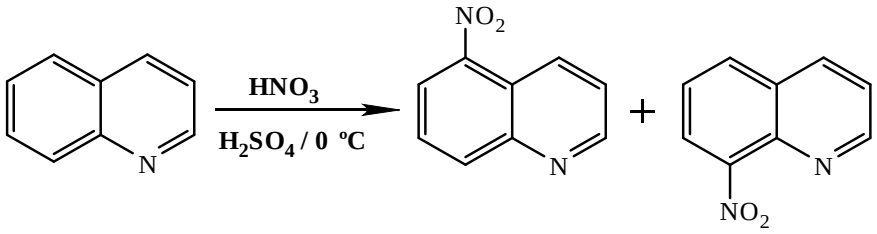


Figure (1.30): Nitration of quinoline.

1.5.1.2.3. Sulfonation:

Sulfonation of quinoline gives largely the 8-sulfonic acid (Beisler, 1970), reaction at higher temperatures produce other isomer, under thermodynamic control, for example both quinoline 8-sulfonic acid and quinoline 5-sulfonic acid are isomerised to the quinoline 6- sulfonic acid.(Mccasland, 1946).

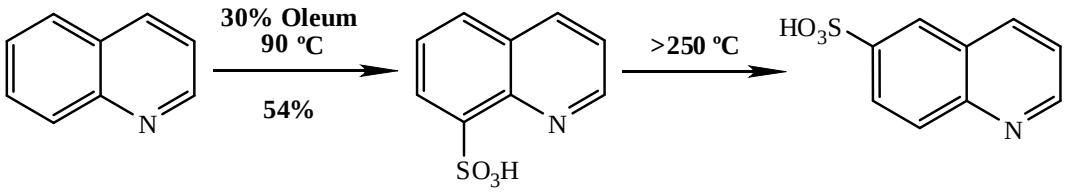


Figure (1.31): Sulfonation of quinoline.

1.5.1.2.4. Halogenation:

Ring substitution of quinoline by halogens is rather complex, products depending on the conditions used (Butler and Gordon, 1975). In concentrated sulfuric acid, quinoline gives a mixture of 5- and 8-bromo derivatives. (Brown and Gouliaev, 2005).

Introduction of halogen to the hetero-rings occurs under mild conditions in which halide addition to a salt initiates the sequence. Thus treatment of quinoline hydrochlorides with bromine produces 3-bromoquinoline.(Kress and Costantino, 1973).

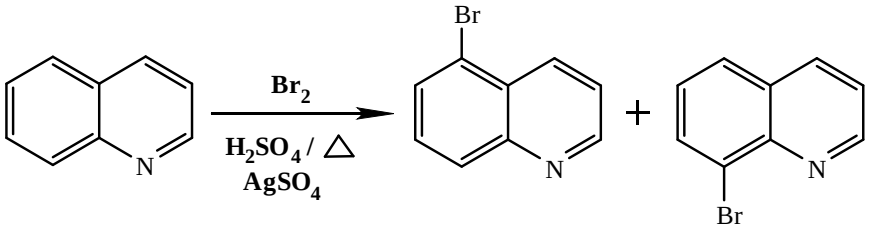


Figure (1.32): Halogenation of quinoline.

1.5.1.2.5. Acylation and alkylation:

There are no generally useful processes for the introduction of carbon substituent by electrophilic substitution of quinolines, except for a few examples in which a ring has a strong electron releasing substituent, for example 4-dimethylaminoquinoline undergoes smooth trifluoroacetylation at C-3.(Okada *et al*, 2000).

1.5.2. Reactions with oxidizing agents:

It requires vigorous conditions to degrade a ring in quinoline, example of attack at ring are known, though degradation of the benzene ring, generating pyridine diacids, ozonolysis can be employed to produce pyridine dialdehydes (Queguiner and Pastour, 1968), or after subsequent hydrogen peroxide treatment, diacids. Electrolytic oxidation of quinoline is the optimal way to convert quinoline into pyridine-2,3-dicarboxylic acid (Quinolinic acid).

1.5.3. Reactions with nucleophilic reagents:

1.5.3.1. Nucleophilic substitution with hydride transfer:

1.5.3.1.1. Alkylation and arylation:

The immediate products of addition of alkyl and aryl Grignard reagents and alkyl- and aryllithiums are dihydro-quinolines and can be characterised as such, but can be oxidised to afford the C-substituted, rearomatised heterocycles; illustrated below is a 2 - arylation of quinoline.(Geissman *et al*, 1946).

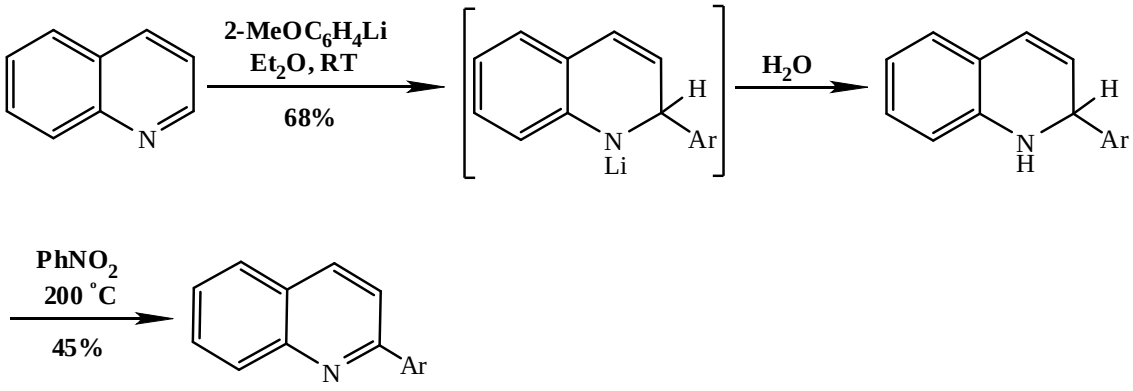


Figure (1.33): Alkylation and arylation of quinoline.

1.5.3.1.2. Amination:

Sodium amide reacts rapidly and completely with quinoline even at - 45 °C, to give dihydro- adducts with initial amide attack at C-2 (main) and C-4 (minor), the quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperatures. Oxidative trapping of the quinoline adducts provides 2- or 4- aminoquinolines, (Tondys *et al*, 1985), oxidative aminations are possible at other quinoline positions, even on the benzene ring, providing a nitro group is present to promote the nucleophilic addition.

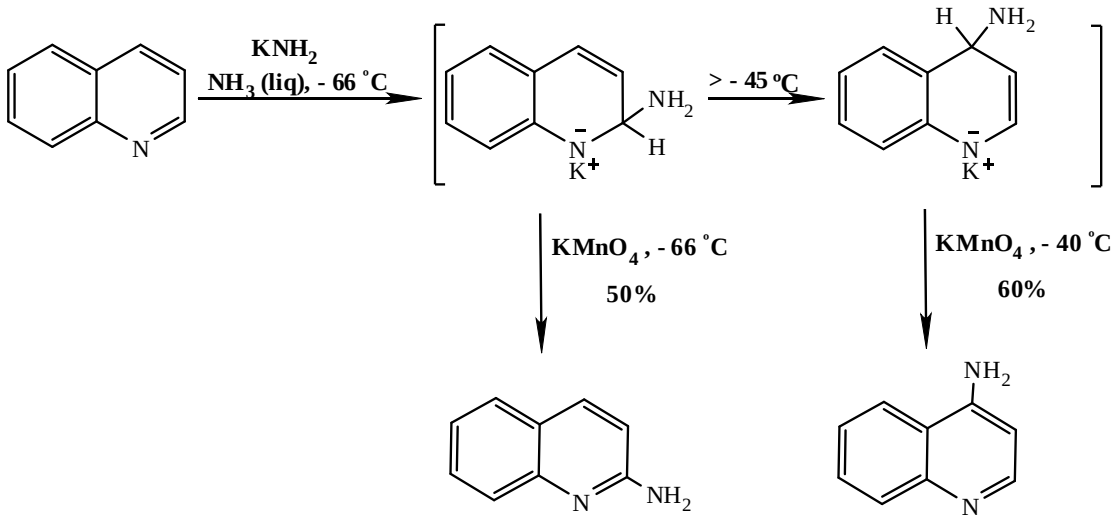


Figure (1.34): Amination of quinoline.

1.5.3.1.3. Hydroxylation:

Quinoline can be directly hydroxylated with potassium hydroxide at higher temperature with the evolution of hydrogen. 2-quinolone (carbostyril) is the isolated products.(Vanderwalle *et al*, 1975).

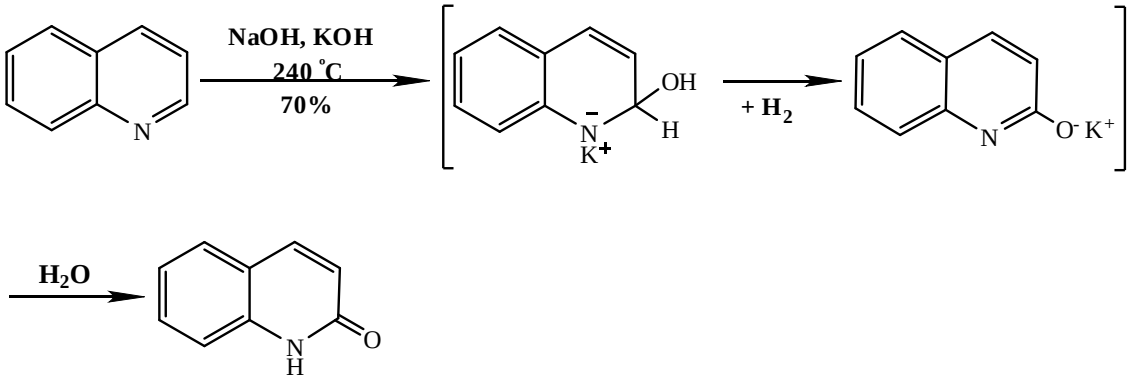


Figure (1.35): Hydroxylation of quinoline.

1.5.3.2. Nucleophilic substitution with displacement of good leaving groups:

The main principle is that a halogen on the homocyclic ring of quinoline and at the quinoline-3 positions, behaves as would a halo-benzene. In contrast, halogen substituent at α-or γ-positions, but not at β-positions, are relatively easily displaced by a wide range of nucleophile via an addition-elimination mechanism facilitated by: electron withdrawal by the substituent and the good leaving ability of the substituent.(Simchen and Kramer, 1969).

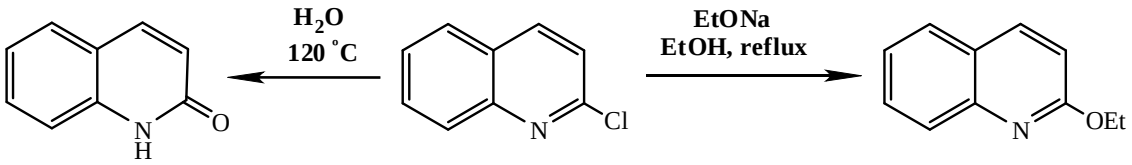


Figure (1.36): Nucleophilic substitution with displacement of good leaving groups.

1.5.4. Metallation and reactions of C-metallated quinolines:

1.5.4.1. Direct ring C-H metallation:

Direct lithiation, i.e. C-deprotonation of quinolines requires an adjacent substituent, such as chlorine, fluorine, or alkoxy. Both 4- and 2-dimethylaminocarbonyloxy quinolines lithiate at C-3, quinolines with an ortho-directing group at C-3 lithiate at C-

4, not at C-2. Quinoline 2-, 3- and 4- carboxylic acids C lithiate (C-3, C-4 and C-3 respectively) are using two mole equivalents of lithium tetramethylpiperidide.

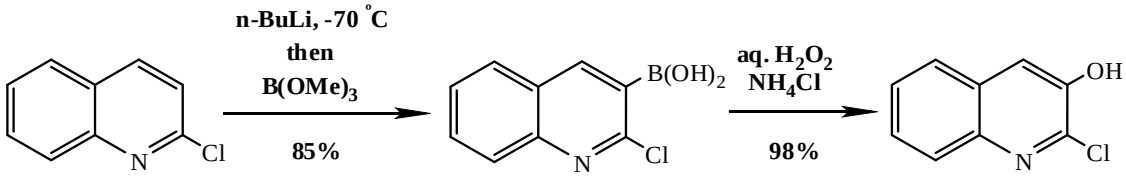


Figure (1.37): Lithiation of quinoline.

1.5.4.2. Metal - halogen exchange:

The use of low temperatures does allow metal-halogen exchange at pyridine and benzene ring positions in quinolines, subsequent reaction with electrophiles generating C-substituted products. It seems that for benzene ring lithiation, two mole equivalents of butyllithium are necessary so that one equivalent can associate with the ring nitrogen.(Wommack *et al*, 1969).

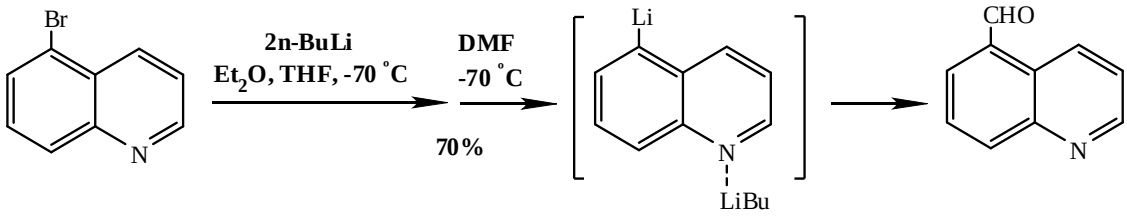


Figure (1.38): Preparation of lithio-quinolines.

1.5.5. Reactions with radicals:

Quinoline is attacked by phenyl radicals generated by decomposition of benzoyl peroxide, all seven monosubstitution products are formed, with 8- phenylquinoline predominating, a much greater degree of specificity occurs when the quinolinium cation is attacked, and by less reactive radicals. Carboxamide and acetyl radicals have been introduced into the quinoline 2- and 4- positions in this way.

1.5.6. Reactions with reducing agents:

Selective reduction of either the pyridine or the benzene rings in quinoline can be achieved: the heterocyclic ring is reduced to the tetrahydro level by sodium cyanoborohydride in acid solution, by sodium borohydride in the presence of nickel (II) chloride, by zinc borohydride (Nose and Kudo, 1984) or, traditionally, by room

temperature and room pressure catalytic hydrogenation in methanol. In strong acid solution it is the benzene ring which is selectively saturated; longer reaction times can then lead to decahydro derivatives. Treatment of quinoline with sodium borohydride in a mixture of acetic acid and acetic anhydride gives good yields of N-acetyl-1,2-dihydro derivatives.

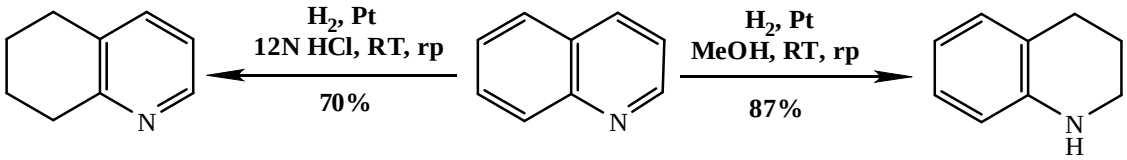


Figure (1.39): Reduction of quinoline.

1.5.7. Oxy - quinolines:

Quinolinols in which the oxygen is at any position other than C-2 or C-4 is true phenols i.e.have a hydroxyl group, though they exist in equilibrium with variable concentrations of zwitterionic structures, with the nitrogen protonated and the oxygen deprotonated. 8-quinolinol has long been used in analysis as a chelating agent, especially for Zn(II), Mg(II) and Al(III) cations; the Cu(II) chelate is used as a fungicide. The position of electrophilic substitution of quinolones depends upon the pH of the reaction medium, each type protonates on carbonyl oxygen, so reactions in strongly acidic media involve attack on this cation and therefore in the benzene ring: the contrast is illustrated below by the nitration of 4-quinolone at different acid strengths. The balance between benzene ring and unprotonated heterocyclic ring selectivity is small. (Kawazoe and Yoshioka, 1968).

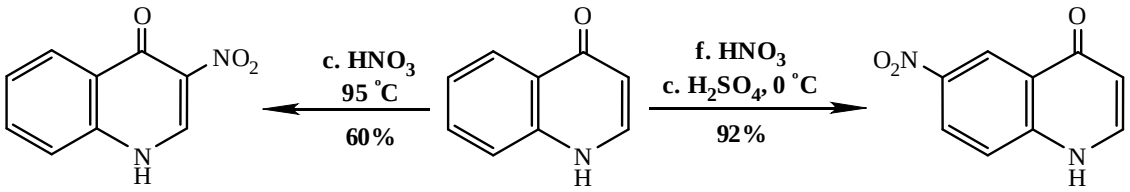


Figure (1.40): Structure of oxy - quinolines.

1.5.8. Amino – quinolines:

Amino-quinolines exist as amino tautomers and all protonate on ring nitrogen. Only 4-amino quinoline shows appreciably enhanced basicity (pK_{aH} 9.2).

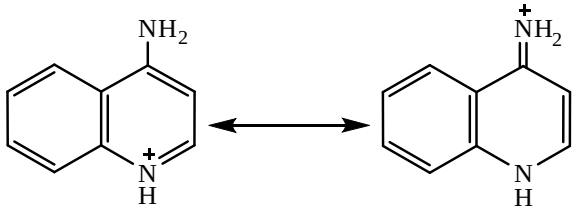


Figure (1.41): 4-amino quinoline.

1.5.9. Quinoline carboxylic acids and esters:

Decarboxylation of quinoline-2-acids, via an ylide that can be trapped with aldehydes as electrophiles, loss of carbon dioxide from N-methylquinolinium-2-acids, and trapping of resulting ylides can be achieved with stronger heating.(Dyson and Hammick, 1937).

1.5.10. Quinoline N-oxides:

The presence of a benzene ring in quinolines gives the additional possibility for electrophilic substitution, for example mixed acid nitration of quinoline N-oxide takes place at C-5 and C-8 via the *O*-protonated species, but at C-4 at lower acid strength.(Yokoyama *et al*,1997).

1.6. Biological importance of quinolines:

Quinolines showed a wide spectrum of biological activities, some modified quinolines are found to be effective as antimalarial drugs, beginning with quinine, systematic modification of quinine led to the potent and inexpensive 4-aminoquinoline drug, chloroquine (CQ), and other related drugs. Rational approach in chemistry and screening efforts produced mefloquine, another quinoline containing compound that was highly active against the CQ-resistant (CQR) strains of *P.Falciparum*, since the development of mefloquine, there have been several reports of new potent quinoline compounds, most of these contain the 7-chloro quinoline nucleus of CQ and vary in the length and nature of their basic amine side chain. It was observed that good antimalarial effects were exerted by alkoxylated chalcone, inparticular, those substituted with electron withdrawing group or those incorporating quinoline rings. (Bawa *et al*, 2010).

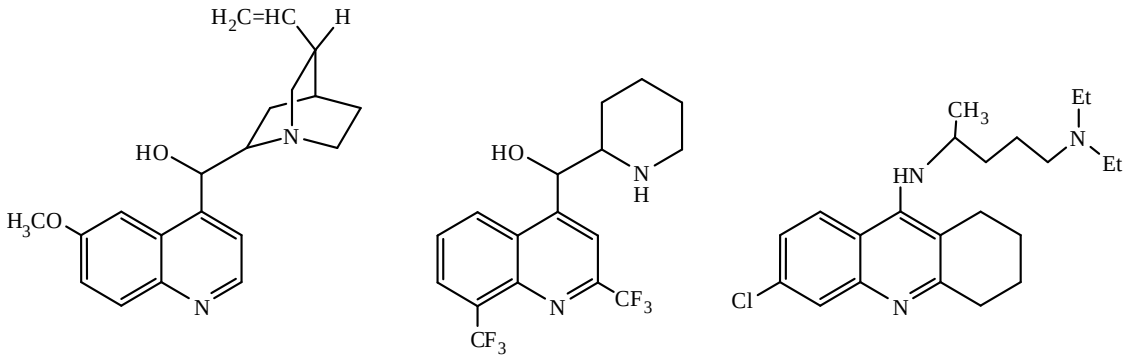


Figure (1.42): Structure of antimalarial drugs.

The molecular basis of the action of these drugs are thought to interfere with haemoglobin digestion in the blood stages of the malaria parasite life cycle, the parasite degrades haemoglobin, in an acidic food vacuole, producing free heme and reactive oxygen species as toxic by products. The heme moieties are neutralized by polymerisation, while the free radical species are detoxified by a vulnerable series of antioxidant mechanisms. (Foley and Tilley, 1998).

Quinolones are broad spectrum antibacterial agents, commonly used in both clinical and veterinary medicine (Tiwari *et al*, 2011), particularly nalidixic acid, have been available for the treatment of urinary tract infections in humans for many years. These drugs are of relatively minor significance because of their limited therapeutic utility and the rabid development of resistance (Goodman and Gilman, 1992). Over the last two decades, research on 4-quinolone-3-carboxylates has led to the discovery of a family of 6-fluoro-7-piperazinyl-4-quinolones active against gram-negative and gram-positives bacteria *in vitro* (Hooper and Wolfson, 1985) as well as intracellular pathogens (Fitzgeorge *et al*, 1988) and trimethoprim / sulfonamide resistant microbes, in addition, these antimicrobials are also active against *mycoplasma* (Sarkozy, 2001), collectively, these compounds are called fluoroquinolones.

The presently available fluoroquinolones with *in vitro* activity against *streptococcus pneumonia* are levofloxacin (levaquin), gatifloxacin (tequin), moxifloxacin, and trovafloxacin, the last three fluoroquinolone have greater *in vitro* activity against *S.aureus* and some enterococcus strains, ciprofloxacin has been shown to be more effective than trimethoprim – sulfamethoxazole and aminoglycosides in seven to ten day courses for the treatment of complicated urinary tract infections and pyelonephritis, also ciprofloxacin or ofloxacin considered as alternative treatment for neisseria

gonorrhoeae urethritis and cervicitis and enteric typhoid fever. Fluoroquinolones have a role in post exposure prophylaxis and chemotherapy for specific agents that could be used in biologic warfare, specific fluoroquinolones are indicated for prophylaxis or treatment of anthrax, cholera, plague, brucellosis, and tularaemia.(Catherine, 2002), beside all that they have been known as anticonvulsant, antiplatelet, And anti HIV.

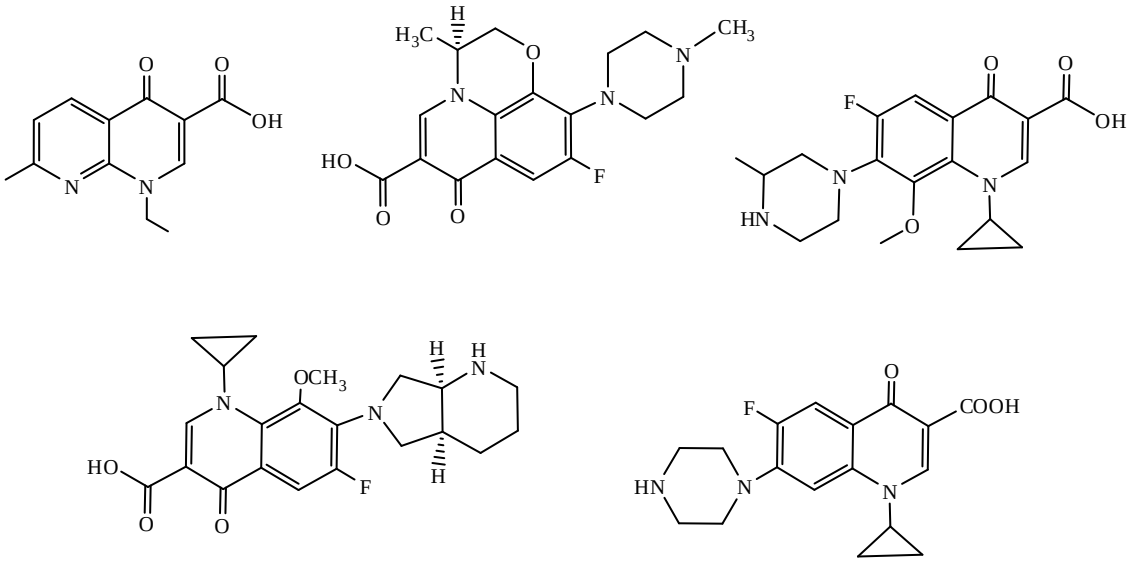


Figure (1.43): Structure of antibacterial drugs.

Quinolines substituted on their carbon 2 is presently a drug candidate for the treatment of visceral leishmaniosis in pre – clinical development (Vieira *et al*, 2011), also quinoline bearing a bromo – substituent were evaluated for their *in vitro* anticancer activity against human breast cancer cell (Mostafa *et al*, 2012), another quinoline derivatives used as flavouring and colouring agent like quinoline yellow, for preparation of nanostructures and polymers.

2-methyl-1,2,3,4-tetrahydroquinoline is present in human brain, a polycyclic system based on tetrahydroquinoline, is a marine alkaloid, a natural antitumor antibiotic, has a complex structure builts on the tetrahydroquinoline system, many relatively simple synthetic of 1,2,3,4-tetrahydoquinolines are already used or have been tested as potential drugs, among them, oxamniquine a schistosomicide, nicainoprl, an antiarrhytmic drug. 2-methyl-5-hydroxyl-1,2,3,4-tetrahydroquinoline, exhibits analgestic activity one eighth as potent as morphine, 1,2,3,4-tetrahydroquinoline-4-carboxylic acid is used in tissue irrigating solutions, some tetrahydroquinolines are potent inhibitors of (H^+ + K^+**)** adenosine triphosphate, blood serum monoamine oxidase, lipoxygenase, bone resorption, and bacterial dihydrofolate reductase. T

Tetrahydroquinolines are potential antidepressants nervous system depressants, besides pharmaceutical applications, there are useful as pesticides, antioxidants and corrosion inhibitors, 2,2,4-trimethyl-8-hydroxy-1,2,3,4-tetrahydroquinoline is a specific reagent for photometric determination of iron (III) salts. Tetrahydroquinolines are used as active components in various types of dyes for hair, for acrylic fibers, for polyesters, and for polyamides, there are also widely used in modern recording technologies: as charge transporting agents for electro photographic photoconductors, as leuco dyes for thermal and pressure sensitive materials, as antiirradiation filter dyes in photography, in the preparation of optical information recording media.

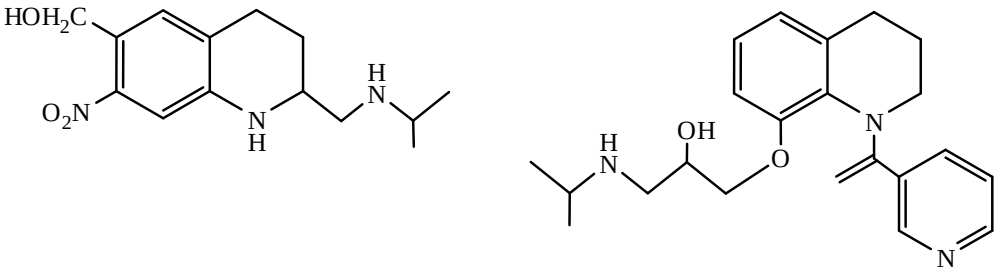


Figure (1.44): Structure of tetrahydroquinolines.

1.7. Aim and objectives:

Quinolines represent a major class of heterocycles, and a number of synthetic approaches have been known since the late 1800s. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties such as antimalarial, antibacterial, antitumor, antifungal, antileishmanial and anti nuclear inhibitors of immune deficiency virus.(Pritam, 2014).

This work aimed to synthesis the structural core of quinoline in a series of 2,3-diaryl-quinoline-4-carboxylic acid derivatives as possible biological active compounds by using Doebner reaction a three component coupling of aromatic amines with an aldehyde and phenyl pyruvic acid.

The main objective of this work is to prepare a series of quinolines linked isoxazyl, the design of these compounds involve isoxazyle ring construction from hydroxyl amine hydrochloride and corresponding quinolyle-chalcones, which were prepared from the corresponding quinolines bearing reactive acetyl group.

The second objective is to test possible approach for quinoline derivative synthesis using aryl amines with acetylacetone as Combes reaction, Knorr reaction between aryl amine and ethylacetoacetate with heating above 100°C and Conrad-Limpach quinoline synthesis a thermal condensation of aryl amine with ethylacetoacetate.

2. Materials and Methods

2.1. Materials:

- Absolute ethanol, C_2H_6O, Density 0.790 – 0.793g/cm^3, Assay 98%, BDH chemicals Ltd, England.
- Acetic anhydride, $C_2H_4O_3$, Density 1.079 – 1.081g/cm^3, Assay 98%, BDH chemicals Ltd, England.
- Acetone, C_3H_6O, Density 0.789 - 0.792g/cm^3, Assay 98%, CDH Laboratory reagent, India.
- Acetyl acetone, $C_5H_8O_2$, Density 0.971 – 0.974g/cm^3, Assay 98%, BDH Laboratory reagent, England.
- Anhydrous sodium acetate, $C_2H_3O_2Na$, Assay 98%, QualiKems fine chemical, India.
- Benzaldehyde, C_7H_6O, Density 1.044 - 1.047g/cm^3, Assay 98.5%, Loba chemie Pvt. Ltd, India.
- Cinnmaldehyde, $C_9H_8O_2$, Density 1.050 –1.052g/cm^3, Assay 98%, Loba chemie Pvt. Ltd, India.
- Chloroform, $CHCl_3$, Density 1.474 – 1.480g/cm^3, Assay 99.5%, Loba chemie Pvt. Ltd, India.
- Drierite, W.A.HAMMOND Drierite Company, U.S.A.
- Ethyl acetoacetate, $C_6H_{10}O_3$, Density 1.025g/cm^3, Assay 99%, SynchemicA, Hopkins and Williams.
- Ethanol, C_2H_6O, Density 0.789g/cm^3, Assay 97%, Alwatania, Sudan.
- Furfural, $C_5H_4O_2$, Density 1.158 – 1.160g/cm^3, Assay 98%, Loba chemie Pvt. Ltd, India.
- Glacial acetic acid, $C_2H_4O_2$, Density 1.048 – 1.051g/cm^3, Assay 99.5%, CDH Laboratory reagent, India.
- Glycine, $C_2H_5NO_2$, Assay 99%, Scientific limited, Northampton, UK.
- Hydrochloric acid, HCl, Density1.18g/cm^3, Assay 35–38%, Loba chemie Pvt. Ltd, India.
- Hydroxyl amine hydrochloride, NH_4OCl, Assay 98%, Loba chemie Pvt. Ltd, India.

- Methanol, CH_4O, Density 0.790 – 0.793g/cm^3, Assay 99.5%, Loba chemie Pvt. Ltd, India.
- P-amino acetophenone, C_8H_9NO, Assay 99.9%, Blulux Laboratories (P) Ltd, India.
- Salicalaldehyde, $C_7H_6O_2$, Density 1.164–1.167g/cm^3, Assay 99%, Loba chemie Pvt. Ltd, India
- Sodium hydroxide, NaOH, CDH Laboratory reagent, India.
- Silica Gel-G for TLC, Techno pharmchem, India.

2.2. Instrumentations:

2.2.1. Infra-red spectroscopy:

Infra-red spectroscopy (IR) was recorded on FTIR-8400s instrument (Shimadzu, Japan) using KBr disc.

2.2.2. ^{1}H Nuclear magnetic resonance spectroscopy:

^{1}H Nuclear magnetic resonance spectroscopy (^{1}HNMR) was recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using DMSO as solvent and operating at 500.13MHz for protons. Employing a 5mm high-resolution broad-band TMS gradients probe. The zg30 pulse program was used. Spectra were recorded over a sweep width of (10330.57 Hz) at 293.4k temperature and time domain data points giving an acquisition time of 1.00 seconds.

2.2.3. ^{13}C Nuclear magnetic resonance spectroscopy:

^{13}C Nuclear magnetic resonance spectroscopy (^{13}CNMR) was recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using DMSO as solvent and operating at 100.62MHz for carbons. Employing a 5mm high-resolution broad-band TMS gradients probe. The zg30 pulse program was used. Spectra were recorded over a sweep width of (24038.46Hz) at 298.8k temperature and time domain data points giving an acquisition time of 2.00 seconds.

2.2.4. Gas chromatography-mass spectroscopy:

Gas chromatography mass spectroscopy (GC-MS) was recorded on QP 2010 GC instrument (Shimadzu, Japan) and the following conditions have been adopted:

- Column oven temp = 100 °C
- Injection temp = 290100 °C
- Injection mode = split
- Total flow = 1.24ml/min
- Ion source temp = 200100 °C
- Solvent cut time = 2.5min
- Start time = 3min
- Oven temp program was illustrated below:

Rate	Temperature (°C)	Hold time (min)
-	100	00.00
30	160	00.00
15	92	20.00

2.3. Thin layer chromatography (TLC):

TLC was carried out using silica gel 60 GF 254 (Merck Germany) precoted plates or coated over glass with different mobile phases.

2.4. Apparatus and equipment:

- Hot plate stirrer, Stuart, Bibby sterilin LTD, UK.
- Melting point apparatus, Gallenkamp, England.
- Sensitive balance, A&D-GR-120, Japan.

2.5. Glassware:

- All glasswares were Pyrex type.

2.6. Synthetic methods:

2.6.1. Synthesis of 2,3-di aryl-quinoline-4-carboxylic acid derivatives (I, II, XXI, XXII, XXIII):

In 1 litre round bottom flask equipped with a reflux condenser were placed 0.236 mol of the required aromatic aldehyde, 41.04g (0.25 mol) of freshly distilled phenyl

pyruvic acid and 200 ml of absolute ethanol. The mixture was heated on a boiling water-bath and a solution of 0.248 mol of the required amine in a 100 ml of absolute ethanol was added slowly with frequent shaking within 1 hour. The mixture was refluxed on a water-bath for 3 hours and left to stand overnight, filtered, washed with little ether and recrystallized from ethanol, for physical and chemical properties see table (2.1.1), (2.2.1), (2.3.1), (2.4.1), (2.6.1), and (2.7.1).

2.6.2. Synthesis of chalcones (III, IV, V, VI, VII, VIII, IX, X, XI):

A mixture of 0.01 mol of the required aromatic aldehyde and 0.01 mol of substituted quinoline was stirred in 30 ml of ethanol at room temperature in the presence of 10 ml of 20% sodium hydroxide solution. The mixture was stirred for 24 hours at RT and kept for overnight at RT. The mixture was poured into crushed ice and acidified with dilute hydrochloric acid. The chalcone derivatives were precipitated out as solid, filtered, dried and recrystallized from ethanol, for physical and chemical properties see table (2.1.2), (2.2.2), (2.3.2), (2.4.2), (2.5.1), (2.6.2), and (2.7.2)

2.6.3. Synthesis of isoxazoles (XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX):

A mixture of 0.02 mol of the required chalcone, 1.39g (0.02 mol) of hydroxylamine hydrochloride and 4.10g (0.05 mol) sodium acetate in 25 ml ethanol was refluxed for 6 hours. The mixture was concentrated by distilling out the solvent and poured into ice water. The precipitate was filtered, washed and recrystallized from ethanol, for physical and chemical properties see table (2.1.3), (2.2.3), (2.3.3), (2.4.3), (2.5.2), and (2.7.3).

2.6.4. Synthesis of 2,4-dimethyl quinoline-6-sulphonamide (XXIV):

A mixture of 2.00g (0.012mol) of sulphanilamide, 3ml (0.029mol) of acetyl acetone and 4g of drierite was refluxed for 4 hours, the precipitate obtained on elution with ether, and then it was filtered, washed and recrystallized from benzene petroleum ether, for physical and chemical properties see table (2.1.4), (2.2.4), (2.3.4), (2.4.4), (2.6.3), and (2.7.4).

2.6.5. Synthesis of 4-methyl-2-hydroxyquinoline-6-sulphonamide (XXV):

A mixture of 1.72g (0.01mol) of sulphanilamide, 1.26ml (0.01mol**)** of ethylacetoacetate was refluxed for 5 minutes. The precipitate was filtered, concentrated sulphuric acid was added to the precipitate and refluxed on a water bath for 15 minutes,

cooled, and poured into saturated solution of sodium carbonate. The precipitate was filtered, washed and recrystallized from acetic acid and water then from ethanol and water, for physical and chemical properties see table (2.1.4), (2.2.4), (2.3.4), (2.4.4), (2.6.3), and (2.7.4).

2.6.6. Synthesis of 2-methyl-4-hydroxyquinoline-6-sulphonamide (XXVI):

To a mixture of 1.72g (0.01mol) of sulphanilamide, 1.26ml (0.01mol) of ethyl acetoacetat was added 3.5ml of absolute ethanol, about 3.5g of drierite, and four drops of glacial acetic acid, the resulting mixture was refluxed for 4 hours. The drierite was filtered and the ethanol was distilled, the mixture poured into petri-dish to dry and recrystallized from water, for physical and chemical properties see table (2.1.4), (2.2.4), (2.3.4), (2.4.4), (2.6.3), and (2.7.4).

2.6.7. Synthesis of acetyl glycine (XXVII):

37.5g (0.5mol) of glycine and 150 ml of water were placed in a 500 ml conical flask; a mechanical stirrer was introduced and stirred vigorously until the solid dissolved. 102g (95 ml, 1mol) of acetic anhydride was added in one portion and stirred vigorously for 15-20 minutes, some acetylglycine crystallised, and the mixture was cooled in refrigerator overnight until the crystals were collected, filtered, washed with ice-cold water and dried, recrystallized from boiling water. Y (g) = 40.00g, Y = 70.4%, m.p = 210C□, IR analysis showed the bands 3352.05 cm^{-1} for NHst.vib., 2941.24 cm^{-1} for C-Hst.vib., 1718.46 cm^{-1} for C=Ost.vib, 1352.01, 1380.94 cm^{-1} for CH_3 bending sym.

2.6.8. Synthesis of 4-benzylidene-2-methyloxazol-5-one (XXVIII):

A mixture of 29g (0.25mol) of acetylglycine, 39.5g (37.5 ml, 0.37mol) of redistilled benzaldehyde, 15g (0.183mol) of anhydrous sodium acetate and 63.5g (59ml, 0.62mol) of acetic anhydride in a 500 ml round bottom flask equipped with a reflux condenser was placed on a water bath with occasional stirring until solution was complete 10-20 minutes. The resulting solution boiled for 1hour, cooled and left in a refrigerator overnight, 60 ml of cold water was added to the solid mass of yellow crystals and stirred, filtered, washed with cold water and dried, recrystallized from ethyl acetate light petroleum. Y (g) = 30.21g, Y = 65.5%, m.p = 149-153C□, IR analysis showed the

bands 1452.30, 1492.80, 1602.74 cm^{-1} for C=Cst.vib, 1654.81 cm^{-1} for C=Ost.vib, 1261.36, 945.05 cm^{-1} for C-H bending, 3072.39 cm^{-1} for C-Hst.vib.

2.6.9. Synthesis of α-acetamidocinnamic acid (XXIX):

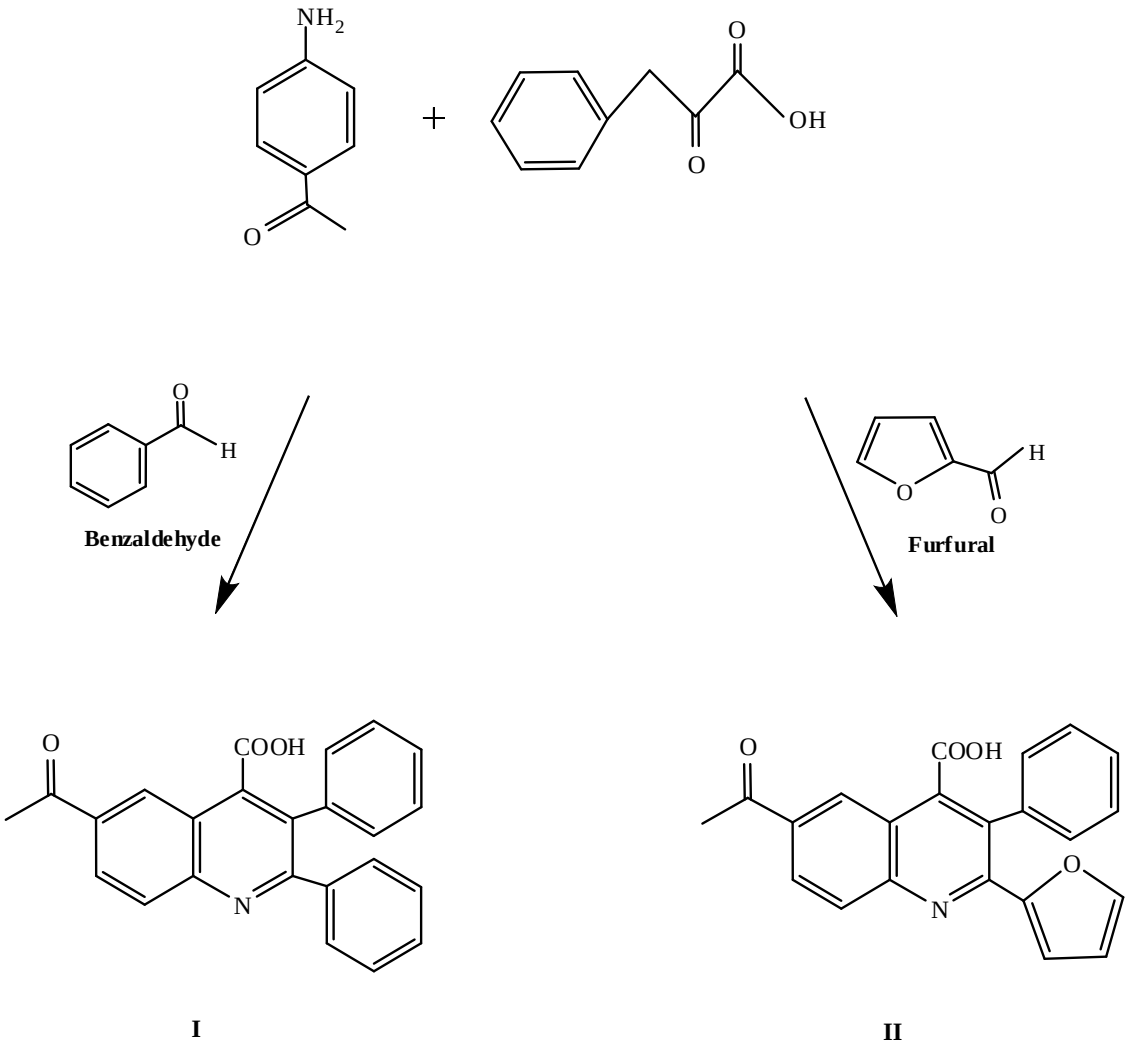
A mixture of 23.5g (0.125mol) of 4-benzylidene-2-methyloxazol-5-one, 90 ml of water and 225 ml of acetone in a 500 ml round bottom flask was boiled under reflux for 4 hours; the mixture was cooled in a refrigerator overnight, filtered, washed with about 100 ml of cold water and dried. Y (g) = 24.37g, Y = 94.1%, m.p = 192-195C□, IR analysis showed the bands 1448.44, 1514.02 cm^{-1} for C=Cst.vib, 1631.67 cm^{-1} for C=Cst.vib., 1654.81 cm^{-1} for C=Ost.vib, 3307.69 cm^{-1} for NHst.vib.

2.6.10. Synthesis of phenyl pyruvic acid (XXX):

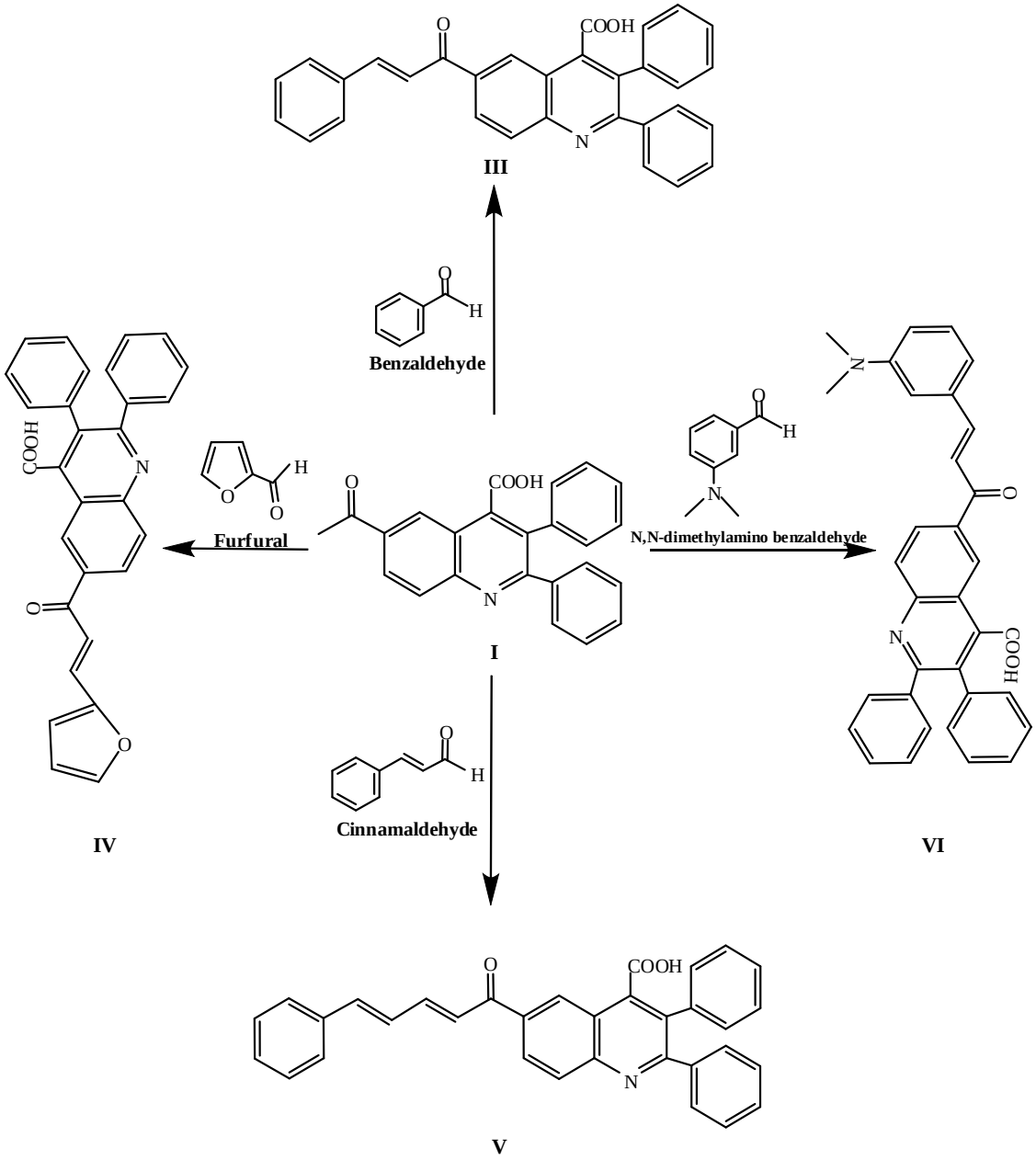
10.3g (0.05mol) of α-acetamidocinnamic acid and 200 ml of 1M hydrochloric acid in 500 ml round bottom flask was boiled steadily under reflux for 3 hours, small quantity of green oil was removed; the filtrate was cooled to room temperature and left at 0 C□ for 48 hours, filtered, washed with a small quantity of ice-cold water and dried. Y (g) = 5.35g, Y = 64.9%, m.p = 153C□, IR analysis showed the bands 1440.73, 1458.08, 1492.80 cm^{-1} for C=Cst.vib, 3475.49 cm^{-1} for OHst.vib, 1679.88 cm^{-1} for C=Ost.vib.

2.7. Assessment of antimicrobial activity:

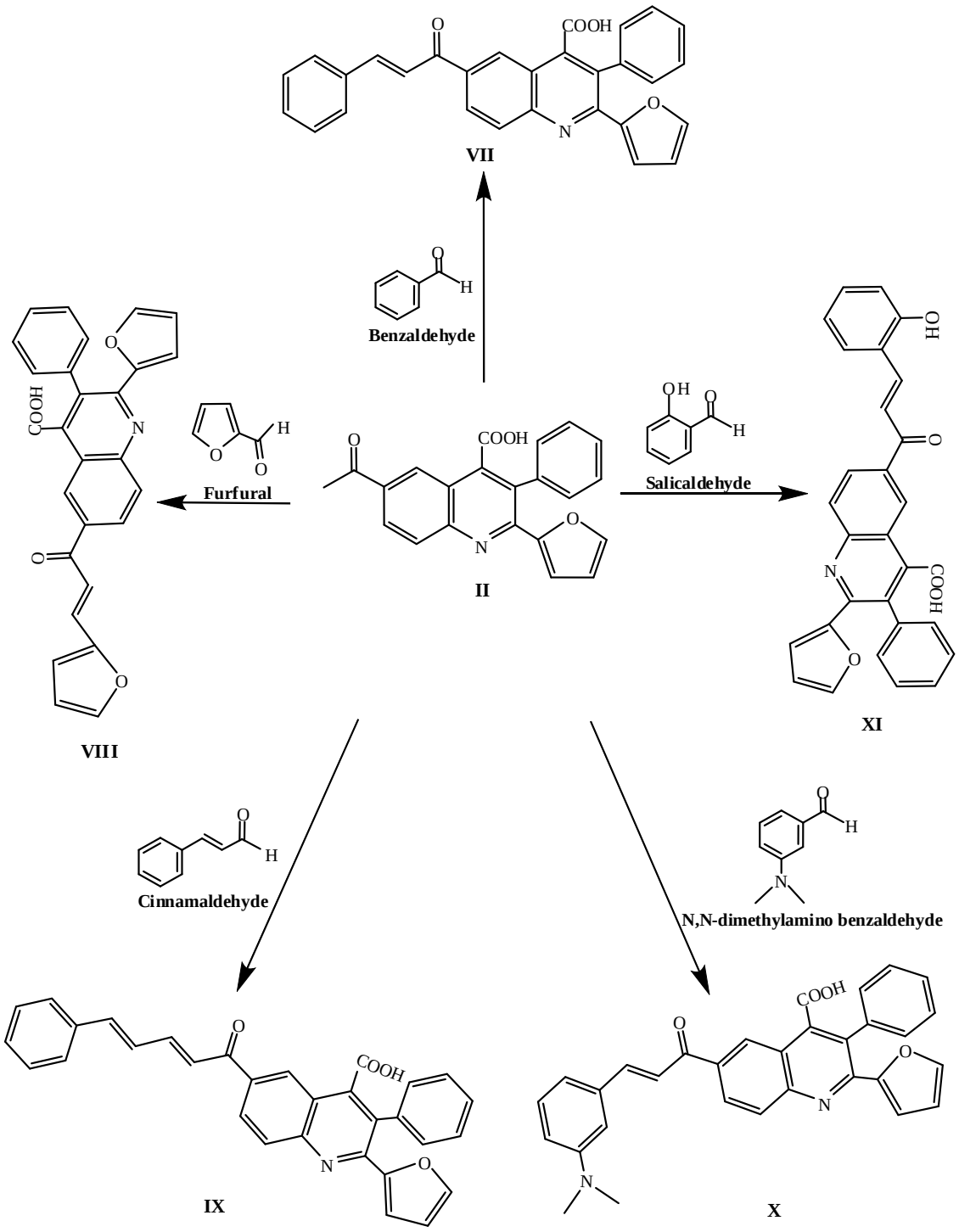
The antibacterial activity was carried out by employing disk diffusion method against *Proteus vulgaris*, *Escherichia coli* (gram negative), *Bacillus subtillis*, *Staphylococus aureus* (gram positive), and for antifungal activity against *Aspergillus niger* and *Candida albicans* by measuring the zone of inhibition in mm. The activities were performed at a conc. of 5mg/ml, using propylene glycol (PRG) as a solvent. (Reeves *et al*, 1978).



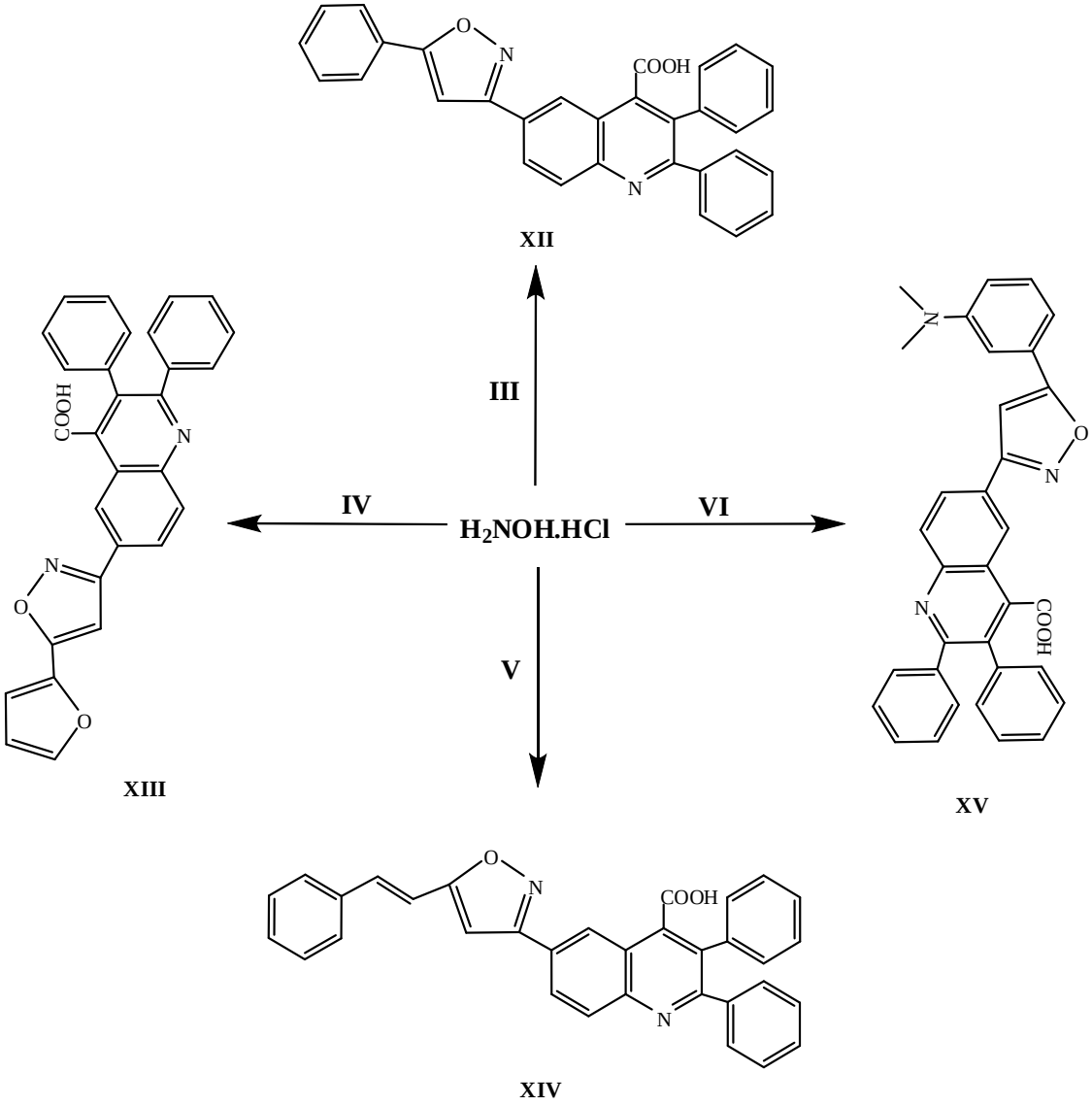
Scheme (2.1): Chemical structure of 2-aryl-3-phenyl-6-acetyl-quinoline-4-carboxylic acid.



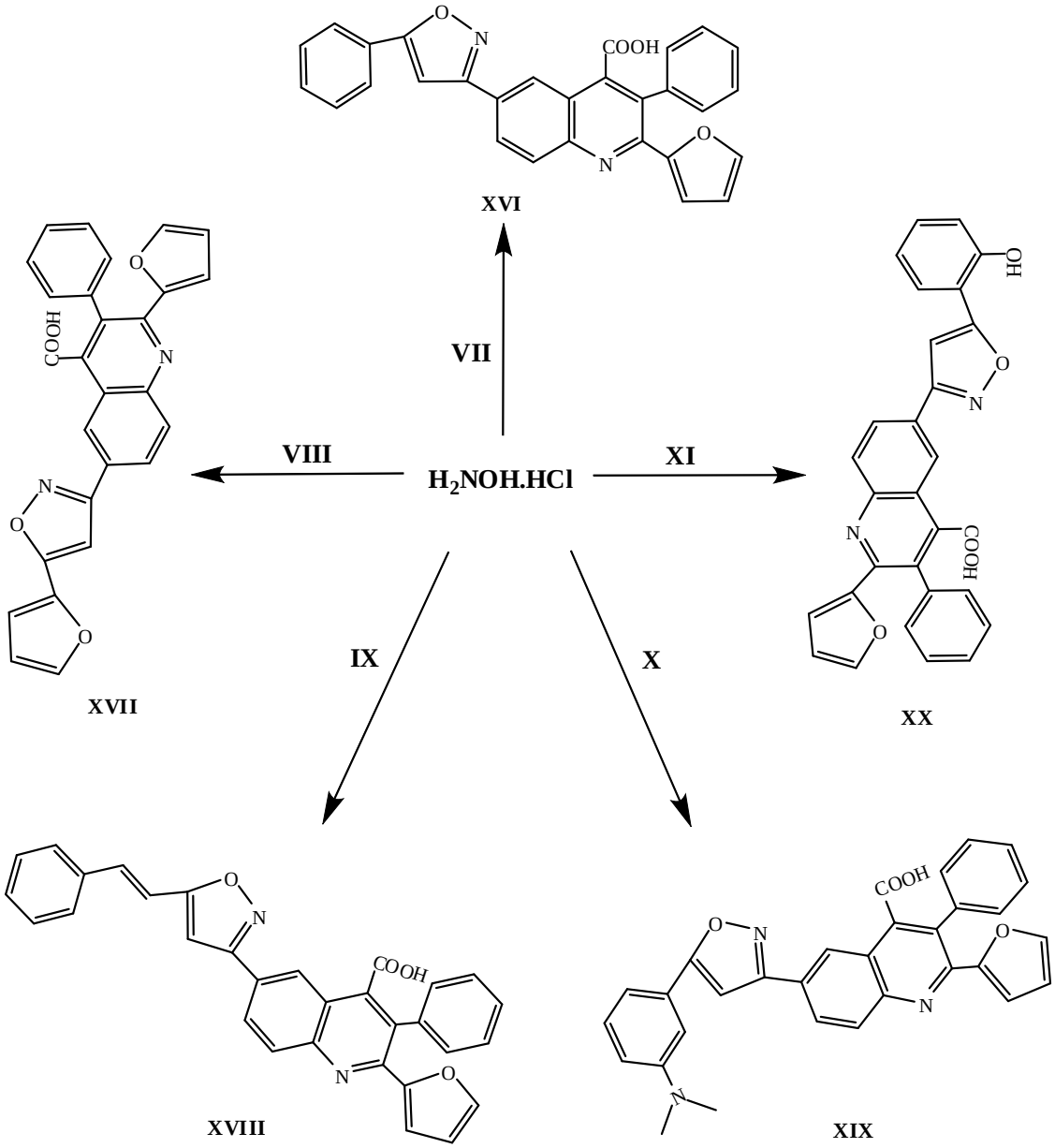
Scheme (2.2): Chemical structure of 2,3-diphenyl-6-(3-aryl-prop-2-enon-1-yl)-quinolin -4-carboxylic acid.



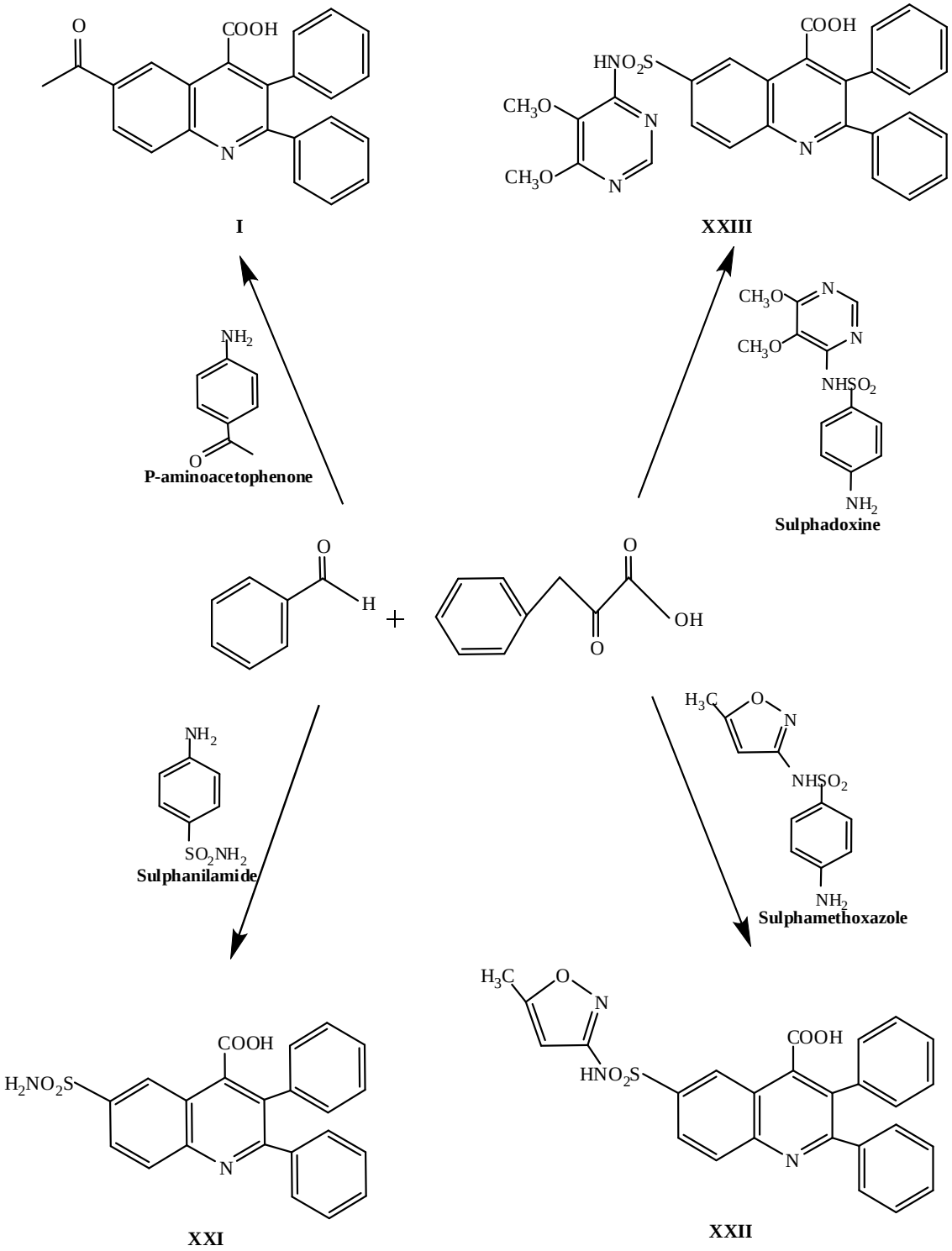
Scheme (2.3): Chemical structure of 2-furyl-3-phenyl-6-(3-aryl-prop-2-enon-1-yl)-quinoline-4-carboxylic acid.



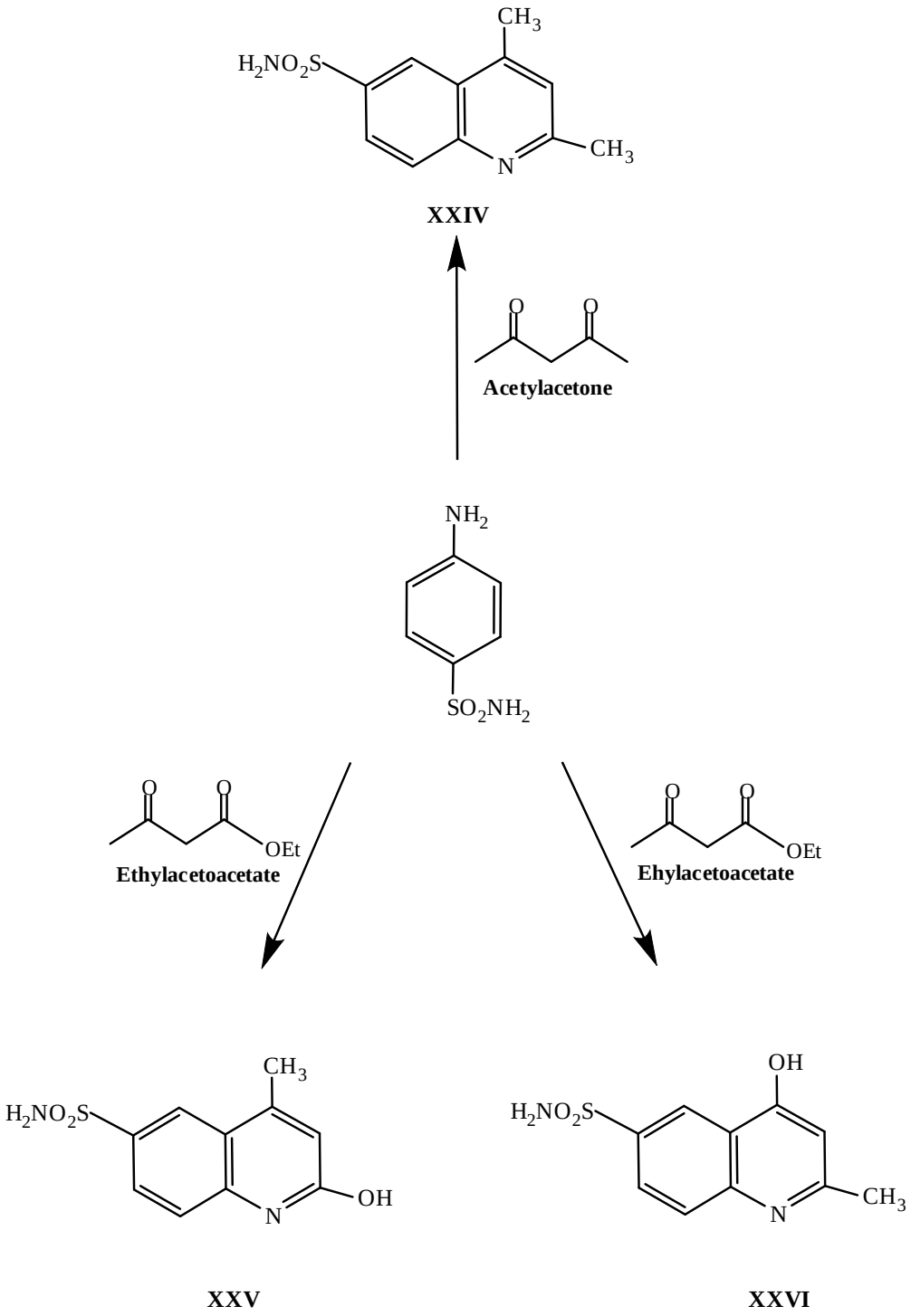
Scheme (2.4): Chemical structure of 2,3-diphenyl-6-(5-aryl-oxazol-3-yl)-quinoline-4-carboxylic acid.



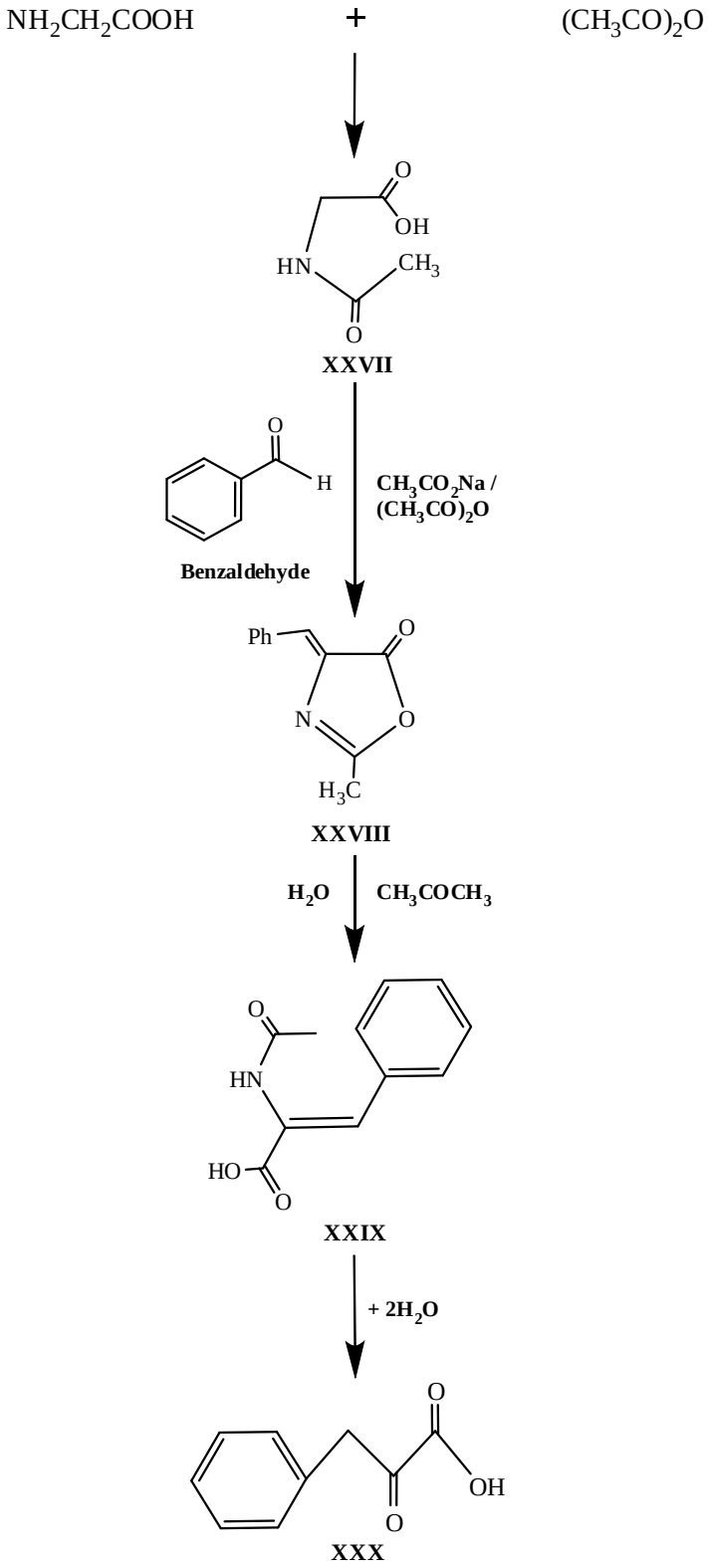
Scheme (2.5): Chemical structure of 2-furyl-3-phenyl-6-(5-aryl-oxazol-3-yl)-quinoline-4-carboxylic acid.



Scheme (2.6): Chemical structure of 2,3-diphenyl-quinoline-4-carboxylic acid derivatives.



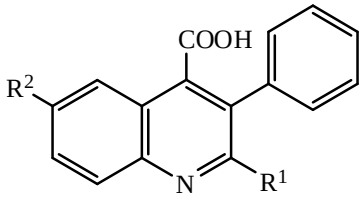
Scheme (2.7): Chemical structure of prepared quinoline derivatives.



Scheme (2.8): Chemical structure of phenyl pyruvic acid and intermediates step synthesis.

Table (2.1): Chemical names of the prepared compounds:

Table (2.1.1): Chemical names of 3-phenyl-quinoline derivatives:



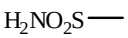
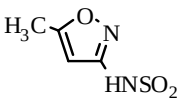
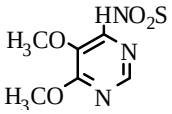
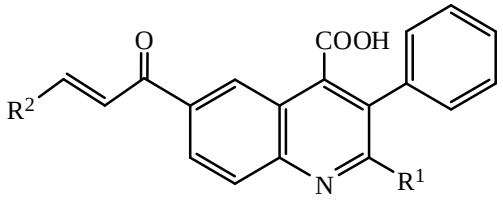
Comp. No	R^1	R^2	Chemical name
I			2,3-Diphenyl-6-acetyl-quinoline-4-carboxylic acid.
II			2-Furyl-3-phenyl-6-acetyl-quinoline-4-carboxylic acid.
XXI			2,3-Diphenyl-6-sulphamido-quinoline-4-carboxylic acid.
XXII			2,3-Diphenyl-6-(5-methyl-3-sulphamido-isoxazole)-quinoline-4-carboxylic acid.
XXIII			2,3-Diphenyl-6-(5,6-dimethoxy-4-sulphamido-pyrimidine)-quinoline-4-carboxylic acid.

Table (2.1.2): Chemical names of the prepared chalcones:



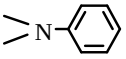
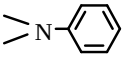
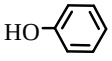
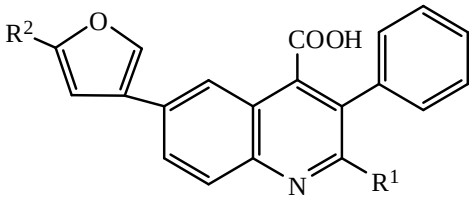
Comp. No	R^1	R^2	Chemical name
III			2,3-Diphenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
IV			2,3-Diphenyl-6-(3-furyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
V			2,3-Diphenyl-6-(3-[2-phenyl ethylene]-prop -2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
VI			2,3-Diphenyl-6-(3-[3-N,N-dimethylamino phenyl]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
VII			2-Furyl-3-phenyl-6-(3-phenyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
VIII			2-Furyl-3-phenyl-6-(3-furyl-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
IX			2-Furyl-3-phenyl-6-(3-[2-phenylethylene]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
X			2-Furyl-3-phenyl-6-(3-[3-N,N-dimethyl amino phenyl]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.
XI			2-Furyl-3-phenyl-6-(3-[2-hydroxyphenyl]-prop-2-en-1-one-1-yl)-quinoline-4-carboxylic acid.

Table (2.1.3): Chemical names of the prepared isoxazoles:



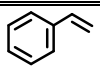
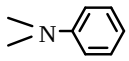
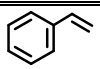
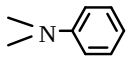
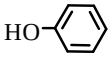
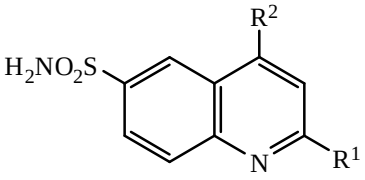
Comp. No	R^1	R^2	Chemical name
XII			2,3-Diphenyl-6-(5-phenyl-oxazole-3-yl)-quinoline-4-carboxylic acid.
XIII			2,3-Diphenyl-6-(5-furyl-oxazole-3-yl)-quinoline-4-carboxylic acid.
XIV			2,3-Diphenyl-6-(5-[2-phenylethylene]-oxazole-3-yl)-quinoline-4-carboxylic acid.
XV			2,3-Diphenyl-6-(5-[3-N,N-dimethylamino phenyl]-oxazole-3-yl)-quinoline-4-carboxylic acid.
XVI			2-Furyl-3-phenyl-6-(5-phenyl-oxazole-3-yl) – quinoline-4-carboxylic acid.
XVII			2-Furyl-3-phenyl-6-(5-furyl-oxazole-3-yl)-quinoline-4-carboxylic acid.
XVIII			2-Furyl-3-phenyl-6-(5-[2-phenylethylene]-oxazole-3-yl)-quinoline-4-carboxylic acid.
XIX			2-Furyl-3-phenyl-6-(5-[3-N,N-dimethyl amino phenyl]-oxazole-3-yl)-quinoline-4-carboxylic acid.
XX			2-Furyl-3-phenyl-6-(5-[2-hydroxyphenyl]-oxazole-3-yl)-quinoline-4-carboxylic acid.

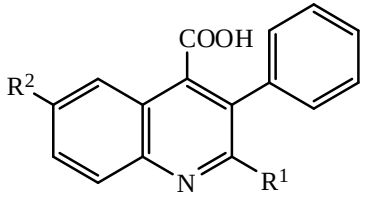
Table (2.1.4): Chemical names of the prepared quinolines derivatives:



Comp. No	R^1	R^2	Chemical name
XXIV	CH_3	CH_3	2,4-Dimethyl quinoline-6-sulphamide.
XXV	OH	CH_3	4-Methyl-2-hydroxyquinoline-6-sulphamide.
XXVI	CH_3	OH	2-Methyl-4-hydroxyquinoline-6-sulphamide.

Table (2.2): Reaction conditions of the prepared compounds:

Table (2.2.1): Reaction conditions of 3-phenyl-quinoline derivatives:



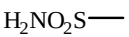
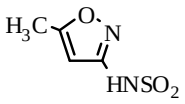
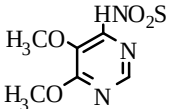
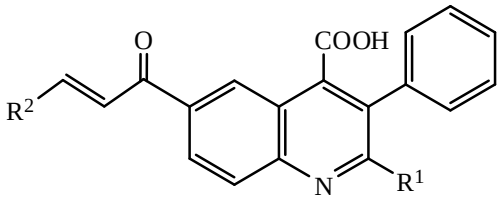
Comp. No	R^1	R^2	Reaction temp(°C)	Time(h)	Rec.solv	Yield(%)	Yield(g)	Color	m.p(°C)
I			Reflux temp.	3	EtOH	80.30	8.42	Beige	249-252
II			Reflux temp.	3	EtOH	45.00	4.64	Pale brown	227-230
XXI			Reflux temp.	3	EtOH	78.00	7.47	Ivory	251-255
XXII			Reflux temp.	3	EtOH	37.00	4.26	Beige	266-268
XXIII			Reflux temp.	3	EtOH	42.60	5.45	White	218-222

Table (2.2.2): Reaction conditions of the prepared chalcones:



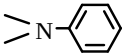
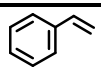
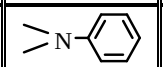
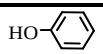
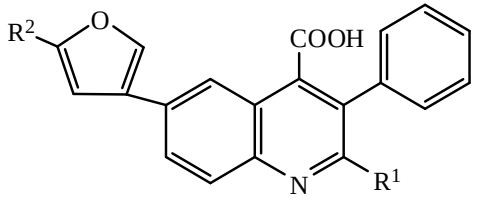
Comp. No	R^1	R^2	Reaction temp(°C)	Time(h)	Rec.solv	Yield(%)	Yield(g)	Color	m.p(°C)
III			Room temp.	24	EtOH	96.00	2.38	Dark yellow	244-247
IV			Room temp.	24	EtOH	81.50	1.98	Brown	215-219
V			Room temp.	24	EtOH	93.00	2.44	Dark yellow	204-208
VI			Room temp.	24	EtOH	88.00	2.38	Orange	198-201
VII			Room temp.	24	EtOH	95.20	2.37	Dark brown	268-271
VIII			Room temp.	24	EtOH	93.00	2.27	Dark yellow	237-240
IX			Room temp.	24	EtOH	92.30	2.43	Bright yellow	225-228
X			Room temp.	24	EtOH	87.00	2.37	Orange-brown	204-207
XI			Room temp.	24	EtOH	84.00	2.17	Grey-brown	184-189

Table (2.2.3): Reaction conditions of the prepared isoxazoles:



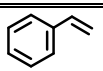
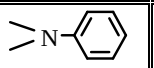
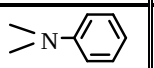
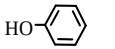
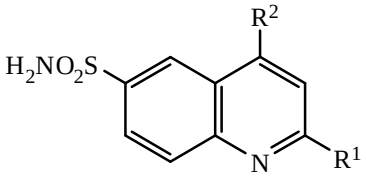
Comp. No	R^1	R^2	Reaction temp(°C)	Time(h)	Rec.solv	Yield(%)	Yield(g)	Color	m.p(°C)
XII			Reflux temp.	6	EtOH	92.20	0.47	Pale yellow	189-192
XIII			Reflux temp.	6	EtOH	95.80	0.69	Bright yellow	181-185
XIV			Reflux temp.	6	EtOH	83.30	0.60	Greenish yellow	244-248
XV			Reflux temp.	6	EtOH	77.80	0.56	Orange	236-239
XVI			Reflux temp.	6	EtOH	84.00	0.43	Pale brown	204-207
XVII			Reflux temp.	6	EtOH	83.30	0.60	Brown- yellow	174-176
XVIII			Reflux temp.	6	EtOH	80.50	0.58	Brown	237-240
XIX			Reflux temp.	6	EtOH	75.00	0.54	Dark orange	231-233
XX			Reflux temp.	6	EtOH	80.60	0.58	Grey-brown	177-180

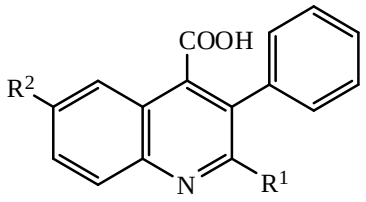
Table (2.2.4): Reaction conditions of the prepared quinolines derivatives:



Comp. No	R^1	R^2	Reaction temp(°C)	Time(h)	Rec.solv	Yield(%)	Yield(g)	Color	m.p(°C)
XXIV	CH_3	CH_3	Reflux temp.	4	Petroleum ether	91.20	2.50	Yellow	176-179
XXV	OH	CH_3	Reflux temp.	15min	EtOH and water	79.80	1.90	Ivory	Dec at 298
XXVI	CH_3	OH	Reflux temp.	3-4	Water	86.10	2.05	Pale pink	168-171

Table (2.3): Infra - red spectral data of the prepared compounds:

Table (2.3.1): Infra - red spectral data of 3-phenyl-quinoline derivatives:



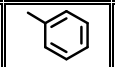
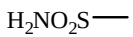
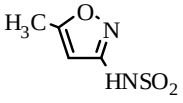
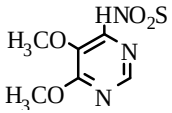
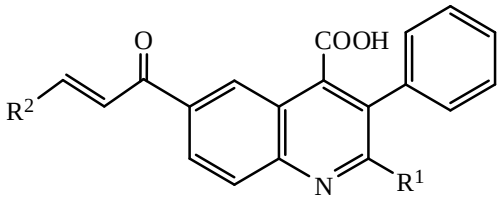
Comp. No	R^1	R^2	$C=C_{st.vib}$	$C-N_{st.vib}$	$C=O_{st.vib}$	$N-H_{st.vib}$	Other
I			1452.30, 1512.09	1369.37	1660.00, 1679.88	–	3000.00-3437.50 ($O-H_{st.vib}$).
II			1512.09, 1600.81	1365.51	1672.17, 1687.60	–	1271 ($C-O_{st.vib}$). 3187.50-3437.50 ($O-H_{st.vib}$).
XXI			1498.59, 1593.09	1369.37	1685.67	3311.55, 3280.00	1311.50asym, 1159.14sym ($SO_{2st.vib}$).
XXII			1496.66, 1591.16	1367.44	1681.81	3259.47	1313.43asym, 1172.64sym ($SO_{2st.vib}$). 929.63 ($N-O_{st.vib}$).
XXIII			1483.16, 1595.02	1365.51	1704.96	3303.83	1311.50asym, 1157.21sym ($SO_{2st.vib}$). 3008.75aro ($C-H_{st.vib}$).

Table (2.3.2): Infra - red spectral data of the prepared chalcones:



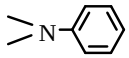
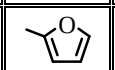
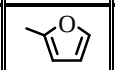
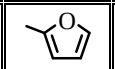
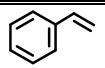
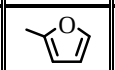
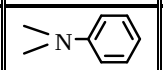
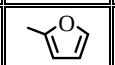
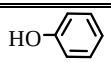
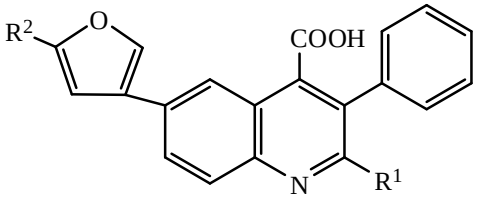
Comp. No	R^1	R^2	$C=C_{st.vib}$(aro)	$C=C_{st.vib}$(olefin)	$C-N_{st.vib}$	$C=O_{st.vib}$	$C-O_{st.vib}$	Other
III			1450.00, 1496.66	1512.09	1369.37	1660.00, 1668.31	1217.00	–
IV			1496.66, 1508.23	1600.81	1369.37	1654.81, 1670.00	1222.79	–
V			1500.00, 1508.23	1598.88	1369.37	1652.88, 1668.31	1255.57	3028.03 ($C-H_{st.vib}$).
VI			1520.00, 1550.00	1596.95	1371.29	1647.10, 1670.24	1215.07	–
VII			1496.66, 1512.09	1596.95	1365.51	1650.00, 1670.24	1218.93	–
VIII			1500.00, 1550.00	1600.81	1367.44	1660.60, 1675.00	1230.50	–
IX			1450.00, 1515.94	1598.88	1363.58	1652.88, 1683.74	1288.43	–
X			1525.59, 1577.66	1596.95	1363.58	1652.55, 1674.10	1230.50	–
XI			1458.08, 1512.09	1598.88	1363.58	1660.00, 1679.88	1274.86	–

Table (2.3.3): Infra - red spectral data of the prepared isoxazoles:



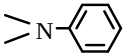
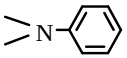
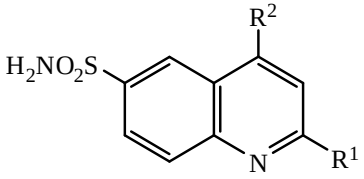
Comp. No	R^1	R^2	$C=C_{st.vib}$(aro)	$C-N_{st.vib}$	$C-O_{st.vib}$	$C=O_{st.vib}$	$N-O_{st.vib}$	Other
XII			1515.94, 1602.74	1369.37	1249.80	1681.81	931.55	2500.00-3400.00 ($O-H_{st.vib}$ bonded).
XIII			1514.02, 1600.81	1367.44	1215.07	1681.81	931,56	2800.00-3520.00 ($O-H_{st.vib}$ bonded).
XIV			1448.44, 1512.09	1363.58	1255.57	1668.38	931.55	1598.88 ($C=C_{st.vib}$ olefin).
XV			1523.66, 1577.66	1367.44	1211.21	1674.10	931.55	–
XVI			1515.94, 1600.18	1367.44	1200.00	1683.74	931.55	–
XVII			1514.02, 1602.74	1365.51	1228.57	1689.53	931.55	–
XVIII			1446.51, 1512.09	1363.58	1286.43	1670.24	931.55	1598.88 ($C=C_{st.vib}$ olefin).
XIX			1577.66, 1600.81	1365.51	1228.57	1676.03	933.48	–
XX			1515.94, 1600.80	1367.44	1215.07	1681.81	931.55	2560.00-3520.00 ($O-H_{st.vib}$ bonded).

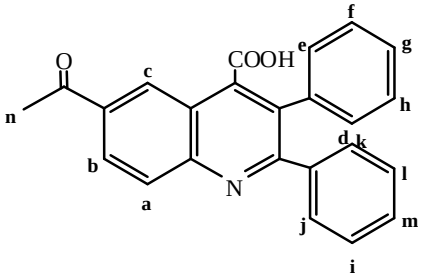
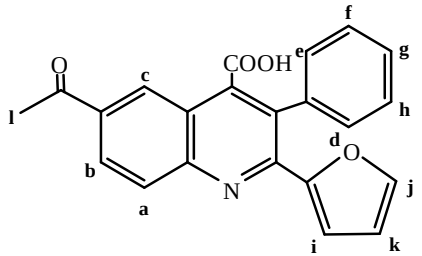
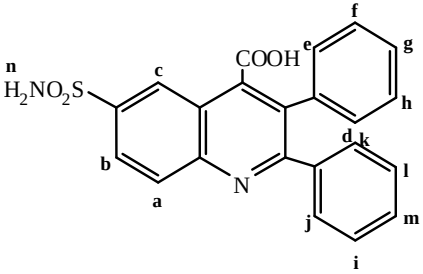
Table (2.3.4): Infra - red spectral data of the prepared quinolines derivatives:



Comp. No	R^1	R^2	$C=C_{st.vib}$(aro)	$N-H_{st.vib}$	$SO_{2st.vib}$	Other
XXIV	CH_3	CH_3	1515.94, 1627.81	3332.76, 3242.12	1330.79asym, 1151.42sym.	3126.40 ($C-H_{st.vib}$).
XXV	OH	CH_3	1598.88, 1629.74	3375.20, 3274.90	1313.43asym, 1149.50sym.	–
XXVI	CH_3	OH	1575.73, 1627.81	3319.26, 3240.19	1309.58asym, 1153.35sym.	–

Table (2.4):^{1}H Nuclear magnetic resonance data of the prepared compounds:

Table (2.4.1):^{1}H Nuclear magnetic resonance data of 3-phenyl-quinoline derivatives:

Comp. No	Structure and signal	Signal	Chemical shift (ppm)
I		a, b c d, e, f, g, h, i, l, m j, k n	7.86-7.92 (m, 2H, Quinoline ring). 10.73 (s, 1H, Quinoline ring). 7.08-7.44 (m, 8H, H-Ar). 7.76 (d, 2H, H-Ar). 2.50 (s, 3H, CH_3).
II		a, b, i, j, d, e, f, g, h c k l	6.90-7.77 (m, 2H, Quinoline ring, 2H, Furyl ring, 5H, H-Ar). 7.95 (s, 1H, Quinoline ring). 6.18 (t, 1H, Furyl ring). 2.57 (s, 3H, CH_3).
XXI		a, b c d, e, f, g, h, i, l, m, n j, k	7.89-7.92 (m, 2H, Quinoline ring). 10.75 (s, 1H, Quinoline ring). 7.09-7.44 (m, 8H, H-Ar, 2H, NH_2). 7.75 (d, 2H, H-Ar).

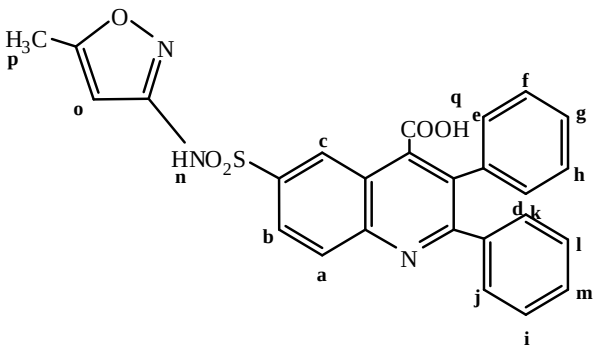
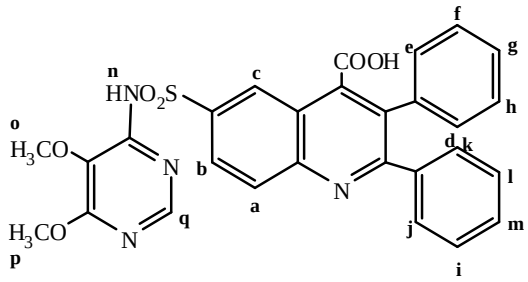
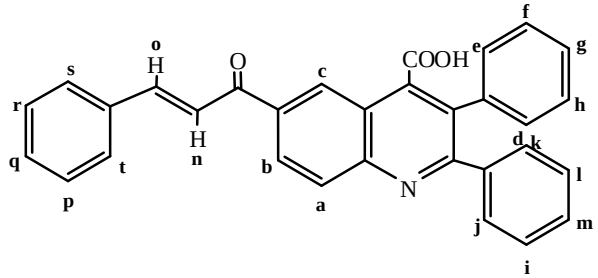
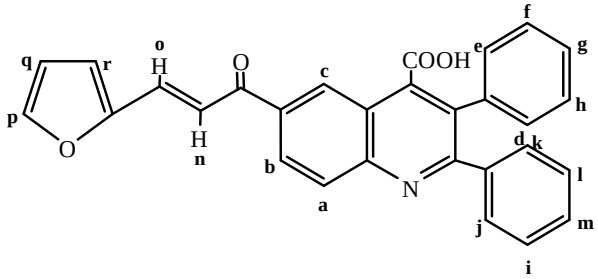
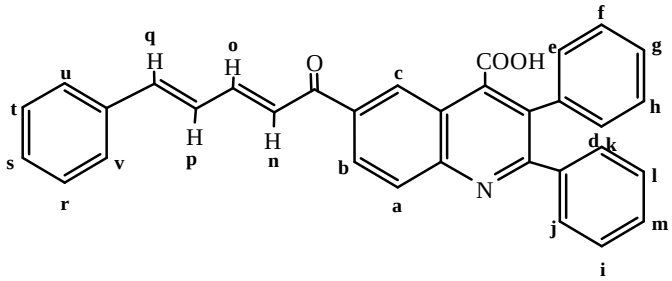
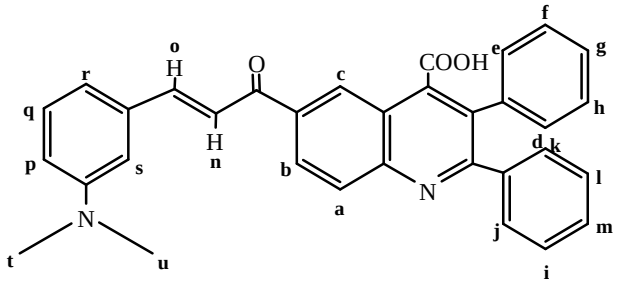
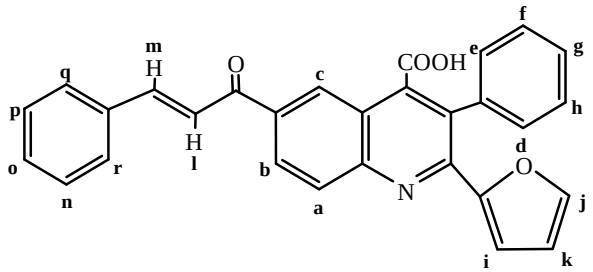
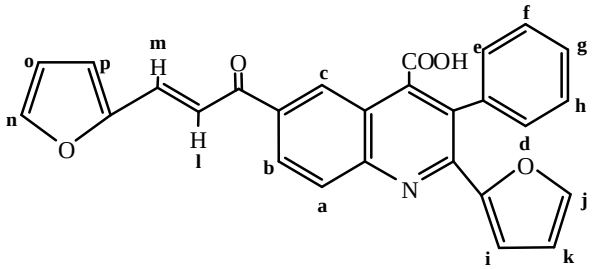
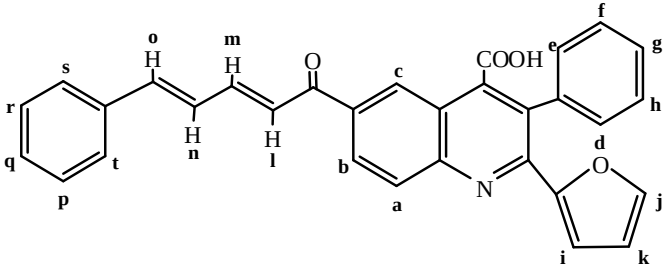
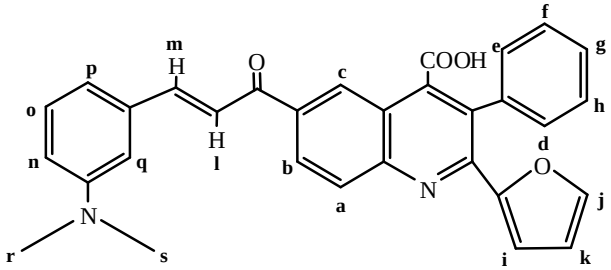
XXII		a, c, j, k	7.73-7.79 (m, 2H, Quinoline ring, 2H, H-Ar).
		b	7.92 (d, 1H, Quinoline ring).
		d, e, f, g, h, i, l, m	7.09-7.43 (m, 8H, H-Ar).
		n	10.76 (s, 1H, NH).
		o	6.62 (s, 1H, Isoxazole ring).
		p	2.29 (s, 3H, CH_3).
		q	11.36 (s, 1H, OH).
XXIII		c	8.10 (s, 1H, Quinoline ring).
		a, b, d, e, f, g, h, i, l, m	7.09-7.43 (m, 2H, Quinoline ring, 8H, H-Ar).
		j, k	7.73 (d, 2H, H-Ar).
		n	10.75 (s, 1H, NH).
		o	3.65 (s, 3H, OCH_3).
		p	3.90 (s, 3H, OCH_3).
		q	7.92 (s, 1H, Pyrimidine ring).
		r	11.09 (s, 1H, OH).

Table (2.4.2):[1]H Nuclear magnetic resonance data of the prepared chalcones:

Comp. No	Structure and signal	Signal	Chemical shift (ppm)
III		a, b, j, k c d, e, f, g, h, i, l, m, n, p, q, r, s, t o	7.81-7.96 (m, 2H, Quinoline ring, 2H, H-Ar). 8.12 (s, 1H, Quinoline ring). 7.08-7.47 (m, 13H, H-Ar, 1H, H-C=). 7.69 (d, 1H, =C-H).
IV		a, b, j, k, p c d, e, f, g, h, i, l, m, n, o, r q	7.77-7.93 (m, 2H, Quinoline ring, 2H, H-Ar, 1H, Furyl ring) 8.02 (s, 1H, Quinoline ring). 7.09-7.52 (m, 8H, H-Ar, 2H, H-C=C-H, 1H, Furyl ring). 6.68 (t, 1H, Furyl ring).
V		a, b, j, k c d, e, f, g, h, i, l, m, n, o, p, q, r, s, t, u, v	7.77-7.96 (m, 2H, Quinoline ring, 2H, H-Ar). 9.52 (s, 1H, Quinoline ring). 7.08- 7.61 (m, 13H, H-Ar, 4H, H-C=C-H).

VI		a	7.91 (d, 1H, Quinoline ring).
		b	7.86 (d, 1H, Quinoline ring).
		c	8.04 (s, 1H, Quinoline ring).
		d, e, f, g, h, i, l, m, n	7.17-7.47 (m, 8H, H-Ar, 1H, H-C=).
		j, k	7.69 (d, 2H, H-Ar).
		o	7.63 (d, 1H, =C-H).
		p	6.75 (d, 1H, H-Ar).
		q, r	7.06 (m, 2H, H-Ar).
		s	6.73 (s, 1H, H-Ar).
		t, u	3.05 (s, 6H, CH_3).
VII		a, b	7.69-7.82 (m, 2H, Quinoline ring).
		c	8.03 (s, 1H, Quinoline ring).
		d, e, f, g, h, i, j, l, m, n, o, p, q, r	7.36-7.42 (m, 10H, H-Ar, 2H, Furyl ring, 2H, H-C=C-H).
		k	6.20 (t, 1H, Furyl ring).

VIII		a, b, c, d, e, f, g, h, i, j, l, m, n, p k, o	7.50-7.88 (m, 3H, Quinoline ring, 5H, H-Ar, 4H, Furyl ring, 2H, H-C=C-H). 6.49-6.68 (m, 2H, Furyl ring).
IX		a b c d, e, f, g, h, i, j, k, l, m, o, p, q, r, s, t n	7.79 (d, 1H, Quinoline ring). 7.69 (d, 1H, Quinoline ring). 7.98 (s, 1H, Quinoline ring). 7.01-7.49 (m, 10H, H-Ar, 3H, Furyl ring, 2H, H-C=C-H, 1H, =C-H). 6.20 (d, 1H, H-C=).
X		c a, b, d, e, f, g, h, i, j, k, l, m, o, p n q r, s	9.74 (s, 1H, Quinoline ring). 7.53-7.98 (m, 2H, Quinoline ring, 7H, H-Ar, 3H, Furyl ring, 2H, H-C=C-H). 6.70 (d, 1H, H-Ar). 6.16 (s, 1H, H-Ar). 3.09 (s, 6H, CH_3).

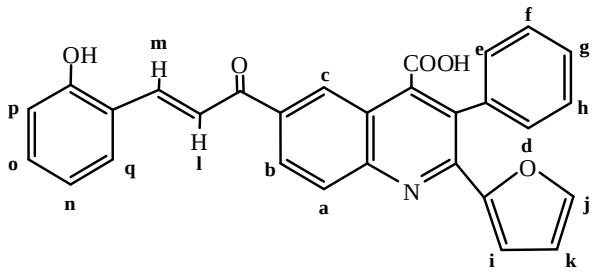
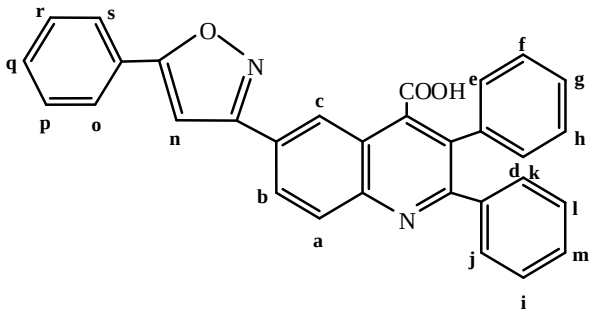
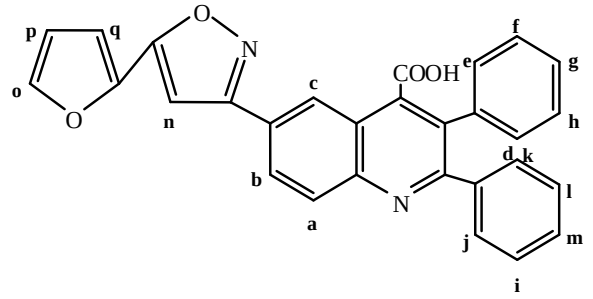
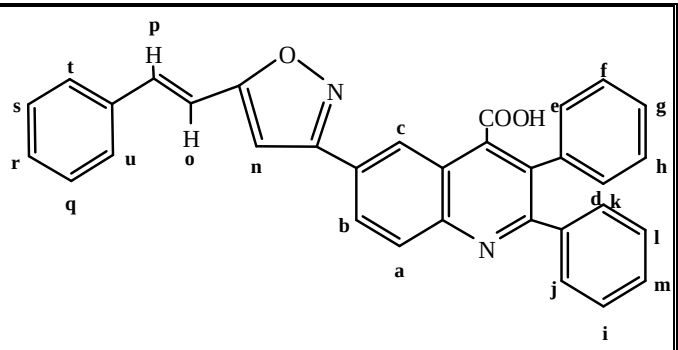
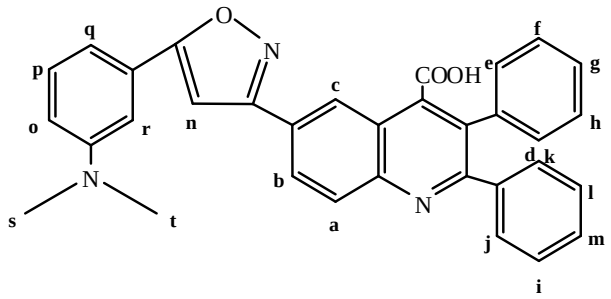
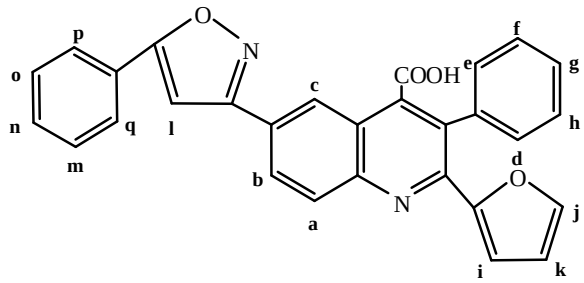
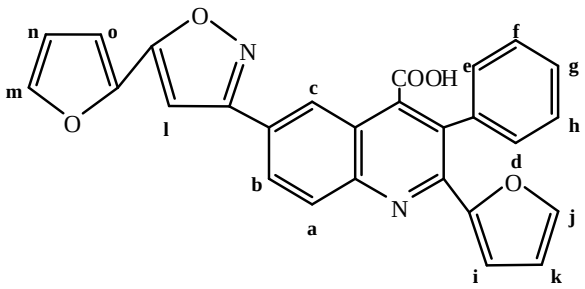
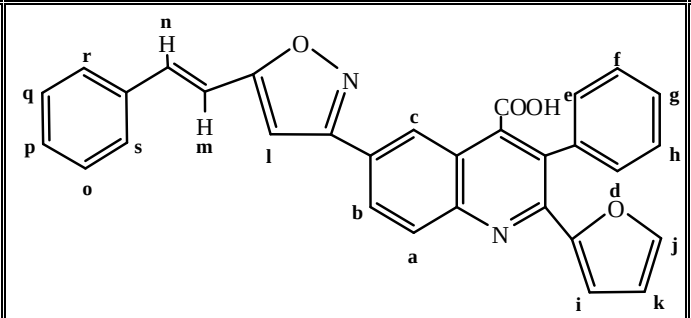
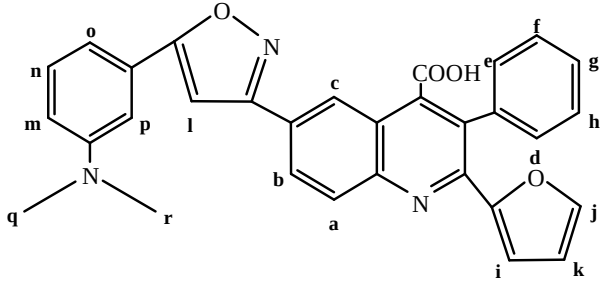
XI		a b, m c d, e, f, g, h, i, j, k, l, n, o, q p	7.95 (d, 1H, Quinoline ring). 7.75-7.80 (m, 1H, Quinoline ring, 1H, =C-H). 8.01 (s, 1H, Quinoline ring). 7.34-7.69 (m, 8H, H-Ar, 3H, Furyl ring, 1H, H-C=). 6.20 (d, 1H, H-Ar).

Table (2.4.3):[1]H Nuclear magnetic resonance data of the prepared isoxazoles:

Comp. No	Structure and signal	Signal	Chemical shift (ppm)
XII		a, b, d, e, f, g, h, i, j, k, l, m, o, p, q, r, s c n	7.41-7.66 (m, 2H, Quinoline ring, 15H, H-Ar). 8.01 (s, 1H, Quinoline ring). 6.00 (s, 1H, Isoxazole ring).
XIII		a, b, d, e, f, g, h, i, j, k, l, m, o, p, q c n	7.17-7.72 (m, 2H, Quinoline ring, 10H, H-Ar, 3H, Furyl ring). 7.96 (s, 1H, Quinoline ring). 6.01 (s, 1H, Isoxazole ring).

XIV		a, b, d, e, f, g, h, i, j, k, l, m, q, r, s, t, u c n o, p	7.31-7.70 (m, 2H, Quinoline ring, 15H, H-Ar). 7.92 (s, 1H, Quinoline ring). 6.01 (s, 1H, Isoxazole ring). 7.00 (q, 2H, H-C=C-H).
XV		a, b, d, e, f, g, h, i, j, k, l, m, p, q, r c n o s, t	7.16-7.76 (m, 2H, Quinoline ring, 13H, H-Ar). 7.94 (s, 1H, Quinoline ring). 6.01 (s, 1H, Isoxazole ring). 6.68 (d, 1H, H-Ar). 3.04 (s, 6H, CH_3).
XVI		a, b, d, e, f, g, h, i, j, m, n, o, p, q c k, l	7.35-7.80 (m, 2H, Quinoline ring, 10H, H-Ar, 2H, Furyl ring). 8.03 (s, 1H, Quinoline ring). 6.00-6.30 (m, 1H, Furyl ring, 1H, Isoxazole ring)

XVII		a, b, d, e, f, g, h, i, j, k, m, o c l, n	7.36-7.80 (m, 2H, Quinoline ring, 5H, H-Ar, 5H, Furyl ring). 8.05 (s, 1H, Quinoline ring). 6.19-6.72 (m, 1H, Isoxazole ring, 1H, Furyl ring).
XVIII		a b c d, e, f, g, h, i, j, o, p, q, r, s k, m, n l	7.69 (d, 1H, Quinoline ring). 7.78 (d, 1H, Quinoline ring). 7.98 (s, 1H, Quinoline ring). 7.29-7.51 (m, 10H, H-Ar, 2H, Furyl ring). 7.01-7.09 (m, 1H, Furyl ring, 2H, H-C=C-H). 6.19 (s, 1H, Isoxazole ring).
XIX		a b c d, e, f, g, h, i, j, n, o k, m, p l q, r	7.69 (d, 1H, Quinoline ring). 7.75 (d, 1H, Quinoline ring). 8.01 (s, 1H, Quinoline ring). 7.32-7.40 (m, 7H, H-Ar, 1H, Furyl ring). 6.50-6.70 (m, 1H, Furyl ring, 2H, H-Ar). 6.19 (s, 1H, Isoxazole ring). 3.05 (s, 6H, CH_3).

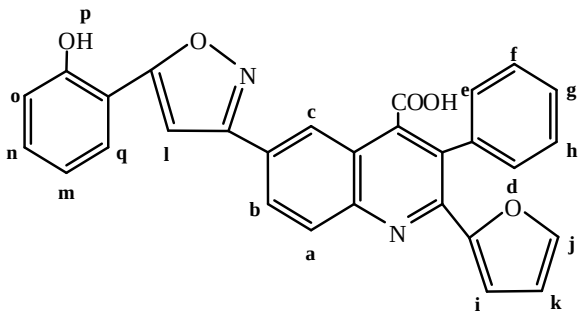
XX		a, b, d, e, f, g, h, i, j, q c k, m, o l n p	7.35-7.79(m, 2H, Quinoline ring, 6H, H-Ar, 2H, Furyl ring) 8.03 (s, 1H, Quinoline ring). 6.82-6.93 (m, 1H, Furyl ring, 2H, H-Ar). 6.19 (s, 1H, Isoxazole ring). 6.97 (t, 1H, H-Ar). 8.22 (s, 1H, OH).

Table (2.4.4):[1]H Nuclear magnetic resonance data of the prepared quinolines derivatives:

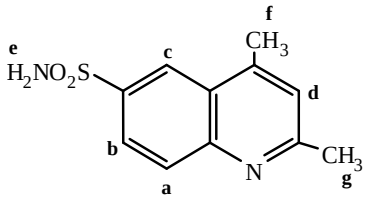
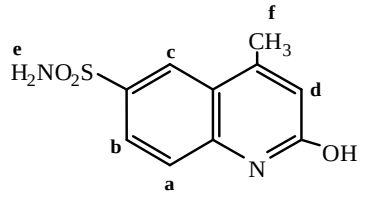
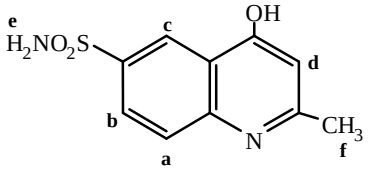
Comp. No	Structure and signal	Signal	Chemical shift (ppm)
XXIV		a, b	7.36 (m, 2H, Quinoline ring).
		c	7.79 (s, 1H, Quinoline ring).
		d	5.35 (s, 1H, Quinoline ring).
		e	6.91 (s, 2H, NH_2).
		f	2.14 (s, 3H, CH_3).
		g	2.04 (s, 3H, CH_3).
XXV		a, b	6.58 (d, 2H, Quinoline ring).
		c	7.44 (s, 1H, Quinoline ring).
		d	5.82 (s, 1H, Quinoline ring).
		e	6.90 (s, 2H, NH_2).
		f	2.51 (s, 3H, CH_3).
XXVI		a, b	6.06-6.58 (m, 2H, Quinoline ring).
		c	7.46 (s, 1H, Quinoline ring).
		d	5.82 (s, 1H, Quinoline ring).
		e	6.91 (s, 2H, NH_2).
		f	2.51 (s, 3H, CH_3).

Table (2.5):^{13}C Nuclear magnetic resonance data of the prepared compounds:

Table (2.5.1):^{13}C Nuclear magnetic resonance data of 3-phenyl-quinoline derivatives:

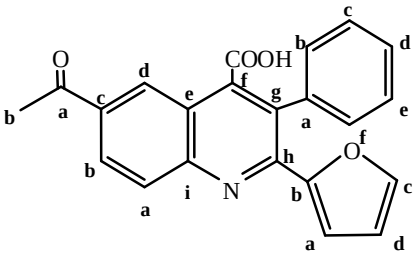
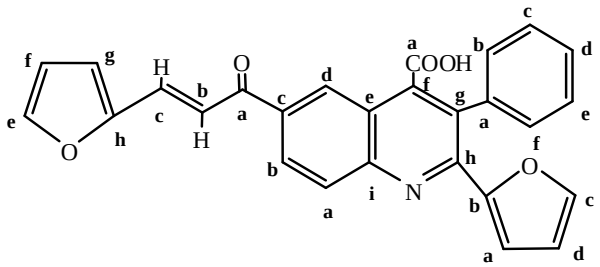
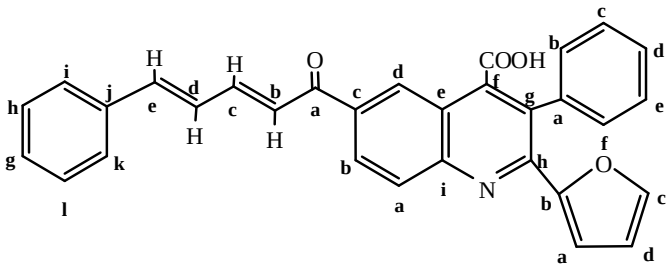
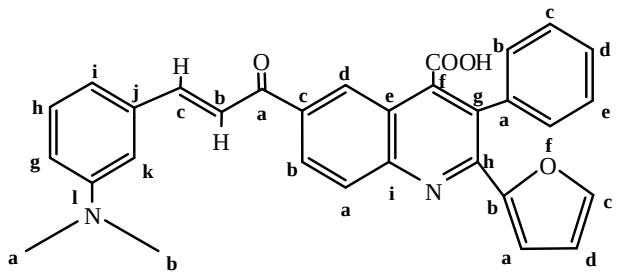
Comp. No	Structure and signal	Signal	Chemical shift (ppm)
II		b	26.49 (CH_3, Acetyl group).
		a	115.00 (C, H-Ar).
		d	121.00 (CH, Furyl ring).
		a, b, d, e, b, c, d, e, f	126.97-128.99 (3CH, C, Quinoline ring, 5CH, H-Ar).
		c, f, g, i	129.00-132.00 (4C, Quinoline ring).
		a	139.00 (CH, Furyl ring).
		c	142.95 (CH, Furyl ring).
		i	143.11 (C, Quinoline ring).
		h, b	148.74 (C, Quinoline ring, C, Furyl ring).
		a	165.52 (C, Carboxylic acid group).
		a	196.66 (C, Acetyl group).

Table (2.5.2):^{13}C Nuclear magnetic resonance data of the prepared chalcones:

Comp. No	Structure and signal	Signal	Chemical shift (ppm)
VIII		c	123.33 (CH, Ethylene group).
		c, e, f, h, i	124.5-132.00 (5C, Quinoline ring).
		a, b, d, b, b, c, d, e, f	127.43-129.83 (3CH, Quinoline ring, CH, Ethylene group, 5CH, H-Ar).
		a	130.00 (C, H-Ar).
		g	132.93 (C, Quinoline ring).
		g	134.00 (CH, Furyl ring).
		a, d, f	136.00-139.00 (3CH, Furyl ring).
		c	142.16 (CH, Furyl ring).
		h	143.00 (C, Furyl ring).
		b	144.00 (C, Furyl ring).
		e	140.05 (CH, Furyl ring).
		a	186.95 (C, C=O).
		a	188.00 (C, Carboxylic acid group).

IX		a	119.00 (C, H-Ar).
		j	119.80 (C, H-Ar).
		f, h, d, e, d, e	123.00-124.95 (CH, 3C, Quinoline ring, 2CH, Ethylene group).
		b	125.43 (CH, Quinoline ring).
		b, c, d, e, f, g, h, i, k, l, a, b, c	127.20-129.15 (10CH, H-Ar, CH, Quinoline ring, 2CH, Ethylene).
		g	132.57 (C, Quinoline ring).
		c	136.04 (C, Quinoline ring).
		a	138.00 (CH, Furyl ring).
		d	139.00 (CH, Furyl ring).
		c	141.35 (CH, Furyl ring).
		b	142.00 (C, Furyl ring).
		i	142.45 (C, Quinoline ring).
		a	187.00 (C, C=O).

X		a, b	40.09 (2CH, CH_3).
		a	109.65 (CH, Furyl ring).
		g	111.71 (CH, H-Ar).
		i	115.90 (CH, H-Ar).
		b	122.00 (CH, Ethylene).
		a, j, e	121.00-122.12 (2C, H-Ar, C, Quinoline ring).
		h	123.00 (CH, Quinoline ring).
		g	124.00 (CH, Quinoline ring).
		a, b, d, h, b, c, d, e, f	127.43-128.87 (3CH, Quinoline ring, 6CH, H-Ar).
		c, f	132.82 (2C, Quinoline ring).
		d	137.00 (CH, Furyl ring).
		k	138.00 (CH, H-Ar).
		c	141.91 (CH, Furyl ring).
		b	143.00 (C, Furyl ring).
		i,c	144.41 (C, Quinoline ring, CH, Ethylene).
		l	151.87 (C, H-Ar).
		a	189.85 (C, C=O).

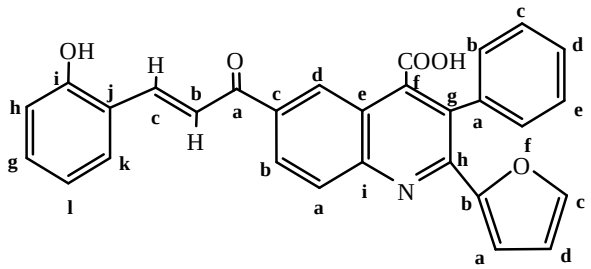
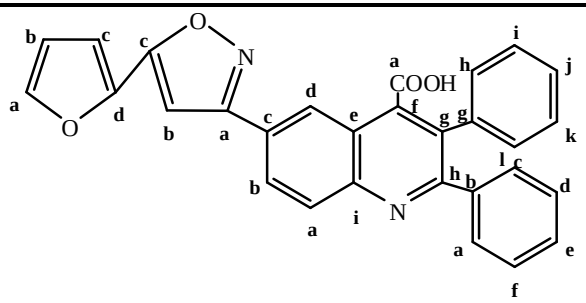
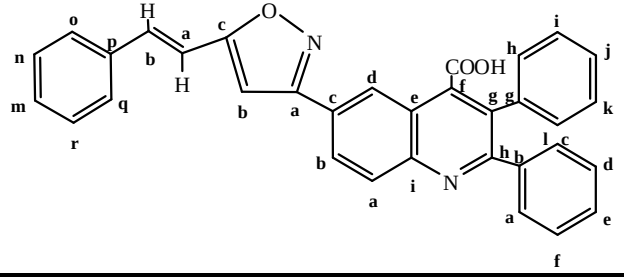
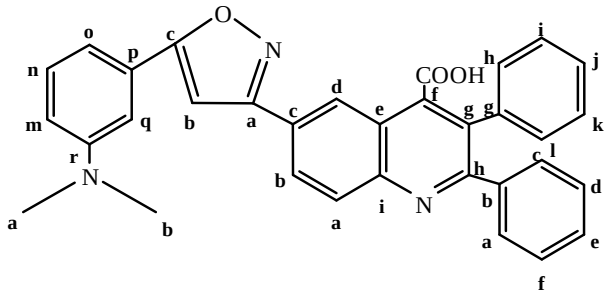
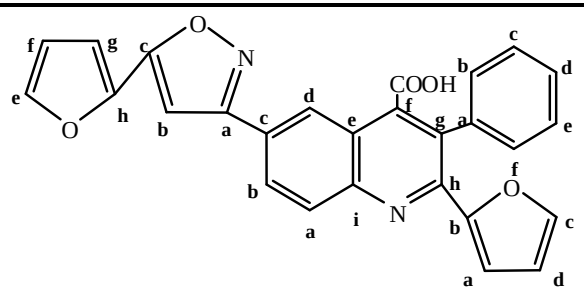
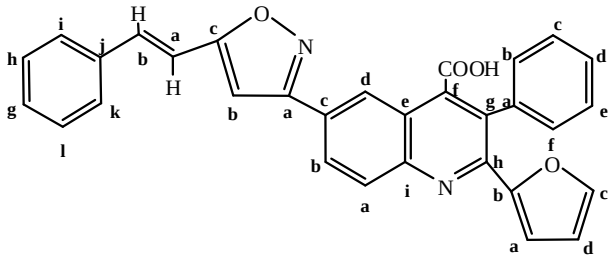
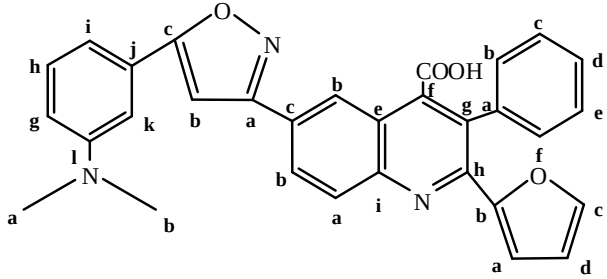
XI		a	110.26 (CH, Furyl ring).
		d	110.76 (CH, Furyl ring).
		a, g, h, i, j	115.00-121.00 (3C, 2CH, H-Ar).
		l	119.84 (CH, H-Ar).
		b	119.94 (CH, Ethylene group).
		a, b, c, d, e, f, g, h, i, b, c, d, e, f, g, k	123.00-129.13 (3CH, 6C, Quinoline ring, 7CH, H-Ar).
		b	141.00 (C, Furyl ring).
		c	142.00 (CH, Ethylene group).
		c	142.67 (CH, Furyl ring).
		a	196.66 (C, C=O).

Table (2.5.3):[13]C Nuclear magnetic resonance data of the prepared isoxazoles:

Comp. No	Structure and signal	Signal	Chemical shift (ppm)
XIII		b	113.08 (CH, Furyl ring).
		c	114.00 (CH, Furyl ring).
		a, b, c, d, e, f, h, i, a, b, c, d, e, f, h, i, j, k, l	123.27-131.50 (3CH, 5C, Quinoline ring, 11CH, H-Ar).
		g	132.90 (C, Quinoline ring).
		g	137.40 (C, H-Ar).
		a	141.12 (CH, Furyl ring).
		d	143.15 (C, Furyl ring).
		b	146.06 (CH, Isoxazole ring).
		c	149.00 (C, Isoxazole ring).
		a	151.18 (C, Isoxazole ring).
		a	166.14 (C, Carboxylic acid group).
XIV		a, b, c, d, e, , f, g, h, i, a, b, c, d, e, f, h, i, j, k, l, m, n, o, q, r	123.53-133.08 (3CH, 6C, Quinoline ring, 15CH, C, H-Ar).
		a, b, c, g, p	135.99-137.30 (CH=CH, Ethylene group, C, Quinoline ring, 2C, H-Ar).

		b	140.98 (CH, Isoxazole ring).
		c	143.89 (C, Isoxazole ring).
		a	150.00 (C, Isoxazole ring).
XV		a, b	40.10 (2CH, CH_3).
		q	111.70 (CH, H-Ar).
		m, o	115.87 (2CH, H-Ar).
		a, b, c, d, e, f, g, h, a,	122.04-133.81 (3CH, 5C, Quinoline ring, 11CH, 2C,
		b, c, d, e, f, h, i, j, k, l,	H-Ar).
		n, p	
		g	137.41 (C, H-Ar).
		i	138.00 (C, Quinoline ring).
		r	140.00 (C, H-Ar).
		b	141.00 (CH, Isoxazole ring).
		c	144.69 (C, Isoxazloe ring).
		a	151.90 (C, Isoxazole ring).
		a	165.88 (C, Carboxylic acid group).

XVII		a, g	110.37 (2CH, Furyl ring).
		d, f	111.40 (2CH, Furyl ring).
		a, b, c, d, e, f, g, h, a, b, c, d, e, f	120.22-133.02 (3CH, 5C, Quinoline ring, 6CH, H-Ar).
		i	139.00 (C, Quinoline ring).
		e, c	140.95 (2CH, Furyl ring).
		b, h	143.21 (2C, Furyl ring).
		b	146.10 (CH, Isoxazole ring).
		c	148.78 (C, Isoxazole ring).
		a	151.18 (C, Isoxazole ring).
		a	165.64 (C, Carboxylic acid group).
XVIII		a	110.38 (CH, Furyl ring).
		a, d	111.43 (CH, Ethylene group, CH, Furyl ring).
		a, b, c, d, e, f, g, h, b, c, d, e, f, g, h, i, l, k	120.22-133.17 (3CH, 5C, Quinoline ring, 10CH, H-Ar).
		i	136.00 (C, Quinoline ring).
		a	140.86 (C, H-Ar).
		j	141.52 (C, H-Ar).
		c	142.96 (CH, Furyl ring).
		b	143.12 (C, Furyl ring).

		b	146.75 (CH, Ethylene group).
		b	143.95 (CH, Isoxazole ring).
		c	149.00 (C, Isoxazole ring).
		a	150.00 (C, Isoxazole ring).
		a	165.55 (C, Carboxylic acid group).
XIX		a, b	40.10 (2CH, CH_3).
		d, k	110.36 (CH, Furyl ring, CH, H-Ar).
		g	111.34 (CH, H-Ar).
		i	111.71 (CH, H-Ar).
		a	119.72 (CH, Furyl ring).
		a, b, c, d, e, f, g, h, a, b, c, d, e, f, h, j	122.05-133.92 (3CH, 5C, Quinoline ring, 6CH, 2C, H-Ar).
		i	139.00 (C, Quinoline ring).
		c	140.48 (CH, Furyl ring).
		b	141.00 (C, Furyl ring).
		l	144.74 (C, H-Ar).
		b	147.00 (CH, Isoxazole ring).
		c	148.86 (C, Isoxazole ring).
		a	151.94 (C, Isoxazole ring).
		a	165.54 (C, Carboxylic acid group).

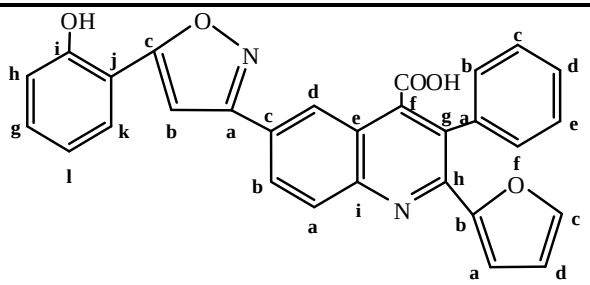
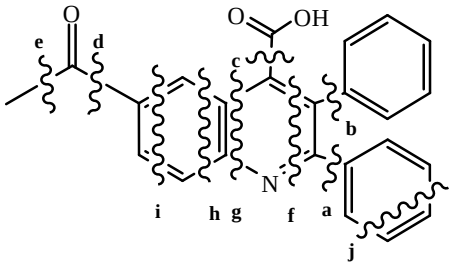
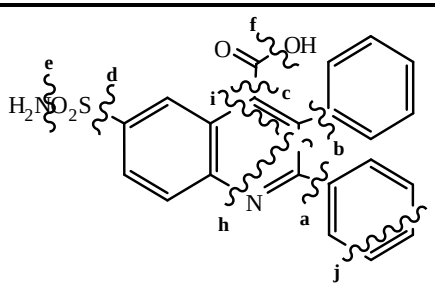
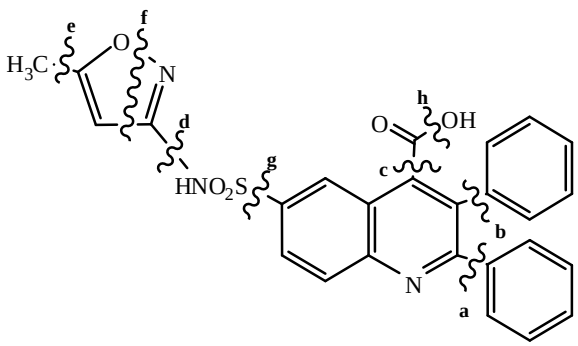
XX		a	110.34 (CH, Furyl ring).
		d	111.13 (CH, Furyl ring).
		j	116.26 (C, H-Ar).
		h	118.84 (CH, H-Ar).
		a, b, ,c, d, e, f, g, h, a, b, c, d, e, f, g, k, l	121.42-137.10 (3CH, 5C, Quinoline ring, 8CH, C, H-Ar).
		i	139.05 (C, Quinoline ring).
		c	142.98 (CH, Furyl ring).
		b	143.45 (C, Furyl ring).
		i	143.07 (C, H-Ar).
		b	148.00 (CH, Isoxazole ring).
		c	149.13 (C, Isoxazole ring).
		a	152.33 (C, Isoxazole ring).
		a	165.37 (C, Carboxylic acid group).

Table (2.6): Gas chromatography – mass spectral data of the prepared compounds:

Table (2.6.1): Gas chromatography – mass spectral data of 3-phenyl-quinoline derivatives:

Comp. No	Structure of compound	Retention time/min	M.wt calculated	$M^{\cdot+}$ m/z	Mass spectral fragmentation	
					Path of fragment lost	m/z
I		14.88	367.40	367	a = $[M^{\cdot+} - ph^{\cdot}]^{\cdot+}$	292
					a+e = $[M^{\cdot+} - (ph^{\cdot}+CH_3^{\cdot})]^{\cdot+}$	276
					a+d = $[M^{\cdot+} - (ph^{\cdot}+CH_3CO^{\cdot})]^{\cdot+}$	247
					a+d = $[M^{\cdot+} - (ph^{\cdot}+CH_3CO^{\cdot}+H^{\cdot})]^{\cdot+}$	246
					a+c+d = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+CH_3CO^{\cdot})]^{\cdot+}$	204
					a+c+d+i = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+CH_3CO^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$	176
					a+b+c+e+g = $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+CH_3^{\cdot}+C_3N^{\cdot})]^{\cdot+}$	102
					b+c+d+f+g+h+i = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+CH_3CO^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$	77
					b+c+d+f+g+h+i+j = $[M^{\cdot+} -(ph^{\cdot}+COOH^{\cdot}+CH_3CO^{\cdot}+C_9H_3N^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$	51

XXI		17.65	404.44	404	a = $[M^{\cdot+} - ph^{\cdot}]^{\cdot+}$ a+c = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot})]^{\cdot+}$ a+b+e+g = $[M^{\cdot+} - (2ph^{\cdot}+NH_2^{\cdot}+C^{\cdot})]^{\cdot+}$ a+b+e+h = $[M^{\cdot+} - (2ph^{\cdot}+NH_2^{\cdot}+CN^{\cdot})]^{\cdot+}$ b+c+d+i = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+H_2NO_2S^{\cdot}+C_2^{\cdot})]^{\cdot+}$ a+b+d+f = $[M^{\cdot+} - (2ph^{\cdot}+H_2NO_2S^{\cdot}+OH^{\cdot})]^{\cdot+}$ b+c+d+g=$[M^{\cdot+} -(ph^{\cdot}+COOH^{\cdot}+H_2NO_2S^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$ b+c+d+g+j = $[M^{\cdot+} -(ph^{\cdot}+COOH^{\cdot}+H_2NO_2S^{\cdot}+C_9H_3N^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$	327 282 222 207 178 152 77 51
XXII		9.98	485.51	485	f = $[M^{\cdot+} - C_3H_4O^{\cdot}]^{\cdot+}$ a+e = $[M^{\cdot+} - (ph^{\cdot}+CH_3^{\cdot})]^{\cdot+}$ a+c+d = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+C_4H_4NO^{\cdot})]^{\cdot+}$ a+b+c+e+g=$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+CH_3^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$	429 393 281 147

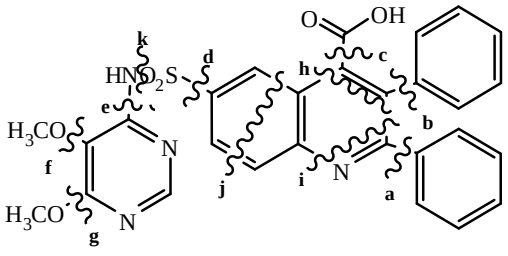
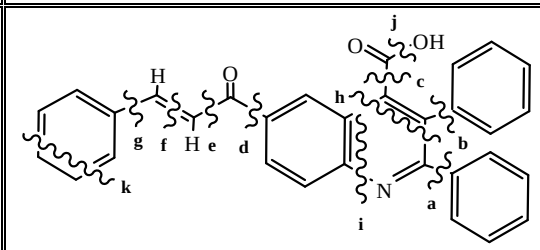
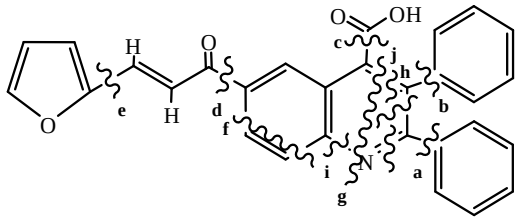
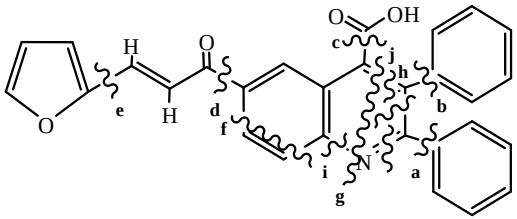
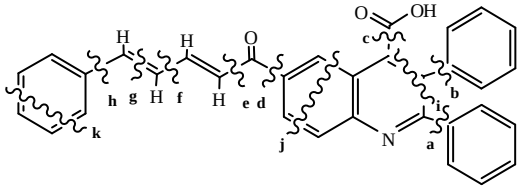
XXIII		17.78	542.56	542	a+b+f+g = **$[M^{\cdot+} - (2ph^{\cdot}+2CH_3O^{\cdot})]^{\cdot+}$** a+b+c+j = **$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_6H_2N^{\cdot})]^{\cdot+}$** a+b+e+f+g+i+k = **$[M^{\cdot+} - (2ph^{\cdot}+C_4HN_2^{\cdot}+2CH_3O^{\cdot}+CN^{\cdot}+NH^{\cdot})]^{\cdot+}$** b+c+d+e+f+g+h = **$[M^{\cdot+}-(ph^{\cdot}+COOH^{\cdot}+HNO_2S^{\cdot}+C_4HN_2^{\cdot}+2CH_3O^{\cdot}+C_2^{\cdot})]^{\cdot}$** a+b+c+d+e+f+g = **$[M^{\cdot+} -(2ph^{\cdot}+COOH^{\cdot}+HNO_2S^{\cdot}+C_4HN_2^{\cdot}+2CH_3O^{\cdot})]^{\cdot+}$** b+c+d+e+f+g+h+i+j+k = **$[M^{\cdot+}- (ph^{\cdot}+COOH^{\cdot}+HNO_2S^{\cdot}+C_4HN_2^{\cdot}+2CH_3O^{\cdot}+ C_9H_3N^{\cdot})]^{\cdot+}$**	327 255 207 178 125 77

Table (2.6.2): Gas chromatography – mass spectral data of the prepared chalcones:

Comp. No	Structure of compound	Retention time/min	M.wt calculated	$M^{\cdot+}$ m/z	Mass spectral fragmentation	
					Path of fragment lost	m/z
III		11.01	455.50	455	a+b+j = $[M^{\cdot+} - (2ph^{\cdot}+OH^{\cdot})]^{\cdot+}$	284
					a+b+c+h = $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_2^{\cdot})]^{\cdot+}$	232
					a+b+g+c+e = $[M^{\cdot+} - (3ph^{\cdot}+COOH^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$	153
					a+b+c+d = $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$	131
					a+b+c+d+e = $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+CO^{\cdot})]^{\cdot+}$	103
					a+b+c+d+f= $[M^{\cdot+} -(2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_2H_2O^{\cdot})]^{\cdot+}$	89
					a+b+c+d+g= $[M^{\cdot+} -(2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_3H_2O^{\cdot})]^{\cdot+}$	77
					a+b+c+d+g+k= $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_3H_2O^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$	51
IV		21.02	445.47	445	a+e = $[M^{\cdot+} - (ph^{\cdot}+C_4H_3O^{\cdot})]^{\cdot+}$	301
					d+e+f = $[M^{\cdot+} - (C_3H_2O^{\cdot}+C_4H_3O^{\cdot}+C_2H_3^{\cdot})]^{\cdot+}$	297
					a+b+e = $[M^{\cdot+} - (2ph^{\cdot}+C_4H_4O^{\cdot})]^{\cdot+}$	223
					a+b+c+g = $[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_2N^{\cdot})]^{\cdot+}$	208
					c+d+e+h=$[M^{\cdot+} -(COOH^{\cdot}+C_3H_2O^{\cdot}+C_4H_3O^{\cdot}+C_7H_3N^{\cdot})]^{\cdot+}$	178
					b+c+d+e+i = $[M^{\cdot+} - (ph^{\cdot}+COOH^{\cdot}+C_3H_2O^{\cdot}+C_4H_3O^{\cdot}+C_8H_3^{\cdot})]^{\cdot+}$	103

IV					a+c+d+e+j = **$[M^{\cdot+}-(ph^{\cdot}+COOH^{\cdot}+C_3H_2O^{\cdot}+C_4H_3O^{\cdot}+C_8H_3N^{\cdot})]^{\cdot+}$** b+c+d+e+f+g+h+i+j = **$[M^{\cdot+}-(ph^{\cdot}+COOH^{\cdot}+C_3H_2O^{\cdot}+C_4H_3O^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$**	89 77
V		12.83	481.54	481	h+g = **$[M^{\cdot+} - (ph^{\cdot}+CH^{\cdot})]^{\cdot+}$** d+h+j = **$[M^{\cdot+} - (C_5H_4O^{\cdot}+ph^{\cdot}+C_3H^{\cdot})]^{\cdot+}$** a+b+c+i = **$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C^{\cdot})]^{\cdot+}$** a+b+h+c+i =**$[M^{\cdot+} - (3ph^{\cdot}+COOH^{\cdot}+C^{\cdot})]^{\cdot+}$** a+b+h+c+e = **$[M^{\cdot+} - (3ph^{\cdot}+COOH^{\cdot}+C_4H_4^{\cdot})]^{\cdot+}$** a+b+c+d+f = **$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_3HO^{\cdot})]^{\cdot+}$** a+b+c+d+h=**$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_5H_4O^{\cdot})]^{\cdot+}$** a+b+c+d+h+k = **$[M^{\cdot+} - (2ph^{\cdot}+COOH^{\cdot}+C_9H_3N^{\cdot}+C_5H_4O^{\cdot}+C_2H_2^{\cdot})]^{\cdot+}$**	391 287 271 193 152 105 77 51

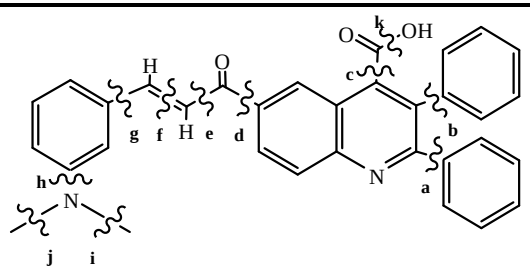
VI		13.93	498.57	498	a+b+i+j = **$[M^{\cdot+} - (2ph^{\cdot} + 2CH_3^{\cdot})]^{\cdot+}$** a+d+g+h = **$[M^{\cdot+} - (ph^{\cdot} + C_3H_2O^{\cdot} + C_6H_4^{\cdot} + C_2H_6N^{\cdot})]^{\cdot+}$** a+b+g+h = **$[M^{\cdot+} - (2ph^{\cdot} + C_6H_5^{\cdot} + C_2H_6N^{\cdot})]^{\cdot+}$** a+b+c+g+h = **$[M^{\cdot+} - (2ph^{\cdot} + COOH^{\cdot} + C_6H_5^{\cdot} + C_2H_6N^{\cdot})]^{\cdot+}$** a+b+c+d+e = **$[M^{\cdot+} - (2ph^{\cdot} + COOH^{\cdot} + C_9H_3N^{\cdot} + CHO^{\cdot})]^{\cdot+}$** a+b+c+d+g= **$[M^{\cdot+} - (2ph^{\cdot} + COOH^{\cdot} + C_9H_3N^{\cdot} + C_3H_2O^{\cdot})]^{\cdot+}$** a+b+c+d+e+h = **$[M^{\cdot+} - (2ph^{\cdot} + COOH^{\cdot} + C_9H_3N^{\cdot} + CO^{\cdot} + C_2H_6N^{\cdot})]^{\cdot+}$**	314 247 223 178 145 120 103

Table (2.6.3): Gas chromatography – mass spectral data of the prepared quinolines derivatives:

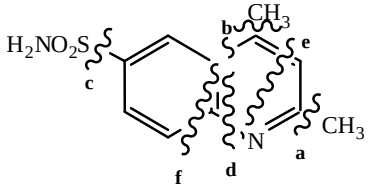
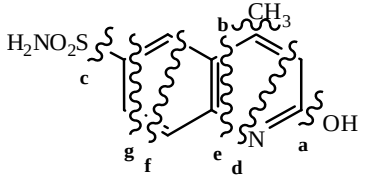
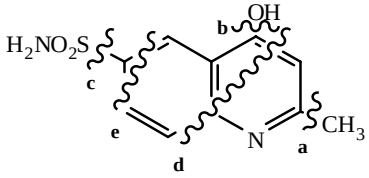
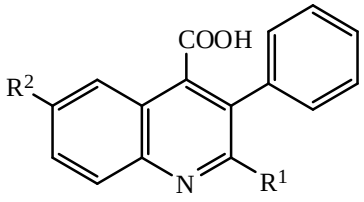
Comp. No	Structure of compound	Retention time/min	M.wt calculated	$M^{\cdot+}$ m/z	Mass spectral fragmentation	
					Path of fragment lost	m/z
XXIV		10.63	236.29	236	a+e = $[M^{\cdot+} - (CH_3^{\cdot}+C_2N^{\cdot})]^{\cdot+}$	183
					c = $[M^{\cdot+} - H_2NO_2S^{\cdot}]^{\cdot+}$	156
					a+c = $[M^{\cdot+} - (CH_3^{\cdot}+H_2NO_2S^{\cdot})]^{\cdot+}$	140
					c+f = $[M^{\cdot+} - (H_2NO_2S^{\cdot}+C_5H_3^{\cdot})]^{\cdot+}$	93
					a+b+c = $[M^{\cdot+} - (2CH_3^{\cdot}+ C_9H_4N^{\cdot})]^{\cdot+}$	80
					a+c+d = $[M^{\cdot+} - (CH_3^{\cdot}+H_2NO_2S^{\cdot}+C_6H_3^{\cdot})]^{\cdot+}$	65
XXV		4.14	238.26	238	a+d = $[M^{\cdot+} - (OH^{\cdot}+C_2N^{\cdot})]^{\cdot+}$	183
					a+b+e = $[M^{\cdot+} - (OH^{\cdot}+CH_3^{\cdot}+C_3HN^{\cdot})]^{\cdot+}$	155
					b+c =$[M^{\cdot+} - (CH_3^{\cdot}+H_2NO_2S^{\cdot})]^{\cdot+}$	143
					c+f = $[M^{\cdot+} - (H_2NO_2S^{\cdot}+C_3H_3^{\cdot})]^{\cdot+}$	119
					a+b+g = $[M^{\cdot+} - (OH^{\cdot}+CH_3^{\cdot}+C_7H_4^{\cdot})]^{\cdot+}$	104
XXVI		10.74	238.26	238	a+d = $[M^{\cdot+} - (CH_3^{\cdot}+C_3HN^{\cdot})]^{\cdot+}$	172
					a+b+d = $[M^{\cdot+} - (CH_3^{\cdot}+OH^{\cdot}+C_3HN^{\cdot})]^{\cdot+}$	156
					a+b+e = $[M^{\cdot+} - (CH_3^{\cdot}+OH^{\cdot}+C_8H_4N^{\cdot})]^{\cdot+}$	92
					a+b+c = $[M^{\cdot+} - (CH_3^{\cdot}+OH^{\cdot}+C_9H_3N^{\cdot})]^{\cdot+}$	80

Table (2.7): Thin layer chromatography data of the prepared compounds:

Table (2.7.1): Thin layer chromatography data of 3-phenyl-quinoline derivatives:



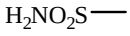
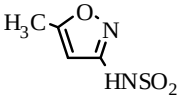
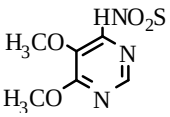
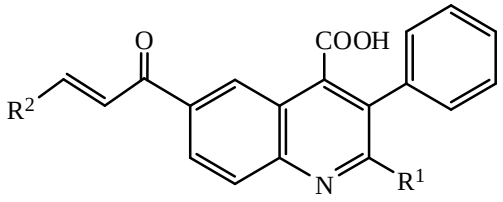
Comp. No	R^1	R^2	Solvent system	R_f value
I			Chloroform 9.8:0.2 Methanol	0.675
II			Chloroform 9.8:0.2 Methanol	0.553
XXI			Chloroform 9.5:0.5 Methanol	0.377
XXII			Chloroform 9.5:0.5 Methanol	0.600
XXIII			Chloroform 9.5:0.5 Methanol	0.813

Table (2.7.2): Thin layer chromatography data of the prepared chalcones:



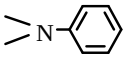
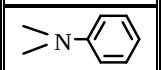
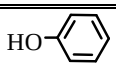
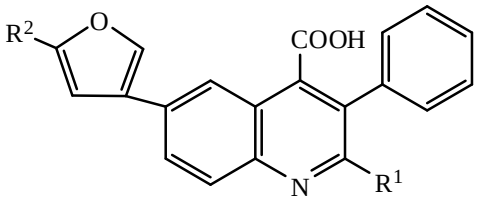
Comp. No	R^1	R^2	Solvent system	R_f value
III			Chloroform 9.8:0.2 Methanol	0.875
IV			Chloroform 9.8:0.2 Methanol	0.811
V			Chloroform 9.8:0.2 Methanol	0.903
VI			Chloroform 9.8:0.2 Methanol	0.806
VII			Chloroform 9.8:0.2 Methanol	0.918
VIII			Chloroform 9.8:0.2 Methanol	0.900
IX			Chloroform 9.8:0.2 Methanol	0.800
X			Chloroform 9.8:0.2 Methanol	0.686
XI			Chloroform 9.8:0.2 Methanol	0.526

Table (2.7.3): Thin layer chromatography data of the prepared isoxazoles:



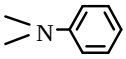
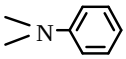
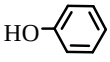
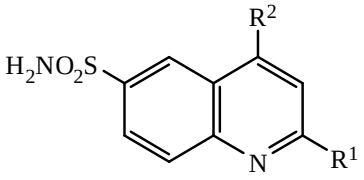
Comp. No	R^1	R^2	Solvent system	R_f value
XII			Chloroform 9.8:0.2 Methanol	0.230
XIII			Chloroform 9.8:0.2 Methanol	0.216
XIV			Chloroform 9.8:0.2 Methanol	0.889
XV			Chloroform 9.8:0.2 Methanol	0.833
XVI			Chloroform 9.8:0.2 Methanol	0.304
XVII			Chloroform 9.8:0.2 Methanol	0.900
XVIII			Chloroform 9.8:0.2 Methanol	0.910
XIX			Chloroform 9.8:0.2 Methanol	0.896
XX			Chloroform 9.8:0.2 Methanol	0.145

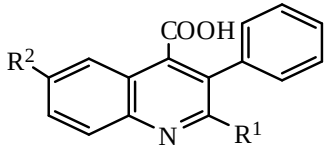
Table (2.7.4): Thin layer chromatography data of the prepared quinolines derivatives:



Comp. No	R^1	R^2	Solvent system	R_f value
XXIV	CH_3	CH_3	Chloroform 9.2:0.8 Methanol	0.797
XXV	OH	CH_3	Chloroform 9.2:0.8 Methanol	0.480
XXVI	CH_3	OH	Chloroform 9.2:0.8 Methanol	0.435

Table (2.8): Antimicrobial activity of the prepared compounds:

Table (2.8.1): Antimicrobial activity of 3-phenyl-quinoline derivatives:



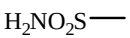
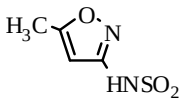
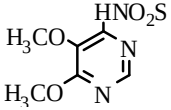
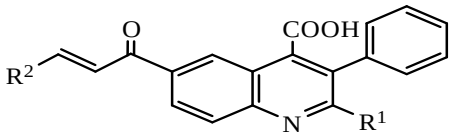
Comp. No	R^1	R^2	Zone of inhibition in (mm)					
			P.vulgaris	***E.coli***	***B.subtillis***	***S.aureus***	***Aspergillus niger***	***Candida albicans***
I			7.00	-	8.00	-	-	-
II			9.00	14.00	-	-	-	6.00
XXI			10.00	13.00	13.00	-	-	10.00
XXII			-	-	11.00	10.00	-	-
XXIII			10.00	-	13.00	8.00	-	-

Table (2.8.2): Antimicrobial activity of the prepared chalcones:



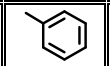
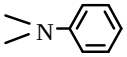
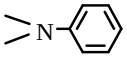
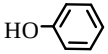
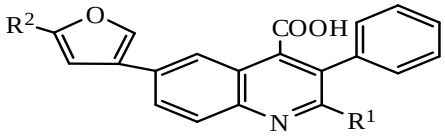
Comp. No	R^1	R^2	Zone of inhibition in (mm)					
			P.vulgaris	***E.coli***	***B.subtillis***	***S.aureus***	***Aspergillus niger***	***Candida albicans***
III			-	-	-	12.00	-	5.00
IV			-	-	-	11.00	-	-
V			-	-	-	9.00	-	9.00
VI			-	-	-	10.00	-	6.00
VII			-	-	-	-	-	8.00
VIII			10.00	-	-	-	-	5.00
IX			-	-	-	-	-	-
X			-	-	-	-	-	-
XI			10.00	-	15.00	12.00	-	11.00

Table (2.8.3): Antimicrobial activity of the prepared isoxazoles:



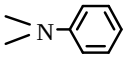
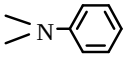
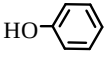
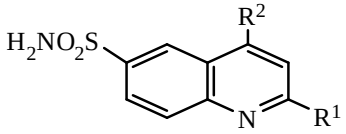
Comp. No	R^1	R^2	Zone of inhibition in (mm)					
			P.vulgaris	***E.coli***	***B.subtillis***	***S.aureus***	***Aspergillus niger***	***Candida albicans***
XII			-	-	-	10.00	-	7.00
XIII			-	-	-	-	-	11.00
XIV			-	-	-	-	-	8.00
XV			-	-	-	-	-	10.00
XVI			8.00	-	7.00	13.00	-	-
XVII			9.00	-	-	7.00	-	9.00
XVIII			6.00	-	-	8.00	-	-
XIX			-	-	-	-	-	-
XX			12.00	11.00	-	6.00	-	-

Table (2.8.4): Antimicrobial activity of the prepared quinoline derivatives:



Comp. No	R^1	R^2	Zone of inhibition in (mm)					
			P.vulgaris	***E.coli***	***B.subtillis***	***S.aureus***	***Aspergillus niger***	***Candida albicans***
XXIV	CH_3	CH_3	16.00	11.00	10.00	-	-	-
XXV	OH	CH_3	9.00	15.00	-	-	-	7.00
XXVI	CH_3	OH	13.00	13.00	8.00	-	-	7.00

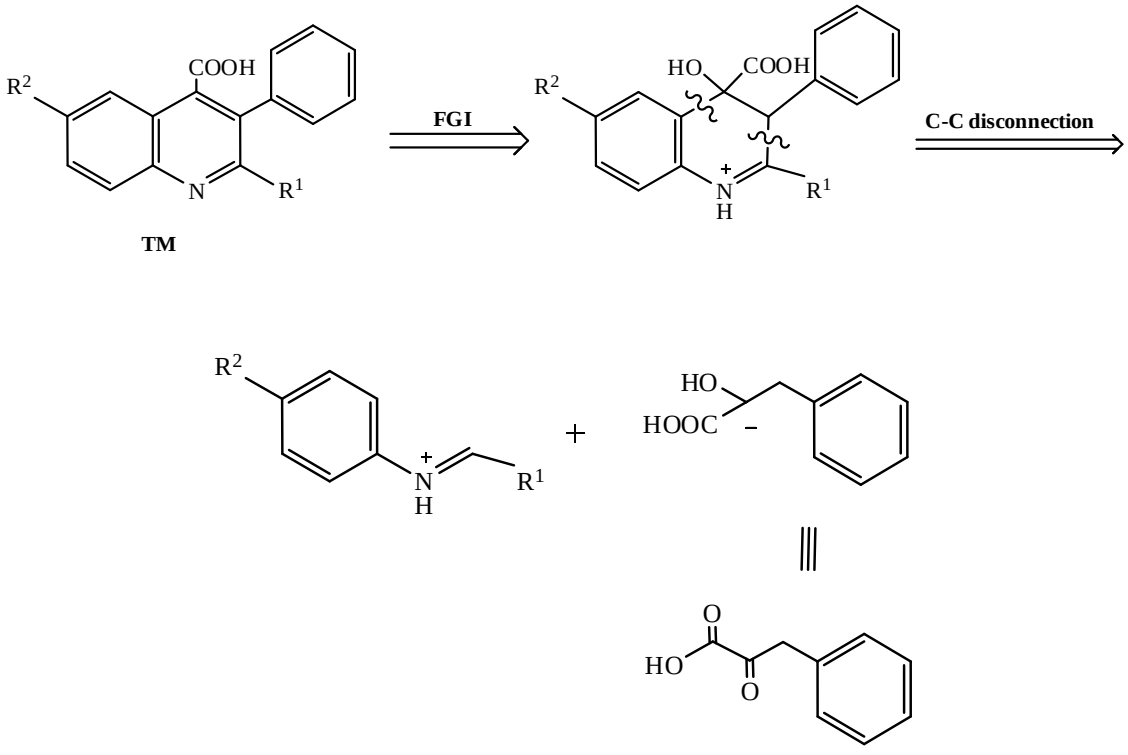
3. Discussion

3.1. Synthetic design:

Retrosynthetic analysis (RSA) is the process of transforming a target molecule through a sequence of progressively simpler structures which leads to simple or commercially available starting materials, this technique helps for solving problems in the planning of organic synthesis.

The synthetic design of this study depends on the appropriate retrosynthetic analysis of the target molecules (TM), through disconnection or functional group interchange (FGI) and functional group removal strategies.

Quinoline derivatives represent the major class of heterocycles; they are prevalent in a variety of pharmacologically active synthetic and natural compounds, the retrosynthetic analysis of quinoline and its derivatives depend on the ring constructed and reactions which build this ring.



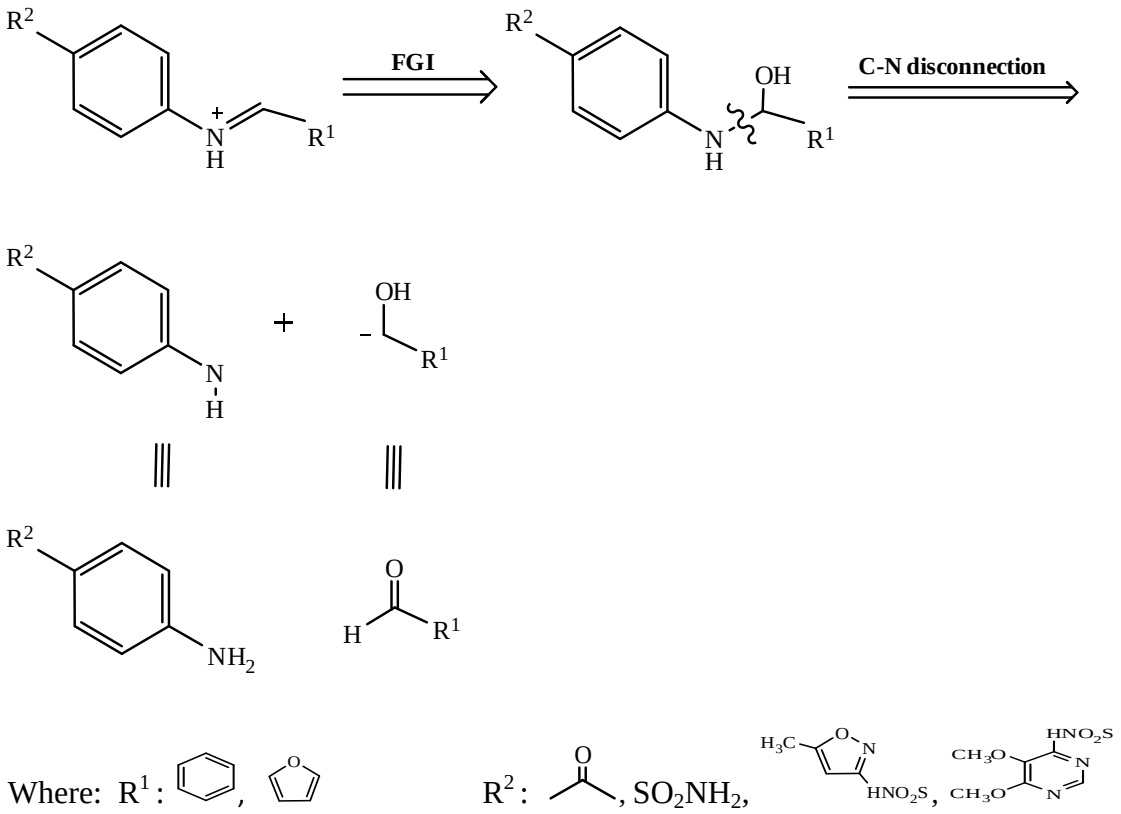


Figure (3.1): Retrosynthetic analysis of quinoline-4-carboxylic acid.

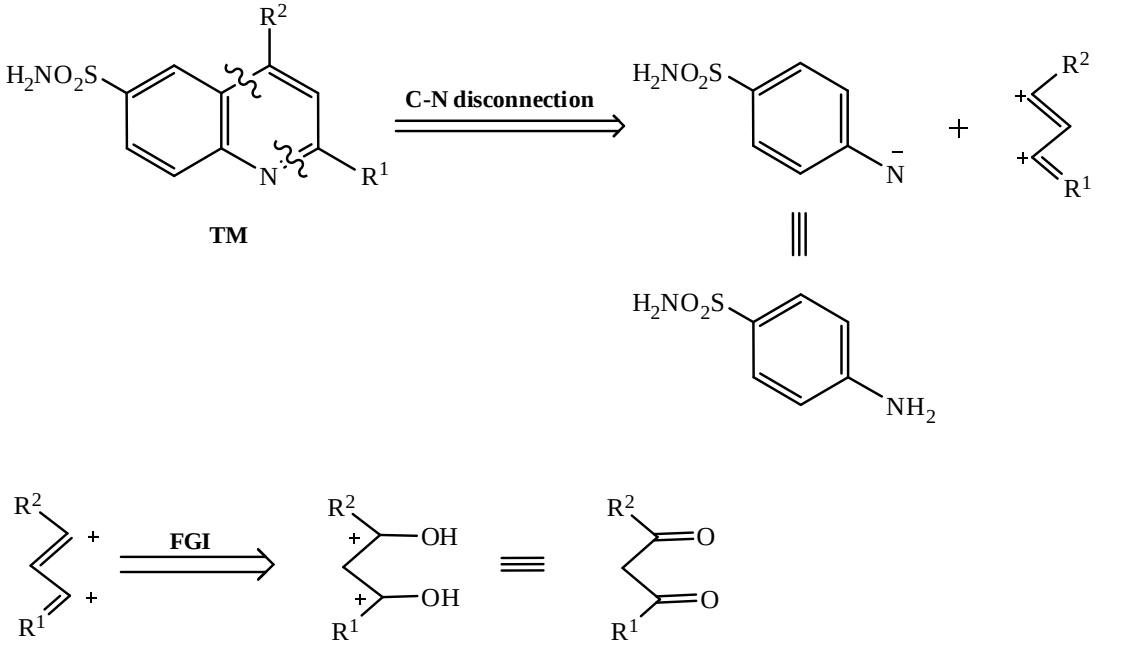
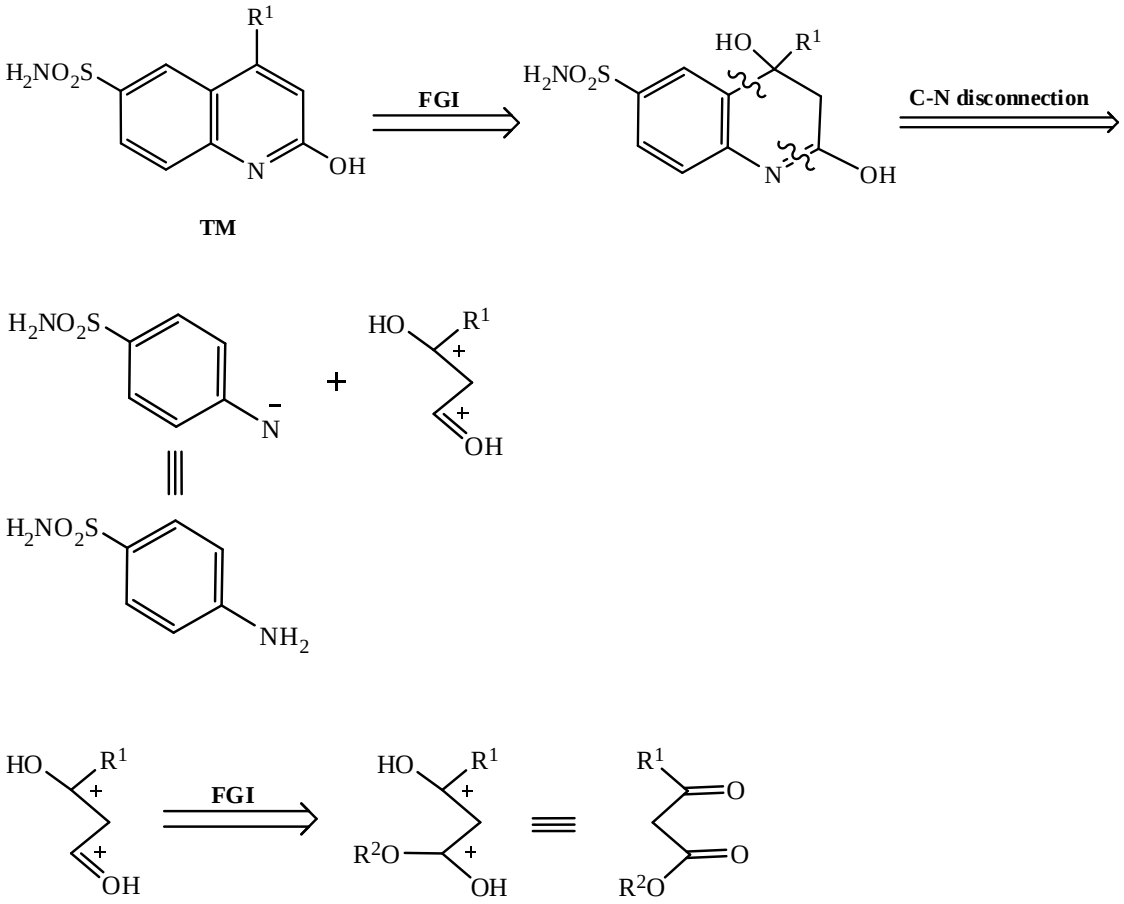
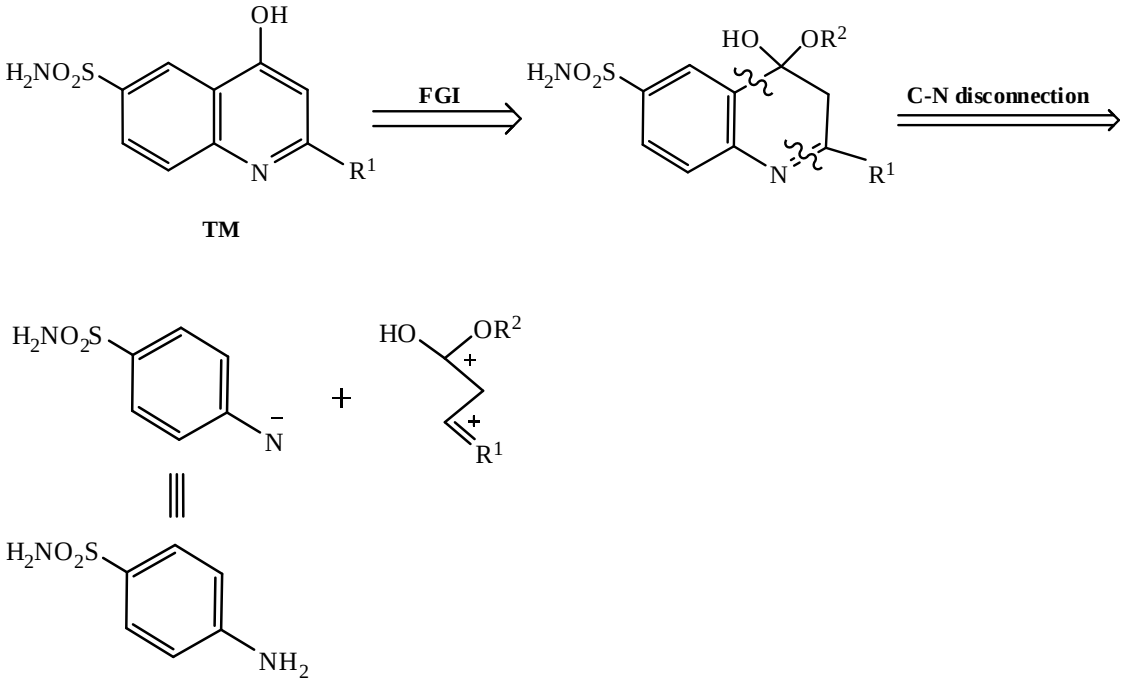


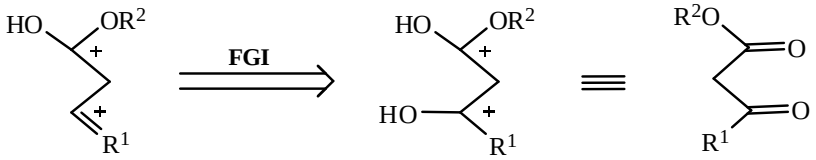
Figure (3.2): Retrosynthetic analysis of 2,4–dialkylquinoline.



Where: R^1: CH_3 R^2:OR

Figure (3.3): Retrosynthetic analysis of 4-alkyl-2-hydroxyquinoline.



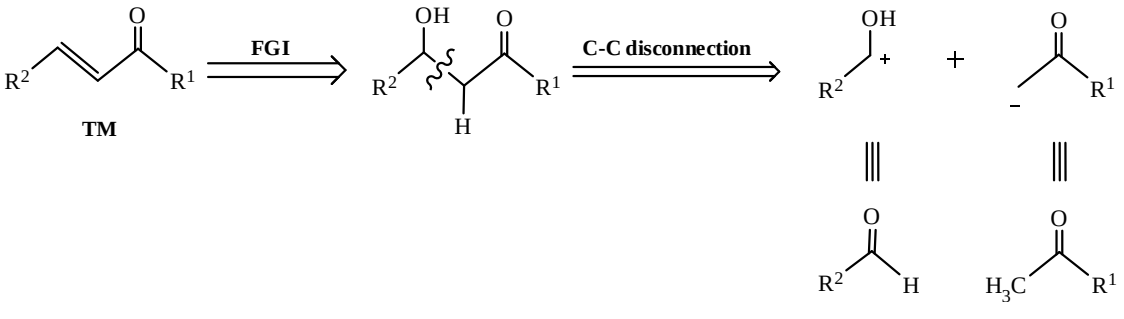


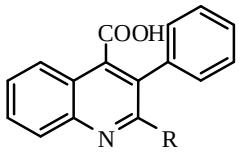
Where: R^1: CH_3 R^2:OR

Figure (3.4): Retrosynthetic analysis of 2-alkyl-4-hydroxyquinoline.

Chalcones belong to a class of α,β-unsatutated aromatic ketones, they are known as benzalacetophenone or benzylidene acetophenone, chalcones are one of the major classes of natural products with wide spread distribution in fruits, vegetables and spices, they have been recently subjects of great interest for their pharmacological applications and biological activities such as anti-cancer, anti-inflammatory, anti-malarial, antimicrobial, and anti-hyperglycemic agent (Rafiee and Rahimi, 2013).

Chalcones are well known intermediates for synthesizing various heterocyclic compounds for example (Isoxazoles, pyrimidines, etc.), compounds with the backbone of chalcones have various biological activities such as antimicrobial, anti-malarial, antileishmanial, and antioxidant. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity.



Where: R^1: 

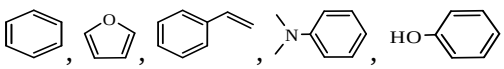
R^2: 

Figure (3.5): Retrosynthetic analysis of chalcones.

Based on the above observation it is worthwhile to prepare newer compounds for their antimicrobial and anti-inflammatory activities, so we prepare isoxazoles as an example of heterocyclic compound with the backbone of chalcones.

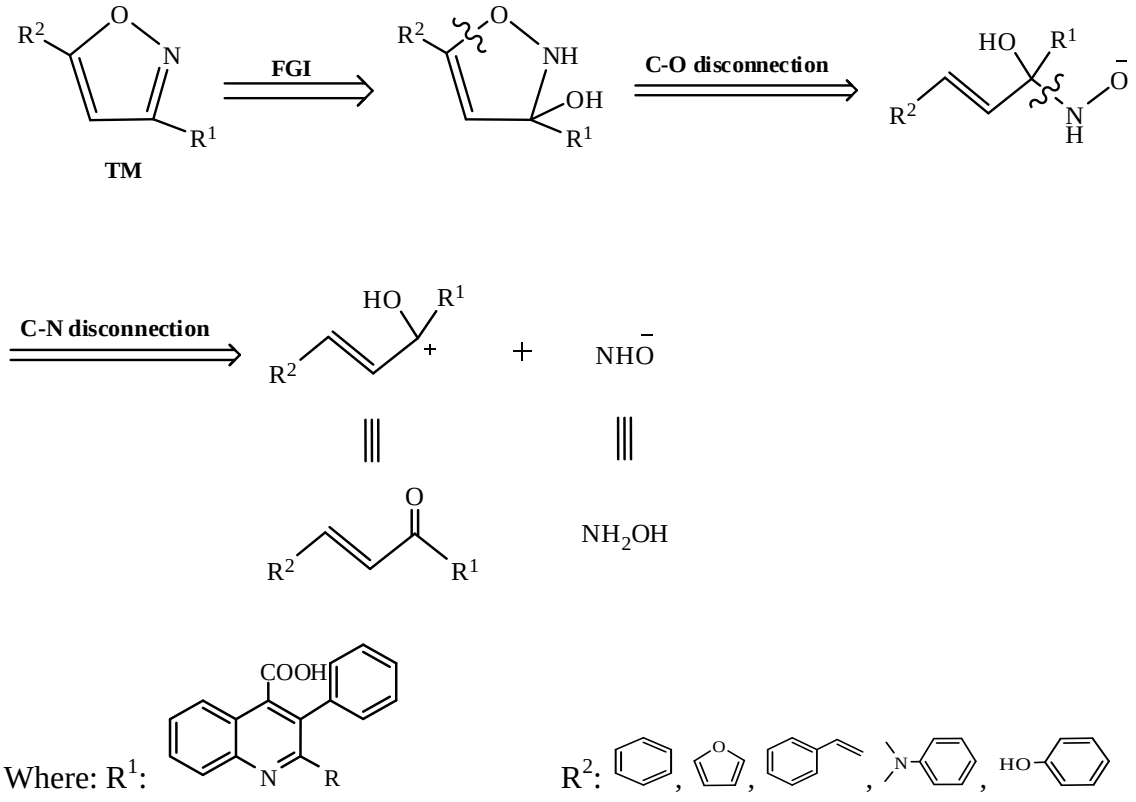


Figure (3.6): Retrosynthetic analysis of isoxazoles.

3.2. Reaction mechanism:

The prepared quinoline derivatives in this study were carried out via four types of reactions Doebner reaction, Combes quinoline synthesis, Knorr quinoline synthesis, and Conrad-Limpach cyclization.

3.2.1. Quinolines from Doebner reaction:

2-aryl-3-phenylquinoline-4-carboxylic acid derivatives were prepared by the Doebner reaction, through the condensation of aromatic amines with phenylpyruvic acid and aromatic aldehydes, mechanism of this reaction involve attack of the nucleophilic NH_2 group in aromatic amines on the electrophilic carbonyl carbon in aromatic aldehydes, followed by condensation reaction, the condensation product attacked by phenylpyruvic acid, subsequent intramolecular condensation and oxidation lead to the target molecule.

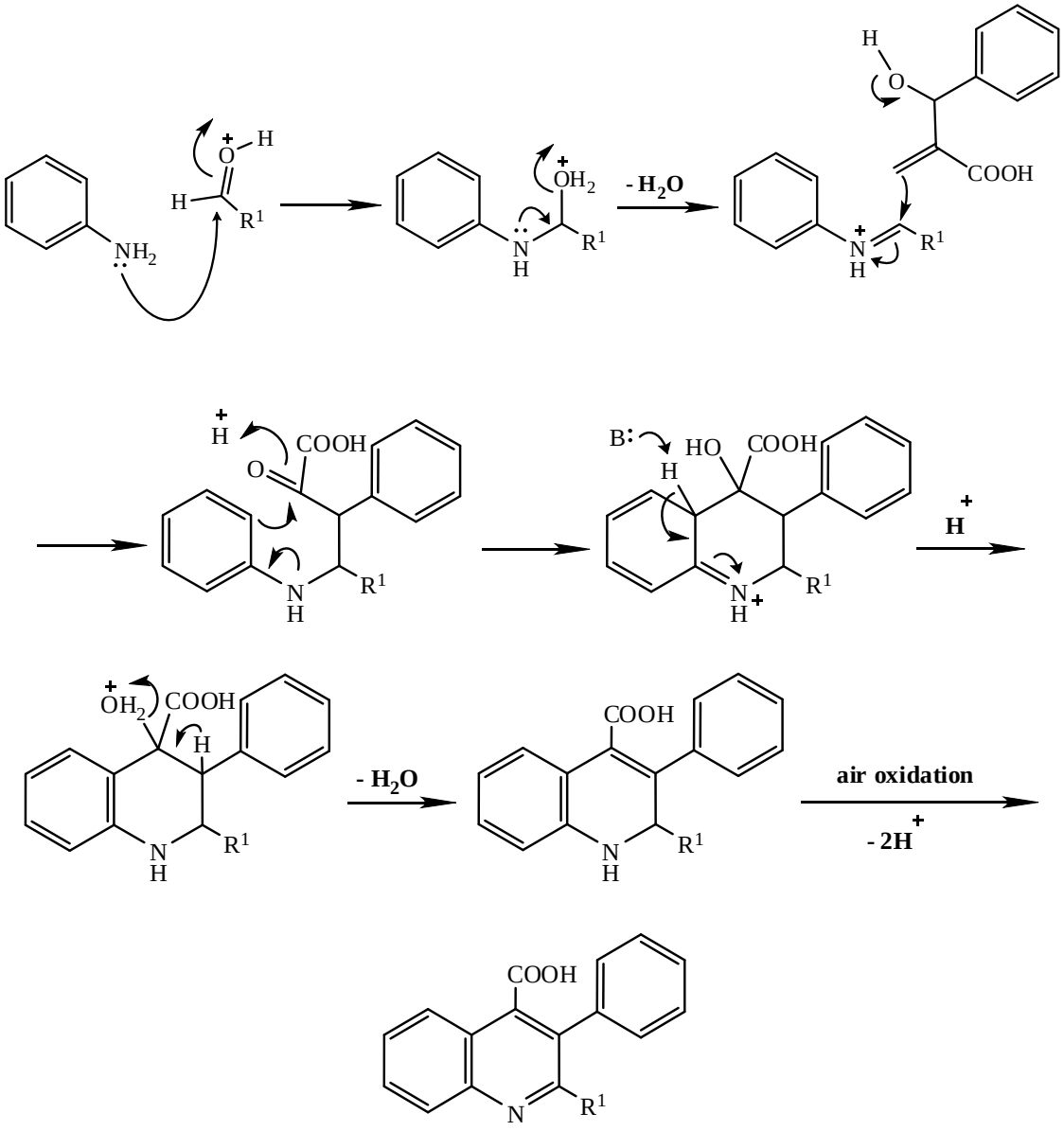


Figure (3.7): Reaction mechanism of quinolines from Doebner reaction.

3.2.2. Quinoline from Combes synthesis:

2,4-dimethylquinoline was prepared through the condensation of aromatic amine with acetylacetone, mechanism of this reaction involves acid-catalyzed condensation of the acetylacetone with the aromatic amine, to form a Schiff base (imine) which isomerizes to the corresponding enamine, the carbonyl oxygen atom of the enamine was protonated to form a carbocation that undergoes an electrophilic aromatic substitution, subsequent proton transfer, elimination of water and deprotonation of the ring nitrogen atom lead to the target molecule.

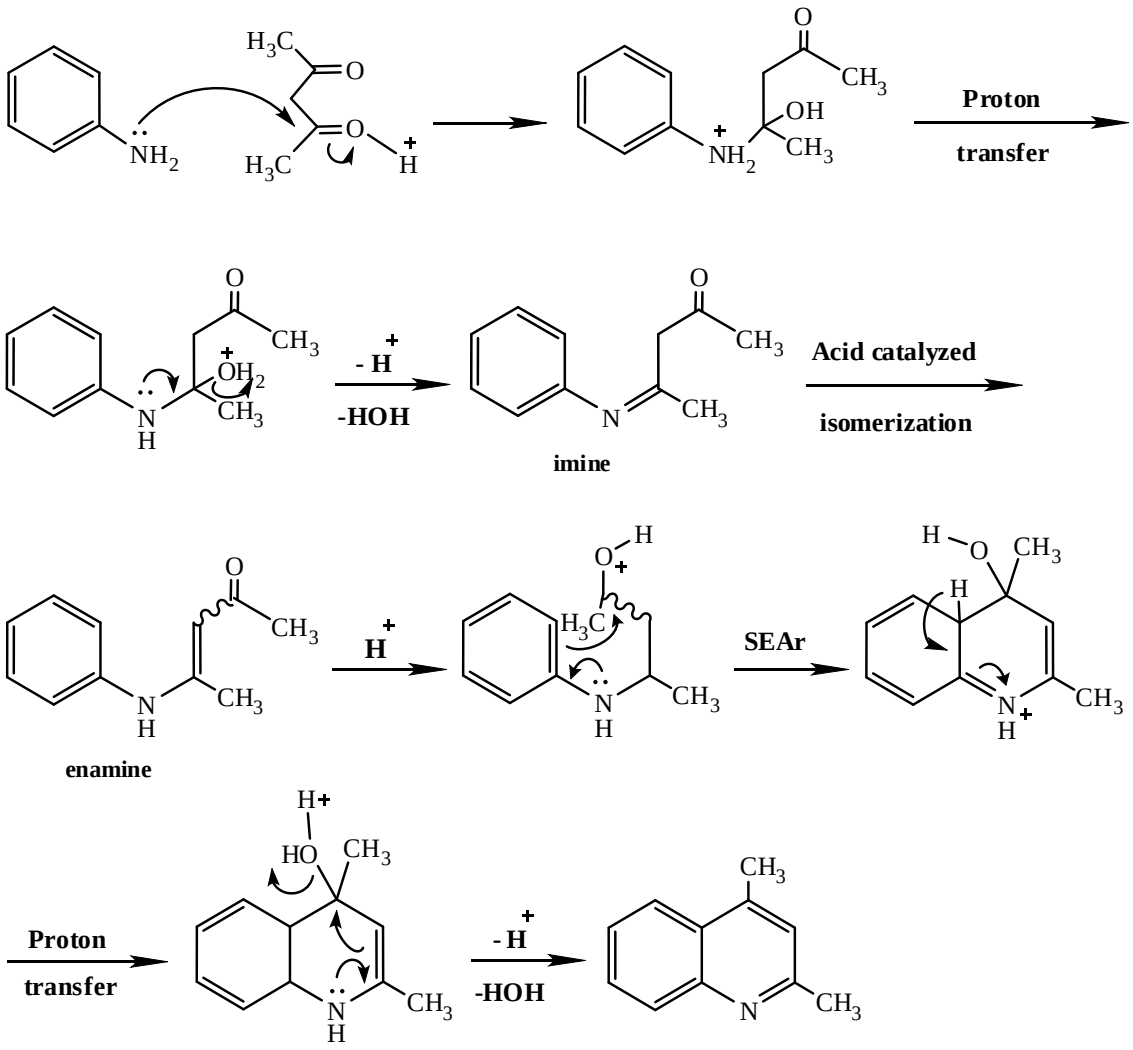
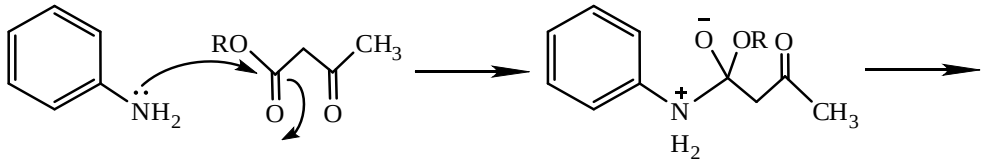


Figure (3.8): Reaction mechanism of quinoline from Combes synthesis.

3.2.3. Quinoline from Knorr synthesis:

4-methyl-2-hydroxyquinoline was prepared from an aromatic amine and ethyl acetoacetate with heating above 100 °C, mechanism of this reaction involves reaction of anilinic nitrogen with ester group of the ethylacetoacetate, to provide the anilide. The latter carried on directly upon warming in presence of acid to form acetanilide, which cyclises with subsequent loss of water to target molecule.



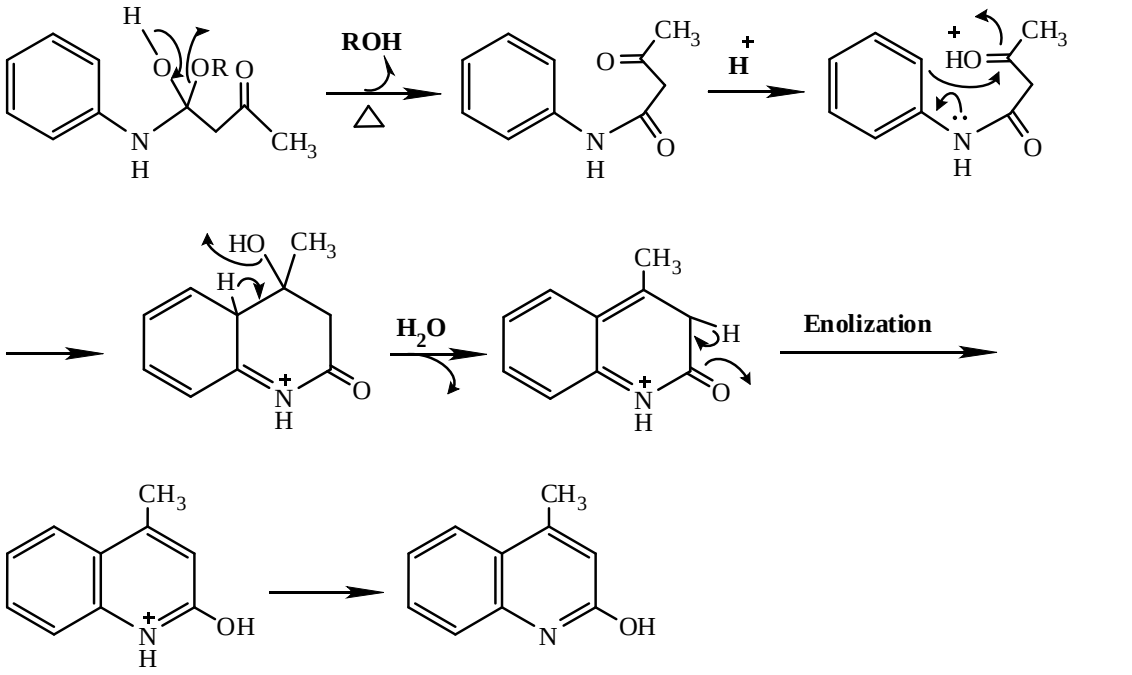
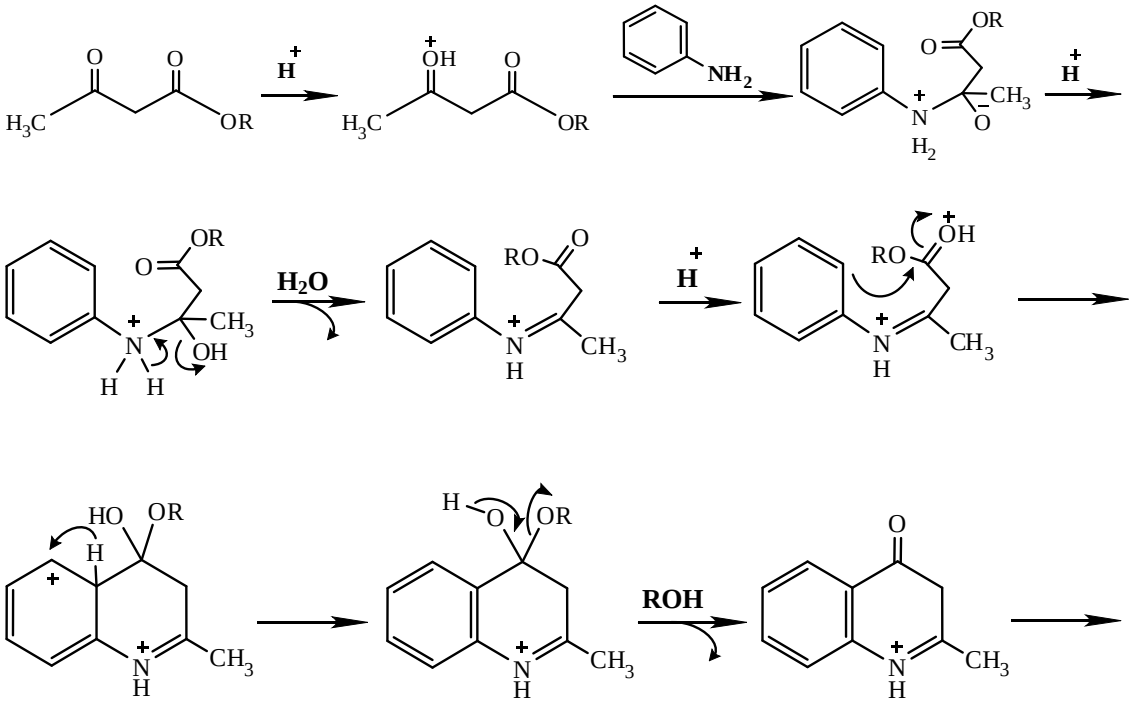


Figure (3.9): Reaction mechanism of quinoline from Knorr synthesis.

3.2.4. Quinoline from Conrad-Limpach cyclization:

2-methyl-4-hydroxyquinoline was prepared from an aromatic amine and ethyl acetoacetat, mechanism of this reaction involves a thermal condensation of aromatic amine with carbonyl group of ethylacetoacetate, followed by cyclization to target molecule.



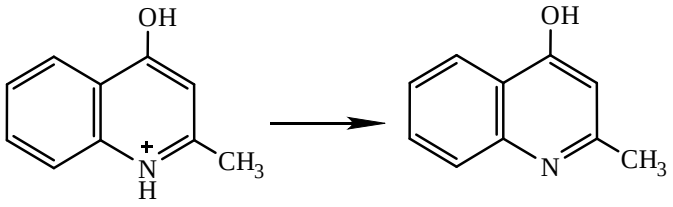


Figure (3.10): Reaction mechanism of quinoline from Conrad-Limpach cyclization.

3.2.5. Chalcone from Claisen-Schmidt condensation:

The prepared chalcones in this study was obtained via Claisen-Schmidt condensation carried out in basic media, in this mechanism the first step is aldol condensation, involving nucleophilic addition of carbanion derived from the keto group attached to quinoline ring, to carbonyl carbon of the aromatic aldehydes. Dehydration of the hydroxy ketones to form chalcones (Yerr et al, 2004).

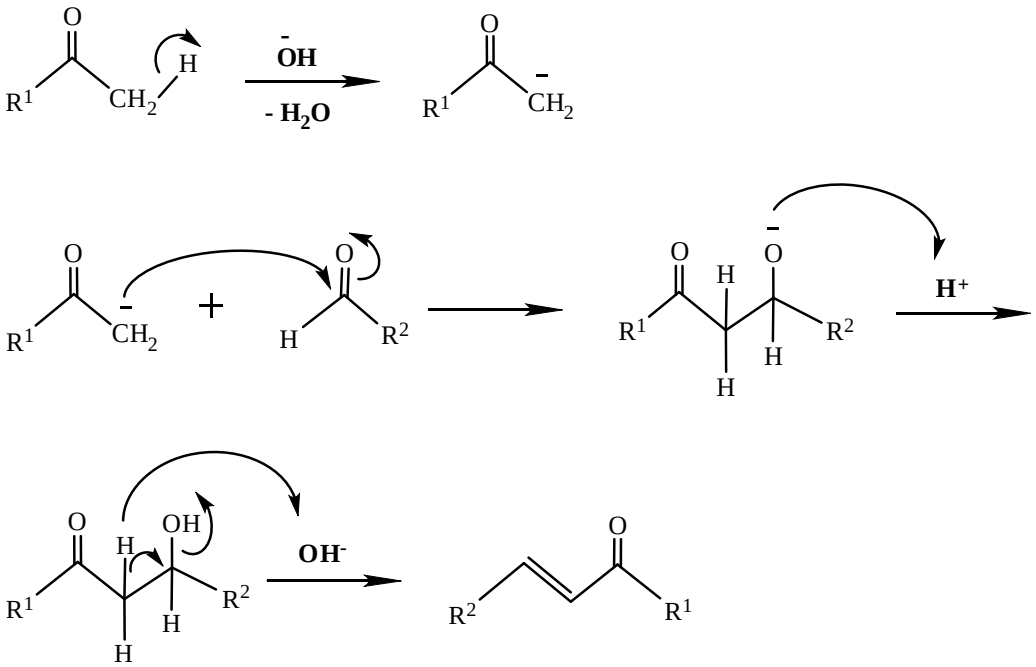


Figure (3.11): Reaction mechanism of chalcones formation.

3.2.6. Isoxazole from cyclization reaction:

The prepared isoxazole derivatives in this study, were prepared by cyclization reaction of chalcones with hydroxylamine hydrochloride in presence of basic catalys, the reaction mechanism is shown below:

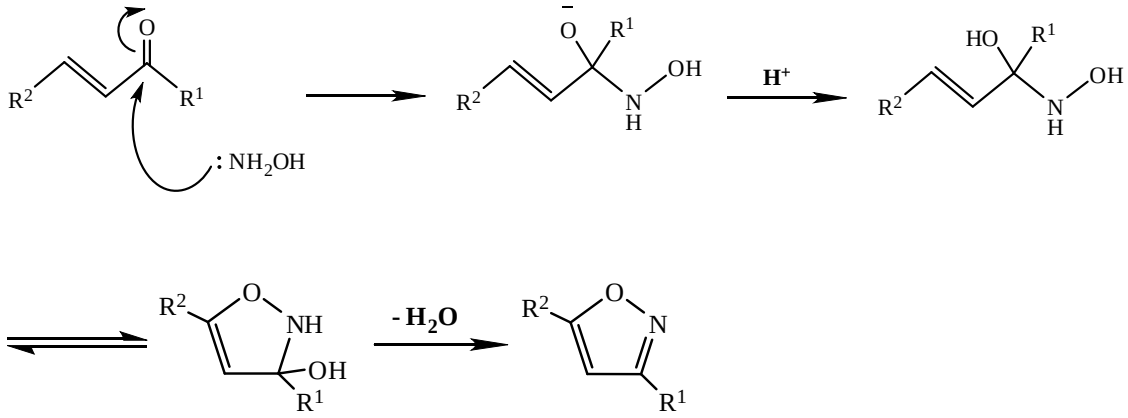


Figure (3.12): Reaction mechanism of isoxazoles formation.

3.3. Spectral characterization:

The chemical structures of the prepared compounds in this study were confirmed using spectroscopic analysis techniques. Infrared spectroscopy is one of the most common spectroscopic techniques, it is used to determine the chemical functional groups in the sample, infrared spectra of prepared compounds have been scanned in KBr pellets by using FT-IR 8400s instrument.

Compounds (**I, II, XXI, XXII, XXIII**) showed the bands of aromatic $C=C_{st.vib}$ which were observed at (1452.30-1600.00cm^{-1}), the band of $C\text{-}N_{st.vib}$ observed at (1365.51-1369.37cm^{-1}), compounds (**I and II**) showed two bands of $C=O_{st.vib}$ for each of them at (1660.00, 1679.88cm^{-1}) and (1672.17, 1687.60cm^{-1}) respectively, bands at (1681.81-1704.96cm^{-1}) observed for $C=O_{st.vib}$ group of carboxylic acid for compounds (**XXI, XXII, XXIII**) which were contain also -NH group, so were observed the absorption band at (3311.55, 3280.00cm^{-1}) for $–NH_2$ for compound (**XXI)**, (3259.47, and 3303.83cm^{-1}) for –NH for compounds (**XXII** and **XXIII)** respectively, also showed two band of $SO_{2st.vib}$ at [(1311.50_{asym}, 1159.14_{sym}), (1313.43_{asym},1172.64_{sym}), and (1311.50_{asym}, 1157.21_{sym})] respectively, the band at range (3000.00-3437.50cm^{-1}) and (3187.50-3437.50cm^{-1}) observed for $–OH_{st.vib}$ for compounds (**I and II**) respectively, compound (**II**) also showed $C\text{-}O_{st.vib}$ band at (1271cm^{-1}), compound (**XXII**) showed absorption band for $N\text{-}O_{st.vib}$ at (929.63$cm^{-1)}$ for isoxazole ring, compound (**XXIII**) showed absorption band for aromatic $C\text{-}H_{st.vib}$ at (3008.75cm^{-1}). Table (2.3.1).

Compounds (**III, IV, V, VI, VII, VIII, IX, X, XI**) showed bands of aromatic $C=C_{st.vib}$ which were observed at (1450.00-1577.66cm^{-1}), the band of olefin $C=C_{st.vib}$

observed at (1512.09-1600.81cm^{-1}), band at (1363.58-1371.29cm^{-1}) observed for C-$N_{st.vib}$, all compounds showed two bands for C=$O_{st.vib}$ the first one at (1647.10-1660.60cm^{-1}) and the second one at (1668.31-1683.74cm^{-1}), C-$O_{st.vib}$ band observed at (1215.07-1288.43cm^{-1}), compound (**V**) showed band at (3028.03cm^{-1}) for C-$H_{st.vib}$. Table (2.3.2).

Compounds(**XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX**) showed bands of aromatic C=$C_{st.vib}$ which were observed at (1446.51-1602.74cm^{-1}), bands at (1363.58-1369.37cm^{-1}) observed for C-$N_{st.vib}$, bands of C-$O_{st.vib}$ observed at (1200.00 - 1286.43cm^{-1}), band at (1668.38- 1689.53cm^{-1}) observed for C=$O_{st.vib}$ group of carboxylic acid, band of N-$O_{st.vib}$ for isoxazole ring observed at range (931.55-933.48cm^{-1}), compounds (**XII, XIII, and XX**) showed band of bonded –$OH_{st.vib}$ at range (2500.00-3400.00cm^{-1}), (2800.00-3520.00cm^{-1}) and (2560.00-3520.00cm^{-1}) respectively, compound (**XIV and XVIII**) observed band at (1598.88 and 1598.88cm^{-1}) respectively indicated to olefin C=$C_{st.vib}$. Table (2.3.3).

Compounds (**XXIV, XXV, XXVI**) showed bands of aromatic C=$C_{st.vib}$ which were observed at (1515.94-1629.74cm^{-1}), compounds showed two bands for –$NH_{2st.vib}$ the first one at (3319.26-3375.20cm^{-1}) the second one at (3240.19-3274.90cm^{-1}), the two band of $SO_{2st.vib}$ observed at [(1330.79$_{asym}$, 1151.42$_{sym}$), (1313.43$_{asym}$, 1149.50$_{sym}$), and (1309.58$_{asym}$, 1153.35$_{sym}$)] respectively, compound (**XXIV**) showed band at (3126.40cm^{-1}) indicated to C-$H_{st.vib}$. Table (2.3.4).

The information about different types and numbers of protons present in compounds and the environment about the protons were elucidated by ^{1}H nuclear magnetic resonance (^{1}H-NMR) technique, the results were reported on δ value (ppm) scale with the signals appear to the left of TMS.

Compound (**I**) showed (m, 1H_a, 1H_b) and (s, 1H_c) for three protons of quinoline ring at δ (7.86-7.92) and (10.73ppm) respectively, (m, 8H) for eight protons of aromatic rings which linked at position two and three in quinoline ring at δ (7.08-7.44ppm), (1H_j, 1H_k) in the aromatic ring at position two in quinoline ring observed as doublet signal at δ (7.76ppm), the last signal was (s, 3H) for three protons of acetyl group at δ(2.50ppm).

Compound (**II**) showed multiplied at δ (6.90-7.77ppm) which indicated to (1H_a, 1H_b) for two protons of quinoline ring, two protons of furyl ring and five protons of

aromatic ring which linked at position two and three in quinoline ring, (s, $1H_c$) for proton of quinoline ring observed at δ (7.95ppm), triplet signal at δ (6.18ppm) observed for ($1H_k$) proton of furyl ring, the last signal was (s, 3H) for three protons of acetyl group at δ (2.57ppm).

Compound (**XXI**) showed (m, $1H_a$, $1H_b$) and (s, $1H_c$) for three protons of quinoline ring at δ (7.89-7.92) and (10.75ppm) respectively, (m, 10H) at δ (7.09-7.44ppm) indicated to eight protons of two aromatic ring which linked at position two and three in quinoline ring, and two protons of SO_2NH_2 group, ($1H_j$, $1H_k$) in aromatic ring at position two in quinoline ring observed as doublet signal at δ (7.75ppm).

Compound (**XXII**) showed multiplied at δ (7.73-7.79ppm) which indicated to ($1H_a$, $1H_c$) for two protons of quinoline ring, and ($1H_j$, $1H_k$) for two protons of aromatic ring at position two in quinoline ring, (d, $1H_b$) for one proton in quinoline ring showed at δ (7.92ppm), (m, 8H) for eight protons of two aromatic ring which linked in position two and three in quinoline ring at δ (7.09-7.43ppm), four singlet signals observed, the first one at δ (10.76ppm) indicated to $HNSO_2$ group, the second one at δ (6.62ppm) for one proton in C_4 in isoxazole ring, the third one at δ (2.29ppm) indicated to three protons of methyl group at C_5 in isoxazole ring, the last one at δ (11.36ppm) indicated to hydroxyl proton of carboxylic acid group at position four in quinoline ring.

Compound (**XXIII**) showed (s,$1H_c$) for one proton of quinoline ring at δ (8.10ppm), multiplied for eight protons of aromatic rings which linked at position two and three in quinoline ring, and two protons of quinoline ring at δ (7.09-7.43ppm), ($1H_j$, $1H_k$) two protons of aromatic ring at position two in quinoline ring observed as doublet signal at δ (7.73ppm), five singlet signals observed, the first one at δ (10.75ppm) indicated to $HNSO_2$ group, the second and third one at δ (3.65ppm) and (3.90ppm) indicated to three protons of methoxy group at C_5 and C_6 respectively in pyrimidine ring, the fourth one observed at δ (7.92ppm) indicated to only proton in pyrimidine ring, the last one observed at δ (11.09ppm) indicated to hydroxyl proton of carboxylic acid group at position four in quinoline ring. Table (2.4.1).

Compound (**III**) showed multiplied at δ (7.81-7.96ppm) which indicated to ($1H_a$, $1H_b$) for two protons of quinoline ring and ($1H_j$, $1H_k$) for two protons of aromatic ring at position two in quinoline ring, (s, $1H_c$) for one proton of quinoline ring at δ (8.12ppm), (m, 14H) indicated to eight protons of aromatic rings which linked at

position two and three in quinoline ring, five protons of aromatic ring which linked with propen-2-one, and ($1H_{\alpha}$) at δ (7.08-7.47ppm), ($1H_{\beta}$) observed as doublet signal at δ (7.69ppm).

Compound (**IV**) showed multiplied at δ (7.77-7.93ppm) which indicated to ($1H_a$, $1H_b$) for two protons of quinoline ring, ($1H_j$, $1H_k$) for two protons of aromatic ring at position two in quinoline ring, and one proton at C_5 in furyl ring, (s, $1H_c$) for one proton of quinoline ring at δ (8.02ppm), (m, 11H) indicated to eight protons of aromatic rings which linked at position two and three in quinoline ring, ($1H_{\alpha}$, $1H_{\beta}$), and ($1H_r$) in furyl ring which linked with propen-2-one at δ (7.09-7.52ppm), (t, $1H_q$) for proton of furyl ring which linked with propen-2-one observed at δ (6.68ppm).

Compound (**V**) showed multiplied at δ (7.77-7.96ppm) which indicated to ($1H_a$, $1H_b$) for two protons of quinoline ring, ($1H_j$, $1H_k$) for two protons of aromatic ring at position two in quinoline ring, (s, $1H_c$) for one proton of quinoline ring at δ (9.52ppm), (m, 17H) indicated to eight protons of aromatic ring which linked at position two and three in quinoline ring, ($2H_{\alpha}$, $2H_{\beta}$), five protons of aromatic ring which linked with propen-2-one observed at δ (7.08-7.61ppm).

Compound (**VI**) showed (d, $1H_a$), (d, $1H_b$), and (s, $1H_c$) for three protons of quinoline ring at δ (7.91ppm), (7.86ppm), and (8.04ppm) respectively, (m, 9H) indicated to eight protons of aromatic rings which linked at position two and three in quinoline ring, and ($1H_{\alpha}$) observed at δ (7.17-7.47ppm), ($1H_j$, $1H_k$) in the aromatic ring at position two in quinoline ring observed as doublet signal at δ (7.69ppm), ($1H_{\beta}$) observed as doublet signal at δ (7.63ppm), (d, $1H_p$), (m, $1H_q$, $1H_r$), and (s, $1H_s$) of four protons in aromatic ring which linked with propen-2-one observed at δ (6.75ppm), (7.06ppm), and (6.73ppm) respectively, singlet signal at δ (3.05ppm) observed for six protons of two methyl group which linked with nitrogen atom.

Compound (**VII**) showed (m, $1H_a$, $1H_b$), and (s, $1H_c$) for three protons of quinoline ring at δ (7.69-7.82ppm), and (8.03ppm) respectively, (m, 14H) indicated to five protons of aromatic ring and two protons of furyl ring which linked at position three and two in quinoline ring, ($1H_{\alpha}$, $1H_{\beta}$), and five protons of aromatic ring which linked with propen-2-one observed at δ (7.36-7.42ppm), (t, $1H_k$) for one proton of furyl ring observed at δ (6.20ppm).

Compound (**VIII**) showed (m, 14H) indicated to three protons of quinoline ring, five protons of aromatic ring and two protons of furyl ring which linked at position three and two in quinoline ring, ($1H_{\alpha}$, $1H_{\beta}$), and two protons of furyl ring which linked with propen-2-one observed at δ (7.50-7.88ppm), multiplied signal at δ (6.49-6.68ppm) observed for ($1H_k$) and ($1H_o$) for furyl ring which linked at position two in quinoline ring, and furyl ring which linked with propen-2-one.

Compound (**IX**) showed (d, $1H_a$), (d, $1H_b$), and (s, $1H_c$) for three protons of quinoline ring at δ (7.79ppm), (7.69ppm), and (7.98ppm) respectively, (m, 16H) indicated to five protons of aromatic ring and three protons of furyl ring which linked at position three and two in quinoline ring, ($1H_{\alpha}$, $1H_{\beta}$), five protons of aromatic ring which linked with propen-2-one, and ($1H_o$) observed at δ (7.01-7.49ppm), ($1H_n$) observed as doublet signal at δ (6.20ppm).

Compound (**X**) showed (s, $1H_c$) which observed for one proton of quinoline ring at δ (9.74ppm), (m, 14H) which indicated to ($1H_a$, $1H_b$) for two protons of quinoline ring, five protons of aromatic ring and three protons of furyl ring which linked at position three and two in quinoline ring, ($1H_{\alpha}$, $1H_{\beta}$), and ($1H_o$, $1H_p$) two protons of aromatic ring which linked with propen-2-one observed at δ (7.53-7.98ppm), (d, $1H_n$) and (s, $1H_q$) for two protons of aromatic ring which linked with propen-2-one observed at δ (6.70ppm) and (6.16ppm) respectively, singlet signal observed at δ (3.09ppm) for six protons of two methyl group which linked with nitrogen atom.

Compound (**XI**) showed (d, $1H_a$) and (s, $1H_c$) for two protons of quinoline ring at δ (7.95ppm) and (8.01ppm) respectively, ($1H_b$) of quinoline ring and ($1H_m$) for H_{β} observed as multiplied signal at δ (7.75-7.80ppm), another multiplied signal observed at δ (7.34-7.69ppm) which indicated to five protons of aromatic ring and three protons of furyl ring which linked at position three and two in quinoline ring, ($1H_{\alpha}$), and ($1H_n$, $1H_o$, $1H_r$) three protons of aromatic ring which linked with propen-2-one, ($1H_p$) for aromatic ring which linked with proppen-2-one observed as doublet signal at δ (6.20ppm). Table (2.4.2).

Compound (**XII**) showed multiplied at δ (7.41-7.66ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, ten protons of aromatic ring which linked at position two and three in quinoline ring, and five protons of aromatic ring which linked at position five in isoxazole ring, the third proton in quinoline ring ($1H_c$) observed at δ

(8.01ppm) as singlet signal, ($1H_n$) the only proton in isoxazole ring showed at δ (6.00ppm) as singlet signal.

Compound (**XIII**) showed multiplied at δ (7.17-7.72ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, ten protons of aromatic ring which linked at position two and three in quinoline ring, and three protons of furyl ring which linked at position five in isoxazole ring, (s, $1H_c$) for proton of quinoline ring observed at δ (7.96ppm), ($1H_n$) the only proton in isoxazole ring showed at δ (6.01ppm) as singlet signal.

Compound (**XIV**) showed multiplied at δ (7.31-7.70ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, ten protons of aromatic rings which linked at position two and three in quinoline ring, and five protons of aromatic ring which linked with ethylene group, (s, $1H_c$) for proton of quinoline ring observed at δ (7.92ppm), two protons of ethylene group which linked at position five in isoxazole ring observed at δ (7.00ppm) as quartet signal, ($1H_n$) the only proton in isoxazole ring showed at δ (6.01ppm) as singlet signal.

Compound (**XV**) showed multiplied at δ (7.16-7.76ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, ten protons of aromatic ring which linked at position two and three in quinoline ring, and three protons of aromatic ring which linked at position five in isoxazole ring, (s, $1H_c$) for proton of quinoline ring observed at δ (7.94ppm), (d, $1H_o$) for proton of aromatic ring which linked at position five in isoxazole ring, observed at δ (6.68ppm), two singlet signals observed the first one at δ (3.04ppm) for six protons of two methyl group which linked with nitrogen atom, the second signal at δ (6.01ppm) for ($1H_n$) the only proton in isoxazole ring.

Compound (**XVI**) showed multiplied at δ (7.35-7.80ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, two protons of furyl ring which linked at position two in quinoline ring, five protons of aromatic ring which linked at position three in quinoline ring, and five protons of aromatic ring which linked at position five in isoxazole ring, (s, $1H_c$) for proton of quinoline ring observed at δ (8.03ppm), multiplied signal observed at δ (6.00-6.30ppm) indicated for ($1H_k$, $1H_l$) protons of furyl ring which linked at position two in quinoline ring, and the only proton in isoxazole ring.

Compound (**XVII**) showed multiplied at δ (7.36-7.80ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, three protons of furyl ring which linked at position two in quinoline ring, five protons of aromatic ring which linked at position three in quinoline ring, and two protons of furyl ring which linked at position five in isoxazole ring, (s, $1H_c$) for proton of quinoline ring observed at δ (8.05ppm), ($1H_n$, $1H_l$) proton of furyl ring which linked at position five in isoxazole ring and the only proton in isoxazole ring showed at δ (6.19-6.72ppm) as multiplied signal.

Compound (**XVIII**) showed (d, $1H_a$), (d, $1H_b$), and (s, $1H_c$) for three protons of quinoline ring at δ (7.69ppm), (7.78ppm), and (7.98ppm) respectively, (m, 12H) indicated to five protons of aromatic ring, and two protons of furyl ring which linked at position three and two in quinoline ring, and five protons of aromatic ring which linked with ethylene group observed at δ (7.29-7.51ppm), another multiplied signal at δ (7.01-7.09ppm) observed for ($1H_k$) proton of furyl ring which linked at position two in quinoline ring and ($1H_\alpha$, $1H_\beta$), ($1H_l$) the only proton in isoxazole ring showed at δ (6.19ppm) as singlet signal.

Compound (**XIX**) showed (d, $1H_a$), (d, $1H_b$), and (s, $1H_c$) for three protons of quinoline ring at δ (7.69ppm), (7.75ppm), and (8.01ppm) respectively, (m, 8H) indicated to five protons of aromatic ring, ($1H_i$) proton of furyl ring which linked at position three and two in quinoline ring, and ($1H_n$, $1H_o$) two protons of aromatic ring which linked at position five in isoxazole ring observed at δ (7.32-7.40ppm), another multiplied signal at δ (6.50-6.70ppm) observed for ($1H_k$) proton of furyl ring which linked at position two in quinoline ring and ($1H_m$, $1H_p$) two protons of aromatic ring which linked at position five in isoxazole ring, two singlet signals observed the first one at δ (3.05ppm) for six protons of two methyl group which linked with nitrogen atom, the second signal at δ (6.19ppm) for ($1H_l$) the only proton in isoxazole ring.

Compound (**XX**) showed multiplied at δ (7.35-7.79ppm) which indicated to ($1H_a$, $1H_b$) two protons of quinoline ring, five protons of aromatic ring and two protons of furyl ring which linked at position three and two in quinoline ring, and ($1H_q$) proton of aromatic ring which linked at position five in isoxazole ring, (s, $1H_c$) for protons of quinoline ring observed at δ (8.03ppm), another multiplied signal at δ (6.82-6.93ppm) observed for ($1H_k$) proton of furyl ring which linked at position two in quinoline ring, and ($1H_m$, $1H_o$) two protons of aromatic ring which linked at position five in isoxazole

ring, triplet signal at δ (6.97ppm) observed for ($1H_n$) proton of aromatic ring which linked at position five in isoxazole ring, two singlet signals observed the first one at δ (8.22ppm) for ($1H_p$) proton of hydroxyl group, the second signal at δ (6.19ppm) for ($1H_l$) the only proton in isoxazole ring.Table (2.4.3).

Compound (**XXIV**) showed (m, $2H_{a,b}$), (s, $1H_c$), and (s, $1H_d$) for four proton of quinoline ring at δ (7.36ppm), (7.79ppm), and (5.35ppm) respectively, three singlet signals observed the first one at δ (6.91ppm) for two proton of SO_2NH_2 group, the second signal at δ (2.14ppm), and third signal at δ (2.04ppm) for six protons of two methyl group in C_4 and C_2 in quinoline ring.

Compound (**XX**V) showed (d, $2H_{a,b}$), (s, $1H_c$), and (s, $1H_d$) for four protons of quinoline ring at δ (6.58ppm), (7.44ppm), and (5.82ppm) respectively, two singlet signals the first one at δ (6.90ppm) for two protons of SO_2NH_2 group, and the second one at δ (2.51ppm) for three protons of methyl group at C_4 in quinoline ring.

Compound (**XXVI**) showed (m, $2H_{a,b}$), (s, $1H_c$), and (s, $1H_d$) for four protons of quinoline ring at δ (6.06-6.58ppm), (7.46ppm), and (5.82ppm) respectively, two singlet signals the first one at δ (2.51ppm) observed for three protons of methyl group at C_2 in quinoline ring, and the second one at δ (6.91ppm)for two protons of SO_2NH_2 group. Table (2.4.4).

Carbon spectra of ^{13}C nuclear magnetic resonance (^{13}C-NMR) technique, can be used to determine the number of non-equivalent carbons and to identify the types of carbon atoms that may be present in a compound, the results were reported on δ value (ppm) scale with signals appear to the left of TMS.

Compound (**II**) showed peak at δ (26.49ppm) for carbon of acetyl group, peak at δ (115.00ppm) for (C_a) of aromatic ring which linked at position three in quinoline ring, peak at δ (121.00ppm) for (CH_d) of furyl ring which linked at position two in quinoline ring, peaks at δ (126.97-128.99ppm) observed for (CH_a, CH_b, CH_d, C_e) for carbons of quinoline ring, and (CH_b, CH_c, CH_d, CH_e, CH_f) for carbons of aromatic ring which linked at position three in quinoline ring, peaks of (C_c, C_f, C_g, C_i) for carbons of quinoline ring observed at δ (129.00-132.00ppm), peak of (CH_a) for furyl ring which linked at position two in quinoline ring observed at δ (139.00ppm), peak at δ (142.95ppm) observed for (CH_c) of furyl ring which linked at position two in quinoline

ring, peaks of (C_h) and (C_i) for quinoline ring observed at δ (148.74ppm) and (143.11ppm) respectively, carbon of carboxylic acid group (C_a) observed at δ (165.52ppm), and carbon of C=O observed at δ (196.66ppm). Table (2.5.1).

Compound (**VIII**) showed peaks at δ (123.33ppm) observed for (CH_β) peaks at δ (124.5o-132.00ppm) observed for (C_c, C_e, C_f, C_h, C_i) of carbons of quinoline ring, peaks at δ (127.43-129.83ppm) observed for (CH_a, CH_b, CH_d) for carbons of quinoline ring, (CH_α), and (CH_b, CH_c, CH_d, CH_e, CH_f) for carbons of aromatic ring which linked at position three in quinoline ring, (C_a) of aromatic ring which linked at position three in quinoline ring observed at δ (130.00ppm), (C_g) of quinoline ring observed at δ (132.93ppm), (CH_g), (CH_a, CH_d, CH_f), (CH_c), (C_h), (C_b), and (CH_e) of two furyl rings which linked at position two in quinoline ring and with propen-2-one observed at (134.00ppm), (136.00-139.00ppm), (142.16ppm), (143.00ppm), (144.00ppm), and (145.00ppm) respectively, carbon of C=O observed at δ (186.95ppm), and carbon of carboxylic acid group (C_a) observed at δ (188.00ppm).

Compound (**IX**) showed peaks at δ (119.00ppm) and (191.80ppm) for (C_a) and (C_j) of two aromatic rings which linked at position three in quinoline ring and linked with propen-2-one respectively, peaks at δ (123.00-124.95ppm) observed for (C_f), (C_h), (CH_d) and (C_e) for carbons of quinoline ring, and for (CH_d, CH_e) of ethylene group, (CH_b) at δ (125.43ppm), (C_g) at δ (132.57ppm), (C_c) at δ (136.04ppm), and (C_i) at δ (142.45ppm) observed for carbons of quinoline ring, (CH_a) at δ (138.00ppm), (CH_d) at δ (139.00ppm), (CH_c) at δ (141.35ppm), and (C_b) at δ (142.00ppm) observed for carbons of furyl ring which linked at posion two in quinoline ring, peaks at δ (127.20-129.15ppm) observed for (CH_b, CH_c, CH_d, CH_e, CH_f, CH_g, CH_h, CH_i, CH_k, CH_l) five carbons of aromatic ring which linked at position three in quinoline ring, and five carbons of aromatic ring which linked with propen-2-one, (CH_a) for carbon of quinoline ring, and (CH_α, CH_β), and carbon of C=O observed at δ (187.00ppm).

Compoud (**X**) showed peak at δ (40.09ppm) for two carbons of two methyl group which linked with nitrogen atom, (CH_a) at δ (109.65ppm), (CH_d) at δ (137.00ppm), (CH_c) at δ (141.91ppm), and (C_b) at δ (143.00ppm) observed for carbons of furyl ring which linked at position two in quinoline ring, (CH_g) at δ (111.71ppm), (CH_i) at δ (115.00ppm), (CH_k) at δ (138.00ppm), and (C_l) at δ (151.87ppm) observed for carbons of aromatic ring which linked with propen-2- one, (CH_α) observed at δ (122.00ppm),

peak at δ (121.00-122.12ppm) observed for (C_e) in quinoline ring and (C_a), (C_j) for two aromatic ring which linked at position three in quinoline ring and linked with propen-2-one, (CH_h), (CH_g), (C_c) and (C_f) of quinoline ring observed at δ (123.00ppm), (124.00ppm), and (132.82ppm) respectively, peaks at δ (127.43-128.87ppm) observed for (CH_a), (CH_b), and (CH_d) for carbons of quinoline ring, (CH_b), (CH_c), (CH_d), (CH_e), (CH_f) five carbons of aromatic ring which linked at position three in quinoline ring, and (CH_h) carbon of aromatic ring which linked with propen-2-one, (C_i) of quinoline ring and (CH_β) observed at δ (144.41ppm), and carbon of C=O observed at δ (189.85ppm).

Compound (**XI**) showed peaks of (CH_a) at δ (110.26ppm), (CH_d) at δ (110.76ppm), (C_b) at δ (141.00ppm), and (CH_c) at δ (142.67ppm) for furyl ring which linked at position two in quinoline ring, (CH_l) for aromatic ring which linked with propen-2-one, and (CH_α) observed at δ (119.84ppm) and (119.94ppm) respectively, peaks at δ (115.00-121.00ppm) observed for (C_a), (CH_g), (CH_h), (C_i), and (C_j) carbons of two aromatic ring which linked at position three in quinoline ring and linked with propen-2-one, peaks at δ (123.00-129.13ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h), and (C_i) for carbons of quinoline ring, (CH_b), (CH_c), (CH_d), (CH_e), and (CH_f) five carbons of aromatic ring which linked at position three in quinoline ring, and (CH_g), (CH_k) two carbons of aromatic ring which linked with propen-2-one, (CH_β) observed at δ (142.00ppm), and carbon of C=O observed at δ (196.66ppm). Table (2.5.2).

Compound (**XIII**) showed peak of (CH_b) at δ (113.08ppm), (CH_c) at δ (114.00ppm), (CH_a) at δ (141.12ppm), and (C_d) at δ (143.15ppm) for carbons of furyl ring which linked at position five in isoxazole ring, peaks of (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_h), (C_i) of quinoline ring and (CH_a), (C_b), (CH_c), (CH_d), (CH_e), (CH_f), (CH_h), (CH_i), (CH_j), (CH_k) and (CH_l) carbons of aromatic ring which linked at position two and three in quinoline ring observed at δ (123.27-131.50ppm), (C_g) of quinoline ring observed at δ (132.90ppm), (C_g) for aromatic ring which linked at position three in quinoline ring observed at δ (137.40ppm), (CH_b), (C_c), and(C_a) for isoxazole ring observed at δ (146.06ppm), (149.00ppm), and (151.18ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (166.14ppm).

Compound (**XIV**) showed peaks at δ (123.53-133.08ppm) for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h), (C_i) for carbons of quinoline ring, and (CH_a), (C_b), (CH_c),

(CH_d), (CH_e), (CH_f), (CH_h), (CH_i), (CH_j), (CH_k), (CH_l), (CH_m), (CH_n), (CH_o), (CH_q), and (CH_r) for carbons of aromatic ring which linked at positon two and three in quinoline ring, and aromatic ring which linked with ethylene group, (CH_α, CH_β), (C_c) for quinoline ring, (C_g) for aromatic ring which linked at position three in quinoline ring, and (C_p) for aromatic ring which linked with ethylene group observed at δ (135.99-137.30ppm), (CH_b), (C_c), and (C_a) for isoxazole ring observed at δ (140.98ppm), (143.89ppm), and (150.00ppm) respectively.

Compound (**XV**) showed peak at δ (40.10ppm) for two carbons of two methyl group which linked with nitrogen atom, peaks of (CH_q) at δ (111.70ppm), (CH_m, CH_o) at δ (115.87ppm), peaks at δ (122.04-133.81ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h) carbons of quinoline ring, (CH_a), (C_b), (CH_c),(CH_d), (CH_e), (CH_f), (CH_h), (CH_i), (CH_j), (CH_k), (CH_l) carbons of aromatic ring which linked at position two and three in quinoline ring, and (CH_n), (C_p) carbons of aromatic ring which linked at position five in isoxazole ring, (C_g) of aromatic ring which linked at position three in quinoline ring, and (C_r) of aromatic ring which linked at position five in isoxazole ring observed at δ (137.41ppm) and (140.00ppm) respectively,(C_i) of quinoline ring observed at δ (138.00ppm), (CH_b), (C_c), and (C_a) for isoxazole ring observed at δ (141.00ppm), (144.69ppm) and (151.90ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (165.88ppm).

Compound (**XVII**) showed peaks of (CH_a), (CH_g) at δ (110.37ppm), (CH_d), (CH_f) at δ (111.40ppm), (CH_e), (CH_c) at δ (140.95ppm), and (C_b), (C_h) at δ (143.12ppm) for furyl ring which linked at position two in quinoline ring, and furyl ring which linked at position five in isoxazole ring, peaks at δ (120.22-133.02ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h) for carbons of quinoline ring, and (C_a), (CH_b), (CH_c), (CH_d), (CH_e), (CH_f) for carbons of aromatic ring which linked at position three in quinoline ring, (C_i) of quinoline ring observed at δ (139.00ppm), (CH_b), (C_c), and(C_a) of isoxazole ring observed at δ (146.10ppm), (148.78ppm), (151.18ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (165.64ppm).

Compound (**XVIII**) showed peaks of (CH_a) at δ (110.38ppm), (CH_c) at δ (142.96ppm), and (CH_b) at δ (143.12ppm) for furyl ring which linked at position two in quinoline ring, (CH_α) and (CH_d) for furyl ring which linked at position two in quinoline ring observed at δ (111.43ppm), and (C_i) at δ (136.00ppm) observed for carbons of

quinoline ring, peaks at δ (120.22-133.17ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h) carbons of quinoline ring, (CH_b), (CH_c), (CH_d), (CH_e), and (CH_f) for carbons of aromatic ring which linked at position three in quinoline ring, and (CH_g), (CH_h), (CH_i), (CH_l), and (CH_k) for carbons of aromatic ring which linked at position five in isoxazole ring, (C_a) of aromatic ring which linked at position three in quinoline ring, and (C_j) of aromatic ring which linked at position five in quinoline ring observed at δ (140.86ppm) and (141.53ppm) respectively, (CH_β) observed at δ (146.75ppm), (CH_b), (C_c), and (C_a) of isoxazole ring observed at δ (143.95ppm), (149.00ppm), and (150.00ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (165.55ppm).

Compound (**XIX**) showed peak at δ (40.10ppm) for two carbons of two methyl group which linked at nitrogen atom, (CH_d) for furyl ring which linked at position two in quinoline ring, and (CH_k) for aromatic ring which linked at position five in isoxazole ring observed at δ (110.36ppm), (CH_g) at δ (111.34ppm), (CH_i) at δ (111.71ppm), (CH_l) at δ (144.74ppm) observed for carbons of aromatic ring which linked at position five in isoxazole ring, (CH_a), (CH_c), (C_b) carbons of furyl ring which linked at postion two in quinoline ring observed at δ (119.72ppm), (140.48ppm), and (141.00ppm) respectively, peaks at δ (122.05-133.92ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h) carbons for quinoline ring, (C_a), (CH_b), (CH_c), (CH_d), (CH_e), and (CH_f) for aromatic ring which linked at position three in quinoline ring, and (CH_h), (C_j) for aromatic ring which linked at position five in isoxazole ring, (C_i) at δ (139.00ppm) observed for quinoline ring, (CH_b), (C_c), and (C_a) of isoxazole ring observed at δ (147.00ppm), (148.86ppm), and (151.94ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (165.54ppm).

Compound (**XX**) showed peaks of (CH_a) at δ (110.34ppm), (CH_d) at δ (111.13ppm), (CH_c) at δ (142.98ppm), and (C_b) at δ (143.45ppm) for carbons of furyl ring which linked at position two in quinoline ring, (C_j), (CH_h), and (C_i) of aromatic ring which linked at position five in isoxazole ring observed at δ (116.26ppm), (118.84ppm), and (143.07ppm) respectively, peaks at δ (121.42-137.10ppm) observed for (CH_a), (CH_b), (C_c), (CH_d), (C_e), (C_f), (C_g), (C_h) carbons of quinoline ring, (CH_a), (CH_b), (CH_c), (CH_d), (CH_e) and (CH_f) for carbons of aromatic ring which linked at position three in quinoline ring, and (CH_g), (CH_k), (CH_l) of aromatic ring which linked at position five in isoxazole ring, (C_i) at δ (139.05ppm) observed for quinoline ring, (CH_b), (C_c), and

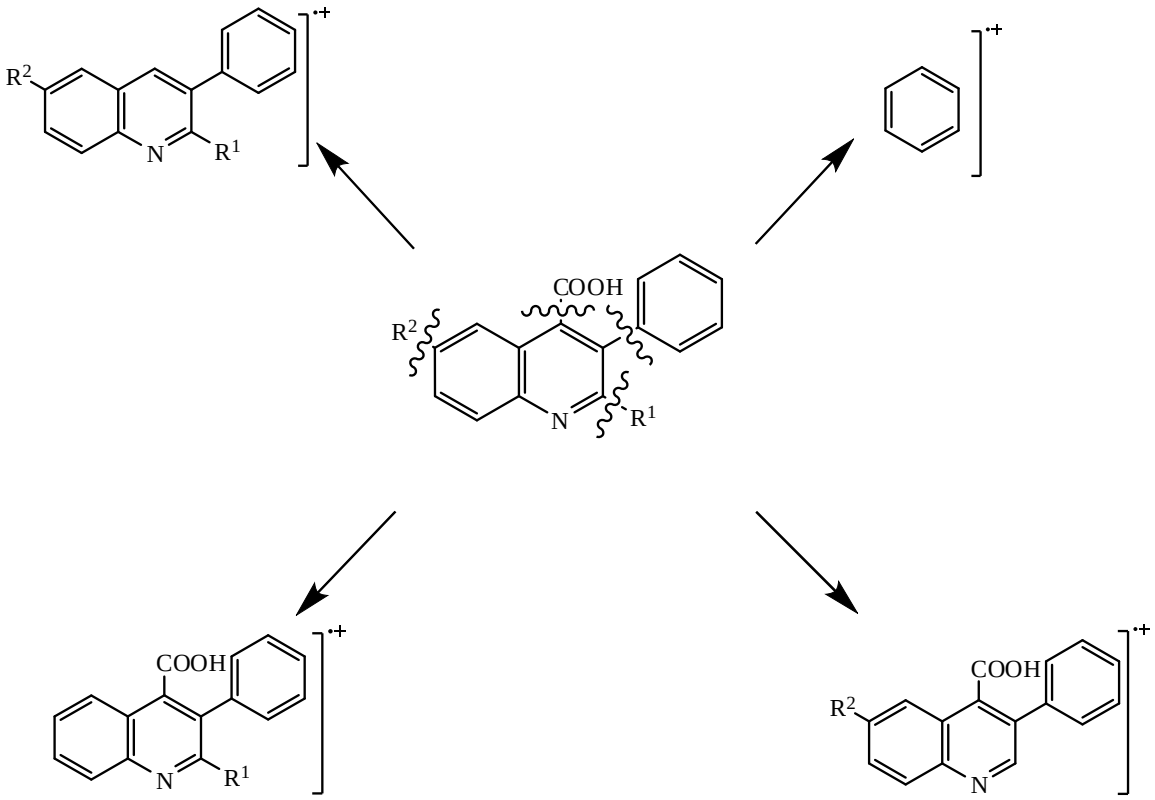
(C_a) of isoxazole ring observed at δ (148.00ppm), (149.00ppm), and (152.33ppm) respectively, and carbon of carboxylic acid group (C_a) observed at δ (165.37ppm). Table (2.5.3).

The technique of gas chromatography with its exceptional separation potential and mass spectrometry which provides unique structural determinations are ideally suited to be used in combination as an analytical technique (**GC-MS**).

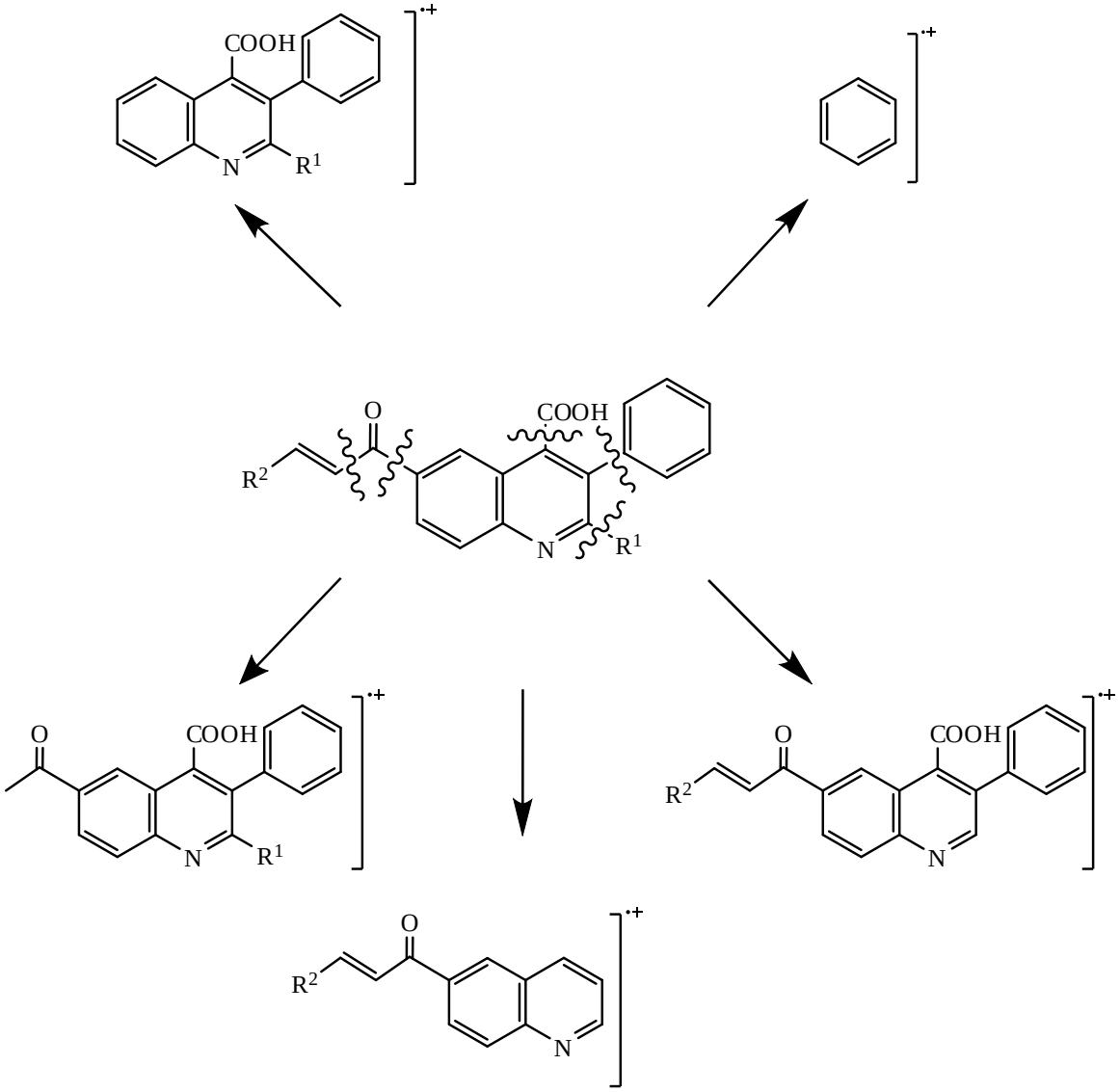
Compound in table (2.6.1) showed this MS spectral analysis, compound (**I**), (**XXI**), (**XXII**), and (**XXIII**) showed retention time (14.88, 17.56, 9.98, and 17.78min) respectively, and base peak at (292, 178m/z), and at (178m/z) for compound (**XXIII**). Scheme (3.1) showed general MS fragmentation of prepared 3-phenyl-quinoline derivatives in table (2.6.1).

Compound in table (2.6.2) showed this MS spectral analysis, compound (**III**), (**IV**), (**V**), and (**VI**) showed retention time (11.01, 21.02, 12.83, and 13.93min) respectively, and base peak at (301, 105, and 223m/z) for compound (**IV**), (**V**), and (**VI**) respectively. Scheme (3.2) showed general MS fragmentation of the prepared chalcones in table (2.6.2).

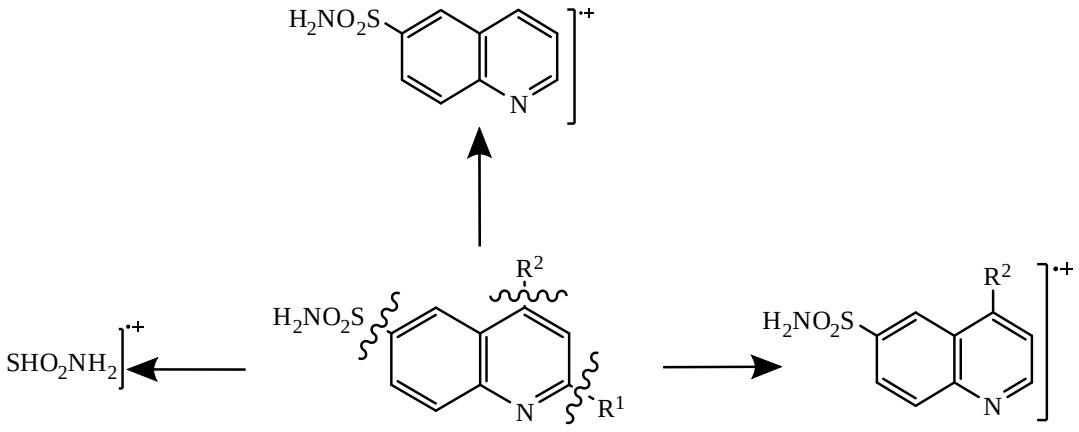
Compound in table (2.6.3) showed this MS spectral analysis, compound (**XXIV**), (**XXV**), and (**XXVI**) showed retention time (10.63, 4.14, and 10.74min) respectively, and base peak at (65, 183, and 172m/z) respectively. Scheme (3.3) showed general MS fragmentation of the prepared quinoline derivatives in table (2.6.3).



Scheme (3.1): General MS fragmentation of prepared 3-phenyl-quinoline derivatives.



Scheme (3.2): General MS fragmentation of the prepared chalcones.



Scheme (3.3): General MS fragmentation of the prepared quinoline derivatives.

Compounds (**I, II, XXI, XXII, and XXIII**) showed significant inhibition against *B.subtillis* followed by *P.vulgaris*. Compound (**II**) bearing acetyl group is more active against *E.coli*, while compound (**XXI**) bearing sulphonamide group is active against *B.subtillis*, *E.coli*, and *P.vulgaris* respectively, none of the 3-phenyl-quinoline derivatives compounds had activity against *Aspergillus niger* while compound (**II**) and (**XXI**) bearing acetyl and sulphonamide groups respectively showed activity against *Candida albicans*. Table (2.8.1).

Compounds (**III, IV, V, VI, VII, VIII, IX, X, XI**) showed significant inhibition against *S.aureus*. Compound (**XI**) bearing hydroxyphenyl group is more active against *B.subtillis*, *S.aureus*, and *P.vulgaris* respectively, none of the prepared chalcones had activity against *E.coli* and *Aspergillus niger* while compounds (**III, V, VI, VII, VIII, and XI**) bearing phenyl, 2-phenyl ethylene, 3-N,N-dimethyl amino phenyl, phenyl, furyl, and hydroxyphenyl groups showed activity against *Candida albicans* the most active one is compound (**XI**). Table (2.8.2).

Compounds (**XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX**) showed significant inhibition against *S.aureus* followed by *P.vulgaris.* Compounds (**XVI**) bearing phenyl group is more active against *S.aureus*, *P.vulgaris*, and *B.subtillis* respectively, compound (**XX**) bearing hydroxyphenyl group is more active against *P.vulgaris*, *E.coli* and *S.aureus* respectively, none of the prepared isoxazoles had activity against *Aspergillus niger* while compounds (**XII, XIII, XVI, XV, XVII**) bearing phenyl, furyl, 2-phenyl ethylene, 3-N,N-dimethyl amino phenyl, and furyl group showed activity against *Candida albicans* the most active one is compounds (**XIII**). Table (2.8.3).

Compounds (**XXIV, XXV, XXVI**) showed significant inhibition against *P.vulgaris* and *E.coli*. Compounds (**XXIV**) bearing two methyl group is more active against *P.vulgaris*, *E.coli*, and *B.subtillis* respectively, compound (**XXVI**) bearing 2-methyl and 4-hydroxyl group is more active against *P.vulgaris*, *E.coli* and *B.subtillis* respectively, none of the prepared quinoline derivatives had activity against *S.aures* and *Aspergillus niger* while compounds (**XXV and XXVI**) bearing 2-hydroxyl, 4-methyl group and 2-methyl, 4-hydroxyl group showed activity against *Candida albicans*. Table (2.8.4).

4. Conclusion and recommendations

The following points can be concluded and recommended according to this study:

- The substituted 2,3-diaryl-6-acetyl-quinoline-4-carboxylic acid could easily be synthesized by Doebner reaction.
- The quinolines bearing active acetyl group reacted by Claisen-Schmidt condensation to give the corresponding chalcones.
- The quinolyle chalcones on condensation with hydroxylamine hydrochloride give the corresponding isoxazole.
- Using of Combes, Knorr, Conrad-Limpach reaction as a different synthetic approach to synthesis newly substituted quinolines.
- It is highly recommended that furyl pyruvic acid to be used instead of phenyl pyruvic acid as a third component of Doebner reaction.
- Using different aromatic aldehydes as a substituent in position two of quinoline is highly recommended.
- Modification on carboxylic acid group in quinoline ring is highly recommended.
- Using microwave irradiation to minimize the time of reactions.

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