بسم الله الرحمن الرحيم

Synthesis of 2-phenyl- and 2,3-diphenyl-quinolin-4-carboxylic acid derivatives

By

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(B. Ed. Chem.)

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My Husband and my parents.

Abstract

Quinoline derivatives are a group of compounds known to possess a wide range of biological activities. The chemistry of quinolines together with their corresponding aldehydes were dealt with in chapter one of this study. Special emphasis was given to the chemistry of benzaldehyde.

Twenty five 2-phenyl-and 2,3-diphenyl-quinolin-4-carboxlic acid derivatives together with their corresponding intermediates were prepared in this work. Basically, the synthetic design of these compounds arised from the appropriate disconnections of the target 2-phenyl- and 2,3-diphenyl-quinolin-4-carboxylic acids. The retro synthesis analysis of these compounds reveals pyruvic acid, aromatic amine and benzaldehyde or phenyl pyruvic acid, aromatic amine and benzaldehyde as possible logical precursors for 2-phenyl- and 2,3-diphenyl-quinolin-4-carboxylic acids respectively. The purity and identities of the synthesized compounds were elucidated through chromatographic and spectroscopic techniques. The compounds were heavily subjected to spectroscopic analysis (UV, IR, GC/MS, ^{1}H-and ^{13}C-NMR).

The appropriate disconnections and the mechanisms of the corresponding reactions were given and discussed in chapter three. The spectral data were interpreted and correlated with the target structures. The prepared 2-phenyl- and 2,3-diphenyl-quinolin-4-carboxylic acid derivatives were screened for their antibacterial activity. The compounds were tested against the standard bacterial organisms *B. subtilis, S. aureus, E. coli* and *P. vulgaris*. Some of these compounds were devoid of antibacterial activity against *S. aureus* and *P. vulgaris*, while others

showed moderate activity. All of the tested compounds showed an activity against *B. subtilis* and *E. coli*. 2,3-diphenyl-6-sulphanilamido-quinolin-4-carboxylic acid showed the highest activity against the four standard tested organisms.

ملخص الأطروحة

الكينولينات و مشتقاتها عبارة عن مجموعة من المركبات عرفت بإمتلاكها لخواص و فعاليات أحيائية عديدة. كمياء الكينولينات و بادئاتها من الالدهيدات لخصت في القسم الأول من هذه الدراسة.

في هذا البحث تم تحضير عدد من المشتقات من نوع ٢-فينيل-كينولين-٤-حمض كاربوكسيلى و أستند التصميم الأساسي للتخليق الكيميائي لهذه المركبات على المبدأ الحديث في الكيمياء التخليقية وهو مبدأ تحليل تخليق الضديد. أوضحت تقنية تحليل تخليق الضديد أن المركبات الهدف يمكن أن تكون المواد البادئه لها هي حمض البيروفيك ، أمين أولي أروماتي و البنزالدهيد للمجموعة الأولي من المركبات المطلوبة، إضافة الي حمض فينيل البيروفيل ، أمين أولي أروماتي و البنزالدهيد للمجموعة الثانية. هوية و نقاوة المركبات المخلقة تم التعرف عليها بالطرق الطيفية و الكروماتوغرافية. تم تعريض المركبات لدراسات طيفية مكثفة شملت طيف الاشعة فوق المرئية، الأشعة تحت الحمراء طيف الرنين النووي المغنطيسي للبروتون و للكربون-١٣ إضافة الي تقنية كروماتوغرافياالغاز المقرونة بطيف الكتلة.

فاصلات تحليل تخليق الضديد و آليات التفاعلات الكيمايائية الموازية لها تم نقاشها في الفصل الثالث من هذه الدراسة. تم أيضا تفسير البيانات الطيفية و ربطها مع البنيات التركيبية.

المركبات المخلقة من عائلة أحادي أو ثنائي فينيل-كينولين-٤- حمض كربوكسيلي تم رصد فعاليتها ضد أربع أنواع من البكتريا موجبة الجرام و سالبة الجرام (*B. subtilis, S. aureus, E. coli* and *P. vulgaris*).

تفاوتت المركبات في مدى فعاليتها ضد الأنواع الأربع من البكتريا مركب ٢،٣-ثنائي فنيل-٦- سلفونااميدو-كينولين-٤-حمض كربوكسيلي كان الأعلى فعالية ضد الأنواع الأربع من البكتريا.

Contents

List of Tables

List of schemes

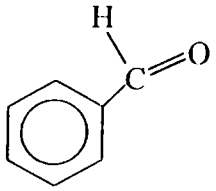
1. Introduction

1.1 Aromatic aldehydes

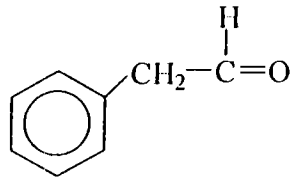
Aromatic aldehydes are characterized by the direct union of an aldehyde group (- CHO) to the aromatic nucleus. Benzaldehyde, $C_6 H_5$ CHO, is the simplest aldehyde of the aromatic series and is a typical representative of such compounds. Aromatic aldehydes have many properties in common with aldehydes of the aliphatic series, though the absence of a hydrogen atom on the alpha carbon precludes certain reactions for which the alpha hydrogen is required.

Other aldehydes, such as phenyl-acetaldehyde and cinnam-aldehyde, are usually studied concurrently with the aromatic aldehydes.

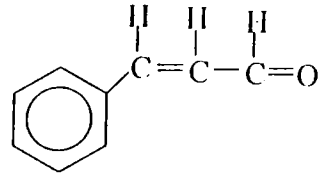
Such aldehydes, however, have the aldehyde group attached to the side chain and are aliphatic in character (Brewster and McEwen, 1963).



Benzaldehyde



Phenylacetaldehyde



Cinnamaldehyde

Benzaldehyde and the homologous aromatic aldehydes are liquids with an aromatic odour. They are easily oxidized to the corresponding carboxylic acids. Molecular oxygen, silver oxide, organic peracids, permanganate and dilute nitric acid are some of the oxidizing agents which have been used.

Aromatic aldehydes show most of the reactions characteristic of the fatty aldehydes. They are hydrogenated to alcohols, give cyanohydrins with HCN, bisulphite compounds with $NaHSO_3$ and form oximes, hydrazones, azines and similar functional derivatives. With

ammonia they give products different in type from those given by the fatty aldehydes, benzaldehyde gives hydrobenzamide, preceded by the formation of an additive compound $(PhCHOH)_2$ NH. With a primary amine an azomethine, ArCH:NR is the normal product. Derivatives of the hydrated form of the aldehyde acetals, $ArCH(OR)_2$, the corresponding thioethers, and the esters $ArCH(O\text{-}COR)_2$ are also readily obtained.

Aromatic aldehydes undergo disproportionation in presence of aqueous alkali, Thus benzaldehyde gives benzyl alcohol and a salt of benzoic acid: (Rodd, 1963).

$$2PhCHO + O\bar{H} \longrightarrow PhC\bar{O}_2 + PhCH_2OH$$

The reaction succeeds with homologues of benzaldehyde, alkoxyhalogen and some nitro-substituted benzaldehydes.

Elimination of the -CHO group occurs to a greater or less extent if the 2:6 positions are occupied by halogen or nitro groups.

In the absence of an excess of alkali or preferably under the influence of a small amount of aluminium alkoxide an ester is formed, benzaldehyde yields benzyl benzoate.

Benzaldehyde and its homologues yield acyloins by the action of a small amount of KCN in boiling alcohol. Benzoin, PhCO-CH(OH). Ph is formed from benzaldehyde (Ide and Buck, 1942).

This dimerisation appears to be characteristic of benzaldehyde and its homologues, halogen and alkoxy substituted benzaldehydes and a few heterocyclic aldehydes.

Reduction of aromatic aldehydes can occur to yield alcohols, hydrocarbons or glycols according to the experimental conditions. Catalytic hydrogenation in the liquid phase with platinum or nickel catalysts gives the alcohols as the first product, although under vigorous

conditions it is possible to obtain smaller or greater yields of hydrocarbon by complete reduction of CO to CH_2.

Reduction to the corresponding alcohol is thought about more conveniently by the Meerwein - ponndorf method of heating the aldehyde with aluminium alkoxides in a primary or secondary alcohol. Reduction of CHO to CH_3 is effected by Clemmensen method.

Aromatic aldehydes condense with a large variety of compounds $CH_2R`R``$ containing an active methylene group with elimination of water, generally to form an unsaturated compound.

$$ArCHO + CH_2R`R`` \longrightarrow ArCH(OH)CHR`R`` \longrightarrow ArCH{:}CR`R``$$

The experimental conditions for these condensations are determined largely by the nature of the reacting substances. Many are brought about by aqueous alkali, alkali metal alkoxides, amines, the alkali salts of weak acids or acetic anhydride and sodium acetate; zinc chloride and acid condensing agents have a limited application.

Aromatic aldehydes also condense with a methyl attached to an aromatic ring and activated by ortho (*o*) and para (*p*) nitro groups and with methyl groups in alpha and beta-positions in pyridine and quinoline compounds. With tertiary aromatic amines and phenols the aldehydes condense to form triaryl methanes. With acyl derivatives of α-amino acids they form azlactones (Carter, 1946).

The only aldehyde that will be discussed in this work is benzaldehyde, the simplest of the series (Rodd, 1963).

1.2 Benzaldehyde

Benzaldehyde is an aromatic flavor compound, consisting of a benzene ring substituted with a carbonyl group containing one hydrogen atom.

Aromatic compounds such as benzaldehyde and vanillin represent a very large market in the flavor industry. The consumer preference for products made with natural ingredients has directed research towards the exploitation of microbial biosynthetic pathways to produce natural flavors. Benzaldehyde as a chemical name is benzoic aldehyde (Niero and Jan, 1998).

1.2.1. Occurrence of benzaldehyde

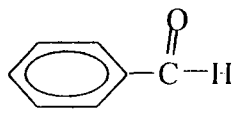
Benzaldehyde occurs in several essential oils, but particularly in oil of bitter almonds, which is practically all benzaldehyde (Stokes, 1979).

Natural benzaldehyde (also known as benzene carbonal) is tight up as a glycoside (amygdalin) in the stones of apricots, peaches, cherries and in almonds and can be released by enzymatic hydrolysis (Niero and Jan, 1998).

1.2.2. Structure of benzaldehyde and physical properties

The molecular formula of benzaldehyde is C_7H_6O. It has all properties of the aliphatic aldehydes which indicates the presence of the -CHO group, although its failure to reduce Fehling's solution might suggest a ketone.

Reduction, however, converts it to a primary alcohol (benzyl-alcohol) of proven structure, and it has aromatic properties. Its structure must there for be (Stokes, 1979):



Benzaldehyde is colourless to yellow viscous transparent liquid, with bitter almond odour, and a burning taste. It has a molecular weight equal (106.13) with melting point (-26°C) and boiling point (179°C).

Benzaldehyde is slightly soluble in water, DMSO, 95% ethanol, acetone, ligroin, oils, fats, ether, benzene, and is volatile in steam. Benzaldehyde has a flashpoint of 62°C (148°F). It is combustible. Fires involving this material can be controlled with a dry chemical, carbon dioxide or Halon extinguisher. A water spray may also be used. The autoigntion temperature is 191°C (377 F) (Weast *et al.*, 1984). Benzaldehyde is sensitive to air, light, and moisture. Solution of this chemical in water, DMSO, 95% ethanol or acetone should be stable for 24 hours under normal room temperature (Hagon *et al.*, 1967).

Benzaldehyde can form explosive peroxides under special conditions. It reacts violently with oxidants, aluminium, iron, bases and phenol causing fire and explosion hazard. It can self-ignite if absorbed in combustible material with large surface area, and it is harmful to aquatic organisms (FAO/WHO, 2001).

1.2.3. Preparation of benzaldehyde

Benzaldehyde can be prepared by one of the following methods, which are general for its homologues as well.

1.2.3.1. Hydrolysis of halogens

By the hydrolysis of benzylidene chloride with aqueous acid.

$$C_6H_5CHCl_2 + H_2O \longrightarrow C_6H_5CHO + 2HCl$$

This is affected by boiling benzyl chloride with aqueous copper or lead nitrate in a current of carbon dioxide.

$$C_6H_5CH_2Cl \xrightarrow{Pb(NO_3)_2} C_6H_5CH(H)-O-\overset{\overset{O}{\parallel}}{\underset{\underset{O}{|}}{N}} \longrightarrow C_6H_5CHO + HNO_3$$

1.2.3.2. Oxidation of toluene

Benzaldehyde can be conveniently prepared in the laboratory by oxidizing toluene with chromium trioxide in acetic anhydride. As the

benzaldehyde is formed, it is converted into benzylidene acetate, thereby preventing further oxidation of the benzaldehyde. Hydrolysis of the acetate with dilute sulphuric or hydrochloric acid gives benzaldehyde.

$$C_6H_5CH_3 \xrightarrow[(CH_3CO_2)O]{CrO_3} C_6H_5CH(OCOCH_3)_2 \xrightarrow{H^+} C_6H_5CHO + 2CH_3CO_2H$$

A better yield of benzaldehyde will be obtained by oxidizing benzyl alcohol with chromium trioxide in acetic anhydride or with acid dichromate (Durrant, 1961).

1.2.3.3. Gattermann-Koch aldehyde synthesis

Benzaldehyde can be synthesized by bubbling a mixture of carbon monoxide and hydrogen chloride through a solution of nitrobenzene, or ether containing benzene, and a catalyst consisting of aluminium chloride and a small amount of cuprous chloride. (Stokes, 1979).

$$C_6H_6 + CO + HCl \xrightarrow{AlCl_3} C_6H_5CHO + HCl$$

1.2.3.4. Gattermann aldehyde synthesis

When benzene is treated with a mixture of hydrogen cyanide, and hydrogen chloride in the presence of aluminium chloride and the complex so produced decomposed with water, benzaldehyde is produced in low yield.

$$HCl + HCN \xrightarrow{AlCl_3} HN{=}CHCl$$

$$C_6H_6 + HN{=}CHCl \xrightarrow{AlCl_3} HCl + \underset{\text{Arylimine}}{C_6H_5CH{=}NH} \xrightarrow{H_2O} C_6H_5CHO + NH_3$$

1.2.3.5. Sommelet's reaction

Benzaldehyde is obtained when benzyl chloride is refluxed with hexamethylenetetramine in aqueous ethanolic solution, followed by acidification and steam distillation:

$$C_6H_5CH_2Cl + (CH_2)_6N_4 \longrightarrow C_6H_5CHO$$

1.2.3.6. Rosenmund reduction

Benzaldehyde is prepared by the catalytic reduction of benzoyl chloride in the presence of a quinolinesulphur poison.

$$C_6H_5COCl + H_2 \xrightarrow{Pd} C_6H_5CHO + HCl$$

1.2.3.7. Stephen's method

When phenyl cyanide is reduced with stannous chloride and hydrochloric acid in ethereal solution, and then hydrolysed with water, benzaldehyde is formed. This method is a general one except for ortho substituted cyanides.

$$C_6H_5CN \xrightarrow[(ii)\ H_2O]{(i)\ SnCl_2 / HCl} C_6H_5CHO$$

1.2.3.8. Grignard reagent reaction

Benzaldehyde can be prepared by the reaction between phenyl magnesium bromide and ethyl formate, or ethyl orthoformate.

$$C_6H_5MgBr + HCO_2C_2H_5 \longrightarrow C_6H_5CHO + MgBr(OC_2H_5)$$

Benzaldehyde also can be obtained from aniline via the diazonium salt formaldoxime (Finar, 1971).

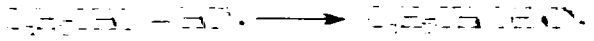
$$C_6H_5N_2Cl \xrightarrow{CH_2=NOH} C_6H_5CH=NOH \xrightarrow{H_2O} C_6H_5CHO$$

1.2.4. Chemical reactions of benzaldehyde

In most of its reactions, benzaldeyde resembles aliphatic aldehydes, but there are a few important differences (Durrant, 1961; Stokes, 1979).

1.2.4.1. Condensation with hydrogen cyanide

Hydrogen cyanide reacts with benzaldehyde to give benzaldehyde cyanohydrin.



1.2.4.2 Condensation with sodium bisulphite

An aqueous solution of sodium bisulphite reacts with benzaldehyde to yield the addition compound.

$$C_6H_5CHO + NaHSO_3 \longrightarrow C_6H_5CH(OH)SO_3Na$$

The hydrogen sulphite compound is readily decomposed by sodium carbonate solution and is used to obtain pure benzaldehyde.

$$2C_6H_5CH(OH)SO_3Na + Na_2CO_3 \longrightarrow 2C_6H_5CHO + 2Na_2SO_3 + CO_2 + H_2O$$

1.2.4.3 Condensation with ammonia

When benzaldehyde is treated with ammonia, colourless crystals of hydrobenzamide are formed.

$$3C_6H_5CHO + 2NH_3 \longrightarrow (C_6H_5CH)_3N_2 + 3H_2O$$

1.2.4.4 Condensation with hydroxylamine

Benzaldehyde reacts directly with hydroxylamine to yield α-benzaldoxime (Durrant, 1961).

$$C_6H_5CHO + H_2NOH \longrightarrow C_6H_5CH{=}NOH + H_2O$$

1.2.4.5 Condensation with hydrazines

Benzaldehyde reacts rapidly with phenylhydrazine to give a phenylhydrazone (Finar, 1971).

$$C_6H_5CHO + H_2N\text{-}NHC_6H_5 \longrightarrow C_6H_5\text{-}CH{=}N\text{-}NHC_6H_5 + H_2O$$

1.2.4.6 Condensation with Grignard reagents

Benzaldehyde reacts with a Grignard reagents, for example, C_2H_5MgBr, to give an intermediate compound which, on treatment with a dilute mineral acid, yields a secondary alcohol (Durrant, 1961).

$$C_6H_5CHO + C_2H_5MgBr \longrightarrow C_6H_5CHC_2H_5OMgBr$$

$$C_6H_5CHC_2H_5OMgBr + HCl \longrightarrow C_6H_5CHOHC_2H_5 + MgBrCl$$

1.2.4.7 The Claisen reaction

In the presence of dilute sodium hydroxide solution, benzaldehyde condenses with acetaldehyde to give cinnamaldehyde.

$$C_6H_5CHO + CH_3CHO \longrightarrow C_6H_5CH{=}CHCHO + H_2O$$

In the presence of sodium hydroxide solution, benzaldehyde condenses with acetone to yield dibenzal acetone.

$$C_6H_5CHO + CH_3COCH_3 + C_6H_5CHO \longrightarrow C_6H_5CH{=}CHCOCH{=}CHC_6H_5 + 2H_2O$$

1.2.4.8 Perkin's reaction

Benzaldehyde reacts with a mixture of acetic anhydride and anhydrous sodium acetate to form acetyl cinnamic acid (Stokes, 1979).

$$C_6H_5CHO + CH_3COO{\bullet}CO{\bullet}CH_3 \longrightarrow C_6H_5CH{=}CHCO{\bullet}O{\bullet}CO{\bullet}CH_3 + H_2O$$

1.2.4.9 Condensation with (aniline) amines

Benzaldehyde condenses readily with aniline in alcoholic solution, to give benzylidene aniline.

$$C_6H_5CHO + C_6H_5NH_2 \longrightarrow C_6H_5CH{=}NC_6H_5 + H_2O$$

1.2.4.10 Benzoin condensation

When a solution of benzaldehyde in ethyl alcohol is treated with potassium cyanide, the benzaldehyde polymerizes to benzoin.

$$C_6H_5CHO + C_6H_5CHO \longrightarrow C_6H_5CHOHCOC_6H_5$$

1.2.4.11 Darzens condensation

Benzaldehyde reacts with a halogenomethylene substance in the presence of a base to form an epoxy containing glycidic ester.

$$C_6H_5CHO + ClCH_2COOC_2H_5 \xrightarrow{Base} C_6H_5CHOCHCOOC_2H_5 + Cl^-$$

1.2.4.12 Cannizzaro reaction

Benzaldehyde reacts with aqueous sodium or potassium hydroxide to give benzyl alcohol and sodium or potassium benzoate. (Durrant, 1961).

$$C_6H_5CHO + NaOH \longrightarrow C_6H_5CO_2H + C_6H_5CH_2OH$$

1.2.4.13 Oxidation reactions

Upon exposure to the air at room temperature benzaldehyde unites with a molecule of oxygen, forming a peroxide, perbenzoic acid, which can oxidize another molecule of the aldehyde.

$$C_6H_5CHO + O_2 \longrightarrow \underset{\text{Perbenzoic acid}}{C_6H_5COO{\bullet}OH}$$

$$C_6H_5COO{\bullet}OH + C_6H_5CHO \longrightarrow \underset{\text{Benzoic acid}}{2C_6H_5COOH}$$

1.2.4.14 Reduction reactions

1.2.4.14.1 Clemensen reductio:

The reduction of benzaldehyde with amalgamated zinc and hydrochloric acid leads to the formation of toluene.

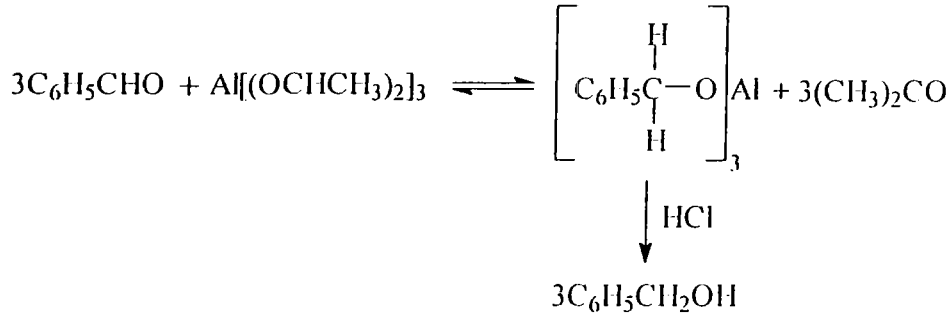
$$C_6H_5CHO \xrightarrow[HCl\ Conc]{Zn(Hg)} C_6H_5CH_3$$

1.2.4.14.2 Wolf-Kishner reduction

This is similar to Clemmenson reduction product but differ in the conditions used.

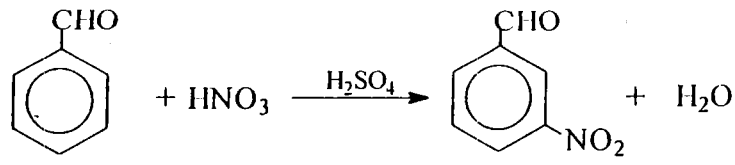
1.2.4.14.3 Meerwein-Ponndorf-Verley reduction

By the use of aluminum isopropoxide, a solution of benzaldehyde in benzene or toluene is reduced to benzyl alcohol.



1.2.4.15 Aromatic properties

Benzaldehyde has the usual aromatic properties, but the substitution reactions require somewhat more drastic conditions than those required for benzene itself. Benzaldehyde can be nitrated in the usual way, to give mainly m-nitrobenzaldehyde (Brewster and McEwen, 1963).



Surprisingly, concentrated nitric acid causes very little oxidation, although the dilute acid oxidizes benzaldehyde easily. Sulphonation of benzaldehyde yields the meta-substituted compound, chlorine in the presence of an iron catalyst gives a nuclear substitution product, m-

chlorobenzaldehyde. Benzaldehyde can also be alkylated by the Friedal-Crafts reaction, but with difficulty (Stokes, 1979).

1.2.4.16 Irradiation of benzaldehyde

Normal irradiation of benzaldehyde in tertiary butyl alcohol as solvent afforded benzil and minor amounts of tert-butyl benzoate (PhCOOt Bu), whereas in the laser-jet mode exclusively ester was observed. On photolysis of benzaldehyde in a 1:1 mixture of tert-butyl peroxide and CCl_4 as solvent, only benzoyl chloride was found on normal irradiation (Adam and Oestrich, 1993).

1.2.4.17 Oscillatory oxidation of benzaldehyde by Air In 1983, Jensen reported oscillatory behavior during the air oxidation of benzaldehyde in aqueous acetic acid catalyzed by a combination of cobaltous and bromide ions. Both electrode potentials and visual observation indicated that the dominant oxidation state of cobalt underwent major repetitive changes with a period of a few minutes (Jensen, 1983; Colussi *et al.*, 1990; Boga *et al*, 1990; Roelofs *et al.*, 1987; Szirovicsa *et al.*, 1989; Bawn and Jolley, 1956; Chalk and Smith, 1957).

1.2.4.18. The reversible addition of hydroxide to substituted benzaldehydes

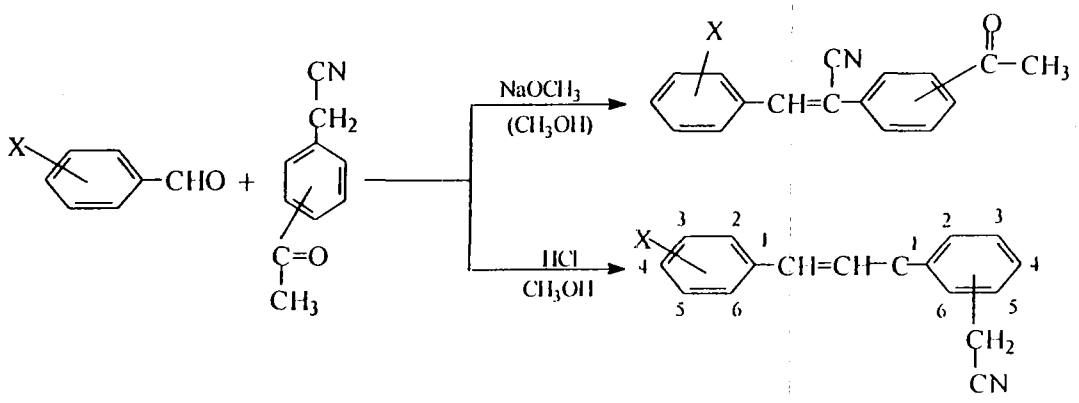
Aliphatic aldehydes and some aliphatic ketones undergo a reversible hydration in neutral aqueous solutions to form the gem-diol (Bell, 1966). Aromatic aldehydes are not hydrated to any appreciable extent, owing to the extra resonance stabilization. However, in basic solutions, mono-and disubstituted benzaldehydes do undergo a reversible addition of hydroxide ion to form the ionized gem-diol. The addition of hydroxide to the substituted benzaldehydes can be viewed as a reversible attack of water which is favored in basic solutions owing to the ionization of the gem-diol formed (Greenzaid, 1973).

1.2.4.19. Condensation of glycine with benzaldehyde

Condensation of glycine with benzaldehyde in ethanolic potassium hydroxide gives the anil of phenyl serine in a good yield (Bolhofer, 1954; Slaw and Fox, 1953; Jones, 1967; Nielsen and Houliham, 1968; Hine *et al.*, 1969; Berndt, 1970; Williams and Bush, 1965; Buckingham *et al.*, 1967; Ogata *et al.*, 1973).

1.2.4.20. Condensations of substituted benzaldehydes with m-or p-acetyl phenyl acetonitrile

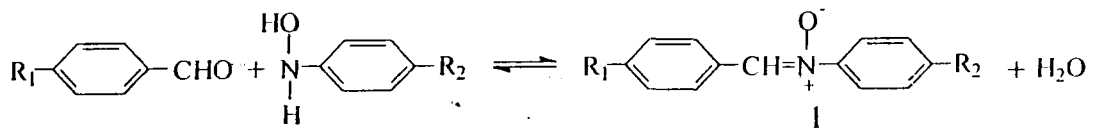
In the presence of alkaline catalysts aromatic aldehydes react with phenylacetonitrile to give α-phenylcinnamonitriles (Roring, 1953)



1.2.4.21. Benzaldehyde on the synthesis of diarylnitrones

Compounds containing the imine N-oxide moiety are most commonly called nitrones (West and Davis, 1989).

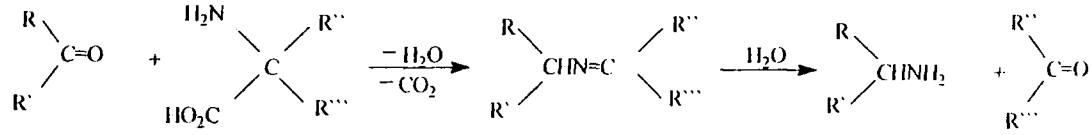
It was reported that acid catalysis can be used to great advantage in the preparation of diaryl nitrones, particularly those whose synthesis is otherwise impeded by electronic effects.



The condensation of arylhydroxylamine with benzaldehyde derivatives offers the most direct approach to the preparation of diarylnitrones (Scott and smith, 1978; Liotla *et al.*, 1974; Ogata and Morimoto, 1965; West and Davis, 1989; Reimann and Jencks, 1966).

1.2.4.22. Synthesis of benzylamines from benzaldehydes

Because of their biological significance, the reactions of α-amino acids with carbonyl compounds have been widely studied (Emerson, 1948; Sayyab and Lowson, 1968; Rizzi, 1971).



1.2.5. Functional derivatives of benzaldehyde

1.2.5.1. Acetals

Ph-CH$(OR)_2$ the ethers of the hydrated aldehyde, are formed by the action of the appropriate alcohol containing a small proportion of dry HCl, or by reaction with orthoformic ester and a little HCl. Other general methods are the reaction of the aryl magnesium bromide with orthoformic esters or of alcoholic solutions of alkoxides on the benzylidene chloride.

The acetals are readily hydrolysed by warm aqueous acid into the aldehyde and alcohol.

1.2.5.2. Benzylidene diacyl esters

Bezylidines are prepared by reaction of benzaldehyde with acyl anhydrides in presence of a little concentrated sulphuric acid, copper sulphate, and zinc chloride, or ferric chloride or by the action of the salts of the carboxylic acids on benzylindene chloride.

Some acid chlorides combine additively with benzaldehyde to give chloroacyl derivatives. Thus oxalyl chloride yields di-α-chlorobenzyl

oxalate, Ph.CHCl.O.CO.CO.O.CHCl.Ph, the corresponding bromo compound, is also known, carbonyl chloride reacts similarly in quinoline.

1.2.5.3. Bisulphites

With sodium bisulphite in saturated aqueous solution a crystalline deposite is formed of benzaldehyde sodium bisulphite, hydrated crystals are easily soluble in water. It is hydrolyzed into its generators by distillation with water or more easily by the action of acids or alkalis. Potassium, ammonium and other salts have been described. They can be formulated as the salts of the sulphurous ester of α-hydroxybenzylalcohol, $PhCH(OH)O.SO_2M$ but are almost certainly α-hydroxysulphonic acid salts, $PhCH(OH)SO_3M$ (Strain,1927).

Benzaldehyde sulphoxylate, the sodium salt Ph.CH(OH).OSONa is prepared by shaking benzaldehyde with an alkaline solution of sodium hydrosulphite. The free acid is unknown, barium, zinc and other salts have been described (Rodd, 1963).

1.2.5.4. Thiobenzaldehydes

Benzaldehyde reacts in alcoholic solution with hydrogen sulphite to give an amorphous thiobenzaldehyde, $(PhCHS)_x$, a white powder which softens on heating at about 85 °C. If the reaction is brought about in presence of some hydrogen chloride or zinc chloride the product is a mixture of two crystalline trimeric thiobenzaldehyde $(PhCHS)_3$.

1.2.5.5. Benzaldehyde dimethyl mercaptal, $phCH(SMe)_2$

Benzaldehyde dimethyl mercaptal is the thioanalogue of the acetal. It is prepared by reaction of methyl mercapton with benzaldehyde in presence of hydrogen chloride. Oxidation gives benzylidene dimethydisulphone, m.p. 163 °C. The diethyl disulphone, m.p. 134 °C, and di-n-butyldisulphone, m.p. 86 °C, are prepared similarly.

1.2.5.6. Selenobenzaldehyde, PhCHSe

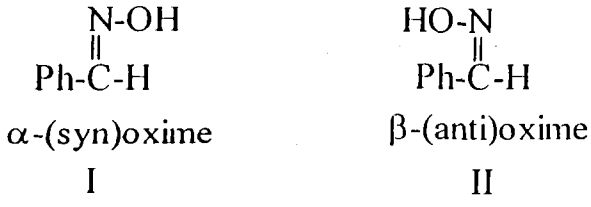
Three forms have been described α-selenobenzaldehyde, m.p. 83 °C, yellow prisms, which is prepared from benzaldeyde and hydrogen selenide in alcohol, the β-and γ-forms, m.p. 205 °C and 166 °C respectively which are formed by the actions of hydrogenselenide on benzaldehyde in alcohol containing hydrogen chloride.

1.2.5.7. Benzaldehyde with ammonias

A concentrated alcoholic solution of benzaldehyde reacts with ammonia at -20 °C to give benzaldehyde ammonia, $[phCH(OH)]_2NH$, m.p. 45 °C. It decomposes rapidly into water, benzaldehyde and hydrobenzamide, $(phCH{:}N)_2CHph$, m.p. 110 °C which is the normal product of the action of concentrated aqueous ammonia on benzaldehyde. It is hydrolysed into benzaldehyde by dilute acid (Stephen, 1925; Bigelow and Eatough, 1947; and Hatt, 1943).

1.2.5.8. Benzaldoximes

Benzaldehyde forms two stereoisomeric oximes represented by the formula I and II below.



α-(syn)oxime I

β-(anti)oxime II

α- or syn-benzaldoxime I, m.p. 34 °C, formed by reaction of benzaldehyde with hydroxylamine. β-or anti-benzaldoxime II, m.p. 127 °C, is best prepared from the α-oxime, it is also obtained by the interaction of benzaldehyde with hydroxylamine hydrochloride in alcohol (Taylor and Roberts, 1933).

1.2.5.9. Ring derivatives of benzaldeyde

1.2.5.9.1.Halogenobenzaldehydes

The more common methods for the preparation of halogen-substituted benzaldehydes include:

The hydrolysis of halogen-substituted benzylidene chlorides.

The Sommelet method from halogen-substituted benzyl chloride.

The oxidation of halogen substituted toluenes.

The diazo reaction from the appropriate aminobenzaldehyde.

The reactions of the halogenobenzaldehydes are similar to those of benzaldehyde.

1.2.5.9.2. Nitrobenzaldehydes

Convenient methods for the preparation of the nitrobenzaldehydes, include the regulated oxidation of the nitro toluenes by manganese dioxide, and sulphuric acid, or by chromium trioxide in acetic anhydride and sulphuric acid, and the oxidation of nitro benzyl chlorides with alkaline chromate. Nitration of benzaldehyde gives a high proportion of m-nitro derivative.

1.2.5.9.3. Aminobenzaldehydes

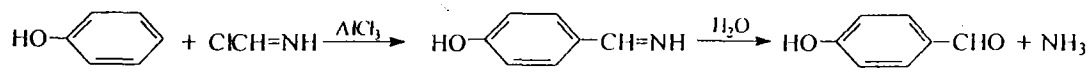
o, m, p-Aminobenzaldehydes can be obtained by the controlled reduction of the corresponding nitrobenzaldehydes. Ferrous sulphate and aqueous ammonia has been used for the preparation of *o* and *m* compounds (Lapworth, 1929).

1.2.5.9.4. Benzaldehyde sulphonic acids

Benzaldehyde-*o*-sulphonic acid is prepared by heating *o*-chlorobenzaldehyde with sodium sulphite at 190-200 °C. It is also obtained by the oxidation of toluene-*o*-sulphonic acid with MnO_2 and sulphuric acid or of stilbene-2:2 disulphonic acid with permanganate (Rodd, 1963)

1.2.5.9.5. Phenolic aldehydes

When phenols or a phenolic ethers are treated with a mixture of hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride, and the complex produced then decomposed with water. *p*-hydroxy-(or alkoxy) benzaldehyde is the main product (Finar, 1971).



1.2.6. The uses and applications of benzaldehyde

Benzaldehyde as one of important aromatic aldehydes, have a wide uses and applications in many fields. It is used for flavouring purposes, and in the manufacture of certain dyes, for example, malachite green (Durrant, 1961).

Benzaldehyde was used as intermediate for numerous of derivatives, included, dyes, odorant in perfumes, flavoring ingredient, intermediate for aromatic alcohols, solvents for oils, resins, some cellulose ethers, cellulose acetate and nitrate, manufacture of benzoic acid, pharmaceuticals, photographic chemistry, manufacture of cinnamic, and mandelic acids. (EPA, 2003).

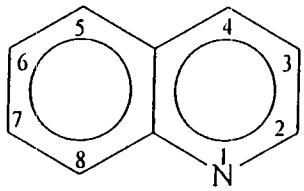
Derivatives of benzaldehyde also were found to have important applications, for example, ortho-nitrobenzaldehyde was used in medicine for killing sebaceous diseases, in curring head exuvium, and dry sebaceous swiat spot, meta-nitrobenzaldehyde was used as organic intermediate, and para-hydroxybenzaldehyde (*p*-formylphenoll or 4-hydroxy benzaldehyde) have many appilications.

In medicine it could be used for making a broad spectrum antibacterical synergist TMP, synthesizing sulfanilamide medicines and other intermediates in shampoo industry, it is mainly used for making raspberry ketone, methyl, bourbonal, anisic aldehyde, and nitrile

perfumes. In agricultural pesticide, it is mainly used for synthesizing new pesticides, herbicides, bromoxynil, hydroxy dichlobenil. In plating industry, it is used as a new nitriles brightening agent for electroplating. Ortho-chlorobenzaldehyde as the important raw material for making up medicines, and it have widely used as raw material of insecticides of mites.

1.3. Quinolines

Quinoline, C_9H_7N, contains a benzene ring and a pyridine ring fused as shown bellow:



The quinoline nucleus is contained in several groups of alkaloids (quinine), in a number of synthetic materials with important physiological properties such as the antimalarial plasmoquin, in the cyanine dyes, and in the analytical reagent, oxine (8-hydroxyquinoline) (Norman, 1968).

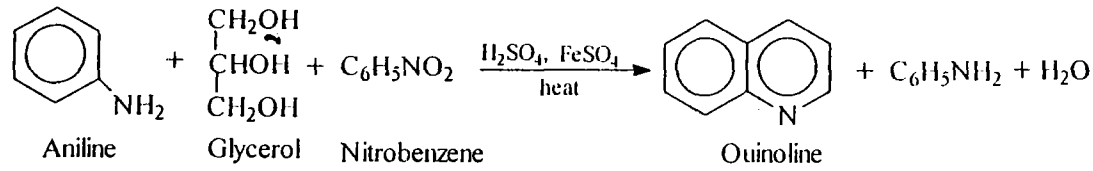
Quinoline is found in coal tar, Although certain derivatives of quinoline can be made from quinoline itself by substitution, most are prepared from benzene derivatives by ring closure (Morrison and Boyd, 1966).

1.3.1. Synthesis of quinoline and quinoline derivatives

Perhaps the most generally useful methods for preparing substituted quinolines include:

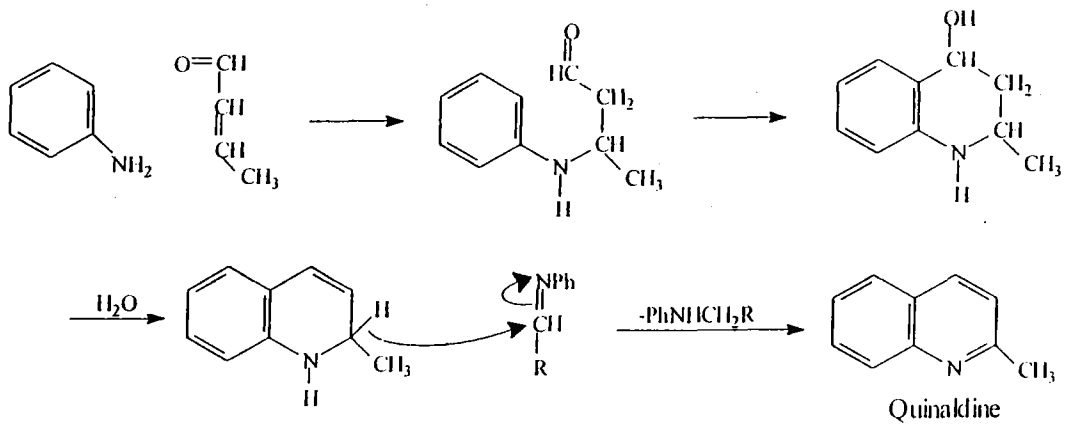
1.3.1.1. Skraup synthesis

In the simplest example, quinoline itself is obtained from the reaction of aniline with glycerol, concentrated sulfuric acid, nitrobenzene and ferrous sulfate (Norman, 1968).



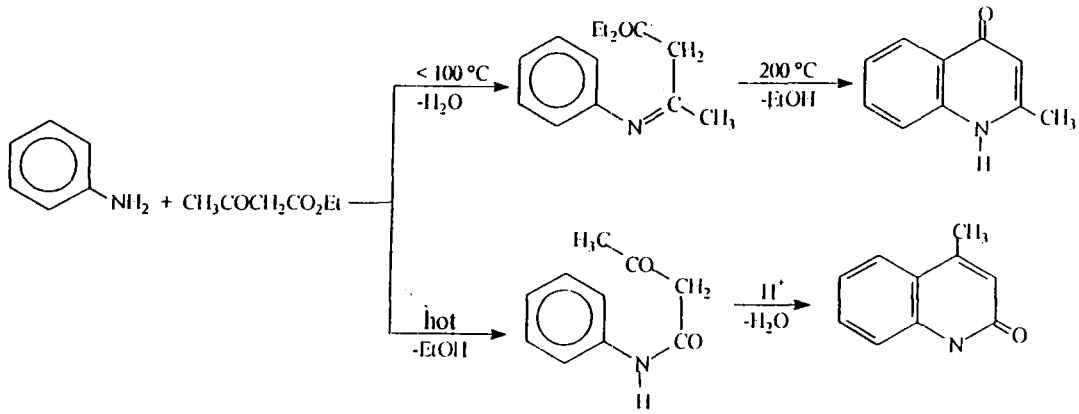
1.3.1.2. The Dobner-Van Miller synthesis

This is very similar to the Skraup method, the difference being that the three-carbon fragment is formed *in situ* by an acid-catalyzed aldol condensation and that no dehydrogenating agent is added. The oxidative step is thought to be brought about by hydride-transfer to the Schiff base which is formed by reaction between the aniline and the aldehyde or ketone.



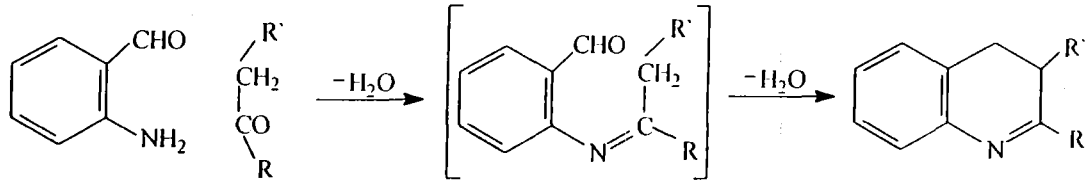
1.3.1.3. The Conradt-Limpach synthesis

β-keto-esters react with anilines in each of two ways: at low temperatures reaction occurs at the keto-group to give a Schiff base, and at high temperatures reaction occurs at the ester group to give an amide. The resulting compound can each be cyclized to quinolines.

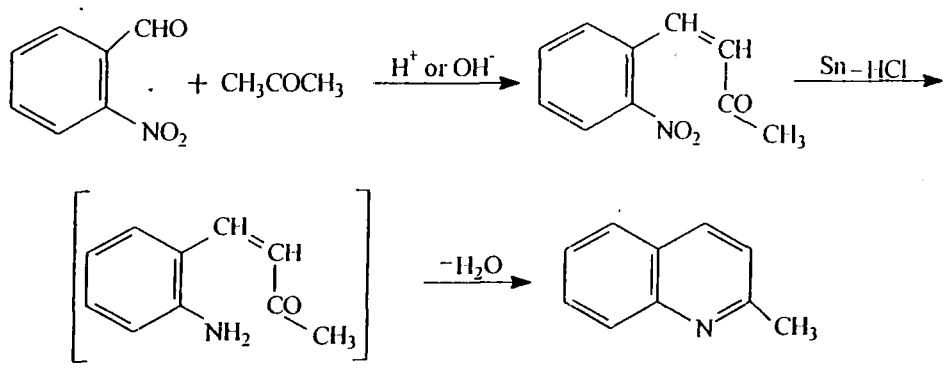


1.3.1.4. The Friedlaender synthesis

An *o*-aminobenzaldehyde is treated with an aldehyde or ketone; formation of the Schiff base is followed by dehydrative cyclization.

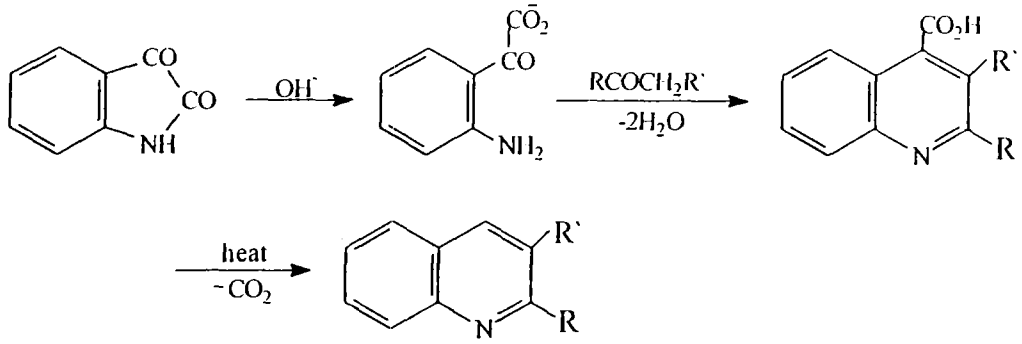


The main problem in this synthesis is that *o*-aminobenzaldehydes are very unstable, readily undergoing self-condensation. One way of overcoming this is to start instead with an *o*-nitrobenzaldehyde, acid or base-catalyzed condensation gives an intermediate which cyclizes spontaneously on reduction. (Morrison and Boyd, 1966)



1.3.1.5. The Pfitzinger synthesis

This is a modification of Friedlaender's method, it employs isatin in place of *o*-aminobenzaldehyde. Reaction with base gives *o*-aminobenzoyl-formate ion which condenses with an aldehyde or ketone to give a -4-carboxyquinoline from which the carboxyl group can be removed thermally (Norman 1968).



1.3.2. Oxidation of quinolines

A variety of methods are available for the oxidation of quinoline and substituted quinolines to quinolinic acids, employing oxidizing agents such as potassium permanganate, manganese dioxide and fuming nitric acid (Koelsch and steinhauer, 1953; Cochran and Little, 1960; Kulka, 1946).

1.3.3. Bromination of quinoline

In rationalizing the selective and facile bromination of quinoline at C-3 by the decomposition of the 1:1 quinoline-bromine complex, it was postulated that C-3 was attacked in preference to C-6 because of the favorable circumstances for a bridged bromonium ion transition state (Eisch, 1962) at C-3 (1); (Mare *et al.*, 1960).

1.3.4. Riessert compound from quinoline reaction

Reaction of a wide variety of 3-,4-,5-,6-, and 7-substituted quinolines with benzoyl chloride and potassium cyanide in methylene chloride- water has resulted in the formation of the appropriate Reissert

compounds. The yields of Reissert compounds were largest when the substituents were electrondonating groups. No Reissert compounds could be obtained from 2-and 8-substituted quinolines with one exception all the Reissert compounds gave benzaldehyde on acid-catalyzed hydrolysis (Mc Ewen and Cobb, 1955; Elliott, 1955; Popp *et al.*, 1961; Walters *et al.*, 1961).

1.3.5 Biological properties

Some derivatives of quinoline-4-carboxylic acid elicited profound changes in the morphology of typical tips of Botrytis cinerea, mainly their branching and the release of the cytoplasmic content. Quinoline derivatives, which elicited morphological changes, increased also the permeability of the plasmalemma of plant cells (Strigacova *et al.*, 2000).

Novel antiplatelet agents for 4-alkoxy derivatives of 2-phenylquinoline as well as related compounds were reported, these compounds demonstrated potent antiplatelet activity (Ko. *et al.*, 2001).

A series of 7-substituted –6-fluoro-1-fluoromethyl 4-oxo-4H- (1,3) thiazeto (3,2-a) quindine-3-carboxylic acid derivatives showed excellent *in vitro* and *in vivo* antibacterial activity against both Gram negative and Gram positive bacteria including quinoline and methicillin-resistant *Staphylococcus aureus* (Matsuoka *et al.*, 1999).

A series of 1-ethyl/benzyl-6-fluoro-7-(substituted piperazin-1-) 1,4-dihydro-4-oxo-quinoline-3-carboxylic acid exhibited significant antibacterial and weak antifungal activities (Ramesh Kumar *et al.*, 2003).

4-(phenylamino)quinoline-3-carboxamides were evaluated for antisecretory activity against histamine-induced gastric acid secretion in rats. Most of the compounds inhibited histamine-induced gastric acid secretion in rats.

Among them, N-allyl-4-(2-ethylphenylamino) quinoline-3-carboxamide was the most potent inhibitor and had the best profile as a candidate antiulcer agent (Uchida *et al.*, 1995). The ethyl acetate extract of cultures of janibacter limosus showed a high biological activity against bacteria and fungi (Asolkar *et al.*, 2004).

The 2-phenylquinoline-4-carboxamide has been found to possess moderate affinity for human neurokinin-3receptor,to investigate the effect of the lipophilic moiety at C-2 of the quinoline ring on the antagonistic activity an enlargement of the aromatic area at this position was suggested. Fifteen compounds were screened for such activity using guinea pig isolated ileum longitudinal muscle preparation and senktide as *selective LNK-3 receptor. Some compounds showed considerable* antagonistic effect (Saudi *et al.*, 2003).

Novel piperazinyloxoauinoline derivatives were found to be potent and selective inhibitors of human immunodeficiency virus (Baba *et al.*, 1997).

Thiazoloquinolone derivatives were highly cytotoxic against mammadlian cells, being comparable in cytotoxicity to the reference drugs. The thiazetoquinolone derivatives were less cytotoxic than the thiazoloquinolone derivatives (Ozaki *et al.*, 1996).

1.4. Retro synthesis

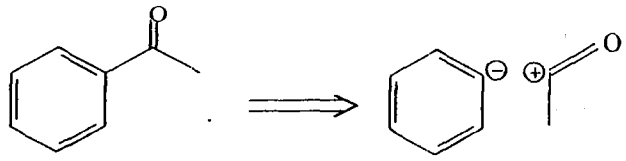
The total synthesis of complex natural products demands a thorough knowledge of reactions that form carbon- carbon bonds as well as those that change one functional group into another. Examination of many syntheses of both large and small molecules, reveals that building up a carbon skeleton by carbon-carbon bond- forming reactions cannot be done successfully unless all aspects of chemical reactivity, functional group interactions, conformations, and stereochemistry are well

understood. When one functional group changes into another, the process was known as functional group interchange (FGI).

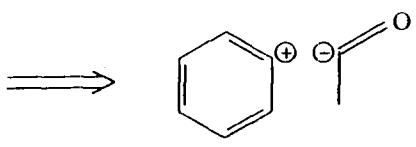
It is common nowadays to show the relationship of two molecules in a synthesis by using a device known as a transform. A transform is defined by Corey and Co workers as the exact reverse of a synthetic reaction to a target structure (Corey and Cheng, 1989)

The target structure is the final molecule one is attempting to prepare. Disconnection of the carbon-carbon bond generates the precursor (the starting material). Both carbon dioxide (CO_2) and cyanide ($C\equiv N$) are reactive fragments that can be converted to CO_2H. Working backward in this manner is termed retrosynthetic analysis or retro synthesis defined by Corey as a problem-solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simple materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis. An idealized fragment, usually a cation or anion, resulting from a disconnection is known as a synthon. Usually synthons don't exist as such, but help in the correct choice of reagent.

In the example:

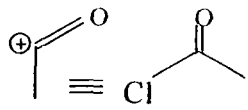


Looks possible because it implies electophilic attack on benzene ring.



Dose not look so good nucleophili attack less usual.

Synthetic equivalent- the actual compounds used to function as synthon (Kngsum and Weiler, 1978).



+ $AlCl_3$ (Friedel Crafts Reagent

Retrosynthetic analysis will only lead to useful results if it is directed towards some goal. The basic goal is to generate precursor that correspond to available starting materials. However, this goal can be used as a guiding principle only when possible starting materials can be identified from the target structure. In general, obvious starting points cannot be found when it comes to complex target structures (and that is where RA is most useful). Stated differently, retro-synthetic analysis is directed towards molecular simplification. Corey has formulated five main types of strategies that lead to the desired simplification.

The early design of synthetic routes for the vast number of simple and complex molecules was a largely intuitive operation. Indeed even the most eminent of synthetic chemists rarely recorded in the literature the thought processes, which led to the realization of the successful synthesis of a complex structure.

1.5. Aim and objectives

Quinolines are a group of compounds associated with different biological activities, such as anti platelet, antibacterial, antimalarial, antiucler inhibitors of immunodeficiency virus etc.....

The present work aimed at synthesizing certain substituted 2-phenyl- and 2, 3-diphenyl-quinolin-4-carboxylic acids, the designing of these compounds include the insertion of certain types of substitutents in the homocyclic ring, these substituents should be to some extend bioisoters to each others. The total synthesis of the target compounds, the

corresponding mechanisms and synthetic routes should be worked from the suitable logical disconnections of the target molecules. The preliminary retrosynthetic analysis reveals aromatic amine, a three-carbon fragment or a two-carbon fragment. The present work aimed to utilize benzadehyde as a suitable precursor in the second two-carbon fragment approach. The identity of the final intermediate compounds should be fully elucidated through spectroscopic techniques e.g. IR, ^{1}H, ^{13}C-NMR, MS and UV. The mechanisms of the reactions and the corresponding retrosynthesis should be pointed out, discussed and form one of the objectives of this work.

The project aimed to screen the compounds for antimicrobial activities and if possible for other biological activities. Standard or modified organic preparative procedures should be followed throughout the synthetic work.

2. Experimental

2.1 Chemicals and reagents

All chemicals and reagents were of general purpose reagent grade supplied by the following manufactures:

A- Reagents

Hydrochloric acid, Nitric acid, Potassium hydrogen sulphate, Sodium carbonate, Sodium hydroxide, and Sulphuric acid (British drug house (BDH) chemical L.T.D, England), Acetic anhydride, Acetic acid and anhydrous sodium acetate, (Koch-Light-Laboratories L.T.d. Colnbrook Bucks, England).

B- Solvents

Absolute ethanol, Acetone, Benzene, Carbon tetrachloride, Chloroform, Diethyl ether, Ethanol, Light petroleum (40-60°) and Methanol, (Riedel-Dehaen AG, Seelze- Hannover, Germany).

C- Starting materials

p-Aminobenzoic acid, Glycine, and Tartaric acid (Koch-Light-Laboratories L.T.d. Colnbrook Bucks. Engalnd). Ammonia (Riedel-Dehaen AG, Seelze- Hannover), and Aniline, Benzaldehyde, Benzoyl chloride, methyl amine, *m*-, *p*-nitroaniline, Sulphanilamide, Sulphadimidine, and *o*-, *m*-, *p*-toludine (Hopkin and Williams L.T.D. Chawell Heath Essex, England).

2.2 Infrared spectrophotometry (IR)

IR analysis was carried out using I.R. satellite FTIR. Spectrometeer, Mattson instrument.

2.3 Ultraviolet-visible spectrophotometer (UV Vis)

UV/VIS was carried out using UV/VIS spectrophotometer; Jenway limited serial No. 2204, England. Model 6505.

2.4 Mass spectrometer (MS)

Mass spectra analysis was carried out at King Saood University- Faculty of Science, using GC/MS. GP 5050A SHIMADZU GC-17A instrument.

2.5 ^{1}H- and ^{13}C- Nuclear magnetic resonance spectrophotometer

^{1}H- and ^{13}C-NMR analysis were carried out at King Saood University- Faculty of Science, using.

a. JEOL ECP 400MHZ instrument.

b. JEOL JNMFX-100MHz instrument.

2.6 Thin Layer Chromatography (TLC)

TLC was carried out with silica gel 60 GF_{254} (Merck, Germany) precoated plates, different mobile phases were attempted.

2.7 General apparatus

Digital Melting point instrument; Electrothemal Engineering Limited. model 9100.

2.8 Preparation of reagents

All of the reagents and the starting materials have been prepared according to the published methods (Furniss *et al.*, 1989).

2.8.1 Preparation of acetylglycine (I)

In 500 ml, conical flask, were placed glycine. (37.5 gm. 0.5 mol), and water (150 ml). The mixture was stirred by mechanical stirrer until the solid have been dissolved. Acetic anhydride (45 ml), in one portion was added. Stirred for (15-20 minutes), the solution became hot with crystalissation of some acetylglycine. The solution was cooled in a refrigerator overnight. The precipitate was collected upon Buchner funnel, washed with ice-cold water and dried at 100 °C. Yield % = 94%, m.p. 204-205, Lit. 207-208 °C.

2.8.2 Preparation of 4-benzylidene-2-methyloxazole-5-ones (II and XXVIII)

In a 500 ml round bottom flask, equipped with a reflux condenser, were placed acetylglycine (29 gm, 0.25 mol), redistilled benzaldehyde, or m-nitrobenzaldehyde (0.37 mol), anhydrous sodium acetate (15 g, 0.183 mol) and acetic anhdride (59 ml). The mixture was warmed on a water bath and stirred by occasional stirring (10-20 minutes), until solution was completed, and boiled for 1 hour. The mixture was cooled and leaved in refrigerator overnight. The solid mass of yellow crystals was transferred with cold water to abuchnner funnel, washed well with cold water, and with a little of ether, recrystalized from carbontetrachloride and dried on air. II, Y% = 76%, m.p. = 150-151, Lit = 150 °C, XXVIII, Y% = 62, m.p. 132-133 °C.

2.8.3. Preparation of α-acetamido cinnamic acid (III)

A mixture of 4-benzylidene-2-methyloxazol-5-one (II) (2.35 g, 0.0125 mol), water (9 ml), and acetone, (22.5 ml), was boiled in a 500 ml round bottomed flask, under reflux for 4 hours. Acetone was removed with a rotary evaporator. The residual solution was diluted with water 20 ml, boiled for (5-10 minutes) and filtered through a hot- water funnel. Decolourized carbon (0.5 g) was added, the solution was boiled for 5 minutes, and was filtered with gentle suction through a warm Buchner funnel. The residual was washed with four portions of boiling water (2.5 ml). The combined filtrate and washings, were placed in refrigerator overnight. The colourless crystals were collected by suction filtration, washed with cold water (10 ml), dried at 100 °C and recrystallized from EtOH. Y% = 86%, m.p. 187-188, Lit 191 °C.

2.8.4. Preparation of benzoylglycine (IV)

In a 500 ml conical flask were placed glycine (12.5 g, 0.165 mol), sodium hydroxide solution (125 ml of 10 percent). Benzoyl chloride (22.5 ml) was added in five portions. The solution was shaken vigorously until all of the benzoyl chloride had reacted. The mixture was transferred to a beaker containing a few grams of crushed ice, concentrated hydrochloric acid was added slowly with stirring, until the mixture was acidic to Congo red paper. The crystalline precipitate was collected as benzoyl glycine, washed with distil-water and air dried. The solid precipitate was placed in the beaker with carbontetrachloride 50 ml, the beaker was covered with watch glass and boiled gently for 10 minutes (fume cupboard). (This to extracts any benzoic acid, which may be present). The mixture was allowed to cool slightly, filtered, washed with carbon tetrachloride (10-20 ml), and dried on air. The dried product was recrystallised from boiling water (about 250ml), and filtered through a hot -water funnel, allowed to crystallized, and dried on oven. Y% = 76%, m.p. = 184-185, Lit = 187 °C.

2.8.5 Preparation of 4-benzylidene-2-phenyloxazol-5-ones (V and XXIV)

In a 500 ml conical flask were placed benzaldehyde or m-nitrobenzaldehyde (0.083 mol), benzoyl glycine (15 g, 0.083 mol), acetic anhydride (25.6 g, 23.8 ml, 0.25 mol), and anhydrous sodium acetate (9.8 g, 0.083 mol). The mixture was heated on an electric hot plate with constant shaking, as soon as the mixture has completely liquefied.

The flask was transferred to a water bath and heated for 2 hours. Then ethanol (33 ml), was added slowly to the flask, the mixture was allowed to stand overnight. The crystalline product was filtered, washed twice with ice-cold alcohol (8.3 ml) and twice with boiling water (8.3

ml), dried at 100 °C and recrystallized from benzene. V (Y% = 64%, m.p. = 165-166, Lit = 167 °C) XXIV (Y% = 71%, m.p. 158-159 °C).

2.8.6 Preparation of pyurvic acid

In a glass mortar were placed tartaric acid, (200 g, 1.33 mol), and freshly fused potassium hydrogen sulphate, (300 g, 2.2 mol). The mixture was grined in to intimate mixture. The mixture was placed in a 1.5 litre round bottomed flask, filtered with a still head and a long air condenser, and heated in an oil bath at 210-220 °C until distilled over.

The distillation was fractionated under reduced pressure and pyruvic acid was collected at 75-80 °C/25 mmHg.

2.8.7 Preparation of m-nitrobenzaldehyde (VII)

In a 500 ml two necked round bottom flask equipped with a mechanical stirrer and a dropping funnel, concentrated sulphuric acid (250 ml), and fuming nitric acid (21.5 ml) were placed. The mixture was stirred, cooled to 0 °C in a bath of ice and salt, and benzaldehyde, (60 ml. 0.59 mol) was added drop wise. The mixture was warmed gradually to 40 °C. After cooling to room temperature, the mixture was poured in a thin stream with vigorous stirring in to finely crushed ice. The mixture was filtered, washed with a little water. The oily layer was pressed out with a wide glass stopper, and dried on air. The crude solid was melted under excess of a solution of sodium carbonate (10 percent), stirred, cooled, filtered, and dried on air, recrystilized from hot toluene and pet-ether. Y% = 50%, m.p. = 58-59, Lit = 58 °C.

2.8.8 Preparation of benzylidene anilines (X and XII)

In a 100 ml round bottomed flask fitted with a reflux condenser, anisaldehyde or benzaldehyde, (0.05 mol), aniline or m-nitroaniline (0.05 mol) and rectified spirit 20 ml, were placed and heated on water bath under reflux for 20 minutes. Water was added until a slight cloudiness

persists, and allowed to cool. The oil which has been separated was induced to crystallize by rubbing with glass rod. The solid deposit product was collected by filtration, washed well with aqueous ethanol. Aqueous methanol was used for recrystallization white plate crystals. X (Y% = 81%, m.p. = 55-56, Lit = 57 °C) ; XII (Y% = 88%, m.p. = 71-72, Lit 72 °C).

2.8.9 Preparation of N- P-methoxybenzyl anilines (XI and XIII)

In a two-necked round bottomed flask fitted with a reflux condenser, in the side neck the stopper was placed, and a magnetic follower was inserted. Benzylidene aniline, X or XII (0.034 mol) and methanol (50 ml) were placed, warmed to about 40 °C, and sodium borohydride (0.6 g, 0.034 mol) was added portion wise with stirring over a period of 30 minutes. The solution was heated under reflux for a further 15 minutes, then water was added, cooled, filtered, and dried on air. The solid amine was collected, and recrystalized from aqueous ethanol. XI (Y% = 90%, m.p. = 46-47, Lit 47) ; XIII (Y% = 90%, m.p. = 102-103, Lit = 106 °C).

2.8.10 Preparation of Phenyl pyruvic acid (XV)

In a 500 ml round-bottomed flask equipped with a reflux condenser, α-acetamidocinnamic acid (10.3 g, 0.05 mol), and hydrochloric acid. (1M, 200 ml), were placed. The mixture was boiled for 3 hours, a small quantity of green oil was removed by rapidly filtering through a small plug of cotton wool. The filtrate was cooled to room temperature and leaved at 0 °C for 48 hours. The crystalline product was collected, washed with ice cold water and dried in a vacuum desiccator over anhydrous calcium chloride and potassium hydroxide pellets. Y% = 55%, m.p. = 156-157, Lit = 157 °C).

2.9 Preparation of quinoline derivatives

2.9.1. Preparation of 2-phenylquinoline-4-carboxylic acids (XIV, XXIV, XXV, XXVI and XXVII)

In a 100 ml round bottomed flask, equipped with a reflux condenser, purified benzaldehyde (0.6 g, 0.5 ml, 0.236 mol), freshly distilled pyruvic acid (1 ml, 0.25 mol), and absolute ethanol (5 ml), were placed. The mixture was heated to boiling point on water bath. A solution of the required pure amine (0.248 mol), and absolute ethanol (2.5 ml), was added slowly, with frequent shaking for 1 hour. The mixture was refluxed on a water bath for 3 hours, then allowed to stand overnight. The crude product was filtered at the pump. XIV (Y% = 51%, m.p. = 209-210, Lit = 210 °C); XXIV (Y% = 66%, m.p. = 190-192 °C) ; XXV (Y% = 77%, m.p. = 244-245 °C) ; XXVI (Y% = 62%, m.p. = 165-167 °C) ; XXVII (Y% = 68%, m.p. = 304-306 °C).

2.9.2. Preparation of 2,3-diphenylquinoline-4-carboxylic acids (XVI, XVII, XVIII, XIX, XX, XXI, XXII and XXIII)

In a 100-ml round bottomed flask, equipped with a reflux condenser, purified benzaldehyde (0.6 m, 0.5 ml, 0.236 mol), phenyl pyruvic acid, (0.5 g, 0.25 mol), and absolute ethanol, (2.5 ml), were placed. The mixture was heated to boiling point on water bath. A solution of the required pure amine (0.248 mol), and absolute ethanol (1.25 ml), was added slowly with frequent shaking for 1 hour. The mixture was refluxed on a water bath for 3 hours. Then allowed to stand overnight. The crude product was filtered at the pump, washed with a little ether and recrystallized from ethanol. XVI (Y% = 55%, 62%, m.p. = 245-146 °C) ; XVII (Y% = 78%, m.p. = 280-282 °C) ; XVIII (Y% = 63% , m.p. = 145-146 °C) ; XIX (Y% = 84%, m.p. = 185-186 °C) ; XX (Y% = 64%, m.p. =

212-214) ; XXI (Y% = 57%, m.p. = 145-147 °C) ; XXII (Y% = 61%, m.p. = 272-273 °C) ; XXIII (Y% = 68%, m.p. 110-112).

2.9.3. Preparation of Methyl-2-phenylquinoline-4-formate(XXX) and Methyl-2,3-diphenylquinoline-4-formate (XXXI)

In a 25 ml round -bottomed flask, fitted with a reflux condenser, 2-phenylquinoline-4-carboxylic acid (XIV) or 2,3-diphenylquinoline-4-carboxylic acid (XVI) (0.3 g), methanol (10 ml), and concentrated sulphuric acid (1 ml), were placed. The mixture was refluxed for 2 hours, cooled to room temperature, then left overnight. Sodium carbonate solution was added to the mixture, and left overnight again, washed with distill water, a pale yellow crystals was collected. XXX (Y% = 50%, m.p. = 58-59 °C) ; XXXI (Y% = 33%, m.p. = 215-216 °C)

2.9.4 Preparation of 2,3-diphenylquinoline-4-carbonyl amides (XXXII, XXXIII and XXXIV)

In one neck round bottomed flask (100 ml), fitted with a reflux condenser which connected with guard tube, 2,3-diphenylquinoline-4-carboxylic acid (XVII) (1.0 g, 0.003 mol), chloroform (25 ml) and thionyl chloride (0.5 ml) was placed, the mixture was stirred by magnetic stirrer for half hour (30 minutes). Ammonia (0.1 ml) was added immediately with continuous stirring. Clear crystals were occurred, the product was allowed to stand for several hours, filtered, and dried on air, white crystals were collected. XXXII (Y% = 55%, m.p. = 240-242 °C) ; XXXIII (Y% = 75%, m.p. = 185-186 °C) ; XXXIV(Y% = 66%, m.p. = 240-242 °C).

2.10. Preparation of benzylidene derivatives

2.10.1 Preparation of benzylidene sulphanilamides (XXXV and XXXVI)

In a 100 ml round-bottomed flask fitted with a reflux condenser, benzaldehyde (5.3 g, 5 ml, 0.05 mol), sulphanilamide (0.05 mol), and rectified spirit (20 ml), were placed and heated on water bath under reflux for 3 hours, then allowed to stand overnight. The precipitate was filtered at the pump and recrystalized from ethanol. XXXV (Y% = 69%, m.p. = 196-198 °C) ; XXXVI (Y% = 72%, m.p. = 194-195 °C).

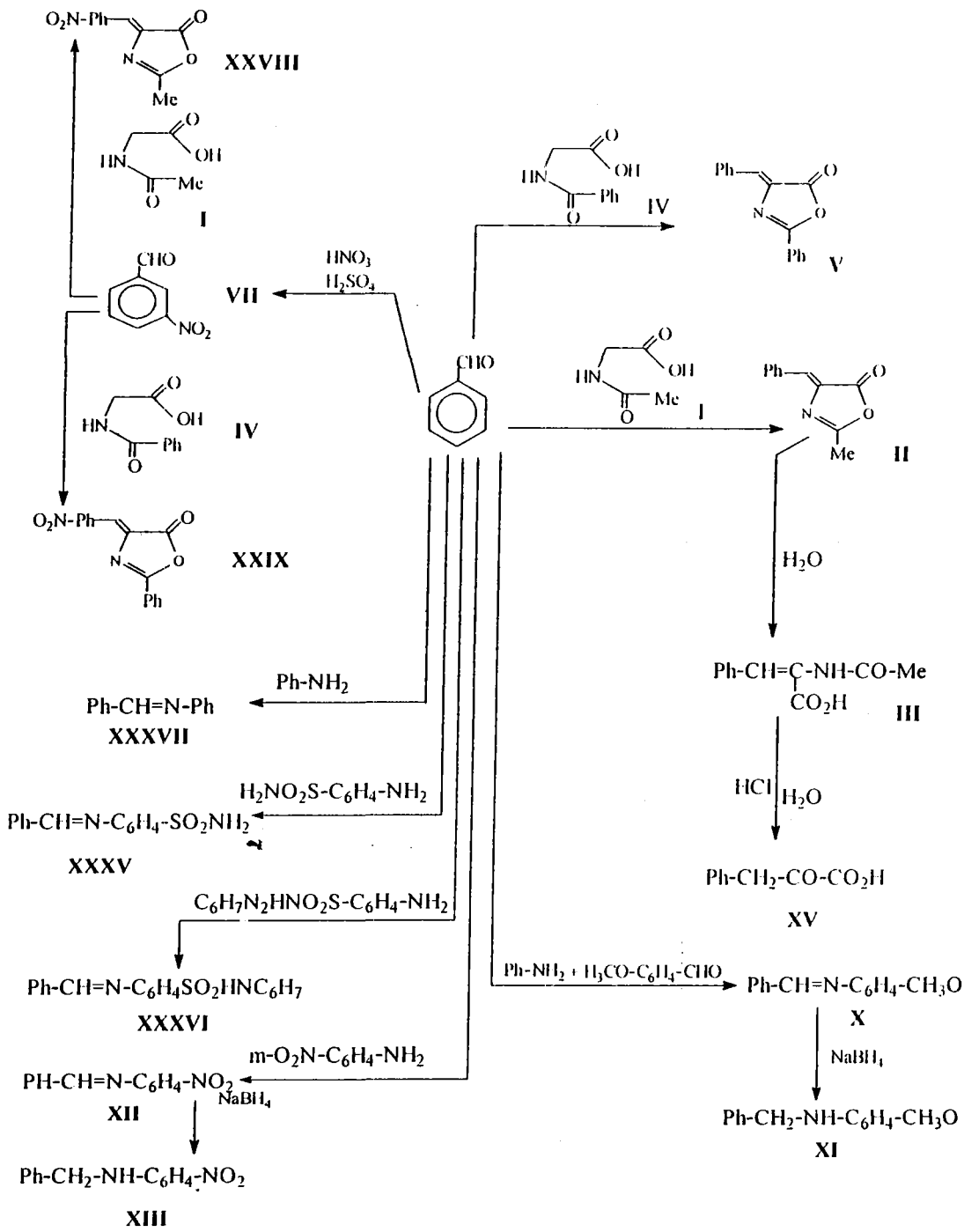
2.10.2 Preparation of benzylidene aniline (XXXVII)

In a 100 ml round-bottomed flask fitted with a reflux condenser, benzaldehyde (5.3 gm, 5 ml, 0.05 mol), aniline (4.6 gm, 4 ml, 0.05 mol), and rectified spirit, 20 ml, were placed and heated on water bath under reflux for 3 hours, and allowed to cool. The oil which separated has been induced to crystallize by rubbing with glass rod. The solid deposit product was collected by filtration, wash well with aqueous ethanol. Aqueous ethanol was used for recrystallization, XXXVII (Y% = 66%, m.p. = 60-62 °C) (Furniss, *et al*, 1989).

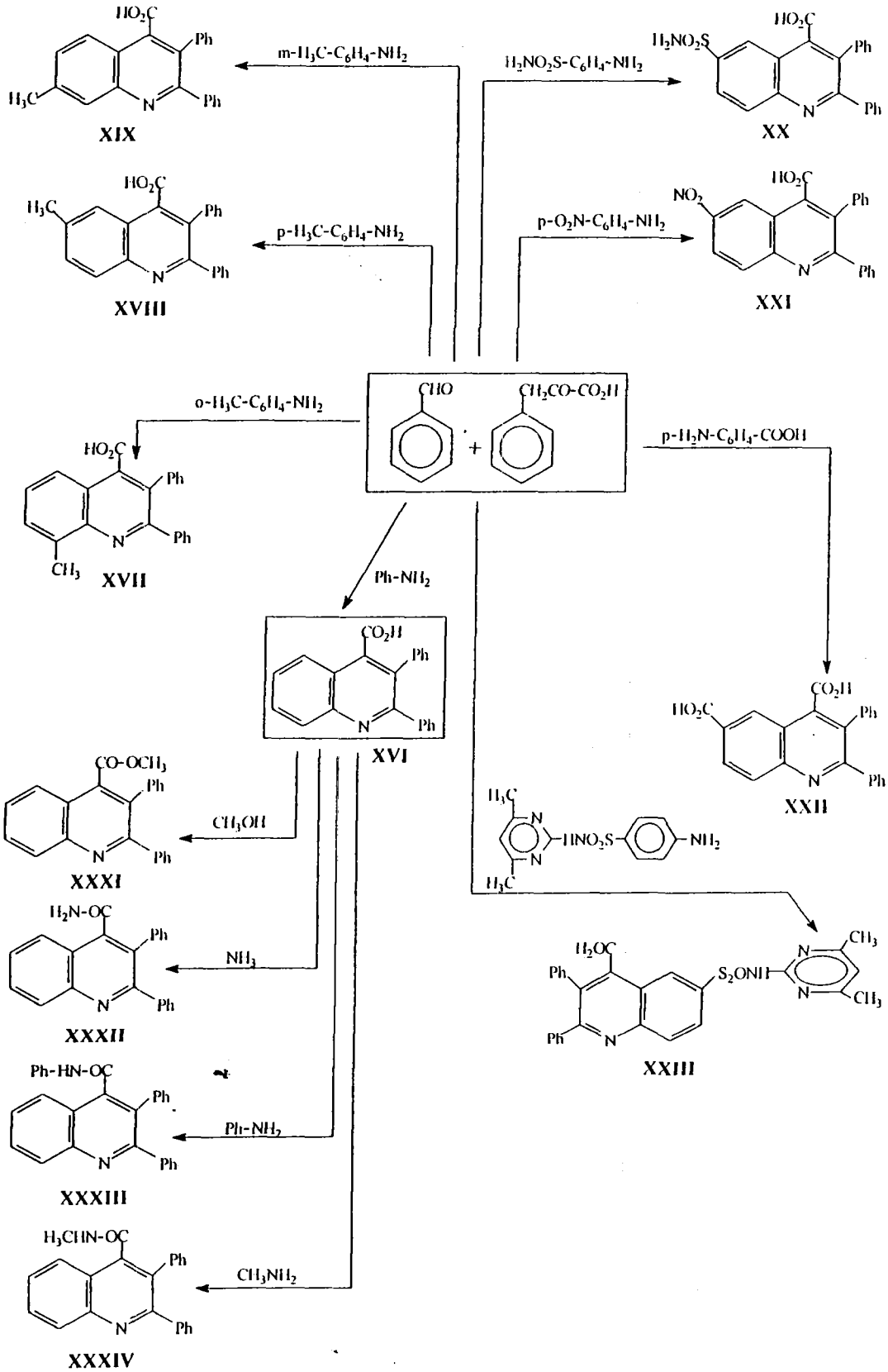
2.11 Antibacterial activity

The standard microbiological two layer agar diffusion technique was adopted with some modification. Nutrient agar (Oxoid) which was used as the culture medium, was reconsitituted, sterilized at 121 °C for 15 minutes and distributed in 15 ml aliquots into sterile Petri-dishes and allowed to set forming the base layer. The organisms (*B. subtilis, S. aureus, E. coli* and *P. vulgaris*) were grown in nutrient broth (Oxoid) at 37 °C for 18 hours. Each bacterial culture was used to introduce to inoculate the agar media. The inoculated medium (1×10^8 cell per ml) was distributed in 10 ml portions onto the surface of the base layer

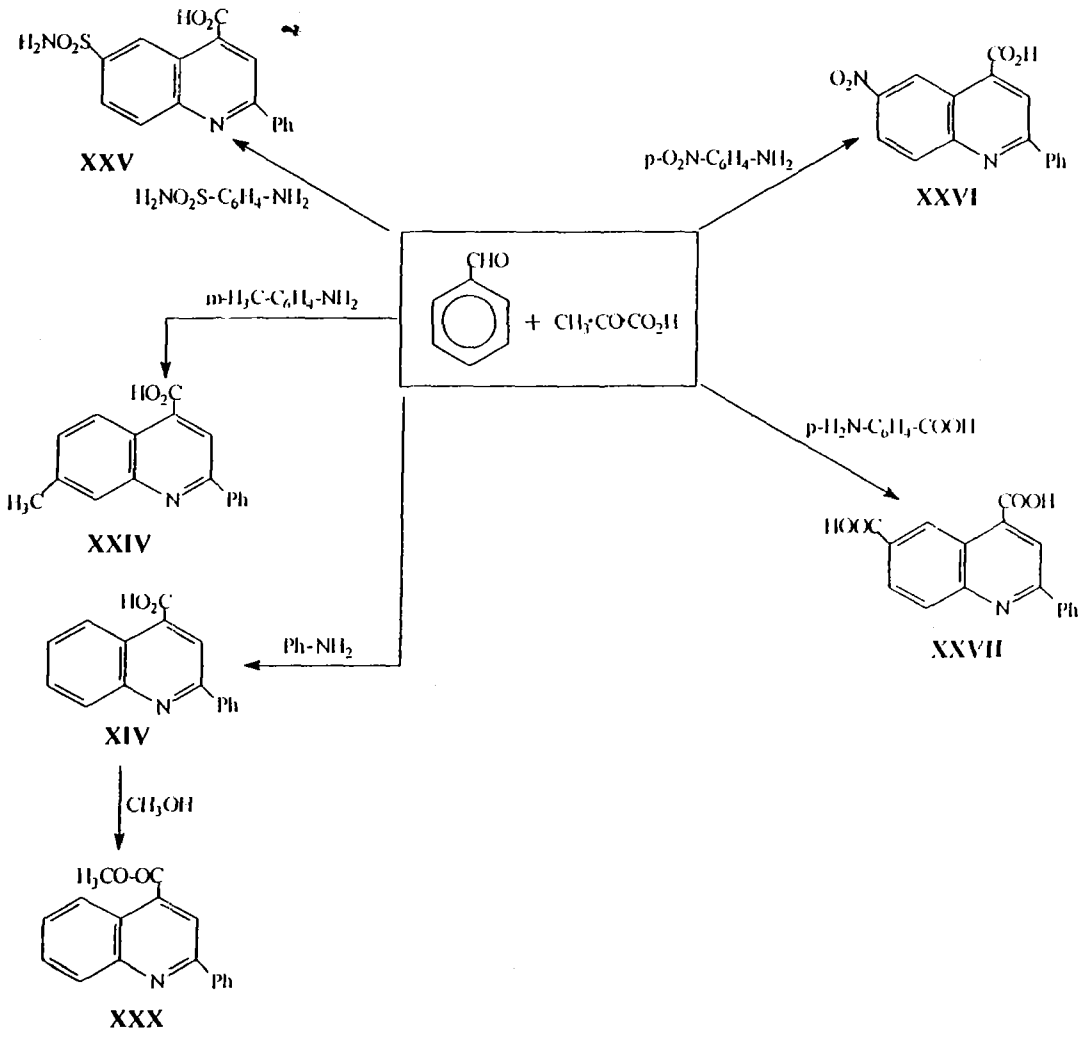
evenly. Five cups 5 mm diameter were cut out using sterile cork borer. 0.2 ml of each solution (5 mg/ml) of the test compound in PEG was added to these cups and allowed to diffuse at room temperature. The plates were incubated at 37 °C for 18 hours. The mean diameters of the inhibition zones are tabulated in table (2-9).



Scheme 2-1: Chemical structures of the prepared intermediates



Scheme 2-2: Chemical structures of the 2,3-diphenylquinoline-4-carboxylic acids and their derivatives

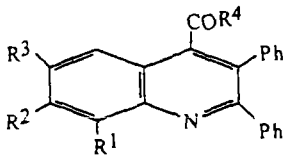


Scheme 2-3: Chemical structures of the 2-phenyl-quinoline-4-carboxylic acids and their derivatives

Table 2-1.a: The chemical names of the prepared intermediate compounds.

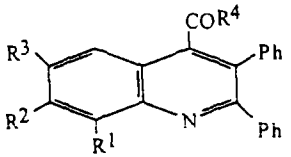
Compounds No.	Names of compounds
I	Acetylglycine
II	4-Benzylidene-2-methyloxazol-5-one.
III	2-Acetamido cinamic acid
IV	Benzoylglycine.
V	4-Benzyledene-2-phenyloxazol-5-one.
VI	Pyruvic acid
VII	*m*-Nitrobenzaldehyde.
X	*p*-Methoxy benzylidene aniline.
XI	N-*p*-Methoxybenzyl aniline.
XII	N-Benzylidene-m-nitroaniline.
XIII	N-Benzyl-m-nitroaniline.
XXVIII	4-Nitrobenzylidene-2-methyloxazol-5-one.
XXIX	4-Nitrobenzylidene-2-phenyloxazol-5-one.
XV	Phenyl pyruvic acid.
XXXV	Bnzylidene sulphanilamide.
XXXVI	Benzylidene sulphadimidine.
XXXVII	Benzylidene aniline.

Table 2-1.b: Chemical names of 2,3-diphenylquinoline-4-carboxylic acids and their derivatives.



Compound No.	R^1	R^2	R^3	R^4	Names for compounds.
XVI	H	H	H	OH	2,3-diphenylquinoline-4-carboxylic acid.
XVII	CH_3	H	H	OH	8-methyl-2,3-diphenylquinoline-4-carboxylic acid.
XVIII	H	H	CH_3	OH	6-methyl-2,3-diphenylquinoline-4-carboxylic acid.
XIX	H	CH_3	H	OH	7-methyl-2,3-diphenylquinoline-4-carboxylic acid.
XX	H	H	S_2ONH_2	OH	2,3-diphenyl-6-sulphonamidoquinoline-4-carboxylic acid.
XXI	H	H	NO_2	OH	6-nitro-2,3-diphenylquinoline-4-carboxylic acid.
XXII	H	H	COOH	OH	2,3-diphenylquinoline-4,6-dicarboxylic acid.
XXIII	H	H	$SO_2NHC_6H_7N_2$	OH	2,3-diphenylquinoline-6-sulphadimidine-4-carboxylic acid.
XXXI	H	H	H	OCH_3	Methyl-2,3-diphenylquinoline-4-formate.
XXXII	H	H	H	NH_2	2,3-diphenylquinoline-4-carbox amide.
XXXIII	H	H	H	NH.Ph	N-phenyl-2,3-diphenylquinoline-4-carbox amide.
XXXIV	H	H	H	$NH.CH_3$	N-methyl-2,3-diphenylquinoline-4-carbox amide.

Table 2-1.c: Chemical names of 2-phenylquinoline -4-carboxylic acids and their derivatives.

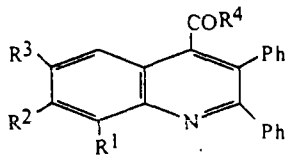


Compounds No.	R^1	R^2	R^3	R^4	Names for compounds.
XIV	H	H	H	OH	2-phenylquinoline-4-carboxylic acid.
XXIV	H	CH_3	H	OH	7-methyl-2-phenylquinoline-4-carboxylic acid.
XXV	H	H	S_2ONH_2	OH	6-sulphonamido-2-phenylquinoline-4-carboxylic acid.
XXVI	H	H	NO_2	OH	6-nitro-2-phenylquinoline-4-carboxylic acid.
XXVII	H	H	COOH	OH	2-phenylquinoline-4,6-dicarboxylic acid.
XXX	H	H	H	OCH_3	Methyl-2-phenylquinoline-4-formate.

Table 2-2.a: Reaction conditions of the prepared intermediate compounds

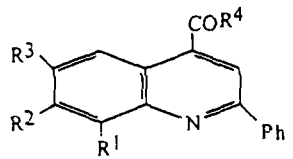
Compound No.	Reaction temp.	Reaction time	Recrystal. solv.	yield %	M.p. °C
I	at room temp.	15-20 minutes	H_2O	94%	204-205 (lit. 207-208)
II	under reflux	1 hour	CCL_4	76%	150-151 (lit. 150)
III	under reflux	4 hour	H_2O	86%	187-188 (lit. 191-192)
IV	at room temp.	4 hour	H_2O	76%	184-185 (lit. 187)
V	under reflux	2 hours	C_6H_6	64%	165-166 (lit. 167-168)
VII	0-5 C°	30 minutes	$C_6H_5CH_3$	50%	58-59 (lit. 58)
X	under reflux	20 minutes	CH_3OH	81%	55-56 (lit. 57-58)
XI	under reflux	15 minutes	CH_3OH	90%	46-47 (lit. 46-47)
XII	under reflux	20 minutes	CH_3OH	88%	71-72 (lit. 71-72)
XIII	under reflux	15 minutes	CH_3OH	90%	102-103 (lit. 106-107)
XXVIII	under reflux	1 hour	CCl_4	62%	130-132
XXIX	under reflux	2 hours	C_6H_6	71%	158-159
XXXV	under reflux	3 hours	CH_3CH_2OH	69%	196-198
XXXVI	under reflux	3 hours	CH_3CH_2OH	72%	194-195
XXXVII	under reflux	3 hours	CH_3CH_2OH	66%	60-62
XV	under reflux	3 hours	CH_3CH_2OH	55%	156-157 (lit. 157)

Table 2-2.b: Reaction conditions of 2,3-diphenyl quinoline-4-carboxylic acids and their derivatives



Compound No.	R1	R2	R3	R4	reaction temp.	reaction time	recrystall solv.	Yield %	m.p. °C
XVI	H	H	H	OH	under reflux	3 hours	CH_3CH_2OH	55%	245-246
XVII	CH_3	H	H	OH	under reflux	3 hours	CH_3CH_2OH	78%	280-282
XVIII	H	H	CH_3	OH	under reflux	3 hours	CH_3CH_2OH	63%	145-146
XIX	H	CH_3	H	OH	under reflux	3 hours	CH_3CH_2OH	84%	185-186
XX	H	H	SO_2NH_2	OH	under reflux	3 hours	CH_3CH_2OH	69%	212-214
XXI	H	H	NO2	OH	under reflux	3 hours	CH_3CH_2OH	57%	145-147
XXII	H	H	CO_2H	OH	under reflux	3 hours	CH_3CH_2OH	61%	272-273
XXIII	H	H	$SO_2NHC_6H_7N_2$	OH	under reflux	3 hours	CH_3CH_2OH	68%	110-112
XXXI	H	H	H	OCH_3	under reflux	2 hours	H_2O	33%	215-216
XXXII	H	H	H	NH_2	at room temp	30 minutes	CH_3CH_2OH	55%	240-242
XXXIII	H	H	H	NHPh	at room temp	30 minutes	CH_3CH_2OH	75%	185-186
XXXIV	H	H	H	$NHCH_3$	at room temp	30 minutes	CH_3CH_2OH	66%	240-242

Table 2-2.c: Reaction conditions of 2-phenyl quinoline-4-carboxylic acids and their derivatives



Compound No	R1	R2	R3	R4	reaction temp	reaction time	recrystall solv.	Yield %	m.p °C
XIV	H	H	H	OH	Under reflux	3hours	CH_3CH_2OH	51%	209-210 (lit. 210)
XXIV	H	CH_3	H	OH	Under reflux	3hours	CH_3CH_2OH	66%	190-192
XXV	H	H	SO_2NH_2	OH	Under reflux	3hours	CH_3CH_2OH	77%	244-145
XXVI	H	H	NO_2	OH	Under reflux	3hours	CH_3CH_2OH	62%	165-167
XXVII	H	H	CO_2H	OH	Under reflux	3hours	CH_3CH_2OH	68%	305-306
XXX	H	H	H	OCH_3	Under reflux	2hours	H_2O	50%	58-59

Table 2-3.a: Infrared data of the intermediate compounds.

Compound No	C=O st.vib.	C=C st.vib. aromatic	N-H bend	C-N st.vib.	C-C	O-H st.vib.	C-H st.vib.	Ar-C C-H bend	C-H st.vib. aromatic	C=N st.vib.	N-O	C-O st.vib.	N-H stvib.
I	1710, 1650	-	1550	1050, 1220	1310	3500, 2600	2930 weak	-	-	-	-	1200	3350
II	1780	1600, 1590	-	-	1340	-	2950	870, 680	3030	1580	-	1260	-
III	1650, 1660	1600	1550	-	1320	3470, 2500	-	780, 680	-	-	-	1220	-
IV	1750, 1700	1610, 1600, 1590	1530	1170	1315	3500, 2600	3050	705, 810	-	-	1210	3210	3350
V	1800	1620, 1600, 1550	-	-	1330	-	2850	680, 720	3020	-	-	1200	-
VII	1700	1690, 1590	-	1105	1310	-	2990, 2750	700, 760	-	-	1530, 1330	-	-
X	-	1620, 1600, 1500	-	-	1320	-	2850	750, 680	3030	1580	-	1150	-
XI	-	1620	1610	1230	1320	-	2850	730	-	-	-	1150	-
XII	-	1620	1570	-	1320	-	2860	710	-	-	1520, 1350	-	-
XIII	-	1620	1575	1150	1320	-	-	670			-	2860-	-

Table 2-3.a continued

Compound No	I.R characteristic bands cm^{-1}														
	C=O st.vib.	C=C st.vib. aromatic	C=N st.vib.	C-C	C-N st.vib.	C-H st.vib. aromatic	C-H bend	O-H st.vib.	C-H st.vib. aliphatic	C-O st.vib.	N-O	N-H st.vib.	N-H of SO_2NH_2 st. vib.	SO_2.st. vib. asym	SO_2.st. vib. sym.
XV	1720, 1700	1620 1480	-	1270 1180	-	3030	850 750	3450-2600	-	1150	-	-	-	-	-
XXVIII	1790	1650, 1600, 1500	1530	1260	1100	3050	850 790 700	-	-	1170	1550, 1350	-	-	-	-
XXIX	1780	1650, 1600, 1550	1520	1165	1260	3080	830 700	-	-	1340	1510, 1320	-	-	-	-
XXXV	-	1620, 1500, 1490	1580	-	-	3020	820 750	-	3150	-	-	3450, 3350	-	1350	1150
XXXVI	-	1600, 1590	1600	-	1100	3100	880 820	-	3160	-	-	-	3300	1300	1130
XXXVII	-	1620 1460	1600 1500	-	-	3050	800 780	-	-	-	-	-	-	-	-

Table 2-3.b: Infrared of 2,3-diphenylquinoline-4-carboxylic acids and their derivatives

Compounds No.	I.R characteristic bands cm^{-1}													
	C=O St. vib.	C=C St. vib.	C=N St. vib.	C-C St. vib.	C-N St. vib.	C-H St. vib.	C-H bend	O-H St. vib..	C-O St. vib.	N-O	N-H St. vib.	SO_2 St.vib		N-H bend of SO_2NH_2
XVI	1670	16151 470 1400	1570	1170	1210	-	730 700	3400- 2600	1280	-	-	asym	sym	-
XVII	1700	1490 1420	1620	1320	1210	3200	740 680	3400- 2600	1280		-	-	-	-
XVIII	1700	1610 1450	1580	1320	1210	3020	780 700	3400- 2600	1250	-	-	-	-	-
XIX	1680	1600 1450 1420	1500	1300	1100	-	850 780 700	3400- 2600	1200	-	-	-	-	-
XX	1690	1480 1450	1580	1160	-	-	880 820 760	3400- 2600	1200	-	3400, 3300	1410 1370	1150	1600
XXI	1690	1500 1400	1490	1180	1160	-	820 780	3400- 2600	1200	1520, 1350	-	-	-	-

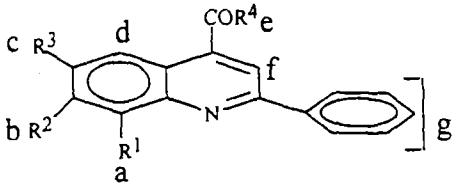
Table 2-3.b cont.

Compounds No.	I.R characteristic bands cm^{-1}													
	C=O St. vib.	C=C St. vib. ar.	C=N St. vib.	C-C St. vib.	C-N St. vib.	C-H St. vib.	C-H St. vib.	O-H St. vib.	C-O St. vib.	N-O St. vib.	N-H St. vib.	SO_2 St.vib		N-H bend of SO_2NH_2
XXII	1700, 1690	1600, 1580	1520	1290	1180	3180	820 780	3300	1220	-	-	-	-	-
XXIII	1700	1600, 1500	1520	1200	1200	3060	750 700	3370	1280	-	3300	1350	1160	1600
XXXI	1720	1570 1450	1530	1120 1230	1320	2960	780 690	-		-	-	-	-	-
XXXII	1680	1600 1430	1510	1200	1220	3050	790 700	-	1320	-	3200			
XXXIII	1770	1600 1470	1520 1500	1100	1190	2900	740	-	1320		3200			1570 amide
XXXIV	1680	1600 1450	1500	1260	1170	3060 broad	760 690	-	1380	-	3060			

Table 2-3.c: Infrared data of 2-phenylquinoline-4-carboxylic acids and their derivatives.

Compound No	I-R characteristic bands cm^{-1}												
	C=O st. vib.	C=C	C=N st. vib.	C-C	C-N st. vib.	C-H st. vib.	C-H bend	O-H st.	O-H bend	C-O st. vib.	N-O	SO_2 st.vib.	N-H
XIV	1680	1600	1600	1230	1210	2820	760 720	-	1350	-	-	-	-
XXIV	1700	1600 1420	1540	1230	1200	2910	890 720	3450	1340	1030	-	-	-
XXV	1700	1600 1480	1530	-	1100	-	820 750	3400- 2600	1330	1170	-	1380 asym. 1160 sym.	1620 bend 3270, 3250 st vib.
XXVI	1770	1670	1520	1200	1130	-	750 700	3350	1330	1150	1520, 1320	-	-
XXVII	1700	1600 1420	1540	1190	1220	-	850 780	3320	1380	1120	-	-	-
XXX	1720	1570 1450 1420	1530	1190 1230	1320	2960	780 690	-	-	-	-	-	-

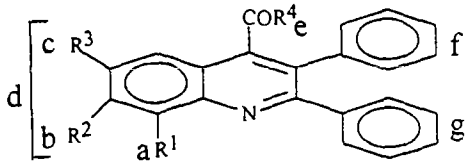
Table 2-4.a: ^{1}H- NMR spectral data of the 2-Phenylquinoline-4-Carboxylic derivatives:



Proton type	Compound No. and chemical shift, intensity and multiplicity					
	XIV	XXIV	XXV	XXVI	XXVII	XXX
R^1	H	H	H	H	H	H
R^2	H	CH_3	H	H	H	H
R^3	H	H	SO_2NH_2	NO_2	COOH	H
R^4	OH	OH	OH	OH	OH	O-CH_3
a	8.67 (1, d)	- 7.96 (1, s)	7.85 (1,d)	7.23 (1,d)	7.70 (1,d)	818-8.57 (4,m)
b	-	2.56 (3,S)	7.76 (1,d)	7.41 (1,d)	7.89 (1,d)	-
c	-	8.27 (1,d)	-	-	10.01(1,S)	-
d	8.13-8.35 (3,m)	8.57 (1,d)	7.27 (1,s)	8.14 (1,s)	7.89 (1,s)	-
e	14.02(1,S)	13.97(1,S)	-	9.38(1,S)	12.89(1,S)	4.02(3,S)
f	8.47 (1,s)	8.40 ((1,s)	7.83 (1,S)	8.13 (1,S)	8.30 (1,s)	8.48 (1,S)
g	7.53-7.90 (5,m)	7.50-7.60 (5,m)	7.30 –745 (5,m)	7.43-7.48 (5,m)	7.40-7.60 (5,m)	7.50-7.87(5,m)

M = multiplet, S = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet. Solvent = DMSO.

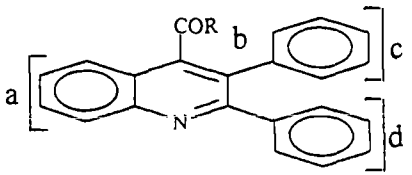
Table 2-4.b: ^{1}H NMR spectral data of the 2,3-diphenyl quinoline-4-carboxylic acid derivatives



Proton type	Compound No. and chemical shift, intensity and multiplicity							
	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII
R^1	H	CH_3	H	H	H	H	H	H
R^2	H	H	H	CH_3	H	H	H	H
R^3	H	H	CH_3	H	SO_2NH_2	NO_2	COOH	$SO_2NHC_6H_7N_2$
R^4	OH	OH	OH	OH	OH	OH	OH	OH
a	-	2.51 (3,d)	-	-	-	-	-	-
b	-	-	-	2.24(3,S)	-	-	-	-
c	-	-	2.50 (3,S)	-	6.64 (2,S)	-	12.82(1,S)	3.37(3,s), 2.50 (3,s), 7.88-8.0 (1,s)
d	7.65-7.75 (4,m)	7.94-8.00 (3,m)	7.50-7.73 (3,m)	7.42-7.73 (3,m)	7.71-7.98 (3,m)	7.72-8.20 (3,m)	7.71-7.92 (3,m)	7.61-7.72 (3,m)
e	10.64 (1,S)	10.67 (1,S)	10.58 (1,S)	10.58 (1,S)	10.03 (1,S)	10.28 (1,S)	10.72 (1,S)	10.02 (1,S)
f	7.03-7.18 (5,m)	7.10-7.30 (5,m)	7.06-7.24 (5,m)	7.06-7.20 (5,m)	7.08-7.22 (5,m)	7.09-7.23 (5,m)	7.07-7.24 (5,m)	7.03-7.24 (5,m)
g	7.28-7.38 (5,m)	7.43-7.64 (5,m)	7.27-7.35 (5,m)	7.28-7.37 (5,m)	7.27-7.47 (5,m)	7.31-7.50 (5,m)	7.30-7.42 (5,m)	7.30-7.42 (5,m)

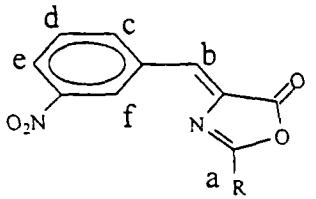
S = singlet, d = doublet, d d = double doublet, t = triplet, q = quartet, m = miltiplet, Solvent = DMSO

Table 2-4.c: ^{1}H.NMR spectral data of the 2,3-diphenylquinoline-4-carbonyl derivatives



Proton type	Compound No. and chemical shift, intensity and multiplicity			
	XXXI	XXXII	XXXIII	XXXIV
R	OCH_3	NH_2	NHPh	$NHCH_3$
a	8.16-8.57 (4,m)	7.64-7.74 (4,m)	7.46-7.50 (4,m)	7.66-7.84 (4,m)
b	4.02 (3,s)	6.54 (2,s)	6.55 (1,s), 7.38-7.40 (5,m)	6.19 (1,s) 2.39 (3,s)
c	7.53-7.88 (10,m)	7.03-7.19 (5,m)	7.15-7.18 (5,m)	7.02-7.17 (5,m)
d		7.27-7.38 (5,m)	7.27-7.31 (5,m)	7.23-7.39 (5,m)

Table 2-4.d: ^{1}H.MMR spectral data of the oxazolone derivatives

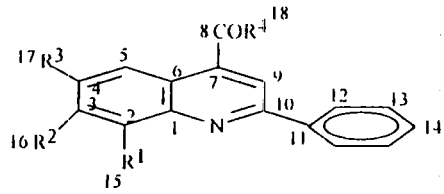


2

Proton type	Compound No. and chemical shift, intensity and multiplicity	
	XXVIII	XXIX
R	CH_3	C_6H_5
a	3.34 (3,s)	7.68-7.81 (5,m)
b	7.40 (1,s)	7.55 (1,s)
c	8.28-8.30 (1,dd)	8.31-8.33 (1,dd)
d	7.76 (1,t)	8.15 (1,d)
e	8.52 (1,d)	8.69 (1,d)
f	9.09 (1,s)	9.23 (1,s)

S = singelet, d = doublet, dd = double doublet, t = triplet, m = multiplet
Solvent = DMSO

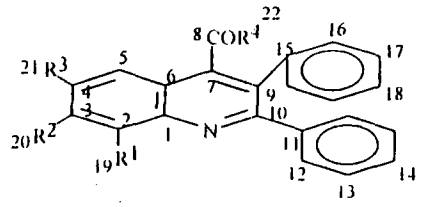
Table (2-5.a): ^{13}C-NMR spectral data of 2-phenyl quinoline –4-carbxylic acid derivatives (Chemical shifts δ-value ppm).



Carbon type	Compound No. and Chemical Shift δ-value ppm					
	XIV	XXIV	XXV	XXVI	XXVII	XXX
R^1	H	H	H	H	H	H
R^2	H	CH_3	H	H	H	H
R^3	H	H	SO_2NH_2	NO_2	COOH	H
R^4	OH	OH	OH	OH	OH	$O.CH_3$
1	138.17	129.23	127.45	127.41	129.47	128.60
2	130.35	140.70	128.63	126.01	130.03	130.41
3	130.54	149.26	129.50	127.86	130.61	130.65
4	130.78	130.44	137.66	140.40	141.44	130.97
5	129.54	130.48	135.73	136.79	129.68	148.89
6	128.34	129.53	127.61	127.53	129.62	129.57
7	138.17	156.20	145.40	129.43	131.36	156.85
8	168.18	168.26	167.08	170.35	167.28	166.85
9	138.46	138.61	140.28	129.64	131.52	138.28
10	148.96	156.28	140.00	148.69	146.56	136.13
11	119.71	118.84	113.83	116.51	116.39	119.90
12	127.78	122.10	116.51	121.20	120.97	123.69
13	124.02	125.64	121.51	121.80	123.37	125.67
14	125.96	127.70	126.28	125.14	127.34	127.77
15	-	-	-	-	-	-
16	-	21.77	-	-	-	-
17	-	-	-	-	167.65	-
18	-	-	-	-	-	53.52

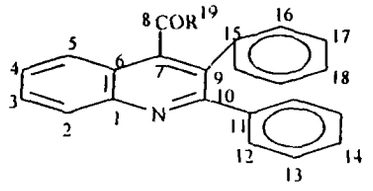
Solvent = DMSO –d6

Table 2-5.b: ^{13}C-NMR spectral data of 2, 3-diphenylquinoline-4-carboxylic acid derivatives (chemical shifts δ-value ppm.)



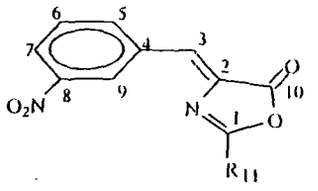
Carbon type	Compound No. and chemical shift δ-value ppm							
	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII
R^1	H	CH_3	H	H	H	H	H	H
R^2	H	H	H	CH_3	H	H	H	H
R^3	H	H	CH_3	H	SO_2NH_2	NO_2	COOH	$SO_2NHC_6H_7N_2$
R^4	OH	OH	OH	OH	OH	OH	OH	OH
1	129.02	129.12	129.11	128.96	131.91	128.55	130.50	129.52
2	128.77	129.00	134.27	128.76	133.44	128.22	131.90	129.72
3	132.19	132.00	134.93	137.38	136.17	129.11	137.80	130.05
4	139.21	138.50	143.66	132.21	141.70	156.00	131.93	133.44
5	138.20	138.32	138.22	138.00	129.22	143.30	130.51	129.82
6	129.16	129.80	132.26	129.00	128.86	-	128.82	129.58
7	137.47	131.30	135.94	138.22	136.15	143.00	131.80	135.15
8	166.00	167.80	165.83	165.93	166.68	166.34	166.34	167.88
9	138.14	133.42	136.69	138.38	137.50	141.37	141.37	136.73
10	143.56	147.40	149.33	143.55	143.24	143.26	143.26	143.17
11			121.52	119.58	121.55	121.16	121.16	126.86
12	122.42	122.00	122.50	123.00	121.83	121.70	124.00	127.96
13	123.09	122.60	122.78	123.03	124.00	125.00	126.68	128.12
14	125.07	126.10	127.69	125.80	126.91	126.96	127.98	128.33
15	127.87	127.32	128.28	127.74	127.96	127.20	128.22	128.83
16	127.87	127.51	128.75	127.85	128.85	128.00	128.55	128.55
17	128.27	128.70	129.00	128.25	129.17	128.20	128.82	129.00
18	128.00	129.00	129.11	128.40	129.48	129.00	129.10	129.52
19	-	21.68	-	-	-	-	-	-
20	-	-	-	21.68	-	-	-	-
21	-	-	21.15	-	-	-	167.29	
22	-	-	-	-	-	-	-	-

Table 2-5.c: ^{13}C-NMR spectral data of 2,3-diphenylquinoline-4-carbonyl derivatives (Chemical shifts δ-value ppm).



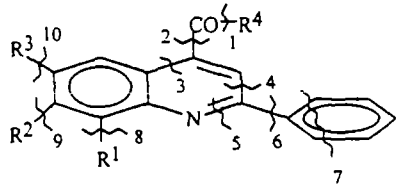
Carbon type	Compound No. And chemical shift δ-value ppm		
	XXXI	XXXII	XXXIV
R	O.CH_3	NH_2	NH.CH_3
1	130.00	130.00	129.62
2	130.40	128.76	128.24
3	130.64	129.02	128.33
4	130.97	129.15	128.64
5	131.00	132.19	128.89
6	136.82	131.82	135.00
7	156.30	137.47	135.59
8	166.84	165.99	169.78
9	138.28	138.15	138.31
10	148.88	143.55	140.62
11	119.90	122.41	122.04
12	123.69	123.09	124.20
13	125.66	125.05	124.53
14	126.00	126.30	126.4
15	127.77	127.86	127.78
16	128.59	127.86	128.18
17	129.59	128.27	128.24
18	129.90	128.41	-
19	53.51	-	25.81

Table 2-5.d: ^{13}C-NMR spectral data of oxazolone derivatives (Chemical shifts δ-value ppm).

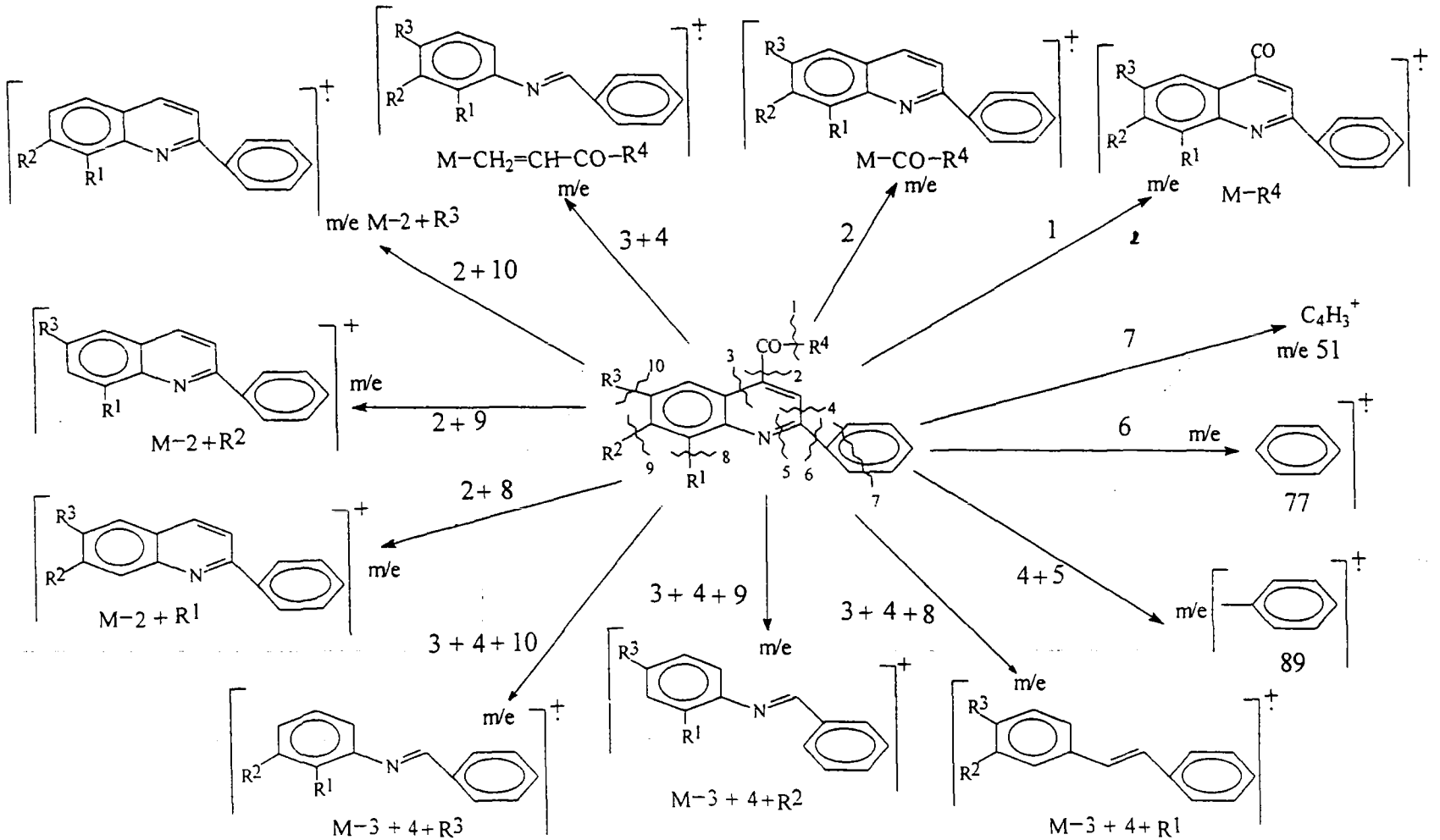


Carbon type	Compound No. And chemical shift	
	XXVIII	XXIX
R	CH_3	Ph
1	105.03	125.42
2	125.52	128.76
3	126.23	130.04
4	127.27	131.07
5	135.18	135.49
6	130.97	134.74
7	138.32	138.48
8	148.66	148.74
9	135.50	135.85
10	168.92	167.00
11	16.13	125.58
12		126.59
13		128.04
14		
15		
16		

Table 2-6.a: Mass spectral data of the 2-phenylquinolline-4-carboxylic acids and their derivatives

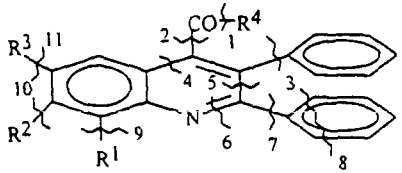


Fragment No.	Compound No. and fragment (m/e) (% relative abundance)					
	XIV	XXIV	XXV	XXVI	XXVII	XXX
R^1	H	H	H	H	H	H
R^2	H	CH^3	H	H	H	H
R^3	H	H	SO_2NH_2	NO_2	COOH	H
R^4	OH	OH	OH	OH	OH	O-CH_3
Molecular Formula	$C_{16}H_{11}NO_2$	$C_{17}H_{13}NO_2$	$C_{16}H_{12}N_2O_4S$	$C_{16}H_{10}N_2O_4$	$C_{17}H_{11}NO_4$	$C_{17}H_{13}NO_2$
Molecular weight	249 (100)	263 (100)	328	294	293 (100)	263 (29)
1	232	-	311	277	276 (7)	232 (3)
2	204 (81)	219 (68)	285	251 (100)	249 (61)	205 (72)
2+8	-	-	-	-	-	-
2+9	-	204 (23)	-	-	-	-
2+10	-	-	205	205(52)	204 (37)	-
3+4	176 (10)	190 (4)	172 (82) (3 + 5)	137 (3) (3 + 5)	220 (5)	176 (8)
3+4+8	-	-	3+5+NH_2 156 (100)	105 (21) (3 + 5 + O_2)	-	-
3+4+9	-	176 (1)	156-SO_2; 92 (66)	91 (3) (105 - N)	-	-
3+4+10	-	-	-	179 (6)	176 (7)	-
4+5	88 (5)	89 (13)	89 (1)	89 (6)	89 (12)	89 (5)
6	77 (4)	77 (7)	77 (5)	77 (19)	77 (13)	77 (8)
7	51 (13)	51 (4)	51 (6)	51 (10)	51 (9)	51 (14)

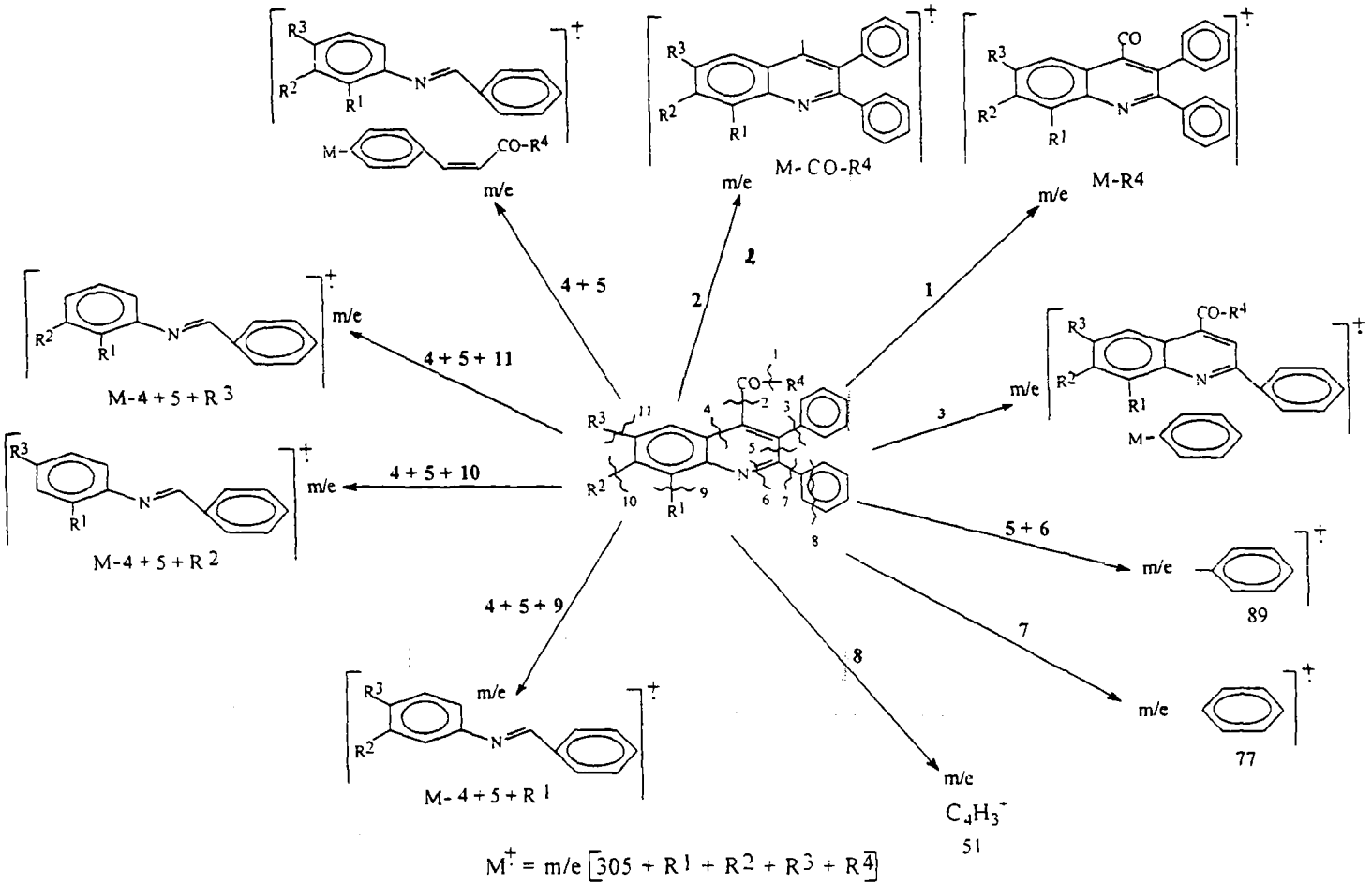


Scheme 2-4: Main fragmentation pathways in the mass spectra of 2-phenylquinolin-4-xarboxylic acid derivatives

Table 2-6.b: Mass Spectral data of the 2,3-diphenyl quinoline-4-carboxylic acid derivatives

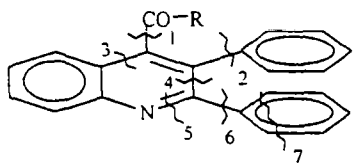


Fragment No	Compound No. and fragment (m/e) (% relative abundance)							
	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII
R^1	H	CH_3	H	H	H	H	H	H
R^2	H	H	H	CH_3	H	H	H	H
R^3	H	H	CH_3	H	SO_2NH_2	NO_2	COOH	$SO_2NHC_6H_7N_2$
R^4	OH	OH	OH	OH	OH	OH	OH	OH
M.F.	$C_{22}H_{15}NO_2$	$C_{23}H_{17}NO_2$	$C_{23}H_{17}NO_2$	$C_{23}H_{17}NO_2$	$C_{22}H_{16}O_4N_2S$	$C_{22}H_{14}N_2O_4$	$C_{23}H_{15}O_4N$	$C_{28}H_{22}O_4N_4S$
M. Wt.	325	339	339	339	404	370	369	518
1	-	-	-	322	-	353	-	-
2	280	294 (1)	-	294	-	325	324	-
3	-	263 (8)	263 (4)	263	327 (35)	294	291	-
2+3	207 (33)	220 (10)	219 (1)	218	282 (3)	278	249	-
4+5	179 (74)	193 (4)	194 (100)	194 (5)	260 (100)	223 (3)	224 (2)	372 (7)
4+5+9	-	179 (100)	-	-	-	-	-	-
4+5+10	-	-	-	179 (100)	-	-	-	-
4+5+11	-	-	179 (3)	-	179 (61)	179 (100)	179 (100)	179 (14)
5+6	89 (4)	89 (38)	89 (14)	89 (9)	89 (10)	89 (5)	89 (4)	89 (4)
7	77 (31)	77 (79)	77 (9)	77 (12)	77 (29)	77 (10)	77 (12)	77 (65)
8	51 (12)	51 (53)	51 (13)	51 (2)	51 (12)	51 (5)	51 (7)	51 (30)

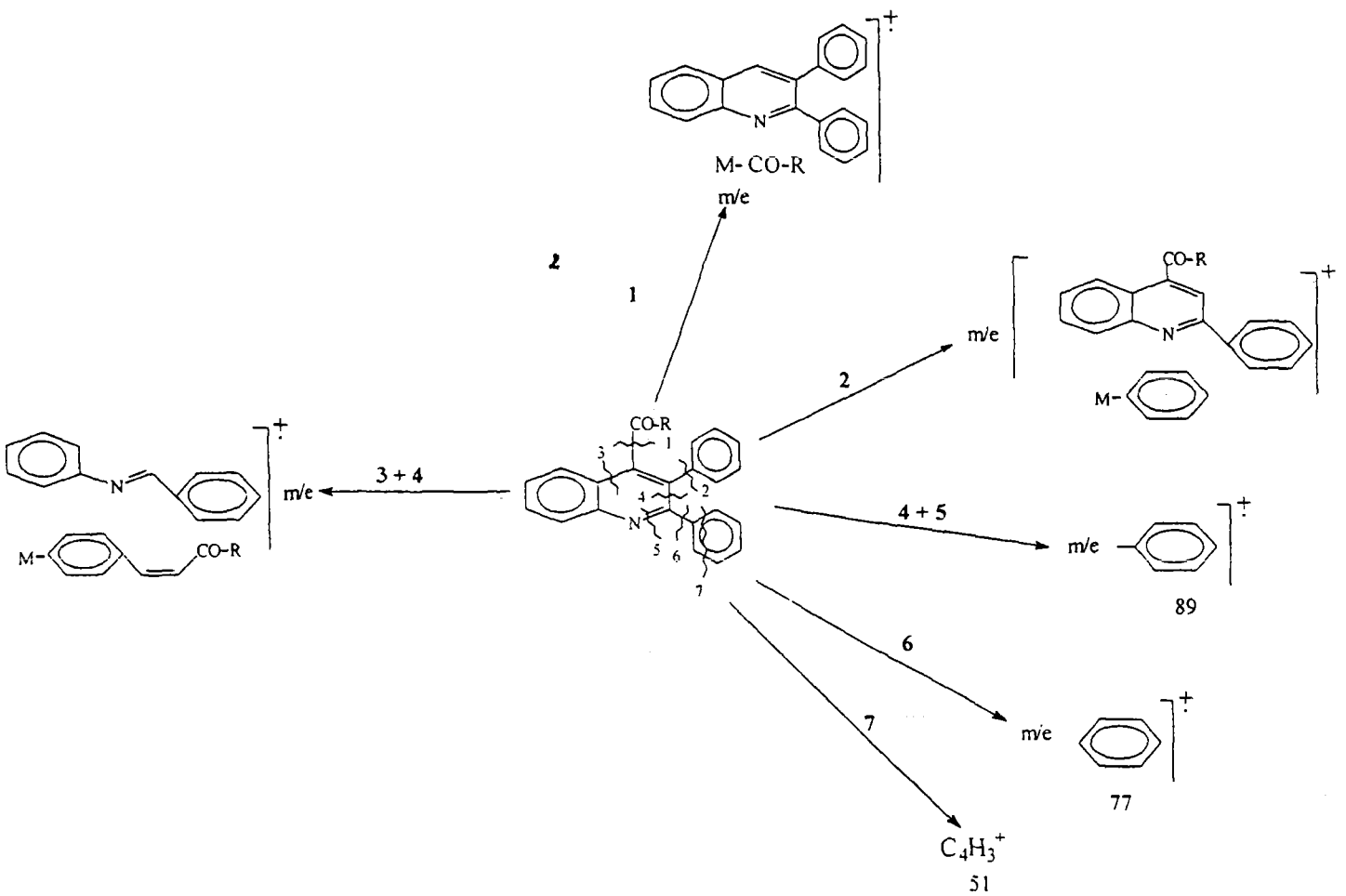


Scheme 2-5: Main fragmentation pathways in the mass spectra of 2,3-diphenylquinolin-4-carboxylic acid derivatives

Table 2-6.C: Mass spectral data of the 2,3-diphenylquinoline-4-carbonyl derivatives



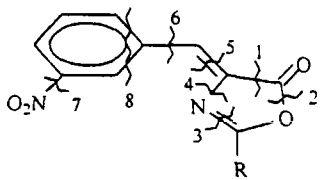
Fragment No.	Compound No. and fragment (m/e) (% relative abundance)			
	XXXI	XXXII	XXXIII	XXXIV
R	O-CH_3	NH_2	NH-C_6H_5	$NHCH_3$
M.F.	$C_{23}H_{17}NO_2$	$C_{22}H_{16}N_2O$	$C_{28}H_{20}N_2O$	$C_{23}H_{18}N_2O$
M.Wt.	339	324	400	338
1	205 (97) (1 + 2)	282 (2)	282 (4)	282 (4)
2	263 (100)	207 (43)	207 (47)	207 (29)
3+4	176 (8)	179 (100)	179 (100)	179 (100)
4+5	88 (4)	89 (6)	89 (4)	89 (2)
6	75 (5)	77 (36)	77 (25)	77 (16)
7	51 (9)	51 (10)	51 (10)	51 (6)



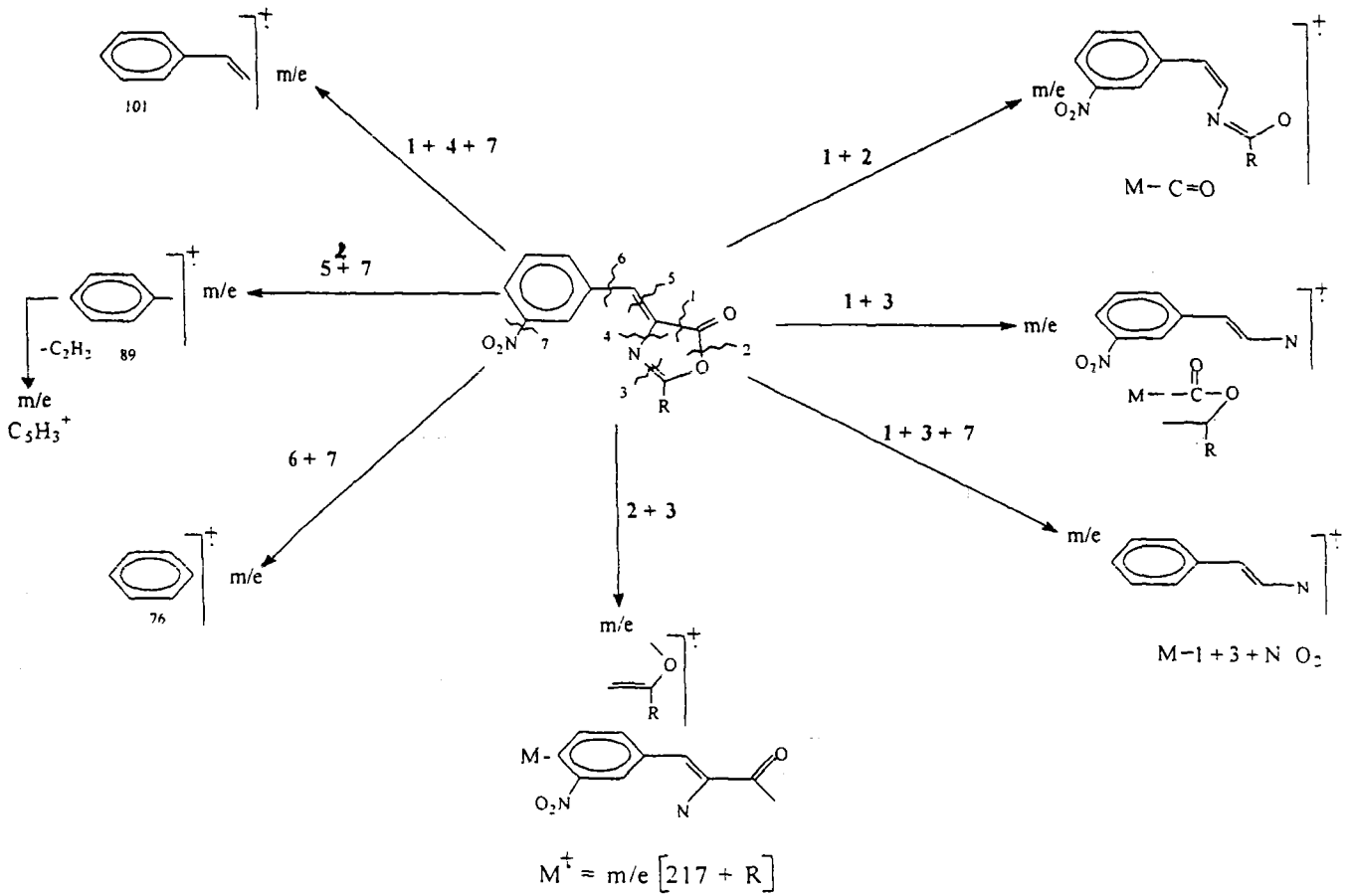
$M^+ = m/e\,[308 + R]$

Scheme 2-6: Main fragmentation pathways in the mass spectra of 2,3-diphenylquinolin-4-carbonyl derivatives

Table 2-6.d: Mass spectral data of the Oxazolones derivatives



Fragment No.	Compound No. and fragment (m/e) (% relative abundance)	
	XXVIII	XXIX
R	CH_3	C_6H_5
M.F	$C_{11}H_8N_2O_4$	$C_{16}H_{10}N_2O_4$
M.W.t	232 (100)	294 (20)
1+2	204 (19)	-
1+3	161 (5)	161
1+3+7	115 (37)	115 (3)
1+4+7	101 (8)	101
5+7	89 (23)	89
6 +7	75 (13)	75 (2)
5 + 7 C_2H_2	63 (28)	63 (1)
2+3	-	105 (100)

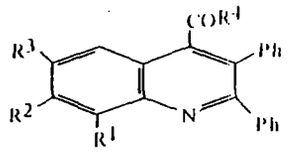


Scheme 2-7: Main fragmentation pathways in the mass spectra of oxazolone derivatives

Table 2-7.a: Ultra violet data of the intermediate compounds.

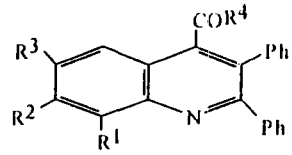
Compounds No.	Solvent used	λ_{max}
I	Acetone	220 , 260
II	Acetone	225 , 265
III	Acetone	230 , 270
IV	Acetone	210 , 260
V	Acetone	210 , 260
VII	Acetone	205 , 265
X	Acetone	210, 225, 235, 270
XI	Acetone	210, 265
XII	Acetone	215, 255
XIII	Acetone	215, 255
V	Acetone	225, 265
XXXV	Acetone	220, 255
XXXVI	Acetone	220, 255
XXXVII	Acetone	215, 235, 270
XXXVIII	Acetone	220, 265
XXXIX	Benzene	205, 210, 220, 255

Table 2-7.b: Ultraviolet data of 2,3 diphenyl quinoline -4-carboxylic acid derivatives.



Compounds No.	R^1	R^2	R^3	R^4	Solvent used	$\lambda_{max.}$
XVI	H	H	H	OH	Benzene	210, 220,
XVII	CH_3	H	H	OH	Acetone	255
XVIII	H	H	CH_3	OH	Acetone	205, 265
XIX	H	CH_3	H	OH	Acetone	210, 265
XX	H	H	SO_2NH_2	OH	Acetone	205, 265
XXI	H	H	NO_2	OH	Acetone	220, 265
XXII	H	H	CO_2H	OH	Benzene	205, 265
XXIII	H	H	$SO_2NHC_6H_7N_2$	OH	Acetone	210, 220,
XXXI	H	H	H	OCH_3	Acetone	255
XXXII	H	H	H	NH_2	Acetone	215, 260
XXXIII	H	H	H	NHph	Acetone	205, 265
XXXIV	H	H	H	$NHCH_3$	Acetone	205, 265
						210, 265
						205, 265

Table 2-7.c: Ultra- violet data of 2-phenylquinoline- 4-carboxylic acid derivatives.

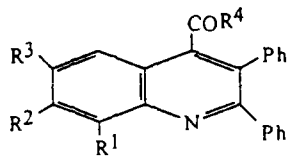


Compound No.	R^1	R^2	R^3	R^4	Solvent used	λ_{max}
XIV	H	H	H	OH	Acetone	205, 265
XXIV	H	CH_3	H	OH	Acetone	205, 265
XXV	H	H	SO_2NH_2	OH	Acetone	210, 265
XXVI	H	H	NO_2	OH	Benzene	205, 265
XXVII	H	H	CO_2H	OCH_3	Acetone	205, 210, 225, 255
XXX	H	H	H	OH	Acetone	215, 265

Table 2-8.a: Thin layer chromatography data of the compounds.

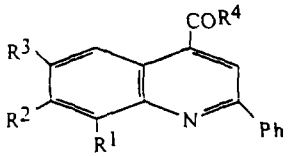
Compound No.	Mobile phase	R_f value
I	chloroform:methanol (9:1)	0.26
II	chloroform:methanol (9:1)	0.96
III	chloroform:methanol (9:1)	0.14
IV	chloroform:methanol (9:1)	0.11
V	chloroform:methanol (9.5 :0.5)	0.88
VI	chloroform:methanol (9.5 :0.5)	0.44
VII	chloroform:methanol (9.5 :0.5)	0.12
X	chloroform:methanol (9.5 :0.5)	0.92
XI	chloroform:methanol (9.5 :0.5)	0.84
XII	chloroform:methanol (9.5 :0.5)	0.92
XIII	chloroform:methanol (9.5 :0.5)	0.84
XV	chloroform:methanol (9.5 :0.5)	0.92
XXXV	chloroform:methanol (9.5 :0.5)	0.72
XXXVI	chloroform:methano (9.5 :0.5)	0.62
XXXVII	chloroform:methano (9.5 :0.5)	0.82

Table 2-8.b: Thin layer chromatography data of 2,3-diphenyquinoline- 4-carboxylic acid derivatives



Compound No.	R^1	R^2	R^3	R^4	Mobile phase	R_f value
XVI	H	H	H	OH	Chloroform : Methanol (9.5:0.5)	0.94
XVII	CH_3	H	H	OH	Chloroform : Methanol (9.5:0.5)	0.74
XVIII	H	H	CH_3	OH	Chloroform : Methanol (9.5:0.5)	0.76
XIX	H	CH_3	H	OH	Chloroform : Methanol (9.5:0.5)	0.72
XX	H	H	SO_2 NH_2	OH	Chloroform : Methanol (9.5:0.5)	0.76
XXI	H	H	NO_2	OH	Chloroform : Methanol (9:1)	0.95
XXII	H	H	CO_2H	OH	Chloroform : Methanol (9.5:0.5)	0.16
XXIII	H	H	$SO_2NHC_6H_7N_2$	OH	Chloroform : Methanol (9:1)	0.94
XXXI	H	H	H	OCH_3	Chloroform : Methanol (9.5:0.5)	0.82
XXXII	H	H	H	NH_2	Chloroform : Methanol (9.5:0.5)	0.64
XXXIII	H	H	H	NHPh	Chloroform : Methanol (9.5:0.5)	0.83
XXXIV	H	H	H	$NHCH_3$	Chloroform : Methanol (9.5:0.5)	0.84

Table 2-8.c: Thin layer chromatography data of 2,phenylquinoline -4-carboxylic acid derivatives.



Compound No.	R^1	R^2	R^3	R^4	Mobile phase	R_f value
XIV	H	H	H	OH	Chloroform : Methanol (9.5: 0.5)	0.72
XXIV	H	CH_3	H	OH	Chloroform : Methanol (9.5: 0.5)	0.78
XXV	H	H	SO_2NH_2	OH	Chloroform : Methanol (9.5: 0.5)	0.87
XXVI	H	H	NO	OH	Chloroform : Methanol (9.5: 0.5)	0.76
XXVII	H	H	CO_2H	OH	Chloroform : Methanol (9.5: 0.5)	0.82
XXX	H	H	H	OCH_3	Chloroform : Methanol (9.5: 0.5)	0.92

Table 2-9: Antibacterial activity of the compounds tested-mean inhibition zones diameter

Comp. No. (5 mg/ml)	Solvent	Mean inhibition zone diameter (mm).			
		B. subtiles	*S. aureus*	*E. coli*	*P. vulgaris*
XVII	polyethylene glycol	17	17	15	20
XVIII	~~	15	-	15	19.5
XX	~~	23.5	22.5	19.5	20
XXI	~~	16	-	16	-
XXIII	~~	20	-	16.5	-
XXIV	~~	20.5	18.5	19.5	20
XXV	~~	21	15	18	-
XXVI	~~	18.5	14.5	16	-
XXVIII	~~	16.5	-	17	20.5
XXIX	~~	20	-	14	22
XXXI	~~	20	-	15	-
XXXIII	~~	14.5	-	16.5	24.5
XXXIV	~~	21	-	17	22.5

3. Discussion

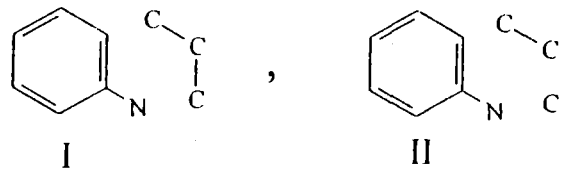
Quinolines were a group of compounds known to possess various functionalities. Quinoline derivatives were used in industry in dyes, rubbers and as antioxidants. Quinoline derivatives possess a wide range of biological activities as antibacterial against, *Staphiococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Proteus vulgaris* (Adkins and Coonradt, 1941; Cormwell and Cram, 1943; Sargent and Small, 1945).

Retrosynthetic analysis is one of the chemical reaction designs technique, it's often applied when a synthetic route to a target molecule has to be developed. The most important character in this technique is to recognize the general structural features of the product, the target molecule, then to disconnect in a logical way to form synthons from which good starting materials are proposed (generated precursors or synthetic equivalents). The importance of the retrosynthetic analysis is to show the relationship of two molecules in a synthesis by using a transform, because, it involve manipulation of the key functional groups as that many functional groups are structural units of the molecule being synthesized. It is common nowadays, that all the new concepts of the chemical synthesis must go onto retrosynthetic analysis as a good technique for solving chemical design problems.

The present work generally depended on the appropriate retrosynthetic analysis, through the disconnection or the functional group interchange (FGI) and functional group removal strategies.

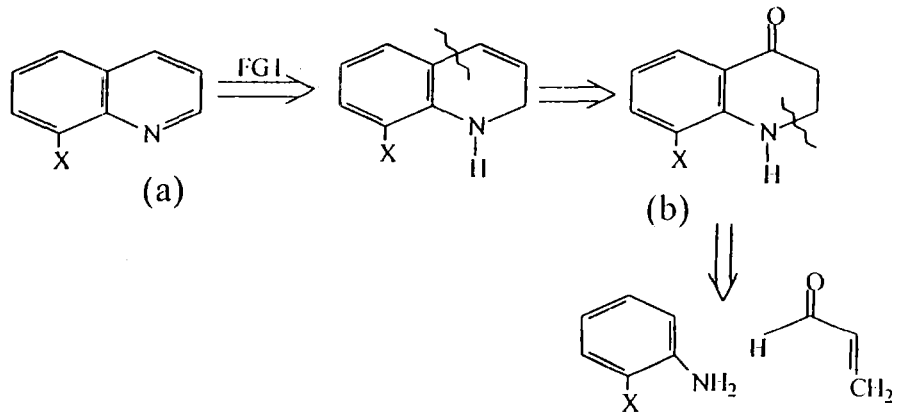
The beauty of the art of retrosynthetic analysis, by which its imaginary hypothesis comes to reality can be seen in the fact that in a one or most of the cases that the total synthesis of any of the quinolines in this work can be simply linked to benzaldehyde as starting material.

The retrosynthetic analysis of quinoline derivatives exemplify two important over all strategies by which the hetero cyclic ring can be constructed, as indicated by (I) and (II) below.



I II

The strategy (I) an important method for quinoline and many of its derivatives (e.g 8-nitro and 8-hydroxyquinoline) by which a carbon skeleton of three atoms was allowed to be condensed with a primary aromatic amine. With quinoline (X = H) the first retrosynthetic transform is reduction to 1,2-dihydroquinoline to facilitate the recognition of the derived synthons then obtained in the following subsequent disconnections.

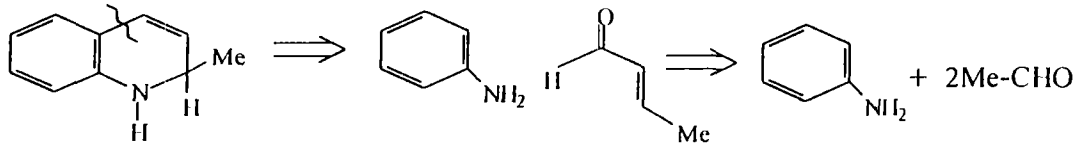


The above analysis reveals that, the reaction involves heating a mixture of an aromatic amine, glycerol, concentrated sulphuric acid and a suitable oxidizing reagent. The over all sequence for (X = H) involves firstly the conversion of glycerol into acrolein by the action of sulphuric acid, then the conjugate 1,4-addition of aniline to acrolein to yield 3-phenylaminopropanal [(b), X=H], followed by an acid catalysed

cyclisation and dehydration to form the 1,2-dihydroquinoline, which is finally oxidized to quinoline.

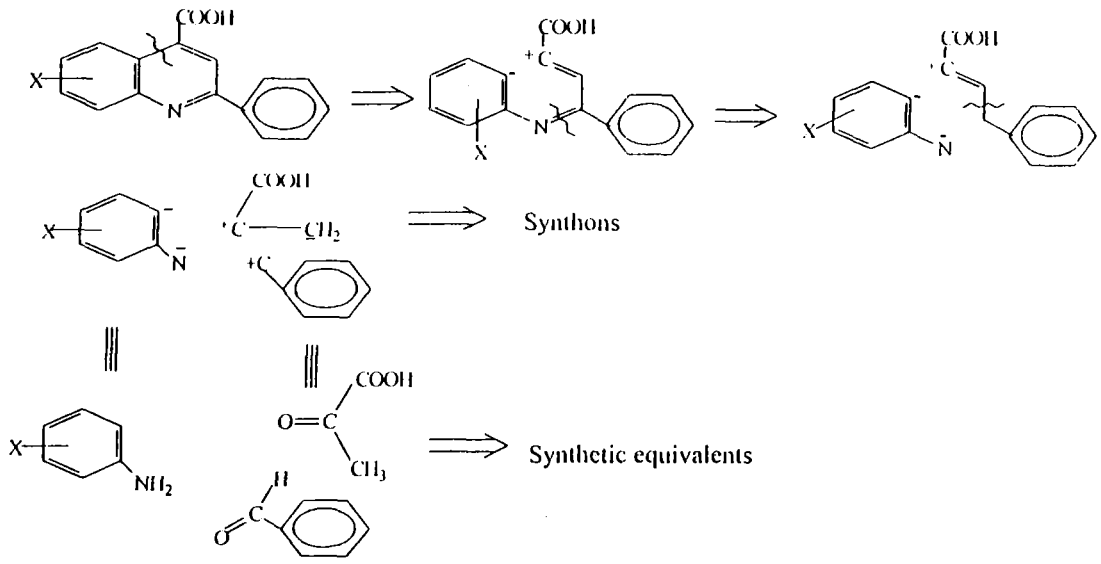
The strategy (II) an important method for retrosynthetic analysis of 1,2-dihydroquinoline and its derivatives, by which an aromatic amine was allowed basically to react with two carbon skeleton one of them consisting from two carbon atoms while the other of one carbon atom.

The retrosynthetic analysis for the 1,2-dihydroquinoline reveals crotonaldehyde as the unsaturated carbonyl component which is in turn formed from acetaldehyde.

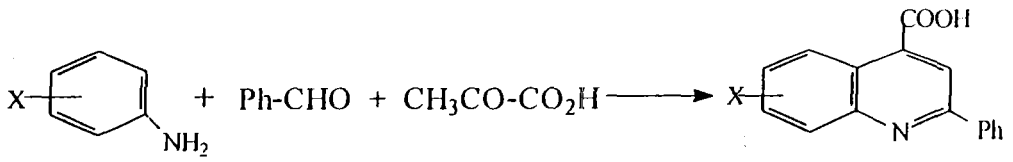


In this case the final dehydrogenation of 1,2-dihydroquinaldine to quinoaldine is effected by anils formed by the condensation of aniline with either acetaldehyde or crotonaldeyde during the course of the reaction (Furniss *et al*, 1989). According to these two approaches for the retrosynthetic analysis of quinolines, the second approach can be adopted in this work.

The retrosynthetic analysis (RA) of 2-phenylquinoline-4-carboxylic acid derivatives (Included XIV, XXIV, XXV, XXVI and XXVII) can be outlined below.

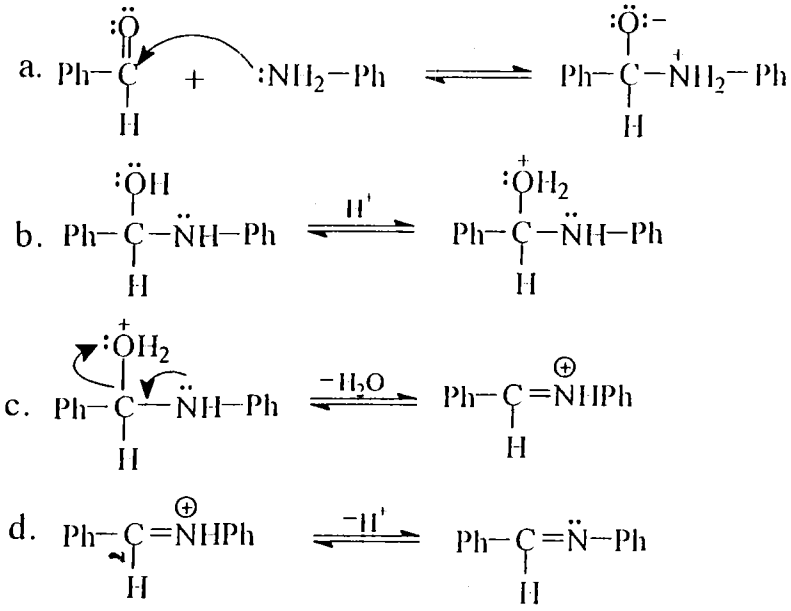


The retrosynthetic analysis for the 2-phenylquinoline-4-carboxylic acid reveals, aniline, pyruvic acid and benzaldehyde as a precursors or synthetic equivalents for the reaction. The same starting materials for this synthesis can be obtained by a similar retrosynthetic analysis for the 1,2-dihydro derivatives, when approached with retrosynthetic analysis strategy requiring two carbon skeletons. This is an example of the Doebner synthesis of quinoline-4-carboxylic acid derivatives, which consists of the condensation of a primary aromatic amine with pyruvic acid and benzaldehyde.

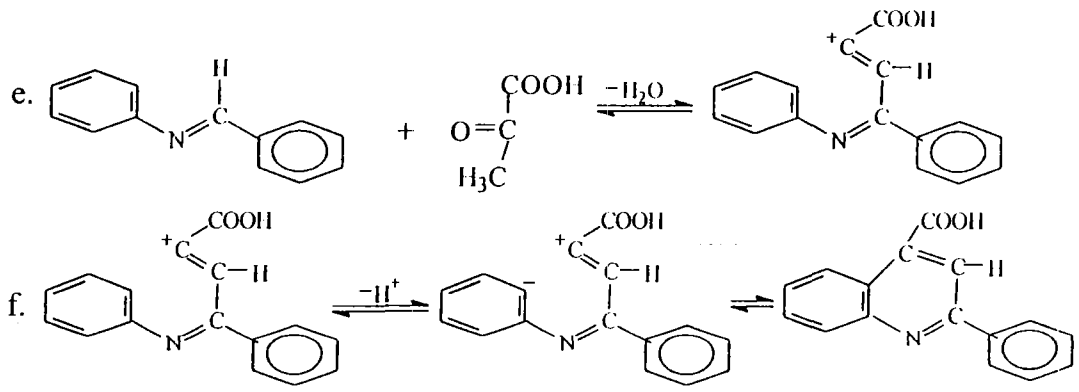


According to this strategy and its corresponding retrosynthetic approach, the mechanism of the reaction can be proposed as outlined below:

Step I



Step II



2-phenylquinoline –4-carboxylic acid derivatives were prepared by the Dobner reaction, an example is the condensation of benzaldehyde, aniline and pyruvic acid in absolute ethanol to give 2-phenylquinolin –4-carboxylic acid (Hancock, 1975). The mechanism of this reaction can be divided into two main steps. In the first step, aniline combines with benzaldehyde to form schiff's base, while in the second step, schiff's base

condense with pyruvic acid (Acheson, 1967). The detailed description of step one includes.

a- Nucleophilic attack on the benzaldehyde by the lone pair electrons of aniline.

b- A H^+ ion is then transfer from nitrogen to oxygen, yielding a neutral carbinolamine.

c- The nitrogen lone-pair electron expel water, giving an iminium ion.

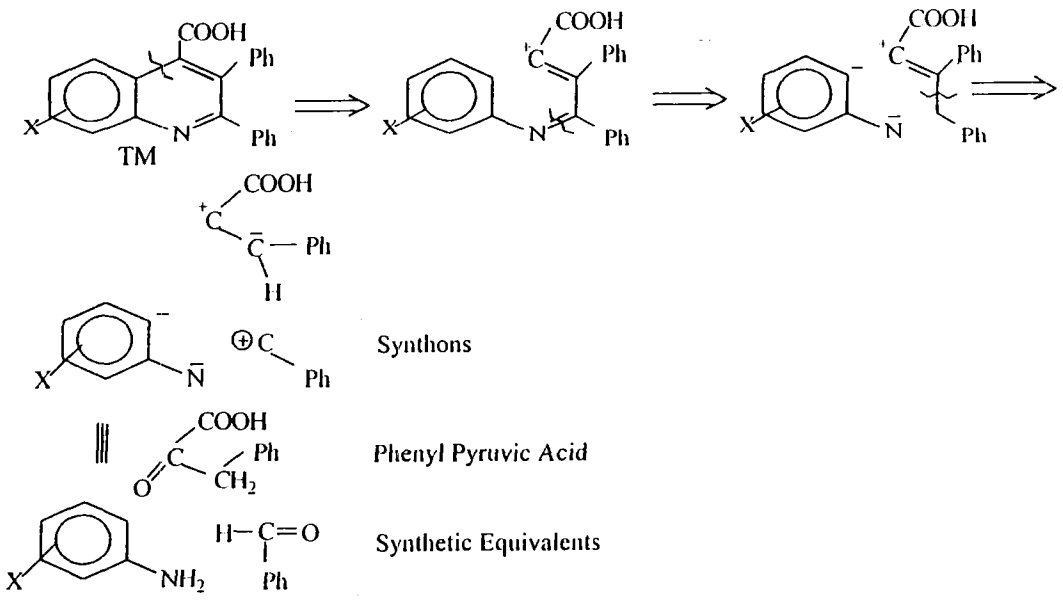
d- Loss of H^+ from nitrogen then gives the benzylidene aniline (Schiff's base) (McMurry, 1984).

The second step involve

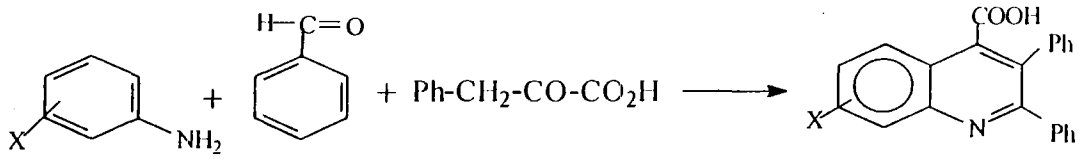
e- Loss of water by condensation of benzylidene aniline and pyruvic acid.

f- Loss of H^+ to gives 2-phenylquinoline-4-carboxylic acid.

The retrosynthetic analysis for the group of 2,3-diphenylquinoline-4-carboxylic acid derivatives which included (XVI, XVII, XVIII, XIX, XX, XXI, XXII and XXIII), can be worked logically as shown below to reveal a two carbon skeleton.

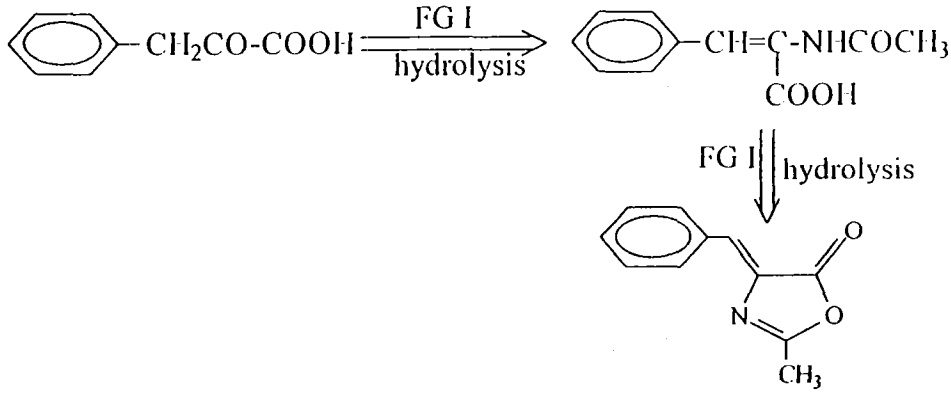


The retrosynthetic analysis for the 2,3-diphenylquinoline –4-carboxylic acid, yields substituted anilines, phenylpyruvic acid and benzaldehyde which can be considered as a general retrosynthetic analysis for the 2,3-diphenylquinoline-4-carboxylic acid derivatives by which the target molecules can be formed through the condensation of a primary aromatic amine with phenylpyruvic acid and benzaldehyde.



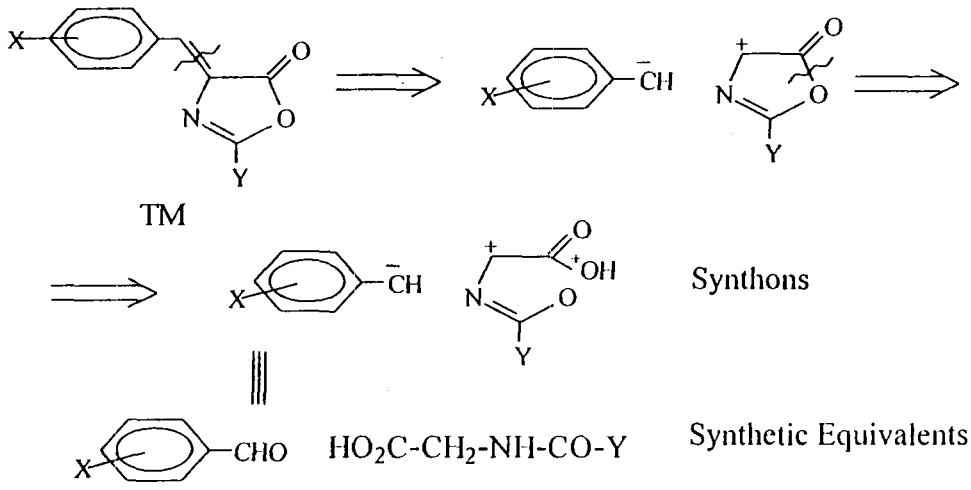
The mechanism of this reaction which include two steps is similar to the mechanism that discussed above for 2-phenylquinoline-4-carboxylic acid, except that in the second step of that mechanism, phenyl pyruvic acid was used instead of pyruvic acid.

Phenyl pyruvic acid, one of the precursors in the above reaction, can be further disconnected and/or worked with functional group interconversion as shown below:



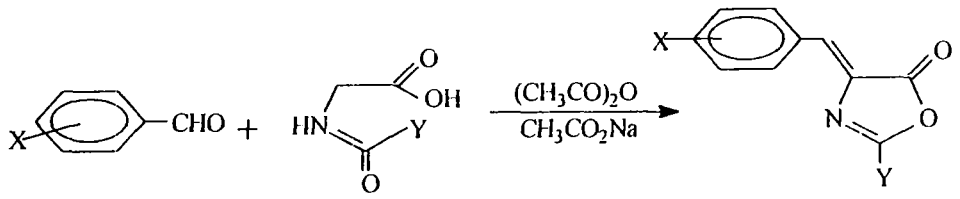
Accordingly phenyl pyruvic acid was obtained from double hydrolysis of benzylidene derivatives, (4-benzylidene-2-methyloxazol-5-one).

The retrosynthetic analysis for the group of 4-benzylidene-2-methyloxazole-5-one derivatives which include (II, V, XXVIII, and XXIX), can be done according to the standard rules for the double bonds and partiall lactone units as follows:

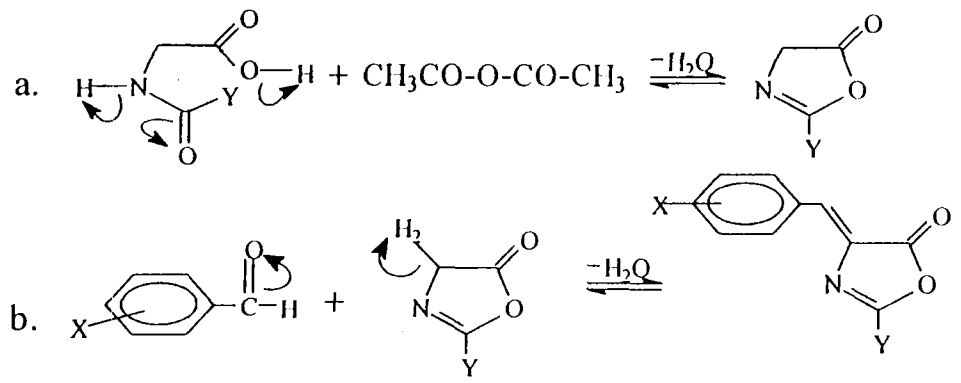


The retrosynthetic analysis for the 4-benzylidene-2-methyloxazol-5-one, reveals, benzaldehyde and N-acetylglycines. The synthetic steps are thus the conversion of N-acetylglycine with acetic anhydride into 2-methyloxazol-5-one, followed by the reaction of the active methylene group with benzaldehyde to afford the corresponding 4-benzylidene derivatives.

The detailed mechanism of the reaction, according to the proposed retrosynthetic analysis, can be summarized below:



Actually this reaction involves two steps:



The mechanism of this reaction involve:

a- Loss of H_2O from Acetylglycines by acetic anhydride to form the corresponding azlactone.

b- Loss of H_2O by condensation between benzaldehyde and azlactone to give 4-benzylidene oxazol-5-one.

This mechanism can be considered as general one for 4-benzylidene derivatives (Bachmann *et al*, 1946).

The retrosynthetic analysis for the acetylglycines reveals, glycine and acid chlorides.

$$\text{R-CO}\{\text{NH-CH}_2\text{-CO}_2\text{H}$$

$$\Downarrow$$

$$\text{R-CO}^+ \quad \text{N}^-\text{H-CH}_2\text{-CO}_2\text{H} \qquad \text{Synthons}$$

$$\Vert$$

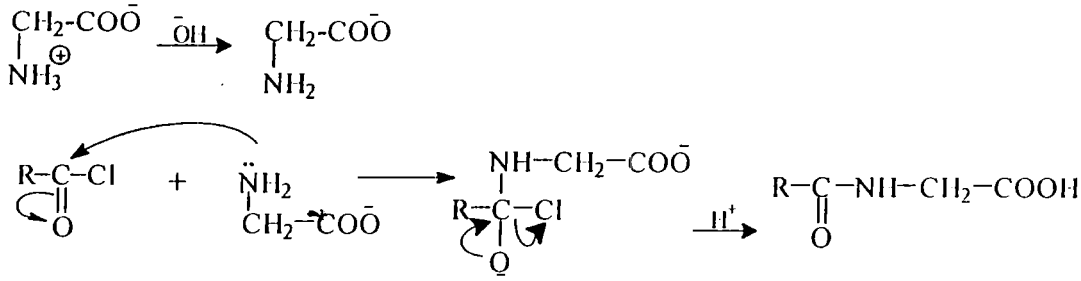
$$\text{R-COCl} \quad \text{H}_2\text{N-CH}_2\text{-CO}_2\text{H} \qquad \text{Synthetic Equivalents}$$

The retrosynthetic analysis for the acetylglycines consists of the condensation of amino acid (glycine) with acid chloride according to Schotton Baumans procedure or technique.

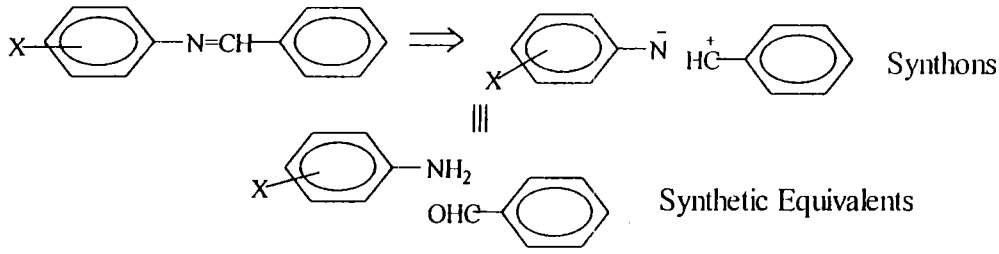
The over all reaction is:

$$\text{H}_2\text{N-CH}_2\text{-CO}_2\text{H} + \text{RCOCl} \longrightarrow \text{R-CO-NH-CH}_2\text{-CO}_2\text{H}$$

The mechanism of this reaction involve nucleophilic acyl substitution:



The retrosynthetic analysis for the benzylidene derivatives which include (XII, XXXV, XXXVI and XXXVIII) can be similarly done as in the case of the intermediates required for quinolines.

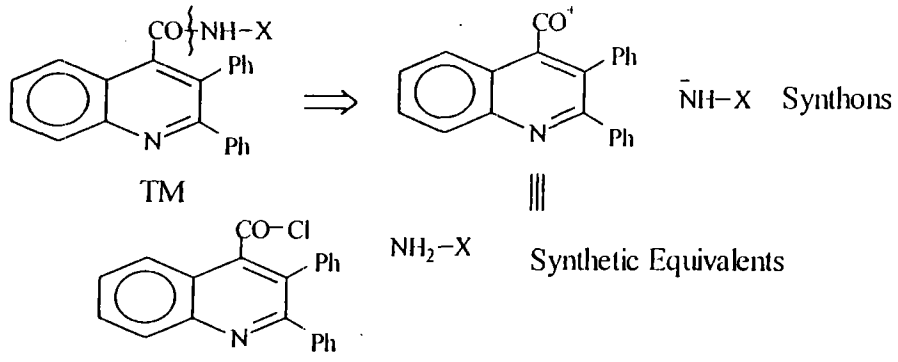


The retrosynthetic analysis for the benzylidene aniline reveals aniline and benzaldehyde.

$$Ph\text{-}CHO + H_2N\text{-}Ph \longrightarrow Ph\text{-}CH{=}N\text{-}Ph$$

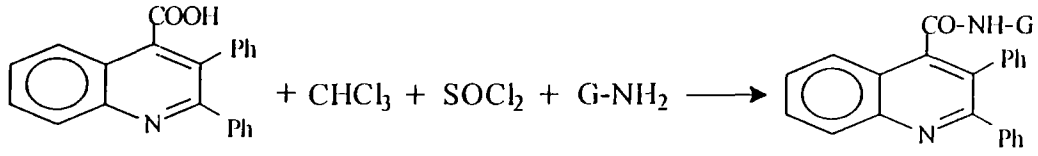
The mechanism of this reaction is similar to the mechanism discussed for the intermediates in the way to quinolines.

The retrosynthetic analysis for the 2,3-diphenyl quinoline-4-carbonyl amide derivatives which include (XXXII, XXXIII and XXXIV), can be done in accordance with the standard rules known for amides, namely the disconnection of the bond between the carbonyl group and nitrogen.

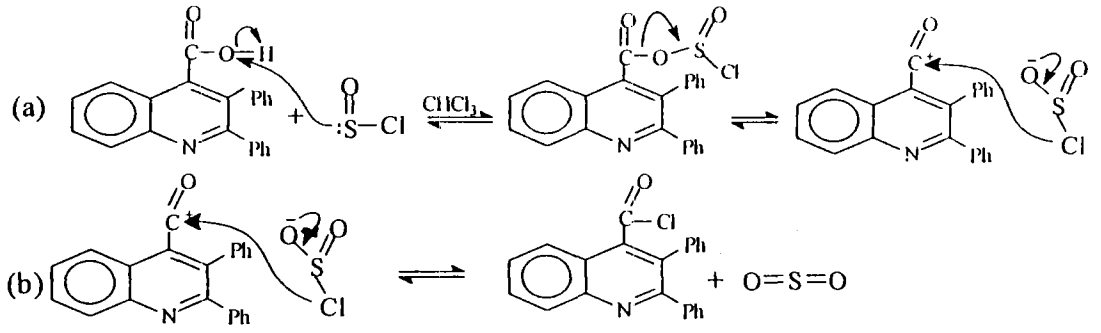


Such analysis of these 2,3-diphenyl quinolin-4-carbonyl amides finally form primary amines and 2,3-diphenylquinolin-4-carboxylic acid through acid chloride.

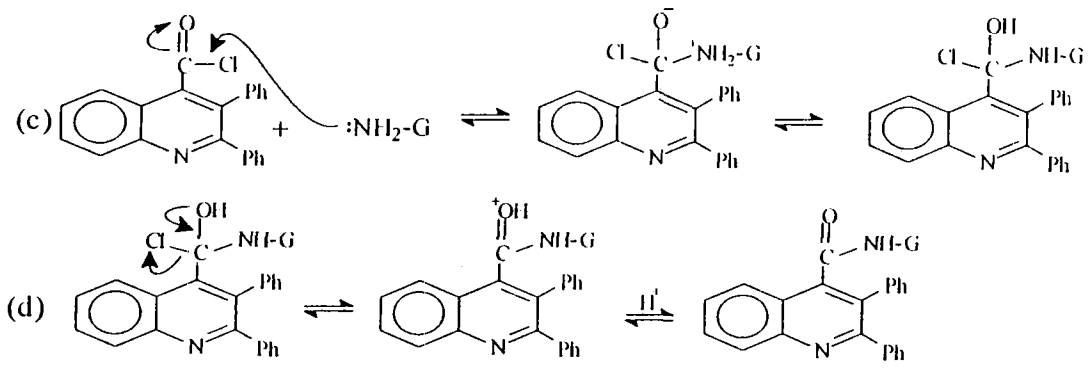
Therefore a two steps reaction was required, firstly the carboxylic acid should be converted to its corresponding acid chloride. Seconded the formation of the amide by the reaction of the acid chloride with amines. It is a known fact that direct reaction between acids and amines to form amides is not a favourite one.



step I:



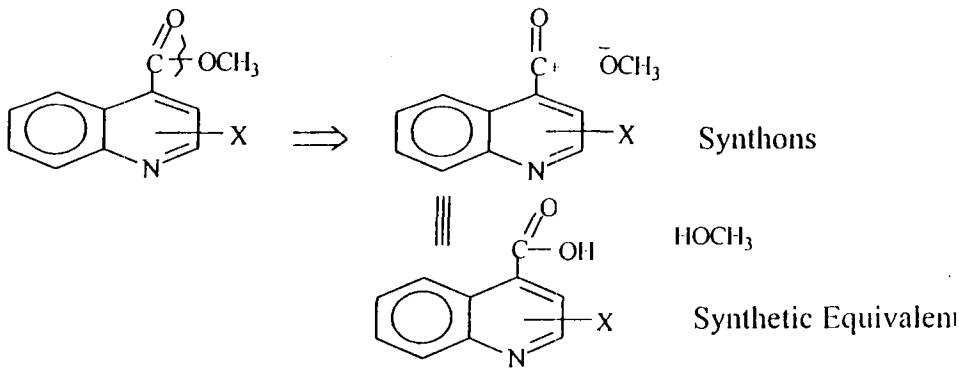
Step II:



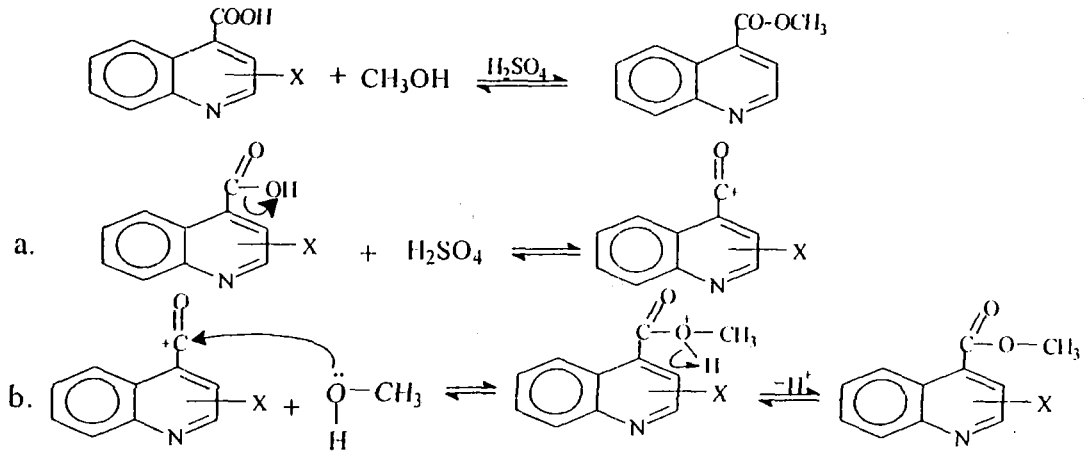
For the mechanism of this reaction it can be seen that two steps were involved.

The first step is the formation of acid chloride by the action of thionyl chloride with 2,3-diphenylquinoline-4-carboxylic acid. In The second step nucleophilic attack on the carbonyl by the lonepair electron of nitrogen and then loss of H^+ to gives 2,3-diphenyl-4-carbonyl amide derivatives (McMurry, 1984).

The retrosynthetic analysis for the group of alkyl quinoline-4-caroxylate derivatives included XXX and XXXI, is shown below:



The retrosynthetic analysis for the alkyl quinoline-4-carboxylate derivatives reveals, quinoline-4-carboxylic acid derivatives and methanol.



The mechanism of this reaction can be explained in terms of protonation of the quinolin-4-carboxylic acid derivatives by concentrated sulphuric acid followed by nucleophilic attack by methanol and loss of H^+ ion to gives quinoline-4-acetyl methyl ester derivatives (Sykes, 1965).

Spectroscopic methods play a vital-role in the development of modern atomic theory. In addition spectroscopic methods have provided perhaps the most widely used tools for the elucidation of the structure of molecular species as well as the quantitative and qualitative determination of both inorganic and organic compounds (Skoog *et al.*, 1996).

Infrared spectroscopy is used to detect and identify the vibrations of molecules, and especially the characteristic vibrations of the double and triple bonds present in many functional groups.

In this work infrared spectroscopic analysis have been carried out using FTIR Mattson spectrometer. The absorption frequencies of the different functional groups associated with the prepared compounds were summarized in table (2-3).

The group of 2-phenyl-and 2,3-diphenyl quinoline-4-carboxylic acid derivatives showed characteristic absorption bands. The O-H st. vib

of the carboxylic acid group appear consistently at 3400-2600cm^{-1} as broad absorption peak. The carbonyl group >C=O st- vib. appear in the range around ≈ 1690 cm^{-1}. The difference in the absorption frequency for the carbonyl group can be attributed to the factors affecting the absorption frequency. It is a well known fact that Hydrogen bonding, direct conjugation and electron-releasing groups tend to decrease the force constant and therefore the absorption frequency, while electron withdrawing groups and ring strain enforce the force constant making the carbonyl group with more double bond character and therefore increasing the absorption frequency. The aromatic system in these compounds showed the C=C st. vib. in the region 1450-1610 cm^{-1}. The C=C–H st. vib. was not observed due to the overlaping with the stronger O-H st.vib.

However the various types of bending which indicate the position of the substituent in the aromatic nucleus was observed in the region of 650-1000 cm^{-1}.

Among the different compounds prepared, additional infrared features and complications appeared due to the presence of certain groups. Therefore some compounds (I, II, III, IV, V, XV, XXIII, XXX, XXXI, XXXII, XXXIII and XXXIV), which included additional –COOH group give rise to additional >C=O at (≈) 1700 cm^{-1}. The compounds containing the SO_2NH_2 group (XX, XXV, and XXXV) or SO_2NH-(XXIII and XXXVI) showed the characteristic asymmetric and symmetric st. vib. of the SO_2 group at ≈ 1350 and 1150cm^{-1} respectively. The N-H st. vib. for this group of compounds appeared at ≈ 3330, 3430cm^{-1}. Compounds (VII, XII, XVII, XXI, XXVI, XXVIII, and XXIX), which contained the nitro group showed the asymmetric and symmetric st. vib. characteristic for this group at ≈ 1520 and 1350cm^{-1} respectively. The C-H st. vib in

compounds (II, III, V, VII, XV, XXVIII, and XXIV), appeared at ≈ 2900-2960cm^{-1}.

The NMR phenomenon is observable because certain nuclei behave like bar magnets for many purposes. Most important among such nuclei are ^{1}H, ^{13}C, ^{19}F, and ^{31}P – all having a nuclear spin of ½, (these with nuclear spin of 1 include deuterium (^{2}H) and ^{14}N). Certain other nuclei which are important in organic chemistry have a nuclear spin of zero and therefore give no nuclear resonance signals, these included ^{12}C and ^{16}O (Williams and Ianfleming, 1964).

The position of an absorption in the NMR spectrum is denoted, not by the absolute frequency value, but by its relationship to the absorption frequency of a reference compound. The normal reference compound for both ^{13}C and ^{1}H spectra is tetramethylsilane [$(CH_3)_4Si$, TMS]. All the protons in TMS are equivalent, and the proton nuclei in the vast majority of organic compounds absorb downfield from the single TMS signal, similarly the vast majority of ^{13}C nuclei in organic compounds absorb downfield from the carbon absorption in TMS.

The position of an absorption peak relative to that of the reference compound is known as the chemical shift. The chemical shift range for ^{13}C in organic compounds is 0-230 ppm, in the absence of electronegative atoms, these resonate in the range 0-60 ppm. Alkenes and benzenoid aromatic systems normally resonate in the range 100-160 ppm and carbonyl carbon resonances appear at a very low field (155 to 230 ppm).

The chemical shift range for ^{1}H in organic compounds exist in the range 0-17 ppm. Aliphatic protons resonate at 1-3 ppm while aromatic protons resonate at 6.5-8 ppm regions (Furniss *et al.*, 1989).

In this work, NMR spectroscopic analysis have been carried out using JEOLECP 400 MHz and JEOL JNMFX-100 MHz instruments. The

chemical shifts of the C^{13} and H^{1} associated with the prepared compounds are summarized in table (2-4 and 2-5).

The group of 2-phenyl quinoline -4-carboxylic acids (XIV, XXV-XXVII and XXX) showed a characteristic features in their ^{1}H-NMR spectra. The homocyclic protons of the parent quinoline ring system appeared in the range of 7.27-8.67 ppm depending upon the effect of the subtituents. These protons sometimes appeared as a multiplet while in other cases revolved into a singlet and a pair of doublets with similar coupling constants. The aromatic ring appeared as a multiplet of five protons in the range of 7.40-7.87 ppm. The unsubtituted proton at position 3 of the quinoline ring system appeared as a singlet at ≃ 8.40 ppm. The acidic protons of the parent carboxylic group or the substitutents appeared as abroad singlet in the range 9.38-14.02 ppm.

Similar situation was observed in the ^{1}H-NMR spectra of 2,3-diphenyl-quinolin-4-carboxylic acid derivatives (XVI, XXII). Additional complication arises from the additional substitutent at position 3 of the quinoline ring system. These substitutents in the phenyl ring were similar to the one at position 2. Both the two substitutents at 2- and -3 were protons of phenyl ring, but still, to some extend they differ in their environment. Such situations results in a possibility of two multiplets for each set of the phenyl groups at 7.03-7.24 and 7.28-7.42 ppm.

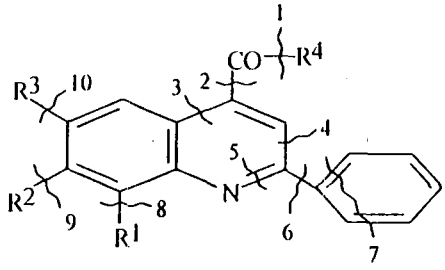
The oxdazalones derivatives XXVIII and XXIX showed a similar ^{1}H-NMR spectra. The conjugated system of the phenyl group beside the ring strain caused the olefinic proton to be strongly deshielded and come to resonance at 7.40 and 7.55 as a singlet. Protons in the *o*-and *p*-position to the nitro group were strongly deshielded and appeared as double doublet 8.28-8.30, doublet 8.52 and a singlet 9.23.

^{13}C-NMR of the prepared 2-phenyl –and, 2,3-diphenyl quinoline-4-carboxylic acid derivatives showed the expected spectra for these compounds. Although the spectra was rich in aromatic carbons, which make assignments difficult, still points can be concluded and signals can be assigned. The carbonyl carbon appeared in the range 166.85-170.35. Phenyl substitutuents at position 2 appeared always at lower value (119-125) compared to that of the quinoline aromatic carbons .

In a typical mass spectrometer, an organic compound under high vacuum is bombarded with electrons. Loss of an electron from the molecule followed by various fission processes gives rise to ions and neutral fragments. The positive ions are expelled from the ionisation chamber and resolved by means of a magnetic or an electric field. The intensity of a peak in the spectrum is thus an indication of the relative number of ions, the larger the peak the more abundant the ion producing it. The most intense peak in the spectrum is known as the base peak. Ions produced in the fragmentation of the organic compounds are separated according to their mass charge ratio (m/z) (formerly m/e). Many compounds gives rise to an ion which corresponds to the removal of a single electron from the molecule, this is known as the molecular ion (M^+) and usually has the highest m/z value in the spectrum, with the exception of a characteristic group of peaks at m/z value of M+1, M+2, M+3,... etc. (Willams and Ianfleming, 1964). The most common use of mass spectrometry by the organic chemist is for the accurate determination of molecular weight. A second important use is to provide information about the structure of compounds by an examination of the fragmentation pattern (Furniss *et al.*, 1989)

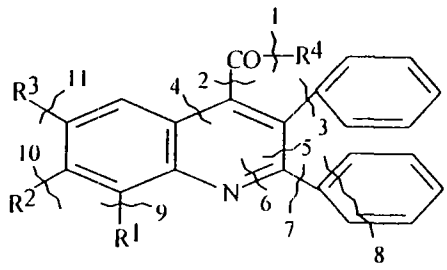
In this work, mass spectroscopic analysis have been carried out using GC/MS-QP 5050A SHIMADZU GC-17A instrument.

The group of 2-phenyl quinoline-4-carboxylic acid derivatives showed a characteristic fragmentation pattern as shown in scheme (2-3) and summarized in the following figure:



These compounds (XIV, XXIV, XXV, XXVI, and XXVII) showed a fragment at m/e 77 which can be simply assigned for the phenyl cation result from the cleavage at position 2 of the quinoline ring system (pathway 6), the phenyl cation $C_6H_5^+$ lost a fragment of C_2H_2 to form an ion at m/e 51 of $C_4H_3^+$ (pathway 7). Basically, the phenyl cation was associated with pathways 4 and 5 which may form similar structure to the stable seven membered tropylluim ion at m/e 89. Due to the presence of the outer carbonyl group and the inner nitrogen atom, cleavage through pathways 3 and 4 can take place and may result in the formation of an ion at m/e [M-CH_2=CHCOR^4]. One of the favored fragmentation routes associated with this group was observed through pathway 2 which form [M-COR^4] with RA over 50% and as can be seen is one of the popular fragments of the carbonyl compounds. The molecular ion was observed in all of the compounds and in most cases form the base peak. With much lower intensity the fragment M-R^4 was observed throughout pathway 1. Fragments associated with the removal of R_1, R_2, R_3 was designated with routes 8,9 and 10 respectively, they are always associated with route 3+4.

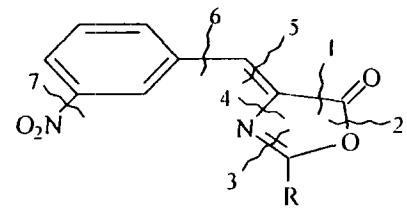
The characteristic fragmentation routes of the group of 2,3-diphenyl quinoline-4-carboxylic acid were given in table (2-6), summarized in scheme (2-4 – 2-7) and in the following figure



A similar situation to that discussed for 2-phenyl quinoline-4-carboxylic acid was observed again for the diphenyl derivatives. Sequence routes 7 and 8 was observed at m/e 77 and 51 due to $C_6H_5^+$ and $C_4H_3^+$ respectively. Beside route 5+6 which form $C_7H_5^+$ at m/e 89. The molecular ion was seen with lower relative abundance. Both of routes 1 and 2 were observed in most of cases which give rise to [M-R^4] and [M-COR^4] respectively. While route 7 forms C_6H_5 at m/e 77, route 3 result in [M-C_6H_5]. Both of route 2+3 occur with the loss of COR^4 and C_6H_5.

In many cases pathway 4+5 occur with higher relative abundance to form [M-C_6H_5Ch=CHCOR^4]. Loss of substituents occur through routes 9, 10 and 11, but associated with 4+5 for each one and form the base peak sometimes.

Compounds (XXVIII and XXIX), the oxazolone derivatives were given in table (2-6) and scheme (2-4 – 2-7), while the following Figure summarized their major fragmentation routes:



The molecular ion of the two compounds was clearly seen and for compound XXVIII it forms the base peak. The base peak of compound XXIX result from the fragmentation through route 2+3. Cleavage through

routes 5+7 form the seven membered tropyllium ion $(C_7H_5)^+$ m/e 89 which followed by removal of C_2H_2 to form $C_5H_3^+$ at m/e 63. Routes 6+7 form the substituted phenyl cation at m/e 75

The visible and ultraviolet spectra of organic compounds are associated with transitions between electronic energy levels. The transition are generally between a bonding or unshared lone-pair orbital (n) and unfilled anti-bonding orbital (π^*). The highest energy separation is found when electrons in σ-bonds are excited, giving rise to absorption in the 120-200 nm range. Above 200 nm, however excitation of electrons from p-, d-orbitals and π-orbitals, and particularly, π-conjugated system, gives rise to readily measured and informative spectra (Williams and Ianfleming, 1964).

The most important transitions in organic compounds are the π-π^* transitions, they are usually associated with the multiple bonds of carbon with carbon, nitrogen, sulphur, etc. n–π^* Transitions are usually associated with groups such as carbonyl, thiocarbonyl, nitroso, etc and generally the intensity of absorption is very much lower than that arising for π-π^*. A chromophore is used to describe the system containing the electrons that are responsible for the absorption in question. λ_{max} is the wavelength of an absorption maximum. In organic compounds there are many types of chromophores, aromatic ring has absorption band at 204 and 256 region, carbonyl has absorption at 280 nm (Skoog *et al.*, 1996).

In this work, ultraviolet spectroscopic analysis have been obtained using uv/vis spectrophotometer, Model 6505, Serial No. 2204, Jenway Limited, England. The ultraviolet-visible spectrum for all chromophores associated with the prepared compounds were summarized in table (2-7).

2-phenyl and 2,3-diphenyl quinoline-4-carboxylic acid derivatives showed λ_{max} (acetone) at 255-270 nm region. 2-phenyl and 2,3-diphenyl quinoline-4-carbonyl derivatives showed λ_{max} (acetone) of 265mm. Oxazolone derivatives showed λ_{max} (acetone) 255 and 265nm region.

Intermediates and starting materials (Acetyl glycine, benzoyl glycin. m-nitrobenzaldeyde, phenyl pyruvic acid, 2-acetamido-cinnamic acid, benzylidene aniline and 2-methyl and 2-phenyl oxazolon-5-one) absorb at 260-270nm region.

Appendixes 1-23 showed some representative spectrum of the different compounds including (^{1}HNMR, ^{13}CNMR, IR, MS and UV).

Thin layer chromatography, a separation technique, was used, in this work, to follow up the reaction course , particularly in the case of new reactions and to check the isolation and purification procedure. The movement of any substance relative to the solvent front in a given chromatographic system is constant and characteristic of the substance. The constant is the R_f value and defined as (Furniss *et al.*, 1989).

$$R_f = \frac{\text{distance moved by substance}}{\text{distance moved by solvent front}}$$

The R_f values for all of the prepared compounds were listed in table (2-8).

All of the obtained compounds were crystalline, colored and soluble in organic solvents.

In this study the antibacterial activities of the synthesized compounds were tested against some bacterial organism.

The antibacterial activity of the compounds was investigated by broth microdilution method using two Gram-positive bacteria (*Bacillus subtilis* NCTC 8236, *Staphylococcus aureus* ATCC 25923) and two

Gram-negative bacteria (*Escherchia coli* ATCC 25922, *Proteus vulgaris* ATCC 6380) by using polyethylene glycol as solvent.

The sensitivity of the compounds prepared and synthesized in this work as antibacterial was studied. It was found that all of the prepared compounds are sensitive against *Basillus subtiles* and *Escherichia coli* bacteria, and most of the compounds are sensitive against *Staphylococcus aureus* and *Proteus vulgaris*. Compound XX showed the highest activity against the four tested standard organism. This compound was characterized by a sulphanilamido group at position 6. Compound XXV showed moderate activity against *B. subtilis, S. aureus* and *E. coli*. Both of compounds XX and XXV bear the sulphanilamido group, they differ in that compound XX is a diphenyl derivative (table 2-9).

4. Conclusions and recommendations:

The following points may be concluded and/ or recommended from the results of this study.

- Benzaldelydes may be considered as a rich precursors for the total synthesis of larger complex heterocyclic ring system.
- Retrosynthetic analysis, the disconnection technique was clearly observed as a powerful analytical/ synthethetic technique as can seen from the logical use of the mentioned approach in this study.
- Various substituted 2-phenyl-2,3-diphenyl-quinolin-4-carboxylic acids derivatives can easily be synthesized through the condensation of benzadehydes, pyruvic or phenyl pyruvic acid and aromatic amines.
- The 2-phenyl-2,3-diphenyl-quinolin-4-carboxylic acids shared a common characteristic features in their spectral data. These compounds showed a characteristic fragmentation pattern in MS. They shared a characteristic pattern in their ^{1}H-and ^{13}C-NMR.
- These compounds were highly recommended for full-scale biological screening against different species. It is a well-known fact that quinoline ring system was associated with different biological activities.
- Further synthetic work may be directed towards the functionalization and/or inter-conversion of the carboxylic acid moiety present in position4.
- Substituted phenyl pyruvic acids may be utilized in some trials instead of phenyl pyruvic acid.

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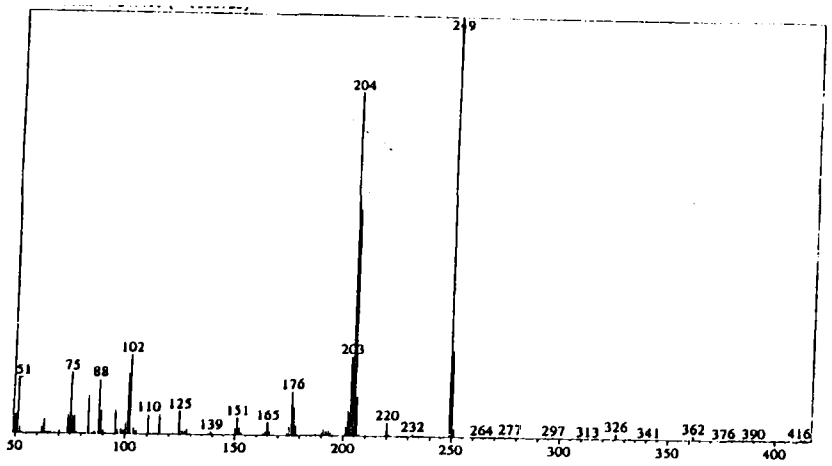
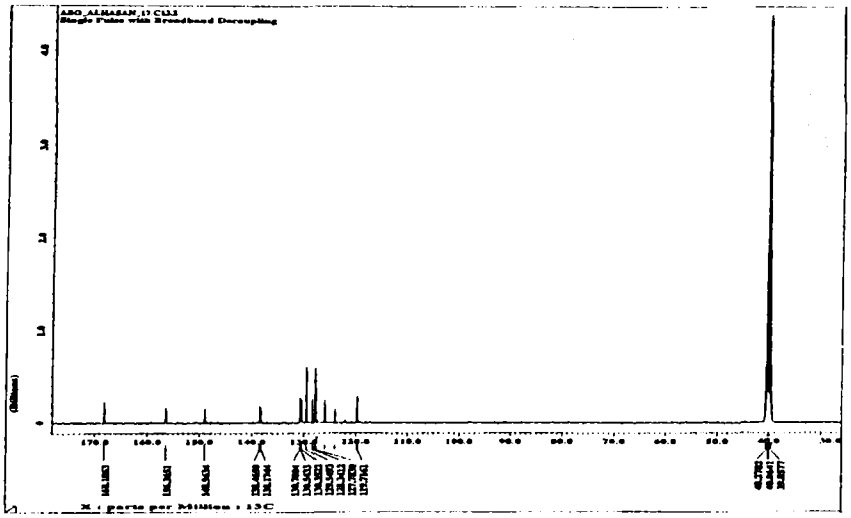
Appendix 1

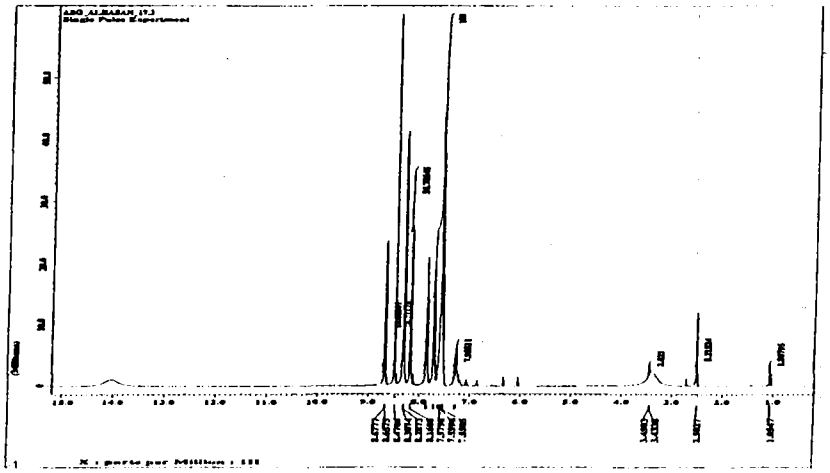
A = MS, B = 13CNMR and C 1HNMR spectra of 2-phenylquinoline-4-carboxylic acid (XIV)



A



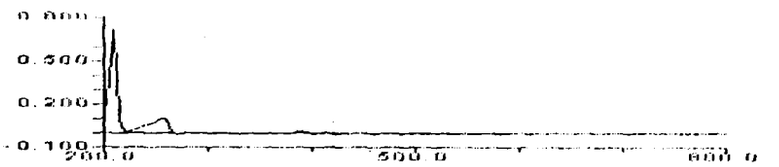
B



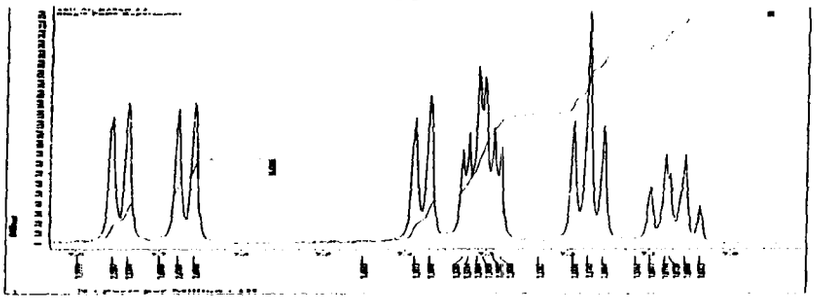
C

Appendix 2

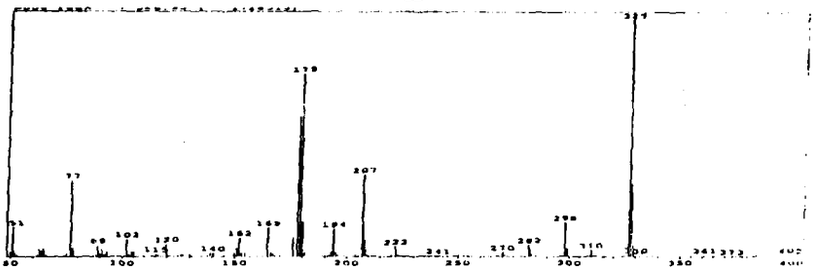
A - UV, B – ^{1}HNMR, C – MS, D – ^{13}CNMR and E – IR spectra of 2,3-diphenylquinoline-4-carboxylic acid (XVI)



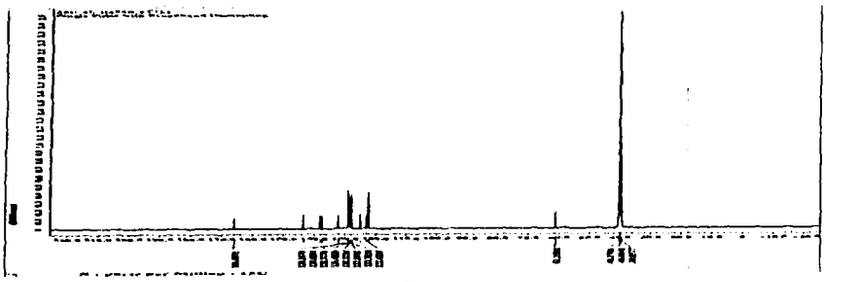
A



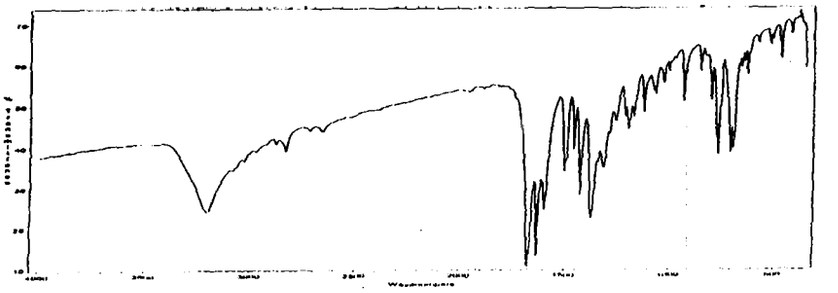
B



C



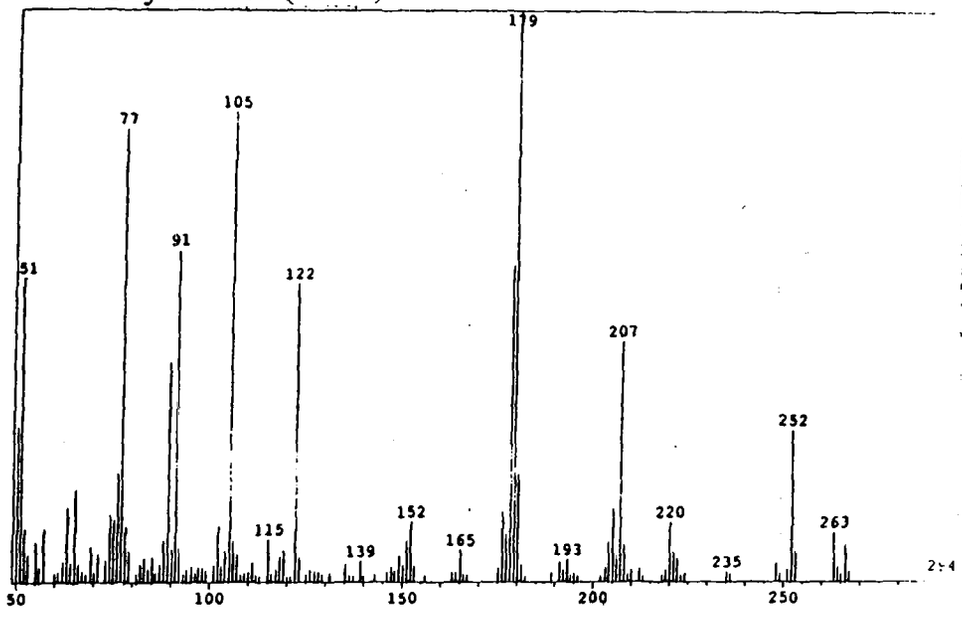
D



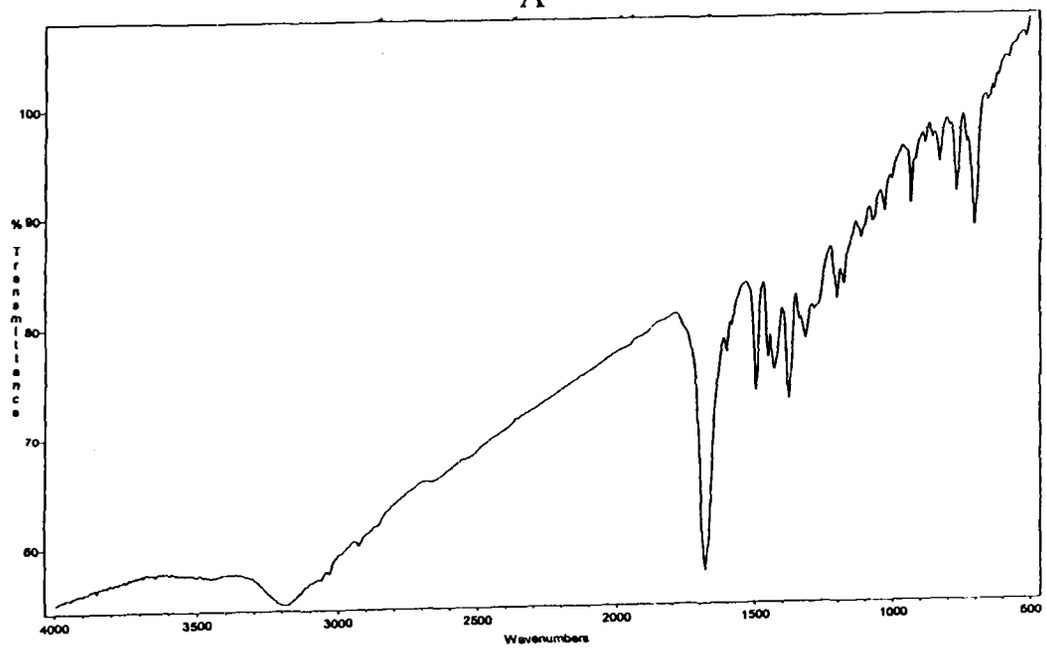
E

Appendix 3

A – MS, and B – IR spectra of 8-methyl-2,3-diphenylquinoline-4-carboxylic acid (XVII)



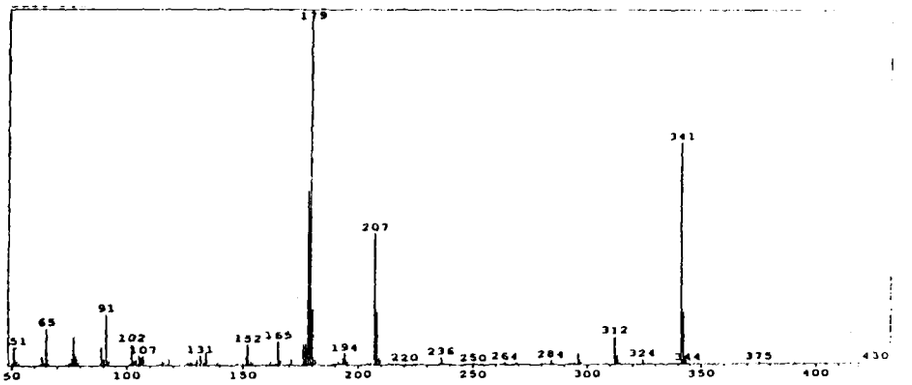
A



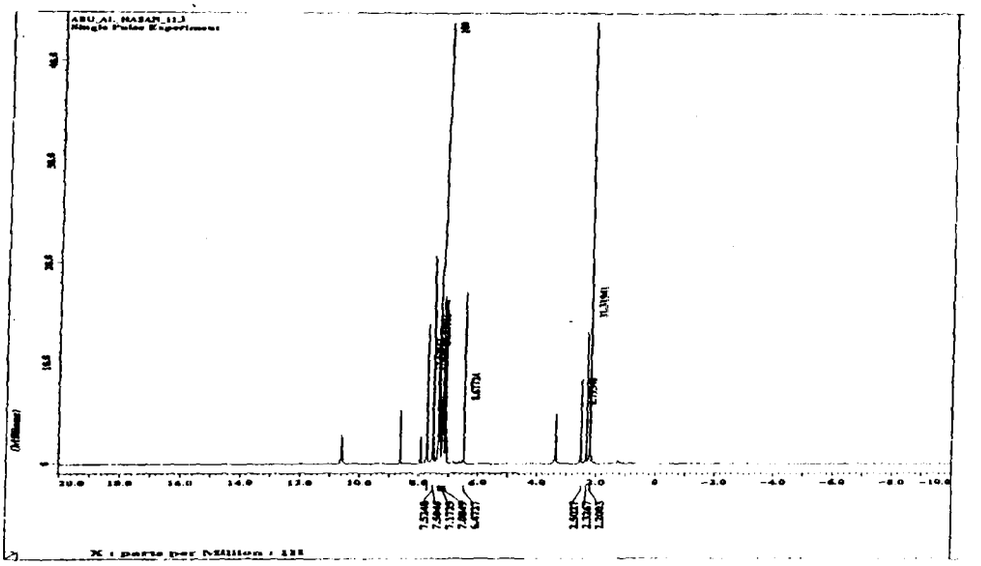
B

Appendix 4

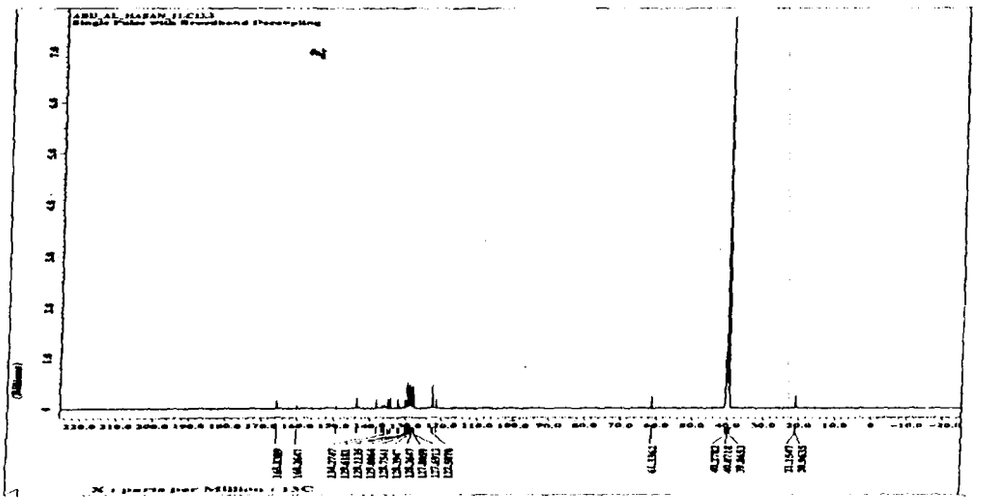
A – MS, B – ^{1}HNMR and C – ^{13}CNMR spectra of 6-methyl-2,3-diphenylquinoline-4-carboxylic acid (XVIII)



A



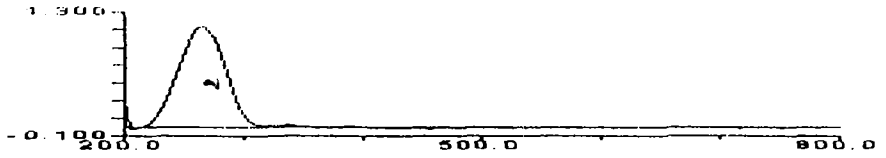
B



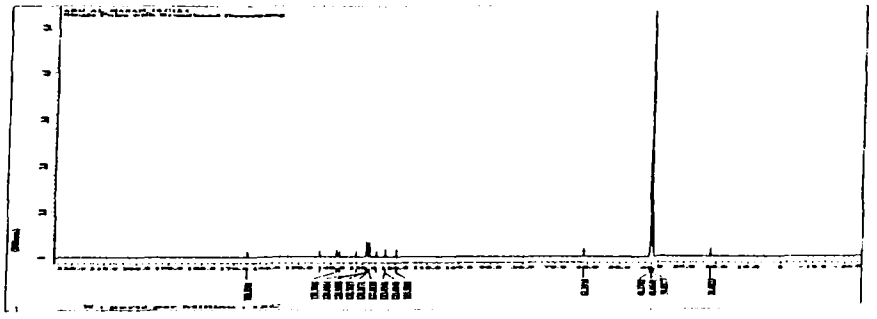
C

Appendix 5

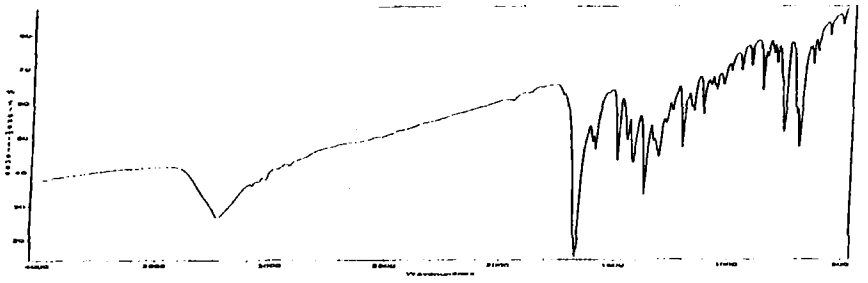
A – UV, B – ^{13}CNMR, C – IR, D – ^{1}HNMR and E – MS spectra of 7-methyl-2,3-diphenylquinoline-4-carboxylic acid (XIX)



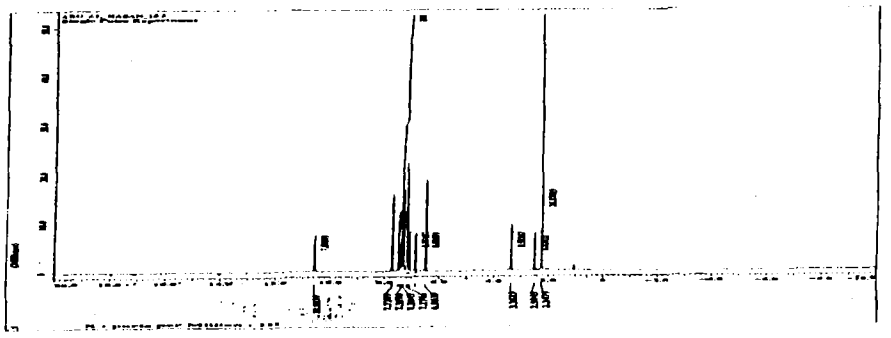
A



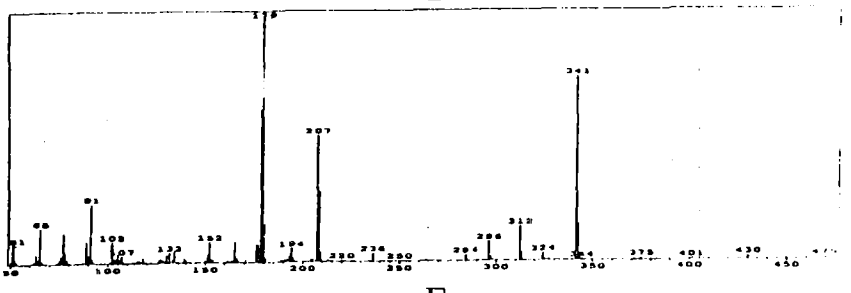
B



C



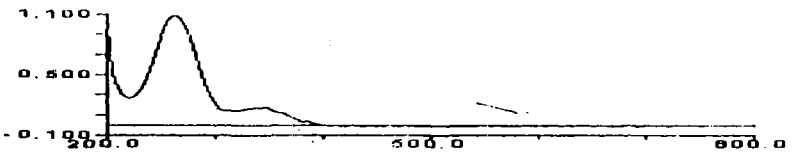
D



E

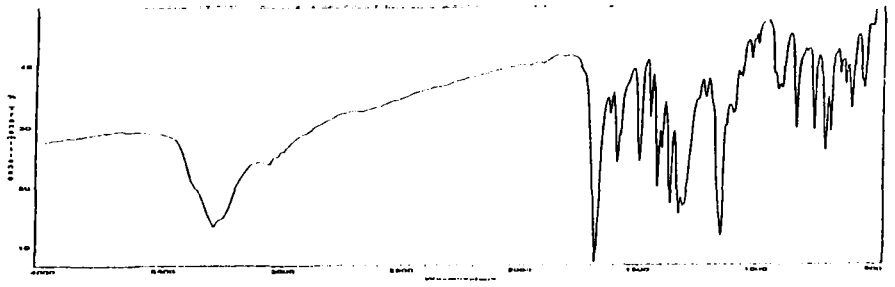
Appendix 6

A – UV, B – ^{13}CNMR, C – IR, D – MS and E – ^{1}HNMR spectra of 2,3-diphenyl-6-sulphonamidoquinoline-4-carboxylic acid (XX)

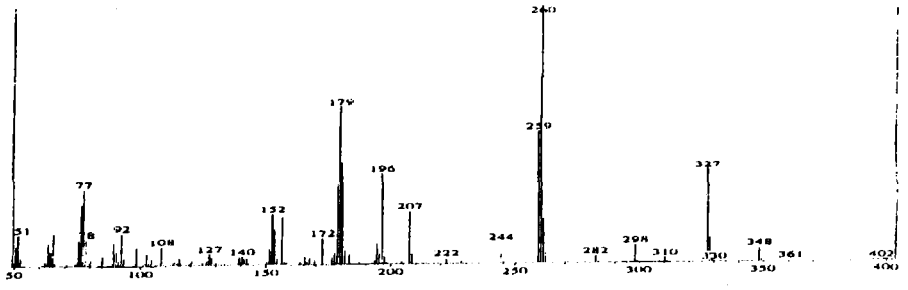


A

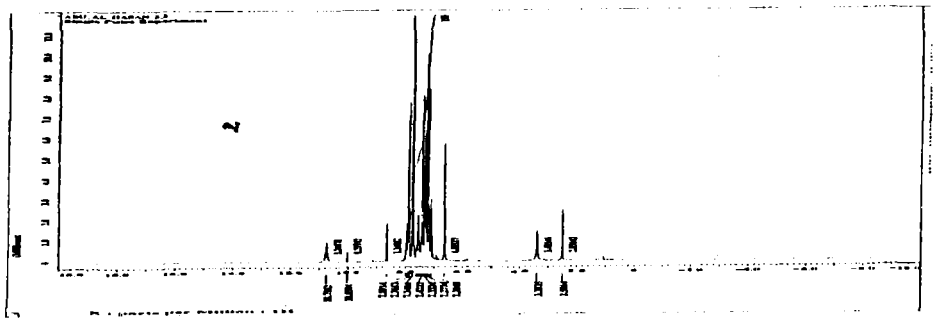
B



C



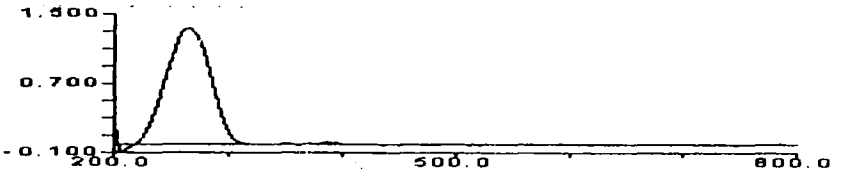
D



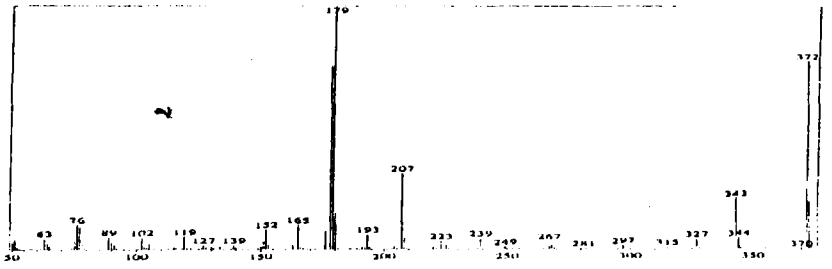
E

Appendix 7

A – UV, B – MS, C – ^{13}CNMR, D – IR and E – ^{1}HNMR spectra of 6-nitro-2,3-diphenylquinoline-4-carboxylic acid (XXI)

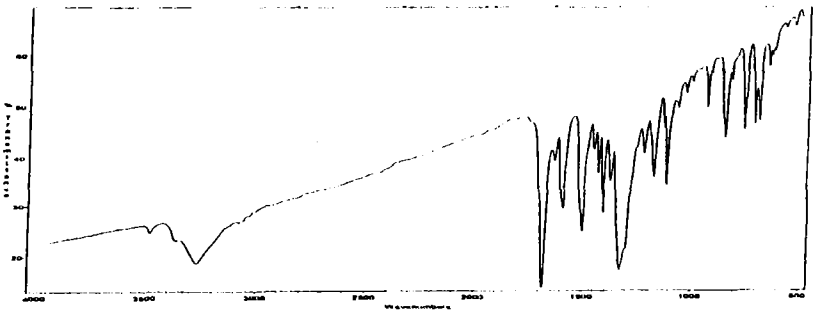


A

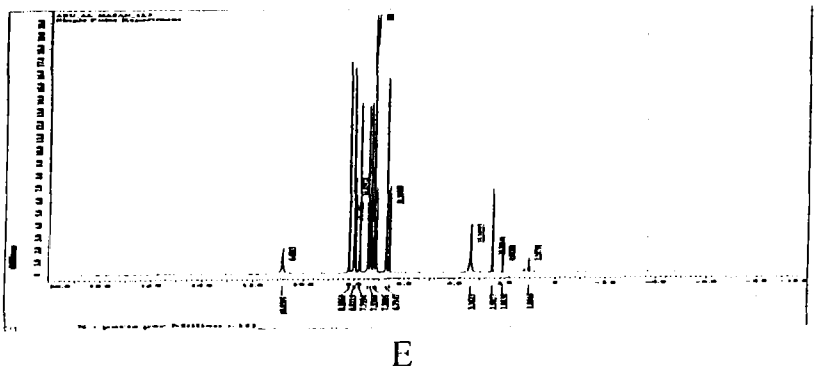


B

C



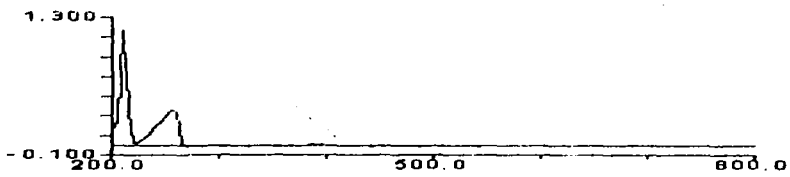
D



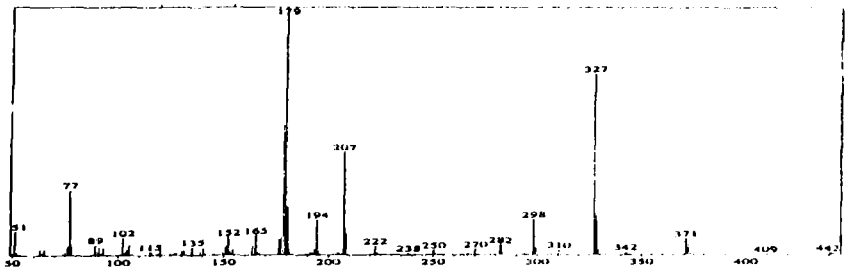
E

Appendix 8

A – UV, B – MS, C – ^{13}CNMR, D – ^{1}HNMR and E – IR spectra of 2,3-diphenylquinoline-4,6-dicarboxylic acid (XXII)

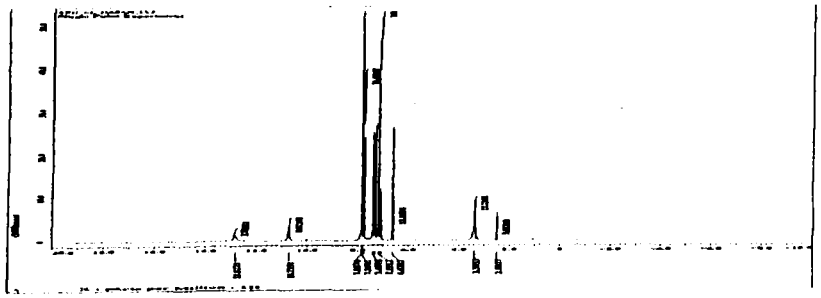


A

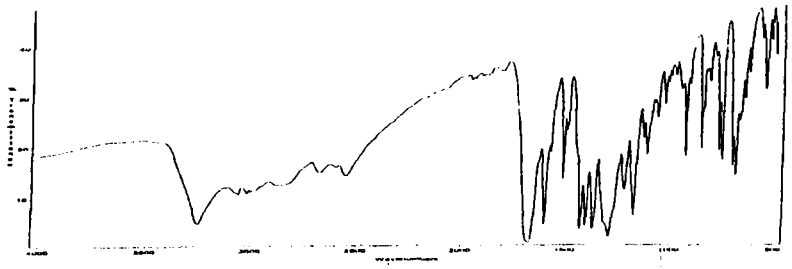


B

C



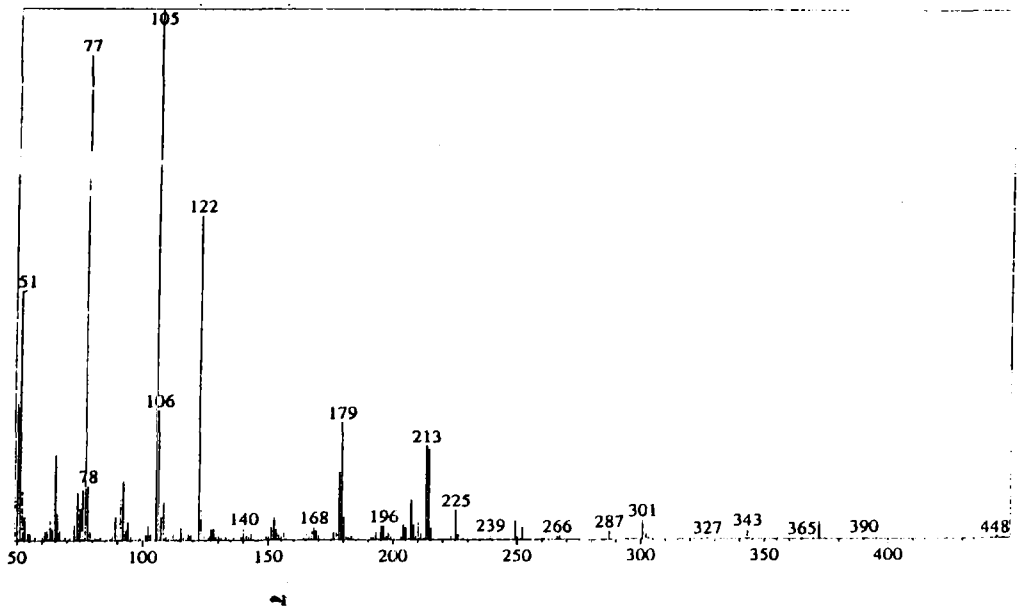
D



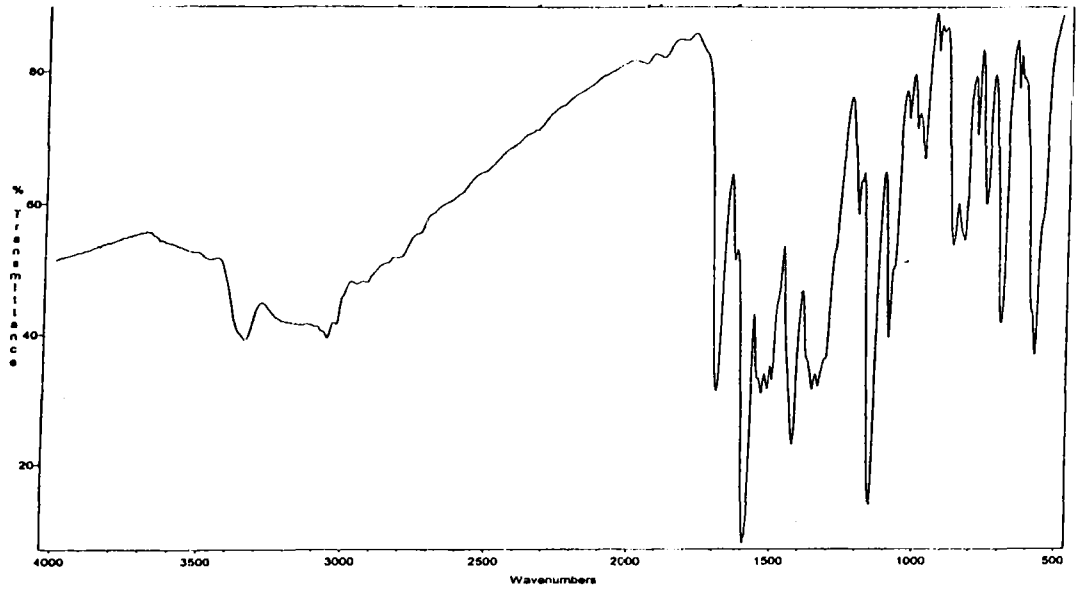
E

Appendix 9

A – MS and B – IR, spectra of 2,3-diphenylquinoline-6-sulphadimidine-4-carboxylic acid (XXIII)



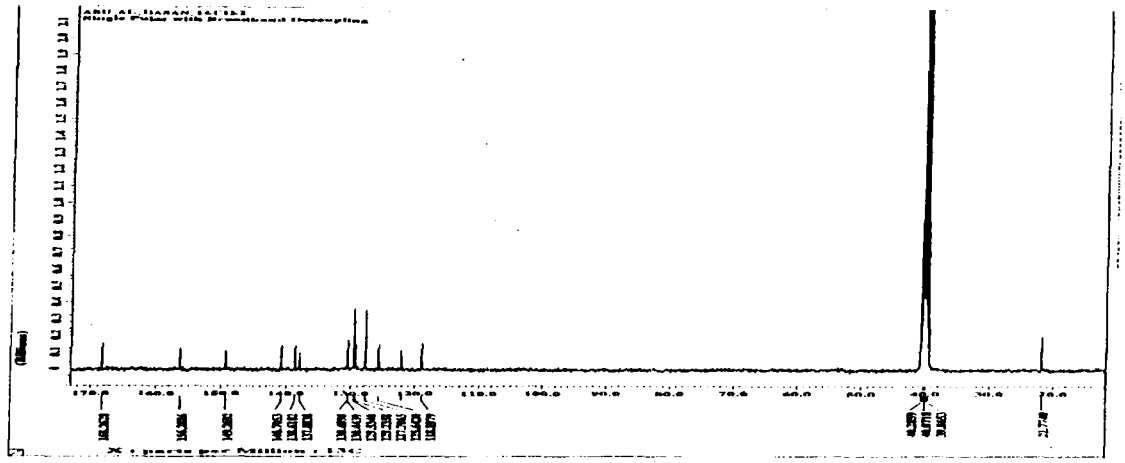
A



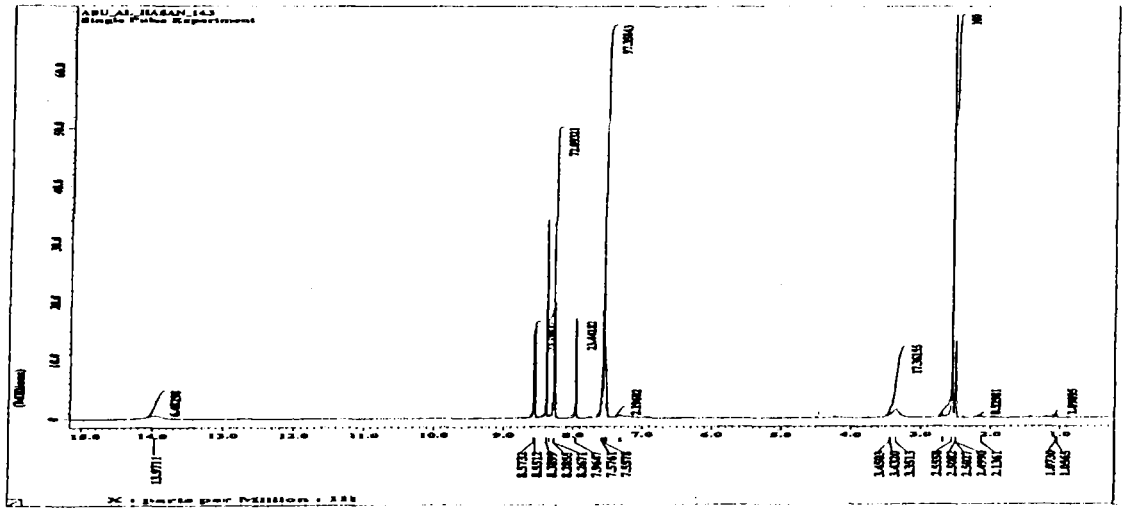
B

Appendix 10

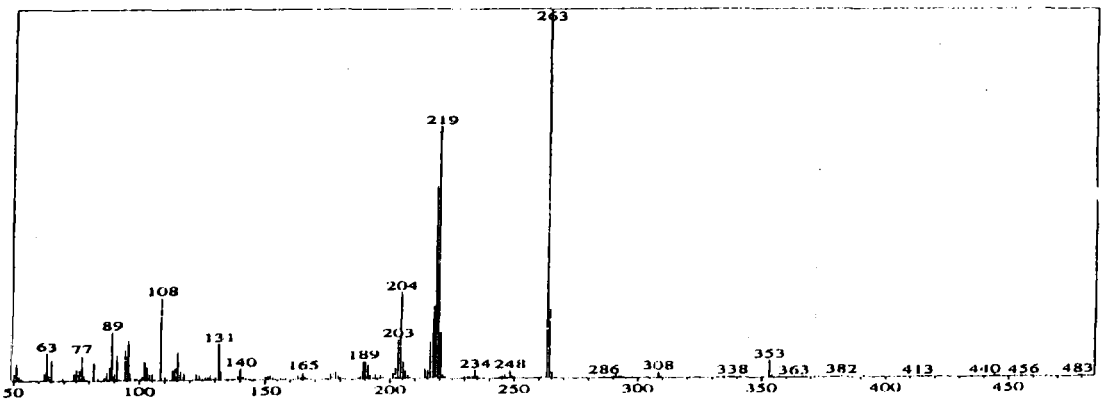
A – ^{13}CNMR, B – ^{1}HNMR, and C – MS spectra of -methyl-2-phenylquinoline-4-carboxylic acid (XXIV)



A



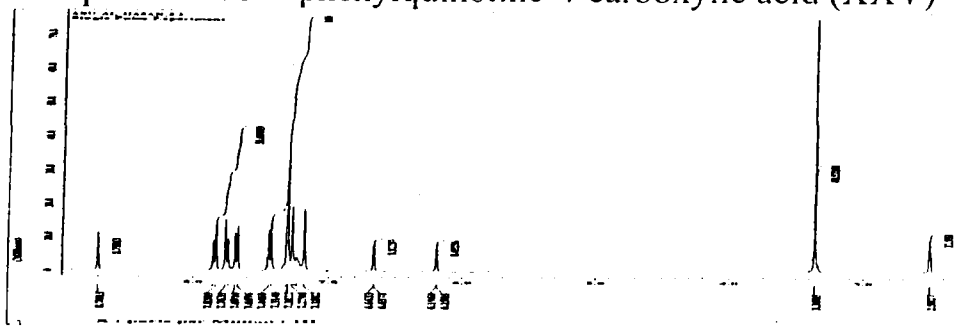
B



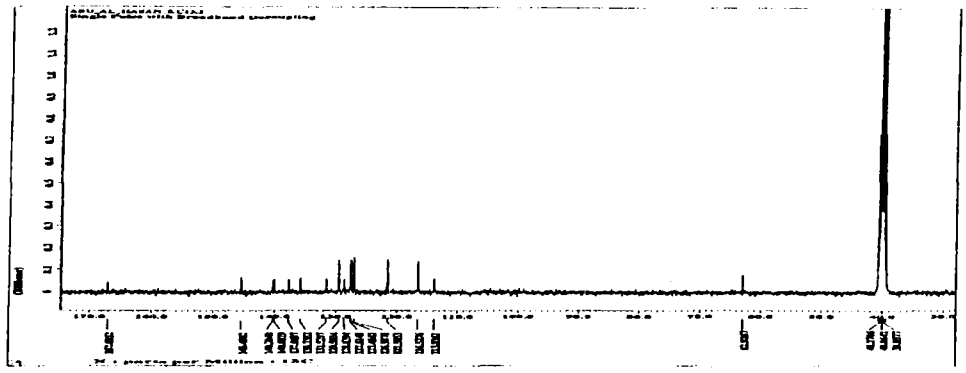
C

Appendix 11

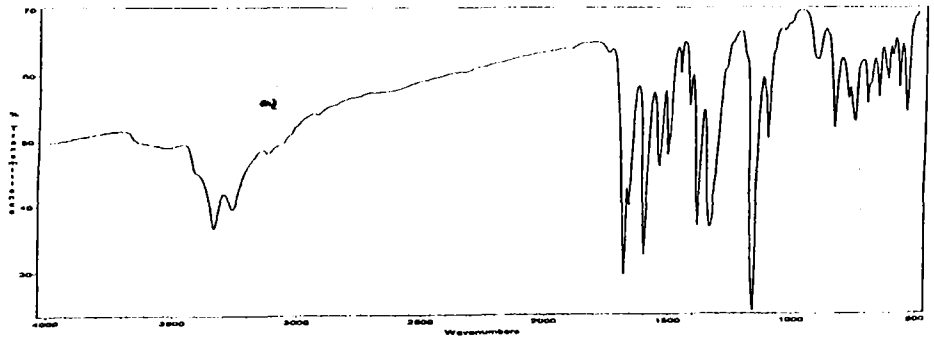
A – ^{1}HNMR, B – ^{13}CNMR, C – IR, and D – MS spectra of 6-sulphonamido-2-phenylquinoline-4-carboxylic acid (XXV)



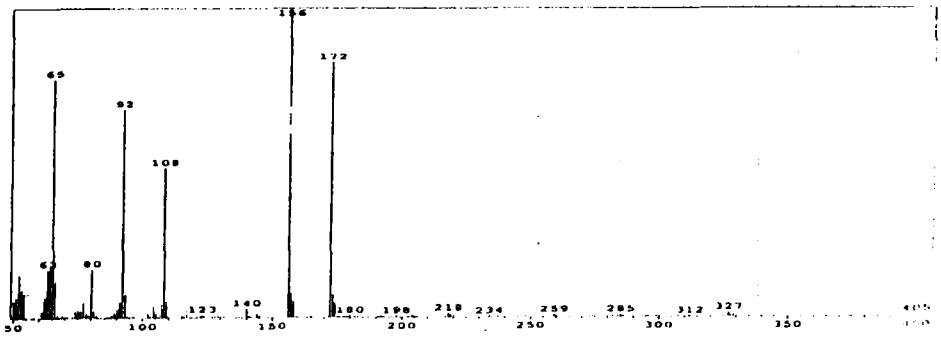
A



B



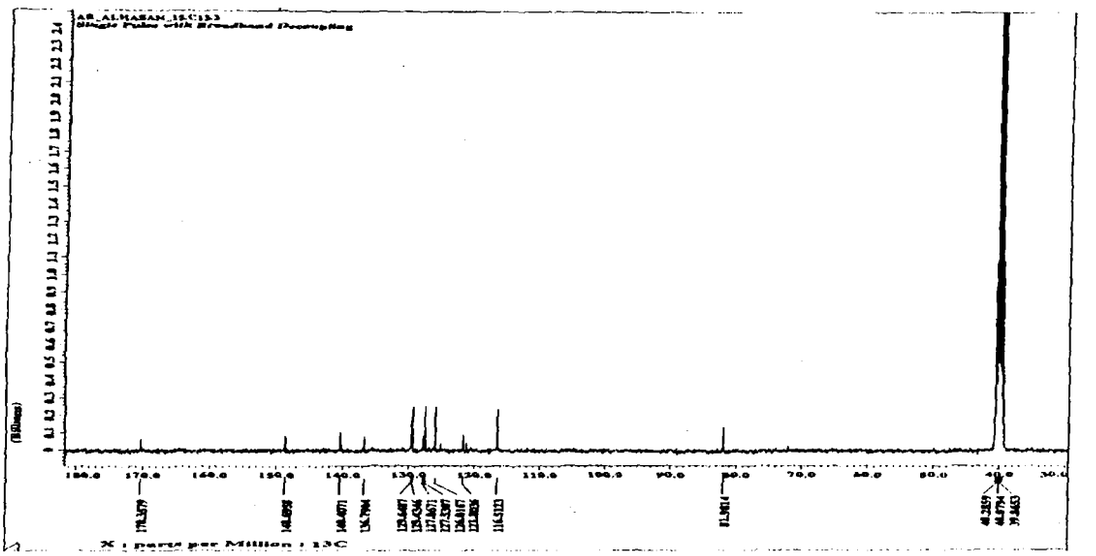
C



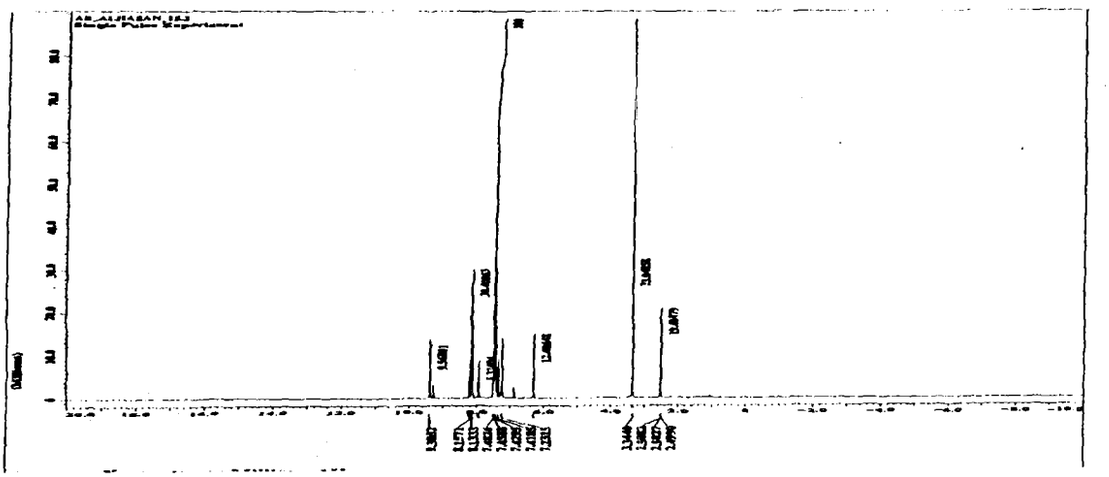
D

Appendix 12

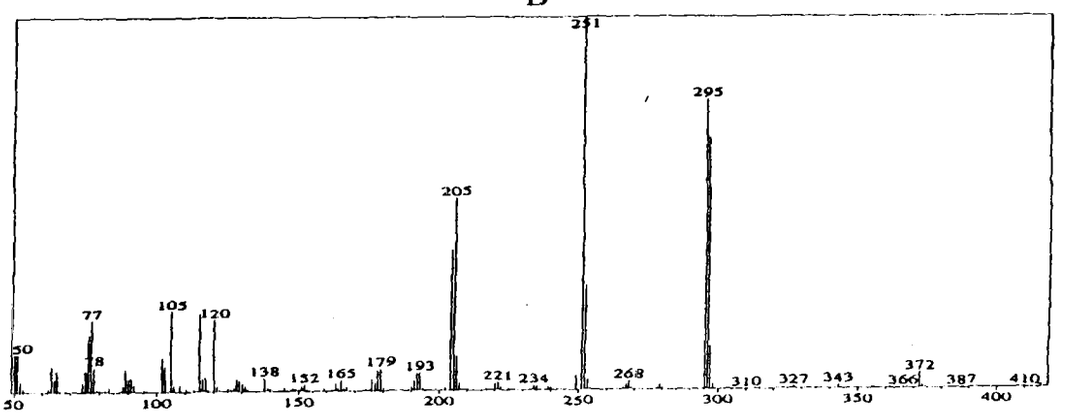
A – ^{13}CNMR; B – ^{1}HNMR and C – MS spectra of 6-nitro-2-phenylquinoline-4-carboxylic acid (XXVI)



A



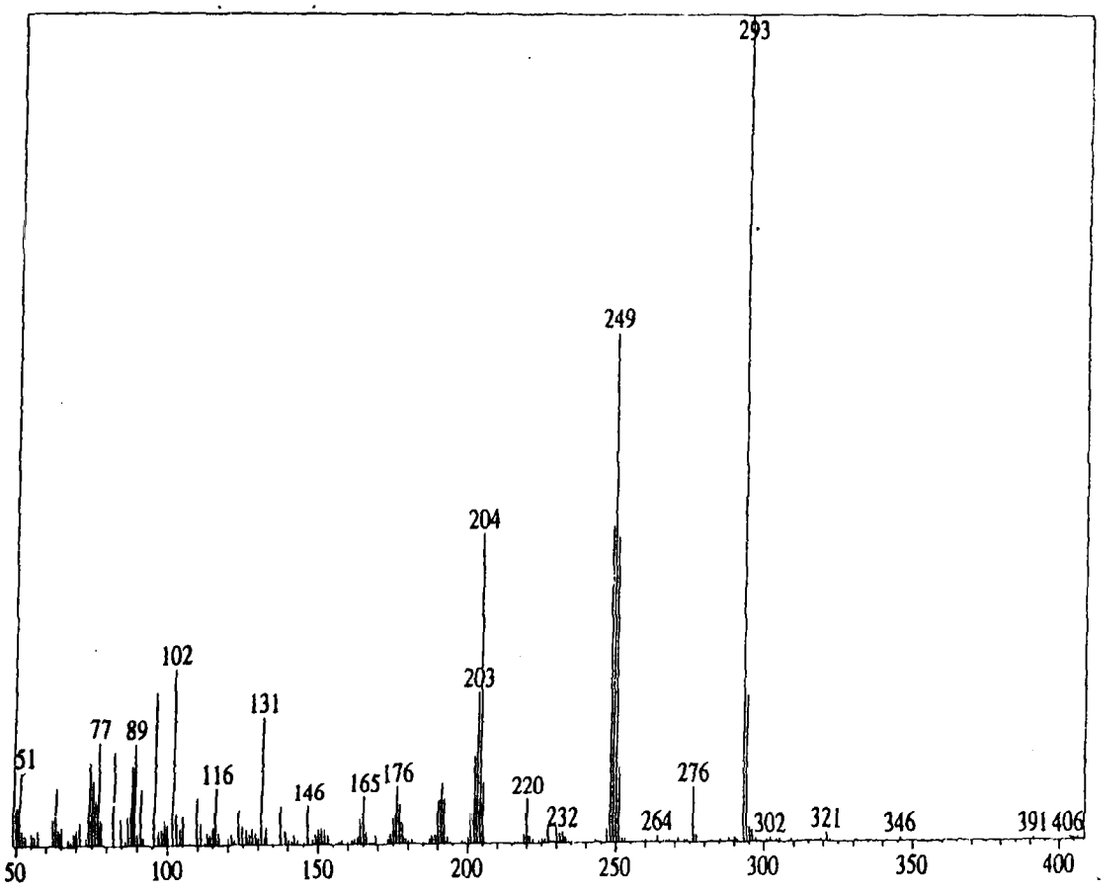
B



C

Appendix 13

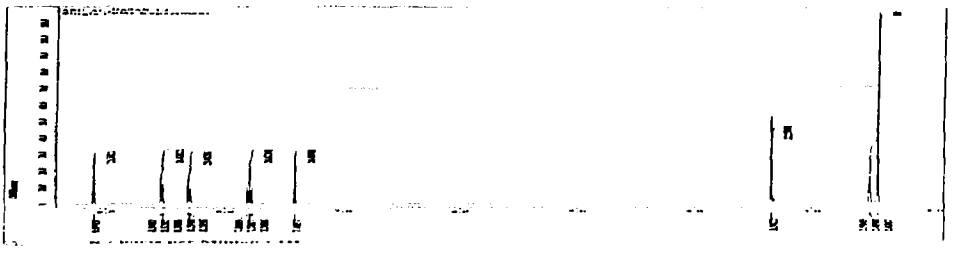
MS spectra of 2-phenylquinoline-4,6-dicarboxylic acid (XXVII)



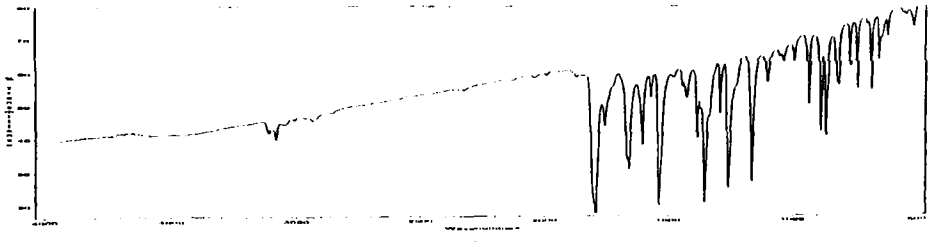
Appendix 14

A – UV, B – ^{1}HNMR, C –IR, D – MS and E – ^{13}CNMR spectra of 4-nitrobenzylidine-2-methyloxazol-5-one (XXVIII)

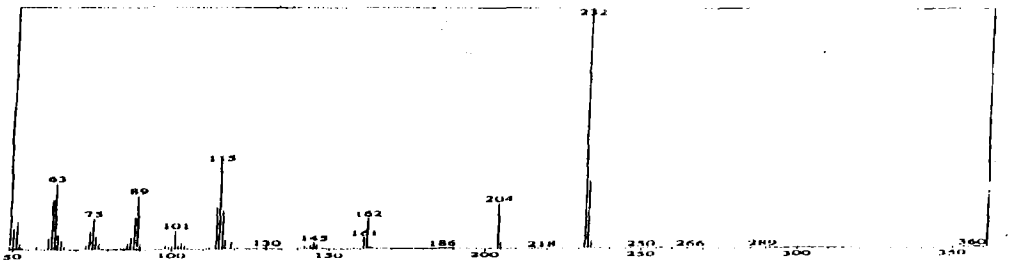
A



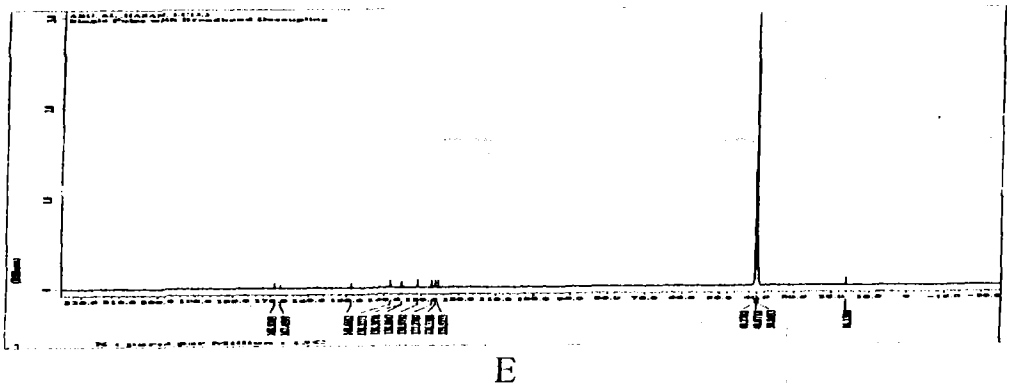
B



C



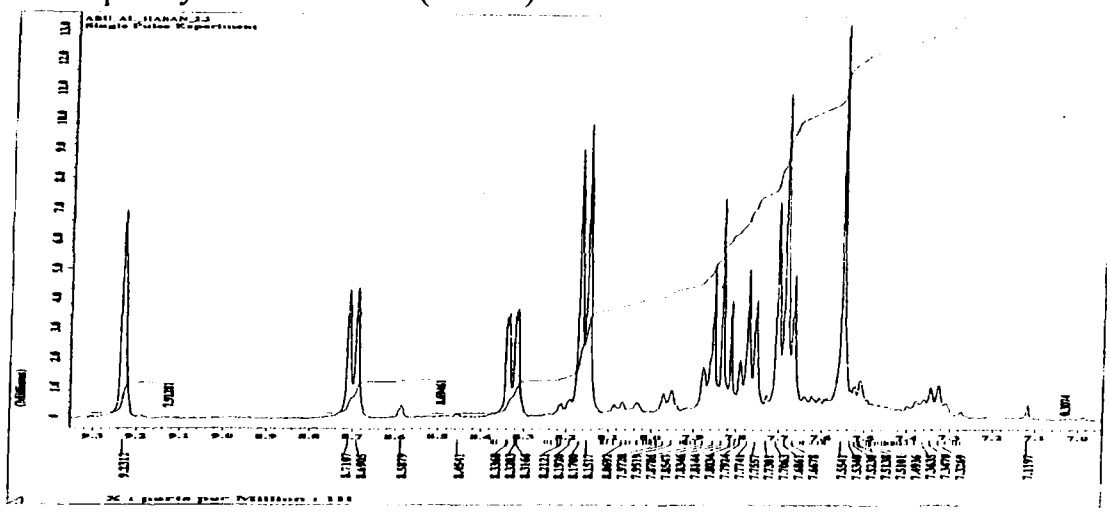
D



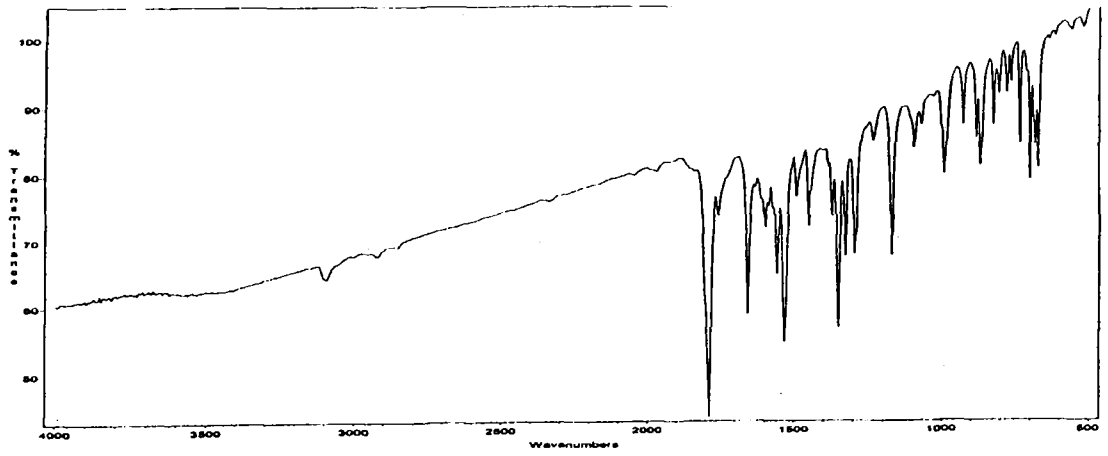
E

Appendix 15

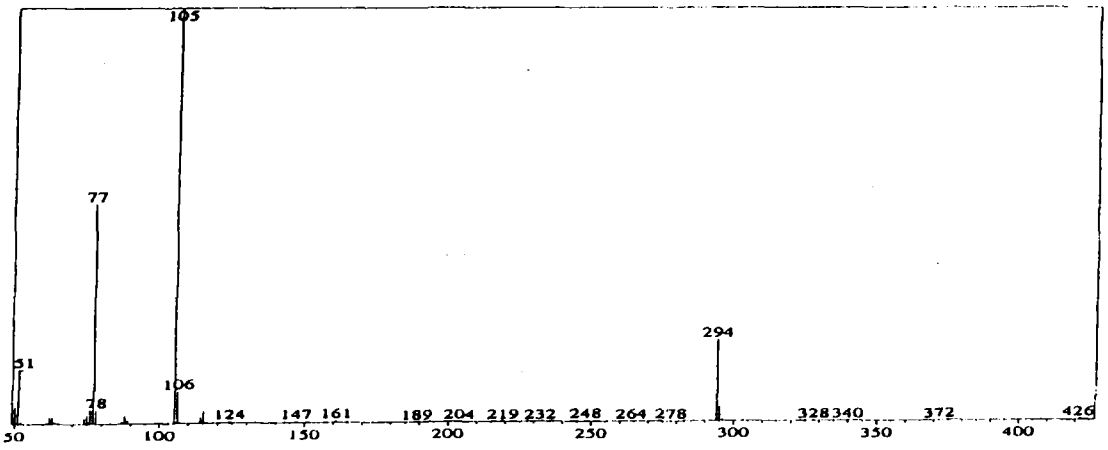
A – ^{1}HNMR, B – IR , and C – MS spectra of 4-Nitrobenzylidene-2-phenyloxazol-5-one (XXIX)



A



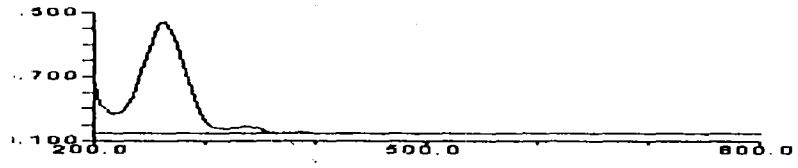
B



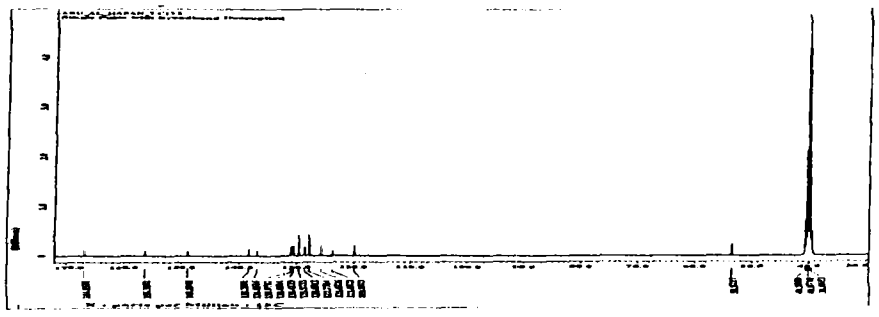
C

Appendix 16

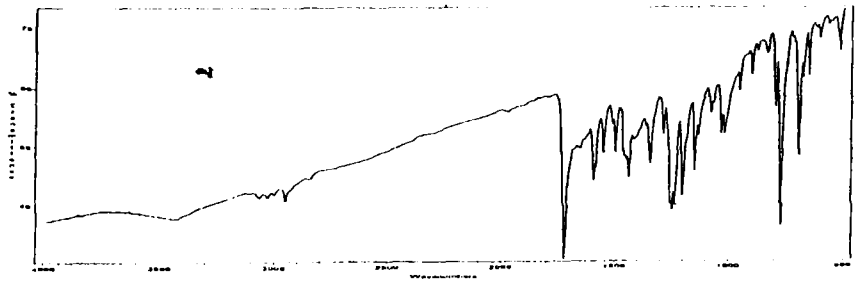
A – UV, B – ^{13}CNMR, C – IR, D – MS and E – ^{1}HNMR spectra of Methyl-2-phenylquinoline-4-formate (XXX)



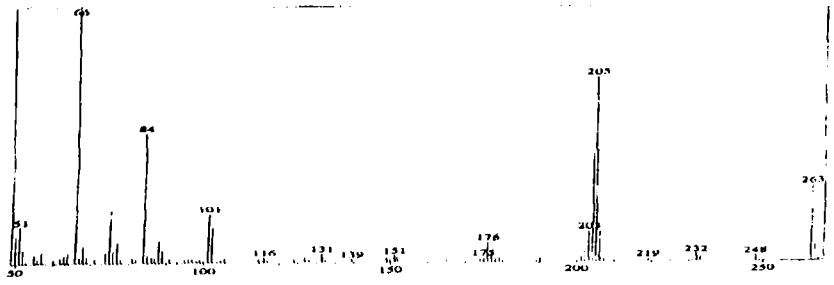
A



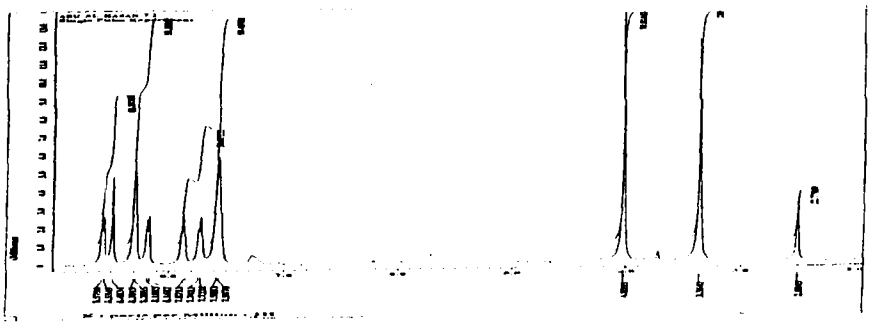
B



C



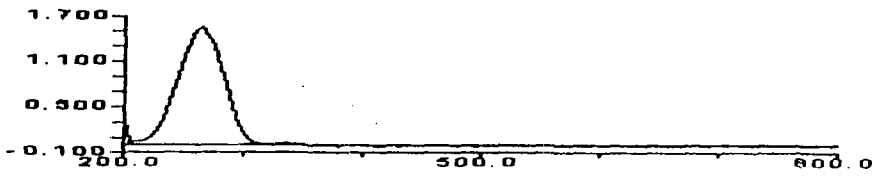
D



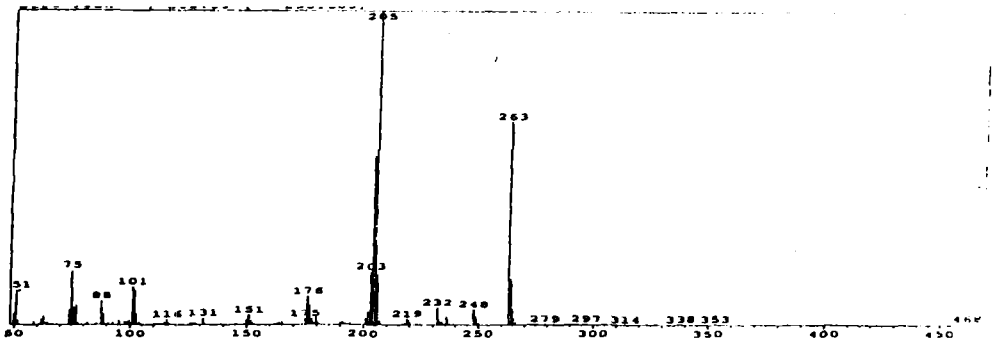
E

Appendix 17

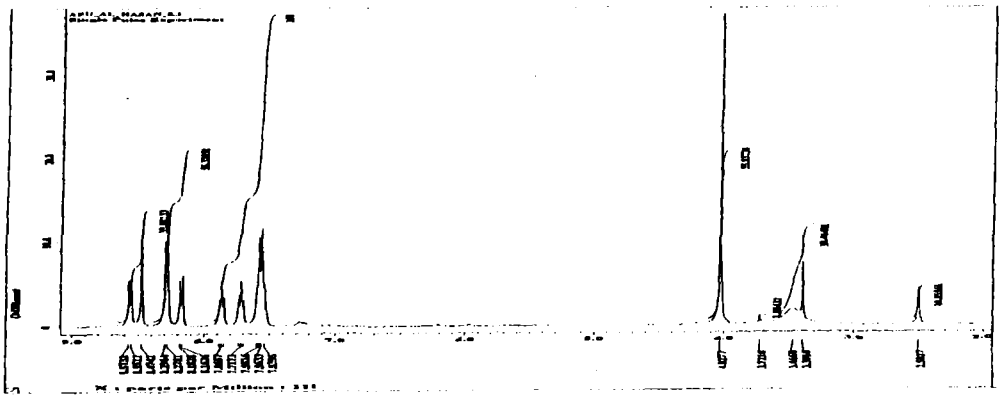
A – UV, B – MS, C – ^{1}HNMR, and D – ^{13}CNMR spectra of Methyl-2,3-diphenylquinoline-4-formate (XXXI)



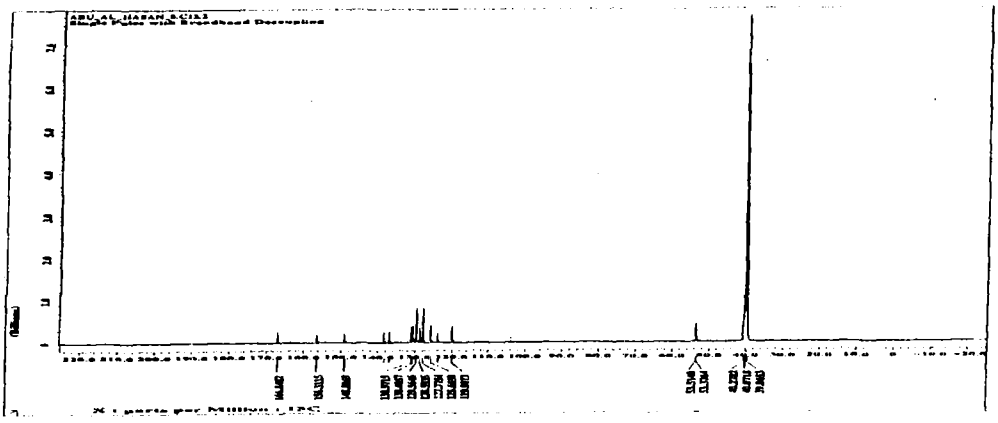
A



B



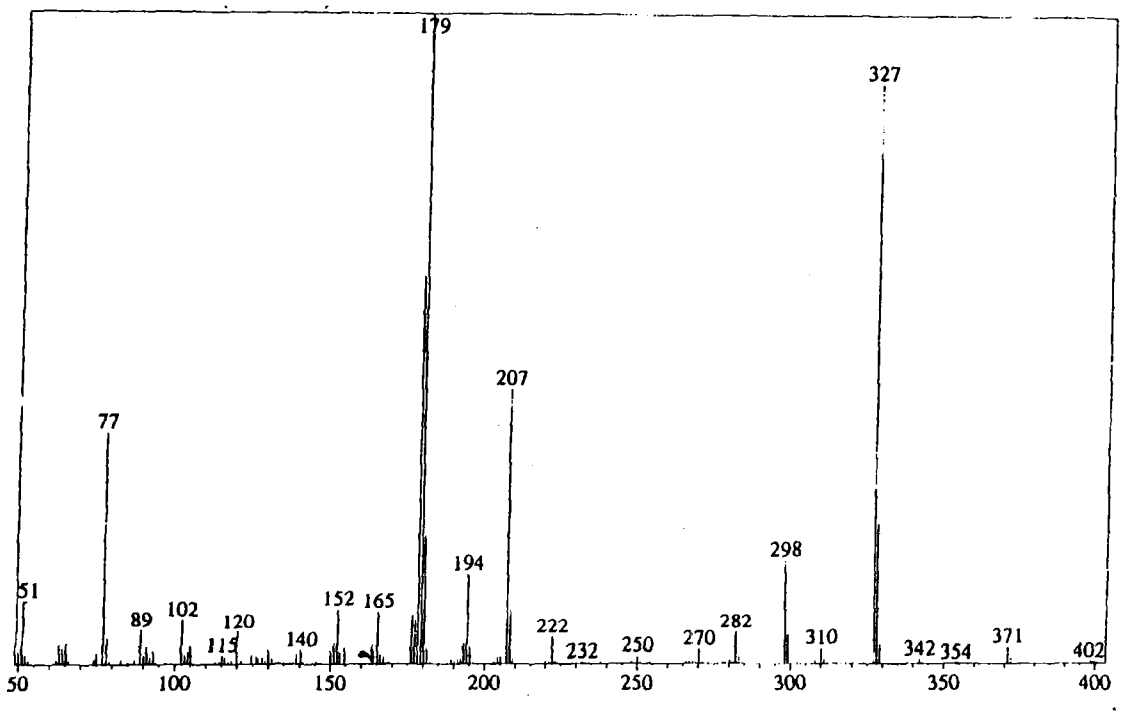
C



D

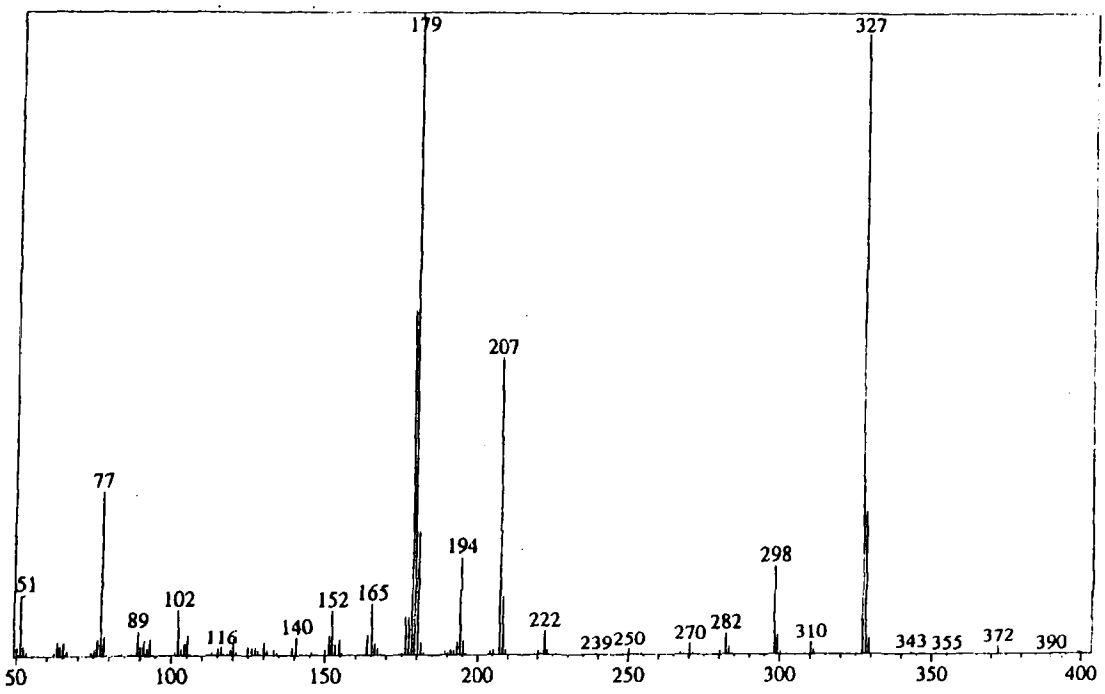
Appendix 18

MS spectra of 2,3-diphenylquinoline-4-carbox amide (XXXII)



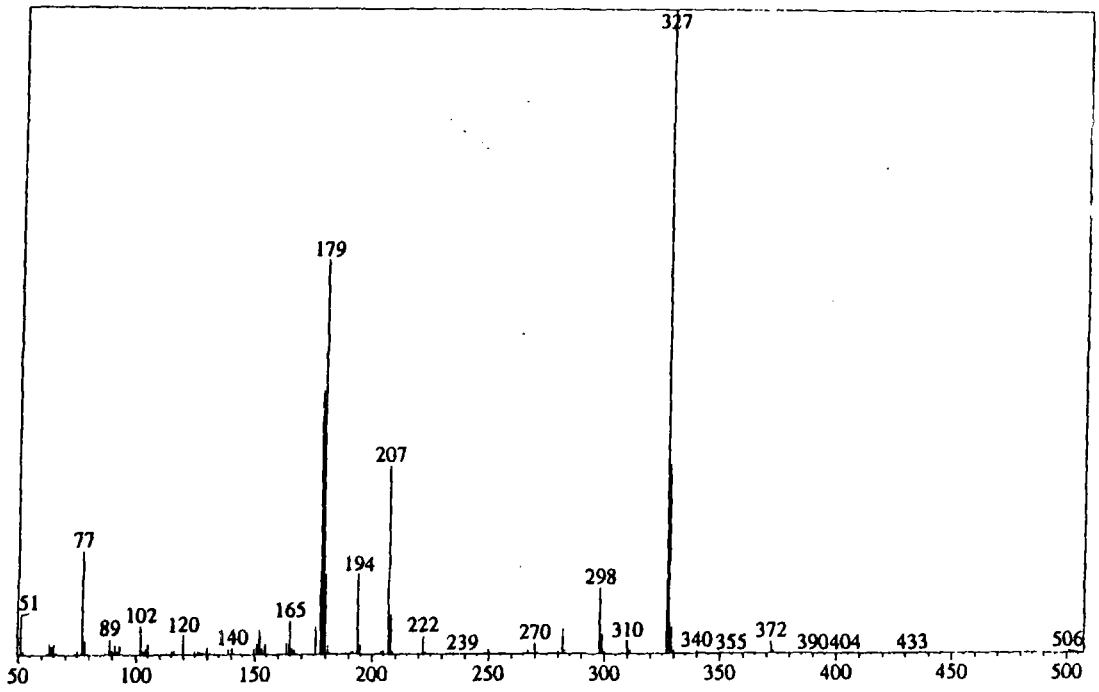
Appendix 19

MS spectra of N-phenyl-2,3-diphenylquinoline-4-carbox amide (XXXIII)

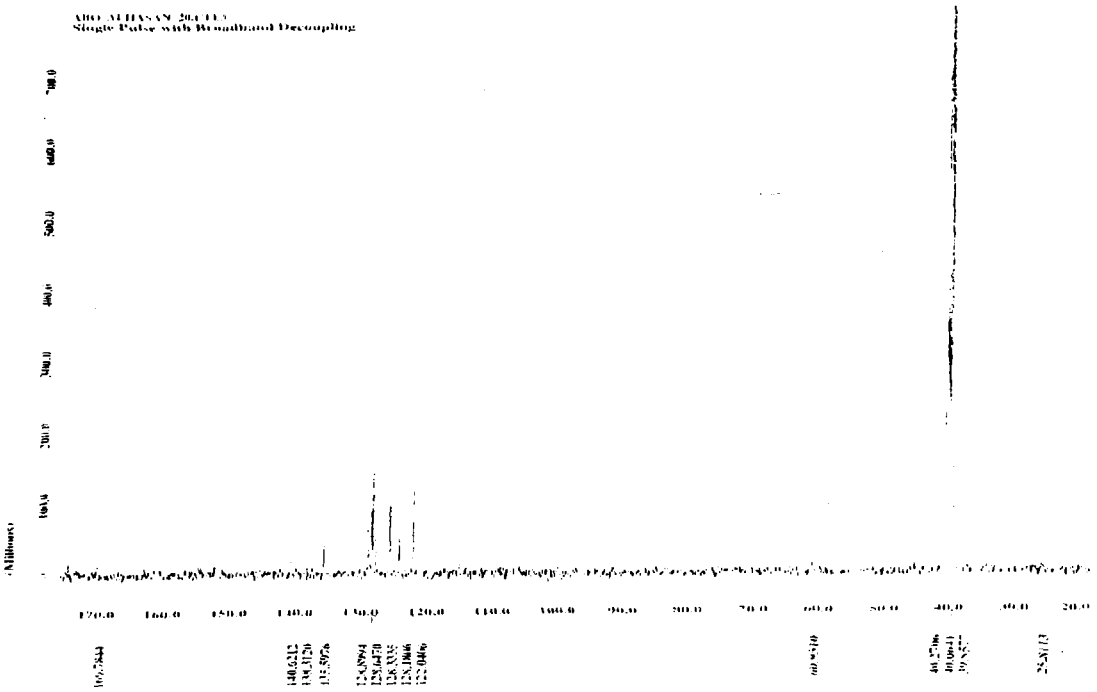


Appendix 20

A – MS UV and B – ^{13}CNMR spectra of N-methyl-2,3-diphenylquinoline-4-carbox amide (XXXIV)



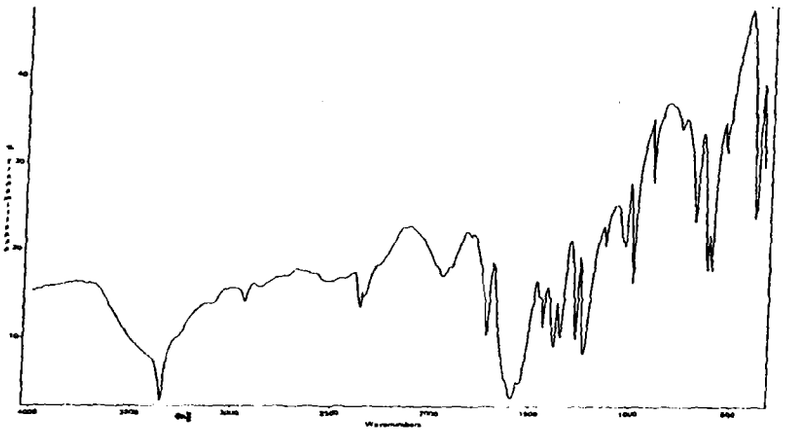
A



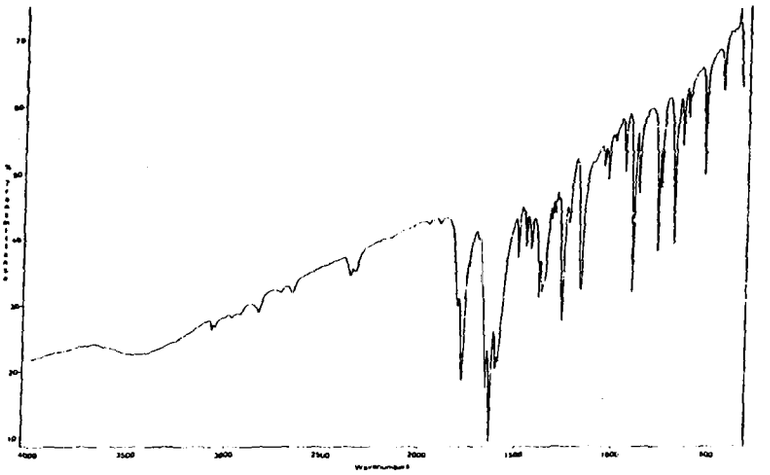
B

Appendix 21

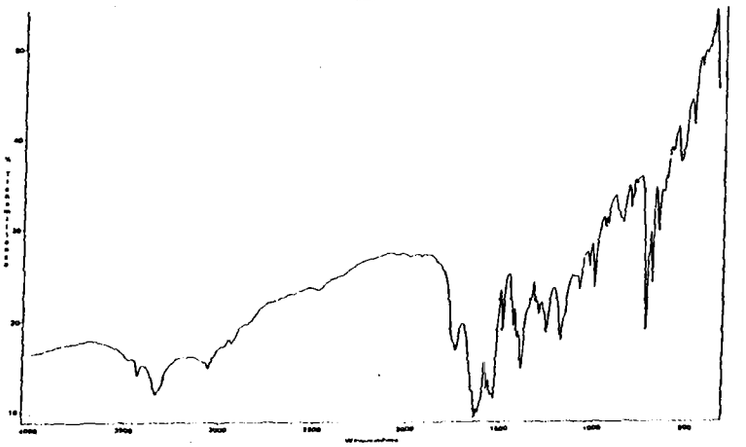
A IR spectra of Acetylglycine (I)
B IR spectra of 4-Benzylidene-2-methyloxazol-5-one (II)
C IR spectra of Benzoylglycine (IV)



A



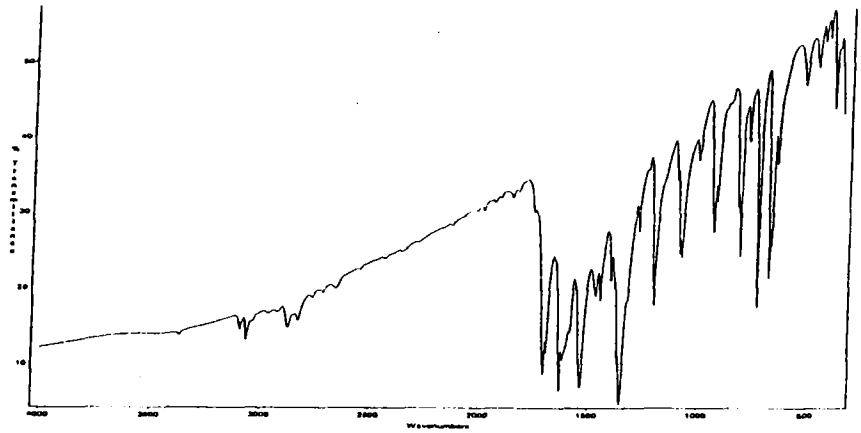
B



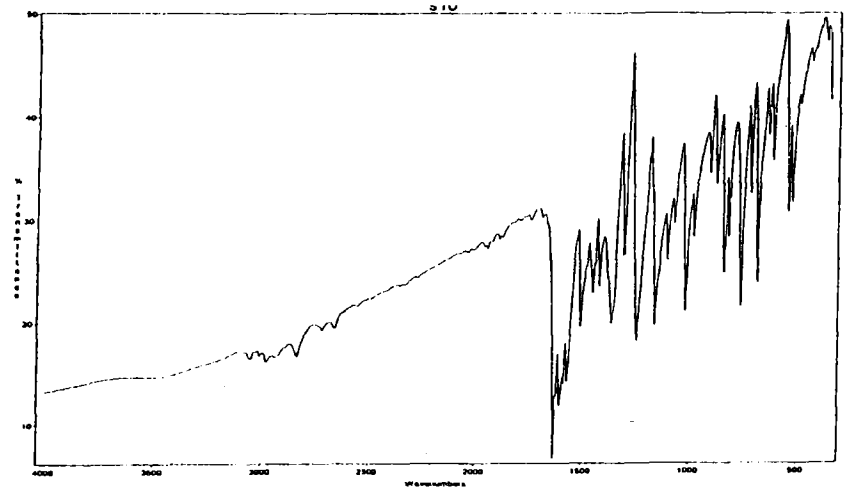
C

Appendix 22

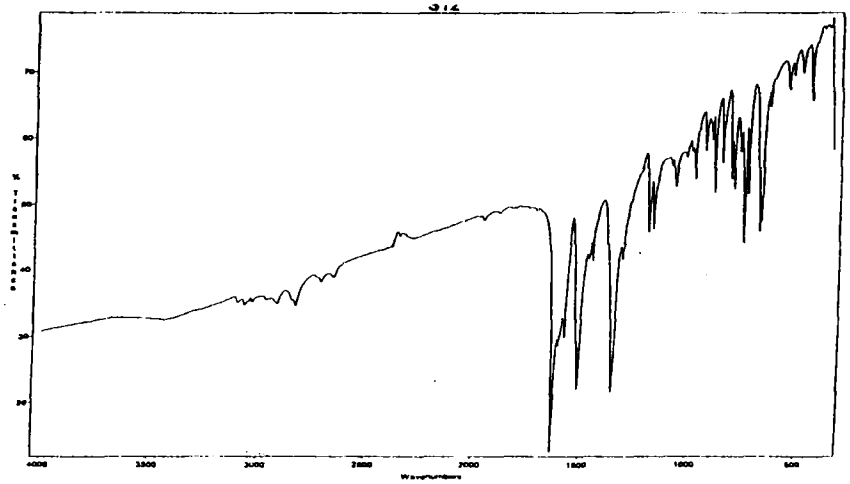
A IR spectra of *m*-Nitrobenzaldehyde (VII)
B IR spectra of *p*-Methoxy benzylidene aniline (X)
C IR spectra of N-Benzylidene-m-nitroaniline (XII)



A



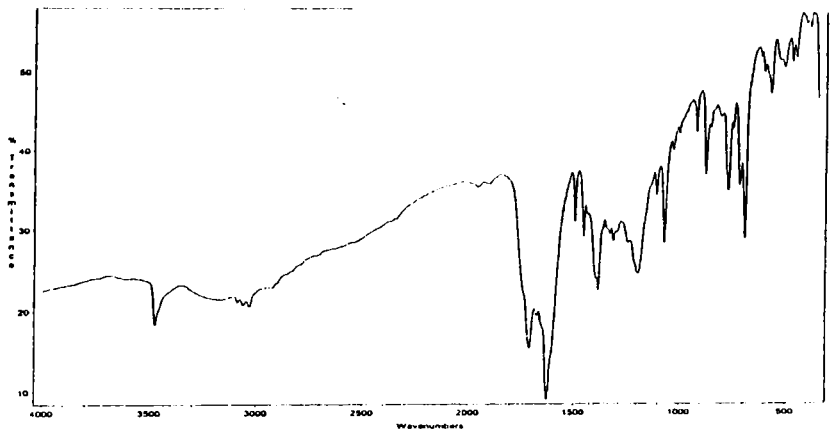
B



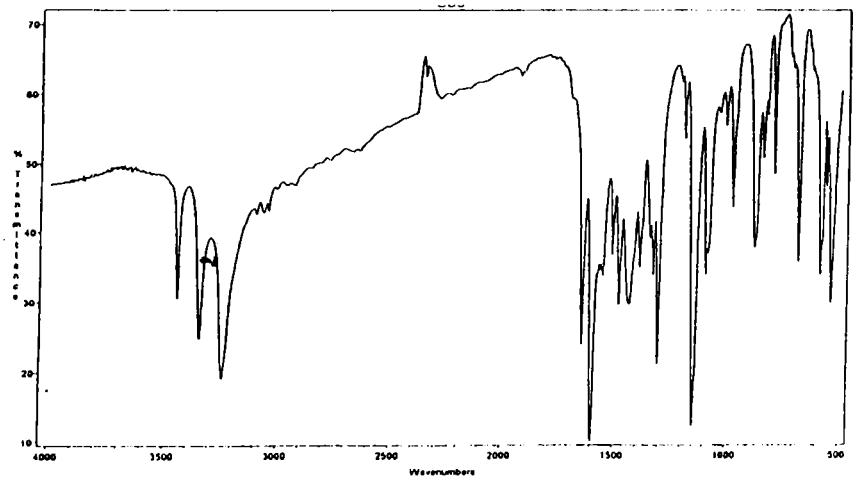
C

Appendix 23

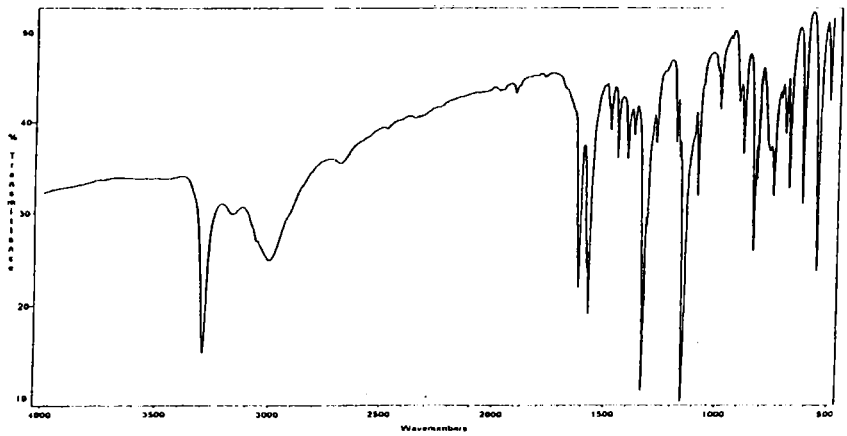
A IR spectra of Phenyl pyruvic acid (XV)
B IR spectra of Bnzylidene sulphanilamide (XXXV)
C IR spectra of Benzylidene sulphadimidine (XXXVI)



A



B



C