بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

Preparation of some 3,6-disubstituted 2-methylquinolin-4-ol and 3,6-disubstituted 4-methylquinolin-2-ol derivatives

تحضير بعض مشتقات ٣,٦- ثنائي مستبدل ٢- ميثيل كينولين-٤-ول و ٣,٦-ثنائي مستبدل ٤- ميثيل كينولين-٢- ول

A Thesis Submitted in The partial Fulfillment for The Requirements of M.Sc. Degree in Chemistry

By:

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استفتاح

بسم الله الرحمن الرحيم

☼ خلق الانسان من علق ☼إقرأ باسم ربك الذي خلق﴾قال تعالى :

☼﴿علّم الانسان ما لم يعلم☼ الذي علّم بالقلم ☼إقرأ وربك الاكرم

صدق الله العظيم

سورة العلق

الايات (1-5)

Dedication

To

My parents

My Brothers and sisters

Acknowledgements

Firstly thanks to Allah almightily for given me the strength to complete this work related.

I would like to offer my great thanks and appreciation to my supervisor **prof. Dr. Ahmed Elsadig Mohammed Saeed** who has exerted his time and efforts for lucid design of this research and help throughout his work.

My thanks are due to **Ustaz munzir hamad** (Central Laboratory University of Khartoum) for his help in IR spectroscopic analysis.

I wish to thanks **Mr. Mohammed kamel** for taking my samples to Cairo for H^1NMR analysis.

To my friends and families, they were a great source of support and encouragement, I wish to thank them all and wish them all the best in their lives.

Finally I am grateful to the chemistry Department and Technical staff for their great help.

Abstract

The chemistry of quinoline derivatives including their preparations, reactions together with a review of their most important biological activity were dealt with in chapter one.

3,6-disubstituted 2-methyl quinolin-4-ol and 3,6-di substituted 4-methyl quinoline-2-ol derivatives were prepared by Conrad Limpach Knorr method, kinetically and thermodynamically.

Eight final compounds were prepared in this work, together with their corresponding intermediates in multiple step synthesis.

In the first step the diazonium ion was formed from the reaction of aromatic amines with nitrous acid and coupling reaction of diazonium products with active methylene compound (ethyl-3-oxobutanoate).

The second step reaction of diazotized dicarbonyl compounds with aromatic amine (aniline, sulphanilamide) in presence of hydrochloric acid in two different conditions (room temperature, 70-80^{o}C), were carried out.

The third step is cyclization using sulphuric acid at high temperature.

The reaction course was followed with thin layer chromatography (TLC), the identity of products was determined through IR, H^{1}NMR.

The retrosynthetic analysis of the compounds was discussed in chapter three together with suitable mechanism of each reaction. The spectral data were interpretated and discussed in the same chapter, the results obtained were agreed will with synthyzed compounds.

المستخلص

كيمياء مشتقات الكينولين بالاضافة الي خواصها وتفاعلاتها مع اهميتها في النشاط البيولوجي تمت مناقشتها في الفصل الاول.

تم تحضير ٦,٣-ثناي مستبدل -٢-ميثيل كينولين-٤-ول و٦,٣-ثناي مستبدل -٤-ميثيل كينولين-٢-ول حركيا وثيرموديناميكيا.

في هذا البحث تم تحضير ثمانية مركبات كناتج نهائي بالاضافة للمركبات الوسيطية المناظرة لها في عة خطوات.

في الخطوة الاولى تم تحضير ملح الديازونيوم من تفاعل الامينات الاروماتية (انيلين وسلفانيل اميد) مع حمض النتروز وبعد ذلك مفاعلة ملح الديازونيوم مع مركبات تحتوي على مجموعة ميثيلين منشطة (ايثيل اسيتو اسيتيت) وتكوين مركبات ازو.

في الخطوة الثانية تمت مفاعلة مركبات ازو ثنائي كاربونيل مع الامينات الاروماتية في وجود حمض الهيدروكلوريك في ظروف مختلفة (درجة حرارة الغرفة و درجة حرارة 70-80 م)

في الخطوة الثالثة تم قفل الحلقة باستخدام حمض الكبريتيك في درجة حرارة عالية.

استخدمت كروماتوغرافيا الطبقة الرقيقة لتحديد اكتمال التفاعل وحددت هوية المركبات بواسطة طيف الاشعة تحت الحمراء و الرنين النووي المغناطيسي.

تمت مناقشة التخليق الرجعي وميكانيكية كل التفاعلات وايضا فسرت النتائج الطيفية في الفصل الثالث وظهرت النتائج بشكل مقبول مع المركبات المحضرة

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Introduction

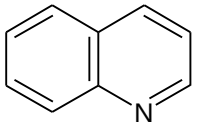
1. Introduction

1.1. Background :

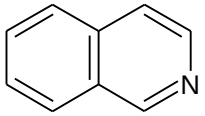
Heterocyclic compounds are compounds that contain rings made up of more than one kind of atom commonly, nitrogen, oxygen, sulphur. in many compounds such as benzene, naphthalene, cyclohexanol, and cyclopentadiene , they are made up only of carbon atoms such compound are called homocyclic compound (Morrison and Boyd, 2002). Heterocyclic compounds are very widely distributed in nature and are essential to life in various way, most of the sugars and their derivatives including vitamin C for instance exist largely in the form of five membered (furan) or six membered (pyran) rings which contain one oxygen atom. Most members of vitamin B group possess nitrogen heterocyclic rings. One example is vitamin B_6, pyridoxine. Most of alkaloids, which are nitrogenous bases occurring in plants and many antibiotics including penicillin, also contain heterocyclic ring systems. A large number of heterocyclic compounds obtainable only by laboratory synthesis have valuable properties as chemotherapeutic agents, drug dyestuffs or copolymers. Heterocyclic compounds may be aliphatic or aromatic in character, depending on their electronic constitution. In general the aliphatic heterocyclic, where specific effects due to the constitution of the compound are excluded are very similar chemically to their open-chain aliphatic analogues, for instance tetrahydrofuran, has many properties characteristic of diethyl ether, pyridine, and benzene.

Six-membered rings, the unsaturated compounds are more stable, when one of the carbons of a benzene ring is replaced by nitrogen; the resulting compound is called pyridine (Paula Bruice., 2003).

The pyridine ring may be fused with the benzene nucleus in different ways with resultant formation of quinoline (1), isoquinoline (2) and quinolinium salts (3).Only the first two have received considerable attention.



(1)



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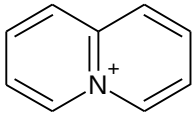
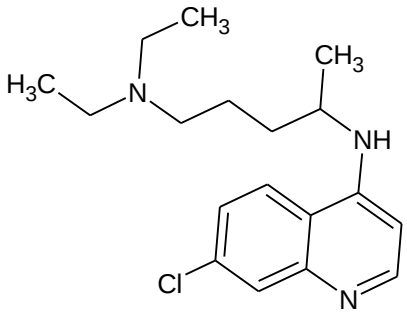


(3)

1.2.Structure of quinoline:

Quinoline is a stable high boiling liquid with a sweetish odour.It finds rather limited use in synthetic chemistry as a basic solvent, especially in Cu-catalyzed decarboxylations. It was first isolated from coal tar bases in 1834, and a little later in the alkaline pyrolysis of cinchonamine, an alkaloid closely related to the famous antimalarial alkaloid quinine.

The word quinoline in fact is derived from the word quinine, which in turn is derived from quinoa, a Spanish version of a local South American name for the bark of quinine containing cinchona species. The subsequent importance of quinoline is linked with malaria in the several successful synthetic antimalarial drugs such as chloroquine, which is also used in the treatment of amoebic dysentery.



Quinoline play no part in fundamental metabolism, they occur relatively rarely in plants as secondary metabolites (alkaloids),quinine being much the best known.An important role played by quinoline compounds was that of providing the first

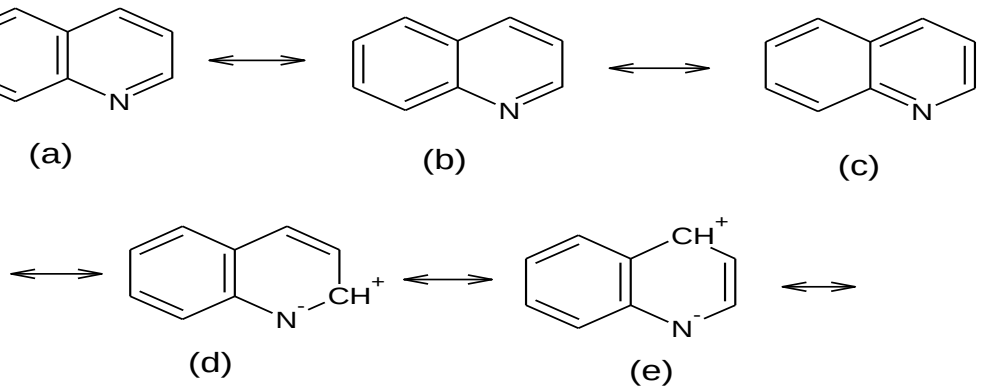
photographic film sensitizers, such as the cyanine dye ‹ethyl red' which extended photography the blue into the green and then in 1904, with pinacyanol, into the red. Since that time, hundreds of sensitizing dyes have been made and investigated, and the quinoline nucleus has been pushed aside by other, more efficient, systems (Joule and Smith, 1978).

1.3. Physical and spectroscopic properties:

Quinoline is a colorless hygroscopic liquid, b.p. 237º and has a characteristic smell resembling that of pyridine. On exposure to air it develops a yellow color.

Quinoline is miscible with organic solvents and is soluble in water to the extent of 0.7%.

Quinoline is highly aromatic and has resonance energy of 47.3kcal/mole and is considered a resonance hybrid of the following contributing structures:



As in the case of naphthalene, structures (a),(b) and (c) are of low energy, however, additional charged structures are also possible because of the introduction of an electronegative nitrogen atom. The dipole moment of quinoline is 2.10D which indicates charge separation in the ring.

Quinoline is weakly basic (pKa 4.94) a value which is intermediate between aniline (pKa 4.58) and pyridine (pKa 5.17). Presence of electron donating group as the 2-and 4- positions of quinoline increase the basicity (2-methylquinoline pKa

5.83). On the other hand, occurrence of hydrogen-bonding of group with ring nitrogen atom decreases the basicity.

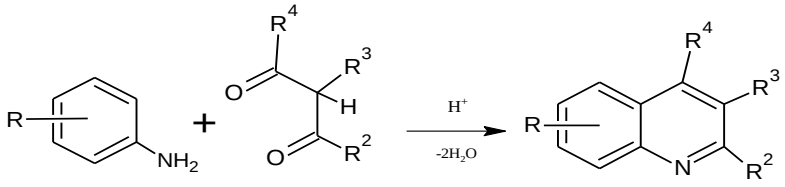
The pyridine ring in quinoline is π electron deficient; therefore, nucleophilic attack takes place at the 2- and 4- position. The π electron densities have been calculated for quinoline by the molecular orbital method and show electron deficiency at these two positions. The electrophilic attack preferably takes place at 5- and 8- positions. The close similarity of absorption bands in u.v. spectrum of quinoline to those of naphthalene further confirms similarities in their structures. The reduce double bond character of 2,3- and 6,7- bonds in quinoline is confirmed by n.m.r. (Bansal, 2014).

1.4. Synthesis of quinolines:

There are three important methods for the construction of quinoline ring system, and all three start with benzene compounds (Joule and Mills,2010).

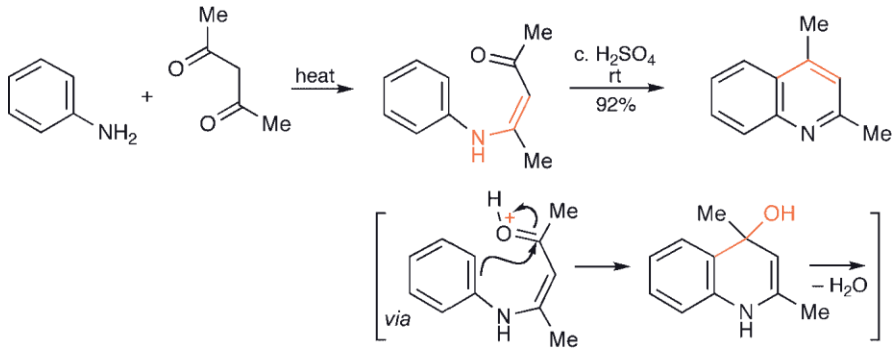
1.4.1. Synthesis of quinoline from aryl amines and 1,3-dicarbonyl compounds.

Anilines react with 1, 3- dicarbonyl compounds to give intermediates which can be cyclized with acid.

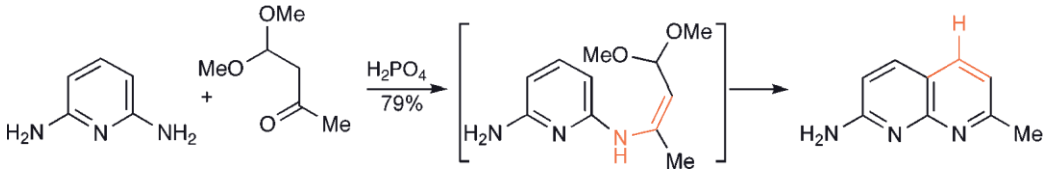


1.4.1.1.The Combes Synthesis:

Condensation of a 1,3 - dicarbonyl compound with an arylamine gives a high yield of a β-amino-enone, which can then be cyclized with concentrated acid. Mechanistically, the cyclization step is an electrophilic substitution by the mesomeric O - protonated amino - enone, followed by loss of water to give the aromatic quinoline.

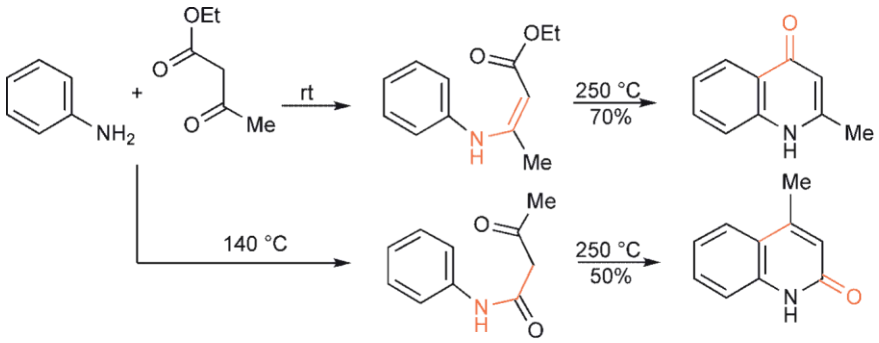


In order to access 4-unsubstituted quinolines, a 1,3- ketoaldehyde, in protected form, guarantees the required regioselectivity; the example below produces a 1,8-naphthyridine (pyrido[2,3- b]pyridine)*(*Litvinov,2006).

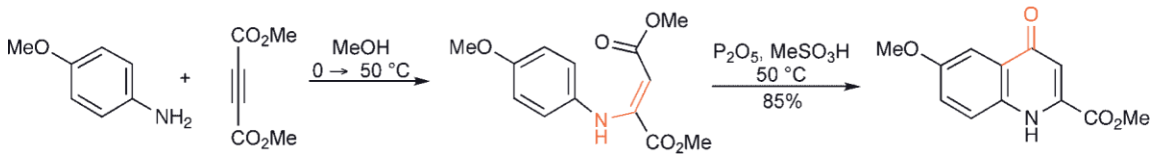


1.4.1.2. Conrad – Limpach – Knorr Reaction:

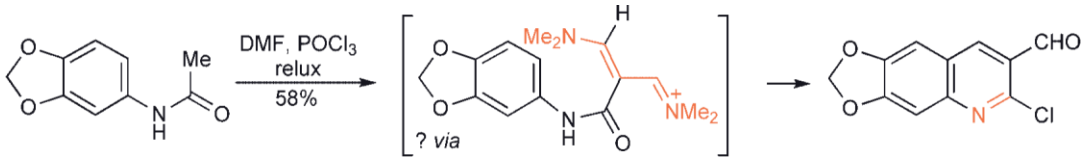
If the 1,3-dicarbonyl component is at the 1, 3- keto acid oxidation levels, then the product is a quinolone. Anilines and β - keto esters react at lower temperatures to give the kinetic product, a β-Aminoacrylate, cyclization of which gives a 4- quinolone. At higher temperatures, β- keto acid anilides are formed and cyclization of these affords 2-quinolones. (Lauer and Kaslow, 1955).



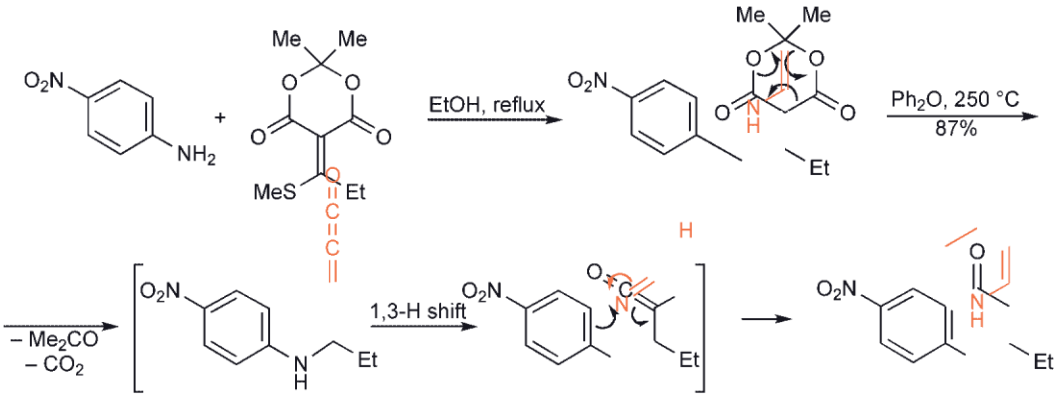
β -Aminoacrylate, for cyclization to 4 - quinolones, are also available via the addition of anilines to acetylenic esters or by displacement of ethoxy from ethoxymethylenemalonate ($EtOCH=C(CO_2Et)_2$.(Zewge*et al*, 2007).



Usefully functionalized quinolines are easily accessible from anilines: the N -acetyl derivative is simply reacted with the Vilsmeier reagent and a 2-chloro - 3 - formyl - quinoline results. One may speculate that a 3 - formyl - anilides, or an equivalent (shown), is involved, placing this useful reaction into the Combes category(Elban*et al*, 2006).

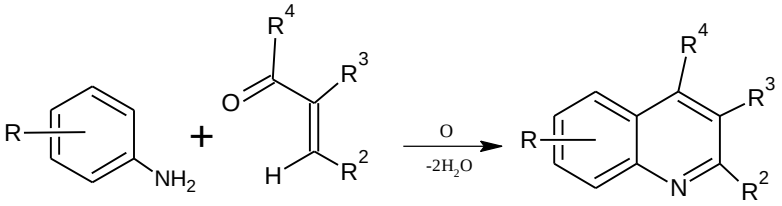


Cyclizationswhere the benzene ring carries an electron- withdrawing group, which would disfavour the electrophilic cyclizing step, can be effected using the variant shown below–the substrate is simply heated strongly–the mechanism of ring closure is probably best viewed as the electro cyclization of a 1,3,5-3- azatriene(Chen *et al*, 1987).



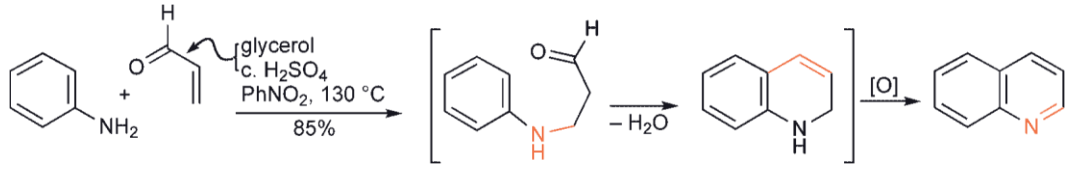
1.4.2. Synthesis of quinoline from aryl amines and α, β-unsaturated carbonyl compounds:

Aryl amines react with α, β- unsaturated carbonyl compound in the presence of an oxidizing agent to give quinolines. When glycerol is used as ansource of acrolein, quinolines carrying no substituent's on the hetero- cyclic ring are produced. (Joule and Mills,2010).

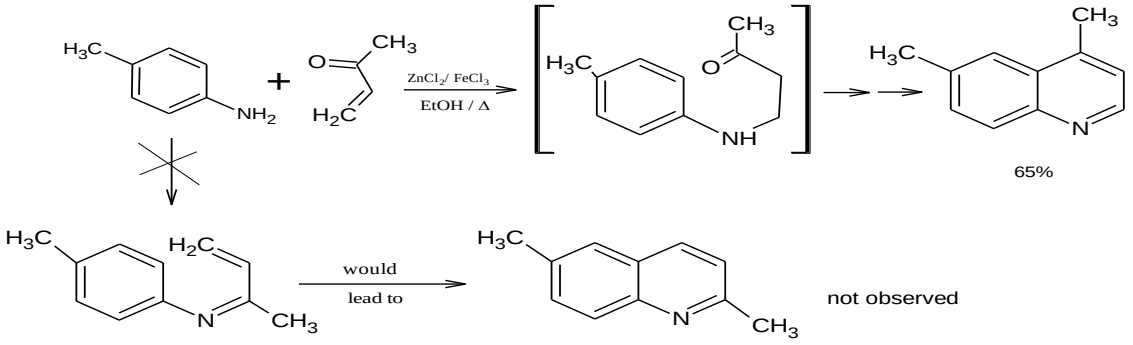


1.4.2.1. The Skraup Synthesis:

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidizing agent are heated together. The reaction has been shown to proceed via dehydration of the glycerol to acrolein, to which aniline adds in a conjugate fashion. Acid-catalyzed cyclization produces a 1,2-dihydro-quinoline. Finally dehydrogenated by the oxidizing agent–the corresponding nitrobenzene or arsenic acid have been used classically. The Skraup synthesis is best for the ring synthesis of quinolines unsubstituted on the hetero ring.(Mosher et al1955).

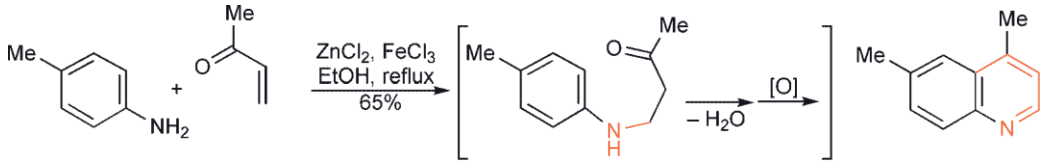


The use of substituted carbonyl components, as in the following example, shows that the intermediates not formed by condensation of amino group with the carbonyl. (Joule and Smith,1978; Manske and Kulka, 1953).

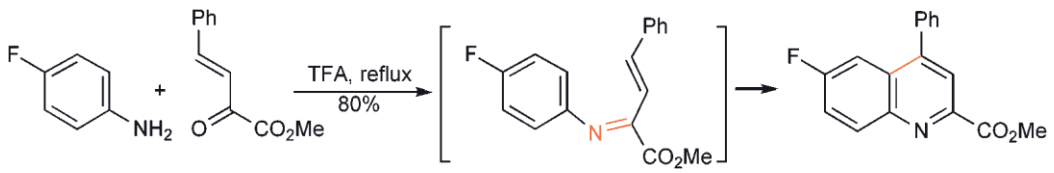


1.4.2.2. Doebner-Miller synthesis:

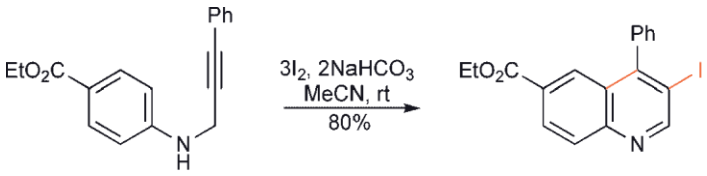
The use of an enone confirms the mechanism, showing that interaction of the aniline amino group with the carbonyl group is not the first step, and this variation is known as the Doebner– Miller synthesis.



Improvements to the regime for Doebner – Miller ring closures include the use of a two - phase organic/ aqueous acid system to minimize alkenes polymerization and the use of indium (III) chloride on silica with microwave irradiation. It is significant that the accepted and proved regiochemistry for these cyclization is reversedwhen the reaction is carried out in trifluoroacetic acid, imines formation being the first step, at least for unsaturated 2-keto esters.(Matsugi and Minamikawa2000; Ranu *et al*,2000; Wu*et al*, 2006).



1-(Aryl amino) prop -2- ynes are at the same oxidation level as the intermediates in the Skraup and Doebner–Miller strategies. The cyclizing step for such substrates requires electrophilic activation of the alkynes, the electrophile ending at the quinoline 3- position (Zhang*et al*, 2005).



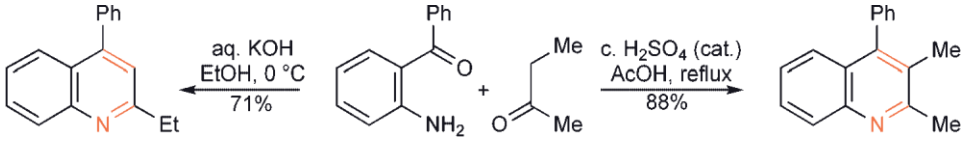
1.4.3. Synthesis of quinoline from acyl aniline and carbonyl compounds:

Acyl-arylamines react with ketones having an α- methylene to give quinolines.

1.4.3.1. The Friedlander synthesis:

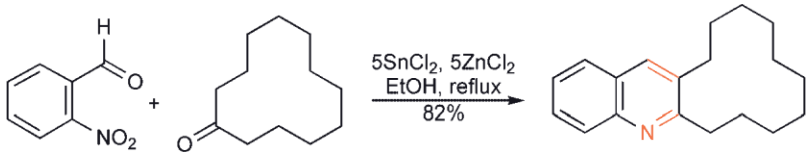
This route has been used extensively for the synthesis of substituted quinolines. In the original sequence, an ortho-acyl-arylamineis condensed with a ketone or aldehyde (which must contain a α-methylene group) by base or acid catalysis to yield the quinoline. The orientation of condensation depends on the regioselectivity of enolate or enol formation(Fehnel,1966).

Control of regiochemistry can be obtained by using a removable phosphonate, to direct enolization, as in $RCOCH_2P(O)(OMe)_2$. 2-Substituted quinolines can be obtained regioselectively from methyl ketones using pyrrolidine as catalyst (Hsiao *et al*,2001; Dormer *et al*, 2003).

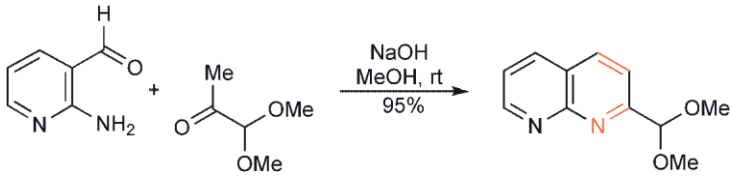


Several improved conditions are available: the use of toluenesulfonic acid, molecular iodine, chloro trimethylsilane, dodecylphophonic acid and sodium tetrachloroaurate (III) ($NaAuCl_4$) all produce excellent yields of structurally varied quinolines. Ortho-Aminobenzyl- alcohol can serve as starting material, being

oxidized to the amino- aldehyde, which then takes part in the condensation, using catalytic copper(II) chloride and potassium hydroxide under oxygen. One can also utilize ortho- nitrobenzaldehyde, carrying out reduction to amine and condensation in one pot utilizing a mixture of tin(II) chloride and zinc chloride. (Ghassamipour and Sardarian, 2009; Cho *et al*, 2006).

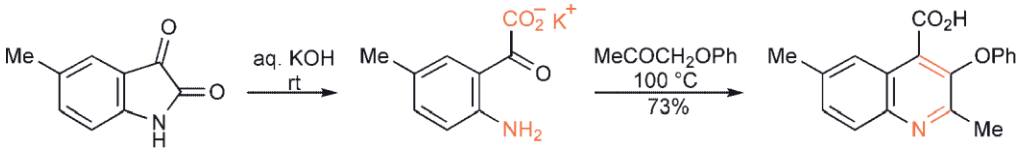


Naphthyridines can also be obtained utilizing the Friedlander strategy.(Yasuda*et al*,2004).



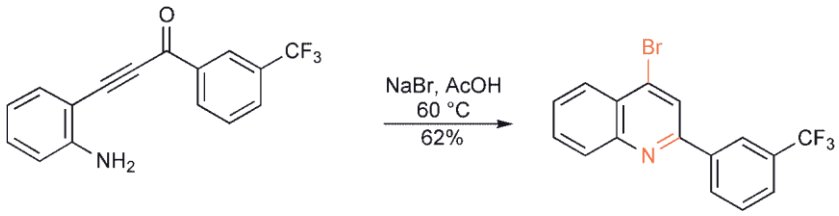
1.4.3.2. The pfitzinger synthesis:

Hydrolysis of isatins, which are easy to synthesis,givesortho- amino aryl-glyoxylates, which react with ketones affording quinoline-4-carboxylic acids. The carboxylic acid group can be removed, if required, by pyrolysis with calcium oxide (Callaway and Henze, 1939).

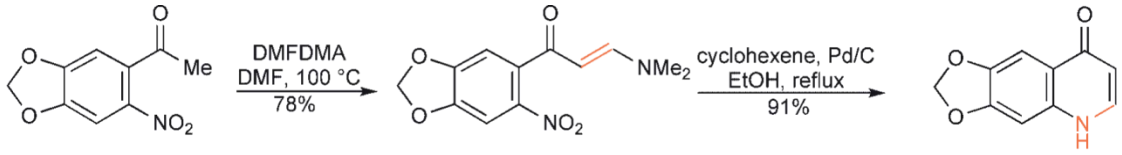


1.4.4. Synthesis of quinolines by Forming the N – C - 2 Bond

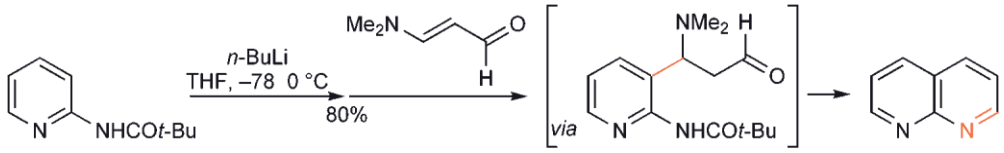
Conjugate addition of a nucleophile to an alkynyl ketone unit ortho to amino allows interaction of the amine and carbonyl groups and thus the formation of a quinoline (Arcadi *et al*, 2007).



The ring closure of ortho-nitroaryl-dimethylaminomethyleneketones is related and produces 4-quinolones via selective reduction of the nitro group and then cyclization (Tois *et al*, 2005).



Dimethylaminomethylene-ketone was used for the related reaction of 3 - lithiated 2- or 4-acylamino-pyridines, probably via the intermediate (Zhichkin *et al*, 2006).

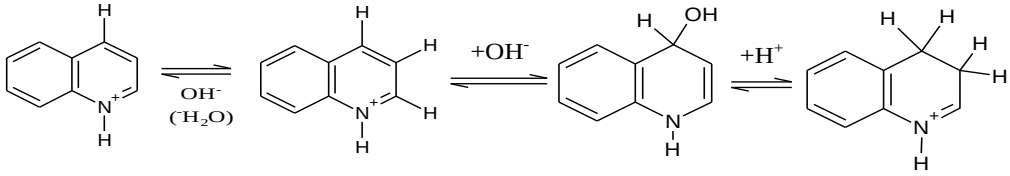


1.5. Chemical Reactions:

Quinoline is a week base and is thus protonated on the ring nitrogen with mineral acids to form water soluble salts (Raj and Bansal,2014).

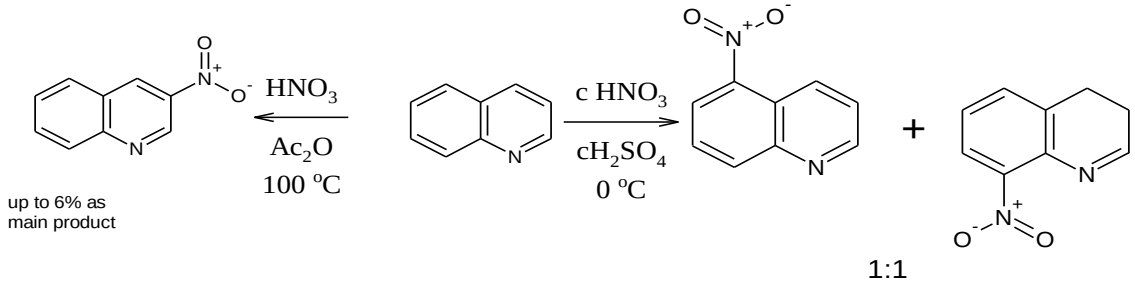
1.5.1. Reaction with electrophilic reagent:

The relative rates of substitution at the various quinoline positions are dependent on the acidity of the medium and the activity of the water in it.

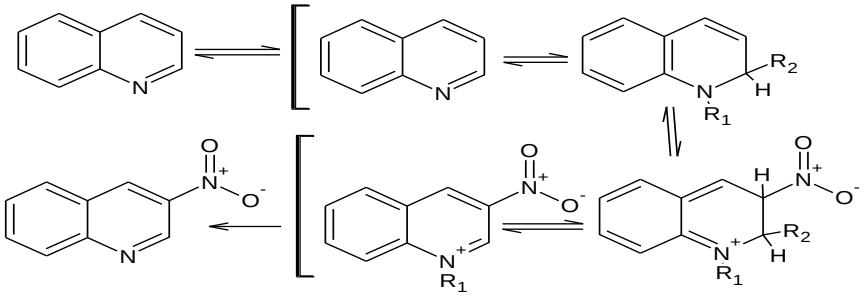


As the acidity increases, with concomitant decrease in water activity, the simple protonation of the homocyclic ring of 1H-quinolinium cation becomes the dominant process, and in 90 per cent sulphuric acid it occurs at 180^{o}C, principally at C8.

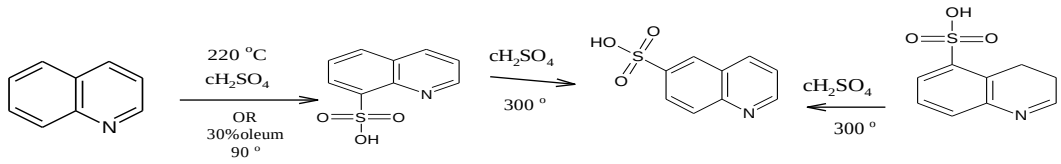
Nitrationoccurs easily; it produces a high yield of a mixture of 5 and 8-nitroquinolines with no detectable quantity of any other isomers (Austin and Ridd,1963).



Kinetic data are consistent with electrophilic attack by the nitrating species on the quinolinium cation. In acetic anhydride nitration proceeds in a totally different manner, and very inefficiently -much quinoline is recovered and much is converted into intractable products. The main product obtained under these conditions is the 3-isomer (1.9-6.6per cent) together with a small quantity of mixture of 6- and 8-nitroquilines (0.7-0.9per cent). A very significant point is that no 5-nitroquinoline is produced. All this seems to be in keeping with electrophilic substitution of a 1,2-adduct, for in such a molecule electron –release from nitrogen would be expected at C3 ,C6 and C8 (Moodie,1963; Dewar and Maitlis,1957).



Sulphonation gives the 8-sulphuric acid with only small quantities of the 5-isomer (Beisler, 1970).

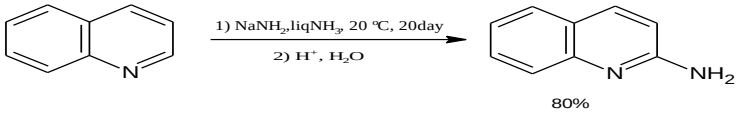


With a very high reaction temperature the 6-sulphuric acid is produced.

1.5.2. Reaction with nucleophilic reagents:

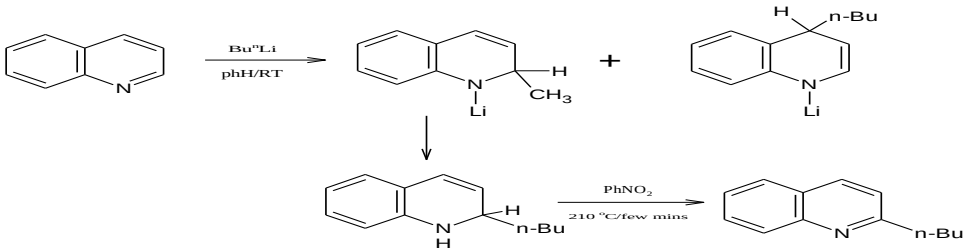
Attack by a nucleophilic occurs in the pyridine ring of quinoline and position-2 is the preferred site for such an attack if the position is occupied then attack may take place at the 4-postion (Jones and Turbini, 1976).

The Chichibabin reaction is an example of a normal attack at C-2.



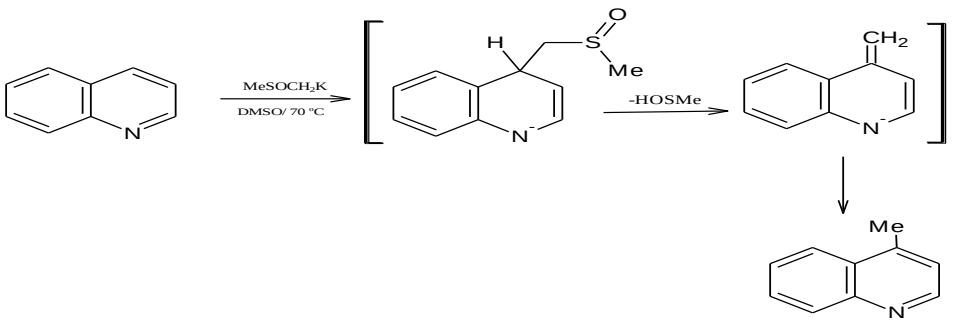
1.5.2.1. Substitution with hydride transfer*:*

The simplest and best-studied of alkylation and arylation reactions with alkyl and aryl-lithium compounds and they lead almost exclusively to addition to C2 with a very small proportion of addition to C4. (Geissman *et al*, 1946).



The N-lithio-1, 2-dihydroquinolines are hydrolysed to the corresponding bases which are reasonably stable compounds. Effective overall substitution and the formation of 2-substitueted quinoline is then achieved only by subsequent oxidation, best by a mild hydride acceptor such as nitrobenzene.

Reaction with methyl sulphinylmethyl potassium provides a novel and high yield alkylation at C4.



Quinoline reacts rapidly with $NaNH_2$ in liquid NH_3 to give a 3:1 mixture of α- and γ-adducts. At RT, reaction goes further to give 2-aminoquinoline: the nature of the cation influences the yield, which is highest (80 per cent), when Ba $(NH_2)_2$ is used. That 4-amino-quinoline is not formed in this reaction suggests that the reversibly formed γ-adduct suffers hydride loss much less readily under these conditions (van der Plas, 2004).

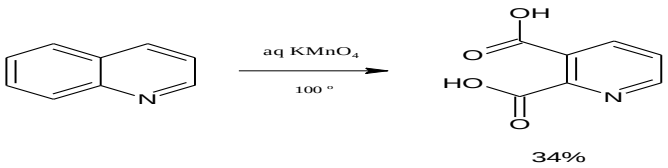
4-aminoquinoline may be obtained in the presence of $NaNO_3$ as hydride acceptor. When substitution cannot occur at C2, as with 2-phenylquinoline, the 4-amino derivative is produced.

When quinoline is heated with KOH or NaOH-KOH, 2-quinolone is produced together with a nearly-quantitative yield of hydrogen.

As with amination, the cation is of importance, for reaction with sodium hydroxide occurs only at about 300º and is much less efficient (Zoltewicz, 1973;Tondys, 1985).

1.5.3. Reaction with oxidizing agents :

Quinoline is resistant to most mild oxidizing agents, even aqueous chromic acid reacts only slowly. Potassium permanganate, however, attacks the homocyclic ring to give pyridine-2,3-dicarboxylic acid as main product. (Cochran and Little,1961).



The alkyl groups of substituted quinolines can be oxidized to the corresponding pyridine carboxylic acid.

1.5.4. Reactions with reducing agents:

Most reducing agents attack the hetero-ring and many of them give high yields of 1, 2-dihydroquinoline.

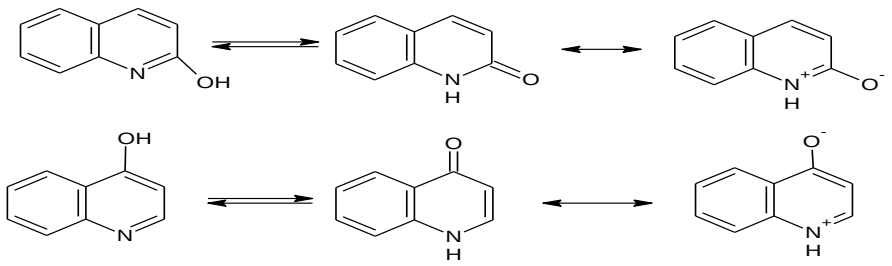
Reduction to 1,2,3,4-tetrahydroquinoline is best achieved by catalytic hydrogenation with raney nickel or palladium or PtO_2, H_2 or ammonium carbonate, though this result is also obtained by reduction with tin-hydrochloric acid and sodium ethanol (Joule and smith, 1978).

Reduction of the isomeric 5,6,7,8-tetrahydroquinoline can be achieved by Pt/H_2 reduction in concentrated hydrochloric acid,which with longer reaction times leads to the decahydroquinolines .

1, 2, 3, 4-tetrahydroquinoline is very easily dehydrogenated to quinoline (Katayama *et al,*1980).

1.5.5. Quinoline derivatives:

1.5.5.1. Hydroxyquinoline or quinolinols: All the hydroxyquinoline are known to exist in tautomeric equilibrium with the corresponding quinolones. The behavior of 2-and 4-hydroxyquinoline is similar to 2-and 4-hydroxy-pyridines.The quinolones have the following mesomeric structures (Ingram, 1965).



The 2- and 4-quinolinols can usually be prepared by the Conrad Limpach or Knorr synthesis while the 3- isomer is most conveniently obtained by diazotizing 3-aminoquinolines followed by hydrolysis.

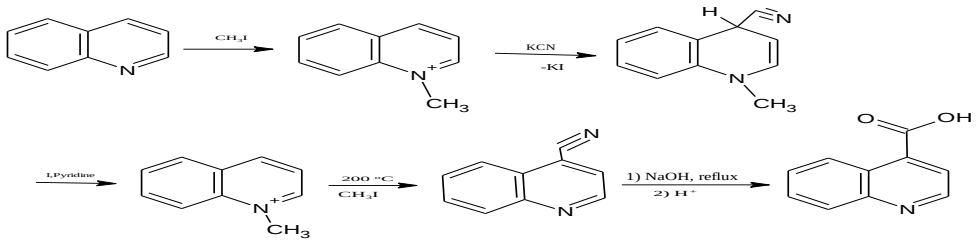
2-hydroxyquinoline is colorless compound, m.p., 199ºC.It is oxidized to isatinby potassium permanganate. The quinolinols behave as typical phenols and when the –OH group is present on the benzene ring they show all the reactions of the corresponding naphthols. i.e. they give violet color with ferric chloride, undergo Reimer-Tiemann reaction and couple with diazonium cations.

8-hydroxquinoline or oxine is best known compound of this group. It can be prepared by fusing quinoline-8-sulphonic acid with potassium hydroxide. This compound is steam volatile and the –OH stretching frequency appears at 3416 cm^{-1} less than the normal –OH group. This is ascribed to the intramolecular hydrogen bond formation in 8-hydroxyquinoline.

1.5.5.2. Quinoline carboxylic acids:

The quinoline carboxylic acid may be prepared by several general methods. 2-quinoline carboxylic acid (quialdinic acid) can be obtained from 1-benzoyl-2-cyano-1, 2-dihydroquinoline on heating with hydrochloric acid.

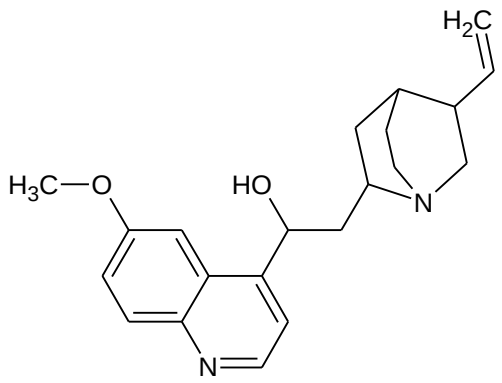
Oxidation of 3-methylquinoline with chromic acid yields the 3-isomer. Quinoline 4-carboxylic acid (cinchoninic acid) is obtained by the oxidation of lipidine or by the following sequence from 4-cyanoquinoline(Cochran and Little, 1961).



Quinoline 6-carboxylic acid was obtained by modified Skraup synthesis on para-amino benzoic acid. Quinoline carboxylic acids can be decarboxylated readily, the 2-isomer particularly decaroxylates at 160ºC. The mechanism of decarboxylations involves the zwiterionic form of the acid. The 4-isomer although stable to fused aqueous potassium hydroxide which converts it to 4-hydroxycarbonyl-2-quinoline can be decarboxylated by heating with copper power (Armarego, 1963).

1.6. Biological activities of quinolines :

Quinoline forms part of the structure of quinine, the quinoline on quinine has a 6-MeO substituent and a side chain attached to C4 (Clayden and Nick, 2014).



Quinine has been standard drug for the treatment of malaria for centuries, it has, however, been superseded by a number of more potent synthetic drugs such as chloroquine, plasmoquin, atebrin.

Many commercially available dyes also contain the quinoline nucleus. The cyanine dyes used for improving the color sensitivity of photographic emulsions (Ven,1952; Hamer, 1963).

4-substituted-7-trifluoromethylquinolines has been found to a good analgesic activity, the activity is attributed to their nitric oxide realizing properties (Abadi *et al*, 2005).

2-(furan-2-yl)-4-phenoxyquinoline derivatives are found to be inhibitors of lysozyme and b.glucuronidase release (Chen *et al*, 2006).

Quinoline derivative with potent anti inflammatory effect in adjuvant arthritis. Certain quinoline derivatives have been treating osteoarthritis, these are amino acetamide inhibitors of aggrcanase -2(Baba *et al*, 1996).

Some of the amido-aniline quinoline act as anti tumour agents by inhibiting CSF-IR kinase Novel 4-hydroxyquinoline are histone acetyl transferase inhibitor. (Scott *et al*, 2009; Mai *et al*, 2009).

A few 3-cyanoquinolines as inhibitor of insulin like growth factor receptor (IGF-IR) for the treatment of cancer (Miller *et al*, 2009).

Phenoxy, phenylthio and phenyloxy substituted quinoline possess anti bacterial activity (Ma *et al*, 2009).

Tetrahydroquinoline are found to have a good degree of activity against fungi Candida albicans, fusariumoxysporum(Gholap*et al*, 2007).

Anilide quinoline derivatives are found to have a good degree of invitro activity against Japanese encephalitis virus (Ghosh *et al*, 2008).

Certain quinoline derivatives act by behaving as HIV-1 Tat-TAR interaction inhibitors (Chen *et al*, 2009).

Substituted 2,4-arylquinolines are a good degree of activity against the nematode *Haemonchus contortus*. These arylquinolines maintain their activity against levamisole, invermectin and thiabendazole resistant strains of Haemonchus contortus (Rossiter and Peron, 2005).

Aim of the project

The main aim of this work is to synthesis a group of 3,6-disubstituted 2-methylquinolin-4-ol and 3,6-disubstituted 4-methylquinolin-2-ol derivatives by Conrad Limpach Knorr method, kinetically and thermodynamically control.

Essentially the synthesis of these compounds was proposed to be worked from suitable disconnection of target quinolines, accordingly. Such retrosynthetic analysis can result in more than one possible route towards the synthesis of the target molecule. Therefore, one of the objectives of this work is to test the different suitable routes for such a synthesis and to verify of the compounds prepared through different routes.

The drawing chemical structures and calculating of molecular properties of prepared compounds by using ChemSketch program (ACD/Lap).

The identity of the prepared compounds can be elucidated with spectroscopic means, suitable reaction mechanism and disconnection protocols can be proposed for each reaction and composing one of the aim of this project.

Chapter two
Materials and methods

Materials ad methods

2.1. Materials:

2.1.1. Solvents:

- Chloroform 99.0% (GC), Alpha chemika India
-dioxane(assay 99.8%), Alpha Chemika-India
- Distilled water
- Ethanol(assay 98%)(B.D.H. England)

2.1.2. Chemicals:

- Aniline (density-1.022g/cm^3)Mumbai-India
- Sulphanilamide 254(H-Mumbai 400002) (CDH-India)
- Hydrochloric acid (assay- 35-38%) Mumbai
- Ethylacetoacetate (density- 1.021g/cm^3)
- Sodium nitrite (23% -New Delhi -India)
- Sodium acetate New Delhi 110002 -India.
- Ethanol assay 98% Alpha chemika- India.
- Sulphuric acid assay 98% Lab chemiepvt. Ltd. India
- Sodium sulphate

2.1.3. Thin layer chromatography (TLC)

Thin layer chromatography (TLC) was carried out using silica gel precoated plates 10×5 cm, also by using silica gel precoated plates5×6.5cm.

2.2. Instruments:

2. 2.1. Infrared spectroscopy:

The instruments used are thermo Nicolette FT IR -84005 (SHIMADZU-Japan) spectrometer, potassium bromide disc are used.

2.2.2. H^1-NMR spectrometry:

-the instruments used are pulse sequence, DMSO solvent, observe 300 MHz

2. 3. General equipments:

- hot plate Magnetic stirrer model L.M.S. 220-230 volts, 50/60 HZ, 550W serial no.010302-1107-0408, melting point apparatus.
- Heater, heating mantel model KM-ME. AC 230V, 50/60HZ, 200W
- Vacuum desiccator
- Water bath.
- All glasses used were of Pyrex type.

. ACD/Lab program:-

ACD/ChemSketch version 2015 is the powerful all purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and chemical properties and design professional reports and presentations.

ACD/ChemSketch includes structure mode for drawing chemical structures, calculating their properties and drow mode or text and graphics processing

In this work the several quinoline derivatives were designed, in order to select compounds to synthesized from different primary amine and diazotized compounds using ChemSketch program(ACD/Lab)to drow chemical structure and calculation of molecular properties (molecular formula, molecular weight, density, polarizability, molar volume and LogP.

2.4. Methods:

2.4.1. Preparation of ethyl 2-(azoaryl) acetoacetate (I, II):

The primary aromatic amine (aniline, sulphonamide) (0.1mole) was dissolved in aqueous hydrochloric acid (80 ml, 1:1, 2.192 mole). The contents were stirred and cooled (0-2ºC), a cold solution of sodium nitrite (7g, 0.101mole) in 30 ml distilled water was slowly added and maintaining the temperature below 5ºC.

The cold diazotized solution was added to a well cooled and stirred mixture of ethylacetoacetate (10 ml, 0.079mole) and sodium acetate (0.079 mole) dissolved in aqueous ethanol 50% (10 ml, 0.217 mole) stirring was continued for 1.5hour and

the resulting yellow crystals were washed with water and recrystallized (yield %, m.p^{o}C I: 63.38% 71-73, II:69.7% 117-120) . For physical, chemical, spectral and chromatographic data (see tables (2.1 – 2.4))

.2.4.2. **Preparation of β-anilinocrotonates (III, IV, V, VI):**

0.005 mole of primary aromatic amines (aniline, sulphanilamide) and diazotized ethyl acetoacetate (0.005 mole) were mixed and trace of Conc. HCl was added and the mixture was shaked well. The mixture left aside for few minutes and the mixture become turbid indicating the liberation of water due to the condensation reaction. At this stage, the mixture was kept inside a vacuum desiccator over Conc. H_2SO_4 and was kept as such for 2-3 days, therefore the ethyl-β-anilinocrotonates which formed as a deep yellow oily liquid , was separated , dried over anhydrous sodium sulphate .

2.4.3. Preparation of 3, 6-substituted 2-methylquinolin-4-ol (VII, VIII, IX, X)

0.002 mole of ethyl-β-anilinocrotonates were dissolved in dioxane solvent and trace amount of conc. Sulphuric acid was added to all contents followed by refluxed at 150 -170^{o} C for 1h and hot mixture was poured in 500ml of ice cold water with constant stirring. Separated solid was filtered, dried, and recrystallized from ethanol.

2.2.4. Preparation of 3,6-substituted 4-methylquinolin-2-ol (XI, XII, XIII, XIV) :

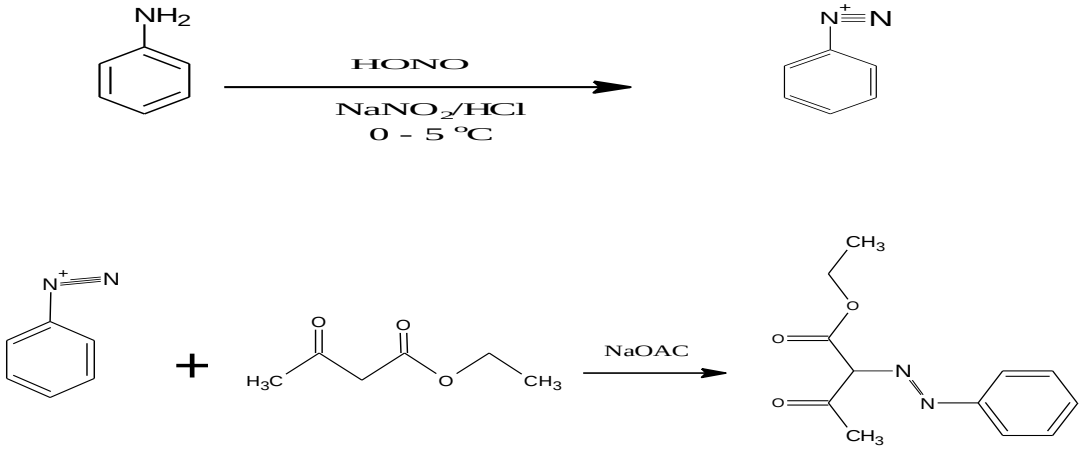
In oven-dry 100mL round bottom flask attached to a reflex condenser was charged 0.008mole of primary aromatic amine (aniline, sulphanilamide) and was added(0.008mole), diazotized ethylacetoacetate, the mixture was dissolved in dioxane solvent and trace of HCl . The mixture was heated at 70-80^{o} C for 3-4 hr., cooled at room temperature and conc. Sulpuric acid (2ml) was added. Then the mixture was refluxed at 150-170 ^{o}C for 1h and hot mixture was poured in 500ml of

ice cold water with constant stirring. Separated solid was filtered, dried, and recrystallized from ethanol.

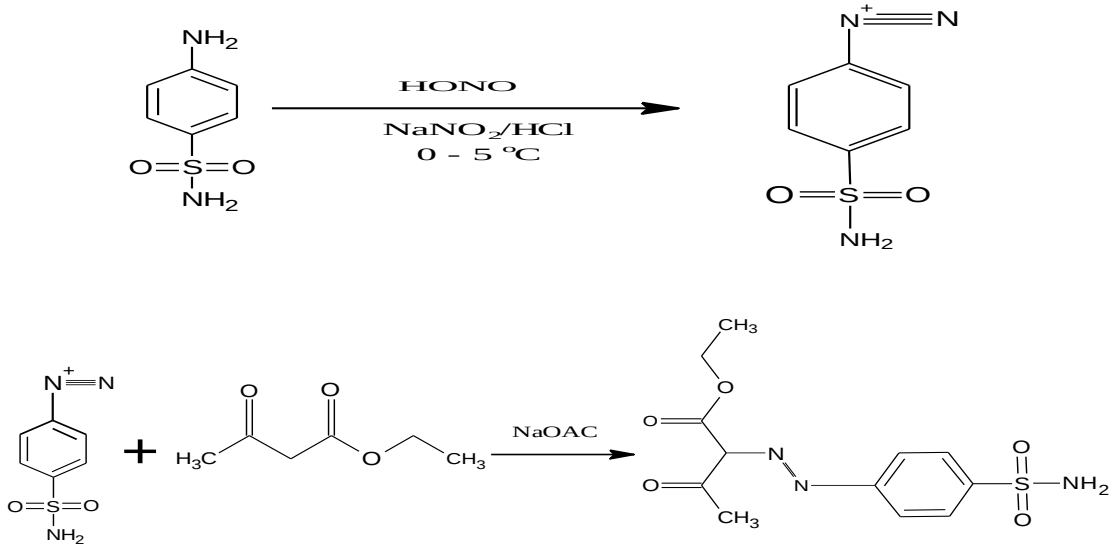
Scheme (1)

Chemical structure of ethyl-2-(azoaryl) acetoacetate (I, II)

- ethyl 3-oxo-2-[phenyldiazenyl]butanoate (I)

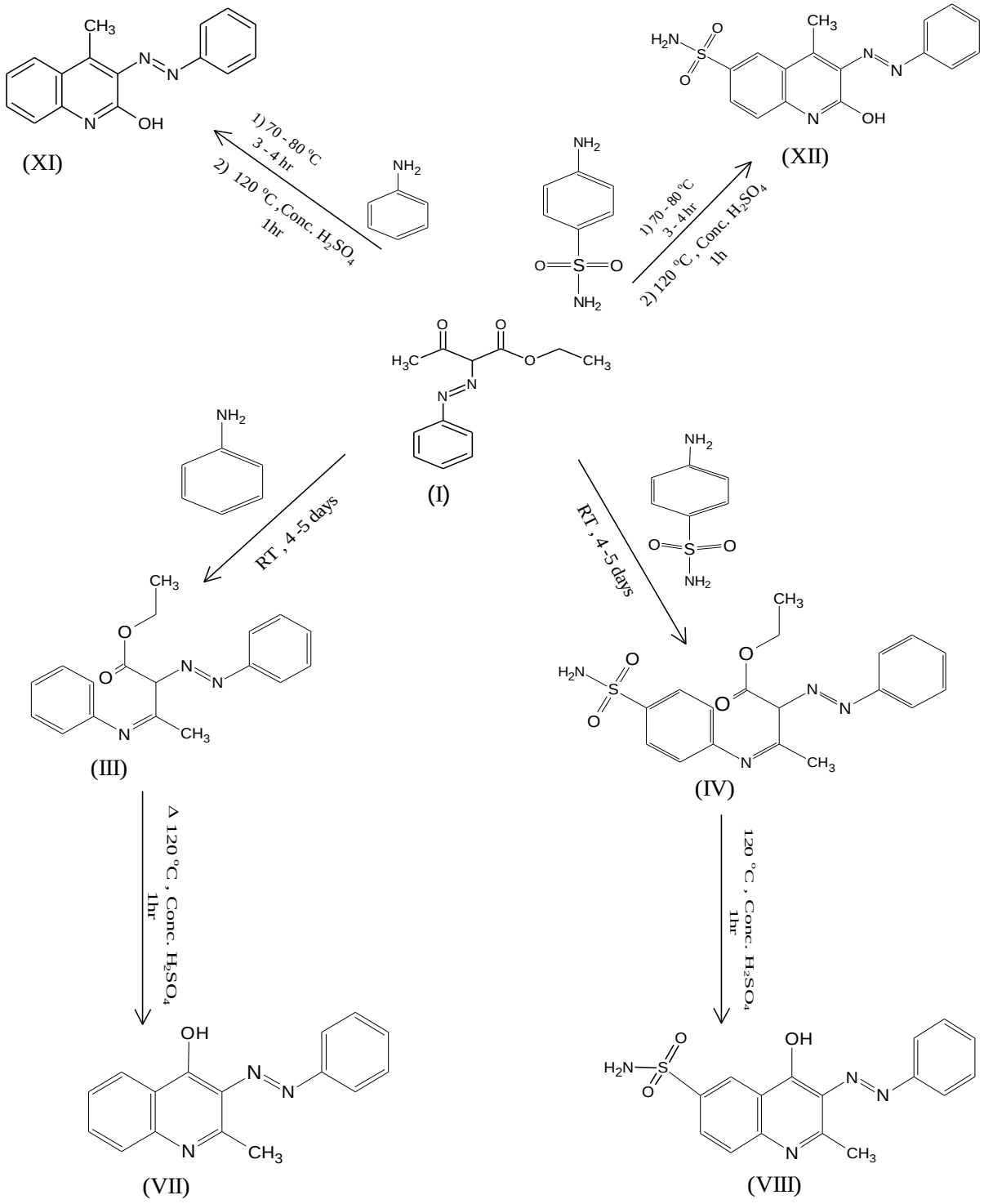


- ethyl-3-oxo-2-((4-sulfamoylphenyl)diazenyl)butanoate (II)



Scheme (2)

- Chemical structure of ethyl-β-anilinocrotonates intermediate and final product from ethyl 3-oxo-2-[phenyldiazenyl]butanoate



- Chemical structure of ethyl-β-anilinocrotonates intermediate and final product from ethyl-3-oxo-2-((4-sulfamoylphenyl)diazenyl)butanoate

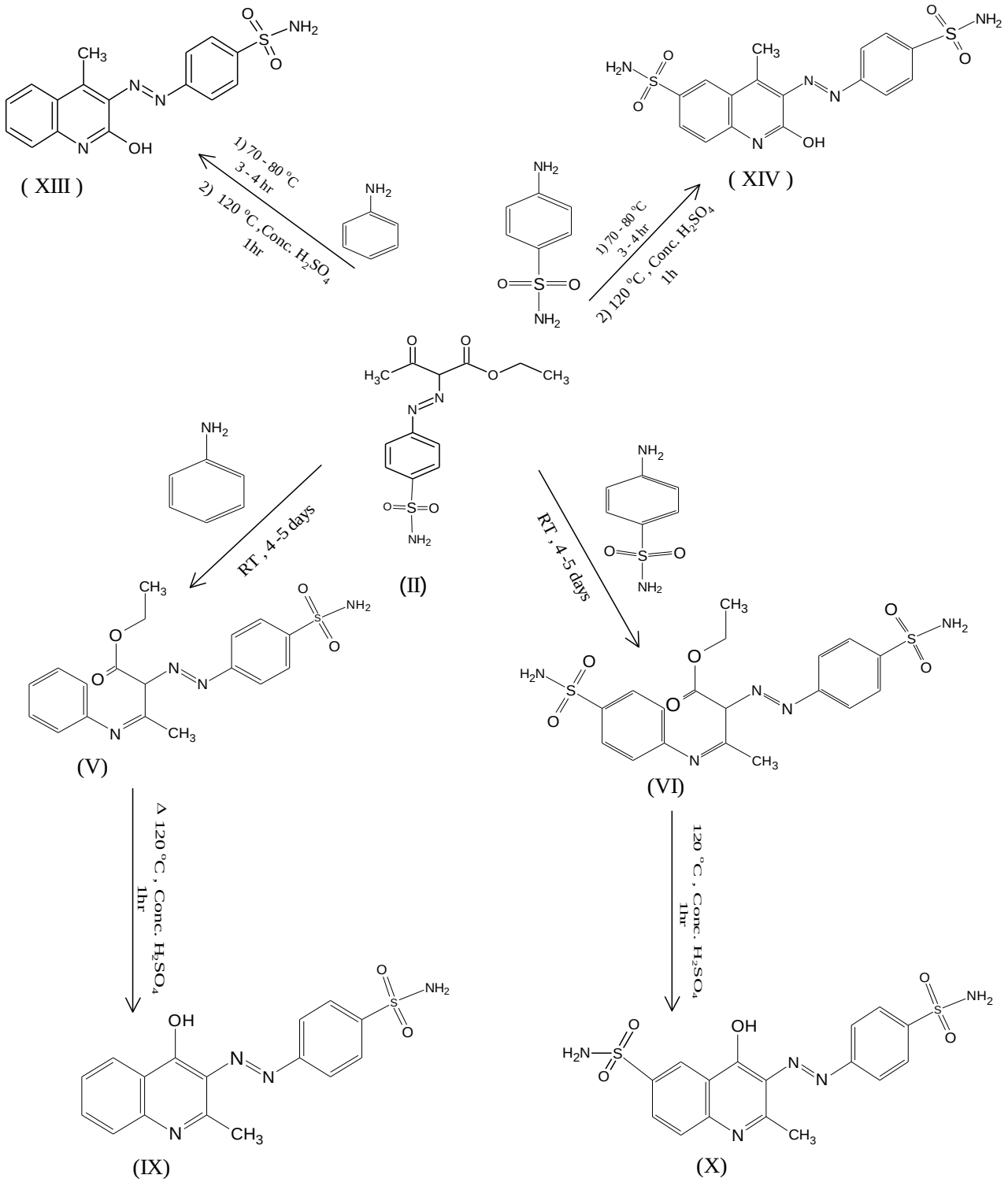
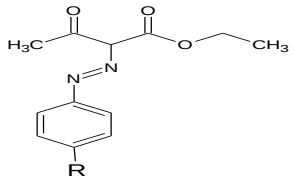

(XIII)
1) 70 - 80 °C
3 - 4 hr
2) 120 °C , Conc. H_2SO_4
1hr
(XIV)
1) 70 - 80 °C
3 - 4 hr
2) 120 °C , Conc. H_2SO_4
1h
(II)
RT , 4 -5 days
RT , 4 -5 days
(V)
(VI)
Δ 120 °C , Conc. H_2SO_4
1hr
120 °C , Conc. H_2SO_4
1hr
(IX)
(X)

Table 2.1a:-

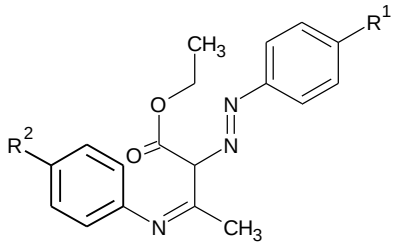
Chemical name of ethyl-2-(azoaryl) acetoacetate



NO.	R	Chemical name
I	-H	ethyl 3-oxo-2-[phenyldiazenyl]butanoate
II	$-SO_2NH_2$	ethyl-3-oxo-2-((4-sulfamoylphenyl)diazenyl)butanoate

Table 2.1b:-

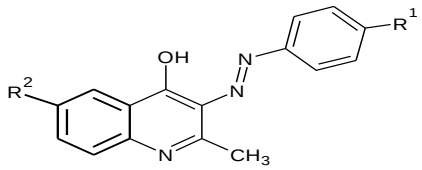
Chemical name of the: ethyl-β-anilinocrotonates Intermediate



NO.	R^1	R^2	Chemical name
III	-H	-H	Ethyl-2-(phenyldiazenyl)-3-(phenylimino)butanoate
IV	-H	$-SO_2NH_2$	Ethyl-2-(phenyldiazenyl)-3-((4-sulphamoylphenyl)imino)butanoate
V	$-SO_2NH_2$	-H	Ethyl-3-(phenylimino)-2-((4-sulphamoylphenyl)diazenyl)butanoate
VI	$-SO_2NH_2$	$-SO_2NH_2$	Ethyl-3-((4- sulphamoylphenyl)imino)-2-((4-sulphamoylphenyl)diazenyl)butanoate

Table 2.1c:-

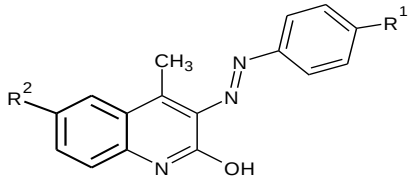
Chemical name of 3,6-(2-methylquinolinones) derivatives



NO.	R^1	R^2	Chemical name
VII	-H	-H	2-methyl-3-(phenyldiazenyl)quinolin-4-ol
VIII	-H	$-SO_2NH_2$	4-hydroxy-2-methyl-3-(phenyldiazenyl)quinoline-6-sulphonamide
IX	$-SO_2NH_2$	-H	4-((4-hydroxy-2-methylquinolin-3-yl)diazenyl)benzene-1-sulphonamide
X	$-SO_2NH_2$	$-SO_2NH_2$	4-hydroxy-2-methyl-3-((4-sulphamoylphenyl)diazenyl)quinoline-6-sulphonamide

Table 2.1d:-

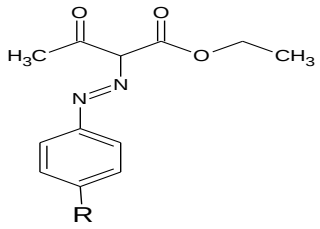
Chemical name of 3,6-(4-methylquinolinones)derivatives



NO.	R^1	R^2	Chemical name
XI	-H	-H	4-methyl-3-(phenyldiazenyl)quinolin-4-ol
XII	-H	$-SO_2NH_2$	2-hydroxy-4-methyl-3-(phenyldiazenyl)quinoline-6-sulphonamide
XIII	$-SO_2NH_2$	-H	4-((2-hydroxy-4-methylquinolin-3-yl)diazenyl)benzene-1-sulphonamide
XIV	$-SO_2NH_2$	$-SO_2NH_2$	2-hydroxy-4-methyl-3-((4-sulphamoylphenyl)diazenyl)quinoline-6-sulphonamide

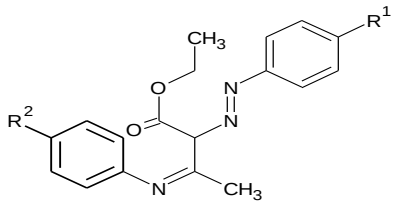
ACD/Lab Data:-

Table 2.2a:- ACD lab data ofethyl-2-(azoaryl) acetoacetate



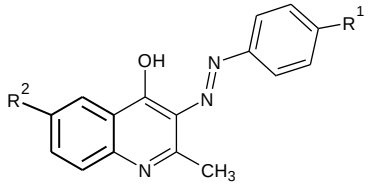
No.	R	Molecular Formula	Molecular Weight	Density g/Cm^3	Polarizability	Molar Volume Cm^3	LogP
I	H	$C_{12}H_{14}N_2O_3$	234.25116	1.13+/-0.1	25.42+/-0.5*10^{-24}	206+/-7	3.54+/-0.62
II	SO_2NH_2	$C_{12}H_{15}N_3O_5S$	313.3296	1.4+/-0.1	30.04+/-0.5*10^{-24}	223.1+/-7	2.11+/-0.62

Table 2.2b:-ACD lab data of ethyl-β-anilinocrotonates Intermediate



No.	R1	R2	Molecular Formula	Molecular Weight	Density g/ Cm^3	Polariz-ability	Molar Volume Cm^3	LogP
III	H	-H	$C_{18}H_{19}N_3O_2$	309.36236	1.09±0.1	36.24±0.5 $x10^{-24}$	281.5±7	4.33±0.37
IV	H	SO_2NH_2	$C_{18}H_{20}N_4O_4S$	388.4408	1.30±0.1	40.87±0.5 $x10^{-24}$	298.4±7	2.81±1.15
V	SO_2NH_2	-H	$C_{18}H_{20}N_4O_4S$	388.4408	1.30±0.1	40.87±0 .5$x10^{-24}$	298.4±7	2.90±0.4
VI	SO_2NH_2	SO_2NH_2	$C_{18}H_{21}N_5O_6S_2$	467.5	1.48±0.1	45.50±0 .5$x10^{-24}$	315.4±7	1.38±1.16

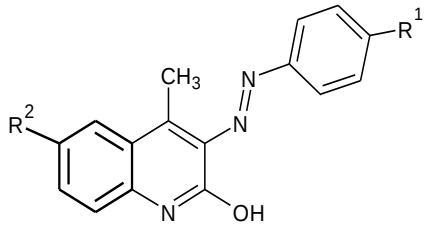
Table 2.2c:-
ACD lab data of 3,6-(2-methylquinolinones) derivatives



No.	R1	R2	Molecular Formula	Molecular Weight	Density g/ Cm^3	Polariz-ability	Molar Volume Cm^3	LogP
VII	H	-H	$C_{16}H_{13}N_3O$	263.2939	1.22±0.1	31.1±0.5x 10^{-24}	215.1±7	4.83±0.37
VIII	H	SO_2NH_2	$C_{16}H_{14}N_4O_3S$	342.3724	1.47±0.1	35.73±0.5 x10^{-24}	232.2±7	3.31±1.15
IX	SO_2NH_2	-H	$C_{16}H_{14}N_4O_3S$	342.3724	1.47±0.1	35.73±0 .5x10^{-24}	232.2±7	3.40±0.4
X	SO_2NH_2	SO_2NH_2	$C_{16}H_{15}N_5O_5S_2$	421.4508	1.69±0.1	40.35±0 .5x10^{-24}	249.2±7	1.88±1.16

Table 2.2d:-

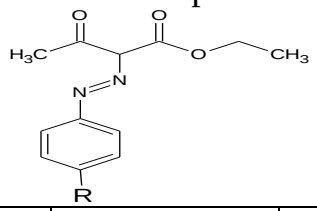
ACD lab data of 3,6-(4-methylquinolinones) derivatives



No.	R1	R2	Molecular Formula	Molecular Weight	Density Cm^3	Polarizability	Molar Volume Cm^3	LogP
XI	H	-H	$C_{16}H_{13}N_3O$	263.2939	1.22 ±0.1	31.1±0.5x10^{-24}	215.1±7	4.33± 0.37
XII	H	SO_2NH_2	$C_{16}H_{14}N_4O_3S$	342.3724	1.47 ±0.1	35.73±0.5x10^{-24}	232.2±7	2.81± 1.15
XIII	SO_2NH_2	-H	$C_{16}H_{14}N_4O_3S$	342.3724	1.47 ±0.1	35.73±0.5x10^{-24}	232.2±7	2.90± 0.4
XIV	SO_2NH_2	SO_2NH_2	$C_{16}H_{15}N_5O_5S_2$	421.4508	1.69 ±0.1	40.35±0.5x10^{-24}	249.2±7	1.38± 1.16

Table 2.3a:-

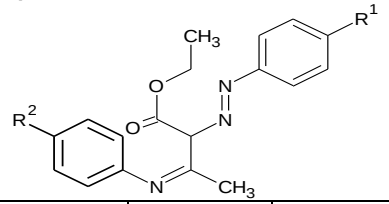
Reaction condition of the intermediate compound:



NO.	R	Molar ratio	Reaction temperature	Recrys-solvent	Y gm	Y%	m.p.^{o}C
I	-H	Aniline: sodium nitrite: ethylacetoacetate 1 : 1.014 : 0.8	0-5ºC	Ethanol	7.9g	61.38%	71-73
II	-SO_2NH_2	Sulphanilamide : sodium nitrite : ethylacetoacetate 1 : 1.014 : 0.8	0-5ºC	Ethanol	8.6177g	69.7%	117-120

Table 2.3b:-

Reaction condition of the intermediate Ethyl-β-anilinocrotonates



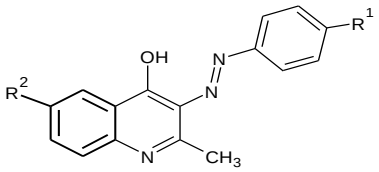
NO.	R1	R2	Molar ratio	React temp	Recryst solvent	Molecular formula	Y%	m.p.^{o}C
III	-H	-H	EPB : aniline 1 1	25ºC	Ethanol	$C_{18}H_{19}N_3O_2$	68%	131-134
IV	-H	-SO2 NH2	EPB : sulphanilamide 1 : 1	25 ºC	Ethanol	$C_{18}H_{20}N_4O_4S$	71%	140-143
V	-SO2 NH2	-H	ESPB : aniline 1 : 1	25ºC	Ethanol	$C_{18}H_{20}N_4O_4S$	73%	165-168
VI	-SO2 NH2	-SO2 NH2	ESPB : sulphanilamide 1 : 1	25 ºC	Ethanol	$C_{18}H_{21}N_5O_6S_2$	76.72 %	195-198

EPB ≡ Ethyl 3-oxo-2-[phenyldiazenyl] butanoate

ESPB ≡Ethyl-3-oxo-2-((4-sulfamoylphenyl) diazenyl) butanoate

Table 2.3c:-

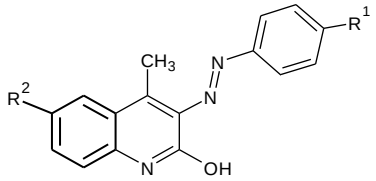
Reaction condition of 3,6-(2-methylquinolinones) derivatives



NO.	R^1	R^2	Recryst. Solvent	Molecular formula	Molecular weight	Y%	m.p.^oC
VII	-H	-H	Ethanol	$C_{16}H_{13}N_3O$	263.29392	67.88%	155-157
VIII	-H	$-SO_2NH_2$	Ethanol	$C_{16}H_{14}N_4O_3S$	342.37236	69.2%	162-165
IX	$-SO_2NH_2$	-H	Ethanol	$C_{16}H_{14}N_4O_3S$	342.37236	67.51%	193-198
X	$-SO_2NH_2$	$-SO_2NH_2$	Ethanol	$C_{16}H_{15}N_5O_5S_2$	421.4508	70%	215-218

Table 2.3d :-

Reaction condition of 3,6-(4-methylquinolinones) derivatives

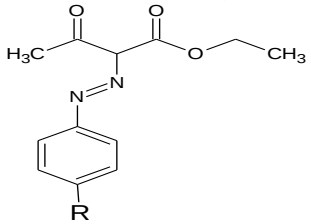


NO.	R^1	R^2	Recryst solvent	Molecular formula	Molecular weigh	Y%	m.p.^oC
XI	-H	-H	Ethanol	$C_{16}H_{13}N_3O$	263.29392	46.9%	166-169
XII	-H	$-SO_2NH_2$	Ethanol	$C_{16}H_{14}N_4O_3S$	342.37236	48%	140-144
XIII	$-SO_2NH_2$	-H	Ethanol	$C_{16}H_{14}N_4O_3S$	342.37236	48.9%	186-190
XIV	$-SO_2NH_2$	$-SO_2NH_2$	Ethanol	$C_{16}H_{15}N_5O_5S_2$	421.4508	49.53%	210-212

Infrared absorption frequencies of intermediate and final product:

Table 2.4a:-

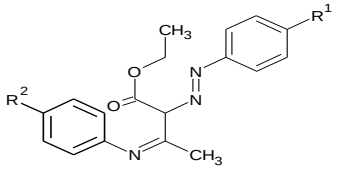
IR Data of ethyl-2-(azoaryl) acetoacetate (I, II):



No.	R	C ═ C aromatic	C=O Keto	C=O ester	N-H St. vib.	N=N	S=O St.vib.	Mono sub-	Para sub-
I	-H	1512.09 1591.16 1600.81	1689.53	1708.81		1625.88		759.90	
II	$-SO_2NH_2$	1521.73 1585.38 1596.95	1668.31	1683.74	3344.34	1635.52	1342.36 1157.21		827 837

Table 2.4b:-

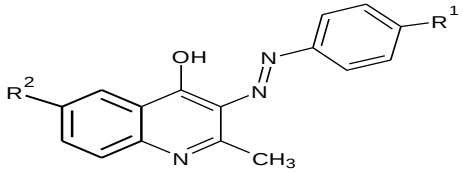
IR Data of ethyl-β-anilinocrotonates (III, IV, V, VI)



Comp. No.	R^1	R^2	C ---- C aromatic	C-H aromatic	C=O ester	N=N	N-H St. vib	S=O St.vib.	N=C	Mono sub-	Para sub-
III	-H	-H	1456.16 1471.59 1541.02	3132.18	1699.17	1602.74	–	–	1652.88	754.12	
IV	-H	$-SO_2NH_2$	1541.02	3132.18	1699.17	1602.74			1647.1	754.12	883.34 910.34
V	$-SO_2NH_2$	-H	1508.23 1533.30 1541.02	3255.62	1716.53	1608.52	3425	1159.14	1652.88		837.05
VI	$-SO_2NH_2$	$-SO_2NH_2$	1456.16 1488.94 1521.73	3265.26	1699.17	1616.24	3375.2	1159.14	1689.53		837.05

Table 2.4c:-

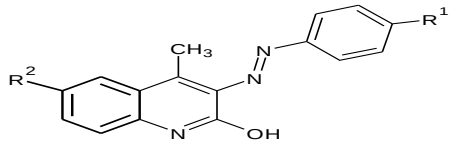
IR Data of 3, 6-(2-methylquinolin-4-ol) derivatives (VII, VIII, IX, X)



NO.	R^1	R^2	C ⎓ C aromatic	C-H Aromatic	O-H	N=N	N-H St. vib	S=O St.vib.	Mono sub-	Para sub-
VII	-H	-H	1492 1600.81		2927.74	1647.1		1172.64	756	
VIII	-H	$-SO_2NH_2$								
IX	$-SO_2NH_2$	-H	1508..23 1652.88		2925.81	1635.52		1172.64	744.47	
X	$-SO_2NH_2$	$-SO_2NH_2$	1647.1		3300 3550		3421.48	1168.78		889.12

Table 2.4d:-

IR Data of 3, 6-(4-methylquinolin-2-ol) derivatives (X I, XII, XIII, X IV)

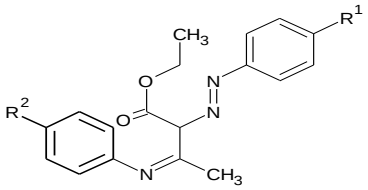


NO.	R^1	R^2	C ⎓ C aromatic	C-H Aromatic	O-H	N=N	N-H St. vib	S=O St.vib.	Mono sub-	Para sub-
X I	-H	-H	1490.87 1498.59 1550.66		3419.56	1595.02			754.12	
XII	-H	$-SO_2NH_2$	1448.44 1508.23 1541.02	3031.89	3132.18	1604.66			754.12	
XIII	$-SO_2NH_2$	-H	1458.08 1525.59 1558.38	3103.026		1616.24	3346.27	1157.21 1325.01		
X IV	$-SO_2NH_2$	$-SO_2NH_2$	1417.58 1456.16 1525.59	3255.62	3000-3360	1614.31	3359.77	1147.57 1159.14 1325.01		837

R_f values of thin layer chromatography of the prepared compounds:-

Table 2.5a:-

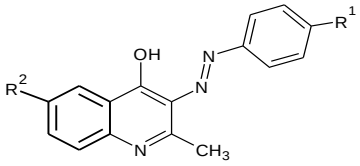
R_f values of intermediates ethyl -β-anilinocrotonates



Compound Number	Mobile phase Chloroform : methanol 9.9 0.1	Mobile phase Chloroform : methanol 9.00 1.00
I	0.71	-
III	0.91	-
IV	0.95	-
II	-	0.62
V	-	0.42
VI	-	0.4

Table 2.5b:-

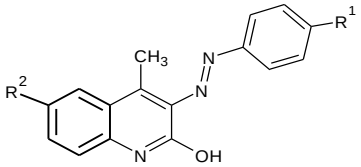
R_f values of 3, 6-(2-methylquinolinones) derivatives



Compound Number	Mobile phase Chloroform : methanol 9.9 0.1	Mobile phase Chloroform : methanol 9.00 ml 1.00 ml	Mobile phase Chloroform : methanol 8.9 ml 1.1 ml
VII	0.84	-	-
VIII	0.88	-	-
IX	-	0.56	-
X	-	-	0.6

Table 2.5c:-

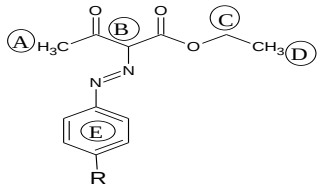
R_f values of 3,6-(4-methylquinolinones) derivatives



Compound Number	Mobile phase Chloroform : methanol 9.9ml 0.1ml	Mobile phase Chloroform : methanol 9.00ml 1.00ml	Mobile phase Chloroform : methanol 8.9m 1.1ml
I	0.71	-	-
XI	0.8	-	-
XII	0.82	-	-
II	-	0.63	0.84
XIII	-	0.53	-
XIV	-	-	0.62

Table 2.6a:-

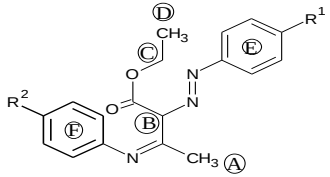
H^1NMR Data ofethyl-2-(azoaryl) acetoacetate (I, II):



Comp. No.	R	solvent	Δ value of chemical shift (ppm)				
			A	B	C	D	E
I	H	DMSO	2.38, s, 3H	3.30, s, H	4.30, q,2H	1.28, t, 3H	7.09-7.46, m, 5H
II	SO_2NH_2	DMSO	2.41, s, 3H	3.32, s, H	4.31, q,2H	1.28, t, 3H	2H, o, R (7.79-7.82, d, 4H) 2H, m, R (7.53-7.56, d, 4H)

Table 2.6b:-

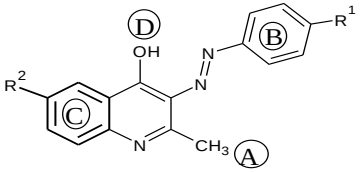
H^1NMR Data ofethyl-β-anilinocrotonates



Comp No.	R1	R2	Δ value of chemical shift (ppm)					
			A	B	C	D	E	F
III	-H	-H	2.49, s, 3H	3.32, s, H	4.32, q, 2H	1.28, t, 3H	7.79-7.84, m, 5H	7.53-7.69, m, 5H
IV	-H	-SO_2NH_2	2.41, s, 3H	3.31, s, H	4.32, q, 2H	1.28, t, 3H	7.25, m, 5H	2H, o, R_2(7.79-7.82, d, 4H) 2H, m, R_2 (7.53-7.56, d, 4H)
V	-SO_2NH_2	-H	2.5, s, 3H	3.38, s, H	-	-	2H, o, R_1 (7.81, d, 4H) 2H, m, R_1 (7.68, d, 4H)	7.36-7.52, m, 5H
VI	-SO_2NH_2	-SO_2NH_2	2.5, s, 3H	3.37, s, H	-	-	2H, o, R_1(7.78-7.81, d, 4H) 2H, m, R_1(7.31-7.34,d ,4H)	2H, o, R_1(7.78-7.81, d, 4H) 2H, m, R_1(7.31-7.34,d ,4H)

Table 2.6c:-

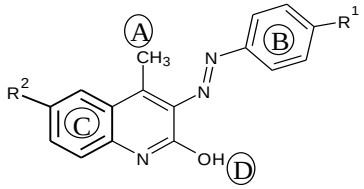
H^1NMR Data of3, 6-(2-methylquinolin-4-ol) derivatives (VII, VIII, IX, X)



Comp. No.	R1	R2	Δ value of chemical shift (ppm)			
			A	B	C	D
VII	-H	-H	2.5, s, 3H	7.59-7.63, m, 5H	7.42-7.48. m, 4H	13.17, s, H
VIII	-H	$-SO_2NH_2$	2.5, s, 3H	7.22-7.25, m, 5H	1H, m, R_2 (7.59-7.62, d, H) 7.42-7.47, m, 2H	13.17, s, H
IX	$-SO_2NH_2$	-H	2.49, s, 3H	2H, o, R_1 (7.82-7.84, d, 4H) 2H, m, R_2 (7.66-7.69, d, 4H)	7.30, m, 4H	12.63, s, H
X	$-SO_2NH_2$	$-SO_2NH_2$	2.49, s, 3H	2H, o, R_1 (7.82-7.85, d, 4H) 2H, m, R_2(7.67-7.69, d, 4H	7.31, m, 3H	12.63, s, H

Table 2.6d:-

H^1NMR Data of3, 6-(4-methylquinolin-2-ol) derivatives (X I, XII, XIII, XIV)



Comp. No.	R1	R2	Δ value of chemical shift (ppm)			
			A	B	C	D
XI	-H	-H	2.49, s, 3H	7.36-7.60, m, 5H	7.36-7.60, m, 4H	13.16, s, H
XII	-H	$-SO_2NH_2$	2.50, s, 3H	7.42-7.47, m, 5H	1H, m, R_2 (7.59-7.62, dd, H) 7.20-7.25, m, 2H	13.17, s, H
XIII	$-SO_2NH_2$	-H	2.50, s, 3H	2H, o, R_1 (7.91-7.93, d, 4H) 2H, m, R_2 (7.61-7.63, d, 4H)	7.21-7.48, m, 4H	12.63, s, H
XIV	$-SO_2NH_2$	$-SO_2NH_2$	2.49, s, 3H	2H, o, R_1 (7.82-7.85, d, 4H) 2H, m, R_2(7.67-7.69, d, 4H	7.31, m, 3H	12.63, s, H

Chapter three

Discussion

3. Discussion

3.1. Introduction:

The quinolines are classes of bicyclic molecules, organic chemical structures that are related to the heteroaromatic coal tar isolate quinoline. Specific quinoline molecules substituted with a hydroxyl functional group at carbons 2 and 4 (C-2 and C-4) are most often observed in isomeric formstermed 2- and 4-quinolones, respectively.

The relative importance of 4-hydroxyquinolines has increased with the discovery that such structures that also bear a methyl or carboxylic acid and other functional groups at particular sites on the ring have very potent antimalarial activity, inhibiting cytochrome complex of *Plasmodia*leads to inhibition of respiration and potent bactericidal activities, inhibiting of a broad spectrum of Gram negative and Gram positive DNA gyrase and topoisomerase enzymes.

Hence, they are very useful in antibacterial therapy. An example of such a 4-quinolone is ciprofloxacin where the ring of quinoline can be traced within this related structure. Ciprofloxacin is second generation fluoroquinolone antibacterial introducedby Bayer AG and still in wide use as the second decade of the new millennium begins.

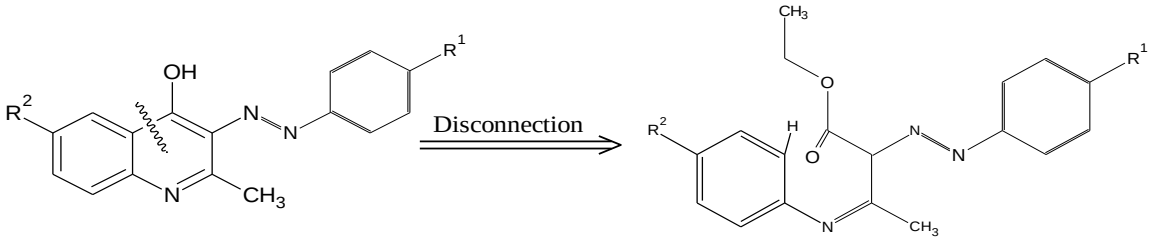
Quinolones and quinoline derivatives are amajor class of alkaloids and have remarkable applications in the field of medicinal chemistry. Quinolones are known to possess cytotoxic, ant mitotic, antibacterial and anti-platelet properties and some serve as cardiovascular protectors.

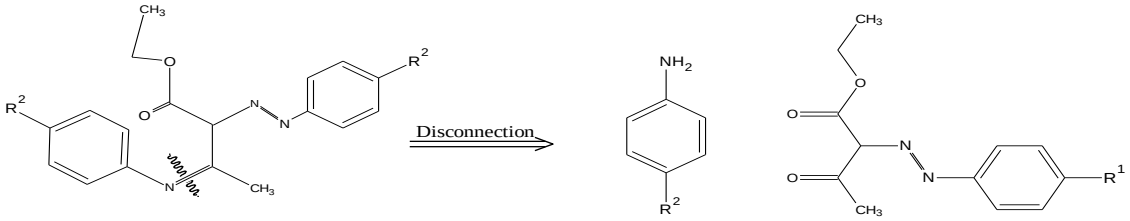
The disconnection approach is the current most widely used technique in designing organic synthesis. By such a technique a target moleculesinterconverted to synthons, from which suitable precursors or synthetic equivalent can be generated.

3.2. Retrosynthetic analysis of final product:

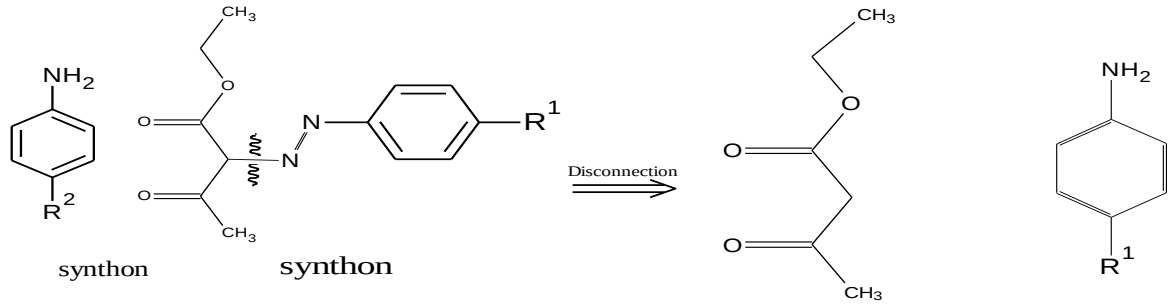
The disconnection approach has been adopted in this work, along with basic concept of the synthetic methods.

A synthons may be defined as a structural unit which becomes an idealized fragment as result of disconnection of carbon- carbon atom or carbon –hetero atom bonds in retro synthetic step. Thus general terms that, the disconnection which would also arise in similar disconnection of a bond joining a group to a cyclic structure.





The appropriate synthetic equivalent for these synthons were



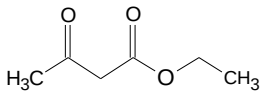
3.3. Reaction mechanism of intermediates and final products:

In the chemical synthesis of specific quinolines, the nitrogen-containing ring is "closed" with diazotized dicarbonyl compound by using one of the standard procedures for Conrad-Limpach reaction method.

Depending on the proposed retro synthetic analysis shown previously (3.2) , the preparation of quinoline derivatives was carried out by the reaction of diazonium salt of aromatic amine, which has been prepared by the reaction of nitrous acid with aromatic amines, and ethyl-3-oxobutanoate this was followed by the reaction with primary amine to give the target product.

Multiple step synthesis to produce compound, through many steps, start with primary materials, and develops to final molecules. In this work the synthesis of the target quinoline derivatives is done though three stages.

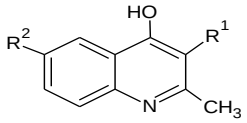
The first step is formation of diazonium ion from the reaction of aromatic amines with nitrous acid. The second stage is reaction of the diazonium product with active methylene compound. Which contain methylene group between two carbonyl groups and that made the acidity of α-Hydrogen very high. As a result of methylene acidity those compound are called active methylene compound.

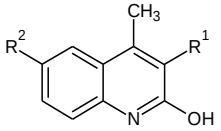


The second step lead to the formation of the diazotized dicarbonyl compound. The third step is formation of ethyl-β-anilinocrotonates from diazotized dicarbonyl compounds with aromatic amine in presence of hydrochloric in two different conditions in room temperature and 70-80^{o}C.

The fourth step is ring closing by using Sulpuric acid in high temperature

There are two of quinoline derivatives synthesized in this work. 2-hydroxy-4-methylquinoline derivative and 4-hydroxy-2-methylquinoline derivative.

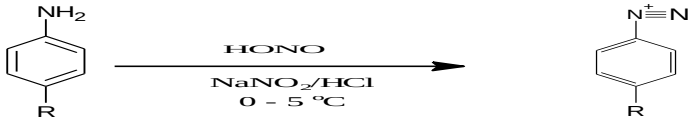




Position 3 (R^1) is always occupied with an azo group N=N and position 6(R^2) is occupied (-H, -SO_2NH_2)

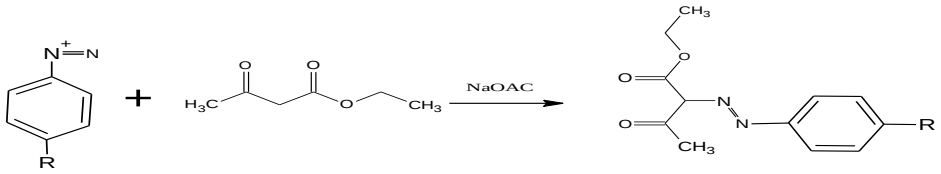
First step:-

Formation of diazonium ion

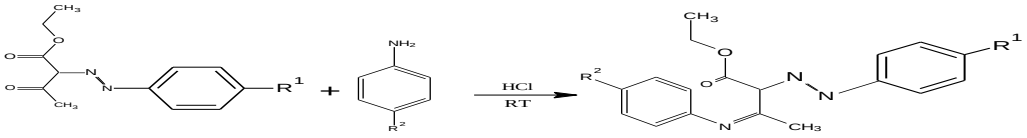


(R= -H, - SO_2NH_2)

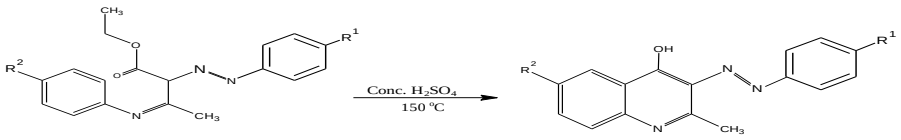
Second step:-



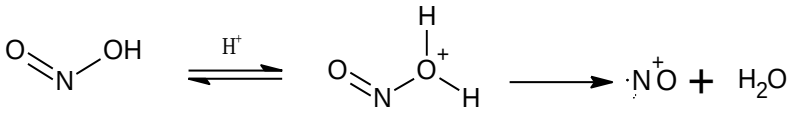
Third step:-



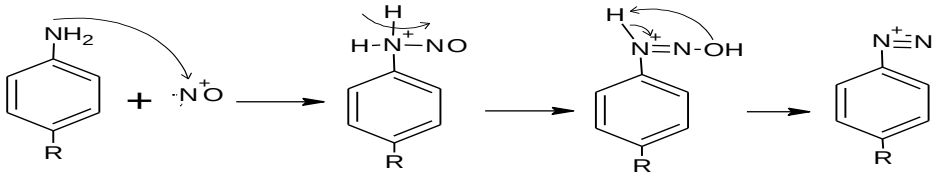
Fourth step:-



The mechanism of reaction of nitrous acid with aromatic amines can be shown below.

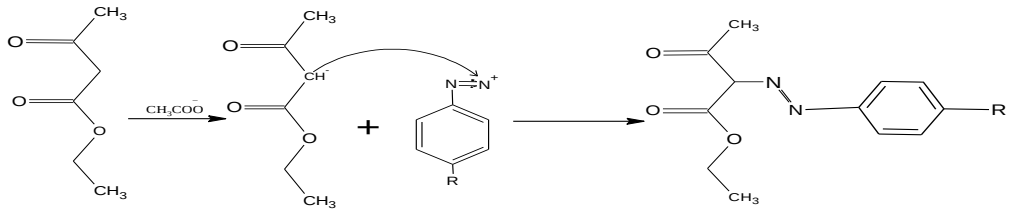


Hydrochloric acid reacts as strong acid with nitrous acid as base the acid proton linked with hydroxyl group in nitrous acid, which make the oxygen positively charged. Oxygen attract electron between oxygen and nitrogen and get released as water molecule the nitrosonium ion which is formed. Reacts with aromatic amine according to the following mechanism.



Nitrosonium ion as in electron electophile attracts the free ion for electron pair on nitrogen of the amine which makes the nitrogen atom charged. A proton is removed to the oxygen, followed by removal of water which leads to formation of the diazonium salt.

The reaction of diazonium salt with ethyl-3-oxobutanoate in the presence of sodium acetate as a base can be justified according to the following mechanism.



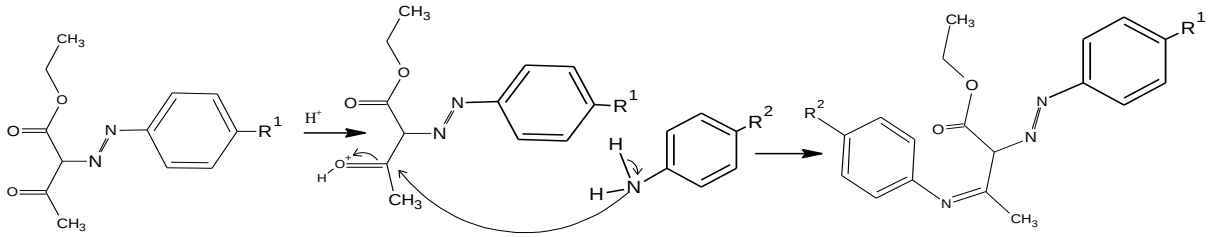
The α-proton in dicarbonyl compound is released by the base and carbanion formed. Diazonium salt, being electrophile attacks the carbanion which leads to the formation of the diazotized ethyl-3-oxobutanoate compound.

There are two pathways described in this work for synthesis of final product.

Firstly pathway synthesis of substituted ethyl-β-anilinocrotonates in room temperature which cyclizes to 4-methylquinolin-2-ol on heating.

Secondly synthesis of anilide by condensation of the primary amine at the ester functions at higher temperatures. This anilide undergoes ring closure on heating in the presence of acid to 2-methylquinolin-4-ol.

The formation of ethyl-β-anilinocrotonates is obtained by reaction of diazotized ethyl-3-oxobutanoate with primary amine in presence of hydrochloric acid according to the following mechanism.

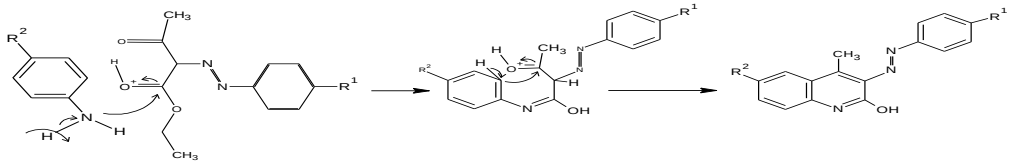


The reaction occurs in acidic medium. The acid proton attacks the carbonyl group oxygen, increasing the positively charge in carbon.

Nitrogen lone pair of electron of primary amines attacks the ketonic carbonyl group as a nuleophile in an addition reaction. The carbocation attracts the Π bond of the oxygen to neutralize the positive charge and one molecular water withdrawn to form the imino group.

The final product is obtained by removal of water molecule and ring closer in ortho phenyl imino position in presence of concentration sulphuric acid at high temperature.

The reaction occurs in strong acidic medium. The acid proton attacks the ester carbonyl group oxygen, increasing the positively charge in carbon, ethyl alcohol is formed as a result of nucleophilic substitution in the ester part.



3.4. Kinetic control and thermodynamic control:-

Product composition at the end of the reaction may be governed by the equilibrium thermodynamics of the system. When this is true, the product composition is governed by thermodynamic control and the stability difference between the competing products, as given by the free-energy difference, determines the product composition. Alternatively product composition may be governed by competing rates of formation of products, which is called kinetic control (Carey and Sundberg, 2007).

Thermodynamic control description quantitatively stability, kinetic control descriptionof reactivity, fundamental thermodynamic equation relates the equilibrium constant for a reaction to the free energy change associated with the reaction(Moore and Pearson, 1981).

$$\Delta G = -RT \ln K$$

Chemical names of synthesized compounds are shown in tables (2.1a, 2.1b, 2.1c, 2.1d).

Reaction temperature, Recrystalization solvent, the percentage yield andmelting points of the synthesized compounds are shown in table (2.3a, 2.3b, 2.3c, 2.3d) characteristic behaviors of the intermediates and their final products are reflected in their melting points, the most synthesized quinolines derivatives gave higher melting point between (155-218) but intermediate compounds show less melting point.

The identity of the prepared compounds has been elucidated with spectroscopic means. The purity of the synthesized compounds has been checked by TLC after repeated Recrystalization. By using chloroform and methane as mobile phase, the

new products showed $R_f$value different from reactants TLC was also performed as a suitable means of for the follow up of the reaction progress. The results of TLC are given in table (2.5a, 2.5b, 2.5c) with mobile, stationary phase and $R_f$values. As it can seen there was a good correlation between the polarity of the intermediates, final products and their corresponding $R_f$values.

3.5. Quantitative structure activity relationship(QSAR):-

The quantitative structure activity relationship (QSAR) paradigm is based on the assumption that, there is an underlying relationship between the molecular structure and biological activity. QSAR attempts to establish correlation between various molecular properties(Hansch and Leo, 1979).

QSAR is general mathematical form is:-

Activity = f (structural properties)

Hansch was first to describe relation of molecule electronic characteristics and to its hydrophobicity this led him to propose that biological activity could be related to the molecular structure.

Hansch and Muir published their brilliant study on the structure activity relationships of plant growth regulators and their dependency on Hammett constant and hydrophobicity (Hansch *et al*, 1962).

Using the octanol/water system, a whole series of partion coefficient were measured and thus new hydrophobic scale was introduced. (Nelson *et al*, 1975).

Fujita and Hansch then combined hydrophobic constant with Hammett electronic constants to yield the linear Hansch equation (Hansch and Leo, 1995).

Log 1/C = A B CK

Limitations in this approach led to the more sophisticated fujita Ban equation that used the logarithm of activity, which brought the activity parameter in line with other free energy related terms (Free and Wilson,1964; Fujita and Ban,1971).

$LogBA = G_iX_i U$

U is defined as the calculated biological activity value of the unsubstituented parent compound of a particular series.

G: represent the biological activity contribution of the substituent's, whereas X_i is ascribed with a value of one when the substituent is present or zero when it is absent .

3.6. Spectral data of synthesized compounds:

Infrared spectroscopy is most suitable technique for the identification of the different functional groups present in molecule. The IR data of the different compounds is shown in table (2.4a, 2.4b, 2.4c, 2.4d).

The intermediate ethyl-2-(azoaryl) acetoacetate compounds (I, II) posses two carbonyl group for ketonic and esteric carbonyl these carbonyl group stretching vibration in the range 1668-1708 cm^{-1}.

-SO_2- stretching vibration of the sulphonamido group in the compound (II) appear at 1342.36 and 1157.21cm^{-1} due to the asymmetric and symmetric stretching vibration respectively. The N-H stretching vibration of the sulphonamido group appears at 3344cm^{-1}while its corresponding bending appears at 1652cm^{-1}, C-H aromatic stretching vibration appears at 3249.83cm^{-1}.

N=N stretching vibration of two compounds at 1625.88cm^{-1} and 1635.52cm^{-1}respectively, =N–C- stretching vibration for two compounds appear at 1367.44cm^{-1}

In the intermediates ethyl-β-anilinocrotonates derivatives (III, IV, V, VI) posses one carbonyl group that stretching vibration appears at 1699.17 – 1716.53cm^{-1}.

The final products of 3,6-methylquinolinol (VII, VIII, IX, X) posses O-H group an stretching vibration appears in range 2927.74 – 3550cm^{-1}, N=C appears at 1652cm^{-1} and absence of carbonyl group.

Proton nuclear magnetic resonance spectroscopy H^1NMR provided and excellent means for quantitative and qualitative analysis of the different protons within a molecule table (2.6a, 2.6b, 2.6c, and 2.6d).

As expected the CH_3 protons (A) in compound (I, II) appear as a singlet at 2.38 ppm and 2.41ppm respectively, while the methyl proton (B) appear at 3.30 ppm and 3.32 ppm as a singlet.This compound contain A_2B_3 system (C, D) which give rise to a quartet and triplet, the protons in (C,D) appears as quartet (CH_2- protons) and triplet (CH_3-protons) at 4.30 ppm and 1.28 ppm respectively, the aromatic ring protons (E) in compound (I) appear as a multiplet at 7.09-7.46ppm but in compound (II) appear as double doublet at 7.53-7.56, 7.79-7.82 ppm.

Compound (III, IV, V, and VI) table (2.6b), the CH_3 protons (A), methyl proton (B) and A_2B_3 system as appeared.

In compound (III), the five protons in aromatic ring (E) appear as multiplet at 7.79-7.84 ppm and five protons in aromatic ring (F) appear as multiplet at 7.53-7.69 ppm.

Compound (IV) the five protons in aromatic (E) appear as a multiplet at 7.25ppm and four protons in aromatic ring (F) appear as double doublet at 7.56, 7.82ppm.

In compound (V) four protons in aromatic ring (E) appear as a double doublet at 7.68, 7.81ppm and five protons in aromatic ring (F) appear as multiplet at 7.36-7.52ppm.

In compound (VI) four protons in aromatic ring (E, F) appears as a double doublet at 7.78-7.81, 7.31-7.34ppm.

Compound VII, VIII, IX, X as a similar CH_3 protons (A) appear at 2.5ppm for VII, VIII and 2.49ppm for IX, X. five protons in aromatic ring (B) in compound (VII, VIII) appear as multiplet at (7.59-7.63ppm),(7.22-7.25ppm) respectively, while four protons in aromatic ring (C) in compound (VII) as a multiplet at 7.42-7.48ppm

and three protons in aromatic ring (C) in compound (VIII) one proton appear as doublet at 7.60ppm and two protons as a multiplet at 7.22-7.47ppm.

Compound IX, X show a similar pattern in four protons in aromatic ring (B) a double doublet at (7.82-7.84, 7.67-7.69ppm), while four protons in aromatic ring (C)in compound (IX) and three protons in aromatic ring (C) in compound (X) appear as a multiplet at 7.30ppm, 7.31ppm.

Also compound XI, XII, XIII, XIV as the similar CH3 protons (A) appear at 2.5ppm, five protons in aromatic ring (B) in compound XI, XII appear as a multiplet at 7.36-7.60 ppm, 7.42-7.47ppm respectively, while four protons in aromatic ring (C) in compound XI appear as multiplet and compound XII appear as double doublet at 7.59-7.62 ppm and multiplet at 7.2-7.25 ppm.

Compound XIII, XIV show a similar in four protons in aromatic ring (B) that appear as a double doublet at 7.62, 7.92ppm and 7.63, 7.68 ppm respectively, while four protons in aromatic ring (C) in compound XIII appear as a multiplet at 7.21-7.48ppm and three protons in aromatic ring (C) in compound XIV appear as a multiplet at 7.31ppm.

3.7. Conclusion and recommendation:-

From the planning prepared in this work the quinolines derivatives were obtained in three steps reaction, firstly formation of diazotized dicarbonyl, secondly formation of ethyl-β-anilinocrotonates in room temperature, thirdly cyclizes to 4-methylquinolin-2-ol and formation of 2-methylquinolin-4-ol.

Such procedure can be considerd as a feasible preparation a large of number of quinoline derivatives.

From the synthetic point of view, the retro synthetic analysis adopted in this work proved to be correct and in good accordance with the proposed mechanism.

Other methods of preparation such as Combes, Skraup, Doebner-Miller, Friedlander and pfitzinger must be use comparatively to Conrad- Limpach method so adopted in this work.

Spectral data obtained for the prepared compounds it can be clearly seen that they are certain features, so it is recommended that all the prepared compounds, are to be fully tested for their spectral properties.

Finally the biological activity of the prepared compounds can be carried out to correlate their anti microbial properties.

Chapter four
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Appendix

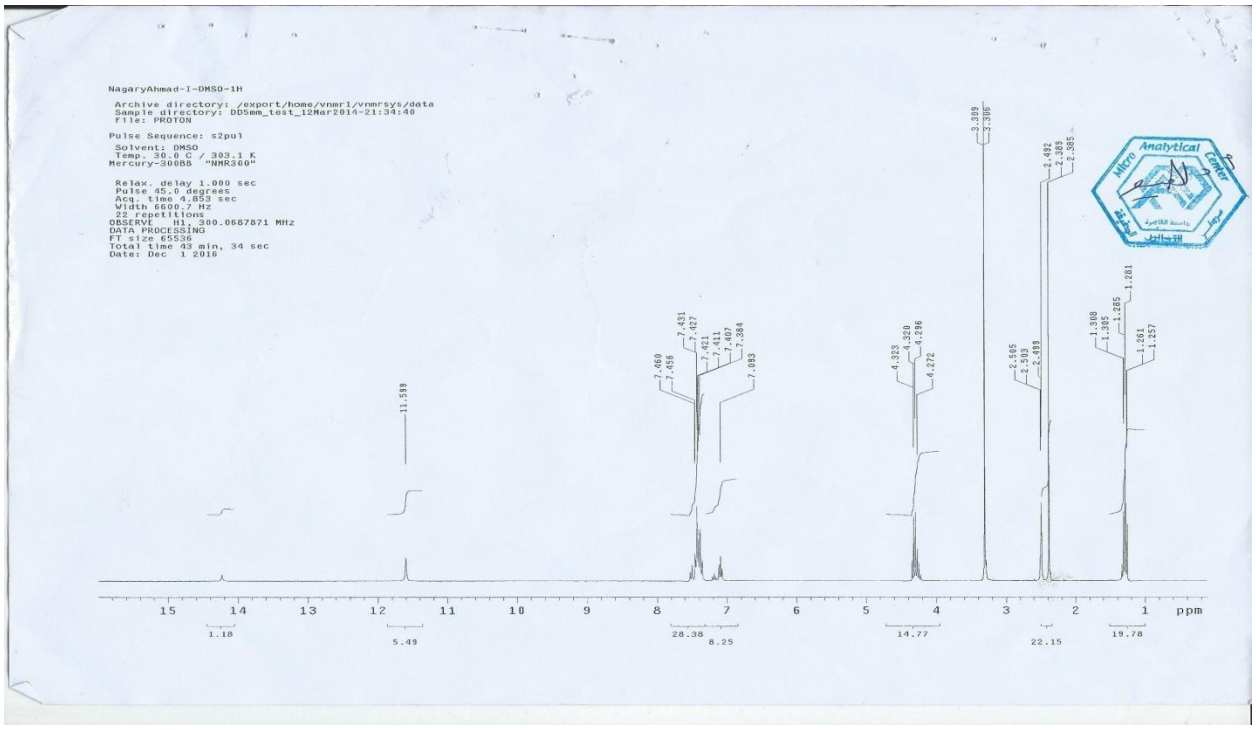

Figure (I) H^1NMR spectrum of ethyl 3-oxo-2-(phenyldiazenyl) butanoate

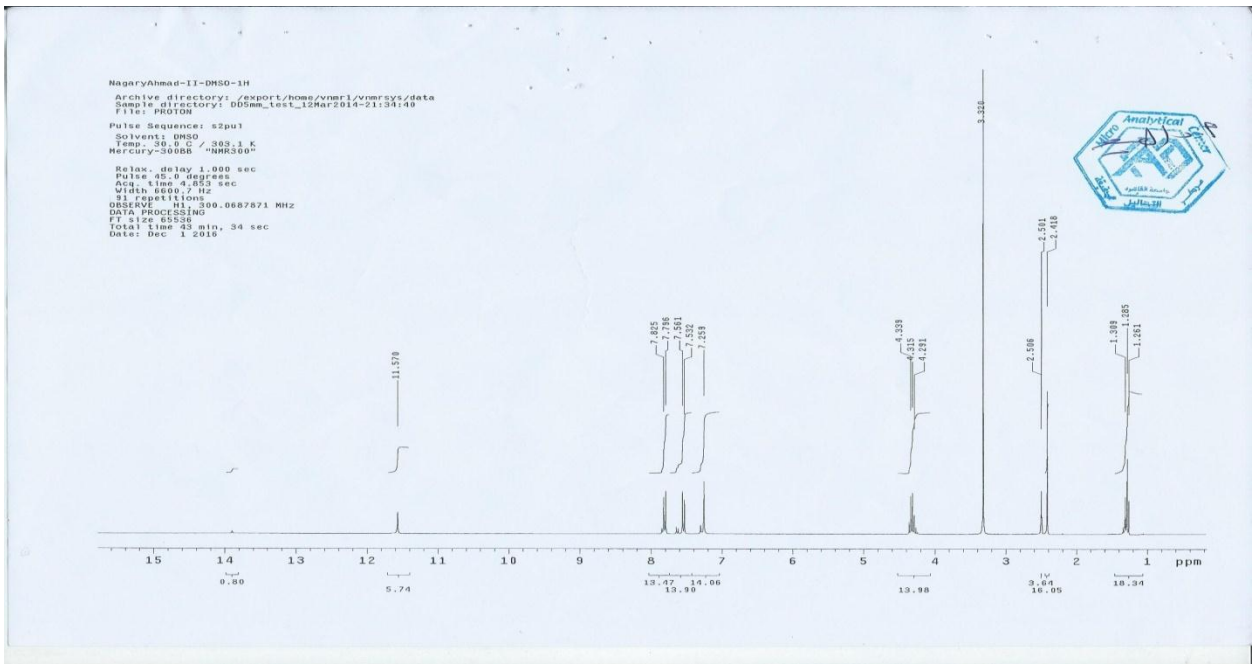

Figure (II) H^1NMR spectrum of ethyl-3-oxo-2-((4-sulfamoylphenyl) diazenyl) butanoate

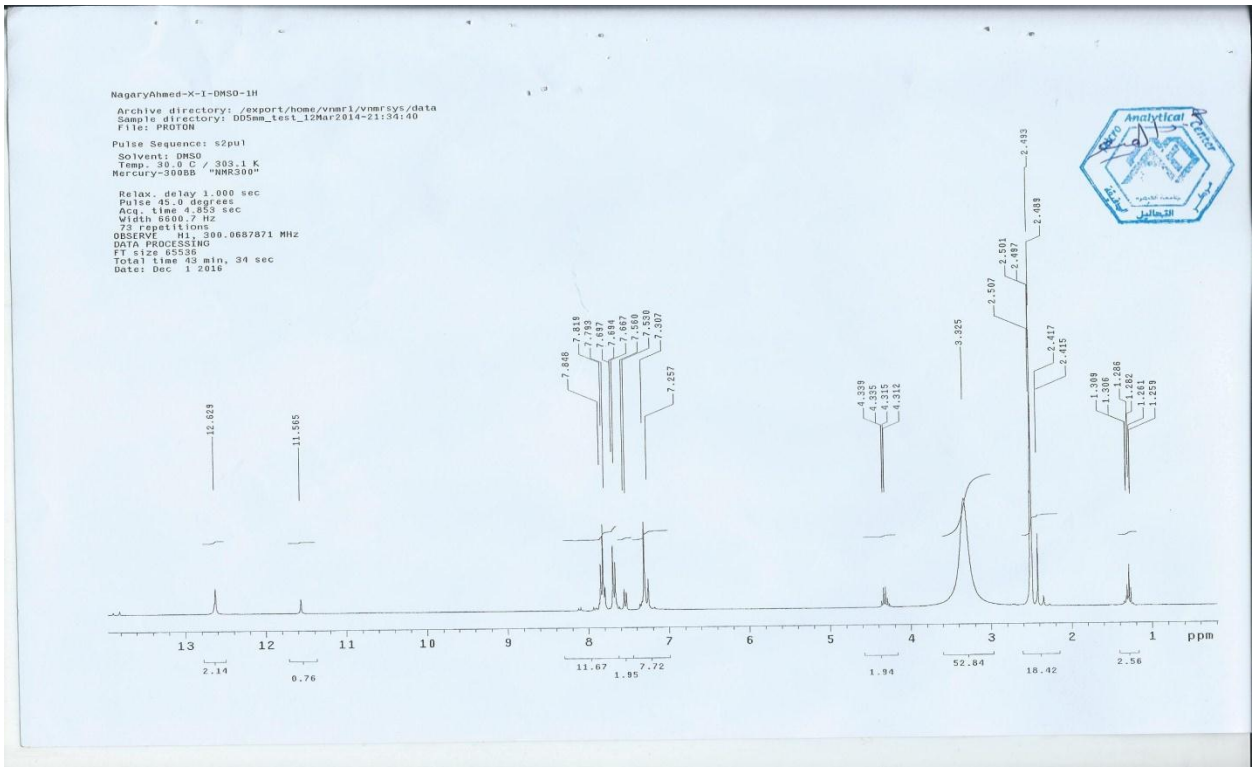

Figure (III) H^1NMR spectrum of ethyl-2-(phenyldiazenyl)-3-(phenylimino) butanoate

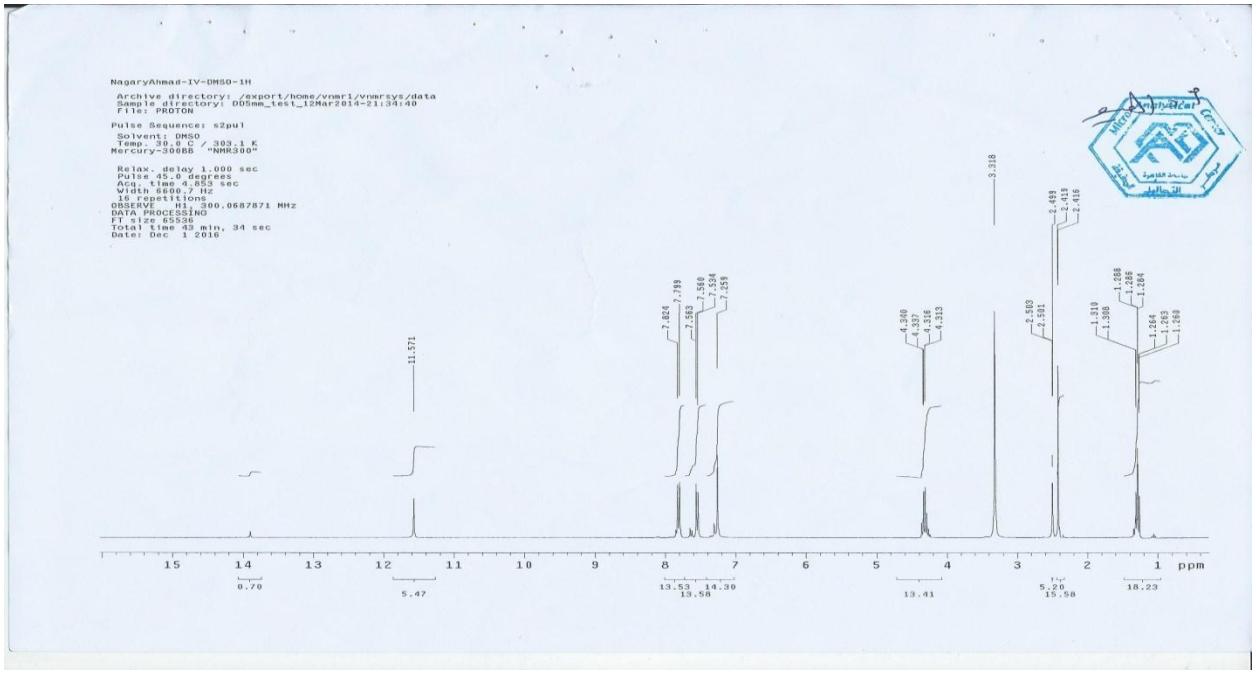

Figure (IV) H^1NMR spectrum of ethyl-2-(phenyldiazenyl)-3-((4-sulphamoyl phenyl) imino) butanoate

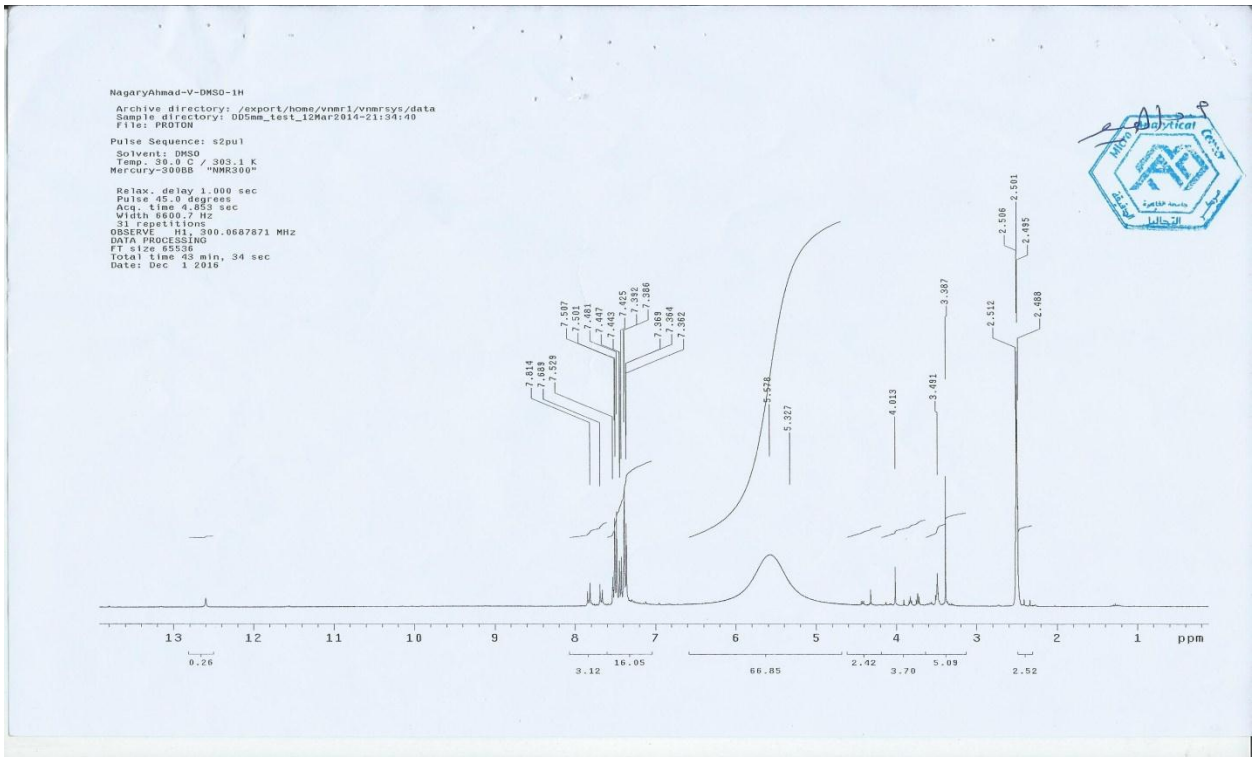

Figure (V) H^1NMR spectrum of ethyl-3-(phenylimino)-2-((4- sulphamoyl phenyl)diazenyl) butanoate

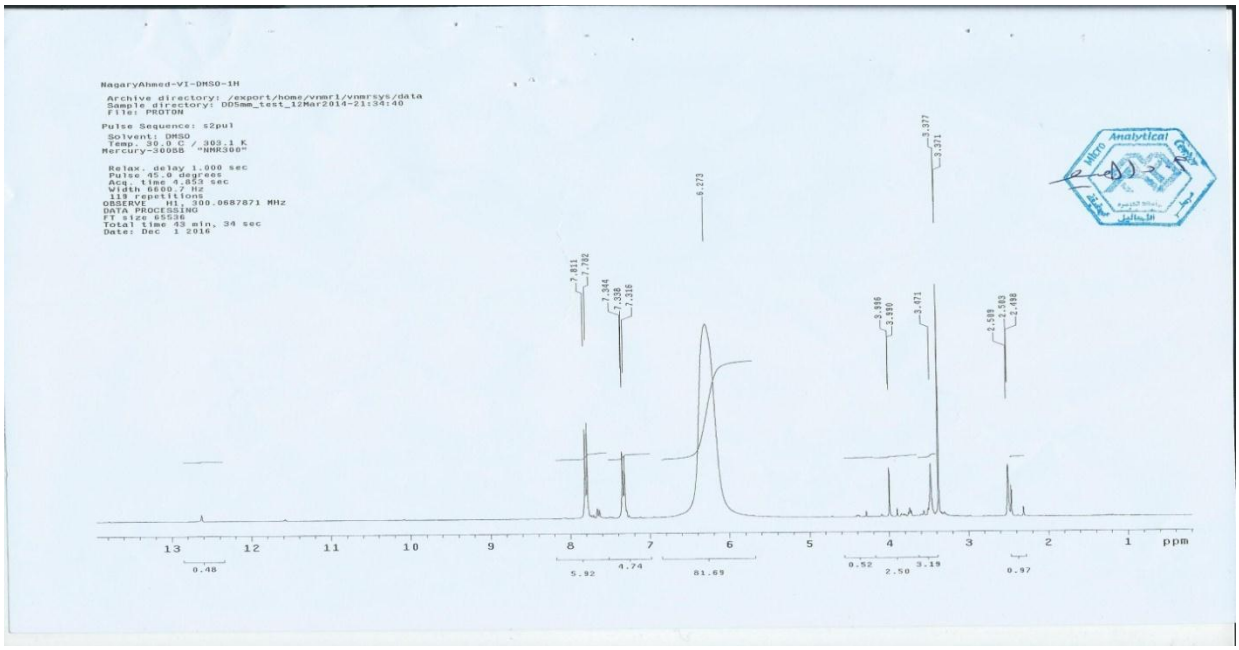

Figure (VI) H^1NMR spectrum of Ethyl-3-((4- sulphamoylphenyl)imino)-2-((4-sulphamoylphenyl) diazenyl)butanoate

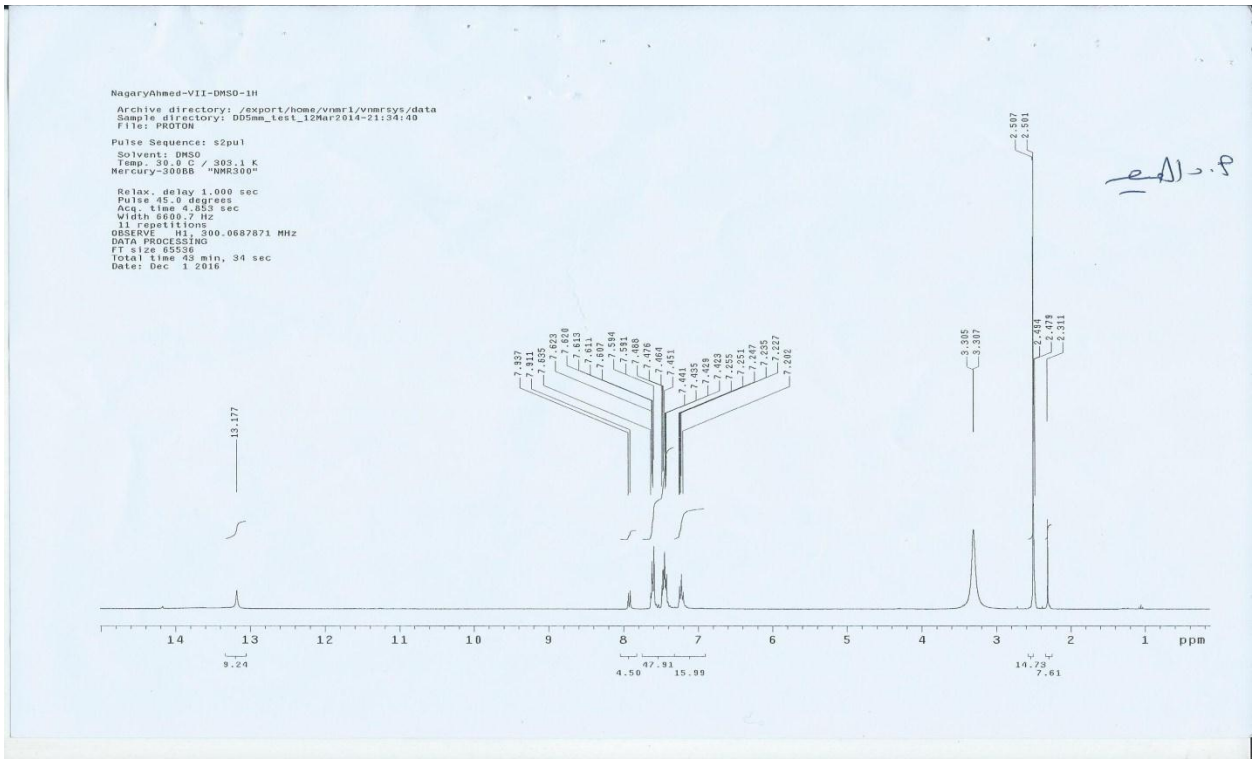

Figure (VII) H^1NMR spectrum of 2-methyl-3-(phenyldiazenyl)quinolin-4-ol

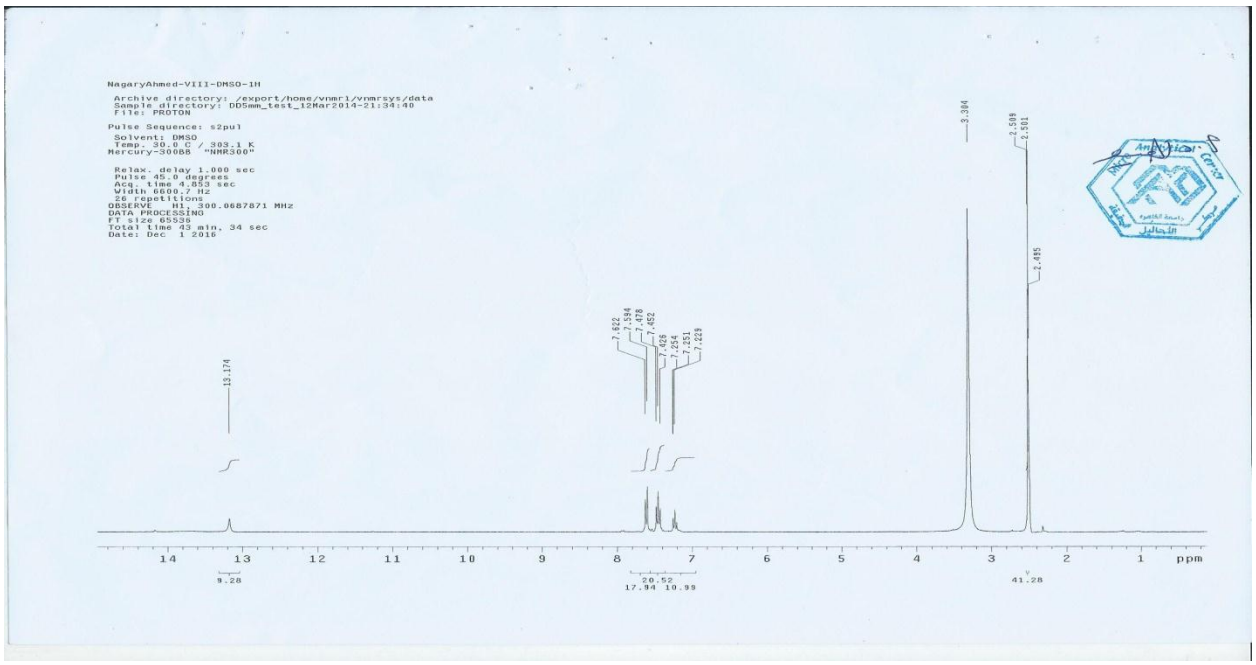

Figure (VIII) H^1NMR spectrum of 4-hydroxy-2-methyl-3-(phenyldiazenyl) quinoline-6-sulphonamide

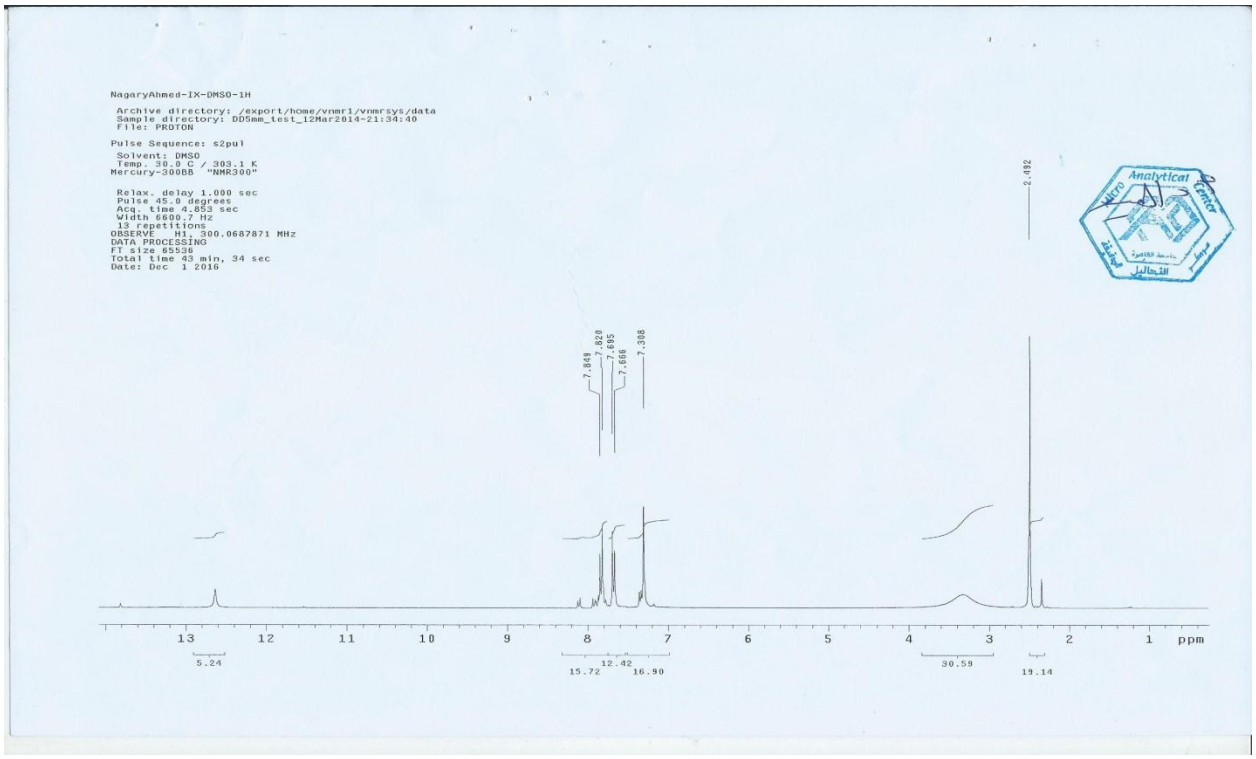

Figure (IX) H^1NMR spectrum of 4-((4-hydroxy-2-methylquinolin-3-yl) diazenyl) benzene-1-sulphonamide

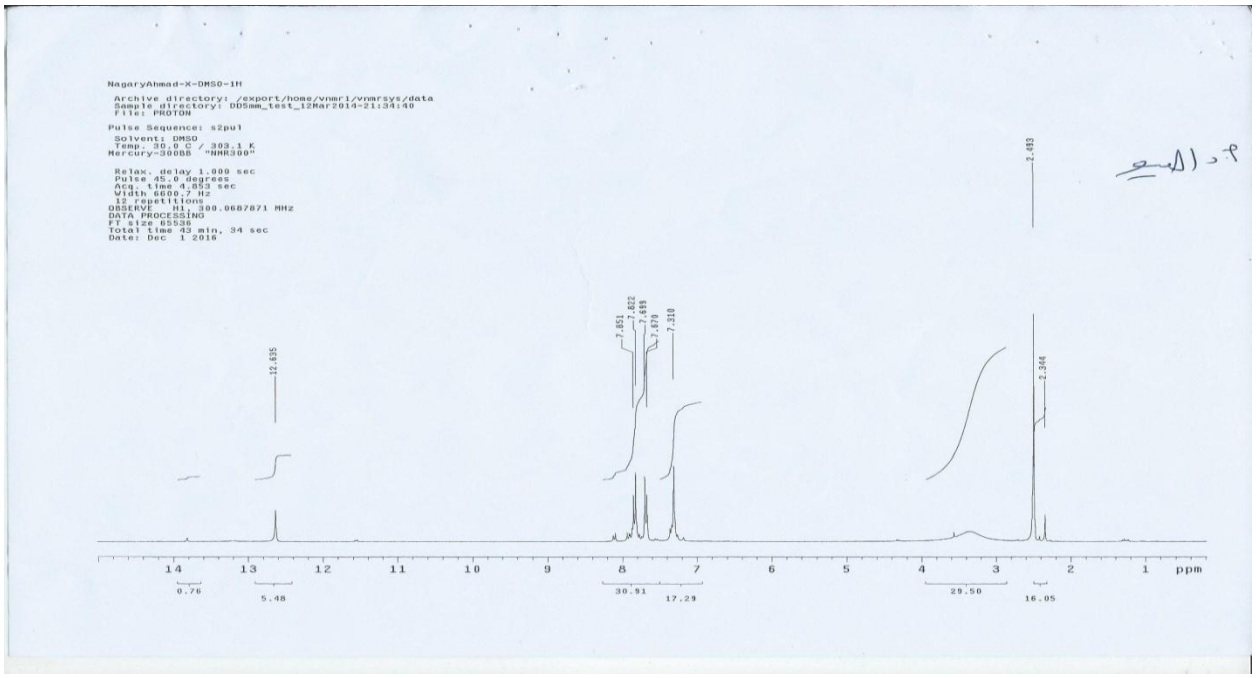

Figure (X) H^1NMR spectrum of 4-hydroxy-2-methyl-3-((4-sulphamoyl phenyl) diazenyl) quinoline-6-sulphonamide

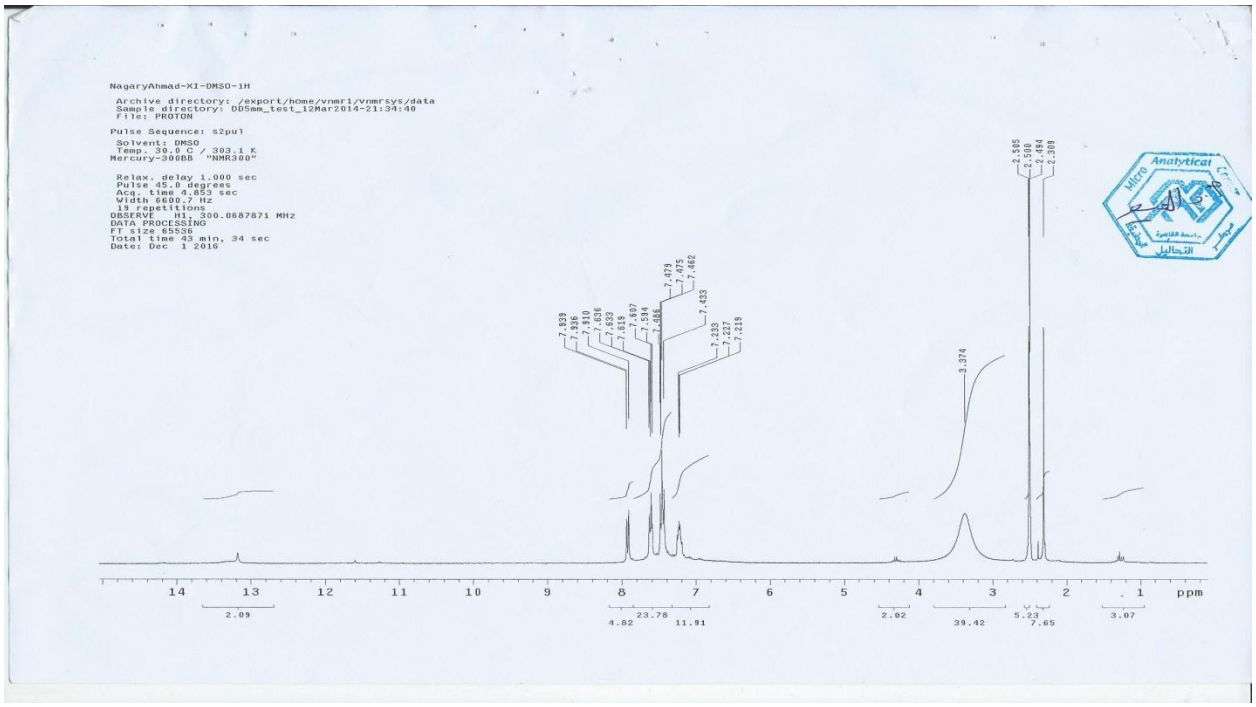

Figure (XI) H^1NMR spectrum of 4-methyl-3-(phenyldiazenyl)quinolin-4-ol

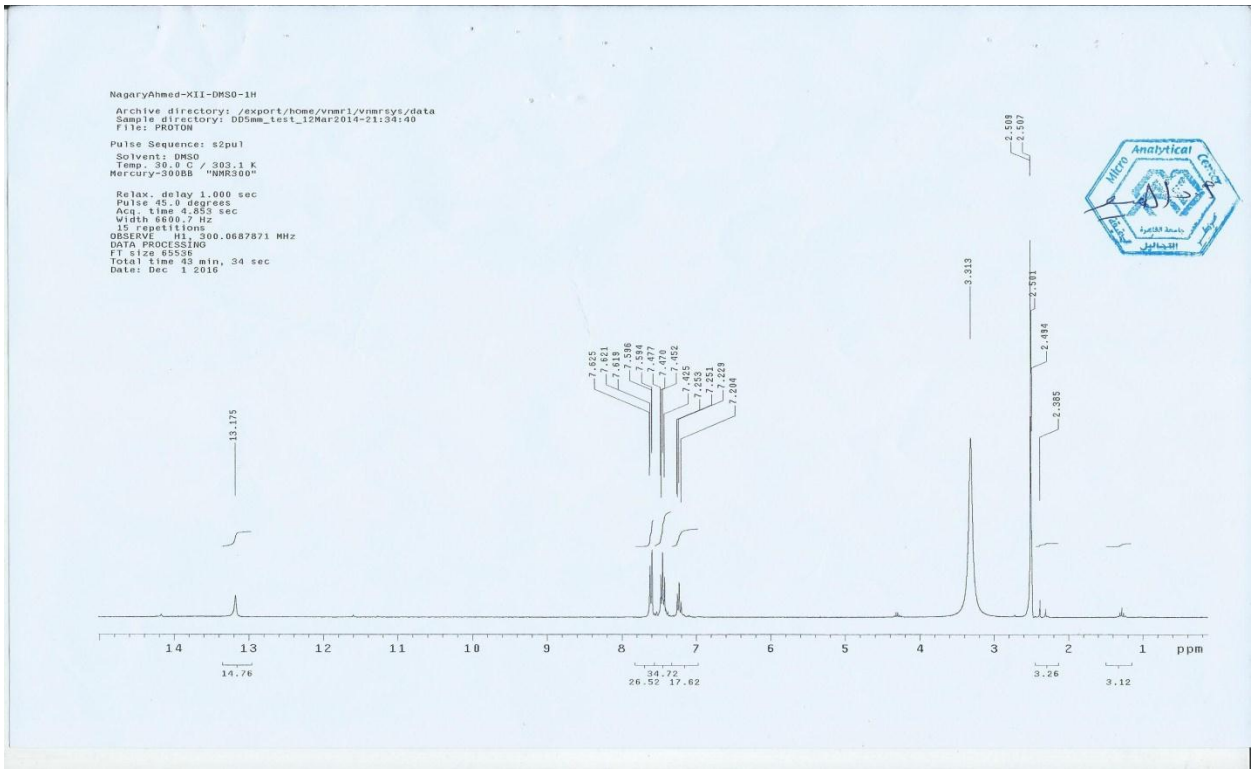

Figure (XII) H^1NMR spectrum of 2-hydroxy-4-methyl-3-(phenyldiazenyl) quinoline-6-sulphonamide

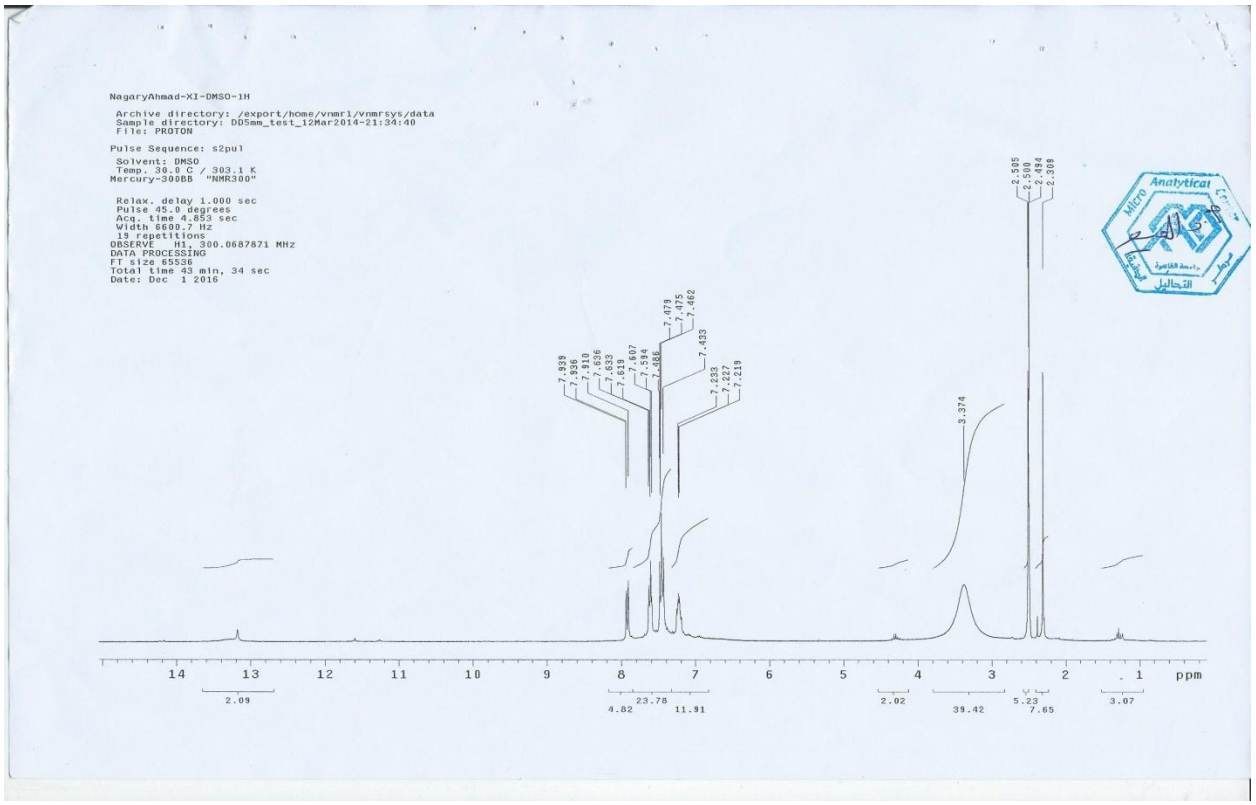

Figure (XIII) H[1]NMR spectrum of 4-((2-hydroxy-4-methylquinolin-3-yl) diazenyl) benzene-1-sulphonamide

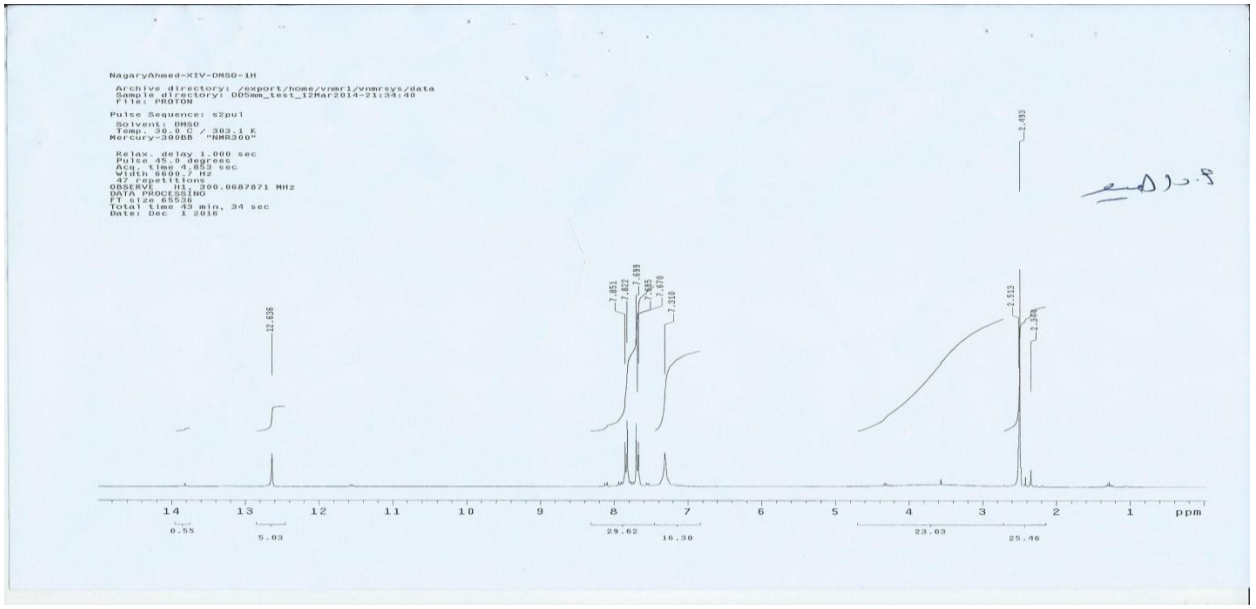

Figure (XIV) H[1]NMR spectrum of 2-hydroxy-4-methyl-3-(4-sulphamoyl phenyl) diazenyl quinoline-6-sulphonamide

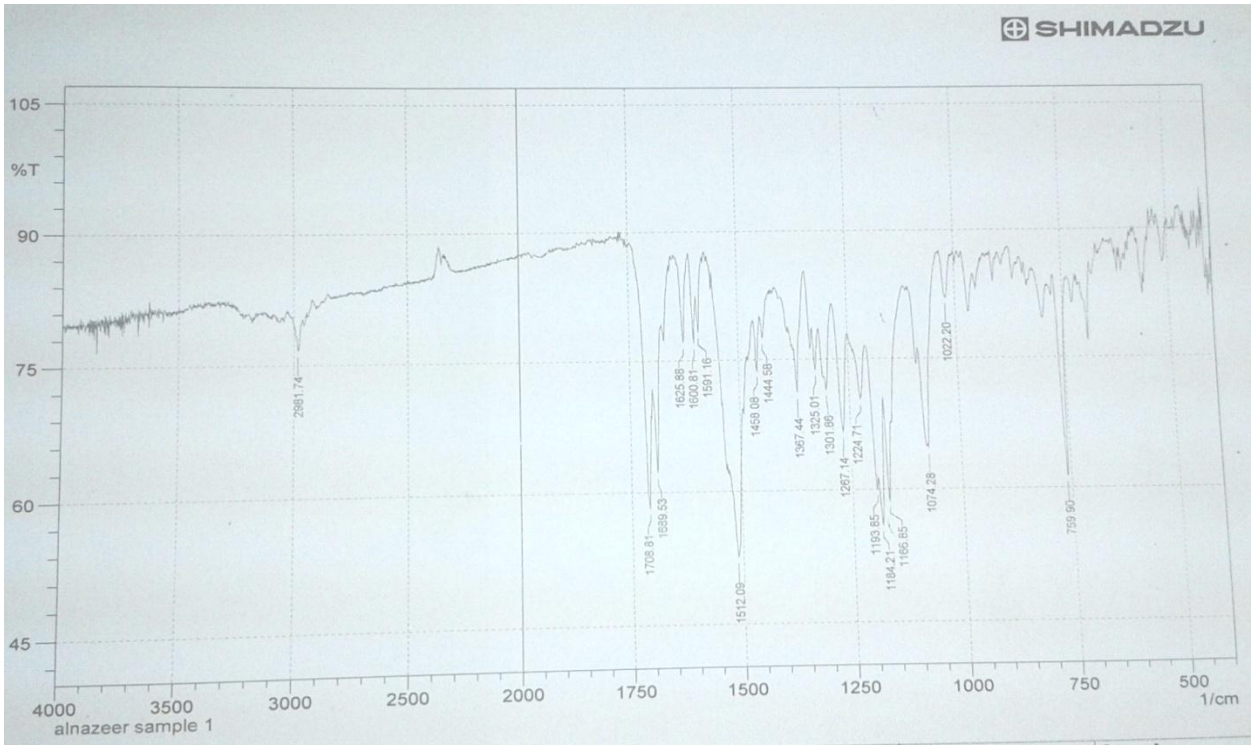

Figure (XV) IR spectrum of ethyl 3-oxo-2-(phenyldiazenyl)butanoate

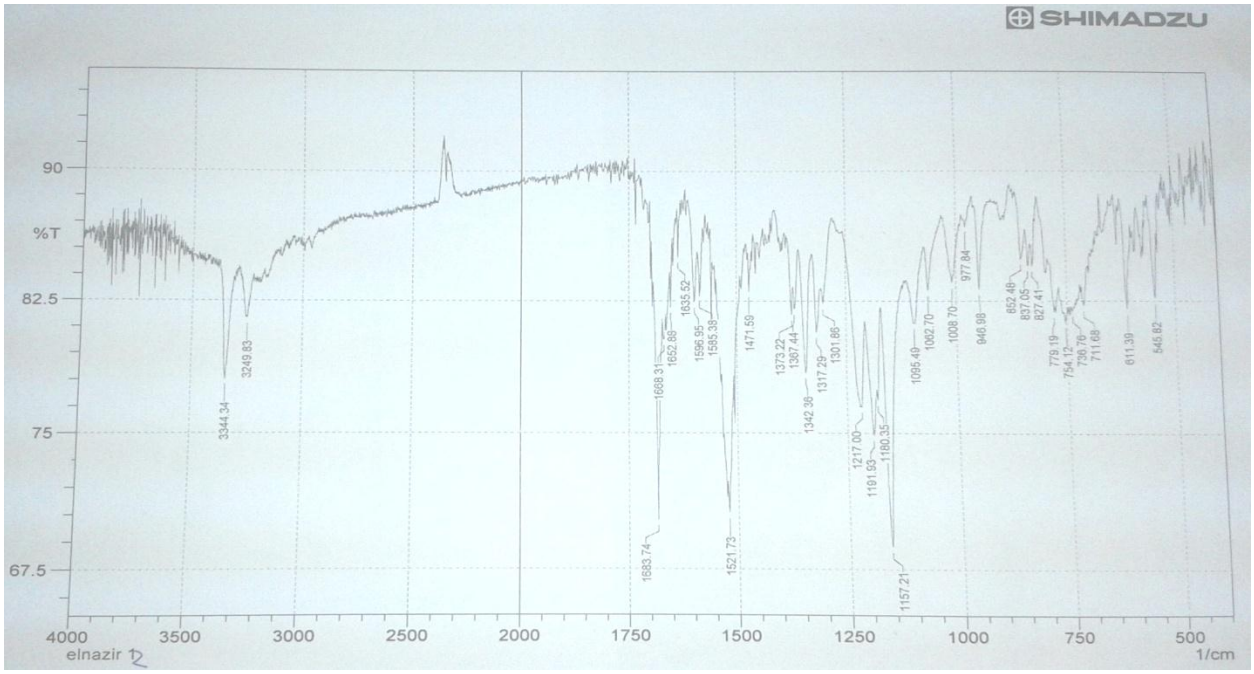

Figure (XVI) IR spectrum of Ethyl-3-oxo-2-((4-sulfamoylphenyl)diazenyl) butanoate

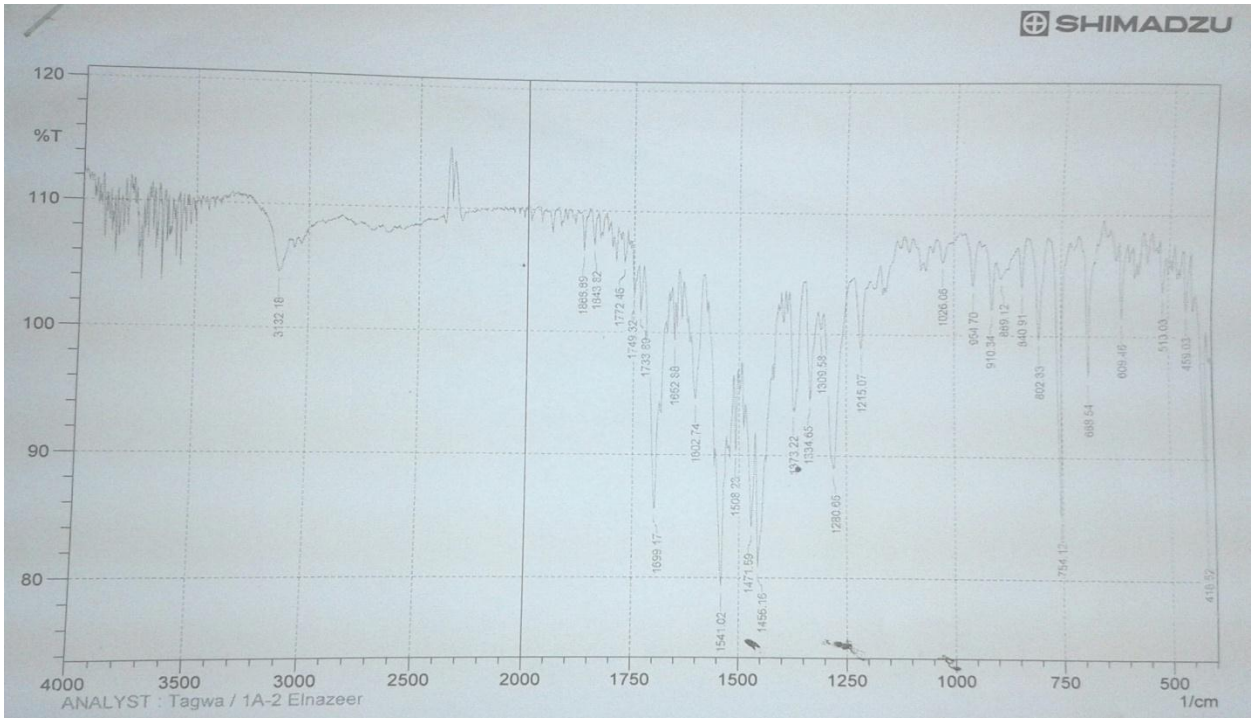

Figure (XVII) IR spectrum of Ethyl-2-(phenyldiazenyl)-3-(phenylimino) butanoate

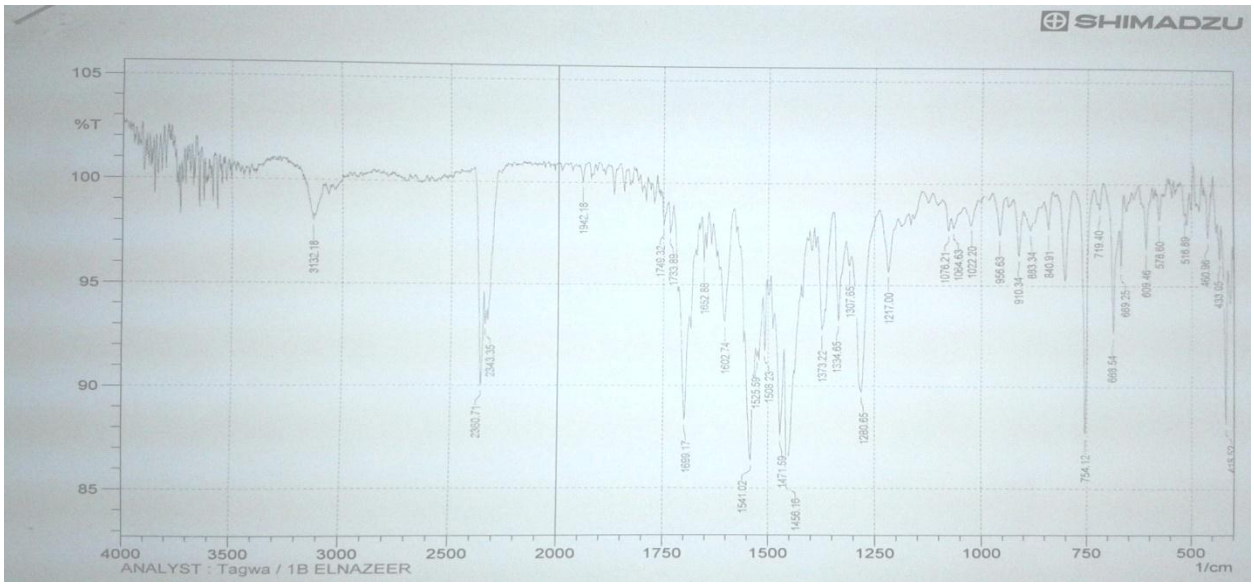

Figure (XVIII) IR spectrum of Ethyl-2-(phenyldiazenyl)-3-((4-sulphamoyl phenyl) imino)butanoate

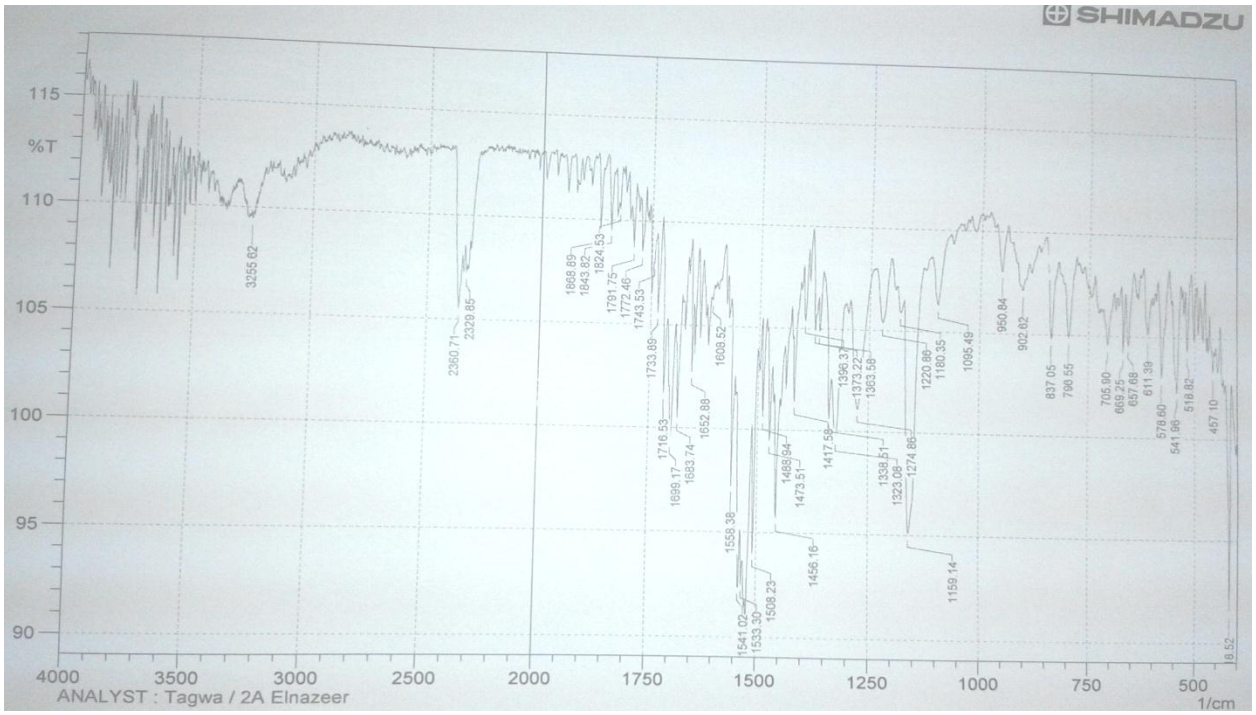

Figure (XIX) IR spectrum of ethyl-3-(phenylimino)-2-((4- sulphamoylphenyl) diazenyl) butanoate

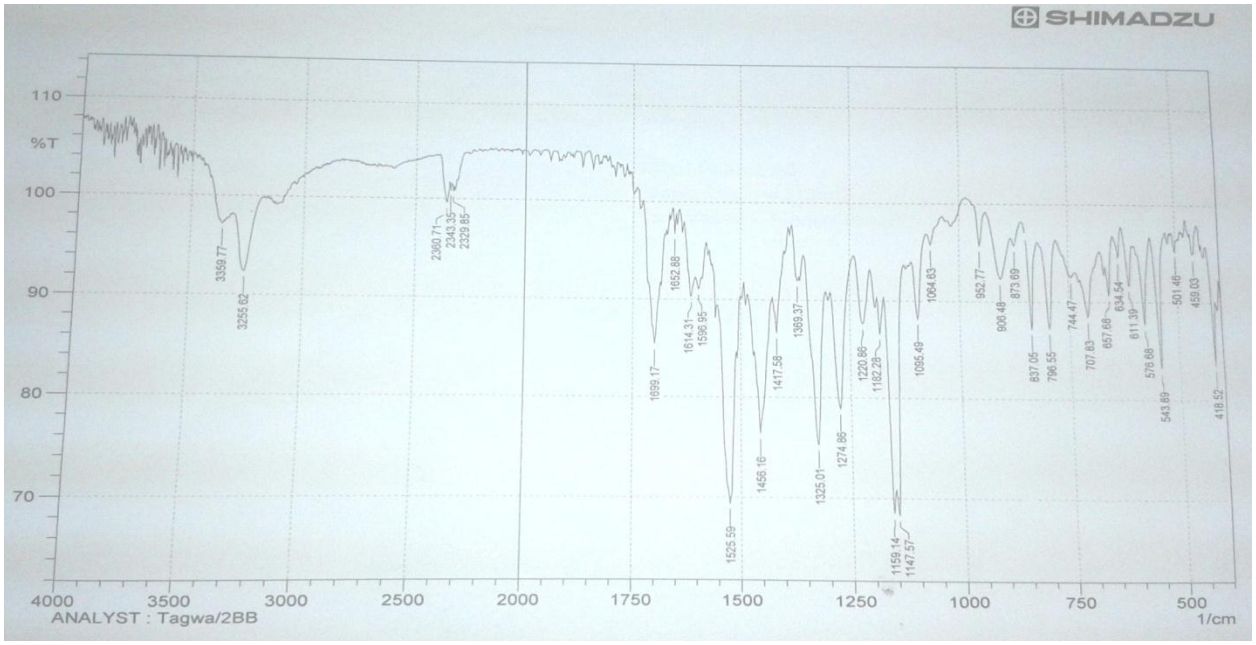

Figure (XX) IR spectrum of ethyl-3-((4- sulphamoylphenyl)imino)-2-((4-sulphamoylphenyl) diazenyl)butanoate

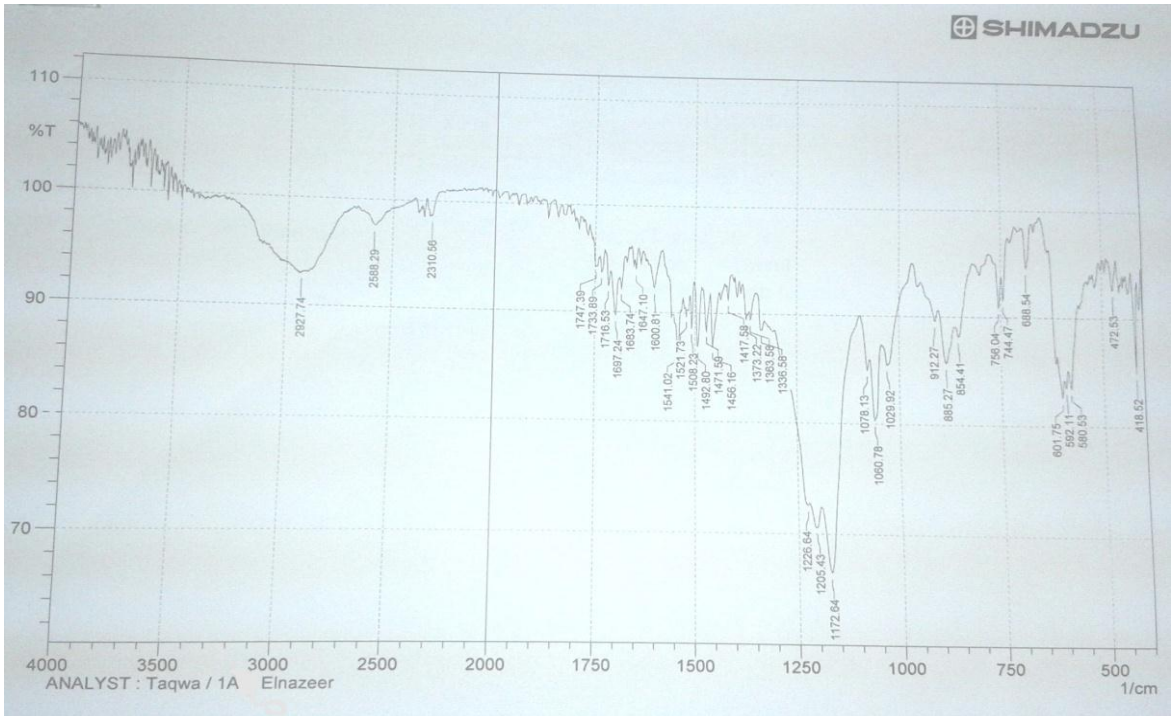

Figure (XXI) IR spectrum of 2-methyl-3-(phenyldiazenyl)quinolin-4-ol

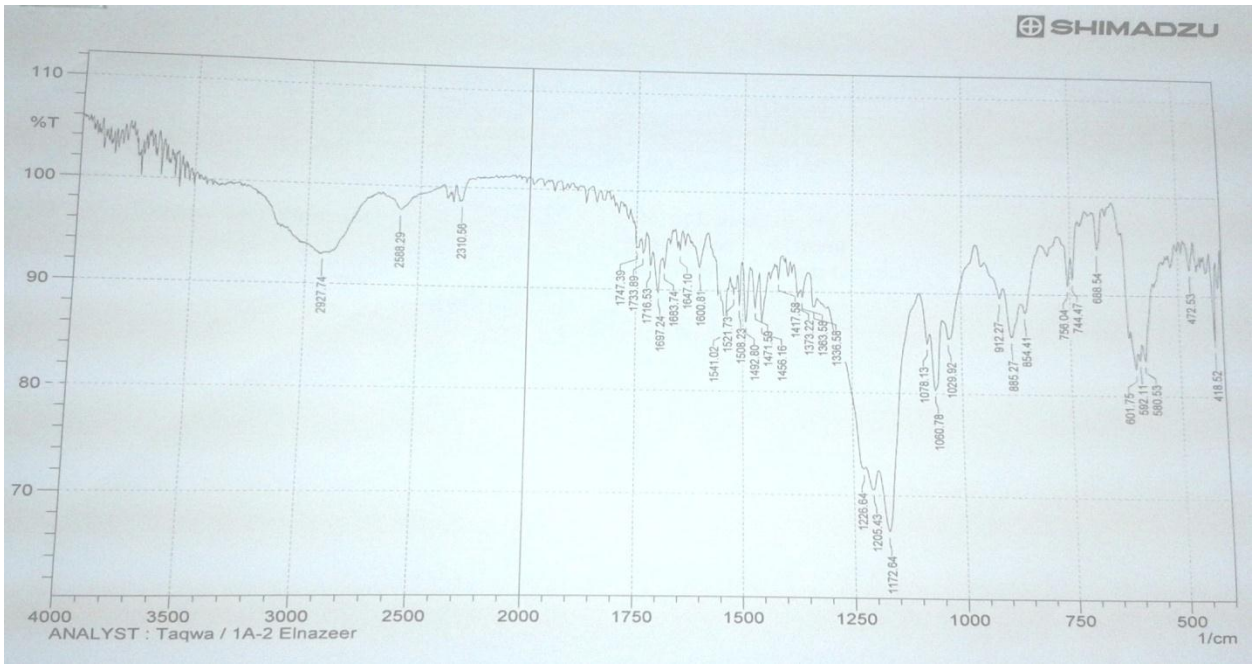

Figure (XXII) IR spectrum of 4-hydroxy-2-methyl-3-(phenyldiazenyl)quinoline-6-sulphonamide

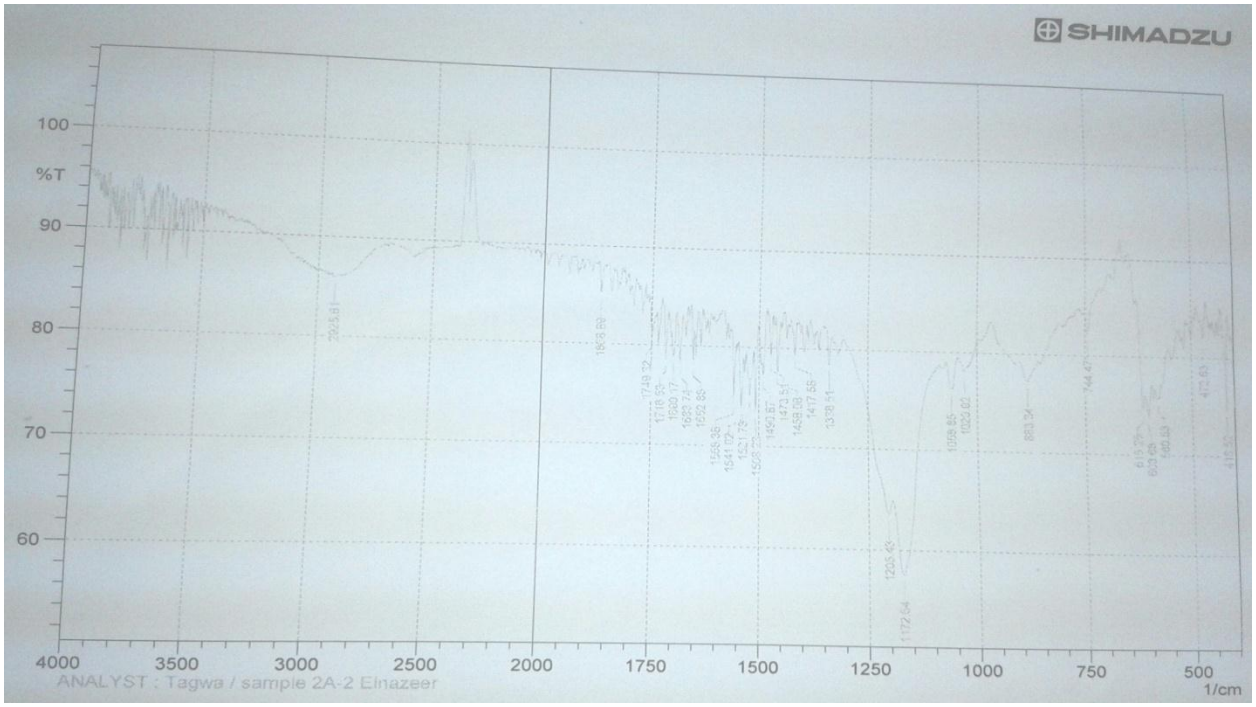

Figure (XXIII) IR spectrum of 4-((4-hydroxy-2-methylquinolin-3-yl)diazenyl) benzene-1-sulphonamide

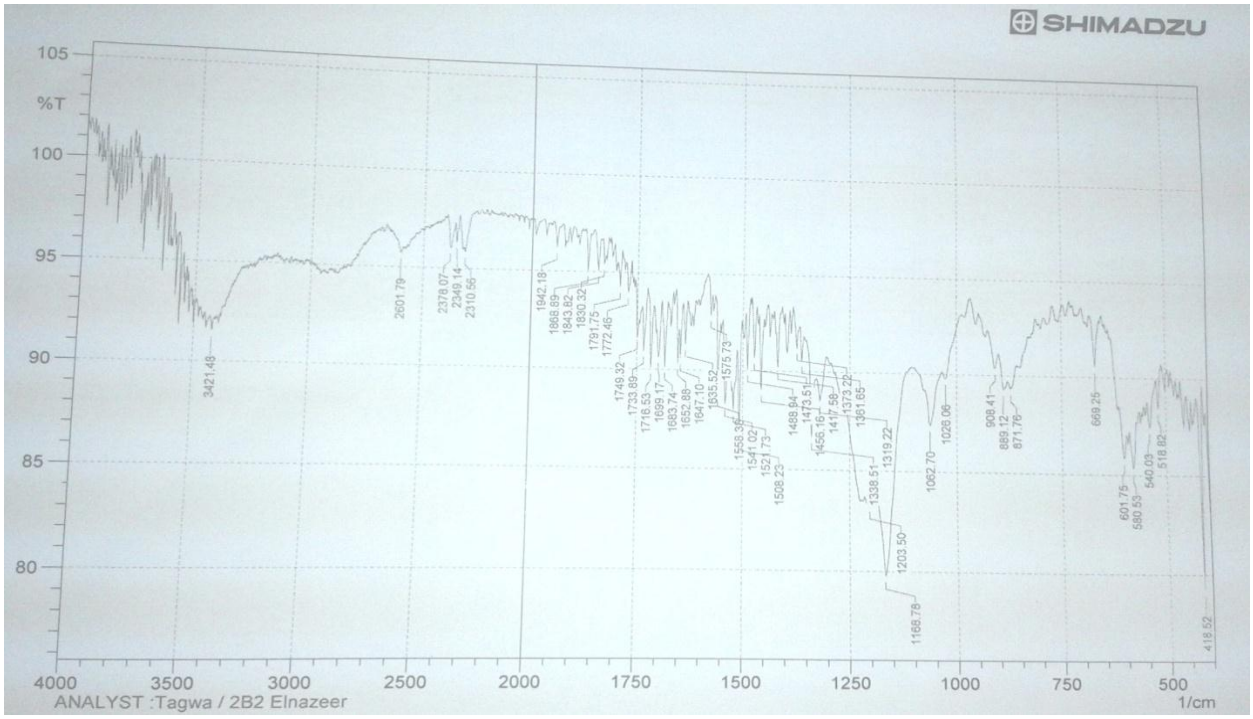

Figure (XXIV) IR spectrum of 4-hydroxy-2-methyl-3-((4-sulphamoylphenyl) diazenyl) quinoline-6-sulphonamide

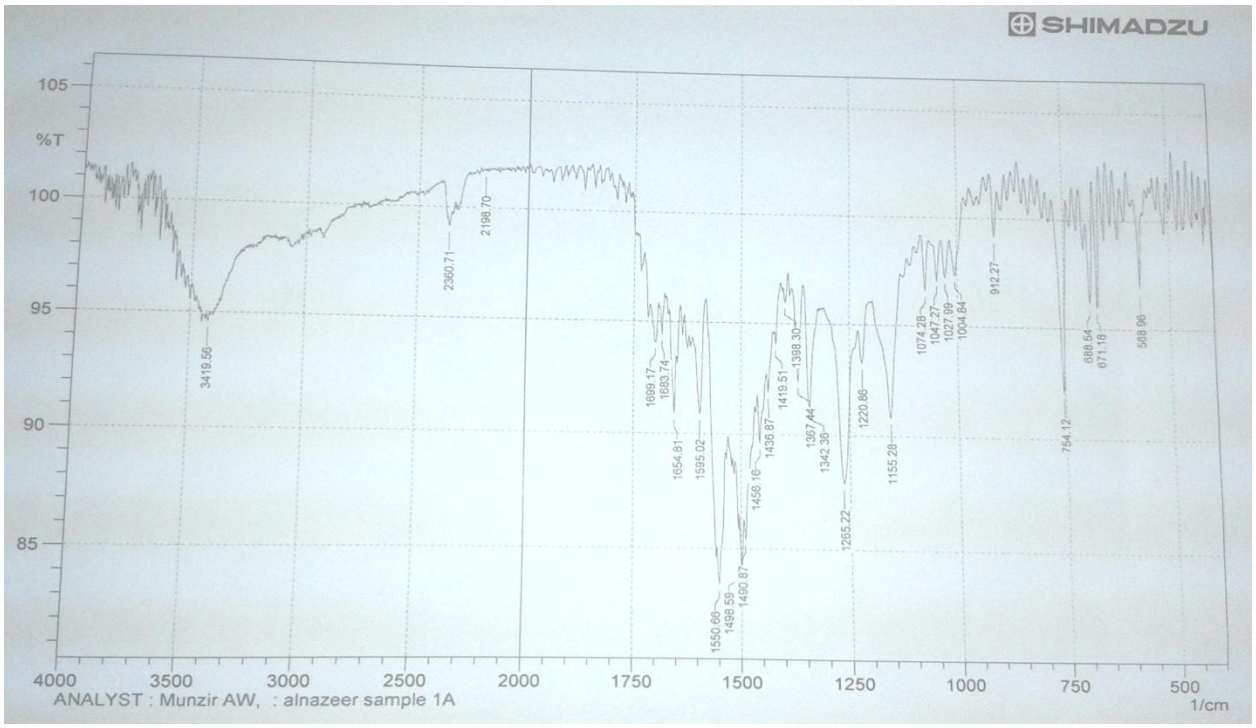

Figure (XXV) IR spectrum of 4-methyl-3-(phenyldiazenyl)quinolin-4-ol

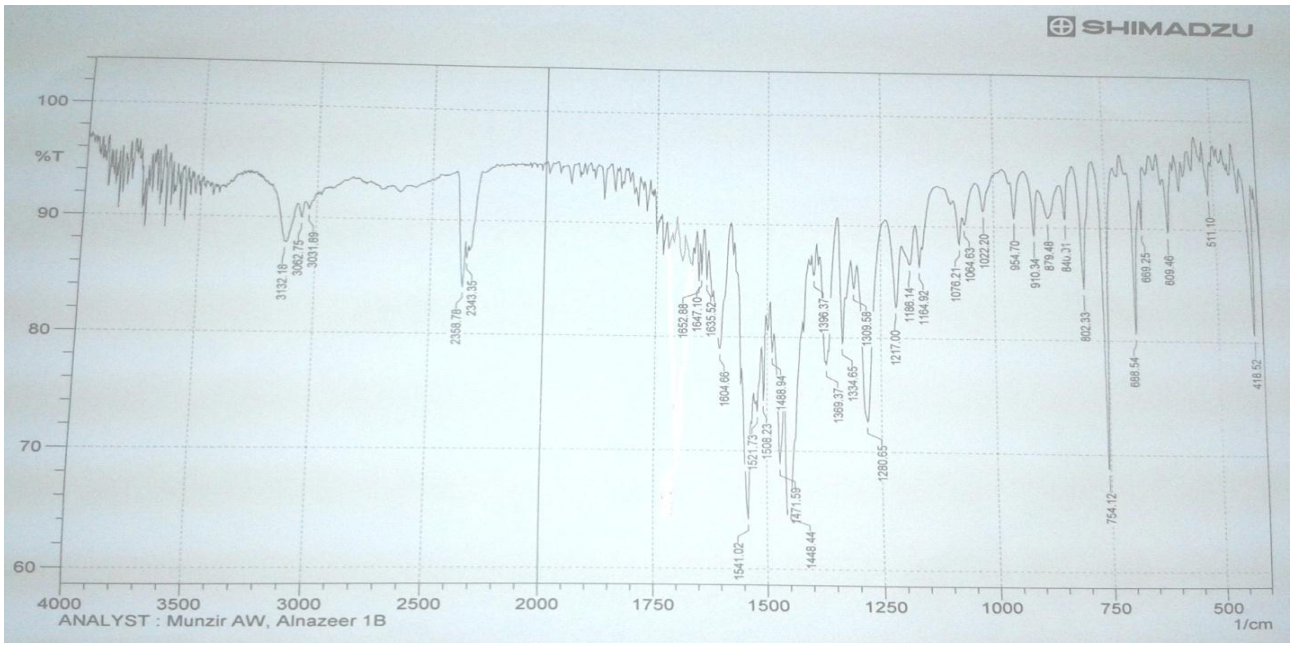

figure (XXVI) IR spectrum of 2-hydroxy-4-methyl-3-(phenyldiazenyl)quinoline-6-sulphonamide

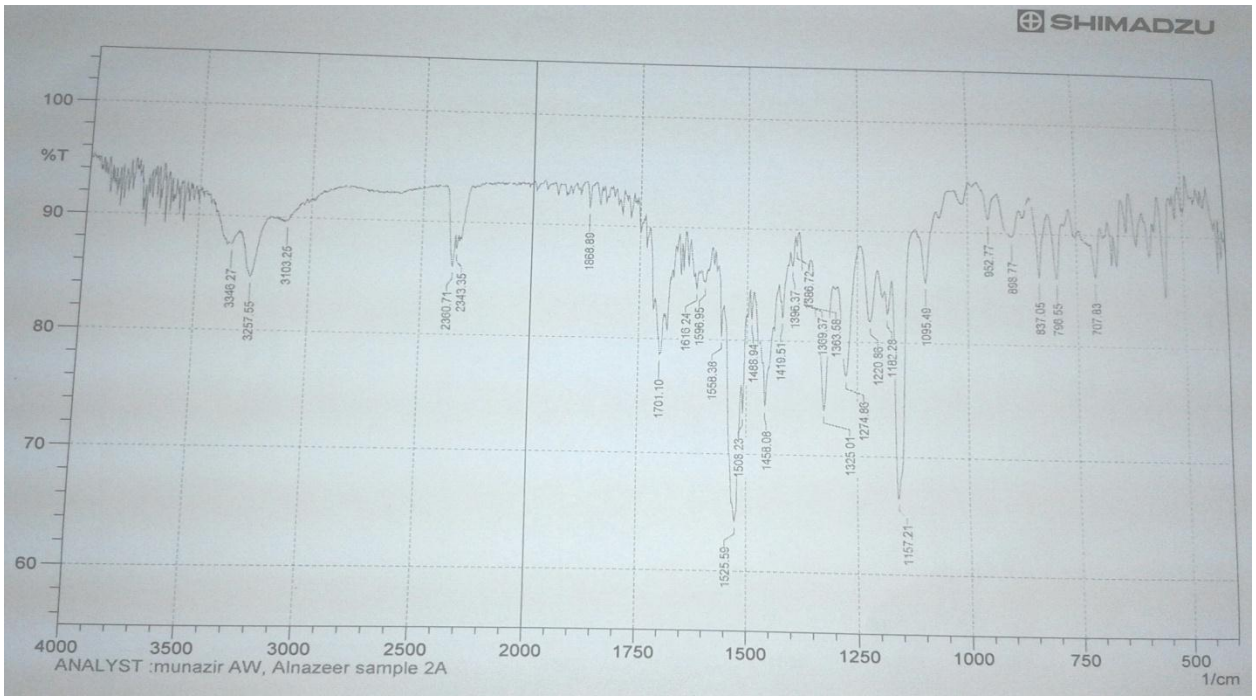

Figure (XXVII) IR spectrum of 4-((2-hydroxy-4-methylquinolin-3-yl)diazenyl) benzene-1-sulphonamide

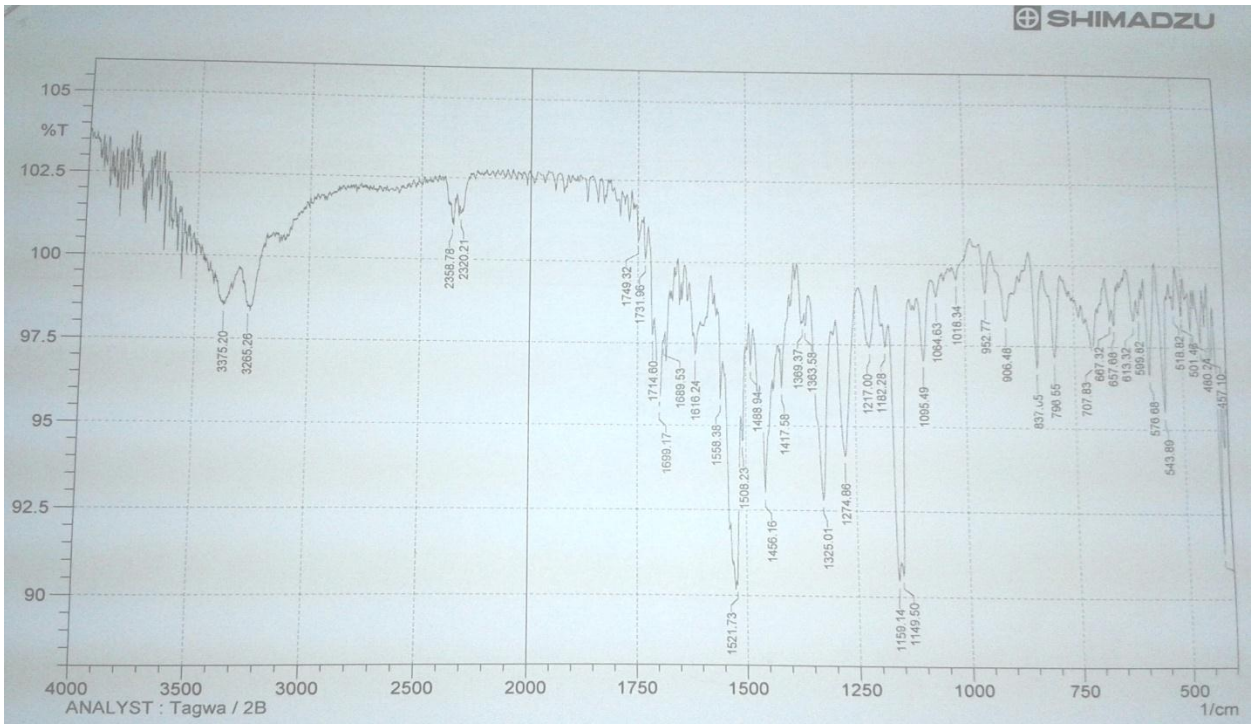

Figure (XXVIII) IR spectrum of 2-hydroxy-4-methyl-3-(4-sulphamoylphenyl) diazenyl quinoline-6-sulphonamides