بسم الله الرحمن الرحيم

SUDAN UNIVERSITY OF SCIENCE AND

TECHNOLGYCOLLEGE OF GRADUATESTUDIES

PREPARATIONOFSOME2-AMINOISOXAZOLYL-*p*-QUINONES DERIVATIVES

تحضير بعض مشتقات ٢-امينوايزواوكسازوليل-براكينون

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(B.Ed Chemistry and Biology, Higher Diploma chemistry,

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A Thesis Submitted for the Fulfillment of the Requirements of the Degree of Ph.D. in Chemistry

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Dedication

To the soul of my father,

To My mother,

My wife, My children,

My brothers and my sisters

Acknowledgements

Thank Alla almighty who guided and helping me to present this work.

I would like to express my deepest thanks and appreciation to Prof .Dr, Ahmed Elsadig Mohammed Saeed for his endless guidance and support. His advices, useful suggestions and encouragement enabled me to carry out my Ph.D. study.His continuous efforts in my career will never be forgotten.

Iwould like to thank teaching and non-teaching staff members of chemistry department in Sudan University of Science and Technology,

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Words are inadequate to thank my most beloved friends and colleagues Dr. Rahma, Dr. Abubker. Raga and Entesar, who always with me.

Abstract

Quinone derivatives are important compounds as they are widely distributed in nature and associated with abroad range of biological activities. Inthis work synthesis of*p*-quinone derivativescontiningα,*β*-unsaturated carbonylor isoxazoleunit was accomplished. Further,intermediate six α,*β*-unsaturated carbonyl compounds, beside six isoxazole derivatives were prepared.*P*-aminoacetamidobezene-suphanamido–p-acetophenone was reacted with some aldehydes (benzealdehyde,salicyaldehyde, anisalaldehyde, furfuraldehyde, acetaldehyde, cinnamaldehyde) in basic medium to furnish the corresponding α,*β*-unsaturated carbonyl derivatives by Clasin–Schemit reaction. The prepared α,*β*-unsaturated carbonyls weretreated with hydroxylamine hydrochloride giving isoxazolesin a cyclization reaction. Hydrolysis of the acetamidoisoxazole and α,*β*-unsaturated carbonyl compounds in hydrochloric acid and ethanol yield the corresponding amino derivatives. Quinone derivatives were prepared by the reaction of amino compounds of α,*β*-unsaturated carbonyls andaminoisoxazoles with different *p*-quinones (1,4-benzoquinoe, 1,4-naphthaquinone, 2-methyl-1,4-naphthaqunone)in a conjugate addition reaction .

The reaction steps and the purity of the products werechecked by using thin layer chromatography (TLC). The chemical structure ofintermediate and final compounds were characterized and confirmed bymeasuring their melting points, FT-IR spectroscopy,UV-Vis and ^{1}H-NMR. The retrosnythetic analysis of the target compounds was discussed in chapter three together with suitable mechanism. The spectral data were discussed in the same chapter.

Some of the prepared compounds showed significant activity at the level of 10 µg/µl against some bacteria and fungi.

الخلاصه

تخليق بعض مشتقات الكينونات مهمة لصناعة الأدويه وبعض المواد العلميه،ونظرا لتطبيقاته الكثيرة واستخداماتها في الأنشطه البيولوجيه. حضرت في هذه الدراسة سلسلة من مشتقات الكينونات بطريقتين اولا تفاعل الكينونات مع مجموعات الكربونيل الغير مشبعه المحضرة من ستهانواع من الدهيدات (بنزالدهيد، ساليسالدهيد، انسيلدهيد فيوفرالداهيد، سينمالهيد، الاسيتالدهيد) في وسط قاعدي بثلاث خطوات. والطريقة الثانيه تفاعل الكينونات مع الأيزواكزولات المحضرة من تكثيف مجموعات الكربونيل الغير مشبعه مع هيدرواكسيل امين هيدروكلوريك في تفاعل حلقي. وبعض اجراء عمليه التحلل المائي لجميع مشتقات الايزواكزولات ومجموعات الكربونيل الغير مشبعه التي المحتوي علي مجموعة الاستواميد.مشتقات الكينونات حضرت من تفاعل ثلاث انواع من الكينون (١و٤ – بنزاكينون، ١ ،٤-نفثاكينون، ٢- مثيل ١، ٤- نفثاكينون) مع مجموعات الايزوكزازول الاميني ومجموعات الكربيونيل الغير مشبعه الاميني في تفاعلات الاضافه الترافقه.خطوات التفاعل ونقاء المركبات المحضرة تم فحصها بإستخدام كرماتغرافيا الطبقه الرقيقه، المركبات النهائيه والوسطيه تم تحديد وزنها النسبى و قياس درجة انصهارها، مع دراسة التحاليل الطيفيه بإستخدام الأجهزه المطيافيه الآتيه، طيف الأشعهفوق البنفسجيه وطيف الأشعة تحت الحمراء والرنين النووي المغنطيسى وطيف الكتله .كما تم دراسه النشاط البيولوجي لبعض المركبات النهائيهضد بعض انواع البكتريا والفطريات في مستوي تركيز ١٠ميكروغرام/ميكرو لتر.

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Chapter One

Introduction

1. Introduction

1.1 Quinones

Quinone is a class of organic compounds that are formally derived from **aromatic compounds such as benzene or naphthalene by conversion of an even** number of –CH= groups into C=O groups with any necessary rearrangement of double bonds, resulting in a fully conjugated cyclic dione structure.(Nic*etal,* 2006). The class includes some heterocyclic compounds.The prototypical member of the class is 1,4-benzoquinone or cyclohexadienedione, often called simply quinone (thus the name of the class). Other important examples are 1,2-benzoquinone (*ortho*-quinone), 1,4-naphthoquinone and 9,10-anthraquinone.

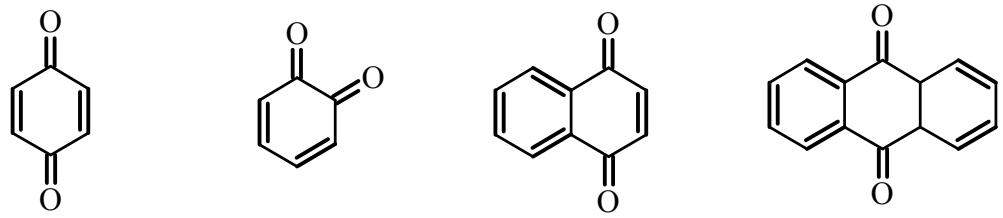


Figure 1.1 Chemical structure of some simple quinones

Quinones are a large class of compounds endowed with rich and fascinating chemistry (Silva *etal*, 2009). 1,4-Benzoquinone or *p*-benzoquinone (Patai and Rappaport,1988) is the basic structure of quinonoid compounds.They are widely distributed in the natural world,being found in bacteria, plants and arthropods and hence quinones are ubiquitous to living systems. Coordination chemistry of quinones is also quite rich from the perspective of designing magnetic materials (Hasegawa *etal*, 2000)and understanding photophysical properties.The studies of quinonoid compounds have focused on a broad

spectrum of topics occurrence in nature, syntheses, (Owton,1999) cycloaddition reactions, photochemistry and pulse radiolysis,computational chemistry, etc.(Kuznetsov,2006).The copiousness of articles describing the aforementioned multi-functional aspects serves as a grand testimonial to the contemporary interest in quinone chemistry. Hence a comprehensive review has been carried out to explore various scientific reports on 1,4-benzoquinones covering their chemical and biological significance.

1.2:- Nomenclature of Quinones:

Quinones are commonly named with a prefix that indicates the parent aromatic hydrocarbon ("benzo-" for benzene, "naphtho-" for naphthalene, "anthra-" for anthracene, etc.) and the "-quinone" suffix. Infix multipliers "-di-", "-tri-", "-tetra-" (etc.) are used when there are 4, 6, 8 (etc.) carbonyls. The position of the carbonyl groups can be indicated before the prefix (as in "1,4,5,8-naphthodiquinone") or after it ("anthra-1,4-quinone").

1.3 Preparation of quinone ring system

Quinones are an important class of compounds, which serve as valuable building blocks in synthesis and are key moieties in the synthesis of biologically active compounds. The immense interest on quinone chemistry has been observed from the middle of 19^{th} century. The most common quinone, benzoquinone was the first synthesized quinone in the late 1830's in Liebig's laboratory as a result of the oxidation of quinic acid with manganese dioxide and sulfuric acid.(Fieser and Fieser, 1956). This reaction involves dehydration, decarboxylation and oxidation.

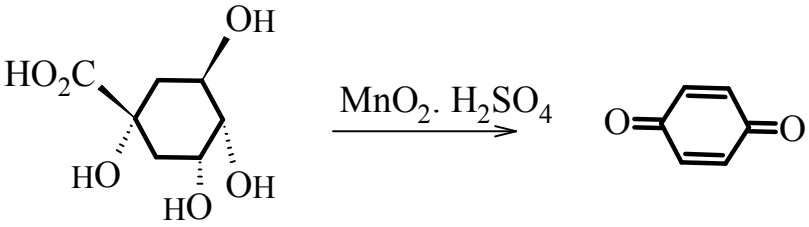


Figure 1.2:First syntheis of 1.4-benzoquinone

1,4-Benzoquinone is prepared by oxidation of diisopropylbenzene via reaction related to the Hock rearrangement:

$C_6H_4(CHMe_2)_2 + 3O_2 \rightarrow C_6H_4O_2 + 2\ OCMe_2 + H_2O$

The reaction proceeds via the bis(hydroperoxide). Acetone is a co product.(Underwood and Walsh;1936)

Another major process involves the direct hydroxylation of phenol by acidic hydrogen peroxide:

$C_6H_5OH + H_2O_2 \rightarrow C_6H_4(OH)_2 + H_2O$

Both hydroquinone and catecholare produced. Subsequent oxidation of the hydroquinone gives the quinone (Gerhard;2000)

Oxidation of phenols to quinones by molecular oxygen catalyzed by a mixture of the cobalt and manganese salts of *p*-amino benzoic acid supported on silica gel is another heterogeneous catalytic method (Hashemi and Ahmadibeni, 1998). 30% aqueous hydrogen peroxide, in the presence of cobalt(II) acetate and manganese(II) acetate serves as an oxidant for a variety of phenols , figure 1.3.(Mostaghim and Ahmadibeni;2003).

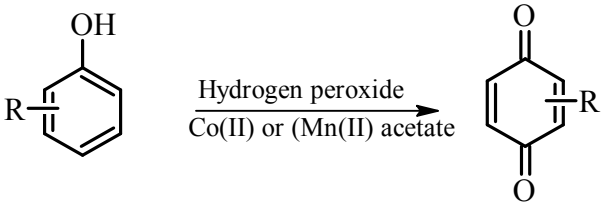


Figure 1.3: Oxidation of phenol by cobalt

Reaction of Sodium perborate and wet Montmorillonite K10 with yielded benzooquinone (Hashemi *et al*., 2005).

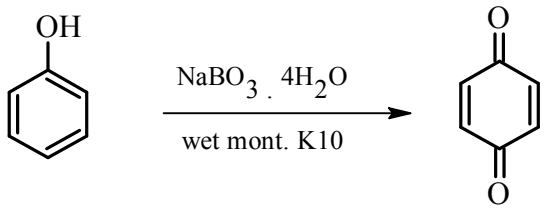
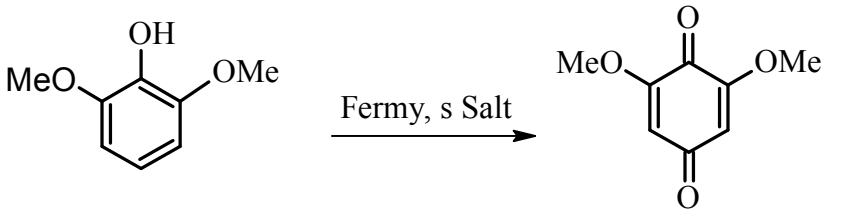


Figure 1.4:Oxidation of phenol by sodium perborate

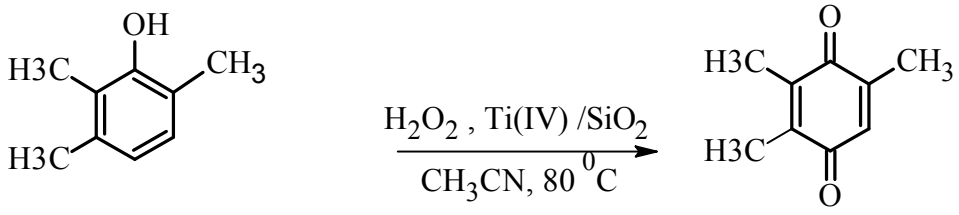
Conversion of 2,6-dimethoxy phenol in to 2,6-dimethoxy quinones by using fremy's salt, required higher reaction time and tedious workup procedure.(Sato *et al*, 1984).



2,6 Dimethoxy phenol 2,6 Dimethoxy quinon

Fiqure 1.5: Conversion of quinone with Fremy salt

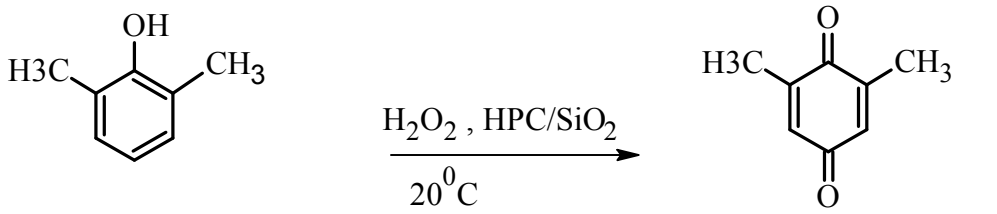
2,3,6-trimethylphenol used as a precursor in the synthesis of vitamin E (Kozhevnikov *et al*., 1995; Kholdeeva *et al*., 2002) is oxidized to 2,3,6-trimethyl-1,4-benzoquinone molecular oxygen, hydrogen peroxide or t-butyl hydroperoxide are being used as common oxygen sources and different catalytic metallophthalocyanins, copper hydroxyl phosphate, copper(II)chloride and titanium silicate were reported for this oxidation. (Sorokin *et al*, 2001; Xiao *et al*, 2002; Sun *et al*, 2005, Xiao *et al,* 2004).figure 1.6



2,3,6 Trimethoxy phenol 2,3,6 Trimethoxy quinone

Figure 1.6: Oxidation using titanium silicate

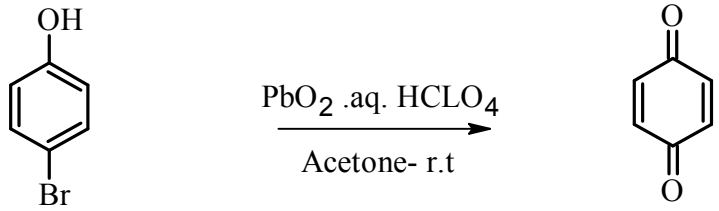
Caceras and co-workers undertook a clean liquid phase oxidation of 2,6–dimethylphenol to 2,6-dimethyl-1,4-benzoquinones using hydrogen peroxide as oxidant and keggin type heteropoly compounds of vanadium and molybdenum supported on silica (HPC/SiO_2) as catalysts figure 1.7 (Caceres *et al*,2008).



2,6 Dimethoxy phenol 2,6 Dimethoxy quinone

Figure 1.7: Hydrogen peroxide as oxidant

Debromination of 4-bromophenol result in quinone formation with perchloric acid in presence of lead oxide at room temperature in acetone solvent (Khan *et al*, 2010)figture 1.8

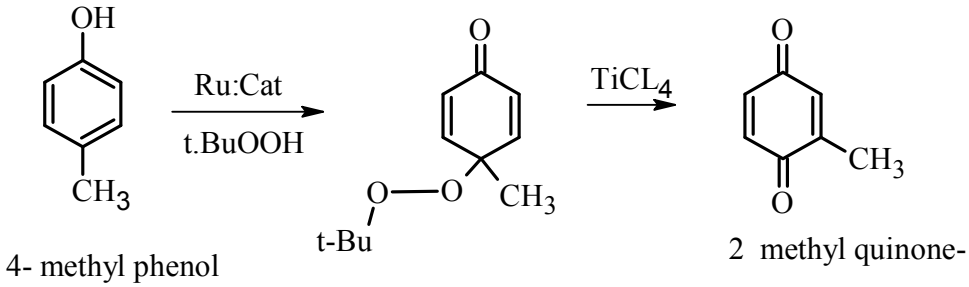


P-bromophenol P- benzoquinone

Figure 1.8: Debromination with perchloric acid

Ruthenium catalyzed oxidation of 4-substituted phenols with t-butyl hydroperoxide in ethyl acetate or benzene followed by treatment with titanium

tetrachloride result in formation of 2-substituted benzoquinone (Murahashi *et al*, 1996).Figure 1.9



4- methyl phenol

2 methyl quinone-

Figure 1.9: Oxidation with butyl hydroperoxide

There are very few methods that are available for the synthesis of quinone compounds using aniline or N-substituted aniline as starting material in the literature. This could be activated by HIO_3 in presence of Mont.k10, and Metal oxides and H_2O_2. (Maiti *et al*,2008)

It has long been known that quinone and substituted quinones may be prepared from aniline and other aryl amines by the action of manganese dioxide and dilute sulfuric acid, or by the action peratures in this range can be maintained only with the use of expensive refrigerating equipment. If the temperature is allowed to rise very far above the preferred range, side-reactions occur to a considerable extent and the yield of pure quinone is sharply reduced. The product is usually separated from the reaction mixture by steam distillation either at normal pressure or at reduced pressure after completion of the reaction.(Jon and Thomas, 1912)

Oxidative degradation of benzamide derivatives to p-quinines could be activated by using fremy's salt with benzamide(See *et al,* 1987).

This is conversion of N-aryl sulphonamides to p-benzoquinone (Wadsworth *et al,* 1989).

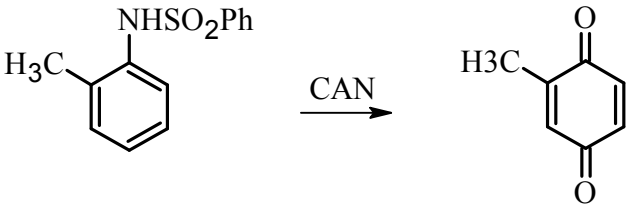


Figure 1.10:Conversion of N-arylsulphonamide

oxone/Iodobenzene mediated by (Zhdankin *et al.*, 2010).More recently reported Oxone and Iodobenzenereaction system for the Synthesis of 1,4-benzoquinone by Hofmann rearrangement

1.4 Reactions of quinones:-

Quinones used as a hydrogen acceptor and oxidant in organic synthesis.(Yang and Sheng; 2004). 1,4-Benzoquinone serves as a dehydrogenation reagent. It is also used as a dienophile in Diels Alderreactions(Oda; *etal*;1996).

1.4.1 Thiele reaction

Benzoquinone reacts with acetic anhydride and sulfuric acid to give the triacetate of hydroxyquinol. This reaction is called the Thielereaction after Johannes Thiele, who first described it in 1898,(Almeida and Correia;1999).

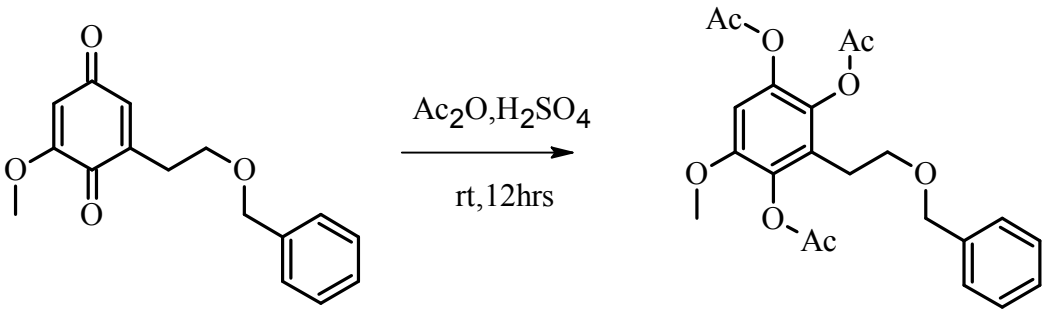


Figure 1.11: Benzoquinone reacts with acetic anhydride

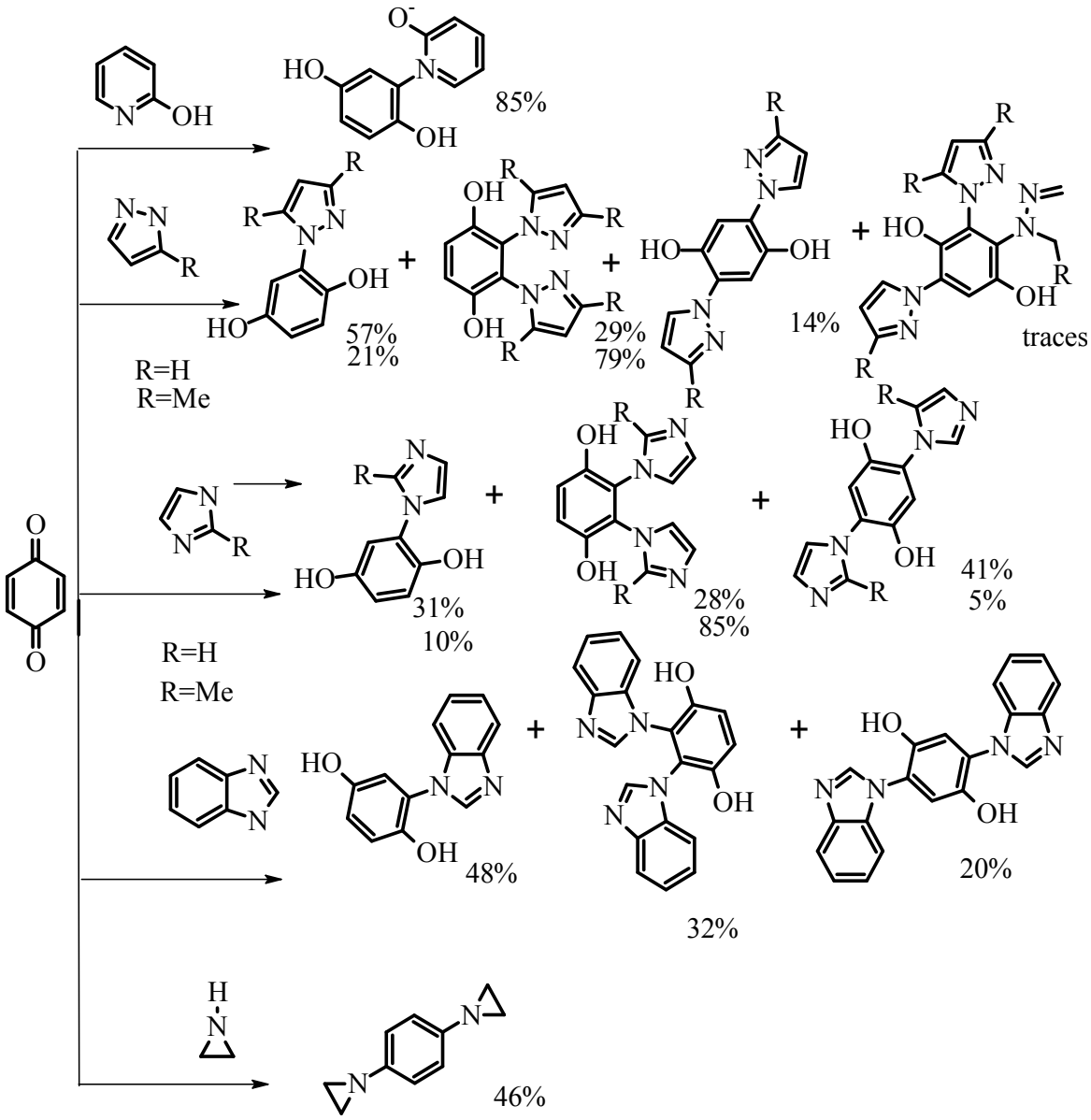
Benzoquinone is also used to suppress double-bond migration during olefin metathesis reactions.

1.4.2 Reactions of *p*-quinone with *S*-Nucleophiles

Conjugate addition of nitrogen, sulfur, oxygen and carbon nucleophiles to *p*-benzoquinone give initially 2-substituted mono-adducts. Depending on the character of the nucleophile, the oxidation potential of the mono-adduct, and possible reversible formation of a charge-transfer complex, the initially formed mono adduct may undergo further nucleophilic addition to give 2,3-, 2,5-and/or 2,6-disubstituted bis-adducts. These bis-adducts can in turn react with a third nucleophile molecule to afford the 2,3,5-trisubstituted adduct. Finally the tris-adduct may react with yet one more equivalent of nucleophile to give a 2,3,5,6-tetrasubstituted *p*-benzoquinone (Ballesteros, *et al. 1992).*

1.4.2.1 Nitrogen nucleophiles:

Conjugate additions of heterocyclic nitrogen nucleophiles including pyridines (Schmidt *et al*, 1990),imidazole and benzimidazole.(Escolastico *et al*, 1994)to *p*-benzoquinones give 2-monosubstituted, 2,3- and 2,5-disubstituted and 2,3,5-trisubstituted hydroquinones figure 1.12. However, conjugate additions of secondary amines to *p*-benzoquinone are reported to produce only 2,5-disubstituted hydroquinones.(Marxer,1955).



(Marxer, A. 1955)

Figure 1.12: Conjugate additions of secondary amides

A group of 19 compounds of the type 2,5-diamino-3,6-dibromo-1,4-benzoquinones were prepared and spectroscopically elucidated through IR,UV-VIS, NMR and MS. Coupling of the intermediate 2,3,5,6-tetra bromo-benzoquinone with the required aryl amines furnished the required compounds. The prepared compounds were found to possess antimicrobial activities when tested against four standardbacterial organisms and two standard fungal organisms.(Saeed andOmer;2009)

1.4.2.2Sulfur nucleophiles

Conjugate addition of one molecule of various sulfur nucleophiles to *p*-benzoquinones are well known figure 1.13,(Ling *et al*, 2002).

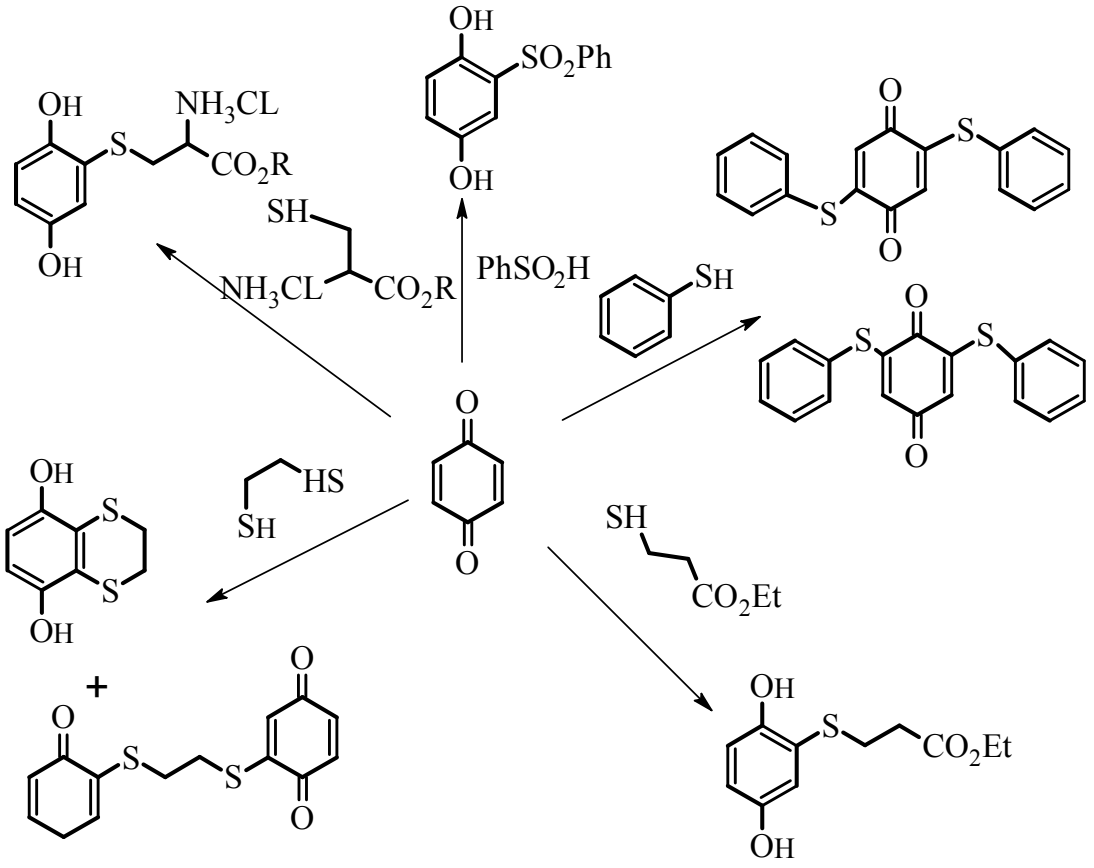


Figure 1.13: Conjugate addition of sulfur

However, double conjugate additions of sulfur nucleophiles to *p*-benzoquinones are rare and thiophenol and *p*-benzoquinone gave both 2,5- and 2,6-bis(phenylthio)benzoquinone and their structures were established by X-ray crystallography (Becker *et al,* 1988).

1.4.2.3Carbon nucleophiles:

Conjugate addition of carbon nucleophiles to *p*-benzoquinones gave 2-monosubstituted, 2,5- and 2,6-disubstituted products similar to thiols figure 1.13, (Yadav *etal*, 2003). Reaction of *p*-benzoquinone with indole in the presence of either 2 mol% bismuth triflate or 5 mol% indium(III) bromide in

acetonitrile at room temperature gave 2,5-bis(3-indolyl)-*p*-hydroquinone.Reaction of *p*-benzoquinone with palladium acetate in acetic acid containing arenes such as benzene, *p*-xylene, and *p*-dichlorobenzene at reflux temperature gave the corresponding 2-aryl-, 2,5-diaryl- and 2,6-diaryl-1,4-benzoquinones(Itahara, 1985).Reaction of *p*-benzoquinone with 4-hydroxycoumarin in aqueous acetic acid gave 3-(1,4-benzoquinonyl)-4-hydroxycoumarin which reacted further with pyridine to give a unique 2,3-disubstituted zwitterionic adduct , figure 1.13, (Jurd,1980; Zhang *etal,* 2004)

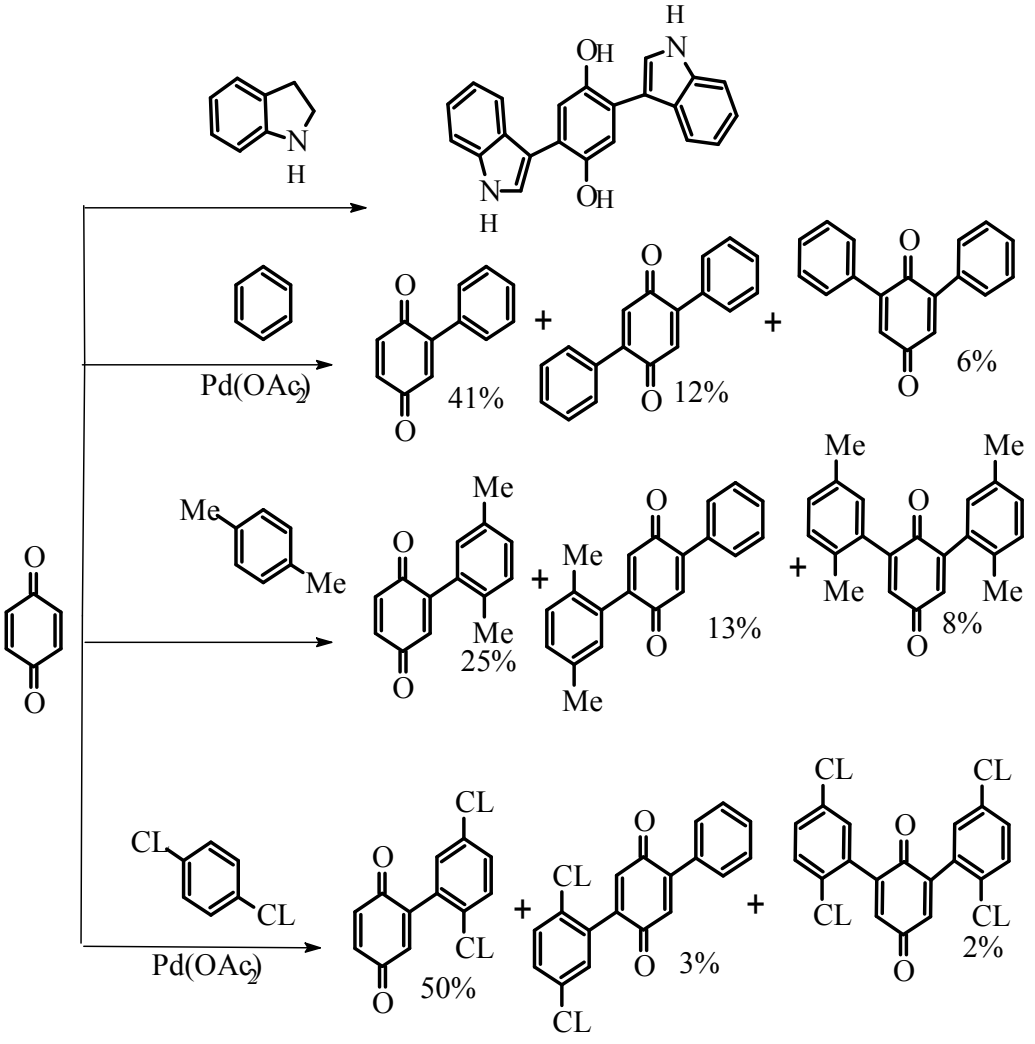


Figure 1.14: Conjugate addition of carbon nucleophiles

Similarly reaction of 3-(1,4-benzoquinonyl)-4-hydroxycoumarin with 4-hydroxycoumarin gave selectively a 2,3-disubstituted quinone product.(Zhang. *et al*; 2006)

1.4.2.4Oxygen nucleophiles:

Conjugate addition of oxygen nucleophiles such as ethanol and phenol with *p*-benzoquinone or activated quinones gave only 2,5-disubstituted products in addition to the 2-monosubstituted adducts figure 1.14, (Musso, and Angew,1963)

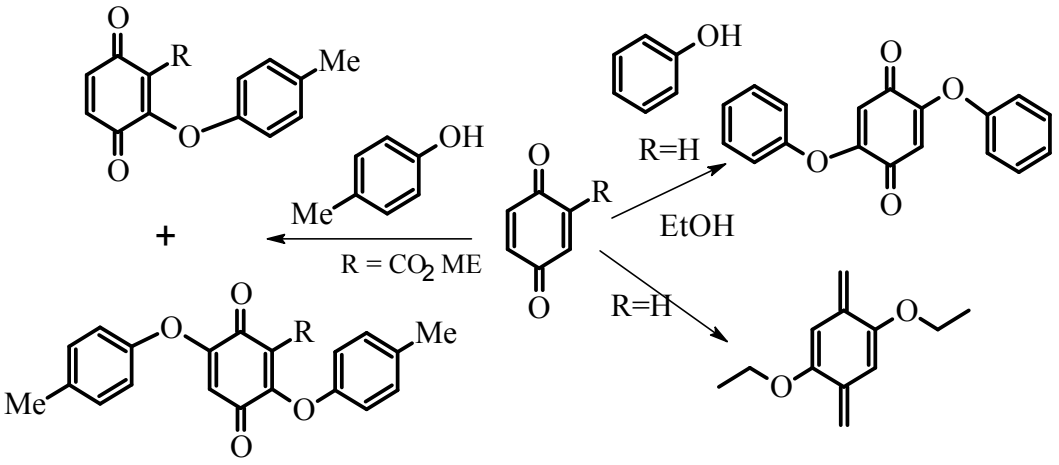


Figure 1.15: Conjugate addition of oxygen nucleophiles

1.4.3 Pulse Radiolytic Studies on 1,4-Benzoquinones

Pulse radiolysis is a method of studying fast chemical reactions in which a sample is subjected to a pulse of ionizing radiation, and the products formed by the resulting reactions are studied stereospecifically. (Wishart *et al*, 2010) Pulse radiolysis technique has been used extensively by several groups to study the electron transfer processes involving quinones. (Pal *et al*,1993). Quinones participate in a range of biological redox processes owing to their efficiency in undergoing reduction. Predominantly, pulse radiolysis is an established

methodology for studying one-electron transfer processes in liquid media. (Wardman,1987).

1.4.4 Quinone Methides:-

Quinone methides are interesting compounds that have been proposed tobe intermediates in a large number of chemical and biological transformations.As in the case of quinones, these also can be classified as p-quinone methides,a-quinone methides and m-quinone methides.

The o-and p-quinone methides are believed to play an important role in avariety of biochemical transformations. They are known to be powerful electrophiles due to the asymmetry introduced by two electronically different substituents, carbonyl and methylidene, as shown in the resonance structures in Figure 1.3. However, m-quinone methides, for which several structures includingthe non-Kekule form may be envisioned, are less widely known.(5)

1.4.5 polyamine-quinone (PAQ) polymers

polyamine-benzoquinone polymers (PAQ) have been shown to adhere to metals with sufficient affinity todisplace water from a wet, rusty steel surface, to become non-wettable by water and resist most organic solvents after being cured chemically or thermally'(kaleem *etal*, 1987). They are also resistant to salt spray, autoclaving and can be easily after biofouling. They adhere onto ordinary paints and all paints except water-based latexes can bind to these coatings, the failure of the latter being due to their in ability to wet the polymer surface. Finally, they can be applied under water. Aromatic poly ether amines yield polymers that are scarcely soluble in even the most powerful solvents except DMSO, DMF and sulphuric acid, but absorb only about0.1% (w/w)

moisture, after being immersed in water for 72 h, rivalling processable polyimides currently used ininsulating electronic components (kaleem *etal,* 1989).The reaction between amines and benzoquinone occurs spontaneously, even below ambient temperature, and takes place, through 1,4- addition, as shown in Scheme 4.The first step during the reaction is the formation of a mono substituted hydroquinone which has to bereoxidized to monosubstituted quinone before the second substitution, again through 1,4- addition, can occur. Benzoquinone, which is present in the solution, can oxidize the monosubstituted hydroquinone because quinone oxidation potential is reduced by electron donating substituents. With diamino compounds one obtains linear polymers.

1.5 Biological activities of quinone

Quinones play pivotal role in biological functions including oxidative phosphorylation and electron transfer (Morton, 1965). Their role as electron transfer agents in primary metabolic processes like photosynthesis and respiration is vital to human life. A large number of chemical derivatives with 1,4-benzoquinone as the basic subunit exhibit prominent pharmacological applications such as antibiotic (Hartley and Reszka.1988) antitumor, (Gupta, 1994), antimalarial,(Silva *etal,* 2009) antineoplastic,(Lin and Sartorelli, 1975)anticoagulant and herbicidal (Dowd and Zheng, 1995) activity. (Gonzalez *et al,* 2005).Wide applications of quinones can also be found in the field of synthetic organic chemistry,**(**Molina**,** 2009**).**

1.6Aim and objectives

This work was aimed to synthesis some *p*–quinone derivatives containing groups like sulphonamides, chalcones, isoxazoles, which were playing an important role in pharmaceutical filed. The idea of synthesis based upon selecting certain synthetic strategic from suitable starting materiel.

The present work aimed at functionalization of sulphonilamido group with certain heterocyclic ring system. The present work test the ring forming reaction of hydroxyl amine with a highly substituted α ,β-unsaturated carbonyl derivatives bearing acetamido benzene sulphanilamido group.

One of aimes of this work is to make use of p–quinones as a carrier in one hand and as potentially reactive functionality in another hand and to couple then with either amino sulphonilamido α ,β-unsaturated carbonyl derivatives or with the corresponding isoxazole derivatives.

The project aimed to establish the structure of the prepared compounds with spectroscopic means through a detailed description of the infrared and nuclear magnetic resonance spectroscopic behavior of the prepared compounds.

Examination of suitable reaction condition at any stage of the multistep synthesis of these compounds is of prime importance and from one of the objectives in this work.

Chapter Two

Materials & methods

2.1 Materials:

2.1.1. Common reagents

Chlorosulphonic acid and hydrochloric acid, were obtained from CDH-laboratory Reagent. Sodium hydroxide hydroxylamine hydrochloride, sodium acetate, sodium acetate, were obtained from Nice Laboratory reagent India.

2.1.2. Chemicals:

Acetanilde, p-aminoacetaphenone, benzealdehyde, salicyaldhyde, anisaldehyde, furfuraldehyde, acetaldehyde, N,N-dimethylbenzealdehyde, cinaldehyde were obtained form Loba-cheme-pvt.Ltd. India. Lawsone (2-hydroxy-1,4-naphthoquinone), was obtained from Alpha – Chemika – India. Menadione (2-methyl-1.4-naphthoquinone), was obtained from Techno-Pharmchem –India. 1,4-naphthoquinone, 1,4-benzoquinone,

2.1.3. Solvents:

Ethanol absolute was obtained from SHAM,LAB, -Syria, glacial acetic acids, acetone, ethyl acetate, chloroform, and methanol, were obtained form Alphachemika-India.

2.1.4 Test Microorganisms:

Escherichia coli (ATCC 25922), *Staphylococcus aureus* (ATCC 292113), *Pseudomonas aeruginosa* (ATCC 29336) *Bacillus subtilis* (ATCC 6633), and the yeast *Candida albicans* (ATCC 10231)

2.1.5.Thin layer chromatography(TLC):

TLC was carried out using precoated plates silica gel GF_{254} for TLC LR, s.d-fine Cheme Limited India (stationary phase)

2.2 Instruments:

2.2.1. **Infrared spectroscopy (IR):**

Infrared spectra were recorded on FT-IR spectrophotometer, 1000 (USA) Perkin Elmer (USA) as KBr disc.

2.2.2.Ultra Violet/visiblespectroscopy (UV-Vis)

UV spectra were recorded on a UV – VIS 1800 spectrophotometer, double beam wavelength 190 – 1100 nm. Shimadzu, Japan,

2.2.3. **Nuclear magnetic resonance (NMR)**

NMR spectra was recorded on UNITY plus-500 spectrophotometers instrument (VARIAN Inc. USA) using DeuteratedAcetone-D6 as a solvent.

2.2.4. General instruments

Electronic balance A & D – GR – 120, Japan

Magnetic hotplate stirrer R000100726 from Bibby Sterilin LTD, UK.

Water bath R000102811 from Bibby Sterilin LTD, UK.

Melting point apparatus were determined using melting point apparatus from Bibby Sterilin, UK.

2.2.5. Glassware

All glassware were Pyrex type

2.3. Synthetic methods:

2.3.1 Synthesis of N-(4-(N-(4-acetylphenyl)sulfamoyl)phenyl)acetamide (I)

A mixture of acetanilide (20g,0.148mole) and chlorosuphonic acid (50ml,90g,0.077mole) were placed in a 50ml round bottom flask equipped with a reflux condenser,the reaction mixture was refluxed at the boiling range for 1 hour. The reaction mixture poured into ice-cold water with continuous stirring

and shaking .The precipitated product was washed with a little cold water, immediately transferred the product to the flask and mixed with p-aminoacetaphenone (8.8g,0.065 mole) and 65ml of sodium hydroxide (2M).

The reaction mixture was stirred for 2 hours at room temperature, filtered and acidified with hydrochloric acid to pH 5.5 the product was filtered and air dried. Y%60,mp 209-214.

2.3.2 Synthesis of p-acetamide α,β–unsaturated carbonyl derivatives(II, III, IV, V, VI, VII)

A mixture of 3.32g, 0.01 mole of compound (I), the required aldehydes (0.01mole), sodium hydroxide (0.02 mole in 10 ml water) and ethanol (15ml) in 150 ml round bottom flask were stirred for 24 hours at room temperature. The mixture was acidified by HCl acid. The precipitated product was filtered and air dried.Chemical and spectral data, table (2.1.1, 2.2.1,2.3.1)

2.3.3. Synthesis of N-(p-acetamide sulfamoyl)phenyl-4-isoxazoles derivatives(VIII, IX, X, XI, XII, XIII).

Mixture of hydroxylamine hydrochloride (0.069g, 0.001 mole), α,β-unsaturated carbonyl (0.001 mole) and sodium acetate (0.5 mole) in ethanol (10ml) in 150 ml round bottom flask equipped with reflux condenser was heated for 6 hours,evaporated and collected product, chemical and spectral data, tables (2.1.2, 2.2.2, 2.3.2)

2.3.4. Synthesis of p-amino- α,β -unsaturated carbonyl derivatives(XIV, XV, XVI, XVII, XVIII, XIX)

Mixture ofacetamidoα,β-unsaturated carbonyl(1g,), hydrocholoric acid 1:1 (10ml) and ethanol (10ml), in 150ml of round bottom flask equipped with a

reflux condenser was heated for 3 hours, filtered while hot, cool and adjusted the pH to 5. The precipitated product was filtered and air dried. Chemical and spectral data tables (2.1.3, 2.2.3, 2.3.3, 2.4.1, 2.5.1, 2.6.1)

2.3.5 Synthesis N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivatives(XXI, XXII, XXIII, XXIV, XXV, XXVI)

Mixture of acetamido isoxazoles (1g), hydrocholoric aicd 1:1 (10ml) and ethanol (10ml), in 150ml of round bottom flask equipped with reflux condenser was heated for 3 hours filtered while hot, cool and adjusted the pH to 5. The precipitated product was filtered and air dried. Chemical and spectral datatables (2.1.4, 2.2.2, 2.3.2, 2.4.4, 2.5.2, 2.6.2. 2.7.2)

2.3.6Synthesisof2-aminosulphanilamido-N^1-(α,β-unsaturated carbonyl)-1,4-quinone derivatives (XXVII, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, XXXIIII, XXXIV, XXXV, XXXVI, XXXVII, XXXVIII, XXXIX, XL, XLI, XLII, XLIII,)

A mixture of p-quinone, 0.002 mole in 3ml of 95% ethanol,3ml glacial acetic acid, were added to 0.001 mole of aminoα,β-unsaturated carbonyl in 2ml of 95% ethanol,2ml glacial acetic acid,1 ml of water and 0.1g sodium acetate, in 150 round bottom flask equipped with reflux condenser. The reaction mixture was heated and stirred for4 hours, poured into ice cold 25ml water and filtered the colored product.

2.3.7 Synthesis of 2-aminosulphanilamido-N^4-phenylisoxazolyl-1,4-quinone derivatives (XLIV, XLV, XLVI, XLVII, XLVIII, XLIX,L,LI,LII,LIII,LIV,LV,LVI,LVII,LVIII,LIX,LX,LXI,)

A mixture of quinones, 0.002 mole in 3ml of 95% ethanol,3ml glacial acetic acid were added to 0.001 mole of isoxazles in 2ml of 95% ethanol,2ml glacial

acetic acid,1 ml of water and 0.1g sodium acetate, in 150 round bottom flask equipped with reflux condenser. The reaction mixture was heated and stirred for4 hours, poured into ice cold 25 ml water and filtered the colored product.

2.3.8 Antimicrobial assay:

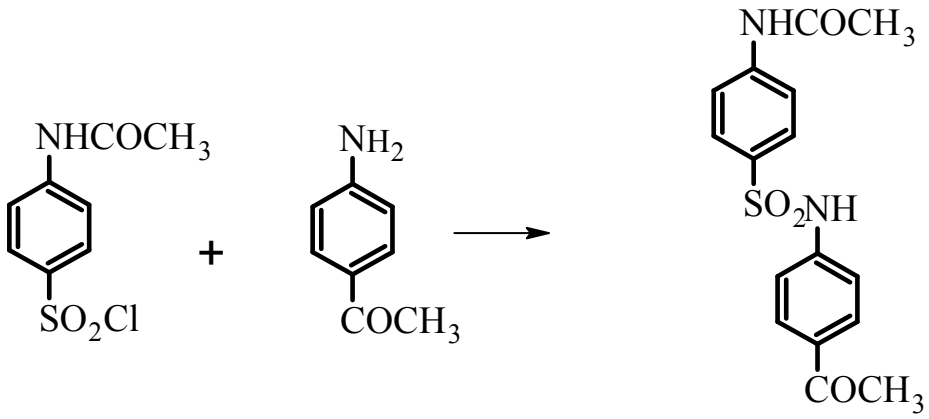
2.3.8.1 Antibacterial assay:

The method is performed according to CLSI methodology (1). Bacterial suspensions were obtained from overnight cultures in Nutrient broth (Scharlau microbiology company SPAIN), cultivated at 37°C for 24 h. The bacterial suspensions were adjusted to an inoculum size 10^8 cfu/mL for inoculation of the agar plates. Suspension of the tested bacteria (100 μLof10^8 cfu/mL) was spread onto solid media plates (Mueller Hinton agar Medium, Scharlau microbiology company SPAIN) Care was taken to ensure proper homogenization. A ditch was made in the plates with the help of a cork borer (8 mm). The test compound (10, 100, 200 µg/100 µl) was introduced aseptically into the well and the plates were incubated at 37°C for 18 h. After incubation at 37°C for 18 hours, the zone of inhibition around the ditch was measured by millimeter scale.

2.3.8.2 Antifungal Assay:

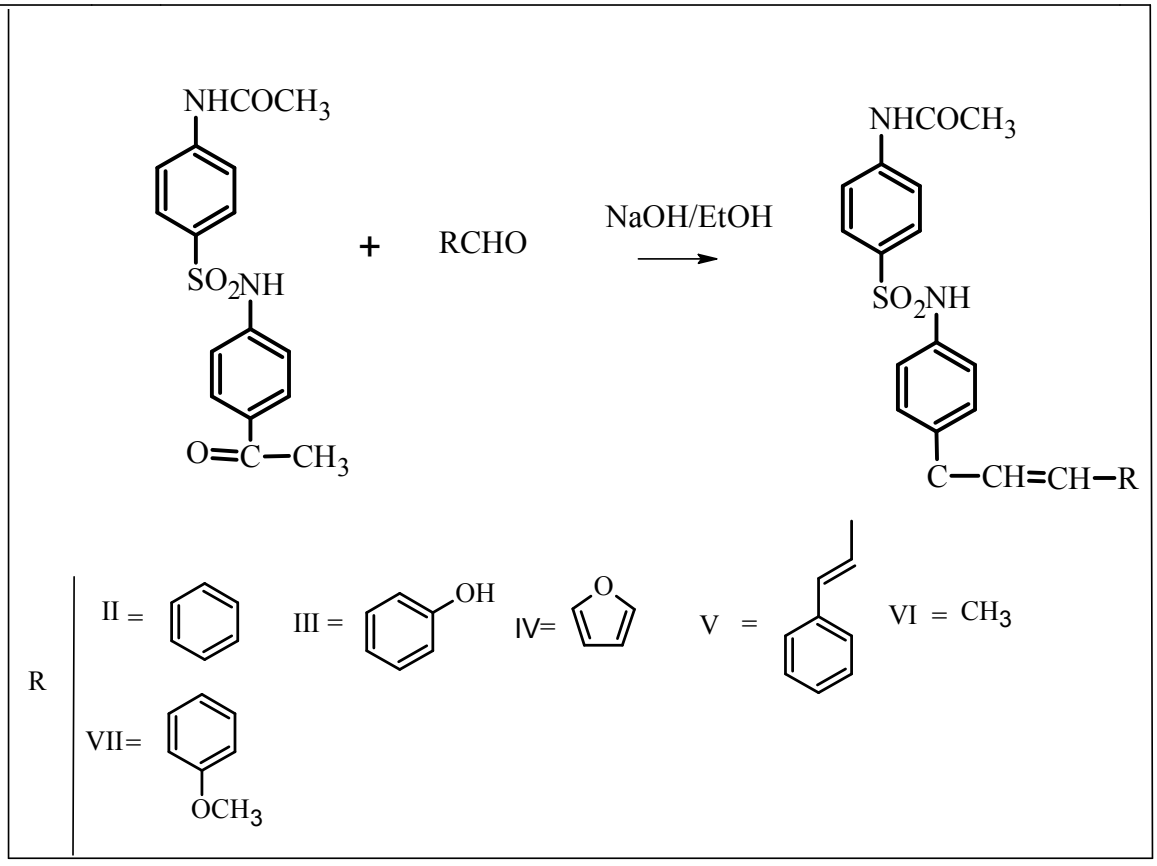
The antifungal activity was determined by Agar ditch diffusion method (2).

The procedure is similar to antibacterial assy. Fungal suspensions were obtained from 48 hours cultures in Sabouraud broth (Oxoid LTD. Basinstoke.company England). Suspension of the tested fungi was spread onto solid Sabouraud agar plates. These plates were incubated at 25 °C for 48 hours. The zone of inhibition around the ditch was measured by millimeter scale.

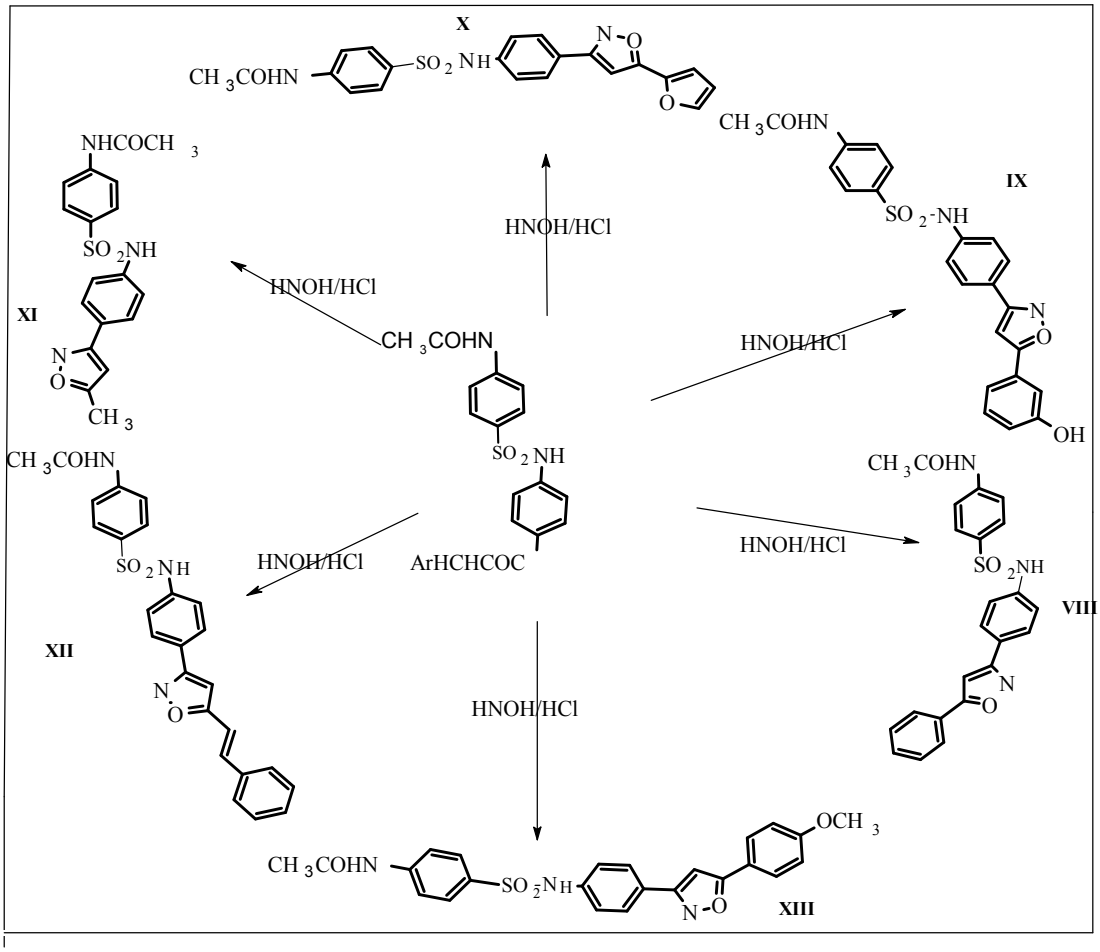


I

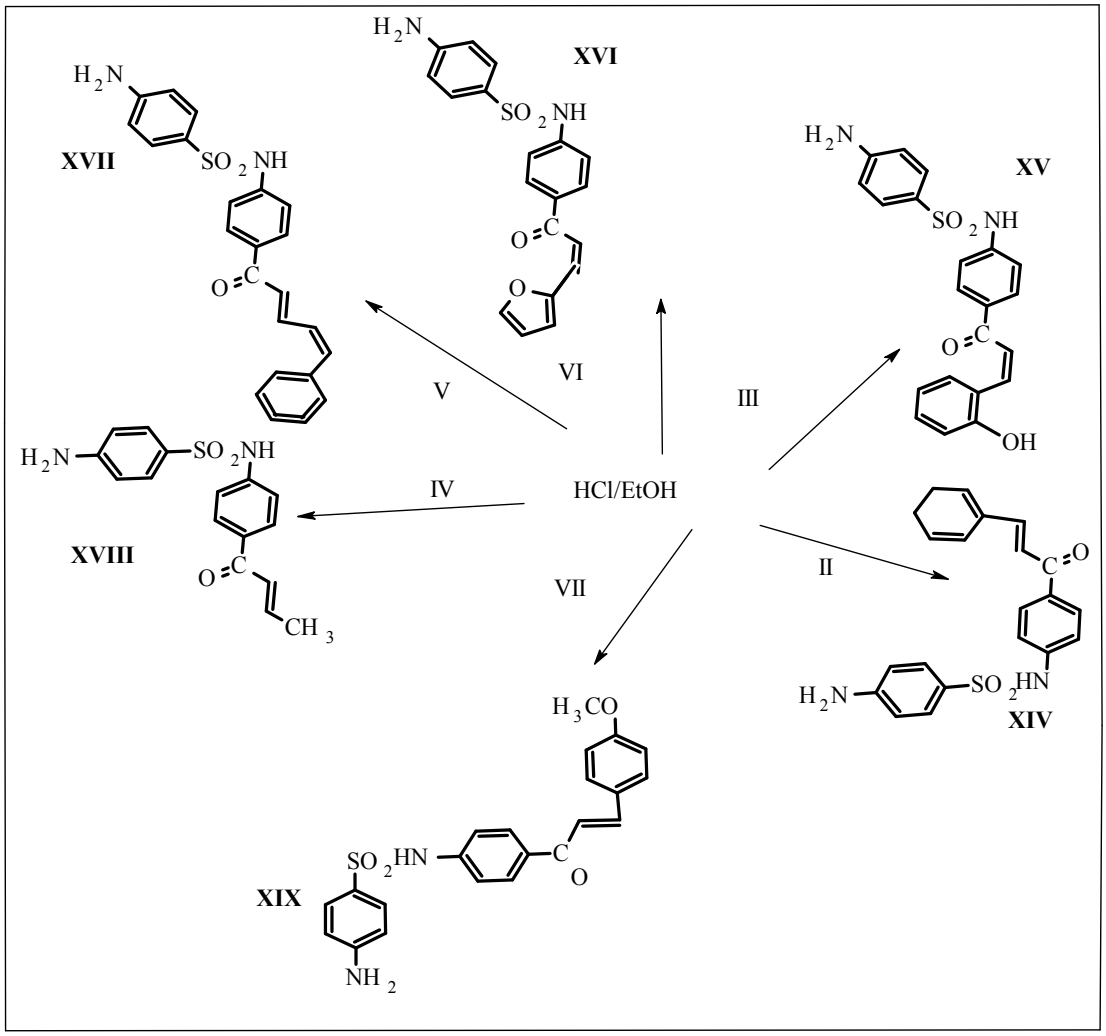
Scheme 2.1:SynthesisN-(4-(N-(4-acetylphenyl)sulfamoyl)phenyl)acetamide



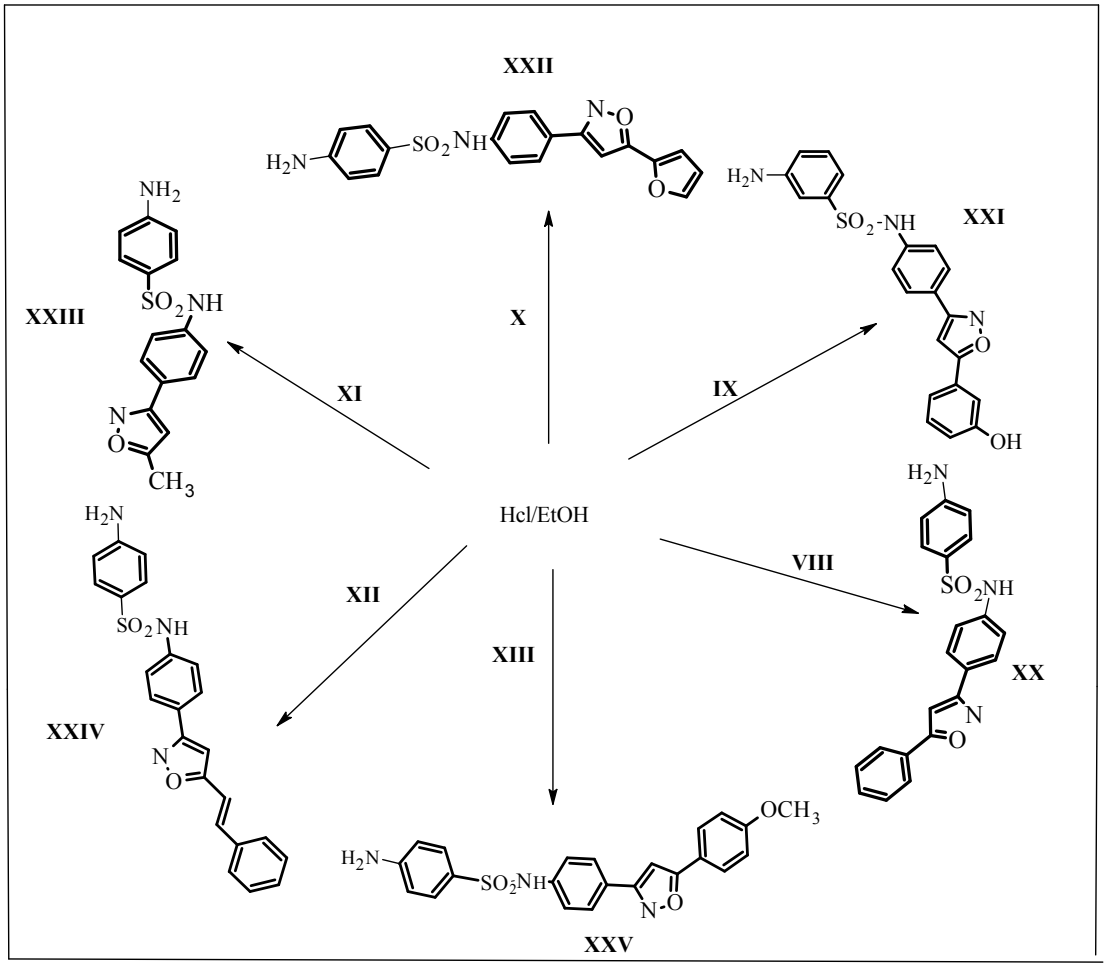
Scheme 2.2: Synthesis of p-acetamide α,β–unsaturated carbonyl derivatives



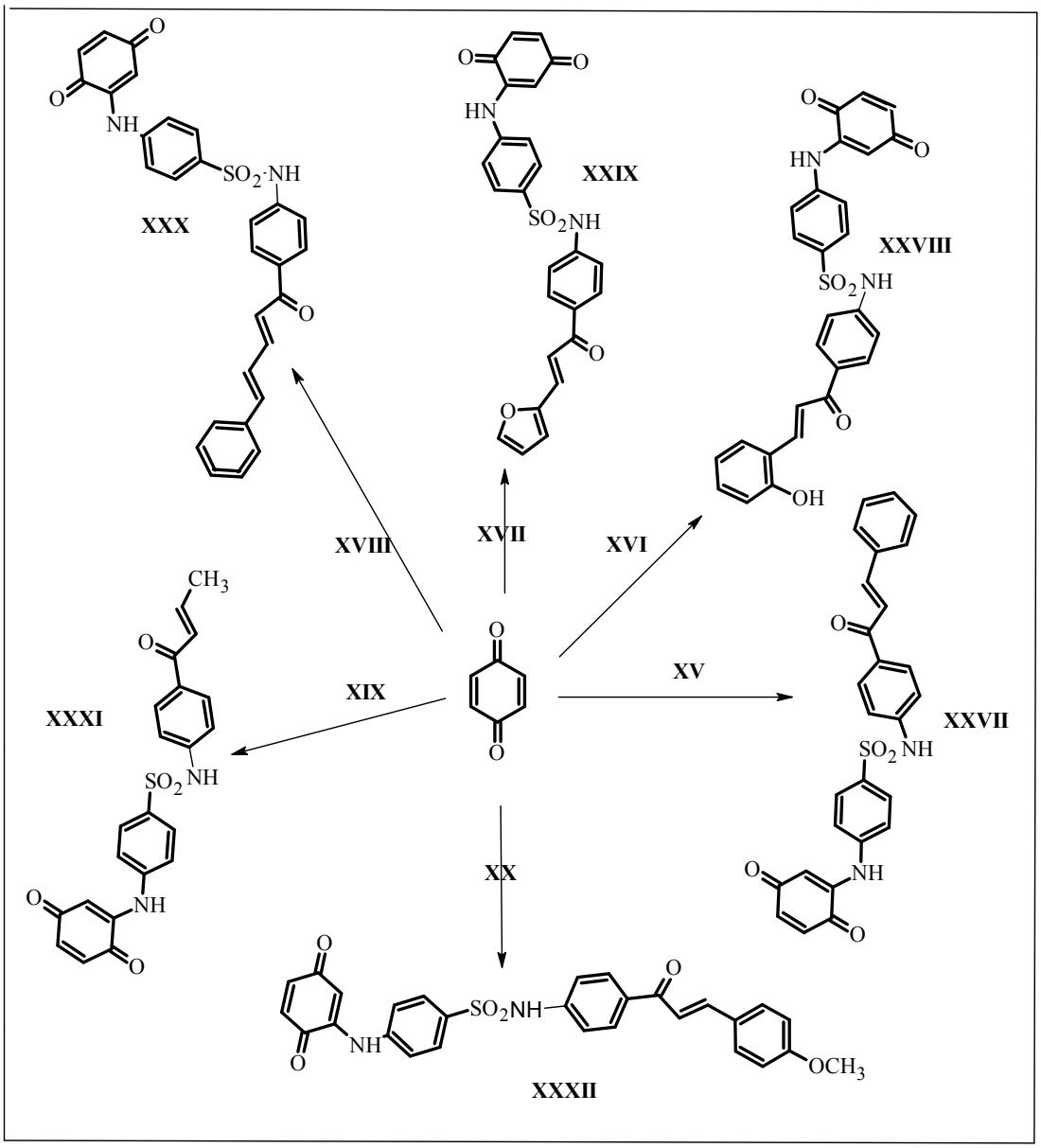
Scheme 2.3: Synthesis of N-(p-acetamide sulflamoyl)phenyl-4-isoxazoles derivatives



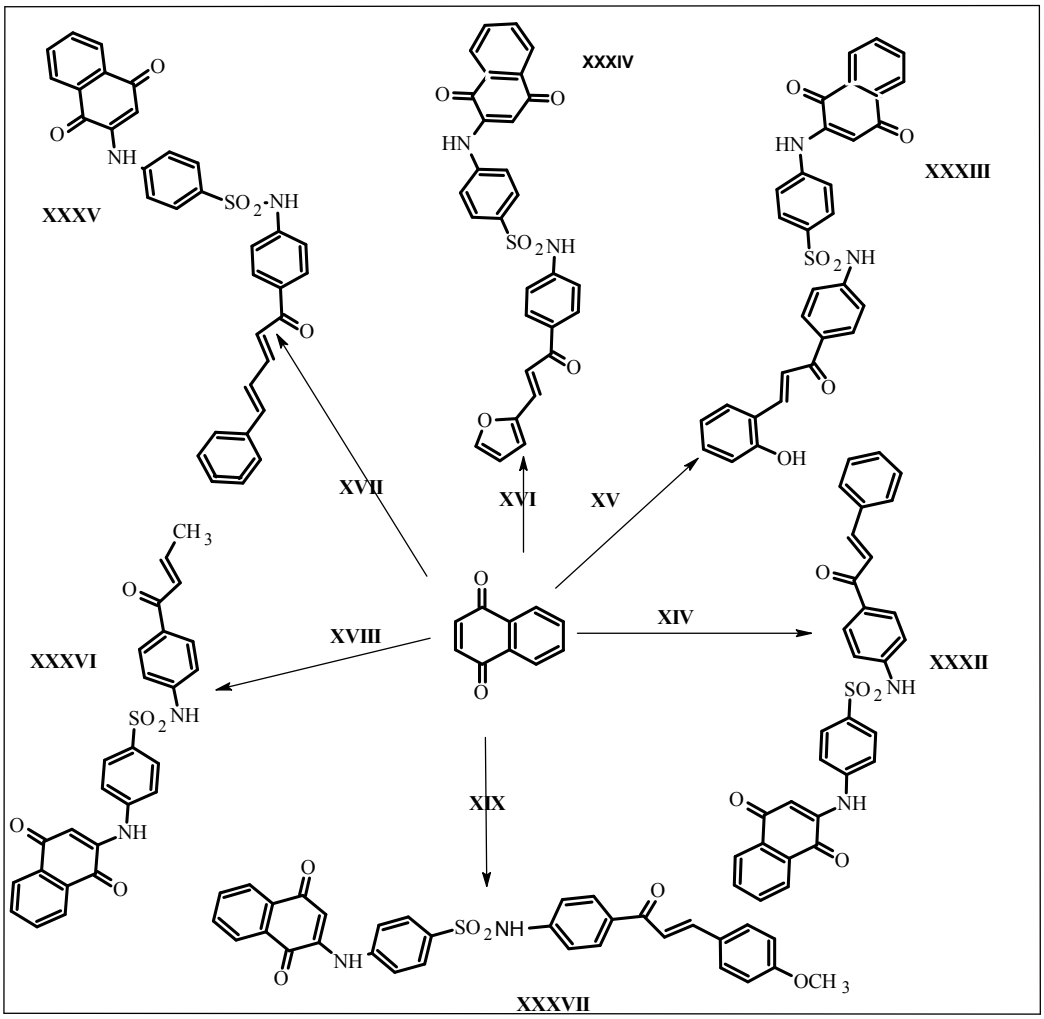
Scheme 2.4: Synthesis of p-amino-α,β-unsaturated carbonyl derivatives



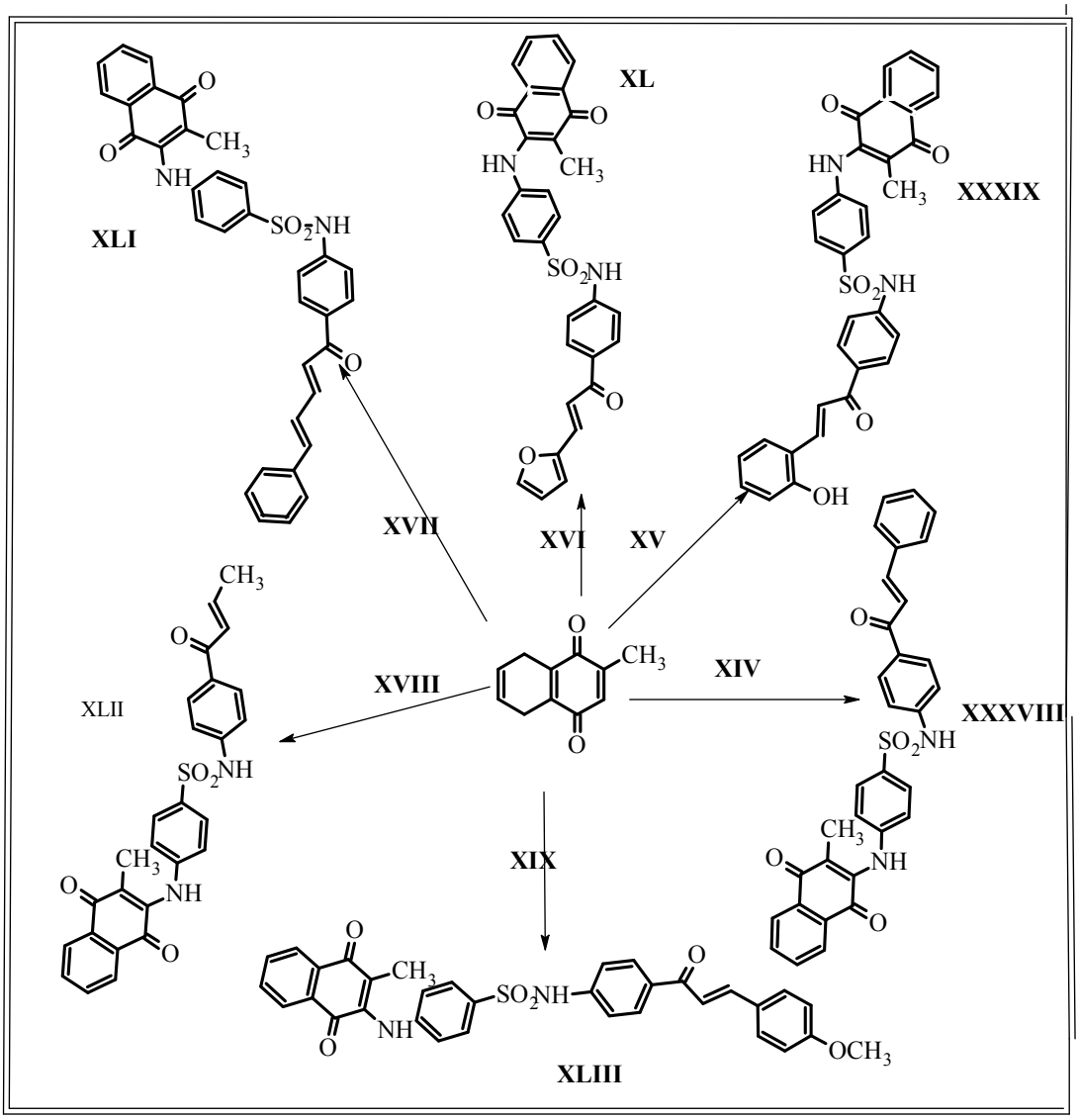
Scheme 2.5: Synthesis N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivatives



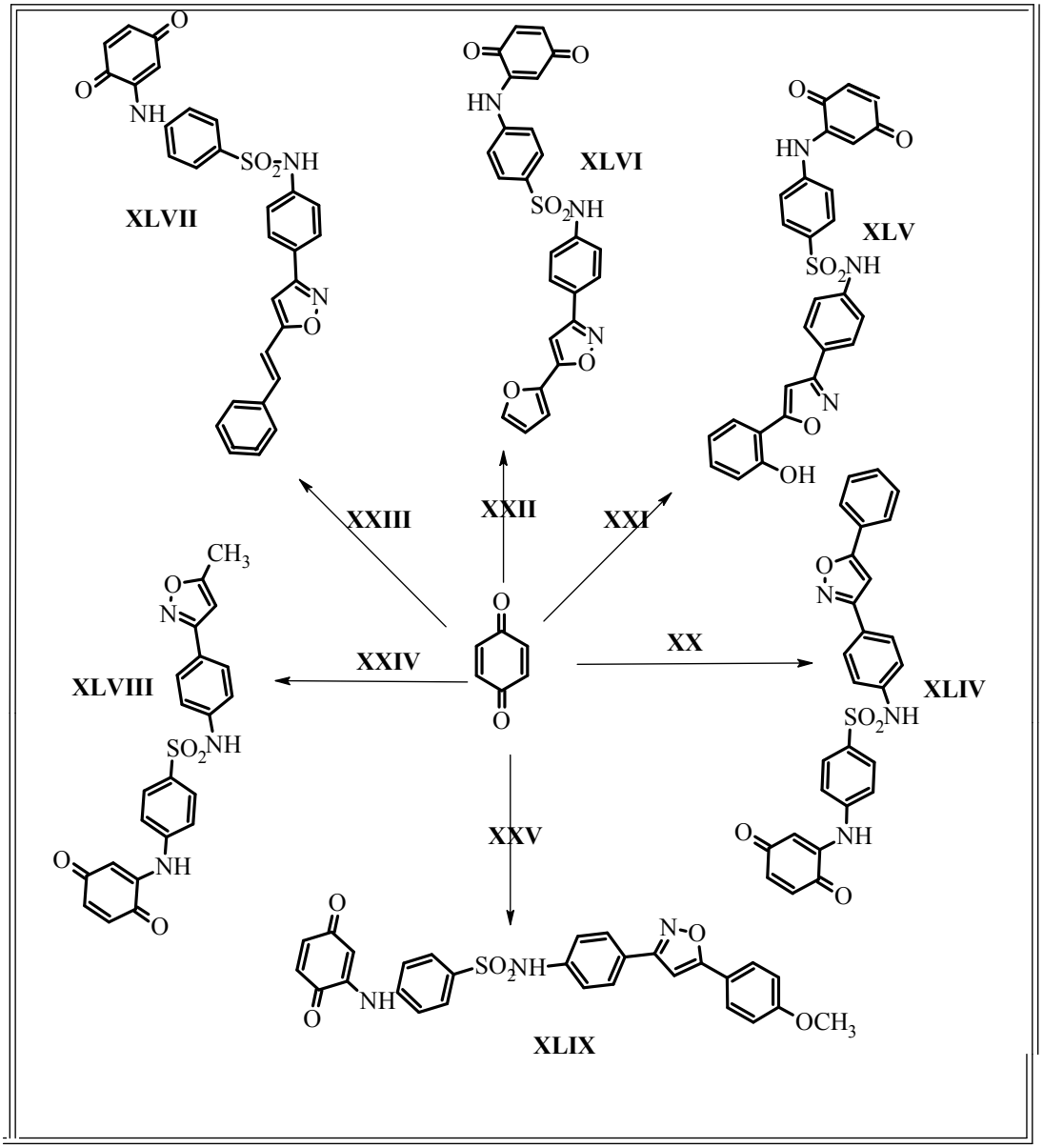
Scheme 2.6: Synthesis of 4-(α,β-unsaturated carbonyl phenyl)-benzenesulphonamide –N- 3,6- benzoquinone



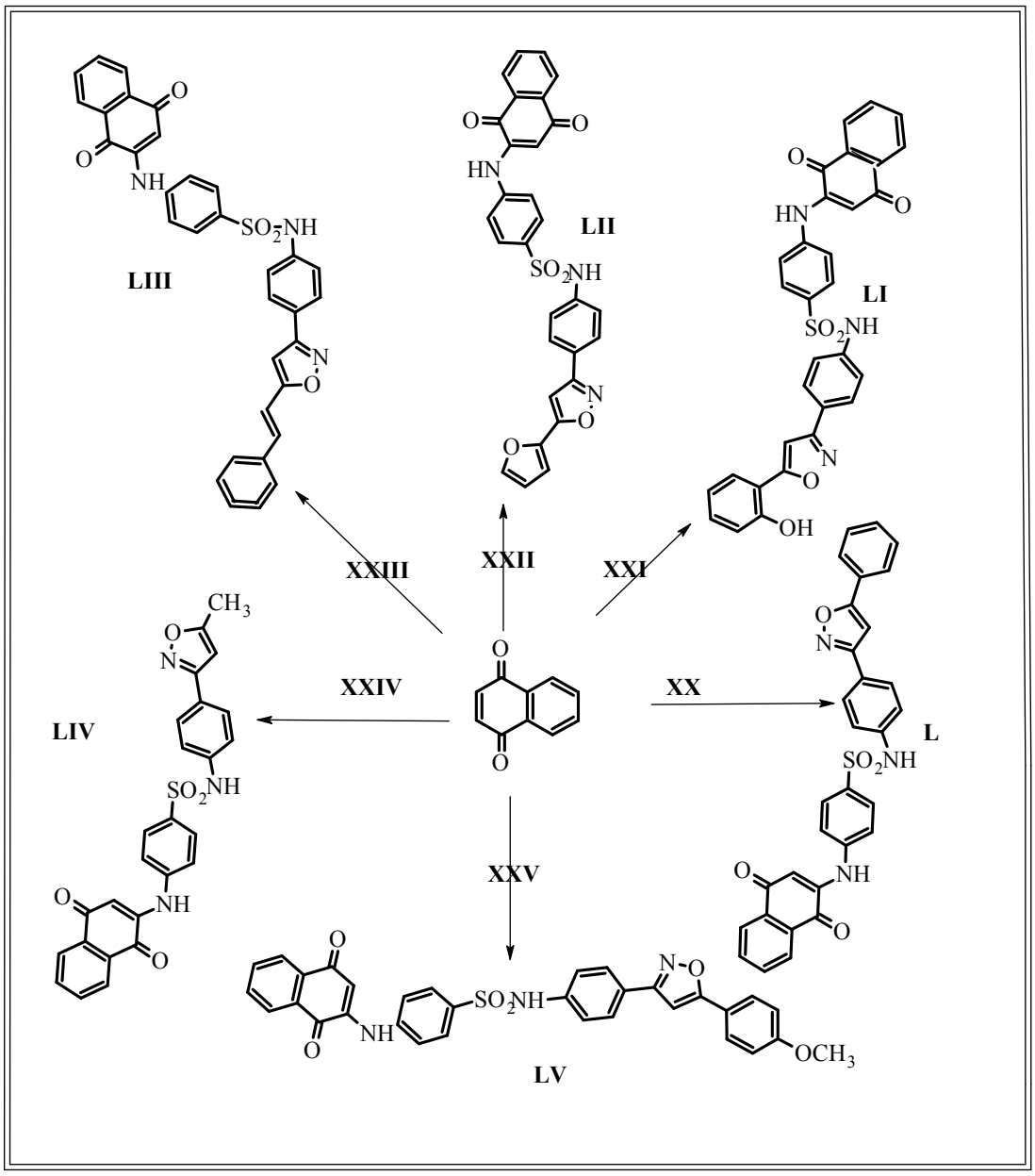
Scheme 2.7: Synthesis of 4-(α,β-unsaturated carbonyl phenyl)-benzenesulphonamide –N- 1,4- naphthaquinone



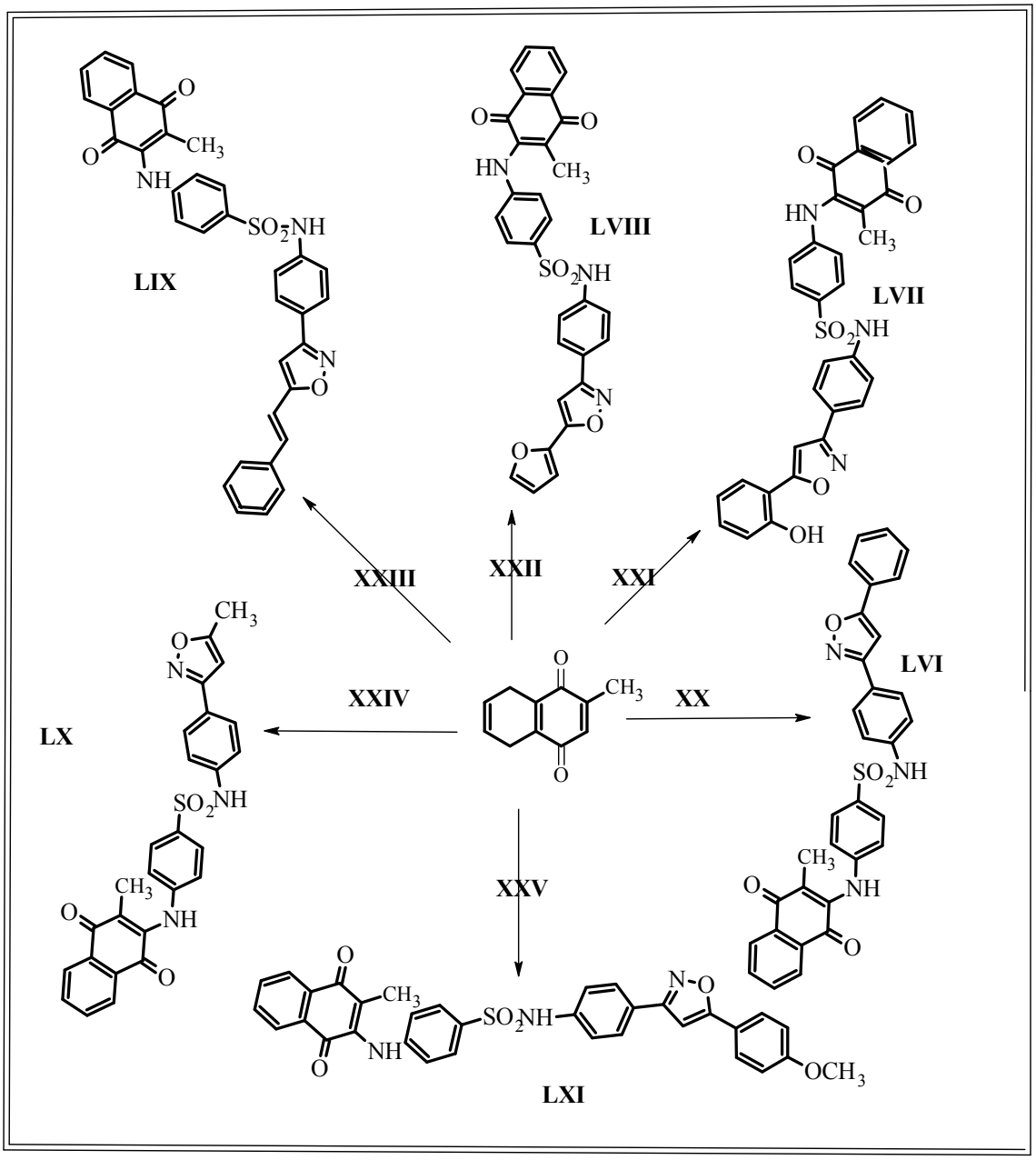
Scheme 2.8: 4-(α,*β*-unsaturated carbonyl phenyl)benzenesulphonamide-N-2-methyl-1,4-naphthaquinone



Scheme 2.9: Synthesis of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



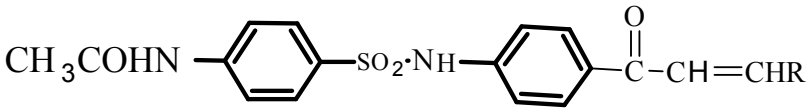
Scheme 2.10: Synthesis of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



Scheme 2.11: Synthesis of N-(p-aminosulfamoyl phenyl-4-isoxazole)-2-methyl-1,4-naphthaquinone

Table. 2.1. Chemicalnames of some synthesized compounds

Table. 2.1.1. Chemical namesof p-acetamide α,β – unsaturated carbonyl derivates



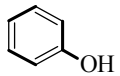
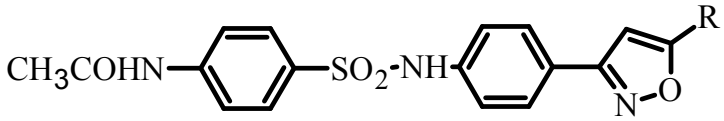
COMP NO	R	Chemical names
II		N^4 -(p-(3-pheny – prop -2-en -1-onlye -phenyl)- acetamidobenzene sulphonamide
III		N^4 -(p-(3-(3-hydroxy pheny)– prop -2-en -1-onlye -phenyl)- acetamidobenzene sulphonamide
IV		N^4 -(p-(3- furan-2-yl– prop -2-en -1-onlye -phenyl)- acetamidobenzene sulphonamide
V		N^4 -(p-(5-phenylpenta-2,4-dienoyl -phenyl)- acetamidobenzene sulphonamide
VI	CH3	N^4 -(p-(4-but-2-enoylpheny)- acetamidobenzene sulphonamide
VII		N^4 -(p- (4-methoxyphenyl) – prop -2-en -1-onlye -phenyl)- acetamidobenzene sulphonamide

Table 2.1.2 chemical names of N-(p-acetamide sulflamoyl)phenyl-4-isoxazoles derivatives



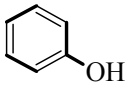
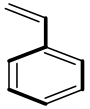
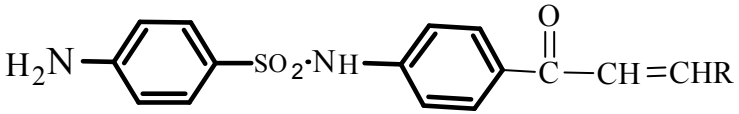
Comp NO	R	Chemical names
VIII		N^4 -(p-(5- phenyl- isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide
IX		N^4 -(p-(5-(4-hydroxyphenyl) - isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide
X		N^4 -(p-(5-(furan-2-yl)-isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide
XI		N^4 -(p-(5- styryl- isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide
XII	CH3	N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide
XIII		N^4 -(p-(5-(4- methoxyphenyl)- isoxazol-3-ye) -phenyl)- acetamidobenzene sulphonamide

Table 2.1.3 chemical names of p-amino- α,β -unsaturated carbonyl derivatives



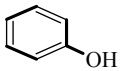
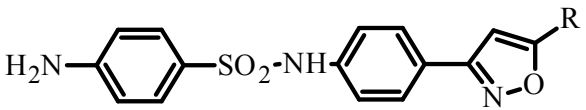
CompNO	R	Chemical names
XIV		N^4 -(p-(3-pheny – prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide
XV		N^4 -(p-(3-(3-hydroxy pheny)– prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide
XVI		N^4 -(p-(3- furan-2-yl– prop -2-en -1-onlye -phenyl)-aminobenzene sulphonamide
XVII		N^4 -(p-(5-phenylpenta-2,4-dienoyl -phenyl)-aminobenzene sulphonamide
XVIII	CH3	N^4 -(p-(4-but-2-enoylphenyl)- aminobenzene sulphonamide
XIX		N^4 -(p- (4-methoxyphenyl) – prop -2-en -1-onlye -phenyl)-aminodobenzene sulphonamide

Table 2.1.4 Chemical names of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivates



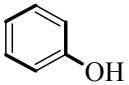
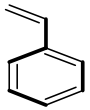
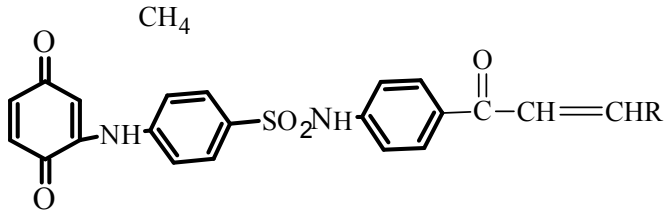
Comp NO	R	Chemical names
XX		N^4 -(p-(5- phenyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide
XXI		N^4 -(p-(5-(4-hydroxyphenyl) - isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide
XXII		N^4 -(p-(5-(furan-2-yl)-isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide
XXIII		N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide
XXIV	CH3	N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide
XXV		N^4 -(p-(5-(4- methoxyphenyl)- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide

Table 2.1.5 Chemical names of 4-(α,β -unsaturated carbonyl phenyl)benzenesulphonamide –N-3,6- benzoquinone



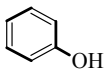
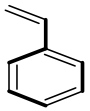
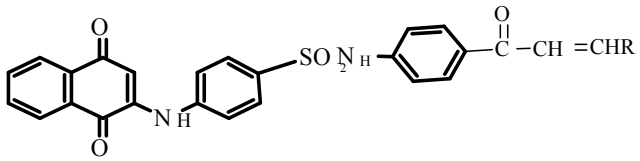
Comp NO	R	Chemical names
XXVI		2-(N^4 -(p-(3-pheny – prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XXVII		2-(N^4 -(p-(3-(3-hydroxy pheny)– prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XXVIII		2-(N^4 -(p-(3- furan-2-yl– prop -2-en -1-onlye -phenyl)-aminobenzene sulphonamide)-1,4-benzoquinone
XXIX		2-(N^4 -(p-(5-phenylpenta-2,4-dienoyl -phenyl)-aminobenzene sulphonamide)-1,4-benzoquinone
XXX	CH3	2-(N^4 -(p-(4-but-2-enoylphenyl)-aminobenzen sulphonamide)-1,4-benzoquinone
XXXI		2-(N^4 -(p- (4-methoxyphenyl) – prop -2-en -1-onlye -phenyl)-aminodobenzene sulphonamide)-1,4-benzoquinone

Table 2.1.6. Chemical names of 4- (α,β-unsaturated carbonyl phenyl)benzenesulphonamide –N- 1,4- naphthaquinone



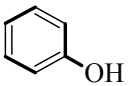
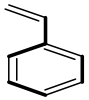
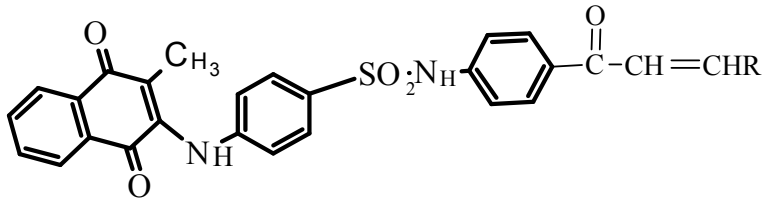
Comp NO	R	Chemical names
XXXII		2-(N^4 -(p-(3-pheny – prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-1,4-naphthaquinone
XXXIII		2-(N^4 -(p-(3-(3-hydroxy pheny)– prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-1,4-naphthaquinone
XXXIV		2-(N^4 -(p-(3- furan-2-yl– prop -2-en -1-onlye -phenyl)-aminobenzene sulphonamide)-1,4-naphthaquinone
XXXV		2-(N^4 -(p-(5-phenylpenta-2,4-dienoyl -phenyl)-aminobenzene sulphonamide)-1,4- naphthaquinone
XXXVI	CH3	2-(N^4-(p-(4-but-2-enoylphenyl)-aminobenzensulphonamide)-1,4- naphthaquinone
XXXVII		2-(N^4 -(p- (4-methoxyphenyl) – prop -2-en -1-onlye -phenyl)-aminodobenzene sulphonamide)-1,4-naphthaquinone

Table 2.1.7. Chemical names of 4-(α,β-unsaturated carbonyl phenyl)benzenesulphonamide –N-2-methyl-1,4-naphthaquinone



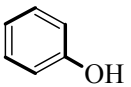
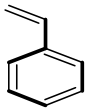
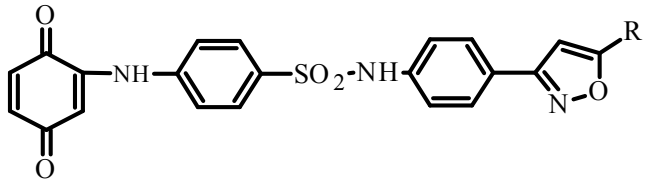
Comp NO	R	Chemical names
XXXVIII		2-(N^4 -(p-(3-pheny – prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-3- methyl -1,4-naphthaquinone
XXXIX		2-(N^4 -(p-(3-(3-hydroxy pheny)– prop -2-en -1-onlye -phenyl)- aminobenzene sulphonamide)-3- methyl -1,4- naphthaquinone
XL		2-(N^4 -(p-(3- furan-2-yl– prop -2-en -1-onlye -phenyl)-aminobenzene sulphonamide)-3- methyl -1,4-naphthaquinone
XLI		2-(N^4 -(p-(5-phenylpenta-2,4-dienoyl -phenyl)-aminobenzene sulphonamide)-3- methyl -1,4-naphthaquinone
XLII	CH3	2-(^{4}-(p-(4-but-2-enoylphenyl)-aminobenzensulphonamide)-3-methyl-1,4- naphthaquinone
XLIII		2-(N^4 -(p- (4-methoxyphenyl) – prop -2-en -1-onlye -phenyl)-aminodobenzene sulphonamide) -3-methyl-1,4- naphthaquinone

Table 2.1.8 Chemical names of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



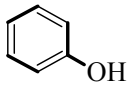
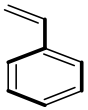
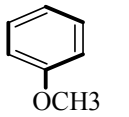
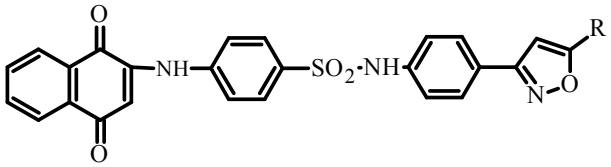
Comp NO	R	Chemical names
XLIV		2-(N^4-(p-(5- phenyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XLV		2-(N^4-(p-(5-(4-hydroxyphenyl) - isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XLVI		2-(N^4-(p-(5-(furan-2-yl)-isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XLVII		2-(N^4-(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XLVIII	CH3	2-(N^4-(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone
XLIX		2-(N^4-(p-(5-(4-methoxyphenyl)- isoxazol-3-ye) -phenyl)-aminobenzene sulphonamide)-1,4-benzoquinone

Table 2.1.9 Chemical names of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



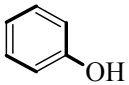
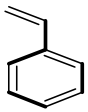
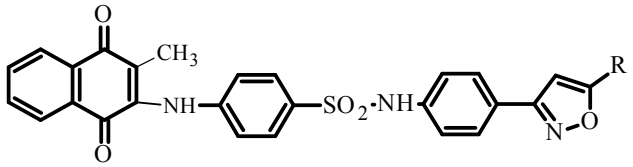
Comp NO	R	Chemical names
L		2-(N^4 -(p-(5- phenyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-naphthaquinone
LI		2-(N^4-(p-(5-(4-hydroxyphenyl) - isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-naphthaquinone
LII		2-(N^4 -(p-(5-(furan-2-yl)-isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4- naphthaquinone
LIII		2-(N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4- naphthaquinone
LIV	CH3	2-(N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4- naphthaquinone
LV		2-(N^4 -(p-(5-(4- methoxyphenyl)- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-naphthaquinone

Table 2.1.10 Chemical names of N-(p-amino sulfamoyl phenyl-4-isoxazole)-2-methyl-1,4-naphthaquinone



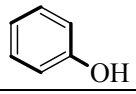
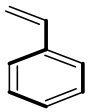
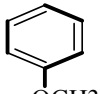
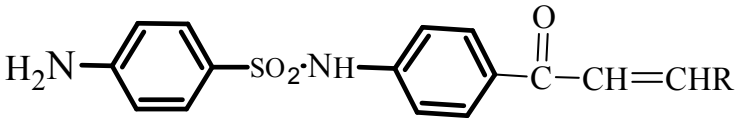
Comp No.	R	Chemical names
LVI		2-(N^4 -(p-(5- phenyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone
LVII		2-(N^4-(p-(5-(4-hydroxyphenyl) - isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone
LVIII		2-(N^4 -(p-(5-(furan-2-yl)-isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone
LIX		2-(N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone
LX	CH3	2-(N^4 -(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone
LXI		2-(N^4 -(p-(5-(4- methoxyphenyl)- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone

Table 2.2. Reactionconditions of some synthesized compounds

Table 2.2.1 Reaction condition of p-amino-α,β-unsaturated carbonyl derivatives



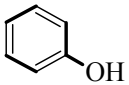
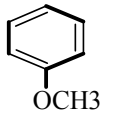
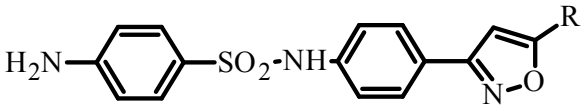
Comp No.	R	Re.Time	Temp	Y%	Recy.solv	m.p
XIV		3hours	80-100 C^0	57%	EtOH	148-153
XV		3hours	80-100 C^0	63%	EtOH	175-180
XVI		3hours	80-100 C^0	66%	EtOH	143-148
XVII		3hours	80-100 C^0	61%	EtOH	139-144
XVIII	CH3	3hours	80-100 C^0	55%	EtOH	164-169
XIX		3hours	80-100 C^0	53%	EtOH	155-160

Table 2.2.2 Reaction condition of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivates



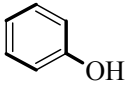
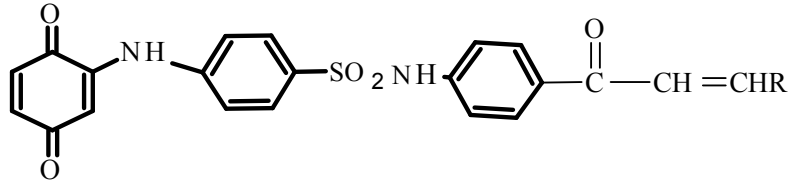
Comp No.	R	Re.Time	Temp	Y%	Recy.solv	M.P
XX		3hours	80-100 C^0	62%	EtOH	166-171
XXI		3hours	80-100 C^0	55%	EtOH	153-158
XXII		3hours	80-100 C^0	58%	EtOH	164-169
XXIII		3hours	80-100 C^0	60%	EtOH	136-141
XXIV	CH3	3hours	80-100 C^0	52%	EtOH	158-162
XXV		3hours	80-100 C^0	61%	EtOH	148-153

Table 2.2.3 Reaction condition 4-(α, β-unsaturated carbonyl phenyl)benzenesulphonamide-N-3,6- benzoquinone



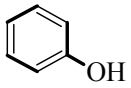
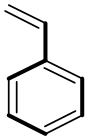
Comp No.	R	Re.Time	Temp	Y%	Recy.solv	M.P
XXVI		4hours	80-100 C^0	70%	EtOH	125-130
XXVII		4hours	80-100 C^0	57%	EtOH	198-203
XXVIII		4hours	80-100 C^0	75%	EtOH	138-143
XXIX		4hours	80-100 C^0	61%	EtOH	116-120
XXX	CH3	4hours	80-100 C^0	77%	EtOH	131-136
XXXI		4hours	80-100 C^0	56%	EtOH	169-174

Table 2.2.4 Reaction condition of 4-(α,β-unsaturated carbonyl phenyl)benzenesulphonamide–N-1,4- naphthaquinone

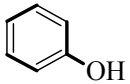
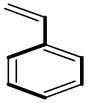
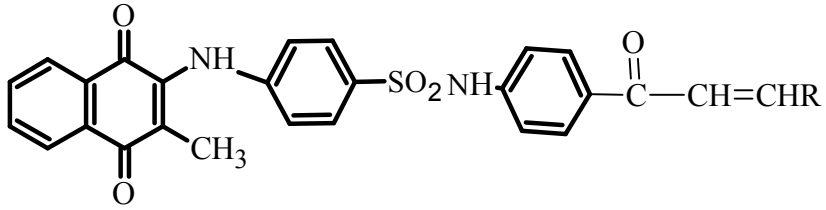
Comp No.	R	Re.Time	Temp	Y%	Recy.solv	M.P
XXXII		4hours	80-100 C^0	75%	EtOH	125-130
XXXIII		4hours	80-100 C^0	65%	EtOH	198-203
XXXIV		4hours	80-100 C^0	77%	EtOH	138-143
XXXV		4hours	80-100 C^0	62%	EtOH	116-120
XXXVI	CH3	4hours	80-100 C^0	70%	EtOH	131-136
XXXVII		4hours	80-100 C^0	57%	EtOH	169-174

Table 2.2.5 Reaction conditions of 4-(α, β-unsaturated carbonyl phenyl)benzenesulphonamide-N-2-methyl-1,4-naphthaquinone



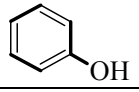
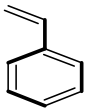
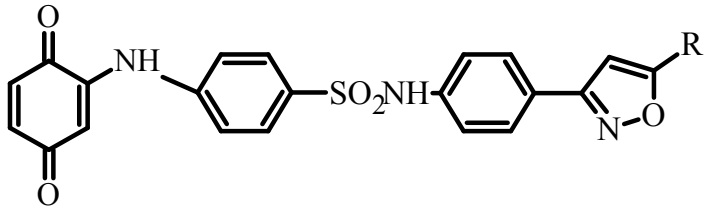
Comp NO	R	Re.Time	Temp	Y%	Recy.solv	M.P
XXXVIII		4hours	80-100 C^0	66%	EtOH	151-156
XXXIX		4hours	80-100 C^0	%70	EtOH	157-162
XL		4hours	80-100 C^0	77%	EtOH	142-147
XLI		4hours	80-100 C^0	72%	EtOH	131-136
XLII	CH3	4hours	80-100 C^0	65%	EtOH	172-177
XLIII		4hours	80-100 C^0	60%	EtOH	178-183

Table 2.2.6 Reaction conditions of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



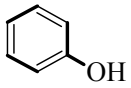
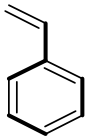
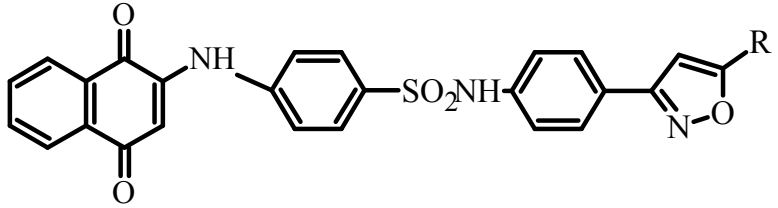
Comp NO	R	Re.Time	Temp	Y%	Recy.solv	M.P
XLIV		4hours	80-100 C^0	58%	EtOH	158-163
XLV		4hours	80-100 C^0	63%	EtOH	117-122
XLVI		4hours	80-100 C^0	66%	EtOH	98-103
XLVII		4hours	80-100 C^0	55%	EtOH	168-173
XLVIII	CH3	4hours	80-100 C^0	61%	EtOH	163-168
XLIX		4hours	80-100 C^0	67%	EtOH	169-174

Table 2.2.7 Reaction conditions of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



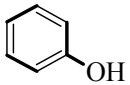
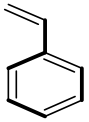
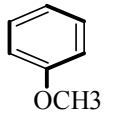
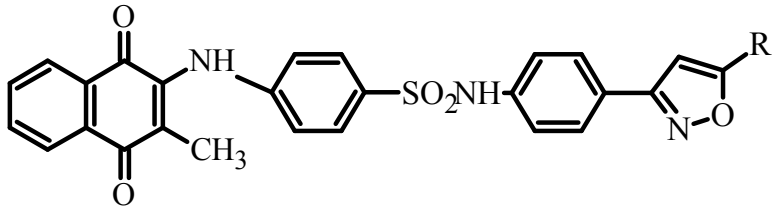
Comp NO	R	Re.Time	Temp	Y%	Recy.solv	M.P
L		4hours	80-100 C^0	68%	EtOH	130-135
LI		4hours	80-100 C^0	65%	EtOH	189-194
LII		4hours	80-100 C^0	60%	EtOH	223-228
LIII		4hours	80-100 C^0	59%	EtOH	177-182
LIV		4hours	80-100 C^0	70%	EtOH	232-237
LV		4hours	80-100 C^0	69%	EtOH	127-132

Table 2.2.8. Reaction conditions of N-(p-amino sulfamoyl phenyl-4-isoxazole)-2- methyl-1,4-naphthaquinone



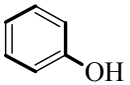
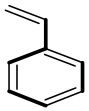
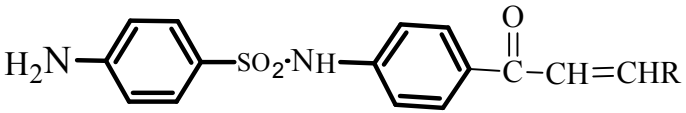
Comp NO	R	Re.Time	Temp	Y%	Recy.solv	M.P
LVI		4hours	80-100 C^0	57%	EtOH	127-132
LVII		4hours	80-100 C^0	62%	EtOH	111-116
LVIII		4hours	80-100 C^0	75%	EtOH	139-144
LIX		4hours	80-100 C^0	59%	EtOH	152-157
LX	CH3	4hours	80- 100 C^0	77%	EtOH	133-138
LXI		4hours	80-100 C^0	62%	EtOH	135-140

Table 2.3.Molecular weight and chemical formula

Table 2.3.1.Molecular weight and chemical formula of p-amino- α,β -unsaturated carbonyl derivates



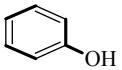
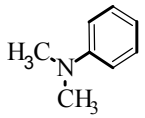
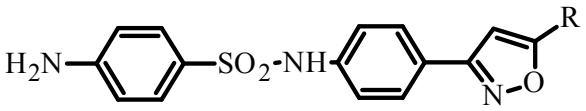
Comp NO	R	Formula	Molecular weight
XIV		$C_{21}H_{18}N_2O_3S$	378
XV		$C_{21}H_{18}N_2O_4S$	394
XVI		$C_{19}H_{16}N_2O_4S$	368
XVII		$C_{23}H_{20}N_2O_3S$	404
XVIII	CH3	$C_{16}H_{16}N2O_3S$	316
XIX		$C_{22}H_{20}N_2O_4S$	408
XIV		$C_{23}H_{23}N_3O_3S$	421

Table 2.3.2.Molecular weight and chemical formula of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivatives



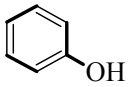
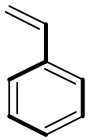
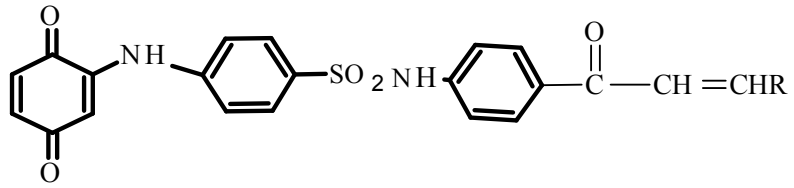
Comp NO	R	Formula	Molecular weight
XX		$C_{21}H_{17}N_3O_3S$	391
XXI		$C_{21}H_{17}N_3O_4S$	407
XXII		$C_{19}H_{15}N_3O_4S$	383
XXIII		$C_{23}H_{19}N_3O_3S$	417
XXIV	CH3	$C_{16}H_{15}N_3O_3S$	329
XXV		$C_{22}H_{19}N_3O_4S$	426

Table 2.3.3 Molecular weight and chemical formula of 4-(α, β-unsaturated carbonyl phenyl)benzenesulphonamide–N-3,6-benzoquinone



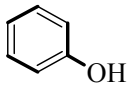
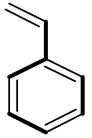
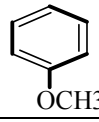
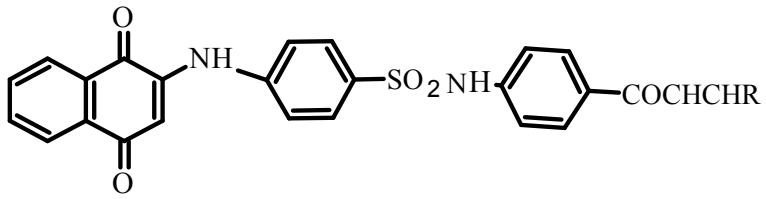
Comp NO	R	Formula	Molecular weight
XXVI		$C_{27}H_{20}N_2O_5S$	484
XXVII		$C_{27}H_{20}N_2O_6S$	500
XXVIII		$C_{25}H_{18}N_2O_6S$	474
XXIX		$C_{29}H_{22}N_2O_5S$	510
XXX	CH3	$C_{22}H_{18}N_2O_5S$	422
XXXI		$C_{28}H_{22}N_2O_6S$	514

Table 2.3.4.Molecular weight and chemical formula of 4-(α, β-unsaturated carbonyl phenyl)benzenesulphonamide–N-1,4-naphthaquinone



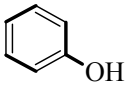
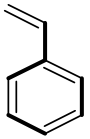
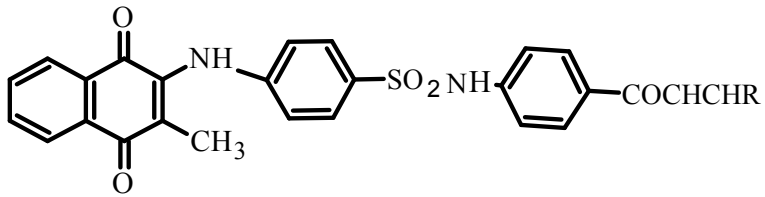
CompNO	R	Formula	Molecular weight
XXXII		$C_{31}H_{22}N_2O_5S$	534
XXXIII		$C_{31}H_{22}N_2O_6S$	550
XXXIV		$C_{29}H_{20}N_2O_6S$	524
XXXV		$C_{33}H_{24}N_2O_5S$	560
XXXVI	CH3	$C_{26}H_{20}N_2O_5S$	472
XXXVII		$C_{32}H_{24}N_2O_6S$	564

Table 2.3.5.Molecular weight and chemical formula of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide -N- 2- methyl -1,4- naphthaquinone



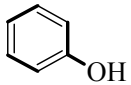
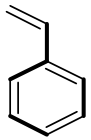
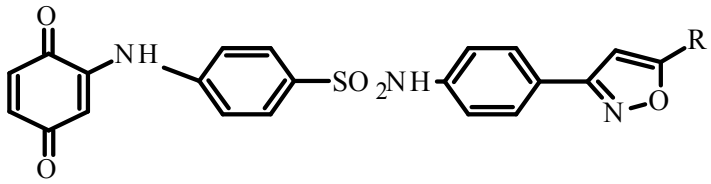
Comp NO	R	Formula	Molecular weight
XXXVIII		$C_{32}H_{24}N_2O_5S$	548
XXXIX		$C_{32}H_{24}N_2O_6S$	564
XL		$C_{30}H_{22}N_2O_6S$	538
XLI		$C_{34}H_{26}N_2O_5S$	574
XLII	CH3	$C_{27}H_{22}N_2O_5S$	486
XLIII		$C_{33}H_{26}N_2O_6S$	578

Table 2.3.6.Molecular weight and chemical formula of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinon



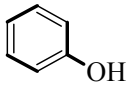
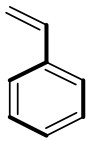
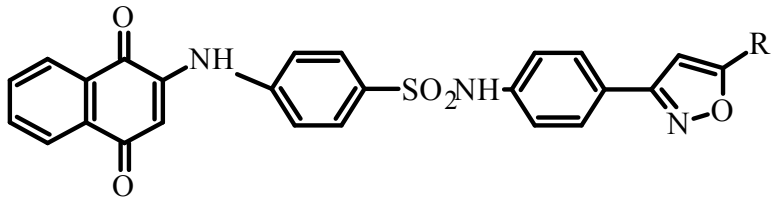
Comp NO	R	Formula	Molecular weight
XLIV		$C_{27}H_{19}N_3O_5S$	497
XLV		$C_{27}H_{19}N_3O_6S$	513
XLVI		$C_{25}H_{17}N_3O_6S$	487
XLVII		$C_{29}H_{21}N_3O_5S$	523
XLVIII	CH3	$C_{22}H_{17}N_3O_5S$	435
XLIX		$C_{28}H_{21}N_3O_6S$	427

Table 2.3.7Molecular weight and chemical formula of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



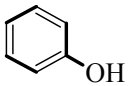
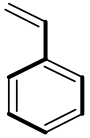
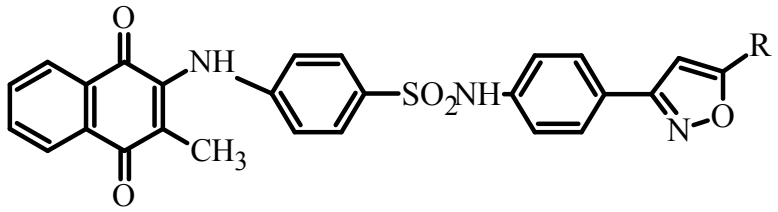
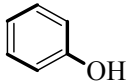
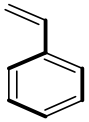
Comp NO	R	Formula	Molecular weight
L		$C_{31}H_{21}N_3O_5S$	547
LI		$C_{31}H_{21}N_3O_6S$	563
LII		$C_{29}H_{19}N_3O_6S$	537
LIII		$C_{33}H_{23}N_3O_5S$	573
LIV		$C_{26}H_{19}N_3O_5S$	485
LV		$C_{32}H_{23}N_3O_6S$	**577**

Table 2.3.8.Molecular weight and chemical formula of N-(p-amino sulfamoyl phenyl-4-isoxazole)- 2- methyl -1,4- naphthaquinone



CompNO	R	Formula	Molecular weight
LVI		$C_{32}H_{23}N_3O_5S$	561
LVII		$C_{32}H_{23}N_3O_6S$	577
LVIII		$C_{30}H_{21}N_3O_6S$	551
LIX		$C_{34}H_{25}N_3O_5S$	587
LX	CH3	$C_{27}H_{21}N_3O_5S$	499
LXI		$C_{33}H_{25}N_3O_6S$	591

Chapter Three

Results and Discussion

3. Results and Discussion

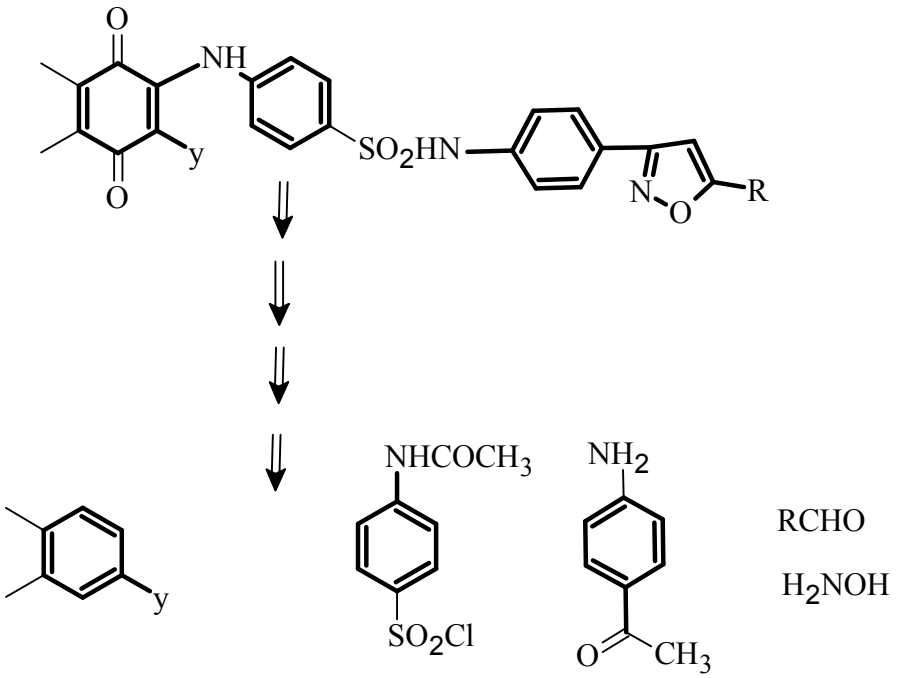
3.1 Introduction

Carbonylgroupis consideredas one of the mostreactivegroupsin organic chemistryduetohigheractivity intheir interactions, leading to a lot ofnew organic compounds. Moreover; thecarbonylgroupis found in manyorganic compounds,aldehydes, ketones, carboxylic acids,esters; amides. Also, alotof natural materialssuch as vitamins, hormones, andsome pharmaceutical productsare in factaldehydesorketones;interested in the carbonyl group played effective role by preparation of α,β-unsaturated carbonyl compoundwhich were prepared when keto compounds interact with different groups of aldehydes based on the base Claisen-Schmidt condenation (Mandge*et al*, 2007).

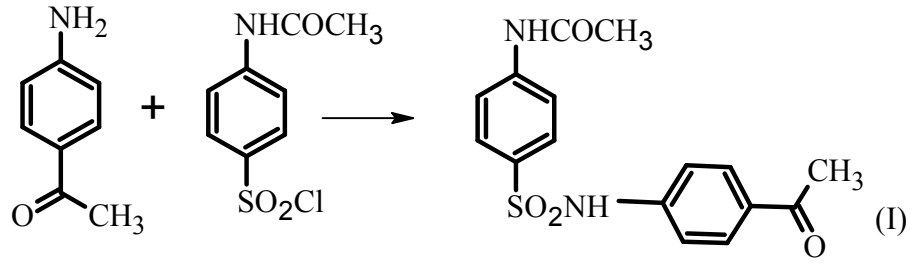
In this study isoxazole compounds were prepared from reaction of α,β-unsaturated carbonyl compound with hydroxylamine hydrochloride.The final products were prepared by the interaction ofα,β-unsaturated carbonyl compounds and isoxazoles with three types of quinones.

3.2 Preparation of some 2-amino isoxazole-*p*–quinine derivatives

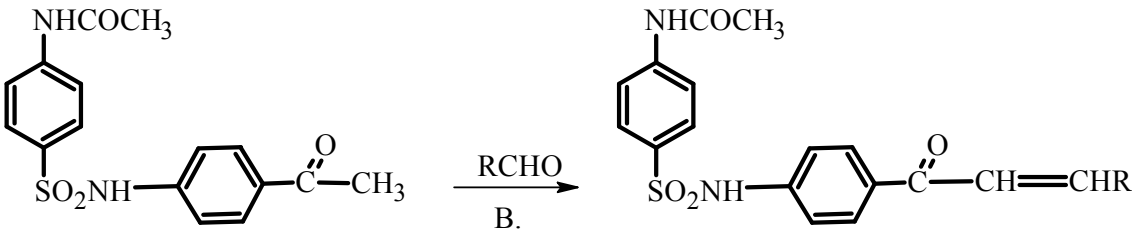
Based upon suitable analysis of the target molecules, synthetic design reveal that the aminoisoxazolesulphanilamido-1,4-quinone derivative can be synthesized from *p*-quinone and *p*-acetamidobenzenesulphonilamide in overall four steps which involve the preparation of reactive α,β-unsaturated carbonyl compound and the corresponding ring closing reaction to isoxazoles.



Synthesis of N^4-(-acetylphenyl)-*p*-acetamidobenzenesulphonilamide is achieved in high quantitative yield, by simple nucleophilic substitution reaction of *p*-amino acetaphenone with*p*–acetamidobenzene sulphonyl chloride.

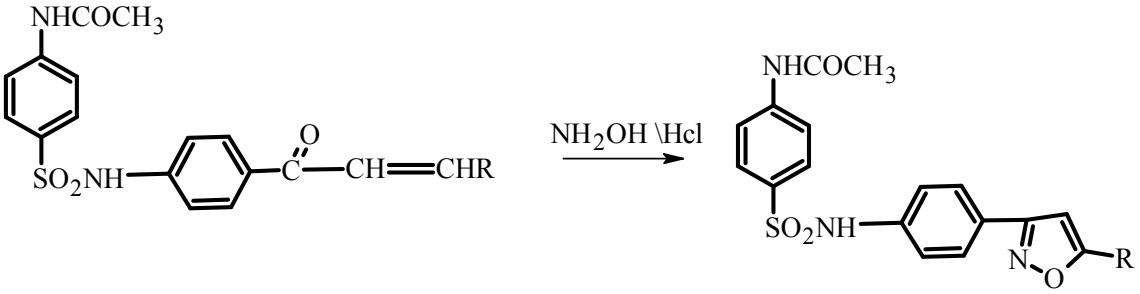


It is a wellknown fact that α—methyl ketones are considered as excellent carbanion precursors. The reaction of compound (I) with substituted aldehydes givesα,*β*-unsaturated carbonyl derivatives according to the adol type reaction and the Claiesen-Schmidt reaction.

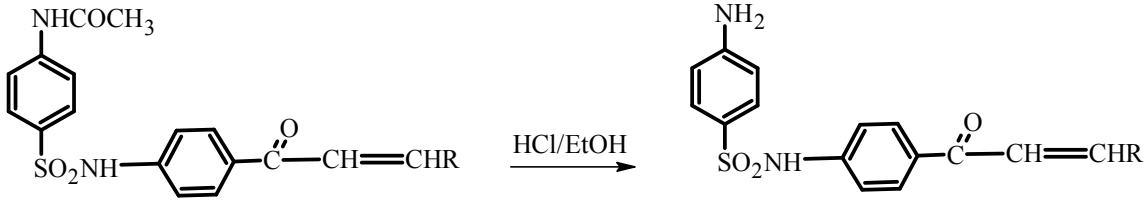


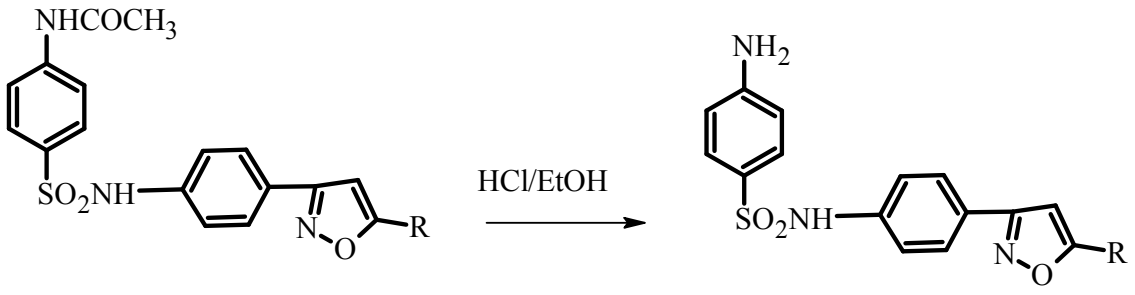
One of the important reactions of α,β-unsaturated carbonyl compounds is their ability to undergo ring forming reactions with a variety of reagents as in the strategies of (3+2) and (3 + 3).

The reaction α,β-unsaturated carbonyl derivatives with hydroxylamine result in Formation of isoxazole ring system. Sodium acetate and ethanol are used to provide suitable pH and to equilibrate the nucleophilicity of the reactive groups.



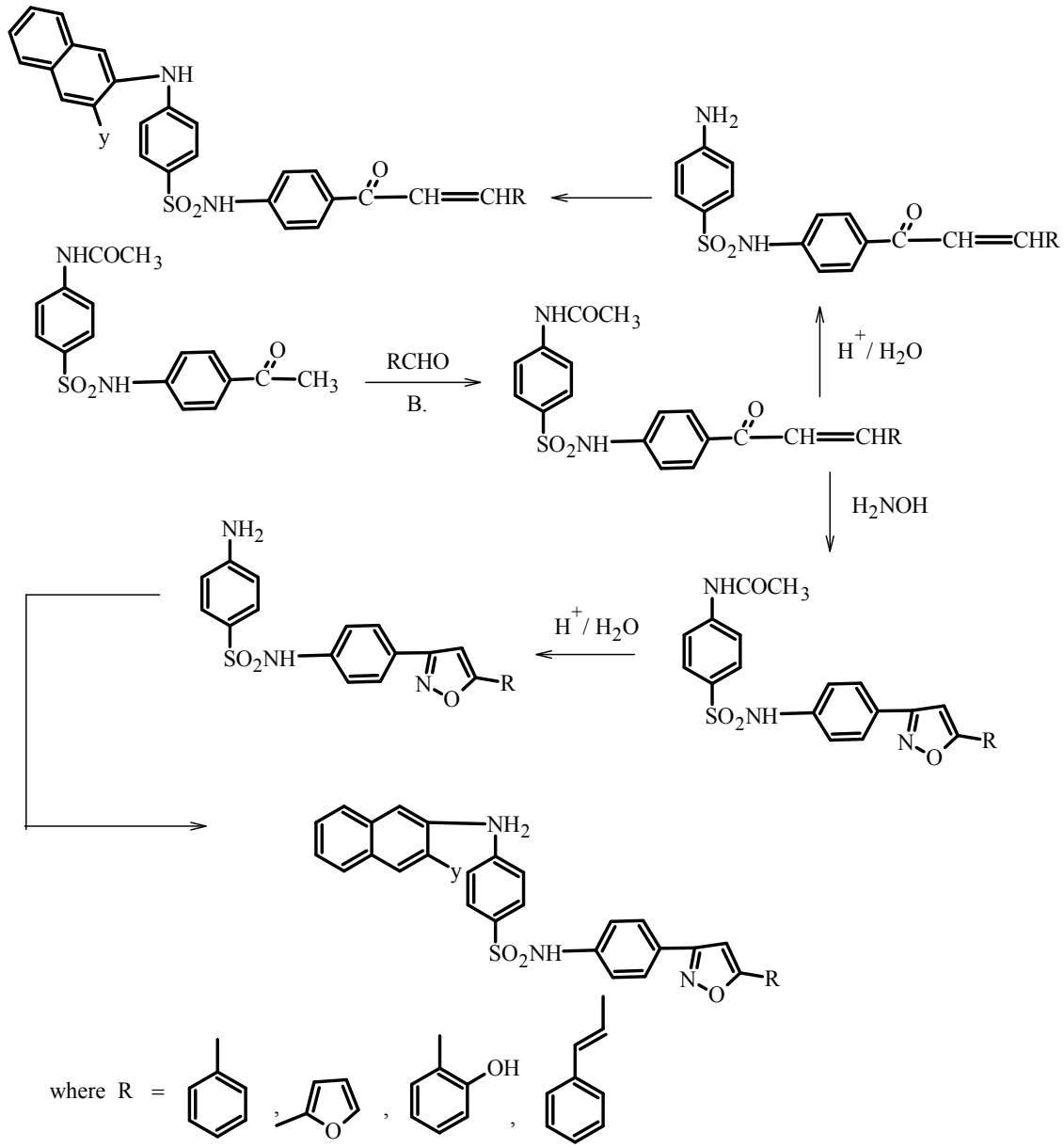
Hydrolysis of the acetaimdo group of bothα,β-unsaturated carbonyl derivatives and isoxazoles derivatives with hydrochloric acid/ethanol(1:1) gives the corresponding primary amino group





The final products of p-quinone derivatives were synthesized by reaction of amino compounds as nuclelophiles with p–quinones using acetic acid and ethanol to provide suitable pH for conjugated addition reaction.

The overall reaction sequence could be summarized in the following scheme



y = H , OH , CH_3- , OR (benzoquinone)

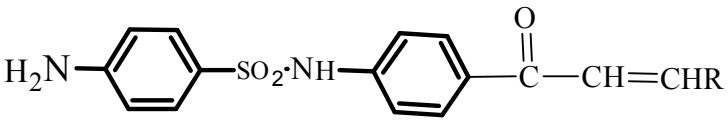
3.3 Spectroscopic analysis

The structures of the various synthesized compounds were assigned onthe basis of their spectral data (IR, NMR, UV and MS). The purity of the synthesized compounds has been checked by TLC after recystallization.

The progress of the synthesis was monitored by TLC.The results of TLC analysis were given in table (3.7), with mobile phase and $\mathbf{R_f}$ values, melting points and percentage yield of synthesized compounds are shown in table(3.2) .

Table 3.1.R_f values of some synthesis compounds (Mobile phaseChloroform :MethanolRatio 9.8: 0.2)

Table 3.1.1. R_f values of p-amino- α, β -unsaturated carbonyl derivates



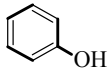
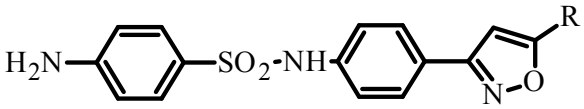
Comp NO	R	R_f value
XV		0.67
XVI		0.77
XVII		0.61
XVIII		0.75
XIX	CH3	0.55
XX		0.72

Table 3.1.2 R_f values of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivates



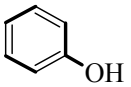
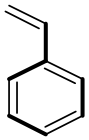
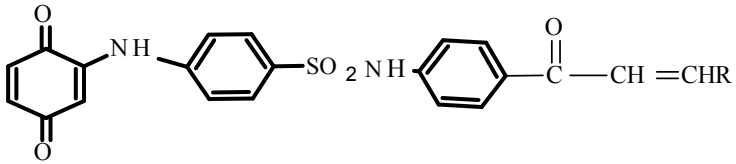
Comp NO	R	R_f value
XX		0.55
XXI		0.62
XXII		0.69
XXIII		0.45
XXIV	CH3	0.57
XXV		0.76

Table 3.1.3 R_f values of of4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 3,6- benzoquinone



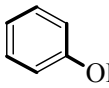
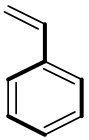
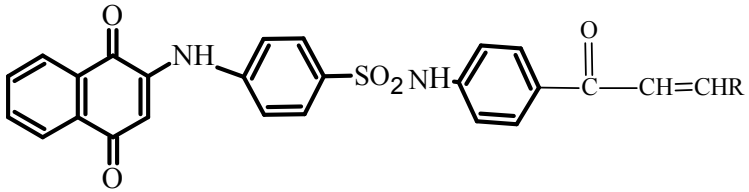
Comp NO	R	R_f value
XXVI		0.79
XXVII		0.18
XXVIII		0.75
XXIX		0.40
XXX	CH3	0.29
XXXI		0.26

Table 3.1.4. R_f values of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 1,4- naphthaquinone



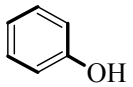
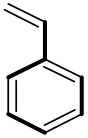
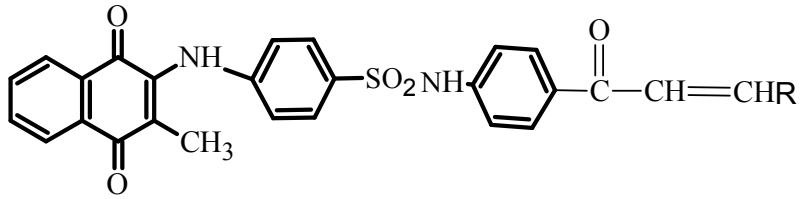
Comp NO	R	R_f value
XXXII		0.78
XXXIII		0.68
XXXIV		0.63
XXXV		0.70
XXXVI	CH3	0.65
XXXVII		0.72

Table 3.1.5. R_f values of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 2- methyl -1,4- naphthaquinone



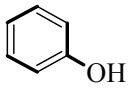
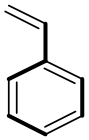
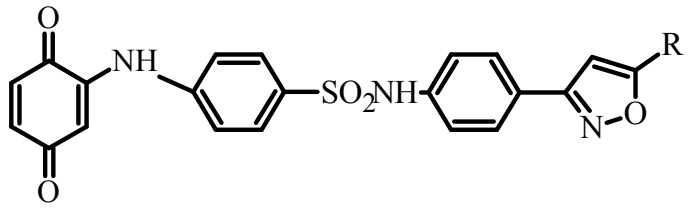
Comp NO	R	R_f value
XXXVIII		0.35
XXXIX		0.37
XL		0.48
XLI		0.26
XLII	CH3	0.53
XLIII		0.63

Table 3.1.6 R_f values of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



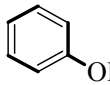
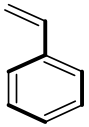
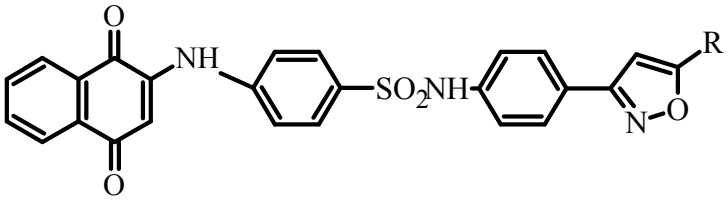
Comp NO	R	R_f value
XLIV		0.45
XLV		0.30
XLVI		0.23
XLVII		0.19
XLVIII	CH3	0.17
XLIX		0.18

Table 3.1.7. R_f values of of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



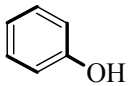
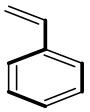
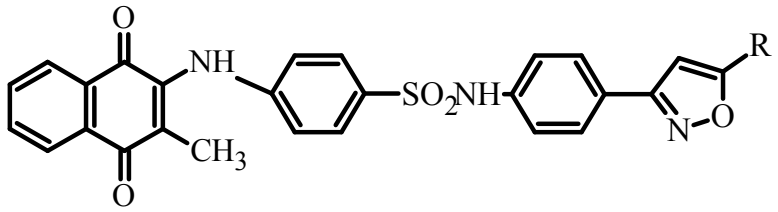
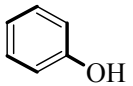
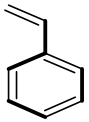
Comp NO	R	R_f value
L		0.77
LI		0.75
LII		0.49
LIII		0.29
LIV	CH3	0.76
LV		0.85

Table 3.1.8 . R_f values of N-(p-amino sulfamoyl phenyl-4-isoxazole)- 2- methyl -1,4- naphthaquinone



Comp NO	R	R_f value
LVI		0.45
LVII		0.35
LVIII		0.40
LIX		0.22
LX	CH3	0.33
LXI		0.53

The group of α,β-unsaturated carbonyl derivatives (XV, XVI, XVII, XVIII, XIX, XXI) showed carbonyl group stretching vibration in the region (1640-1680) cm^{-1}, the decreased wave number of absorption was attributed to the direct conjugated system. Carbon-carbon doublebond st–vib for the aliphatic and aromatic group were observed as sharp bonds near (1523-1598) and was sometimes overlapped with the carbonyl group bonds, the characteristic stretching vibration of C- H aromatic was seen in the region(3045–3116) cm^{-1}.

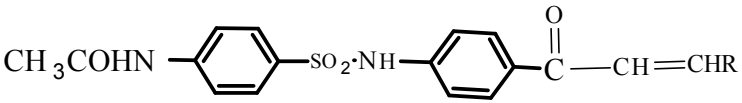
In all of the prepared compounds medium intensity bands at near 1350 and near 1150 cm^{-1} were always attributed to the presence of the $–SO_2$ – asymmetric and symmetric st .vib. The data were tabulated in tabe 3.2.

Compounds (XV, XVI, XVII, XVIII, XIX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII) showed additional common feature. The secondary amines group bands st. vib appeared in the region of (3200–3300) cm^{-1} while in all cases this may overlapped with the primary amine asymmetric and symmetric st.vib bands in the region of (3300-3500) cm^{-1}. Beside the presence of the above common groups in the prepared compounds, the carbon–nitrogen double bond, nitrogen–oxygen bond and carbon–oxygen single bonds for prepared isoxazoles heterocyclic group were observed bands near (1630–1641) cm^{-1} for N=C , (918 - 921) cm^{-1} for N-O and st.vib bands in region (1089–1093) cm^{-1} due to C-O group.

The final *p*-quinone derivatives showed characteristic carbonyl group stretching vibration bands (1680–1640) cm^{-1} and in most cases the second carbonyl appeared as a shoulder to principal bands.

Table.3.2 IR data of some synthesized compounds

Table.3.2.1. IR data of p-acetamide α, β–unsaturated carbonyl derivates



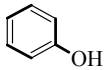
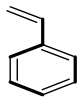
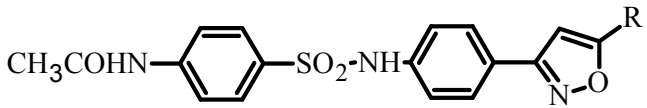
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	C=O St-vib	C=C St-vib	OH St-vib	C=C Aromatic	Others
II		3353.98 3242.12	1336.58 1155.28	3053.11 3112.89	2927.74 2864.09	1656.74	1525.59		1598.88	
III		3315.41 3257.55	1325.01 1157.21	3045.39 3116.75	2933.53 2866.02	1670	1527.52	3577	1595.02	
VI		3350.12 3230.54	1334.65 1155.28	3116.75 3047.32	2929.67 2858.31	1652.88	1537.16		1598.88	C-O 1089.71 719.4
V		3475.49 3321.19	1330.79 1155.28	3114.82 3045.39	2937.39 2869.88	1670.24	1529.45		1595.02	
VI	CH3	3321.19 3267.19	1328.86 1153.35	3116.75 3047.32	2935.46 2873.74	1670.24	1529.45		1595.02	
VII		3317.34	1330.79 1157.21	3116.75 3045.39	2935.46 2867.95	1672.17	1523.66		1595.02	C-O 1091.63 717.47

Table 3.2.2 IR data of N-(p-acetamide sulflamoyl)phenyl-4-isoxazoles derivatives



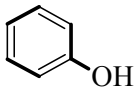
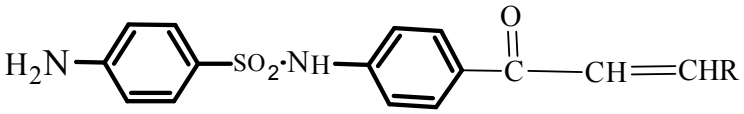
Comp No	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	C=O St-vib	C=N St-vib	C-O Str-vib	C=C Aromatic	N-O Str-vib	OTHRES
IX		3375.2 3263.33	1330.37 1155.28	3056.96	2866.02	1681.81	1630	1091.63 727.11	1596.95 1531.37	921.91 698.18	
X		3346.27 3188.11	1315.36 1157.21	3060	2939.31 2875.67	1687.6	1639.38	1093.56 725.18	1593.09	923.84 756.04	O-H Str.vib 3434.98
XI		3286.48	1348.15 1155.28	3040	2860	1677.95	1641.31	1089.71 746.4	1595.02	918.05 690.47	C=C 1564.16
XII		3320	1330.79 1153.35	3107.11	2900.74	1680		1089.71 750.26	1598.88	919.98 675.04	C=C 1539.09
XIII	CH3	3348.19 3282.62	1325.01 1153.35	3020	2931.6	1687.6	1639.38	1091.63 678.9	1593.09	921.91 727.11	C=C 1541.02
XIV		3280.69	1326.93 1161.07	3120	2842.88	1685.67	1637.45	1093.56 723.26	1595.02	919.98 638.39	

Table 3.2.3 IR data of p-amino- α, β -unsaturated carbonyl derivates



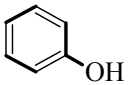
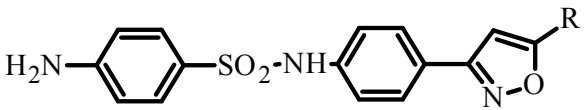
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	C=O St-vib	C=C St-vib	OH St-vib	C=C Aromatic	Others
XIV		3349.27 3417.63	1338.51 1149.5	3040 3141.82	2916.17 2854.45	1659.67	1633.59		1595.02	
XV		3236.33 3423.41	1319.22 1151.42	3040	2820	1679.88	1620	3352.05	1595.02	
XVI		3398.34	1346.22 1159.14	3026.10	2848.67	1680	1654.81		1600.81	
XVII		3342.41 3409.91	1319.22 1151.42	3101.32	2916.17 2854.45	1652.88	1610		1595.02	
XVIII	CH3	3350.12	1311.5 1159.14	3070.46 3018.39	2912.31 2856.38	1690	1658.67		1600.81	
XIX		3421.48	1342.36 1164.92	3046.68	2910.38 2839.02	1695	1652.88		1598.88	

Table 3.2.4 IR data of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivates



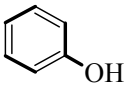
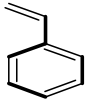
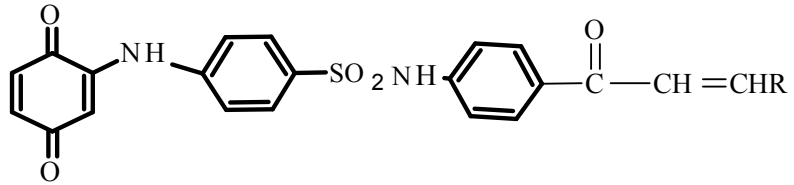
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	C=O St-vib	N=C St-vib	C-O St-vib	C=C Aromatic	N-O
XX		3375.2 3263.33	1330.37 1155.28	3056.96	2866.02	1681.81	1630	1091.63 727.11	1596.95 1535.37	931.91 688.18
XXI		3346.27 3178.11	1315.36 1157.21	3060.12	2939.31 2875.67	1687.6	1639.38	1093.56 725.18	1593.09	920.84 746.04
XXII		3286.48	1348.15 1155.28	3040.00	2860	1677.95	1641.31	1089.71 746.4	1591.02	918.05 694.47
XXIII		3310.00	1334.79 1153.35	3107.11	2910.74	16750		1090.71 750.26	1598.88	798 675.04
XXIV		3348.19 3282.62	1325.01 1153.35	3020.08	2931.60	1687.6	1639.38	1091.63 678.9	1593.09	921.91 727.11
XXV		3280.69	1326.93 1161.07	3123.09	2842.88	1685.67	1637.45	1093.56 723.26	1595.02	919.98 638.39

Table 3.2.5 IR data of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 3,6- benzoquinone



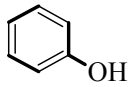
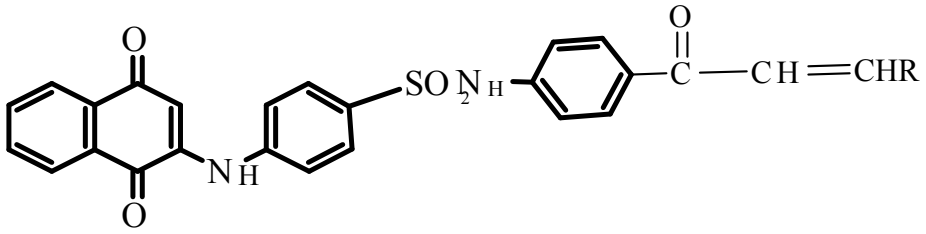
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	O-H Str-vib	C=O St-vib	C=C St-vib	C=C Aromatic
XXVI		3375.2 3234.4	1338.51 1151.42	3100	2927.74 2858.31		1650.95	1504.37	1595.02
XXVII		3205.47	1313.43 1155.28	3040	2925.81	3346.27	1685.67	1533.3	1593.09
XXVIII		3234.4 3373.27	1319.22 1153.35	3041.53	2925.81 2856.38		1650 1670 1690	1508.23	1595.95
XXIX		3375.2 3232.47	1321.15 1151.42	3031.89	2927.74 2867.95		1677.95	1506.3	1595.95
XXX	CH3	3242.12 3377.12	1319.22 1151.42	3056.96	2927.74 2869.88		1680	1504.37	1596.95
XXXI		3342.41 3375.2	1338.51 1151.42	3035.75	2929.67 2837.07		1654.81	1510.16	1596.95

Table 3.2.6 IR data of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 1,4- naphthaquinone



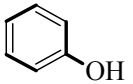
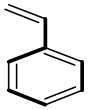
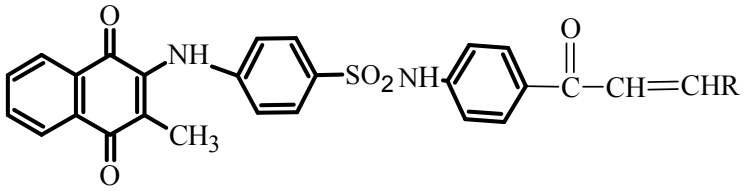
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	O-H Str-vib	C=O St-vib	C=C St-vib	C=C Aromatic
XXXII		3346.27 3232.47	1332.72 1149.5	3062.75	2929.67 2854.45		1660.6	1573.81 1506.3	1593.09
XXXIII		3296.12	1332.72 1157.21	3064.68	2931.6	3386.77	1670.24	1570 1510.16	1591.16
XXXIV		3307.69 3257.55	1330.79 1147.57	3058.89 3028,03	2880 2960		1660.6	1587.31 1517.87	1602.74
XXXV		3305,76 3255.62	1328.86 1151.42	3060.82	2960 2870		1660.6	1523.66	1591.16
XXXVI	CH3	3296.12 3184.26	1332.72 1159.14	3060.82	2947.03		1677.95	1573.81 1541.02	1589.23
XXXVII		3307.69 3234.4	1332.72 1155.28	3066.61	2929.67 2837.09		1658.67	1571.88	1593.03

Table 3.2.7 IR data of 4-(α, β-unsaturated carbonyl phenyl)benzenesulphonamide–N-2-methyl-1,4-naphthaquinone



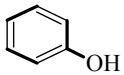
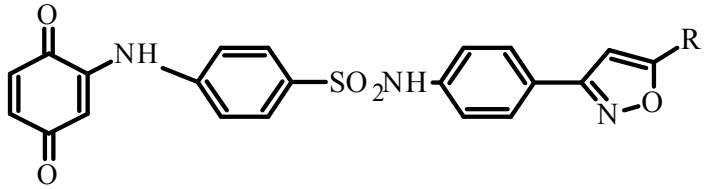
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	O-H Str-vib	C=O St-vib	C=C St-vib	C=N St.vib	C=C Aromatic	N-O St.vib	C-O St.vib
XXXVIII		3377.12 3240.19	1338.51 1151.42	3031.89	2921.96 2856.38		1652.88	1502.44		1596.95		
XXXIX		3380.98 3222.83	1340.43 1153.35	3040	2914.24 2860.24		1650.95	1548.73		1596.95		
XL		3265.26 3348.19	1319.22 1149.5	3039.6	2921.96 2862.17		1706.88 1679.88	1637.45 1500.52		1596.95		
XLI		3402.2	1338.51 1157.21	3012.6			1647.1	1608.52 1524		1575.73		
XLII	CH3	3380.98 3224.76	1325.01 1155.28	3035.75	2977.75 2921,96		1710.74 1654.81	1483.16		1596.95		
XLIII		3375.2 3263.33	1330.37 1155.28	3056.96								

Table 3.2.8 IR data N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



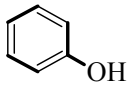
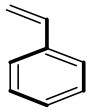
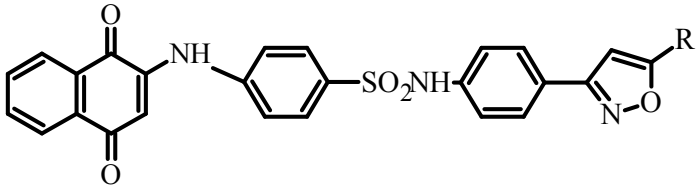
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	O-H Str-vib	C=O St-vib	C=C St-vib	C=N St.vib	C=C Aromatic	N-O St.vib	C-O St.vib
XLIV		3327.20 3269.83	1335.58 1153.35	3064.81			1679.32 1688.72 46		1644.45	1595.02	917.27 688.54	1089.71 725.18
XLV		3375.20 3230.45	1338.51 1149.5	3054.89		3471.63	1680 1647.1		1623.95	1595.02	910.34 678.90	1089.71 1035.7 732.9
XLVI		3230.54 3371.34	1319.22 1151.42	3041.53			1680 1720		1640	1595.95	912.27 692.4	1091.63 1027.99 736.76
XLVII		3222.38 3346.27	1357.79 115195	3040.53	2918.10 286024		1679.88	1510.16	1633.59	1595.95	916.12 709.76	1091.63 730.79
XLVIII	CH3	3222.83 3346.27	1325.01 1151.42	3043.46 3132.18	2860.24 2921.96		1679.88		1633.59	1595.95	916.12 707.83	1091.63 730.9
XLIX		3342.41 3230.54	1320. 1151.42	3109.04 3012	2931.6 2839.12		1708,81		1656.74	1596.96	981.7 678.90	1091.63 1029.92 730.97

Table 3.2.9 IR data of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



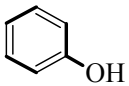
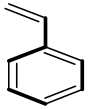
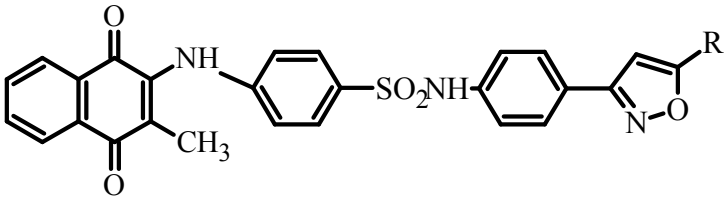
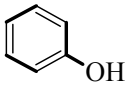
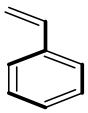
Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C=O St-vib	C=C St-vib	C=N St-vib	C=C Aromatic	N-O Str-vib	C-O Str-vib	OTHERS
L		3337.20 3249.83	1336.58 1153.35	3062.81	1749.32 1772.46		1664.45	1595.02	912.27 688.54	1089.71 725.18	
LI		3373.27	1336.58 1155.28	3120	1699.17 1714.6		1670.24	1595.02	916.12 688.54	1091.63 725.18	O-H Str-vib 3566.14
LII		3463.92 3298.05	1336.58 1157.21	3020	1677.95 1739.67		1618.17	1593.09	916.12 694.33	1093.56 721.33	
LIII		3380.98	1336.58 1155.28	3031.89	1672.17 1716.53	1573.81	1633.59	1593.09	914.2 692.4	1091.63 723.26	
LIV	CH3	3442.7 3298.05	1336.58 1157.21	3050	1676.03 1741.6		1620.09	1593.09	916.12 690.47	1093.56 723.26	C-H aliph 2950.89
LV		3444.63 3392.55	1336.58 1153.35	3040	1677.95 1739.67		1645.17	1595.02	918.05 680.83	1091.63 721.33	C-H aliph 2927.74

Table 3.2.10.IR data of N-(p-amino sulfamoyl phenyl-4-isoxazole)- 2- methyl -1,4- naphthaquinone



Comp NO	R	NH St-Vib	SO_2 St –vib	C-H St-vib Aromatic	C-H St-vib liphatic	C=O St-vib	C=C St-vib	C=N St-vib	C=C Aromatic	N-O Str-vib	-O Str-vib
LVI		3325.50	1322.05 1153.00	3070.60	2900.00 2876.55	1673.70 1680		1635.60	1596.00	927.00	1091.63
LVII		3300.00	1320.22 1153.50	3040.09	2937.80 2877.07	1670.00 1685.70		1640.00	1595.05	934.08 675.08	1091.63 743.65
LVIII		3386.77	1321.15 1153.35	3055.03	2921.96 2860.24	1680 1650.95		1630	1596.95	914.12 676.97	1091.63 744.47
LIX		3357.84	1311.5 1159.14	3068.53 3020.32	2916.17 2858.31	1658.67	1508.23	1600.81	1595	931.55 698.18	1091.63
LX	CH3	3436.91	1317.29 1161.07	3031	2918.1 2856.38	1650.95 1701.1		1600.81	1581.51	916.12 694.33	1091.63 740.61
LXI		3257.55 3417.63	1338.51 1172.64	3014.53	2918.1 2839.02	1716.53 1650.95		1605	1585	931.55 698.18	1091.63 740.61

The ^{1}H NMR spectra of α,β-unsaturated carbonyl showed two doublets near δ 6.50–7,07 and δ7.80 -8.09 ppm for -CH=CH- protons. The highly deshielded signal is attributed to the proton adjacent to the ring system.These compounds showeda number of multiplets and double doublets in the regionδ6.69 – 8.06 ppm which were being assigned for aromatic proton.Detailedanalysis of these signals were tabulated in table (3.3.1).

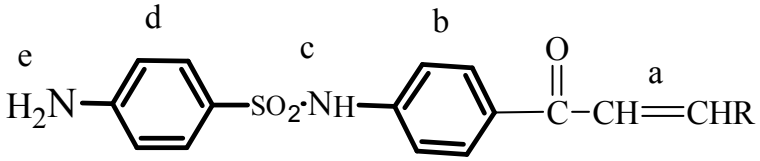
All of the prepared compounds showed a singlet or multiplets near δ8.9 – 10.04 ppm due to proton of this group (-SO_2NH-), the primary amine protons were observed as a singlet near δ3.97-5.4 ppm, some compound showed multiplets chemical shift near δ3.80-3.95 ppm for –OCH_3 protonsand near δ 2.50–2.83 ppm –CH_3 protons.

The ^{1}H NMR spectra of the isoxazoles compounds showed a singlet or multipltes chemical shift near δ6.30 -6.49 ppm which were assigned for heterocyclic ring protons, but the other chemical shifts of these compounds were in the range expected forα,β-unsaturated carbonyl compounds, detailed analysis of these signals were tabulated in table (3.3.2)

The ^{1}H NMR spectra of the final p–quinone derivative showed a singlet for the secondary amine and N-H protons near δ3.80-5.50 ppm while the resonance at δ8.90 – 1.20 ppmaccount for (-SO_2NH-), proton. The signals atδ6.65–8.23 ppm were assigned for aromatic protons. Detailed analysis of these signals were tabulated in table (3.3)

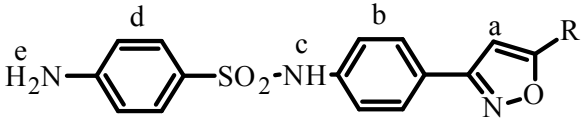
Table 3.3.[1]H-NMR data of some synthesis compounds

Table 3.3.1.[1]H-NMR data of p-amino- α, β -unsaturated carbonyl derivates



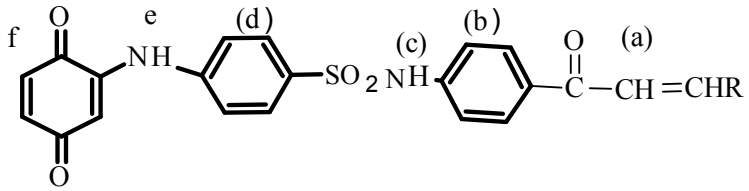
Comp NO	R	Chemical shift					
		A	B	C	D	E	R
XIV		8.07-8.09 (m,2H,CH=CH)	7.61-7.83 (m,4H,Ar-H)	10,02 (s,1H,NH-S)	7.33-7.39 (m,4H,Ar-H)	5.54 (s.2H,$NH_{2)}$	7.46-7.59 (m,5H,Ar-H)
XVI		7.80-7.89 (m,2H,CH=CH)	7.75-7.60 (m,4H,Ar-H)	9.25 (s,1H,NH-S)	6.8-7.33 (m,4H,Ar-H)	5.40-5.50 (m,2H,$NH_{2)}$	7.93-8.01 (m,3H)
XVIII	CH3	6.69-6.70 (m,2H,CH=CH)	7.80-7.89 (m,4H,Ar-H)	9.56 (s,1H,NH-S)	7.30-7.60 (m,4H,Ar-H)		2.08 (s,3H,$CH_{3)}$
XIX							

Table 3.3.2.[1]H-NMR data of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivates



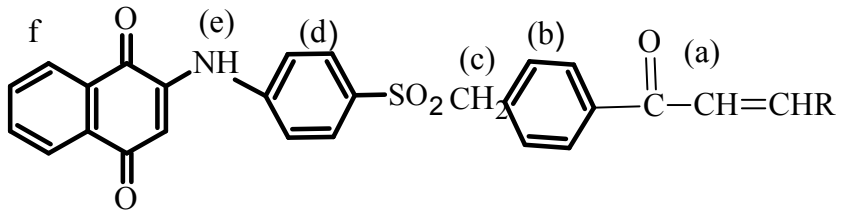
Comp NO	R	Chemical shift					
		A	B	C	d	E	R
XX		6.70-6.72 (m,1H)	7.38-7.46 (m,4H,Ar-H)		7.59-7.83 (m,4H,Ar-H)	5.70-5.80 (m,2H,NH_2)	7.86-8.06 (m,5H,Ar-H)
XXII		6.66-6.70 (m,1H)	7.22-7.57 (m,4H,Ar-H)	10,20 (s,1H,NH-S)	7.59-7.87 (m,4H,Ar-H)		7.89.7.91 (m,3H)
XXIV	CH3	5.30 (s,1H)	6.69-7.31 (m,4H,Ar-H)	10.11 (s,1H,NH-S)	7.57-7.89 (m,4H,Ar-H)	5,50 (s,2H,NH_2)	2.79-2.83 (m,3H,CH_3)
XXV		6.68-6.89 (m,1H)	7.02-7.58 (m,4H,Ar-H)	9.96 (s,1H,NH-S)	7,71-7.80 (m,4H,Ar-H)	5.50- 5.60 (m,2H,NH_2)	7.89- 8.06 (m,4H,Ar-H) 3.80-3.93 (m,3H,CH_3-O)

Table 3.3.3.^{1}H-NMR data of 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 3,6- benzoquinone



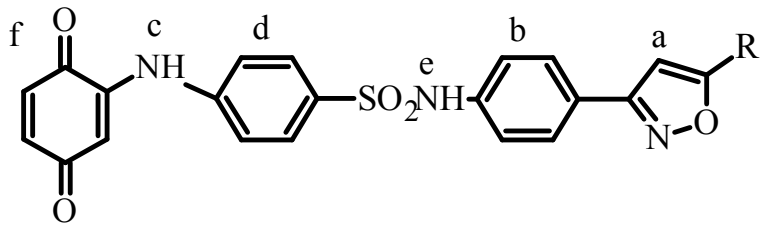
Comp NO	R	Chemical shift						
		A	B	C	D	E	R^1	R
XXVI		(8.0-8.09) (m,2H, CH=CH)	(7.41-7.5) (m,4H, Ar-H)	(10.04) (s,1H, NH-S)	(7.37-7.39) (m,4H, Ar-H)	(4.00) (s,1H, NH-R^1)	(6.69-6.71) (m,3H, Ar-H)	7.80-7.89 (m,5H,Ar-H)
XXVIII		(7.87-7.98) (m,2H, CH=CH)	(7.41-7.64) (m,4H, Ar-H)	(9.29) (s,1H,NH-S)	(7.33-7.37) (m,4H, Ar-H)	(5.50) (s.1H, NH-R^1)	(6-99-6.71) (m,6H, Ar-H)	
XXX	CH3	(6.69) (s, 2H, CH=CH)	(7.60-7.87) (m,4H, Ar-H)		(7.33-7.54) (m,4H,Ar-H)	(4.20) (s,1H, NH-R^1)	(6.70-6.71) (m,3H)Ar-H	(2.50) (s,3H, CH_3)
XXXI		(8.05-8.09) (m,2H, CH=CH)	(7.72-7.80) (m,4H)Ar-H	(9.30) (s,1H,NH-S)	(7.37-7.58) (m,4H , Ar-H)	(5.50) (s,1H, NH-R^1)	(6.69-6.71) (m,3H, Ar-H)	(7.00-7.30) (m,4H, Ar-H) (3.80-3.90) (m,3H, CH_3)

Table 3.3.4.[1]H-NMR of data 4- (α, β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 1,4- naphthaquinone



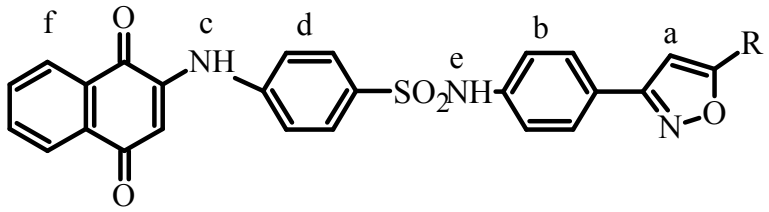
CompNO	R	Chemical shift						
		A	B	C	D	E	R^1	R
XXXII		7.07 (s, 2H, CH=CH)	7.81-7.87 (m.5H, Ar-H)	9.3(s, 1H, NH-S)	7.37-7.46 (m, 4H, Ar-H)	5.5 (s, 1H, NH-C)	8.00- 8.12(m, 4H, Ar-H)	7.59-7.80(m, 5H, Ar-H)
XXXIV		7.90-7.91(m, 2H, CH=CH)	7.40-7.60(m, 8H, Ar-H)	8.9(s, 1H, NH-S)	7.30-7.39 (m,5H, Ar-H)	4.50(s, 1H, NH-C)	7.80-7.89 (m, 4H, Ar-H)	8.06-8.08(m,3H)
XXXVI	CH3	6.47(s, 2H, CH=CH)	7.40-7.67 (m,4H, Ar-H)	10.20(s,1 H, NH-S)	7.07 (s, 4H, Ar-H)	4.50(s,1H,N H-C)	7.97-799(m, 4H,Ar-H)	2.51 (s,1H, CH_3)
XXXVII	 OCH3	7.43-7.59(m, 2H, CH=CH)	7.77-7.85(m, 4H,Ar-H)	8.80(s,1H , NH-S)	7.65-7-75(m, 4H, Ar-H)	5.70(S,1H, NH-C)	8.07-8.23(m,4H, Ar-H)	7.60-7.63(m, 4H,Ar-H) 3.87(s, 3H,CH_3

Table 3.3.5.[1]H-NMR data of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone



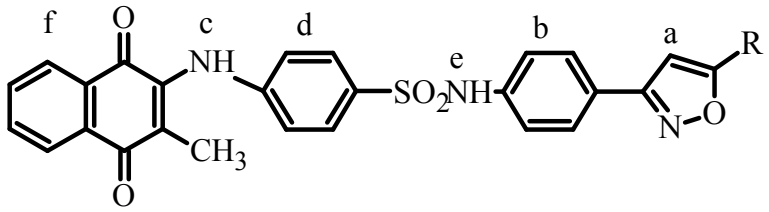
CompNO	R	Chemical shift						
		A	B	C	D	E	R^1	R
XLIV		6.79 (s,1H)	7.37 (s,4H,Ar-H)	9.18 (s,1H,NH-S)	7.57 (s,4H,Ar-H)	5,53 (s,1H,NH)	6.68 (s,3H,Ar-H)	7.87 (s,5H,Ar-H)
XLVI		6.3 (s,1H)	7.21-7.40 (m,4H,Ar-H)	10.20 (s,1H,NH-S)	7.60-7.87 (m,4H,Ar-H)	5,53 (s,1H,NH)	6.64-6.70 (m,3H,Ar-H)	7.88-8.08 (m,3H)
XLVIII	CH3	6.70 (s,1H)	7.30-7.59 (m,4H,Ar-H)	9.19 (s,1H,NH-S)	7.86-7.87 (m,4H,Ar-H)	3.80 (s,1H,NH)	6.68-6.69 (m,3H,Ar-H)	2.48 (s,3H,CH_3)
XLIX		6.60 (s,1H)	7.38-7.60 (m,4H,Ar-H)	9.40 (s,1H,NH-S)	7.70-7.84 (m,4H,Ar-H)	4.40 (s,1H,NH)	6.68-6.99 (m,3H,Ar-H)	8.00-8.05 (m,4H,Ar-H) 3.85(,s,3H, CH_3

Table 3.3.6[1]H-NMR of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone



Comp. NO	R	Chemical shift						
		A	B	C	D	E	R^1	R
L		6.48 (s,1H)	6.99-7.39 (m,4H,Ar-H)	8,9 (s,1H,NH-S)	7.46-7.83 (m,4H,Ar-H)	5.54 (s.1H,NH)	7.95-8.07 (m,5H,Ar-H)	8.08-8.12 (m,5H,Ar-H)
LII		6.45-6.49 (m,1H)	7.60-7.80 (m,4H,Ar-H)	10.23 (s,1H,NH-S)	7.85-7.95 (m,4H,Ar-H)	3.90 (s,1H,NH)	7.97-8.04 (m,5H,Ar-H)	7.07-7.40 (m,3H,)
LIV	CH3	6.47 (s,1H)	7.37-7.41 (m,4H,Ar-H)	8.92 (s,1H,NH-S)	7.85-7.94 (m,4H,Ar-H)	3.92 (s,1H,NH)	7.97-8.20 (m,5H,Ar-H)	2.82 (s,3H,CH_3)
LV		6.50 (s,1H)	7.17-7.30 (m,4H,Ar-H)		7.35-7.50 (m,4H,Ar-H)	5.40 (s,1H,NH)	7.90-8.04 (m,5H,Ar-H)	7.60-7.85 (m,4H,Ar-H) 3.84-3.91 (m,3H,CH_3-O)

Table 3.3.7.[1]H-NMR data of N-(p-amino sulfamoyl phenyl-4-isoxazole)- 2- methyl -1,4- naphthaquinone



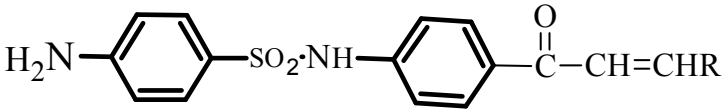
CompNO	R	Chemical shift						
		A	B	C	D	E	R^1	R
LVI		6.30 (s,1H)	6.69-7.20 (m,4H,Ar-H)	10.08 (s,1H,NH -S)	7.35-7.77 (m,4H,Ar-H)	4.30 (s,1H,NH)	7.85-7.95 (m.5H,Ar-H) 2.84(s,3H,CH_3)	7.99-8.25 (m,5H,Ar-H)
LVIII		5.69 (s,1H)	7.29-7.36 (m,4H,Ar-H)		7.56-7.60 (m,4H,Ar-H)		7.85-7.95 (m,5H,Ar-H) 2.82 -2.84 (m,3H,CH_3)	6.69-6.89 (m,3H)
LXI		6.35 (s,1H)	6.75-7.30 (m,4H,Ar-H)	9.92 (s,1H.NH -S)	7.40-7.70 (m,4H,Ar-H)	4.20 (s,1H,NH)	7.90-8.20 (m,5H.Ar-H) 2.60 (s,3H,CH_3)	7.75-7.89 (m,4H,Ar-H) 3.86-3.95 (m,3H,CH_3-O)

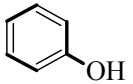
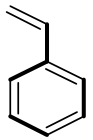
Ultraviolet–visible spectroscopy was carried out using the solvent used and the wavelength λmaxof the compounds were given in table. (table3.5). The spectra of the compounds were given in appendix (UV spectra)

Ultraviolet spectra of the synthesized compounds showed one to three main bands due to$\pi - \pi^*$ transition which sometimes overlapped with$n - \pi^*$ transition.

Table 3.5 UV data of some synthesis compounds

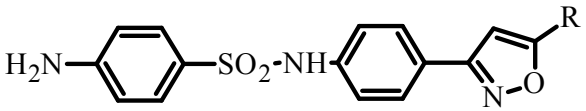
Table 3.5.1 UV data of p-amino- α,β -unsaturated carbonyl derivatives

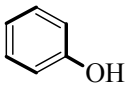
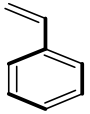


Comp NO	R	Nm
XV		272
XVI		268,204
XVII		266.5
XVIII		267
XIX	CH3	267
XX		345.5,268

Solvent Ethanol

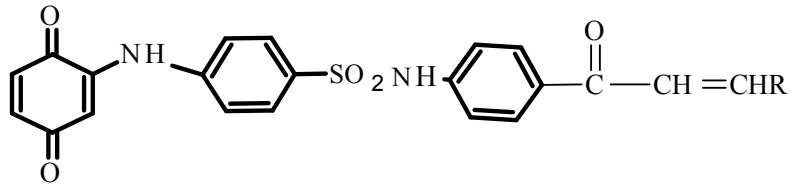
Table 3.5.2 UV data of N-(p-amino sulfamoyl)phenyl-4-isoxazoles derivatives

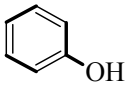
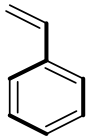


Comp NO	R	Nm
XX		296,270
XXI		265,208
XXII		340,263
XXIII		268,207
XXIV	CH_3	267
XXV		271.226,206

Solvent Ethanol

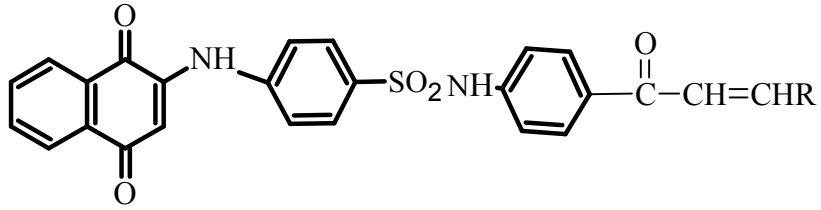
Table 3.5.3 UV data of 4- (α,β -unsaturated carbonyl phenyl)benzenesulphonamide –N- 3,6- benzoquinone

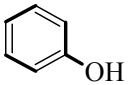
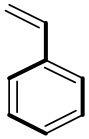


Comp NO	R	Nm
XXVI		265,223.5
XXVII		258.5
XXVIII		259.5
XXIX		258.5
XXX	CH_3	340,264
XXXI		350,261

Solvent Ethanol

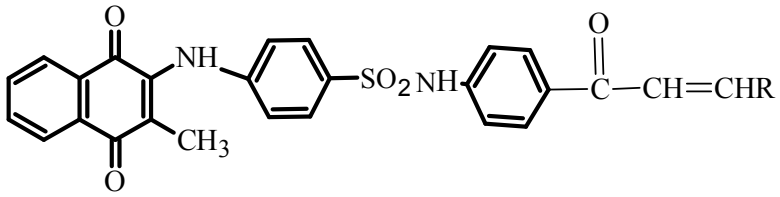
Table 3.5.4 UV data 4-(α,β-unsaturated carbonyl phenyl)benzenesulphonamide–N-1,4-naphthaquinone

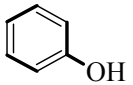
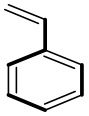


CompNO	R	Nm
XXXII		294,252.5,226
XXXIII		271.5,251.5
XXXIV		339.5,246
XXXV		333,246
XXXVI	CH3	279.5
XXXVII		340.5,277.5,241

Solvent Ethanol

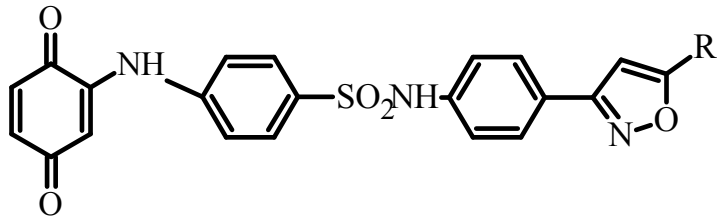
Table 3.5.5 UV data of 4-(α,β-unsaturated carbonyl phenyl)benzenesulphonamide–N-2-methyl-1,4-naphthaquinone

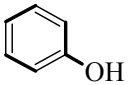
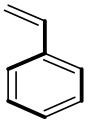


Comp NO	R	Nm
XXXVIII		264.5
XXXIX		
XL		261.5
XLI		266
XLII	CH3	260.5
XLIII		263

Solvent Ethanol

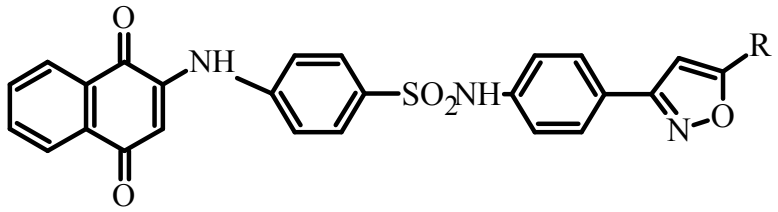
Table 3.5.6 UV data of N-(p-amino sulfamoyl phenyl-4-isoxazole)-3,6-benzoquinone

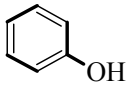
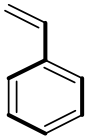


Comp NO	R	Nm
XLIV		265
XLV		293.5,273
XLVI		339.5,270.5,210.5
XLVII		267,209
XLVIII	CH3	267.5,213
XLIX		270.5,213.5

Solvent Ethanol

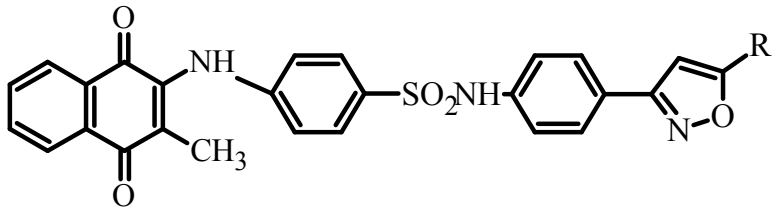
Table 3.5.7 UV data of N-(p-amino sulfamoyl phenyl-4-isoxazole)-1,4-naphthaquinone

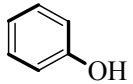
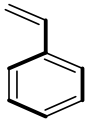


Comp NO	R	Nm
L		277
LI		278
LII		277,226
LIII		274
LIV	CH3	278,226

Solvent Ethanol

Table 3.5.8.UV dataof N-(p-amino sulfamoyl phenyl-4-isoxazole)-2-methyl-1,4-naphthaquinone



Comp NO	R	Nm
LVI		264
LVII		267
LVIII		263
LIX		265
LX		265
LXI		265

Solvent Ethanol

3.6 tested exhibited considerable antibacterial and antifungal activity.

Table 3.6.1tested of some compounds for antibacterial and antifungal activity

Diameter of zone of inhibition (mm)																		
	XLVII			XLIX			L			XXX			XXXI			XXXII		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Escherichia coli	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Staphylococcus aureus	16	16	14	30	28	22	30	22	22	18	17	16	16	12	12	0	0	0
Pseudomonas aeruginosa	20	20	20	0	0	0	20	18	17	20	18	18	16	18	20	0	0	0
Bacillus subtilis	17	17	15	30	30	25	20	20	17	17	17	14	16	16	16	22	22	21
Candida albicans	12	12	14	18	18	16	18	18	18	20	20	20	16	18	16	16	16	16

Table 3.6.2tested of some compounds for antibacterial and antifungal activity

Diameter of zone of inhibition (mm)															
	XXXIX			XLI			XLIII			XXXIV			XXXVII		
	1	2	3	1	2	1	2	3	1	2	1	2	3	1	2
Escherichia coli	0	0	0	0	0	0	0	0	0	15	15	12	0	0	0
Staphylococcus aureus	20	18	18	18	18	16	16	14	11	22	26	19	21	18	16
Pseudomonas aeruginosa	0	0	0	20	18	18	15	15	18	0	0	0	18	18	18
Bacillus subtilis	22	18	16	21	20	20	0	0	0	27	26	23	23	23	22
Candida albicans	24	24	21	18	18	18	18	18	18	17	15	15	20	20	16

The concentration 1=1mg/0.5ml, 2 = 1mg\1ml, 3= 0.1mg\1ml

Some of prepared compounds were tested for antibacterial activity against *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 292113), *Pseudomonas aeruginosa* (ATCC 29336) *Bacillus subtilis* (ATCC 6633), and antifungal activity against the yeast *Candida albicans* (ATCC 10231). Results of antibacterial and antifungal study were presented in table 1 and 2. Data analysis revealed that most of the compounds showed excellent antibacterial activity against the entire test organism except *Escherichia coli* (ATCC 25922), only compound (XXXIV) gave good result with it. Also all tested compound showed good antifungal activity against the yeast *Candida albicans* (ATCC 10231).

The three benzoquinone isoxazole derivatives tested showed promising antifungal activity against C.albicans. Compound XLVII showed the highest activity this compound possess an electron donating group (OCH_3). Compound exhibited significant antibacterial activity against the tow gram positive bacteria while totally devoid of activity against –gram negative bacteria. Of all the tested compounds only compound XXXIV showed activity against E.coli but surprising, devoid of activity against P. aeruginosa .

Conclusion and recommendation

The following points may be concluded and recommended from this work α,β-unsaturated carbonyl compound can be prepared from α– methyl ketones withsubstituted aldehydes by Claiesen_Schmidt reaction

The reaction of α,β unsaturated carbonyl derivatives with hydroxyl amide resulted information of isoxazole ring system.

The *p*–quinone derivatives compounds were prepared by reaction of quinone with isoxazoles derivatives compounds in conjugated addition reactions.

α,β -unsaturated carbonyl compounds in this study prepared could be reacted with different reagents to give heterocyclic compounds containing one or two hertro atoms.

All synthesized compounds in study were purified by recrystallization and TLC techniques, IR, UV, and ^{1}H-NMR, spectral analysis for some of the prepared compounds was highly recommended.

All the final compounds prepared in this work werenew.

Based upon the promising antimicrobial activity of some of the prepared compounds, it is highly recommended that p-quinone derivatives to be screened and evaluated for probable other biological activities e.g. antitumor, antimalarial.

It is recommended to modeling the structure activity relation of these compounds with suitable software programme.

It is highly recommended to complete the mass spectral analysis beside 13C-NMR

Overall fifty six compounds were successfully prepared in this work. These compounds were classified as either p-quinone isoxazoyl derivatives or p-quinone α,β-unsaturated carbonyl derivatives.

Further intermediates were six α,β-unsaturated carbonyl compounds and six isoxazoles derivatives.

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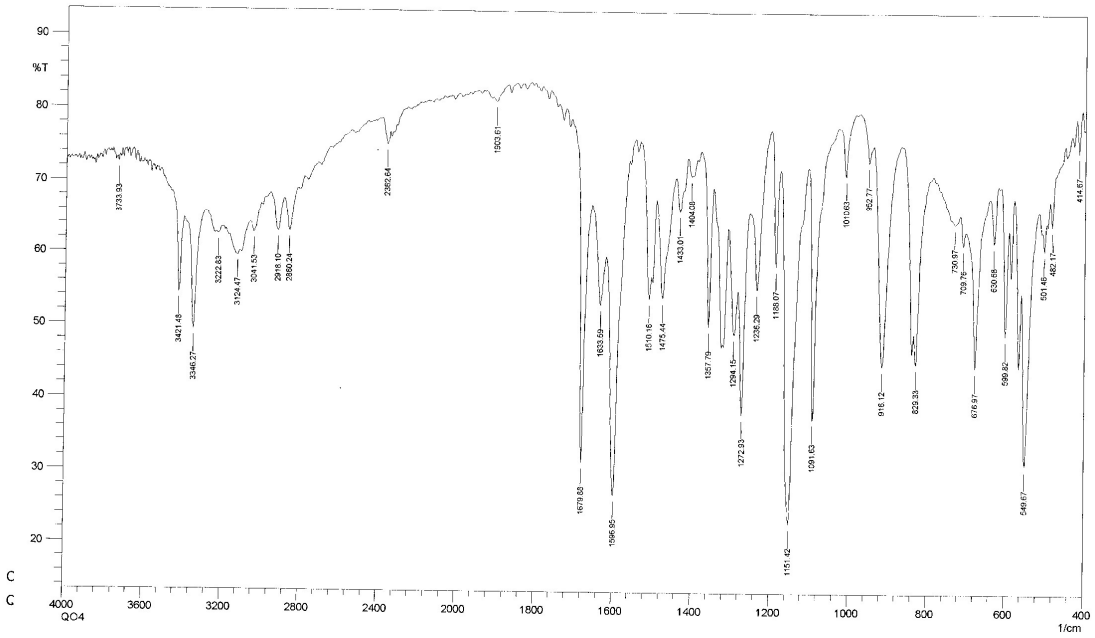
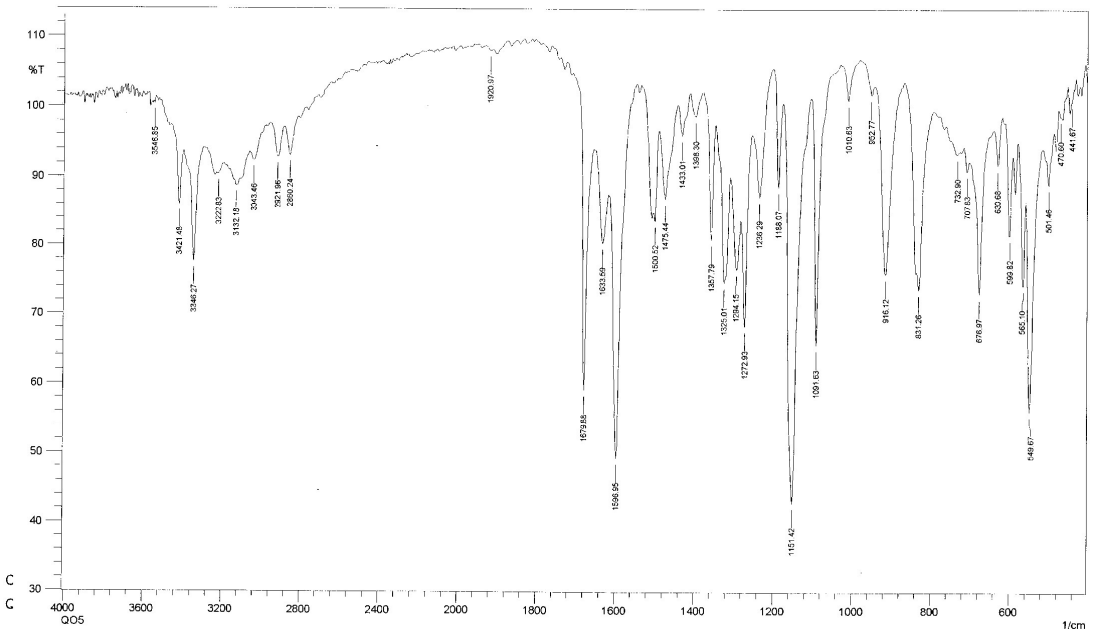
Appendixes

IR Spectra appendixes



I R Spectra of 2-(N^4-(p-(5- methyl- isoxazol-3-ye) -phenyl)- aminobenzene sulphonamide)-1,4-benzoquinone (XLVII)



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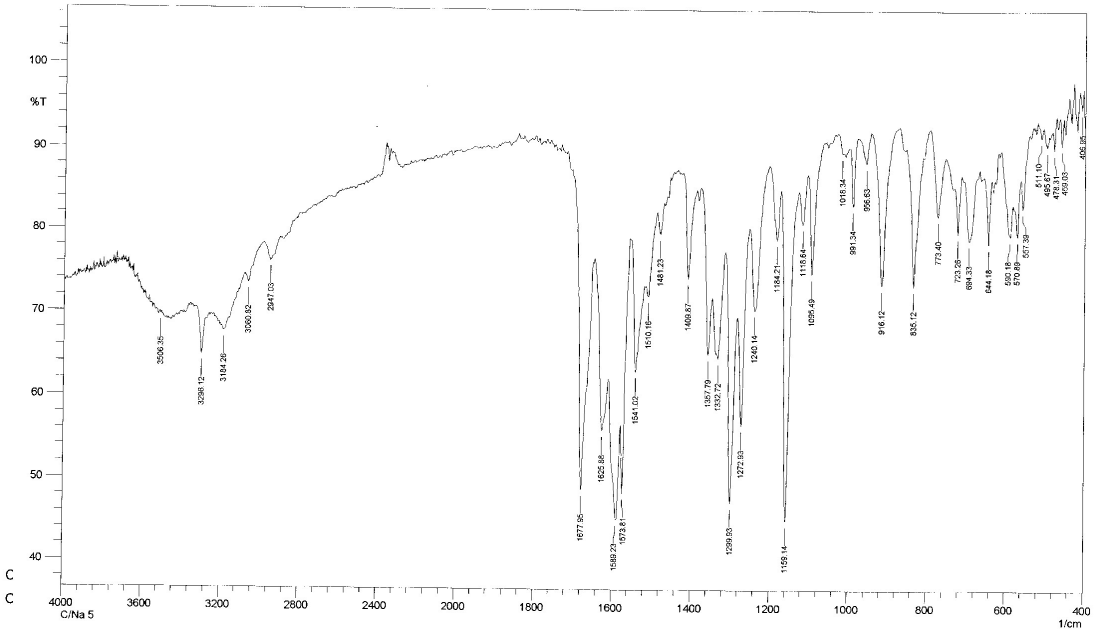

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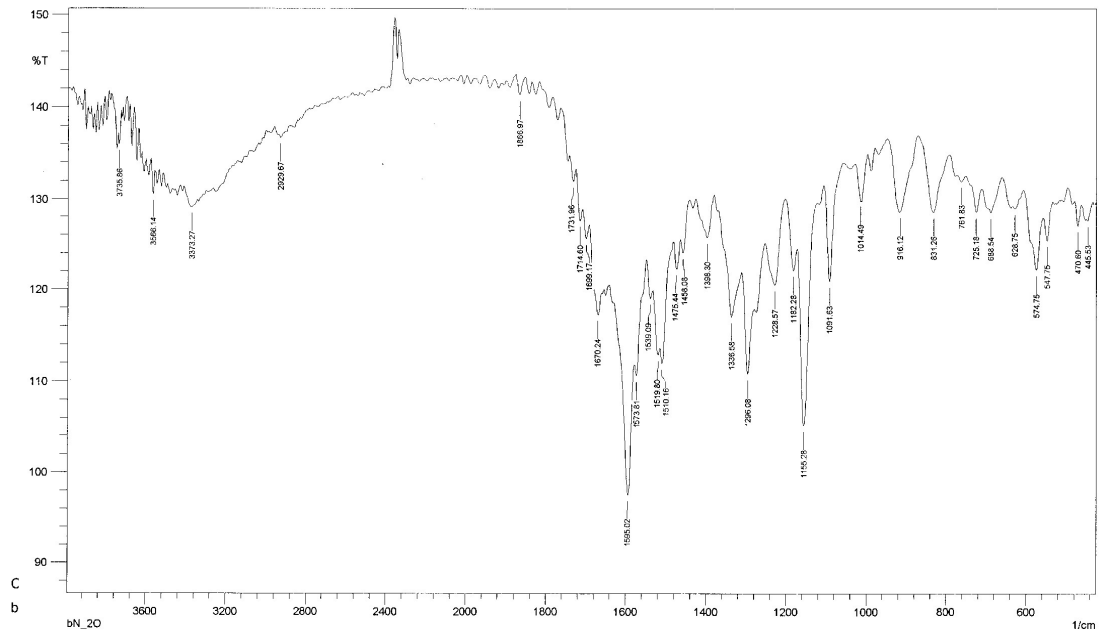

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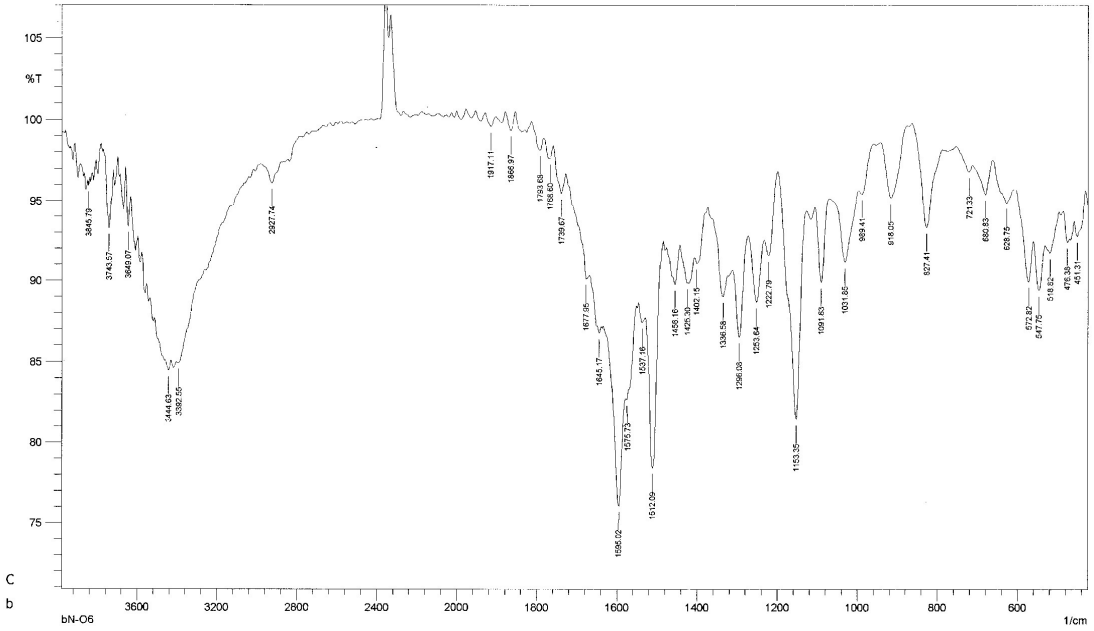

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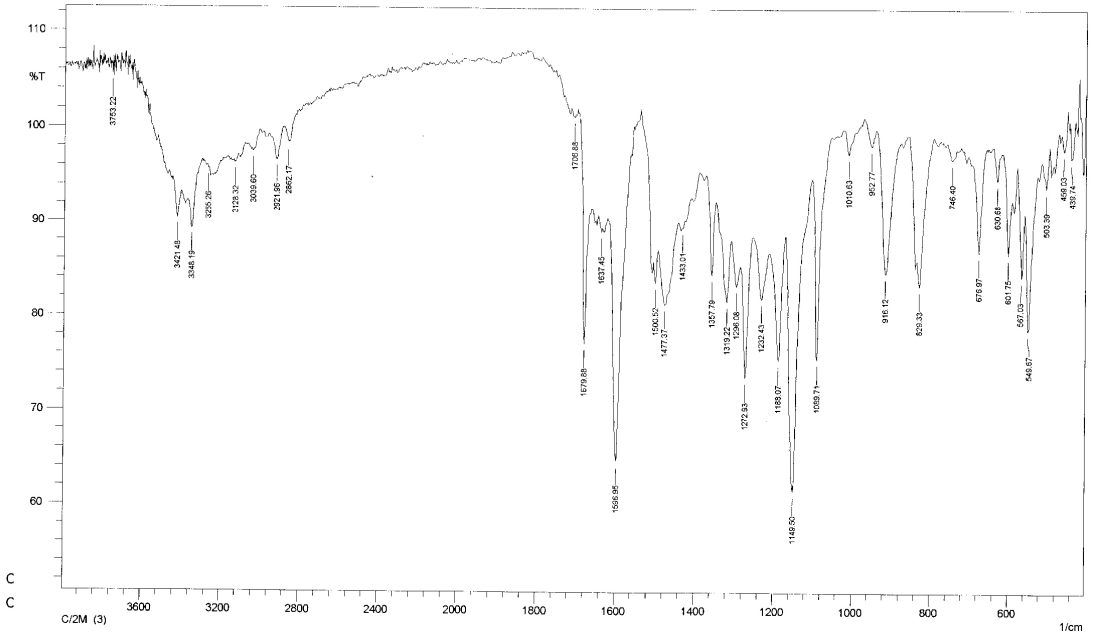

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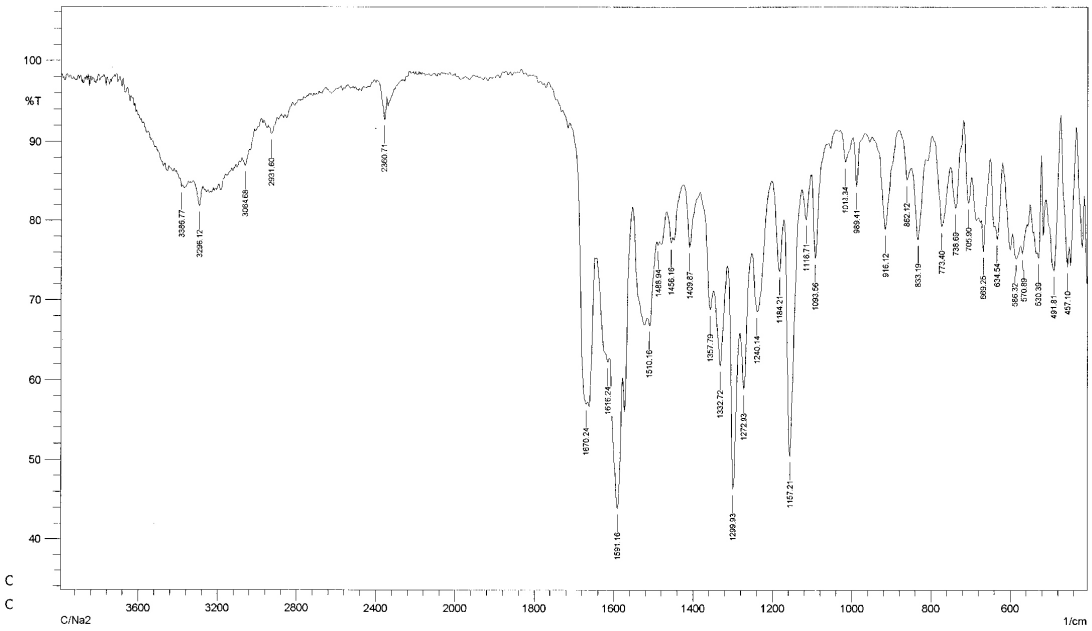

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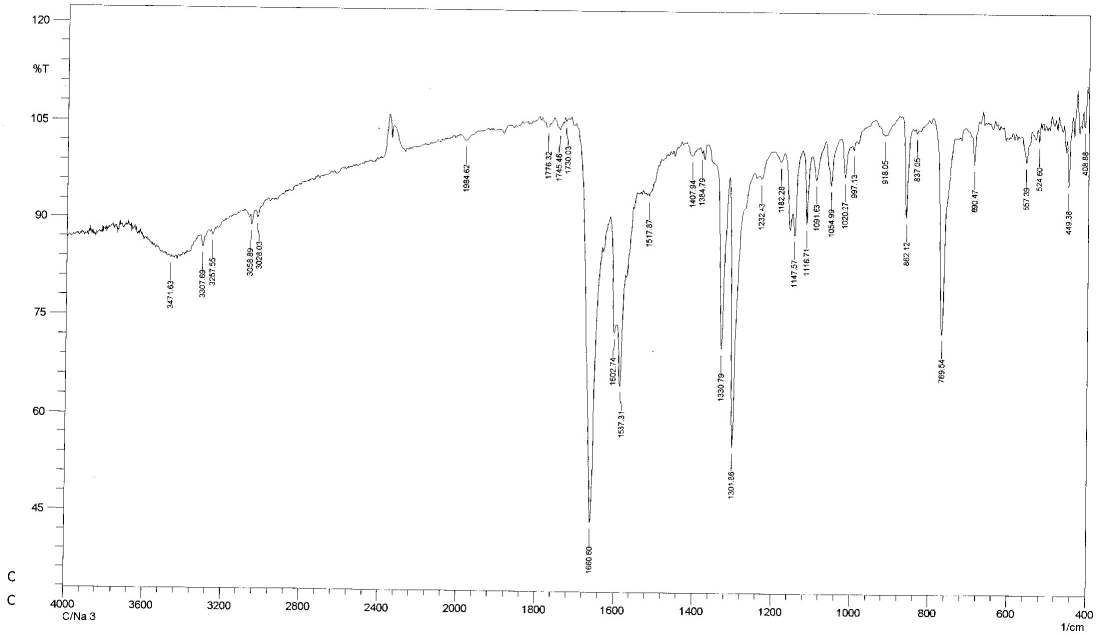

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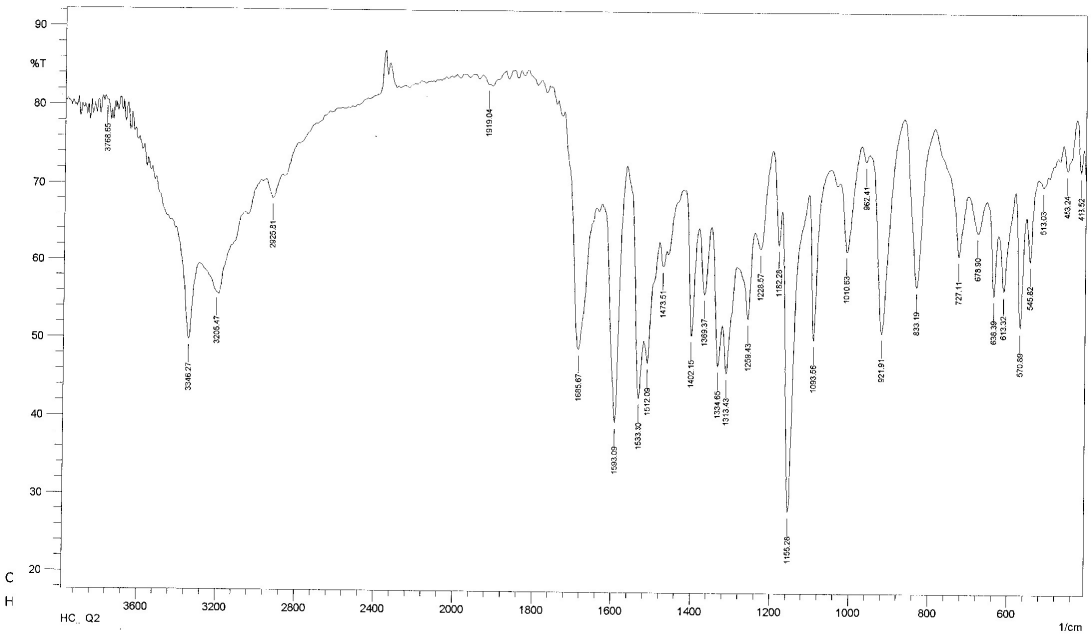

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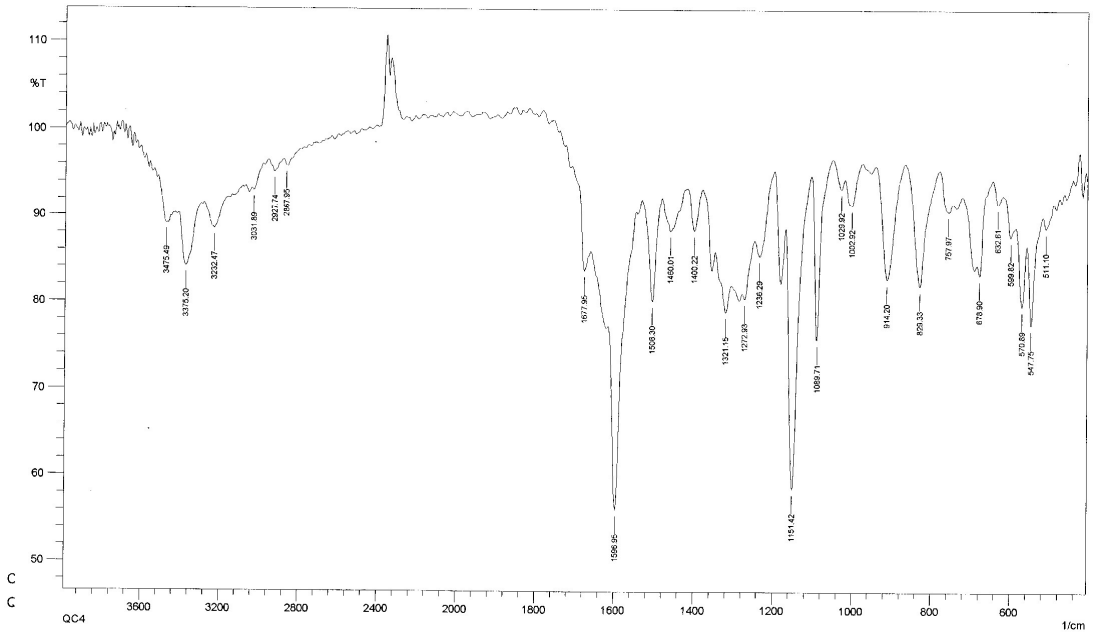

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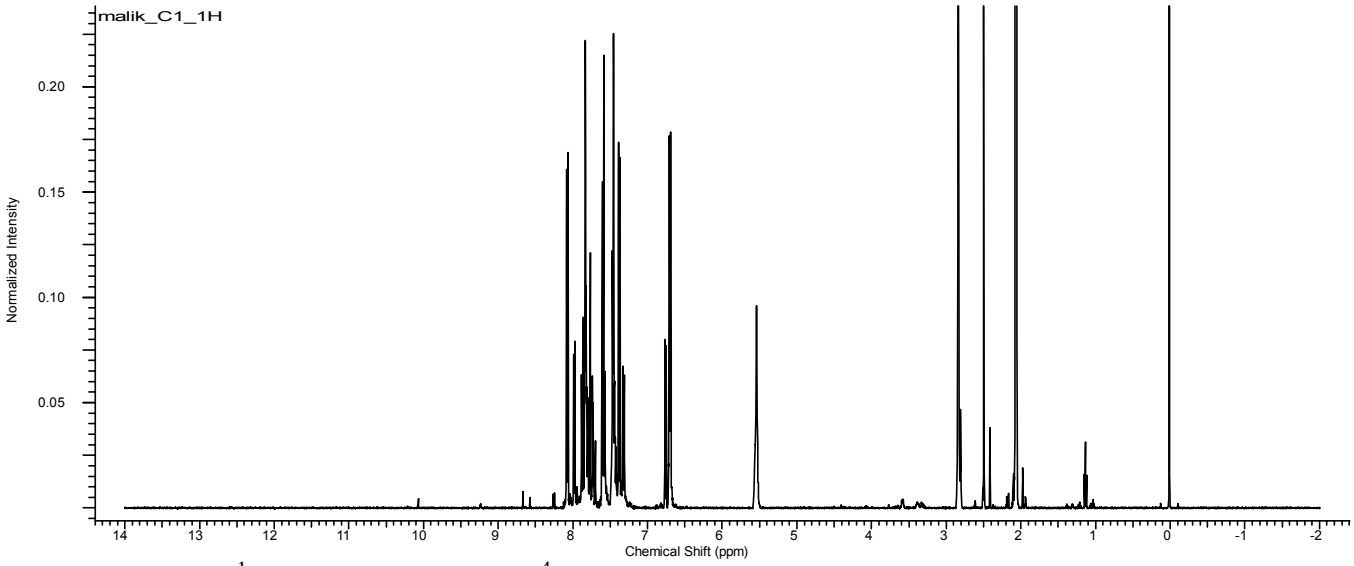
H^1NMR Spectra appendixes



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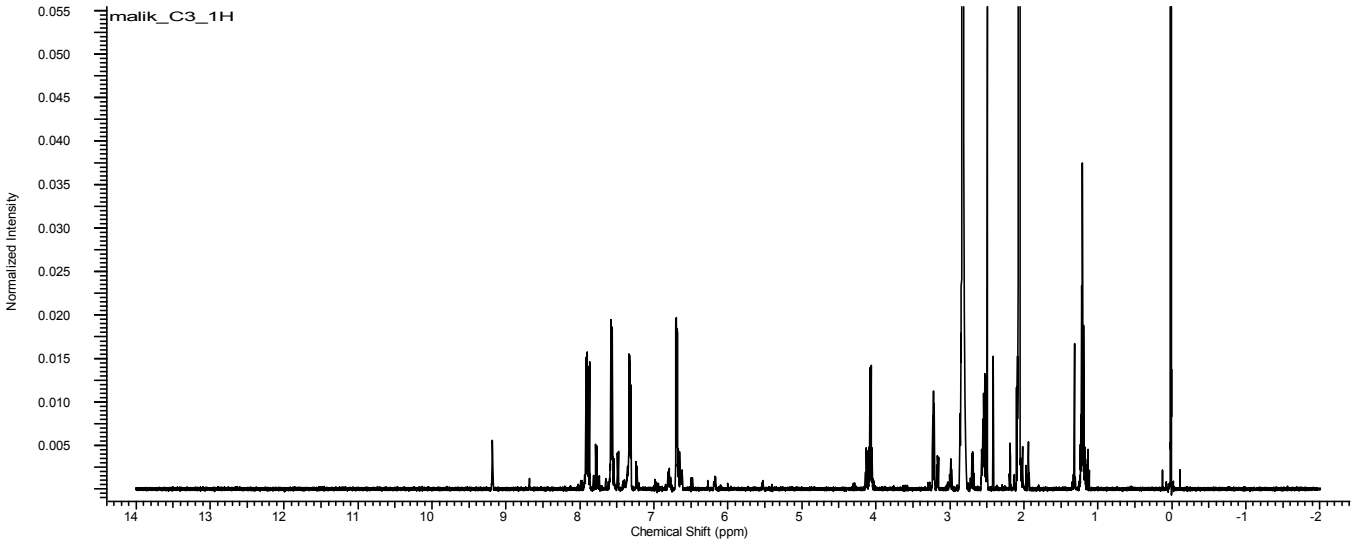

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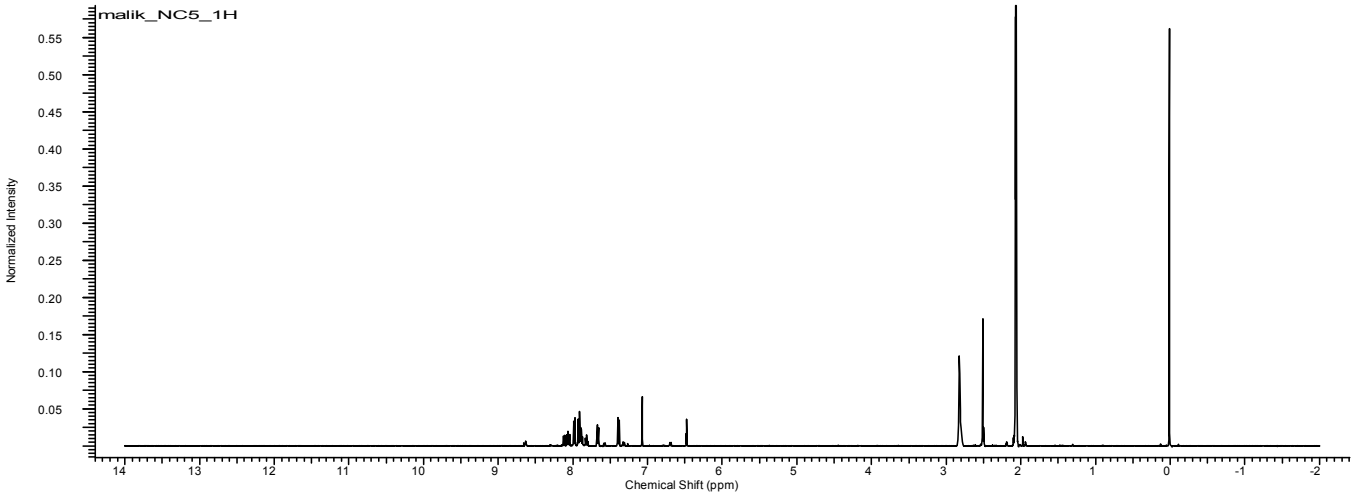
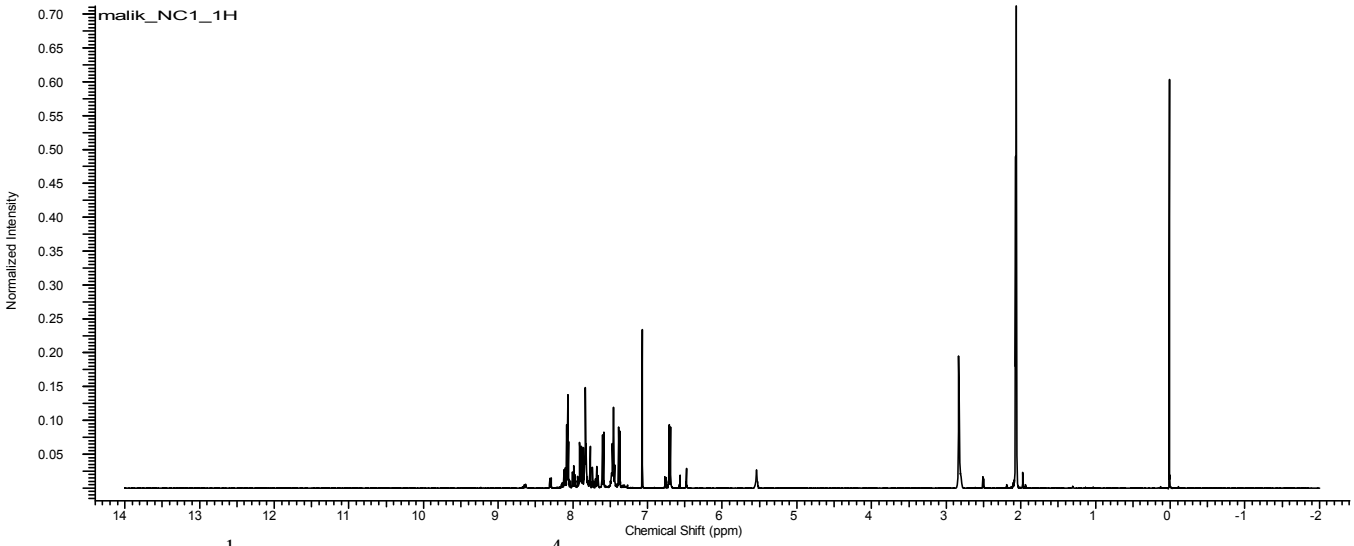


H^1NMR spectra of 2-(N^4-(p-(4-but-2-enoylphenyl)-aminobenzensulphonamide)-1,4- naphthaquinone(XXXVI)



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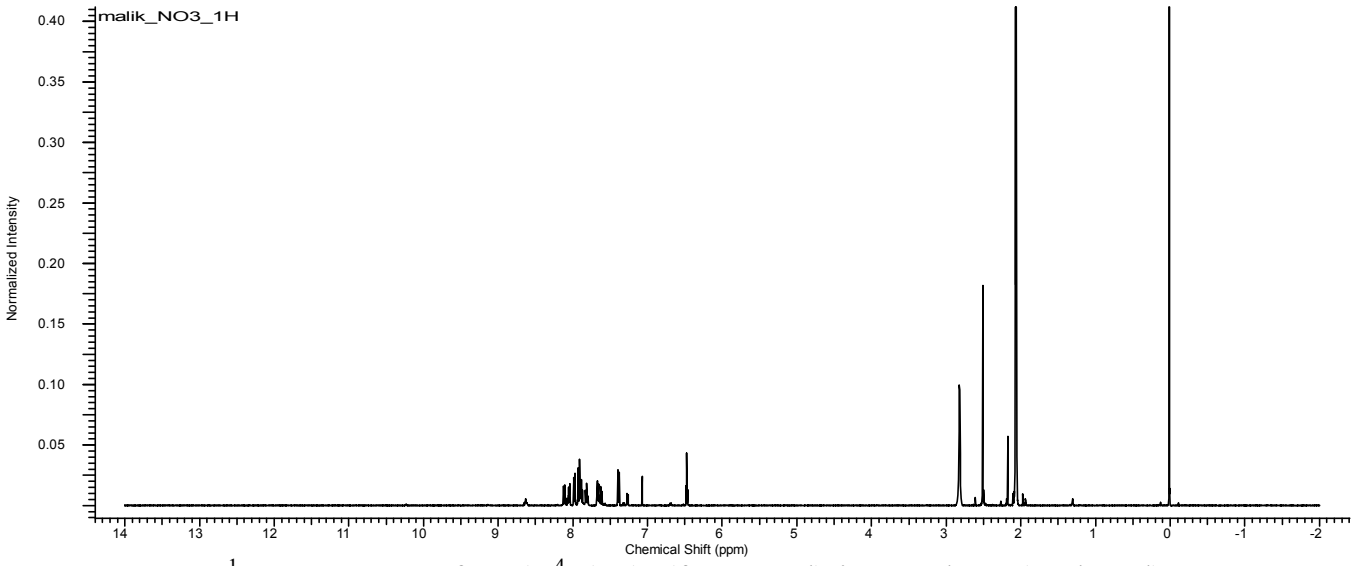

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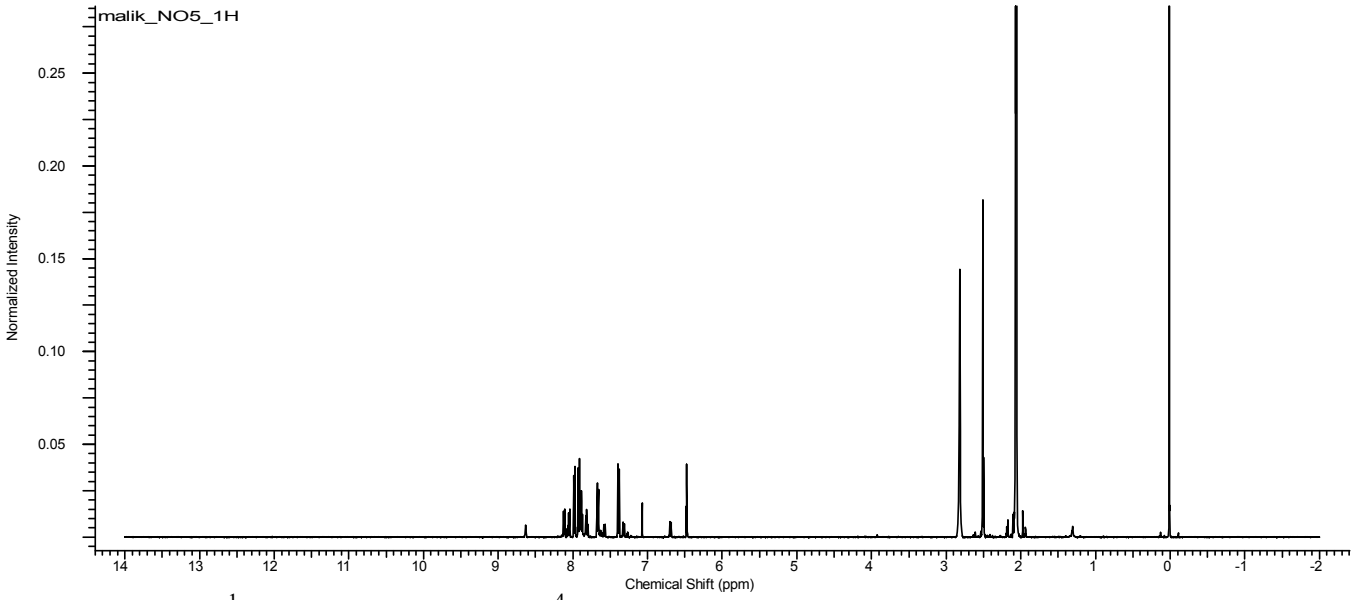

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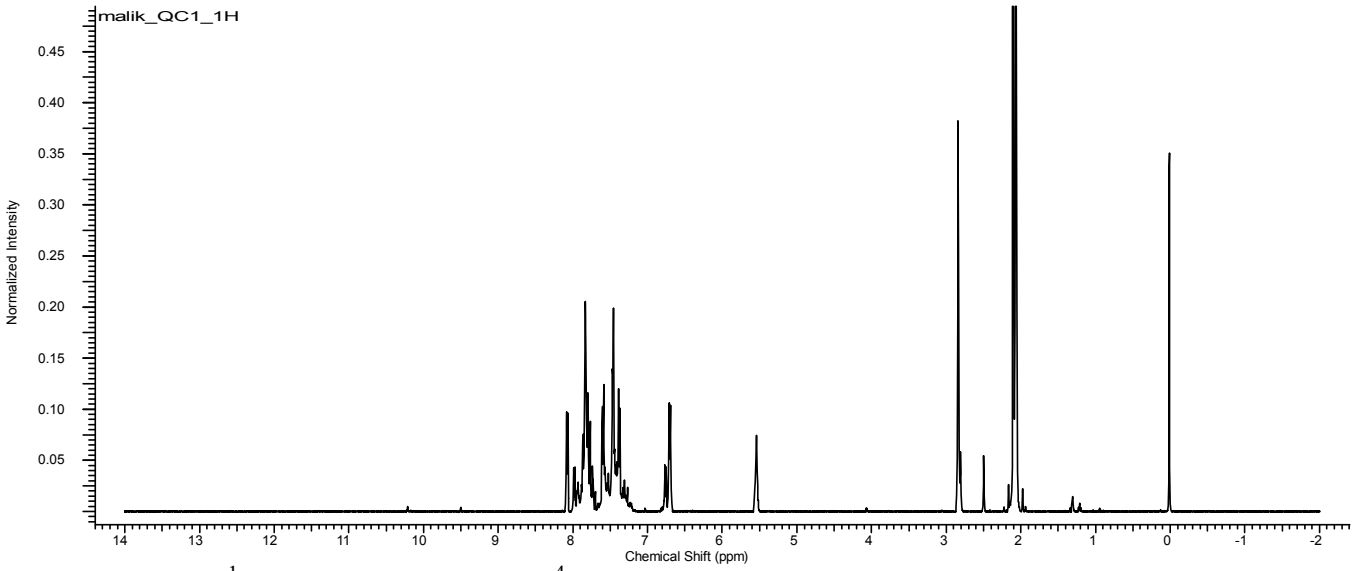

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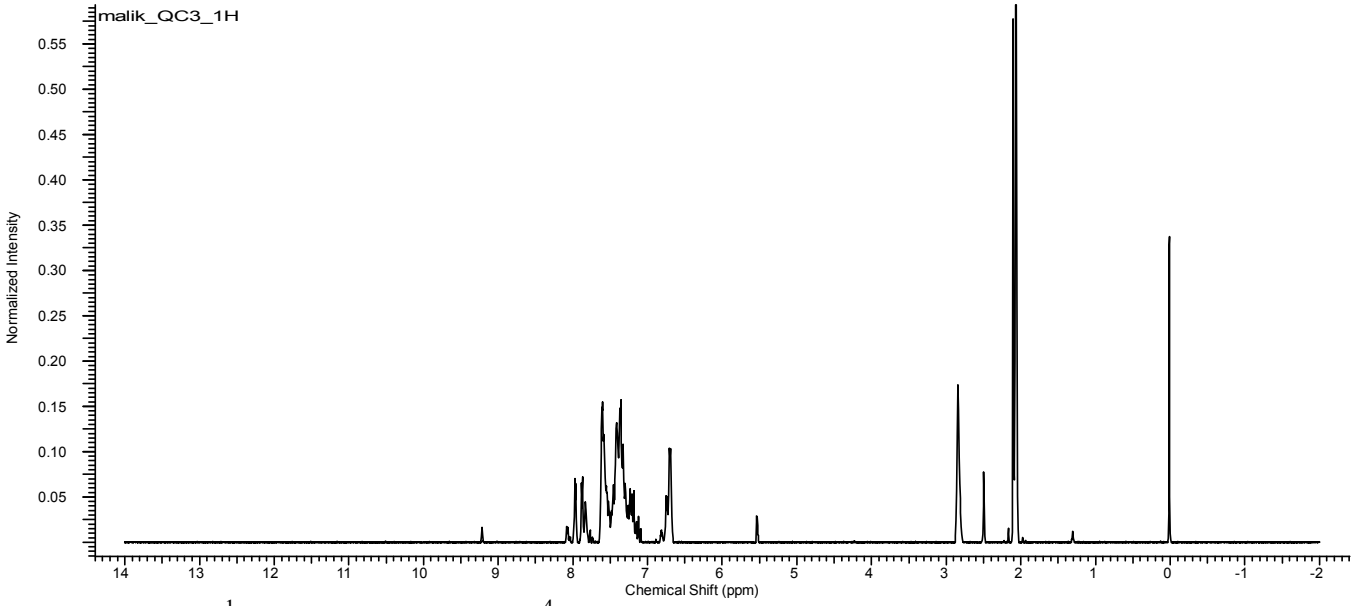

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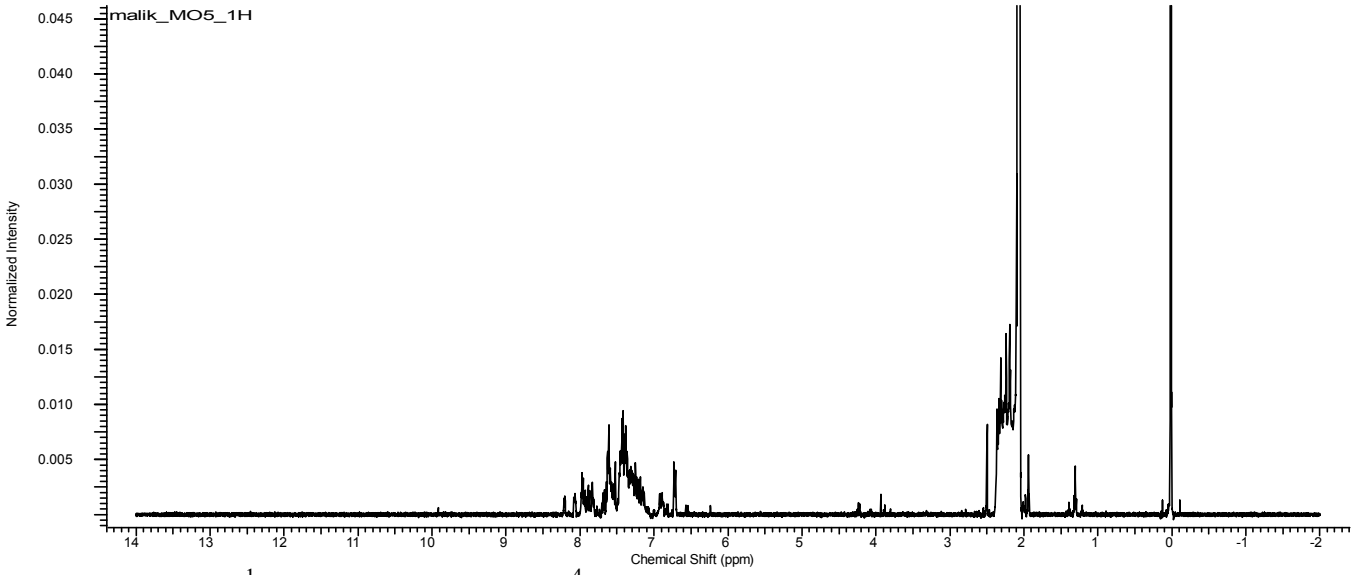

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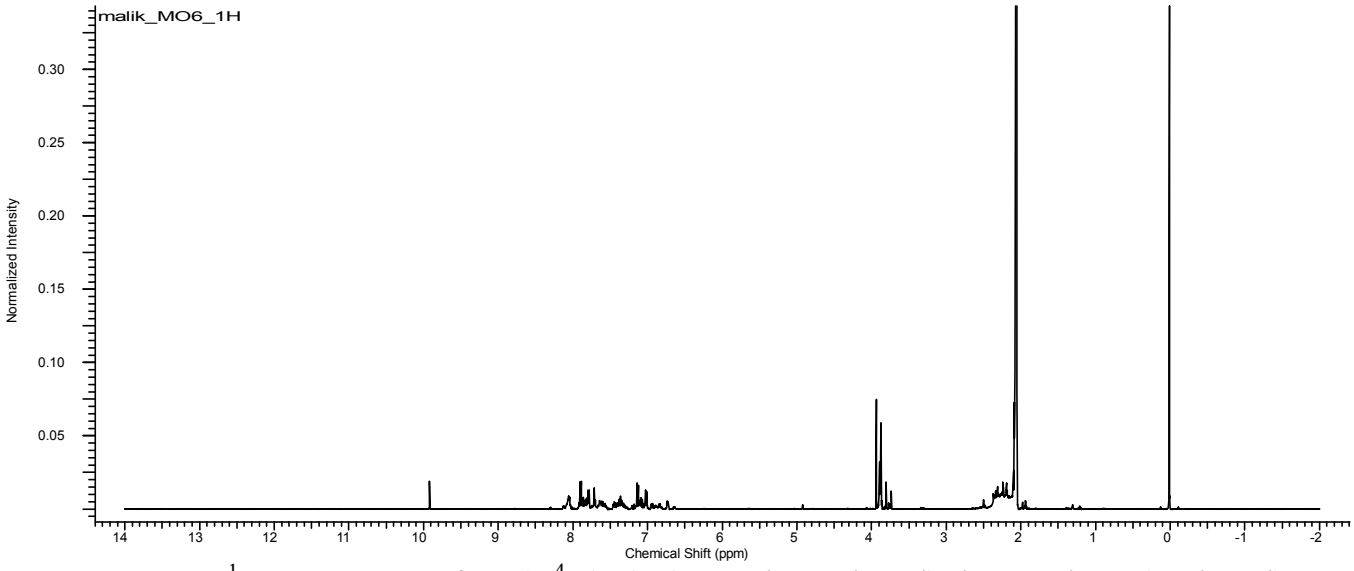
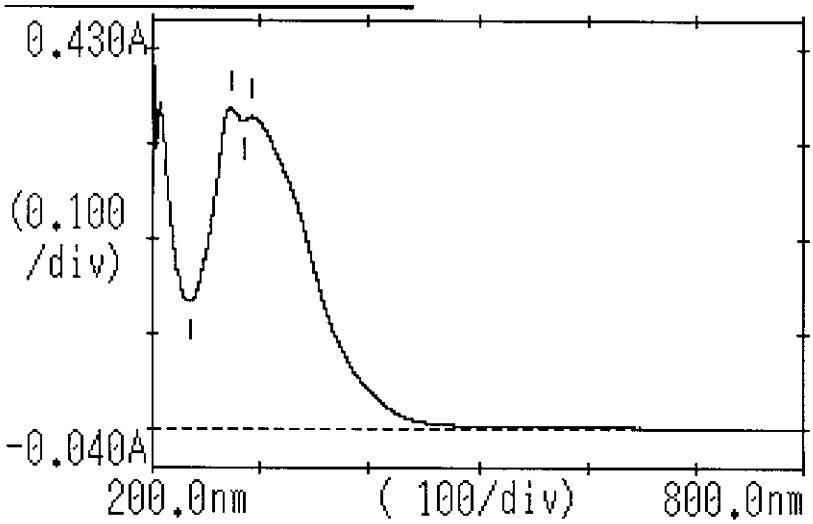


H^1NMR spectra of 2-(N^4-(p-(5-(4- methoxyphenyl)- isoxazol-3-ye) -phenyl)-aminobenzene sulphonamide)-3-methyl-1,4-naphthaquinone (LXI)

UV Spectra appendixes



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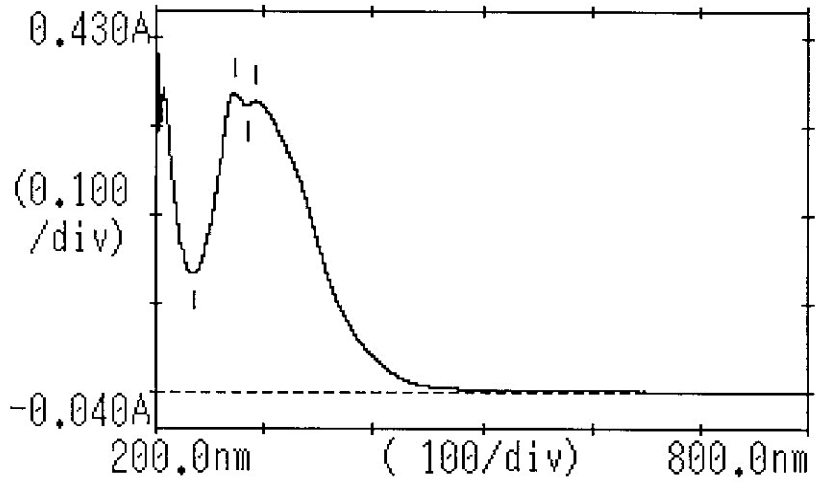

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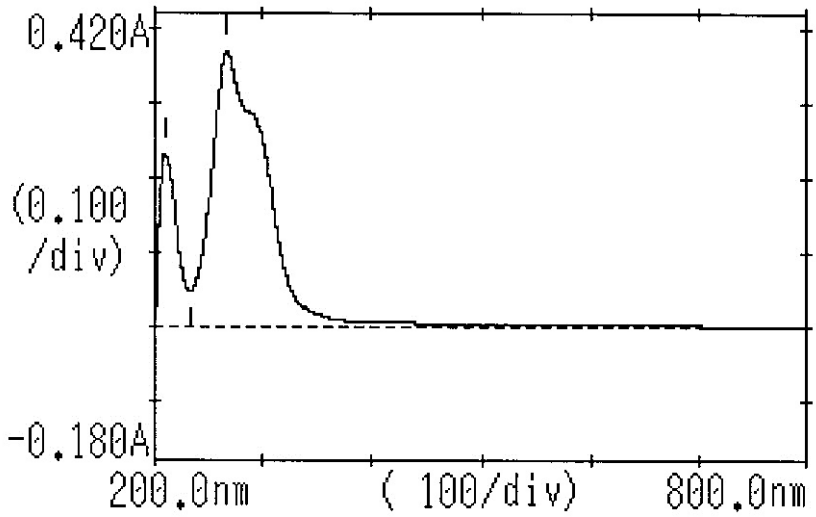

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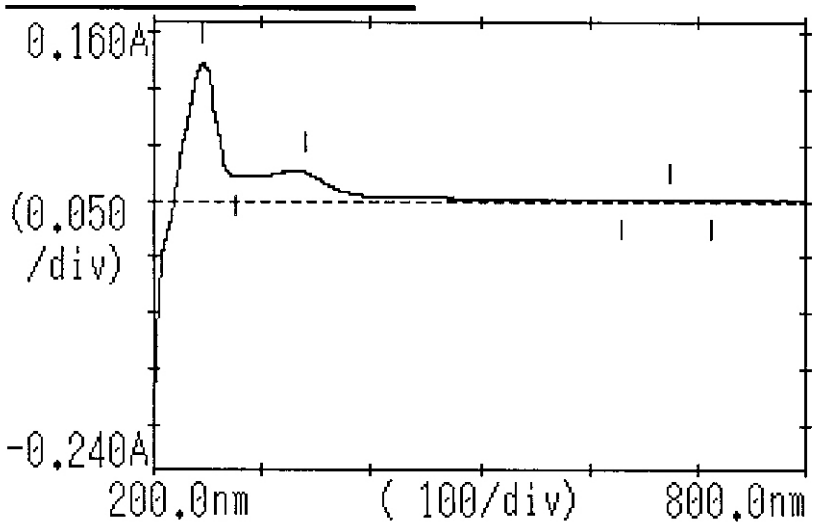

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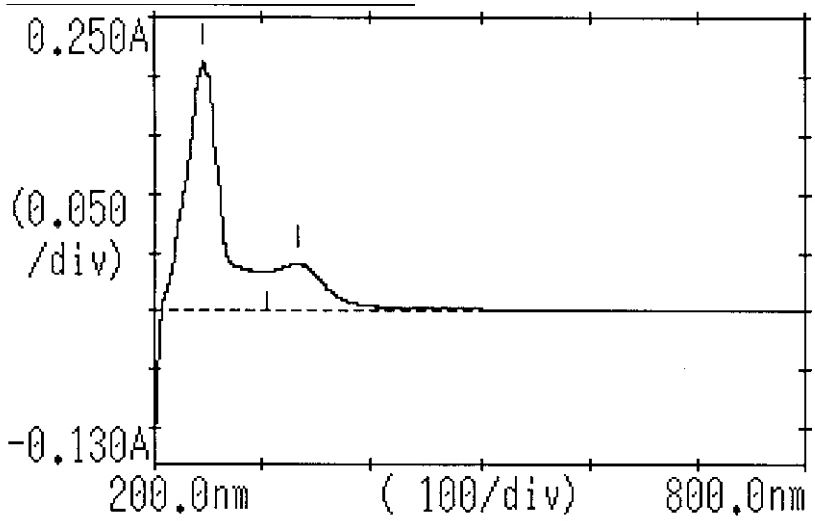

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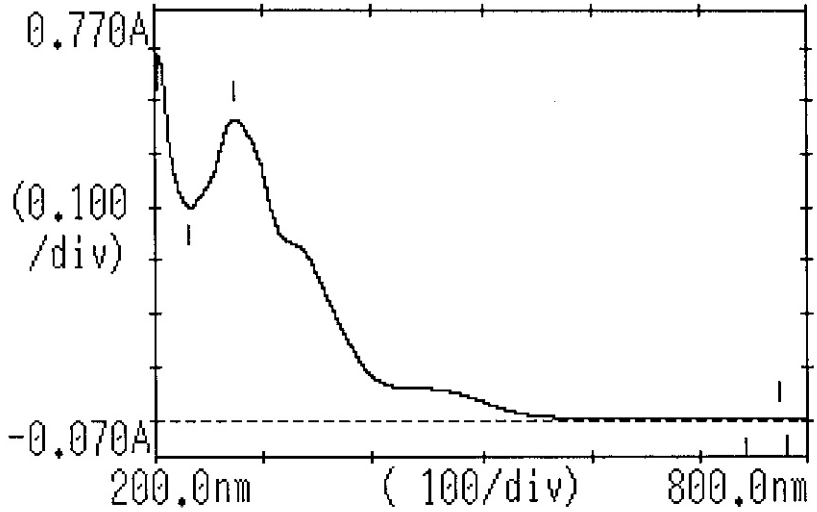

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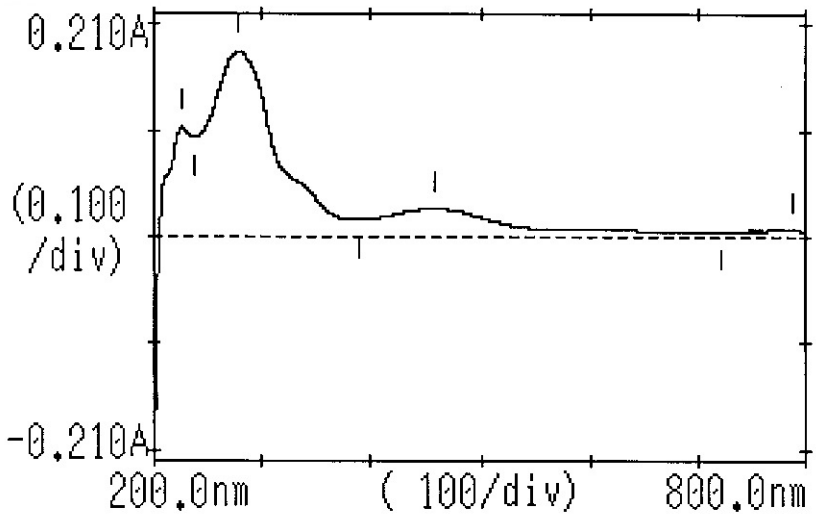

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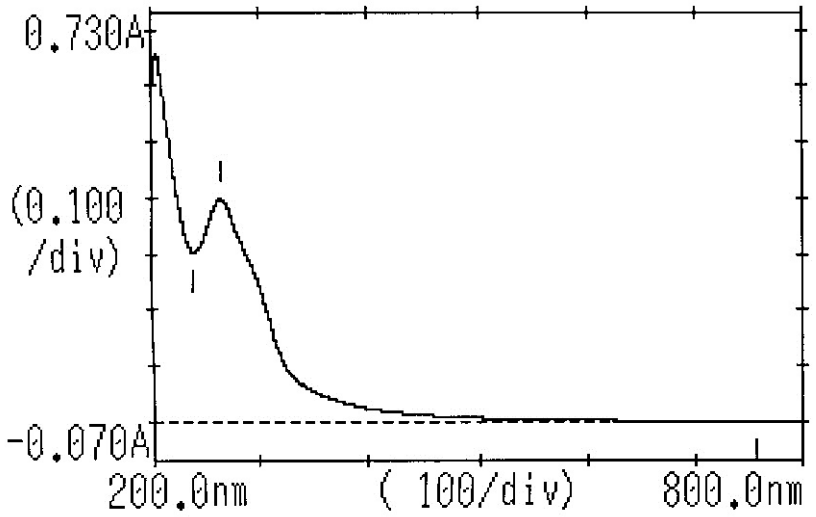

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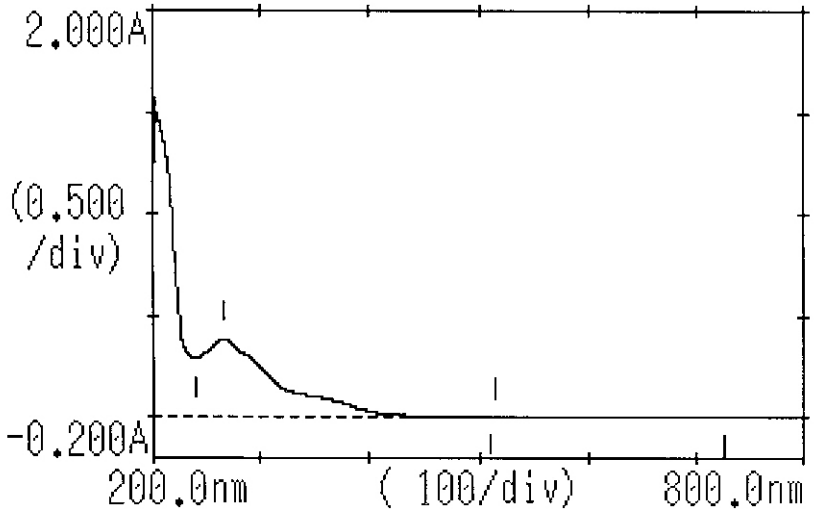

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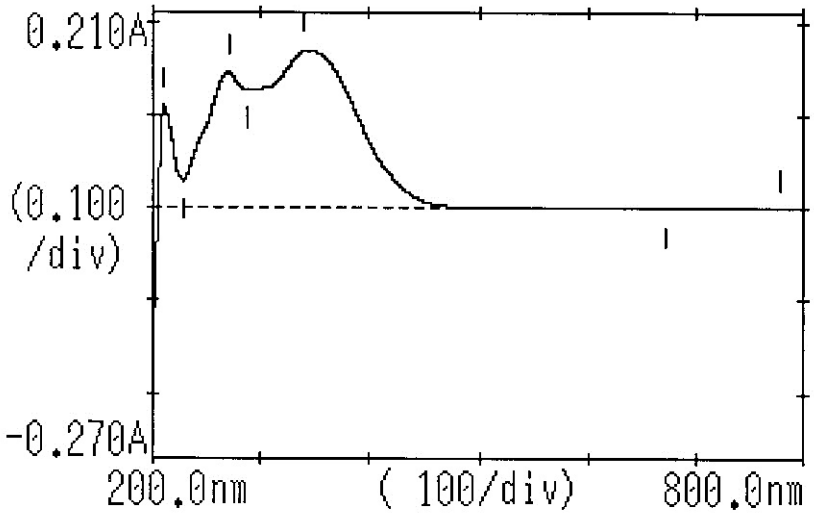

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