T.C.
ISTANBUL UNIVERSITY-CERRAHPASA
INSTITUTE OF GRADUATE STUDIES

Ph.D. THESIS

THE SYNTHESIS OF NEW POTENTIAL BIOACTIVE QUINONE AND BUTADIENE COMPOUNDS

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ISTANBUL- June, 2020

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This thesis is supported by the project numbered FDK-2017-24871 of Istanbul University-Cerrahpaşa Scientific Research Projects Executive Secreteriat.

FOREWORD

Praise and thanks to God who gave me the ability to overcome many difficulties and enabled me to complete my thesis.

All the love and appreciation to my supervisor Prof. Dr. M.Çiğdem SAYIL, and my Co-supervisor Assoc. Prof. Dr. Nahide Gulsah DENIZ for unlimited their love and support, they never spare me any effort or useful comments. Without their knowledge and common sense, I could not finish my thesis, I am really grateful to them.

My sincere thanks to all members of the department of organic chemistry for their continuous assistance and encouragement.

My dear husband, my children, my parents, my sisters, and my friends, thank you very much for your trust, patience and support for me throughout the years of study and intensive work.

Last but not least, I feel indebted to my government, which has provided me with great financial support to continue my higher education

June 2020 Aesha F. SH. ABDASSALAM

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LIST OF SYMBOLS AND ABBREVIATIONS

Abbreviation	Explanation
Vit K3	: Vitamin K3
TEA	: Triethylamine
Abs.	: Absolute
TLC	: Thin-layer chromatography
EtAc	: Ethylacetate
R_f	: Retention factor
MIC	: Minimum Inhibition Concentration
APT	: ^{13}C Attached-Proton-Test
MS[+ESI]	: Electrospray Ionisation Mass Spectrometry
R.T	: Room temperature

ÖZET

YENİ POTANSİYEL BİYOAKTİF KİNON VE BUTADİEN BİLEŞİKLERİNİN SENTEZİ

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Birçok araştırmacı, özellikle biyolojik ve terapötik olarak çeşitli alanlarda uygulanabilen çoklu özellikleri nedeniyle naftakinon ve 1,3,4,4-pentakloro-2-nitro-1,3-bütadien ve türevlerinin sentezi ile ilgilenmiştir.

Bu çalışmada, 2-metil-1,4-naftakinon (**la)**, 2,3-dikloro-5-nitro-1,4-naftakinon **(1b),** 2-nitro-1,3,4,4-tetrakloro-1-mono (oktiltiyo/heksiltiyo)-1,3-bütadien (**1d**, **1e)** farklı reaksiyon ortamında farklı N-nükleofiller ile birkaç yeni bileşik sentezlendi ve araştırıldı.

Çalışmamızın ilk aşamasında; yeni N-sübstitüe veya N,N-sübstitüe naftakinon bileşikleri, 2-metil-1,4-naftakinonun (K3 Vitamini) **(la),** piperazinler, morfolinler ve alifatik veya aromatik aminlerle bazik veya ılımlı ortamda reaksiyona sokulmasıyla sentezlendi, 2-metil-3-N-sübstitüe-l,4-naftakinonlar **2, 3, 5, 6, 7, 8, 9, 10, 12** ve **14**, nükleofillerin 2-metil-1,4-naftakinonun sadece 2-konumundaki reaksiyonu sonucu elde edildi, ilaveten, nükleofillerin 2-metil-1,4-naftakinon ile tepkimesi ile 2 ve 3-konumundaki metil grubu üzerinden 2-N-sübstitüe-3-N-sübstitüe-metil-1,4-naftakinon bileşikleri **4, 11** ve **13** sentezlendi.

İkinci aşamada; yeni regioizomerler, 2,3-dikloro-5-nitro-1,4-naftakinonun **(lb)**, aynı nükleofiller ile reaksiyonu yoluyla sentezlendi. Regioizomerler (2-amino-3-kloro-5-nitro-naftalen-1,4-dion) ve (3-amino-2-kloro-5-nitro-naftalen-1,4-dion) kolon kromatografisiyle farklı oranlarda çözücüler kullanarak ayrıldı. Sentezlenmiş regioizomerler **15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 28, 29, 30, 31, 32, 33, 35, 36** farklı renk, farklı erime noktası, farklı tutma faktörüne sahiptir (R_f) ve yeni regioizomerlerin ^{1}H NMR spektrumlarına göre (2-amino-3-kloro-5-nitro-naftalen-1,4-dion) izomerinin aromatik protonlarının kimyasal kayması (3-amino-2-kloro-5-nitro-naftalen-1,4-dion) izomerinin aromatik protonlarına göre daha düşük alanda gözlenmiştir. Ayrıca, regioizomer karışımı söz konusu olduğunda, yüksek R_f bileşeninin 2-amino-3-kloro-5-nitro-naftalen-1,4-dion izomerine ve düşük R_f bileşeninin 3-amino-2-kloro-5-nitro-naftalin-1,4-dion izomerine ait olduğu gözükmüştür.

Son aşamada; yeni S- ve N,S- sübstitüe nitro bütadien bileşikleri, farklı reaksiyon koşulları altında başarıyla sentezlenmiştir. 2-nitropentakloro-l,3-bütadienin **(1c)** çözücü içermeyen ortamda tiyoller (oktantiol, heksantiol) ile reaksiyonları yapıldı. Bu reaksiyonların bir sonucu olarak, 2-nitro-1,3,4,4-tetrakloro-1-mono (oktiltiyo/heksiltiyo)-1,3-bütadien **(1d, 1e)** elde edildi ve piperazin, morfolin ve piperidin türevleri ile reaksiyona sokularak yeni **37, 38, 39, 40, 41, 42 ve 43** bileşikleri iyi bir verim ile elde edildi.

Yeni bileşiklerin saflaştırılması kromatografik yöntemlerle gerçekleştirildi ve yapıları FTIR, ^{1}H NMR, ^{13}C NMR ve Kütle spektroskopisi gibi spektral yöntemlerle karakterize edildi.

Haziran 2020, 252 sayfa.

Anahtar kelimeler: Sentez, Naftakinonlar, K3 Vitamini, Polihalonitrobutadienler, Spektroskopi

SUMMARY

THE SYNTHESIS OF NEW POTENTIAL BIOACTIVE QUINONE AND BUTADIENE COMPOUNDS

Ph.D. THESIS

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Many researchers have been interested in the synthesis of naphthoquinone and 1,3,4,4 pentachloro-2-nitro 1,3-butadiene and their derivatives due to their multiple properties, which can be applied in several fields, particularly in biological and therapeutic applications.

In this study, reactions of 2-methyl-1,4-naphthoquinone **(1a)** and 2,3-dichloro-5-nitro-1,4-naphthoquinone **(1b),** 2-nitro-1,3,4,4-tetrachloro-1-mono(octylthio/hexylthio)-1,3-butadiene **(1d, 1e)** with different N-nucleophiles at different reaction medium, several new compounds were synthesized and investigated.

In the first stage of our study; the new N-substituted or N,N-substituted naphthoquinone compounds were synthesized by the reaction of 2-methyl-1,4-naphthoquinone (Vitamin K3) **(1a)** with piperazines, morpholines and aliphatic or aromatic amines in basic or moderate medium, 2-methyl-3-N-substituted-1,4-naphthoquinones **2, 3, 5, 6, 7, 8, 9, 10, 12** and 1**4** were obtained as a result of reaction of nucleophiles at only 2-position of 2-methyl-1,4-naphthoquinone, additionally, the 2-N-substituted-3-N-substituted-methyl-1,4-

naphthoquinone compounds **4, 11** and **13** were formed when the reaction of nucleophiles take place on the 2-position and methyl group at 3-position of 2-methyl-1,4-naphthoquinone.

In the second stage; new regioisomers were synthesized by the reaction of 2,3-dichloro-5-nitro-1,4-naphthoquinone **(1b)**, with same nucleophiles. The regioisomers (2-amino-3-chloro-5-nitro-naphthalene-1,4-dione) and (3-amino-2-chloro-5-nitro-naphthalene-1,4-dione) were separated by column chromatography using a different ratio of solvents. The synthesized regioisomers **15, 16, 17, 18, 20, 21, 22, 23, 24, 25, 28, 29, 30, 31, 32, 33, 35, 36** have different color, different melting point, different retention factor (R_f), and chemical shift of naphthoquinone protons. According to the ^1H NMR spectra of the new regioisomers were indicated that, the peaks of the 2-amino-3-chloro-5-nitro-naphthalene-1,4-dione isomer of aromatic protons are shifted more down field than the aromatic protons of the 3-amino-2-chloro-5-nitro-naphthalene-1,4-dione isomer. Also, it has been found that, In the case of mixture regioisomers, the higher R_f component was shown to be the 2-amino-3-chloro-5-nitro-naphthalene-1,4-dione isomer and the lower R_f component the 3-amino-2-chloro-5-nitro-naphthalene-1,4-dione isomer.

In the last stage; novel S- and N, S-substituted nitro butadiene compounds have been successfully synthesized under different reaction conditions. The reactions of 2-nitropentachloro-1,3-butadiene **(1c)** with octanethiol, hexanethiol in solvent-free were done. As a result of these reactions, 2-nitro-1,3,4,4-tetrachloro-1-mono(octylthio/hexylthio)-1,3-butadiene **(1d, 1e)** were obtained and reacted with piperazine, morpholine and piperidine derivatives to give new compounds **37, 38, 39, 40, 41, 42** and **43** in a good yield.

The purification of new compounds was performed by chromatographic methods and their structures were characterized by spectral techniques as FTIR, ^1H, ^{13}C NMR, and Mass spectroscopy.

June 2020, 252 pages.

Keywords: Synthesis, Naphthoquinones, Vitamin K3, Polyhalonitrobutadienes, Spectroscopy

1. INTRODUCTION

The quinone compounds are colored compounds due to their conjugation system and are used as natural pigments. The research fields of quinone compounds are broad and important around the world due to its high biological properties [1]. A considerable number of natural and synthetic of quinones specially, One of the interesting biological properties of 1,4-naphthoquinone derivatives has been used as antimalarials [2-4], antifungal [5-8], antibacterial [9-12], antitumor [13, 14], and antiallergic activities [15, 16], due to their redox potentials [17]. Also, a large-scale application of quinones in synthetic organic chemistry [18, 19]. The reactions of 1,4-naphthoquinones with amines and other N-nucleophilic reagents give derivatives of 2-aryl or alkylamino-1,4-naphthoquinone have known many years ago [20], this reaction is the most investigated type of Michael addition to quinones.

It is known that nitrogen-substituted polyhalo-1,3-butadienes have been created as primary sources for synthesis of derivatives that have multiple biological properties [21, 22], because of their activity towards nucleophilic substitution reaction. Also, some thio-substituted dienes display high biological activity such as herbicide, insecticide, and fungicide [23]. These years, some of N,S-substituted nitrodienes obtained by reaction of thiols, amines or piperazines with nitrodienes [24-26].

New amino naphthoquinone derivatives and N,S-substituted butadiene compounds were created in this research. A new naphthoquinone compounds were obtained using vitamin K3 “2-methyl-1,4-naphthoquinone” and “2,3-dichloro-5-nitro-1,4-naphthoquinone” compounds as starting material with some N-nucleophiles (amines and their derivatives). In the synthesis of new halobutadienes, 2-nitropentachlor-1,3-butadiene compound and (mono-thio) substituted nitrobutadienes synthesized and used as starting material. New N,S-substituted-2-nitro-1,3-butadiene compounds also synthesized by reaction of (mono-thio) substituted 2-nitrodiene compounds with same N-nucleophiles.

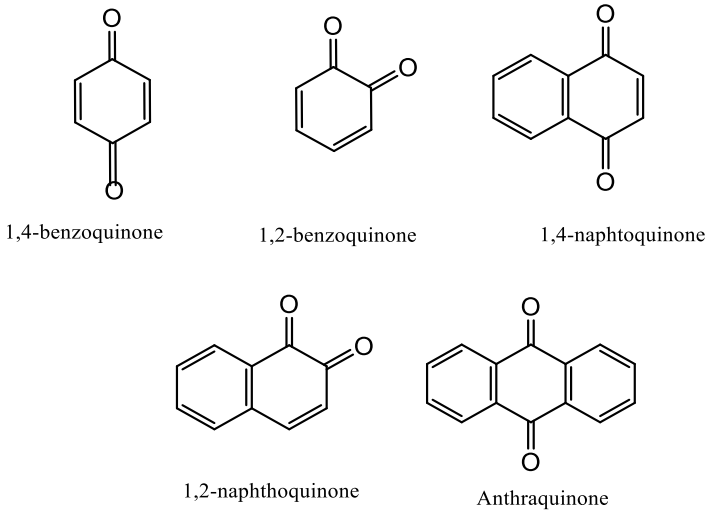
The newly synthesized compounds in this study, are expected to contribute to the literature and researchers in organic chemistry. We hope that all compounds will exhibit high biological activity and antioxidant agents.

Physical and chemical properties, synthesis methods, reactions and usage areas of quinone, butadiene, amine and thiol compounds were discussed in the first part of my thesis.

1.1. GENERAL INFORMATION ABOUT QUINONES AND 1,4-NAPHTHOQUINONE COMPOUNDS

Quinone, is the common name given to group of cyclic organic compounds. It has a conjugated cyclic with di carbonyl groups on an aromatic ring. 1,4-Naphthoquinones are part of quinone families containing benzoquinones (ortho, para-benzoquinone) and anthraquinones. p-benzoquinone or 1,4-benzoquinone is the simplest member of quinones, it is so called quinone. The quinones are not aromatic compounds, but are readily obtained from aromatic compounds and can be readily converted to aromatic compounds. In the aromatic rings, according to the classical spelling, there are three double bonds in the conjugation system, however, the quinones have two conjugated double bonds. Therefore, ring systems can be classified into two classes, benzenoid and quinoid rings. The benzenoid compounds, can be changed to quinoid systems by oxidation [27].

The most of quinones like structures are known, the most famous of them are 1,2- and 1,4-benzo/naphthoquinone. Generally, the 1,2-quinone is harder to prepare and more reactive than 1,4-quinone. Some structure of quinones are shown in (1.1).



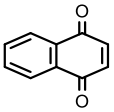
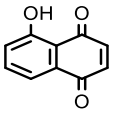
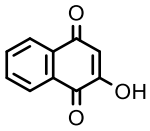
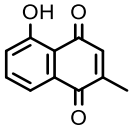
(1.1)

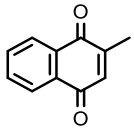
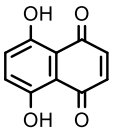
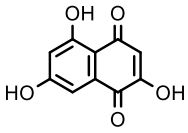
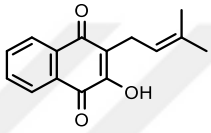
1.1.1. Physical and Chemical Properties of Quinones.

The quinones contained only two double bonds, and because they have 4π electrons in the ring, they are not aromatic compounds.

P-benzoquinone is a bright yellow crystal with a melting point of 115.7ºC, easily to sublimate. It can be distilled by water vapor. It has a strange odor that causes sneezing. However, it soluble in alcohol, water, ether, chloroform and some other organic solvents [28]. 1,4-naphthoquinone is brownish green powder or yellow needles, triclinic crystalline class of crystalline organic compounds has a melting point of 125-128°C. It is easily soluble in polar organic solvents, whereas, in water, it is slightly soluble, also it gives a brown-red solution in alkaline media. Anthraquinone, melting at 284-285ºC, odorless, non-volatile with water vapor, has a yellow crystal. Phenanthrenequinone, melting at 209ºC, odorless, volatile, and orange crystals. The most widespread and simplest naphthoquinones in nature are, plumbagin, lawsone, juglone and lapachol (Table 1.1).

Table 1.1: Some chemical Structurs and physical properties of 1,4-naphthoquinones in nature

Systematic (Trivial) Name	Chemical Structure	Molecular Weight	Melting Point [°C]
1,4-naphthoquinone		158.15	119-122
5-hydroxy-1,4-naphthoquinone (juglone)		174.14	155
2-hydroxy-1,4-naphthoquinone (lawsone)		174.15	192-195
5-Hydroxy-2-methyl-1,4-naphthoquinone (Plumbagin)		188.18	78-79

2-Methyl-1,4-naphthoquinone (Menadione)		172.18	105-107
5,8-Dihydroxy-1,4-naphthoquinone (Naphthazarin)		190.16	237
2,5,7-Trihydroxy-1,4-naphthoquinone (Flaviolin)		206.17	164-168.5
2-Hydroxy-3-(3-methyl-but-2-enyl)-1,4- naphthoquinone (Lapachol)		242.27	141-143

All of quinones are highly conjugated system and thus, show colorful properties. Most quinone compounds can be isolated from plants as natural dyes [29]. An example of natural dye sources extracted from the plant roots of *Rubia tinctorum L,* the dyeing ingredients are anthraquinones, that may contribute to increasing the plant's ability to resistant fungi in the soil (Fig. 1.1). It has a wide dyeing spectrum in colors, red, orange, brown, lilac and pink. The color quality of the fabrics is more stable and clearer than synthetic dyes.



Figure 1.1: An overview of *Rubia tinctorum L* and structure of Alizarin dye.

The redox process from hydroquinone form to quinone form can be seen as steps of proton and electron transfers. Firstly, deprotonation leads to a phenoxide ion which is changed to phenoxy radical by one-electron oxidation. In the second step, dissociation of the second

hydroxyl group forms the radical anion semiquinone, followed by the second one-electron oxidation to generate the p-benzoquinone (Fig.1.2). All intermediates are stabilized by resonance. Similar redox processes are commonly observed in nature.

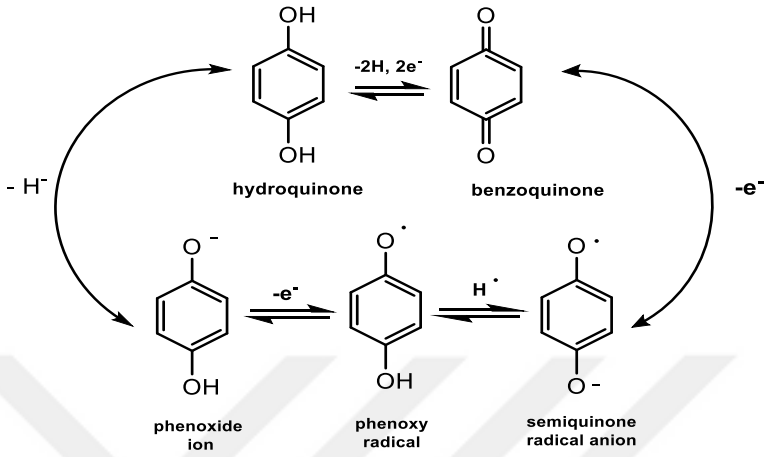
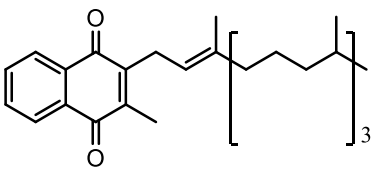
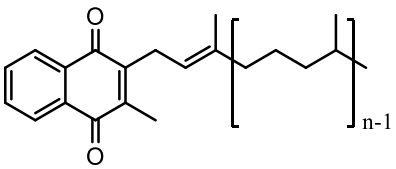


Figure 1.2: Redox forms of quinones.

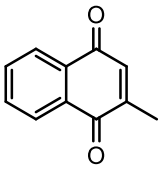
1,4-Naphthoquinone and its derivatives have antitumor and antibacterial properties due to their aromatic stability. There are many known natural organic substances contain the naphthoquinone in their main structure, especially vitamin K groups. Vitamins K, have basic structure consists of 2-methyl-1,4-naphthoquinone and different side chain in (C-3) position. There are two kinks of Vit-K in the nature: Vit K1, K2. Vit K1 is called phylloquinone, its chemical name is "2-methyl-3-suppository-1,4-naphthoquinone, green plants are rich in this vitamin, and vitamin K2 is a group of menaquinone compounds that can be made by bacteria inside the intestine. The chemical name is "2-methyl-3-difarnesyl-1,4-naphthoquinone". There are also other naphthoquinone compounds having a different number of carbons in the side chain that showing vitamin K activity. However, there is no need for a side chain for vitamin K effect to occur. Menadione (Vit K3) or “2- methyl-1,4-naphthoquinone” is the synthetic form without side chain in (C-3) position and has same effect of vitamin K group. Generally, vitamin K regulates blood clotting properties [30]. Section (1.2) shows the chemical structure of vitamin K group.



(Vitamin K1)



(Vitamin K2)

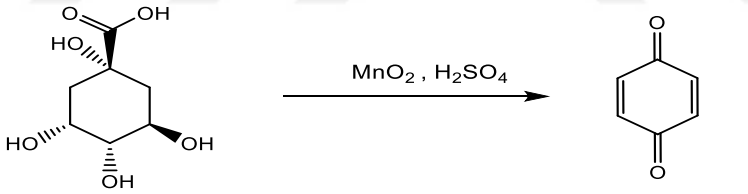


(Vitamin K3)

(1.2)

1.1.2. The General Synthesis of Quinones

Since the middle of the 19th century, researchers have been studied the different properties of several quinones. The most common is p-quinone which was discovered in the late 1830s by Liebig as the chemical oxidation product of quinic acid with sulfuric acid and manganese dioxide. The reaction involves a dehydration, decarboxylation, and finally, oxidation [31] (1.3).

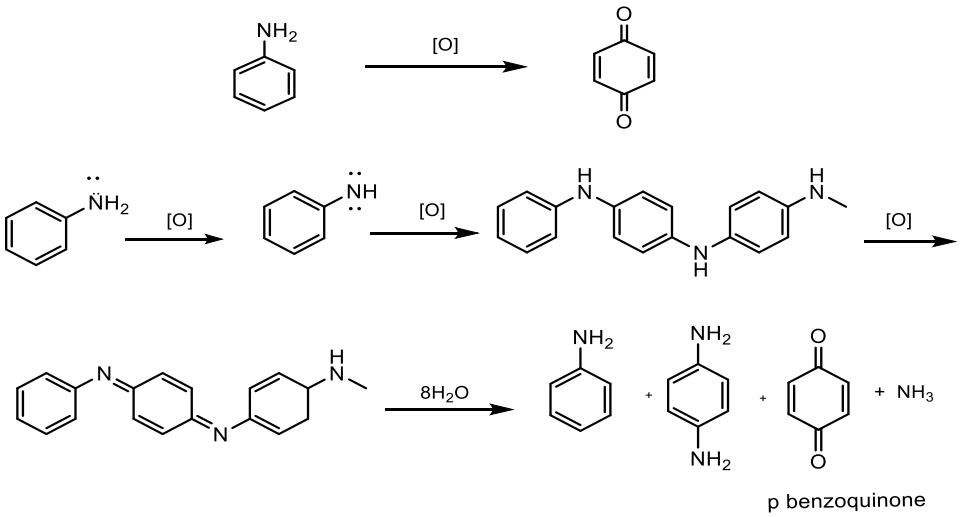


quinic acid

p-benzoquinone

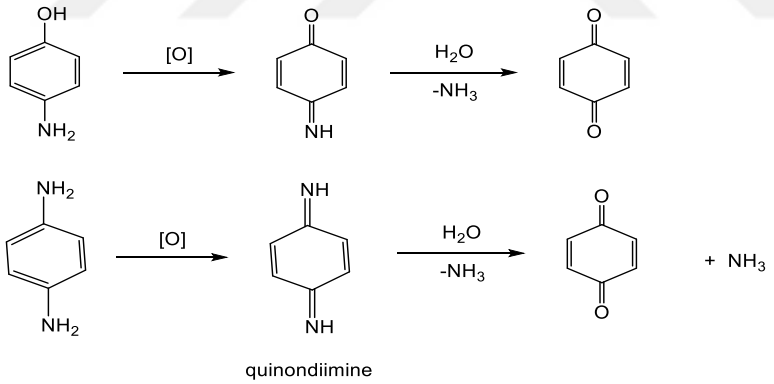
(1.3)

The same product can be obtained using the same reagents of sulfuric acid and manganese dioxide or in acidic dichromate solution with aniline through the free radical condensation mechanism. In the dichromate solution First, a dark intermediate product called aniline black is formed, more oxidation and hydrolysis give the benzoquinone (1.4).



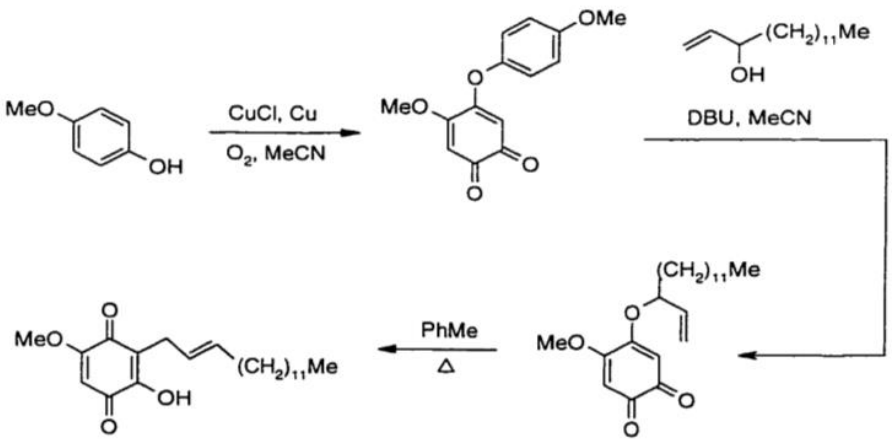
(1.4)

Acidic dichromate (VI), by oxidation of aminophenols and diamines in the presence of permanganate, intermediates of quinonimine and quinondimine are obtained. Then by hydrolysis of these intermediates quinone compound can be obtained (1.5).



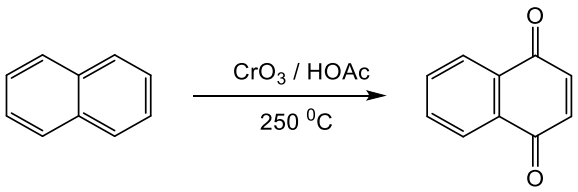
(1.5)

An asymmetric and biologically active compound of alkyl hydroxy methoxyquinone can be synthesized from para- methoxy phenol. The alkyl chain can be introduced into the hydroxy group by Claisen rearranging [32] (1.6).



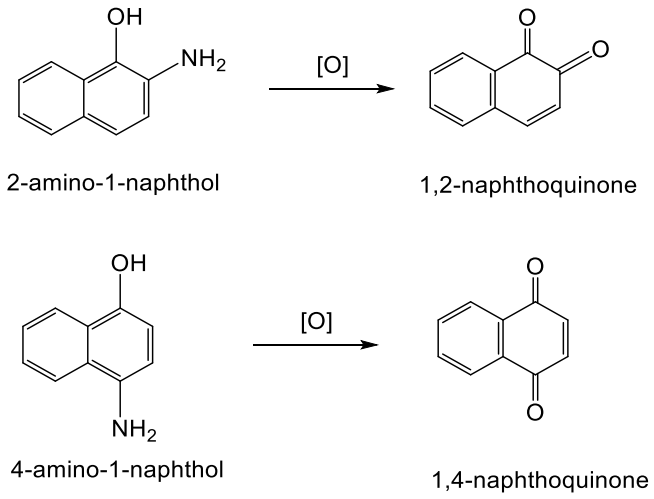
(1.6)

The synthesis of naphthoquinones also can be performed by oxidation reactions. However, they may also be synthesized by cycloaddition and electrophilic reactions. Naphthoquinones are known to be synthesized by some plants. But naphthoquinones, naphthalene and naphthalene derivatives. These by the oxidation reactions are difficult to synthesize naphthoquinones, because the structure of the naphtha is stable and this makes the reaction difficult to perform. Although, the oxidation reaction of naphthalene was performed using dichromate catalyzed with acetic acid [33].



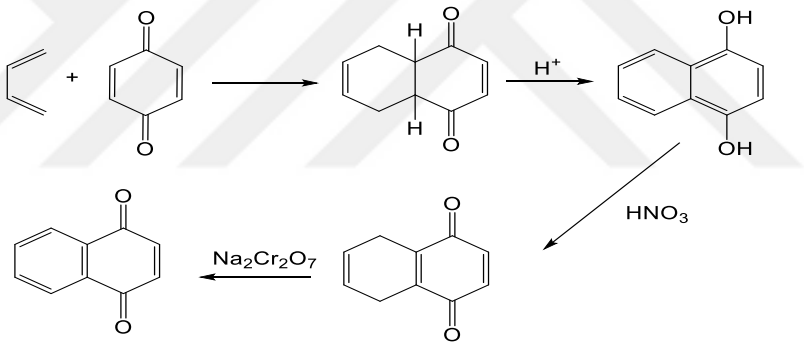
(1.7)

Naphthoquinones, also can be synthesized from naphthalene containing $–NH_2$ and –OH groups in their structure by oxidation reaction in a similar manner (1.8).



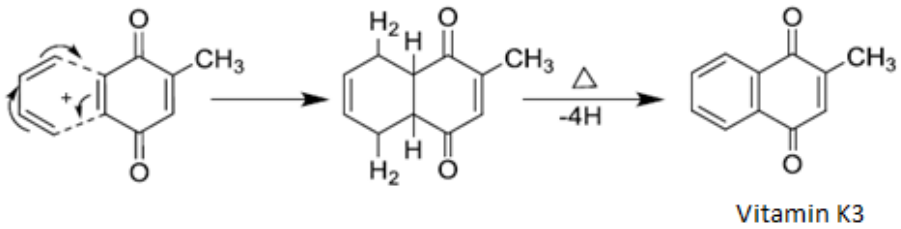
(1.8)

The 1,4-naphthoquinones also obtained from Diels-Alder reaction of 1,3-butadiene with p-benzoquinone or their derivatives in order to add a new ring to the benzoquinones [34].



(1.9)

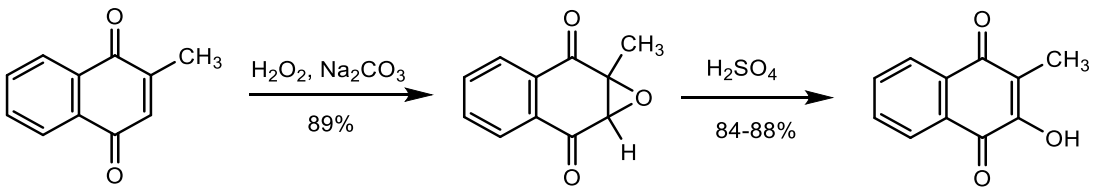
2-methyl-1,4-naphthoquinone (Vitamin K3) can be synthesized using same method, by reacting 1,3-butadiene with methyl benzoquinone (1.10).



(1.10)

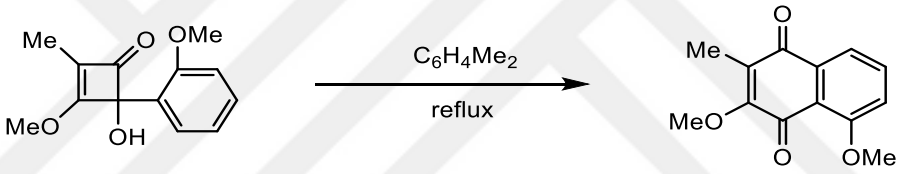
2-methyl-1,4-naphthoquinone can be oxidizing under the hydrogen peroxide reagent. The epoxide ring breaks down easily in a cold medium with existence of H_2SO_4 giving 2-methyl-

3-hydroxy-1,4-naphthoquinone. This reaction refers the oxidation-reduction of naphthoquinones (1.11).



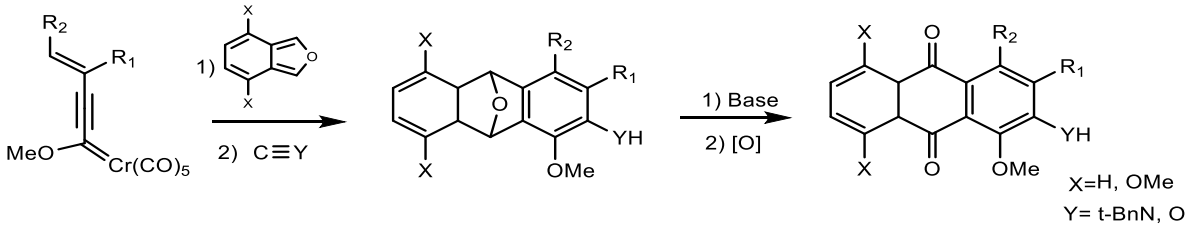
(1.11)

Another interesting method, which requires rearrangement of hydrocyclobutenone derivatives [35].



(1.12)

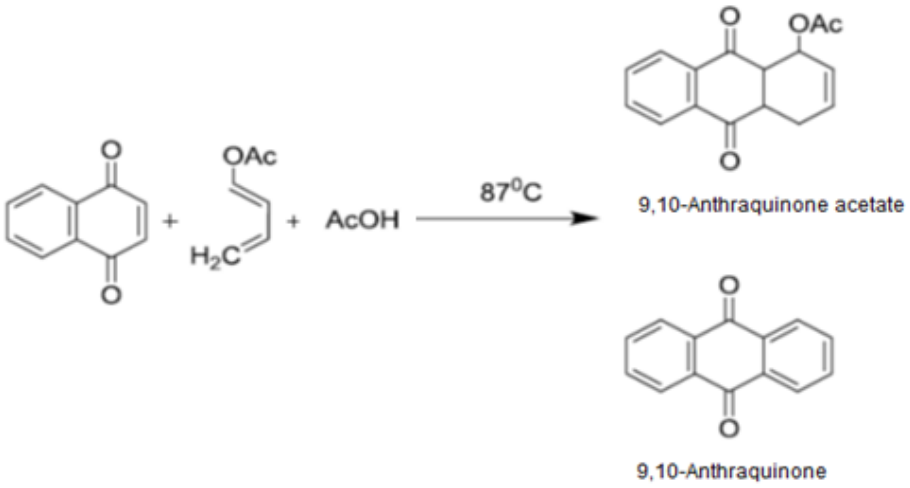
Moreover, anthraquinone synthesized from carbene complexes in the presence of isobenzofurans, in this reaction, the organometallic species behave as good dienophiles according to the Diels–Alder reaction [36].



(1.13)

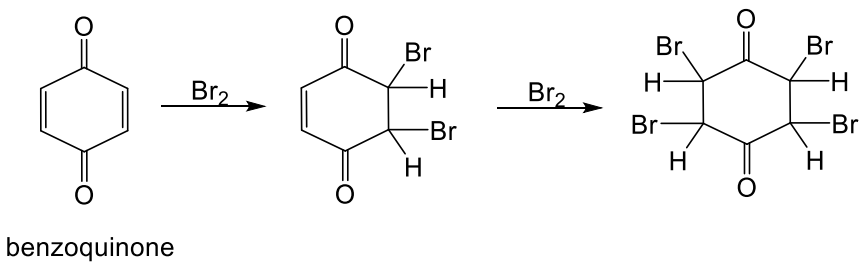
1.1.3. Reactions of Quinones

The quinones are cyclic unsaturated diketones, they are not aromatic compounds because they contain 4 π electrons. Therefore, they give reactions of the carbonyl group and their specific addition to α,β-unsaturated ketones. Naphthoquinones give the Diels-Alder addition reaction very easily with dienes. Diels alder addition products as starting materials to synthesize natural naphthoquinones frequently used. Reaction of 1,4-naphthoquinone with 1,3-butadienyl acetate gives anthraquinone acetate and 9,10-anthraquinone (1.14) [37].



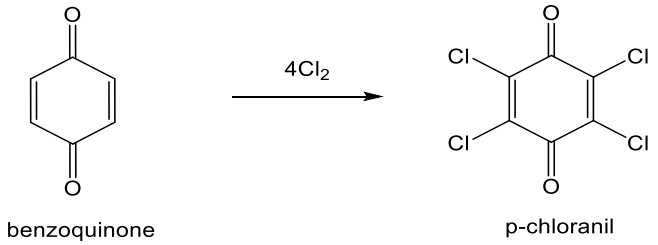
(1.14)

Quinones also reacted with halogens, for example, the bromine addition to the pi-bond of p-benzoquinone to lead the formation of 2,3,5,6- tetrabromo-1,4-benzoquinone (1.15).



(1.15)

When the p-benzoquinone reacts with chlorine atom the p-chloranil is formed [38].



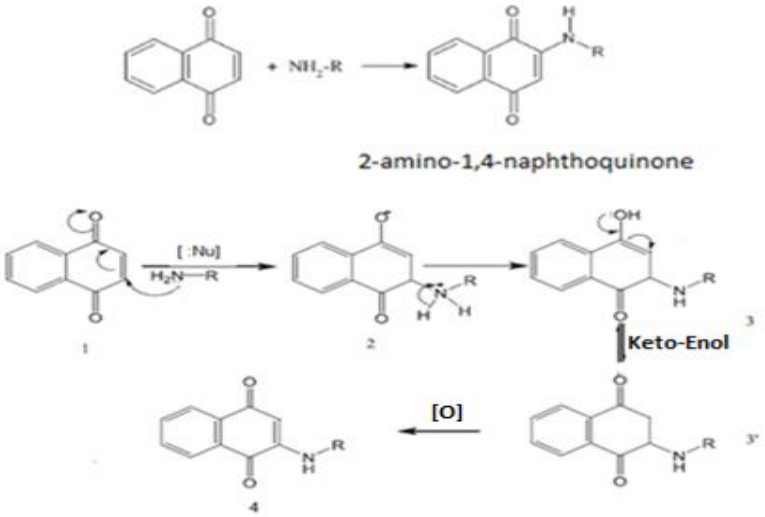
(1.16)

The Nucleophilic Reactions of Quinones

Many nucleophiles which contain nitrogen, sulfur and oxygen are used to produce mono or disubstituted of quinone derivatives. Usually, 2-substituted and 2,3-disubstituted-1,4-naphthoquinones or both of them can be obtained by the Michael addition reactions according to the reaction conditions [39, 40]. Heterocyclic derivatives, difunctional can also be obtained [41].

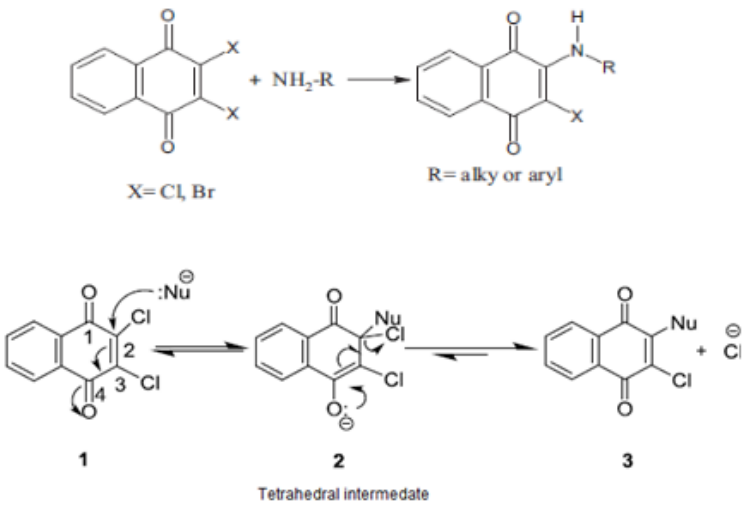
Reaction of Naphthoquinones with N-Nucleophiles

It was recently known that the amino-naphthoquinone compounds improve the biological activities of these derivatives, moreover, were used as starting materials for synthesis of many compounds. Two main methods that describe how to make alkyl/aryl amino derivatives of naphthoquinone. First type: the reaction requires Michael addition reaction of the amino compound with 1,4-naphthoquinone ring to produce 2-amino-1,4-naphthoquinone (1.17).



(1.17)

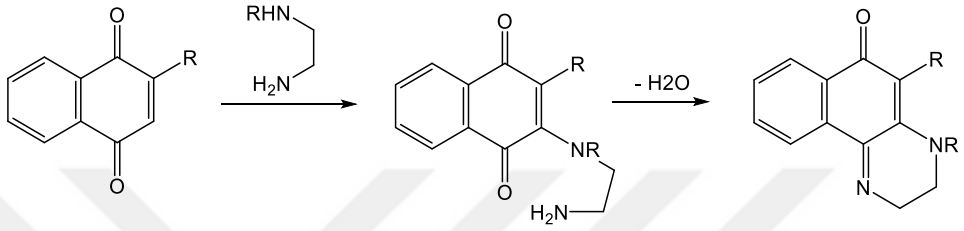
The second type involves a nucleophilic substitution reaction between the nucleophile with mono or dihalogenated of 1,4-naphthoquinone derivatives to generate the corresponding amino derivative. The mechanism of nucleophiles with 2,3-dichloro-1,4-naphthoquinone starts with a nucleophilic attack on the carbon atom in C2 position and / or C3 forming the tetrahedral intermediate (2), which easily converted to 2-substituted-3-chloro-1,4-naphthoquinones (3) [42]. The substitution of the second chlorine atom may occur due to the electronegativity effect of the other substituent in the quinone structure. Especially when the electron-donating group such as amine is attached to the C2 atom. The proposed mechanism is shown below (1.18).



(1.18)

However, both methods practically are low efficiency, and give a large number of products, especially with primary amines. Ultrasonic radiation has been used in some cases because of its powerful effect in improving and speeding up the organic reactions [43].

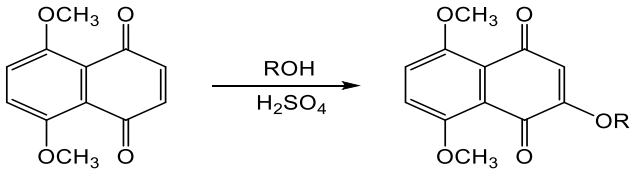
When 1,4-naphthoquinones react with diamines, this reaction leads to the formation of one amino substituted, and then after dehydration heterocyclic naphthoquinone derivative is produced.



(1.19)

Reaction of Naphthoquinones with O-Nucleophiles

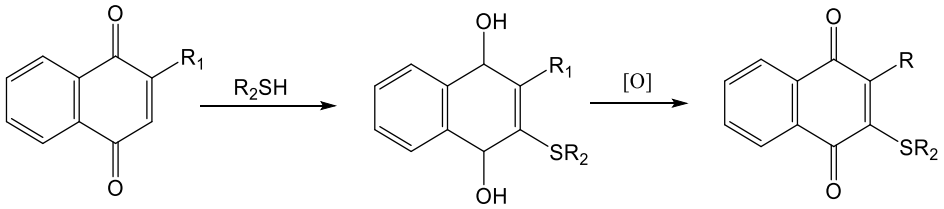
Another example of the Michael addition reaction; When 1,4-Naphthoquinones having specific electron-donor substituents at 5 and 8 positions react with alcohols to give 2-alkoxy derivatives in the existence of sulfuric acid and iron sulfate as catalyst (1.20).



(1.20)

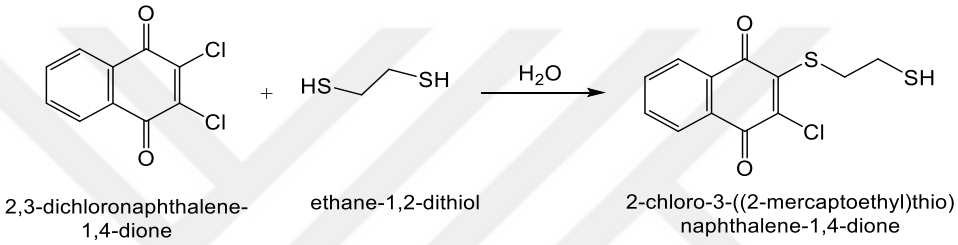
Reaction of Naphthoquinones with S-Nucleophiles

The reaction of thiol compounds with naphthoquinones can be achieved also by Michael addition and followed by oxidation by air to form alkyl thio or aryl thioquinones (1.21).



(1.21)

Reaction of ethane-1,2-dithiol with 2,3-dichloro-1,4-naphthoquinone with in aqueous medium without using any base as a catalyst. 2-Chloro-3-((2-mercaptoethyl)thio)naphthalene-1,4-dione obtained as product [44].



(1.22)

1.1.4. Different Uses of Naphthoquinone and Their Applications in Different Fields

Naphthoquinones have a wide range of uses. Some important applications and uses of naphthoquinone were shown in (Fig. 1.3).

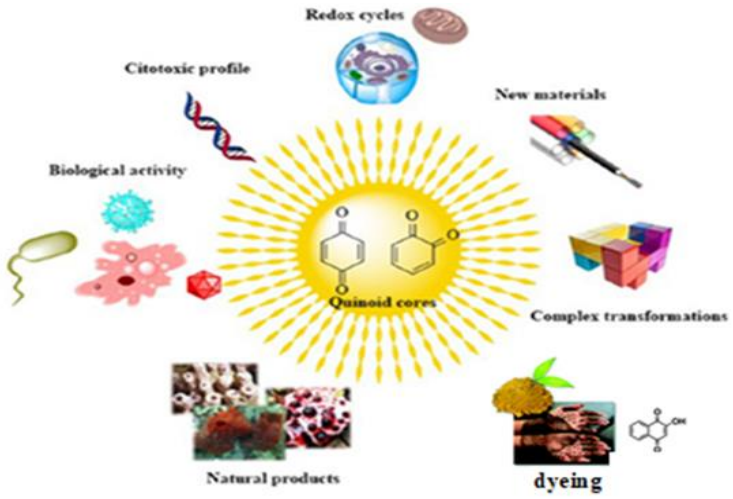


Figure 1.3: Diagram showing some applications of naphthoquinones.

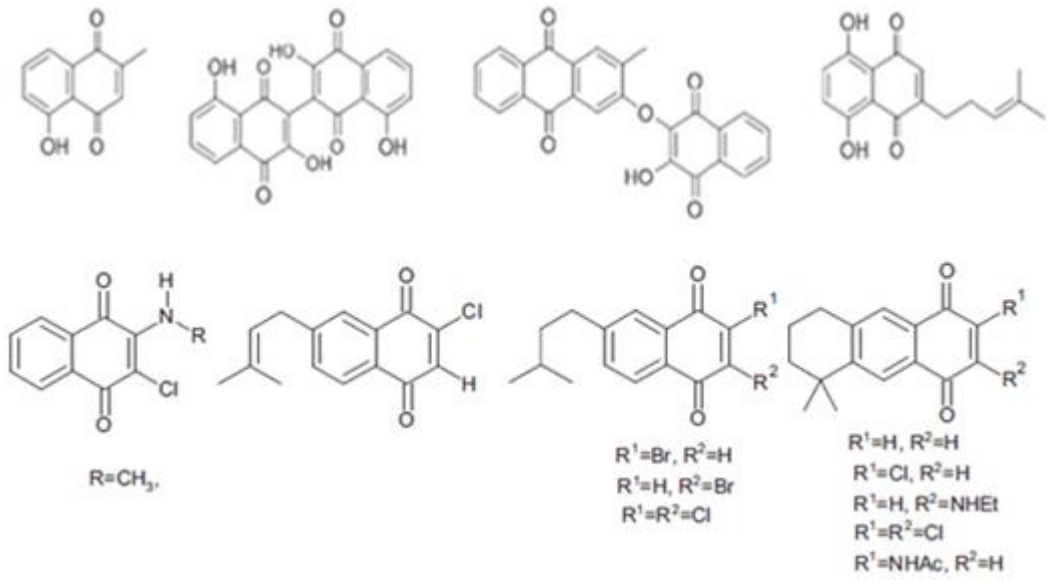
1.1.4.1. ***Biological Activities***

The high biological activities of naphthoquinone derivatives, either synthetic or natural, have a clear effect on some diseases, such as antifungal, antibacterial, anticancer, antiparasitic and antiviral. That is why naphthoquinone compounds are interesting for study. In this section, we summarize some of these activities:

- ***Antifungal activities***

Fungal infections are responsible for major diseases in humans, and major organ transplants, Leukemia or HIV infection leads to poor immune system in patients [45]. This increases the need to discover new antifungal compounds today. Many reports in the literature reveal the antifungal potential of novel compounds such as naphthoquinones.

The following naphthoquinone derivatives have anti-fungal properties obtained synthetically or isolated from plant roots [46].



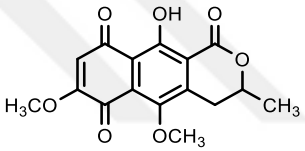
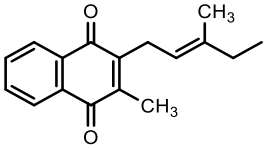
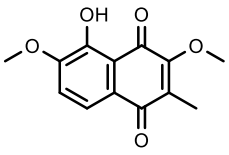
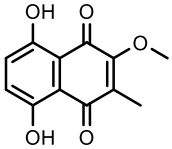
(1.23)

- ***Antibacterial activities***

An example of some antibiotic medications. tolypomycin and damavaricin have a ring of quinone as pharmaceuticals, which are an essential part of their composition. Naphthoquinone

derivatives have been used as antibacterial agents for several years ago, there are many reports of 60s of chemical compounds synthesized with 1,4-naphthoquinone structure and have antibacterial properties [47]. Later, in the 80s, there are studies on inhibition of bacteria, along with vitamin K and 1,4-naphthoquinone. It has been suggested that pharmaceuticals compete in the electronic transport system. Another suggestion is the production of ROS and radical semiquinone and cytotoxicity of naphthoquinone [48, 49]. Table 1.2 shows the properties of naphthoquinones extracted from natural plants and their biological activity against various bacterial infections including for examples; Mycobacterium tuberculosis and Helicobacter pylori (chronic gastritis and peptic ulcer). Furthermore, a Minimum statement of Inhibition Concentration (MIC) measured by μg/mL of naphthoquinones and using the antibacterial drug as a control reference in determining antibacterial tests [50-52].

Table 1.2: Antibacterial activities of some extracted naphthoquinones

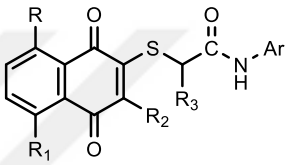
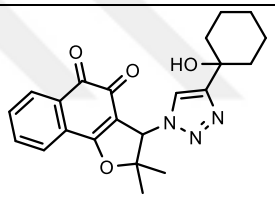
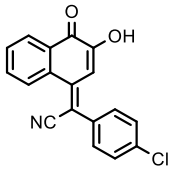
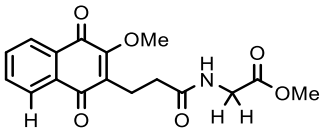
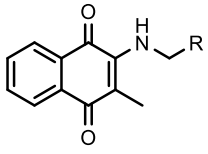
Compound name, source	**Bacteria, MIC***	**Control, MIC***	**Structure**	**Ref.**
5-methoxy-3,4-dehydroxanthomegnin, *Paepalanthus latipes*	H. *pylori*, 64.0 μg/mL	Metronidazole, > 254.0 μg/mL Amoxicillin 2.0 μg/mL,		[50]
Trigonoheterona, *Trigonostemon heterophyllus*	*S. aureus*, 7.8 μg/mL	Mitomycin, 60.0 μg/mL		[51]
5-hydroxy-3,6-dimethoxy-2 methylnaphthalene-1,4-dione and 5,8-dihydroxy-3-methoxy-2-methylnaphthalene-1,4-dione, *Aloe secundiflora*	*M. tuberculosis*, 3.5 μg/mL *M. tuberculosis*, 3.5 μg/mL	rifampicin, 0.05 μg/mL rifampicin, 0.05 μg/mL	 	[52]

MIC*= Minimum Inhibition Concentration

Some of the active compounds are extracted from “Euclea natalensis” roots, and are used by african peoples in South Africa for the treatment of oral and respiratory diseases. From these

roots, 6 types of naphthoquinones called Isodiospirin, Diospirin, Mamegakinone, 7-Methyljuglone, Shinanolone and Neodyospyrin were isolated and tested against M. tuberculosis and some compounds such as ethambutol isoniazid and rifampicin [53]. Table 1.3, showing the synthetic derivatives of naphthoquinone with antibacterial activity, Minimum Inhibition Concentration MICs and using drug controls [54-58].

Table 1.3: Antibacterial activity of the synthetic naphthoquinones.

Compound name, source	Bacteria, MIC	Control, MIC	Structure	Ref.
1,4-Naphthoquinone-[3,2-c]-1H-pyrazoles and their 1,4-naphthohydroquinone derivatives ρ-/ σ-anisidilo, phenyl and methyl	*Streptococcus faecalis,* 25.0 μg/mL *Klebsiella pneumoniae y* *Escherichia coli,* 6.2 μg/mL	Gentamycin, 0.4 μg/mL kanamycin, 16.0-32.0 μg/mL	 R, R_1, R_2, R_3 = H, Ar = p-anisyl	[54]
Arylamine 1,2,3-triazole of nor-β-Lapachone	*Enterococcus faecalis,* *8.0-16.0* μg/mL	Vancomycin, 2.0 μg/mL chloramphenicol, 12.0 μg/mL		[55]
2-hydroxy-1, 4-naphthoquinone derivatives with cyano and 4-chlorophenyl moiety in C-4	*S. aureus,* *16.0-64.0* μg/mL	Ciprofloxacin and gentamicin, 0.25μg/mL		[56]
Amide derivatives of plumbagin, juglone, lawsone, menadione with amino acids	*S. aureus,* 3.9-125 μg/mL	Streptomycin, 3.9 μg/mL		[57]
2-ethylamino-3-methyl-1,4-naphthoquinone	*Pseudomonas aeruginosa,* 0.6 μg/mL *S. aureus,* 0.3 μg/mL	Vitamin K, 0.15	 R= CH_3, C_2H_5, C_3H_7	[58]

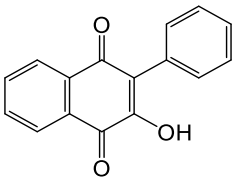
The hybrids of triazoles and triazole chromene naphthoquinone derivatives were prepared, then tested against tuberculosis, the derivative is found to be more active than the most tuberculosis drugs. According to these results, the activity of antimycobacterial is particularly increased, when the substitute on the ring of aniline is chlorine or fluorine atom in the synthesized derivatives [59].

A new series of carbazole fragments 6,11 debt has been tested containing 1.4 derivatives of naphthoquinone. And most of them showed good activity against bacteria. [60].

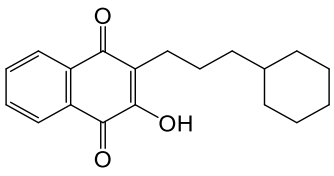
- ***Antiparasitic activities***

Several research reports have been published dealing with naphthoquinones and their synthetic derivatives that have the potential to prevent progress of parasites such as *"Leishmania",* which is found in the tropics and subtropics and is caused by the primitive leishmaniasis. More than one million people die every year from this disease in Africa. The 5-Hydroxy-2-methyl-1,4-naphthoquinone, 2-methoxy-1,4- naphthoquinone showed anti-leishmania activities [61].

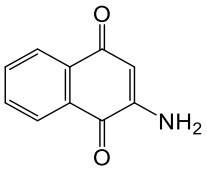
Malaria is a fatal infectious disease for humans, especially children, caused by primary plasmodium parasites. Among the research published to eliminate the disease. The compounds in (1.24) have been present and used since the 1950s to treat malaria [62, 63, 64].



2-hydroxy-3-phenyl-1,4-naphthoquinone



2-hydroxy-3-cyclohexylpropyl-1,4-naphthoquinone



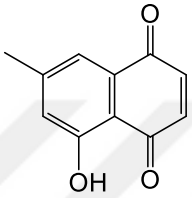
2-amino-1,4-naphthoquinone

(1.24)

Currently, the focus on the atovaquone structure to synthesize new antimalarial drugs. For example, thirty-six novel phenylsulfanylmethyl-1,4-naphthoquinone derivatives can be substituted with various substituents, these derivatives consist of three components, Lawsone derivatives, aldehydes, and thiols.[65].

- ***Antiviral activities***

There are limited reports published about naphthoquinone compounds that can be used as antiviral agents. Some of these reports have shown that naphthoquinone derivatives have activity against HIV. For example, some 1,4-naphthoquinone derivatives and 5-hydroxy-7-methylnaphthalene-1,4-dione derivatives separated from "*Euclea natalensis"* roots. It has been found that 5-hydroxy-7-methyl-1,4-naphthoqinone is one of the most inhibitors of HIV-1 activity [66].

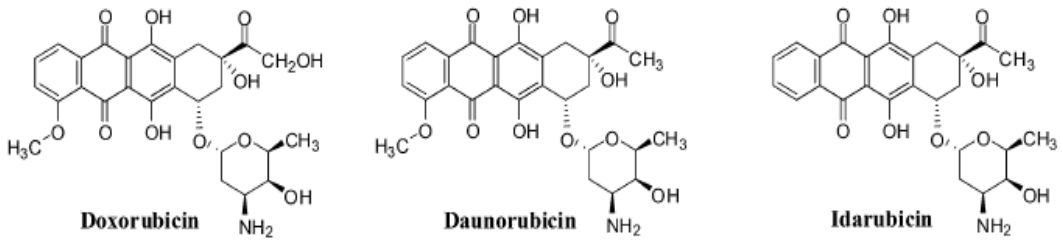


5-hydroxy-7-methylnaphthalene-1,4-dione

(1.25)

- ***Anticancer activities***

Cancer is a type of noncommunicable disease, which causing the death, and the growth of its cells has not yet been controlled so far, there more than a hundred different types of cancer each organized by the type of cell that was initially affected. Among the applications used for naphthoquinone in the medical field, it used as an anti-cancer. There are several reports published in this area [67]. The anthracyclines, such as daunorubicin, doxorubicin, and idarubicin are quinone-derivatives holding antitumor agents which used for treatment of cancers, such as breast, lymphomas, leukemias, uterine, lung, and ovarian cancers (1.26).



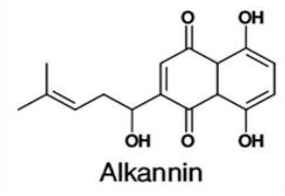
(1.26)

1.1.4.2. ***Naphthoquinones as Dyes***

Quinones were first used in the paint industry in the past. The Egyptians have got the paint by grinding the leaves of the tree called "henna". The main component of this tree is the naphthoquinone compound called “Lawsone”. It is one of the naphthoquinone dyes extracted from the leaves of *Laosonia* plant, a henna plant was used from a long time ago to prepare hair dyes and skin pigments. It also reacts strongly with light. Also, besides the beauty properties of henna, 2-Hydroxy-1,4-naphthoquinone shows antimicrobial and antioxidant effects.

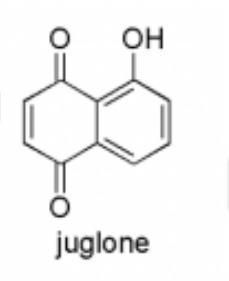


Alkanna has been known since ancient times especially in Southeast Europe and Asia Minor. The root of *Tinctoria* gives a red dye called alkanet. The Greek historians Theophrastus and Pliny, who introduced the blood-red dye that can be obtained from the roots of this plant. This blood-red colorant has been used in textile food and cosmetic products. The main coloring component of the alkanna is naphthoquinone alkannin.





One of the most famous members, Walnut, or Juglans regia, represents important tree species found in warm areas and is commercially grown in the United States, South Latin America, Asia, and Central and South Europe. Moreover, besides the extensive use of leaves and bark in traditional medicine, walnuts have been used to produce colorants and brown dyes for dyeing different types of textiles [68, 69]. It is known that the main ingredient in walnuts is juglone.



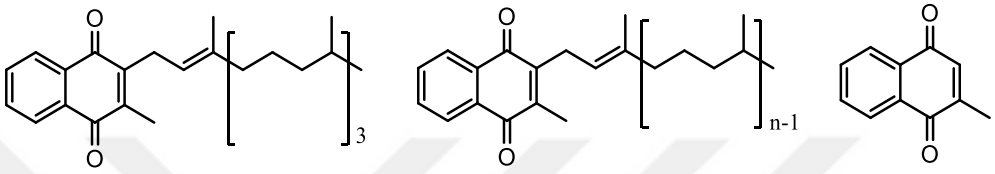




1.1.4.3. ***Naphthoquinones as Vitamins***

Many quinones are found in the structure of vitamins and affect enhancing their biological activity. They also play significant role in maintaining clotting blood properties, vitamin K is also important in maintaining carbohydrate storage in the body and healthy structure bone [70]. In the case of vitamin K deficiency in the body affects calcium balance, may lead to vascular calcification and bone dysfunction. These days, vitamin K is broadly used in Asian, especially for the treatment of osteoporosis [71]. As mentioned before there are three types of vitamin K, (Vit K1, K2, K3). Vitamin K1 found in plants. The vitamin K3 is the synthetic form of vitamin K which converted into the human body to vitamin K2, which has same biological properties of vitamin K3 [72]. Vitamin K group is found in the following foods: leafy vegetables, such as, spinach, green turnip, parsley, green lettuce. Vegetables such as broccoli, cauliflower and cabbage. Fish, eggs, grains, liver and meat. Menadione sodium bisulfate is routinely given to new babies immediately after born to avoid any serious bleeding that could threaten their lives. Nutter et al., 1992 has reported that, the most important pharmacological properties of vitamin K3 are anti-cancer activity, oxidative stress induces cancer cells by producing hydroxyl radicals and DNA breaks [73,74].

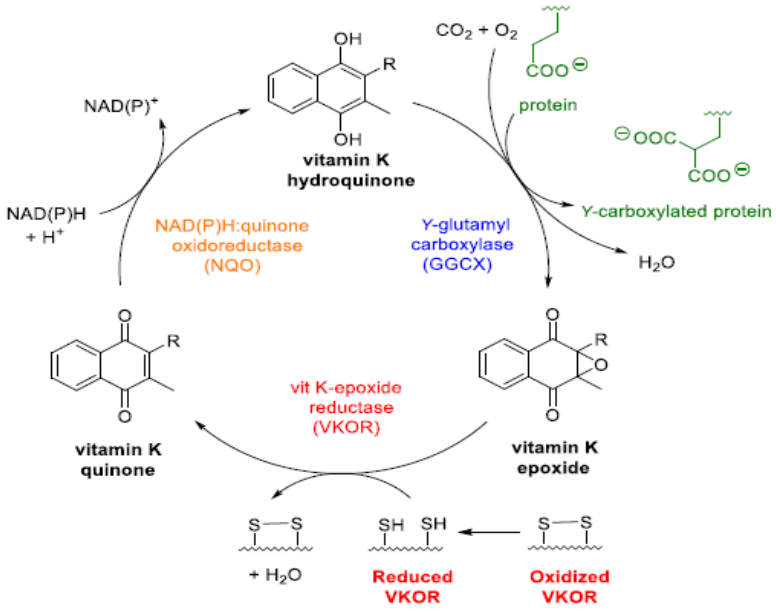




(Vitamin K1) (Vitamin K2) (Vitamin K3)
Menadione

(1.27)

Vitamin K plays a pivotal role with gamma carboxyl proteins in the body's metabolism. Vitamin K is soluble in fat and the body keeps only small amounts of it. Instead, these vitamins are recycled through a process called the vitamin K cycle (1.28).



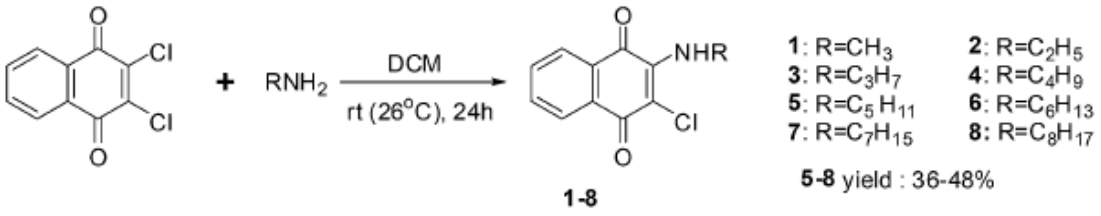
(1.28)

By NAD(P)H: quinone oxidoreductase (NQO), vitamin K is reduced to vitamin K hydroquinone. Enzyme gamma glutamyl carboxylase (GGCX) used in this process to generate Vit K-epoxide, which is converted back to Vit K again by Vit K-epoxide reductase (VKOR) [75].

1.1.5. Some Previously Studies of Naphthoquinone Derivatives and Their Various Applications

As mentioned before the 1,4-naphthoquinones having an amine at position 2 has been the subject of many years, because of their important biological properties. Because of the importance of these derivatives, there are many studies on the synthesis of these derivatives by traditional or modern ways to get the best properties and yields. Some of these studies will be briefly presented.

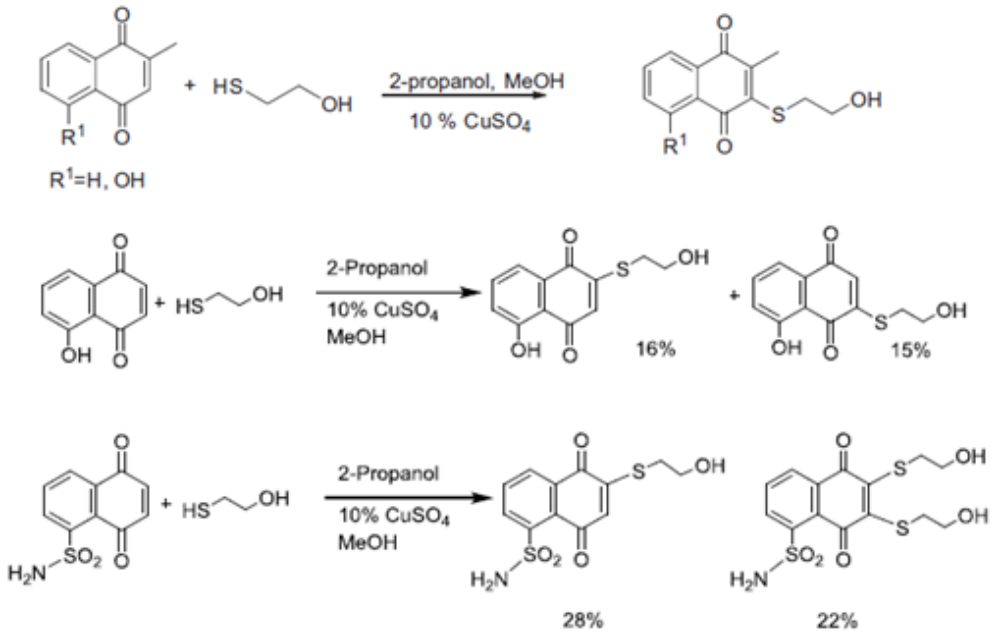
2-Chloro-3(n-alkaylamino)-1,4-naphthoquinone side chain derivatives of 1-8 (from methyl to octyl) were investigated, (Salunke-Gawali et al. 2013) reported that the derivatives including methyl until butyl are found to be antidepressant, antiproliferative, colon, brain and pancreas cell lines, cells were examined in the panel [76]. Also, was reported that the 2-chloro-3-propylamino-1,4-naphthoquinone is very active in the colon cell line.



(1.29)

Phenylamino-1,4-naphthoquinones were created by (Benites et al. 2010) to investigate the anticancer activity and the structure–activity relationships of Severe Acute Respiratory Syndrome (SARs). According to the SAR analysis a series of aminonaphthoquinone. It was found the (CH_3) group introduced into the nitrogen atom coming from the donor phenylamino group and / or the addition of chlorine [77]. Thiolated derivatives of plumbagin, menadione, juglone and 1,4-naphthoquinone, synthesized for use in the study of anticancer properties

(Bhasin, D. et al. 2013). Derivatives were examined towards depression and gave promising results [78].



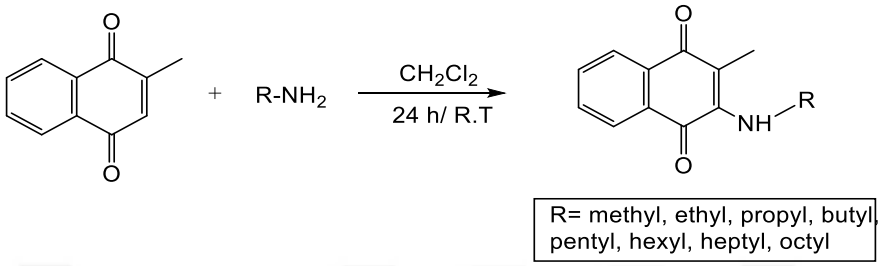
(1.30)

Studies that are interested in dyeing properties are not many, especially, 1,4-naphthoquinone containing heteroatomic substituted compounds in the publications. The color can be formed in 1,4-naphthoquinone compounds by inserting amino or hydroxyl groups into the quinoid ring in the position (2, 3), or in the aromatic ring in the position (5,8), or both of them. (Sayil, C. et al. 2016) interested in synthesizing some dyes of naphthoquinones substituted in positions 2, 3, and verified. In addition to studying their spectral properties and testing pigmentation on polyester fibers [68, 69].

1.1.6. Vitamin K3 (2-Methyl-1,4-Naphthoquinone) and Its Applications

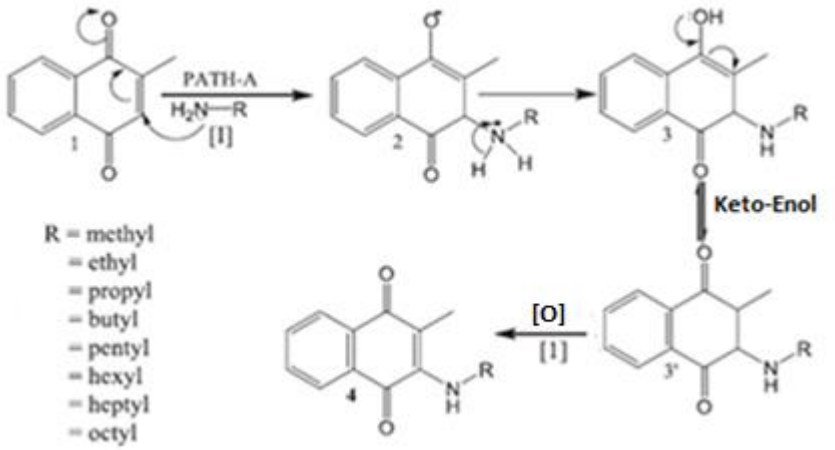
Aminonaphthoquinone derivatives of vitamin K3 represent an important part of natural antibiotics [79,80]. Many of them are toxic to different types of cancer cells because of their redox potential [81-84]. For example; Vitamin K3 derivative, 2-methyl-3-(n-alkylamino)-1,4-naphthoquinone, (n: methyl to octyl) homologized side chain derivatives by synthesizing their activities against some cancer cells by different methods were investigated. 1 to 4 are {n:

methyl, ethyl, propyl, and butyl} antiproliferative colon, brain and pancreas cell lines, and 2-propylamino-3-methyl-1,4-naphthoquinon was to have antibacterial properties (Chadar and Salunke-Gawali et al. 2015) [85] (1.31).



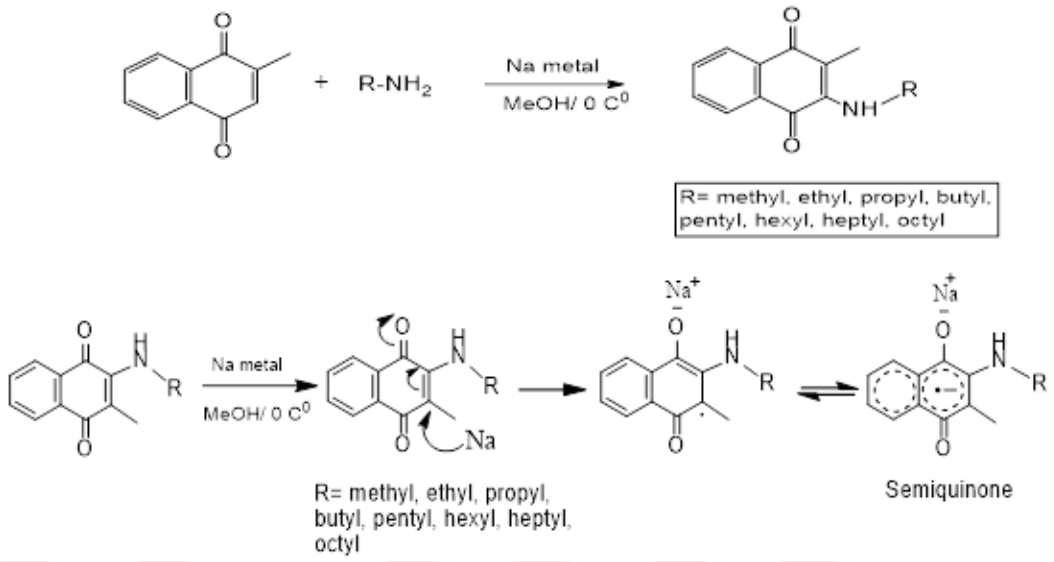
(1.31)

The proposed reaction mechanism of n-alkylamino derivatives of vitamin K3 is shown below [85].



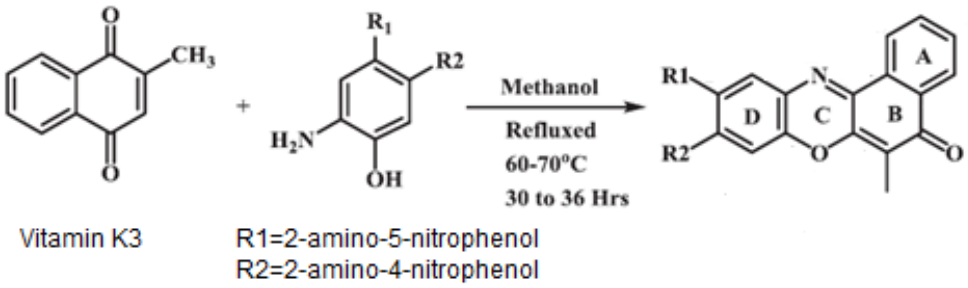
(1.32)

Sodium metal in this reaction used as reducing agent to generate naphthosemiquinone radical, the proposed mechanism for electron reduction of n-alkylamino derivatives of vitamin K3 with sodium metal is shown below [86].



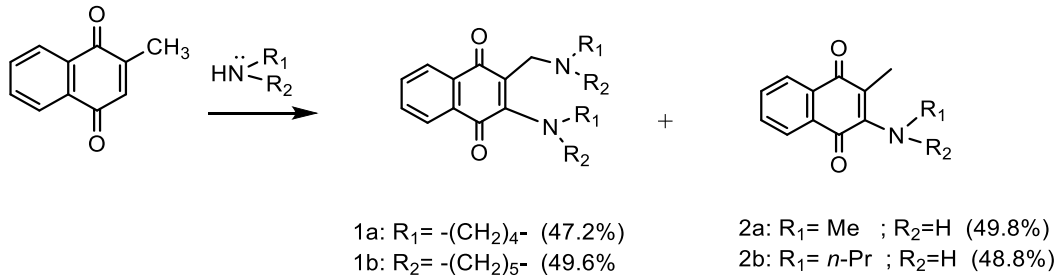
(1.33)

The phenoxazone system is a molecule formed by displacement reaction or rearrangement of an o-aminophenol compound. Phenoxazine and benzo[α]phenoxazine derivatives, which contain heterogeneous atoms of nitrogen and oxygen, consisting of three to five rings, are molecules with high fluorescent properties. Because of their high absorption, they have a wide range of biological applications. Benzo[α]phenoxazine derivatives of vitamin K3 have been previously synthesized and characterized [87].



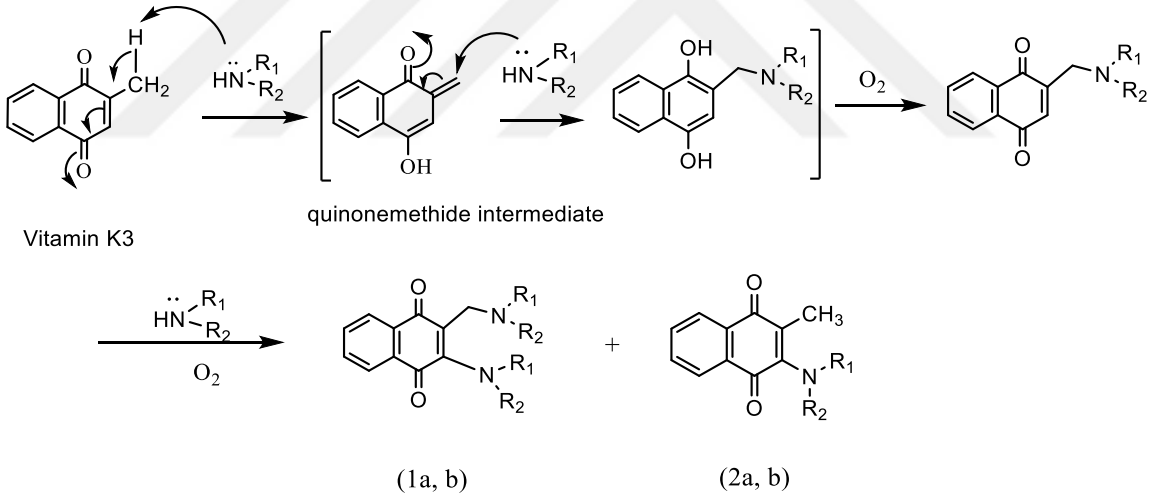
(1.34)

It has reported that, the reaction of 2-methyl-1,4-nahpthoquinoms combined with primary amines or cyclic amines gave more than one product. For example; (Ohta et al 1994) has examine the reaction of vitamin K3 with primary (methyl, n-propyl) amines and cyclic amines as pyrrolidines, piperidines and use them as a solvent and kept for 24 hours in the dark place, the reaction gave the diamino compounds (1a, b) and monoamino compounds (2a, b) [88].



(1.35)

The diamino-substituted products (1a, b) produced of a large excess of nucleophile. In this case, it is presumed that, during the elimination reaction, the methyl group loss a proton by nucleophilic attack, and the quinonemethide intermediate is formed, then an autooxidation steps, followed by nucleophilic attack on naphthoquinone system forming an adduct (1a, b). A proposed mechanism is shown below [88].



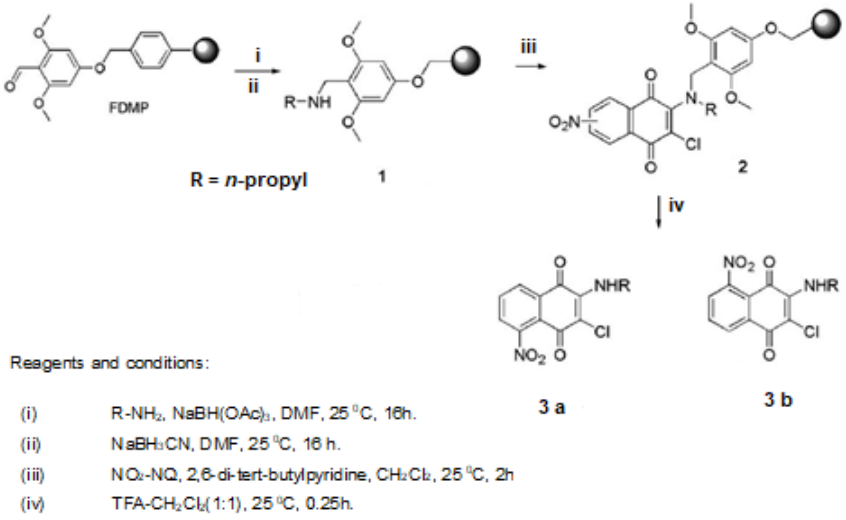
(1.36)

1.1.7. 2,3-Dichloro-5-Nitro-1.4-Naphthoquinone and Its Applications

Studies on nitronapthoquinone derivatives are rare in the literature, and the nitro group associated with the aromatic ring in the quinone system is known to increase the biological activity of naphthoquinone due to its electron-withdrawing properties. Recently, it has been

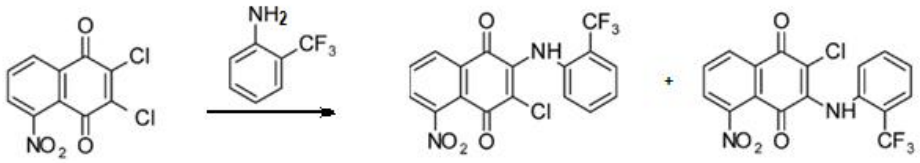
reported that the 2,3-dichloro-5-nitronaphthalene-1,4-dione derivative is more active towards amines and the reaction provides a mixture of two regioisomers.

(Blackburn, 2005) has treated 2,3-dichloro-5-nitronaphthalene-1,4-dione linked with resin amine (FDMP) giving very colorful products have good yield. FDMP resin under some reducing process and reacted to 2,3-dichloro-5-nitronaphthalene-1,4-dione in existence of 2,6-di-*tert*-butylpyridine giving the radish resin-quinone 2. Treatment by trifluoracetic acid led to the rapid formation of regioisomeric mixtures of nitroquinons. As a comparison between the regioisomers 3a, b, the retention factor (R_f) of the 5-nitro isomer (3a) was found to be higher than the 8-nitro isomer (3b). Also, in the ^{1}H NMR, the proton signal of naphthoquinone ring showed the first isomer (3a) are shifted more downfield than the naphthoquinone peaks of the second isomer (3b) [89].



(1.37)

Some derivatives synthesized, studied, and examined the biological activities by (Samant, and Chakaingesu, 2013). They found that, two regioisomers of nitronapthoquinone derivatives, 3-chloro-5-nitro-2-((2-(trifluoromethyl)phenyl)amino)naphthalene-1,4-dione (a), 2-chloro-5-nitro-3-((2-(trifluoromethyl)phenyl)amino)naphthalene-1,4-dione (b) demonstrated strong active against the sleeping sickness disease (African human trypanosomiasis) with low cytotoxicity in vitro [90].



a b

Substrate	% Total conversion[a] (% selectivity)	Isolated yield (%)	IC_{50} versus *T. brucei*[b] (μM)	IC_{50} versus L-6 rat skeletal myoblast cells[b] (μM)
a $R^1 = NO_2$, $R^2 = 2\text{-}CF_3$	60 (45)	24	0.07 ± 0.01	75 ± 5
b $R^1 = NO_2$, $R^2 = 2\text{-}CF_3$	60 (46)	24	0.05 ± 0.01	95 ± 5

Nitro substituted aminonaphthoquinones containing -CF_3 group

(1.38)

Another study describing the formation of 2 and 3-amino-5-nitro-1,4-naphthoquinones as mixtures of regioisomers with high purities. Also, as like previous literature, the H NMR spectra of these isomers were indicated that the peaks of the 2-amino isomer of aromatic protons are shifted more down field than the aromatic protons of the 3-amino isomer [91].

1.2. POLYHALONITROBUTADIENE COMPOUNDS

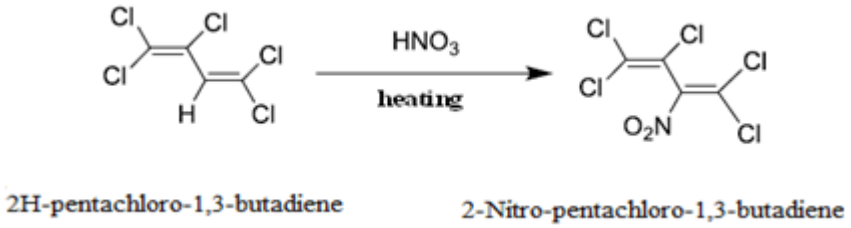
The 1,3-butadiene compounds are hydrocarbons containing two conjugated double bonds in their structure is an important component of the petrochemical industry. Especially, in polymeric industries, usually ethylene used as a monomer to produce the synthetic rubber. Rubbers and latexes are used to make many materials: such as plastic, tires, carpets, papers, coatings, gloves, and foams. Polyhalobutadiene compounds containing different halogen atoms (chlorine, fluorine, bromine, iodine). It has been synthesized and studied for many years and has wide uses [92]. The chemistry of nitro compounds also has long been studied extensively. Research with nitro compounds mainly relates to the synthesis of their derivatives used as unusual intermediate compounds. Because of their high reactivity in S_N reactions, polyhalonitrobutadienes have been shown in many studies to have many properties such as heat transfer and cooling, lubrication and agglomeration on an industrial basis as well as medical and pharmaceutical effects such as antitumor, bactericidal, fungicide and algicide [93].

1.2.1. General Synthesis Methods of Nitropentachloro-1,3-Butadiene

Typically, there are two main ways of synthesizing halonitrobutadienes: (I) through direct nitration of halogenated butadiene derivatives, using different nitration agents; (II) the synthesis from aliphatic nitrocompounds by removing small molecules (proton, halides, acetic acid, etc.).

Synthesis of 2-nitropentachloro-1,3-butadiene

Direct nitrification of 1,1,2,4,4-pentachloro-1,3-butadiene and concentrated nitric acid (57-68% at 80-90 °C) by electrophilic attack on the hydrogen atom giving the replacement of the hydrogen atom with (NO_2) group, then nitrodichlorovinyl group occurs. To obtained 2-nitropentachlorobuta-1,3-diene in a yield of 40% [94]. In case of presence a mixture of HNO_3, H_3PO_4 (10:1), the yield increases up to 55-65% (more details in the result section).



2H-pentachloro-1,3-butadiene 2-Nitro-pentachloro-1,3-butadiene

(1.39)

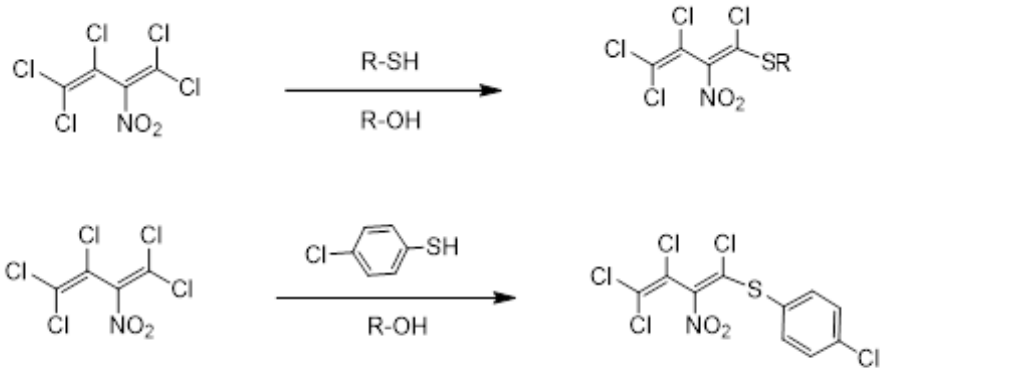
Usually, 2-nitroperchloro-1,3-butadiene used as the primary source for the synthesis. The preferred center in nucleophilic substitution reactions is (C-1) atom of the nitrodichlorovinyl part. The carbon (C-1) that activated by withdrawing NO_2 group allows for any attacks by different nucleophiles (N-, S- and O-) in S_NVin processes. Additionally, internal carbon atom C-3 is suitable for nucleophile attack under harsh conditions.

1.2.2. Reactions of Halonitropentachloro-1,3-Butadiene Compounds

As mentioned above the preferred reactions of halonitrobutadienes is a nucleophilic substitution reaction with thiols, dithiols and amines. We will review some of these famous interactions.

1.2.2.1. *Reaction of Halonitropentachloro-1,3-Butadiene with Thiols*

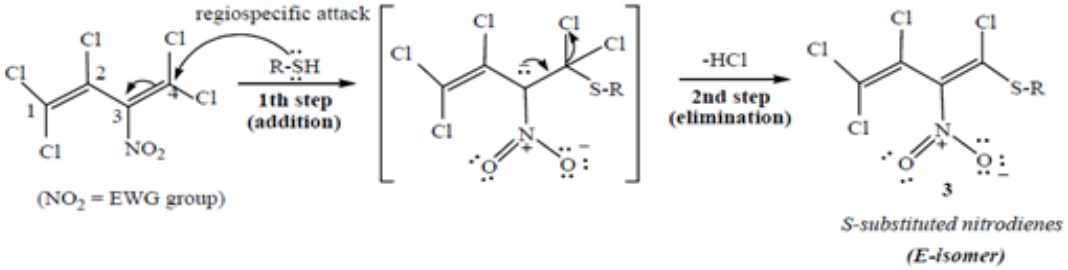
Reaction of 2-nitropentachloro-1,3-butadienes with thiols (alkyl or aryl) resulting mono, di, or tris (thio)-substituted nitrobutadiene depending of the medium conditions. Under moderate conditions, such as alcohols, mono (alkylthio)-1,3,4,4-tetra-chloro-2-nitrobuta-1,3-diene displacement of one geminal Cl atom in nitrodichlorovinyl moiety. It is reported that mono-thio and N,S-substituted-1,3-butadiene compounds were obtained as (E) isomer. In our previously works, crystal structures of mono-thio and N,S-substituted-1,3-butadienes were determined as (E) isomer by single crystal diffraction methods (XRD). The structure was established that the nitro and thio groups are in the same direction, confirming that the shape is (E) isomer [95].



(*E*) -1,3,4,4-Tetrachloro-4- (4-chlorophenylsulfanyl) -2-nitrobuta-1,3-diene

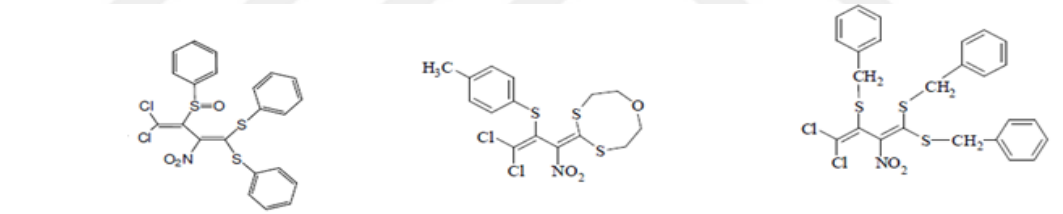
(1.40)

The substitution reaction begins with a mechanism of addition-elimination (S_NVin) reaction. Firstly, the addition of S-nucleophile to the nitrodichlorovinyl fragment occurs. Secondly, a stabilization of intermediate by the removal of HCl [96]. A proposed mechanism is shown below.



(1.41)

If pentachloro-2-nitro-1,3-butadiene reacted with one equivalent molar of thiols at room temperature in diethyl ether gives single isomer of 1,3,4,4-tetrachloro-2-nitro-mono (thio)-1,3-butadiene in good yield. Whereas, using two molar equivalents of same thiol in basic medium (two molar equivalents sodium ethoxide at 0°C in ethanol) offers the di (thio)-substituted trichloronitrobutadiene [97,98]. With three molar thiols, structure of the compound tris (thio)-substituted-2-nitro-1,3-butadiene It has been seen that; two thiol groups are replaced by two chlorine atoms on carbon C1, the third thiol group is replaced with chlorine atom at carbon C3 [99, 100, 101].



dichloro-2-nitro-1,1-bis(phenylsulfanyl)-3-(phenylsulfinyl) -buta-1,3-diene compound

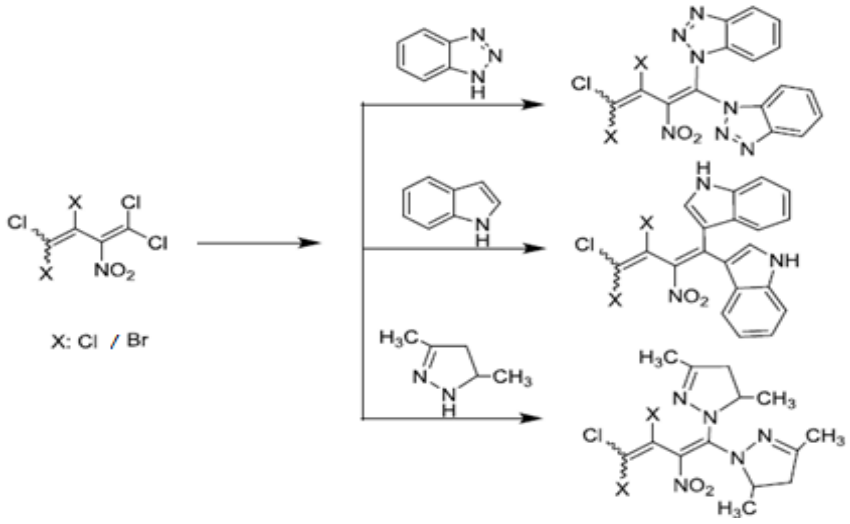
1,1-Didhloro-3-(6,1,3-oxadithiaoctocan-2-ylidine)-3-nitro-2-(4-methylphenyl-sufanyl)propene

2,4.4-Tris(benzylsulfanyl)-1,1-dichloro-3-nitrobuta-1,3-diene

(1.42)

1.2.2.2. ***Reaction of Halonitropentachloro-1,3-Butadiene with Amines***

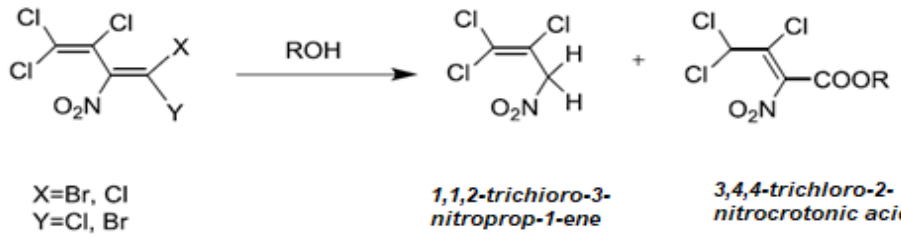
The reaction of (primary/secondary) amines with polyhalo-2-nitro-1,3-butadienes easily occurs under moderate conditions (in ethanol, ether, or dichloromethane, 1:4 diene: amine), the amine takes place of two chlorine atoms in the dichloronitrovinyl section, leading to the formation of corresponding 1,1-diamino-3,4,4-trihalogeno-2-nitro-1,3-butadienes. For example; nitrodienes with benzo-triazole, 3,5-dimethylpyrazole and amphoteric N-nucleophiles such as indole reactions take more time and lead to the formation of 1,1-disubstituted derivatives [102].



(1.43)

1.2.2.3. ***Reaction of Halonitropentachloro-1,3-Butadiene with Alcohols***

Reactions of polyhalonitrobutadienes with O-nucleophiles such as alcohols, have unexpected and insignificant results. Methyl, ethyl and isopropyl alcohol as strong nucleophiles, with 2-nitropentahalogenobutadienes give 1,1,2-trichloro-3-nitroprop-1-ene and esters of 3,4,4-trichloro-2-nitrocrotonic acid.

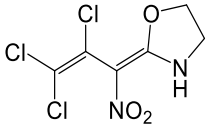
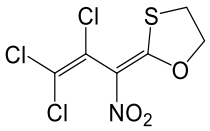
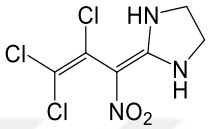
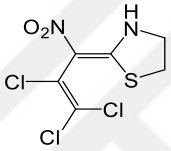
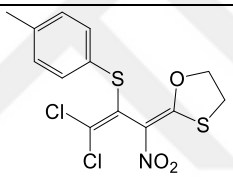


(1.44)

1.2.2.4. ***Reaction of Halonitropentachloro-1,3-Butadiene with Polyfunctional Nucleophiles***

Polyhalonitrobutadienes are a variety of compounds that allow the synthesis of a range of heterocyclic systems, easily reacts with bifunctional nucleophiles. Previously inaccessible, side chain nitrodienes for synthesis of heterocyclic compounds containing radical of trihalogeno-1-nitropropenylidine, based preparative methods have been developed. Some of polyhalonitrobutadienes including heterocyclic system were shown in table 1.4.

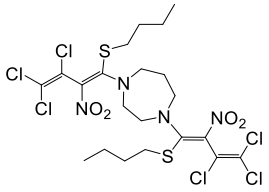
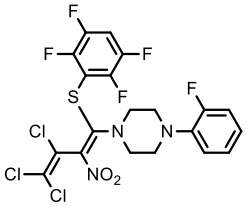
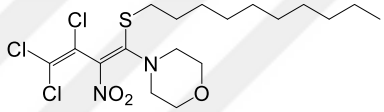
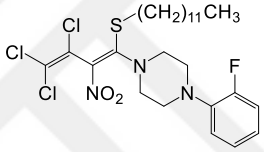
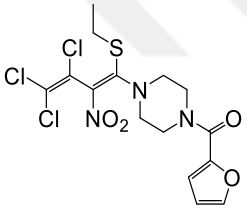
Table 1.4: Polyhalonitrobutadiene compounds including heterocyclic system.

Chemical Name	Chemical Structure	Ref.
2-(2,3,3-trichloro-1-nitroallylidene) oxazolidine		[103]
2-(2,3,3-trichloro-1-nitroallylidene)-1,3-oxathiolane		[103]
2-(2,3,3-trichloro-1-nitroallylidene)imidazolidine		[104]
2-(2,3,3-trichloro-1-nitroallylidene)thiazolidine		[104]
2-(3,3-dichloro-1-nitro-2-(p-tolylthio)allylidene)-1,3-oxathiolane		[97]

Novel N, S-substituted halonitrobutadienes derivatives, by reacting of (mono-thio) substituted halonitro-1,3-butadienes with amines, piperazines, morpholines, etc. were synthesized and studied, due to its biological activities [100, 105]. Especially piperazine derivatives, have number of different therapeutic areas including anti-cancer [106], antibacterial, antifungals antimalarials and antidepressants as well as HIV inhibitors [107, 108]. Thus, mono-thio nitrobutadiene compounds have received the attention of many researchers and have been heavily synthesized.

Additionally, the interaction of S-substituted-3-nitro-butadienes with some piperazines at room temperature in chloroform were synthesized. the products obtained in good yields, and crystal structure of compounds showed that the N, S-substituted-2-nitro-polyhalo-1,3-butadiene compounds were *E*-isomers, some *E*-isomer structures were shown in table 1.5.

Table 1.5: E-isomer structure of N,S-substituted-2-nitro-polyhalo-1,3-butadiene compounds

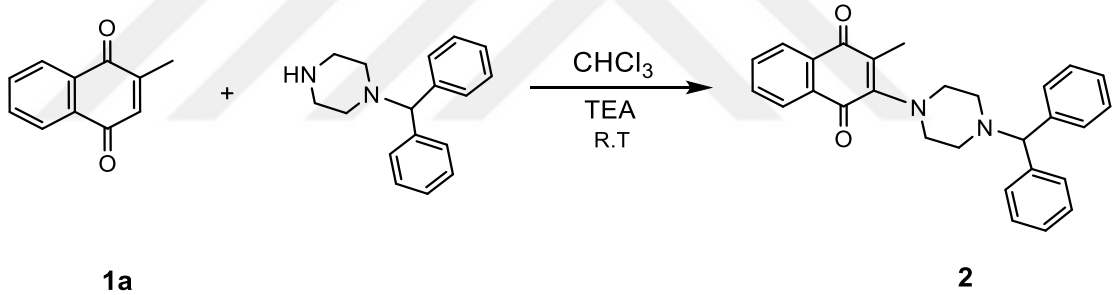
Chemical Name	*E*-Isomer Structure	Ref.
1,4-bis((*E*)-1-(butylthio)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl)-1,4-diazepane		[109]
(E)-1-(2-fluorophenyl)-4-(3,4,4-trichloro-2-nitro-1-((2,3,5,6-tetrafluorophenyl)thio)buta-1,3-dien-1-yl)piperazine		[110]
(E)-4-(3,4,4-trichloro-1-(decylthio)-2-nitrobuta-1,3-dien-1-yl)morpholine		[111]
(E)-1-(2-fluorophenyl)-4-(3,4,4-trichloro-1-(dodecylthio)-2-nitrobuta-1,3-dien-1-yl)piperazine		[105]
(E)-[4-(1-(2-Furoyl)piperazin-1-yl)]-4-(ethyl-sulfanyl)-1,1,2-trichloro-3-nitro-1,3-butadiene		[26]

2. MATERIALS AND METHODS

2.1. SYNTHESIS OF NEW N-SUBSTITUTED DERIVATIVES OF 2-METHYL-1,4-NAPHTHOQUINONE (VITAMIN K3)

2.1.1. Synthesis of 2-(4-benzhydrylpiperazin-1-yl)-3-methylnaphthalene-1,4-dione (2)

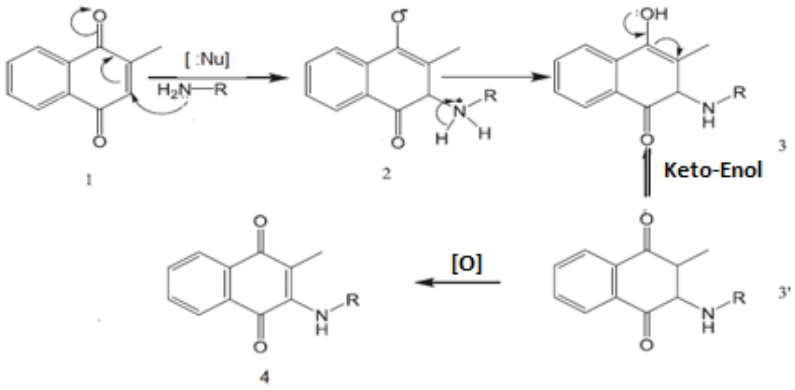
A new compound **(2)** obtained by reacting 2-methyl-1,4-naphthoquinone **(1a)** and 1-(diphenylmethyl)piperazine in chloroform at room temperature in presence of triethylamine (TEA) as general procedure 1.



1a **2**

(2.1)

The suggested mechanism (2.2) showing the formation of product 2-(N-substituted)-3-methyl-1,4-naphthoquinone. It requires the Michael addition of nucleophiles (amines, piperazines or morpholines, etc.) to the active site of 2-methyl-1,4-naphthoquinone (1), this leads to the generation of an intermediate (Enol form 3), which directly change into the more stable (Keto form 3`), then immediately converted into the major product (4) [39].



(2.2)

According to the IR spectrum of compound **2**; stretching bands for (C-H_{arom}) appeared at ν = 3219 cm^{-1} and stretching bands for (C-H_{aliph}) was observed at ν = 2979, 2904 cm^{-1}, (C=O) band appeared at ν = 1661 cm^{-1}, (C=C) was observed at ν = 1590 cm^{-1} (Figure 2.1).

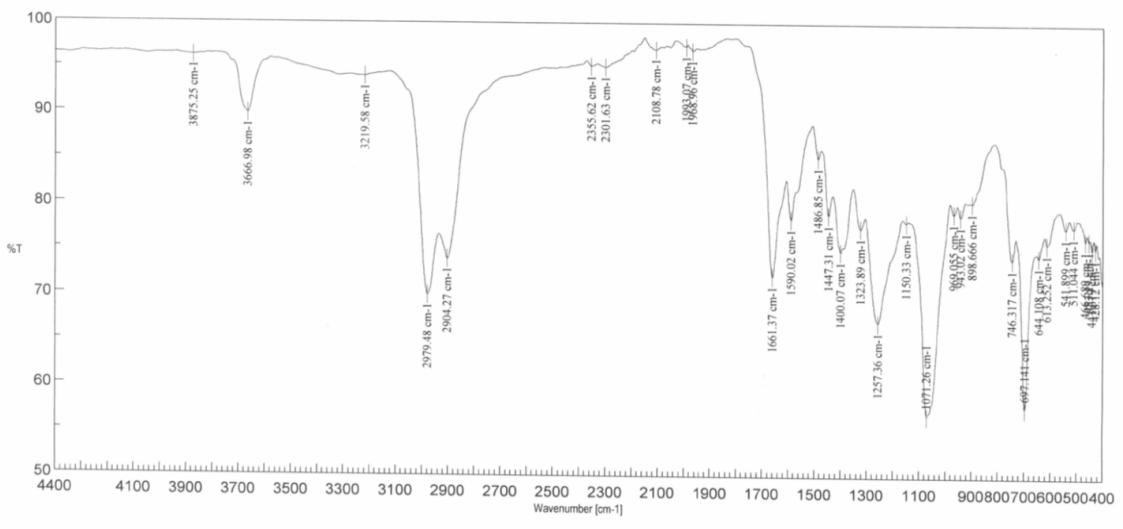


Figure 2.1: FTIR (KBr) spectrum concerning the compound **2.**

According to the ^{1}H NMR spectrum of compound **2**; (CH_3) were shown at δ = 2.00 ppm as a singlet. Piperazine ring protons at δ = 2.51 and 3.43 ppm as a broad singlet. A proton of (-CH<) was seen at δ = 4.32 ppm as singlet, protons in the two aromatic rings take place at δ = 7.27-7.77 ppm as multiplet. The doublet at δ = 7.80 ppm, doublet of doublets at δ = 8.00 ppm related to the naphthoquinone protons (Figure 2.2).

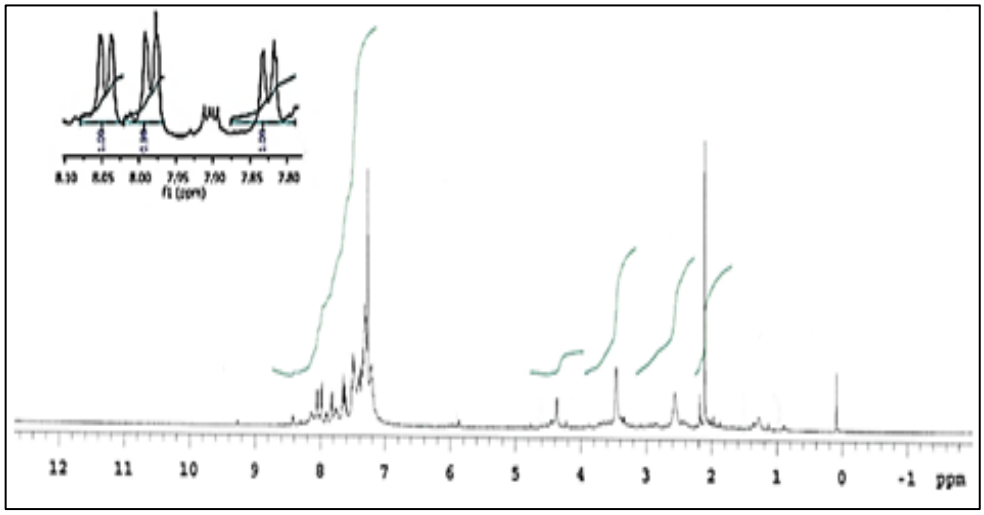


Figure 2.2: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **2**.

According to; ^{13}C (APT) NMR spectrum concerning the compound **2**; carbon signal of methyl group (CH_3) appeared at δ = 13.60 ppm, (CH_2-N-CH_2) carbon appeared at δ = 52.91, 53.82 ppm, carbon signal of (-CH<) at δ = 76.80 ppm, signals at δ = 125.75, 126.19, 126.55, 127.58, 127.73, 127.77, 128.01, 128.3, 128.50, 128.63, 128.85, 130.07, 132.53, 134.8 ppm are belongs to (CH_{arom}, C_{arom}), (=C-N) at δ = 168.24 ppm, signals at δ = 183.62, 185.40 ppm for carbonyl groups (C=O) (Figure 2.3).

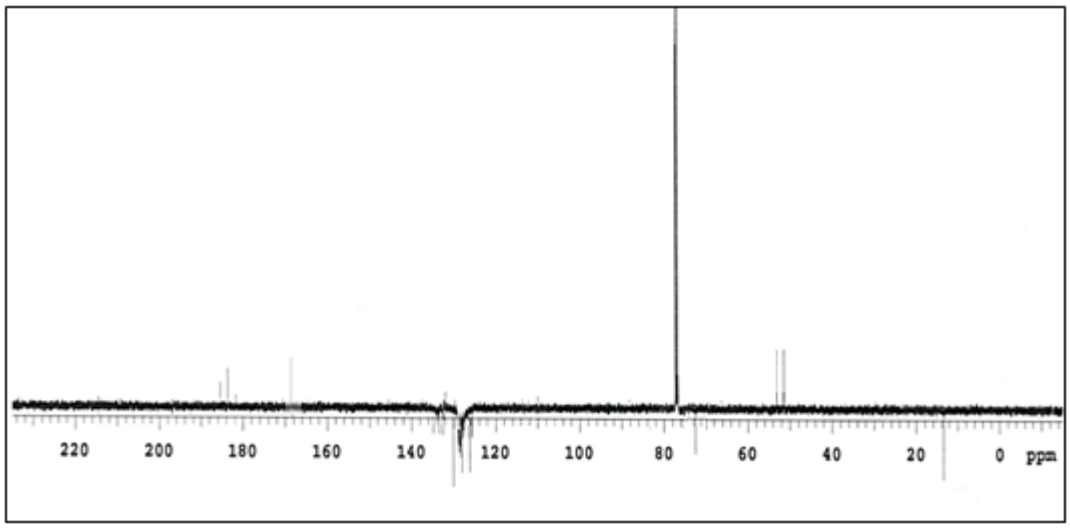


Figure 2.3: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **2**.

According to (+ESI) mass spectrum concerning the compound **2**; the molecular ion peak of a new compound ($C_{28}H_{26}N_2O_2$, M_w = 422.5 g/mol) was shown at *m/z* (100%) = 423.1$[M]^+$ (Figure 2.4).

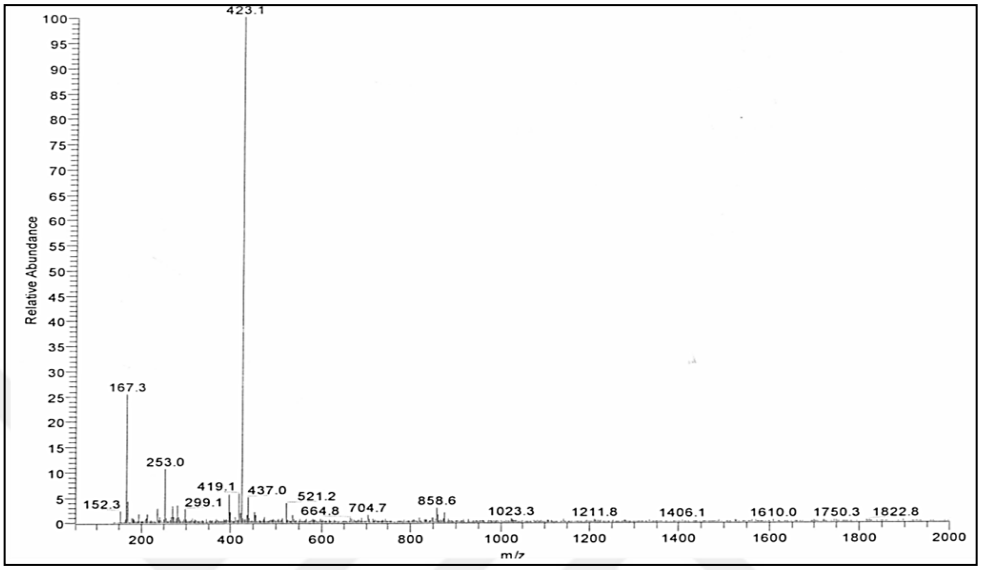
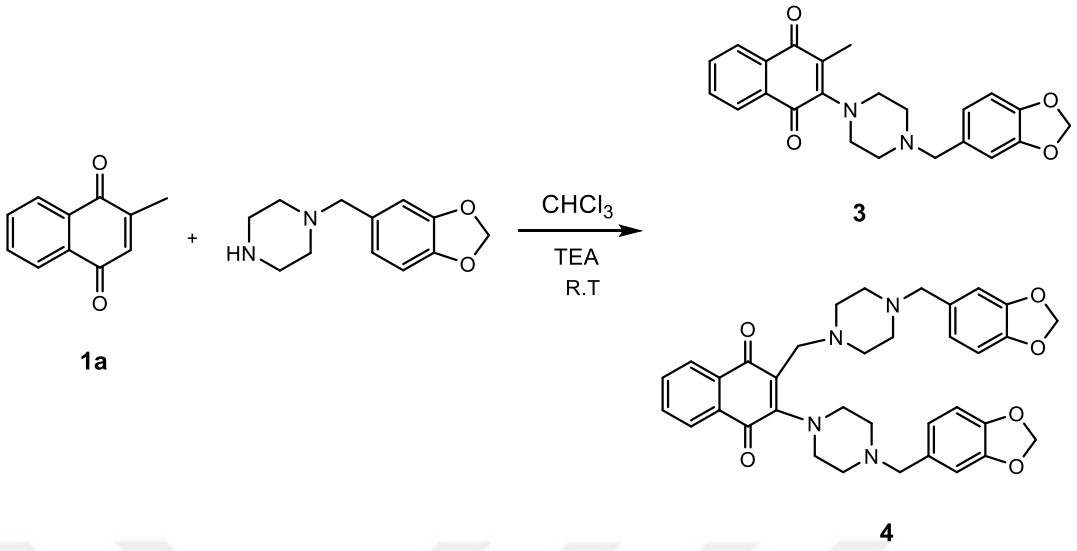


Figure 2.4: Mass spectrum [+ESI] of compound **2**.

All results obtained from the mass spectrum and other data prove the correct proposed structure for the new compound **(2)**.

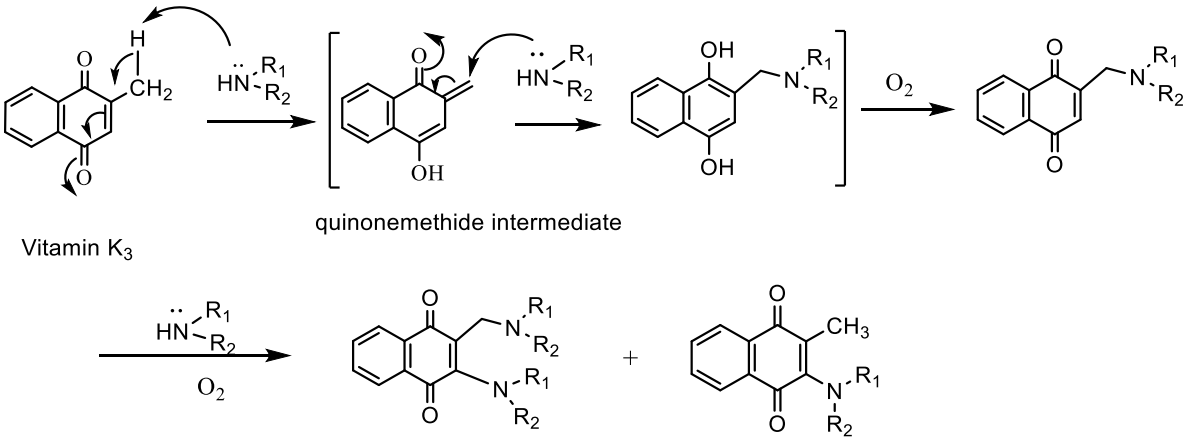
2.1.2. Synthesis of 2-(4-((benzo[d][1,3]dioxol-6-yl)methyl)piperazin-1-yl)-3methylnaphthalene-1,4-dione and 2-(4-((benzo[d][1,3]dioxol-6-yl)methyl)piperazin-1-yl)-3-((4-((benzo[d][1,3]dioxol-6-yl)methyl)piperazin-1-yl)methyl)naphthalene-1,4-dione (3, 4)

The new compounds **(3, 4)** were obtained by reacting the compound **(1a)** and 1-piperonylpiperazine in chloroform at (25 ^{0}C) in the existence of triethylamine (TEA) according procedure 1.



(2.3)

In this reaction we assumed that, the diamino-substituted product (4) produced of a large excess of nucleophile. In this case, it is presumed that, during the elimination reaction, the methyl group loss a proton, and the quinonemethide intermediate is formed, then an autooxidation steps, followed by nucleophilic attack on naphthoquinone system forming an adduct (4) [88]. Proposed mechanism is shown below (2.4).



(2.4)

According to the IR spectrum of compound **3**; stretching bands for (C-H_{arom}) appeared at ν = 3093 cm^{-1} and stretching bands for (C-H_{aliph}) observed at ν = 2979, 2902 cm^{-1}, (C=O) bands were seen at ν = 1661 and 1630 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1590, 1563 cm^{-1} (Figure 2.5).

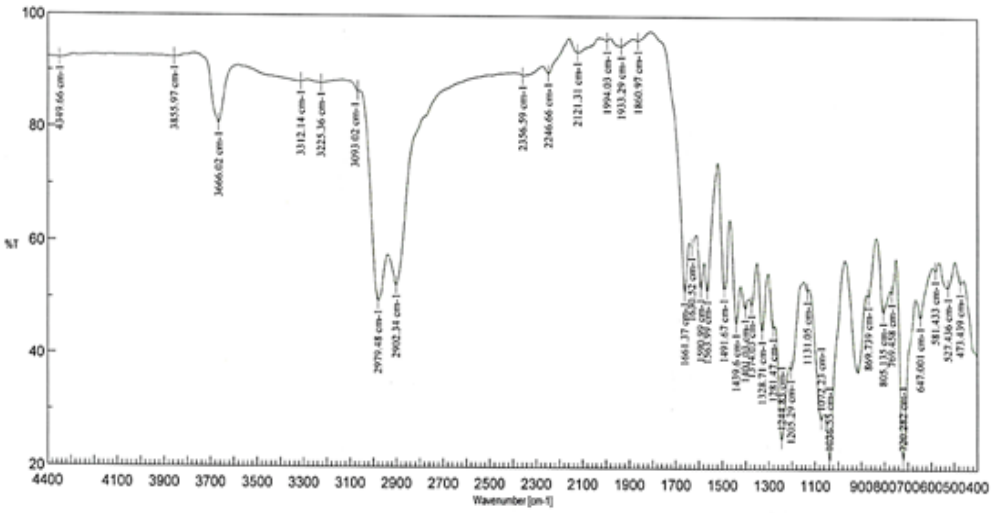


Figure 2.5: FTIR (KBr) spectrum concerning the compound **3.**

According to ^{1}H NMR spectrum concerning the compound **3**; (CH_3) protons were seen at δ = 2.01 ppm as singlet, piperazine ring protons detected at δ = 2.56 and 3.37 ppm as a broad singlet. Protons of methylene group (N-CH_2-C_{arom}) and (O–CH_2–O), were seen at δ = 3.50, 5.86 ppm as singlet. Protons of aromatic ring (CH_{arom}), two of them appeared as multiplet at δ = 6.71-6.78 ppm and one proton at δ = 6.81 ppm as a singlet. The multiplet and doublet at δ = 7.55 -7.84 and 7.89-7.99 ppm are belonging to naphthoquinone protons (Figure 2.6).

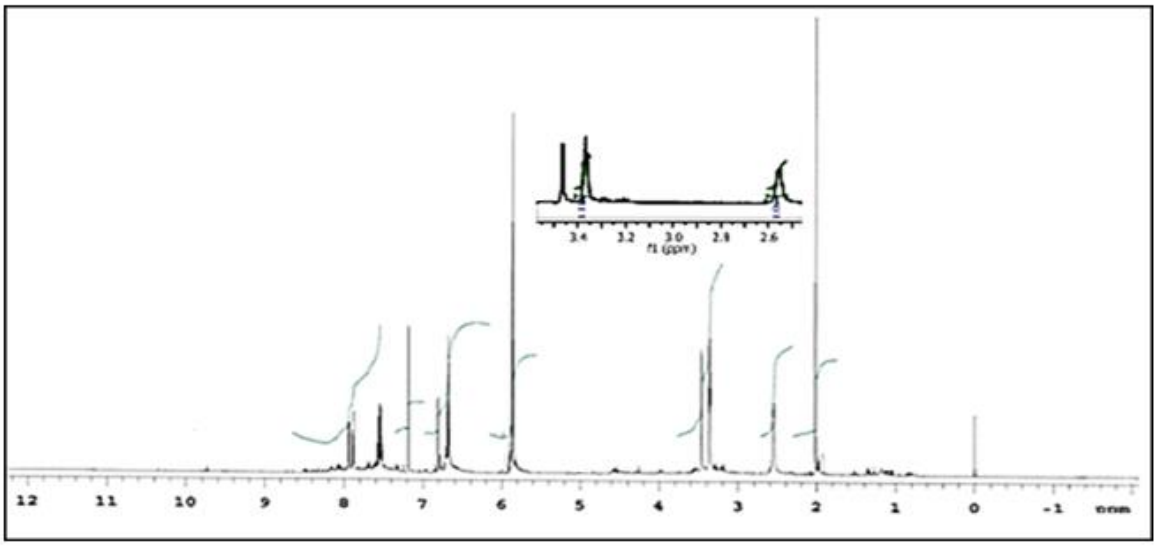


Figure 2.6: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **3**.

According to ^{13}C (APT) NMR spectrum concerning the compound **3**; Carbon signal of methyl group (CH_3) was appeared at δ = 13.58 ppm. The piperazine carbons (CH_2-N-CH_2) gave two signals at δ = 50.98, 53.57 ppm. Carbons of the methylene group (N-CH_2-C_{arom}) and (O–CH_2–O), were seen at δ = 62.69, 100.90 ppm. Aromatic carbon (CH_{arom}, C_{arom}) signals were observed at δ = 107.96, 109.71, 122.61, 125.74, 126.16, 128.55, 131.99, 132.37, 132.62 and 133.43 ppm. Carbons of (=C-O) were appeared at δ =146.92, 147.73 ppm and (=C-N) at δ = 151.52 ppm. Signals at δ = 183.54, 185.40 ppm for carbonyl groups (C=O) (Figure 2.7).

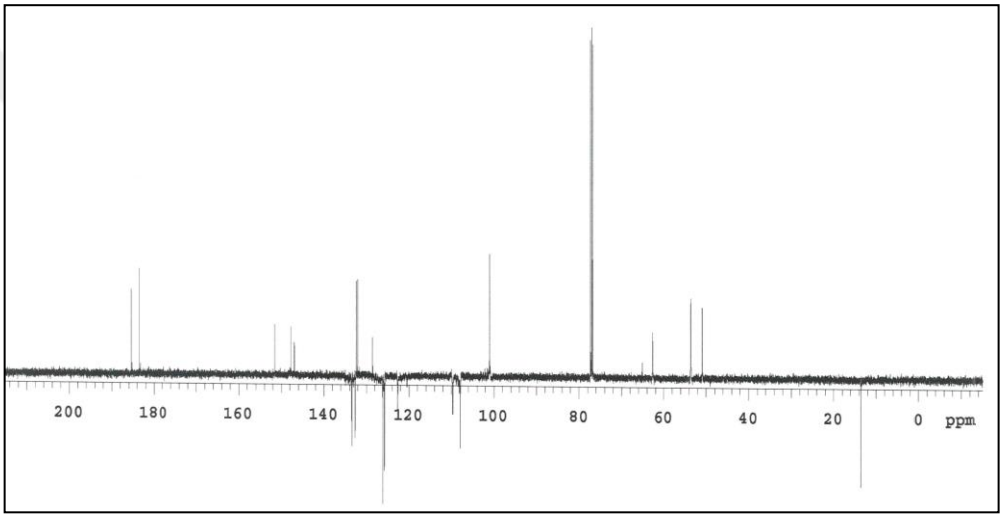


Figure 2.7: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **3**.

According to (+ESI) mass spectrum concerning the compound **3**; the molecular ion peak of a new compound $C_{23}H_{22}N_2O_4$, M_w = 390.45 g/mol), was shown at *m/z* (100%) = 391.1 $[M+H]^+$(Figure 2.8).

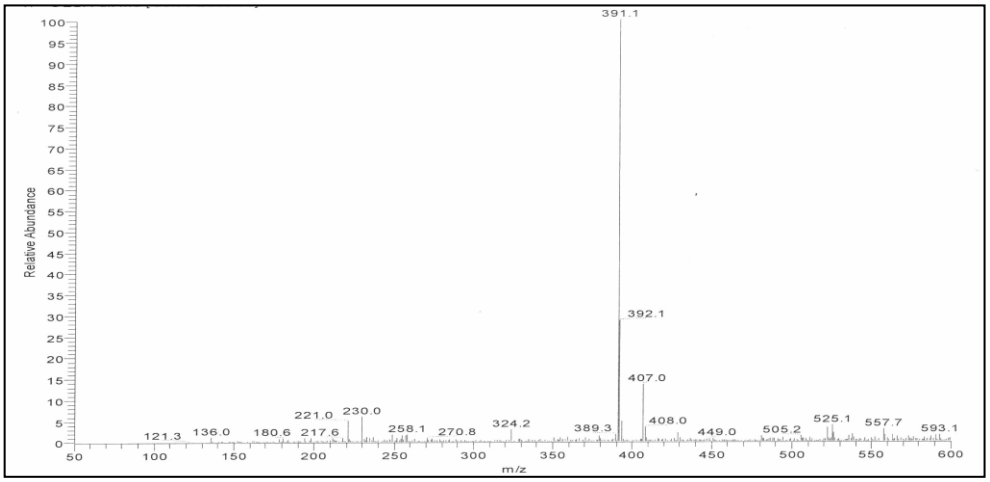


Figure 2.8: Mass spectrum [+ESI] concerning the compound **3**.

According to the IR spectrum of compound **4;** Stretching bands for (C-H_{arom}) observed at ν = 3069 cm^{-1} and stretching bands for (C-H_{aliph}) appeared at ν = 2978, 2900, 2815, 2774 cm^{-1}. (C=O) band appeared at ν = 1661 and 1630 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1587, 1565 cm^{-1} (Figure 2.9).

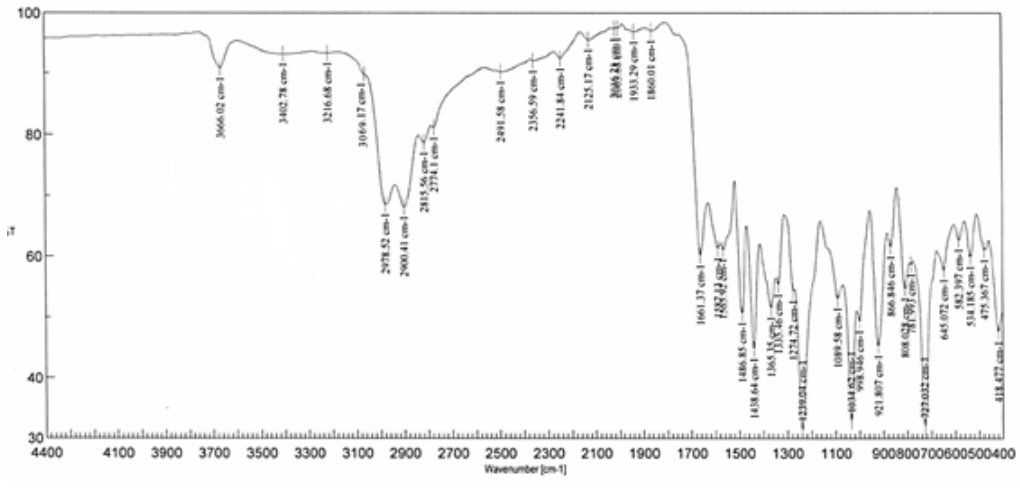


Figure 2.9: FTIR (KBr) spectrum concerning the compound **4**.

According to the ^{1}H NMR spectrum concerning the compound **4**; piperazine rings were seen at δ= 2.61, 3.10 ppm, and δ = 3.62, 3.86 ppm as a singlet. Protons of (N–CH_2–C_{naphth}), (N-CH_2-C_{arom}) and (O–CH_2–O) were seen as a singlet at δ=3.44, 3.50, 5.90 ppm, respectively.

Protons of phenyl rings were shown as multiplet at δ = 6.70-6.89 ppm. The triplet, multiplet and doublet of doublet at δ = 7.65 ,7.75 and (8.00-8.18) ppm are belonging to naphthoquinone protons (Figure 2.10).

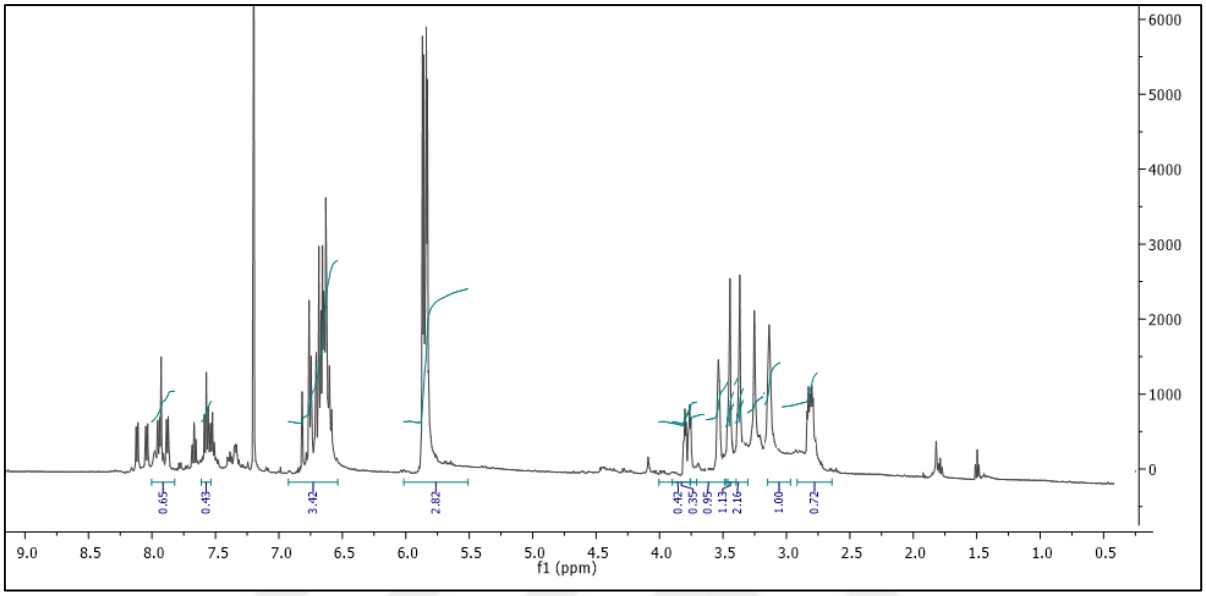


Figure 2.10: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **4**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **4**; The carbons in piperazine rings (CH_2-N-CH_2) gave signals at δ = 51.91, 53.21, 58,30 ppm. Carbons of methylene groups (N–CH_2–C_{naphth}), (N-CH_2-C_{arom}) and (O–CH_2–O) appeared at δ = 46.14, 62.69 and 100.94 ppm, respectively. Signals at δ =107.79, 109.34, 122.44, 125.86, 126.24, 130.68, 131.39, 132.36, 133.56 and 135.17 ppm for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) was appeared at δ =146.96 ppm and (=C-O) at δ = 153.89 ppm. The last two signals at δ =182.31, 184.20 ppm related to carbon of carbonyl groups (Figure 2.11).

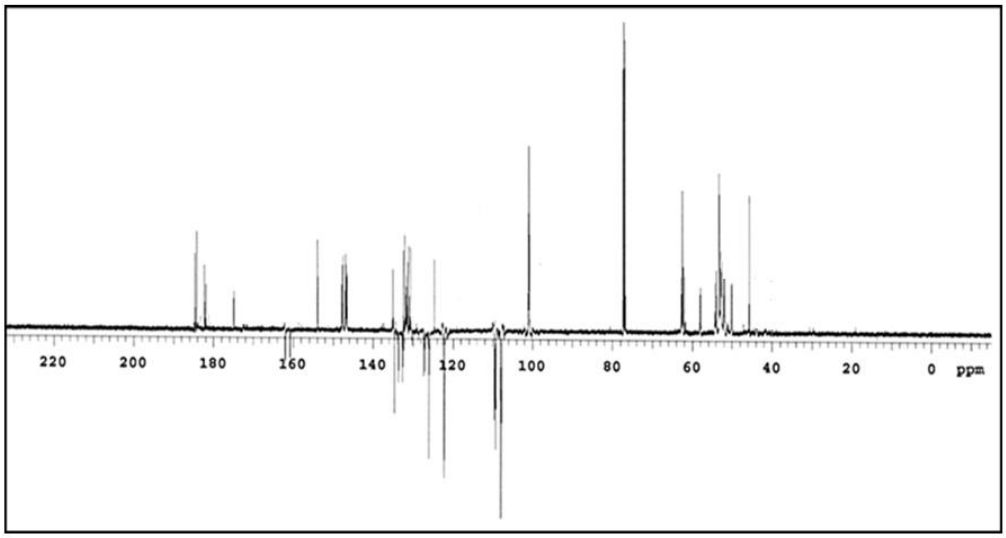


Figure 2.11: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **4**.

According to (+ESI) mass spectrum concerning the compound **4**; the molecular ion peak of a new compound ($C_{35}H_{36}N_4O_6$, M_w = 608.70 g/mol) was shown at *m/z* (100%) =609.0$[M]^+$ (Figure 2.12).

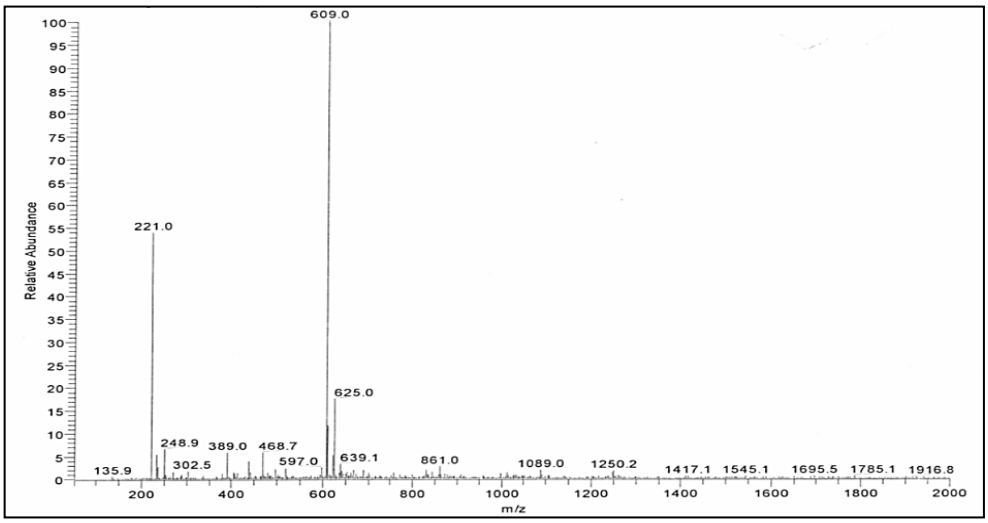
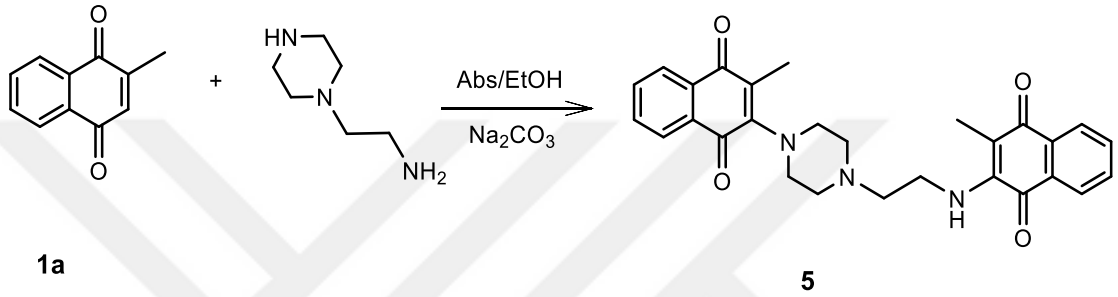


Figure 2.12: Mass spectrum [+ESI] concerning the compound 4**.**

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new compounds **(3, 4)**.

2.1.3. Synthesis of 2-methyl-3-(4-(2-((3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)ethyl)piperazin-1-yl)naphthalene-1,4-dione (5)

The new compound **(5)** was formed by reacting the starting compound **(1a)** and 1-(2-aminoethyl)piperazine in Abs. Ethanol, then refluxed 8h in the existence of Na_2CO_3 as general procedure 2.



(2.5)

According to the IR spectrum of compound **5**; a broad and weak stretching band for (NH) group appeared at ν = 3310 cm^{-1} and stretching bands for($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) observed at ν = 3078, 2968, 2906 cm^{-1}, (C=O) bands appeared around ν = 1661 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1594, 1563 cm^{-1} (Figure 2.13).

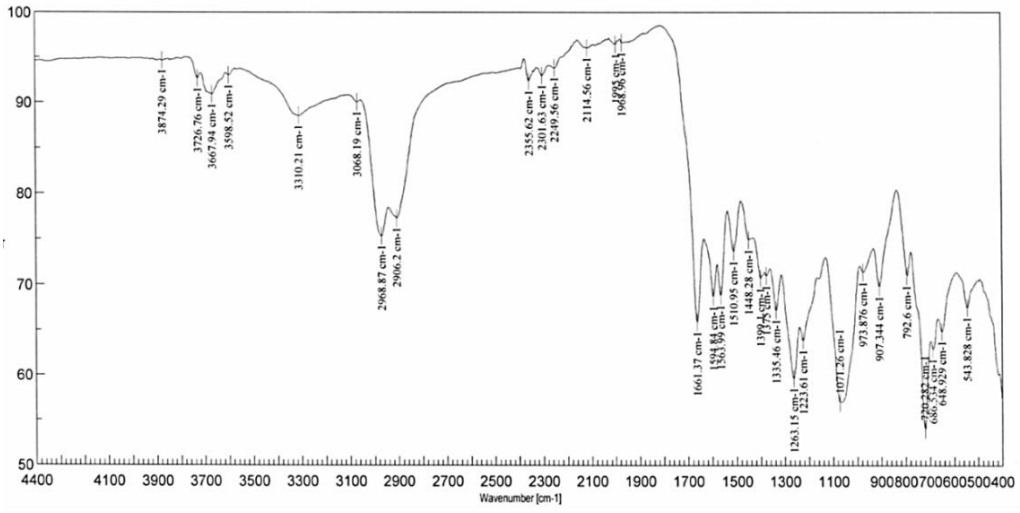


Figure 2.13: FTIR (KBr) spectrum concerning the compound **5**.

According to the ^{1}H NMR spectrum concerning the compound **5**; protons (CH_3) were shown at δ = 1.94, 2.05 ppm as singlet. Piperazine ring were seen at δ =2.60, 3.40 ppm as a singlet. Protons of (C**H**$_2$-NH) at δ =2.70 ppm as a triplet and (CH_2-N_{piper}) at δ =3.65 ppm as a multiplet. (NH) Proton at δ = 6.36 ppm was observed as a broad singlet. Protons of naphthoquinone were seen at δ = 7.51-7.61 and 7.91-7.98 ppm as a multiplet (Figure 2.14).

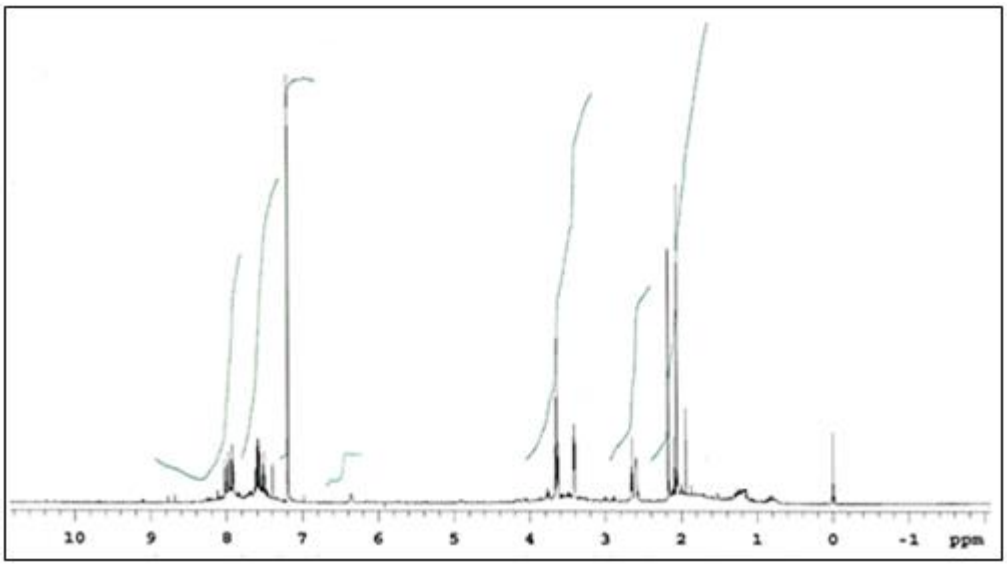


Figure 2.14: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **5**.

According to the ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **5**; the carbon signal of methyl groups (CH_3) appeared at δ = 11.06, 13.60 ppm. The piperazine carbons (CH_2 -N-CH_2) gave two signals at δ = 51.20, 53.48 ppm. Carbons of the methylene groups (N-CH_2CH_2-NH) were seen at 41.57, 57.16 ppm. Aromatic carbon (CH_{arom}, C_{arom}) signals were observed at δ = 125.78, 126.20, 128.71, 130.51, 131.82, 132.67, 133.48, 134 ppm. Carbons of (=C-N) and (=C-NH), were appeared at δ =146.61, 151.51 ppm. Signals at δ = 182.56, 183.48, 183.65, 185.47 ppm for carbonyl groups (C=O) (Figure 2.15).

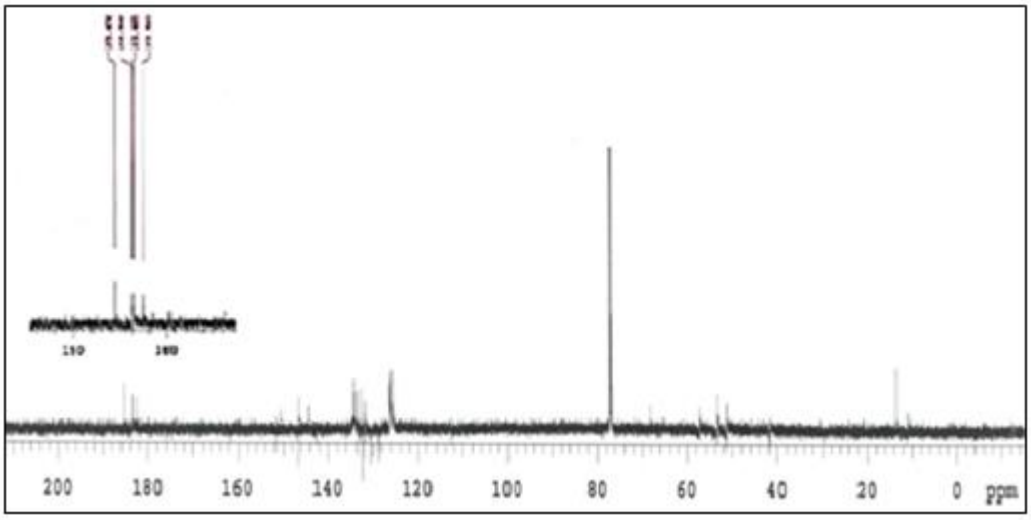


Figure 2.15: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **5.**

According to (+ESI) mass spectrum concerning the compound **5**; the molecular ion peak of a new compound ($C_{28}H_{27}N_3O_4$, Mw = 469.53 g/mol). was obtained at m/z (100%) =470.2$[M+H]^+$ (Figure 2.16).

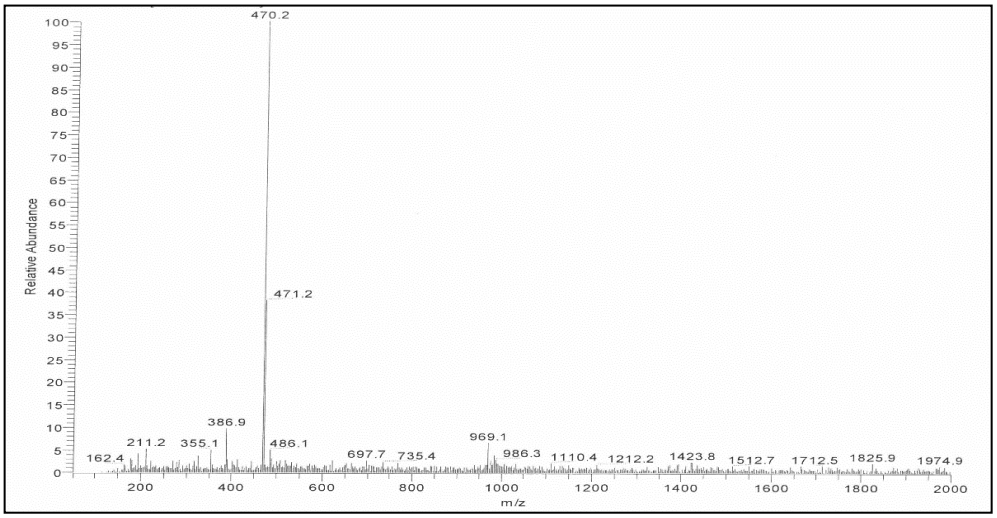
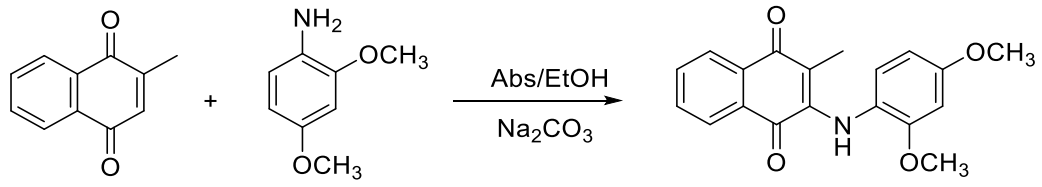


Figure 2.16: Mass spectrum [+ESI] concerning the compound **5**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of compound **(5)**.

2.1.4. Synthesis of 2-((2, 4-dimethoxyphenyl)amino)-3-methylnaphthalene-1,4-dione (6)

The new compound **(6)** obtained when the starting compound **(1a)** mixed with 2,4-dimethoxyaniline in Abs. Ethanol and refluxed 8h in the existence of Na_2CO_3, as general procedure 2.



1a **6**

(2.6)

According to IR spectrum of compound **6**; the (NH) band was observed at ν = 3338 cm^{-1} (C-H_{arom}) band appeared at ν = 3063 cm^{-1} and (C-H_{aliph}) bands observed at ν = 2970, 2913 cm^{-1}, carbonyl group band (C=O) appeared at ν = 1724, 1661 cm^{-1}, and the band of carbon-carbon double bonds (C=C) were seen at ν = 1597, 1567 cm^{-1} (Figure 2.17).

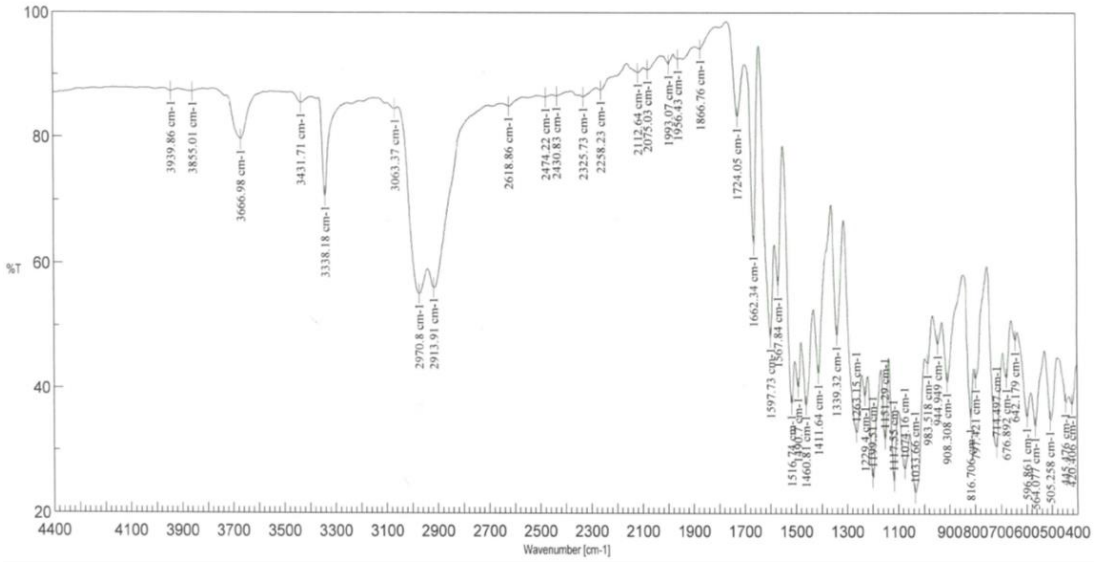


Figure 2.17: FTIR (KBr) spectrum concerning the compound **6**.

According to the ^{1}H NMR spectrum concerning the compound **6**; (CH_3) protons were shown as a singlet at δ =1.73 ppm. Protons of methoxy groups (-OCH_3) appeared at δ = 3.85 ppm as a singlet. Protons of the aromatic ring (CH_{arom}), two of them appeared as multiplet at δ = 6.44-6.48 ppm and one proton at δ = 6.81 ppm as a doublet. (NH) proton was seen at δ = 7.22 ppm as a singlet. The multiplet at δ = 7.61-7.73 ppm and the doublet of doublet at δ = 8.08, 8.18 ppm related to the naphthoquinone protons (Figure 2.18).

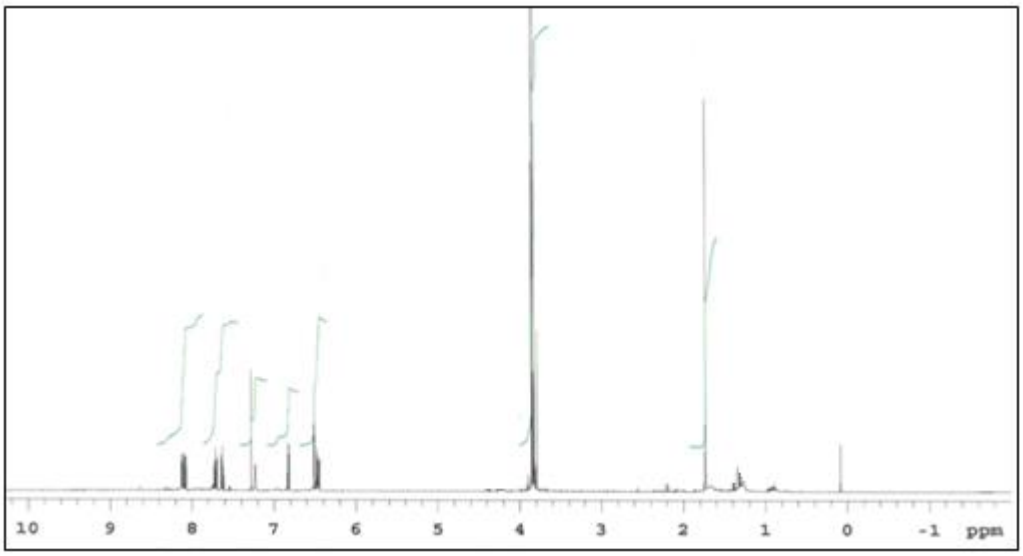


Figure 2.18: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **6**.

According to ^{13}C (APT) NMR spectrum concerning the compound **6**; the signal of methyl group (CH_3) observed at δ = 13.31 ppm. The carbons of methoxy (CH_3O-) gave two signals at δ = 55.52, 55.70 ppm. Aromatic carbon (CH_{arom}, C_{arom}) signals were seen at δ = 98.95, 103.36, 116,41, 121.96, 124.36, 126.07, 130.49, 132.09, 133.46, 134.25, 143.07 ppm. Carbons of (=C-O) appeared at δ = 153.55, 157.80 ppm. Signals at δ = 182.53, 184.21 are belonging to carbonyl groups (C=O) (Figure 2.19).

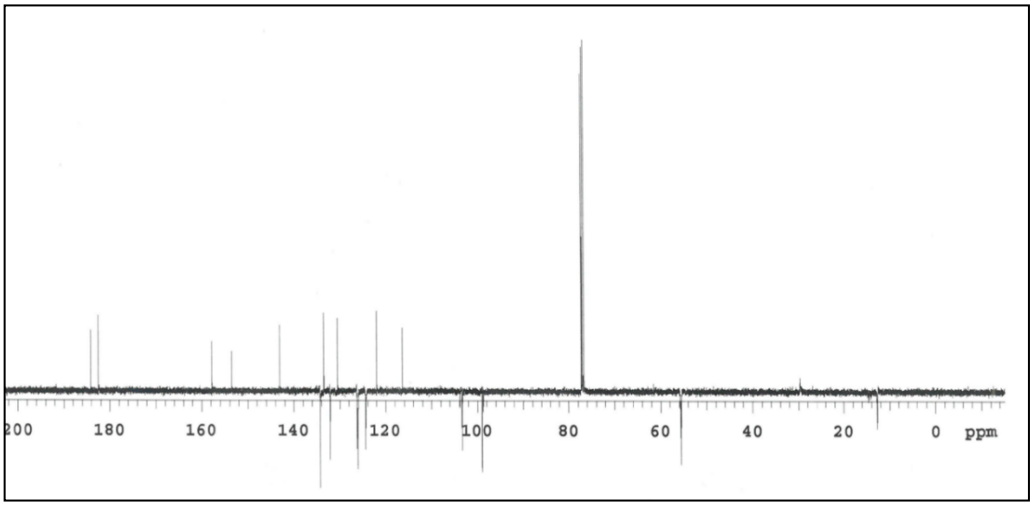


Figure 2.19: ^{13}C (APT) NMR spectrum concerning the compound **6**.

According to (+ESI) mass spectrum concerning the compound **6**; the molecular ion peak of a new compound ($C_{19}H_{17}NO_4$, M_w = 323.43 g/mol) was shown at *m/z* (100%) = 324.1 $[M+H]^+$ (Figure 2.20).

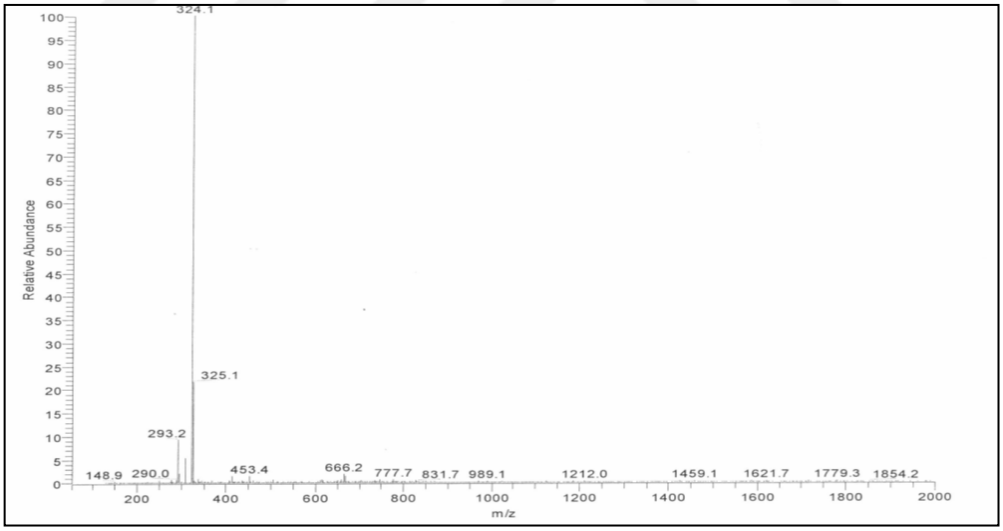
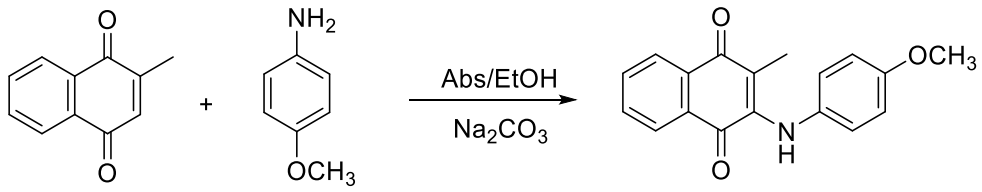


Figure 2.20: Mass spectrum [+ESI] concerning the compound **6**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(6)**.

2.1.5. Synthesis of 2-((4-methoxyphenyl) amino)-3-methylnaphthalene-1,4-dione (7)

The new compound **(7)** obtained when 4-methoxyaniline added to the starting compound **(1a)** in Abs. Ethanol and refluxed 8 h in the existence of Na_2CO_3, according procedure 2.



1a **7**

(2.7)

According to IR spectrum of compound **7**; (NH) band was shown at ν = 3248 cm^{-1}, stretching bands for (C-H_{aliph}) observed at ν = 2966, 2916 cm^{-1}, carbonyl group band (C=O) appeared at ν = 1718, 1664 cm^{-1}. The band of carbon-carbon double bond (C=C) was seen at ν = 1594, 1563 cm^{-1}, (C-O) band at 1072 cm^{-1} (Figure 2.21).

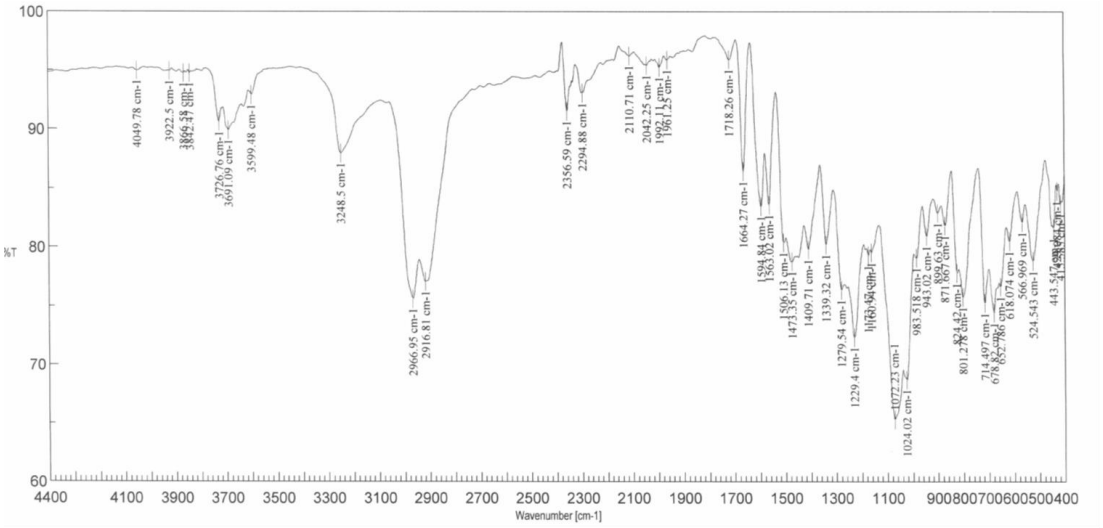


Figure 2.21: FTIR (KBr) spectrum concerning the compoun **7**.

According to the ^{1}H NMR of compound **7**; protons of methyl group (CH_3) observed as a singlet at δ = 1.63 ppm. Methoxy groups (-OCH_3) were seen at δ = 3.74 ppm as singlet. Protons of the aromatic ring (CH_{arom}) were taking place at δ= 6.87-6.80 and 6.89-6.91 ppm as multiplet. (NH) proton was seen at δ = 7.27 ppm as a singlet. The multiplet and doublet at δ = 7.55-7.66 and 8.05, 8.12 ppm related to the naphthoquinone protons rspectively (Figure 2.22).

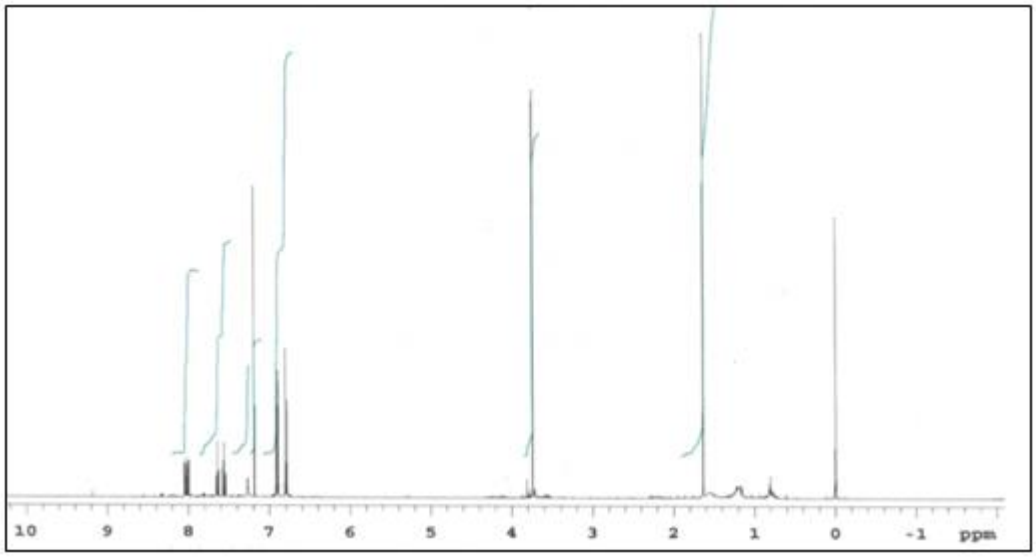


Figure 2.22: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **7**.

According to ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **7**; Carbon signal in (CH_3) was seen at δ = 13.22 ppm. The carbons of (CH_3O-) group gave a signal at δ = 55.45 ppm. Signals at. Aromatic carbon (CH_{arom}, C_{arom}) signals were seen at δ = 114.12, 116.73, 124.86, 126.12, 130.83, 132.22, 133.39 ppm. Carbons of (=**C**-N)$_{naphth}$ and (**C**-O)$_{ph}$ appeared at δ = 143.10, 156.48 ppm. Signals at δ = 182.60, 184.35 ppm for carbonyl groups (C=O) (Figure 2.23).

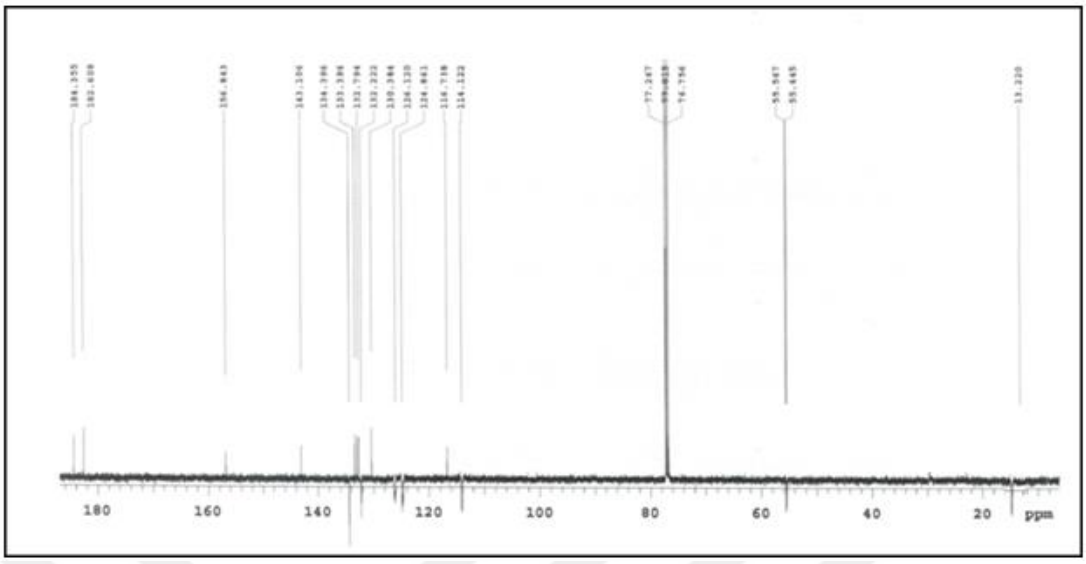


Figure 2.23: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **7**.

According to (+ESI) mass spectrum concerning the compound **7**; the molecular ion peak of a new compound ($C_{18}H_{15}NO_3$, M_w = 293.32 g/mol) was seen at *m/z* (100%) = 294.1 $[M+H]^+$(Figure 2.24).

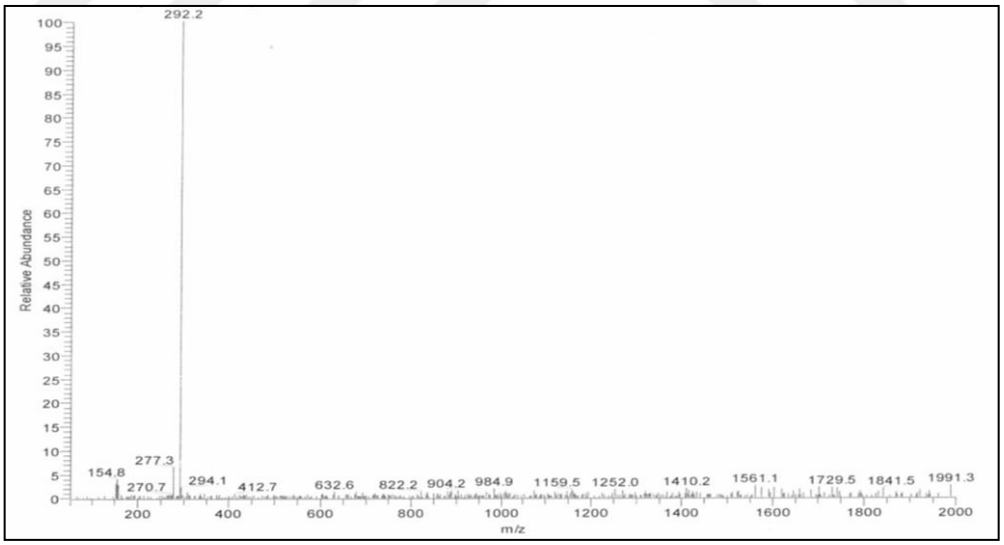
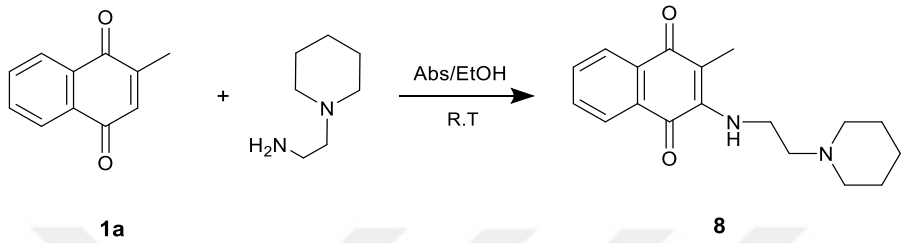


Figure 2.24: Mass spectrum [+ESI] concerning the compound **7**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(7)**.

2.1.6. Synthesis of 2-methyl-3-((2-(piperidin-1-yl)ethyl)amino) naphthalene-1,4-dione (8)

The new compound **(8)** obtained when 1-(2-aminoethyl)piperidine added to the starting compound **(1a)** in Abs. Ethanol at (25 ^{0}C) as general procedure 3.



1a **8**

(2.8)

According to IR spectrum of compound **8**; (NH) band was observed at ν = 3276 cm^{-1}. Band corresponding (C-H$_{arom}$) appeared at ν = 3070 cm^{-1} and stretching bands for (C-H$_{aliph}$) were observed at ν = 2980, 2923, 2855, 2793, 2760 cm^{-1}. The (C=O) band detected at ν = 1668 cm^{-1}. Also, the bands of carbon-carbon double bond (C=C) were seen at ν = 1597, 1561 cm^{-1} (Figure 2.25).

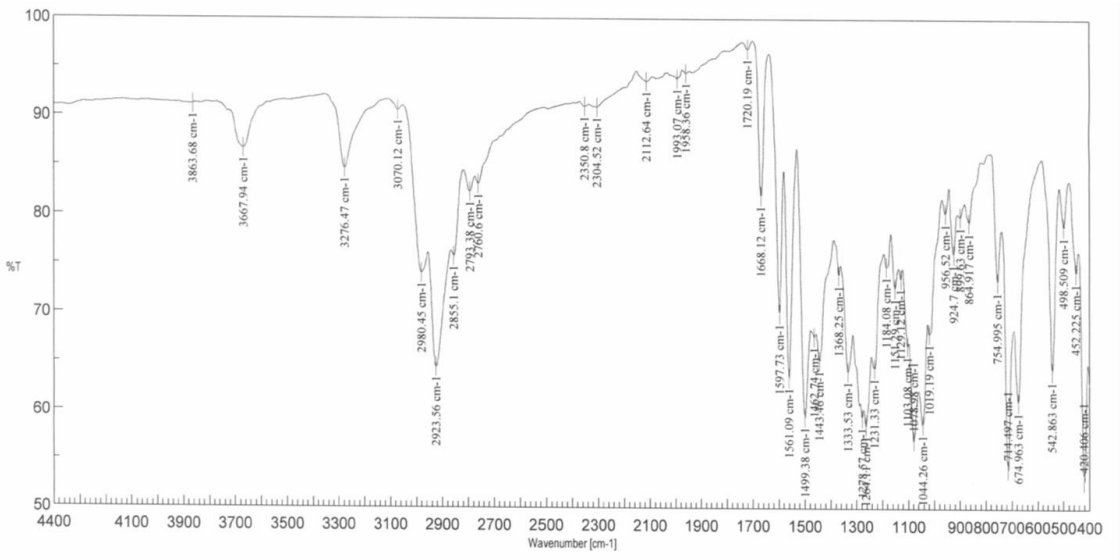


Figure 2.25: FTIR (KBr) spectrum concerning the compound **8**.

According to ^{1}H NMR spectrum concerning the compound **8**; six protons of piperidine ring $(CH_2)_{piperi}$ appeared at δ =1.39, 1.55 ppm as a multiplet and other protons $(N\text{-}CH_2)_{piperi}$ appeared as a broad singlet at δ = 2.37 ppm. Methyl protons (CH_3) observed at δ=2.13 ppm as singlet too. Protons of ($CH_2C\mathbf{H_2}$-N) were seen at δ = 2.52 ppm as a triplet, whereas, (HN-C$\mathbf{H}_2$) as a multiplet at δ = 3.60 ppm. (NH) proton was seen at δ = 6.37 ppm as a singlet. The multiplet at δ = 7.46- 7.98 and doublet at δ = 8.00, 8.09 ppm related to the naphthoquinone protons (Figure 2.26).

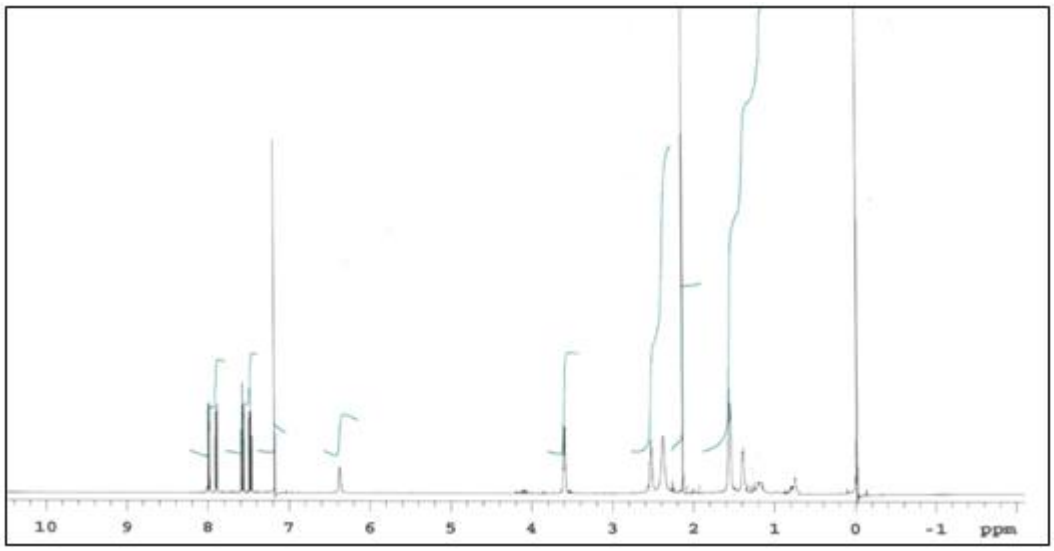


Figure 2.26: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **8**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **8**; Carbon signal for (CH_3) group was seen at δ=10.90 ppm. Carbons (CH_2) in piperidine gave two signals at δ = 24.34, 26.01 ppm. Signals at δ = 41.84, 45.13 ppm for (HN-CH_2) and $(N\text{-}CH_2)_{piperi}$. The carbons of (N-CH_2) and (=**C**-CH_3) observed at δ =57.64, 125.83 ppm. Aromatic carbon (CH_{arom}, C_{arom}) signals were seen at δ = 126.86, 126.04, 130.59, 131.86, 133.51, 134.07 ppm. Carbon of (=**C**-NH) appeared at δ = 146.73 ppm. Signals at δ = 182.62, 183.31 ppm for carbonyl groups (C=O) (Figure 2.27).

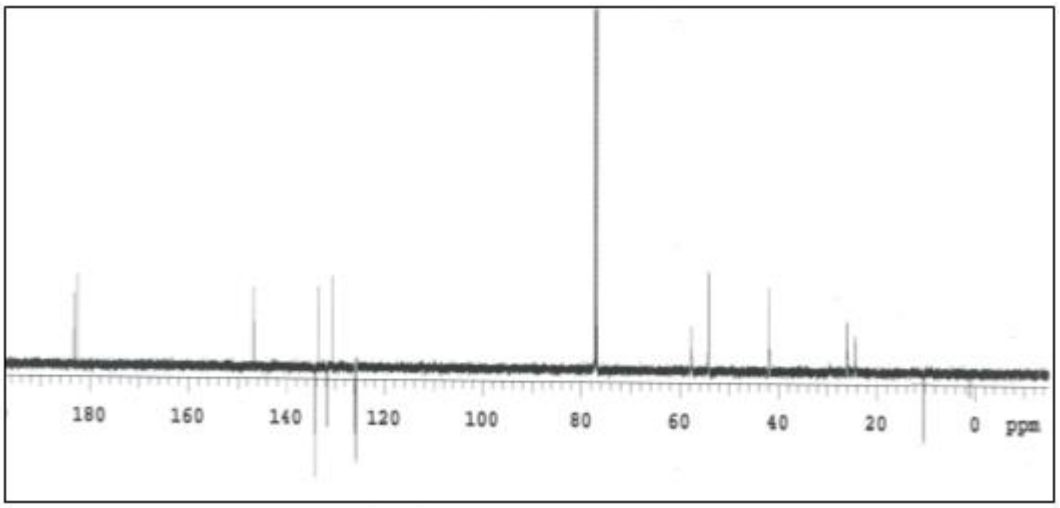


Figure 2.27: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **8**.

According to (+ESI) mass spectrum concerning the compound **8**; the molecular ion peak of a new compound ($C_{18}H_{22}N_2O_2$, M_w = 298.38 g/mol) was seen at *m/z* (100%) = 294.2$[M\text{-}4H]^+$ (Figure 2.28).

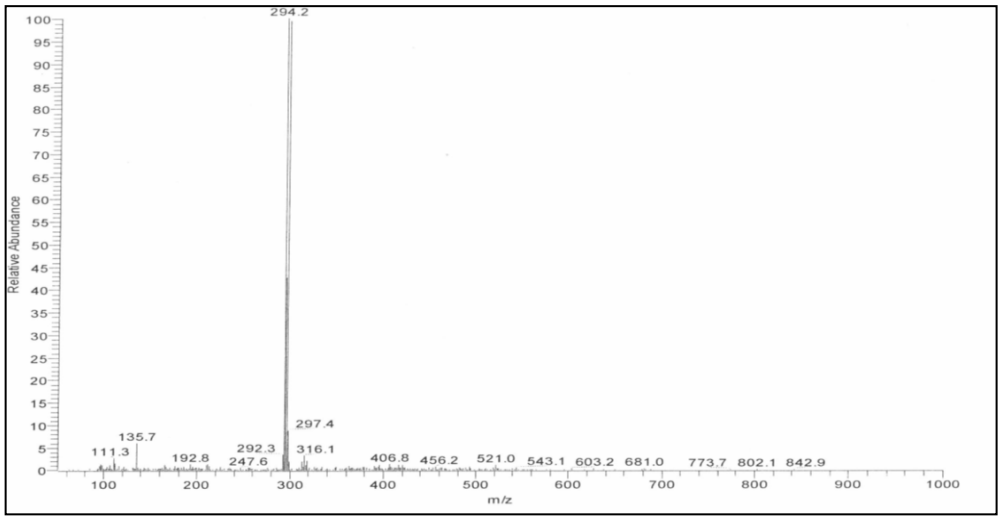
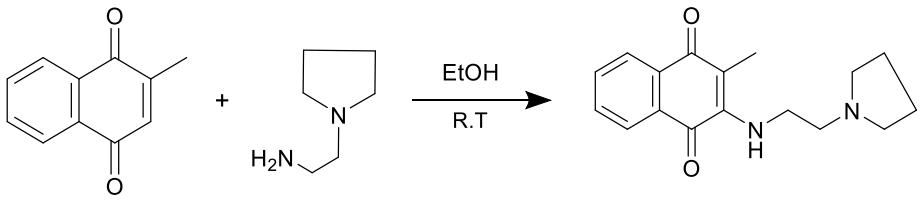


Figure 2.28: Mass spectrum [+ESI] concerning the compound **8**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(8)**.

2.1.7. Synthesis of 2-methyl-3-[(2-(pyrrolidin-1-yl)ethyl)amino]naphthalene-1,4-dione (9)

The new compound **(9)** obtained when 1-(2-aminoethyl)pyrrolidine added to the starting compound **(1a)** and Abs. Ethanol at (25 ^{0}C) as general procedure 3.



1a **9**

(2.9)

According to the IR spectrum of compound **9**; (NH) band was observed at ν = 3332 cm^{-1}. Stretching bands for (C-H$_{arom}$), (C-H$_{aliph}$), carbonyl group (C=O), (C=C) were observed at ν = 3067 cm^{-1}, ν = 2952, 2876, 2794 cm^{-1}, ν =1661 cm^{-1}, ν = 1596, 1563 cm^{-1}, respectively (Figure 2.29).

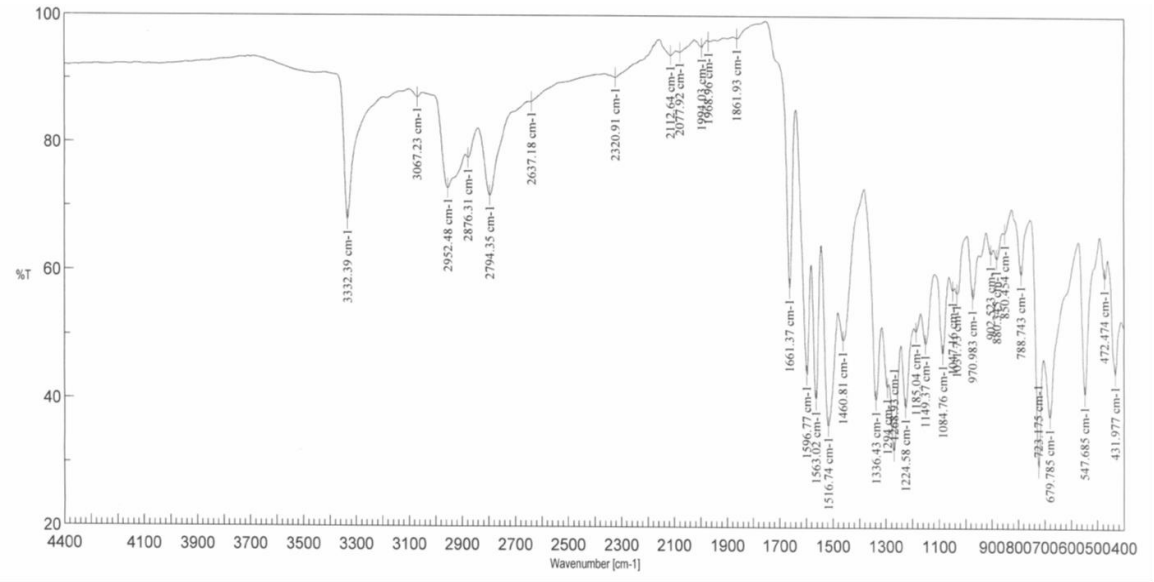


Figure 2.29: FTIR (KBr) spectrum concerning the compound **9**.

According to the ^{1}H NMR spectrum concerning the compound **9**; the protoms in pyrrolidine ring $(CH_2\text{-}CH_2)_{pyrol}$, $(CH_2\text{-}N\text{-}CH_2)_{pyrrol}$ were shown at δ = 1.73, 2.50 ppm as multiplet and a

broad singlet. Methyl protons (CH_3) observed at δ = 2.13 ppm as singlet. Protons in (CH_2-N) were seen as a triplet at δ = 2.67 ppm and two protons of HN-(C**H**$_2$) were seen as doublet of doublets at δ =3.60 ppm. (NH) proton was seen at δ = 6.22 ppm as a singlet. The multiplet at δ = 7.46-7.85 ppm and doublet of doublet at δ =7.99, 8.03 ppm related to the naphthoquinone protons (Figure 2.30).

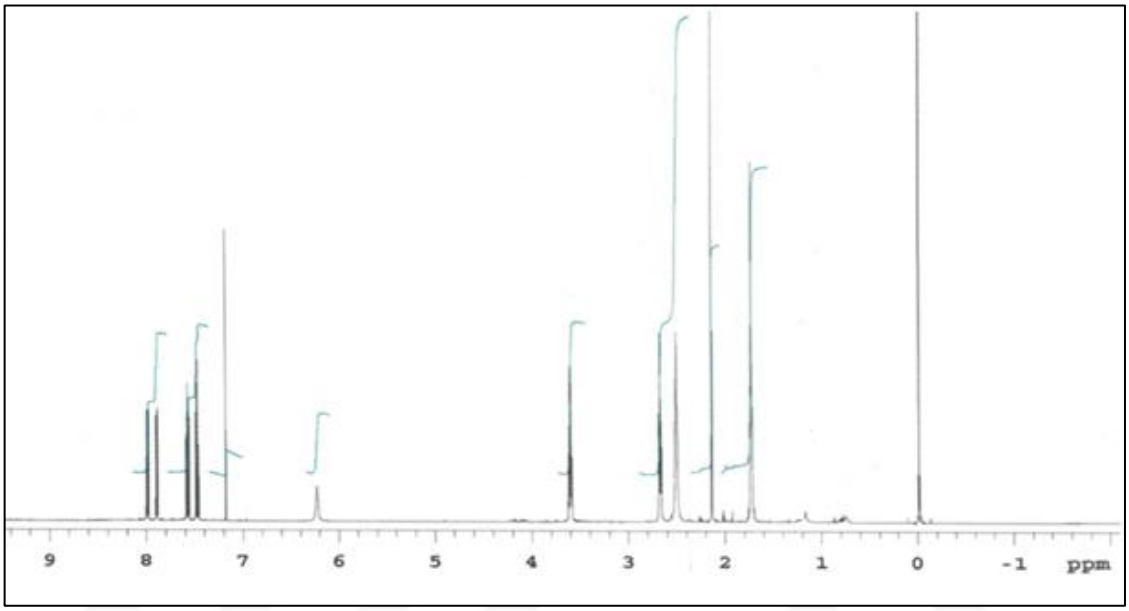


Figure 2.30: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **9**.

According to^{13}C (APT) NMR spectrum concerning the compound **9**; carbon signal for (CH_3) was seen at δ = 10.60 ppm. Carbons of pyrrolidine (**C**H_2-CH_2) gave one signal at δ = 23.50 ppm. The signal at δ = 53.78 ppm for (CH_2-N-CH_2)$_{pyrrol}$. (HN-**C**H_2-**C**H_2-N) gave two signals at δ = 43.90, 55.29 ppm. (=**C**-CH_3) was observed at δ =112.24 ppm. Aromatic carbon (CH_{arom}, C_{arom}) signals were seen at δ= 125.83 130.48, 131.56, 133.47. 134.10 ppm. The carbon of (HN-C_{naphth}) appeared at δ = 146.61 ppm. Signals at δ = 182.51, 183.35 ppm for carbonyl groups (C=O) (Figure 2.31).

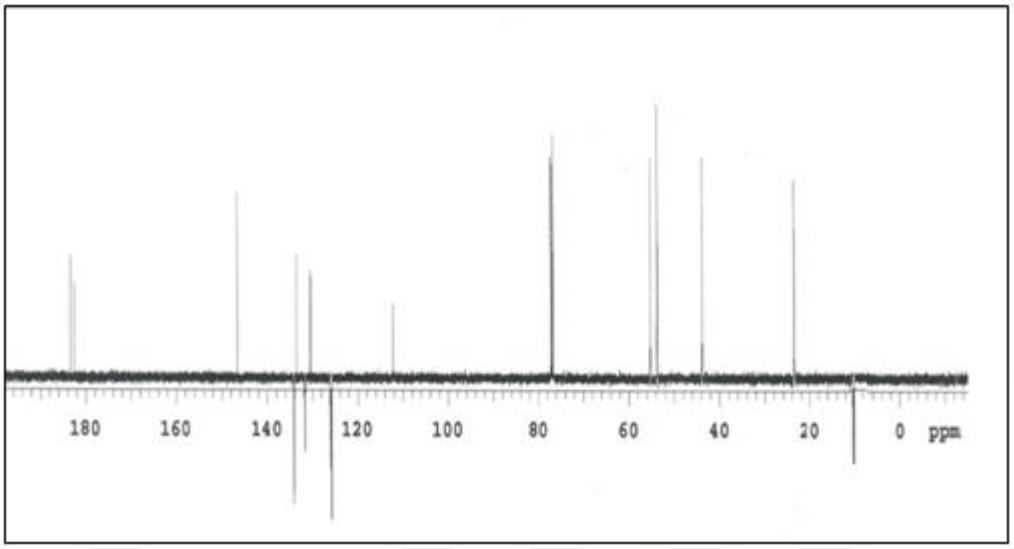


Figure 2.31: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **9**.

According to (+ESI) mass spectrum concerning the compound **9**; the molecular ion peak of a new compound ($C_{17}H_{20}N_2O_2$, M_w=284.35 g/mol) was seen at *m/z* (100%) = 281.6$[M-2H]^+$ (Figure 2.32).

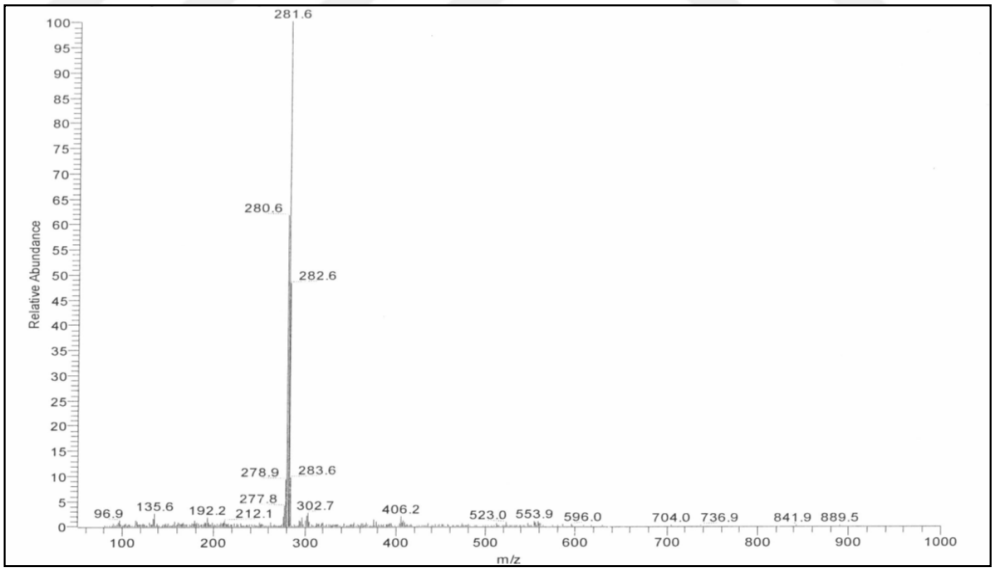
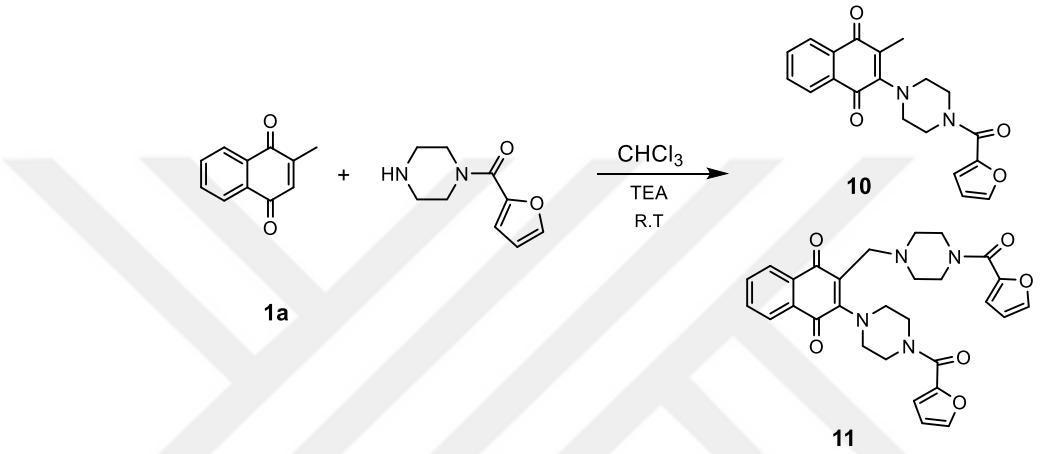


Figure 2.32: Mass spectrum [+ESI] concerning the compound **9**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(9)**.

2.1.8. Synthesis of 2-(4-(furan-2-carbonyl)piperazin-1-yl)-3-methylnaphthalene-1,4-dione and 2-(4-(furan-2-carbonyl)piperazin-1-yl)-3-((4-(furan-2-carbonyl) piperazin-1-yl)methyl) naphthalene-1,4-dione (10, 11)

The new compounds **(10, 11)** obtained when 1-(2-furoyl)piperazine added to a mixture of the starting compound **(1a)** and chloroform with the existence of triethylamine (TEA) at (25 ^{0}C) according to general procedure 1.



(2.10)

According to the IR spectrum of compound **10**; (C-H_{arom}) band was appeared at ν = 3227 cm^{-1} and (C-H_{aliph}) was observed at ν = 2971 cm^{-1}. Band of (C=O) at ν = 1661 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1592, 1563 cm^{-1} (Figure 2.33).

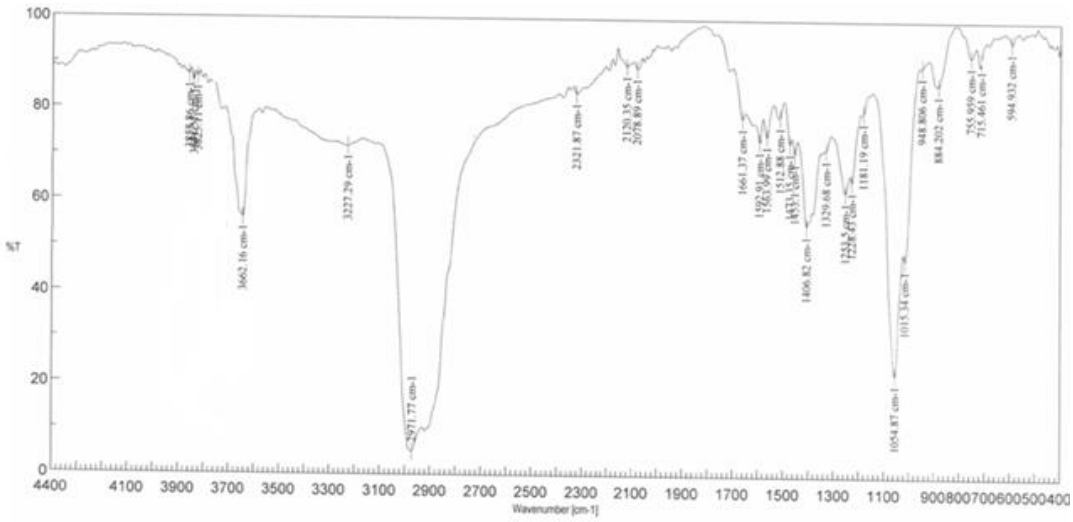


Figure 2.33: FTIR (KBr) spectrum concerning the compound **10**.

According to ^{1}H NMR spectrum concerning the compound **10**; (CH_3) protons were seen as singlet at δ =1.16 ppm. Protons of piperazine ring appeared at δ =3.01 ppm and 3.96 ppm as abroad singlet. Protons of furan ring (CH_{furan}) were seen at δ = 6.40 and 6.51 ppm as a multiplet, Protons of naphthoquinone (CH_{naphth}), two of them were appeared at δ = 7.56-7.68 ppm as a multiplet and the other at δ = 8.05-8.11 ppm as also multiplet (Figure 2.34).

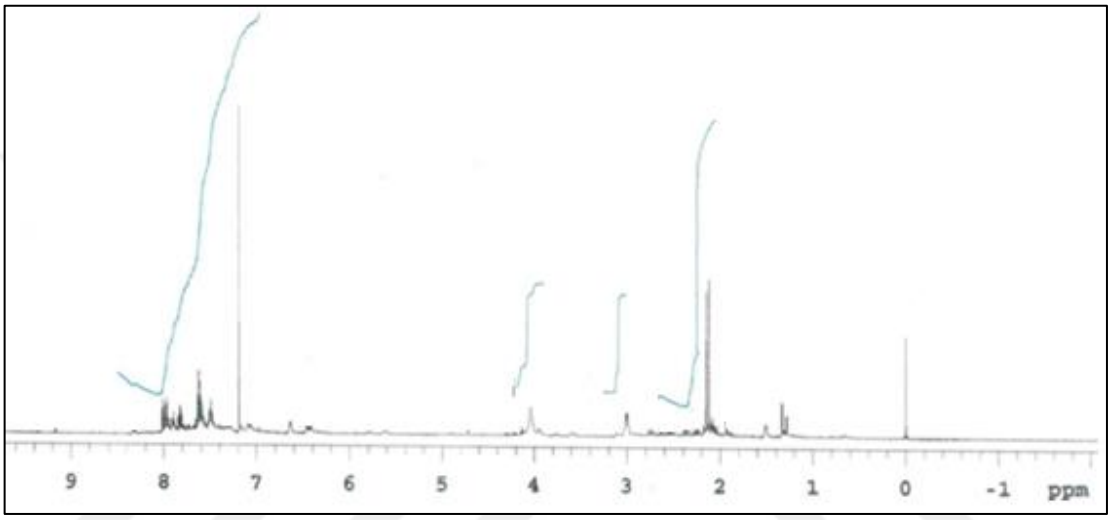


Figure 2.34: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **10**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **10**; carbon (CH_3) signal was found at δ = 13.54 ppm. Carbons in piperazine ring (N-**C**H_2)$_{piper}$ gave two signals at δ = 40.11 and 54.76 ppm. Furan ring gave four signals, (**C**H-**C**H)$_{furan}$ at δ=112.80, 117.88 ppm and (**C**-O-**C**H)$_{furan}$ at δ = 143.12, 144.66 ppm. Signals at δ = 126.74, 126.75, 127.55, 127.43, 128.03, 131.91, 132.69, ppm for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) were appeared at δ =146.42 ppm. The last signals at δ =160.01, 182.41, 183.23 ppm related to the carbon of carbonyl groups (Figure 2.35).

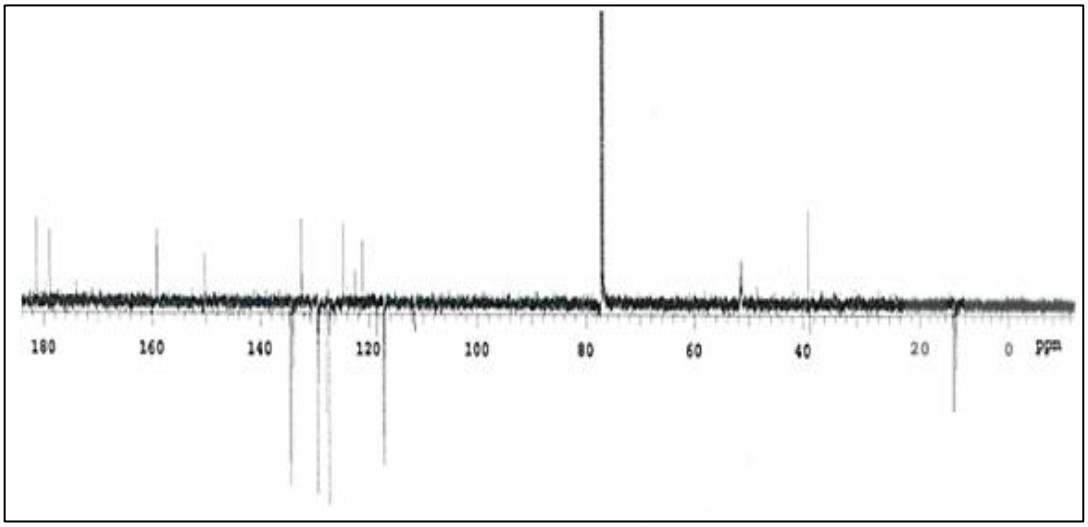


Figure 2.35: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **10**.

According to (+ESI) mass spectrum concerning the compound **10**; the molecular ion peak of a new compound ($C_{20}H_{18}N_2O_4$, M_w = 350.13 g/mol) was seen at *m/z* (100%) =349.1 $[M-H]^+$ (Figure 2.36).

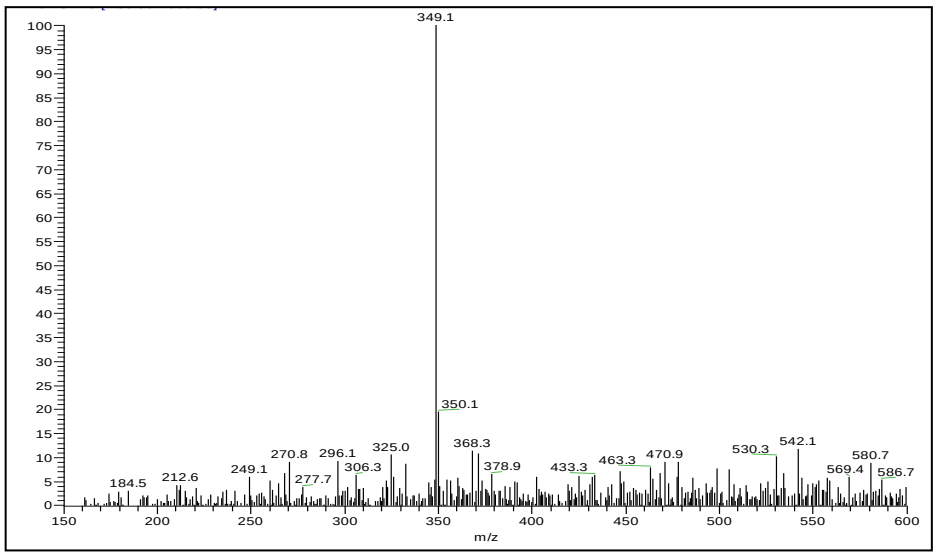


Figure 2.36: Mass spectrum [+ESI] concerning the compound **10**.

According to the IR spectrum of compound **11**; ($C\text{-}H_{arom}$), ($C\text{-}H_{aliph}$) bands were appeared at ν = 3116, 2961, 2912 cm^{-1} respectively. Bands of (C=O) were shown at ν =1667, 1617 cm^{-1}. (C=C) band was seen at ν = 1556, cm^{-1} (Figure 2.37).

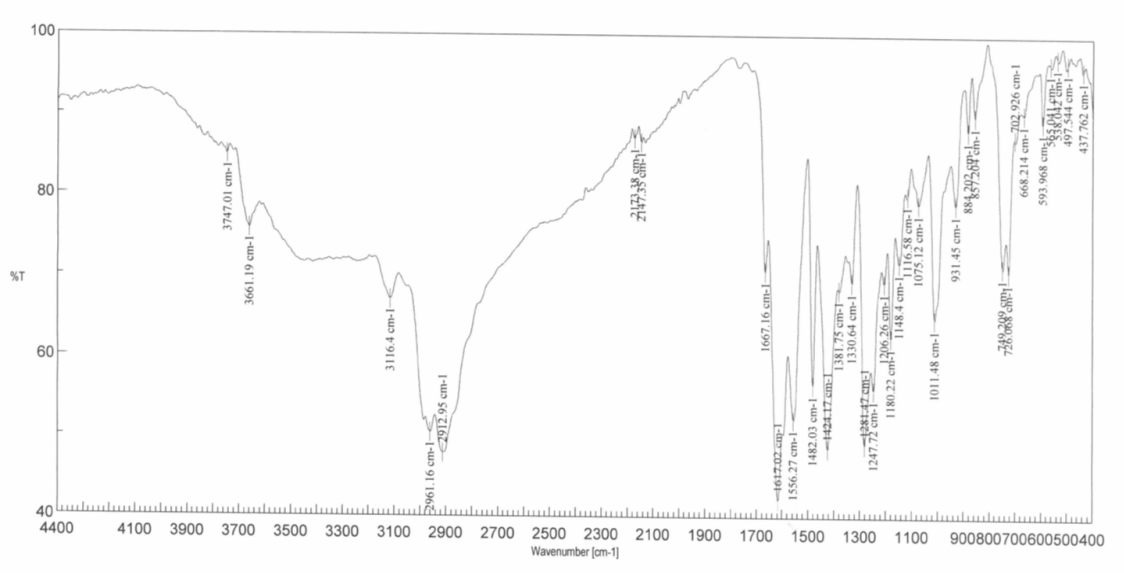


Figure 2.37: FTIR (KBr) spectrum concerning the compound **11**.

According to ^{1}H NMR spectrum concerning the compound **11**; piperazine ring CH_2-(N-$(CH_2)_2)_{piper}$ were seen as singlet at δ=2.50, 3.12 ppm, and the other protons of piperazine ring O=C-(N-$(CH_2)_2)_{piper}$ at δ = 3.60-3.84 ppm. The singlet at δ = 3.48 ppm is corresponding to protons of the methylene group (CH_2). Last protons of piperazine ring that bonded to naphthoquinone were seen at δ = 3.71 ppm as also multiplet. Furan ring protons (CH_{furan}) were seen at δ = 6.32- 6.48, 6.91 and 6.89-7.12 ppm as a multiplet, doublet and multiplet respectively, Protons of naphthoquinone (CH_{naphth}), two of them appeared at δ =7.38-7.66 ppm as a multiplet and the others at δ = 7.90, 8.00 ppm as a doublet (Figure 2.38).

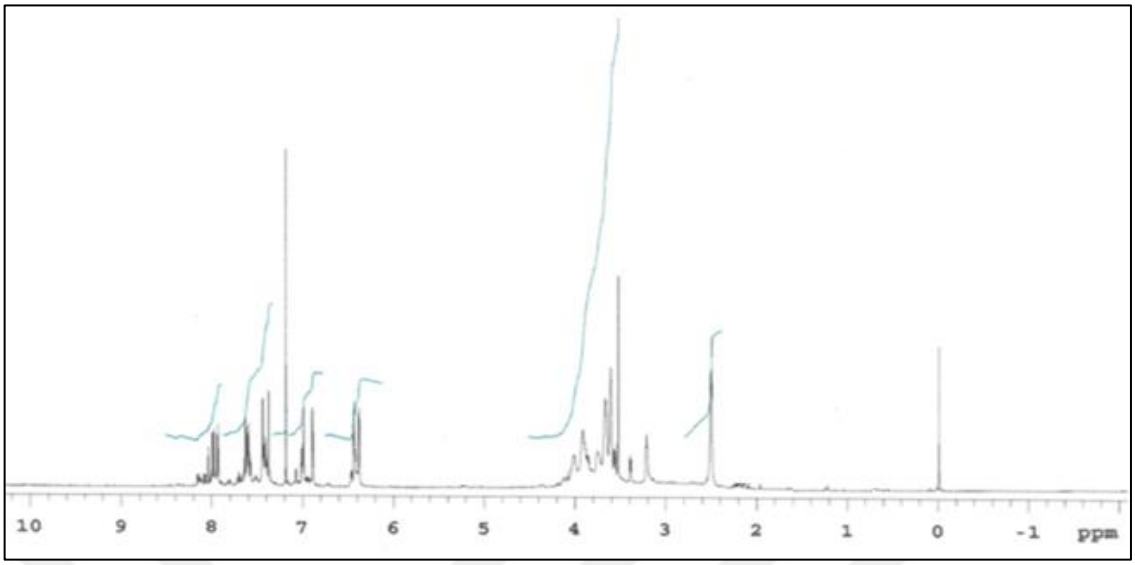


Figure 2.38: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **11**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **11**; (CH_2) group signal was found at δ = 43.93 ppm. Carbons in piperazine ring $(N\text{-}CH_2)_{piper}$ gave three signals at δ = 51.99, 53.20 and 53.43 ppm, a signal at δ = 109.96 ppm for ($\mathbf{C}_{naphtth}\text{-}CH_2$), carbon signals of furan ($\mathbf{C}H\text{-}\mathbf{C}H)_{furan}$, $(C\text{-}O\text{-}\mathbf{C}H)_{furan}$ were observed at 111.80, 117.88 ppm. Signals at δ = 126.28, 127.55, 132.12, 131.55, 132.95, 134.91 for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) were appeared at δ =147.72 ppm. The last signals at δ =162.30, 183.90, 184.77 ppm related to the carbon of carbonyl groups (Figure 2.39).

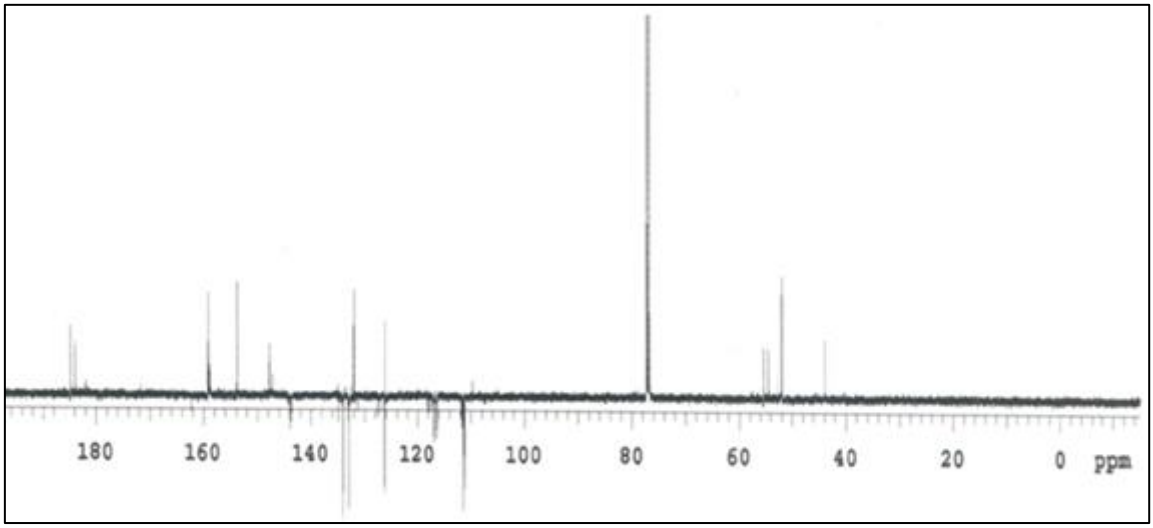


Figure 2.39: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **11**.

According to (+ESI) mass spectrum concerning the compound **11**; the molecular ion peak of a new compound ($C_{29}H_{28}N_4O_6$, M_w = 528.56 g/mol) was found at *m/z* (100%) =529.1 $[M]^+$ (Figure 2.40).

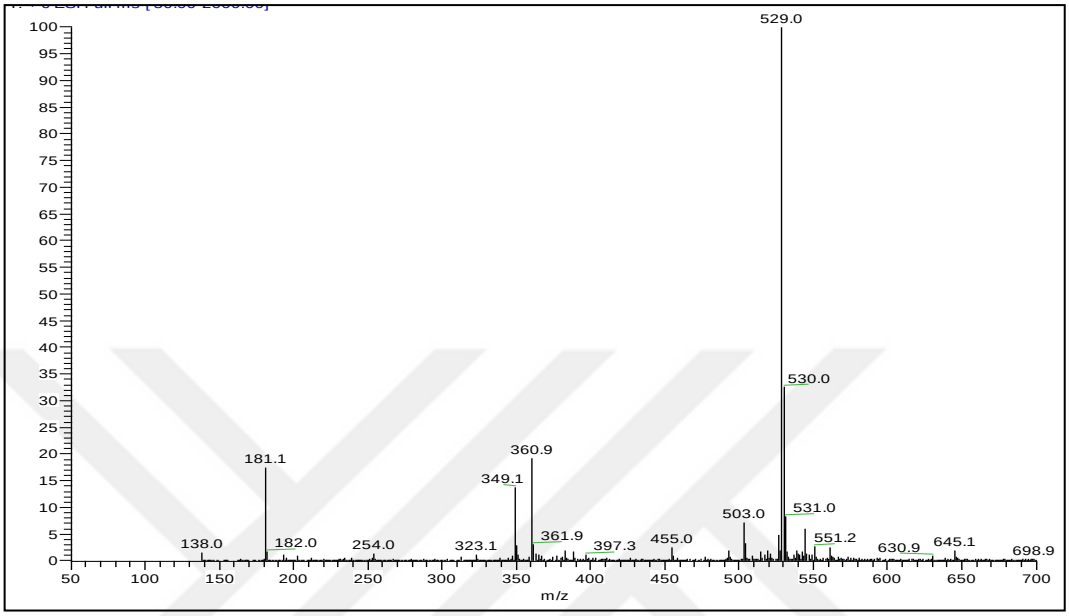
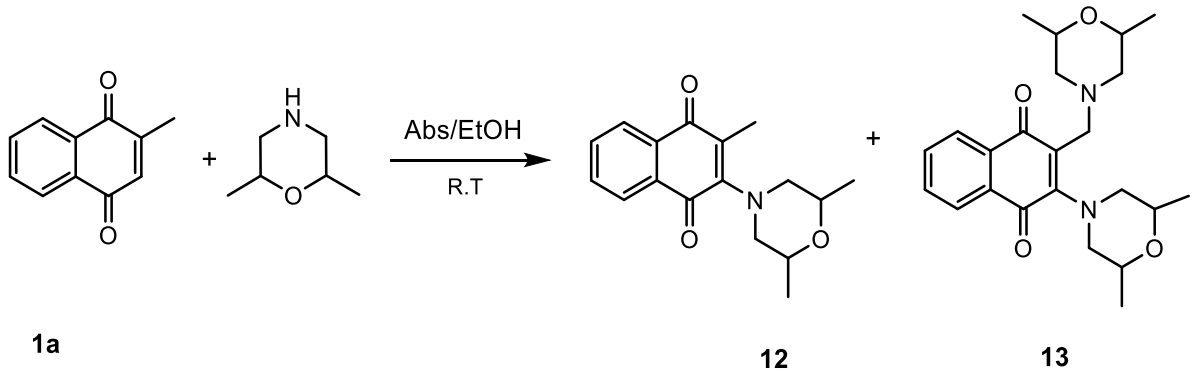


Figure 2.40: Mass spectrum [+ESI] concerning the compound **11**.

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new compounds **(10, 11)**.

2.1.9. Synthesis of 2-methyl-3-(2,6-dimethylmorpholino)naphthalene-1,4-dione and 2-(2,6-dimethylmorpholino)-3-((2,6-dimethylmorpholino)methyl)naphthalene-1,4-dione (12, 13)

The new compounds of **(12, 13)** were obtained when reaction of the starting compound **(1a)** with 2,6-dimethylmorpholine take place in Abs. Ethanol at (25 ^{0}C) for 6 hours as general procedure 3.



1a **12** **13**

(2.11)

According to the IR spectrum of compound **12**; stretching band for (C-H_{aliph}) was observed at ν = 2971, 2930 cm^{-1}. (C=O) band at ν = 1668 cm^{-1}, and the bands of carbon-carbon double bonds (C=C) was seen at ν = 1590, 1546 cm^{-1} (Figure 3.41).

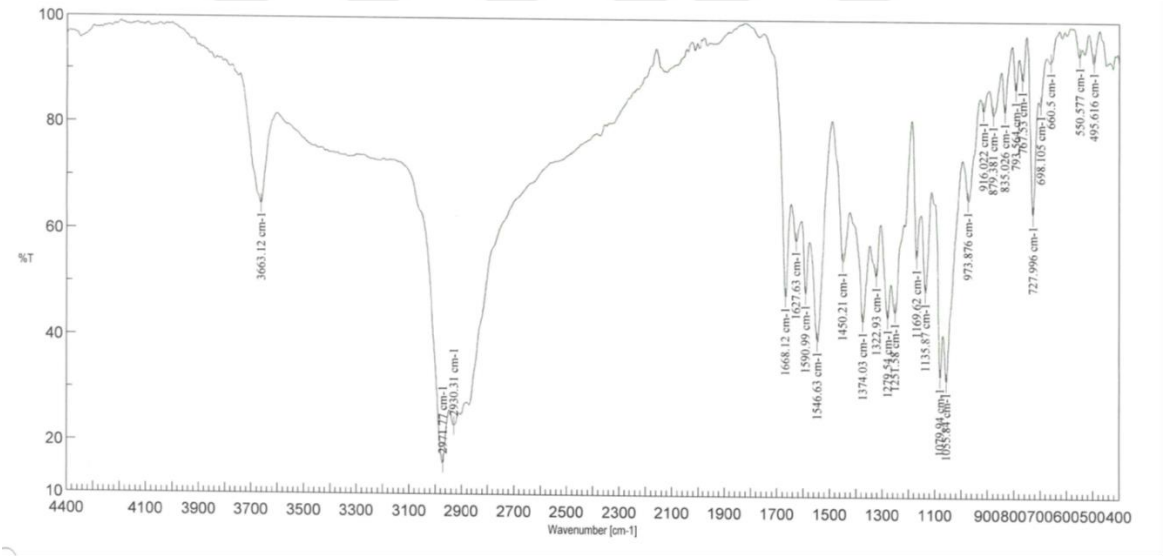


Figure 2.41: FTIR (KBr) spectrum concerning the compound **12**.

According to ^{1}H NMR spectrum concerning the compound **12**; two (CH_3) groups of morpholine ring were observed as singlet at δ=1.07 ppm, whereas, protons of methyl group that bonded to naphthoquinone ring was seen at δ =2.10 ppm as singlet too. Morpholine ring (CH_2-N-CH_2) and (CH) were found at δ =3.40, 3.89 and δ = 4.10 ppm respectively. Signals at δ = 7.57-7.62, 7.98 and 8.00 ppm are corresponding to naphthoquinone protons (Figure 2.42).

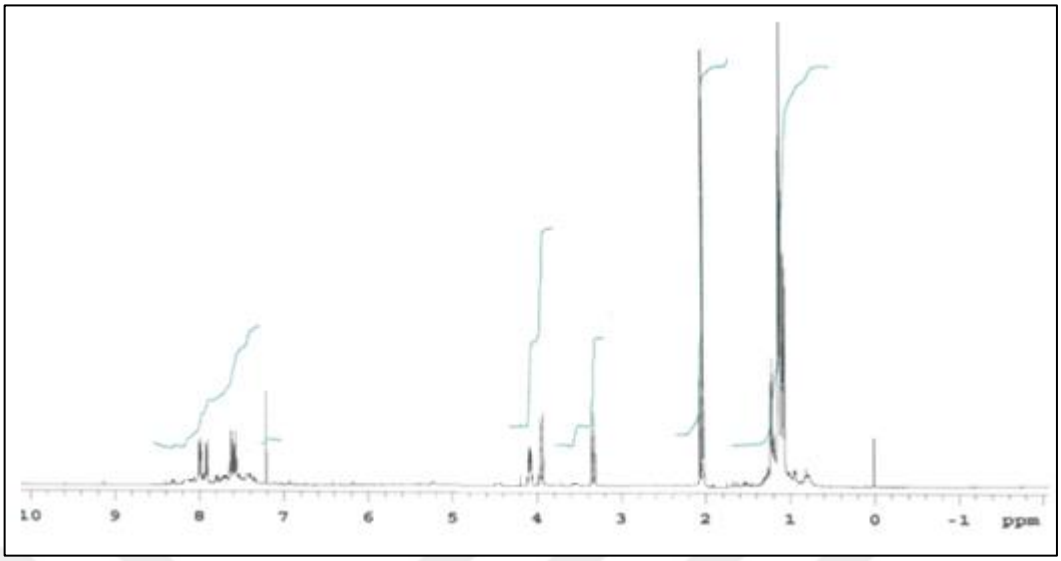


Figure 2.42: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **12**.

According to ^{13}C (APT) NMR spectrum concerning the compound **12**; carbon signal of methyl group in naphthoquinone (CH_3) was found at δ = 9.33 ppm, while methyl groups in morpholine rings $(CH_3)_{morph}$ at δ =18.75 ppm, signals of $(\mathbf{C}H_2\text{-}N\text{-}\mathbf{C}H_2)_{morph}$ at δ = 52.46 ppm whereas $(\mathbf{C}H\text{-}O\text{-}\mathbf{C}H)_{morph}$ at δ =71.98 ppm, a signal at δ = 109.35 ppm related to $(\mathbf{C}_{naphth}\text{-}CH_3)$, aromatic carbons ($CH_{arom}$, C_{arom}) were seen at δ =124.09, 126.13, 131.36, 132.31, 133,86, 134.91 ppm, (=C-N) was appeared at δ =153.91 ppm, however, signals corresponding to carbonyl groups (C=O) were detected at δ =182.09, 184.76 ppm (Figure 2.43).

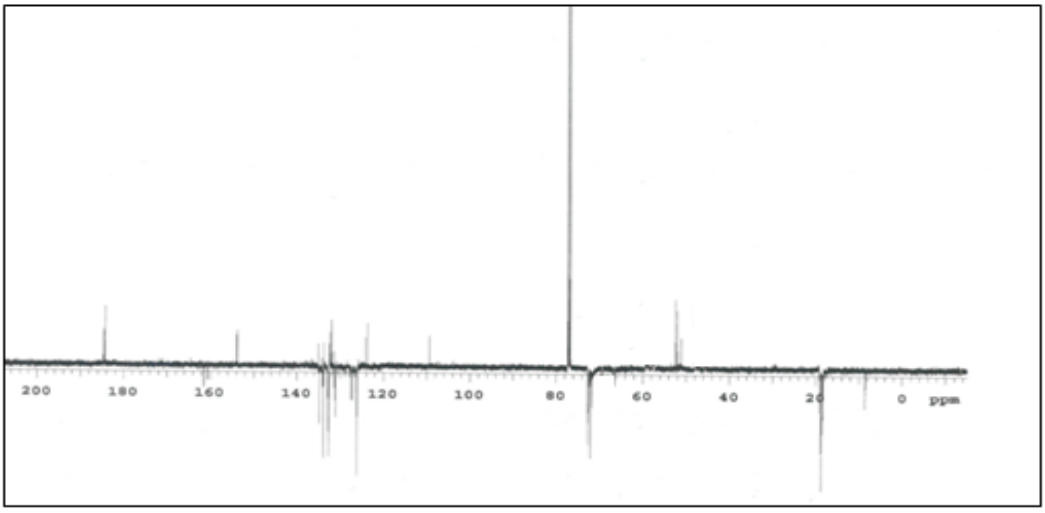


Figure 2.43: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **12**.

According to (+ESI) mass spectrum concerning the compound **12**; the molecular ion peak of a new compound ($C_{17}H_{19}NO_3$, M_w = 285.34 g/mol) was seen at *m/z* (100%) = 284.1 $[M-H]^+$ (Figure 2.44).

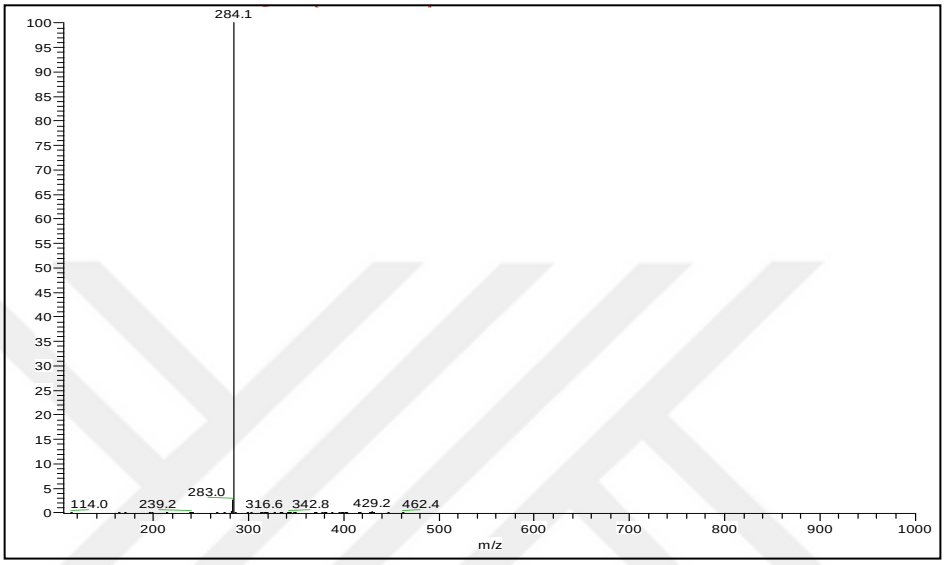


Figure 2.44: Mass spectrum [+ESI] concerning the compound **12**.

According to the IR spectrum of compound **13**; stretching band for ($C\text{-}H_{aliph}$) was observed at ν = 2972, 2929 cm^{-1}. Carbonyl group bands (C=O) at ν =1785, 1669 cm^{-1}, and the bands of carbon-carbon double bonds (C=C) was seen at ν = 1591, 1538 cm^{-1} (Figure 2.45).

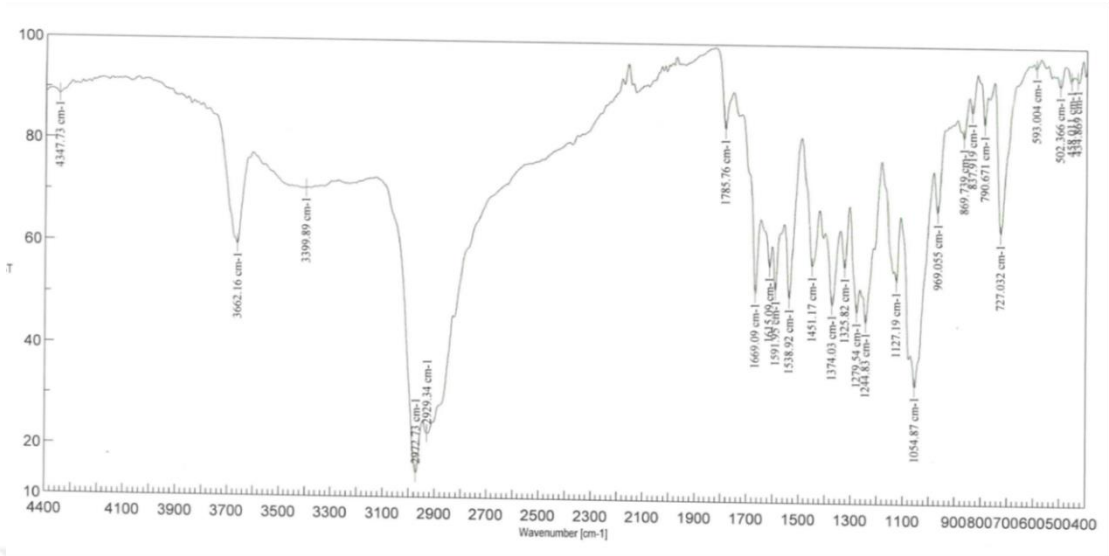


Figure 2.45: FTIR (KBr) spectrum concerning the compound **13**.

According to the ^{1}H NMR spectrum concerning the compound **13**; four methyl groups (CH_3) of morpholine ring were observed at δ = 1.05-1.18 and 1.22-1.31 ppm as a multiplet, whereas, methylene group that bonded to naphthoquinone ring was found as singlet at δ = 3.71 ppm. Morpholine ring protons (CH_2-N-CH_2) and $(CH)_{morph}$ were found at δ= 1.87-2.05, 2.55-2.79, 3.12-3.32, 3.62-3.82 and 4.18 ppm as a multiplet. Signals at δ = 7.55-7.68 and 7.92-8.09 ppm are corresponding to naphthoquinone protons (Figure 2.46).

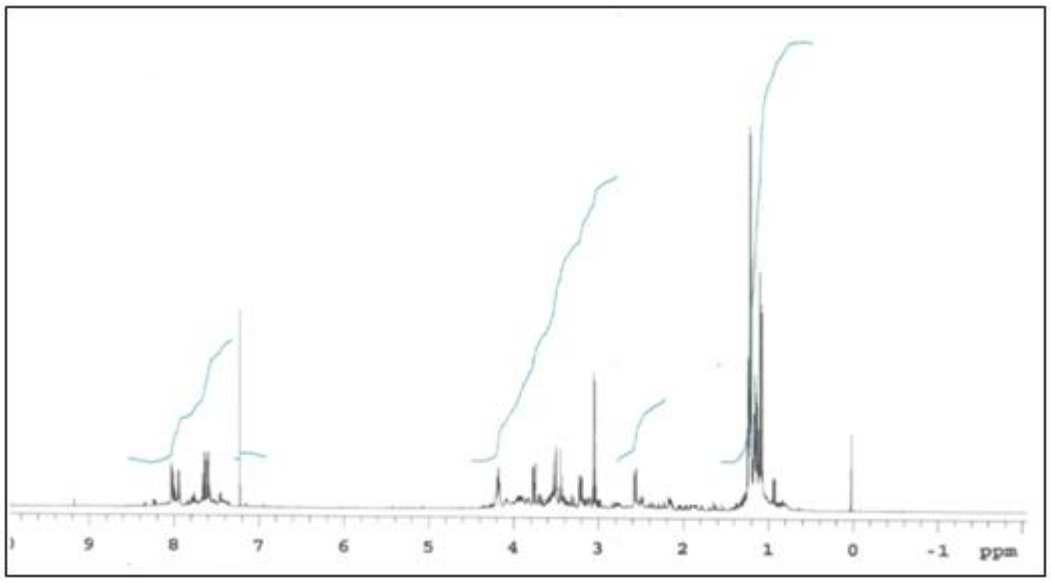


Figure 2.46: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **13**.

According to ^{13}C (APT) NMR spectrum concerning the compound **13**; four methyl groups (CH_3) of morpholine ring gave one signal at δ =18.72 ppm, methylene group (CH_2) at δ = 45.49 ppm, (**C**H_2-N-**C**H_2)$_{morph}$ at δ = 56.62 ppm whereas CH_2-(-N-(**C**H_2-)$_2$)$_{morph}$ at δ = 59.47 ppm, two signals corresponding to (**C**H-O-**C**H)$_{morph}$ were found at δ = 67.11, 71.92 ppm, aromatic carbons (CH_{arom}, C_{arom}) were seen at δ =123.92, 126.16, 130.55, 132.09, 132.61, 133,85 ppm, (=C-N) was appeared at δ =154.18 ppm, however, signals of carbonyl groups (C=O) were detected at δ =183.93, 184.57 ppm (Figure 2.47).

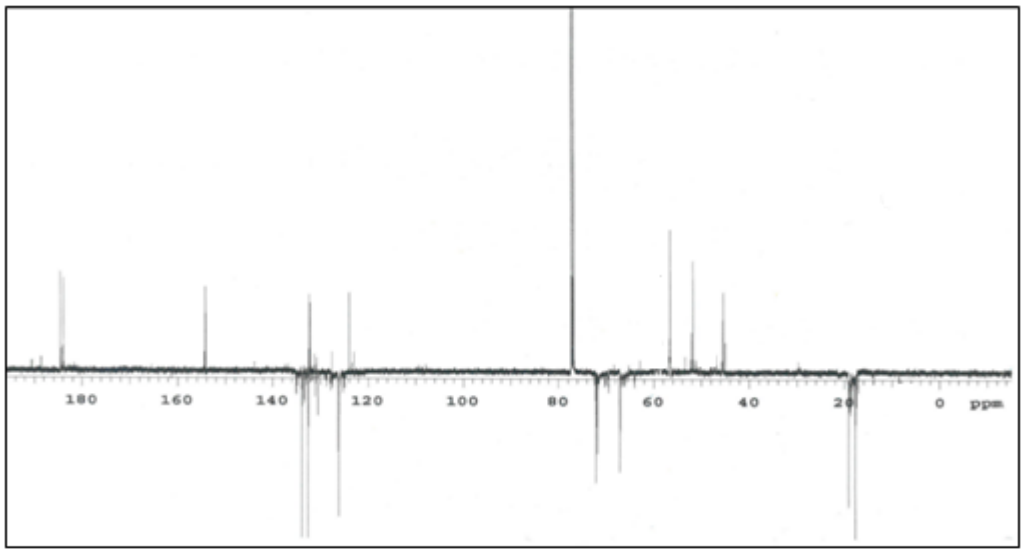


Figure 2.47: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **13**.

According to (+ESI) mass spectrum concerning the compound **13**; the molecular ion peak of a new compound ($C_{23}H_{30}N_2O_4$, M_w = 398.5 g/mol). was seen at *m/z* (100%) =399.1 $[M]^+$ (Figure 2.48).

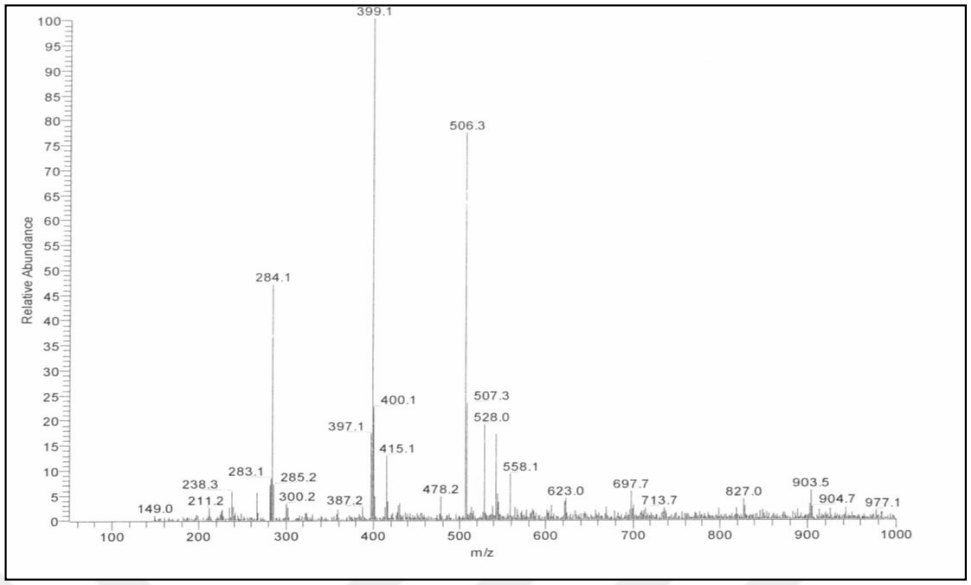
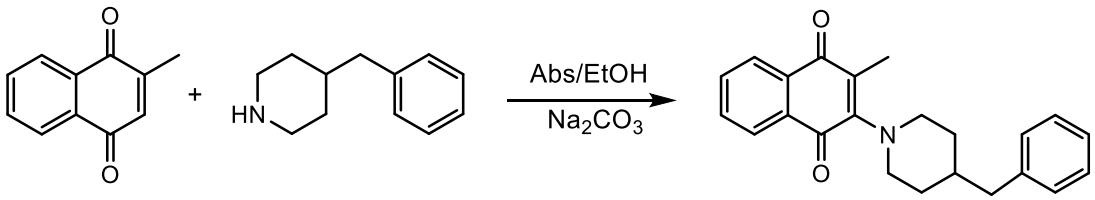


Figure 2.48: Mass spectrum [+ESI] concerning the compound **13**.

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new compounds **(12, 13)**.

2.1.10. Synthesis of 2-(4-benzylpiperidin-1-yl)-3-methylnaphthalene-1,4-dione (14)

The new compounds **(14)** obtained by reacting between the starting compound **(1a)** with 4-benzylpiperidine in Abs. Ethanol then refluxed 24 h in the presence of Na_2CO_3 as general procedure 2.



1a **14**

(2.12)

According to the IR spectrum of compound **14**; stretching band for (C-H_{aliph}) was observed at ν = 2956, 2922, 2853 cm^{-1}. Carbonyl group bands (C=O) at ν = 1722, 1667 cm^{-1}. The bands of carbon-carbon double bonds (C=C) was seen at ν = 1596 cm^{-1} (Figure: 2.49).

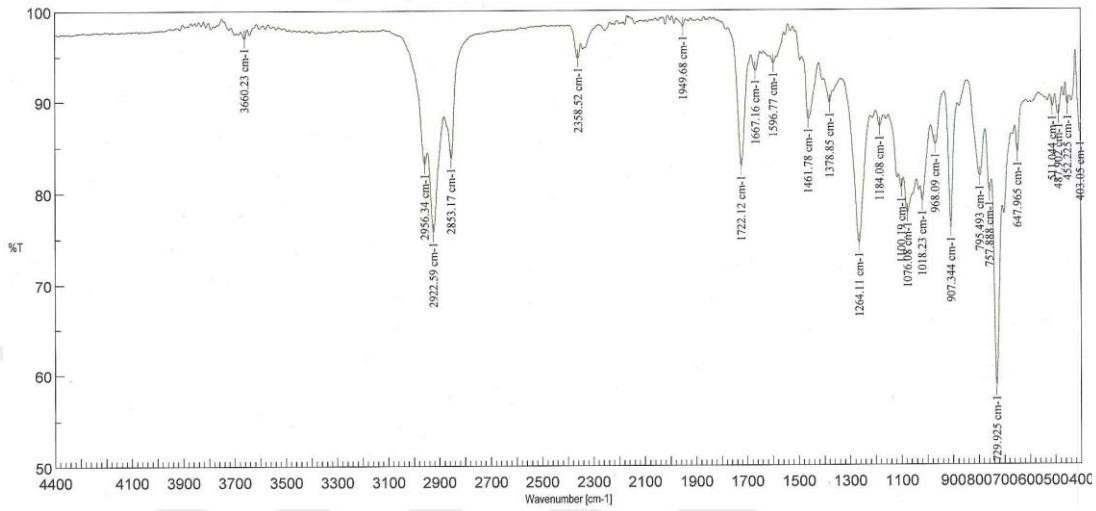


Figure 2.49: FTIR (KBr) spectrum concerning the compound **14**.

According to the ^{1}H NMR spectrum concerning the compound **14**; protons of (CH_3) was seen as a singlet at δ=2.11 ppm, protons of methylene (CH_2) in benzylpiperidine as a doublet at δ = 2.50 ppm. Protons of piperidine ring (C**H**$_2$-CH-C**H**$_2$)$_{piperi}$, (CH$_2$-C**H**-CH$_2$)$_{piperi}$ and (C**H**$_2$-N-C**H**$_2$)$_{piperi}$, were seen around δ = 1.04-1.36, 1.61-1.69 and 3.10, 4.32 ppm as a multiplet respectively. Protons of aromatic ring (CH_{arom}) at δ = 7.07-7.20 ppm as a multiplet and the (CH_{naphth}) of naphthoquinone at δ = 7.50-7.64 and 7.84-7.94 ppm as also multiplet (Figure 2.50).

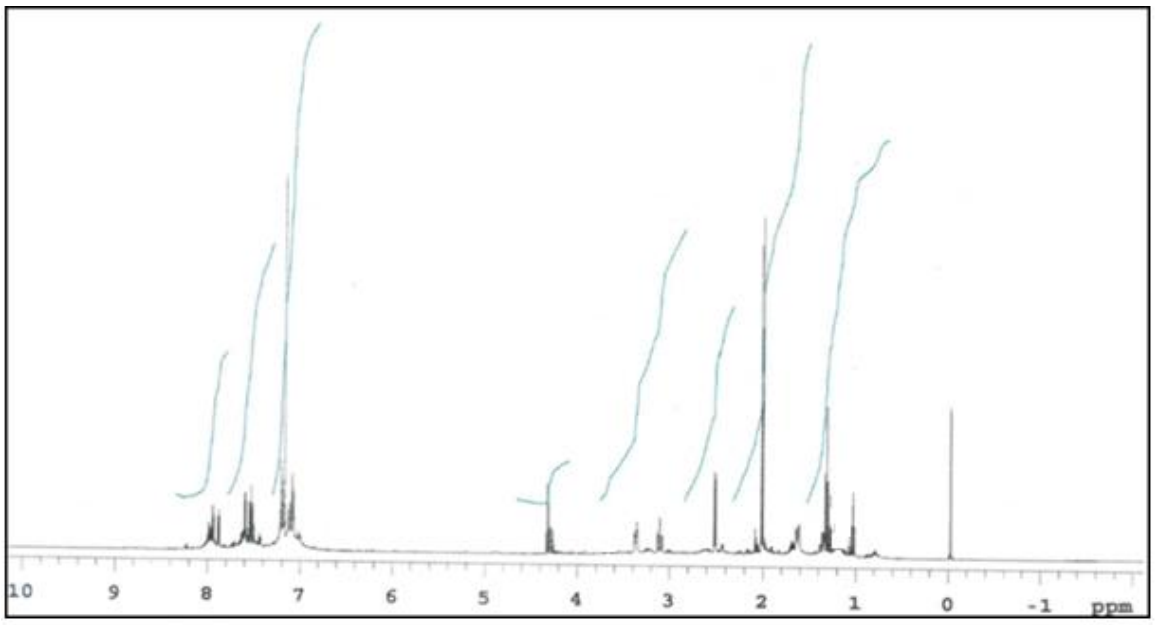


Figure 2.50: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **14**.

According to ^{13}C (APT) NMR spectrum concerning the compound **14**; carbon signal of methyl group (CH_3) was found at δ = 13.58 ppm, signal at δ = 43.32 ppm is corresponding to methylene group in benzylpiperidine. Carbons in piperidine ring (**C**H_2-CH-**C**H_2)$_{piperi}$, (CH_2-**C**H-CH_2)$_{piperi}$ and (**C**H_2-N-**C**H_2)$_{piperi}$ gave three signals at δ =33.21, 37.99 and 52.00 ppm respectively. Signals at δ =125.68, 126.12, 126.34, 128.24, 128.84, 129.01, 132.13, 132.48, 133.19, 133.67 ppm for aromatic carbons (CH_{arom}, C_{arom}). (CH_2-**C**$_{ph}$), (=C-N-) were appeared at δ =140.26 and 153.10 ppm. The last signals at δ =183.90, 185.45 ppm related to carbon of carbonyl groups (Figure 2.51).

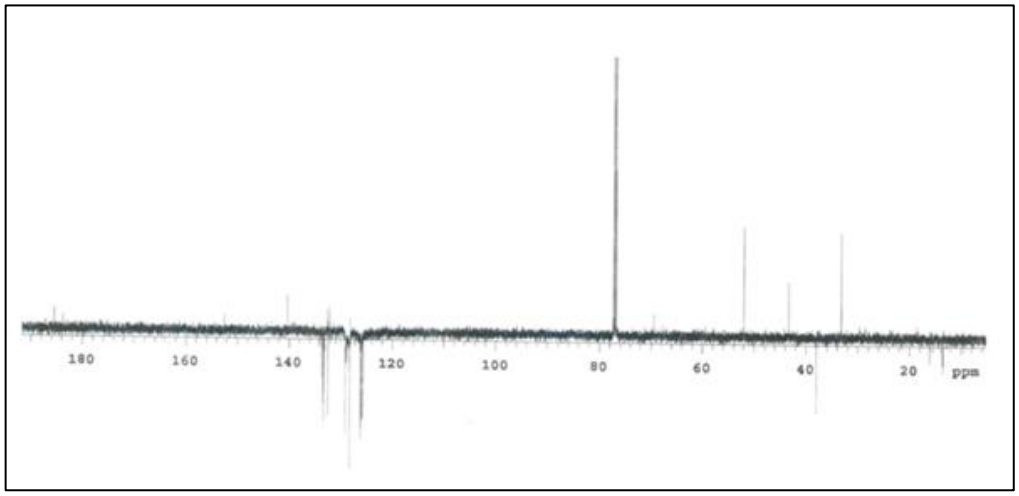


Figure 2.51: ^{13}C (APT) NMR (CDCl3) spectrum concerning the compound **14.**

According to (+ESI) mass spectrum concerning the compound **14**; the molecular ion peak of a new compound ($C_{23}H_{23}NO_2$, M_w =345.34 g/mol). was seen at *m/z* (100%) =346.30 $[M+H]^+$ (Figure 2.52).

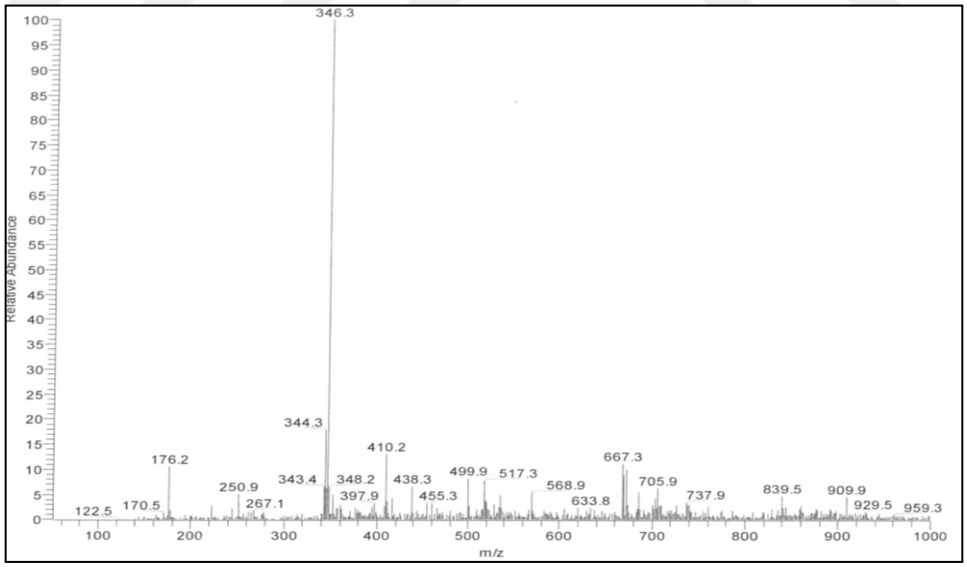
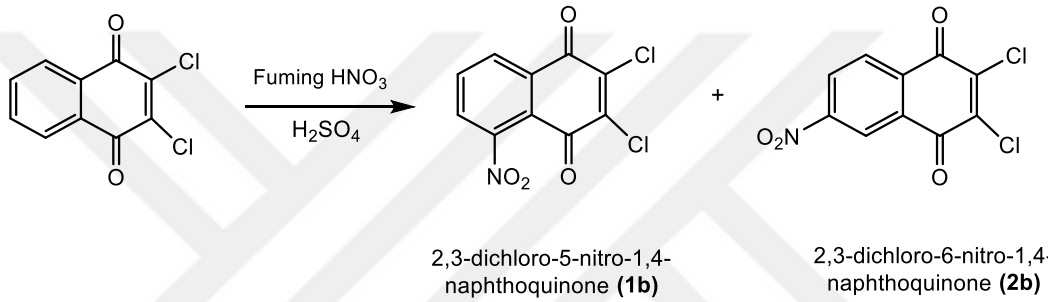


Figure 2.52: Mass spectrum[+ESI] concerning the compound **14.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(14).**

2.2. SYNTHESIS OF NEW REGIO ISOMERS OF 2,3-DICHLORO-5-NITRO-1,4-NAPHTHOQUINONE DERIVATIVES

The synthesis of the regio-isomer of 2,3-dichloro-5/6-nitro-1,4-naphthoquinone was performed by the reported experiment [112,113], the method is explained in detail in the result section. The reaction below (2.13) is summering the formation of 2,3-dichloro-5/6-nitro-1,4-naphthoquinone isomers. The mixture of isomer was separated by chromatographic device using EtAc/hexane (1:6). **(1b** and **2b)** isomers were characterized and only one isomer **(1b)** was used as starting material.



(2.13)

According to the ^{1}H NMR spectrum of **(2b)** isomer; three protons of nitro-naphthoquinone ring appeared at δ = 8.44 ppm as a doublet, 8.63 ppm as doublet of doublet and last protone at δ = 9.01 ppm as a doublet too (Figure 2.53).

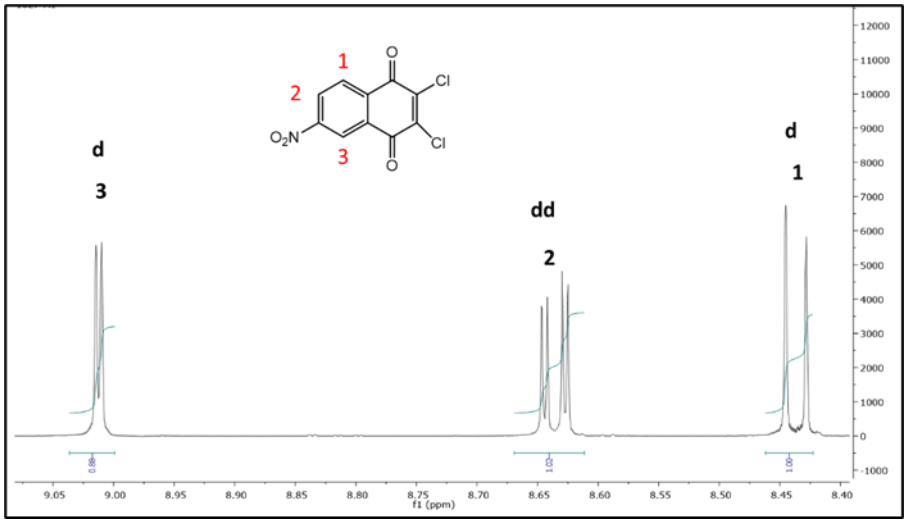


Figure 2.53: ^{1}H NMR($CDCl_3$) spectrum concerning the isomer **(2b)**.

According to ^{13}C (APT) NMR spectrum of isomer **(2b)**; five signals of carbon in nitro-naphthoquinone ring (CH_{arom}, C_{arom}) were detected at δ = 122.94, 128.27, 128.70, 132.10, 134.30 ppm. Carbon signal at δ = 144.13 and 144.42 ppm are related to (=C-Cl), (C-NO_2) signal at δ = 151.39 ppm. A very close signals of carbonyl group were observed at δ = 174.21 and 174.61 ppm (Figure 2.54).

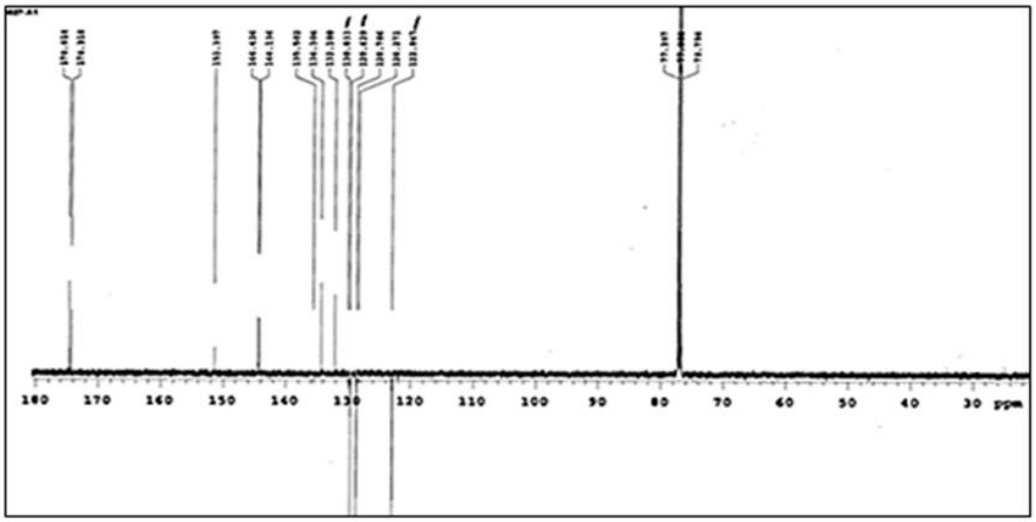


Figure 2.54: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the isomer **(2b)**.

According to (+ESI) mass spectrum of **(2b)** isomer; the molecular ion peak of 6-nitro isomer compound ($C_{10}H_3Cl_2NO_4$, M_w= 272.04 g/mol) was seen at *m/z* (100%) = 271.1 $[M-H]^+$ (Figure 2.55).

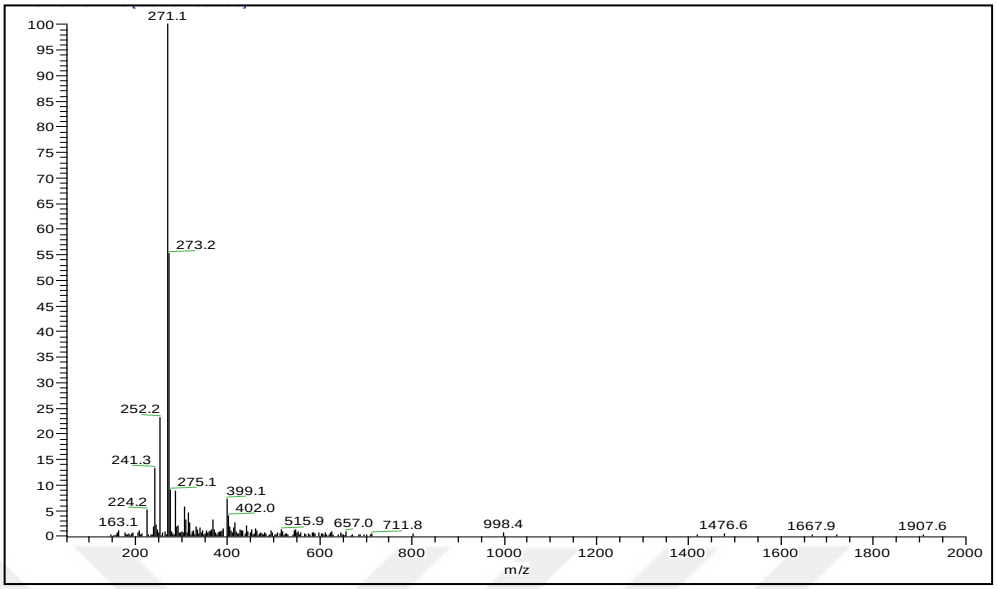


Figure 2.55: Mass spectrum [+ESI] concerning the isomer **(2b)**.

According to ^{1}H NMR spectrum of second isomer **(1b)**; three protons of nitro-naphthoquinone ring appeared at δ =7.81 and 8.42 ppm as doublet of doublet and as a triplet at δ = 7.98 ppm (Figure 2.56).

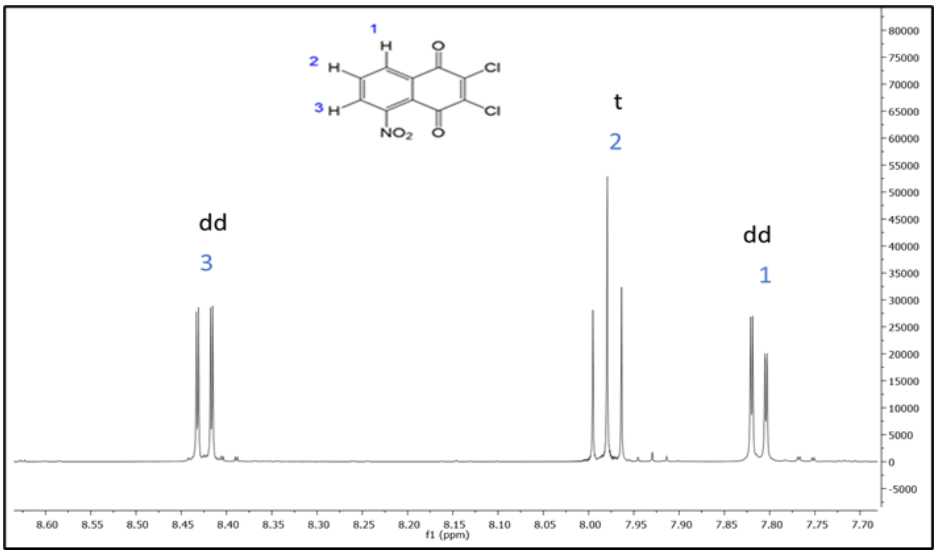


Figure 2.56: ^{1}H NMR ($CDCl_3$) spectrum concerning the isomer **(1b)**.

According to ^{13}C (APT) NMR spectrum of second isomer **(1b)**; five signals of carbon in nitro-naphthoquinone ring (CH_{arom}, C_{arom}) were detected at δ = 121.95, 128.26, 130.04, 131.75, 135.53 ppm. Carbon signal at δ = 143.35 and 143.82 ppm are related to (=C-Cl) and (C-NO_2). Signals of carbonyl group were observed at δ = 172.63 and 174.29 ppm (Figure 2.57).

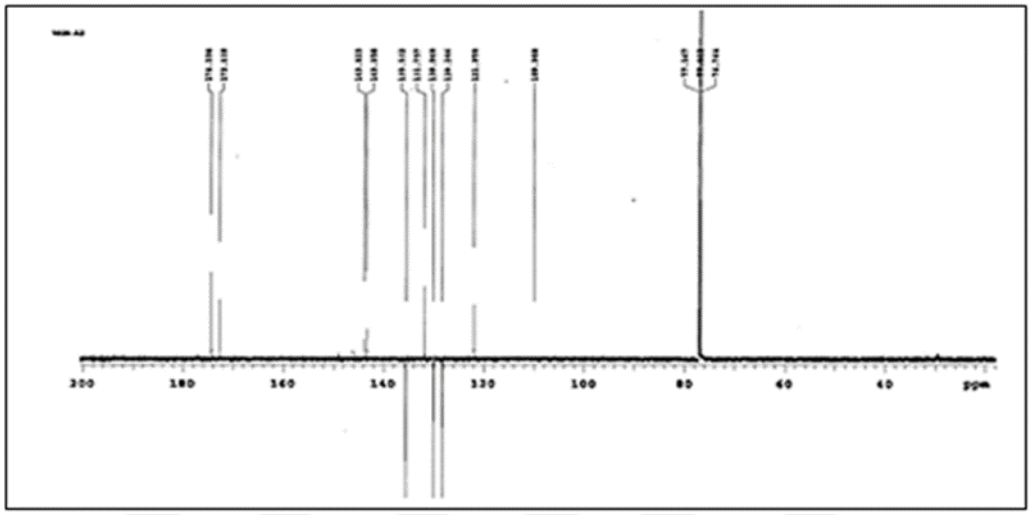


Figure 2.57: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the isomer **(1b).**

According to (+ESI) mass spectrum of **(1b)** isomer; the molecular ion peak of 5-nitro isomer ($C_{10}H_3Cl_2NO_4$, M_w= 272.04 g/mol) was seen at *m/z* (75%) = 271.1 $[M-H]^+$ (Figure 2.58).

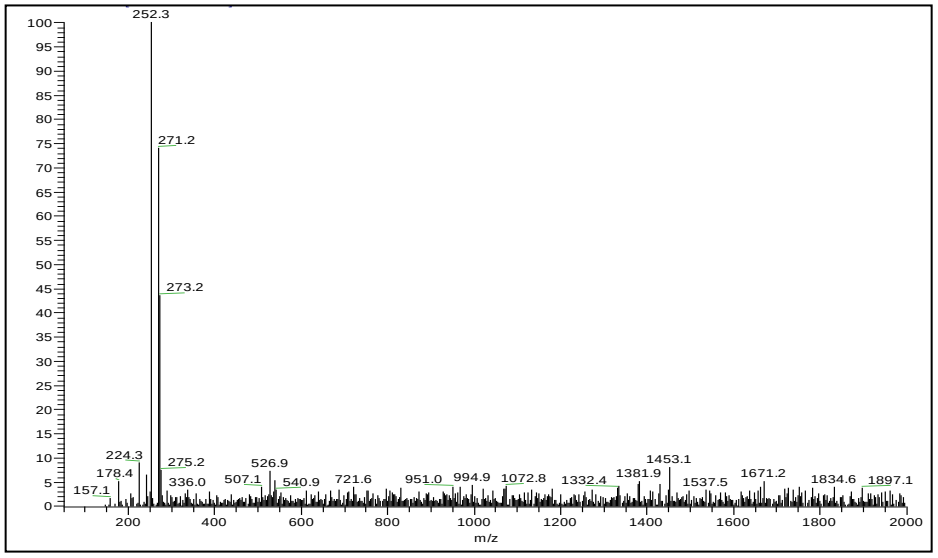


Figure 2.58: Mass spectrum [+ESI] concerning the isomer **(1b)**.

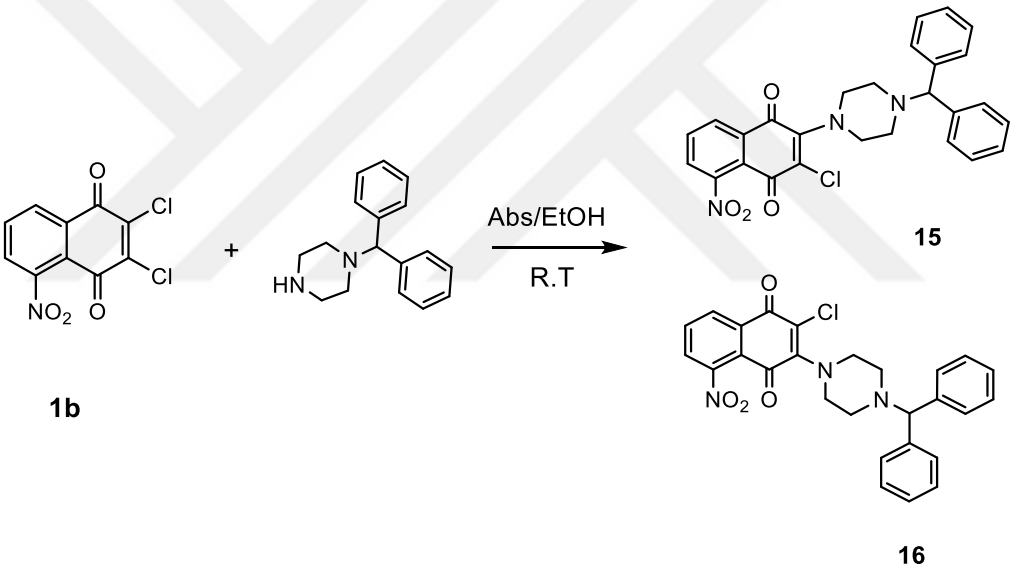
All the obtained results from mass spectra and other data prove the correct proposed structure of the isomer compounds **(1b, 2b)**.

2.2.1. Synthesis of 2-(4-benzhydrylpiperazine-1-yl)-3-chloro-5-nitronaphthalene-1,4-dion and 3-(4-benzhydrylpiperazin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione (15, 16)

New isomer compounds (**15**, **16**) were obtained by reacting the starting compound **(1b)** and 1-(diphenylmethyl)piperazine in Abs.Ethanol for 3-4 hours according procedure 4.

Isomer **15**; Red solid, R_f: 0.37 (1:3, EtAc /Hexane), M.p.: 183-184°C.

Isomer **16**; Red oil, R_f: 0.27 (1:3, EtAc /Hexane).



(2.14)

According to the IR spectrum of compound **15**; stretching band for (C-H_{arom}) was detected at ν = 3085 cm^{-1} and stretching bands for (C-H_{aliph}) were observed at ν = 2978, 2906, 2803, 2756 cm^{-1}. Carbonyl group bands (C=O) at ν = 1679, 1644 cm^{-1}. (C=C) band were seen at ν = 1589 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were seen at ν = 1446, 1285 cm^{-1} respectively (Figure 2.59).

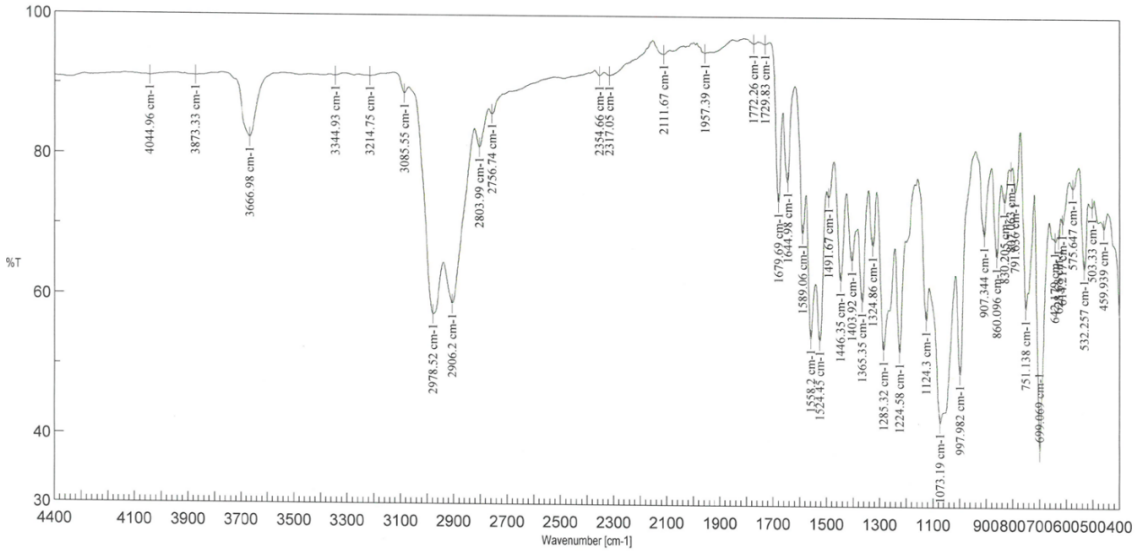


Figure 2.59: FTIR (KBr) spectrum concerning the compound **15**.

According to ^{1}H NMR spectrum concerning the compound **15**; piperazine (CH_2NCH_2) were seen at δ= 2.64 and 3.62 ppm as a broad singlet. A proton of (-CH<) was seen as singlet at δ = 4.34 ppm. Ten protons in the two aromatic rings take place at δ = 7.20 -7.77 ppm as a multiplet. The three protons of nitro-naphthoquinone were detected at δ = 7.80, 8.32 and 8.39 ppm as a multiplet, triplet and doublet of doublets respectively (Figure 2.60).

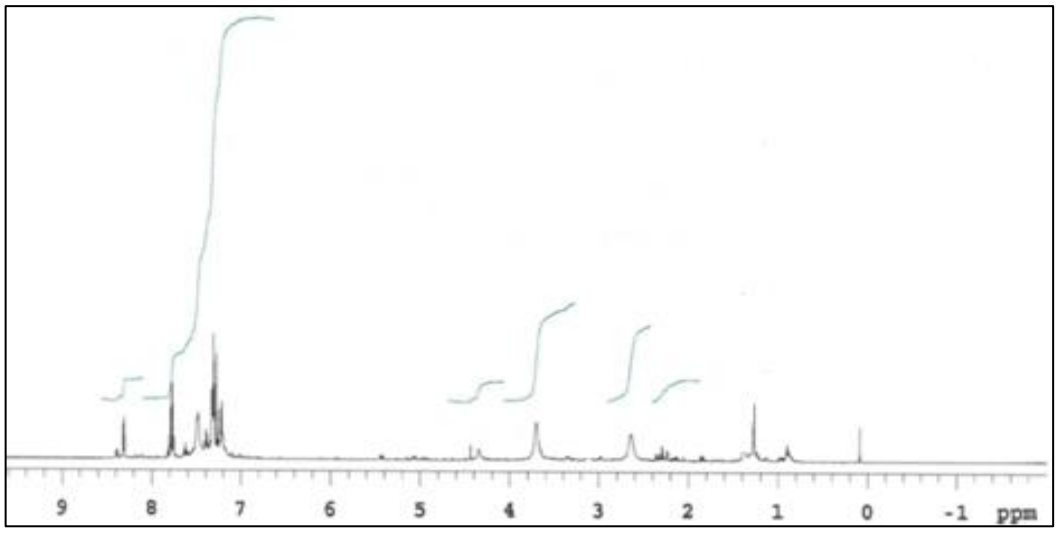


Figure 2.60: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **15**.

According to ^{13}C (APT) NMR spectrum concerning the compound **15**; piperazine (N-CH_2) ring signal appeared at δ = 45.83, 52.64 and 56.10 ppm, carbon signal of (–CH<) at δ = 76.77 ppm and (=C-Cl) signal at δ = 109.98 ppm, signals at δ =126.09, 127.05, 127.96, 128.79, 129.37 and 130.04 ppm are belonging to (CH_{arom}, C_{arom}). Carbon signal at δ = 148.39 ppm is related to (=C-N). Signals of carbonyl groups at δ = 175.73 and 179.12 ppm (Figure 2.61).

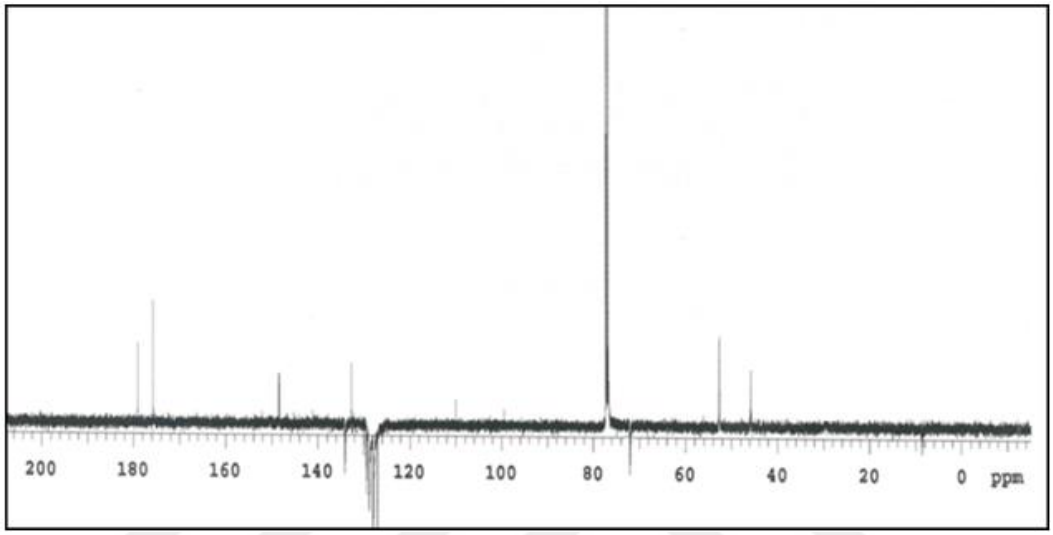


Figure 2.61: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **15**.

According to (+ESI) mass spectrum concerning the compounds **15**; the molecular ion peak of a new regio-isomer compound ($C_{27}H2_2N_3O_4Cl$, Mw= 487.93g/mol) was seen at m/z (100%) = 487.9 $[M]^+$. A small peak at m/z = 510.1 referred to $[M+Na]^+$ (Figure 2.62).

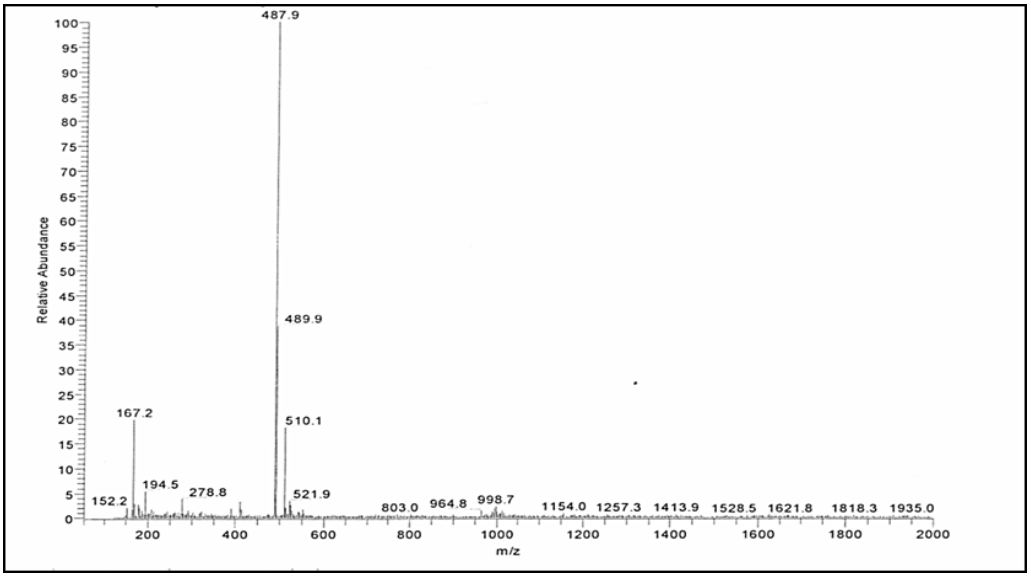


Figure 2.62: Mass spectrum [+ESI] concerning the compound **15**.

According to the IR spectrum of compound **16**; stretching band for (C-H_{arom}) was detected at ν = 3084 cm^{-1} and stretching bands for (C-H_{aliph}) were observed at ν = 2979, 2905 cm^{-1}. Carbonyl group band (C=O) at ν = 1653 cm^{-1}. (C=C) band was seen at ν = 1590 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were seen at ν = 1536, 1377 cm^{-1} respectively (Figure 2.63).

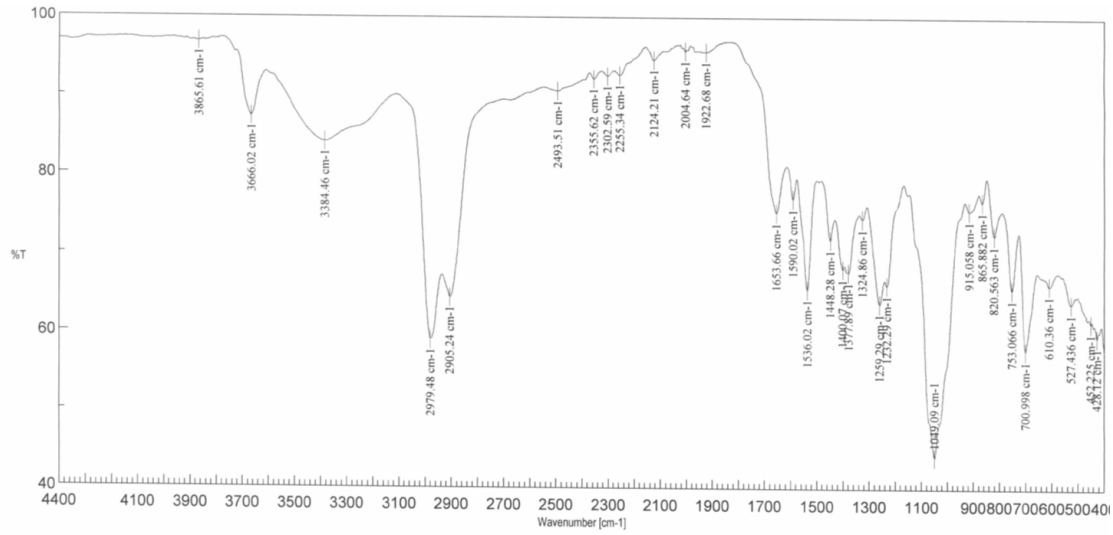


Figure 2.63: FTIR (KBr) spectrum concerning the compound **16**.

According to ^{1}H NMR spectrum concerning the compound **16**; piperazine (CH_2NCH_2) were seen at δ = 2.56 and 3.56 ppm as a broad singlet. A proton of (-CH<) was seen as singlet at δ = 4.32 ppm. Ten protons in the two aromatic rings take place at δ =7.11- 7.67 ppm as a multiplet. The three protons of nitro quinone was detected at δ = 7.76, 7.85 and 8.24 ppm as a multiplet, triplet and doublet of doublet respectively (Figure 2.64).

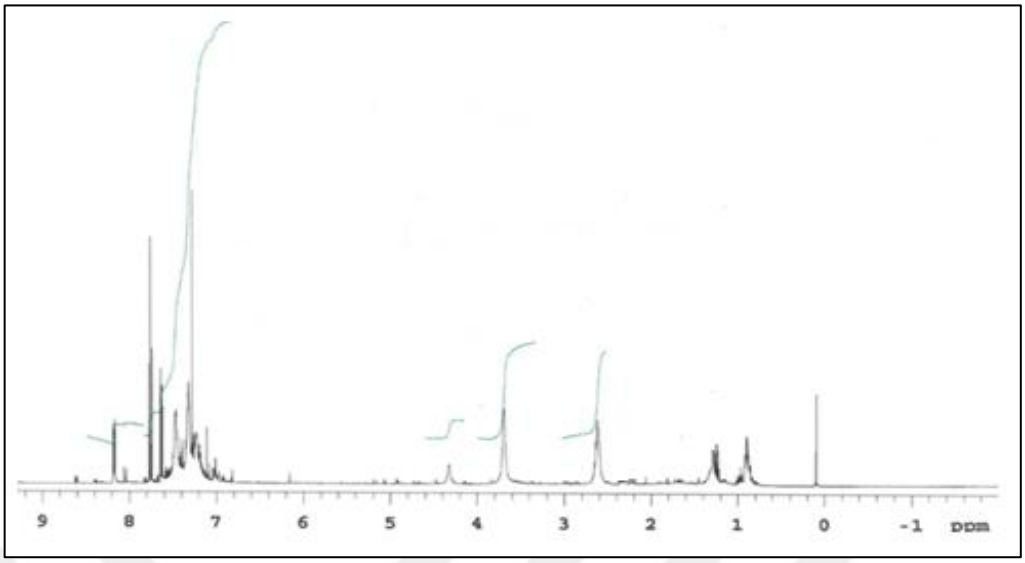


Figure 2.64: ^{1}H NMR ($CDCl_3$) concerning the compound **16**.

According to ^{13}C (APT) NMR spectrum concerning the compound **16**; piperazine (N-CH_2) ring signals were appeared at δ = 52.56, 56.21 ppm, carbon signal of (–CH<) at δ = 77.25 ppm and (=C-Cl) signal at δ = 110.15 ppm, signals at δ =127.95, 129.00, 129.49, 130.05, 133.07 ppm are belonging to (CH_{arom}, C_{arom}). Carbon signal at δ = 148.03 ppm is related to (=C-N). Signals of carbonyl groups at δ = 179.57, 180.12 ppm (Figure 2.65).

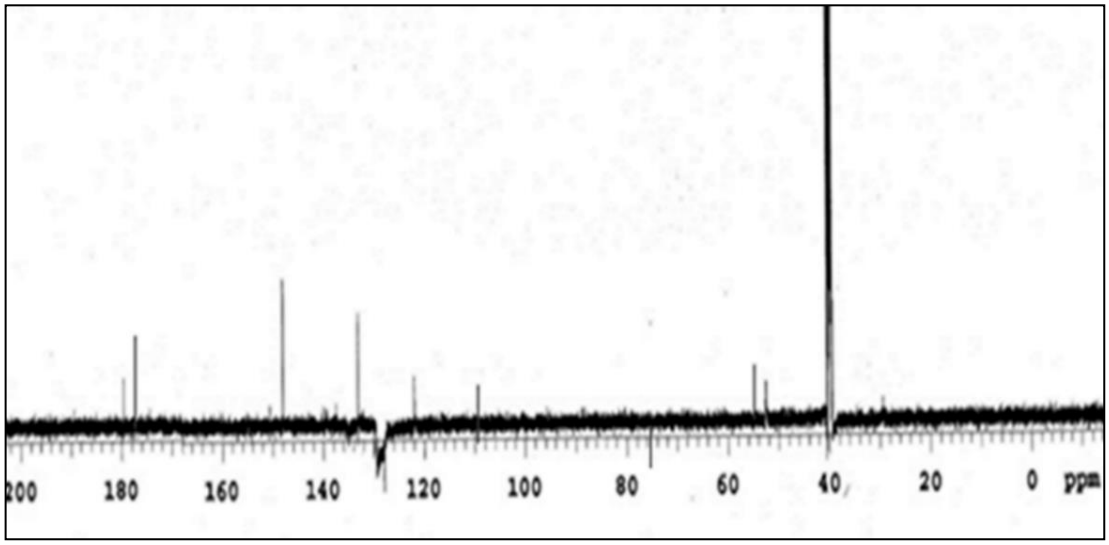


Figure 2.65: ^{13}C (APT) NMR (DMSO-d_6) spectrum concerning the compound **16**.

According to (+ESI) mass spectrum concerning the compound **16**; the molecular ion peak of a new regio-isomer compound ($C_{27}H_{22}N_3O_4Cl$, M_w= 487.93g/mol) was seen at *m/z* (100%) = 487.8 $[M]^+$. A small peak at *m/z* = 510.5 referred to $[M+Na]^+$ (Figure 2.66).

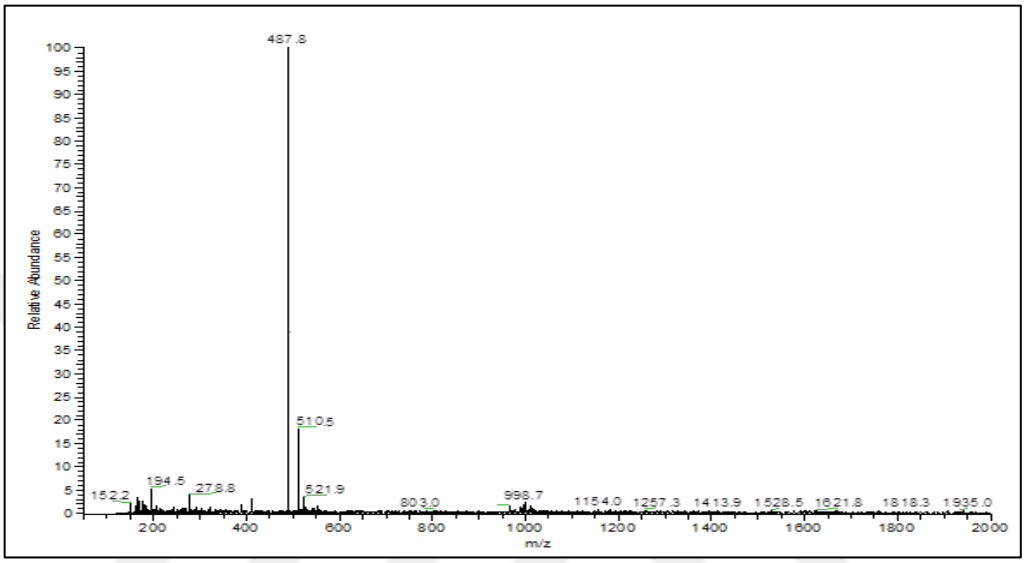


Figure 2.66: Mass spectrum [+ESI] concerning the compound **16**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(15, 16)**; we observed that the proton of naphthoquinone peaks (δ=7.80, 8.32 ,and 8.39 ppm) for the first isomer 2-(4-benzhydrylpiperazine-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione **(15)** are shifted more downfield than the naphthoquinone peaks (δ=7.76, 7.85 and 8.24 ppm) of the second isomer 3-(4-benzhydrylpiperazin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione **(16)**. Also, it found that the isomer **(15)** has a higher R_f component than the isomer **(16)** [89], [91].

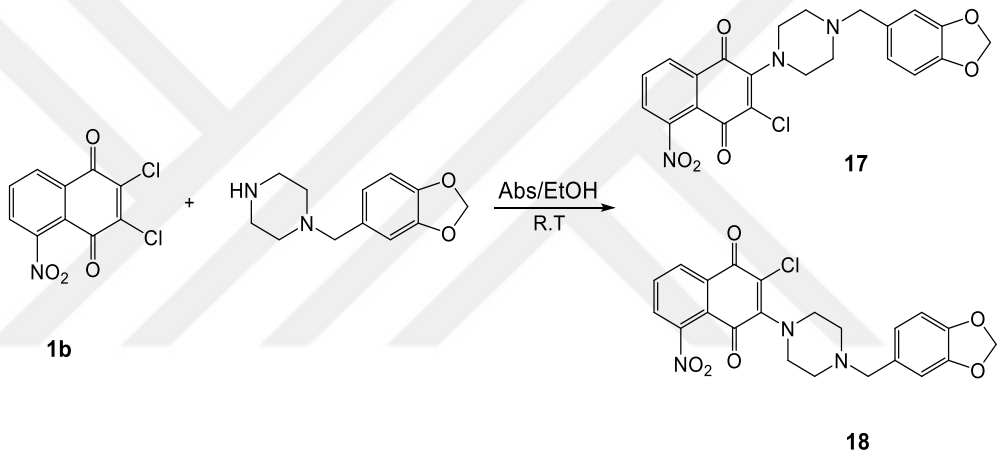
The previous results obtained from mass spectra and spectral data confirm the proposed correct structure of new regioisomers **(15, 16)**.

2.2.2. Synthesis of 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione and 3-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione (17, 18)

The new isomer compounds of **(17, 18)** were obtained by the starting compound **(1b)** with 1-piperonylpiperazine in Abs. Ethanol for 3-4 hours as general prosedure 4.

Isomer **17**; Red solid, R_f: 0.80 (1:3 EtAc/Hexane), M.p.: 131-132°C.

Isomer **18**; Pink solid, R_f: 0.37 (1:3 EtAc/Hexane), M.p.: 89-91°C.



(2.15)

According to the IR spectrum of compound **17**; stretching band for (C-H_{arom}) was detected at ν = 3094 cm^{-1} and stretching bands for (C-H_{aliph}) were observed at ν = 2912, 2809, 2772, 2659 cm^{-1}. Carbonyl group band (C=O) at ν = 1679, 1640 cm^{-1}. Bands of carbon-carbon double bond (C=C) were seen at ν = 1590, 1555 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at ν = 1494, 1438 cm^{-1} respectively (Figure 2.67).

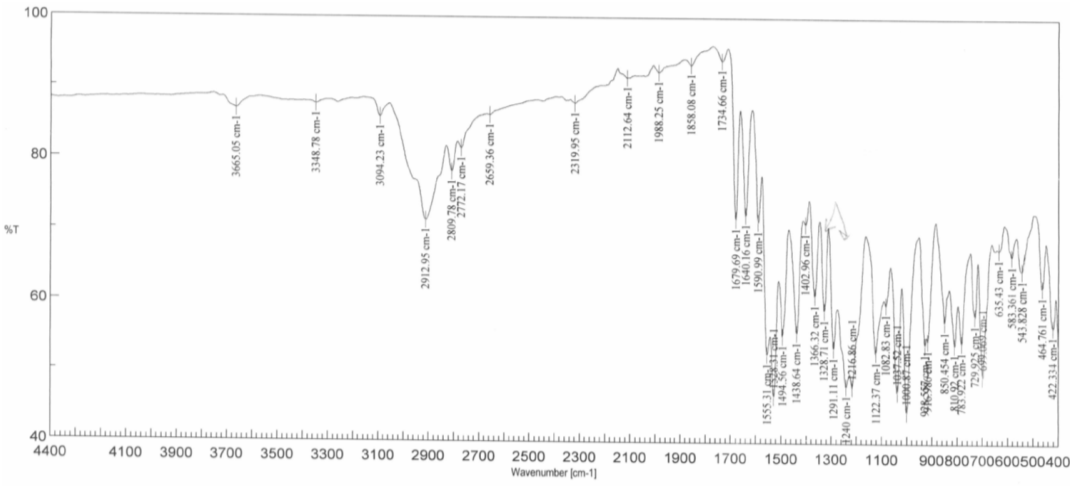


Figure 2.67: FTIR (KBr) spectrum concerning the compound **17**.

According to the ^{1}H NMR spectrum concerning the compound **17**; a singlet at δ =3.52 ppm is corresponding to protons of the methylene group. Piperazine (CH_2NCH_2) were seen at δ = 2.56 and 3.64 ppm as a broad singlet. Protons of ($O\text{-}CH_2\text{-}O$) were seen at δ =5.97 ppm as a singlet. The protons in aromatic rings take place at δ = 6.74-6.90 ppm as a multiplet. The three protons of nitro naphthoquinone were detected at δ = 7.76-7.82 ppm as a multiplet and 8.34 ppm as doublet of doublet (Figure 2.68).

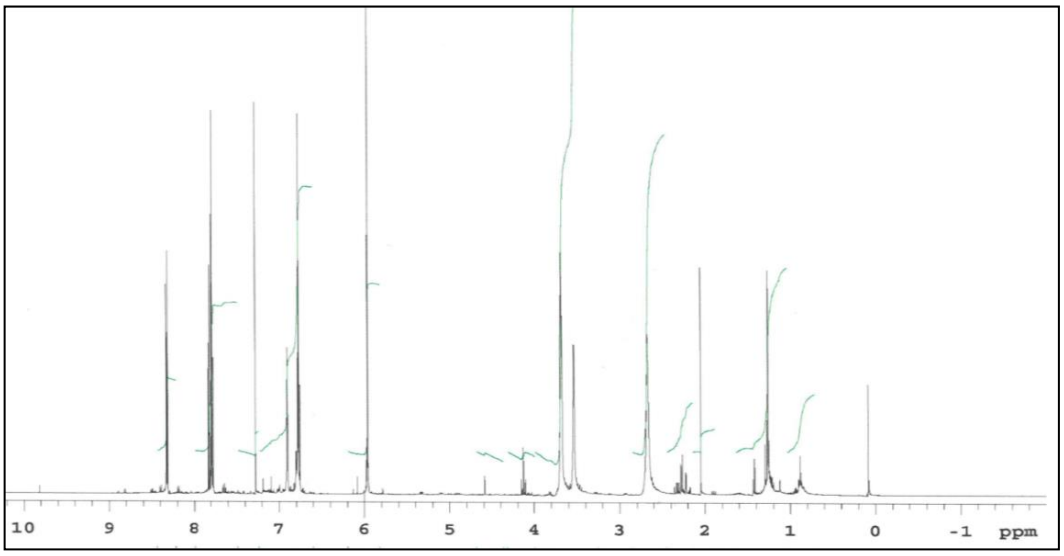


Figure 2.68: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **17**.

According to ^{13}C (APT) NMR spectrum concerning the compound **17**; piperazine (N-CH_2) ring signal were appeared at δ = 51.15, 53.31 ppm, carbon signal of (CH_2) at δ = 62.43 ppm. Signals at δ = 101.12 and 108.01 ppm are related to carbon of (O-CH_2-O) and (=C-Cl) respectively. Signals at δ = 109.56, 122.60, 127.07, 129.42, 130.49, 132.64, 134.17 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 148.40 and 150.40 ppm are related to (C-NO_2) and (=C-N). Signals of carbonyl groups were seen at δ = 175.74, 179.07 ppm (Figure 2.69).

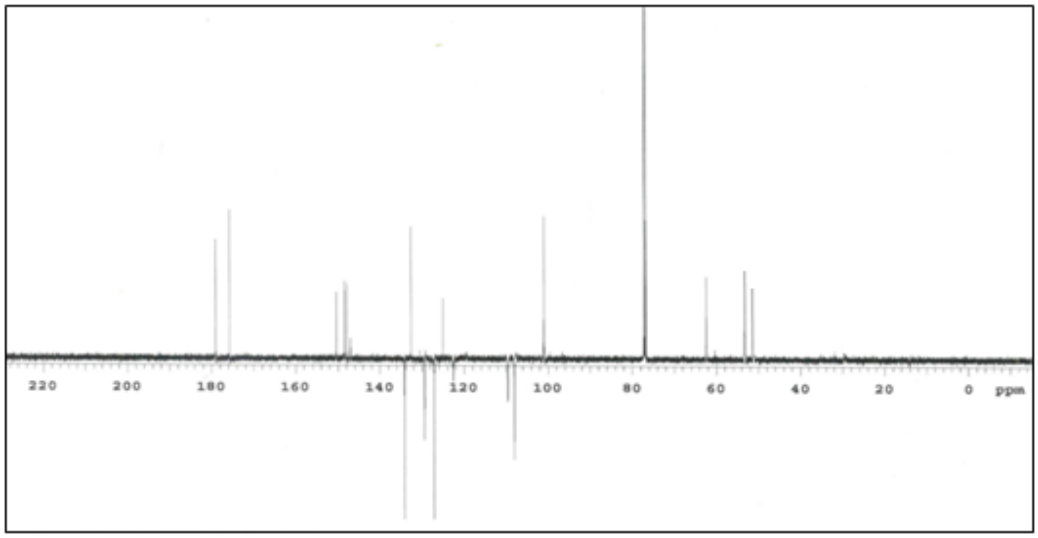


Figure 2.69: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **17**.

According to (+ESI) mass spectrum concerning the compound **17**; the molecular ion peak of a new regio-isomer compound ($C_{22}H_{18}N_3O_6Cl$, M_w= 455.85 g/mol) was seen at *m/z* (100%) = 456.0 $[M]^+$ (Figure 2.70).

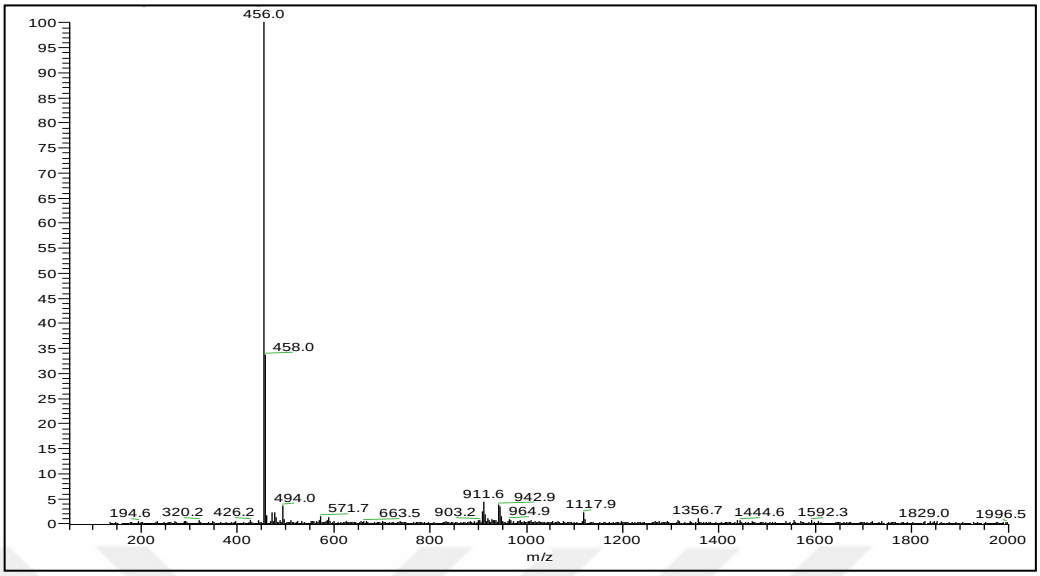


Figure 2.70: Mass spectrum [+ESI] concerning the compound **17.**

According to the IR spectrum of compound **18**; stretching band for (C-H_{arom}) was detected at ν = 3079 cm^{-1} and stretching bands for (C-H_{aliph}) were observed at ν = 2905, 2811, 2772, 2659 cm^{-1}. Carbonyl group bands (C=O) at ν = 1676, 1644 cm^{-1}. Bands of carbon-carbon double bond (C=C) were seen at ν = 1590, 15357 cm^{-1}. Stretching (asymmetric, symmetric) band of (C-NO_2) were appeared at ν = 1492, 1438 cm^{-1} respectively (Figure 2.71).

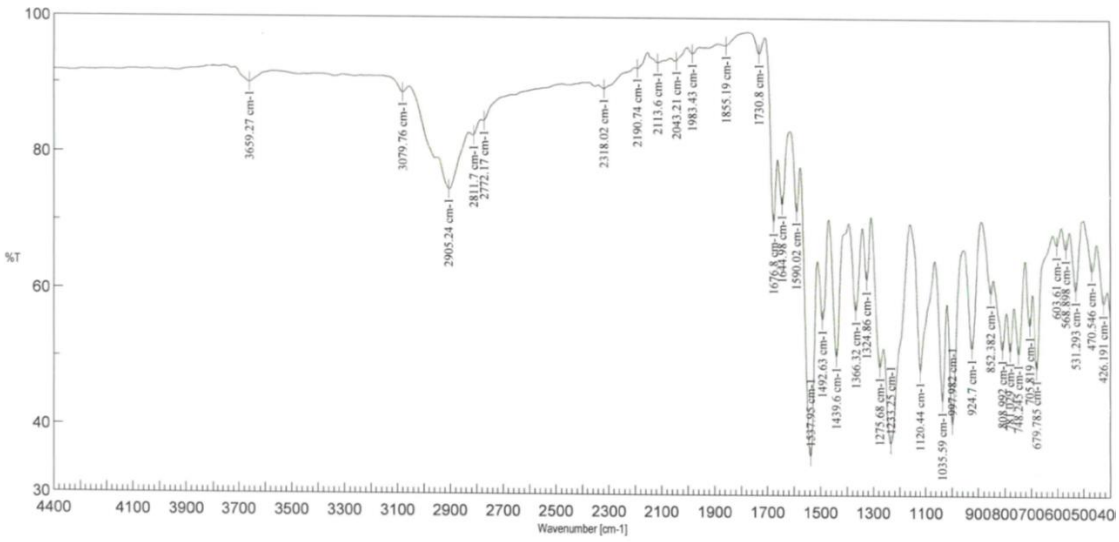


Figure 2.71: FTIR (KBr) spectrum concerning the compound **18**.

According to the ^{1}H NMR spectrum concerning the compound **18**; a singlet at δ =3.62 ppm is corresponding to protons of methylene group. Piperazine (CH_2NCH_2) were seen at δ 2.52 and 3.64 ppm as a broad singlet, protons of (O-CH_2-O) were seen at δ =5.97 ppm as a singlet. The protons in aromatic rings take place at δ = 6.74-6.94 ppm as a multiplet. The three protons of nitro naphthoquinone were detected at δ = 7.67, 7.82 and 8.21 ppm as doublet of doublet, triplet and doublet of doublet respectively (Figure 2.72).

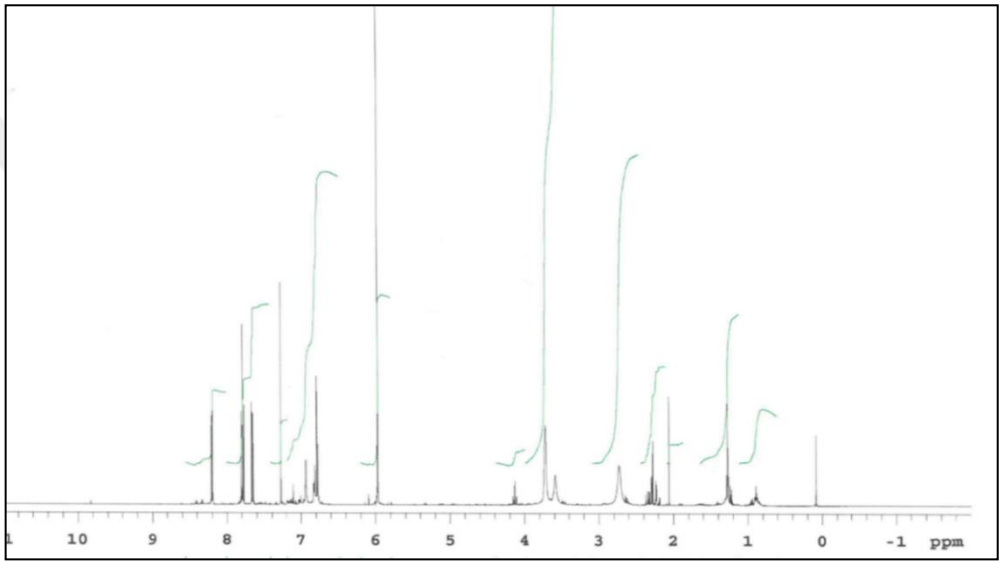


Figure 2.72: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **18**.

According to ^{13}C (APT) NMR spectrum concerning the compound **18**; piperazine (N-CH_2) ring signals were appeared at δ = 53.26 ppm, carbon signal of (CH_2) at δ = 62.39 ppm. Signal at δ = 101.08 and 108.07 ppm are related to carbon of (O-CH_2-O) and (=C-Cl) respectively. Signals at δ =109.73, 122.67, 127.63, 129.16, 132.32, 133.70 ppm are belonging to (CH_{arom}, C_{arom}). Carbon signal at δ = 148.35 and 149.33 ppm are related to (C-NO_2) and (=C-N). Signals of carbonyl groups were seen at δ = 173.97, 179.84 ppm (Figure 2.73).

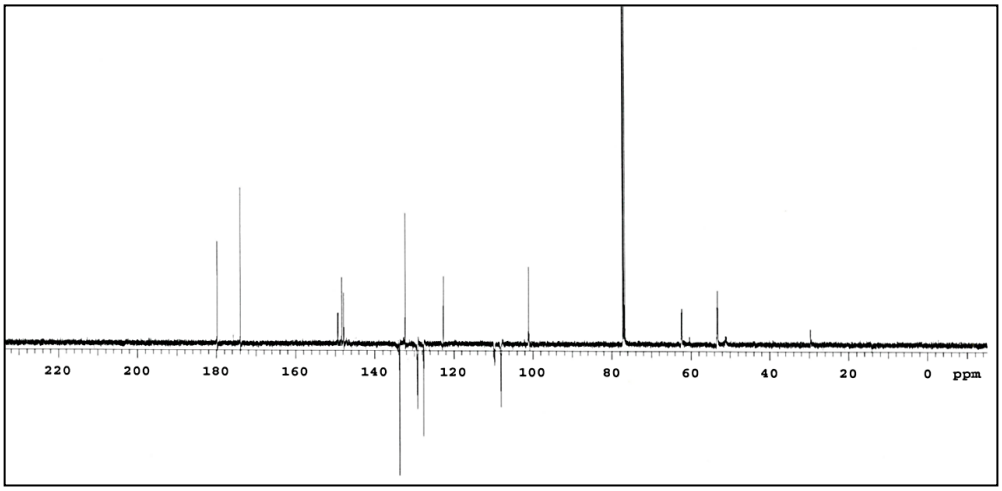


Figure 2.73: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **18**.

According to the (+ESI) mass spectrum concerning the compound **18**; the molecular ion peak of a new regioisomer compound ($C_{22}H_{18}N_3O_6Cl$, M_w= 455.85 g/mol) was seen at *m/z* (100%) = 456.0 $[M]^+$. A small peak at *m/z* = 478.0 referred to $[M+Na]^+$ (Figure 2.74).

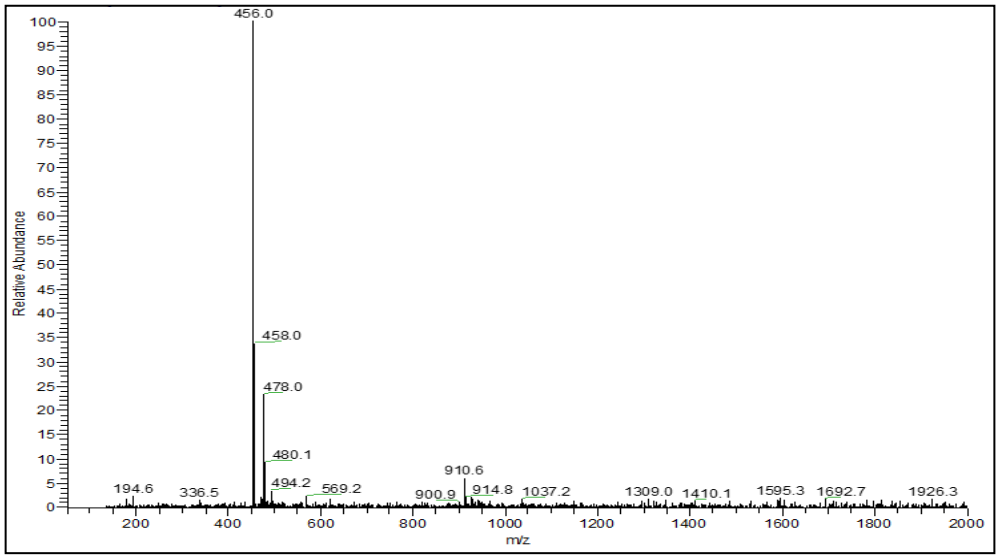


Figure 2.74: Mass spectrum [+ESI] concerning the compound **18**.

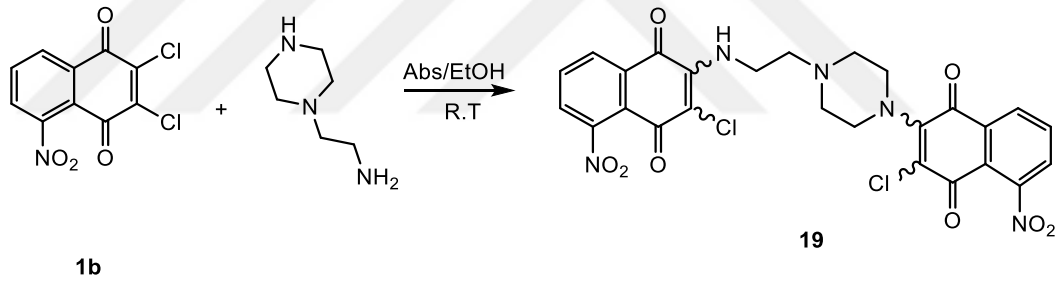
As a comparison between the ^1H NMR spectra of the synthesized new regioisomers **(17, 18)**; we observed that the proton of naphthoquinone peaks (δ=7.76-7.82 and 8.34 ppm) for the first

isomer **(17)** are shifted more downfield than the naphthoquinone peaks at δ = 7.67, 7.82 and 8.21) of the second isomer **(18)**. Also, it found that the isomer **(17)** has a higher R_f component than the isomer **(18)** [89], [91].

All the previous results obtained from mass spectra and spectral data confirm the proposed correct structure of new regioisomers **(17, 18)**.

2.2.3. Synthesis of 2-chloro-3-(4-(2-((3-chloro-5-nitro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)ethyl)piperazin-1-yl)-5-nitronaphthalene-1,4-dione (19)

The new compound (**19**) was obtained from reaction of compound **(1b)** and 2-(1-piperazinyl)ethylamine in Abs. Ethanol for 3-4 hours as general procedure 4.



1b **19**

(2.16)

IR spectrum of compound **19**; stretching a broad band of (NH) was appeared at 3258 cm^{-1}. (C-H_{arom}), (C-H_{aliph}) bands were detected at ν = 3076, 2964 and 2922 cm^{-1} respectively. (C=O) band at ν = 1676 cm^{-1}. (C=C) band was seen at ν = 1590 cm^{-1}. Stretching (asymmetric, symmetric) band for (C-NO_2) were appeared at ν = 1534, 1447 cm^{-1} respectively (Figure 2.75).

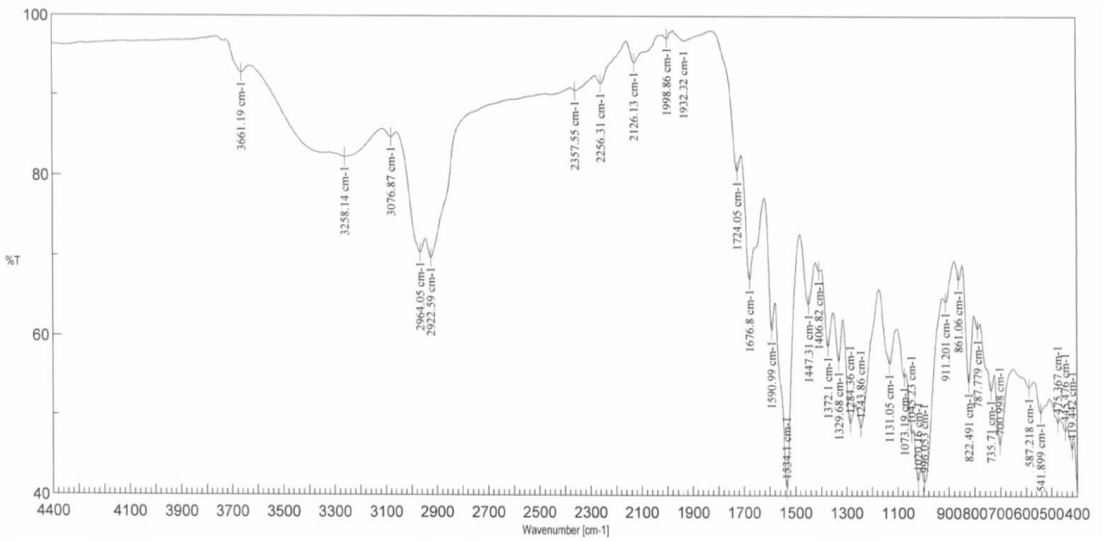


Figure 2.75: FTIR (KBr) spectrum concerning the compound **19**.

According to the ^{1}H NMR spectrum concerning the compound **19**; Methylene protons of ($CH_2C\mathbf{H}_2$-N) and (HN-C$\mathbf{H}_2CH_2$) were appeared at δ = 2.64, 3.32 ppm as a multiplet, whereas, piperazine ring protons were seen at δ = 3.50, 3.81 ppm as a broad singlet. (NH) proton was seen at δ = 7.50 ppm as a broad singlet. One proton of nitro naphthoquinone was seen at δ = 7.99 and 8.11 ppm as a doublet of doublet and other protons at δ = 8.01-8.08, 8.19-8.23 ppm as a multiplet (Figure 2.76).

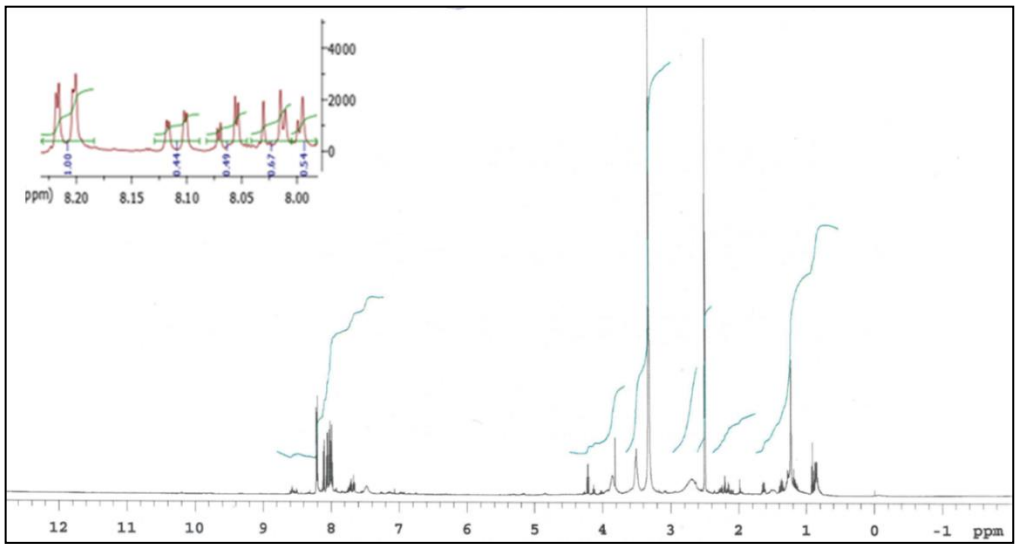


Figure 2.76: ^{1}H NMR (DMSO-d_6) spectrum concerning the compound **19**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **19**; carbon signals of (CH_2-NH) group was detected at δ = 40.68 ppm. Carbon signals of piperazine (N-CH_2) ring were appeared at δ = 53.65, 55.15 ppm, carbon signal of (N–CH_2) at δ = 59.82 ppm. Signal at δ = 98.44, 99.55 ppm are belonging to (=C-Cl). Signals at δ = 127.18, 128.80, 129.42, 130.84, 132.58, 134.53 ppm for aromatic carbon (CH_{arom}, C_{arom}). Signal at δ = 148.52 ppm is related to (=C-N). Signals of carbonyl groups were seen at δ = 175.84, 178.97, 190.32 ppm (Figure 2.77).

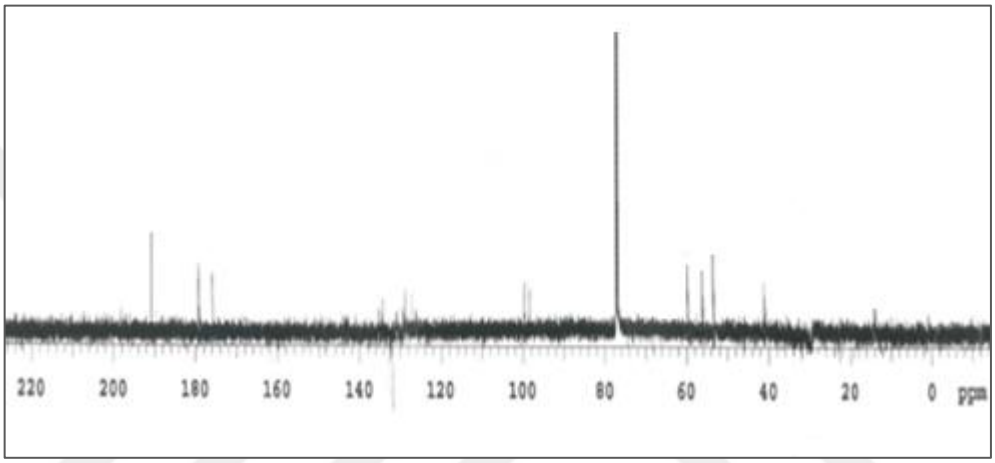


Figure 2.77: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **19**.

According to (+ESI) mass spectrum concerning the compound **19**; the molecular ion peak of a new compound ($C_{26}H_{19}N_5O_8Cl_2$, M_w= 600.36 g/mol) was seen at *m/z* (100%) = 600.0 $[M]^+$ (Figure 2.78).

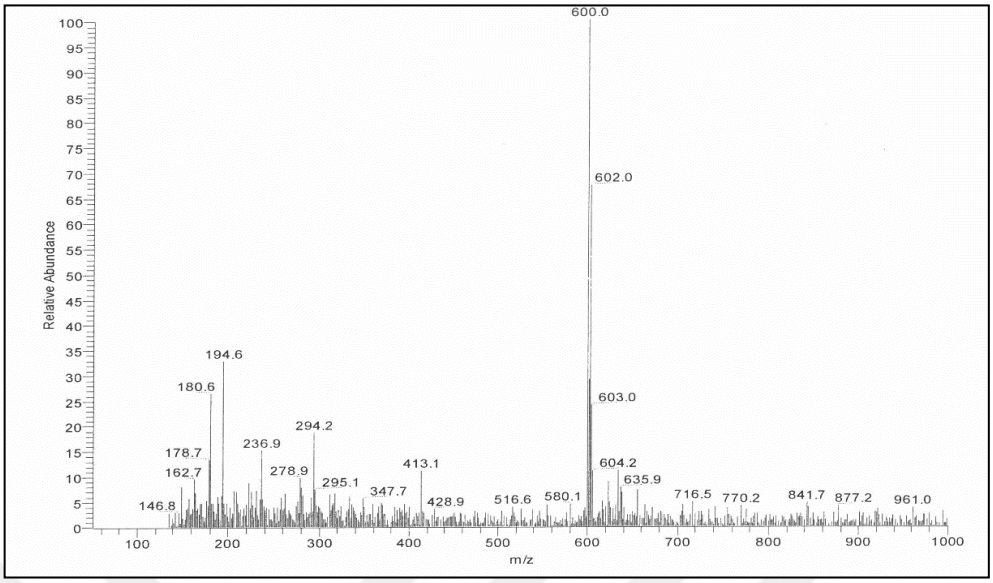


Figure 2.78: Mass spectrum [+ESI] concerning the compound **19**.

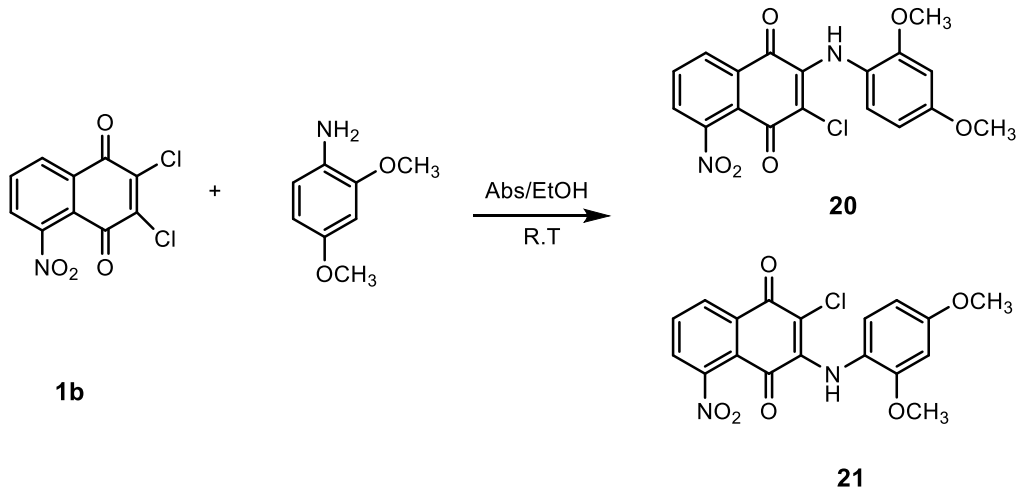
All the previous obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(19)**.

2.2.4. Synthesis of 3-chloro-2-((2,4-dimethoxyphenyl)amino)-5-nitronaphthalene-1,4-dione and 2-chloro-3-((2,4-dimethoxyphenyl)amino)-5-nitronaphthalene-1,4-dione (20, 21)

The new regioisomer compounds (**20**, **21**) were obtained by the reaction of compound **(1b)** with 2,4-dimethoxyaniline in absolute ethanol for 3-4 hours according procedure 4.

Isomer **20**; Red solid, R_f: 0.52 (1:4 EtAc/Hexane), M.p.: 205-206°C.

Isomer **21**; Red solid, R_f: 0.35 (1:4 EtAc/Hexane), M.p.: 198-199°C.



(2.17)

According to IR spectrum concerning the compound **20**; (NH) band observed at ν = 3316 cm^{-1} (C-H_{arom}), (C-H_{aliph}) bands appeared at ν = 3083, 2967 and 2917 cm^{-1} respectively, band for (C=O) appeared at ν = 1675 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1585, 1554 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1534, 1370 cm^{-1} respectively (Figure 2.79).

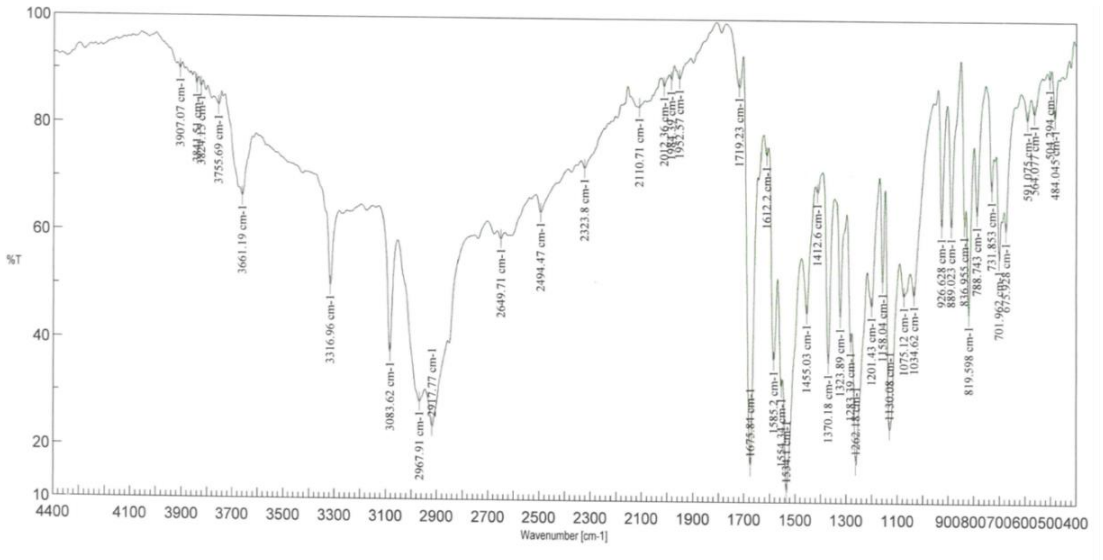


Figure 2.79: FTIR (KBr) spectrum concerning the compound **20.**

According to the ^{1}H NMR spectrum concerning the compound **20**; (CH_3-O) protons were seen as a singlet at δ = 3.84 ppm, whereas, protons of aromatic ring at δ = 6.42, 6.93 ppm as a multiplet. (NH) proton was seen at δ = 7.51 ppm as a broad singlet. One proton of nitro naphthoquinone was seen at δ = 7.73 ppm as doublet, another proton at δ = 8.02 ppm as a triplet last one as doublet at δ = 8.40 ppm (Figure 2.80).

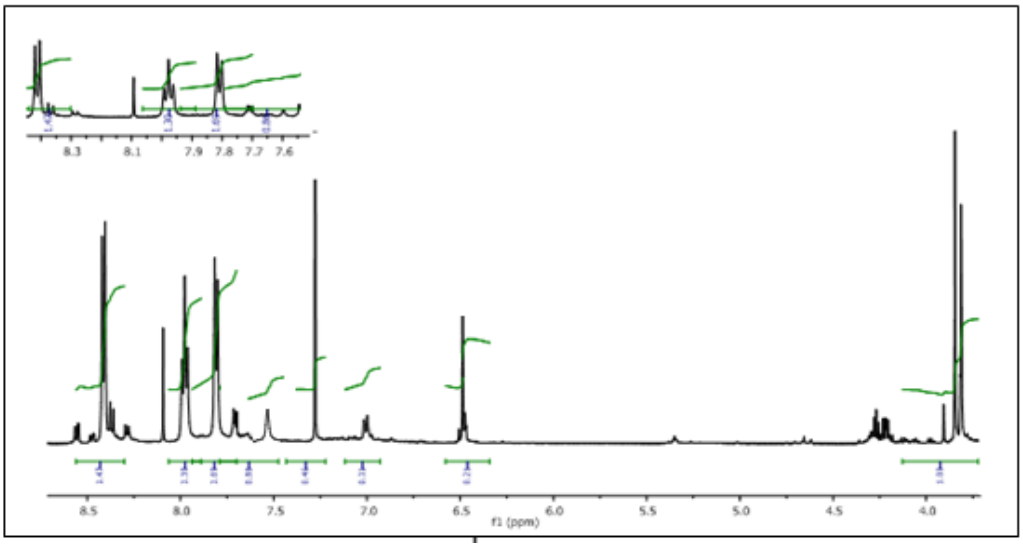


Figure 2.80: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **20**.

According to ^{13}C (APT) NMR spectrum concerning the compound **20**; methoxy (CH_3-O) group signal was detected at δ = 55.58 ppm. Carbon signals in aromatic ring (CH_{arom}) were appeared at δ = 98.65, 103,54 ppm, carbon signal of (=C-Cl) at δ = 113.79 ppm. Signals at δ = 121.17, 126.85, 128.30, 128.87, 130,88, 131.73, 135.60 ppm for aromatic carbon (CH_{arom}, C_{arom}). Signal at δ = 143.34, 148.93 ppm were related to (C-NO_2) and (=C-N). (=**C**-OCH_3) signals at δ = 154.57, 159.64 ppm. Two carbonyl groups were seen at δ = 172.65, 174.28 ppm (Figure 2.81).

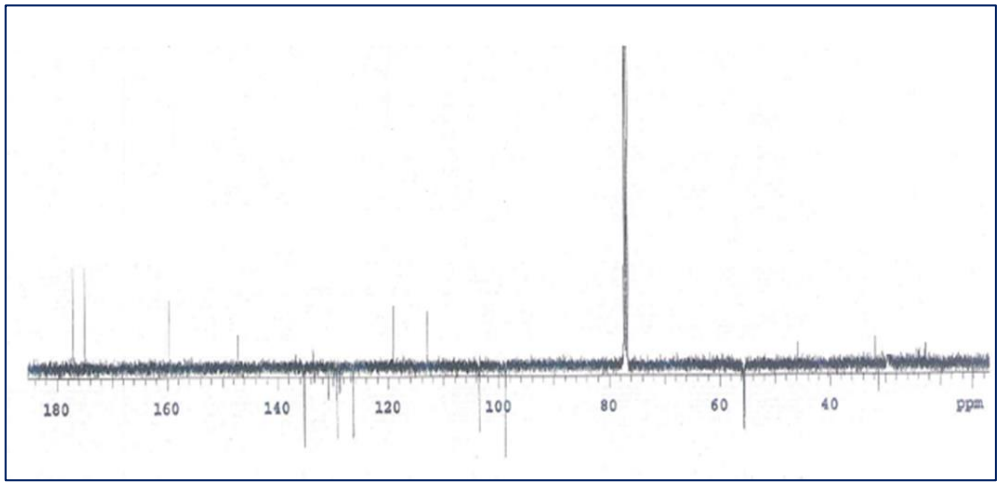


Figure 2.81: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **20**.

According to (+ESI) mass spectrum concerning the compound **20**; the molecular ion peak of a new compound ($C_{18}H_{13}ClN_2O_6$, M_w = 388.73 g/mol) was seen at *m/z* (100%) = 387.2 $[M-H]^+$ (Figure 2.82).

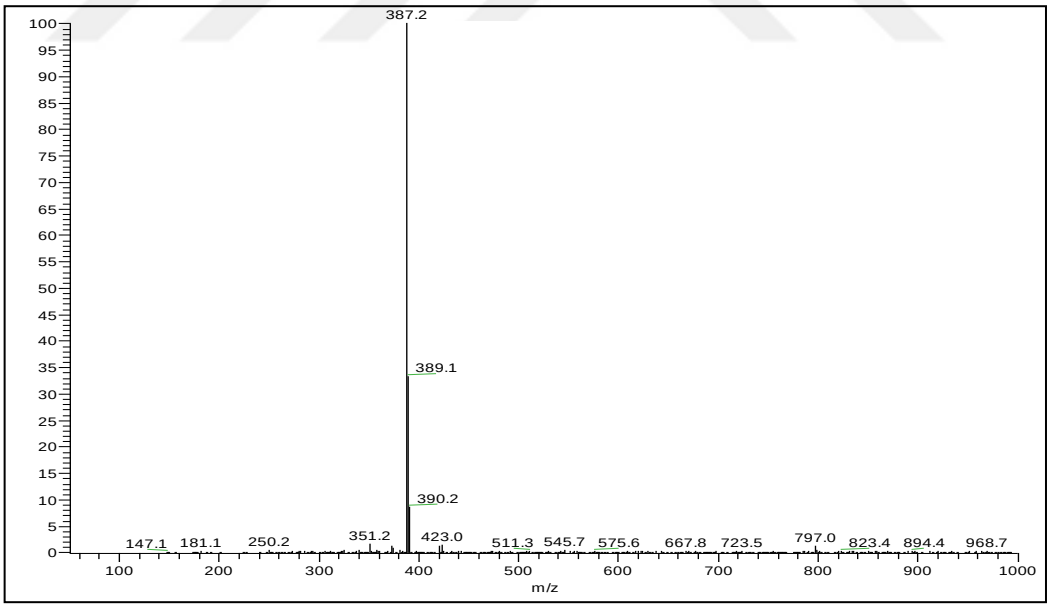


Figure 2.82: Mass spectrum[+ESI] concerning the compound **20**.

According to the IR spectrum of compound **21**; the amino group band (NH) was observed at ν = 3308 cm^{-1}, ($C-H_{arom}$), ($C-H_{aliph}$) bands appeared at ν = 3090 and 2970 cm^{-1}, (C=O) bands

appeared at ν = 1679, 1640 cm^{-1}. The band of carbon-carbon double bonds (C=C) were seen at ν = 1590, 1563 cm^{-1}. Stretching (asymmetric, symmetric) band for (C-NO_2) were appeared at ν = 1455, 1339 cm^{-1} respectively (Figure 2.83).

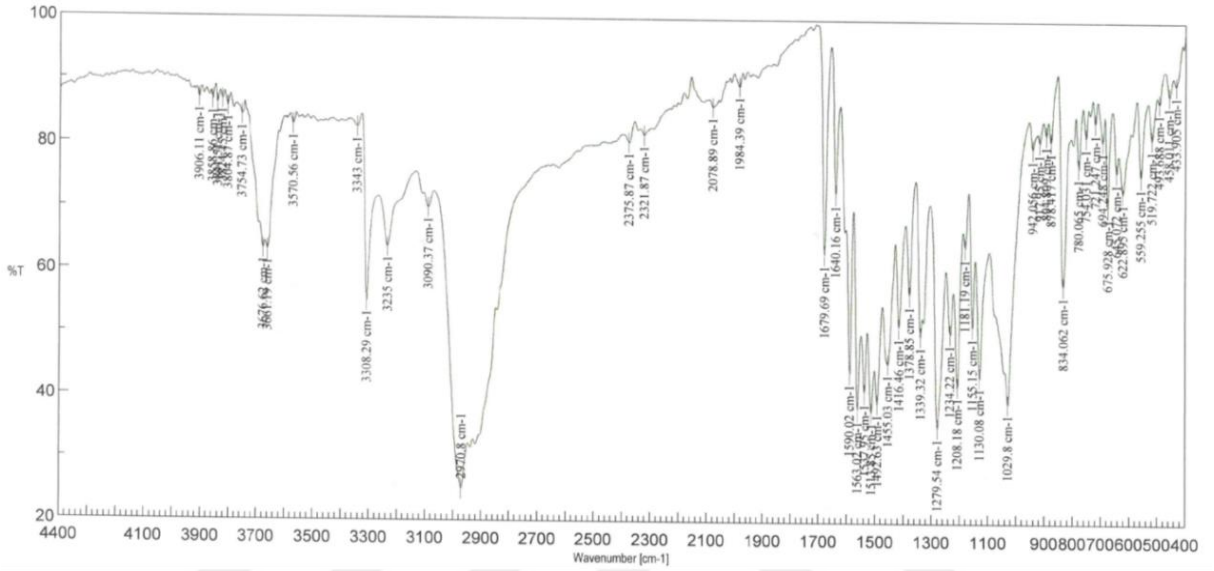


Figure 2.83: FTIR (KBr) spectrum concerning the compound **21**.

According to ^{1}H NMR spectrum concerning the compound **21**; (NH) proton was seen at δ = 7.54 ppm as a broad singlet. Methoxy protons of (CH_3-O) were found as singlet at δ = 3.82 ppm, whereas, protons of aromatic ring at δ = 6.48 ppm as a doublet of doublet, δ = 7.00 ppm as a multiplet. Two protons of nitro naphthoquinone were seen at δ = 7.69, 7.87 and 8.29 ppm as doublet of doublet, triplet and doublet of doublet respectively (Figure 2.84).

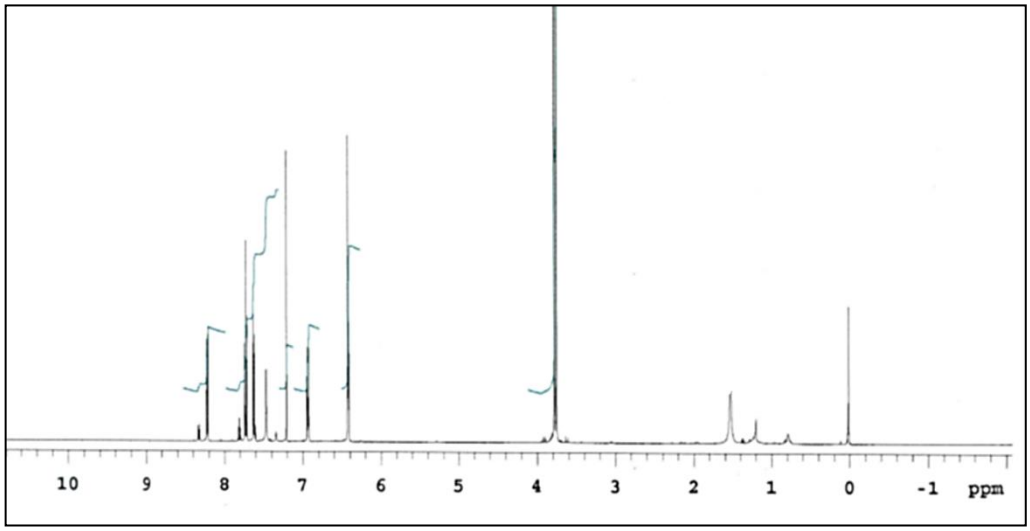


Figure 2.84: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **21**.

According to ^{13}C (APT) NMR spectrum concerning the compound **21**; methoxy group (CH_3-O) signal was detected at δ = 55.68 ppm. Carbon signals in aromatic ring (CH_{arom}) were appeared at δ = 98.67, 103,60 ppm, carbon signal of (=C-Cl) at δ = 113.34 ppm. Signals at δ = 120.17, 123.71, 126.84, 128.95, 131,05, 133.37, 135.24 ppm for aromatic carbon (CH_{arom}, C_{arom}). Signal at δ = 142.86, 148.72 ppm were related to (C-NO_2) and (=C-N). Signals at δ = 154.11, 159.49 ppm for (=**C**-OCH_3). Two carbonyl groups were seen at δ = 173.29, 178.67 ppm (Figure 2.85).

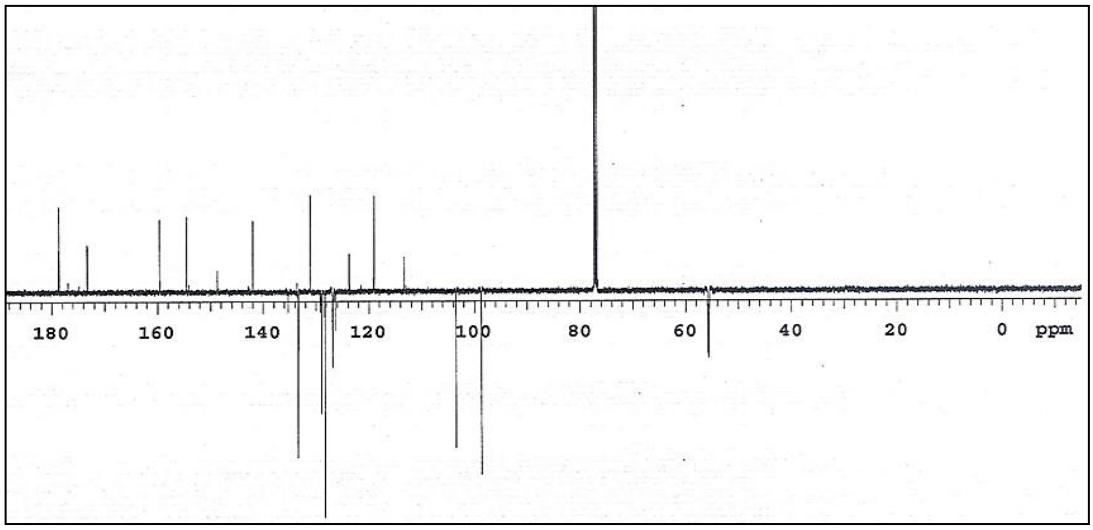


Figure 2.85: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **21**.

According to (+ESI) mass spectrum concerning the compound **21**; the ion molecular peak of a new compound ($C_{18}H_{13}ClN_2O_6$, M_w = 388.73 g/mol) was seen at *m/z* (100%) = 387.5 $[M-H]^+$ (Figure 2.86).

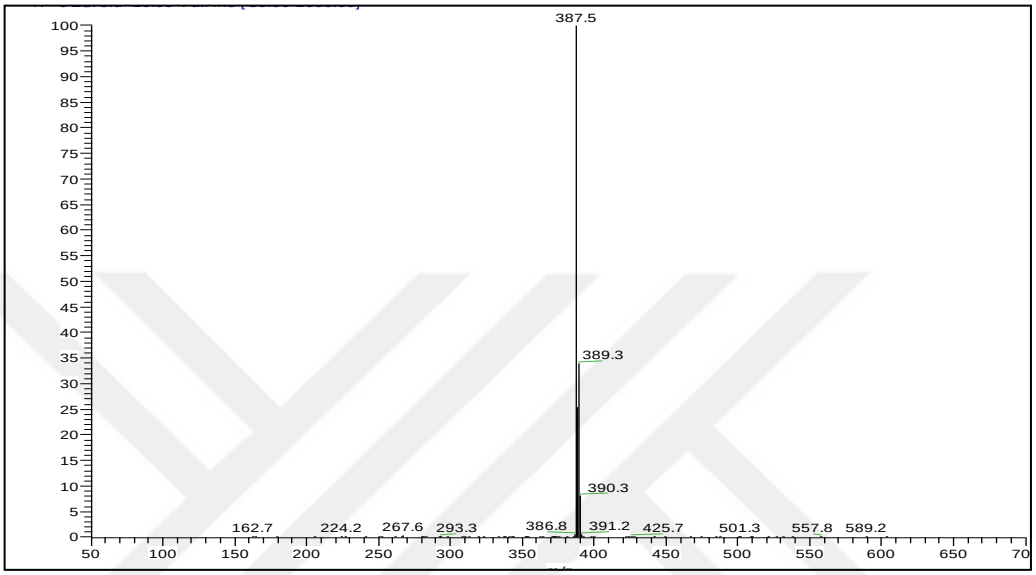


Figure 2.86: Mass spectrum [+ESI] concerning the compound **21**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(20, 21)**; we observed that the proton of naphthoquinone peaks (δ=7.72, 8.02 and 8.40 ppm) for the first isomer **(20)** are shifted more downfield than the naphthoquinone peaks (δ=7.69, 7.87 and 8.29 ppm) of the second isomer **(21)**. Also, it found that the isomer **(20)** has a higher R_f component than the isomer **(21)** [89], [91].

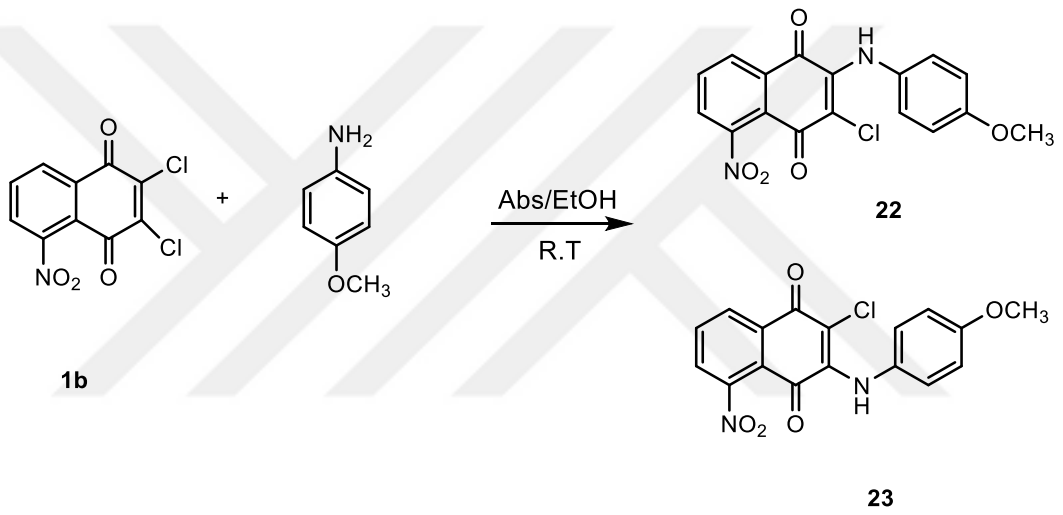
The previous results obtained from mass spectra and spectral data confirm the proposed correct structure of new regioisomers **(20, 21)**.

2.2.5. Synthesis of 3-chloro-2-((4-methoxyphenyl)amino)-5-nitronaphthalene-1,4-dione and 2-chloro-3-((4-methoxyphenyl)amino)-5-nitronaphthalene-1,4-dione (22, 23)

The new isomer compounds (**22**, **23**) were obtained by reacting the 4-methoxyaniline with starting material **(1b)** in pure ethanol for 3-4 hours as general procedure 4.

Isomer **22**; Red solid, R_f: 0.51(1:4 EtAc/Hexane), M.p.: 167-168°C.

Isomer **23**; Red solid, R_f: 0.33 (1:4 EtAc/Hexane), M.p.: 129-131°C.



(2.18)

According to IR spectrum concerning the compound **22**; the (NH) band observed at ν = 3226 cm^{-1}, stretching band for (C-H_{arom}) appeared at ν = 3084cm^{-1} and stretching bands for (C-H_{aliph}) observed at ν = 2919, 2850 cm^{-1}, carbonyl group band (C=O) appeared at ν = 1684, 1636 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1590, 1563 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1532, 1376 cm^{-1} respectively (Figure 2.87).

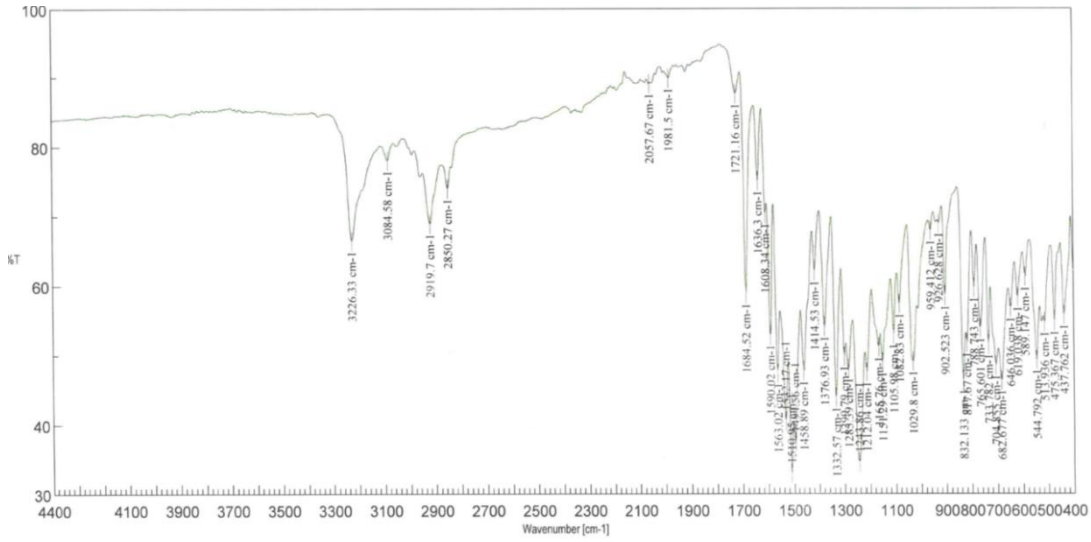


Figure 2.87: FTIR (KBr) spectrum concerning the compound **22**.

According to the ^{1}H NMR spectrum concerning the compound **22**; Methoxy (CH_3-O) protons were seen at δ = 3.85 ppm as a singlet. Proton of (NH) observed at δ =5.38 ppm as a broad singlet. Whereas, protons of aromatic ring at δ = 6.85-6.94 and 7.04-7.10 ppm as a multiplet, protons of nitro naphthoquinone were seen at δ = 7.81, 7.97 and 8.33-8.42 ppm as a doublet of doublet, triplet, multiplet respectively (Figure 2.88).

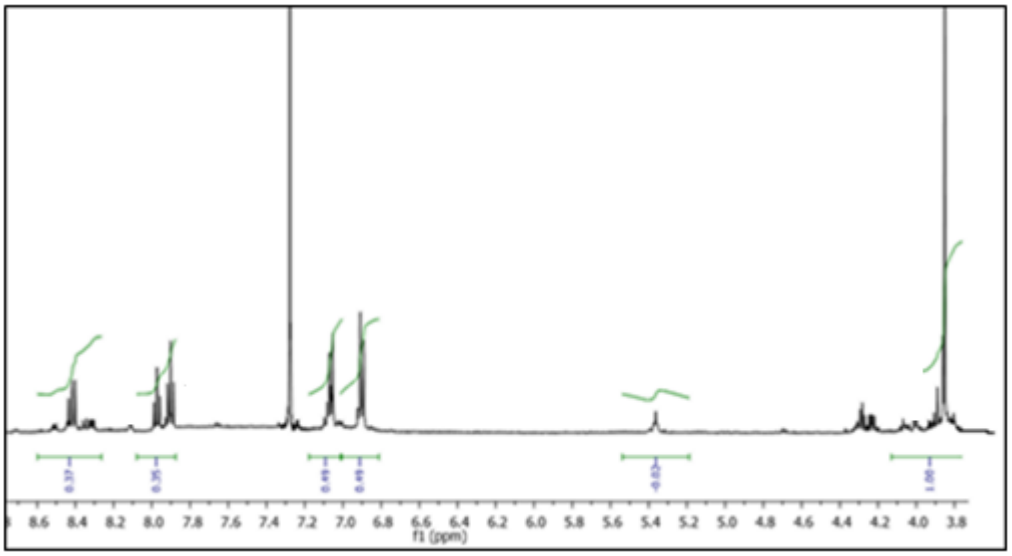


Figure 2.88: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **22**.

According to ^{13}C (APT) NMR spectrum concerning the compound **22**; methoxy group (CH_3-O) signal was detected at δ = 55.53 ppm. Carbon signals in aromatic ring (CH_{arom}) were appeared at δ = 111,70 ppm, carbon signal of (=C-Cl) at δ = 113.36 ppm. Signals at δ = 119.17, 123.17, 126.84, 127.14, 128.95, 131.37, 135.24 ppm for aromatic carbon (CH_{arom}, C_{arom}). Signal at δ = 144.86, 148.93 ppm are related to (C-NO_2) and (=C-N). Signals at δ = 158.64 ppm for (=**C**-OCH_3). Two carbonyl groups were seen at δ = 173.29, 178.91 ppm (Figure 2.89).

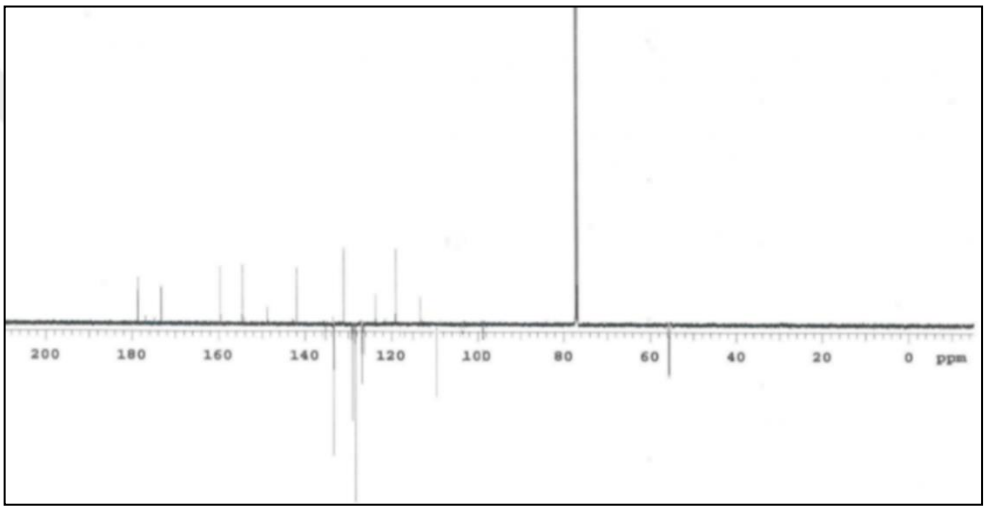


Figure 2.89: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **22**.

According to (+ESI) mass spectrum concerning the compound **22**; the molecular ion peak of a new compound ($C_{17}H_{11}ClN_2O_3$, M_w = 358.73 g/mol) was seen at *m/z* (100%) = 357.1 $[M-H]^+$ (Figure 2.90).

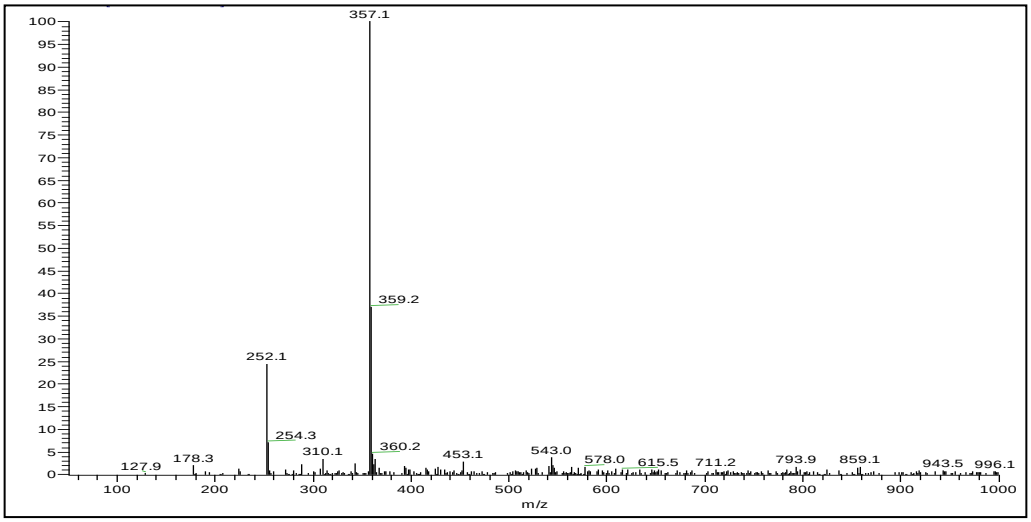


Figure 2.90: Mass spectrum [+ESI] concerning the compound **22**.

According to IR spectrum concerning the compound **23**; (NH) band appeared at ν =3289 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) bands appeared at ν = 3102, 3002 cm^{-1} and 2918, 2843 cm^{-1} respectively. (C=O) bands appeared at ν=1680, 1644 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1590, 1552 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at ν = 1542, 1329 cm^{-1} respectively (Figure 2.91).

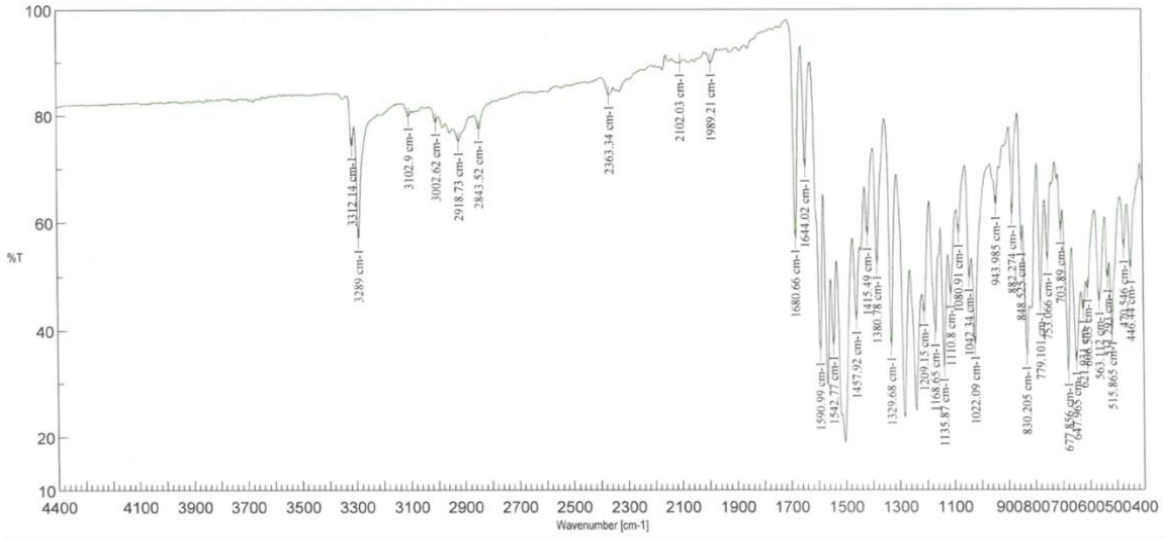


Figure 2.91: FTIR (KBr) spectrum concerning the compound **23**.

According to the ^{1}H NMR spectrum concerning the compound **23**; Methoxy (CH_3-O) protons were seen as a singlet at δ = 3.86 ppm, whereas, protons of aromatic ring at δ = 6.74-6.98 and 7.06-7.17 ppm as a multiplet. (NH) proton was seen as a broad singlet at δ = 6.15 ppm. three protons for nitro naphthoquinone were seen at δ = 7.63-7.74 and 8.06-8.41 ppm as a multiplet (Figure 2.92).

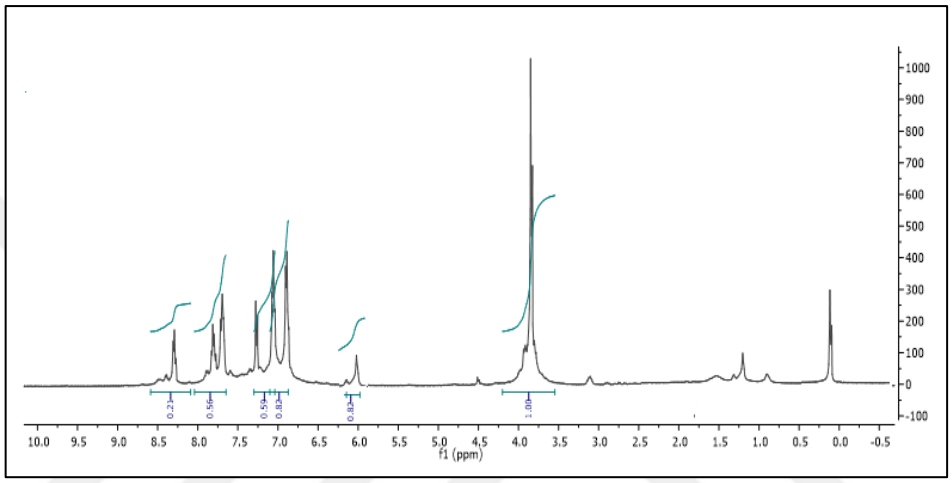


Figure 2.92: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **23**.

According to ^{13}C NMR spectrum concerning the compound **23**; methoxy group (CH_3-O) signal was detected at δ = 55.49 ppm. Carbon signal of (=C-Cl) at δ = 112.04 ppm. Signals at δ = 113.66, 123.12, 126.60, 128.46, 129.17, 131.90, 132.01, 134.60 ppm for aromatic carbon (CH_{arom}, C_{arom}). Signal at δ = 144.25, 148.23 ppm are related to (C-NO_2) and (=C-N). Signals at δ = 157.36 ppm for (=**C**-OCH_3). Two carbonyl groups were seen at δ = 173.66, 178.92 ppm (Figure 2.93).

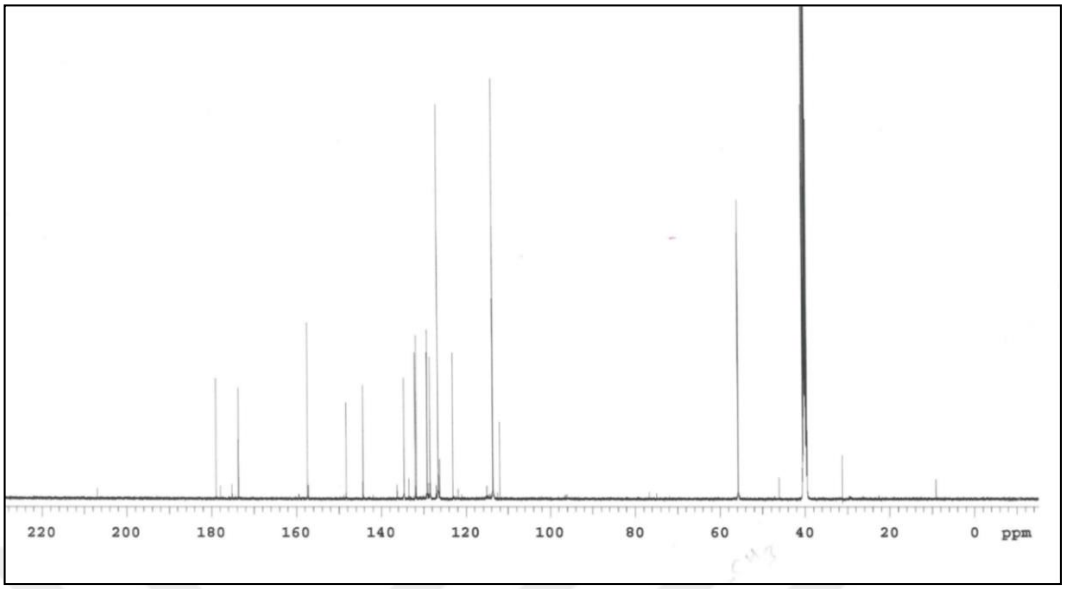


Figure 2.93: ^{13}C NMR (DMSO-d_6) spectrum concerning the compound **23.**

According to (+ESI) mass spectrum concerning the compound **23**; the molecular ion peak of a new compound ($C_{17}H_{11}ClN_2O_3$, M_w = 358.73 g/mol) was seen at *m/z* (100%) = 357.2 $[M-H]^+$ (Figure 2.94).

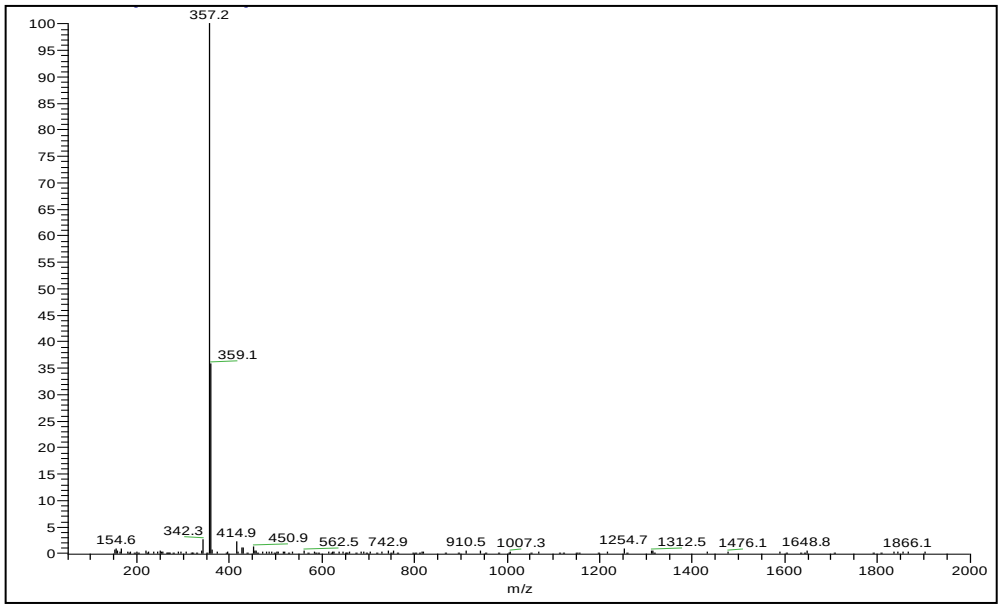


Figure 2.94: Mass spectrum [+ESI] concerning the compound **23**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(22, 23)**; we observed that the proton of naphthoquinone peaks (δ=7.81, 7.97 and 8.33-8.42 ppm) for the first isomer **(22)** are shifted more downfield than the naphthoquinone peaks (δ=7.63-7.74 and 8.06-8.41ppm) of the second isomer **(23)**. Also, it found that the isomer **(22)** has a higher R_f component than the isomer **(23)** [89], [91].

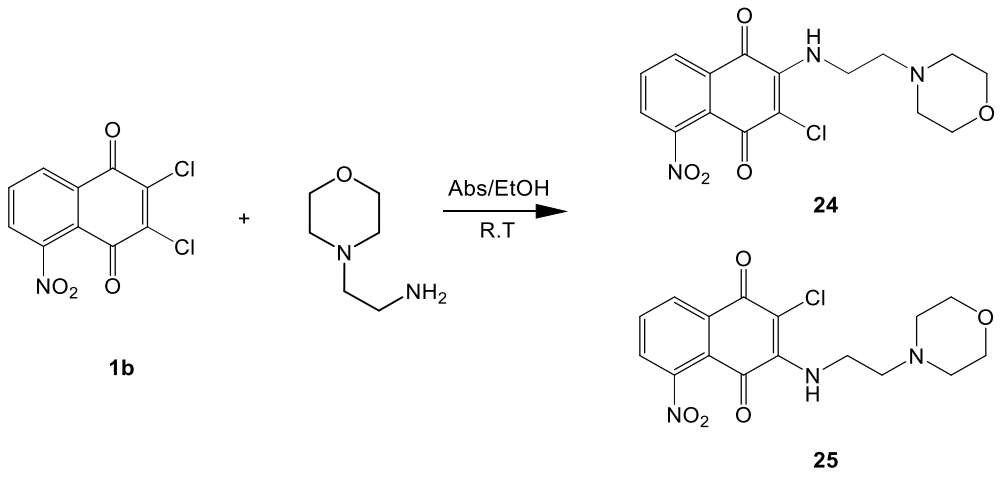
The previous results obtained from mass spectra and spectral data confirm the proposed correct structure of new regioisomers **(22, 23)**.

2.2.6. Synthesis of 3-chloro-2-((2-morpholinoethyl)amino)-5-nitronaphthalene-1,4-dione and 2-chloro-3-((2-morpholinoethyl)amino)-5-nitronaphthalene-1,4-dione (24, 25)

The new isomer compounds (**24**, **25**) were obtained by the reaction of **(1b)** as starting material with 4-(2-aminoethyl) morpholine in Abs. Ethanol for 3-4 hours as general procedure 4.

Isomer **24**; Red solid, R_f: 0.50 (1:2 EtAc/Hexane), M.p.: 178-179°C.

Isomer **25**; Red solid, R_f: 0.33 (1:2 EtAc/Hexane), M.p.: 173-174°C.



(2.19)

According to IR spectrum concerning the compound **24**; (NH) band observed at ν =3292 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3096, 2918, 2852, 2813 cm^{-1} respectively. (C=O) appeared at ν = 1690 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1591, 1561 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1519, 1338 cm^{-1} respectively (Figure 2.95).

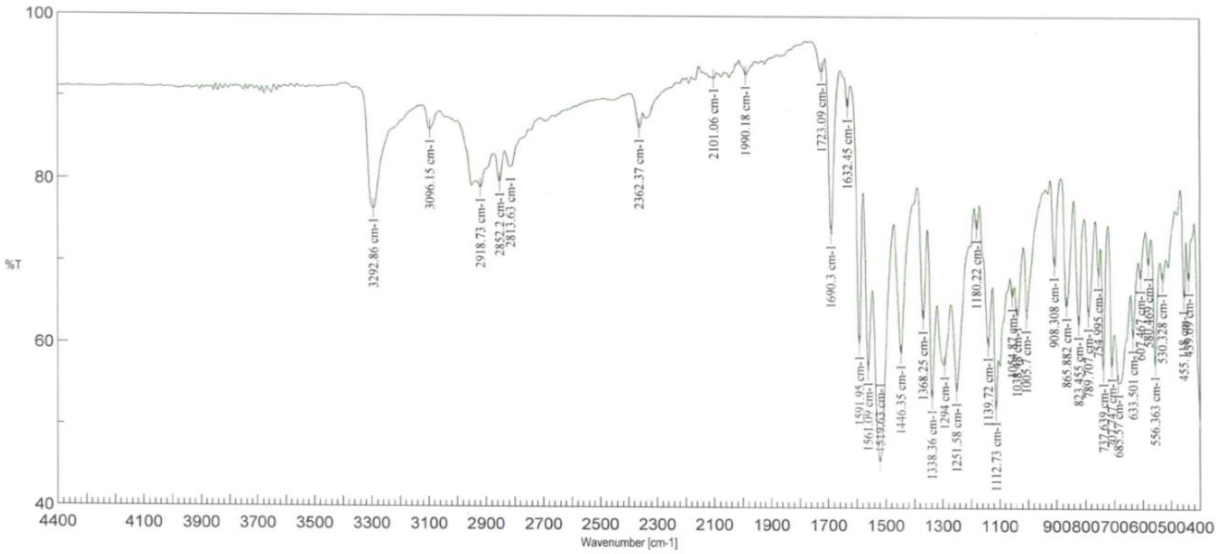


Figure 2.95: FTIR (KBr) spectrum concerning the compound **24**.

According to the ^1H NMR spectrum concerning the compound **24**; morpholine ring protons (C**H**$_2$-N-C**H**$_2$) and (C**H**$_2$-O-C**H**$_2$) were appeared at δ = 2.50 and 3.75 ppm as a triplet, (N-C**H**$_2$$CH_2$) was seen at δ = 2.58 ppm as a triplet. The two protons that bonded to amino group (HN-C**H**$_2$) were appeared as a quartet at δ = 3.85 ppm. (NH) proton was seen at δ = 6.94 ppm as a broad singlet. Three protons of nitro naphthoquinone were seen at δ = 7.65 and 8.36 ppm as doublet of doublet and as a triplet at δ = 7.86 ppm (Figure 2.96).

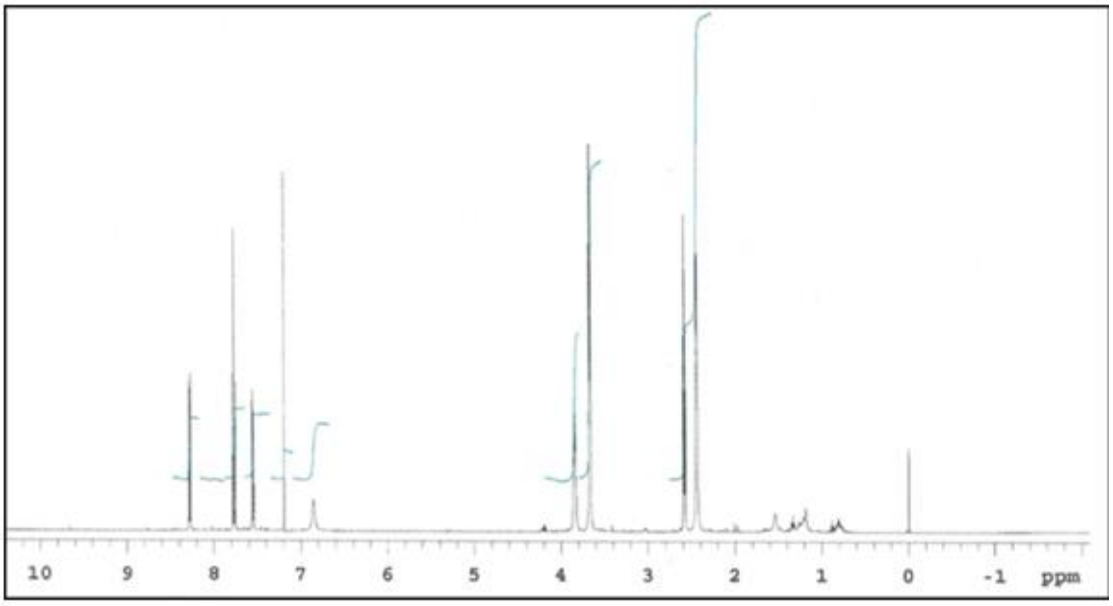


Figure 2.96: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **24**.

According to ^{13}C (APT) NMR spectrum concerning the compound **24**; (HN-**C**H_2-CH_2) and (NH-CH_2-**C**H_2) signals were appeared at δ = 40.87 and 56.50 ppm. Signals at δ = 52.93, 66.94 ppm, are related to carbons of morpholine ring (CH_2-N-CH_2)$_{morph}$ and (CH_2-O-CH_2)$_{morph}$, (=C-Cl) at δ =110.36 ppm. Signals at δ =123.22, 126.09, 129.02, 133.54, 135.24 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 142.61 and 148.93 ppm are related to (C-NO_2) and (=C-N). Signals of carbonyl groups were seen at δ = 178.69, 181.51 ppm (Figure 2.97).

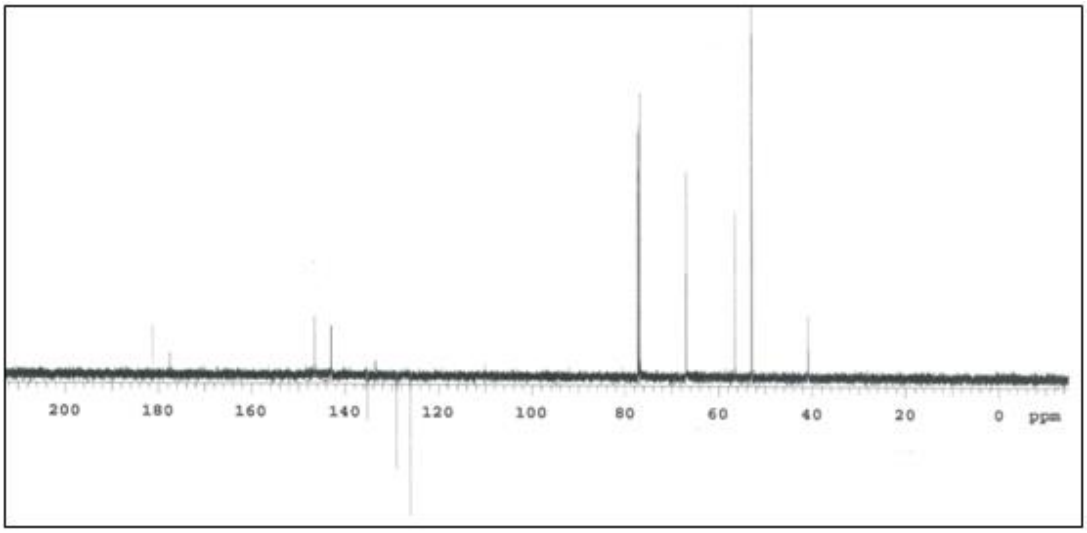


Figure 2.97: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **24**.

According to (+ESI) mass spectrum concerning the compound **24**; the molecular ion peak of a new compound ($C_{16}H_{16}ClN_3O_5$, M_w = 365.77 g/mol) was seen at *m/z* (100%) = 366.2 $[M]^+$ (Figure 2.98).

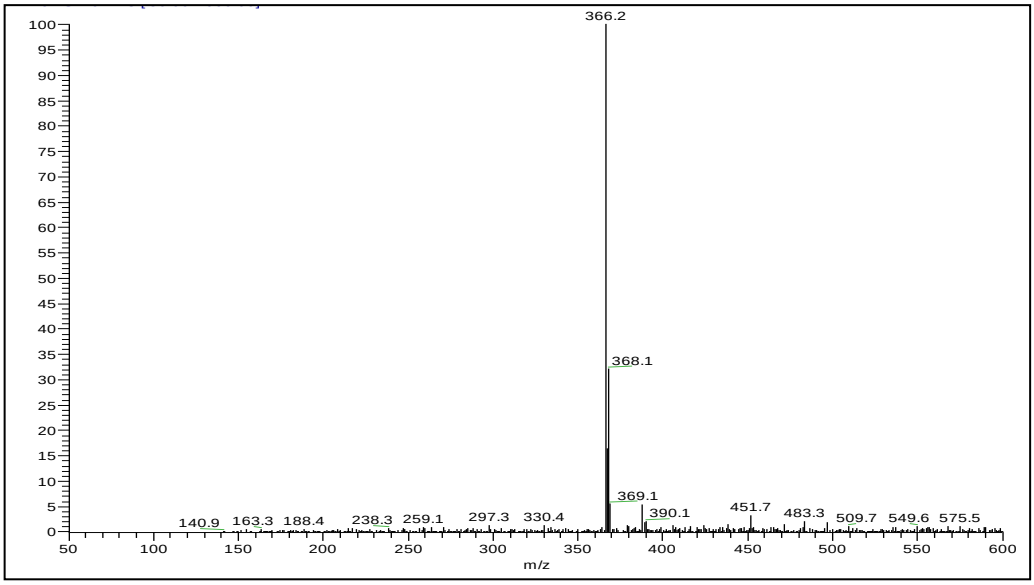


Figure 2.98: Mass spectrum [+ESI] concerning the compound **24**.

According to IR spectrum concerning the compound **25**; the (NH) band observed around ν = 3275 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) bands appeared at ν = 3080, 2957, 2894 and 2822 cm^{-1} respectively. (C=O) band appeared at ν = 1679 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1609, 1572 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at ν = 1535, 1330 cm^{-1} respectively (Figure 2.99).

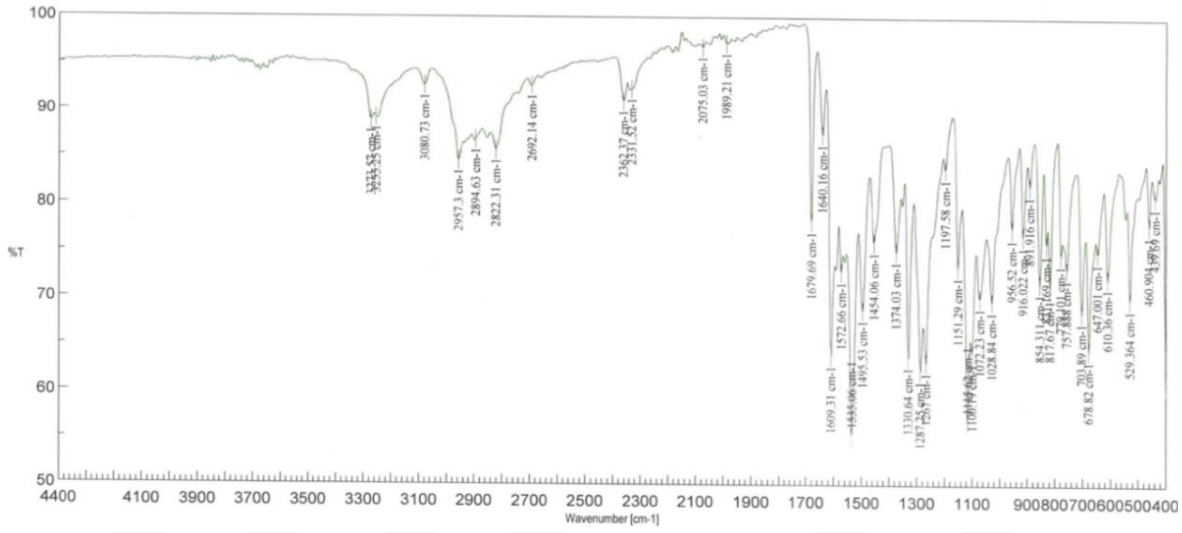


Figure 2.99: FTIR (KBr) spectrum concerning the compound **25**.

According to ^{1}H NMR spectrum concerning the compound **25**; protons of morpholine ring (C**H**$_2$-N-C**H**$_2$) and (C**H**$_2$OC**H**$_2$) were appeared at δ =2.62 and 3.70 ppm as abroad singlet, (N-C**H**$_2$CH$_2$) was seen as a broad singlet at δ = 2.73 ppm. The two protons that bonded to amino group (HN-C**H**$_2$) were detected at δ = 3.94 ppm as multiplet. (NH) proton was seen at δ = 7.06 ppm as a broad singlet. Two protons of nitro naphthoquinone were seen at δ = 7.66 and 8.23 ppm as doublet of doublet and at δ = 7.81 ppm as triplet (Figure 2.100).

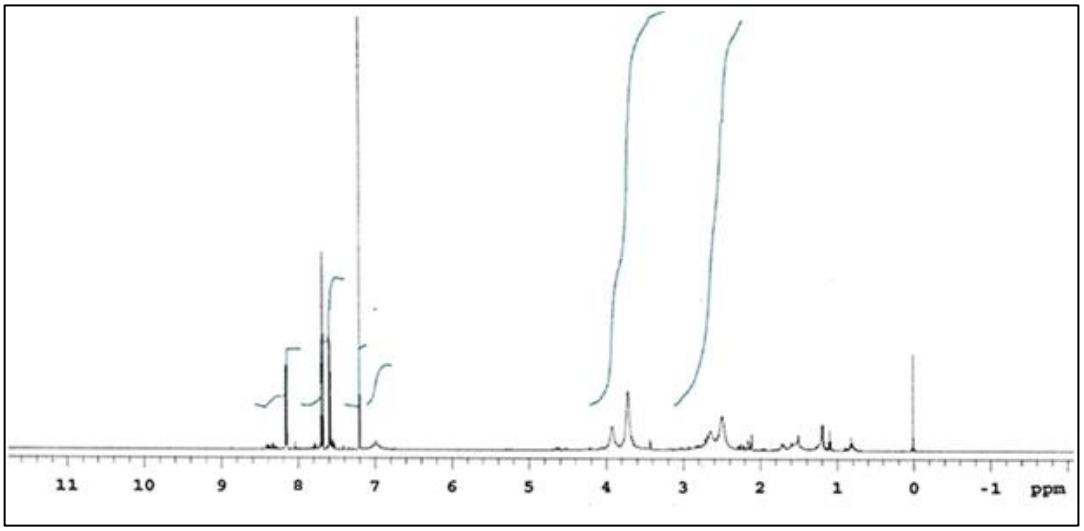


Figure 2.100: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **25**.

According to ^{13}C NMR spectrum concerning the compound **25**; (HN-**C**H_2-CH_2) and (NH-CH_2-**C**H_2), signals were appeared at δ = 48.49 and 57.13 ppm. Signals at δ = 53.28, 66.45 ppm are related to carbons of morpholine ring $(CH_2\text{-}N\text{-}CH_2)_{morph}$ and $(CH_2\text{-}O\text{-}CH_2)_{morph}$, (=C-Cl) at δ =98.63 ppm. Signals at δ =122.98, 128.71, 129.50, 133.30, 134.24 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 148.83 and 160.45 ppm are related to (C-NO_2) and (=C-N). Signals of carbonyl groups were seen at δ = 175.26, 176.76 ppm (Figure 2.101).

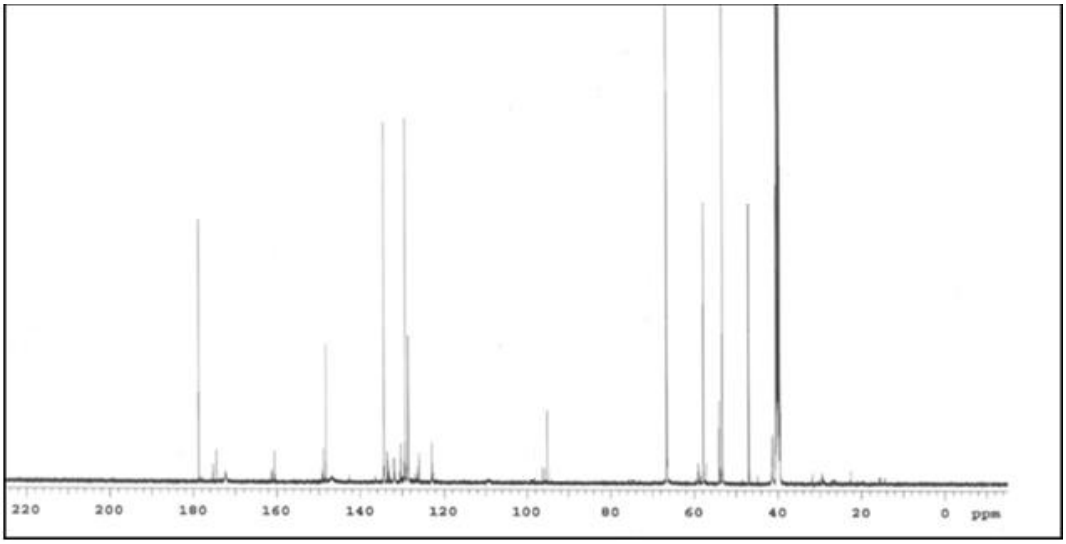


Figure 2.101: ^{13}C NMR (DMSO-d_6) spectrum concerning the compound **25**.

According to (+ESI) mass spectrum concerning the compound **25**; the molecular ion peak of a new compound ($C_{16}H_{16}ClN_3O_5$, M_w = 365.77 g/mol) was seen at *m/z* (100%) = 364.7 $[M\text{-}H]^+$ (Figure 2.102).

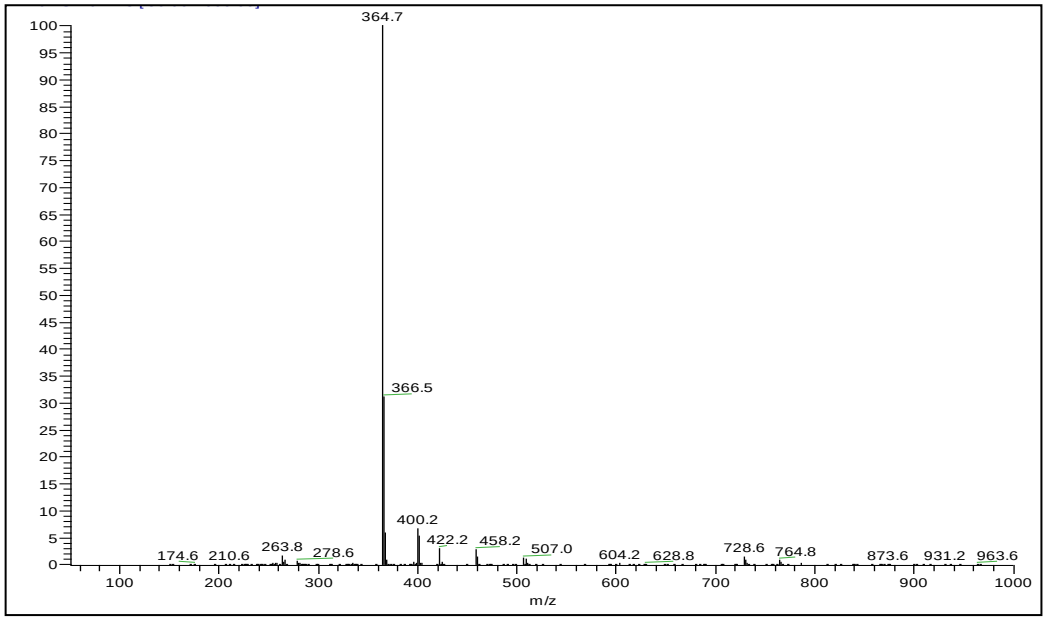


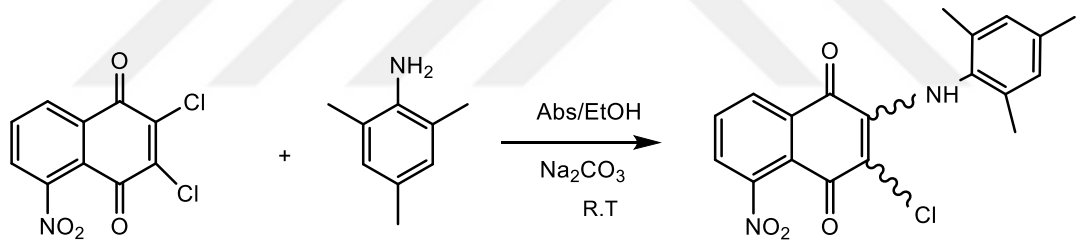
Figure 2.102: Mass spectrum [+ESI] concerning the compound **25**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(24, 25)**; we observed that the proton of naphthoquinone peaks (δ=7.65, 7.86 and 8.36 ppm) for the first isomer **(24)** are shifted more downfield than the naphthoquinone peaks (δ=7.66, 7.81and 8.23 ppm) of the second isomer **(25)**. Also, it found that the isomer **(24)** has a higher R_f component than the isomer **(25)** [89], [91].

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new regio-isomers **(24, 25)**.

2.2.7. Synthesis of 3-chloro-2-(mesitylamino)-5-nitronaphthalene-1,4-dione (26)

The new compound **(26)** obtained by refluxing the compound **(1b)** and 2,4,6-trimethylaniline in absolute ethanol in presence of sodium carbonate about 8 h as general procedure 4.



1b **26** (2.20)

According to IR spectrum concerning the compound **26**; (NH) band observed around ν = 3272 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3091, 2982 and 2904 cm^{-1} respectively. (C=O) appeared at ν = 1676, 1658 cm^{-1}. The (C=C) band was seen at ν = 1588 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1535, 1365 cm^{-1} respectively (Figure 2.103).

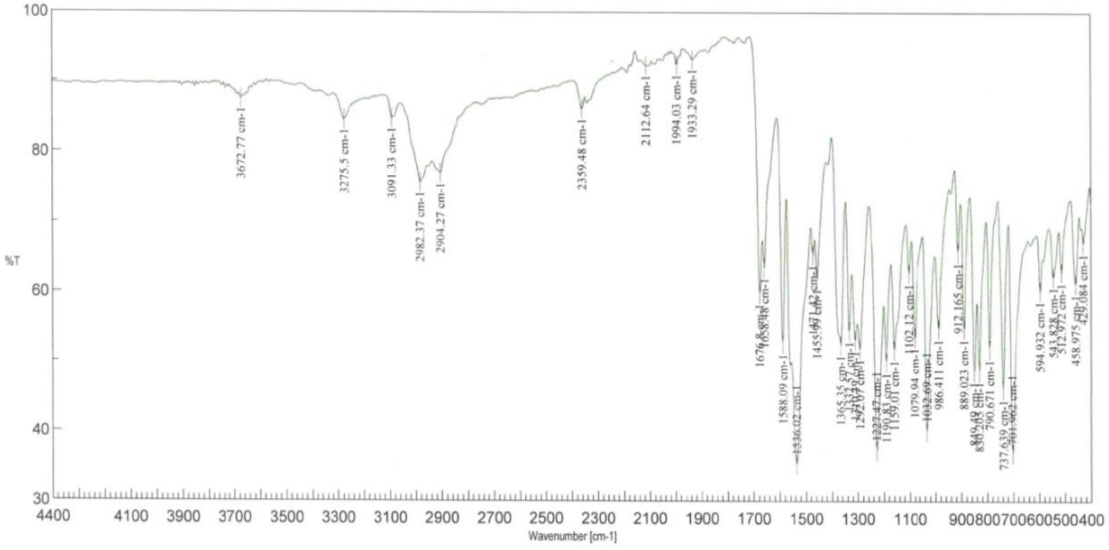


Figure 2.103: FTIR (KBr) spectrum concerning the compound **26**.

According to ^{1}H NMR spectrum concerning the compound **26**; (CH_3) protons in aromatic ring were appeared at δ = 1.31-1.37 and 2.04-2.12 ppm as a multiplet, protons of aromatic ring at δ = 6.85 ppm as a singlet. (NH) was seen around δ = 5.20 ppm as singlet. Protons of nitro naphthoquinone were seen at δ = 7.71-7.79, 7.85-7.92 and 8.31-8.35 ppm as a multiplet (Figure 2.104).

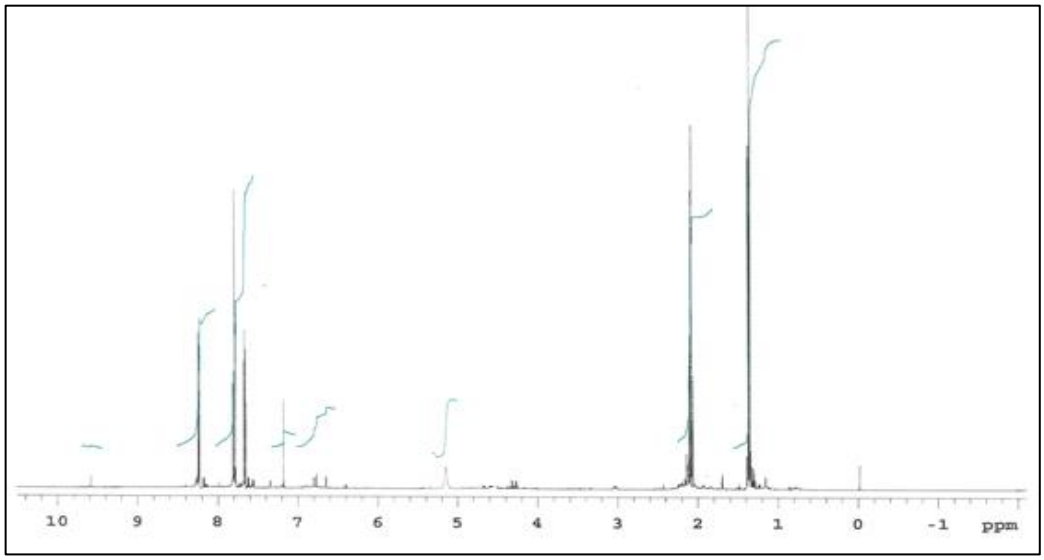


Figure 2.104: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **26**.

According to ^{13}C (APT) NMR spectrum concerning the compound **26**; methyl group (CH_3) signals were appeared at δ = 15.93 and 16.47 ppm. Signals at δ = 111.95 ppm is related to (=C-Cl). Signals of aromatic carbons (CH_{arom}, C_{arom}), were seen at δ =123.20, 126.66, 127.22, 129.03, 133.54, 134.92, 135.24 ppm. Signals at δ = 148.56 and 156.85 ppm are related to (C-NO_2) and (=C-N). Signals of carbonyl groups were seen at δ = 176.44, 177.73 ppm (Figure 2.105).

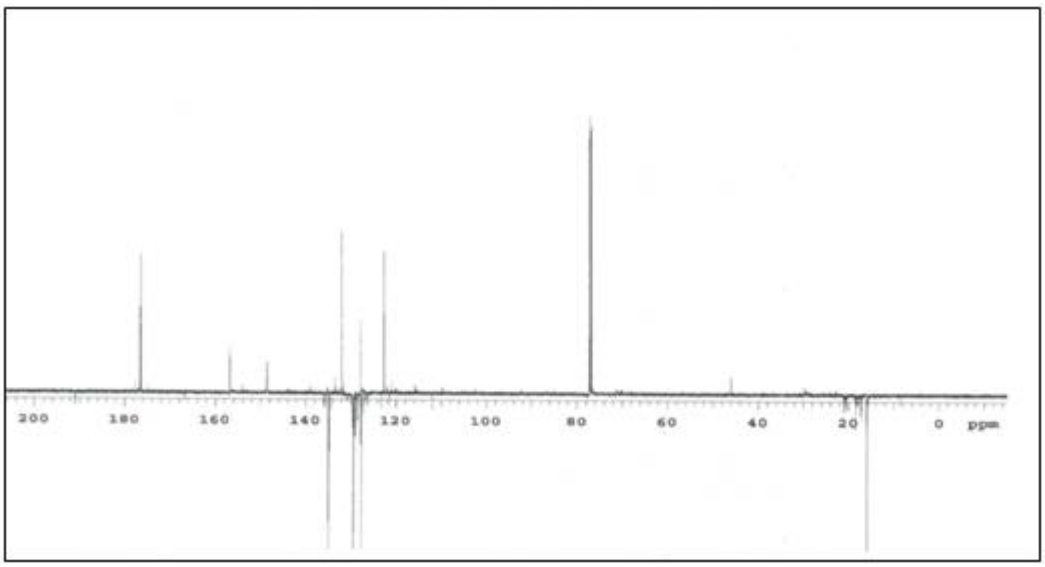


Figure 2.105: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **26**.

According to (+ESI) mass spectrum concerning the compound **26**; the molecular ion peak of a new compound ($C_{19}H_{15}ClN_2O_4$, M_w = 370.79 g/mol) was seen at *m/z* (100%) = 369.1 $[M-H]^+$ (Figure 2.106).

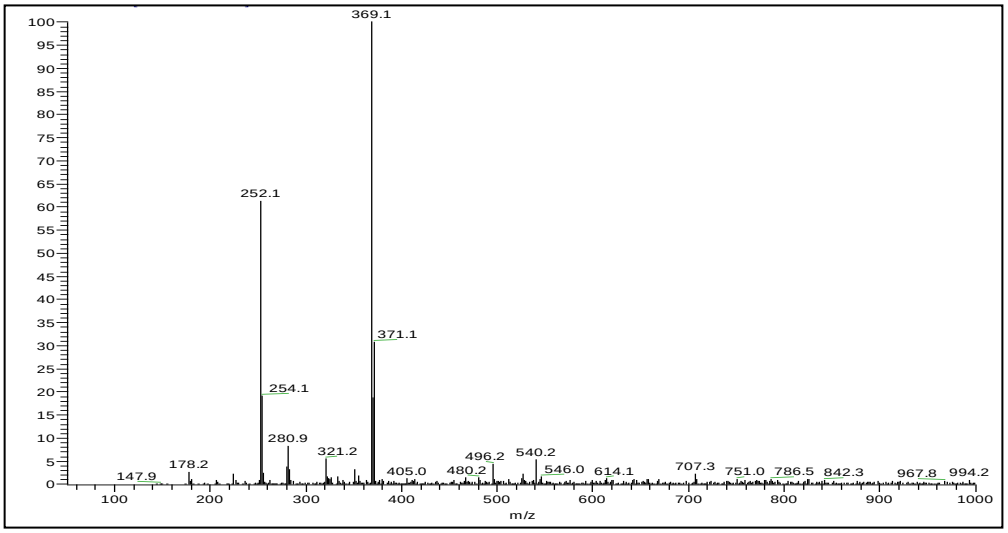
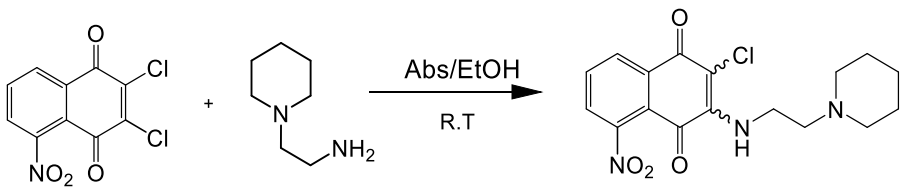


Figure 2.106: Mass spectrum [+ESI] concerning the compound **26**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(26)**.

2.2.8. Synthesis of 2-chloro-5-nitro-3-((2-(piperidin-1-yl)ethyl)amino)naphthalene-1,4-dione (27)

The new compound **(27)** obtained by the reacting compound **(1b)** with 2-(piperidin-1-yl)ethan-1-amine in Abs. Ethanol about 3-4 hours as general procedure 4.



1b **27**

(2.21)

According to IR spectrum concerning the compound **27**; (NH) band observed around ν = 3277 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3115, 2929, 2894 and 2851 cm^{-1} respectively.

(C=O) appeared at ν = 1683 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1591, 1556 cm^{-1}. Stretching asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1520, 1336 cm^{-1} respectively (Figure 2.107).

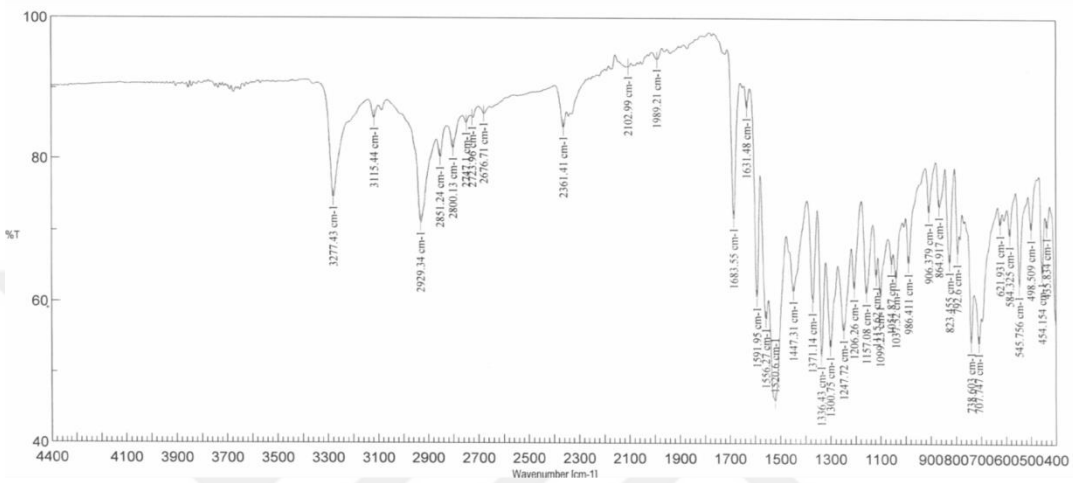


Figure 2.107: FTIR (KBr) spectrum concerning the compound **27**.

According to ^{1}H NMR spectrum concerning the compound **27**; a broad singlet at δ = 1.45-1.60 and 1.62-1.81 ppm are corresponding to piperidine ring protons (CH_2) and (C**H**$_2$-CH_2-C**H**$_2$), whereas, other protons in the ring (C**H**$_2$-N-C**H**$_2$) at δ = 2.52 ppm as broad singlet too. The two protons out of ring (CH_2-N) and that bonded to amine group (HN-C**H**$_2$) were appeared at δ = 2.68 and 3.88 ppm also as broad singlet. (NH) proton was seen at δ = 7.16 ppm as a broad singlet. Two protons of nitro naphthoquinone were seen at δ = 7.69 and 8.34 ppm as a doublet of doublet, last one as a triplet at δ = 7.81 ppm (Figure 2.108).

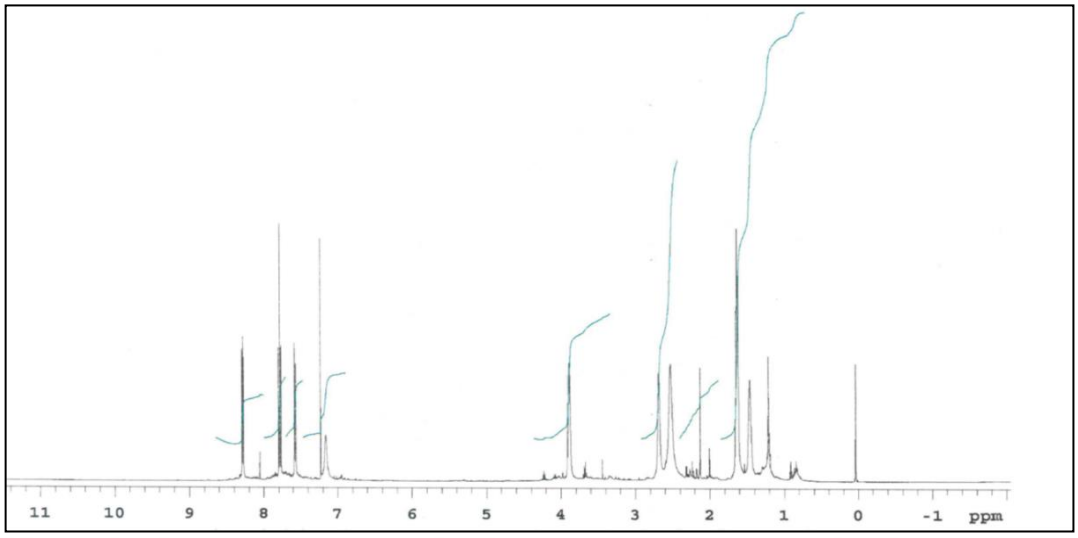


Figure 2.108: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **27**.

According to ^{13}C (APT) NMR spectrum concerning the compound **27**; piperidine ring (C-**C**H_2-C), (**C**H_2-CH_2-**C**H_2), and (CH_2-N-CH_2) signals were appeared at δ = 23.87, 25.43 and 54.04 ppm respectevely. Signals at δ = 41.01 and 56.88 ppm are related to carbons of (CH_2-N) and (HN-CH_2). Signals at δ =126.06, 128.97, 129.46, 133.52, 135.14 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 148.36 ppm are related to (=C-N). Carbonyl group was seen at δ = 177.59 ppm (Figure 2.109).

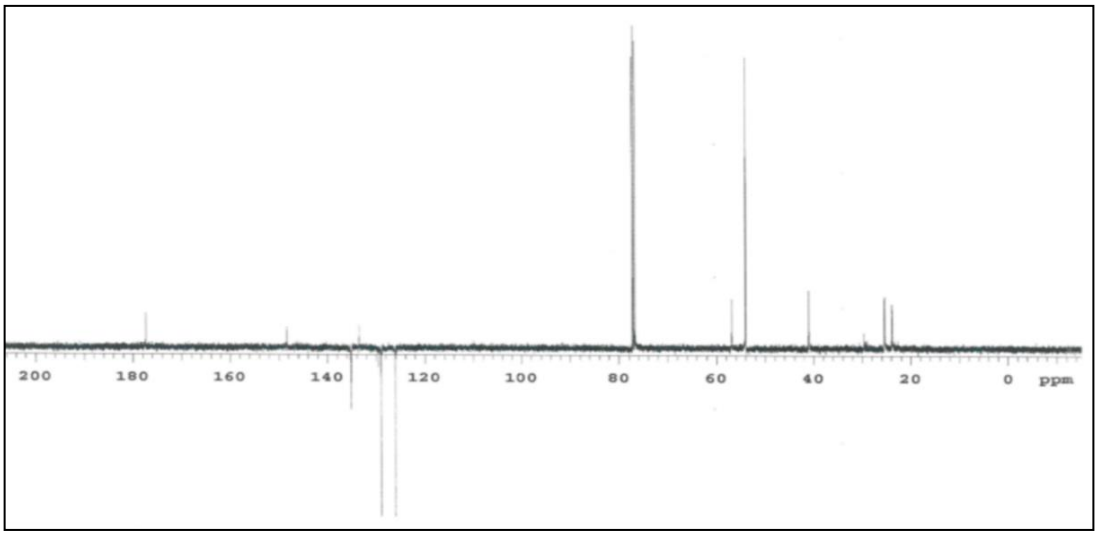


Figure 2.109: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **27**.

According to (+ESI) mass spectrum concerning the compound **27**; the molecular ion peak of a new compound ($C_{17}H_{18}ClN_3O_4$, M_w = 363.80 g/mol) was seen at *m/z* (100%) = 364.2 $[M]^+$ (Figure 2.110).

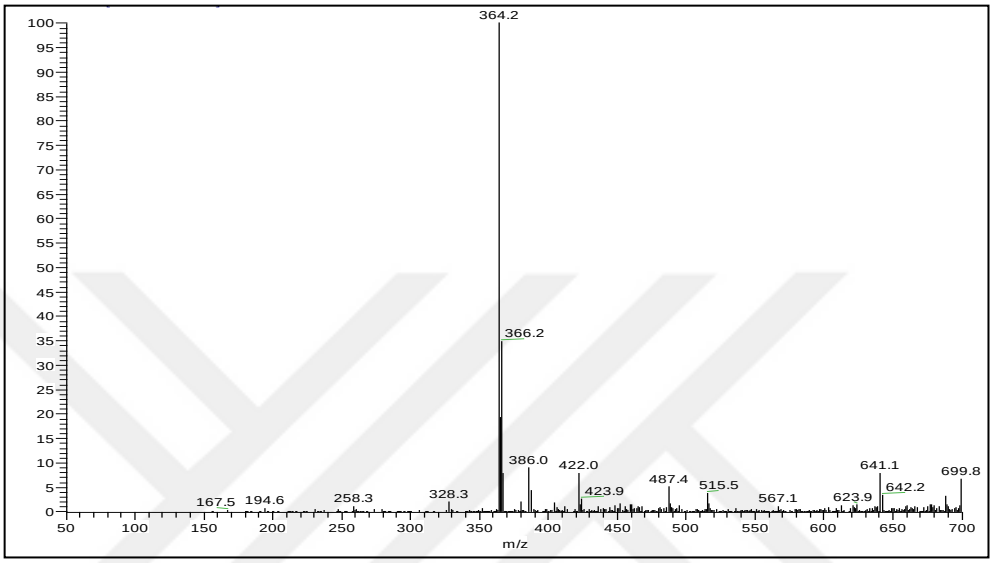


Figure 2.110: Mass spectrum [+ESI] concerning the compound **27**.

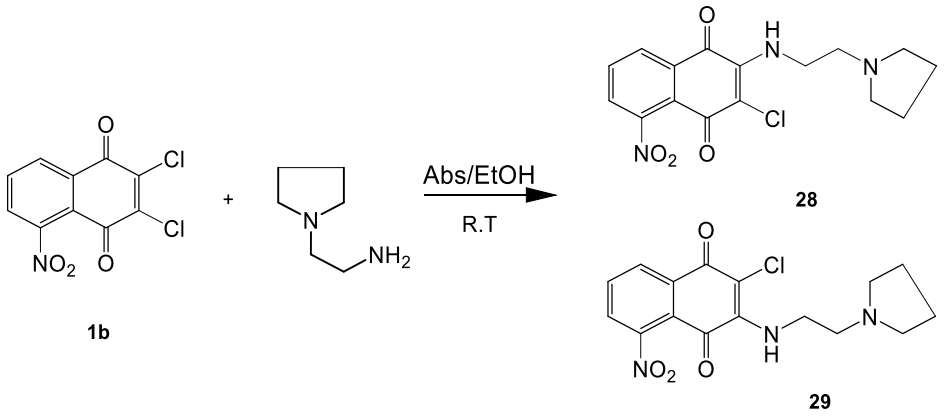
All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(27)**.

2.2.9. Synthesis of 3-chloro-5-nitro-2-((2-(pyrrolidin-1-yl)ethyl)amino)naphthalene-1,4-dione and 2-chloro-5-nitro-3-((2-(pyrrolidin-1-yl)ethyl)amino)naphthalene-1,4-dione (28, 29)

The new isomer compounds (**28**, **29**) obtained by reacting the compound **(1b)** with 2-(pyrrodin-1-yl)ethane-1-amine in Abs. Ethanol about 3-4 hours as general procedure 4.

Isomer **28**; Red solid, R_f: 0.71 (1:2 EtAc/Hexane), M.p.: 146-147°C.

Isomer **29**; Red solid, R_f: 0.33 (1:2 EtAc/Hexane), M.p.: 132-133°C.



(2.22)

According to IR spectrum concerning the compound **28**; the (NH) band observed around ν = 3281 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3112, 2958, 2871, 2789 cm^{-1} respectively. (C=O) appeared at ν = 1681 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1591, 1559 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at ν = 1525, 1335 respectively cm^{-1} (Figure 2.111).

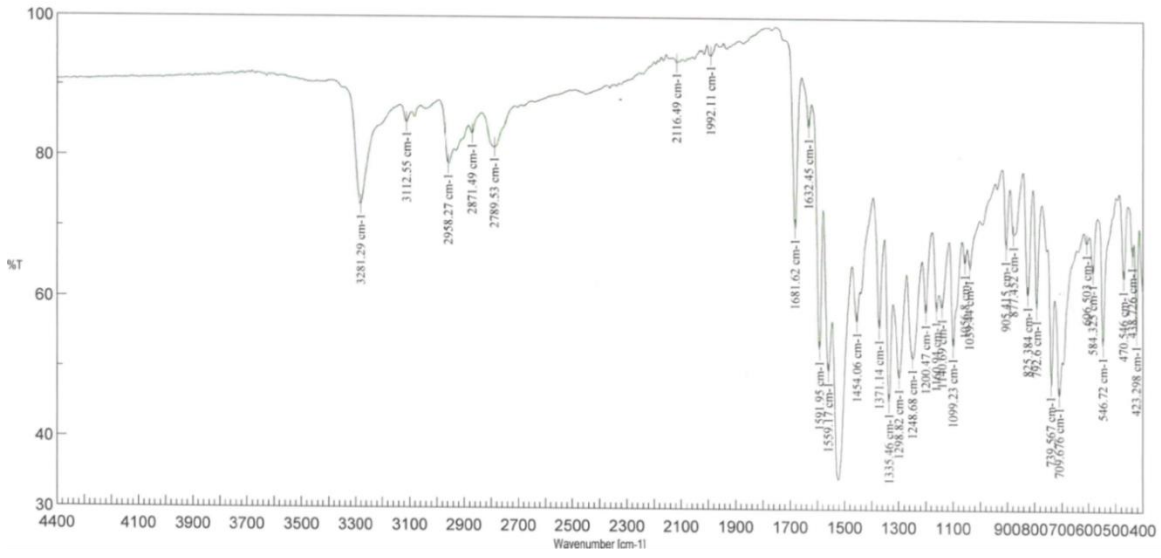


Figure 2.111: FTIR (KBr) spectrum concerning the compound **28**.

According to the ^{1}H NMR spectrum concerning the compound **28**; pyrrolidine ring protons (C**H**$_2$-C**H**$_2$) and (C**H**$_2$-N-C**H**$_2$) were appeared as broad singlet at δ = 1.72 and 2.51 ppm. The two protons out of ring (C**H**$_2$-N) and that bonded to amino group (HN-C**H**$_2$) were appeared at

δ = 2.61-2.70 and 3.82 ppm also as broad singlet. Proton (NH) was seen as a broad singlet around δ = 6.96 ppm. Two protons of nitro naphthoquinone were seen at δ = 7.61 and 8.32 ppm as a doublet, one proton as a triplet at δ = 7.79 ppm (Figure 2.112).

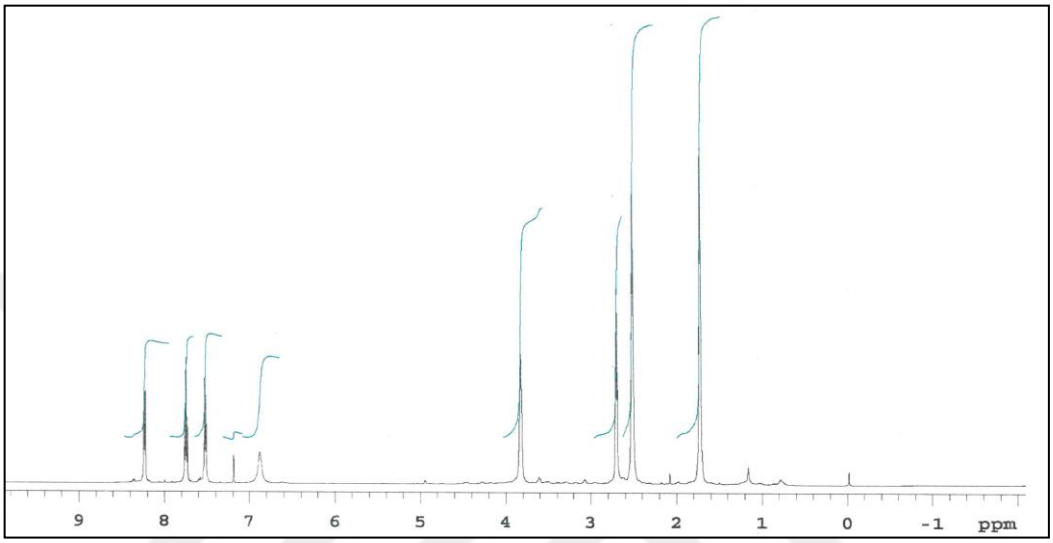


Figure 2.112: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **28**.

According to ^{13}C (APT) NMR spectrum concerning the compound **28**; pyrrolidine ring (**C**H_2-**C**H_2) and (**C**H_2-N-**C**H_2) signals were appeared at δ = 23.34 and 54.11 ppm. Signals at δ = 43.24 and 55.32 ppm are related to carbons of (**C**H_2-N) and (HN-**C**H_2). (=C-Cl) at δ =109.98 ppm Signals at δ = 126.02, 128.88, 130.91, 133.43, 135.37 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 148.23 ppm are related to (=C-N). Carbonyl groups were seen at δ = 173.95 and 177.32 ppm (Figure 2.113).

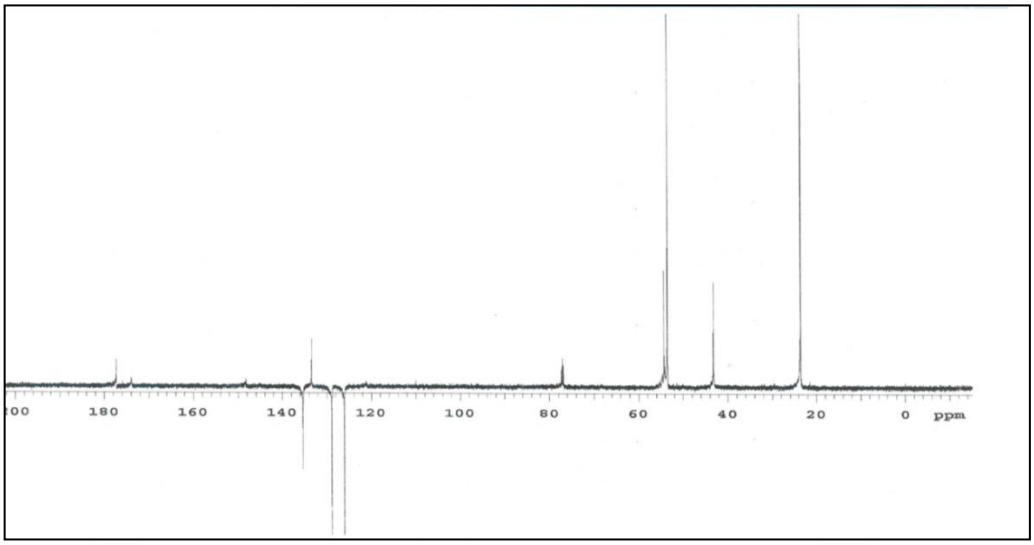


Figure 2.113: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **28**.

According to (+ESI) mass spectrum concerning the compound **28**; the molecular ion peak of a new compound ($C_{16}H_{16}ClN_3O_4$, M_w = 349.77 g/mol) was seen at *m/z* (100%) = 349.5 $[M]^+$ (Figure 2.114).

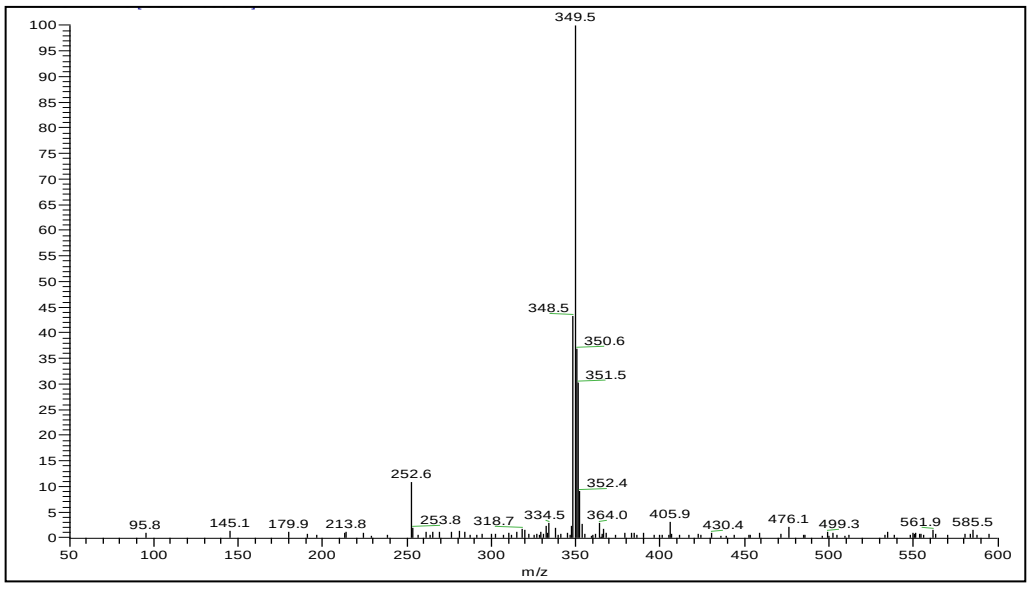


Figure 2.114: Mass spectrum [+ESI] concerning the compound **28**.

According to IR spectrum of compound **29**; (NH) band observed around ν = 3241 cm^{-1}, (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3072 and 2968 cm^{-1}, band of (C=O) appeared at ν =

1681 cm^{-1}, the (C=C) bond was seen at ν = 1590, cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1531, 1372 cm^{-1} (Figure 2.115).

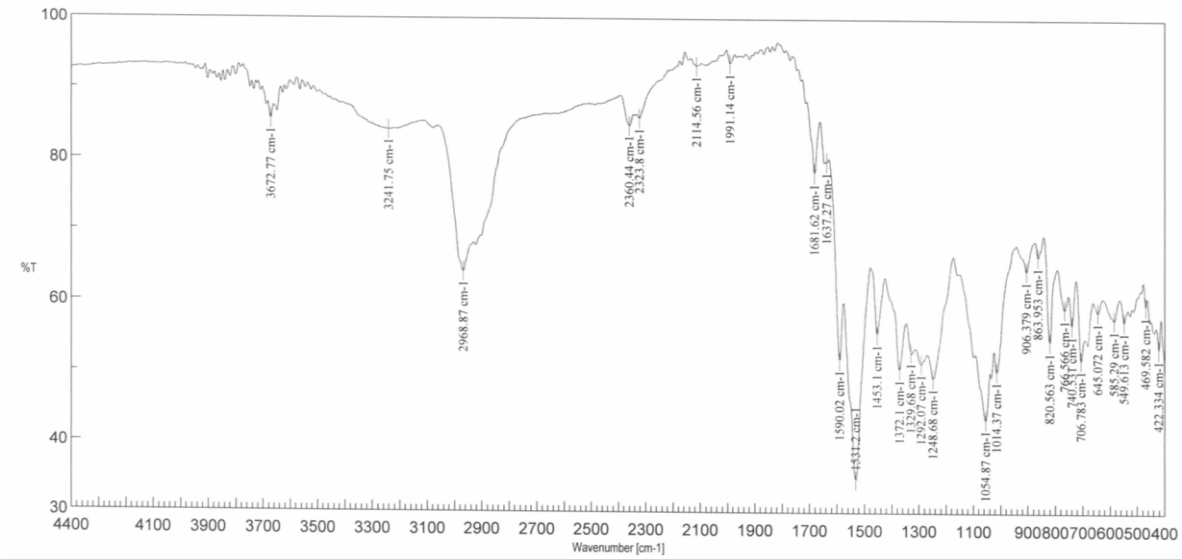


Figure 2.115: FTIR (KBr) spectrum concerning the compound **29**.

According to ^{1}H NMR spectrum concerning the compound **29**; (NH) proton was seen at δ = 6.93 ppm as a broad singlet. Protons of pyrrolidine ring (C**H**$_2$-C**H**$_2$) and (C**H**$_2$-N-C**H**$_2$) were appeared as broad singlet at δ = 1.70 and 2.48 ppm. Two protons out of ring (C**H**$_2$-N) and that bonded to amino group (HN-C**H**$_2$) were appeared at δ = 2.58-2.69 and 3.60 ppm also as a broad singlet, two protons of nitro naphthoquinone were seen at δ = 7.47 and 8.29 ppm as a doublet, one proton as a triplet at δ = 7.76 ppm (Figure 2.116).

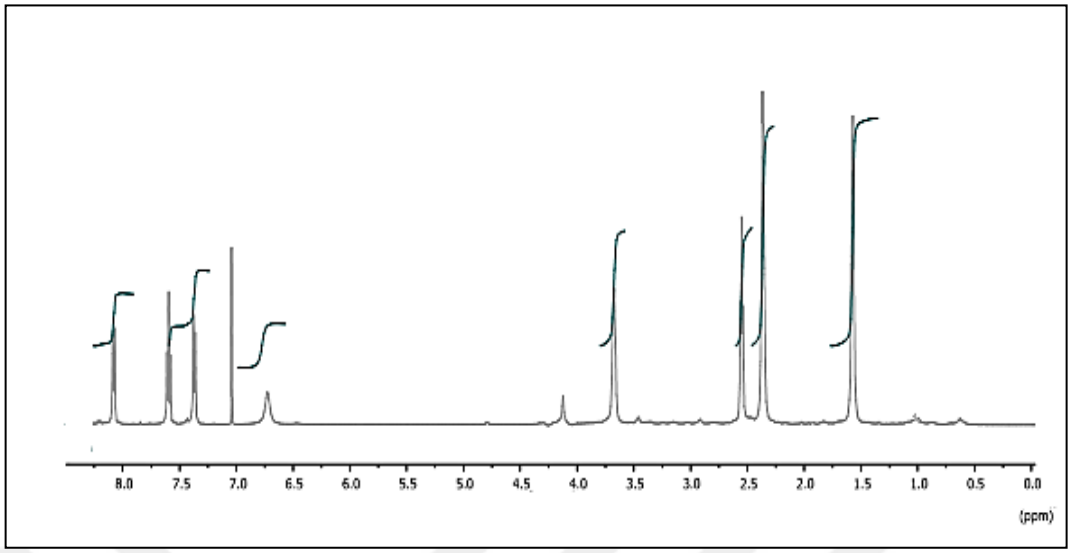


Figure 2.116: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **29**.

According to ^{13}C NMR spectrum concerning the compound **29**; pyrrolidine ring (**C**H_2-**C**H_2) and (**C**H_2-N-**C**H_2) signals were seen at δ = 23.83 and 54.05 ppm. Signals at δ = 45.17 and 60.90 ppm are related to carbons of (**C**H_2-N) and (HN-**C**H_2). (=C-Cl) at δ =103.93 ppm Signals at δ = 122.02, 126.05, 128.16, 131.35, 136.42 ppm are belonging to (CH_{arom}, C_{arom}). Signals at δ = 148.03 and 166.72 ppm are related to (=C-N) and (**C**-NO_2). Carbonyl groups were seen at δ = 172.46 and 181.90 ppm (Figure 2.117).

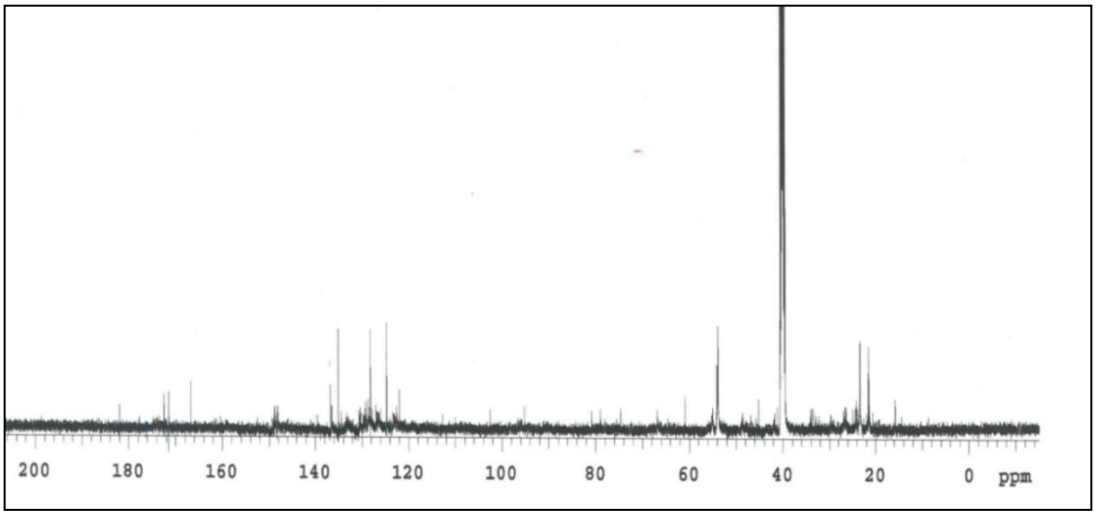


Figure 2.117: ^{13}C NMR (DMSO-d_6) spectrum concerning the compound **29**.

According to (+ESI) mass spectrum concerning the compound **29**; the molecular ion peak of a new compound ($C_{16}H_{16}ClN_3O_4$, M_w = 349.77 g/mol) was seen at *m/z* (100%) = 348.5 $[M]^+$ (Figure 2.118).

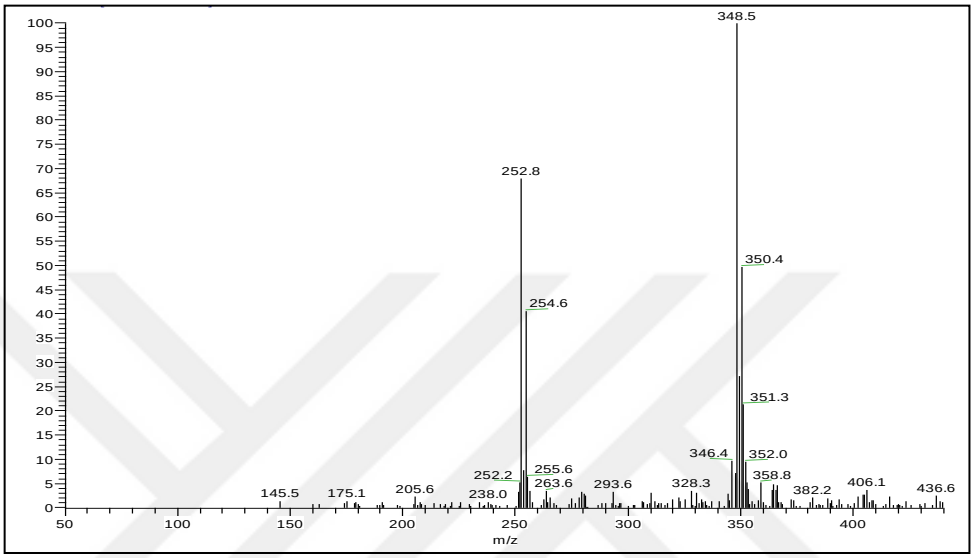


Figure 2.118: Mass spectrum [+ESI] concerning the compound **29**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(28, 29)**; we observed that the proton of naphthoquinone peaks (δ=7.61, 7.79 and 8.32 ppm) for the first isomer **(28)** are shifted more downfield than the naphthoquinone peaks (δ= 7.47, 7.76 and 8.29 ppm) of the second isomer **(29)**. Also, it found that the isomer **(28)** has a higher R_f component than the isomer **(29)** [89], [91].

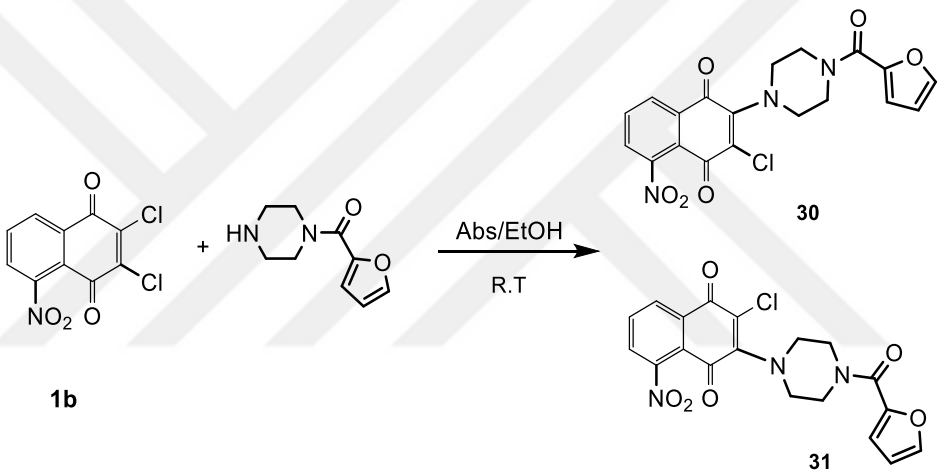
All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new regio-isomers **(28, 29)**.

2.2.10. Synthesis of 3-chloro-2-(4-(furan-2-carbonyl)piperazin-1-yl)-5-nitronaphthalene-1,4-dione and 2-chloro-3-(4-(furan-2-carbonyl)piperazin-1-yl)-5-nitronaphthalene-1,4-dione (30, 31)

The new isomer compounds (**30**, **31**) obtained by reacting the compound **(1b)** with 1-(2-furoyl) piperazine in Abs. Ethanol for 3-4 hours as general procedure 4.

Isomer **30**; Purple solid, R_f: 0.61 (1:2 EtAc/PET), M.p.: 148-149°C.

Isomer **31**; Red solid, R_f: 0.45 (1:2 EtAc/PET), M.p.: 178-180°C.



(2.23)

According to the IR spectrum of compound **30**; stretching bands of ($C\text{-}H_{arom}$) appeared at ν = 3141 and 3101 cm^{-1} and stretching bands of ($C\text{-}H_{aliph}$) observed at ν = 2927, 2855 cm^{-1}, carbonyl group bands (C=O) appeared at ν = 1724, 1677, 1648 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1610, 1588 cm^{-1}. Stretching (asymmetric, symmetric) bands of ($C\text{-}NO_2$) were appeared at ν = 1522, 1416 cm^{-1} respectively (Figure 2.119).

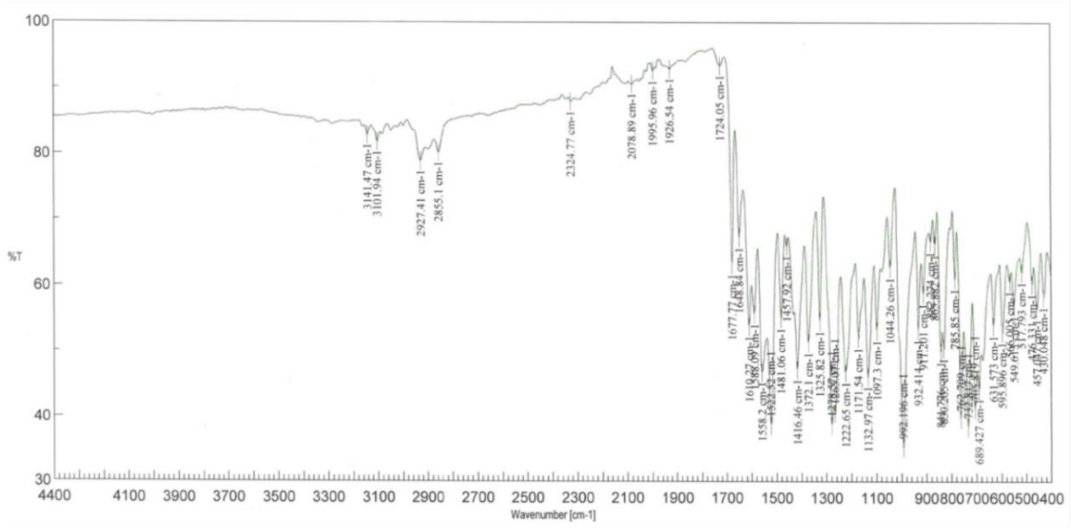


Figure 2.119: FTIR (KBr) spectrum concerning the compound **30**.

According to ^{1}H NMR spectrum concerning the compound **30**; piperazine (CH_2NCH_2) were detected at δ = 3.62 ppm and 3.94 ppm as a broad singlet. Protons of furan ring (CH_{furan}) were seen at δ = 6.50- 6.56, 7.10 and 7.44-7.49 ppm as a multiplet. Protons of naphthoquinone, two of them ware appeared at δ = 7.72-7.80, 8.12-8.18 ppm as a multiplet and the other at 8.35 ppm as a doublet of doublet (Figure 2.120).

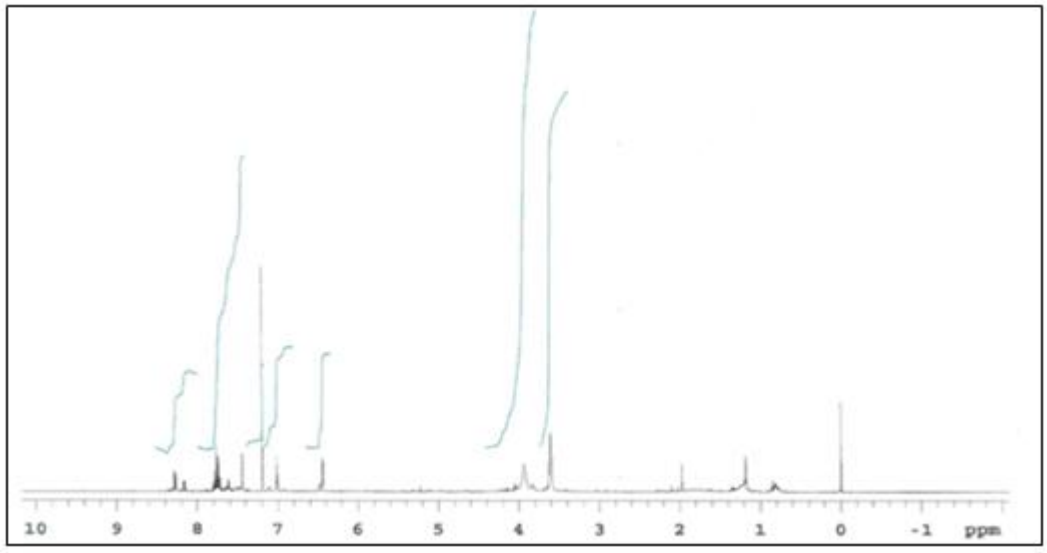


Figure 2.120: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **30**.

According to the ^{13}C (APT) NMR spectrum concerning the compound **30**; carbons in piperazine ring (**C**H_2-N-**C**H_2)$_{piper}$ gave two signals at δ = 40.73, 51.41 ppm. (=C-Cl) at 111.52 ppm. Furan ring gave four signals (C_{furan}, CH_{furan}) at δ =111.89, 117.27, 147.57, 148.54 ppm. Signals at δ =122.58, 124.74, 127.97, 130.87, 134.99 ppm for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) was appeared at δ = 150.26 ppm. The last signals at δ =159.15, 175.88 and 179.81 ppm related to carbon of carbonyl groups (Figure 2.121).

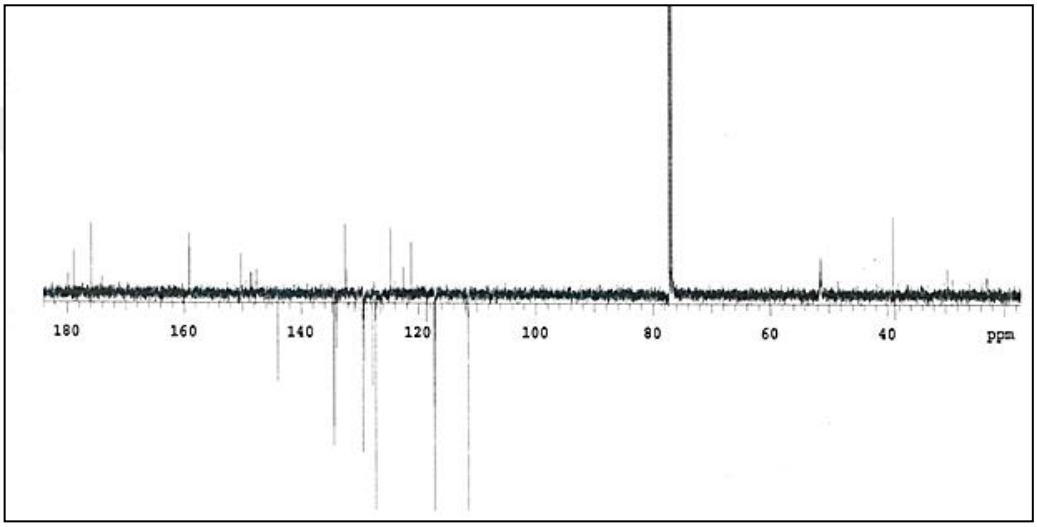


Figure 2.121: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **30**.

According to (+ESI) mass spectrum concerning the compound **30**; the molecular ion peak of a new compound ($C_{19}H_{14}ClN_3O_6$, M_w = 415.79 g/mol) was seen at *m/z* (100%) = 415.3 $[M-H]^+$ (Figure 2.122).

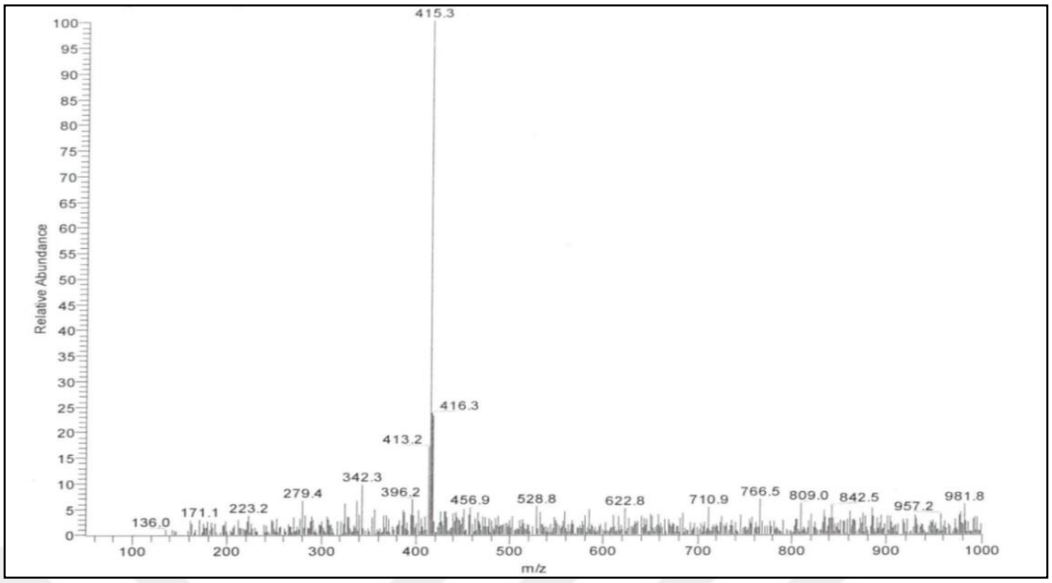


Figure 2.122: Mass spectrum [+ESI] concerning the compound **30**.

According to the IR spectrum of compound **31**; stretching bands of (C-H_{arom}) appeared at ν = 3137 and 3068 cm^{-1} and stretching band of (C-H_{aliph}) observed at ν = 2921 cm^{-1}, carbonyl group bands (C=O) appeared at ν = 1724, 1682, 1646 cm^{-1}, the bands of carbon-carbon double bond (C=C) were seen at ν = 1617, 1589 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at ν = 1538, 1428 cm^{-1} respectively (Figure 2.123).

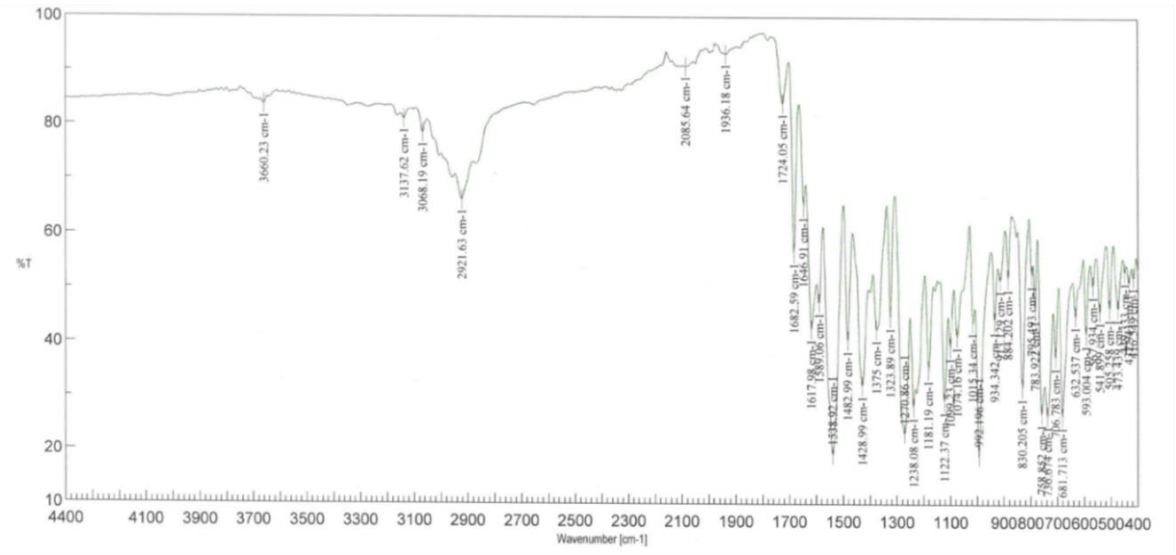


Figure 2.123: FTIR (KBr) spectrum concerning the compound **31**.

According to ^{1}H NMR spectrum concerning the compound **31**; piperazine ring appeared at δ =3.64 and 3.90 ppm as a singlet and abroad singlet respectively. Protons of furan ring (CH_{furan}) were seen at δ = 6.42-6.48, 7.00 and 7.42-7.48 ppm as a multiplet, Protons of naphthoquinone, two of them were appeared at δ = 7.60-7.68 and 7.72-7.80 ppm as multiplet and the other at δ = 8.30 ppm as doublet of doublet (Figure 2.124).

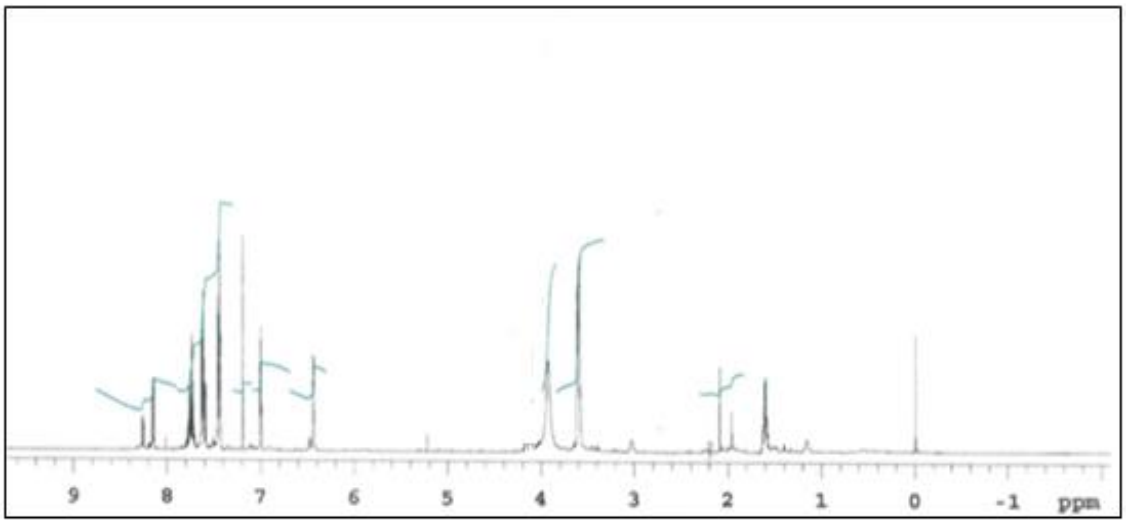


Figure 2.124: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **31**.

According to ^{13}C (APT) NMR spectrum concerning the compound **31**; carbons in piperazine ring ($\mathbf{C}H_2$-N-$\mathbf{C}H_2)_{piper}$ gave two signals at δ = 45.91, 51.34 ppm. (=C-Cl) at 111.44 ppm. Furan ring gave four signals (C_{furan}, CH_{furan}) at δ =111.54, 117.26, 147.56, 149.33 ppm. Signals at δ =122.53, 124.74, 127.76, 129.25, 132.24, 134.43 ppm for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) was appeared at δ =159.15 ppm. The last signals at δ =167.74, 174.09 and 179.78 ppm related to carbon of carbonyl groups (Figure 2.125).

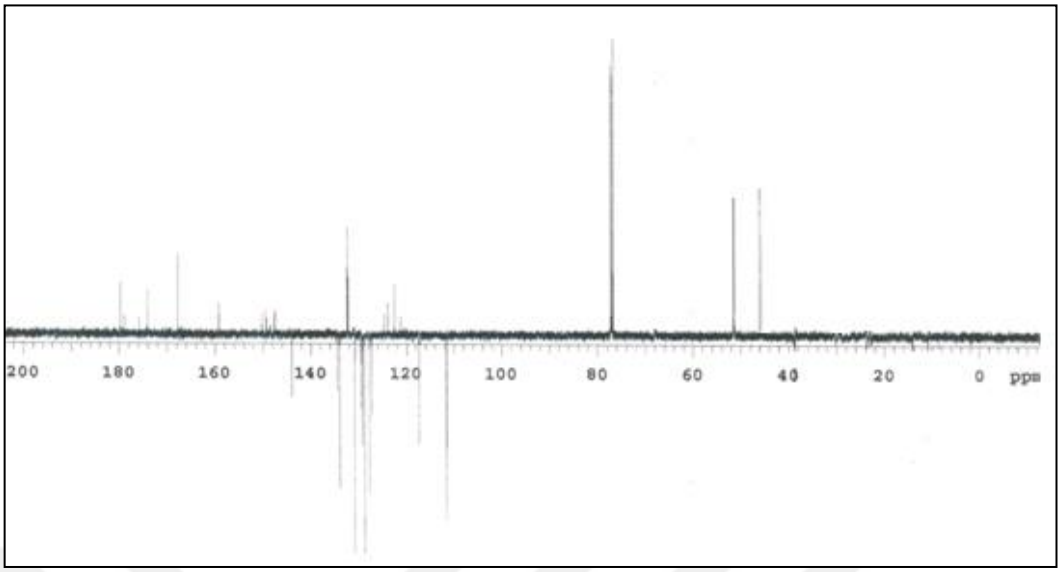


Figure 2.125: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **31**.

According to (+ESI) mass spectrum concerning the compound **31**; the molecular ion peak of a new compound ($C_{19}H_{14}ClN_3O_6$, M_w = 415.79 g/mol) was seen at *m/z* (100%) = 413.2 $[M-3H]^+$ (Figure 2.126).

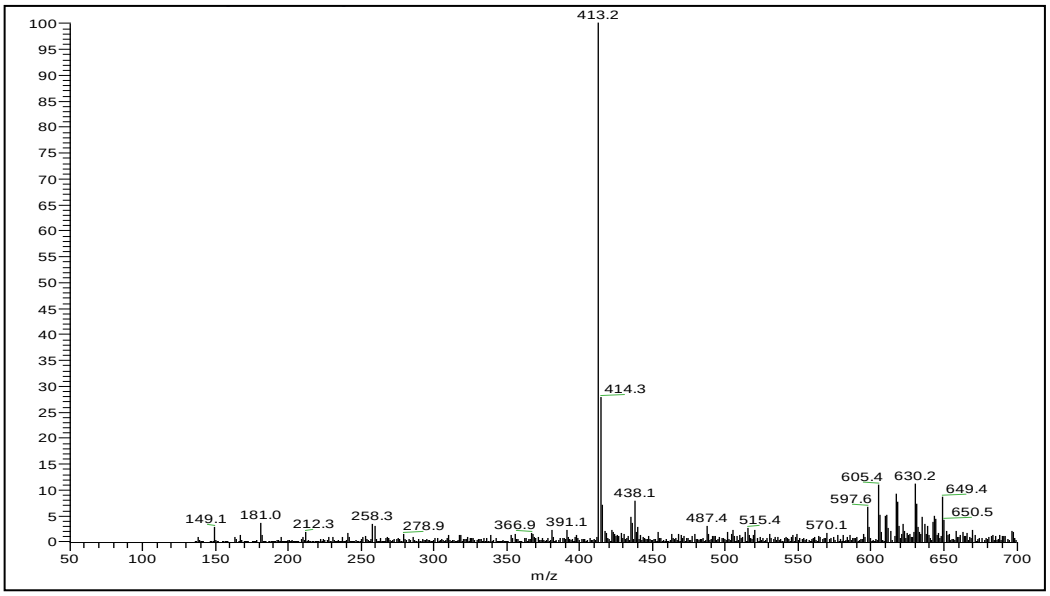


Figure 2.126: Mass spectrum [+ESI] concerning the compound **31**.

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(30, 31)**; we observed that the proton of naphthoquinone peaks (δ=7.72-7.80, 8.12-8.18 and 8.35 ppm) for the first isomer **(30)** are shifted more downfield than the naphthoquinone peaks (δ=7.60-7.68, 7.72-7.80 and 8.30 ppm) of the second isomer **(31)**. Also, it found that the isomer **(30)** has a higher R_f component than the isomer **(31)** [89], [91].

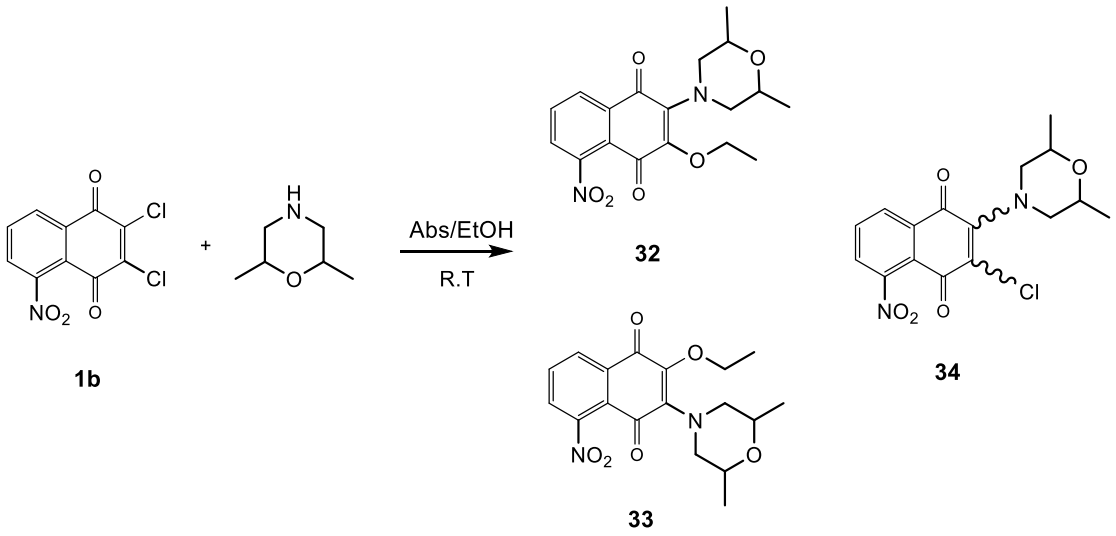
All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new regio-isomers **(30, 31)**.

2.2.11. Synthesis of 2-(2,6-dimethylmorpholino)-3-ethoxy-5-nitronaphthalene-1,4-dione, 3-(2,6-dimethylmorpholino)-2-ethoxy-5-nitronaphthalene-1,4-dione and 3-chloro-2-(2,6-dimethylmorpholino)-5-nitronaphthalene-1,4-dione (32, 33, 34)

The new isomer compounds (**32**, **33**) and compound **(34)** obtained by reaction of starting compound **(1b)** with 2,6-dimethylmorpholine in Abs. Ethanol about 3-4 h, as procedure 4.

Isomer **32**; Pink solid, R_f: 0.51 (1:4 EtAc/PET), M.p.: 146-147°C.

Isomer **33**; Pink solid, R_f: 0.40 (1:4 EtAc/PET), M.p.: 155-156°C.



(2.24)

According to the IR spectrum of compound **32**; stretching bands of ($C-H_{arom}$) appeared at ν =3082 cm^{-1} and stretching bands of ($C-H_{aliph}$) observed at ν = 2963, 2889 and 2865 cm^{-1}, (C=O) appeared at ν = 1680 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen

at ν = 1642, 1591 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at 1526, 1370 cm^{-1} respectively. C-O band was appeared at ν = 1219 cm^{-1}. (Figure 2.127).

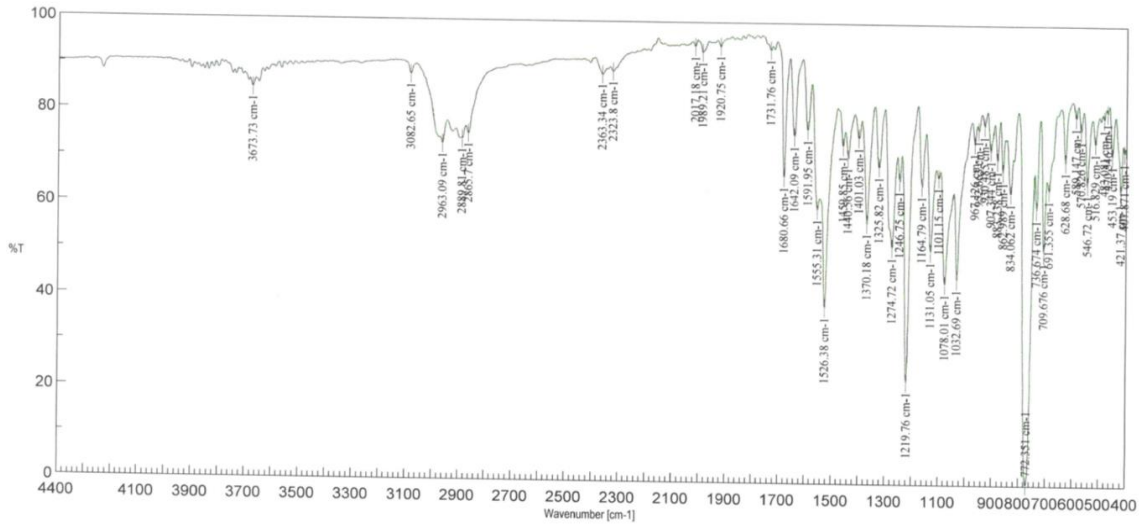


Figure 2.127: FTIR (KBr) spectrum concerning the compound **32**.

According to the ^{1}H NMR spectrum concerning the compound **32**; two methyl groups (CH_3) in morpholine ring were seen as a singlet at δ = 1.14 ppm, whereas, protons of methyl in ethoxy group (O-$CH_2C\mathbf{H}_3$) detected at δ = 1.31-1.33 ppm as a multiplet. Morpholine ring protons (CH_2-N-CH_2) and (CH) were found at δ = 3.00 and δ = 3.59-3.64 ppm. (O-C$\mathbf{H}_2CH_3$) signal was seen at 3.74-3.80 ppm as a multiplet. Signals at δ =7.76-7.85 and 8.35 ppm are corresponding to naphthoquinone protons (Figure 2.128).

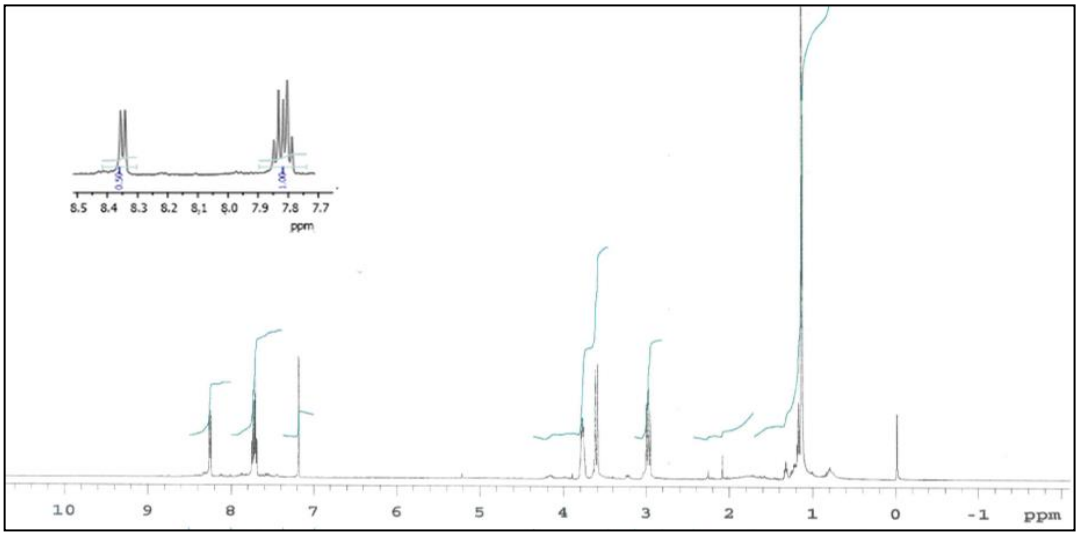


Figure 2.128: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **32**.

According to ^{13}C (APT) NMR spectrum concerning the compound **32**; methyl group signal in ethoxy (CH_3) was found at δ = 17.37 ppm, while methyl groups in morpholine ring $(CH_3)_{morph}$ at δ =18.59 ppm, signals of $(CH_2)_{ethoxy}$ and $(\mathbf{C}H_2\text{-}N\text{-}\mathbf{C}H_2)_{morph}$ at δ = 56.03 and 56.87 ppm whereas $(\mathbf{C}H\text{-}O\text{-}\mathbf{C}H)_{morph}$ at δ = 72.47 ppm. Aromatic carbons (CH_{arom}, C_{arom}) were seen at δ =122.69, 127.16, 129.18, 130.91, 132.34, 134.22 ppm, (=C-N-) was appeared at δ =148.91 ppm, however, signals corresponding to carbonyl groups (C=O) were detected at δ =173.98, and 179.90 ppm (Figure 2.129).

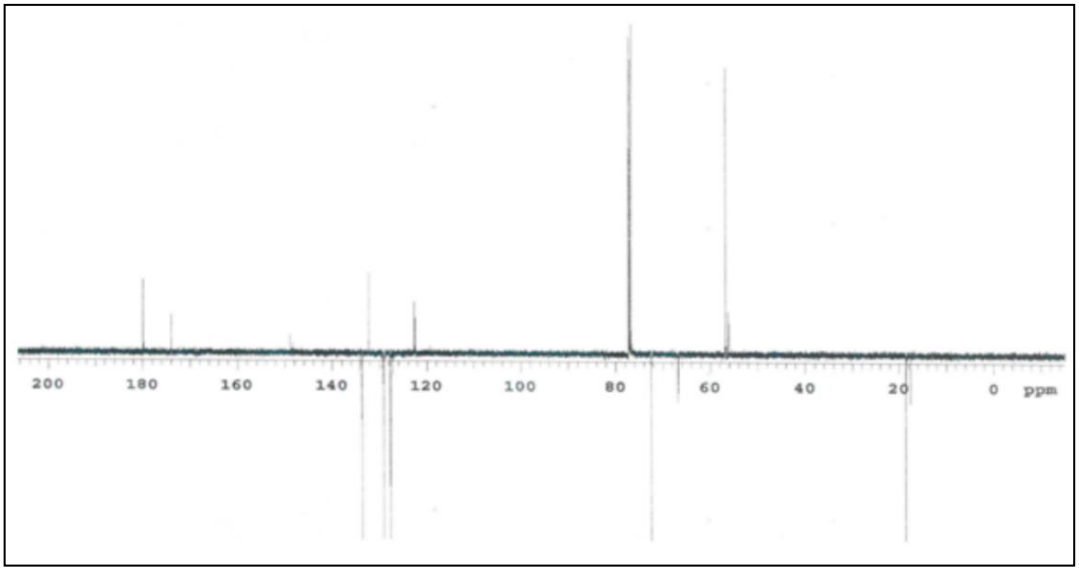


Figure 2.129: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **32**.

According to (+ESI) mass spectrum concerning the compound **32**; the molecular ion peak of a new compound ($C_{18}H_{20}N_2O_6$, M_w = 360.37 g/mol) was seen at *m/z* (100%) = 361.7 $[M+2H]^+$. Peak of $[M+Na]^+$was shown at *m/z* = 381.6. (Figure 2.130).

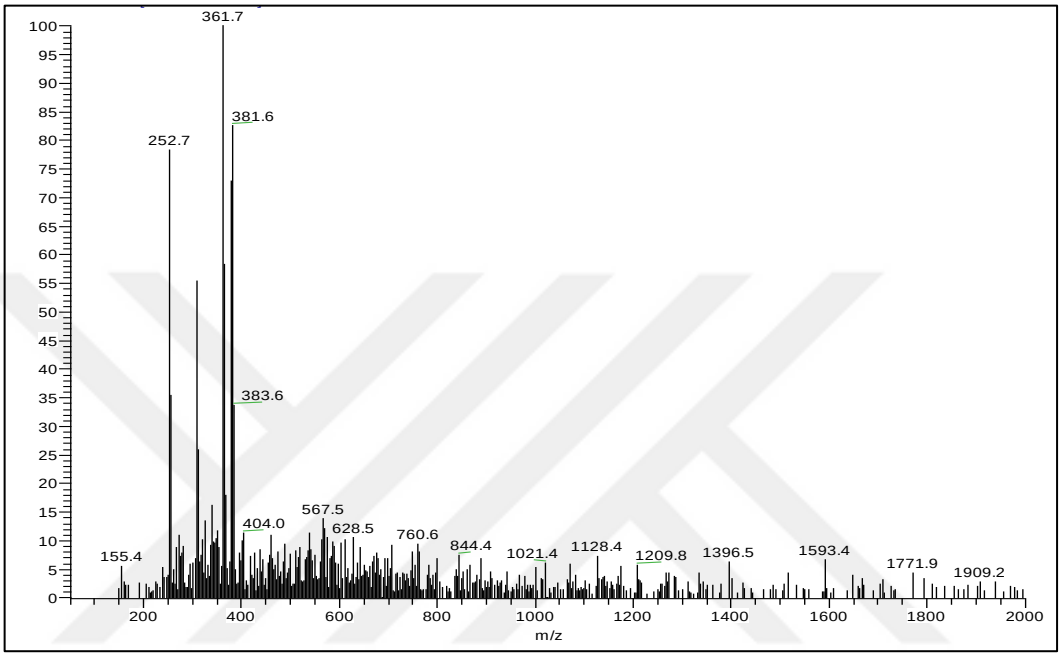


Figure 2.130: Mass spectrum [+ESI] concerning the compound **32**.

According to the IR spectrum of compound **33**; stretching bands of ($C\text{-}H_{arom}$) appeared at ν =3083 cm^{-1} and stretching bands of ($C\text{-}H_{aliph}$) observed at ν = 2972, 2904 cm^{-1}, (C=O) appeared at ν = 1679 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1646, 1592 cm^{-1}. Stretching (asymmetric, symmetric) bands for ($C\text{-}NO_2$) were appeared at 1527, 1370 cm^{-1} respectively. C-O band was appeared at ν = 1219 cm^{-1}. (Figure 2.131).

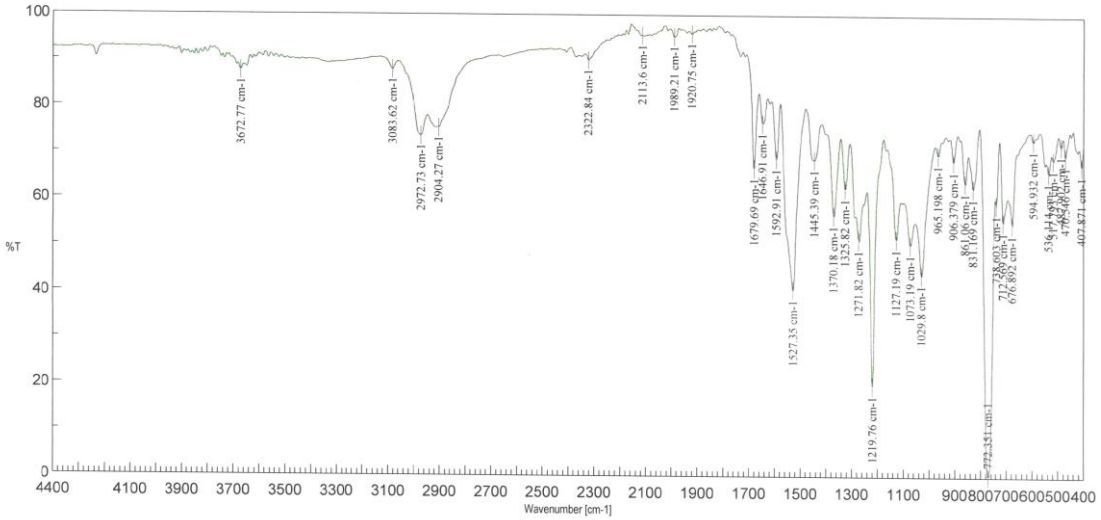


Figure 2.131: FTIR (KBr) spectrum concerning the compound **33**.

According to the ^{1}H NMR spectrum concerning the compound **33**; two methyl groups (CH_3) in morpholine ring were observed as a singlet around δ=1.20 ppm, whereas, protons of methyl in ethoxy group (O-CH_2C**H**$_3$) detected at δ=1.32-1.35 ppm as triplet. Morpholine ring protons (CH_2-N-CH_2) and (CH) were found at δ = 3.23-3.27 and δ = 3.46-3.67 ppm as a triplet. (O-C**H**$_2$$CH_3$) signal was seen at 4.17-4.21 ppm as a multiplet. Signals at δ =7.79-7.84 and 8.33 ppm are corresponding to naphthoquinone protons (Figure 2.132).

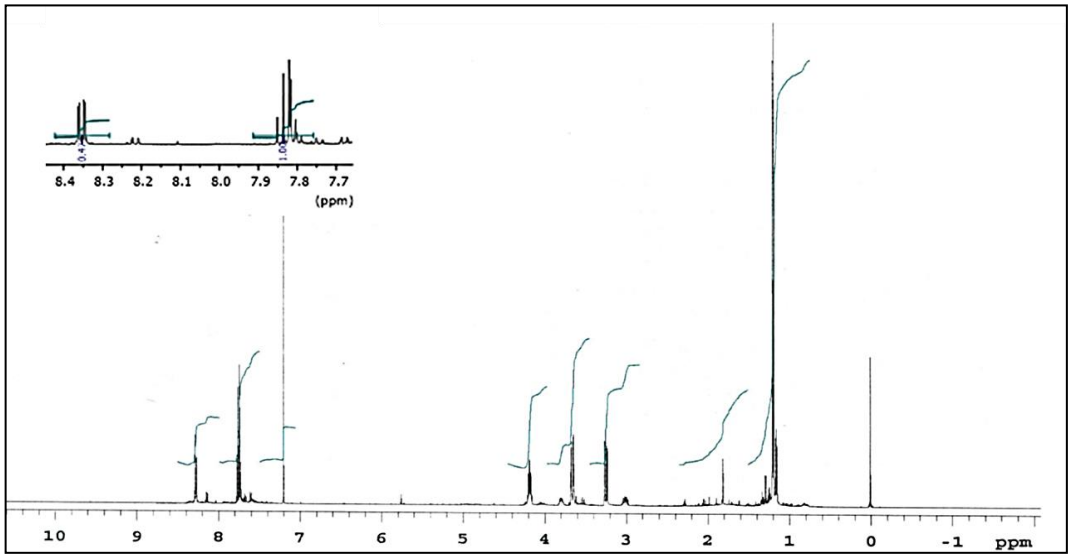


Figure 2.132: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **33**.

According to ^{13}C (APT) NMR spectrum concerning the compound **33**; carbon signal of methyl groups in morpholine ring $(CH_3)_{morph}$ was found at δ = 17.57 ppm, while methyl group in ethoxy (CH_3) at δ =18.59 ppm, signals of ($\mathbf{C}H_2$-N-$\mathbf{C}H_2$)$_{morph}$ and $(CH_2)_{ethoxy}$ at δ = 56.04 and 56.87 ppm whereas, ($\mathbf{C}$H-O-$\mathbf{C}$H)$_{morph}$ at δ = 66.78 ppm. Aromatic carbons (CH_{arom}, C_{arom}) were seen at δ =119.37, 125.18, 127.69, 129.47, 132.66, 134.19 ppm, (=C-N) was appeared at δ =150.87 ppm, however, signal corresponding to carbonyl groups (C=O) were detected at δ = 176.63, 179.05 ppm (Figure 2.133).

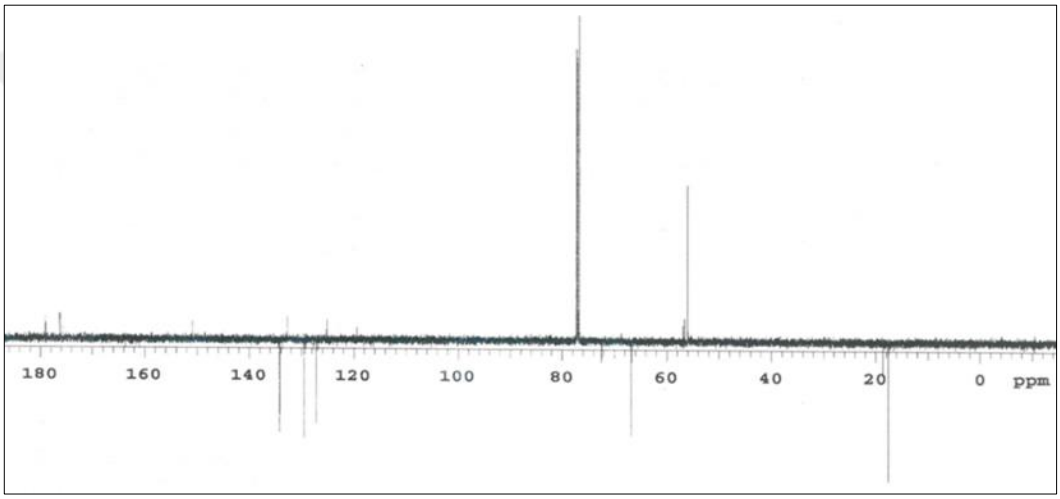


Figure 2.133: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **33**.

According to (+ESI) mass spectrum concerning the compound **33**; the molecular ion peak of a new compound ($C_{18}H_{20}N_2O_6$, M_w = 360.37 g/mol) was seen at *m/z* (100%) = 361.7 $[M+2H]^+$. $[M+Na]^+$ peak appeared at *m/z* = 381.7 (Figure 2.134).

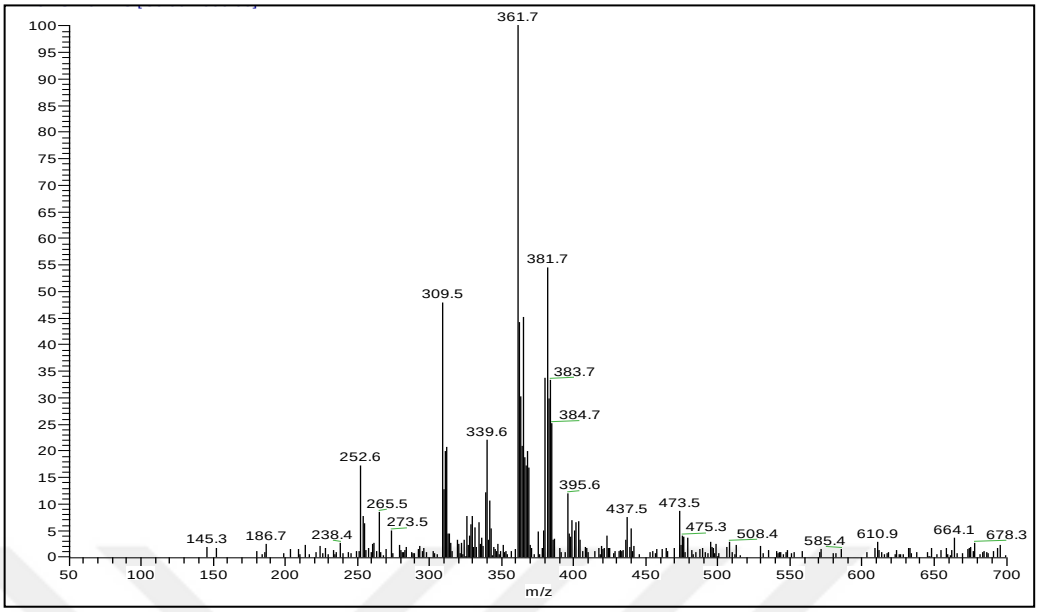


Figure 2.134: Mass spectrum [+ESI] concerning the compound **33**.

According to the IR spectrum of compound **34**; stretching bands of (C-H_{arom}) appeared at ν =3093 and 3035 cm^{-1} and stretching bands of (C-H_{aliph}) observed at ν = 2972, 2927 and 2900 cm^{-1}, (C=O) appeared at ν = 1684 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1632, 1590 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at 1530, 1371 cm^{-1} respectively (Figure 2.135).

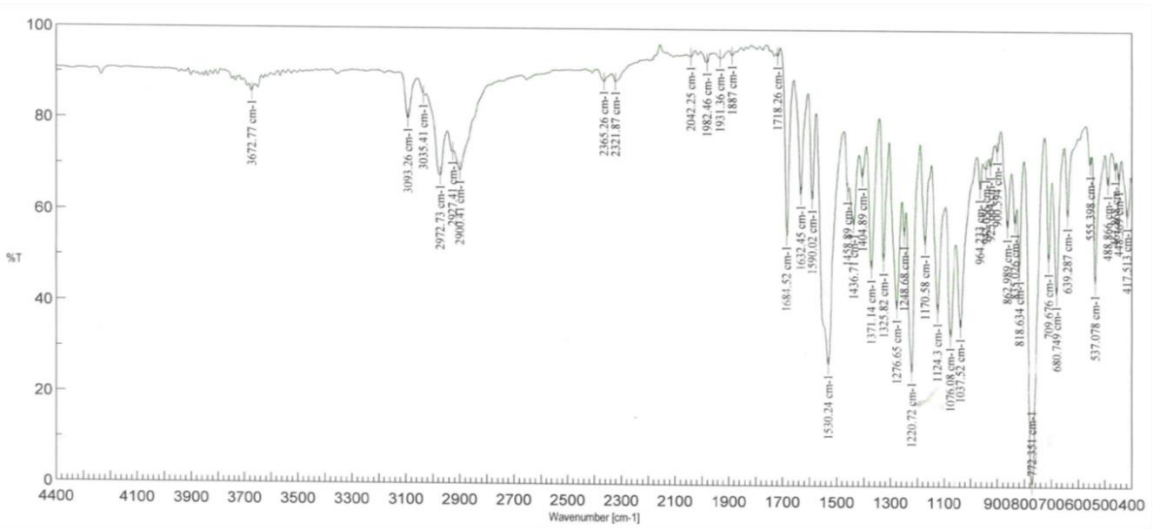


Figure 2.135: FTIR (KBr) spectrum concerning the compound **34**.

According to the ^{1}H NMR spectrum concerning the compound **34**; two methyl groups (CH_3) in morpholine ring were observed as a singlet around δ=1.20 ppm. Morpholine ring protons (CH_2-N-CH_2) and (CH) were found at δ=3.01-3.66 and δ=3.77-3.85 ppm as a triplet. Protons corresponding to naphthoquinone were seen at δ =7.68, 7.79 and 8.22 ppm as doublet of doublet, triplet and doublet of doublet respectively (Figure 2.136).

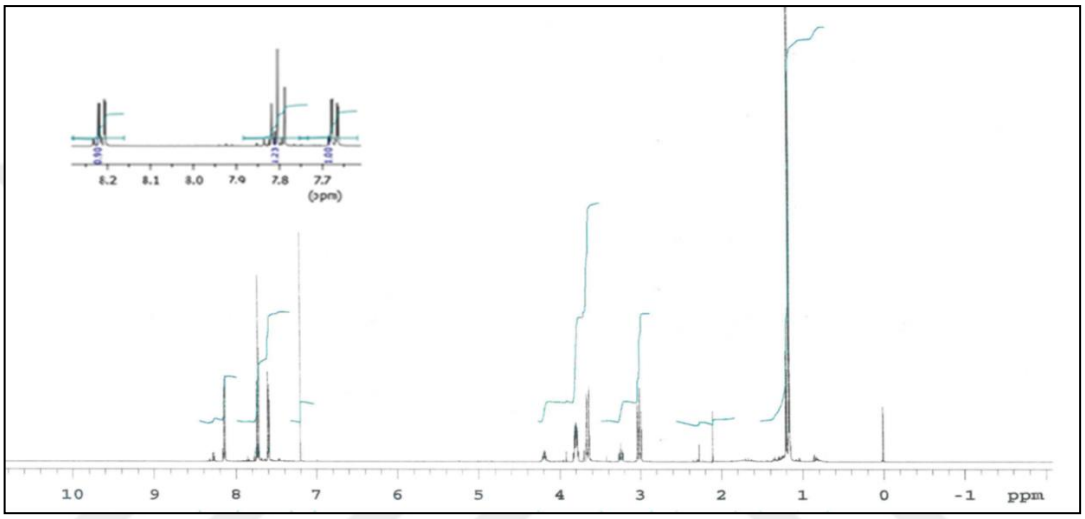


Figure 2.136: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **34**.

According to ^{13}C (APT) NMR spectrum concerning the compound **34**; methyl groups in morpholine ring (CH_3) were found at δ = 18.59 ppm, signals of $(CH_2\text{-}N\text{-}CH_2)_{morph}$ at δ = 56.64 ppm, whereas, $(CH\text{-}O\text{-}CH)_{morph}$ at δ = 72.40 ppm. (=C-Cl) at 111.15 ppm. Aromatic carbons (CH_{arom}, C_{arom}) were seen at δ = 119.61, 124.90, 127.11, 129.42, 132.63, 134.22 ppm, (=C-N) was appeared at δ =149.93 ppm, however, signal corresponding to carbonyl groups (C=O) were detected at δ =175.78, 179.10 ppm (Figure 2.137).

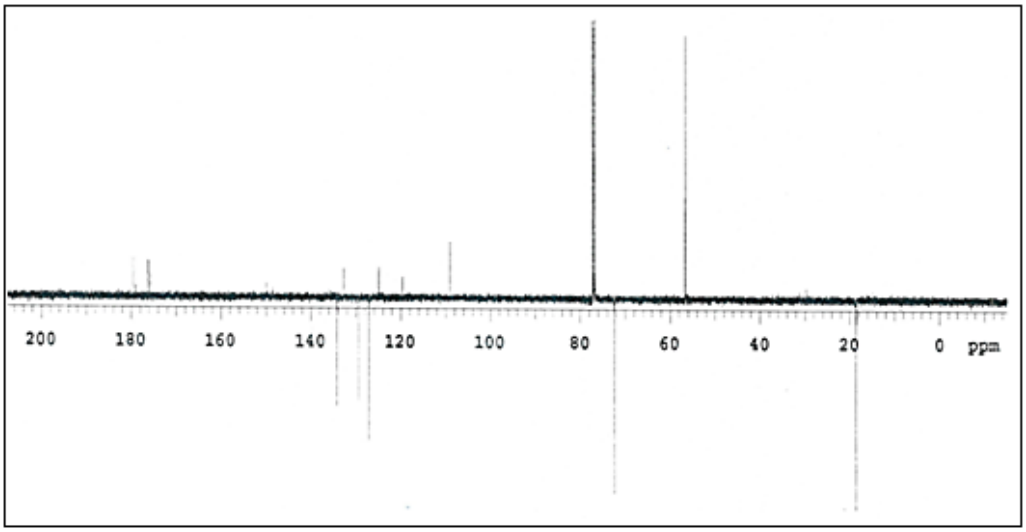


Figure 2.137: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **34**.

According to (+ESI) mass spectrum concerning the compound **34**; the molecular ion peak of a new compound ($C_{16}H_{15}ClN_2O_5$), M_w = 350.76 g/mol) was seen at *m/z* (100%) = 350.4 $[M-H]^+$ (Figure 2.138).

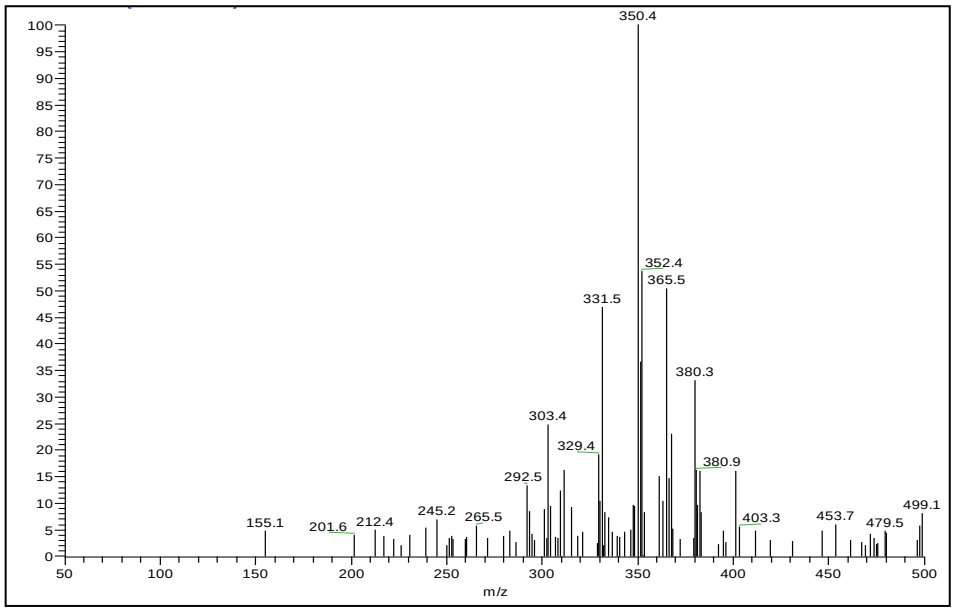


Figure 2.138: Mass spectrum [+ESI] concerning the compound **34.**

As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(32, 33)**; we observed that the proton of naphthoquinone peaks (δ=7.76-7.85 and 8.35 ppm) for the first isomer **(32)** are shifted more downfield than the naphthoquinone peaks (δ=7.79-7.84 and 8.33 ppm) of the second isomer **(33)**. Also, it found that the isomer **(32)** has a higher R_f component than the isomer **(33)** [89], [91].

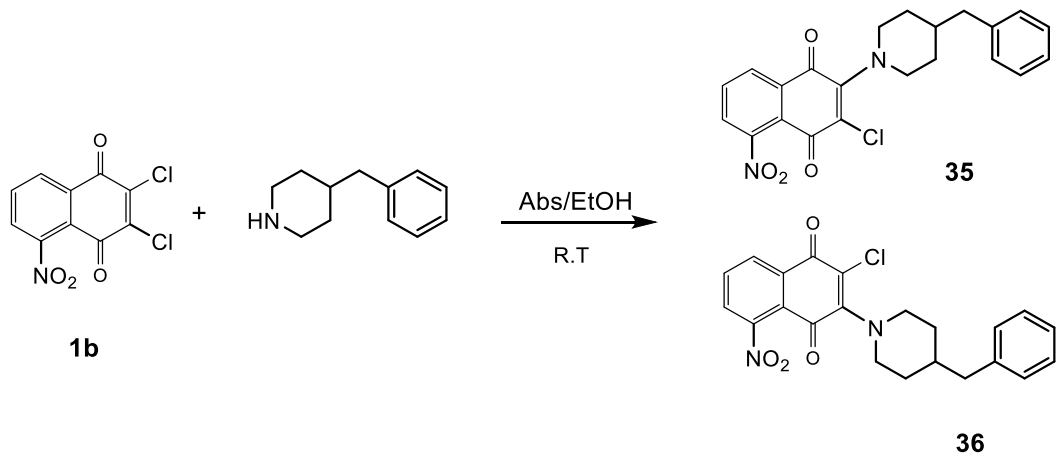
All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new regio-isomers **(32, 33)** and a new compound **(34)**.

2.2.12. Synthesis of 2-(4-benzylpiperidin-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione and 3-(4-benzylpiperidin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione (35, 36)

The new isomer compounds (**35**, **36**) obtained by reacting the compound **(1b)** with 4-benzylpiperidine in Abs. Ethanol at room temperature for 3-4 hoursas general procedure 4.

Isomer **35**; Red solid, R_f: 0.46 (1:1 $CHCl_3$/PET), M.p.: 153-154°C.

Isomer **36**; Red oil, R_f: 0.37 (1:1 $CHCl_3$/PET).



(2.25)

According to the IR spectrum of compound **35**; stretching bands of (C-H) observed at ν = 2952, 2920 and 2853 cm^{-1}, (C=O) appeared at ν = 1718 cm^{-1}, and the bands of carbon-carbon double bond (C=C) were seen at ν = 1606, 1594 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at 1453, 1375 cm^{-1} respectively (Figure 2.139).

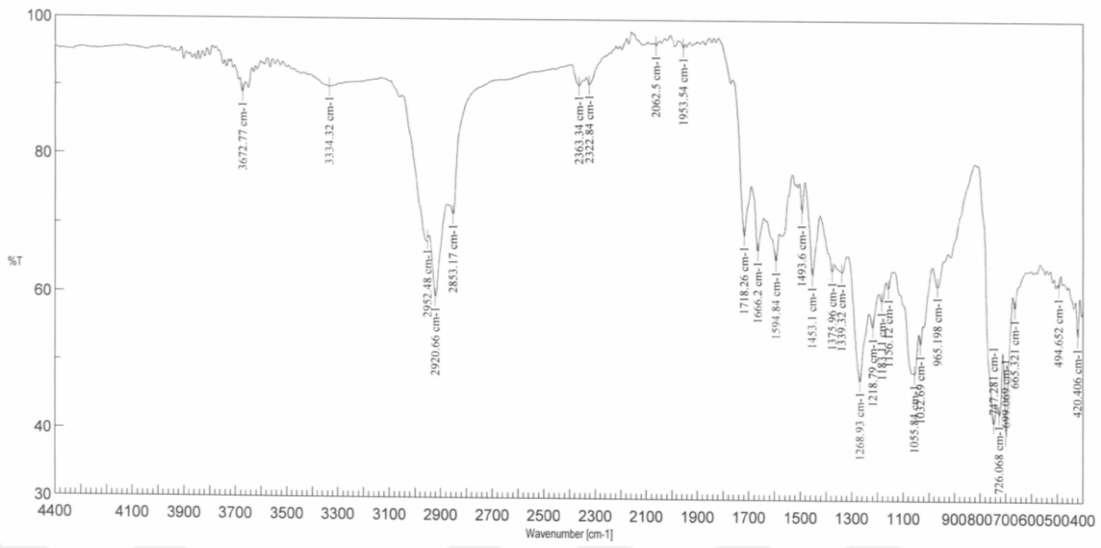


Figure 2.139: FTIR (KBr) spectrum concerning the compound **35**.

According to ^{1}H NMR spectrum concerning the compound **35**; piperidine ring protons (C**H**$_2$-CH-CH$_2$)$_{piper}$), (C**H**$_2$-C**H**-)$_{piper}$) and (C**H**$_2$-N-C**H**$_2$)$_{piper}$), were seen at δ = 1.46-1.59, 1.66-1.93 and 3.12-3.19, 3.69-3.81 ppm as a multiplet respectively. Protons of methylene (C**H**$_2$) in benzylpiperidine as a doublt at δ = 2.53 ppm. Protons of aromatic ring (CH$_{arom}$) at δ = 7.07-7.25 ppm as a multiplet. Two protons of nitro naphthoquinone at δ = 7.70-7.74 ppm as also multiplet, last proton of nitro naphthoquinone was seen at δ = 8.26-8.37 ppm as a doublet of doublet (Figure 2.140).

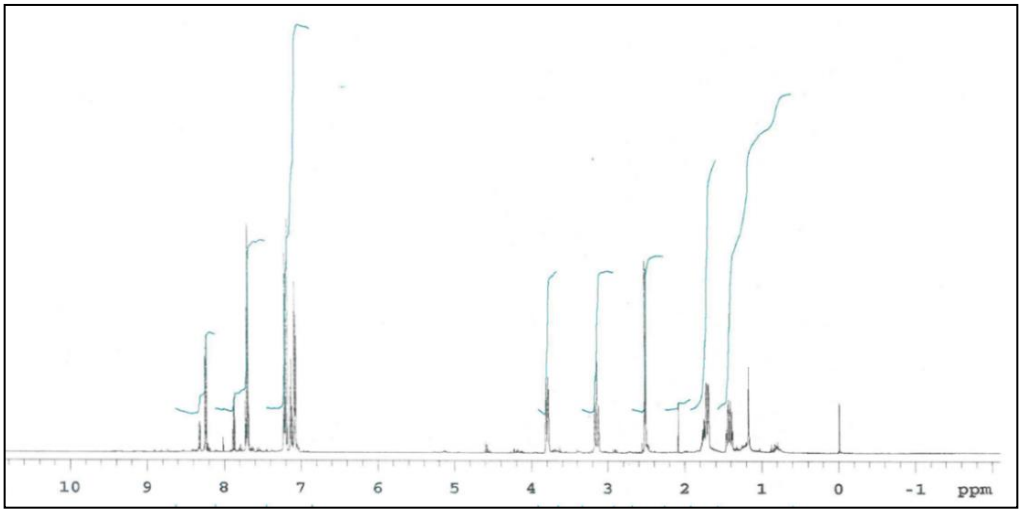


Figure 2.140: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **35**.

According to ^{13}C (APT) NMR spectrum concerning the compound **35**; signal at δ = 42.95 is corresponding to methylene group in benzylpiperidine. Carbons in piperidine ring (**C**H_2-CH-**C**H_2) $_{piperi}$, (CH_2-**C**H-CH_2)$_{piperi}$ and (**C**H_2-N-**C**H_2)$_{piperi}$ gave three signals at δ =33.06, 37.65 and 52.20 ppm respectively. (=C-Cl) at δ =119.98 ppm. Signals at δ = 125.79, 126.95, 128.27, 129.08, 130.02, 132.80, 135.51, 140.00 ppm for aromatic carbons (CH_{arom}, C_{arom}). (=C-N) was appeared at δ = 151.10 ppm. The last signals at δ =175.69, 179.36 ppm related to carbon of carbonyl groups (Figure 2.141).

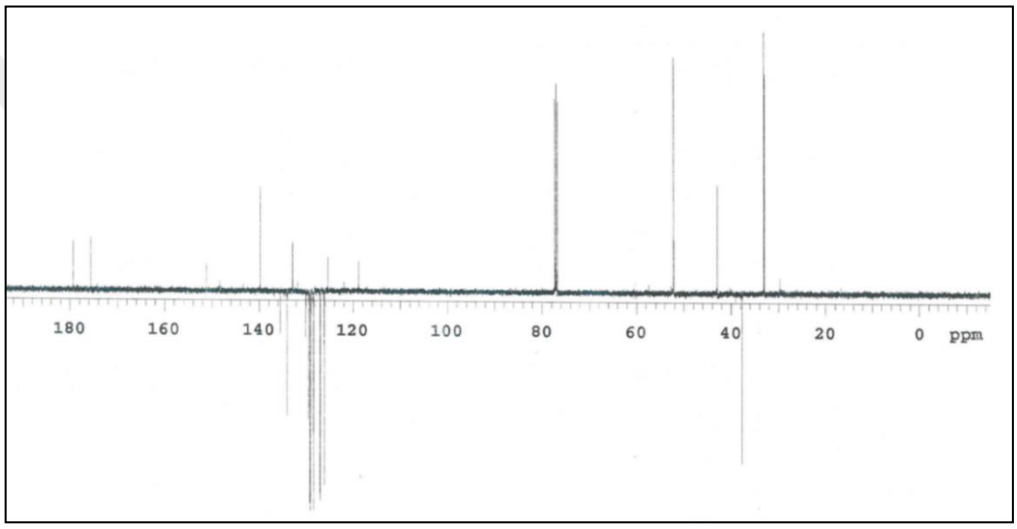


Figure 2.141: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **35**.

According to (+ESI) mass spectrum concerning the compound **35**; the molecular ion peak of a new isomer ($C_{22}H_{19}ClN_2O_4$), M_w = 410.85 g/mol) was seen at *m/z* (100%) = 411.1 $[M]^+$. A fragmentation of $[M+Na]^+$ was seen at *m/z* = 433.2 as a very small peak (Figure 2.142)

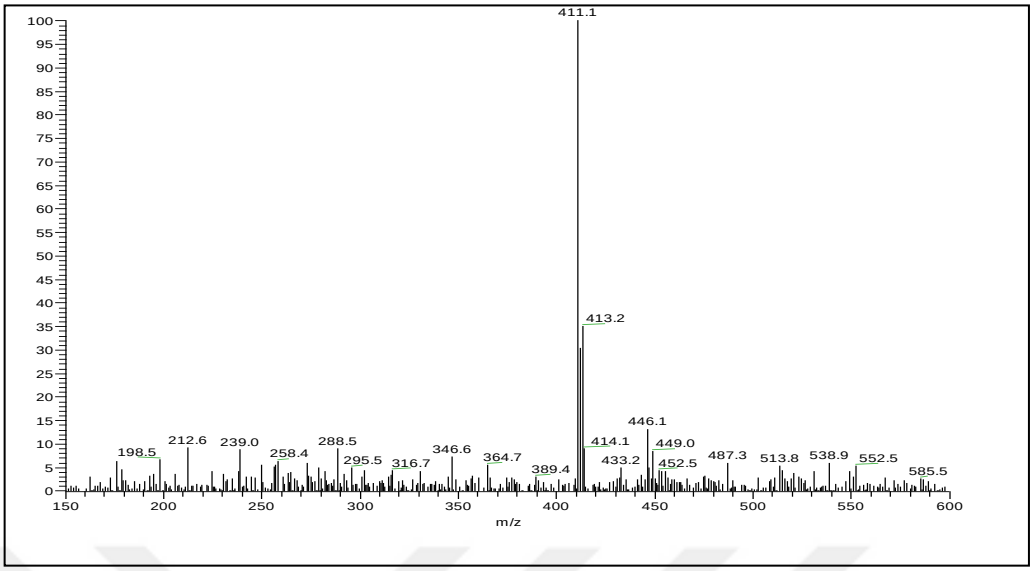


Figure 2.142: Mass spectrum [+ESI] concerning the compound **35**.

According to the IR spectrum of compound **36**; stretching bands of ($C\text{-}H_{arom}$) appeared at ν =3060 cm^{-1} and stretching bands of ($C\text{-}H_{aliph}$) observed at ν = 2970, 2919 cm^{-1}, (C=O) appeared at ν =1717 and 1664 cm^{-1}. The bands of carbon-carbon double bond (C=C) were seen at ν = 1592, 1561 cm^{-1}. Stretching (asymmetric, symmetric) bands of ($C\text{-}NO_2$) were appeared at 1452, 1329 cm^{-1} respectively (Figure 2.143).

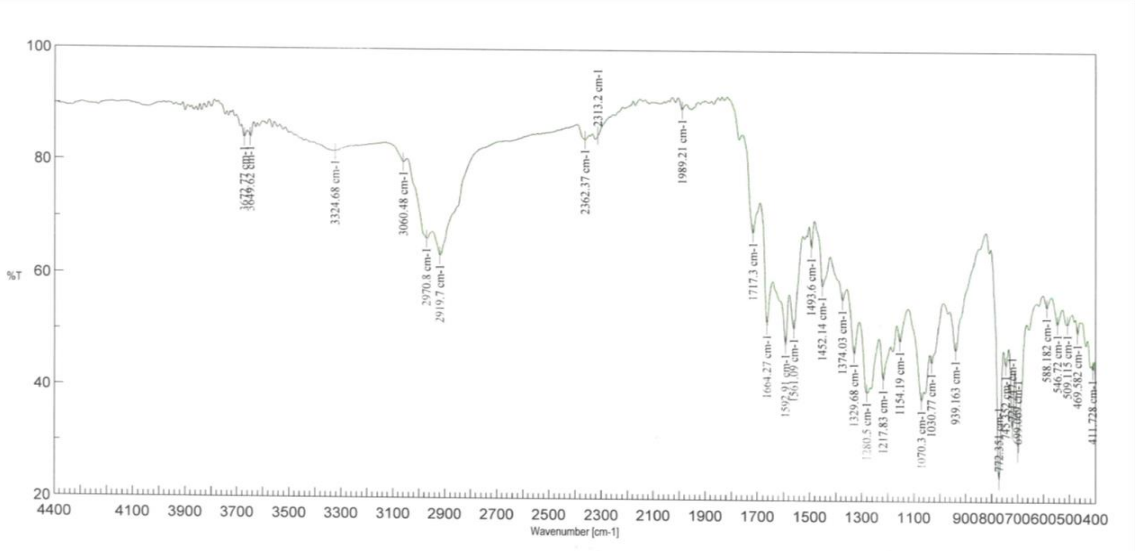


Figure 2.143: FTIR (KBr) spectrum concerning the compound **36**.

According to ^{1}H NMR spectrum concerning the compound **36**; piperidine ring (C**H**$_2$-CH-CH$_2$)$_{piperi}$), (C**H**$_2$-C**H**-)$_{piperi}$) and (C**H**$_2$-N-C**H**$_2$)$_{piperi}$), were seen at δ = 1.38-1.43, 1.69-1.81 and 3.12-3.18, 3.77-3.80 ppm as a multiplet respectively. Protons of methylene (C**H**$_2$) in benzylpiperidine as a multiplet at δ = 2.50-2.55 ppm. Protons of aromatic ring (CH$_{arom}$) at δ = 7.05-7.25 ppm as a multiplet. Two protons of nitro naphthoquinone at δ = 7.62, 7.64-8.72 ppm as also a multiplet, last proton of nitro naphthoquinone was seen at δ = 8.22 ppm as a doublet (Figure 2.144).

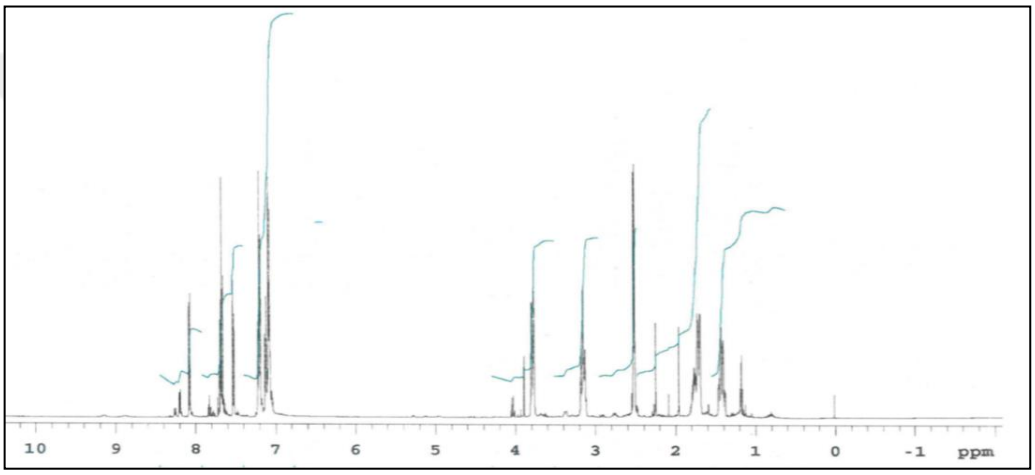


Figure 2.144: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **36.**

According to ^{13}C (APT) NMR spectrum concerning the compound **36;** signal at δ=42.92 is corresponding to methylene group in benzylpiperidine. Carbons in piperidine ring (**C**H$_2$-CH-**C**H$_2$) $_{piper}$, (CH$_2$-**C**H-CH$_2$)$_{piper}$ and (**C**H$_2$-N-**C**H$_2$)$_{piper}$ gave three signals at δ =33.05, 37.60 and 52.20 ppm respectively. (=C-Cl) at δ =119.90 ppm. Signals at δ = 122.70, 126.08, 127.01, 128.33, 129.63, 133.61, 134.14, 139.87 ppm for aromatic carbons (CH$_{arom}$, C$_{arom}$). (C-NO$_2$) and (=C-N) were appeared at δ = 148.23 and 151.11 ppm. The last signals at δ =173.89, 179.35 ppm related to carbon of carbonyl groups (Figure 2.145).

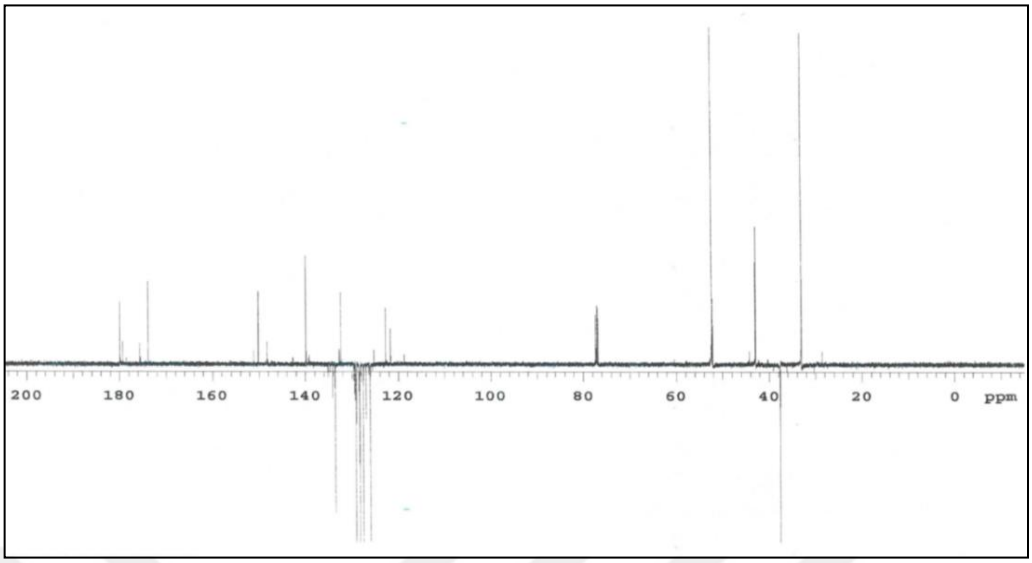


Figure 2.145: ^{13}C (APT) NMR ($CDCl_3$) spectrum concerning the compound **36.**

According to (+ESI) mass spectrum concerning the compound **36**; the molecular ion peak of a new compound ($C_{22}H_{19}ClN_2O_4$), M_w = 410.85 g/mol) was seen at *m/z* (100%) = 411.2 $[M]^+$. Fragmentation of $[M+Na]^+$ observed at *m/z* = 433.1 (Figure 2.146).

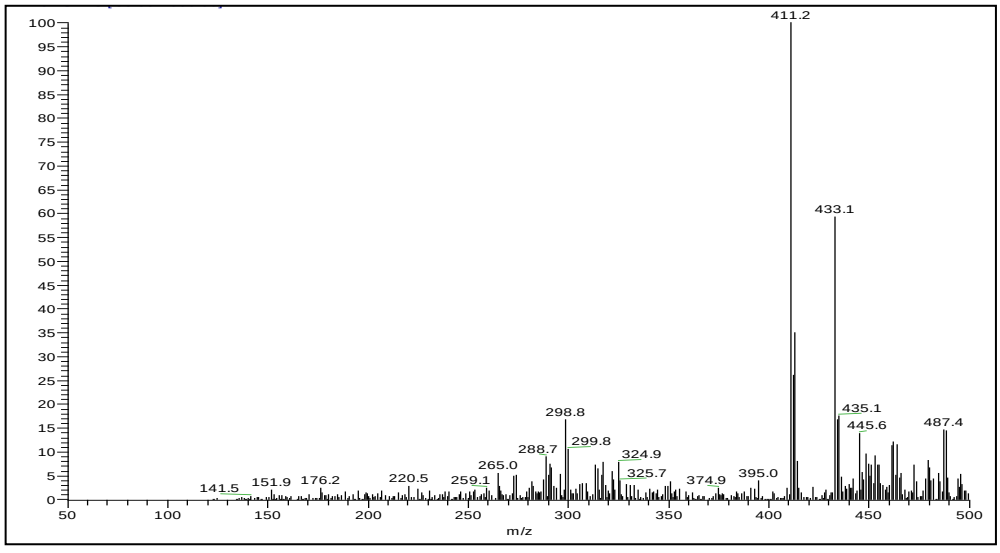


Figure 2.146: Mass spectrum [+ESI] concerning the compound **36.**

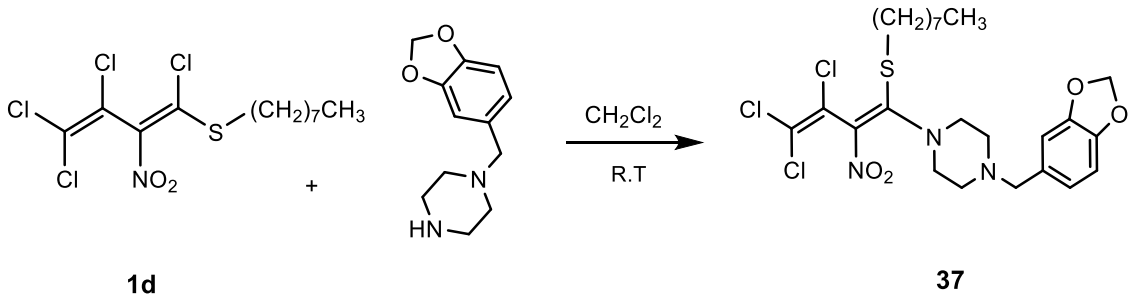
As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(35, 36)**; we observed that the proton of naphthoquinone peaks (δ=7.70-7.74 and 8.26-8.37 ppm) for the first isomer **(35)** are shifted more downfield than the naphthoquinone peaks (δ=7.62, 7.64-8.72 and 8.22 ppm) of the second isomer **(36)**. Also, it found that the isomer **(35)** has a higher R_f component than the isomer **(36)** [89], [91].

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new regio-isomers **(35, 36)**.

2.3. SYNTHESIS OF NEW BUTADIENE DERIVATIVES

2.3.1. Synthesis of (E)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(3,4,4-trichloro-2-nitro-1-(octylthio)buta-1,3-dien-1-yl)piperazine (37)

The new compound (**37**) was formed when the compound **(1d)** mixed [114] with 1-piperonylpiperazine in dichloromethane at room temperature for 12 hours as general procedure 6.



1d **37**

(2.26)

According to the IR spectrum of compound **37**; stretching bands for (C-H) were detected at ν = 2922, 2854, 2774 cm^{-1}. Bands of carbon-carbon double bond (C=C) were seen at ν = 1524, 1503 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at 1438, 1269 cm^{-1} respectively (Figure 2.147).

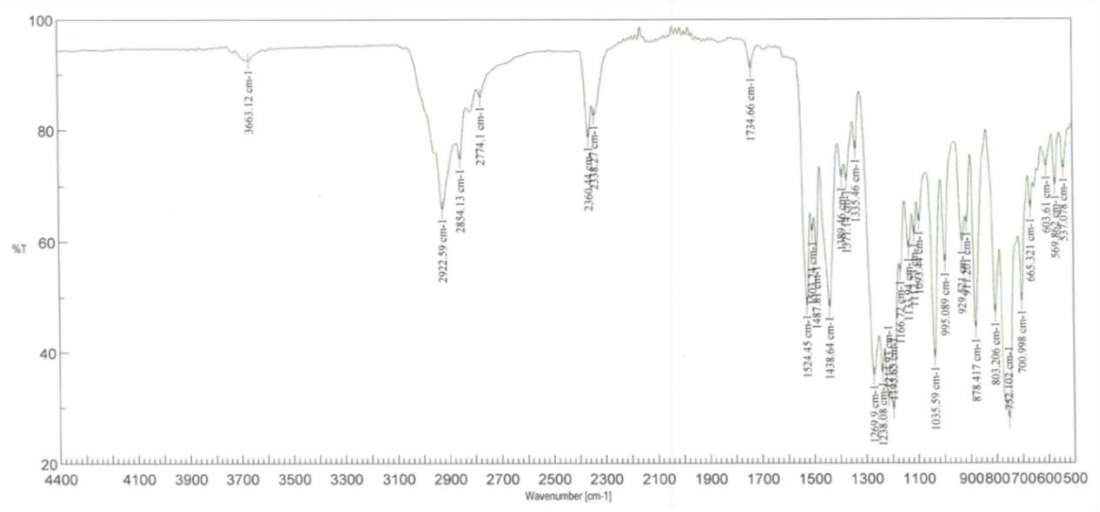


Figure 2.147: FTIR (KBr) spectrum concerning the compound **37.**

According to ^{1}H NMR spectrum concerning the compound **37**; a triplet at δ=0.88 ppm is corresponding to protons of methyl group, whereas, protons of (CH_2) at δ = 1.28-1.36 ppm as multiplet, Protons of (S-CH_2-C**H**$_2$) were seen as a multiplet at δ =1.53-1.55 ppm, (S-C**H**$_2$) at δ = 2.92 ppm as a triplet. Piperazine ring detected at δ =2.55 and 3.65 ppm as a broad singlet. A proton of (N-C**H**$_2$) and (O-CH_2-O) were seen at δ = 3.45 and 5.88 ppm as a singlet. The protons in aromatic rings appeared as a multiplet around δ = 6.61-7.25 ppm. (Figure 2.148).

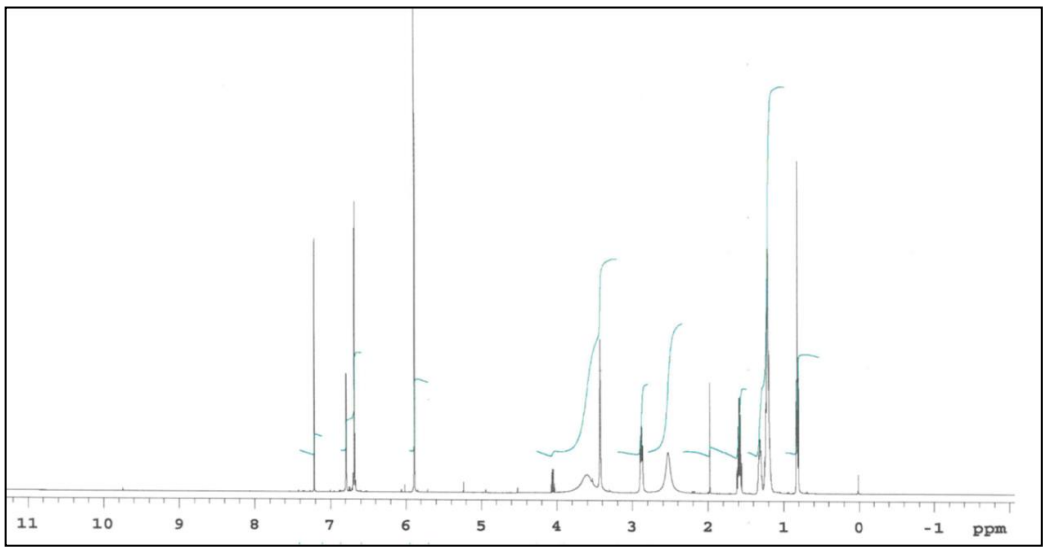


Figure 2.148: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **37**.

According to ^{13}C NMR spectrum concerning the compound **37**; (CH_3) carbon signal was appeared at δ = 14.09 ppm, (CH_2) signals at δ = 22.04, 28.65, 28.97, 29.00, 29.69 ppm. Signals of (S-CH_2-**C**H_2) and (S-**C**H_2) were appeared at δ = 31.69 and 35.48 ppm. piperazine (N-**C**H_2) ring were appeared at δ = 52.37, 53.31 ppm, carbon signal of (N–**C**H_2) at δ = 62.04 ppm. Signal at δ = 101.04 ppm is related to carbon of (O-**C**H_2-O). Signals at δ =108.02, 117.79, 122.27, 124.14, 126.92, 147.05, 147.87, 169.30 are belonging to (CH_{arom}, C_{arom}, C_{butad}) carbons (Figure 2.149).

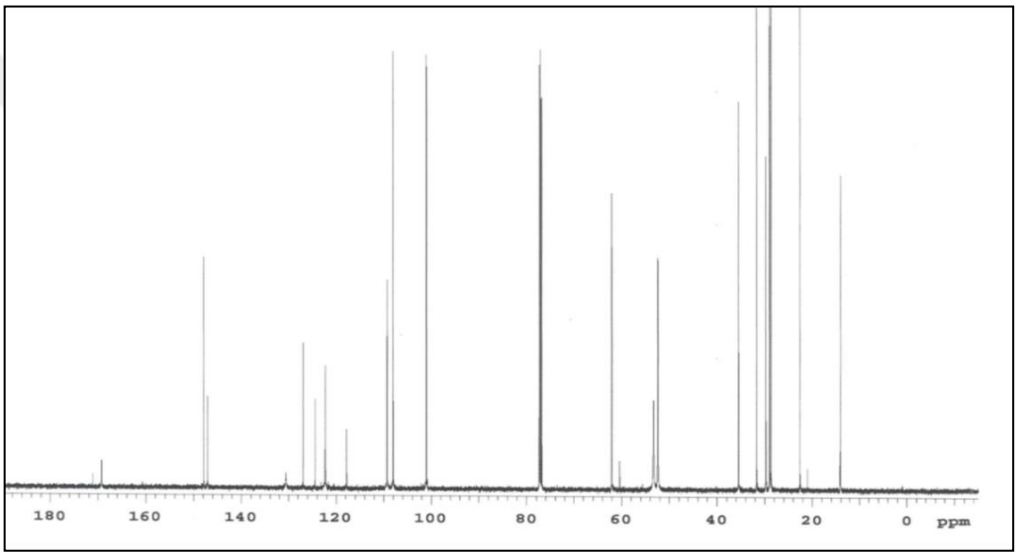


Figure 2.149: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **37**.

According to (+ESI) mass spectrum concerning the compound **37**; the molecular ion peak of a new compound ($C_{24}H_{32}Cl_3N_3O_4S$), M_w = 564.95 g/mol) was seen at *m/z* (100%) = 566.0 $[M+H]^+$. A small peak at *m/z* = 586.0 related to $[M+Na]^+$ (Figure 2.150).

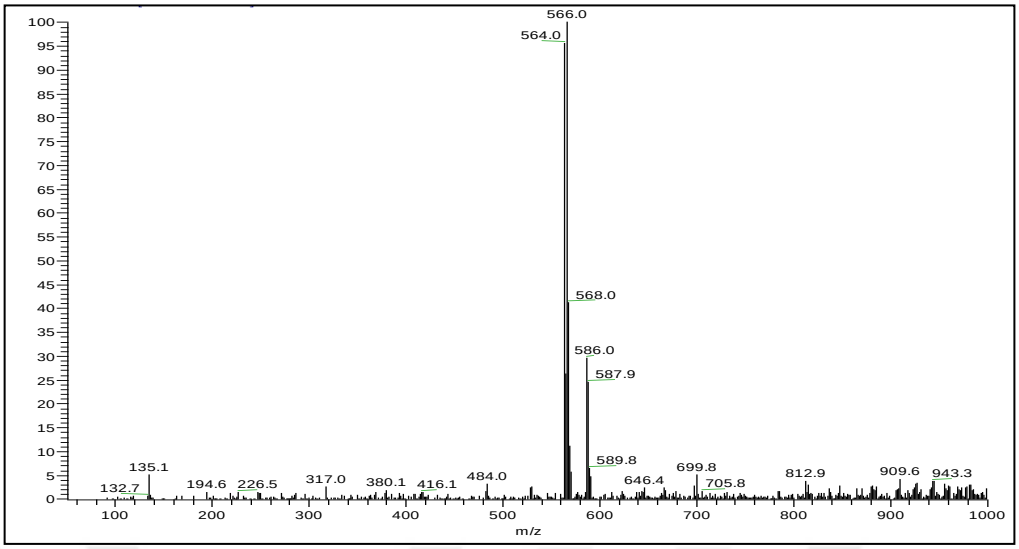
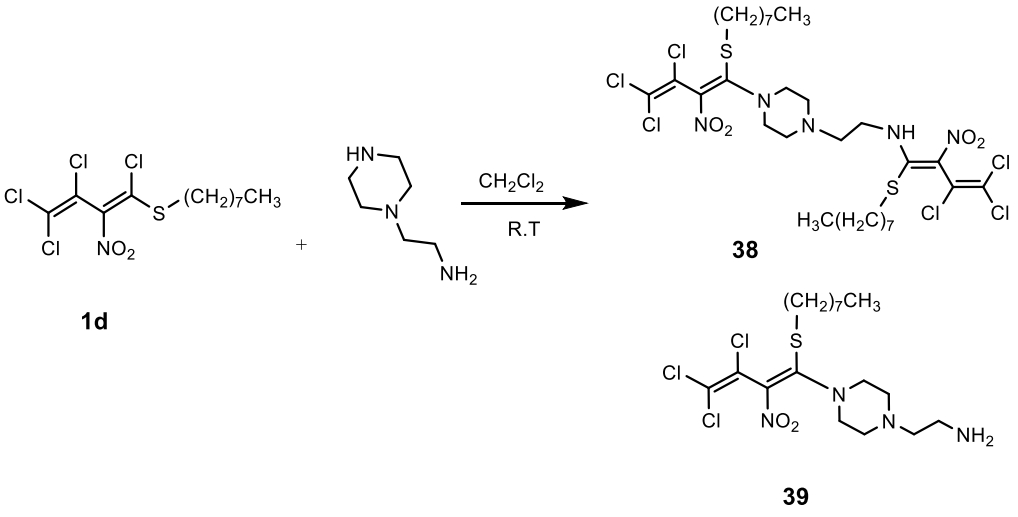


Figure 2.150: Mass spectrum [+ESI] concerning the compound **37**.

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(37)**.

2.3.2. Synthesis of (E)-3,4,4-trichloro-2-nitro-1-(octylthio)-N-(2-(4-((E)-3,4,4-trichloro-2-nitro-1-(octylthio)buta-1,3-dien-1-yl)piperazin-1-yl)ethyl)buta-1,3-dien-1-amine and (E)-2-(4-(3,4,4-trichloro-2-nitro-1-(octylthio)buta-1,3-dien-1-yl)piperazin-1-yl)ethan-1-amine 38, 39)

The new compounds (**38, 39**) were formed when the compound **(1d)** interacted with 1-(2-aminoethyl)piperazine in dichloromethane at room temperature for 12 hours as general procedure 6.



(2.27)

According to IR spectrum concerning the compound **38**; stretching bands for (C-H) were detected at ν = 2956, 2921, 2852 cm^{-1}. (C=C) group was seen at ν = 1557 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at 1526, 1280 cm^{-1} (Figure 2.151).

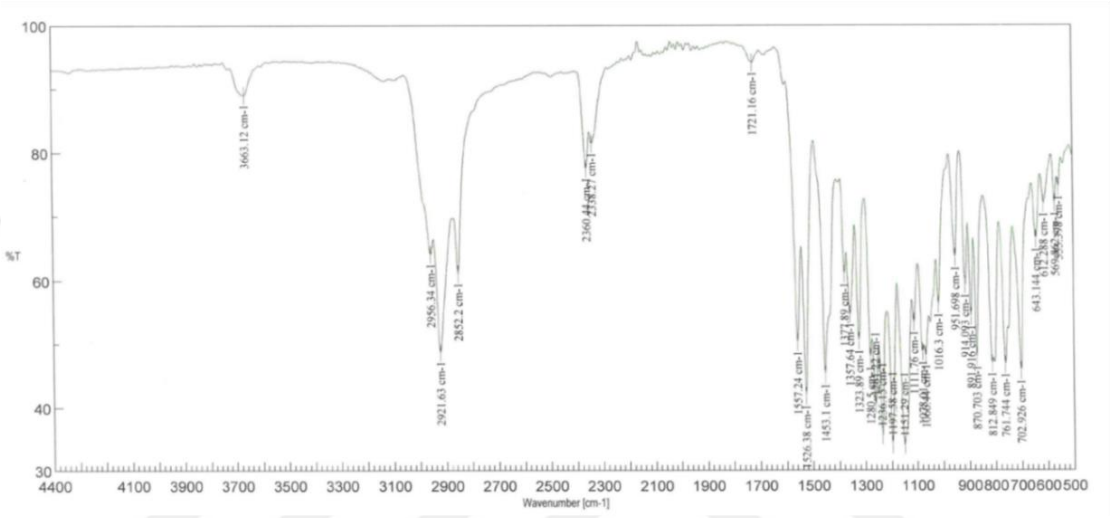


Figure 2.151: FTIR (KBr) spectrum concerning the compound **38.**

According to ^{1}H NMR spectrum concerning the compound **38**; A multiplet at δ=0.89 ppm is corresponding to protons of methyl groups, whereas, protons of (C**H**$_2$) at δ = 1.10-1.29 ppm as a multiplet. Protons of (CH_2-CH_3) were detected at δ =1.38 ppm as multiplet. Protons of (S-CH_2-C**H**$_2$) were seen at δ =1.50-1.65 ppm as a multiplet too, (S-C**H**$_2$) at δ =2.94 ppm as a multiplet. Protons of piperazine ring were seen at δ = 2.68 and 3.80 ppm as abroad singlet. (HN-C**H**$_2$) was appeared at δ = 3.50 ppm as a multiplet. (N-H) proton was seen at δ = 11.04 ppm (Figure 2.152).

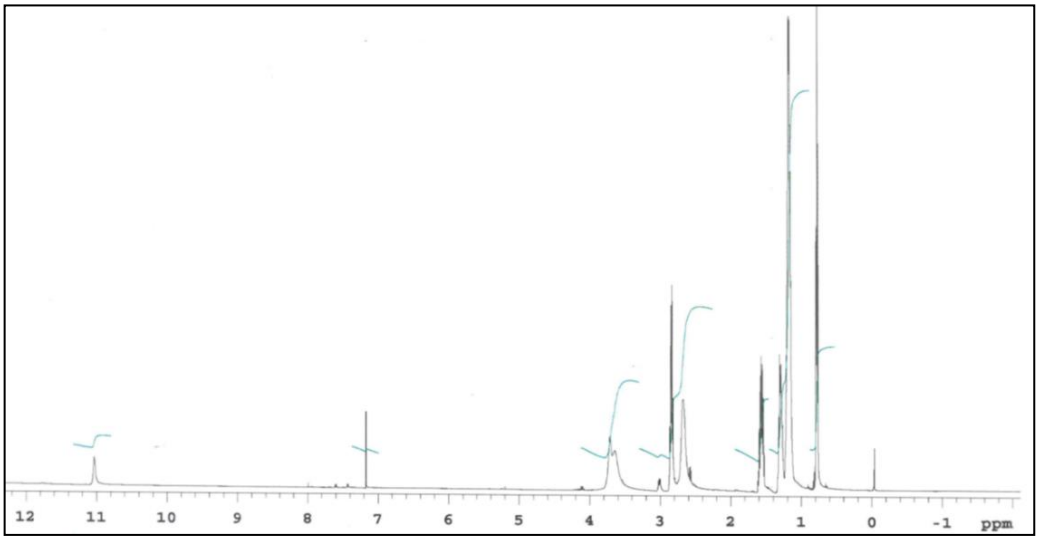


Figure 2.152: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **38.**

According to ^{13}C NMR spectrum concerning the compound **38**; ($2CH_3$) signals were seen at δ = 14.08 ppm, ($2\mathbf{C}H_2CH_3$) at δ = 22.59, 22.73 ppm, ($8\mathbf{C}H_2$) signals at δ = 28.52, 28.63, 28.66, 28.95, 28.97, 29.01, 29.16, 29.70 ppm. Signals of ($2S\text{-}CH_2\text{-}\mathbf{C}H_2$) and ($2S\text{-}\mathbf{C}H_2$) were appeared at δ = 31.70, 31.77, 35.50 and 35.54 ppm. ($HN\text{-}\mathbf{C}H_2$) was appeared at δ = 39.22 ppm. Carbon signals in piperazine ring were seen at δ = 52.21, 53.24 ppm, carbon signal of ($HN–CH_2\mathbf{C}H_2$) δ = 55.78 ppm. Signal at δ =118.02, 120.19, 126.02, 128.54 162.30 ppm are belonging to (C_{butad}) carbons (Figure 2.153).

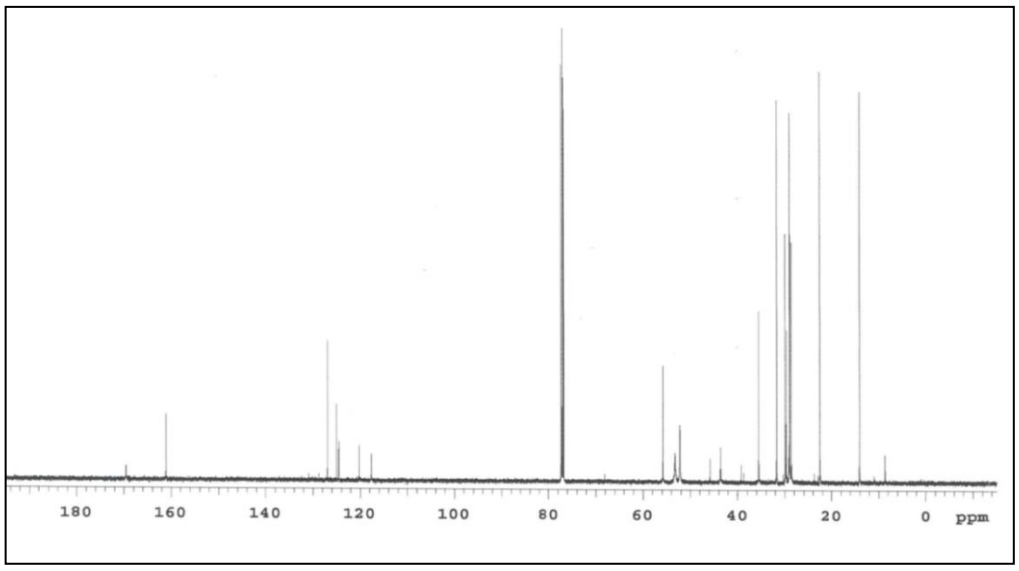


Figure 2.153: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **38.**

According to (+ESI) mass spectrum concerning the compound **38**; the molecular ion peak of a new compound ($C_{30}H_{47}Cl_6N_5O_4S_2$), M_w = 818.56 g/mol) was seen at *m/z* (100%) = 816.2 $[M-3H]^+$, $[M]^+$ at *m/z* (60%) =818.1 (Figure 2.154).

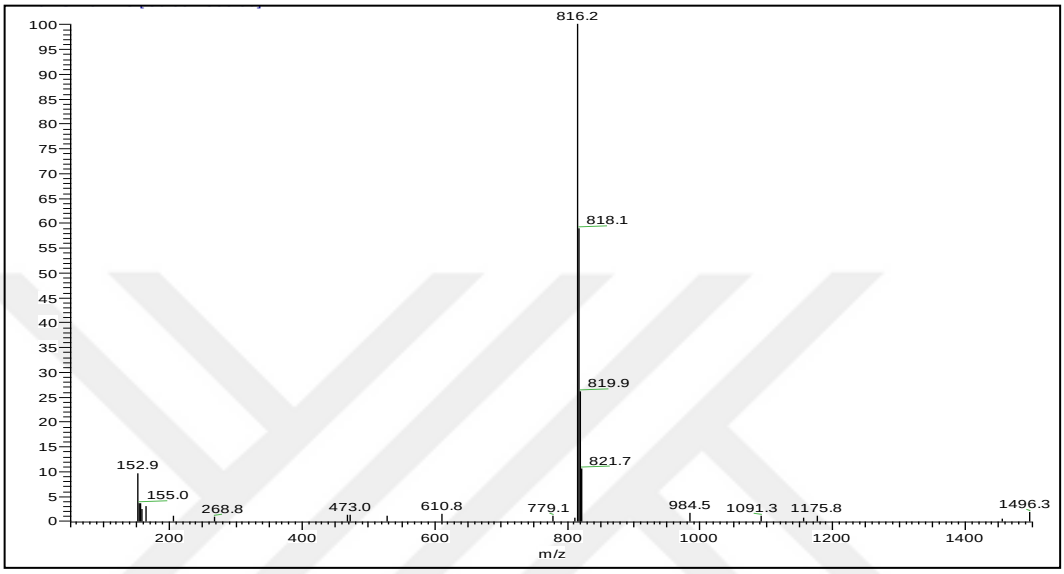


Figure 2.154: Mass spectrum [+ESI] concerning the compound **38.**

According to the IR spectrum concerning the compound **39**; stretching bands for (C-H) were detected at ν =2922, 2852 cm^{-1}. (C=C) band was seen at ν = 1600 cm^{-1}. Stretching (asymmetric, symmetric) bands for ($C-NO_2$) were appeared at 1525, 1267 cm^{-1} respectively **(**Figure 2.155).

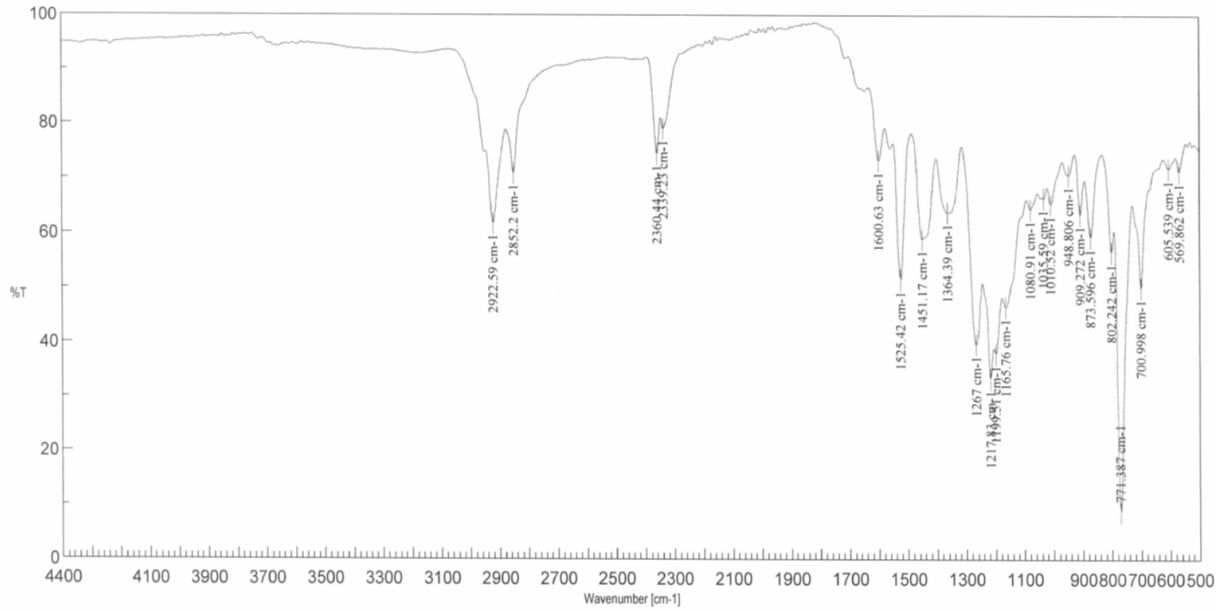


Figure 2.155: FTIR (KBr) spectrum concerning the compound **39.**

According to ^{1}H NMR spectrum concerning the compound **39**; A multiplet at δ=0.81 ppm is corresponding to protons of methyl group, whereas, protons of (C**H**$_2$) at δ = 1.11-1.31 ppm as a multiplet, (C**H**$_2$CH$_3$) at δ =1.48 ppm. (S-CH$_2$-C**H**$_2$) protons were seen at δ=1.57-1.60 ppm as multiplet, (N-CH$_2$)$_{piper}$), (S-C**H**$_2$) at δ = 2.61- 2.77 and 2.80 ppm as a multiplet. Protons of piperazine ring (C**H**$_2$-N-C**H**$_2$) were appeared at 2.93, 3.50 ppm as abroad singlet and (HN-C**H**$_2$) was seen at δ = 4.01 ppm as a multiplet. (NH$_2$) protons were seen at δ = 11.01 ppm. (Figure 2.156).

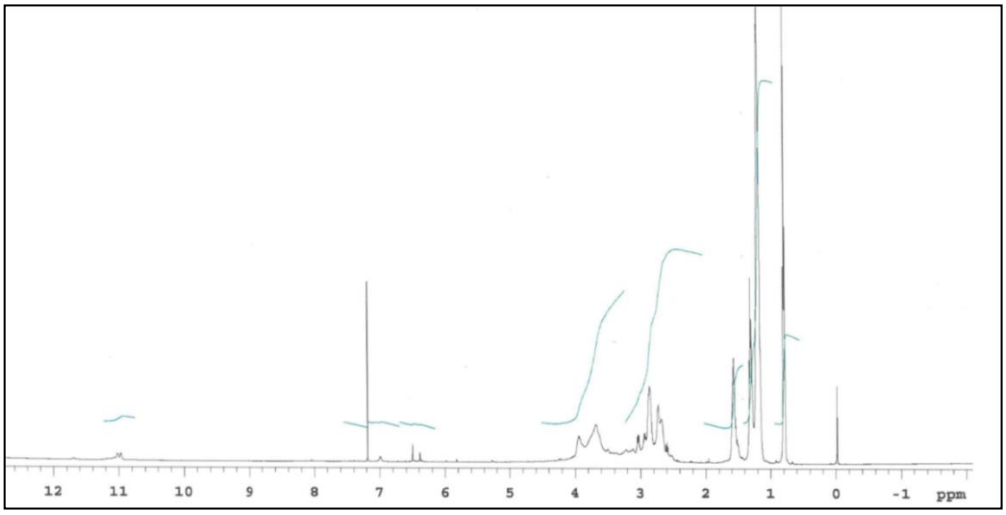


Figure 2.156: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **39.**

According to ^{13}C NMR spectrum concerning the compound **39**; (CH_3) signal appeared at δ = 14.08 ppm, (**C**H_2CH_3) at δ = 22.64 ppm, (**C**H_2) signals at δ = 28.17, 28.37, 28.52, 28.67 ppm. Signals of (S-CH_2-**C**H_2) and (S-**C**H_2) were appeared at δ = 31.20, 35.56 ppm. (HN-**C**H_2) was appeared at δ = 41.45 ppm. Carbon signals in piperazine ring were seen at δ = 52.87, 53.40 ppm, carbon signal of (HN–CH_2**C**H_2) δ = 65.78 ppm. Signal at δ = 115.06, 118.48, 124.54, 126.49 169.71 ppm are belonging to (C_{butad}) carbons (Figure 2.157).

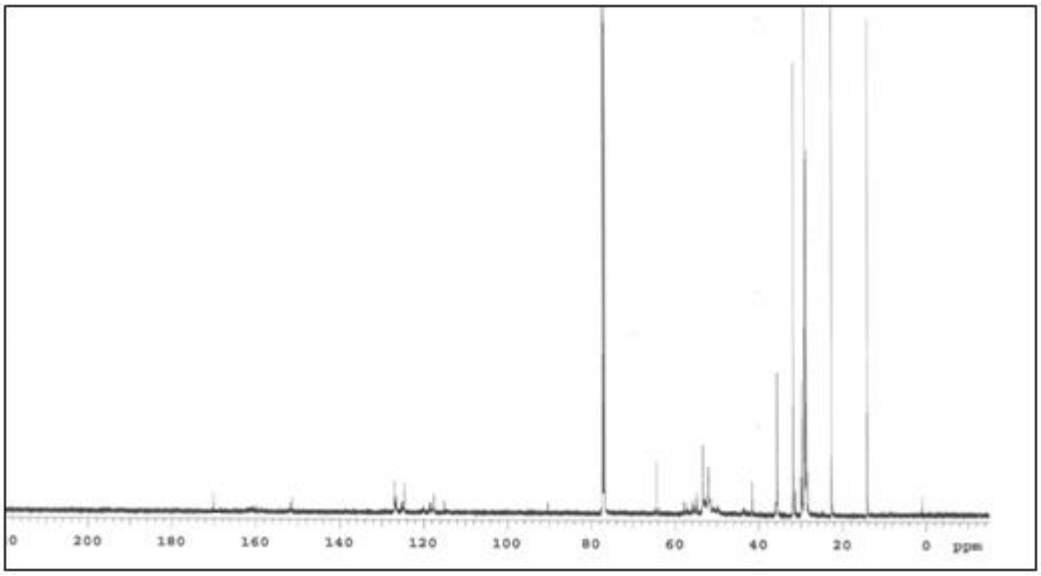


Figure 2.157: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **39.**

According to (+ESI) mass spectrum concerning the compound **39**; the molecular ion peak of a new compound ($C_{18}H_{31}Cl_3N_4O_2S$), M_w = 473.88 g/mol) was seen at *m/z* (100%) = 475.1 $[M+H]^+$ (Figure 2.158).

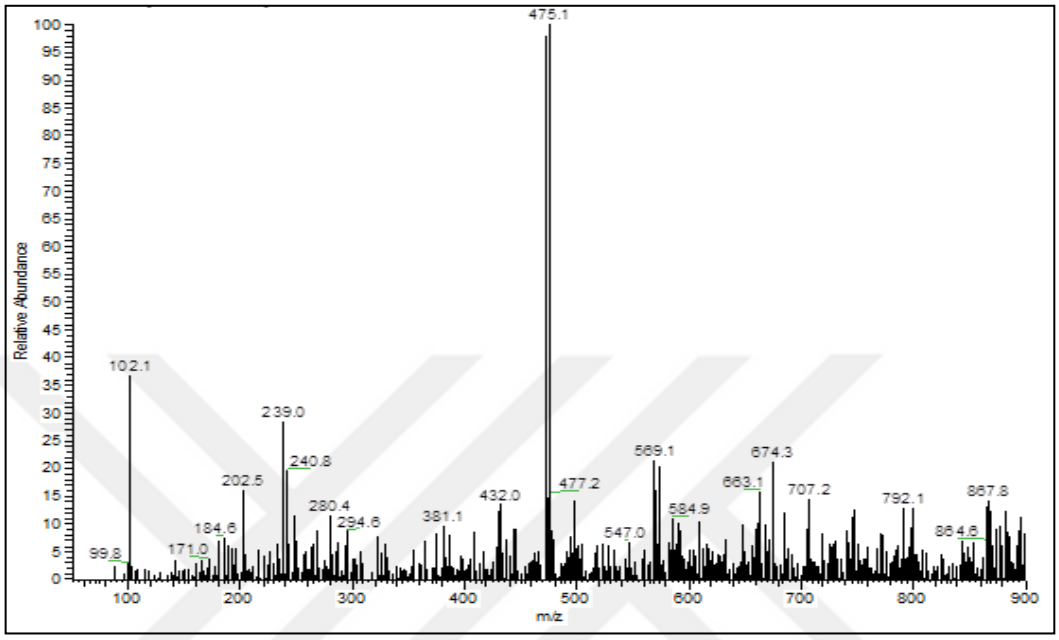
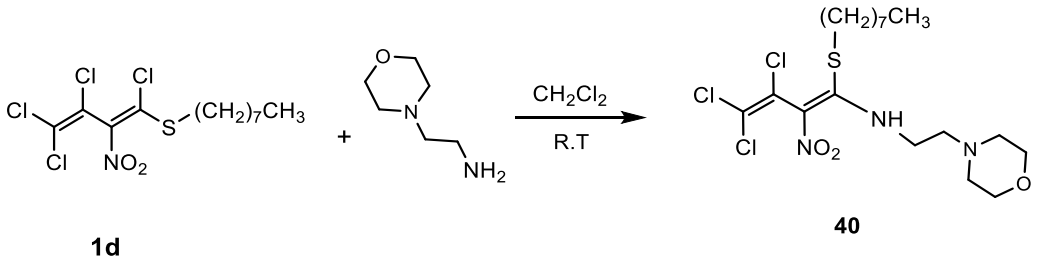


Figure 2.158: Mass spectrum [+ESI] concerning the compound **39.**

All the obtained results from mass spectra and spectroscopic data confirm the correct proposed structure of the new compounds **(38, 39)**.

2.3.3. Synthesis of (E)-3,4,4-trichloro-N-(2-morpholinoethyl)-2-nitro-1-(octylthio)buta-1,3-dien-1-amine (40)

The new compound (**40**) was formed when the compound **(1d)** reacted with 4-(2-aminoethyl)morpholine in dichloromethane at room temperature for 12 hours as general procedure 6.



(2.28)

According to IR spectrum concerning the compound **40**; N-H band appeared at ν = 3143 cm^{-1}. Stretching bands for (C-H) was detected at ν = 2954, 2923, 2854 cm^{-1}. Bands of carbon-carbon double bond (C=C) were seen at ν = 1673, 1556 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at 1443, 1297 cm^{-1} respectively (Figure 2.159).

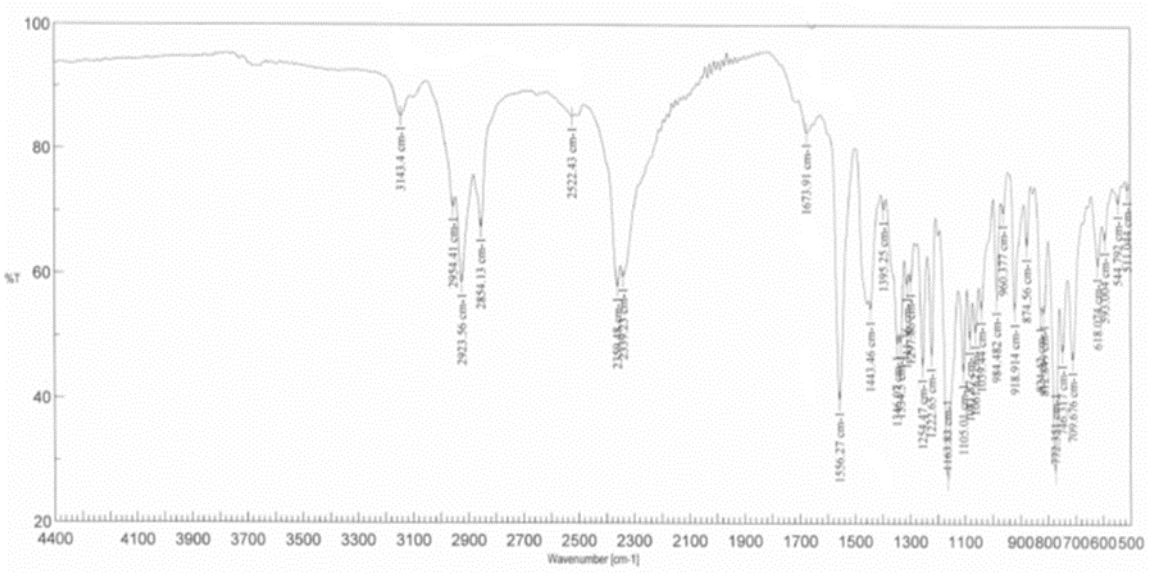


Figure 2.159: FTIR (KBr) spectrum concerning the compound **40.**

According to ^{1}H NMR spectrum concerning the compound **40**; multiplet at δ = 0.86 ppm is corresponding to protons of methyl group, whereas, protons of (C**H**$_2$) at δ = 1.12-1.38 ppm as multiplet, Protons of (S-CH_2-C**H**$_2$) were seen at δ =1.50-1.65 ppm as multiplet, (S-C**H**$_2$) at δ = 2.93 ppm as a triplet. Protons of morpholine ring (C**H**$_2$-N-C**H**$_2$) and (C**H**$_2$-O-C**H**$_2$) were appeared at δ = 3.08 and 3.90 ppm as a triplet and a singlet respectively, (HN-CH_2C**H**$_2$) was seen as broad singlet at δ =3.22 ppm. two protons that bonded with amine group (HN-C**H**$_2$)

were shown at δ = 4.10 ppm as singlet. (N-H) proton was seen at δ = 10.94 ppm (Figure 2.160).

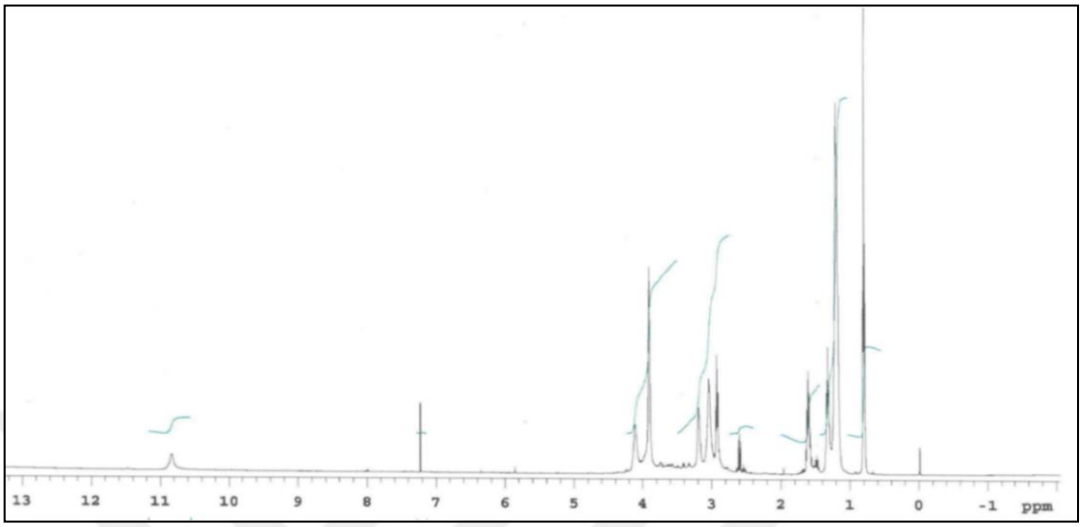


Figure 2.160: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **40.**

According to the ^{13}C NMR spectrum concerning the compound **40**; (CH_3) carbon signal appeared at δ = 14.05 ppm, (**C**H_2CH_3) at δ = 22.56 ppm, (**C**H_2) signals at δ = 28.48, 28.86, 29.01, 29.30 ppm. Signals of (S-CH_2-**C**H_2) and (S-**C**H_2) were appeared at δ = 31.68 and 35.56 ppm. (HN-**C**H_2) was appeared at δ = 41.80 ppm. Carbon signals in morpholine ring were seen at δ = 52.73, 53.67 ppm, carbon signal of (HN–**C**H_2CH_2) and at δ = 56.50 ppm, δ = 64.64 ppm related to (CH_2-O-CH_2)$_{mrpho}$. Signal at δ =121.02, 124.19, 128.02, 162.30 ppm are belonging to (C_{butad}) carbons (Figure 2.161).

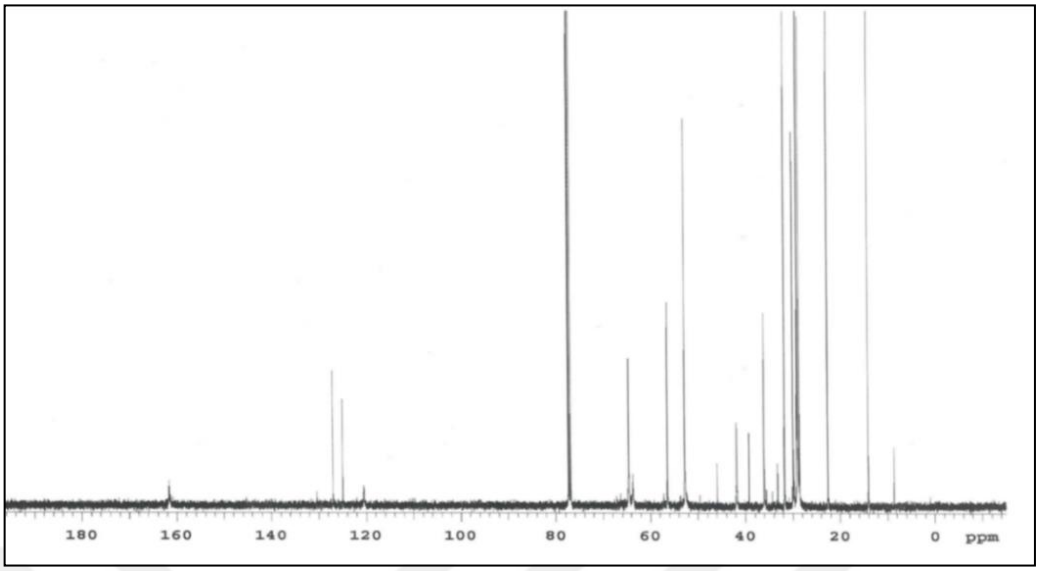


Figure 2.161: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **40.**

According to (+ESI) mass spectrum concerning the compound **40**; the molecular ion peak of a new compound ($C_{18}H_{30}Cl_3N_3O_3S$), M_w = 474.87 g/mol) was seen at *m/z* (100%) = 473.9 $[M-H]^+$ (Figure 2.162).

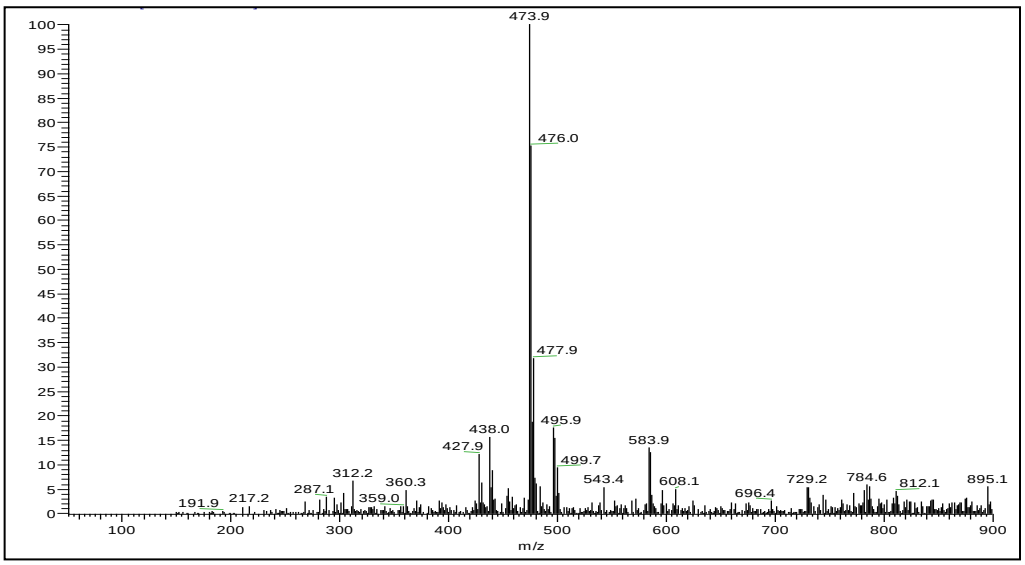
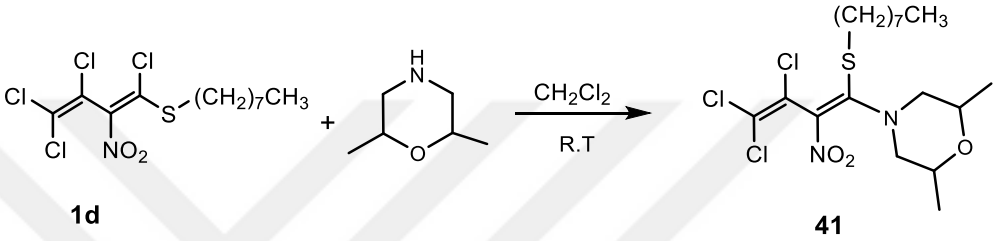


Figure 2.162: Mass spectrum [+ESI] concerning the compound **40.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(40)**.

2.3.4. Synthesis of (E)-2,6-dimethyl-4-(3,4,4-trichloro-2-nitro-1-(octylthio)buta-1,3-dien-1-yl)morpholine (41)

The new compound (**41**) was formed when the compound **(1d)** reacted with 2,6-dimethylmorpholine in dichloromethane at room temperature for 12 hours as general procedure 6.



(2.29)

According to the IR spectrum concerning the compound **41**; stretching band for (C-H) were detected at ν = 2924, 2854 cm^{-1}. (C=C) bands were seen at ν =1662, 1596 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) appeared at 1523, 1269 cm^{-1} respectively (Figure 2.163).

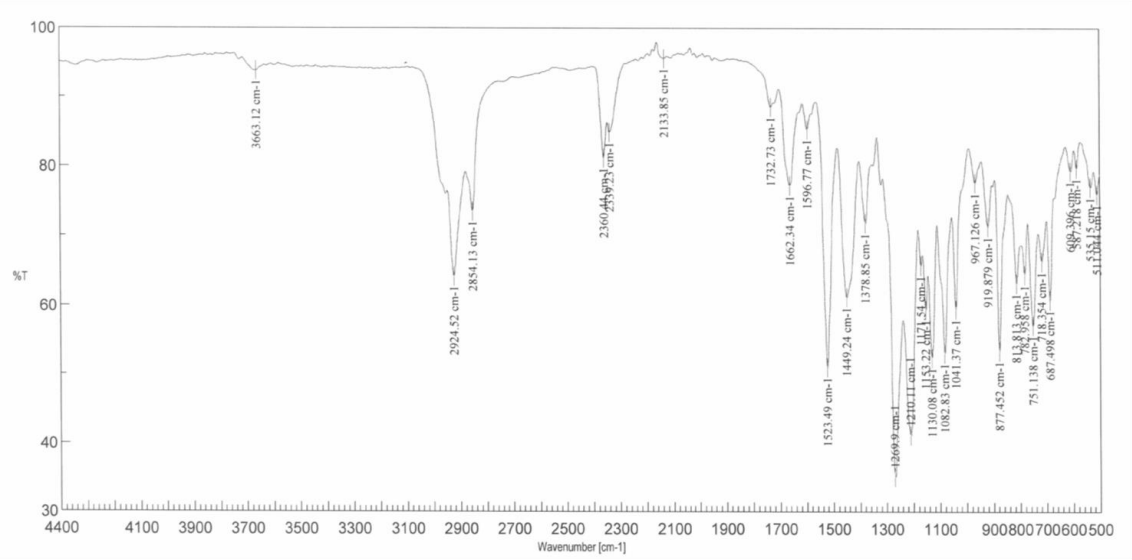


Figure 2.163: FTIR (KBr) spectrum concerning the compound **41.**

According to ^{1}H NMR spectrum concerning the compound **41**; triplet around δ = 0.82 ppm is corresponding to protons of methyl group, whereas, protons of (C**H**$_2$) and (2CH$_3$)$_{morph}$ at δ =1.11-1.29 ppm as a multiplet. Protons of (C**H**$_2$-CH$_3$) were appeared at δ =1.30-1.41 ppm as a multiplet, (S-CH$_2$C**H**$_2$) at δ = 1.53-1.63 ppm as also multiplet. Protons of morpholine ring (C**H**$_2$-N-C**H**$_2$) were appeared at δ = 2.90 and 3.50 ppm as a broad singlet. (S-C**H**$_2$) and (C**H**-O-C**H**)$_{morph}$ were seen at δ =3.06 and 4.10 ppm as a multiplet. (Figure 2.164).

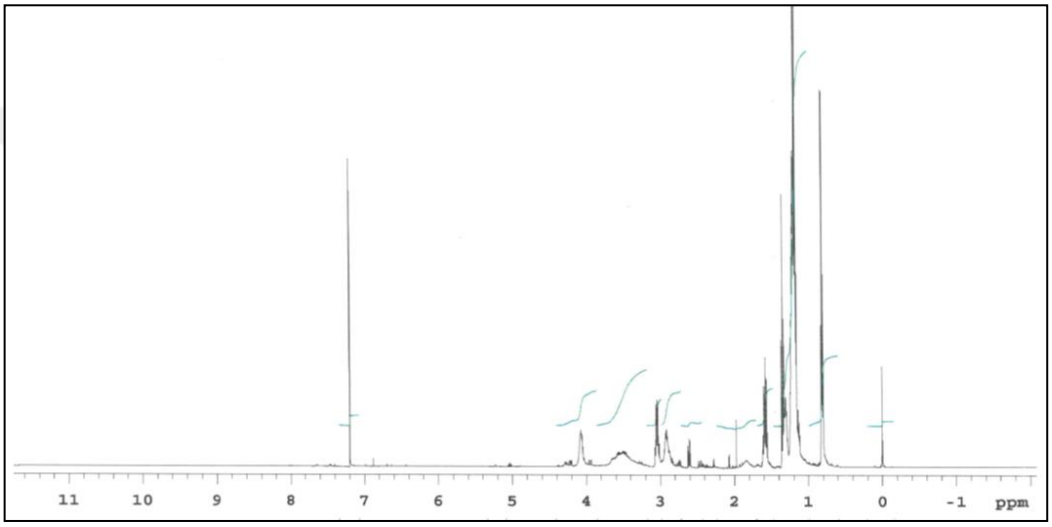


Figure 2.164: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **41.**

According to the ^{13}C NMR spectrum concerning the compound **41;** (CH$_3$) carbon signal appeared at δ = 11.05 and 14.06 ppm, (**C**H$_2$CH$_3$) at δ = 22.58 ppm, (**C**H$_2$) signals at δ = 28.53, 28.64, 29.05, 29.23 ppm. Signals of (S-CH$_2$-**C**H$_2$) and (S-**C**H$_2$) were appeared at δ = 31.80 and 39.22 ppm. Carbon signals in morpholine ring were seen at δ = 51.78, 52.04 ppm, δ = 71.64 ppm related to (CH-O-CH)$_{mrpho}$. Signal at δ =115.02, 118.19, 122.02, 124.30 ppm are belonging to (C$_{butad}$) carbons (Figure 2.165).

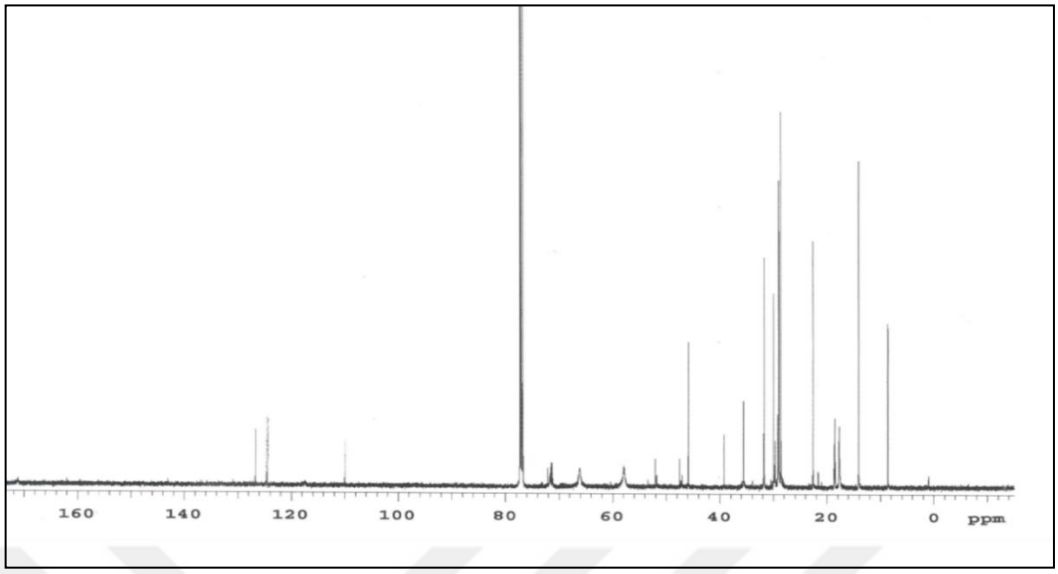


Figure 2.165: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **41.**

According to (+ESI) mass spectrum concerning the compound **41**; the molecular ion peak of a new compound ($C_{18}H_{29}Cl_3N_2O_3S$), M_w = 459.87 g/mol) was seen at *m/z* (100%) = 482.9 $[M+Na]^+$ and at *m/z* (61%) = 459.0 $[M-H]^+$ (Figure 2.166).

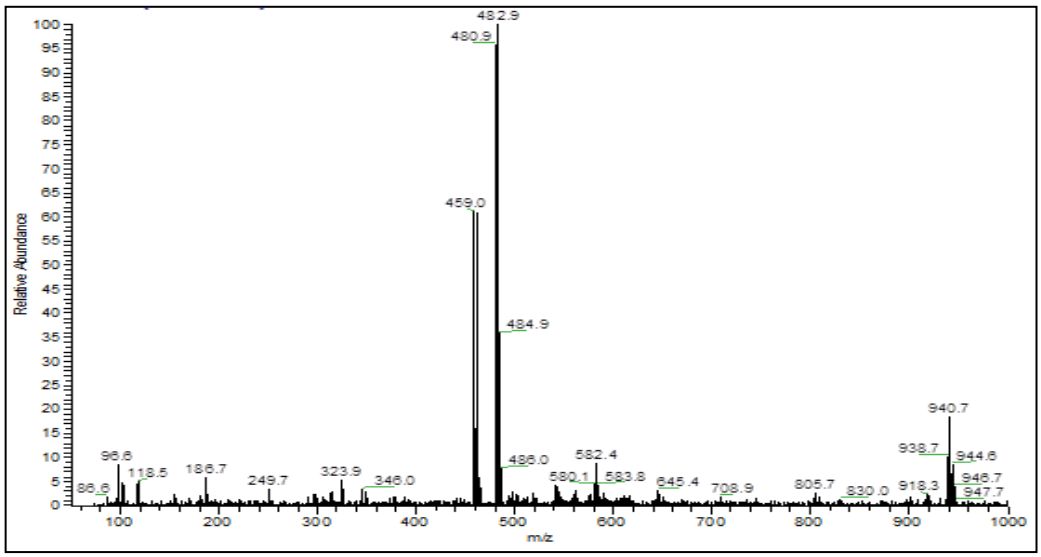
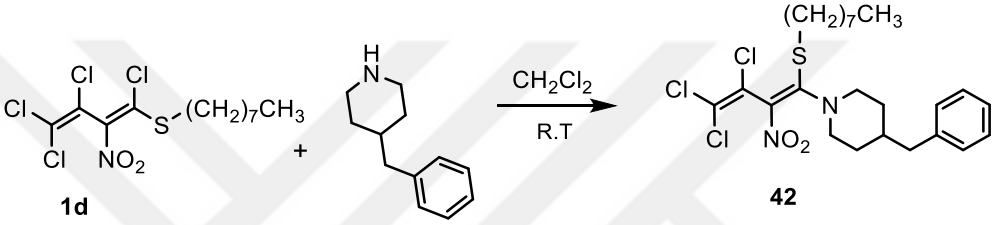


Figure 2.166: Mass spectrum [+ESI] concerning the compound **41.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(41)**.

2.3.5. Synthesis of (E)-4-benzyl-1-(3,4,4-trichloro-2-nitro-1-(octylthio)buta-1,3-dien-1-yl)piperidine (42)

The new compound (**42**) was formed when the compound **(1d)** reacted with 4-benzylpiperidine in dichloromethane at room temperature for 12 hours as general procedure 6.



(2.30)

According to the IR spectrum concerning the compound **42**; stretching band for (C-H) were detected at ν = 2921, 2852 cm^{-1}. (C=C) bands were seen at ν = 1674, 1598 cm^{-1}. Stretching (asymmetric, symmetric) bands of (C-NO_2) were appeared at 1523, 1260 cm^{-1} respectively (Figure 2.167).

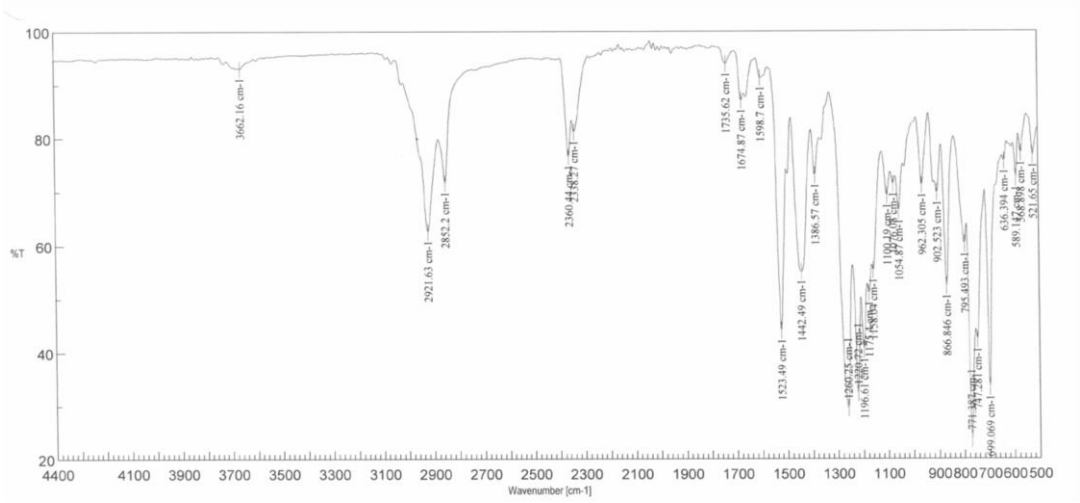


Figure 2.167: FTIR (KBr) spectrum concerning the compound **42.**

According to ^{1}H NMR spectrum concerning the compound **42**; triplet around δ = 0.85 ppm is corresponding to protons of methyl group, whereas, protons of (C**H**$_2$) at δ =1.14-1.27 ppm as multiplet. Protons of (C**H**$_2$-CH$_3$) were appeared at δ =1.38-1.40 ppm as a multiplet, (S-CH$_2$C**H**$_2$) at δ = 1.55-1.61 ppm as a multiplet. Protons of piperidine ring (C**H**$_2$-C**H**-C**H**$_2$) were appeared at δ = 1.85 and 1.90 ppm as a multiplet. A doublet at δ =2.52 ppm for (-C**H**$_2$-). (S-C**H**$_2$) was seen at δ =2.88 as triplet. (C**H**$_2$-N-C**H**$_2$)$_{piperi}$ at δ =3.20-4.10 ppm as a broad multiplet. Aromatic protons take place at δ =7.20-7.25 ppm as multiplet too (Figure 2.168).

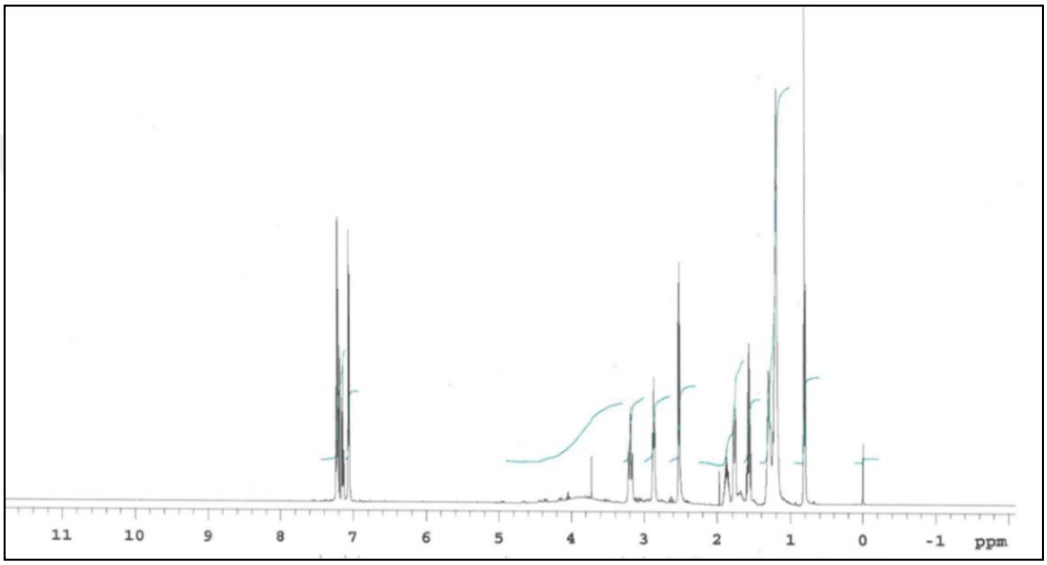


Figure 2.168: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **42.**

According to ^{13}C NMR spectrum concerning the compound **42;** (CH$_3$) carbon signal was appeared at δ = 14.09 ppm, (**C**H$_2$CH$_3$) at δ = 22.61 ppm, (**C**H$_2$) signals at δ = 28.68, 28.99, 29.03, 29.77 ppm. Signals of (**C**H$_2$-CH-**C**H$_2$) in piperidine ring at δ = 31.71 ppm. (S-CH$_2$-**C**H$_2$) and (S-**C**H$_2$) were appeared at δ = 32.25 and 35.33 ppm. (CH$_2$-**C**H-CH$_2$)$_{piperi}$, (**C**H$_2$-N-**C**H$_2$)$_{piperi}$ and (-**C**H$_2$-) were seen at δ = 37.50, 42.37 and 54.01 ppm respectively. Signals at δ =124.17, 126.36, 127.09, 128.47, 128.56, 128,98, 129.02, 139.18, 169.2 ppm are belonging to (C$_{butad,}$ CH$_{arom}$) (Figure 2.169).

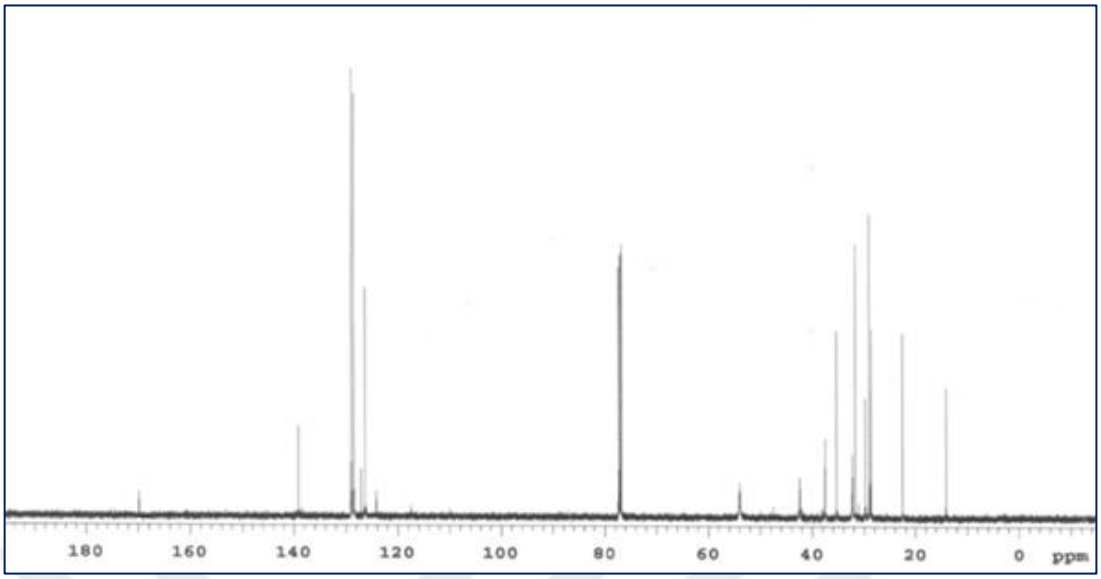


Figure 2.169: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **42.**

According to (+ESI) mass spectrum concerning the compound **42**; the molecular ion peak of a new compound ($C_{24}H_{33}Cl_3N_2O_2S$), M_w = 519.95 g/mol) was seen at *m/z* (35%) = 521.1 $[M+H]^+$ and $[M+Na]^+$ at *m/z* (100%) = 543.0 (Figure 2.170).

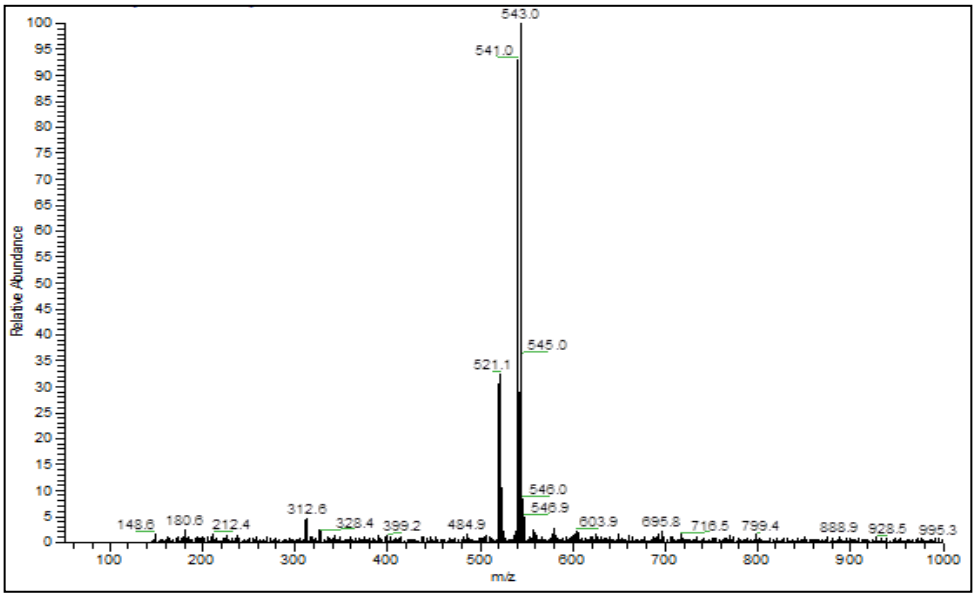
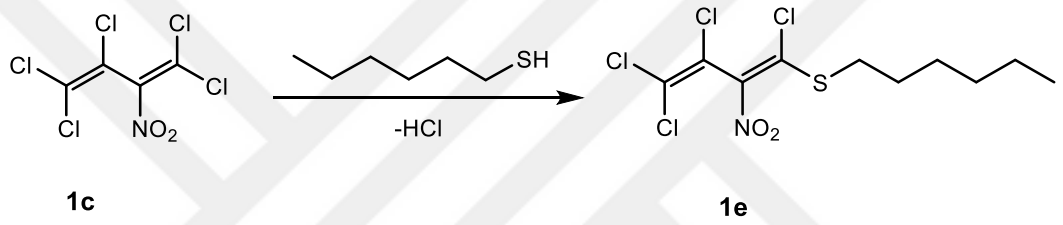


Figure 2.170: Mass spectrum [+ESI] concerning the compound **42.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(42)**.

2.3.6. **Synthesis of 2-nitro-1,3,4,4-tetrachlor-1-(hexylsulfanyl)-1,3-butadiene (1e)**

The reaction of 2-nitropentachloro-1,3-butadiene **(1c)** [94] with 1-hexanethiol in a solvent-free medium at room temperature 12 hours according general procedure 5. A new compound **(1e)** was obtained as a mono(thio) substituted compound.



1c **1e**

(2.31)

According to IR spectrum concerning the compound **1e**; stretching band for (C-H) were detected at ν = 2957, 2925, 2858 cm^{-1}. (C=C) band was seen at ν = 1601 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at 1528, 1287cm^{-1} respectively (Figure 2.171).

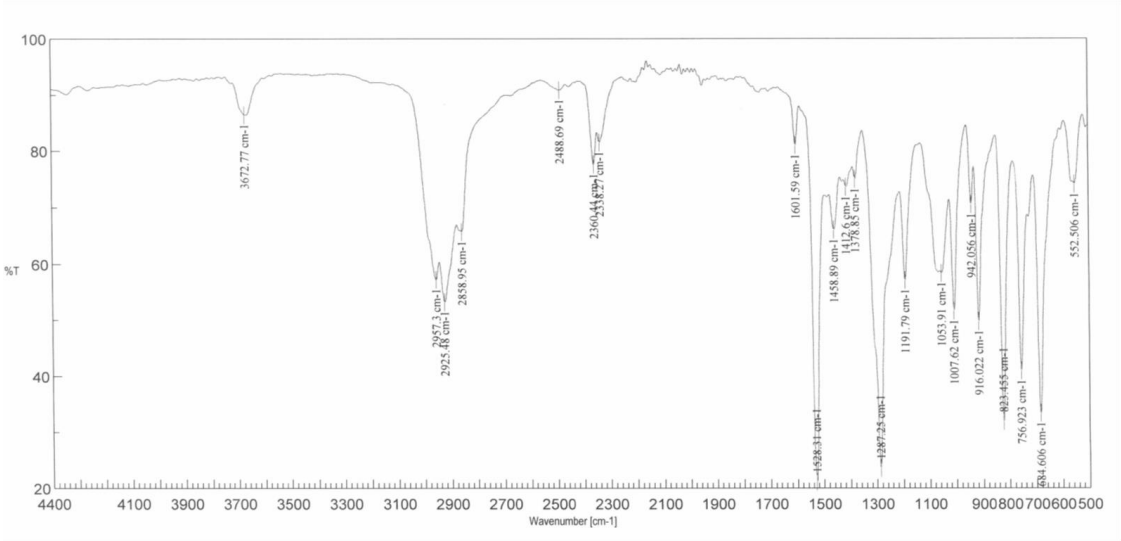


Figure 2.171: FTIR (KBr) spectrum concerning the compound **1e.**

According to ^{1}H NMR spectrum concerning the compound **1e**; multiplet at δ = 0.81 ppm is corresponding to protons of methyl group, whereas, protons of (2C**H**$_2$) at δ =1.19-1.30 ppm as a multiplet. Protons of (C**H**$_2$-CH$_3$) were appeared at δ =1.37-1.40 ppm as a multiplet, (S-CH$_2$C**H**$_2$) at δ = 1.62-1.71 ppm as a multiplet. A triplet at δ =3.02 ppm is related to (S-C**H**$_2$) (Figure 2.172).

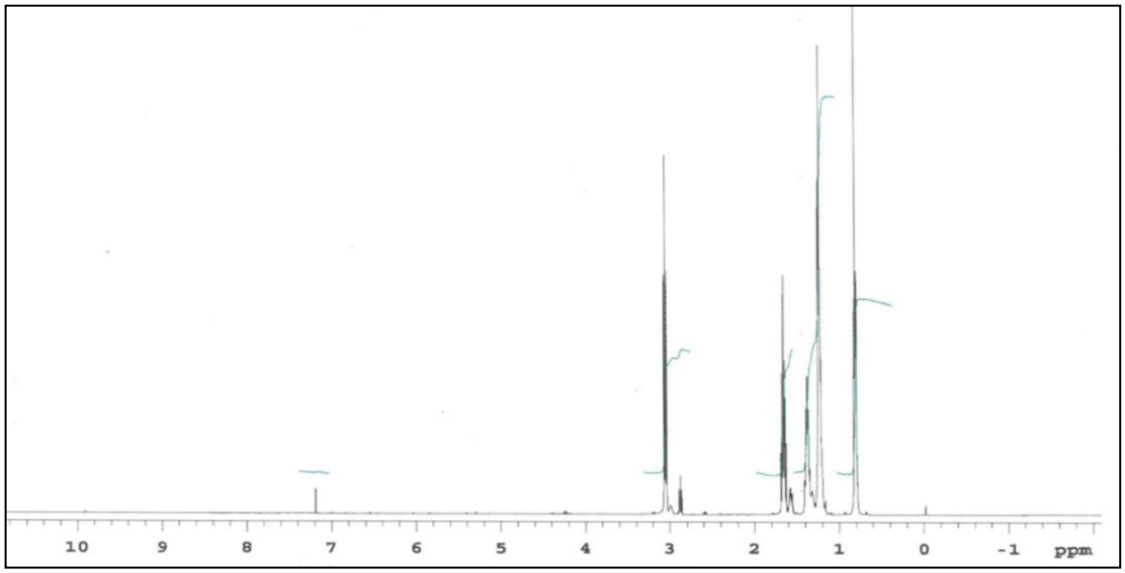


Figure 2.172: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **1e.**

According to ^{13}C NMR spectrum concerning the compound **1e;** (CH_3) was appeared at δ = 13.96 ppm, (**C**H_2CH_3) at δ = 22.47 ppm, (2**C**H_2) signals at δ = 28.36, 29.36 ppm. Signals of (S-CH_2-**C**H_2) was seen at δ =31.06 ppm and (S-**C**H_2) at δ = 36.07 ppm. Signals at δ =121.61, 128.55, 138.53, 158.53 ppm are belonging to carbons of butadiene (Figure 2.173).

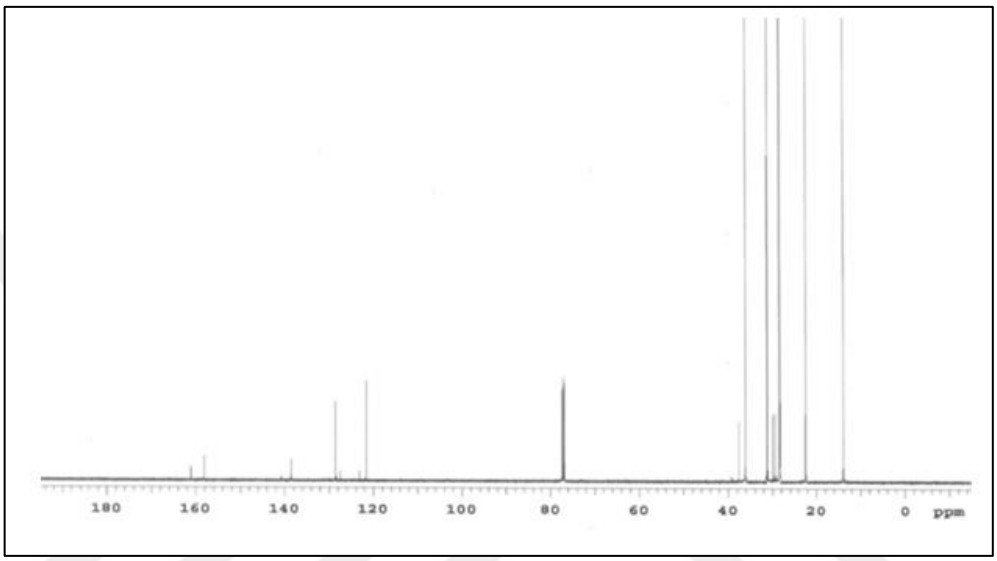


Figure 2.173: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **1e.**

According to (+ESI) mass spectrum concerning the compound **1e**; the molecular ion peak of a new compound ($C_{10}H_{13}Cl_4NO_2S$), M_w = 353.08g/mol) was seen at *m/z* (100%) = 353.9 $[M+H]^+$ (Figure 2.174).

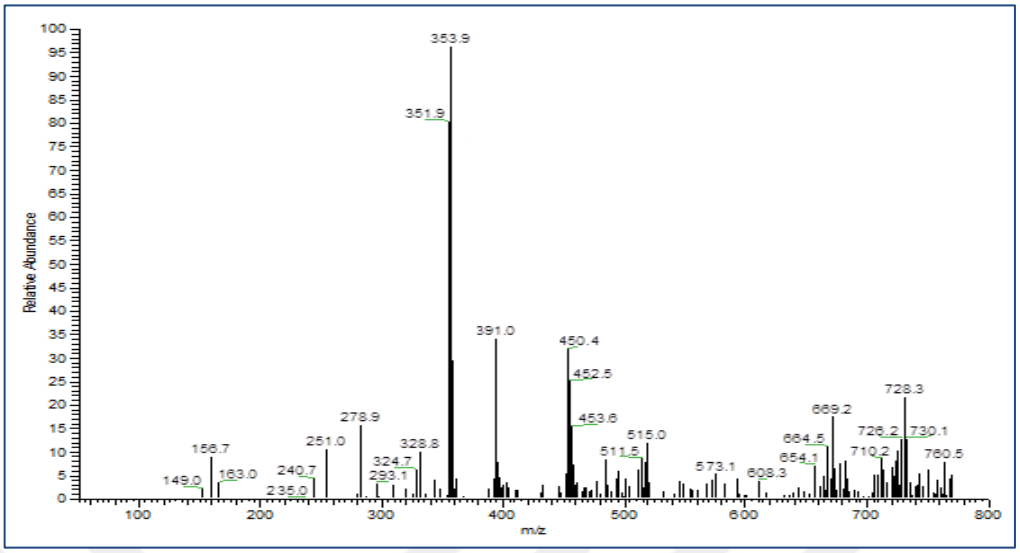
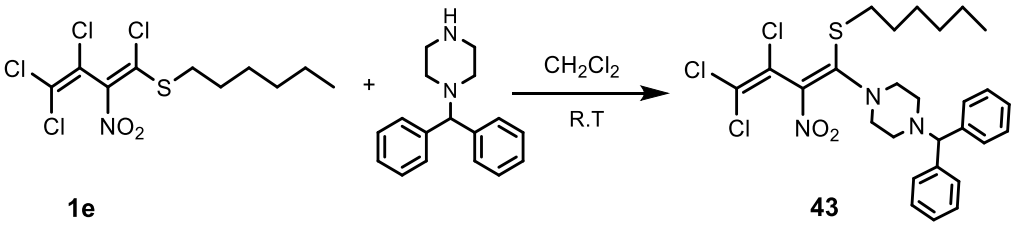


Figure 2.174: Mass spectrum [+ESI] concerning the compound **1e.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(1e)**.

2.3.7. Synthesis of (E)-1-benzhydryl-4-(3,4,4-trichloro-1-(hexylthio)-2-nitrobuta-1,3-dien-1-yl)piperazine (43)

The new compound (**43**) was formed when the compound **(1e)** reacted with 1-(diphenylmethyl)piperazine in dichloromethane at room temperature for 12 hours as general procedure 6.



(2.32)

According to IR spectrum concerning the compound **43**; stretching band for (C-H) were detected at ν = 2957, 2924, 2812 cm^{-1}. (C=C) band was seen at ν = 1595 cm^{-1}. Stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at 1524, 1268 cm^{-1} respectively (Figure 2.175).

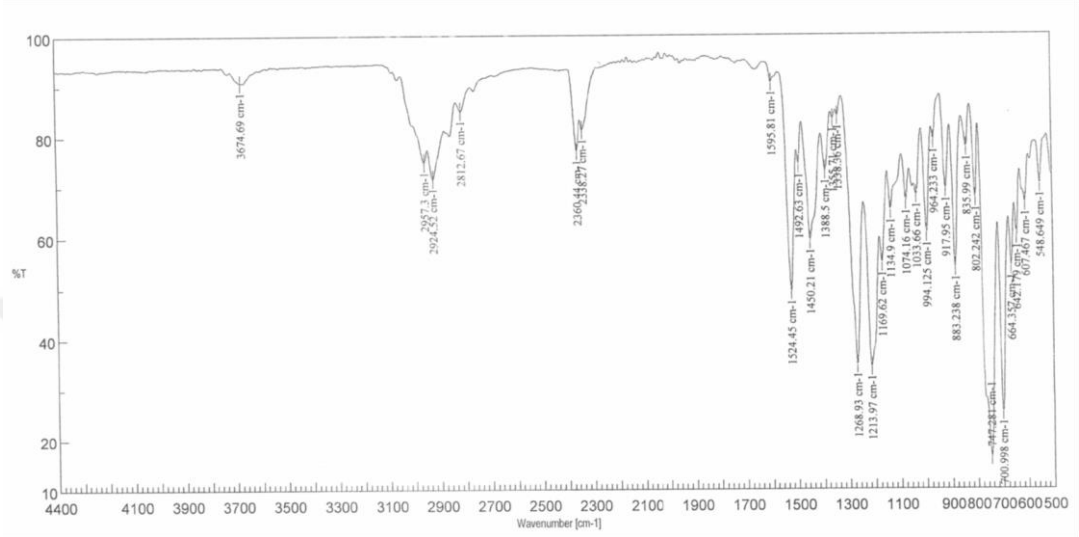


Figure 2.175: FTIR (KBr) spectrum concerning the compound **43.**

According to ^1H NMR spectrum concerning the compound **43**; triplet at δ = 0.89 ppm is corresponding to protons of methyl group, whereas, protons of (2C**H**$_2$) at δ =1.19 ppm as multiplet. Protons of (C**H**$_2$-CH_3) were found at δ =1.22 ppm as multiplet, (S-CH_2C**H**$_2$) at δ = 1.52 ppm as a multiplet. Piperazine ring were seen at 2.50 and 3.50 ppm as abroad singlet. A triplet at δ =2.81 ppm is related to (S-C**H**$_2$). A singlet at δ =4.20 ppm is corresponding to (CH<), aromatic protons are taking place at 7.10-7.38 ppm (Figure 2.176).

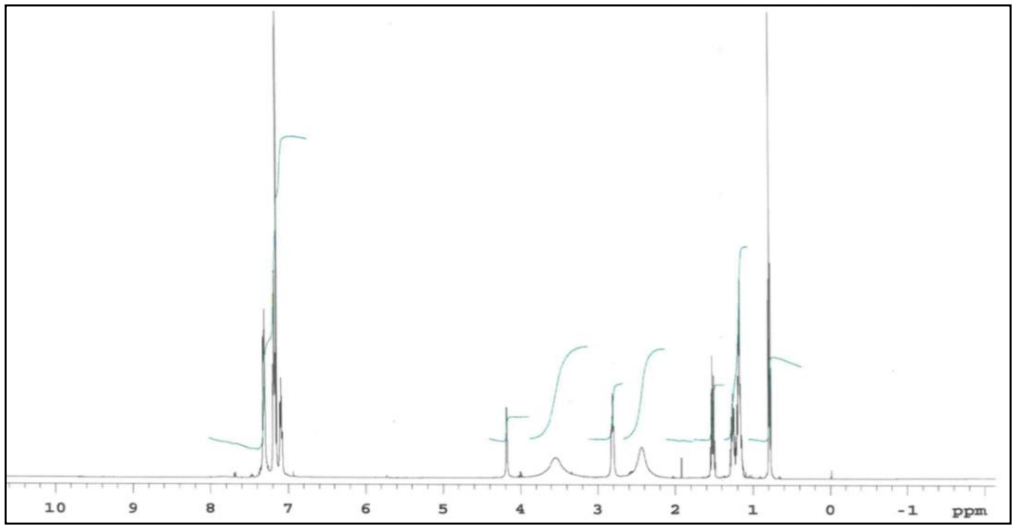


Figure 2.176: ^{1}H NMR ($CDCl_3$) spectrum concerning the compound **43.**

According to the ^{13}C NMR spectrum concerning the compound **43**; (CH_3) carbon signal was appeared at δ = 14.04 ppm, (**C**H_2CH_3) at δ = 22.43 ppm, (2**C**H_2) signals at δ = 28.30, 29.39 ppm. Signals of (S-CH_2-**C**H_2) was seen at δ =31.06 ppm and (S-**C**H_2) at δ = 35.50 ppm. Signals at δ = 51.60 and 53.57 ppm are related to piperazine ring. (**C**H<) at δ =75.79 ppm. Signals at δ =117.80, 124.38, 126.55, 127.00, 128.43, 128.82, 130.04, 141.60, 168.97 ppm are belonging to carbons of butadiene and aromatic rings (C_{butad}, CH_{arom}) (Figure 2.177).

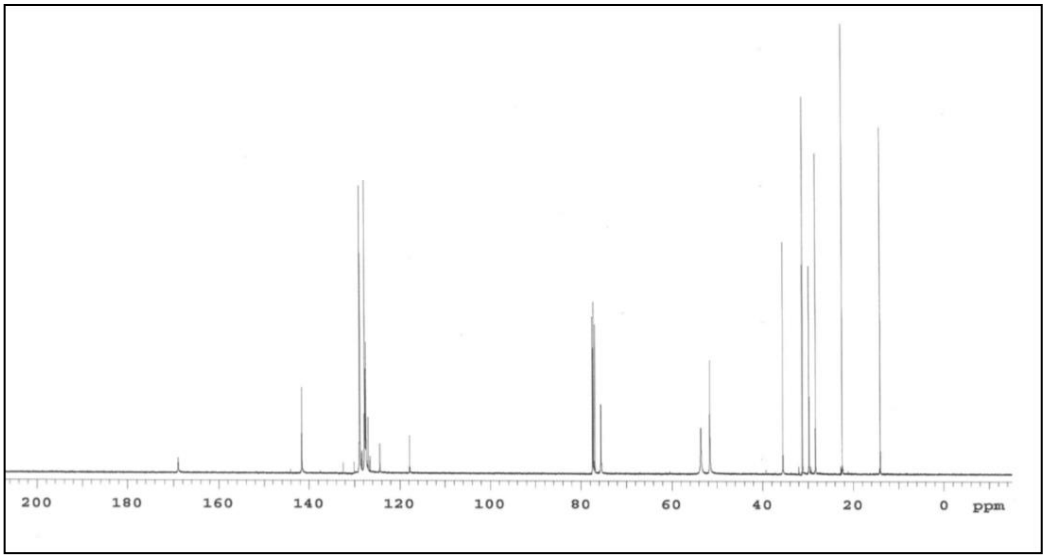


Figure 2.177: ^{13}C NMR ($CDCl_3$) spectrum concerning the compound **43.**

According to (+ESI) mass spectrum concerning the compound **43**; the molecular ion peak of a new compound ($C_{27}H_{32}Cl_3N_3O_2S$), M_w = 568.08 g/mol) was seen at *m/z* (100%) = 567.9 $[M]^+$ (Figure 2.178).

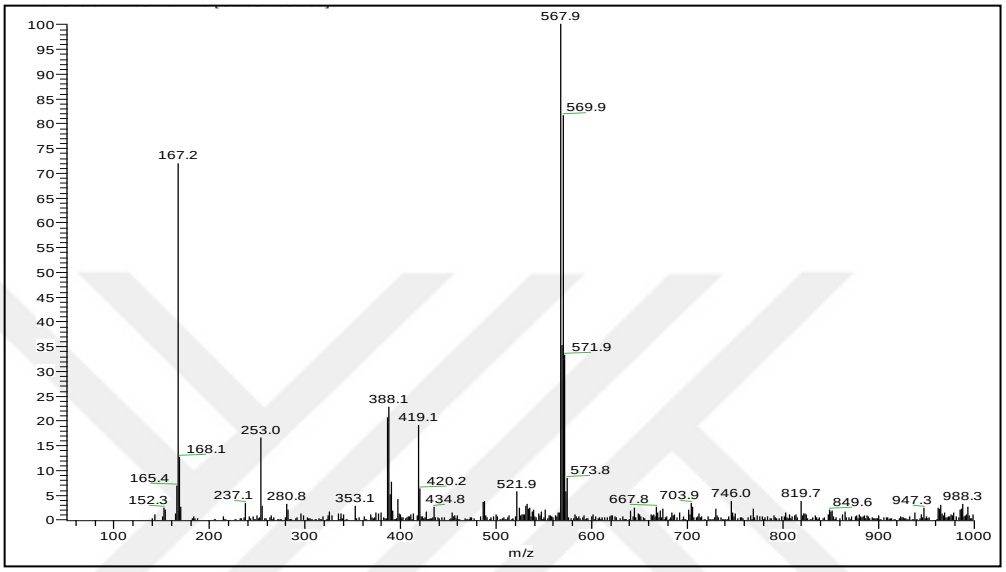


Figure 2.178: Mass spectrum [+ESI] concerning the compound **43.**

All the obtained results from mass spectrum and other data prove the correct proposed structure of new compound **(43)**.

3. RESULTS

3.1. EQUIPMENTS AND CHEMICAL SUBSTANCES THAT USED IN THE EXPERIMENTS

Column chromatography filler; Kieselgel 60 (63-200 μm) (Fluka).

Thin Layer Chromatography (TLC) plates: Silica 60 F 254 (Merck, Darmstadt).

Rotavapor: Büchi Heating Bath B-490.

UV lamb: CAMAC Muttenz-Schweiz 29200. Ultraviolet light (254 nm).

Drying apparatus: Chem-Dry-Laboratory Devices Inc.

Melting point device: Büchi SMP 20 (B-540).

FT-IR Spectrometer: Perkin Elmer Precisely Spectrum One FT-IR spectrometry.

^{1}H, ^{13}C NMR Spectrometer: Varian UNITY INOVA (499.83 MHz for ^{1}H, 125 MHz for ^{13}C).

MS spectrometer: Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer, electrospray ionization (+ESI) mode.

Silica gel 60 (Fluka), particle size (63-200 μm).

Technical solvents such as hexane, petroleum ether, chloroform, methylene chloride, ethyl acetate and ethanol were used without extra purification. The mentioned brands of the substances that have been used are shown in the table 3.1.

Table 3.1: The chemical substances that used in the experimental part.

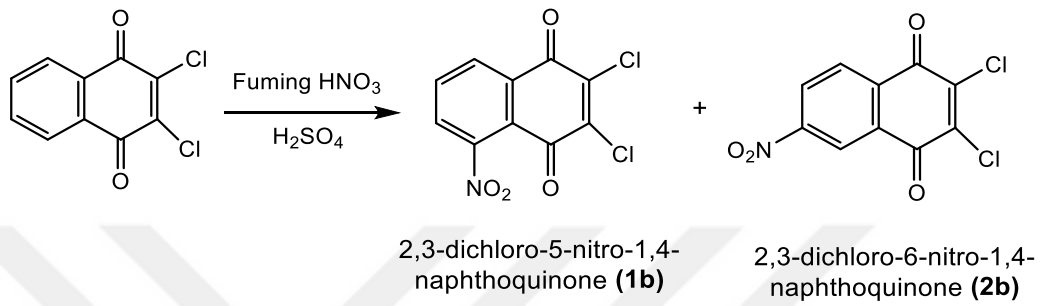
Chemical Substances	Company Name
Na_2CO_3, Na_2SO, $CaCl_2$, HNO_3, H_2SO_4	Merck
Triethylamine TEA	Merck
1-(piperonyl)piperazine	Aldrich
1-(diphenylmethyl)piperazine	Fluka
1-(2-aminoethyl)piperazine	Acros Organics
2,4-dimethoxyaniline,	Merck
Trimethyl aniline, 4-methoxyaniline	Merck
2,6-dimethylmorpholine	Merck
1-(2-aminoethyl)pyrrolidine	Aldrich
1-(2-aminoethyl)piperidine	Aldrich
4-(2-aminoethyl)morpholine	Aldrich
1-(2-furoyl)piperazine	Aldrich
4-benzylpiperidine	Aldrich
1-hexanethiol, 1-octanethiol	Aldrich

3.2. SYNTHESIS OF STARTING MATERIALS

3.2.1. Preparation of 2,3-dichloro-5-nitro-1,4-naphthoquinone and 2,3-dichloro-6-nitro-1,4-naphthoquinone (1b, 2b)

A mixture of 2,3-dichloro-1,4-naphthoquinone and sulphuric acid was prepared by mixing 50 g of 2,3-dichloro-1,4-naphthoquinone with 65 ml of 98% H_2SO_4, then 130 ml of fuming HNO_3 added slowly with stirring. The temperature is increased after adding 31 ml of HNO_3, in this case, it was necessary to cooling the reaction and keep the temperature below 100ºC, (because at temperature above of 120ºC, the reaction can be decomposed). The remining of nitric acid was added drop-wise with keeping the temperature between (80-90ºC) for about 7 h and then the solution was transferred into ice when the yellow product precipitated. The precipitate was filtered and washed several times by water then stirred with 1N Na_2CO_3 solution about 8 h. The solid formed was precipitated and washed several times by water, then dried and recrystallized with $CHCl_3$. At this stage the yellow product is a mixture of the

isomer in which nitro group is substituted at position 5 and 6. These isomers ware separated by chromatographic column using Hexane/EtAc (6:1 v/v). The physical properties and characterization methods have been described befor. The reaction (3.1) showing the isomer formation of 5/6 nitro naphthoquinone from 2,3-dichloro-1,4-naphthoquinone [112, 113].



(3.1)

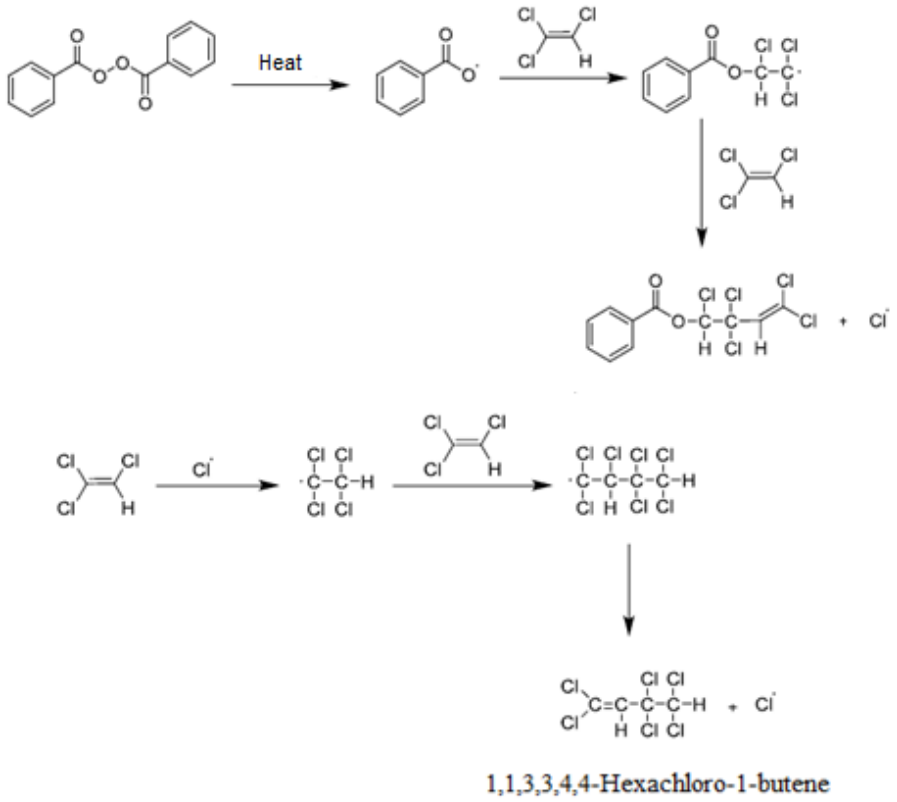
3.2.2. **Preparation of 2-nitro-pentachloro-1,3-butadiene (1c)**

Three steps are required to synthesis this compound**.**

3.2.2.1. ***Preparation of 1,1,3,3,4,4-hexachloro-1-butene***

Trichlorethylene, in the presence of benzoyl peroxide free radical dimerization forming 1,1,3,3,4,4-hexachloro-1-buten [115].

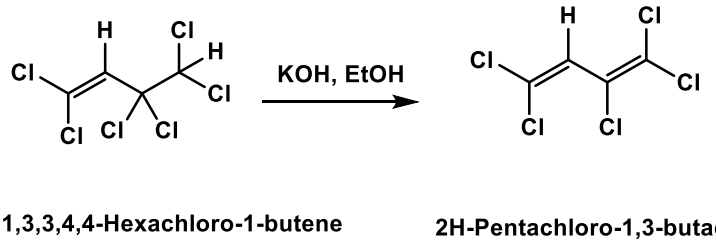
358 ml of trichlorethylene (Cl_2C=CHCl) was puted into flask, heated and stirred for 96 h. At this time 11.616 g of benzoyl peroxide was added to the flask. Remaining boiling point to high boiling vacuum. Distillation yielded 1,1,3,3,4,4-hexachloro-1-butene., yield: 315 g, 60%, B.p.: 102-108 °C



(3.2)

3.2.2.2. ***Preparation of 2H-Pentachlorobutadiene***

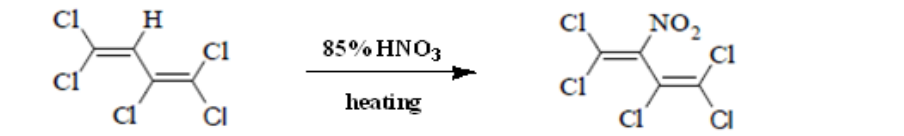
3g of KOH disolved in water (10 ml), then added to 25 ml of ethanol. This mixture added to 13.2 g of hexachloro-1-butene (Cl_2C=CH-CCl_2-$CHCl_2$) and cooled over 6 hours. The precipitating salt is eliminated and the filter is then extracted using 1,1,2,4,4-pentachlorobuta-1,3-diene were obtained by distillation, which is a colorless, liquid, B.p.: 76-78 $^{\circ}$C, Yield: 8.52 g, 75% [116].



(3.3)

3.2.2.3. Preparation of 2-nitro-pentachloro-1,3-butadiene (1c)

22.7 g of 2H-pentachloro-1,3-butadiene stirred at 90 °C. 50 ml of 85% HNO_3 was added slowly with heating for 12 hours at 90-93 °C, cooled and diluted with 150 ml of H_2O. The separated oil is extracted by ether. Ether layer washed by water, rinsed with solution of 3% KOH and washed again, dried with $MgSO_4$, then dried under vacuum. 2-nitro-pentachloro-1,3-butadiene **(1c)** was obtained as a yellowish oil (B.p.: 69-71°C, Yield: 12 g, 44.3% [94, 117].



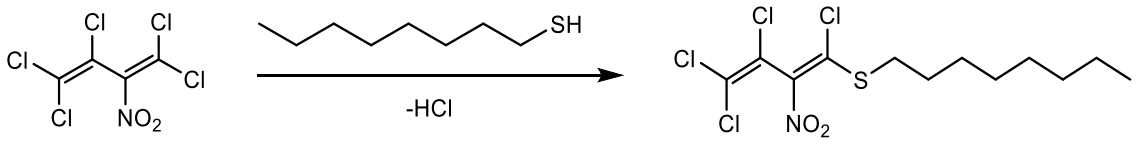
2H-pentachloro-1,3-butadiene 2-Nitro-pentachloro-1,3-butadiene **(1c)**

(3.4)

3.2.3. Preparation of 2-nitro-1,3,4,4-tetrachloro-1-(octylsulfanyl)-1,3-butadiene (1d)

Reaction of 2-nitropentachloro-1,3-butadiene **(1c)** with 1-octanethiol in a solvent-free medium as general procedure 5. A compound **(1d)** was obtained as a mono (thio) substituted compound [114].

1 g (3.68 mmol) 2-nitro-pentachloro-1,3-butadiene **(1c)**, 0.54 g (3.69 mmol) of 1-octanethiol, stirred 24 hours without solvent. According procedure 5. The mixture is then extracted with (30 ml of $CHCl_3$), and washed using (4×30 ml, H_2O) then dried with Na_2SO_4. purified by chromatographic system. **(1d)** was obtained as yellow oil.



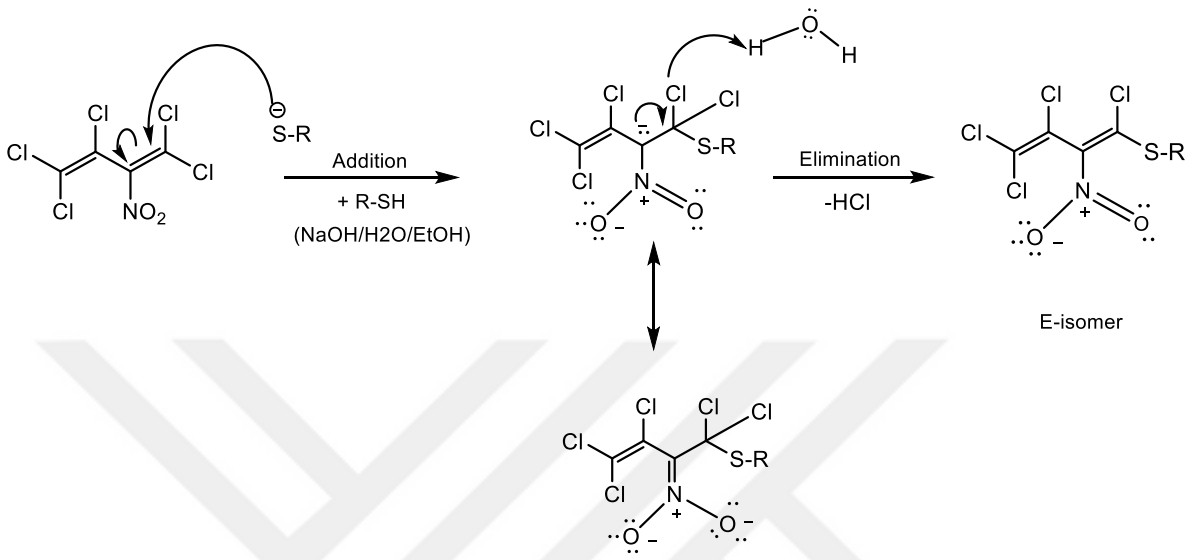
1c

(E)-2-nitro-1,3,4,4-tetrachloro-1-(octylsulfanyl)-1,3-butadiene

(1d)

(3.5)

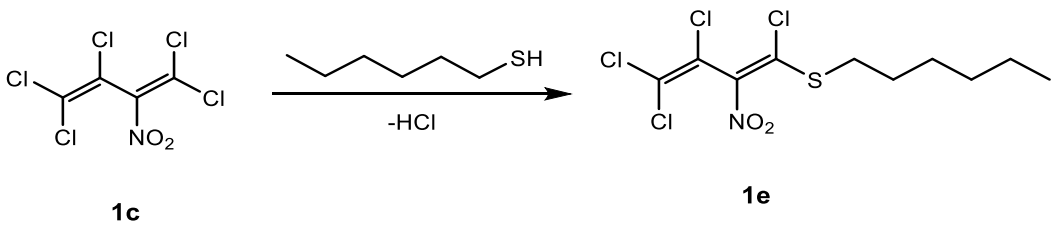
The general proposed mechanism of mono (thio) substituted (E)-nitrodiene compounds is shown in (3.6) [96].



(3.6)

3.2.4. Preparation of 2-nitro-1,3,4,4-tetrachloro-1-(hexylsulfanyl)-1,3-butadiene (1e)

The reaction of 2-nitropentachloro-1,3-butadiene **(1c)** with 1-hexanethiol in a solvent-free medium according procedure 5. A new compound **(1e)** was obtained as mono (thio) substituted compound.



1c **1e**

(3.7)

1 g (3.69 mmol) of compound **(1c)** and 0.44 g (3.70 mmol) of 1-hexanethiol, stirred 24 hours without solvent. The mixture is then extracted with (30 ml, $CHCl_3$), washed using (4×30 ml, H_2O), then after purification **(1e)** was obtained as yellowish oily.

3.3. GENERAL PROCEDURES

3.3.1. General Synthesis Methods of Naphthoquinone Compounds

Procedure 1

2-Methyl-1,4-naphthoquinone **(1a)** and nucleophiles (amines, piperazines, etc.) were stirred in chloroform (25-30 ml) at (25 ^{0}C) for approximately 8 h with presence of tri ethyl amine (TEA). The reaction mixture was monitoring with (TLC) until disappearance of starting naphthoquinone. Then extracted using (30 ml $CHCl_3$), washed three times with water, then dried using Na_2SO_4. To get rid of excess solvent, evaporator system was used. The crude dark residue purified using chromatographic device and dried using vacuum oven at the end.

Procedure 2

Vitamin K3 **(1a)** and nucleophiles (amines, piperazines, etc.) were refluxed in (50 ml) of absolute ethanol with existence of Na_2CO_3 (0.2 g) for 8 hours. The reaction mixture was monitoring by usage of (TLC) till disappearance of starting substances. Then mixture extracted using (30 ml $CHCl_3$), with H_2O washed three times, then Na_2SO4 used for drying. After evaporation. The product purified by chromatographic system and dried using vacuum oven at the end [118].

Procedure 3

2-Methyl-1,4-naphthoquinone **(1a)** and nucleophiles (amines, piperazines, etc.) were stirred in (25-30 ml) of absolute ethanol for (4-8 h/R.T). The mixture was monitoring by (TLC) until lossing of starting material. The mixture then extracted using (30 ml $CHCl_3$), washed with H_2O three times, then dried using Na_2SO_4. After evaporation. The crude dark residue was purified with chromatographic system and dried using vacuum oven at the end [119].

Procedure 4

A compound **(1b)** and nuchleophiles (amines, piperazines, etc.) were stirred in 25 ml of absolute ethanol for 3-4 h (or 8 h in prisince of Na_2CO_3 /R.T). Using (TLC) the mixture was monitoring to exammin the end of reactants. For the extraction (30 ml of $CHCl_3$) were added, then washed with (3×30 ml of H_2O), and dried with Na_2SO_4. Evaporator system was used to remove the extra amount of solvent, then purified using column chromatography [89, 120].

3.3.2. General Synthesis Methods of Pentachloro-2-Nitro-1,3-Butadiene Compounds

Procedure 5

The butadiene **(1c)** with thiols were mixed in an equimolar ratio in a solvent-free medium at room temperature with a magnetic stirrer between 12-48 hours. The reaction progress was controlled using (TLC). Reaction mixture was extracted with chloroform and washed with (3×50 ml) of water, then Na_2SO_4 was used as a dryer. After evaporation, the crude product mixture purified using chromatographic system [97].

Procedure 6

Butadienes **(1d, 1e)** compound with equimolar ratios of nucleophile were dissolved and stirred in CH_2Cl_2 around (12-24 h/R.T). (TLC) card was used for the monotoring of reaction. Then extracted with chloroform, washed by (3×50 ml water), then dried with Na_2SO_4. The product after evaporation, purified using chromatographic system.

3.4. GENERAL SYNTHESIS OF NEW NAPHTHOQUINONE AND BUTADIENE COMPOUNDS

3.4.1. Experiment 1: Synthesis of a new compound (2)

According to procedure 1, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was added to 1-(diphenylmethyl)piperazine (1.46 g, 5.7 mmol) and mixed in chloroform with presence of TEA. The product **(2)** was synthesized as a new compound.

Compound 2: Red solid, yield: 0.349 g, (15 %), R_f :0.90 (EtAc/$CHCl_3$) (1:7 v/v); M.p: 100-101°C. **FT-IR (cm^{-1})**: *v* = 3219 (C-H_{arom}), 2979, 2904, (C-H_{aliph}), 1661 (C=O), 1590 (C=C). **^{1}H NMR (*ppm*)**: δ = 2.00 (s, 3H, CH_3), 2.51 (s, br, 4H, H_{piper}), 3.43 (br, s, 4H, H_{piper}), 4.32 (s, 1H,-CH<), 7.27-7.77 (m, 10H, H_{arom}), 7.80 (d, *J* = 5.44 Hz, 2H, H_{naphth}), 8.00 (dd, *J* = 6.84, 2.93 Hz, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 13.60 (CH_3), 52.91, 53.82 (CH_2-N-CH_2), 76.80 (–CH<), 125.75, 126.19, 126.55, 127.58, 127.73, 127.77, 128.01, 128.3, 128.50, 128.63, 128.85, 130.07, 132.53, 134.8 (CH_{arom}, C_{arom}), 168.24 (=C-N), 183.62, 185.40 (C=O); $C_{28}H_{26}N_2O_2$ (M_w= 422.5 g/mol). **MS (+ESI)**: *m/z* = 423.1$[M]^+$.

3.4.2. Experiment 2: Synthesis of new compounds (3, 4)

According to procedure 1, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with (1.27 g, 5.7 mmol) 1-piperonylpiperazine in chloroform with presence of TEA (3 ml) at room temperature. The products **(3, 4)** were synthesized as new compounds.

Compound 3: Red oily, yield: 0.351g, (18 %), R_f: 0.54 (EtAc/$CHCl_3$) (1:2 v/v). **FT-IR (*cm*$^{-1}$)**: *v* = 3093 (C-H_{arom}), 2979, 2902, (C-H_{aliph}), 1661, 1630 (C=O), 1590, 1563 (C=C). **^{1}H NMR (*ppm*)**: δ = 2.01 (s, 3H, CH_3), 2.56 (br, s, 4H, H_{piper}), 3.37 (t, *J*= 7.3, 4H, H_{piper}), 3.50 (s, 2H, N–CH_2–C_{arom}), 5.86 (s, 2H, O–CH_2–O), 6.71-6.78 (m, 2H, CH_{arom}), 6.81 (s, 1H, CH_{arom}), 7.55-7.84 (m, 2H, H_{naphth}), 7.89-7.99 (d, *J* = 5.85 Hz, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 13.58 (CH_3), 50.98, 53.57 (CH_2-N-CH_2)$_{piper}$, 62.69 (CH_2), 100.90 (O-CH_2-O), 107.96, 109.71, 122.61, 125.74, 126.16, 128.55, 131.99, 132.37, 132.62, 133.43 (CH_{arom}, C_{arom}), 146.92, 147.73 (=C-O), 151.52 (=C-N), 183.54, 185.40 (C=O). $C_{23}H_{22}N_2O_4$ (M_w = 390.45 g/mol). **MS (+ESI)**: *m/z* = 391.1 $[M+H]^+$.

Compound 4: Red oily, yield: 0.400 g (21%), R_f: 0.72 (EtAc/$CHCl_3$) (1:2 v/v). FT-IR **(*cm*$^{-1}$)**: *v* = 3069 (C-H_{arom}), 2978, 2900, 2815, 2774 (C-H_{aliph}), 1661, 1630 (C=O), 1587, 1565 (C=C), 1293 (C-N). **^{1}H NMR (*ppm*):** δ =2.61, 3.10 (s, 8H, H_{piper}), 3.62, 3.86 (s, 8H, H_{piper}), 3.44 (s, 2H, N–CH_2–C_{naphth}), 3.50 (s, 4H, N-CH_2-C_{arom}), 5.90 (s, 4H, O–CH_2–O), 6.70-6.89 (m, 6H, CH_{arom}), 7.65 (t, *J* = 7.33 Hz, 1H, H_{naphth}), 7.75 (m, 2H, H_{naphth}), 8.00- 8.18 (dd, *J* = 7.32, 0.89 Hz, 1H, CH_{naphth}). **^{13}C(APT) NMR (*ppm*):** δ = 43.82, (N-CH_2-C_{naphth}), 51.91, 53.21, 58.03 (CH_2-N-CH_2)$_{piper}$, 62.69 (N–CH_2-C_{arom}), 100.94 (O-CH_2-O), 107.79, 109.34, 122.44, 125.86, 126.24, 130.68, 131.39, 132.36, 133.56, 135.17 (CH_{arom}, C_{arom}), 146.96, (=C-N), 153.89 (=C-O), 182.31, 184.20 (C=O). $C_{35}H_{36}N_4O_6$ (M_w = 608.70 g/mol). **MS (+ESI)**: *m/z* = 609.0 $[M]^+$.

3.4.3. Experiment 3: Synthesis of a new compound (5)

According to procedure 2, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with 0.75g (5.8 mmol) of 1-(2-aminoethyl)piperazine in absolute ethanol with presence of Na_2CO_3 (0.2 g). The product **(5)** was obtained as a new compound.

Compound 5: Red solid, yield: 0.558 g, (24%), R_f : 0.62 (EtAc/$CHCl_3$) (1:5 v/v): M.p.: 177-178°C. **FT-IR (*cm*$^{-1}$)**: *v* = 3310 (N-H), 3078 (C-H_{arom}), 2968, 2906, (C-H_{aliph}), 1661 (C=O),

1594, 1563 (C=C). **^{1}H NMR (*ppm*)**: δ = 1.94, (s, 3H, CH3), 2.05 (s, 3H, CH_3), 2.60 (s, 4H, H_{piper}), 2.70 (t, *J* = 7.32, 2H, C**H**$_2$-NH), 3.40 (t, *J*= 4.8 Hz, 4H, H_{piper}), 3.65 (m, 2H, CH_2-N_{piper}), 6.36 (br, s, 1H, N-H), 7.51-7.61 (m, 4H, H_{naphth}), 7.91-7.98 (m, 4H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 11.06, 13.60 (CH_3), 41.57 (CH_2-NH), 51.20, 53.48 (CH_2-N)$_{piper}$ 57.16 (N-CH_2-), 125.78, 126.20, 128.71, 130.51, 131.82, 132.67, 133.48, 134. (CH_{arom}, C_{arom}), 146.61, (=C-NH), 151.51 (=C-N), 182.56, 183.48, 183.65, 185.47 (C=O. $C_{28}H_{27}N_3O_4$, (M_w = 469.53 g/mol). **MS (+ESI)**: m/z = 470.2 $[M+H]^+$.

3.4.4. Experiment 4: Synthesis of a new compound 6)

According to procedure 2, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was refluxed with 0.89 g (5.8 mmol) of 2,4-dimethoxyaniline in absolute ethanol with presence of Na_2CO_3 (0.2 g). The product **(6)** was obtained as a new compound.

Compound 6: Red oily, yield: 0.456 g, (24 %), R_f: 0.50 ($CHCl_3$/hexane) (1:4 v/v). **FT-IR (*cm^{-1}*)**: *v* =3338 (N-H), 3063 (C-H_{arom}), 2970, 2913, (C-H_{aliph}), 1724, 1662 (C=O), 1597,1567 (C=C). **^{1}H NMR (*ppm*)**: δ = 1.73 (s, 3H, CH_3), 3.85 (s, 6H, -OCH_3) 6.44-6.48 (m, 2H, H_{arom}), 6.81 (d, *J* = 9.27 Hz, 1H, H_{arom}), 7.22 (s, 1H, -NH), 7.61-7.73 (m, 2H, H_{naphth}), 8.08-8.18 (dd, *J* = 8.19, 0.98 Hz, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 13.31 (CH_3), 55.52, 55.70 (O-CH_3), 98.95, 103.36, 116,41, 121.96, 124.36, 126.07, 130.49, 132.09, 133.46, 134.25, 143.07 ppm (CH_{arom}, C_{arom}), 153.55, 157.80 ppm (=C-O), 182.53, 184.21 ppm (C=O. $C_{19}H_{17}NO_4$. (M_w = 323.43 g/mol). **MS (+ESI)**: *m/z* = 324.1$[M+H]^+$.

3.4.5. Experiment 5: Synthesis of a new compound (7)

According to procedure 2, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was refluxed with 0.70 g (5.6 mmol) of 4-methoxyaniline in absolute ethanol with presence of Na_2CO_3(0.2 g). The product **(7)** was obtained as a new compound.

Compound 7: Purple solid, yield: 0.351 g (21%), R_f: 0.80 ($CHCl_3$/hexane) (1:4 v/v); M.p.: 69-70°C. **FT-IR (*cm^{-1}*):** *v* = 3248 (N-H), 2966, 2916, (C-H_{aliph}), 1718, 1664 (C=O), 1594, 1563 (C=C), 1072, (C-O). **^{1}H NMR (*ppm*)**: δ = 1.63 (s, 3H, CH_3), 3.74 (s, 3H, -OCH_3), 6.87-6.80 (m, 2H, H_{arom}), 6.89-6.91 (m, 2H, H_{arom}), 7.27 (s, 1H, NH), 7.55-7.66 (m, 2H, H_{naphth}), 8.05, 8.12 (d, *J* = 8.2 Hz, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ=13.22 (CH_3), 55.45 (O-CH_3), 114.12,

116.73, 124.86, 126.12, 130.83, 132.22, 133.39, (CH_{arom}-C_{arom}), 143.10 (=C-N)$_{naphth}$,156.48 (C-O)$_{ph}$, 182.60, 184.35 (C=O). $C_{18}H_{15}NO_3$ (M_w =293.32 g/mol). **MS (+ESI)**: *m/z* =294.1 $[M+H]^+$.

3.4.6. Experiment 6: Synthesis of a new compound (8)

According to procedure 3, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with 0.74 g (5.7mmol) of 1-(2-aminoethyl)piperidine room temperature in ethanol. The product **(8)** obtained as new compound.

Compound 8: Red solid, yield: 0.901 g (53 %) R_f: 0.35, (EtAc/hexane) (1:4 v/v); M.p.: 61-62°C. **FT-IR (*cm*$^{-1}$)**: *v* = 3276 (N-H), 3070 (C-H_{arom}), 2980, 2923, 2855. 2793, 2760 (C-H_{aliph}), 1668 (C=O), 1597,1561 (C=C). **^{1}H NMR (*ppm*)**: δ = 1.39 (br, s, 2H $CH_2C\mathbf{H_2}CH_{2piperi}$), 1.55 (m, 4H, $C\mathbf{H_2}CH_2C\mathbf{H_2}_{piperi}$), 2.13 (s, 3H, CH_3), 2.37 (br, s, 4H, $C\mathbf{H_2}$-N-$C\mathbf{H_2}_{piperi}$), 2.52 (t, *J*= 6.34 Hz, 2H, $CH_2C\mathbf{H_2}$-N), 3.60 (m, 2H, NH-$C\mathbf{H_2}$), 6.37 (s, 1H, NH), 7.46-7.98 (m, 2H, H_{naphth}), 8.00, 8.09 (dd, *J* =7.8, 0.97 Hz, 2H, H_{naphth}). **^{13}C(APT) NMR** (*ppm*): δ = 10.90 (CH_3), 24.34 (C-CH_2-C)$_{piperi}$, 26.01 (C-CH_2-C)$_{piperi}$, 41.84 (HN-CH_2), 45.13 (N-CH_2)$_{piperi}$, 57.64 (N-CH_2). 125.83 (=C-CH_3), 126.86, 126.04, 130.59, 131.86, 133.51. 134.07 (CH_{arom}, C_{arom}), 146.73 (=C-NH), 182.62, 183.31 (C=O). $C_{18}H_{22}N_2O_2$ (M_w =298.38 g/mol). **MS (+ESI):** *m/z* = 294.2 $[M-4H]^+$.

3.4.7. Experiment 7: Synthesis of a new compound (9)

According to general procedure 3; 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with 0.74g (6.4 mmol) of 1-(2-aminoethyl)pyrrolidine room temperature in absolute ethanol. The compund **(9)** was obtained.

Compound 9: Red solid, yield: 0.712 g (43 %), R_f: 0.33 ($CHCl_3$/PET) (1:2 v/v); M.p.: 83-84 °C. **FT-IR (*cm*$^{-1}$)**: *v* = 3332 (N-H), 3067 (C-H_{arom}), 2952, 2876, 2855. 2794 (C-H_{alipha}), 1661 (C=O), 1596, 1563 (C=C). **^{1}H NMR (*ppm*)**: ^{1}H-NMR (*ppm*): δ = 1.73 (m, 4H, CH_2-CH_2)$_{pyrroli}$, 2.13 (s, 3H, CH_3), 2.50 (br, s, 4H, CH_2-N-CH_2)$_{pyrroli}$, 2.67 (t, *J*= 6.34 Hz, 2H, $CH_2C\mathbf{H_2}$-N), 3.60 (dd, *J*= 11.7, 5.8, 2H, HN-$C\mathbf{H_2}$), 6.22 (s, 1H, NH), 7.46-7.85 (m, 2H, $H_{naphth.}$), 7.99, 8.03 (dd, *J*= 7.8, 0.97 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 10.60 (CH_3), 23.50 (CH_2-

$CH_2)_{pyrroli}$ 43.90 (HN-**C**H_2-CH_2-N)$_{aliph.}$, 53.78 (CH_2-N-CH_2-)$_{pyrroli}$, 55.29 (HN-CH_2-**C**H_2-N)$_{aliph}$, 112.24 (=C-CH_3), 125.83, 130.48, 131.56, 133.47, 134.10 (CH_{arom}, $C_{arom.}$), 146.61 (=C-NH)$_{naphth.}$, 182.51, 183.35 (C=O). $C_{17}H_{20}N_2O_2$ (M_w=284.35 g/mol). **MS (+ESI)**: m/z = 281.6 $[M-2H]^+$.

3.4.8. Experiment 8: Synthesis of new compounds (10, 11)

According to general procedure 1; 1.0 g (5.8 mmol) of vitamin K3 **(1a)** mixed with (1.04 g, 5.7 mmol) 1-(2-furoyl)piperazine in chloroform at room temperature with presence of TEA (3 ml). Products **(10, 11)** were obtained as new compounds.

Compound 10: Purple oily, yield: 0.563 g (28 %), R_f: 0.83 (EtAc/PET) (1:2 v/v); **FT-IR (*cm*$^{-1}$)**: *v* = 3227 (C-H_{arom}), 2971 (C-H_{aliph}), 1661 (C=O), 1592,1563 (C=C). **^{1}H NMR (*ppm*)**: δ = 1.16 (s, 3H, CH_3), 3.01 (s, 4H, $CH_2)_{piper}$, 3.96 (s, 4H, $CH_2)_{piper}$, 6.40 (m, 1H, CH_{furan}), 6.51 (m, 2H, CH_{furan}), 7.56-7.68 (m, 2H, $H_{naphth.}$), 8.05-8.11 (m, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 13.54 (CH_3), 40.11, 54.76, (N-CH_2) $_{piper}$, 112.80, 117.88 (CH-CH)$_{furan}$, 126.74, 126.75, 127.55, 127.43, 128.03, 131.91, 132.69, (CH_{arom}, C_{arom}), 143.12, 144.66 (**C**-O-**C**H)$_{furan}$, 146.42, (=C-N), 160.01, 182.41, 183.23 (C=O) $C_{20}H_{18}N_2O_4$ (M_w = 350.13 g/mol). **MS (+ESI)**: *m/z* = 349.1 $[M-H]^+$.

Compound 11: Red oily, yield: 0.712 g (35 %), R_f: 0.33 (EtAc/PET) (1:2 v/v); **FT-IR (*cm*$^{-1}$)**: *v* = 3116 (C-H_{arom}), 2961, 2912 (C-H_{alipha}), 1667, 1617 (C=O), 1556 (C=C). **^{1}H NMR (*ppm*)**: δ = 2.50, 3.12 (s, 8H, CH_2-(N-$(CH_2)_2$) $_{piper}$, 3.60-3.84 (s, 8H, O=C-(N-$(CH_2)_2)_{piper}$, 3.48 (s, 2H, $(CH_2)_{aliph}$, δ = 3.71 (m, 4H, NQ-(N-$(CH_2)_2$) $_{piper}$, 6.32, 6.48 (m, 2H, CH_{furan}), 6.91 (d, *J* = 4.5 Hz, 2H, CH_{furan}), 6.89-7.12 (m, 2H, CH_{furan}), 7.38-7.66 (m, 2H, $H_{naphth.}$), 7.90 (d, *J* = 7.3 Hz, 1H, H_{naphth}), 8.00 (d, *J* = 6.4 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 43.93 (CH_2), 51.99, 53.20, 53.43 (N-CH_2-) $_{piper}$, 109.96 (C_{naphth}-CH_2), 111.80, 117.88 (CH-CH)$_{furan}$, 126.28, 127.55, 132.12, 131.55, 132.95, 134.91, (CH_{arom}, C_{arom}), 147.10 (C-O-CH)$_{furan}$, 147.72 (=C-N), 153.87 (C-O-CH)$_{furan}$, 162.30, 183.90, 184.77 (C=O). $C_{29}H_{28}N_4O_6$ (M_w = 528.56 g/mol), **MS (+ESI)**: *m/z* =529.1 $[M]^+$.

3.4.9. Experiment 9: Synthesis of new compounds (12, 13)

According to procedure 3, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with0.668 g (5.8 mmol) of 2,6-dimethylmorpholine in absolute ethanol at room temperature for 6 hours. Products **(12, 13)** were obtained as new compounds.

Compound 12: Red oily, yield: 0.362 g (22 %); R_f: 0.33 (EtAc/PET) (1:6 v/v). **FT-IR (*cm*$^{-1}$)**: *v* = 2971, 2930 (C-H_{aliph}), 1668 (C=O), 1590, 1546 (C=C). **^{1}H NMR (*ppm*)**: δ =1.07 (s, 6H, $CH_3)_{morph}$, 2.10 (s, 3H, $CH_3)_{naphth,}$ 3.40, 3.89 (m, 4H, N-$CH_2)_{morph,}$ 4.10 (m, 2H, CH-O-CH)$_{morph}$, 7.57-7.62 (m, 2H, H)$_{naphth}$, 7.98 (d, *J*= 7.81 Hz, 1H, H_{naphth}), 8.00 (d, *J*= 7.52 Hz, 1H, $H_{naphtha}$). **^{13}C(APT) NMR (*ppm*)**: δ = 9.33 $(CH_3)_{naphth}$, 18.75 $(CH_3)_{morph}$ 52.46 (CH_2-N-CH_2) $_{morph}$, 71.98 (CH-O-CH)$_{morph,}$ 109.35 (C_{naphth}-CH_3), 124.09, 126.13, 131.36, 132.31, 133,86, 134.91, (CH_{arom}, C_{arom}), 153.91(=C-N) 182.09, 184.76 (C=O). $C_{17}H_{19}NO_3$ (M_w=285.34 g/mol), **MS (+ESI)**: *m/z* =284.1 $[M-H]^+$.

Compound 13: Red oily, yield: 0.352 g (15 %); R_f: 0.26 (EtAc/PET) (1:6 v/v). **FT-IR (*cm*$^{-1}$)**: *v* = 2972, 2929 (C-H_{aliph}), 1785, 1669 (C=O), 1591, 1538 (C=C). **^{1}H NMR (*ppm*)**: δ =1.05-1.18 (m, 6H, CH_3) $_{morph}$, 1.22-1.31 (m, 6H, CH_3) $_{morph}$, 1.87-2.05, 2.55-2.79 (m, 4H, (CH_2-N-CH_2) $_{morph}$) 3.12-3.32, 3.62-3.82 (m, 4H, (CH_2-N-CH_2) $_{morph}$) 3.71 (m, 2H, $CH_2)_{morph,}$ 4.18 (m, 4H, CH)$_{morph}$, 7.55-7.68 (m, 2H, H_{naphth}), 7.92-8.09 (m, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 18.72 $(CH_3)_{morph,}$ 45.49 (CH_2), 56.62 (**C**H_2-N- **C**H_2) $_{morph}$, 59.47 CH_2-(N-(**C**$H_2)_2$) $_{morph,}$ 67.11, 71.92 (**C**H-O-**C**H)$_{morph,}$ 123.92, 126.16, 130.55, 132.09, 132.61, 133,85 (CH_{arom}, C_{arom}), 154.18 (=C-N) 183.93, 184.57 (C=O). $C_{23}H_{30}N_2O_4$ (M_w = 398.5 g/mol). **MS (+ESI)**: *m/z* = 399.1 $[M]^+$.

3.4.10. Experiment 10: Synthesis of new compound (14)

According to procedure 2, 1.0 g (5.8 mmol) of 2-methyl-1,4-naphthoquinone **(1a)** was reacted with 1.0 g (5.7 mmol) of 4-benzylpiperidine in 50 ml of absolute ethanol at room temperature with presence of Na_2CO_3 (0.2 g), Product **(14)** was obtained as a new compound.

Compound 14: Red oily, yield: 0.612 g (32 %); R_f: 0.71 (EtAc/PET) (1:6 v/v). **FT-IR (*cm*$^{-1}$)**: *v* = 2956, 2922, 2853 (C-H_{aliph}), 1722, 1667(C=O), 1596 (C=C). **^{1}H NMR (*ppm*)**: δ = 1.04-1.21, 1.26-1.36 (m, 4H, (C**H**$_2$-CH-C**H**$_2)_{piperi}$), 1.61-1.69 (m, 1H, , (CH_2-C**H**-$CH_2)_{piperi}$), 2.11

(s, 3H, CH_3), 2.50 (2H, d, *J*= 0.86 Hz, CH_2), 3.10, 4.32 (m, 4H, $(CH_2\text{-N-}CH_2)_{piperi}$), 7.07-7.20 (m, 5H, CH_{arom}), 7.50-7.64 (m, 2H, H_{naphth}.), 7.84-7.94 (m, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 13.58 (CH_3), 33.21 ($\mathbf{C}H_2\text{-CH-}\mathbf{C}H_2)_{piperi}$, 37.99 ($CH_2\text{-}\mathbf{C}H\text{-}CH_2)_{piperi}$, 43.32 ($CH_2$), 52.00 $(CH_2\text{-N-}CH_2)_{piper}$, 125.68, 126.12, 126.34, 128.24, 128.84, 129.01, 132.13, 132.48, 133.19, 133.67 (CH_{arom}, C_{arom}), 140.26 ($CH_2\text{-}\mathbf{C}_{ph}$) 153.10 (=C-N), 183.90, 185.45 (C=O). $C_{23}H_{23}NO_2$ (M_w =345.34 g/mol). **MS (+ESI)**: *m/z* = 346.30 $[M+H]^+$.

3.4.11. Experiment 11: Synthesis of isomer (1b, 2b)

According to procedure that mentioned before [114, 115] the product was obtained as a yellowish crystal mixture of two isomers (yield: 58%), using hexane /EtAc (6:1 v/v) the isomer were isolated and purified.

Isomer (2b): Light yellow crystal, yield: 3 g (14%); R_f: 0.6 (EtAc/Hexane) (1:6 v/v); M.p.: 179-180°C. **^{1}H NMR (*ppm*)**: δ = 8.44 (d, *J*= 7.8 Hz, 1H, H_{naphth}), 8.63 (dd, *J*= 10.7, 2.4 Hz, 1H, H_{naphth}), 9.01 (d, *J* = 2.46 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 122.94, 128.27, 128.70, 132.10, 134.30 (CH_{arom}, C_{arom}), 144.13, 144.42 (=C-Cl), 151.39 (C-NO_2), 174.21, 174.61 (C=O). $C_{10}H_3Cl_2NO_4$ (M_w= 272.04 g/mol). **MS (+ESI)**: *m/z* = 271.1 $[M-H]^+$.

Isomer (1b): Dark yellow crystal, yield: 12 g (42 %); R_f: 0.3 (EtAc/Hexane) (1:6 v/v); M.p.: 149-150°C. **^{1}H NMR (*ppm*)**: δ = 7. 81 (dd, *J* = 9.2, 0.98 Hz, 1H, H_{naphth}), 7.98 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.42 (dd, *J* = 8.6, 0.98 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 121.95, 128.26, 130.04, 131.75, 135.53 (CH_{arom}, C_{arom}), 143.35 (=C-Cl), 143.82 (C-NO_2), 172.63, 174.29 (C=O). $C_{10}H_3Cl_2NO_4$ (M_w= 272.04 g/mol). **MS (+ESI)**: *m/z* = 271.2 $[M-H]^+$.

3.4.12. Experiment 12: Synthesis of regioisomers (15, 16)

According to procedure 4, 0.30 g (1 mmol) of the isolated isomer **(1b)** was reacted with 0.28 g (1 mmol) of 1-(diphenylmethyl)piperazine in absolute ethanol at room temperature for 4 hours. Products **(15, 16)** were obtained as a new regioisomer compounds.

Compound 15: Red solid, yield: 0.122 g (24 %); R_f : 0.37 (EtAc /Hexane) (1:3 v/v); M.p: 183-184°C. **FT-IR (cm^{-1}):** *v* = 3085 (C-H_{arom}), 2978, 2906, 2803, 2756 (C-H_{aliph}), 1679, 1644 (C=O), 1589, 1558, 1524 (C=C), 1446, 1285 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.64 (br, s, 4H, H_{piper}), 3.62 (br, s, 4H, H_{piper}), 4.34 (s, 1H, –CH<), 7.20-7.77 (m, 10H, H_{arom}) 7.80-7.82 (m,

1H, H_{naphth}), 8.32 (t, *J* =7.8 Hz, 1H, H_{naphth}), 8.39 (dd, *J* = 7.2, 1.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 45.83, 52.64, 56.10 $(N\text{-}CH_2)_{piper}$ 76.77 (–CH<), 109.98 (=C-Cl), 126.09, 127.05, 127.96, 128.79, 129.37, 130.04 (CH_{arom}, C_{arom}), 148.39 (=C-N), 175.73,179.12 ppm (C=O. $C_{27}H_{22}N_3O_4Cl$ (M_w= 487.94 g/mol). **MS (+ESI)**: *m/z* = 487.9 $[M]^+$.

Compound 16: Pink oily, yield: 0.111 g (22 %); R_f: 0.27 (EtAc/Hexane) (1:3 v/v). **FT-IR (*cm^{-1}*):** *v* = 3084 (C-H_{arom}), 2979, 2905 (C-H), 1653, (C=O), 1590, 1532 (C=C), 1536, 1377(C-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.56 (br, s, 4H, H_{piper}), 3.56 (br, s, 4H, H_{piper}), 4.32 (1H, s, –CH<), 7.11-7.67 (m, 10H, H_{arom}) 7.76-7.80 (m, 1H, H_{naphth}), 7.85 (t, 1H, *J* = 7.3, 1.2 Hz, H_{naphth}) 8.24 (dd, *J* = 7.2, 1.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 52.56, 56.21 $(N\text{-}CH_2)_{piper}$, 77.25(–CH<), 110.15 (=C-Cl), 127.95, 129.00, 129.49, 130.05, 133.07 (CH_{arom}, C_{arom}), 148.03 (=C-N), 179.57, 180.12 (C=O). $C_{27}H_{22}N_3O_4Cl$ (M_w = 487.94 g/mol). **MS (+ESI)**: *m/z* = 487.9 $[M]^+$.

3.4.13. Experiment 13: Synthesis of regioisomers (17, 18)

According to procedure 4, 0.30 g (one mmol) of starting **(1b)** was added to 0.25 g (one mmol) of 1-piperonylpiperazine in absolute ethanol and stirred for 4 hours. The product separated and purified, products **(17, 18)** were obtained as a new regioisomer compounds.

Compound 17: Red solid, yield: 0.110 g (20%); R_f: 0.80 (EtAc/Hexane) (1:3 v/v) M.p: 131-132°C. **FT-IR (*cm^{-1}*)**: v = 3094 (C-H_{arom}), 2912, 2809, 2772, 2659 (C-H_{aliph}), 1679, 1640 (C=O), 1590, 1555 (C=C), 1494, 1438, 1240 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.56 (br, s, 4H, H_{piper}), 3.52 (s, 2H, CH_2), 3.64 (br, s, 4H, H_{piper}), 5.96 (s, 2H, O-CH_2-O), 6.74-6.94 (m, 3H, CH_{arom}), 7.76-7.82 (m, 2H, H_{naphth}), 8.34 (dd, *J* = 9.27, 1.46 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 51.15, 53.31 $(N\text{-}CH_2)_{pipre}$, 62.43 (CH_2), 101.12 (O-CH_2-O), 108.01, 109.56, 122.60, 127.07, 129.42, 130.49, 132.64, 134.17 (CH_{arom}, C_{arom}), 148.40 (C-NO_2), 150.40 (=C-N)), 175.74, 179.07 (C=O). $C_{22}H_{18}N_3O_6Cl$ (M_w = 455.85 g/mol). **MS (+ESI)**: *m/z* = 456.0 $[M]^+$.

Compound 18: Pink solid, yield: 0.223 g (44 %); M.p: 89-91°C; R_f: 0.73 (EtAc/Hexane) (1:3 v/v). **FT-IR (*cm^{-1}*)**: v = 3079 (C-H_{arom}), 2905, 2811, 2772 (C-H_{aliph}), 1676, 1644 (C=O), 1590, 1537 (C=C), 1492, 1439, 1235 (C_{arom}-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.52 (br, s, 4H, H_{piper}), 3.62 (s, 2H, CH_2), 3.64 (br,s, 4H, H_{piper}), 5.97 (s, 2H, O-CH_2-O), 6.74-6.94 (m, 3H,

CH_{arom}), 7.67 (dd, *J* = 9.2, 1.4 Hz, 1H, H_{naphth}), 7.82 (t, *J* =7.8 Hz, 1H, H_{naphth}), 8.21 (dd, *J* = 9.2, 1.4 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 53.26 (N-CH_2), 62.39 (CH_2), 101.08 (O-CH_2-O), 108.07, 109.73, 122.67, 127.63, 129.16, 132.32, 133.70 (CH_{arom}, C_{arom}), 148.35 (C-NO_2), 149.33 (=C-N), 173.97,179.84 (C=O). $C_{22}H_{18}N_3O_6Cl$ (M_w= 455.85 g/mol). **MS (+ESI)**: *m/z* = 456.0 $[M]^+$.

3.4.14. Experiment 14: Synthesis of compound (19)

According to procedure 4, 0.54 g (2 mmol) of **(1b)** was reacted with 0.12 g (1 mmol) of 2-(1-piperazinyl)ethylamine in absolute ethanol for 4 h. The product was separated. Only one new compound was obtained **(19)**.

Compound (19): Pink solid, yield: 0.122 g (40%), M.p.:143-144°C; R_f: 0.57 (EtAc /Hexane) (1:3 v/v). **FT-IR (*cm^{-1}*)**: v = 3258 (N-H), 3076 (C-H_{arom}), 2964, 2922 (C-H_{aliph}), 1676 (C=O), 1590, (C=C), 1534, 1447 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.64 (m, 2H, C**H**$_2$ -N), 3.32 (2H, C**H**$_2$-NH) 3.50 (br, s, 4H, H_{piper}), 3.81 (br, s, 4H, H_{piper}), 7.50 (br, s, 1H, NH), 7.99 (dd, *J* = 7.1, 4.9 Hz, 1H, H_{naphth}), 8.01-8.03 (m, 1H,H_{naphth}), 8.05– 8.08 (m, 1H, H_{naphth}) 8.11 (dd, *J* = 7.9, 1.1 Hz, 1H, H_{naphth}), 8.19-8.23(m, 2H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ =40.68 (CH_2-NH), 53.65, 55.15 (N-CH_2)$_{piper}$, 59.82 (CH_2-N), 98.44, 99.55 (=C-Cl), 127.18, 128.80, 129.42, 130.84, 132.58, 134.53 (CH_{arom}, C_{arom}), 148.52 (=C-N), 175.84, 178.97, 190.32 (C=O). $C_{26}H_{19}N_5O_8Cl_2$ (M_w= 600. 36 g/mol). **MS (+ESI)**: *m/z* = 600.0 $[M]^+$.

3.4.15. Experiment 15: Synthesis of regioisomers (20, 21)

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was added to 0.30 g (2.0 mmol) 2,4-dimethoxyaniline in (25 ml) absolute ethanol about 4 h. The products were separated and purified. Products **(22, 23)** were obtained as a new regioisomer compounds.

Compound (20): Red solid, yield: 0.251 g (32%); M.p.: 205-206 °C; R_f : 0.52 (EtAc/Hexane) (1:4 v/v). **FT-IR (*cm^{-1}*)**: v = 3316 (N-H), 3083 (C-H_{arom}), 2967, 2917 (C-H), 1675 (C=O), 1585, 1554 (C=C), 1534, 1370 (C -NO_2). **^{1}H NMR (*ppm*)**: δ = 3.84 (s, 6H, O-CH_3), 6.42 (m, 2H, H_{arom}), 6.93 (m, 1H, H_{arom}), 7.51 (s, 1H, N-H), 7.73 (d, *J* = 7.8 Hz, 1H, H_{naphth}), 8.02 (t, *J*

= 7.3 Hz, 1H, H_{naphth}), 8.40 (d, *J* = 7.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 55.58 (O-CH_3), 98.65, 103,54 (CH_{arom}), 113.79 (=C-Cl), 121.17, 126.85, 128.30, 128.87, 130,88, 131.73, 135.60 (CH_{arom}, C_{arom}), 143.34 (C-NO_2), 148.93 (=C-N), 154.57, 159.64 (=**C**-OCH_3), 172.65, 174.28 (C=O). $C_{18}H_{13}ClN_2O_6$ (M_w= 388.73 g/mol). **MS (+ESI)**: *m/z* = 387.2 $[M-H]^+$.

Compound (21): Red solid, yield: 0.357 g (46%); M.p.:198-199°C; R_f: 0.35; (EtAc/Hexane) (1:4 v/v). **FT-IR (*cm^{-1}*)**: v = 3308 (N-H), 3090 (C-H_{arom}), 2970 (C-H), 1679, 1640 (C=O), 1590, 1563 (C=C), 1455, 1339 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 3.82 (s, 6H, O-CH_3), 6.48 (dd, *J* = 6.9, 2.4 Hz, 2H, H_{arom}), 7.00 (m, 1H, H_{arom}), 7.54 (s, 1H, N-H), 7.69 (dd, *J* = 9.2, 1.4 Hz, 1H, H_{naphth}), 7.87 (t, 7.8 Hz, 1H, H_{naphth}), 8.29 (dd, *J* = 8.8, 1.2 Hz 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 55.68 (O-CH_3), 98.67, 103,60 (CH_{arom}), 113.34 (=C-Cl), 120.17, 123.71, 126.84, 128.95, 131,05, 133.37, 135.24 (CH_{arom}, C_{arom}), 142.86 (C-NO_2), 148.72 (=C-N), 154.11, 159.49 (=**C**-O-CH_3), 173.29, 178.67 (C=O). $C_{18}H_{13}ClN_2O_6$ (M_w= 388.73 g/mol). **MS (+ESI)**: *m/z* = 387.5 $[M-H]^+$.

3.4.16. Experiment 16: Synthesis of regioisomers (22, 23)

According to procedure 4, 0.50 g (1.80 mmol) of compound **(1b)** was added to 0.22 g (1.80 mmol) of 4-methoxyaniline in (25 ml) absolute ethanol about 4 h. The products were separated and purified. Products **(22, 23)** were obtained as a new regioisomer compounds.

Compound (22): Red solid, yield: 0.157 g (24%); M.p.: 167-168 °C; R_f : 0.51 (EtAc/Hexane) (1:4 v/v). **FT-IR (*cm^{-1}*)**: v = 3226 (N-H), 3084 (C-H_{arom}), 2919, 2850 (C-H), 1684, 1636 (C=O), 1590, 1563 (C=C), 1532, 1376 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 3.85 (s, 3H, O-CH_3), 5.38 (br, s, 1H, NH), 6.85-6.94 (m, 2H, H_{arom}), 7.04-7.10 (m, 2H, H_{arom}), 7.81 (dd, *J* = 7.9, 1.2 Hz, 1H, H_{naphth}), 7. 97 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.33-8.42 (m, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 55.53 (O-CH_3), 111,70 (CH_{arom}), 113.36 (=C-Cl), 119.17, 123.17, 126.84, 127.14, 128.95, 131.37, 135.24 (CH_{arom}, C_{arom}), 144.86 (C-NO_2), 148.93 (=C-N), 158.64 (=**C**-OCH_3), 173.29, 178.91 (C=O). $C_{17}H_{11}ClN_2O_3$ (M_w= 358.73 g/mol). **MS (+ESI)**: *m/z* = 357.1[M-H] $^+$.

Compound (23): Red solid, yield: 0.355 g (54%); M.p.:129-131 °C; R_f: 0.33 (EtAc/Hexane) (1:4 v/v). **FT-IR (*cm^{-1}*)**: v = 3289 (N-H), 3102, 3002 (C-H_{arom}), 2918, 2843 (C-H), 1680,

1644 (C=O), 1590, 1542 (C=C), 1500, 1329 (C -NO_2). **^{1}H NMR (*ppm*)**: δ = 3.86 (s, 3H, O-CH_3), 6.74-6.98 (m, 2H, H_{arom}), 7.06-7.17 (m, 2H, H_{arom}), 6.15 (s, 1H, N-H), 7.63-7.74 (m, 2H, H_{naphth}), 8.06-8.41 (m, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 55.49 (O-CH_3), 112,04 (=C-Cl), 113.66 (CH_{arom}), 123.12, 126.60, 128.46, 129.17, 131.90, 132.01, 134.60 (CH_{arom}, C_{arom}), 144.25 (C-NO_2), 148.23 (=C-N), 157.36 (=**C**-O-CH_3), 173.66, 178.92 (C=O). $C_{17}H_{11}ClN_2O_3$ (M_w= 358.73 g/mol). **MS (+ESI)**: *m/z* = 357.2 $[M-H]^+$.

3.4.17. Experiment 17: Synthesis of regioisomers (24. 25)

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was added to 0.24 g (1.80 mmol) of 4-(2-aminoethyl) morpholine in (25 ml) ethanol about 4 h. The products were separated and purified. Products **(24, 25)** were obtained as a new regioisomer compounds.

Compound (24): Red solid, yield: 0.231 g (34%); M.p.:178-179 °C; R_f: 0.50 (EtAc/Hexane) (1:2 v/v). **FT-IR (*cm^{-1}*)**: v = 3292 (N-H), 3096 (C-H_{arom}), 2918, 2852, 2813 (C-H), 1690 (C=O), 1591, 1561 (C=C), 1519, 1338 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 2.50 (t, *J*= 6.1, 4H, (C**H**$_2$-N-C**H**$_2$)$_{morph}$), 2.58 (t, *J* = 6.0 Hz, 2H, N-C**H**$_2$CH$_2$), 3.75 (t, *J*= 6.1, 4H, C**H**$_2$-O-C**H**$_2$), 3.85 (m, 2H, HN-C**H**$_2$), 6.94 (br, s, 1H, N-H), 7.65 (dd, *J* = 7.9, 0.98 Hz, 1H, H_{naphth}), 7.86 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.36 (dd, *J* = 7.8, 1.5 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 40.87 (NH-**C**H$_2$-CH$_2$), 52,93 (CH$_2$-N-CH$_2$)$_{morph}$, 56.50 (NH-CH$_2$-**C**H$_2$), 66.94 (CH$_2$-O-CH$_2$)$_{morph}$, 110.36 (=C-Cl), 123.22, 126.09, 129.02, 133.54, 135.24 (CH_{arom}, C_{arom}), 142.16 (C-NO_2), 148.93 (=C-N), 178.69, 181.51 (C=O). $C_{16}H_{16}N_3O_5Cl$ (M_w= 365.77g/mol). **MS (+ESI)**: *m/z* = 366.2 $[M]^+$.

Compound (25): Red solid, yield: 0.221 g (32%); M.p.:173-174 °C; R_f: 0.33 (EtAc/Hexane) (1:2 v/v). **FT-IR (*cm^{-1}*)**: v = 3275 (N-H), 3080 (C-H_{arom}), 2957, 2894, 2822 (C-H), 1679, 1640 (C=O), 1609, 1572 (C=C), 1535, 1330 (C-NO_2). **^{1}H NMR (*ppm*)**: δ =2.62 (br, s, 4H, (C**H**$_2$-N-C**H**$_2$)$_{morph}$), 2.73 (br, s, 2H, N-C**H**$_2$CH$_2$), 3.70 (br, s, 4H, CH$_2$-O-CH$_2$), 3.94 (m, 2H, HN-C**H**$_2$), 7. 06 (br, s, 1H, N-H), 7.66 (dd, *J* = 7.9, 0.98 Hz, 1H, H_{naphth}), 7.81 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.23 (dd, *J* = 7.8, 1.5 Hz, 1H, H_{naphth}). **^{13}C NMR (*ppm*)**: δ = 48.49 (NH-**C**H$_2$-CH$_2$), 53,28 (CH$_2$-N-CH$_2$)$_{morph}$, 57.13 (NH-CH$_2$-**C**H$_2$), 66.45 (CH$_2$-O-CH$_2$)$_{morph}$, 98.63 (=C-Cl), 122.98, 128.71, 129.50, 133.30, 134.24 (CH_{arom}, C_{arom}), 148.83 (C-NO_2), 160.45 (=C-N), 175.26, 176.76 (C=O). $C_{16}H_{16}N_3O_5Cl$ (M_w= 365.77g/mol). **MS (+ESI)**: *m/z* = 364.7 $[M-H]^+$.

3.4.18. Experiment 18: Synthesis of new compound (26)

According to procedure 2; 0.50 g (1.80 mmol) of **(1b)** was mixed with 0.26 g (1.9 mmol) of 2,4,6-trimethylaniline and refluxed in 50 ml absolute ethanol for 24 h with presence of Na_2CO_3 (0.2 g), The mixture was separated and purified. One product was obtained as a new compound **(26)**.

Compound (26): Red solid, yield: 0.298 g (44%); M.p.:171-172°C; R_f : 0.60 (EtAc/PET) (1:4 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3272 (N-H), 3091 (C-H_{arom}), 2982, 2904 (C-H), 1676, 1658 (C=O), 1588 (C=C), 1535, 1365 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 1.31-1.37 (m, 6H, C**H**$_3$), 2.04-2.12 (m, 3H, CH_3), 6.85 (s, 2H, H_{arom}) 5.20 (s, 1H, NH), 7.71-7.79 (m, 1H, H_{naphth}), 7.85-7.92 (m, 1H, H_{naphth}), 8.31-8.35 (m, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 15.93, 16.47 (CH_3), 111.95 (=C-Cl), 123.20, 126.66, 127.22, 129.03, 133.54, 134.92, 135.24 (CH_{arom}, C_{arom}), 148.56 (C-NO_2), 156.85 (=C-N), 176.44, 177.73 (C=O). $C_{19}H_{15}Cl\ N_2O_4$ (M_w= 370.79 g/mol). **MS (+ESI)**: *m/z* = 369.1 $[M-2H]^+$.

3.4.19. Experiment 19: Synthesis of new compound (27)

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was mixed with 0.24 g (1.80 mmol) of 2-(piperidin-1-yl)ethan-1-amine in (25 ml) absolute ethanol about 4 h. The product was separated and purified. One product was obtained as a new compound **(27)**.

Compound (27): Red solid, yield: 0.200 g (33%); M.p:184-185°C; R_f : 0.28 (EtAc/Hexane) (1:2 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3277 (N-H), 3115 (C-H_{arom}), 2929, 2851 (C-H), 1683 (C=O), 1591, 1556 (C=C), 1520, 1336 (C-NO_2). **^{1}H NMR (*ppm*)**:δ =1.45-1.60 (br, s, 2H, $(CH_2)_{piperi}$), 1.62-1.81 (br, s, 4H, C**H**$_2$-CH_2-C**H**$_2$)$_{piperi}$, 2.52 (br, s, 4H, C**H**$_2$-N-C**H**$_2$)$_{piperi}$, 2.68 (br, s, 2H, C**H**$_2$-N), 3.88 (br, s, 2H, HN-C**H**$_2$), 7.16 (br, s, 1H, N-H), 7.69 (dd, *J* = 7.8, 1.2 Hz, 1H, H_{naphth}), 7.81 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.34 (dd, *J* = 7.9, 1.2 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 23.87 (C-**C**H_2-C)$_{piperi}$, 25.43 (**C**-CH_2-**C**)$_{piperi}$, 41.01 (N-CH_2), 54.04 (**C**H_2-N-**C**H_2)$_{piperi}$., 56.88 (HN-CH_2), 126.06, 128.97, 129.46, 133.52, 135.14 (C_{arom}, CH_{arom}), 148.36 (=C-N) 177.59 (C=O). $C_{17}H_{18}ClN_3O_4$ (M_w= 363.80 g/mol). **MS (+ESI)**: *m/z* = 364.2 $[M]^+$.

3.4.20. Experiment 20: Synthesis regioisomers (28, 29)

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was mixed with 0.24 g (1.80 mmol) of 2-(pyrrodin-1-yl)ethane-1-amine in (25 ml) ethanol for about 4 h. Product was separated and purified. Products **(28, 29)** were obtained as a new regioisomer compounds.

Compound (28): Red solid, yield: 0.280 g (46%); R_f : 0.71 (EtAc/Hexane) (1:2 v/v) M.p.:146-147°C. **FT-IR (*cm*$^{-1}$)**: v = 3281 (N-H), 3112 (C-H_{arom}), 2958, 2871, 2789 (C-H), 1681 (C=O), 1591, 1559 (C=C), 1525, 1335 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 1.72 (br, s, 4H, CH_2-$CH_2)_{pyrro}$, 2.51 (br, s, 4H, C**H**$_2$-N-C**H**$_2)_{pyrro}$, 2.61-2.70 (m, 2H, (C**H**$_2$-N), 3.82 (br, s, 2H, HN-C**H**$_2$), 6.96 (br, s, 1H, N-H), 7.61 (d, *J* = 7.8 Hz, 1H, H_{naphth}), 7.79 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.32 (d, *J* = 7.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 23.34 (**C**H_2-**C**$H_2)_{pyroo}$, 43.24 (**N**-CH_2), 54.11 (**C**H_2-N-**C**$H_2)_{pyrro}$., 55.32 (HN-**C**H_2), 109.98 (=C-Cl), 126.02, 128.88, 130.91, 133.43, 135.37 (C_{arom}, CH_{arom}), 148.23 (=C-N) 173.95, 177.32 (C=O). $C_{16}H_{16}ClN_3O_4$ (M_w= 349.77 g/mol). **MS (+ESI)**: *m/z* = 349.5 $[M]^+$.

Compound (29): Red solid, yield: 0.220 g (35%); R_f : 0.33; (EtAc/Hexane) (1:2 v/v); M.p.: 132-133°C. **FT-IR (*cm*$^{-1}$)**: v = 3241 (N-H), 3072 (C-H_{arom}), 2968 (C-H), 1681 (C=O), 1590 (C=C), 1531, 1372 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 1.70 (br, s, 4H, CH_2-$CH_2)_{pyrro}$, 2.48 (br, s, 4H, C**H**$_2$-N-C**H**$_2)_{pyrro}$, 2.58-2.69 (m, 2H, (C**H**$_2$-N), 3.60 (br, s, 2H, HN-C**H**$_2$), 6.93 (br, s, 1H, N-H), 7.47 (d, *J* = 7.8 Hz, 1H, H_{naphth}), 7.76 (t, *J* = 7.8 Hz, 1H, H_{naphth}), 8.29 (d, *J* = 7.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 23.83 (**C**H_2-**C**$H_2)_{pyrro}$, 45.17 (**N**-CH_2), 54.05 (**C**H_2-N-**C**$H_2)_{pyrro}$, 60.90 (HN-**C**H_2), 103.93 (=C-Cl), 122.02, 126.05, 128.16, 131.35, 136.42 (C_{arom}, CH_{arom}), 148.03 (=C-N), 166.72 (C-NO_2), 172.46, 181.90 (C=O). $C_{16}H_{16}ClN_3O_4$ (M_w= 349.77 g/mol). **MS (+ESI)**: *m/z* = 348.5 $[M-H]^+$.

3.4.21. Experiment 21: Synthesis of regioisomers (30, 31)

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was mixed with 0.33 g (1.80 mmol) of 1-(2-furoyl)piperazine in (25ml) absolute ethanol about 4 h. Product was separated and purified. Products **(30, 31)** were obtained as a new regioisomer compounds.

Compound (30): Purple solid, yield: 0.350 g (46 %);M.p.:148-149°C; R_f: 0.61 (EtAc/PET) (1:2 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3141, 3101 (C-H_{arom}), 2927, 2855 (C-H), 1724, 1677, 1648 (C=O), 1610, 1588 (C=C), 1522, 1416 (C-NO_2). **^{1}H NMR (*ppm*)**: δ =3.62 (br, s, 4H, (C**H**$_2$-N-C**H**$_2$)$_{piper}$), 3.94 (br, s, 4H, C**H**$_2$-N-C**H**$_2$)$_{piper}$, 6.50-6.56 (m, 1H, (C**H**$_{furan}$), 7.10 (m, 1H, C**H**$_{furan}$), 7.44-7.49 (m, 1H, C**H**$_{furan}$), 7.72-7.80 (m, 1H, H_{naphth}), 8.12-8.18 (m, 1H, H_{naphth}), 8.35 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: 40.73 (C**H**$_2$-N-C**H**$_2$)$_{piper}$ 51.41 (**C**H$_2$-N-**C**H$_2$)$_{piper}$, 111.52 (C-Cl), 111.89, 117.27, 147.57, 148.54 (C$_{furan}$, CH$_{furan}$), 122.58, 124.74, 127.97, 130.87, 134.99 (C$_{arom}$, CH$_{arom}$), 150.26 (=C-N) 159.15, 175.88, 179.81 (C=O). $C_{19}H_{14}ClN_3O_6$ (M_w= 415.79 g/mol). **MS (+ESI)**: *m/z* = 415.3[M-H]$^+$.

Compound 31: Red solid, yield: 0.211 g (28 %); M.p.:178-180°C; R_f: 0.45 (EtAc/PET) (1:2 v/v). **FT-IR (*cm*$^{-1}$)**: *v* = 3137, 3068 (C-H_{arom}), 2921 (C-H_{alipha}), 1724, 1682, 1646 (C=O), 1617,1589 (C=C). 1538, 1428 (C-NO_2). **^{1}H NMR (*ppm*)**: δ=3.64 (br, s, 4H, CH$_2$-N-CH$_2$)$_{piper}$, 3.90 (br, s, 4H, C**H**$_2$-N-C**H**$_2$)$_{piper}$, 6.42-6.48 (m, 1H, (C**H**$_{furan}$), 7.00 (m, 1H, C**H**$_{furan}$), 7.42-7.48 (m, 1H, C**H**$_{furan}$), 7.60-7.68 (m, 1H, H_{naphth}), 7.72-7.80 (m, 1H, H_{naphth}), 8.30 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 45.91 (C**H**$_2$-N-C**H**$_2$)$_{piper}$, 51.34 (**C**H$_2$-N-**C**H$_2$-)$_{piper}$, 111.44 (=C-Cl), 111.54, 117.26, 147.56, 149.33 (C$_{furan}$, CH$_{furan}$), 122.53, 127.76, 129.25, 132.24, 134.43 (C$_{arom}$, CH$_{arom}$), 159.15 (=C-N) 167.74, 174.09, 179.78 (C=O). $C_{19}H_{14}ClN_3O_6$ (M_w= 415.79 g/mol). **MS (+ESI)**: *m/z* = 413.2 [M-3H]$^+$.

3.4.22. **Experiment 22: Synthesis of compounds (32, 33, 34)**

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was added to 0.21 g (1.80 mmol) of 2,6-dimethylmorpholine in (25 ml) absolute ethanol about 4 h. Product was separated and purified. Products **(32, 33)** were obtained as a new regioisomer compounds and a new compound **(34).**

Compound (32): Pink solid, yield: 0.160 g (25%); M.p:146-147°C; R_f: 0.5 (EtAc/PET) (1:4 v/v). **FT-IR (*cm*$^{-1}$)**: v =3082 (C-H_{arom}), 2963, 2889, 2865 (C-H), 1680 (C=O), 1642, 1591(C=C), 1526, 1370 (C-NO_2), 1219 (C-O). **^{1}H NMR (*ppm*)**: δ =1.14 (s, 6H, CH$_3$)$_{morph}$, 1.31-1.33 (m, 3H, (O-CH$_2$C**H**$_3$), 3.00 (m, 4H, (C**H**$_2$-N-C**H**$_2$)$_{morph}$), 2.59-3.64 (m, 2H, CH)$_{morph.}$ 3.74-3.80 (m, 2H, (O-C**H**$_2$CH$_3$), 7.76-7.85 (m, 2H, CH$_{naphth}$), 8.35 (dd, *J* = 7.8, 1.4 Hz, 1H, CH$_{naphtha}$). **^{13}C(APT) NMR (*ppm*)**: δ= 17.37 (**C**H$_3$)$_{ethoxy}$, 18.59 (CH$_3$)$_{morph}$, 56.03 (CH$_2$)$_{ethoxy,}$

56.87 (**C**H_2-N-**C**H_2-)$_{morph}$, 72.47 (**C**H-O-**C**H)$_{morph}$, 122.69, 127.16, 129.18, 130.91, 132.34, 134.22 (C_{arom}, CH_{arom}), 148.91 (=C-N) 173.98, 179.90 (C=O). $C_{18}H_{20}N_2O_6$ (M_w= 360.37 g/mol). **MS (+ESI)**: *m/z* = 361.7$[M+H]^+$.

Compound (33): Pink solid, yield: 0.110 g (17%); M.p.:155-156°C; R_f: 0.40 (EtAc/PET) (1:4 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3083 (C-H_{arom}), 2972, 2904 (C-H), 1679 (C=O), 1646, 1592 (C=C), 1527, 1370 (C-NO_2), 1219 (C-O). **^{1}H NMR (*ppm*)**: δ =1.20 (s, 6H, CH_3)$_{morph}$, 1.32-1.35 (m, 3H, (O-CH_2C**H**$_3$), 3.23-3.27 (m, 4H, C**H**$_2$-N-C**H**$_2$)$_{morph}$, 3.46-3.67 (m, 2H, CH)$_{morph.}$ 4.17-4.21 (m, 2H, O-C**H**$_2$$CH_3$), 7.79-7.84 (m, 2H, CH_{naphth}), 8.33 (dd, *J* = 7.4, 1.4 Hz, 1H, $CH_{naphtha}$). **^{13}C(APT) NMR (*ppm*)**: δ= 17.57 $(CH_3)_{morph}$, 18.59 (**C**H_3)$_{ethoxy}$, 56.04 (**C**H_2-N-**C**H_2)$_{morph}$, 56.87 $(CH_2)_{ethoxy,}$ 66.78 (**C**H-O-**C**H)$_{morph}$, 119.37, 125.18, 127.69, 129.47, 132.66, 134.19 (C_{arom}, CH_{arom}), 150.87 (=C-N) 176.63, 179.05 (C=O). $C_{18}H_{20}N_2O_6$ (M_w= 360.37 g/mol). **MS (+ESI)**: *m/z* = 361.7$[M+2H]^+$.

Compound (34): Pink solid, yield: 0.143 g (23%); M.p.:159-160°C; R_f : 0.35 (EtAc/PET) (1:4 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3093, 3035 (C-H_{arom}), 2972, 2927, 2900 (C-H), 1684 (C=O), 1632, 1590 (C=C), 1530, 1371 (C-NO_2). **^{1}H NMR (*ppm*)**: δ =1.20 (s, 6H, CH_3)$_{morph}$, 3.01, 3.66 (m, 4H, (C**H**$_2$-N-C**H**$_2$)$_{morph}$), 3.77-3.85 (m, 2H, CH)$_{morph.}$), 7.68 (dd, *J* = 7.8, 1.2 Hz 1H, CH_{naphth}), 7.79 (t, *J* = 7.8, 1H, CH_{naphth}), 8.22 (dd, *J* = 7.8, 1.4 Hz, 1H, $CH_{naphtha}$). **^{13}C(APT) NMR (*ppm*)**: δ= 18.59 $(CH_3)_{morph}$, 56.64 (**C**H_2-N-**C**H_2-)$_{morph}$, 72.40 (**C**H-O-**C**H)$_{morph}$, 111.15 (=C-Cl), 119.61, 124.90, 127.11, 129.42, 132.63, 134.22 (C_{arom}, CH_{arom}), 149.93 (=C-N) 175.78, 179.10 (C=O). $C_{16}H_{15}ClN_2O_5$ (M_w= 350.76 g/mol). **MS (+ESI)**: *m/z* = 350.4 $[M-H]^+$.

3.4.23. **Experiment 23: Synthesis of regioisomer (35, 36)**

According to procedure 4, 0.50 g (1.80 mmol) of **(1b)** was mixed with 0.32 g (1.80 mmol) of 4-benzylpiperidine in (25 ml) absolute ethanol about 4 h. Products were purified and separated. Products **(35, 36)** were obtained as a new regioisomer compounds.

Compound (35): Red solid, yield: 0.332 g (44%); M.p.:153-154°C; R_f: 0.46 ($CHCl_3$/PET) (1:1 v/v). **FT-IR (*cm*$^{-1}$)**: v = 2952, 2920, 2853 (C-H), 1718 (C=O), 1606, 1594(C=C), 1453, 1375 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 1.46-1.59 (m, 2H, CH_2)$_{piperi}$, 1.66-1.93 (m, 3H, C**H**$_2$-C**H**)$_{piperi}$, 2.53-2.71 (m, 2H, (C**H**$_2$), 3.12-3.19 (m, 2H, N-C**H**$_2$)$_{piperi}$, 3.69-3.81 (m, 2H, N-C**H**$_2$)$_{piperi}$, 7.07-7.25 (m 5H, H_{arom}), 7.70-7.74 (m, 2H, H_{naphth}), 8.26-8.37 (dd, *J* = 6.8, 2.4 Hz,

1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ= 33.06 (**C**H_2-CH-**C**H_2)$_{piperi}$, 37.65 (CH_2-**C**H-CH_2)$_{piperi}$, 42.95 (**C**H_2), 52.20 (**C**H_2-N-**C**H_2)$_{piperi}$, 119.98 (=C-Cl), 125.79, 126.95, 128.27, 129.08, 130.02, 132.80, 135.51, 140.00 (C_{arom}, CH_{arom}), 151.10 (=C-N) 175.69, 179.36 (C=O). $C_{22}H_{19}ClN_2O_4$ (M_w= 410.85 g/mol). **MS (+ESI)**: *m/z* = 411.1 $[M]^+$, *m/z* =433.2 $[M+Na]^+$.

Compound (36): Red oil, yield: 0.226 g (30%); R_f: 0.37 ($CHCl_3$/PET) (1:1 v/v). **FT-IR (*cm^{-1}*)**: v = 3060 (C-H_{arom}), 2970, 2919 (C-H), 1717, 1664 (C=O), 1592, 1561 (C=C), 1452, 1329 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 1.38-1.43 (m, 2H, CH_2)$_{piperi}$, 1.69-1.81 (m, 3H, (C**H**$_2$-C**H**)$_{piperi}$), 2.50-2.55 (m, 2H, (C**H**$_2$), 3.12-3.18 (m, 2H, (N-C**H**$_2$)$_{piperi}$), 3.77-3.80 (m, 2H, (N-C**H**$_2$)$_{piperi}$, 7.05-7.25 (m 5H, H_{arom}), 7.62 (m, 1H, H_{naphth}), 7.64-8.72 (m, 1H, H_{naphth}) 8.22 (d, *J* = 7.8 Hz, 1H, H_{naphth}). **^{13}C(APT) NMR (*ppm*)**: δ = 33.05 (**C**H_2-CH-**C**H_2)$_{piperi}$, 37.60 (CH_2-**C**H-CH_2)$_{piperi}$, 42.92 (**C**H_2), 52.20 (**C**H_2-N-**C**H_2)$_{piperi}$, 119.90 (=C-Cl), 122.70, 126.08, 127.01, 128.33, 129.63, 133.61, 134.14, 139.87 (C_{arom}, CH_{arom}), 148.23 (C-NO_2), 151.11 (=C-N) 173.89, 179.35 (C=O). $C_{22}H_{19}ClN_2O_4$ (M_w= 410.85 g/mol). **MS (+ESI)**: *m/z* = 411.2 $[M]^+$, *m/z* =433.1 $[M+Na]^+$.

3.4.24. Experiment 24: Synthesis of new compound (37)

According to procedure 6, 1.0 g (2.62 mmol) of the starting compound **(1d)** was reacted with 0.58 g (2.62 mmol) of 1-piperonylpiperazine in CH_2Cl_2 (25 ml) about 24 h. Producct was separated and purified. Product **(37)** was obtained as a new compound.

Compound (37): Yellow oil, yield: 1.11 g (68%); R_f: 0.52 (EtAc/$CHCl_3$) (1:5 v/v). **FT-IR (*cm^{-1}*)**: v = 2922, 2854, 2774 (C-H), 1524, 1503 (C=C), 1438, 1269 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 0.88 (t, *J* =6.8 Hz, 3H, CH_3), 1.28-1.36 (m, 10H, C**H**$_2$), 1.53-1.55 (m, 2H, (S-CH_2-C**H**$_2$), 2.92 (t, *J* = 7.3 Hz, 2H, S-C**H**$_2$), 2.55 (s, br, 4H, C**H**$_2$-N-C**H**$_2$)$_{piper}$, 3.45 (s, 2H, N-C**H**$_2$), 3.65 (s, br, 4H, C**H**$_2$-N-C**H**$_2$)$_{piper}$ 5.88 (s, 2H, O-C**H**$_2$-O), 6.61-7.25 (m 3H, H_{arom}). **^{13}C NMR (*ppm*)**: δ = 14.09 (CH3), 22.04, 28.65, 28.97, 29.00, 29.69, (CH2), 31.69 (S-CH2-**C**H2), 35.48 (S-**C**H2), 52.37, 53.31 (**C**H_2-N-**C**H_2)$_{piper}$, 62.04 (N-CH2), 101.04 (O-CH2-O), 108.02, 117.79, 122.27, 124.14, 126.92, 147.05, 147.87, 169.30 (CH_{arom}, C_{arom}, C_{butad}). $C_{24}H_{32}Cl_3N_3O_4S$ (M_w= 564.95 g/mol). **MS (+ESI)**: *m/z* = 566.0$[M+H]^+$.

3.4.25. Experiment 25: Synthesis of new compounds (38, 39)

According to procedure 6, 1.0 g (2.62 mmol) of compound **(1d)** was reacted with 0.34 g (2.62 mmol) of 1-(2-aminoethyl) piperazine in dichloromethane (25 ml) about 24 h. The products were separated and purified. Products **(38, 39)** were obtained as a new compounds.

Compound (38): Yellow oil, yield: 0.46 g (21%); R_f: 0.75 ($CHCl_3$). **FT-IR (*cm*$^{-1}$)**: v = 2956, 2921, 2852 (C-H), 1557, (C=C), 1526, 1280 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 11.04 (s, 1H, N-H), 0.89 (m, 6H, CH_3) 1.10-1.29 (m, 16H, C**H**$_2$), 1.38 (m, 4H, C**H**$_2$$CH_3$), 1.50-1.65 (m, 4H, S-$CH_2$-C**H**$_2$), 2.68, 3.80 (br, s, 8H, N-CH_2)$_{piper}$, 2.94 (m, 4H, S-C**H**$_2$), 3.50 (m, 4H, C**H**$_2$C**H**$_2$-NH). **^{13}C NMR (*ppm*):** δ = 14.08 (2**C**H_3), 22.59, 22.73 (2**C**H_2CH_3), 28.52, 28.63, 28.66, 28.95, 28.97, 29.01, 29.16, 29.70 (8CH_2), 31.70, 31.77 (2S-CH_2-**C**H_2), 35.50, 35.54 (2S-**C**H_2), 39.22 (HN-**C**H_2) 52.21, 53.24 (**C**H_2-N-**C**H_2)$_{piper}$, 55.78 (HN-CH_2**C**H_2), 118.02, 120.19, 126.02, 128.54, 162.30 (C_{butad}). $C_{30}H_{47}Cl_6N_5O_4S_2$ (M_w= 818.56 g/mol). **MS (+ESI)**: *m/z* = 816.2$[M-3H]^+$.

Compound (39): Yellowish oily, yield: 0.21 g (17%); R_f: 0.52 ($CHCl_3$). **FT-IR (*cm*$^{-1}$)**: v = 2922, 2852 (C-H), 1600 (C=C), 1525, 1267 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 11.01 (2H, NH_2), 0.81 (m, 3H, CH_3), 1.11-1.31 (m, 8H, C**H**$_2$), 1.48 (m, 2H, C**H**$_2$$CH_3$), 1.57-1.60 (m, 2H, S-$CH_2$-C**H**$_2$), 2.61-2.77 (m, 2H, N-$CH_2$)$_{piper}$, 2.80 (m, 2H, S-C**H**$_2$), 2.93, 3.50 (br, s, 8H, C**H**$_2$-N)$_{piper}$, 4.01 (m, 2H,C**H**$_2$-NH_2). **^{13}C NMR (*ppm*)**: δ = 14.08 (**C**H_3), 22.64 (**C**H_2CH_3), 28.17, 28.37, 28.52, 28.67 (CH_2), 31.20 (S-CH_2-**C**H_2), 35.56 (S-**C**H_2), 41.45 (HN-**C**H_2) 65.78 (HN-CH_2**C**H_2), 52.87, 53.40 (**C**H_2-N-**C**H_2)$_{piper}$, 115.06, 118.48, 124.54, 126.49, 169.71 (C_{butad}). $C_{18}H_{31}Cl_3N_4O_2S$ (M_w= 473.88 g/mol). **MS (+ESI)**: *m/z* = 475.1$[M+H]^+$.

3.4.26. Experiment 26: Synthesis of new compound (40)

According to procedure 6, 1.0 g (2.62 mmol) of **(1d)** was reacted with 0.34 g (2.62 mmol) of 4-(2-aminoethyl) morpholine in dichloromethane (25 ml) about 24 h. The Product **(40)** was separated and obtained as a new compound.

Compound (40): Yellow oil, yield: 0.570 g (45%); R_f: 0.51 (EtAc/$CHCl_3$) (1:5 v/v). **FT-IR (*cm*$^{-1}$)**: v = 3143 (N-H), v = 2954, 2923, 2854 (C-H), 1673, 1556 (C=C), 1443, 1297 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 10.94 (s, 1H, N-H), 0.86 (m, 3H, CH_3) 1.12-1.38 (m, 10H, C**H**$_2$), 1.50-1.65 (m, 2H, S-CH_2-C**H**$_2$), 2.93 (m, 2H, S-C**H**$_2$), 3.08 (m, 4H, C**H**$_2$-N-C**H**$_2$)$_{morph}$, 3.90 (s, 4H, C**H**$_2$-O-C**H**$_2$)$_{morph}$, 3.22 (br, s, 2H, HN-CH_2C**H**$_2$), 4.10 (br, s, 2H, HN-C**H**$_2$). **^{13}C NMR**

(*ppm*): δ = 14.05 (**C**CH_3), 22.56 (**C**H_2CH_3), 28.48, 28.86, 29.01, 29.30, ($4CH_2$), 31.68 (S-CH_2-**C**H_2), 35.56 (S-**C**H_2), 41.80 (HN-**C**H_2) 52.73, 53.67 (**C**H_2-N-**C**$H_2)_{morph}$, 56.50 (HN-CH_2**C**H_2), 64.64 (CH_2-O-$CH_2)_{morph}$, 121.02, 124.19, 128.02, 162.30 (C_{butad}). $C_{18}H_{30}Cl_3N_3O_3S$ (M_w= 474.87 g/mol). **MS (+ESI)**: *m/z* = 473.9$[M-H]^+$.

3.4.27. **Experiment 27: Synthesis of new compound (41)**

According to procedure 6, 1.0 g (2.62 mmol) of compound **(1d)** was reacted with 0.30 g (2.62 mmol) of 2,6-dimethylmorpholine in dichloromethane (25 ml) about 24 h. The Product **(41)** was separated and purified then obtained as a new compound.

Compound (41): Yellow oil, yield: 0.400 g (28%); R_f: 0.45 (PET/$CHCl_3$) (1:1 v/v). **FT-IR (*cm*$^{-1}$)**: v = 2924, 2854 (C-H), 1662, 1596 (C=C), 1523, 1269 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 0.82 (t, *J* = 6.8 Hz, 3H, CH_3) 1.11-1.29 (m, 14H, 4C**H**$_2$,2C**H**$_3$)$_{morph}$, 1.30-1.41 (m, 2H, C**H**$_2$-CH_3), 1.53-1.63 (m, 2H, S-CH_2C**H**$_2$), 2.90, 3.50 (br, s, 4H, C**H**$_2$-N-C**H**$_2)_{morph}$, 3.06 (m, 2H, S-C**H**$_2$), 4.10 (m, 2H, C**H**-O-C**H**)$_{morph}$. **^{13}C NMR (*ppm*)**: δ = 11.05 (**C**H_3), 14.06 $(CH_3)_{morph}$, 22.68 (**C**H_2CH_3), 28.53, 28.64, 29.05, 29.23 ($4CH_2$), 31.80 (S-CH_2-**C**H_2), 39.22 (S-**C**H_2), 51.78, 52.04 (**C**H_2-N-**C**$H_2)_{morph}$, 71.64 (CH-O-CH)$_{morph}$, 115.02, 118.19, 122.02, 124.30 (C_{butad}). $C_{18}H_{29}Cl_3N_2O_3S$ (M_w= 459.60 g/mol). **MS (+ESI):** *m/z* = 459.0 $[M]^+$, *m/z* = 482.9 $[M+Na]^+$.

3.4.28. **Experiment 28: Synthesis of new compound (42)**

According to procedure 6; 1.0 g (2.62 mmol) of startig matirial **(1d)** was reacted with 0.46 g (2.62 mmol) of 4-benzylpiperidine in dichloromethane (25 ml) for about 24 h. The product **(42)** was separated and purified, then obtained as a new compound.

Compound (42): Yellow oil, yield: 0.610 g (44%); R_f: 0.44 ($CHCl_3$). **FT-IR (*cm*$^{-1}$)**: v = 2921, 2852 (C-H), 1674, 1598 (C=C), 1523, 1260 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 0.85 (t, *J* = 7.3 Hz, 3H, CH_3), 1.14-1.27 (m, 8H, 4C**H**$_2$), 1.38-1.40 (m, 2H, C**H**$_2$-CH_3), 1.55-1.61 (m, 2H, S-CH_2C**H**$_2$), 1.85, 1.90 (m, 5H, C**H**$_2$-C**H**-C**H**$_2)_{piperi}$, 2.52 (d, *J* = 7.3 Hz, 2H, C**H**$_2$), 2.88 (t, *J* = 6.8 Hz, 2H, (S-CH_2), 3.20- 4.10 (m, 4H, C**H**$_2$-N-C**H**$_2)_{piperi}$, 7.20-7.25 (m, 5H, CH_{arom}). **^{13}C NMR (*ppm*)**: δ = 14.09 (**C**H_3), 22.61 (**C**H_2CH_3), 28.68, 28.99, 29.03, 29.77 ($4CH_2$), 31.71,

(**C**H_2-CH-**C**H_2), 32.25 (**C**$H_2$$CH_2$-S) 35.33 (S-**C**$H_2$), 37.50 ($CH_2$-**C**H-$CH_2$)$_{piperi}$, 42.37 (**C**$H_2$) 54.01, (**C**$H_2$-N-**C**$H_2$)$_{piperi}$, 124.17, 126.36, 127.09, 128.47, 128.56, 128,98, 129.02, 139.18, 169.2 ($C_{butad,}$ CH_{arom}). $C_{24}H_{33}Cl_3N_2O_2S$ (M_w= 519.95 g/mol). **MS (+ESI)**: *m/z* = 543.0 $[M+Na]^+$.

3.4.29. Experiment 29: Synthesis of a new compound (1e)

According to procedure 5; 1 g (3.69 mmol) of compound **(1c)** was mixed with 0.44 g (3.70 mmol) of 1-hexanethiol, stirred 24 hours without solvent. The mixture was separated and purified. Product **(1e)** was obtained as a new compound.

Compound (1e): Yellow oil, yield: 1.04 g (80%); R_f : 0.66 (PET). **FT-IR (*cm*$^{-1}$)**: v = 2957, 2925, 2858 (C-H), 1601 (C=C), 1528, 1287 (C-NO_2). **^{1}H NMR (*ppm*)**: δ = 0.81 (m, 3H, CH_3) 1.19-1.30 (m, 4H, 2C**H**$_2$), 1.37-1.40 (m, 2H, C**H**$_2$-CH_3), 1.62-1.71 (m, 2H, S-CH_2C**H**$_2$), 3.02 (t, *J* = 7.3 Hz, 2H, (S-CH_2). **^{13}C NMR (*ppm*)**: δ = 13.96 (**C**H_3), 22.47 (**C**$H_2$$CH_3$), 28.36, 29.36 (2**C**$H_2$), 31.06 (**C**$H_2$$CH_2$-S) 36.07 (S-**C**$H_2$), 121.61, 128.55, 138.53, 158.53 (C_{butad}). $C_{10}H_{13}Cl_4NO_2S$ (M_w= 353.08 g/mol). **MS (+ESI)**: *m/z* =353.9 $[M+H]^+$.

3.4.30. Experiment 30: Synthesis of a new compound (43)

According to procedure 6, 1.0 g (2.83 mmol) of the compound **(1e)** was reacted with 0.71g (2.81 mmol) of 1-(diphenylmethyl)piperazine in dichloromethane (25 ml) about 24 h. The product was separated and purified. Product **(43)** was obtained as a new compound.

Compound (43): Yellow oil, yield: 1.01 g (67%); R_f: 0.53 ($CHCl_3$). **FT-IR (*cm*$^{-1}$)**: v = 2975, 2924, 2812 (C-H), 1595 (C=C), 1524, 1268 (C -NO_2). **^{1}H NMR (*ppm*)**: δ = 0.89 (t, *J*= 6.8 Hz, 3H, CH_3) 1.19 (m, 4H, 2C**H**$_2$), 1.22 (m, 2H, C**H**$_2$-CH_3), 1.52 (m, 2H, S-CH_2C**H**$_2$), 2.50, 3.50 (br, s, 8H, (CH_2-N-CH_2)$_{pipera}$), 2.81 (t, *J*= 7.3 Hz, 2H, (S-CH_2), 4.20 (s, 1H, -CH<), 7.10-7.38 (m, 10H, H_{arom}). **^{13}C NMR (*ppm*)**: δ=14.04 (**C**H_3), 22.43 (**C**$H_2$$CH_3$), 28.30, 29.39 (2×**C**$H_2$), 31.06 (**C**$H_2$$CH_2$-S) 35.50 (S-**C**$H_2$), 51.60, 53.57 (**C**$H_2$-N-**C**$H_2$), 75.79 (**C**H<), 117.80, 124.38, 126.55, 127.00, 128.43, 128.82, 130.04, 141.60, 168.97 (C_{butad}, CH_{arom}). $C_{27}H_{32}Cl_3N_3O_2S$ (M_w= 568.08 g/mol). **MS (+ESI)**: *m/z* =567.9$[M]^+$.

4. DISCUSSION

The aim of my study to synthesize some new powerful bioactive quinone and butadiene compounds.

In the first part, the synthesis of new biologically active *N*-substituted naphthoquinone compounds was investigated, we used 2-methyl-1,4-naphthoquinone **(1a)** and 5-nitro-2,3-dichloro-5-nitro-1,4-naphthoquinone **(1b)** as starting materials with some nucleophiles. The new compounds **(2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14)** were obtained by the reaction of **(1a)** with some nucleophiles such as amines, piperazines, piperidines or morpholines. However, the new compounds **(15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, and 36)** were obtained by the reaction of **(1b)** with same nucleophiles.

In the second part, some N,S-substituted butadiene compounds **(37, 38, 39, 40, 41, 42, and 43)** were synthesized by the reaction of some (mono-thio)substituted compounds, 2-nitro-1,3,4,4-tetrachloro-1-(octylsulfanyl)-1,3-butadiene **(1d)** and 2-nitro-1,3,4,4-tetrachloro-1-(hexylsulfanyl)-1,3-butadiene **(1e)** with some piperazines, morpholines, piperidines and pyrrolidines as nucleophiles.

Using column chromatography, all synthesized compounds were purified and separated. Its chemical composition has been confirmed by spectral methods (MS, FTIR, and ^{1}H, ^{13}C NMR).

The reaction of vitamin K3 **(1a)** with 1-(diphenylmethyl)piperazine gave the new compound **(2)**. The reaction carried out in chloroform/TEA at room temperature. In the IR spectrum of compound **2**; stretching bands for (C-H_{arom}) and (C-H_{aliph}) appeared at ν = 3219, 2979, 2904 cm^{-1} and (C=O) group appeared at ν = 1661 cm^{-1}. ^{1}H NMR spectrum shows that the methyl group was seen as a singlet at δ = 2.00 ppm, protons of piperazine were seen also as two broad singlet at δ =2.51, 3.43 ppm. According to APT spectrum; two signals of (C=O) were found at δ =183.62, 185.40 ppm.

The new compounds **(3, 4)** were formed when **(1a)** reacted with 1-piperonylpiperazine, this reaction carried out in $CHCl_3$ in the exestence of TEA. We obtained an expected compound **(3)** by the Michael addition on the naphthoquinone system [39]. Additionally, unexpected

compound **(4)**, in this compound, we assumed that the diamino substituted product formed of a large excess of piperazine. In this case, it is presumed that, during the elimination reaction, the methyl group loss a proton by nucleophilic attack, and the quinonemethide intermediate is formed, proposed mechanism was shown in the material and method part [88]. According to the IR spectrum of compound **(3)**; characteristic stretching bands for ($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) were seen at ν = 3093, 2979, 2902 cm^{-1} and (C=C) at ν = 1590, 1563 cm^{-1}. In ^{1}H NMR spectrum; the chemical shift for (CH_3) appeared at δ = 2.01 ppm, the singlet at δ =2.56, 3.37 ppm are related to piperazine ring, the protons of naphthoquinone around δ = 8.00 ppm. The ^{13}C(APT) NMR showed two signals for carbons of piperazine ring at δ = 50.98 and 53.57 ppm and two signals for carbonyl group at δ = 183.54 and 185.40 ppm. According to IR spectrum of new compound **(4)**; stretching bands for ($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) were seen at ν = 3069, 2978, 2900 cm^{-1}, (C=O) group at ν = 1661 cm^{-1}. In ^{1}H NMR; protons of methyl group disappeared ta around δ = 2.00 ppm, however, the protons of methylene that bonded to quinone ring appeared as a singlet at δ = 3.44 ppm, piperazine rings were seen at δ = 3.10 and δ = 3.62 ppm. Carbon signals related to piperazine ring were detected by ^{13}C(APT) NMR at δ = 51.91, 53.21, 58.30 ppm, furthermore, two carbon signals at δ =182.31, 184.20 ppm for carbonyl group.

A new compound **(5)** obtained by the reaction **(1a)** with 1-(2-aminoethyl)piperazine, this reaction refluxed in ethanol and Na_2CO_3. In this compound, the nucleophile take place between two naphthoquinone compounds as a bridge, because the 1-(2-aminoethyl) piperazine contains two active sites. In the IR spectrum; a broad and weak stretching band for (N-H) group appeared at ν = 3310 cm^{-1}, characteristic stretching bands for ($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) were observed at ν = 3078, 2968, 2906 cm^{-1} and (C=O) at ν = 1661 cm^{-1}. Protons of methyl groups were shown as a singlet at δ = 1.94 and 2.05 ppm according to ^{1}H NMR spectrum, and N-H at δ = 6.36 ppm. Two methyl group signals at δ = 11.06, 13.60 ppm, and four signals for carbonyl at δ = 182.56, 183.48, 183.65 and 185.47 ppm, as were shown in the APT spectrum of a new compound.

Reaction of **(1a)** with 2,4-dimethoxy aniline or 4-methoxyaniline gave the new compounds **(6)**, **(7)** under same conditions (reflux in ethanol /Na_2CO_3). In IR spectrum for compound **(6)**, characteristic stretching bands for (N-H) was seen at ν = 3338 cm^{-1}. According to ^{1}H NMR spectrum, protons of methyl group and ($O\text{-}CH_3$) were detected at δ =1.73, 3.85 and 3.85 as a singlet respectively. (N-H) was shown as a singlet too at δ = 7.22 ppm. In ^{13}C(APT) NMR

spectrum; signals of methoxy groups appeared at δ = 55.52, 55.71 ppm, two signals at δ = 182.53, 184.21 ppm related to carbonyl groups.

IR spectrum concerning the compound **(7)**, characteristic stretching band for (N-H) was seen at ν = 3248 cm^{-1}. According to ^{1}H NMR spectrum; protons of methyl group and methoxy group were observed at δ =1.63 and 3.74 as a singlet respectively. NH was shown as singlet too at δ = 7.27 ppm. In ^{13}C(APT) NMR spectrum; signal of methoxy group appeared at δ = 55.45 ppm, two signals at δ = 182.60, 184.35 ppm related to carbonyl groups.

The new compounds **(8)** was obtained from the reaction of **(1a)** with 1-(2-aminoethyl) piperidine in ethanol at room temperature. As was shown in IR spectrum; characteristic stretching band of (NH) was seen at ν = 3276 cm^{-1}, and (C=O) band at ν = 1668 cm^{-1}. In ^{1}H NMR spectrum; piperidine protons were appered between δ = 1.39-2.37 ppm as a broad singlet and (NH) peak was seen at δ = 6.37 ppm. The carbons of piperidine gave signals between δ = 24.34- 45.13 ppm, and carbonyl group gave two signals at δ =182.62, 183.31 ppm as were shown in ^{13}C(APT) NMR spectrum.

The new compounds **(9)** was obtained from the reaction of **(1a)** with 1-(2-aminoethyl) pyrrolidine in ethanol at room temperature. As was shown in IR spectrum; characteristic stretching band of (N-H) was seen at ν = 3332 cm^{-1}, and (C=O) band at ν =1661 cm^{-1}. Pyrrolidine protons were appered at δ = 1.73 and 2.50 ppm as a broud singlet, and (N-H) peak was seen at δ = 6.22 ppm according to ^{1}H NMR spectra. Carbons of pyrrolidine gave signals between δ = 23.50, 53.78 ppm, and carbonyl group gave two signals at δ =182.51, 183.35 ppm as were shown in ^{13}C(APT) NMR spectrum.

According the IR spectrum of compound **(10)**; characteristic stretching bands for($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) and carbonyl group were seen at *ν* = 3227, 2971 cm^{-1}, 1661 cm^{-1}. As we observed in ^{1}H NMR; protons of (CH_3) were seen at δ = 1.16 ppm as a singlet, and piperazine ring at δ = 3.01, 3.96 ppm as abroad singlet. The carbons of piperazine gave signals at δ = 40.11, 54.76 ppm, and carbonyl group gave three small signals at δ =160.01, 182.41and 183.23 ppm as were shown in ^{13}C(APT) NMR spectrum.

In IR spectra of new compound **(11)**; stretching bands for ($C\text{-}H_{arom}$) and ($C\text{-}H_{aliph}$) were seen at *ν* = 3116, 2961, 2912 cm^{-1}, and carbonyl groups at *ν* = 1667, 1617 cm^{-1}. In ^{1}H NMR; protons of methylene that bonded to quinone ring appeared as a singlet at δ = 3.48 ppm. Three carbon signals related to piperazine ring were detected by ^{13}C(APT) NMR at δ = 51.99, 53.20,

51.91 and 53.43 ppm, furthermore, three carbon signals at δ =162.30, 183.90 and 184.77 ppm for carbonyl groups.

The new compounds **(12, 13)** were obtained from the reaction of **(1a)** with 2,6-dimethylmorpholine. According to IR spectra of compound **(12)**; stretching bands for (C-H_{aliph}) were observed at ν = 2971, 2930 cm^{-1}, and (C=O) at ν = 1668 cm^{-1}. According to ^{1}H NMR spectra; methyl groups of morpholine ring and naphthoquinone were seen at δ = 1.07, 1.30 ppm as a singlet respectively. APT spectra shows; the signals at δ = 9.33, 18.75 ppm are related to $(CH_3)_{naphth}$ and $(CH_3)_{morph}$, carbonyl group signals were detected at δ =182.09, 184.76 ppm. IR spectra of new unknown compound **(13)**; stretching bands for (C-H_{aliph}) were seen at ν = 2972, 2929 cm^{-1}, and carbonyl groups at ν = 1785, 1669 cm^{-1}. In ^{1}H NMR, protons of $(CH_3)_{morph}$ appeared as multiplets between δ = 1.05-1.31 ppm, whereas, methylene that bonded to quinone ring appeared as singlet at δ = 3.71 ppm. Two signals for $(CH_3)_{morph,}$ $(CH_2)_{naphth}$ were detected by ^{13}C(APT) NMR at δ = 18.72, 45.49 ppm, however, two carbon signals at δ =183.93, 184.57 ppm for carbonyl groups.

Reacting of vitamin K3 **(1a)** and 4-benzylpiperidine (reflux in EtOH /Na_2CO_3), gave a new unknown compound **(14)**. As was shown in IR spectrum of compound **(14)**; characteristic stretching bands for (C-H_{aliph}) were observed at ν = 2956, 2922, 2853 cm^{-1}, and (C=O) group at ν = 1667 cm^{-1}. According to ^{1}H NMR; methyl group in naphthoquinone was seen at δ = 2.11 ppm as a singlet, and (CH_2) in benzylpiperidine as a doublet at δ = 2.50 ppm. In the ^{13}C(APT) NMR spectrum; signals at δ = 13.58, 43.32 ppm are related to $(CH_3)_{naphth,}$ and $(CH_2)_{benzyl}$, carbonyl group signals were detected at δ =183.90, 185.45 ppm.

As we known the reactions of naphthoquinones with amines such as aliphatic (primary, secondary or cyclic) amines and aromatic amines with electron donating groups are highly reactive providing a good yield of naphthoquinone amino derivatives. Reaction of amines with 2,3-dichloro-1,4 naphthoquinone gives mono-amino derivatives. If a nitrogen atom is available in heterogeneous rings, then two halogen atoms can be replaced by N such as piperazine, morpholine, piperidine etc. [121]. The substitution of the chlorine atom with the nitrogen atom in the aromatic amines supported by activated electronic groups depends on the density of electrons around the quinone ring. The second substitution of the chlorine atom can be carried out with the quinone unit containing an electron withdrawing group (EWG) [122] or using a catalyst [123]. The compound **(1b)** has been known to be much easier to interact

with the variety of amines, providing mono-substituted quinone derivatives as regioisomeric mixture [89]. We decided to study the effect of the electron withdrawing group (NO_2) at the quinone ring in this substitution. All new regioisomers which obtained have different colors, melting point, R_f, and chemical shift of naphthoquinone protons [89, 91, 124].

The new regioisomers **(15, 16)** were synthesized from the reacting of **(1b)** and 1-(diphenylmethyl)piperazine in ethanol at room temperature. ^{1}H NMR spectrum of regioisomers **15** and **16**, the signals for protons of the naphthoquinone ring are observed as different pattern [89, 91, 124]. ^{1}H NMR of isomer 15, signals concerning one proton of the naphthoquinone ring is shown in the range δ = 7.80 ppm as multiplet. The other proton detected at δ = 8.32 ppm as a triplet, last one is at δ = 8.39 ppm as doublet of doublet. Whereas, ^{1}H NMR signal of the hydrogen atoms at naphthoquinone ring of isomer 16 is detected as multiplets, triplet and doublets of doublets at δ= 7.76, 7.85, and 8.24 ppm, respectively.

The new regioisomers **(17, 18)** were synthesized when reaction of **(1b)** with 1-piperonylpiperazine take place in pure ethanol. In the IR spectrum of compounds **(17** and **18)**; stretching (asymmetric, symmetric) of (C-NO_2) were appeared around ν = 1494, 1438 cm^{-1}, ν = 1492, 1438 cm^{-}1 respectively. It was shown in the ^{1}H NMR spectra, protons of nitro naphthoquinone were detected at δ = 7.76-7.82 and 8.34 ppm as a multiplet and doublet of doublet in isomer **(17)** whereas in isomer **(18)** were detected at less chemical shift at δ = 7.67, 7.82 and 8.21 ppm as a doublet of doublet, triplet and doublet of doublet respectively. According ^{13}C(APT) NMR; two signals of carbonyl groups were seen at δ = 175.74, 179.07 ppm in isomer **(17)**, and in isomer **(18)** at δ = 173.97, 179.84 ppm.

The new compound **(19)** was obtained when 2-(1-piperazinyl)ethylamine reacted with **(1b)** at room temperature using ethanol as medium. The proposed structure is the presence of nucleophile between two naphthoquinone rings as a bridge. In the IR spectra; (N-H) band was appeared at 3258 cm^{-1}. Piperazine ring were seen as a broad singlet at δ = 3.50, 3.81 ppm in ^{1}H NMR. Carbonyl groups at δ = 175.84, 178.97, 190.32 ppm as were seen in ^{13}C(APT) NMR,

The known compound **(1b)** was reacted with 2,4-dimethoxyaniline and new regioisomer compounds **(20, 21)** were obtained. As was shown in IR spectra; (N-H) bands for compounds

(20, 21) were observed at ν = 3316 cm^{-1}, 3308 cm^{-1} respectively. Protons of nitro naphthoquinone were seen between δ = 7.73-8.40 ppm in isomer **(20)** whereas, in isomer **(21)** the protons of naphthoquinone were seen at less chemical shift between δ = 7.69 - 8.29 ppm, as was observed in their ^{1}H NMR spectrum. In the APT spectrum; signals of methoxy group (CH_3-O) and carbonyl group for isomer **(20**) were detected at δ = 55.58 ppm and δ = 172.65, 174.28 ppm respectively, while in isomer **(21)** at δ = 55.68 ppm and δ = 173.29, 178.67 ppm respectively.

The new isomer compounds (**22**, **23**) obtained by the reaction of **(1b)** and 4-methoxyaniline. As was shown in IR spectra; the (N-H) bands for compounds **(22, 23)** were observed at ν = 3226, 3289 cm^{-1} respectively. Protons of nitro naphthoquinone were seen at δ = 7.81, 7.97 and 8.33-8.42 ppm as a doublet of doublet, triplet and multiplet in isomer **(22)** whereas, in isomer **(23)** the protons of naphthoquinone were seen at less chemical shift between δ = 7.63-8.41 ppm as a triplet, as was observed in their ^{1}H NMR spectra. In the APT spectrum; signals of methoxy (CH_3-O) and carbonyl group for isomer **(22**) were detected at δ = 55.53 ppm and δ = 173.29, 178.91 ppm respectively, while in isomer **(23)** at δ = 55.49 ppm and δ = 173.66, 178.92 ppm respectively.

The known compound **(1b)** was reacted with 4-(2-aminoethyl)morpholine and new regioisomer compounds **(24, 25)** were obtained. As was shown in IR spectra for **(24, 25)** isomers; asymmetric and symmetric stretching of (C-NO_2) were appeared at ν = 1519, 1338 cm^{-1} and 1535, 1330 cm^{-1} respectively. According to ^{1}H NMR spectra; (N-H) protons for the two isomers were seen at δ = 6.94 and 6.07 ppm as a broad singlet respectively. In the ^{13}C(APT) NMR spectra, carbonyl signals for isomer **(24)** were seen at δ = 178.69, 181.51 ppm, and at δ = 175.26, 176.76 ppm for another isomer.

One new isomer **(26)** was obtained by refluxing the titled compound **(1b)** and 2,4,6-trimethylaniline in ethanol and sodium carbonate. The band of (N-H) was seen around ν = 3272 cm^{-1} as was shown in the IR spectrum. Protons of methyl groups (CH_3) in ^{1}H NMR spectrum were appeared at δ = 1.31-1.37 and 2.04-2.12 ppm as a multiplet. Two signals at δ = 176.44, 177.73 ppm were related to carbonyl groups as was seen in the ^{13}C(APT) NMR spectrum.

One new isomer **(27)** was obtained by reacting the titled compound **(1b)** with 2-(piperidin-1-yl)ethan-1-amine in ethanol. The band of (N-H) was seen around at ν = 3277 cm^{-1} as was shown according to IR spectra. Nitro naphthoquinone protons were detected around δ = 7.69-8.34 ppm. A signal at δ = 177.59 ppm was related to carbonyl group as was seen in the ^{13}C(APT) NMR spectrum.

The known compound **(1b)** was reacted with 2-(pyrrodin-1-yl)ethane-1-amine in ethanol and new regioisomer compounds **(28, 29)** were obtained. As was shown in IR spectra for **(28, 29)** isomers; asymmetric and symmetric stretching of (C-NO_2) appeared at ν = 1525, 1335 cm^{-1} and 1531, 1372 cm^{-1} respectively. According to ^1H NMR spectra; (N-H) protons for the two isomers were observed at δ = 6.96 and 6.93 ppm as a broad singlet respectively. In the ^{13}C(APT) NMR spectra, carbonyl signals for isomer **(28)** were seen at δ = 173.95, 177.32 ppm, and for isomer **(29)** were detected by ^{13}C NMR spectrum at δ = 172.46, 181.90 ppm.

The new isomer compounds (**30**, **31**) obtained by the reaction between **(1b)** and 1-(2-furoyl)piperazine in ethanol at room temperature. As was shown in IR spectra for **(30, 31)** isomers; asymmetric and symmetric stretching of (C-NO_2) appeared at ν = 1522, 1416 cm^{-1} and 1538, 1428 cm^{-1} respectively. piperazine ring (CH_2NCH_2) observed at δ = 3.62, 3.94, 3.58-3.64 and 3.90 ppm as a broad singlet for two isomers respectively. As were shown in APT-NMR; three expected carbonyl signals were observed for two isomers.

The new isomer compounds (**32**, **33**) and compound **(34)** obtained by reaction between **(1b)** and 2,6-dimethylmorpholine in ethanol. In this reaction, the solvent reacted as a nucleuphil (O-CH_2CH_3) and substituted with one chlorine, while the other chlorine replaced with morpholine to form an isomer **(32, 33)**. According to IR spectra for these isomers, C-O bands were appeared at ν = 1219 cm^{-1}. Signals at δ =7.76-7.85 and 8.35 ppm are corresponding to naphthoquinone protons for first isomer and at δ =7.79-7.84 and 8.34 ppm for second isomer. As were shown in the ^{13}C(APT) NMR, an expected carbonyl signals were observed for two isomers. In compound **(34)**, stretching (asymmetric, symmetric) bands for (C-NO_2) were appeared at 1530, 1371 cm^{-1}. Two methyl groups (CH_3) in morpholine ring were observed at δ = 1.20 ppm as a singlet however, signal corresponding to carbonyl groups (C=O) were detected at δ =175.78, 179.10 ppm.

The compound **(1b)** was reacted with 4-benzylpiperidine in ethanol and new regioisomer compounds **(35, 36)** were obtained. In IR spectra, carbonyl group bands (C=O) appeared at ν = 1718, 1717 cm^{-1} respectively. Protons of nitro naphthoquinone appeared between δ = 7.70-8.37 ppm in isomer **(35)**, whereas, in another isomer between δ = 7.62-8.22 ppm as were seen in their ^{1}H NMR spectra. Signals corresponding to carbonyl group (C=O) in isomer **(35, 36)** were detected at δ =175.69, 179.36 and δ =173.89, 179.35 ppm respectively.

The ^{1}H NMR spectra of the synthesized new regioisomers of nitronaphthoqinoe were indicated that the proton peaks of naphthoquinone for the (2-amino) isomer are shifted more downfield than the aromatic protons of the (3-amino) isomer. Also, it has been found that, the retention factor R_f of (2-amino-) isomer is higher than R_f of isomer (3-amino) by ^{1}H, ^{13}C (HMBC) analysis [89].

In the second part, we used nitro polyhalo-1,3-butadienes due to its prominent activity in nucleophilic substitution reactions as strong electrophiles due to the existence of a nitro group in its composition. It is also known to be used as starting materials for preparing bioactive derivatives containing heterogeneous rings [95]. Often, the preferred and most active synthesis is 2-nitropentercloro-1,3-butadiene **(1c)**, which can be obtained by inserting an active group such as a nitro instead of a hydrogen atom in the 2H-pentachloro-1,3-butadiene compound.

In **(1c)** the presence of the nitro group (electron withdrawal) associated with the carbon atom number 2 makes the carbon atom C_1 in part (Cl_2C = C-NO_2) one of the best and most active sites toward nucleophiles in (S_N-Vinylic) reactions. Additionally, in some cases the C_3, can be attacked by nucleophiles too. Recently, some *N, S*-substituted of nitrodiene derevatives were synthesized by the interaction of thiols and amines with nitrodienes[125].

In this section, *S*- and *N, S*-substituted nitro butadienes have been prepared and achieved.

The reactions of **(1c)** with octanethiol and hexanethiol in solvent-free were done. As a result of these reactions **(1d** and **1e)** were synthesized and used as starting materials.

The reaction of mono (thio) substituted-2-nitro-butadiene **(1d, 1e)** with piperazine, morpholine, piperidine derivatives unknown compounds **37, 38, 39, 40, 41, 42** and **43** were synthesized.

(1d) when reacted with 1-piperonylpiperazine in CH_2Cl_2, a new compound **(37)** was synthesized. As was seen In ^{1}H NMR; piperazine ring observed at δ= 2.55 and 3.65 ppm as a

broad singlet, (S-C**H**$_2$) at δ = 2.92 ppm as a triplet. According to ^{13}C NMR piperazine ring signals appeared at δ = 52.37, 53.31 ppm.

The novel compounds **(38, 39)** were obtained as a result of the reaction between **(1d)** and 1-(2-aminoethyl)piperazine in CH_2Cl_2. The structure of the new compound **(38)** indicate that the nucleophile reacted with two moles of **(1d)** to form a bridge [126]. According to ^{1}H NMR; proton (N-H) was seen at δ = 11.04 ppm as a broad singlet, piperazine ring observed also as abroad singlet at δ = 2.68, 3.80 ppm, whereas, in compound **(39)**, proton (NH_2) was seen at δ = 11.01 ppm, and piperazine ring at δ = 2.93, 3.50 ppm as abroad singlet too.

The new compound (**40**) was obtained from reaction **(1d)** with 4-(2-aminoethyl)morpholine in CH_2Cl_2. As was shown in IR spectrum; (N-H) band appeared at ν = 3143 cm^{-1}. Proton (N-H) was seen at δ = 10.94 ppm as a broad singlet, carbon signals in morpholine ring were seen at δ = 52.73, 53.67 ppm, as were observed in ^{1}H,^{13}C NMR spectra.

Compound (**41**) was obtained from the reaction of **(1d)** with 2,6-dimethylmorpholine in CH_2Cl_2. As was shown in the IR spectrum; carbon-carbon double bond (C=C) were seen at ν = 1662, 1596 cm^{-1}. Protons of morpholine ring appeared at δ = 2.90 and 4.10 ppm as a broad singlet, carbon signals in morpholine ring were seen at δ = 51.78, 52.04 ppm, as were observed in ^{1}H,^{13}C NMR spectra.

The new compound (**42**) was obtained from the reaction of **(1d)** with 4-benzylpiperidine in CH_2Cl_2. As was shown in the IR spectrum; Asymmetric and symmetric stretching of the nitro group (C-NO_2). were appeared at 1523, 1260 cm^{-1}. In ^{1}H NMR; aromatic protons take place at δ =7.20-7.25 ppm as a multiplet. The base peak of a new compound was seen whit sodium ion $[M+Na]^+$ at *m/z* (100%) = 543.

Reaction of **(1c)** with hexanethiol in solvent-free has done, as a result of reaction a new compound **(1e)** was obtained as a yellowish oily, yield: 1.040 g (80%); R_f: 0.66; (PET). According to the IR spectrum of compound **(1e)**; (C=C) bond were seen at ν =1601 cm^{-1}, stretching (asymmetric, symmetric) bands of (NO_2) were appeared at 1528, 1287cm^{-1}. A triplet at δ =3.02 ppm is related to (S-C**H**$_2$), carbon signals of hexylthio were appeared between δ =13.96 and 36.07 ppm, as we observed in ^{1}H,^{13}C NMR spectra.

Compound (**43**) was obtained as a new compound when the compound **(1e)** reacted with 1-(diphenylmethyl)piperazine in CH_2Cl_2. According to the IR spectrum of compound **43**; carbon-carbon double bond was seen at ν = 1595 cm^{-1}. Protons of piperazine ring were seen at

2.50 and 3.50 ppm, the signals at δ = 51.60 and 53.57 ppm are related to piperazine ring as were shown in ^{1}H,^{13}C NMR spectra.

According to the previous studies of crystal structures, it was noted that all the *S*-substituted and *N*, *S*-substituted nitrodienes, were *E*-isomers [26], [105], [109], [111], [127].

5. CONCLUSION AND RECOMMENDATIONS

The goal of my study was to synthesize new quinone and butadiene compounds **(2- 43)** from the reactions of 2-methyl-1,4-naphthoquinone **(1a)** and 2,3-dichloro-5-nitro-1,4-naphthoquinone **(1b),** 2-nitro-1,3,4,4-tetrachloro-1-(octylsulfanyl)-1,3-butadiene **1d)** and 2-nitro-1,3,4,4-tetrachloro-1-(hexylsulfanyl)-1,3-butadiene **(1e)** with different N-nucleophiles. The new compounds were successfully synthesized and their structures were proved using ^{1}H,^{13}C NMR, FTIR and mass spectroscopy.

In the first stage; the new *N*-substituted or *N,N*-substituted naphthoquinone compounds were synthesized by Michael addition reaction between Vit.K3 **(1a)** and N-nucleophiles at different conditions in one step. The 2-methyl-3-N-substituted 1,4-naphthoquinones **2, 3, 5, 6, 7, 8, 9, 10, 12** and **14** were obtained as a result of reaction of nucleophiles at only 2-position of 2-methyl-1,4-naphthoquinone, however, the 2-N-substituted-3-N-substituted-methyl-1,4-naphthoquinone compounds **4, 11** and **13** were formed when the reaction of nucleophiles take place on the 2-position and (CH_3) group at 3-position of 2-methyl-1,4-naphthoquinone.

All the synthesized new naphthoquinone compounds have formed in solid or oily with a moderate yield and variety of colors, red, pink and purple. According to the (+ESI) mass spectra, the compounds obtained were pure, due to the presence of a single molecular ion peak. Also, the main characteristic functional groups have identified by the FTIR spectra. Generally, the occurrence of absorption bands at 1560-1660 cm^{-1} indicate to (C=O) stretching mode of naphthoquinone, and the (NH) bands at around 3200-3300 cm^{-1}. Moreover, the structural formulas of thirteen compounds proved with ^{1}H NMR spectra. The ^{1}H NMR spectra displayed signals for all the protons in their characteristic regions, naphthoquinone protons were observed in the region 7.50-8.09 ppm, and NH protons between 6-7 ppm.

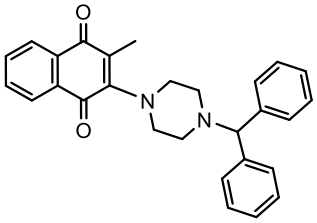
In the second stage; new regioisomers were synthesized by reacting of **(1b)**, with some nucleophiles such as amines, piperazines, or morpholines. The regioisomers were separated by column chromatography using a different ratio of solvents. The obtained regioisomers have different colure, different melting point, different retention factor (R_f), and chemical shift of naphthoquinone protons. The ^{1}H NMR spectra of the synthesized new regioisomers

were indicated that, the peaks of the (2-amino) isomer of aromatic protons are shifted more down field than the aromatic protons of the (3-amino) isomer. Also, it has been found the (2-amino) isomer has a higher R_f than (3-amino) isomer. As a comparison between the ^{1}H NMR spectra of the synthesized new regioisomers **(17, 18)**; we found that the proton of naphthoquinone peaks (δ =7.76-8.34 ppm) for the first isomer **(17)** are shifted more downfield than the naphthoquinone peaks (δ =7.67-8.21 ppm) of the second isomer **(18)**. Also, it found that the isomer **(17)** has a higher R_f component than the isomer **(18)** [128].

In the last stage; new *S*-, and *N*,*S*-substituted nitro butadiene compounds have been successfully synthesized under different reactions. Reaction of (mono-thio) substituted-2-nitro-butadienes **(1d, 1e)** with piperazine, morpholine, piperidine derivatives gave new compounds **37, 38, 39, 40, 41, 42** and **43**.

Naphthoquinone derivatives are famous due to their excellent pharmacological properties, as antifungal, antibacterial, and antitumor agents. Therefore, we consider evaluating the biological activity, such as antifungal, antibacterial and anticancer properties of the newly synthesized naphthoquinone compounds. We also plan to investigate the antioxidant capacity and biological evaluations of these compounds in the future.

5.1. THE CHEMICAL STRUCTURE OF NEW NAPHTHOQUINONE AND BUTADIENE COMPOUNDS.



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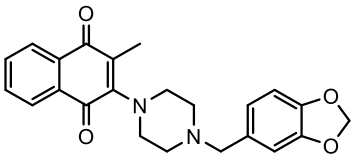

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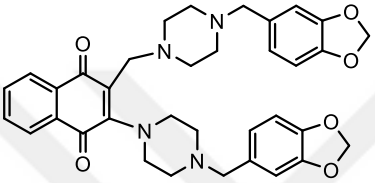

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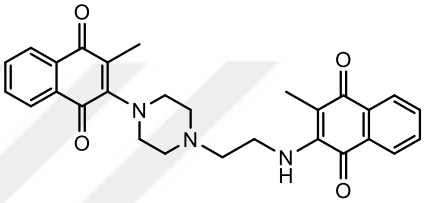

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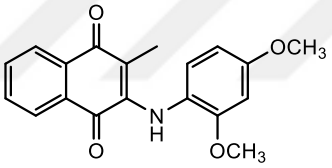

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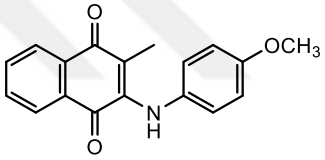

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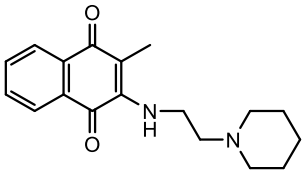

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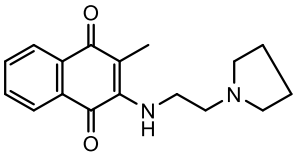

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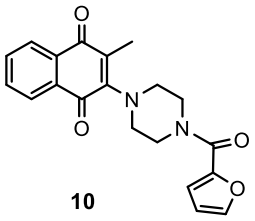

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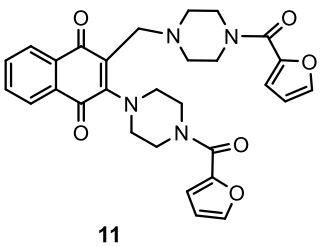

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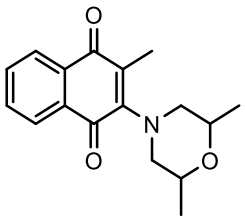

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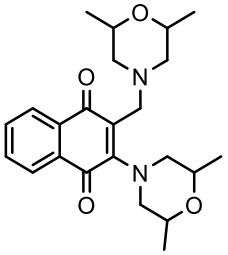

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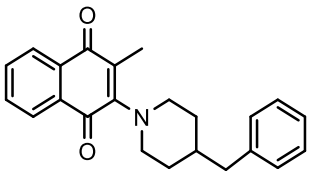

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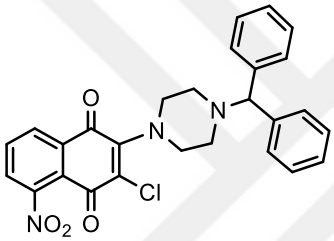

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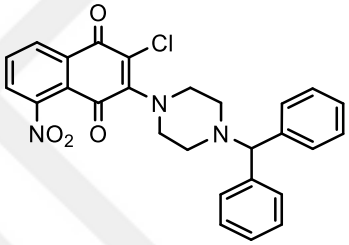

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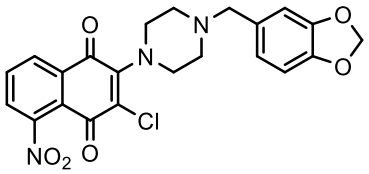

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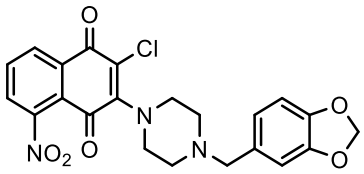

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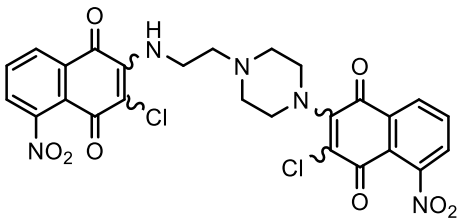

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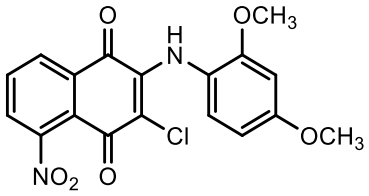

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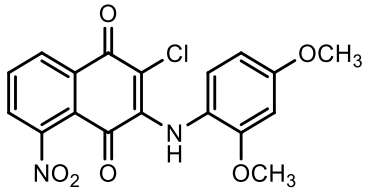

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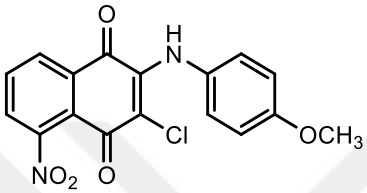

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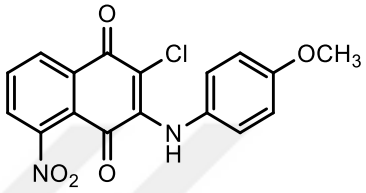

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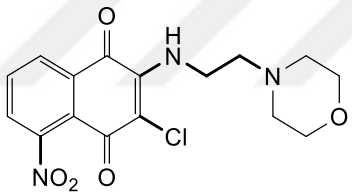

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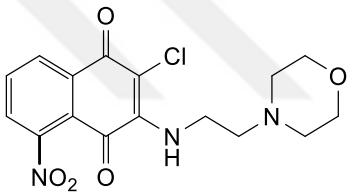

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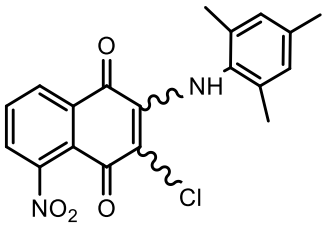

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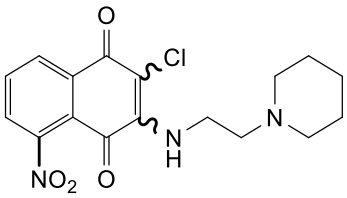

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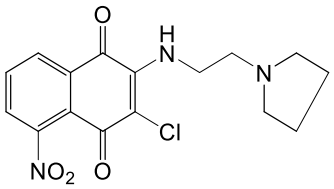

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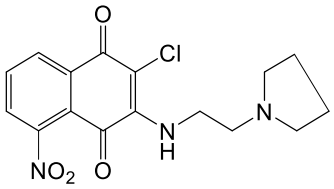

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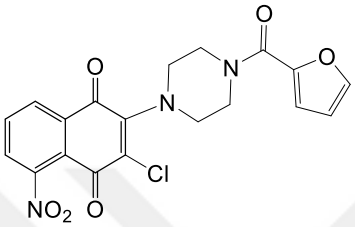

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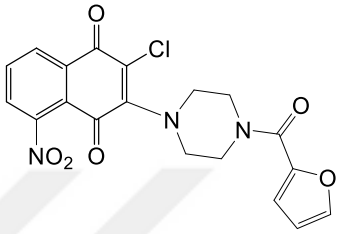

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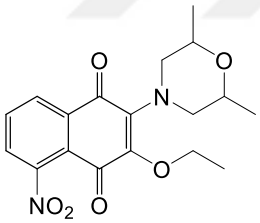

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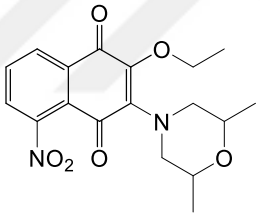

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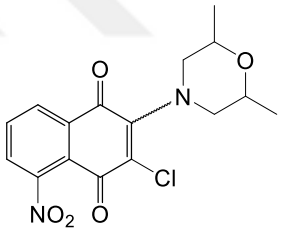

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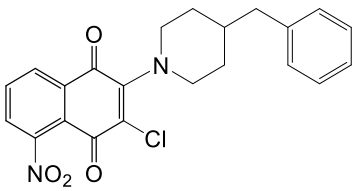

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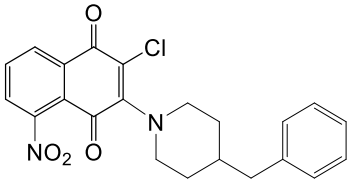

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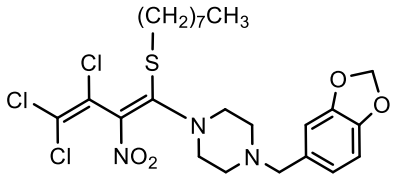

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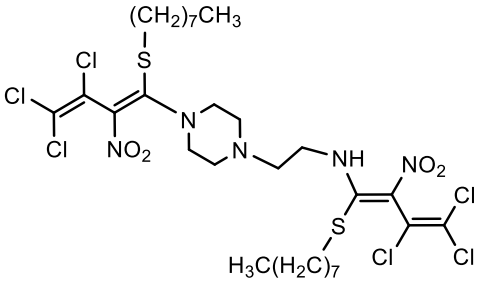

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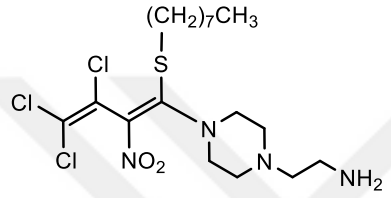

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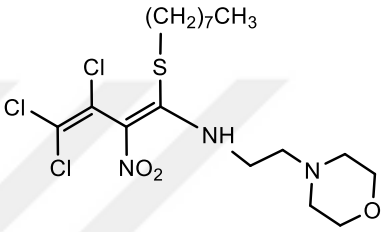

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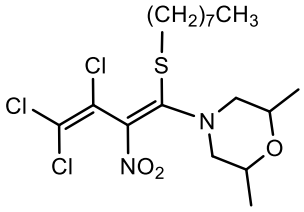

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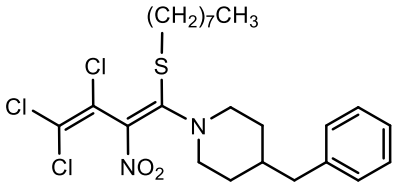

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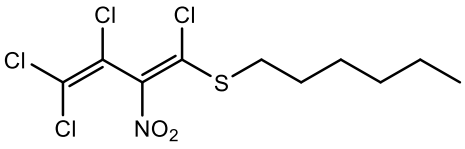

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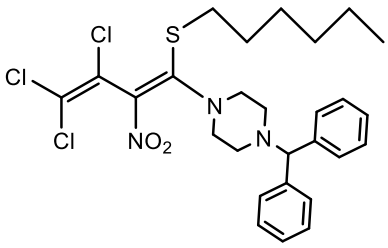

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B. Sc.	
University	Alzawia University
Faculty	Faculty of Science
Department	Chemistry
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M. Sc.	
University	Masaryk University, Czech Republic
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Programme	Analytical Chemistry

Ph. D.	
University	Istanbul University-Cerrahpasa
Institute	Institute of Graduate Studies
Department	Department of Chemistry
Programme	Chemistry Programme

Publications

F.Sh. Abdassalam A., Kurban S., Deniz N.G., Sayil C., 2019, Synthesis and characterization of new naphtho- and tetracyclic diazaquinone derivatives, *Journal of the Chemical Society of Pakistan*, vol.41, no.5, pp.834-840.

F.Sh. Abdassalam A., Deniz N.G., Sayil C., Synthesis of new mono-, and bis-substituted 2-nitrohalo-1,3-dienes, *Euroanalysis* 2019, İSTANBUL, TÜRKIYE, 1-5 Eylül 2019, pp.396-396.

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Sayil Ç., Deniz N.G., F.Sh. Abdassalam A., Synthesis of new derivatives from naphthoquinone containing an electron-withdrawing group (EWG) in the aromatic ring, *International Conference on Innovations in Natural Science and Engineering* (ICINSE 2018), Lefkoşe, KUZEY KIBRIS TÜRK CUM., 3-6 Ocak 2018, pp.118-118.

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