Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Kerbala College of Science
Department of Chemistry

Synthesis and studies of biological activity of -1,3-oxazepine-4,7-dione derivitives "

A Thesis

Submitted to the Council of the College of Science, University of Kerbala in Partial fulfillment of the Requirements for the Degree of Master in Chemistry.

By

Sawsan KhdeaurAbbas

B. Sc. Chemistry, College of Science

Babylon University (2002)

Supervised by

Asst. Prof. Dr.Zeid Hassan Abood Al-a' arajy

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بسم الله الرحمن الرحيم

الرَّحْمَنُ{1} عَلَّمَ الْقُرْآنَ{2} خَلَقَ الْإِنسَانَ{3} عَلَّمَهُ الْبَيَانَ{4}

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I certify that this thesis was prepared under my supervision in the Department of Chemistry, College of Science, University of Kerbala in partial fulfillment of the requirements for the degree of Master in Organic Chemistry .

Signature :

Name : Dr. Zeid Hassan Abood

Title : Asst. Prof.

Address : Department of Chemistry

College of science

Kerbala University

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Signature:

Dr. Baker Abdl- Zahra Juda

Head of the Chemistry Department

College of Science

Kerbala University

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Name : Majed Jari Mohammed

Title : Asst. Prof.

Address :Kufa University / College of Science

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Address :Kufa University/
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Title : Asst. Prof.
Address : Kerbala University / College of Science
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Name : Sabah Wajed Ali

Title : Asst. Prof.

Address : Kerbala University/ College of education
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To the jewel, my real friend, ***Shamma Ibrahim****,who has been really a great friend and sister in helping me and for her warm feelings , I wish her more success.*

I'd like to thank my dearest friend, who has been with me all the time and for warm feeling and helping. Finally I'd like to thank my friend ***Sara*** *For her help, for her love.*

Sawsan

Dedication

To my

Parents

my Brothers and sisters For love

To my faithful friend and the rose of my life ……

Shamma Ibrahim

To all those who stood by my side ……

To everyone who has a place in my heart ……

To everyone who has supported me even with a word ……

Abstract

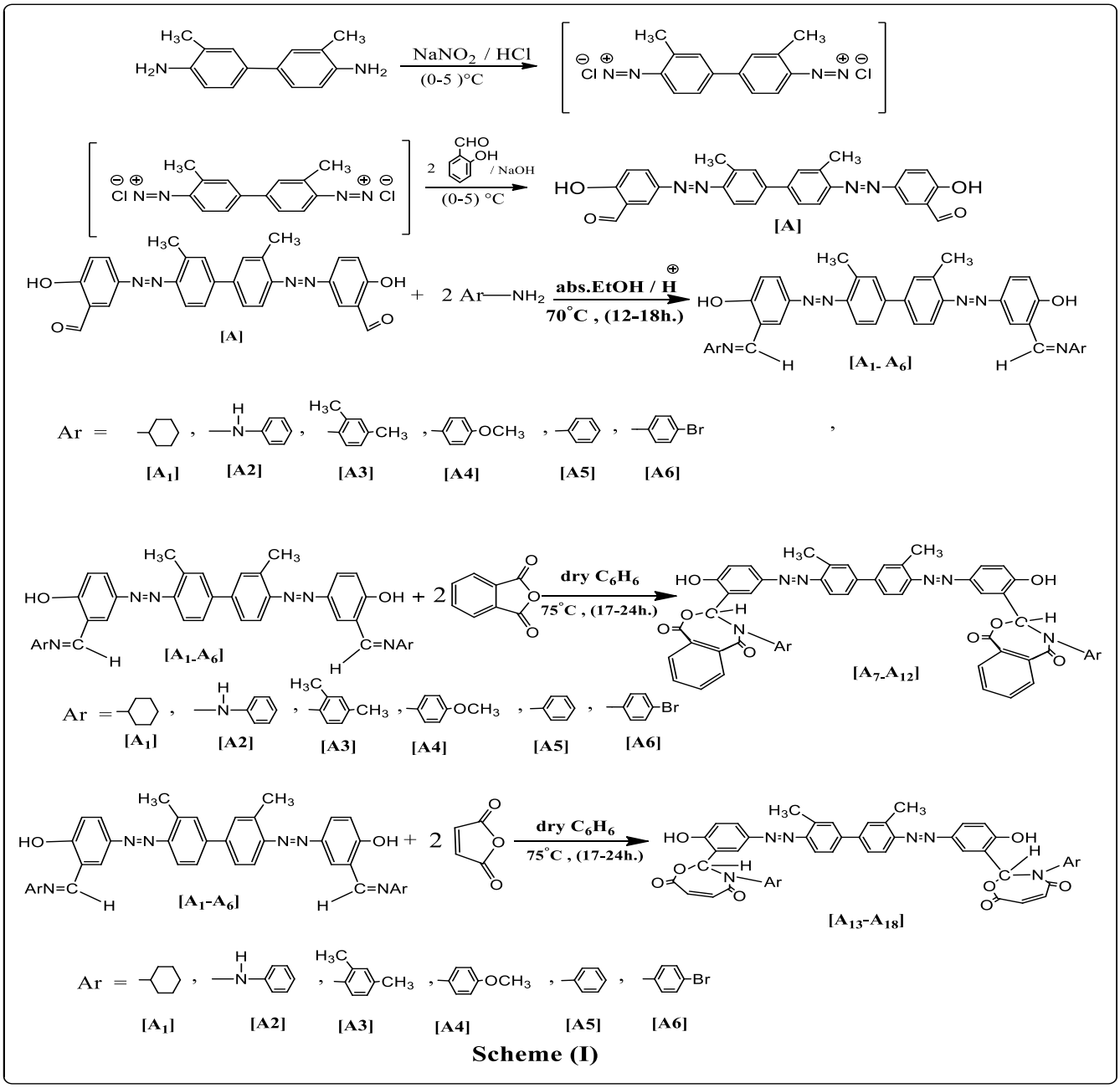
In this work two series of new bisazo bis-1,3-oxazepine - 4,7- dione [A_7-A_{18}] and bis -1,3-oxazepine -4,7-dione [B_6-B_{15}] derivatives have been synthesized via [2+5] cycloaddition reaction of phthalic and maleic anhydrides to some synthesized bisazoimine [A_1-A_6] and bisimine [B_1-B_5] derivatives .

In the first line, ***o***-Toludine was converted to the corresponding bis-azoaldehyde derivative [A] via coupling reaction with phenoxide anion of 2-hydroxybenzaldehyde . Aldehyde groups in bis-azoaldehyde derivative [A] was condensed with different primary amines a one hydrazine (cyclohexyl amine, phenylhydrazine, 2,4-dimethylaniline, 4-methoxyaniline, aniline and 4-bromoaniline) in presense of glacial acetic acid as a catalyst in absolute ethanol to give bisazoimine derivatives [A_1-A_6] respectively. The resulting bisazoimine derivatives [A_1-A_6] were then introduced in [2+5] cycloaddition reaction with each of phthalic anhydride and maleic anhydride in dry benzene to give new bisazo bis-1,3-oxazepine-4,7-dione derivatives [A_7-A_{12}] and [A_{13}-A_{18}] respectively as shown in scheme (I).

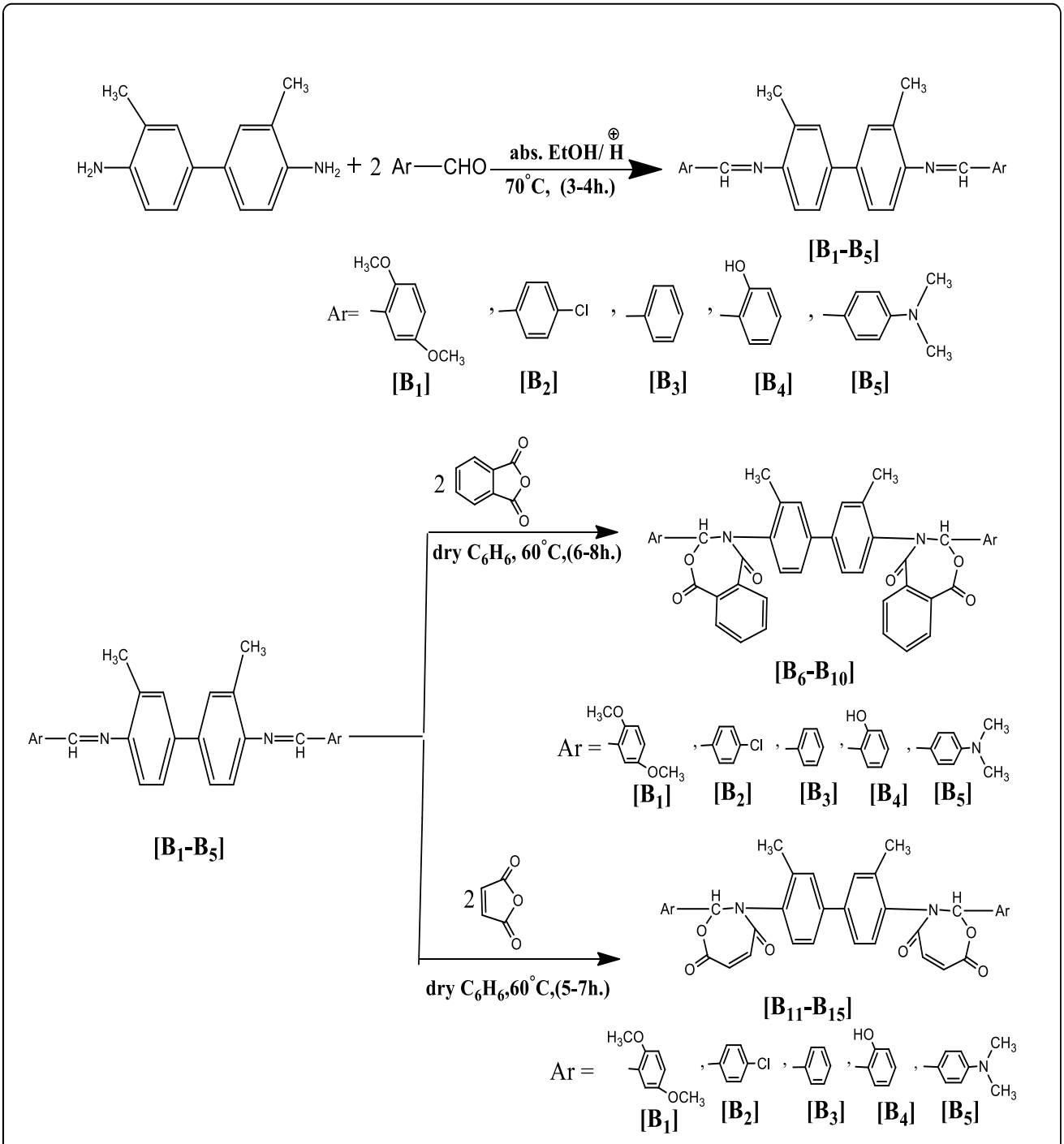
In the second line , ***o***-Toludine was directly condensed with different benzaldehyde derivatives (2,5-dimethoxybenzaldehyde, 4-chlorobenzaldehyde, benzaldehyde, 2-hydroxybenzaldehyde and 4-*N*,*N*-dimethylaminobenzaldehyde) in presense of glacial acetic acid as a catalyst in absolute ethanol to give bisimine derivatives [B_1-B_5]. The resulting bisimine derivatives [B_1-B_5] were then introduced in [2+5] cycloaddition reaction with each of phthalic anhydride and maleic anhydride in dry benzene to give new bis-1,3-oxazepine-4,7-dione derivatives [B_6-B_{10}] and [B_{11}-B_{15}] respectively as shown in scheme (II).

All the synthesized target compounds [A_7-A_{18}] and [B_6-B_{15}] have been characterized by (C.H.N.) elementary micro analysis and the spectroscopic methods including FT-IR ,^{1}H NMR for compounds [A_7, A_8, A_9, A_{10}, A_{11}, A_{13}, A_{14}, A_{15}, A_{16}, A_{17}, B_7, B_8, B_{11}, B_{12}, B_{13} and B_{15}] .

The last step included preliminary evaluation of antibacterial activity of all target compounds [A_7-A_{18}] and [B_6-B_{15}] which were tested against *Staphylococcus aureous* (Gram positive) and *Escherichia coli* (Gram negative), these activities have been determined in ***vitro*** using disc diffusion method (Agar), the results revealed that some of compounds showed measurable activity as shown in table (3-7).



Scheme (I)


abs. EtOH/ H⊕
70°C, (3-4h.)
[B1-B5]
Ar=
[B1]
[B2]
[B3]
[B4]
[B5]
2
dry C6H6, 60°C,(6-8h.)
[B6-B10]
[B1-B5]
dry C6H6,60°C,(5-7h.)
[B11-B15]

Scheme(II)

Abbreviations

Symbol	Name
h	Hour
Ar	Aryl
DMSO	Dimethyl Sulfoxide
Ph	Phenyl
Abs.	Absolute
R_f	Retention Factor
TLC	Thin Layer Chromatograghy
M.f.	Molecular Formula
M.Wt.	Molecular Weight
T.S	Transition State
FT-IR	Fourier Transform Infrared
^{1}HNMR	Proton Nuclear Magnetic Resonance
Δ	Heat
Et	Ethyl
Me	Methyl
M.p.	Melting Point
Et_2O	Diethyl ether
EtOAc	Ethyl acetate

Str.vib.	**Stretching vibration**
δ	**Bending in IR**
δ	**Chemical shift in NMR**
o.o.p.	**Out of plane**
ppm	**Part per million**
R.t.	**Reaction time**
br.	**Broad**

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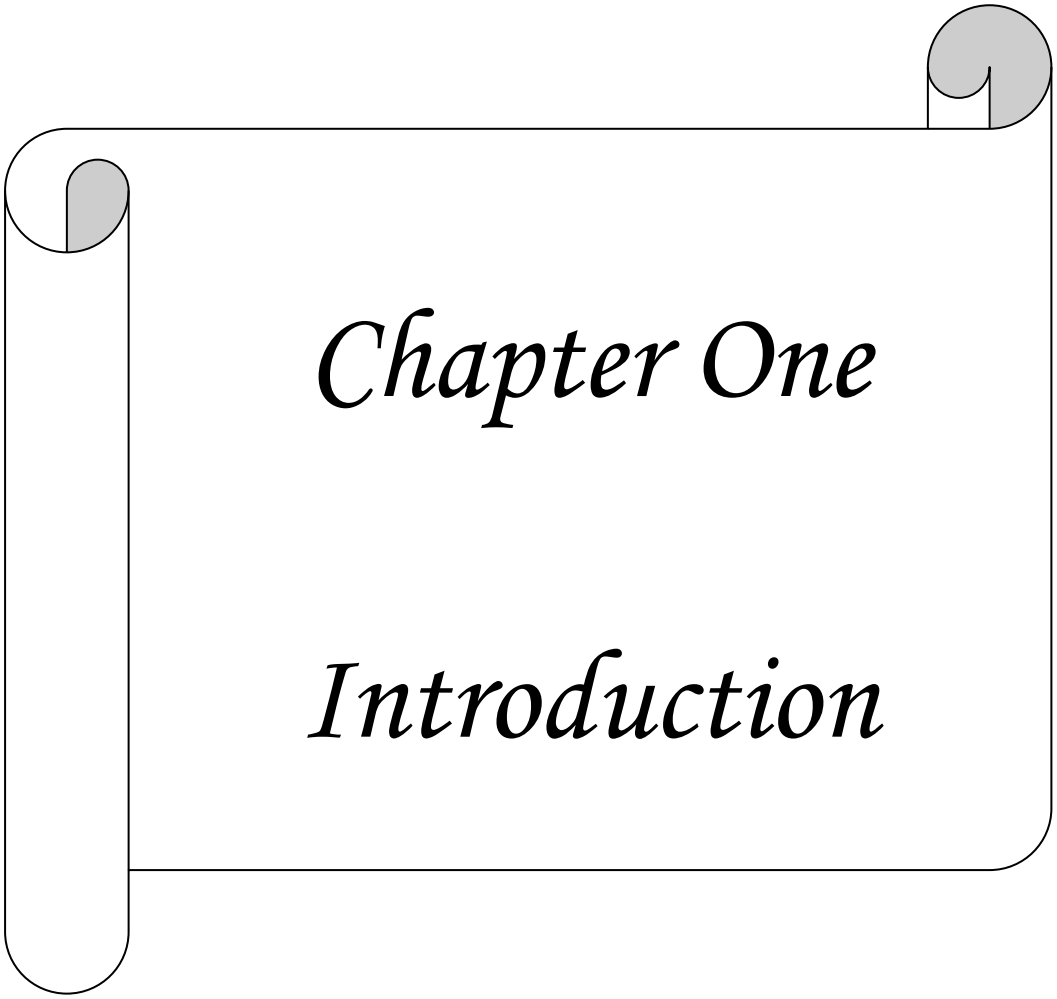


Chapter One

Introduction

1.1. Azo compounds

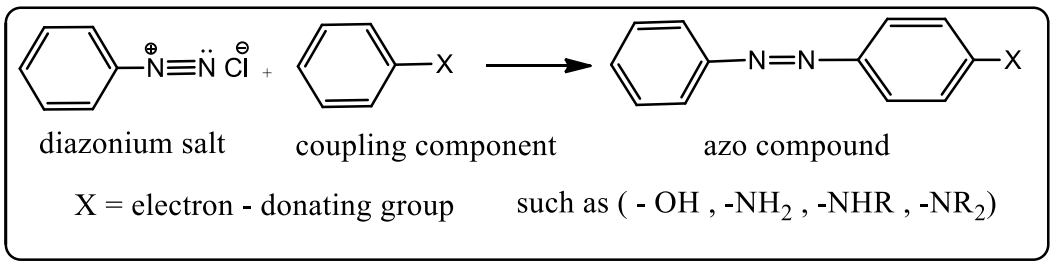
Azo compounds are characterized by the presence of azo group (—N=N—) which links two sp^2 hybridized carbon atoms[1] . Often , these carbons are part of an extended delocalized electron system involving the aromatic rings , called a chromophore[2] . Most azo compounds contain only one azo group , but some contain two, three or more azo groups[3].

Aliphatic azo compounds (R_1-N=N-R_2) (R_1 and /or R_2 = alkyl groups) are rather unstable . At an elevated temperature or by irradiating two carbon - nitrogen (R-N) bonds are cleaved simultaneously with the loss of nitrogen gas to generate carbon-centered radicals . owing to this process some aliphatic azo compounds are utilized as radical initiators[4].

Electrochemical studies show that the type of the substituted groups on the aromatic ring play an important role on the transformation of the potential of these compounds. However, an electron with drawing groups, such as (NO_2), have the ability to distribute negative charge to azo compound, by the effect of resonance, forming more stable complexes. Nevertheless, the position of these substitutions on the aromatic ring has also effect on the stability of these complexes[5].

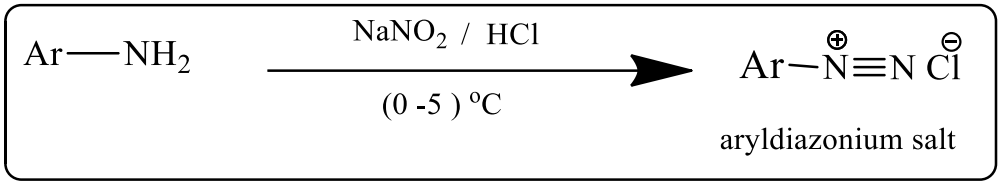
1.2. Synthesis of azo compounds

In general , the preparation of an azo compound requires two organic compounds a diazonium salt and a coupling component[6].This method was well- known as azo coupling as indicated in scheme (1-1).



Scheme (1-1) : Synthesis of an azo compound by using the azo coupling method

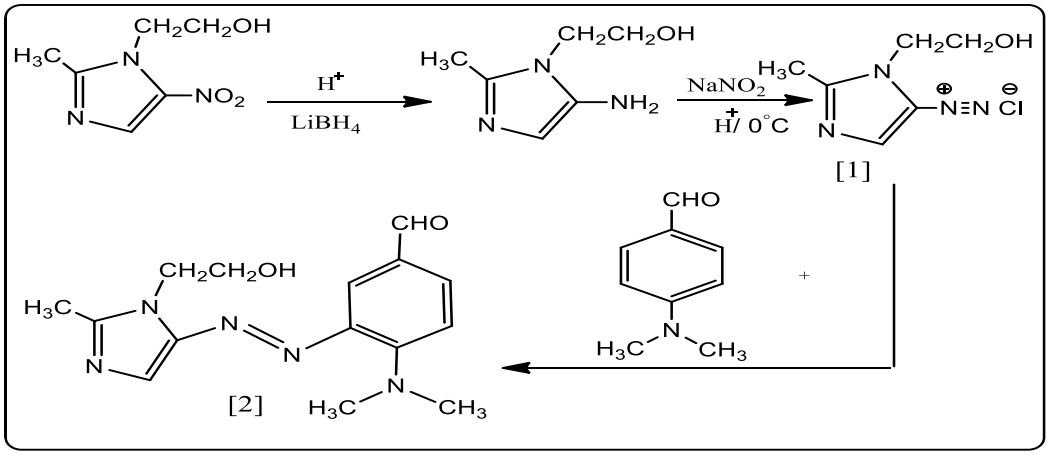
Aryldiazonium salts are prepared by treating an acidic solution of aniline and their derivitives with presence of sodium nitrite and hydrochloric acid. Scheme (1-2).



Scheme (1-2) : Formation of aryldiazonium salt

Diazonium salts are unstable and can be explosive when dry[7].Therefore, they are always prepared as needed under acidic condition with good stirring, kept at near 0°C, otherwise they react with water to produce a phenol, and must be used immediately in the coupling reaction.

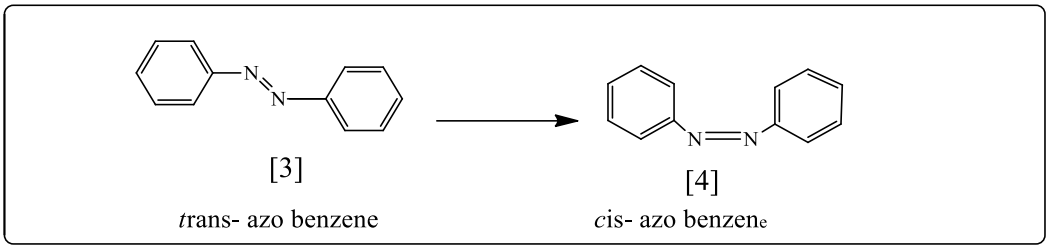
Adegoke et al.[8]prepared the new azo compound [2]. The procedure involves coupling of diazotized nitroimidazol [1] with *p-N,N*-dimethylaminobenzaldehyde to form a greenish-yellow solution. Scheme (1-3).



Scheme (1-3) : Formation of azo compond [2] via coupling reaction

1.3. Isomerism in azo compounds

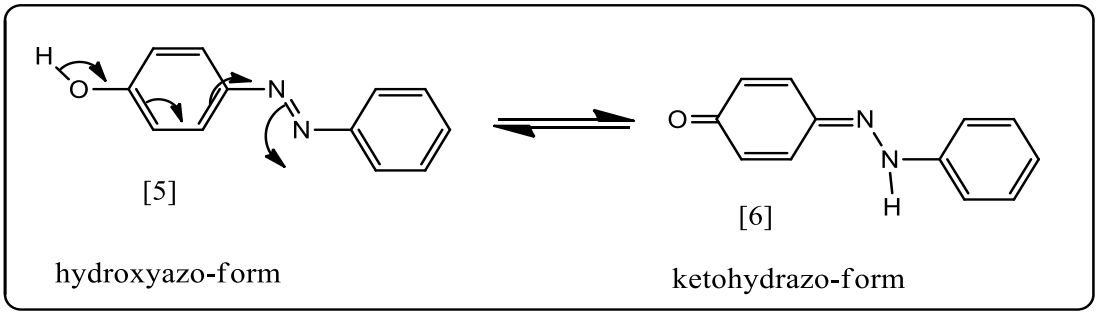
As with any double bond, the planar ($^{-}N{=}N^{-}$) bond usually exists in two geometrical isomers *cis* and *trans* . The *trans* isomer is considered to be the more preferable one[9].Scheme (1-4) .



Scheme (1-4) : Structures of trans and cis-azobenzene

The change from *trans* to *cis* will be effected by exposure to UV-radiation . This can lead to photochromism , a light induced reversible color change in some dyes .This effect was considered a nuisance and has largely been eliminated by careful development of more stable dyes. But photochromic dyes are beginning to make a comeback in technology like sunglasses and sunroofs in cars[10,11].

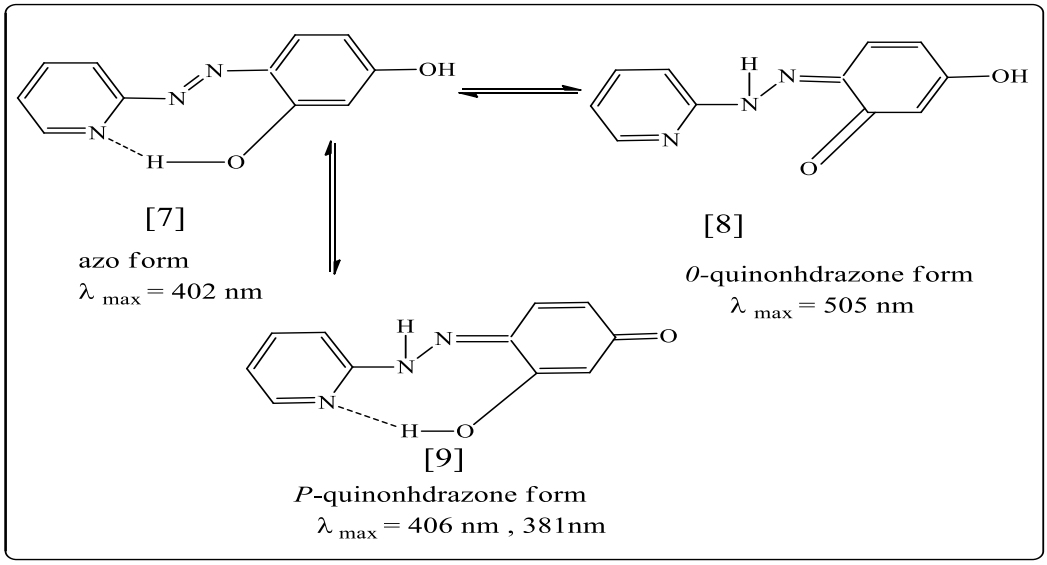
The aromatic azo compounds were identified to be more stable than the aliphatic one . This is in fact because of the presence of a tautomeric equilibrium form.This involves the removal of a hydrogen from one part of the molecule , and the addition of a hydrogen to a different part of the molecule ,this is common when there is an (-OH) group *ortho* or *para* to the azo group[12]as shown in .Scheme (1-5).



Scheme (1-5) : Tautomerism in azo compound [5]

Tautomeric forms can be identified through their characteristic spectra . Ketohydrazones are normally bathochromic compared to their counterpart hydroxyazo forms. Ketohydrazones also have higher molar extinction coefficients. However , not all azo compounds show tautomerism and some tautomeric forms are more stable than others[13].

Many authors[13-16] have investigated the intramolecular hydrogen bonding in some azo compounds . They related the low dissociation constant to the electrostatic effects of the ring substituent on the electronegativity of the azo nitrogen acting as a proton acceptor . The deprotonation of the *ortho*- hydroxy group usually proceeds more slowly when the hydrogen bond becomes stronger[17].Scheme (1-6).

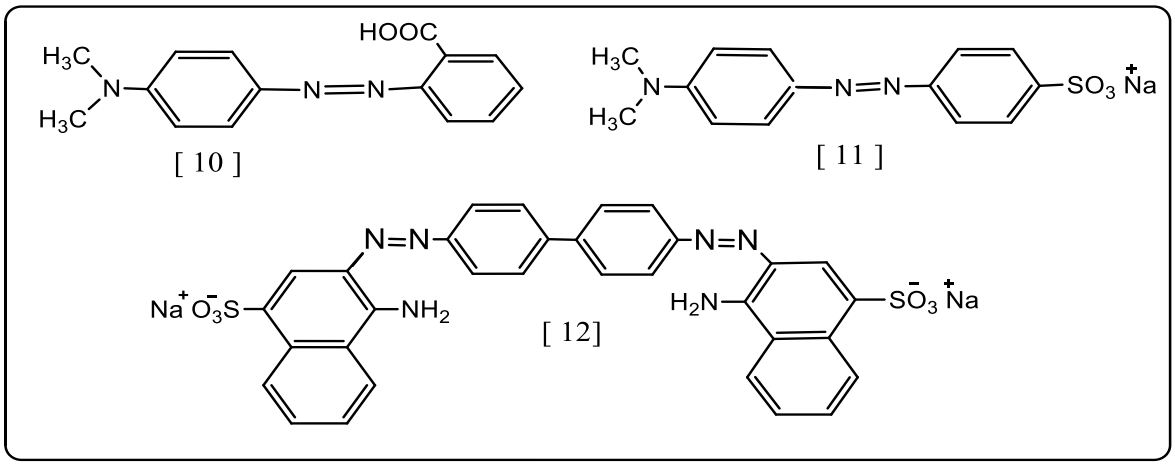


Scheme (1-6) : Tautomerism in azo compound [7]

1.4. Importance of azo compounds

Azo compounds constitute one of the largest classes of industrially synthesized organic compounds. Aliphatic azo compound , like azobisisobutyronitrile (AIBN), can be as radical initiators in polymerization of alkenes to make plastics[18].

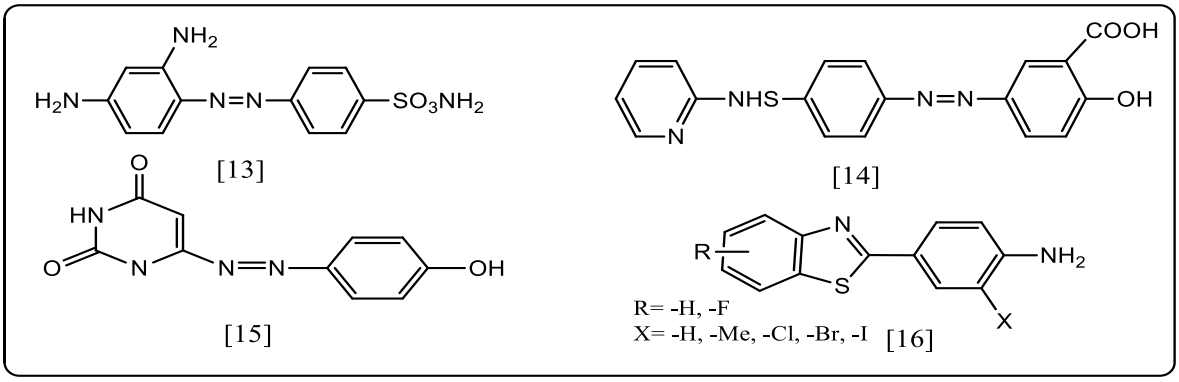
Aromatic azo compounds are used as acid-base indicators such as methyl red [10], methyl orange [11] and congo red [12] [19]as shown in scheme (1-7).



Scheme (1-7) : Using of azo compounds as indicators

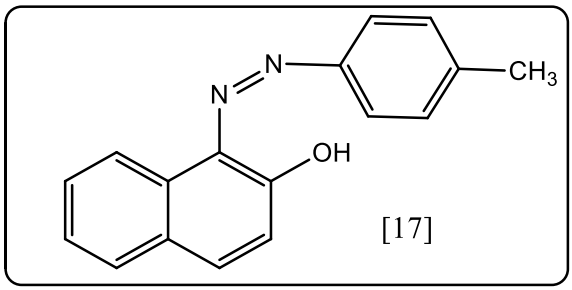
Azo compounds are important in the synthesis of drugs, cosmetics and azo dyes [(20)]. Azo dyes form (60-70 %) of all synthetic dyes used as commercial colorants . Azo dyes have several advantages over other commercial dyes including their wide color range, good color fastness and they can be synthesized cheaply because the starting materials are readily available and inexpensive compounds. Azo compounds show a variety of interesting biological activities including antibacterial [(21)], antifungal[(22)]and anticancer[(23)].

Some azo dyes were published as antimicrobial agents[(24)], for example ; prontosil [13] , salicylazosulfopyriden [14] and 6-(4-hydroxy phenyazo) uracil [15] in 1998, Bradshow et al.[(25)]showed that 2-(3- substituted 4-amino phenyl)benzothiazole derivatives [16] were a novel class of potent and selective antitumour agents which exhibit nanomolar inhibitory activity against a range of human breast,ovarian,colon and renal cell lines in vitro as shown in scheme (1-8).



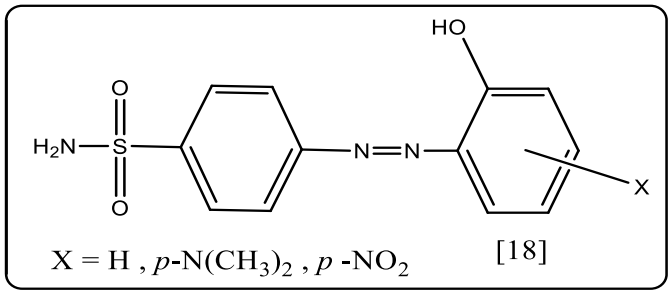
Scheme (1-8) : Some of azo derivatives which used as antimicrobial agents

Mkpenie et al.[26]prepared 1-(4-methylphenylazo)-2-naphthol [17] and studied the inhibition effect on the biological activities of some bacteria like *Escherichia.coli* and *Staphylococcus.aureus*.



compound [17]

Mossalamy[27] prepared sulfonamide azo dyes [18] by the reaction sulfonamide with derivatives of phenol and were used as ligands.

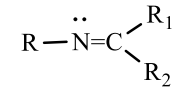


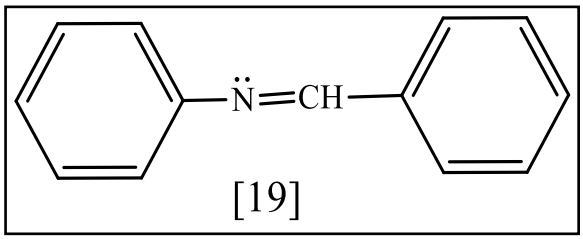
compound [18]

1.5. Schiff bases

Schiff bases are compounds which contain an azomethine group $\left(-\overset{\cdot\cdot}{N}=\overset{|}{C}-\right)$ .They are named after Schiff who prepared a number of these bases via condensation of aliphatic and aromatic aldehydes and ketones

with primary aromatic amines, primary aliphatic amines and amino acids[28].

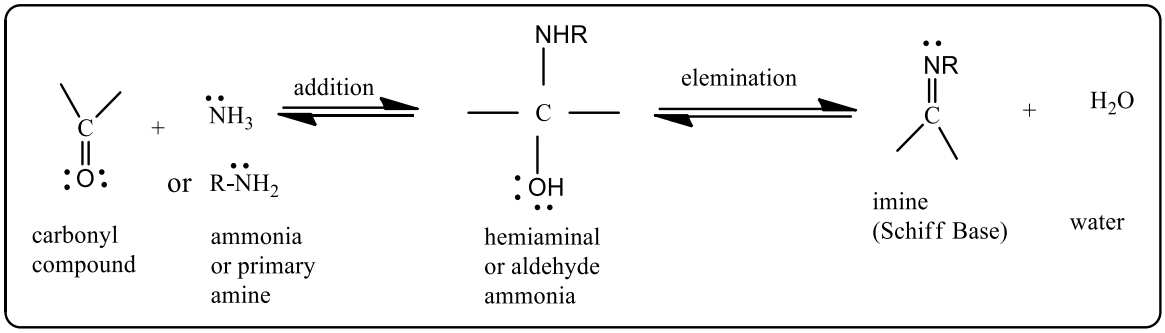
The general formula of these Schiff bases is  and their nomenclature depends on the nature of the groups R , R_1, R_2 [29]. The compound C_6H_5-Ṅ=CHC_6H_5 [19], for example, is named as*N*-benzyli- deneaniline (an old name), or *N*-benzylidenebenzeneamine (systematic name) and it is anaromatic Schiff base , while the compound (C_4H_9-Ṅ=CH-C_2H_5) is named as *N*-propylidenebutylamine, and it is an aliphatic Schiff base. There are other names for starting material such as azomethine Schiff base**,** anil**,** imine**,** ketimine**,** benzylideneaniline**,** benzalaniline (or benzaniline)**,** benzalanil (or benzanil)**,** and as the Schiff base of benzaldehyde and aniline[30]**.** Aromatic Schiff bases are considered as a chromophores due to conjugation of the electron pair on the nitrogen atom with the benzene ring of aniline and benzaldehyde [31].



compound [19]

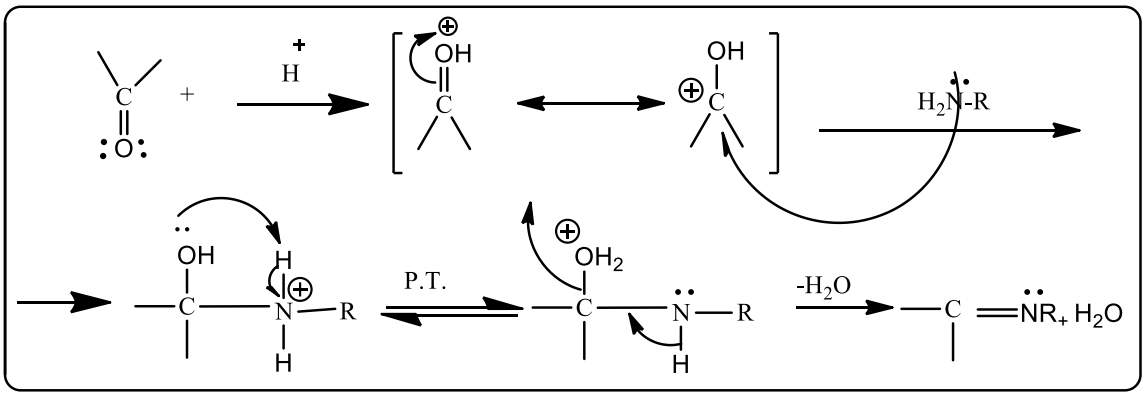
1.6. **Synthesis of Schiff bases**

Ammonia or primary amines add to the carbonyl group of aldehydes or Ketones to give hemiaminals (also called "aldehyde ammonias ") which decompose to the imines or Schiff bases [32,33] as shown in scheme (1-9).



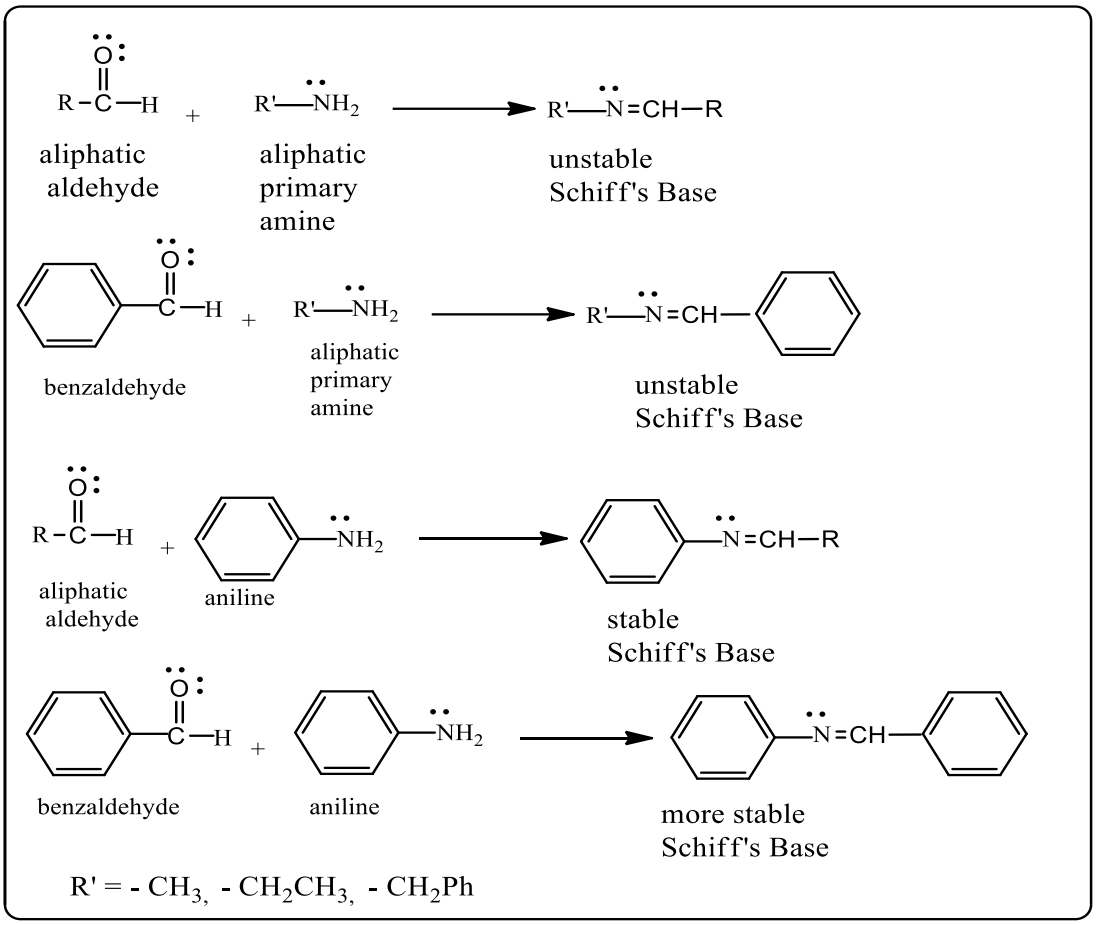
Scheme (1-9) : Formation of Schiff bases through condensation of aldehydes or ketones with ammonia or primary amines

The reaction may be catalyzed by protonating the carbonyl group[34]the reaction is believed to follow the mechanism shown in scheme (1-10).



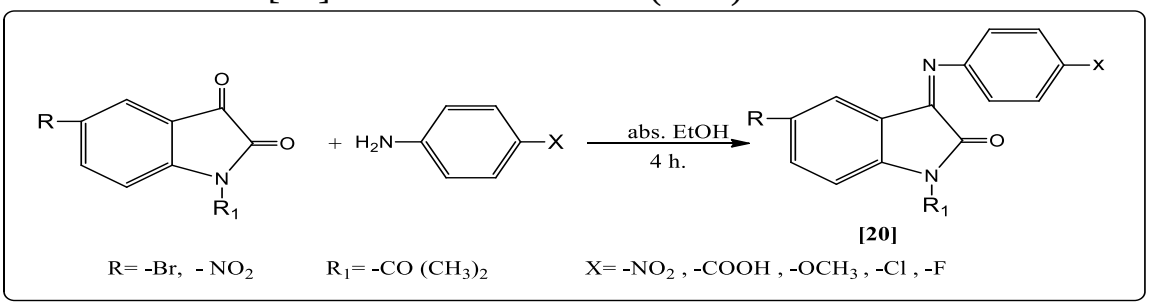
nmine formatioiMechanism of) :01-Scheme (1

In general, the resulting imine is unstable [32] . The stability of the final product depends on the nature of the starting aldehyde or ketone and the amine . It can be concluded that the stabilized Schiff bases may be prepared from the following types of compounds as shown in scheme (1-11)[35] .



Scheme (1-11) : Effect of the structure on the stability of Schiff bases

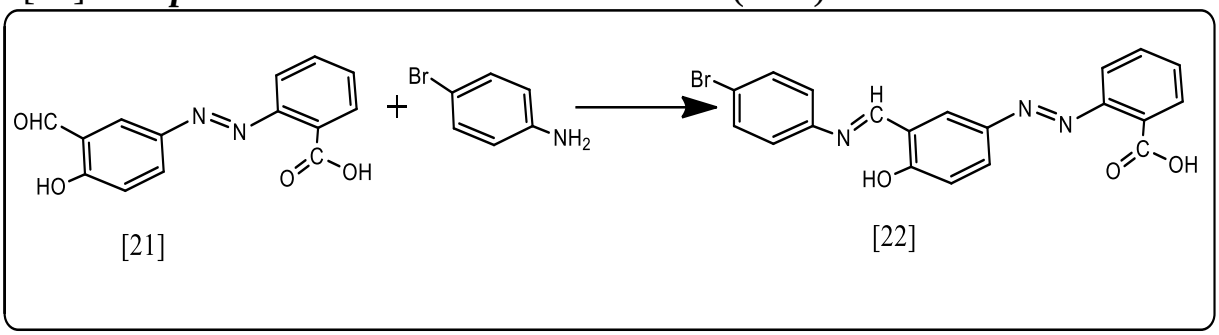
Verma et al. [36] synthesized Schiff bases of *N*-methyl and *N*-acetyl isatin derivatives [20] as shown in scheme (1-12).



Scheme (1-12): Synthesis of *N*- methyl and *N*- acetyl isatin derivatives

Compounds containing each azo and imine groups are called azoimines or azo Schiff bases which are prepared starting from azoaldehydes and primary amines through catalytic condensation reaction . Basu et al. [37]prepared new azo Schiff base derivative [22] via

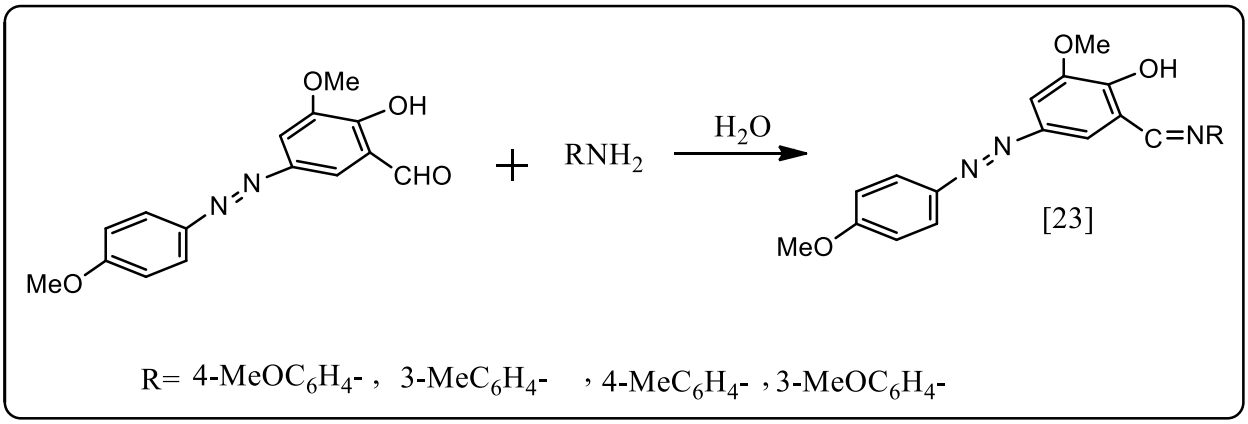
acid-catalysed condensation reaction between azoaldehydes derivative [21] with ***p***- bromoaniline as shown in scheme (1-13) .



[21] [22]

Scheme (1-13) : Structure of azo Schiff base derivative [22]

Zarei et al.[38] prepared azo Schiff bases derivatives [23] with free solvent in green method and high yield as shown in scheme (1-14).



Scheme(1-14): Synthesis of azo Schiff base derivatives[23]

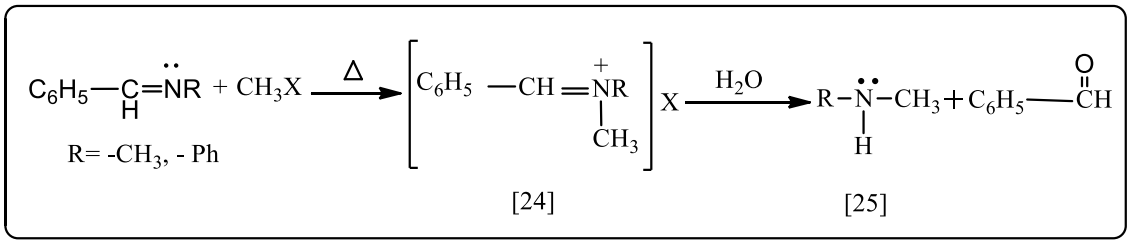
1.7. Reactions of Schiff bases

1.7.1. Addition reactions

Schiff bases undergo addition reactions to the azomethine group, the reagents are added to the polarized double bond $\left(\rangle C^{\delta+}=N^{\delta-}-\right)$ so,nucleo-philic reagents attack the carbon atom of the azomethine linkage**.**

1.7.1.1. Addition of alkyl halides

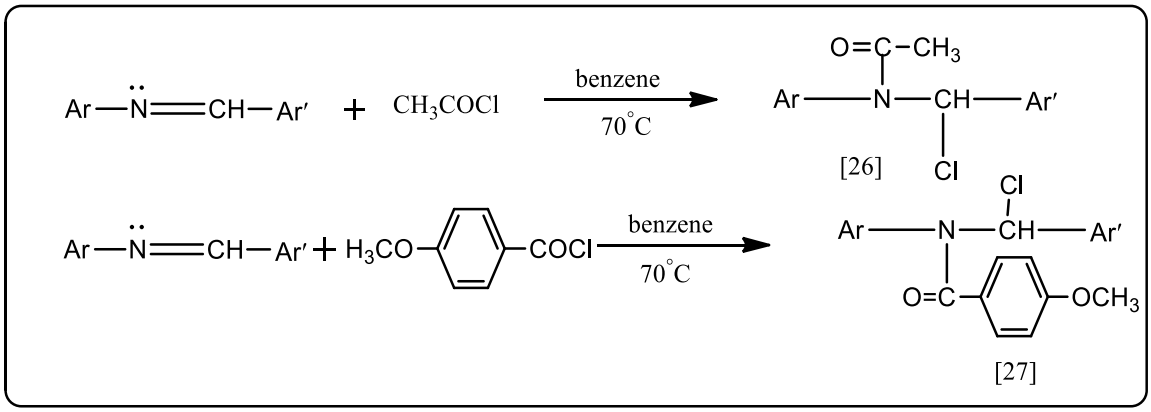
The alkylation of Schiff bases with alkyl halides results in a quaternary iminium salts [24], which are converted to secondary amines [25] uponhydrolysis[39]. The alkylation is used to synthesis of secondary amines as shown in scheme (1-15) .



Scheme (1-15) : Alkylation of imines to the secondaryamines [25] through reaction with alkyl halides

1.7.1.2. Addition of carboxylic acid chlorides

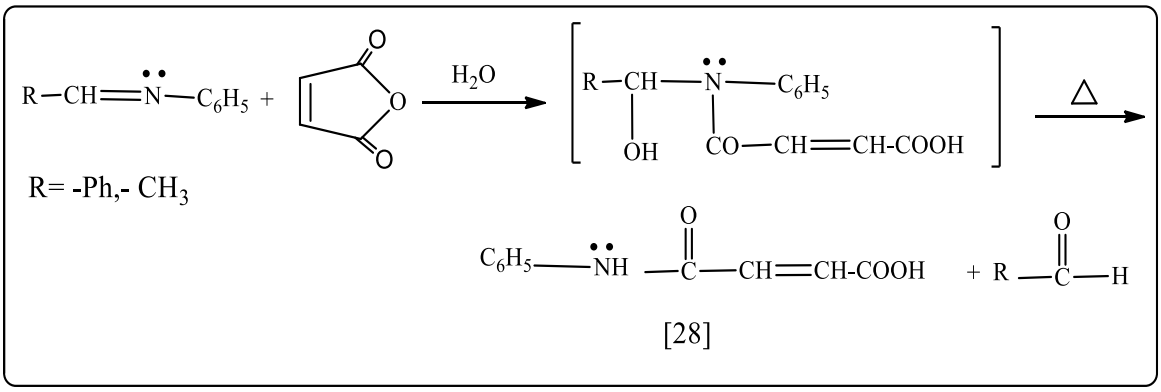
It is found that acidchlorides such as acetyl chloride and ***p***-anisoyl chloride are added to Schiff bases to give the addition products [26][40] and [27][41] respectively as shown in scheme (1-16).



Scheme (1-16) : Addition of acetyl chloride and *p*-anisoylchloride to azomethine group to give the addition products [26] and [27] respectively

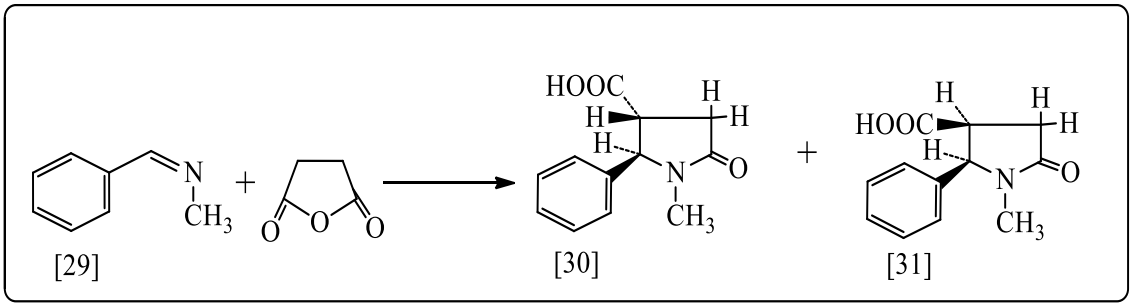
1.7.1.3. Addition of maleic andsuccinic anhydrides

Anils react with maleic anhydride in the presence of water to form maleanilic acid [28] and aldehydes[42]. When an anil is heated with maleic anhydride in toluene, maleanilic acid [28] is also obtained[43]. Whereas the formation of a condensation product has been reported when the mixture is heated without using the solvent. Crotonaldehydeanil and cinnamaldehydeanil react with maleic anhydride in xylene to form an addition products[44].Scheme (1-17).



Scheme (1-17) : Fomation of maleanilic acid [28] from anils

The condensation of benzylidenemethylamine [29] with succinic anhydride yields *trans*- and *cis*- 1-methyl4-carboxy-5-phenyl-2- pyrrolidin-one [30] and [31] respectively[45] . Scheme (1-18).

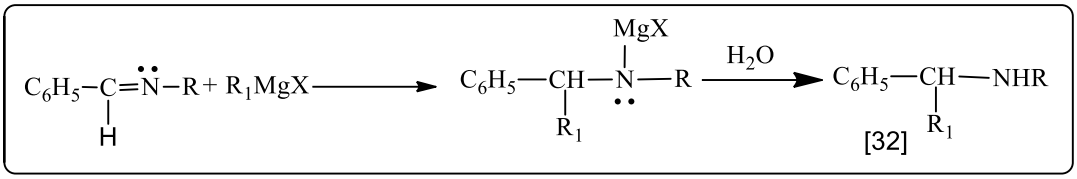


Scheme (1-18) : Addition of succinic anhydride to imine [29]

1.7.1.4. Addition of Grignard reagents

Grignard reagents react with azomethine compounds to form addition products which on hydrolysis result in secondary amines [32]. The reaction

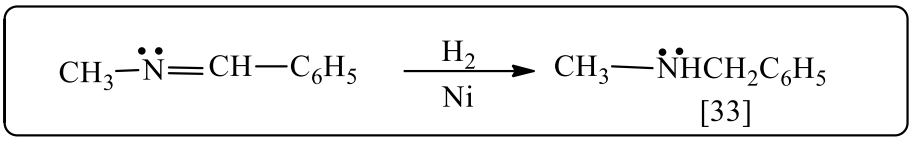
is usually applied to the Schiff bases which are prepared from aryl aldehydes[46]as shown in scheme (1-19)**.**



Scheme (1-19) : Addition of Grignard reagents to imines

1.7.1.5. Addition of hydrogen

Schiff bases can be hydrogenated in the presence of catalyst to give the corresponding secondary amines[47] [33]**.** Scheme (1-20).



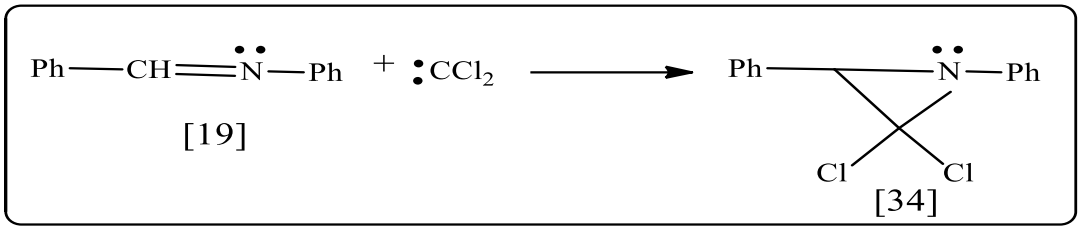
Scheme (1-20) : Hydrogenation of imines

1.7.2. Cycloaddition reactions

For several years, the Diels- Alder reaction was the only widely useful example of the so-called cycloaddition reactions[48]. The extensive generalization by Huisgen and his school of the concept of 1,3-dipolar cycloadditions, first recognized by Schmidt, has opened new avenues for investigations[49]. The dimerazation of olefins, as well as the addition of carbenes and nitrenes to unsaturated centers has extended the series to include three-, four-, five- and six-membered ring systems. Huisgen et al.[48 ,49] have reviewed cycloaddition reactions of alkenes, and here we will deal with the various cycloaddition of the azomethine bond ().

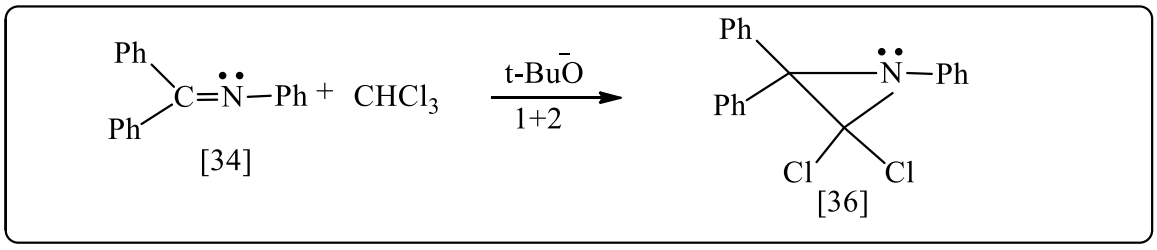
1.7.2.1. Formation of three-membered rings

Dichlorocarbene added to *N*-benzylideneaniline [19] to give the corresponding dichloroaziridine[50] [34]. Scheme (1-21).



Scheme (1-21) : Synthesis of aziridine ring via cycloaddition of dichlorocarbene to azomethine bond

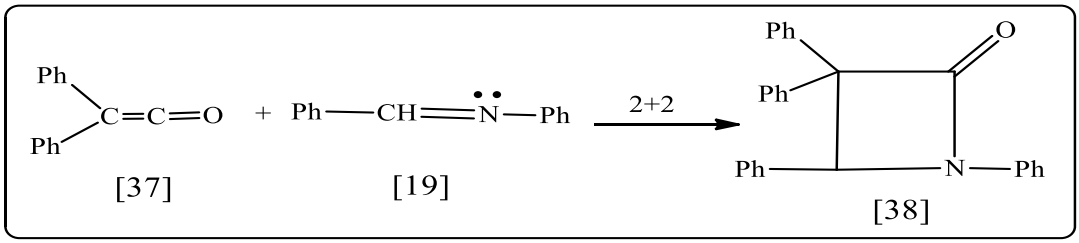
Deyrup and Grunewald[51]have shown that the reaction of diphenylmethyleneaniline [35] with chloroform and potassium t-butoxide gave 3,3- dichloro-1,2,2-triphenylaziridine [36] as shown in scheme (1-22).



Scheme (1-22) : Synthesis of aziridine ring via cycloaddition of cloroform toazomethine bond

1.7.2.2. Formation of four- membered rings

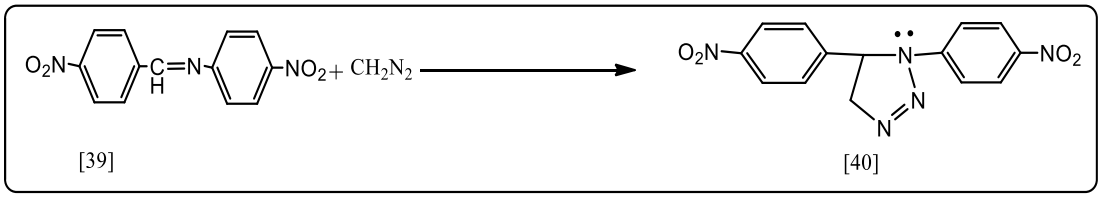
Staudinger[52]reported the formation of 1,3,3,4-tetraphenyl-2-azetidinone [38] via [2+2] cycloaddition of diphenylketene [37] with *N*-benzylideneaniline [19]. Scheme (1-23)**.**



Scheme (1-23) : Synthesis of azetidine ring through [2+2] cycloaddition of ketene to azomethine bond

1.7.2.3. Formation of five-membered rings

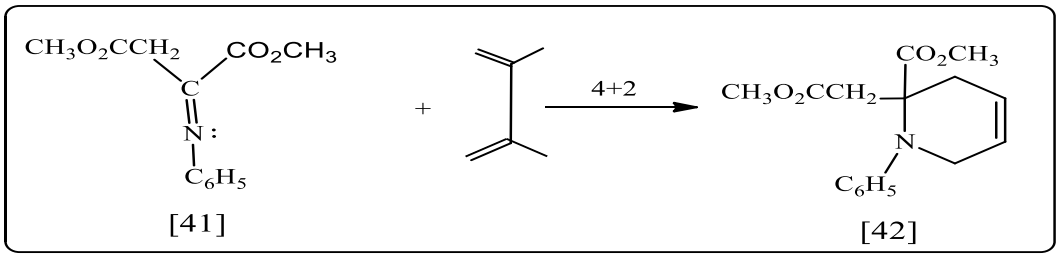
Buckley[53] reported the reaction of diazomethane with *p*-nitro-*N*-(*p*-nitrobenzylidene) aniline [39] and assigned the 1,2,3-triazoline structure [40] via 1,3-dipolar cycloaddition. Scheme (1-24) **.**



Scheme (1-24) : Formation of 1,2,3-triazoline ring via1,3-dipolar cycloaddition of diazomethane to imine group

1.7.2.4. Formation of six-membered rings

Alder[54] mentions that the reaction of imino form of dimethyl anilinomaleate [41] with *c*is dienes gives tetrahydropyridine [42]. The influence of an electron-withdrawing groups attached to imine bond is the key factor to do the reaction as shown in scheme (1-25)**.**



Scheme (1-25) : Formation of tetrahydropyridine derivative [42] via [4+2] cycloaddition of imino group to *c*is 2,3- dimethyl-1,3-butadiene

1.8. Schiff bases uses

Schiff bases are starting materials for the preparation of a large number of heterocyclic compounds[55] and their complexes[56].They are also used to prepare super - conducting polymers [57].

Schiff bases are reported to show a variety of interesting biological actions including antibacterial[58],antifungal[59],antivirus(MHV)[60],

anticonvulsant[36],anticancerand herbicidal activities[38], it is also known that the presence of an azo moiety in different types of Schiff bases can

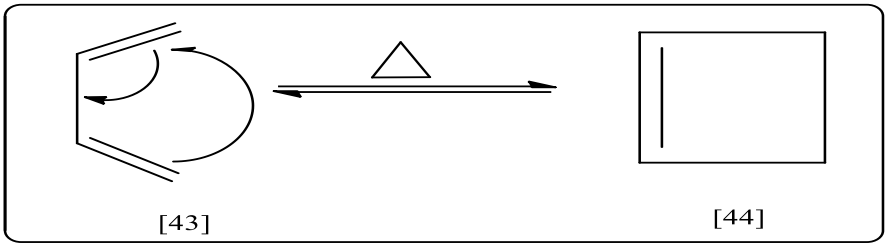
lead them to exhibit pesticidal activities[61]. Both Schiff bases and azo compounds are important structures in the medicinal and pharmaceutical fields [60]. And it has been suggested that the azomethine linkage might be responsible for biological activities displayed by Schiff bases [62]. In the light of the interesting variety of biological activities seen in compounds containing azo and azomethine linkage. So many methods were reported for the synthesis of Schiff bases .

1.9. Pericyclic reactions

Pericyclic reaction represents an important class of concerted (single step) processes involving π-systems, a concerted rearrangement of the electrons takes place that causes σ and π-bonds are broken and formed simultaneously. While the classical organic reactions involve several steps or rearrangement with side reactions and relatively low yield, the pericyclic reaction is one step-process and takes place through a single transition state (T.S) with relatively high yield and no side reactions[63].Concerted reactions include three major classes :

1.9.1. Electrocyclic reactions

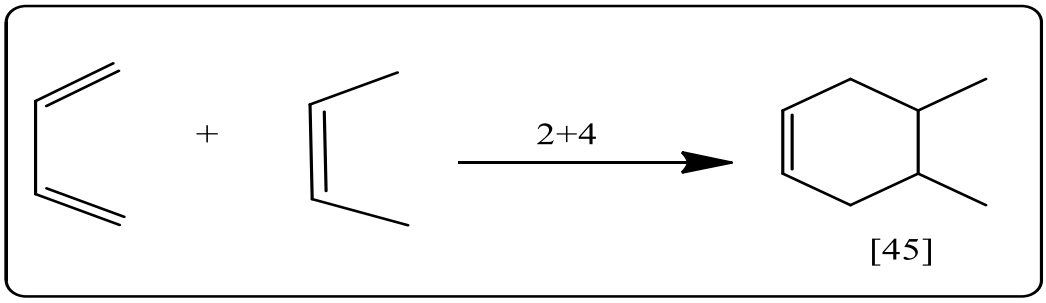
Electrocyclic reactions is a pericyclic process that involve the cyclization of a conjugated polyene. One π-bond is broken, the other π-bond is changed position then a new σ-bond is formed and a cyclic compound is resulted. For example *c*is 1,3-butadiene [43] can be converted to acyclobutene [44][64]under heating as shown in scheme (1-26)



Scheme (1-26) : Conversion of *c*is1,3- butadiene to cyclobutene under heating

1.9.2. Cycloaddition reactions

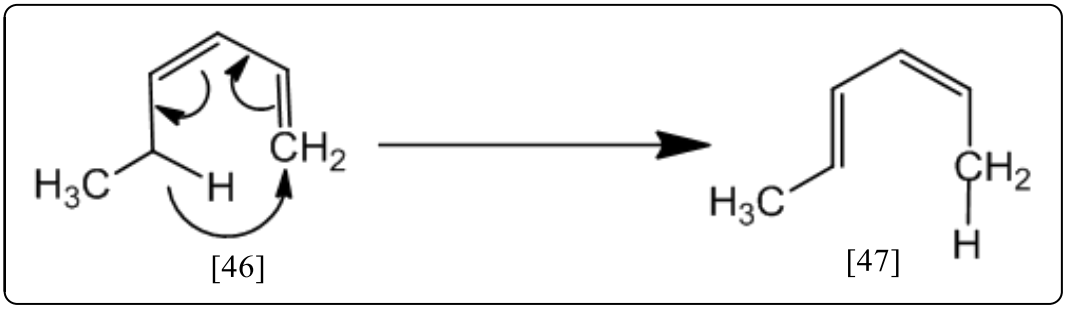
There is number of reactions of alkenes and polyene in which two molecules form a cyclic product [45]. These reactions are called cycloadditon reactions. The Diels-Alder reaction is one type of this reaction[65].Scheme (1-27).



Scheme (1- 27) : Formation of six- membered ring via [2+4] cycloaddtion of alkene and cis 1,3-butadiene

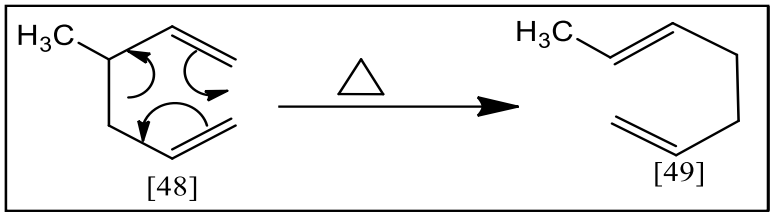
1.9.3. Sigmatropic rearrangements

Sigmatropic rearrangements are unimolecular processes, like electrocyclic reactions, and involve the movement of a σ-bond with the simultaneous rearrangement of the π-system[66]. Scheme (1-28)



Scheme (1-28) : Sigmatropic rearrangement reaction

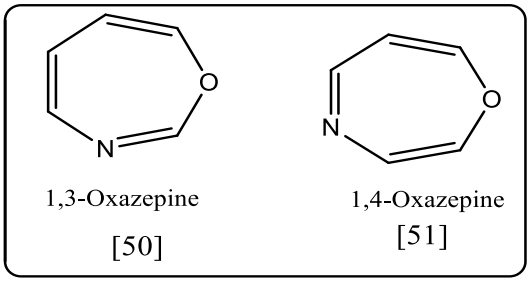
The Cope rearrangement is important example on sigmatropic rearrangement[67].Scheme (1-29).



Scheme (1-29) : Cope rearrangement reaction

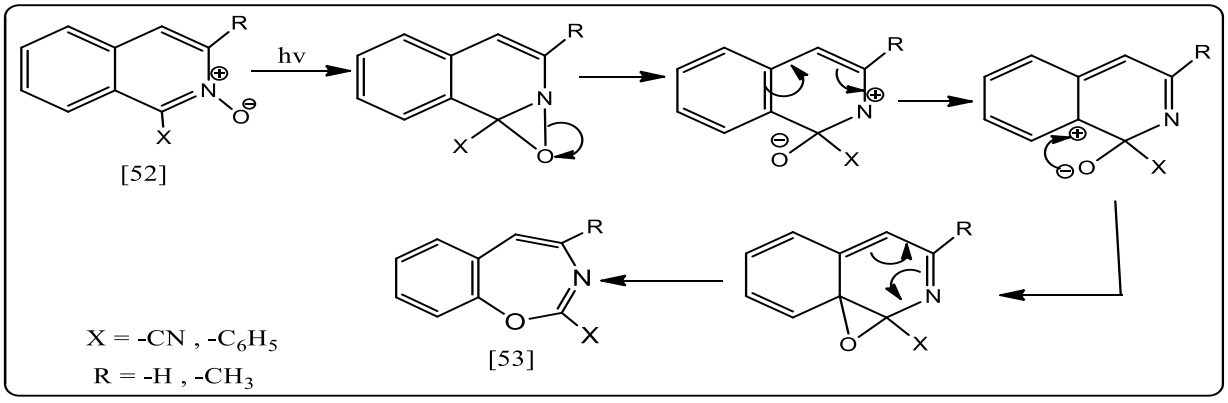
1.10. Synthesis of 1,3- and 1,4-oxazepines

Oxazepine is non-homologous seven-membered ring that contains two hetero atom (oxygen and nitrogen) as shown in Scheme (1-30).



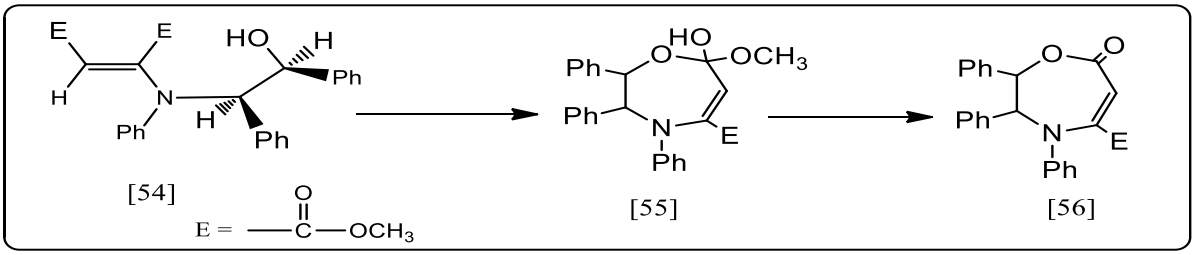
Scheme (1-30) : Structures of 1,3- and 1,4- oxazepine rings

For a long time, the synthesis of 1,3- and 1,4-oxazepine rings were based on two limited classical types of reaction, the first reaction is called (Valence-bond isomerization) which is carried out via irradiation of polyaryl pyridiine *N*-oxides [52]. This irradiation results in ring expansion to 1,3-oxazepine derivatives[68] [53] as shown in scheme (1-31).



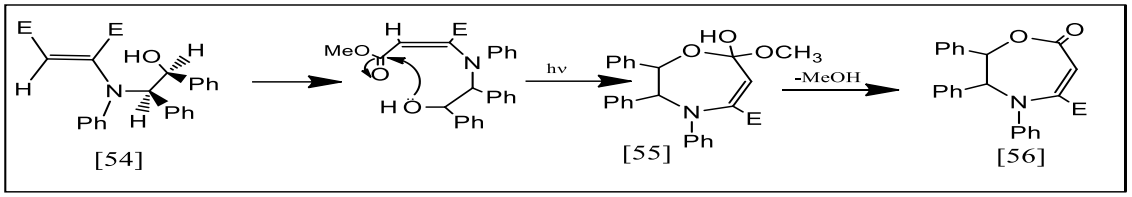
Scheme (1-31) : Mechanism of pyridine ring expansion to seven-membered1,3-oxazepine ring

The second reaction is called (Enamine condensation) which is carried out via irradiation of enamine derivative [54] to produced 2,3,6-trihydro-5-methoxy carbonyl-2,3,4-triphenyl-1,4-oxazepin-7-one [55] and [56] as its hemiacetal[69].Scheme (1-32) .



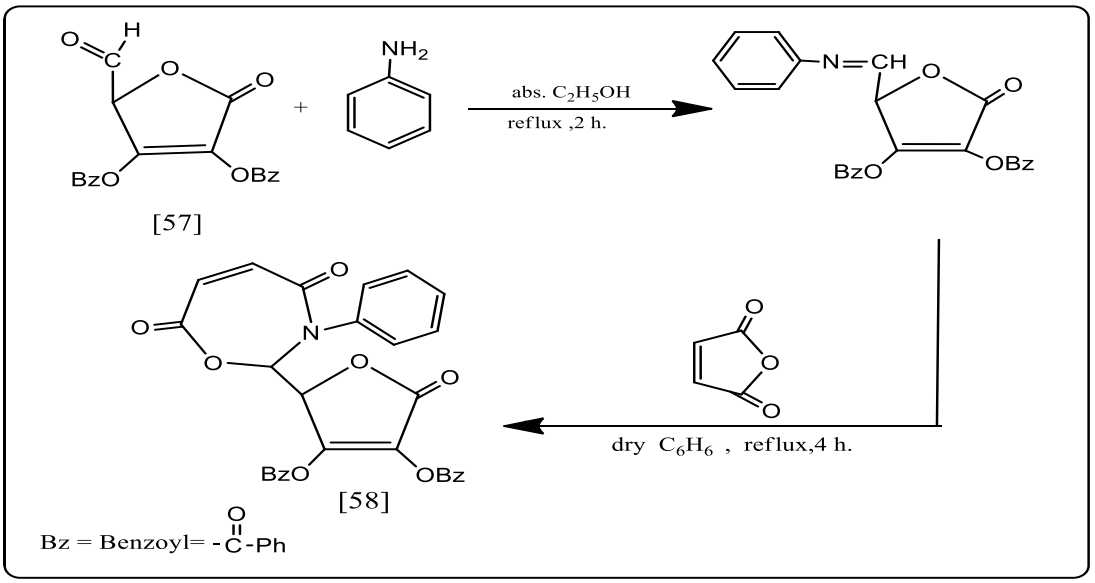
Scheme (1-32) : Formation of 1,4- oxazepines [55] and [56] via irradiation of enamines derivative [54]

The[69] mechanism of this reaction is shown in scheme (1-33) .



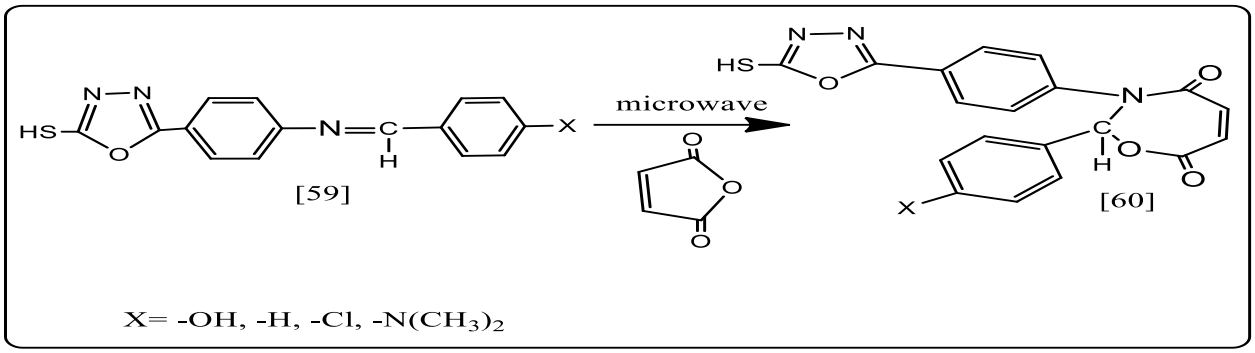
Scheme (1-33) : Mechanism of irradiation of enaminederivative [54] to produce 1,4-oxazepine ring

Recently, pericyclic reactions are used in synthesise of 1,3-oxazepine ring[70,71].Jawad[72]prepared new 1,3-oxazepine derivative [58] starting from L-Ascorbic acid [57] .Scheme (1-34) .



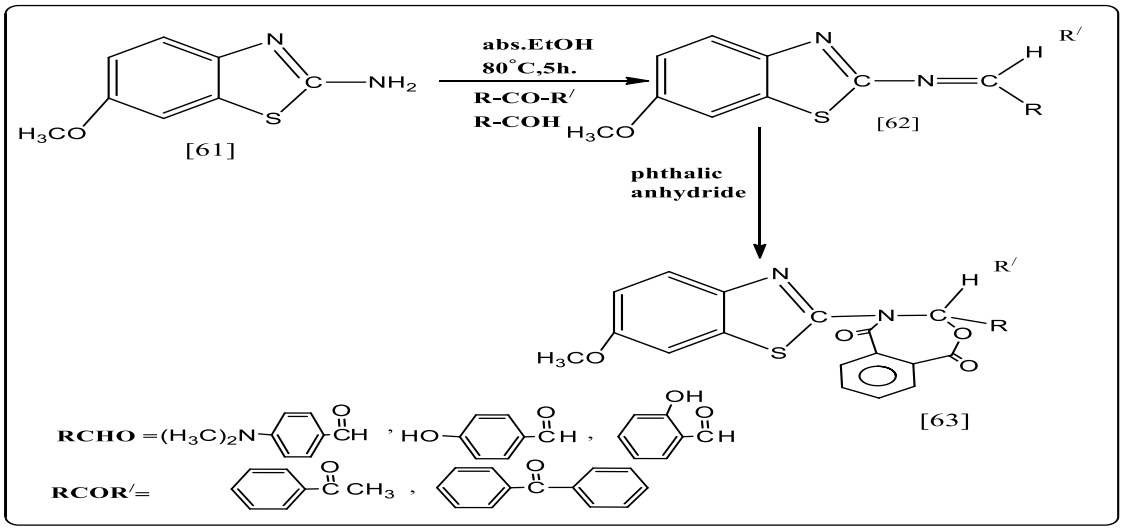
Scheme (1-34) : Formation of 1,3-oxazepine derivatives [58] through cycloaddition reaction of imino ascorbic acid to maleic anhydride

Hameed[73]synthesis of four new 1,3,4-oxadiazole derivatives containing 1,3-oxazepine moiety [60] by microwave assisted organic synthesis method through the addition reaction of 2-[4-(arylidene) phenyl-1,3,4-oxadiazole-5-thiol] [59] with maleic anhydride under variable microwave power (180,510) watt.Scheme (1-35).



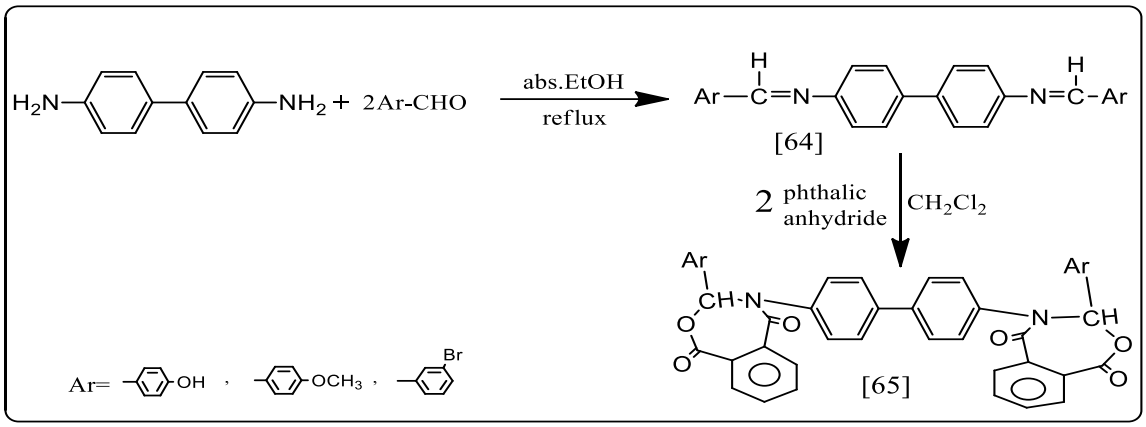
Scheme (1-35) : Synthesis of 1,3-oxazepines [60] through addition of maleic anhydride to imines [59] under variable microwave power

Yousif[74]synthesis of several Schiff bases [62] by condensation of 6- methoxy -2- amino benzothiazole [61] with some aldehydes and ketones (2- hydroxyl benzaldehyde, 4- hydroxyl benzaldehyde, 4- *N*,*N* –dimethy amino acetophenone, benzophenone) to obtain Schiff bases which were found to react with phthalic anhydride to give1,3- oxazepine derivatives [63] .Scheme (1-36).



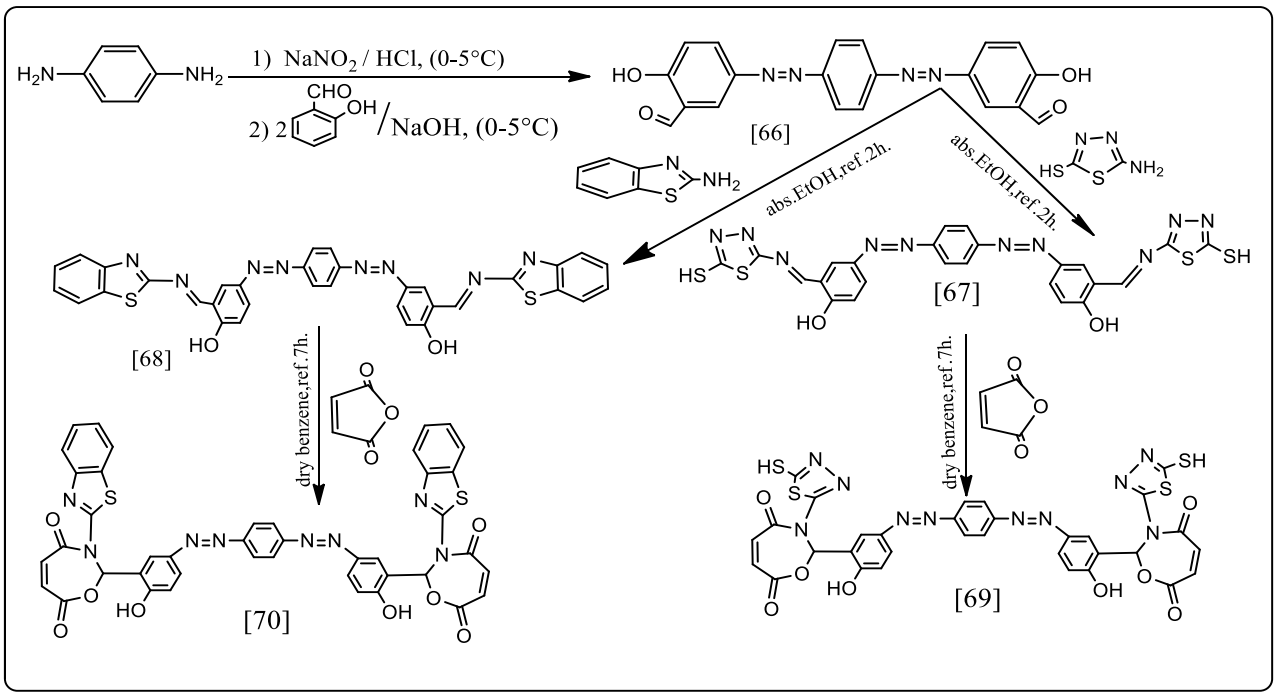
Scheme (1-36) : Formation of 1,3-oxazepine derivatives [63] containing benzothiazole moiety

Mahrath et al.[75] synthesized new bis- 1,3 oxazepine 4,7- dione derivatives [65] via [2+5] cycloaddition of phthalic anhydride to imines [64]. Scheme (1-37).



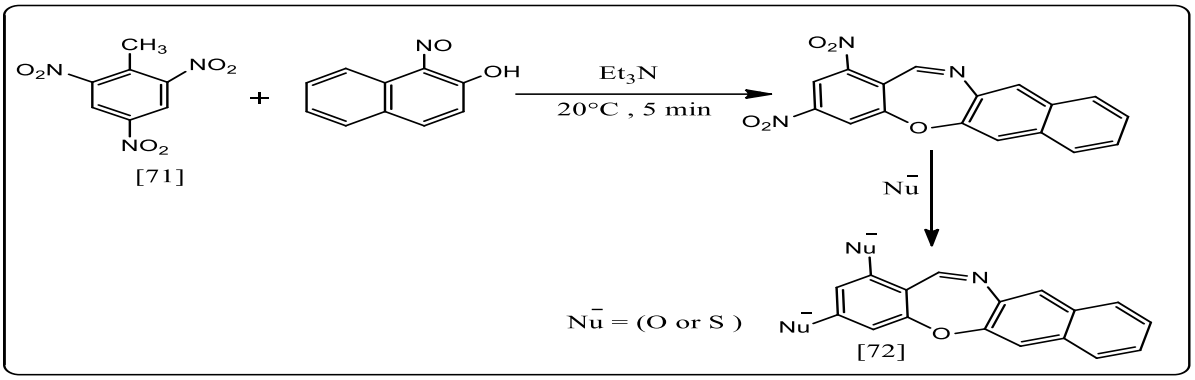
Scheme (1-37) : Synthesis of bis - 1,3- oxazepine derivatives [65] via [2+5] cycloaddition of phthalic anhydride to bis-imines [64]

Abood[76] synthesized new bis-1,3–oxazepine-4,7- dione derivatives [69] and [70] containing two azo groups and 1,3,4-thiadiazole or benzothiazole moieties as shown in scheme (1-38).



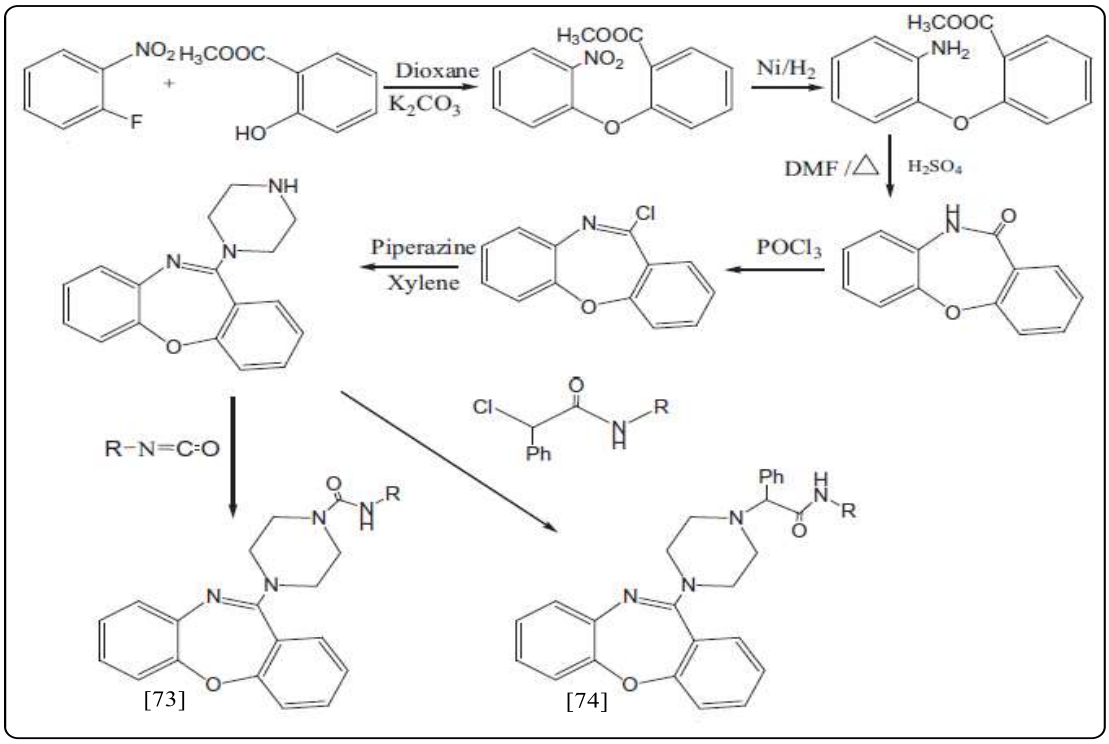
Scheme (1-38) : Synthesis of bis-1,3-oxazepine derivatives containing two azo groups and 1,3,4-thiadiazole or benzothiazole moieties [67] and [68]

Samet et al.[77]synthesized of benzo [f] naphthol [b][1,4] oxazepines [72] from TNT [71] as shown in scheme (1-39).



Scheme (1-39) : Synthesis of benzo [f] naphthol [b] [1,4] oxazepines [72] from TNT [71]

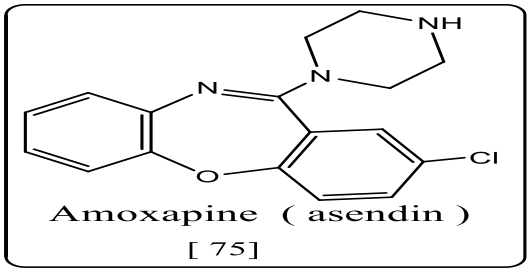
Jain et al.[78] synthesized a series of new substituted N-11-(40-N-aryl carboxamido / N-(aryl)-a-phenyl-acetamido-piperazinyl) -dibenz [b,f] [1,4]-oxazepine derivatives [73] and [74] were designed on a revised structural model the present study demonstrates significant antipsychotic activity as shown in scheme (1-40).



Scheme (1-40) : Synthesis of dibenz[b,f][1,4]-oxazepine derivatives [73] and [74]

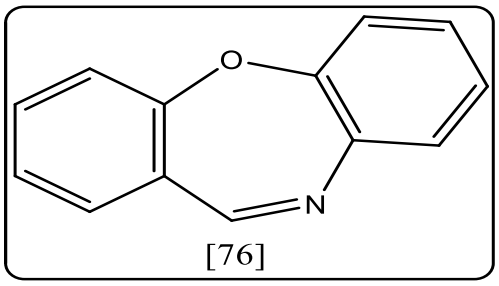
1.11. Importance of oxazepine

Oxazepine and their derivatives have some important biological pharmacological activities[79] such as enzyme inhibitors[80], analgesic[81], antidepressant[82]and psychoactive drug[83] . Amoxapine [75] is a group of drugs called tricyclic antidepressants. It is used to treat symptoms of depression, anxiety and agitation [84].



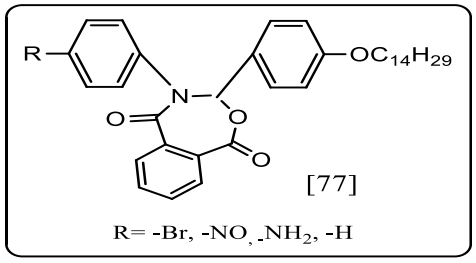
compound [75]

Dibenz [b,f]-1,4-oxazepine [76] is used in chemical weapons as tear gas. Tear gas is the common name for a low concentration substance, cause pain in eyes, flow of tears and difficulty in keeping eyes open. It is used mainly in military exercises and in riot control[85].



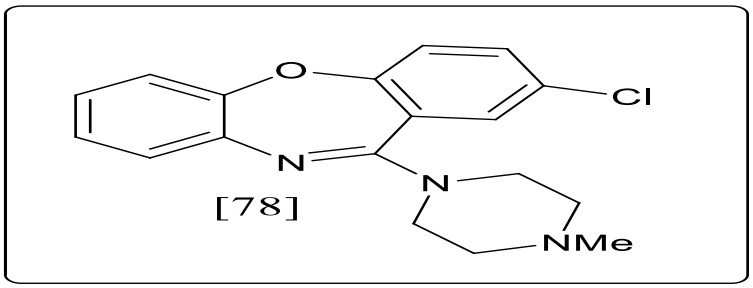
compound [76]

Guan etal.[86] prepared new1,3- oxazepine- 4,7- dione derivatives [77] and study their liguid crystalline properties.



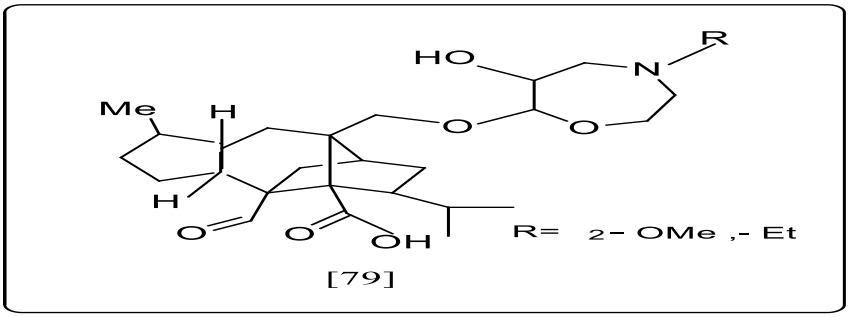
compound [77]

Aiello et al.[87]prepared2- Chloro-11(4-methyl-piperazin-1-yl) dibenzo[b,f] [1,4]oxazepine [78] and used it as anti-psychoactive.



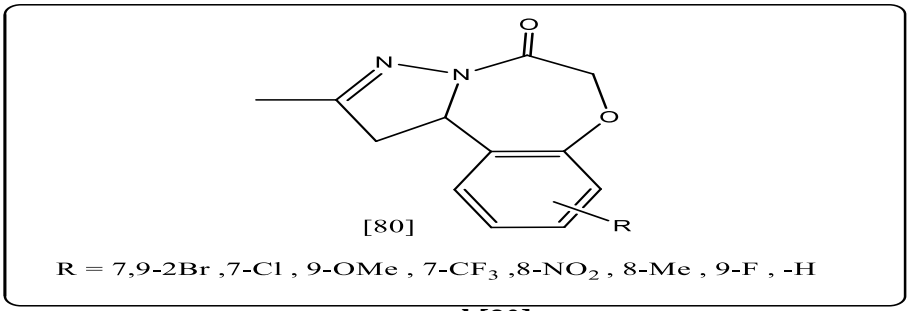
compound [78]

Serrano et al.[88] evaluated the biological activity of 1,4-oxazepine derivative [79], medically- known as Sordarin which showed antifungal activity against three types of fungi *are candida albicans,candida glabrata and cryptococcus neoformas*.



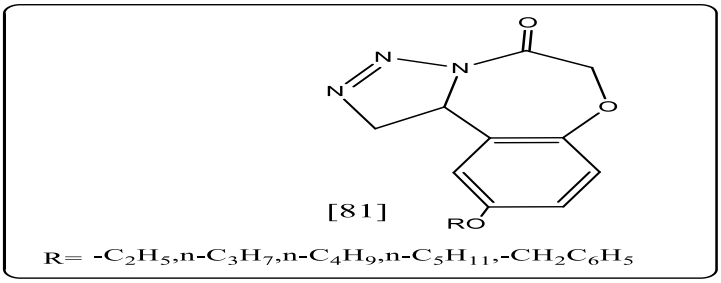
compound [79]

Xin-Hua Liu et al.[89] synthesized eight novel 4,5-tetrahydropyrazolo [1,5-d][1,4] oxazepine derivatives [80] to be screened for anticancer activity.



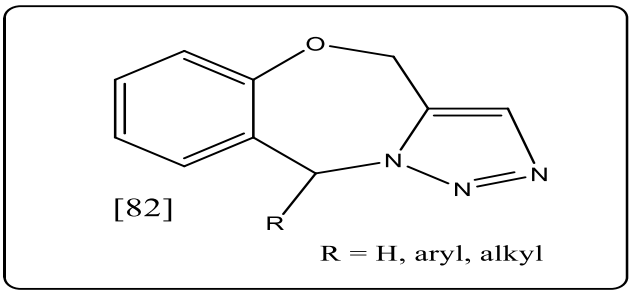
compound [80]

Xian-Qing Denget al.[90]synthesized novel series of 10-alkoxy-5, 6-dihydro-triazolo[4,3-d] benzo[f][1,4] oxazepine derivatives [81] were screened for their anticonvulsant activities by the maximal electroshock (MES) test.



compound [81]

Seennaiah et al.[91]synthesized a series of [1,2,3-triazolo [5,1-c][1,4] benzoxazepine derivatives [82] as antibacterial.



compound [82]

Aim of the study

This work aims to synthesis the preliminary evaluation of antibactrial activity of two new series of bis-1,3-oxazepine-4,7-dione derivatives, the first series contains azo groups while the second does not.

Chapter Two

Experimental part

2. Experimental part

2.1. Materials

Table (2-1) shows the utilized chemicals in the experimental course of the thesis.

Table (2-1) : Chemicals and their manufactures

Chemical	M.Wt. g/mol	Purity %	Supplied from
o-Tolidine	212	99	Merck
Sodium nitrite	69	99	BDH
Hydrochloric acid (Conc.)	36.5	99	Merck
4-*N*,*N* Dimethylaminobenzaldehyde	149	99	Merck
Ethanol(absolute)	46	99.9	BDH
Sodium hydroxide	40	99	BDH
4- Clorobenzaldehyde	140	99	Merck
4-Methoxyaniline	123	99	Fluka
2-Hydroxybenzaldehyde	122	99	BDH
Glacial acetic acid	60	99.9	GCC
Maleic anhydride	98	99	BDH
Phthalic anhydride	148	99	BDH
Benzene	78	99.9	GCC
Methanol	32	95	BDH
benzaldehyde	106	99	Merk
Ethyl acetate	88	99	BDH

Dimethyl sulfoxide	78	99	BDH
Diethyl ether	72	99	BDH
Chloroform	118	99	BDH
2,5- Dimethoxybenzaldehyde	166	99	Merk
2,4- Dimethylaniline	121	99	Merk
2,4- Dinitrophenylhydrazine	198	99	Merk
Aniline	93	99	BDH
Phenylhydrazine	108	99	BDH
Cyclohexyl amine	99	99	BDH
4- Bromoaniline	172	98	BDH
n- Hexane	86	99	Scharla, Spain
Iodine	254	99.5	GCC, Germany

2.2. Instrumentations

1. Thin layer chromatography (TLC) was performed on aluminum plates and coated with 0.25 mm layer of silica gel 60 F_{254}, compounds were detected by iodine vapor.
2. Melting points were recorded using status melting point apparatus, UK.

3. FT-IR spectra were recorded using Fourier transform infrared SHIMADZU FT-IR-8400S infrared spectrophotometer by KBr disc, University of Kerbala.

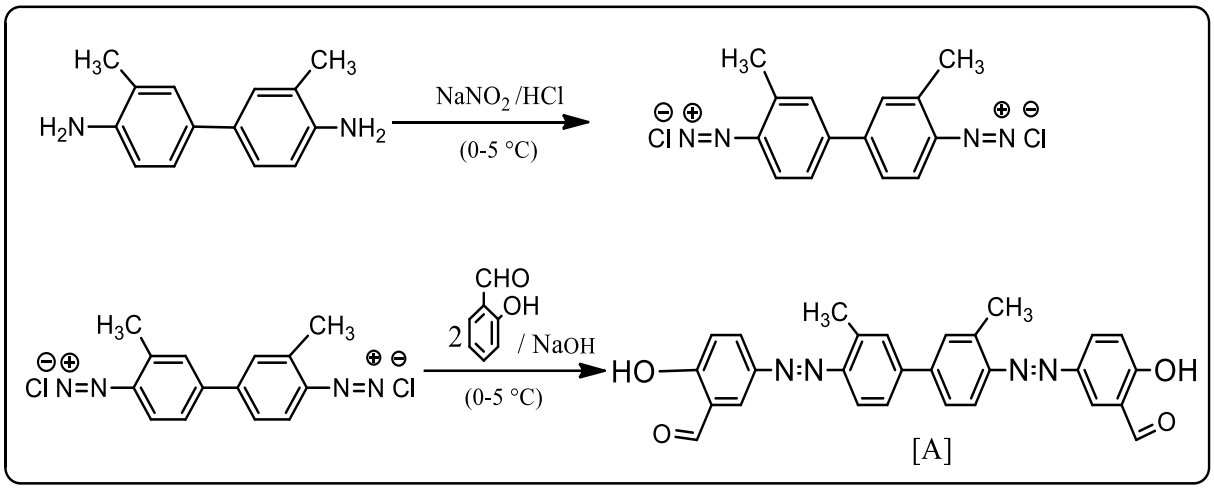
4. ^{1}H NMR spectra were recorded on Fourier transform Varian spectrometer , operating at 300 MH_Z with tetramethylsilane as internal standard and DMSO-d_6 as solvent , measurements were made at Metu Central Laboratory ,Orta DoGu Teknik Üniversitesi, Turkey.

5. The elemental analyses were recorded using E.A.G.E.R.-100, Carlo Erba, Italy, measurements were made at Metu Central Laboratory , Orta DoGu Teknik Üniversitesi , Turkey.
6. Autoclave was used to sterilize agar media, supplied from Prestige Medical-England

7. Incubator was used to maintain different temperature required for the growth of organism, supplied from Memert-Germany

2.3. Synthesis methods

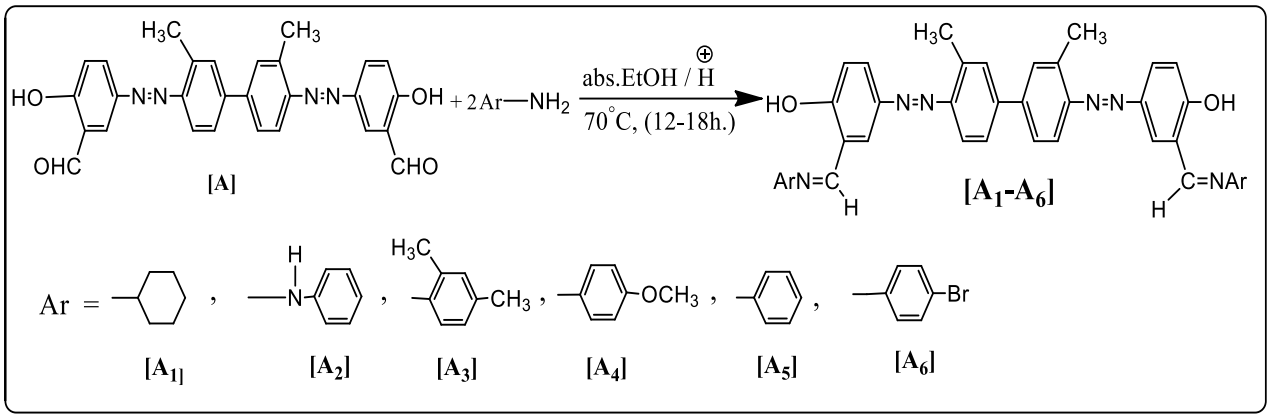
2.3.1. Synthesis of 5,5'-((3,3'-dimethyl-[1,1'-biphenyl]-4, 4'-diyl) bis (diazene-2,1diyl))bis(2-hydroxybenzaldehyde) [A]



Scheme (2-1) : Synthesis of bis-azoaldehyde derivative [A]

o-Toludine (2.12 g ,0.01mol) was dissolved in mixture of concentrated hydrochloric acid (6.4 mL) with distilled water (6.4 mL). The mixture was cooled at 0 ^{0}C in ice-water bath. Then a solution of sodium nitrite (1.6 g) dissolved in distilled water (8 mL) was prepared. This solution was added a dropwise to the mixture with stirring. In another beaker asoultin of 2- hydroxybenzaldehyde (2.6 g) dissolved in (20 mL) of (10 %w\v) sodium hydroxide solution was prepared and then coold in ice-water bath to (0-5^{0}C) and stirred vigorously. The cold diazonium chloride was added to the coupling agent in small portions and stirred after each addition, after the addition was completed, the reaction mixture was occasional stirred at 0^{0}C for 1hours. The orange product was precipitated ,filtered, washed well with distilled water and recrystallized from ethanol, yield (61 %), m.p. >300^{0}C and R_f = 0.72 (chloroform : benzene,1:1).

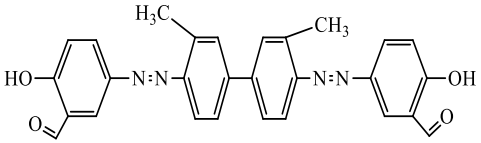
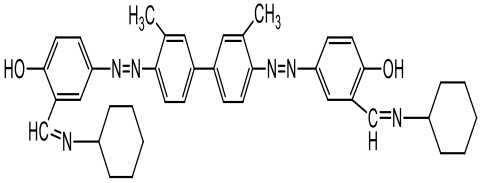
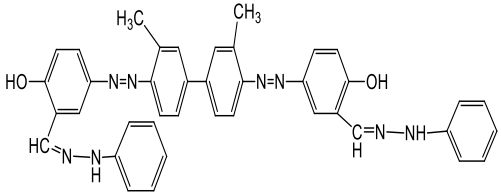
2.3.2. General procedure for Synthesis of bis-azoimine derivatives [A_1-A_6]

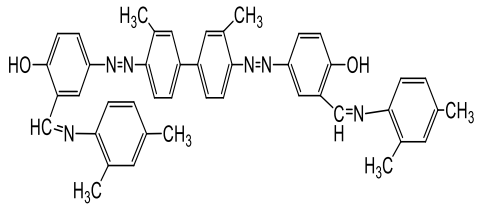
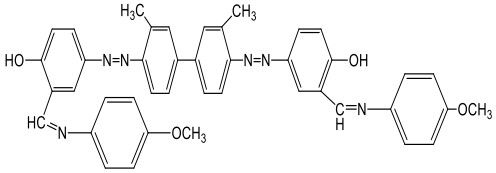
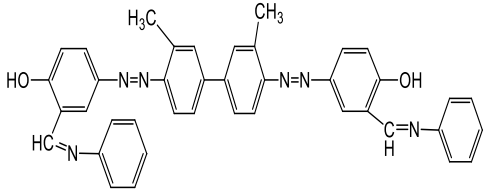
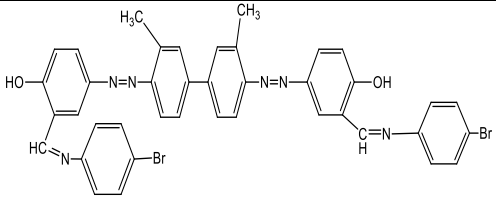


Scheme (2-2) : Synthesis of bis - azoimines [A_1-A_6]

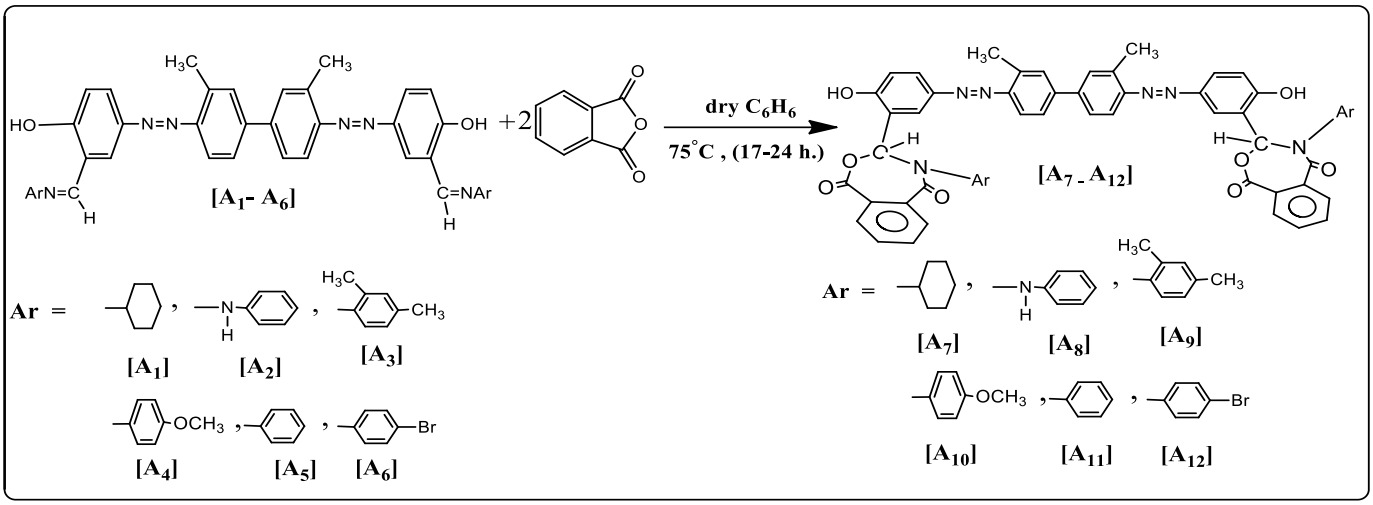
Bis-azoaldehyde derivative [A] (0.956g ,0.002 mol) was dissolved in absolute ethanol (20 mL) containing two drops of glacial acetic acid, then equimolar amount (0.004mol) of primary aromatic amines (cyclohexylamine, phenylhydrazine, 2,4-dimethylaniline, 4-methoxyaniline ,aniline and 4-bromoaniline) were added. The reaction mixture was refluxed with stirring on a water bath at 70^0C for (12-18 h.) . TLC (Et_2O:*n*-hexane , 2 : 1) showed that the reaction was completed. The mixture was allowed to cool to room temperature and the colored precipitate was filtered , then recrystallized from ethanol. Table (2-2) shows the structures , molecular formulas, molecular weights, melting points, yield% and R_f values of the synthesized compounds [A] and [A_1-A_6].

Table (2-2) : The physical properties of compounds [A] and [A_1-A_6]

Com. no.	Structural formula	Name	M.F.	M.Wt. g/mol	M.p. ^{0}C	Color	Yield %	R.T. (*h*.)	R_f
A		5,5'-((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis (diazene-2,1-diyl))bis(2-hydroxybenzaldehyde)	$C_{28}H_{20}N_4O_4$	478	>300 dec.	Pale orange	61	-	0.78 (cloroform:benzene) 1:1
A_1		2-((Z)-(cyclohexylimino) methyl)-4-((4'-((3-((cyclohexylimino)methyl)-4- hydroxyphenyl)diazenyl) -3,3'-dimethyl-[1,1'-bi phenyl]-4-yl)diazenyl) phenol	$C_{40}H_{44}N_6O_2$	640	150-152	red	91	12	0.85 (Et_2O: *n*-hexane) 2:1
A_2		4-((4'-((4-hydroxy-3-((2-phenylhydrazono) methyl) phenyl) diazenyl)-3,3'-di methyl-[1,1'-biphenyl] -4-yl)diazenyl)-2-((Z)-(2-phenylhydrazono)methyl) phenol	$C_{40}H_{34}N_8O_2$	658	240-242	red	83	16	0.79 (Et_2O:*n*-hexane) 2:1

A_3		2- (((2,4-dimethylphenyl) imino) methyl)-4-((4'-((3-((Z) -((2,4-dimethylphenyl) imino) methyl)-4-hydroxy phenyl)diazenyl)-3,3'-dime thyl-[1,1'-biphenyl]-4-yl) diazenyl)phenol	$C_{44}H_{40}N_6O_2$	684	248-250	orange	79	15	0.71 (Et_2O: *n*-hexane) 2:1
A_4		4-((4'-((4-hydroxy-3-(((4-methoxyphenyl)imino)methyl)phenyl)diazenyl)-3,3'-dimethyl-[1,1'-biphenyl] -4-yl)diazenyl)-2-((Z)-((4-methoxyphenyl)imino) methyl)phenol	$C_{42}H_{36}N_6O_4$	688	230-232	orange	87	13	0.85 (Et_2O: *n*-hexane) 2:1
A_5		4-((4'-((4-hydroxy-3-((Z)-(phenylimino)methyl)phenyl)diazenyl)-3,3'dimethyl[1,1'-biphenyl]-4-yl) diazenyl) -2-((phenyl imino)methyl) phenol	$C_{40}H_{32}N_6O_2$	628	170-172	dark orange	89	16	0.67 (Et_2O:*n*-hexane) 2:1
A_6		2-(((4-bromophenyl) imino)methyl)-4-((4'-((3-((Z)-((4-bromophenyl)imino)methyl)-4-hydroxy phenyl)diazenyl)-3,3'-dimethyl-[1,1'-biphenyl]-4-yl)diazenyl)phenol	$C_{40}H_{30}N_6O_2Br_2$	786	210-212	brown	79	18	0.65 (Et_2O:*n*-hexane) 2:1

2.3.3. General procedure for synthesis of bisazobis -1,3-oxazepine-4,7-dione derivatives [A_7-A_{12}]



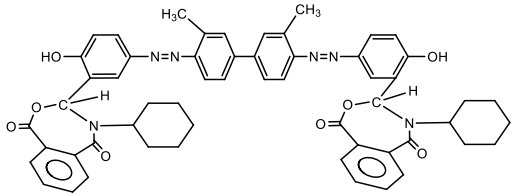
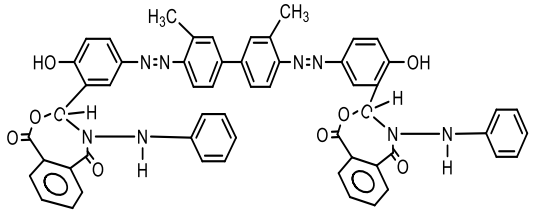
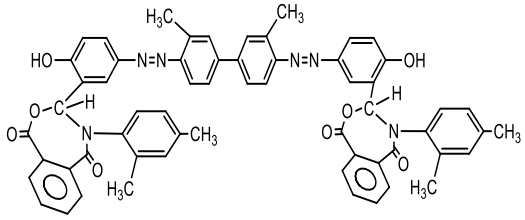
Scheme (2- 3) : Synthesis ofbisazobis-1,3 oxazepine- 4,7-dione derivatives [A_7-A_{12}]

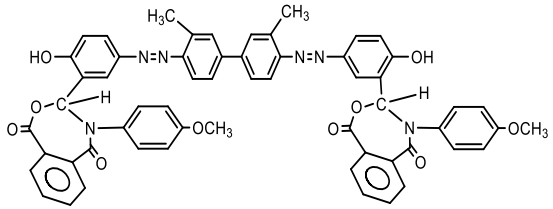
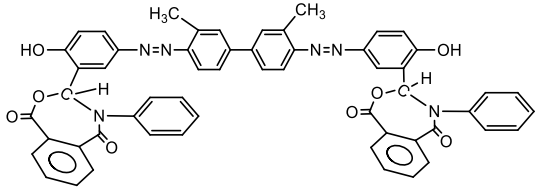
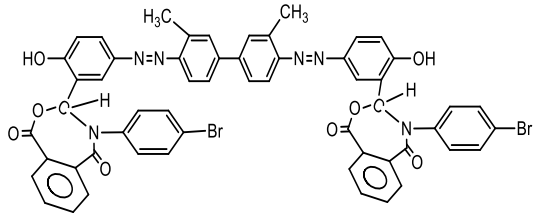
A mixture of equimolar amounts of bis-azoimines [A_1-A_6] (0.0006 mol) and phthalic anhydride (0.1776g, 0.0012mol) in dry benzene (20 mL) was refluxed with stirring on a water bath at 75^0C for (17-24 h.) . TLC (EtOAc : *n*-hexane , 2 : 1) showed that the reaction was completed . Then, the solvent was removed under reduced pressure and the resulting colored solid was washed well with ether and recrystallized from ethanol.

Table (2-3) shows the structures , molecular formulas , molecular weights , melting points, yield% and R_f values of the synthesized compounds [A_7-A_{12}].

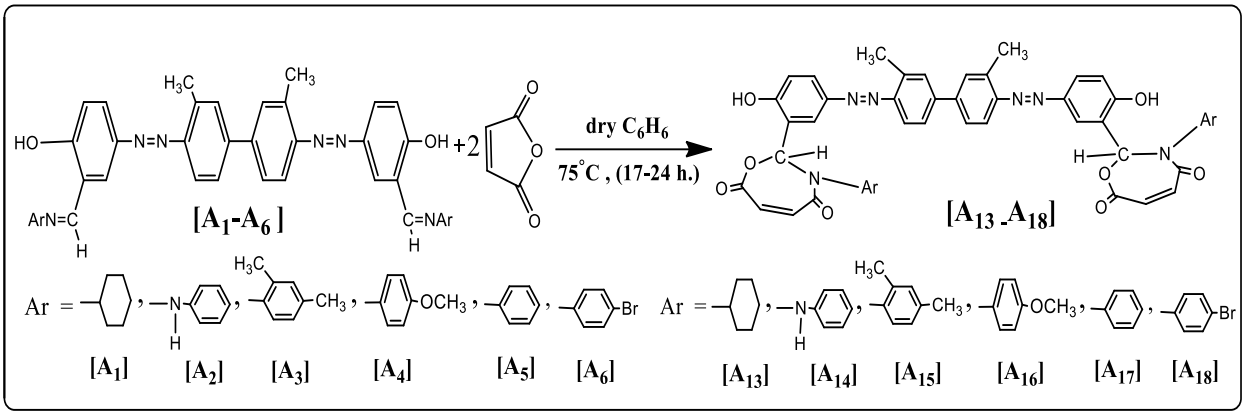
The (C.H.N.) elementary microanalysis data of the synthesized compounds [A_7-A_{12}] was lisited in table (2-5).

Table (2-3): The physical properties of compounds [A_7-A_{12}]

Com. no.	Structural formula	Name	M.F.	M.Wt. g/mol	M.P. ^{0}C	Color	Yield %	R.T. *(h)*.	R_f
A_7		3,3'-(((3,3'-dimethyl-[1,1'-bi phenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(4-cyclohexyl-3,4-dihydrobenzo[e][1,3] oxazepine-1,5(6H,9H)-dione)	$C_{56}H_{52}N_6O_8$	936	222-224	dark brown	68	17	0.69 (EtOAc:*n*-hexane) **3:1**
A_8		3-(5-((4'-((3-(1,5-dioxo-4-(phenylamino)-1,3,4,5,5a,6,9,9a -octahydrobenzo[e][1,3] oxazepine -3-yl)-4-hydroxy phenyl) diazenyl)-3,3'-dimethyl-[1,1'-biphenyl]-4-yl) diazenyl)-2-hydroxyphenyl)-4-(phenylamino)-3,4-dihydro benzo[e] [1 ,3]oxazepine-1,5 (6H,9H)-dione	$C_{56}H_{42}N_8O_8$	954	232-233	dark red	68	24	0.74 (EtOAc:*n*-hexane) **3:1**
A_9		3,3'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(4-(2,4-dimethyl phenyl)-3,4,5a,6,9,9a-hexa hydro benzo[e][1,3]oxazepine-1,5-dione)	$C_{60}H_{48}N_6O_8$	980	230-232	orange	63	23	0.54 (EtOAc:*n*-hexane) **3:1**

A_{10}		3,3'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(4-(4-methoxy phenyl)octahydrobenzo[e][1,3] oxazepine-1,5-dione)	$C_{58}H_{44}N_6O_{10}$	984	188-190	dark brown	68	24	0.71 (EtOAc:*n*-hexane) **3:1**
A_{11}		3-(5-((4'-((3-(1,5-dioxo-4-phenyl de cahydrobenzo[e][1,3] oxazepin-3-yl)-4-hydroxy Phenyl) diazenyl) -3,3'-di methyl -[1,1'-biphenyl]-4-yl) diazenyl)-2-hydroxyphenyl)-4-phenyl-3,4,5a,6 ,9,9a-hexahydrobenzo [e][1,3] oxazepine-1,5-dione	$C_{56}H_{40}N_6O_8$	924	221-222	orange	63	23	0.76 (EtOAc:*n*-hexane) **3:1**
A_{12}		4-(4-bromophenyl)-3-(5-((4'-((3-(4-(4- bromophenyl)-1,5-dioxo decahydrobenzo[e][1,3]oxazepin-3-yl)-4-hydroxy phenyl)di azenyl)-3,3'-di methyl -[1,1'-biphenyl]-4-yl)di azenyl)-2-hydroxy phenyl) -3,4,5a, 6,9,9a-hexahydrobenzo [e] [1,3] oxazepine-1,5-dione	$C_{56}H_{38}N_6O_8$ Br_2	1082	245-247	brown	73	22	0.78 (EtOAc:*n*-hexane) **3:1**

2.3.4.General procedure for synthesis of bisazobis -1,3-oxazepine-4,7-dione derivatives [A_{13} –A_{18}]



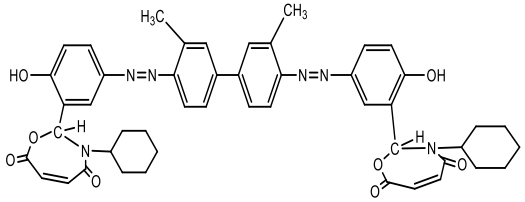
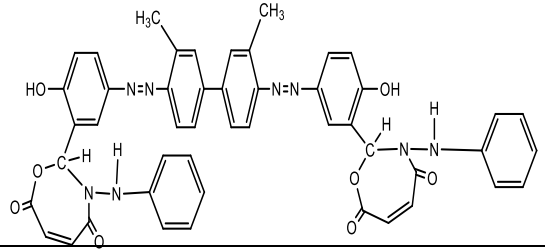
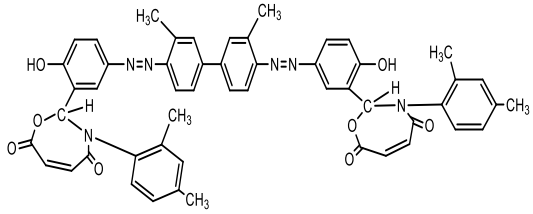
Scheme (2- 4) : Synthesis of bisazo bis- 1,3 oxazepine- 4,7-dione derivatives [A_{13}-A_{18}]

A mixture of equimolar amounts of bis- azoimines [A_1-A_6] (0.0006 mol) and maleic anhydride (0.1176g, 0.0012 mol) in dry benzene (20 mL) was refluxed with stirring on a water bath at 75°C for (17-24h.) . TLC (EtOAc :*n*- hexane , 2 : 1) showed that the reaction was completed . Then, the solvent was removed under reduced pressure and the resulting colored crystalline solid was washed well with ether and recrystallized from ethanol.

Table (2-4) shows the structures , molecular formulas , molecular weights , melting points, yield % and R_f values of the synthesized compounds [A_{13}-A_{18}].

Table (2-5) shows the (C.H.N.) elementary microanalysis data of the synthesized compounds [A_{13}-A_{18}].

Table (2-4) : The physical properties of compounds [A_{13}-A_{18}]

Com. no.	Structural formula	Name	M.F.	M.Wt .g/mol	M.P. ^{0}C	Color	Yield %	R.T. *(h.)*	R_f
A_{13}		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis (diazene-2,1-diyl)) bis (2-hydroxy-5,1-phenylene)) bis (3-cyclohexyl-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{48}H_{48}N_6O_8$	836	200-202	brown	74	17	0.81 (EtOAc:*n*-hexane) **3:1**
A_{14}		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis (diazene-2,1-diyl)) bis (2-hydroxy-5,1-phenylene)) bis(3-(phenylamino)-2,3-di hydro-1,3-oxazepine-4,7-dione)	$C_{48}H_{38}N_8O_8$	854	203-205	dark brown	59	24	0.63 (EtOAc:*n*-hexane) **3:1**
A_{15}		2,2'- (((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis (di azene-2,1-diyl)) bis(2-hydroxy -5,1-phenylene)) bis(3-(2,4-dimethylphenyl)-2 ,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{52}H_{44}N_6O_8$	880	176-177	orange	66	21	0.58 (EtOAc:*n*-hexane) **3:1**

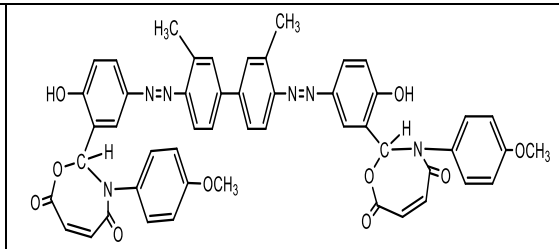
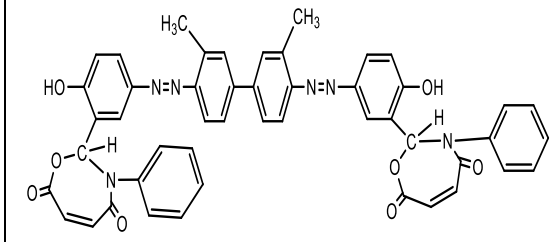
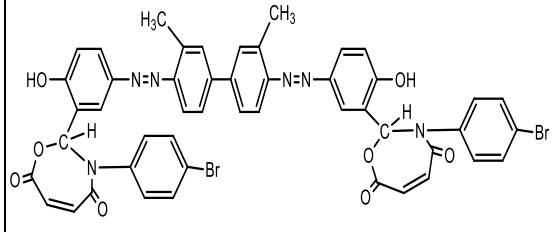
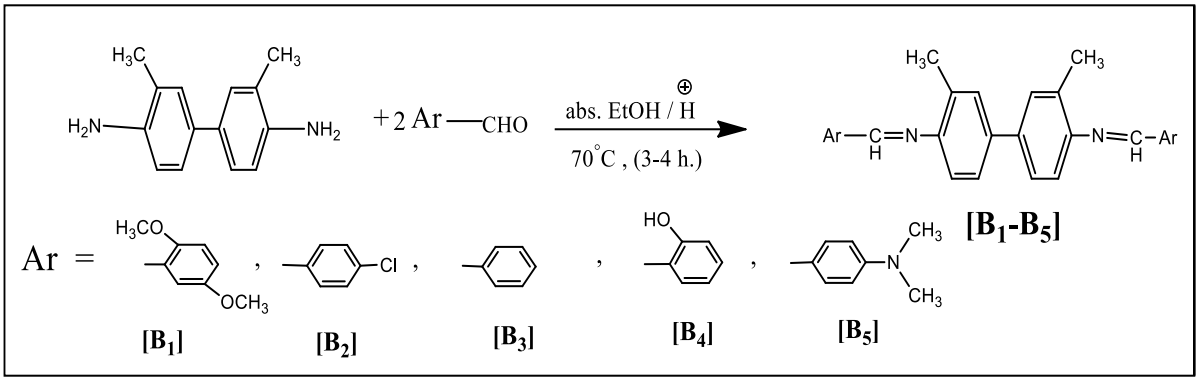
A_{16}		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(3-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{50}H_{40}N_6O_{10}$	884	185 -187	brown	63	20	0.77 (EtOAc:*n*-hexane) **3:1**
A_{17}		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(3-phenyl-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{48}H_{36}N_6O_8$	824	217-219	red	63	21	0.65 (EtOAc:*n*-hexane) **3:1**
A_{18}		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(diazene-2,1-diyl))bis(2-hydroxy-5,1-phenylene))bis(3-(4-bromophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{48}H_{34}N_6O_8\ Br_2$	982	235-237	red	61	22	0.68 (EtOAc:*n*-hexane) **3:1**

Table (2-5) : (C.H.N.) analysis data of bisazobis -1,3- oxazepine-4,7-dione derivatives [A_7 - A_{18}]

Com. no.	M.Wt. g/mol	Calculated / Found		
		C %	H %	N %
A_7	936	71.79 71.10	5.55 5.38	8.97 8.45
A_8	954	70.44 69.75	4.40 4.12	11.74 11.32
A_9	980	73.46 73.17	4.89 4.48	8.57 8.93
A_{10}	984	70.73 70.38	4.47 4.28	8.53 8.34
A_{11}	924	72.72 72.48	4.32 4.21	9.09 8.53
A_{12}	1082	62.10 61.55	3.51 2.86	7.76 6.09
A_{13}	836	68.89 68.23	5.74 5.14	10.04 10.24
A_{14}	854	67.44 67.15	4.44 4.03	13.11 12.92
A_{15}	880	70.90 70.50	5.00 5.05	9.54 9.10
A_{16}	884	67.87 67.24	4.52 4.16	9.50 9.22
A_{17}	824	69.90 69.33	4.36 4.19	10.19 9.91
A_{18}	982	58.65 58.05	3.46 3.62	8.55 8.28

2.3.5. General procedure for Synthesis of bis imine derivatives [B_1-B_5]

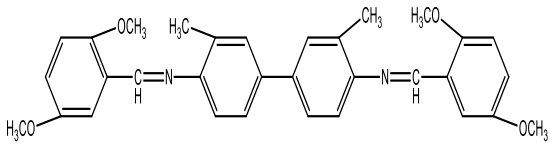
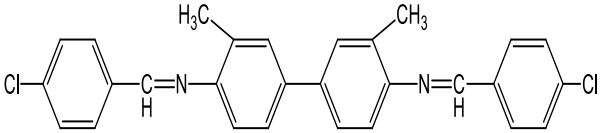
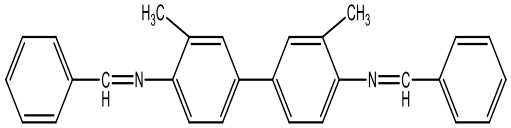
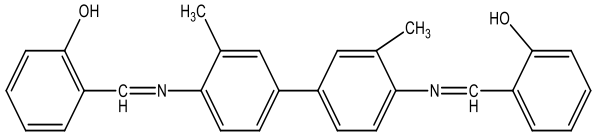
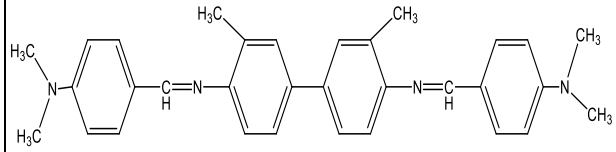


Scheme (2-5) : Synthesis of bisimines [B_1 - B_5]

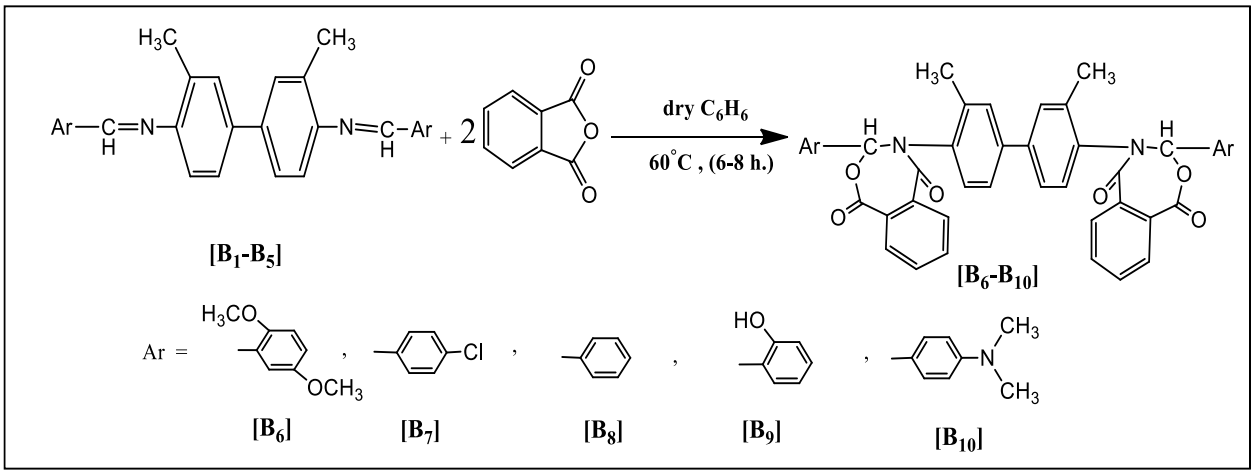
o-Toludine (1.06g ,0.005mol) was dissolved in absolute ethanol (20mL) containing two drops of glacial acetic acid, then equimolar amount (0.010mol) of aromatic aldehydes (2,5-dimethoxybenzaldehyde , 4-chlorobenzaldehyde , benzaldehyde, 2-hydroxybenzaldehyde and 4-*N*,*N*-dimethylaminobenzaldehyde) were added. The reaction mixture was refluxed with stirring on a water bath at 70°C for (3-4 h.) . TLC (Et_2O: *n*-hexane , 2 : 1) showed that the reaction was completed . The mixture was then allowed to cool down to room temperature and the colored precipitate was filtered , then recrystallized from ethanol.

Table (2-6) shows the structures , molecular formulas, molecular weights, melting points, yield % and R_f values of the synthesized compounds [B_1-B_5].

Table (2-6) : The physical properties of compounds [B_1-B_5]

Com. no.	Structural formula	Name	M.F.	M.Wt. g/mol	M.P.^{0}C	Color	Yield %	R.T. *(h.)*	R_f
B_1		N4,N4'-bis(2,5-dimethoxy benzylidene)-3,3'-di methyl -[1,1'-biphenyl]-4,4'-diamine	$C_{32}H_{32}N_2O_4$	508	188 -186	Pale green	92	3	0.73 (Et_2O: *n*-hexane) 2:1
B_2		N4,N4'-bis(4-chloro benzylidene)-3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine	$C_{28}H_{22}N_2Cl_2$	457	138-142	dark green	64	3.25	0.79 (Et_2O: *n*-hexane) 2:1
B_3		N4,N4'-dibenzylidene-3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine	$C_{28}H_{24}N_2$	388	161-163	Greenish yellow	86	3.5	0.81 (Et_2O: *n*-hexane) 2:1
B_4		2,2'-(((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis(azanylylidene)) bis(methanylylidene)) diphenol	$C_{28}H_{24}N_2O_2$	420	198-202	yellow	76	4	0.82 (Et_2O: *n*-hexane) 2:1
B_5		N4,N4'-bis(4-(dimethylamino)benzylidene)-3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diamine	$C_{32}H_{34}N_4$	474	260 (dec.)	red	83	4	0.76 (Et_2O: *n*-hexane) 2:1

2.3.6.General procedure for synthesis of bis-1,3-oxazepine-4,7-dione derivatives [B_6- B_{10}]



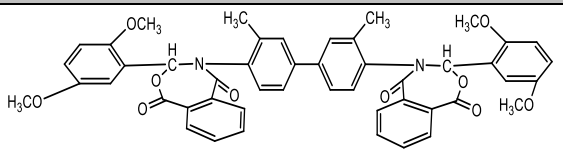
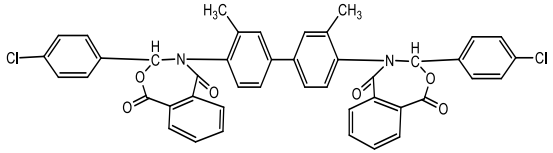
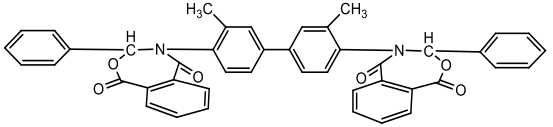
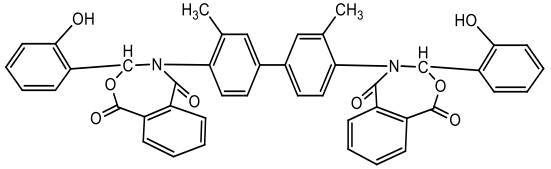
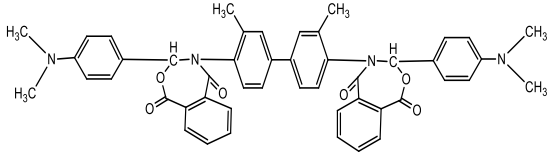
Scheme (2-6) : Synthesis of bis-1,3-oxazapine-4,7-dione derivatives [B_6-B_{10}]

A mixture of equimolar amounts of Schiff bases derivatives [B_1-B_5] (0.0006 mol) and phthalic anhydride (0.1776 g ,0.0012mol) in dry benzene (20 mL) was refluxed with stirring on a water bath at 60^0C for (6-8 h.) .TLC (EtOAc : *n*-hexane , 2 : 1) showed that the reaction was completed . Then, the solvent was removed under reduced pressure and the resulting colored crystalline solid was recrystallized from ethanol .

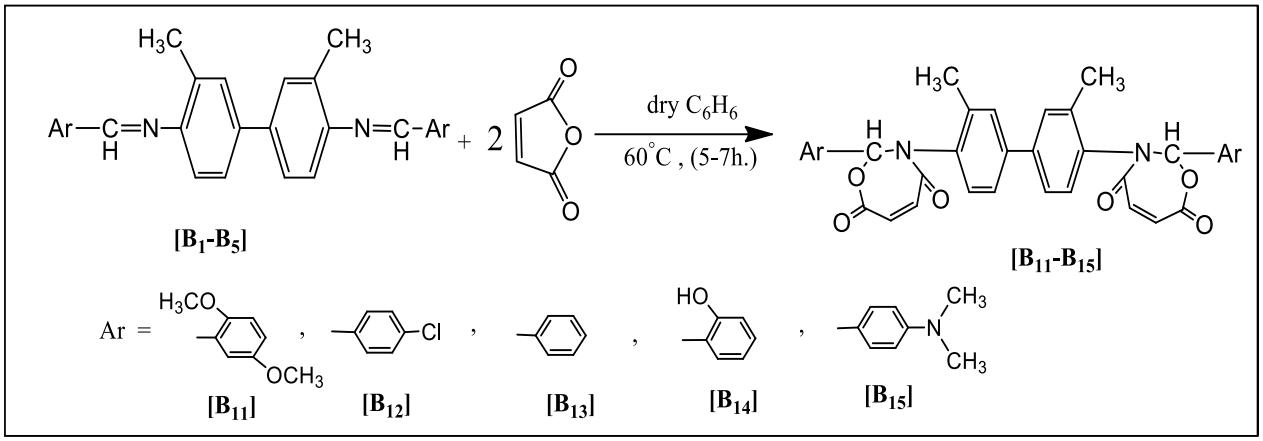
Table (2-7) shows the structures , molecular formulas , molecular weights , melting points, yield % and R_f values of the synthesized compounds [B_6-B_{10}].

The (C.H.N.) elementary microanalysis data of the synthesized compounds [B_6-B_{10}] was lisited in table (2-9)

Table (2-7) : The physical properties of compounds [B_6-B_{10}]

Com. no.	Structural formula	Name	M.F.	M.Wt. g/mol	M.P.^{0}C	Color	Yield %	R.T. *(h.)*	R_f
B_6		4,4'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(3-(2,5-dimethoxyphenyl)-3,4-dihydro benzo [e][1,3] oxazepine-1,5-dione)	$C_{48}H_{40}N_2O_{10}$	804	216-218	grew	73	6	0.86 (EtOAc:*n*-hexane) **2:1**
B_7		4,4'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(3-(4-chlorophenyl)-3,4-dihydro benzo [e][1,3]oxazepine-1,5-dione)	$C_{44}H_{30}N_2O_6Cl_2$	753	240-242	Pale yallow	68	6.25	0.61 (EtOAc:*n*-hexane) **2:1**
B_8		4,4'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(3-phenyl-3,4-dihydrobenzo[e] [1,3]oxazepine-1,5-dione)	$C_{44}H_{32}N_2O_6$	684	225-228	grew	71	7	0.76 (EtOAc:*n*-hexane) **2:1**
B_9		4,4'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(3-(2-hydroxyphenyl)-3,4-di hydrobenzo[e][1,3] oxazepine-1,5-dione)	$C_{44}H_{32}N_2O_8$	716	212-214	orange	59	7.5	0.83 (EtOAc:*n*-hexane) **2:1**
B_{10}		4,4'-(3,3'-dimethyl-[1,1'-bi phenyl]-4,4'-diyl)bis(3-(4-(di methylamino)phenyl)-3,4-di hydrobenzo[e][1,3] oxazepine-1,5-dione)	$C_{48}H_{42}N_4O_6$	770	238-240	red	78	8	0.59 (EtOAc:*n*-hexane) **2:1**

2.3.7.General procedure for Synthesis of bis -1,3-oxazepine-4,7-dione derivatives [B_{11}-B_{15}]



Scheme (2-7) : Synthesis of bis-1,3-oxazapine-4,7-dione derivatives [B_{11}-B_{15}]

Amixture of equimolar amounts (0.0006 mol) of Schiff bases derivatives [B_1-B_5] and maleic anhydride (, 0.1176g ,0.0012 mol) in dry benzene (20 mL) was refluxed with stirring on a water bath at 60°C for (5-7 h.) . TLC (ethyl acetate :*n* -hexane , 2 : 1) showed that the reaction was completed . Then, the solvent was removed under reduced pressure and the resulting colored crystalline solid was recrystallized from ethanol .

Table (2-8) shows the structures, molecular formulas, molecular weights, melting points, yield % and R_f values of the synthesized compounds [B_{11}-B_{15}].

Table (2-9) shows the (C.H.N.) elementary microanalysis data of the synthesized compounds [B_{11}-B_{15}].

Table (2-8) : The physical properties of compounds [B_{11}-B_{15}]

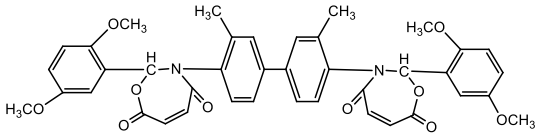
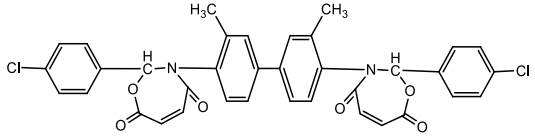
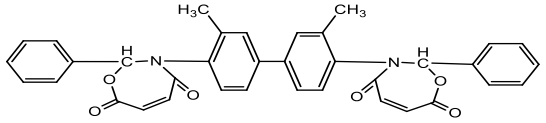
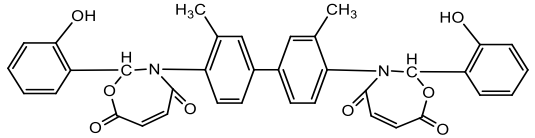
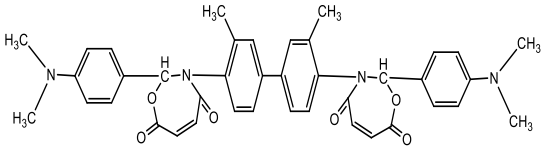
Com. no.	Structural formula	Name	M.F.	M.Wt. g/mol	M.P.^{0}C	Color	Yield %	R.T. *(h.)*	R_f
B_{11}		3,3'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis (2-(2,5-dimethoxyphenyl) -2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{40}H_{36}N_2O_{10}$	704	178 (dec.)	orange	78	5	0.63 (EtOAc:*n*-hexane) **2:1**
B_{12}		3,3'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(2-(4-chlorophenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{36}H_{26}N_2O_6Cl_2$	653	196 (dec.)	Pale yellow	82	6	0.69 (EtOAc:*n*-hexane) **2:1**
B_{13}		3,3'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(2-phenyl-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{36}H_{28}N_2O_6$	584	198 (dec.)	grew	73	6	0.71 (EtOAc:*n*-hexane) **2:1**
B_{14}		3,3'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(2-(2-hydroxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione)	$C_{36}H_{28}N_2O_8$	616	195 (dec.)	grew	61	6.5	0.66 (EtOAc:*n*-hexane) **2:1**
B_{15}		3,3'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis (2(4-(dimethylamino) phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione	$C_{40}H_{38}N_4O_6$	670	162-164	red	87	7	0.76 (EtOAc:*n*-hexane) **2:1**

Table (2-9) : (C.H.N.) analysis data of bis -1,3- oxazepine-4,7- dione derivatives [B_6-B_{15}]

Com.	M.Wt.	Calculated /Found		
		C %	H %	N %
B_6	804	71.64 71.09	4.97 5.04	3.48 3.42
B_7	753	70.11 70.74	3.98 4.85	3.71 3.96
B_8	684	77.19 77.68	4.67 4.34	4.09 4.23
B_9	716	73.74 73.49	4.46 4.48	3.91 3.77
B_{10}	770	74.80 74.55	5.45 5.56	7.27 7.09
B_{11}	704	68.18 68.45	5.11 5.43	3.97 4.88
B_{12}	653	66.15 66.23	3.98 4.38	4.28 4.41
B_{13}	584	73.97 73.75	4.79 4.42	4.79 4.52
B_{14}	616	70.12 69.24	4.54 4.13	4.54 4.28
B_{15}	670	71.64 70.65	5.67 5.62	8.35 8.31

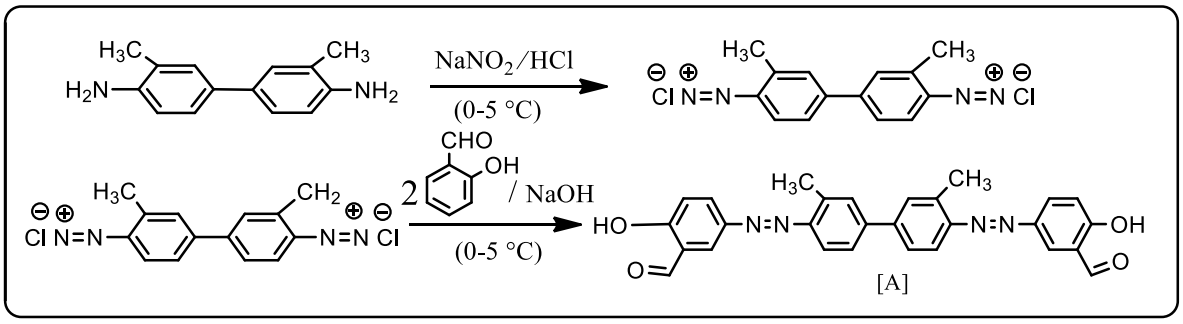
Chapter Three

Results and Discussion

3- Results and Discussion

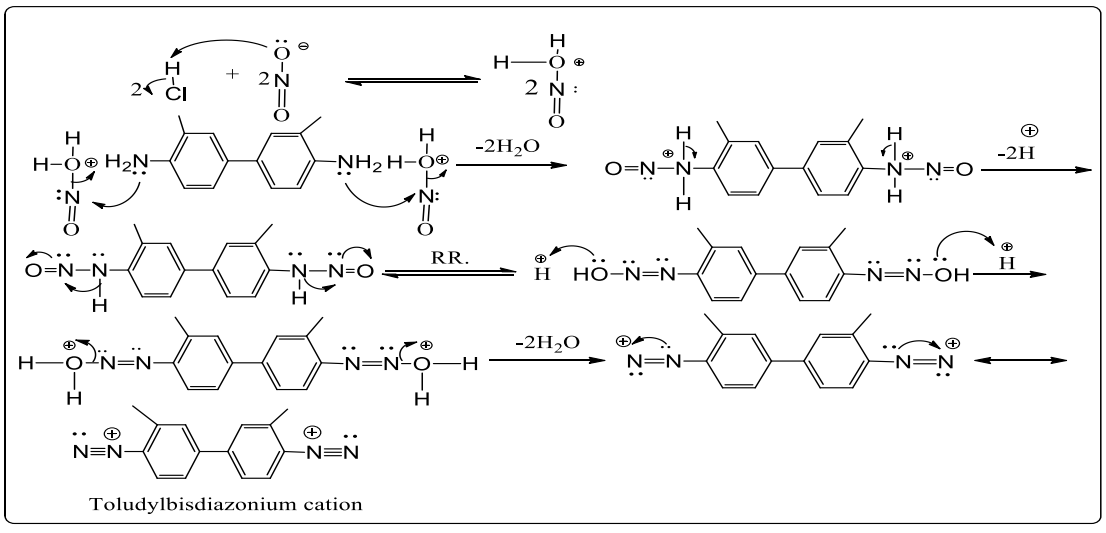
3.1. Synthesis of 5,5'-((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl) bis(diazene-2,1diyl))bis (2-hydroxybenzaldehyde) [A]

A coupling reaction between the bis diazonium salt of *o*- toludine and equimolar quantity of phenoxide salt of 2-hydroxybenzaldehyde as coupling reagent at (0-5)°C afforded bis-azoaldehyde derivative[92] [A] as indicated in scheme (3-1).

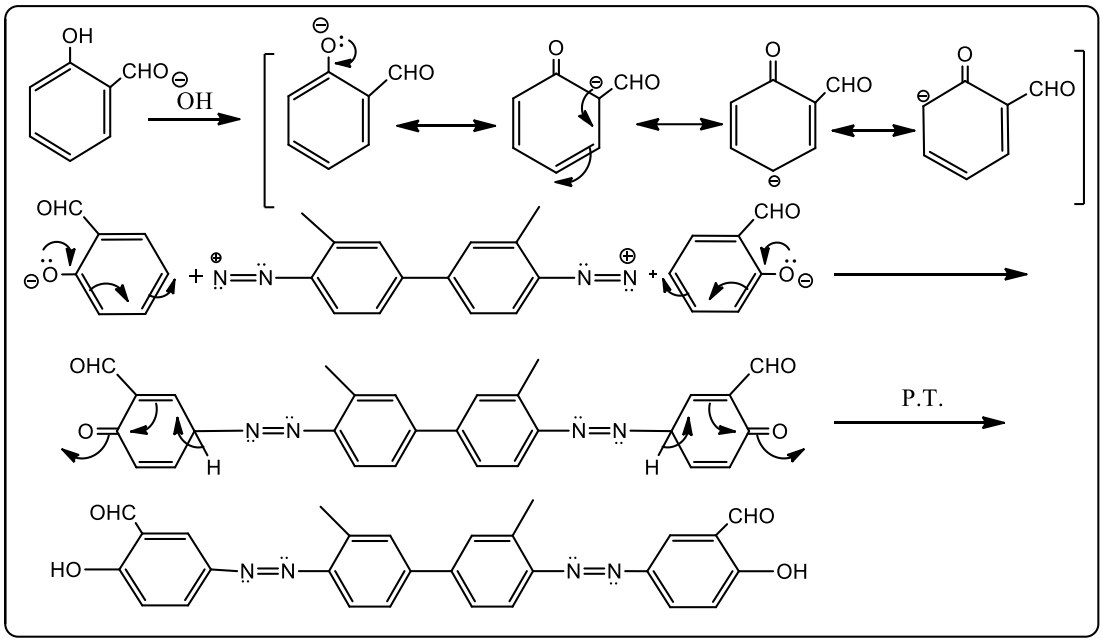


Scheme (3-1) : Synthesis of bis-azoaldehyde derivative [A]

The coupling reaction is an electrophilic substitution in aromatic systems which proceeds according to the proposed mechanism[93] shown in schemes (3-2 and 3-2a).



Scheme (3-2): Mecansim of formation of *o* - tolidylbisdiazonium cation

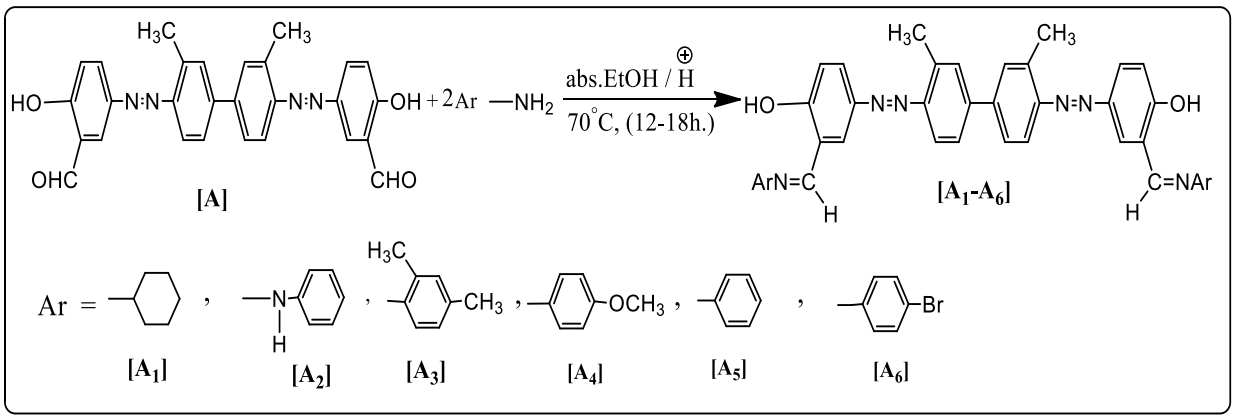


Scheme(3-2a): Mechanism of coupling reaction

The FT-IR spectra, figure (3-2) of bis-azoaldehyde derivative [A] showed disappearance of the sharp bands at (3468,3410) cm^{-1} and (3373,3338) cm^{-1} attributed to the asymmetric and symmetric stretching vibrations of amino groups ($-NH_2$) in *o*-toludine, the spectrum also showed disappearance of the sharp and strong band at 1624 cm^{-1} due to the scissoring bending vibration of ($-NH_2$) groups and appearance of sharp and strong band at 1653cm^{-1}assigned to the stretching vibration of carbonyl groups[(94)](C=O) ,this band was shifted towards lower frequency due to intramolecular hydrogen bonding with ***ortho***-hydroxy group[(95)], the spectrum also appeared broad band at 3416cm^{-1} attributed to the stretching vibration of hydroxy group. Other bands with their interpretation were summarized in table (3-1).

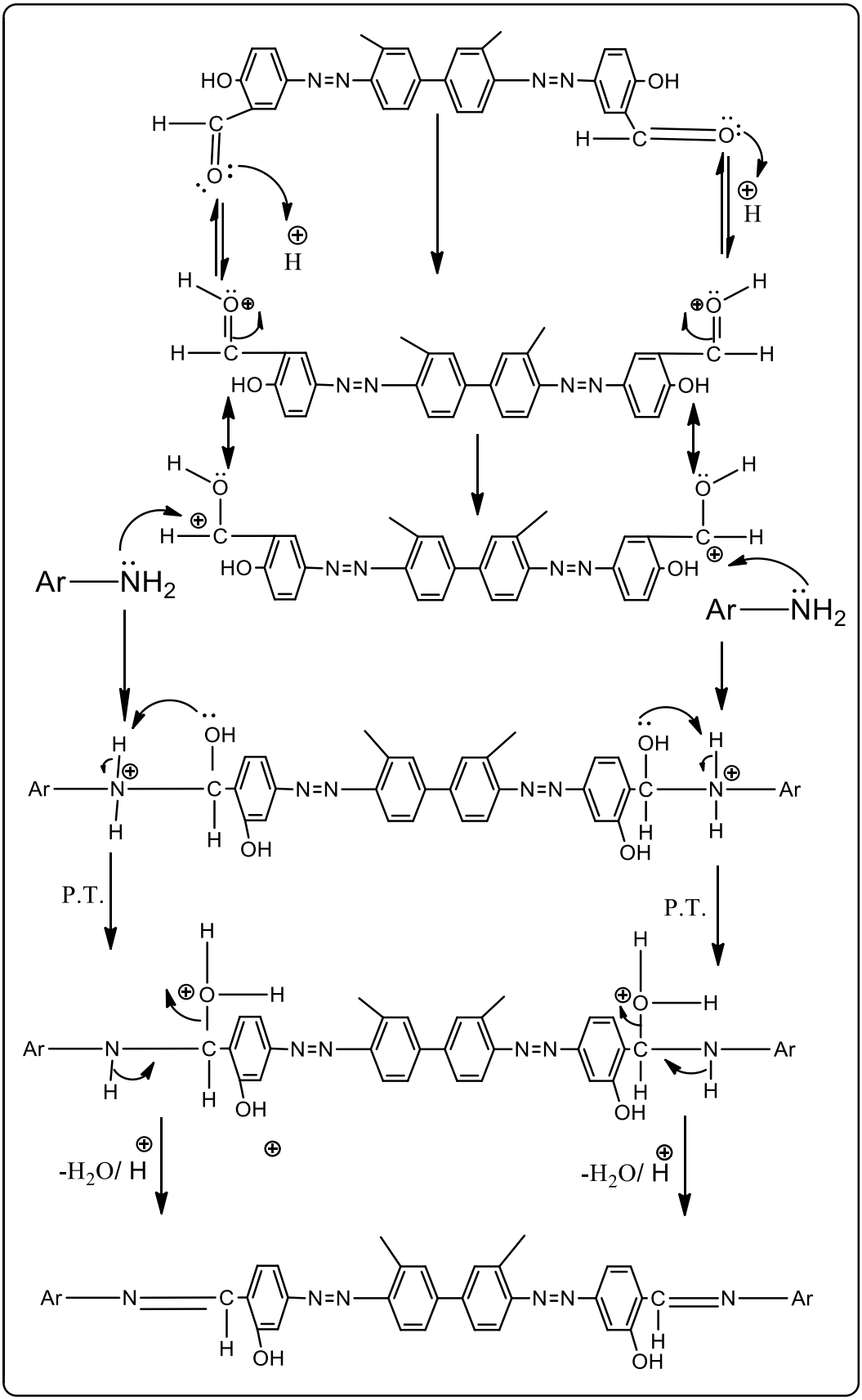
3.2. Synthesis of bis-azoimine derivatives [A_1-A_6]

A condensation reactions between bis-azoaldehyde derivative [A] and some selective primary amines and a hydrazine (cyclohexyl amine, phenylhydrazine, 2,4-dimethylaniline, 4-methoxyaniline, aniline and 4-bromoaniline) respectively in the presence of two drops of glacial acetic acid as catalyst in absolute ethanol resulted formation of bis-azoimines [A_1-A_6] as shown in scheme (3-3).



Scheme (3-3) : Synthesis of bis – azoimine derivatives [A_1-A_6]

The condensation reaction [96] proceeds via elimination of two H_2O molecules as shown in the following proposed mechanism .Scheme (3-4).



Scheme (3-4) : Mechanism of formation of bis-azoimines [A_1-A_6]

FT-IR spectrum, figures (3-3) - (3-8) at **υ** (cm^{-1}) (KBr) of all synthesized bis-azoimines compounds [A_1-A_6] illustrate good evidence that the reactions happened successfully by disappearing the strong band at 1653cm^{-1} belong to the stretching vibration of (C=O) group and appearing strong band at lower frequencies at the general range (1629-1600) cm^{-1}attributed to the stretching vibration of imine groups[97](C=N). Other characteristic bands with their interpretation were summarized in table (3-1).

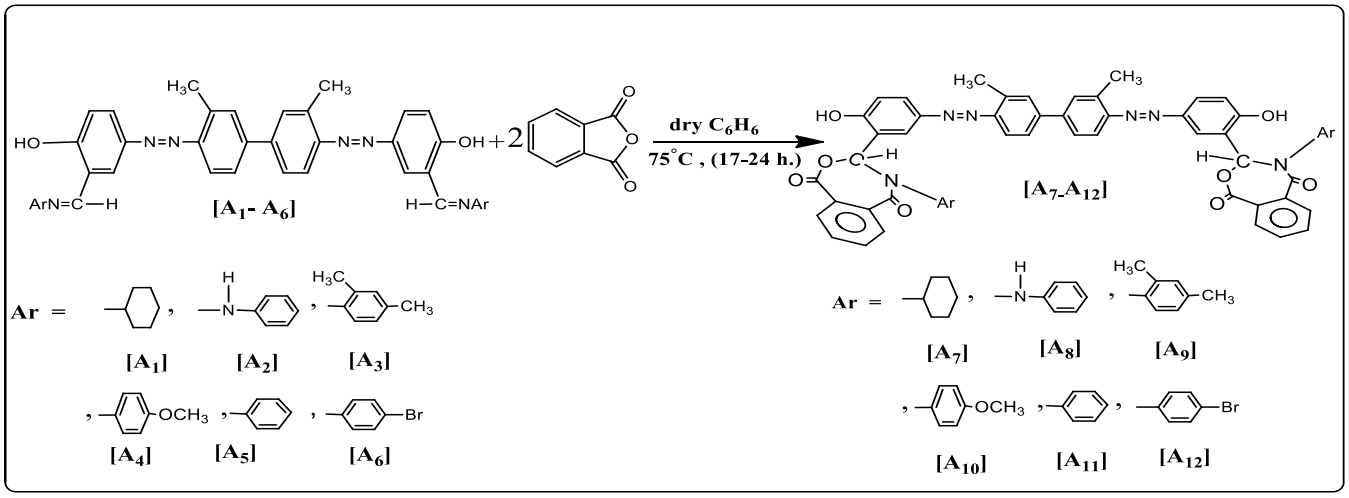
Table (3-1) : FT-IR data of the synthesized bis - azoimine derivatives [A_1-A_6] in cm^{-1}

Com. no.	FT-IR bands
[A]	3416 and 3251 (υ_{O-H}), 3045 ($\upsilon_{C-H,benzene\ rings}$), 2922 ($\upsilon_{as.C-Hm,CH_3}$), 2835 ($\upsilon_{s.C-H,CH_3}$),2758($\upsilon_{C-H,aldehyde}$),1653 ($\upsilon_{C=O}$),1602, 1518 and 1471($\upsilon_{C=C,benzene\ rings}$),1461($\delta_{as.C-H,\ CH_3}$),1375($\delta_{s.C-H,\ CH_3}$),1329 and1278 ($\upsilon_{C-N}$),1103($\upsilon_{C-O,phenol}$),895,837,756 and 698($\delta_{o.o.p\ C-H,\ benzene\ rings}$).
A_1	3444 (υ_{O-H}),3036 ($\upsilon_{C-H,\ benzene\ rings}$),2928 ($\upsilon_{as.C-H,CH_2,cyclohexane}$), 2854 ($\upsilon_{s.C-H,CH_2,cyclohexane}$),1629 ($\upsilon_{C=N}$), 1598 and 1489($\upsilon_{C=C\ ,benzene\ rings}$),1448 ($\delta_{sciss.C-H,CH_2,\ cyclohexane}$),1379 ($\delta_{s.C-H,\ CH_3}$),1346 and 1284 ($\upsilon_{C-N}$),1103($\upsilon_{C-O,phenol}$), 889 ,833,749 and 692($\delta_{\ o.o.p\ C-H,\ benzene\ rings}$).
A_2	3423 (υ_{O-H}) ,3307(υ_{N-H}) ,3034 and 3001 ($\upsilon_{C-H,\ benzene\ rings}$),2943 ($\upsilon_{as.C-H,CH_3}$), 2899 ($\upsilon_{s.C-H,CH_3}$), 1600 ($\upsilon_{C=N}$),1572 and1489 ($\upsilon_{C=C,benzene\ rings}$),1442($\delta_{s.C-H,CH_3}$),1398($\delta_{s.C-H,CH_3}$),1348 and 1288 (υ_{C-N}),1105($\upsilon_{C-O,phenol}$),852,827,786,746 and 690($\delta_{o.o.p\ C-H,benzene\ rings}$).

A_3	3435(υ_{O-H}),3037 and 3010 ($\upsilon_{C-H,benzene\ rings}$),2970 ($\upsilon_{as.C-H,CH_3}$), 2872 ($\upsilon_{s.C-H,CH_3}$) ,2812 ($\upsilon_{C-H,imine}$) ,1612 ($\upsilon_{C=N}$),1582and1487($\upsilon_{C=C,\ benzene\ rings}$),1442 ($\delta_{as.C-H,\ CH_3}$),1396 ($\delta_{s.C-H,CH_3}$), 1350, 1282 ($\upsilon_{C-N}$), 1105($\upsilon_{C-O,phenol}$),896 ,835 ,823 ,717 and 671($\delta_{o.o.p.\ C-H\ ,benzene\ rings}$).
A_4	3433 (υ_{O-H}), 3041 and 3001($\upsilon_{C-H,benzene\ rings}$), 2943 ($\upsilon_{as.C-H,CH_3}$),2899 ($\upsilon_{s.C-H,CH_3}$) ,2833 ($\upsilon_{C-H,imine}$) , 1618 ($\upsilon_{C=N}$), 1599,1506 and 1485 ($\upsilon_{C=C,benzene\ rings}$),1442 ($\delta_{as.C-H,\ CH3}$),1398($\delta_{s.C-H,CH_3}$) 1348 and 1288 (υ_{C-N}),1105 ($\upsilon_{C-O,phenol}$),1031 ($\upsilon_{s.C-O-C,ether}$) 902, 877, 835, 788,756and717($\delta_{o.o.p\ C-H\ ,benzene\ rings}$).
A_5	3431(υ_{O-H}), 3034 ($\upsilon_{C-H,\ benzene\ rings}$), 2920 ($\upsilon_{as.C-H,CH_3}$),2848 ($\upsilon_{s.C-H,CH_3}$) ,1618 ($\upsilon_{C=N}$), 1593, 1572 and 1485 ($\upsilon_{C=C,benzene\ rings}$),1456 ($\upsilon_{as.C-H,\ CH_3}$),1438 ($\upsilon_{N=N}$),1398 ($\upsilon_{s.C-H,\ CH_3}$),1350 and 1282 ($\upsilon_{C-N}$), 1103 ($\upsilon_{C-O,phenol}$),895 ,871 ,821, 783, 758 and 690 ($\delta_{o.o.p.C-H\ ,benzene\ rings}$).
A_6	3433 (υ_{O-H}),3041 ($\upsilon_{C-H,benzene\ rings}$), 2953 ($\upsilon_{as.C-H,CH_3}$), 2922 ($\upsilon_{s.C-H,CH_3}$),1616 ($\upsilon_{C=N}$), 1587, 1572 and 1483 ($\upsilon_{C=C,benzene\ rings}$), 1458 ($\delta_{as.C-H,\ CH_3}$),1435 ($\upsilon_{N=N}$),1394 ($\delta_{s.C-H,\ CH_3}$),1350 and 1282 ($\upsilon_{C-N}$) ,1103 ($\upsilon_{C-O,phenol}$),1072 (υ_{C-Br}), 889, 875, 825, 777, 740 and 694 ($\delta_{o.o.p.C-H\ ,benzene\ rings}$).

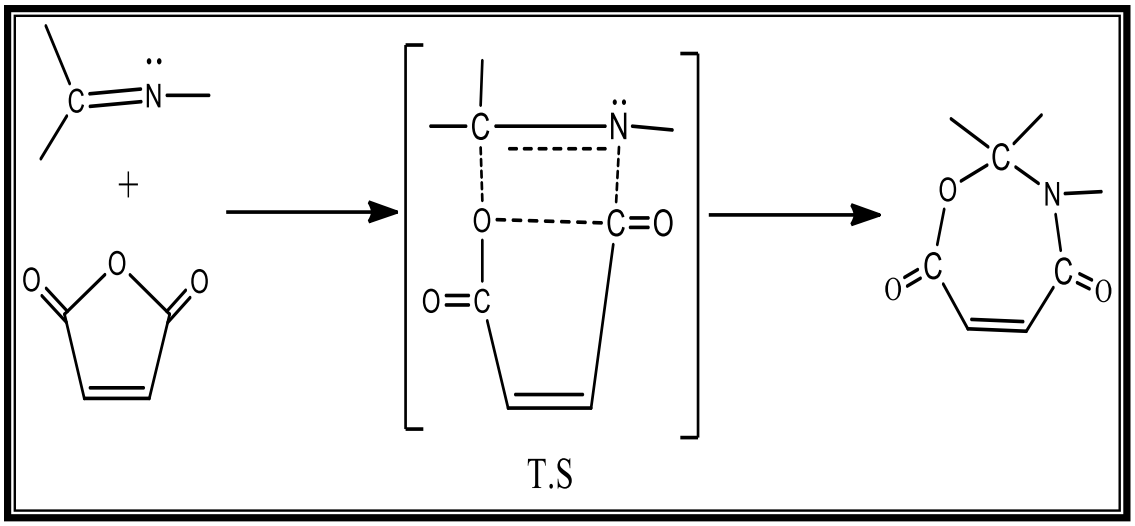
3.3.Synthesis of bisazobis -1,3-oxazepine-4,7-dione derivatives [A_7-A_{12}]

This series of bis-1,3-oxazepine derivatives was obtained via a (5+2 ⟶ 7) cycloaddition reaction between equimolar amount of phathalic anhydride as five-membered component and the synthesized bis-azoimines [A_1-A_6] as two-membered components[98] in dry benzene as indicated in scheme (3-5).



Scheme (3- 5) : Synthesis of bisazo bis -1,3 oxazepine- 4,7-dione derivatives [A_7-A_{12}]

This type of cycloaddition reactions involves addition of five atom from the first compnent (Maleic anhydride) to two atoms from the second compnent (imine group) to form a seven-membered 1,3-oxazepine ring.The cycloaddition is believed to proceed via formation of four-membered cyclic transition state (i.e.concerted process)[99] in which the participating orbitals should be in the same plane[100] as indicated in scheme (3-6).



Scheme (3-6) : Approximate transition state geometryfor addition of Maleic anhydride to imine groups

The (C.H.N.) elementery microanalysis, table (2-5) of bisazo bis -1,3 oxazepines [A_7-A_{12}] showed good agreement between the calculated and found values.

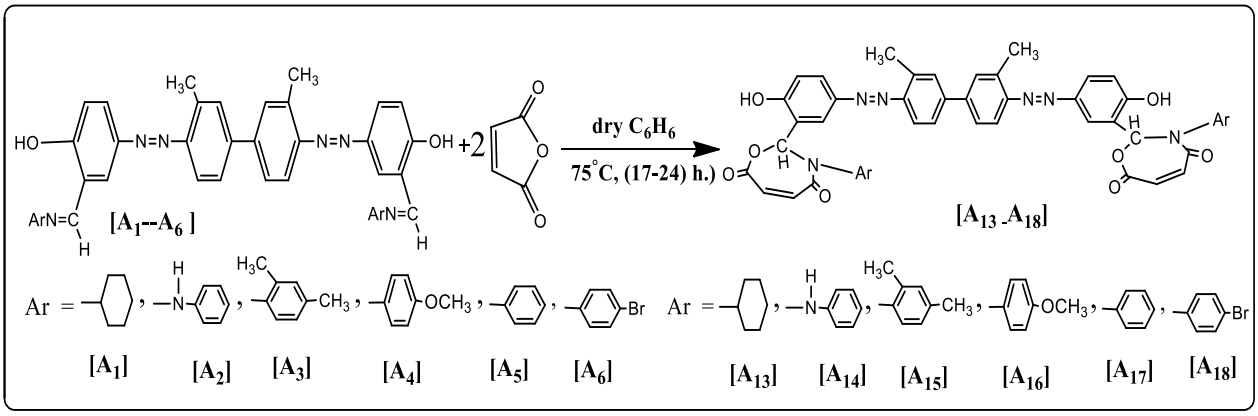
The FT-IR spectrum, figures (3-9) - (3-14) of compounds [A_7-A_{12}] illustrate good evidence that the cycloaddition reactions happened successfully through disappearing the strong band at the general range (1629-1600) cm^{-1} which attributed to υ (C=N) and appearing of one or two bands at frequency relatively higher than that of (C=N) group at (1714 and 1656) cm^{-1},1693cm^{-1},1689cm^{-1},1691cm^{-1},(1707and1680) cm^{-1} ,(1716 and 1649) $cm^{-1}$and (1716and1656) respectively attributed to the stretching vibrations of carbonyl groups (O=C-O) and (O=C-N) inside oxazepine ring respectively.It is important to refer that appearance only one band for (C=O) groups insideoxazepine ring due to the vibration coupling interactions. Other caracteristic bands with their interpretation were summarized in table (3-2).

Table (3-2): FT-IR data of the synthesized bisazo bis -1,3-oxazepine-4,7-dione derivatives [A_7-A_{12}]

Com. no.	FT-IR bands
A_7	3363 (υ_{O-H}), 3051 ($\upsilon_{C-H,benzene\ rings}$),2928 ($\upsilon_{as.C-H,CH_2,cyclohexane}$) ,2854 ($\upsilon_{s.C-H,CH_2,cyclohexane}$), 1714 ($\upsilon_{C=O,O=C-O,oxazepine}$), 1656 ($\upsilon_{C=O,\ O=C-N\ ,oxazepine}$),1597 and 1481($\upsilon_{C=C,benzene\ rings}$), 1452 ($\delta_{sciss.C-H,CH_2\ cyclohexane}$), 1371($\delta_{s.C-H,CH_3}$), 1278 ($\upsilon_{C-N}$), 1103 ($\upsilon_{C-O,phenol}$),891, 831,759 and 702 ($\delta_{o.o.p.C-H,benzene\ rings}$).
A_8	3497 (υ_{O-H}), 3288 (υ_{N-H}), 3034 ($\upsilon_{C-H,benzene\ rings}$), 2953 ($\upsilon_{as.C-H,CH3}$) ,2874 ($\upsilon_{s.C-H,CH_3}$), 1693 ($\upsilon_{C=O,O=C-OandO=C-N,oxazepine,\ vib.coupling}$), 1597,1572 and 1487 ($\upsilon_{C=C,benzene\ rings}$), 1396 ($\delta_{s.C-H,\ CH_3}$), 1274 ($\upsilon_{C-N}$), 1115 ($\upsilon_{.C-O,phenol}$), 806,748,694 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
A_9	3406(υ_{O-H}), 3080and 3012($\upsilon_{C-H,\ benzene\ rings}$),2974($\upsilon_{as.\ C-H,CH_3}$) ,2897 ($\upsilon_{\ s.C-H,CH_3}$), 2816($\upsilon_{C-H,oxazepine}$), 1691 ($\upsilon_{C=O,O=C-O\ and\ O=C-N\ ,oxazepine,vib.coupling}$), 1587 and 1404 ($\upsilon_{C=C,benzene\ rings}$),1494($\upsilon_{as.NO_2}$), 1280 (υ_{C-N}),1070 ($\upsilon_{C-O,phenol}$),908,829,800,740 and 673($\delta_{o.o.p.C-H,\ benzene\ rings}$).
A_{10}	3427(υ_{O-H}), 3101and 3014($\upsilon_{C-H,\ benzene\ rings}$),2923 ($\upsilon_{as.\ C-H,CH_3}$) ,2870($\upsilon_{s.C-H,CH_3}$), 1707 ($\upsilon_{C=O,O=C-O\ ,oxazepine}$), 1680($\upsilon_{C=O,O=C-N\ ,oxazepine}$),1514($\upsilon_{C=C,benzene\ rings}$),1394($\delta_{s.C-H,CH_3}$), 1284and1255($\upsilon_{C-N}$),1072($\upsilon_{C-O,phenol}$),1030($\upsilon_{s.C-O-C,ether}$) 902, 827,787 ,759 and 702 ($\delta_{o.o.p.C-H,benzene\ rings}$).
A_{11}	3319 (υ_{O-H}),3130 and 3055 ($\upsilon_{C-H,\ benzene\ rings}$),2985 and 2923($\upsilon_{as.\ C-H,CH_3}$) ,2875($\upsilon_{\ s.C-H,CH_3}$),1716 ($\upsilon_{C=O,O=C-O,oxazepine}$),1649 ($\upsilon_{C=O,\ O=C-N,oxazepine}$), 1602,1543,1506,1491 and 1454($\upsilon_{C=C,benzenerings}$), 1440 ($\delta_{as.C-H,\ CH_3}$) , 1394($\delta_{s.C-H,\ CH_3}$), 1330 and 1242 ($\upsilon_{C-N}$), 1087 ($\upsilon_{.C-O\ ,phenol}$) ,891,827,750 and 690 ($\delta_{o.o.p.C-H,benzenerings}$).
A_{12}	3315(υ_{O-H}), 3055 ($\upsilon_{C-H,benzene\ rings}$), 2924 ($\upsilon_{as.C-H,CH_3}$),2860 ($\upsilon_{s.\ C-H\ ,CH_3}$), 1716($\upsilon_{C=O,O=C-O,oxazepine}$),1656($\upsilon_{C=O,\ O=C-N\ ,oxazepine}$), 1610,1548 and 1485 ($\upsilon_{C=C}$),1386 ($\delta_{s.C-H,\ CH_3}$) 1282 and 1247 ($\upsilon_{C-N}$),1111($\upsilon_{C-O,phenol}$), 1074 ($\upsilon_{C-Br}$),885, 819, 796, 763, 732 and 698 ($\delta_{o.o.p.C-H,benzene\ rings}$).

3.4. Synthesis of bisazobis -1,3-oxazepine-4,7-dione derivatives [A_{13}-A_{18}]

The synthesized bisimines [A_1-A_6] were also introduced in (5+2 ⟶ 7) cycloaddition reaction with maleic anhydride as five-membered component to obtain a second series of bis-1,2-disubstituted-1,3-oxazepine-4,7-dione derivatives [A_{13}-A_{18}] as indicated in scheme (3-7).



Scheme (3-7) : Synthesis of bisazo bis- 1,3 oxazepine- 4,7-dione derivatives [A_{13}-A_{18}]

The (C.H.N.) elementery microanalysis table (2-5) of bisazo bis -1,3 oxazepines [A_{13}-A_{18}] showed good agreement between the calculated and found values.

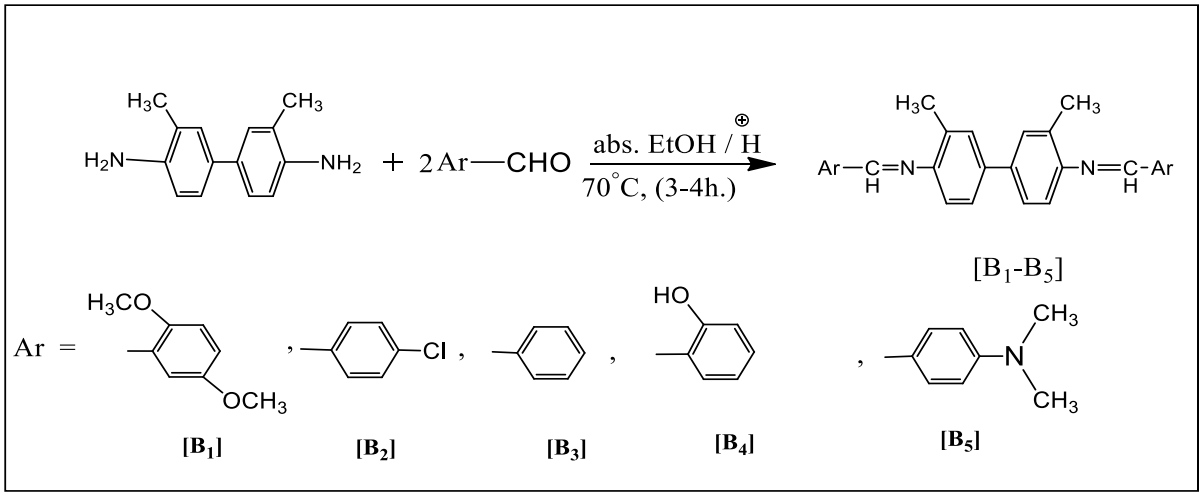
The FT-IR spectrum, figures (3-15) - (3-20) of compounds [A_{13}-A_{18}] provide good evidence that cycloaddition reactions took place successfully through disappearing the strong band at the general range (1629-1600) cm^{-1} which assigned to υ (C=N) and appearing one or two bands at frequency relatively higher than that of (C=N) group at (1703 and 1656) cm^{-1},1691cm^{-1},(1716 and 1641) cm^{-1},1701cm^{-1}, 1699cm^{-1} and 1705 cm^{-1} respectively attributed to the stretching vibrations of carbonyl groups (O=C-O) and (O=C-N) inside oxazepine ring respectively.It is important to refer that appearance only oneband for (C=O) groups inside oxazepine with their interpretation were lisited in table (3-3).

Table (3-3) : FT-IR data of the synthesized bisazobis -1,3-oxazepine-4,7-dione derivatives [A_{13}-A_{18}]

Com. no.	FT-IR bands
A_{13}	3236 (υ_{O-H}), 3055 ($\upsilon_{C-H,\ benzene\ rings}$), 2935 ($\upsilon_{as.C-H,CH_2,cyclohexane}$), 2858 ($\upsilon_{s.C-H,CH_2,cyclohexane}$), 1703 ($\upsilon_{C=O,O=C-O,oxazepine}$), 1656 ($\upsilon_{C=O,\ O=C-N\ ,oxazepine}$), 1591,1523 and 1481 ($\upsilon_{C=C,benzene\ rings}$),1375($\delta_{s.C-H,\ CH_3}$), 1313and 1280 ($\upsilon_{C-N}$),1097 ($\upsilon_{C-O,phenol}$), 846, 742 and 704 ($\delta_{o.o.p.C-H,benzene\ rings}$).
A_{14}	3498 (υ_{O-H}), 3360 (υ_{N-H}),3095($\upsilon_{C-H,\ benzene\ rings}$),2939 ($\upsilon_{as.C-H,CH_3}$) ,2838 ($\upsilon_{s.C-H,CH_3}$), 1691 ($\upsilon_{C=O,O=C-O and\ O=C-N,oxazepine,vib.coupling}$), 1572 and 1516 ($\upsilon_{C=C,benzene\ rings}$), 1392 ($\delta_{s.C-H,\ CH_3}$)1365 and 1267 ($\upsilon_{C-N}$),1118($\upsilon_{C-O,phenol}$), 869,749 and716 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
A_{15}	3429 (υ_{O-H}), 3087 and 3019 ($\upsilon_{C-H,benzene\ rings}$),2976 and 2920 ($\upsilon_{as.C-H\ ,CH_3}$),2860 ($\upsilon_{s.C-H,CH_3}$), 1716 ($\upsilon_{C=O,O=C-O,oxazepine}$), 1641 ($\upsilon_{C=O,\ O=C-N,oxazepine}$),1604, 1547 and 1489 ($\upsilon_{C=C,benzene\ rings}$),1458($\delta_{as.C-H,\ CH_3}$),1379 ($\delta_{s.C-H,CH_3}$),1344 and 1287($\upsilon_{C-N}$),1105($\upsilon_{C-O,phenol}$), 893,854,825, 810, 767 and 712 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
A_{16}	3265 and 3203 (υ_{O-H}),3063 and 3018($\upsilon_{C-H,\ benzene\ rings}$), 2952 and 2922($\upsilon_{as.C-H,CH_3}$), 2843 ($\upsilon_{s.C-H,CH_3}$), 1701 ($\upsilon_{C=O,O=C-O and\ O=C-N\ ,oxazepine,vib.coupling}$), 1622($\upsilon_{C=C,oxazepine}$), 1550,1523,1506 and 1404 ($\upsilon_{C=C,benzene\ rings}$), 1325 ($\delta_{s.C-H,\ CH_3}$), 1305and1278 ($\upsilon_{C-N}$),1176($\upsilon_{C-O,phenol}$), 1033 ($\upsilon_{s.C-O-C,ether}$), 887,833,817,803, and 756 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
A_{17}	3275 and 3207 (υ_{O-H}),3101and3009($\upsilon_{C-H,\ benzene\ rings}$),2879 ($\upsilon_{s.C-H,CH_3}$) ,2854 ($\upsilon_{C-H,oxazepine}$),1699 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$), 1626 ($\upsilon_{C=C,oxazepine}$), 1545 and 1494 ($\upsilon_{C=C,benzenerings}$), 1448 ($\delta_{as.C-H,\ CH_3}$), 1325and1269 ($\upsilon_{C-N}$),1153($\upsilon_{.C-O,phenol}$),900,850, 832,759 and 715 ($\delta_{o.o.p.C-H,benzene\ rings}$).
A_{18}	3510, 3425, 3357, (υ_{O-H}), 3080 and 3014($\upsilon_{C-H,benzenerings}$), 2942($\upsilon_{as.C-H\ ,CH_3}$), 2870($\upsilon_{s.C-H,CH_3}$),1705($\upsilon_{C=O,O=C-O and\ O=C-N,oxazepine,vib.coupling}$),1624 ($\upsilon_{C=C\ ,\ oxazepine}$), 1576,1543,1516 and 1491 ($\upsilon_{C=C,benzene\ rings}$), 1392 ($\delta_{s.C-H,\ CH_3}$) , 1315 and 1257 ($\upsilon_{C-N}$),1107 ($\upsilon_{C-O,phenol}$),1074($\upsilon_{C-Br}$), 900 ,858, 82,767, 736 and 682($\delta_{o.o.p.C-H,benzenerings}$).

3.5. Synthesis of bisimine derivatives [B_1-B_5]

A condensation reaction between *o*- Tolidine and equimolar quantity of aromatic aldehydes (2,5-dimethoxybenzaldehyde, 4-chlorobenzaldehyde, benzaldehyde, 2- hydroxybenzaldehyde and 4-*N* , *N*- dimethylaminobenzaldehyde) respectively in presense of glacial acetic acid as catalyst in absolute ethanol afforded bisimine derivatives [B_1-B_5] as indicated in scheme (3-8).



Scheme (3-8) : Synthesis of bisiminederivatives [B_1- B_5]

FT-IR spectrum, figures (3-21) - (3-25) of all synthesized bisimine derivatives [B_1-B_5] illustrate good evidence that the condensation reactions happened successfully by disappearing the sharp bands at (3468,3410) $cm^{-1}$and (3373,3338) cm^{-1}which attributed to the asymmetric and symmetric stretching vibrations of the two amino (-NH_2) groups in *o*-tolidine,also disappearing the sharp and strong band at 1624cm^{-1} due to the scissoring bending vibration of (-NH_2) groups and appearing sharp and medium-strong band at lower frequencies at the general range (1627-1593) cm^{-1} assigned to

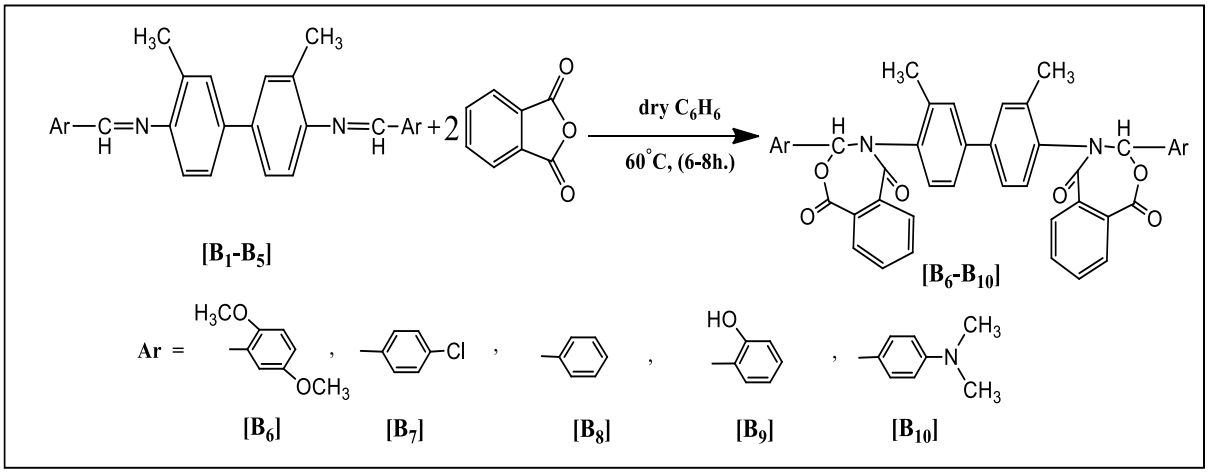
the stretching vibration of imine (C=N) group[101]. Other data of functional groups were shown in table (3- 4).

Table (3-4): FT-IR data of the synthesized bisimine derivatives [B_1-B_5]

Com. no.	FT-IR bands
B_1	3055 and 3007($\upsilon_{C-H,benzene\ rings}$), 2949 and 2916 ($\upsilon_{as.C-H,CH_3}$),2833 ($\upsilon_{s.C-H,CH_3}$),1620 ($\upsilon_{C=N}$),1595 and1494 ($\upsilon_{C=C,benzene\ rings}$),1456 ($\delta_{as.C-H,CH_3}$),1369($\delta_{s.C-H,\ CH_3}$),1301 and 1267 ($\upsilon_{C-N}$),1217($\upsilon_{as.C-O-C,ether}$),1039 ($\upsilon_{s.C-O-C,ether}$), 866,808 and 705 ($\delta_{o.o.p.C-H,benzene\ rings}$).
B_2	3061 and 3022($\upsilon_{C-H,benzene\ rings}$),2972 ($\upsilon_{as.C-H,CH_3}$), 2874 ($\upsilon_{s.C-H,CH_3}$),1622 ($\upsilon_{C=N}$),1593,1562 and1485 ($\upsilon_{C=C,benzenerings}$),1444 ($\delta_{as.C-H,CH_3}$),1361($\delta_{s.C-H,\ CH_3}$), 1286 ($\upsilon_{C-N}$),1087($\upsilon_{C-Cl}$), 877,825and 730 ($\upsilon_{C-H\ o.o.p.,\ benzene\ rings}$).
B_3	3059 and 3024($\upsilon_{C-H,benzene\ rings}$),2984 ($\upsilon_{as.C-H,CH_3}$), 2918 ($\upsilon_{s.C-H,CH_3}$),1627 ($\upsilon_{C=N}$),1608,1572 and1483 ($\upsilon_{C=C,benzene\ rings}$),1448($\delta_{as.C-H,CH_3}$),1371($\delta_{s.C-H,\ CH_3}$), 1307($\upsilon_{C-N}$), 877,812, 758,708 and 690 ($\delta_{o.o.p.C-Hbenzene\ rings}$).
B_4	3421(υ_{O-H}), 3055 and 3032($\upsilon_{C-H,benzene\ rings}$), 2985 and 2939 ($\upsilon_{as.C-H,CH_3}$), 2904 ($\upsilon_{s.C-H,CH_3}$),2715 ($\upsilon_{C-H,imine\ group}$),1612 ($\upsilon_{C=N}$),1566 and 1483 ($\upsilon_{C=C,benzene\ rings}$), 1454 ($\delta_{as.C-H,CH_3}$),1367($\delta_{s.C-H,\ CH_3}$),1301and1278 ($\upsilon_{C-N}$),1182($\upsilon_{C-O,\ phenol}$), 890,868, 853,808 and 750 ($\delta_{o.o.p.C-H,benzene\ rings}$).
B_5	3049 and 3012($\upsilon_{C-H,benzene\ rings}$), 2983 and 2945($\upsilon_{as.C-H,CH_3}$), 2897 and 2862 ($\upsilon_{s.C-H,CH_3}$), 2810 ($\upsilon_{C-H,imine\ group}$),1593 ($\upsilon_{C=N}$),1525 and1479 ($\upsilon_{C=C,benzene\ rings}$),1437 ($\delta_{as.C-H,CH_3}$),1361($\delta_{s.C-H,\ CH_3}$),1315 and 1228($\upsilon_{C-N}$), 877,815and 715($\delta_{o.o.p.C-H,benzenerings}$).

3.6. Synthesis of bis -1,3-oxazepine-4,7-dione derivatives[B_6-B_{10}]

A (5+2 ⟶ 7) cycloaddition reaction of equimolar amount of phathalic anhydride and the synthesized bisimines [B_1-B_5] was used for synthesis a series of bis-1,2-disubstituted-1,3-oxazepine-4,7-dione derivatives [B_6-B_{10}] as shown in scheme (3-9).



Scheme (3-9) : Synthesis of bis-1,3-oxazapine-4,7-dionederivatives [B_6–B_{10}]

The (C.H.N.) elementary microanalysis, table (2-9) of the synthesized compounds [B_6-B_{10}] showed good agreement between the caculated and found values.

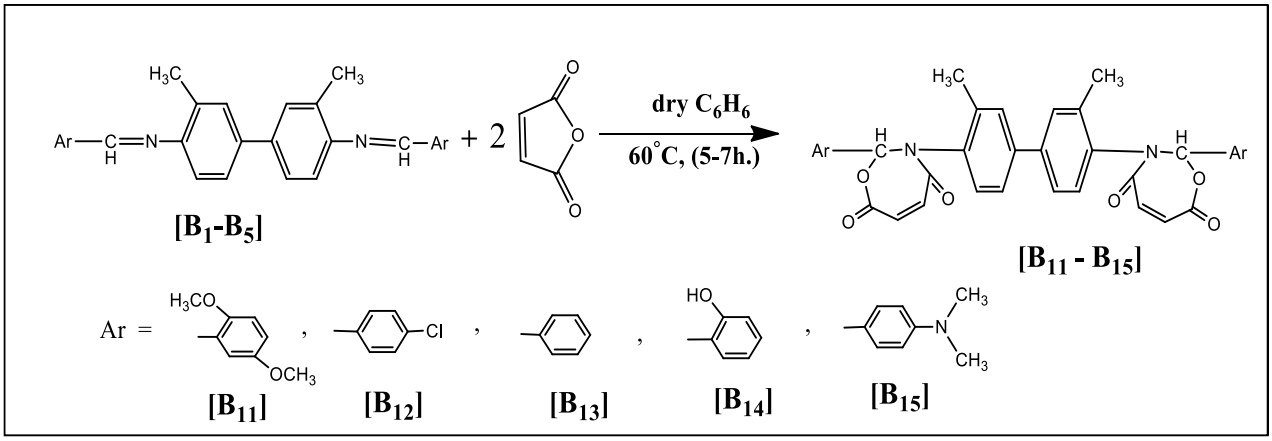
The FT-IR spectrum, figures (3-26) - (3-30) of compounds [B_6-B_{10}] illustrate good evidence that the cycloaddition reactions took place successfully by disappearing the band at the general range (1627-1593) cm^{-1} which attributed to υ (C=N) and appearing one or two bands at (1701,1658) cm^{-1}, (1699,1654) cm^{-1}, (1695,1637) cm^{-1},1693 $cm^{-1}$and (1697,1660) cm^{-1}, the first one assigned to stretching vibration of (C=O) group in (O=C-O) inside oxazepine ring while the second attributed to the streching vibration of (C=O)[102] group in (O=C-N) inside oxazepine ring. Other characteristic bands with their interpretation were listed in table (3-5).

Table (3-5) : FT-IR data of the synthesized bis -1,3-oxazepine-4,7-dione derivatives [B_6- B_{10}]

Com. no.	FT-IR bands
B_6	3026($\upsilon_{C-H,benzene\ rings}$), 2897 ($\upsilon_{as.C-H,CH_3}$), 2835 ($\upsilon_{s.C-H,CH_3}$), 1701 ($\upsilon_{C=O,O=C-O,oxazepine}$), 1658 ($\upsilon_{C=O,O=C-N,oxazepine}$),1589,1519 and 1496 ($\upsilon_{C=C,benzene\ rings}$), 1450 ($\delta_{as.C-H,\ CH_3}$), 1390 ($\delta_{s.C-H,\ CH_3}$),1286 ($\upsilon_{C-N}$) ,1222 ($\upsilon_{as.C-O-C,ether}$),1074 ($\upsilon_{s.C-O-C,\ oxazepine}$),1039($\upsilon_{s.C-O-C,ether}$), 914,808,742 and 705 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
B_7	3026 ($\upsilon_{C-H,benzene\ rings}$),2928 ($\upsilon_{as.C-H,CH_3}$), 2893 ($\upsilon_{s.C-H\ ,CH_3}$),1699 ($\upsilon_{C=O,O=C-O,oxazepine}$), 1654 ($\upsilon_{C=O,O=C-N,oxazepine}$), 1589, 1518 and 1491($\upsilon_{C=C,benzene\ rings}$), 1448 ($\delta_{as.C-H,\ CH_3}$),1310 and1290 ($\upsilon_{C-N}$) ,1080 (υ_{C-Cl}), 912 , 879 , 808, 740 ,700 and 680 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
B_8	3167 and 3030 ($\upsilon_{C-H,benzene\ rings}$), 2868$_{br}$ ($\upsilon_{as.\ and\ s.C-H,CH_3,interacted}$), 1695 ($\upsilon_{C=O,O=C-O,oxazepine}$) ,1637($\upsilon_{C=O,O=C-N,oxazepine}$),1587,1529 and 1491 ($\upsilon_{C=C,benzene\ rings}$),1446 ($\delta_{as.C-H,CH_3}$),1361($\delta_{s.C-H,\ CH_3}$),1311 and 1276 ($\upsilon_{C-N}$),1072 ($\upsilon_{as.C-O,oxazepine}$), 910, 877, 806, 761 and 698($\delta_{o.o.p.C-H,benzene\ rings}$).
B_9	3437 (υ_{O-H}), 3086 and 3022 ($\upsilon_{C-H,\ benzene\ rings}$), 2989 ($\upsilon_{as.\ C-H,CH_3}$), 2885 ($\upsilon_{s.C-H,CH_3}$), 1693 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,\ oxazepine,vib.coupling}$) ,1587, 1518 and1500 ($\upsilon_{C=C,benzene\ rings}$), 1446 ($\delta_{as.C-H,\ CH_3}$),1371 ($\delta_{s.C-H,\ CH_3}$) ,1285 and 1278 ($\upsilon_{C-N}$), 1072 ($\upsilon_{as.C-O,oxazepine}$), 910,794,738 ,700 and 682 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).
B_{10}	3103 and 3024 ($\upsilon_{C-H,benzene\ rings}$), 2980 and 2899 ($\upsilon_{as.C-H\ ,CH_3}$), 2862 and 2812 ($\delta_{s.C-H,CH_3}$), 1697 ($\upsilon_{C=O,O=C-Ooxazepine}$), 1660 ($\upsilon_{C=O,O=C-N\ ,oxazepine}$),1589,1545, 1525 and 1481($\upsilon_{C=C,benzene\ rings}$),1437($\delta_{as.C-H\ ,\ CH_3}$), 1361($\delta_{s.C-H,\ CH_3}$), 1313,1278 and 1232 ($\upsilon_{C-N}$), 879, 815 and 740 ($\delta_{o.o.p.C-H,benzene\ rings}$).

3.7. Synthesis of bis -1,3-oxazepine-4,7-dione derivatives [B_{11}-B_{15}]

The synthesized bisimines [B_1-B_5] were also introduced in (5+2⟶7) cycloaddition reaction with maleic anhydride as five-membered component to produce a series of bis-1,2-disubstituted-1,3-oxazepine-4,7-dione derivatives [B_{11}-B_{15}] as indicated in scheme (3-10).



Scheme (3-10) : Synthesis of bis-1,3-oxazapine-4,7-dionederivatives [B_{11}-B_{15}]

The (C.H.N.) elementary microanalysis, table (2-9) of the synthesized compounds [B_{11}-B_{15}] showed closeness between the calculated and found values.

The FT-IR spectrum, figures (3-31) - (3-35) of compounds [B_{11}-B_{15}] provide good evidence that cycloaddition reactions happened successfully through disappearing the band around (1627-1593) cm^{-1} which assigned to the stretching vibrations of (C=N) groups and appearing strong band at (1712,1705,1712,1710 and 1710) cm^{-1} respectively belong to υ (C=O) in (O=C-O) and (O=C-N) groups inside oxazepine ring due to the vibration coubling. Moreover, the spectra of compounds [B_{11}-B_{14}] appeared medium band at (1629,1627,1623 and 1622) cm^{-1} respectively which attributed to υ (C=C) inside oxazepine ring. Other caracteristic bands with their interpretation were summarized in table (3-6).

Table (3-6) : FT-IR data of the synthesized bis -1,3-oxazepine-4,7-dione derivatives [B_{11}-B_{15}]

Com. no.	FT-IR bands
B_{11}	3051and 3001($\upsilon_{C-H,benzene\ rings}$), 2986 ($\upsilon_{as.C-H,CH_3}$), 2841 ($\upsilon_{s.C-H\ ,CH_3}$) ,1712 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$), 1629 ($\upsilon_{C=C,oxazepine}$), 1573 ,1529 and 1492 ($\upsilon_{C=C,benzene\ rings}$),1451($\delta_{as.C-H,CH_3}$),1359 ($\delta_{s.C-H,\ CH_3}$), 1305 and 1278 ($\upsilon_{C-N}$), 1219($\upsilon_{as.C-O-C,ether}$), 848, 813and 716($\delta_{o.o.p.C-H,benzene\ rings}$).
B_{12}	3041($\upsilon_{C-H,benzene\ rings}$),2980 ($\upsilon_{as.C-H,CH_3}$),2861 ($\upsilon_{s.C-H,CH_3}$) ,1705 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$),1627 ($\upsilon_{C=C,oxazepine}$), 1587,1566 ,1533 and 1489 ($\upsilon_{C=C,benzene\ rings}$),1450($\delta_{as.C-H,\ CH_3}$),1355 ($\delta_{s.C-H,\ CH_3}$),1292 ($\upsilon_{C-N}$),1091($\upsilon_{C-Cl}$), 892, 852 and 825($\delta_{o.o.p.C-H,\ benzene\ rings}$).
B_{13}	3049 ($\upsilon_{C-H,benzene\ rings}$), 2929 ($\upsilon_{as.C-H,CH_3}$), 2860 ($\upsilon_{s.C-H\ ,CH_3}$), 1710 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$),1623 ($\upsilon_{C=C,oxazepine}$), 1554, 1533 and 1492 ($\upsilon_{C=C,benzene\ rings}$), 1301 ($\upsilon_{C-N}$),889, 850, 821, 752 and 690 ($\delta_{o.o.p.C-H,benzene\ rings}$).
B_{14}	3392(υ_{O-H}), 3051($\upsilon_{C-H,benzene\ rings}$), 2985 ($\upsilon_{as.C-H,CH_3}$),2874 ($\upsilon_{s.C-H\ ,CH_3}$),1710 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$),1622 ($\upsilon_{C=C,oxazepine}$), 1575, 1529 and 1489 ($\upsilon_{C=C,benzene\ rings}$),1434($\delta_{as.C-H,\ CH_3}$),1381 ($\delta_{s.C-H,\ CH_3}$),1271 ($\upsilon_{C-N}$),1152 ($\upsilon_{C-O,phenol}$), 856,817,771,750,711 and 682 ($\delta_{o.o.p.C-H,benzene\ rings}$).
B_{15}	3039($\upsilon_{C-H,\ benzene\ rings}$), 2982 and 2939 ($\upsilon_{as.C-H,CH_3}$), 2899 ($\upsilon_{s.C-H\ ,CH_3}$), 1710 ($\upsilon_{C=O,O=C-O\ and\ O=C-N,oxazepine,vib.coupling}$),1589 ($\upsilon_{C=C,oxazepine}$),1535 and 1489 ($\upsilon_{C=C,benzene\ rings}$),1448 ($\delta_{as.C-H,\ CH_3}$), 1392 ($\delta_{C-H,\ N(CH_3)_2}$),1359 ($\delta_{s.C-H,\ CH_3}$),1307 ($\upsilon_{C-N}$), 848, 817,781 and 723 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).

^{1}H NMR spectra

^{1}H NMR spectra, figure (3-36), (μHz, DMSO-d_6) of compound [A_7] showed the following signals in δ (ppm) : The signal at (1.061-1.344) ppm attributed to protons (a) in cyclohexane rings, (quintet,4H,4×Ha). The signal at (1.401-1.591) ppm belong to protons (b) in cyclohexane rings, (quintet,8H,8×Hb). The signal at 1.70 ppm due to protons (c) in cyclohexane rings, (quartet,8H,8×Hc). The signal at 1.811 ppm assigned to protons (d) in cyclohexane rings, (quintet,2H,2×Hd).The signal at (2.442-2.569) ppm attributed to DMSO solvent. The singlet signal at 2.889 ppm assigned to methyl groups protons, (6H,2×CH_3). The signal at (3.675-3.690) ppm due to H_2O in DMSO.The signals of aromatic protons and protons of (C-H) groups inside oxazepine rings appeared at the range (6.850-9.140) ppm.The signals of phenolic hydroxy groups protons appeared at 10.447 ppm as sharp, (11.382-11.993), 14.114 and 14.665 ppm as broad, (2H,2×H-O).

^{1}H NMR spectra, figure (3-37), (μHz, DMSO-d_6) of compound [A_8] showed the following signals at δ (ppm): The signal at (2.403-2.569) ppm attributed to DMSO solvent.The singlet signal at 2.735 ppm assigned to methyl groups protons, (6H,2×CH_3). The broad signal at (3.228-3.496) ppm attributed to H_2O in DMSO. The two signals at (4.221-4.293) ppm and 4.526 ppm belong to protons of (N-H) groups, (2H,2×N-H). The signals of aromatic protons [101] and (C-H) protonsof oxazepine rings appeared at the range (6.769-8.257) ppm. The two signals at 10.627 ppm and 11.143 ppm assigned to protons of phenolic hydroxy groups, (2H,2×H-O).

^{1}H NMR spectra, figure (3-38), (μHz, DMSO-d_6) of compound [A_9] showed the following signals at δ (ppm): The signal at (2.437-2.570) ppm due to DMSO solvent. The singlet signal at 2.636 ppm attributed to methyl group protons (a), (s,3H, 3×Ha). The signal at (2.705- 2.728) ppm assigned to methyl group protons (b) (s,3H, 3×Hb).The signal at (2.771-2.796) ppm attributed to methyl group protons (c), (s, 6H , 6×Hc).The broad signal at (3.145-3.625) ppm due to the H_2O in DMSO solvent. The signals of aromatic protons and (C-H) protons of oxazepine rings[(104)] appeared at the range (7.157-7.880) ppm. The signal of phenolic hydroxy groups protons appeared asbroad at the range (12.894-13.482) ppm , (2H,2×O-H).

^{1}H NMR spectra, figure (3-39), (μHz, DMSO-d_6) of compound [A_{10}] showed the following signals at δ (ppm): The signal at (2.437-2.570) ppm due to DMSO solvent. The two signals at (2.722- 2.728) ppm and (2.771-2.795) ppm attributed to methyl groups protons, (6H, 2×CH_3) .The signal of H_2O in DMSO solvent[(104)] appeared as broad at (3.091-3.547) ppm. The singlet signals at 3.733 ppm and 3.819 ppm attributed to methoxy groups protons, (6H, 2×CH_3O). The signals of aromatic protons and (C-H) protons of oxazepine rings appeared at the range (6.918-9.179) ppm. The broad signal at the range (12.939-13.334) ppm assigned to the phenolic hydroxy groups protons, (2H,2×O-H).

^{1}H NMR spectra, figure (3-40), (μHz, DMSO-d_6) of compound [A_{11}] showed the following signals at δ (ppm): The signal at (2.436-2.569) ppm due to DMSO solvent. The singlet signal at 2.787 ppm assigned to methyl groups protons, (6H, 2×CH_3) .The signal of H_2O in DMSO solvent appeared at (3.274- 3.404) ppm. The signals of aromatic protons and (C-H)

protons inside oxazepine rings appeared at the range (7.044 - 9.189) ppm. The two signals at 10.329 ppm and 10.386 ppm assigned to phenolic hydroxy groups protons, (2H,2×O-H).

^{1}H NMR spectra, figure (3-41), (μHz, DMSO-d_6) of compound [A_{13}] showed the following signals at δ (ppm) : The signal at (1.021-1.352) ppm attributed to protons (a) in cyclohexane rings, (quintet,4H,4×Ha). The signal at (1.395-1.582) ppm belong to protons (b) in cyclohexane rings, (quartet,8H,8×Hb). The signal at (1.684-1.800) ppm attributed to protons (c) in cyclohexane rings, (quartet,8H,8×Hc). The signal at 1.885 ppm due to protons (d) in cyclohexane rings,(quintet,2H,2×Hd).The signal of DMSO solvent appeared at (2.439-2.570) ppm. The two signals at (2.713-2.736) ppm and 2.878 ppm assigned to methyl groups protons, (6H,2×CH_3). The broad signal at (3.338-3.613) ppm belong to H_2O in DMSO solvent. The spectrrum illustrates good evidence that the cycloaddition reaction happened successfully and formed the desired product, oxazepine derivative [A_{13}] , by appearing two doublet signals at (6.220-6.261) ppm and (6.446-6.488) ppm assigned to olefinic (C-H) protons (e and f) respectively inside oxazepine rings. The signal at 6.088 ppm may be due to olefinc (C-H) proton (e) in *cis* position to (C=O) group, so its signal is shifted towards high field region .The signals of aromatic protons and protons of (C-H) inside oxazepine rings appeared at the range (6.848-9.202) ppm. The two signals at 10.374 ppm and 11.625 ppm belong to protons of phenolic hydroxy groups, (2H, 2×H-O).

^{1}H NMR spectra, figure (3-42), (μHz, DMSO-d_6) of compound [A_{14}] showed the following signals at δ (ppm) : The signal at (2.404 - 2.575) ppm attributed to DMSO solvent. The signal at (2.729- 2.774) ppm assigned to methyl groups protons, (6H , 2×CH_3). The broad signal at (3.120 -3.501) ppm attributed to H_2O in DMSO. The signal of (N-H) protons may be interacted with the broad signal of H_2O in DMSO.The spectrum provides good evidence that the cycloaddition reaction proceeded successfully and give the desired oxazepine derivative [A_{14}] by appearing two signals at 5.973 ppm and 6.106 ppm attributed to olefinic (C-H) protons inside oxazepine rings, the first signal assigned to (C-H) protons (a), (2H, 2×Ha) while the second signal belong to (C-H) protons (b), (2H, 2×Hb). The signals of aromatic protons and (C-H) protons of oxazepine rings appeared at the range (6.773 -8.617) ppm.The two signals at 10.594 ppm and 11.123 ppm assigned to the phenolic hydroxy groups protons , (2H, 2×H-O).

^{1}H NMR spectra, figure (3-43), (μHz, DMSO-d_6) of compound [A_{15}] showed the following signals at δ (ppm): The signal at (2.430 - 2.575) ppm due to DMSO solvent . The signal at (2.723 -2.735) ppm attributed to methyl groups protons (a), (6H, 6×Ha). The signal at (2.770 -2.793) ppm attributed to methyl groups protons (b), (6H, 6×Hb). The signal of H_2O in DMSO solvent appeared at the range (3.136-3.921) ppm. The two signals at 6.178 ppm and 6.311ppm assigned to olefinic (C-H) protons in structure of oxazepine rings which provide good evidence that the cycloaddition reaction proceeded successfully and yielded the desired oxazepine derivative [A_{15}]. The signals at the range (7.155- 9.148) ppm attributed to aromatic protons and (C-H)

protons of oxazepine rings. The singlet signal at 10.391 ppm belong to the phenolic hydroxy groups protons, (2H, 2×H-O) .

^{1}H NMR spectra, figure (3-44), (μH$_z$, DMSO-d$_6$) of compound [A$_{16}$] showed the following signals at δ (ppm): The signal at (2.437 - 2.570) ppm attributed to DMSO solvent. The singlet signal at (2.765 - 2.785) ppm assigned to methyl groups protons, (6H, 2×CH_3). The signal at the range (3.308-3.665) ppm belong to H_2O in DMSO solvent. The two signals at (3.798-3.813) ppm and (3.880-3.969) ppm belong to methoxy groups protons, (6H, 6×H_3C-O). The spectrum illustrates good evidence that the cycloaddition reaction happened successfully and formed oxazepine derivative [A$_{16}$] by appearing two signals for olefinic (C-H) protons inside oxazepine rings, the first signal appeared as triplet at (6.211- 6.282) ppm attributed to olefinic (C-H) protons (a), (2H ,2×Ha) while the second signal appeared at the range (6.382- 6.515) ppm belong to olefinic (C-H) protons (b), (2H,2×Hb). The signals of aromatic protons and (C-H) protons of oxazepine rings appeared at the range (6.833- 9.165) ppm. The two signals at (10.388 -10.479) ppm and at (13.356-13.555) ppm belong to the phenolic hydroxy groups protons, (2H, 2×O-H).

^{1}H NMR spectra, figure (3-45), (μH$_z$, DMSO-d$_6$) of compound [A$_{17}$] showed the following signals at δ (ppm): The signal at (2.436 -2.570) ppm belong to DMSO solvent. The signal at (2.739 -2.780) ppm assigned to methyl groups protons, (6H, 2×CH_3). The broad signal at (3.307-3.496) ppm attributed to H_2O in DMSO solvent. The signals at the range (6.196 -6.498) ppm attributed to olefinic (C-H) protons inside oxazepine rings ,(4H, 4×C-H) which provide good evidence that the cycloaddition

reaction happened successfully and yielded the desired oxazepine derivative [A_{17}]. The signals of aromatic protons and (C-H) protons of oxazepine rings appeared at the range (7.065 -9.180) ppm .The two signals at 10.395 ppm and 11.524 ppm assigned to the phenolic hydroxy groups protons, (2H, 2×H-O).

^{1}H NMR spectra, figure (3-46), (μHz, DMSO-d_6) of compound [B_7] showed the following signals at δ (ppm): The singlet signals at 2.154 ppm and 2.355 ppm attributed to methyl groups protons, (6H, 2×CH_3) . The singlet signal at 2.505 ppm belong to DMSO solvent. The singlet signal at 3.369 ppm due to H_2O in DMSO solvent.The signals at the range (6.713 - 8.617) ppm attributed to aromatic protons and (C-H) protons of oxazepine rings.

^{1}H NMR spectra, figure (3-47), (μHz, DMSO-d_6) of compound [B_8] showed the following signals at δ (ppm): The signals at 2.154 ppm and (2.305 -2.417) ppm attributed to methyl groups protons, (6H, 2×CH_3) . The singlet signal at 2.518 ppm due to DMSO solvent. The singlet signal at 3.407 ppm belong to H_2O in DMSO solvent. The signals of aromatic protons and protons of (C-H) inside oxazepine rings appeared at the range (6.738 -8.592) ppm.

^{1}H NMR spectra, figure (3-48), (μHz, DMSO-d_6) of compound [B_{11}] showed the following signals at δ (ppm) : The signals at (2.160 - 2.371) ppm attributed to methyl groups protons, (6H, 2×CH_3) . The signal at (2.504 -2.571) ppm belong to DMSO solvent. The signal of H_2O in DMSO solvent appeared at 3.391 ppm.The two signals at (3.759 -3.789) ppm and (3.856 -3.880) ppm assigned to methoxy groups protons, (12H, 4×O-CH_3). The spectrum illustrates good evidence that the cycloaddition

reaction happened successfully and formed the desired oxazepine derivative [B_{11}] by appearing two signals at (6.239 -6.342) ppm and (6.595 -6.632) ppm assigned to olefinic (C-H) protons (a), (2H , 2×Ha) and olefinic (C-H) protons (b), (2H, 2×Hb) respectivly inside oxazepine rings .The signals of aromatic protons and (C-H) protons inside oxazepine rings appeared at the range (7.132 -8.768) ppm.

^{1}H NMR spectra, figure (3-49) , (μH_z, DMSO-d_6) of compound [B_{12}] showed the following signals at δ (ppm) : The signals at (2.260 -2.283) ppm and (2.430 -2.437) ppm attributed to methyl groups protons, (6H,2×CH_3) . The signal of DMSO solvent appeared at (2.443 -2.575) ppm. The broad signal at (3.338 -3.616) ppm due to H_2O in DMSO solvent. The spectrum provides good evidence that the cycloaddition reaction proceeded successfully and gave the desired oxazepine derivative [B_{12}] by appearing signals of olefinic (C-H) protons at (6.156 -6.407) ppm for protons (a), (2H, 2×Ha) and (6.597 -6.698) ppm for protons (b), (2H, 2×Hb). The signals of aromatic protons and (C-H) protons inside oxazepine rings appeared at the range (7.169 -8.606) ppm.

^{1}H NMR spectra, figure (3-50) , (μH_z, DMSO-d_6) of compound [B_{13}] showed the following signals at δ (ppm) : The signals at (2.155 -2.390) ppm attributed to methyl groups protons, (6H, 2×CH_3) .The singlet signal at 2.510 ppm belong to DMSO solvent. The broad signal at 3.398 ppm due to H_2O in DMSO solvent. The spectrum showed appearance of two signals at (6.238 -6.346) ppm for olefinic (C-H) protons (a), (2H, 2×Ha) and (6.598 -6.634) ppm for olefinic (C-H) protons (b), (2H, 2×Hb) which is considered good evidence that the

cycloaddition reaction took place successfully and yielded the desired oxazepine derivative [B_{13}]. The signals of aromatic protons and (C-H) protons inside oxazepine rings appeared at the range (7.511-8.591) ppm.

^{1}H NMR spectra, figure (3-51), (μHz, DMSO-d_6) of compound [B_{15}] showed the following signals at δ (ppm): The signals at (2.167 - 2.392) ppm assigned to methyl groups protons (a), (6H , 2×CH_3) .The singlet signal at 2.505 ppm belong to DMSO solvent. The singlet signal at 3.069 ppm attributed to methyl groups protons (b), (12H , 4×H_3C-N) . The broad signal at 3.469 ppm due to H_2O in DMSO solvent.The spectrum illustrates good evidence that the cycloaddition reaction happened successfully and produced the desired oxazepine derivative [B_{15}] by appearing signals of olefinic (C-H) protons at (6.225 -6.350) ppm for olefinic protons (c) ,(2H, 2×Hc) and 6.626 ppm for protons (d) , (2H, 2×Hd). The signals of aromatic protons and (C-H) protons inside oxazepine rings appeared at the range (6.826-8.454) ppm.

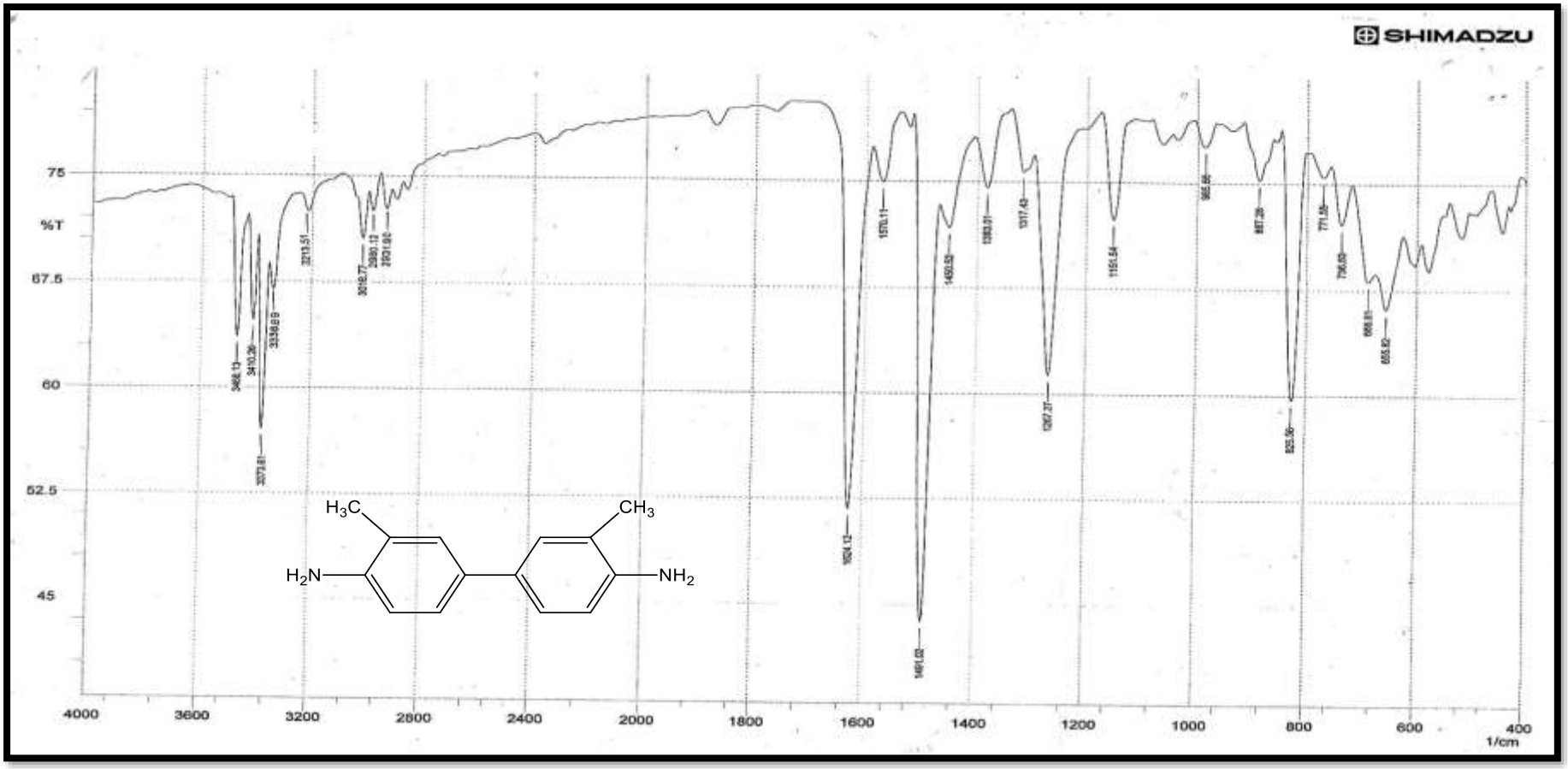


Figure (3-1) : FT-IR spectrum of *o*- toludine

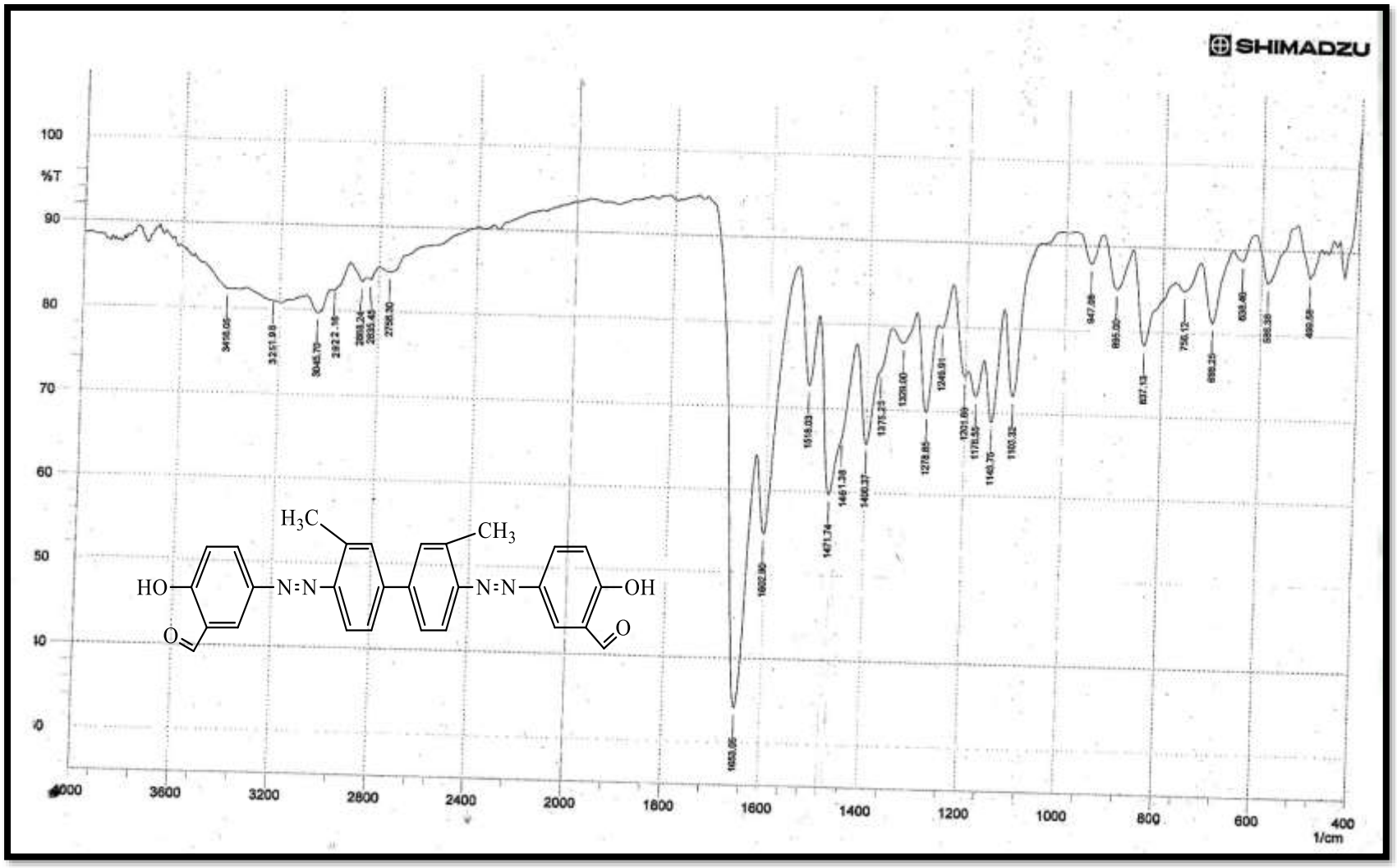


Figure (3-2) : FT-IR spectrum of compound [A]

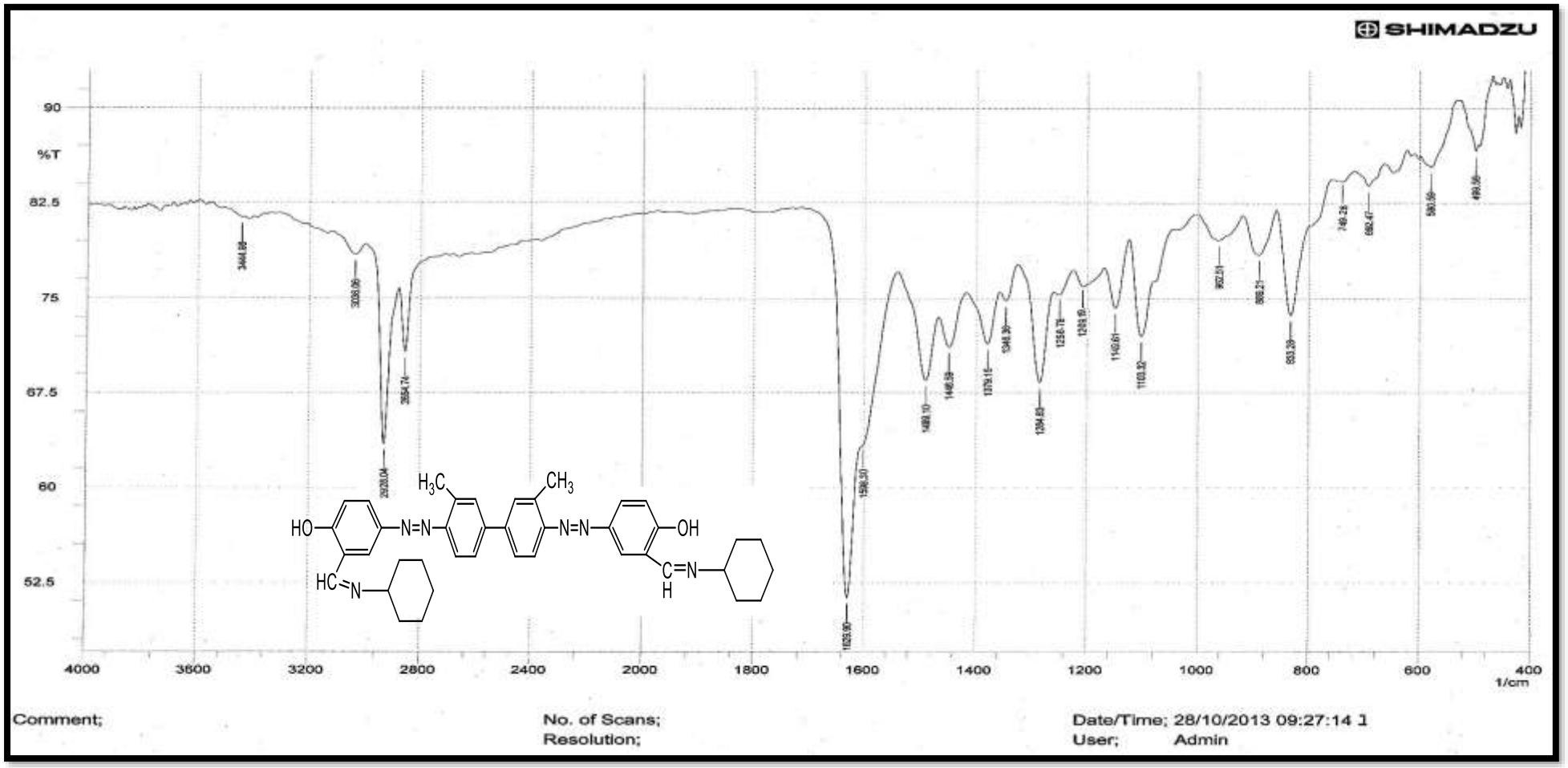


Figure (3-3) : FT-IR spectrum of compound [A_1]

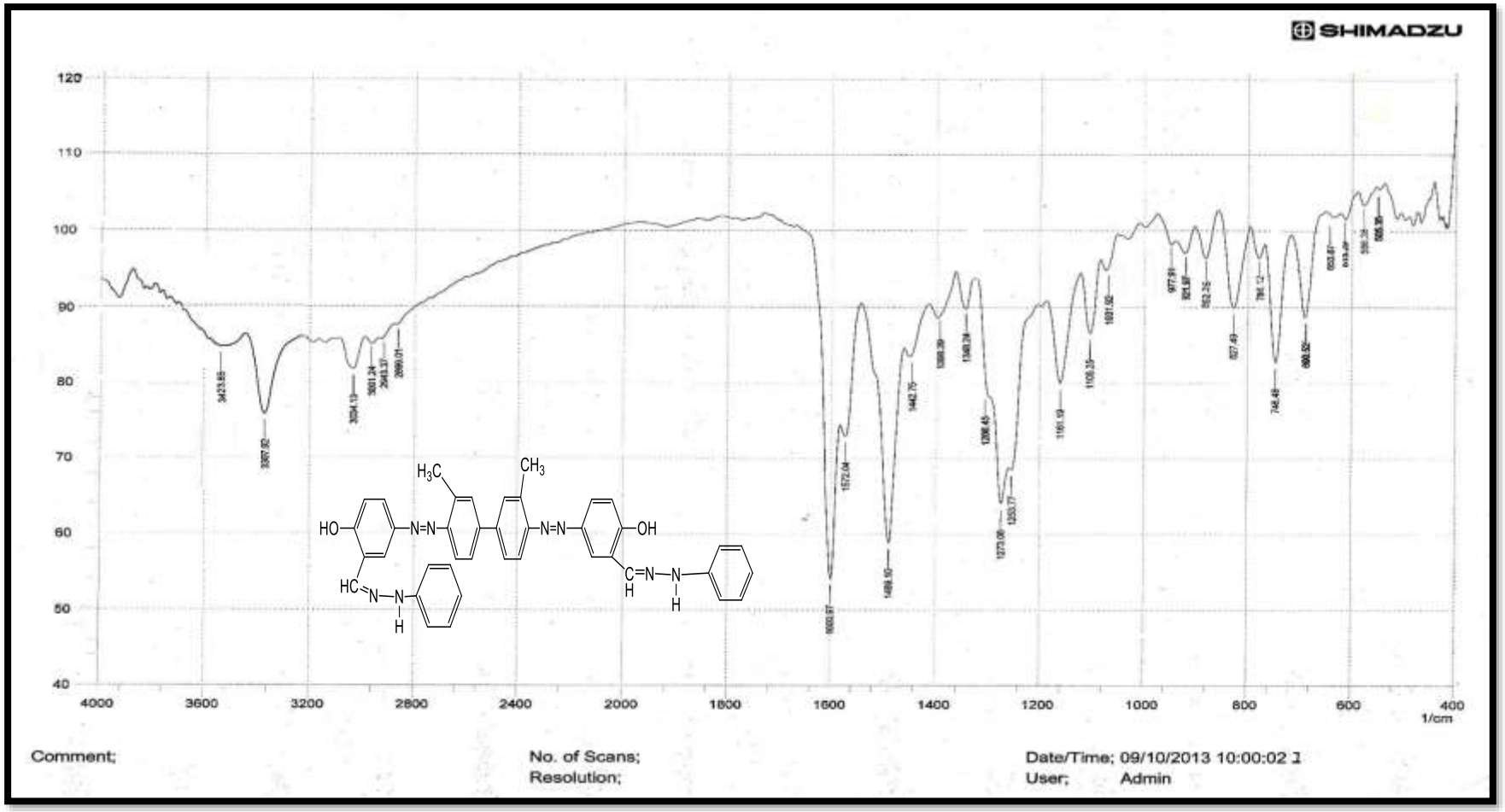


Figure (3-4) : FT-IR spectrum compound [A_2]

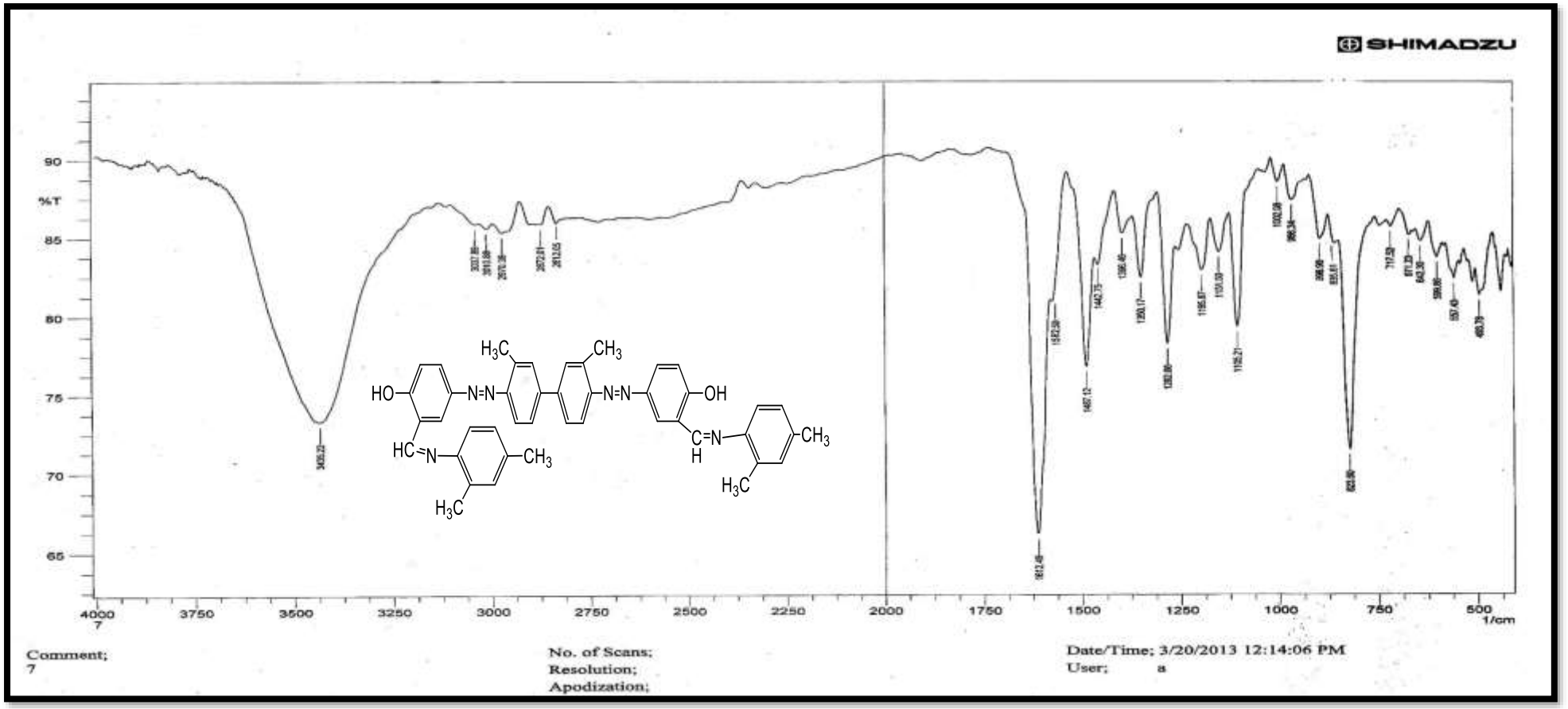


Figure (3-5) : FT-IR spectrum of compound [A_3]

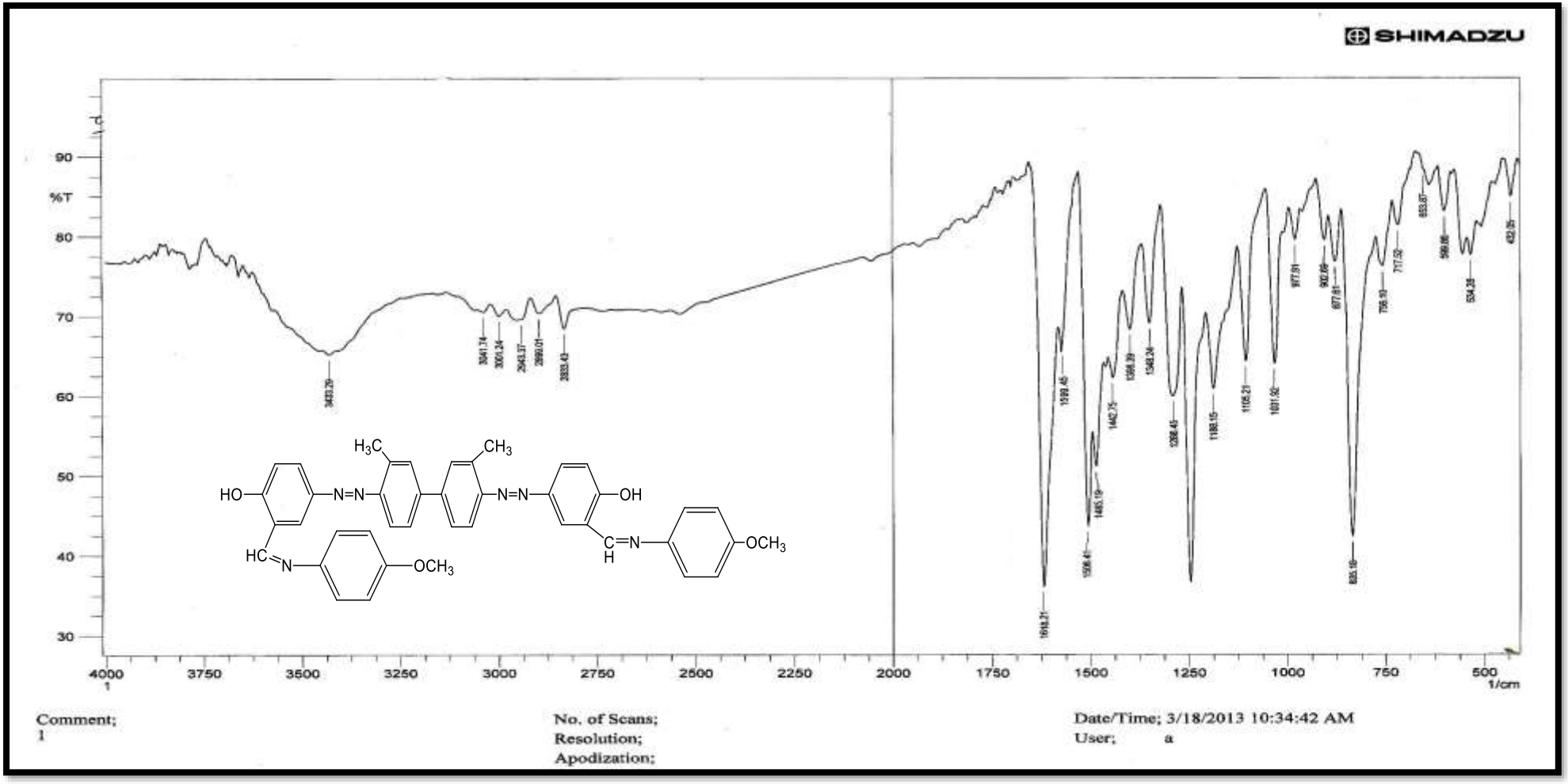


Figure (3-6) : FT-IR spectrum of compound [A_4]

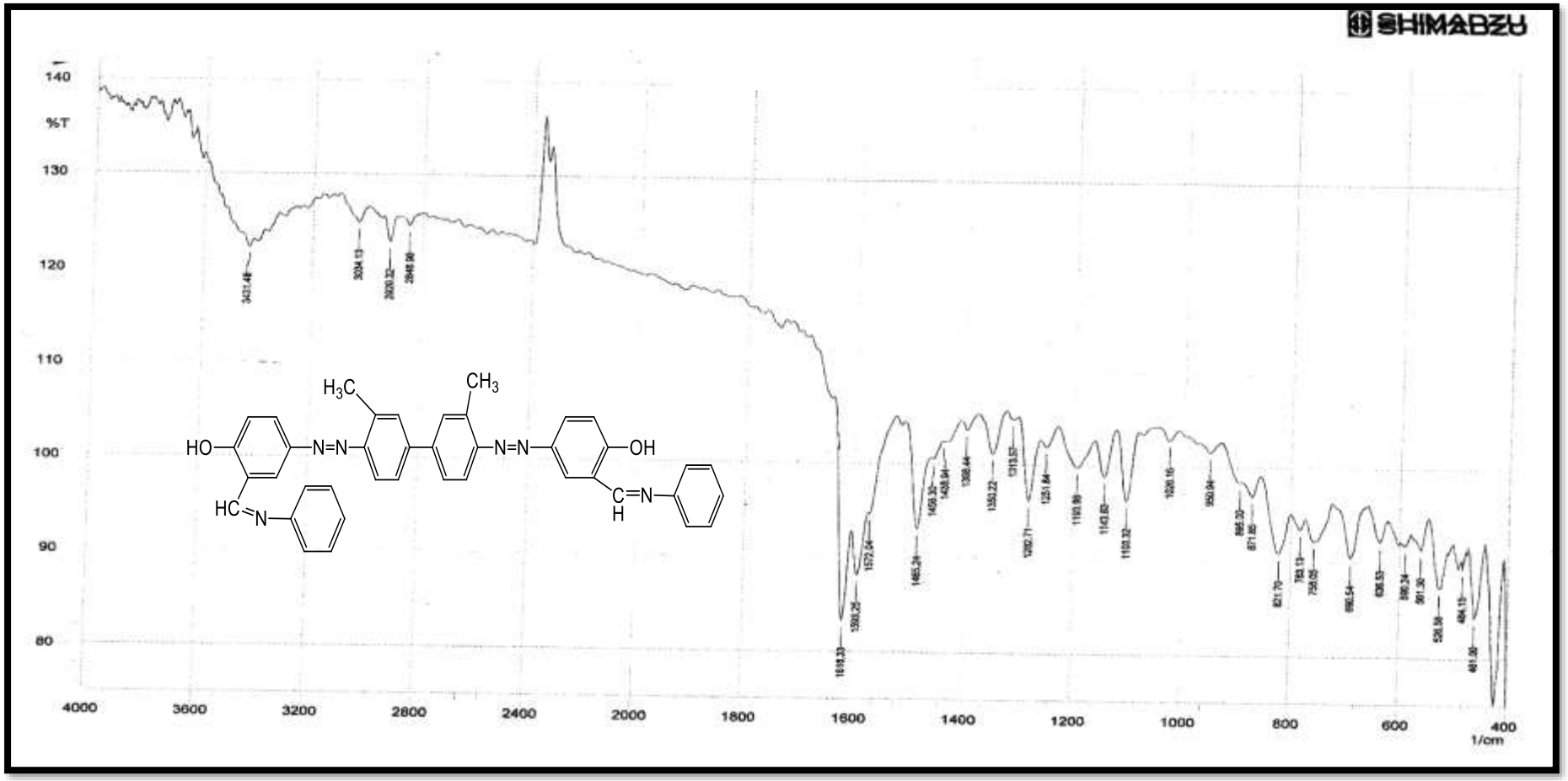


Figure (3-7) : FT-IR spectrum of compound [A_5]

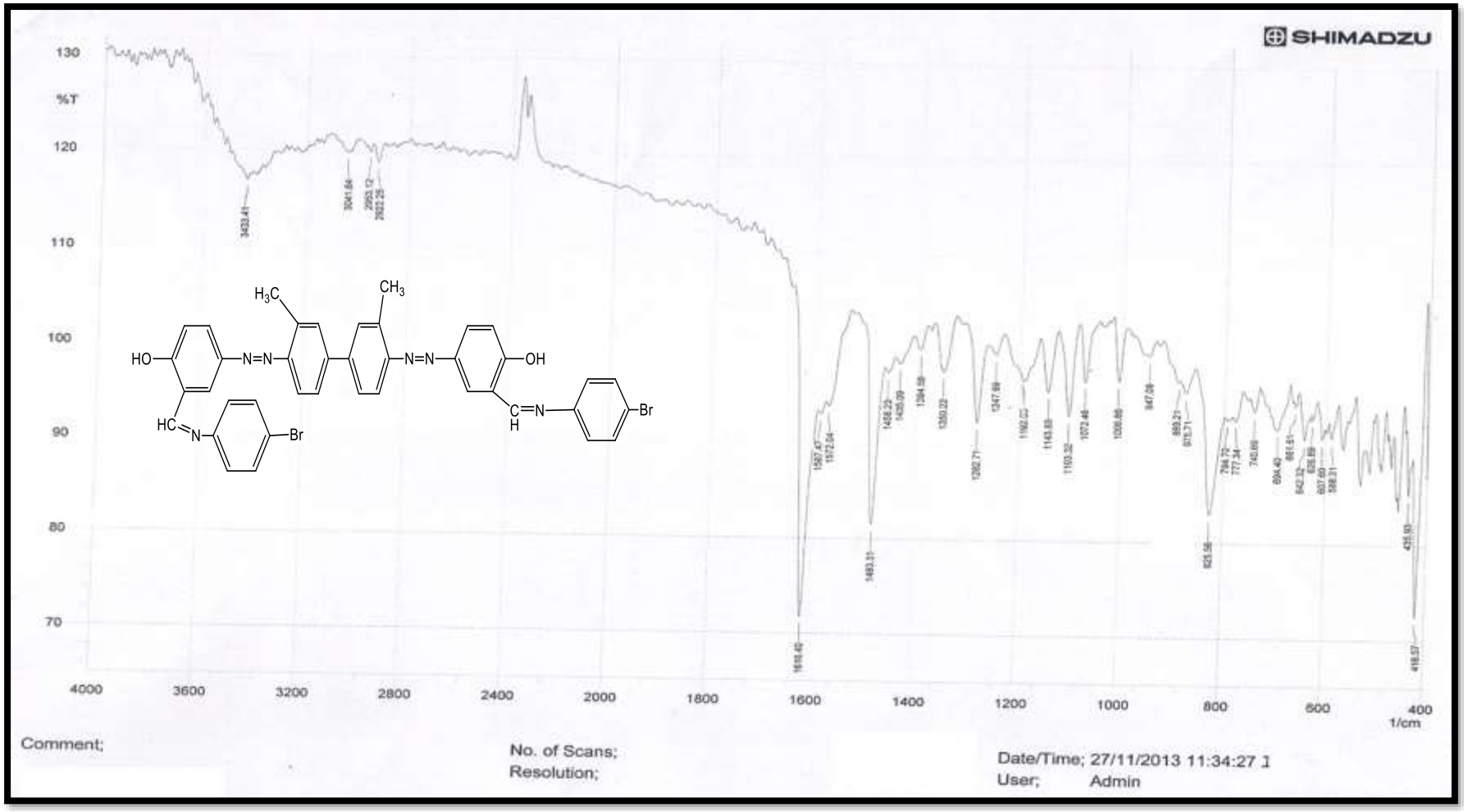


Figure (3-8) : FT-IR spectrum of compound [A_6]

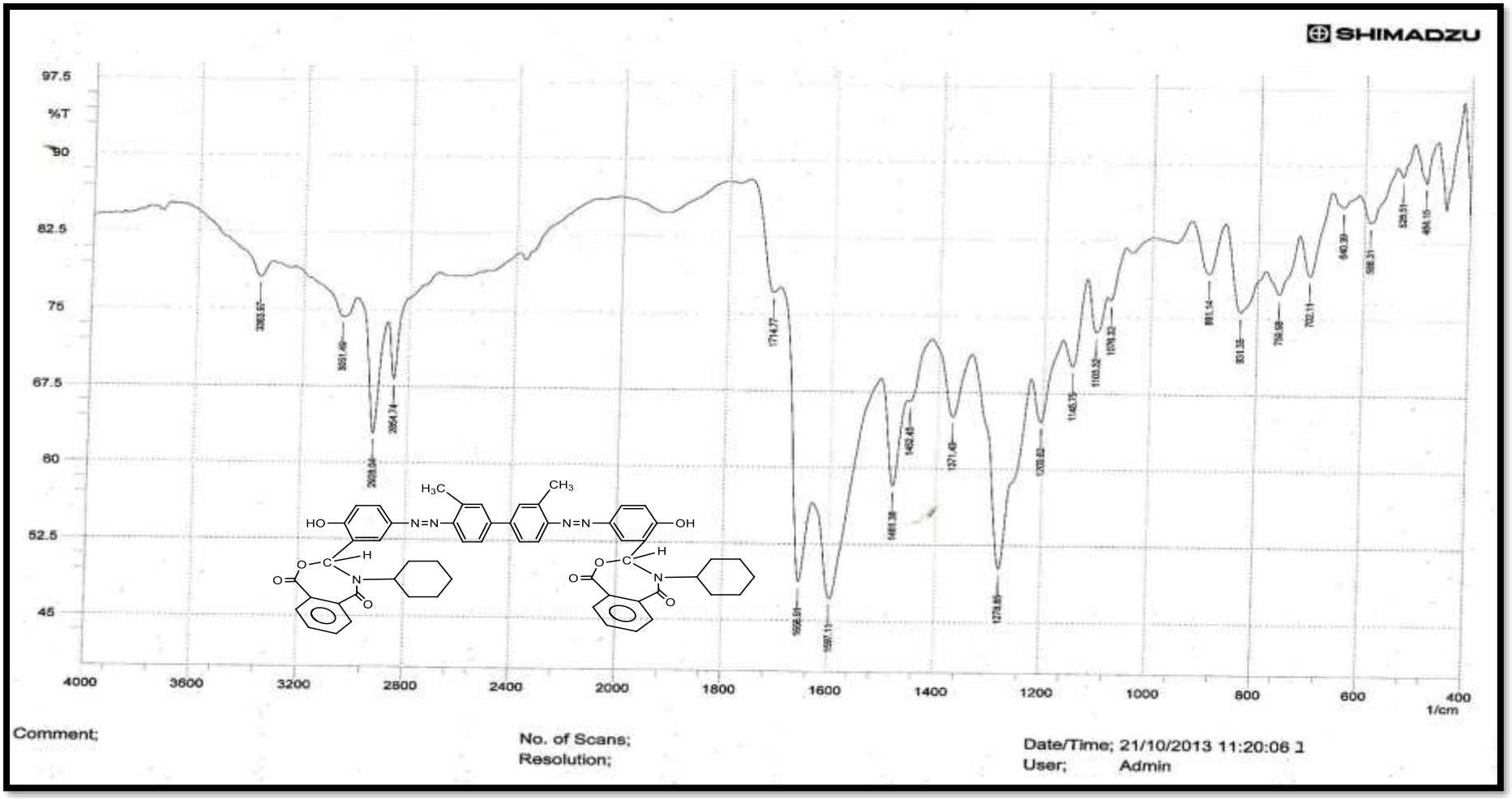


Figure (3-9) : FT-IR spectrum of compound [A_7]

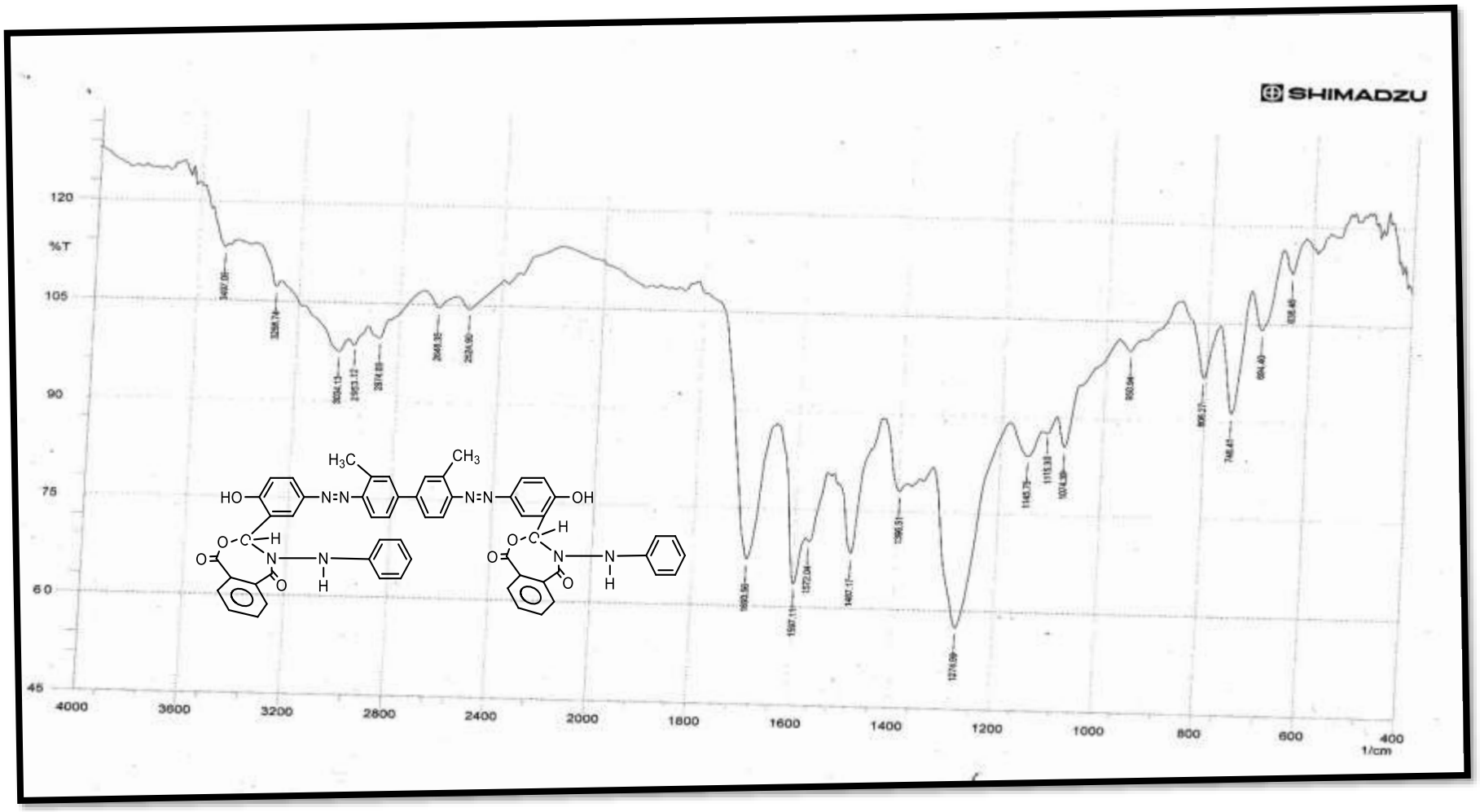


Figure (3-10) : FT-IR spectrum of compound [A_8]

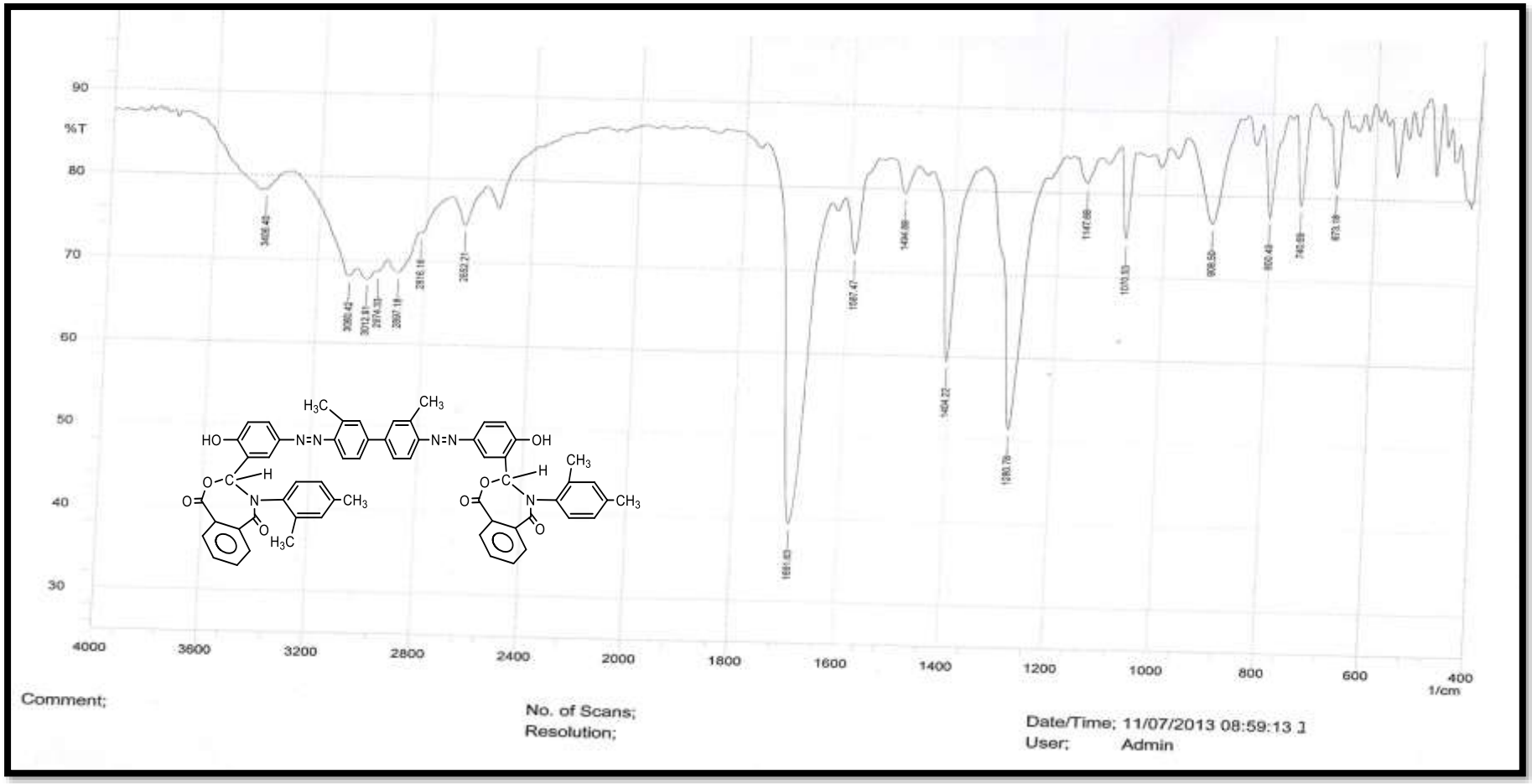


Figure (3-11) : FT-IR spectrum of compound [A_9]

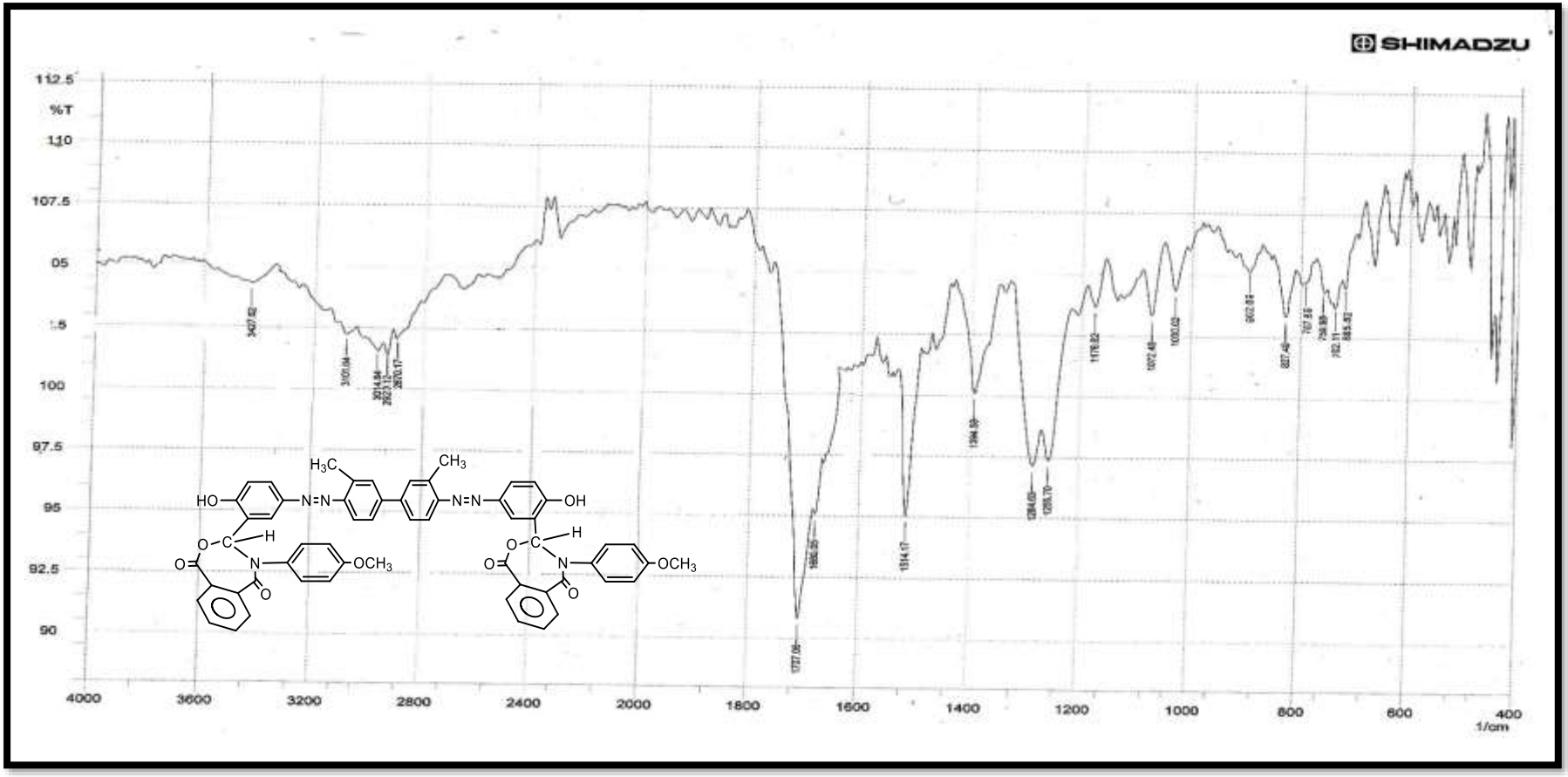


Figure (3-12) : FT-IR spectrum of compound [A_{10}]

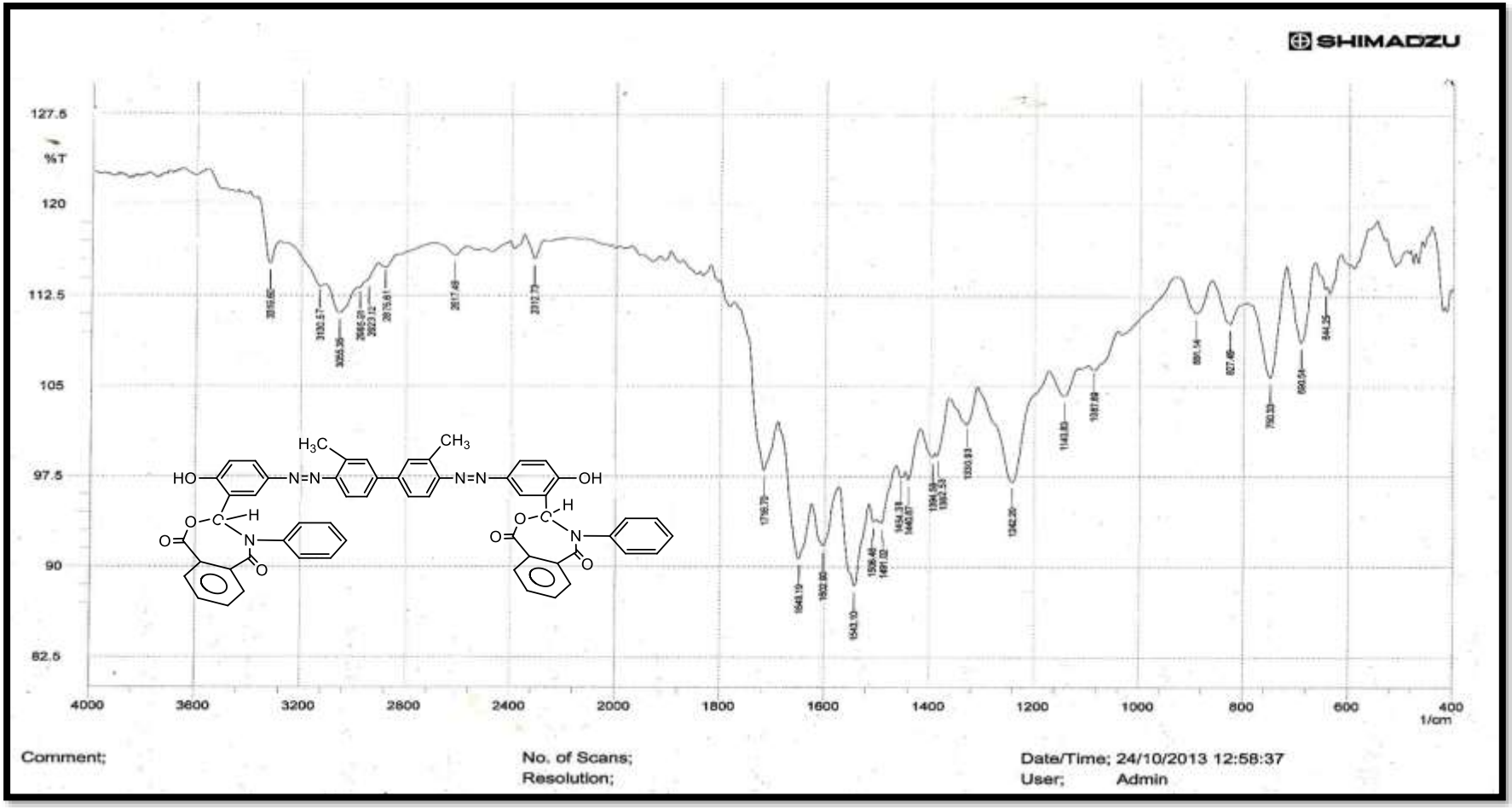


Figure (3-13) : FT-IR spectrum of compound [A_{11}]

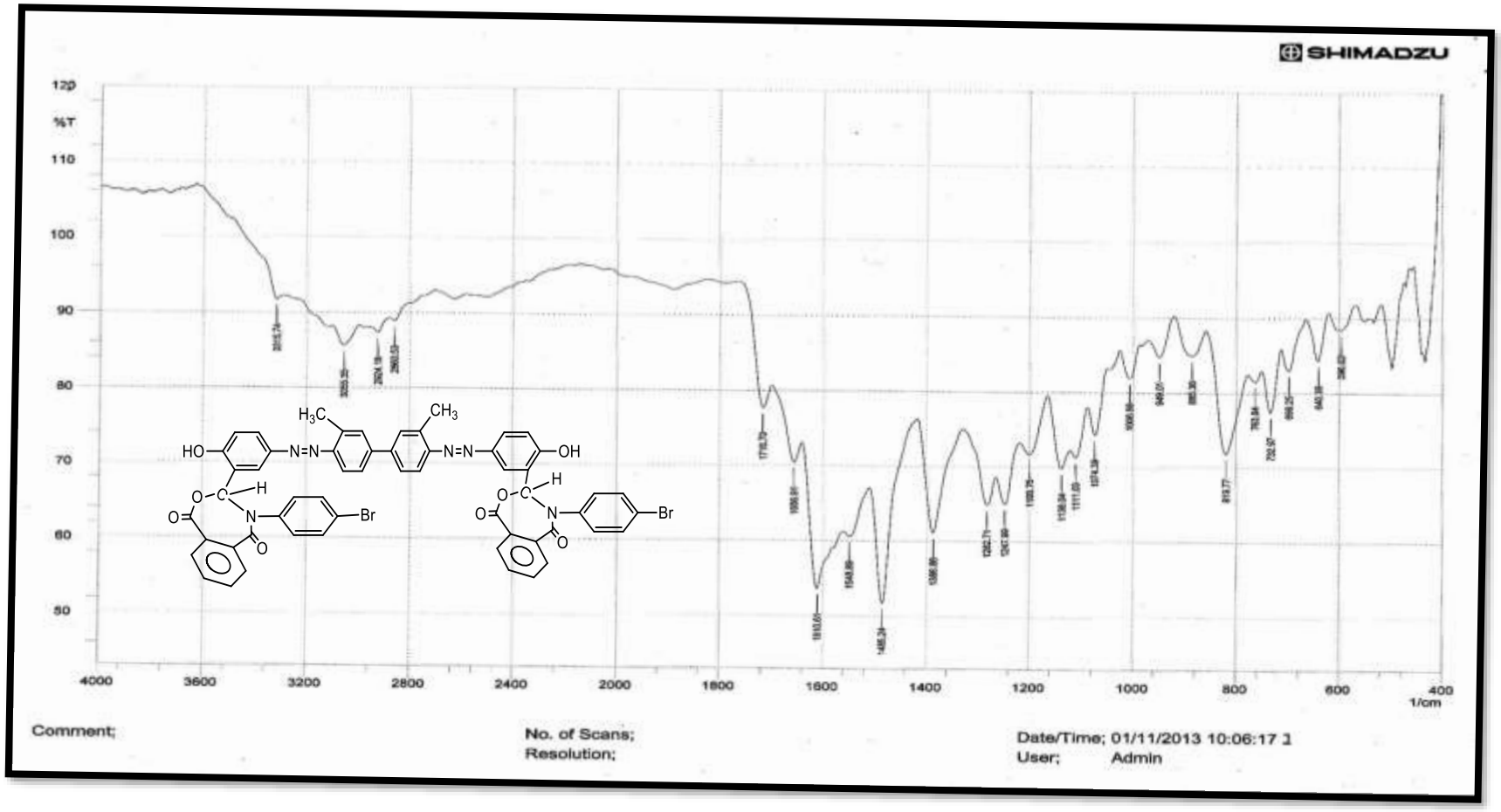


Figure (3-14) : FT-IR spectrum of compound [A_{12}]

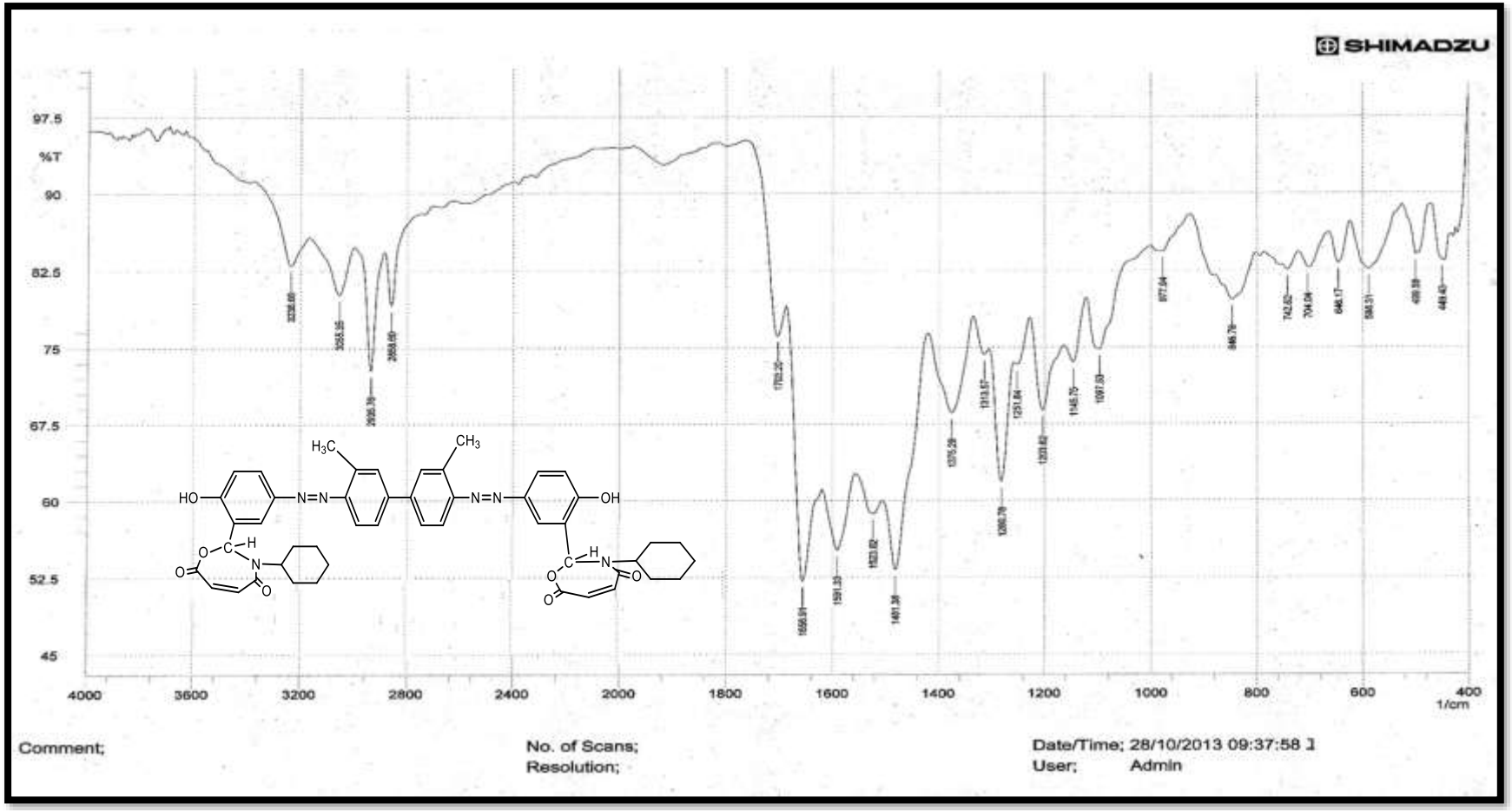


Figure (3-15) : FT-IR spectrum of compound [A_{13}]

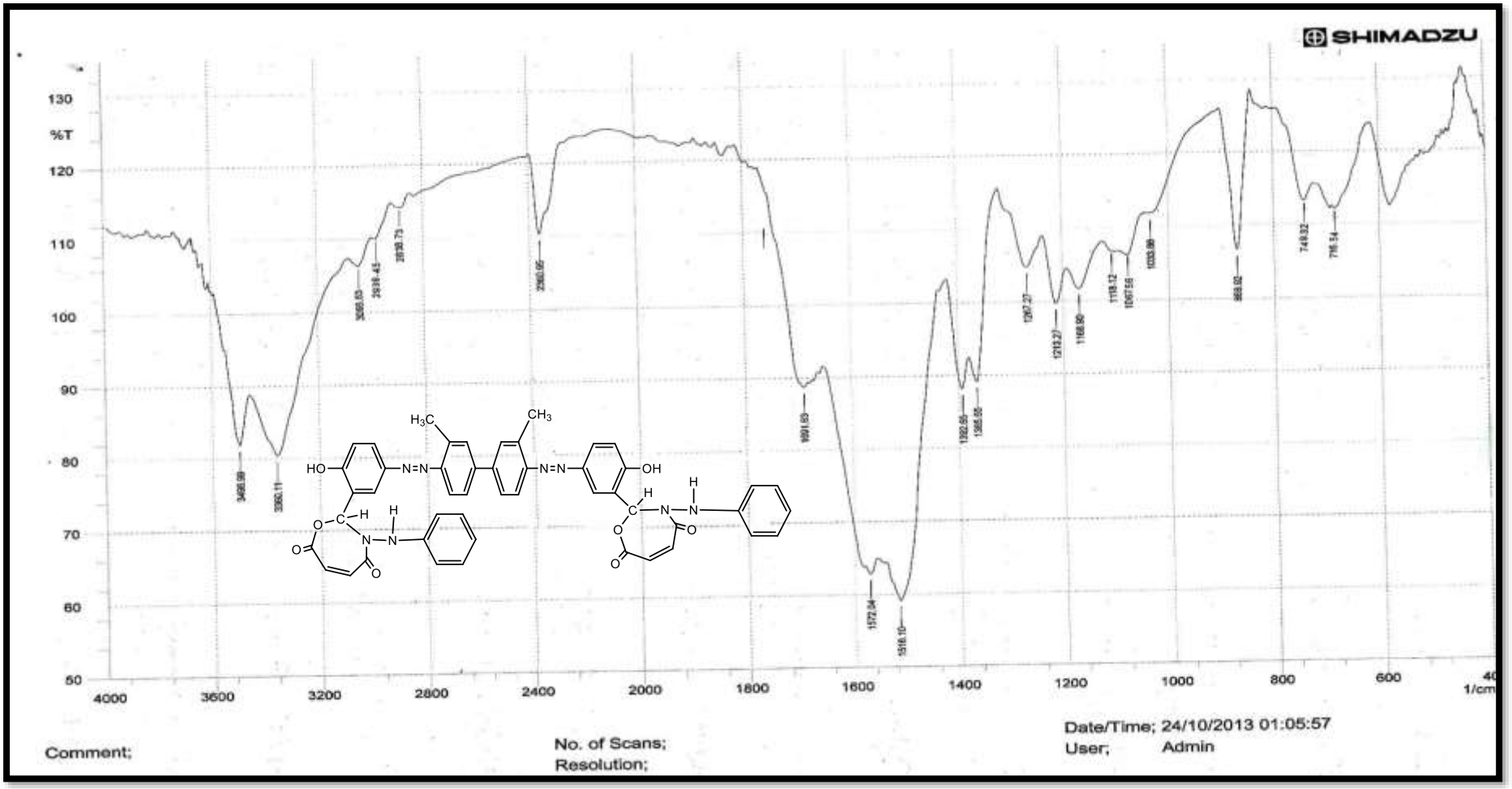


Figure (3-16) : FT-IR spectrum of compound [A_{14}]

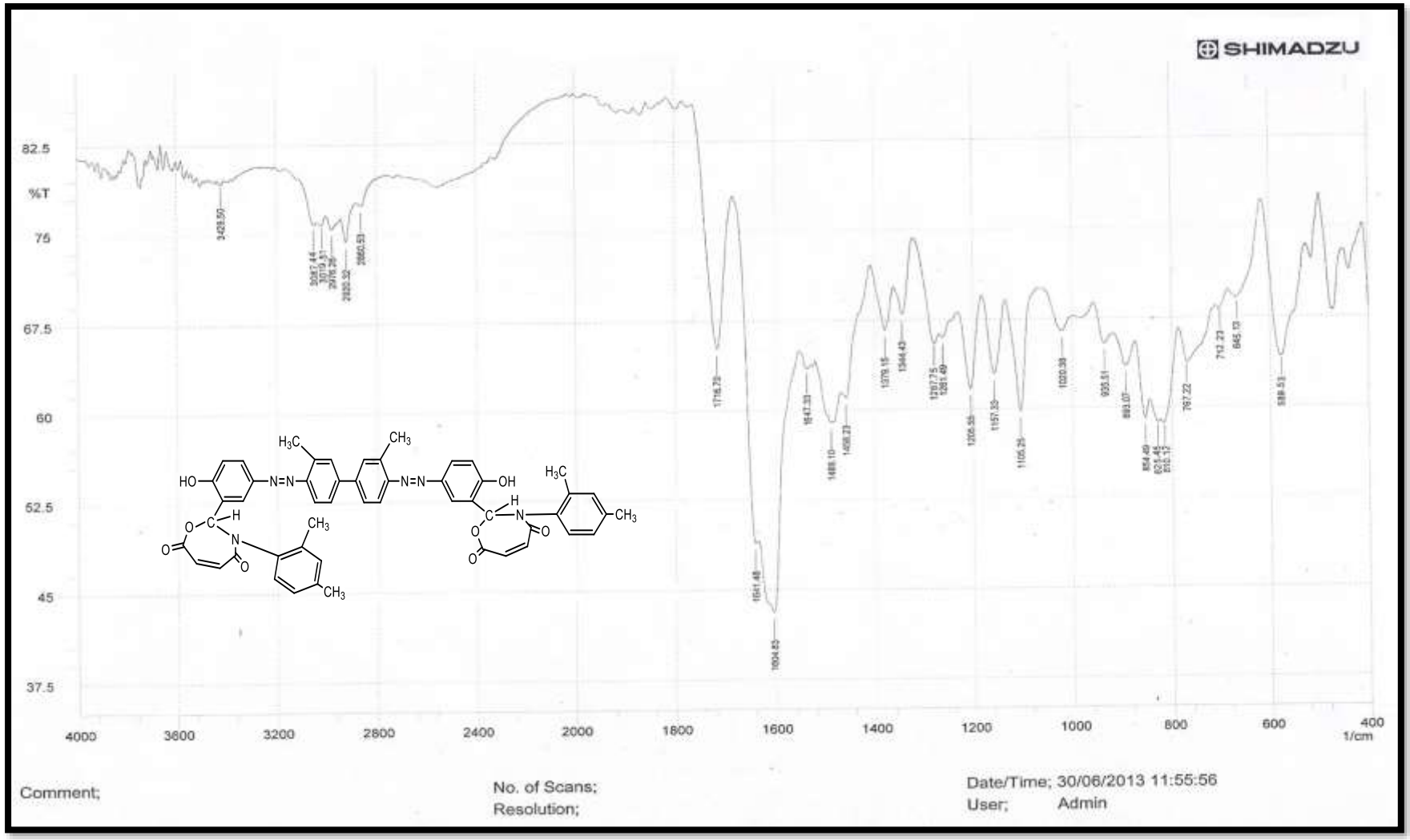


Figure (3-17) : FT-IR spectrum of compound [A_{15}]

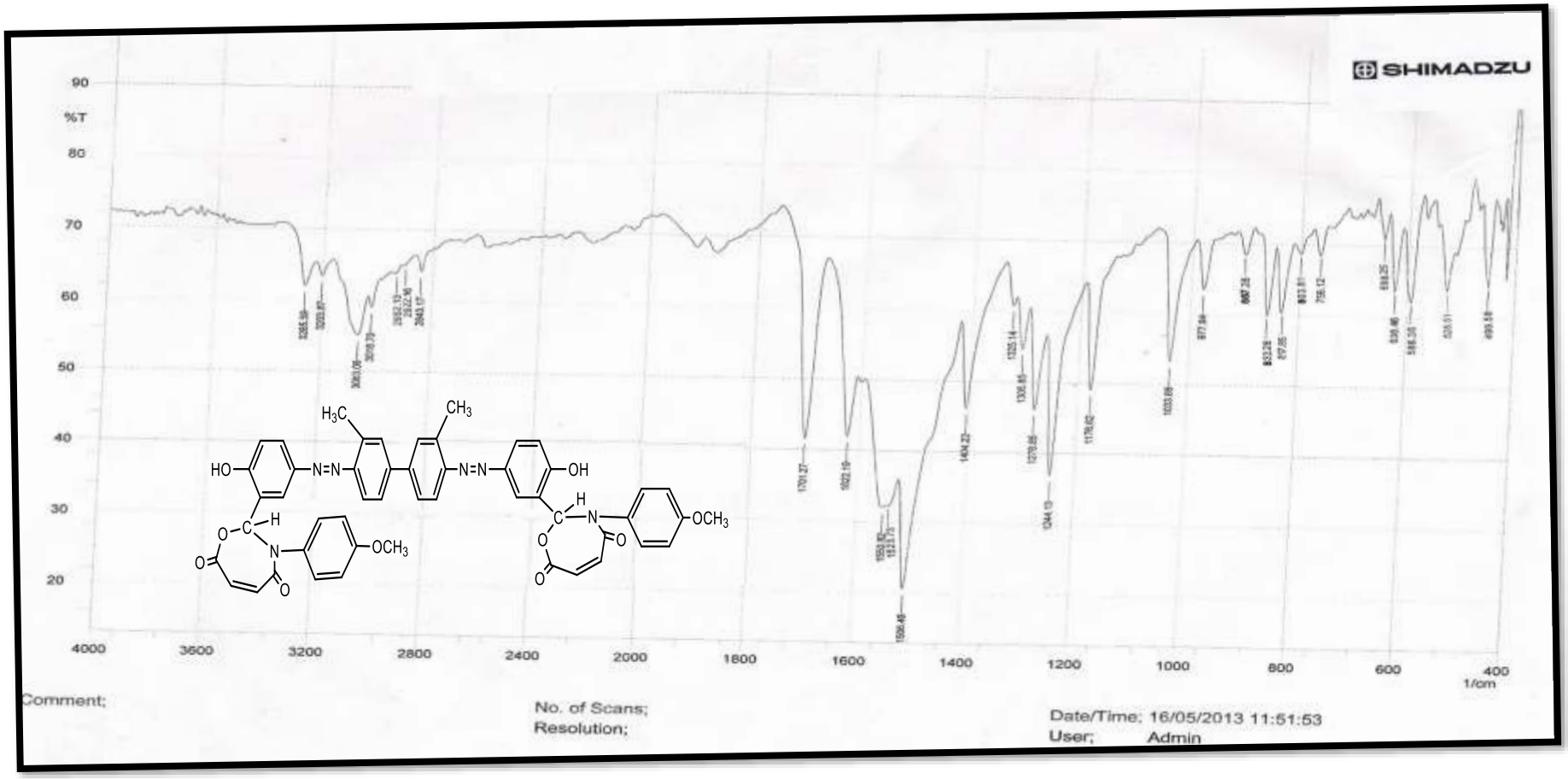


Figure (3-18) : FT-IR spectrum of compound [A_{16}]

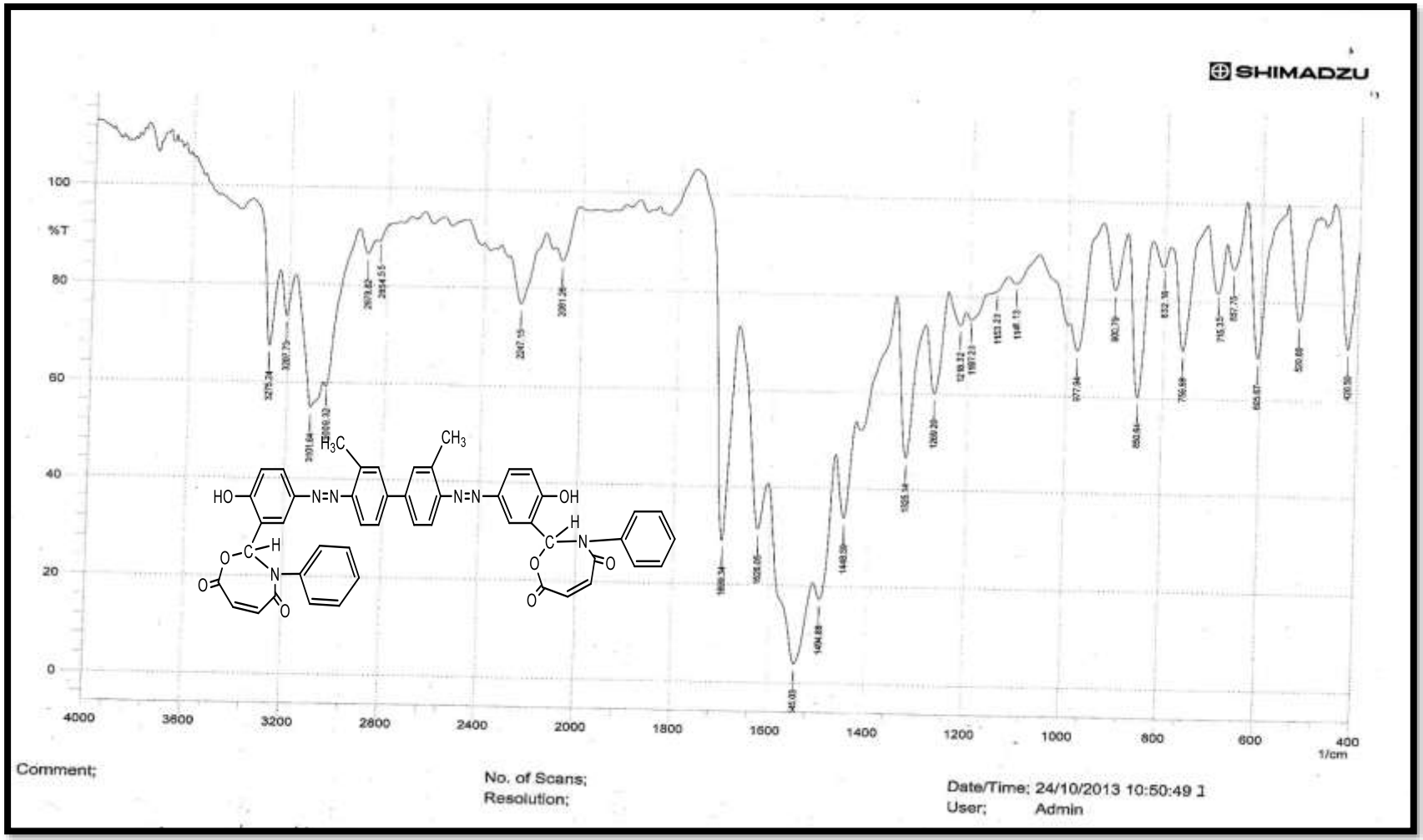


Figure (3-19) : FT-IR spectrum of compound [A_{17}]

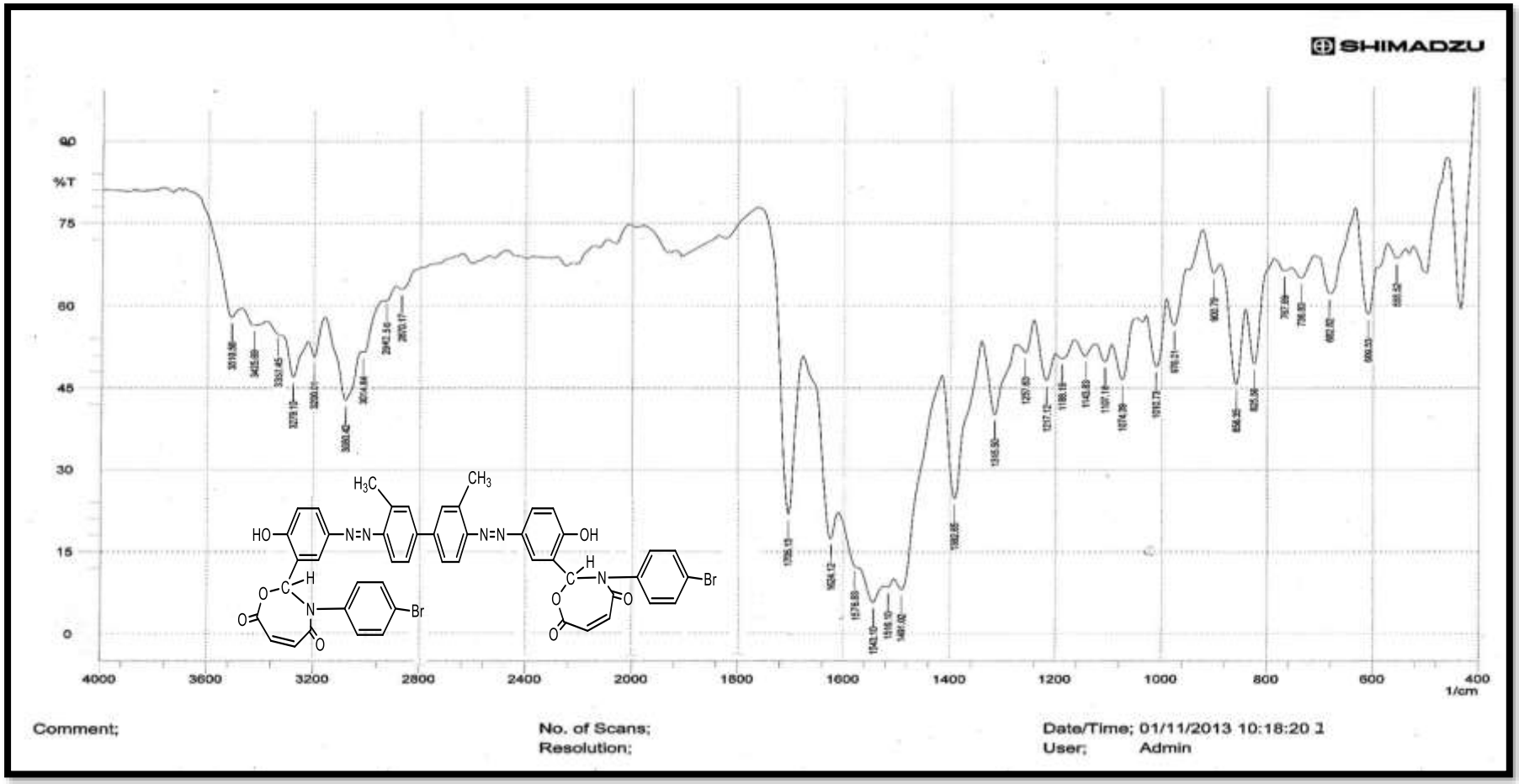


Figure (3-20) : FT-IR spectrum of compound [A_{18}]

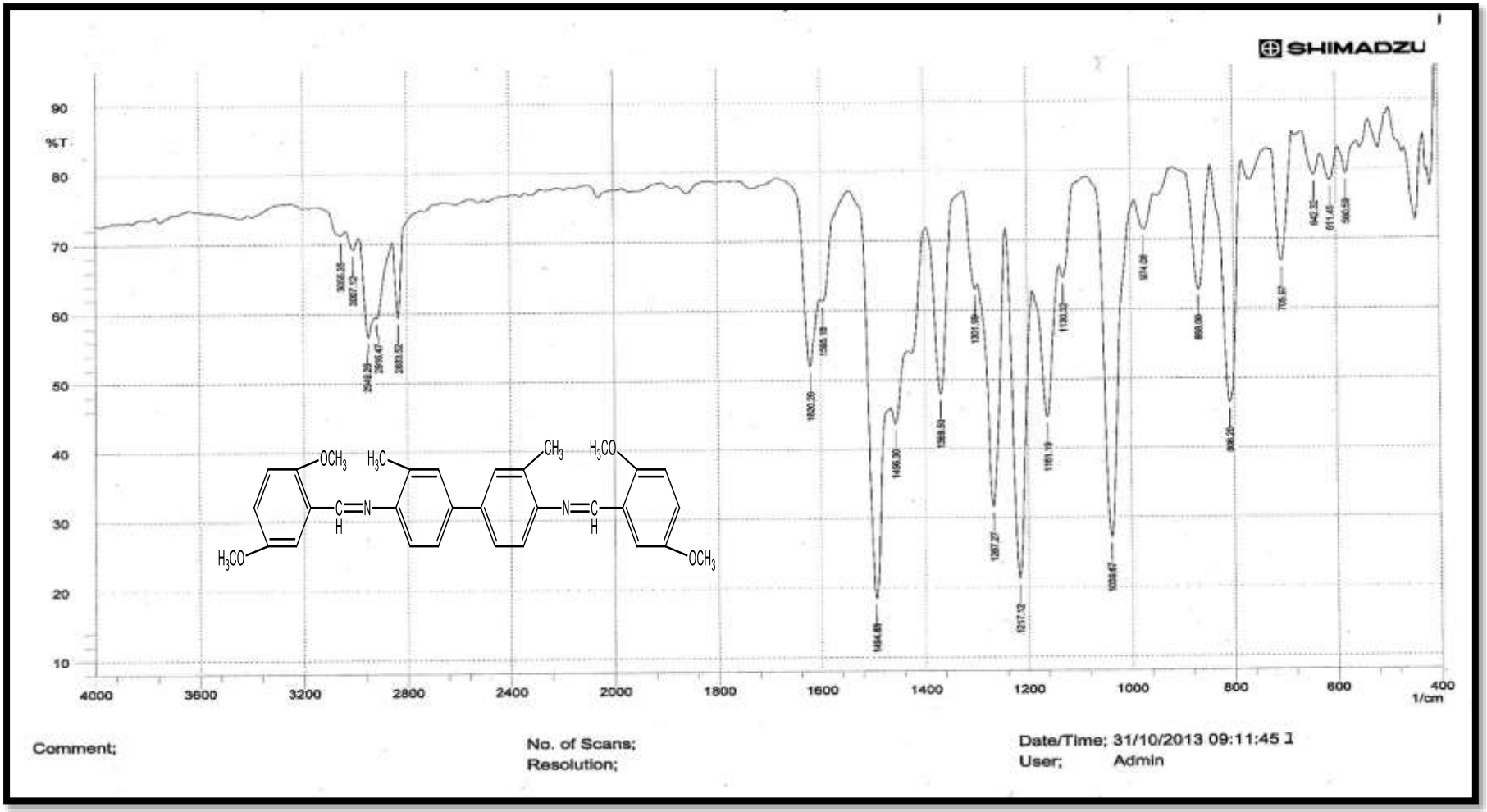


Figure (3-21) : FT-IR spectrum of compound [B_1]

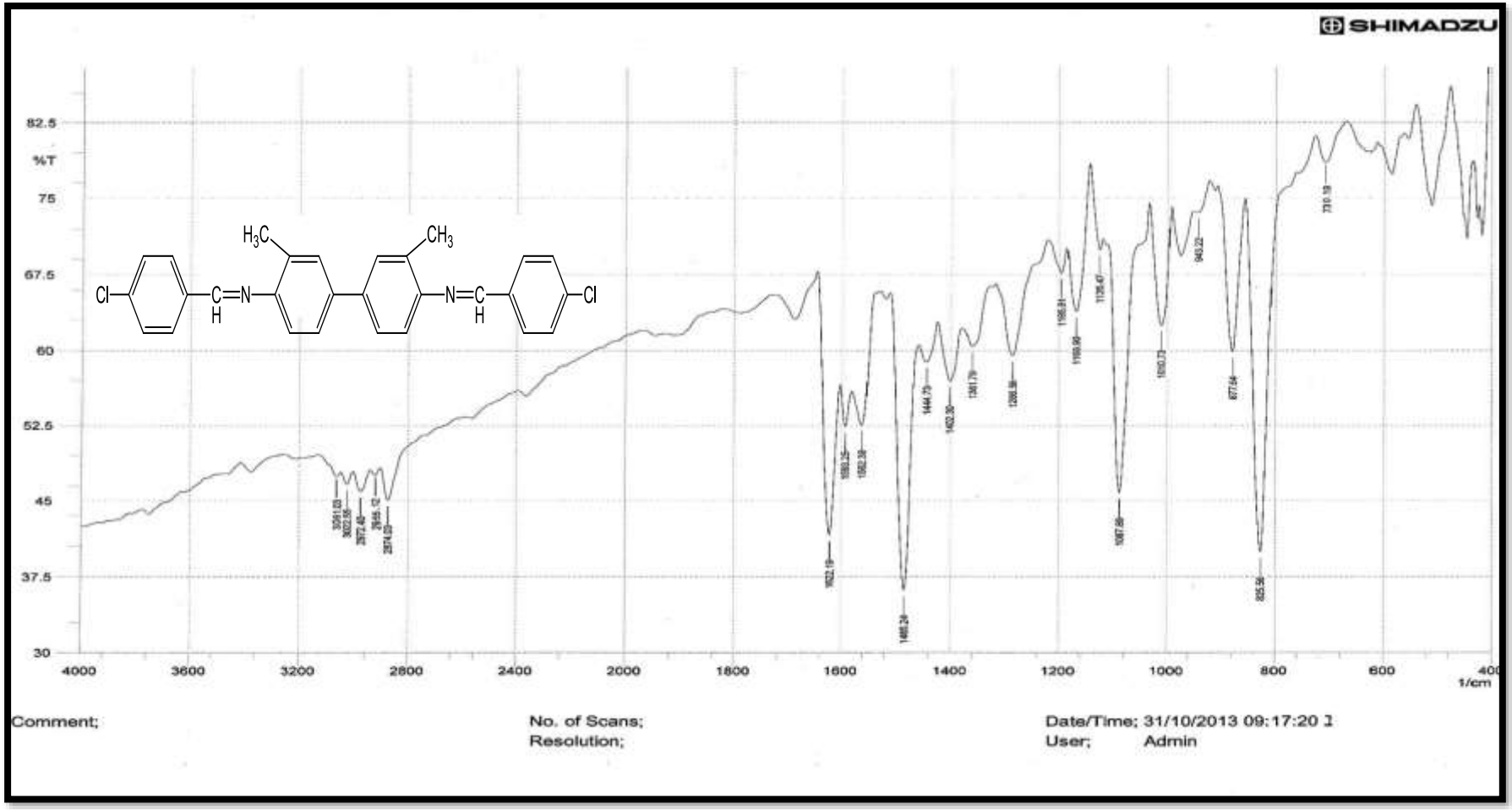


Figure (3-22) : FT-IR spectrum of compound [B_2]

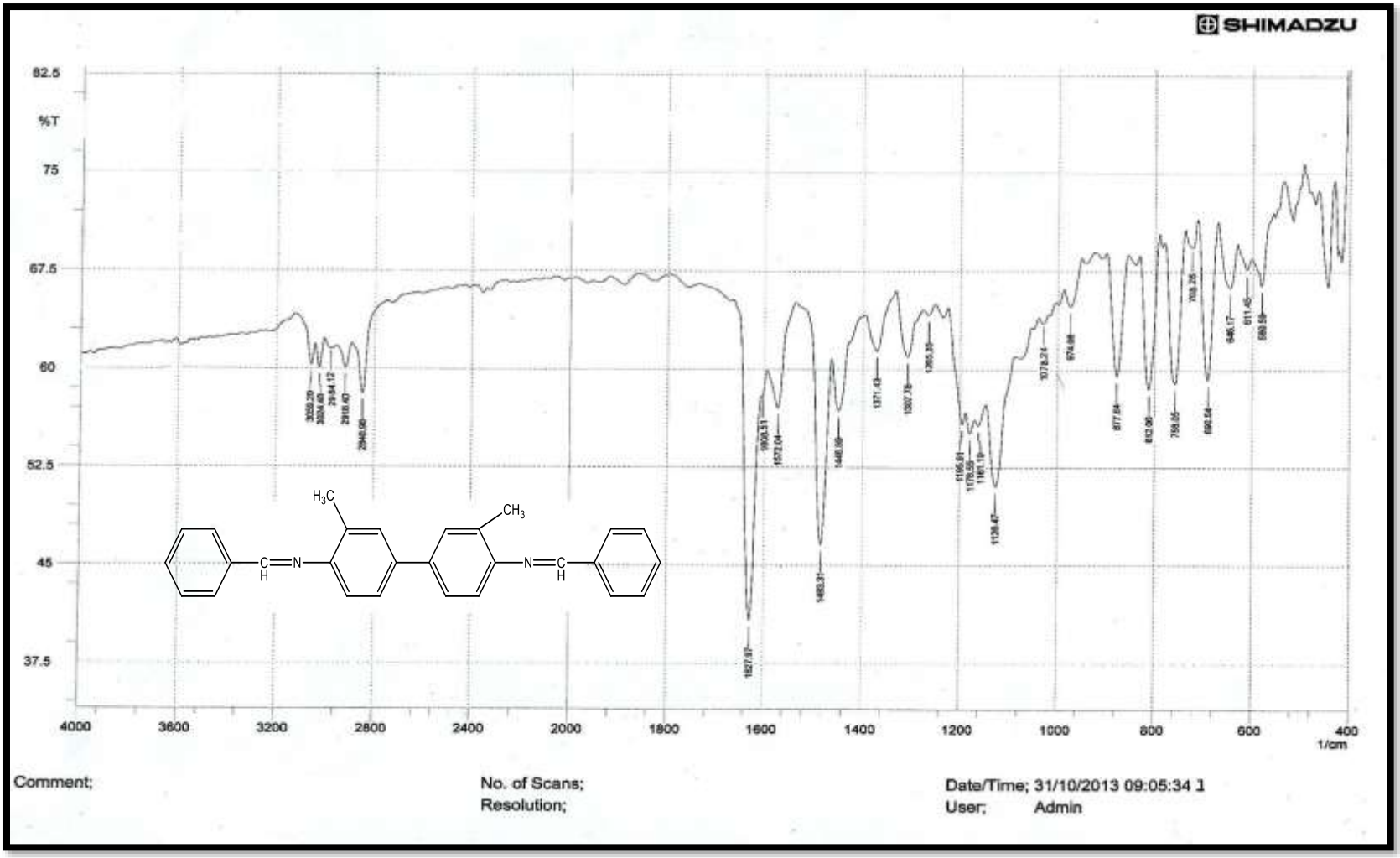


Figure (3-23) : FT-IR spectrum of compound [B_3]

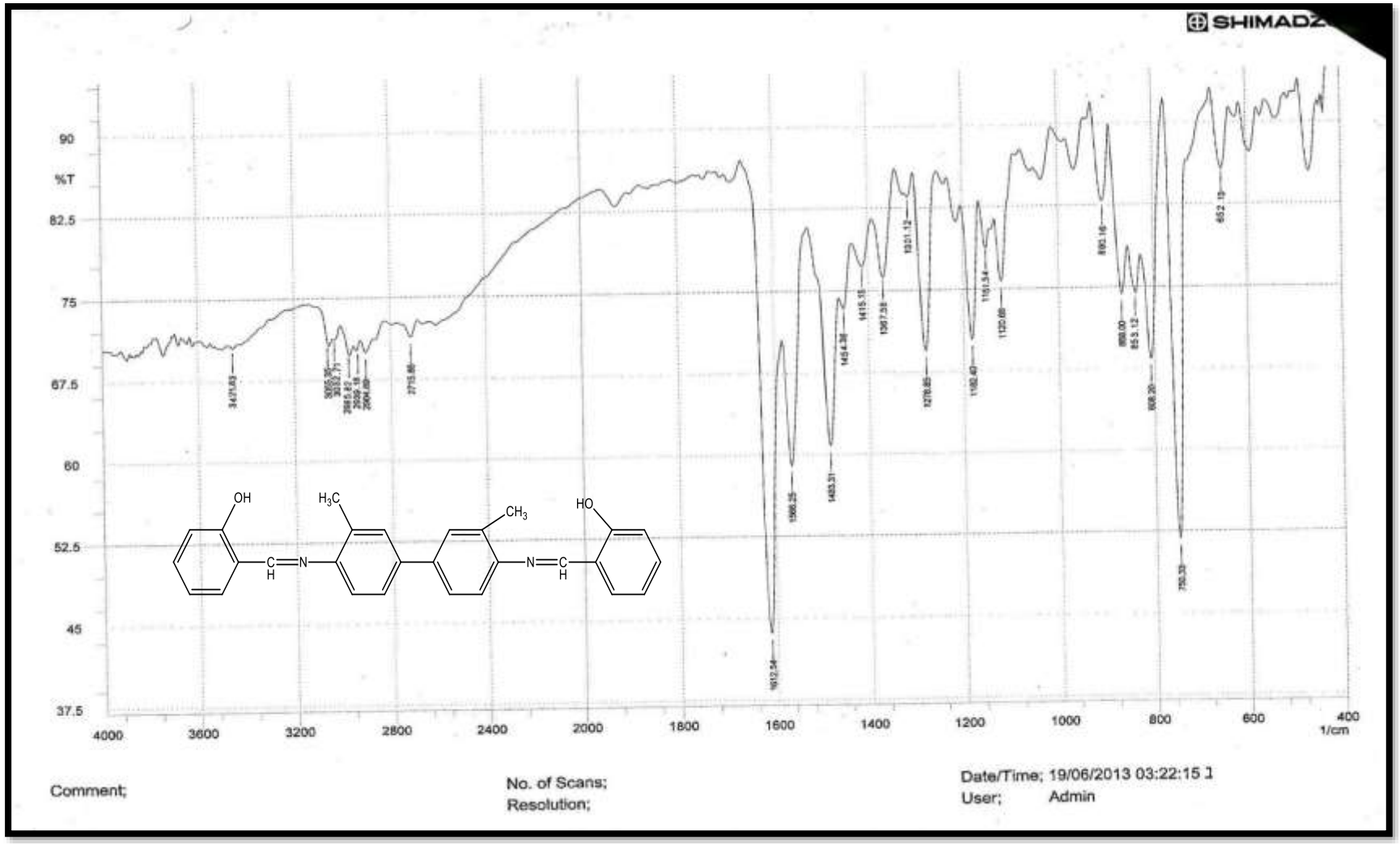


Figure (3-24) : FT-IR spectrum of compound [B_4]

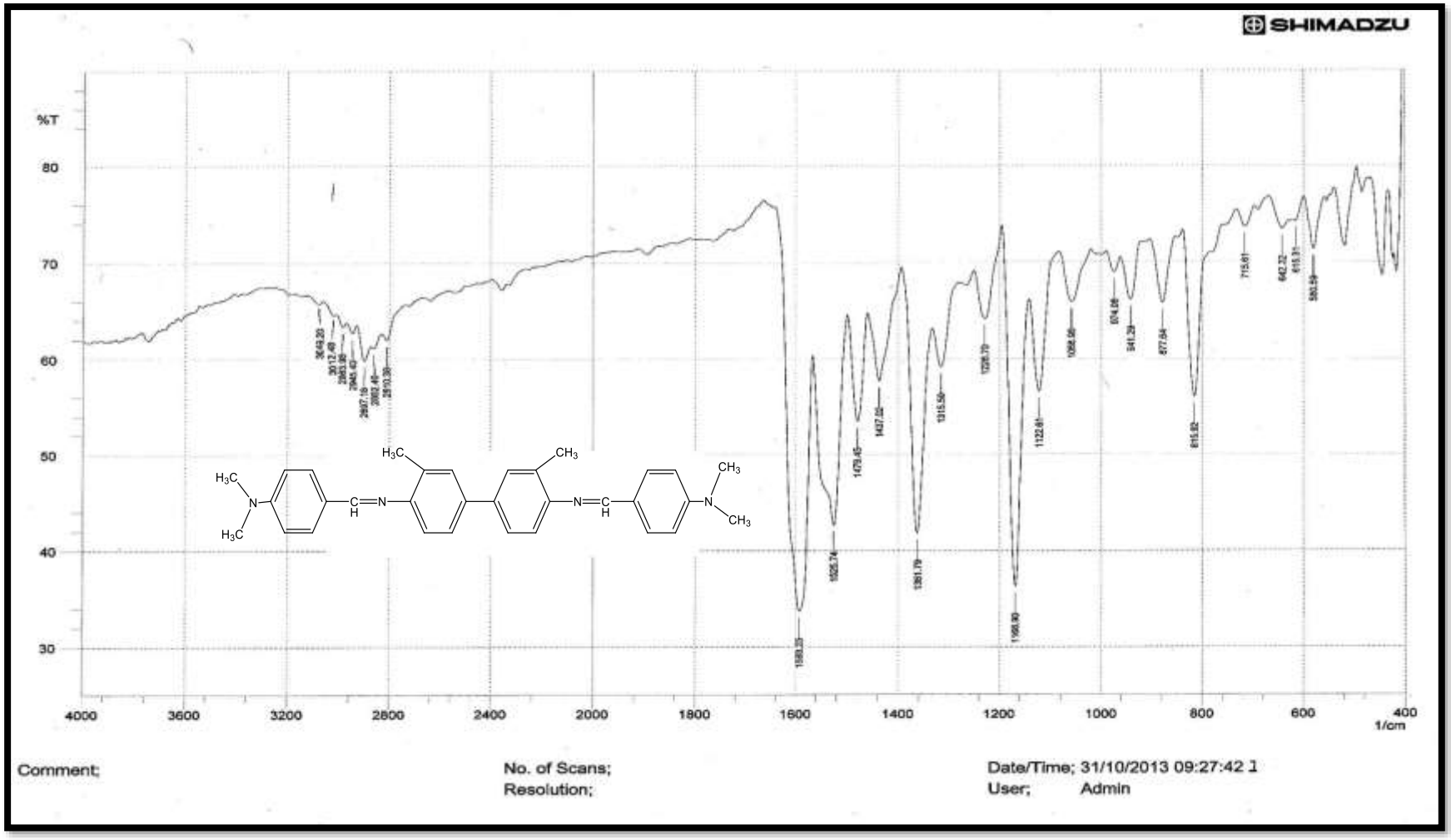


Figure (3-25) : FT-IR spectrum of compound [B_5]

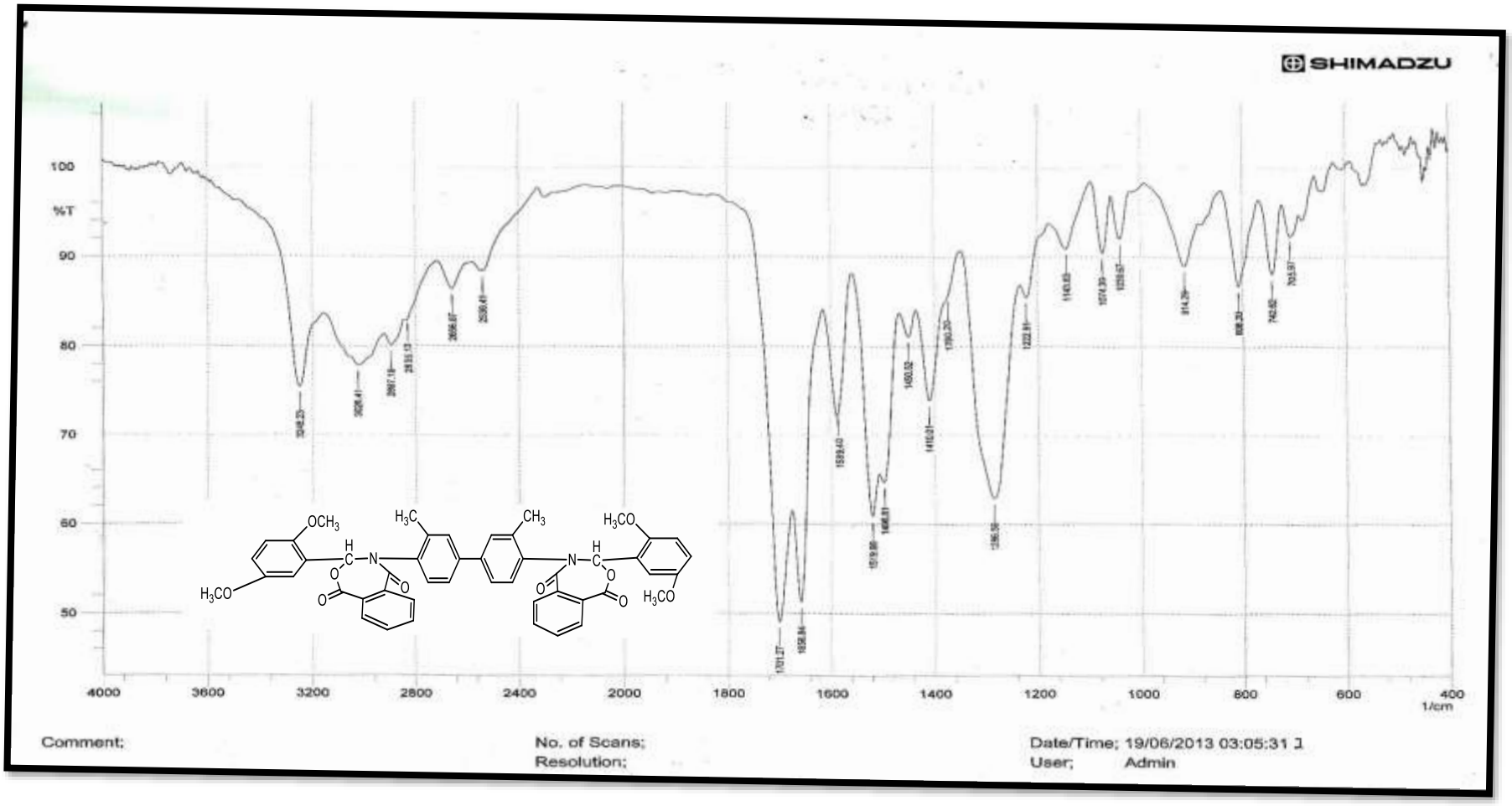


Figure (3-26) : FT-IR spectrum of compound [B_6]

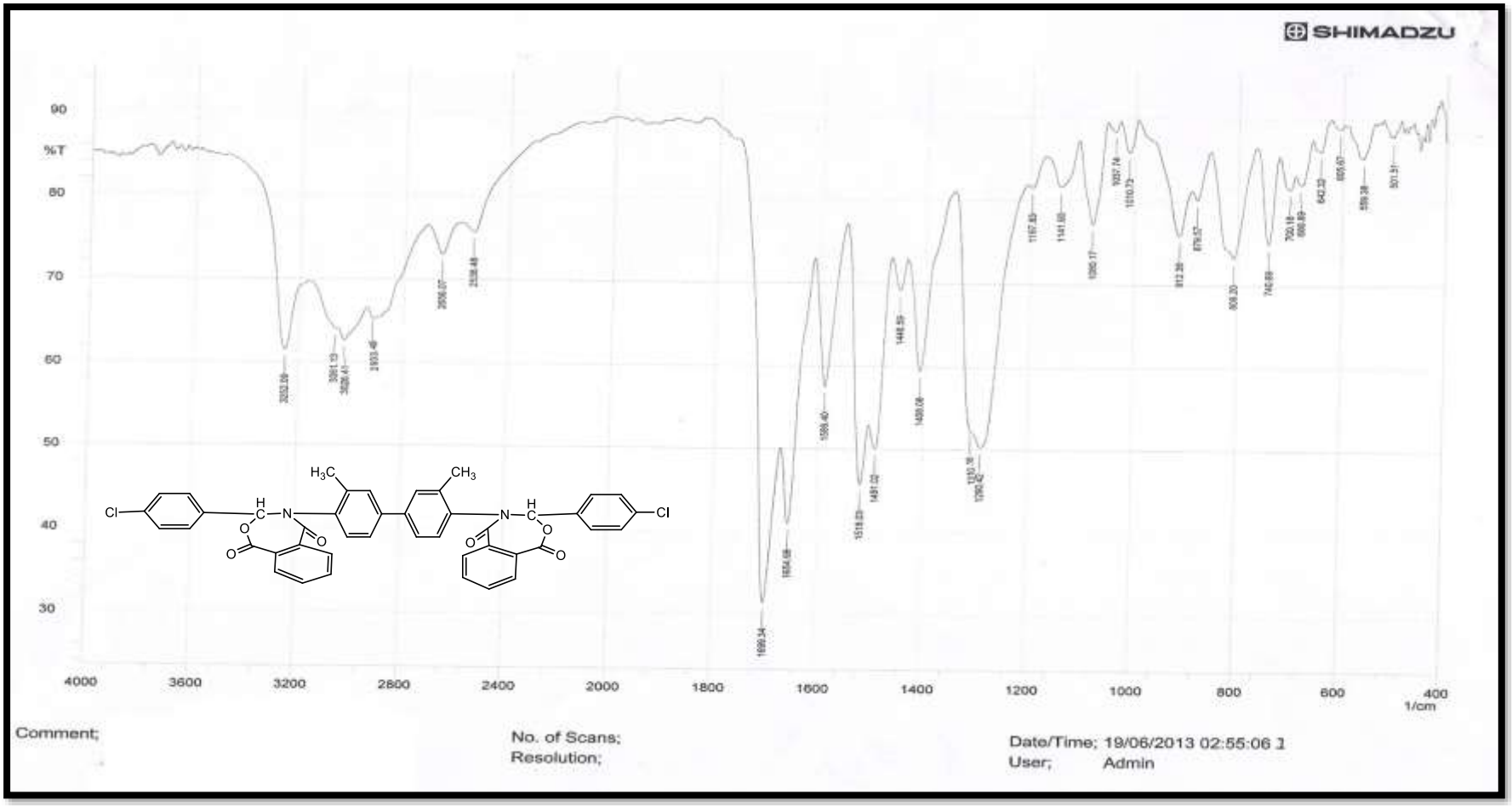


Figure (3-27) : FT-IR spectrum of compound [B_7]

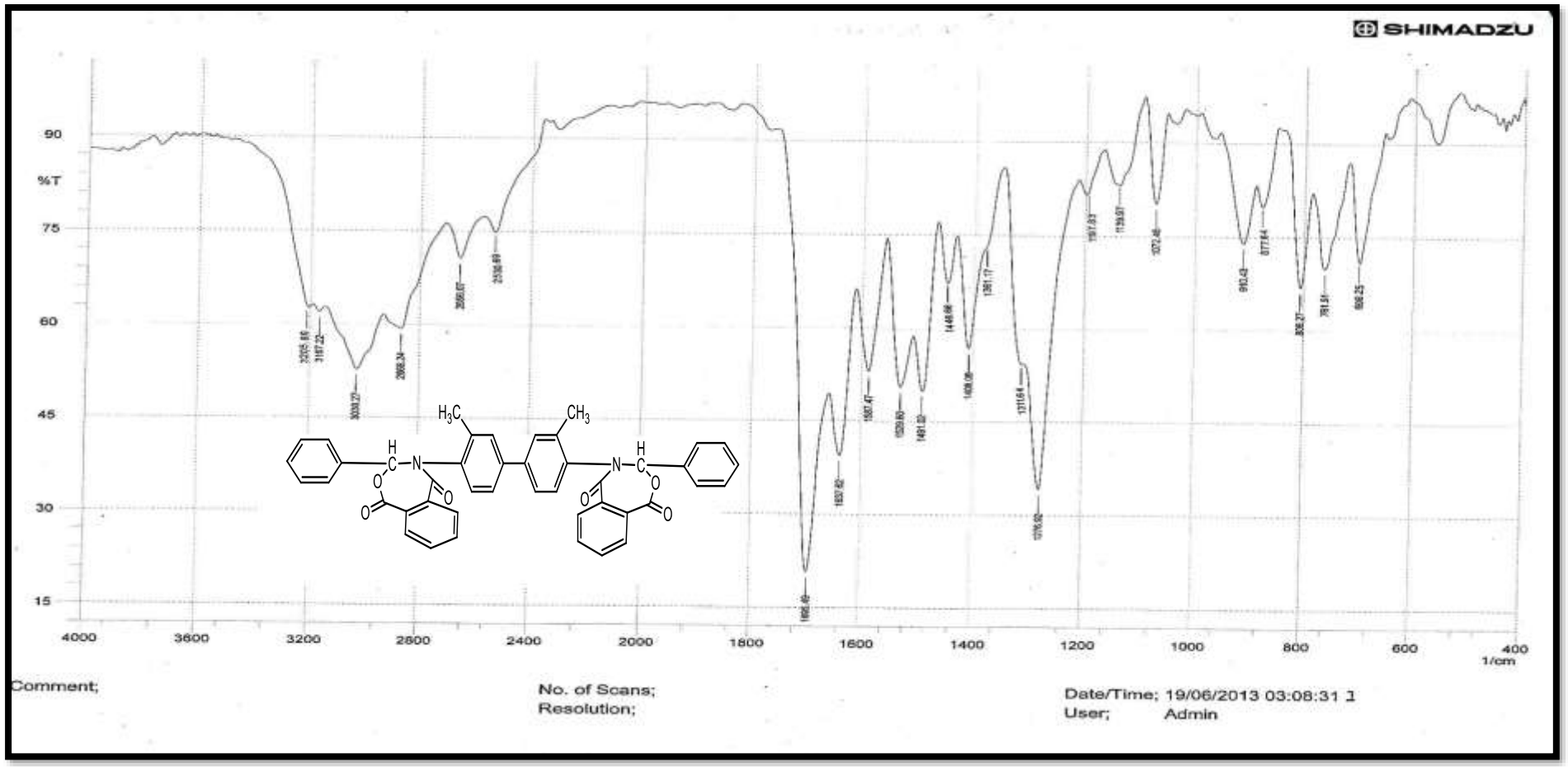


Figure (3-28) : FT-IR sbectrum of compound [B_8]

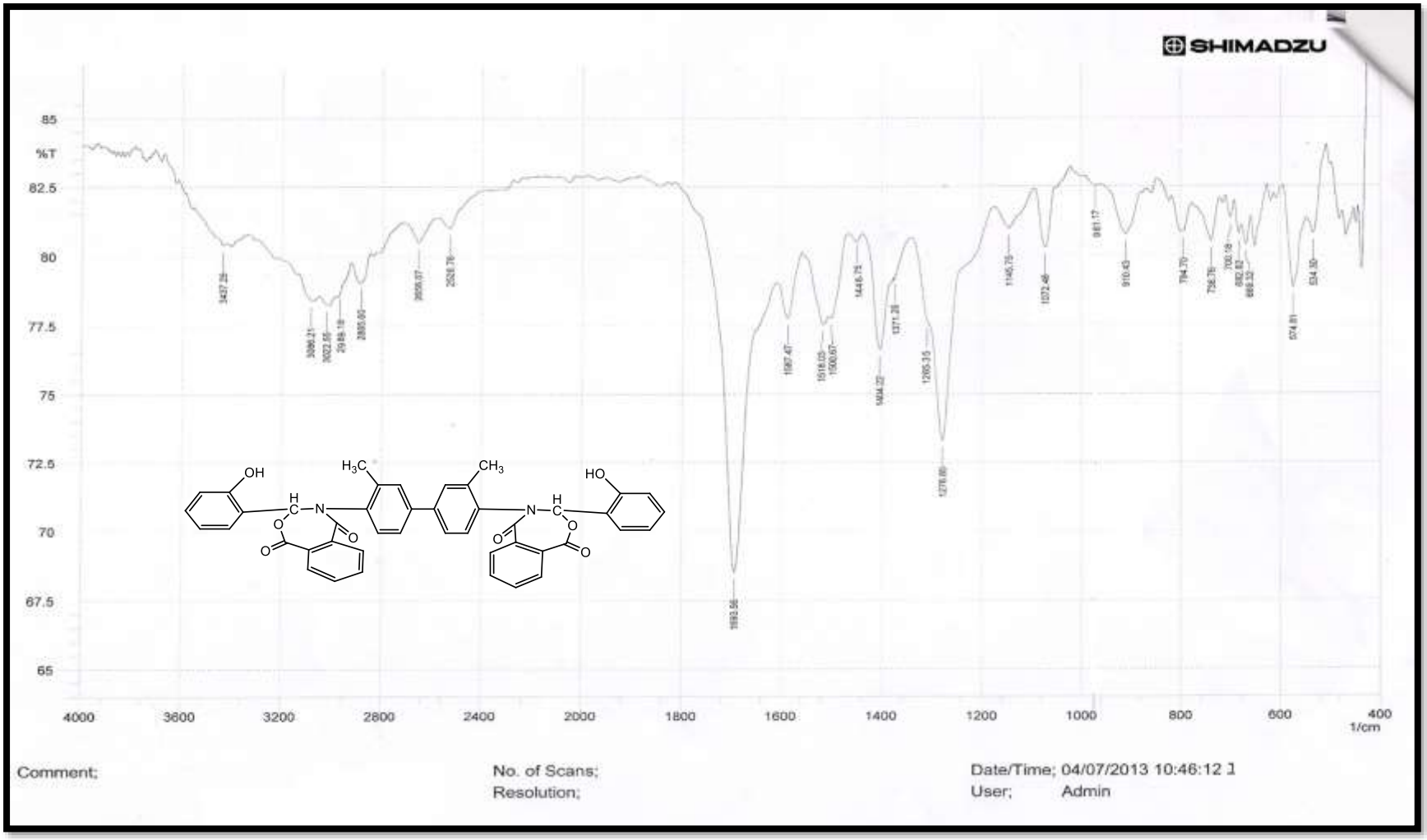


Figure (3-29) : FT-IR spectrum of compound [B_9]

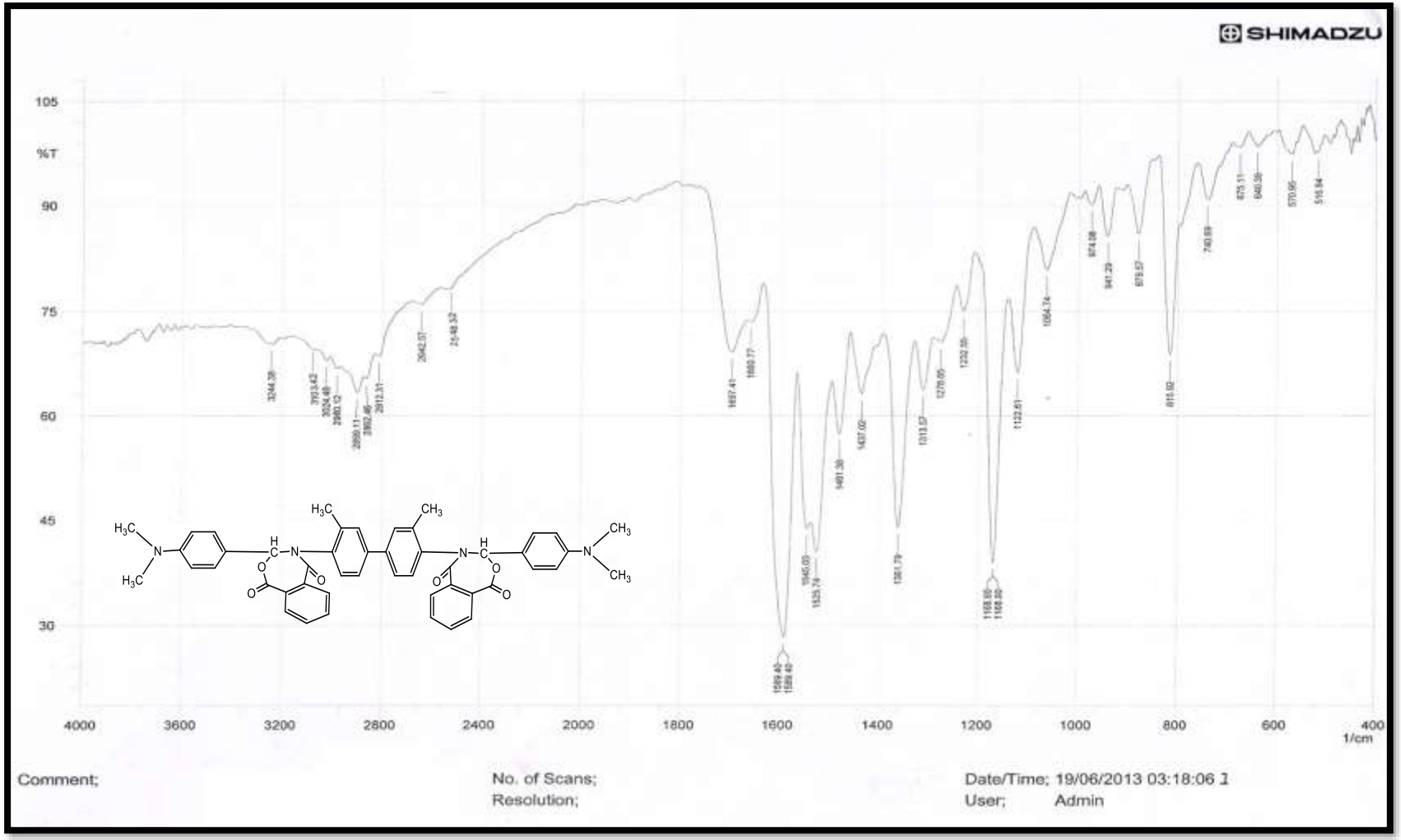


Figure (3-30) : FT-IR spectrum of compound [B_{10}]

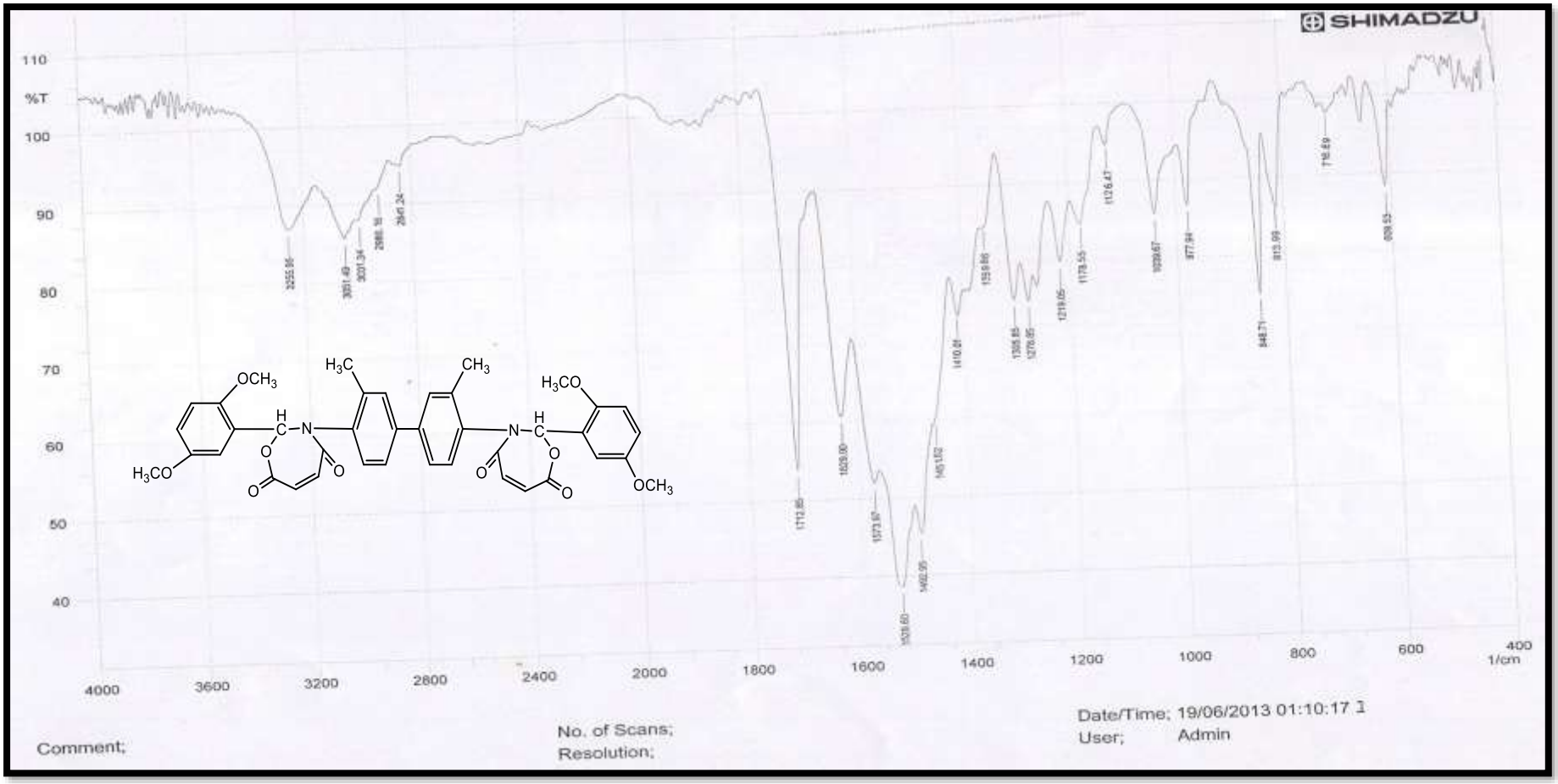


Figure (3-31) :FT-IR spectrum of compound [B_{11}]

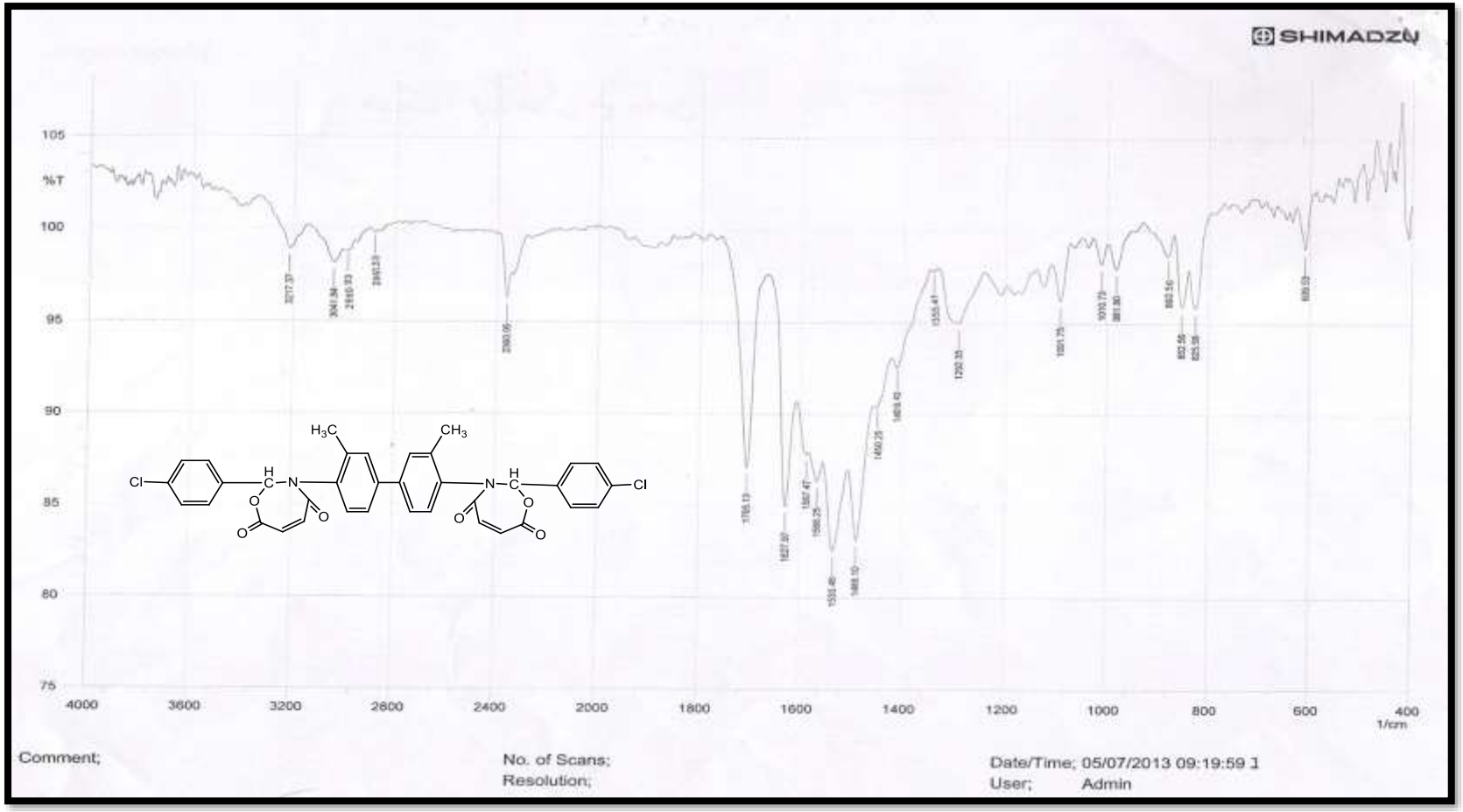


Figure (3-32) :FT-IR spectrum of compound [B_{12}]

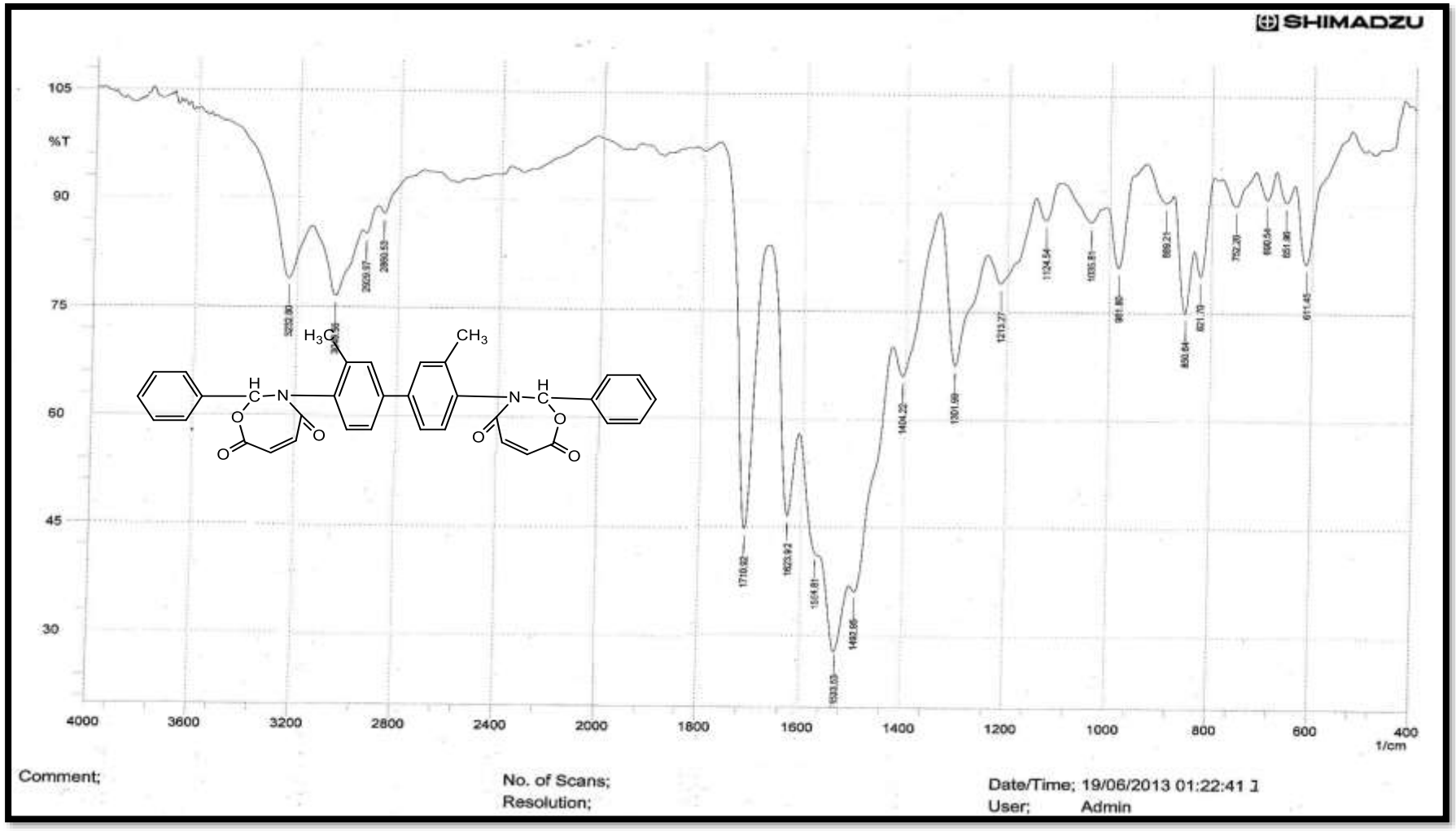


Figure (3-33) : FT-IR spectrum of compound [B_{13}]

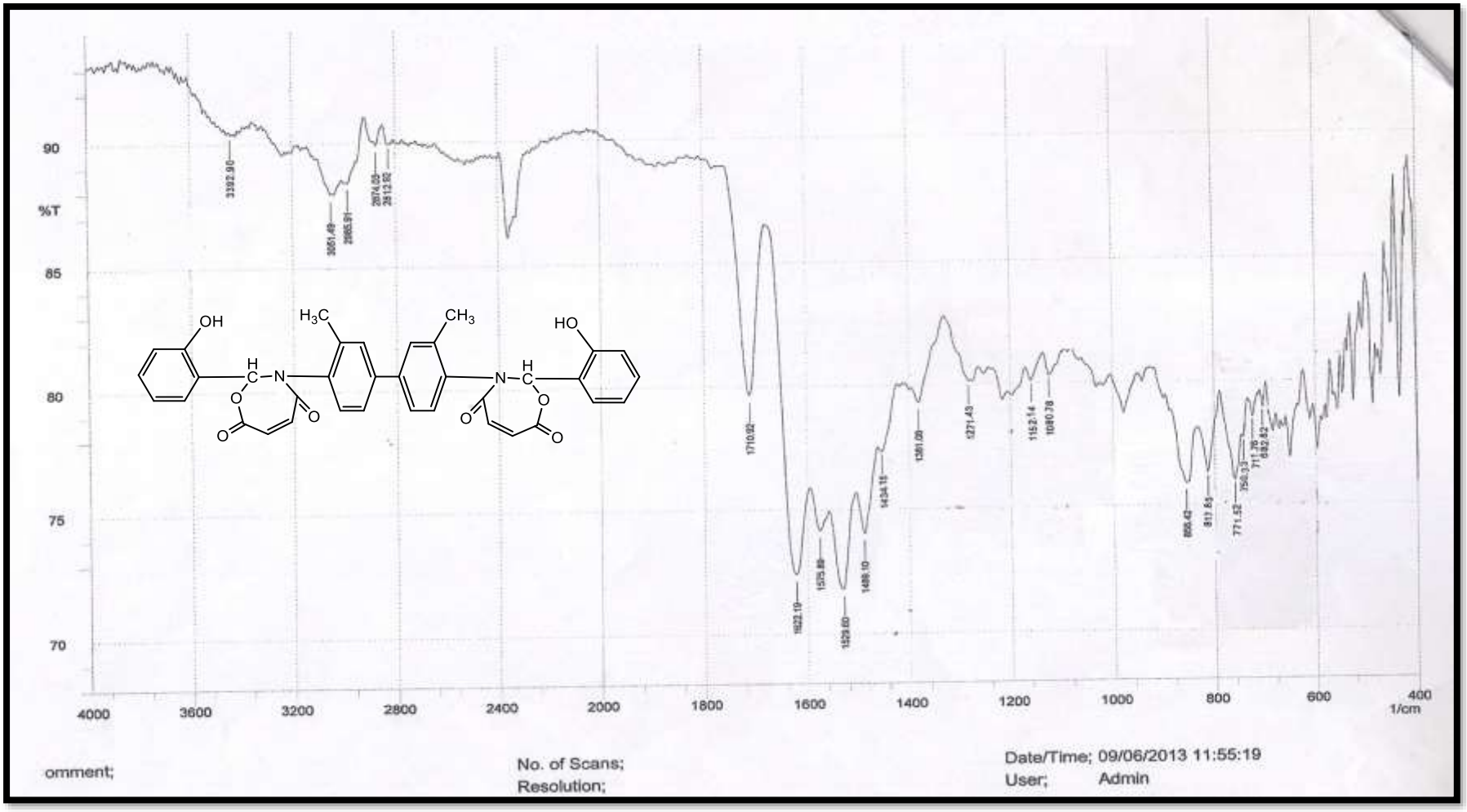


Figure (3-34) : FT-IR spectrum of compound [B_{14}]

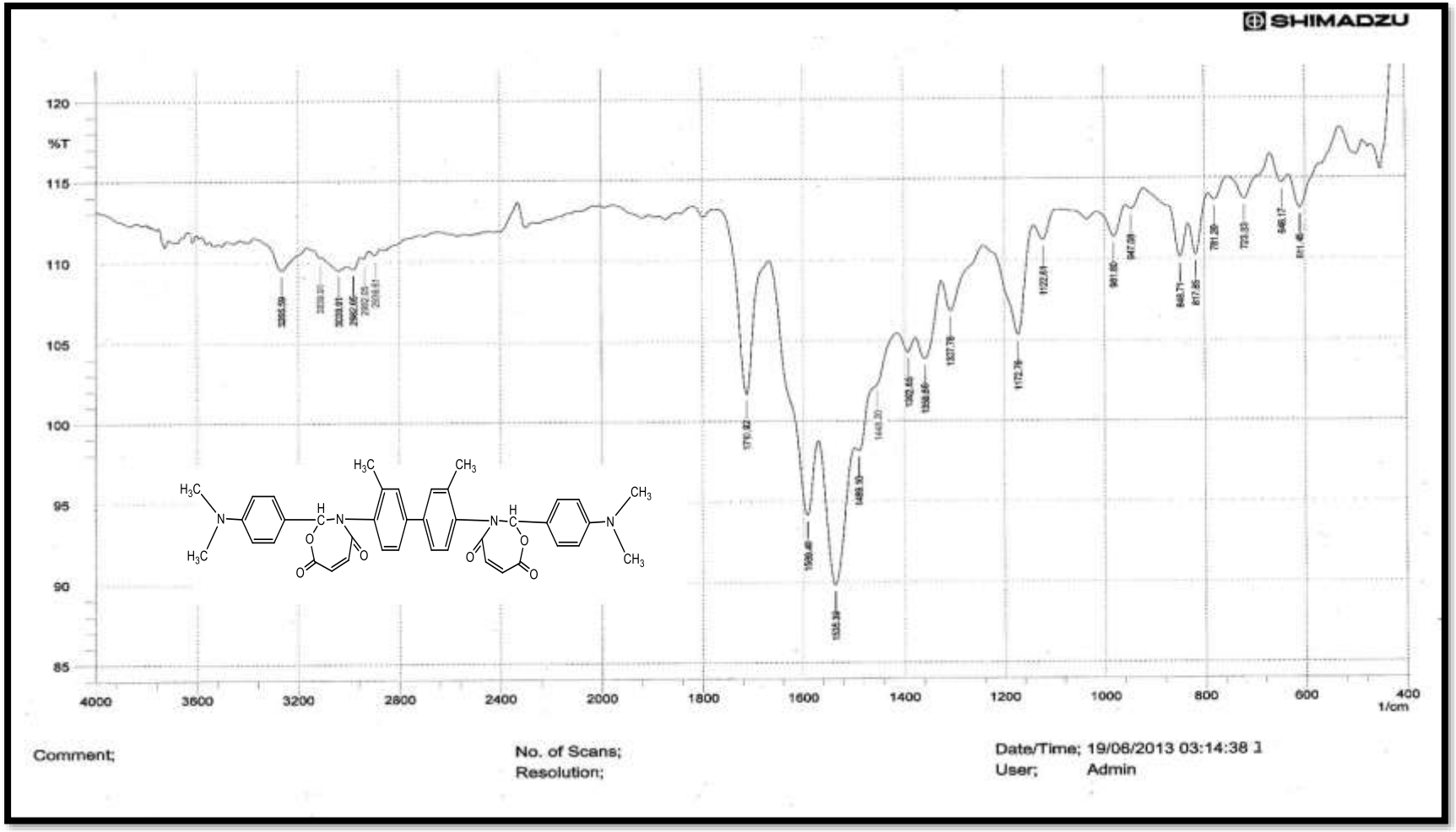


Figure (3-35) : FT-IR spectrum of compound [B_{15}]

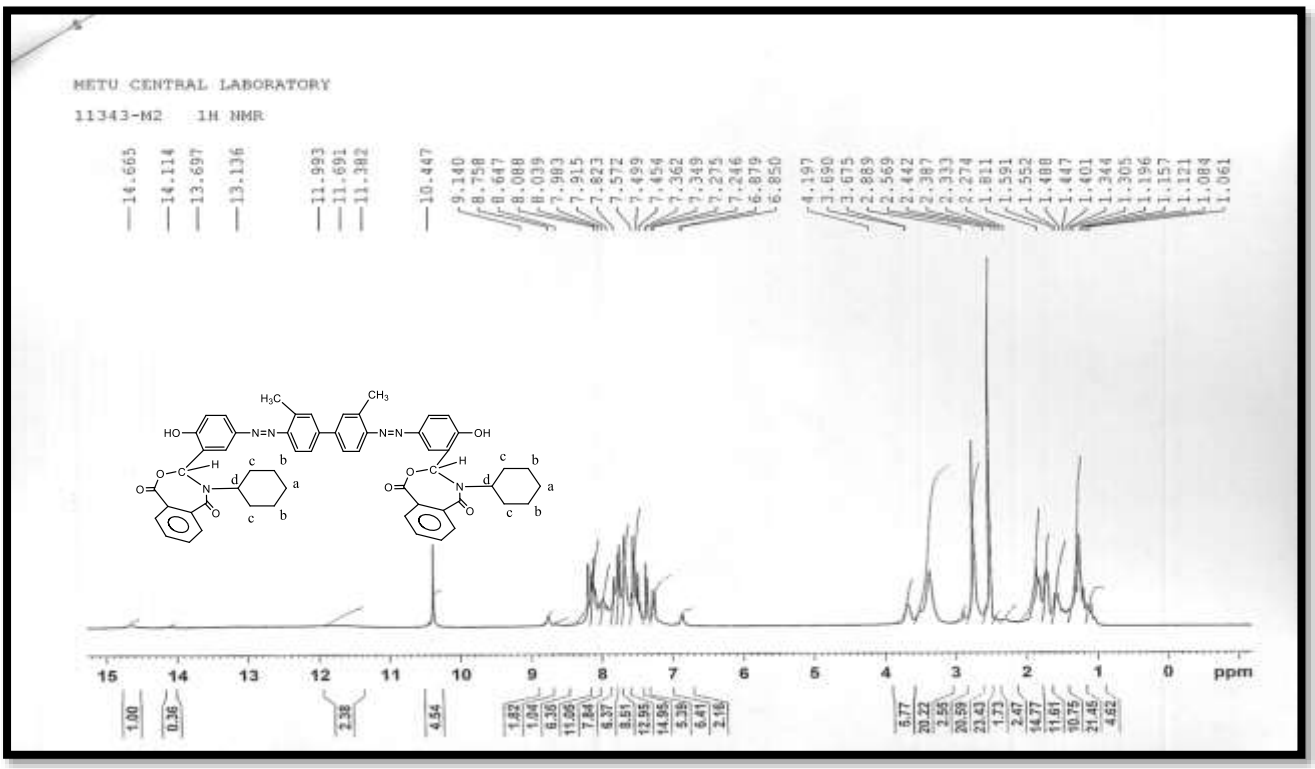


Figure (3-36) : ^{1}H NMR spectrum of compound [A_7]

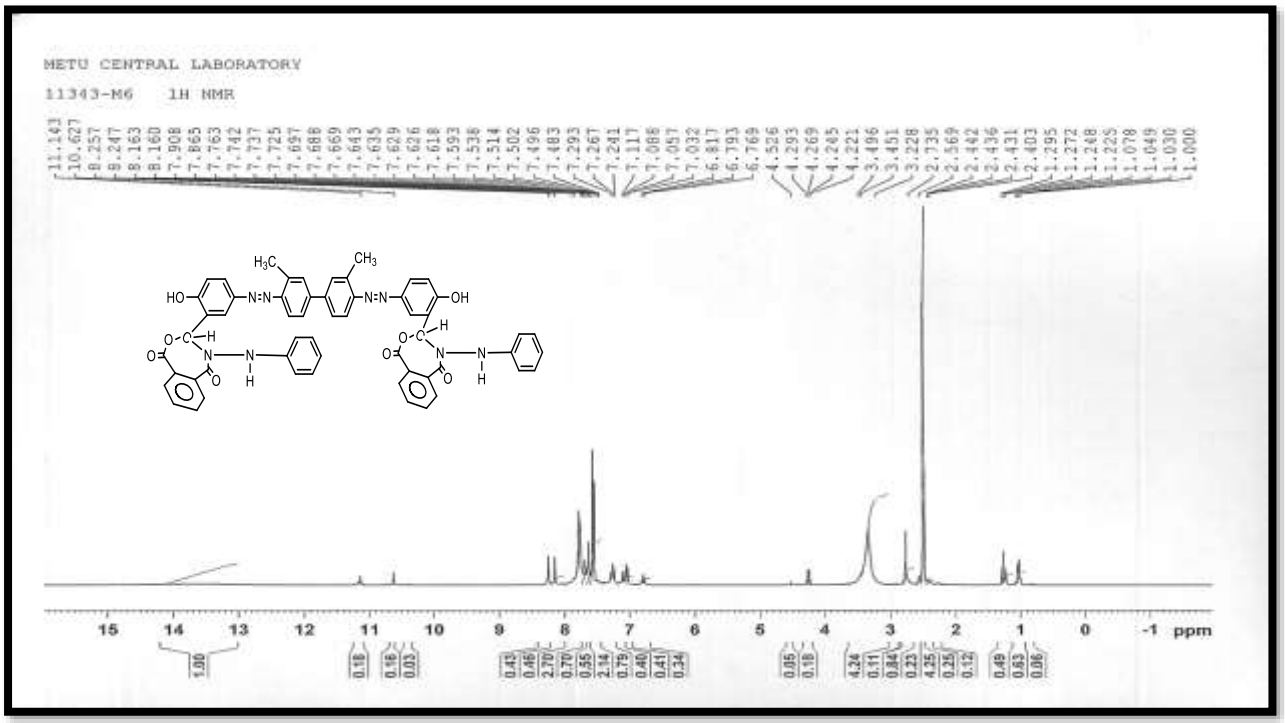


Figure (3-37) : ^{1}H NMR spectrum of compound [A_8]

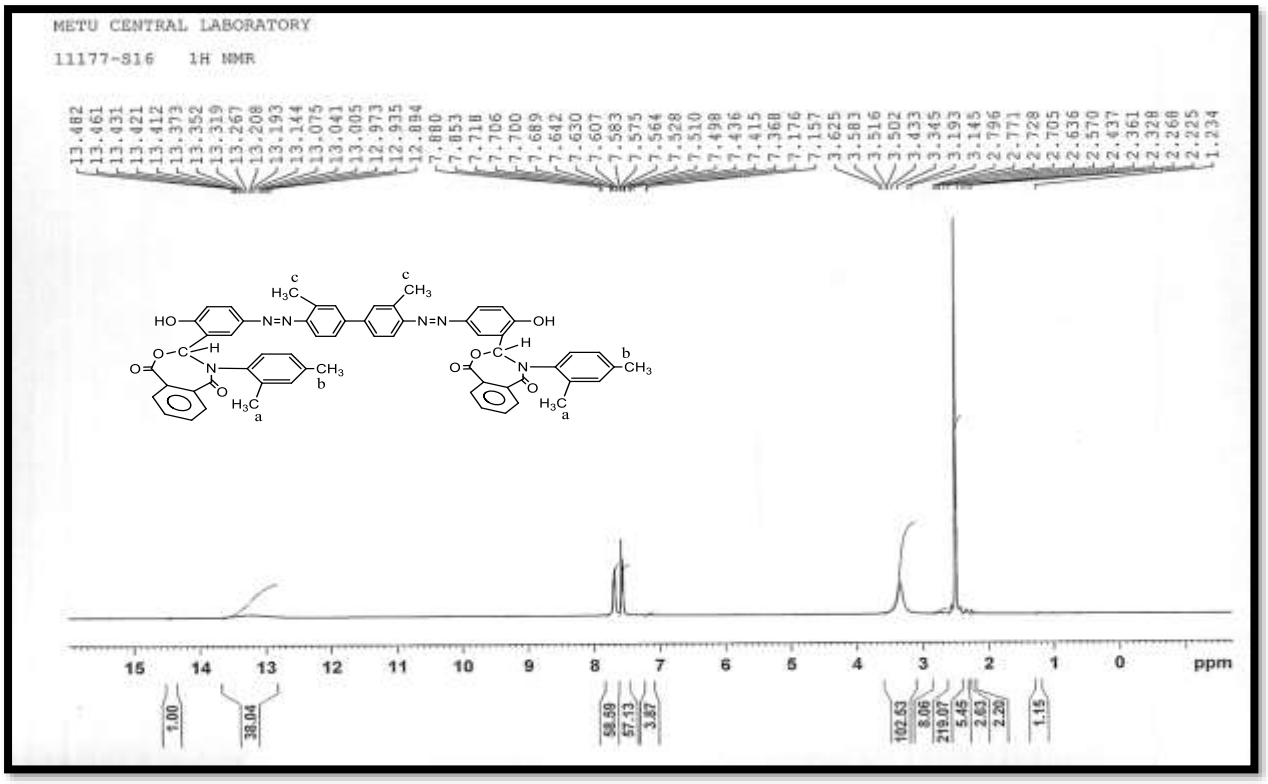


Figure (3-38) : ^{1}H NMR spectrum of compound [A_9]

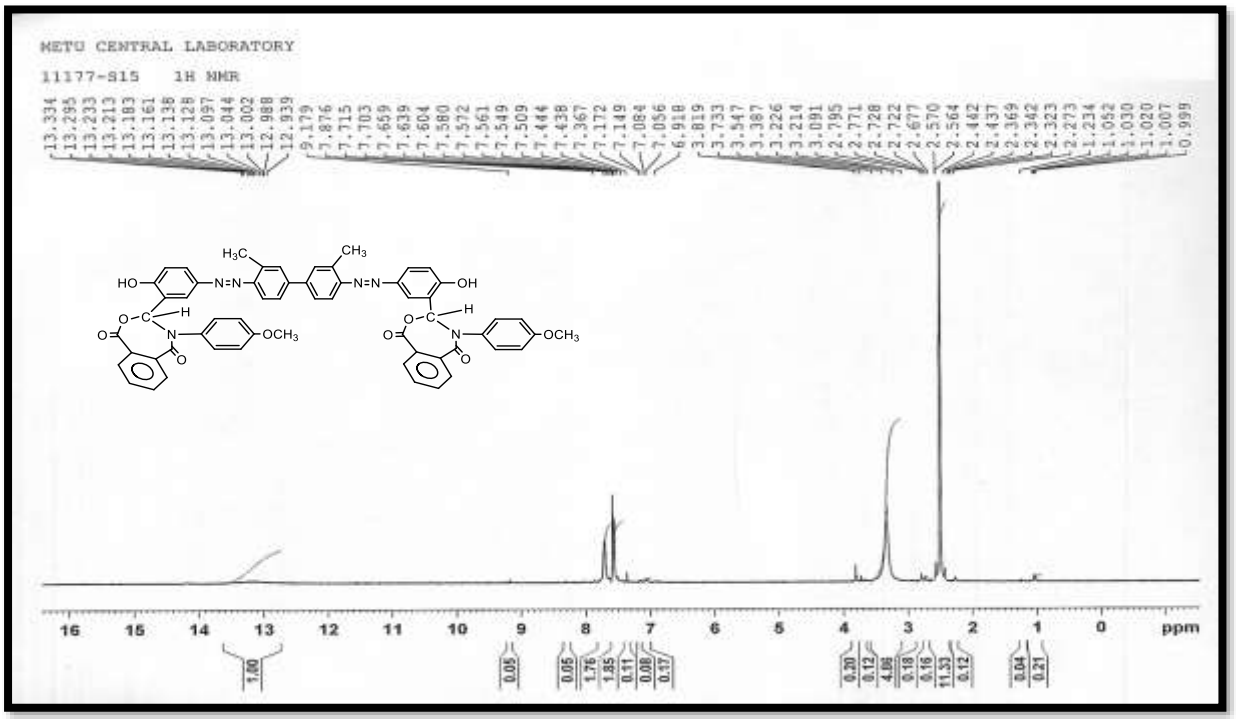


Figure (3-39) : ^{1}H NMR spectrum of compound [A_{10}]

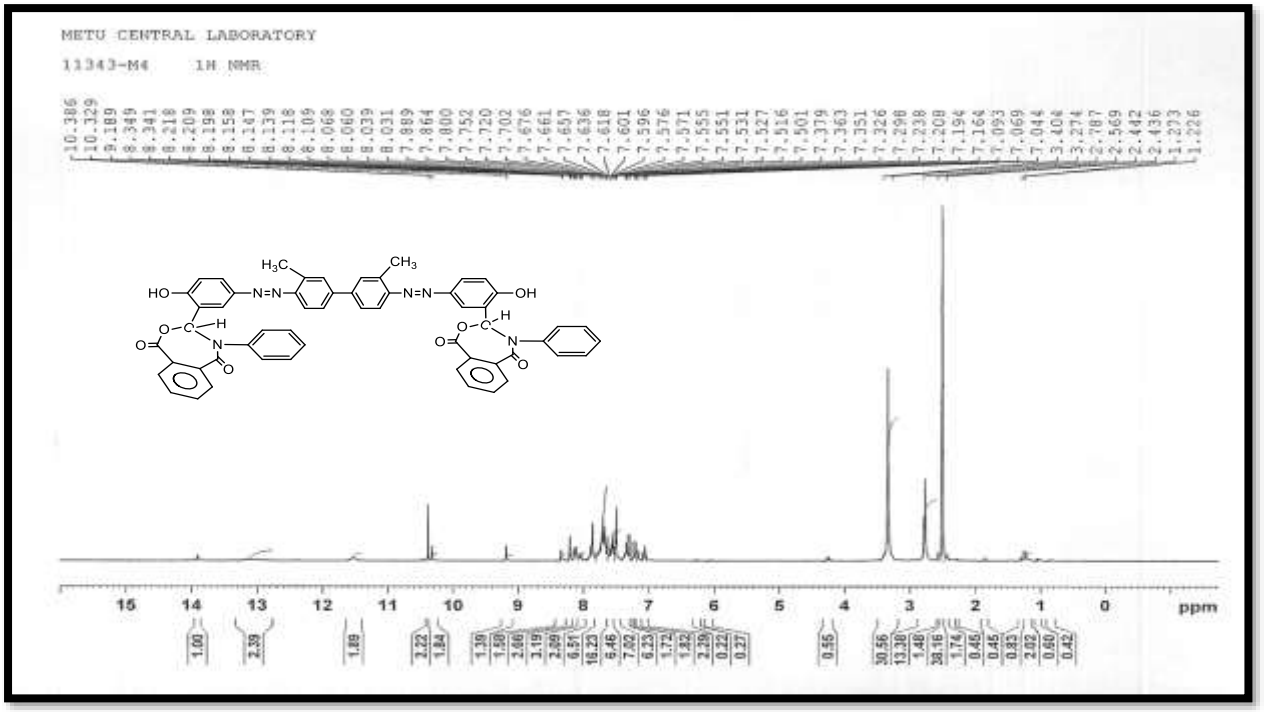


Figure (3-40) : ^{1}H NMR spectrum of compound [A_{11}]

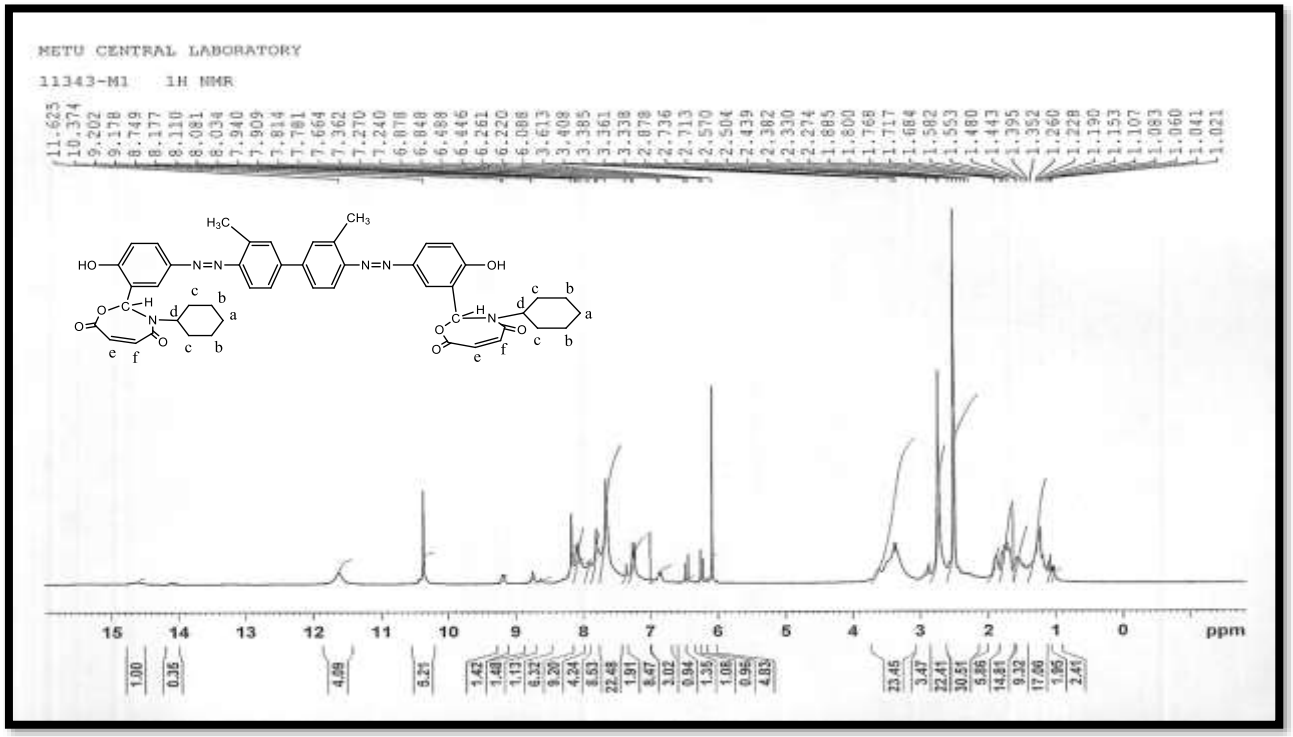


Figure (3-41) : ^{1}H NMR spectrum of compound [A_{13}]

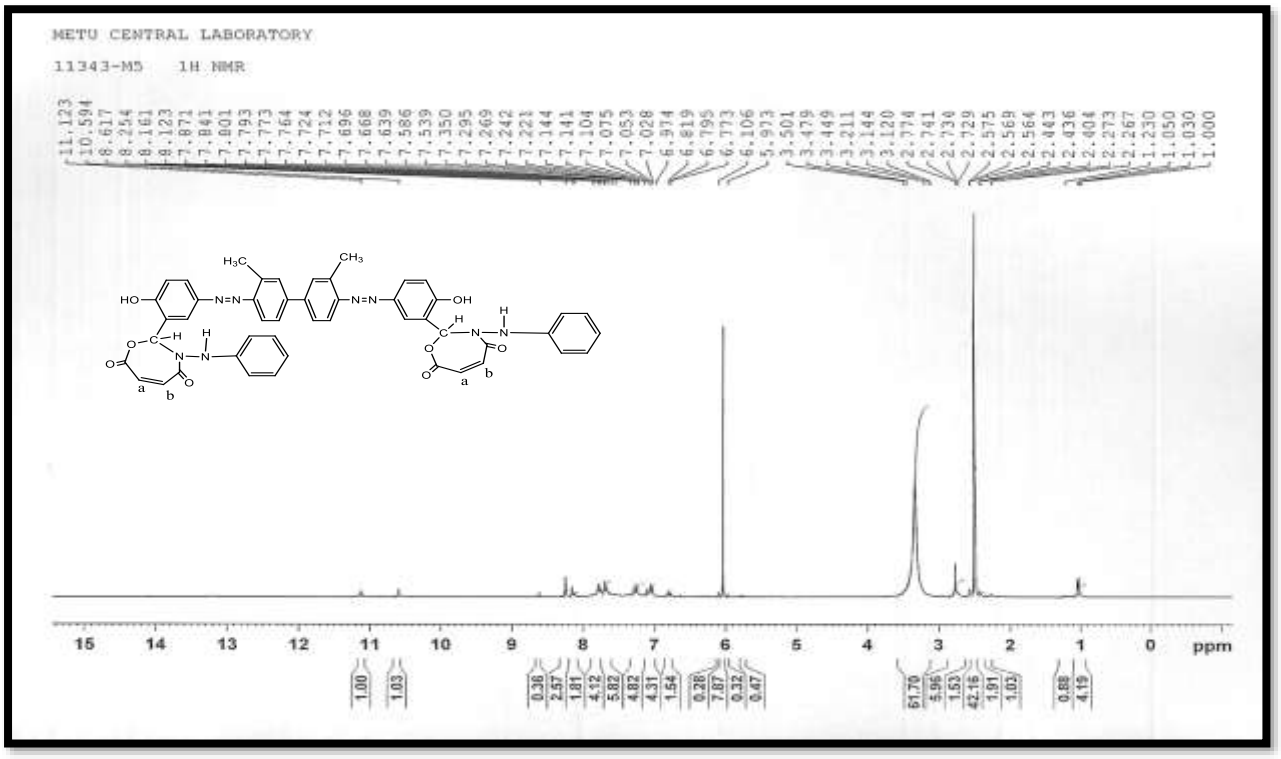


Figure (3-42) : ^{1}H NMR spectrum of compound [A_{14}]

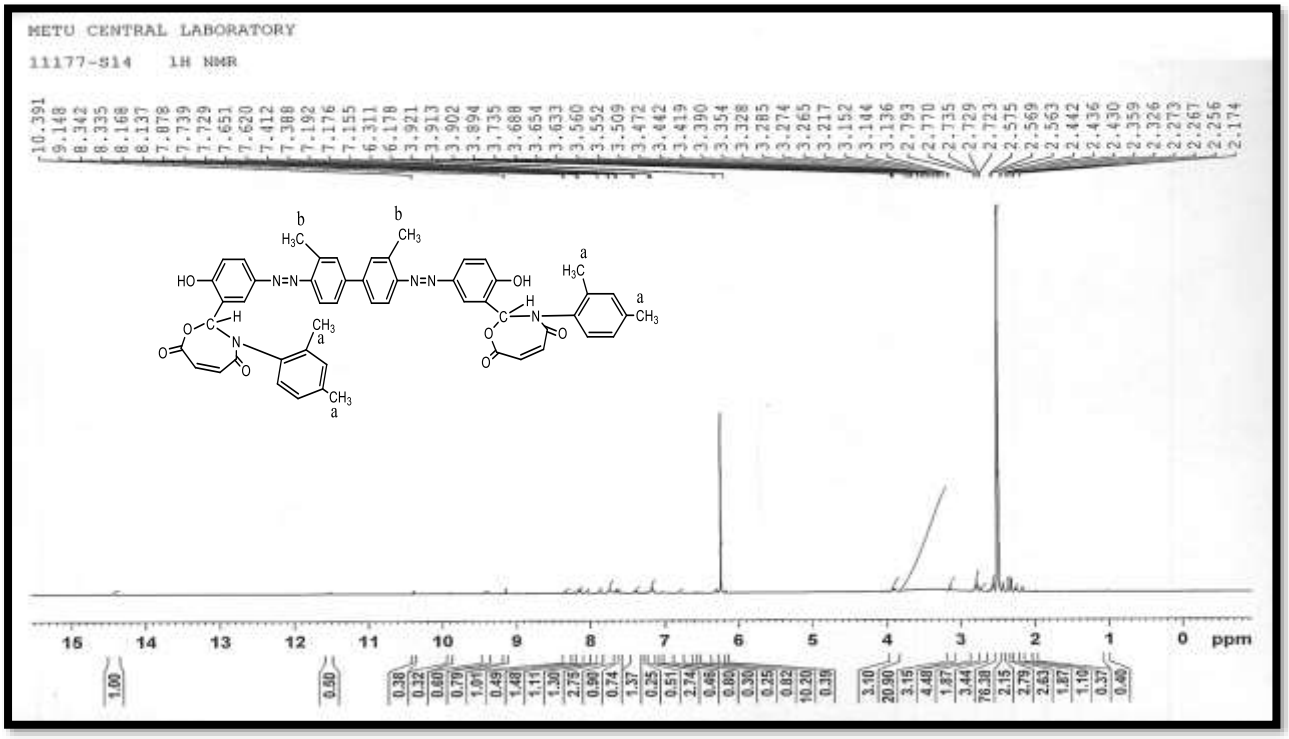


Figure (3-43) : ^{1}H NMR spectrum of compound [A_{15}]

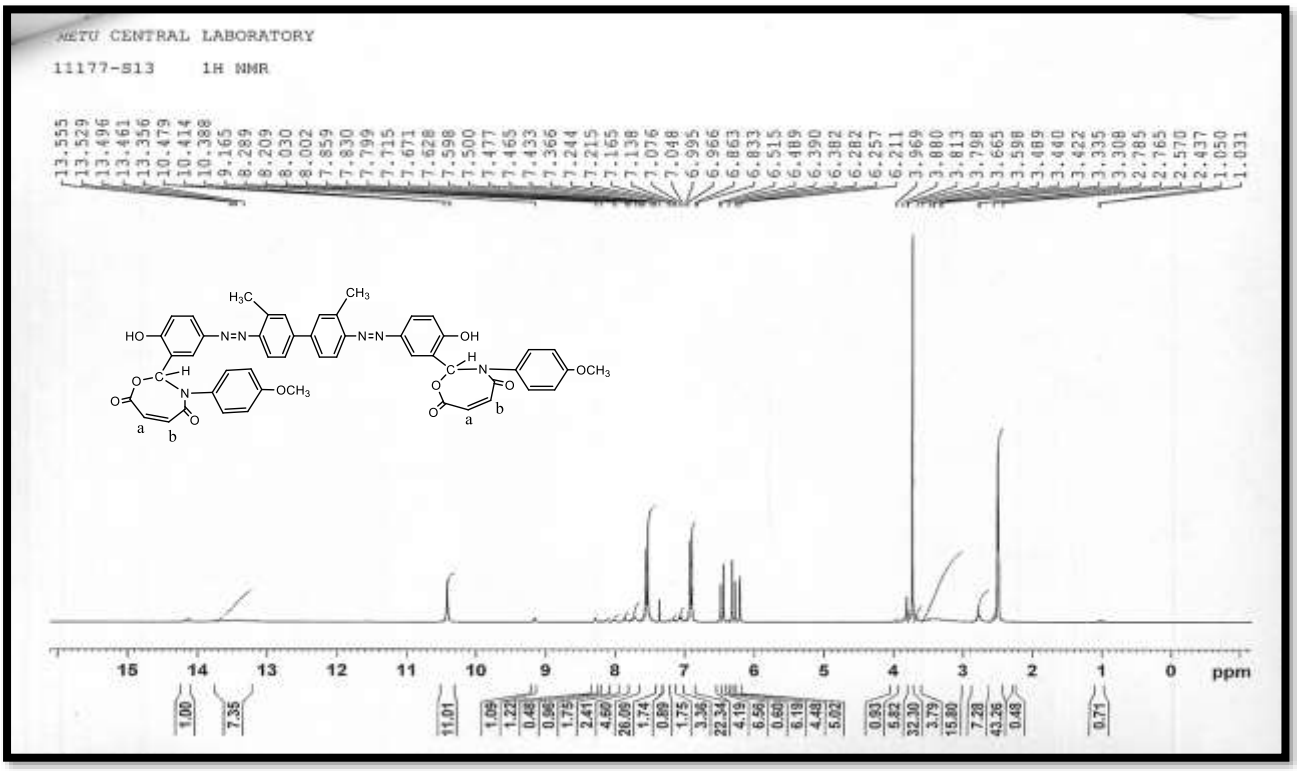


Figure (3-44) : ^{1}H NMR spectrum of compound [A_{16}]

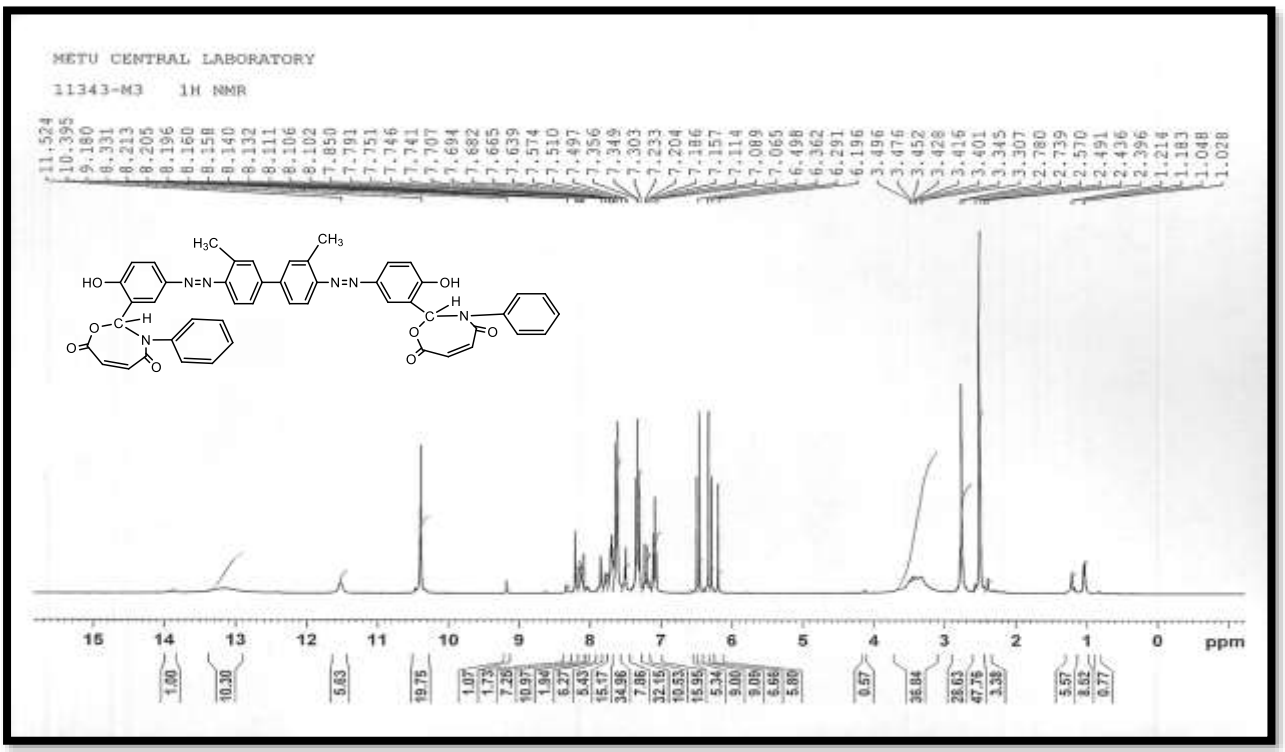


Figure (3-45) : ^{1}H NMR spectrum of compound [A_{17}]

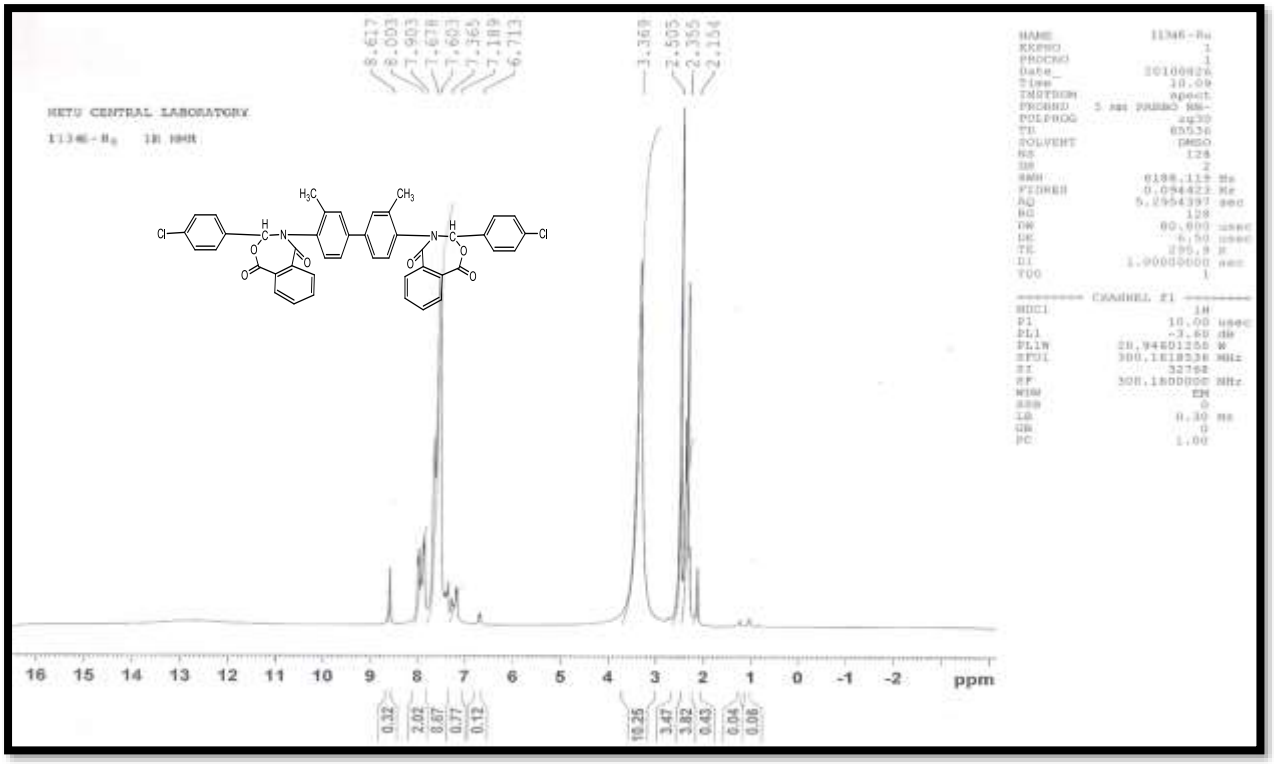


Figure (3-46) : ^{1}H NMR spectrum of compound [B$_{7}$]

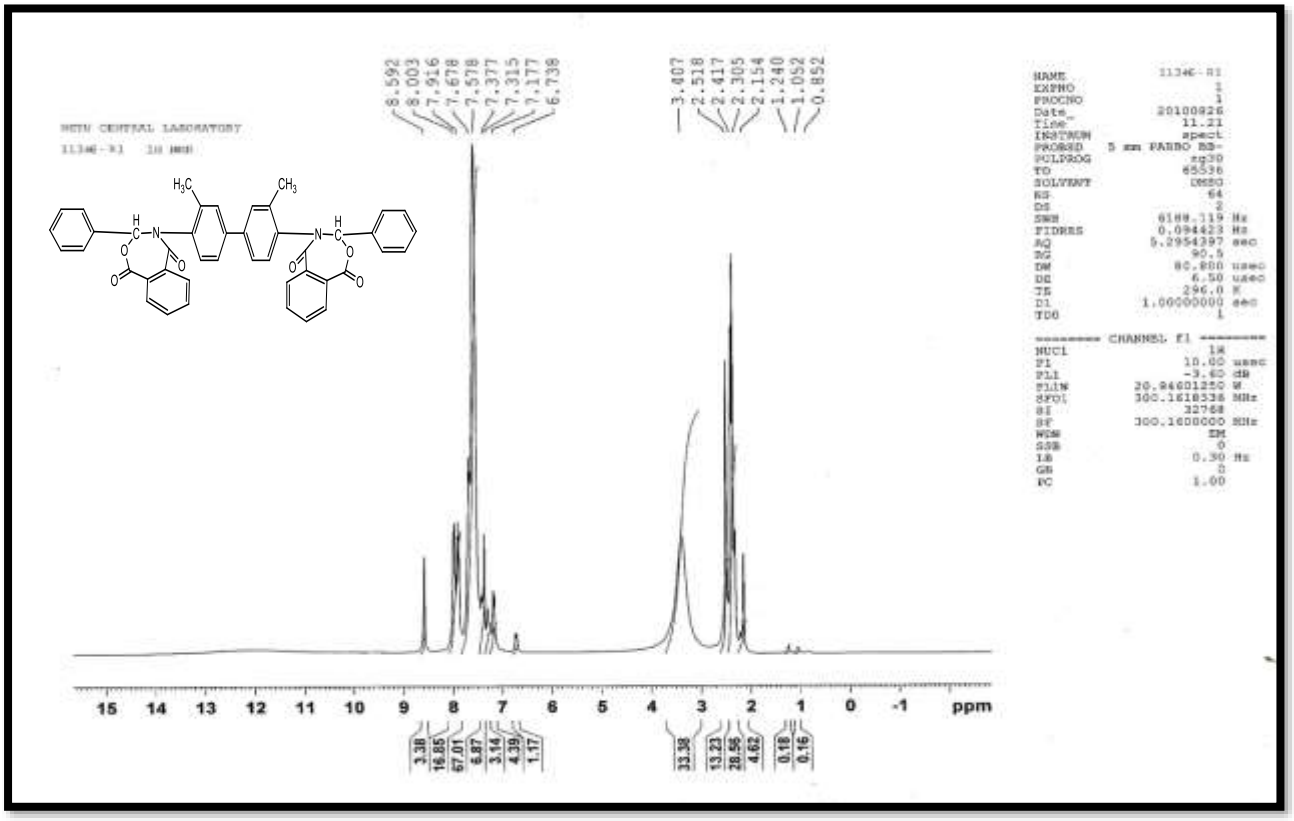


Figure (3-47) : ^{1}H NMR spectrum of compound [B$_{8}$]

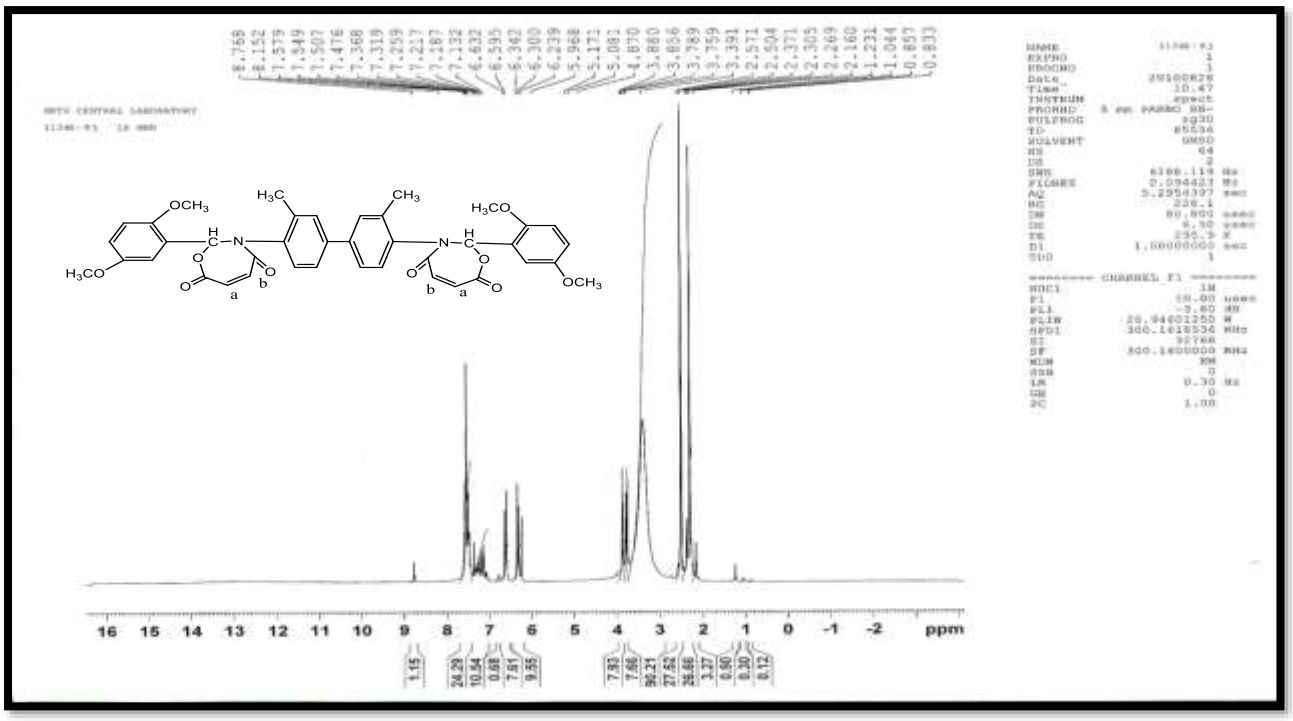


Figure (3-48) : ^{1}H NMR spectrum of compound [B_{11}]

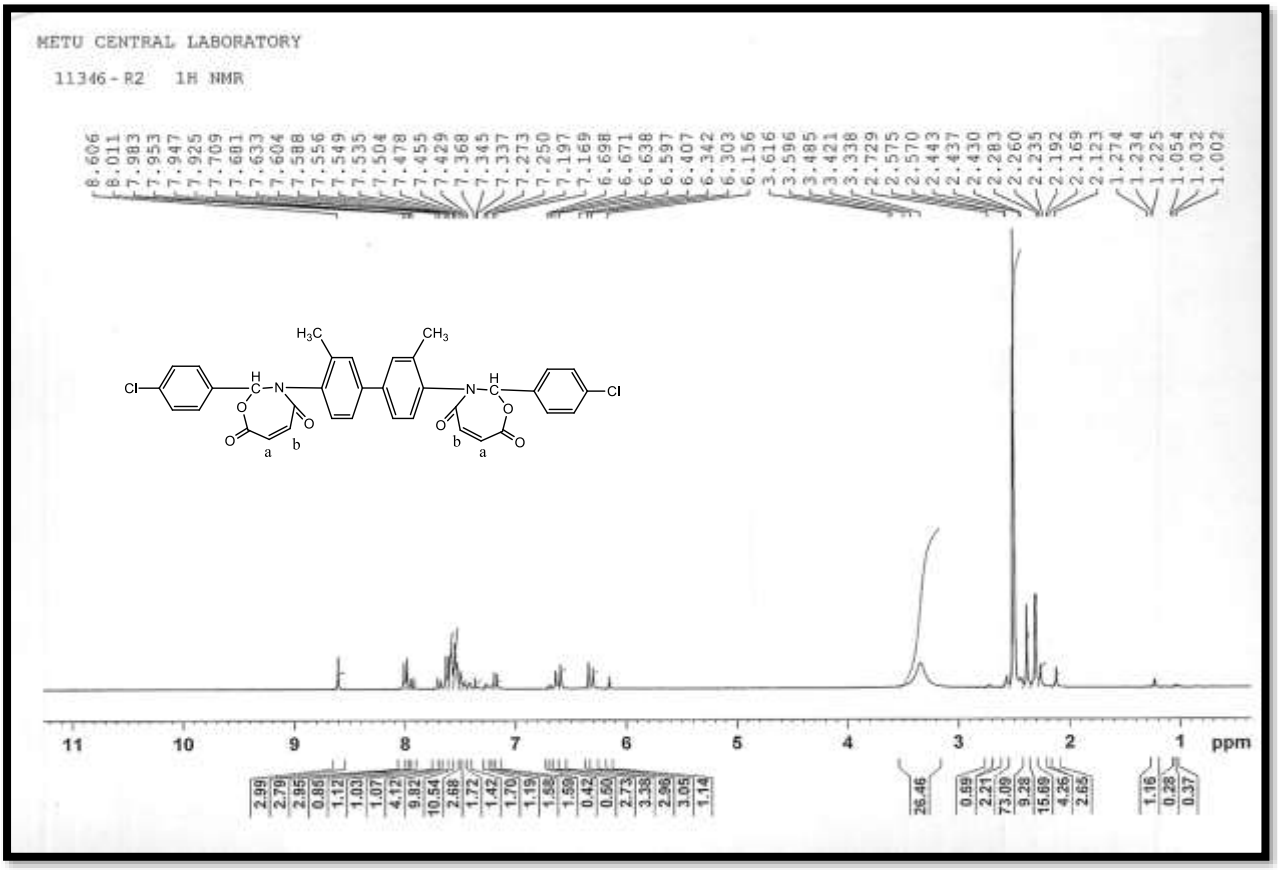


Figure (3-49) : ^{1}H NMR spectrum of compound [B_{12}]

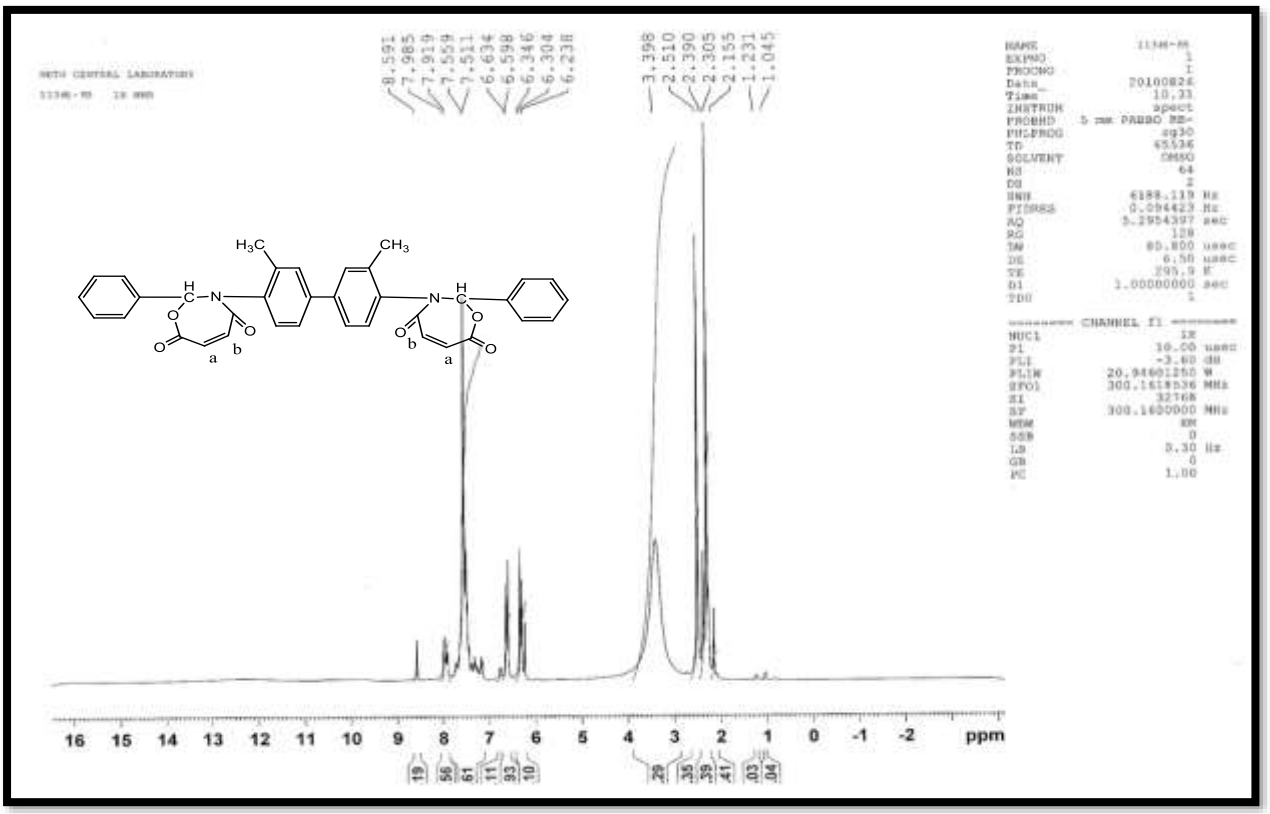


Figure (3-50) : ^{1}H NMR spectrum of compound [B$_{13}$]

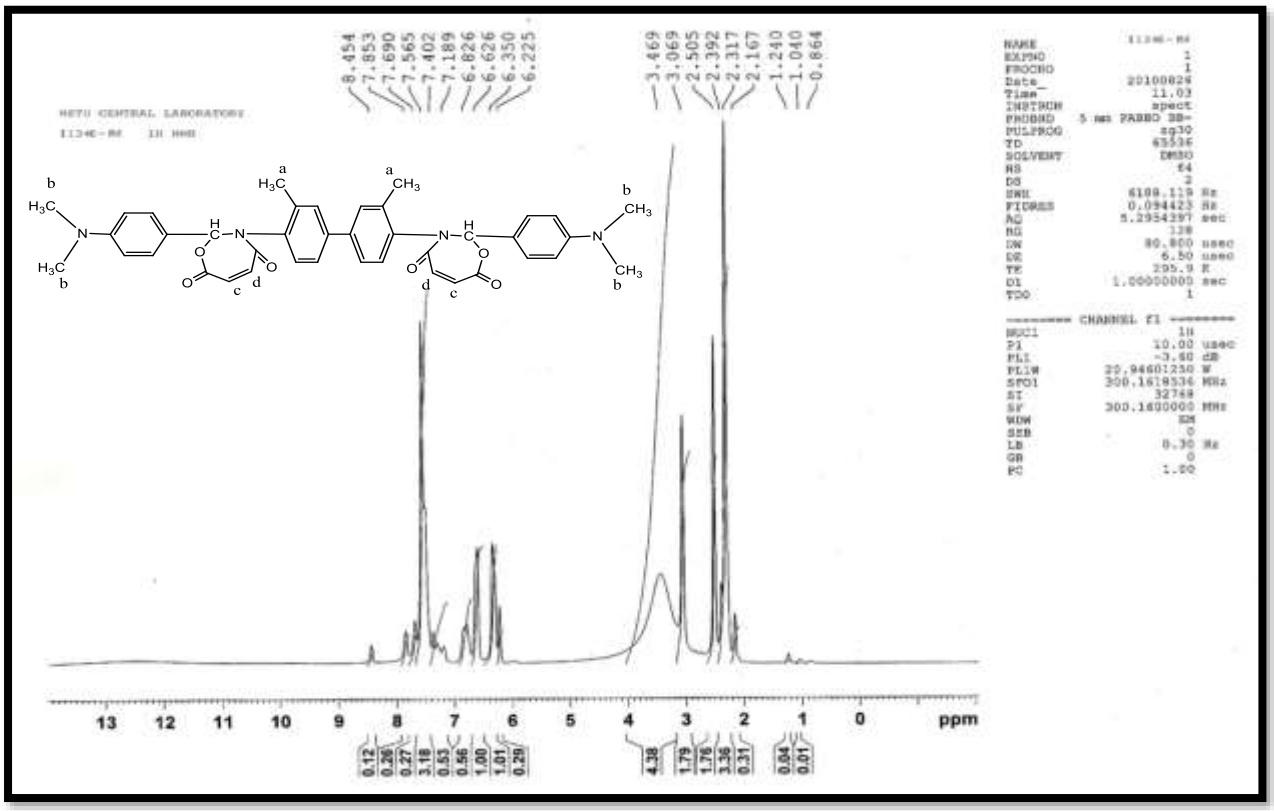


Figure (3-51) : ^{1}H NMR spectrum of compound [B$_{15}$]

Conclusions

1. The Formation of azoimine derivatives [A_1-A_6] by the reaction of bis-azoaldehyde derivative [A] with primary amines is more difficult than that of direct reaction between ***o***- tolidine and aldehydes, the reason may be due to the intramolecular hydrogen bonding between carbonyl group and ***o***- hydroxy group which leads to form a six- membered ring gives higher stabilization for carbonyl group, so the rate of reaction will be decreased.
2. The Reaction rate of bis-azoimine derivatives [A_1-A_6] with both cyclic anhydrides is slower than that of bisimine derivatives [B_1-B_5] with the same cyclic anhydrides, the reason may be due to the further conjugation with azo groups which leads to increase the stability of these bisimine derivatives and decrease the characteristic of π- bond in (C=N) group, so the rate of reaction will be decreased.
3. The cycloaddition reaction between cyclic anhydrides and bis-azoimine derivatives containing strong electron with - drawing group, such as nitro or chloro, in ***p***- position to imine group never take place, the reason may be attributed to decrease the characteristic of π- bond in (C=N) group due to the further conjugation with nitro group and decreasing the electronic density of benzene ring in case of chlorine atom which leads to increase strength of the conjugation.
4. Four compounds appeared higher inhibithion against Gram- positive bacteria (*Staphylococcus aureous*), while only one compound showed higher inhibithion against Gram- negative bacteria (*Escherichia coli*) ,also seven compounds showed medium inhibition against the positive bacteria, while two compounds

appeared medium inhibition against the negative bacteria, moreover, seven compounds showed no inhibition against the positive bacteria, while fourteen compounds showed no inhibition against the negative bacteria. These results indicate that the synthesized bis-1,3-oxazepine compounds are more reactive against Gram- positive bacteria than the other.

Prospective studies

1. Introducing the synthesized bis- azoimine derivatives in a cycloaddition reaction type [2+3→5] with soduim azide or organic azides to obtain new bis tetrazole derivatives.
2. Introducing the synthesized bis- azoimine derivatives in a cycloaddition reaction type [2+5→7] with succinic anhydride to obtain new bis-1,3- oxazepane-4,7-dione derivatives.
3. Using the synthesized bis- azoimine derivatives as starting material for the synthesis of *β*- Lactam derivatives via the reaction with chloroacetyl chloride.
4. Treatment of the synthesized bis-1,3- oxazepine derivatives with various primary amines or hydrazines to obtain new bis-1,3-diazepine derivatives.
5. Study the liquid crystalline properties of the synthesized bis-1,3-oxazepine-4,7-dione derivatives.

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الخلاصة

تم من خلال هذا العمل تحضير سلسلتين جديدتين من مشتقات ثنائية الازوثنائية1 ،3- اوكسازبين-4،7- دايـون [A_7-A_{18}] ومشـتقات ثنائيـة3,1- اوكسـازبين- 4،7- دايـون [B_6-B_{15}] وذلـك بأستعمال تفاعل الاضـافة الحلقيـة [2+5] لانهدريـدات الفثالـك و الماليـك الـى بعـض الايمينـات الثنائية الحاوية على مجموعتي أزو[A_1-A_6] والايمينات الثنائية [B_6-B_{15}] المحضرة .

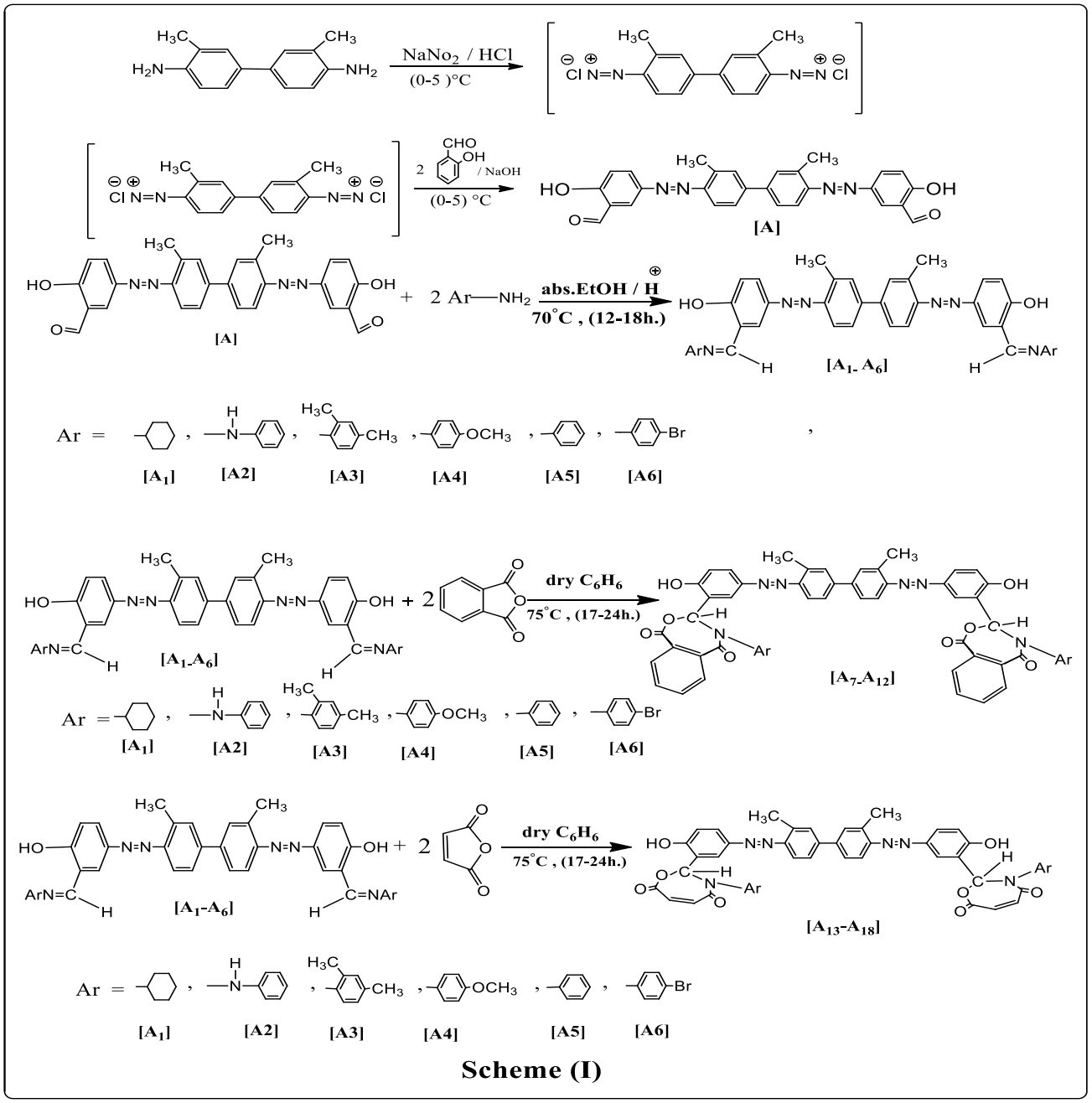
تم في الخط الأول من البحث تحويل مركب اورثـو- توليدين إلـى مشـتق ثنـائي ألازوالديهايـد [A]وذلـك مـن خـلال تفاعـل الازدواج مـع ايـون الفينوكسـيد السـالب لمركـب 2- هيدروكسـي بنزالديهايـد. ان تكـاثف مجمـوعتي الالديهايـد فـي مشـتق الأزوالديهايـد الثنـائي المحضـر [A] مـع مجموعتي أمـين فـي امينـات اوليـة متنوعـة ومشـتق هيـدرازين واحـد (سايكلوهكسـيل امـين ,فنيـل هيـدرازين ,4,2- ثنـائي مثيـل انيلـين,4- ميثوكسـيإنيلين, انيلـين,4- برومـوانيلين) بوجـود حـامض الخليك الثلجي كعامل مساعد في الأيثانول المطلق أدى إلى تكوين مشتقات الازوايمين الثنائية -[A_1 A_6] على التتالي .تم إدخـال مشـتقات الازوايمـين الثنائيـة المحضـرة [A_1-A_6] فـي تفاعـل إضـافة حلقية [2+5] مع كل من انهدريد الفثالك وانهدريد ألماليك فـي البنـزين الجـاف فـتم الحصـول علـى مشتقات 3،1- اوكسازبين -7,4- دايون ثنائية جديدة حاوية في تركيبها على مجموعتي أزو -[A_7 A_{12}و [A_{13}- A_{18}]على التتالي وكما موضح في مخطط (I).

تم في الخط الثاني من البحث تحضيرمشتقات ايمين ثنائية [B_1-B_5] عن طريـق التكـاثف المباشـر بـين اورثـو - توليـدين ومشـتقات بنزالديهايـد متنوعـة (2،5- ثنـائي ميثوكسـي بنزالديهايـد,4- كلوروبنزالديهايد, بنزالديهايد,2- هيدروكسي بنزالديهايد,*N*,*N*-4-ثنائي مثيل أمينوبنزالديهايد) على التتالي بوجود حامض الخليك الثلجي كعامل مساعد في الايثانول المطلق. تم إدخال مشتقات الايمين الثنائيـة المحضـرة [B_1-B_5] لاحقـا فـي تفاعـل إضـافة حلقيـة [2+5] مـع كـل مـن انهدريـدالفثالك وانهدريد الماليك في البنزين الجاف فتم الحصـول علـى مشـتقات 3،1- اوكسـازبين -4،7- دايـون ثنائية جديدة [B_6-B_{10}] و [B_{11}-B_{15}] على التتالي وكما موضح في مخطط (II).

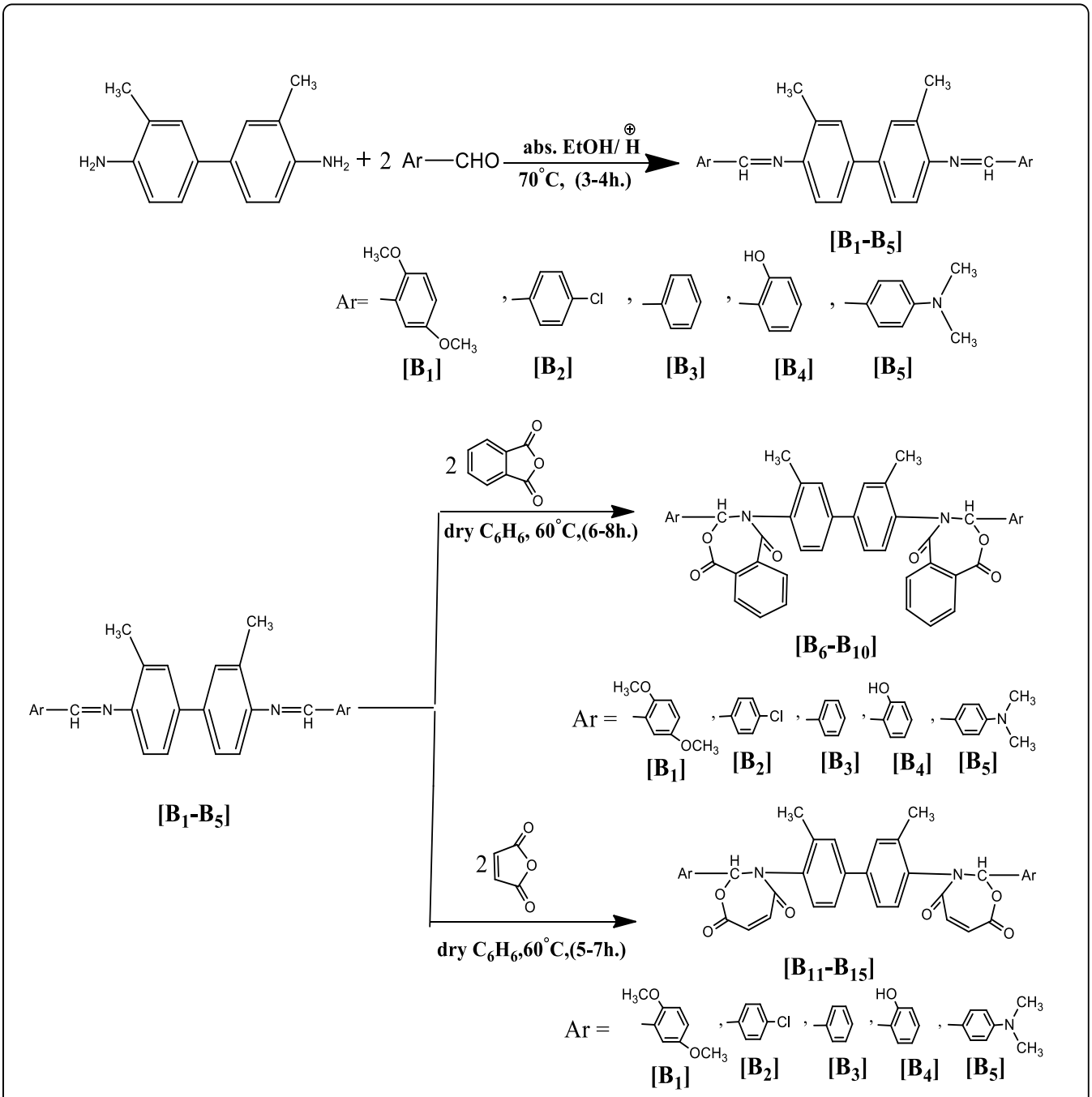
تم تشخيص جميع مركبات الاوكسازبين [A_7-A_{18}] و[B_6-B_{15}] المحضرة بوساطة التحليل الكمي العنصري الدقيق (C.H.N.) وكذلك بالطرق الطيفية المتضمنة مطيافية الأشعة تحت الحمـراء وتـم تشخيص مركبات الاوكسازيبن [A_{17}, A_{16}, A_{15}, A_{14}, A_{13}, A_{11} , A_{10} , A_9 , A_8 , A_7] و

[B_7, B_8, B_{11}, B_{12}, B_{13}, B_{15}] بمطيافية الرنين النووي المغناطيسي للبروتون ^{1}H NMR.

تضمت الخطوة الأخيرة من البحث تقييم أولي للفعالية ضد البكتريا لجميع المركبات النهائية [A_7-A_{18}] و[B_6-B_{15}] والتي اختبرت فعاليتها ضد بكتريا *(Staphylococcus aureous)* الموجبة لصبغة كرام وبكتريا *(Escherichia coli)* السالبة لصبغة كرام. تم تعيين هذه الفعاليات خارج الجسم باستعمال طريقة الانتشار في الوسط الغذائي (الاكار). دلت النتائج المستحصلة بأن بعض المركبات أظهرت فعالية عالية وكما موضح في جدول (7-3).



Scheme (I)


abs. EtOH/ H⊕
70°C, (3-4h.)
[B1-B5]
Ar=
[B1]
[B2]
[B3]
[B4]
[B5]
2
dry C6H6, 60°C,(6-8h.)
[B6-B10]
[B1-B5]
Ar =
[B1]
[B2]
[B3]
[B4]
[B5]
2
dry C6H6,60°C,(5-7h.)
[B11-B15]
Ar =
[B1]
[B2]
[B3]
[B4]
[B5]

Scheme(II)

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
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كلية العلوم
قسم الكيمياء

تحضير ودراسة الفعالية البايلوجية لمشتقات 3،1-أوكسازبين-7،4-دايون

رسالة مقدمة إلى

مجلس كلية العلوم - جامعة كربلاء

كجزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل

سوسن خضير عباس

بكالوريوس علوم كيمياء (2002) جامعة بابل

بأشراف

أ. م. د. زيد حسن عبود الاعرجي

1435 هـ 2014م