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University of Baghdad
College of Education for Pure Science-Ibn-Al-Haitham
Department of Chemistry

Synthesis and Spectroscopic Characterization of New Heterocyclic Compounds Including Five to Seven Members Ring with Evaluate their Biological Activity

A thesis
Submitted to the Council of College of Education for Pure Science-Ibn-AlHaitham University of Baghdad, in partial Fulfillment of the Requirements for the Degree of Master of Science in Chemistry

By

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(B. Sc., 2011)

Supervised By

Assist. Prof. Dr. Amina A. Fayad

2019 A.D. **1441 A.H**

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ ﴿١﴾ خَلَقَ
الْإِنسَانَ مِنْ عَلَقٍ ﴿٢﴾ اقْرَأْ وَرَبُّكَ
الْأَكْرَمُ ﴿٣﴾ الَّذِي عَلَّمَ بِالْقَلَمِ ﴿٤﴾
عَلَّمَ الْإِنسَانَ مَا لَمْ يَعْلَمْ ﴿٥﴾

﴿ سورة العلق ﴾

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We, the examining committee certify that we have read this thesis entitled "**Synthesis and Spectroscopic Characterization of New Heterocyclic Compound Including Five to Seven Members Ring with Evaluate their Biological Activity**" and examined the student "**Abdul Gabar Abdul Maged M. Said**" in its contents and that in our opinion, it is accepted for the Degree of Master of Science in Chemistry.

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Dean of college of Education for Pure Science /

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Dedication

This thesis is dedicated to :

Our first Teacher and Prophet Muhammad {peace and blessings of Allaah be upon him }

Who supported me after Allah. My dear's Father

My beloved Mother

My brothers and sisters

To everyone who left a beautiful imprint in myself

To all those who helped me to work until finish this thesis

Abdul-Gabbar

ACKNOWLEDGMENT

Praise be to God, and God's blessing and peace be upon our Prophet Mohammed

I owe a deep debt of gratitude to my supervisor ***Assist. Prof. Dr. Amina A. Fayad*** *for her guidance and help throughout the period of the research, I wish her health and happiness.*

I'm very grateful to ***Dr. Basim H. Alzedy*** *to his assistance.*

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Sincere thanks are to the deanery of College of Education for Pure Science/ Ibn-AlHaitham, Department presidency, and all my virtuous professors in the Department of Chemistry .

Abdul Gabar

Summary

This work involves the synthesis of five to seven memberrings heterocyclic compounds.

In the first part of this work, the initial step was to synthesize the oxime **[A]** as starting material for the preparation of Schiff bases. 4-Aminacetophenone was converted into the oxime by reacted it's with equivalent amounts of $NH_2OH.HCl$ and CH_3COONa in abs.EtOH. Then enter the oxime in a condensation reaction with the aldehyde (N,N-dimethylamino banzaldehyde), added a few drops G.A.A and refluxed at 78 ^oC, to synthesizes Schiff base **[A1]**. The hydrogen atom in (-OH) group compound **[A1]** was then replaced through reactions with benzenesulfonyl chloride and 4-methylbenzenesulfonyl chloride using pyridine at 0 °C as a medium of interaction.

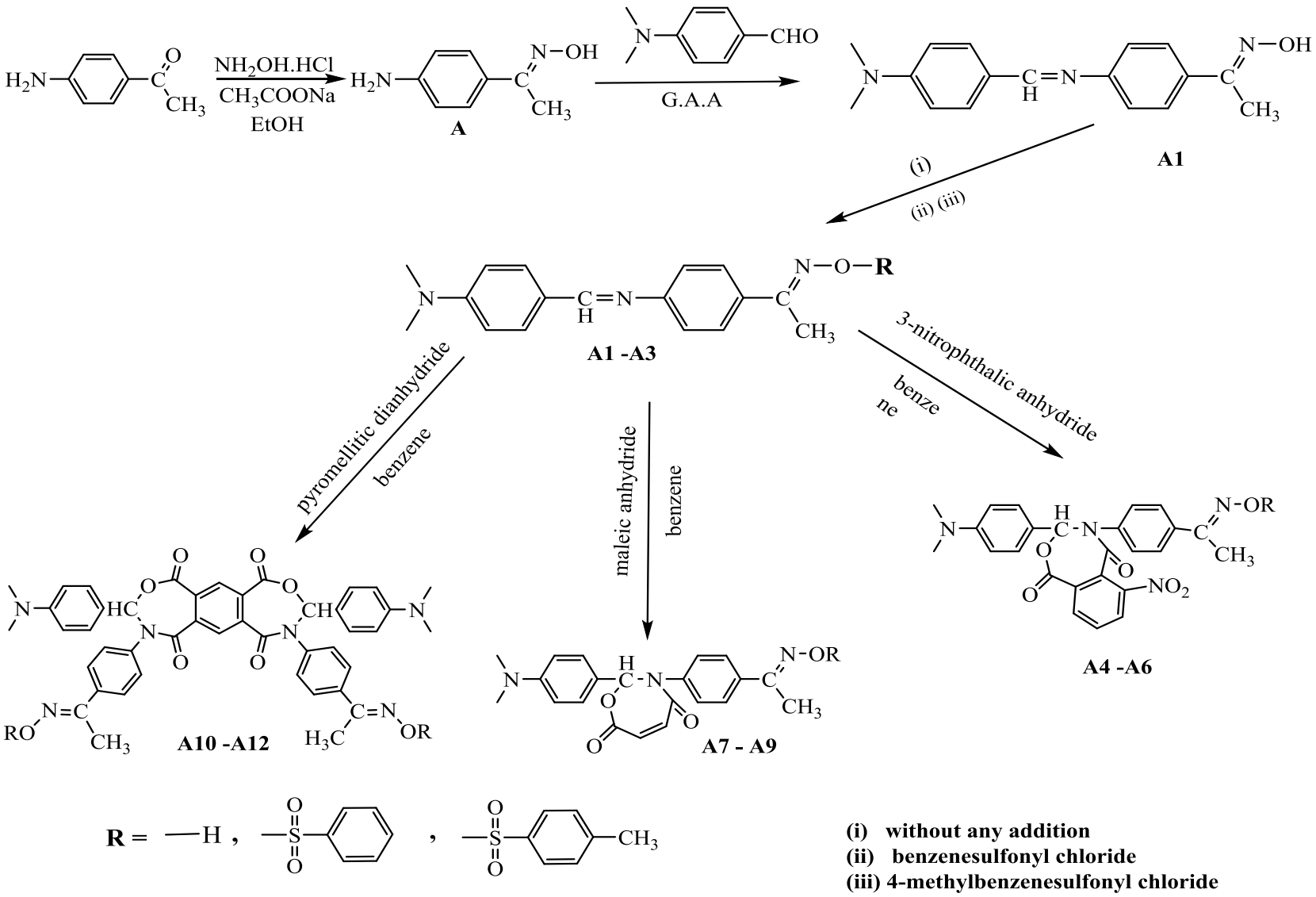
Schiff bases derivatives **[A1-A3]**, which cyclic addition reaction with (maleic anhydride, 3-nitrophthalic anhydride, and pyromellitic dianhydride), for preparation 1,3-oxazepine derivatives **[A4-A12]**, **Scheme [I]**.

In the second part, same Schiff bases **[A1-A3]** were reacted with acetyl chloride using benzene as a solvent to obtain the N-acyl derivatives **[A13-A15]**. In turn, these product's reacted with urea and thiourea in same solvent with Na_2CO_3 catalyst to give compounds **[A16-A18]**, **[A19-A21]** respectively and the last step added diethyl malonate to synthesis pyrimidine **[A22-A27]**; as well as sodium azide and thioglycolic acid for prepared tetrazole **[A28-A30]** and thiazolidin-4-one **[A31-A33**] respectively, **Scheme [II].**

The third part of this work involved the preparation of Schiff base **[B1]** from 4-aminobenzenesulfonamide by reaction with 4-hydroxyacetophenone in benzene with 3 mL of G.A.A. The compound **[B1]** converted to the ester **[B2]** and then the acid hydrazide derivative **[B3]** by treatment of hydrazine hydrate with ester. The pyrazoline and pyrazole derivatives **[B4, B5]** were obtained from the reaction of the **[B3]** with diethyl malonate and acetylacetone as shown in **Scheme [III].**

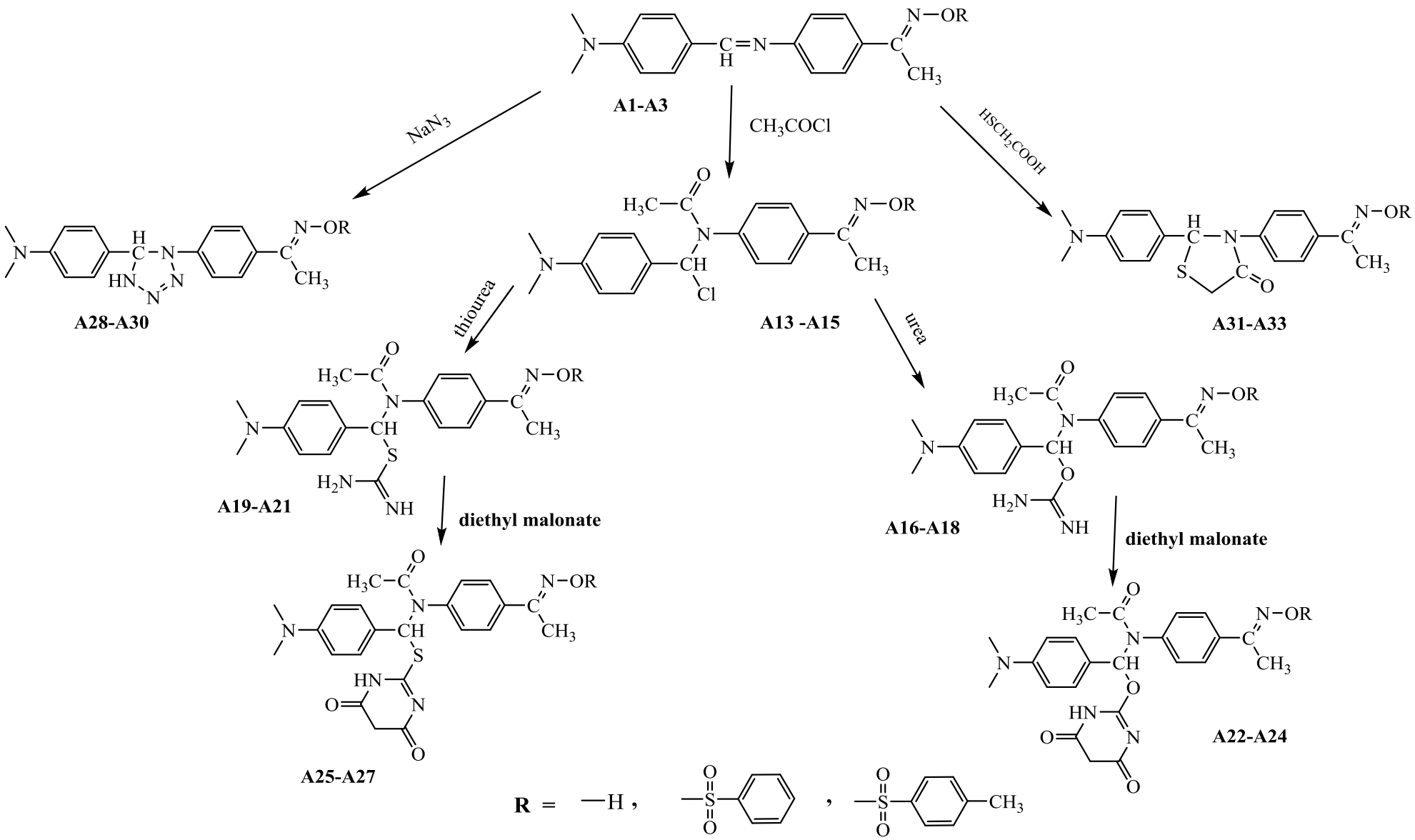
Finally, the fourth part Schiff base [B1] reacted cyclic addition reaction with (maleic anhydride, 3-nitrophthalic anhydride, and pyromellitic dianhydride) to prepared 1,3-oxazepine derivatives **[B6-B8]** as well as with sodium azide and thioglycolic acid for the synthesis heterocyclic rings; tetrazole **[B9]**, thiazolidin-4-one **[B10]**. Besides, **[B1]** was also treated with acetyl chloride to synthesis a acetamide **[B11]** in acetone as a solvent at temperature 0°C, then add the product to urea and thiourea in acetone and sodium carbonate as a catalyst and during the course of the reaction directly added equivalent amounts of diethylmalonate to prepared the derived pyrimidine **[B12, B13]** as shown in **Scheme [IV].**

The physical properties of synthesized compounds checked by (TLC, melting point), where's the chemical structures were identified by using different methods of spectroscopic such as (FTIR, ^{1}HNMR, ^{13}CNMR and C.H.N.S), and evaluate the biological activity against four types of bacteria such as (***Staphylococcus aureus, Bacillus Subtilis***) gram-positive and (***E. coli, Pseudomonas aeruginosa***) gram-negative and one type of fungal such as ***(Candida albicans*)**.


NH2OH.HCl
CH3COONa
EtOH
A
G.A.A
A1
(i)
(ii) (iii)
A1 -A3
pyromellitic dianhydride
benzene
maleic anhydride
benzene
3-nitrophthalic anhydride
benzene
A10 -A12
A7 - A9
A4 -A6
R =
(i) without any addition
(ii) benzenesulfonyl chloride
(iii) 4-methylbenzenesulfonyl chloride

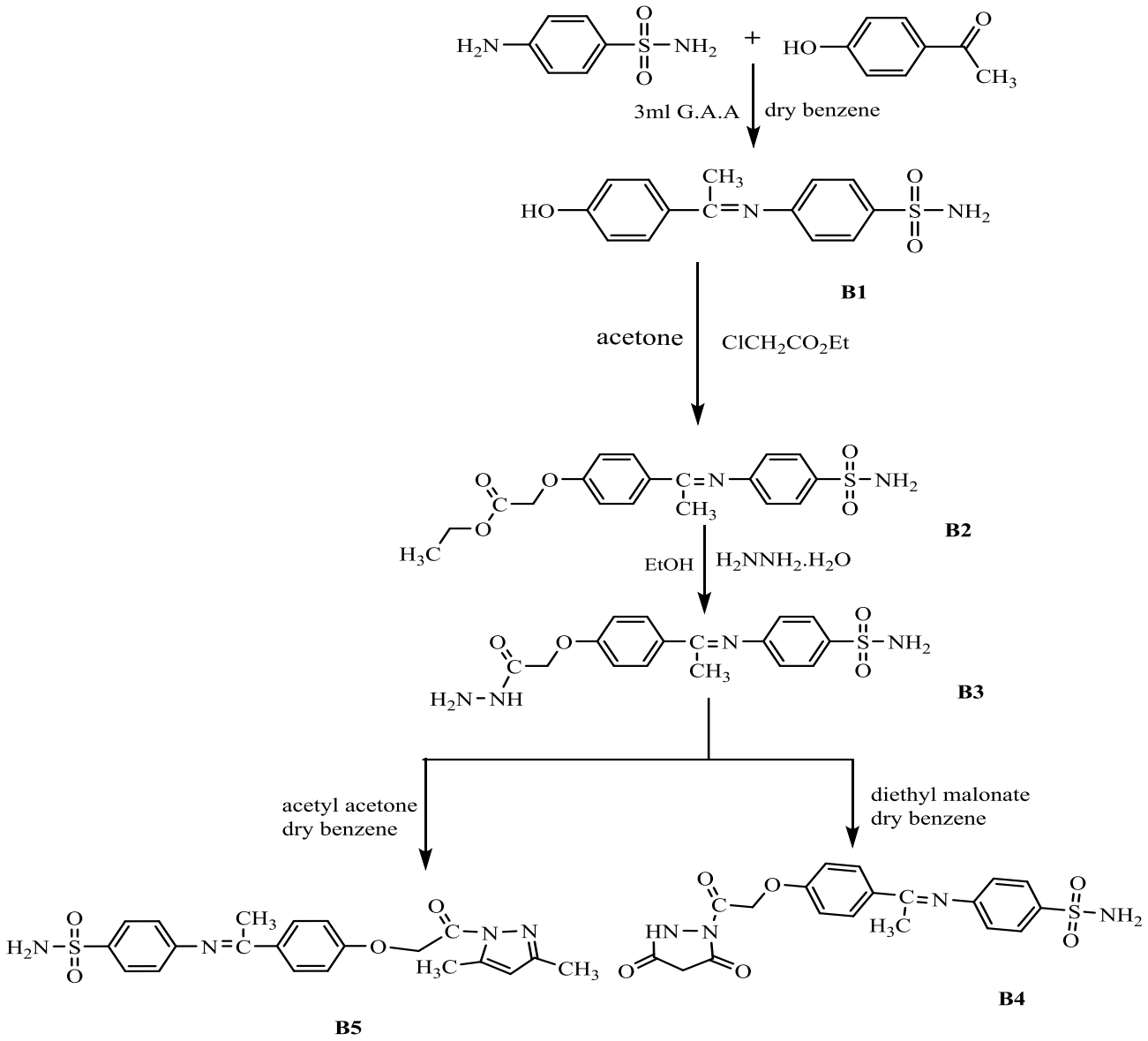
Scheme I

III


A1-A3
NaN3
CH3COCl
HSCH2COOH
A28-A30
A13 -A15
A31-A33
thiourea
urea
A19-A21
A16-A18
diethyl malonate
diethyl malonate
A25-A27
A22-A24
R = —H , , —CH3

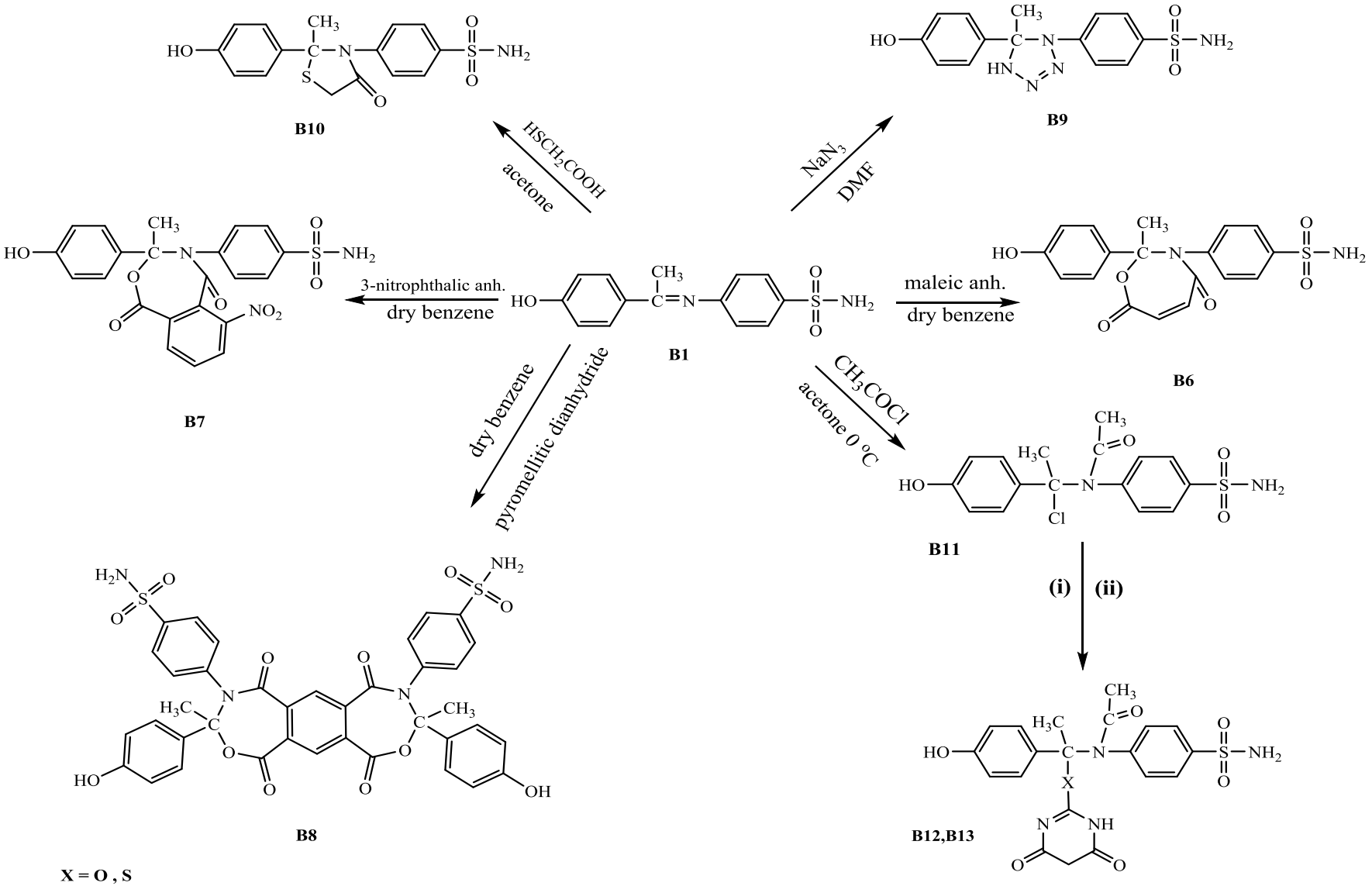
Scheme II

IV


3ml G.A.A
dry benzene
B1
acetone
ClCH2CO2Et
B2
EtOH
H2NNH2.H2O
B3
acetyl acetone
dry benzene
diethyl malonate
dry benzene
B5
B4

Scheme III

V



X = O , S

(i) urea , thiourea , Na_2CO_3 , 4hrs , (ii) diethyl malonate, 4hrs

Scheme IV

VI

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List of abbreviations

Absolute	abs.
N,N-Dimethylformamide	DMF
Glacial acetic acid	G.A.A
Pyridine	Py
Hours	hrs
Deuterated dimethylsulfoxide	DMSO-d_6
Gram	gm
Degree centigrade	^{o}C
Wave number	cm^{-1}
Proton Nuclear Magnetic Resonanc	^{1}HMNR
Carbon Nuclear Magnetic Resonanc	^{13}CNMR
Fourier Transform Infrared	FTIR
Symmetric	sym.
Asymmetric	asym.
Chemical shift	δ
Part per million	ppm
Stretching	str.
Vibration	vib.
Melting point	M.p.
Figure	Fig.
Stannum	Sn
Human Immunodeficiency Virus	HIV

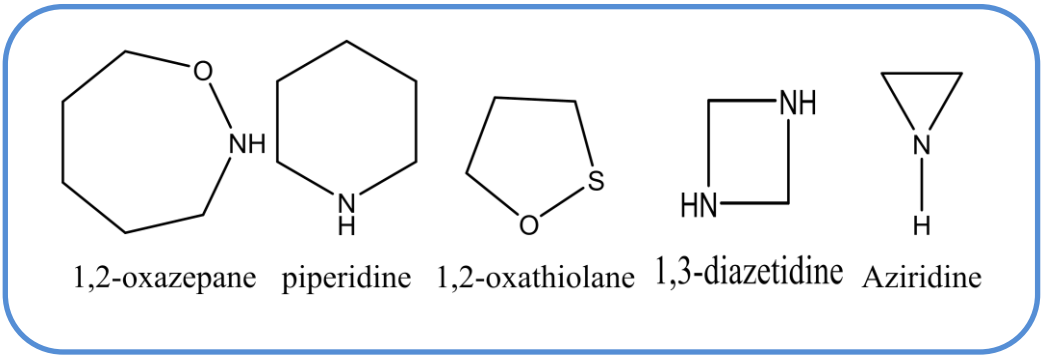
Chapter One

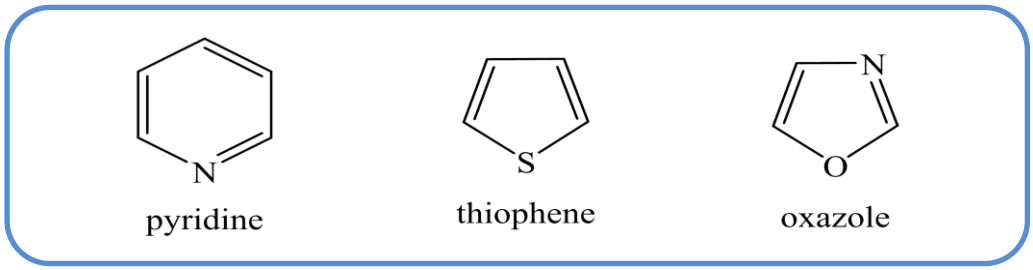
Introduction

1. Introduction

1.1 Heterocyclic Compounds

Heterocyclic compounds are an important type of organic compounds that contain carbon ring and at least one different atom. The most common atoms entering these compounds are N, O, S. These compounds can be classified according to the size of the ring: three, four, five, six and seven [1].



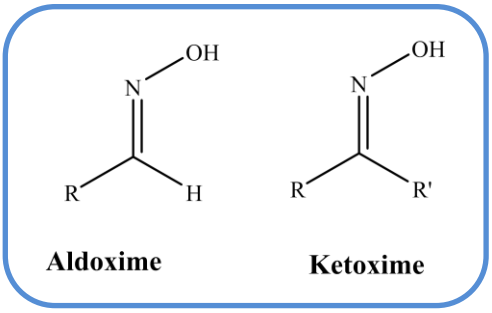


The different atoms that enter heterocyclic compounds give unique chemical and physical properties [2]. The heterocyclic rings are great importance in the pharmaceutical industry, which has proved to be good antibiotics for many diseases and also involved in the synthesis of many essential substances for life such as DNA, RNA amino acids, hormones, and vitamins, etc [3,4].

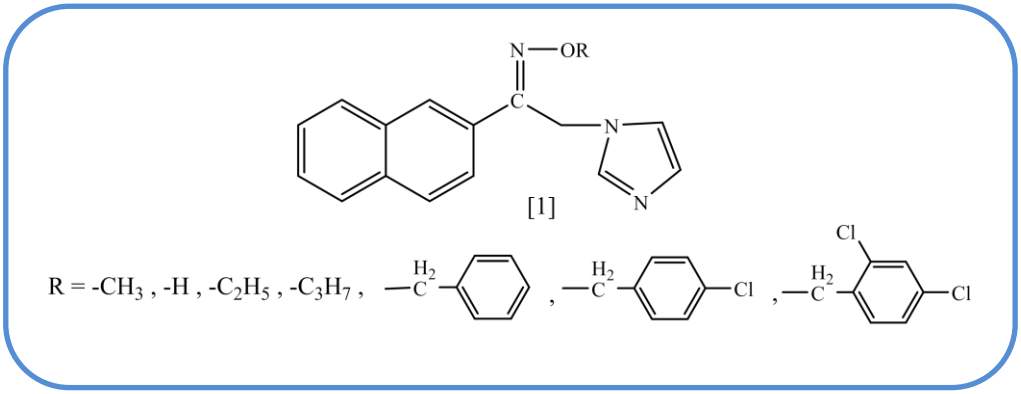
1.2 Oxime

Oxime is a chemical compound belongs to the imines, with the general formula RR'C=N-OH, where R is an organic group and R' may be hydrogen, forming an aldoxime, or any organic group, forming a ketoxime. Oximes are usually generated by reaction of hydroxylamine, and ketones or aldehydes.

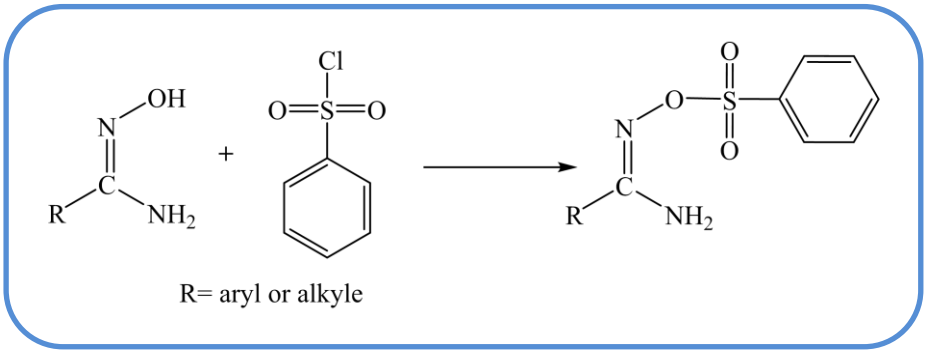
The source of oxime date back to a 19th century; of the words oxygen and imine. Amidoximes are oximes of amides with general formula RR'C=NOH where R is an organic group and R'= NH_2 [5].



Oxime[1] has many interactions in which various derivatives have been obtained through several reactions such as its reaction with alkyl halides or aryl [6].



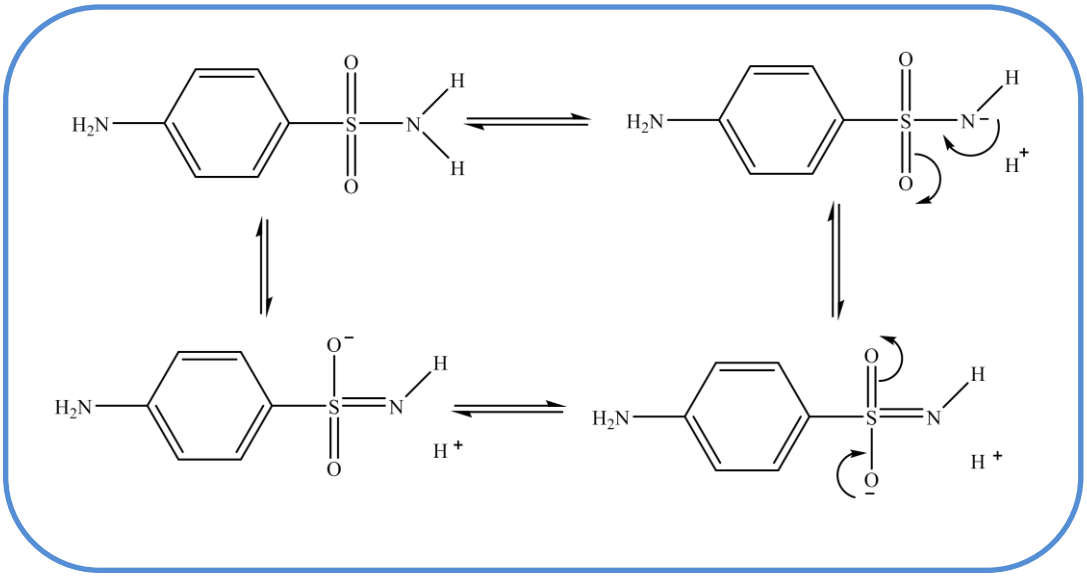
Oxime reacts with benzene sulfonyl chloride to replace the hydrogen atom to prepare the corresponding derivative [7].



1.3 Sulfonamide Compound

The primary sulfonamide structure consists of benzenesulfonamide and amine at the site of the para. There are a relationships between the structure

and activity of this compound. A large number of derivatives were synthesized, and differences in ortho and meta positions were found to be less effective than in para position Scheme (1.1). Sulfonamide is a stable compound under normal conditions of temperature, pressure, and light [8].

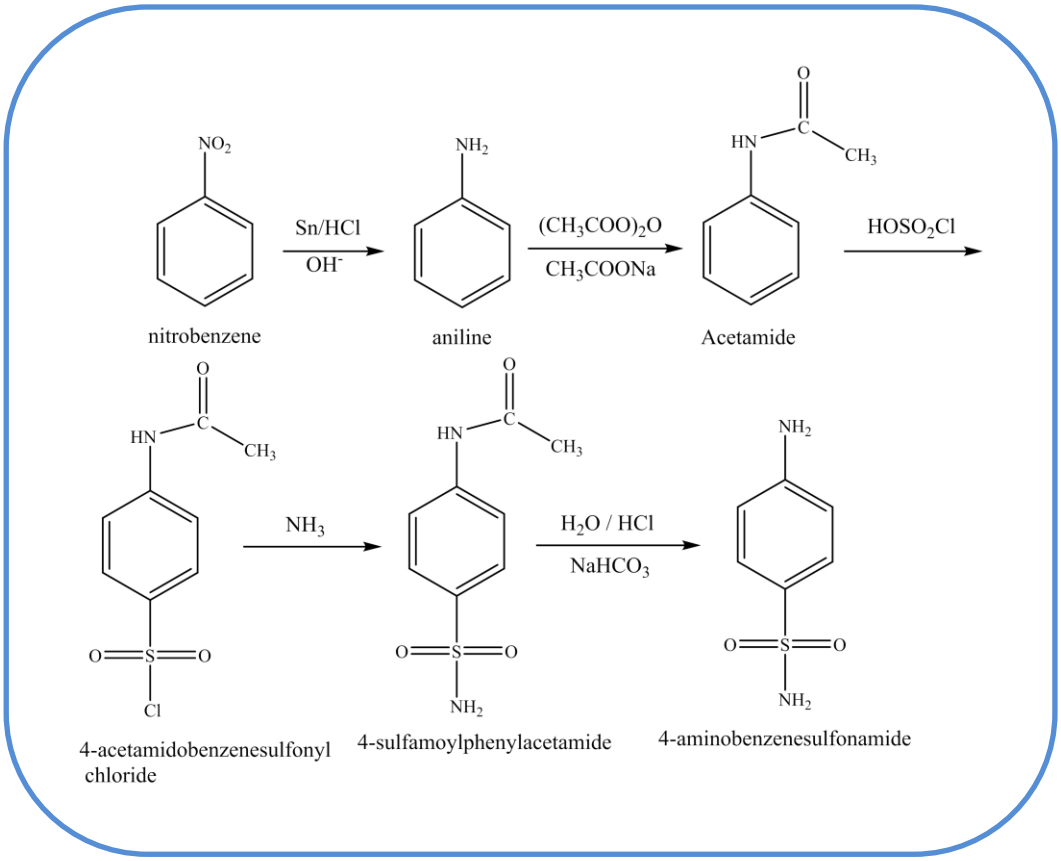


Scheme (1.1): Activity of benzenesulfonamide

1.3.1 Sulfonamide Synthesis

Synthesis of sulfonamide from the common method is the reaction of appropriate aliphatic or aromatic compounds [9,10]. Sulfonyl chloride and the adequate amine can be started from nitrobenzene and using Sn and hydrochloric acid as a reducing agent to give the aniline after the use of NaOH.

Acetylchloride or acetic anhydride can be used with a sodium acetate base that gives the acetamide derivative, a low solubility component. $HOSO_2Cl$ and ammonia then added to give 4-acetamidobenzenesulfonamide. Acidic hydrolysis opens the protection group of acetamide given 4-aminobenzene sulfonamide Scheme (1.2) showed synthesis of sulfonamide [11].



Scheme (1.2): Synthesis of sulfonamide

1.3.2 Biological Activity of Sulfonamide

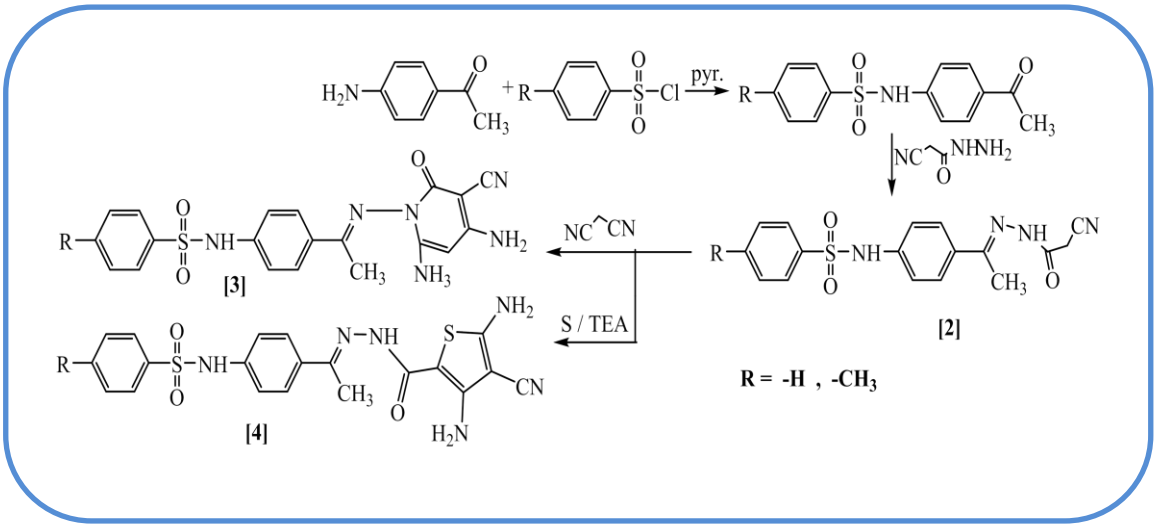
The sulfonamide group is considered to be an active group in pharmacology, where it has proven to be very effective against a large number of pathogens [12].

Although sulfone compounds were not used very often at the beginning of their droughts due to the toxic effect of humans until, sulfisoxaide, sulfamethoxazole, sulfacetamide, mafenide, and sulfadiazine silver was prepared, these compounds are now used in clinical medicine [13].

1.3.2.1 Anti-Cancer Activity

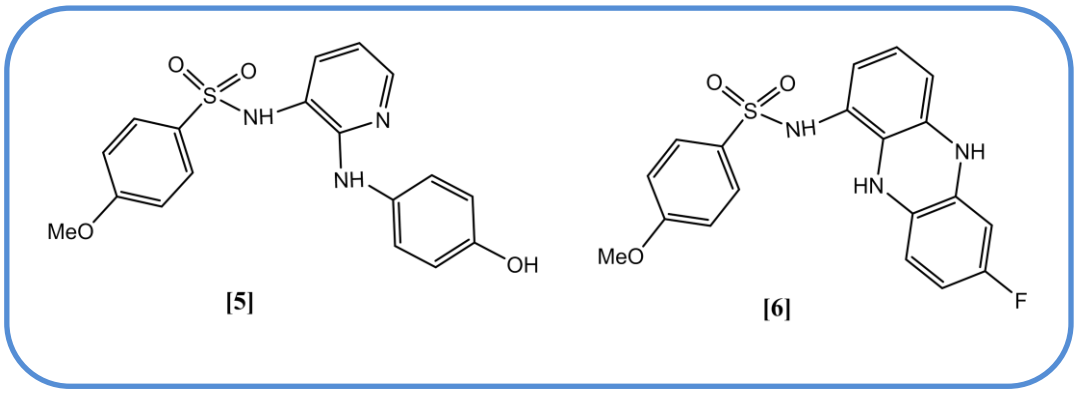
M. G. Mostafa et al. [14] were prepared of a new group of sulfonamide compounds starting from (4-(1-(2-(2-cyanoacetyl)hydrazono) ethyl)phenyl)-4-methyl substituted benzenesulfonamide [2] and inserted in the synthesis of the resulting materials in order to obtain activity against cancer cells.

A new series of compounds**[2], [3], [4]** that have been proven to be effective in the laboratory, Scheme (1.3).



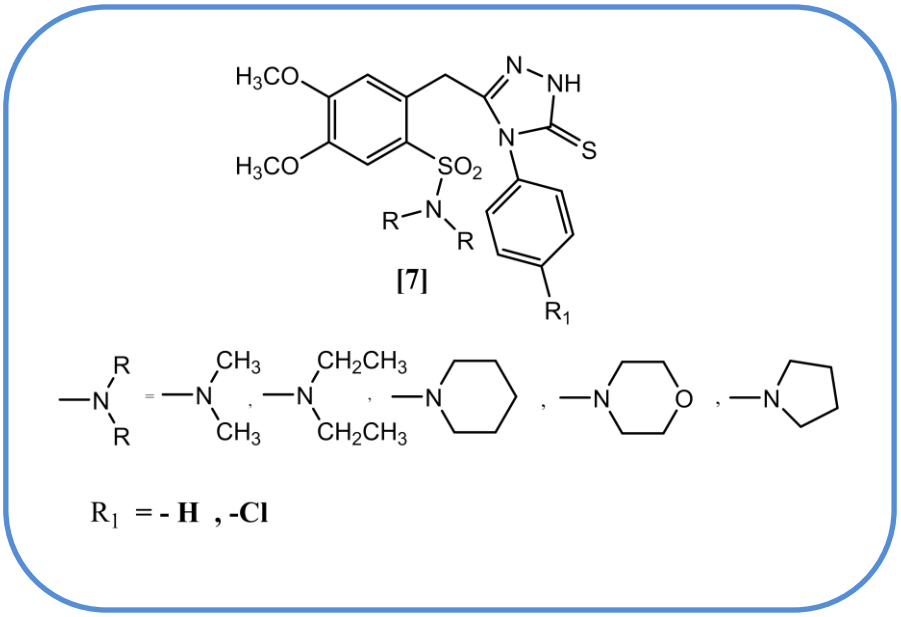
Scheme (1.3): Preparation of anti-cancer compounds

Y. Luo et al. [15] were designed and synthesized compounds [5,6] and evaluated them anti-tubulin activities and anticancer activities were found to be a good inhibitor (0.88 μM)**.**



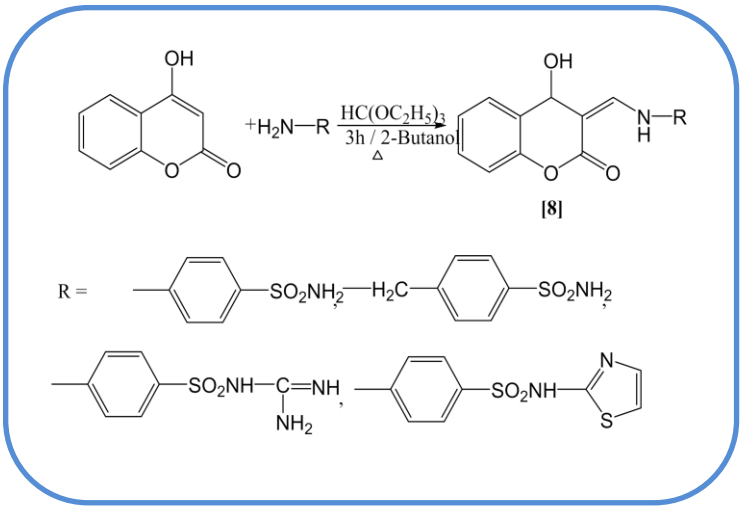
1.3.2.2 Antifungal Activity

R. E. Iraj et al.[16] prepared a new set of compounds derived from 5-(2-substituted sulfamoyl)-4,5-dimethoxy-benzyl-4-aryl-s-triazole-3-thiones [7]. Measured activity in *vitro* antifungal and yielded positive results compared to the commercial fungicide bifonazole **.**



1.3.2.3 Antibacterial Activity

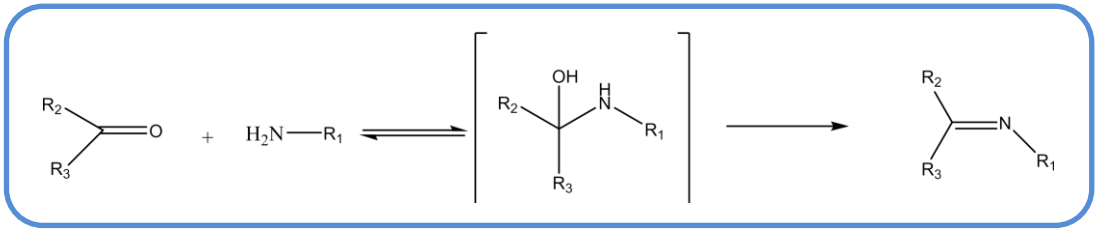
H. C. Zahid et al. [17] were synthesized compound [8] by reaction of 4-hydroxycoumarin with sulfonamide compounds and tested *in-vitro* anti-bacterial activity against a number of gram-negative bacteria (*S. Typhi and E. coli, S. flexneri, P. aeruginosa*) and two gram-positive bacteria (*B. subtilis and S. aureus*).



1.4 Schiff Bases

Azomethine or imines compounds have a general chemical formula *R*1*R*2*C=NR*3 and are called Schiff bases relative to the Hugo Joseph Schiff, one of the founders of modern chemistry [18,19]. The way to prepare these compounds is the reaction of the carbonyl group (aldehyde or ketone) with the

primary amine through the Schiff method discovered by which the water molecule is removed by condensation and this reaction uses acid as a catalyst, Scheme (1.4) [20].



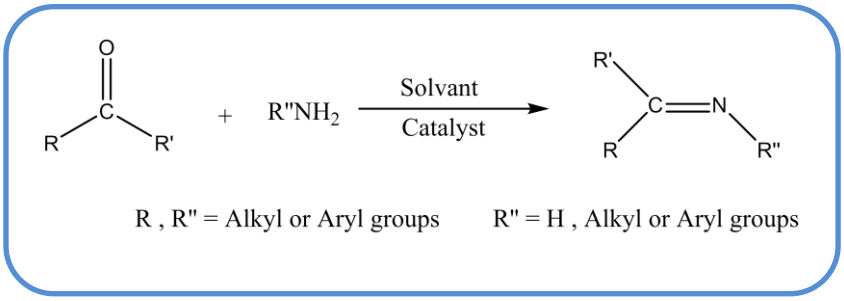
Scheme (1.4): The mechanism of preparing Schiff base

Reaction of aldehydes with primary amines to prepare imines faster than ketones that require high temperature and harsh conditions [21].

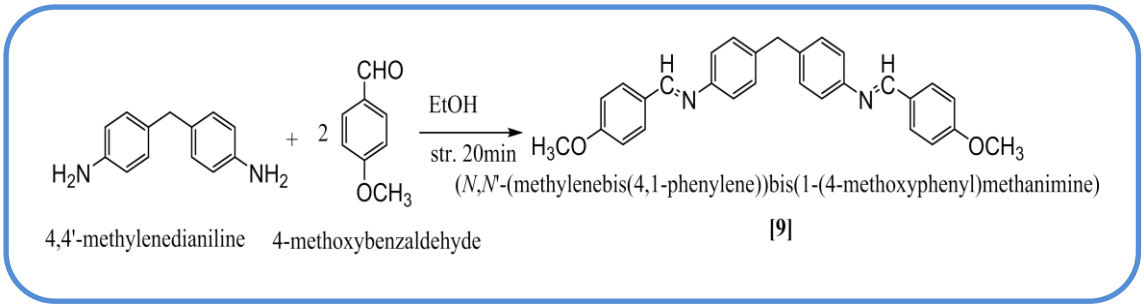
1.4.1 Synthesis Methods of Imine Compounds

❖ **Condensation Reactions (Thermal Condensation)**

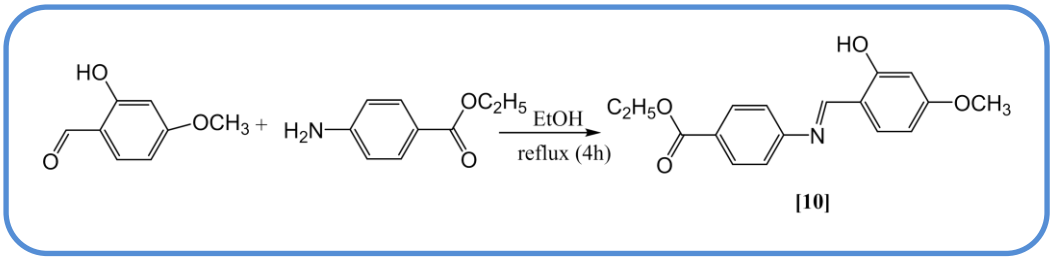
The method of direct condensation is one of the most important ways to synthesize Schiff bases. The interaction between primary amines with aldehyde or ketone is characterized by the presence of acids or bases. The first part of the reaction consists of unstable intermediate compounds (Carbinolamine) accompanied by the deletion of a water molecule [22].



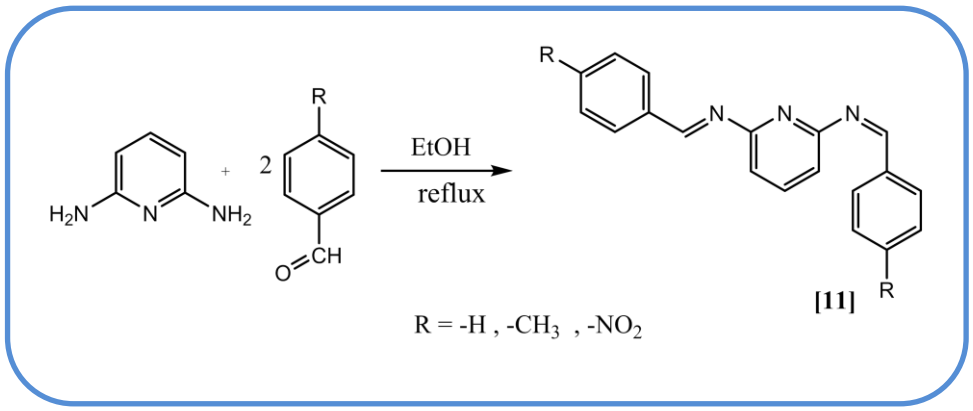
H. H. Sabah [23] was synthesized Schiff base [9] by condensation (4,4`-methylenedianiline) with *p*-methoxybenzaldehyde without any catalyst and stirring at room temperature.



E. Plahontu et al.[24] prepared Schiff base ethyl 4-[(E)-(2- hydroxy-4-methoxyphenyl)methyleneamino]benzoate] [10] by a reaction of ethyl 4-aminobenzoate with 2-hydroxy-4-methoxybenzaldehyde.

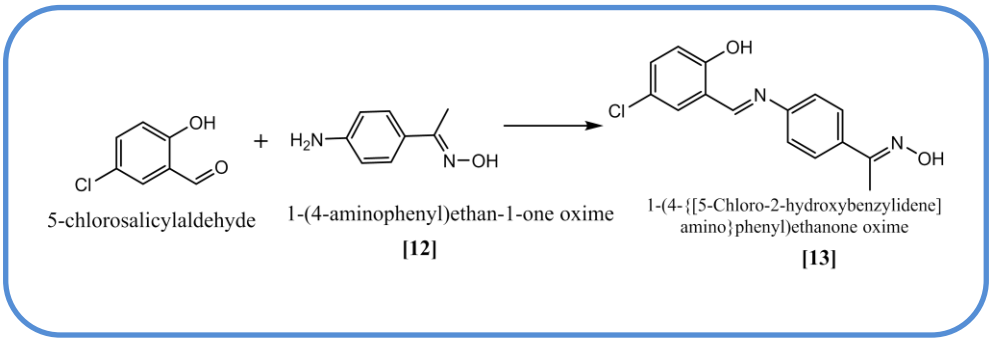


B. Dohare et al. [25] synthesized Schiff bases [11] from the reaction various substituted aromatic aldehyde with 2,6–diaminopyridine in ethanol.



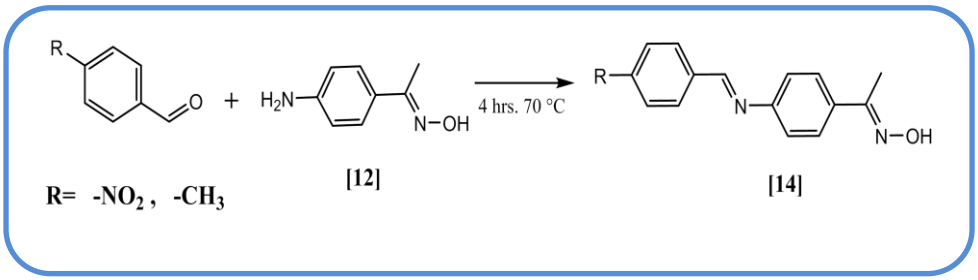
1.4.2 Schiff bases for Oxime Derivatives

Li Zhao et al. [26] were prepared 1-(4-{[-5-Chloro-2-hydroxybenzyli-dene]amino}phenyl)ethanone oxime [13] was prepared from reaction of 4-aminophenylethanone oxime [12] reaction with 5-chlorosalicylaldehyde.



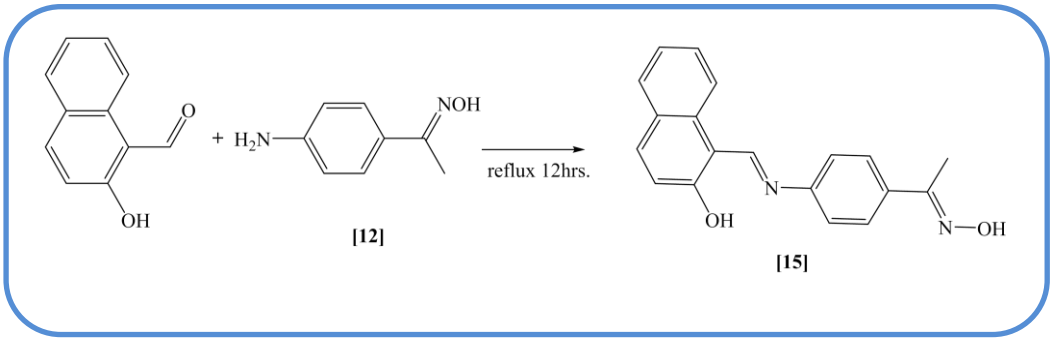
5-chlorosalicylaldehyde 1-(4-aminophenyl)ethan-1-one oxime [12] 1-(4-{[5-Chloro-2-hydroxybenzylidene] amino}phenyl)ethanone oxime [13]

L. Zhao et al. [26, 27] was synthesized azomethine [14] from reaction oxime [12] with *p*-substituted benzaldehyde and refluxed at 4 hrs. at 70 °C.



R= -NO_2 , -CH_3 [12] [14]

A. Karakurt et al.[28] were prepared 1-(4-(((2-hydroxynaphthalen-1-yl)methylene)amino)phenyl)ethan-1-one oxime [15] by treatment of 2-hydroxy-1-naphthaldehyde with oxime [12] and refluxed for 12 hrs.

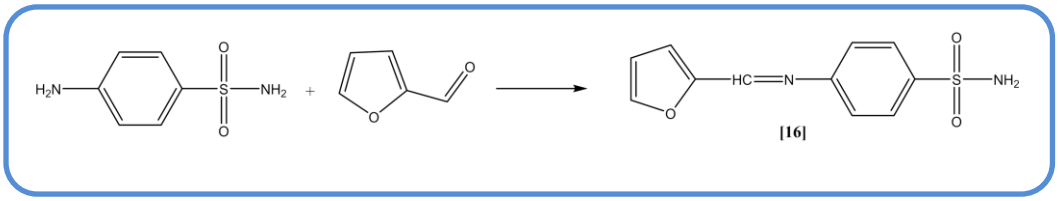


[12] [15]

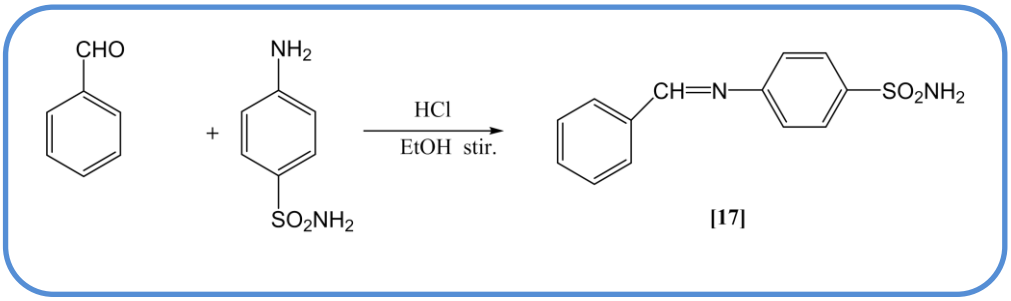
1.4.3 Schiff Bases of Sulfonamide Derivatives

Schiff bases of sulfonamides were synthesized from 4-amino benzenesulfonamide and substituted aromatic ketone and aldehydes.

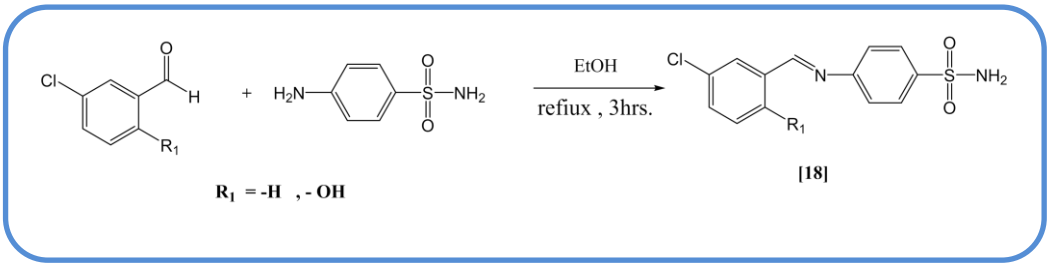
M. Sekhar et al. [29] synthesized Schiff base 4-((furan-2-ylmethylene)amino)benzenesulfonamide [16] from reacted of 4-aminobenzene sulfonamide and furan-2-carbaldehyde**.**



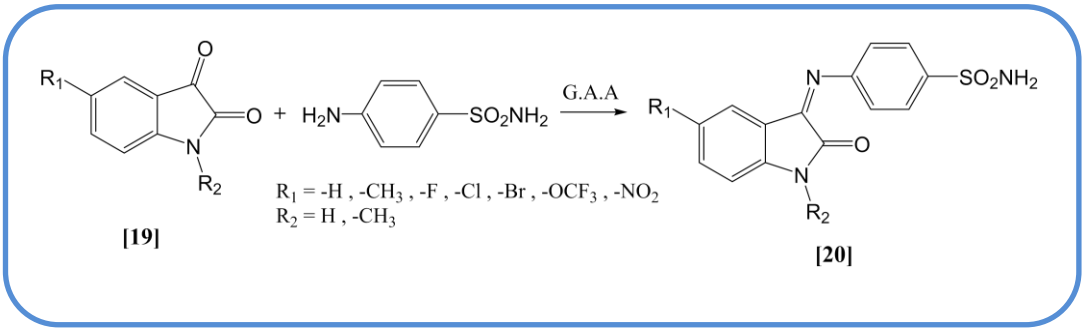
S. Kumar et al. [30] were prepared Schiff base [17] of by condensation 4-aminobenzenesulfonamides with aldehyde using concentrated hydrochloric acid as a catalyst and ethanol.



M. Kratky et al. [31] synthesized new Schiff bases [18] from treatment of 5-chlorosalicyladehyde with sulfonamide and measured the biological activity of these compounds.



G. A. Ozlen et al. [32] were synthesized imine compounds [20] from reaction of diketone compounds (dione) [19] with sulfonamide derivatives in presence of drops of G.A.A.

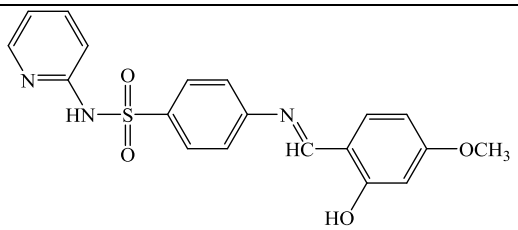
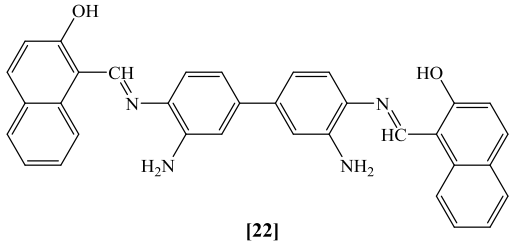


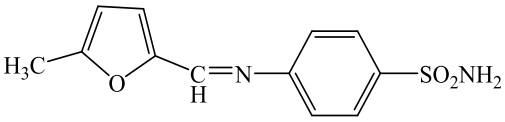
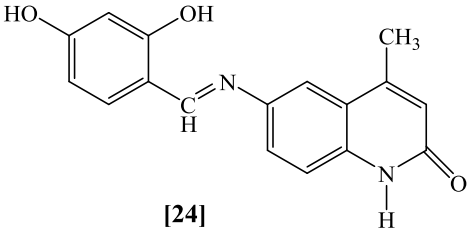
[19] [20]

1.4.4 Schiff Bases Activity

Schiff bases give many applications in the public life and the medical and pharmaceutical fields especially for having biological activities [33-35], such as anti-inflammatory, analgesic [36], antimicrobial [37], antibacterial, antifungal [38], antitumor [39]. Table (1.1) displayed Schiff bases activity.

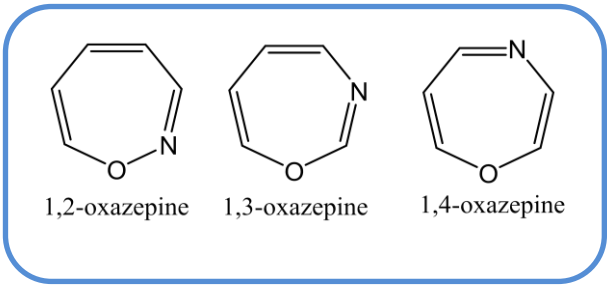
Table (1.1): Biological activity of some Schiff bases

Comp. name	Structure	Biological Activity	Rf.
4-((2-hydroxy-4-methoxybenzylidene)amino)-N-(pyridin-2-yl)benzenesulfonamide	 [21]	antitumor	(39)
1,1'-(((3,3'-diamino-[1,1'-biphenyl]-4,4'-diyl)bis(azanylidene))bis(methanylidene))bis(naphthalen-2-ol)	 [22]	anti-inflammatory analgesic	(40)

4-(((5-methylfuran-2-yl)methylene)amino)benzenesulfonamide	 [23]	antifungal antibacterial	(41)
(E)-6-((2,4-dihydroxybenzylidene)amino)-4-methylquinolin-2(1H)-one	 [24]	anticancer	(42)

1.5 Oxazepine

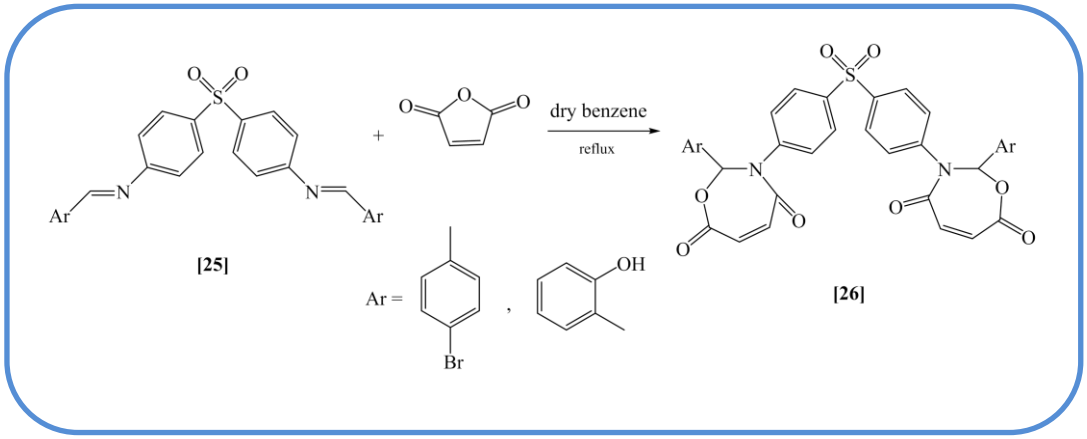
Oxazepine are heterocyclic compounds consisting of seven members ring from five carbon, nitrogen ,and oxygen elements in positions; 1,3 [43] . There are three isomers for oxazepine compounds 1,2 and 1,3 and 1,4-oxazepine [44].



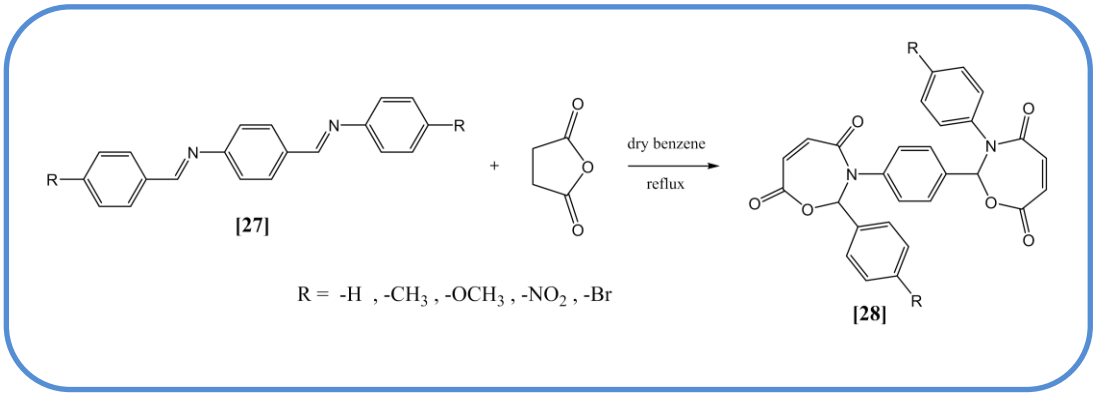
There are different ways for synthesis oxazepine, such as direct addition to double bond succinic anhydride or phthalic anhydride or maleic anhydride [45].

1.5.1 Synthesis of 1,3-Oxazepine Derivatives

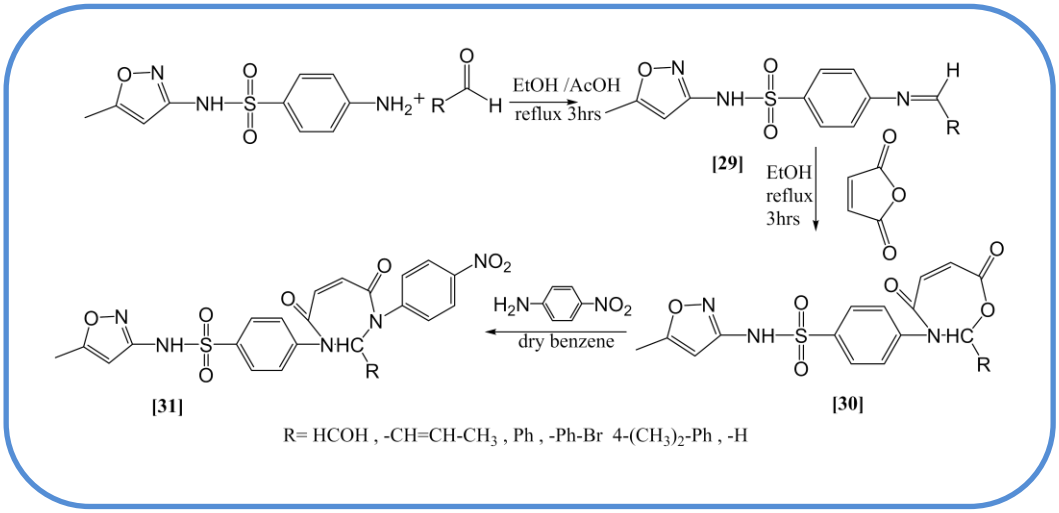
S. T. F. Ali et al. [46] were synthesized compounds [26] from reacting of Schiff bases [25] with maleic anhydride in dry benzene as a solvent.



F. H. Jumaa et al. [47] were synthesized oxazepines [28] from the reaction of phthalic or maleic anhydride with Schiff bases [27] in dry benzene.

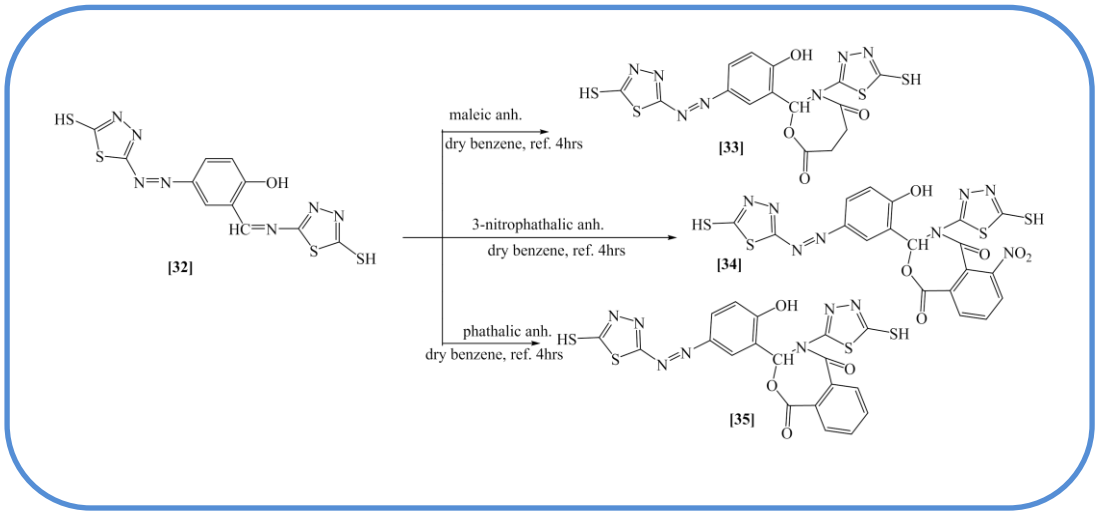


I. A. Yass. [48] ware prepared oxazepines derivatives [30,31] in water bath by reacted of imine compounds [29] with maleic anhydride in absolute ethanol. The mixture was refluxed for 3hrs. Scheme (1.5).



Scheme (1.5): Prepared oxazepines derivatives

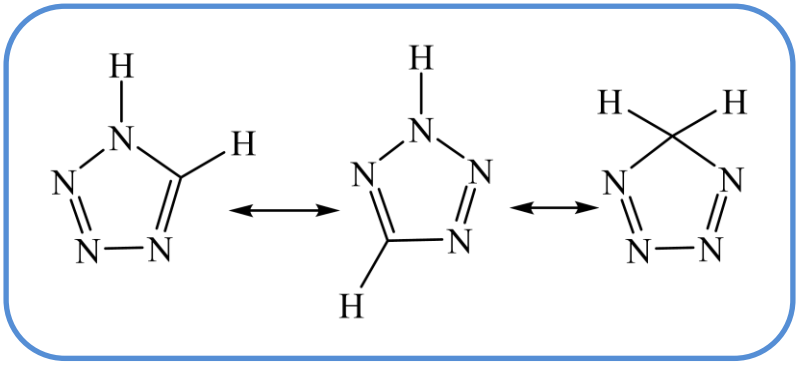
R. T. Haiwal [49] were synthesized oxazepine compounds [33-35] by treatment of imine compounds [32] with (maleic, phthalic, 3-nitrophthalic) anhydride in dry benzene and refluxed at 80ºC, Scheme (1.6).



Scheme (1.6): Preparing oxazepine compounds [33-35]

1.6 Tetrazole

It is a type of small heterocyclic organic rings containing carbon and four N atoms, its molecular formula $C_2N_4H_2$ [50]**.** This compound possesses several isomers due to the delocalization of H atom on N and this is called the tautomerization [51].

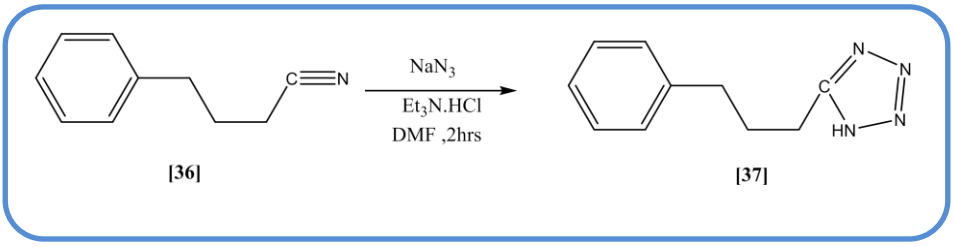


Tetrazole, an aromatic azabirol group, is stable in metabolism and has acidic behavior much similar to the carboxylic group [52].

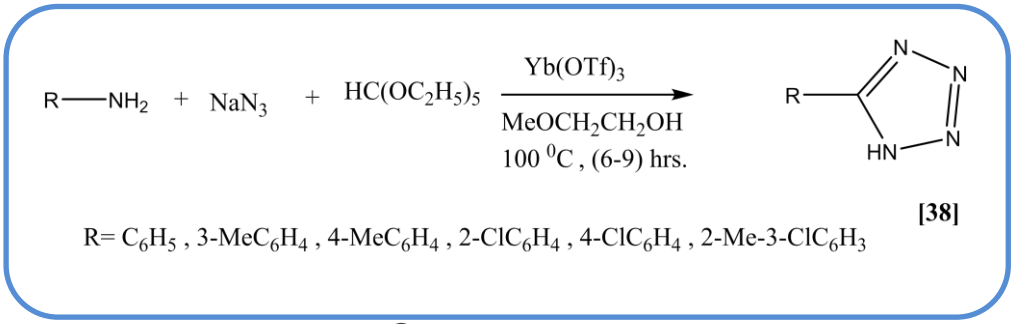
1.6.1 Synthesis of Tetrazole Derivatives

The tetrazole preparation was to a large reported in the literature survey. The major synthetic methods of tetrazoles could be by a reaction of substituted amines with NaN_3.

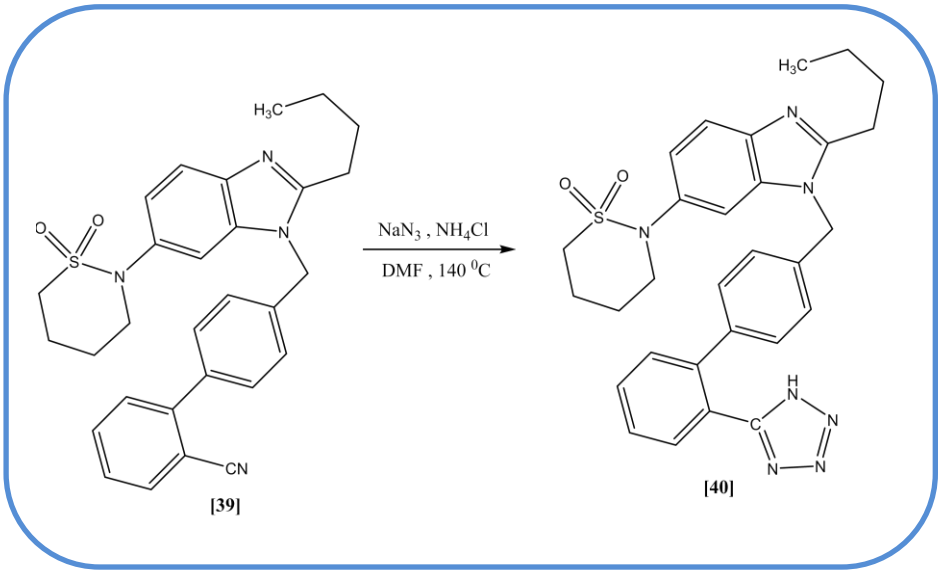
H. K. Eyama et al. [53] were synthesized of 5-(3-phenylpropyl)-1H-tetrazole [37] from reaction of 3-phenylpropionitrile [36] with sodium azide at 130 ^{0}C in 2 hrs.



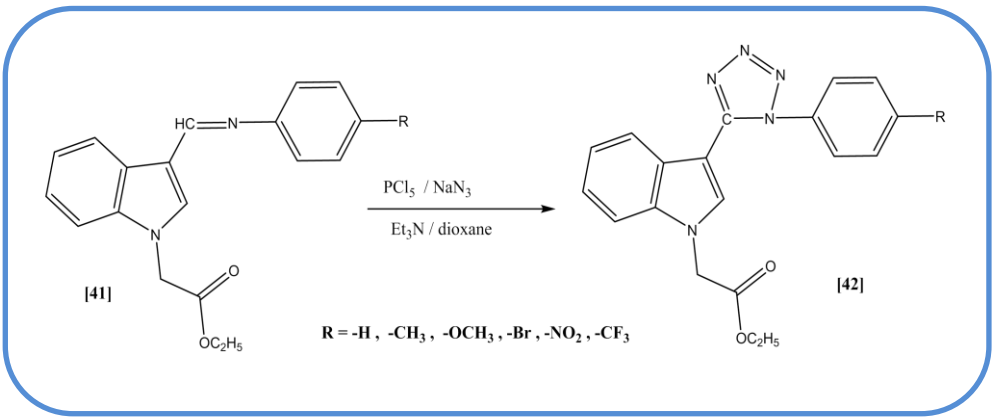
W. K. Su et al. [54] were synthesis of 5-substituted 1H-tetrazole derivatives [38] from sodium azide, amines, and triethylformate in 100 ^{0}C for 6-9 hrs.



U. J. Ries et al. [55] were prepared 1H-tetrazole derivative [40] by reaction of aryl nitrile [39] with ammonium salt and sodium azide and refluxed at 140 ^{0}C in DMF.



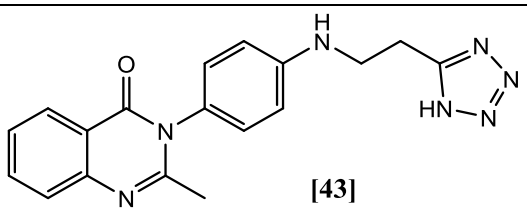
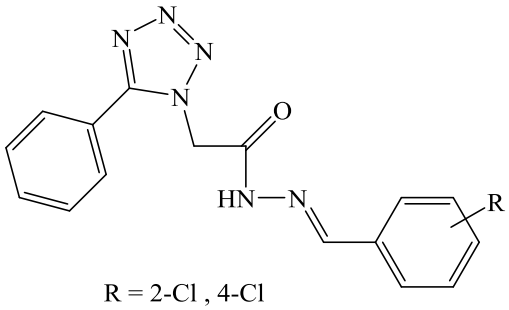
S. Muralikrishna et al. [56] Ethyl 2-(3-(1-phenyl-1H-tetrazol-5-yl)-1H-indol-1-yl)acetate [42] synthesized from mixed Schiff bases[41] and PCl_5 was heated at 100 C for 1 h.

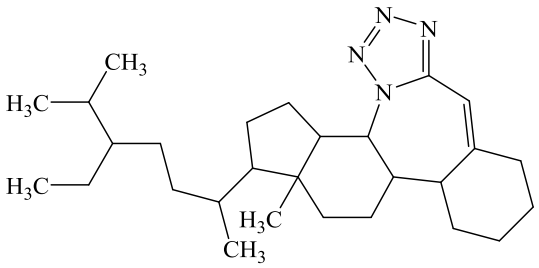
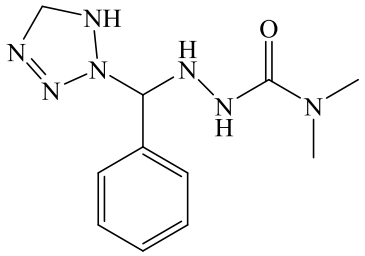
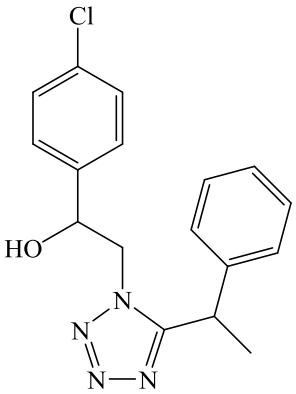


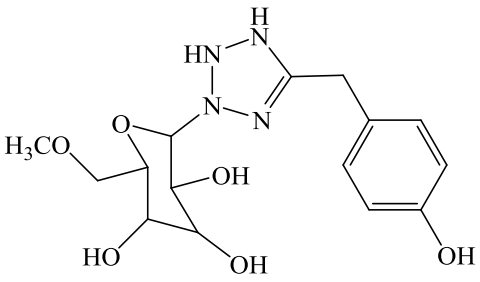
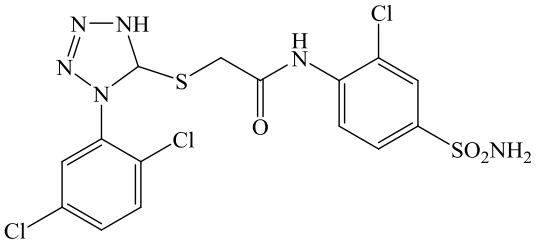
1.6.2 Pharmacological Activity of Tetrazole

Tetrazole compounds received significant attention to their pharmacutecal properties. Many of these researches have been published on the antifungal, and bacteriological properties of these derivatives. These compounds also offer anti-inflammatory [57], anti-cancer [58], analgesic [59], anticonvulsant [60], anti-hypertensive [61], antifungal and antimicrobial agents [62].

Table(1.2): Pharmacological activity of tetrazoles derivatives

Comp. name	Structure	Biological Activity	Rf.
3-(4-((2-(1H-tetrazol-5-yl)ethyl)amino)phenyl)-2-methylquinazolin-4(3H)-one	 **[43]**	antibacterial	(63)
(E)-N'-substituted benzylidene-2-(5-phenyl-1H-tetrazol-1-yl)acetohydrazide	 R = 2-Cl , 4-Cl **[44]**	antifungal	(64)

1-(5-ethyl-6-methylheptan-2-yl)-14a-methyl-1,2,3,3a,3b,9,10,11,12,12a,12b,13,14,14a-tetradecahydrobenzo[d]indeno[5,4-f]tetrazolo[1,5-a]azepine	 **[45]**	anticancer	(65)
2-((1,5-dihydro-2H-tetrazol-2-yl)(phenyl)methyl)-N,N-dimethylhydrazine-1-carboxamide	 **[46]**	anti-inflammatory	(66)
1-(4-chlorophenyl)-2-(5-(1-phenylethyl)-1H-tetrazol-1-yl)ethan-1-ol	 **[47]**	anticonvulsant	(67)

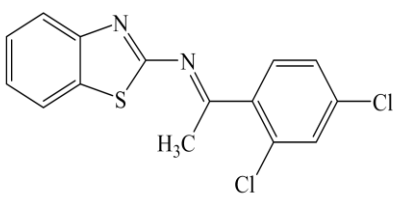
(2R,3S,5S,6S)-2-(5-(4-hydroxybenzyl)-3,4-dihydro-2H-tetrazol-2-yl)-6-(methoxymethyl)tetrahydro-2H-pyran-3,4,5-triol	 **[48]**	anti-diabetic	(68)
N-(2-chloro-4-sulfamoylphenyl)-2-((1-(2,5-dichlorophenyl)-4,5-dihydro-1H-tetrazol-5-yl)thio)acetamide	 **[49]**	anti HIV	(69)

1.7 Thiazolidinone

Thiazolidinone is the derivative of thiazolidine, it is a heterocyclic compound containing sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 4, in a five-member ring [70].

1.7.1 Synthesis of Thiazolidin-4-one

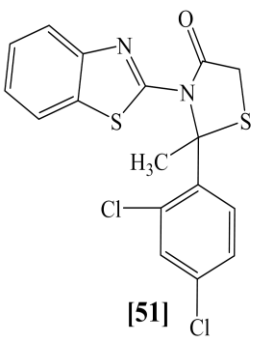
K. R. Desai et al. [71] synthesis of thiazolidinone [51] from thiolactic acid added to (N-(benzo[d]thiazol-2-yl)-1-(2,4-dichlorophenyl)ethan-1-imine) [50].



[50]

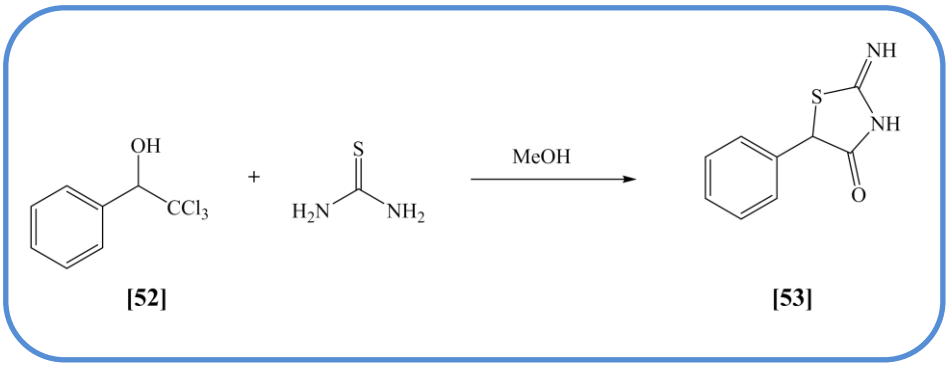
$HSCH_2COOH$

15 - 16 hrs

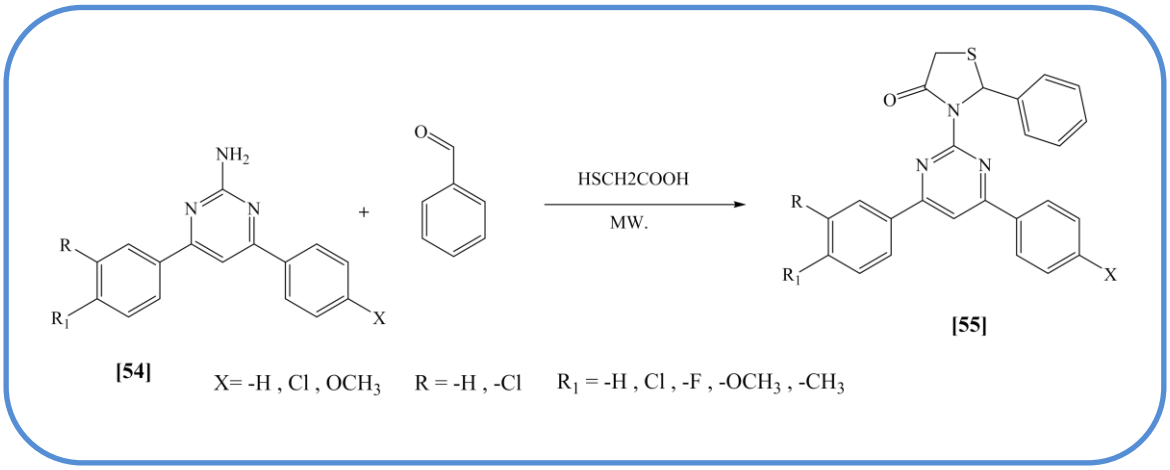


[51]

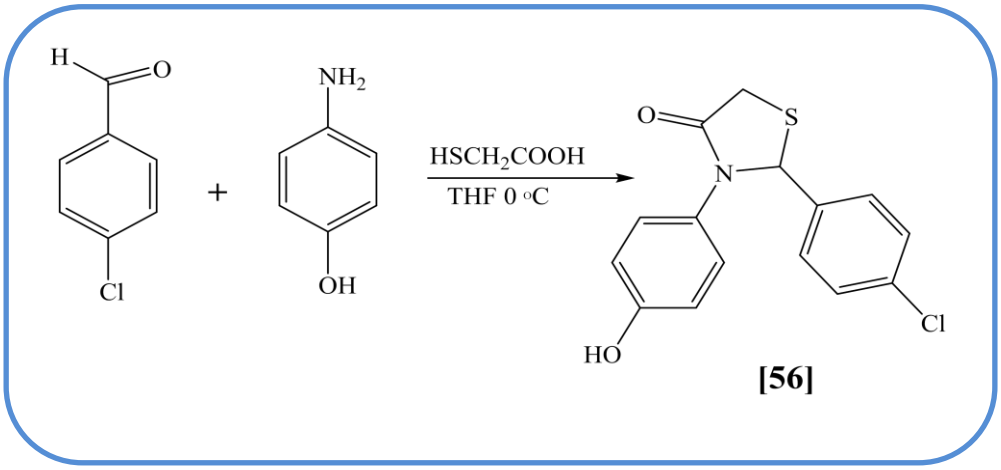
J. Blanchet et al. [72] were synthesized of 2-aminothiazolidin-4-one [53] from (2,2,2-trichloro-1-phenylethan-1-ol) [52] with thio-urea and refluxed in MeOH.



V. Kanagarajan et al. [73] were prepared 2-phenyl-3-(4,6-diarylpyrimidin-2-yl) thiazolidin-4-ones [55] by the addition of benzaldehyde, and thioglycolic acid to 2-amino-4,6-diarylpyrimidines[54] in the microwave.

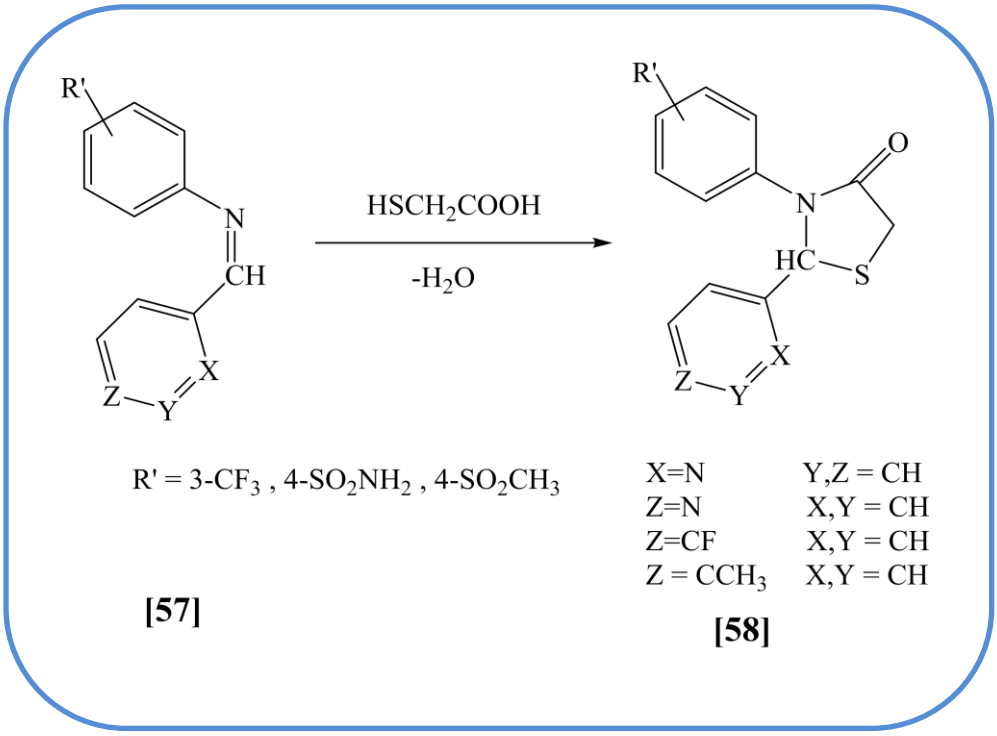


M. Sala, et al. [74] Prepared 2-(4-chlorophenyl)-3-(4-hydroxyphenyl)thiazolidin-4-one[56] from reacted of 4-aminophenol, 4-chlorobenzaldehyde and 2-mercaptoacetic acid in THF at 0 °C.



[56]

I. Vazzana et al. [75] prepared thiazolidinone [58] from treatment of Schiff base [57] with α-mercaptoacetic acid and refluxed for (7-30) hrs.



R' = 3-CF_3 , 4-SO_2NH_2 , 4-SO_2CH_3

[57]

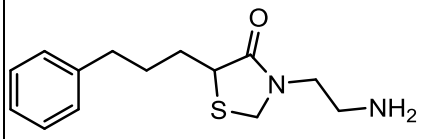
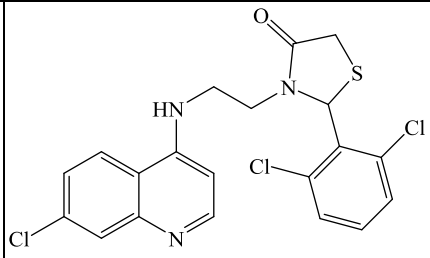
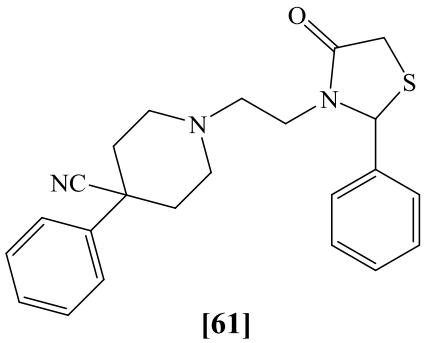
X=N	Y,Z = CH
Z=N	X,Y = CH
Z=CF	X,Y = CH
Z = CCH_3	X,Y = CH

[58]

1.7.2 Biological Activities of 1,3-Thiazolidin-4-one

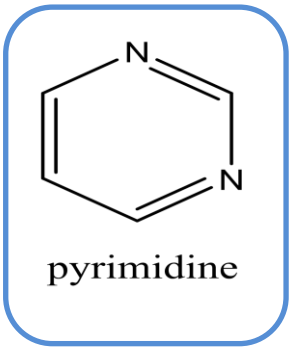
Thiazolidine-4-one is widely used for anti-disease drugs. This compound a number of activities such as anti-cancer, anti-arthritic, anti-inflammatory, anti-diabetic, anti-melanoma and anti-microbial. Among all of these, anti-diabetic activity has been widely carried out and a significant number of drugs are already available in the market such as rosiglitazone, pioglitazone, lobeglitazone, and troglitazone drugs [76,77].

Table(1.3): Biological activity of 1,3-thazolidine-4-one

Comp. name	Structure	Biological Activity	Rf.
3-(2-aminoethyl)-5-(3-phenylpropyl) thiazolidin-4-one	 **[59]**	anti-cancer	(77)
3-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(2,6-dichlorophenyl)thiazolidin-4-one	 **[60]**	anti-malarial	(78)
1-(2-(4-oxo-2-phenylthiazolidin-3-yl)ethyl)-4-phenylpiperidine-4-carbonitrile	 **[61]**	anti-yellow fever virus	(79)

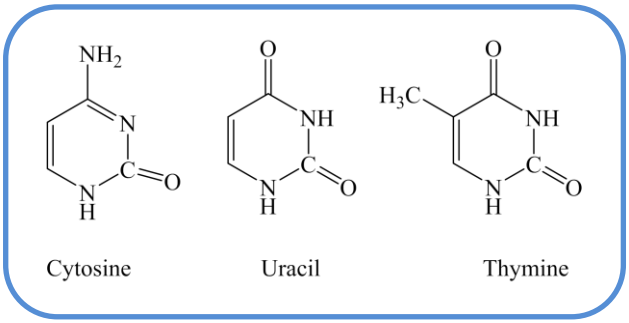
1.8 Pyrimidine

Pyrimidine of aromatic organic compounds, a six-member ring containing two nitrogen atoms in positions 3 and 1. Pyrimidine contains many similar properties with pyridine. The number of nitrogen atoms in the ring increases as the electronic resonance of the ring becomes less active [80].



pyrimidine

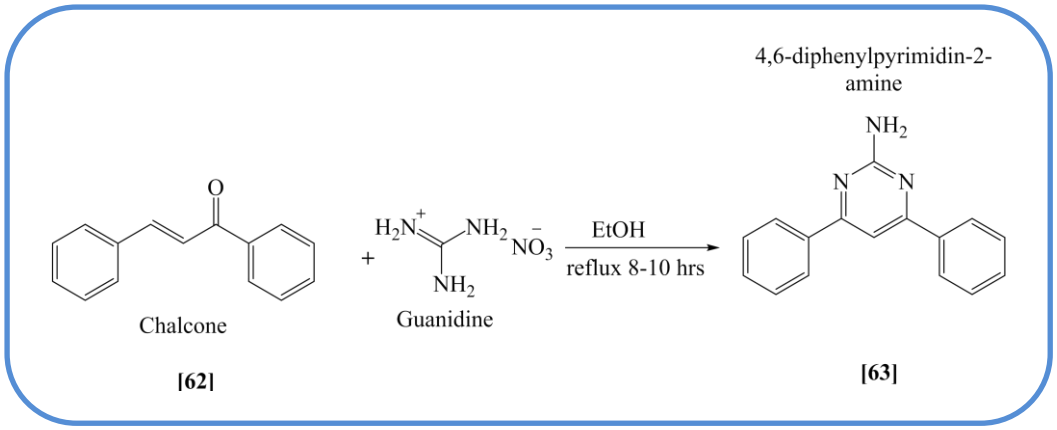
Pyrimidines are a type of diazine isomers are a class of heterocyclic and unsaturated compounds. The name diazine, according to the Hansch-Friedman system. Cytosine, Uracil, and Thymine these compounds are the basic bases of DNA and RNA. These compounds are derived from pyrimidine obtained from the decomposition of the above acids [81].



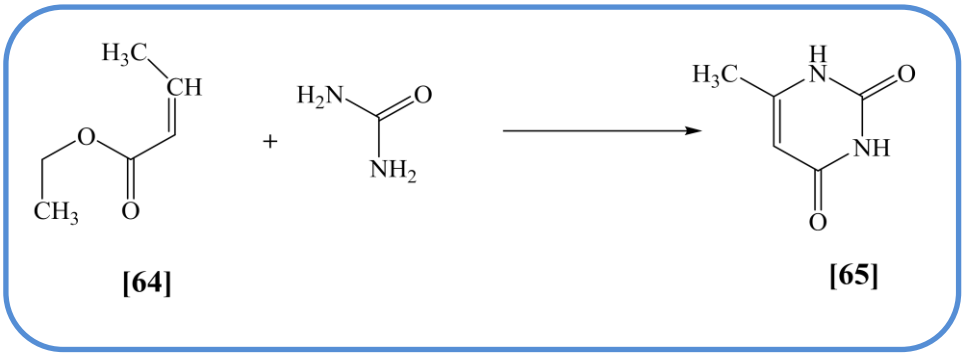
Cytosine Uracil Thymine

1.8.1 Synthesis of Pyrimidines

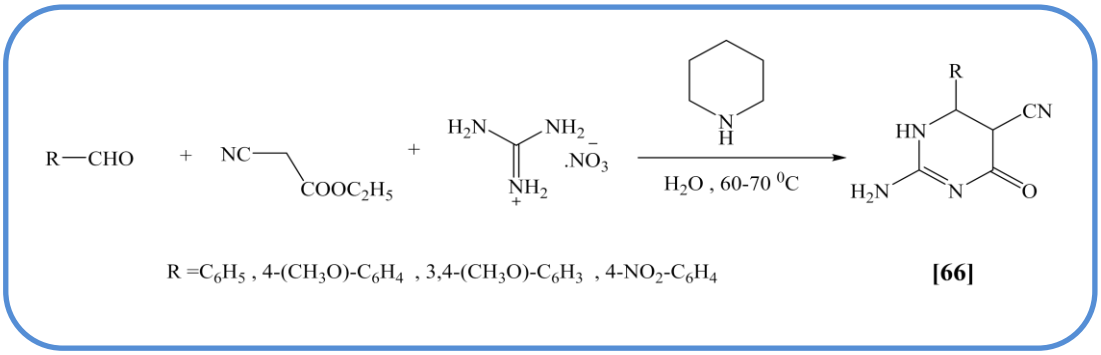
N. R. El-Rayyes et al. [82] were used the method of synthesis is through chalcone [62] was condensed with guanidine nitrate in the ethanol and aqueous NaOH and refluxed the reaction to 8-10 hrs.



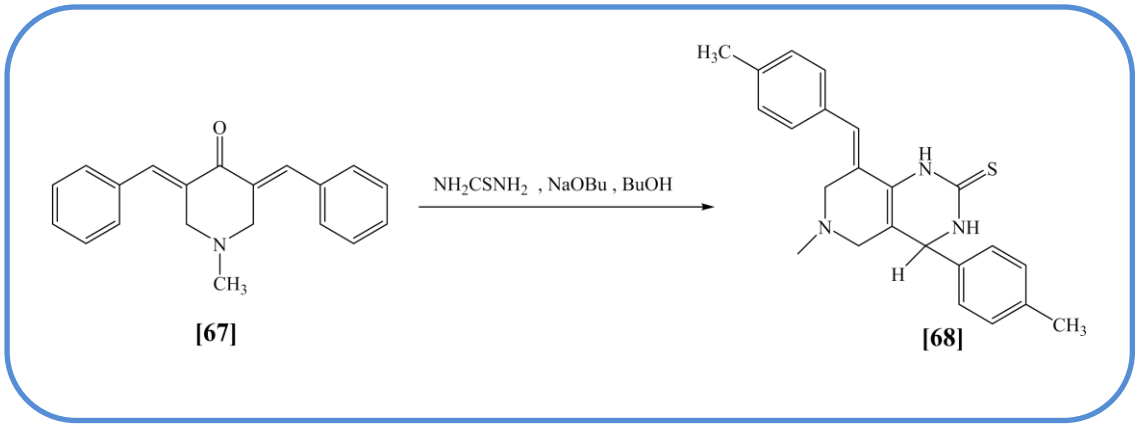
G. Bringmann et al. (83) were synthesized of pyrimidine[65] from the condensation of ureas or amidines with ethyl crotonate [64] or unsaturated compounds in the basic conditions.



B. Anjna et al. (84) synthesized 2-amino-4-oxo-6-aryl-tetrahy dropyrimidine-5-carbonitrile [66] and its derivative by three-component aromatic aldehydes, ethyl cyanoacetate, and guanidine nitrate by piperidine as a catalyst in an aqueous medium under the refluxing condition.



H. I. El-Subbagh et al. [85] were prepared pyrimidine [78] from reaction of 3,5-di((E)-benzylidene)-1-methylpiperidin-4-one[67] with thiourea in basic medium of butanol as a solvent and the mixture was refluxed for 10 hrs.

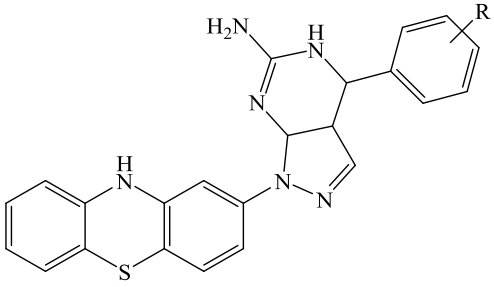
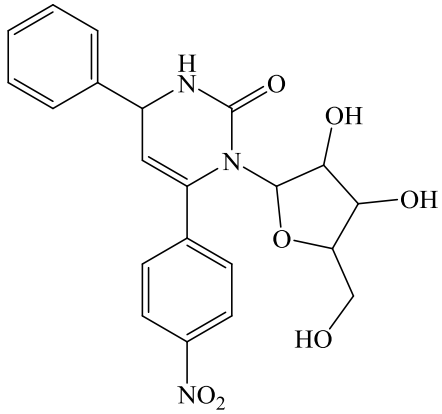
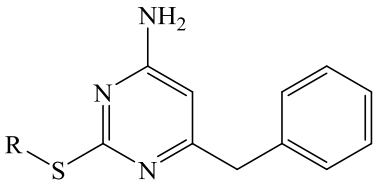


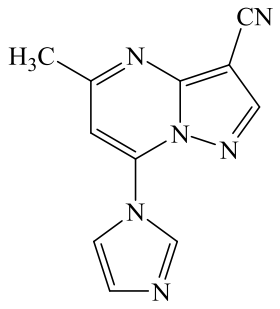
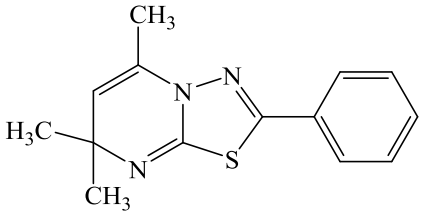
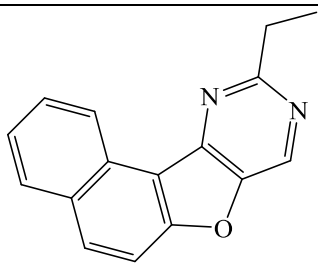
[67] **[68]**

1.8.2 Pharmacological Activities of Pyrimidines

Pyrimidine derivatives chemistry plays an important role in medicine and many biological activities. A wide range of pharmacological studies was conducted on pyrimidine and its derivatives. However, the need for further research remains for the importance of biological compounds. Pyrimidine derivatives have been used for many activities, such as antioxidants, antimicrobial, anti-inflammatory, antibiotic, antimicrobial, anticonvulsants, antispasmodics, anti-cancer, antifungal, and sedative activity [86]. The next Table displayed the biological activities.

Table (1.4): The pharmacological activities of pyrimidine

Comp. name	Structure	Biological Activity	Rf.
1-(10H-phenothiazin-2-yl)-4-phenyl-3a,4,5,7a-tetrahydro-1H-pyrazolo[3,4-d]pyrimidin-6-amine	 R= -H , OH , Cl , NO_2 , OCH_3 **[69]**	anti-tubercular activity	(87)
1-(3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-(4-nitrophenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one	 **[70]**	antioxidant activity	(86)
6-benzyl-2-(substitutedthio)pyrimidin-4-amine	 R = $-CH_2C_6H_5$, $-CH_2CH_2CH_2C_6H_5$ $-CH_2CH_2C_6H_5$, $-CH_2$ (m-OCH_3)C_6H_4 **[71]**	anti-HIV activity	(88)

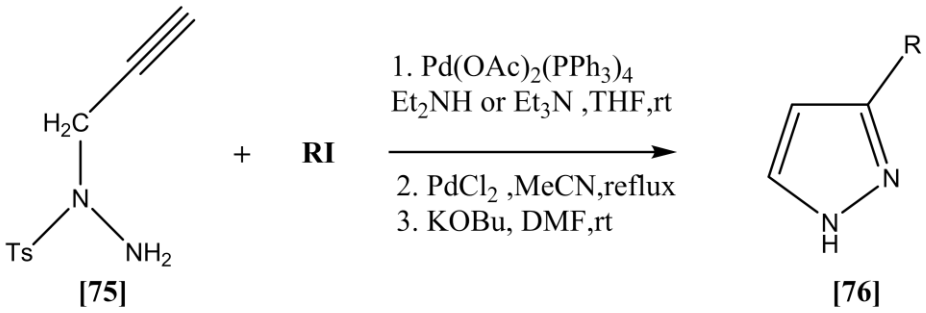
7-(1H-imidazol-1-yl)-5-methylpyrazolo[1,5-a]pyrimidine-3-carbonitrile	 **[72]**	hypnotic activity	(89)
5,7,7-trimethyl-2-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine	 **[73]**	herbicidal activity	(90)
10-ethylnaphtho[1',2':4,5]furo[3,2-d]pyrimidine	 **[74]**	anthelmintic activity	(91)

1.9 Pyrazoles

Pyrazoles contained of the heterocyclic rings, it is classified as the diazole family of five members containing two nitrogen and three carbons. Classified as alkaloids although they are rare in nature [92]. It has many interactions and biological activities will be detail in Table (5.1).

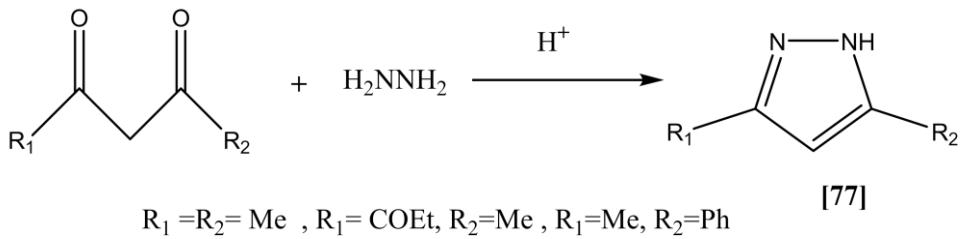
1.9.1 Synthesis of Pyrazole Derivatives

S. Cacchi et al. [93] was prepared 3-(5)aryl/vinyl-1H-pyrazole derivatives [76] from N-tosyl-N-propargylhydrazine [75] and aryl or vinyl iodides**.**



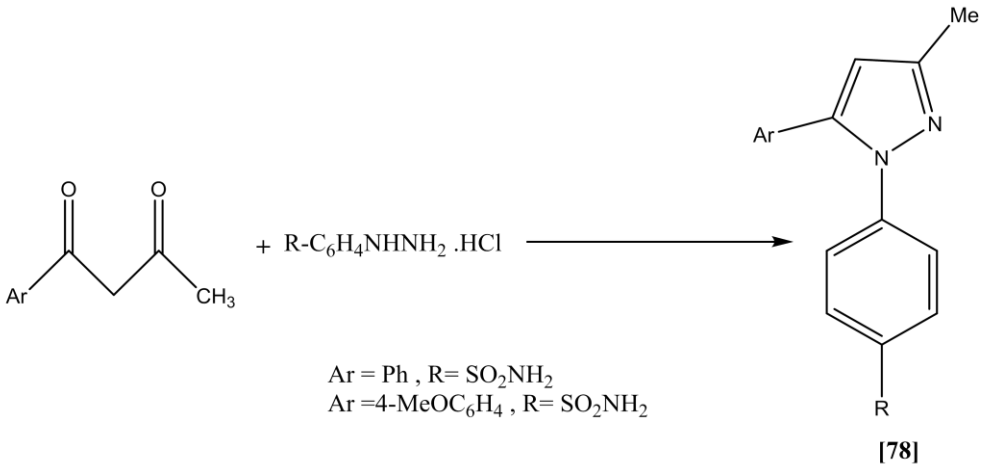
R = ph , 2-NO_2-C_6H_4 , 4-$MeCOC_6H_4$, 3-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$

X. Zhong et al. [94] synthesized 3,5-disubstituted pyrazole [77] from mixed diketone with hydrazide and few drops of H_2SO_4**.**



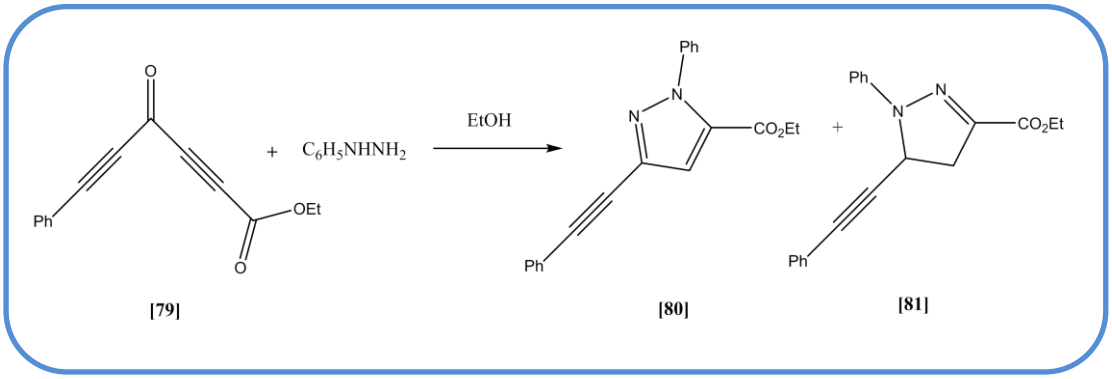
R_1 =R_2= Me , R_1= COEt, R_2=Me , R_1=Me, R_2=Ph

F. Gosselin et al. [95] prepared the compound [78] by reaction 1-arylbutane-1,3-dione with arylhydrazide hydrochloride in N,N-dimethylacetamide

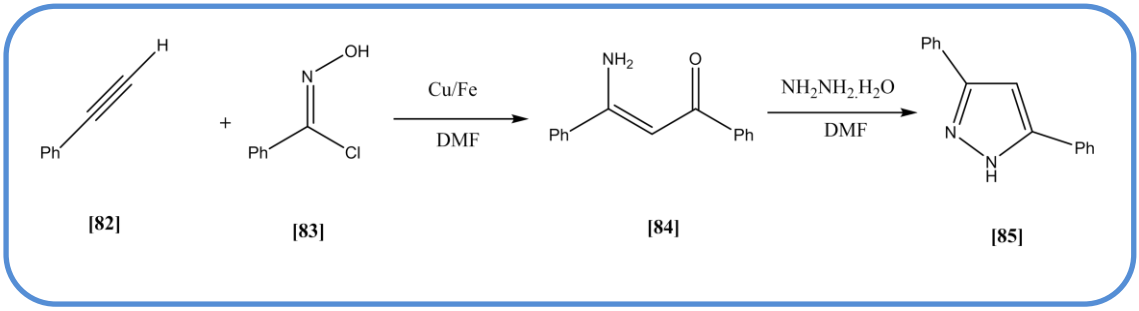


Ar = Ph , R= SO_2NH_2
Ar =4-$MeOC_6H_4$, R= SO_2NH_2

J. E. Baldwin et al. [96] synthesized pyrazole derivative [80,81] by used EtOH as solvent and dissolved it ethyl 4-oxo-6-phenylhexa-2,5-diynoate [79], phenylhydrazine.



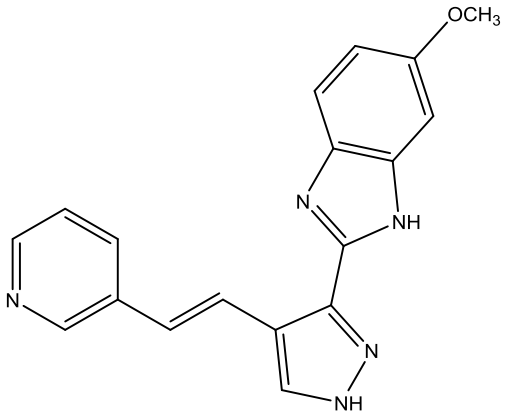
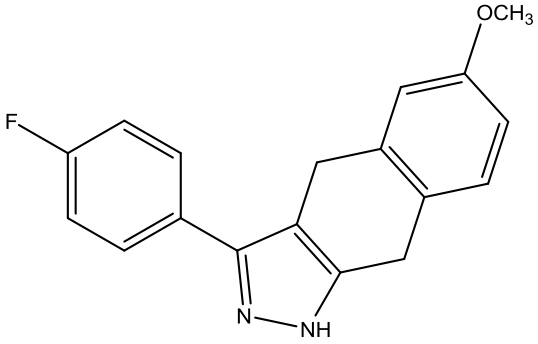
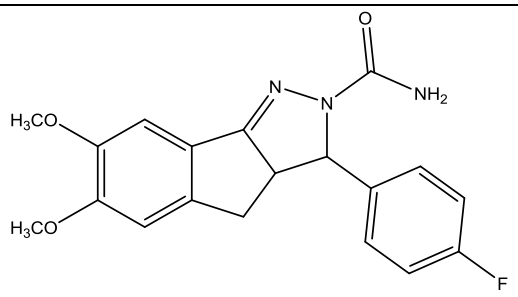
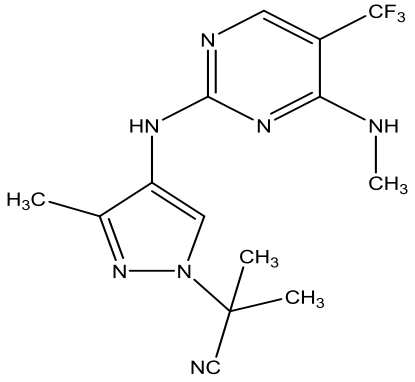
S. Kovacs et al. [97] Synthesized of 3,5-substituted pyrazole [85] by a reaction of the coupling between any alkyne [82] and any oxime [83] in the DMF, where a product beta-aminoenone [84] is produced with the addition of hydrazine, which produces the corresponding pyrazole.



1.9.2 Pharmacological Activities of Pyrazole

All studies have shown that pyrazole derivatives played an important role in the pharmaceutical industry and have been shown in literature survey revealed to have worked as an antibiotic against antifungal, anticancer, anti-tubercular, anticonvulsant , antipyretic, anti-bacterial, anti-inflammatory, and analgesic [98]. Table (1.5) shows the pharmacological activity of pyrazole.

Table (1.5): The biological activities of pyrazole derivatives

Comp.name	Structure	Biological Activity	Rf.
6-methoxy-2-(4-(2-(pyridin-3-yl)vinyl)-1H-pyrazol-3-yl)-1H-benzo[d]imidazole		antitumor	(99)
3-(4-fluorophenyl)-6-methoxy-4,9-dihydro-1H-benzo[f]indazole		anticancer	(100)
3-(4-fluorophenyl)-6,7-dimethoxy-3a,4-dihydroindeno[1,2-c]pyrazole-2(3H)-carboxamide		anti-tubercular	(101)
2-methyl-2-(3-methyl-4-((4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)propanenitrile		anti-parkinson	(102)

The aim of this study

1) Synthesis of new Schiff bases derived from oxime and sulfonamide compounds.

2) Synthesis of 1,3-oxazepine derivatives of azomethine compounds.

3) Synthesis of tetrazole and thiazolidin-4-one compounds from azomethine compounds.

4) Synthesis of the pyrazole compounds.

5) Synthesis of the pyrimidine compounds.

6) Spectroscopic characterization of the prepared compounds by FTIR, ^{1}H-NMR, and ^{13}CNMR.

7) Evaluate their biological Activity against four types of bacteria such as (***Staphylococcus aureus, Bacillus Subtilis***) gram-positive and (***E. coli, pseudomonas aeruginosa***) gram-negative and one type of fungal such as ***(Candida albicans)*** and comparison with penicillin as an antibiotic.

Chapter two

Experimental part

2.1 Chemicals

Table (2.1) shows all the used chemicals in experimental couse of this work.

Table (2.1): Chemicals and their manufactures

No.	Chemicals	Company supplied from
1	2-Mercaptoacetic acid	Aldrich
2	3-Nitrophthalic anhydride	SEGMA
3	4-Aminoacetophenone	BDH
4	4-Aminobenzenesulphonamide 99%	Aldrich
5	4-Hydroxyacetophenone	Aldrich
6	4-Methylbenzenesulfonyl chloride	Aldrich
7	Acetone 99%	Alfa aesar
8	Acetyl chloride	Himedia & Merck
9	Benzene 99.5%	BDH
10	Benzenesulfonyl chloride	BDH
11	Diethyl malonate	Merck
12	Diethylether 99%	Merck
13	Dimethylformamide (DMF) 99%	BDH
14	Dimethylsulphoxide (DMSO)99%	BDH
15	Ethanol absolute 99.8%	Merck
16	Ethyl chloroacetate 99.8%	Merck
17	Glacial acetic acid 99.8%	Aldrich
18	Hydroxylamine hydrochloride , 99%	Aldrich
19	Maleic anhydride	Riedel-De Haen
20	Methanol 99.99% HPLC	Fluka
21	N,N-Dimethylaminobenzaldehyde97%	Aldrich
22	Potassium hydroxide	BDH
23	Pyromellitic dianhydride	Fluka
24	Sodium acetate 99.9%	SEGMA
25	Sodium azide	Aldrich
26	Sodium carbonate	BDH
27	Thiourea	Riedel-De Haen
28	Urea	Fluka
29	Acetyl acetone	Merck

2.2 Instruments

2.2.1 Spectroscopy

i) Fourier transform infrared spectrophotometer (FTIR)

FT-IR spectra were measured by using KBr disc by a SHIMADZU FT-IR spectroscopy at Ibn Sinaa company; Baghdad, Iraq. In addition, some spectra were carried at the College of Pure Science, University of Baghdad (Center Lab).

ii) Nuclear magnetic resonace (^{1}HNMR & ^{13}CNMR)

^{1}HNMR & ^{13}CNMR spectra were accomplished by Ultra Shield 300 MH_Z, Bruker, in Sharif university of technology, Tehran / Iran. Reported in δ(ppm) and DMSO was used as a solvent with TMS as an internal standard.

iii) Elemental microanalysis

Elemental micro-analyses (C.H.N.S) of some compounds were performed on a EuroEA Elemental Analyzer (Euro vector- Italy model) at Central Service Laboratory - College of Education for Pure Science (Ibn Al-Haitham).

2.2.2 Melting point measurements

The melting points were measured in open capillaries, to used (Stuart) melting point (SMP30,England).

2.2.3 Thin layer chromatography (TLC).

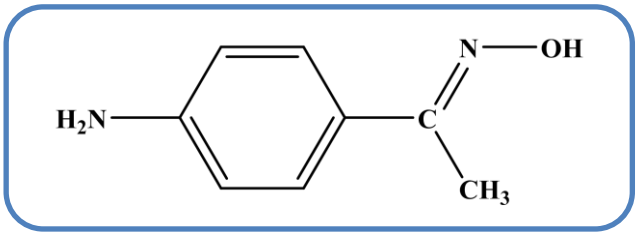
TLC was execution on aluminum plates coated with a layer silica gel provided by MACHEREY-NAGEL. The spot was detected by burn a plate. The completed reaction and the purity of new compoundes were checked by using; (benzene: methanol) (9:1).

2.2.4 Evaluate biological activity.

Biological activities evaluating were specified in Market Research and Consumer Protection Center; University of Baghdad.

2.3 Synthesis of compounds

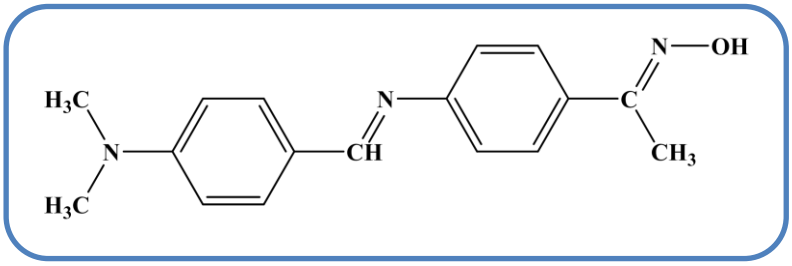
2.3.1 Preparation of compound [A] (103)



In 20 mL ethanol, dissolved (5.5 gm, 40 mmol) of 4-amino acetophenone in a round flask. With the mixture of ethanol and a minimum amount of water until the solution is clear dissolved (2.77 gm 40 mmol) of $H_2NOH.HCl$ and (3.28 gm, 40 mmol) of CH_3COONa, and gradually added the mixture to the flask then refluxed for 6 hours.

After the reflexes, the solution was left at room temperature and added to ice water.The crystals were filtered, left dry then re-crystallized by ethanol **.** R*f* and physical properties as shown in Table (2.2)

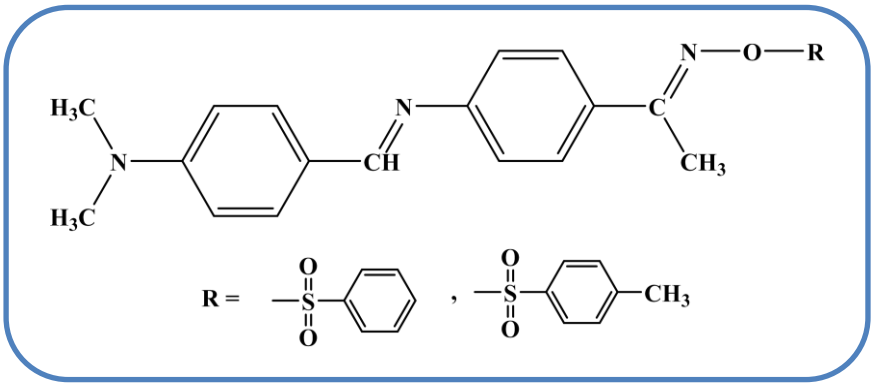
2.3.2 Synthesis of compound [A1] (104)



4-(Dimethylamino)benzaldehyde (10 gm, 67 mmol) was dissolved in 30 mL ethanol. A few drops of G.A.A were added to the solution and left to stir for 5 minutes. Added (10.06 gm, 67 mmol) of the prepared oxime to the round flask and refluxed at 78 ^{o}C for 3hrs. Filtered the solution and

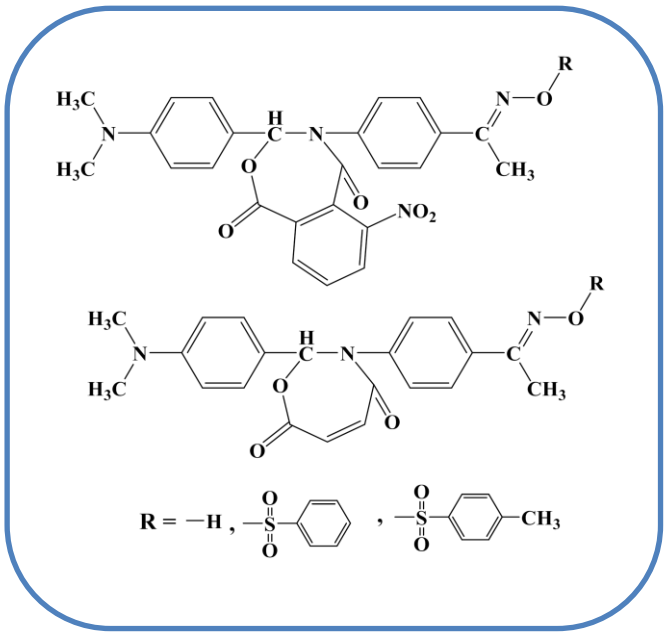
recrystallized the yellow precipitates by ethanol. R*f* and physical properties as shown in Table (2.2).

2.3.3 Synthesis of compounds [A2, A3] [6, 105]



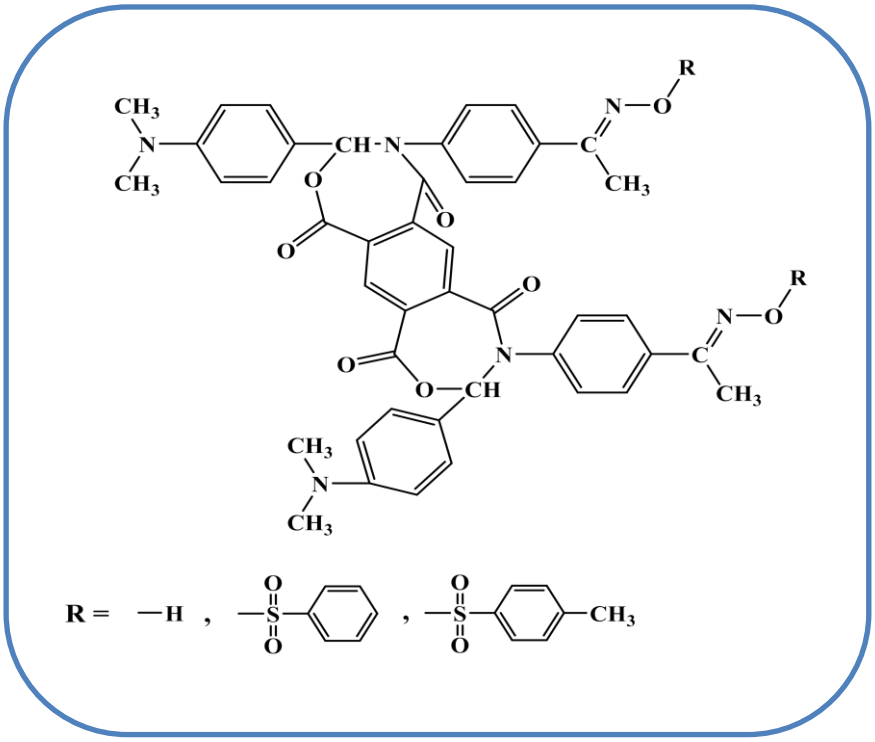
Schiff base **[A1]** (10 mmol) was dissolved in 20 mL of pyridine in an ice bath (0 ^{o}C) and mixed with (10 mmol) of (benzenesulfonyl chloride, 4-methylbenzenesulfonyl chloride) and it has been left to stirring for 2 hrs until the reaction was completed. The precipitate (Maronite) was washed with a diluted solution of cold water and hydrochloric acid, filtered and recrystallized in ethanol. R*f* and physical properties as shown in Table (2.2).

2.3.4 Synthesis of compounds [A4 –A9] (106)



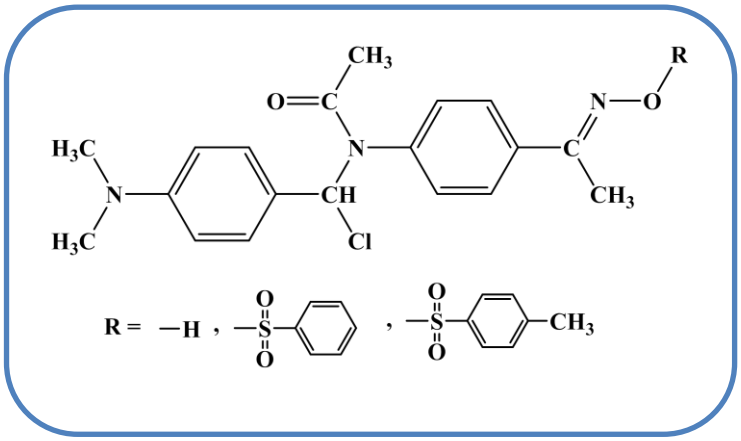
A mixture of Schiff bases [A1-A3] (1 mmol) was dissolved in 15 mL dry benzene at 80 ^{o}C in a water bath and refluxed for 5 minutes. After that, (maleic anhydride, 3-nitrophthalic anhydride) (1 mmol) was added to the round flask and it has been left to reflux for 6 hours. After completing the reaction, the product was filtered, and recrystallized by benzene. R*f* and physical properties in the Table (2.2).

2.3.5 Synthesis of compounds [A10-A12]



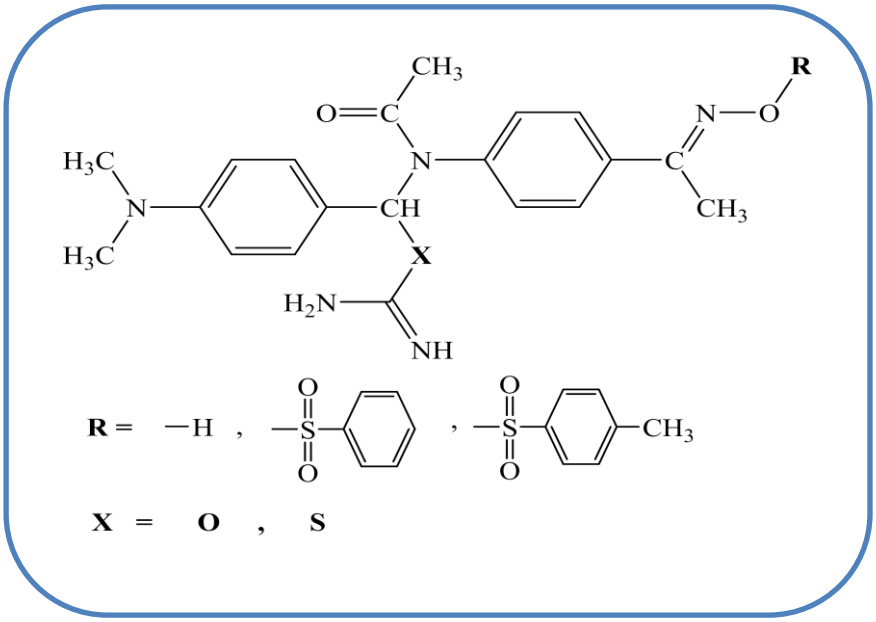
A mixture of Schiff bases [A1-A3] (2 mmol) was dissolved in 15 mL dry benzene at 70 °C in a water bath and refluxed for 5 minutes. After that, pyromellitic dianhydride (1mmol) was added to the mixture and it has been left to reflux for 8 hrs. After completing the reaction, filtered and recrystallized by dry benzene. R*f* and physical properties as shown in Table (2.2).

2.3.6 Synthesis of compounds [A13-A15]



In dry benzene 10 mL, Schiff bases [A1-A3] (10 mmol) was dissolved at 0 ^{o}C and acetyl chloride (10 mmol) was added to the droplets and it has been left to stirring for (1-2) hrs. The precipitate was then filtered and re-crystallized by benzene. The Table (2.2) displayed R*f* and physical properties.

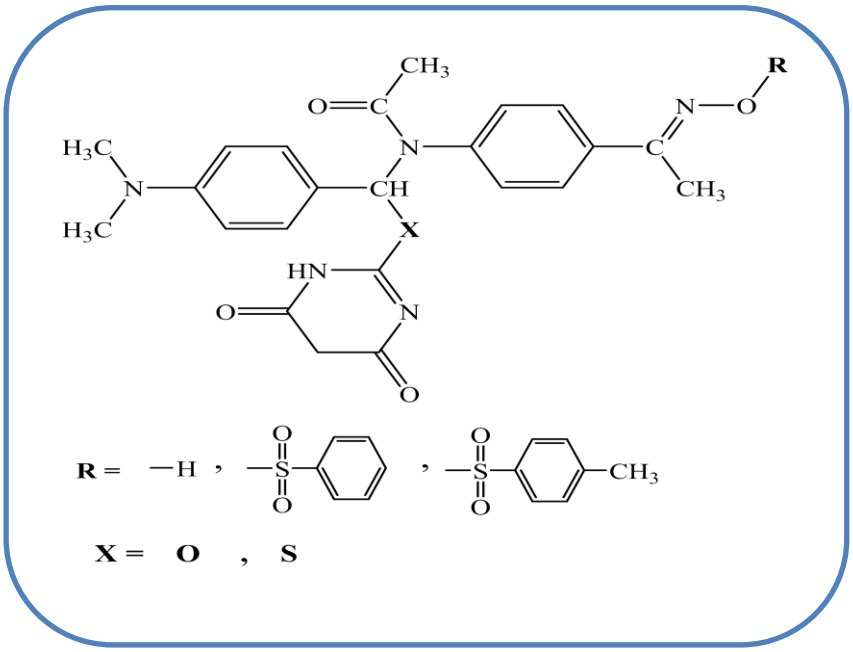
2.3.7 Synthesis of compounds [A16-A21]



The compounds **[A13-A15]** (1 mmol) were dissolved in 20 mL benzene with Na_2CO_3 as a catalyst in a round flask and added (urea or thiourea) (1 mmol) to the mixture. Continue on the reflux for 4-6 hrs.

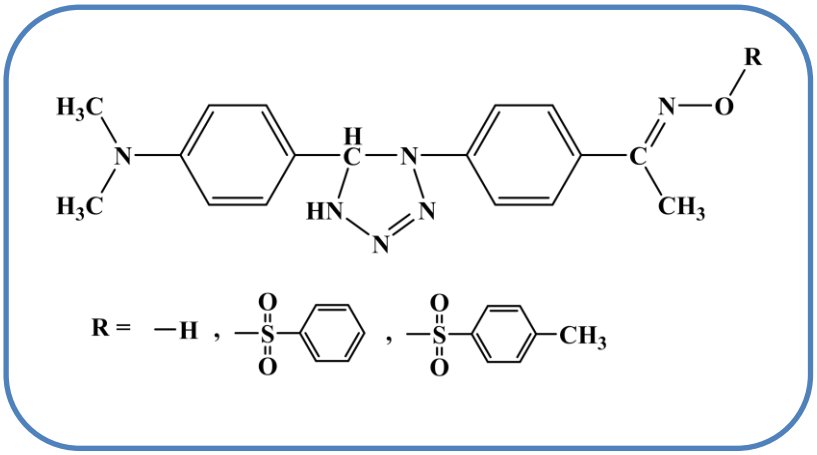
(monitored by TLC; benzene: methanol, 9:1) Then the solution was left at room temperature the product has been filtered and re-crystallized by acetone. The Table (2.2) displayed physical properties and R*f*.

2.3.8 Synthesis of compounds [A22-A27]



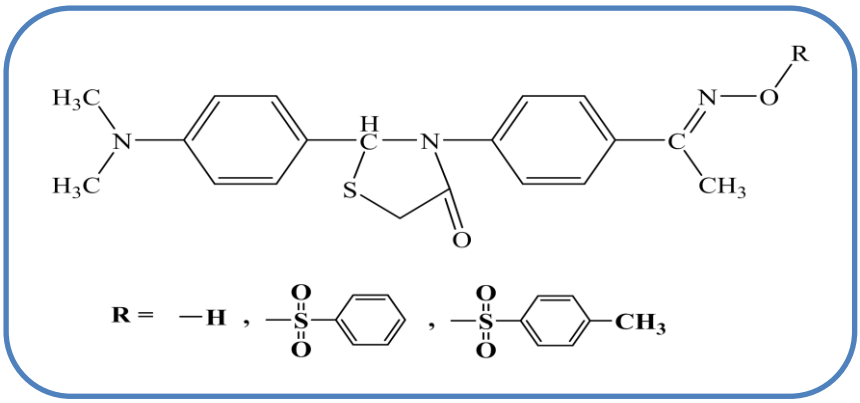
The compounds **[A16-A21]** (1mmol) were dissolved in 20 mL dry benzene with Na_2CO_3 as a catalyst in a round flask and added diethyl malonate (1mmol) to the mixture. It was refluxed for 4 hrs and then be filtered and dried. R*f* and physical properties as shown in Table (2.2).

2.3.9 Synthesis of compounds [A28–A30]



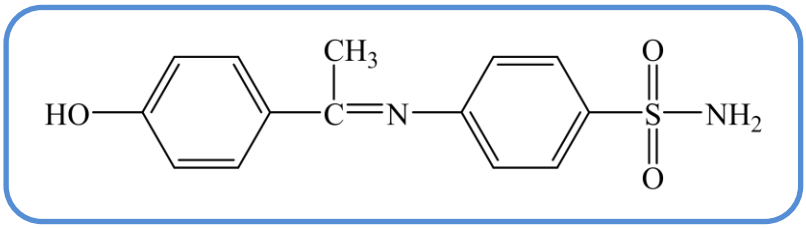
A mixture of Schiff bases [A1, A2, A3] (1 mmol) was dissolved in 10 mL DMF at the round flask. After that, sodium azide (1 mmol) was added to the mixture and it's been left to reflux for 20 hours, (monitored by TLC; methanol: benzene, 1:9) after complete that, filtered, dried, and recrystallized by EtOH. R*f* and physical properties as shown in Table (2.2).

2.3.10 Synthesis of compounds [A31-A33]



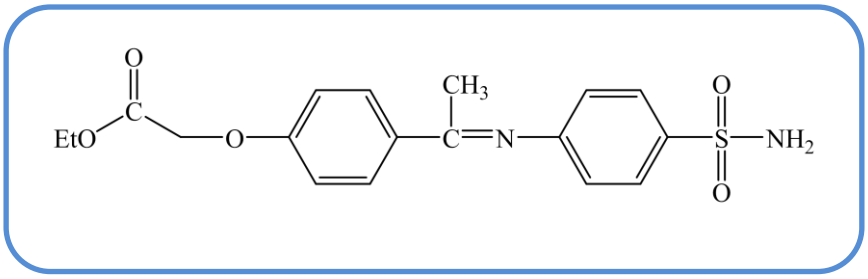
The Schiff bases [A1, A2, A3] (1 mmol) were dissolved in 20 mL acetone and thioglycolic acid (1 mmol) was added. The reflux was left for 12 hrs. (monitored by TLC; methanol: benzene, 1:9). Then the solvent evaporated washed the precipitate with water. The product was recrystallized by ethanol. The Table (2.2) displayed R*f* and physical properties.

2.3.11 Synthesis of compounds [B1]



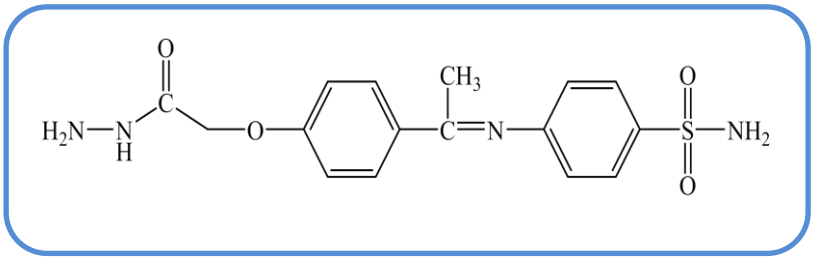
In dry benzene (30 ml), added 4-hydroxy acetophenone (50 mmol) and 3 mL G.A.A in a water bath at 80 °C and added 4-aminobenzine-sulfonamide (50 mmol) to the mixture. It has been left for 48 hrs. in refluxed. The yellow product filtered re-crystallization in dry benzene. The Table (2.3) displayed physical properties and R*f*.

2.3.12 Synthesis of compound [B2]



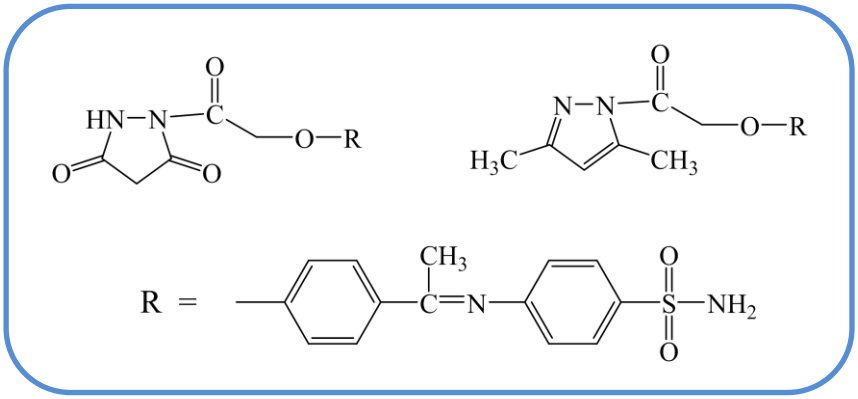
The ester compound **[B2]** was synthesized by dissolved (10 mmol) of the compound [B1] in 20 mL of acetone and added it an increase of potassium hydroxide and sodium carbonate. Ethyl chloroacetate (10 mmol) was then added to the mixture and refluxed for 6 hrs. and the White color product re-crystallization in EtOH. R*f*, Physical properties as shown in the Table (2.3).

2.3.13 Synthesis of compound [B3] [107]



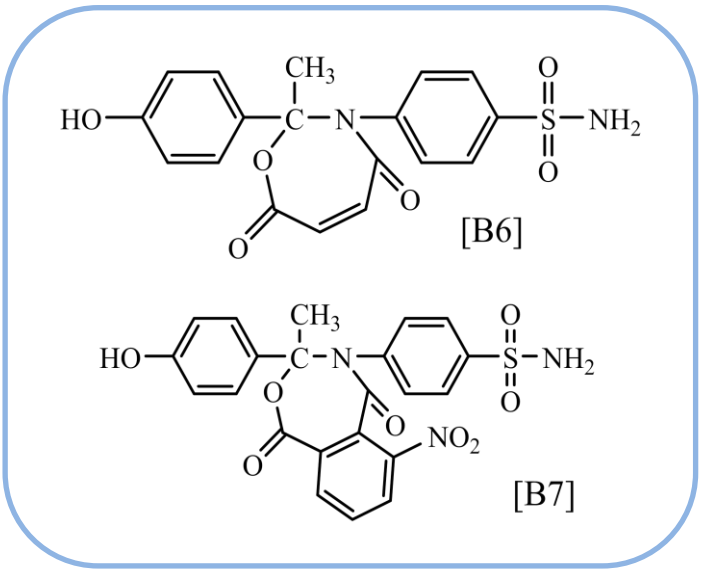
The compound [B2] (10 mmol) was dissolved in the ethanol 15 mL and added it hydrazine hydrate (10 mmol). Refluxed the mixture for 3 hrs., filtered the precipitate and recrystallized by ethanol. The Table (2.3) displayed R*f* and physical properties.

2.3.14 Synthesis of compounds [B4] [B5]



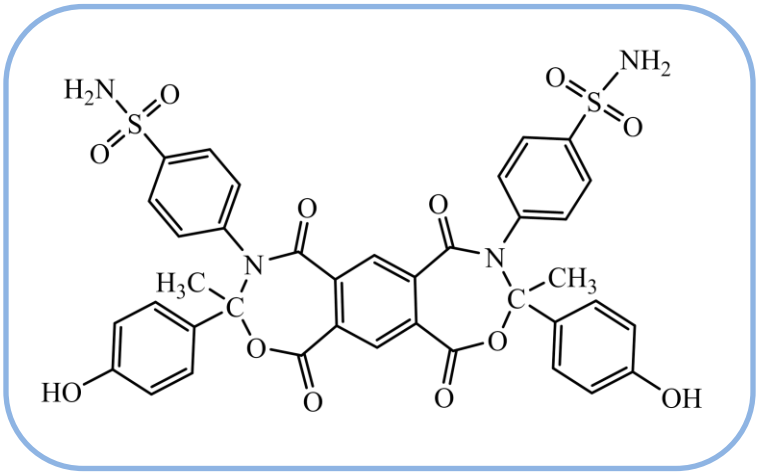
In a round flask, added (10 mmol) 4-((1-(4-(2-hydrazinyl-2-oxoethoxy)phenyl)ethylidene)amino)benzenesulfonamide was placed (10mmol) of sodium carbonate with a small amount in dry benzene in a water bath 80 °C after 5 minutes, then added (diethyl malonate, acetyl acetone) (10mmol) in droplets to the mixture and refluxed for 4-5 hrs. collected, filtered the precipitate, and re-crystallized by dry benzene. The Table (2.3) displayed R*f* and physical properties.

2.3.15 Synthesis of compounds [B6][B7] (108)



A Schiff base (10 mmol) was dissolved in 15 mL dry benzene at 80C° in a water bath. After 5 minutes, (3-nitrophthalic anhydride, maleic anhydride) (10 mmol) was added to a round flask and Leave it to reflux for 8 hours. After completing the reaction, the product was filtered and recrystallized by dry benzene. R*f* and physical properties has shown in Table (2.3).

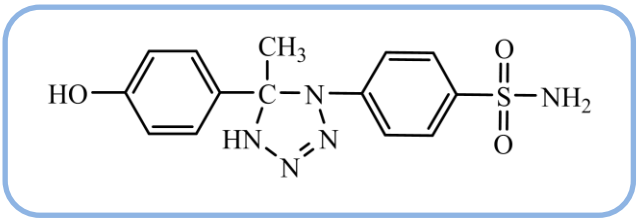
2.3.16 Synthesis of compound [B8]



Schiff base [B1] (2 mmol) was dissolved in 15 mL benzene at 80 °C in a water bath and refluxed for 5 minutes. After that, pyromalitic dianhydride (1 mmol) was added to the mixture and

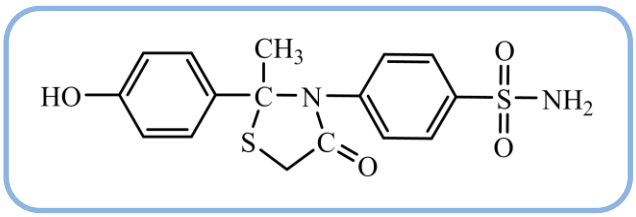
left to refluxed for 12 hrs. after completing the reaction, filtered and recrystallized by dry benzene. The Table (2.3) displayed R*f* and physical properties.

2.3.17 Synthesis of compound [B9]



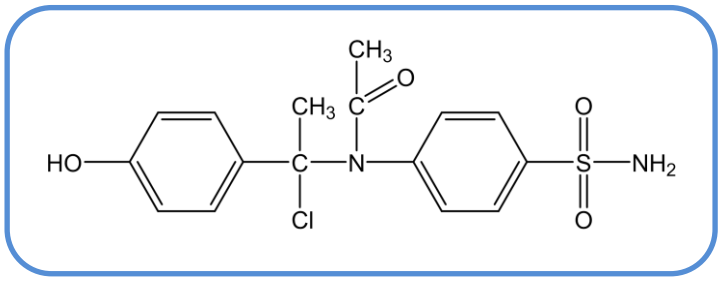
Schiff base (1 mmol) was dissolved in 10 mL DMF at the round flask after that, sodium azide (1 mmol) was added to the mixture and left to reflux for 48 hrs. (monitored by TLC; methanol: benzene, 1:9) after completing, filtered and recrystallized by ethanol. R*f* and physical properties as shown in a Table (2.3).

2.3.18 Synthesis of compound [B10]



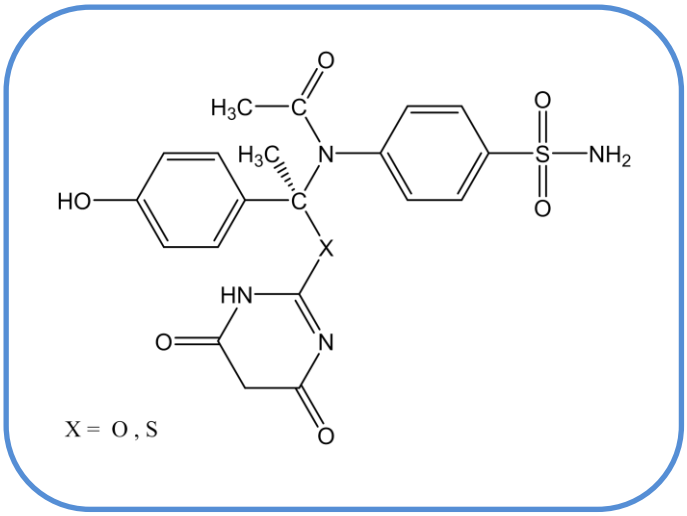
The Schiff base (1 mmol) was dissolved in 15 mL acetone and thioglycolic acid (1 mmol.) was added. The reflux was left for 10 hrs (monitored by TLC; methanol: benzene, 1:9). The solvent evaporated, then washed the precipitate with water, the product was re-crystallized by ethanol. R*f* and physical properties as shown in a Table (2.3).

2.3.19 Synthesis of compound [B11]



In acetone as a solvent (10 mL) the compound [B1] was dissolved at 0 °C and acetyl chloride (10 mmol) was added to the droplets and it has been left to stirring for (4) hrs. The precipitate was then filtered and re-crystallized by acetone. The Table (2.2) displayed R*f* and physical properties.

2.3.20 Synthesis of compounds [B12, B13]



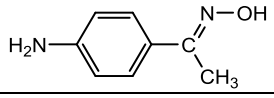
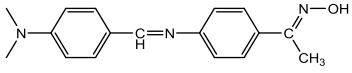
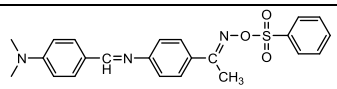
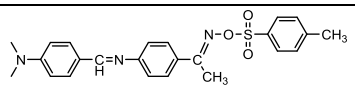
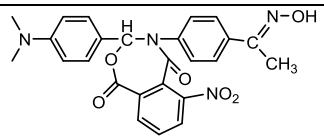
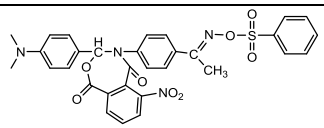
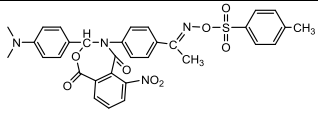
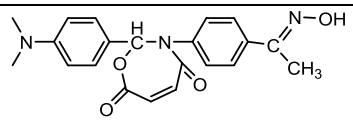
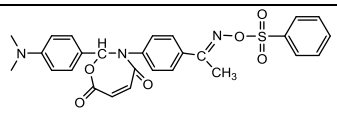
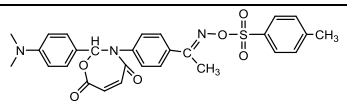
The compound **[B11]** (1 mmol) was dissolved in 20 mL acetone with Na_2CO_3 as a catalyst in a round flask and added (urea or thiourea) (1 mmol) to the mixture. Continued the refluxed for 4 hrs., the endpoint of the reaction was checked by (TLC; benzene: methanol, 9:1) and the color of this reaction changed from white to yellow gives good evidence for the end of the reaction. In the same flask, added diethyl malonate (1 mmol) to the mixture. The reaction was continued reflux for another 4 hours until appearance

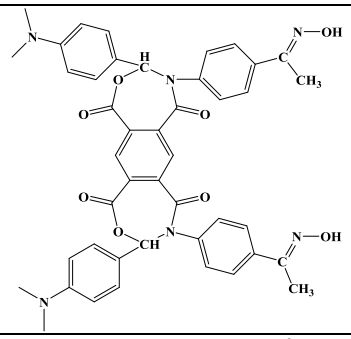
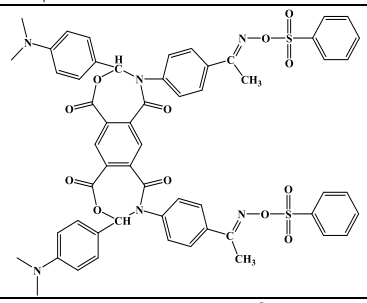
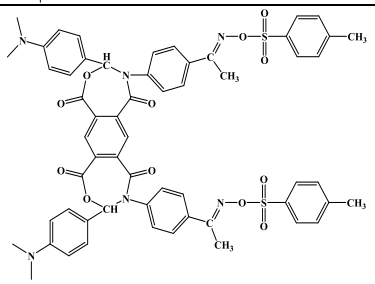
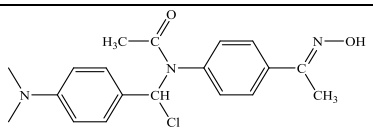
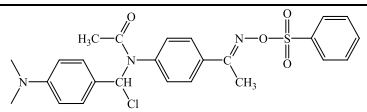
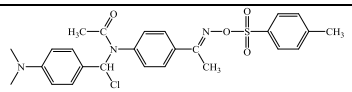
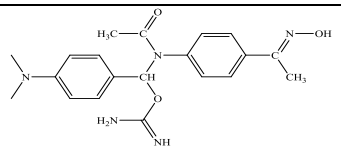
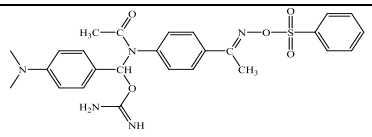
the brown precipitate, then filtered and left to dried. R*f* and physical properties as shown in the Table (2.3).

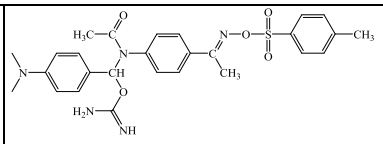
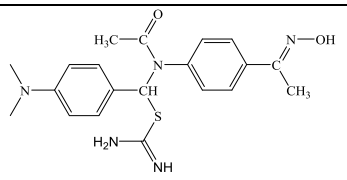
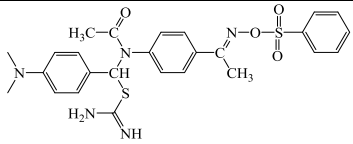
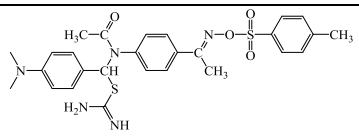
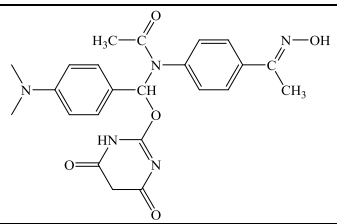
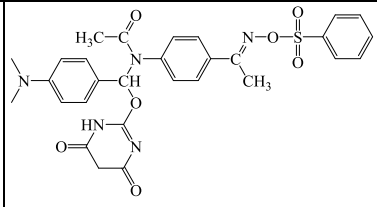
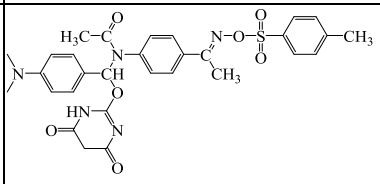
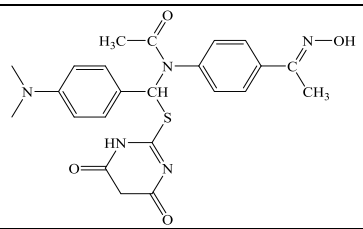
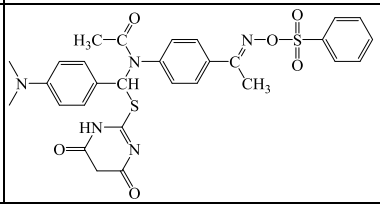
2.4 Biological evaluation

Antibacterial and antifungal activity was screened for some compounds synthesized against four kinds of bacteria **(*Staphylococcus aureus, Bacillus cereus*)** gram (+) and, **(*E. coli, pseudomonas aeruginosa*)** gram (-) and one kind of fungi **(*Candida albicans*)** in agar diffusion method. These sterilized agar media were poured into Petri dishes, and allowed to solidify, on the surface of the media microbial suspensions were spread with the help of the disinfected triangular loop. [A stainless steel cylinder of (pre-sterilized) used to bore activities]. The prepared compounds (10^{-2}M) were placed serially using micro pipette and allowed to diffuse for an hour. DMSO was applied as solvent, and control for all the compounds. These plates were incubated at 37 ^{o}C for (24 hrs.). The zone inhibition spotted around the cup was measured in mm unit. [109]

Table (2.2): Structures and physical properties

Com. No.	Nomenclature	Structural formula	M. wt. g/mol	M.p. °C	Yield%	Color	R*f*
A	(E)-1-(4-aminophenyl)ethan-1-one oxime		150	128-130	70	Golden brown	0.56
A1	(E)-1-(4-((4-1 (dimethylamino)benzylidene)amino)phenyl)ethan-1-one oxime		281	244 - 246	68	Shiny-yellow	0.52
A2	(E)-1-(4-((4-1 (dimethylamino)benzylidene)amino)phenyl)ethan-1-one O-phenylsulfonyl oxime		421	252-250	51	Brown	0.35
A3	(E)-1-(4-((4-1 (dimethylamino)benzylidene)amino)phenyl)ethan-1-one O-tosyl oxime		435	265-263	72	Reddish black	0.63
A4	(E)-3-(4-(dimethylamino)phenyl)-4-(4-(1-(hydroxyimino)ethyl)phenyl)-6-nitro-3,4-dihydrobenzo [1,3]oxazepine-1,5-dione		474	164-166	80	Pale-orange	0.42
A5	(E)-3-(4-(dimethylamino)phenyl)-6-nitro-4-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)-3,4-dihydrobenzo[1,3]oxazepine-1,5-dione		614	143-145	78	Dark-brown	0.84
A6	(E)-3-(4-(dimethylamino)phenyl)-6-nitro-4-(4-(1-((tosyloxy)imino)ethyl)phenyl)-3,4-dihydrobenzo [1,3]oxazepine-1,5-dione		628	179-181	83	Reddish black	0.57
A7	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-(hydroxyimino)ethyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione		379	168-170	84	Orange	0.40
A8	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione		519	183-185	76	Reddish black	0.72
A9	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-((tosyloxy)imino)ethyl)-phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione		533	200-203	80	Mat-red	0.49

A10	bis(4--3,9 (dimethylamino)phenyl)-4,8-bis(4-((E)-1-(hydroxyimino)ethyl)phenyl)-8,9-dihydro-1H,3H-benzo[1,2-e:5,4-e']bis([1,3]oxazepine)-1,5,7,11(4H)-tetraone		780	>300	75	Mat-red	0.62
A11	bis(4--3,9 (dimethylamino)phenyl)-4,8-bis(4-((E)-1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)-8,9-dihydro-1H,3H-benzo[1,2-e:5,4-e']bis([1,3]oxazepine)-1,5,7,11(4H)-tetraone		1061	>300	68	Mat-red	0.74
A12	bis(4--3,9 (dimethylamino)phenyl)-4,8-bis(4-((E)-1-((tosyloxy)imino)ethyl)phenyl)-8,9-dihydro-1H,3H-benzo[1,2-e:5,4-e']bis([1,3]oxazepine)-1,5,7,11(4H)-tetraone		1089	>300	70	Mat-red	0.60
A13	(E)-N-(chloro(4-(dimethylamino)phenyl)methyl)-N-(4-(1-(hydroxyimino)ethyl)phenyl)acetamide		359	219-221	62	Strong orange	0.80
A14	(E)-N-(chloro(4-(dimethylamino)phenyl)methyl)-N-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)acetamide		500	238-240	59	Strong orange	0.39
A15	(E)-N-(chloro(4-(dimethylamino)phenyl)methyl)-N-(4-(1-((tosyloxy)imino)ethyl)phenyl)acetamide		514	251 - 253	67	Strong orange	0.68
A16	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-(hydroxyimino)ethyl)phenyl)acetamido)methyl carbamimidate		383	231 - 233	87	Yellow	0.58
A17	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)acetamido)methyl carbamimidate		523	222-224	80	Yellow	0.32

A18	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-((tosyloxy)imino)ethyl)phenyl)acetamido)methyl carbamimidate		537	194-192	83	Yellow	0.45
A19	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-(hydroxyimino)ethyl)phenyl)acetamido)methyl carbamimidothioate		399	205-207	87	Yellow	0.70
A20	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)acetamido)methyl carbamimidothioate		539	212-210	81	Pale-Yellow	0.86
A21	(E)-(4-(dimethylamino)phenyl)(N-(4-(1-((tosyloxy)imino)ethyl)phenyl)acetamido)methyl carbamimidothioate		553	176-178	79	Pale-Yellow	0.33
A22	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)oxy)methyl)-N-(4-(1-(hydroxyimino)ethyl)phenyl)acetamide		451	264-266	63	White	0.27
A23	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)oxy)methyl)-N-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)acetamide		591	278 - 282	51	Milky	0.50
A24	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)oxy)methyl)-N-(4-(1-((tosyloxy)imino)ethyl)phenyl)acetamide		605	295-297	57	Milky	0.77
A25	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)thio)methyl)-N-(4-(1-(hydroxyimino)ethyl)phenyl)acetamide		467	273 - 275	53	White	0.30
A26	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)thio)methyl)-N-(4-(1-(((phenylsulfonyl)oxy)imino)e		607	286-288	54	Off-white	0.79

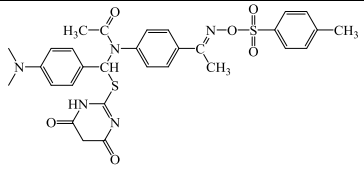
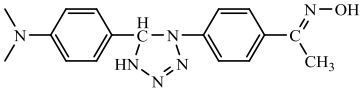
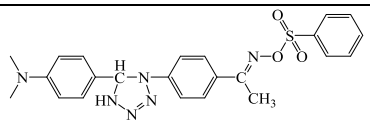
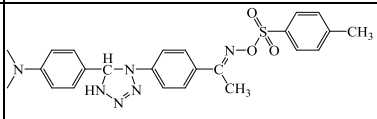
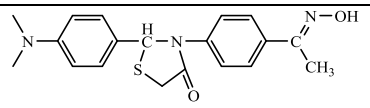
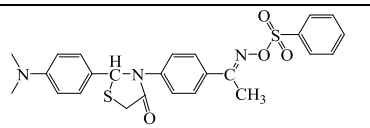
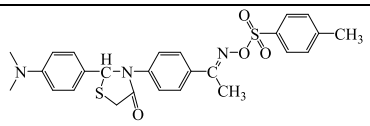
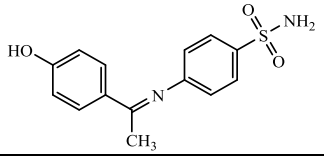
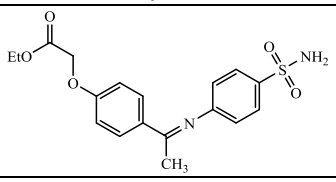
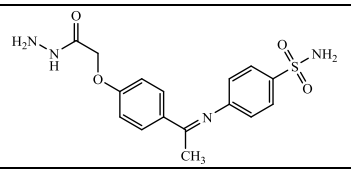
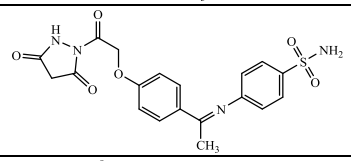
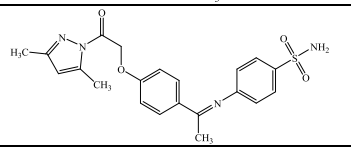
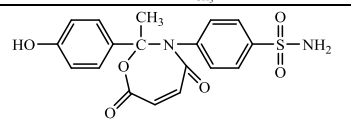
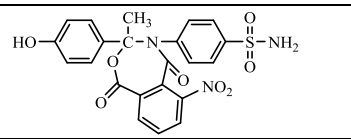
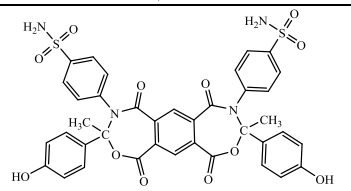
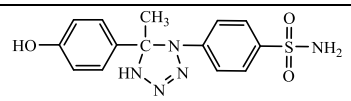
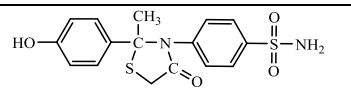
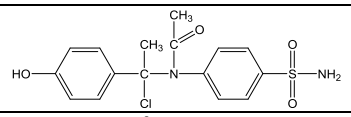
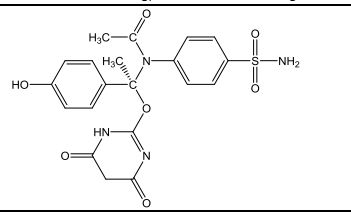
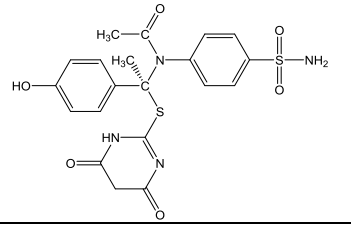
	thyl)phenyl)acetamide						
A27	(E)-N-((4-(dimethylamino)phenyl)((4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yl)thio)methyl)-N-(4-(1-((tosyloxy)imino)ethyl)phenyl)acetamide		621	290-293	52	White	0.85
A28	(E)-1-(4-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-tetrazol-1-yl)phenyl)ethan-1-one oxime		324	224-222	66	Yellow	0.29
A29	(E)-1-(4-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-tetrazol-1-yl)phenyl)ethan-1-one O-phenylsulfonyl oxime		464	238-236	62	Brown	0.66
A30	(E)-1-(4-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-tetrazol-1-yl)phenyl)ethan-1-one O-tosyl oxime		478	255-253	69	Reddish black	0.25
A31	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-(hydroxyimino)ethyl)phenyl)thiazolidin-4-one		355	198-196	54	Red-black	0.56
A32	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-(((phenylsulfonyl)oxy)imino)ethyl)phenyl)thiazolidin-4-one		495	219-216	53	Grayish-green	0.41
A33	(E)-2-(4-(dimethylamino)phenyl)-3-(4-(1-((tosyloxy)imino)ethyl)phenyl)thiazolidin-4-one		509	237-234	55	Grayish-green	0.51

Table (2.3): Structures and physical properties

Com. No.	**Nomenclatre**	**Structural formula**	**M. wt. g/mol**	**M.p. ^{0}C**	**Yield%**	**Color**	**R*f***
B1	-4)-1))-4 hydroxyphenyl)ethylidene)amino)benzenesulfonamide		290	230-232	77	Yellow	o.41
B2	ethyl 2-(4-(1-((4-sulfamoylphenyl)imino)ethyl) phenoxy)acetate		376	>300	80	Off-white	0.36

B3	hydrazinyl-2--2)-4)-1))-4 oxoethoxy)phenyl)ethylidene) amino)benzenesulfonamide		362	>300	57	White	0.48
B4	-3,5)-2)-4)-1))-4 dioxopyrazolidin-1-yl)-2-oxoethoxy)phenyl)ethylidene) amino)benzenesulfonamide		430	>300	66	Yellow	0.57
B5	dimethyl-1H--3,5)-2)-4)-1))-4 pyrazol-1-yl)-2-oxoethoxy)phenyl)ethylidene) amino)benzenesulfonamide		426	>300	71	Yellow	0.59
B6	hydroxyphenyl)-2--4)-2)-4 methyl-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2H)-yl)benzenesulfonamide		388	189-191	84	Orange	0.67
B7	hydroxyphenyl)-3--4)-3)-4 methyl-6-nitro-1,5-dioxo-1,5-dihydrobenzo[e][1,3]oxazepin-4(3H)-yl)benzenesulfonamide		483	198-200	81	Yeddish black	0.74
B8	bis(4--3,9)-'4,4 hydroxyphenyl)-3,9-dimethyl-1,5,7,11-tetraoxo-7,11-dihydro-1H,3H-benzo[1,2-e:5,4-e']bis([1,3]oxazepine)-4,8(5H,9H)-diyl)dibenzenesulfonamide		843	>300	78	Yellow	0.66
B9	hydroxyphenyl)-5--4)-5)-4 methyl-4,5-dihydro-1H-tetrazol-1-yl)benzenesulfonamide		333	274-277	62	White	0.52
B10	hydroxyphenyl)-2--4)-2)-4 methyl-4-oxothiazolidin-3-yl)benzenesulfonamide		364	256-258	59	Pale-yellow	0.77
B11	N-(1-chloro-1-(4-hydroxyphenyl)ethyl)-N-(4-sulfamoylphenyl)acetamide		368	209-211	69	White	0.43
B12	S)-N-(1-((4,6-dioxo-1,4,5,6-) tetrahydropyrimidin-2-yl)oxy)-1-(4-hydroxyphenyl)ethyl)-N-(4-sulfamoylphenyl)acetamide		460	267-269	73	Brouwn	0.69
B13	S)-N-(1-((4,6-dioxo-1,4,5,6-) tetrahydropyrimidin-2-yl)thio)-1-(4-hydroxyphenyl)ethyl)-N-(4-sulfamoylphenyl)acetamide		476	263-265	75	Brouwn	0.71

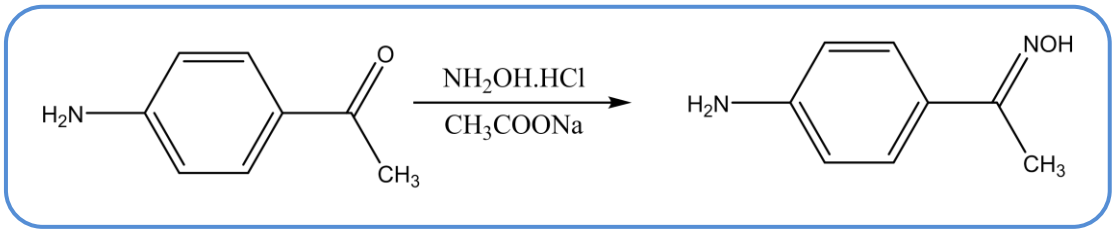
Chapter three

Results and Discussion

3.1 Results and Discussion

3.1.1 Preparation and characterization of compound [A]

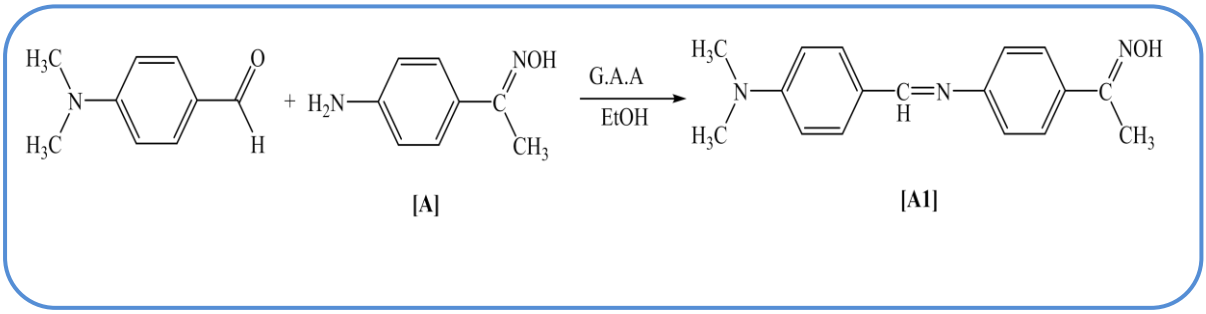
Oxime [A] was prepared by refluxing equimolar 4-amino acetophenone with $H_2NOH.HCl$ and CH_3COONa in ethanol **(**m.p 128-130) [(103)].



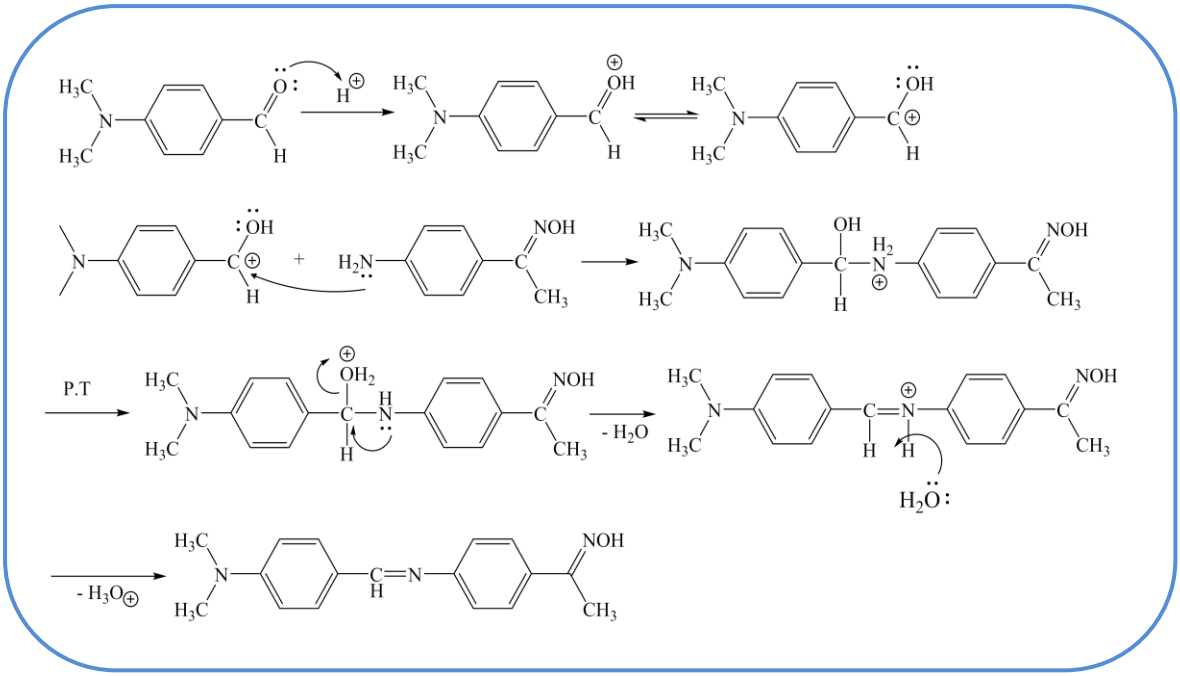
This structure was characterized by m.p and FT-IR spectrum. **Fig.(3.1)** This Figure showed the disappearance of absorption bands of [-C=O] group of the starting material, with the appearance of new absorption str.band due to (-C=N-) at (1627 cm^{-1}), absorption vibration band due to;-C-N at(1303 cm^{-1}) and (-O-H) stretching appeared at (3182 cm^{-1}).

3.1.2 Synthesis and characterization of compound [A1]

Schiff base [A1] was prepared by refluxing of oxime [A] with 4-(N,N-dimethylamino)benzaldehyde in abs. EtOH with few drops of G.A.A.



The mechanism of this reaction outlined as follows in the Scheme (3.1) [(110)]



Scheme (3.1): The mechanism of synthesis compound [A1]

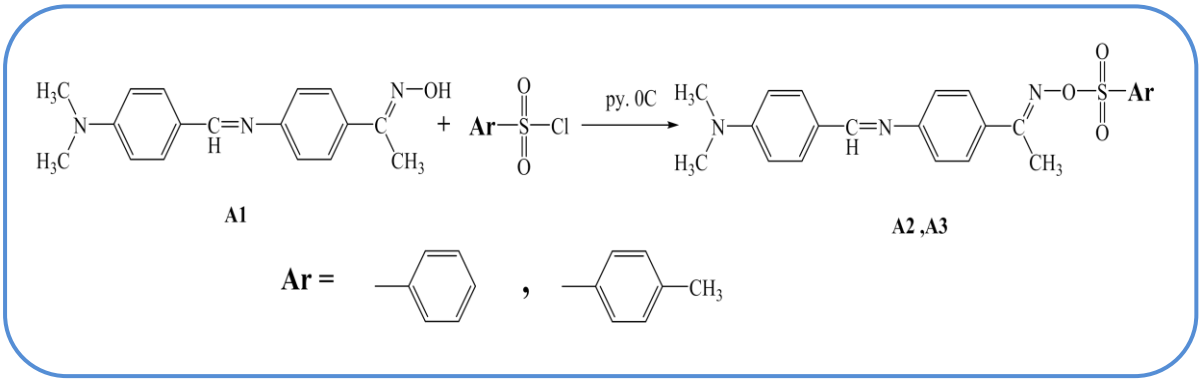
The compound [A1] was characterized by m.p., FT-IR, ^{13}CNMR, and ^{1}HNMR spectroscopy. The FT-IR spectrum displayed the disappearance of absorption bands for [-NH_2] and C=O group together with the appearance of the new absorption band at 1608 cm^{-1} which is assigned to the azomethine group, [118] **Fig. (3-2)** showed FT-IR spectrum.

The ^{1}HNMR spectrum (in a solvent DMSO) of compound [A1], **Fig. (3.3)** showed a singlet signal at δ(11.12) ppm be to a (1H) of the N=OH group, single signal at δ(8.44) ppm to a one proton of (CH=N) Schiff bases group, doublet doublet signals in the range δ(6.80-7.76) ppm for 8 aromatic protons, and two singlet signal at δ(3.02, 2.17) ppm for 6 and 3 protons for the methyl groups [$(CH_3)_2$N], (CH_3-C=N) respectively present in the compound.

The ^{13}CNMR spectrum (in a solvent DMSO) of compound [A1], **Fig. (3.4)** displayed a signal at δ(159.43) ppm expected to be the carbon of (C=N) Schiff bases group. A signal at δ(152.02) ppm to carbon of (-C=NOH) oxime, many signal in the range δ(133.03-110.91) ppm for aromatic carbon atoms, the signal at δ(39.49) ppm from the (N, N-dimethylamino) groups, and signal in a position δ(10.19) ppm from [CH_3-C=NOH].

3.1.3 Synthesis and characterization of compounds [A2, A3]

Schiff bases derivatives [A2, A3] was prepared by reacting of Schiff base [A1] with benzenselfonyl chloride and 4-methylbenzenselfonyl chloride in pyridine at 0°C.



The compound [A2 and A3] was characterized by m.p, FT-IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The FT-IR spectrum **Figures (3.5),(3.6)** showed, evanescence of absorption band due to the (-OH) and the appearance of the new absorption band at (1373, 1369) asy. and (1161,1165) sy. cm^{-1} due to the (S=O) groups, band in the (844-837) cm^{-1} to the C-S group, The FT-IR absorption bands data of these were shown compounds in the Table (3.1).

Table (3.1): Characteristic FT-IR absorption bands of Schiff bases [A1-A2]

Comp. No.	FT-IR spectra (cm^{-1})							
	υC-H Arom.	υC-H Aliph.	υC=N Schiff b.	υC=N Oxime	υC=C Arom.	υS=O	υC-S	Others
A1	3078	2900	1608	1627	1585	-	-	υ O-H 3221
A2	3062	2908	1651	1670	1600	1673 asy. 1161 sy.	844	-
A3	3062	2897	1608	overlap	1589	1369 asy. 1165 sy.	833	-

The ^{1}HNMR spectrum (DMSO solvent), **Figure (3.7)** of compound [A2] showed a singlet signal at δ(9.68) ppm to a proton of CH=N of (Schiff base). doublet doublet and multipet signals in the range δ(8.59-6.77) ppm for thirteen protons in the aromatic ring. A singlet signal at δ(3.03) ppm is attributed to six protons of the [$(CH_3)_2N$], and a singlet signal in the position δ(2.17ppm) is attributed to (CH_3-C=N) groups. The spectrum did not show a signal for OH proton.

The ^{1}HNMR spectrum (in DMSO solvent) **Figure (3.8)** of compound **[A3]** displayed a single signal at δ(8.90) ppm a attributed to one proton of (-CH=N) group. Doublet doublet signals in the range (8.06-6.79) ppm for twelve aromatic protons. The single signal at δ(3.05 ppm) was refers to six protons of the methyl groups related to the nitrogen atom, and a single signal in the position δ(2.19 ppm) is attributed for three protons of the (-CH_3-C=N); and a single signal in the position δ(2.33 ppm) at CH_3-tosyl. The spectrum did not show any signal for the proton -OH group.

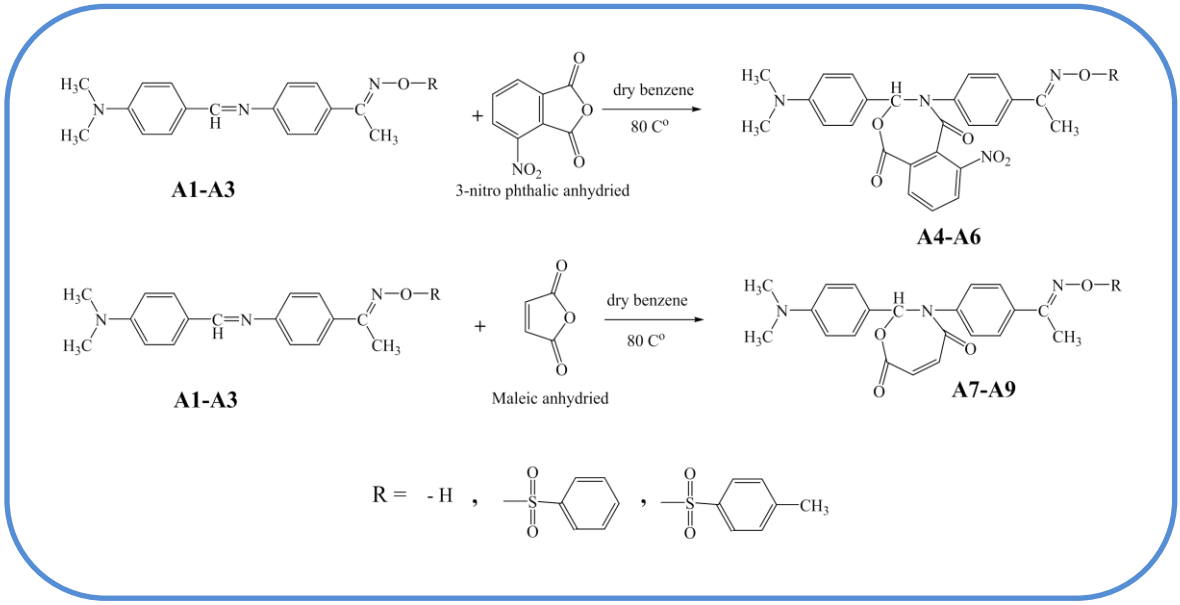
The ^{13}CNMR spectrum (in DMSO solvent), **Fig. (3.9)** of **[A2]** showed signals to carbon atom as follows at signal at positions δ(159.03) ppm expected to be for the carbon (-C=N) Schiff base group. The signal at δ(152.07) ppm to carbon of (-C=NOH) in oxime, the signals in the range δ(137.49-118.89) ppm for aromatic carbon atoms, the signal at δ(39.13) ppm form the (N,N-dimethylamino) group, and signal in a position δ(10.72) ppm from [CH_3-C=NOH].

The ^{13}CNMR spectrum**, Fig. (3.10)** of compound **[A3]** displayed; a signal in δ(151.61) ppm expected to be for the carbon of (C=N) Schiff bases group. A signal at δ(142.75) ppm to (-C=NOH) oxime, many signals in the region of δ(137.63 -118.37) ppm for aromatic carbon atoms, the signal at δ(39.31) ppm from the (N,N-dimethylamino) groups, a signal at δ(20.37) ppm for (CH_3-tosyl) and signal in a position δ(10.72) ppm from [CH_3-C=NOH].

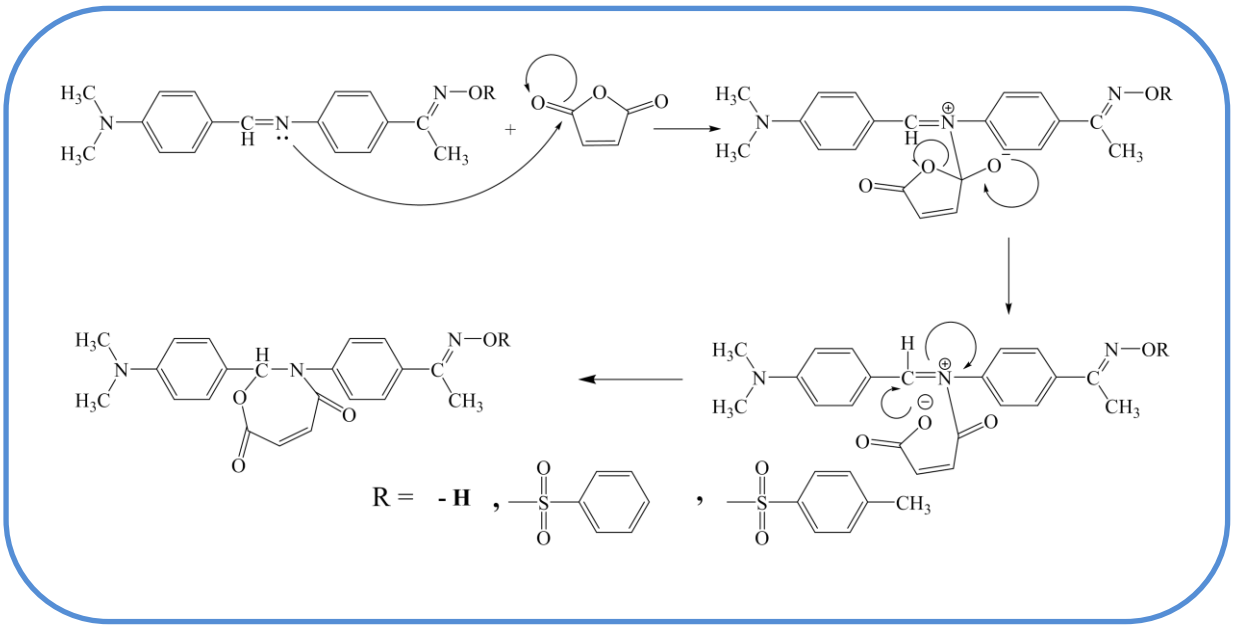
The elemental analysis (C.H.N.S) of compound **[A3]** was found [N=10.06, C=66.46, H=6.23, S=7.09] calculated [N=9.65, C=66.19, H=5.79, S=7.36].

3.1.4 Synthesis and characterization of compounds [A4-A9]

Oxazepines ring was prepared from dissolved Schiff bases [A1-A3] in dry benzene, (maleic anhydride, 3-nitrophthalic anhydride) was added to the round flask and left to refluxed for 6 hrs.



The mechanism for this reaction as shown in scheme (3.2) [111].



Scheme (3.2): The mechanism of synthesis compound [A7-A9]

The compounds [A4 – A9] was characterized by m.p, FTIR, and some of the them in ^{1}HNMR, and ^{13}CNMR spectroscopy. The FTIR spectra **Figs. (3.11)-(3.14),** showed the disappearance of a band imine in (1608 and 1651) cm^{-1} in [A1, A2, and A3]. The spectra showed the appearance of new two bands in the range, (1712-1697) cm^{-1} belong to υ(O-C=O) group of lactone and (1681-1658) cm^{-1} refers to (-N-C=O) of lactam in the 1,3-oxazepine ring. The spectrum showed another band in the region (3082-3039) cm^{-1} belong to υCH aromatic, (2920-2850) cm^{-1} belong to υCH aliphatic, and (1597-1589,

1454-1435) cm^{-1} belongs to ν(C=C) of aromatic rings. Besides, all main absorption data of these compounds were given in the Table (3.2).

Table (3.2): Characteristic FT-IR absorption bands of compounds [A4-A9]

Com. NO.	FTIR spectra (cm^{-1})							
	υ(CH) aromatic	**υ(C-H) aliphatic**	**υ(C=O) lactone**	**υ(C=O) lactam**	**υ(C=C) oxazepine ring**	**υ(C-O)**	**υ(C-N)**	**Other absorption band**
A4	3050	2897	1712	1681	---	1172	1192	**υ(OH)** 3221
A5	3043	2881	1703	1647	---	1180	1200	**υ(C-S)** 840
A6	3039	2920	1702	1668	---	1168	1230	**υ(C-S)** 813 υ(NO_2) asy.1546 sy.1369
A7	3082	2893	1697	overlap	overlap	1168	overlap	**υ(OH)** 3244
A8	3062	3850	1712	1685	1639	1161	overlap	**υ(C-S)** 844
A9	3039	2873	1701	1678	1658	1168	1230	**υ(C-S)** 837

The ^{1}HNMR spectrum, **Figure (3.15)** of compound **[A4]** showed single signal at δ(11.14) ppm to be refers to (1H) of (C=N-OH). Multiplet signals in range δ(8.48-8.22) ppm is attributed to three protons of the (3-nitrophthalic) ring. A single signal at δ(6.54) ppm for to the one proton of (O-CH-N) in 1,3-oxazepine ring. The signals in the range δ(7.79-7.23 ppm) for eight protons in aromatic rings. A single signal in the position δ(3.04ppm) is attributed to 6 protons of the [$(CH_3)_2$-N] group and a single signal at δ(2.17) ppm is attributed to (3H) of (CH_3-C=N).

The ^{1}HNMR spectrum (in DMSO) **Figure (3-16)** of **[A6]** showed the Multiplet signals at δ(8.31-8.01) ppm is attributed to three protons of the (nitro phthalic) ring. A single signal at δ(6.59 ppm), for the (1H) of (O-CH-N) oxazepine ring. The range of signals in δ(7.81-7.11) ppm for twelve aromatics protons. The single signal at δ(3.04 ppm) is referred to 6 protons of the [$(CH_3)_2$-N] groups. A single signal in the position δ(2.18 ppm) is attributable to three protons of the (CH_3-C=N) group, and a single signal in the position δ(2.28 ppm) at CH_3-tosyl.

The ^{1}HNMR spectrum(in DMSO) **Fig.(3.17)** of compound **[A7]** displayed a single signal in position δ(11.11) related to the (C=N-OH). A singlet signal at δ(6.54) ppm for (O-CH-N) group in the oxazipene ring. The signals in range δ(7.85-6.80 ppm) for eight proton in aromatic rings. The doublet signals in δ(6.78 ppm) to (CH=CH) in the oxazipiene ring and signal in the position at (3.04, and 2.17) ppm are for the methyl groups as mentioned earlier.

The ^{1}H-NMR spectrum, **Figure (3.18)** of compound **[A9]** displayed a single signal at δ(6.60) be to the one proton of (O-CH-N) group in the oxazepine ring. Signals in the range δ(8.03-6.80) ppm for twelve aromatic protons. The doublet signals in the δ(6.78 ppm) to (CH=CH) in the oxazepine ring and signals in the position at (3.05, 2.18 and 2.33) ppm for the methyl groups as mentioned earlier.

The ^{13}C-NMR spectrum (in DMSO) of **[A4]** in the **Fig. (3.19)** showed the signal to carbon atoms as follows at δ(10.90) ppm, for a carbon of (methyl oxime), a signal at δ(39.45) ppm, of [$(CH_3)_2$N-]. Besides appearance signal at δ(110.51) ppm of CH of 1,3-oxazepine. The signals at regions δ(120.22-152.25 ppm) of aromatic atoms of the benzene ring. The signal at (δ159.33) ppm for (C=NOH), another signal in position δ(165.40 ppm) assigned (N-C=O) for lactam and s. at δ (189.30 ppm) refer to a (-O-C=O) for lactone group.

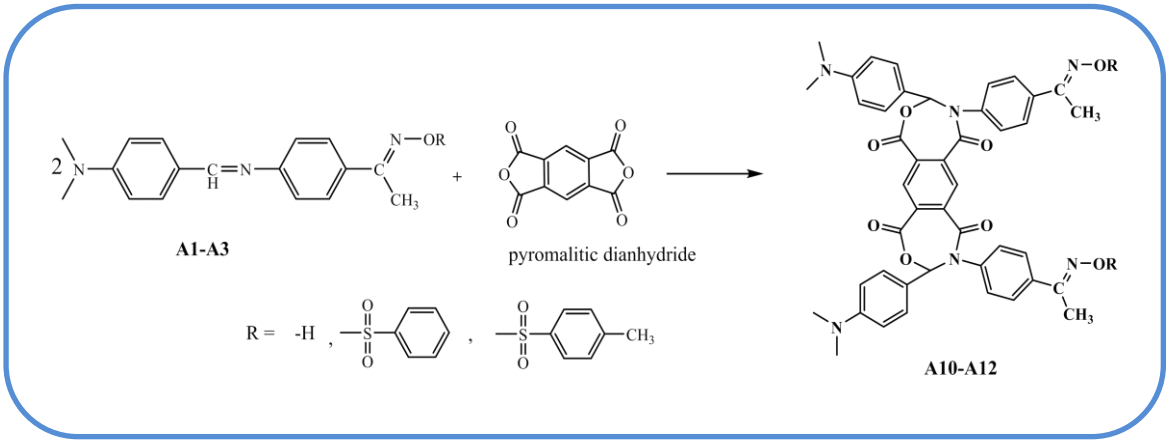
The ^{13}CNMR spectrum of **[A7]** (in DMSO) **Fig. (3.20)** showed; at δ(10.89 ppm) related to the carbon atom of (CH_3-C=N) group, signal at δ (39.49) ppm to [$(CH_3)_2$N-]. Besides appearance signal at δ(110.52) ppm of (CH) of 1,3-oxazepine ring. The signals at δ(120.01-153.67) ppm of aromatic carbon atoms and C=C of oxazepine. Also, a signal at δ(159.08) ppm to (C=NOH), in addition a signal in δ(166.48 ppm) assigned to C=O for lactam, and signal at δ (189.29) ppm refers to the (O-C=O) lactone-group.

The elemental analysis (C.H.N.S) of compound [A6] was found [N=8.52, C=60.83, H=4.62, S= 4.82] calculated [N8.91 , C=61.1 , H=4.49 , S=5.10].

The elemental analysis (C.H.N) of compound [A7] was found [N=10.30, C=66.20, H=5.25] calculated [N=11.08, C=66.48, H=5.58].

3.1.5 Synthesis and characterization of compounds [A10-A12]

Schiff bases [A1-A3] was dissolved in dry benzene at 70 °C in a water bath and pyromalitic dianhydride was added to the mixture and left to reflexed for 8 hrs.



The compound **[A10 – A12]** was characterized by m.p, FT-IR, and some of them by ^{1}HNMR,^{13}CNMR spectroscopy. The FTIR spectra of these compound **Figs. (3.21)-(3.23)**, showed the disappearance of a band of imine at (1608) and(1651) cm^{-1} of compounds [A1-A3]. The spectrum showed the appearance of new two bands in the range, (1716-1708) cm^{-1} belong to υ(C=O) group of lactone and (1658-1656) cm^{-1} refers to δ(N-C=O) of lactam group in 1,3-oxazepine heterocyclic ring. Also, showed new band in the range (3059-3028) cm^{-1} belong to υCH aromatic, (2929-2889) cm^{-1} belong to υCH aliphatic, (1600-1596, 1452-1435) cm^{-1} belongs to aromatic rings. Besides, all main absorption bands of these compounds were listed in Table (3.3).

Table (3.3): Characteristic FTIR absorption bands of compounds [A10-A12]

Com. No.	FT-IR spectra (cm^{-1})							
	υ(CH) aromatic	**υ(CH) aliphatic**	**υ(C=O) lactone**	**υ(C=O) lactam**	**υ(C-O)**	**υ(S=O)**	**υ(C-N)**	**Other absorption band**
A10	3059	2889	1712	1658	1168	-	1222	**υ(OH)** 3221
A11	3028	2916	1708	1658	1165	1381 asy. overlap sy.	1226	**υ(C-S)** 844 overlap
A12	overlap	2929	1716	1656	1166	1361 asy.	1228	**υ(C-S)** 837

The ^{1}HNMR spectrum (in DMSO), **Figure (3-24)** of compound **[A10]** displayed a single signal at δ(11.16) be to the two protons of 2(OH) groups in a compound. A single signal at δ(6.79) (O-CH-N) group in the oxazepine ring.

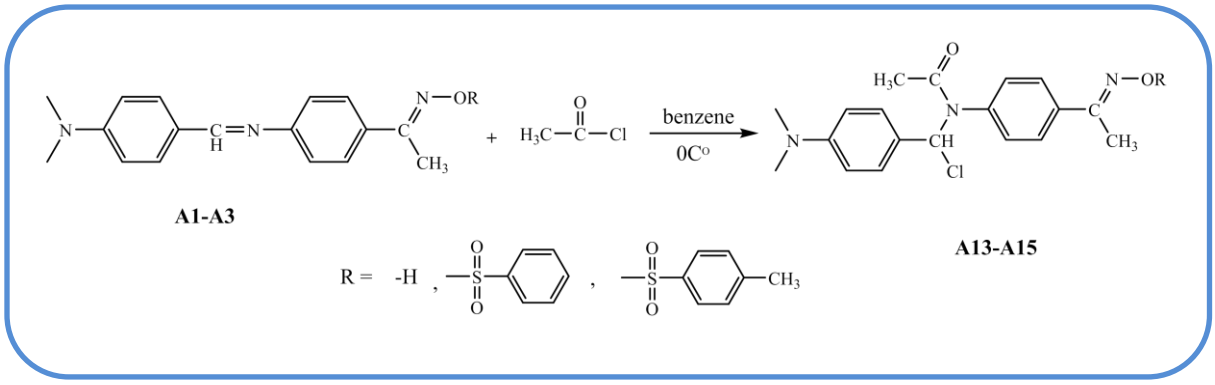
Doublet doublet signals in the range δ(8.52-6.80) ppm for the eighteen aromatic protons and signals in the position at (3.05, and 2.17) ppm for the methyl groups as mentioned earlier.

^{1}HNMR spectrum (in DMSO) **Figure (3.25)** of compound **[A12]** displayed the single signal at δ(6.75) ppm for the two protons of (O-CH-N) groups in the oxazepine rings. Many signals in the range δ(8.33-6.78 ppm) for eighteen aromatic ring's protons, and signals in a position (3.05,2.16 and 2.33) ppm for the methyl groups as mentioned earlier.

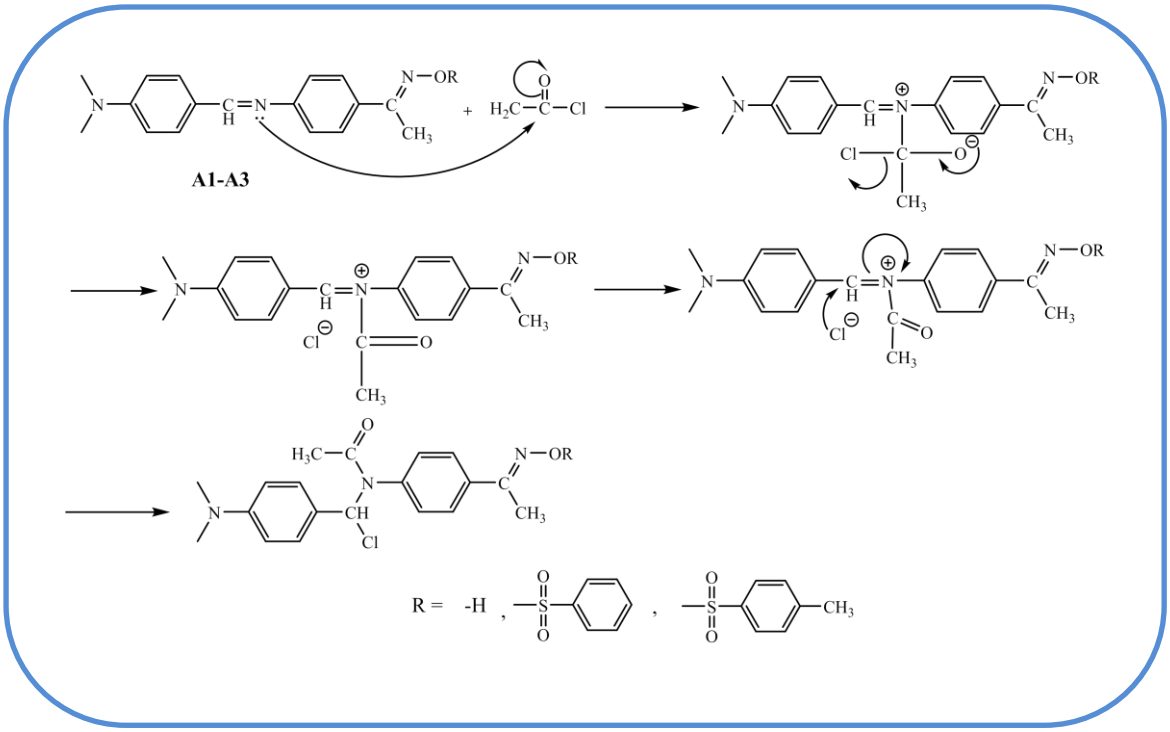
The ^{13}CNMR spectrum (in DMSO a solvent) of **[A12]** in **Fig. (3.26)** displayed the signals at δ(10.86) and δ(20.22) ppm to a carbon atom of (CH_3-tosyl), (CH_3-C=N) groups respectively, a signal at δ (38.49) ppm for [$(CH_3)_2$N-]. Besides appearance signal at δ(110.53) ppm of (CH) oxazepine ring. The signals at δ(118.74-134.72) ppm of aromatic carbons atoms. The signal at δ(137) ppm is to (-C=N-OH), else signal that appeared at δ(166.72) ppm may be assigned to (-N-C=O) for lactam and signal at δ(189.30) ppm refers to a carbon atom of carbonyl lactone group.

3.1.6 Synthesis of compounds [A13-A15]

Acetamide derivatives prepared Schiff bases were dissolved at 0 °C in dry benzene and acetyl chloride was added to the droplets and left to stir for one hour led to getting N-acetyl compounds.



The mechanism for this reaction as shown in the Scheme **(3.3)** [112]**.**



Scheme (3.3): The mechanism of synthesis compounds [A13-A15]

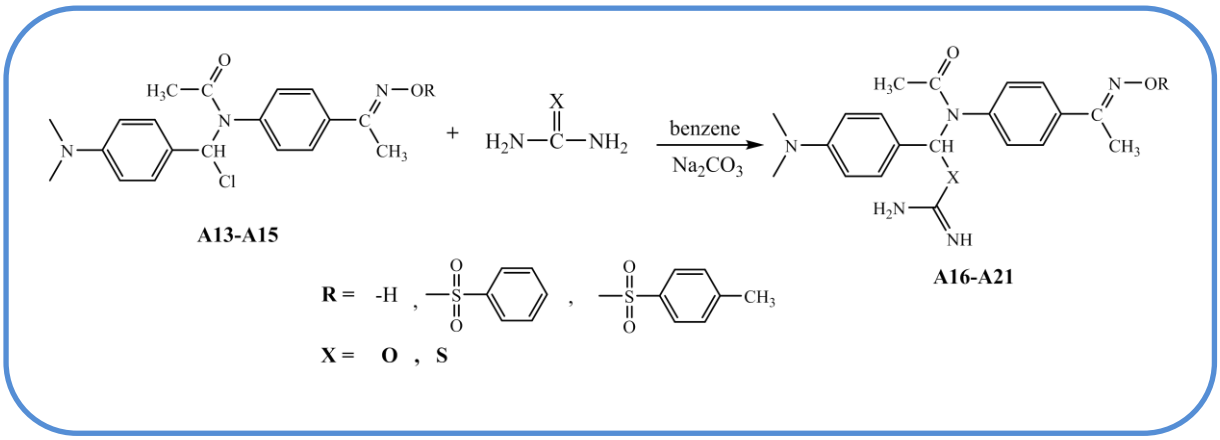
These compounds **[A13 -A15]** characterized by m. p. and FTIR**.** The FT-IR spectra displayed the disappearance band υ(C=N) azomethine at (1608 and 1651 cm^{-1}) for compounds [A1- A3]. The spectra showed the appearance of new stretching band refers (-N-C=O) at (1670-1651) cm^{-1}, **Figs (3.27) (3.29).** Besides, All absorption data of compounds were given in Table (3.4).

Table (3.4): Characteristic FT-IR absorption bands of compounds [A13-A15]

Comp. No.	FT-IR spectra (cm^{-1})								
	υC-H arom.	**υC-H aliph.**	**υC=C arom**	**υC=N oxime**	**υC=O**	**υC-N**	**υC-S**	**υS=O**	**Others**
A13	3059	2889	1600	overlap	1656	1261	-	-	υ O-H 3201 υC-Cl 694
A14	3066	2866	1600	1639	1666	1230	837	1361asy. 1161 sy.	υC-Cl 686
A15	3005	2912	1600	1639	1670	1238	overlap	1361asy. 1161 sy.	υC-Cl 686

3.1.7 Synthesis and characterization of compounds [A16-A21]

These compounds were prepared from the reaction of [A12-15] with urea and thiourea in dry benzene. These compounds were characterized by m.p., IR and ^{1}HNMR of compound [A18].



The FTIR spectra of compounds, **Figs. (3.30)-(3.35)**, were displayed the disappearance stretching band (686, 694) cm^{-1} to (C-Cl) of N-acetyl compounds, and some band due to starting material and show a new three bands in ranges; (3456-3178), (3282-3224) cm^{-1} str. bands due to (asym., sym.) of (NH_2), (-NH) group respectively. All main absorption data of these compounds are listed in the Table (3.5).

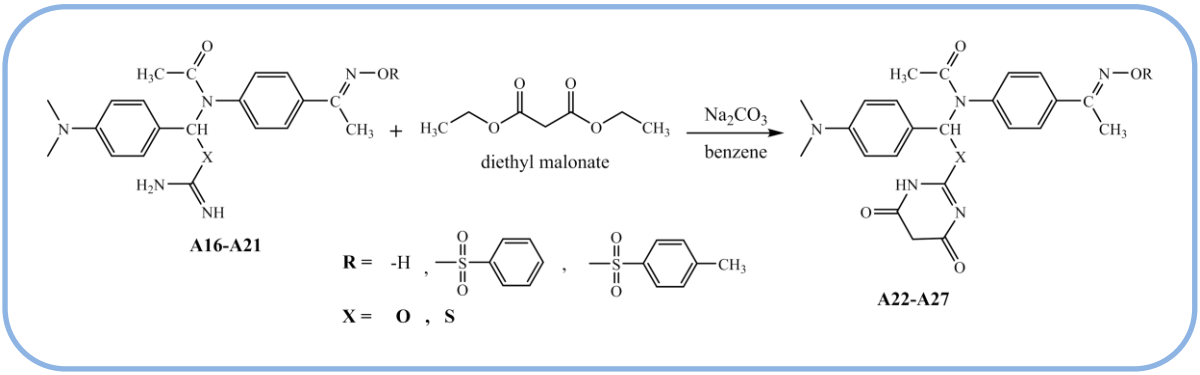
Table (3.5): Characteristic FTIR absorption bands of [A16-A21]

Comp. No,	FT-IR spectra (cm^{-1})							
	υNH_2, NH	υCH Aromatic	υCH Aliph.	υ(C=O)	υ(C=C)	υ(C=NH)	υS=O	Other
A16	3456, 3332 overlap	overlap	2850, 2904	1674	1585	1612	-	υO-H 3232
A17	3440, 3224	overlap	2893	1666	overlap	1616	1369asy. 1168 sy.	
A18	3456, 3361	3066	2831, 2937	1668	1593	overlap	1363asy. 1163 sy.	
A19	3375, overlap	3078	2893	1689	1585	1612	-	υ O-H 3190
A20	3382, 3182	overlap	2956	overlap	overlap	1614	1367asy. 1182 sy.	
A21	3383, 3178	overlap	2893	overlap	overlap	1616	1385asy. 1165 sy.	

The ^{1}HNMR spectrum of compound **[A18], Figure (3.36)** showed a single signal at δ(8.51) be to the (1H) of (-NH) in a compound, the rang of signals at δ(7.96-6.55) ppm for twelve aromatic proton. A single signal at (δ5.45 ppm) to be (-NH_2) and signals in the position at (2.99, 2.76, 2.32 and 2.09) ppm are for the methyl groups.

3.1.8 Synthesis and characterization of compounds [A22-A27]

The preparation of pyrimidine derivatives through the reaction of the previously recorded compounds **[A16-A21]** with the diethyl malonate.



These compounds were identified by FT-IR, ^{1}HNMR spectroscopy**.** FTIR spectrum of compounds [A22-A27], **Figures (3.37)-(3.41)** showed the appearance of a new str.band refers to υ(-C=O) at (1778-1728) cm^{-1}, it also didn't show the appearance of two streching bands of the (-NH_2) group. All data listed in the Table (3.6).

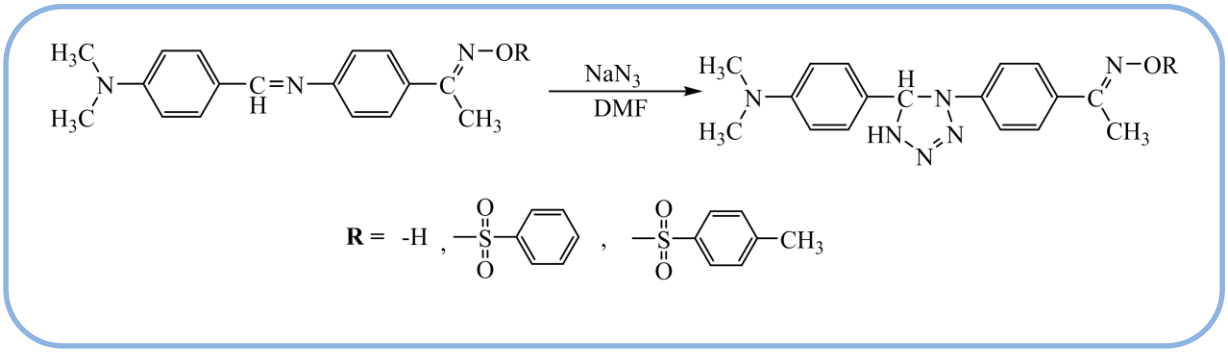
Table (3.6): Characteristic FTIR absorption bands of [A22-A27]

Comp. No.	FT-IR spectra (cm^{-1})							
	υNH	υCH arom.	υCH alph.	υ(C=O)	υ(C=O) pyrmidine	υC=C	υ(C=N pyrmidine	Other
A22	overlap	3082	2900	overlap	overlap	1585	1612	υO-H 3228
A23	3428	3016	2893	1666	1774	1593	1616	
A24	3414	overlap	2889, 2947	1675	1774	1554	1616	
A25	3410	3024	2881	1685	1771	1573	1604	υO-H 3201
A26	3379	overlap	2816, 2893	overlap	1728	overlap	1612	
A27	3479	overlap	2924	1660-1670	1778	overlap	1610	

The ^{1}HNMR spectrum (in DMSO as a solvent) **Figure (3.42)** of compound **[A24]** displayed the single signal at δ(10.73) it is expected to be a (1H) of (-NH) group in a pyrimidine, the singlet signal in a position δ(6.69) ppm refers to one proton for a group (O-CH-N). The range of signals in δ(7.96-6.71) ppm to twelve aromatic protons. A singlet signal at δ(3.53) ppm for (CH_2) in a pyrimidine ring and signals in a position (2.99, 2.09, 2.33 and 2.00) ppm for the methyl groups.

3.1.9 Synthesis and characterization of compounds [A28–A30]

Tetrazole derivatives were prepared by reaction of Schiff bases [A1-A3] with sodium azide in DMF as a solvent.



Identified these compounds by FT-IR and ^{1}HNMR spectroscopy**.** The FTIR spectra, **Figs. (3-43)(3-45),** displayed the disappearance band υ(-C=N) imine of [A1-A3] with the appearance of a new band at 1550-1552 cm^{-1} due to N=N stretching, and a new band at (3394-3251) cm^{-1} due to NH stretching. All absorption data bands of these compounds are listed in Table (3.7)

Table (3.7): Characteristic FT-IR absorption bands of compounds [A28-A30]

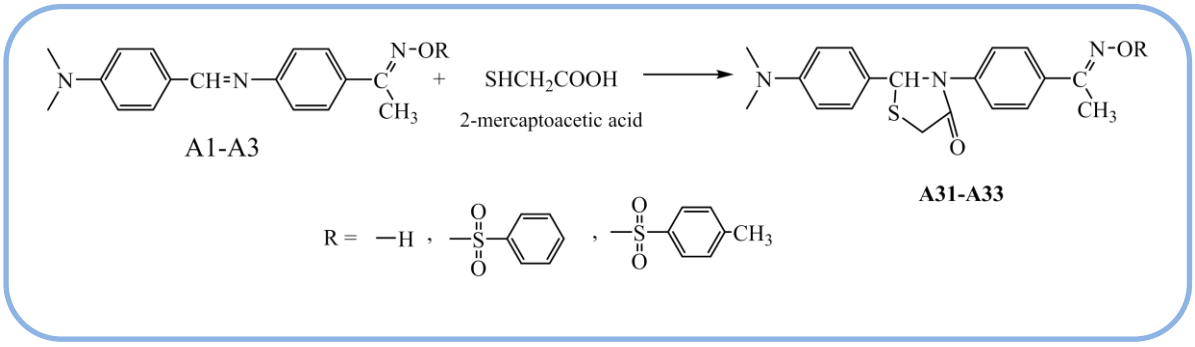
No.		FTIR spectra (cm^{-1})							
	υNH	υC-H arom.	υCH aliph.	υN=N	υC=N oxime	υC=C	υC-N	υS=O	Others
A28	overlap	3005	2947	overlap	1627	1577	overlap	-	υ O-H 3176
A29	3394	3055	2902	1552	1652	1596	1334	1373asy. 1164 sy.	υC-S 837
A30	3251	3032	2904	1550	1654	1593	1334	1385asy. 1161 sy.	υC-S 837

^{1}HNMR spectrum (in DMSO) of **[A29] Figure (3.46)** displayed a single signal at δ(10.80) ppm be to a proton of the (C-NH-N) in tetrazole ring, a

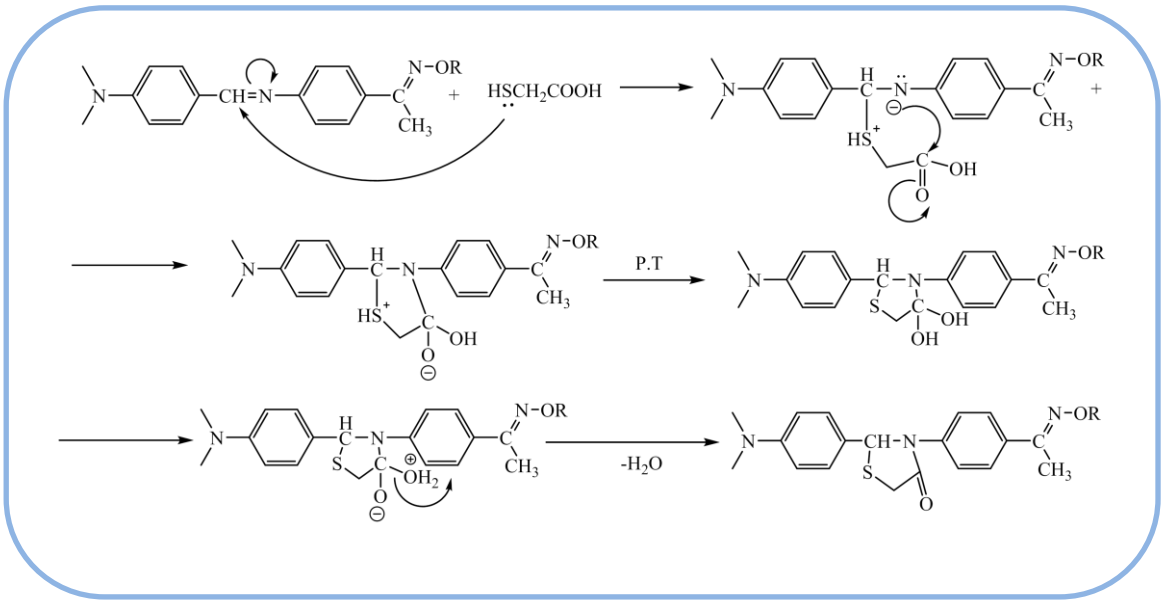
singlet signal at (δ5.45) ppm is attributed to the (1H) of [N-CH-N]. The range of signals δ(8.51-6.50 ppm) related to twelve protons. Single signal in the position δ(3.02and 2.16 ppm) is attributed to ($(CH_3)_2N$) and (CH_3-C=N) groups respectively.

3.1.10 Synthesis and characterization of compounds [A31-A33]

The Schiff bases [A1-A3] were dissolved in acetone then Thioglycolic acid was added, and refluxed to 12 hrs.



The mechanism suggested for this reaction as shown in the Scheme **(3.4)**



Scheme (3.4): The mechanism of synthesis compounds [A31-A33]

Identify these compounds by FTIR and ¹HNMR spectroscopy. The spectra, **Figures (3.47) (3.49),** showed the disappearance of absorption stretching band due to imine group [A1-A3]. The appearance a new band at

1714-1726 cm^{-1} due to (N-C=O) stretching, and a new bands at (837-850) cm^{-1} due to C-S stretching. All absorption data of it in the Table (3.8).

Table (3.8): Characteristic FTIR absorption bands of [A22-A27]

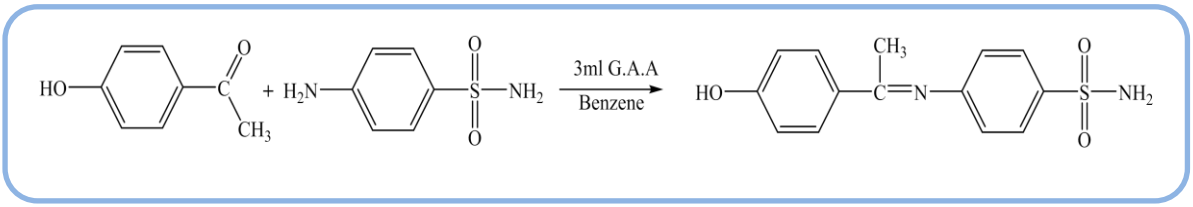
Comp. No.		FTIR spectra (cm^{-1})						
	υCH arom.	υCH Aliph.	υC=O	υC=N oxime	υ(C=C)	υC-N	υC-S	Other
A31	3047	2897	overlap	1670	1597	1323	837	υ O-H 3271
A32	3064	2866	1726	1662	1602	1336	850	-
A33	3049	2867	1714	1670	1596	1338	846	-

The ^{1}HNMR spectrum of compound **[A31] Figure (3.50),** showed a singlet signal at δ (11.07) ppm to (1H) of the (-N=OH). Many signals in the range δ(7.96-7.19) ppm for eight aromatic protons, single signal at (6.68ppm) to; (S-CH-N-), signal at(δ3.74) ppm related to (-CH_2) thiazolidin-one ring appeared and two singlet signal at δ (3.04 , 2.13) ppm for 6 and 3 protons respectively for methyl groups present in the compound.

The ^{13}CNMR spectrum of compound **[A33]** As shown in Fig(3.51) showed**;** signal in δ(195.87) ppm expected to be for the carbon carbonyl group in the thiazolidin-4-one ring. A signal at δ(143.12) ppm to carbon of (C=N) oxime, many signals in the region of δ(129.21-111.40) ppm due to aromatic ring, the signal in the position δ(51.97) ppm be to the (S-CH-N) and the signal at δ(40.56) ppm for CH_2, in addition, three signals in δ(39.37, 25.76 and 20.36) ppm for (N,N-dimethylamino), (CH_3-tosyl) and [CH_3-C=N] respectively.

3.1.11 Synthesis and characterization of compound [B1]

This compound was prepared by reacted of 4-hydroxyacetophenone with 4-aminobenzenesulfonamide in dry benzene and G.A.A as a catalyst.



The compound **[B1]** was identify by: melting point, FTIR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The FTIR spectrum showed the disappearance of absorption str. band of NH_2 and C=O groups. The appearance of a new band

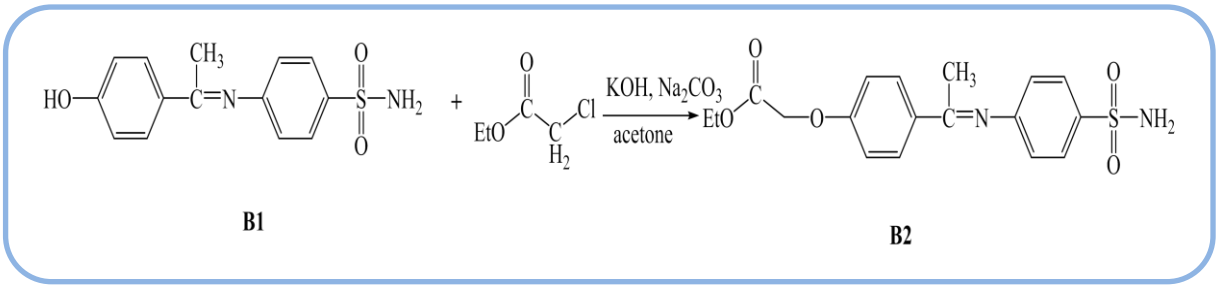
at 1645 cm^{-1} which is expected to the azomethine group. **Figure (3.52)** showed the FT-IR spectrum.

The ^{1}HNMR spectrum (in a solvent DMSO) of compound **[B1]** showed the singlet signal in (δ10.38 ppm), to the (-OH) proton group, single signal in a δ(5.81) ppm to the two protons of ($-NH_2$), doublt doublt signals in the range δ(6.60-7.84) ppm for eight aromatic protons, and singlet signal at δ(1.91) ppm for 3 protons of the methyl group in the compound**, Fig. (3.53).**

The ^{13}CNMR spectrum of **[B1]** showed the signal at δ(161.48) ppm expected to be for the carbon of (C=N) Schiff base group. The range of signals in the δ(151.37-111.93) ppm related to carbons rings, and signal in the position δ(25.66) ppm for the CH_3, **Figure (3.54)** showed the ^{13}CNMR spectrum of [B1].

3.1.12 Synthesis and characterization of compound [B2]

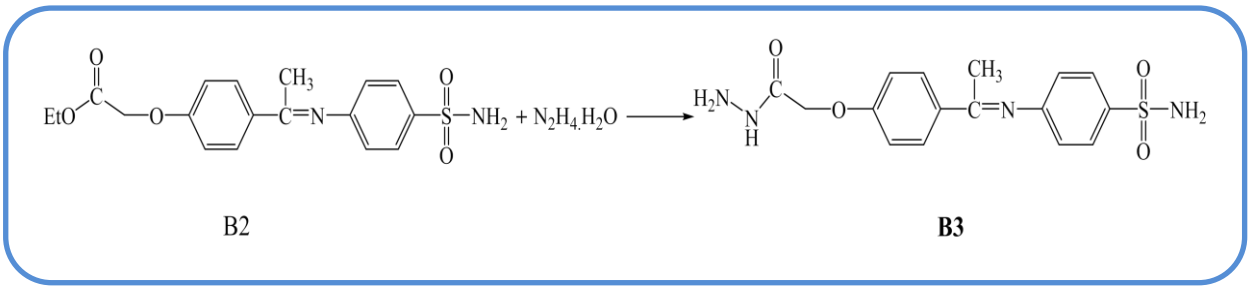
This compound prepared from dissolved Schiff base **[B1]** in acetone and added to it an increase of KOH and Na_2CO_3 as a catalyst, then ethyl chloroacetate was added to the mixture then refluxed for 6 hrs.



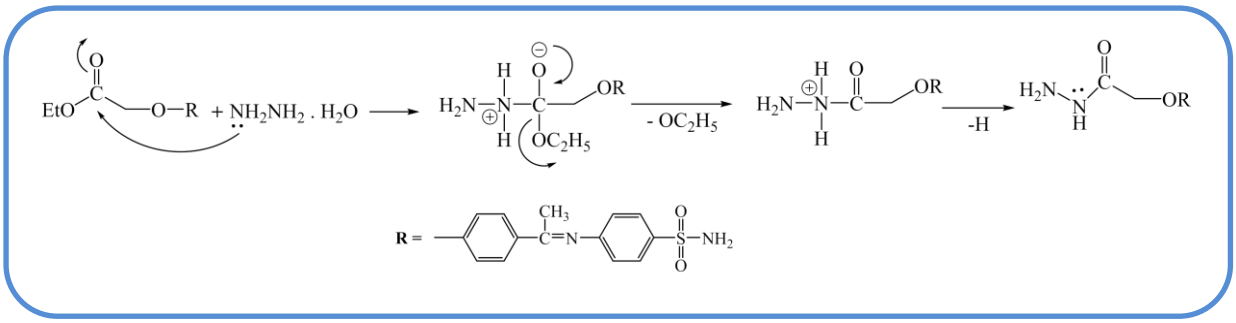
This compound **[B2]** was identify by m.p, and FT-IR spectroscopy. The FT-IR displayed a disappearance of (-OH) absorption streching band, and appearance of the new absorption band at 1759 cm^{-1} due to the (O-C=O) for ester group, and streching band at 1311 cm^{-1} refer to -C-O, **Fig.(3.55)**

3.1.13 Synthesis and characterization of compound [B3]

The acid hydrazide **[B3]** prepared by refluxed the ester **[B2]** with hydrazine hydrate in solvent EtOH.



The mechanism for this reaction as shown in Scheme (3.5) [113]

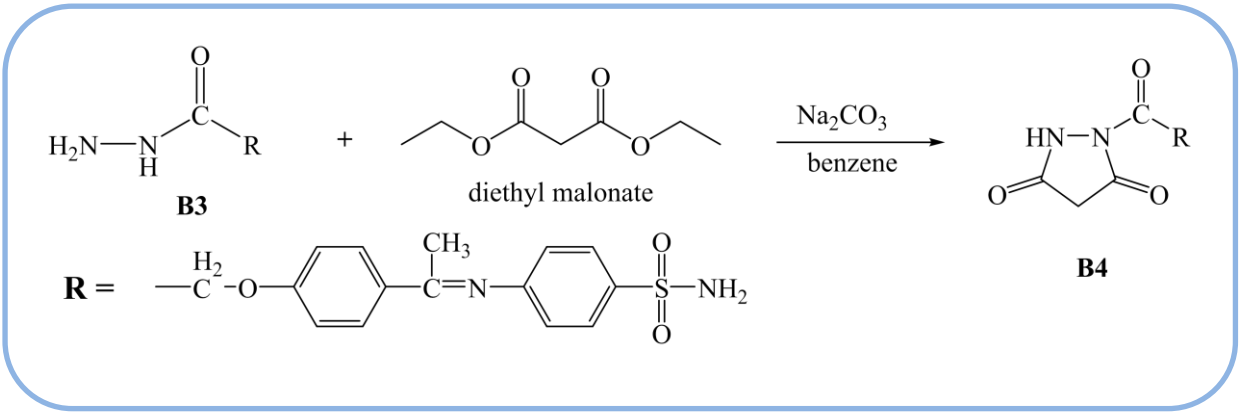


Scheme (3.5): The mechanism of synthesis compound [B3]

The FTIR spectrum of compound **[B3]**, showed the str. bands in (3313, 3282, 3236) cm^{-1} referred to [NH] and [NH_2] (asym.; sym.) groups. Also, evanescence of the stretching band of (-O-C=O) ester group, and the appearance of the absorption band at 1665 cm^{-1} attributed to (-N-C=O) amide group. **Fig(3.56).**

3.1.14 Synthesis and compound [B4]

The acid hydrazide **[B3]** was dissolved in benzene with a small amount of sodium carbonate then added (diethyl malonate) droplets to the mixture and refluxed for 4-5 hrs.

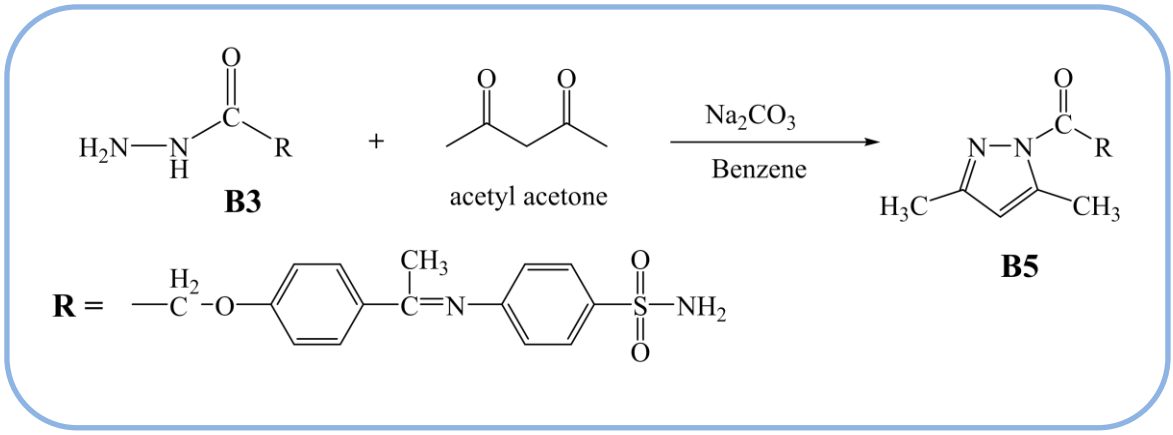


The FTIR spectrum of compound **[B4]**, showed disappearance of stretching band due to (NH_2, NH and C=O amide) for compoumd [B3] and appearance of new broad absorption band at (3282) cm^{-1} for (NH, NH_2) groups and stretching band at (1776, 1730) cm^{-1} of (C=O) of pyrazolidine ring **Fig. (3.57).**

The ^{1}HNMR spectrum (in DMSO) of **[B4]** displayed a single signal at (δ11.19) ppm be to the one proton of the (NH) group, doublet doubet signals in the range δ(8.48-7.60 ppm) for eight ring's protons. Singlet signal at δ(5.83) ppm to the (2H) of (NH_2), in addition a signal in the position of δ(3.57) ppm for two protons ($CO-CH_2-O$), the signal at δ(2.85 ppm) refers to ($CO-CH_2-CO$) finally, singlet signal at δ(2.00) ppm for 3 protons of the ($CH_3-C=N$) group **Figure (3.58)**.

3.1.15 Synthesis and characterization of compound [B5]

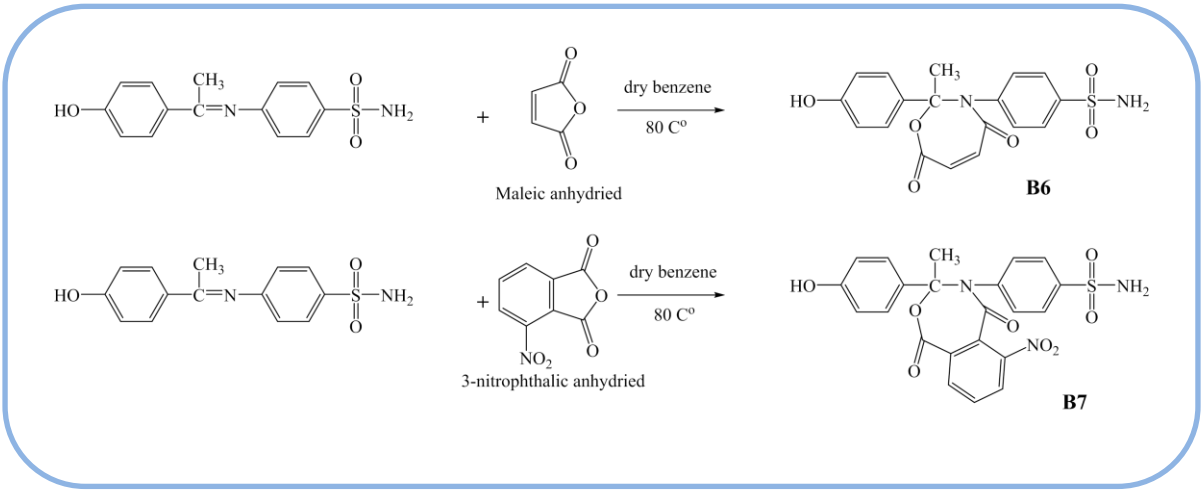
In dry benzene dissolved acid hydrazide **[B3]** with a small amount of Na_2CO_3 then added acetylacetone droplets to the flask and refluxed for 7 hrs.



FT-IR spectrum of compound **Figure (3.59) [B5]** displayed a stretching bands at (3460,3344) cm^{-1} refer to NH_2 (asym., sy.). Showed str. band at (3066) cm^{-1} due to CH aromatic, and band in the (2889-2839) cm^{-1} to be (CH) aliphatic group. The absorption band at (1670) cm^{-1} due to (-N-C=O) besides, the appearance of the new absorption band at 1608 cm^{-1} refers to (-N=C) in pyrazole heterocyclic ring.

3.1.16 Synthesis and characterization of compounds [B6, B7]

1,3-oxazepine **[B6, B7]** were prepared by refluxed the Schiff base **[B1]** with (maleic anhydride, 3-nitrophthalic anhydride) in dry benzene as a solvent.



The FT-IR spectra of **[B6 , B7]** showed the evanescence bands of (-N=C-) imine group in the position (1645) cm^{-1} of compound **[B1]**, and showed the appearance of a new two bands in a range, (1716,1701cm^{-1}) refers to υ(O-C=O) of lactone and υ(1681, 1664) cm^{-1} refer to υ(-N-C=O) of lactam. The absorption bands of two compounds listed in the Table (3.9), **Fig. (3.60)**.

Table (3.9): Characteristic FT-IR absorption bands of [B6, B7]

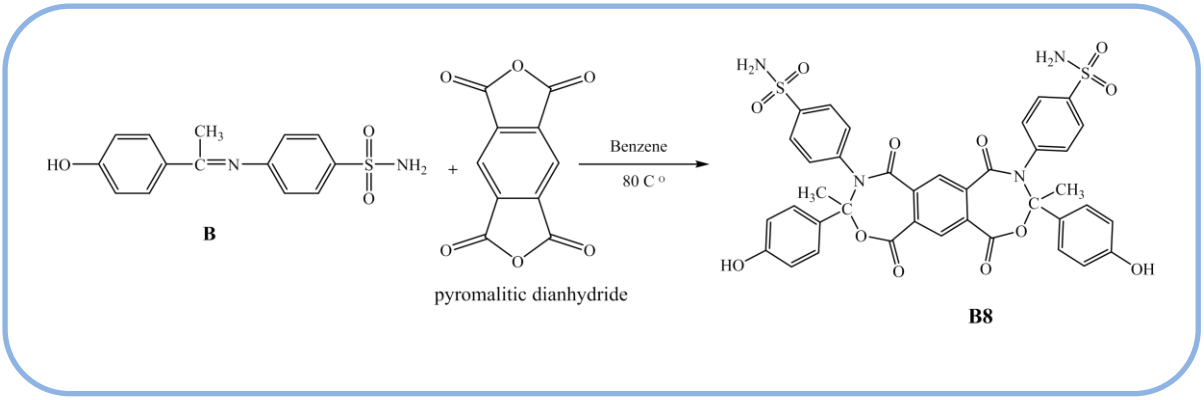
Com. No.	FT-IR spectra cm^{-1}							
	υCH aromatic	**υCH Aliphatic**	**υ(C=O) lactone**	**υ(C=O) lactam**	**υ(C=C)**	**υC-O**	**υC-N**	**Other absorption band**
B6	3020	2887	1701	1664	1577	1327	1248	υ(C=C) 1631
B7	3060	2908	1716	1681	1597	1338	1253	υ(NO_2) asy. 1535 sy. 1338

The ^{1}HNMR spectrum (in a solvent DMSO) of compound **Fig. (3.61) [B7]** displayed the singlet signal at (δ11.04 ppm) for (1H) the hydroxyl group. The signals in the δ(8.30-7.54 ppm) for eleven aromatic ring's protons; singlet signal at δ(6.59 ppm) to the two protons of (-NH_2), and singlet signal at δ(2.47) ppm for (CH_3) in the compound.

The ^{13}CNMR spectrum of compound **[B7], Fig. (3.62)** showed signals at δ(189.10, 165.41) ppm expected for lactone and lactam carbonyl groups respectively. Many signal in the range δ(151.36 -126.88 ppm) attributed to aromatic rings carbons. Also, the signal at δ(111.90)ppm refers to [O-C(CH_3)-N] in 1,3-oxazepine ring and signal in the position δ(26.00) ppm form the CH_3,

3.1.17 Synthesis and characterization of compound [B8]

The compound [B8] was synthesized by reacted the Schiff base [B1] (0.02mmol) with pyromellitic dianhydride (0.01mmol) in dry benzene at 80 °C.



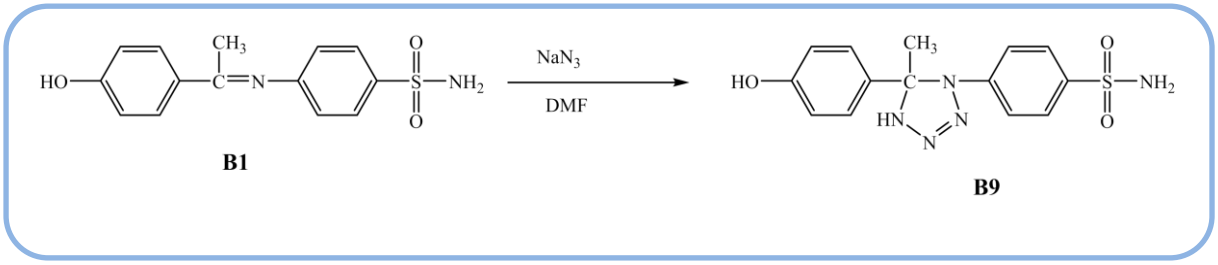
The FT-IR spectra of **[B8] , Figure (3.63)** displayed the disappearance band of imine group υ(-C=N) in (1645) cm^{-1} of compound **[B1]** and showed the new appearance bands in (1708) cm^{-1} attributed to υ(-O-C=O) of lactone group, and band in (1666 cm^{-1}) refer to υ(N-CO) lactam for oxazepine ring and another band such as [(υ C-O at 1331cm^{-1})(υ C-N at 1276 cm^{-1})].

The ^{1}HNMR spectrum of [B8]; displayed the single signal at δ(10.35) related to (2H) of hydrogen hydroxyl groups. Doublet doublet and singlet signals in the position δ(8.40-6.90) ppm to the eighteen of aromatic protons. The single signal at δ(6.60 ppm) for four protons of 2[-SO_2-NH_2]. The signal at δ(1.91) ppm refers to methyl groups in the compound.

The ^{13}CNMR spectrum of **[B8]**; showed signal at δ(195.50) ppm for the carbonyl of lactone group, signals at δ(166.74 ppm) carbonyl's lactam in oxazipine ring. The many signals in the rang δ(141.5-126.16 ppm) to aromatic carbon's atoms. The two signals at δ(114.61) ppm related to [-N-C(CH_3)-O-], and signal in position δ(25.66 ppm) for methyl group.

3.1.18 Synthesis and characterization of compound [B9]

This compound was prepared from the reaction of the Schiff base and sodium azide in DMF as a solvent.

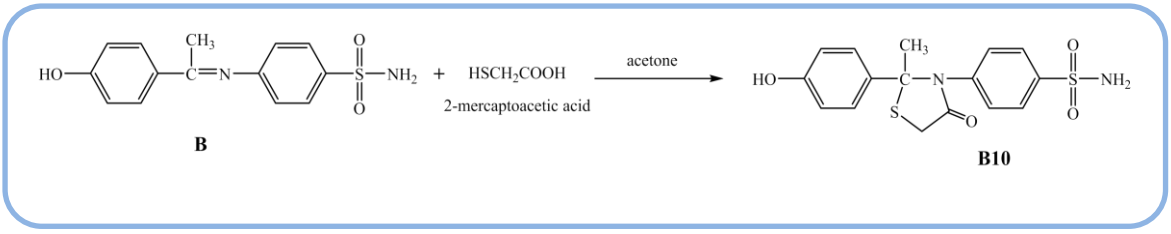


B1 B9

The FT-IR spectrum to this compound displayed the disappearance of absorption band that (C=N) stretching of azomethine for **[B]** with the appearance of a new band at 1560 cm^{-1} overlap refer to N=N stretching, and a new band at (3475) cm^{-1} due to NH stretching, **Fig.(3.64).**

3.1.19 Synthesis and characterization of compound [B10]

The compound [B10] was prepared by refluxed the compound [B1] with thioglycolic acid in acetone for 10 hrs.



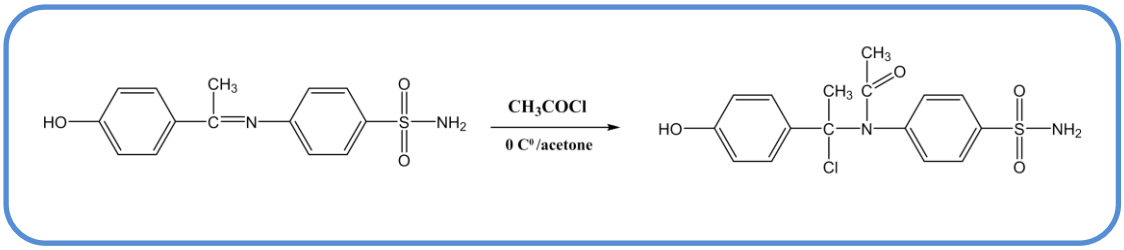
B B10

FT-IR spectrum of compound [B10], **Fig. (3.65)** displayed the evanescence of the absorption azomethine band for **[B1]** with the showed a new band at 1662 cm^{-1} of carbonyl (N-C=O) and a new band at (844) cm^{-1} due to (C-S).

The ^{1}HNMR spectrum (in DMSO as a solvent), **Figure (3.66)** of compound **[B10]** showed the singlet signal at δ(10.33 ppm), refers to (1H) of the -OH group. Doublet doublet signals in δ(7.86-6.60) ppm for eight aromatic protons; single signal in the position δ(5.85) ppm to the two protons of (NH_2), in addition singlet signal in the δ(3.45) ppm related to (-S-CH_2-CO), and single signal at δ(2.05) ppm to (3H) attributed to(C-CH_3) group.

3.1.20 Synthesis and characterization of compound [B11]

The compound **[B11]** was prepared by dissolved [B] in acetone before that added droplets from CH_3COCl and has been left stirring 4hrs.

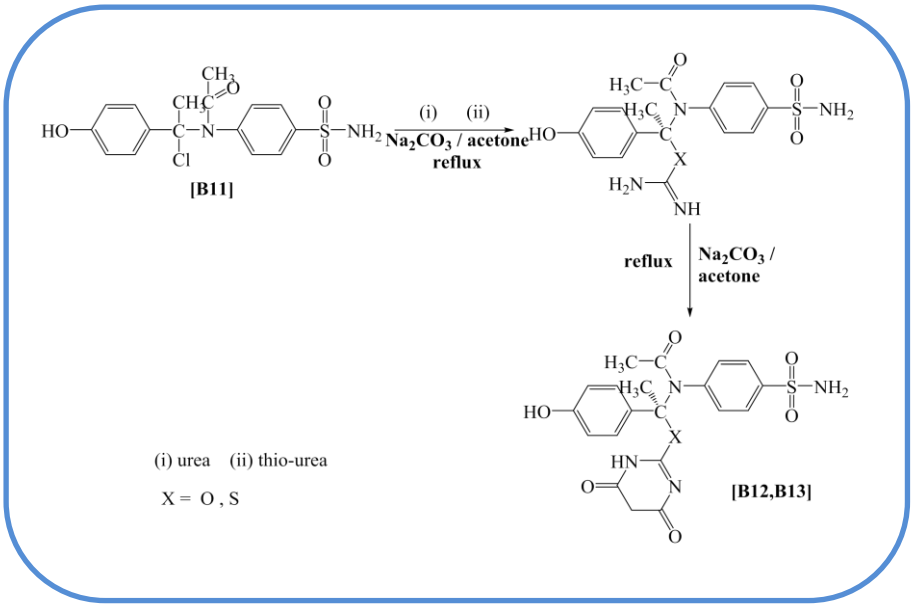


The FTIR spectrum displayed a disappearance ν(-C=N) band of azomethine in [B] and showed the new appearance str.band related to (νN-C=O) in 1667 cm^{-1}, **Fig.(3.67).**

The ^{1}HNMR spectrum in DMSO, **Fig. (3.68)** displayed the single signal at δ(10.62) ppm refers to the one proton of the hydroxyl group, the doublet doublet signals at δ(7.71-6.94) ppm related to (8H) of aromatic ring's. The single signal in the position δ(5.85 ppm) refers to two protons of ($-NH_2$), and the signals at δ(2.05 and 1.76) ppm to be (3H) for [CH_3-C-Cl], [CH_3-CO-N] respectively.

3.1.21 Synthesis and characterization of compounds [B12-B13]

The compounds **[B12, B13]** were prepared by dissolved [B11] in acetone with Na_2CO_3 as a catalyst, added (urea or thiourea) to the mixture and refluxed for 4 hrs. Then added diethylmalonate to the mixture the reaction continued for another 4 hrs. Scheme (3.6): showed the reaction of compound [B12-B13]



Scheme (3.6): The reaction of synthesis compounds [B12, B13]

FTIR spectrum of compounds **[B12, B13]**, showed the appearance new streching band referred to (υC=O),at (1778,1774) cm^{-1}**, Figures (3.69),(3.70).** All data of these compounds listed in the Table: (3.10).

Table (3.10): Characteristic FTIR absorption bands of [B12-B13]

Comp. No.	FT-IR spectra (cm-1)							
	υNH $υNH_2$	υ(C-H) arom.	υCH Aliph.	υC=O	υC=O pyrmidine	υC=C	υC=N pyrmidine	Other
B12	3441-3340	Overlap	2816	1651	1778	1585	overlap	υO-H 3228
B13	3379-3275	3097	Overlap	1651	1774	1585	1616	υO-H 3178

The ^{1}HNMR spectrum of [B12]; displayed the single signal at δ(11.01) ppm refer to (1H) of (-NH) group, and the single signal at δ(10.41) ppm related to one proton of a hydroxyl group. Doublet doublet signals in the position δ(7.13-8.31) ppm to the eight of aromatic's protons. A single signal at δ(5.80 ppm) to be two protons of(SO_2-NH_2). Signal at δ(2.96 ppm) to (2H; -CH_2), and signals in (2.08 and 1.67) ppm refer to [O-C-CH_3] and [N-CO-CH_3].

The ^{1}HNMR spectrum (in DMSO) of [B13] **Figure (3.71)** displayed two singlet signal at δ(11.81, 10.00) ppm it is expected to be (-NH and OH) groups. Doublet douublet signals in δ(7.80-6.64 ppm) for eight aromatic protons in the two rings, also single signal in the position δ(5.81) ppm to the

two protons of (-NH_2) in addition, A singlet signal at δ(3.58) ppm be to (CO-CH_2-CO) in a pyrimidine ring and signals in a position δ(2.85 and 2.00) ppm for the methyl groups in a compound.

The ^{13}CNMR spectrum of [B12]; showed signal at δ(160) ppm to be the carbonyl group of [N-CO-CH_3], signals at (183 and 169) related to carbonyl's pyrimidine ring. the signal at δ(157 ppm) to the [O-C=N] and many signals in the rang δ(150-130 ppm) to aromatic carbon atoms. The two signals at δ(105 and 38) ppm refer to [N-C(CH_3)-O] and (CH_2) respectively. Signals at δ(25, 20) ppm for the methyl groups.

3.2 Biological activity assay

Antibacterial and antifungal activity was performed for some compounds prepared in concentration (10^{-2} M) against four kinds of bacteria **(*Staphylococcus aureus, Bacillus Cereus)*** gram (+) and ***(E.coli, Pseudomonas aeruginosa)*** gram (-), and a kind of fungal,(***Candida albicans)*** through in a nutrient agar medium. DMSO was applied as a solvent for all the compounds, and as a control. These prepared compounds exhibited different biological activity.

3.2.1 Conclusions

- The compounds showed different activity against ***Bacillus Cereus*** where **[A29, A33][B1, B10, B13]** recorded high inhibition zoon while other compounds showed moderate to weak inhibition zoon.
- For ***Staphylococcus aureus*** **[A2, A29, A33, B1, B10]** showed good effectiveness, while **[A3, B6, B8, B13]** recorded Equal to effectiveness to ampicillin.
- For ***E. Coli*** Prepared compounds **[A1, A3, A12, A29, B10]** recorded the high inhibition zoon and the rest of the compounds range from medium to weak.
- For ***pseudomonas aerug.*** compounds **[A29, B1, B8]** were seen as good activity.
- For ***Candida albicans*** the compounds **[A3, A28, A33, B1, B21]** recorded good activity, where the **[A7, A22, B8]** was almost equal as

well as and displayed the remaining group of compounds weak inhibition zoon, **Fig. (3.72-3.78)**. Biological investigation data were given in **Table (3.11)**.

Table(3.11): The inhibition zones of some prepared compounds

Compound No.	Inhibition zone (mm.)				
	Gram Positive(+)		Gram Negative(-)		*Candida albicans*
	Bacillus cereus	*Staphylococcus aureus*	*E. Coli*	*Pseudomonas aerug.*	
A1	-	-	18	15	10
A2	16	20	17	13	14
A3	15	17	19	15	19
A4	14	-	16	12	13
A7	13	15	14	11	17
A9	-	10	15	-	-
A10	13	15	16	10	10
A12	14	15	18	14	11
A25	13	13	17	14	-
A22	11	14	12	16	15
A23	-	-	14	-	13
A28	-	13	16	14	18
A29	25	20	21	19	14
A33	19	22	17	16	18
B1	21	25	16	22	19
B4	-	13	14	10	13
B6	14	16	17	15	12
B8	14	17	15	21	16
B10	22	20	25	18	21
B13	19	16	13	15	11
Ampicillin 10^{-2} M	16	17	15	18	16
DMSO	--	--	--	--	--

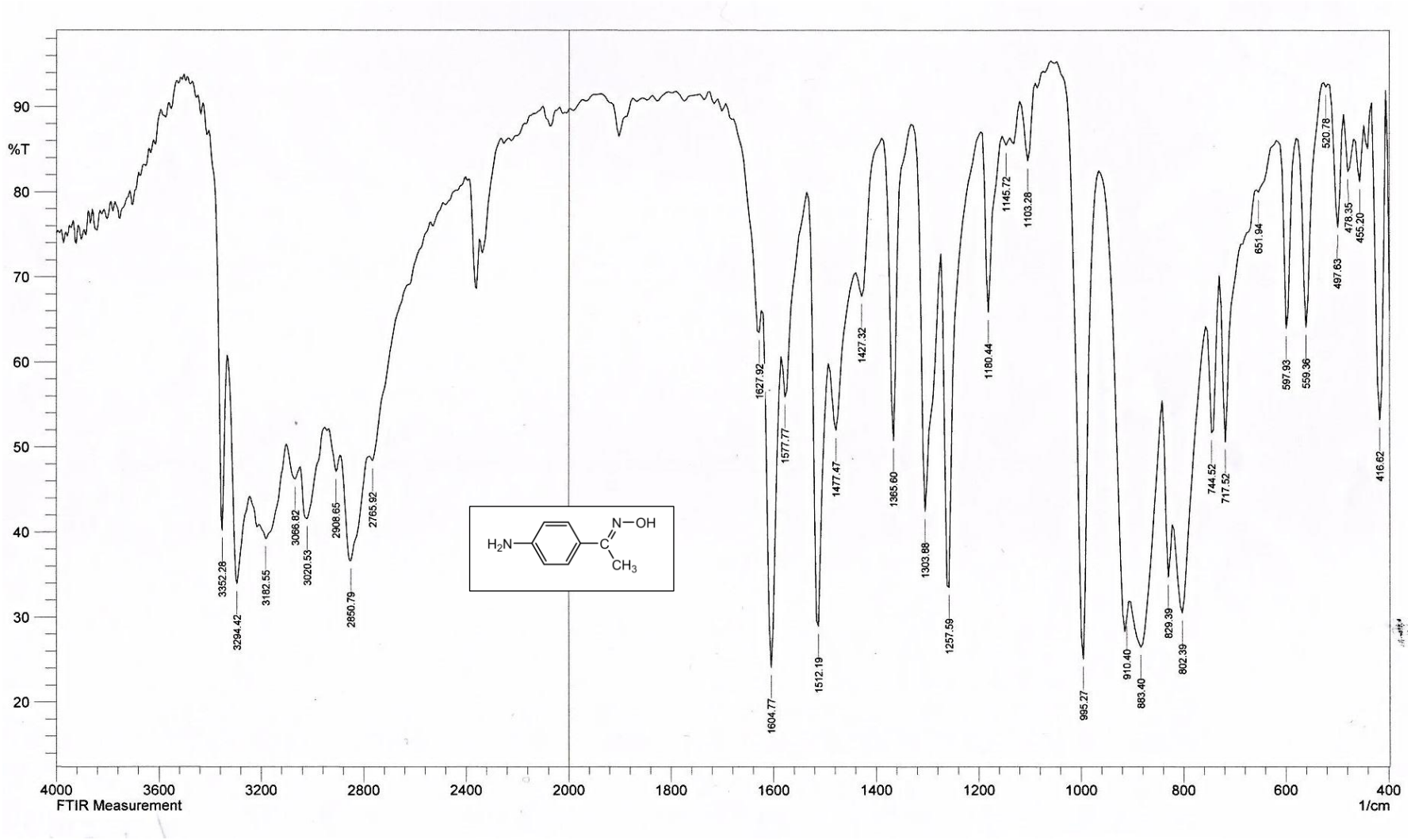


Fig. (3.1) FTIR spectrum of [A]

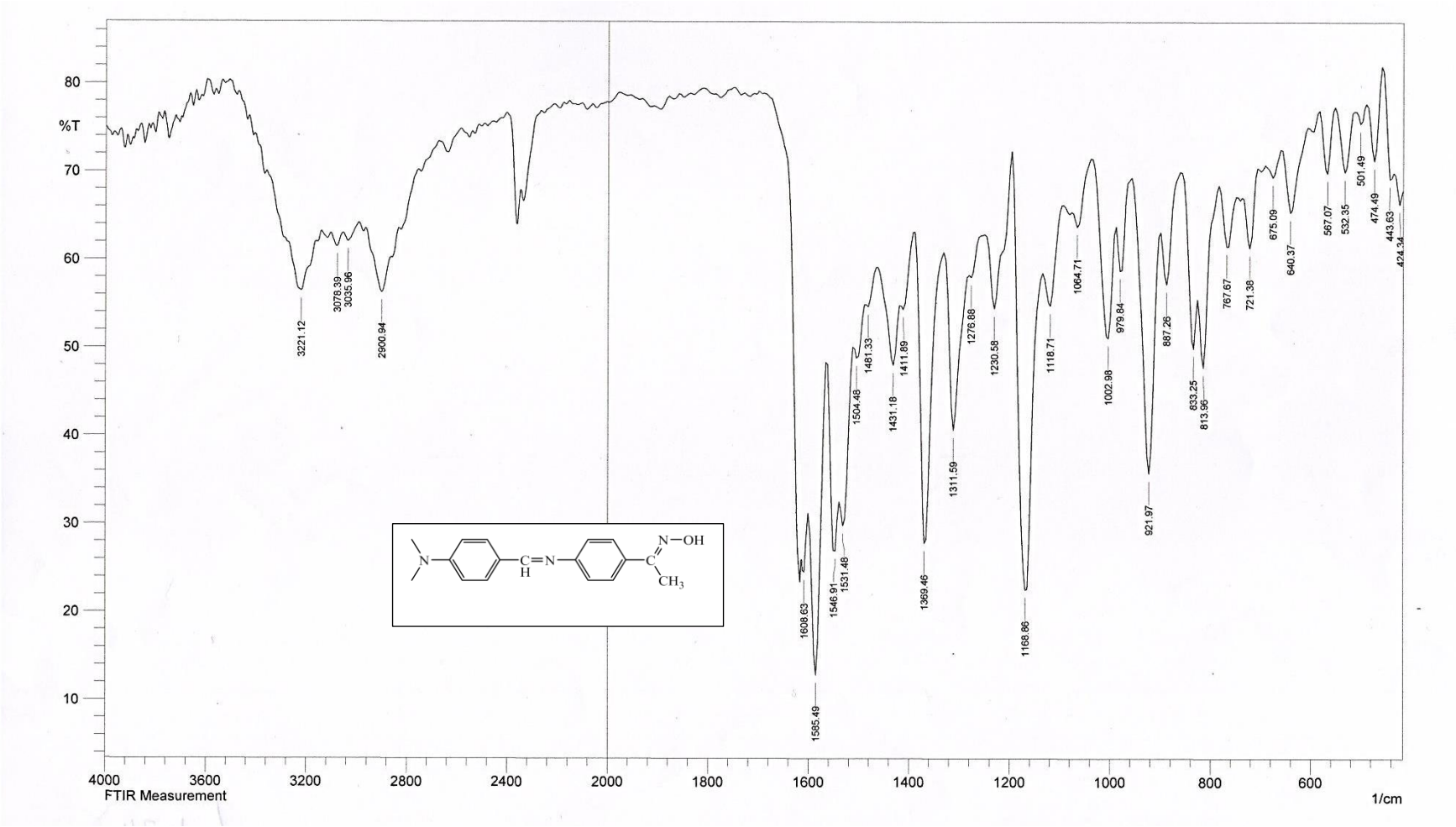


Fig. (3.2) FTIR spectrum of [A1]

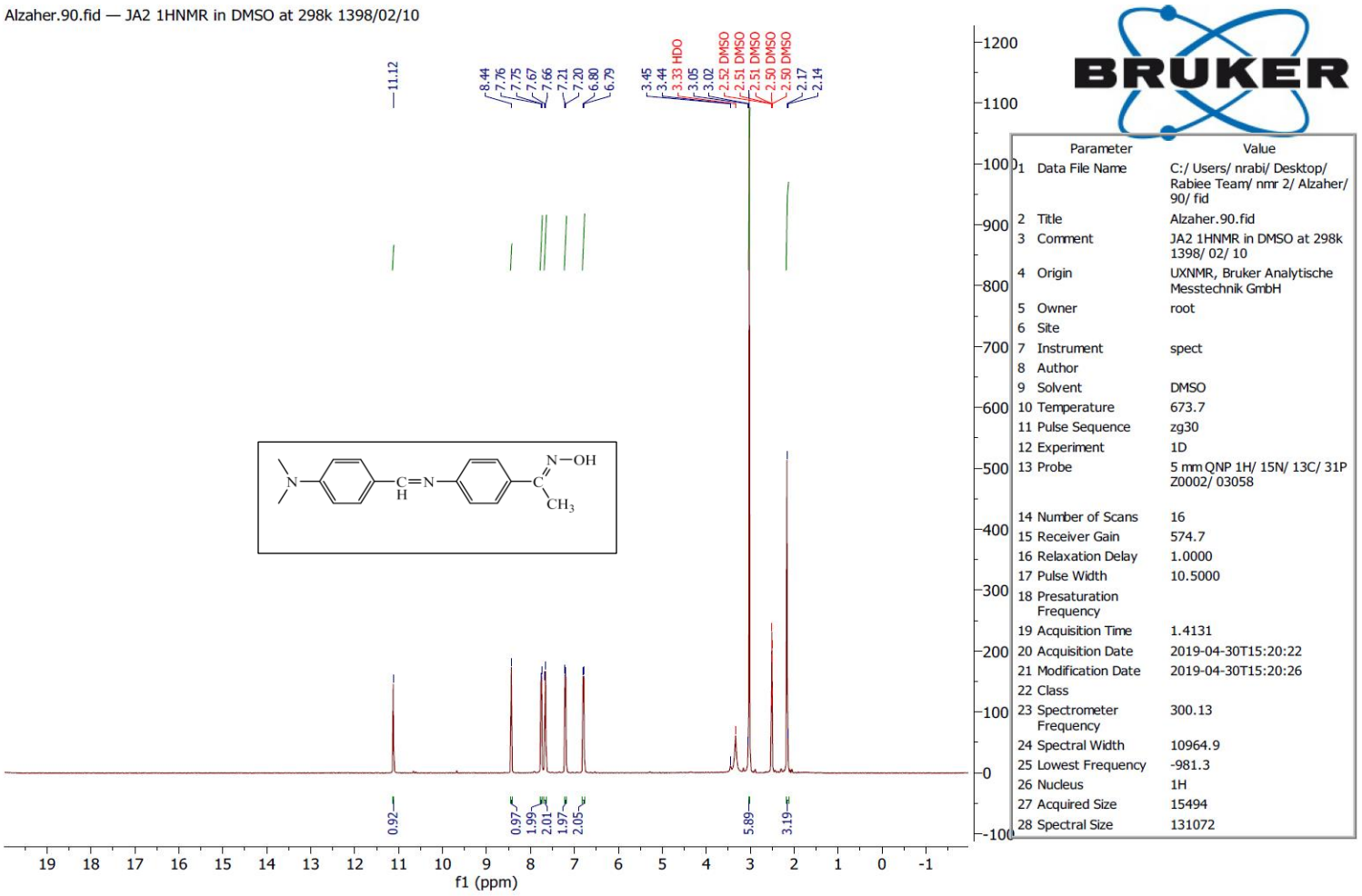


Fig. (3.3) ^{1}HNMR spectrum of [A1]

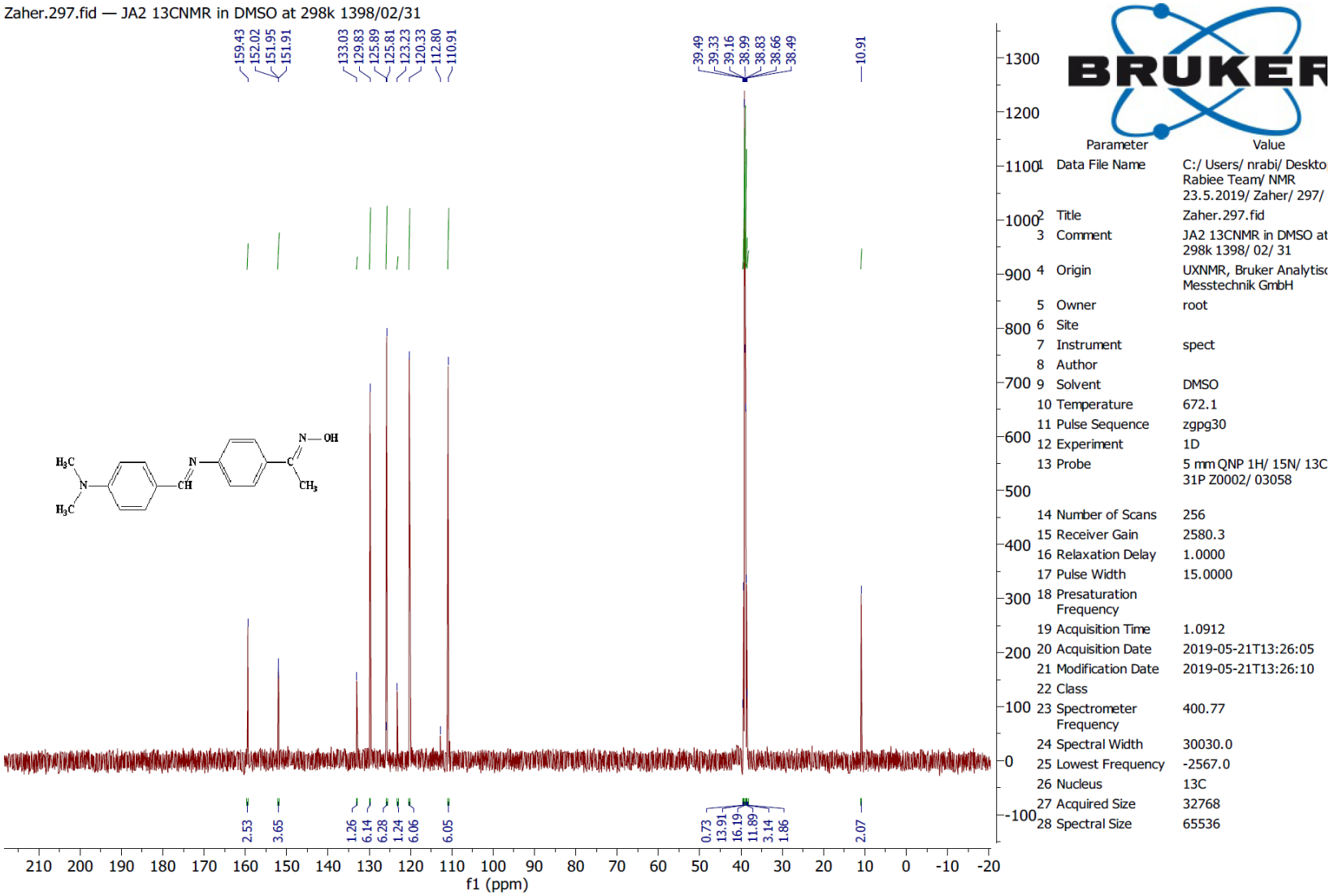


Fig. (3.4) ^{13}CNMR spectrum of [A1]

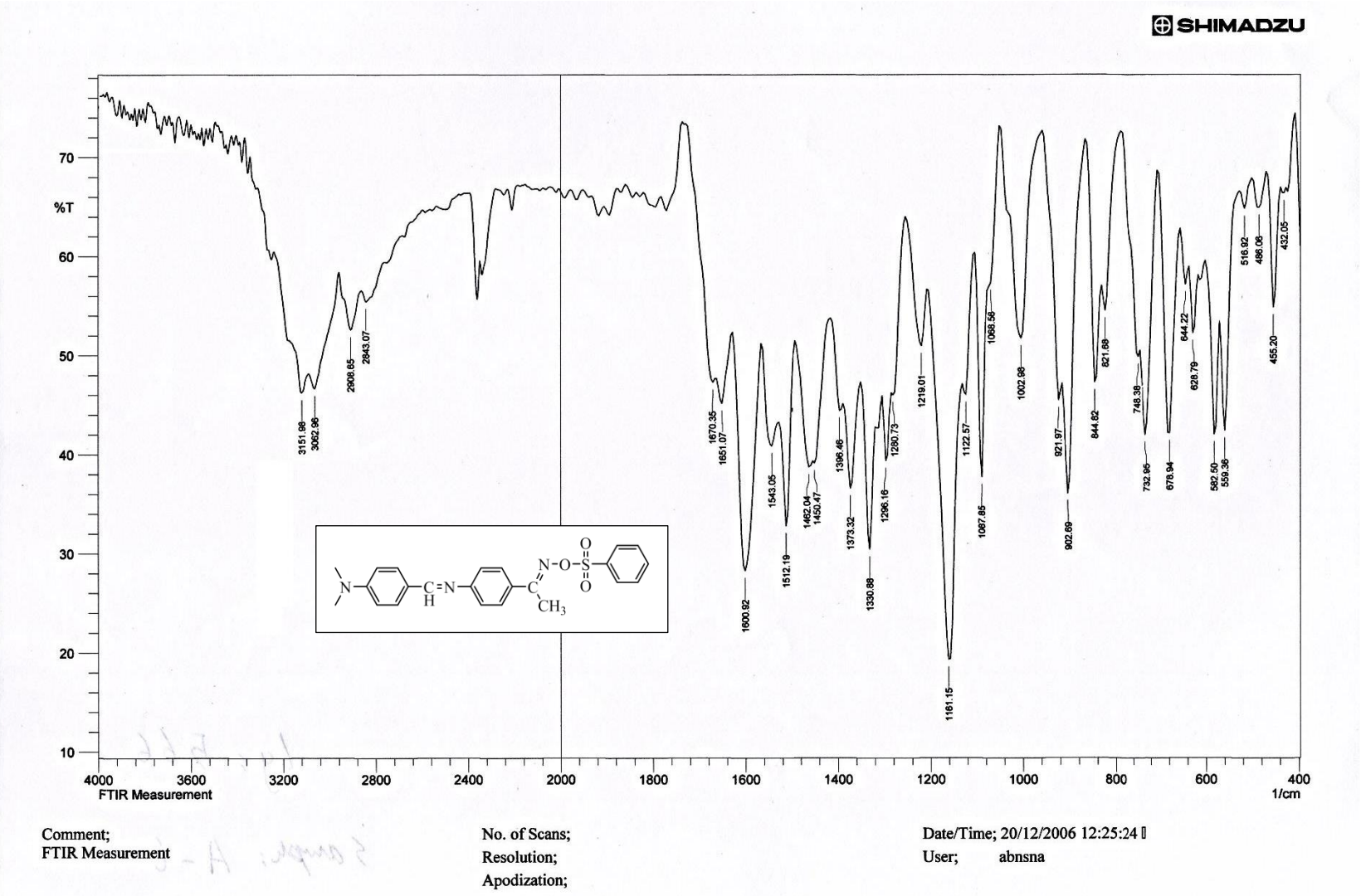


Fig. (3.5) FTIR spectrum of [A2]

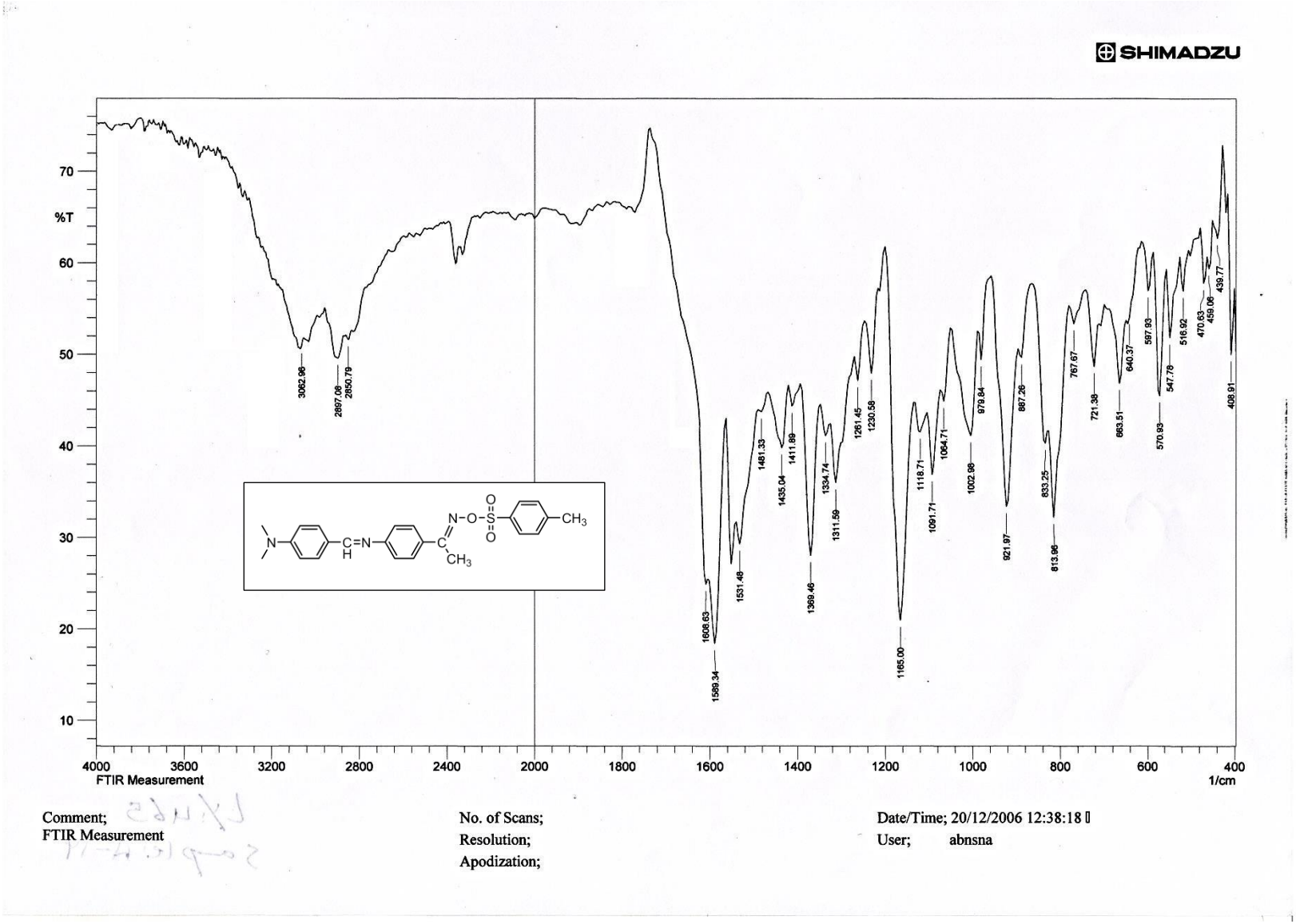


Fig. (3.6) FT-IR spectrum of [A3]

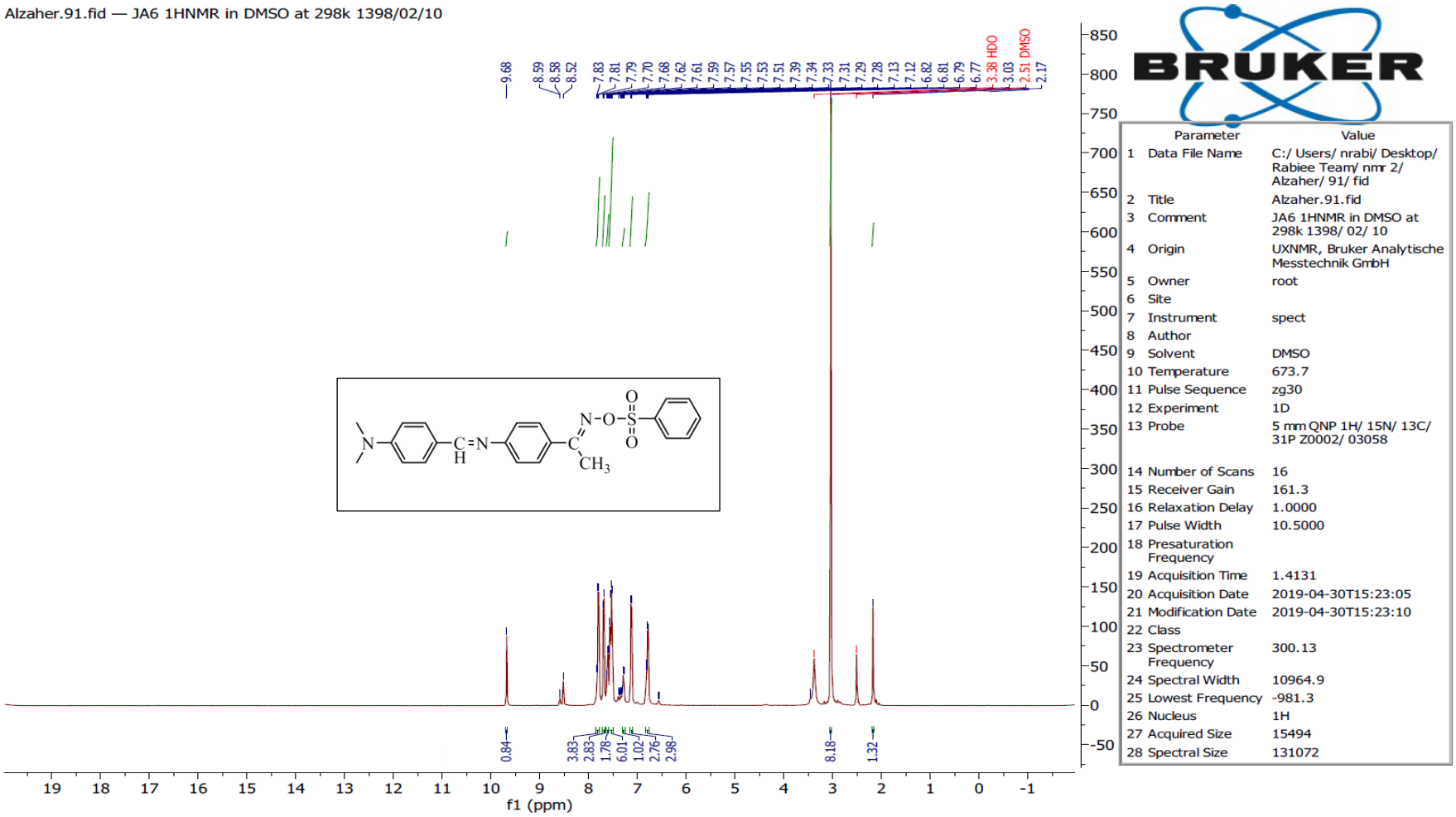


Fig. (3.7) ^{1}HNMR spectrum of [A2]

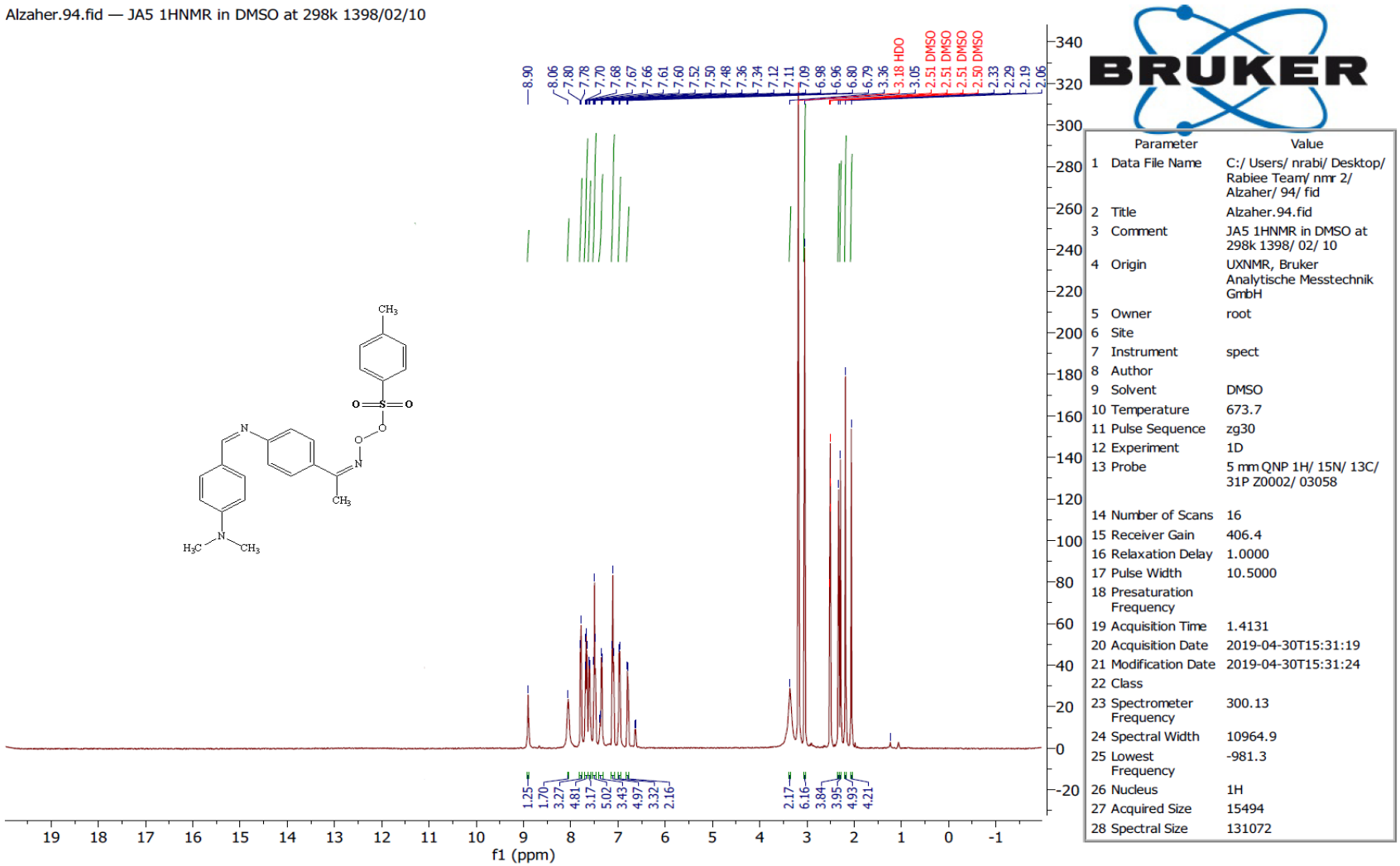


Fig. (3.8) ^{1}HNMR spectrum of [A3]

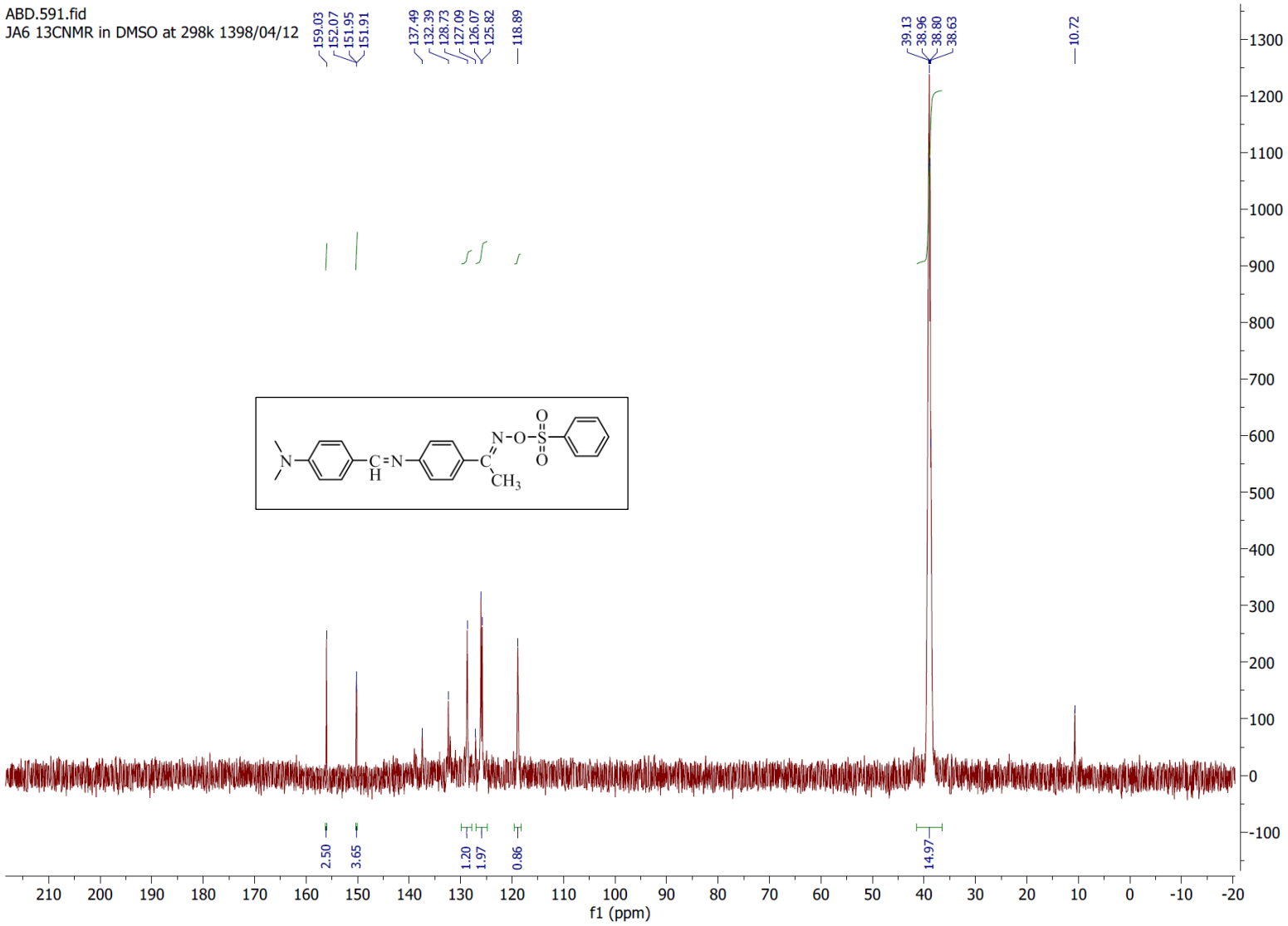


Fig. (3.9) ^{13}CNMR spectrum of [A2]

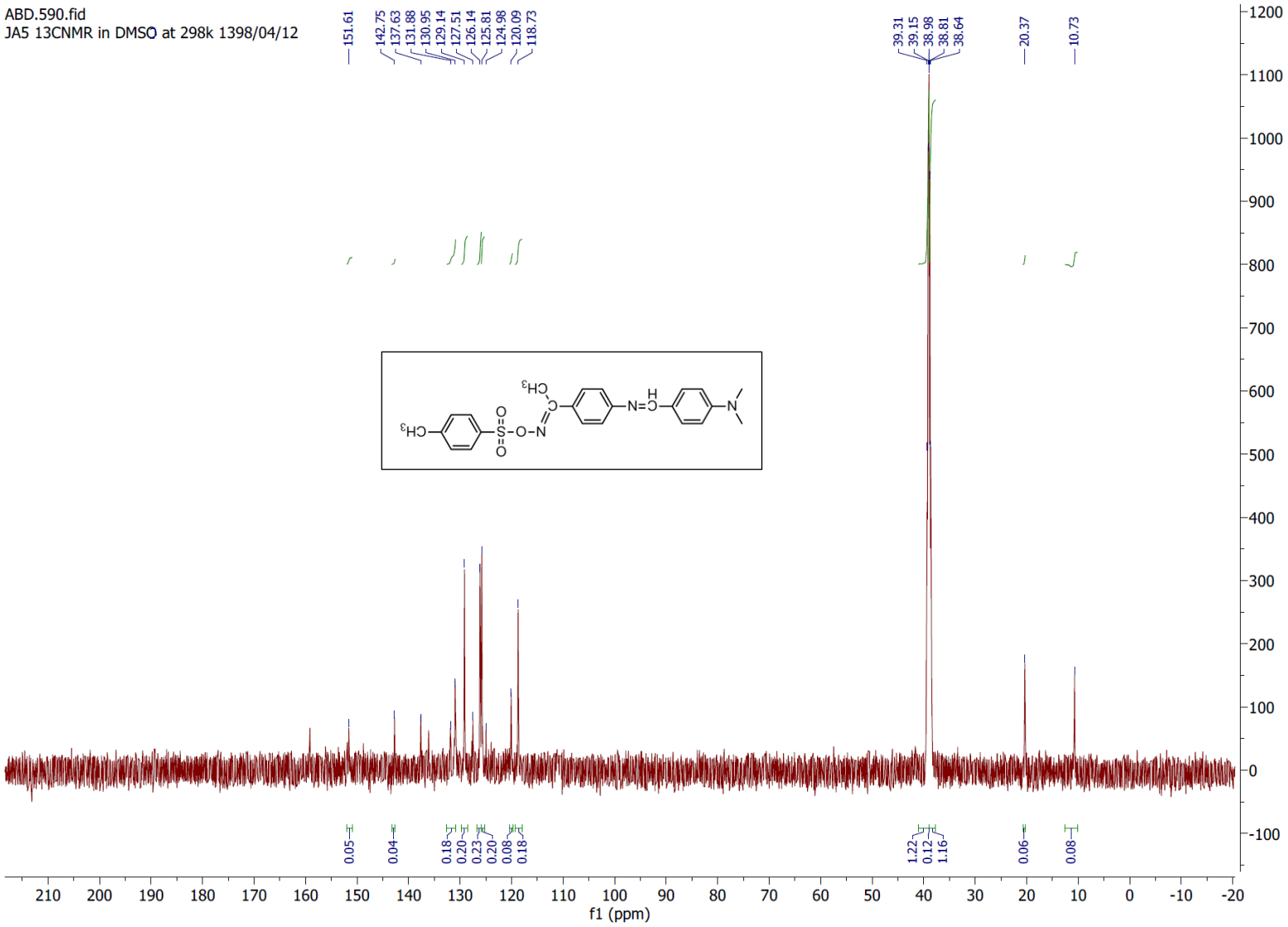


Fig. (3.10) ^{13}CNMR spectrum of [A3]

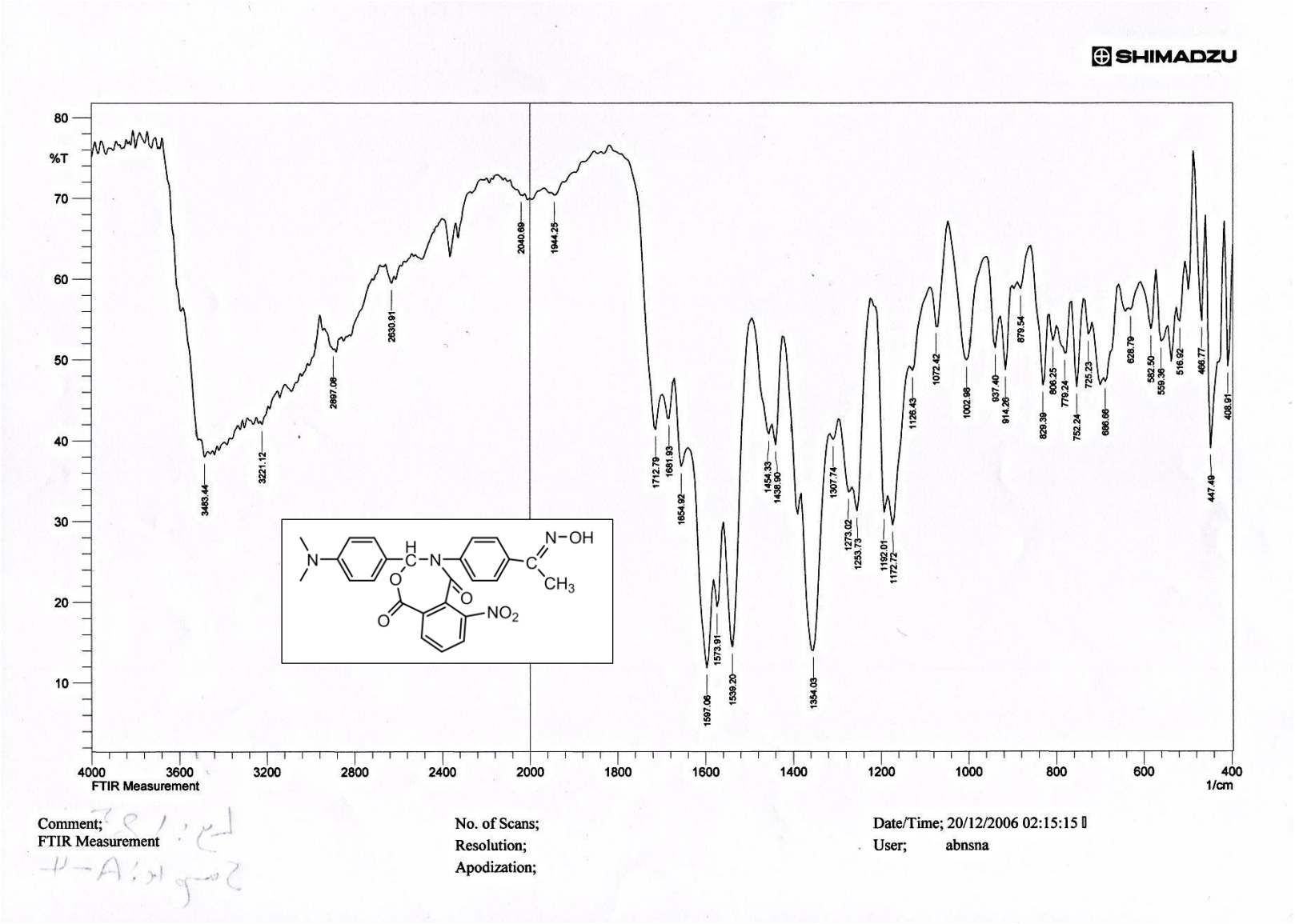


Fig. (3.11) FTIR spectrum of [A4]

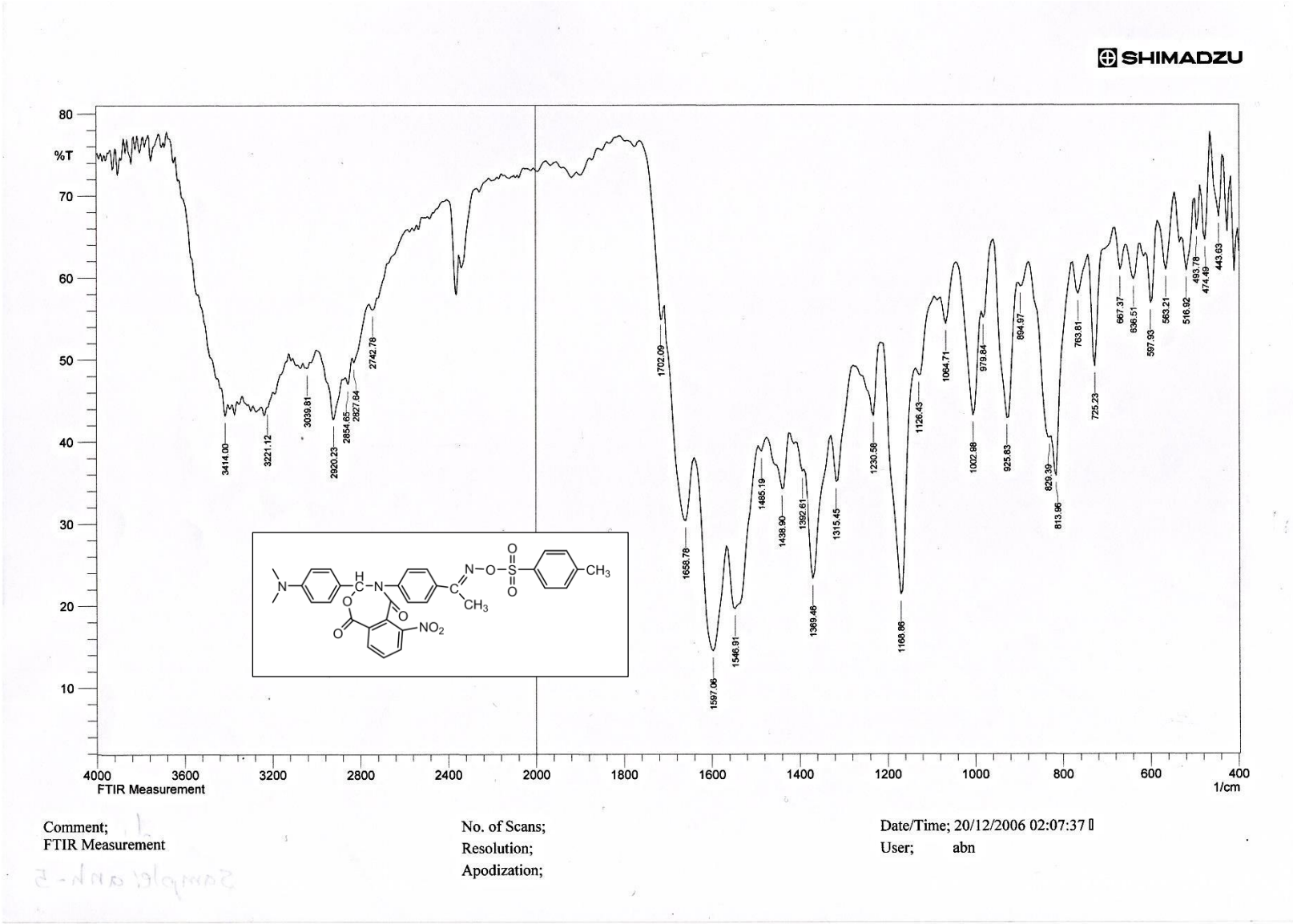


Fig. (3.12) FTIR spectrum of [A6]

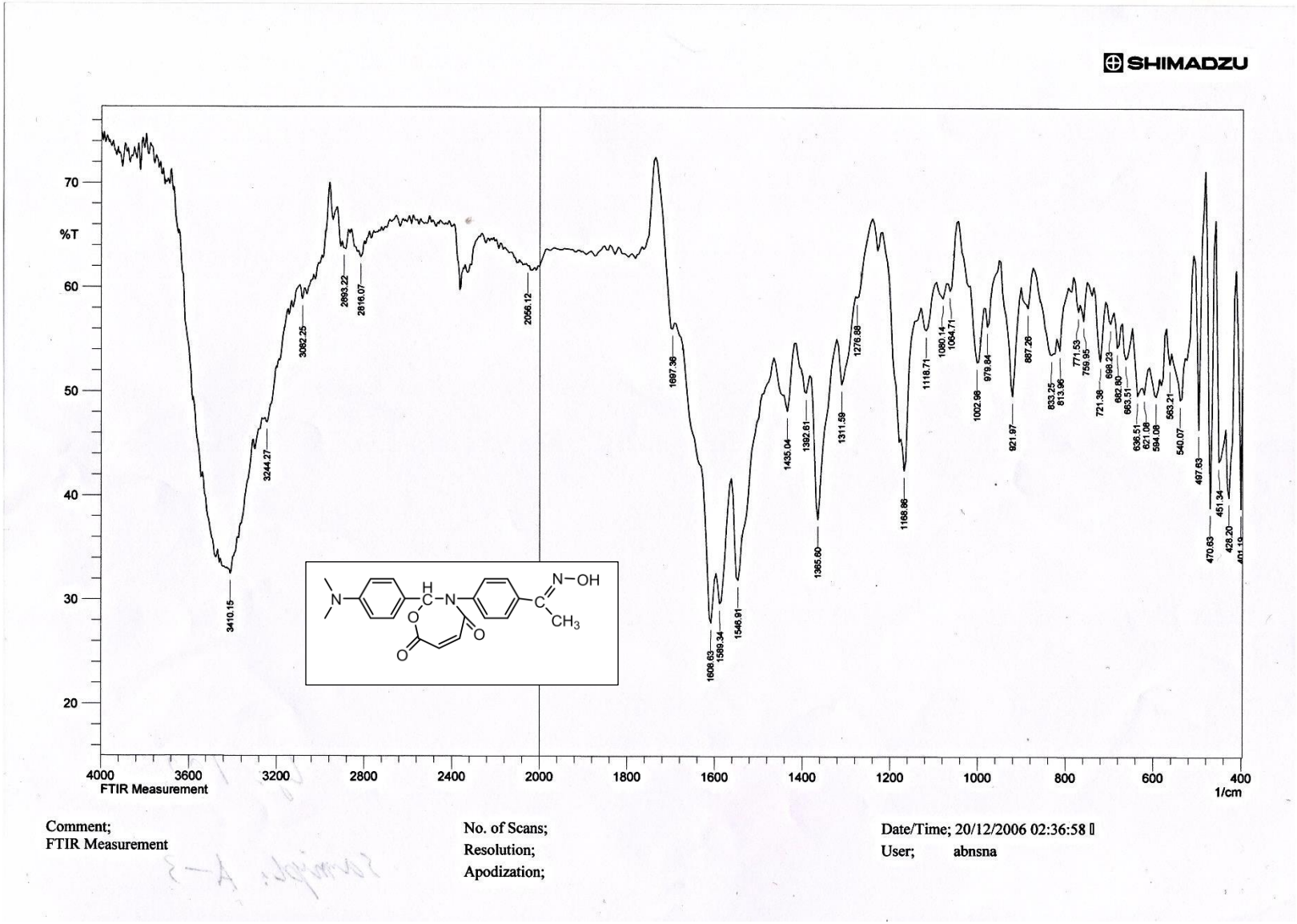


Fig. (3.13) FTIR spectrum of [A7]

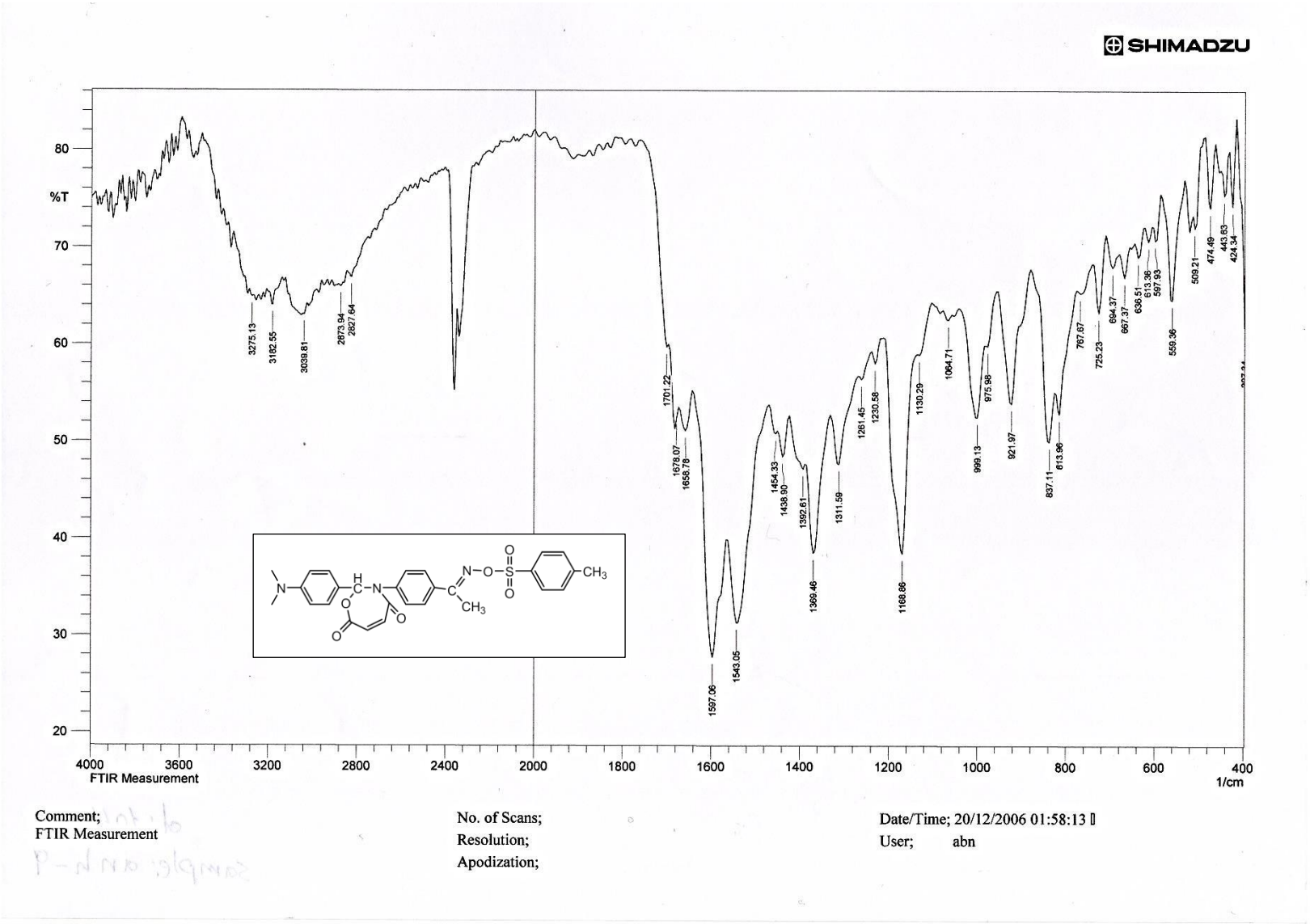


Fig. (3.14) FTIR spectrum of [A9]

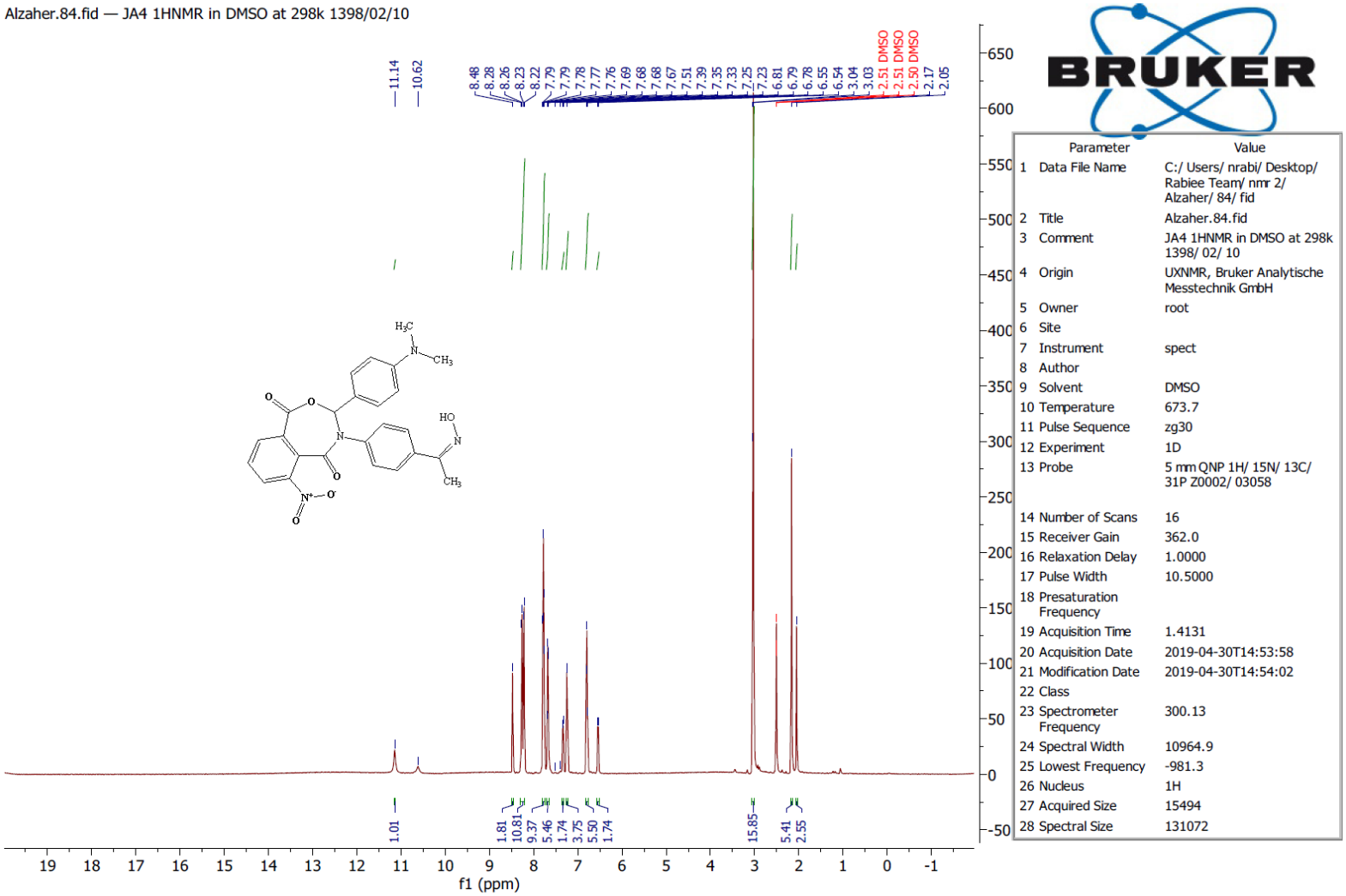


Fig. (3.15) [1]HNMR spectrum of [A4]

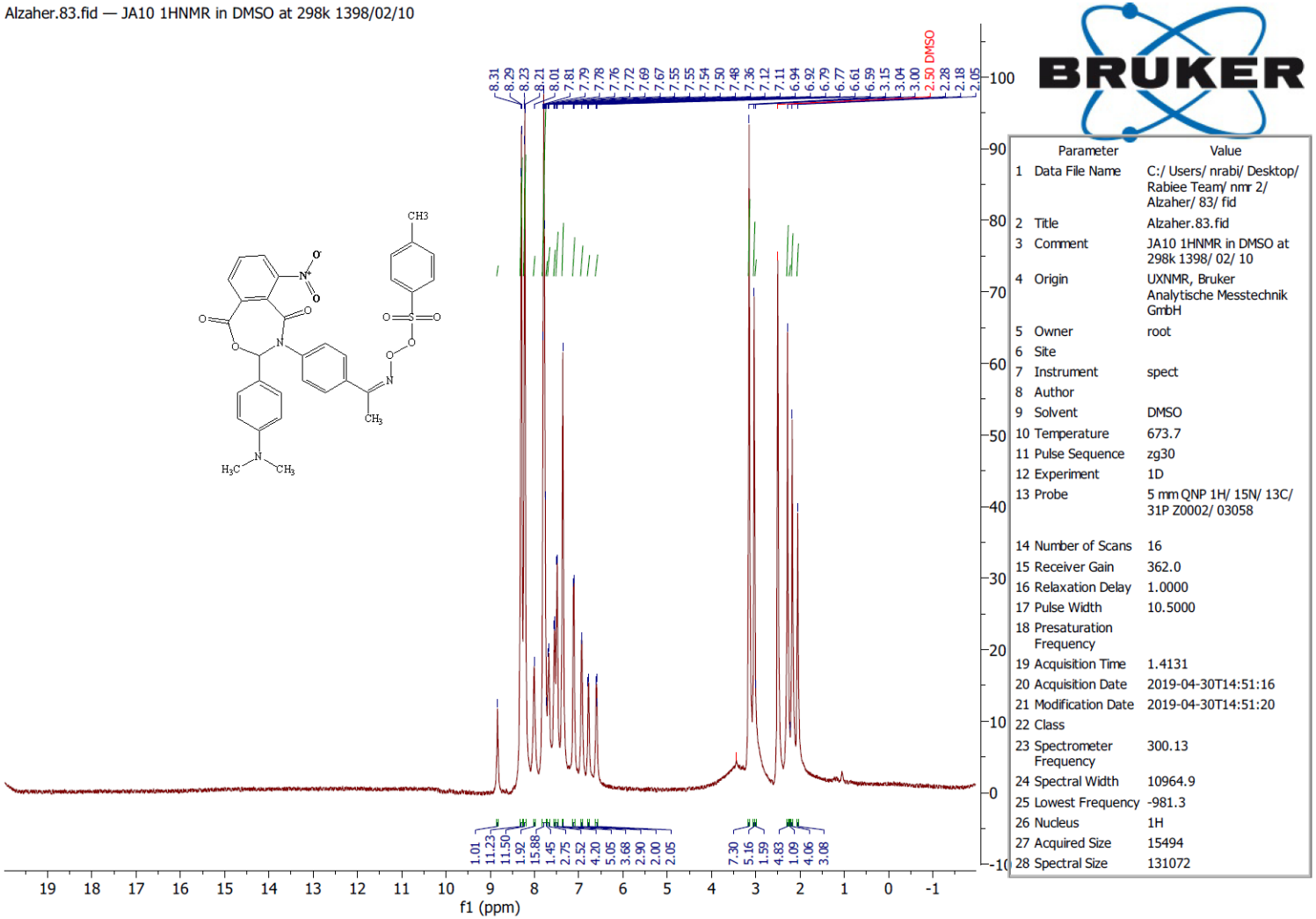


Fig. (3.16) ^{1}HNMR spectrum of [A6]

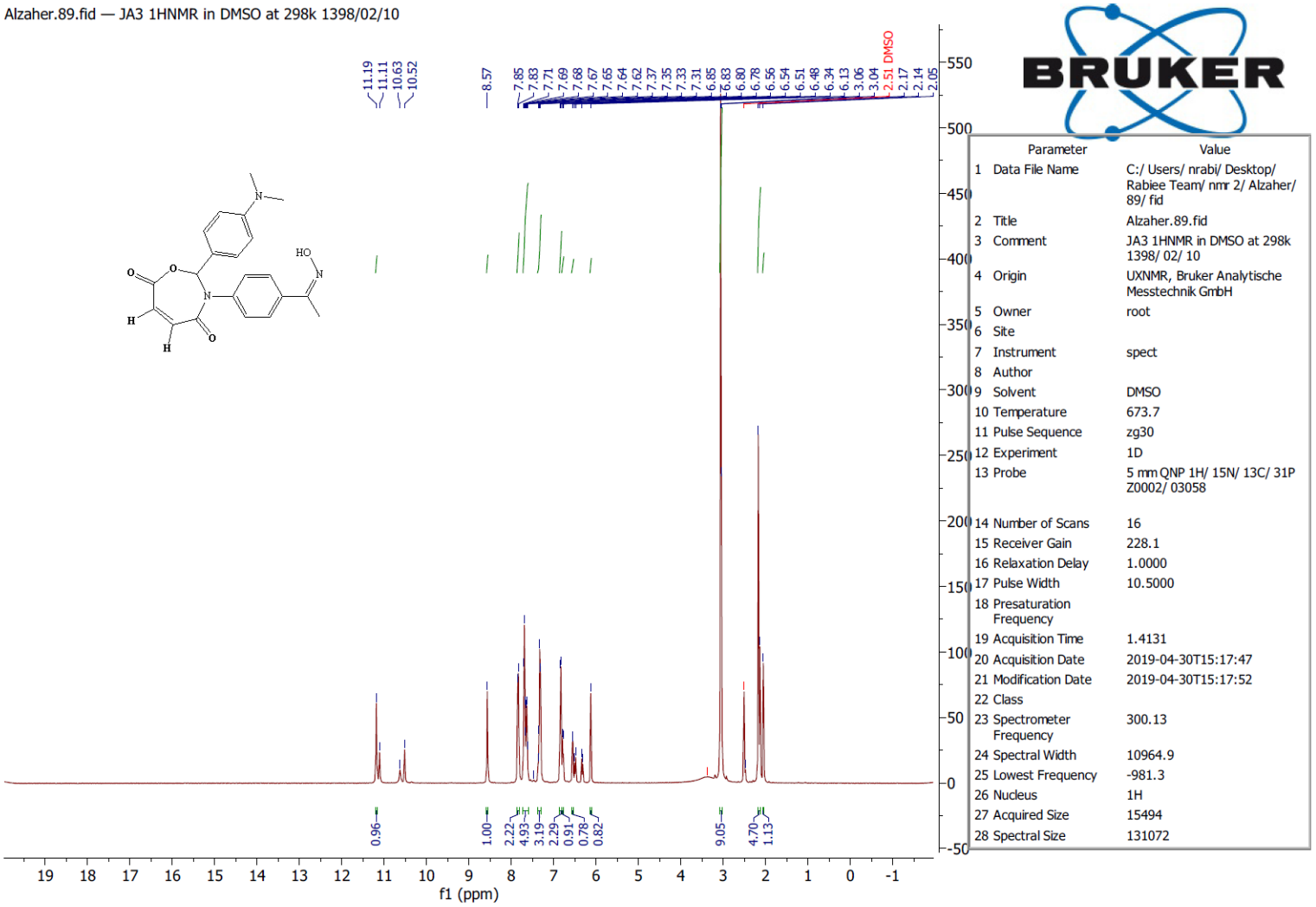


Fig. (3.17) ^{1}HNMR spectrum of [A7]

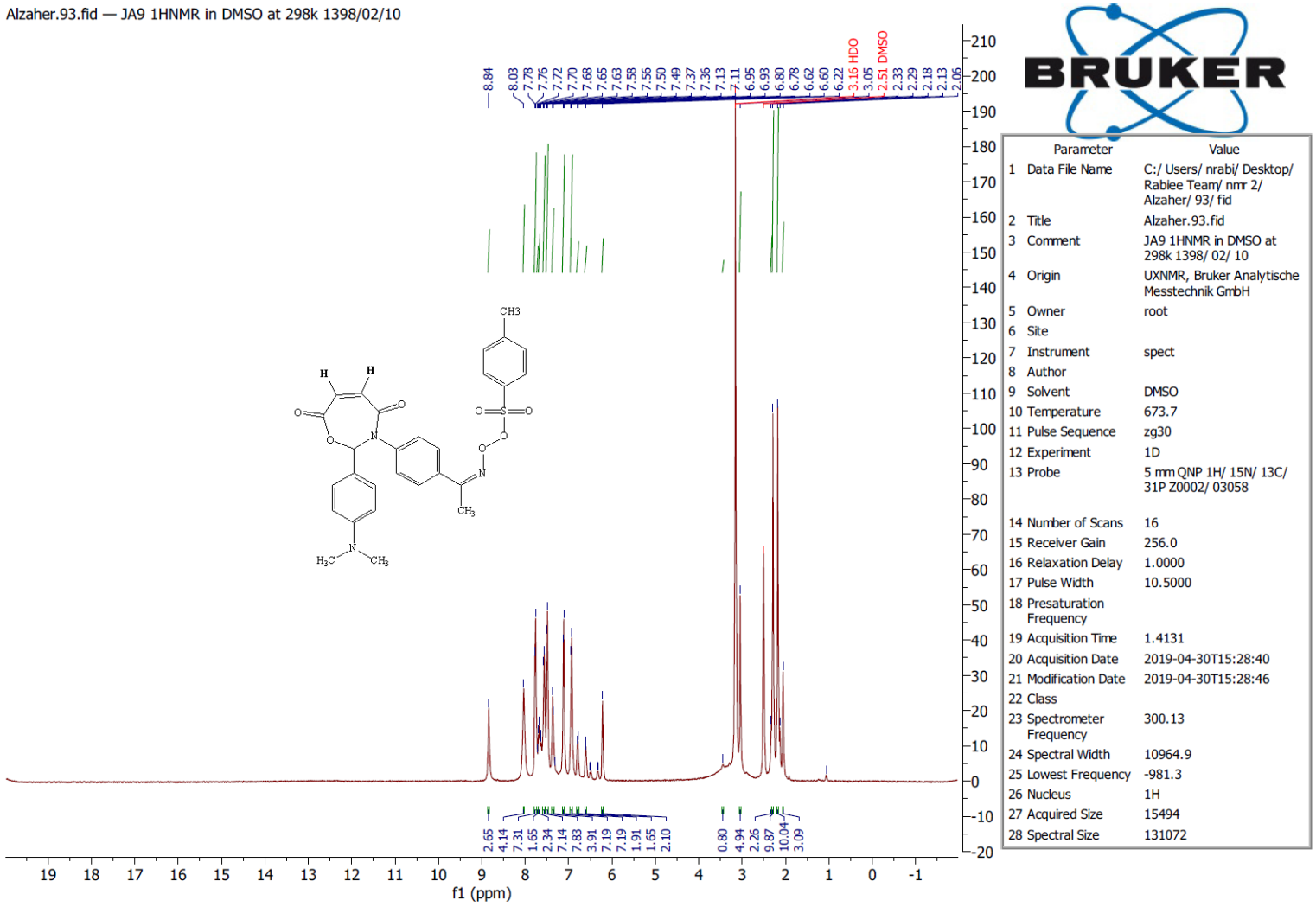


Fig. (3.18) ^{1}HNMR spectrum of [A9]

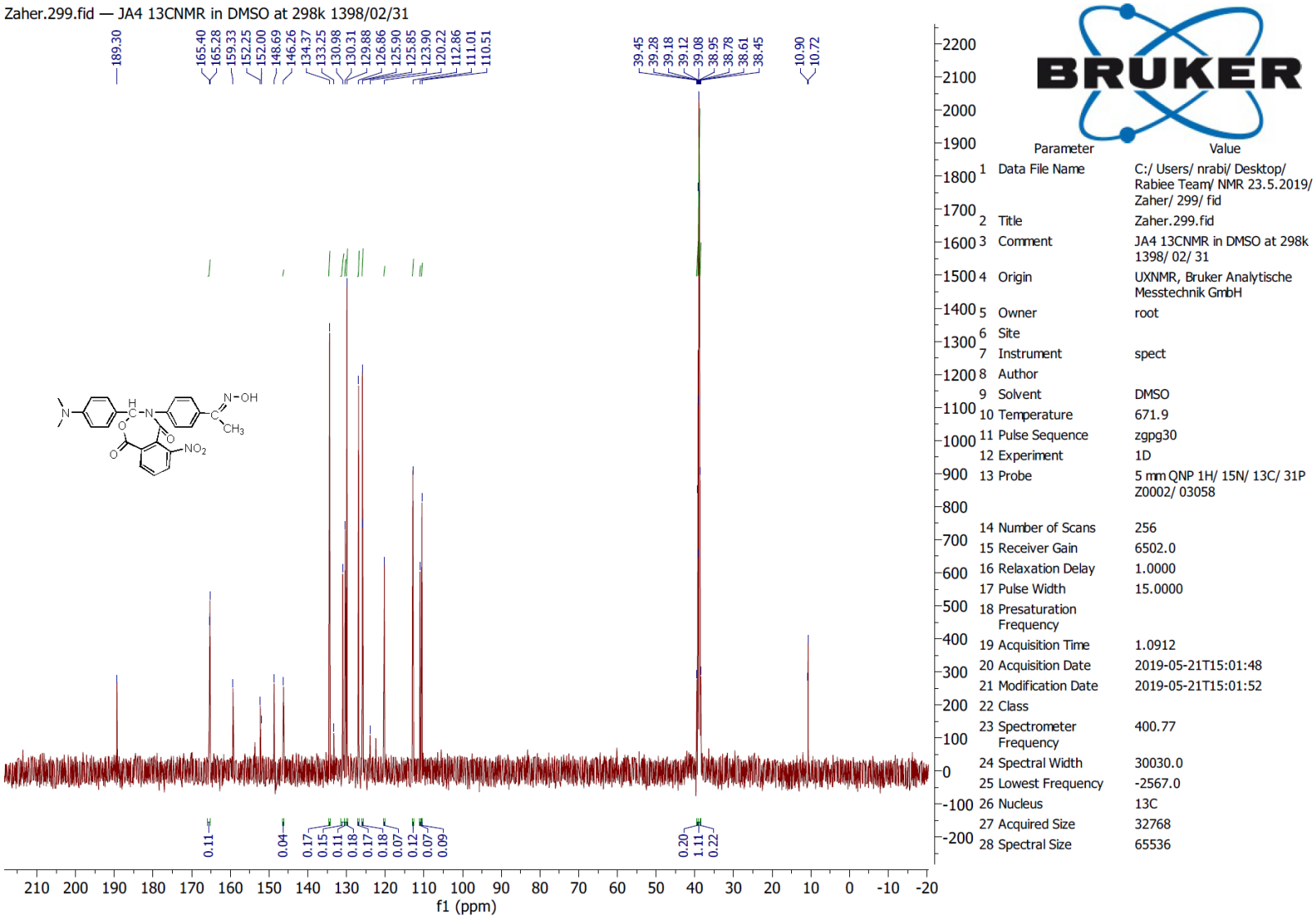


Fig. (3.19) ^{13}CNMR spectrum of [A4]

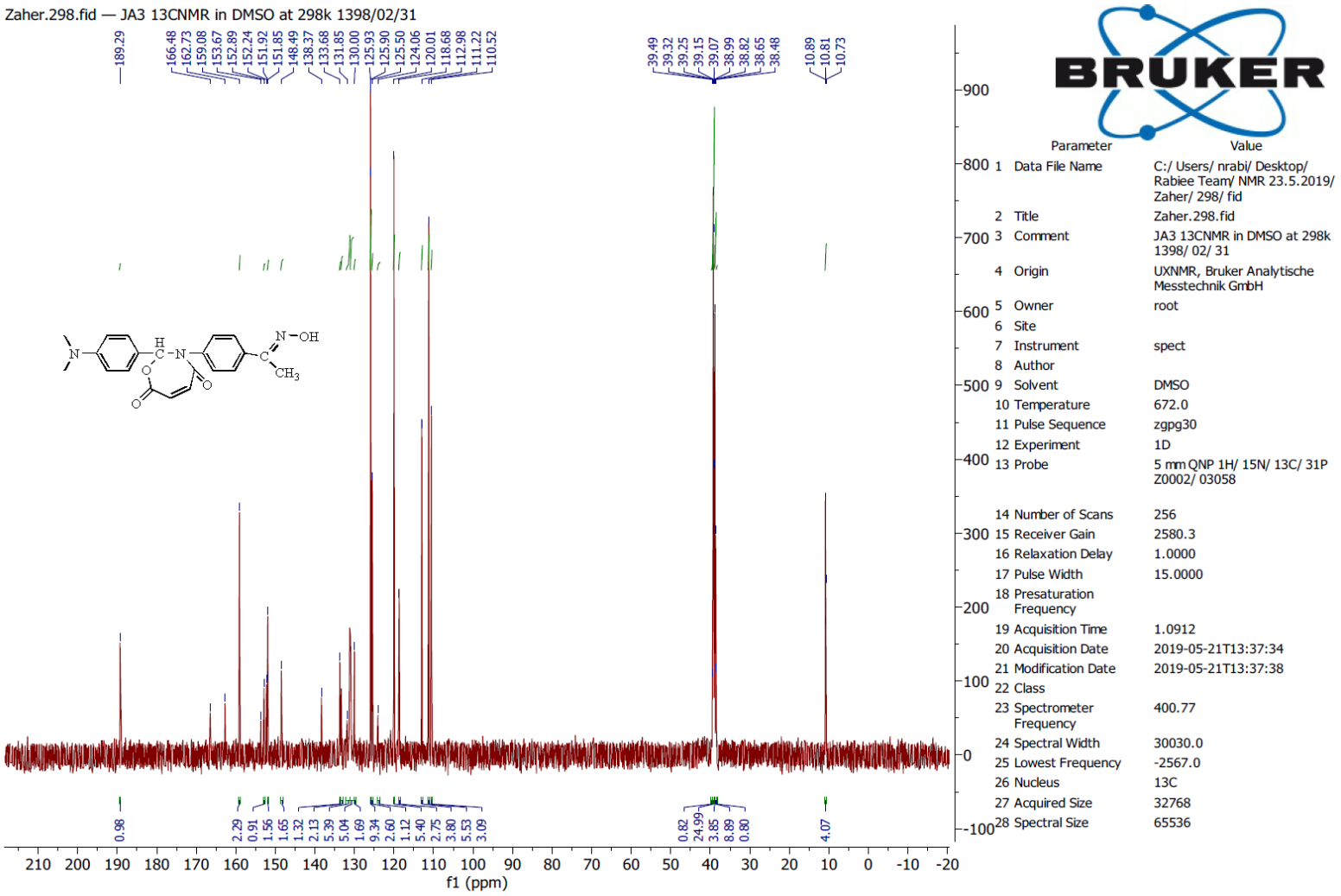


Fig. (3.20) ^{13}CNMR spectrum of [A7]

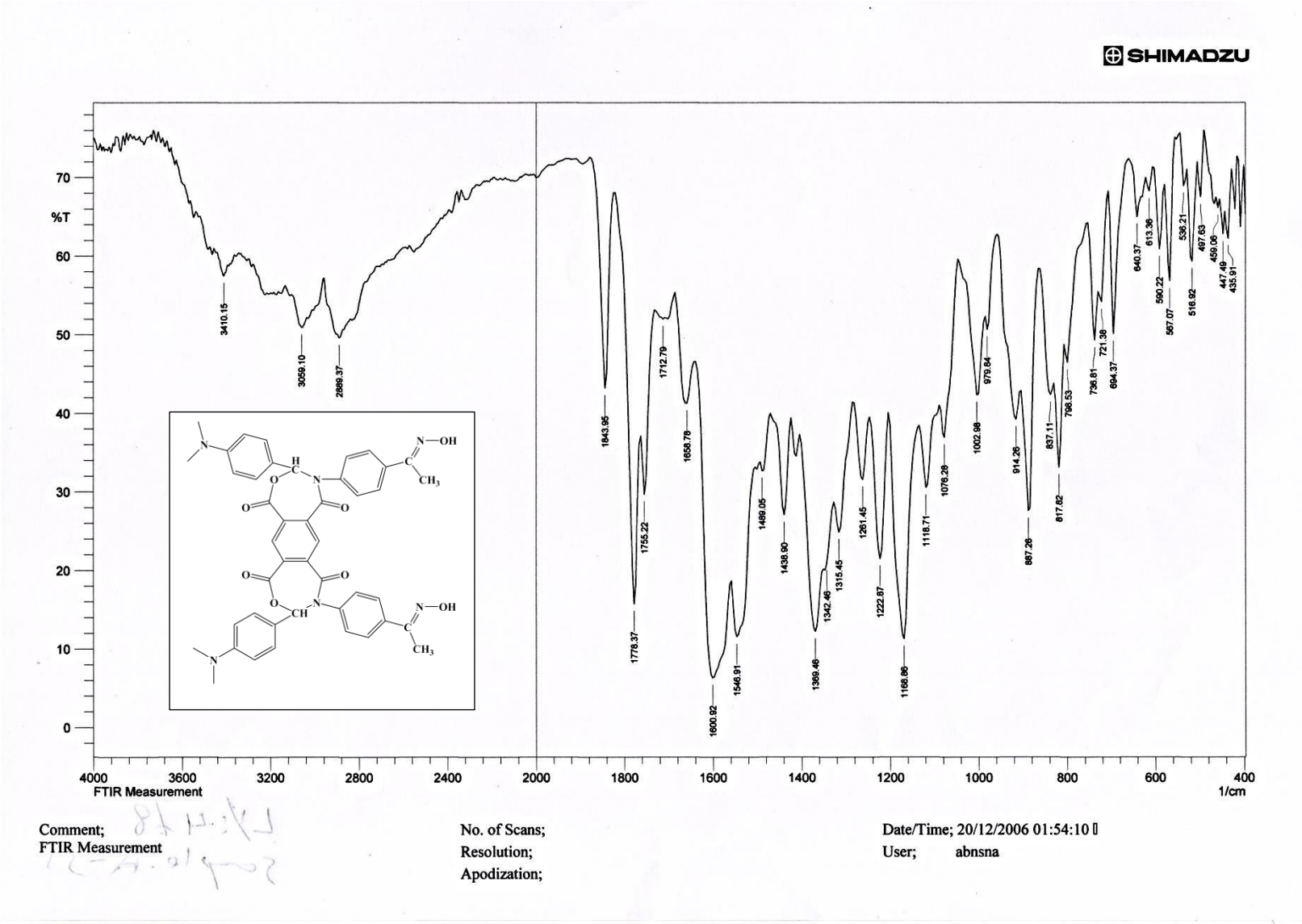


Fig. (3.21) FTIR spectrum of [A10]

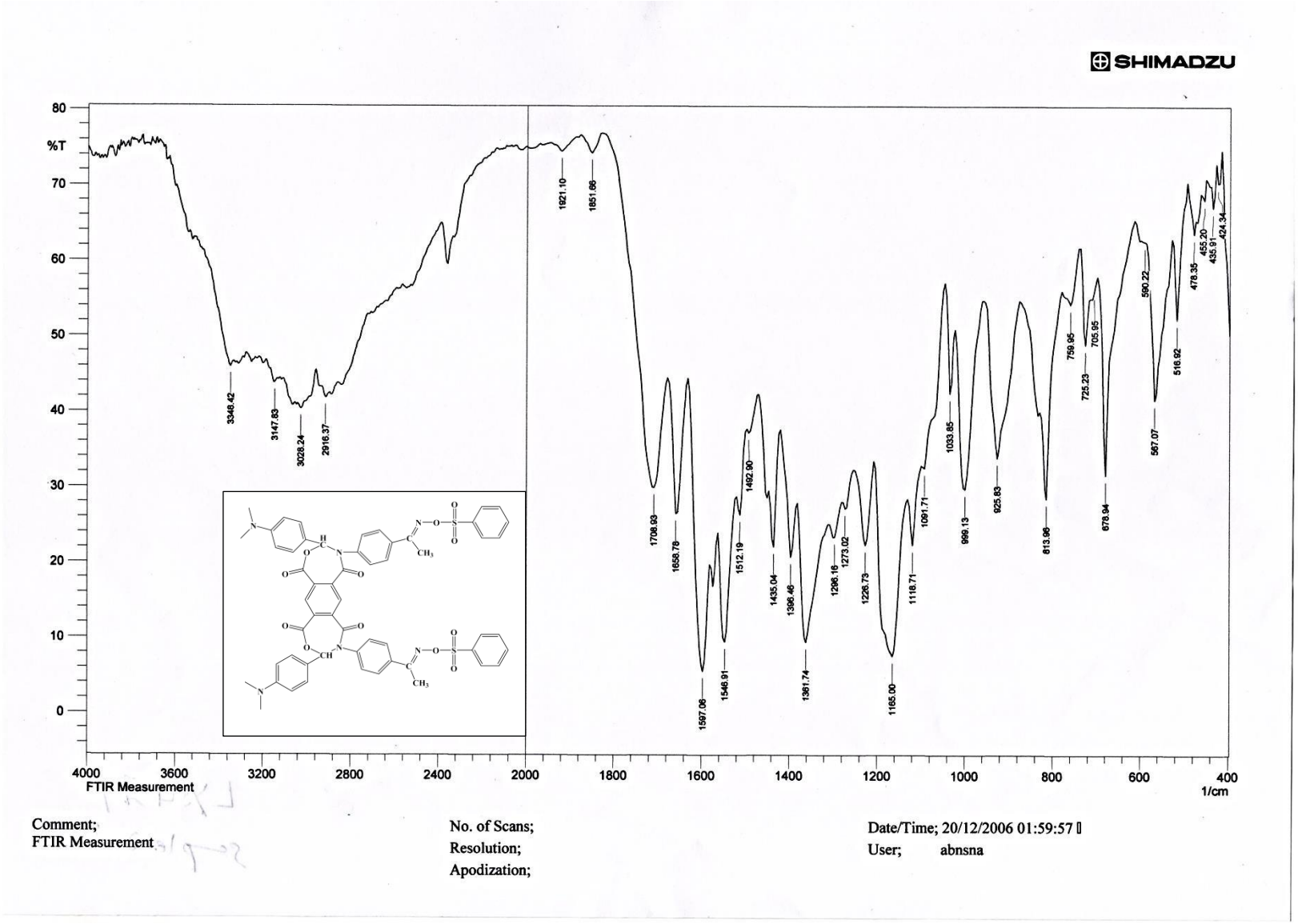


Fig. (3.22) FTIR spectrum of [A11]

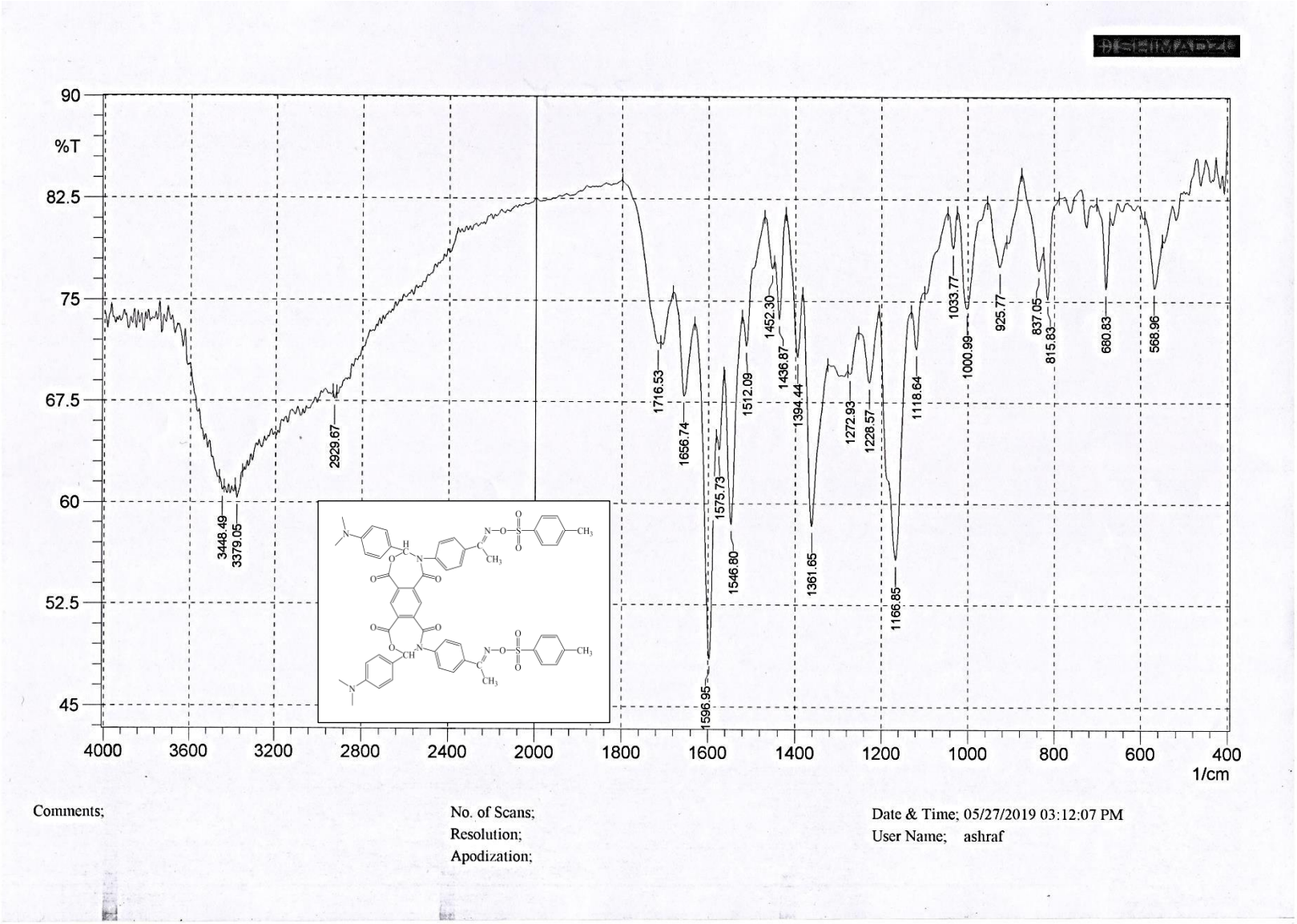


Fig. (3.23) FTIR spectrum of [A12]

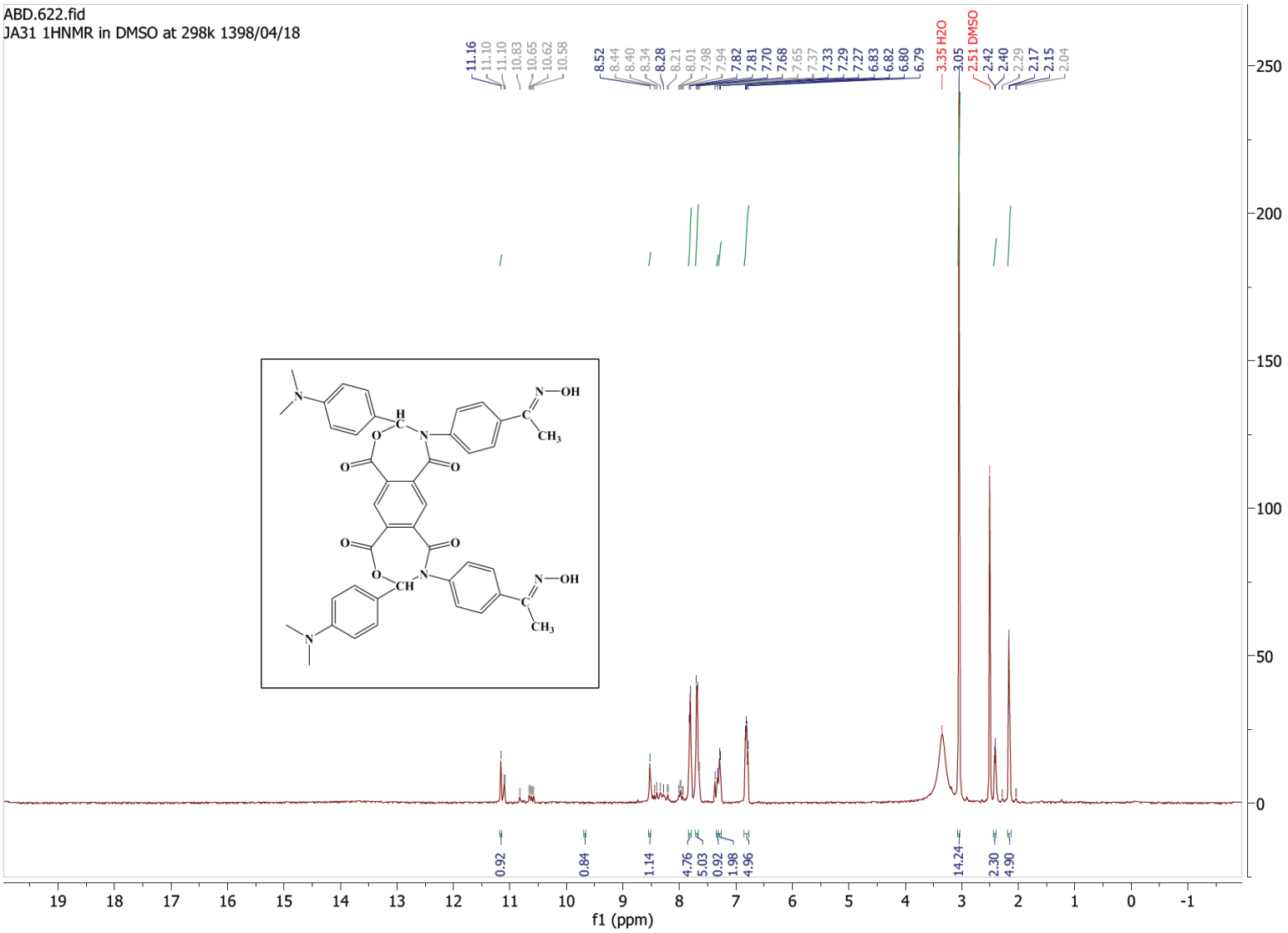


Fig. (3.24) [1]HNMR spectrum of [A10]

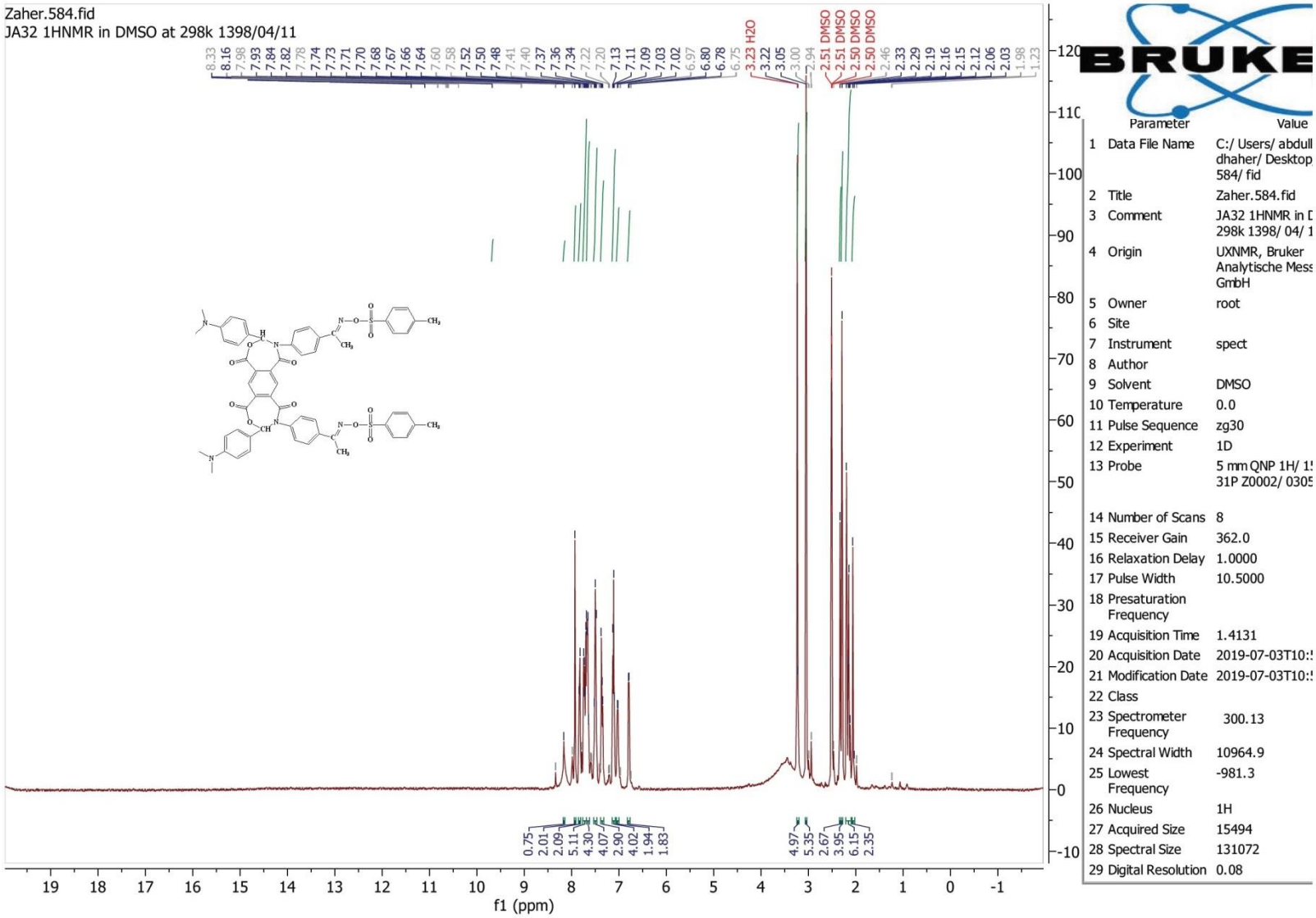


Fig. (3.25) ^{1}HNMR spectrum of [A12]

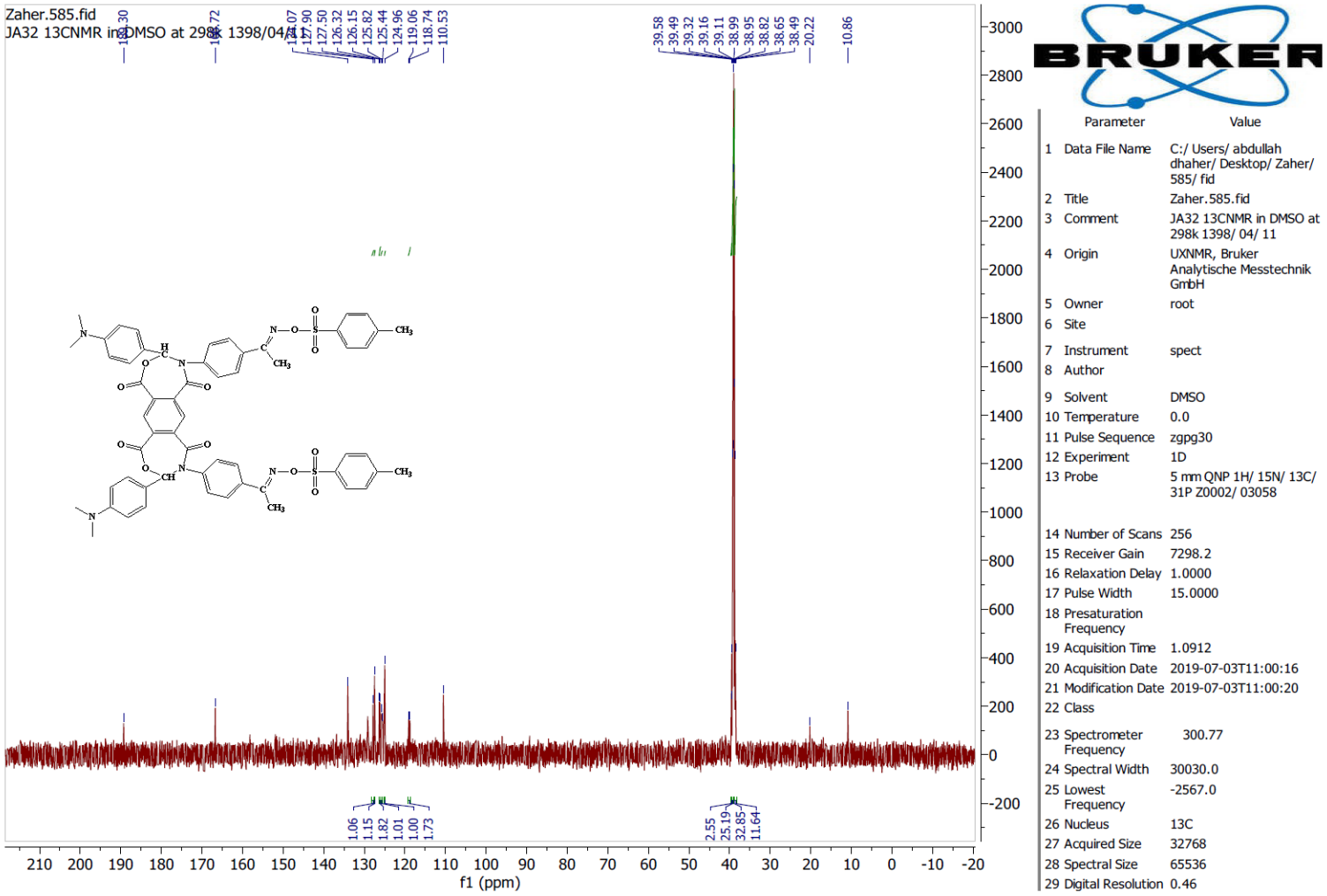


Fig. (3.26) ^{13}CNMR spectrum of [A12]

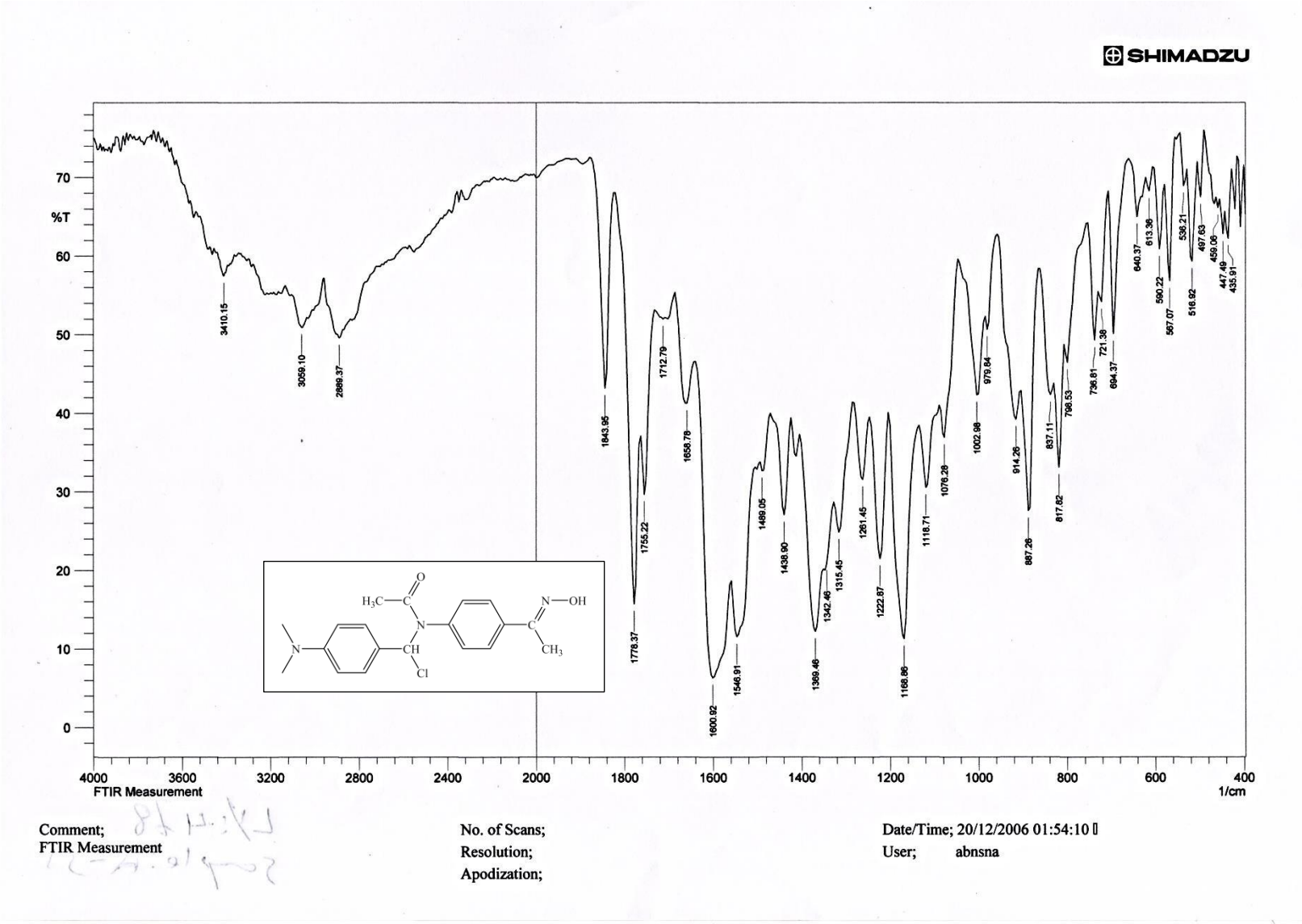


Fig. (3.27) FTIR spectrum of [A13]

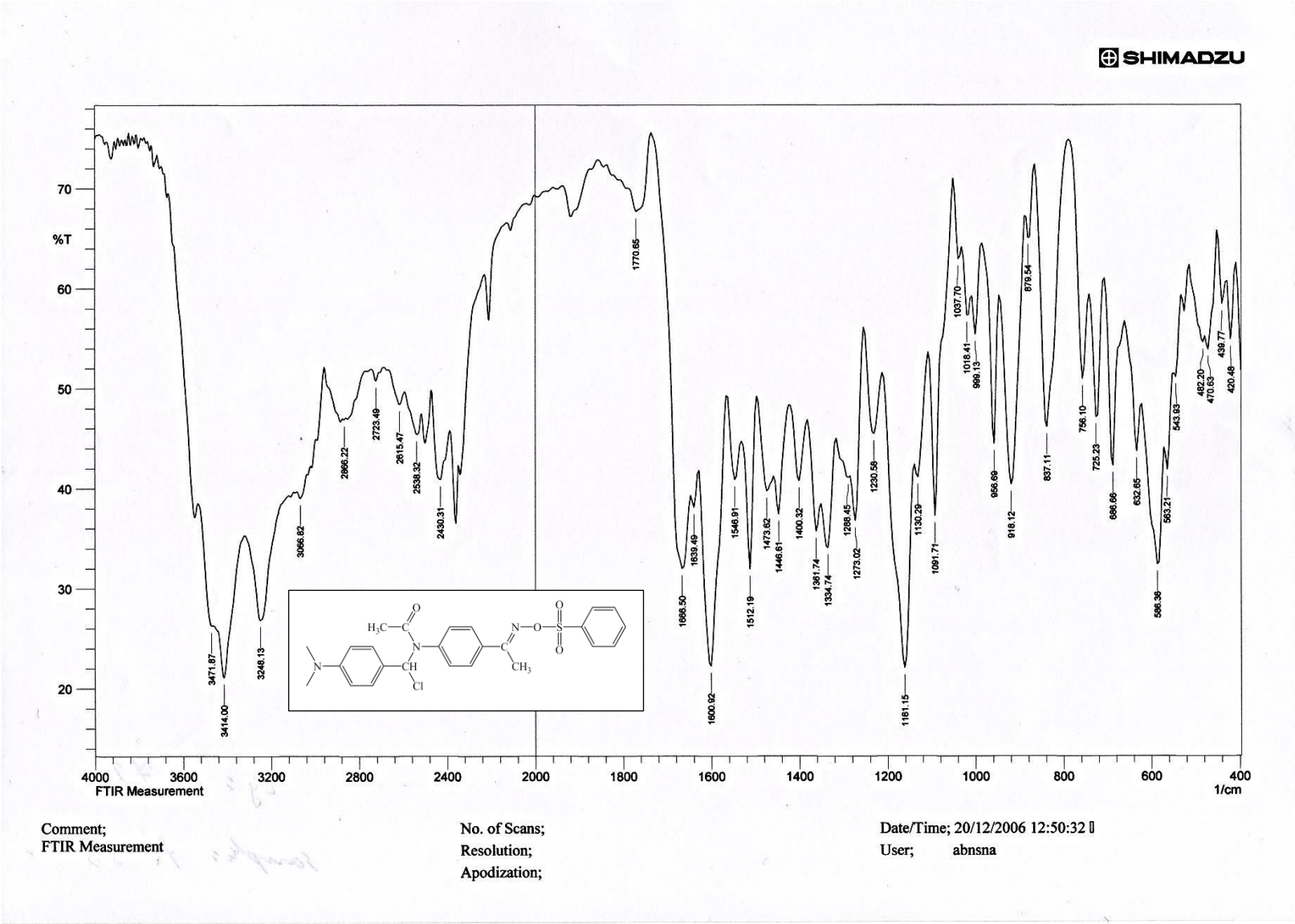


Fig.(3.28) FTIR spectrum of [A14]

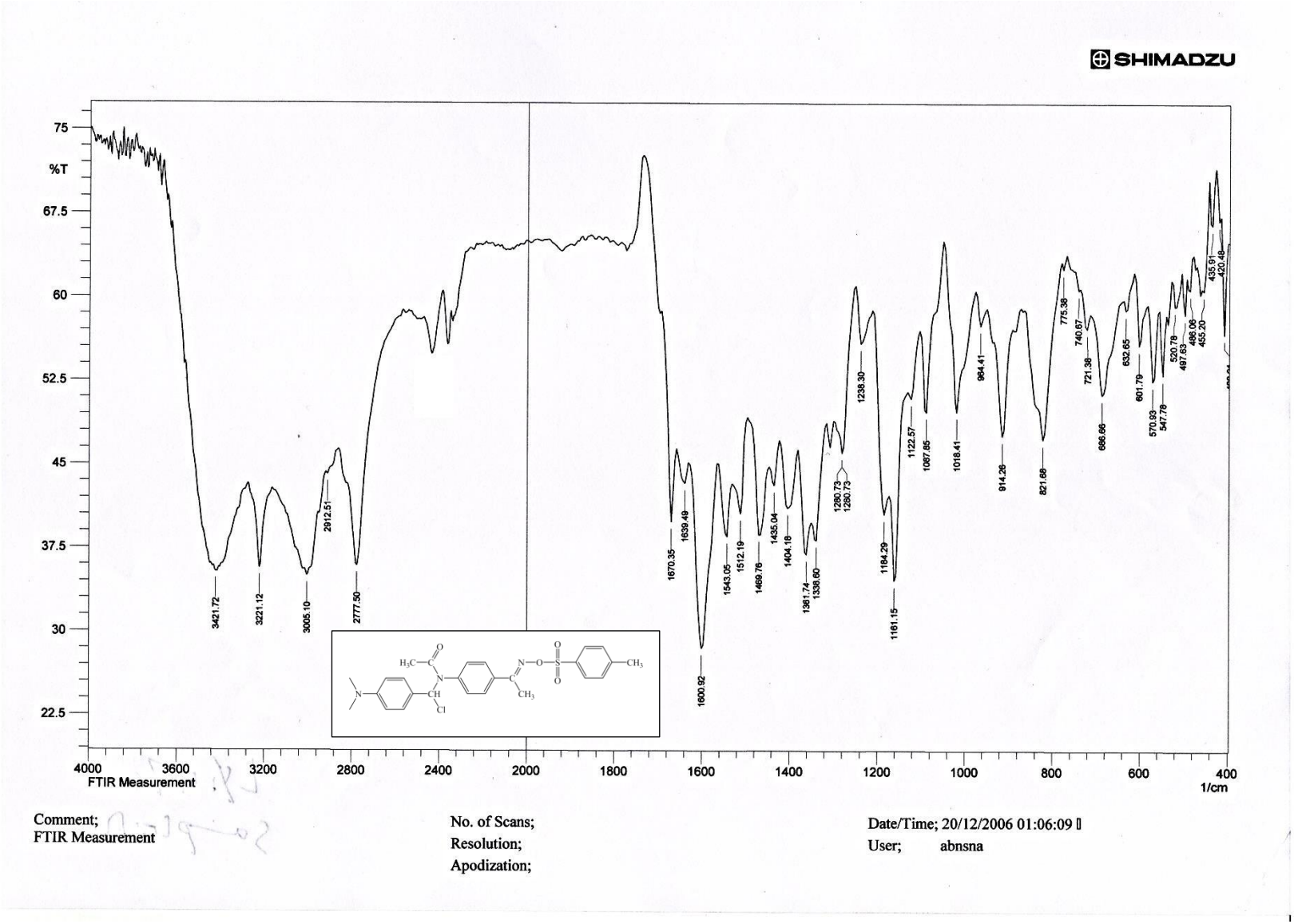


Fig. (3.29) FTIR spectrum of [A15]

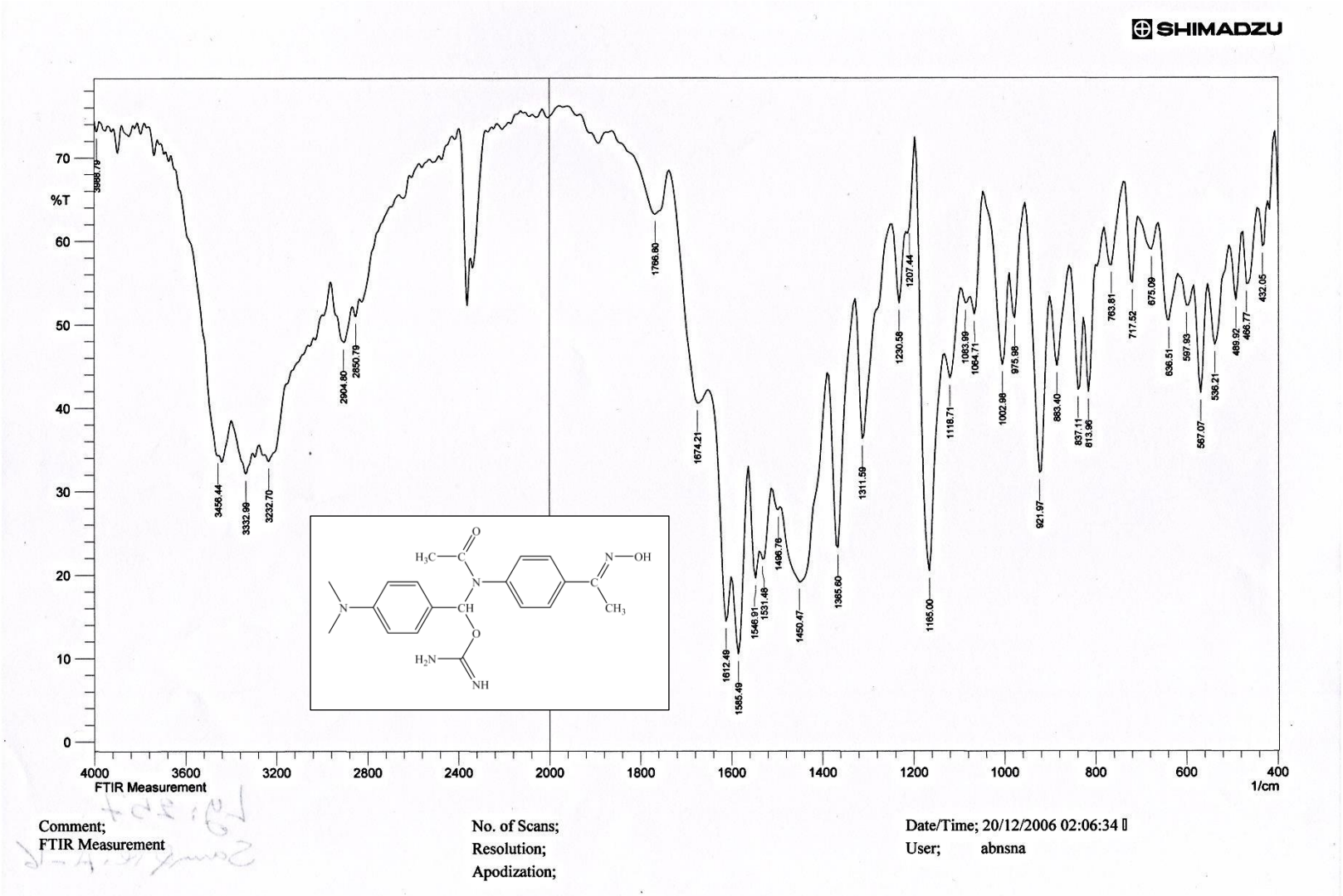


Fig. (3.30) FTIR spectrum of [A16]

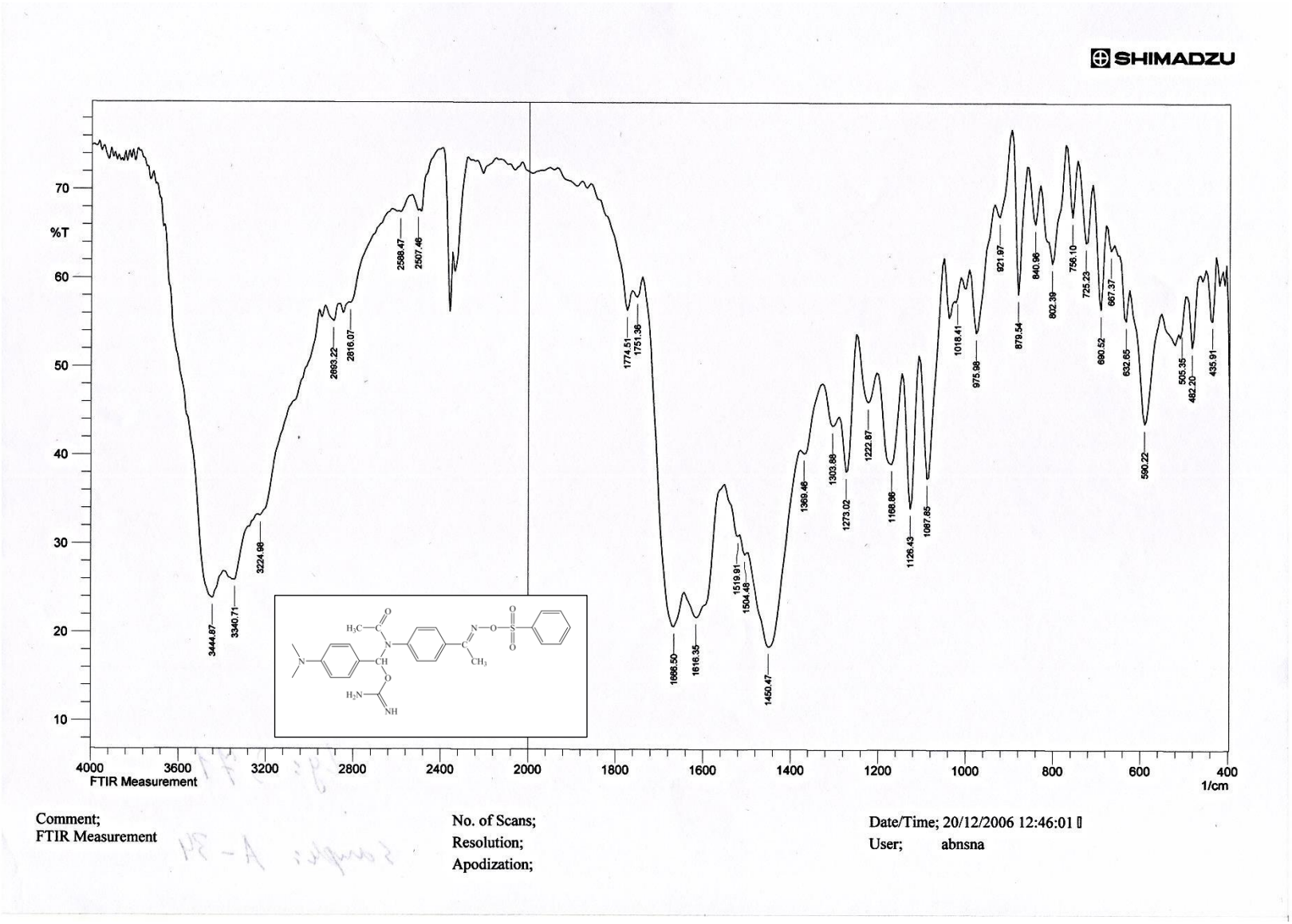


Fig. (3.31) FTIR spectrum of [A17]

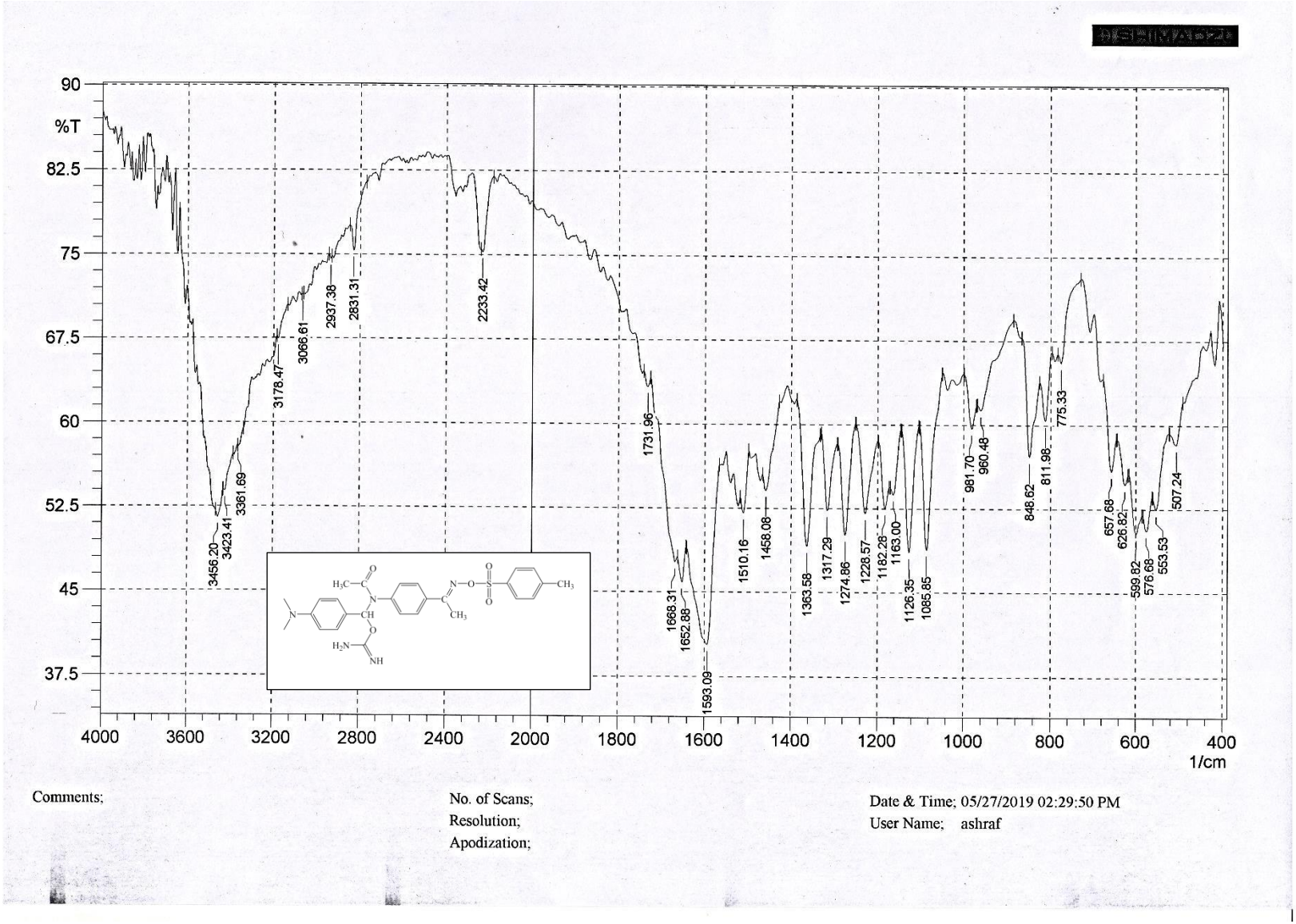


Fig. (3.32) FTIR spectrum of [A18]

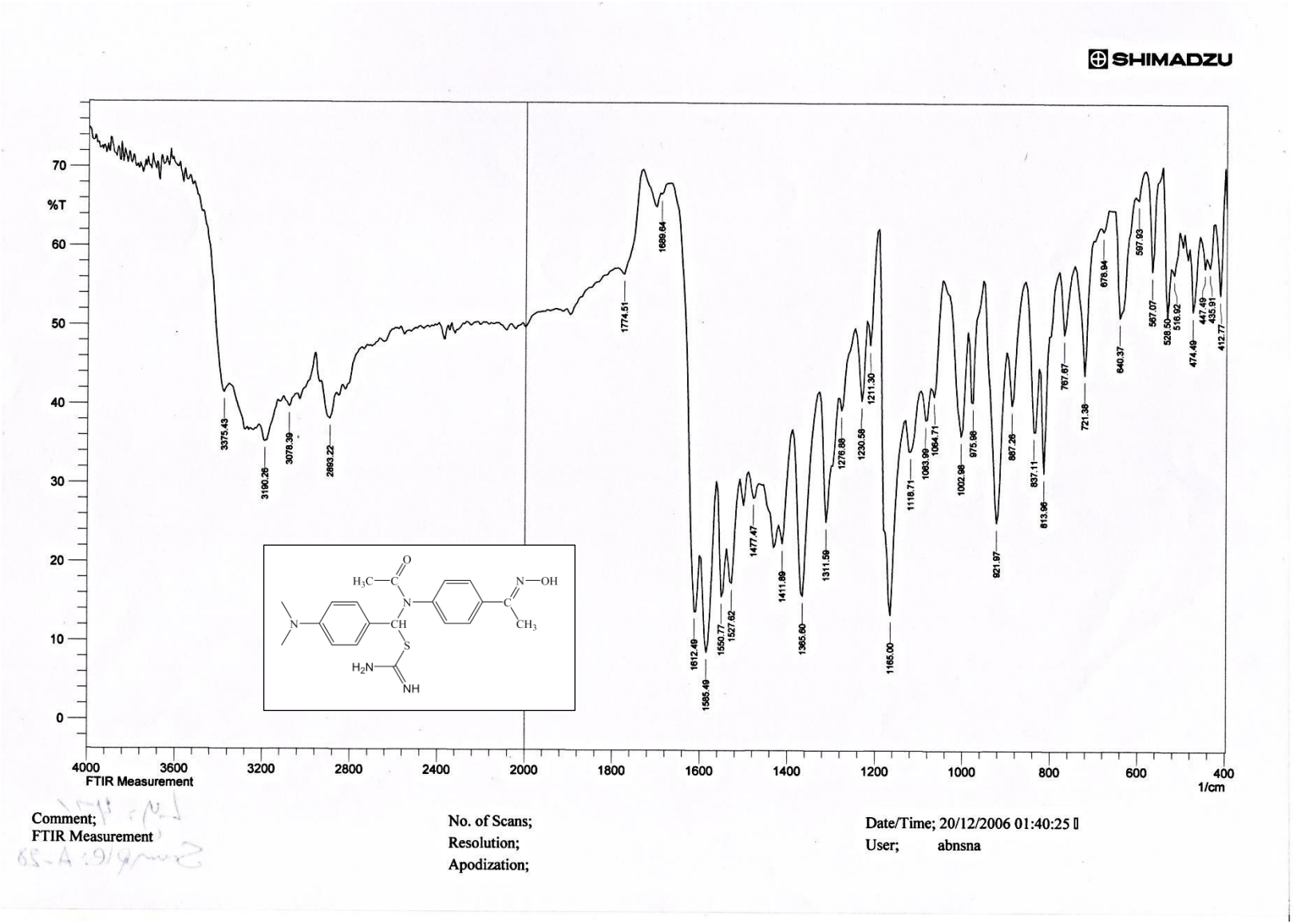


Fig. (3.33) FTIR spectrum of [A19]

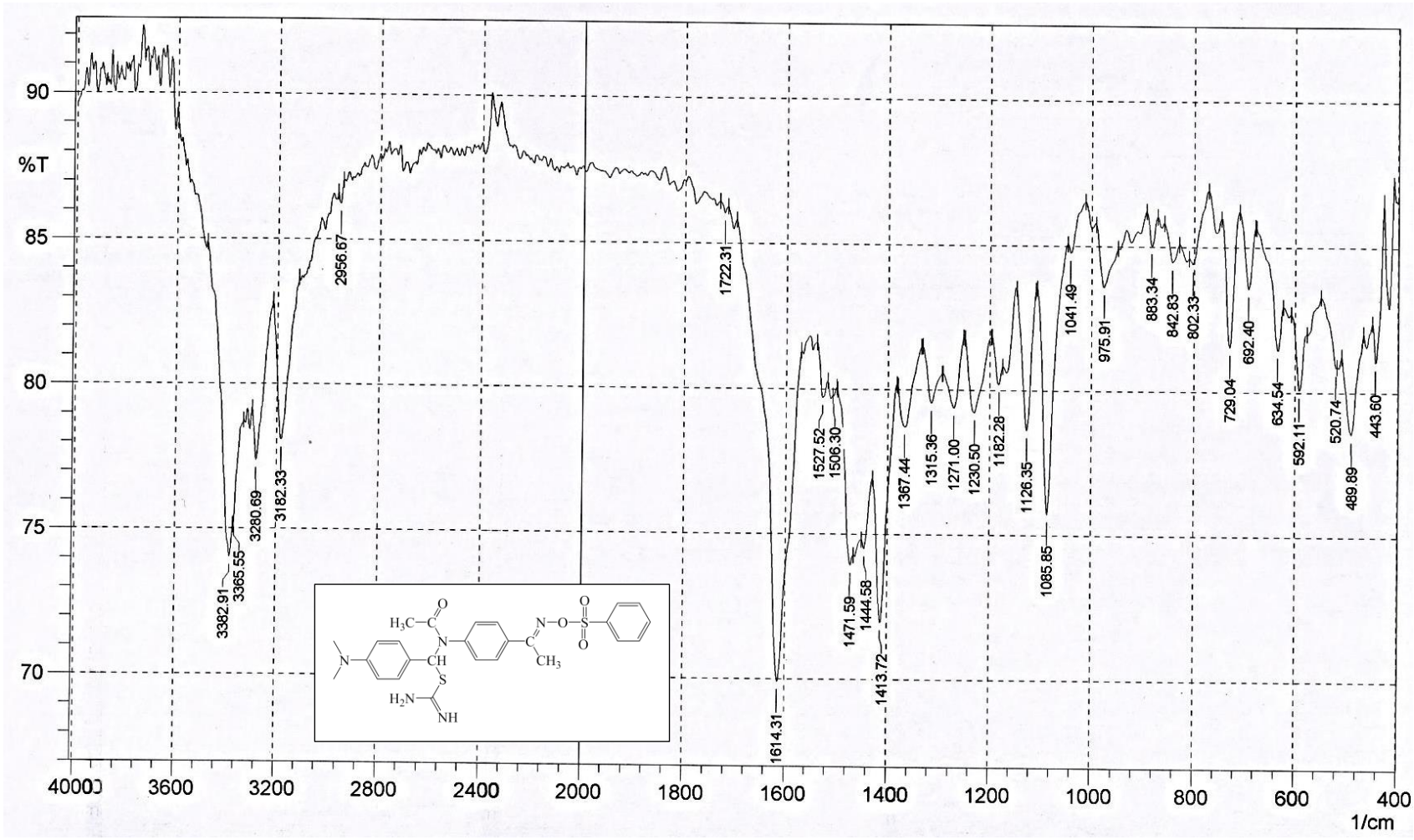


Fig. (3.34) FT-IR spectrum of [A20]

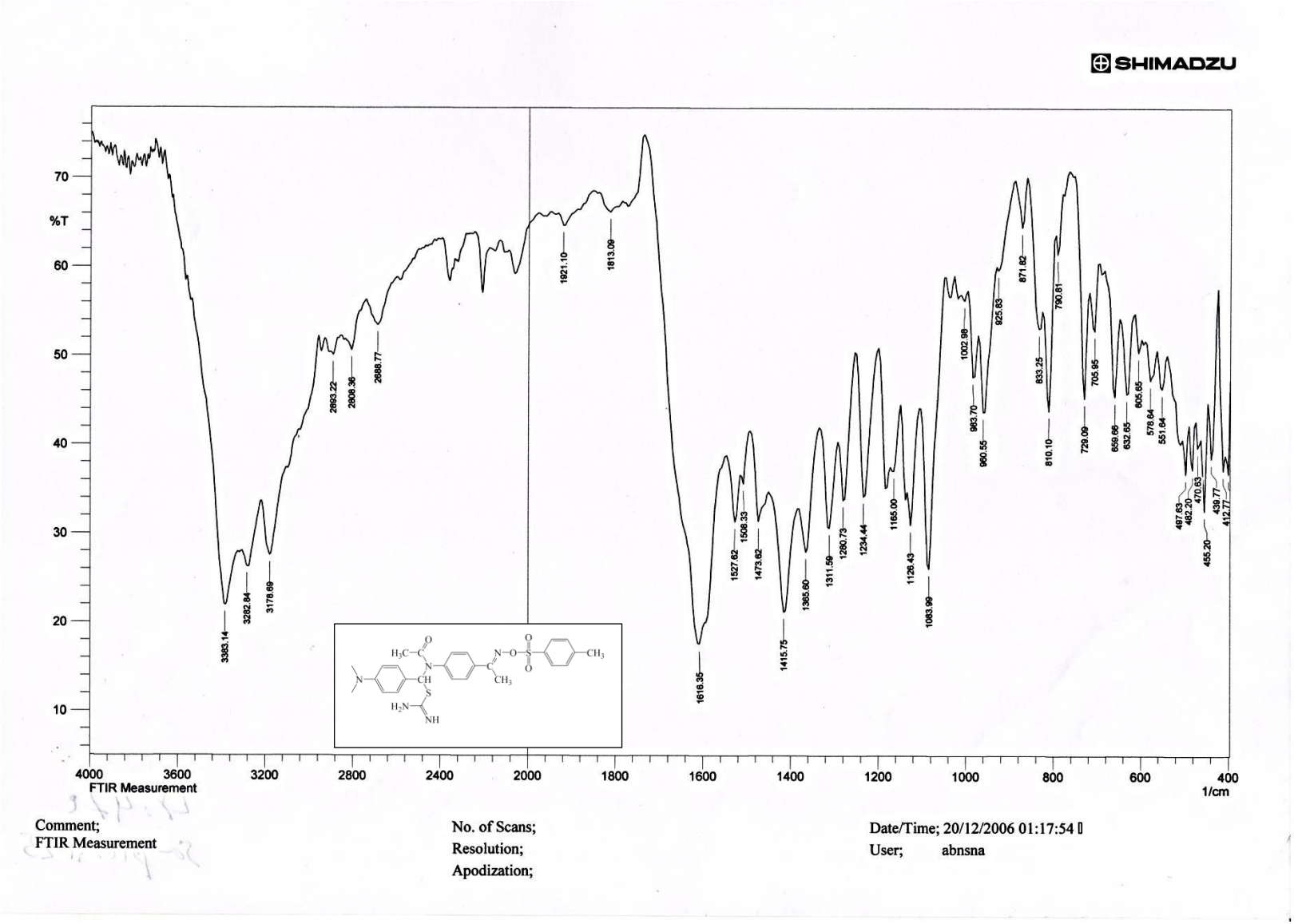


Fig. (3.35) FTIR spectrum of [A21]

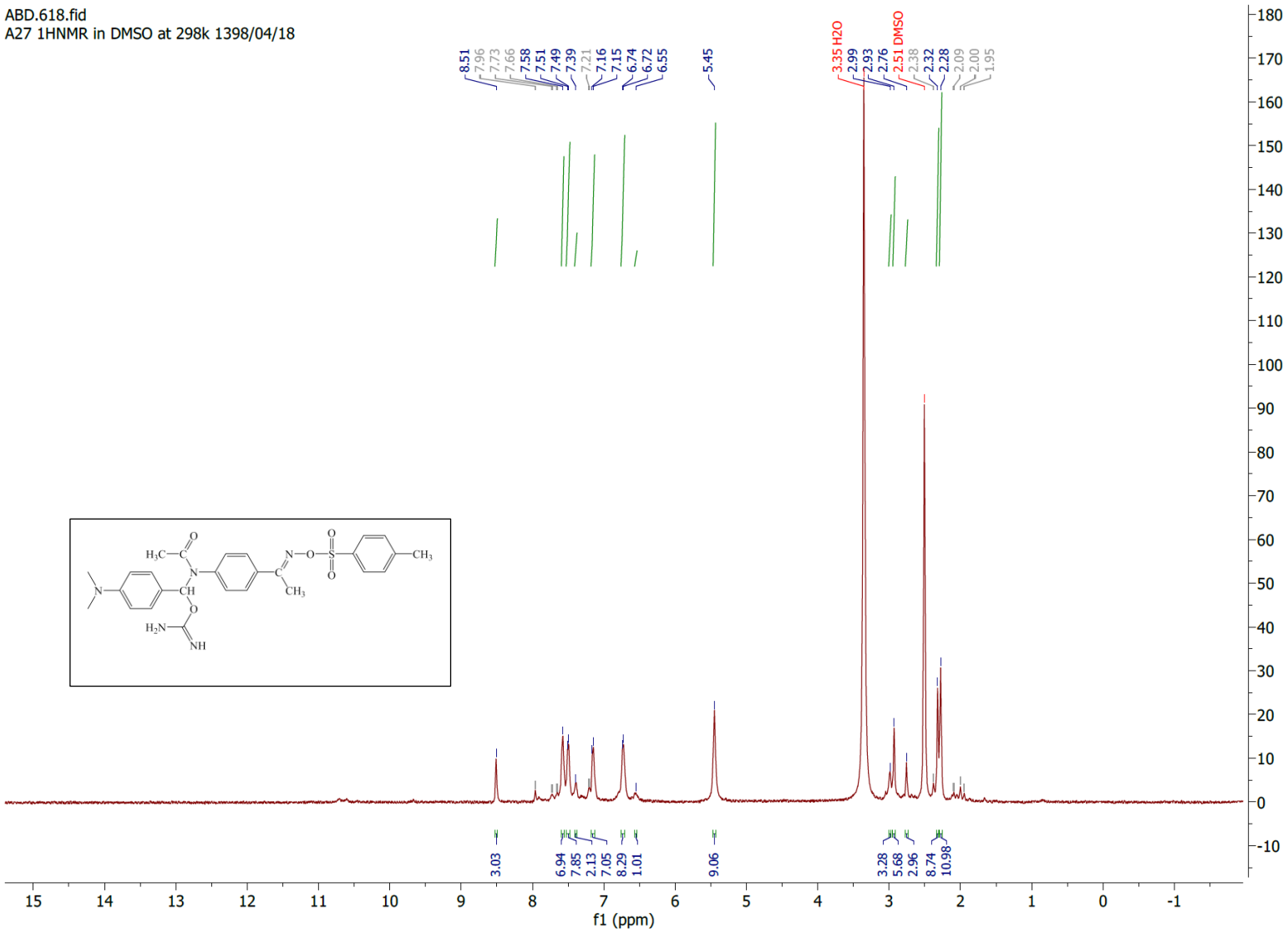


Fig. (3.36) [1]HNMR spectrum of [A18]

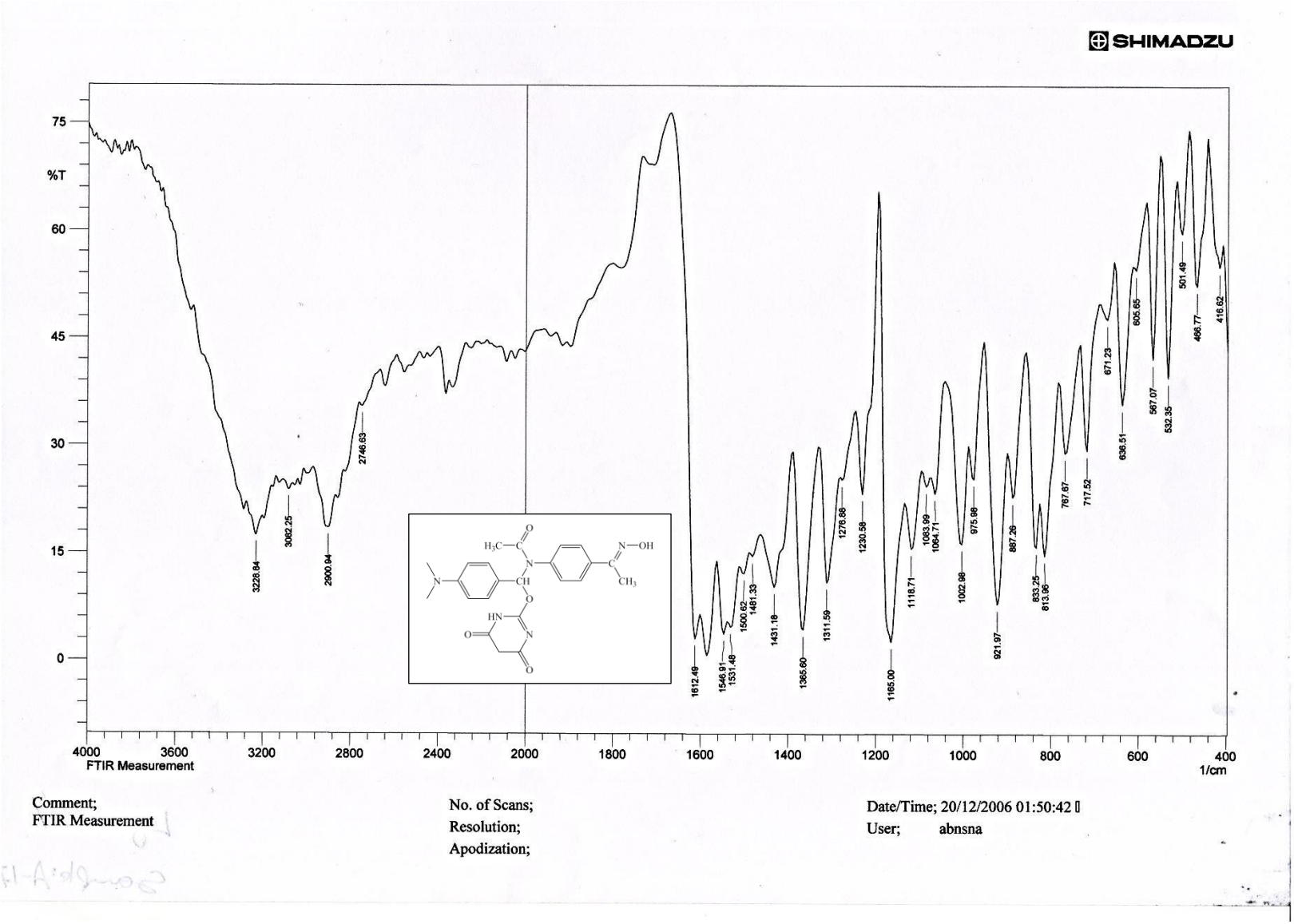


Fig. (3.37) FTIR spectrum of [A22]

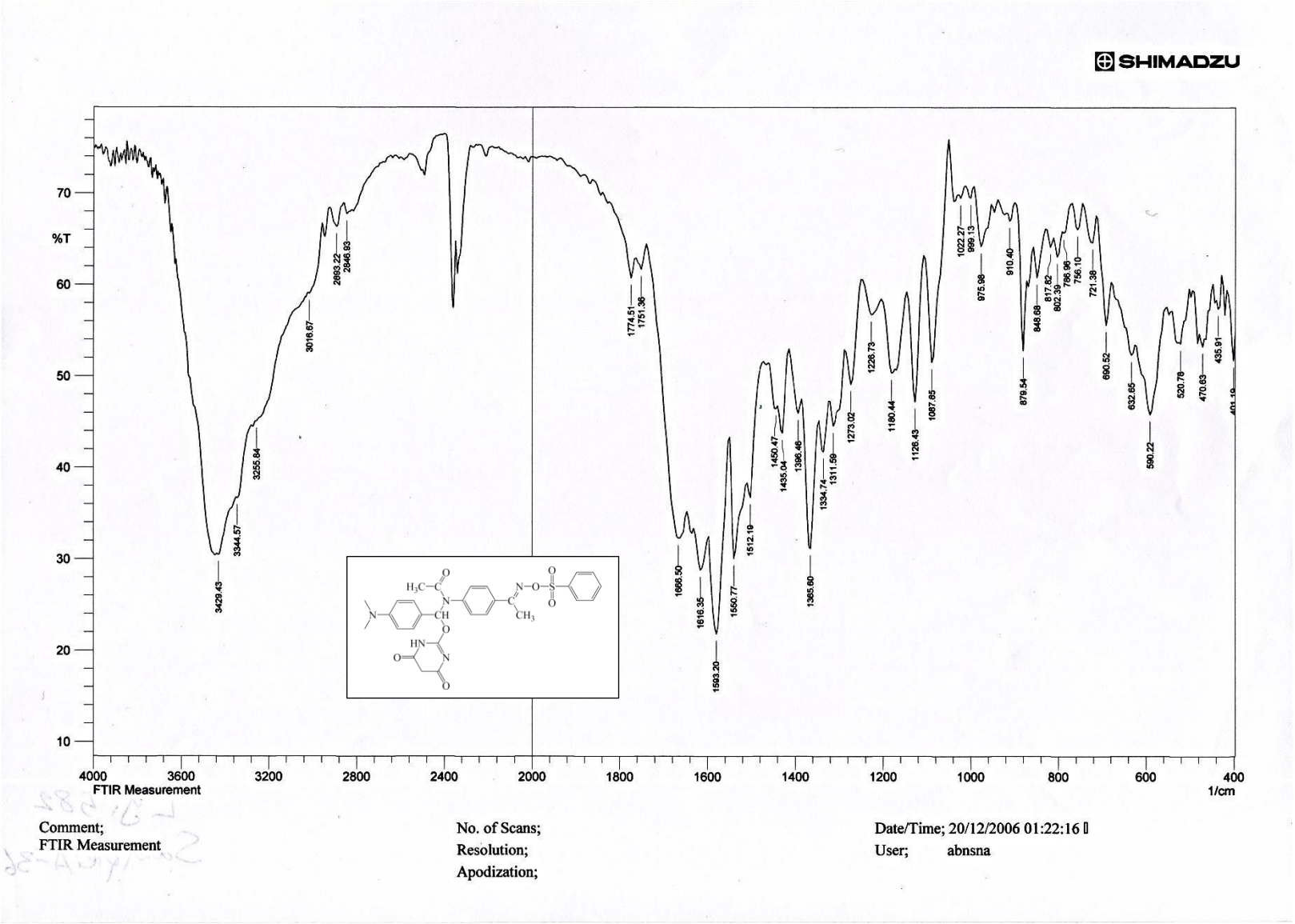


Fig. (3.38) FTIR spectrum of [A23]

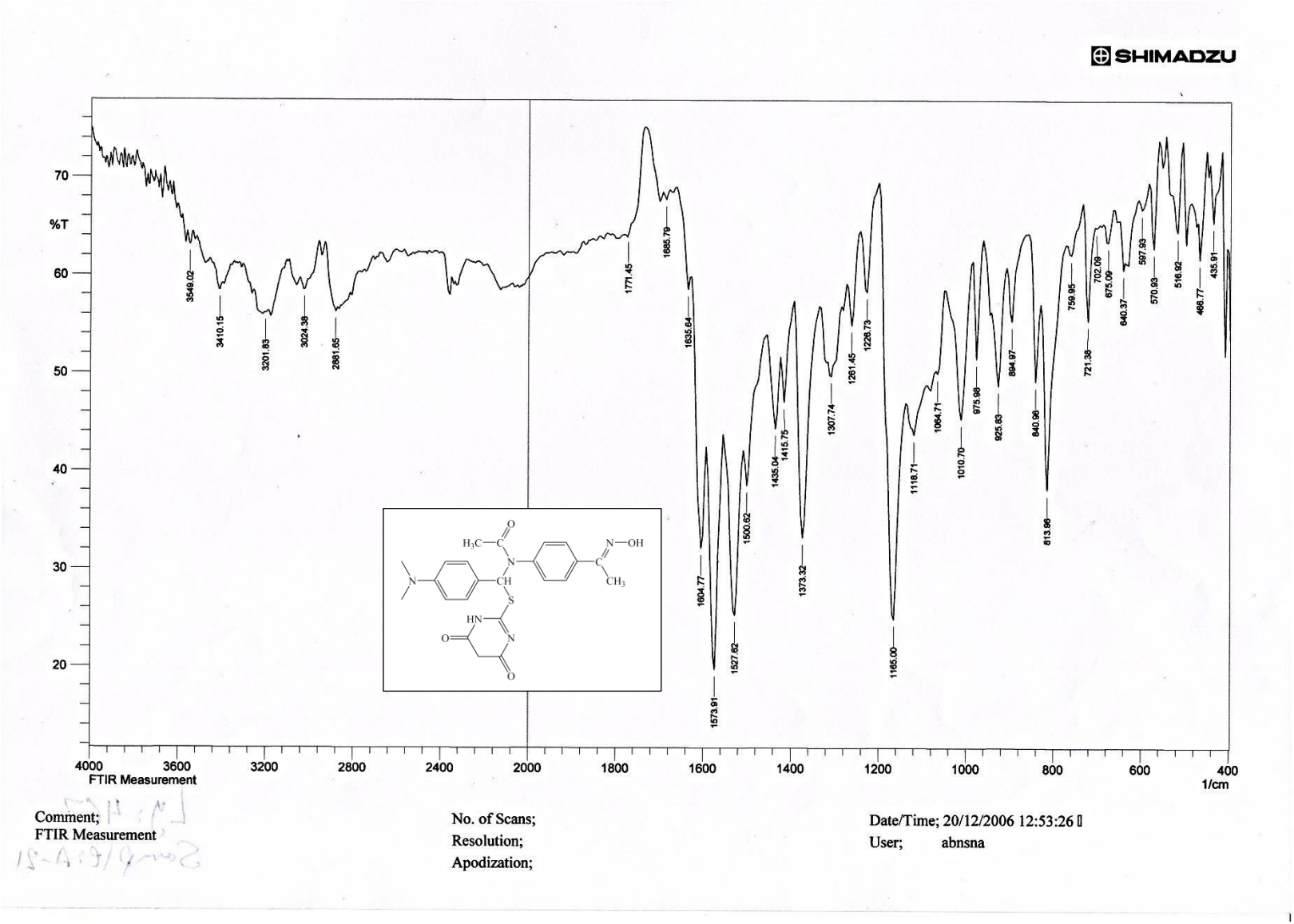


Fig. (3.39) FTIR spectrum of [A25]

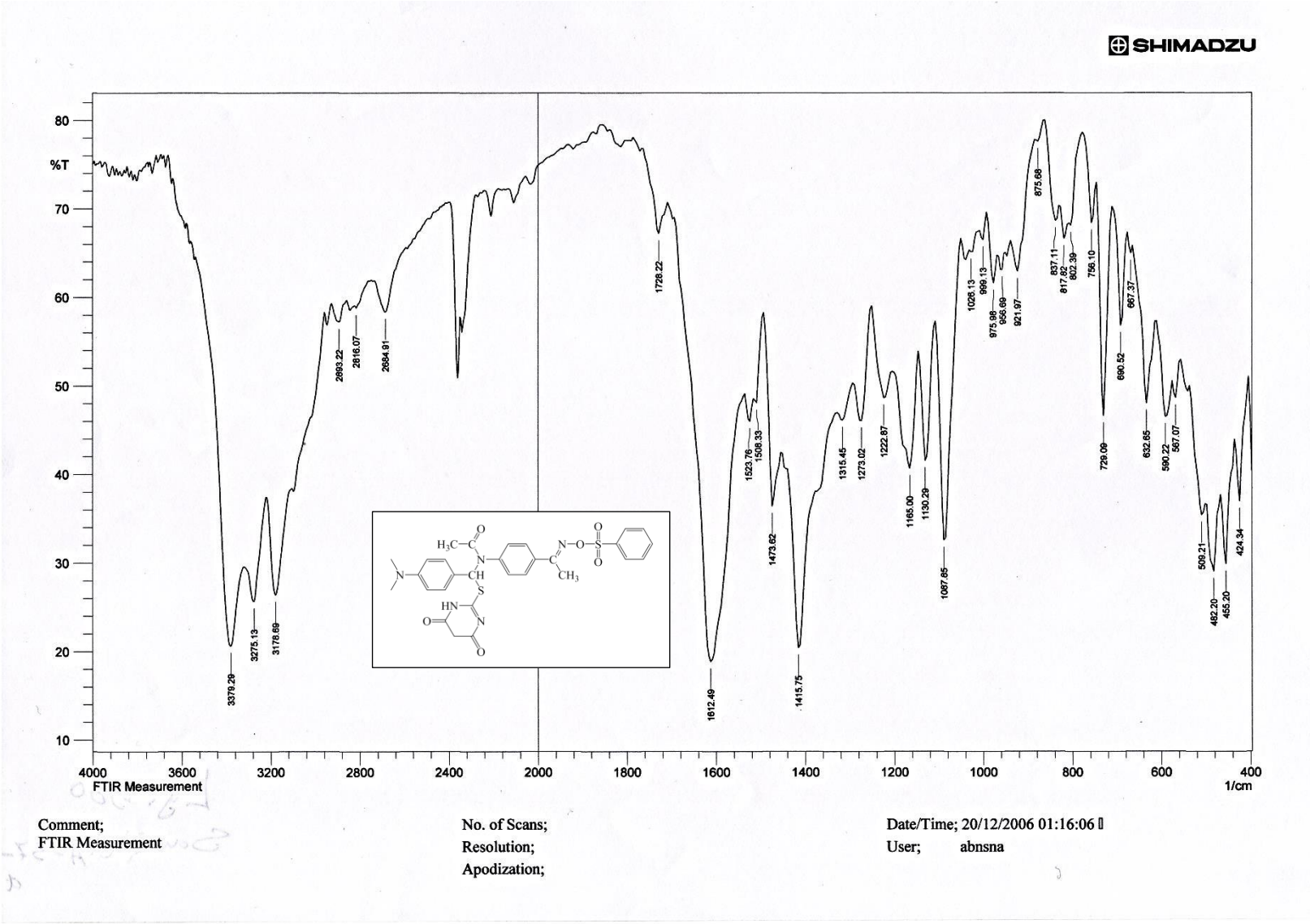


Fig. (3.40) FTIR spectrum of [A26]

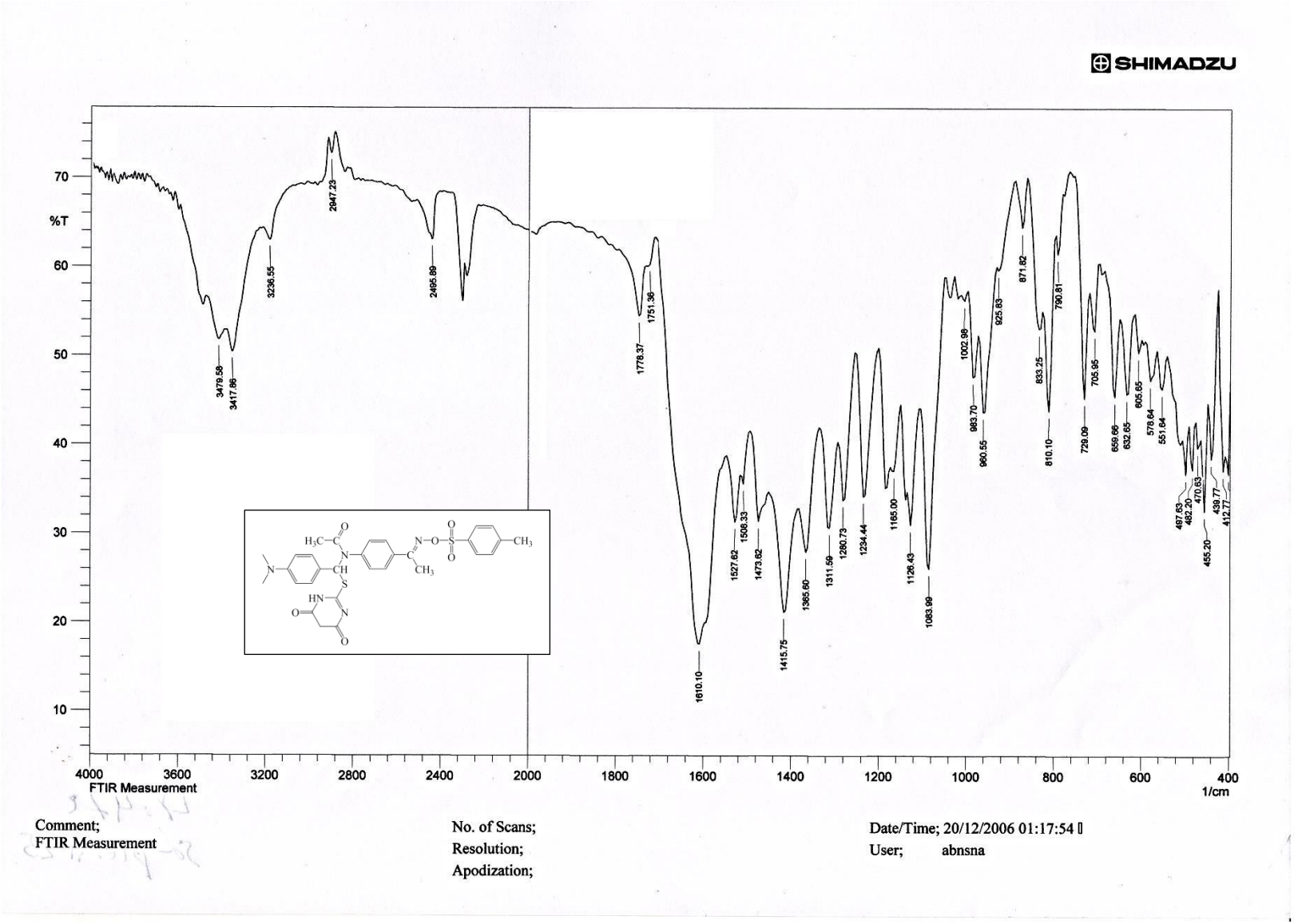


Fig. (3.41) FTIR spectrum of [A27]

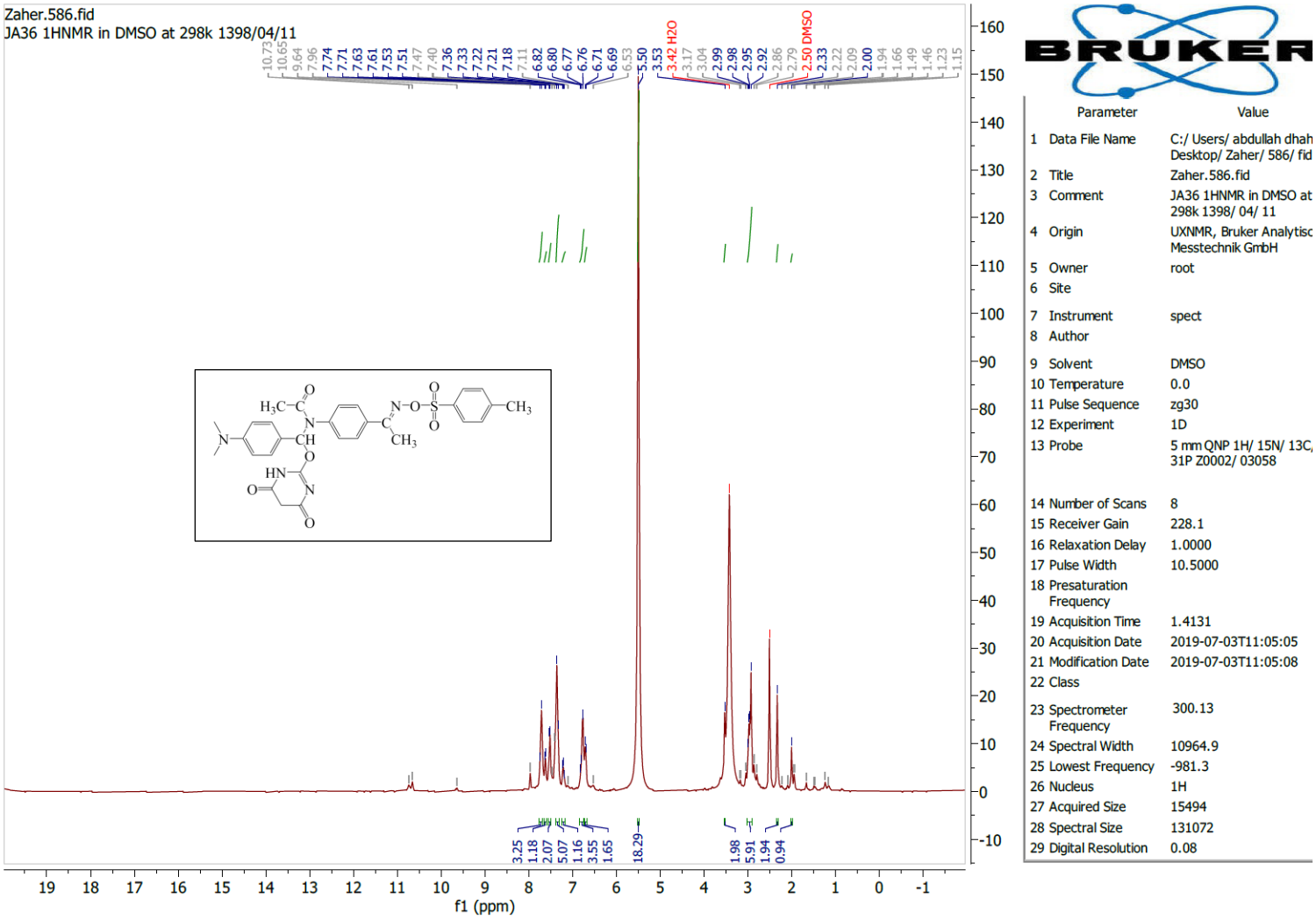


Fig. (3.42) ^{1}HNMR spectrum of [A24]

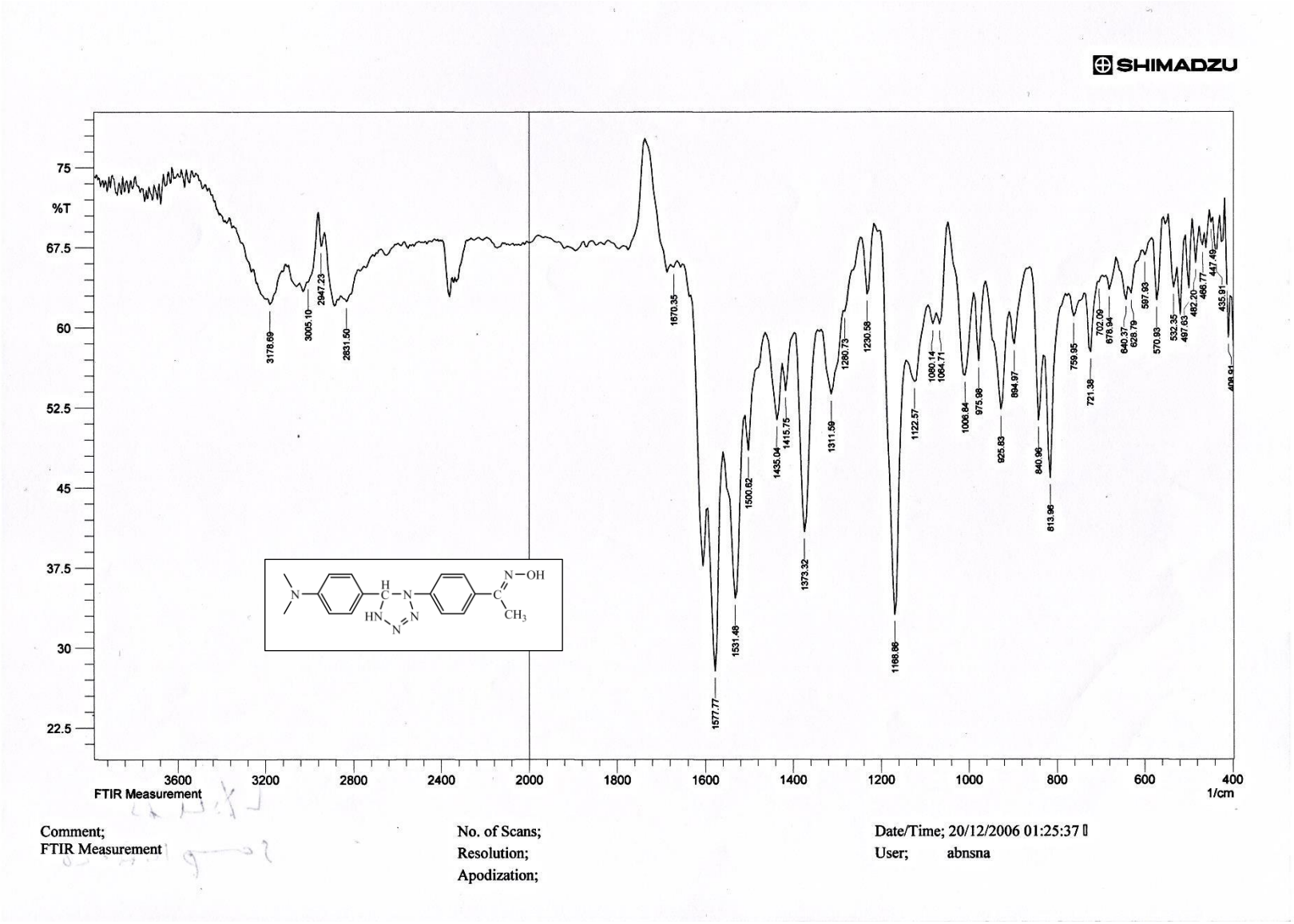


Fig. (3.43) FTIR spectrum of [A28]

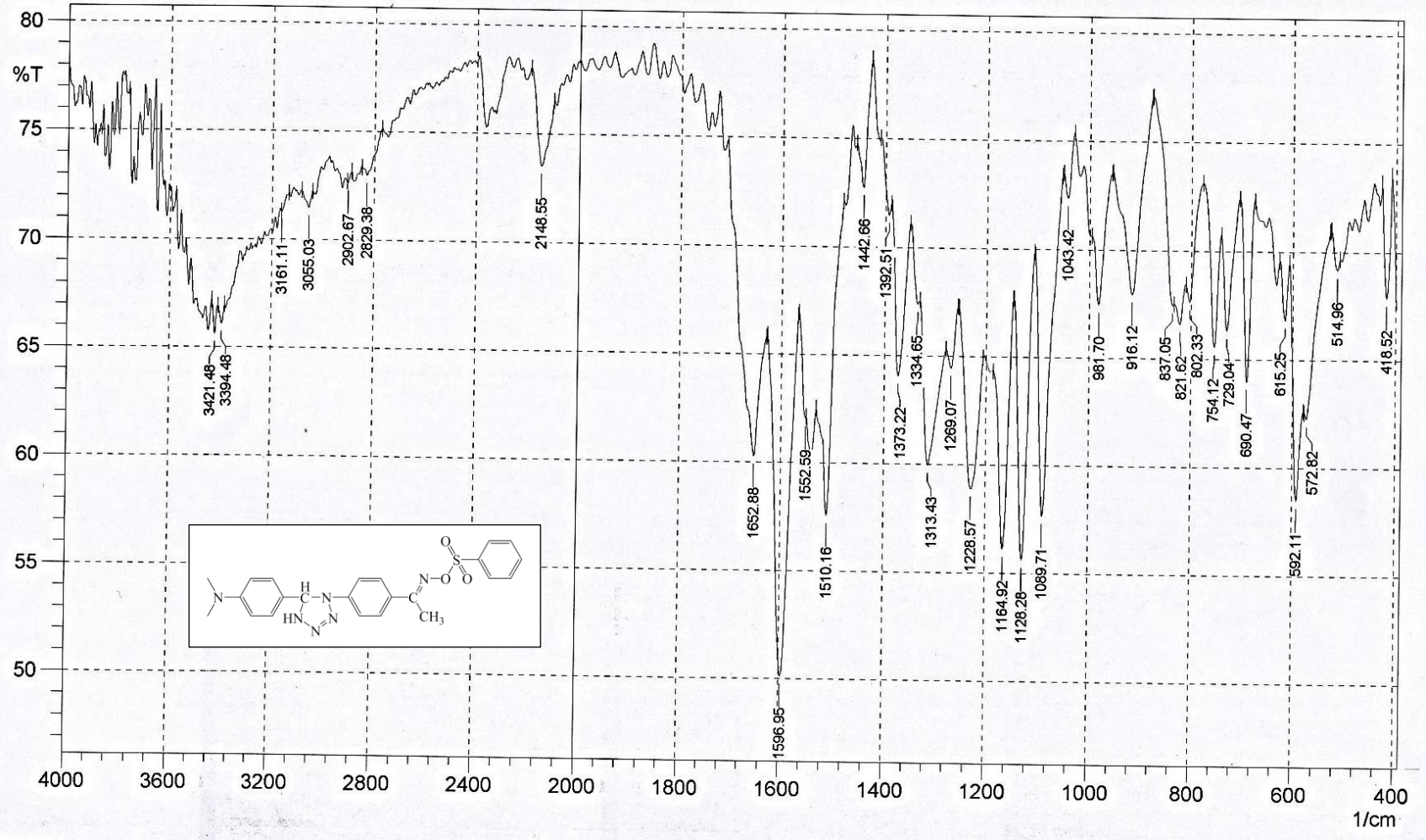


Fig. (3.44) FTIR spectrum of [A29]

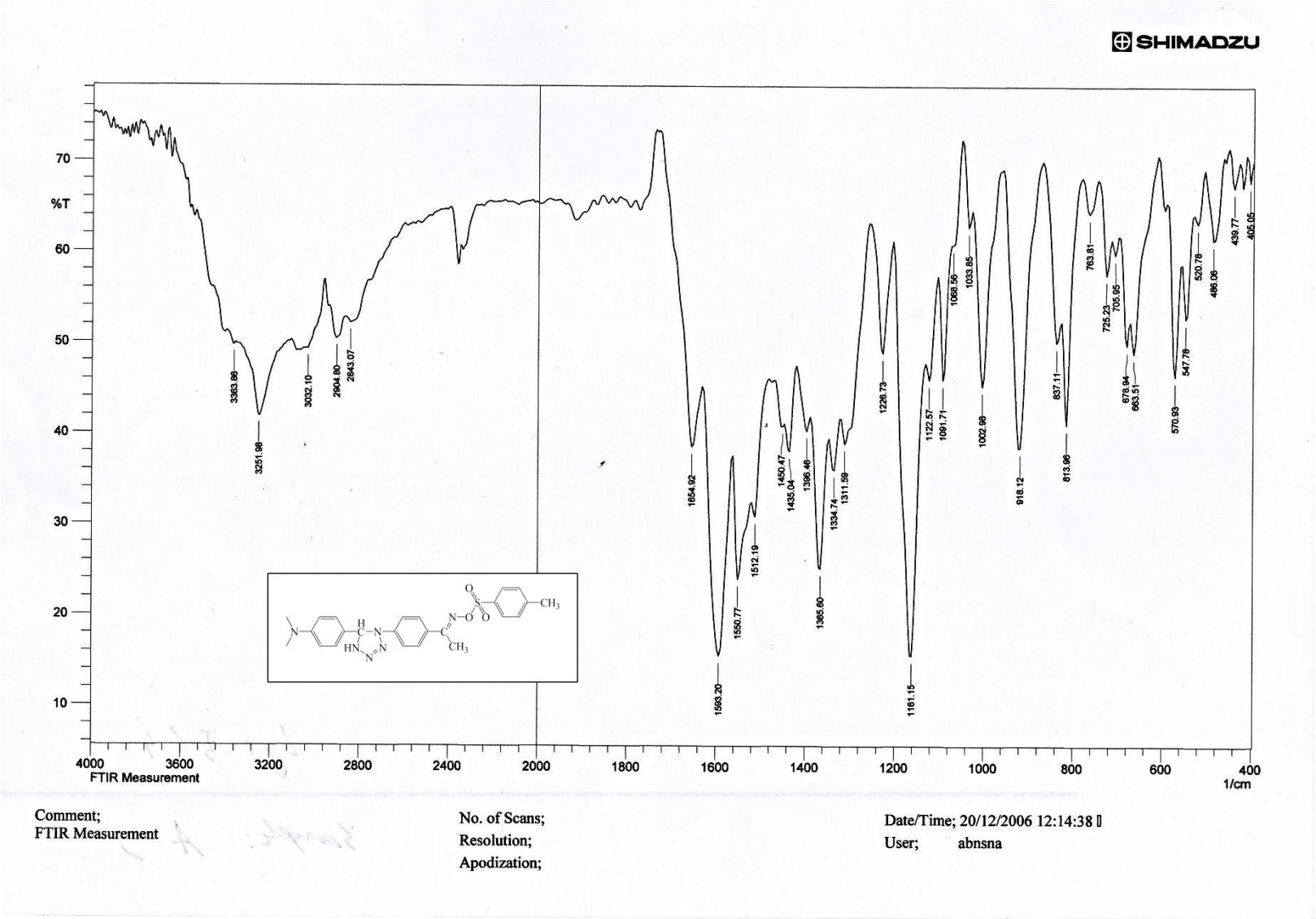


Fig. (3.45) FTIR spectrum of [A30]

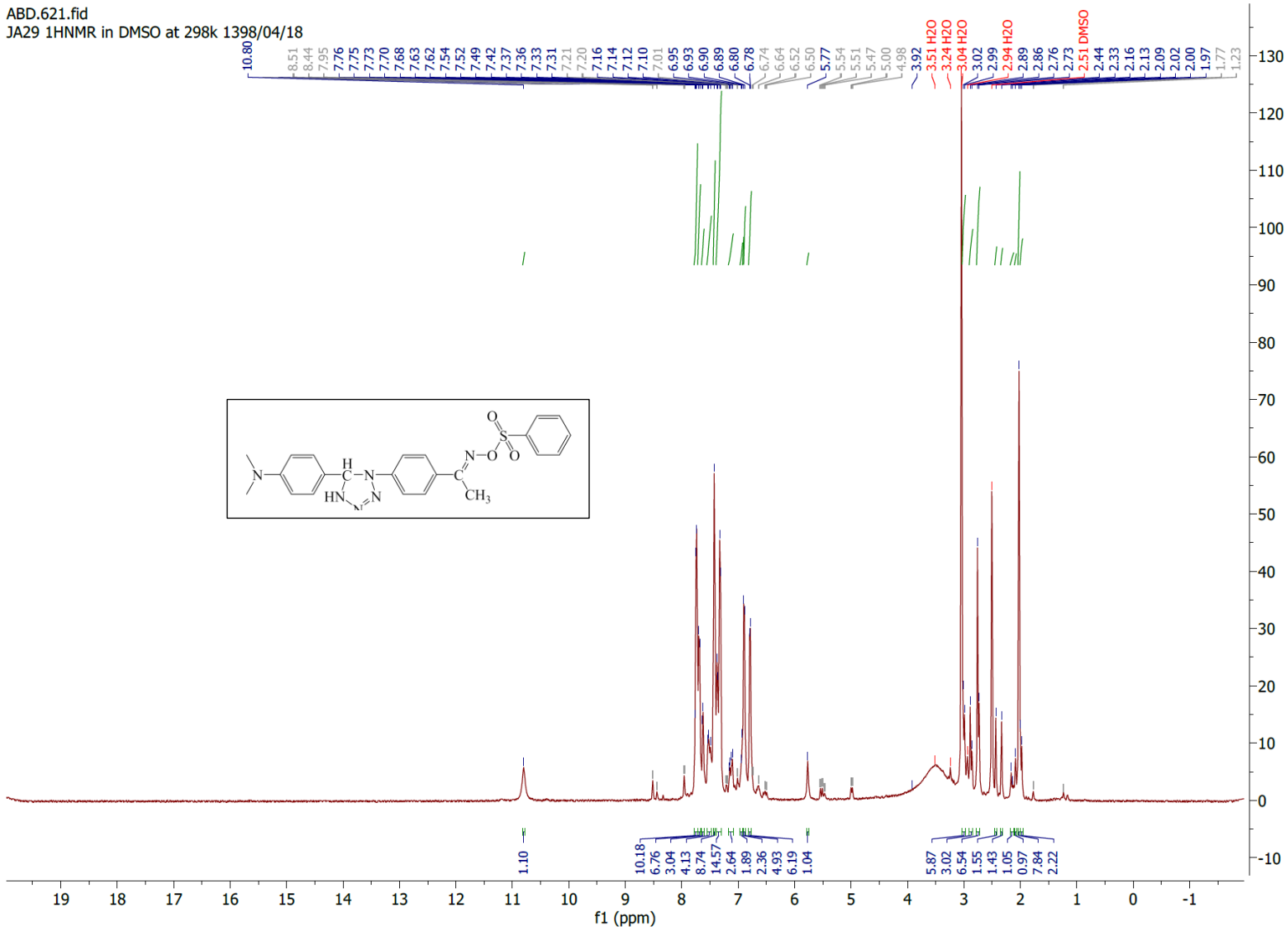


Fig. (3.46) [1]HNMR spectrum of compound [A29]

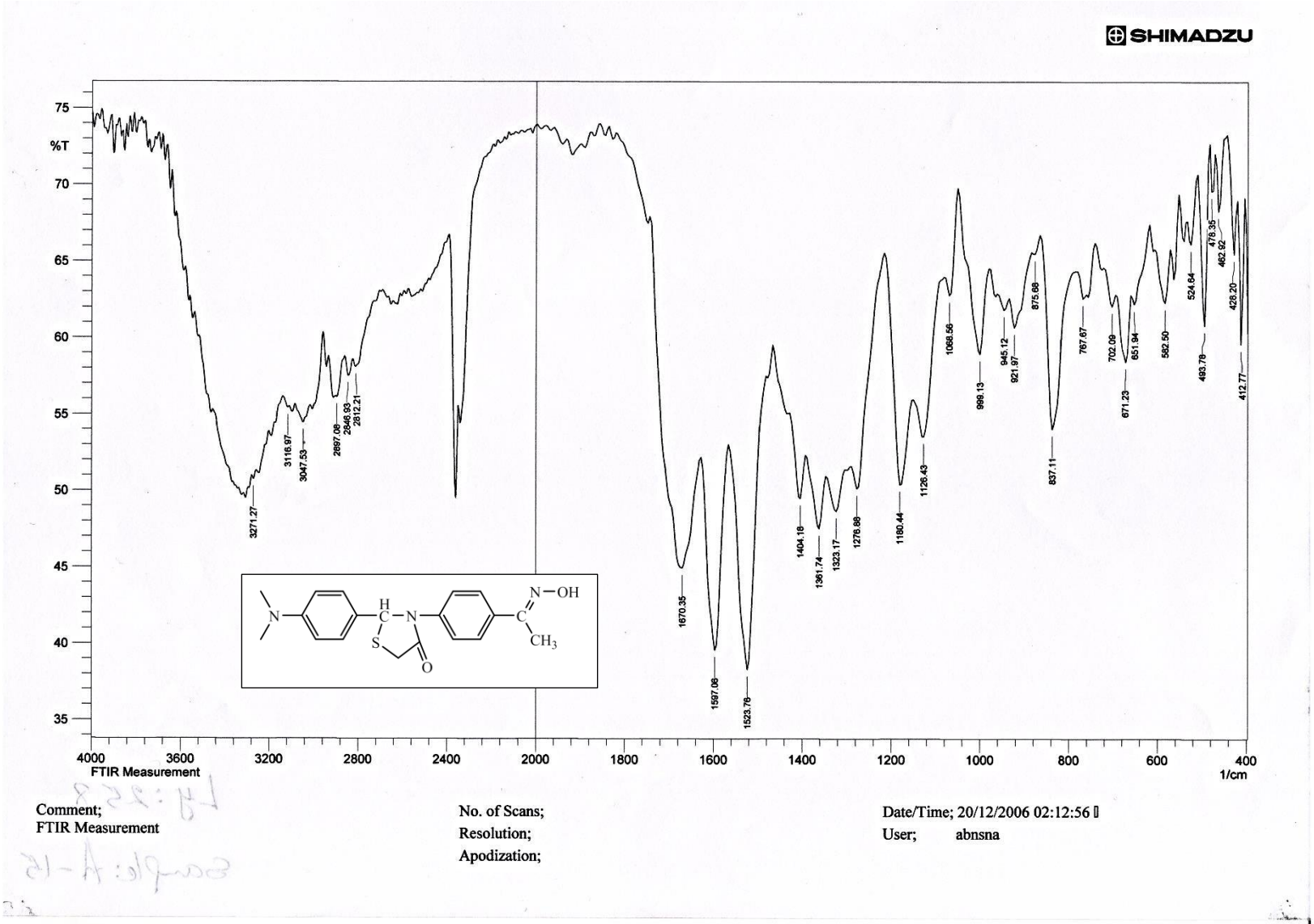


Fig. (3.47) FTIR spectrum of [A31]

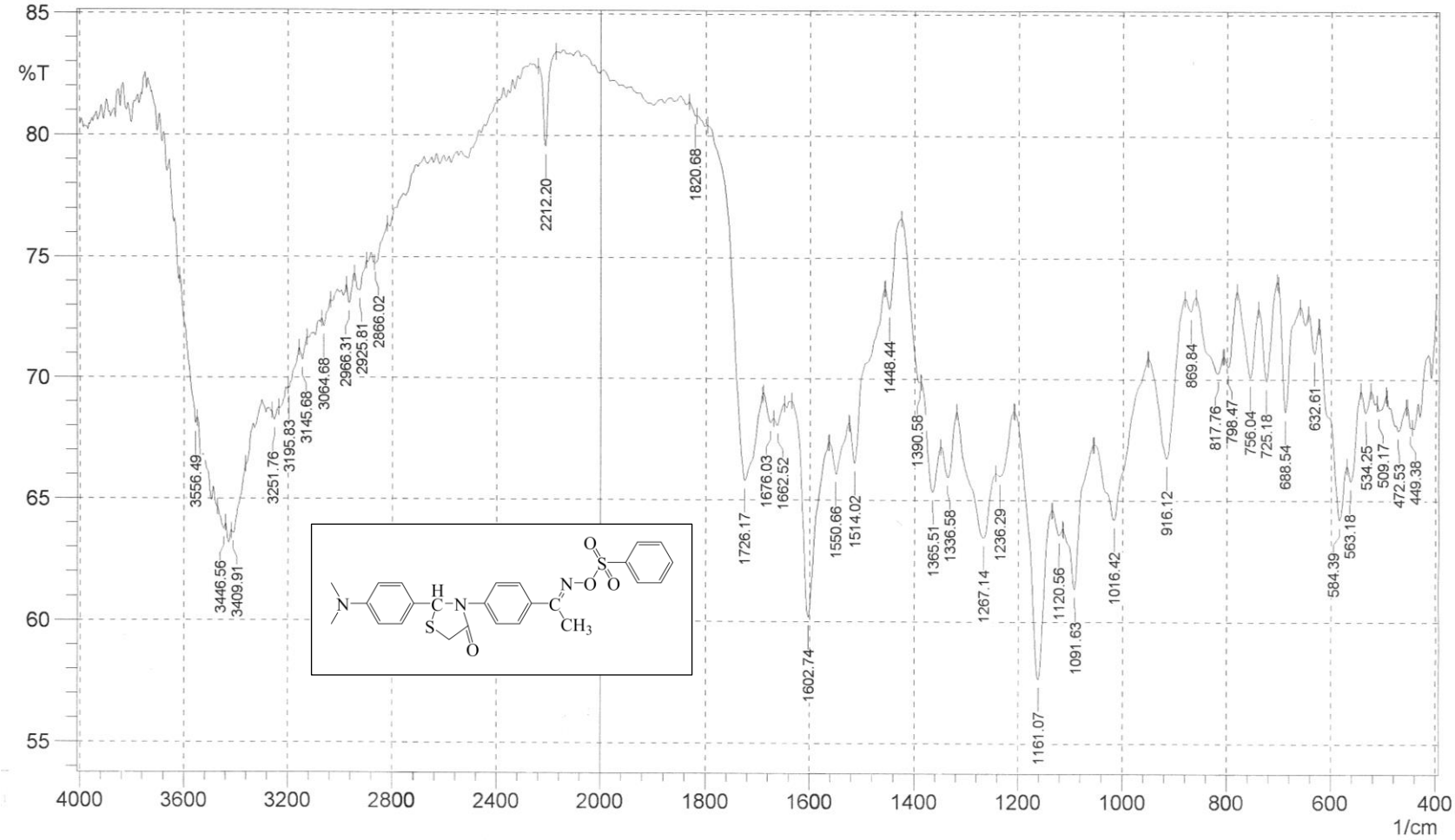


Fig. (3.48) FTIR spectrum of [A32]

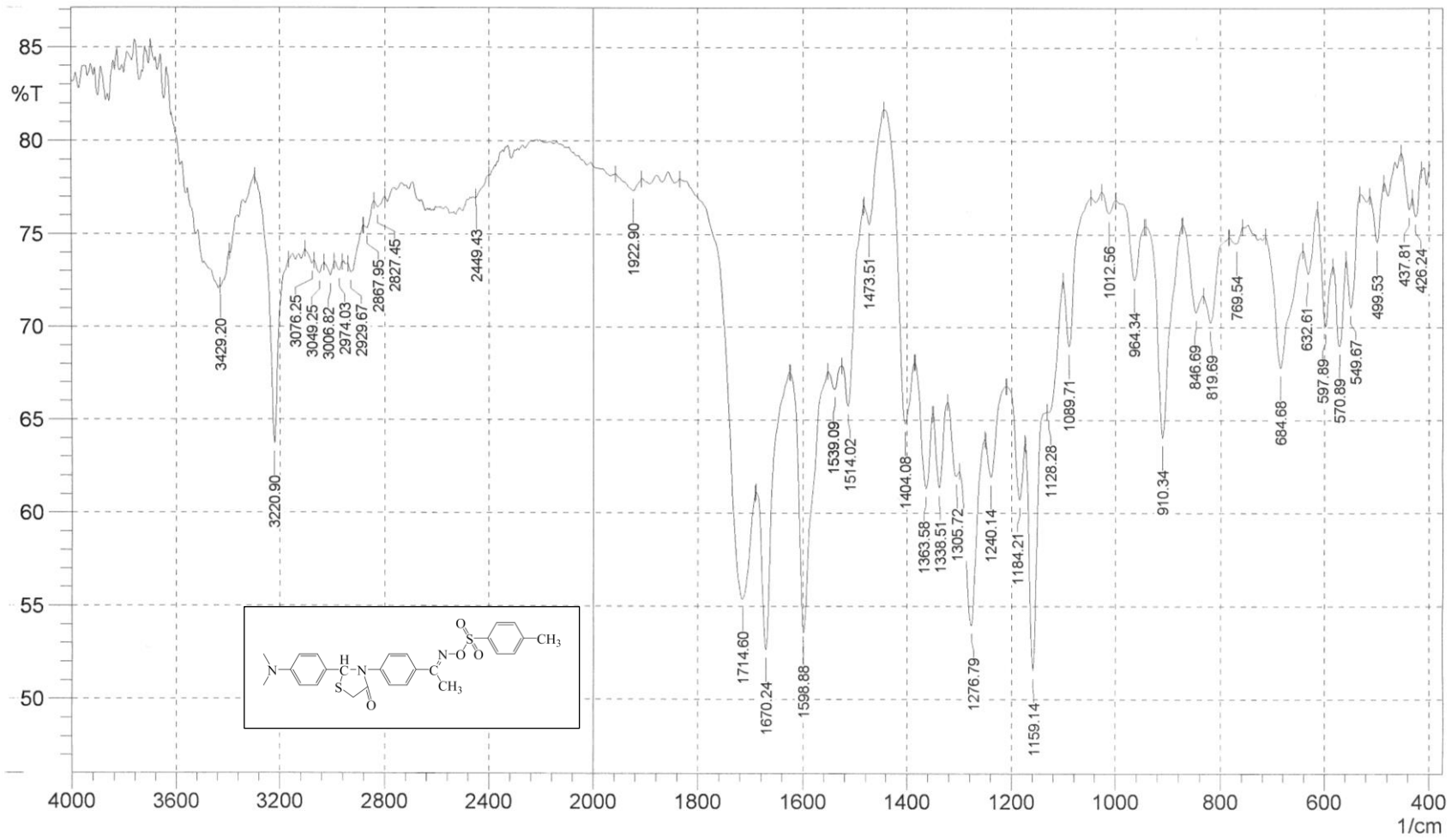


Fig. (3.49) FTIR spectrum of [A33]

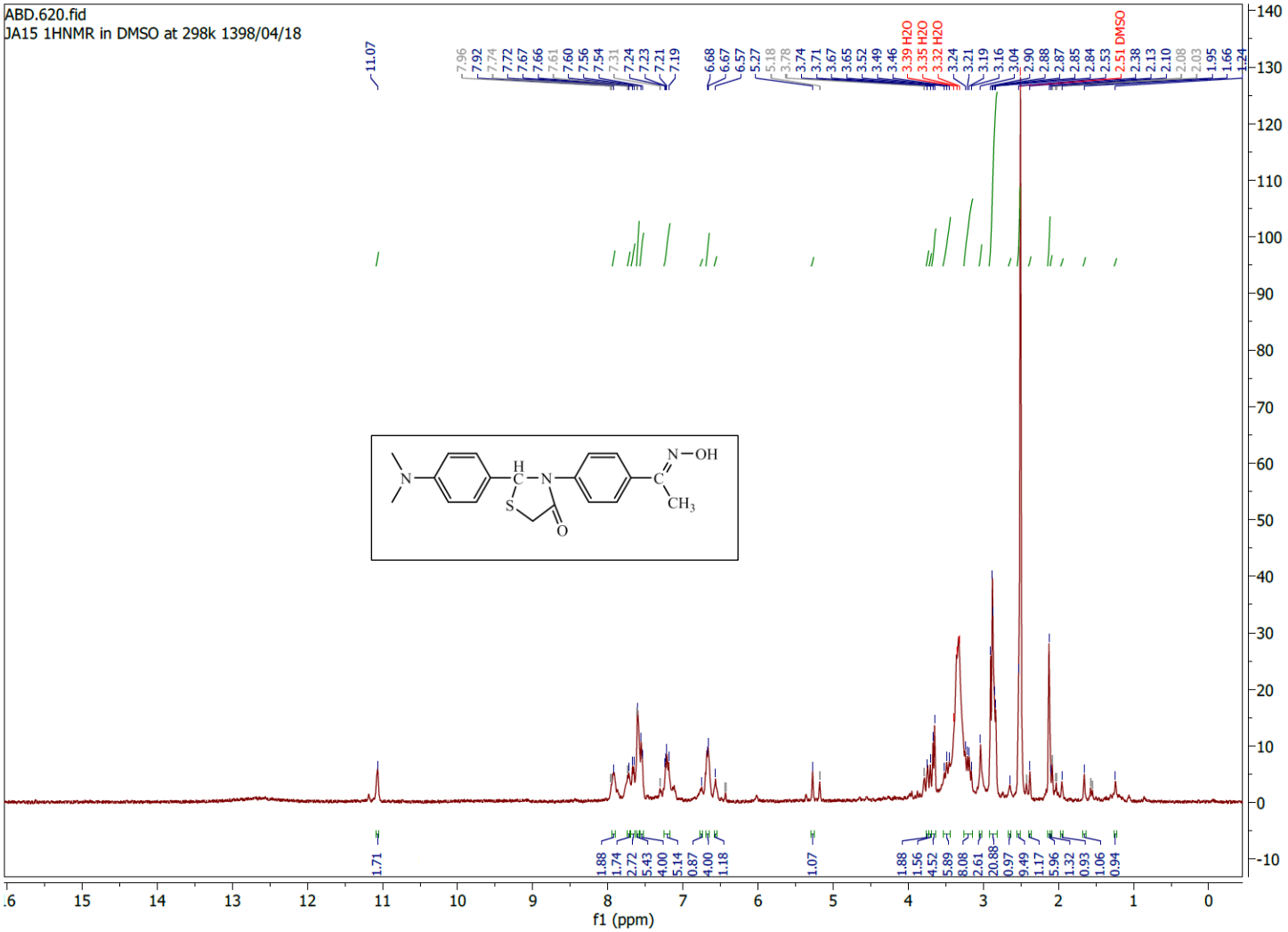


Fig. (3.50) ^{1}HNMR spectrum of [A31]

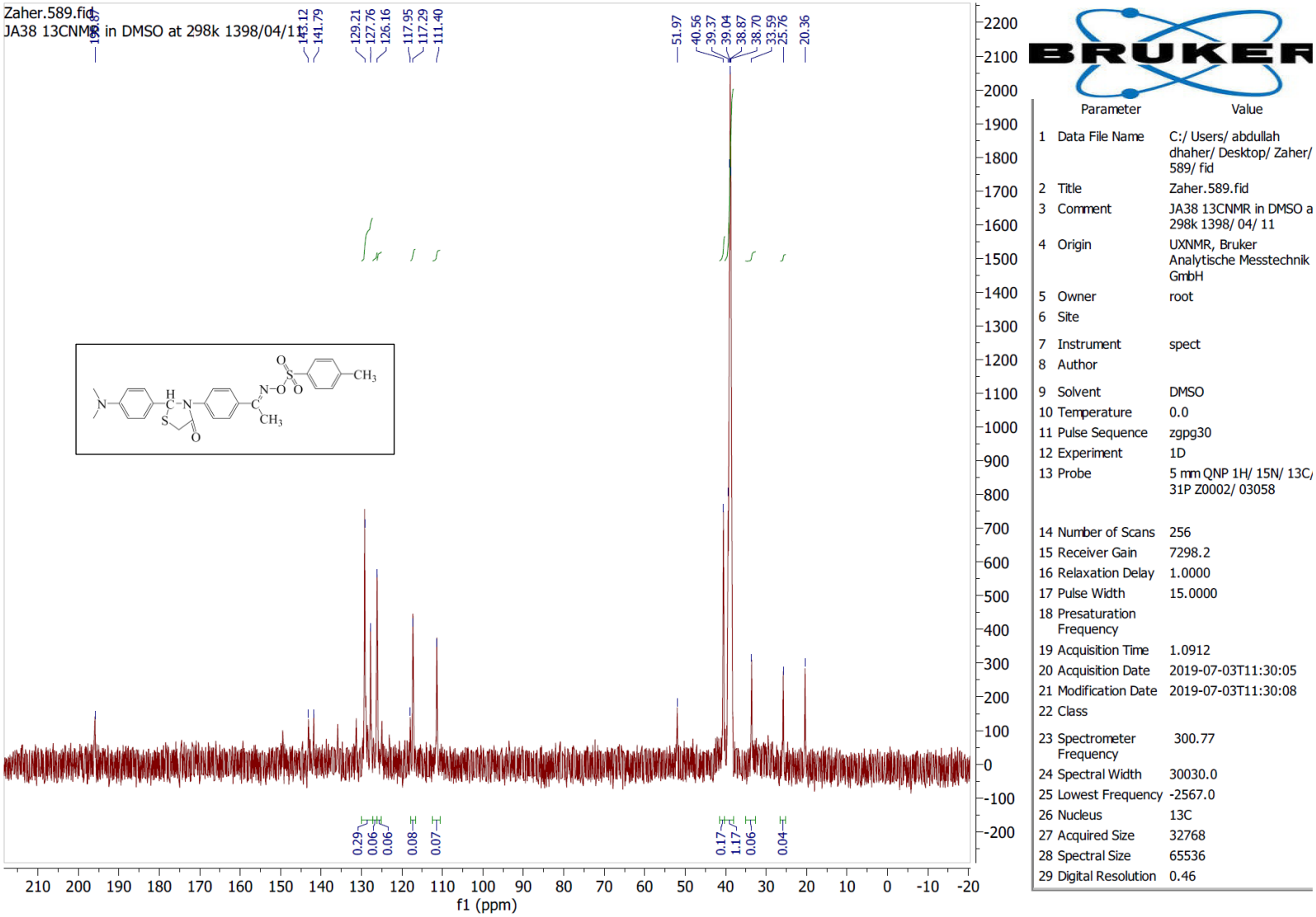


Fig. (3.51) ^{13}CNMR spectrum of [A33]

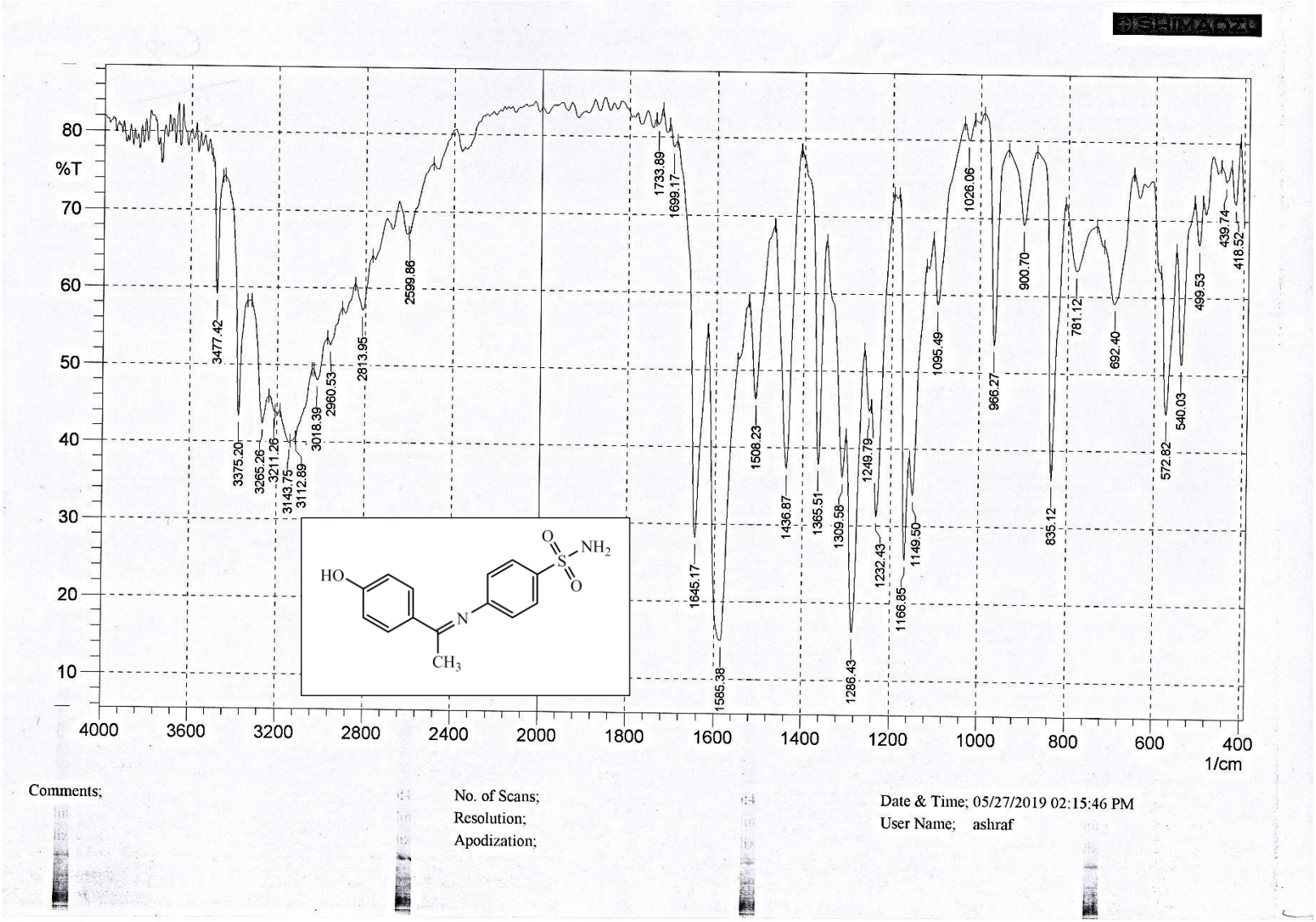


Fig. (3.52) FTIR spectrum of [B1]

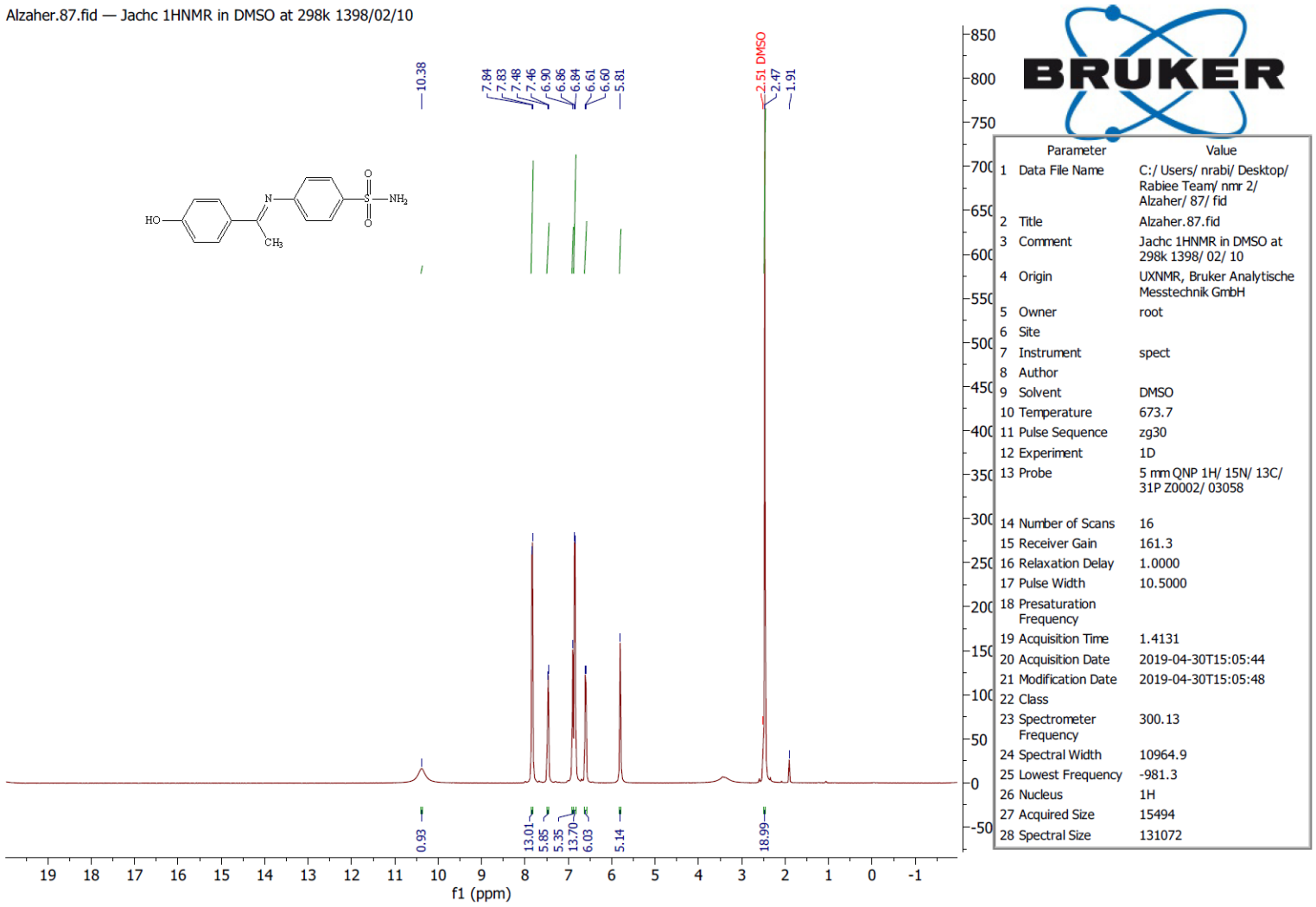


Fig. (3.53) ^{1}HNMR spectrum of [B1]

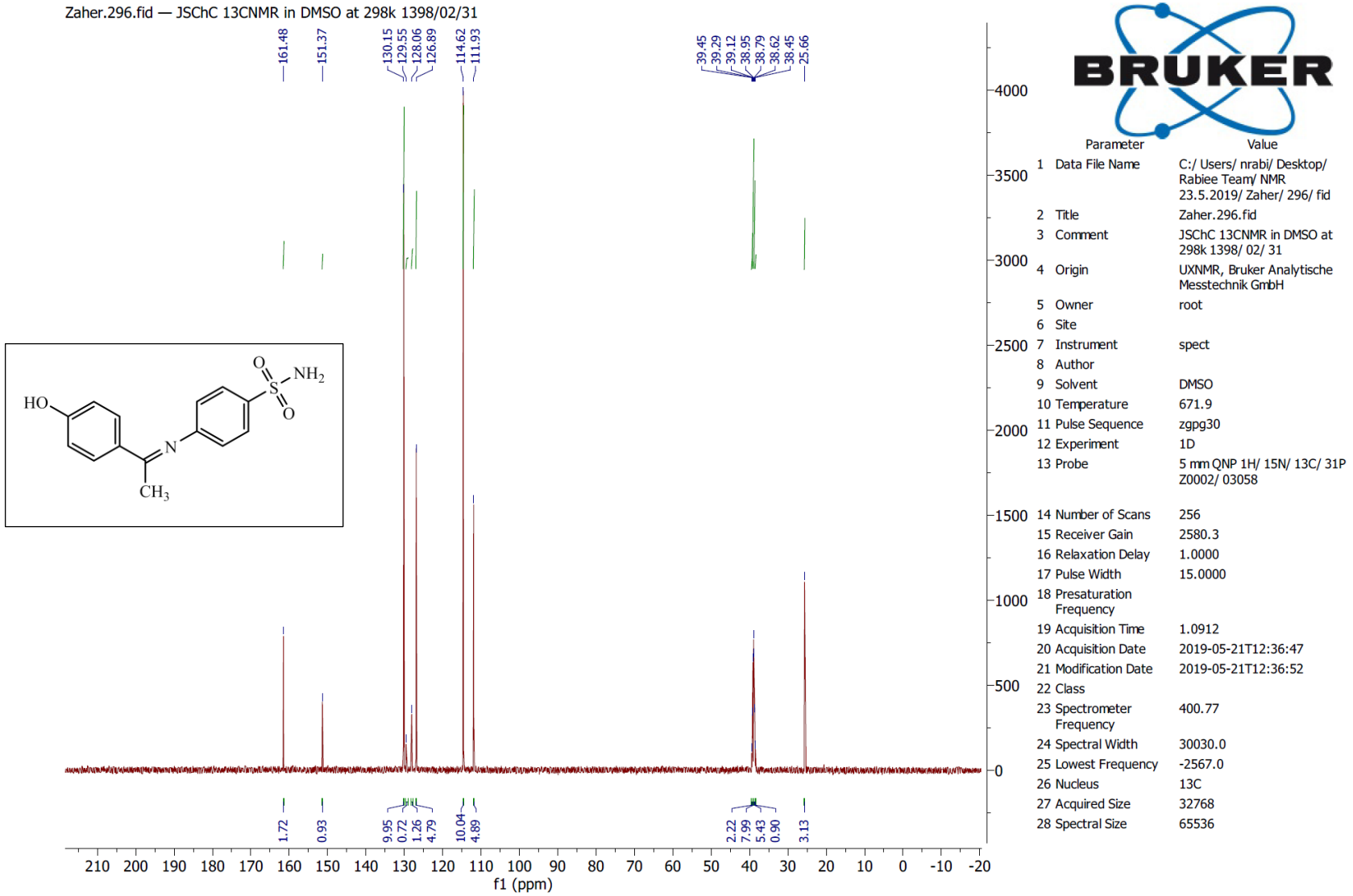


Fig. (3.54) ^{13}CNMR spectrum of [B1]

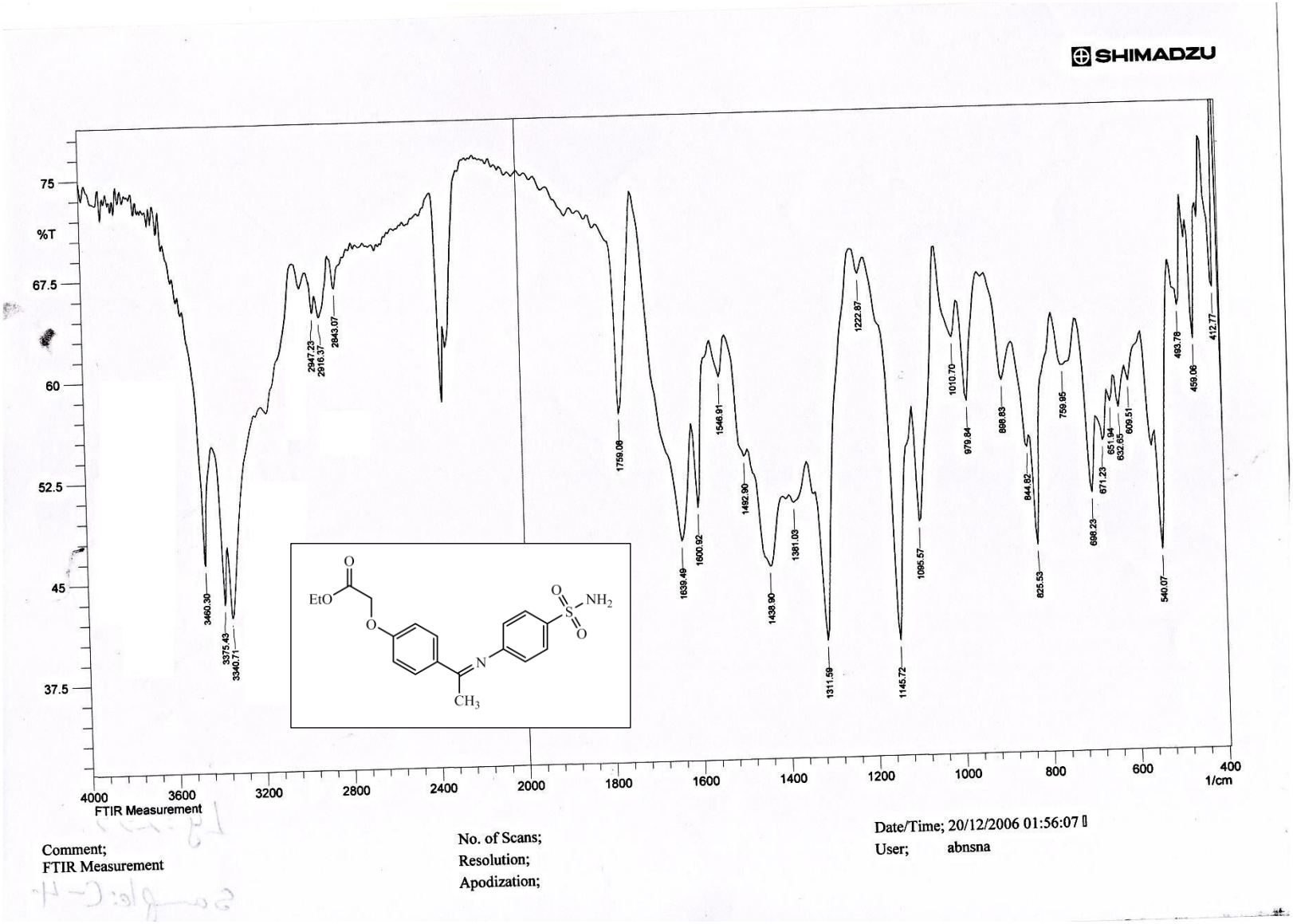


Fig. (3.55) FTIR spectrum of [B2]

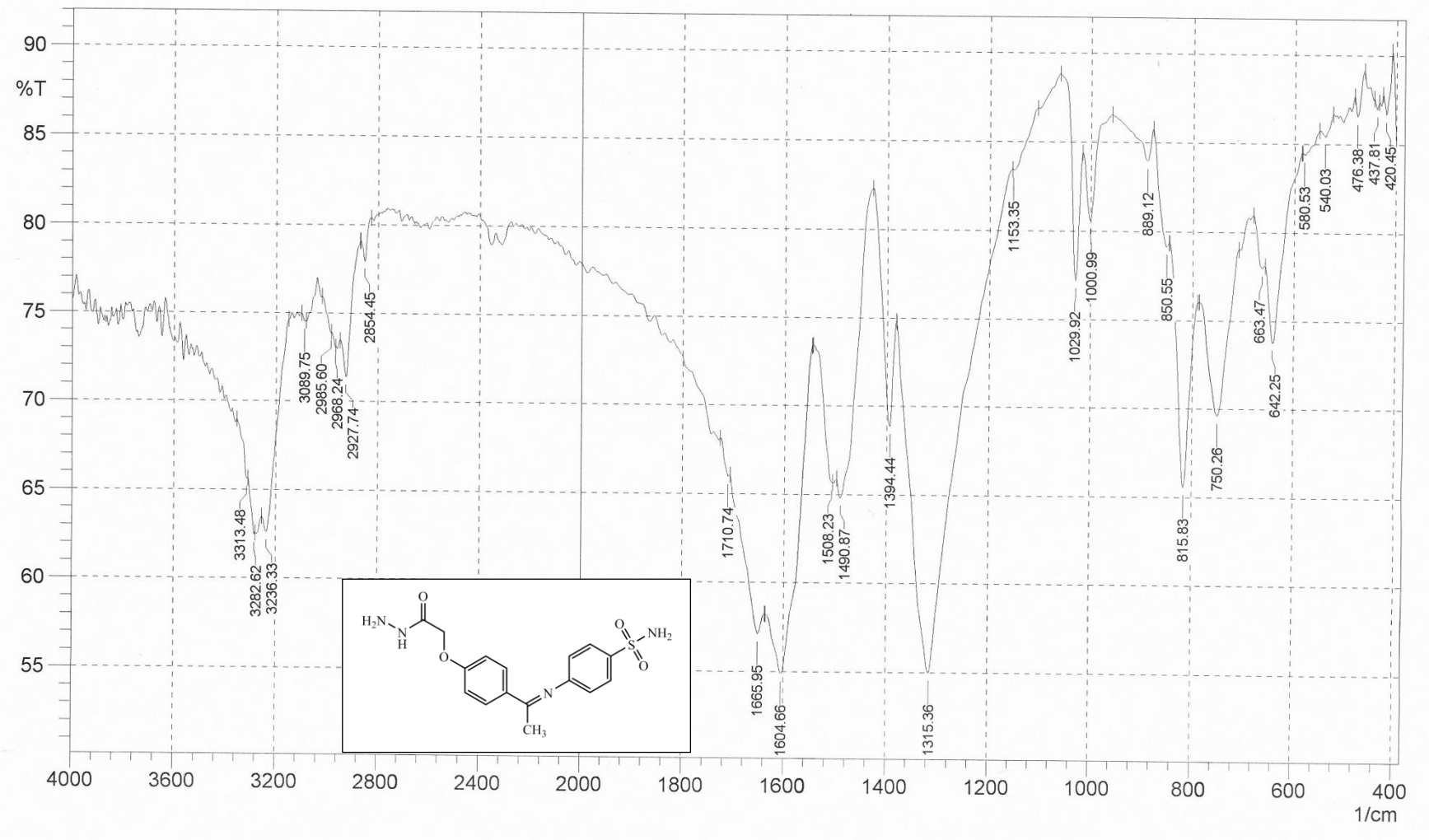


Fig. (3.56) FTIR spectrum of [B3]

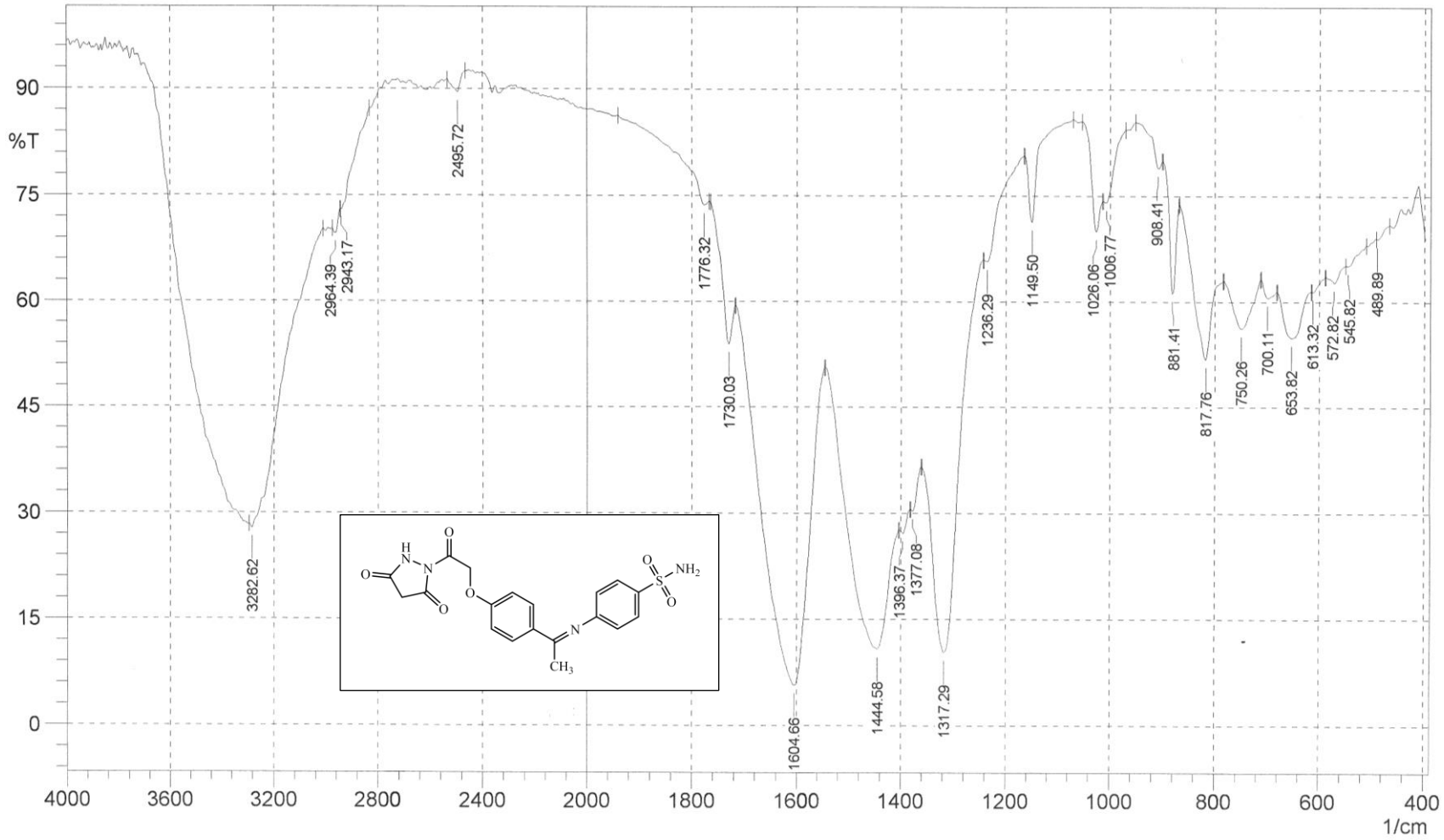


Fig. (3.57) FTIR spectrum of [B4]

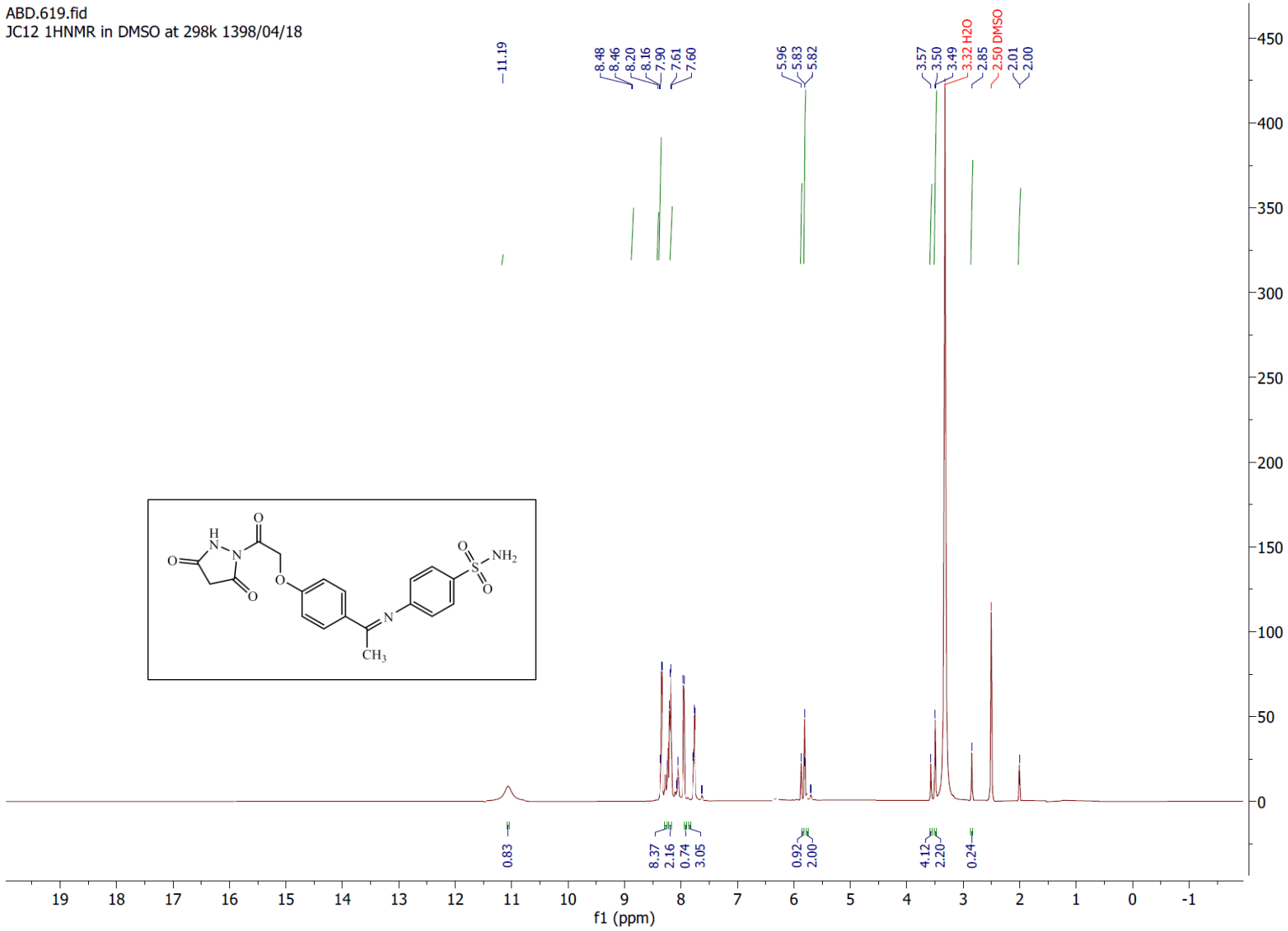


Fig. (3.58) [1]HNMR spectrum of [B4]

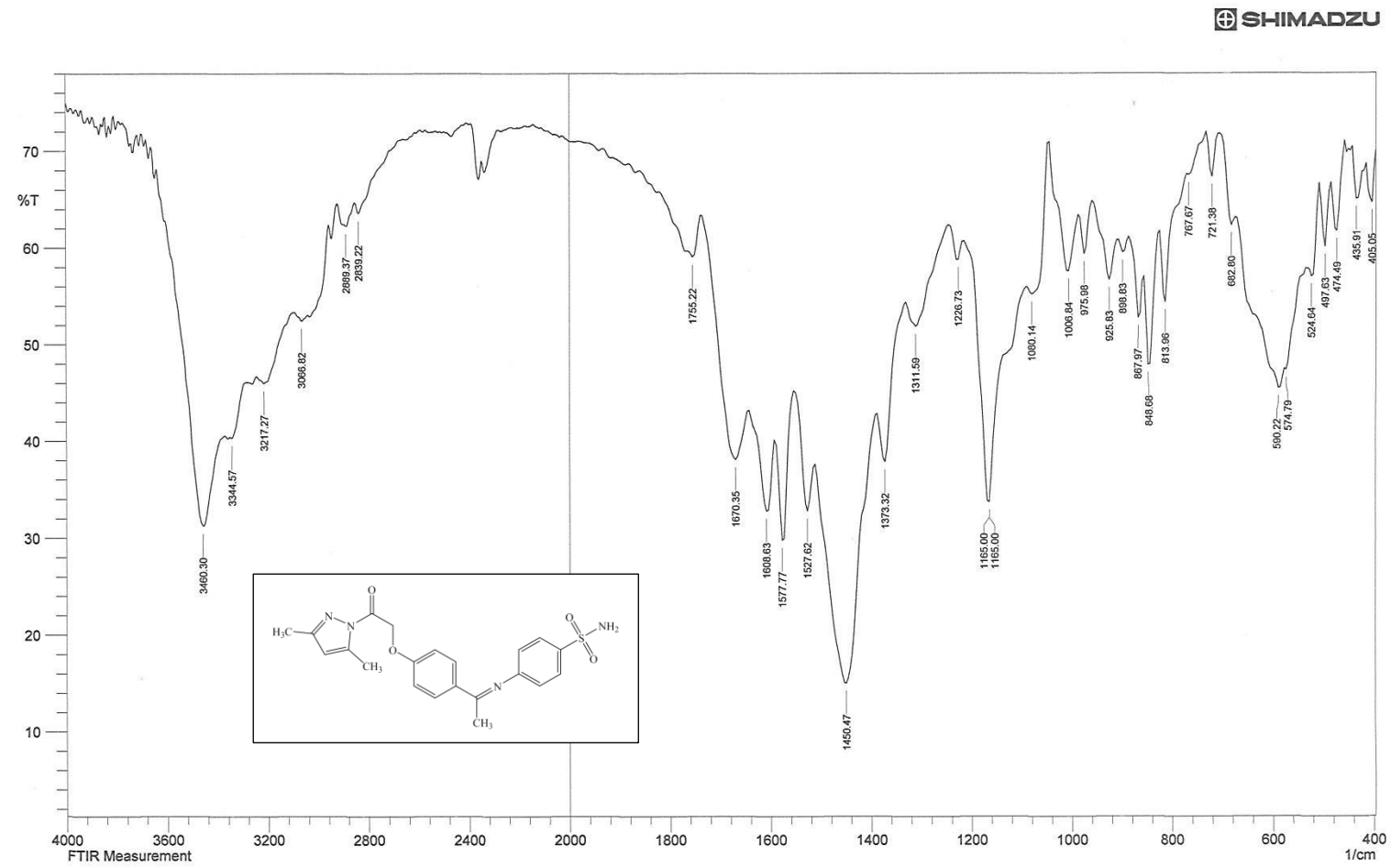


Fig. (3.59) FTIR spectrum of [B5]

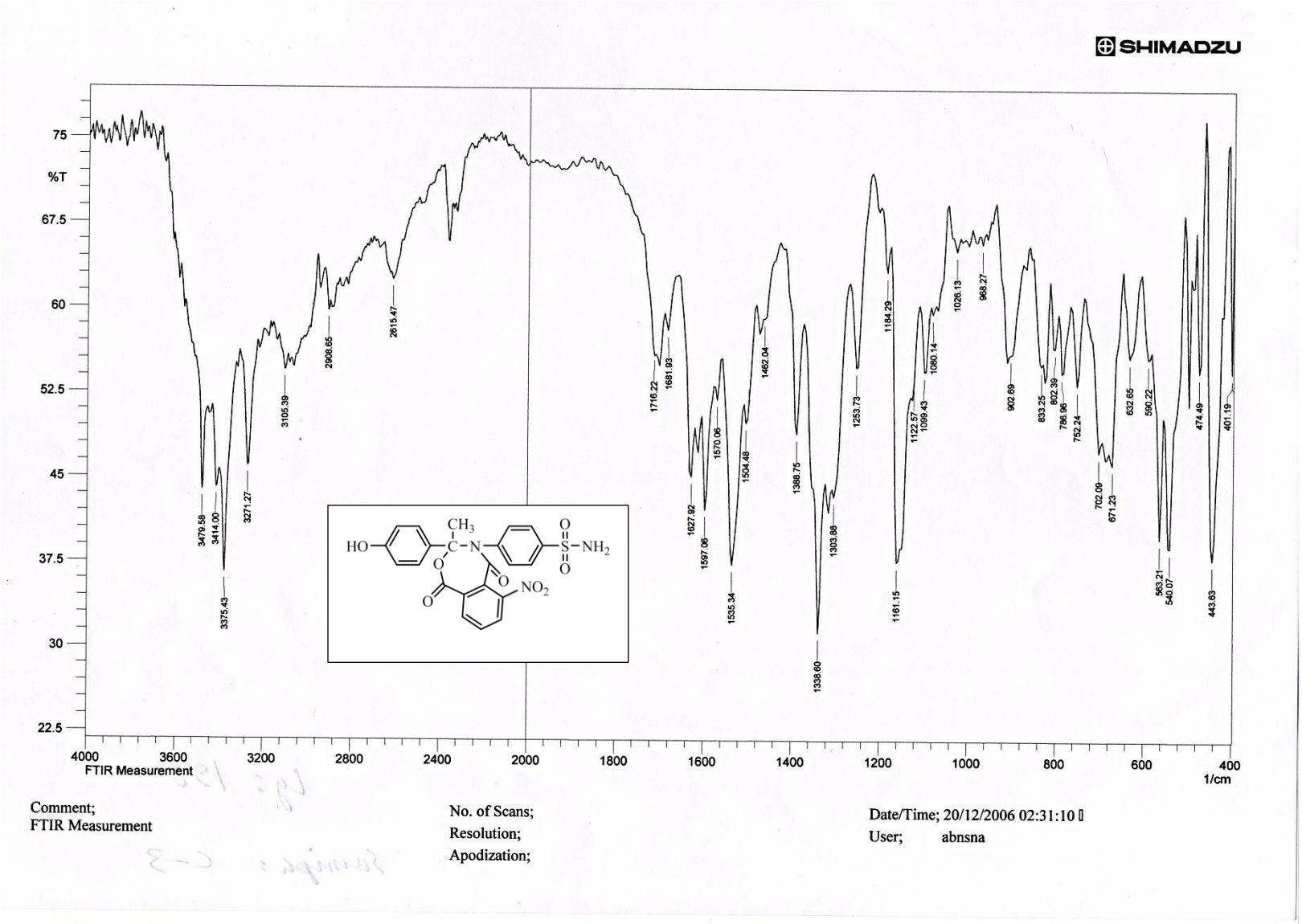


Fig. (3.60) FTIR spectrum of [B7]

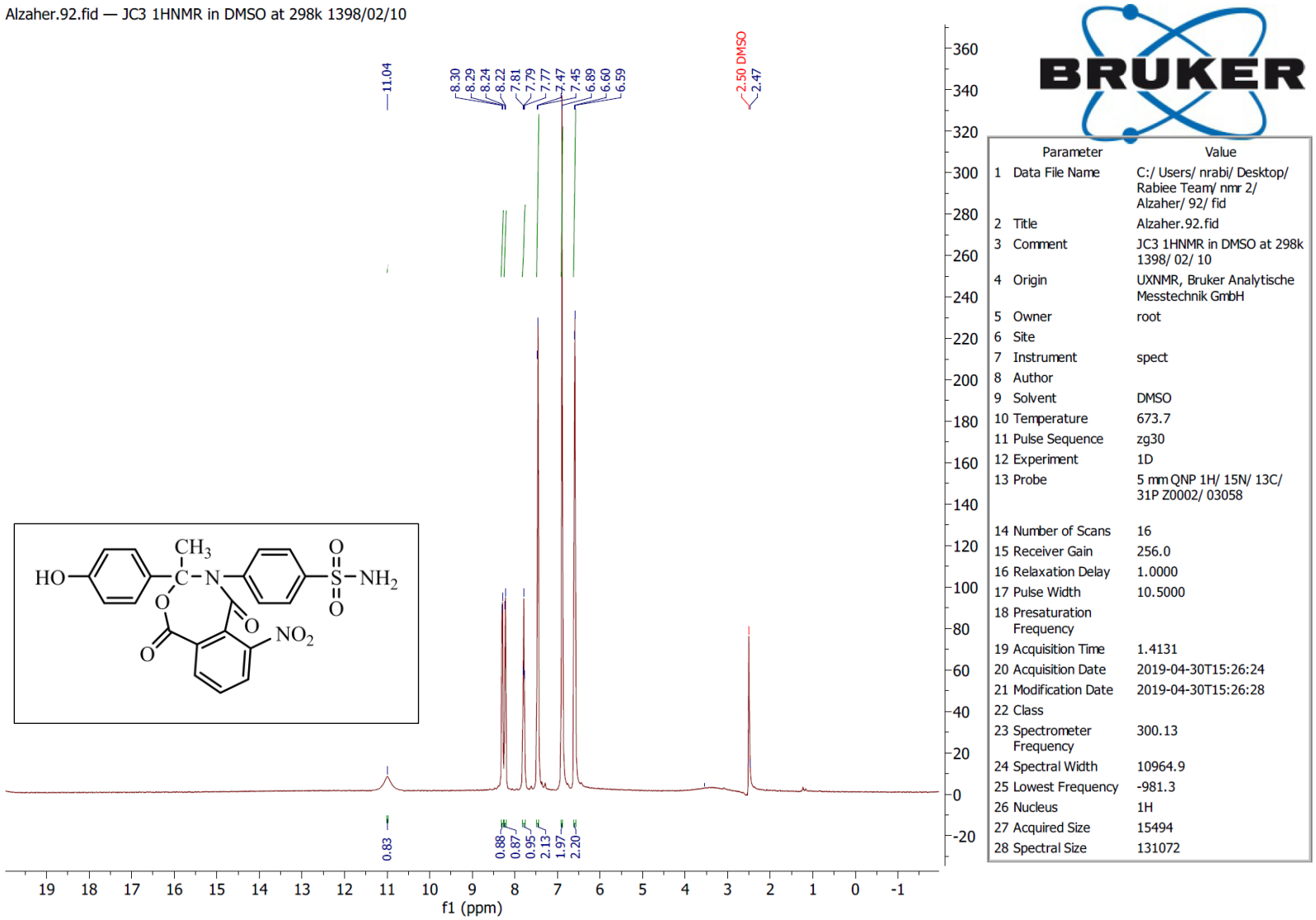


Fig. (3.61) ^{1}HNMR spectrum of [B7]

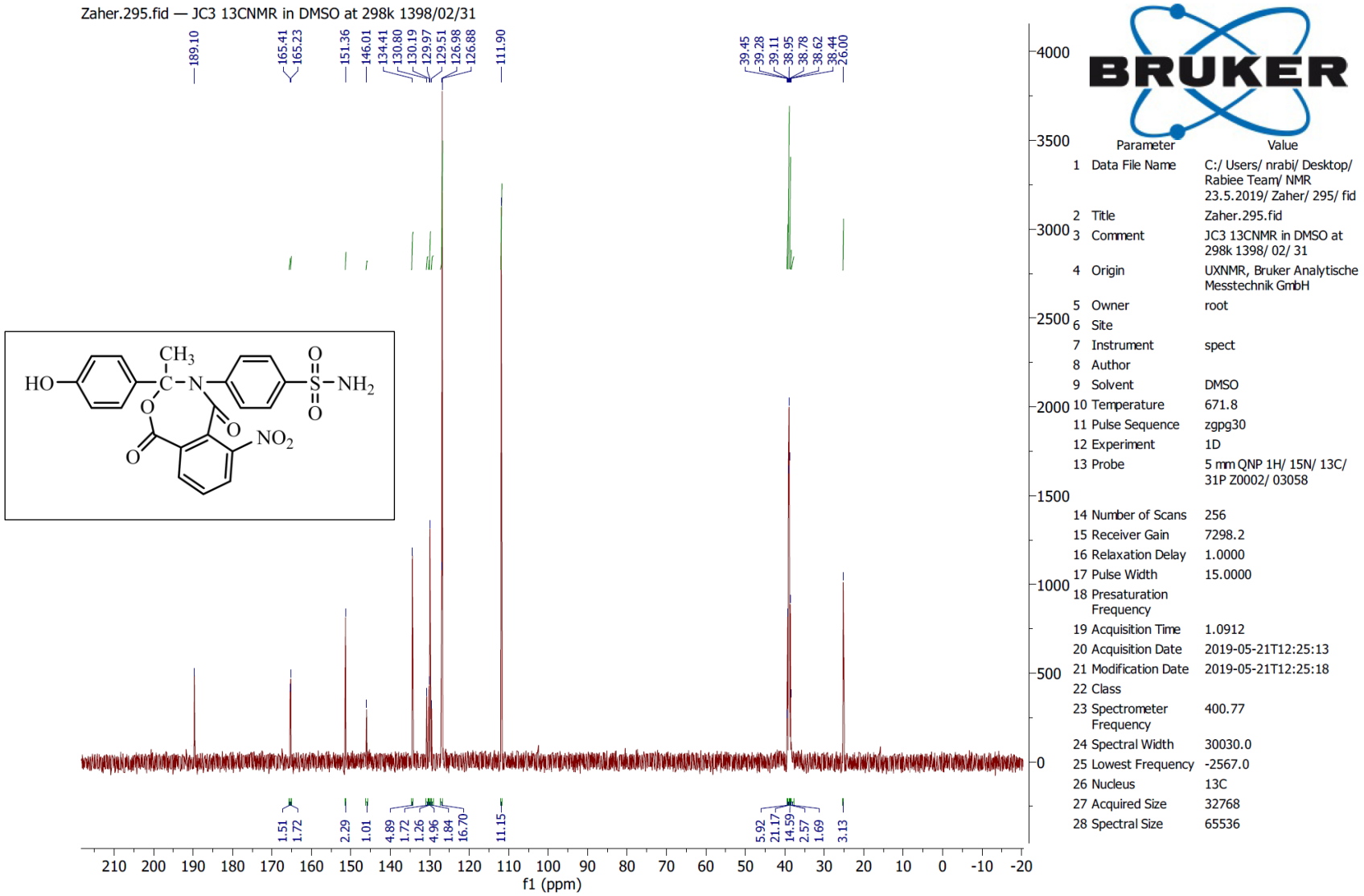


Fig. (3.62) ^{13}CNMR spectrum of [B7]

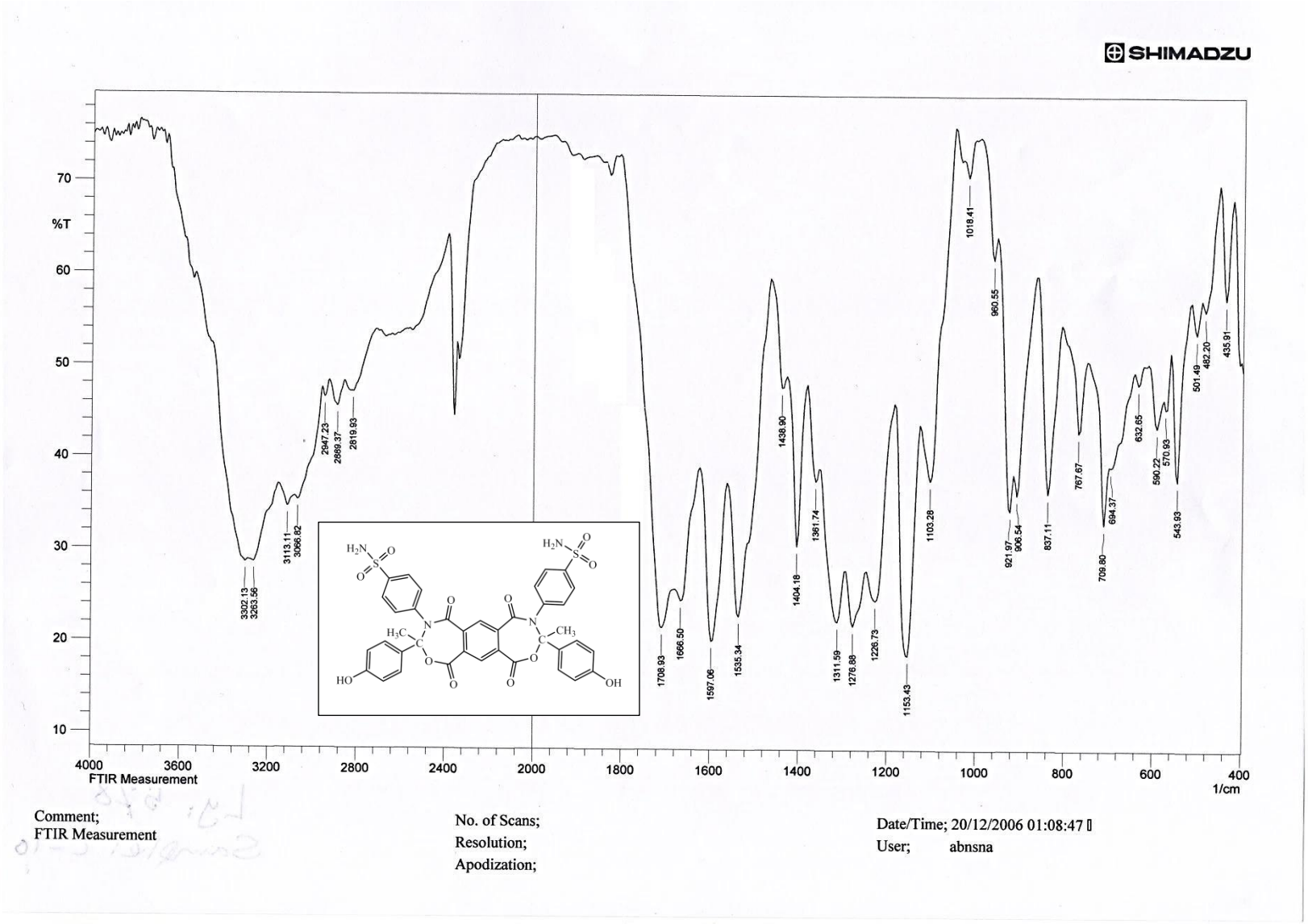


Fig. (3.63) FTIR spectrum of [B8]

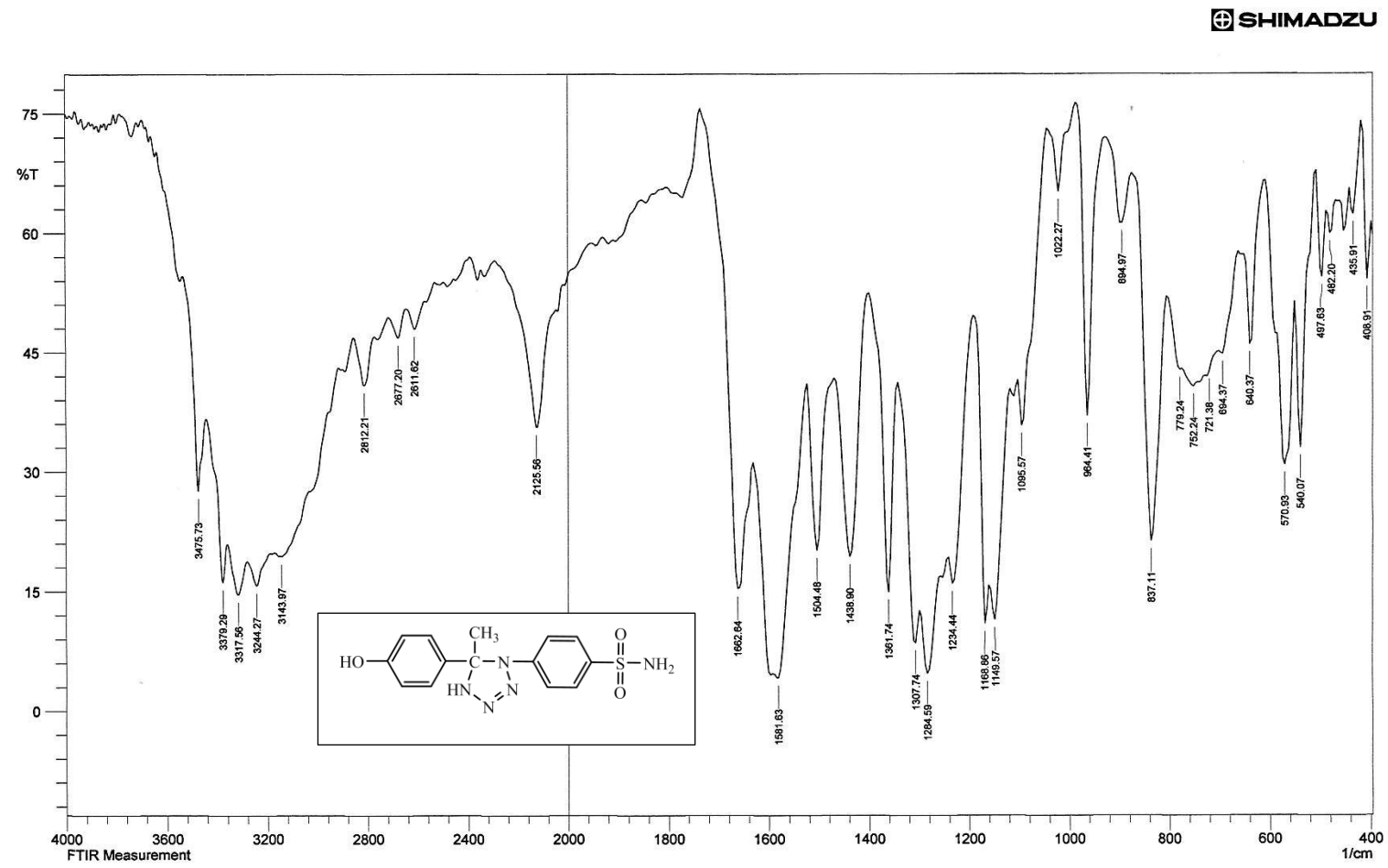


Fig. (3.64) FTIR spectrum of [B9]

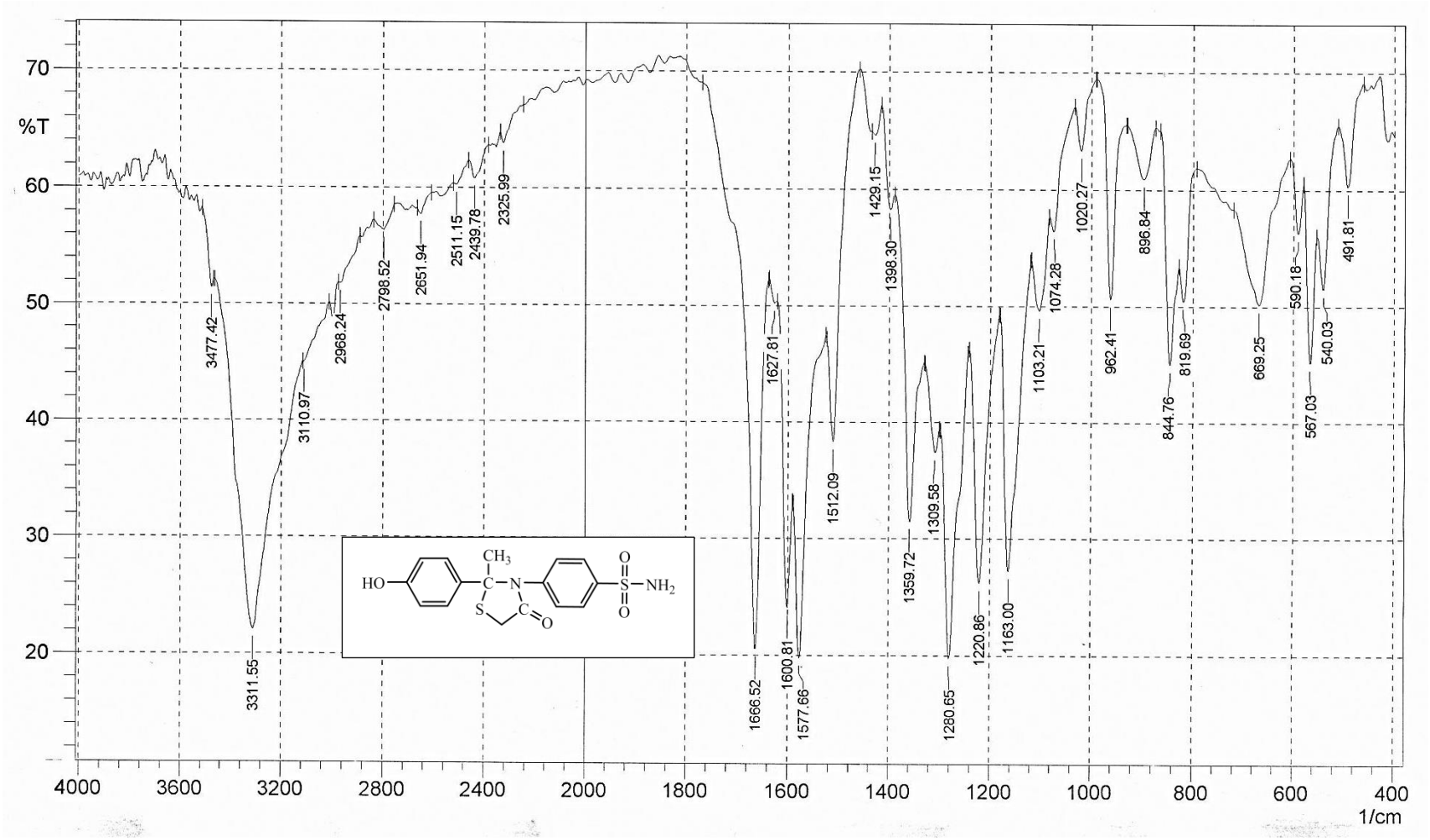


Fig. (3.65) FTIR spectrum of [B10]

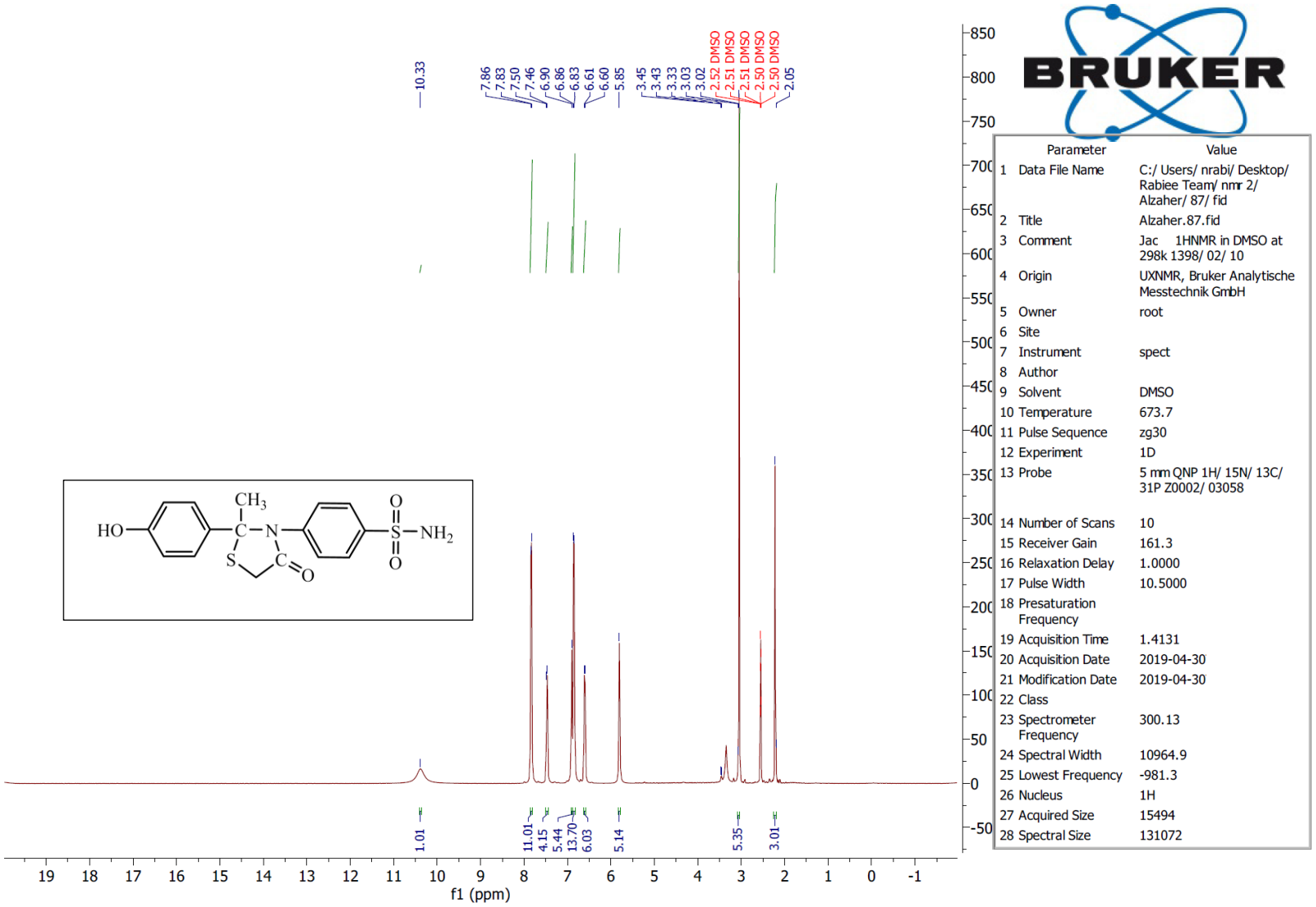


Fig. (3.66) ^{1}HNMR spectrum of [B10]

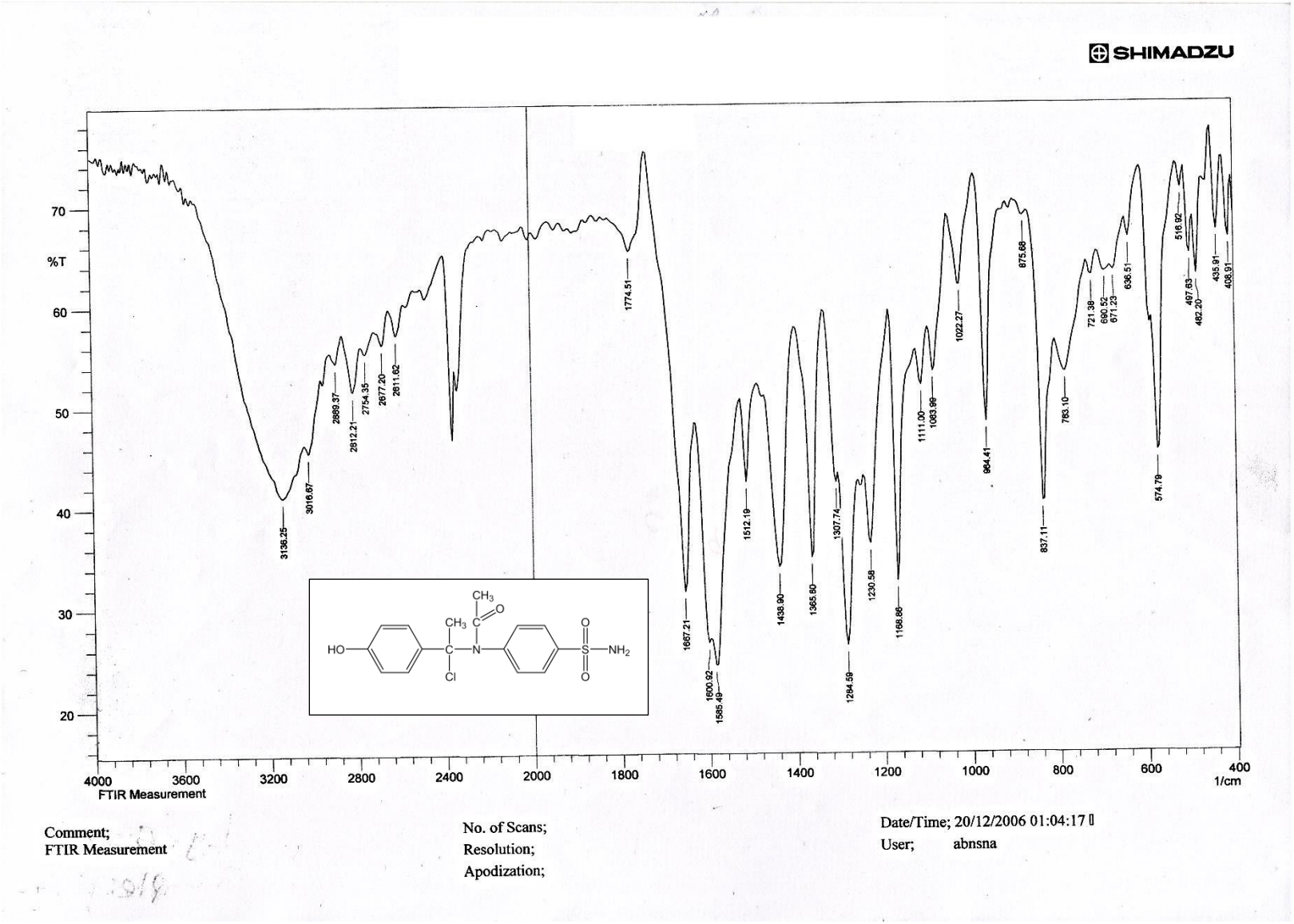


Fig. (3.67) FTIR spectrum of [B11]

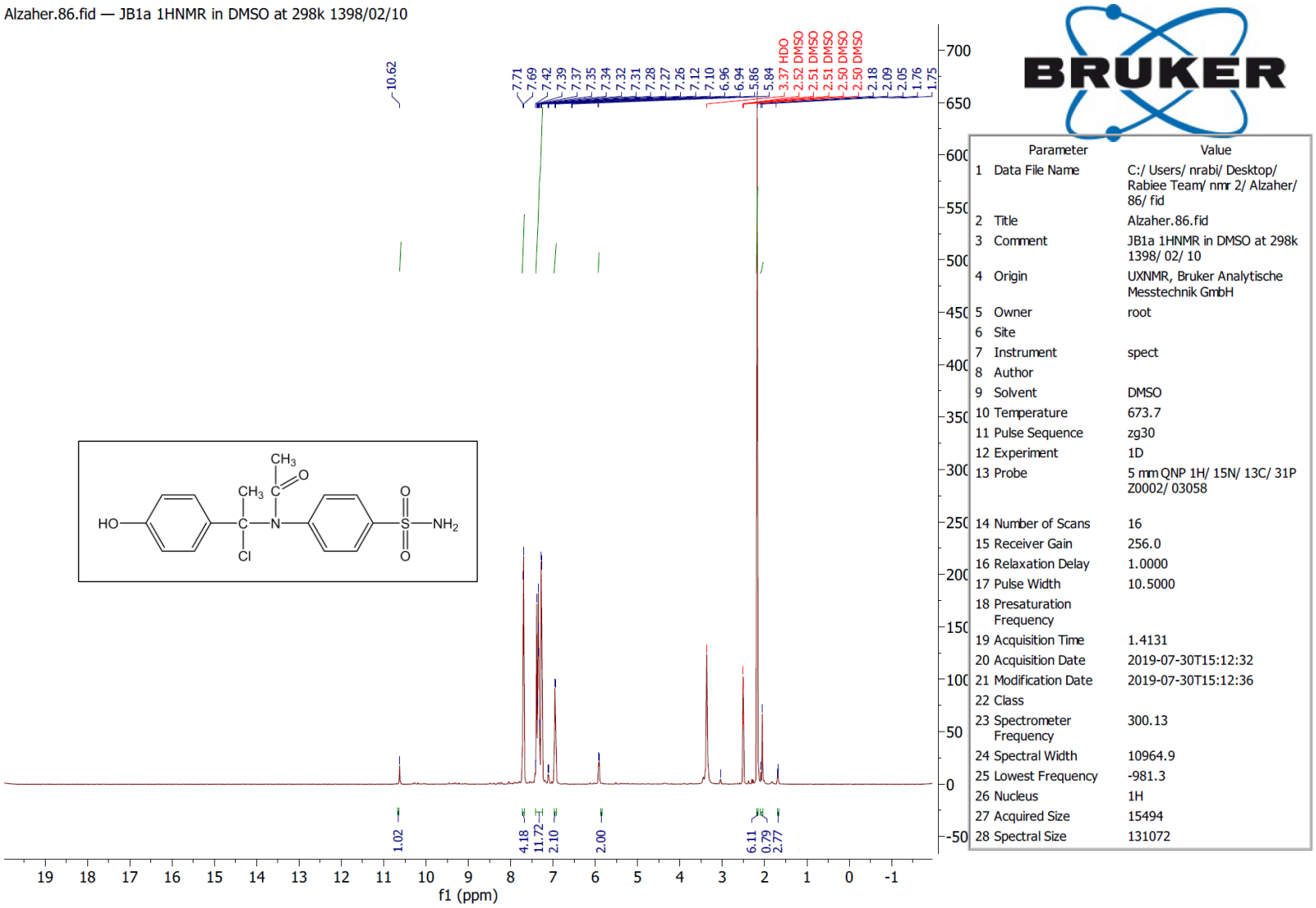


Fig. (3.68) ^{1}HNMR spectrum of [B11]

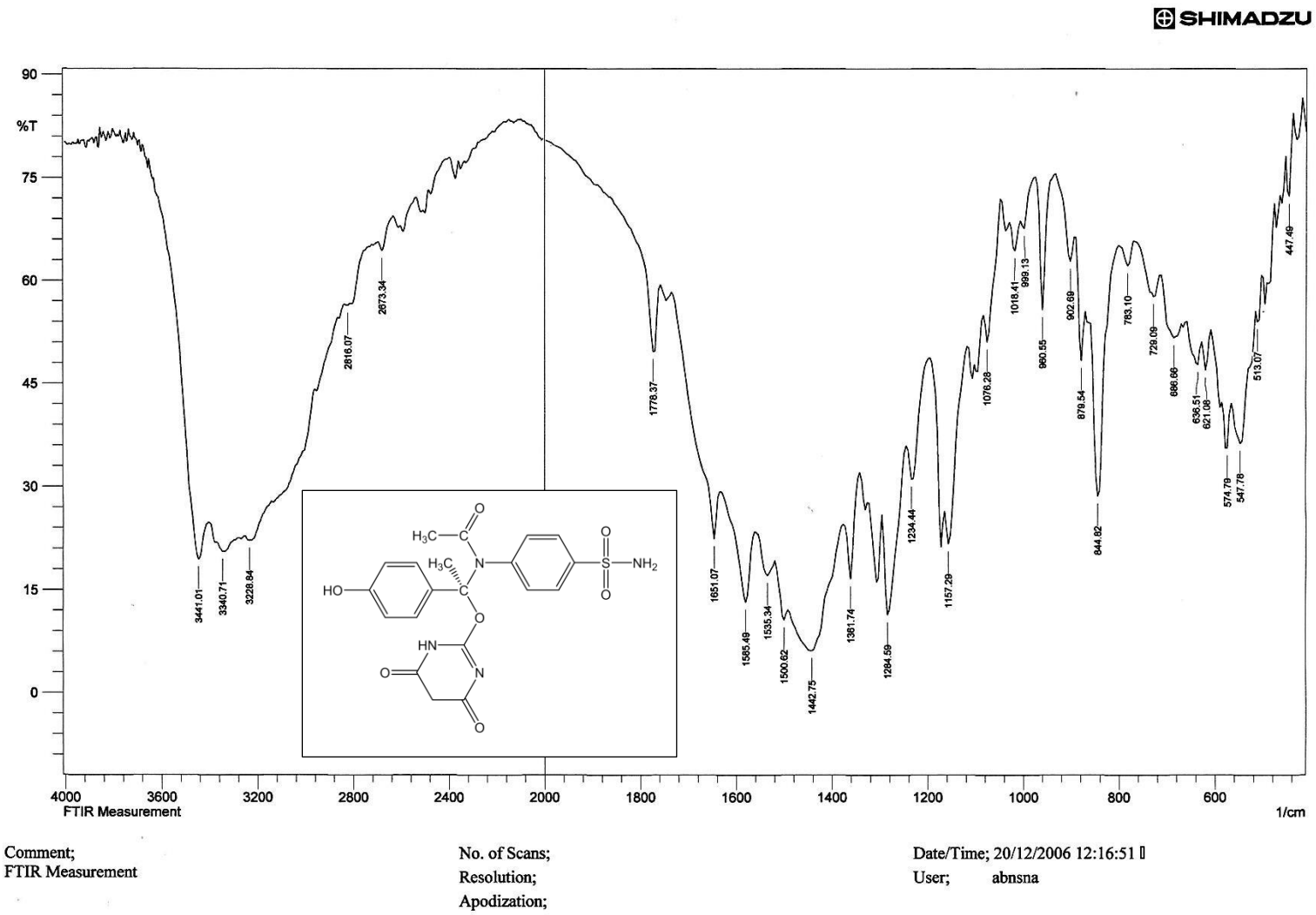


Fig. (3.69) FTIR spectrum of [B12]

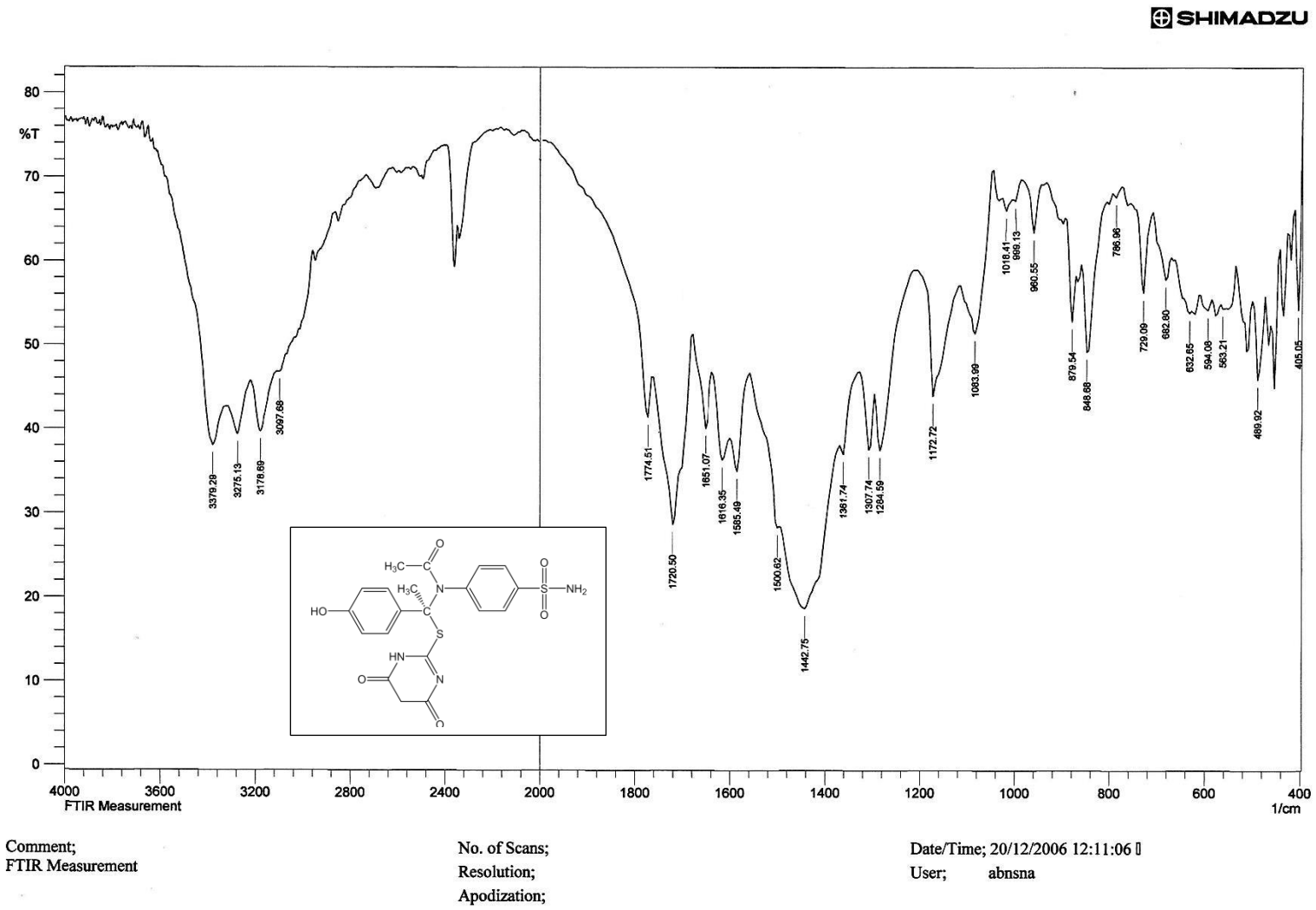


Fig. (3.70) FTIR spectrum of [B13]

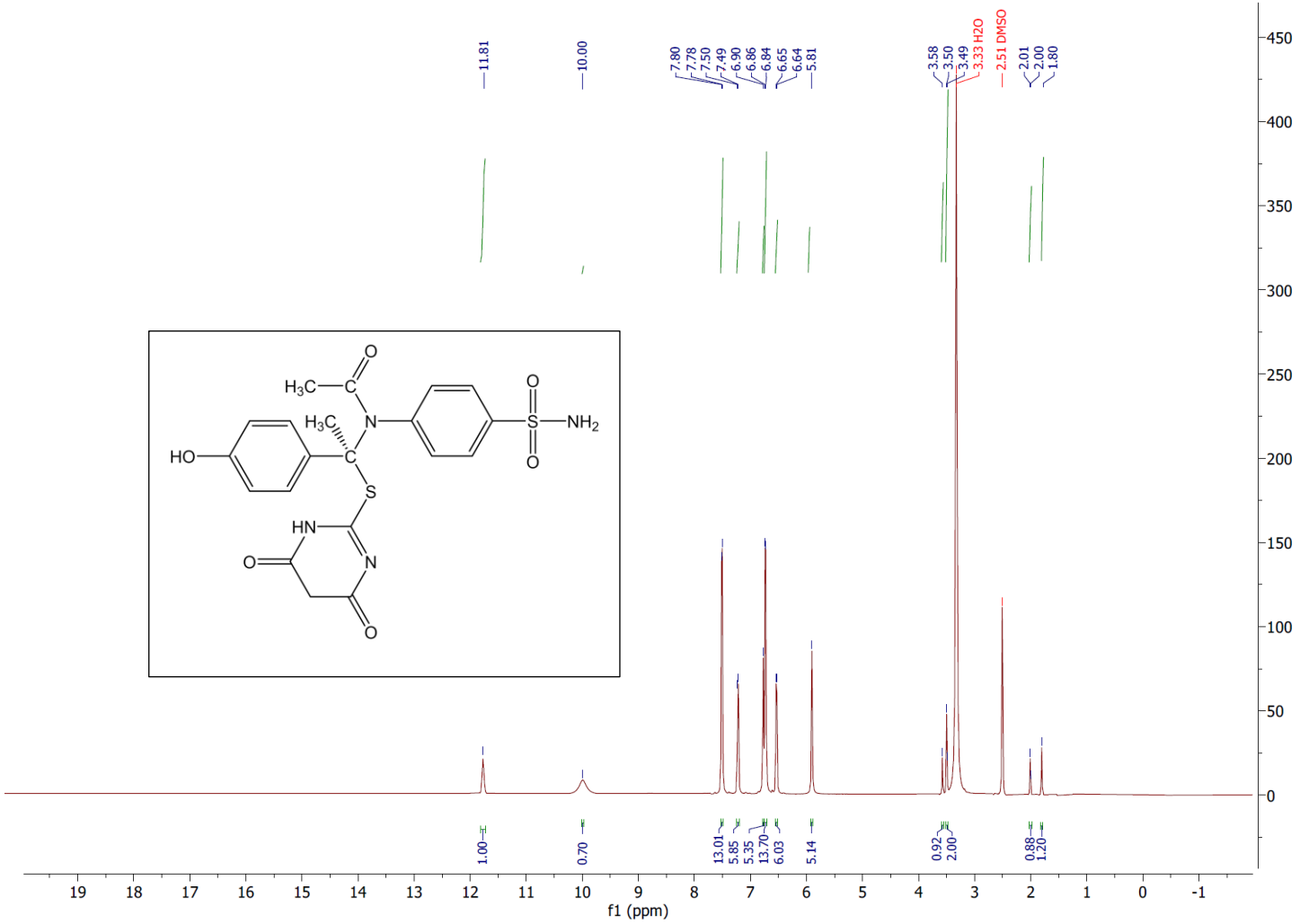


Fig. (3.71) ^{1}HNMR spectrum of [B13]

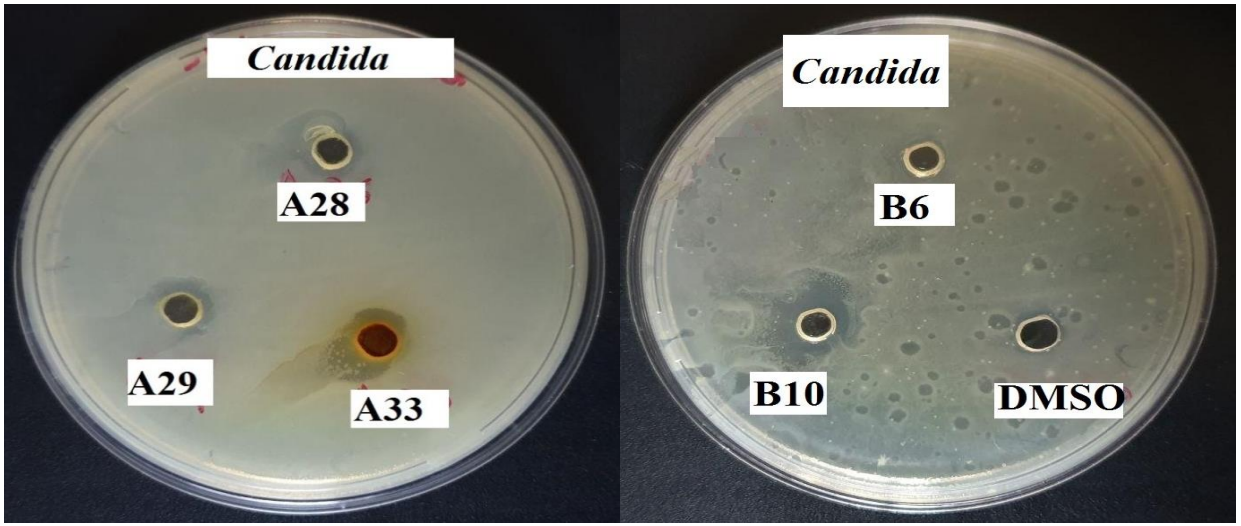


Fig. (3.72) Biological activity of fungal

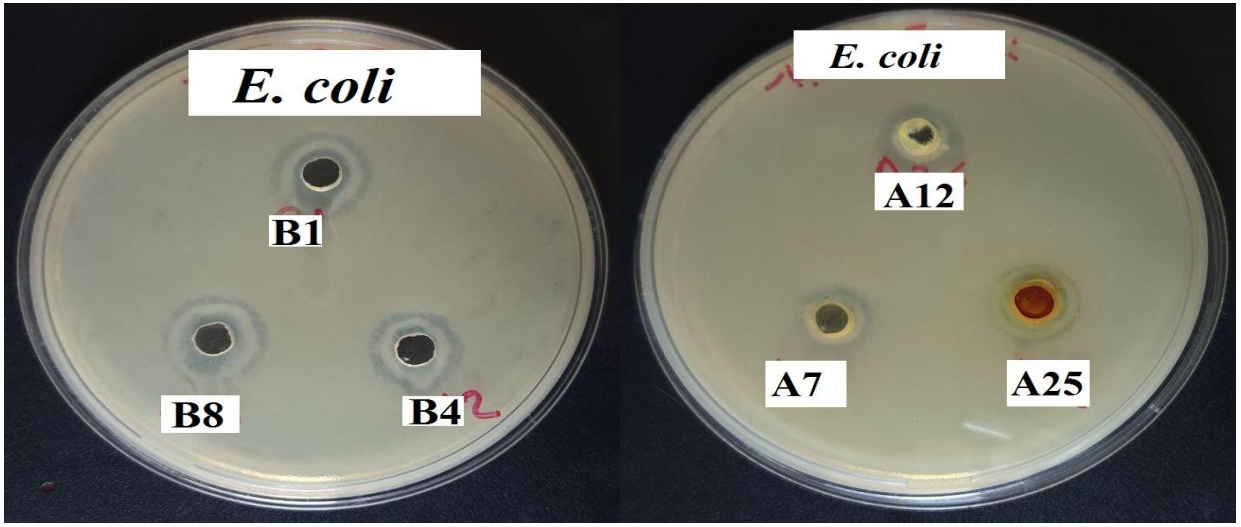


Fig. (3.73) Biological activity of ***E. coli***

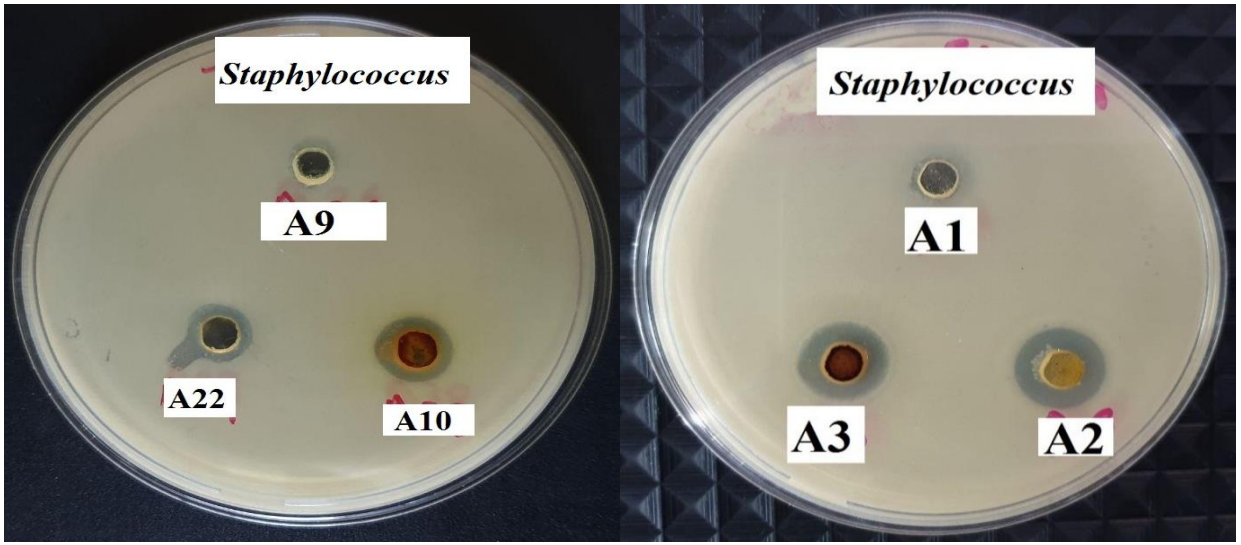


Fig. (3.74) Biological activity of ***Staphylococcus***

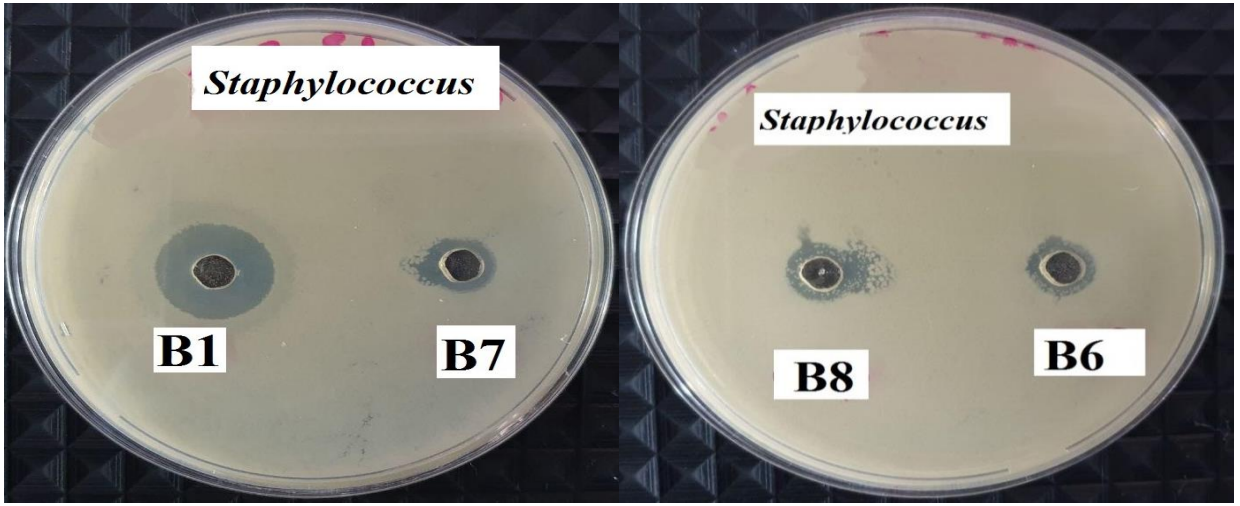


Fig. (3.75) Biological activity of ***Staphylococcus***

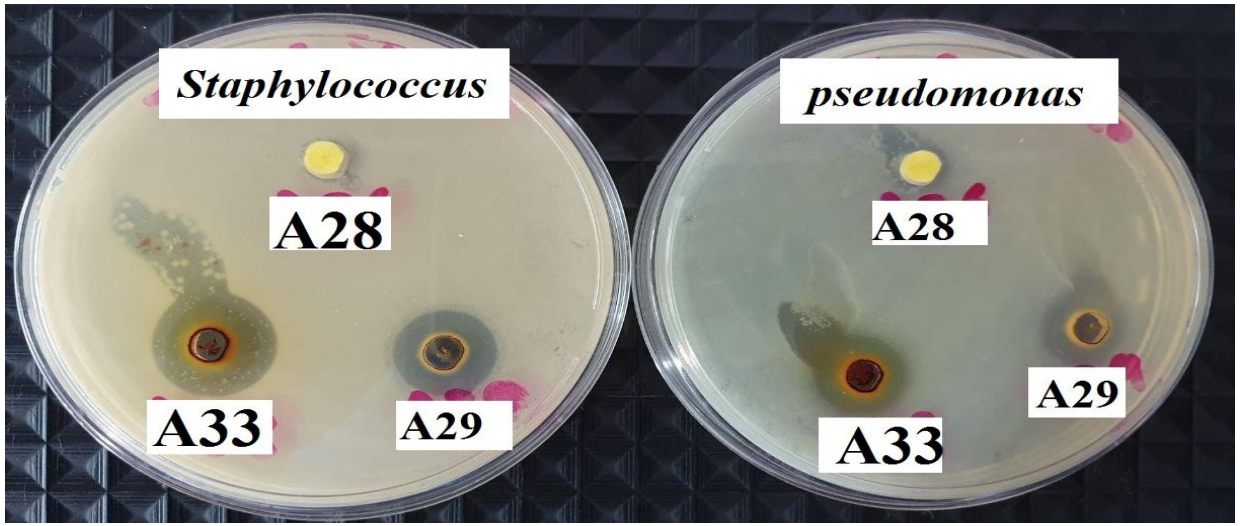


Fig. (3.76) Biological activity of bacterial

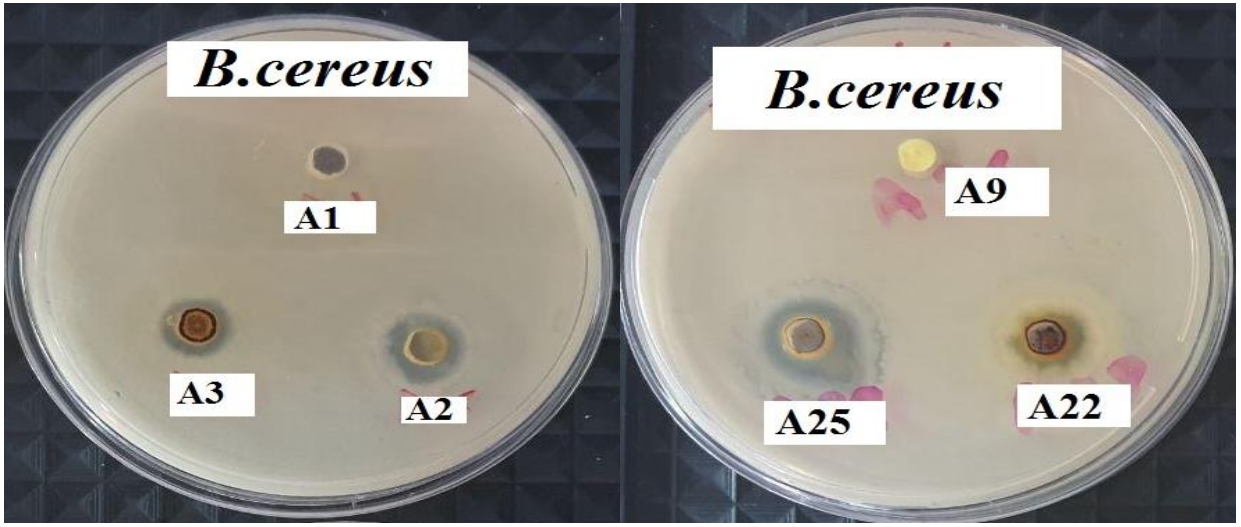


Fig. (3.77) Biological activity of ***B. cereus***

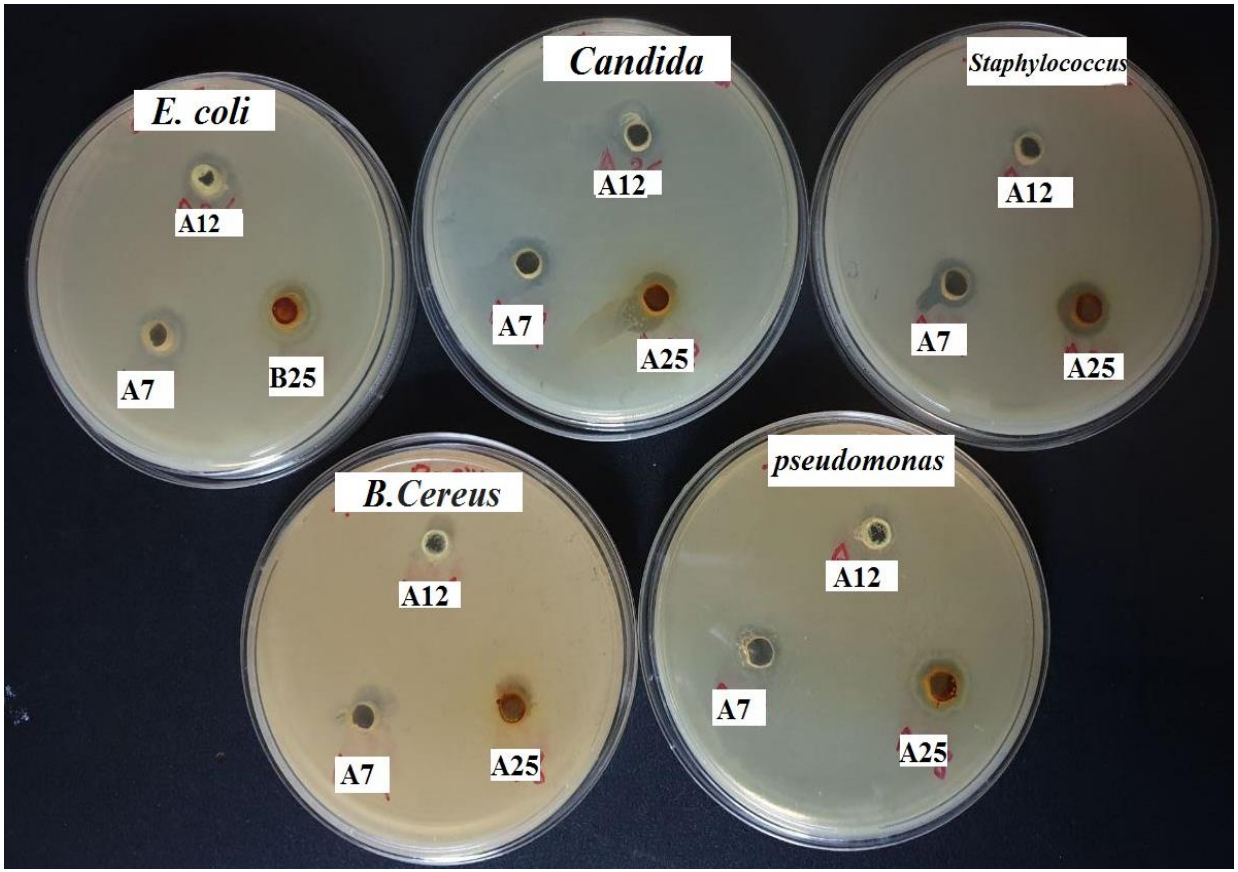


Fig. (3.78) Biological activity of some prepared compounds

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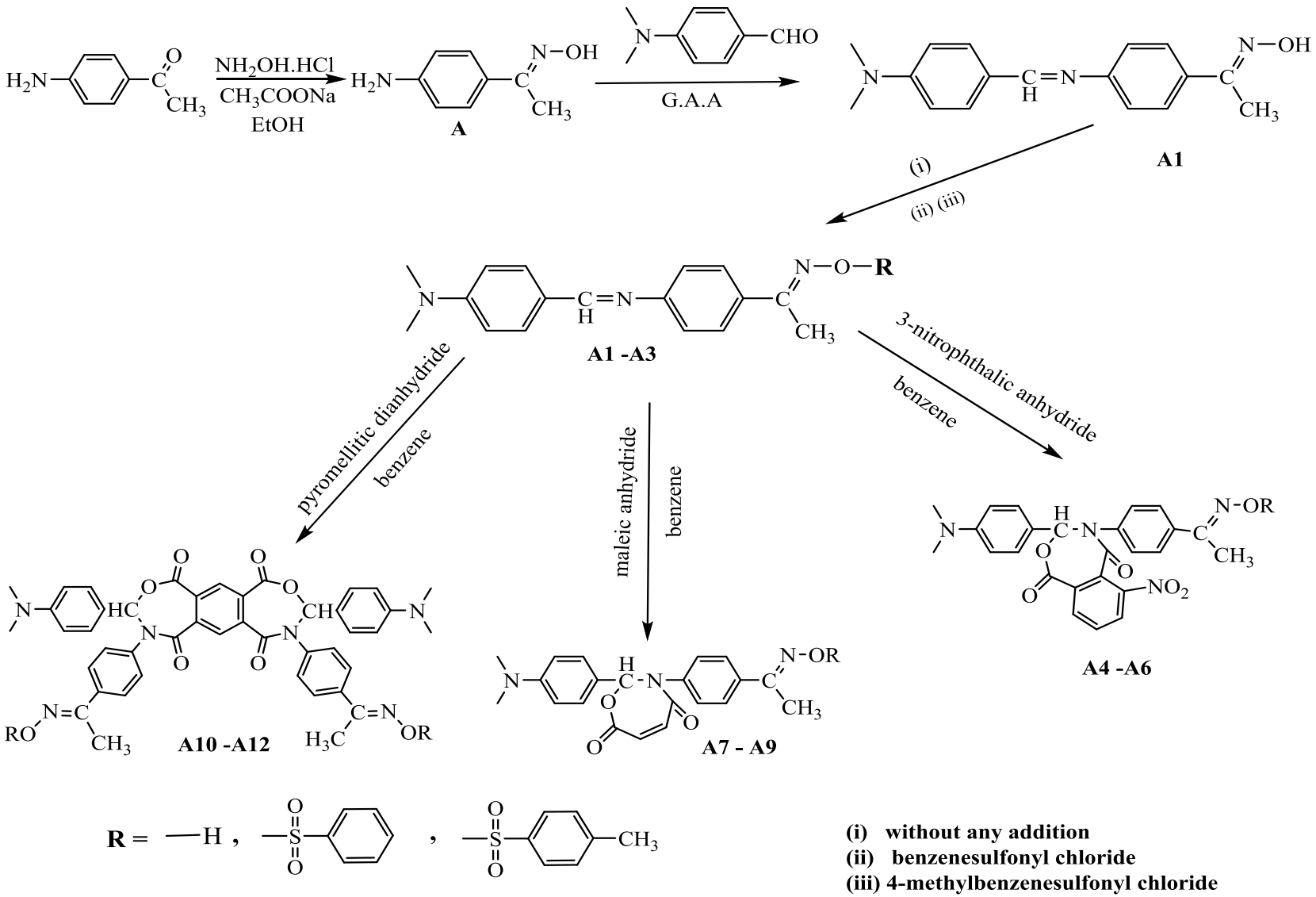
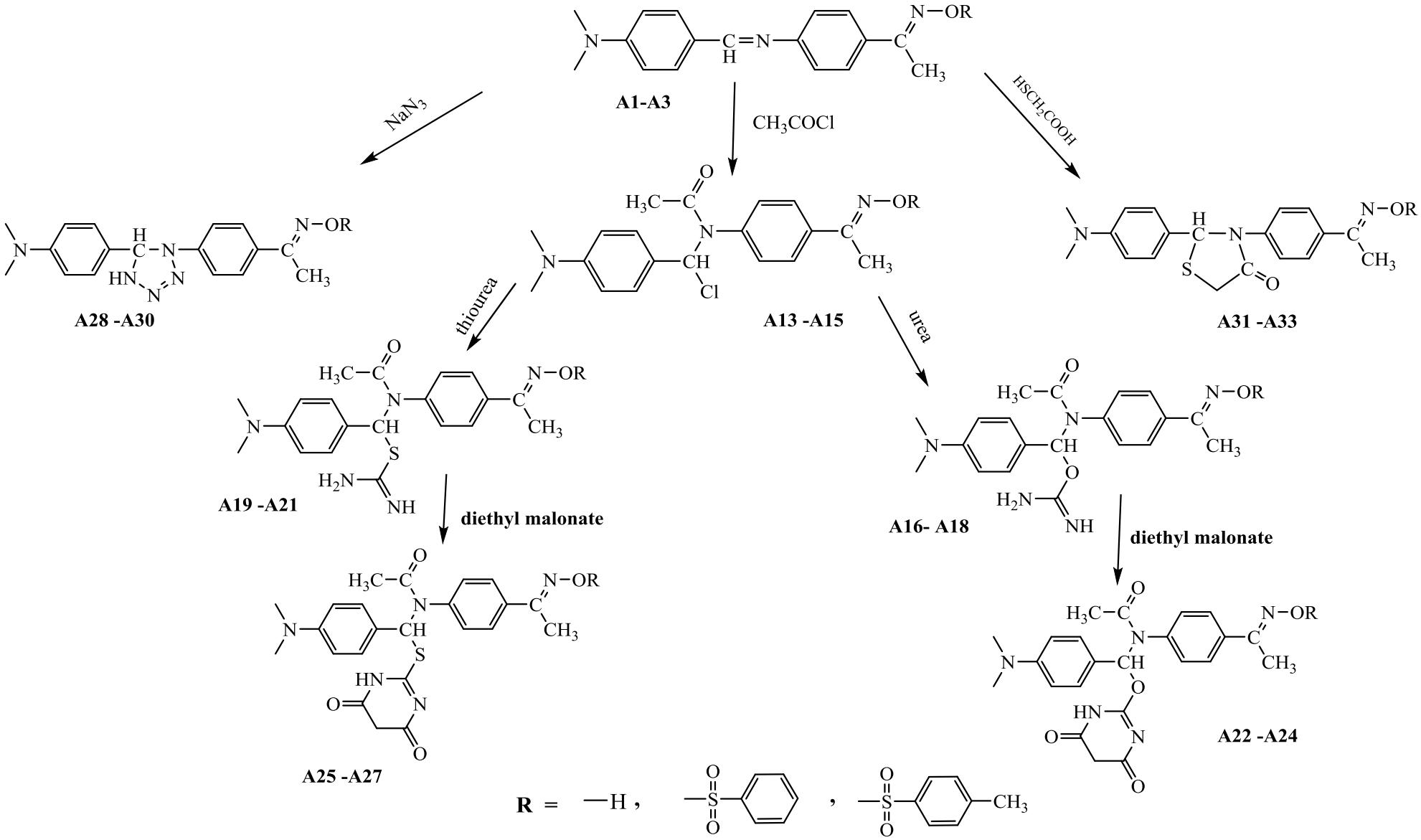
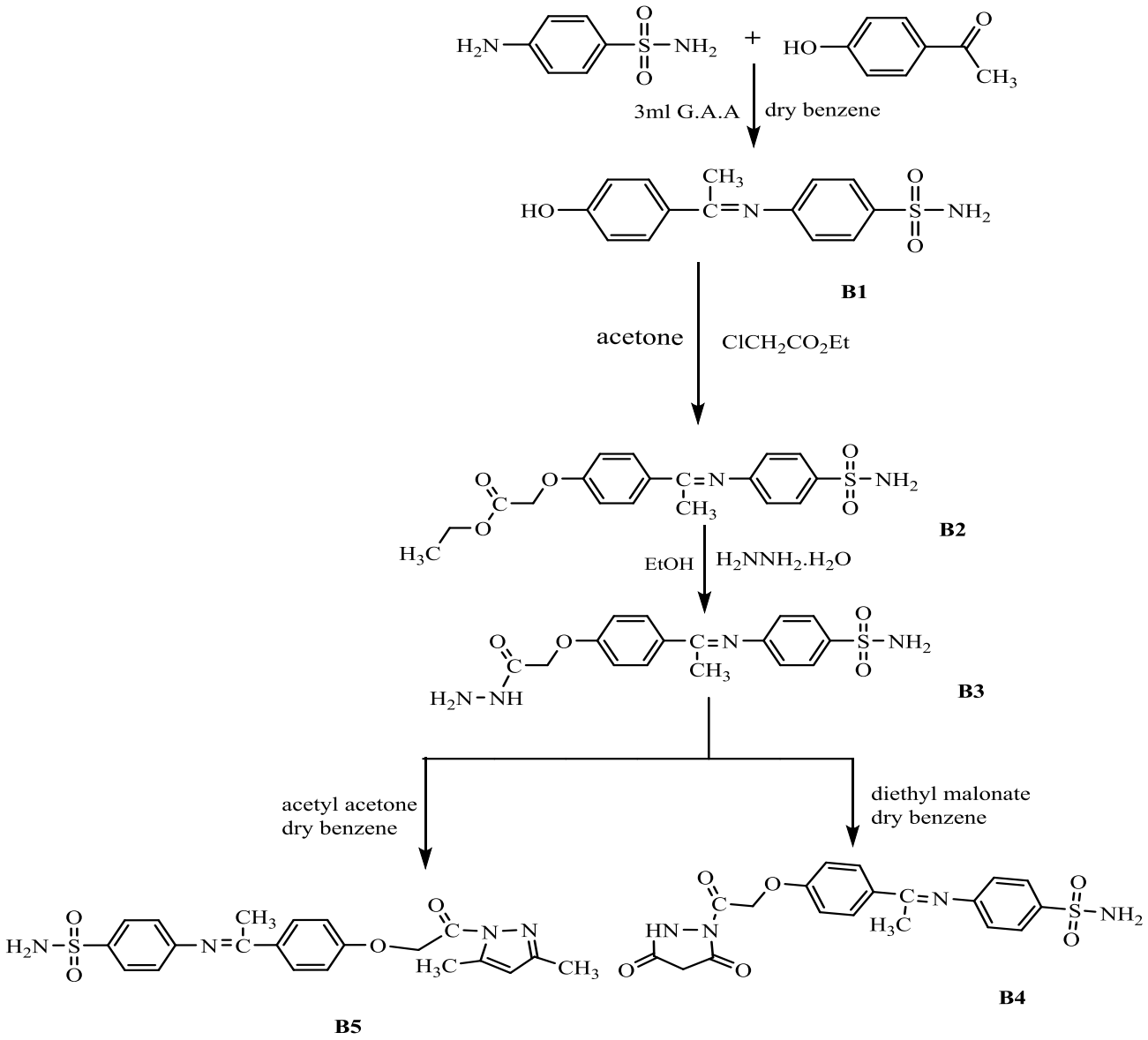

NH2OH.HCl
CH3COONa
EtOH
A
G.A.A
A1
(i)
(ii) (iii)
A1 -A3
pyromellitic dianhydride
benzene
maleic anhydride
benzene
3-nitrophthalic anhydride
benzene
A10 -A12
A7 - A9
A4 -A6
R =
(i) without any addition
(ii) benzenesulfonyl chloride
(iii) 4-methylbenzenesulfonyl chloride

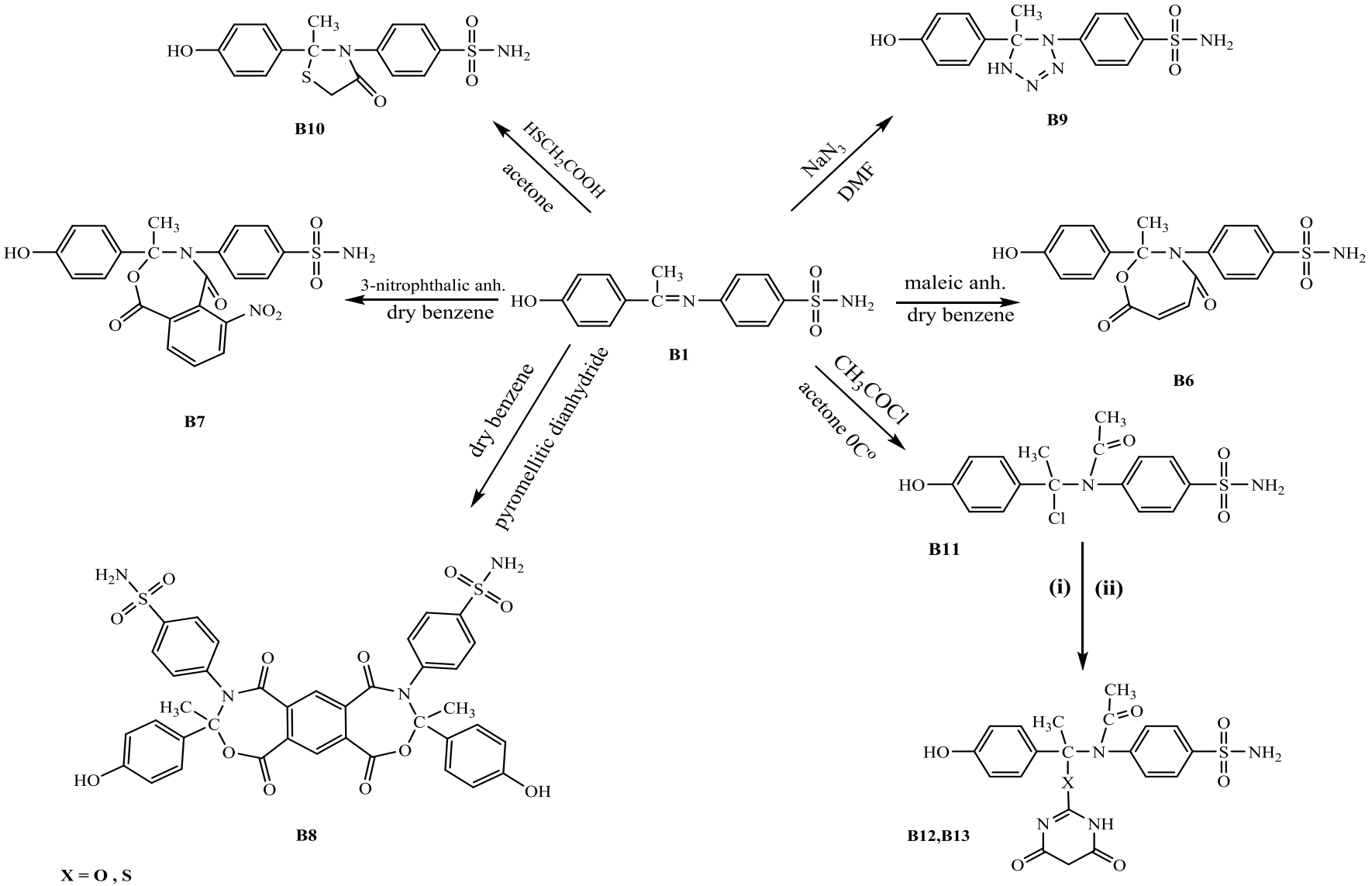
مخطط I


A1-A3
NaN3
CH3COCl
HSCH2COOH
A28 -A30
A13 -A15
A31 -A33
thiourea
urea
A19 -A21
A16- A18
diethyl malonate
diethyl malonate
A25 -A27
A22 -A24
R = —H ,
,

مخطط II


3ml G.A.A
dry benzene
B1
acetone
ClCH2CO2Et
B2
EtOH
H2NNH2.H2O
B3
acetyl acetone
dry benzene
diethyl malonate
dry benzene
B5
B4

مخطط III



X = O , S

(i) urea , thiourea , Na_2CO_3 , 4hrs , (ii) diethyl malonate, 4hrs

مخطط IV

الخلاصة

يتضمن هذا العمل تحضير حلقات غير متجانسة خماسية الى سباعية ابتداء من قواعد شيف المحضرة من الأوكزيم كمادة اولية.

في **الجزء الأول** من هذا العمل كانت الخطوة الأولى هي تحضير الأوكزيم [A] كمادة اولية والتي منها يتم تحضير قواعد شف. تم تحويل 4-أمينواسيتوفينون إلى الأوكزيم عن طريق إذابته في الايثانول المطلق مع كميات مكافئة من $NH_2OH.HCl$ و CH_3COONa. ثم أدخل الأوكزيم في تفاعل تكثيف مع الالديهايد (N,N-dimethylaminobanzaldehyde) ، مع أضافه بضع قطرات من حامض الخليك الثلجي مع التصعيد العكسي بدرجة 78 مئوية ، تم نجاح التفاعل في الحصول على قاعدة شف [A1]. بعد ذلك تم استبدال ذرة هيدروجين الهيدروكسيل في المركب A1 من خلال تفاعلات مع بنزين سلفونيل كلورايد و مثيل بنزين سلفونيل كلورايد باستخدام البيريدين بدرجة صفر مئوية كوسط للتفاعل.

مشتقات قواعد شف الثلاثة المشتقة [A1-A3] ، والتي تفاعلت مع إضافة (Maleic anhydride، 3-nitrophthalic anhydride، pyromellitic dianhydride) لتحضير مشتقات 1,3-oxazepine [A4-A12] **مخطط [I].**

الجزء الثاني: تم تفاعل قواعد شف نفسها [A1-A3] مع كلوريد حامض الخليك باستخدام البنزين كمذيب للحصول على مشتقات N-acyl [A13-A15]. بعد ذلك، تم مفاعلة هذه النواتج مع اليوريا للحصول على المركبات [A16-A18] وثايو يوريا للحصول على المركبات [A19-A21] في المذيب نفسه مع Na_2CO_3 كعامل مساعد واخيرا يضاف ثنائي اثيل المالونيت وتعتبر هذه الخطوة جزء من تفاعلات الغلق الحلقي لتحضير البيرميدين [A22-A27] وكذلك تم تفاعل قواعد شف نفسها مع أزيد الصوديوم و2-ثايو حامض الخليك لإعداد التترازول [A28-A30] والثايازوليدينون [A31-A33] على التوالي. **مخطط [II]**

تضمن **الجزء الثالث** من هذا العمل تحضير قاعدة شف [B1] من تفاعل 4 - أمينوبنزين سلفونيل امايد مع 4-هيدروكسي اسيتوفينون في البنزين مع 3 مل من G.A.A. المركب [B1] ادخل في العديد من التفاعلات ، بما في ذلك تحضير من الإستر [B2] ثم حامض الهايدرازيد المشتق [B3] بواسطة تفاعل الهيدرازين المائي مع الاستر. تم الحصول على مشتقات البيرازوليدين والبيرازول من تفاعل [B3] مع ثنائي إيثيل مالونيت واسيتايل اسيتون **مخطط [III].**

في **الجزء الرابع** ادخلت قاعدة شيف [B1] في تفاعلات التحليق المباشر مع (انهدريد الماليك ، 3- نايتروفثاليك انهيدريد ، بايروملتك ثنائي الانهيدريد) لتحضير حلقة الاوكسازيبين [B6–B8] وكذلك مع أزيد الصوديوم و 2- ثايو حمض الخليك لتحضير الحلقات غير المتجانسة ؛ التترازول [B9] و الثيازوليدينون [B10]. بالإضافة إلى ذلك ، تمت معاملة [B1] أيضًا مع كلوريد حامض الخليك لتحضير مشتقات الاسيتامايد [B11] في الأسيتون كمذيب ودرجة حرارة 0 درجة مئوية ، أضيف الناتج إلى اليوريا وثايو يوريا في الأسيتون وكربونات الصوديوم كعامل مساعد وخلال التفاعل يضاف مباشرة كميات مكافئة من داي إثيل مالونيت لتحضير مشتق البيرميدين [B12، B13]. **مخطط [IV]**

تم التأكيد من المركبات المحضرة عن طريق الخواص الفيزيائية التي تم فحصها بواسطة (كروموتوغرافيا الطبقة الرقيقة ، نقطة الانصهار)في حين تم تحديد التراكيب الكيميائية باستخدام طرق مختلفة من التحليل الطيفي مثل (^{1}HNMR, C.H.N.S، ^{13}CNMR، FT-IR) وتقييم الأنشطة البيولوجية ضد اربعة انواع من البكتريا ***Staphylococcus aureus)*** (***Bacillus Subtilis***, ***E. coli, Pseudomonas aeruginosa***, ونوع واحد من الفطريات ***Candida albicans***.

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تحضير وتشخيص طيفي لمركبات حلقية غير متجانسة جديدة تحتوي على حلقات خماسية الى سباعية مع تقدير فعاليتها البايولوجية

رسالة مقدمة الى

مجلس كلية التربية للعلوم الصرفة أبن الهيثم - جامعة بغداد

وهي جزء من متطلبات نيل درجة ماجستير علوم

في الكيمياء

من قبل

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(بكالوريوس في علوم الكيمياء-2011)

بأشراف

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