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Ministry of Higher Education
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University of Kerbala
College of Science
Department of Chemistry

Synthesis of 1,5-Disubstituted Tetrazoles and Study of Their Antibacterial Activity

A Thesis
Submitted to the Council of the College of Science
University of Kerbala, in Partial Fulfillment of the
Requirements for the Degree of Master of Science in
Chemistry

By

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1436 A.H **2015 A.D**

﴿فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۗ وَلَا تَعْجَلْ بِالْقُرْآنِ مِنْ قَبْلِ أَنْ يُقْضَىٰ إِلَيْكَ وَحْيُهُ ۖ وَقُلْ رَبِّ زِدْنِي عِلْمًا﴾

صَدَقَ اللهُ العَلِيُّ العَظِيم

طه (١١٤)

Dedication

To Almighty Allah

To the Prophet of mercy and the light of the
Worlds…Mohammad

To the infallible Imams

To my family
I present my modest Gift

Acknowledgment

*Initially, I am most grateful to **Allah**, who gave me the strength and guidance throughout my life especially during this work.*

*I wish to express my deepest gratitude and sincere appreciation to my supervisor **Asst. Prof. Dr. Zeid Hassan Abood Al-a`arajy** for his immense guidance, Kind support, Constant encouragement throughout the progress of the dissertation work, I wish him a long life with best health.*

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Finally, I would like to express my thanks to all individuals who helped me in one way or another in the fulfillment of this work.

Nooralhuda

Supervisor Certification

I certify that this thesis is conducted under my supervision at the department of chemistry, College of science, University of Kerbala, as a partial fulfillment of the requirements for the degree of Master in chemistry.

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Report of the Head of Chemistry Department Chairman of Postgraduate Studies Committee

According to the recommendation presented by the Chairman of the Postgraduate Studies Committee, I forward this thesis for discussion.

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Report of Linguistic Evaluator

I certify that the linguistic evaluation of this thesis was carried out by me and it is linguistically sound.

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*We, the examining committee, certify that we have read this thesis "***Synthesis of 1,5-disubstituted tetrazoles and study of their antibacterial activity***"* and *examined the student* (Nooralhuda Mohammed Abdul Hussein) *in its contents and that in our opinion, it is adequate as a thesis for the degree of Master of Science in chemistry.*

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Date: **/ / 2015**

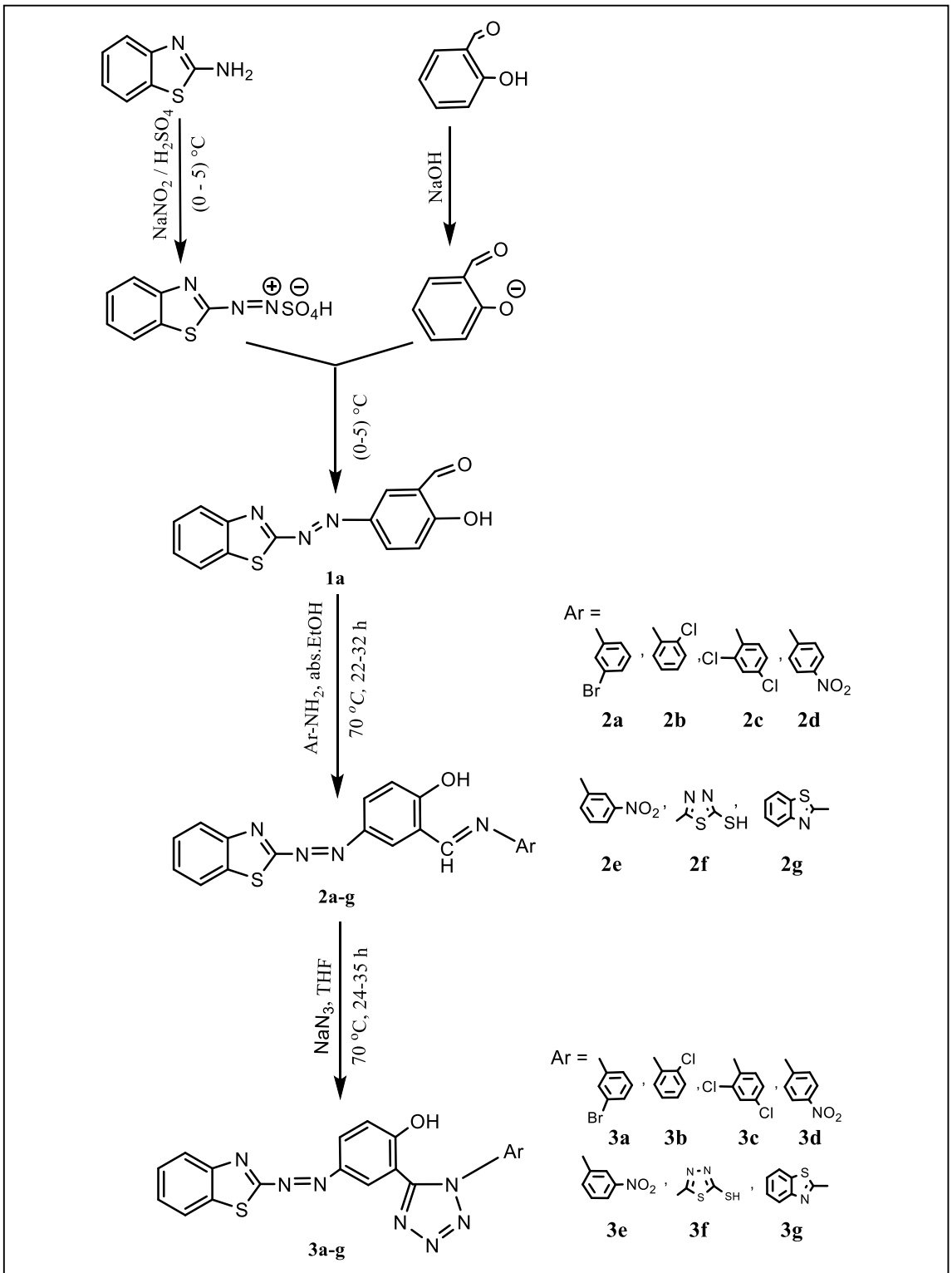
Abstract

In this work two series of new 1,5-disubstituted tetrazole derivatives containing azo group and benzothiazole moiety have been synthesized. At first, the primary aromatic amine 2-aminobenzothiazole was converted to the corresponding azoaldehyde derivative containing benzothiazole moiety **1a** via coupling reaction of its diazonium salt with 2-hydroxy benzaldehyde, which dissolved in sodium hydroxide solution, as coupling reagent. Next, the resulting azoaldehyde **1a** was respectively introduced in acid-catalyzed condensation reactions with the primary aromatic amines (3-bromoaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline, 3-nitro aniline, 2-amino-5-mercapto-1,3,4-thiadiazole and 2-aminobenzothiazole) in absolute ethanol to give seven azoimines containing benzothiazole moiety **2a-g** respectively. Later, the synthesized azoimines **2a-g** were respectively introduced in [3+2] cycloaddition reactions with sodium azide in tetrahydrofuran to obtain seven new 1,5-disubstituted tetrazole derivatives **3a-g**.

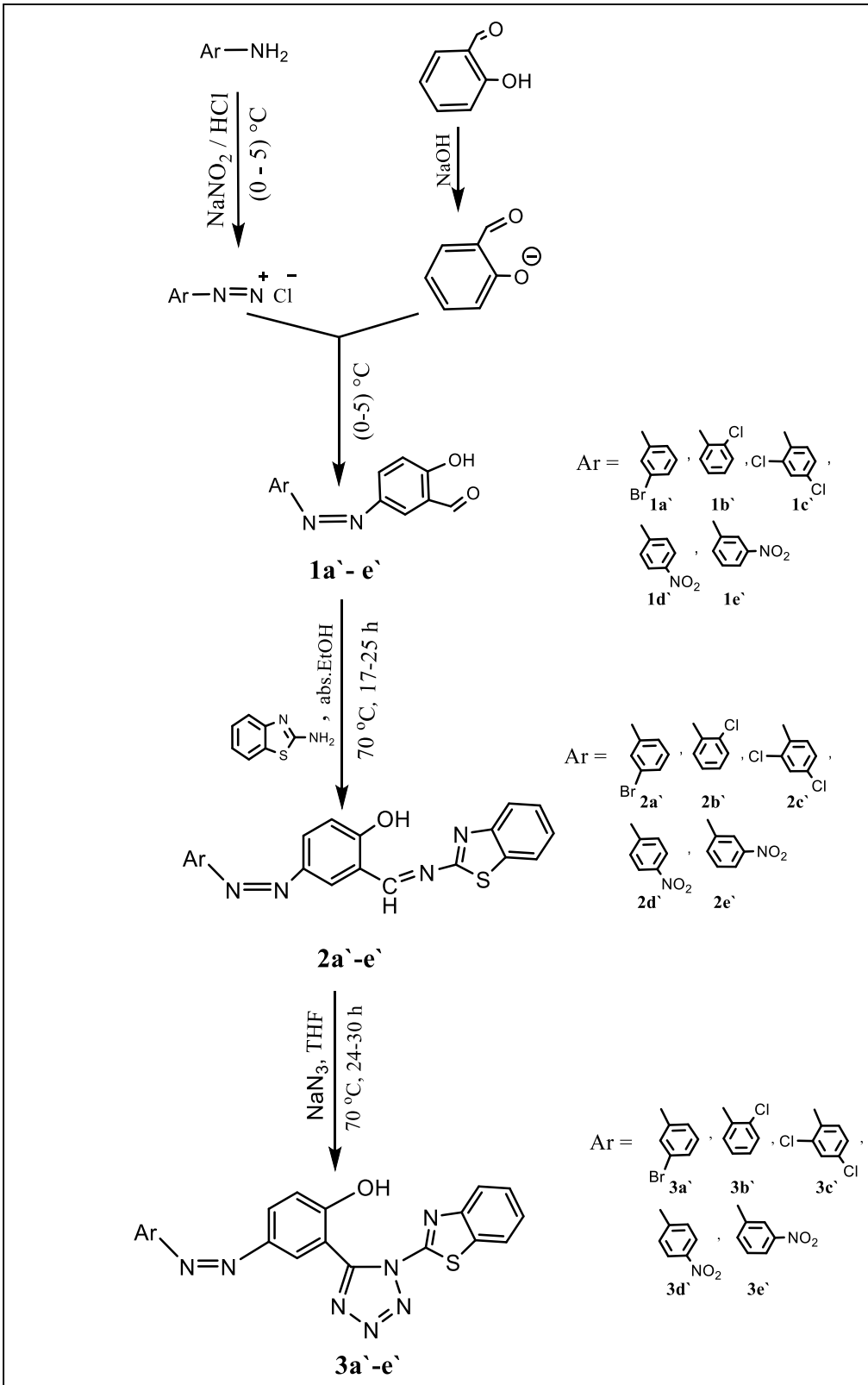
Then, azoaldehyde derivatives **1a`-e`** were prepared through coupling reactions of the diazonium salts for the primary aromatic amines (3-bromo aniline, 2-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline and 3-nitro aniline) with 2-hydroxybenzaldehyde, which dissolved in sodium hydroxide solution, as coupling reagent. Next, the resulting azoaldehydes **1a`-e`** were introduced in acid-catalyzed condensation reactions with 2-aminobenzothiazole in absolute ethanol to obtain five azoimines containing benzothiazole moiety **2a`-e`** respectively. Later, treatment of the resulting azoimines **2a`-e`** with sodium azide under the same cycloaddition [3+2] reaction conditions afforded five new 1,5-disubstituted tetrazole derivatives **3a`-e`** respectively.

The structures of all new synthesized tetrazoles have been confirmed by the spectroscopic means including FT-IR, ^{1}H NMR and Mass. All new synthesized tetrazoles have been tested for their antibacterial activity

against two types of bacteria, ***Staphylococcus aureous*** (Gram-positive) and ***Escherichia coli*** (Gram-negative). The results indicated that all synthesized tetrazoles except compound **3d** showed medium-high activity against Gram-positive bacteria. On the other hand, all tetrazoles showed no effect against Gram-negative bacteria.



Scheme (I)


Ar—NH2
NaNO2 / HCl
(0 - 5) °C
NaOH
Ar—N=N+ Cl−
(0-5) °C
1a`- e`
Ar =
1a`
1b`
1c`
1d`
1e`
, abs.EtOH
70 °C, 17-25 h
2a`-e`
2a`
2b`
2c`
2d`
2e`
NaN3, THF
70 °C, 24-30 h
3a`-e`
3a`
3b`
3c`
3d`
3e`

Scheme (II)

Table of contents

List of tables

List of figures

Abbreviations

Symbol	Definition
Abs.	Absolute
AcOH	Acetic acid
APAZA	5-aminosalicylic acid linked to one molecule of 4-aminophenyl acetic acid by an azo bond
aq	aqua
br	Broad
Cat.	Catalyst
d	doublet
DBUF	1,8-diazabicyclo [5.4.0]undec-7-ene based fluorinated
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPTB	A mixture of dipropylene glycol tert-butyl ethers and di-tert-butyl ethers
eq	equals
Et_2O	Diethyl ether
$Et_3N.HCl$	Triethylammonium chloride
EtOAc	Ethyl acetate
EtOH	Ethanol
FAAH	Fatty acid amide hydrolase
FT-IR	Fourier Transform Infrared
GABA	γ-aminobutyric acid
^1H NMR	Proton Nuclear Magnetic Resonance
h	Hour
HIV	Human immunodeficiency virus
ILs	Ionic Liquids
LLC	Lewis lung carcinoma
m	Multiplet
m/ z	Mass/charge

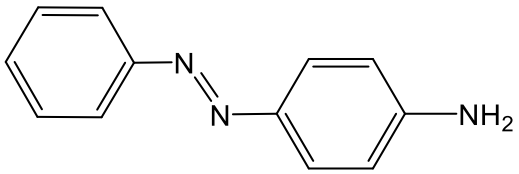
MeCN	Acetonitrile
MeOH	Methanol
min.	Minute
MW	Microwave
MZNSS	Mesoporous ZnS nanospheres
NBS	*N*-bromosuccinimide
o.o.p.	Out of plane
P.t.	Proton transfers
ppm	part per million
PTSA	*p*-toluenesulfonic acid
r.t	Room temperature
Rec.	Recrystallization
ref	Reflux
R_f	Retention factor
s	Singlet
Str.vib.(υ)	Stretching vibration
t	triplet
TBAB	Tetrabutylammonium bromide
TBAF.xH_2O	Tetrabutyl ammonium fluoride hydrate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
$TMSN_3$	Trimethylsilyl azide
W	Watt
$Yb(OTf)_3$	Ytterbium Triflate Hydrate
$Zn(OTf)_2$	Zn triflates
δ	Bending in IR and chemical shift in NMR

Chapter One

Introduction

1.1. Azo compounds

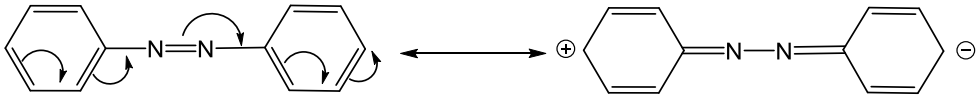
Azo compounds illustrate the largest class of compounds amongst all known families of dyes, and characterized by the presence of the azo group (–N=N–) in their structure, conjugated with two, distinct or identical, mono- or polycyclic aromatic systems. In 1858 Griss[1] represents that the treating of an aromatic amine with nitrous acid resulted in an unstable salt (diazonium salt) which developed the azo coupling reaction and obtained first azo dye - Aniline Yellow[2] (1) as shown in figure (1-1).



(1)

Fig. (1-1): Structure of azo dye - aniline yellow **(1)**

Usually, although not exclusively azo dyes are conjugated with two, distinct or identical, mono- or polycyclic aromatic systems and which are distinguished greatly use and proliferation because of their high stability, which comes back to the phenomenon of resonance as shown in azo benzene (2).[2,3] Scheme (1-1).

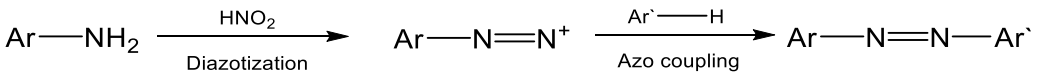


(2)

Scheme (1-1)

1.1.1. Synthesis of azo compounds

However, almost without exception, azo compounds are made on an industrial scale by the same reaction sequence in two phases: diazotization and azo coupling[3], as illustrated in scheme (1-2).



Scheme (1-2)

In diazotization, primary aromatic amines reacted with nitrous acid to form aryldiazonium salts which, unlike their aliphatic counterparts, are stable at 0°C and can be kept in solution for short periods without decomposition. Diazotization is the conversion of a primary amine to a diazonium ion[4].

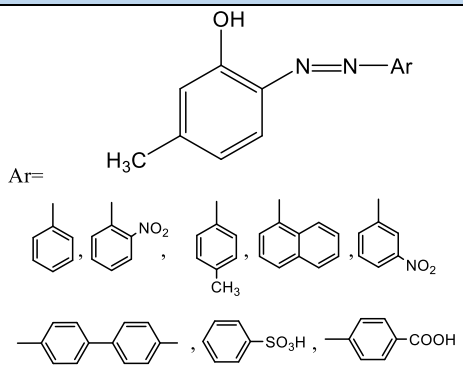
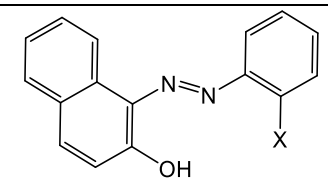
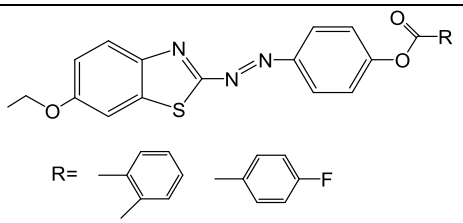
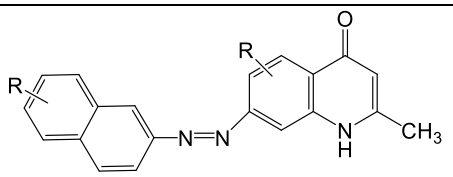
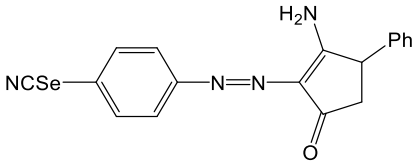
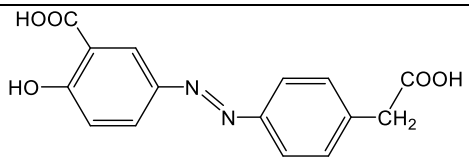
The comparatively unstable diazonium salt thus formed is reacted with a coupling component, which may be a phenol, an aromatic amine or a β-ketoacid derivative, to form the azo compounds. This method was well-known as azo coupling[2].

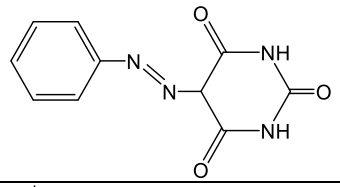
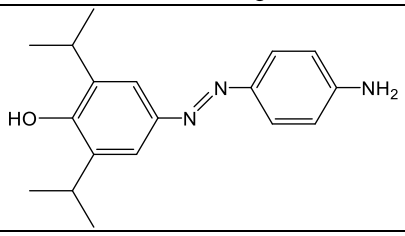
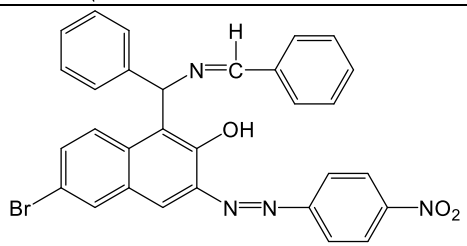
There are other methods for the synthesis of azo compounds described in literature such as: coupling of primary arylamines with nitroso compounds (Mills reaction)[5], rearrangement of an aromatic azoxy compounds in acidic medium (Wallach reaction)[6,7], reduction of azoxy benzenes[8,9], reductive coupling of aromatic nitro derivatives[10,11], oxidation of primary aromatic amines[12], oxidation of hydrazo derivatives using various oxidizing agents[13-20].

1.1.2. The biological activity of azo compounds

Azo compounds have been studied more than any other class of dyes due to their popular application, as biological activities[21], pharmaceutical[22], cosmetic[23] and food[24]. Table (1-1) shows biological activities for some azo derivatives.

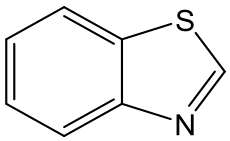
Table (1-1): The biological activities for some azo compounds

Com. no.	Structure	Biological activity	Refe.
(3)		Antimicrobial constituents against four microorganisms viz., *Salmonella typhi*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.	25
(4)	 X = -H, -OH, $-OCH_3$, -Cl, -COOH, $-NO_2$	Antibacterial constituents against six strains of bacteria *Bacillus cereus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter cloacae*, *Enterococcus faecalis* and one species of fungi against *Candida, albicans*.	26
(5)		The synthesized compounds, have antioxidant activity.	27
(6)	 R= H, 2-OH, 3-OH, 4-OH, $2-NO_2$,$3-NO_2$, $3-NO_2$, 2-Cl ,3-Cl, $3-OCH_3$, $4-OCH_3$, $3,4,5-(OCH_3)$, $-N(CH_3)_2$	These compounds have antibacterial activity against *E. coli* and *S. aureus* and antifungal activity against *C. albicans* and *A. niger* Showing good result.	28
(7)		Anti-tumor.	29
(8)		Using resulting prodrug, APAZA ™ (Biocon Ltd) is a potent inhibitor of toxin A-induced colonic inflammation in rat model of experimental colitis.	30

Com. no.	Structure	Biological activity	Refe.
(9)		Antibacterial activity against *Bacillus subtilis* and antifungal activity against *Aspergillus Niger*.	31
(10)		The azopropofols, in its dark-adapted form, has an effect on $GABA_A$ receptors.	32
(11)		Antibacterial activities against nine different bacterial strains *(E. coil (mixed), Salmonella sp., B. subtilis, P.vulageris, Pseudomonas sp., S.aureus, E. coil (+ve strai,), Rhodococci* and *B. stearothermopelus).*	33

1.2. Benzothiazoles

Benzothiazole (12) is fused ring system made of benzene ring fused with thiazole ring. Thiazole ring is a five-membered ring consisting of one nitrogen and one Sulphur atom in the ring. Figure (1-2).

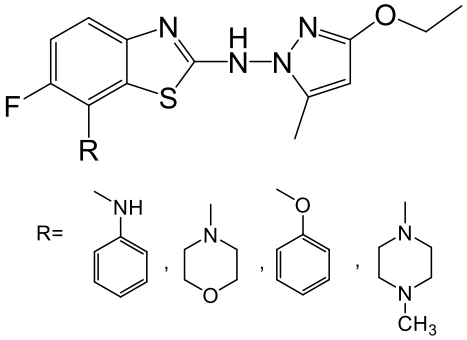
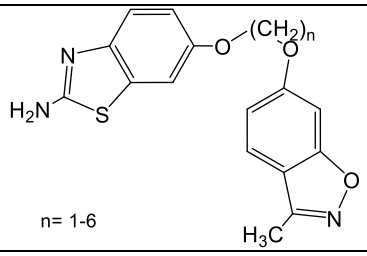
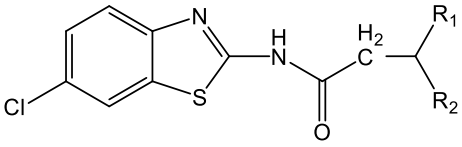
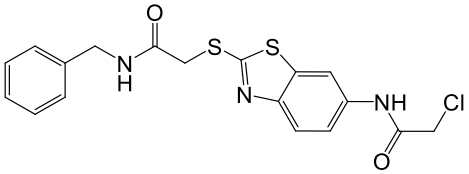
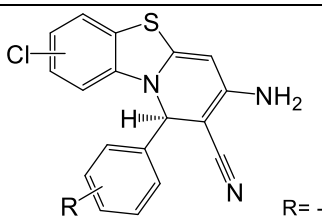
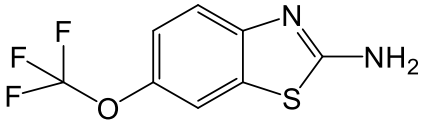


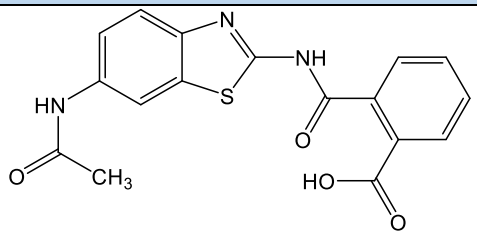
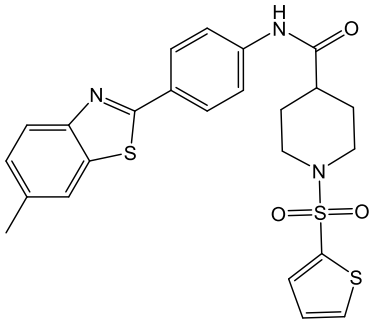
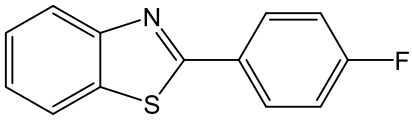
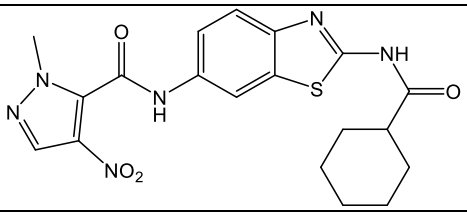
(12)

Fig. (1-2): Structure of benzothiazole **(12)**

Benzothiazole derivatives have been studied and found to have various chemical reactivity, biological and pharmacological activities such as anti-bacterial[34] and anti-fungal[35]. Benzothiazole nucleus containing molecules are also reported as anti-diabetic[36], anti-tumor[37] and anti-inflammatory[38]. Table (1-2) shows biological activities for some benzothiazole derivatives.

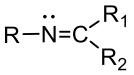
Table (1-2): The biological activities for some benzothiazole derivatives

Com. no.	Structure	Biological activity	Refe.
(13)		The synthesized compounds give anti-bacterial activities against *B.subtilis* , *S.aureus* and *E.coli* and for anti-fungal activities against *Candida albicans.*	34
(14)		Anti-bacterial activity and anti-fungal activity.	35
(15)	 R_1, R_2 = dimethylamino, 4- fluoroanilino, diethylamino, 3-chloroanilino, diethanolamino, 4-pyridino, morpholino, 2-pyridino, piperidino, 4-sulfanilido	Antidiabetic activity.	36
(16)		Antitumor activity.	37
(17)	 R= -Cl, 3,4,5-OCH_3	Anti-inflammatory activity.	38
(18)		Anticonvulsant, anxiolytic effects and neuroprotective.	39

Com. no.	Structure	Biological activity	Refe.
(19)		Anti- inflammatory activity.	40
(20)		Anti-inflammatory drugs, Fatty acid amide hydrolase (FAAH) inhibitor.	41
(21)		Anti-Alzheimer's activity.	42
(22)		Antitumor activity against an LLC xenograft model.	43

1.3. Schiff bases

Schiff bases have been known since 1864. The reaction is named in relation to scientist Schiff's who prepared these compounds from simple condensation between aldehydes and ketones with primary amines[44].

The general formula of Schiff bases is  nitrogen analogs of aldehydes and ketones called Schiff bases, azomethines or imines but imine is the preferred name[45]. Schiff bases are characterized by (C=N) group (imine) which are important compounds in the medical and pharmaceutical fields[46] . If aldehydes and ketones react with primary amines, this leads to the formation of imines and with secondary amines to form enamines[47]. Figure (1-3).

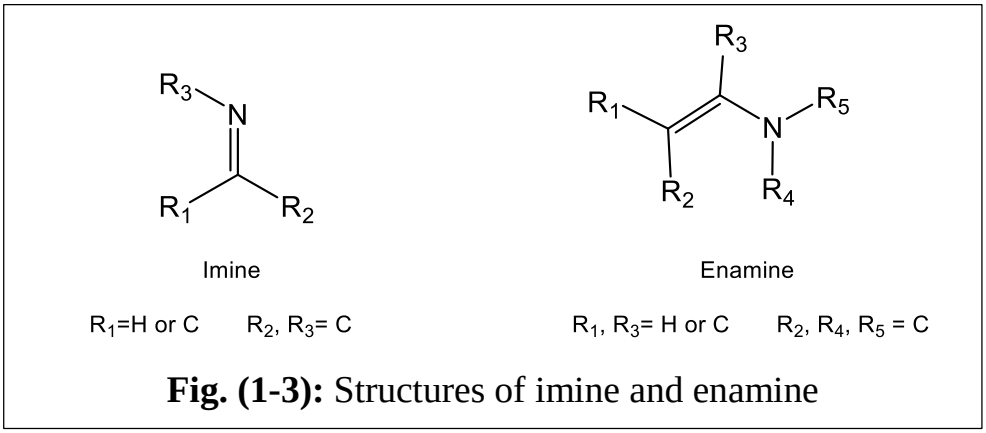
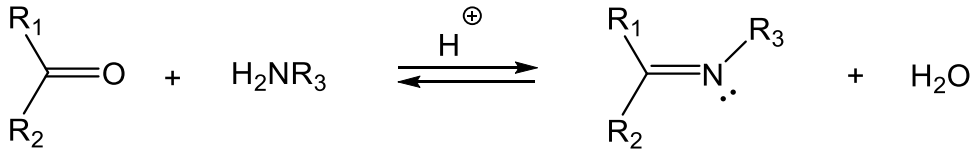


Fig. (1-3): Structures of imine and enamine

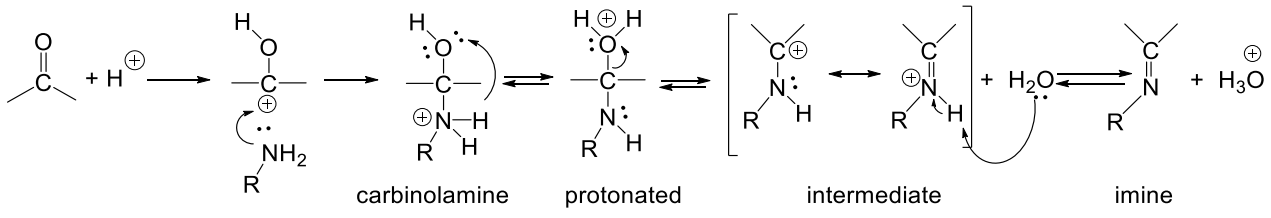
1.3.1. Synthesis of Schiff bases

These compounds can be prepared via condensation of ketones or aldehydes with primary amines. The reaction is usually led forward by elimination water[48] because of the equilibrium constants are undesirable. A general equation for the formation of an imine was shown in scheme (1-3).



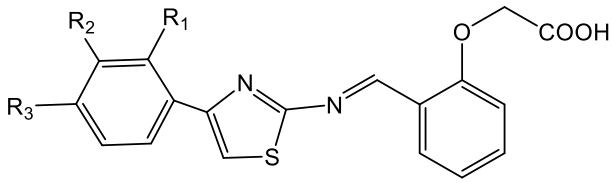
Scheme (1-3)

Imine formation is acid catalyzed, generally takes place fastest at range of pH = 4-5 and is slow down at very high or very low values of pH. The important step is when the protonated aminoalcohol losing a molecule of water leads to form an iminium ion as intermediate. The acid converts a poor leaving group (-OH group) to a good leaving group ($-\overset{\oplus}{O}H_2$ group) via protonating the alcohol group[47,48].



Scheme (1-4)

Siddiqui[49] et al. prepared five novel Schiff bases (23) from *o*-formylphenoxy acetic acid and a series of aminothiazoles. Figure (1-4).

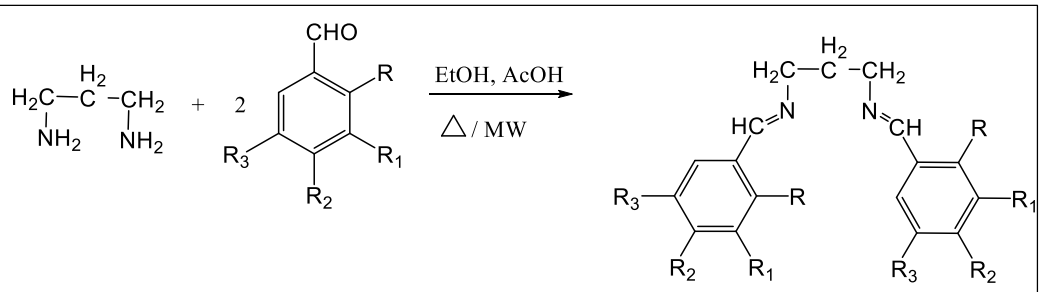


R_1= -Br, -H, -F
R_2= -H, -F
R_3= -H, -Br, -F

(23)

Fig. (1-4): Structures of Schiff bases **(23)**

Shinde[50] et al. introduced 1,3-diamine propane in condensation with different halogeno substituted benzaldehydes under microwave irradiation affording novel series of bis-imines (24). Scheme (1-5).

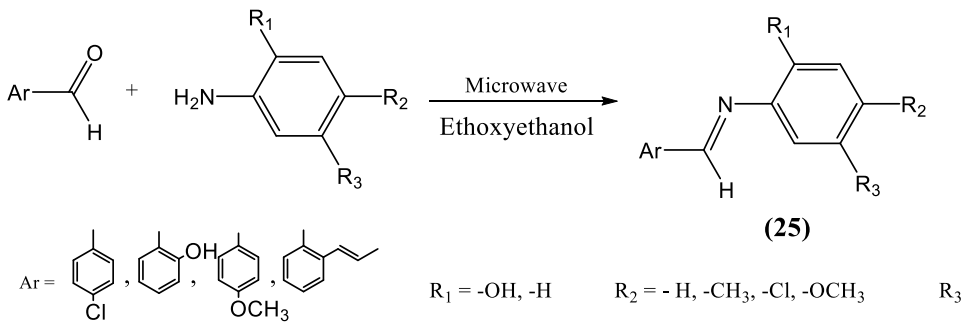


R = -H , - OH
R_2 = -H , - I , - OH , - OMe , -Cl , - F
R_1 =- H , - Br , - OEt , - OMe , - Cl, -F
R_3 = -H , -Br , -Cl , -I , -OMe

(24)

Scheme (1-5)

Bekdemir and Efil[51] synthesized some imine derivatives (25) via reaction of aromatic aldehydes and aromatic amines (in 1:1 molar ratio) in presence of ethoxyethanol as a wetting reagent under solvent-free conditions using microwave heating. Scheme (1-6).

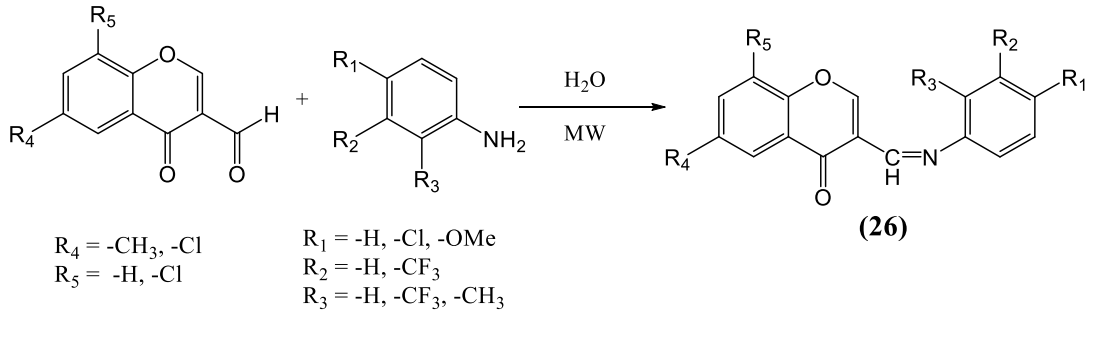


(25)

R_1 = -OH, -H R_2 = - H, -CH_3, -Cl, -OCH_3 R_3 = -H, -Cl

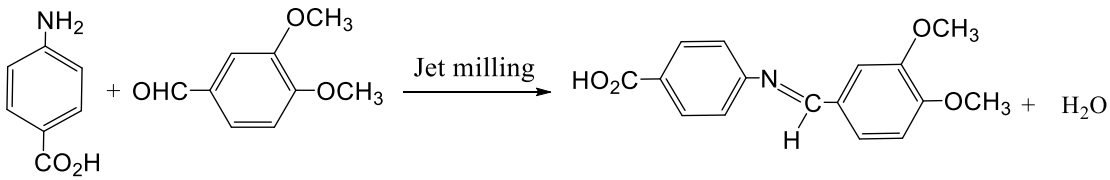
Scheme (1-6)

Mhaske[52] et al. reported synthesis of Schiff bases (26) derived from 3-formyl chromones and various aromatic anilines under microwave irradiation in water. Scheme (1-7).



Scheme (1-7)

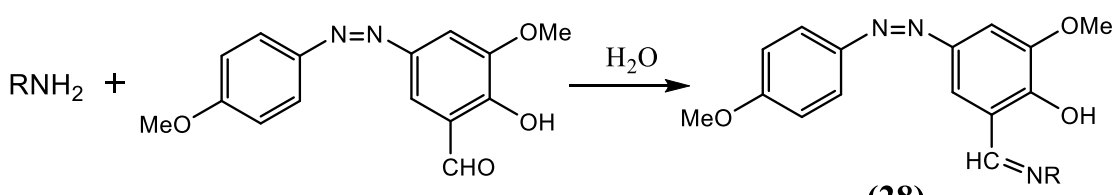
Cai[53] et al. prepared Schiff base (27) derived from 3,4-dimethoxybenz aldehyde and *p*-aminobenzoic acid by supersonic speed gas impacting method. Scheme (1-8).



(27)

Scheme (1-8)

Azoimines (28) were synthesized in high yields using green method in free-solvent or using aqueous slurry[54] scheme (1-9).



(28)

R= 4-MeOC$_6$H$_4$- ,3-MeC$_6$H$_4$-, 4-MeC$_6$H$_4$-, 3-MeOC$_6$H$_4$-

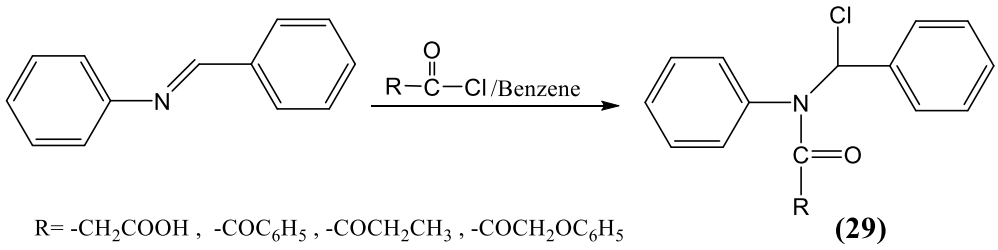
Scheme (1-9)

1.3.2. Reactions of imines

Imines are very important class used as intermediates in organic synthesis for formation of heterocyclic derivatives. In organic synthesis, there are different types of reactions that have been found by Schiff bases, such as:

1.3.2.1. Addition reactions

The C=N group of imines may react with nucleophiles at the carbon atom, or they may react at the nitrogen atom with electrophiles, including proton. Aromatic Schiff's bases were treated with α-chloroacetic acid or acid chlorides to give the addition products[55] (29) as shown in scheme (1-10).



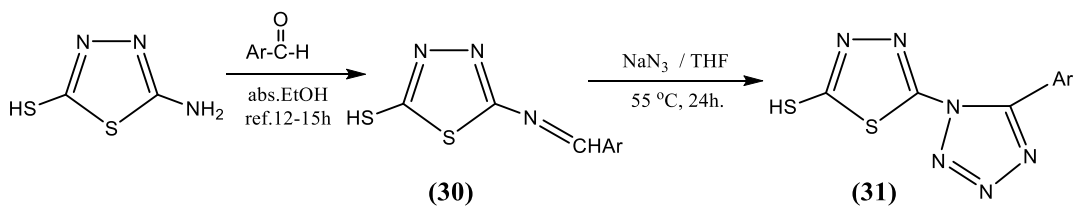
R= -CH_2COOH , -COC_6H_5 , -$COCH_2CH_3$, -$COCH_2OC_6H_5$ **(29)**

Scheme (1-10)

1.3.2.2. Cycloaddition reactions

Imines could be introduced in cycloaddition reactions with various reagents to yield three[56,57], four[58-60], five[61], six[62] and seven[63]-membered rings.

Salih[64] prepared some of tetrazole derivatives (31) via using [2+3] cycloaddition reaction of imines (30) with sodium azide in tetrahydrofuran. Scheme (1-11).

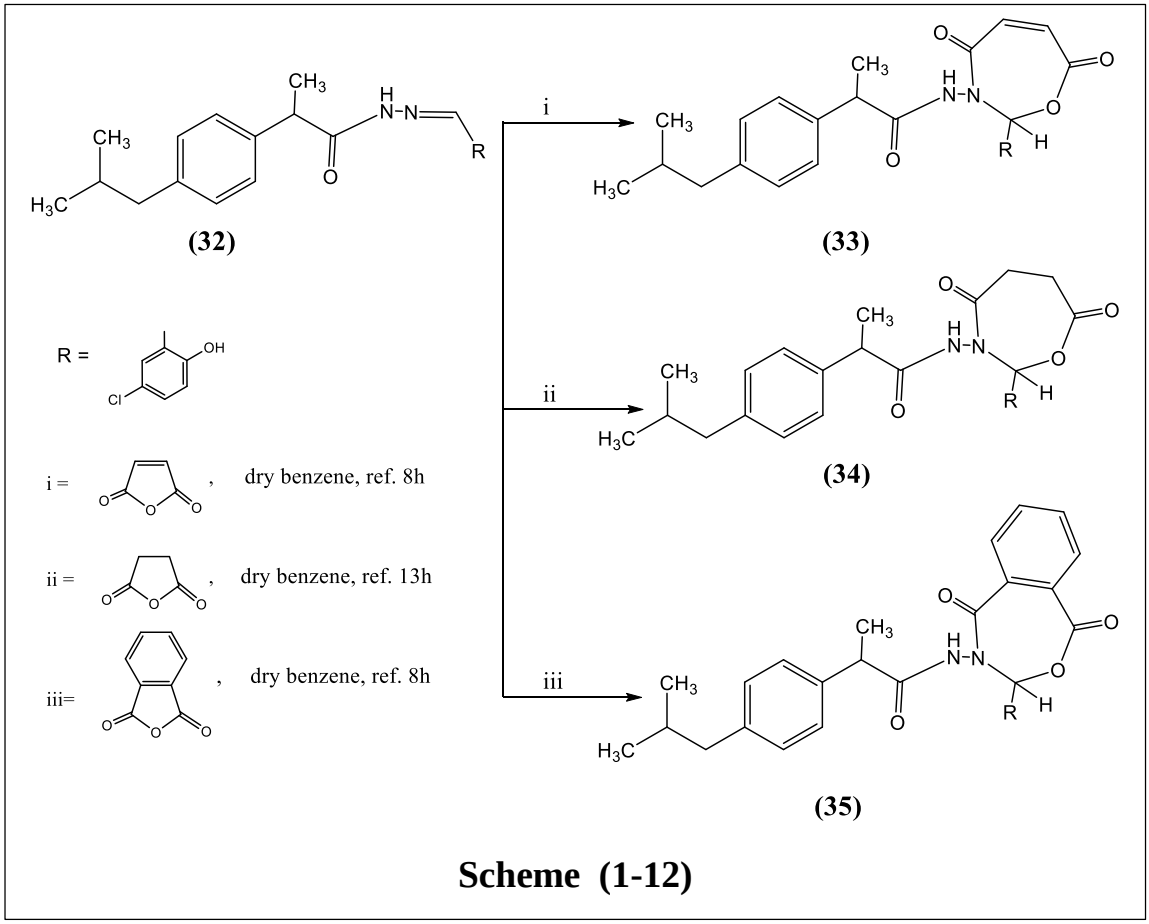


(30) **(31)**

Ar = C_6H_5-, *p*-$CH_3C_6H_4$-, *p*-$CH_3OC_6H_4$-, *p*-$NO_2C_6H_4$-, *m*-$CH_3C_6H_4$-

Scheme (1-11)

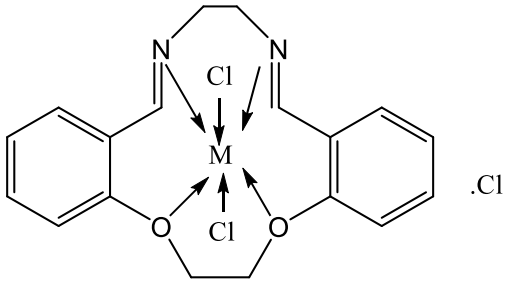
A new 1,3 oxazepine derivatives (33-35) have been prepared through using [5+2] cycloaddition reaction of imine derivative (32) with maleic, succinic and phthalic anhydrides respectively[65]. Scheme (1-12).



Scheme (1-12)

1.3.2.3. Formation of complexes

Khalill[66] et al. synthesized a novel Schiff base metal complexes (36) and used them in determining iron in different kinds of natural water as shown in figure (1-5).



(36)

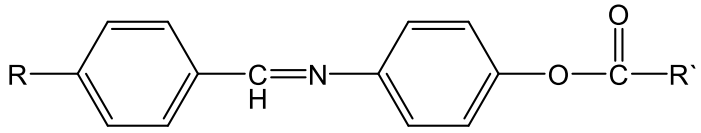
M = Ni(II), Co(II), Cu(II) , Zn(II), Cr(III) , Fe(III)

Fig. (1-5): Structures of Schiff base metal complexes **(36)**

1.3.3. The biological activity of Schiff bases

Schiff bases are very important compounds in pharmaceutics and medicines, its analogues have shown a large group of biological activities such as anti-inflammatory[67], antifungal and antibacterial activity[68].

Noureen[69] et al. reported the synthesis of some Schiff base esters (37) as promising new antitumor. Figure (1-6).



R= -H, $-OCH_3$, - Cl, $-CH_3$ **(37)**

R`= $-(CH_2)_{10}CH_3$, $-(CH_2)_{12}CH_3$

Fig. (1-6): Structures of Schiff base esters **(37)**

1.4. Tetrazoles

The first tetrazole was prepared by the Swedish chemist Bladin[70] in 1885. Tetrazoles are a representative class of poly-aza-heterocyclic compounds, which consists of a 5-membered ring of one carbon and four nitrogen atoms[71]. They are unknown in nature. Tetrazoles are divided into three categories depending on the number of the substituents: **(i)** parent tetrazole (simplest tetrazole), **(ii)** monosubstituted tetrazoles (1- or 2- or 5-substituted) and **(iii)** disubstituted tetrazoles (1,5- or 2,5-disubstituted)[72] . Figure (1-7).

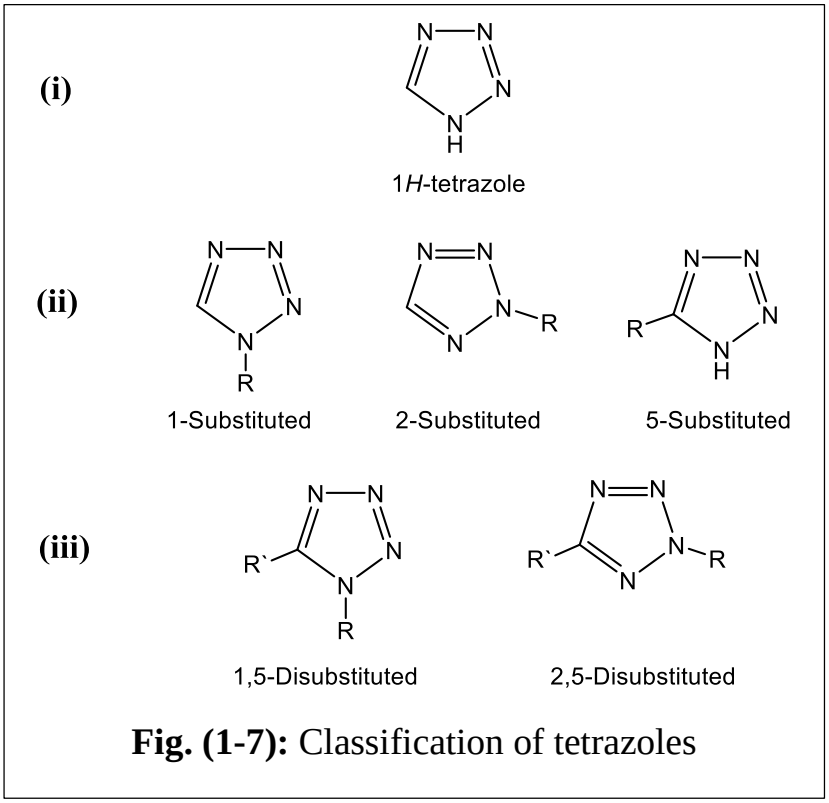


Fig. (1-7): Classification of tetrazoles

Tetrazoles are a class of heterocycles with a wide range of applications which are currently receiving great attention, therefore the literature on tetrazole is expanding rapidly. This functional group has a role in coordination chemistry as a ligand[73] as well as in various materials sciences applications including nanomaterials[74] and specialty explosives[75]. Extensive work was also carried out in the field of medicinal chemistry[76]. Neutral N*H*-tetrazoles with no functional substituents at the carbon atom of the hetero ring can exist in 1*H*- and 2*H*-tautomeric forms[77]. Figure (1-8).

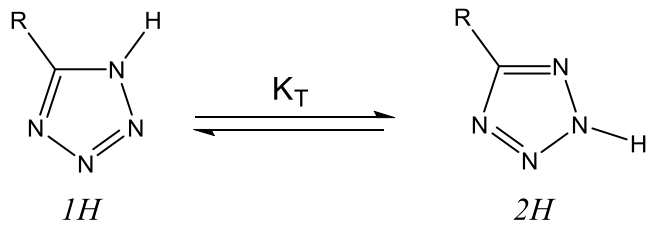
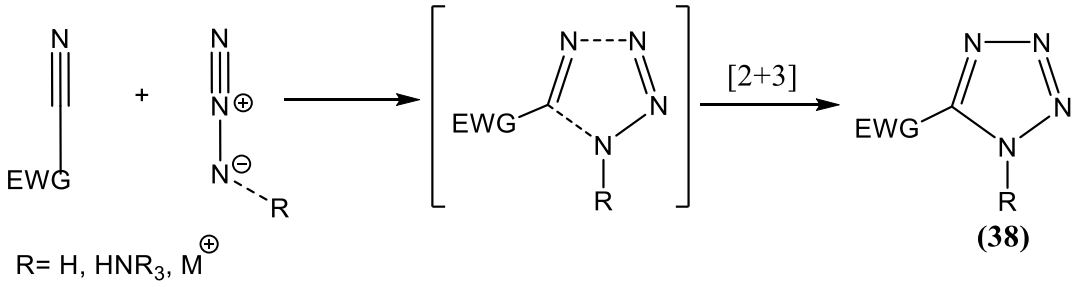


Fig. (1-8): 1*H*- and 2*H*-tautomeric forms of neutral N*H*-tetrazoles with no functional substituents at the carbon atom

Tetrazole derivatives also strangest stable although tetrazole itself (m.p 158 °C, decomposes above180 °C) is classified as an explosive, at least for shipping. The ring systems of tetrazoles are very resistant to reduction[78].

1.4.1. Synthesis of tetrazoles

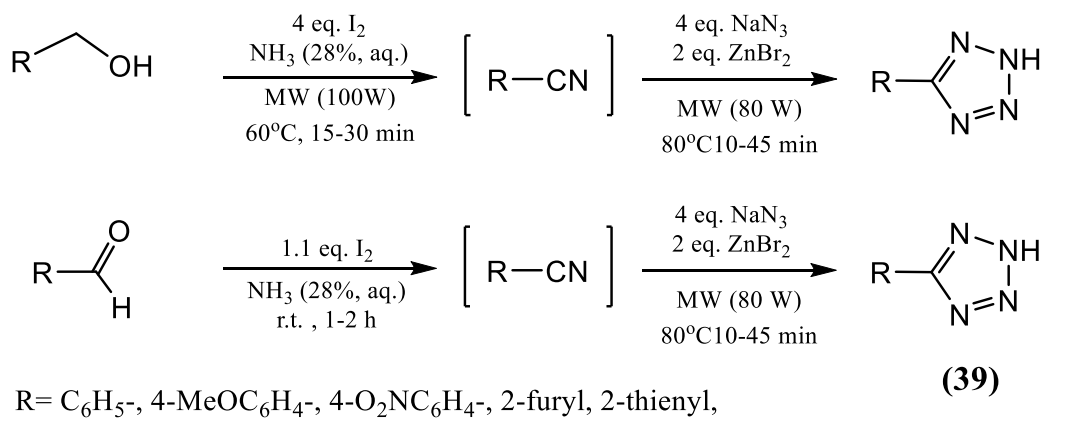
Tetrazoles can be synthesized by a number of methods and the synthesis of tetrazoles by the Huisgen[79] 1,3-dipolar cycloaddition reaction between nitriles and azides (azide ion or hydrazoic acid) is a well-known process. Scheme (1-13).



Scheme (1-13)

A [2+3] cycloaddition is the most likely pathway for the bimolecular addition of non-ionic azides to nitriles. In the concerted cycloaddition , two different isomers of tetrazole, the 1,5- and the 2,5-disubstituted, can be formed. Generally the TS1 is the preferred transition state by using electron-withdrawing substituents R[80].

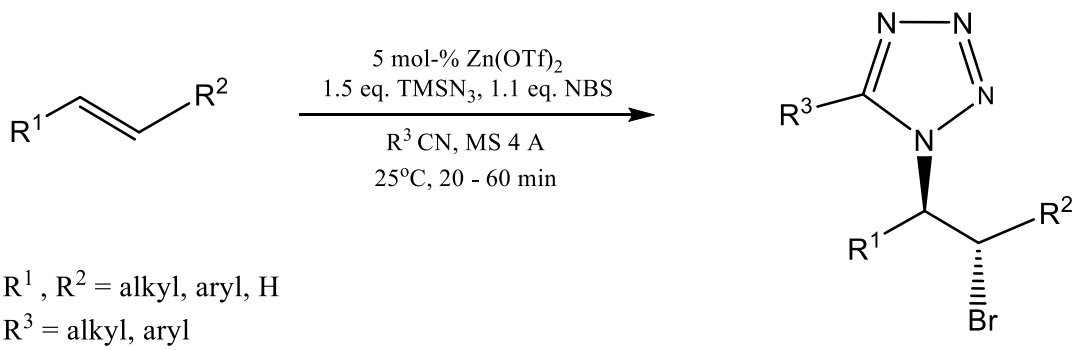
Shie and Fang[81] treating a series of aldehydes and primary alcohols using microwave irradiation with iodine in aqueous media which leads to produce the corresponding tetrazoles (39) at excellent yield. Scheme (1-14).



R= C_6H_5-, 4-$MeOC_6H_4$-, 4-$O_2NC_6H_4$-, 2-furyl, 2-thienyl,

Scheme (1-14)

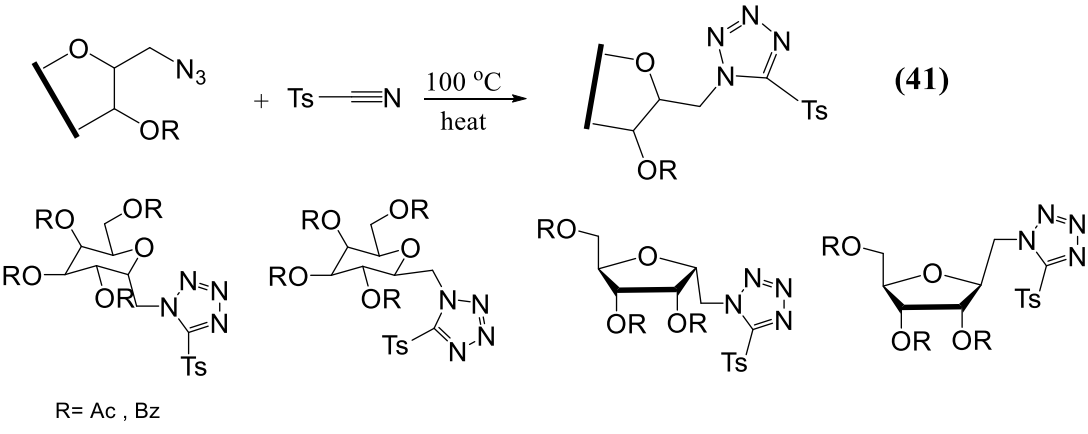
Hajra[82] et al. synthesized of 1,5-disubstituted tetrazoles (40) with metal triflate catalyzed reactions of NBS, $TMSN_3$, alkenes and nitriles includes an additional α-bromo functionality of the N1-alkyl substituent. Scheme (1-15).



(40)

Scheme (1-15)

Aldhoun[83] et al. have developed an efficient and a click way for the formation of 1-glycosylmethyl-5-tosyl tetrazoles (41) from the reaction of benzylated or acetylated glycosylmethyl azides (azidomethyl glycosides) with TsCN at 100 °C. Scheme (1-16).

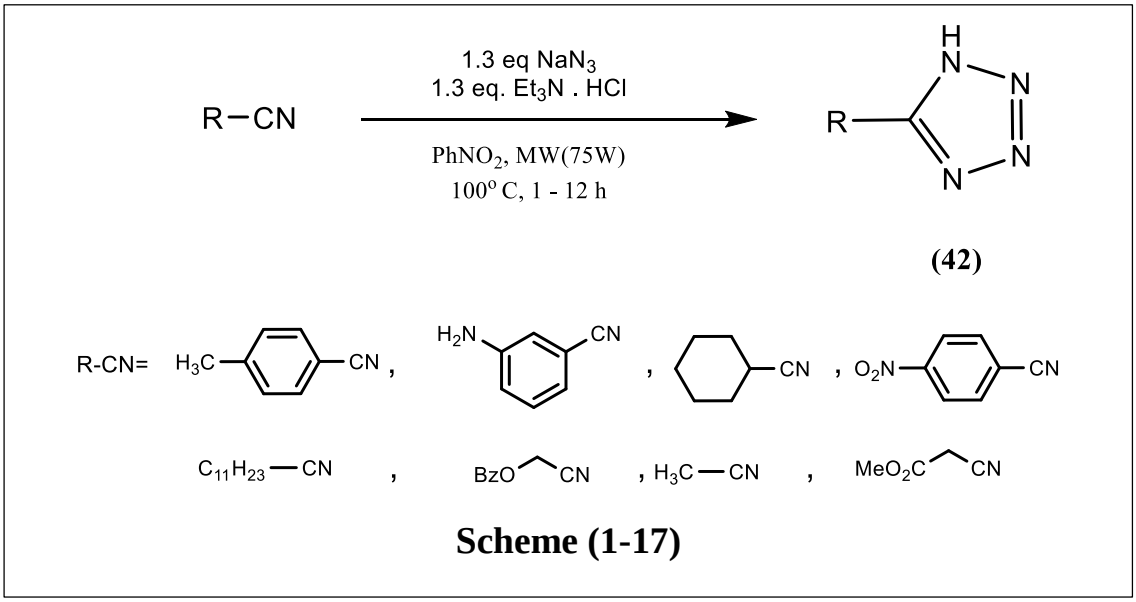


(41)

Scheme (1-16)

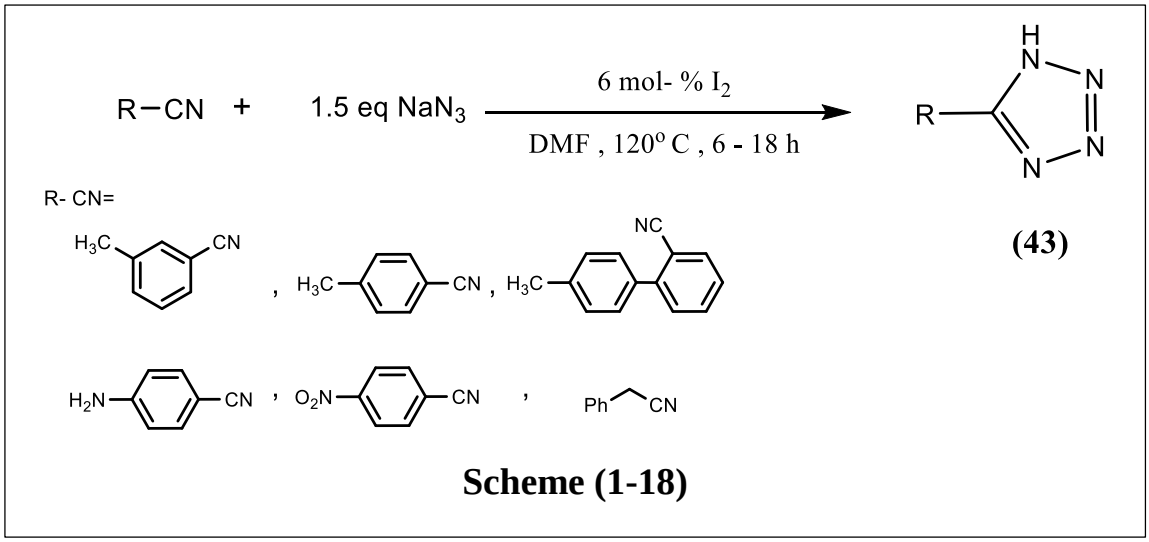
By treating triethylammonium chloride, nitriles and sodium azide in nitrobenzene using microwave irradiation, 5-substituted tetrazoles (42) were synthesized and gave very good yields and short reaction times. Also

sterically hindered tetrazoles, overtime those stopped by electron-donating groups, can be prepared[84]. Scheme (1-17).



Scheme (1-17)

Treating of organic nitriles with NaN_3 in the heterogeneous catalyst such as iodine or silica-supported sodium hydrogen sulfate enables an interesting synthesis of 5-substituted 1*H*-tetrazoles[85] (43). Scheme (1-18).



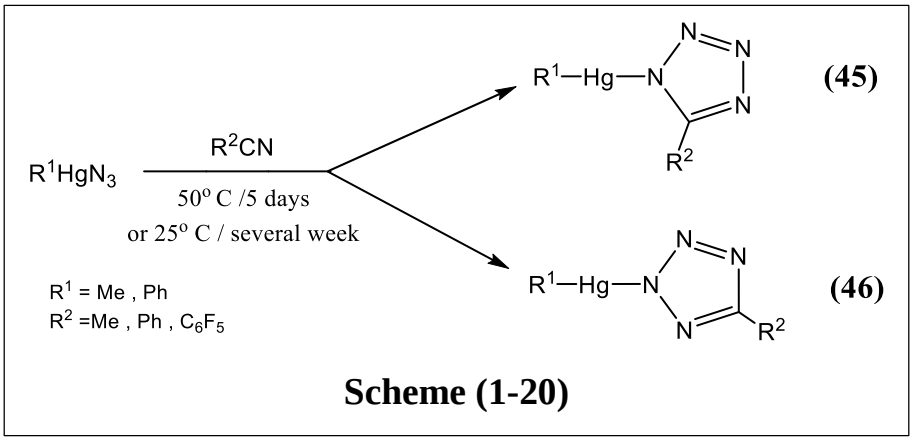
Scheme (1-18)

Leiming Lang[86] et al. synthesized of 5-substituted 1*H*-tetrazoles (44) via mesoporous ZnS nanospheres as a novel heterogeneous catalyst from sodium azide and various nitriles that showed excellent catalytic performance due to high surface area and fine mesoporous structure. Scheme (1-19).

(44)

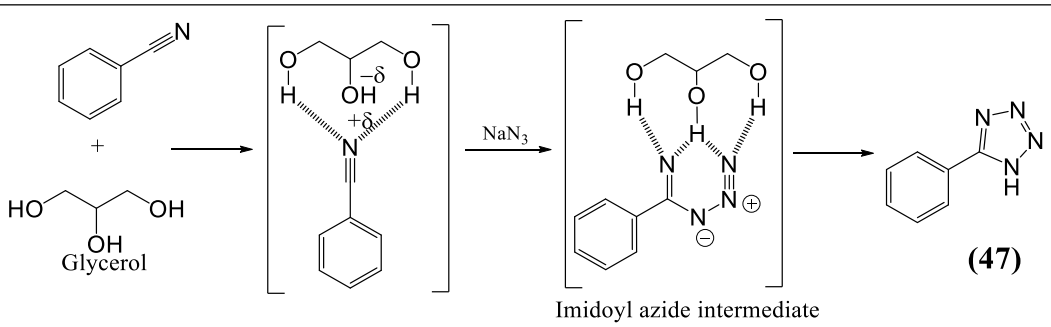
Scheme (1-19)

Klapötke[87] et al. described the 1,3-dipolar cycloaddition reaction of organomercury(II) azides with organonitriles, this reaction has a simple work up procedure, without the need for a catalyst and quantitative yields. Scheme (1-20).



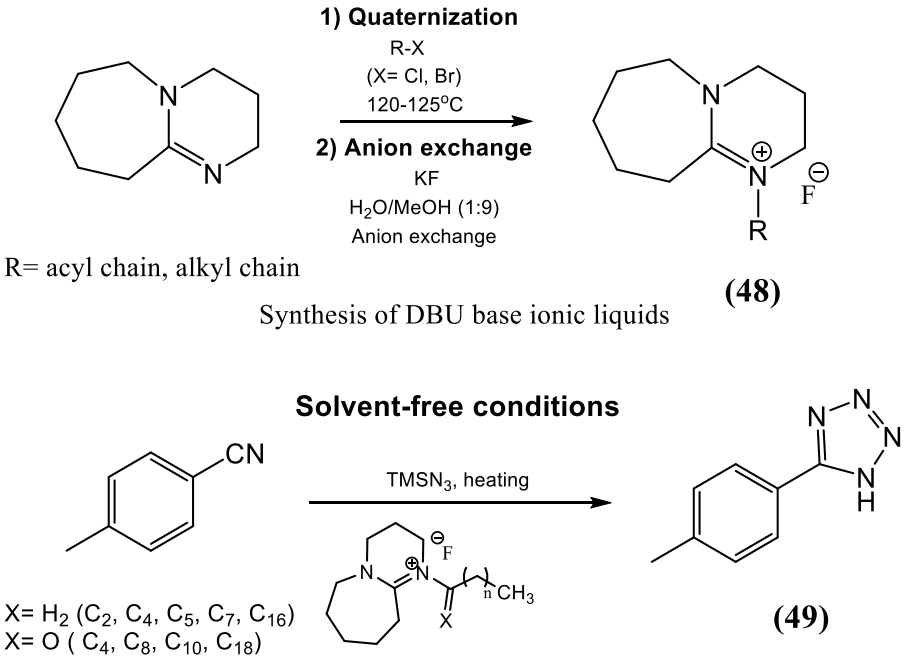
Scheme (1-20)

Nandre[88] et al. for the first time have developed using of glycerol without catalyst in the synthesis of 5-substituted 1*H*-tetrazole (47). Therefore, glycerol was specified as more effective solvent for this conversion because of solubility of sodium azide and organic nitriles at 110 °C. Scheme (1-21).



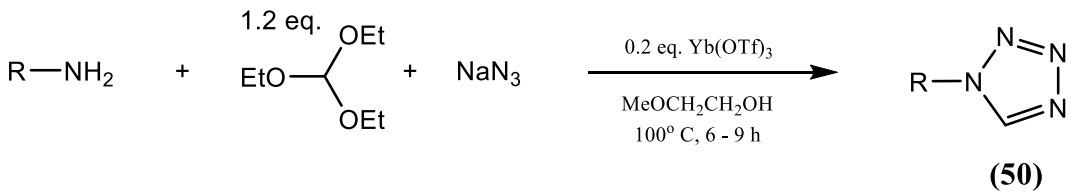
Scheme (1-21)

Hameed[89] et al. have synthesized novel 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU)-based fluorinated ILs (DBUF-ILs) (48) by solvent-free quaternization and subsequent anion (F) exchange reactions. And the click chemistry reaction for tetrazole (49) formation is performed under solvent-free thermal and microwave irradiation. Scheme (1-22).



Scheme (1-22)

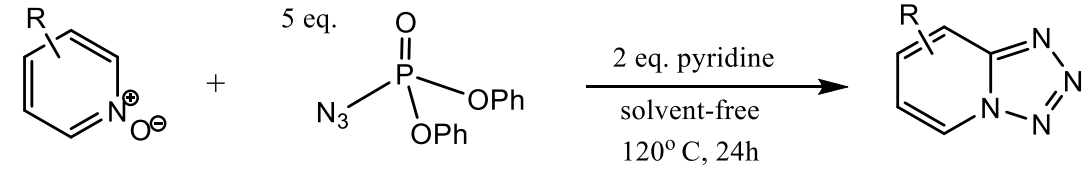
Su[90] et al. synthesized a group of 1-substituted 1*H*-1,2,3,4-tetrazole compounds (50) from sodium azide, amines and triethylortho formate by $Yb(OTf)_3$ as catalyst in good yields. Scheme (1-23).



R= C_6H_5-, 3-MeC_6H_4-, 4-MeC_6H_4-, 2-ClC_6H_4-, 4-ClC_6H_4-, 2-Me-3-ClC_6H_3-, 2-Me-5-ClC_6H_3-, 2,4-ClC_6H_3-, 3,5-ClC_6H_3-, 2-$C_5H_4N_6$-, 2-(4-MeC_5H_3N), $C_6H_5CH_2$-, 4-CH_3O–$C_6H_4CH_2$-, (S)-1-Phenylethylamine, Furfurylamine

Scheme (1-23)

The reaction of pyridine *N*-oxides in sulfonyl or phosphoryl azides by heating and pyridine in solvent-free condition have been transformed to tetrazolo[1,5-a]pyridines[91] (51). Diphenyl phosphorazidate (DPPA) was suitable reagent and gave well to excellent yield. Scheme (1-24).

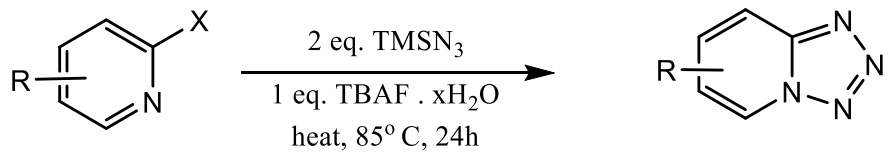


R= H-, Me-, MeO-,Cl-, F-

(51)

Scheme (1-24)

2-Halopyridines reacted with trimethylsilyl azide and tetrabutyl ammonium fluoride hydrate gave tetrazolo[1,5-a]pyridines[92] (52). Scheme (1-25).

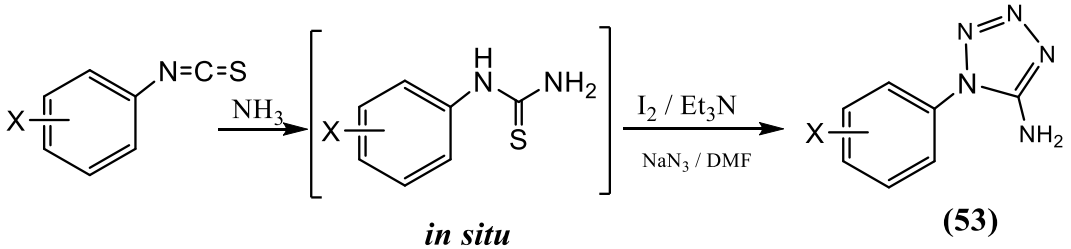


X= Br , Cl
R= $EtCO_2$-, Br-, CH_3-

(52)

Scheme (1-25)

Yella[93] et al. developed a one-pot, tandem process to forming a series of 1-aryl-1*H*-tetrazole-5-amine (53) from their corresponding isothio cyanates, the reaction is carried out at room temperature in DMF. Scheme (1-26).



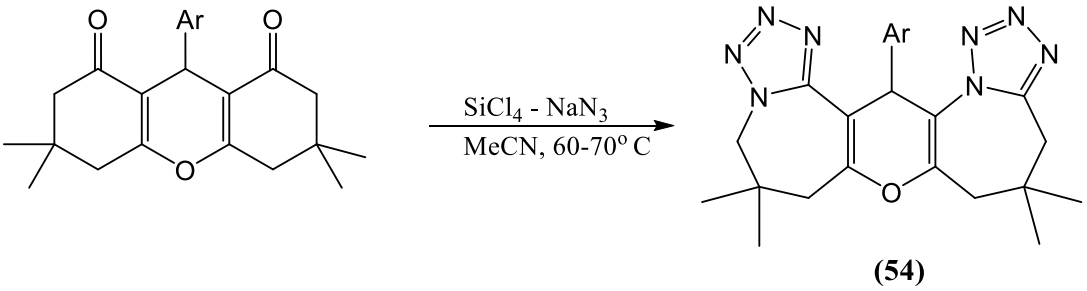
in situ

(53)

X= H ,*o*-Cl ,*m*-Cl,*m*-NO_2 ,*p*-Br, *p*-CH_3

Scheme (1-26)

Soliman and Salama[94] synthesized aryl-pyrano-bis-tetrazoloazepine derivatives (54). Scheme (1-27).



(54)

Ar = Ph , 4-$MeOC_6H_4$,4-BrC_6H_4 , 4-ClC_6H_4 , 4-NCC_6H_4 , 4-HO-3-$MeOC_6H_3$

Scheme (1-27)

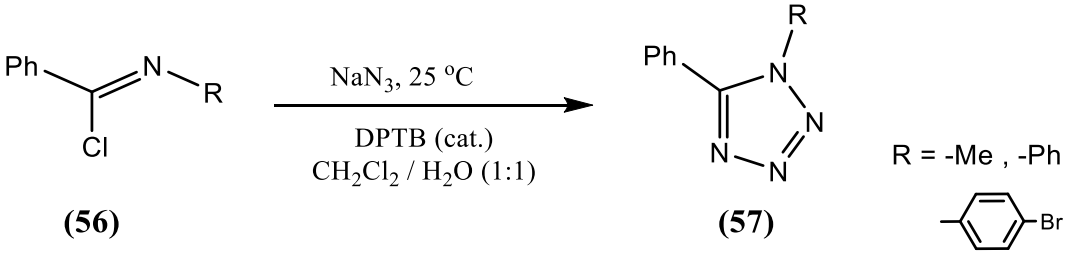
Rokade[95] et al. found a mild and convenient method copper-catalyzed oxidative transformation of secondary alcohols to 1,5-disubstituted tetrazoles (55) by employing $TMSN_3$ as a nitrogen source. Scheme (1-28).

(55)

R = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 1-napthyl, 2-napthyl, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 3-ClC6H4, 4-ClC6H42, 4-ClC6H3, 2-FC6H4, 2-FC6H4, 2-BrC6H4, 3-BrC6H4

Scheme (1-28)

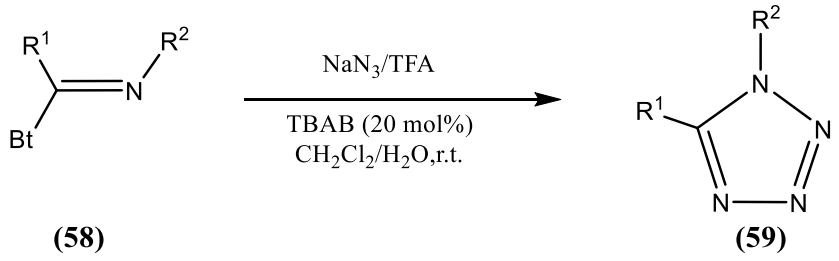
1,5-disubstituted tetrazoles (57) were also synthesized via the reaction of imidoyl chlorides (56) with sodium azide[96] as shown in scheme (1-29).



(56) **(57)**

Scheme (1-29)

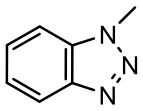
Katritzky[97] et al. synthesized 1,5-disubstituted tetrazoles (59) in high yields from imidoylbenzotriazoles (58) including short reaction times and mild reaction conditions. Scheme (1-30).



(58) **(59)**

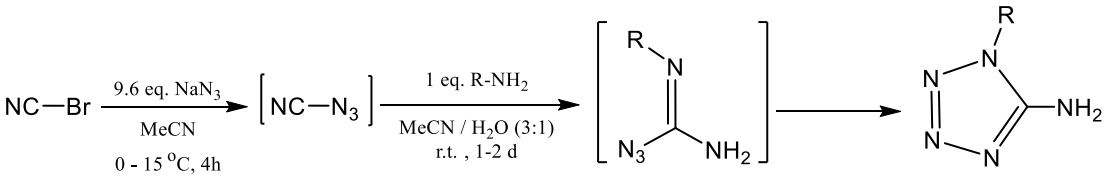
R^1= Me, Bn, $PhCH_2CH_2$, Ph, *p*-Tolyl, *p*-Methoxyphenyl, *p*-Chlorophenyl, *p*-Nitrophenyl, 2-Furyl, 2-Thienyl

R^2= Ph, *p*-Tolyl , Bn, Me,Cyclohexyl,CH_2CO_2Et

Bt= 

Scheme (1-30)

The reaction of primary amines and cyanogen azide in acetonitrile/water gives the intermediate imidoyl azides. These intermediates after cyclization, generated 1-substituted aminotetrazoles (60) in good yield[98]. Scheme (1-31).

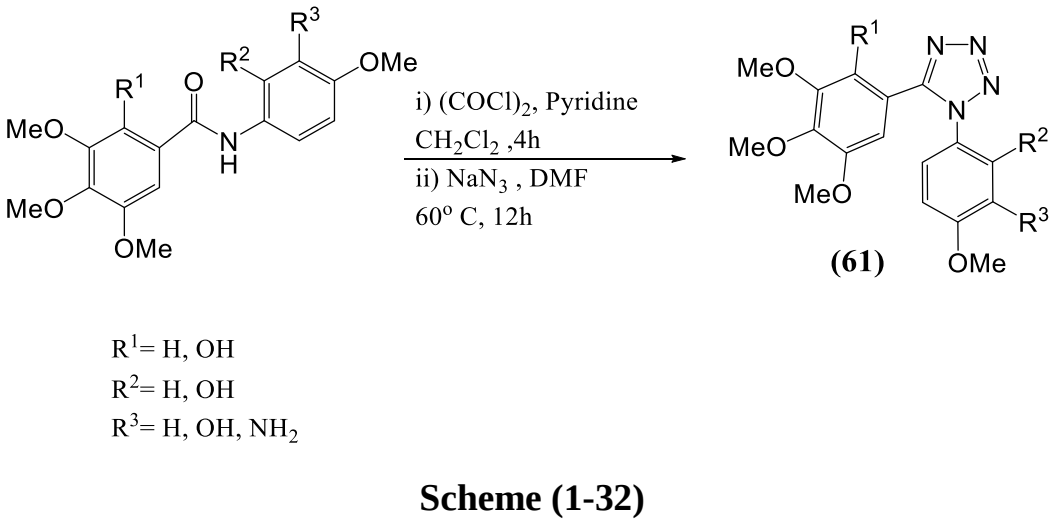


(60)

R= alkyl, benzyl

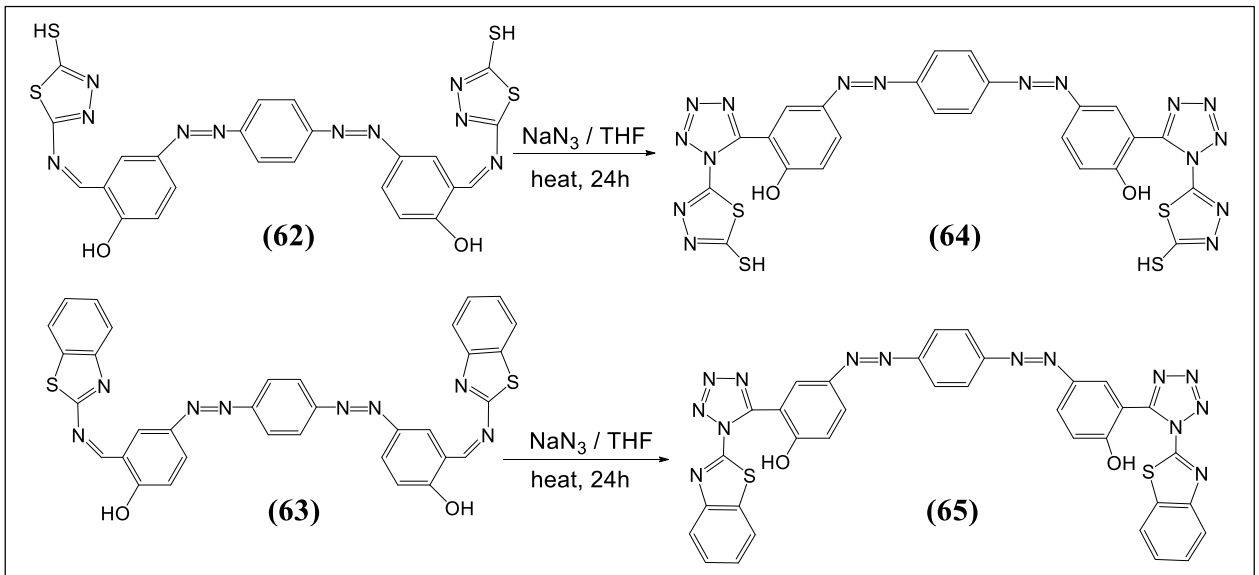
Scheme (1-31)

Amides were converted to imidoyl chlorides with $(COCl)_2$ in the presence of quinoline then reacted with NaN_3 in DMF at 60 °C to form the corresponding benzyloxy protected tetrazoles[99] (61). Scheme (1-32).



Scheme (1-32)

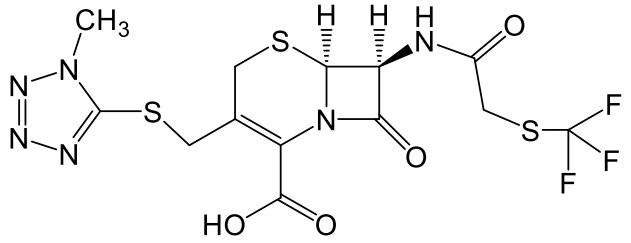
Abood[100] synthesized two new bis-1,5-disubstituted tetrazoles (64) and (65) via treatment of bis- imines (62) and (63) with sodium azide under [3+2] cycloaddition conditions. Scheme (1-33).



Scheme (1-33)

1.4.2. Biological importance of tetrazoles

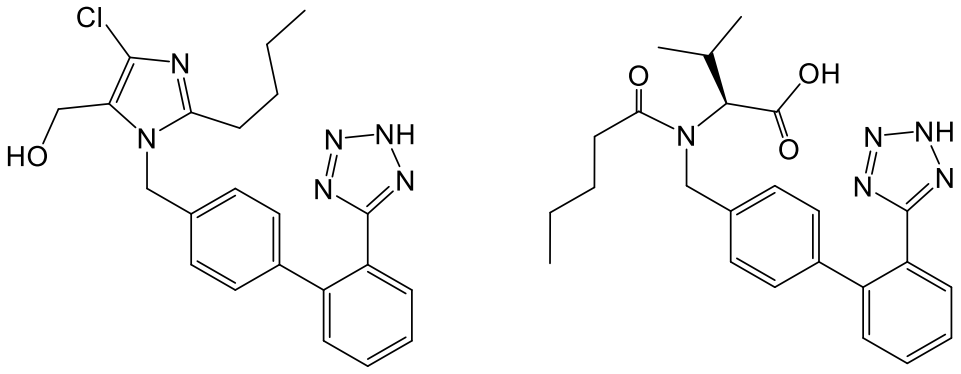
The tetrazoles are representative of active pharmacophores for several therapeutic active molecules such as antiallergic[101], anti-inflammatory[102], antibiotic[103], antihypertensive[104] and antitubercular agents[76]. The β-lactam antibiotics[105] (66) of the cephalosporin class is an example of drugs containing a 1,5-disubstituted tetrazole moiety. Figure (1-9).



(66)

Fig. (1-9): Structure of β-lactam antibiotic containing a 1,5-disubstituted tetrazole

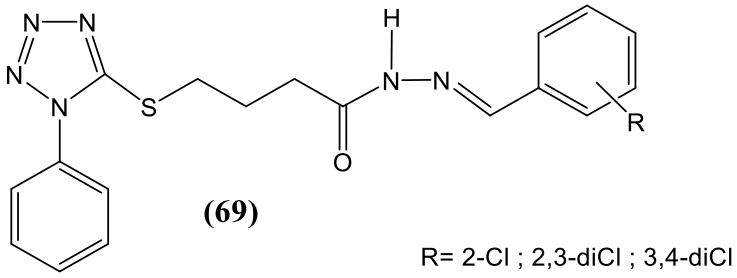
Losartan (67) is a sartan derivative that was the first nonpeptide angiotensin receptor antagonist to appear on the market followed by Valsartan (68) which includes the regulation of blood pressure and volume homeostasis[106,107]. Figure (1-10).



(67) **(68)**

Fig. (1-10): Structures of Losartan **(67)** and Valsartan **(68)**

Kaplancıklı[108] et al. synthesized a new class of tetrazole-hydrazone derivatives includes chloro-substituted phenyl moiety (69) to perform anticancer activity screening. Three compounds showed significant anticancer activity. Figure (1-11).

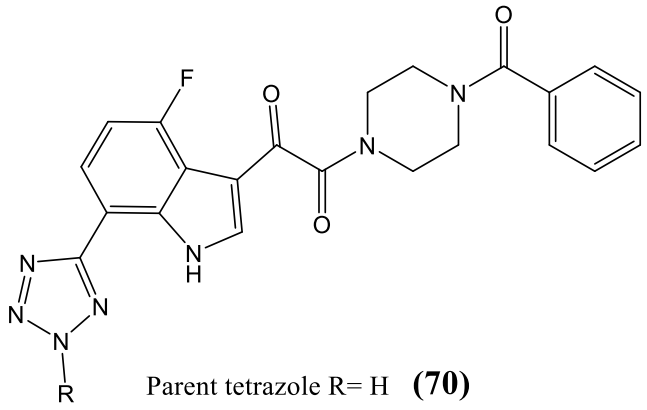


(69)

R= 2-Cl ; 2,3-diCl ; 3,4-diCl

Fig. (1-11): Structures of compounds **(69)**

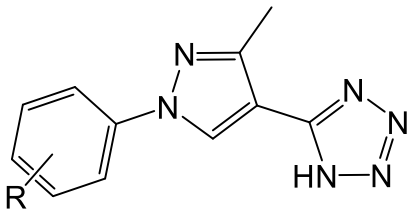
Yeung[109] et al. prepared potential prodrug (71) of the parent tetrazole 7-(2*H*-tetrazol-5-yl)-1*H*-indole (70) which is found to be an effective inhibitor of HIV-1 attachment, the simple *N*-methyl tetrazole which represents a novel example of a methyl tetrazole that acts as a prodrug for a free NH tetrazole-containing compound. Figure (1-12).



Parent tetrazole R= H **(70)**
and Prodrug R= Me **(71)**

Fig. (1-12): Structures of compounds **(70)** and **(71)**

Faria[110] et al. synthesized new groups of 5-(1-aryl-3-methyl-1*H*-pyrazol-4-yl)-1*H*-tetrazole derivatives (72), thus refer to that the pyrazole-tetrazole that are a new structural class of azoles with antileishmanial activity. Figure (1-13).

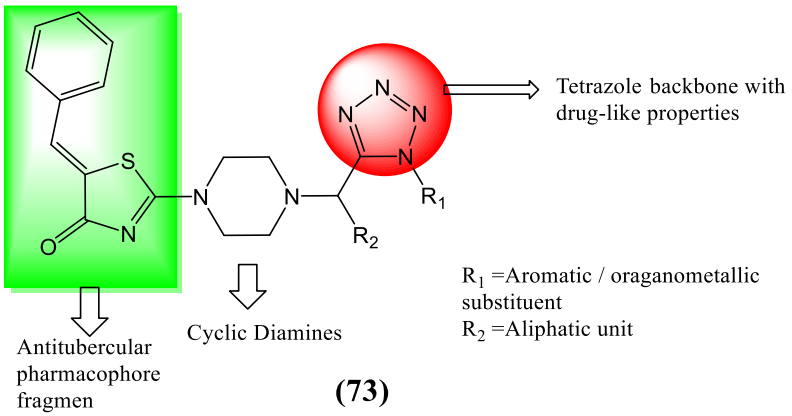


R = 3-Cl ; 3,4-diCl

(72)

Fig. (1-13): Structures of compounds **(72)**

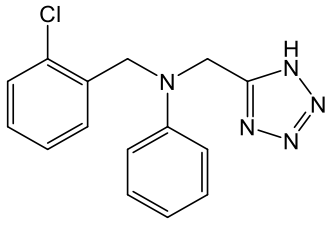
Chauhan[111] et al. synthesized new class of thiazolone piperazine tetrazole derivatives (73) as potent antitubercular agents as shown in figure (1-14).



(73)

Fig. (1-14): Structures of potent antitubercular agents **(73)**

Dai[112] et al. synthesized a series of tetrazole derivatives and it found that compound (74) has stronger antifungal efficiency in comparison with the reference drug Fluconazole. Figure (1-15).



(74)

Fig. (1-15): Structures of compounds **(74)**

Aim of the study

The present work aims to synthesize two new series of tetrazoles containing the biologically active benzothiazole moiety and azo group, then all series will be tested for their antibacterial activity against *Staphylococcus aureous* (Gram-positive) and *Escherichia coli* (Gram-negative).

Chapter Two

Experimental Part

2.1. Materials

All chemicals, reagents and solvents were purchased from the commercial sources summarized in table (2-1**).**

Table (2-1): Chemicals and their commercial sources

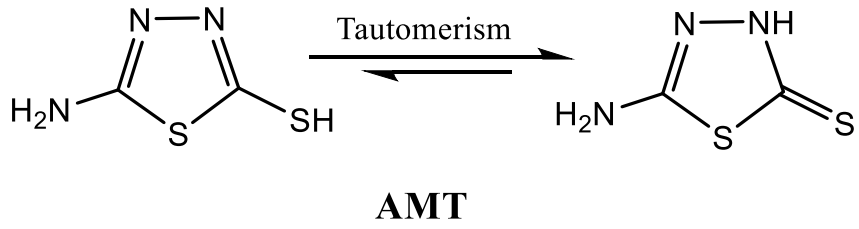
Chemicals	Molecular formula	M.Wt. g/mol	Purity %	Supplied from
2,4-Dichloroaniline	$C_6H_5NCl_2$	162.01	95	BDH, England
2-Aminobenzothiazole	$C_7H_6N_2S$	150.20	97	Sigma Aldrich
2-Hydroxy benzaldehyde	$C_7H_6O_2$	122.12	98	S.D.Fine.india
3-Bromoaniline	C_6H_6NBr	172.02	96	Fluka, Germany
3-Nitroaniline	$C_6H_6N_2O_2$	138.12	98	Fluka
4-Chloroaniline	C_6H_6NCl	127.57	99	Fluka
4-Nitroaniline	$C_6H_6N_2O_2$	138.12	99	Fluka
Carbon disulfide	CS_2	75.94	99	Scharlau, Spain
Diethyl ether	$C_4H_{10}O$	74.12	98	Scharlau, Spain
Dimethyl sulfoxide	$(CH_3)_2SO$	78	99	BDH
Ethanol absolute	C_2H_6O	46.06	99.9	Scharlau, Spain
Ethyl acetate	$C_4H_8O_2$	88.10	99	Scharlau, Spain
Glacial acetic acid	CH_3COOH	60	99.9	GCC
Hydrochloric acid (Conc.)	HCl	36.46	99	Merck, Germany
Iodine	I_2	253.80	99.5	GCC, Germany
n-Hexane	C_6H_{14}	86.17	99	Scharlau, Spain
Sodium azide	NaN_3	65.01	99	Fluka, Germany
Sodium carbonate (anhydrous)	Na_2CO_3	105.98	99	Merck, Germany
Sodium hydroxide	NaOH	39.99	99	BDH, England
Sodium nitrite	$NaNO_2$	68.99	99	BDH, England
Sulfuric acid	H_2SO_4	98.08	98	Merck, Germany
Teterahyrofuran	C_4H_8O	72.11	99.9	Scharlau, Spain
Thiosemicarbazide	CH_5N_3S	91.13	98	Redial de hean

2.2. Instrumentations

1. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The reactions were monitored by TLC and visualized by development of the TLC plates with Iodine vapor.
2. Melting points were recorded using an Electro thermal Stuart SMP 30 capillary melting point apparatus, UK.
3. Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide discs in Kerbala University.
4. ^{1}H NMR spectra was collected on NMR spectrometer 400 MHz, Avance III 400 Bruker, Germany at 400 MHz in DMSO-d_6 as solvent and TMS as an internal standard at Esfahan University, Iran.
5. Mass spectra were obtained on MS ACQUISITION PARAMETERS Agilent 5975c with Triple-axis direct insert probe SIS at Tehran University, Iran.
6. Autoclave was used to sterilize agar media, supplied from Prestige Medical-England.
7. Incubator was used to maintain different temperature required for the growth of organism, supplied from Binder - Germany.

2.3. Preparation methods

2.3.1. Preparation of 2-amino-5-mercapto-1,3,4-thiadiazole (AMT) [113]

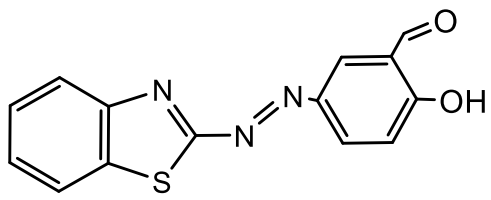


AMT

Fig. (2-1): Structure of **(AMT)**

A mixture of thiosemicarbazide (9.1g, 0.1mol) and anhydrous sodium carbonate (5.3 g, 0.05 mol) was dissolved in absolute ethanol (50 mL), to this solution carbon disulfide (7.6 g, 0.1 mol) was added. The mixture of the reaction was refluxed with stirring on the water bath for 24 h in 65 ºC. At room temperature, the mixture was allowed to cool down. Most of the solvent was removed under reduced pressure, the residue was dissolved in distilled water (150 mL) and the solution was acidified carefully with concentrated hydrochloric acid to give pale yellow precipitate that was filtered under reduced pressure, washed well with cold distilled water and recrystallized from distilled water to form white needles crystals, yield (10.906g, 82%), m.p. 230-232 ºC, Lit. 231 °C.

2.3.2. Preparation of azoaldehyde derivative 1a[114]

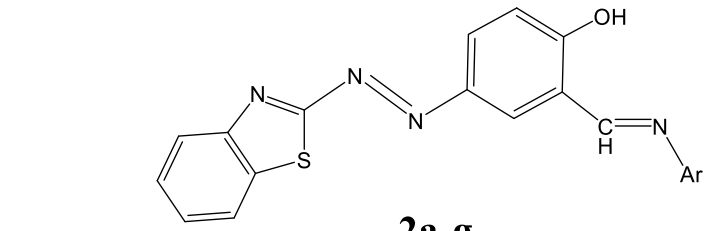


1a

Fig. (2-2): Structure of azoaldehyde derivative **1a**

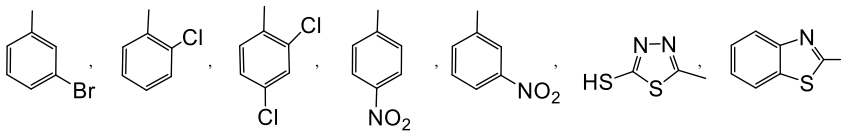
A solution of 2-aminobenzothiazole (8.1 g, 0.054 mol) in H_2SO_4 (12mL) was cooled to 0°C. To this solution a cold solution of sodium nitrite (3.726 g, 0.054 mol) dissolved in distilled water (20 mL) was added drop wise with constant stirring. When the addition was completed, the resultant reaction mixture was left in ice-chest for 1h. The ice cold solution of diazonium bisulfate was then added drop wise to the cold solution of 2-hydroxy benzaldehyde (6.588 g, 0.054 mol) dissolved in (44 mL) of (10% w/v) sodium hydroxide with constant shaking. A dark dye resulted which darkened on adding more alkaline solution of phenol derivative. When the addition was completed, the resultant reaction mixture was vigorously stirred. A saturated solution of the last compound in water was neutralized with concentrated hydrochloric acid. A solid separated out which was allowed to stand at room temperature for 30 min., then filtered off and washed well with distilled water. The precipitated substance was collected and recrystallized from ethanol to yield **1a** as a dark brown solid (7.79 g, 51%). The physical properties of compound **1a** was given in table (2-2).

2.3.3. General procedure for the preparation of azoimine derivatives 2a-g



2a-g

Ar =

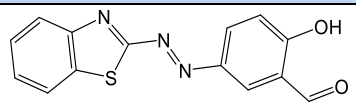
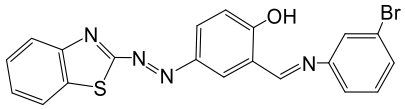
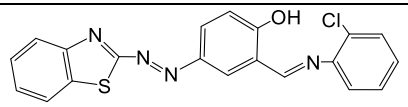
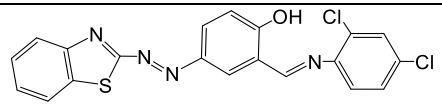
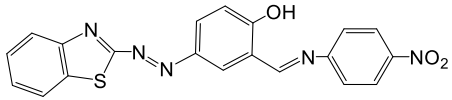
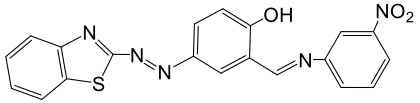
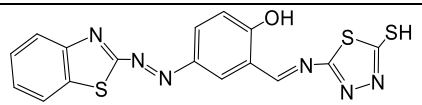
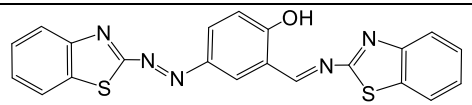


2a **2b** **2c** **2d** **2e** **2f** **2g**

Fig. (2-3): Structures of azoimines **2a-g**

Azoaldehyde derivative **1a** (1.132 g, 0.004 mol) was dissolved in absolute ethanol (30 mL) containing two drops of glacial acetic acid, then equimolar amount (0.004 mol) of (3-bromoaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline, 3-nitroaniline, 2-amino-5-mercapto-1,3,4-thiadiazole and 2-aminobenzothiazole respectively) were added. The reaction mixture was refluxed with stirring on a water bath at 70 ^{o}C for 22-32 h. TLC (*n*- hexane: EtOAc) showed that the reactions were completed. The mixture was then allowed to cool down to room temperature and the colored precipitate was filtered, then recrystallized from ethanol. Table (2-2) shows physical properties and other characteristics for the synthesized compounds **2a-g**.

Table (2-2): Physical properties and other characteristics for the synthesized azoaldehyde derivative 1a and azoimine derivatives 2a-g

Com. no.	Structure	Molecular formula	Color	M.Wt. g/mol	Reaction time (h)	Yield %	m.p. °C	R_f
1a		$C_{14}H_9N_3O_2S$	Dark brown	283.31	-	51	141-143	0.68 *n*-hexane : EtOAc 1 : 3
2a		$C_{20}H_{13}N_4OSBr$	Dark brown	437.32	24	66	173-175	0.78 *n*-hexane : EtOAc 1 : 2
2b		$C_{20}H_{13}N_4OSCl$	Reddish brown	392.86	26	55	206-208	0.73 *n*-hexane : EtOAc 1 : 3
2c		$C_{20}H_{12}N_4OSCl_2$	Brown	427.30	28	67	163-165	0.75 *n*-hexane : EtOAc 1 : 2
2d		$C_{20}H_{13}N_5O_3S$	Brown	403.42	31	71	220-222	0.88 *n*-hexane: EtOAc 1 : 2
2e		$C_{20}H_{13}N_5O_3S$	Dark brown	403.42	27	70	175-177	0.7 *n*-hexane : EtOAc 1 : 2
2f		$C_{16}H_{10}N_6OS_3$	Brown	398.48	22	85	198-200	0.71 *n*-hexane : EtOAc 1 : 2
2g		$C_{21}H_{13}N_5OS_2$	Brown	415.48	32	50	204-206	0.73 *n*-hexane : EtOAc 1 : 3

2.3.4. General procedure for the preparation of 1,5-disubstituted tetrazole derivatives 3a-g

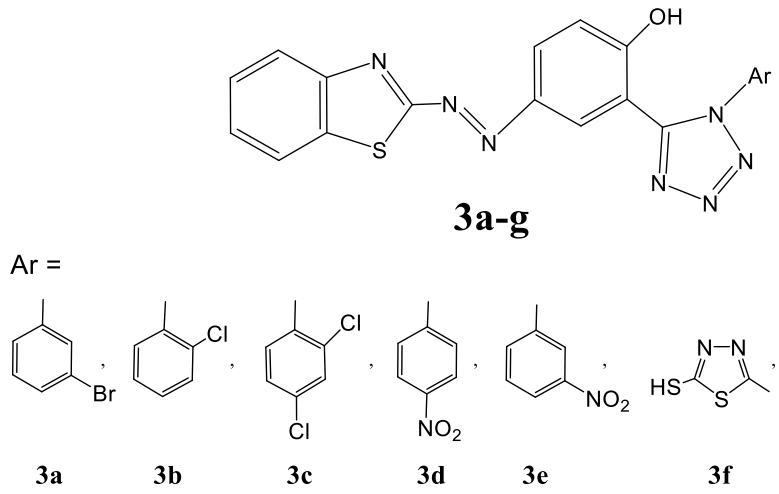
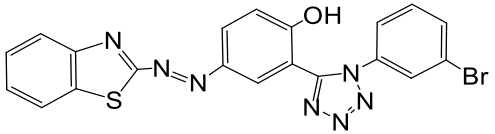
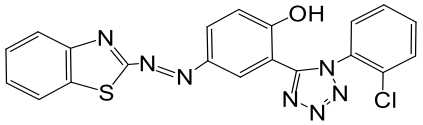
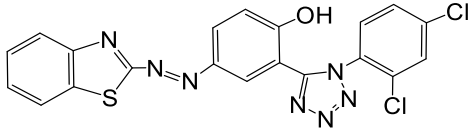
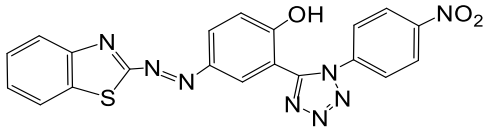
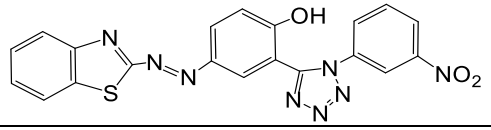
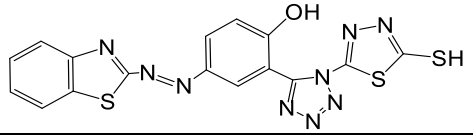
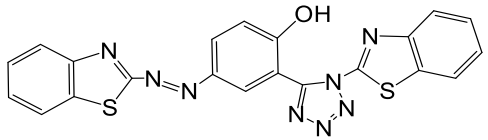


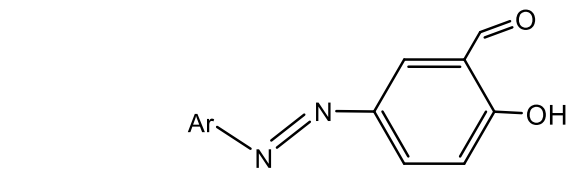
Fig. (2- 4): Structures of 1,5-disubstituted tetrazoles **3a-g**

A mixture of imine derivatives **2a-g** (0.001 mol) and sodium azide (0.065 g, 0.001 mol) in tetrahydrofuran (20 mL) was refluxed with stirring on a water bath at 70 ºC for 24-35h. TLC (*n*- hexane: EtOAc) showed that the reactions were completed. The reaction mixture was then allowed to cool down to room temperature. The solvent was removed by evaporation under reduced pressure and the colored precipitate was recrystallized from ethanol. Table (2-3) shows physical properties and other characteristics for the synthesized compounds **3a-g**.

Table (2-3): Physical properties and other characteristics for the synthesized 1,5-disubstituted tetrazole derivatives 3a-g

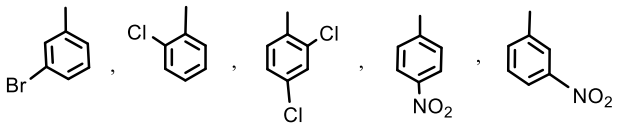
Com. no.	Structure	Molecular formula	Color	M.Wt. g/mol	Reaction time (h)	Yield %	m.p. °C	R_f
3a		$C_{20}H_{12}N_7OSBr$	Dark purple	478.33	26	63	135-137	0.51 *n*-hexane : EtOAc 1 : 2
3b		$C_{20}H_{12}N_7OSCl$	Dark red	433.87	28	77	130-132	0.56 *n*-hexane : EtOAc 1 : 2
3c		$C_{20}H_{11}N_7OSCl_2$	Dark purple	468.32	31	79	128-130	0.65 *n*-hexane : EtOAc 1 : 2
3d		$C_{20}H_{12}N_8O_3S$	Dark brown	444.43	34	73	201-203	0.52 *n*-hexane : EtOAc 1 : 2
3e		$C_{20}H_{12}N_8O_3S$	Black	444.43	29	60	149-151	0.62 *n*-hexane : EtOAc 1 : 2
3f		$C_{16}H_9N_9OS_3$	Purple	439.49	24	88	116-118	0.58 *n*-hexane : EtOAc 1 : 2
3g		$C_{21}H_{12}N_8OS_2$	Brown	456.50	35	75	152-154	0.60 *n*-hexane : EtOAc 1 : 2

2.3.5. Preparation of azoaldehyde derivatives 1a`-e`[115]



1a`-e`

Ar =

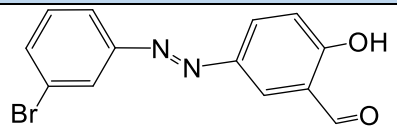
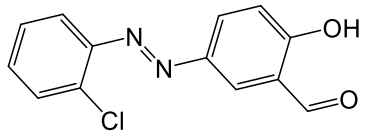
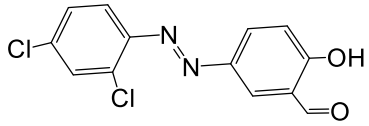
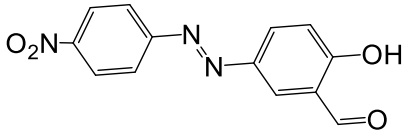
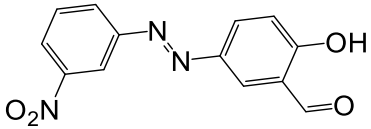


1a`** **1b` **1c`** **1d`** **1e`**

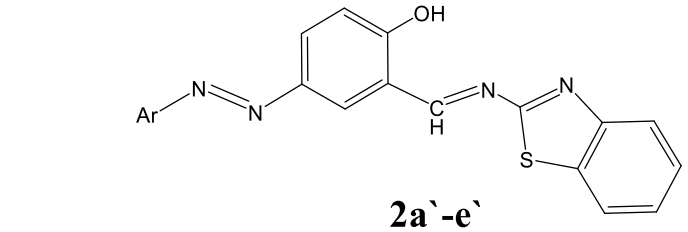
Fig. (2-5): Structures of azoaldehyde derivatives **1a`-e`**

Aromatic amines (3-bromoaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline and 3-nitroaniline respectively) (0.025 mol) were dissolved in a mixture of concentrated hydrochloric acid (8 mL) and distilled water (8 mL). The mixture was cooled at (0 °C) in an ice bath, then a solution of sodium nitrite (1.725 g, 0.025 mol) dissolved in distilled water (10 mL) was added drop wise to the mixture with stirring. The temperature of the ice bath was controlled between (0-5 °C) during the addition. A solution of 2-hydroxybenzaldehyde (3.05 g, 0.025 mol) dissolved in (20 mL) of (10%w/v) sodium hydroxide solution was prepared and cooled to (5 °C) by immersion in an ice bath and stirred vigorously, then the diazonium salt solution was added very slowly to the phenoxide solution, a colored precipitate soon separated. When all the diazonuim salt solution has been added, the mixture was allowed to stand in an ice bath for (30 min.) with occasional stirring, then the solution was filtered and the precipitate was washed well with distilled water, dried upon filter paper then in oven and recrystallized from ethanol. The physical properties and other characteristics for the synthesized azoaldehyde derivatives **1a`-e`**are shown in table (2-4).

Table (2-4): Physical properties and other characteristics for the synthesized azoaldehyde derivatives 1a`-e`

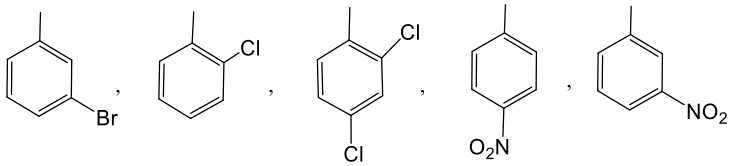
Com. no.	Structure	Molecular formula	Color	M.Wt. g/mol	Yield %	m.p. °C	R_f
1a`		$C_{13}H_9N_2O_2Br$	Yellow	305.13	82	136-138	0.66 *n*-hexane:EtOAc 1 : 2
1b`		$C_{13}H_9N_2O_2Cl$	Orang	260.68	89	143-145	0.72 *n*-hexane:EtOAc 1 : 2
1c`		$C_{13}H_8N_2O_2Cl_2$	Brown	295.12	75	161-163	0.68 *n*-hexane : Et_2O 1 : 2
1d`		$C_{13}H_9N_3O_4$	Brown	271.23	85	113-115	0.65 *n*-hexane : Et_2O 1 : 2
1e`		$C_{13}H_9N_3O_4$	Red	271.23	90	104-106	0.74 *n*-hexane : EtOAc 2 : 3

2.3.6. General procedure for the preparation of azoimine derivatives 2a`-e`



2a`-e`

Ar =

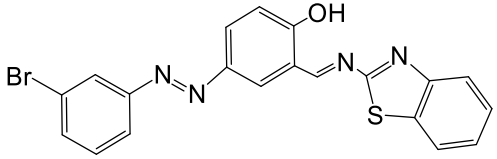
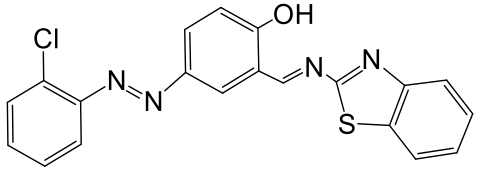
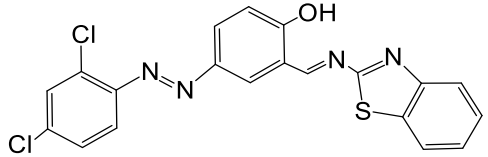
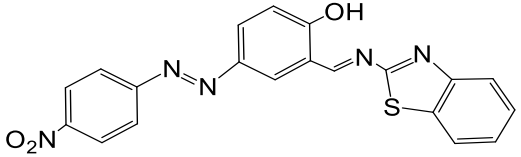
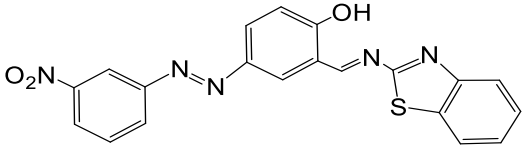


2a`** **2b` **2c`** **2d`** **2e`**

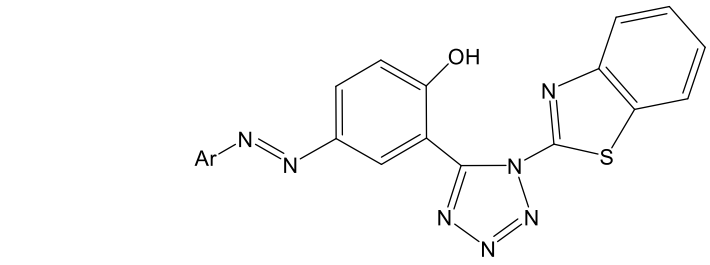
Fig. (2-6): Structures of azoimines **2a`-e`**

Azoaldehyde derivatives **1a`-e`** (0.004 mol) was dissolved in absolute ethanol (30 ml) containing two drops of glacial acetic acid, then equimolar amount (0.6 g, 0.004mol) of 2-aminobenzothiazole was added. The reaction mixture was refluxed with stirring on a water bath at 70 ^{o}C for 17-25 h. TLC (*n*- hexane: EtOAc) showed that the reactions were completed. The mixture was then allowed to cool down to room temperature and the colored precipitate was filtered, then recrystallized from ethanol. Table (2-5) shows physical properties and other characteristics for the synthesized compounds **2a`-e`**.

Table (2-5): Physical properties and other characteristics for the synthesized azoimine derivatives 2a`-e`

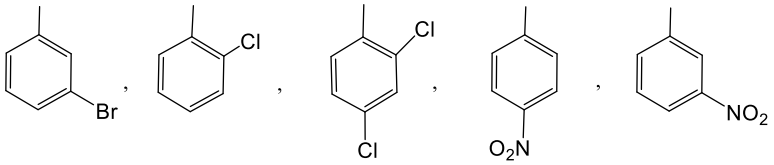
Com. no.	Structure	Molecular formula	Color	M.Wt. g/mol	Reaction time (h)	Yield %	m.p. °C	R_f
2a`		$C_{20}H_{13}N_4OSBr$	Red	437.32	25	80	223-225	0.78 *n*-hexane : EtOAc 1 : 2
2b`		$C_{20}H_{13}N_4OSCl$	Orang	392.86	22	57	190-192	0.67 *n*-hexane : EtOAc 1 : 2
2c`		$C_{20}H_{12}N_4OSCl_2$	Dark brown	427.30	20	51	218-220	0.73 *n*-hexane : EtOAc 1 : 2
2d`		$C_{20}H_{13}N_5O_3S$	Yellow	403.42	17	76	273-275	0.7 *n*-hexane : EtOAc 1 : 2
2e`		$C_{20}H_{13}N_5O_3S$	Light brown	403.42	21	72	238-240	0.67 *n*-hexane : EtOAc 2 : 3

2.3.7. General procedure for the preparation of 1,5-disubstituted tetrazole derivatives 3a`-e`



3a`-e`

Ar =

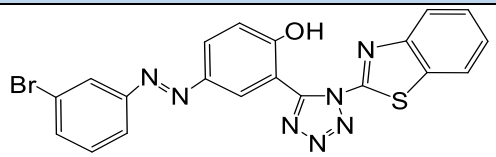
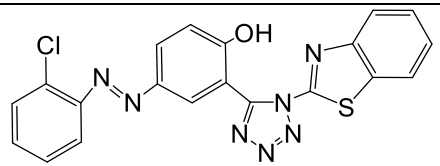
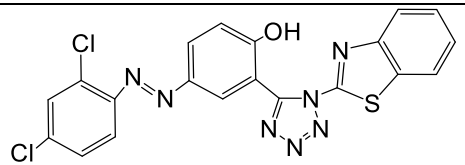
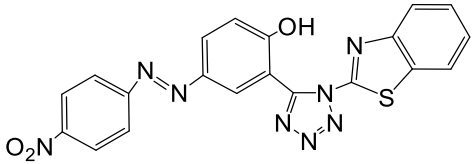
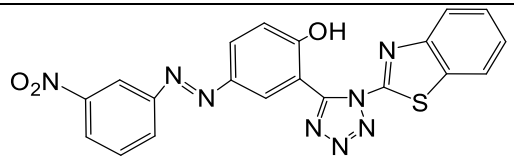


3a`** **3b` **3c`** **3d`** **3e`**

Fig. (2-7): Structures of 1,5-disubstituted tetrazoles **3a`-e`**

A mixture of imine derivatives **2a`-e`** (0.001 mol) and sodium azide (0.065 g, 0.001 mol) in tetrahydrofuran (20mL) was refluxed with stirring on a water bath at 70ºC for 24-30 h. TLC (*n*- hexane: EtOAc) showed that the reactions were completed. The reaction mixture was then allowed to cool down to room temperature. The solvent was removed by evaporation under reduced pressure and the colored precipitate was recrystallized from ethanol. Table (2-6) shows physical properties and other characteristics for the synthesized compounds **3a`-e`**.

Table (2-6): Physical properties and other characteristics for the synthesized 1,5-disubstituted tetrazole derivatives 3a`-e`

Com. no.	Structure	Molecular formula	Color	M.Wt. g/mol	Reaction time (h)	Yield %	m.p. °C	R_f
3a`		$C_{20}H_{12}N_7OSBr$	Dark brown	478.33	30	68	110-112	0.67 *n*-hexane : EtOAc 1 : 2
3b`		$C_{20}H_{12}N_7OSCl$	Black	433.87	28	60	132-134	0.7 *n*-hexane : EtOAc 1 : 2
3c`		$C_{20}H_{11}N_7OSCl_2$	Dark brown	468.32	26	75	113-115	0.7 *n*-hexane : EtOAc 1 : 2
3d`		$C_{20}H_{12}N_8O_3S$	Brown-black	444.43	24	69	135-137	0.49 *n*-hexane : EtOAc 1 : 2
3e`		$C_{20}H_{12}N_8O_3S$	Dark brown	444.43	27	58	123-125	0.65 *n*-hexane : EtOAc 1 : 2

2.4. Antibacterial test method

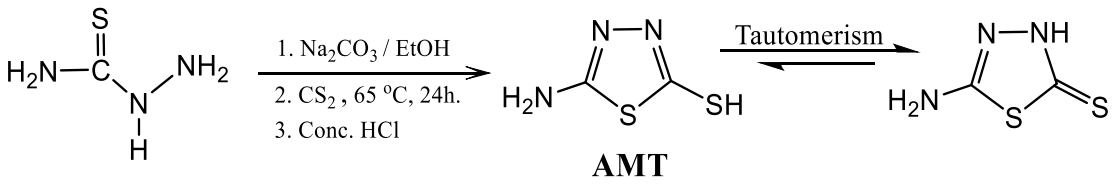
The antibacterial test has been carried out according to the disc diffusion method[116]. All synthesized tetrazoles have been examined for their antibacterial activity in vitro against one type of Gram-positive bacteria (***Staphylococcus aureous***) and one type of Gram-negative bacteria (***Escherichia coli***). Prepared agar and petri dishes have been sterilized by autoclaving for 15 min. at 121°C. The agar plates have been surface-inoculated uniformly from both culture of the tested bacteria. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 40 µL of the prepared compounds (5mg of the compound dissolved in 1mL of DMSO solvent). These plates have been incubated at 37 ^{o}C for 24 h for both bacteria. The zones of bacterial growth inhibition around the discs have been measured in (mm).

Chapter Three

Results and Discussion

3.1. Synthesis of 2-Amino-5-mercaptro-1,3,4-thiadiazole (AMT) [113]

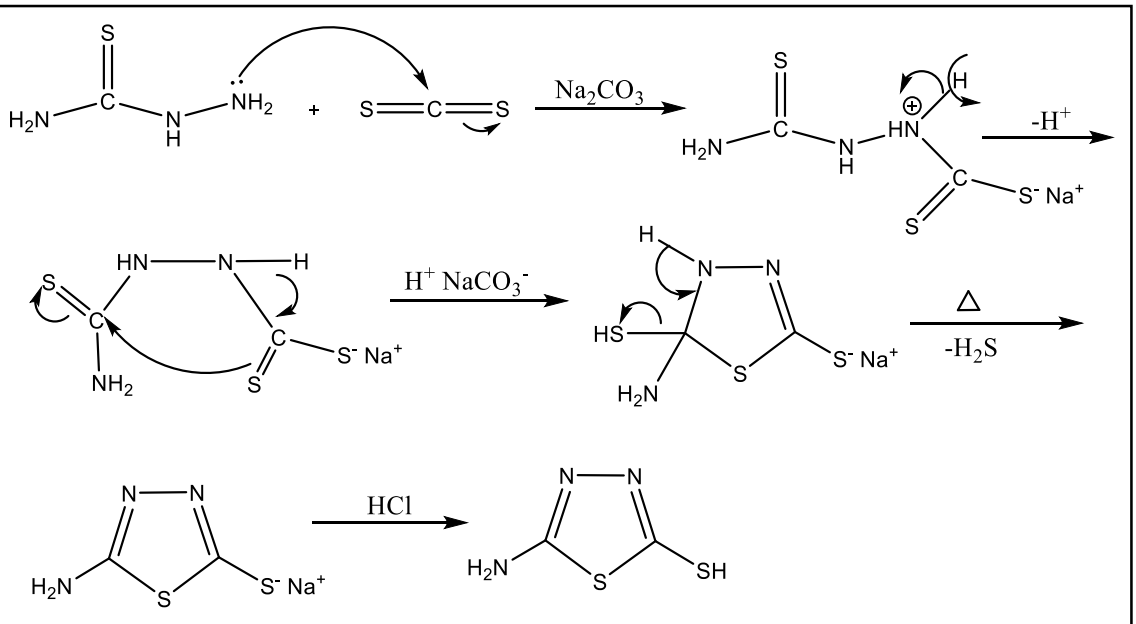
(**AMT**) was prepared through the reaction of thiosemicarbazide with carbon disulfide in the presence of anhydrous sodium carbonate in absolute ethanol as shown in scheme (3-1).



AMT

Scheme (3-1)

The proposed mechanism[113] for this reaction was shown in scheme (3-2).

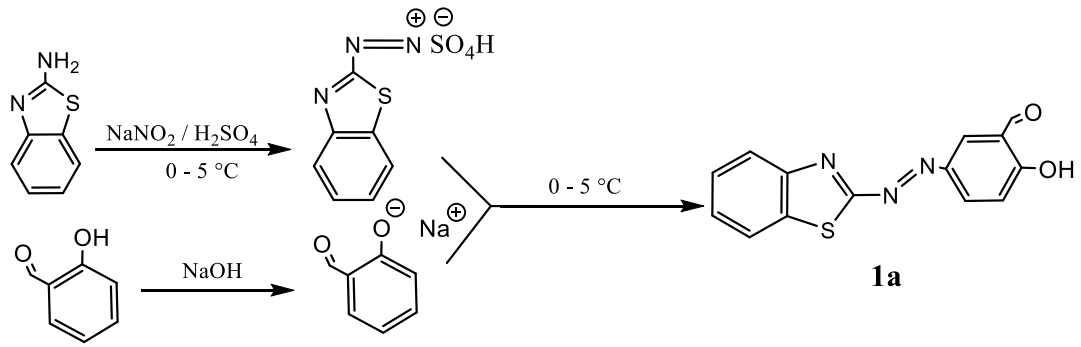


Scheme (3-2)

(**AMT**) was identified by its melting point and FT-IR spectrum. FT-IR spectrum, figure (3-1) of (**AMT)** showed the following bands at $\bar{\upsilon}$ (cm^{-1}) (KBr): 3336 (υ as. N-H, NH_2), 3267 (υ S. N-H, NH_2), 3095 (υ N-H, thioketone form), 2922 and 2773 (υ N-H, intramolecularly hydrogen bonded)[117] ,2584 (υ S-H), 1602 (υ C=N), 1543 (δ N-H), 1491 (υ C-N), 1172 (υ C=S), 669 (υ C-S).

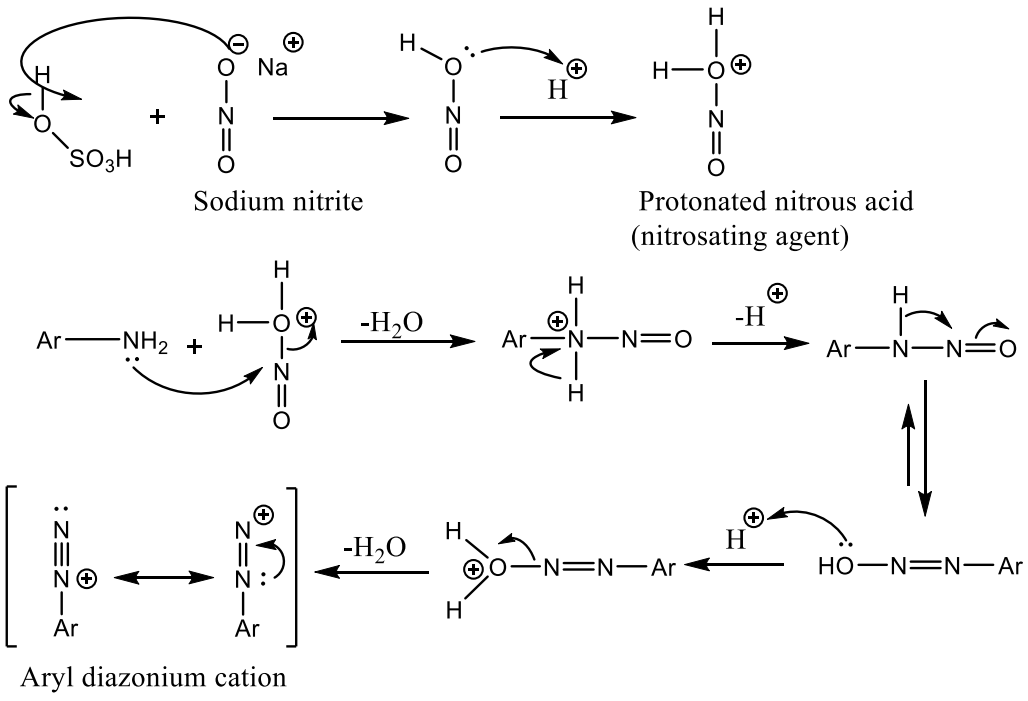
3.2. Synthesis of azoaldehyde derivative 1a

A coupling reaction between the diazonium salt of 2-aminobenzothiazole generated by using H_2SO_4 instead of HCl and 2-hydroxybenzaldehyde dissolved in NaOH solution at (0-5) ^oC afforded azoaldehyde derivative **1a**. Scheme (3-3).

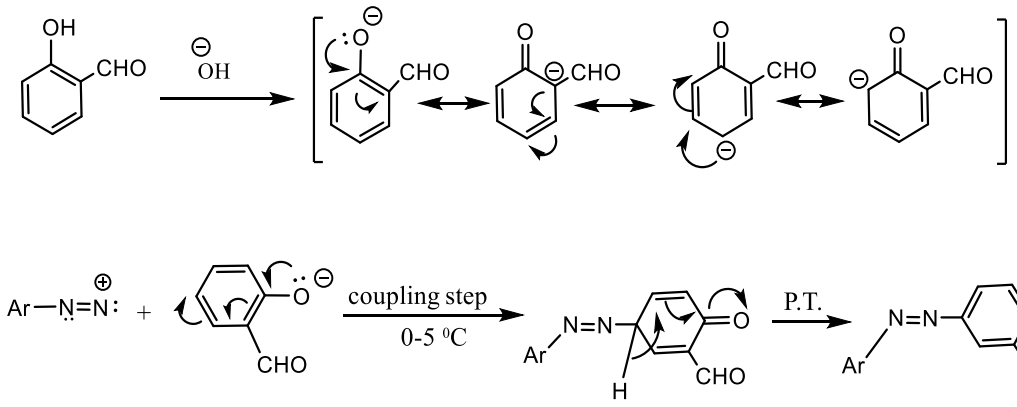


Scheme (3-3)

The coupling reaction is an electrophilic substitution reaction in aromatic systems proceeds according to the mechanism[118] described in schemes (3-4 and 3-4a).



Scheme (3-4)



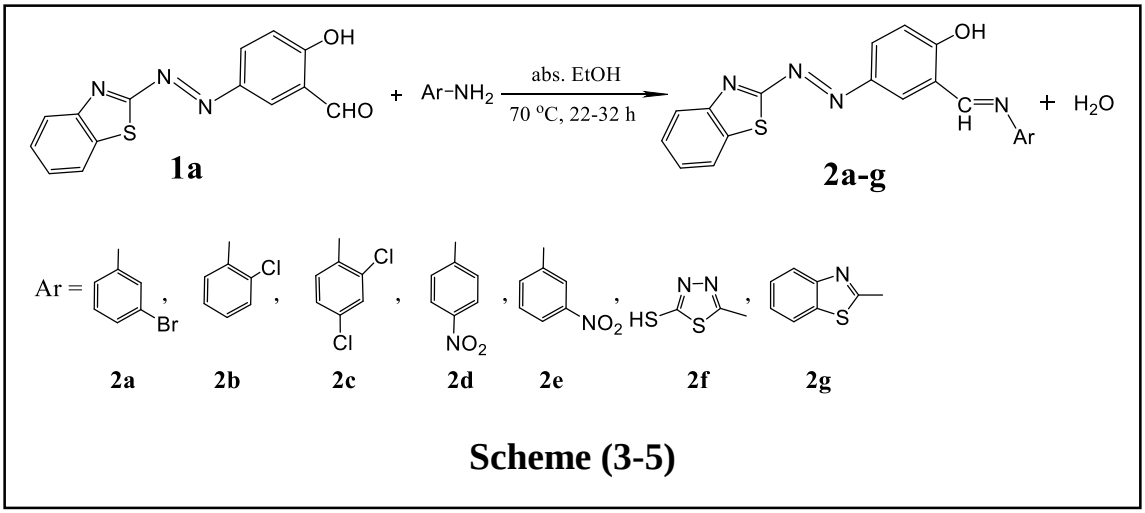
Scheme (3-4a)

FT-IR spectrum of azoaldehyde derivative **1a**, figure (3-3) showed disappearance the sharp bands at 3398 cm^{-1} and 3273 cm^{-1} attributed to asymmetric and symmetric stretching vibrations of (-NH_2) group in benzothiazole, figure (3-2), also disappearing the sharp strong band at 1641 cm^{-1} for bending vibration of (-NH_2) group in the same ring and appearing strong band at 1651cm^{-1} attributed to the stretching vibration of (C=O) group which gives good evidence that the reaction proceeded successfully and yielded the desired azoaldehyde **1a**. The intramolecular hydrogen bonding between carbonyl group oxygen atom and *o*-hydroxy group causes a shifting in the stretching vibration of carbonyl group towards lower frequency. The band of azo group (N=N) stretching did not appear due to decrease the dipole moment value of this group in azoaldehyde derivative **1a**. Other bands were listed in table (3-1).

3.3. Synthesis of azoimine derivatives 2a-g

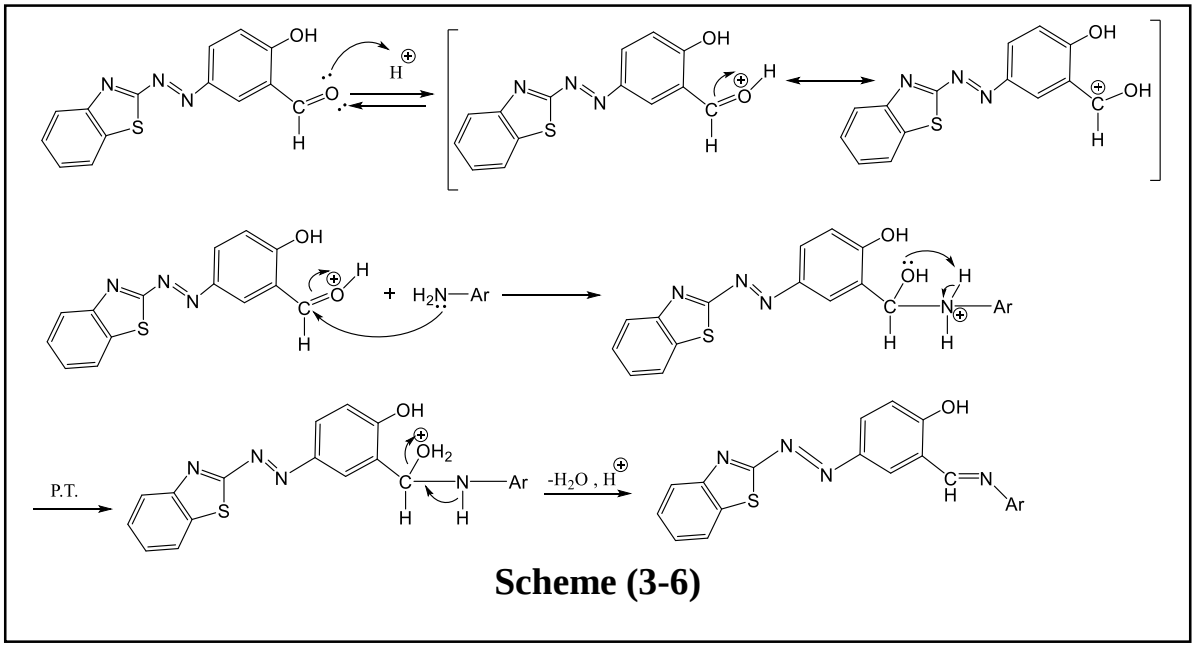
A condensation reaction occurs between azoaldehyde derivative **1a** and the primary aromatic amines (3-bromoaniline, 2-chloroaniline, 2,4-dichloro aniline, 4-nitroaniline, 3-nitroaniline, 2-amino-5-mercapto-1,3,4-thiadiazole and 2-aminobenzothiazole) respectively in the presence of glacial acetic acid

as catalyst in absolute ethanol resulted formation of azoimines **2a-g** as shown in scheme (3-5).



Scheme (3-5)

The reaction mechanism was well-known and shown in scheme (3-6).



Scheme (3-6)

(TLC) showed that rate of the reaction of azoaldehyde derivative **1a** with the selected aromatic amines is relatively increased with decreasing strength of the electron-withdrawing group substituted in benzene ring of the aromatic amine due to the relatively less decreasing in the electronic density on the amine group nitrogen atom. It is also found that the reaction of azoaldehyde derivative **1a** with **AMT** was completed in a relatively shorter time than the others, while its reaction with 2-aminobenzothiazole required relatively

longer time than the others to complete. The reason may be attributed to the weaker resonance of the electron lone-pair of amine group nitrogen atom with π-electrons system of 1,3,4-thiadiazole ring than with benzene or benzothiazole, so the electronic density on amino group nitrogen atom in **AMT** will be relatively higher.

In general, the reaction of azoaldehyde derivative **1a** with the selected aromatic amines required relatively long times for completion, the reason may be related with presence of the electron-withdrawing groups and steric hindrance effects coming from the bulky size of azoaldehyde molecule which is also contained hydroxyl group in ***ortho*** position to carbonyl group.

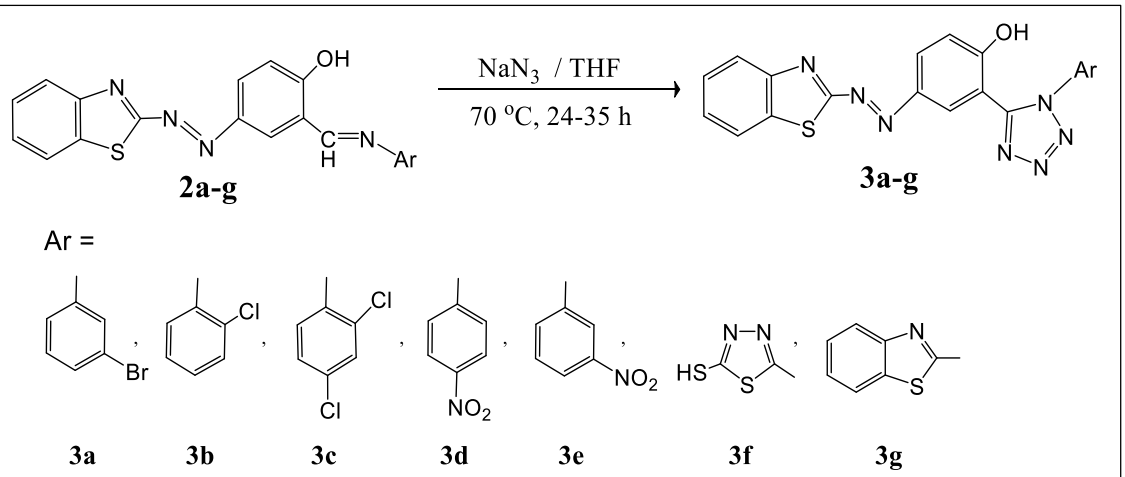
FT-IR spectra, figures (3-4) -(3-10) at $\bar{\upsilon}$ (cm^{-1}) (KBr) of the synthesized azoimines **2a-g** illustrate good evidence that the reactions happened successfully by disappearing the strong band at $1651cm^{-1}$ belong to the stretching vibration of (C=O) group and appearing medium-strong band at lower frequency at the range (1602-1622) cm^{-1} attributed to the stretching vibration of imine group (C=N). Also, the spectra were devoid of the sharp bands for asymmetric and symmetric stretching vibrations of ($-NH_2$) group at the general range (3400-3250) cm^{-1}. Other characteristic bands with their interpretation were summarized in table (3-1).

Table (3-1): FT-IR data of the synthesized azoaldehyde derivative 1a and azoimine derivatives 2a-g in cm^{-1}

Com. no.	FT-IR bands	Fig. no.	Page no.
1a	3269_{br} (υ_{O-H}), 3064 ($\upsilon_{C-H,\ benzene\ rings}$), 2868 and 2756 ($\upsilon_{C-H,\ aldehyde}$), 1651 ($\upsilon_{C=O}$), 1593 and 1464 ($\upsilon_{C=C,\ benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$),750 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-3)	90
2a	3379_{br} (υ_{O-H}), 3064 ($\upsilon_{C-H,\ benzene\ rings}$), 1606 ($\upsilon_{C=N}$), 1577 and 1477 ($\upsilon_{C=C,\ benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 752 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-4)	91
2b	3317_{br} and 3178_{br} (υ_{O-H}), 3063 ($\upsilon_{C-H,\ benzene\ rings}$), 1608 ($\upsilon_{C=N}$), 1523, 1477 and 1446 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 750 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-5)	92
2c	3309_{br} (υ_{O-H}), 3063 ($\upsilon_{C-H,\ benzene\ rings}$), 1610 ($\upsilon_{C=N}$), 1543 and 1475 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 752 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-6)	93
2d	3371_{br} (υ_{O-H}), 3064 ($\upsilon_{C-H,\ benzene\ rings}$), 1608 ($\upsilon_{C=N}$), 1589 and 1448 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$),1514 ($\upsilon_{as.\ NO_2}$), 1404 ($\upsilon_{N=N}$), 1336 ($\upsilon_{s.\ NO_2}$), 758 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-7)	94
2e	3340_{br} (υ_{O-H}), 3064 ($\upsilon_{C-H,\ benzene\ rings}$), 1612 ($\upsilon_{C=N}$), 1483 and 1442 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$),1525 ($\upsilon_{as.\ NO_2}$), 1399 ($\upsilon_{N=N}$), 1348 ($\upsilon_{s\ NO_2}$), 752 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-8)	95
2f	3273 (υ_{O-H}), 3082 ($\upsilon_{C-H,\ benzene\ rings}$), 1622 ($\upsilon_{C=N}$), 1498($\upsilon_{C=C,benzene}$, $\upsilon_{C=N,\ thiadiazole}$ and $\upsilon_{C=N,\ benzothiazole\ ,\ vib.\ coupling}$), 1132 ($\upsilon_{C=S\ ,\ thioketone\ form}$) , 746 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-9)	96
2g	3317_{br} and 3182_{br} (υ_{O-H}), 3061 ($\upsilon_{C-H,\ benzene\ rings}$), 1602 ($\upsilon_{C=N}$), 1523 and 1454 ($\upsilon_{C=C,benzene}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 748 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-10)	97

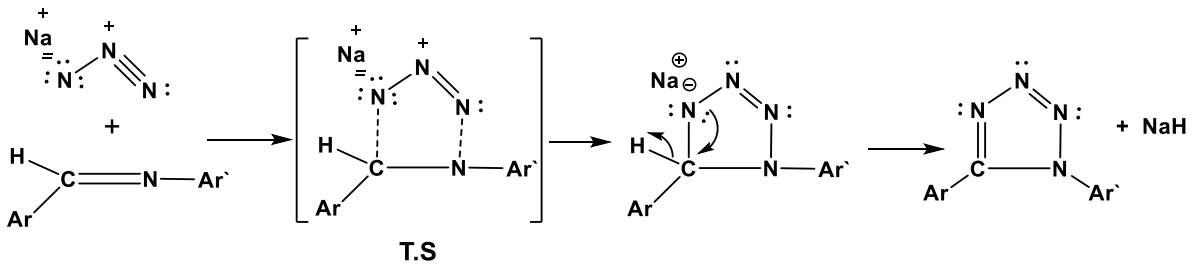
3.4. Synthesis of 1,5-disubstituted tetrazole derivatives 3a-g

The reaction of azoimine derivatives **2a-g** with sodium azide in tetrahydrofuran produced a series of 1,5-disubstituted tetrazoles **3a-g** respectively as shown in scheme (3-7).



Scheme (3-7)

This reaction was classified as [3+2] cycloaddition. The common features of this type of reactions are best accommodated by the transition state geometry in which the dipolarphile molecule and its ligands lie in one plane, and the azide as a 1,3- dipolar group lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form σ bonds, as shown in scheme (3-8)[80].



Scheme (3-8)

TLC technique showed that the rate of reaction is relatively increased with decreasing strength of the electron-withdrawing group substituted in benzene ring which is directly bonded with imine group nitrogen atom, the reason may be attributed to the relatively less decreasing in the electronic density on the imine group nitrogen atom, also the stability of the cyclic transition state for azide addition may be increased when the imine derivative is substituted with electron-withdrawing groups, have mesomeric effect such

as chlorine and bromine, in benzene ring which is directly bonded with imine group nitrogen atom.

It is also found that reaction of imine derivative **2f**, which containing thiadiazole moiety directly bonded with imine group nitrogen atom, with sodium azide was completed in a relatively shorter time than the others, while reaction of imine derivative **2g**, which containing benzothiazole moiety directly bonded with imine group nitrogen atom, with sodium azide required relatively longer time than the others to complete. The reason may be attributed to increase the electronic density on the imine group nitrogen atom in imine derivative **2f** which is caused by the electron-donating resonance of thiadiazole ring, while the electronic density on imine group nitrogen atom in imine derivative **2g** is decreased due to the electron-withdrawing resonance of benzothiazole ring, so expected that the cyclic transition state for azide addition to imine derivative **2f** will be the more stable due to the electron-donating resonance of thiadiazole ring, while the cyclic transition state for azide addition to imine derivative **2g** will be the less stable due to the electron-withdrawing resonance of benzothiazole ring.

Due to presence of polarized groups such as phenolic O-H, nitro group NO_2, sulfhydryl group S-H in addition of four nitrogen atoms in tetrazole ring, the synthesized tetrazoles showed good solubility in water.

FT-IR spectra of 1,5-disubstituted tetrazoles **3a-g**, figures (3-11)-(3-17) showed a disappearance of the medium-strong band at the range (1602-1622) cm^{-1} which is attributed to the stretching vibration of (C=N) group in azoimine derivatives and the appearance of broad strong band at lower frequency at the range (1564-1575) cm^{-1} attributed to the stretching vibration of (C=N) inside tetrazole ring which is interacted with stretching vibrations of (C=C) and (C=N) in benzene and benzothiazole rings respectively. Beside this, the FT-IR spectra of these derivatives were devoid of a strong band at 2133 cm^{-1}

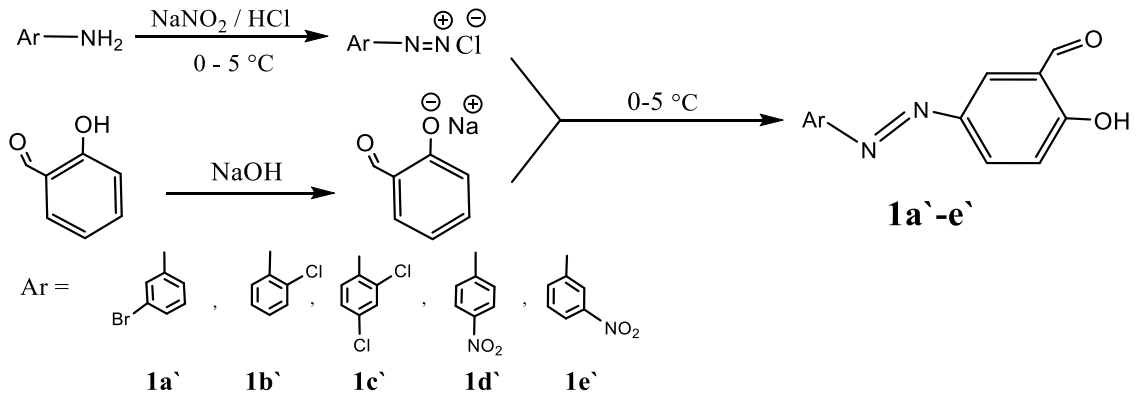
attributed to the stretching vibration of azide group in sodium azide. It is clear that FT-IR data refer to the successful proceeding of cycloaddition reactions and forming tetrazole ring. Other characteristic bands with their interpretation were listed in table (3-2).

Table (3-2) : FT-IR data of the synthesized tetrazole derivatives 3a-g in cm^{-1}

Com. no.	FT-IR bands	Fig. no.	Page no.
3a	3425_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1570_{br} ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$, benzene rings and $\upsilon_{C=N}$, benzothiazole, vib. coupling), 1408 ($\upsilon_{N=N}$), 758 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-11)	98
3b	3408_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1570_{br} ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$, benzene rings and $\upsilon_{C=N}$, benzothiazole, vib. coupling), 1410 ($\upsilon_{N=N}$), 758 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-12)	99
3c	3410_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1568_{br} ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$, benzene rings and $\upsilon_{C=N}$, benzothiazole, vib. coupling), 1404 ($\upsilon_{N=N}$), 756 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-13)	100
3d	3425_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1575_{br} ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$, benzene rings, $\upsilon_{C=N}$, benzothiazole and $\upsilon_{as.\ NO_2}$, vib. coupling), 1413 ($\upsilon_{N=N}$),1305 ($\upsilon_{s.\ NO_2}$), 756 and 709 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-14)	101
3e	3410_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1575_{br} ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$, benzene rings, $\upsilon_{C=N}$, benzothiazole and $\upsilon_{as.\ NO_2}$, vib. coupling), 1408 ($\upsilon_{N=N}$), 1346 ($\upsilon_{s.\ NO_2}$), 744 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-15)	102
3f	3406_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1564 ($\upsilon_{C=N}$, tetrazole, $\upsilon_{C=C}$,benzene rings, $\upsilon_{C=N}$, benzothiazole and $\upsilon_{C=N}$, thiadiazole, vib. coupling), 1408 ($\upsilon_{N=N}$), 756 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-16)	103
3g	3417_{br} (υ_{O-H} and υ_{C-H}, benzene rings, vib. coupling), 1566 ($\upsilon_{C=N}$, tetrazole), 1440 ($\upsilon_{C=C}$, benzene rings and $\upsilon_{C=N}$, benzothiazole, vib. coupling), 1406 ($\upsilon_{N=N}$), 756 ($\delta_{o.o.p\ C-H}$, benzene rings).	(3-17)	104

3.5. Synthesis of azoaldehyde derivatives 1a`-e`

A coupling reaction between the diazonium salts of the primary aromatic amines (3-bromoaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-nitroaniline and 3-nitroaniline) with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution at (0-5) ^{o}C afforded different azoaldehyde derivatives **1a`-e`** respectively. Scheme (3-9).



Scheme (3-9)

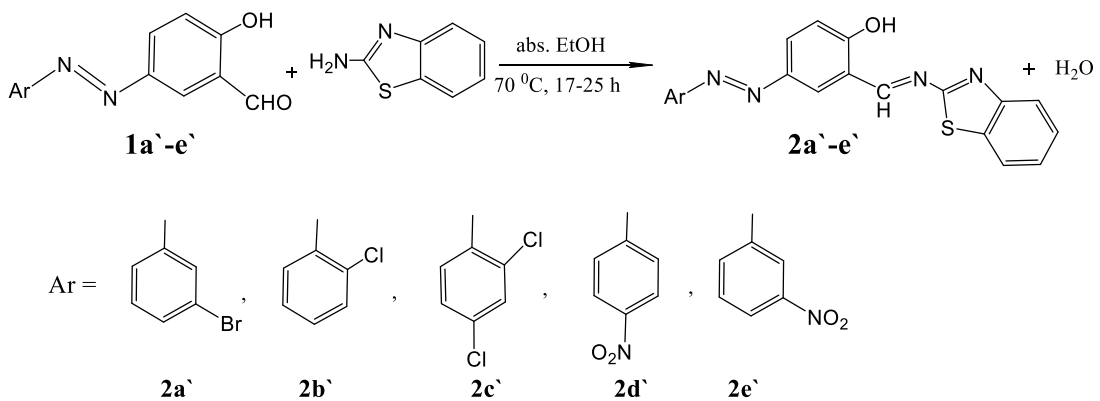
The synthesized azoaldehydes **1a`-e`** were characterized by their melting points and FT-IR spectra at υ (cm^{-1}) (KBr). FT-IR spectra, figures (3-18)-(3-22) of azoaldehyde derivatives **1a`-e`** were devoid of the sharp bands at the general range (3400-3250) cm^{-1} attributed to asymmetric and symmetric stretching vibrations of (-NH_2) group and appearance of strong band at the range (1656-1664) cm^{-1} attributed to the stretching vibration of (C=O) group which gives good evidence that the reactions proceeded successfully and yielded the desired azoaldehydes **1a`-e`**. The intramolecular hydrogen bonding between carbonyl group oxygen atom and *o*-hydroxy group causes shifting the stretching vibrations of carbonyl groups towards lower frequencies. The spectra also showed appearance of characteristic weak band at the range (1402-1425) cm^{-1} assigned to azo group (N=N) stretching. The relative increasing in dipole moment of azo group in azoaldehyde derivatives **1a`-e`**caused appearance of azo group stretching band. Other characteristic bands were shown in table (3-3).

Table (3-3): FT-IR data of the synthesized azoaldehyde derivatives 1a`-e` in cm^{-1}

Com. no.	FT-IR bands	Fig. no.	Page no.
1a`	3192 (υ_{O-H}), 3068 ($\upsilon_{C-H,\ benzene\ rings}$), 2872 ($\upsilon_{C-H,\ aldehyde}$), 1656 ($\upsilon_{C=O}$), 1573 and 1481 ($\upsilon_{C=C,\ benzene\ rings}$), 1413 ($\upsilon_{N=N}$), 833, 732 and 673 ($\delta_{o.o.p.\ C-H,\ benzene\ rings}$).	(3-18)	105
1b`	3194 (υ_{O-H}), 3057 ($\upsilon_{C-H,\ benzene\ rings}$), 2843 and 2740 ($\upsilon_{C-H,\ aldehyde}$), 1664 ($\upsilon_{C=O}$), 1573 and 1475 ($\upsilon_{C=C\ benzene\ rings}$), 1425 ($\upsilon_{N=N}$), 767 and 742 ($\delta_{o.o.p.\ C-H,\ aromatic\ rings}$).	(3-19)	106
1c`	3412 (υ_{O-H}), 3088 ($\upsilon_{C-H,\ benzene\ rings}$), 2856 ($\upsilon_{C-H,\ aldehyde}$), 1662 ($\upsilon_{C=O}$), 1575, 1518 and 1475 ($\upsilon_{C=C,\ benzene\ rings}$), 1402 ($\upsilon_{N=N}$), 831 and 771 ($\delta_{o.o.p.\ C-H,\ benzene\ rings}$).	(3-20)	107
1d`	3161 (υ_{O-H}), 3103 ($\upsilon_{C-H,\ benzene\ rings}$), 2870 ($\upsilon_{C-H,\ aldehyde}$), 1660 ($\upsilon_{C=O}$), 1581 and 1481 ($\upsilon_{C=C,\ benzene\ rings}$), 1523 ($\upsilon_{as.\ NO_2}$), 1423 ($\upsilon_{N=N}$), 1340 ($\upsilon_{s.\ NO_2}$), 854 and 759 ($\delta_{o.o.p.C-H,\ benzene\ rings}$).	(3-21)	108
1e`	3182 (υ_{O-H}), 3086 ($\upsilon_{C-H,\ benzene\ rings}$), 2860 and 2748 ($\upsilon_{C-H,\ aldehyde}$), 1660 ($\upsilon_{C=O}$), 1575 and 1483 ($\upsilon_{C=C,\ benzene\ rings}$), 1525($\upsilon_{as.\ NO_2}$), 1425 ($\upsilon_{N=N}$), 1350 ($\upsilon_{s.\ NO_2}$), 810, 742 and 673 ($\delta_{s\ o.o.p.\ C-H,\ benzene\ rings}$).	(3-22)	109

3.6. Synthesis of azoimine derivatives 2a`-e`

A condensation reaction between azoaldehyde derivatives **1a`-e`** and 2-aminobenzothiazole in the presence of glacial acetic acid as catalyst in absolute ethanol resulted in the formation of azoimines **2a`-e`** as shown in scheme (3-10).



Scheme (3-10)

(TLC) showed that the rate of reaction of 2-aminobenzothiazole with the synthesized azoaldehyde derivatives **1a`-e`** is relatively increased with increasing strength of electron-withdrawing group substituted in benzene ring which is directly bonded with azo group due to decrease the electronic density on the carbonyl group carbon atom (increasing the electrophilicity).

In general, the reaction of 2-aminobenzothiazole with the synthesized azoaldehyde derivatives **1a`-e`** required relatively long times for completion, the reason may be related with decreasing nucleophilicity of amino group in 2-aminobenzothiazole due to the resonance with benzothiazole ring and presence of steric hindrance effects caused by the bulky size of both benzothiazole moiety and azoaldehydes molecules which are also contained hydroxyl group in ***ortho*** position to carbonyl group.

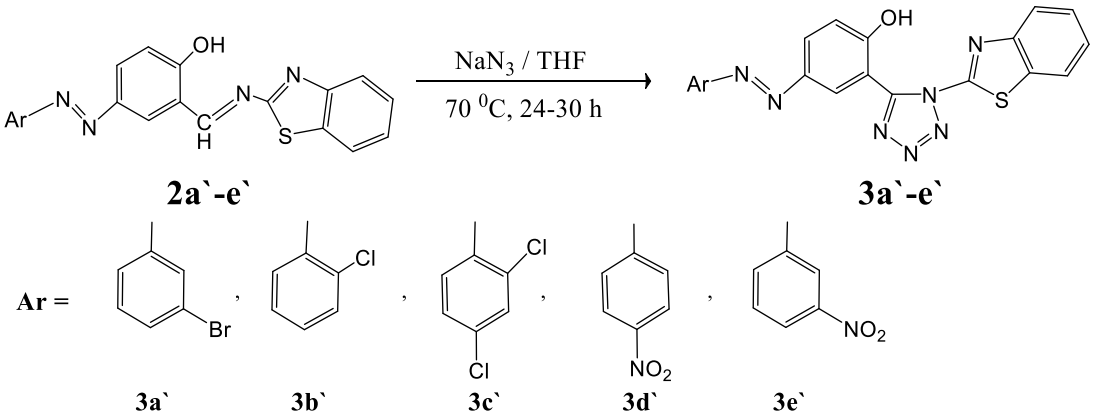
FT-IR spectra, figures (3-23)-(3-27) at $\bar{\upsilon}$ (cm^{-1}) (KBr) of the synthesized azoimine derivatives **2a`-e`** illustrate good evidence that the reactions happened successfully by causing the disappearance of the sharp bands at 3398 cm^{-1} and 3273 cm^{-1} attributed to the asymmetric and symmetric stretching vibrations of ($-NH_2$) group in benzothiazole, also causing disappearance of the sharp strong band at 1641 cm^{-1} assigned to the bending vibration of ($-NH_2$) group in the same ring. The spectrum also showed the disappearance of the sharp strong band at the range (1656-1664) cm^{-1} belong to the stretching vibration of (C=O) group and appearing medium-strong band at lower frequency at the range (1600-1608) cm^{-1} attributed to the stretching vibration of imine group (C=N). Other characteristic bands with their interpretation were summarized in table (3-4).

Table (3-4): FT-IR data of the synthesized azoimine derivatives 2a`-e` in cm^{-1}

Com. no.	FT-IR bands	Fig. no.	Page no.
2a`	3443 (υ_{O-H}), 3059 ($\upsilon_{C-H,\ benzene\ rings}$), 1606 ($\upsilon_{C=N}$), 1568 and 1489 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 1415 ($\upsilon_{N=N}$), 831, 754 and 675 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-23)	110
2b`	3373 (υ_{O-H}), 3057 ($\upsilon_{C-H,\ benzene\ rings}$), 1608 ($\upsilon_{C=N}$), 1568, 1494 and 1475 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 1427 ($\upsilon_{N=N}$), 756 ($\delta_{o.o.p\ C-H,\ benzene\ rings}$).	(3-24)	111
2c`	3419 (υ_{O-H}), 3061 ($\upsilon_{C-H,\ benzene\ rings}$), 1600 ($\upsilon_{C=N}$), 1568 and1479 ($\upsilon_{C=C,benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 1425 ($\upsilon_{N=N}$), 752 and 673 ($\delta_{o.o.p\ C-H,benzene\ rings}$).	(3-25)	112
2d`	3448 (υ_{O-H}), 3103 and 3074 ($\upsilon_{C-H,\ benzene\ rings}$), 1606 ($\upsilon_{C=N}$), 1568, 1494 and 1454($\upsilon_{C=C,\ benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 1523 ($\upsilon_{as.\ NO_2}$), 1429 ($\upsilon_{N=N}$), 1342 ($\upsilon_{s.\ NO_2}$), 856, 763 and 686 ($\delta_{o.o.p.\ C-H,benzene\ rings}$).	(3-26)	113
2e`	3377 (υ_{O-H}), 3084 ($\upsilon_{C-H,\ benzene\ rings}$), 1608 ($\upsilon_{C=N}$), 1568 and 1492 ($\upsilon_{C=C,\ benzene\ rings}$ and $\upsilon_{C=N,\ benzothiazole,\ vib.\ coupling}$), 1527 ($\upsilon_{as.\ NO_2}$), 1427 ($\upsilon_{N=N}$), 1348 ($\upsilon_{s.\ NO_2}$), 808, 759 and 675 ($\delta_{o.o.p\ C-H,benzene\ rings}$).	(3-27)	114

3.7. Synthesis of 1,5-disubstituted tetrazole derivatives 3a`-e`

This series of tetrazoles resulted from the reaction of sodium azide with azoimine derivatives **2a`-e`** in tetrahydrofuran as indicated in scheme (3-11).



Scheme (3-11)

TLC technique showed that the rate of reaction is decreased a lot in presence of electron-donating groups substituted in benzene ring, while it is relatively increased in presence of electron-withdrawing groups. Also, the rate is relatively increased with increasing strength of the electron-withdrawing group, the reason may be assigned to decreasing the electronic density on imine group carbon atom (increasing the electrophilicity), also stability of the cyclic transition state for azide addition may be increased when the imine derivative is substituted with electron-withdrawing groups, especially by resonance, in benzene ring which is directly bonded with azo group, so it expected that the cyclic transition state for azide addition to imine derivative **2d`** which is substituted with nitro group in ***para*** position will be the more stable than the others.

The synthesized tetrazoles showed good solubility in water due to presence of polarized groups such as phenolic O-H, nitro group NO_2 in addition of four nitrogen atoms in tetrazole ring.

FT-IR spectra of tetrazoles **3a`-e`,** figures (3-28)-(3-32) showed the disappearance of the medium-strong band at the range (1600-1608) cm^{-1} which attributed to the stretching vibration of (C=N) group in azoimine derivatives and appearance of broad strong band at lower frequency at the range (1573-1595) cm^{-1} attributed to the stretching vibration of (C=N) inside tetrazole ring which is interacted with stretching vibrations of (C=C) and (C=N) in benzene and benzothiazole rings respectively. Beside this, the FT-IR spectra of these derivatives were devoid of a strong band at 2133 cm^{-1} attributed to the stretching vibration of azide group. It is clear that FT-IR data refer to the successful proceeding of cycloaddition reactions and forming tetrazole ring. Other characteristic bands with their interpretation were listed in table (3-5).

Table (3-5): FT-IR data of the synthesized tetrazole derivatives 3a`-e` in cm^{-1}

Com. no.	FT-IR bands	Fig. no.	Page no.
3a`	3398_{br} (υ_{O-H} and $\upsilon_{C-H, benzene rings, vib. coupling}$), 1577 ($\upsilon_{C=N, tetrazole}$), 1454 ($\upsilon_{C=C, benzene rings}$ and $\upsilon_{C=N, benzothiazole, vib. coupling}$), 1423 ($\upsilon_{N=N}$), 765 and 684 ($\delta_{o.o.p\ C-H,\ benzene rings}$).	(3-28)	115
3b`	3396_{br} (υ_{O-H} and $\upsilon_{C-H, benzene rings, vib. coupling}$), 1573 ($\upsilon_{C=N, tetrazole}$, $\upsilon_{C=C, benzene rings}$ and $\upsilon_{C=N, benzothiazole, vib. coupling}$), 1415 ($\upsilon_{N=N}$), 752 ($\delta_{o.o.p\ C-H,\ benzene rings}$).	(3-29)	116
3c`	3398_{br} (υ_{O-H} and $\upsilon_{C-H, benzene rings, vib. coupling}$), 1587 ($\upsilon_{C=N, tetrazole}$), 1548 and 1448 ($\upsilon_{C=C, benzene rings}$ and $\upsilon_{C=N, benzothiazole, vib. coupling}$), 815 and 754 ($\delta_{o.o.p\ C-H,\ benzene rings}$).	(3-30)	117
3d`	3377_{br} (υ_{O-H} and $\upsilon_{C-H, benzene rings, vib. coupling}$), 1591 ($\upsilon_{C=N, tetrazole}$), 1525 ($\upsilon_{as.\ NO_2}$), 1454 ($\upsilon_{C=C, benzene rings}$ and $\upsilon_{C=N, benzothiazole, vib. coupling}$), 1400 ($\upsilon_{N=N}$), 1334 ($\upsilon_{s.\ NO_2}$), 850 and 750 ($\delta_{o.o.p\ C-H,\ benzene rings}$)	(3-31)	118
3e`	3427_{br} (υ_{O-H} and $\upsilon_{C-H, benzene rings, vib. coupling}$), 1595 ($\upsilon_{C=N, tetrazole}$), 1531 ($\upsilon_{as.\ NO_2}$), 1479 and 1450 ($\upsilon_{C=C, benzene rings}$ and $\upsilon_{C=N, benzothiazole, vib. coupling}$), 1406 ($\upsilon_{N=N}$), 1350 ($\upsilon_{s.\ NO_2}$), 806 and 734($\delta_{o.o.p\ C-H,\ benzene rings}$).	(3-32)	119

^{1}H NMR spectra of tetrazoles 3a-g and 3a`-e`

^{1}H NMR spectrum of compound **3a**, figure (3-33) showed twelve signals, overall integration = 12H, attributed to eleven nonequivalent types of aromatic protons in addition of phenolic (O-H) proton at the following chemical shifts in (ppm): δ = 6.99 (s, 1H, H_a), 7.17 (s, 1H, H_b), 7.28 (s, 1H, H_c), 7.60 (s, 1H, H_d), 7.72 (s, 1H, H_e), 7.80 (s, 1H, H_f), 7.98 (s, 1H, H_g), 8.20 (s, 1H, H_h), 8.50 (s, 1H, H_i), 8.59 (s, 1H, H_j), 8.90 (s, 1H, H_k), 9.32 (br, 1H, O-H). The singlet signals around 2.50 ppm and 3.40 ppm are assigned to DMSO and absorbed HDO in DMSO, respectively.

^{1}H NMR spectrum of compound **3b**, figure (3-34) appeared eleven signals, overall integration = 12H, back to ten nonequivalent types of aromatic protons in addition of phenolic (O-H) proton around the following chemical shifts: δ (ppm) = 7.08 (s, 1H, H_a), 7.23 (s, 1H, H_b), 7.44 (s, 1H, H_c), 7.58 (s, 1H, H_d), 7.60 (s, 1H, H_e), 7.69 (d, *J* = 8.4 Hz, 1H, H_f), 7.88 (s, 2H, $2H_g$), 8.22 (d, *J* = 8.3 Hz, 1H, H_h), 8.57 (s, 1H, H_i), 8.58 (s, 1H, H_j), 9.43 (s, 1H, O-H). The singlet signals around 2.59 ppm and 3.42 ppm assigned to DMSO and absorbed HDO in DMSO, respectively.

^{1}H NMR spectrum of compound **3c**, figure (3-35) showed eleven signals, overall integration = 11H, belong to ten nonequivalent types of aromatic protons in addition of phenolic (O-H) proton at δ (ppm) = 7.15 (s, 1H, H_a), 7.28 (s, 1H, H_b), 7.54 (s, 1H, H_c), 7.60 (s, 1H, H_d), 7.75 (d, *J* = 6.9 Hz, 1H, H_e), 7.85 (d, *J* = 8.4 Hz, 1H, H_f), 7.94 (s, 1H, H_g), 8.04 (s, 1H, H_h), 8.13 (s, 1H, H_i), 8.50 (s, 1H, H_j), 9.47 (s, 1H, O-H). The singlet signals around 2.51 ppm and 3.39 ppm are due to DMSO and absorbed HDO in DMSO, respectively.

^{1}H NMR spectrum of compound **3d**, figure (3-36): showed eleven signals, overall integration = 12H, due to ten nonequivalent types of aromatic protons in addition of phenolic (O-H) proton at the following chemical shifts δ (ppm) = 6.81 (d, *J* = 9.7 Hz, 1H, H_a), 7.04 (d, *J* = 9.2 Hz, 1H, H_b), 7.25 (s, 1H, H_c), 7.77 (s, 1H, H_d), 7.87 (s, 1H, H_e), 8.04 (s, 1H, H_f), 8.29 (s, 1H, H_g), 8.36, 8.37 (ss, 2H, H_h and $H_{h`}$), 8.94 (s, 2H, $2H_i$), 10.08 (br, 1H, O-H). The singlet signals of DMSO and absorbed HDO in DMSO appeared at 2.50 ppm and 3.39 ppm, respectively.

^{1}H NMR spectrum of compound **3e**, figure (3-37): showed nine signals, overall integration = 12H, belong to eight nonequivalent types of aromatic protons in addition of phenolic (O-H) proton around the following chemical shifts δ (ppm) = 7.13 (s, 1H, H_a), 7.28 (s, 1H, H_b), 7.38 (s, 1H, H_c), 7.51 (s,

1H, H_d), 7.66 (s, 1H, H_e), 7.75 (s, 1H, H_f), 7.85 (s, 1H, H_g), 8.49 (s_{br}, 4H, $4H_h$), 9.46 (s, 1H, O-H). The singlet signals of DMSO and absorbed HDO in DMSO appeared around 2.50 ppm and 3.40 ppm, respectively.

^{1}H NMR spectrum of compound **3f**, figure (3-38): appeared ten signals, overall integration = 9H, belong to seven nonequivalent types of aromatic protons in addition of phenolic (O-H) proton and S-H, N-H proton in each thiol and thione tautomeric forms, respectively as follow: δ (ppm) = 3.75 (s, 1H, S-H)[119], 7.24 (s, 1H, H_a), 7.39 (s, 1H, H_b), 7.53 (d, *J* = 7.0 Hz, 1H, H_c), 7.61 (s, 1H, H_d), 7.78 (s, 1H, H_e), 8.18 (s, 1H, H_f), 8.51 (s, 1H, H_g), 8.74 (s, N-H, thione form), 9.37 (s, 1H, O-H). The singlet signals of DMSO and absorbed HDO in DMSO appeared at 2.52 ppm and 3.39 ppm, respectively.

^{1}H NMR spectrum of compound **3g**, figure (3-39) showed ten signals, overall integration = 12H, attributed to nine nonequivalent types of aromatic protons in addition of phenolic (O-H) proton as follow: δ (ppm) = 7.06 (s, 1H, H_a), 7.26 (s, 1H, H_b), 7.43 (d, *J* = 8.3 Hz, 2H, $2H_c$), 7.63 (s, 1H, H_d), 7.73 (s, 1H, H_e), 7.75 (d, *J* = 7.4 Hz, 2H, $2H_f$), 7.94 (s, 1H, H_g), 8.14 (s, 1H, H_h), 8.5 (s, 1H, H_i), 9.47 (s, 1H, O-H). DMSO and absorbed HDO in DMSO appeared singlet signals at 2.51 ppm and 3.41 ppm, respectively.

^{1}H NMR spectrum of compound **3a`**, figure (3-40) showed twelve signals, overall integration = 12H, due to eleven nonequivalent types of aromatic protons in addition of phenolic (O-H) proton as follow: δ (ppm) = 7.00 (s, 1H, H_a), 7.18 (s, 1H, H_b), 7.25 (s, 1H, H_c), 7.41 (d, *J* = 7.8 Hz, 1H, H_d), 7.64 (d, *J* = 7.9 Hz, 1H, H_e), 7.76 (s, 1H, H_f), 7.77 (s, 1H, H_g), 8.09 (s, 1H, H_h), 8.49 (s, 1H, H_i), 8.50 (s, 1H, H_j), 8.52 (s, 1H, H_k), 9.34 (s, 1H, O-H). DMSO and absorbed HDO in DMSO showed two singlet signals at 2.51 ppm and 3.39 ppm, respectively.

^{1}H NMR spectrum of compound **3b`**, figure (3-41) appeared eleven signals, overall integration = 12H, attributed to ten nonequivalent types of

aromatic protons in addition of phenolic (O-H) proton at δ (ppm) = 7.00 (s, 1H, H_a), 7.18 (s, 1H, H_b), 7.22 (s, 1H, H_c), 7.32 (d, *J* = 7.8 Hz, 1H, H_d), 7.49 (s, 1H, H_e), 7.52 (s, 1H, H_f), 7.58 (s, 1H, H_g), 7.64 (s, 1H, H_h), 7.71 (d, *J* = 7.3 Hz, 1H, H_i), 8.50 (s, 2H, $2H_j$), 9.36 (s, 1H, O-H). The singlet signals at 2.50 ppm and 3.41 ppm assigned to DMSO and absorbed HDO in DMSO.

^{1}H NMR spectrum of compound **3c`**, figure (3-42) showed nine signals, overall integration = 11H, attributed to eight nonequivalent types of aromatic protons in addition of phenolic (O-H) proton at δ (ppm) = 7.18 (s, 1H, H_a), 7.31 (d, *J* = 8.3 Hz, 1H, H_b), 7.44 (d, *J* = 8.4 Hz, 1H, H_c), 7.62 (s, 1H, H_d), 7.74 (d, *J* = 8.0 Hz, 1H, H_e), 7.97 (d, *J* = 7.8 Hz, 1H, H_f), 8.35 (s, 2H, $2H_g$), 8.62 (s, 2H, $2H_h$), 9.34 (s, 1H, O-H). The singlet signals at 2.51 ppm and 3.40 ppm assigned to DMSO and absorbed HDO in DMSO, respectively.

^{1}H NMR spectrum of compound **3d`**, figure (3-43) appeared to ten signals, overall integration = 12H, belong to nine nonequivalent types of aromatic protons in addition of phenolic (O-H) proton as follow: δ (ppm) = 7.06(s, 1H, H_a), 7.25 (d, *J* = 7.5 Hz, 1H, H_b), 7.43 (d, *J* = 7.4 Hz, 1H, H_c), 7.64 (s, 1H, H_d), 7.71 (s, 2H, $2H_e$), 7.81 (s, 1H, H_f), 8.20 (s, 1H, H_g), 8.23 (s, 1H, H_h), 8.48 (s, 2H, $2H_i$), 9.43 (s, 1H, O-H). The singlet signals for DMSO and absorbed HDO in DMSO appeared around 2.51 ppm and 3.41 ppm, respectively.

^{1}H NMR spectrum of compound **3e`**, figure (3-44) showed twelve signals, overall integration = 12H, attributed to eleven nonequivalent types of aromatic protons in addition of phenolic (O-H) proton at δ (ppm) = 7.06 (s, 1H, H_a), 7.21 (s, 1H, H_b), 7.27 (s, 1H, H_c), 7.42 (s, 1H, H_d), 7.70 (d, *J* = 8.2 Hz, 1H, H_e), 7.88 (s, 1H, H_f), 7.95 (s, 1H, H_g), 8.06 (d, *J* = 6.3 Hz, 1H, H_h), 8.27 (s, 1H, H_i), 8.33 (s, 1H, H_j), 8.49 (s, 1H, H_k), 9.41 (s, 1H, O-H). The singlet signals back to DMSO and absorbed HDO in DMSO appeared around 2.50 ppm and 3.41 ppm, respectively.

Mass spectra of the synthesized tetrazoles 3a-g and 3a`-e`

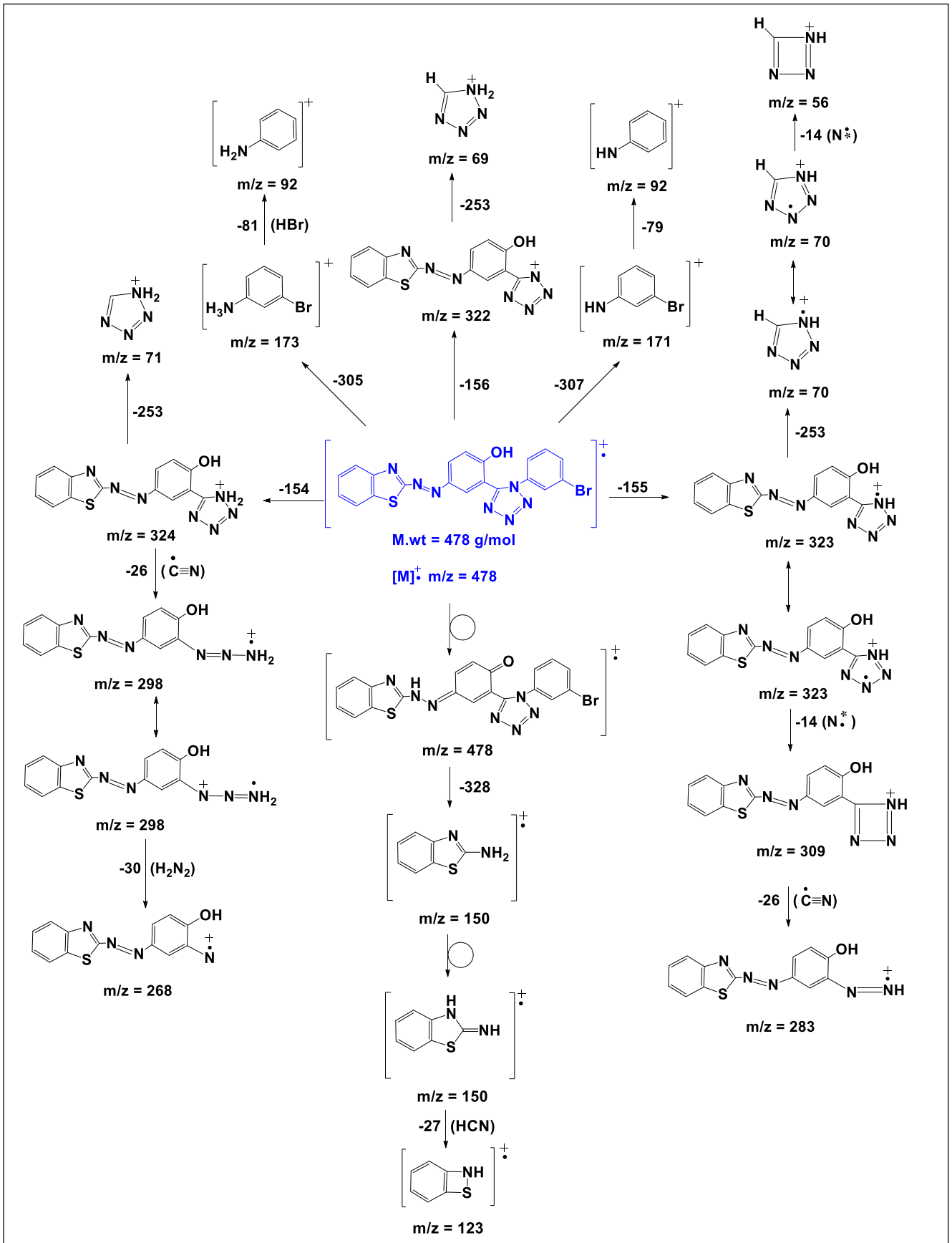
All mass spectra of the synthesized tetrazoles, figures (3-45)- (3-56) appeared the molecular ion peak at (m/z) value is equal to the corresponding calculated mass as indicated in table (3-6) below.

Table (3-6): The estimated molecular weight (g/mol) and measured molecular ion mass (m/z) of the synthesized tetrazoles 3a-g and 3a`-e`

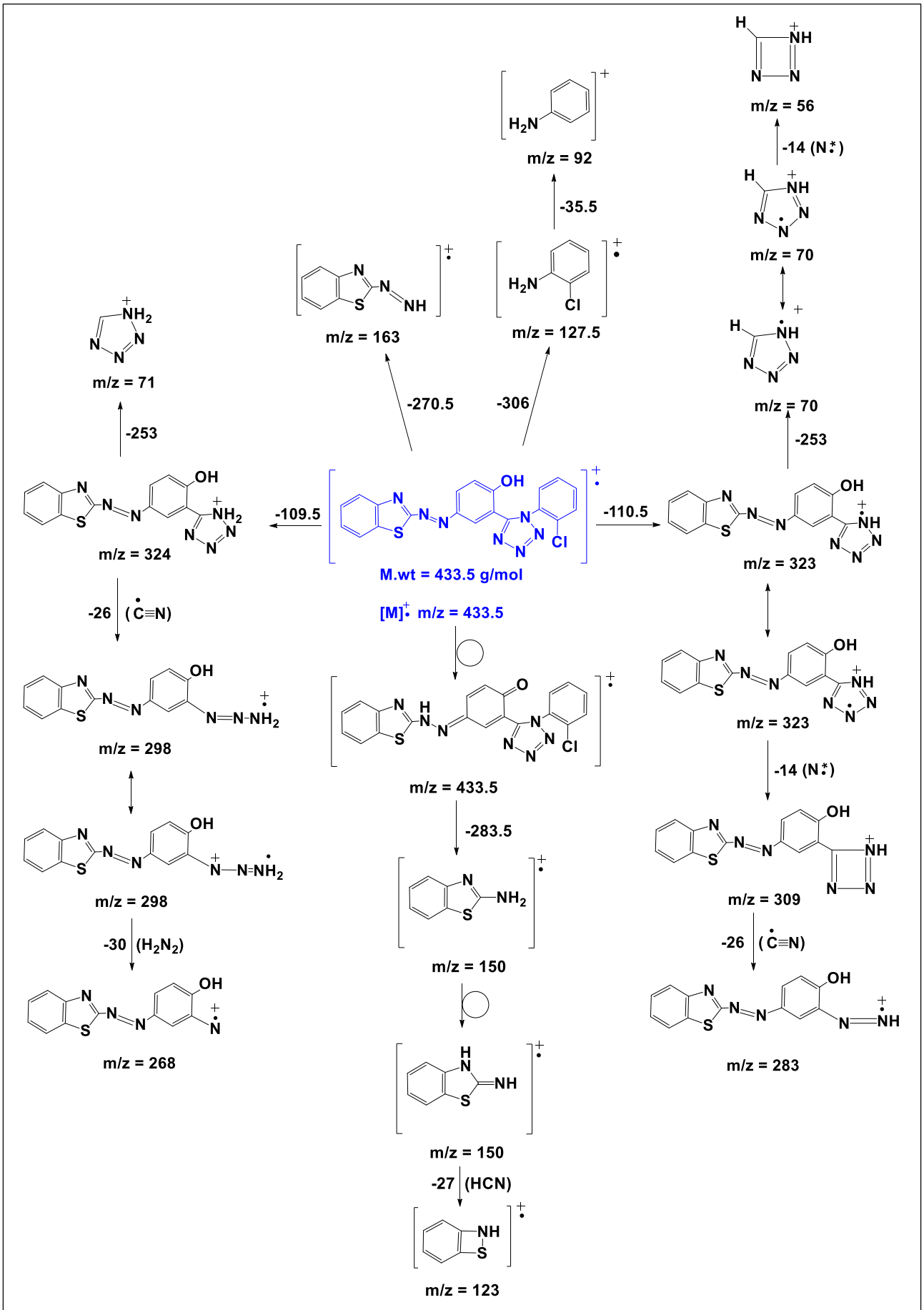
Com. no.	Molecular weight (g/mol)	Molecular ion mass (m/z)
3a	478.33	478.35
3b	433.87	433.90
3c	468.32	468.40
3d	444.43	444.35
3e	444.43	444.50
3f	439.49	439.45
3g	456.50	456.40
3a`	478.33	478.40
3b`	433.87	433.70
3c`	468.32	468.35
3d`	444.43	444.45
3e`	444.43	444.45

Fragmentation pathways and rearrangements of the synthesized 1,5-disubstituted tetrazoles 3a-g and 3a`-e`

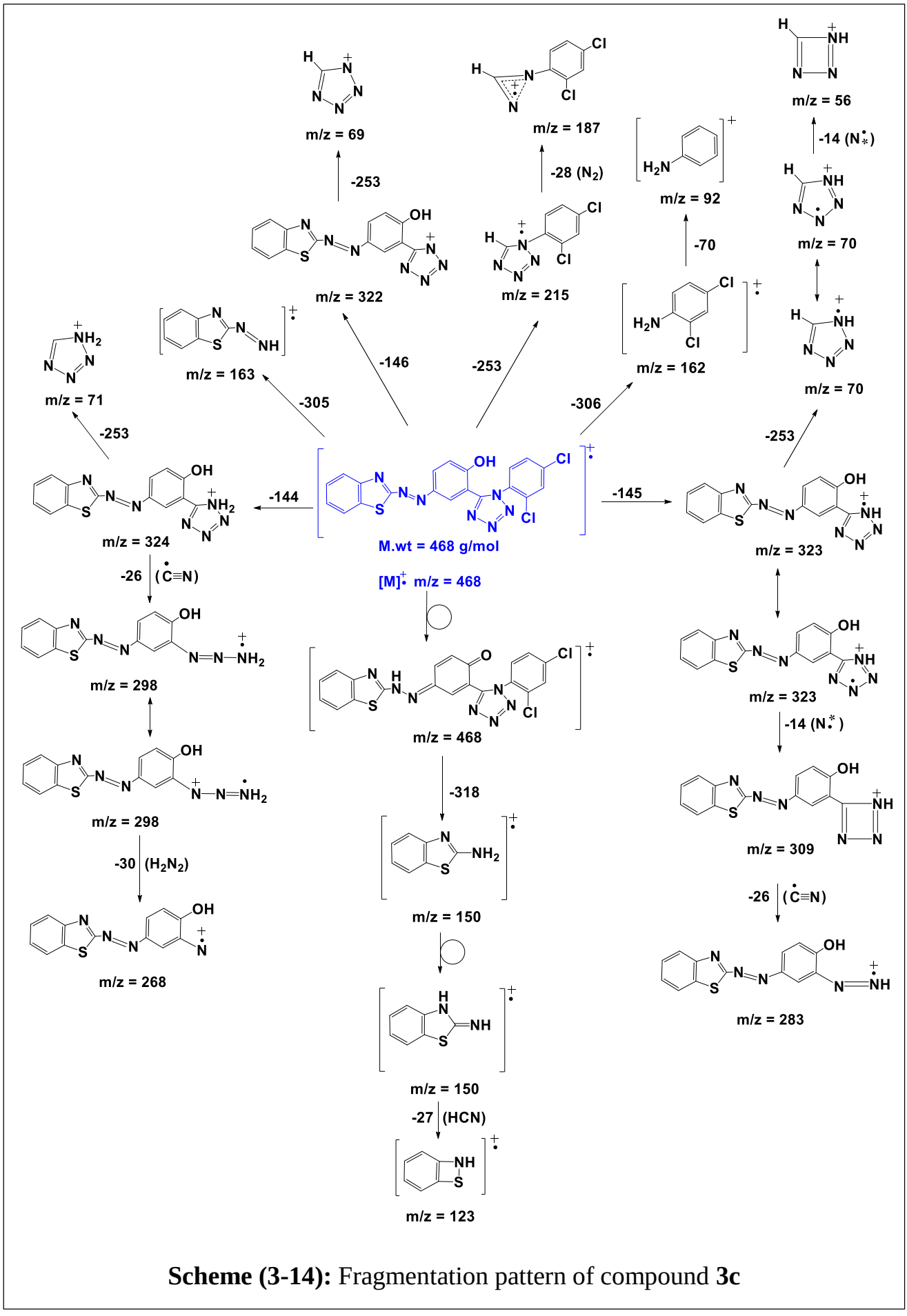
The mass spectral fragmentation pattern of parent tetrazole, all isomers of monomethyl- and dimethyltetrazole, as well as deuterated analogs was studied by Forkey and Carpenter[120]. Moreover, the fragmentation pattern of 1-(*o*-, *m*-, and *p*-tolyl)-5-phenyltetrazoles were studied and shown to consist of a sequence of reactions, namely, initial tautomeric conversion to an azide structure, followed by elimination of a molecule of nitrogen, and rearrangement of the resulting nitrene intermediate to a cation-radical derivative of a methyl-substituted 2-phenylbenzimidazole compound[121]. Also, the mass spectrometric behavior of 1-aryl-5-(1-acyl-2-dialkylamino vinyl)-1*H*-tetrazoles was studied, especially using 1-phenyl-5-(1-benzoyl-2-dimethylaminovinyl)-1*H*-tetrazole and its *D*- and ^{15}N-labeled derivatives[122]. The fragmentation pattern of the synthesized 1,5-disubstituted tetrazoles **3a-g** and **3a`-e`**, schemes (3-12)- (3-23), was suggested depending on the above mentioned reports and other references[123-125]. The mass spectra of the synthesized 1,5-disubstituted tetrazoles showed several significant co-fragments which refer to presence of tetrazole ring such as fragments at (m/z = 69, 70, and 71) which assigned to tetrazolyl cation, tetrazolyl radical cation, and tetrazolium cation, respectively. Also, the fragment at (m/z =56) resulting from the loss of nitrogen radical from tetrazolyl radical cation. Moreover, the fragment at (m/z =57) coming from the loss of nitrogen radical and gain of hydrogen radical from tetrazolyl radical cation. Other significant co-fragments for tetrazole ring were shown in schemes (3-12)- (3-23).



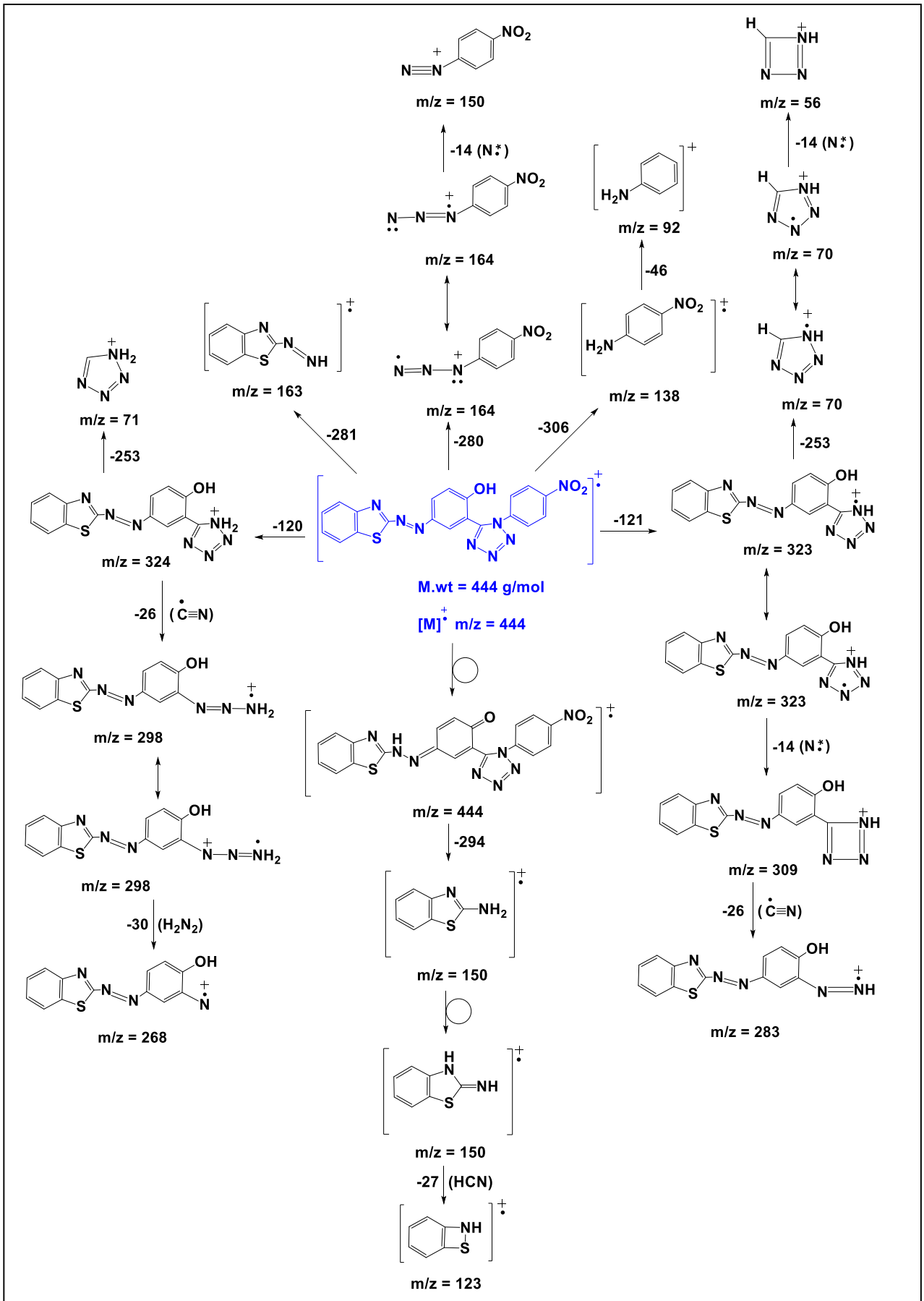
Scheme (3-12): Fragmentation pattern of compound **3a**



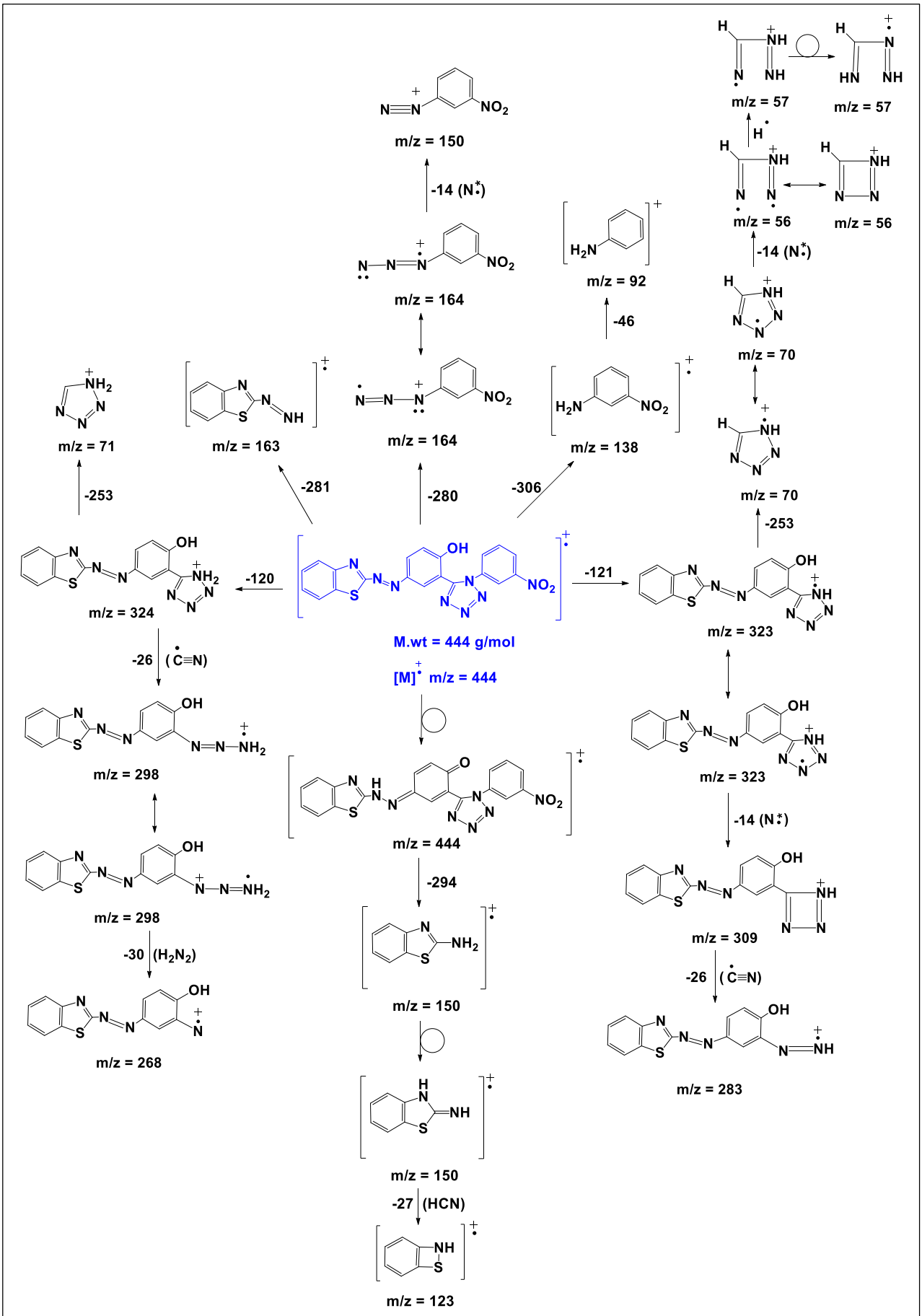
Scheme (3-13): Fragmentation pattern of compound **3b**



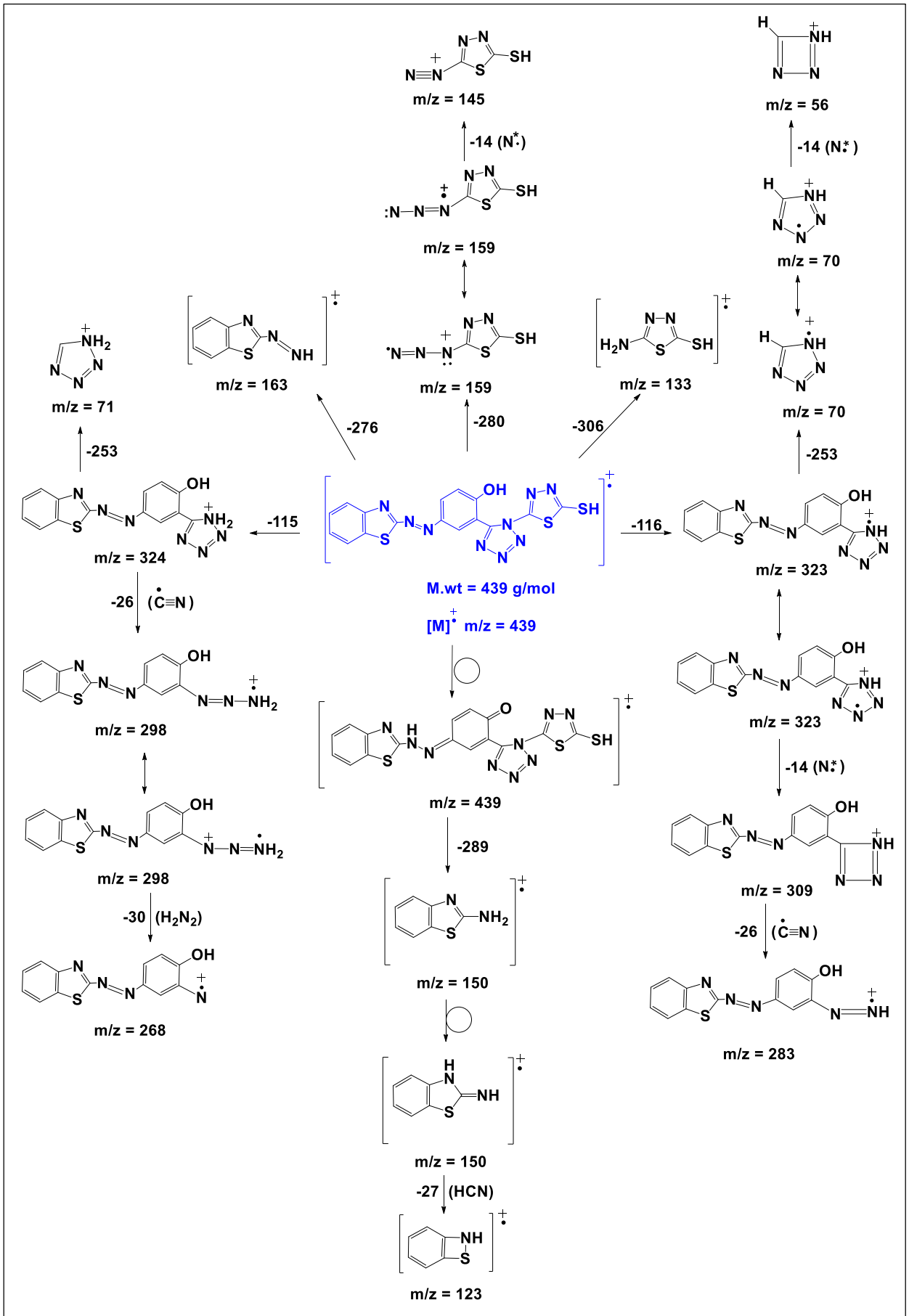
Scheme (3-14): Fragmentation pattern of compound **3c**



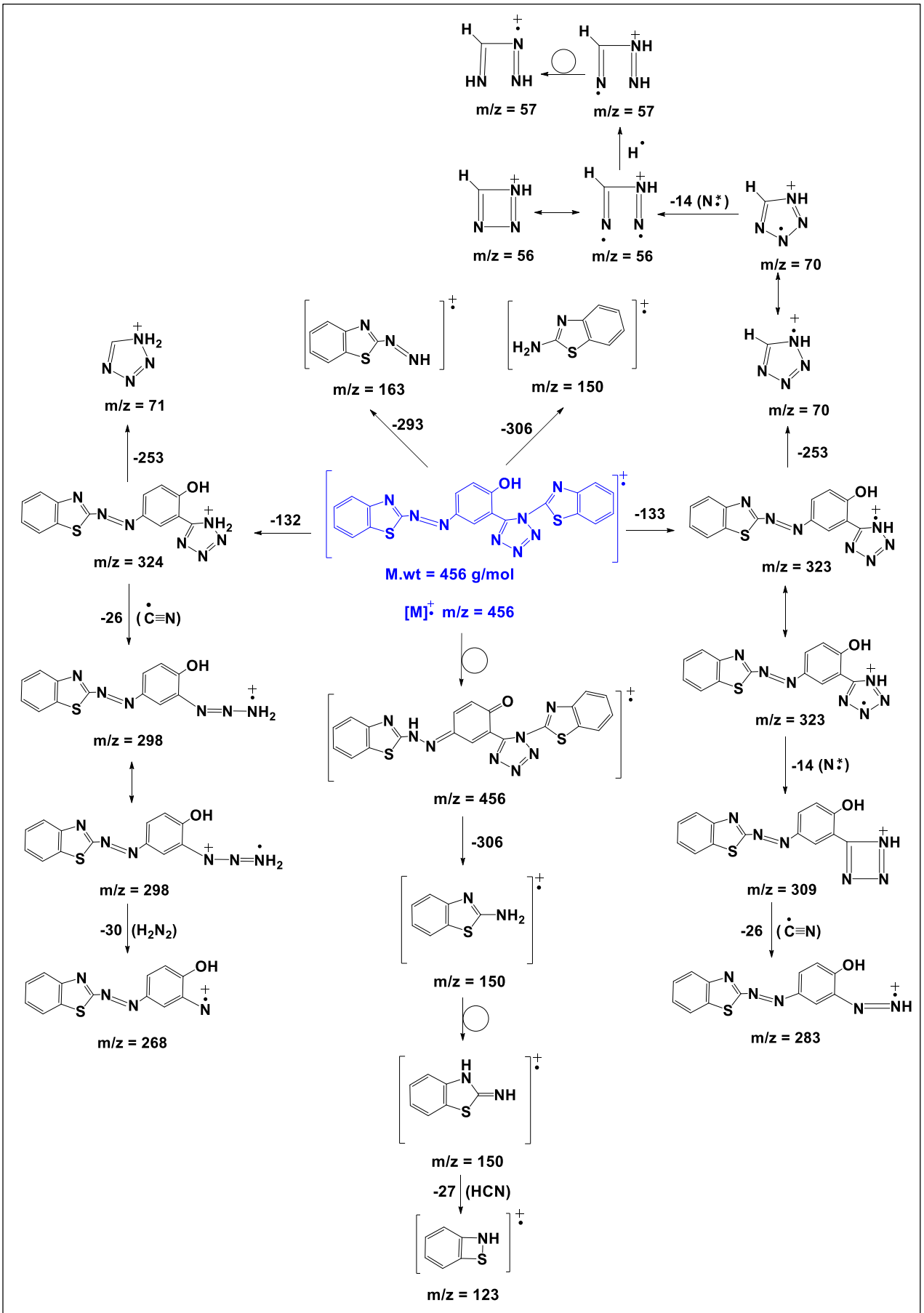
Scheme (3-15): Fragmentation pattern of compound **3d**



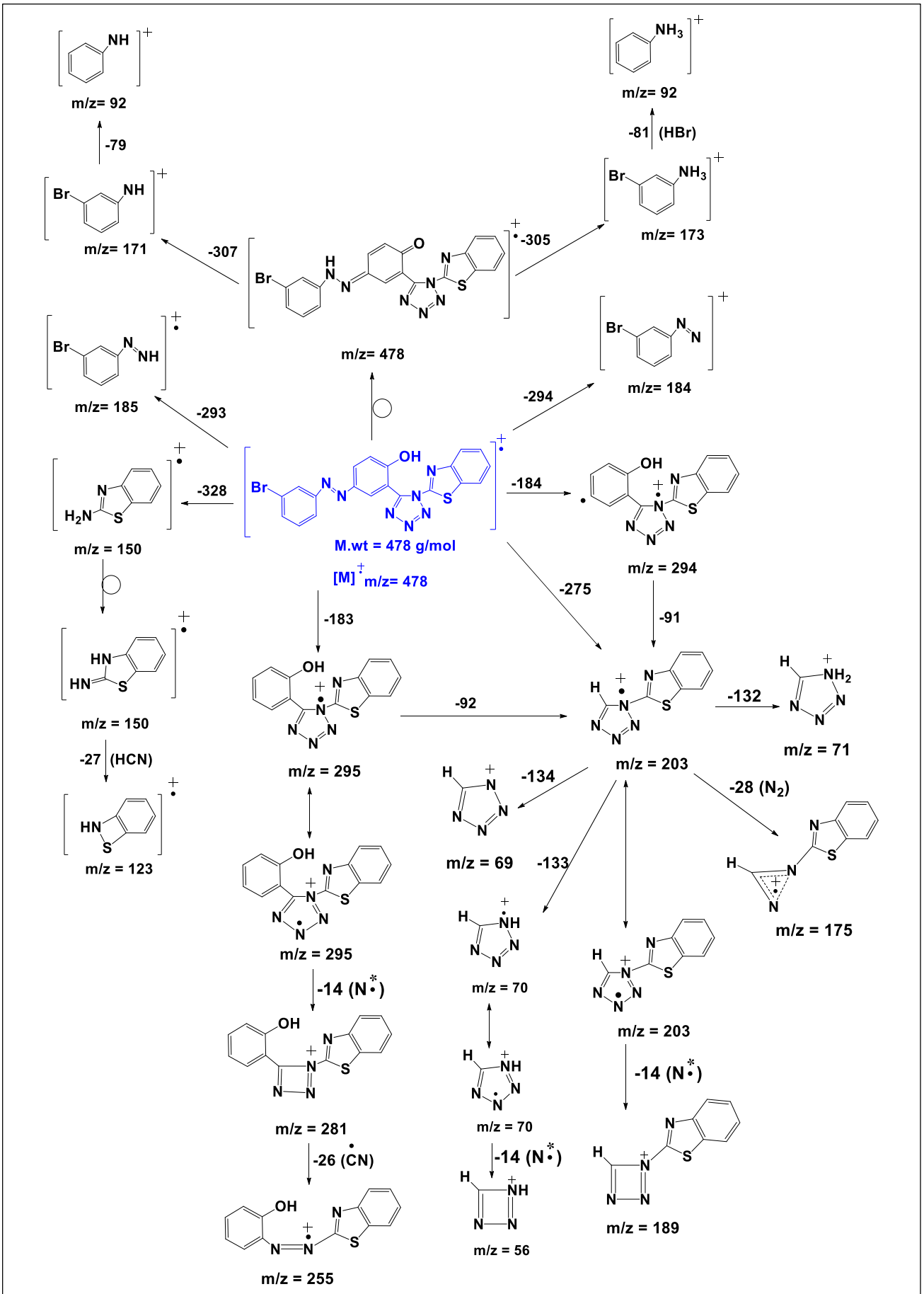
Scheme (3-16): Fragmentation pattern of compound **3e**



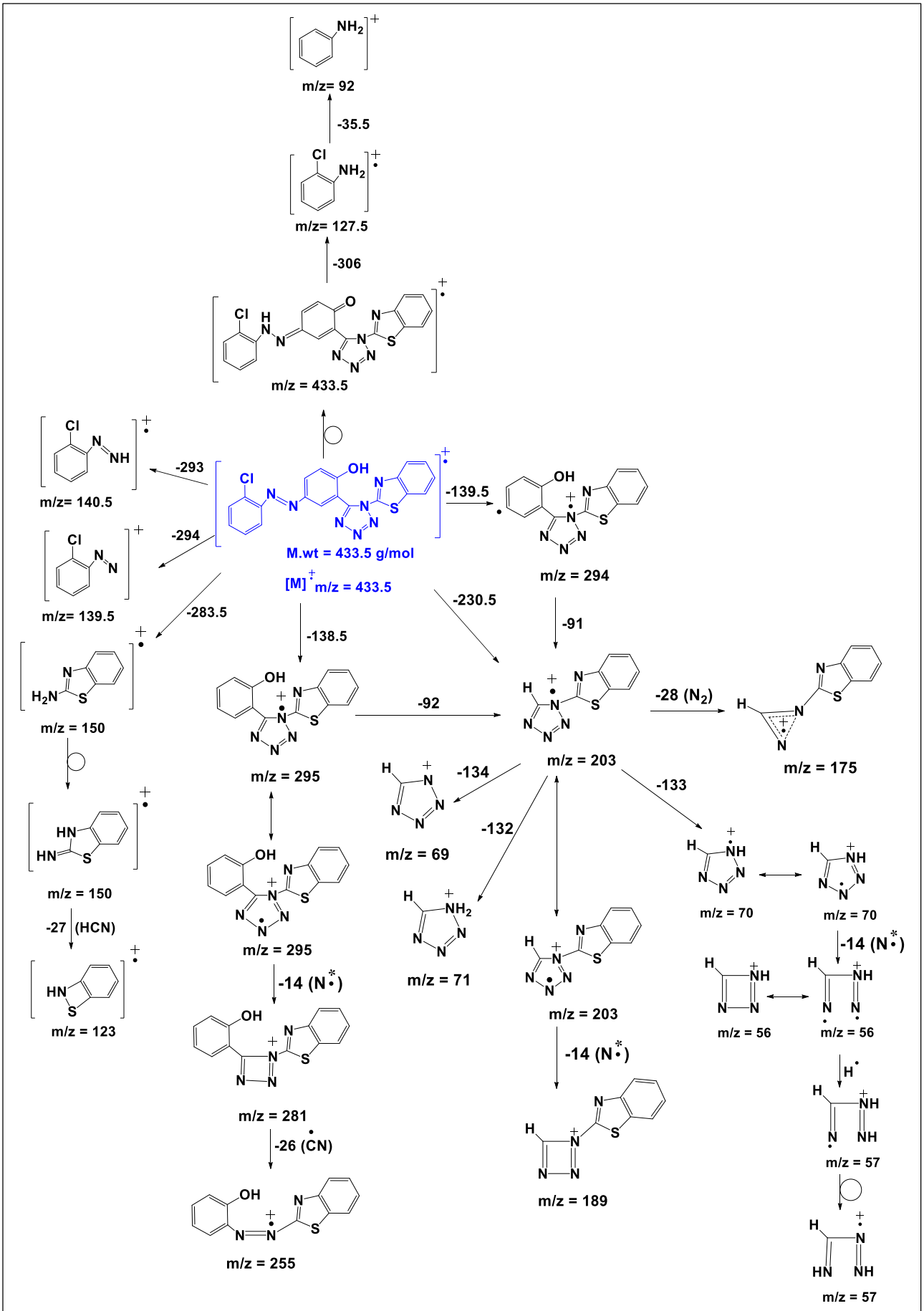
Scheme (3-17): Fragmentation pattern of compound **3f**



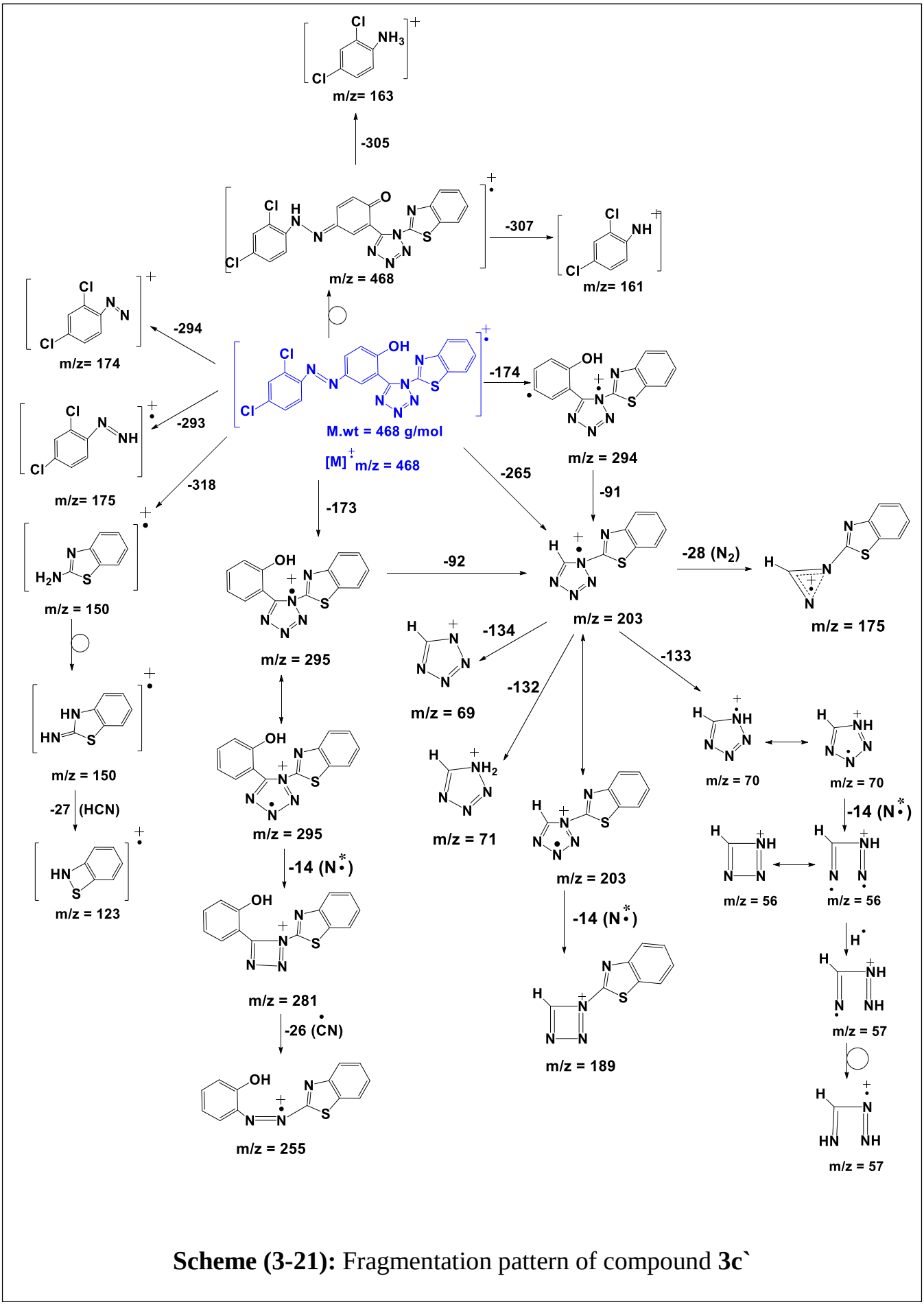
Scheme (3-18): Fragmentation pattern of compound **3g**



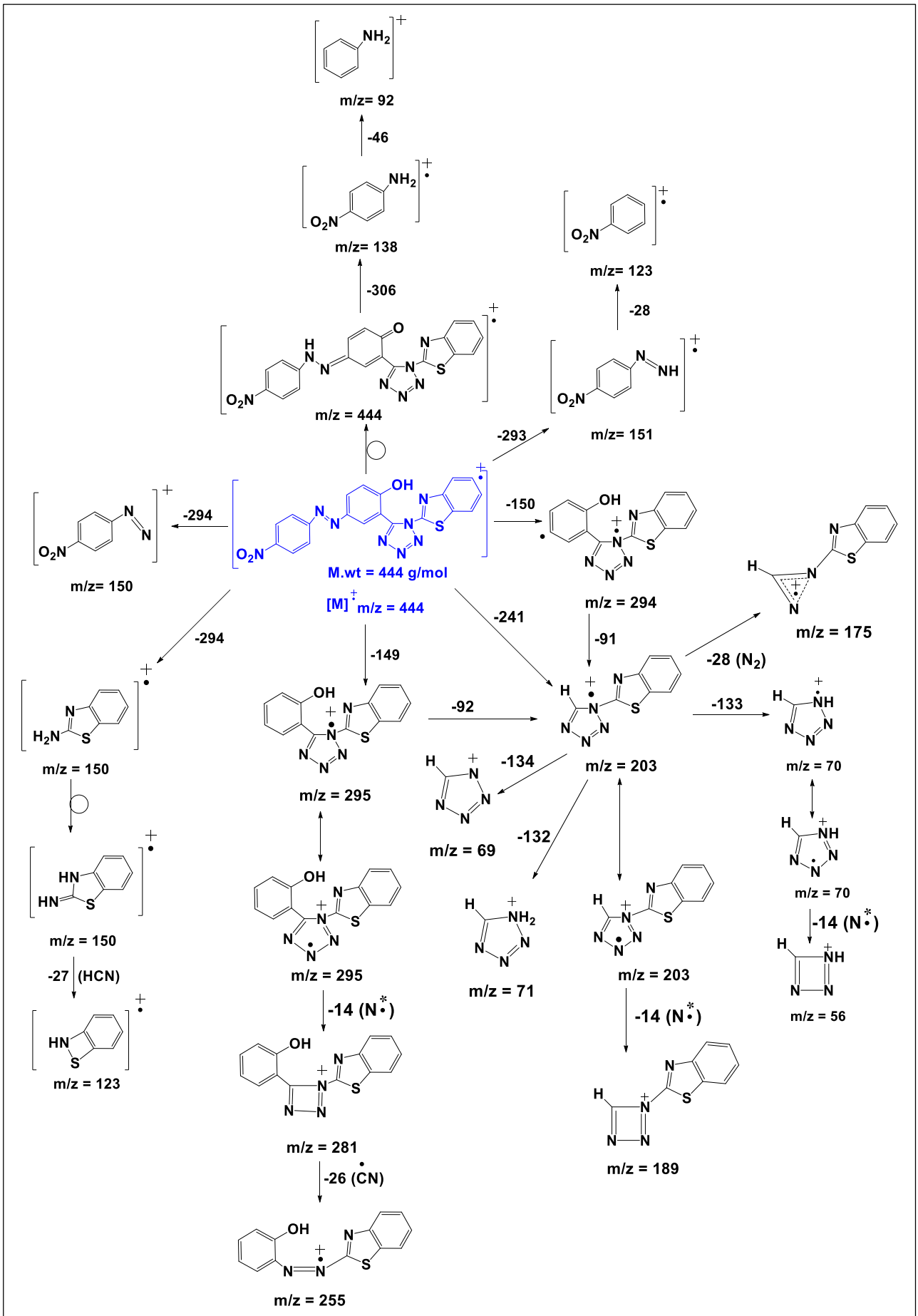
Scheme (3-19): Fragmentation pattern of compound **3a`**



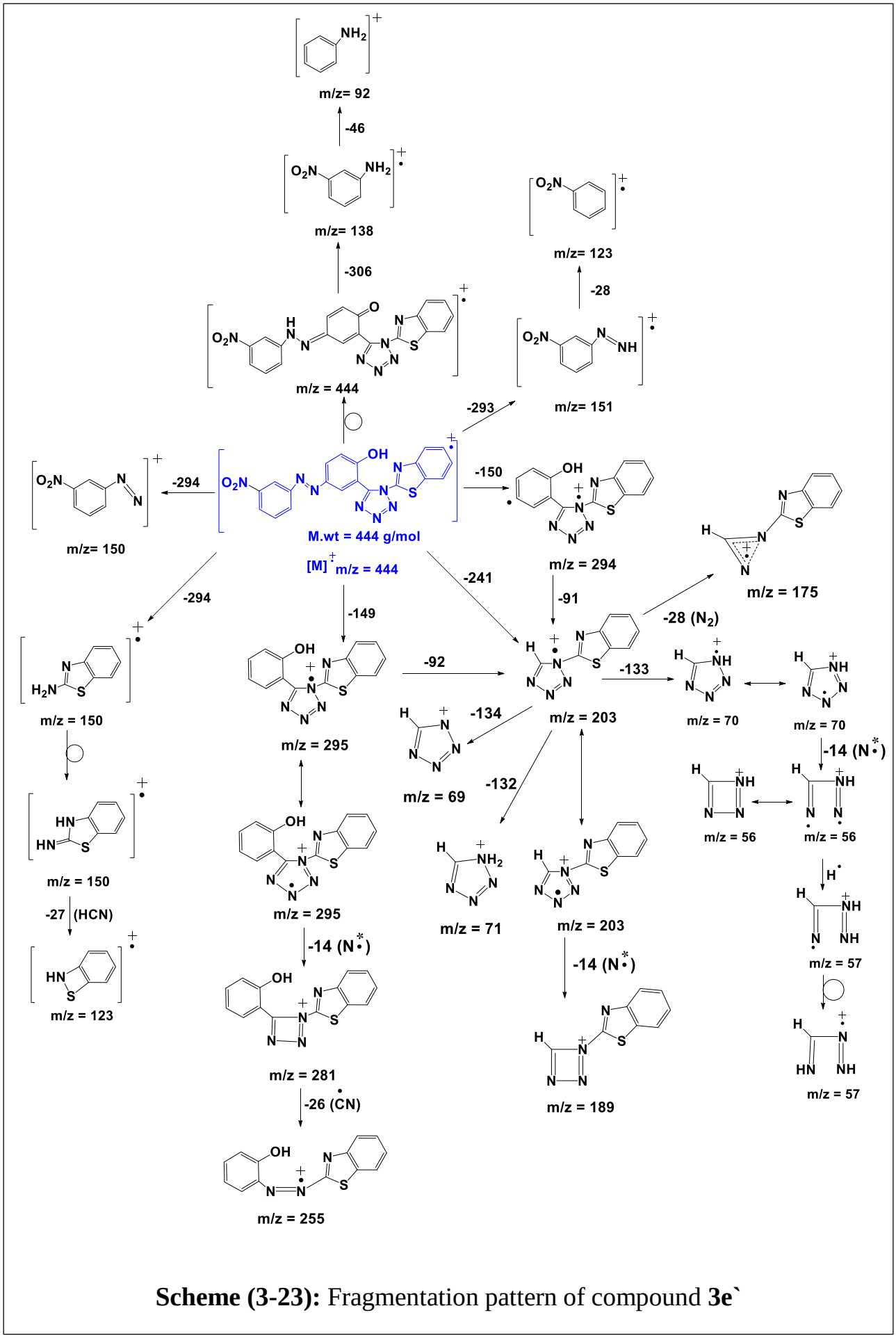
Scheme (3-20): Fragmentation pattern of compound **3b`**



Scheme (3-21): Fragmentation pattern of compound **3c`**



Scheme (3-22): Fragmentation pattern of compound **3d`**



Scheme (3-23): Fragmentation pattern of compound **3e`**

3.8. Antibacterial activity

In this work, the antibacterial activity of all synthesized tetrazoles has been tested. The results of antibacterial action have been described in table (3-7) and photographs of growth inhibition zones have been illustrated in figures (3-57)-(3-58).

Table (3-7): The antibacterial activity for synthesized tetrazole derivatives

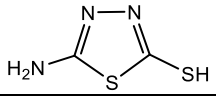
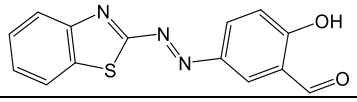
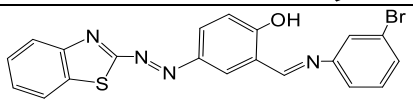
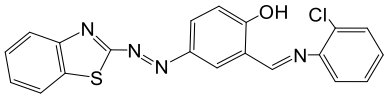
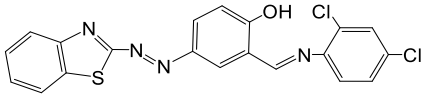
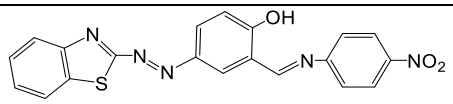
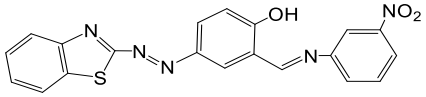
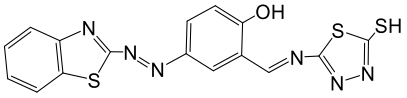
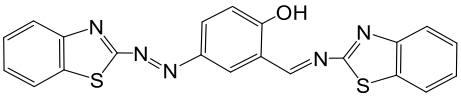
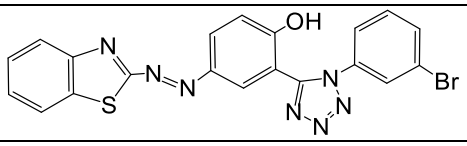
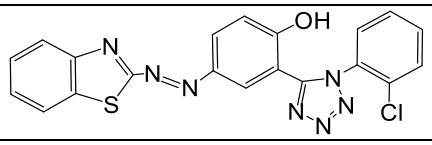
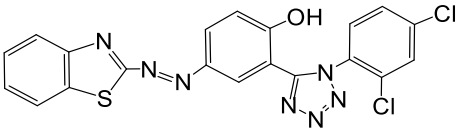
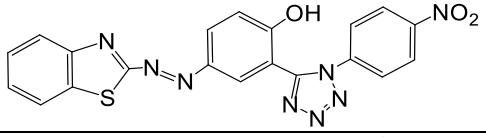
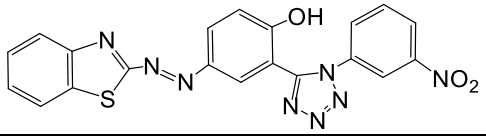
Bacteria	***Staphylococcus aureous*** **(Gram-positive)**	***Escherichia coli*** **(Gram-negative)**
Com. no.	**Diameter of inhibition zone in (mm)**	
3a	15	0
3b	14	0
3c	15	0
3d	0	0
3e	16	0
3f	13	0
3g	15	0
3a`	16	0
3b`	16	0
3c`	12	0
3d`	14	0
3e`	12	0
DMSO	-	-

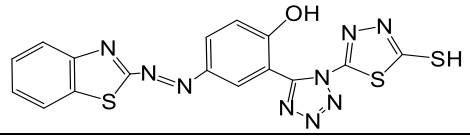
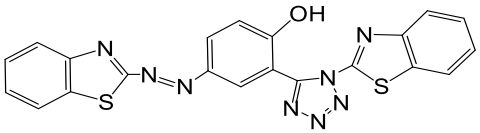
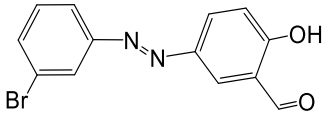
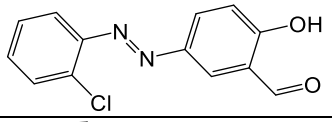
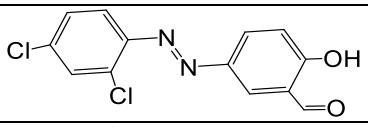
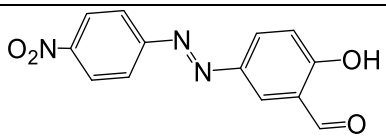
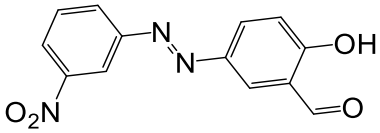
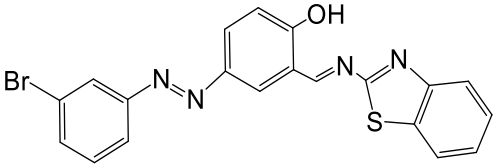
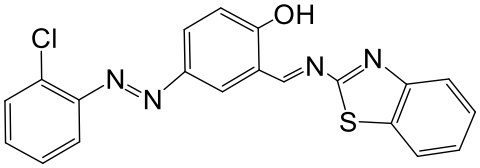
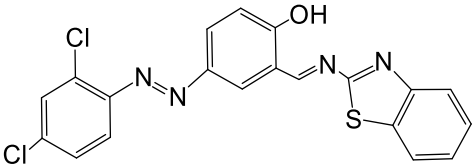
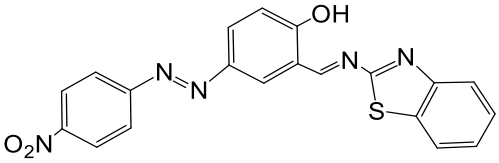
Gentamycin as control drug	***Staphylococcus aureous* (Gram-positive)**	***Escherichia coli* (Gram-negative)**
	Diameter of inhibition zone in (mm)	
10 *M*g/mL	18	15
100 *M*g/mL	23	19

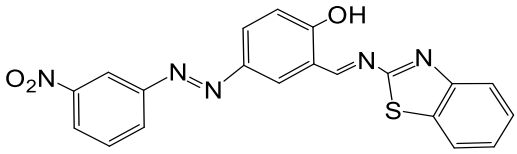
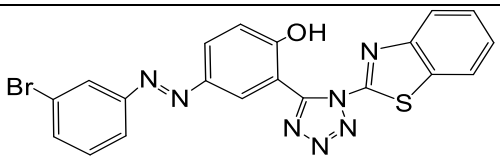
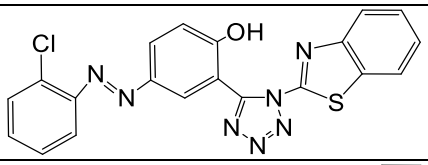
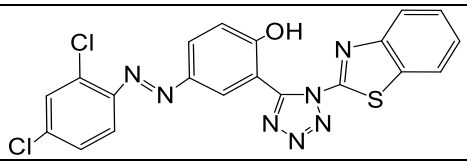
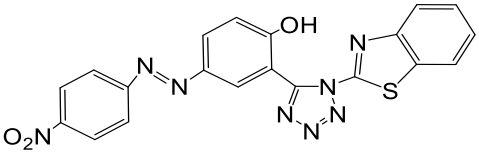
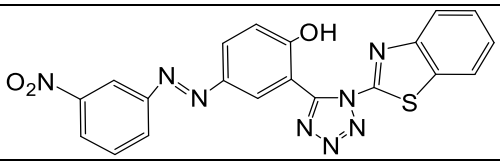
Highly active	(inhibition zone > 15 mm)
Moderately active	(inhibition zone 11-15 mm)
Slightly active	(inhibition zone 5-10 mm)
Inactive	(inhibition zone < 5 mm)

From the data observed, it is found that just one tetrazole **3d** showed no effect against Gram-positive bacteria while the others (**11** tetrazoles) showed medium-high effect towards the same bacteria. All tetrazoles showed no effect against Gram-negative bacteria.

Table (3-8): Names of the synthesized compounds

Com. symbol	Structure	Name
AMT		5-amino-1,3,4-thiadiazole-2-thiol
1a		*(E)*-5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxybenzaldehyde
2a		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((3-bromophenyl)imino) methyl)phenol
2b		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((2-chlorophenyl)imino) methyl)phenol
2c		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((2,4-dichlorophenyl)imino) methyl)phenol
2d		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((4-nitrophenyl)imino)methyl)phenol
2e		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((3-nitrophenyl)imino)methyl) phenol
2f		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)phenol
2g		4-((*E*)-benzo[d]thiazol-2-yldiazenyl)-2-((*E*)-(benzo[d]thiazol-2-ylimino) methyl)phenol
3a		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(3-bromophenyl)-1*H*-tetrazol-5-yl)phenol
3b		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(2-chlorophenyl)-1*H*-tetrazol-5-yl)phenol
3c		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(2,4-dichlorophenyl)-1*H*-tetrazol -5-yl)phenol
3d		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(4-nitrophenyl)-1*H*-tetrazol-5-yl)phenol
3e		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(3-nitrophenyl)-1*H*-tetrazol-5-yl)phenol

Com. symbol	Structure	Name
3f		(*E*)-4-(benzo[d]thiazol-2-yldiazenyl)-2-(1-(5-mercapto-1,3,4-thiadiazol-2-yl)-1*H*-tetrazol-5-yl)phenol
3g		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H*-tetrazol-5-yl)-4-(benzo[d] thiazol-2-yldiazenyl)phenol
1a`		(*E*)-5-((3-bromophenyl)diazenyl)-2-hydroxybenzaldehyde
1b`		(*E*)-5-((2-chlorophenyl)diazenyl)-2-hydroxybenzaldehyde
1c`		(*E*)-5-((2,4-dichlorophenyl) diazenyl)-2-hydroxybenzaldehyde
1d`		(*E*)-2-hydroxy-5-((4-nitrophenyl) diazenyl)benzaldehyde
1e`		(*E*)-2-hydroxy-5-((3-nitrophenyl) diazenyl)benzaldehyde
2a`		2-((*E*)-(benzo[d]thiazol-2-ylimino) methyl)-4-((*E*)-(3-bromophenyl) diazenyl)phenol
2b`		2-((*E*)-(benzo[d]thiazol-2-ylimino) methyl)-4-((*E*)-(2-chlorophenyl) diazenyl)phenol
2c`		2-((*E*)-(benzo[d]thiazol-2-ylimino) methyl)-4-((*E*)-(2,4-dichlorophenyl)diazenyl)phenol
2d`		2-((*E*)-(benzo[d]thiazol-2-ylimino)methyl)-4-((*E*)-(4-nitrophenyl) diazenyl)phenol

Com. symbol	Structure	Name
2e`		2-((*E*)-(benzo[d]thiazol-2-ylimino) methyl)-4-((*E*)-(3-nitrophenyl) diazenyl)phenol
3a`		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H* -tetrazol-5-yl)-4-((3-bromophenyl) diazenyl)phenol
3b`		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H* -tetrazol-5-yl)-4-((2-chlorophenyl)diazenyl)phenol
3c`		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H* -tetrazol-5-yl)-4-((2,4-dichlorophenyl)diazenyl)phenol
3d`		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H* -tetrazol-5-yl)-4-((4-nitrophenyl) diazenyl)phenol
3e`		(*E*)-2-(1-(benzo[d]thiazol-2-yl)-1*H* -tetrazol-5-yl)-4-((3-nitrophenyl) diazenyl)phenol

Conclusions and Future work

Conclusions

1. The cycloaddition reaction of all imines with sodium azide has been considered a new general method for the synthesis of tetrazoles.
2. The rates of cycloaddition reactions for formation of 1,5-disubstituted tetrazoles **3a-g** are relatively increased with decreasing the strength of the electron with-drawing group that substituted in benzene ring.
3. The rates of cycloaddition reactions for formation of 1,5-disubstituted tetrazoles **3a`-e`** are relatively increased with increasing the strength of the electron with-drawing group that substituted in benzene ring.
4. All synthesized tetrazoles have relatively high solubility in water.
5. All synthesized tetrazoles have biological activity against Gram-positive bacteria only.

Future work

1. Synthesis of different azoimines or hydrazones via introducing the synthesized azoaldehydes in a condensation reactions with other primary amines or hydrazines which could be used as precursors for the synthesis of new 1,5-disubstituted tetrazoles.
2. Using the synthesized azoimines as precursors for the synthesis of β-Lactam derivatives via reaction with chloroacetyl chloride.
3. Using the synthesized azoimines as precursors for the synthesis of 1,3-oxazepines and 1,3-oxazepanes via [5+2] cycloaddition reaction with unsaturated and saturated cyclic anhydrides.
4. Evaluation the toxicity and minimum-influenced concentration for the new synthesized tetrazoles.
5. Study the biological activity of the synthesized tetrazoles against other types of bacteria in addition of fungi, virus and some diseases of the animal tissues.

References

References

1. Zollinger, H. "Color: A Multidisciplinary Approach" Verlag Helvetic Chimica Acta, Switzerland, **1999,** p. 44.
2. Christie, R. M. "Colour Chemistry" The Royal Society of Chemistry, UK, **2001,** pp. 6-45.
3. Brown, W. H.; Iverson, B. L.; Anslyn, E. V.; Foote, C. S.; Novak, B. M. "Organic Chemistry", 7th Ed., WADSWORTH Cengage Learning, USA, **2013**, pp. 989-992.
4. Smith, M. B. "March's advanced organic chemistry" 7th Ed., Wiley & Sons, Inc, New Jersey, **2013**, p.597.
5. Davey, H. H.; Lee, R. D.; Marks, T. J. *J. Org. Chem.* **1999**, 27, 4976-4987.
6. Wallach, O.; Belli, E.; *C. Ber. Acc. Chem. Res.* **1880**, 13, 525-539.
7. Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.*, **1983**, 56, 643-656.
8. Merino, E. *Chem. Soc. Rev.* **2011**, 40, 3835-3853.
9. Yus, M.; Alonso, F.; Radivoy, G. *Tetrahedron* **2000**, 56, 8673-8678.
10. Hamon, F.; Djedaini-Pilard, F.; Barbot, F.; Len, C. *Tetrahedron lett.* **2009**, 65, 1010-1012.
11. Hecht, S.; Khan, A. *Chem. Eur. J.* **2006**, 12, 4764 - 4774.
12. Gilbert, A. M.; Failli, A.; Shumsky, J.; Yang, Y.; Severin, A.; Singh, G.; Hu, W.; Keeney, D.; Petersen, P. J.; Katz, A. H. *J. Med. Chem.* **2006**, 49, 6027- 6036.
13. Drug, E.; Gozin, M. *J. Am. Chem. Soc.* **2007,** 129, 13784-13785.
14. Mihara, M.; Nakai, T.; Iwai, T.; Ito, T.; Mizuno, T. *Syn. Lett.* **2007**, 13, 2124- 2126.
15. Hirano, M.; Yakabe, S.; Chikamori, H.; Clark, J. H.; Morimoto, T. *J. Chem. Soc.* **1998**, 770-771.
16. Dimroth, K.; Tuncher, W. *Synthesis* **1977**, 5, 339-340.
17. Grirrane, A.; Corma, A.; García, H. *Science* **2008**, 322, 1661-1664.

18. Barth, M.; Tasadaque, S.; Shah, A.; Rademann, J. *Tetrahedron Lett.* **2004**, 60, 8703-8709.
19. Farhadi, S.; Zaringhadam, P.; Sahamieh, R. Z. *Acta Chim. Slov.* **2007**, 54, 647-652.
20. Hyatt, J. A. *Tetrahedron Lett.* **1977**, 18, 141-146.
21. Weglarz-Tomczak, E.; Górecki, Ł. *CHEMIK* **2012,** 66(12), 1298-1307.
22. Shams, H. Z.; Mohareb, R. M.; Helal, M. H.; El-Sayed Mahmoud, A. *Molecules* **2011**, 16, 6271-6305.
23. Wang, Lai. H.; Huang**,** S. J. *Russian Journal of Electrochemistry* **2010**, 46(12), 1414–1418.
24. Baltac, T.; Vlad, G.; Sebe, I. *REV. CHIM.* **2012**, 63, 18-21.
25. Rathod, K. M.; Thakre, N. S. *Chem. Sci. Trans.* **2013**, 2(1), 25-28.
26. Swati, Ginni, Karnawat, R.; Sharma, I. K.; Verma, P. S. *Internat. J. Applied Biology and Pharmaceutical Technology* **2011**, 2, 332-338.
27. Mahesh, B.; Belagali, S. L. *Internat. J. Current Engineering and Technology*, **2014**, 4(4), 2711-2715.
28. Narule, M. N.; Khan, T. K.H. *Internat. J. Adv. Res. Chemi. Sci.* **2014,** 1(1), 28-47.
29. Shaaban, S.; Arafat, M. A.; Gaffer, H. E.; Hamama, W. S. *Der Pharma Chemica* **2014**, 6(3),186-193.
30. Mcvey, D. C.; Liddle, R. A.; Riggs-Sauthier, J.; Ekwuribe, N.; Vigna, S. R. *Digestive Diseases and Sciences* **2005**, 50, 565–573.
31. Ehsan, S.; Ishfaq, A.; Khan, B.; Saghir, T.; Ghafoor, S. *Internat. J. Sci. Res* **2014**, 3(12), 368- 373.
32. Stein, M.; Middendorp, S. J.; Carta, V.; Pejo, E.; Raines, D. E.; Forman, S. A.; Sigel, E.; Trauner, D. *Angew. Chem. Int. Ed.* **2012**, 51, 10500-10504.
33. Chopde, H. N.; Meshram, J. S.; Pagadala, R.; Mungole, A. J. *Int. J. ChemTech. Res.* **2010**, 2(3), 1823-1830.
34. Rekha, S.; Bisht, P.; Chandrashekhara, S.; Shantharam, U.; Chandy, V.; Tyagi, S. *Journal of Drug Discovery and Therapeutics* **2013**, 1(5), 29-36.

35. Kumbhare, R. M.; Ingle, V. N. *Indian J. Chem.* **2009**, 48B, 996-1000.
36. Mariappan, G.; Prabhat, P.; Sutharson, L.; Banerjee, J.; Patangia, U.; Nath, S. *Journal of the Korean Chemical Society* **2012**, 56, 251-256.
37. Peng, X.; Xie, G.; Wang, Z.; Lin, H.; Zhou, H.T.; Xiang, P.; Jiang, Y.; Yang, S.; Wei, Y.; Yu, L.; Zhao, Y. *Cell death and disease* **2014**, 5, 1-10.
38. Yadav, M. *The Pharma Research* **2013**, 9(02), 12-20.
39. Bryson, H. M.; Fulton, B.; Benfield, P. *Drugs* **1996,** 52, 549-563.
40. Verma, A. K.; Martin, A.; Singh, A. K. *Indian J. Pharm. Biol. Res.* **2014**, 2(3), 84-89.
41. Wang, X.; Sarris, K.; Kage, K.; Zhang, D.; Brown, S. P.; Kolasa, T.; Surowy, C.; El Kouhen, O. F.; Muchmore, S. W.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2009**, 52, 170–180.
42. Hofmann, A. W. *Chem. Ber.* **1887**, 20, 1784-1788.
43. Yoshida, M.; Hayakawa, I.; Hayashi, N.; Agatsuma, T.; Oda, Y.; Tanzawa, F.; Iwasaki, S.; Koyama, K.; Furukawa, H.; Kurakata, S.; Sugano, Y. *Bioorga. Med. Chem. Lett.* **2005**, 15, 3328–3332.
44. Schiff, H. *Justus Liebigs Annalen der Chemie***, 1864**, 131(1), 118-119.
45. Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry Part B: Reactions and Synthesis" 5th Ed., Springer Science Business Media, LLC, **2007**, p.46.
46. Srivastava, K. P.; Singh, A.; Singh, S. K. *Am. Internat. J. Res. Sci., Tech., Enginee. & Math.* **2014**, 6, 286-292.
47. Solomons, T.W. G.; Fryhle**,** C. B. "Organic Chemistry" 10th Ed., John Wiley & Sons, Inc. **2009**, p.751.
48. Wade, L. G. "Organic Chemistry" 7th Ed., Pearson Prentice Hall, **2010,** p.842.
49. Siddiqui, H. L.; Iqbal, A.; Ahmad, S.; Weaver, G. W. *Molecules* **2006**, 11, 206-211.
50. Shinde, A.; Zangade, S.; Chavan, S.; Vibhute, Y. *Org. Commun.* **2014**, 7(2), 60-67.

51. Bekdemir, Y.; Efil, K. *Hindawi Publishing Corporation Organic Chemistry International* **2014**, 2014, 1-5.
52. Mhaske, G.; Nilkanth, P.; Auti, A.; Davange, S.; Shelke, S. *I. Internat. J. of Innovative Res. Sci. Enginee. Tech.* **2014**, 3, 8156- 8162.
53. Cai, Y.H.; Luo, W. *Hindawi Publishing Corporation Journal of Chemistry* **2014**, 2014, 1-5.
54. Zarei, M.; Jarrahpour, A. *Iranian J. Sci. Tech.* **2011**, 38, 235-242.
55. Hello, K. M. *Nat. J. Chem.* **2008**, 30, 297-305.
56. Kadaba, P. K.; Edwards, J. O. *J. Org. Chem.* **1960**, 25, 1431-1433.
57. Deyrup, D.H.; Greenwald, R.B. *Tetrahedron Lett.* **1965**, 6(5), 321-324.
58. Staundinger, H. *Justus Liebigs Annalen der Chemie* **1907**, 356, 51-123.
59. Wadher, S.; Karande, N.; Sonawanne, S.; Yeole, P. *Int. J. Chem. Tech. Res.* **2009**, 1(4), 1303-1307.
60. Sharma, M.; Kohli, D.; Sharma, S.; Sharma, D. *Chemica. Sinica.* **2010**, 1(1), 92-105.
61. Bckley, G.K. *J.Chem.Soc*. **1954**, 1850-1851.
62. Alder, K. "Newer Methods of Preparative Organic Chemistry", Interscience, New York, **1948**, p.504.
63. Hanoon, H. D. *Nat. J. Chem.* **2011**, 41, 77-89.
64. Salih, N. A. Ph. D. Thesis, College of Science, Al-Nahrain University of Baghdad (**2005)**.
65. Khadhim, M. J.; Ghanim, H. T. *Int. J. Adv. Res.* **2014**, 2(10), 24-39.
66. Khalill, M. M. H.; Ismail, E. H.; Mohamed, G. G.; Zayed, E. M.; Badr, A. *Open J. Inorg. Chem.* **2012**, 2, 13-21.
67. Alama, M. S.; Choi, J. H.; Lee, D. U. *Bioorg. Med. Chem.* **2012**, 20, 4103–4108.
68. Jarrahpour, A. A.; Motamedifar, M.; Pakshir, K.; Hadi, N.; Zarei, M. *Molecules* **2004**, 9, 815-824.
69. Noureen, A.; Saleem, S.; Fatima, T.; Siddiqi, H. M.; Mirza, B. *Pak. J. Pharm. Sci.* **2013**, 26(1), 113-124.

70. Bladin, J. A. *Berichte der deutschen chemischen Gesellschaft* **1885**, 18(1), 1544-1551.
71. Butler, R.N.; In: Katritzky, A.R.; Rees, C.W.; Scriven E.F.V. (Eds.), "Comprehensive Heterocyclic Chemistry II", Vol. 4, Pergamon, Oxford, UK, **1996**.
72. Sarvary A.; Maleki, A. *Mol. Divers.* **2015**, 19(1), 189-212.
73. Rokade, B. V.; Gadde, K.; Prabhu, K.R. *Adv. Synth. Catal.* **2014**, 356(5), 946-950.
74. Xue, H.; Gao, Y.; Twamley, B.; Shreeve, J. N. M. *Adv. Mater.* **2005**, 17(17), 2142–2146.
75. Sabatini, J. J.; Raab, J. M.; Hann Jr, R. K.; Damavarapu, R.; Klapçtke, T.M. *Chem. Asian J.* **2012**, 7, 1657-1663.
76. Karabanovich, G.; Roh, J.; Soukup, O.; Pávková, I.; Pasdiorová, M.; Tambor, V.; Stolaˇr´ıková, J.; Vejsová, M.; Vávrová, K.; Klimeˇsová, V.; Hrabálek, A. *Med. Chem. Commun.* **2015**, 6, 174-181.
77. Trifonov, R.E.; Ostrovskii, V. A. *Russian J. Org. Chem.* **2006**, 42(11), 1585-1605.
78. Joule, J. A.; Mills, K. "Heterocyclic Chemistry" 5th Et., John Wiley & Sons Ltd, United Kingdom **2010,** p.561.
79. Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, 348(16), 2337-2361.
80. Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K.B. *J. Am. Chem. Soc.* **2002**, 124, 12210-12216.
81. Shie, J. J.; Fang, J. M. *J. Org. Chem.* **2007**, 72. 3141-3144.
82. Hajra, S.; Sinha, D.; Bhowmick, M. *J. Org. Chem*. **2007**. 72. 1852- 1855.
83. Aldhoun, M.; Massi, A.; Dondoni, A. *J. Org. Chem.* **2008**, 73, 9565–9575.
84. Roh. J.; Artamonova, T.V.; Vavrova, K.; Koldobskii, G. I.; Hrabalek, A. *Synthesis* **2009**, 13, 2175-2178.
85. Das, B.; Reddy, C. R; Kumar, D. N.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 3, 391-394.

86. Lang, L.; Li, B.; Liu, W.; Jiang, L.; Xu, Z.; Yin, G. *Chem. Commun.* **2010**, 46, 448-450.
87. Klapötke, T. M.; Krumm, B.; Moll, R. *Eur. J. Inorg. Chem.* **2011**, 3, 422-428.
88. Nandre, K. P.; Salunke, J. K.; Nandre, J. P.; Patil, V. S.; Borse, A. U.; Bhosale, S. V. *Chinese Chemical Lett.* **2012,** 23(2), 161-164.
89. Hameed, A.; Ali, S. A.; Khan, A. A.; Moin, S. T.; Khan, K. M.; Hashim, J.; Basha, F. Z.; Malik, M. I. *RSC Adv.* **2014**, 4, 64128–64137.
90. Su, W. K.; Hong, Z.; Shan, W. G.; Zhang, X. X. *Eur. J. Org. Chem.* **2006**, 12, 2723- 2726.
91. Keith, J. M. *J. Org. Chem.* **2006**, 71, 9540- 9543.
92. Laha, J. K.; Cuny, G. D. *Synthesis,* **2008**, 24, 4002-4006.
93. Yella, R.; Khatun, N.; Rout, S. K.; Patel, B. K. *Org. Biomol. Chem.* **2011**, 9, 3235-3245.
94. Soliman, H. A.; Salama, T. A. *Chinese Chemical Lett.* **2013**, 24, 404-406.
95. Rokade, B. V.; Gadde, K.; Prabhu, K. R. *Adv. Synth. Catal.* **2014**, 356(5), 946-950.
96. Artamonova, T. V.; Zhivich, A. B.; Dubinskii, M. Yu.; Koldobskii, G. I. *Synthesis* **1996**, 12, 1428-1430.
97. Katritzky, A. R.; Cai, C.; Meher, N. K. *Synthesis* **2007**, 8, 1204-1208.
98. Joo, Y. H.; Shreeve, J. M. *Org. Lett.* **2008**, 10, 4665- 4667.
99. Jedhe, G. S.; Paul, D.; Gonnade, R. G.; Santra, M. K.; Hamel, E.; Nguyen, T. L.; Sanjayan, G. J. *Bioorg. Med. Chem. Lett.* **2013**, 23, 4680-4684.
100. Abood, Z. H. *Iraqi Nat. J. Chem.* **2013,** 50, 207-246.
101. Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, 29, 538-549.
102. Rajasekaran, A.; Thampi, P.P. *Eur. J. Med. Chem.* **2004**, 39, 273–279.

103. Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Yamasaki, K.; Nakagawa, K. *Chemical & Pharmaceutical Bulletin* **1989**, 37(4), 958-961.
104. Powers, R. A.; Shoichet, B. K. *J. Med. Chem.* **2002**, 45, 3222-3234.
105. Actor, P.; Ur, J. V.; Guarini, J. R.; Zajac, I.; Phillips, L.; Sachs, C. S.; Demarinis, R. M.; Hoover, J. R. E.; Weisbach, J. A. *The Journal of Antibiotics* **1975**, 28(6), 471-476.
106. Duncia, J. V.; Pierce, M. E.; Santella, J. B. *J. Org. Chem.* **1991**, 56, 2395-2400.
107. Osborne, H. B.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Larsen, P. K. *J. Med. Chem.* **2000**, 43, 2609- 2645.
108. Kaplancıkl, Z. A.; Yurttas, L.; Ozdemir, A.; Turan-Zitouni, G.; Ciftci, G. A.; Yıldırım, S. U.; Mohsen, U. A. *Med. Chem. Res.* **2014**, 23, 1067-1075.
109. Yeung, K. S.; Qiu, Z.; Yang, Z.; Zadjura, L.; Arienzo, C. J.; Browning, M. R.; Hansel, S.; Huang, X. S.; Eggers, B. J.; Riccardi, K.; Lin, P. F.; Meanwell, N. A.; Kadow, J. F. *Bioorg. Med. Chem. Lett.* **2013**, 23, 209-212.
110. Faria, J. V.; dos Santos, M. S.; Bernardino, A. M.R.; Becker, K. M.; Machado, G. M.C.; Rodrigues, R. F.; Canto-Cavalheiro, M. M.; Leon, L. L. *Bioorg. Med. Chem. Lett.* **2013**, 23, 6310-6312.
111. Chauhan, K.; Sharma, M.; Trivedi, P.; Chaturvedi, V.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2014**, 24, 4166-4170.
112. Dai, L. L.; Zhang, H. Z.; Nagarajan, S.; Rasheed, S.; Zhou, C. H. *Med. Chem. Commun.* **2015**, 6, 147-154.
113. Sharma, B.; Verma, A.; Prajapati, S.; Sharma, U. K. *J. Med. Chem.* **2013**, 1, 1-17.
114. Kumar, P.; Kriplani, S. P.; Gupta, G. N.; Ojha, K.G. *E-Journal of Chemistry* **2007**, 4, 14-20.

115. Acton, Q. A. “Azo Compounds: Advances in Research and Application” Scholarly Paper Edition, Atlanta **2011**, pp.42-117.
116. Egorove, N.S. “Antibiotics Scientific Approach”, Mir. Publishers, Moscow, **1985**.
117. Nejati, K.; Rezvani, Z.; Seyedahmadian, M. *Dyes and Pigments* **2009**, 83(3), 304-311.
118. Sykes, P. “A Guidebook to Mechanism in Organic Chemistry”, 6th Ed., Longman, **1985**. pp.115-134.
119. Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. “SPECTROMETRIC IDENTIFICATION OF ORGANICCOMPOUNDS” 7th Ed., JOHN WILEY & SONS. INC. Printed in the United States of America, **2005**, p.127.
120. Forkey, D. M.; Carpent, W. R. *Organic Mass Spectrometry* **1969**, 2(5), 433-445.
121. Shurukhin, Y. V.; Dovgilevich, A. V.; Grandberg, I. I.; Baskunov, B. P. *Chemistry of Heterocyclic Compounds* **1988**, 24(7), 760-764.
122. Fischer, G. W.; Herrmann, M.; Moder, M. *J. Heterocyclic Chem.* **1996**, 33(3), 815-823.
123. Světlík, J.; Martvoň, A.; Leško, J. *Chemical Papers* **1979**, 33(4), 521-527.
124. Shurukhin, Y. V.; Klyuev, N. A.; Grandberg, I. I. *Chemistry of Heterocyclic Compounds* **1985,** 21(6), 605-620.
125. Liu, W.; Guo, Y.; Han, C.; Huang, X. *Life Science Journal*, **2008**, 5(2), 25-29.

Appendix

A. Spectroscopic figures

A.1. FT-IR spectra

A.1.1. FT-IR spectra of the synthesized AMT, 2-Aminobenzothiazole and azoaldehyde derivative 1a

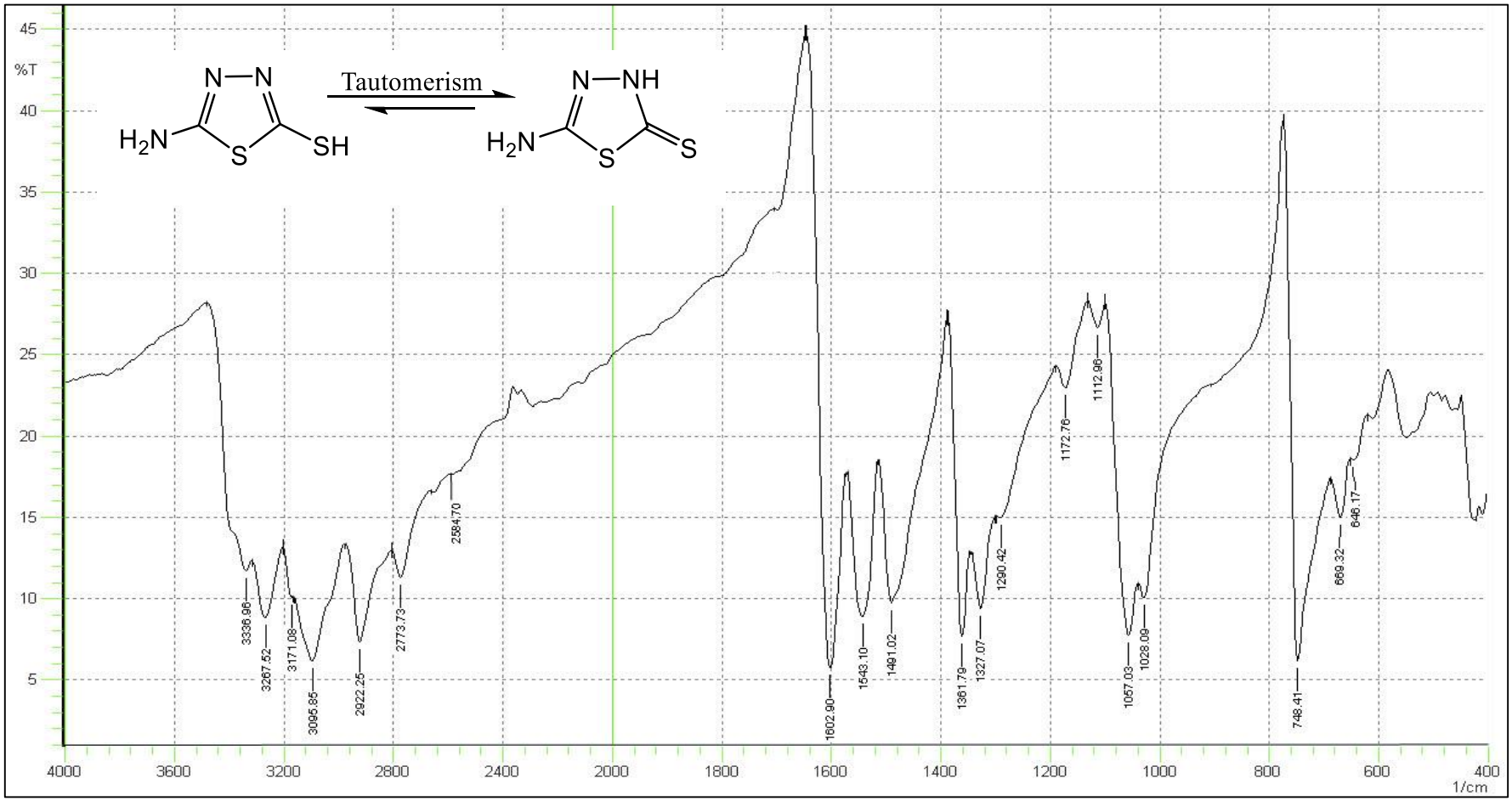


Fig. (3-1): FT-IR spectrum of compound **AMT**

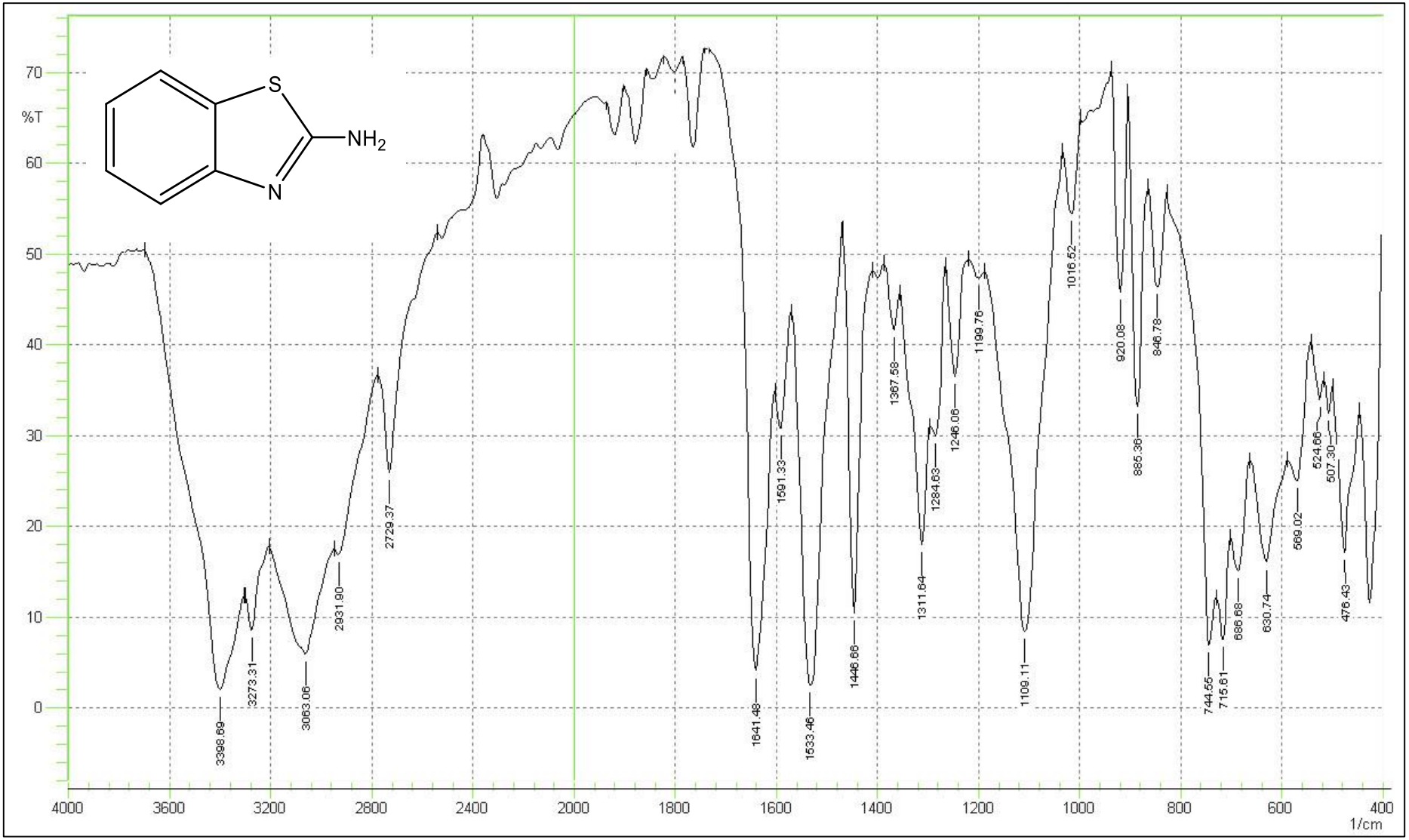


Fig. (3-2): FT-IR spectrum of **2-Aminobenzothiazole**

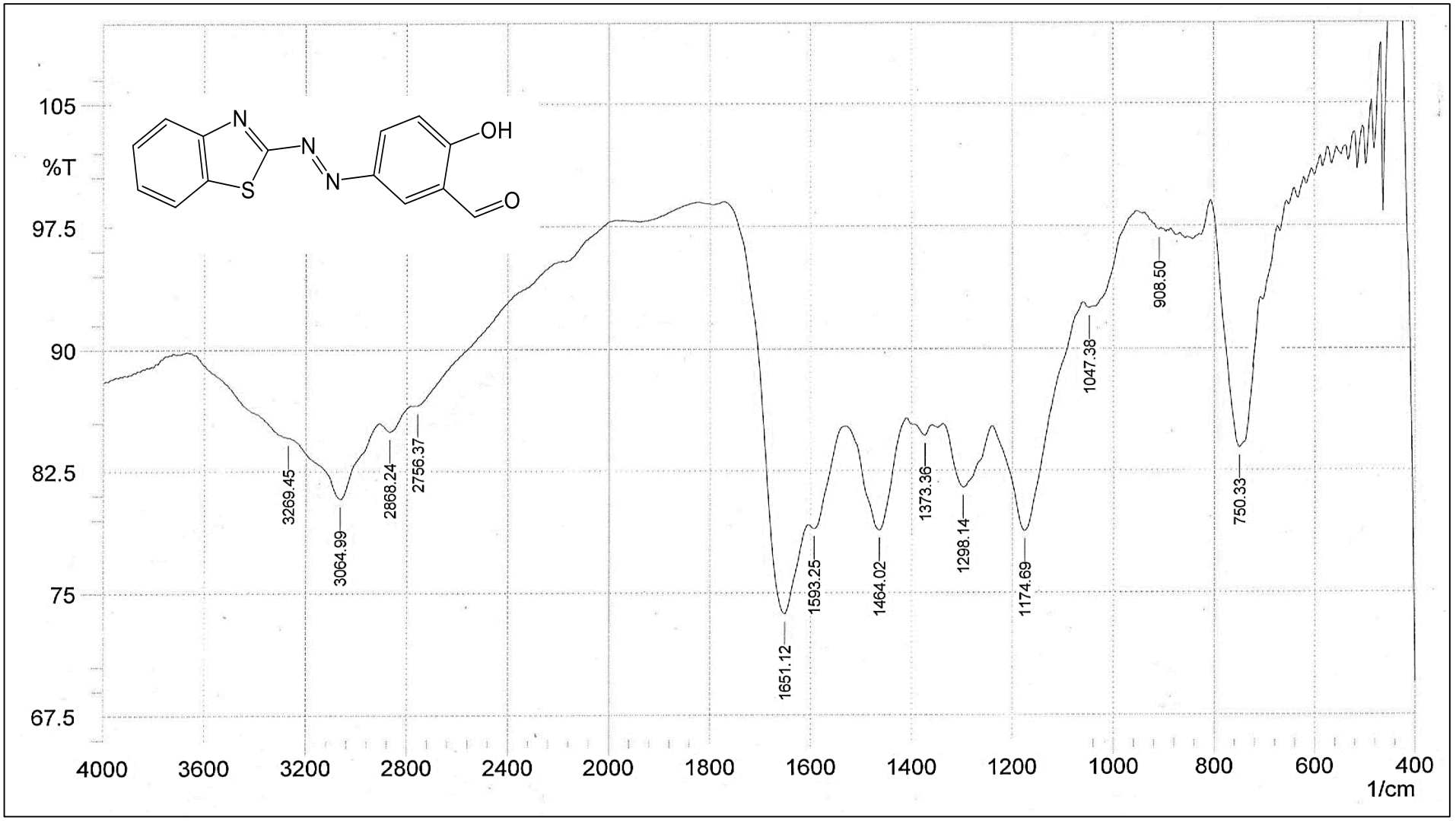


Fig. (3-3): FT-IR spectrum of compound **1a**

A.1.2. FT-IR spectra of the synthesized azoimine derivatives 2a-g

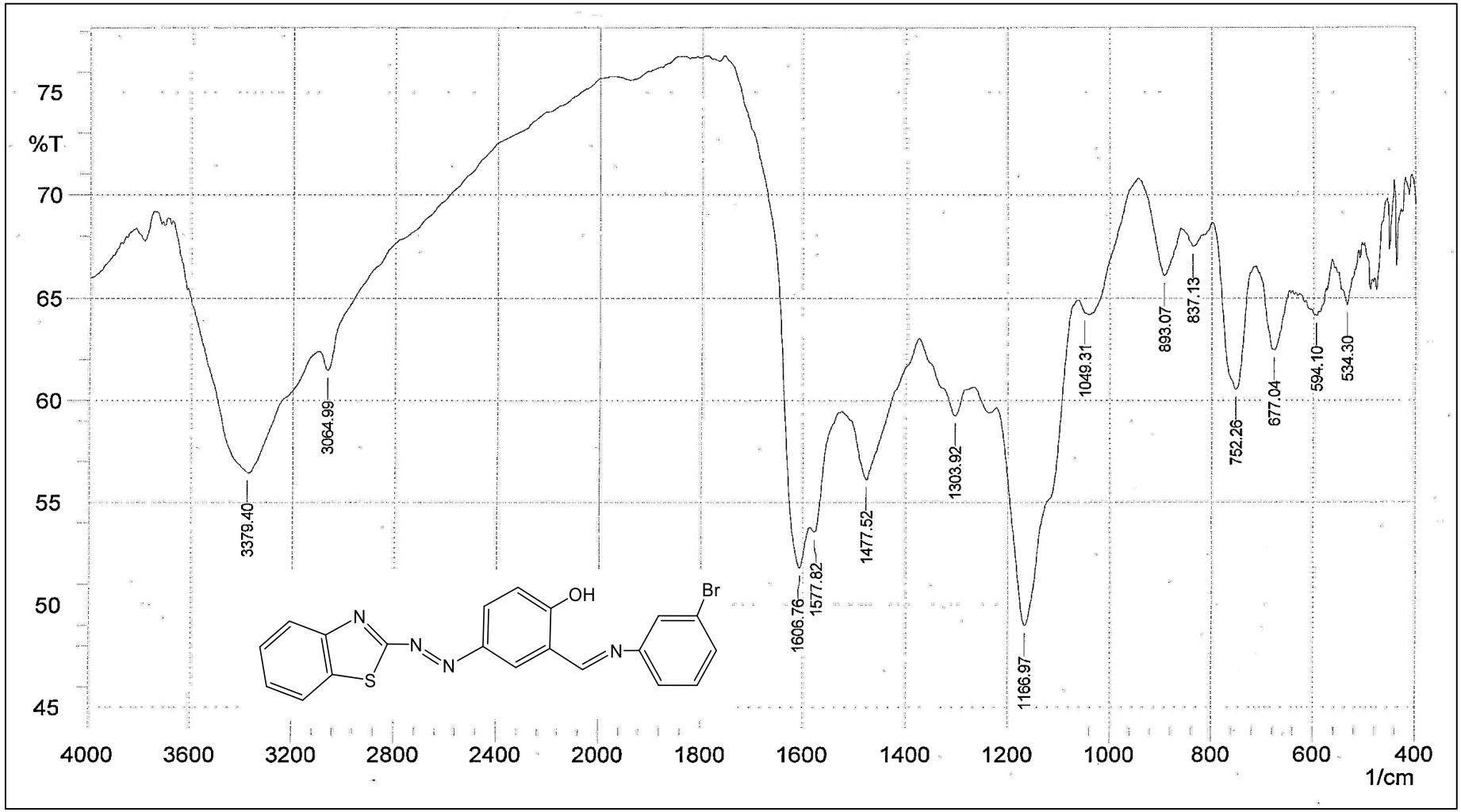


Fig. (3-4): FT-IR spectrum of compound **2a**

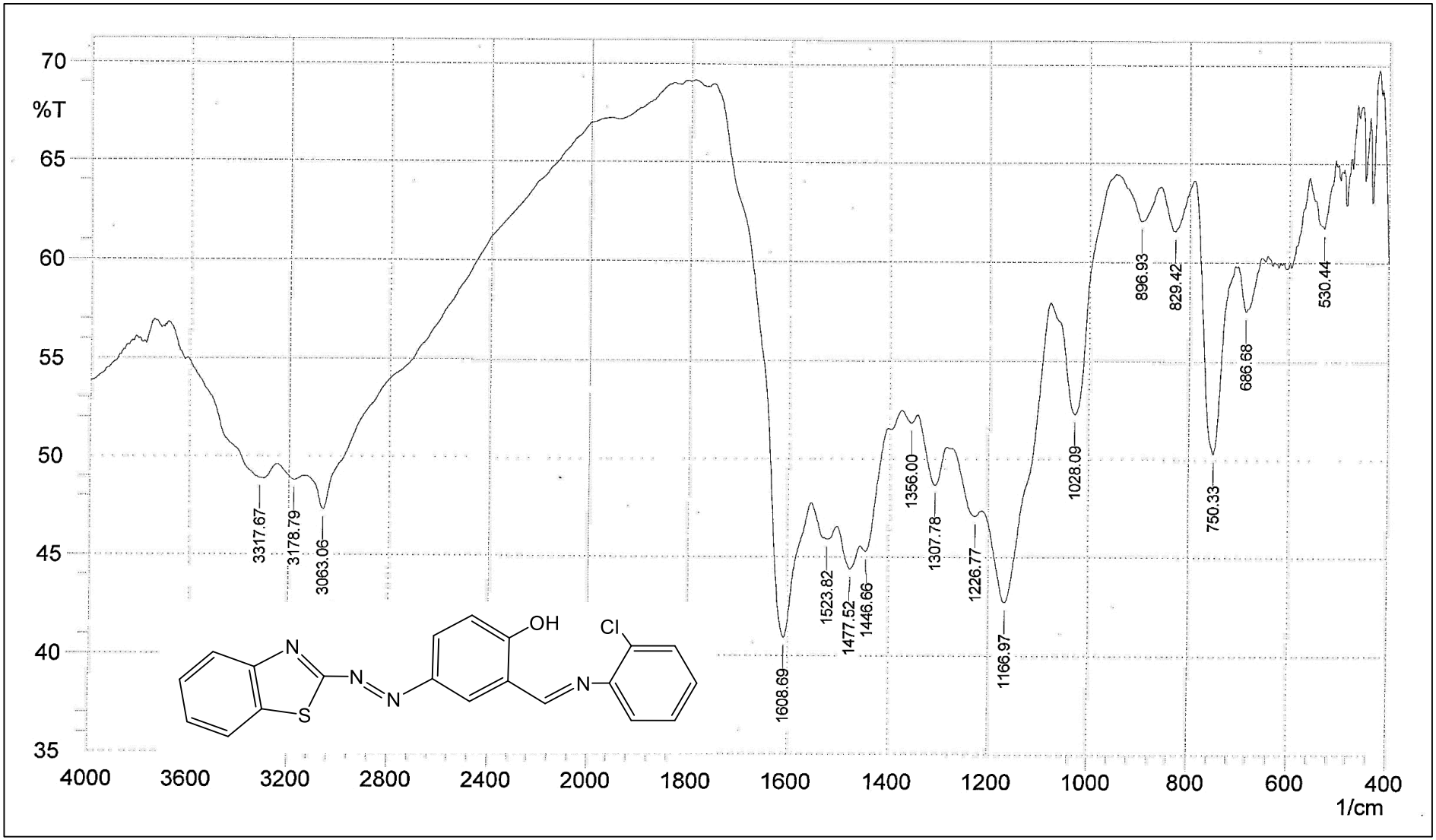


Fig. (3-5): FT-IR spectrum of compound **2b**

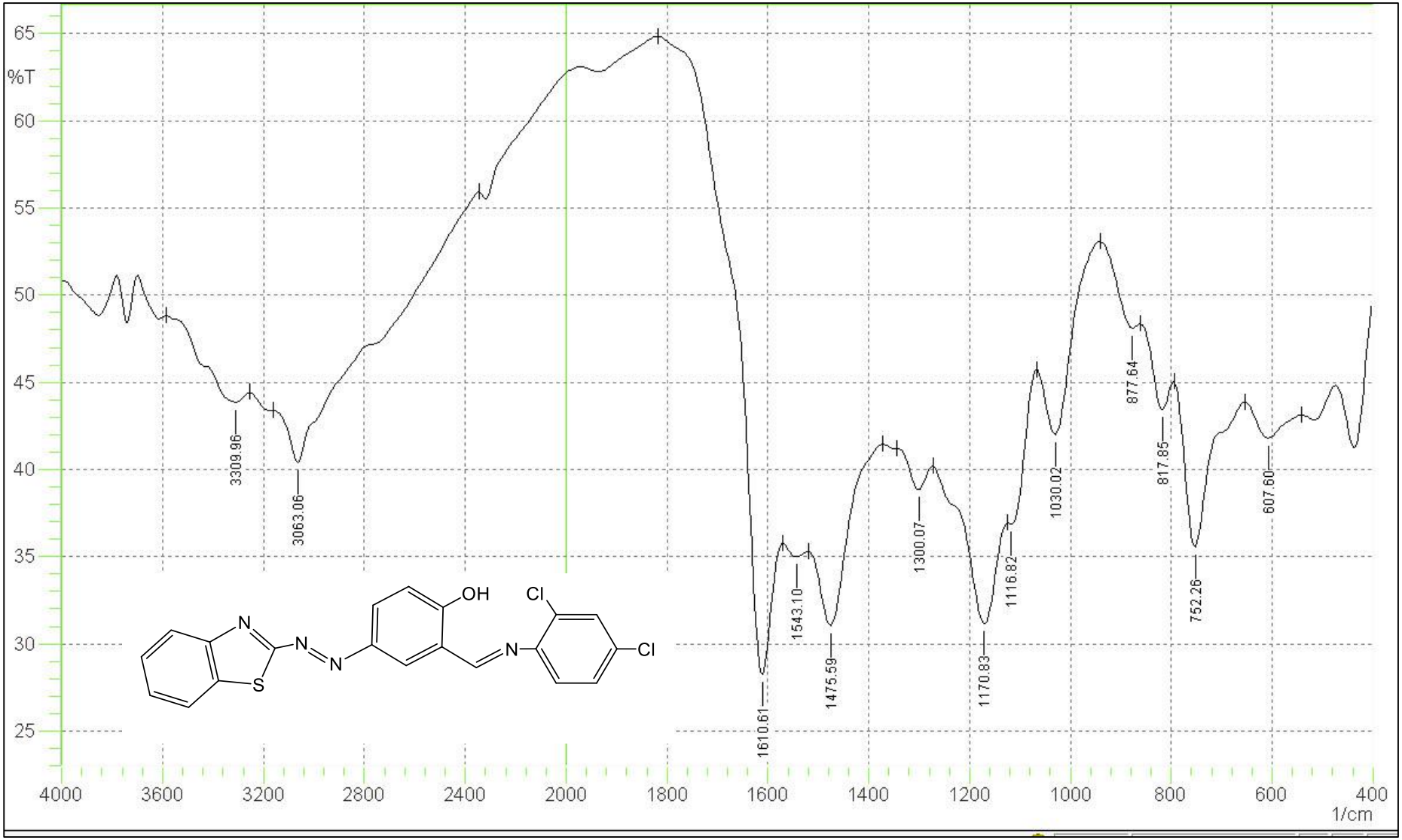


Fig. (3-6): FT-IR spectrum of compound **2c**

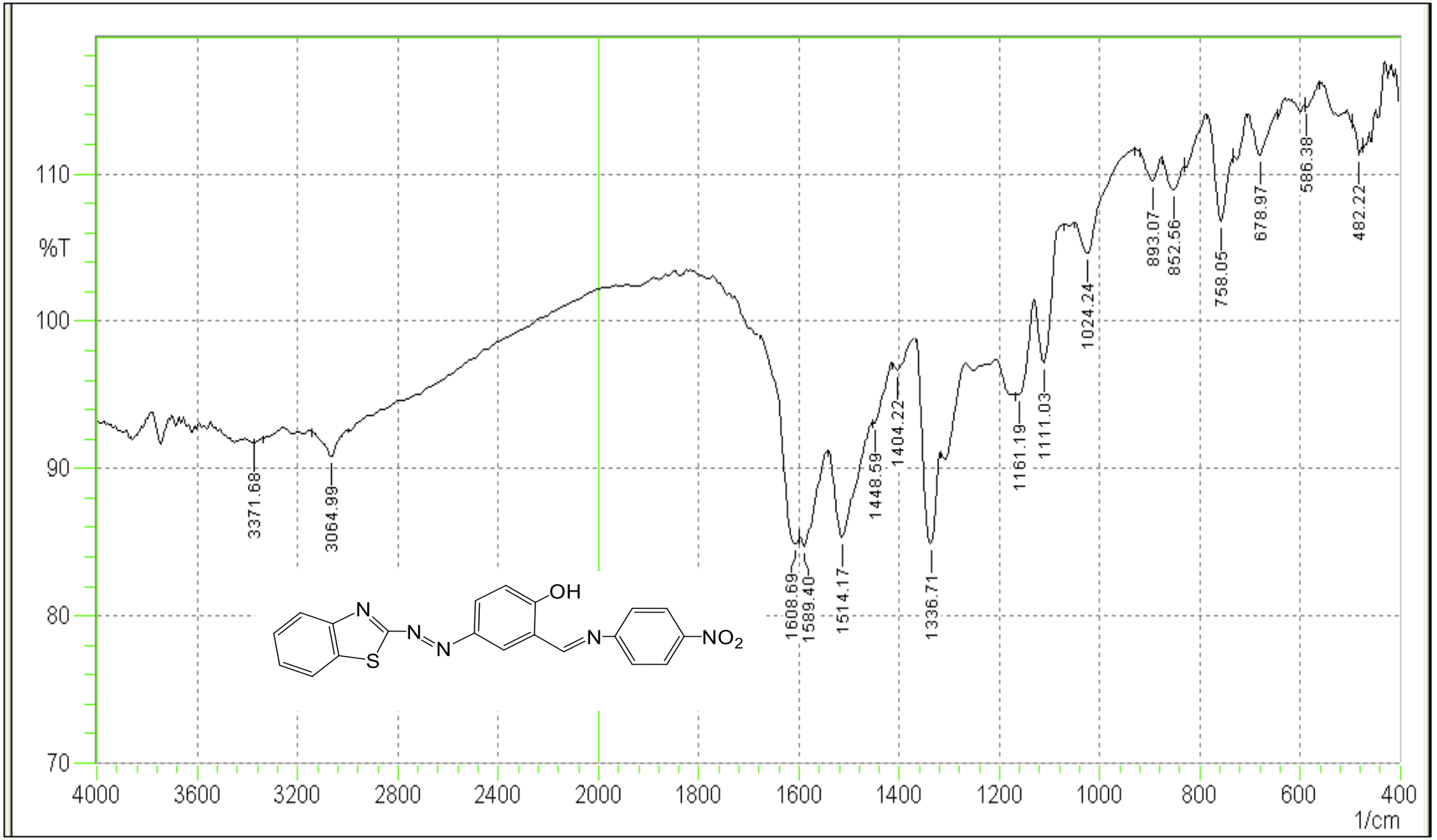


Fig. (3-7): FT-IR spectrum of compound **2d**

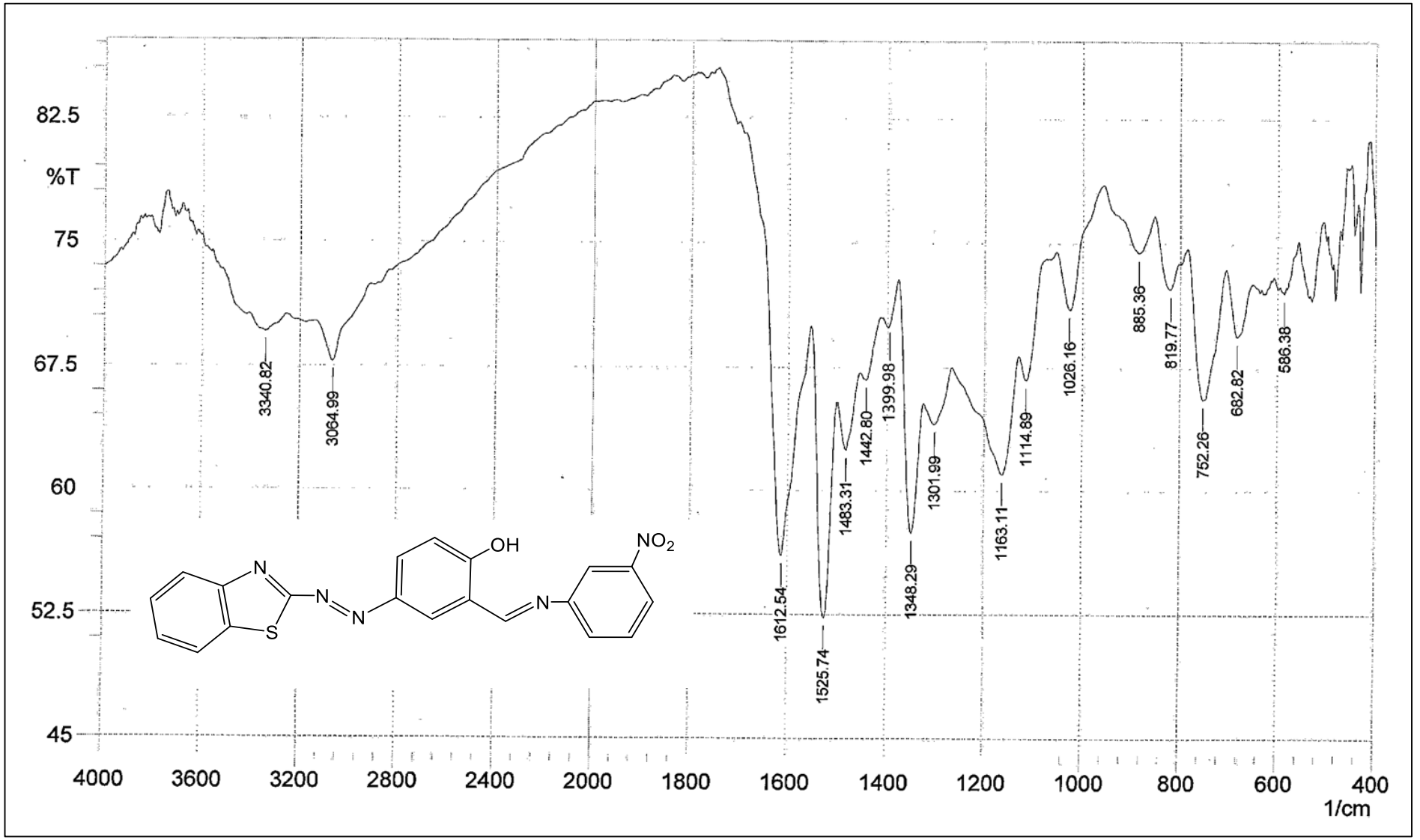


Fig. (3-8): FT-IR spectrum of compound **2e**

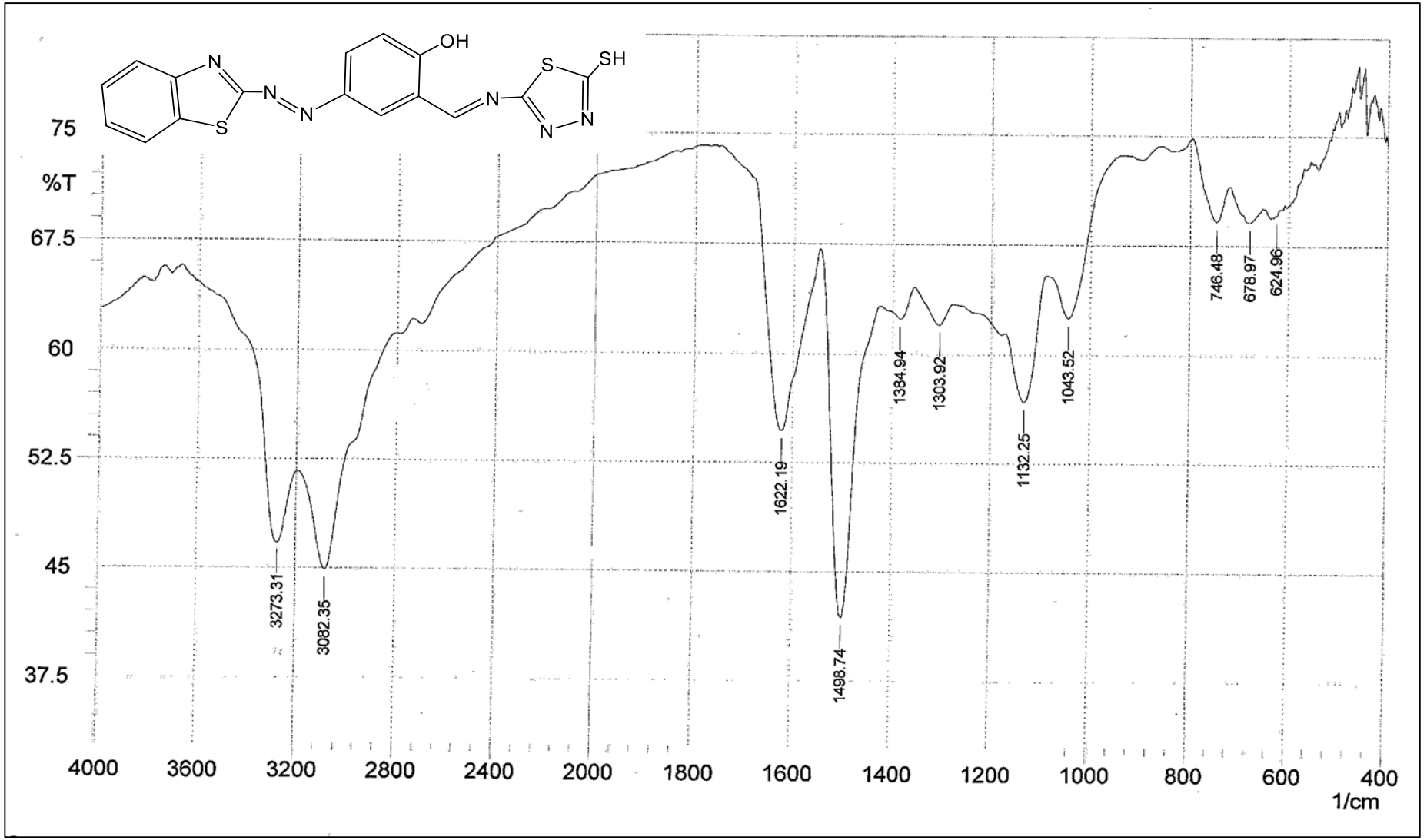


Fig. (3-9): FT-IR spectrum of compound **2f**

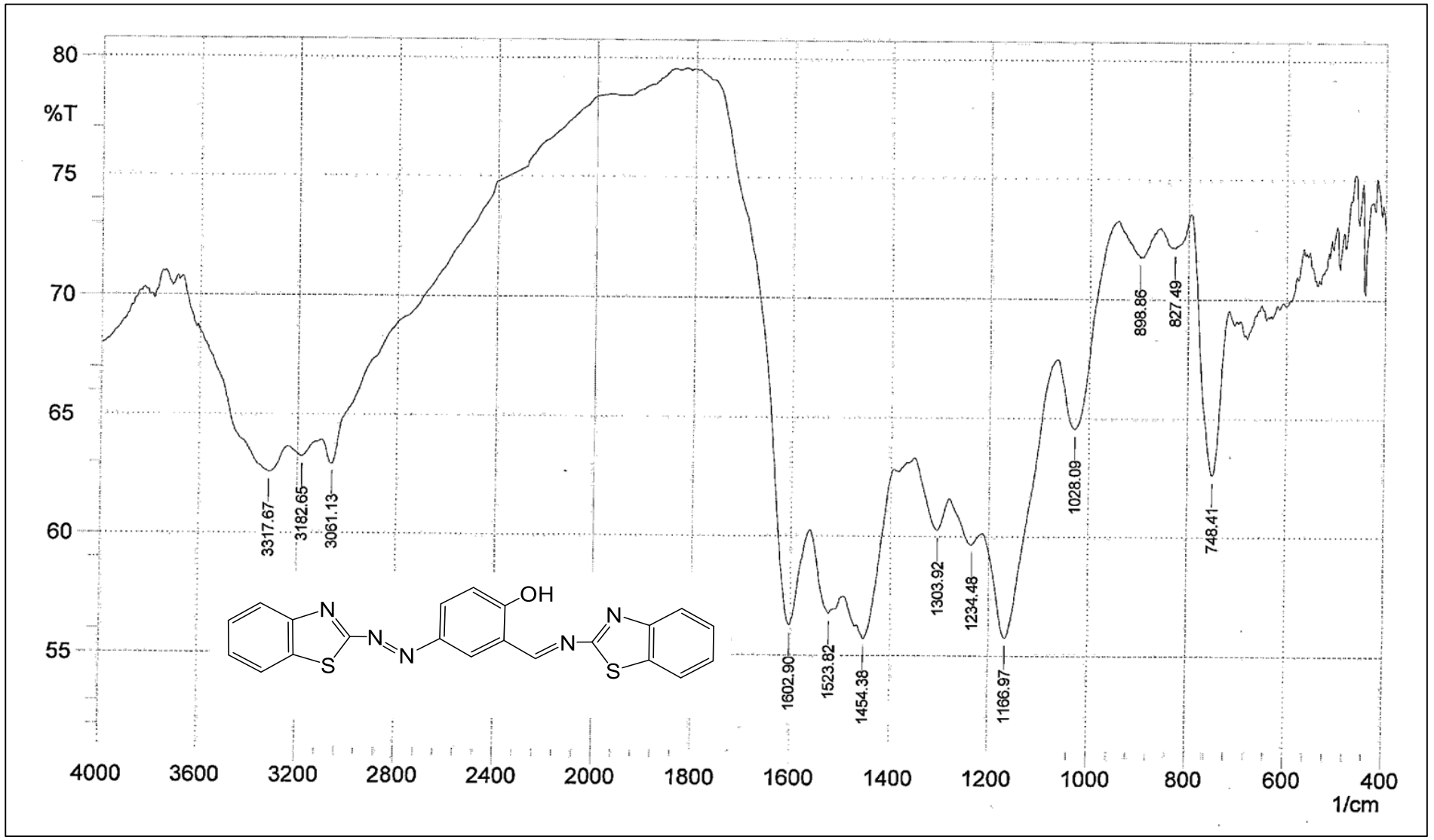


Fig. (3-10): FT-IR spectrum of compound **2g**

A.1.3. FT-IR spectra of the synthesized tetrazole derivatives 3a-g

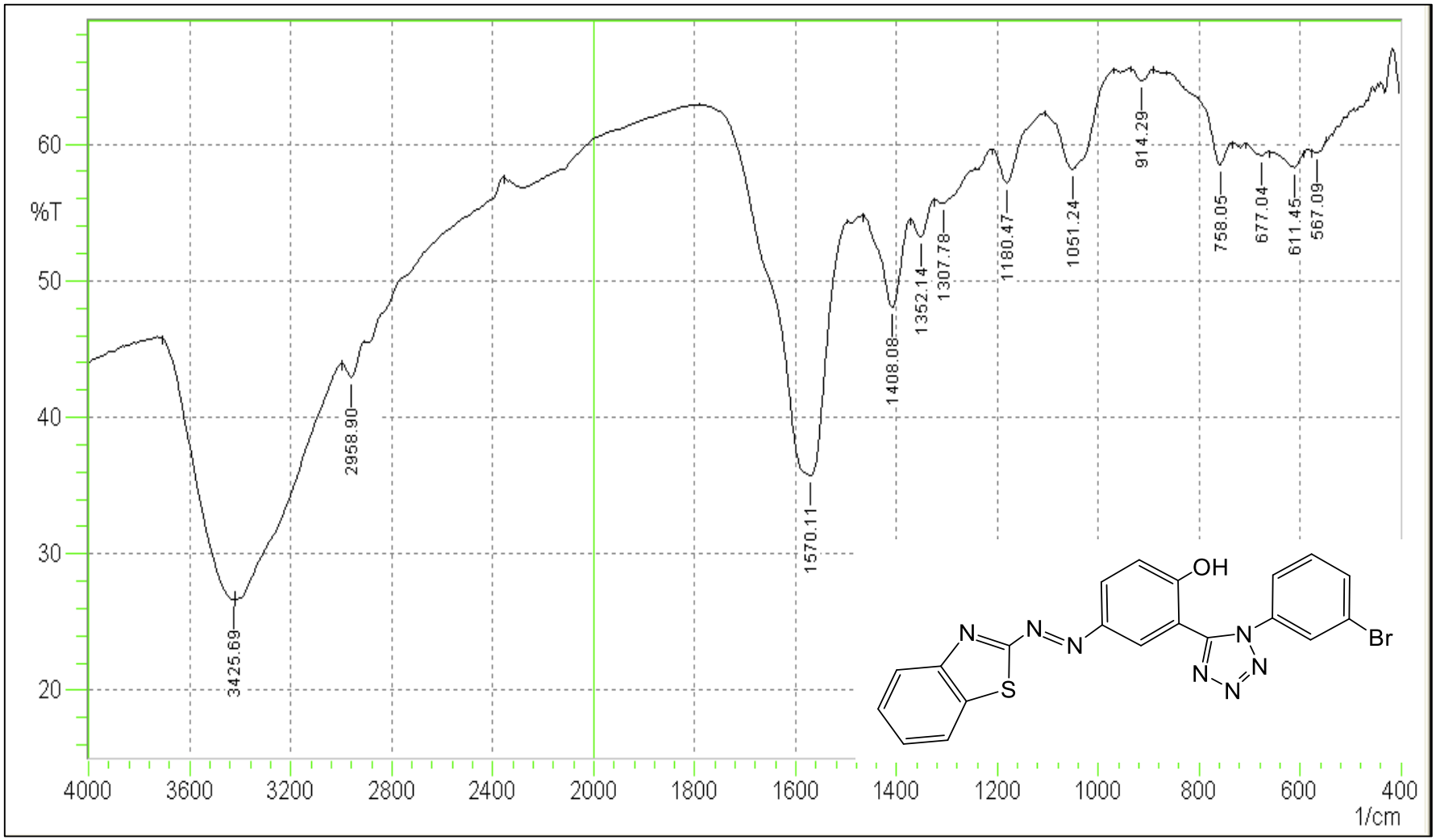


Fig. (3-11): FT-IR spectrum of compound **3a**

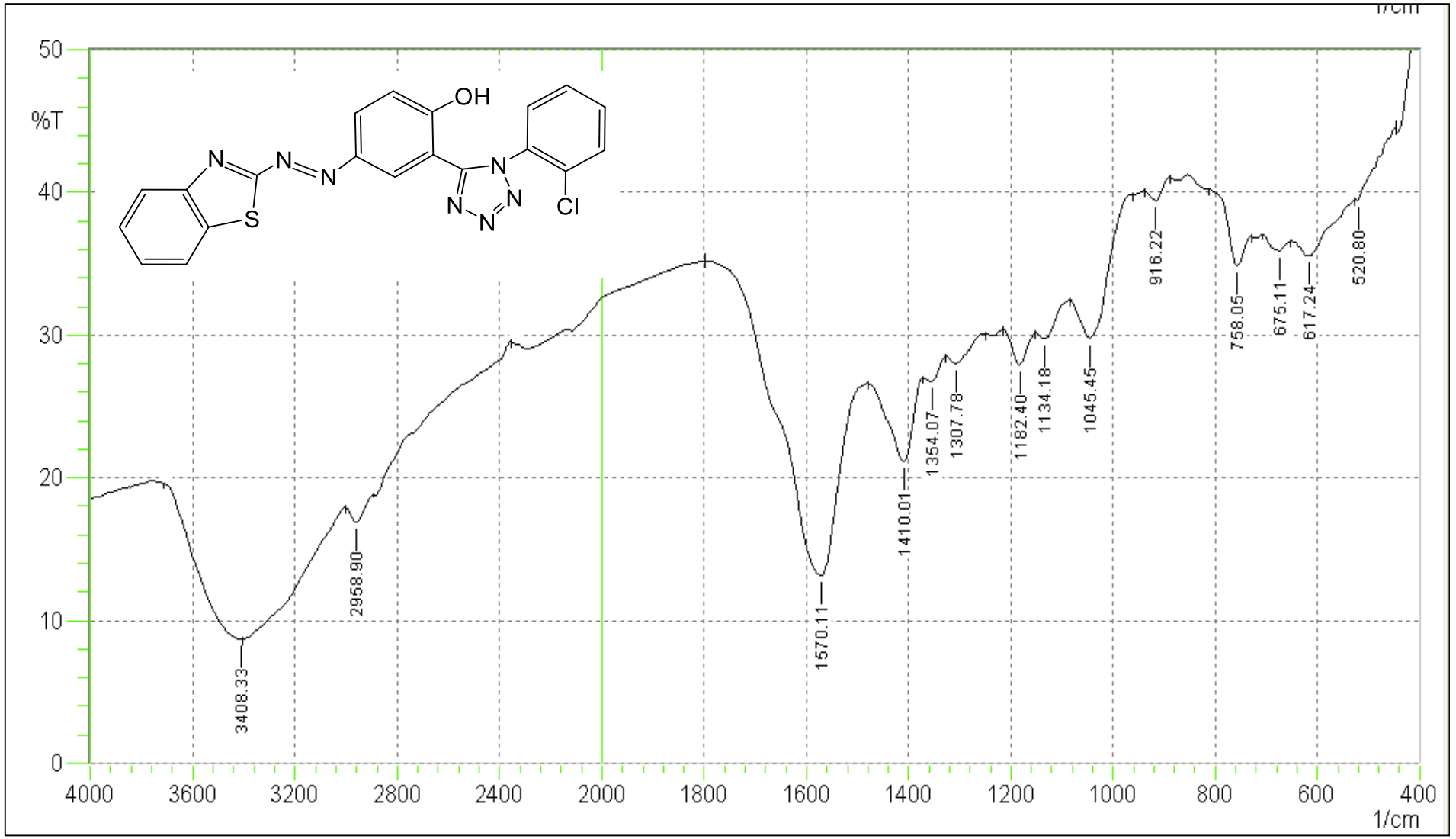


Fig. (3-12): FT-IR spectrum of compound **3b**

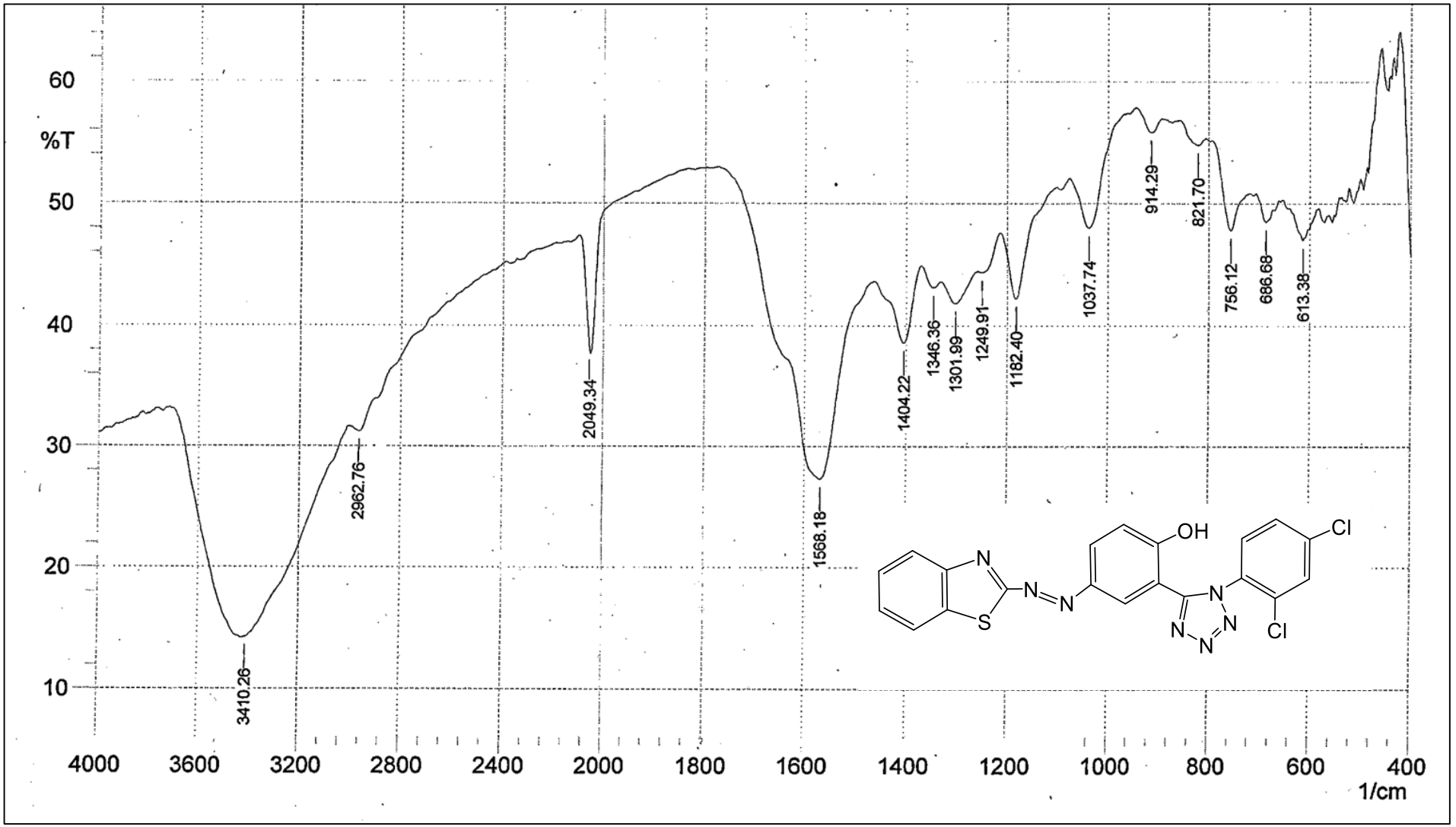


Fig. (3-13): FT-IR spectrum of compound **3c**

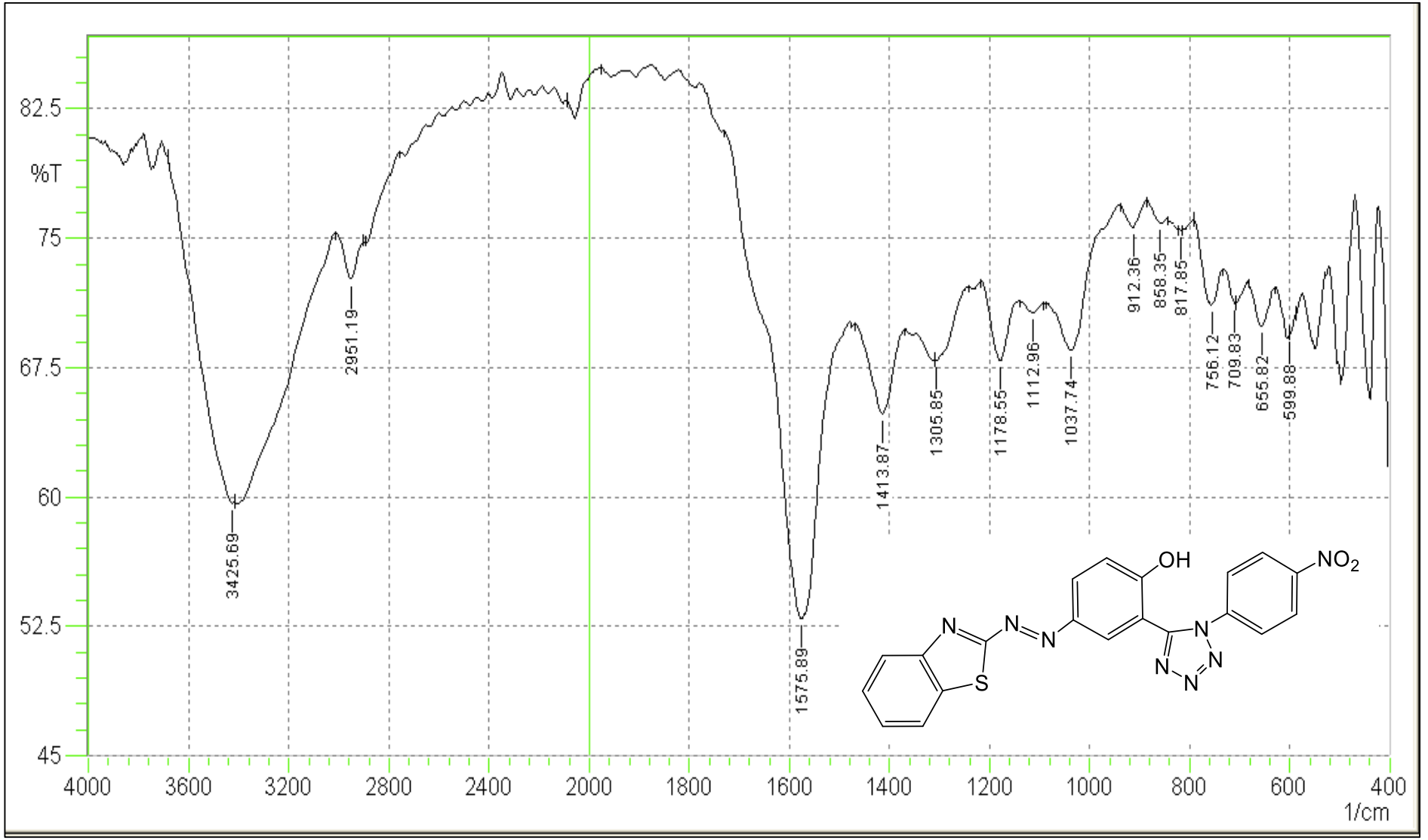


Fig. (3-14): FT-IR spectrum of compound **3d**

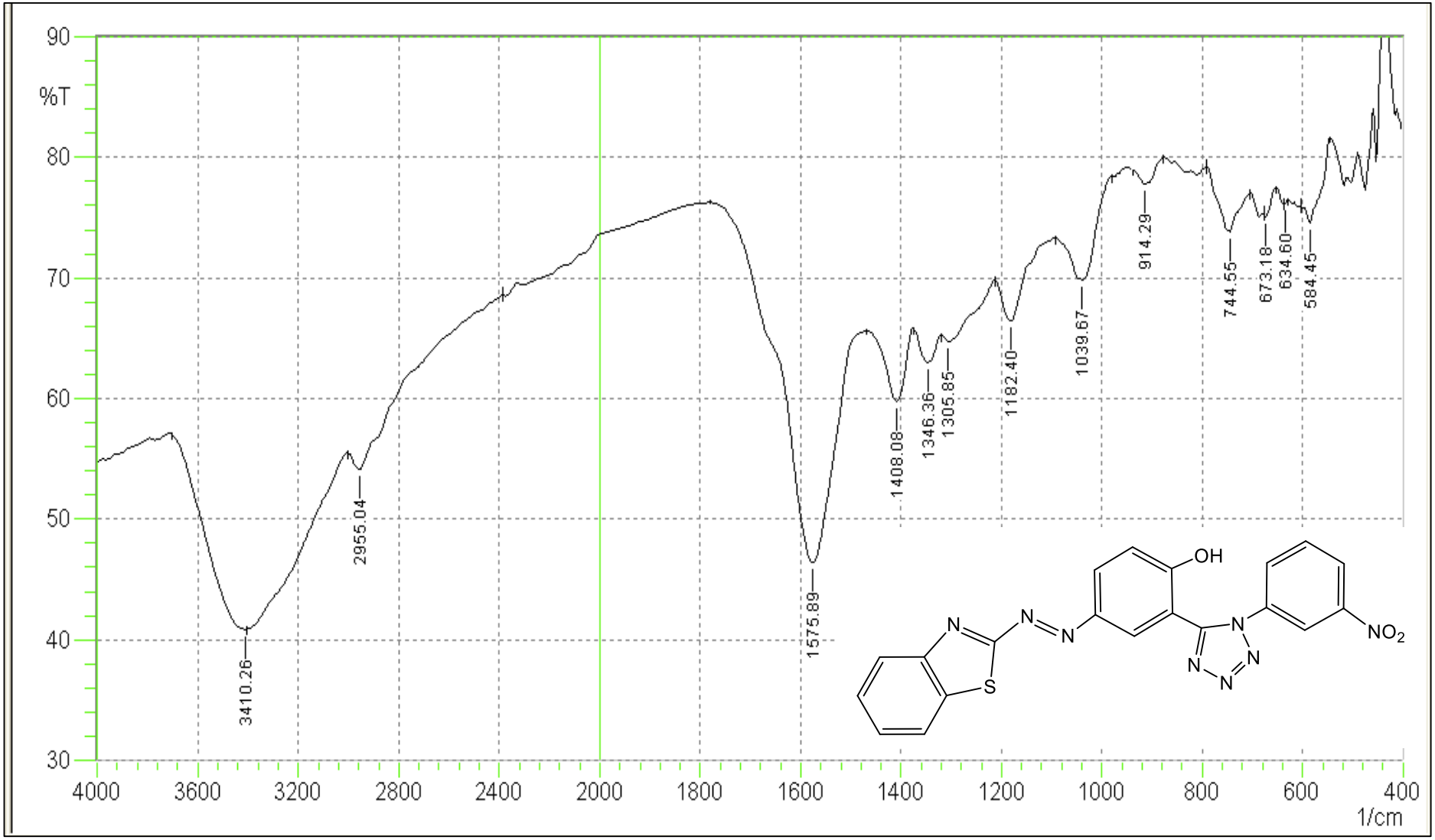


Fig. (3-15): FT-IR spectrum of compound **3e**

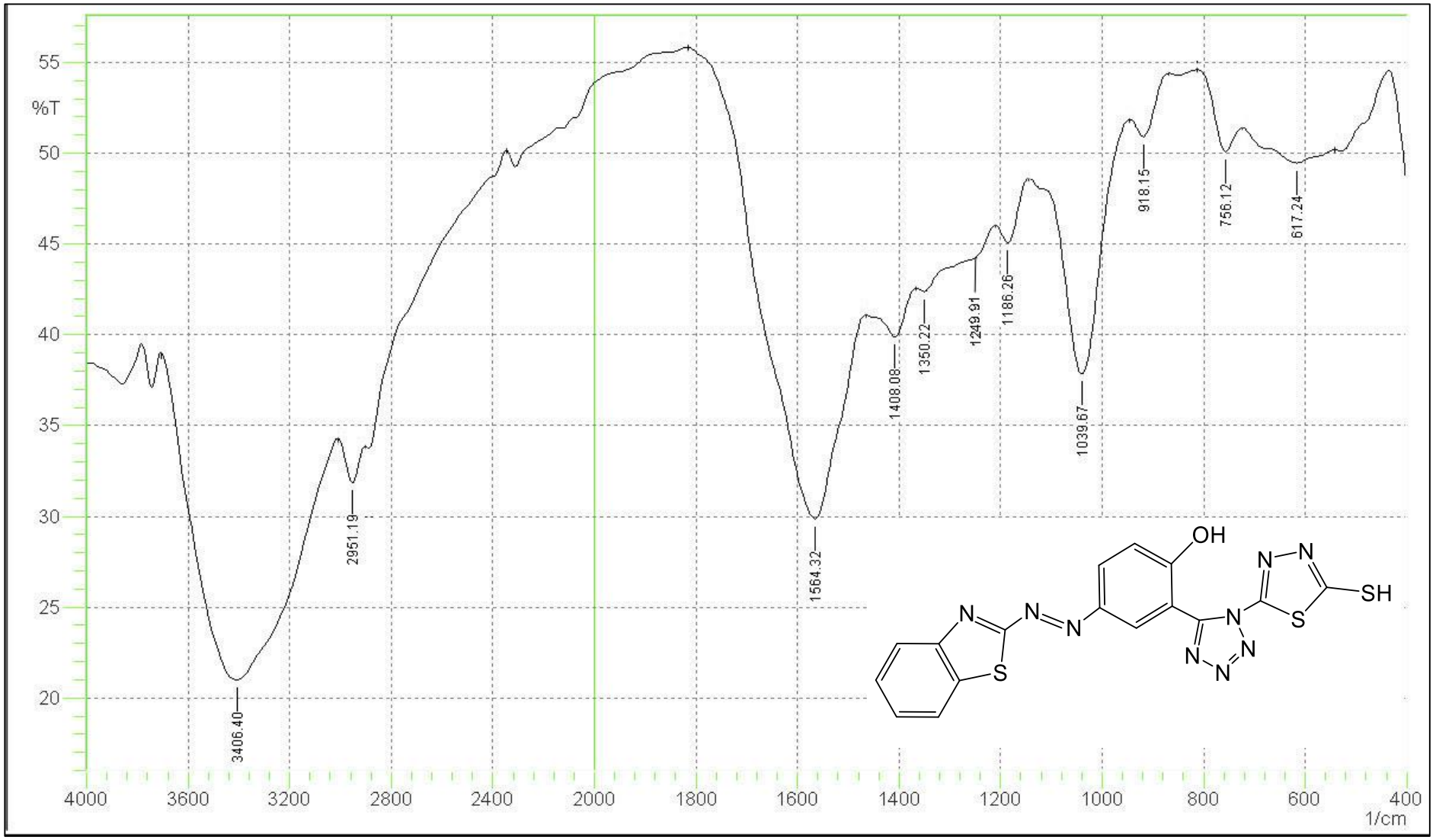


Fig. (3-16): FT-IR spectrum of compound **3f**

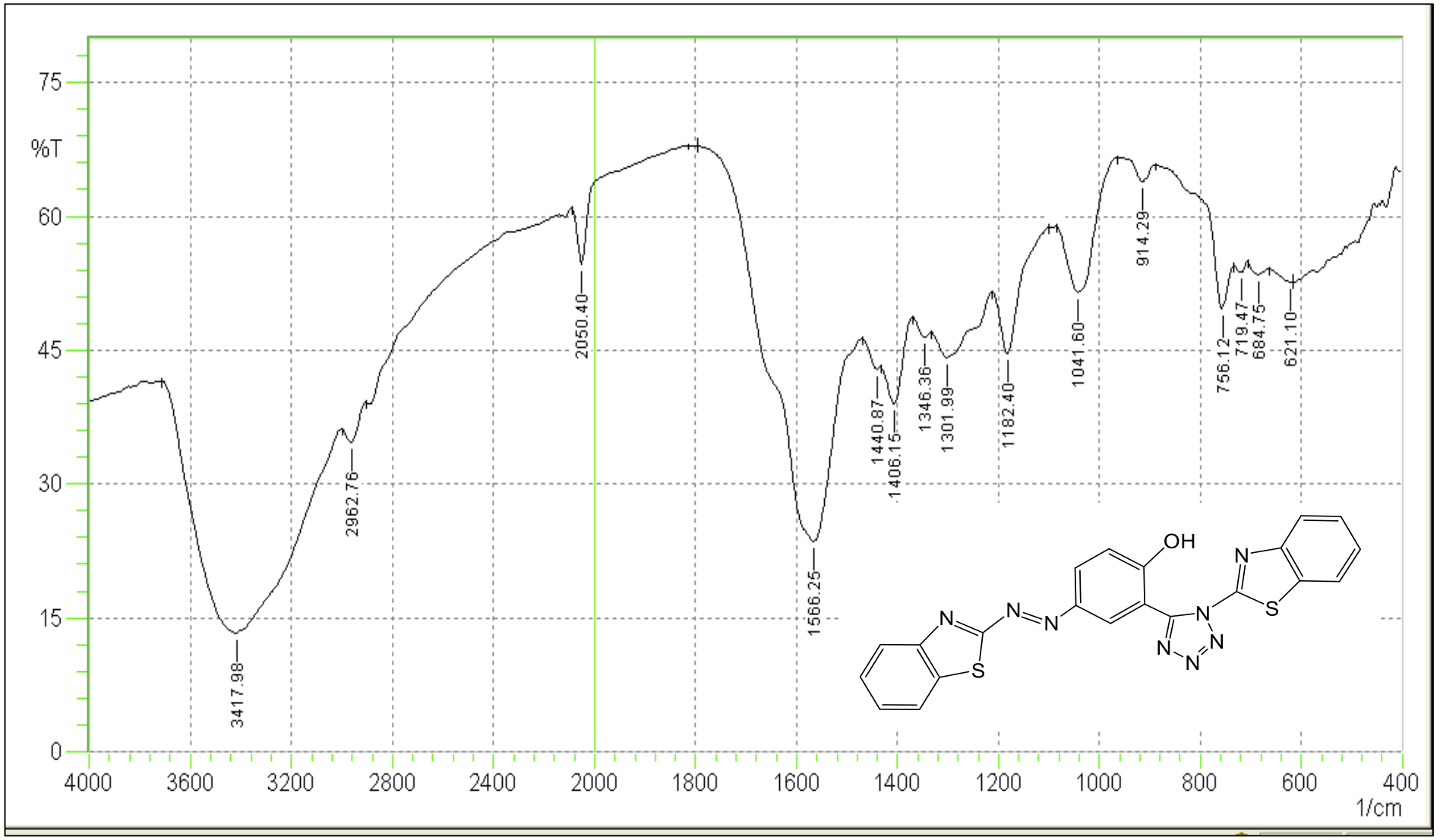


Fig. (3-17): FT-IR spectrum of compound **3g**

A.1.4. FT-IR spectra of the synthesized azoaldehyde derivatives 1a`-e`

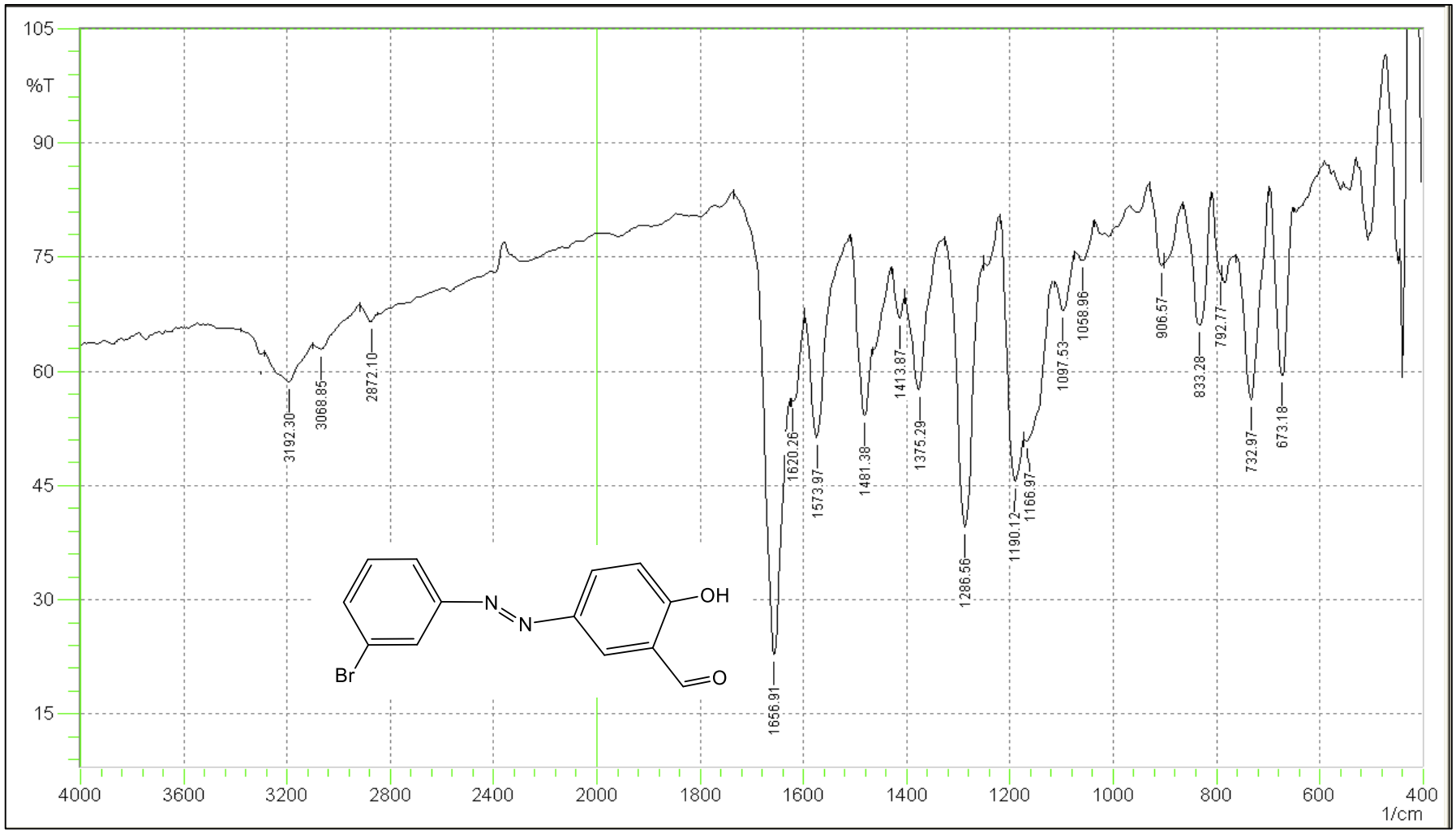


Fig. (3-18): FT-IR spectrum of compound **1a`**

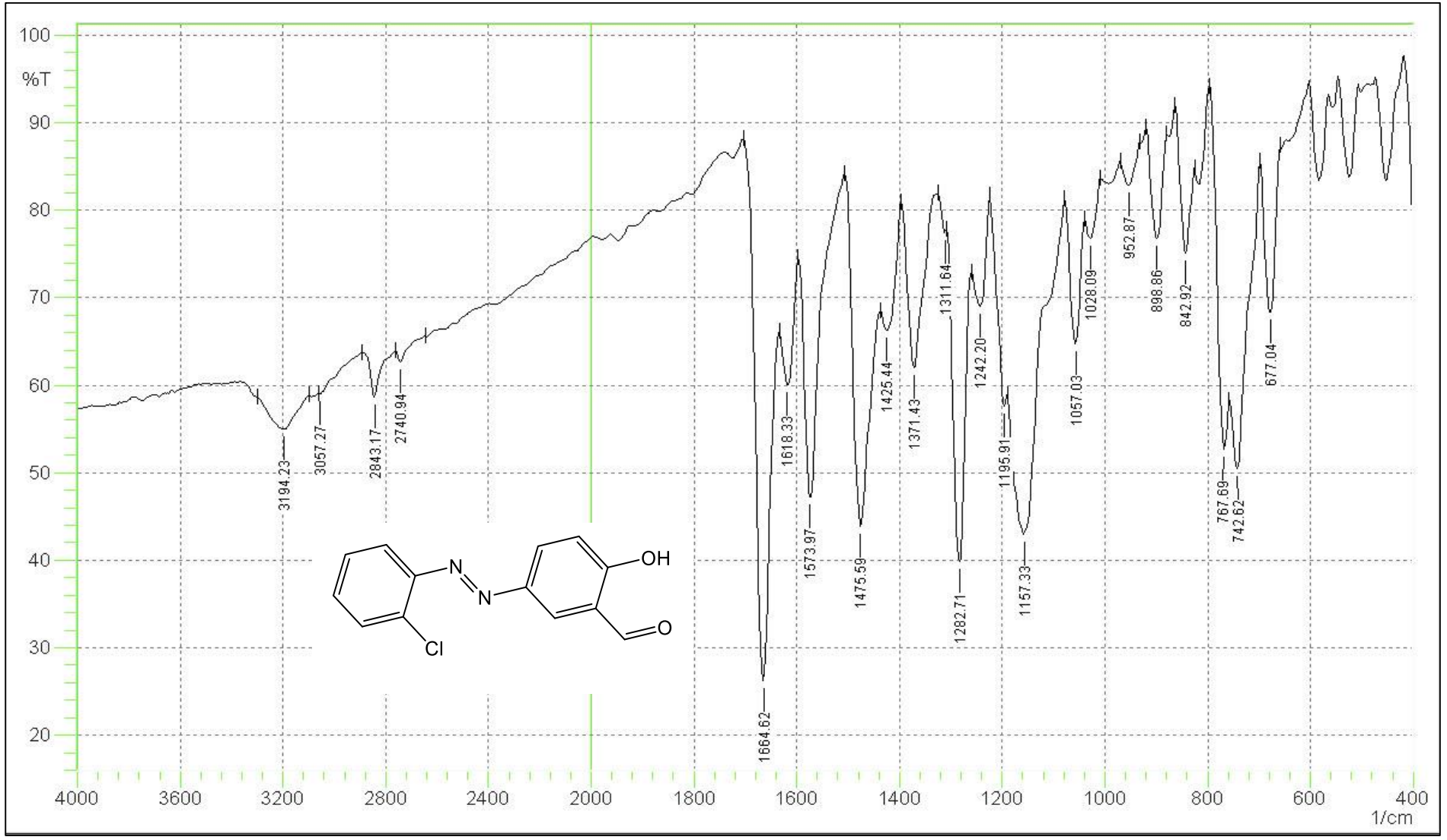


Fig. (3-19): FT-IR spectrum of compound **1b`**

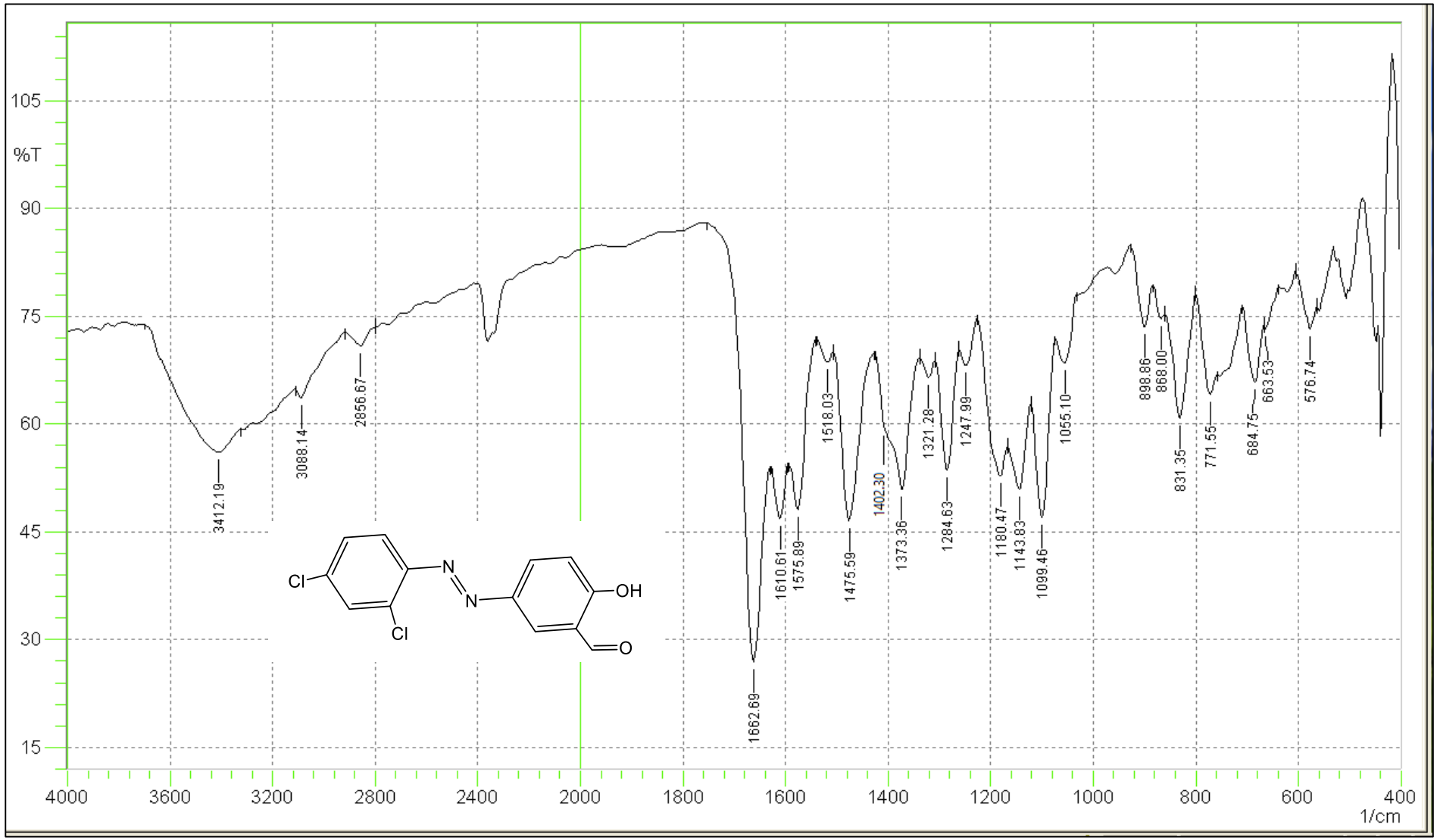


Fig. (3-20): FT-IR spectrum of compound **1c`**

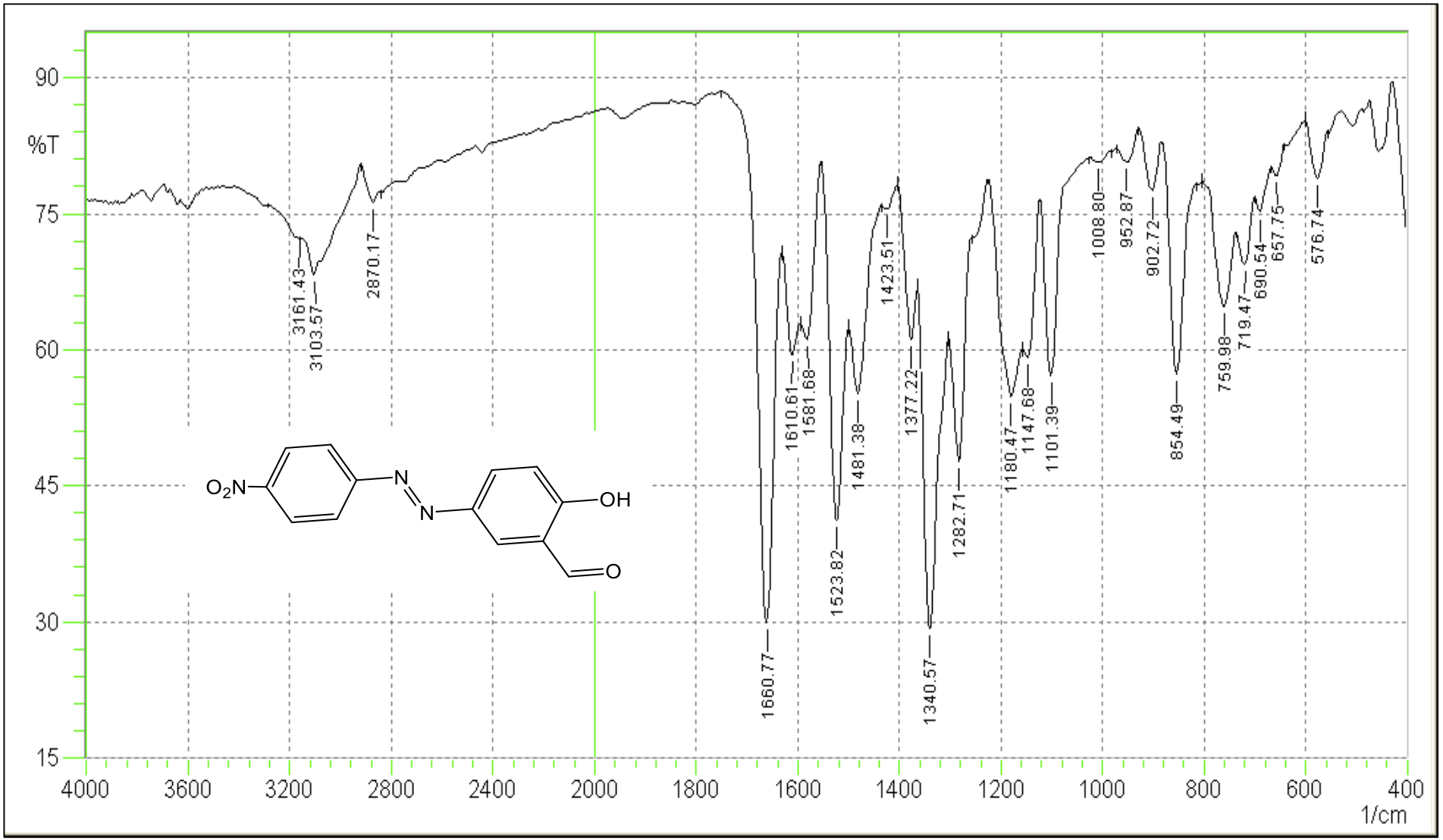


Fig. (3-21): FT-IR spectrum of compound **1d`**

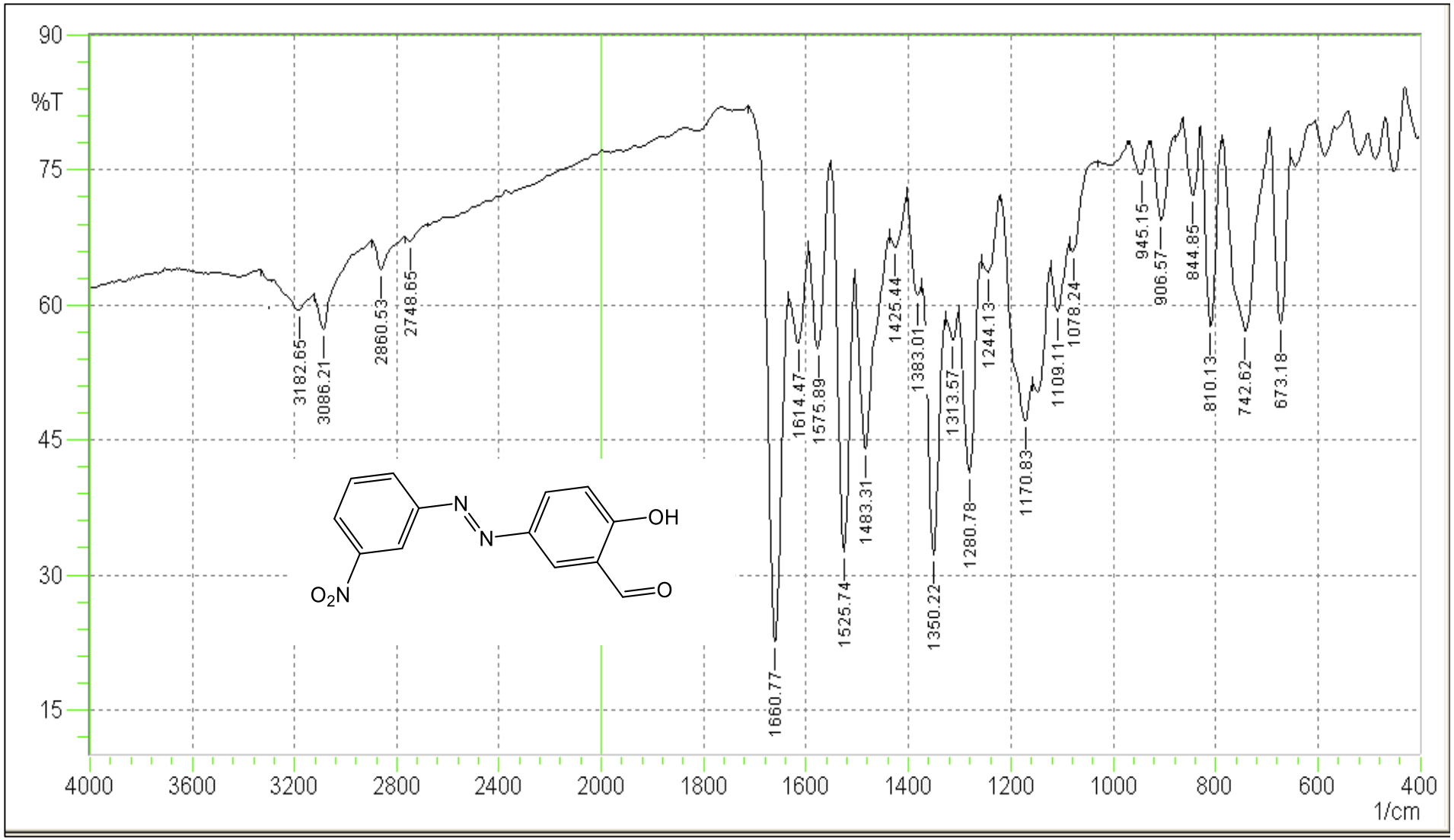


Fig. (3-22): FT-IR spectrum of compound **1e`**

A.1.5. FT-IR spectra of the synthesized azoimine derivatives 2a`-e`

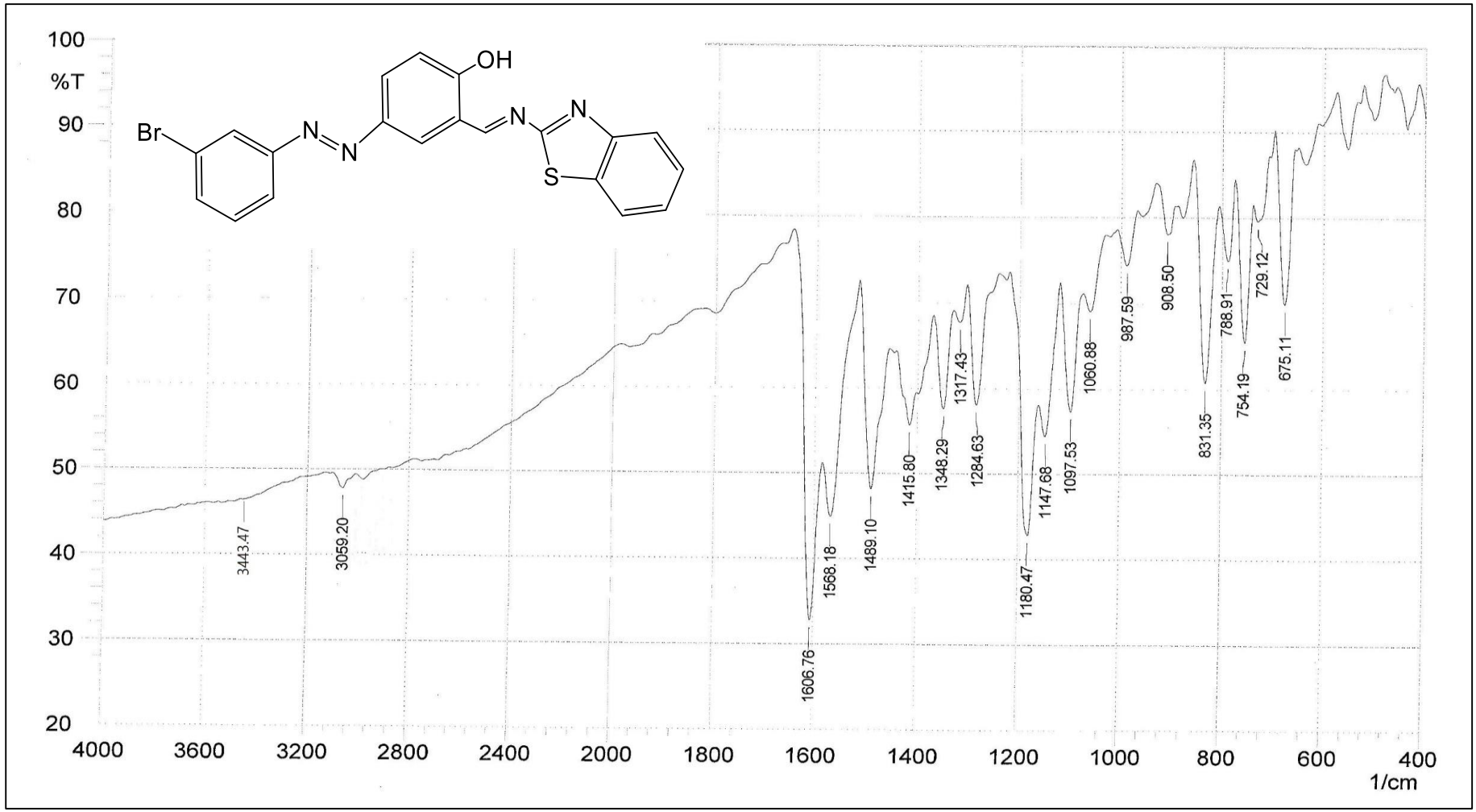


Fig. (3-23): FT-IR spectrum of compound **2a`**

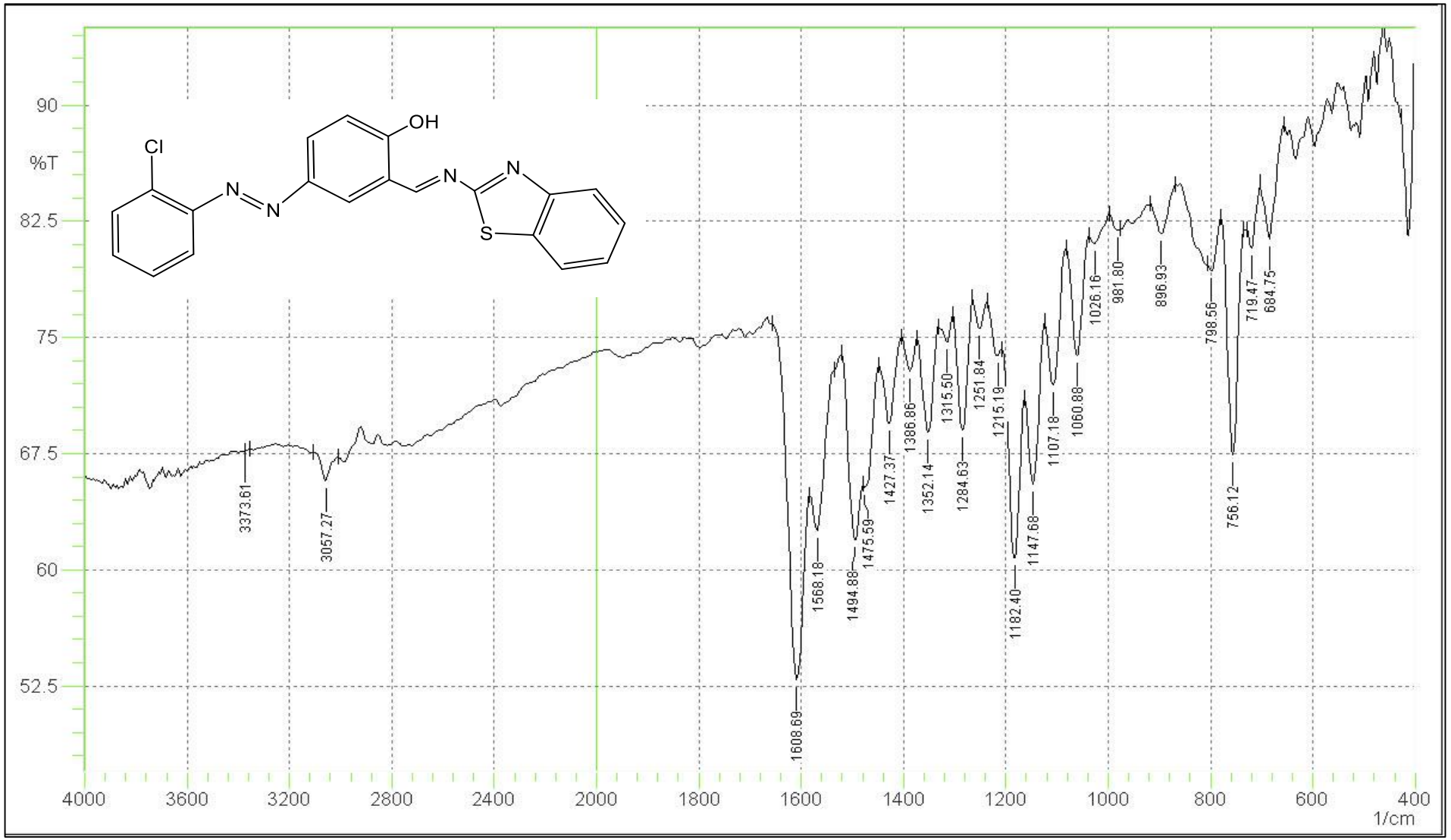


Fig. (3-24): FT-IR spectrum of compound **2b`**

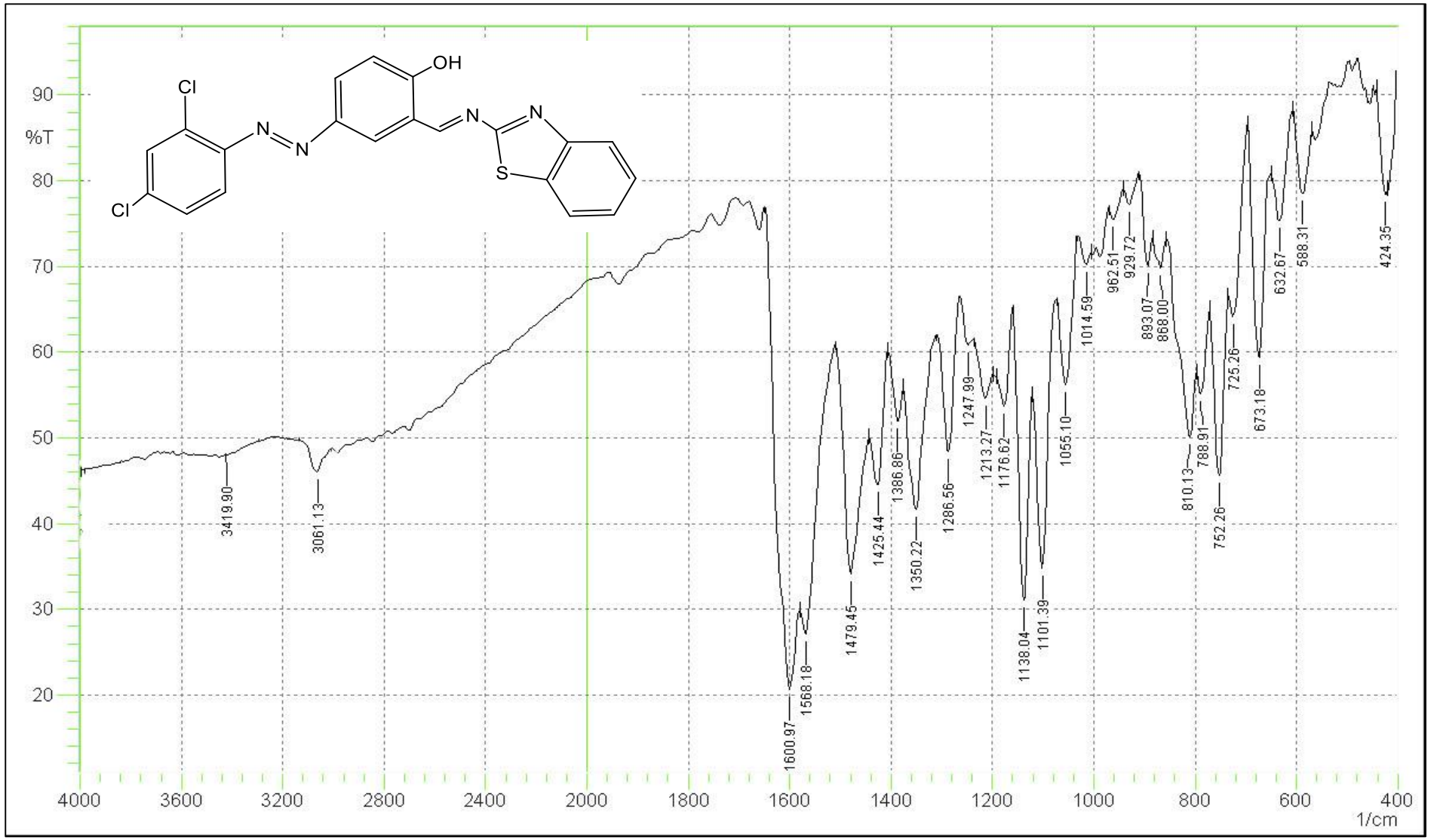


Fig. (3-25): FT-IR spectrum of compound **2c`**

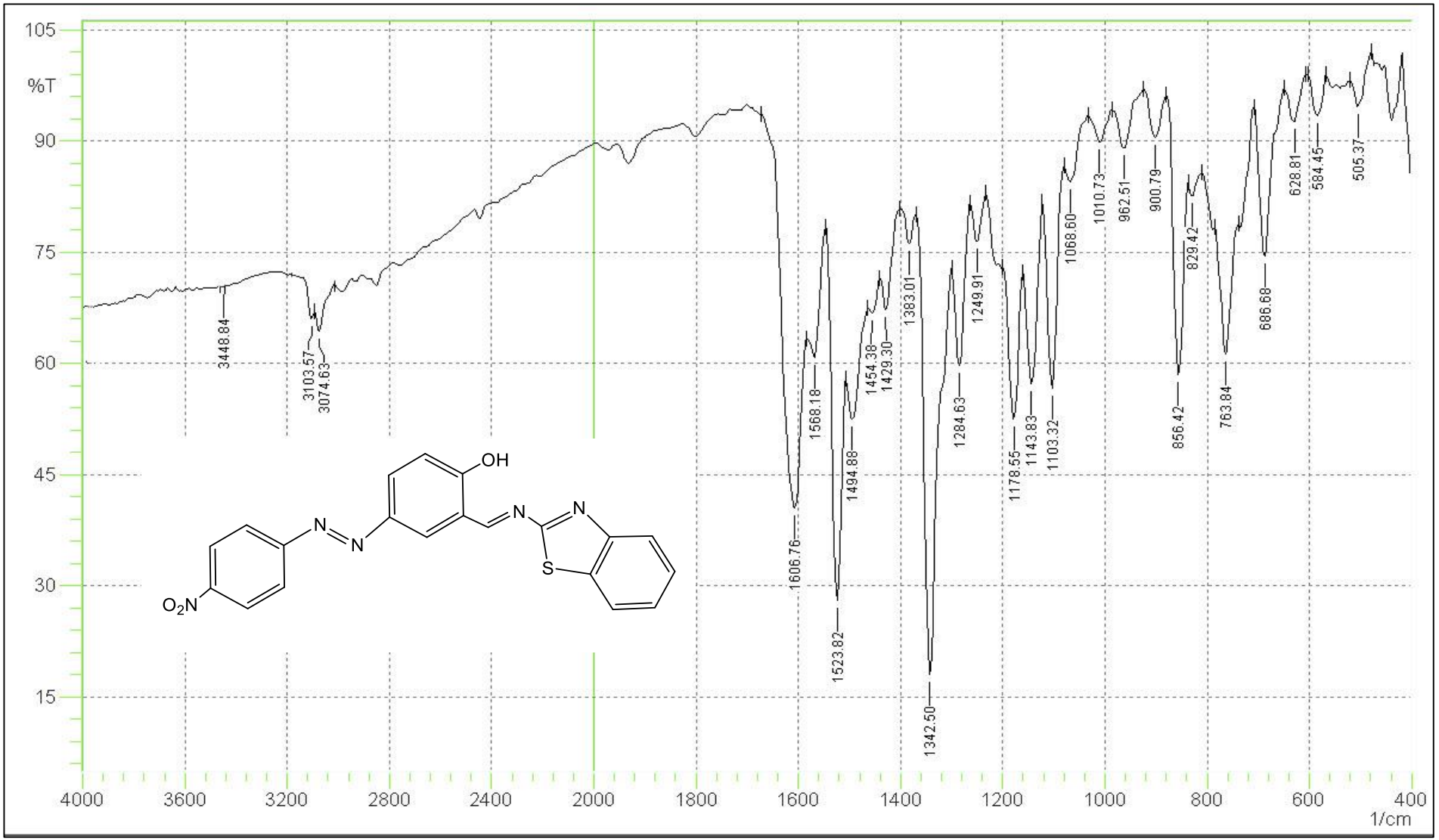


Fig. (3-26): FT-IR spectrum of compound **2d`**

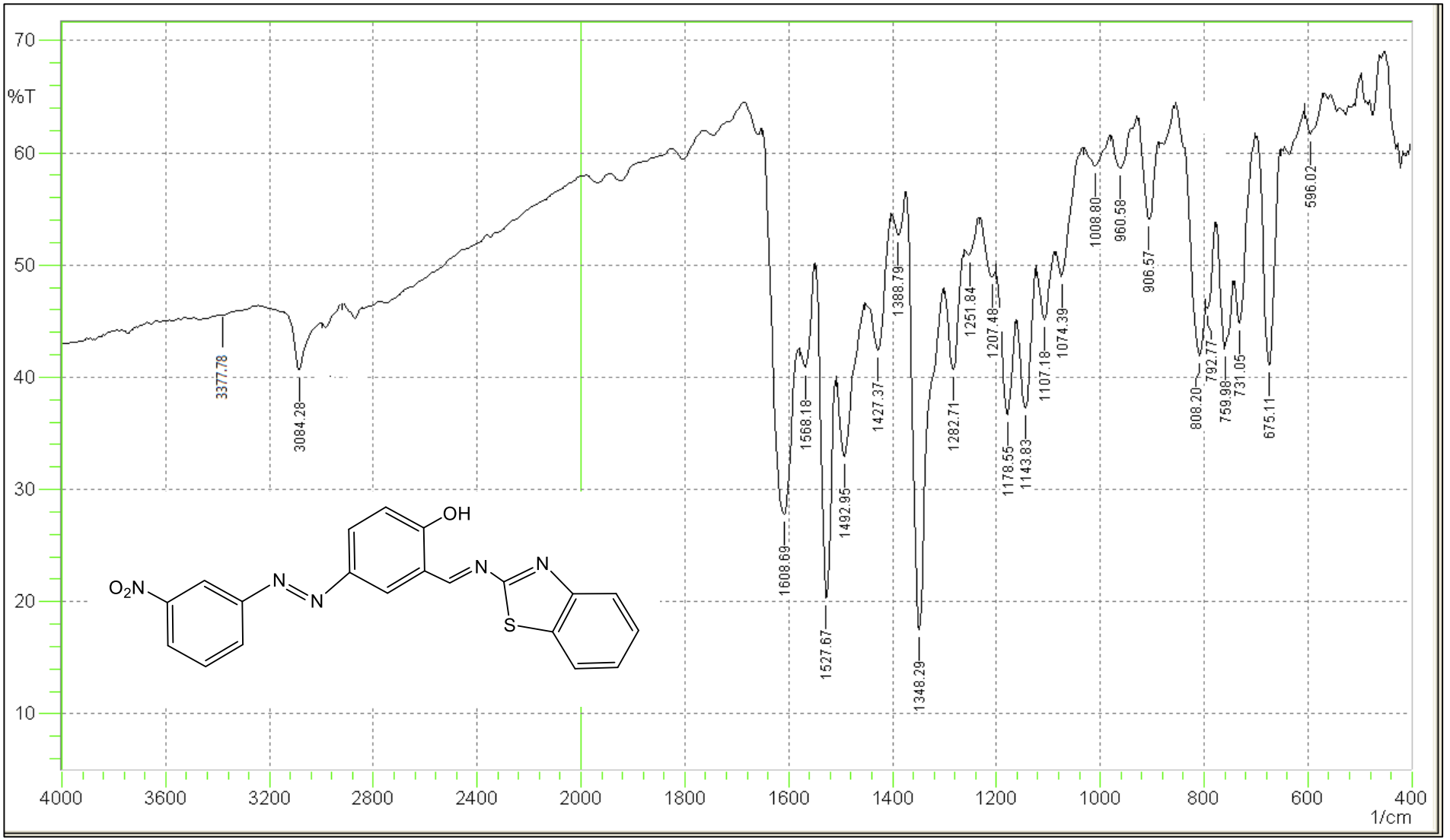


Fig. (3-27): FT-IR spectrum of compound **2e`**

A.1.6. FT-IR spectra of the synthesized tetrazole derivatives 3a`-e`

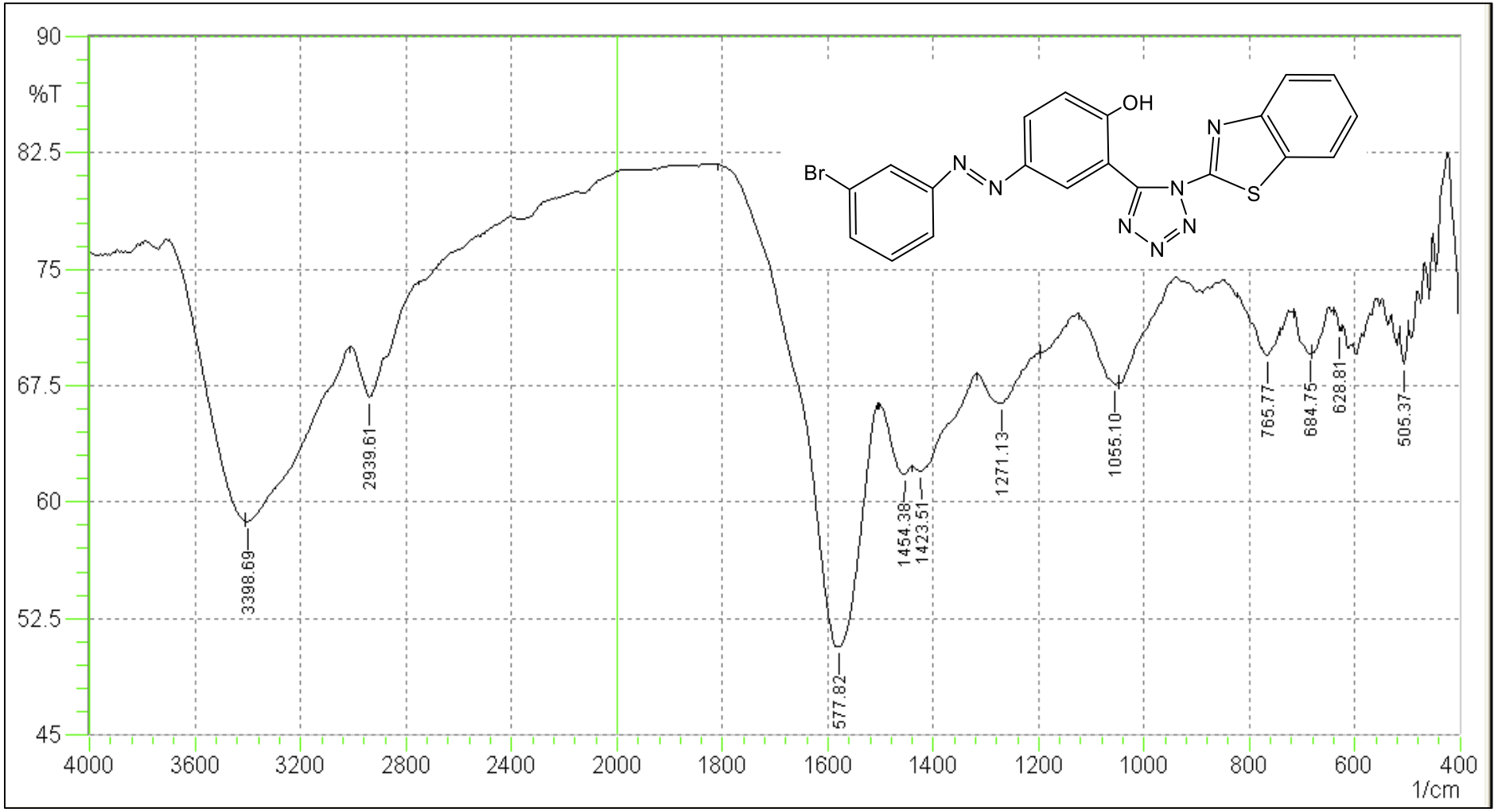


Fig. (3-28): FT-IR spectrum of compound **3a`**

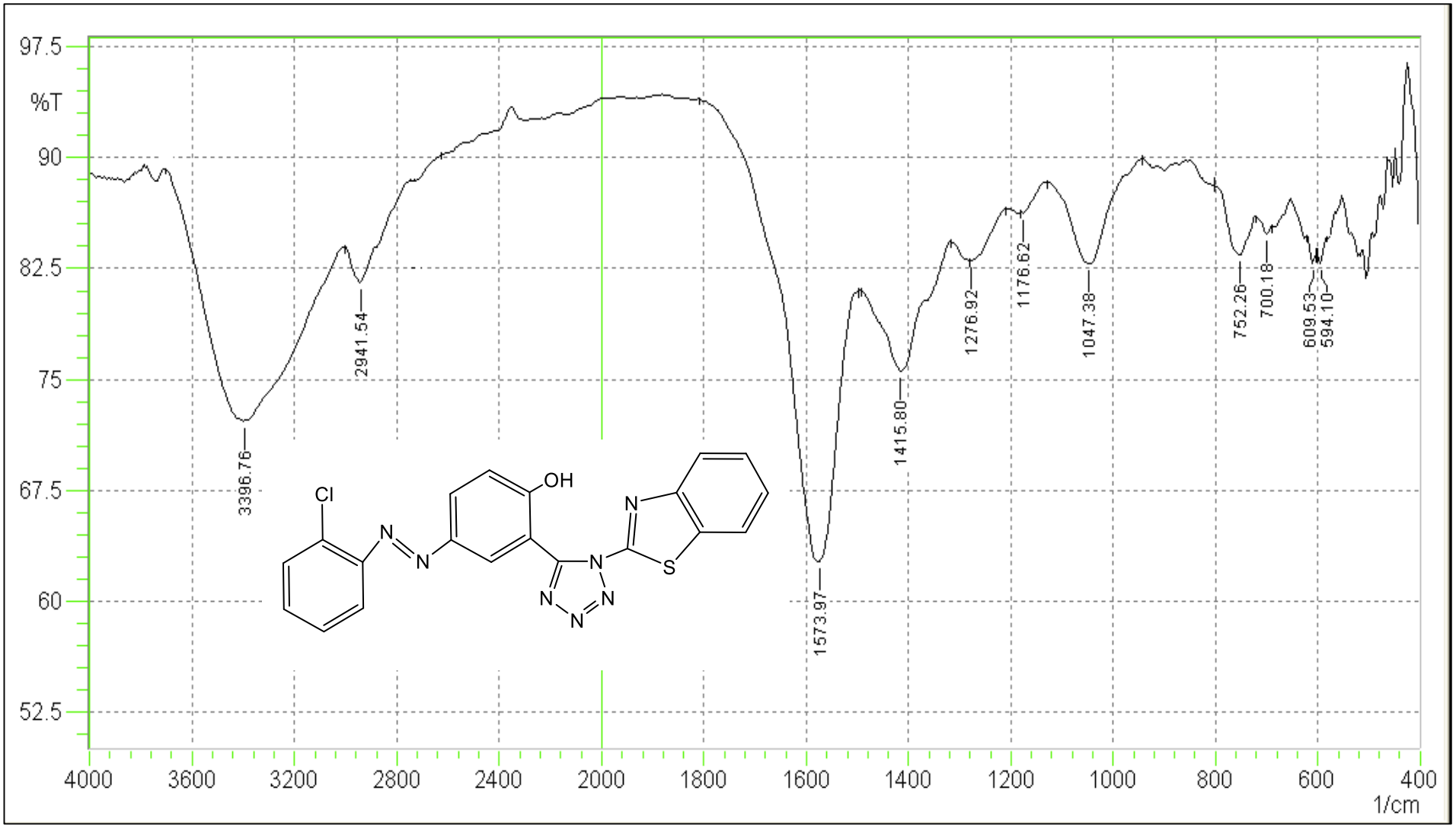


Fig. (3-29): FT-IR spectrum of compound **3b`**

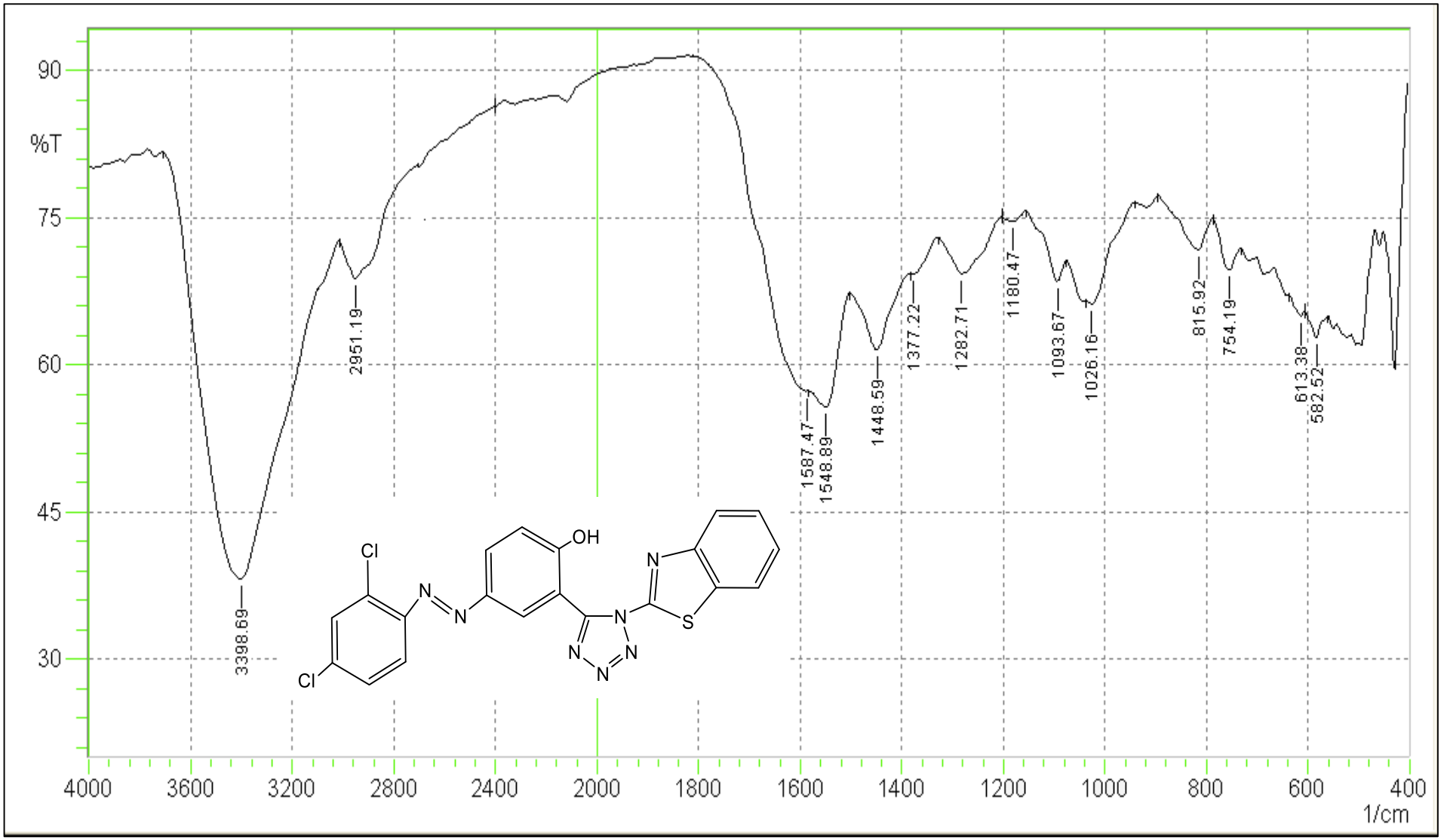


Fig. (3-30): FT-IR spectrum of compound **3c`**

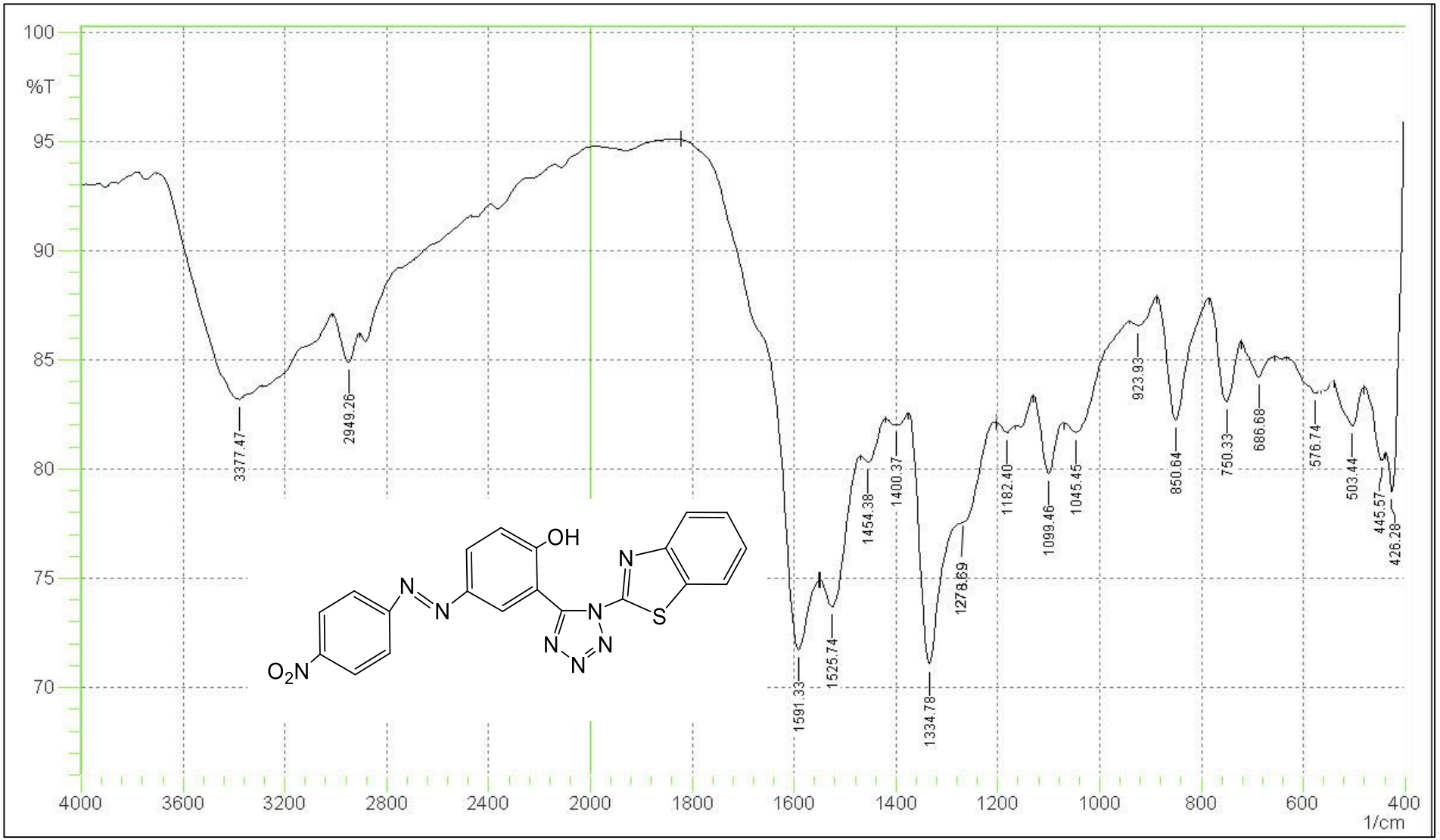


Fig. (3-31): FT-IR spectrum of compound **3d`**

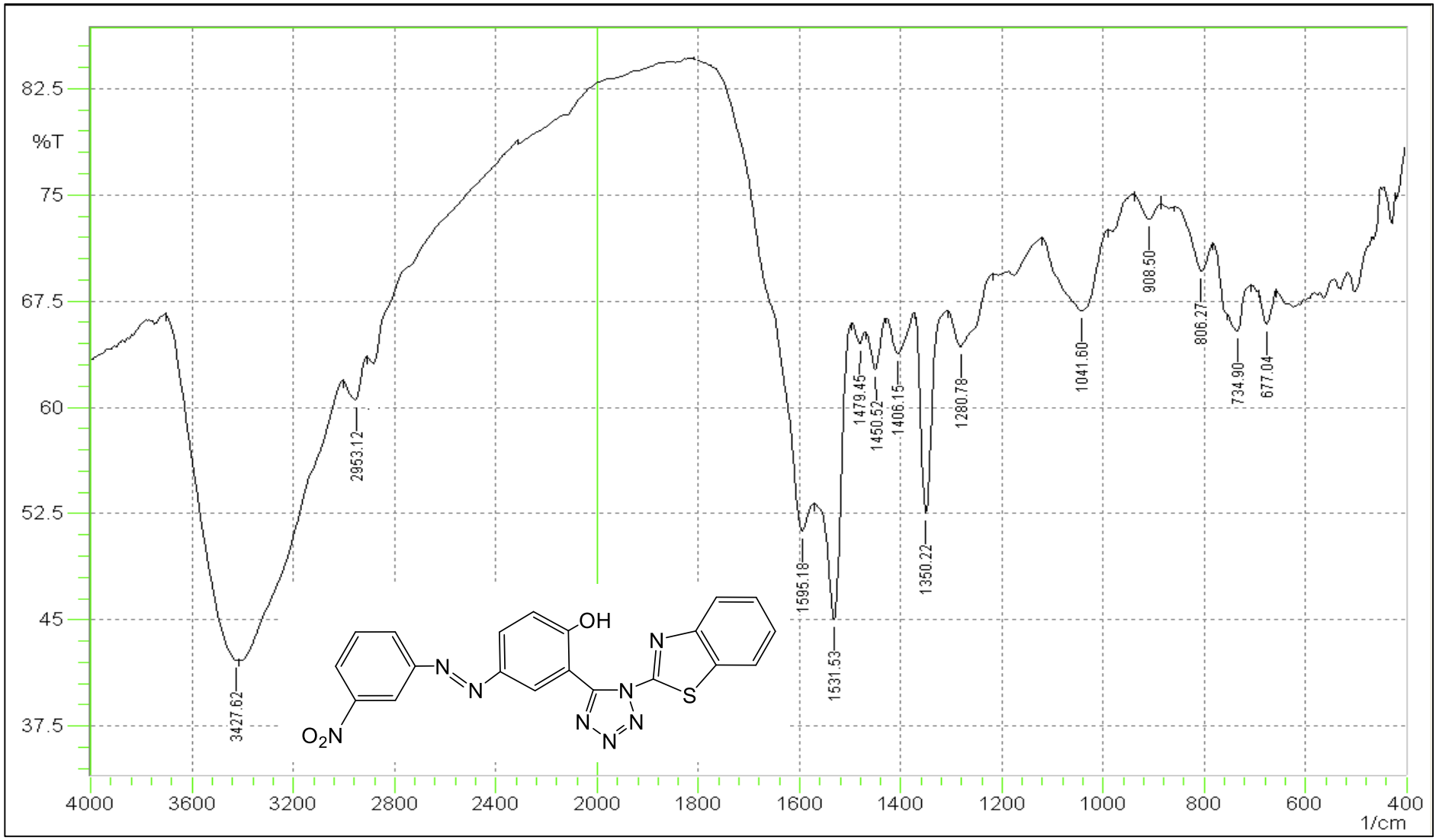


Fig. (3-32): FT-IR spectra of compound **3e`**

A.2. ^{1}H NMR spectra

A.2.1. ^{1}H NMR spectra of the synthesized tetrazole derivatives 3a-g

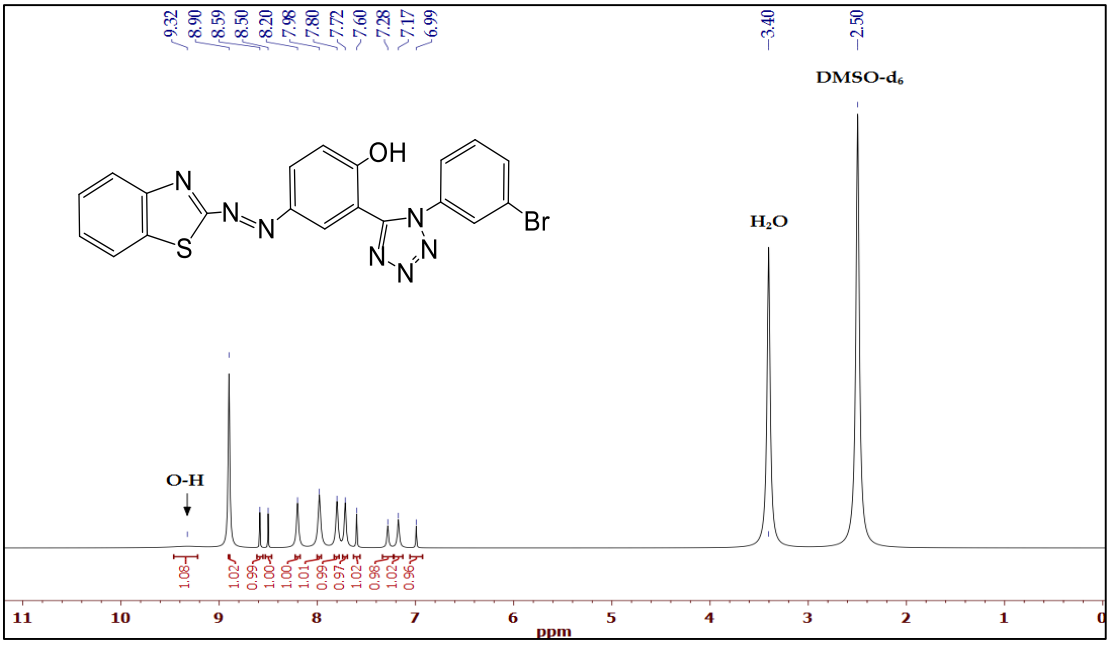


Fig. (3-33): ^{1}H NMR spectrum of compound **3a**

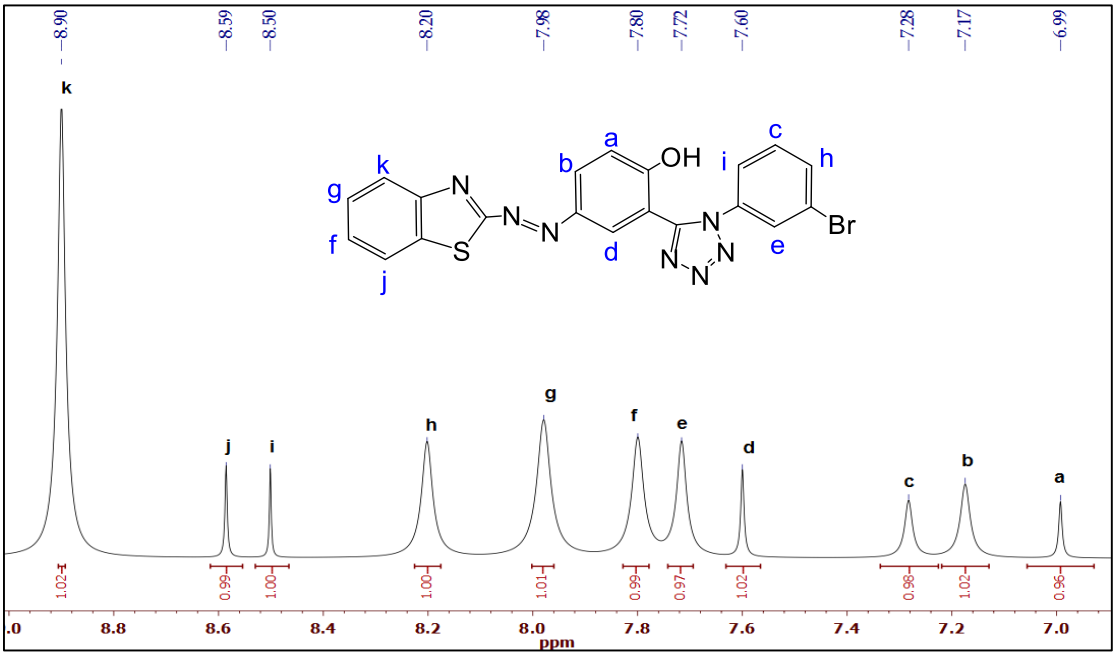


Fig. (3-33a): Expanded ^{1}H NMR spectrum of compound **3a** in ppm

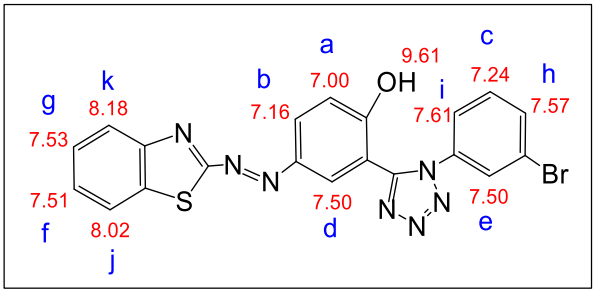


Fig. (3-33b): Theoretical δ (ppm) values of compound **3a**

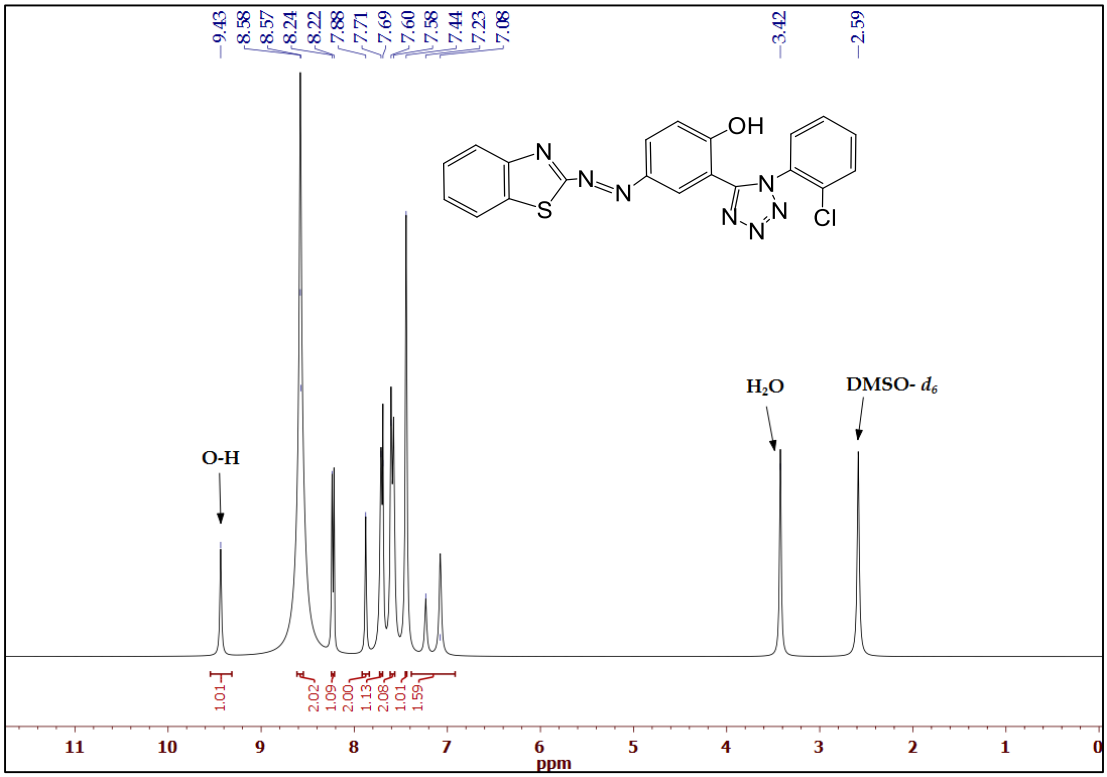


Fig. (3-34): ^{1}H NMR spectrum of compound **3b**

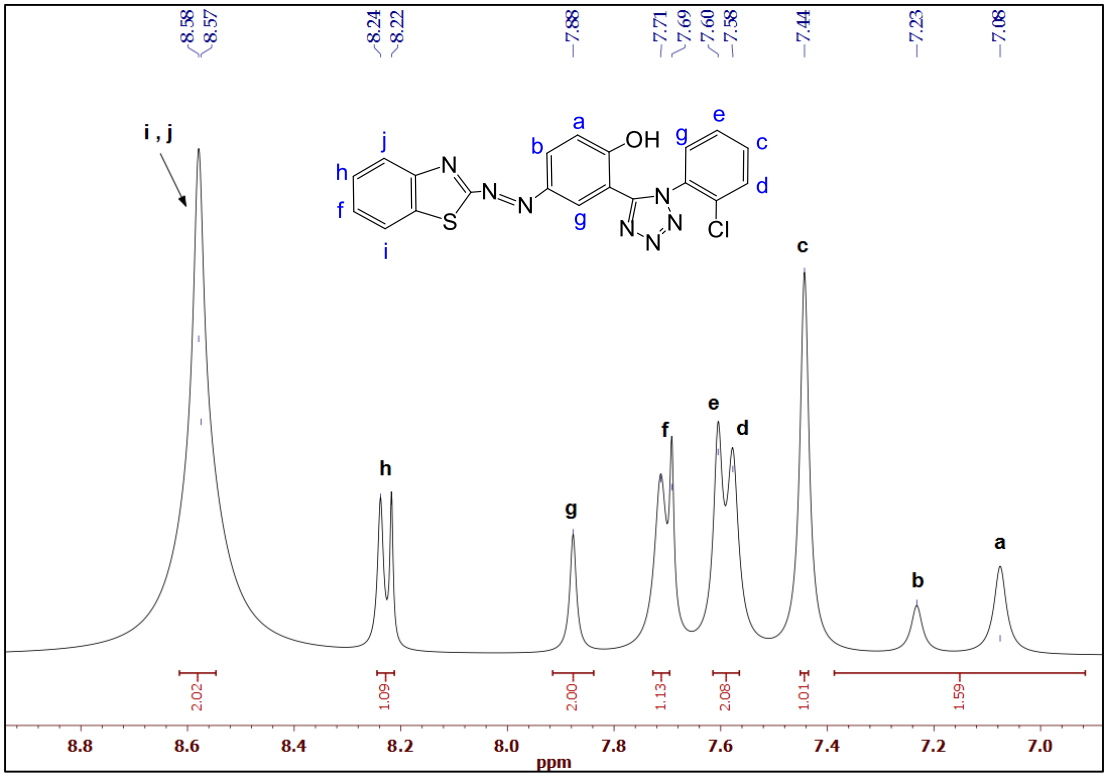


Fig. (3-34a): Expanded ^{1}H NMR spectrum of compound **3b** in ppm

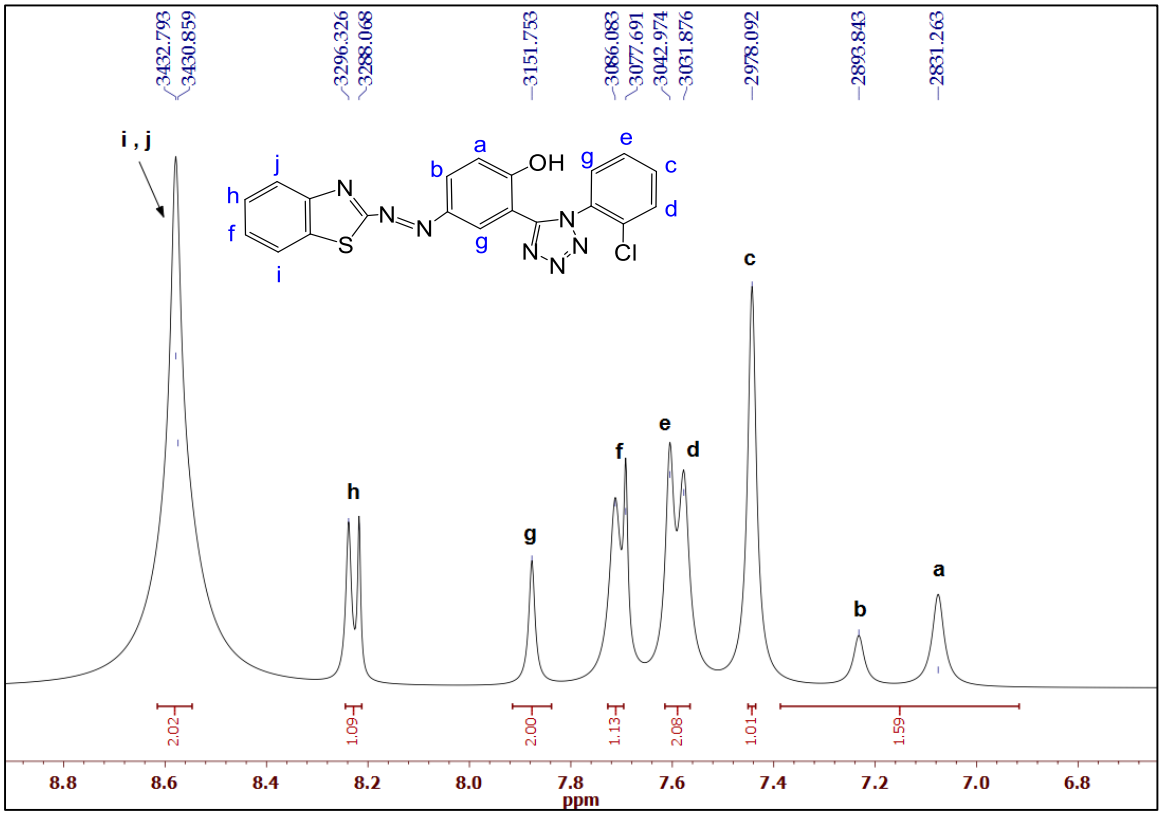


Fig. (3-34b): Expanded ^{1}H NMR spectrum of compound **3b** in Hz

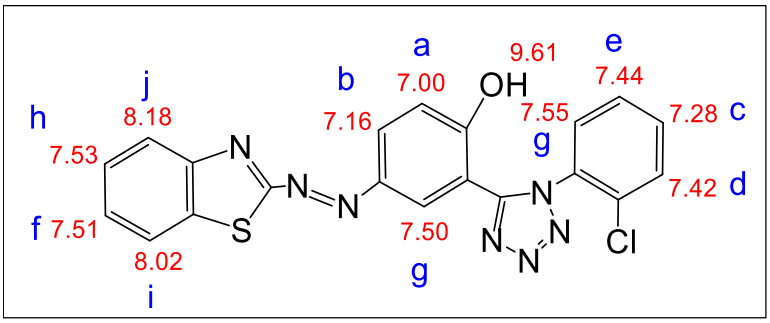


Fig. (3-34c): Theoretical δ (ppm) values of compound **3b**

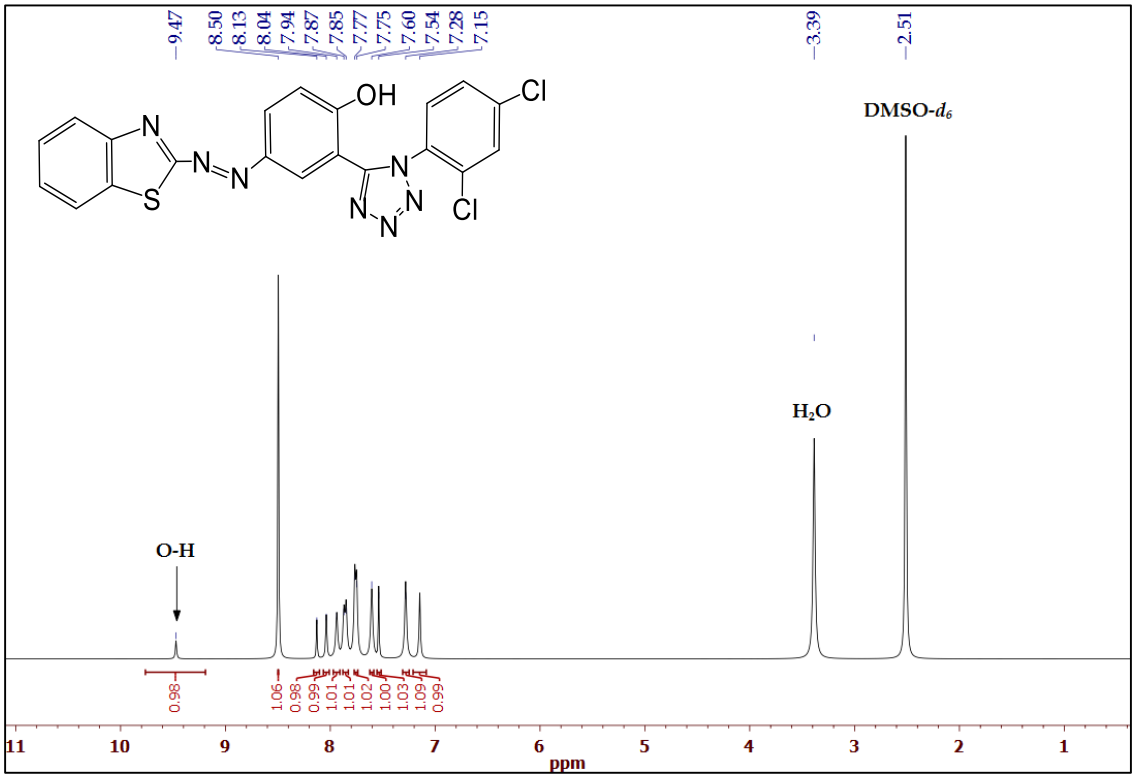


Fig. (3-35): ^{1}H NMR spectrum of compound **3c**

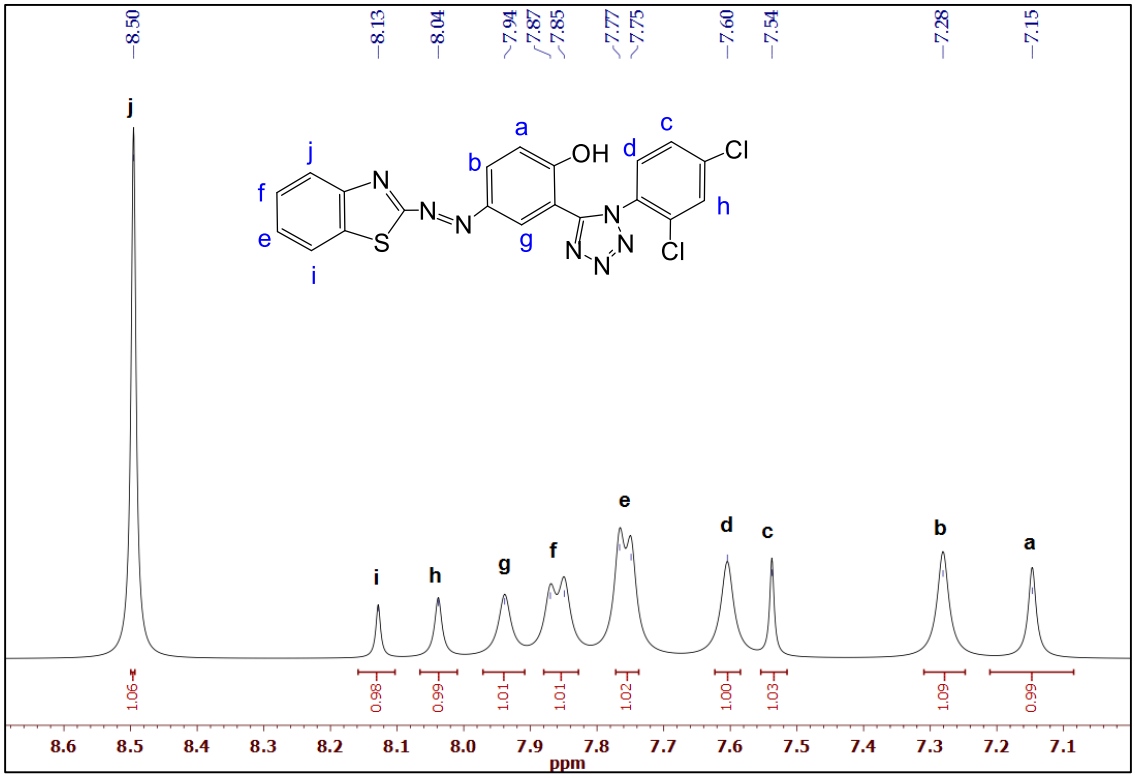


Fig. (3-35a): Expanded ^{1}H NMR spectrum of compound **3c** in ppm

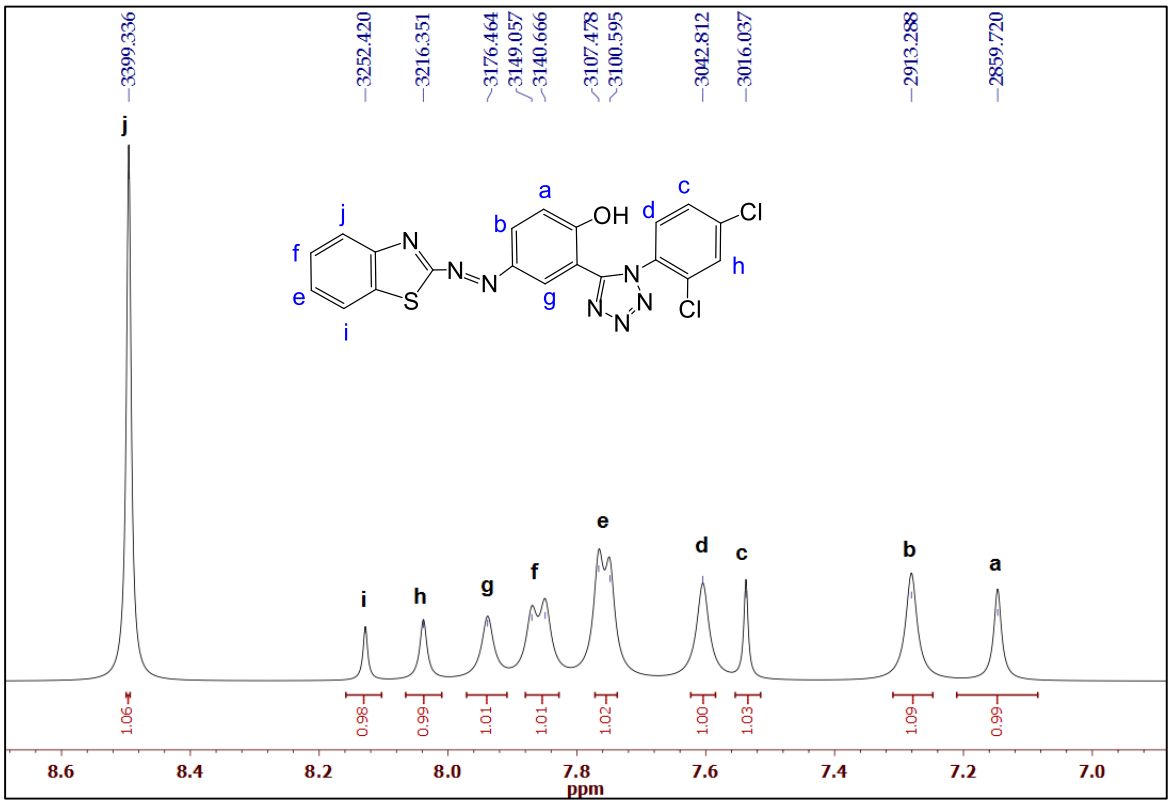


Fig. (3-35b): Expanded ^{1}H NMR spectrum of compound **3c** in Hz

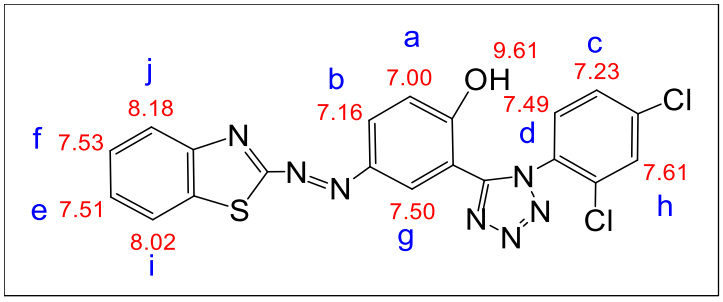


Fig. (3-35c): Theoretical δ (ppm) values of compound **3c**

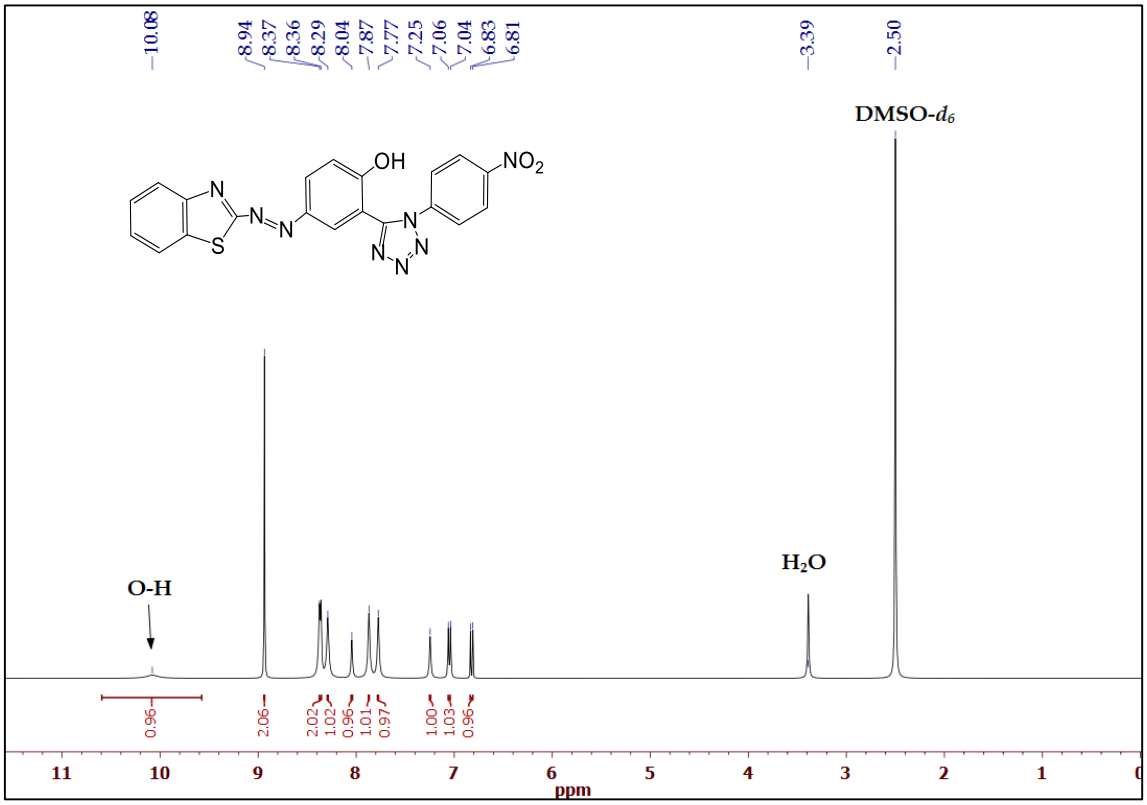


Fig. (3-36): ^{1}H NMR spectrum of compound **3d**

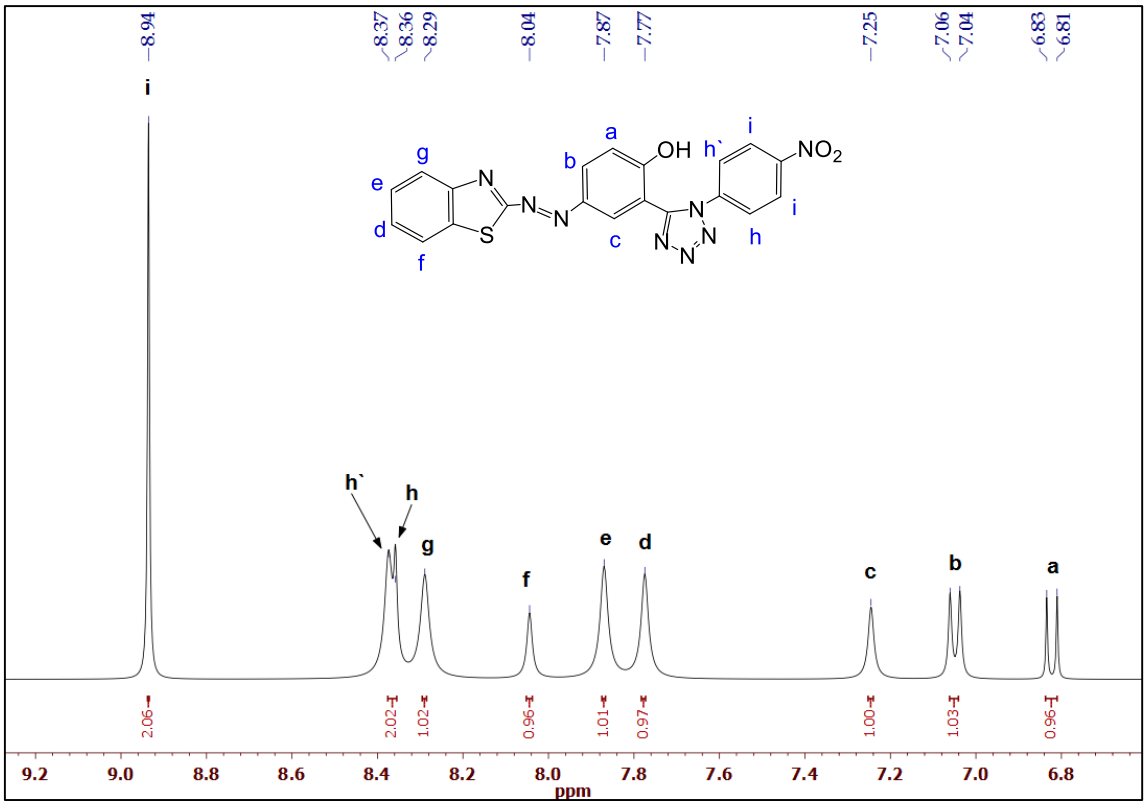


Fig. (3-36a): Expanded ^{1}H NMR spectrum of compound **3d** in ppm

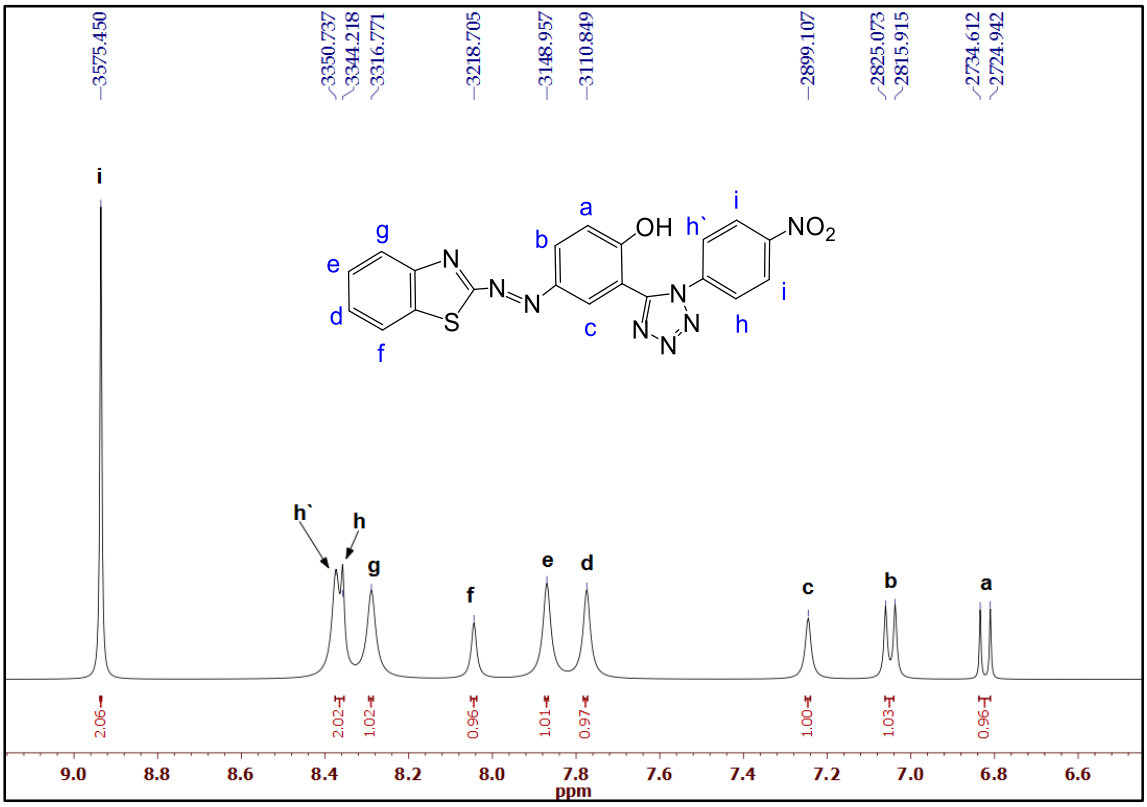


Fig. (3-36b): Expanded ^{1}H NMR spectrum of compound **3d** in Hz

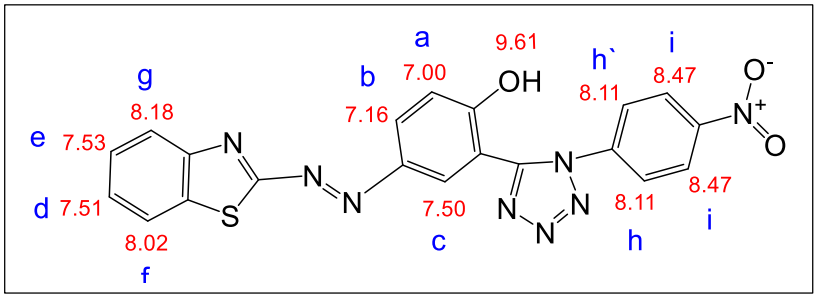


Fig. (3-36c): Theoretical δ (ppm) values of compound **3d**

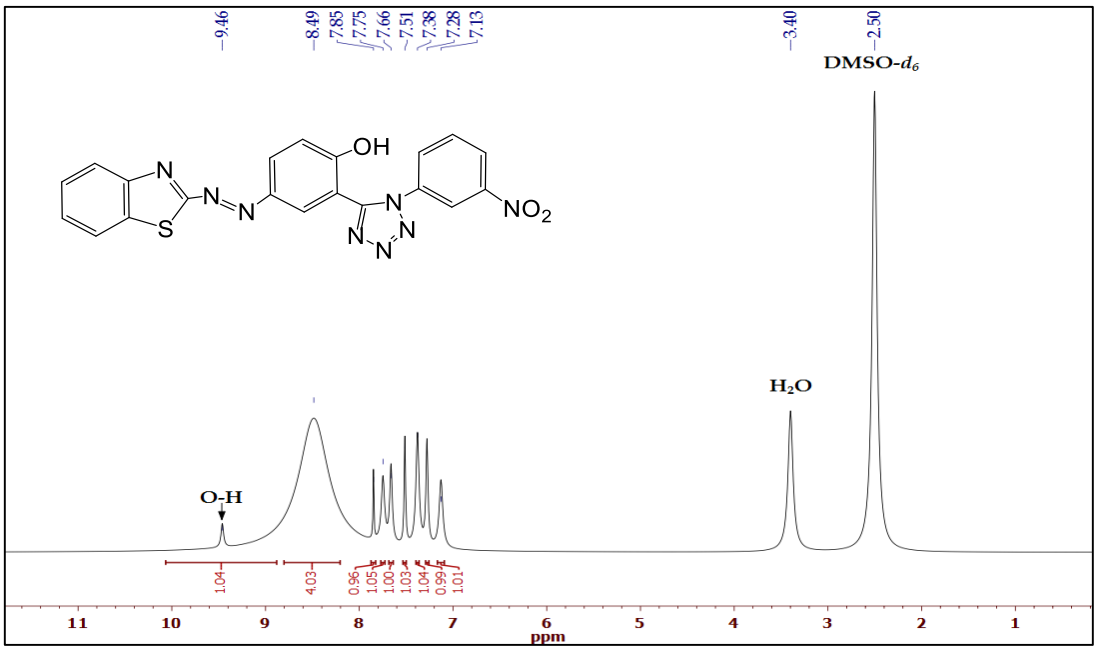


Fig. (3-37): ^{1}H NMR spectrum of compound **3e**

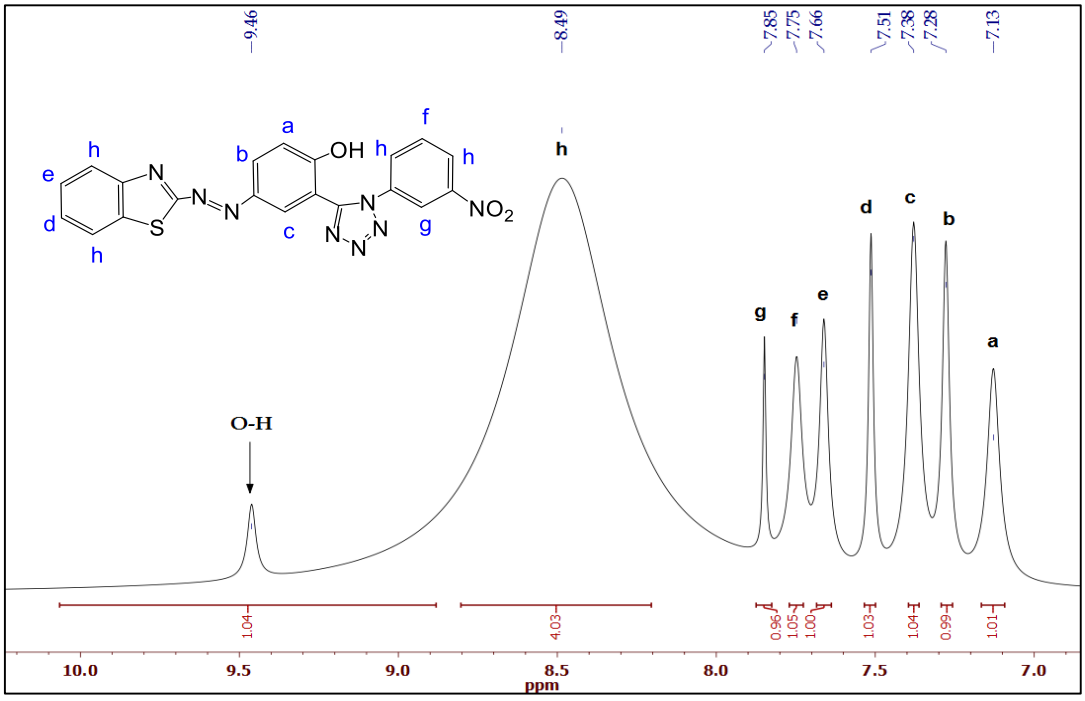


Fig. (3-37a): Expanded ^{1}H NMR spectrum of compound **3e** in ppm

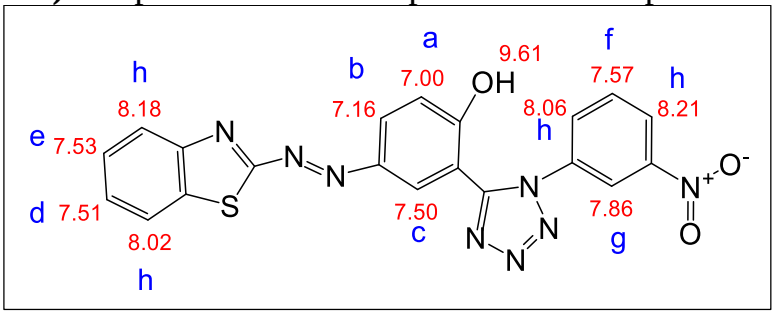


Fig. (3-37b): Theoretical δ (ppm) values of compound **3e**

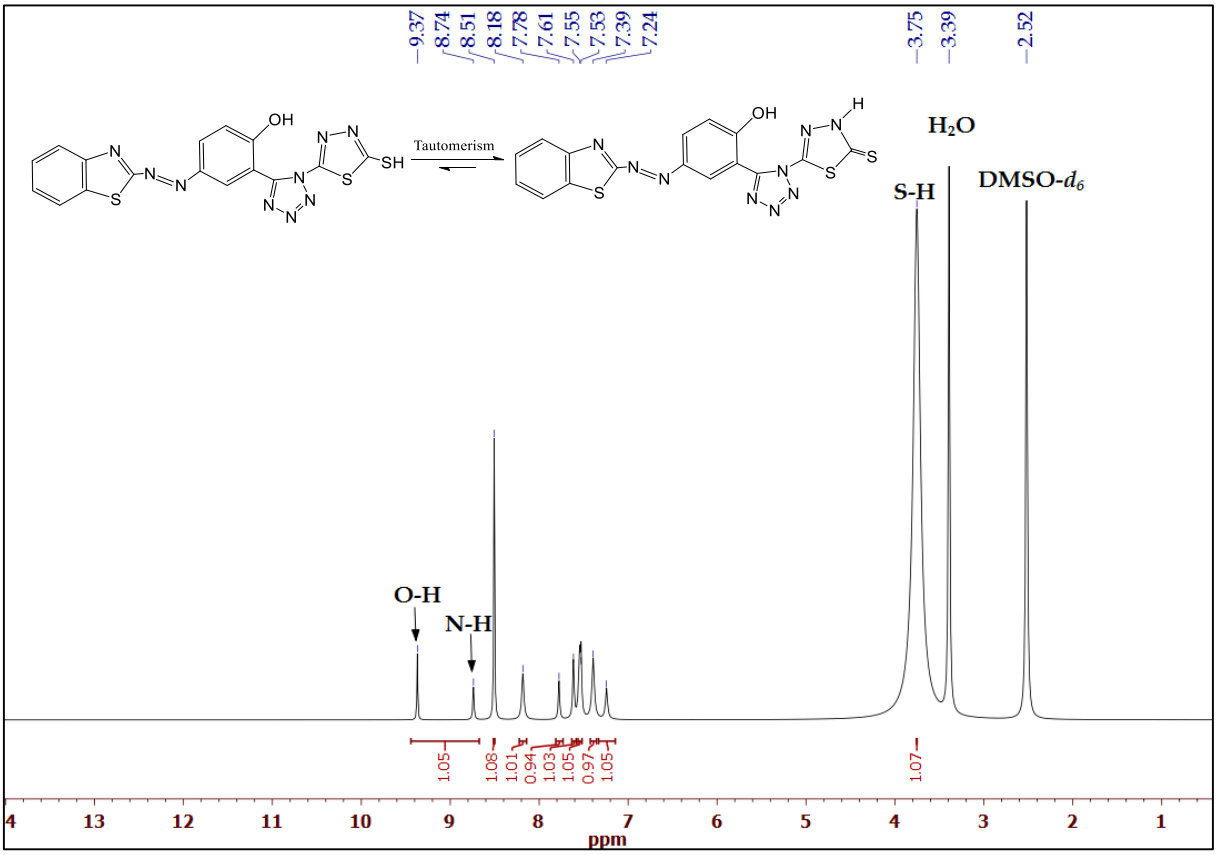


Fig. (3-38): ^{1}H NMR spectrum of compound **3f**

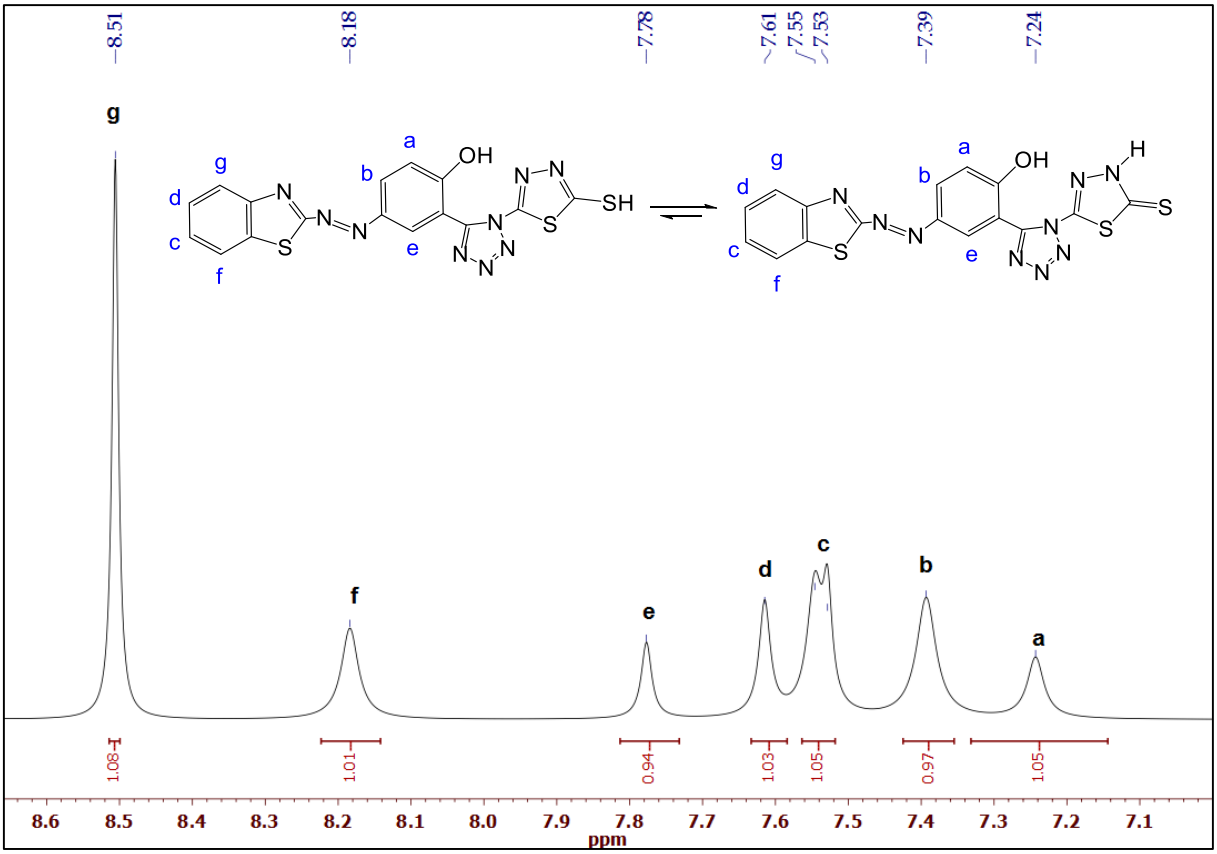


Fig. (3-38a): Expanded ^{1}H NMR spectrum of compound **3f** in ppm

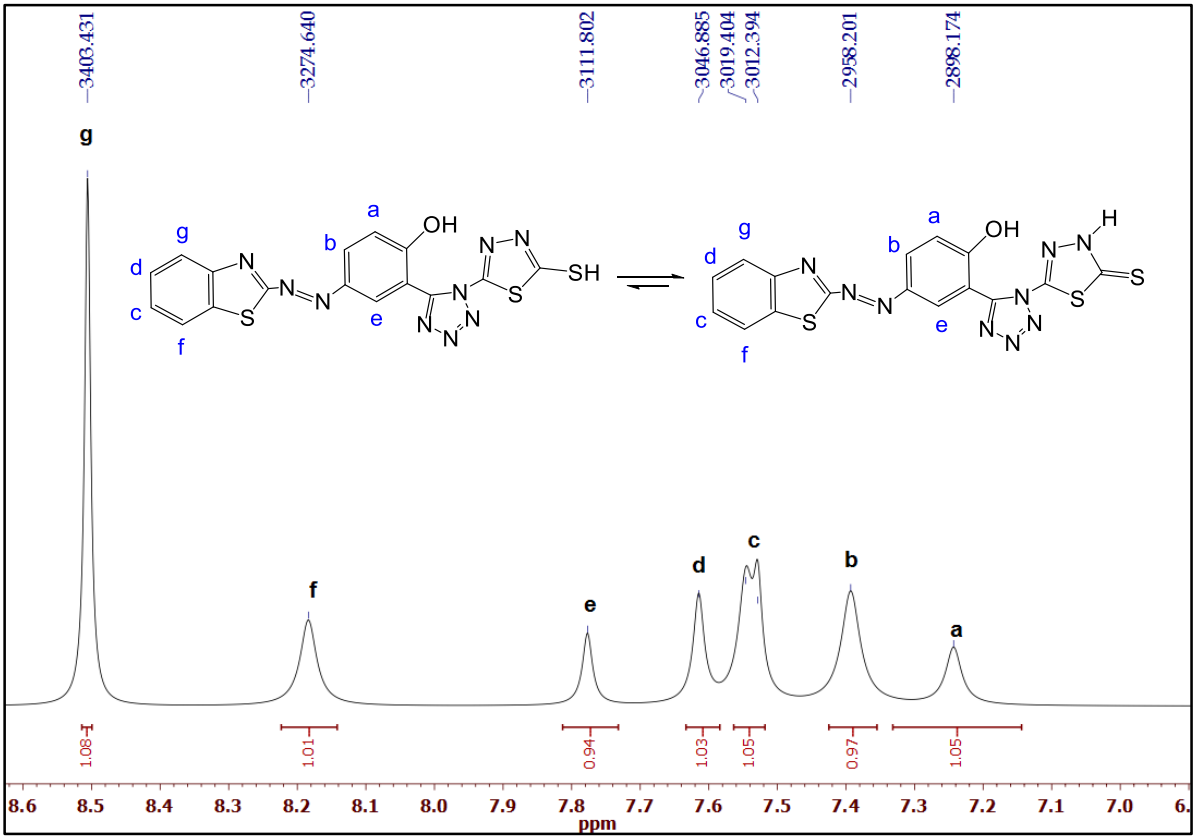


Fig. (3-38b): Expanded ^{1}H NMR spectrum of compound **3f** in Hz

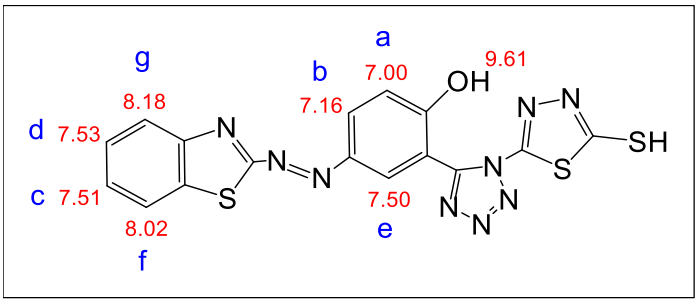


Fig. (3-38c): Theoretical δ (ppm) values of compound **3f**

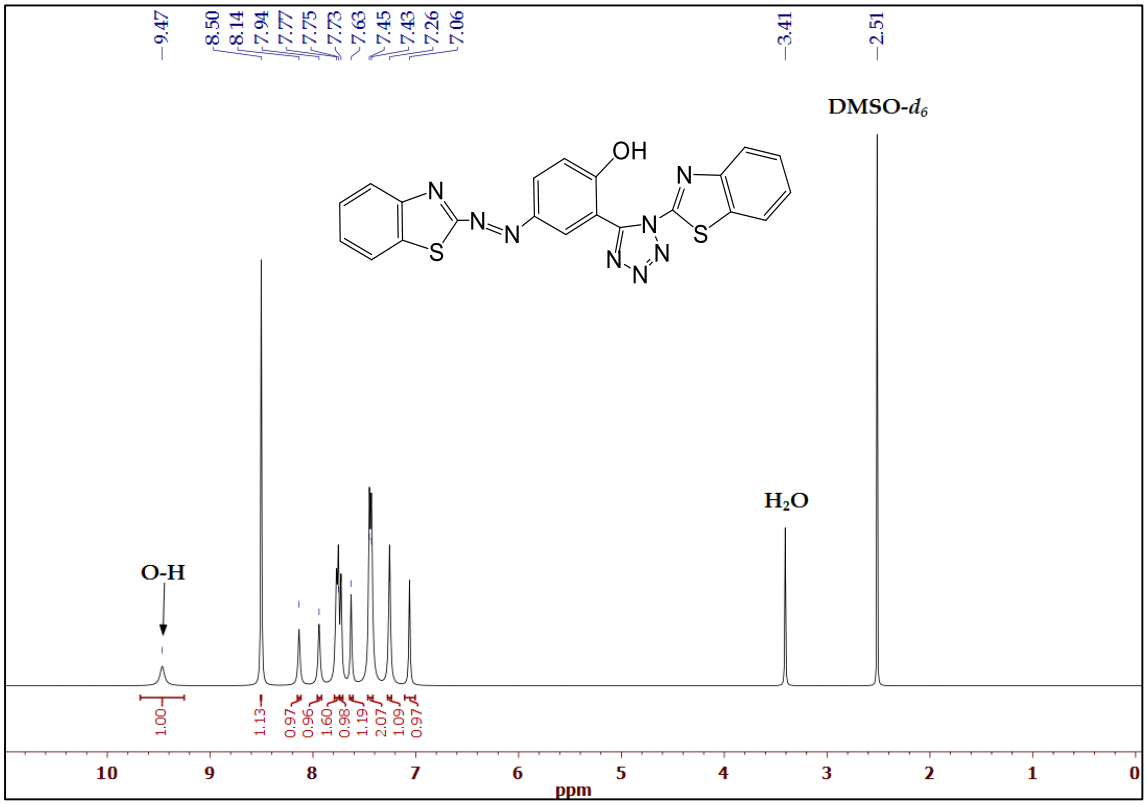


Fig. (3-39): ^{1}H NMR spectrum of compound **3g**

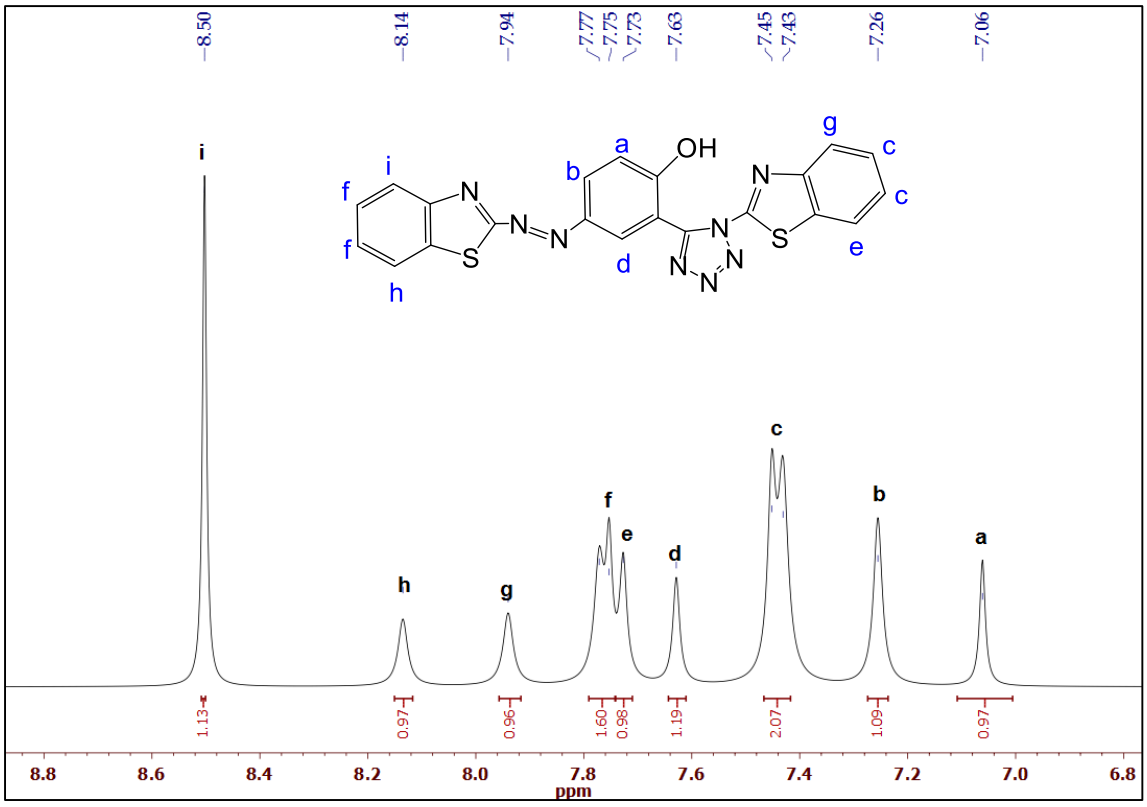


Fig. (3-39a): Expanded ^{1}H NMR spectrum of compound **3g** in ppm

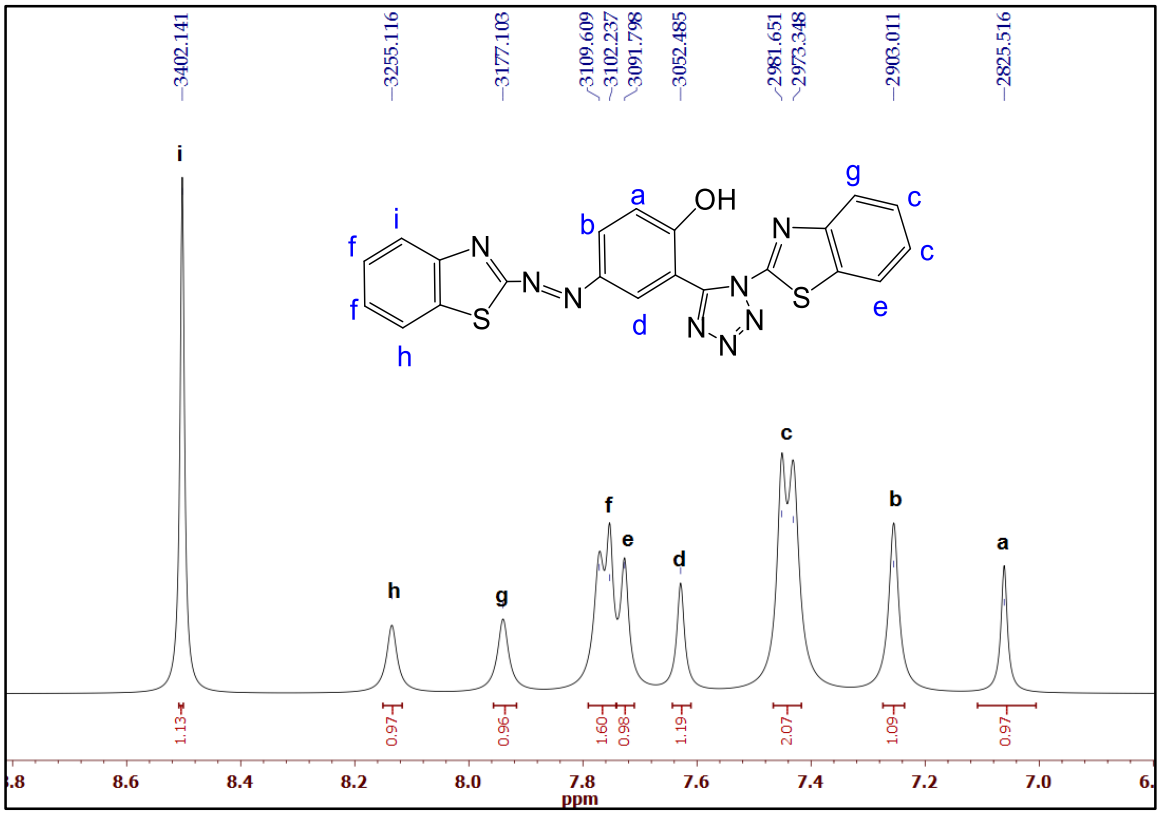


Fig. (3-39b): Expanded ^{1}H NMR spectrum of compound **3g** in Hz

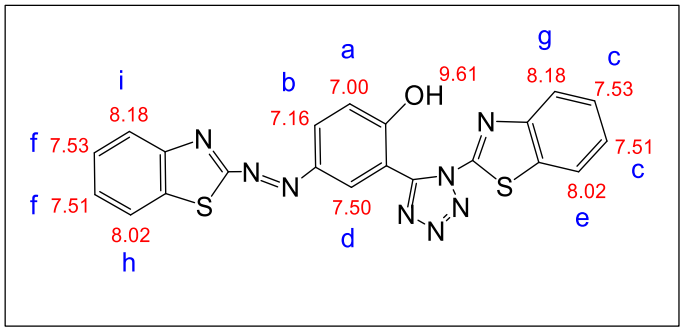


Fig. (3-39c): Theoretical δ (ppm) values of compound **3g**

A.2.2. ^{1}H NMR spectra of the synthesized tetrazole derivatives 3a`-e`

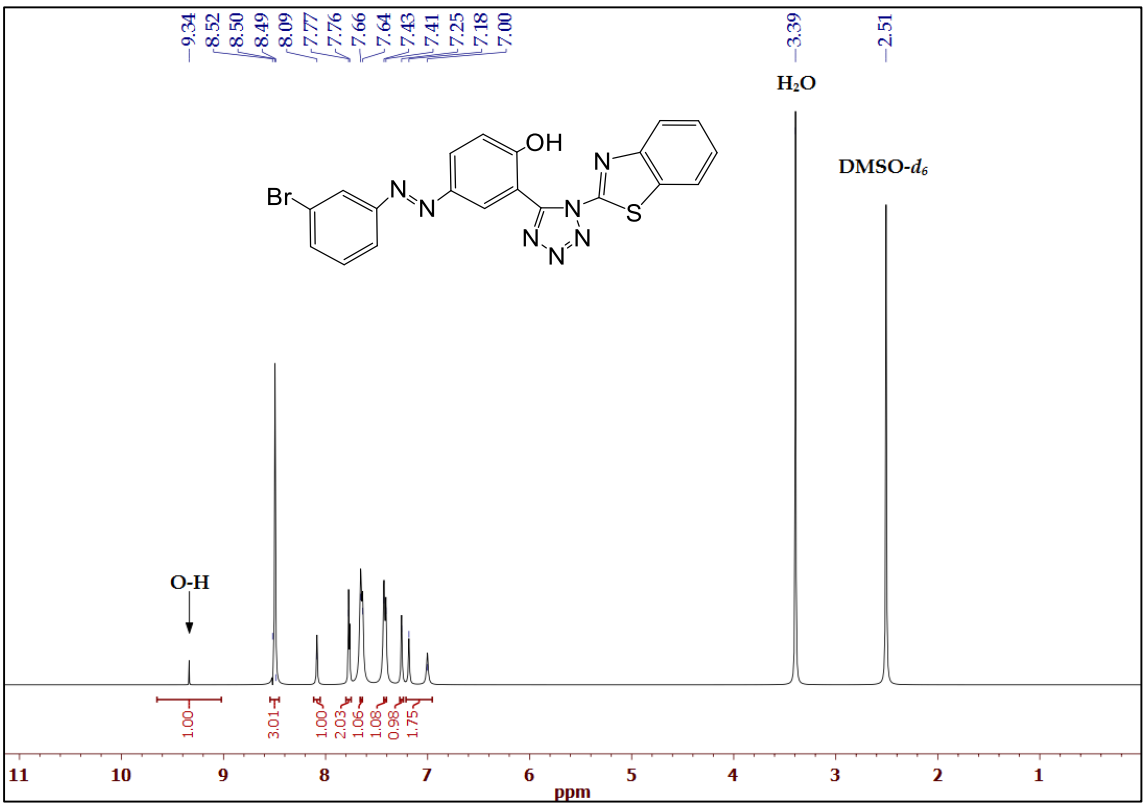


Fig. (3-40): ^{1}H NMR spectrum of compound **3a`**

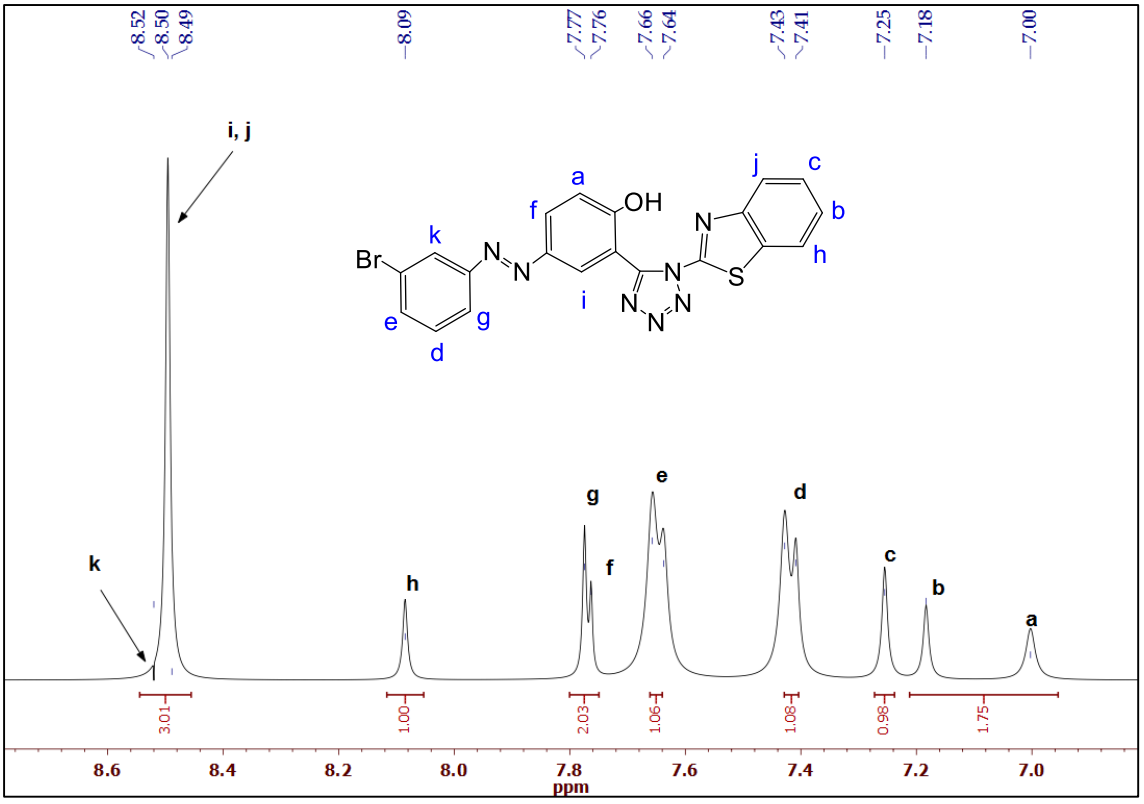


Fig. (3-40a): Expanded ^{1}H NMR spectrum of compound **3a`** in ppm

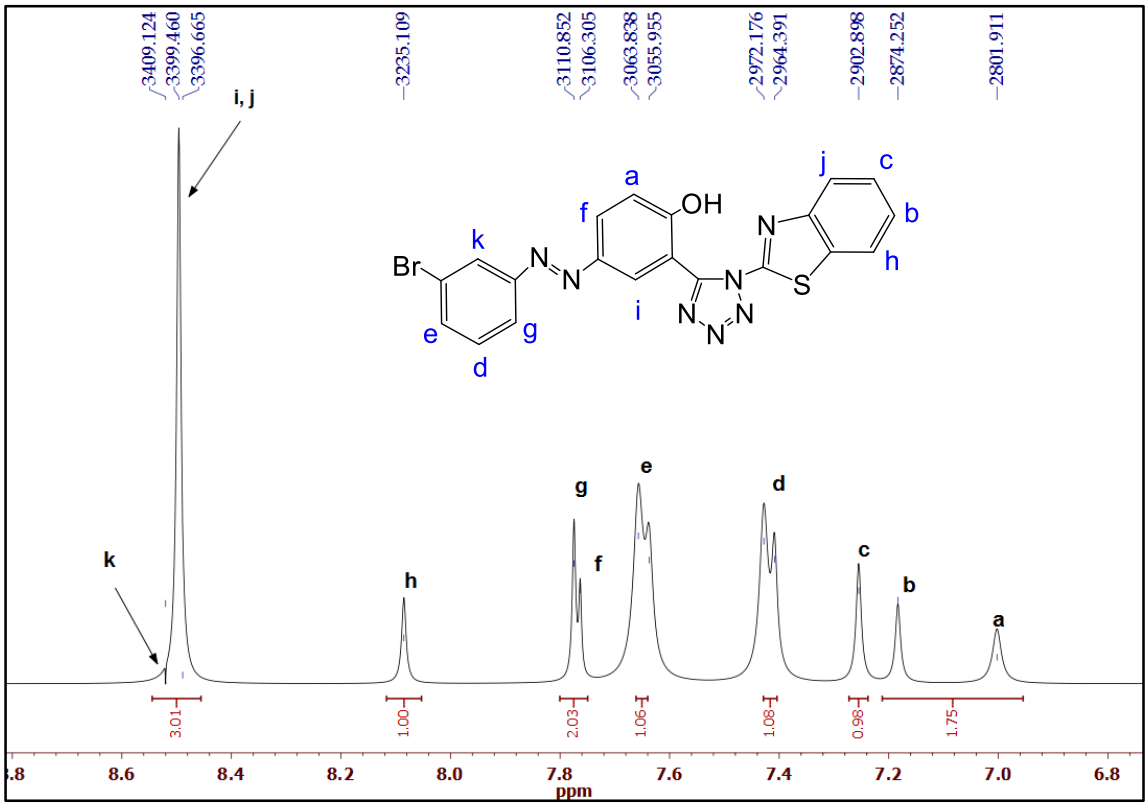


Fig. (3-40b): Expanded ^{1}H NMR spectrum of compound **3a`** in Hz

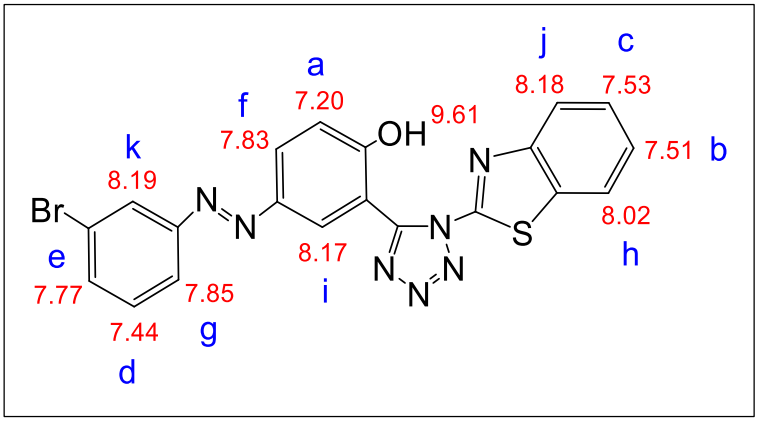


Fig. (3-40c): Theoretical δ (ppm) values of compound **3a`**

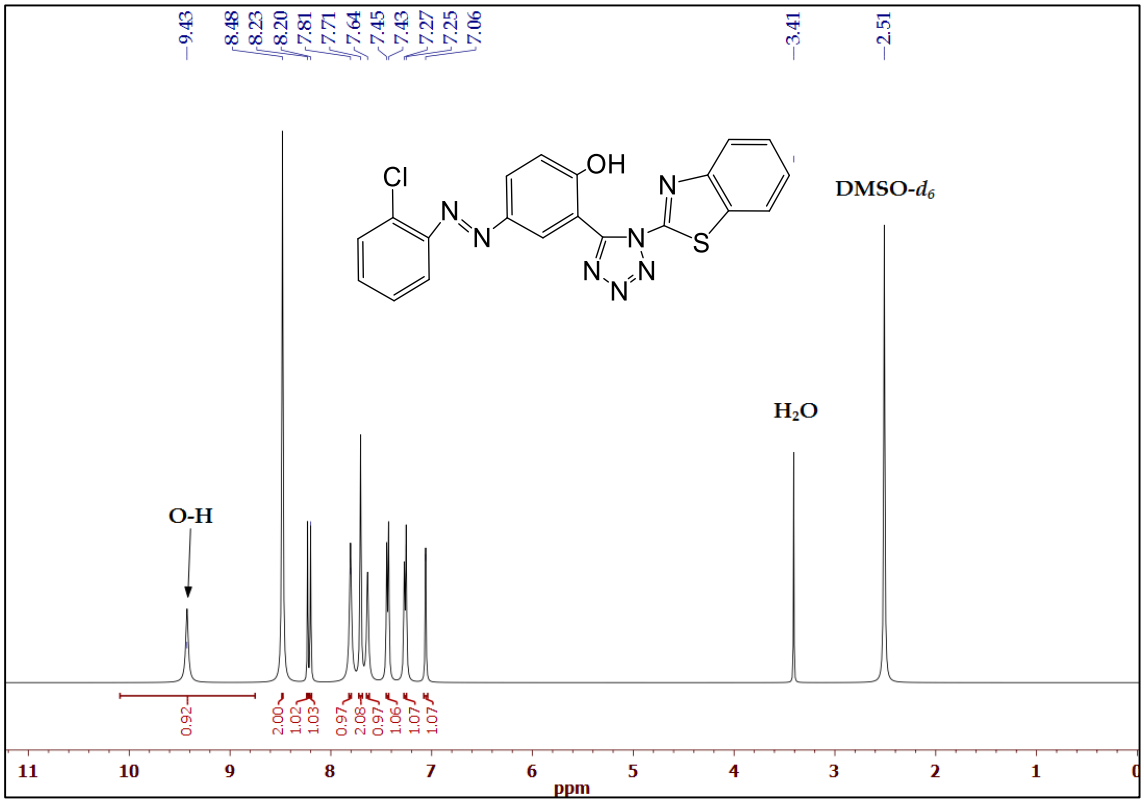


Fig. (3-41): ^{1}H NMR spectrum of compound **3b`**

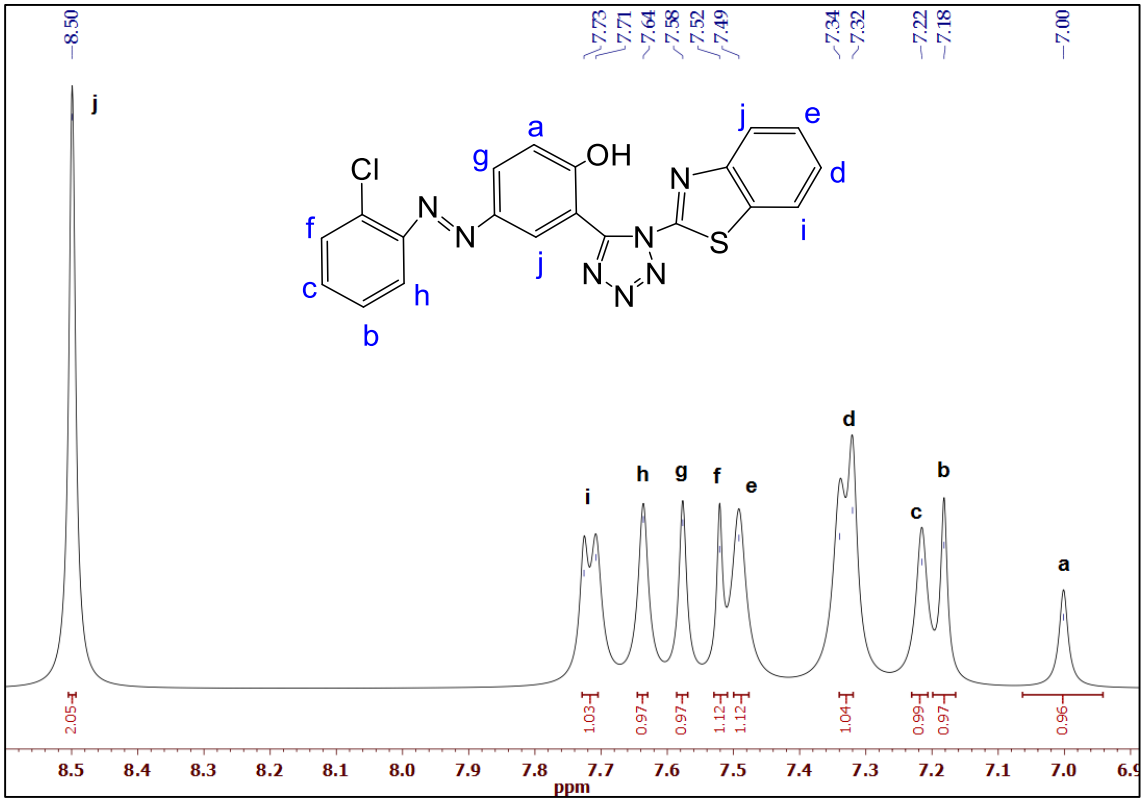


Fig. (3-41a): Expanded ^{1}H NMR spectrum of compound **3b`** in ppm

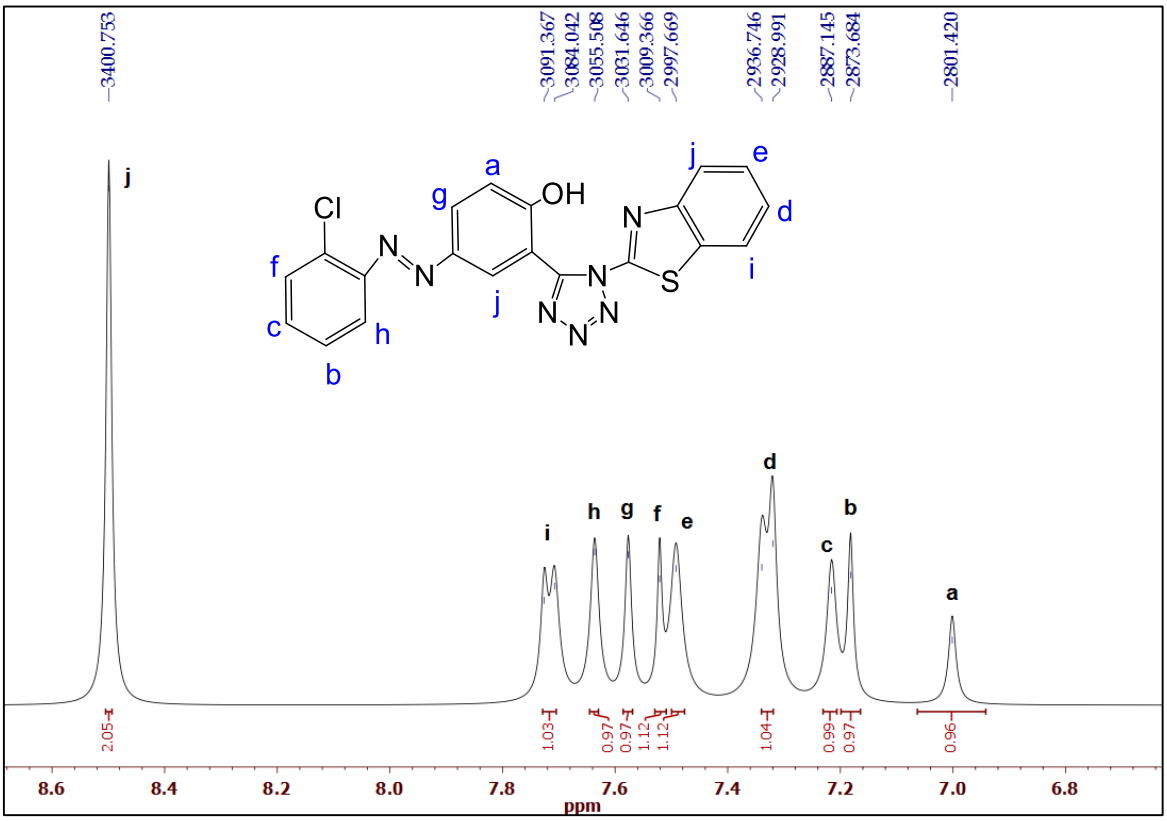


Fig. (3-41b): Expanded ^{1}H NMR spectrum of compound **3b`** in Hz

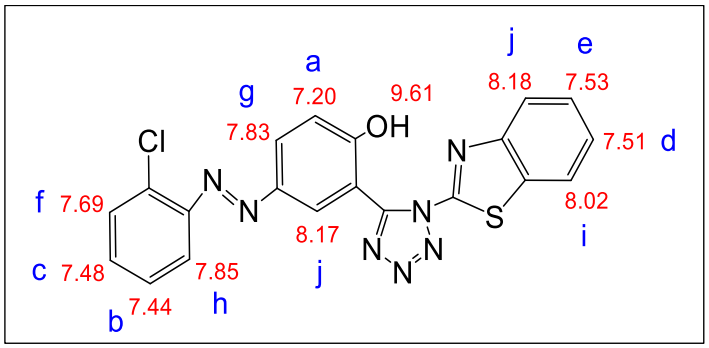


Fig. (3-41c): Theoretical δ (ppm) values of compound **3b`**

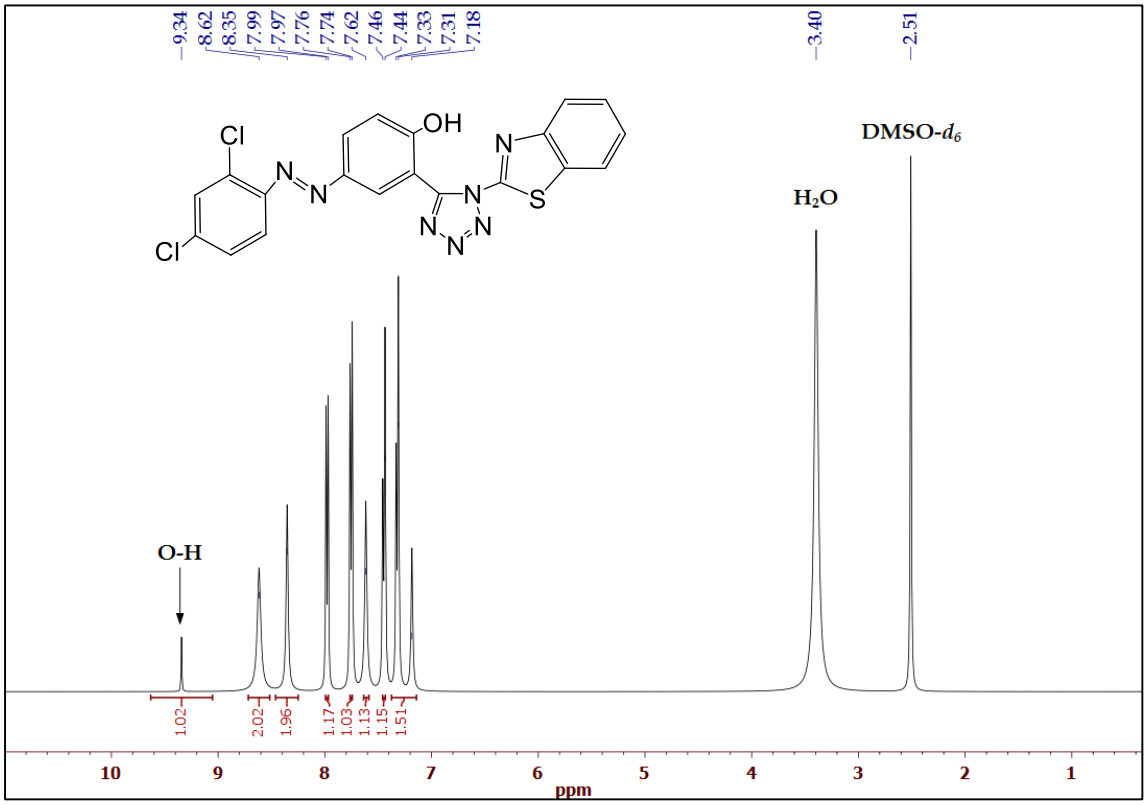


Fig. (3-42): ^{1}H NMR spectrum of compound **3c`**

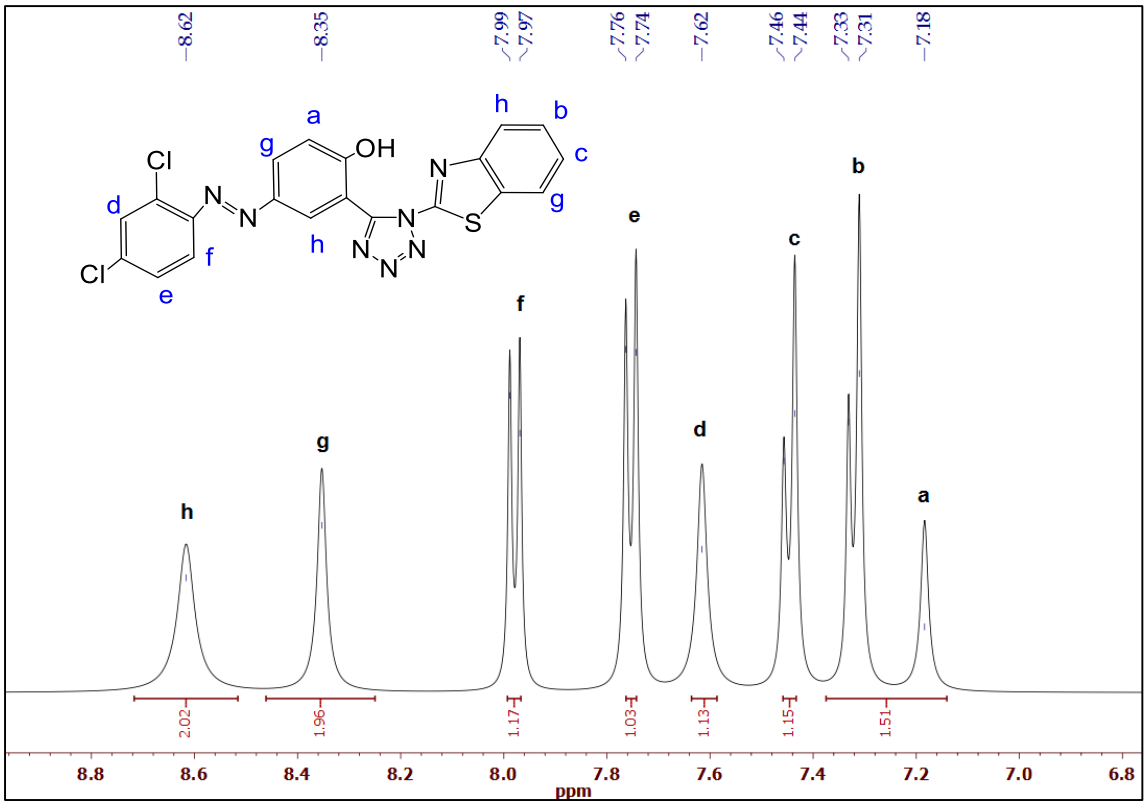


Fig. (3-42a): Expanded ^{1}H NMR spectrum of compound **3c`** in ppm

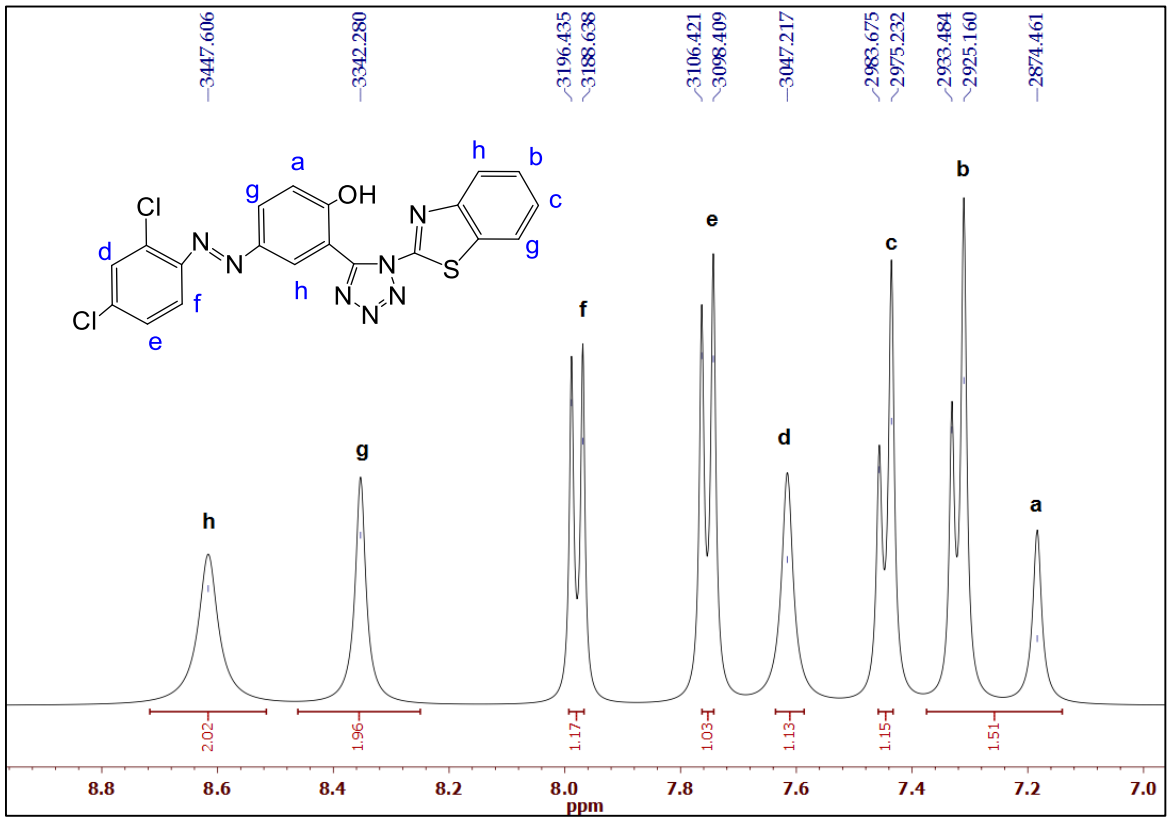


Fig. (3-42b): Expanded ^{1}H NMR spectrum of compound **3c`** in Hz

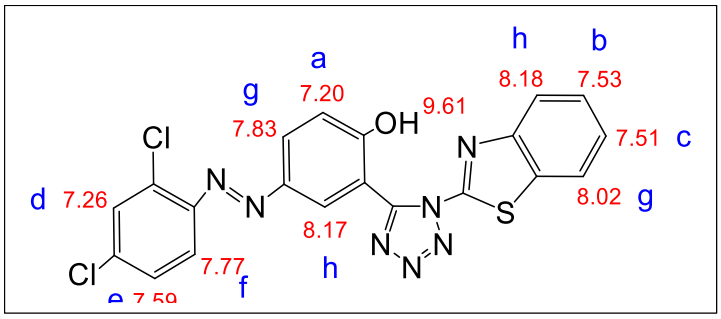


Fig. (3-42c): Theoretical δ (ppm) values of compound **3c`**

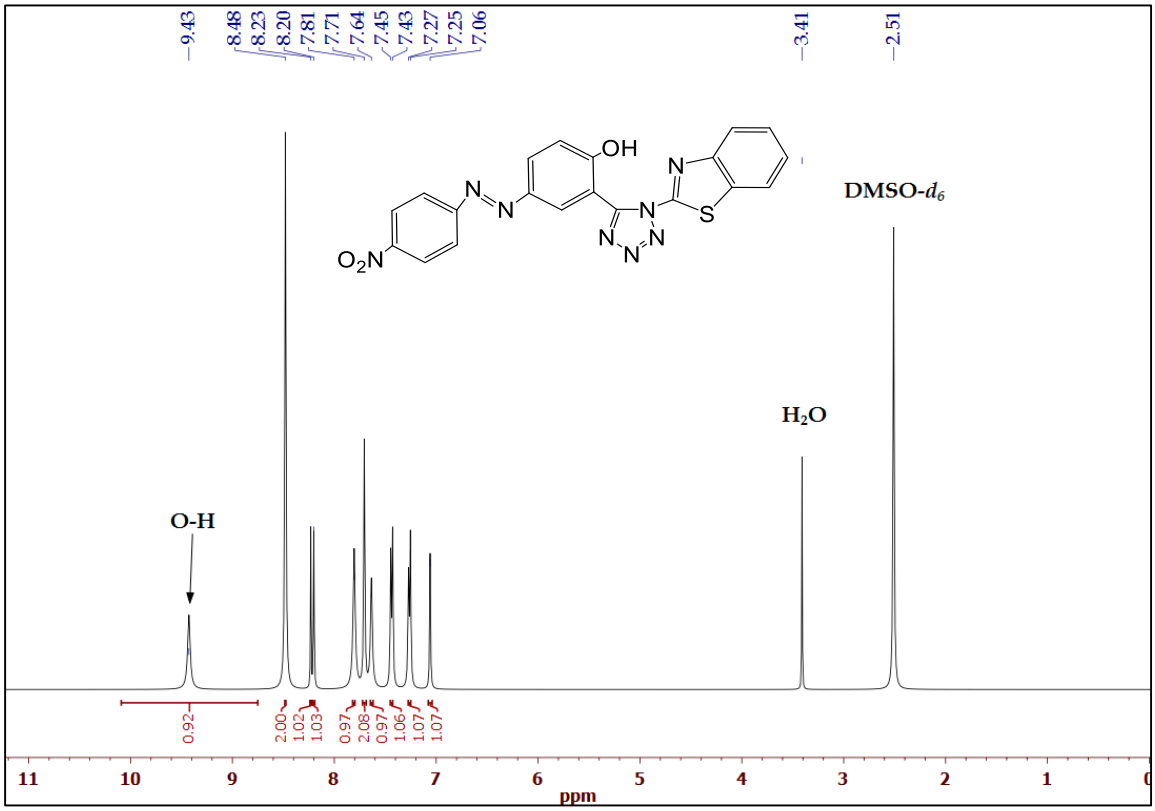


Fig. (3-43): ^{1}H NMR spectrum of compound **3d`**

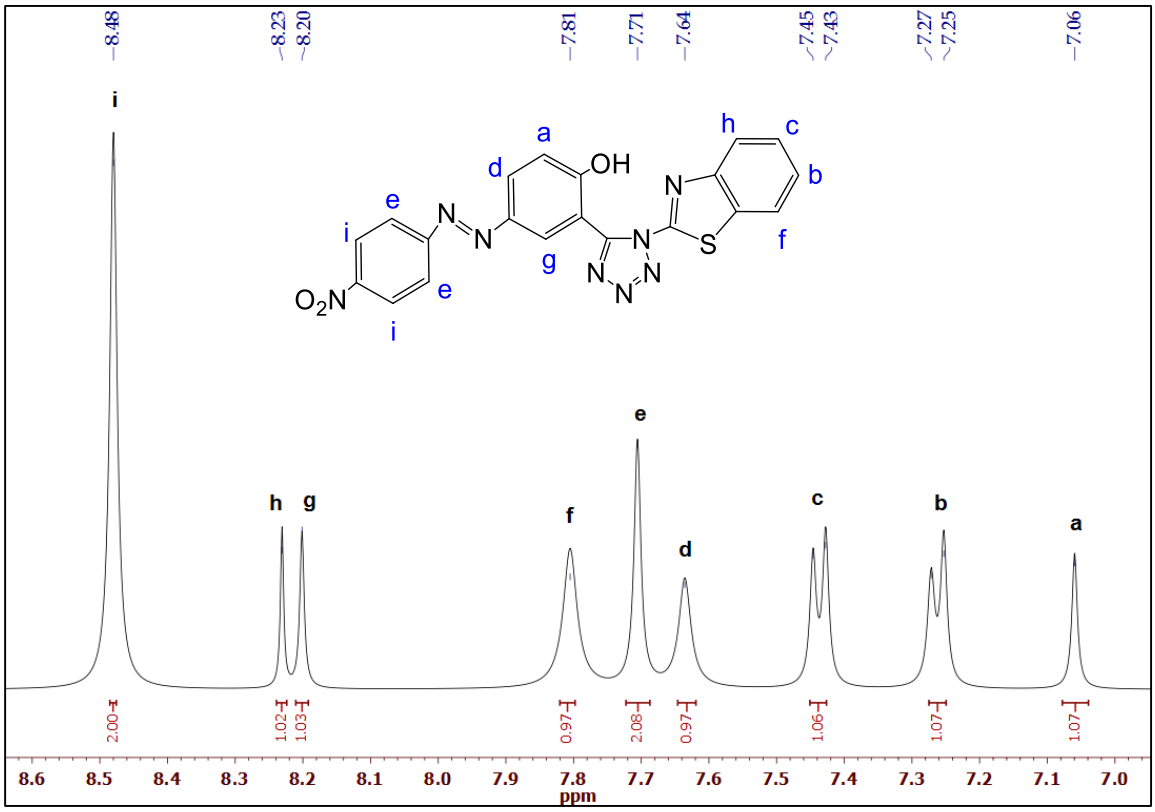


Fig. (3-43a): Expanded ^{1}H NMR spectrum of compound **3d`** in ppm

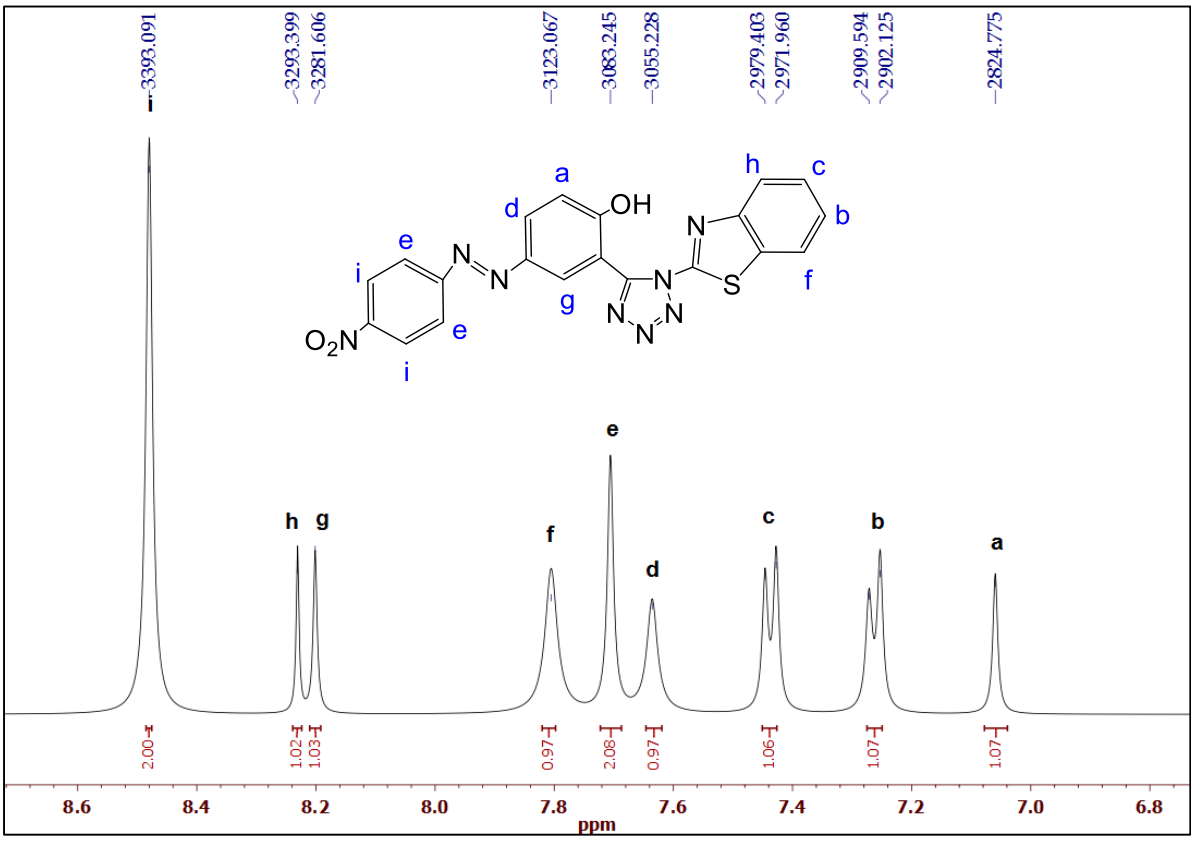


Fig. (3-43b): Expanded ^{1}H NMR spectrum of compound **3d`** in Hz

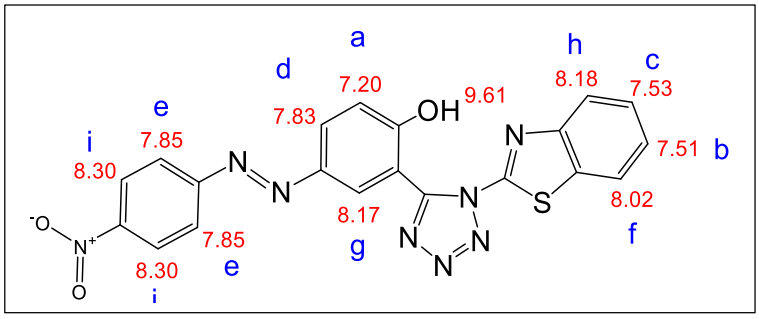


Fig. (3-43c): Theoretical δ (ppm) values of compound **3d`**

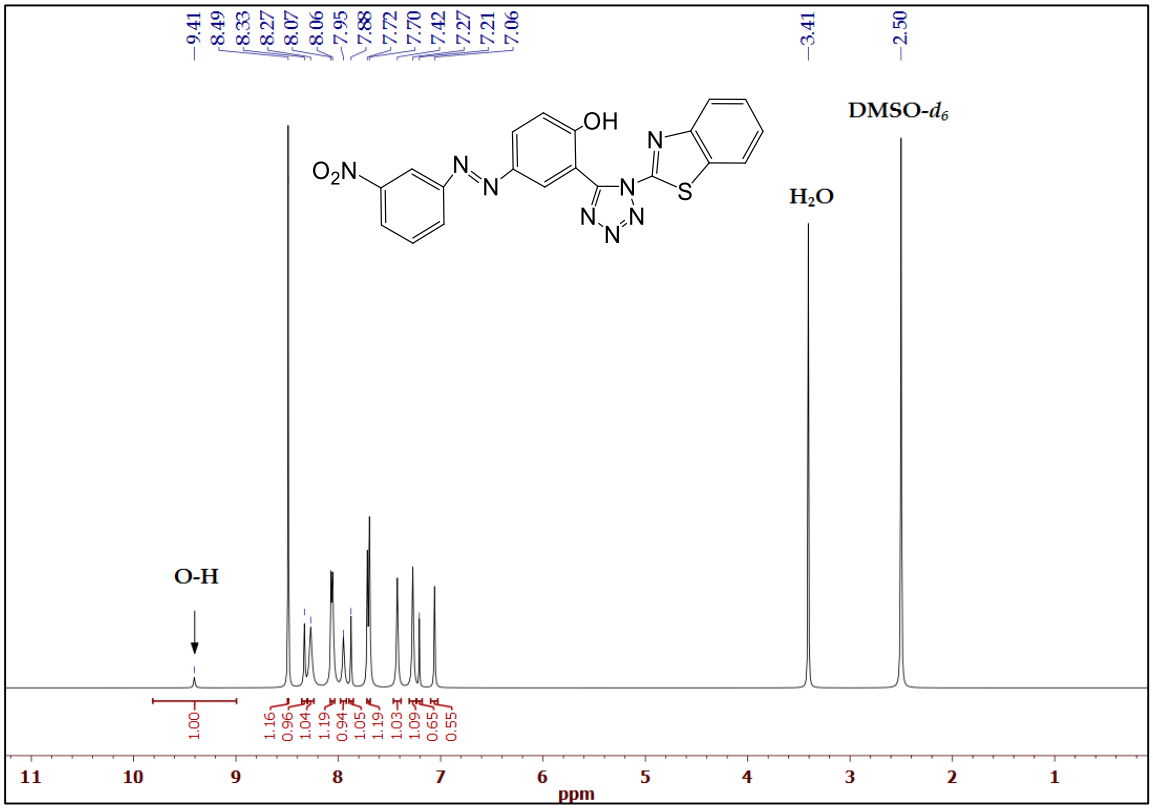


Fig. (3-44): ^{1}H NMR spectrum of compound **3e`**

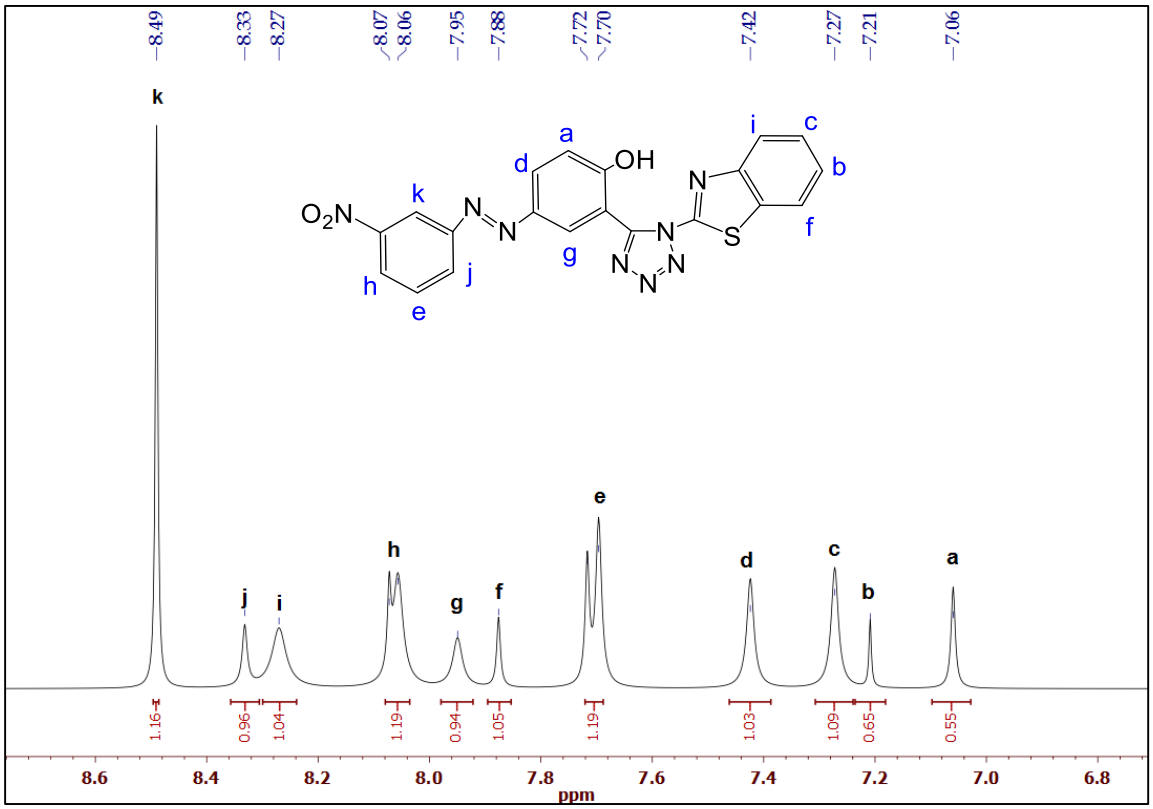


Fig. (3-44a): Expanded ^{1}H NMR spectrum of compound **3e`** in ppm

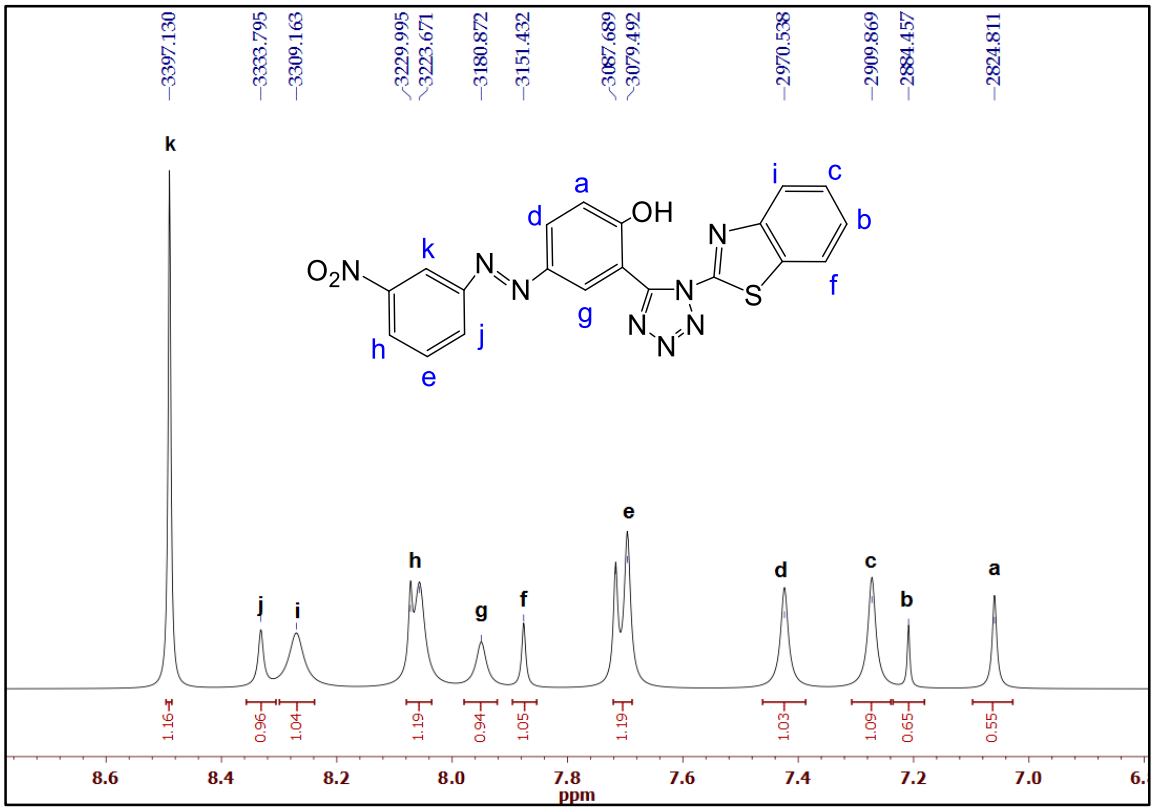


Fig. (3-44b): Expanded ^{1}H NMR spectrum of compound **3e`** in Hz

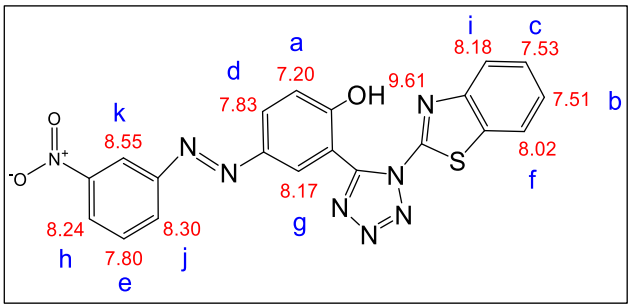


Fig. (3-44c): Theoretical δ (ppm) values of compound **3e`**

A.3. Mass spectra

A.3.1. Mass spectra of the synthesized tetrazole derivatives 3a-g

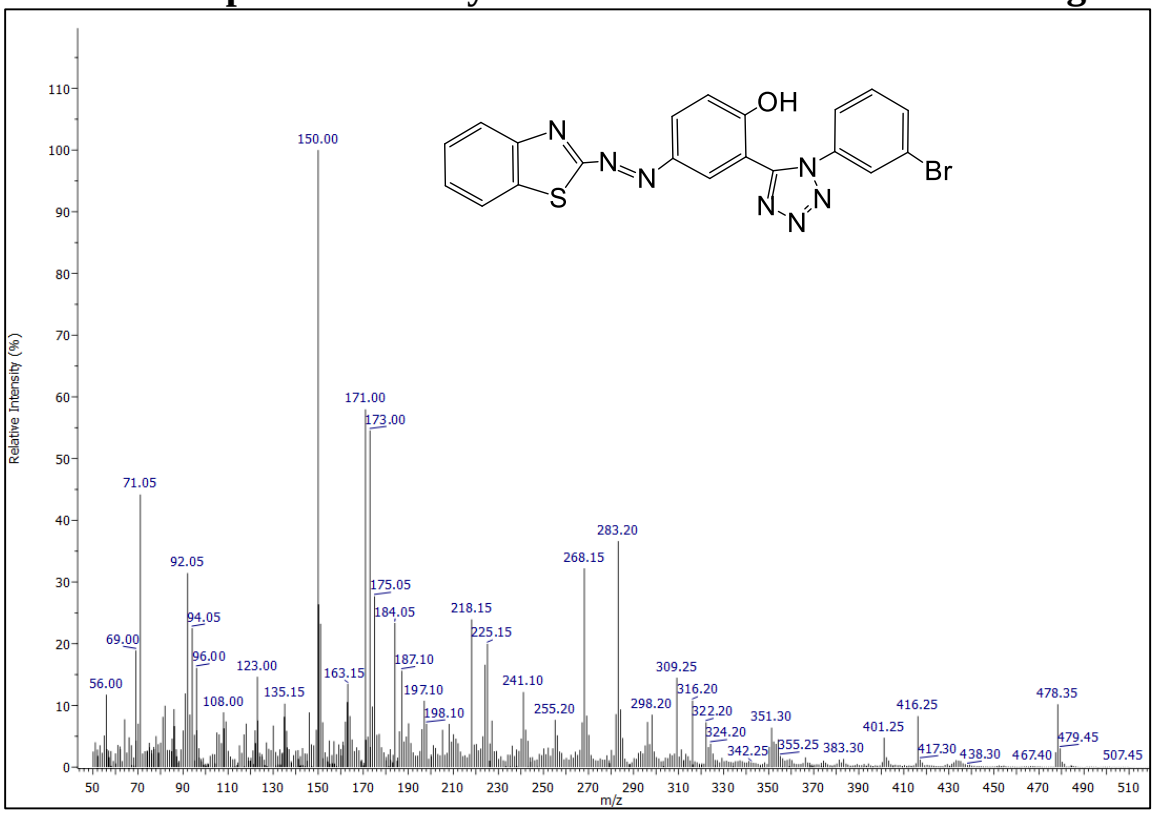


Fig. (3-45): Mass spectrum of compound **3a**

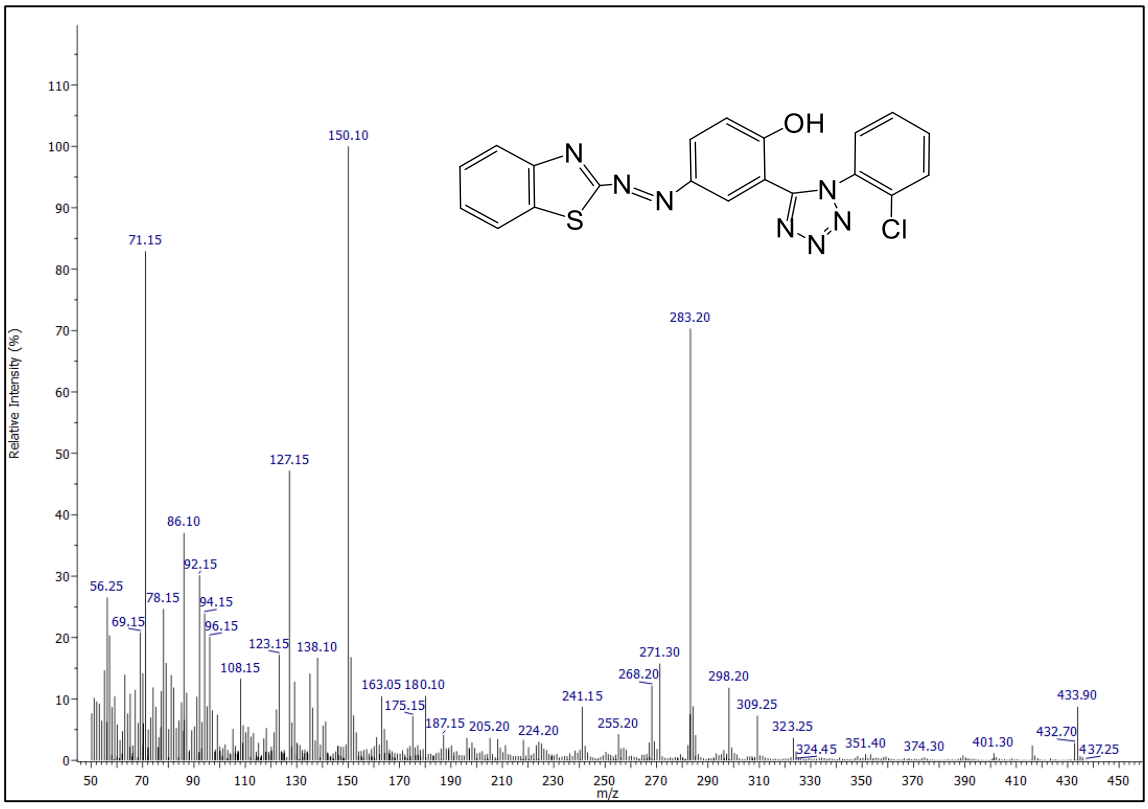


Fig. (3-46): Mass spectrum of compound **3b**

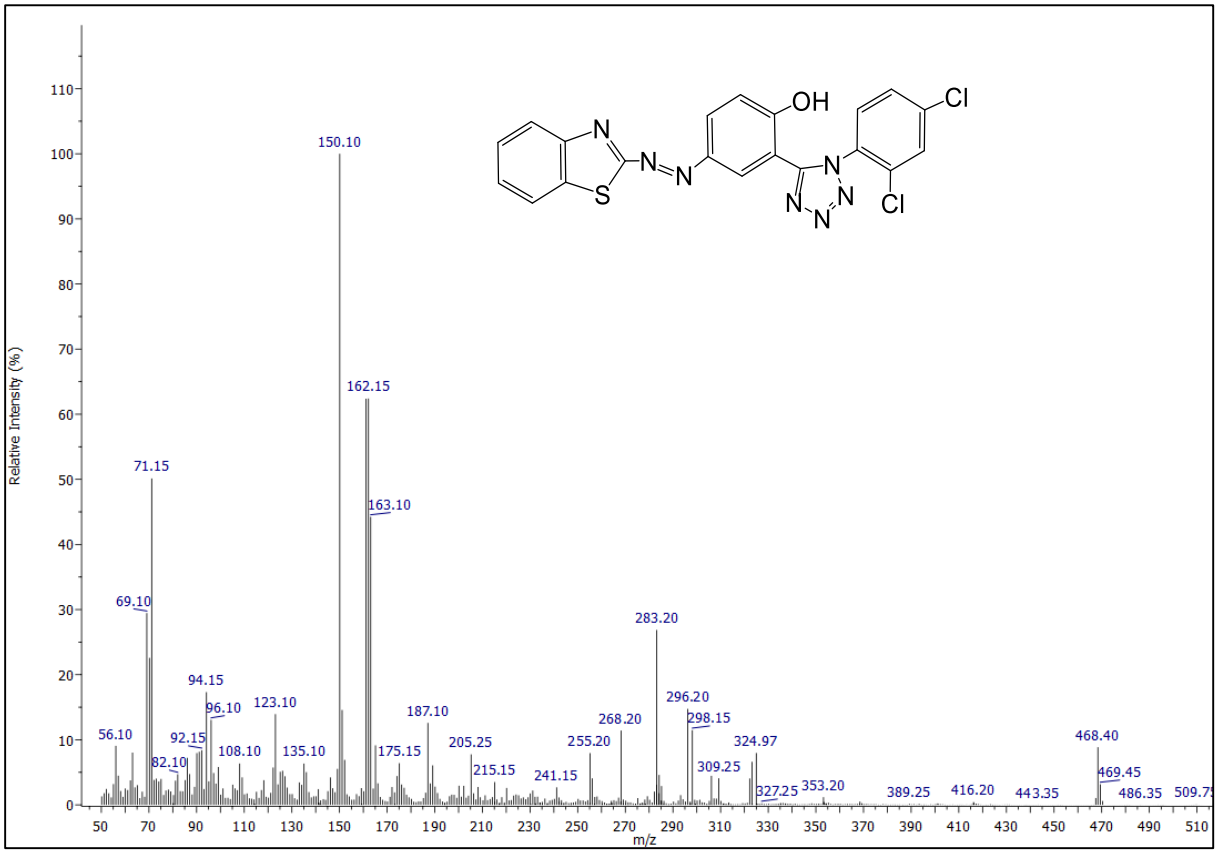


Fig. (3-47): Mass spectrum of compound **3c**

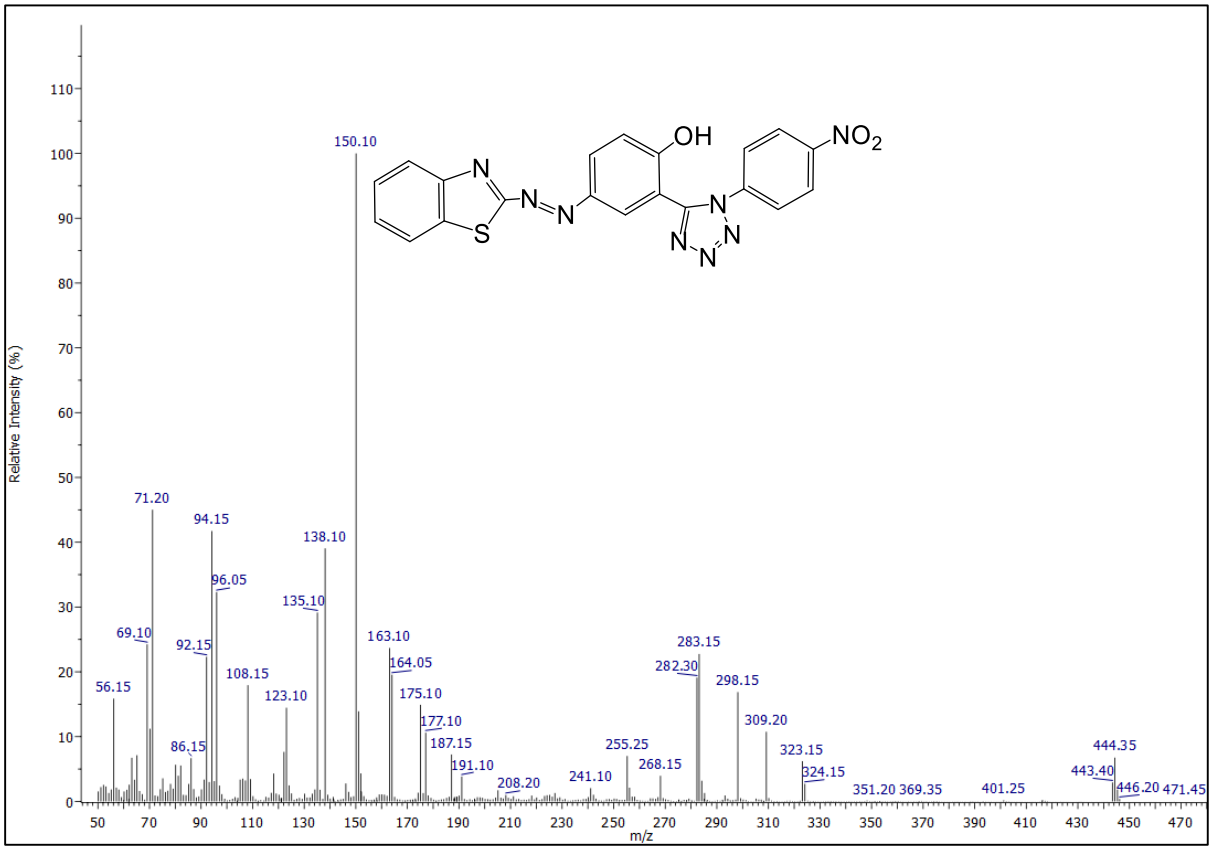


Fig. (3-48): Mass spectrum of compound **3d**

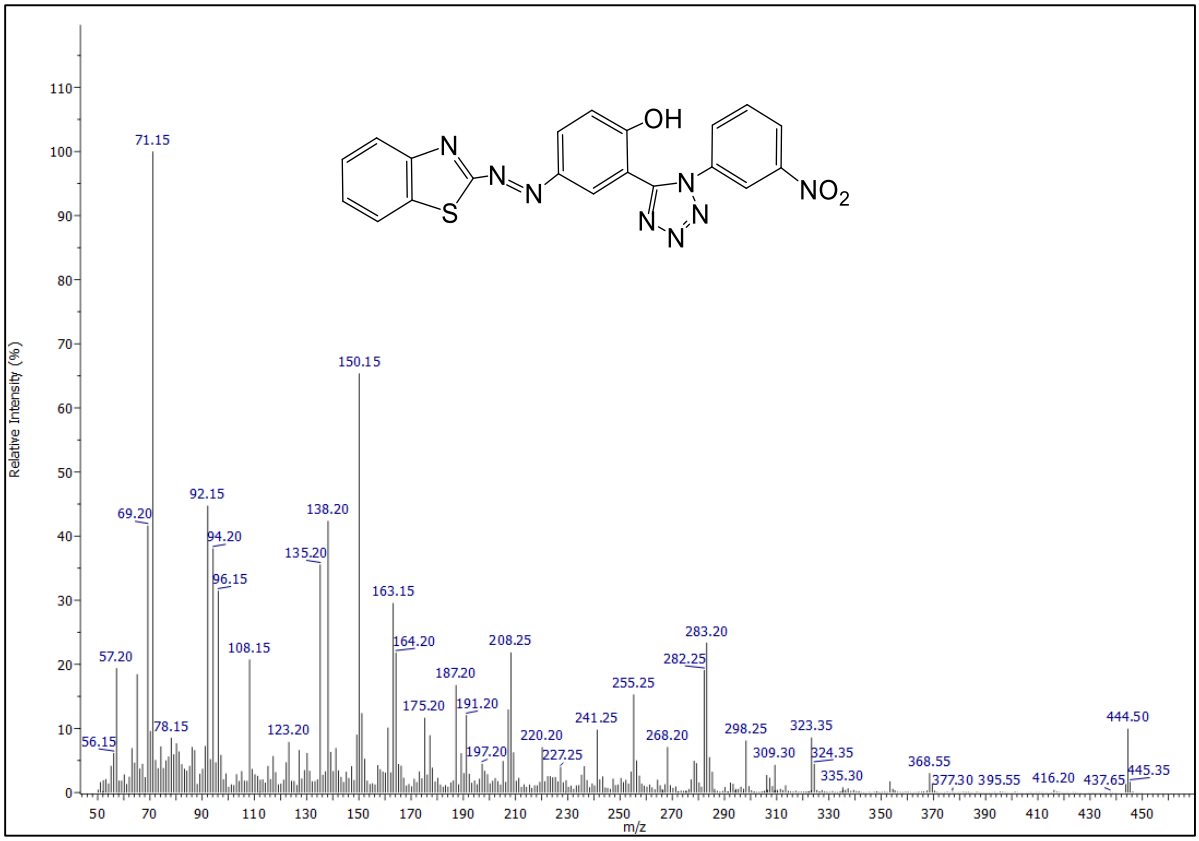


Fig. (3-49): Mass spectrum of compound **3e**

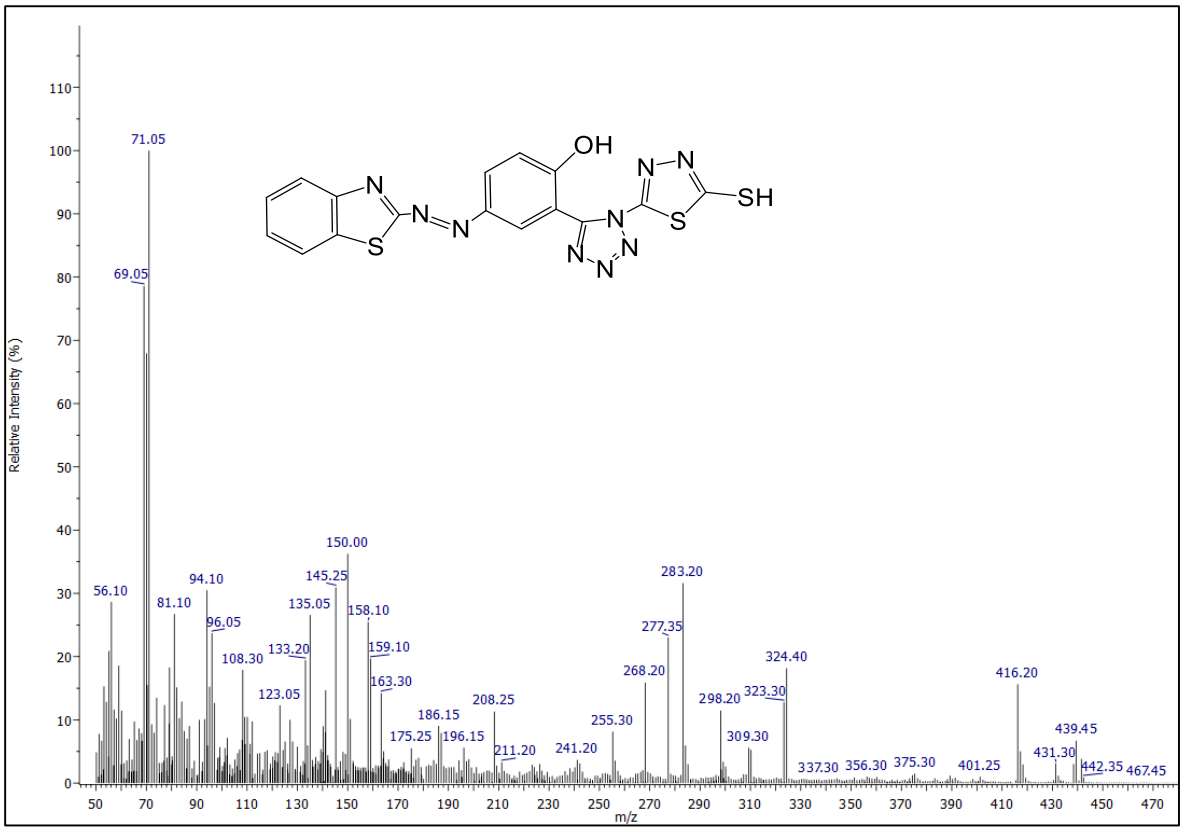


Fig. (3-50): Mass spectrum of compound **3f**

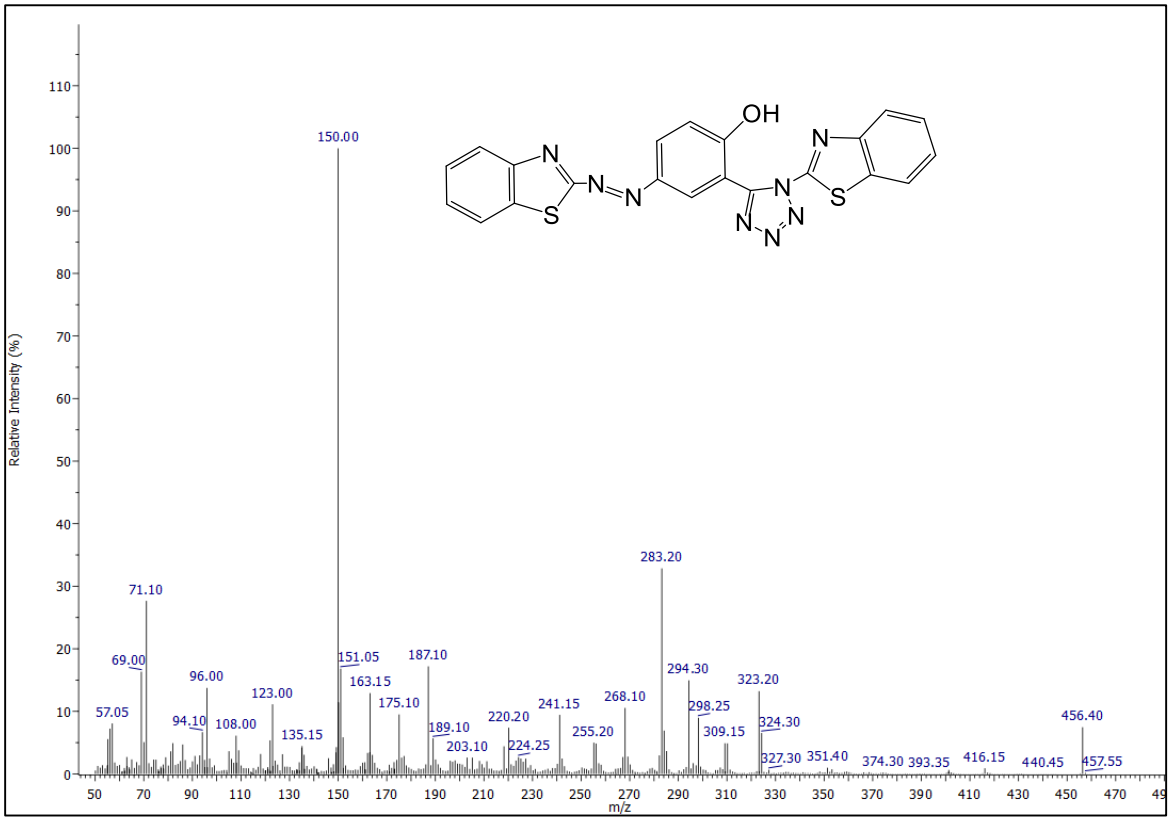


Fig. (3-51): Mass spectrum of compound **3g**

A.3.2. Mass spectra of the synthesized tetrazole derivatives 3a`-e`

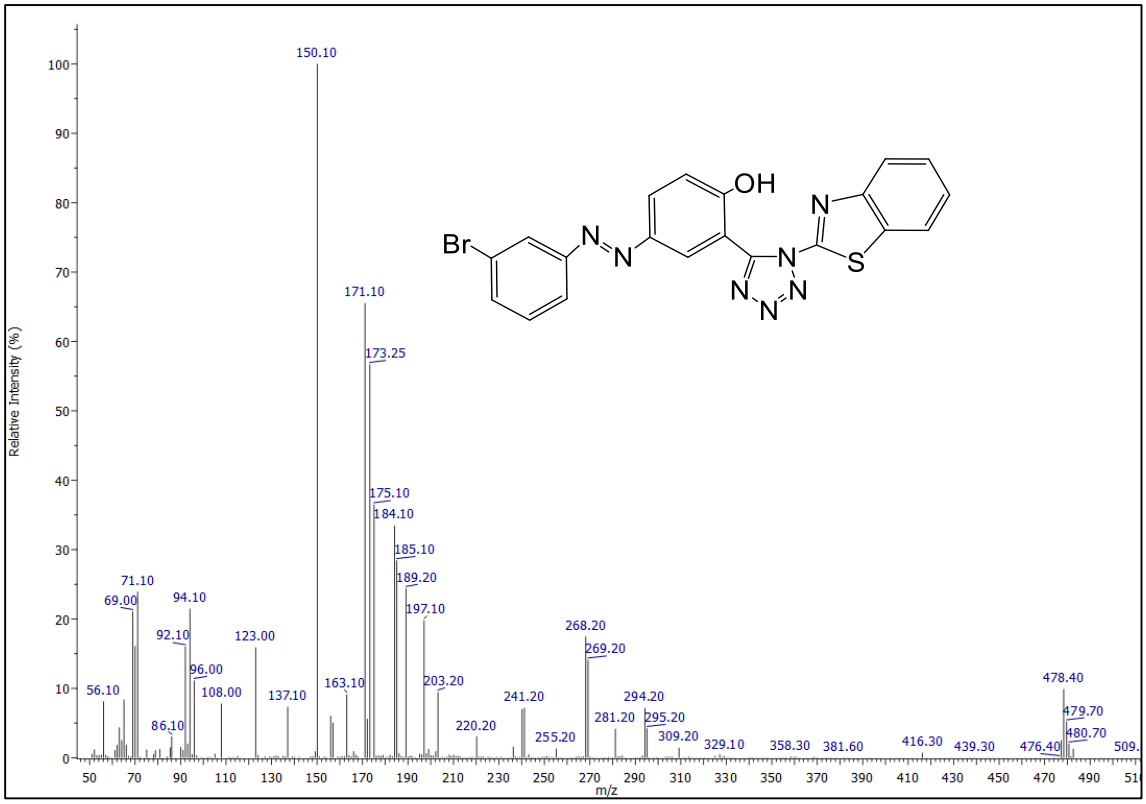


Fig. (3-52): Mass spectrum of compound **3a`**

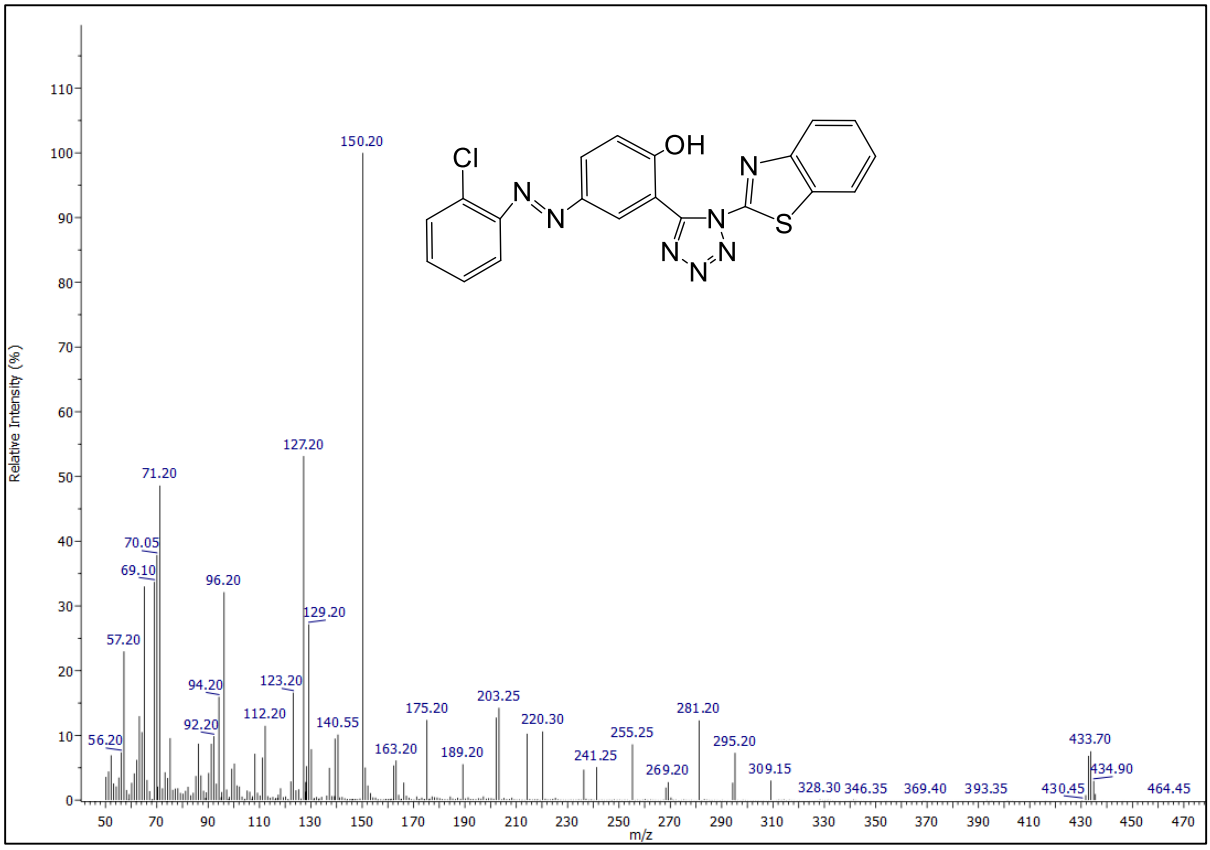


Fig. (3-53): Mass spectrum of compound **3b`**

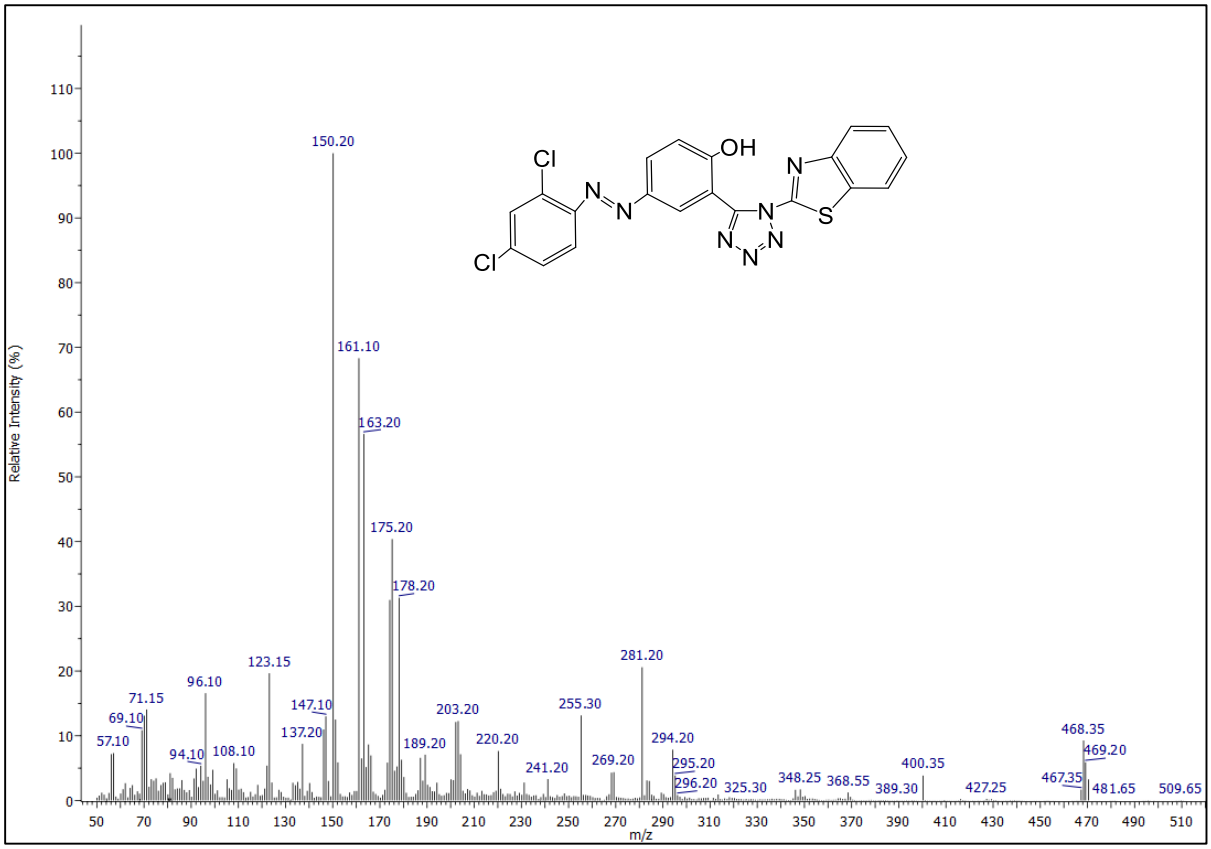


Fig. (3-54): Mass spectrum of compound **3c`**

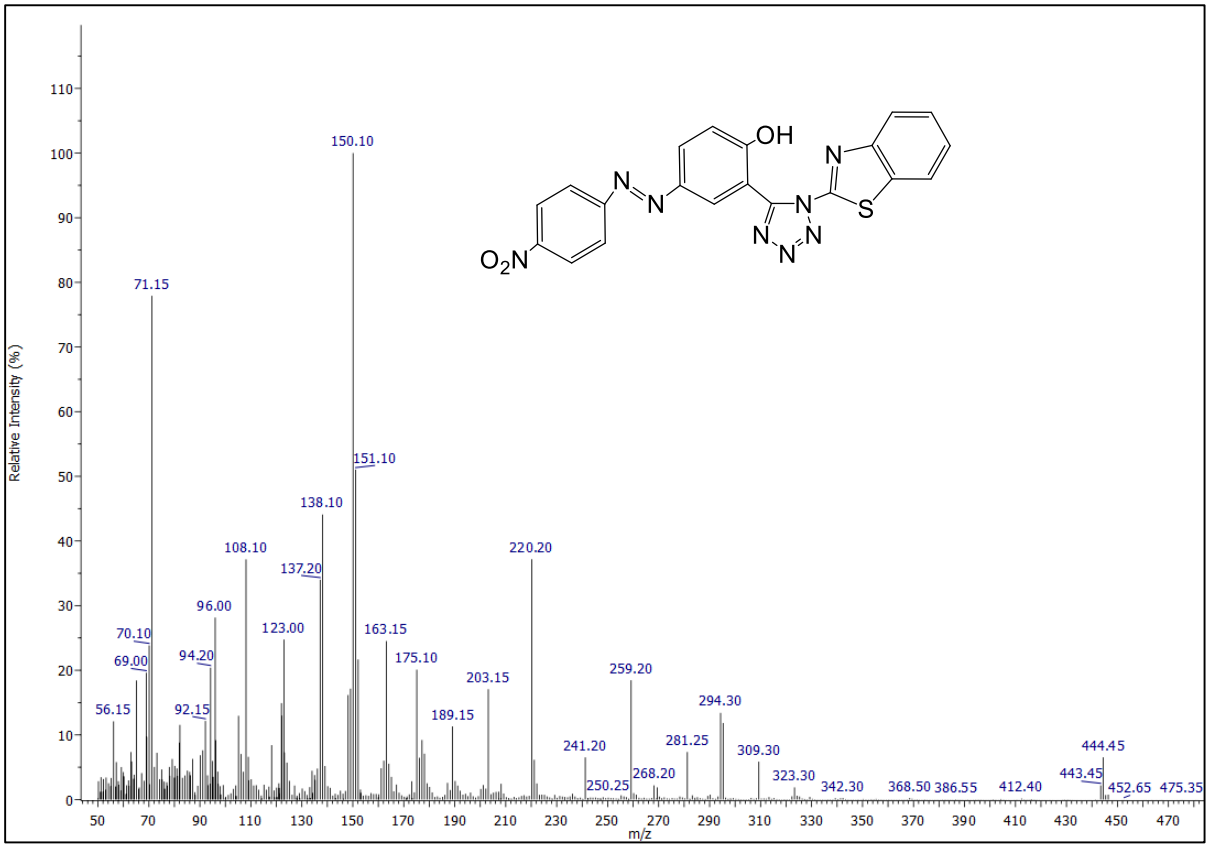


Fig. (3-55): Mass spectrum of compound **3d`**

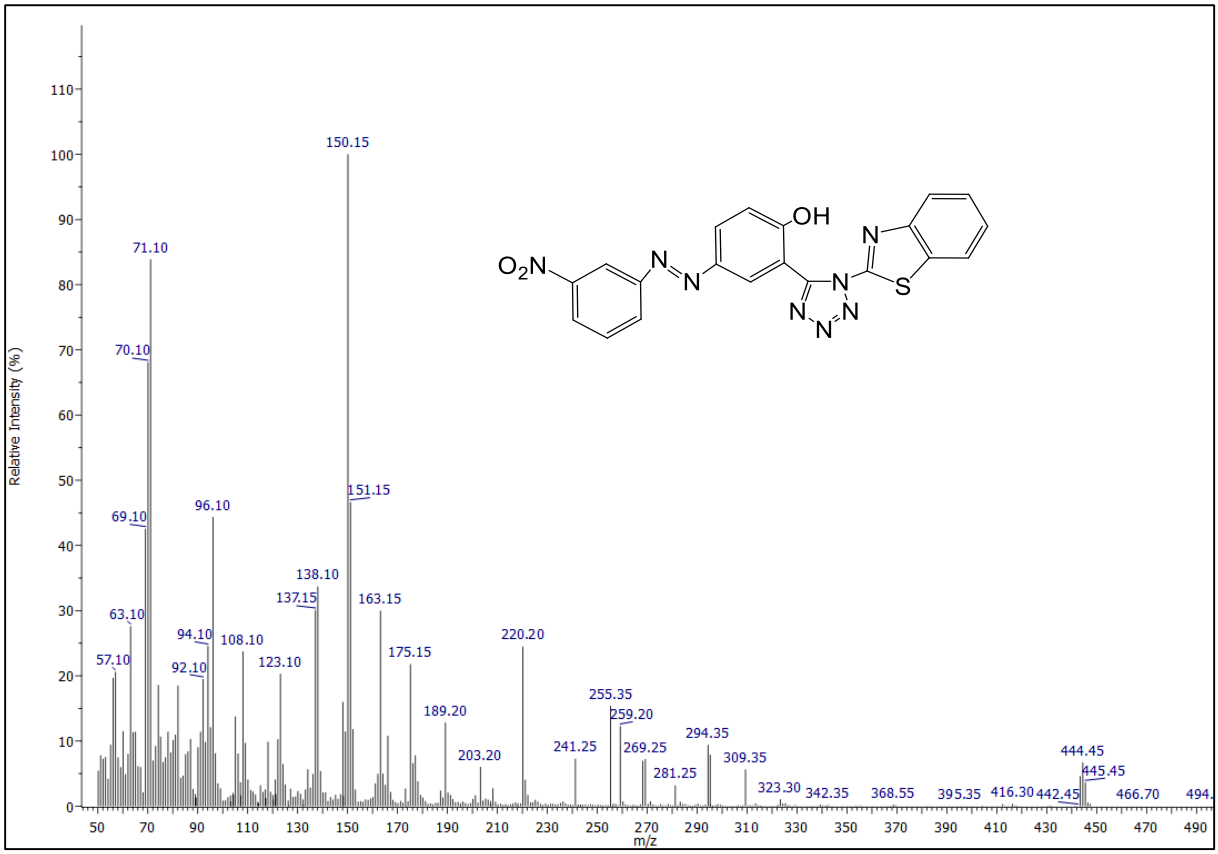


Fig. (3-56): Mass spectrum of compound **3e`**

B. Antibacterial photographs

B.1. Antibacterial photographs of tetrazole derivatives 3a-g and 3a`-e` against *staphylococcus aureous*

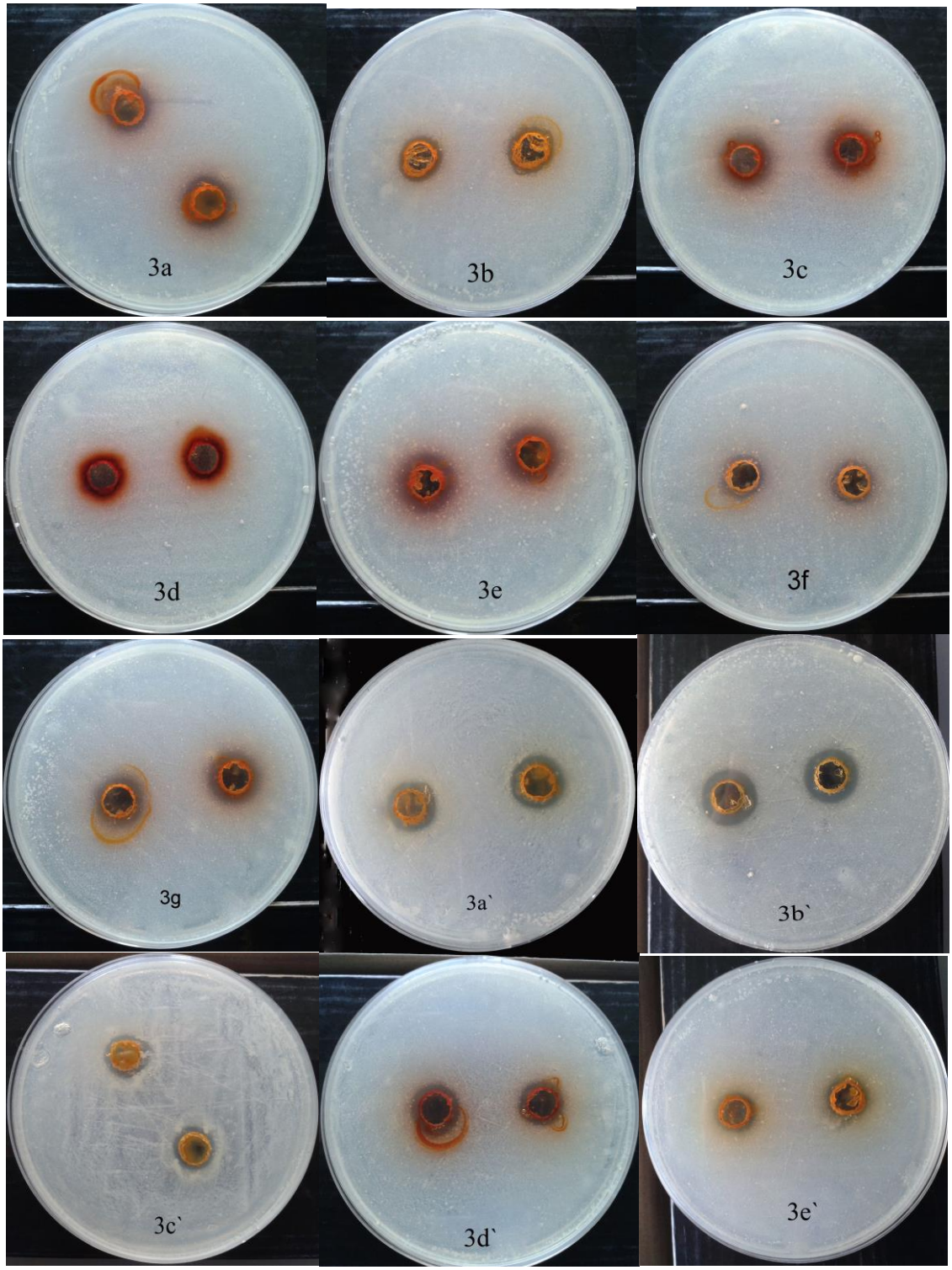


Fig. (3-57): Antibacterial activity of tetrazoles **3a-g** and **3a`-e`** against *staphylococcus aureous*

B.2. Antibacterial photographs of tetrazole derivatives 3a-g and 3a`-e` against *Escherichia coli*

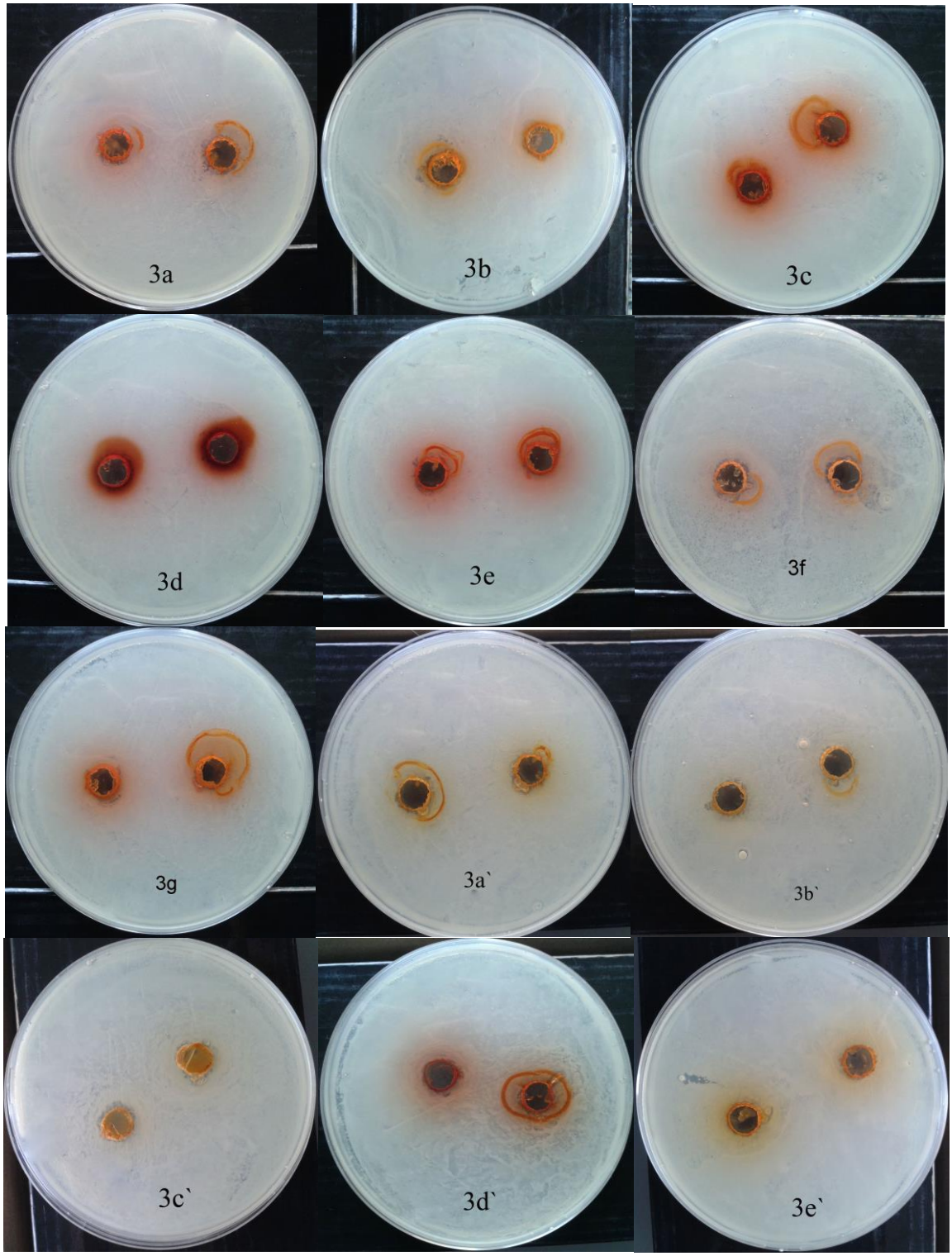


Fig. (3-58): Antibacterial activity of tetrazoles **3a-g** and **3a`-e`** against *Escherichia coli*

الخلاصة

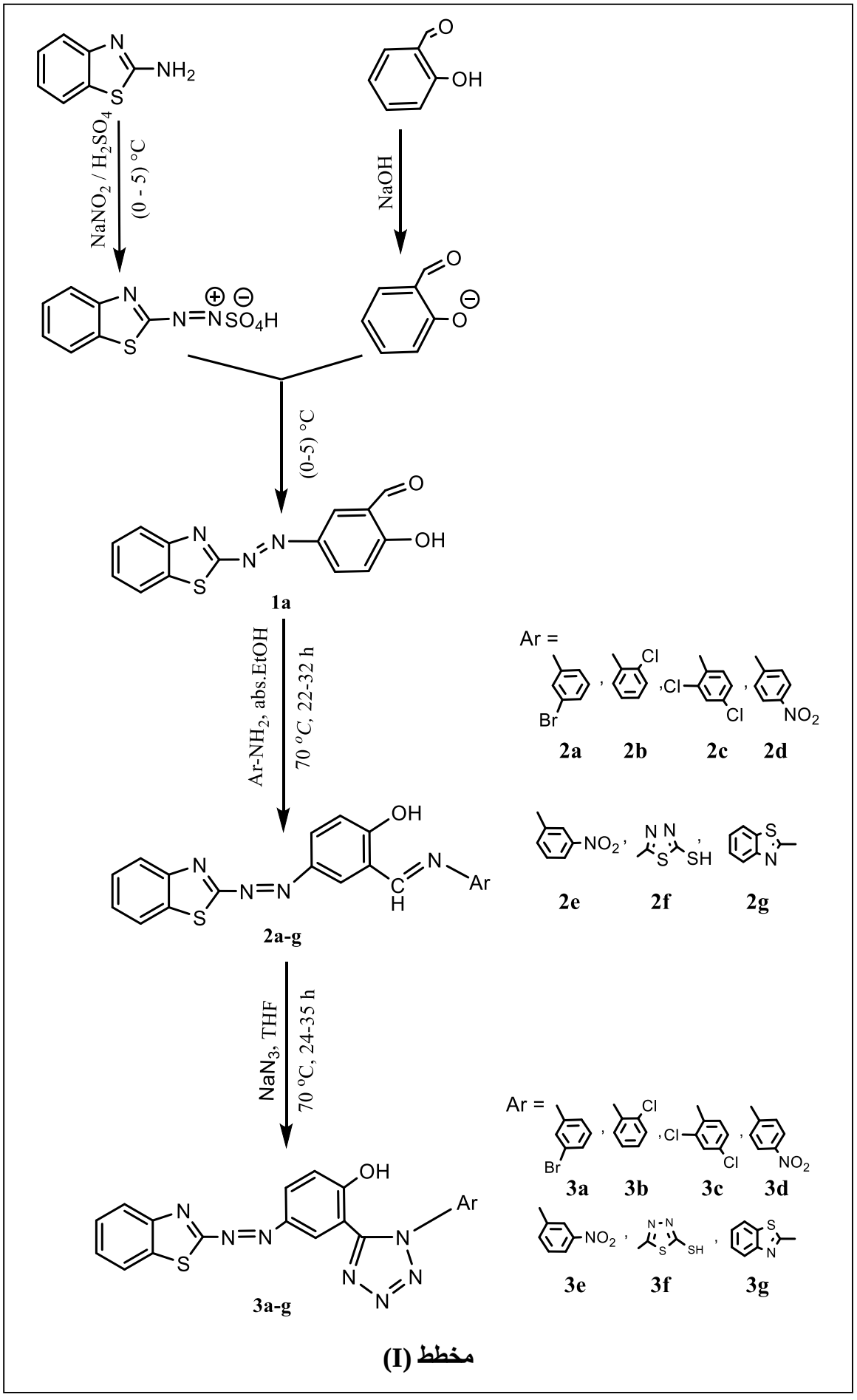
الخلاصة :

تم من خلال هذا العمل تحضير سلسلتين جديدتين من مشتقات التترازول ثنائية التعويض في الموقعين 5،2 الحاوية على وحدة البنزوثيازول و مجموعة الازو. في البداية تم تحويل الأمين الأولي الاروماتي 2-امينوبنزوثيازول الى مشتق الأزوالديهايد المقابل الحاوي على وحدة البنزوثيازول **1a** عن طريق تفاعل الازدواج مابين ملح الدايازونيوم لهذا الامين ومركب 2-هيدروكسي بنزالديهايد المذاب في محلول هيدروكسيد الصوديوم ككاشف ازدواج. تم بعد ذلك ادخال مشتق الازوالديهايد الناتج في تفاعلات تكثيفية محفزة بحامض مع الامينات الاولية الاروماتية (3-بروموانيلين، 2-كلوروانيلين، 4،2-ثنائي كلوروانيلين، 4-نايتروانيلين، 3-نايتروانيلين، 2-امينو5-مركبتو-1،3،4-ثايادايازول و 2-امينوبنزوثيازول) على التوالي في الايثانول المطلق فتم الحصول على سبع ازوايمينات حاوية على وحدة البنزوثيازول **2a-g** تم ادخال الازوايمينات الناتجة **2a-g** لاحقا و على التوالي في تفاعلات الاضافة الحلقية [3+2] مع ازيد الصوديوم في التتراهيدروفيوران فتم الحصول على سبع مشتقات تترازول ثنائية التعويض في الموقعين 5،1 **3a-g,**.

بعد ذلك، تم تحضير الديهايدات حاوية على مجموعة الازو **1a`-e`** عن طريق تفاعلات ازدواج ما بين املاح الدايازونيوم للامينات الاولية الاروماتية (3-بروموانيلين، 2-كلوروانيلين، 4،2-ثنائي كلوروانيلين، 4-نايتروانيلين و 3-نايتروانيلين) على التوالي و مركب 2-هيدروكسي بنزالديهايد المذاب في محلول هيدروكسيد الصوديوم ككاشف ازدواج. تم لاحقا ادخال الازوالديهايدات الناتجة **1a`-e`** و على التوالي في تفاعلات تكثيفية محفزة بحامض مع 2-امينوبنزوثيازول في الايثانول المطلق فتم الحصول على خمس ازوايمينات حاوية على وحدة البنزوثايازول **2a`-e`**. ان معاملة الازوايمينات الناتجة **2a`-e`** مع ازيد الصوديوم تحت نفس شروط الاضافة الحلقية [3+2] اعطت خمس مشتقات تترازول ثنائية التعويض في الموقعين 5،1 **3a`-e`,** على التوالي.

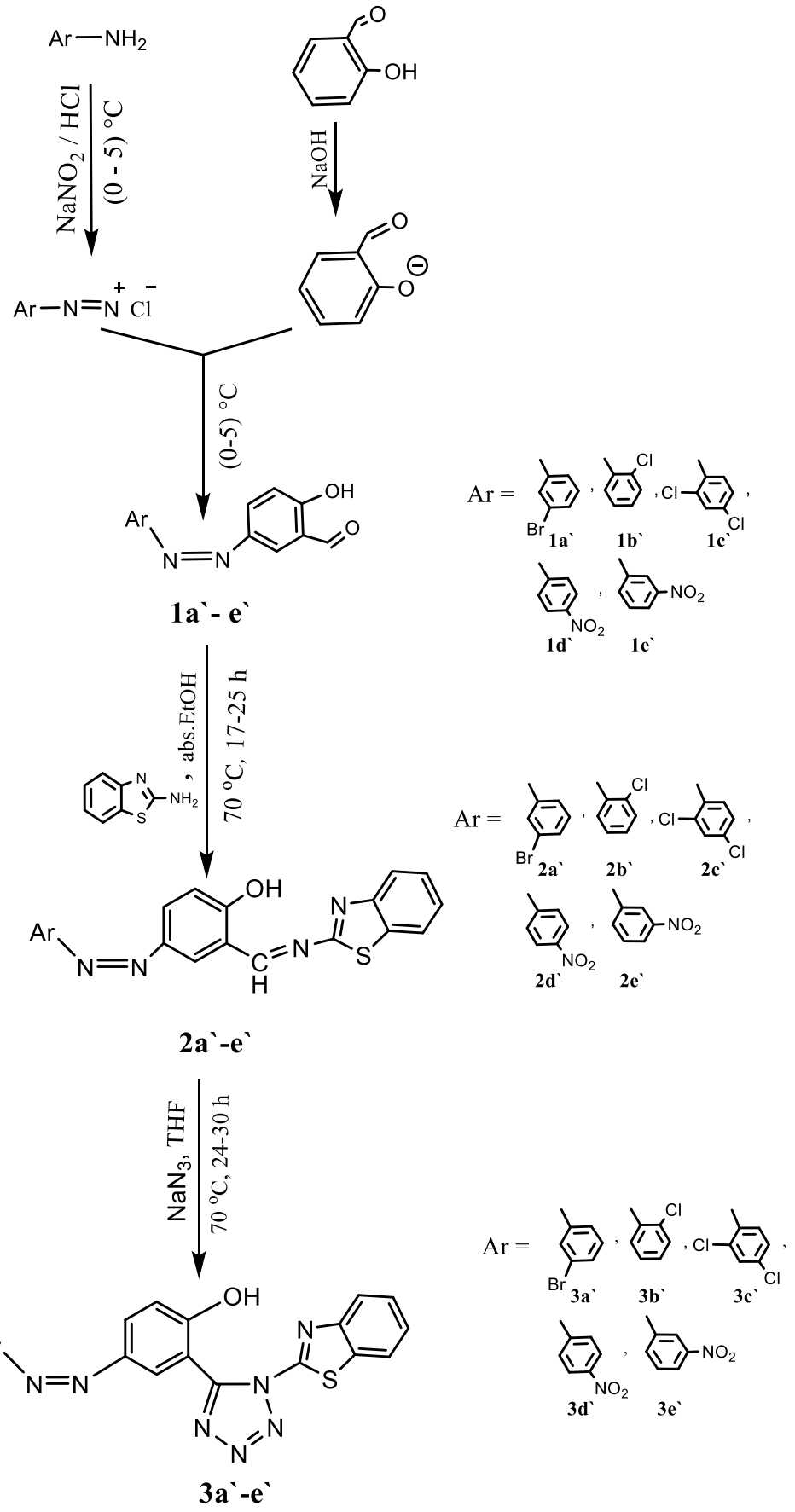
شخصت تراكيب جميع مركبات التترازول الجديدة المحضرة بوساطة االطرائق الطيفية المتضمنة مطيافية الأشعة تحت الحمراء والرنين النووي المغناطسي للبروتون بالاضافة الى مطيافية الكتلة.
تم فحص الفعالية البايولوجية لكافة المركبات الجديدة المحضرة ضد نوعين من البكتريا هما (***Staphylococcus aureous***) الموجبة لصبغة كرام و (***Escherichia coli***) السالبة لصبغة كرام، وقد بينت نتائج الاختبار الاولي بأن جميع مركبات التترازول المحضرة فيما ماعدا **3d** أظهرت فعالية تثبيطية متوسطة-عالية تجاه البكتريا الموجبة لصبغة كرام. من جهة اخرى وجد أن كافة المركبات التترازول لم تظهر اي تاثير تجاه البكتريا السالبة لصبغة كرام.

الخلاصة



مخطط (I)

الخلاصة



مخطط (II)

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة كربلاء/ كلية العلوم
قسم الكيمياء

تحضير تترازولات ثنائية التعويض في الموقعين 1،5 و دراسة فعاليتها ضد البكتريا

رسالة مقدمة إلى
مجلس كلية العلوم - جامعة كربلاء
كجزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل

نورالهدى محمد عبد الحسين الرماحي

بكالوريوس علوم كيمياء (٢٠١٠)
جامعة كربلاء/ كلية العلوم

بإشراف

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د. زيد حسن عبود الأعرجي

١٤٣٦ هـ **٢٠١٥ م**