University of Kerbala
College of Science
Department of Chemistry

Synthesis and Evaluation of Antibacterial Activities for Some New Thiazolidinone Derivatives of Thiadiazole

A Thesis

Submitted to the Council of the College of Science, University of Kerbala as a Partial Fulfillment of the requirements for Master degree of Science in Chemistry

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2023 AD **1444 AH**

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(سورة المجادلة آية 11)

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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 Master degree of Science in chemistry.

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Examination Committee Certification

We, the examining committee, certify that we have read this thesis "Synthesis and Evaluation of Antibacterial Activities for Some New Thiazolidinone Derivatives of Thiadiazole" and examined the student (Haneen Hadi Abbas) 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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Dedication

I humbly dedicate this research to Allah, thanking him for the gifts he gave to me and the blessings he surrounded me by.

Secondly, to my beloved parents who were my source of strength and inspiration, making me love learning and teaching me to choose my dreams. And to my husband, who has always supported me.

Finally, to what book, person, word is credited with educating me.

Haneen Hadi

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With affection and deep appreciation I acknowledge my family: father, mother and husband for their patience, support and enthusiastic encouragement during doing the research.

Last, I would like to express my thanks to the people who helped me, in a way and another to fulfillment of this work.

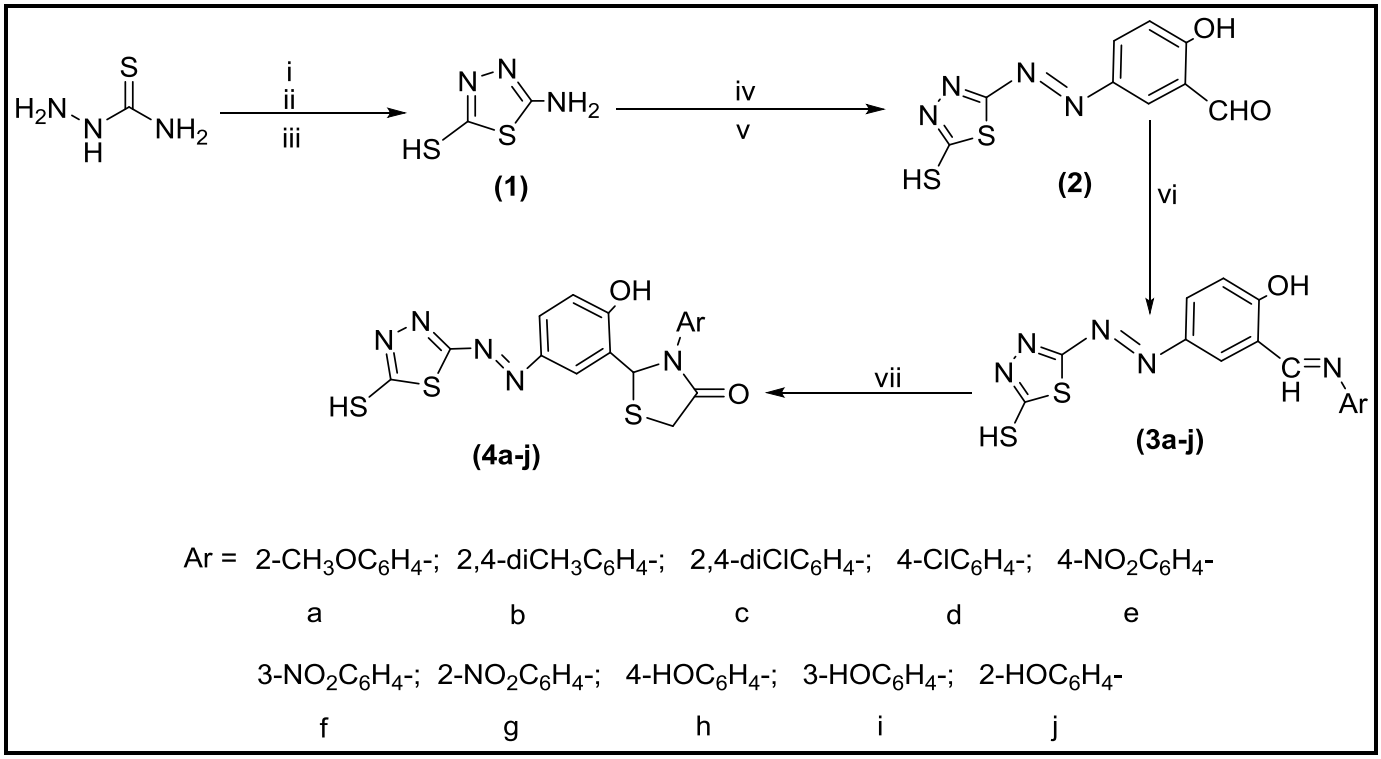
Haneen Hadi

Abstract

Thiazolidines represent a very powerful class of heterocyclic compounds in pharmaceutical field and coerce researchers to synthesize and test novel drugs In this work, new 1,3-thiazolidin-4-one derivatives bearing 1,3,4-thiadiazole moiety have been synthesized as outlined in Scheme (I).

The starting compound 2-amino-5-mercapto-1,3,4-thiadiazole **(1)** has been prepared by refluxing thiosemicarbazide and carbon disulfide in presence of anhydrous sodium carbonate in absolute ethyl alcohol. 2-Amino-5-mercapto-1,3,4-thiadiazole **(1)** was converted to the corresponding 2-thiadiazolyldiazonium chloride salt which was combined with salicylaldehyde through azo-coupling reaction affording azothiadiazolic aldehyde compound **(2)**. Condensation of aldehyde function in compound **(2)** with various anilines (2-methoxyaniline, 2,4-dimethylaniline, 2,4-dichloroaniline, 4-chloroaniline, 4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-aminophenol, 3-aminophenol, and 2-aminophenol), through microwave technique produced imine derivatives **(3a-j)**, respectively. Imine compounds have been reacted with α-mercaptoacetic acid using microwave irradiation method in dimethylfomamide to yield the desired 1,3-thiazolidin-4-one derivatives of 1,3,4-thiadiazole **(4a-j)**, correspondingly.

The structures of the desired 4-thiazolidinone compounds characterized from IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques in addition to (CHNS) elemental microanalysis measurements.. The preliminary antibacterial study results pointed that most of newly thiazolidinone derivatives **(4a**, **4d**, **4e**, **4h**, **4i**, and **4j)** own effect greater than the reference drug (amoxicillin-clavulanate) against Gram-positive bacteria (*staphylococcus aurous*), while compounds **(4e**, **4h**, and **4j)** appeared better activity than standard antibiotic towards Gram-negative bacteria (*Escherichia coli*), Figures (3-43) and (3-44).



Scheme (I): Synthesis of 1,3-thiazolidin-4-one derivatives, Reagents and conditions (i) Na2CO3/ EtOH; (ii) CS2, 65 oC, 24 hrs; (iii) Conc. HCl; (iv) Conc. HCl, NaNO2, 0 oC; (v) 2-hydroxybenzaldehyde, NaOH 10% , 5oC; (vi) Ar-NH2, EtOH, MW (300W), (10 min); (vii) α-mercaptoacetic acid, DMF, MW (300W), (15 min).

Table of contents

List of tables

List of figures

Abbreviations

Symbol	Definition
^{1}H NMR	Proton Nuclear Magnetic Resonance
Abs.	Absolute
Ac	Acetyl
Aq	Aqueous
Ar	Aryl
Bn	Benzyl
CAC	Chloroacetyl chloride
CFTR	cystic fibrosis transmembrane conductance regulator
Conc.	Concentrated
D	Deutrated
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ERGs	Electron releasing groups
Et	Ethyl
et al.	et alli
EtOAc	Ethyl acetate

EtOH	Ethanol
EWGs	Electron-withdrawing groups
FT-IR	Fourier Transform Infrared
FSH	Follicle stimulating hormone
FDA	Food and Drug Administration
H	Hour
HIV	human immunodeficiency virus
Lit.	Literature
M.Wt	Molecular weight
Me	Methyl
MHz	Megahertz
MIC	Minimum influenced concentration
Min	Minute
Mm	Millimeter
Mp	Melting point
MW	Microwave
n	Normal
NSAID	Non-steroidal anti-inflammatory drugs
Ph	Phenyl
Ppm	Part per million
QSAR	Quantitative Structure–Activity Relationships
R_f	Retention factor
Rt	Room temperature
S_NAr	Nucleophilic substitution in aromatic rings
Str	Stretching
t-Bu	Tertiary butyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
W	Watt

Chapter One

Introduction

1.1. Thiadiazoles

Heterocyclic compounds are thought to be the base of modern medicinal chemical research (1). Thiadiazole is a five-membered heterocyclic compound (2). It has a hydrogen-binding domain, a sulfur atom, and a nitrogen system with two electron donors (3). In nature, they exist in four isomeric forms, namely 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole; and 1,3,4-thiadiazole (4, 5).

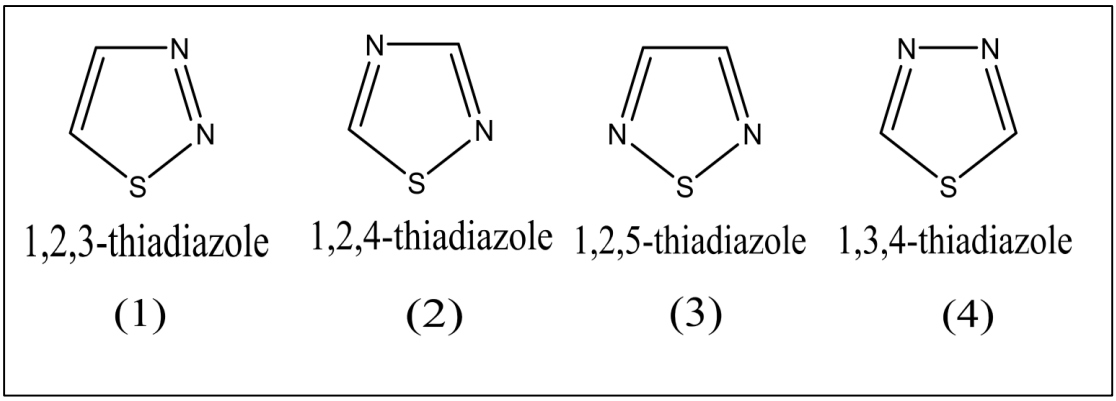


Figure (1-1): Isomers of thiadiazole

One of the factors that makes it easier for the thiadiazole ring to cross biological membranes is the distribution of positive and negative charges (6). The structure of thiadiazole functions as a "two electron donor site" and a "hydrogen bonding site" (7). The sulfur atom in the ring increases the pharmacokinetic characteristics and biological activity of the ring, which increases the lipophilicity (8). One of the isomers, the 1,3,4-thiadiazole ring, contains a sulfur atom that, by inductive action, gives the ring a weakly basic characteristic and a high level of aromaticity (9). 1,3,4-Thiadiazole, first was described by Fischer in 1882 and developed by Bush, and then Goerdler et al., shown by the now known version (10). Thiadiazoles have become more significant due to the presence of mesoionic molecules and compounds containing sulfur (11).

According to their double bonds, 1,3,4-thiadiazoles can exist in three different states: (5) is the aromatic state with the neutral version (12); (6) is the version mesoionic state (13); (7) is the non-aromatic state (14),

reduced version, as tetrahydro-1,3,4-thiadiazoles (15), figure (1-2).

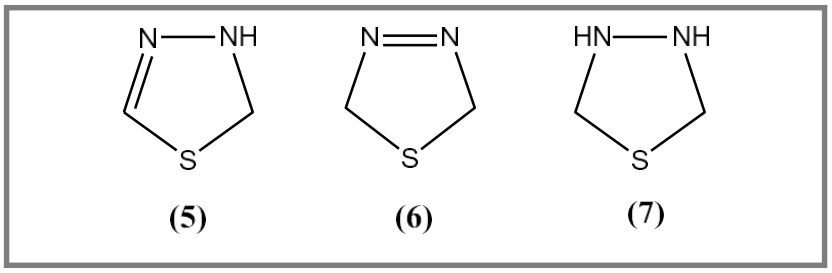


Figure (1-2): Three versions of bonds on 1,3,4-thiadiazole: (2,3-dihydro-1,3,4-thiadiazole; 2,5-dihydro-1,3,4-thiadiazole; and 1,3,4-thiadiazolidine)

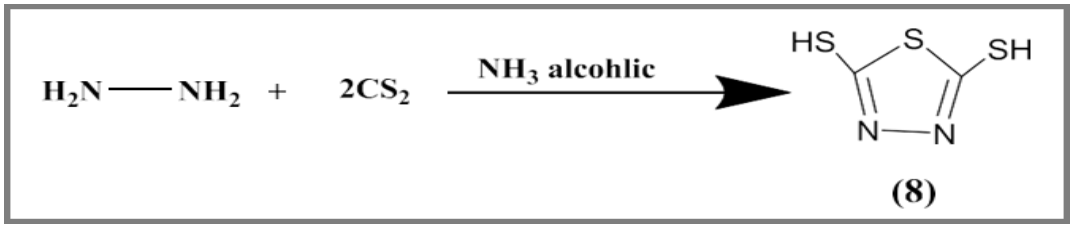
1.2. 1,3,4-Thiadiazoles

1,3,4-thiadizole is a hetrocyclic organic compound that has a five-membered ring having one sulphur and two nitrogen atoms (16). During recent years , there has been intense investigation of different classes of thiadiazole compounds (17). 1,3,4-thiadizole have a wide range of applications in pharmaceutical chemistry and biological activities (18, 19), including antimicrobial (20, 21), anti-inflammatory (22), anti-diabetic (23), antiviral (24), anticovid19 (25), anticancer agents (26) and inhibitors for urease enzyme (27). Many antiviral drugs were reported to append the 1,3,4-thiadiazole in their constructors (28) like acetazolamide (29)and furidiazine (triafur) (24).

1.2.1. Synthesis of 1,3,4-thiadiazoles

Different reactions involving synthesis of 1,3,4-thiadiazoles were reported since the late nineteenth century (30). The first authors that described the way of synthesis of a thiadiazole, was Bush in 1894 in which the reaction of hydrazine sulfate ($N_2H_4.H_2SO_4$) with carbon disulfide (CS_2) in alcoholic solution of KOH. In accordance with Losanitch, the discovery of hydrazine prompted the development of 1,3,4-thiadizole compounds that was synthesized by treating the 2,5-dithiol-

1,3,4-thiadiazole hydrazine salt with strong HCl (8). Losanitch modified this procedure to synthesize compound (8), which was produced by treating (CS_2) with ($N_2H_4.H_2SO_4$) in alcoholic ammonia and yielding 60% of the product (31), scheme (1-1).



Scheme (1-1): Synthesis of 2,5-dithiol-1,3,4-thiadiazole

The derivatives resulting from 2-amino-5-substituted-1,3,4-thiadiazoles have been the subject of numerous studies among the various modification patterns obtained for the thiadiazole. The most common way to obtain these compounds is through the conversion of 1,3,4-oxadiazoles through the cyclization of acylhydrazines, dithiocarbazates, thiosemicarbazides, and thiosemicarbazones (31). .

The synthesis of the effective thiosemicarbazides or dithiocarbazides, that can then be converted into 1,3,4-thiadiazoles, must first be produced in order to initiate the reactions of acylhydrazide with sulfur reagents (CS_2, isothiocyanate, or dithiocarbamates) to synthesize thiadiazoles (32).

After being cyclized in an acidic medium to form *N*-substituted 2-amino-5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazoles (11), acylhydrazine (9) was reacted with substituted isothiocynate in ethanolic sodium hydroxide solution (32), scheme (1-2).

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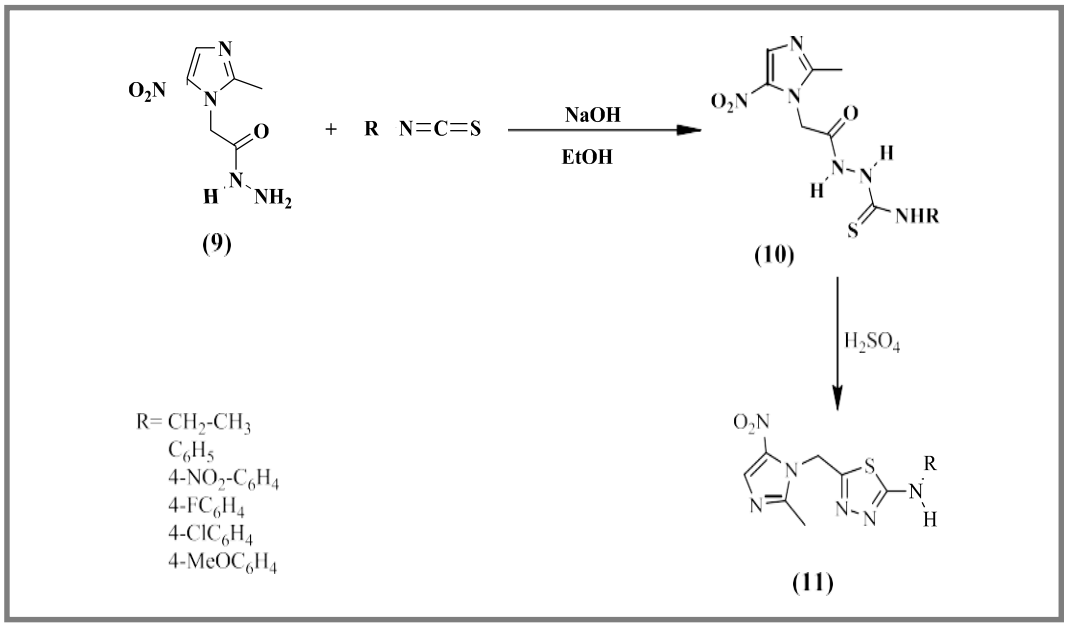
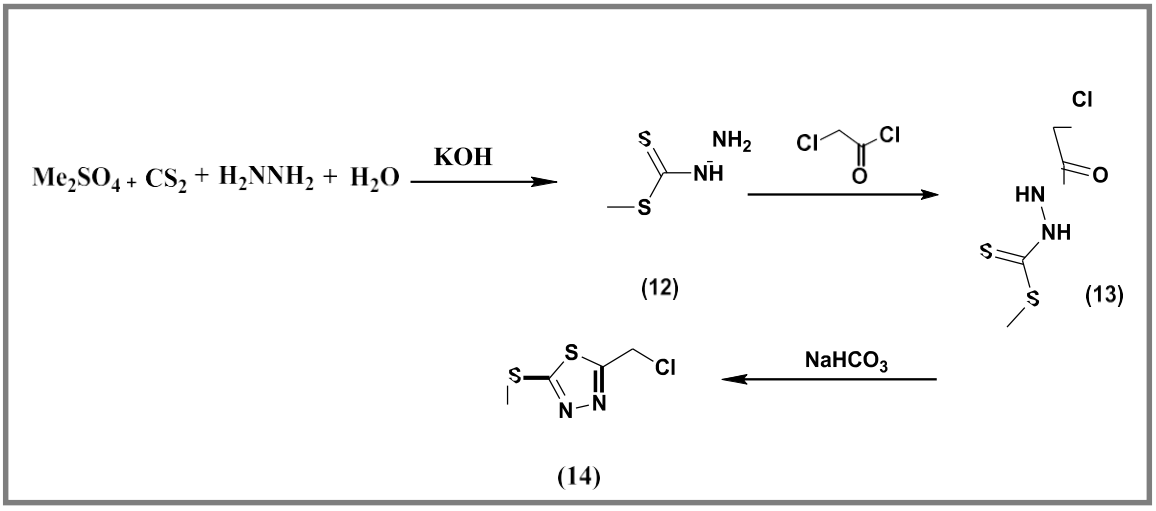


Scheme (1-2): Synthesis of 1,3,4-thiadiazole from isothiocynate

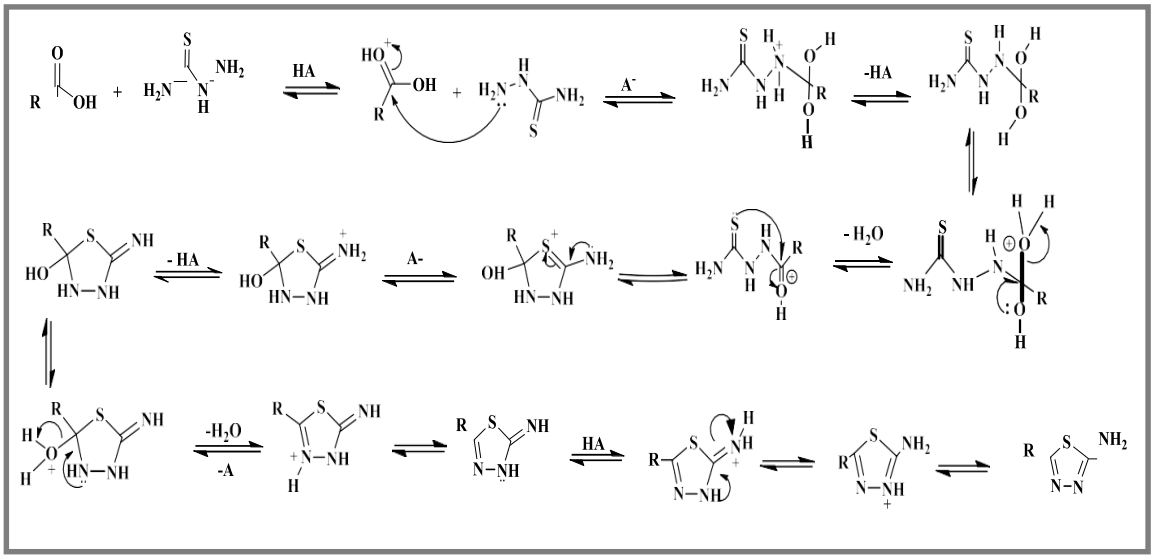
(5-methylthio-1,3,4-thiadiazol-2-yl)methylchloride (14), from dithiocarbazate (13) and 10% sodium bicarbonate, was synthesized by Wang at low temperature of -15 °C, with a yield of 78% (33), as shown in scheme (1-3). .



Scheme (1-3): Synthesis of 1,3,4-thiadiazoles from dithiocarbazate

Thiosemicarbazide cyclization with carboxylic acids in the presence of metallic acid as catalyst, which has been extensively employed and is effective in the synthesis of 1,3,4-thiadiazoles, is the starting point for

several syntheses of 1,3,4-thiadiazoles. The mechanism for this reaction shown in scheme (1-4) (34) .



Scheme (1-4): Mechanism of cyclization of thiosemicarbazides with carboxylic acids

The thiosemicarbazide nitrogen electron pair attacks the carboxylic acid sp^2 carbon nucleophilically in the first step of the suggested mechanism, which is followed by the dehydration of the intermediate. The carbonyl is attacked by an electron pair from the sulfur atom, which leads to cyclization. The resulting intermediate is then dehydrated. The aromatic heterocycle is then created by an electron migration (31).

Oxidizing aryl thiosemicarbazone (15) with an aqueous solution of ferric chloride produces 1,3,4-thiadiazole derivative (16) by Young and Eyre in 1901, Figure (1-3). The authors claim that as compared to the oxidation of semicarbazone, the oxidation of thiosemicarbazone using ferric chloride takes place at gentler reaction temperatures (70–80 °C) (35).

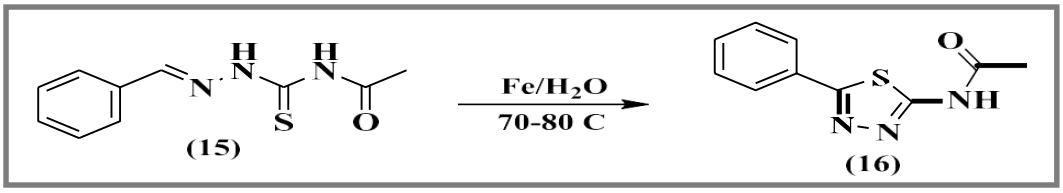
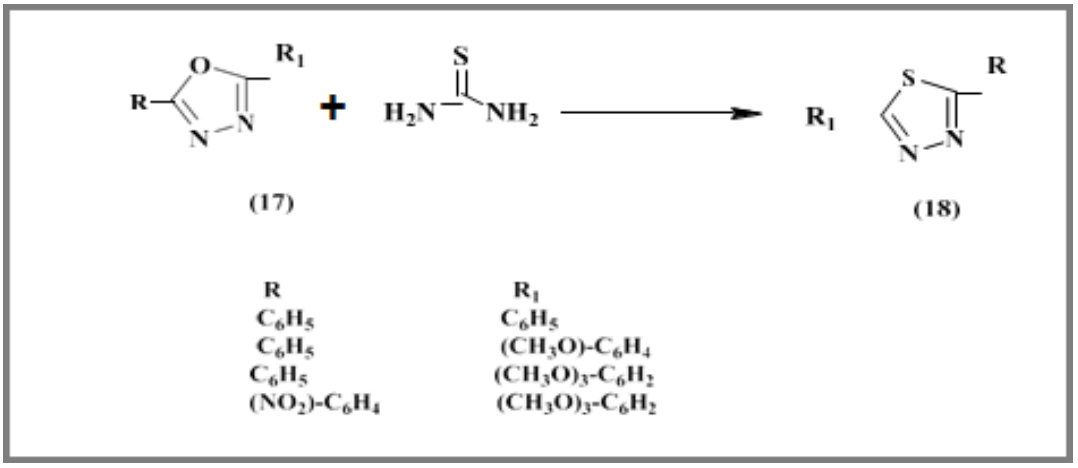


Figure (1-3): Oxidation of phenylthiosemicarbazone with $FeCl_3$ toproduce 1,3,4-thiadiazole

The conversion of 1,3,4-oxadiazoles to 1,3,4-thiadiazoles is related to an alternative process that has been mentioned in the literature. A bioisosteric equivalent of the 1,3,4-thiadiazole ring is the 1,3,4-oxadiazole ring. A strategy known as bioisosterism, or the substitution of oxygen for sulfur in the heterocyclic ring, is an illustration. One of the best methods for creating bioactive compounds is the concept of bioisosterism (36), scheme (1-5).



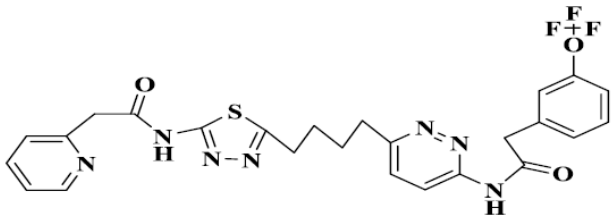
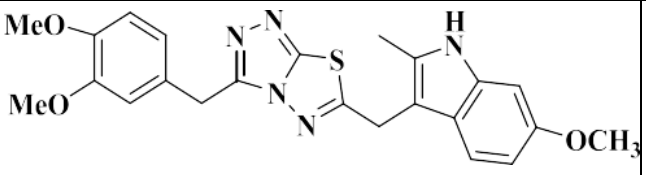
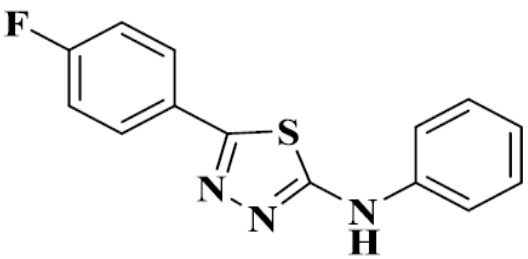
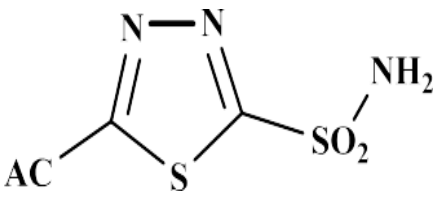
Scheme (1-5): Conversion of aryl-1,3,4-oxadiazoles to aryl-1,3,4-thiadiazoles

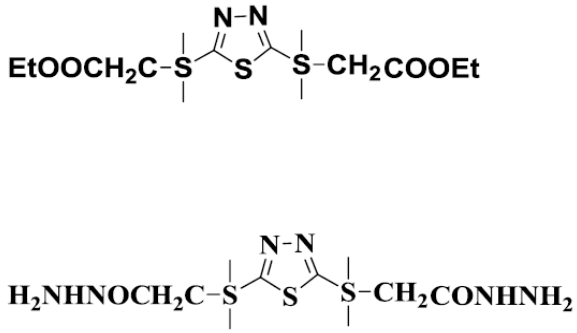
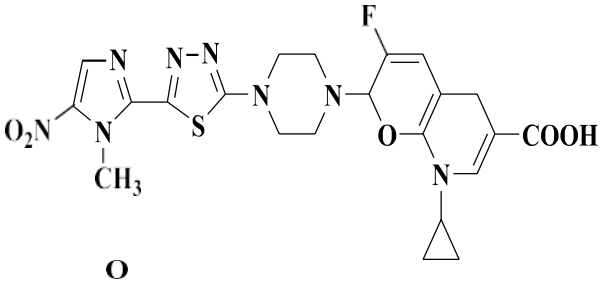
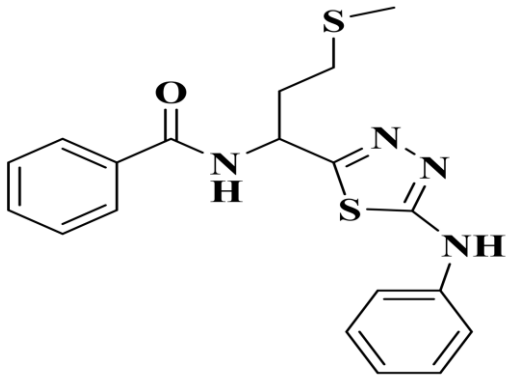
1.2.2. Biological activities of 1,3,4-thiaziazoles

Many microorganisms are highly resistant to drugs in most parts of the world (37). Synthesis of new anti-infective compounds has become important for the treatment of bacterial infections (38). 1,3,4-Thiadiazoles possess a wide range of pharmaceutical activities (39), including: anti-inflammatory (16, 20), antifungal (40), antibacterial (24), analgesic(23) and antituberculous (41). Moreover, 1,3,4-thiadiazoles are also an important class of azoles with important antiviral biological properties and anticancer drugs. Some studies have shown that two or three heteroatoms, such as nitrogen and sulfur, are expected to have antimicrobial activity (42). A few 1,3,4-thiadiazole scaffold-containing medicinal chemistry medications acetazolamide (29) and methazolamide

(43), for example they are powerful carbonic anhydrase inhibitors, pharmaceuticals used to treat glaucoma, an eye-related illness that causes optic nerve damage. Sulfamethizole has antimicrobial properties (44). Azeteta is a phosphorus-containing medication used to treat cancer. As a result, 1,3,4-thiadiazole has a variety of pharmacological effects, including anti-inflammatory, anticonvulsant agents (45).

Table (1-1): The biological activities for some 1,3,4-thiadiazole derivatives

Entry	Structure	Biological activity	Ref.
(19)		This compound has proven effective cells in the lung.	(46)
(20)		Compound showed good anit-inflammatory and analgesic.	(47)
(21)		This compound showed inhibition against mycobacteriumtuberculosis and vitro growing mycobacteriumtuberculosis.	(47)
(22)		Was the first nonmercurial diuretic drug, used clinically there after as anti-glaucoma, antiepileptic oranti-ulcer.	(48)

(23) **(24)**		Showed a high degree of antibacterial activities vs bacterial species Gram-positive and Gram negative in addition to fungi	(49)
(25)		Showed outstanding activity Against Staphylococcus epidermidis and Staphylococcus aureus.	(50)
(26)		Showed potent inhibition of Influenza AH3N2 virus	(50)

1.3. 1,3-Thiazolidinones

Another crucial heterocyclic ring in biology is the thiazolidinone (51), which has a carbonyl group at the 2, 4, or 5 positions, a sulfur atom at position 1, and a nitrogen atom at position 3 (52), figure (1-3). There are several pharmacological features connected to the different derivatives,

including 2-thiazolidinone (A), 4-thiazolidinone (B), 5-thiazolidinone (C), 2-thioxo-4-thiazolidinone (D), and thiazolidine-2,4-dione (E) (53).

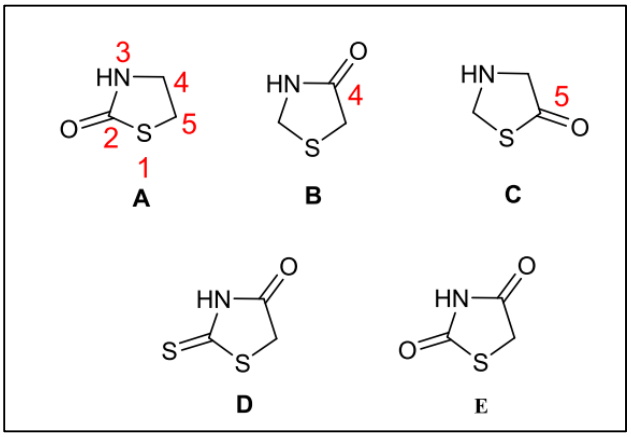
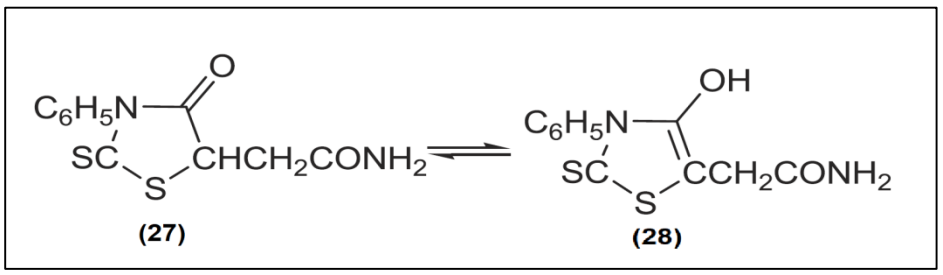


Figure (1-4): Structures of the various 1,3-thiazolidinone derivatives

Numerous thiazolidinone derivatives have biological action when they are present in their optically pure state (54). Therefore, it is important to research the optical activity connected to thiazolidinones. Regarding the rhodanine series, scheme (1-6). The cyclized product has little optical activity because the tautomer's equilibrium was quickly reached, however when the two hydrogen atoms on the methylene carbon are exchanged with alkyl or substituted alkyl groups , This type of tautomerism is optically active and constrained. The creation of rhodanine derivatives using active amines and thiourea using these active amines, provides cyclized products that are optically active (55).



Scheme (1-6): Tautomerism in the rhodanine derivatives

In diluted alkali solution, the antibiotic 2-(5-Carboxypentyl)-4-thiazolidinone (29) quickly loses optical activity to produce the racemate. By fractionally crystallizing its brucine salt, this racemic combination can be solved (56).

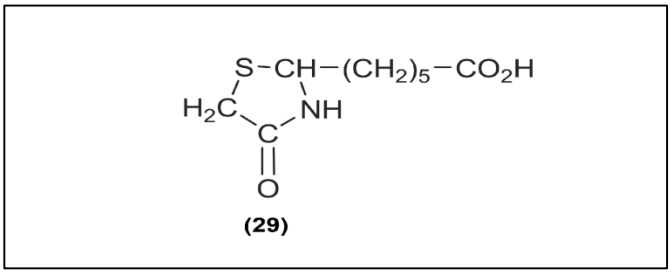


Figure (1-5): Structure of compound (29)

1.4. 4-Thiazolidinones (1,3-thiazolidin-4-ones)

The most significant and extensively researched compounds are 4-thiazolidinones and their derivatives (53). Several synthetic pathways to this significant class of compounds are given in this review, along with their biological functions (57). The 4-thiazolidinones that do not include aryl or alkyl substituents are very soluble in water, however the addition of substituents significantly reduces the water solubility, limiting the compounds utility in aqueous condition (58). Additionally, polarity is seen for several derivatives: Rhodanine (30B) has a dipole moment of 2.20 D, 2,4-thiazolidinedione (30A) of 2.03 D, and 3-ethylrhodanine (30C) of 1.75 D (59), figure (1-6).

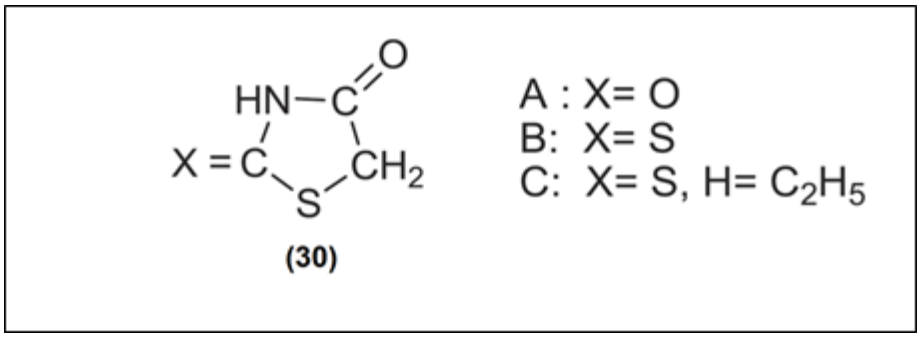


Figure (1-6): Structures of compounds (30)

Scaffolds made of 4-thiazolidinone are favored structures used in medication development . Epalrestat and glitazones are two of this class of heterocycles most popular compounds, It has significantly aided in the treatment of diabetes. 4-thiazolidinone derivatives have been the subject of ongoing study by medicinal chemists over the past ten years and have recently made a comeback to the global pharmaceutical market. As a result, the FDA authorized Ponvory, a 5-ylidene derivative of the medication 2-(alkyl)imino-4-thiazolidinone Ponesimod, in 2021 as a possible therapy for psoriasis and multiple sclerosis (60), figure (1-7).

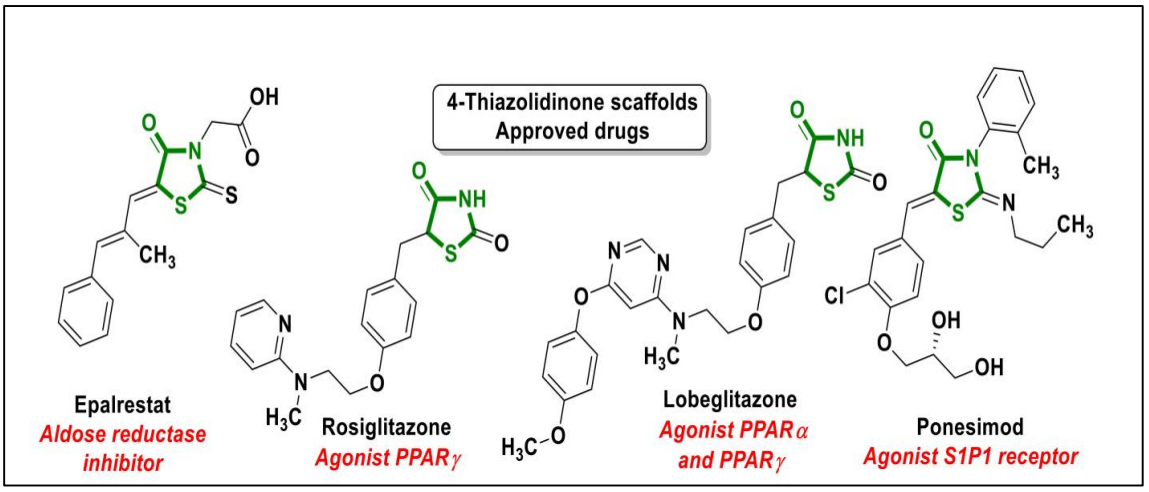
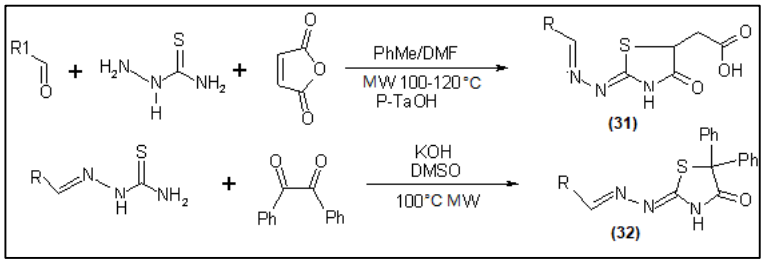


Figure (1-7): The profile of 4-thiazolidinone-bearing molecules in medicinal chemistry

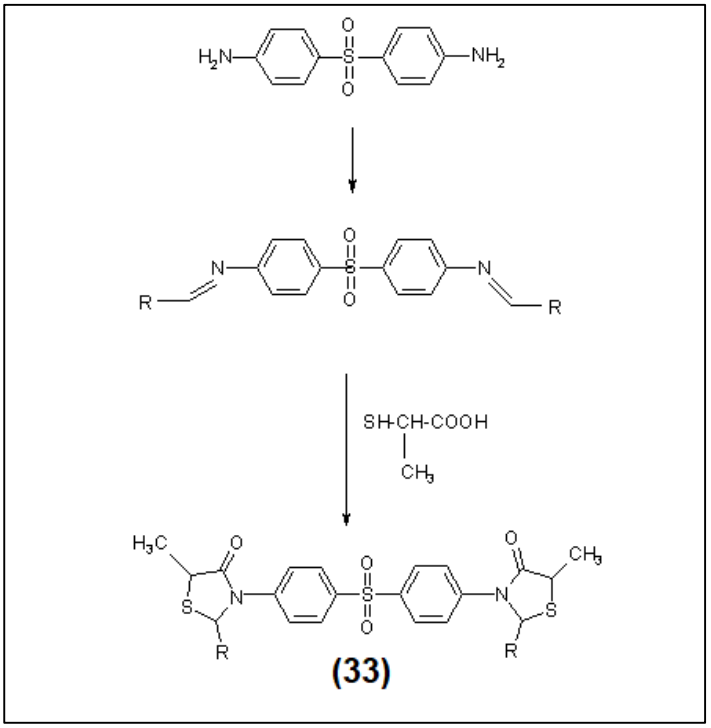
1.4.1. Synthesis of 4-thiazolidinones

Due to the importance of 4-thiazolidinones, several synthetic methods were developed to prepare 4-thiazolidinone rings. A tandem method for the synthesis of 2-hydrazolyl-4-thiazolidinones (31) from commercially available materials in a three-component reaction was developed. The reaction combines aldehydes, thiosemicarbazide, and maleic anhydride and is effectively assisted by microwave irradiation. A new type of compounds, 2-hydrazolyl-5,5-diphenyl-4-thiazolidinones (32), has also been reported for synthesis, obtained by benzylic treatment of thiosemicarbazones in basic medium (61), scheme (1-7).



Scheme (1-7): Microwave irradiation-assisted synthesis of 4-thiazolidinone derivatives (31) and (32)

4,4'-diaminodiphenylsulphone and different aromatic or heterocyclic aldehydes were condensd to produce imine compounds as intermediates for the synthesis of a variety of 4-thiazolidinones. 4-thiazolidinone derivatives (33) were produced when Schiff's bases were cyclocondensed with 2-mercaptopropionic acid, scheme (1-8).



Scheme (1-8): Cyclocondensation of imines with 2-mercaptopropanoic acid gave 4-thiazolidinones (33)

An developing method, microwave-assisted organic synthesis, which uses a safe heating source and greatly reduces reaction time, has enormous potential for industrial operations (62).

By enhancing chemical yield and product selectivity, the reaction's yield may increase, which improves the "atom economy" and allows for solvent-free processes. Microwave-assisted organic synthesis of various heterocyclic units is an efficient and environmentally friendly synthetic approach, making it an effective tool for green chemistry methods (63).

Over the past decades, various researchers have worked on microwave-assisted organic synthesis (64). Figure (1-8) shows the heat transfer mechanism by conventional heating and microwave heating. The effectiveness of microwave irradiation as a heating method depends on the ability of analogs to convert electromagnetic energy into heat (65).

Microwave technology may be used to create or transform complex clusters of bioactive fragments as well as simple fragments. Thus, the basic underlying idea of heating in microwave ovens is based on the collision of the substance's polar bodies with the electromagnetic waves of a specific frequency. Electromagnetic radiation can produce warmth by impact, conduction, or infrequently both. Utilized in process chemistry for the manufacture of fine compounds, the microwave heating technology effectively decreases reaction times from days to hours, hours to minutes (66).

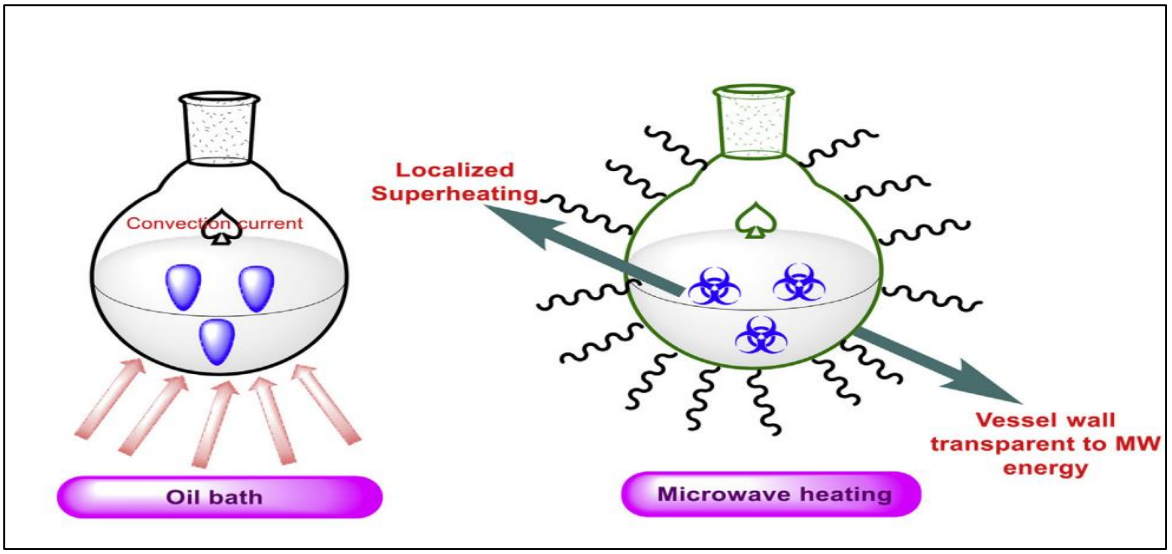
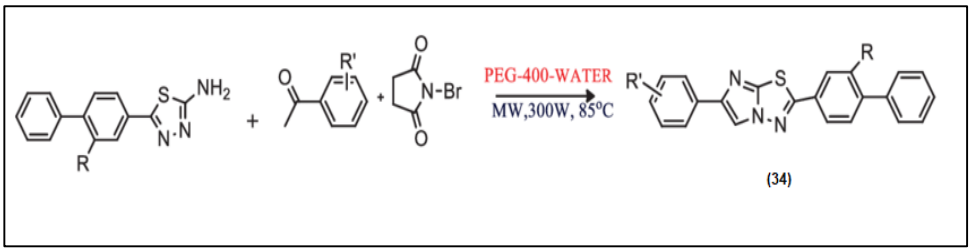


Figure (1-8): Mechanism of heating for conventional and microwave heatin

The main benefit of microwave heating over traditional heating is that the microwaves immediately couple with the ionic or dipole molecules of the reaction mixture, and the energy transfer takes place in less than one millisecond with a corresponding rise in temperature (67). However, with traditional heating, heat is transferred slowly through the reaction vessels' walls, activating the reaction mixture's molecules. The reactants were progressively activated by the conventional heating approach, which used an external heating source (68). Heat first penetrates the vessel walls before reaching the reactants and solvents. This way of transferring energy through the responding mechanism is time-consuming and inefficient. Microwaves, on the other hand, directly couple with the entire reaction mixture, quickly raising the temperature. This heating technique heats the reaction mixture rather than the vessel (69).

An example of the use of microwaves in organic synthesis is synthesis of benzo[d]imidazo [2,1-b]thiazoles (34) from the condensation of aromatic ketones, NBS (*N*-bromosuccinimide) and 5-(Biphenyl-4-yl)-1,3,4- thiadiazol-2-amine using PEG (polyethylene glycol)-400 and water as a green reaction medium under microwave irradiation at 80–85 ºC. The product was produced with good to outstanding yield (94-98%) and took the shortest amount of time, scheme (1-9).



Scheme: (1-9) One-pot microwave synthesis of compound (34)

In less than ten years, microwave-assisted organic synthesis has already become significant in synthetic organic chemistry. Microwave irradiation is used in organic synthesis more frequently than ever in medical and

educational settings since it is a cutting-edge tool for the discovery and development of new medications. Examples of several exemplary microwave-assisted organic synthesis processes were shown in figure (1-8).

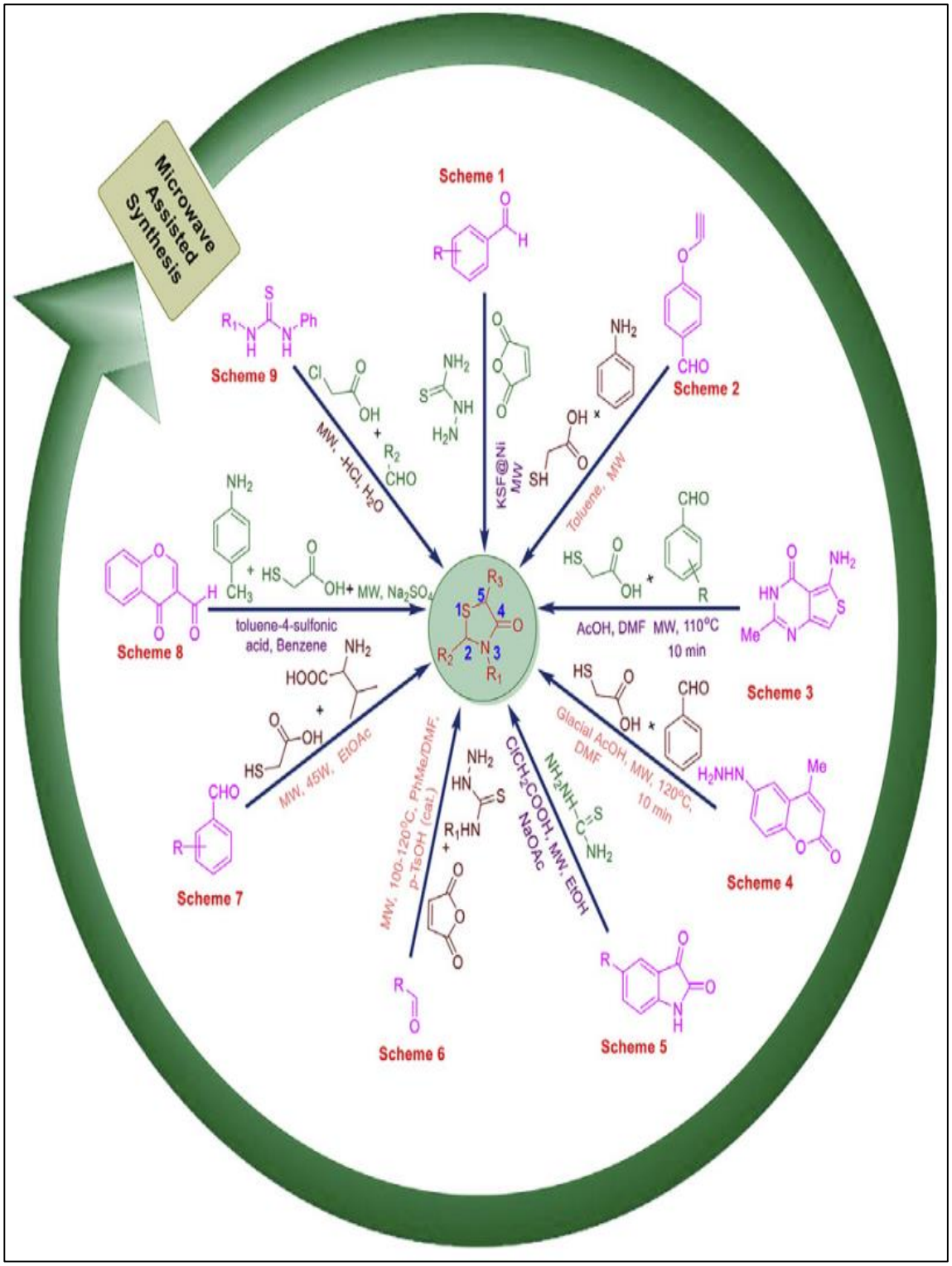
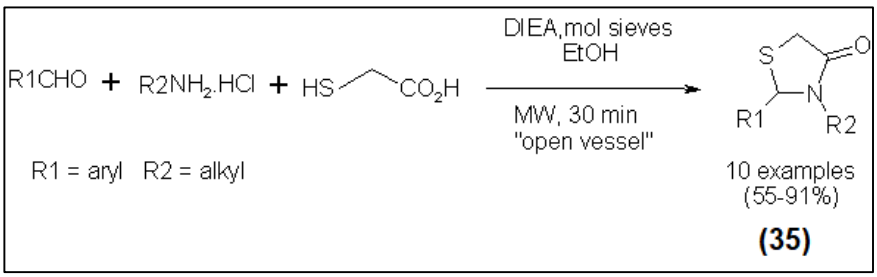


Figure (1-9): Graphical representation of few examples of microwave assisted synthesis of thiazolidin-4-ones

In scheme 1 of figure (1-9), Mahmoodi et al. (2017) proposed a practical one-pot three-component process to synthesize thiazolidin-4-ones from benzaldehydes, thiosemicarbazide, and maleic anhydride using KSF@Ni as heterogeneous catalyst under microwave irradiation (70). In scheme 2, Kumar et al. (2015) presented the reaction of propargyloxybenzaldehyde, aniline, and thioglycolic acid in toluene using the microwave irradiation approach to produce a new series of thiazolidin-4-one derivatives(67).In scheme 3, El-Azab et al. (2015) detailed the synthesis of 4-thiazolidinones through microwave irradiation of a combination of benzaldehyde, thioglycolic acid, and 5-amino-2-methylthieno[3,4-d]pyrimidin-4(3*H*)-one in DMF using glacial acetic acid as catalyst(71). According to scheme 4, El-Azab et al. (2014) created a novel series of thiazolidin-4-ones using the microwave irradiation of 6-hydrazinyl-4-methyl-2*H*-chromen-2-one, benzaldehyde, and thioglycolic acid(72). In scheme 5, Raguvanshi et al. (2010) created a series of thiazolidinone analogues by reacting 1*H*-indole-2,3-dione with thiosemicarbazide in ethanol with a catalytic quantity of chloroacetic acid in a standard home microwave oven at 160 W(73). The synthesis of 1,3-thiazolidin-4-ones was described by Cunico et al. (2008) in scheme 6 by reacting arene aldehydes and valine with an excess of mercaptoacetic acid in ethyl acetate under MW irradiation at 45 W in a home microwave oven for six minutes(65). In scheme 7, Saiz et al. (2009) reported a tandem approach for producing 2-hydrazolyl-4-thiazolidinones by the reaction of aldehyde, thiosemicarbazide, and maleic anhydride while being exposed to microwave radiation(74). In scheme 8, Zhou et al. (2007) developed a one-pot liquid-phase combinatorial synthesis of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinone analogues via a reaction between 3-formyl chromone, primary amine, and mercaptoacetic acid while being microwave-irradiated(75). According to scheme 9, Kasmi-Mir et al. (2006) created a solvent-free one-pot method of producing 5-arylidene-2-imino-4-

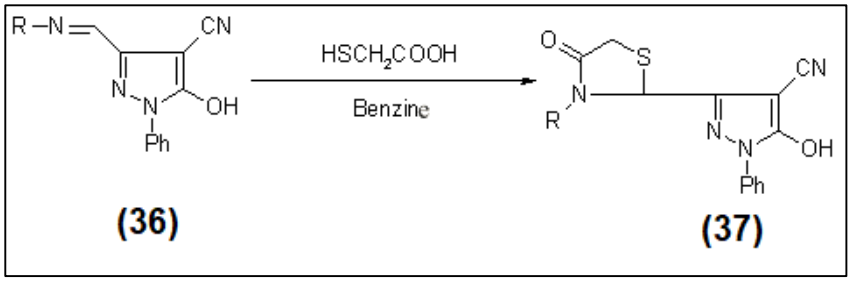
thiazolidinones by condensation of thiourea with chloroacetic acid and an aldehyde while being microwaved(76).

By using the microwave-induced organic reaction enhancement (MORE) chemical approach, certain 4-thiazolidinone derivatives (35) prepared using microwave irradiation, starting with thiazolidin-4-ones are made by condensing aromatic aldehydes, amines, and mercaptoacetic acid in ethanol. The best method involves microwave irradiating a mixture of aldehyde, amine hydrochloride, and mercaptoacetic acid (molar ratio 1:2:3) while it was being exposed to 1.25 equivalents of *N*,*N*-diisopropylethylamine (DIEA) base in ethanol at 120°C for 30 minutes (77), scheme (1-10).



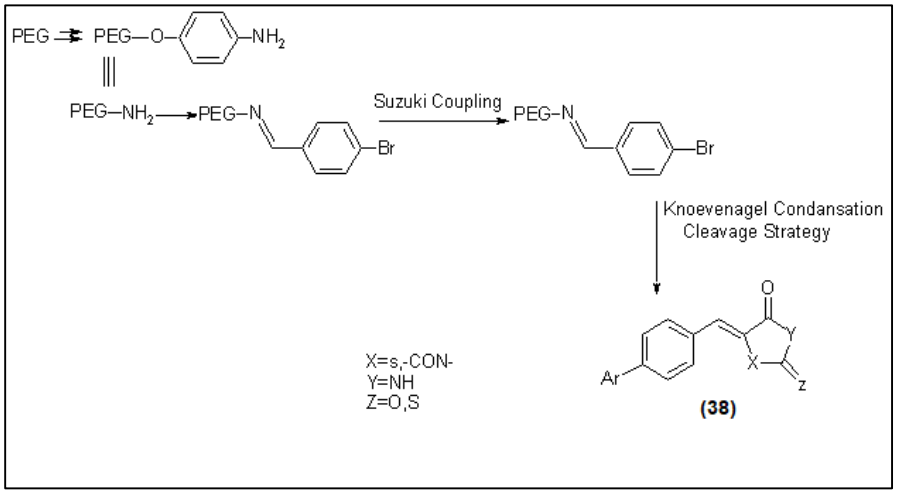
Scheme (1-10): A mixture of aldehyde, amine hydrochloride, and mercaptoacetic acid was irradiated by microwave to afford 4-thiazolidinone derivatives (35)

Thioglycolic acid had a successful cycloaddition reaction with the Schiff's base derivatives (36). It was added to (36) using a water separator and added to boiling benzene to produce 4-thiazolidinone derivatives (37) (78), scheme (1-11).



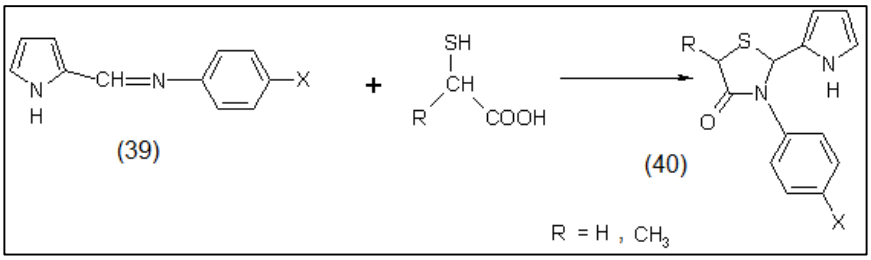
Scheme (1-11): Cycloaddition of thioglycolic acid to Schiff's bases yielding 4-thiazolidinone derivatives (37)

The synthesis of 5-arylidene 1,3-thiazolidin-4-ones and pyrimidinones (38) on soluble polymer supports utilizing aniline as a traceless linker was described as effective procedure (79), scheme (1-12).



Scheme (1-12): Synthesis of 4-thiazolidinone derivatives (38) by reacting Aldehyde with polyethylene glycol (PEG)-aniline to give imine linkage followed by Knoevenagel condensation

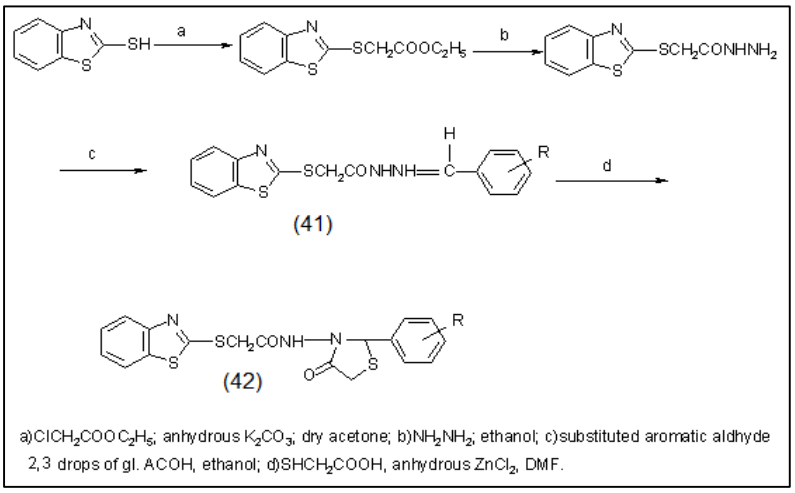
3-aryl-2-(2-pyrrolyl)-1,3-thiazolidin-4-ones and 5-methyl-3-aryl-2-(2-pyrrolyl)-1,3-thiazolidin-4-ones (40) were prepared in excellent yields by refluxing equimolar concentrations of the imines (39) with thioglycolic or thiolacetic acids in dry benzene (80), scheme (1-13).



Scheme (1-13): Refluxing imines (39) and thioglycolic or thiolacetic acids in dry benzene to give 4-thiazolidinones (40)

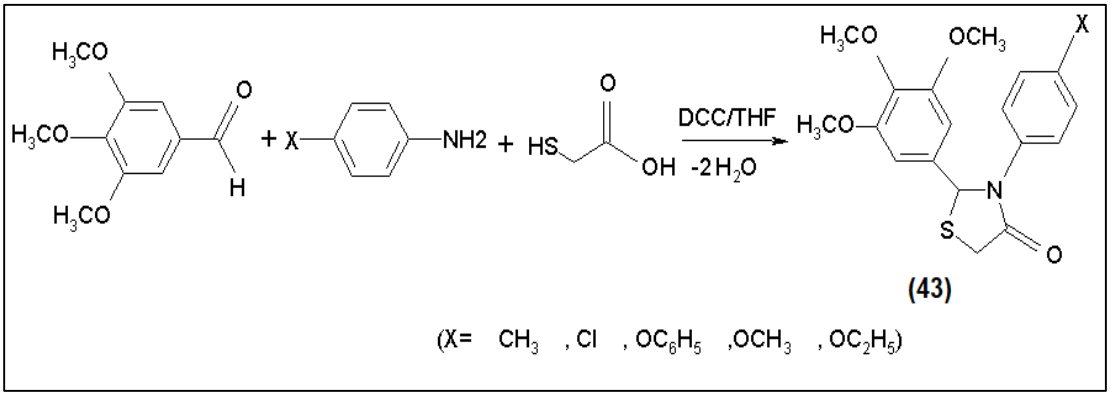
4-thiazolidinones (42) were produced in good yields, that are described and compared to conventional synthesis techniques, through heterocyclization reaction of 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide (41) with $SHCH_2COOH$ in DMF in the presence of a catalytic amount of anhydrous $ZnCl_2$ under microwave

irradiation (81), scheme (1-14).



Scheme (1-14): Treatment of 2-(benzothiazol-2-ylthio)-*N'*-benzylideneacetohydrazides (41) with mercaptoacetic acid gave 4-thiazolidinone derivatives (42)

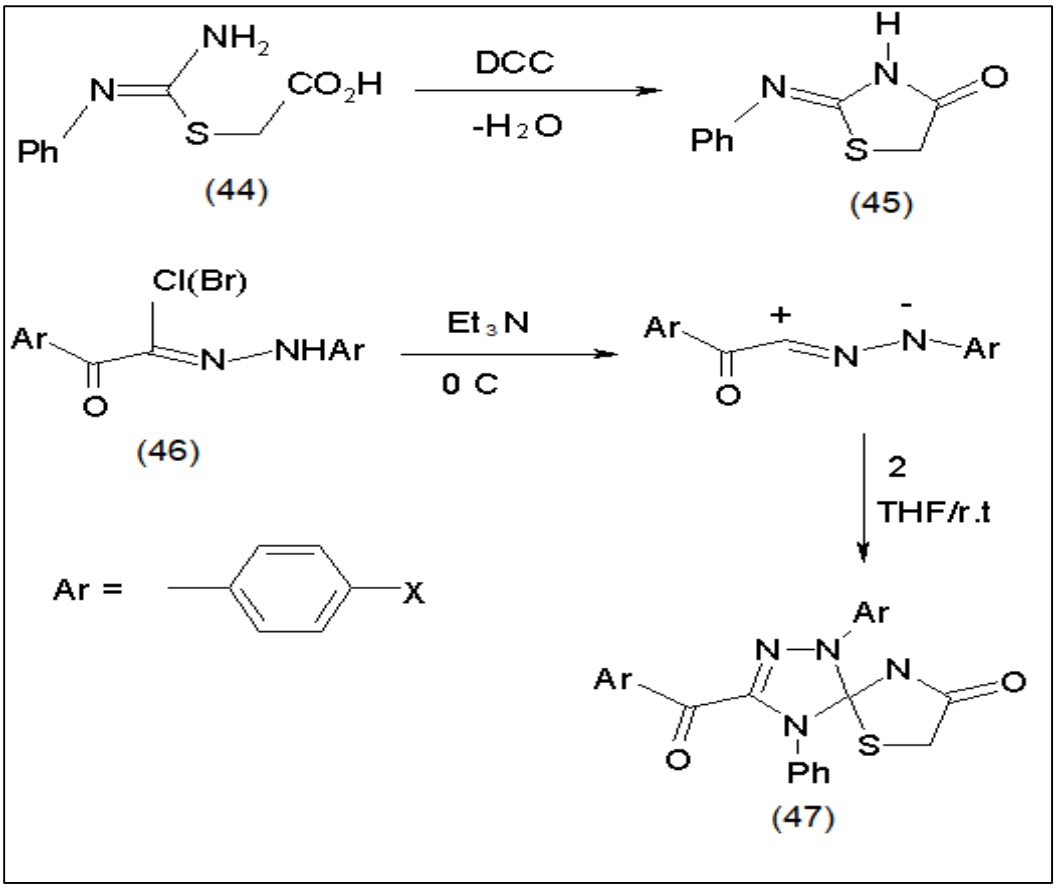
A one-pot, three-component condensation procedure involving an aromatic amine, an aldehyde, and a mercaptoacetic acid was used to create the 4-thiazolidinones (43) (82), scheme (1-15).



Scheme (1-15): Reaction of an aldehyde, an aromatic amine, and mercaptoacetic acid to give 4-thiazolidinones (43)

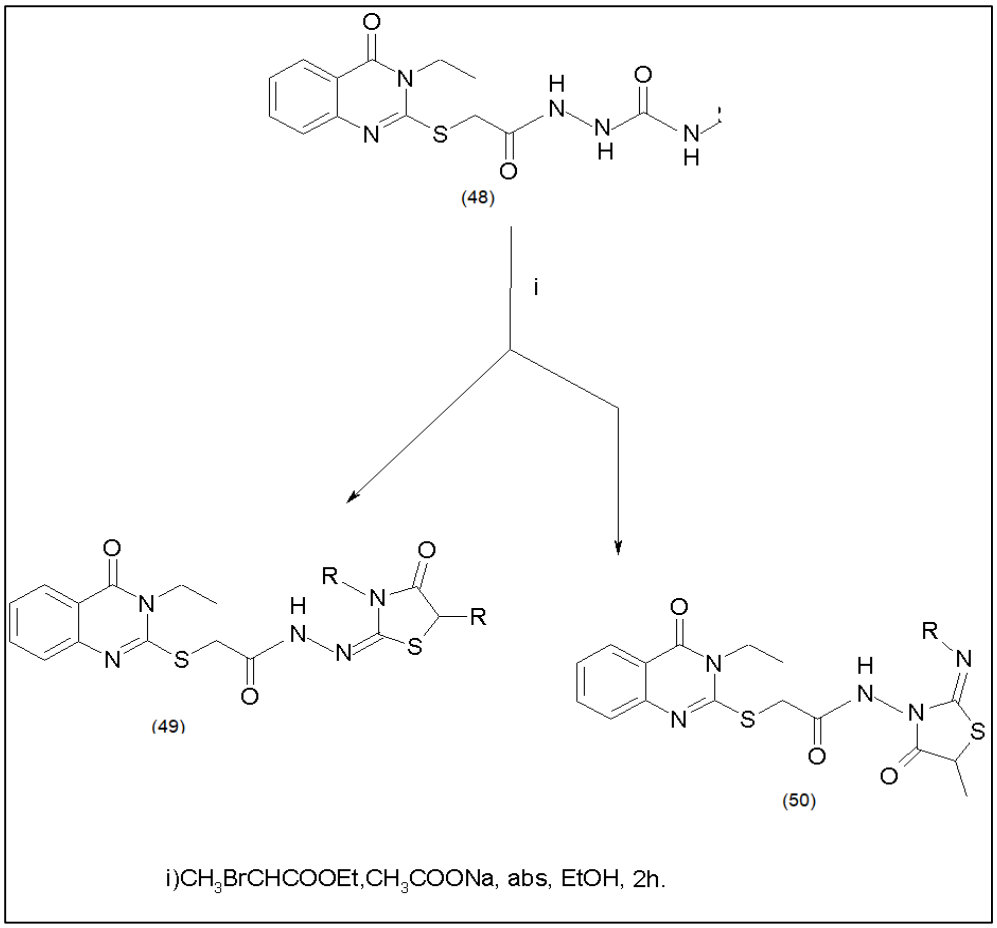
By thermally cyclizing 4-amino-5-phenyl-3,5-thiaaza-4-pentenoic acid (44) with DCC (*N*,*N'*-Dicyclohexylcarbodiimide) as a dehydrating agent, 2-phenylimino-1,3-thiazolidin-4-one (45) was produced. 6-aryl-9-phenyl-8-substituted-1,4,6,7,9-thiatetrazaspiro-[4.4]non-7-en-3-ones (47) were produced as a result of treating 2-phenylimino-1,3-thiazolidin-4-one (45) with different hydrazonoyl halides (46) (nitrilimines 4 precursor) (83),

scheme (1-16).



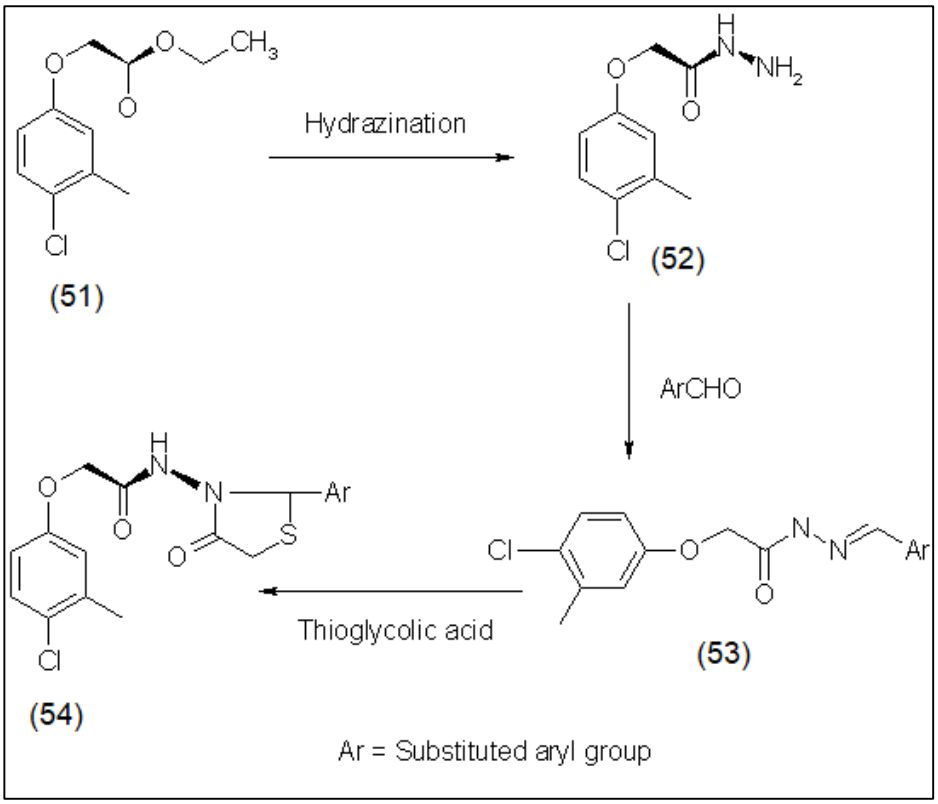
Scheme (1-16): Cyclization of 4-amino-5-phenyl-3,5-thiaaza-4-pentenoic acid (44) using DCC as dehydrating agent

Two regioisomer series, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacety-lhydrazono)-3-alkyl/3- aryl-5-methyl-4-thiazolidinones (49) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4 thiazolidinones (50), were synthesized through cyclization of 1-(3-ethyl-4(3*H*)-quinazolinone-2-ylmercapto-acetyl)-4-alkyl/aryl thiosemicarbazides (48) with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium (84), scheme (1-17).



Scheme (1-17): Synthesis of 4-thiazolidinones (49) and (50) by reacting 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercapto-acetyl)-4-alkyl/aryl thiosemicarbazides (48) with ethyl 2-bromopropionate

Hydrazination of 2-(4-chloro-3-methylphenoxy) acetate (51) produced the corresponding hydrazide derivative (52). The condensation of hydrazide derivative (52) with various aromatic aldehydes produced *N*-(substituted benzylidiene)-2-(4-chloro-3-methylphenoxy) acetamides (53). Thioglycolic acid was used to cyclize compounds (53), which produced 2-(4-chloro-3-methylphenoxy)-*N*-(4-oxo-2-arylthiazolidin-3-yl) acetamides (54) (85), scheme (1-18).



Scheme (1-18): Synthesis of 2-(4- chloro- 3-methylphenoxy)-*N*-(4-oxo-2-arylthiazolidin-3-yl) acetamides (54) via cyclization of compounds (53) with thioglycolic acid

1.5. Biological activities of 1,3-Thiazolidin-4-ones

Because it exhibits several biological properties, including those that are antibacterial, antiviral, anti-inflammatory, antidiabetic, anti-cancer, anticonvulsant, FSH agonist, and CFTR inhibitor, 4-thiazolidinone has been referred to as a "magic moiety (86). There is a ton of research on the anti-inflammation, anti-cancer, anti-tumor, anticonvulsant and antidiabetic, activities. But in this study, we've gone into length into a few different biological processes connected to this moiety, including antibacterial (and the various targets identified), antituberculosis, antioxidant, antiviral (a number of infections), and FSH agonist (with various targets).

1.5.1. Anticancer drug-4-thiazolidinones hybrids

According to Tura et al. a variety of unique hybrid compounds with an imatinib (Gleevec) moiety were designed and created. The FDA-approved

protein kinase inhibitor imatinib (55) which revolutionized how most instances of chronic myeloid leukemia (CML) were treated, was the first of its kind. Using the K562 (chronic myeloid leukemia), PC3 (prostate cancer), and SHSY-5Y (neuroblastoma) cell lines, Türe et al. obtained 5-benzylidene-2-arylimino-4-thiazolidinones-bearing imatinib analogs (56a-c) and tested them for their antimitotic activity (87). The three most potent cytotoxic hybrids were then found. Cell death by apoptosis was brought on by compounds (56a-c). Furthermore, compounds (56b) and (56c) resulted in cycle arrest in the G0/G1 phase, but compound (56a) prevented cell cycle progression in the G2/M phase. Imatinib was shown to be less genotoxic than hybrid molecules (56a) and (56c), which were tested against K562 cells (88), figure (1-10).

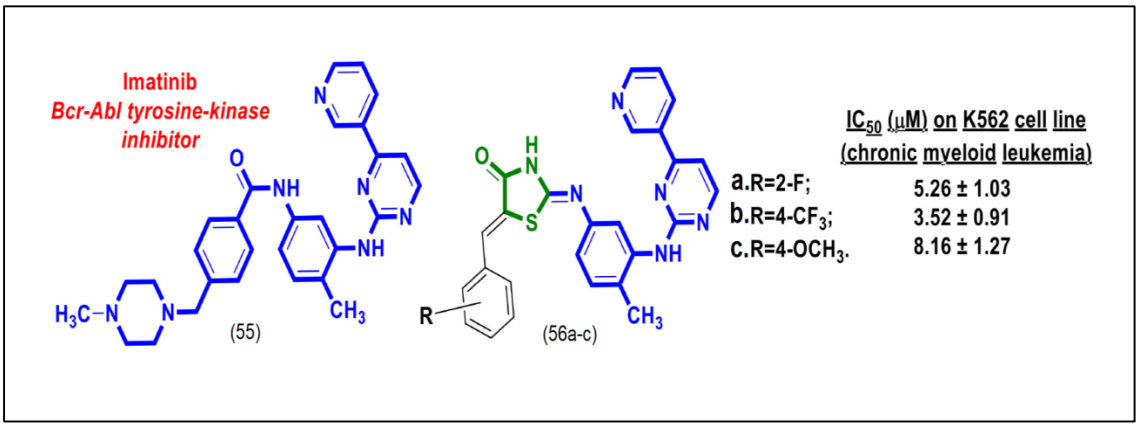


Figure (1-10): Structures of imatinib (55) and 4-thiazolidinones-bearing imatinib analogs (56a-c) with anticancer activity

1.5.2. NSAID-4-Thiazolidinones Hybrids

Using prospective NSAIDs for treating cancer or the use of NSAID scaffolds or molecules for developing novel antimitotic medicines have attracted more attention in recent decades. Piotr Roszczenko. and others employed a hybridization strategy to create novel, potential anti-cancer medicines (57a-b, 58a-b and 59) by combining the anti-inflammatory medication 5-aminosalicylic acid with the scaffold 5-ylidene-4-thiazolidinone, Figure (1-11) (87). Two compounds, (57a and 57b), were discovered to be effective in some forms of cancer when compared to the

impact of doxorubicin after being evaluated on a panel of seven cancer cell lines using synthesized hybrids (reference drug), with IC50 values of 0.31 and 0.30 M, respectively, on the MCF7 line showing the greatest activity level. Additionally, for compounds (57a and 57b), tumor selectivity and little effects on healthy fibroblasts were seen. The generation of DNA damage was discovered by in vitro investigations of the molecular mechanisms of action for compounds (57a and 57b). Cell cycle arrest in the G2/M phase, as well as the induction of apoptosis as shown by annexin-V staining and caspases activation. Furthermore, it was discovered that both substances alter the expression and activity of various components of the DNA damage response system, including cyclins, cyclin-dependent kinases, and CDC25 phosphatase (89).

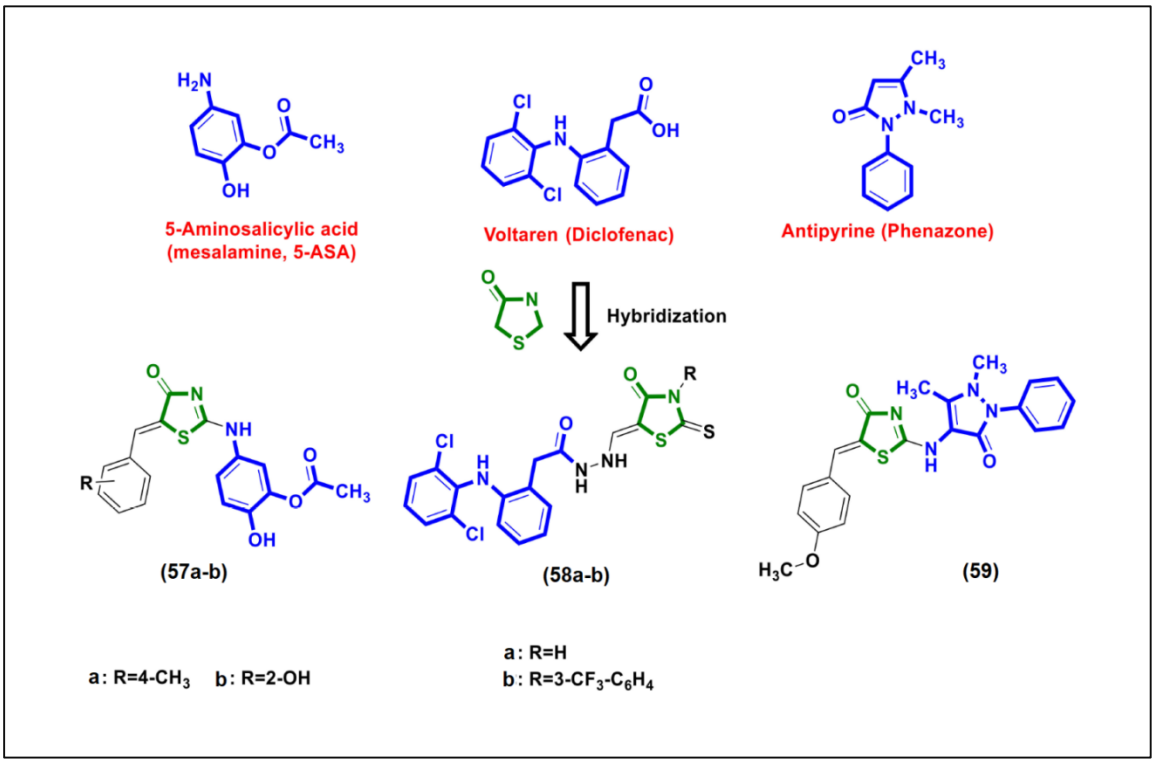


Figure (1-11): 4-Thiazolidinone-bearing hybrids molecules combined with NSAIDs scaffolds (57-59) possessing anticancer activity

1.5.3. Antibacterial drug-4-thiazolidinone hybrids

Eldehna et al. developed a number of new 4-thiazolidinone-sulfanilamide hybrids (60 and 61) as potential hCA inhibitors. The novel hybrids' inhibitory potency athwart hCA I, II, IV, and IX was assessed in vitro, and

all compounds were active to varying degrees. Additionally, the anti-proliferative properties of each substance were tested against the colorectal and MCF-7 breast cancer strains (90). Hybrid (60), figure (1-12), was the most effective against MCF-7 of the Caco-2 cell lines, with an IC50 of 3.96 0.21 M. Deep investigations revealed that hybrid (60) induced the intrinsic mitochondrial apoptotic pathway in MCF-7 cells, as demonstrated by the up-regulation of active caspase-3 and caspase-9, cytochrome C, and p53 levels, as well as the increased expression of the pro-apoptotic protein Bax and the decreased expression of the anti-apoptotic protein Bcl-2 (91).

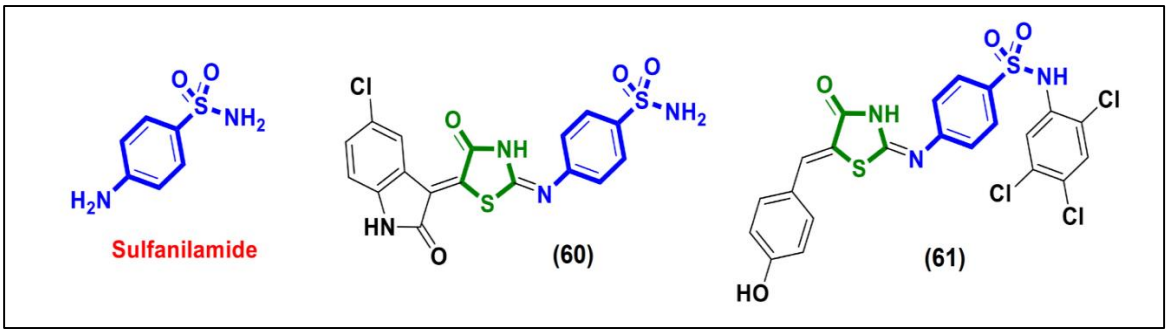


Figure (1-12): Sulfanilamide-bearing hybrids with 4-thiazolidinone scaffolds (60 and 61) as potential anticancer agents

1.5.4. Antiviral activity

The 4-thiazolidinone derivatives have antiviral action against a number of dangerous diseases. 3% of the world's population is thought to be infected with the hepatitis C virus (HCV), making it a significant human disease for global public health (92). Anti-HCV drugs are attracted to the HCV nonstructural protein 5B (NS5B) as a target. 28 brand-new 2-heteroarylimino-5-arylidene-4-thiazolidinones were tested by Küçükgüzel et al. as HCV NS5B polymerase non-nucleoside inhibitors. The derivative with R1 = Cl and R2 = 2,6-dichlorophenyl (62) was shown to be the most powerful in vitro. The thumb pocket-II of NS5B and the co-crystal structure of PF-868554-NS5B (PDB ID: 3FRZ) were used in further molecular docking investigations (93), figure (1-13).

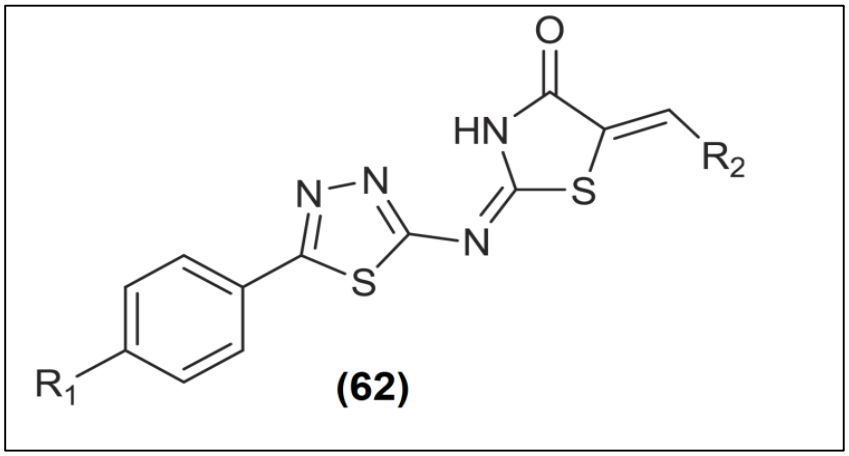


Figure (1-13): Structure of 4-thiazolidinone derivative bearing 1,3,4-thiadiazole unit (62) that showed powerful antiviral activity

1.5.5. Anti-tuberculosis activity

The second-leading cause of infectious disease death worldwide, tuberculosis is fatal illness. Multi- and extensively drug-resistant TB are the results of incomplete medication therapy (94). New anti-tuberculosis medications must thus be created immediately, especially for use against the disease's difficult-to-treat multidrug-resistant and other latent forms. In recent years, the 4-thiazolidinone scaffold has served as the catalyst for the discovery of a number of innovative anti-tubercular drugs. One of the earliest known active 1,3-thiazolidin-4-one derivative (63) against Mycobacterium TB is an actithiazic acid, (-)-2-(5-carboxypentyl) thiazolidin-4-one (95). Additionally, it has been discovered that a variety of 2,3-disubstituted or 2,3,5-trisubstituted-4- thiazolidinones as well as 1,3-thiazolidin-4-ones based on piperidone, isonicotinyl hydrazide derivatives containing the 4-thiazolidinone nucleus, and others have anti-tuberculosis activity (96), figure (1-14).

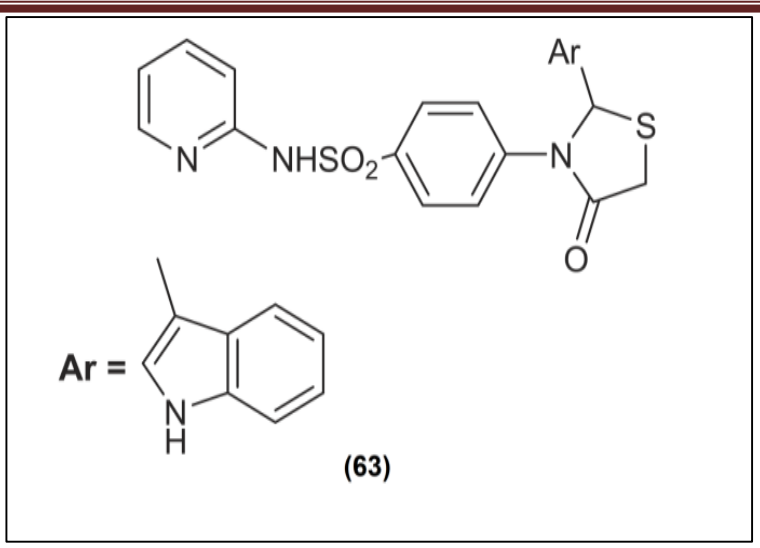


Figure (1-14): Structure of 4-thiazolidinone derivative (63) as active drug against Mycobacterium TB

1.5.6. The anti-HIV activity

Thiazolidinones' anti-HIV properties have also been the subject of much research. A lot of 4-thiazolidinones specifically block HIV-1 reverse transcriptase, preventing it from integrating viral genetic material into the host genome. The anti-HIV activity of 2,3-diaryl substituted 4-thiazolidinone, produced by the reterosynthetic opening of thiazolobenzimidazole, was reported by Barreca et al. (97). The bioactivity of the 4-thiazolidinone skeleton was subsequently rationalized by the structure-property relationship (QSAR) method (98). As selective HIV reverse transcriptase inhibitors, 2-(aryl)-3-furan-2-ylmethyl-thiazolidin-4-one derivatives (64), figure (1-15), have also been investigated. Utilizing these derivatives, QSAR investigations revealed the significance of the compounds' dipole moment, lipophilicity, and out-of-plane energy stored in explaining the activity (99).

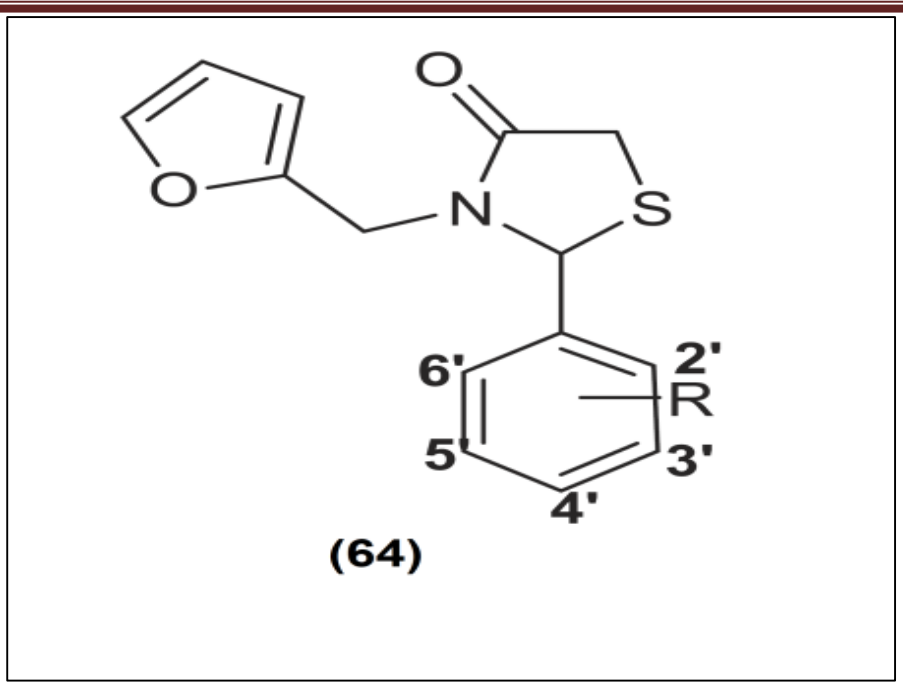


Figure (1-15): Structure of 2-(aryl)-3-furan-2-ylmethyl-thiazolidin-4-one derivatives (64)

1.6. Natural compounds scaffold-4-thiazolidinones hybrids

When designing anticancer treatments, structural motifs of natural products are usually a great place to look for compounds that are similar to drugs (100).

1.6.1. Monoterpene-4-thiazolidinone hybrids

Zielińska et al. created 4-acetyl-1-methylcyclohexenothiosemicarbazones and hybrids of 4-acetyl-1-methylcyclohexeno-2-imino-4-thiazolidinones (65a-b) based on the molecule's hydrazone linker and monoterpene backbone structure of limona ketone, figure (1-16), (101). On the HT-1080, A549, and MCF-7 cell lines, the cytotoxicity of the produced compounds was assessed. The most cytotoxic compounds on HT-1080 lines were compound (65a) and compound (65b) with IC50 values of 15.85 M and 16.13 M, respectively. These substances were discovered to form dependable ligand-caspase-3 complexes using molecular docking. Additionally, it was discovered that compound (65b) was the most effective at inducing apoptosis and caspase-3/7 activation, as well as

inhibiting the S-phase cell cycle in HT-1080 cells. In contrast, compound (65a) showed a lower degree of apoptosis induction than compound (65b), which in turn caused G0/G1 phase arrest in the same cells (102).

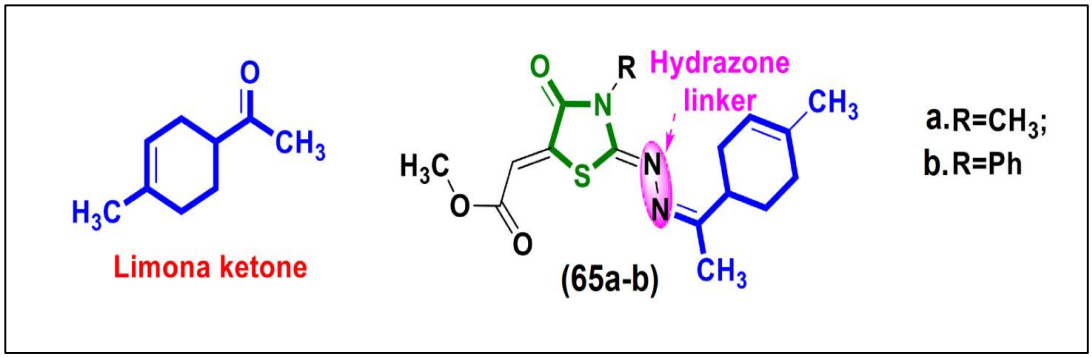


Figure (1-16): Structures of 4-thiazolidinone hybrids with limona ketone (65a-b)

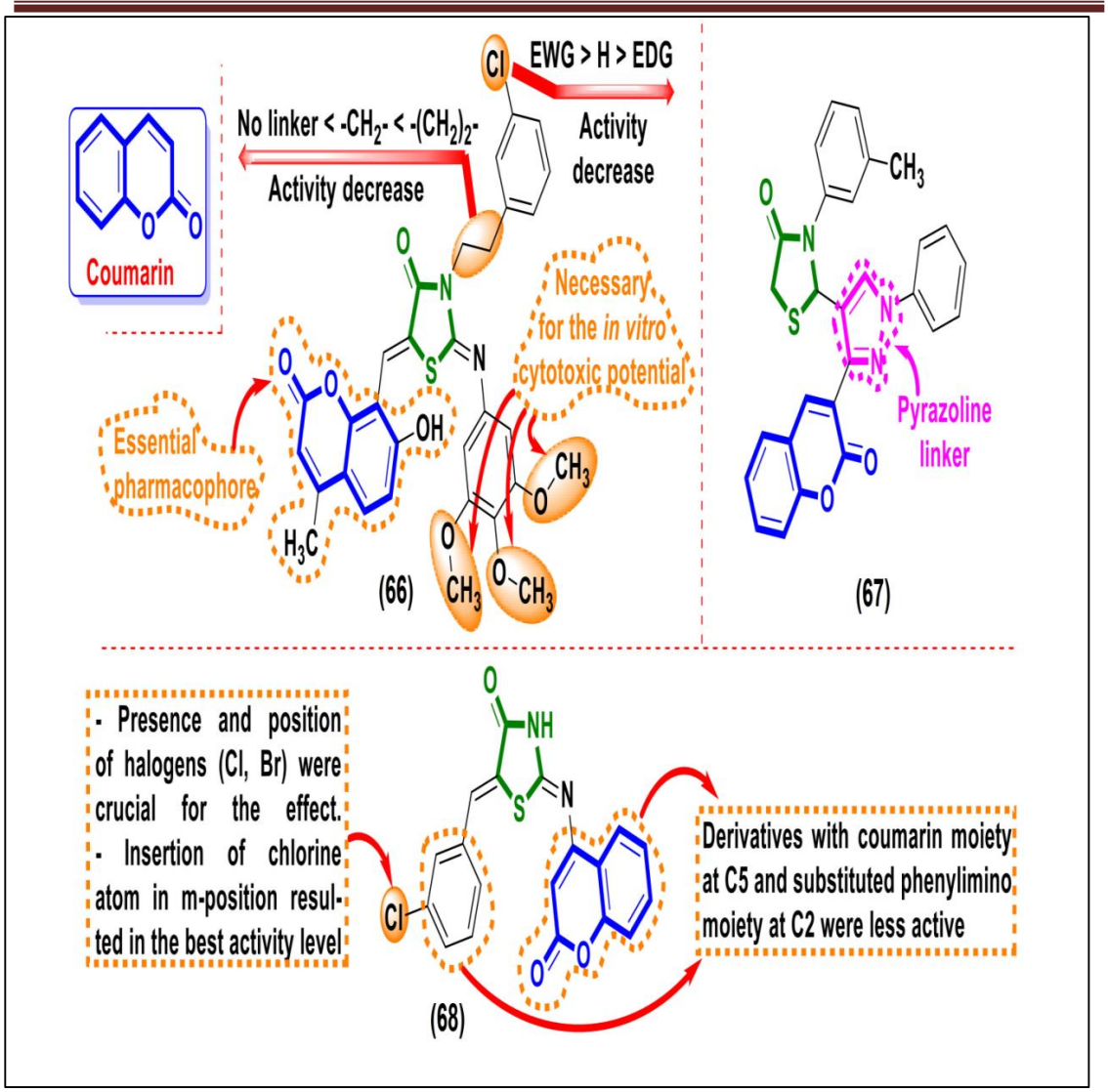
1.6.2. Coumarin 4-thiazolidinones hybrids

An appealing path in the development of anticancer drugs is the use of the coumarin motif. Zaki et al. reported the synthesis of new 4-thiazolidinone-umbelliferone (7-hydroxycoumarin) molecular hybrids (66-68) as potent cytotoxic agents. The most potent copound is (66), figure (1-16), (103) which had an IC50 value of 0.96 1.09 M and a selectivity index of 51.7, was the most active. Apoptosis was induced by the annexin-v/PI dual staining experiment, it affected several stages of the cell cycle, it effectively bound to CTDNA, and it inhibited tubulin polymerization at IC50 value of 2.65 0.47 M. In silico tests showed that compound (66) had a strong binding affinity for the /-tubulin receptor and had exceptional protein-ligand interactions and binding energy (104).

Figure (1-17): Structures of 4-thiazolidinone hybrids with coumarin motifs (66-68) in the molecules and empirical SAR correlations

1.6.3. Hybrids of 4-thiazolidinones with steroidal skeleton

In order to achieve and create beneficial pharmacological features, including strong anticancer activity, structural tuning of steroids, which are substantial and physiologically relevant natural chemicals, is possible. A



number of mono- and bis-4-thiazolidinone-containing hybrids with androstene derivatives were created by Tratrat et al. (105). Six cancer lines were used in the anticancer activity investigations for the synthesized hybrids: MDA-MB-453 (breast carcinoma), K562 (chronic myelogenous leukemia), HeLa (cervical adenocarcinoma), and MDA-MB-361 (melanoma) (breast adenocarcinoma), MRC-5, LS174 (colon adenocarcinoma), and A549 (lung carcinoma) (normal lung fibroblast line). On all tested lines, every one of the discovered compounds displayed selective, concentration-dependent cytotoxicity (106). The K562 and HeLa cell lines showed the greatest reaction to the test substance, with an average IC50 fluctuating about 10 M and an IC50 for the cisplatin reference compound for these lines of 5.7 M and 5.2 M, respectively. These

substances showed less toxicity to normal cells when compared to the positive control. Figure (1-18) shows that hybrids (69) and (70) were the most active, inhibiting the cell cycle in the sub-G1, S, and G2/M phases of HeLa cells and inducing apoptosis via both intrinsic and extrinsic pathways (107).

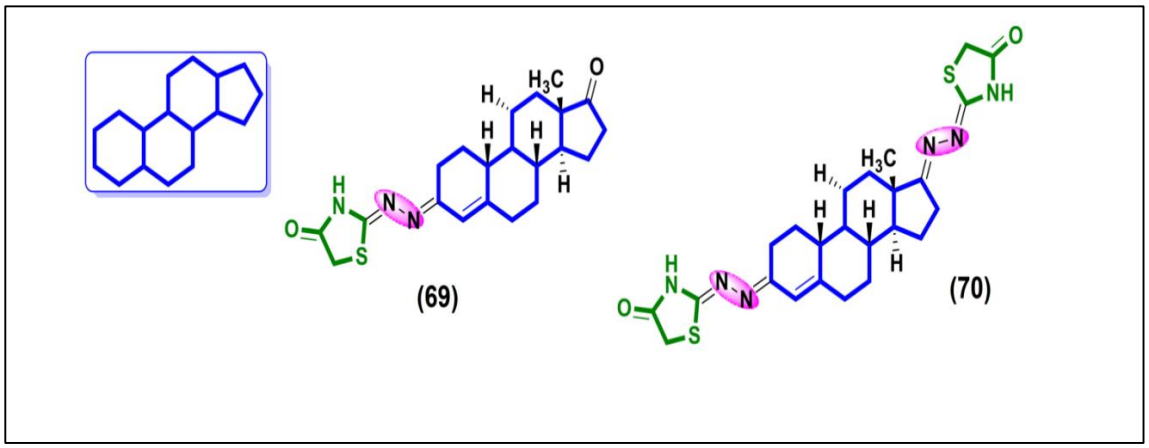


Figure (1-18): Structures of steroid-4-thiazolidinone hybrids (69) and (70)

1.7. The basics of microwave heating

A type of electromagnetic radiation that falls in between radio waves and infrared radiation is microwave irradiation (108). Its frequencies range from 300 (0.001 m) to 0.3 (1 m) GHz, and its wavelengths are 0.001–1 m (109). Numerous fields, including radio astronomy, communications, navigation, radar technology, spectroscopy, and heating, use microwaves. To avoid interferences (110), which are held by the Federal Communications Commission, two operating frequencies of micro-waves typically employed in industrial, scientific, and medical equipment are 0.915 and 2.450 GHz. Additionally, one of the microwave network analyzers that are commercially available is permitted to function at a variety of frequencies between 0.1 and 20 GHz (111). The first microwave oven to be sold commercially was created by Raytheon in 1947. Despite the widespread usage of microwave ovens for heating meals, research on using them to process materials is still in its early stages. Higher production quality, shorter processing times, lower prices,

innovative product development, and less risks are just a few advantages of microwave assisted research (112). Typically, energy is transferred to the materials during traditional thermal processing either through convection, radiation, or heat conduction through the surface of the materials. Thermal gradients are used to transfer energy during this process (54). The principle that electromagnetic energy changes to thermal energy, as opposed to heat transmission, is demonstrated by microwave irradiation, where energy is directly transmitted to materials through the interaction of microwaves with molecules. Therefore, an object's ability to interact with the microwave depends on its chemical structure. Additionally, composites or multi-phase materials having a larger dielectric loss and a variety of dielectric characteristics will be selectively heated by microwaves (113).

1.7.1. Appearance of the microwave

The publication trends over the past ten years make clear how quickly microwave syntheses technology has advanced. In all relevant study fields from 2010 to 2017 (114), a search of the terms "microwave" and "microwave, reaction" in the science direct search engine produced the corresponding results. This heating technology has become more and more popular and practical due to the expanding variety and accessibility of microwave equipment. Before 1990, controlled equipment utilizing a closed pressure vessel reactor led to a breakthrough in microwave technology (115). Microwave reactors are now available from a large number of well-known companies for a wide range of applications. By using safer reaction conditions and solvents, lowering the risk of accidents, avoiding product waste, and shortening the reaction time, microwave heating technology represents sustainable "green chemistry" for chemical reactions (116). For instance, using various microwave frequencies, it is possible to effectively synthesize nanoparticles in a lot

less time than when using conventional synthesis, which excludes the use of microwaves. Microwave heating applications in industry, particularly in drying and other thermal treatment procedures, underwent significant development and became commercially available in 1968. Due to its simplicity of use and low cost, manufacturers quickly discovered a variety of applications for microwave technology. It is easy to convert a common home microwave oven for use in chemical studies; up until the 1990s, this sort of laboratory equipment was the standard .However, in a domestic microwave oven, the irradiation power is generally controlled by on- and off-cycles of the magnetron without monitoring the reaction temperature. The lack of temperature and pressure control and even homogenous stirring liquid samples makes performing reproducible chemical synthesis troublesome in such devices (117). Consequently, specialized microwave devices created for laboratories and industry have emerged recently. Metals, especially steels with strong chemical resistance in the form of sheets, screens, and other shapes, are the primary structural materials utilized in the production of microwave devices (118). The safety of usage, efficiency, and durability of microwave devices are determined by the tight fit of all metal parts and by how well they are grounded and sealed. Microwave heating relies on a substance's capacity to absorb microwave energy and transform the electromagnetic energy into heat. Each reagent or solvent has a unique interaction with microwave energy (119). The polarity of the solvent is important because microwave irradiation depends mostly on the lattice parameter of a particular chemical; as a result, the more arctic the reactant, the better the reactions are at converting microwaves into heat. When compared to other techniques that do not involve microwaves, microwave irradiation enhances the homogeneity of the produced muck; the smaller the particle, the narrower the grain size distribution (120).

1.7.2. Basic microwave equipment

The three fundamental types of microwave equipment used in chemical processing are traveling-wave devices, mono (or single)-mode equipment, and multimode equipment. The most popular applicators are multimode ones, which are used in everything from home ovens to small-scale industrial dryers (121). They usually resemble a closed, rectangular Faraday cage, at least two of whose dimensions are longer than half the wavelength. A wide range of resonance modes emerge inside the cavity as a result of the microwaves' reflection off the hollow walls. Such reflections result in wave interference. Microwave activation and solvent-free conditions provide clean chemical reactions with increased reaction speeds, higher yields, and easier manipulation (118), figure (1-19).

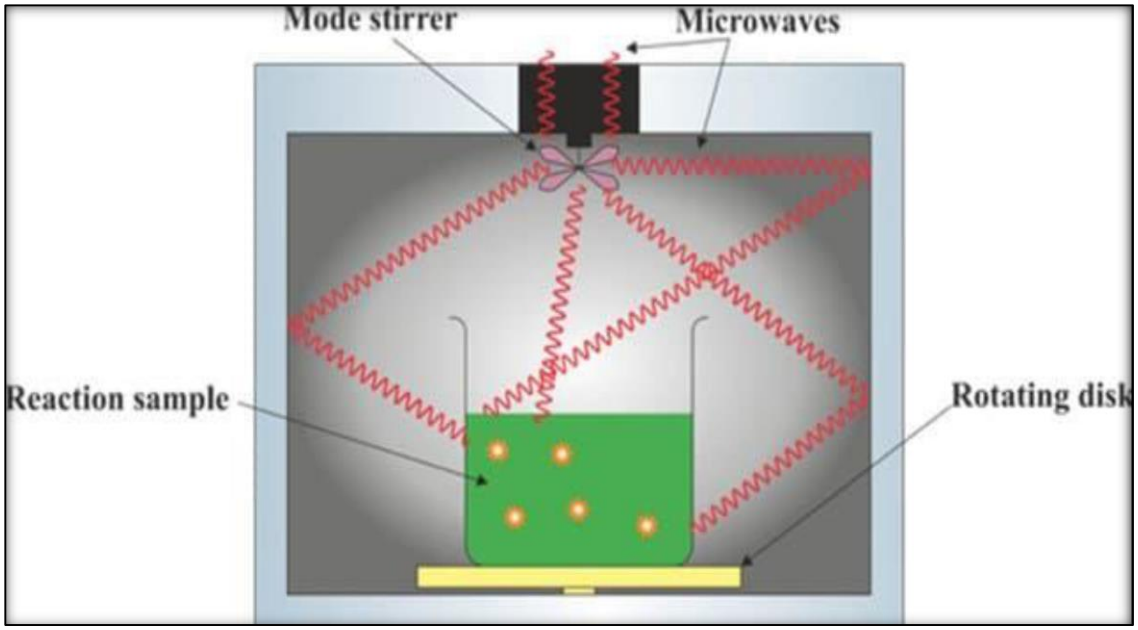


Figure (1-19): Domestic microwave oven

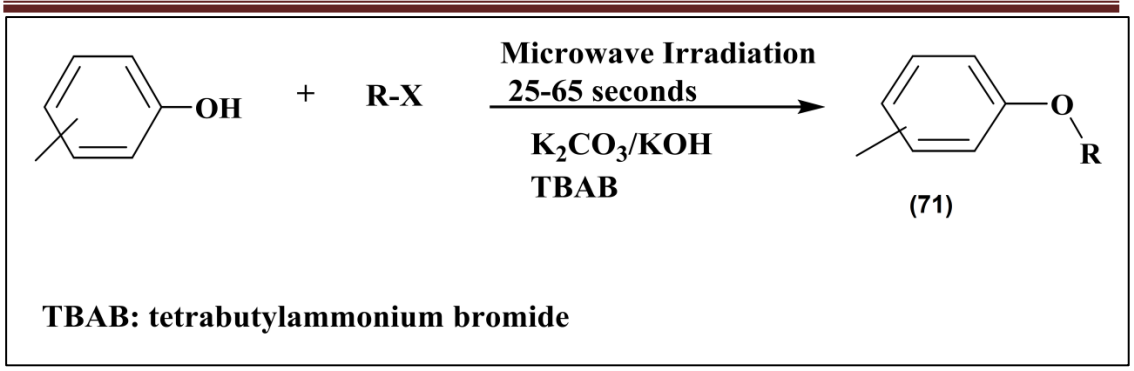
1.7.3. Microwave in organic synthesis

A wide range of organic reactions can be sped up with the help of the synthetic approach, which also produces high yields, higher selectivity,

fewer side products, and faster work-up and purification of the end products. Since many organic processes may be carried out without the use of solvents, microwave-assisted organic synthesis (MAOS) is regarded as a "green" method. Organic synthesis has been revolutionized by MAOS. Small molecules can be synthesized in a small portion of the time needed by conventional thermal techniques (122). This method has so quickly become recognized as a useful tool for expediting the drug discovery and development procedures. The study of chemical processes as a result of microwave radiation is known as (MAOS). Any substance that contains mobile electric charges will typically be heated by microwave radiation because it has high energy electric fields. It was discovered that microwave irradiation sped up reaction times and increased yields of the desired products (123). One of the most extensively studied uses of microwaves in chemical reactions is microwave-aided organic synthesis. A wide variety of organic reactions aided by microwave irradiation, such as Diels-Alder reactions between dienes and dienophiles, have been successfully carried out by chemists using both conventional and MW assisted methods, with and without solid support. Hydrogenation of lactams, Heck, Suzuki, and Mannish reactions, as well as hydrolysis, dehydration, esterification, epoxidation, reductions, condensations, and cycloaddition reactions (124).

1.7.3.1. Alkylation

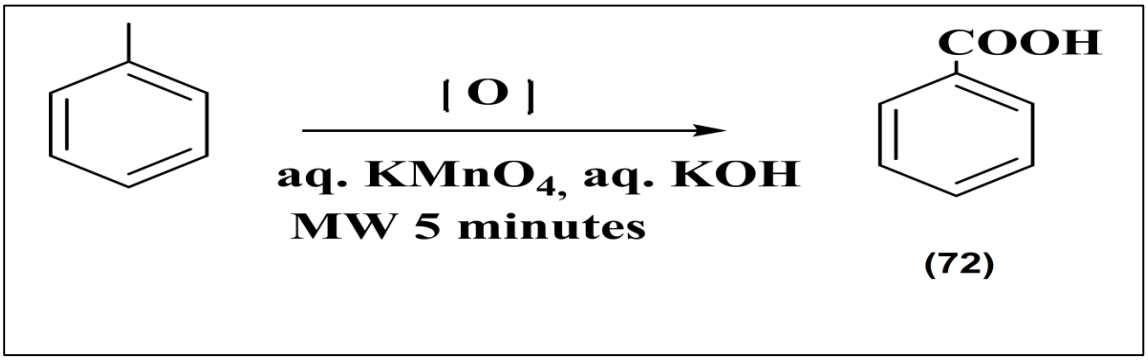
In order to *O*-alkylate phenols, Dariusz et al. employed microwave heating under solvent-free PTC conditions (125), scheme(1-19).



Scheme (1-19): Alkylation of phenols via microwave method

1.7.3.2. Oxidation

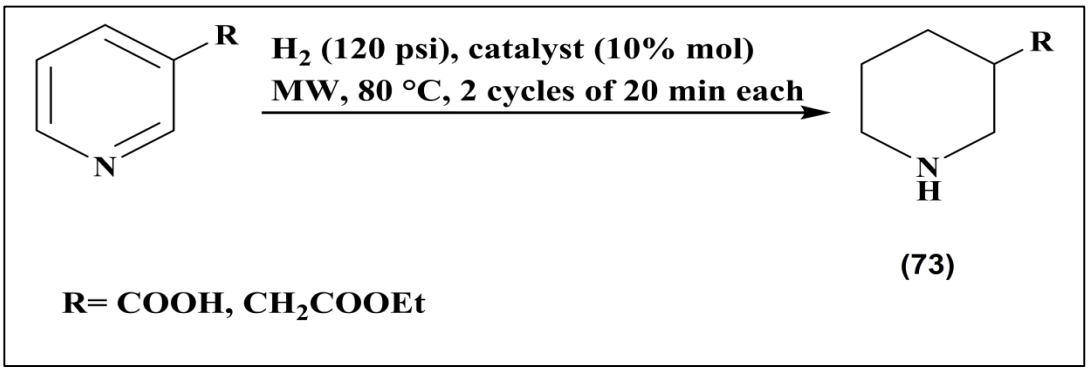
By using microwave radiation and $KMnO_4$, Grewal et al. converted toluene to benzoic acid (72) (126), scheme (1-20).



Scheme (1-21): Oxidation of arenas using microwave technique

1.7.3.3. Reduction

Optimization of the process for microwave-assisted hydrogenation by Piras et al. resulted in the conversion of the substituted pyridines into the matching piperidines (73) (127), scheme(1-21).



Scheme (1-21): Reduction of pyridines by microwave irradiation

Aims of the study

1,3-Thiazolidin-4-ones represent very powerful kind of heterocyclic derivatives in pharmaceutical field and encourage researchers to explore novel drug candidates, so the present work aims to synthesize a series of new 1,3-thiazolidin-4-one derivatives containing 1,3,4-thiadiazole moiety using microwave heating method and then evaluate their antibacterial activity athwart Gram-positive and Gram-negative bacteria.Inaddition as well as comparing effects with amoxicillin-clavulanate as a standard drug.

Chapter Two

Experimental Part

2.1. Materials

The chemicals used were supplied by the following companies as outlined in table (2-1**).**

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

Chemicals	Molecular formula	M.Wt g/mol	Purity %	Supplied companies
Thiosemicarbazide	CH_5N_3S	91.13	98	Redial de jean
Sodium carbonate (anhydrous)	Na_2CO_3	105.98	99	Merck, Germany
Ethanol (absolute)	CS_2	75.94	99	Scharlau, Spain
Carbon disulfide	C_2H_6O	46.06	99.9	Scharlau, Spain
Hydrochloric acid (Conc.)	HCl	36.46	99	Merck, Germany
Sodium nitrite	$NaNO_2$	68.99	99	BDH, England
2-Hydroxy benzaldehyde	$C_7H_6O_2$	122.12	98	SD Fine, India
Sodium hydroxide	NaOH	39.99	99	BDH, England
4-Chloroaniline	C_6H_6NCl	127.57	99	BDH, England
2,4-Dichloroaniline	$C_6H_5NCl_2$	162.01	95	BDH, England
4-Nitroaniline	$C_6H_6N_2O_2$	138.12	98	Fluka
3-Nitroaniline	$C_6H_6N_2O_2$	138.12	99	Fluka
2-Nitroaniline	C_7H_9NO	123.16	98	BDH, England
2-Methoxyaniline	C_7H_9NO	123.16	98	BDH, England
4-Aminophenol	C_6H_7NO	109.13	99	BDH, England
3-Aminophenol	C_6H_7NO	109.13	99	BDH, England
2-Aminophenol	C_6H_7NO	109.13	99	BDH, England
2,4-dimethylaniline	$C_8H_{11}N$	121.18	99	Fluka
α-Chloroacetic acid	$C_2H_2Cl_2O$	112.94	99	Fluka

N,*N*-Dimethylformamide	C_3H_7NO	73.10	99.8	Sigma-Aldrich
Diethyl ether	$C_4H_{10}O$	74.12	99.5	Scharlau, Spain
n-Hexane	C_6H_{14}	86.17	99	Scharlau, Spain
Ethyl acetate	$C_4H_8O_2$	88.10	99	BDH, England
Iodine	I_2	253.80	99.5	GCC, Germany
Dimethyl sulfoxide	C_2H_6OS	78.13	99	BDH, England

2.2. Equipment

1. Monitoring reactions done by TLC test using silica plate (60 F_{254}**)** and iodine as developer.
2. Melting points have been measured via Electro thermal Stuart SMP 30 capillary melting point apparatus.
3. (FTIR) spectra have been deduced using SHIMADZU FTIR–8400S Infrared Spectrophotometer at University of Kerbala.
4. ^{1}H NMR spectra have been deduced on Avance III Bruker, Germany at 400 MHz NMR spectrometer using DMSO-d_6 as solvent and TMS as reference at University of Basra.
5. ^{13}C NMR spectra have been recorded on Avance III Bruker, Germany at 100 MHz NMR spectrometer using DMSO-d_6 as solvent and TMS as reference at University of Basra.
6. Elemental analyses measurements were done by Perkin Elmer 300A at Tehran University, Iran.
7. Domestic microwave oven in crucible was used to carried out reactions.
8. Autoclave, supplied from Prestige Medical-England, was used to sterilize agar media,.

9. Incubator, supplied from Binder-Germany, was used to maintain different degrees of temperature required to growth organism,.

2.3. Preparation methods

2.3.1. Preparation of 2-Amino-5-mercapto-1,3,4-thiadiazole (1)

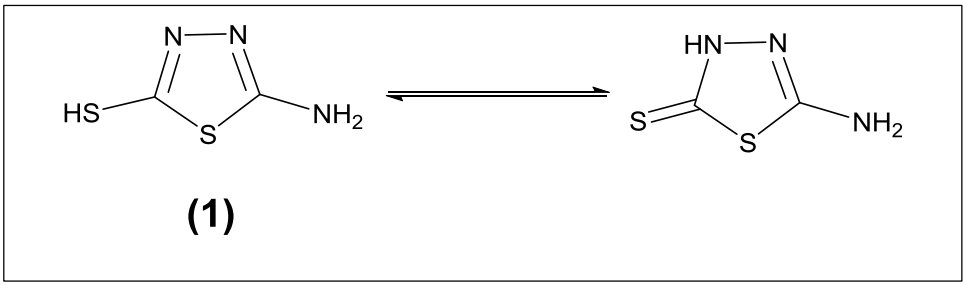


Figure (2-1): Structure of compound (1)

(9.1g , 100 mmol) of thiosemicarbazide and (5.3 g, 50 mmol) of anhydrous sodium carbonate in (50 mL) of absolute ethyl alcohol were stirred for (10 min), then (10 mL) of carbon disulfide was added. The mixture was left under reflux around 70 ºC for (24 hrs). At end of reaction, the solvent was evaporated under vacuum and the solid was dissolved in (100 mL) of distilled water and filtered then neatly acidified using conc. (HCl) affording yellow solid that filtered and dried, then purified via recrystallization using distilled water yielding white crystalline product, (10.64 g, 80%), mp 230-232ºC, Lit. 231°C.

2.3.2. Preparation of 2-Hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)benzaldehyde (2)

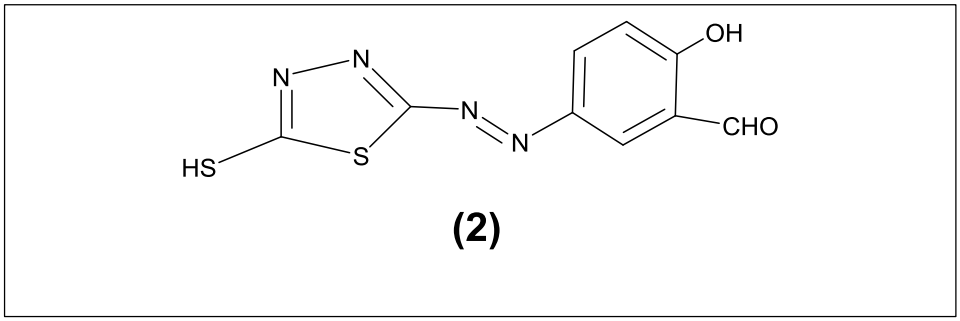
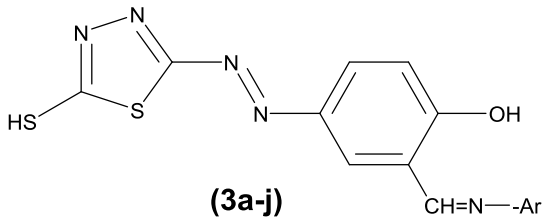


Figure (2-2): Structure of compound (2)

2-Amino-5-mercapto-1,3,4-thiadiazole (1) (3.99 g, 30 mmol) was dissolved in hydrochloric acid (12 mL) and distilled water (25 mL), after that sodium nitrite (2.07 g, 30 mmol) in (25 mL) of distilled water was added drop wise with stirring at (0°C). Phenoxide salt solution was prepared through dissolving salicylaldehyde (3.66 g, 30 mol) in (25 mL) of sodium hydroxide 10%w/v at (0ºC). The diazonium salt solution was added slowly to sodium pheoxide salt solution. The mixture was left one hour for completing precipitation process. The orange solid product was recrystallized by ethyl alcohol giving (2), yield (4.4 g, 55%), m.p. 169-171 ºC.

2.3.3. General procedure for the preparation of imines (3a-j)



(3a-j)

Ar= (a) 2-OCH_3-Ph-, (b) 2,4-di-CH_3-Ph-, (c) 2,4-di-Cl-Ph-, (d) 4-Cl-Ph-, (e) 4-NO_2-Ph-
(f) 3-NO_2-Ph-, (g) 2-NO_2-Ph-, (h) 4-OH-Ph-, (i) 3-OH-Ph-, (j) 2-OH-Ph-

Figure (2-3): Structures of compounds (3a-j)

A mixture of azothiadiazole-aldehyde (2) (0.283 g, 1 mmol), and some aromatic primary amines (1 mmol) dissolved in ethyl alcohol (1 mL) was heated by microwave oven at (300W) for (10 minutes). End of reactions was detected using TLC (*n*-hexane: Ethyl acetate, 1:2). The crude yields were purified via recrystallization from ethyl alcohol. Some physical properties and other characteristics for compounds (3a-j) were shown in table (2-2).

*4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)-2-(((2-methoxyphenyl)imino)methyl)phenol **(3a)**

*2-(((2,4-dimethylphenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3b)**

*2-(((2,4-dichlorophenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3c)**

*2-(((4-chlorophenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3d)**

*4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)-2-(((4-nitrophenyl)imino)methyl)phenol **(3e)**

*4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)-2-(((3-nitrophenyl)imino)methyl)phenol **(3f)**

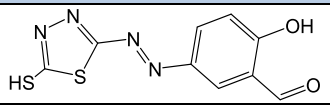
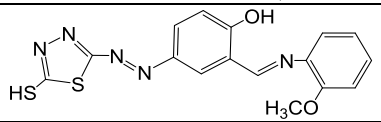
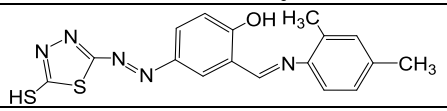
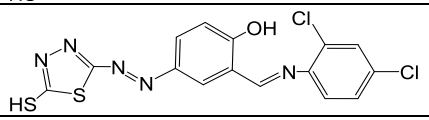
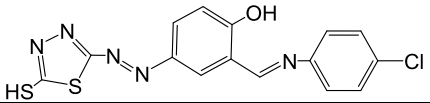
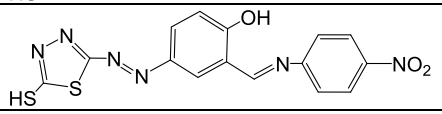
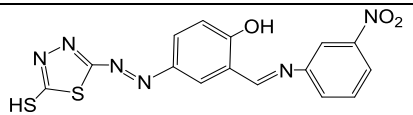
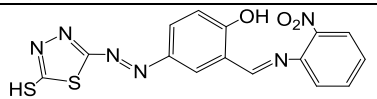
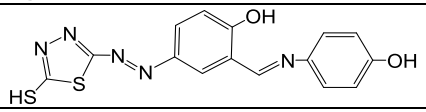
*4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)-2-(((2-nitrophenyl)imino)methyl)phenol **(3g)**

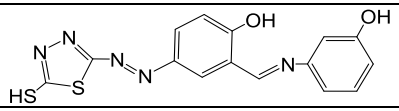
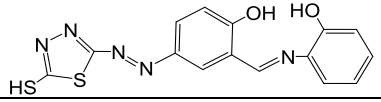
*2-(((4-hydroxyphenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3h)**

*2-(((3-hydroxyphenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3i)**

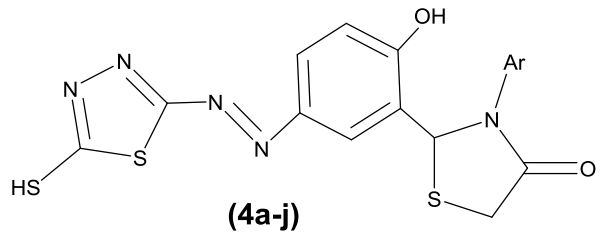
*2-(((2-hydroxyphenyl)imino)methyl)-4-((*E*)-(5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenol **(3j)**

Table (2-2): Some physical properties of imine derivatives (3a-j)

Comp. No	Structure	Formula	M.Wt	Color	M.P. °C	R_f *n*-hexane : EtOAc 1 : 2	Yield %
2		$C_9H_6N_4O_2S_2$	266.29	Orange	169-171	o.68	55
3a		$C_{16}H_{13}N_5O_2S_2$	371.43	Red	152-154	0.67	76
3b		$C_{17}H_{15}N_5OS_2$	369.46	Orange	132-134	0.82	80
3c		$C_{15}H_9N_5OS_2Cl_2$	410.29	Yellow	129-131	0.86	83
3d		$C_{15}H_{10}N_5OS_2Cl$	375.85	Yellow	121-123	0.84	72
3e		$C_{15}H_{10}N_6O_3S_2$	386.40	Red	118-120	0.75	89
3f		$C_{15}H_{10}N_6O_3S_2$	386.40	Yellow	141-143	0.72	85
3g		$C_{15}H_{10}N_6O_3S_2$	386.40	Orange	138-140	0.63	61
3h		$C_{15}H_{11}N_5O_2S_2$	357.41	Dark red	160-162	0.71	68

3i		$C_{15}H_{11}N_5O_2S_2$	357.41	Dark red	169-171	0.69	73
3j		$C_{15}H_{11}N_5O_2S_2$	357.41	Dark red	154-156	0.62	76

2.3.4. General procedure for the preparation of 1,3-Thiazoliidin-4-ones (4a-j)



(4a-j)

Ar= (a) 2-OCH_3-Ph-, (b) 2,4-di-CH_3-Ph-, (c) 2,4-di-Cl-Ph-, (d) 4-Cl-Ph-, (e) 4-NO_2-Ph-
(f) 3-NO_2-Ph-, (g) 2-NO_2-Ph-, (h) 4-OH-Ph-, (i) 3-OH-Ph-, (j) 2-OH-Ph-

Figure (2-3): Structures of compounds (4a-j)

A mixture of each Schiff bases (3a–j) (1 mmol), mercaptoacetic acid (1 mmol) and (DMF) as solvent (1 mL) has been heated around (300W) for (15 min). Completion of reactions has been monitored using thin-layer chromatography (*n*-hexane: Ethyl acetate, 1:2). The crude products were purified through recrystallization from ethanol. Some properties of compounds (4a-j) were listed in table (2-3).

*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(2-methoxyphenyl)thiazolidin-4-one **(4a)**

*(*E*)-3-(2,4-dimethylphenyl)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)thiazolidin-4-one **(4b)**

***(*E*)-3-(2,4-dichlorophenyl)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)thiazolidin-4-one **(4c)**

*(*E*)-3-(4-chlorophenyl)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)thiazolidin-4-one **(4d)**

*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(4-nitrophenyl)thiazolidin-4-one (**4e**)

*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(3-nitrophenyl)thiazolidin-4-one **(4f)**

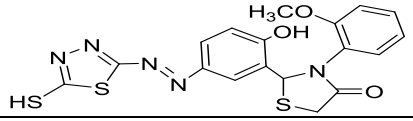
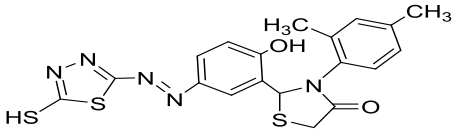
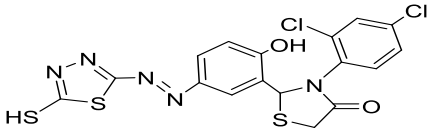
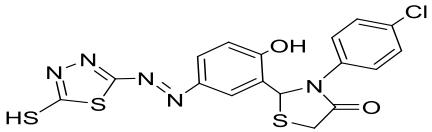
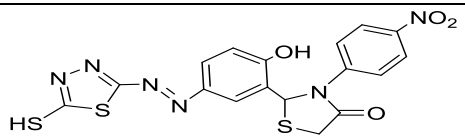
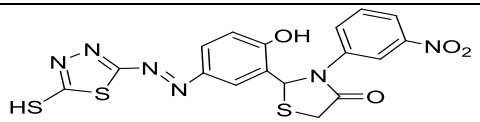
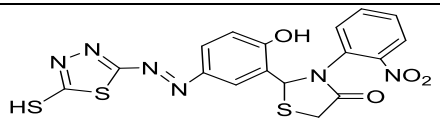
*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(2-nitrophenyl)thiazolidin-4-one **(4g)**

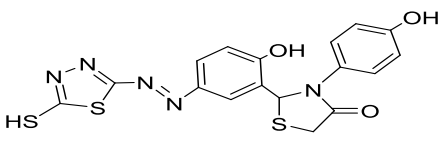
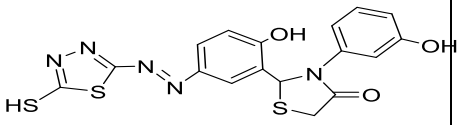
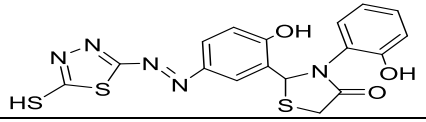
*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(4-hydroxyphenyl)thiazolidin-4-one **(4h)**

*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(3-hydroxyphenyl)thiazolidin-4-one **(4i)**

*(*E*)-2-(2-hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)phenyl)-3-(2-hydroxyphenyl)thiazolidin-4-one **(4j)**

Table (2-3): Some physical properties of 1,3-thiazolidin-4-one derivatives (4a-j)

Comp. No	Structure	Formula	M.Wt	Color	mp °C	R_f *n*-hexane: EtOAc 1 : 2	Yield %
4a		$C_{18}H_{15}N_5O_3S_3$	445.53	Dark red	176-178	0.69	72
4b		$C_{19}H_{17}N_5O_2S_3$	443.56	Dark red	143-145	0.78	78
4c		$C_{17}H_{11}Cl_2N_5O_2S_3$	484.39	Dark red	164-166	0.81	87
4d		$C_{17}H_{11}N_6O_4S_2Cl$	449.95	Dark red	150-152	0.62	81
4e		$C_{17}H_{12}N_6O_4S_3$	460.50	Dark red	184-186	0.74	90
4f		$C_{17}H_{12}N_6O_4S_3$	460.50	Dark red	178-180	0.69	63
4g		$C_{17}H_{12}N_6O_4S_3$	460.50	Dark red	183-185	0.70	58

4h		$C_{17}H_{13}N_5O_3S_3$	431.50	Dark red	227-229	0.74	87
4i		$C_{17}H_{13}N_5O_3S_3$	431.50	Dark red	229-231	0.82	85
4j		$C_{17}H_{13}N_5O_3S_3$	431.50	Dark red	226-228	0.69	87

2.4. Antibacterial Study

2.4.1. Preparing McFarland solution

McFarland solution (tube No. 0.5) consists of solution (A) which was prepared by dissolving 1.75g of Barium chloride $BaCl_2.H_2O$ in 100 ml of distilled water and solution (B) which was prepared by adding 1 ml of concentrated H_2SO_4 in 100 ml of distilled water. Immediately, 0.5 ml of solution (A) was added to 99.5 ml of solution (B). This resulting solution was used for comparison to give the approximately number of germ cells (1.5×10^8 cell /ml) in bacterial cell suspension which is used in antibacterial activity (130).

2.4.2. Preparing bacterial suspension

Brain heart infusion broth (BHI) broth were inoculated with tested bacterial isolates and incubated at 37 ^oC for 24h, then their turbidity was compared against standard McFarland solution No. (0.5).

Then an amount of 0.1 ml of isolates broth containing approximately (1.5×10^8 cell /ml), was spread it onto Muller Hinton agar plate by using a cotton swab and the plate approximately 60^o for each direction then plates were kept to stand upside down at room temperature for 15 min, the plat put in an incubation at 37 C for 24 h and by sterile rule the diameter of inhibition zone was determine (130).

2.4.3. Preparing implant mediums (Agar)

The Muller Hinton agar medium was prepared by dissolving 38 g in 1000 ml of distilled water, boiled to dissolve the agar completely, sterilized by autoclave at 121 ^oC for 15 min and allowed to cool down to 45 ^oC. After that, the agar will pour into petridishes so it will be ready to be use (130).

2.4.4. Antibacterial tests method

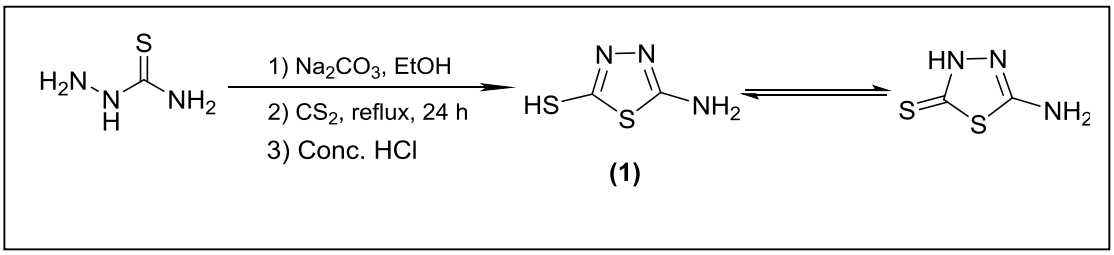
The antibacterial test has been done in order to disc diffusion method [128]. The antibacterial effect of all target 1,3-thiazolidin-4-one compounds **(4a-j)** have been examined *in vitro* athwart *Staphylococcus aurous* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria). The agar plates have been surface-inoculated uniformly from both culture of the tested bacteria. In the solidified medium suitably spaced apart holes were made all 6 mm in diameter. The holes were filled with 40 µL of the prepared compounds (20 mg of each compound dissolved in 1mL of DMSO). The plates have been incubated at 37 ^{o}C for 24 hrs for both bacteria. The zones of inhibition of bacterial growth around the discs have been determined in (mm).

Chapter Three

Results and Discussion

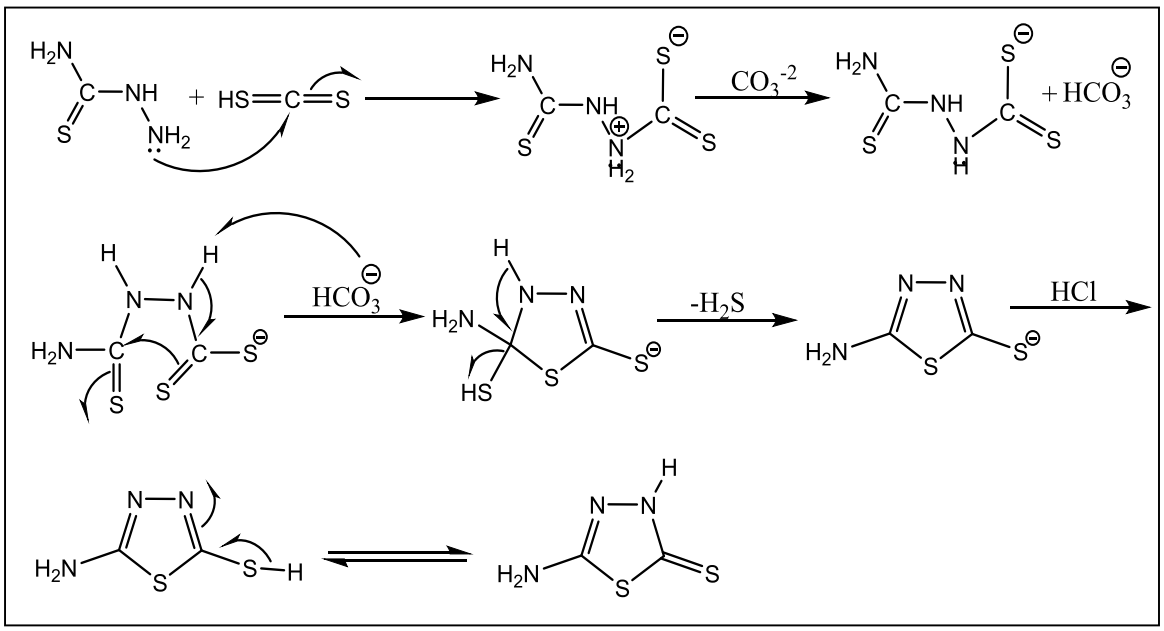
3.1. Synthesis of 2-Amino-1,3,4-thiadiazole-5-thiol (1)

The initial compound 2-Amino-5-mercapto-1,3,4-thiadiazole (1) has been prepared via cyclization reaction of thiosemicarbazide with carbon disulfide in basic medium using absolute ethyl alcohol as solent, the producing sulfide salt was acidified to result compound (1) as shown in scheme (3-1).



Scheme (3-1): Synthesis of 2-Amino-1,3,4-thiadiazole-5-thiol (1)

The mechanism suggested for forming compound (1) was outlined in scheme (3-2) .



Scheme (3-2): Reaction mechanism for foring compound (1)

Infrared spectrum of compound **(**1**)** appeared two sharp peaks around 3394 and 3275 cm^{-1} assigned to (NH_2) stretching, (N-H) stretching. of thione form pointed at 3093 cm^{-1}, the two peaks around 2920 and 2777 cm^{-1} attributed to intramolecularly hydrogen bonded of (N-H) stretching, the shoulder at 2565

cm^{-1} for (S-H) stretching, (C=N) stretching of thiadiazole ring recorded at 1597 scm^{-1}, bending of (N-H) as strong peak around 1535 cm^{-1}, (C-N) stretching. pointed peak at 1498 cm^{-1}, (C=S) stretching. appeared around 1064 cm^{-1}, (C-S) stretching. pointed at 671 cm^{-1}

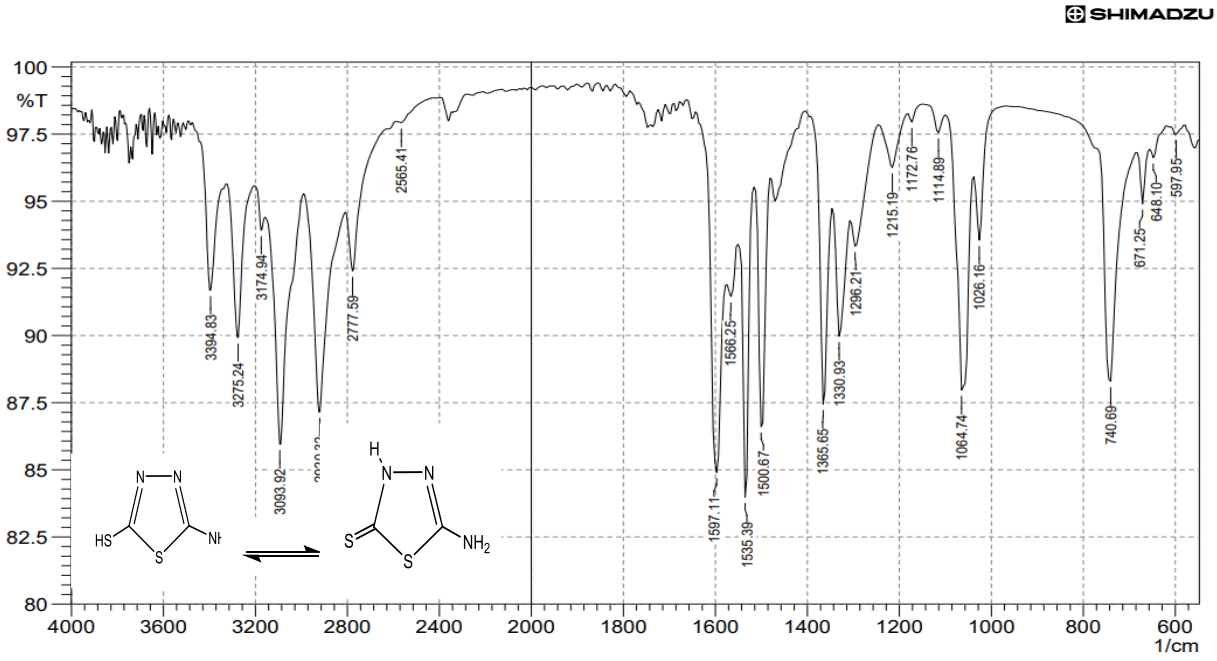
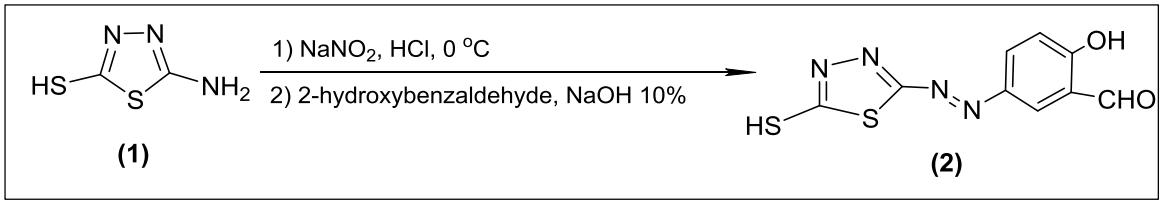


Figure (3-1): FT-IR spectrum of compound (1)

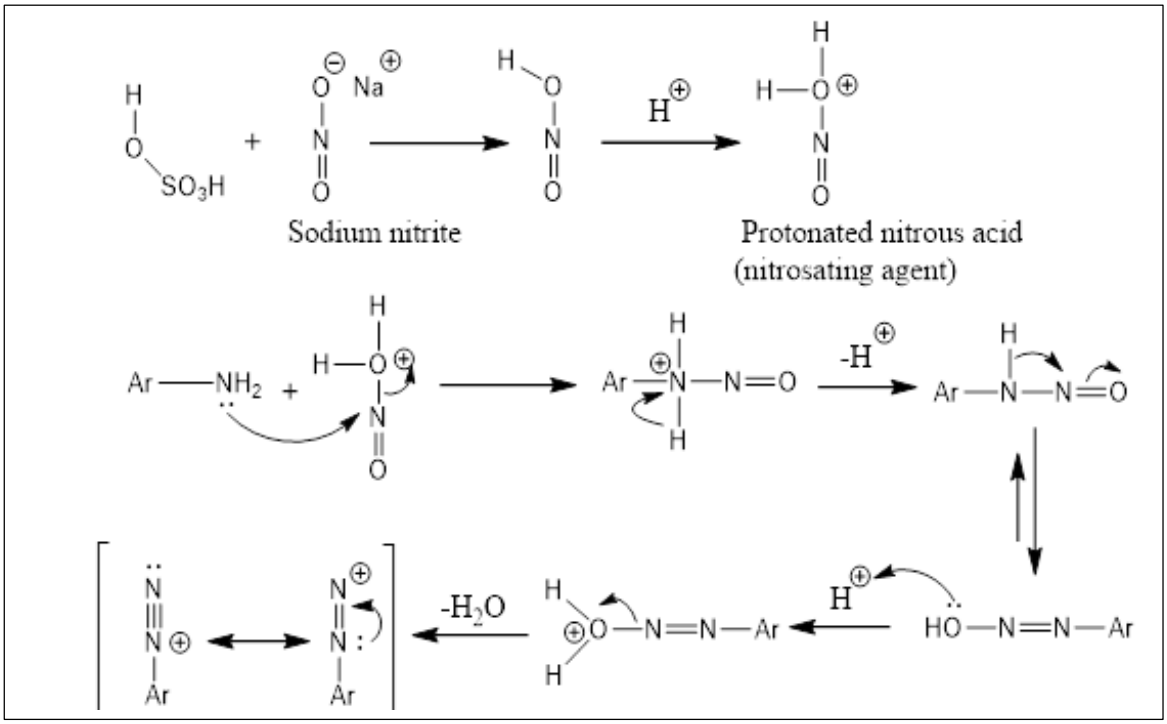
3.2. Synthesis of 2-Hydroxy-5-((5-mercapto-1,3,4-thiadiazol-2-yl)diazenyl)benzaldehyde (2)

Amino function in 2-amino-5-mercapto-1,3,4-thiadiazole **(1)** was converted to azo group via reaction with nitrous acid, the forming diazonium salt was coupled with *o*-hydroxybenzaldehyed dissolved in sodium hydroxide solution giving aldehyde derivative **(2)**, scheme (3-3).

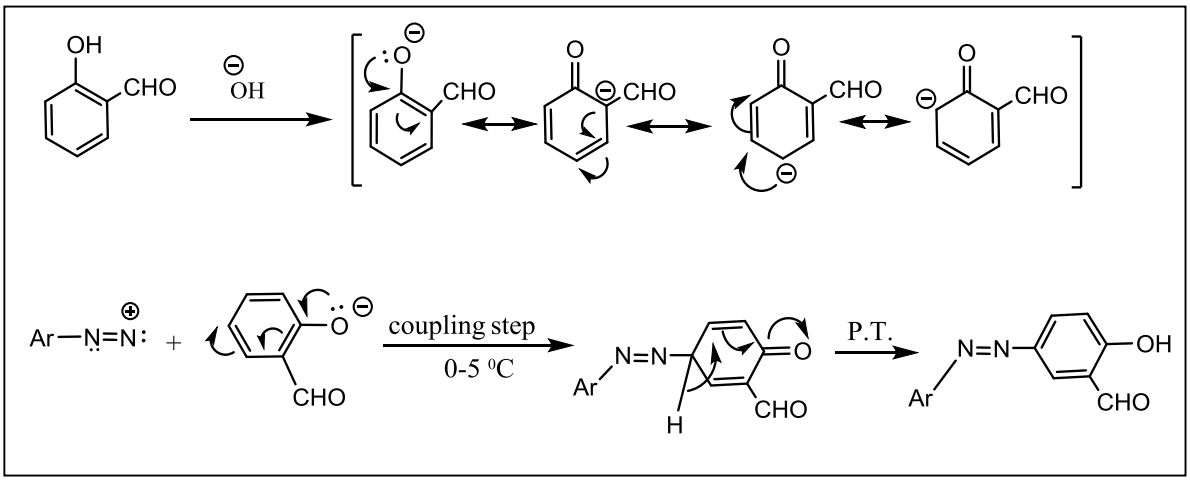


Scheme (3-3): Synthesis of compound (2)

The reaction mechanisms were indicated in schemes (3-4) and (3-5).



Scheme (3-4): Mechanism of Diazotization of primary amine



Scheme (3-5): Mechanism of azo-coupling reaction

Infrared spectrum of compound (2) showed bands of (O-H) str, (C=O) str, and (N=N) str around 3128 cm^{-1}, 1647 cm^{-1}, and 1427 cm^{-1}, while the sharp bands of (NH_2) str around (3394 cm^{-1}, and 3275 cm^{-1}) were disappeared, the band of thiadiazolic (C=N) str was overlapped with carbonyl absorption at1647 cm^{-1}. Other peaks were found in table (3-1).

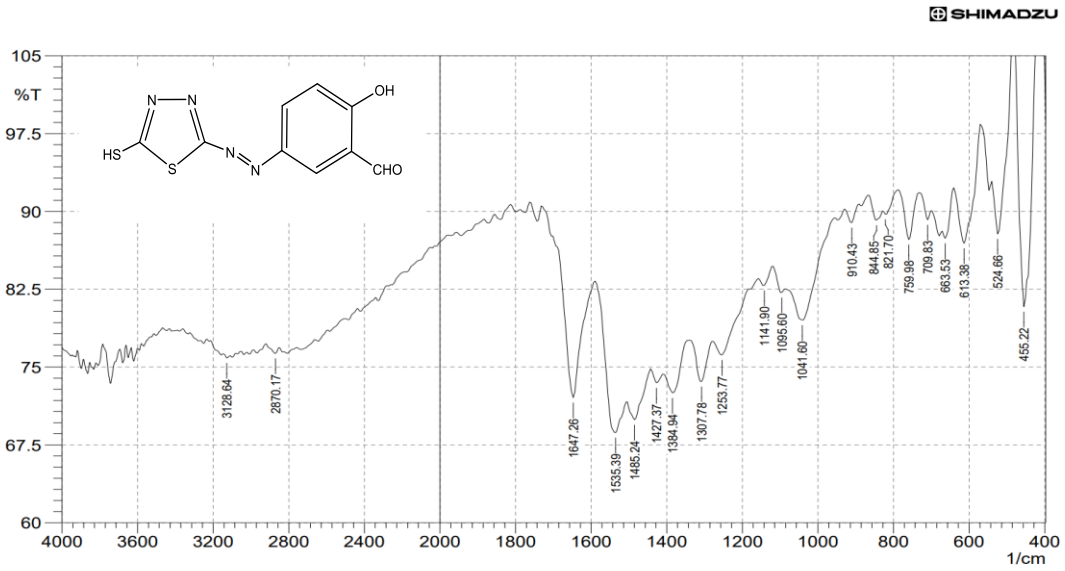
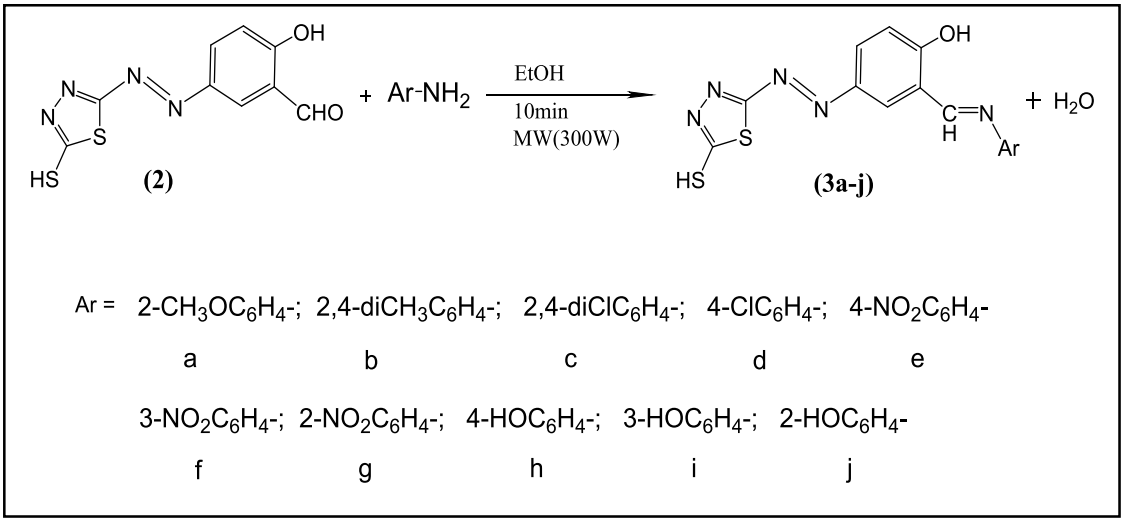


Figure (3-2): FT-IR spectrum of compound (2)

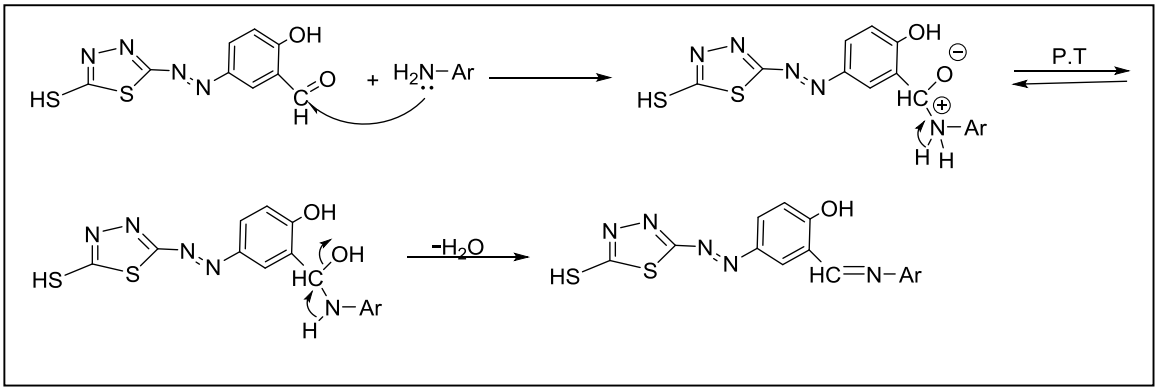
3.3. Synthesis of imine derivatives (3a-j)

Schiff bases **(3a-j)** were synthesized through condensation reaction between Azoaldehyde **(2)** and some aniline derivatives (2-methoxyaniline, 2,4-dimethylaniline, 2,4-dichloroaniline, 4-chloroaniline, 4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-aminophenol, 3-aminophenol, and 2-aminophenol) in very small amounts of absolute ethyl alcohol under microwave irradiation yielding Schiff bases **(3a-j)** as platforms for preparing target compounds, scheme (3-6).



Scheme (3-6): Synthesis of imines (3a-j)

The condensation of amino function with carbonyl group without catalyst was shown in scheme (3-7).



Scheme (3-7): Mechanism of imine formation without catalyst

(IR) data of compounds (3a-j) pointed the absence of (C=O) stretching at 1647 cm^{-1} and appearance of (C=N) stretching of imines around 1612 cm^{-1}, 1600 cm-1, 1612 cm^{-1}, 1612 cm^{-1}, 1597 cm^{-1}, 1604 cm^{-1}, 1620 cm^{-1}, 1608 cm^{-1}, 1597 cm^{-1}, and 1608 cm^{-1} correspondingly. It is important to refer that absorption of (C=N) str of thiadiazole ring may be overlapped with peak of Schiff bases (C=N) str. Other peaks were interpreted in table (3-1).

Table (3-1): IR data of imine compounds (3a-j) in cm^{-1}

Com .NO	ν(O-H)	ν(N-H) thione form	νC-H) aroma.	ν(C=O)	ν(C=N) imine	ν(C=N) thiadiazole	ν(C=C) benzene	ν(N=N)	ν(C=S) thione form	Others
2	3128	3128 overla-pped	3050	1647	-	overlapped with carbonyl	1535 1485	1427	1041	2870 (CH)str aldehyde
3a	3275	3128	3047	-	1612	overlapped with ν(C=N) imine	1531 1500 1458	1420	1053	2835 (CH_3)str
3b	3375	3147	3028	-	1600	overlapped with ν(C=N) imine	1531 1500 1446	-	1057	2916 (CH_3)str
3c	3286	3151	3050	-	1612	overlapped with ν(C=N) imine	1535 1485	1423	1053	1103 (C-Cl)str
3d	3163	3109	3050	-	1612	overlapped with ν(C=N) imine	1539 1492	1427	1057	1095 (C-Cl)str
3e	3313	3178	3050	-	1597	overlapped with ν(C=N) imine	1450	1427	1057	1500 1269 (NO_2)str
3f	3275	3120	3078	-	1604	overlapped with ν(C=N) imine	1485	1427	1053	1523 1265 (NO_2)str
3g	3302	3113	3082	-	1620	overlapped with ν(C=N) imine	1562	1431	1099	1500 1249 (NO_2)str
3h	3336 3279	3140	3028	-	1608	overlapped with ν(C=N) imine	1554 1508	-	1053	
3i	3360	3163	3050	-	1597	overlapped with ν(C=N) imine	1535 1496	1427	1053	
3j	3236	3140	overla-pped with N-H	-	1608	overlapped with ν(C=N) imine	1535 1496 1462	1431	1057	

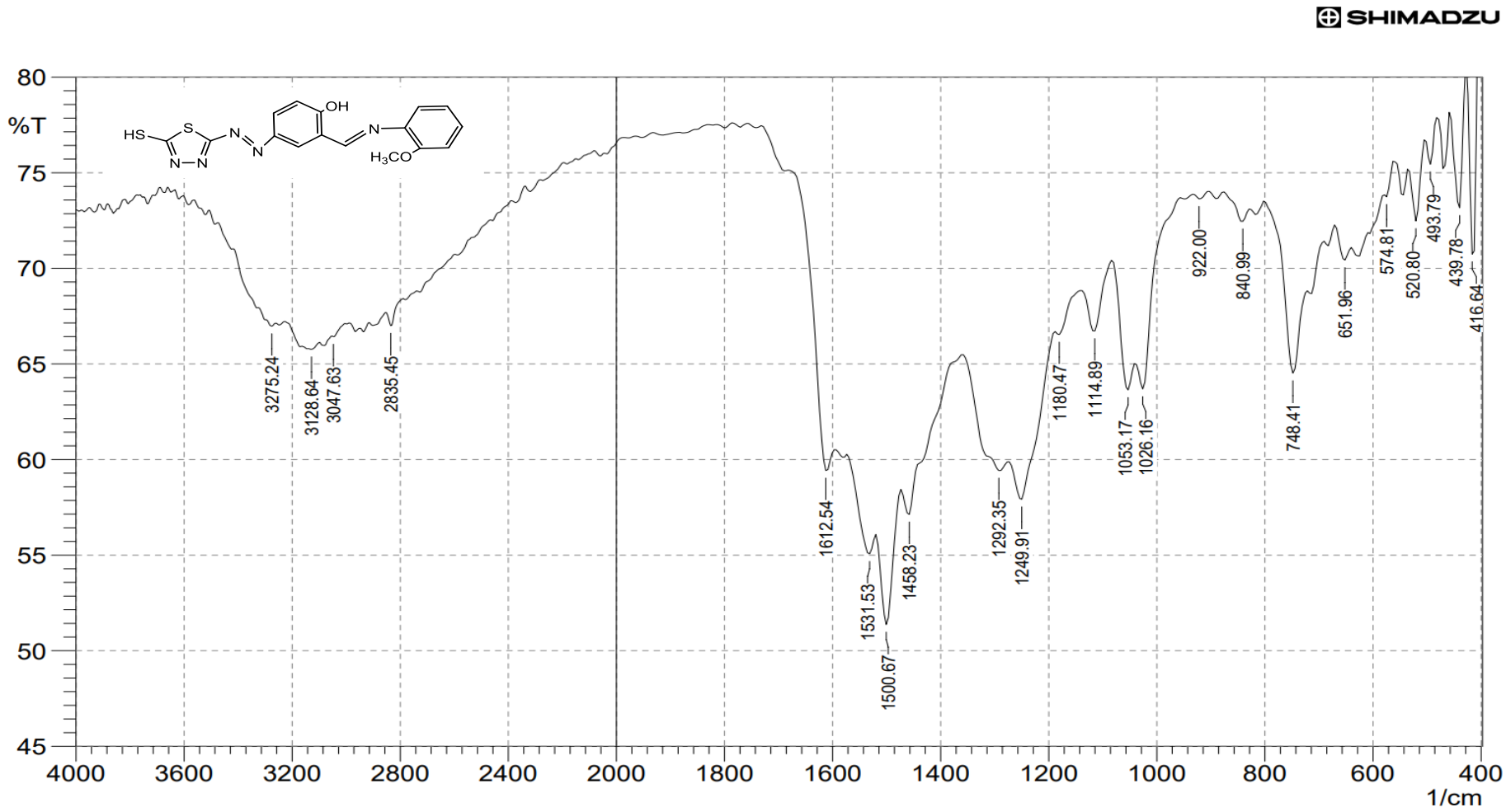


Figure (3-3): FT-IR spectrum of compound (3a)

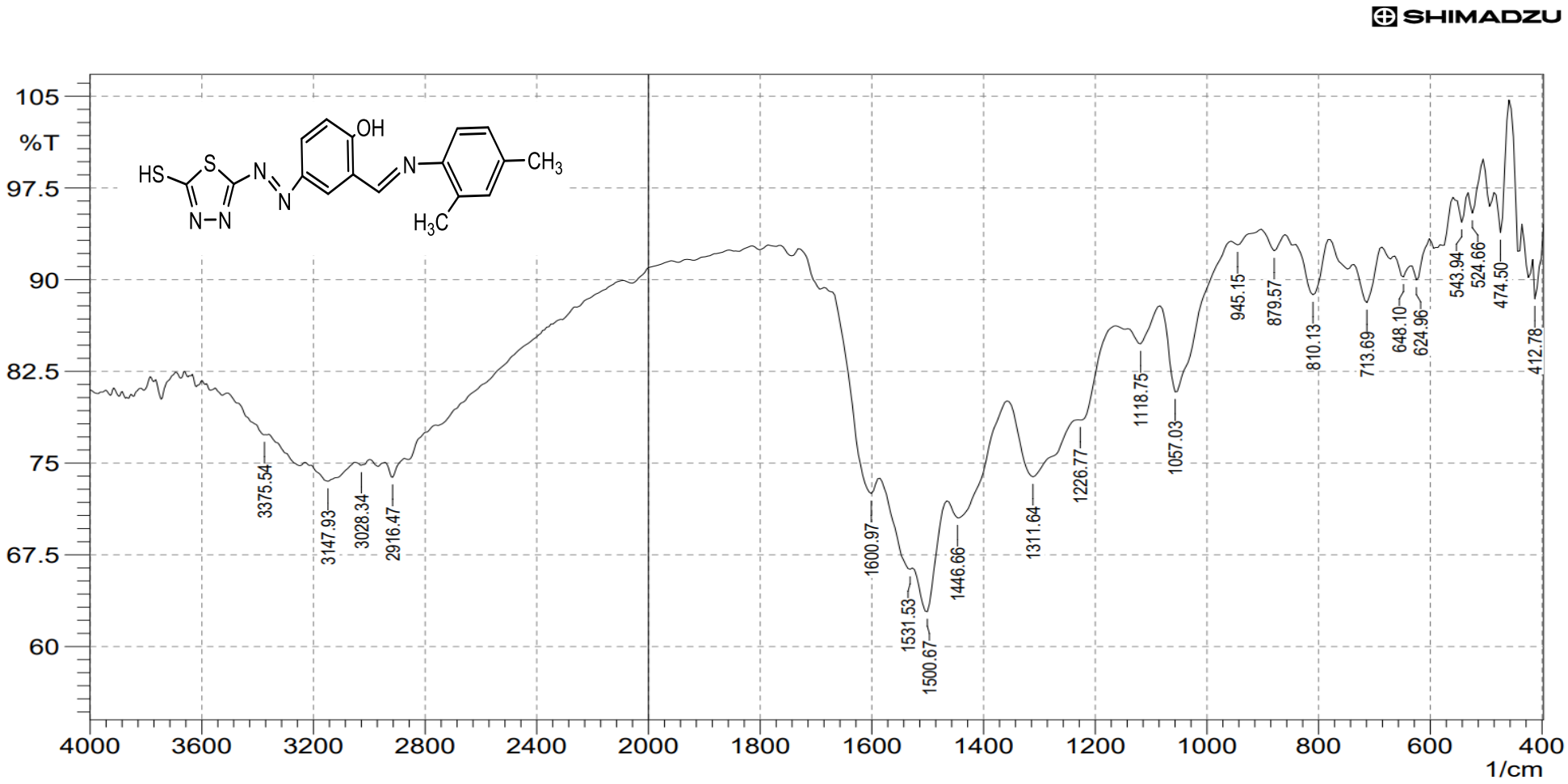


Figure (3-4): FT-IR spectrum of compound (3b)

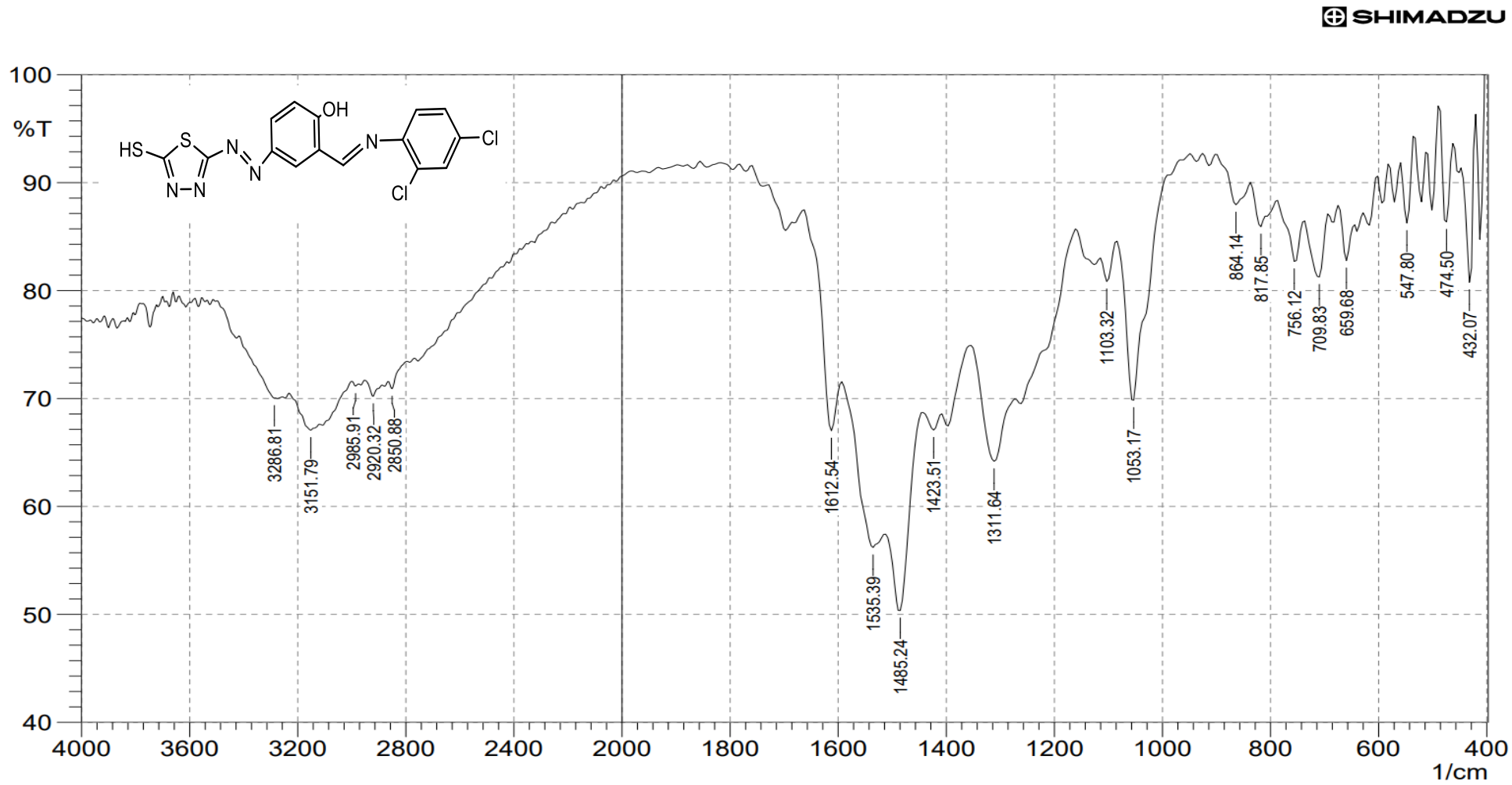


Figure (3-5): FT-IR spectrum of compound (3c)

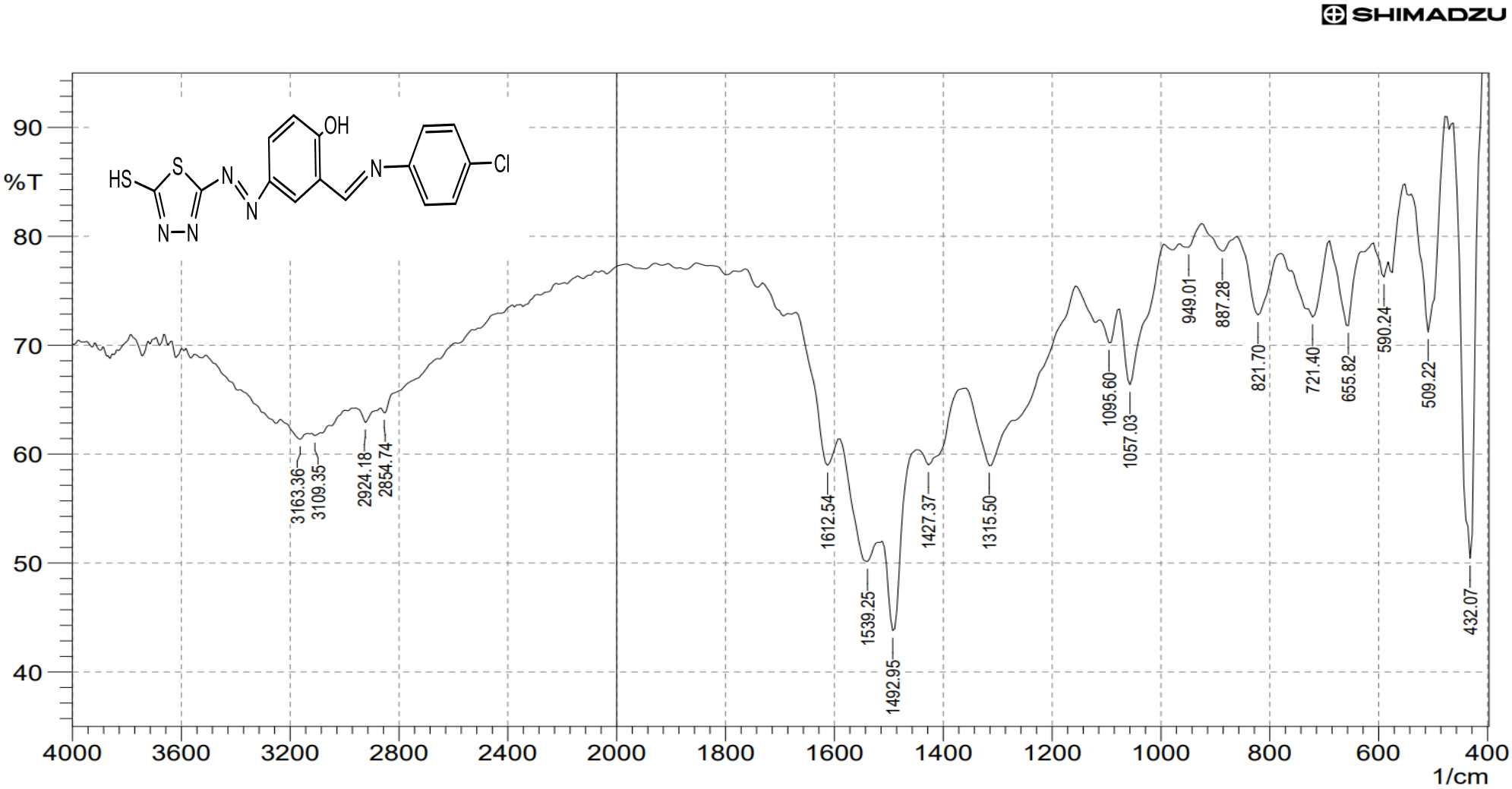


Figure (3-6): FT-IR spectrum of compound (3d)

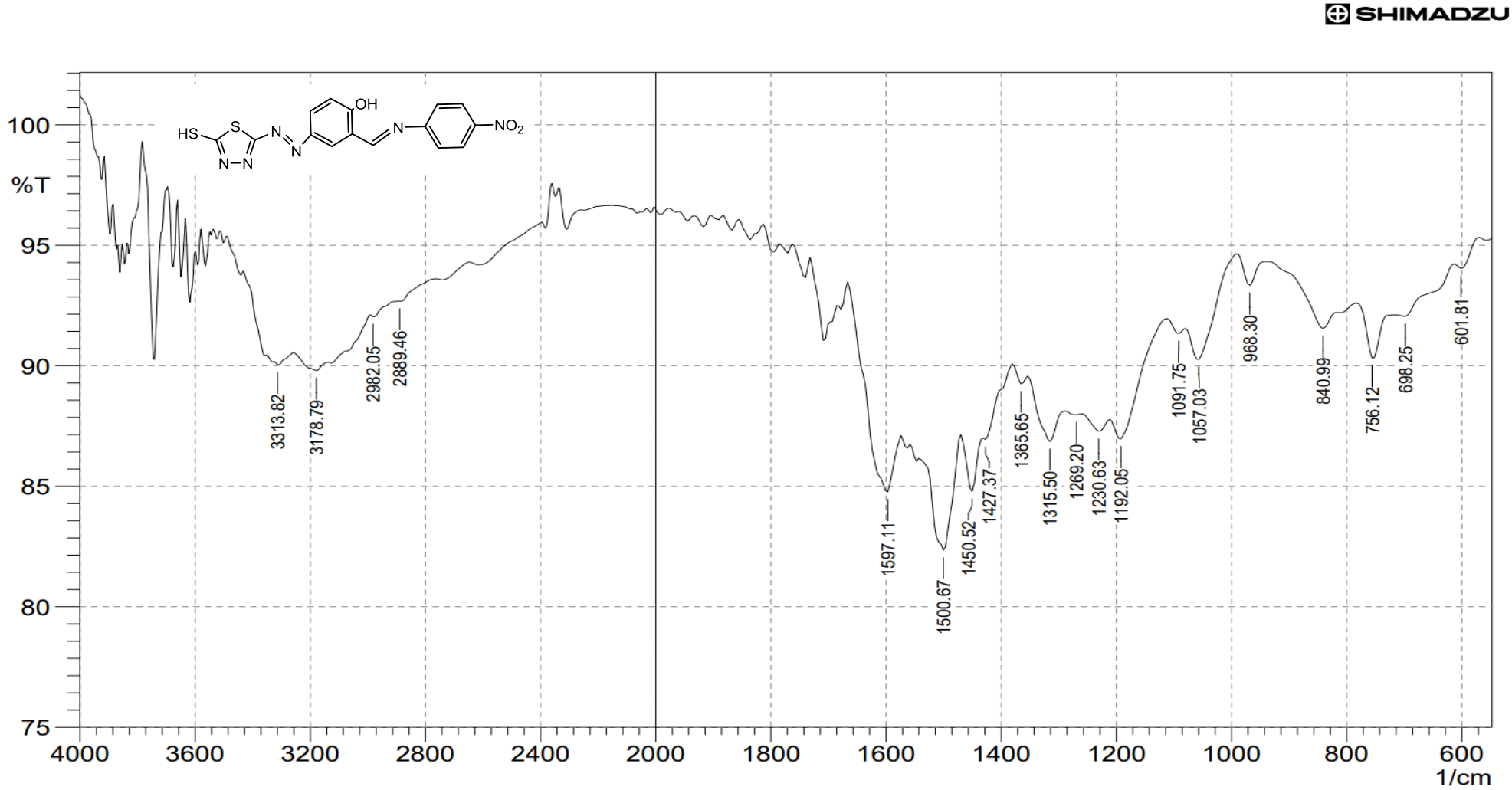


Figure (3-7): FT-IR spectrum of compound (3e)

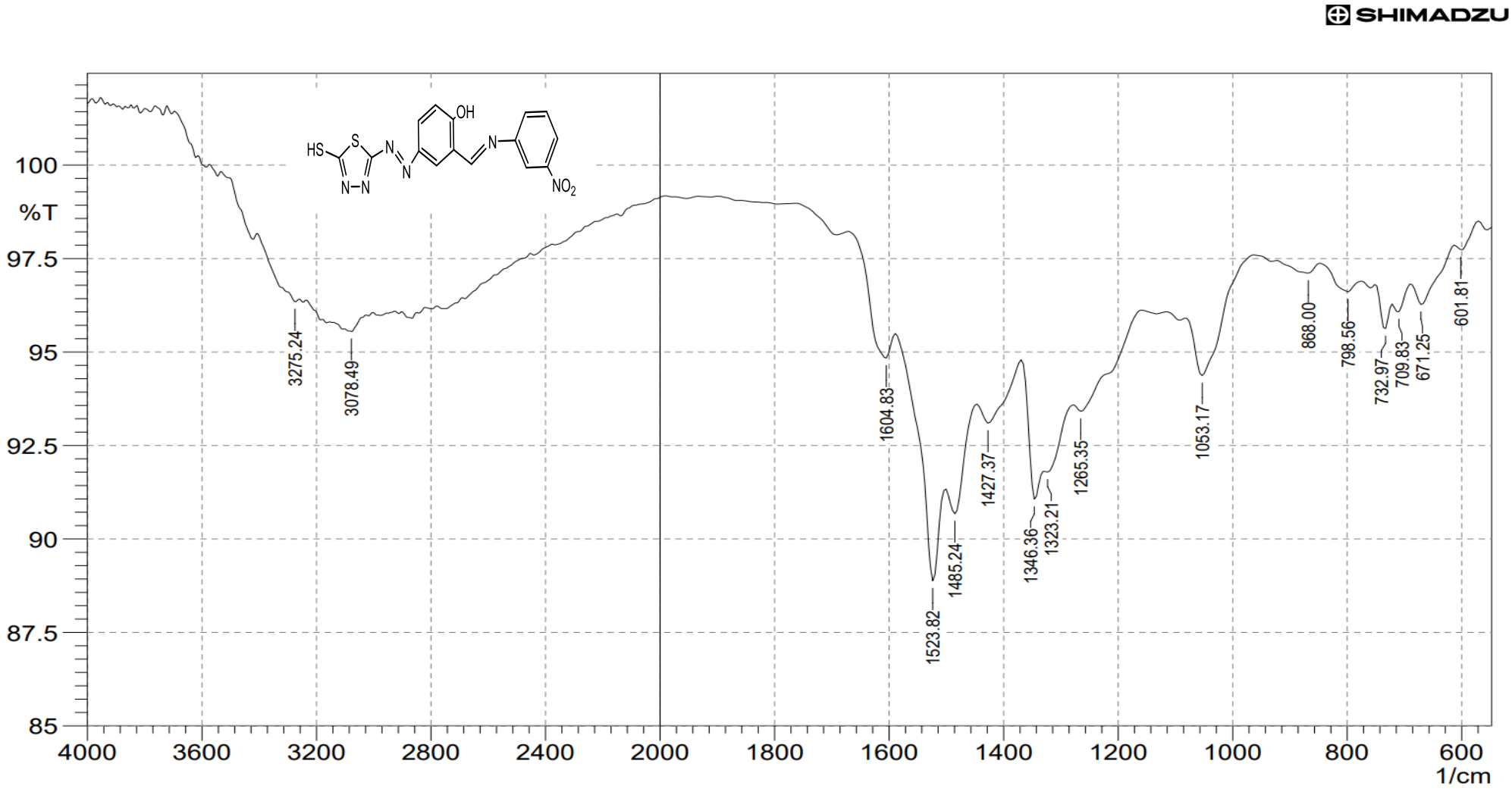


Figure (3-8): FT-IR spectrum of compound (3f)

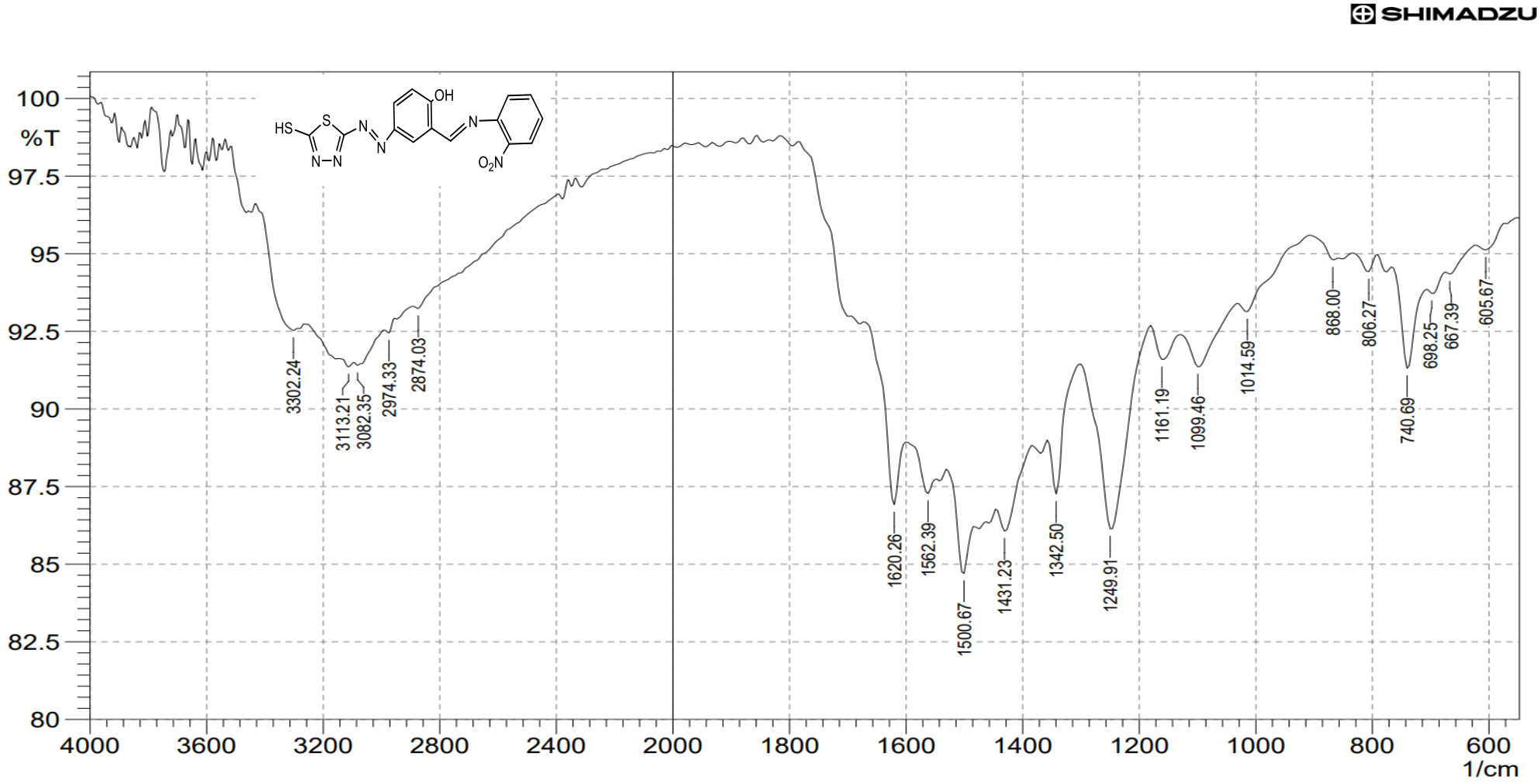


Figure (3-9): FT-IR spectrum of compound (3g)

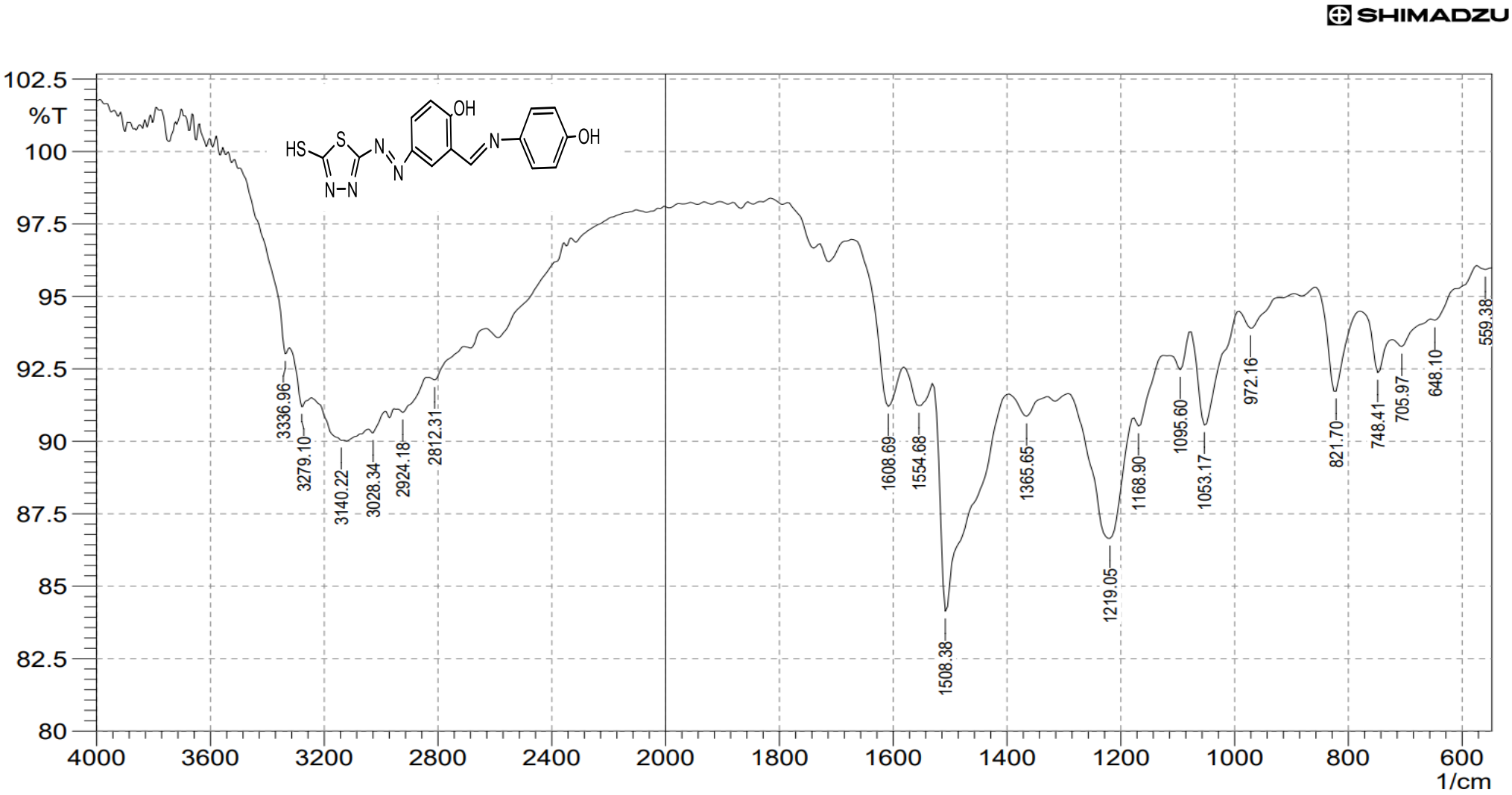


Figure (3-10): FT-IR spectrum of compound (3h)

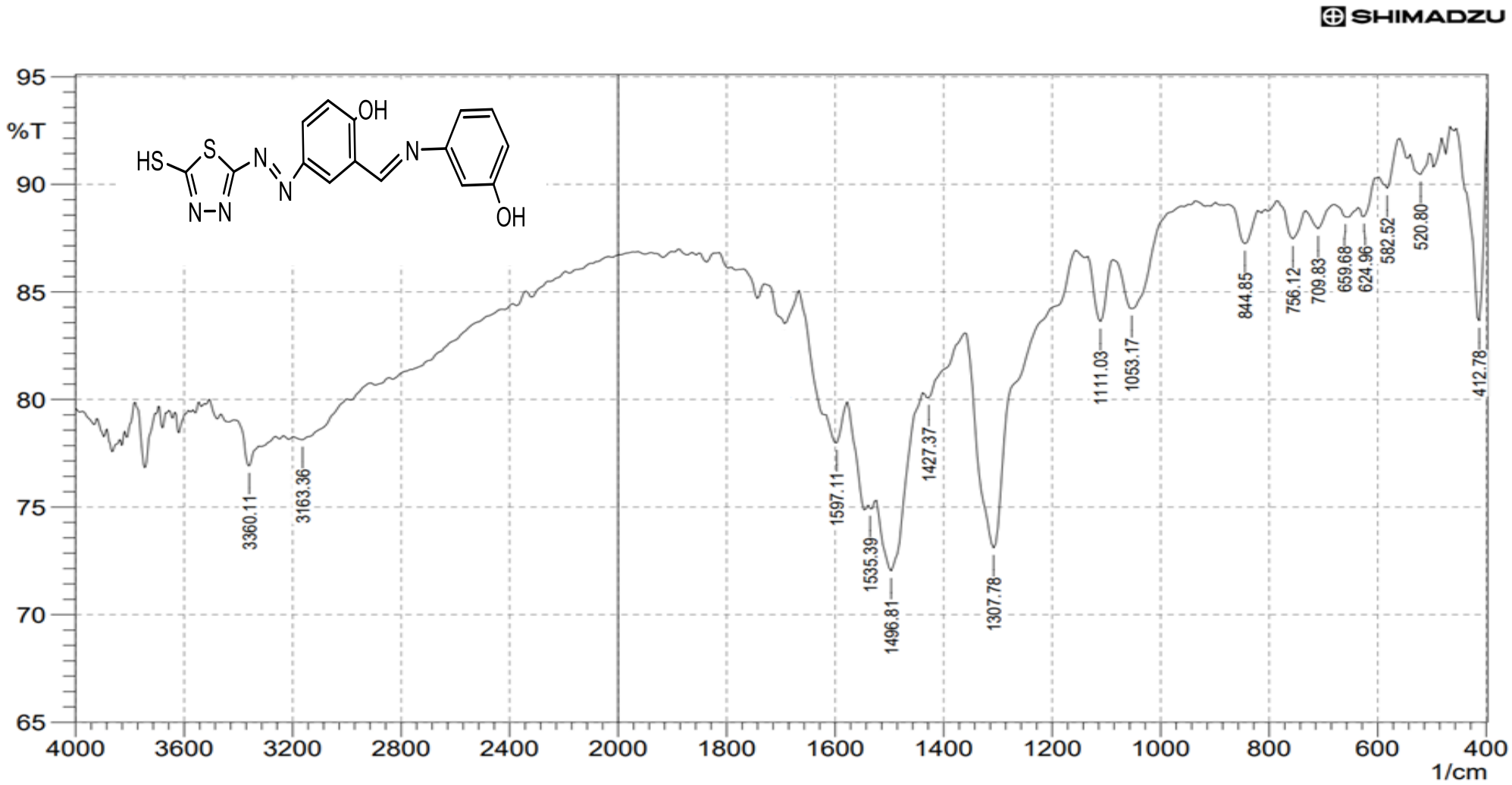


Figure (3-11): FT-IR spectrum of compound (3i)

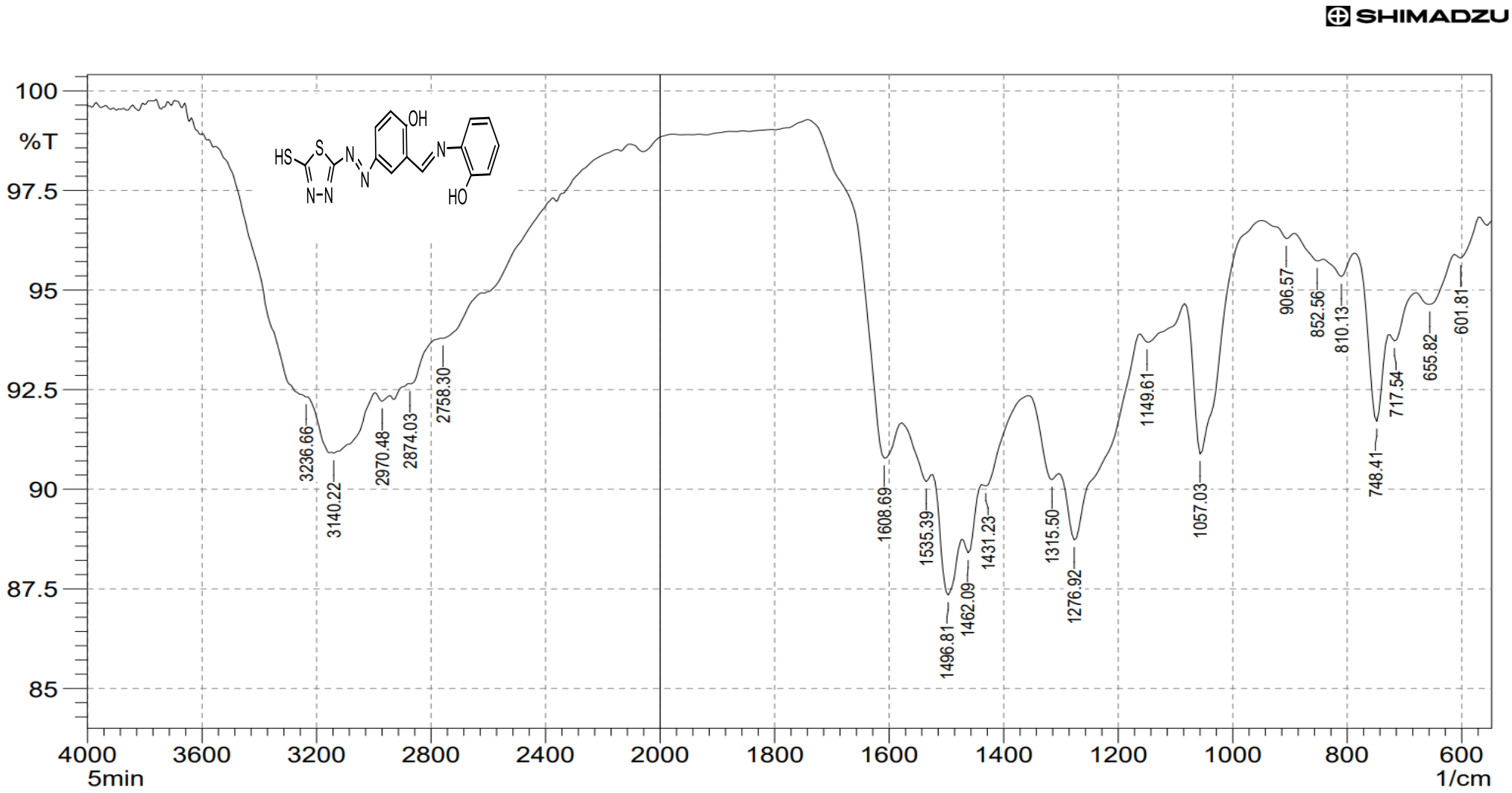
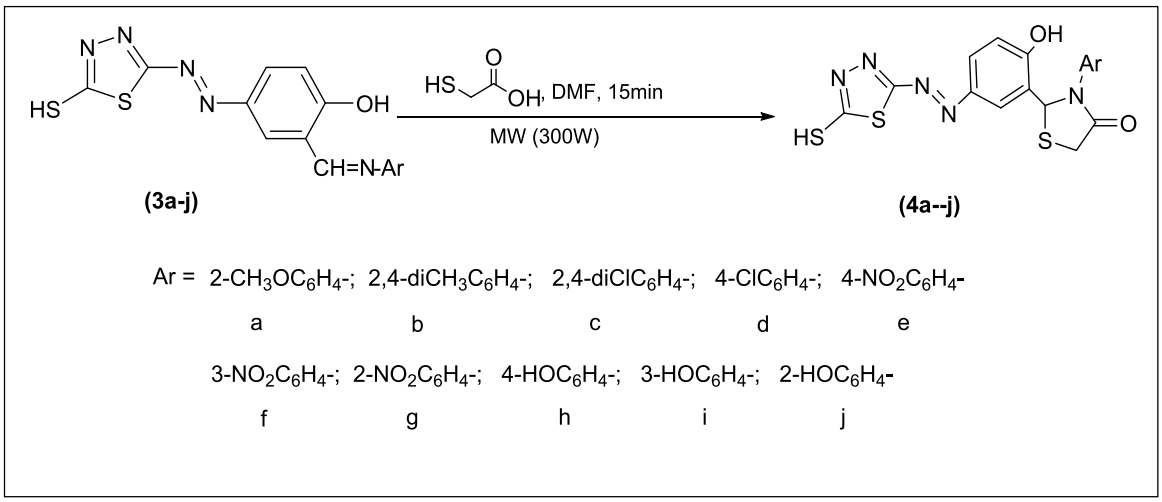


Figure (3-12): FT-IR spectrum of compound (3j)

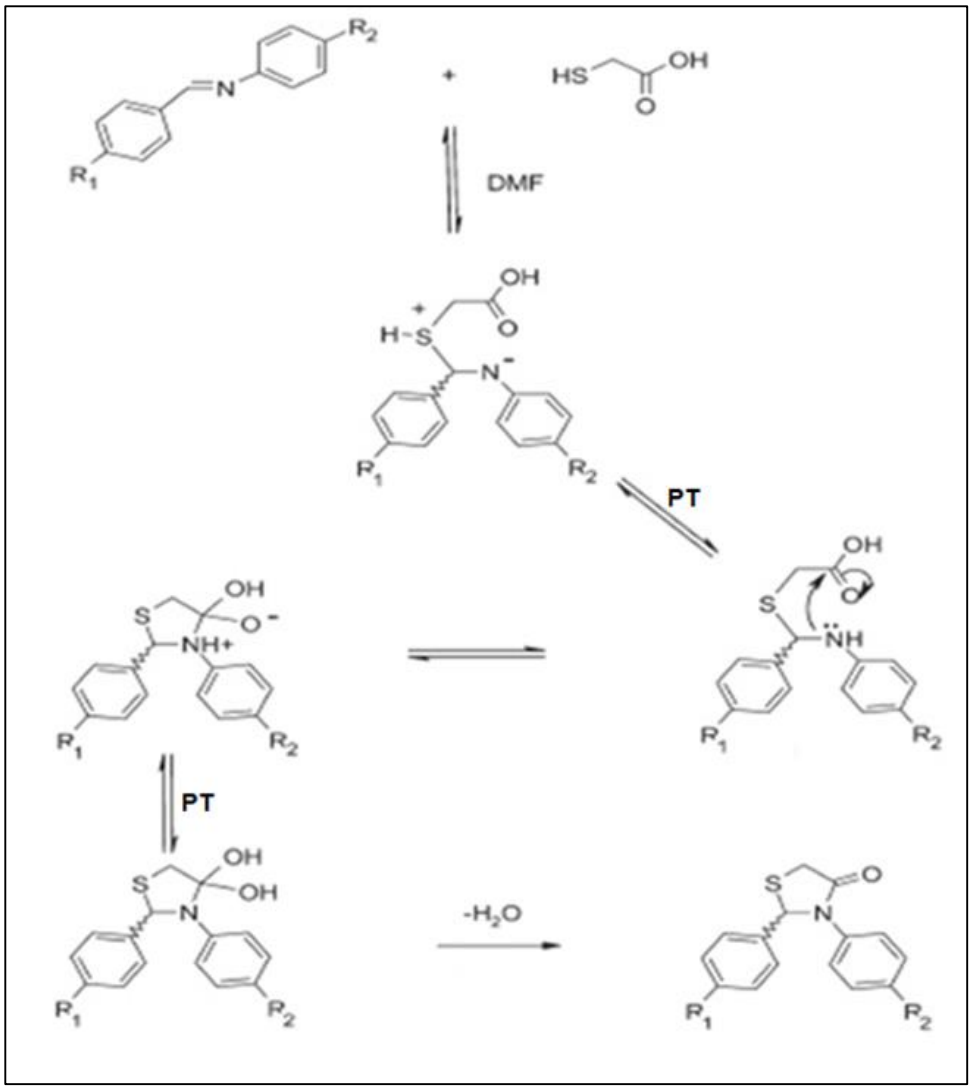
3.4. Synthesis of 1,3-Thiazolidin-4-ones (4a-j)

The latter step involving ring closure of Schiff bases **(3a-j)** and 2-mercaptoacetic acid using small amounts of dimethylformamide as solvent by microwave irradiation to give the desired 1,3-thiazolidin-4-one derivatives **(4a-j)**, scheme (3-8).



Scheme (3-8): Synthesis 1,3-Thiazolidin-4-ones (4a-j)

The proposed reaction mechanism for ring closure to form 1,3-Thiazolidin-4-one in solvent (DMF) was outlined in scheme (3-9) (130).



Scheme (3-9): Mechanism of 1,3-thiazolidin-4-one formation in DMF

IR, ^{1}H NMR, and ^{13}C NMR spectral means have been utilized for deducing chemical structures of the target compounds synthesized, in addition of (CHNS) elemental microanalysis measurements.

Infrared spectrum of thiazolidin-4-one derivative (4a) showed appearing band for (C=O) stretching of thiazolidinone ring around 1643 cm^{-1}, on the other hand the spectrum showed peak around 1612 cm^{-1} assigned to (C=N) group of thiadiazole ring, table (3-2).

Proton magnetic resonance of (4a) pointed singlet signal at δ 3.84 ppm for (OCH_3) hydrogens, protons of (CH_2) hydrogens of thiazolidine appeared as

multiplet around δ 3.90 ppm, while (CH) proton of thiazolidine appeared as singlet at δ 6.24 ppm [130, 132]. The aromatic hydrogens indicated around 7.06–7.47 ppm. The (O-H) hydrogen appeared at δ 9.68 ppm, while (S-H) proton signal was recorded around 13.78 ppm.

^{13}C NMR spectrum of compound (4a) appeared signals of (CH_2) and (CH) carbons of thiazolidinone ring around δ 33.96 ppm and 58.42 ppm, respectively. The signal at δ 55.0 ppm assigned to (OCH_3) carbon, the aromatic carbons signals indicated around the scope δ 113.57-155.74 ppm, the signal at δ 168.20 ppm for (C-SH) carbon of thiadiazole ring, while the signal around δ 170.57 ppm due to (C=O) carbon of thiazolidinone unit, the signal of (C-N=N) carbon of thiadiazole ring pointed at 174.76 ppm.

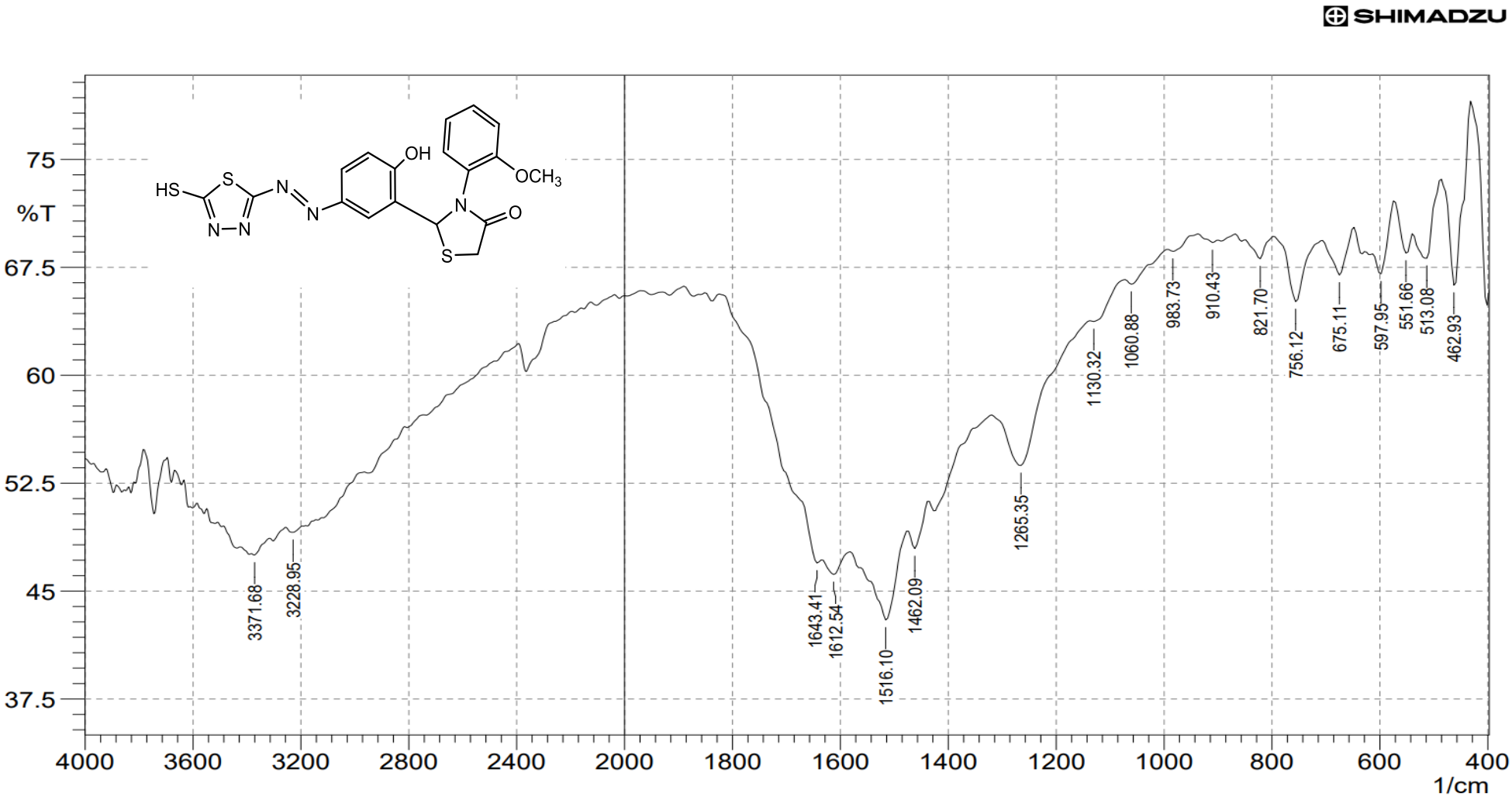


Figure (3-13): FT-IR spectrum of compound (4a)

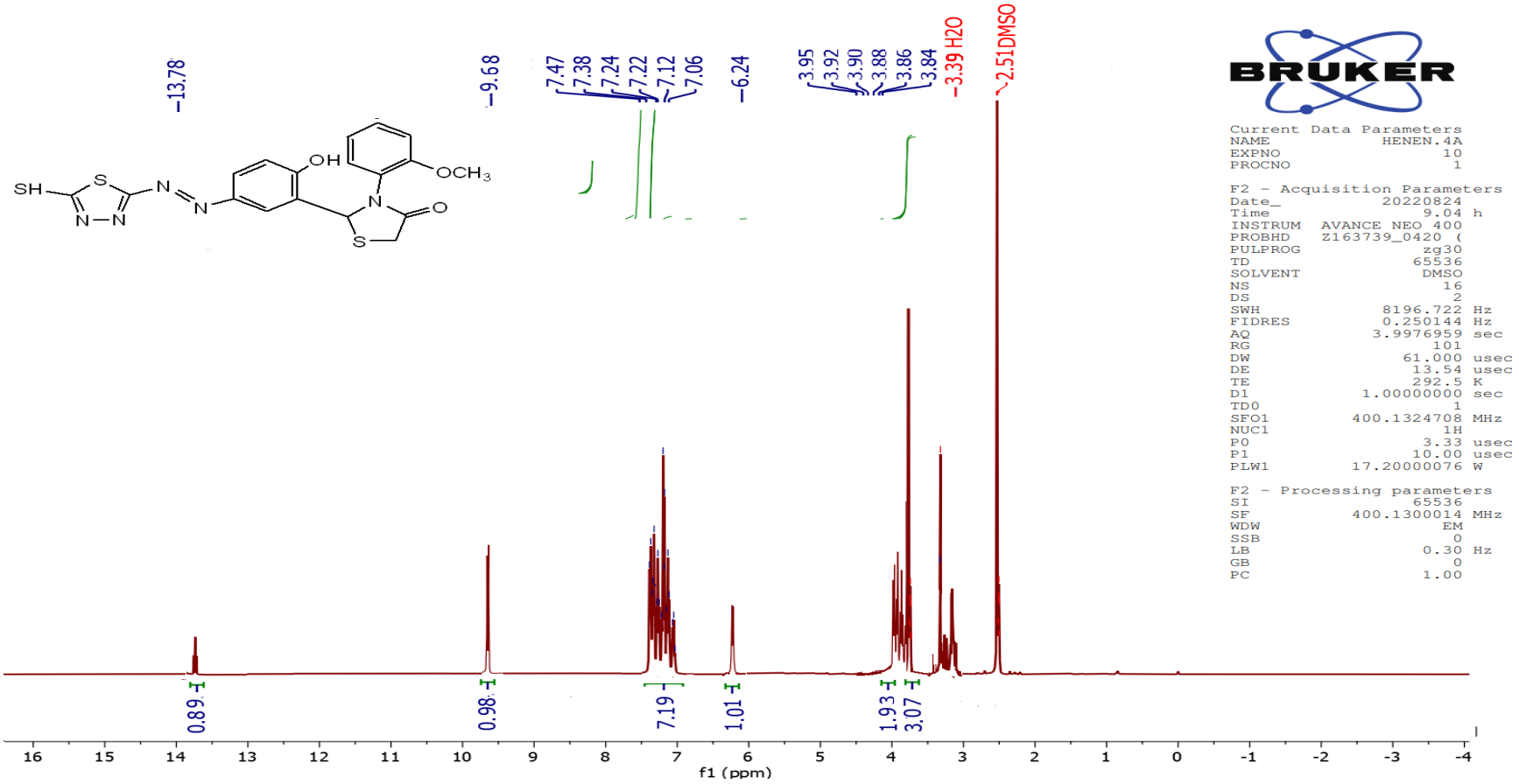


Figure (3-14): ^{1}H NMR spectrum of compound (4a)

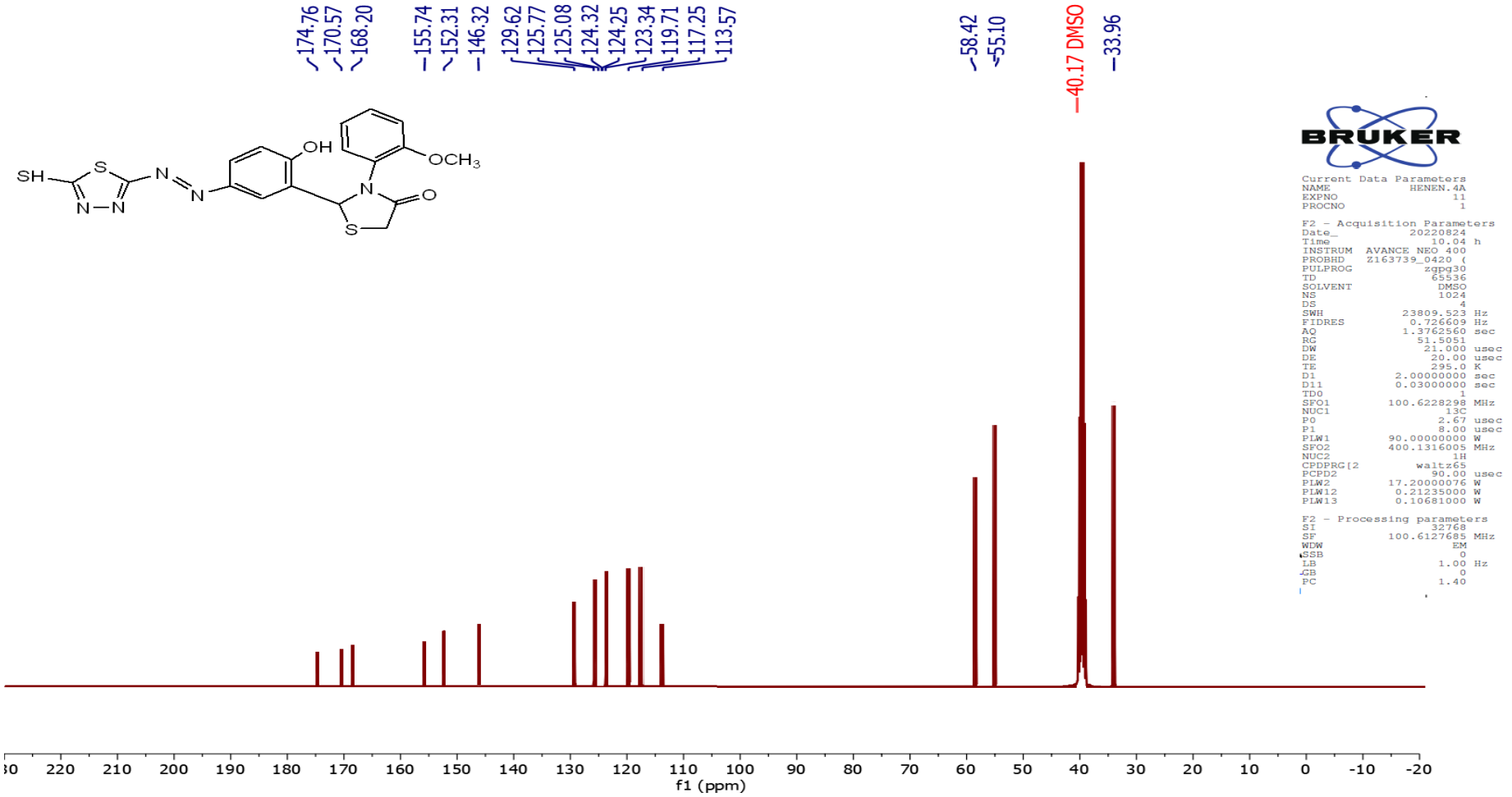


Figure (3-15): ^{13}C NMR spectrum of compound (4a)

Infrared of thiazolidin-4-one derivative (4b) showed appearing band for (C=O) stretching of thiazolidinone ring around 1658 cm^{-1}), whereas imine (C=N) stretching was disappeared, (table 2).

^{1}H NMR of compound (4b) pointed two singlet signals around δ 2.34 ppm and 2.67 ppm assigned to methyl groups hydrogens, the multiplet signal around δ 3.73 ppm for (CH_2) hydrogens of thiazolidine, peak of (CH) proton of thiazolidine recorded as singlet around δ 5.95 ppm. The signals of aromatic protons pointed around 6.89–7.36 ppm. The singlet around δ 9.54 for (O-H) proton, signal of sulfhydryl proton signal was indicated at 13.60 ppm.

^{13}C NMR of compound (4b) showed signals of methyl groups carbons around δ 18.20 ppm and 20.80 ppm, the signals around δ 33.89 ppm and 58.55 ppm belong to (CH_2) and (CH) carbons of thiazolidinone moiety, respectively. The signals of aromatic carbons recorded at the range δ 117.20-155.77 ppm, the signal of (C-SH) carbon of thiadiazole unit recorded at δ 168.58 ppm, the signal of (C=O) carbon of thiazolidinone appeared at δ 170.54 ppm, the signal of (C-N=N) carbon for thiadiazole recorded at 174.72 ppm.

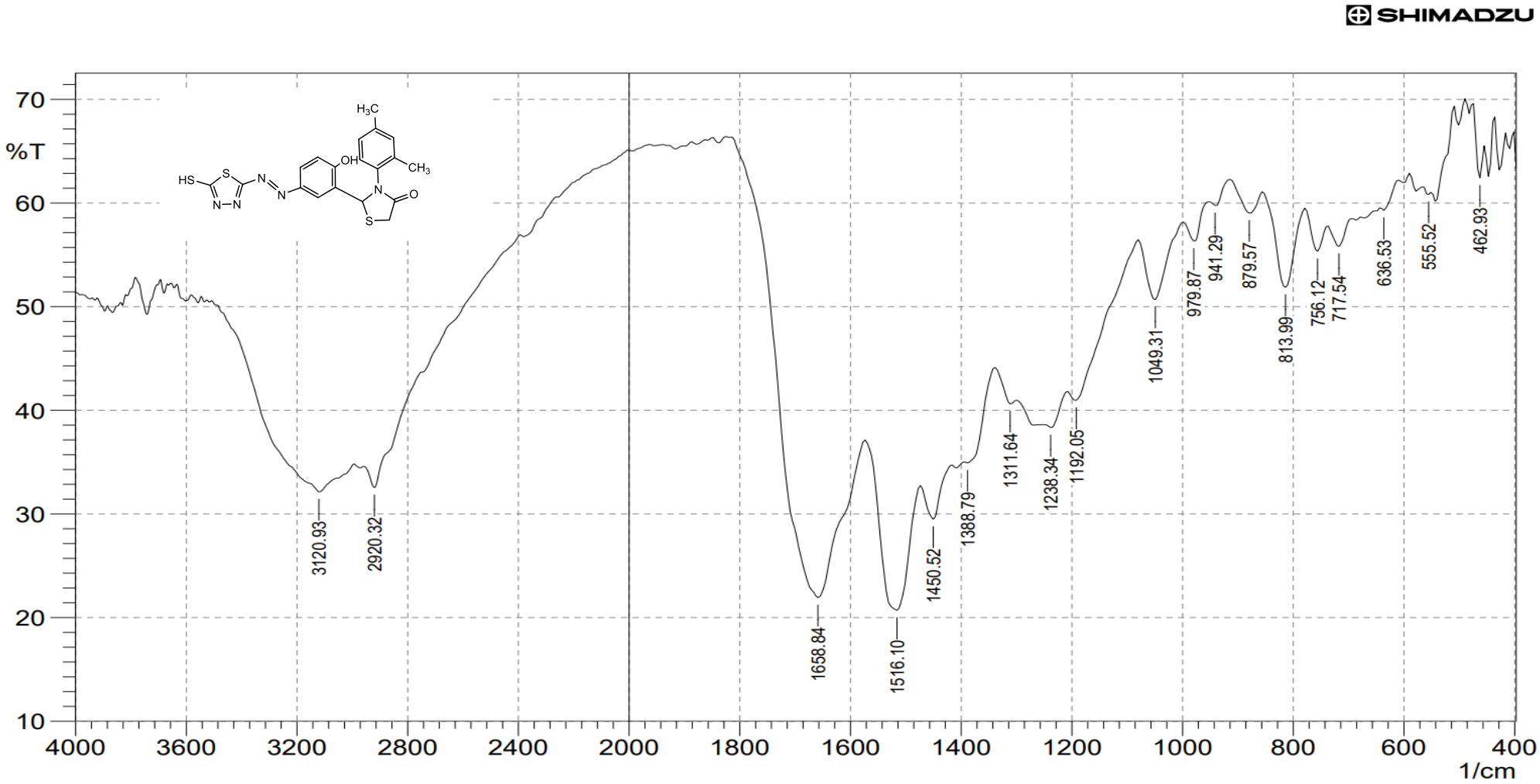


Figure (3-16): FT-IR spectrum of compound (4b)

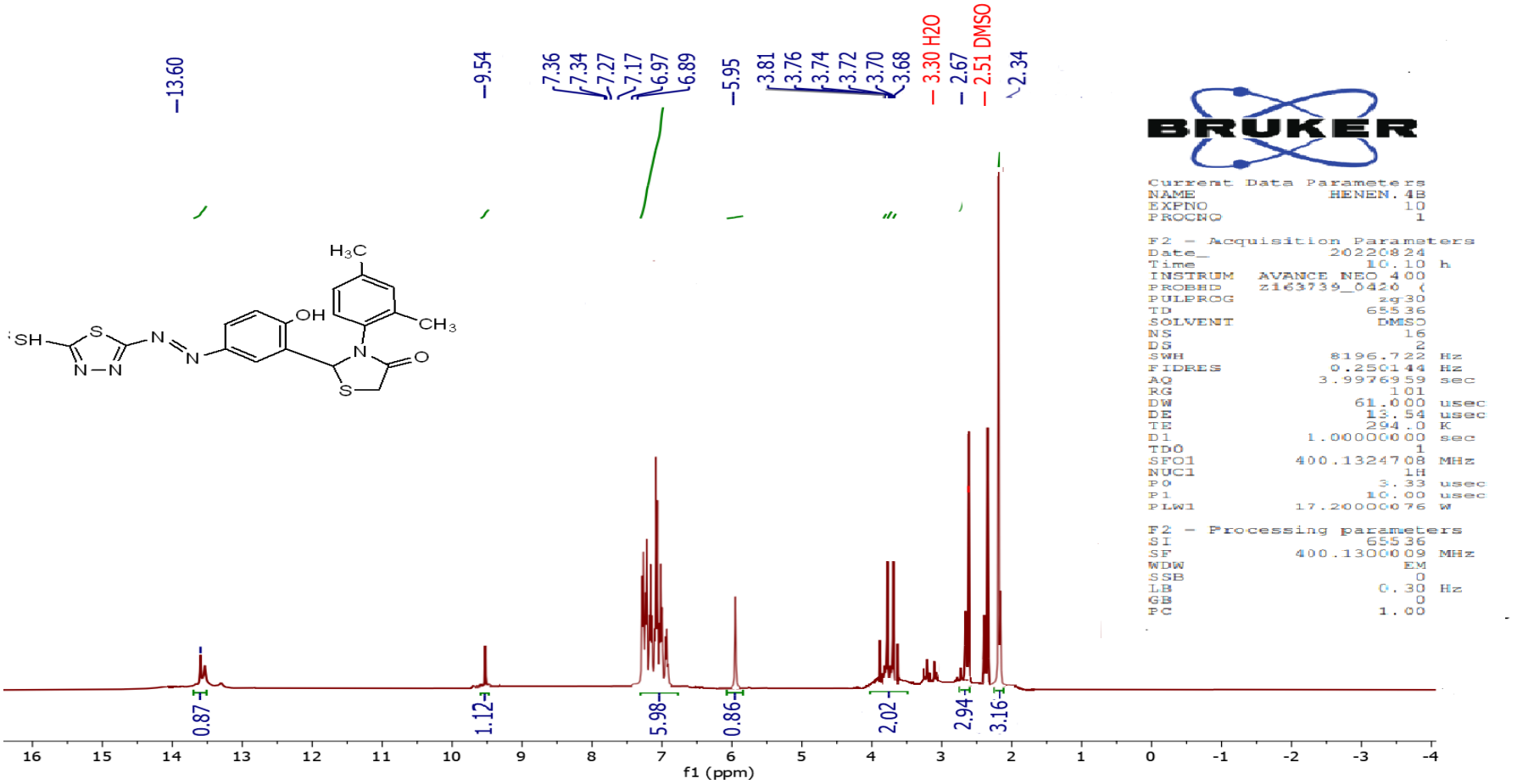


Figure (3-17): ^{1}H NMR spectrum of compound (4b

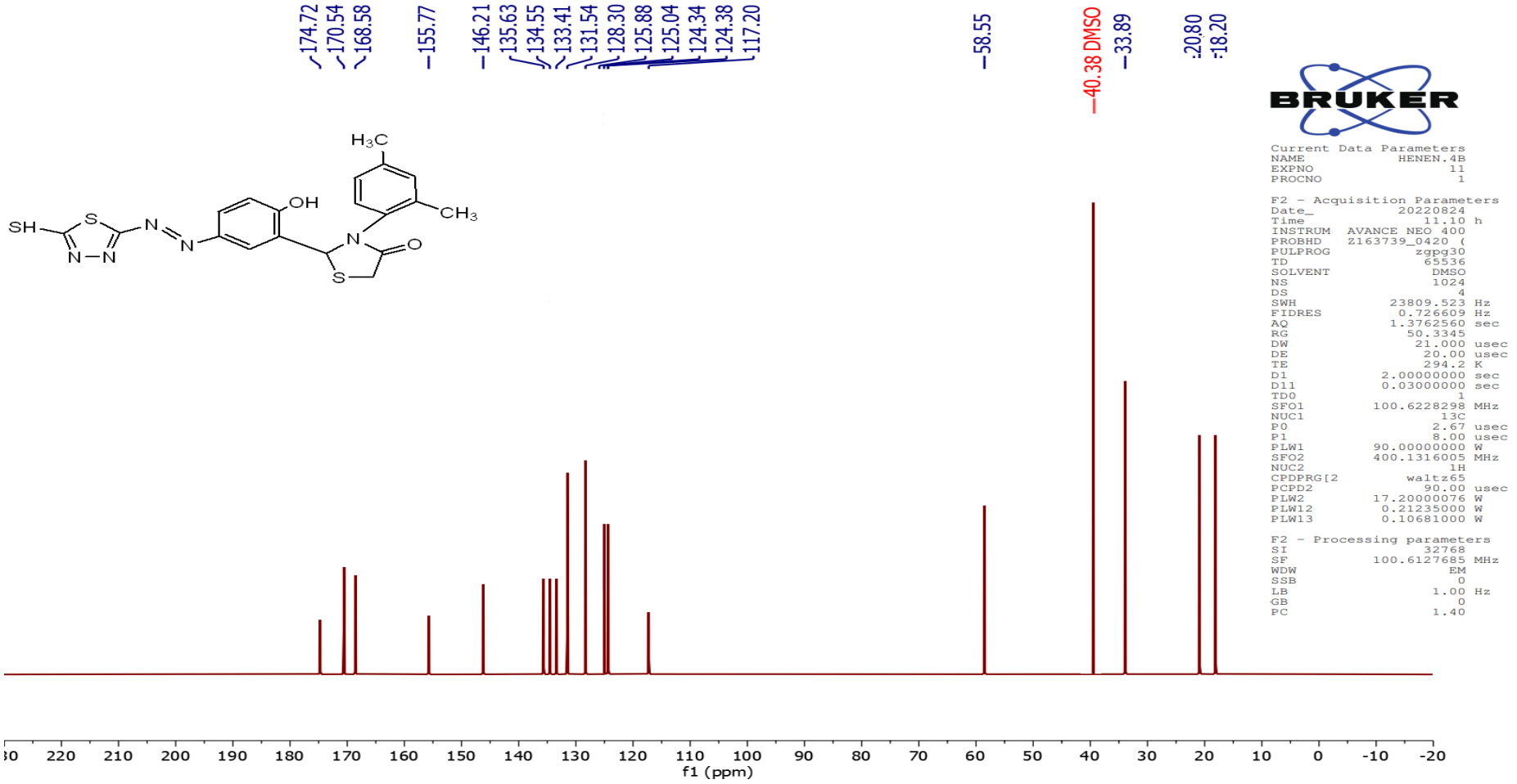


Figure (3-18): ^{13}C NMR spectrum of compound (4b)

Infrared of thiazolidin-4-one compound (4c) indicated appearance of peak for (C=O) stretching of thiazolidinone ring around 1647 cm^{-1}), the spectrum also appeared (C=N) stretching of thiadiazole moiety around 1581 cm^{-1}, (table 2).

^{1}H NMR of compound (4c) showed the multiplet signal for (CH_2) protons of thiazolidine around δ 3.93 ppm, (CH) proton of thiazolidine recorded at 6.16 ppm as singlet. The multiplet signals around 6.93–7.43 ppm for aromatic hydrogens. The(O-H) hydrogen resonated around δ 9.61 ppm, thiolic proton was recorded at 13.05 ppm.

^{13}C NMR of compound (4c) pointed two signals for (CH_2) and (CH) carbons of thiazolidine unit around δ 33.72 ppm and 58.58 ppm, respectively, the signals of aromatic carbons recorded around δ 117.24-155.69 ppm. The signal around δ 168.54 ppm recorded to (C-SH) carbon of thiadiazole, the signal around δ 170.20 ppm due to (C=O) carbon of thiazolidinone, the signal of (C-N=N) carbon of thiadiazole ring indicated around 174.69 ppm.

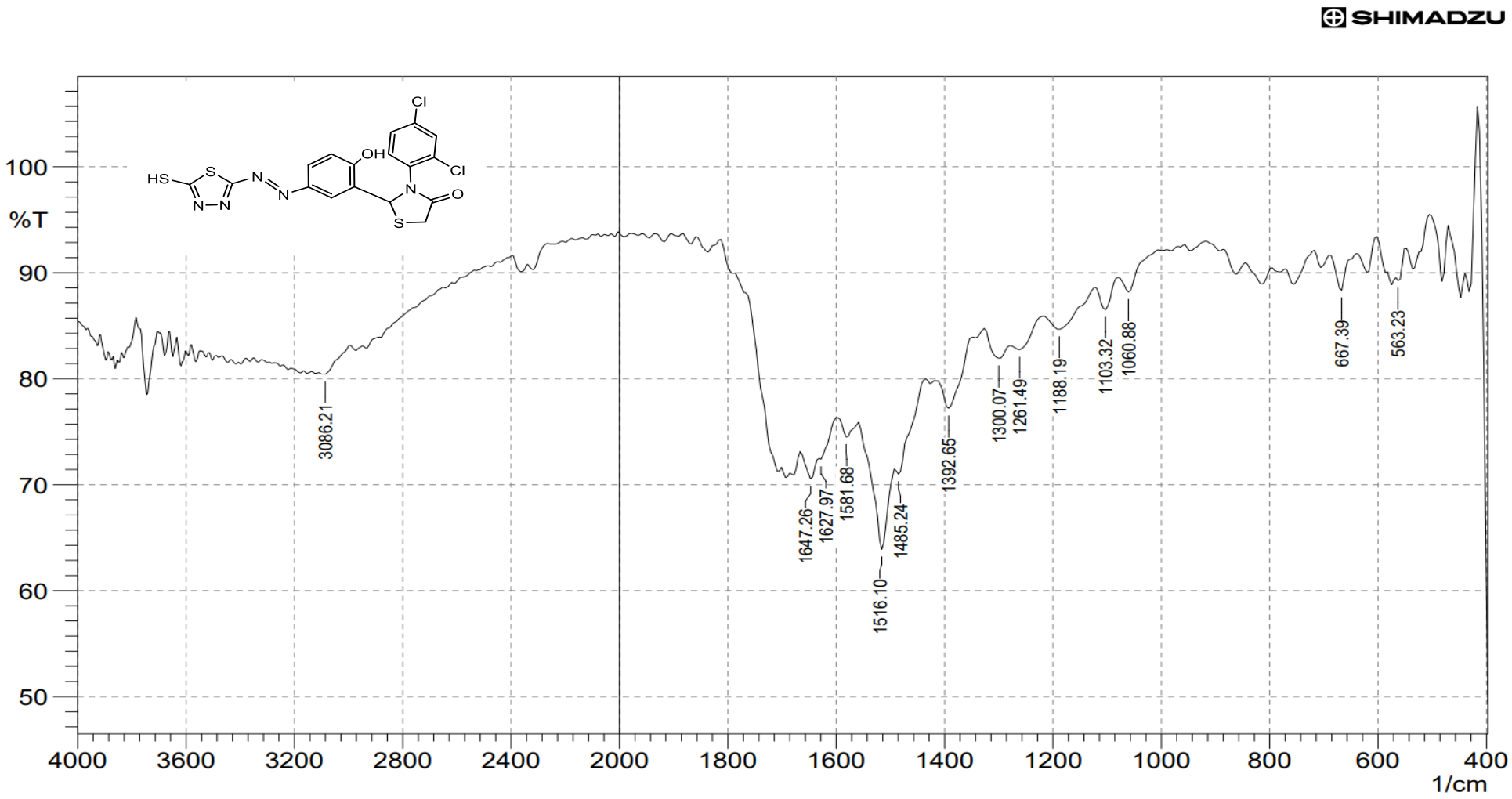


Figure (3-19): FT-IR spectrum of compound (4c)

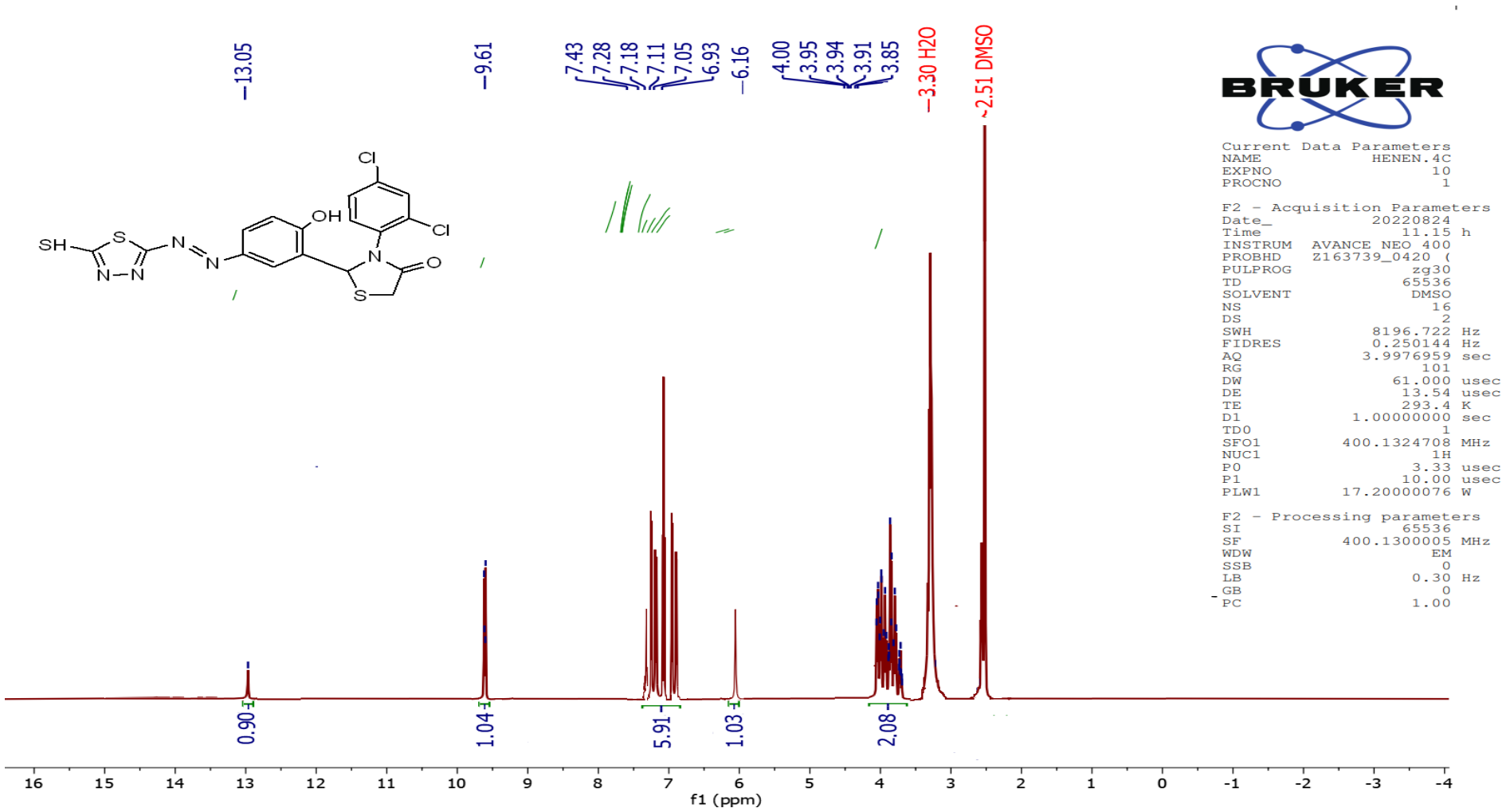


Figure (3-20): ^{1}H NMR spectrum of compound (4c)

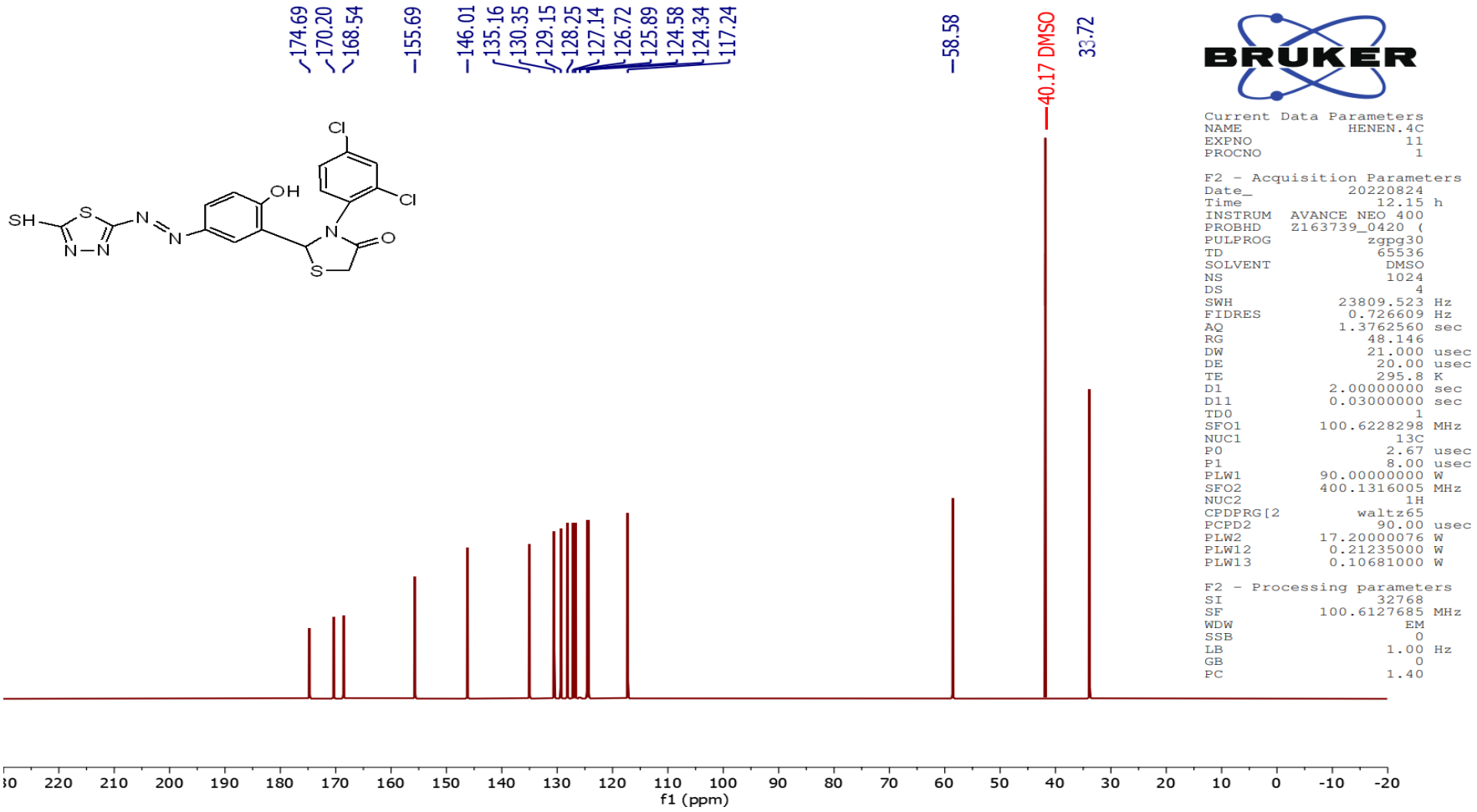


Figure (3-21):^{13}C NMR spectrum of compound (4c)

Infrared spectrum of thiazolidin-4-one derivative (4d) pointed peak at 1712 cm^{-1} assigned to (C=O) stretching of thiazolidinone unit, while peak around 1600 cm^{-1} assigned to (C=N) group of thiadiazole ring, table (3-2).

1H NMR of compound (4d) recorded signal of (CH_2) hydrogens of thiazolidine as multiplet at δ 3.98 ppm, the singlet around 6.55 ppm due to (CH) proton of thiazolidine. The multiplet signals for aromatic protons recorded around 6.91–7.48 ppm. proton of (O-H) pointed singlet at δ 9.15 ppm, sulfhydryl proton appered singlet at 13.52 ppm.

^{13}C NMR of compound (4d) showed signals of (CH_2) and (CH) carbons of thiazolidine at δ 33.83 ppm and 57.88 ppm, respectively, the signals around δ 117.24-155.57 ppm for aromatic carbons, the signal at δ 168.55 ppm assigned to (C-SH) carbon of thiadiazole, the signal of (C=O) carbon of thiazolidinone pointed around δ 171.74 ppm, the signal at 174.20 ppm due to (C-N=N) carbon of thiadiazole moiety.

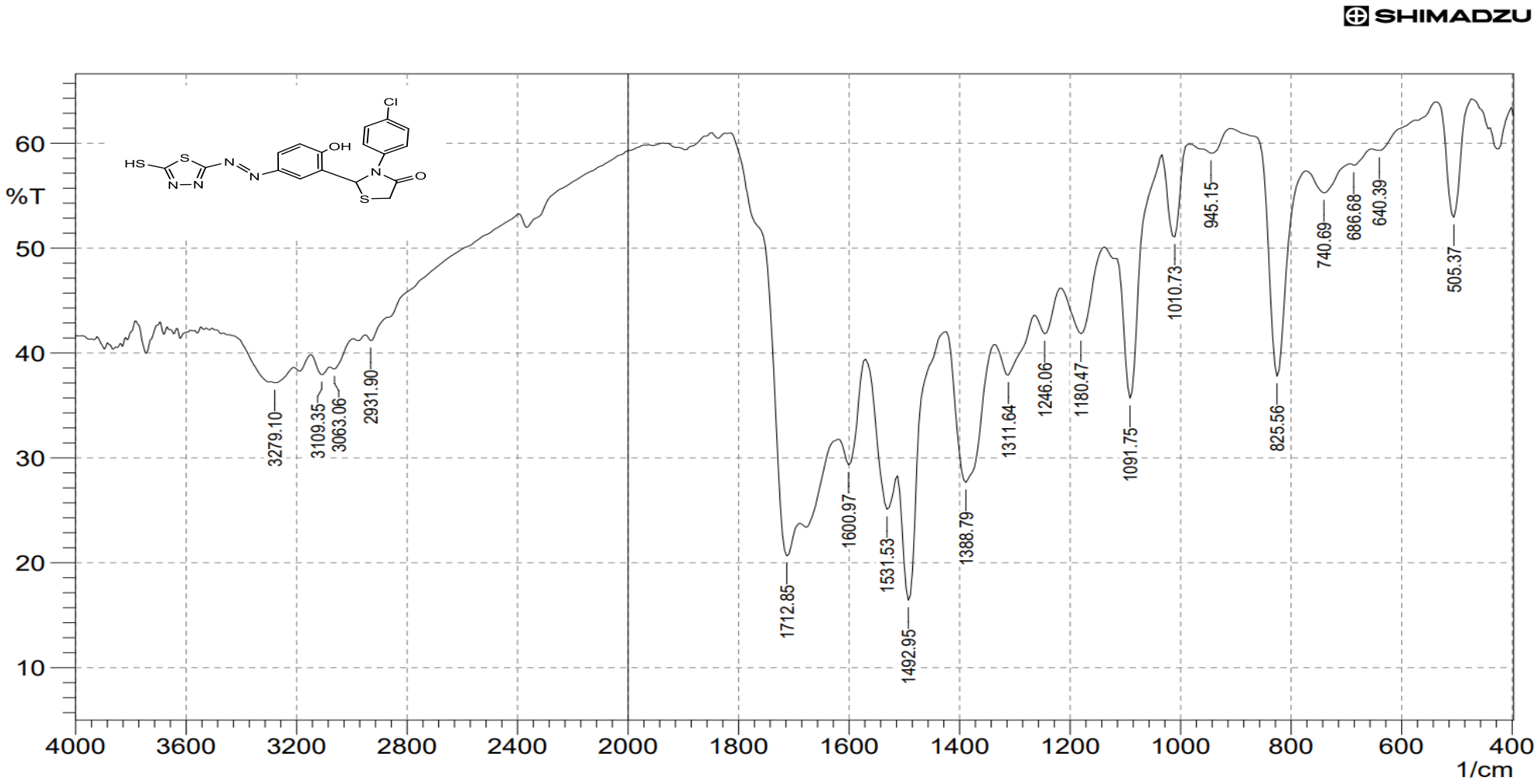


Figure (3-22): FT-IR spectrum of compound (4d)

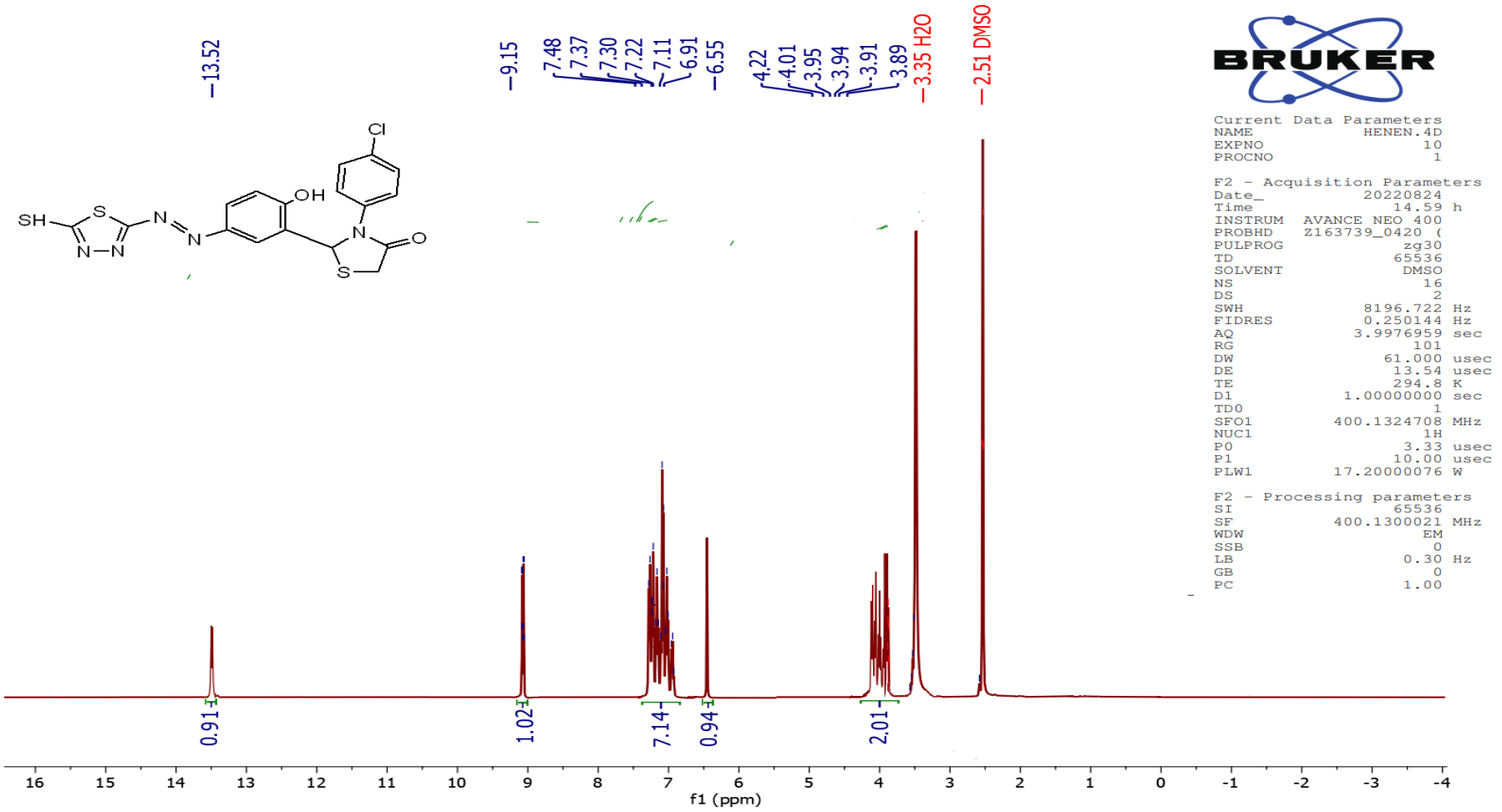


Figure (3-23): ^{1}H NMR spectrum of compound (4d)

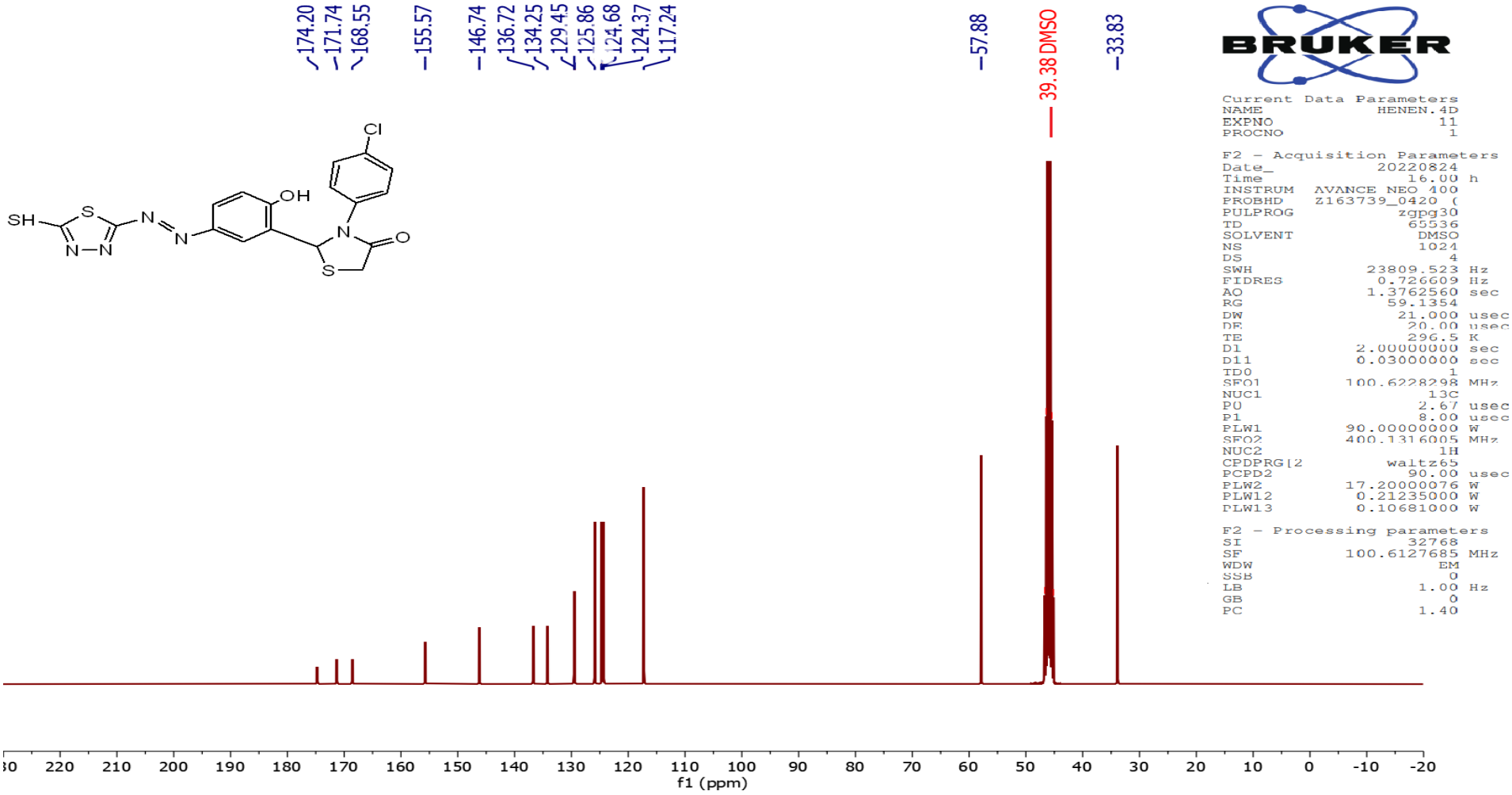


Figure (3-24): ^{13}C NMR spectrum of compound (4d)

Infrared of thiazolidin-4-one compound (4e) showed appearing band for (C=O) stretching of thiazolidinone ring around 1670 cm^{-1}), whereas peak at 1608 cm^{-1} due to (C=N) group of thiadiazole ring, (table 2).

^{1}H NMR of compound (4e) recorded multiplet signal for methylenic hydrogen of thiazolidine around δ 3.90 ppm while proton of (CH) appeared as singlet at δ 6.48 ppm. The aromatic hydrogens indicated multiplet signals around 6.85–7.34 ppm, the singlet at δ 9.79 ppm for hydroxyl proton. The singlet of (SH) proton was recorded at δ 13.96 ppm.

^{13}C NMR compound (4e) pointed two signals around δ 33.82 ppm and 57.85 ppm for (CH_2) and (CH) carbons of thiazolidinone ring, respectively. The aromatic carbons recorded signals around δ 117.24-155.70 ppm, the(C-SH) carbon of thiadiazole recorded signal at δ 168.77 ppm, the signal of carbonyl group carbon recorded around δ 171.24 ppm, the signal around δ 174.64 ppm attributed to(C-N=N) carbon of thiadiazole moiety.

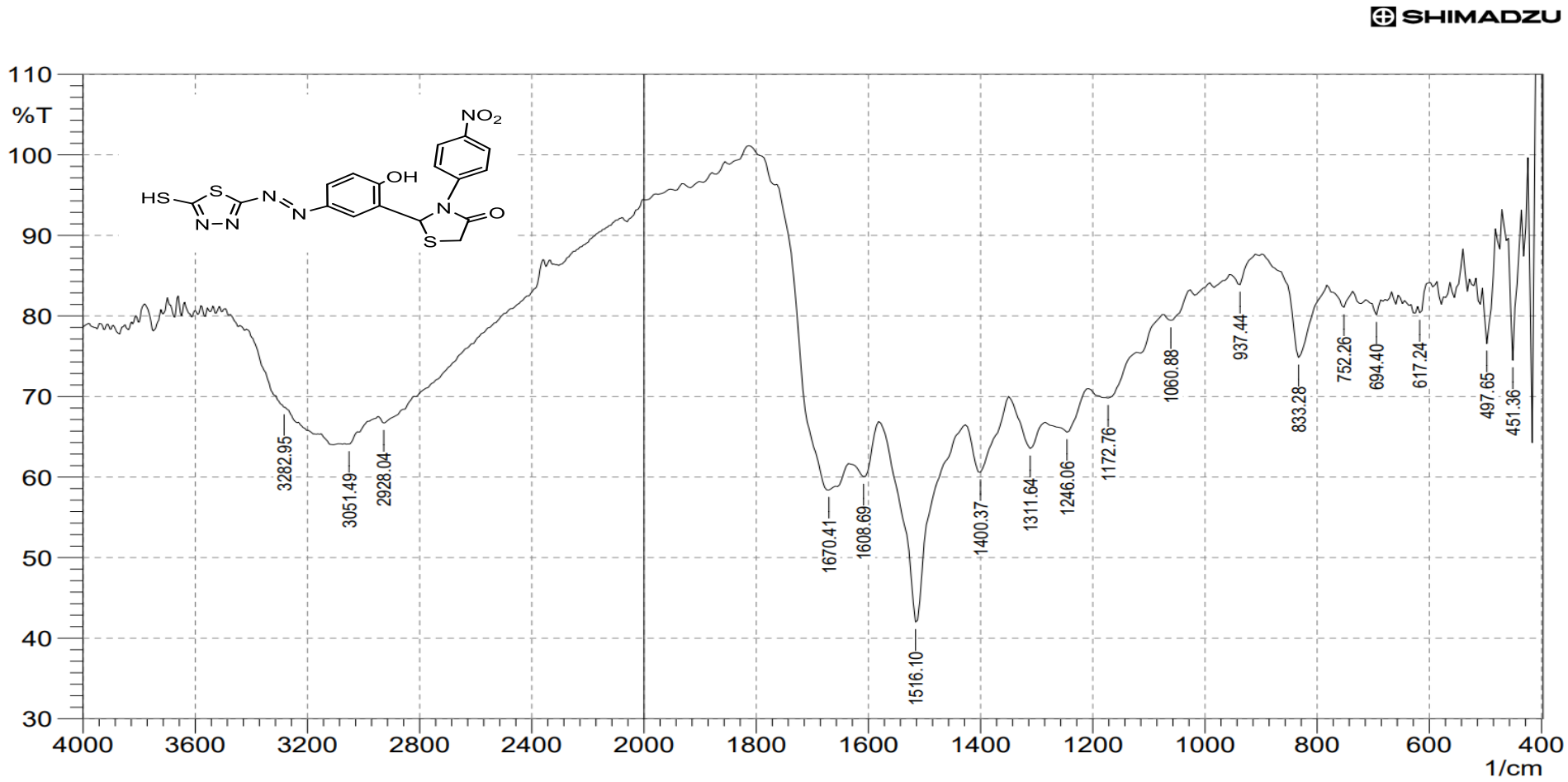


Figure (3-25): FT-IR spectrum of compound (4e)

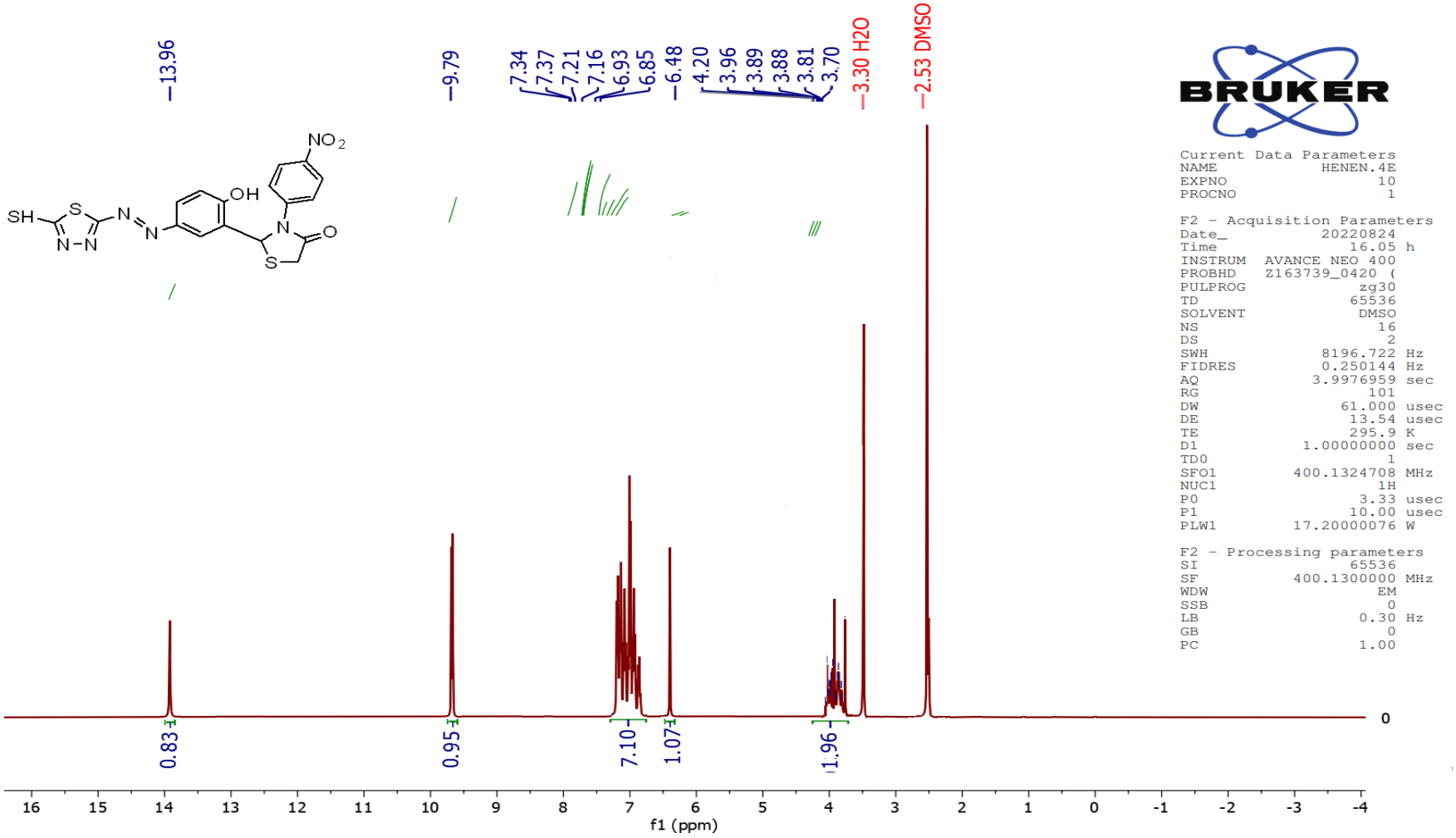


Figure (3-26): ^{1}H NMR spectrum of compound (4e)

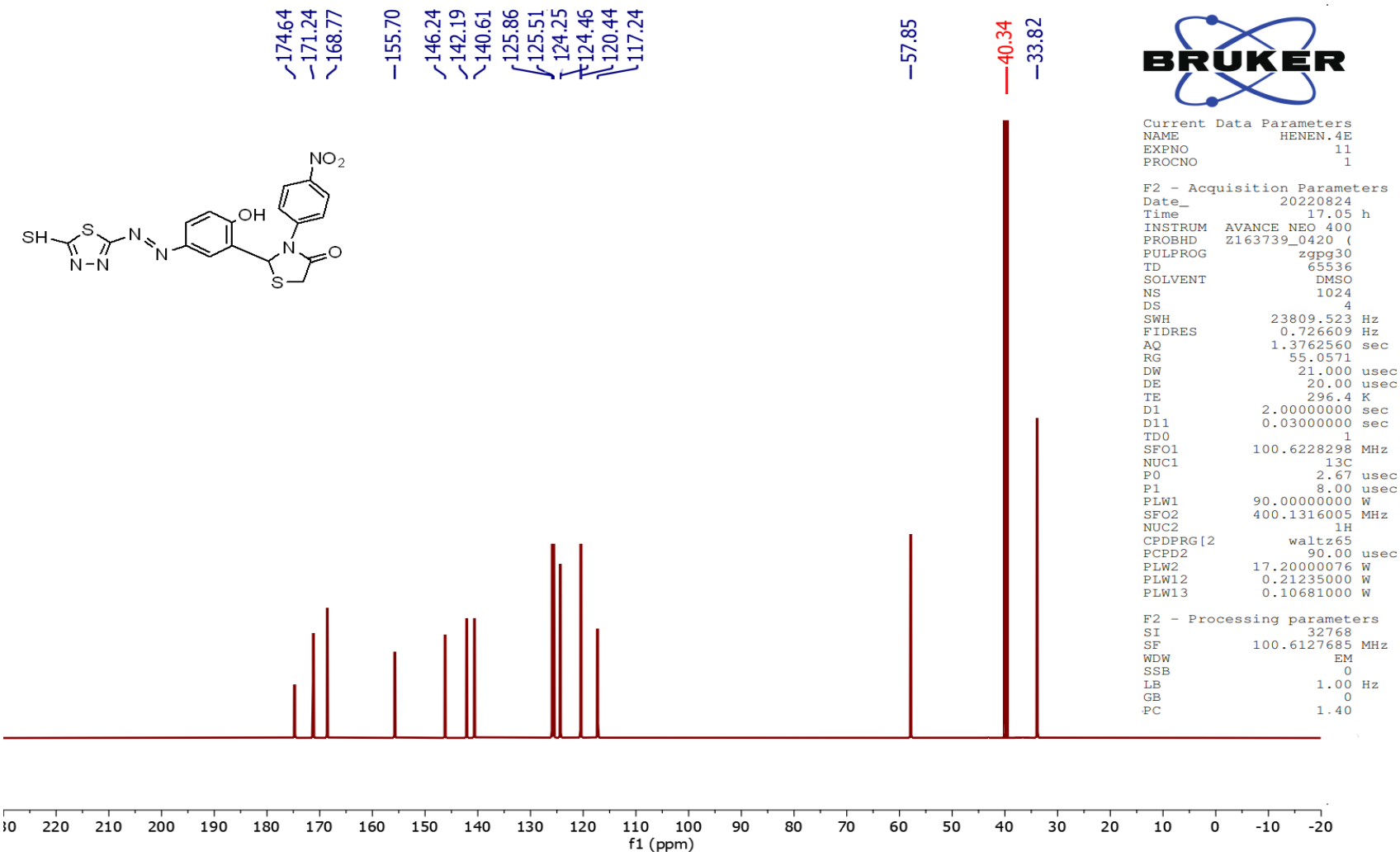


Figure (3-27): ^{13}C NMR spectrum of compound **(4e)**

(IR) spectrum of thiazolidin-4-one derivative (4f) appeared peak around 1674 cm^{-1} for (C=O) stretching of thiazolidinone ring around, the peak at 1616 cm^{-1} attributed to (C=N) group of thiadiazole ring, table (3-2).

^{1}H NMR of compound (4f) recorded multiple peak for thiazolidinone (CH_2) hydrogens around δ 3.99 ppm, while the signal of (CH) hydrogen for the same ring was recorded as singlet at δ 6.29 ppm[50]. The (Ar-H) signals were recorded around δ 6.88–7.37 ppm. The singlet signal around δ 9.89 ppm assigned to proton of hydroxyl group (O-H). The sulfhydryl proton (S-H) pointed at δ 13.15 ppm.

^{13}C NMR spectrum of compound (4f) appeared signal around δ 33.85 ppm attributed to (CH_2) carbon of thiazolidinone ring, whereas signal of (CH) carbon in the same ring was pointed at 57.83 ppm. The aromatic carbons of benzene rings were recorded at 116.29 -148.80 ppm, the signal around δ 168.53 ppm recorded for (C-SH) carbon of thiadiazole ring. The signal of carbonyl group carbon of thiazolidinone moiety indicated around δ 171.24 ppm. The signal around 174.71 ppm assigned to (C-N=N) carbon of thiadiazole unit.

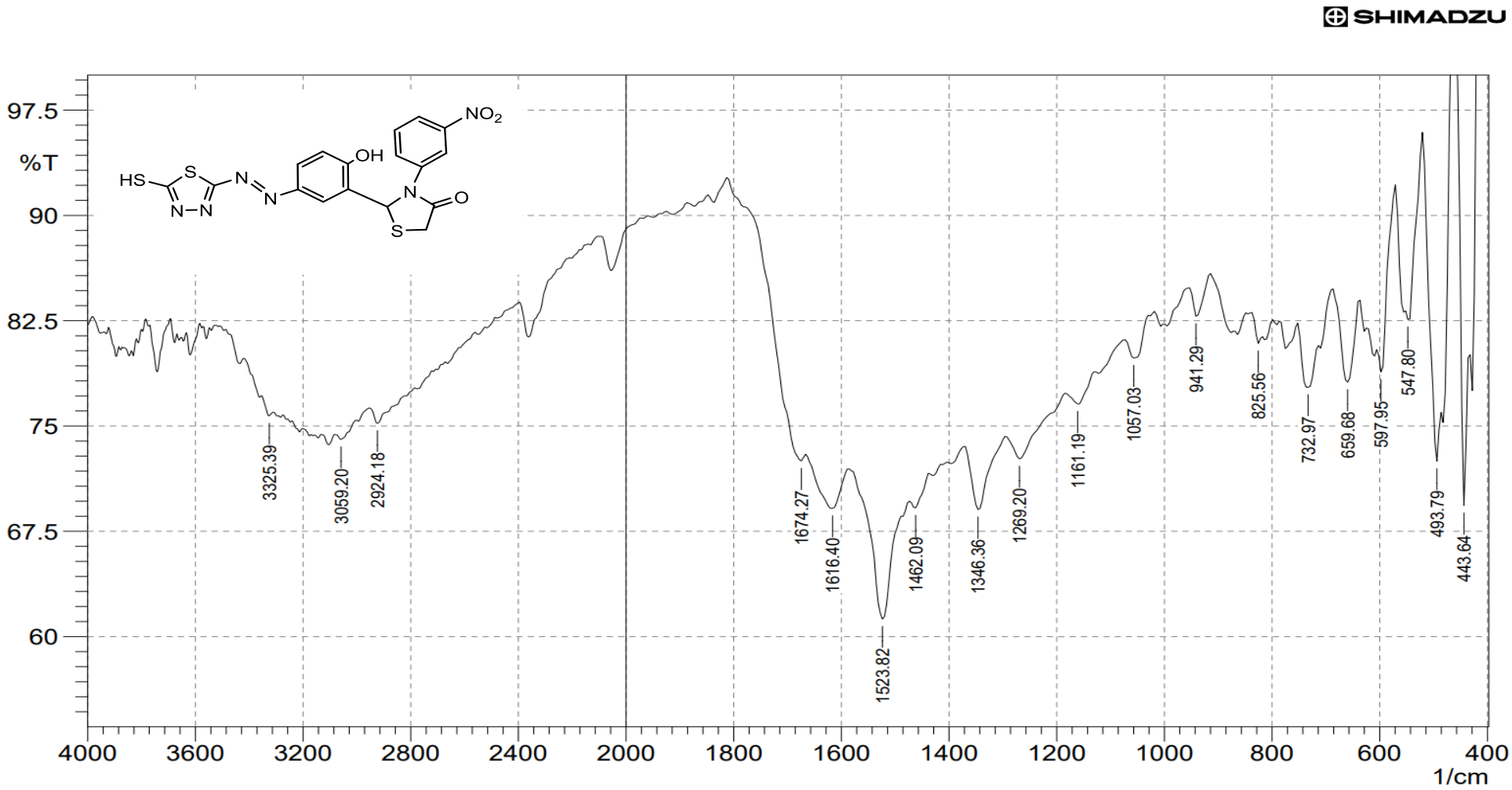


Figure (3-28): FT-IR spectrum of compound (4f)

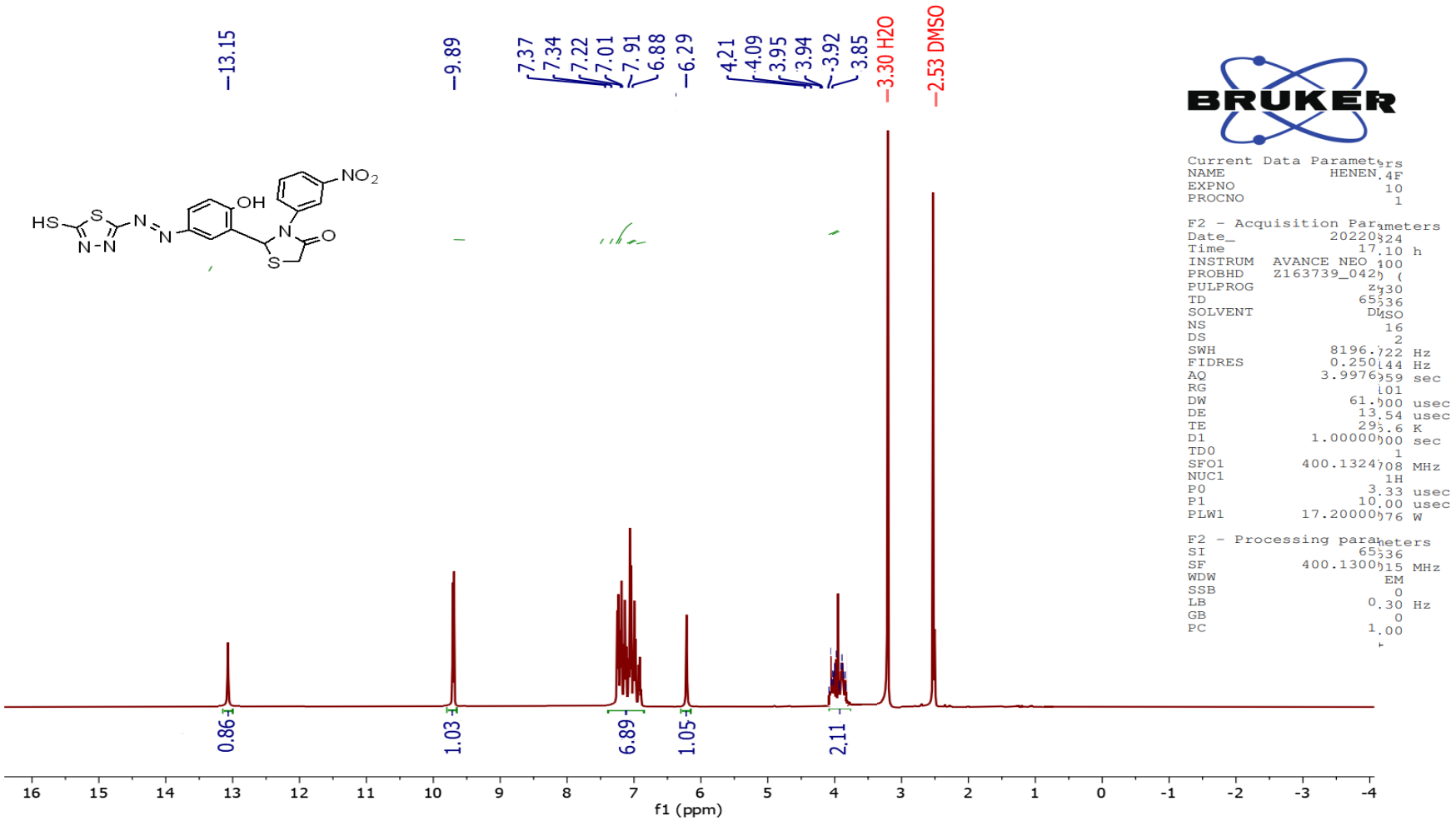


Figure (3-29): ^{1}H NMR spectrum of compound (4f)

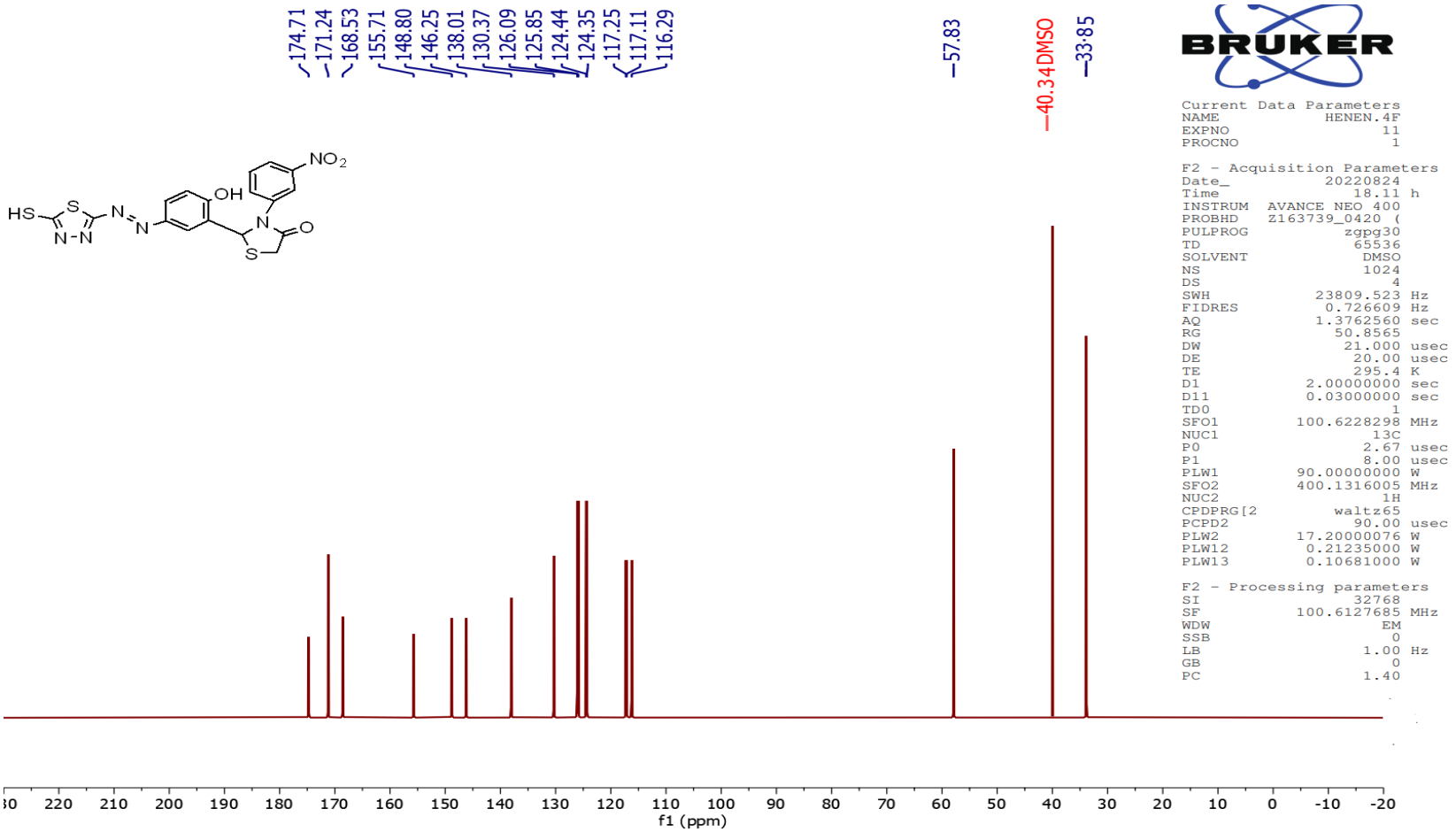


Figure (3-30):^{13}C NMR spectrum of compound (4f)

(IR) spectrum of thiazolidin-4-one copound (4g) indicated appearing peak for (C=O) stretching of thiazolidinone ring at 1643 cm^{-1}), whereas imine (C=N) stretching of thiadiazole unit appeared around1624 cm^{-1}, (table 2).

^{1}H NMR spectrum of compound (4g) appeared signal of (CH_2) protons of thiazolidinone unit as multiplet around δ 3.90 ppm. The singlet peak at δ 6.48 ppm for (CH) proton of thiazolidinone ring. The signals of aromatic hydrogens as multiplet around δ 7.02–7.44 ppm. The signal of (O-H) proton recorded at δ 9.91 ppm. Thiolic (S-H) hydrogen appeared at δ 13.88 ppm.

^{13}C NMR of derivative (4g) recorded two lines around δ 33.49 ppm and 58.41 ppm assigned to (CH_2) and (CH) carbons of thiazolidinone moiety, correspondingly. The aromatic carbons appeared signals at δ 117.21-155.74 ppm, the (C-SH) carbon of thiadiazole recorded signal at δ 168.56 ppm, the signal of carbonyl group carbon recorded around δ 170.44 ppm, the signal around δ 174.79 ppm attributed to (C-N=N) carbon of thiadiazole moiety.

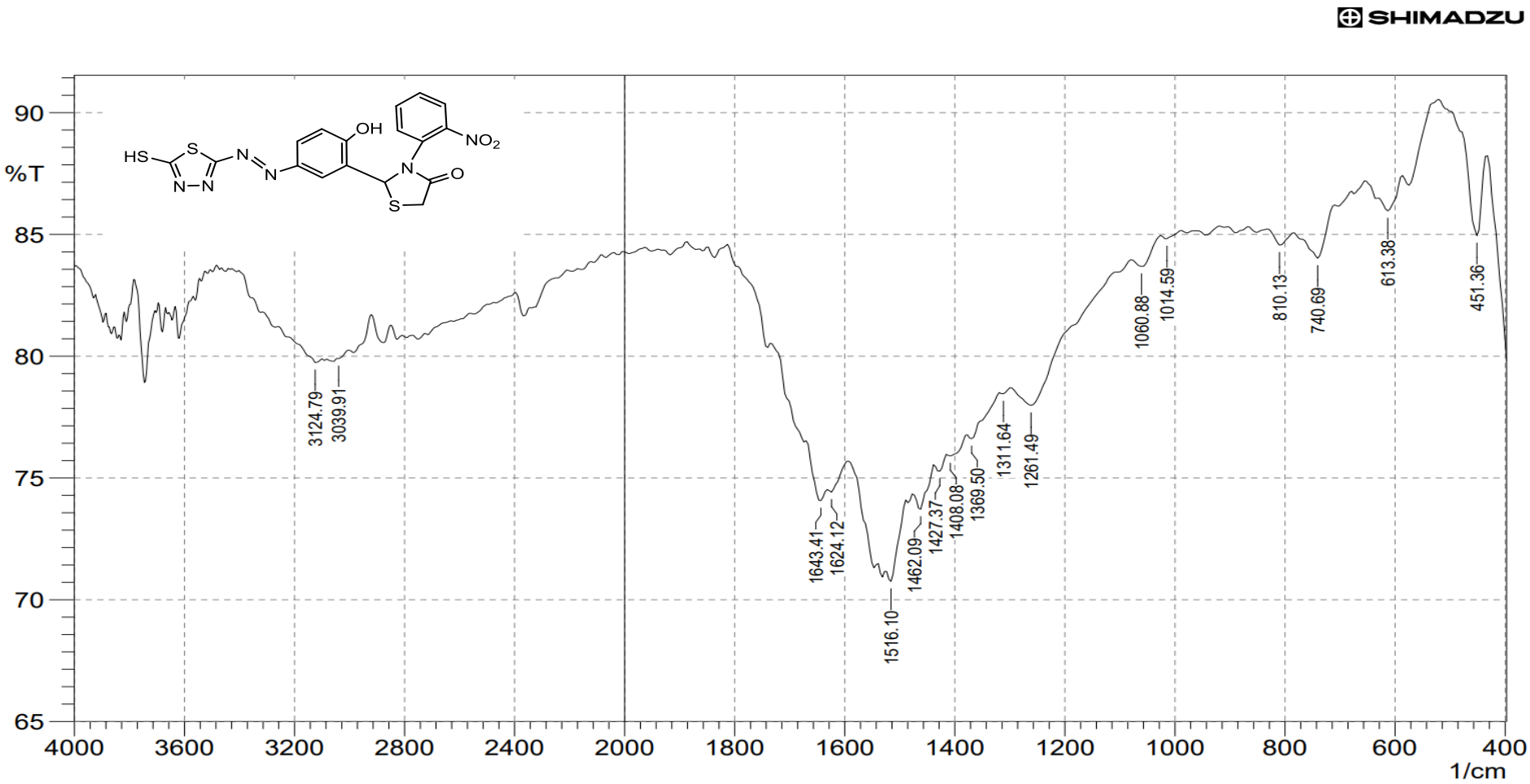


Figure (3-31): FT-IR spectrum of compound (4g)

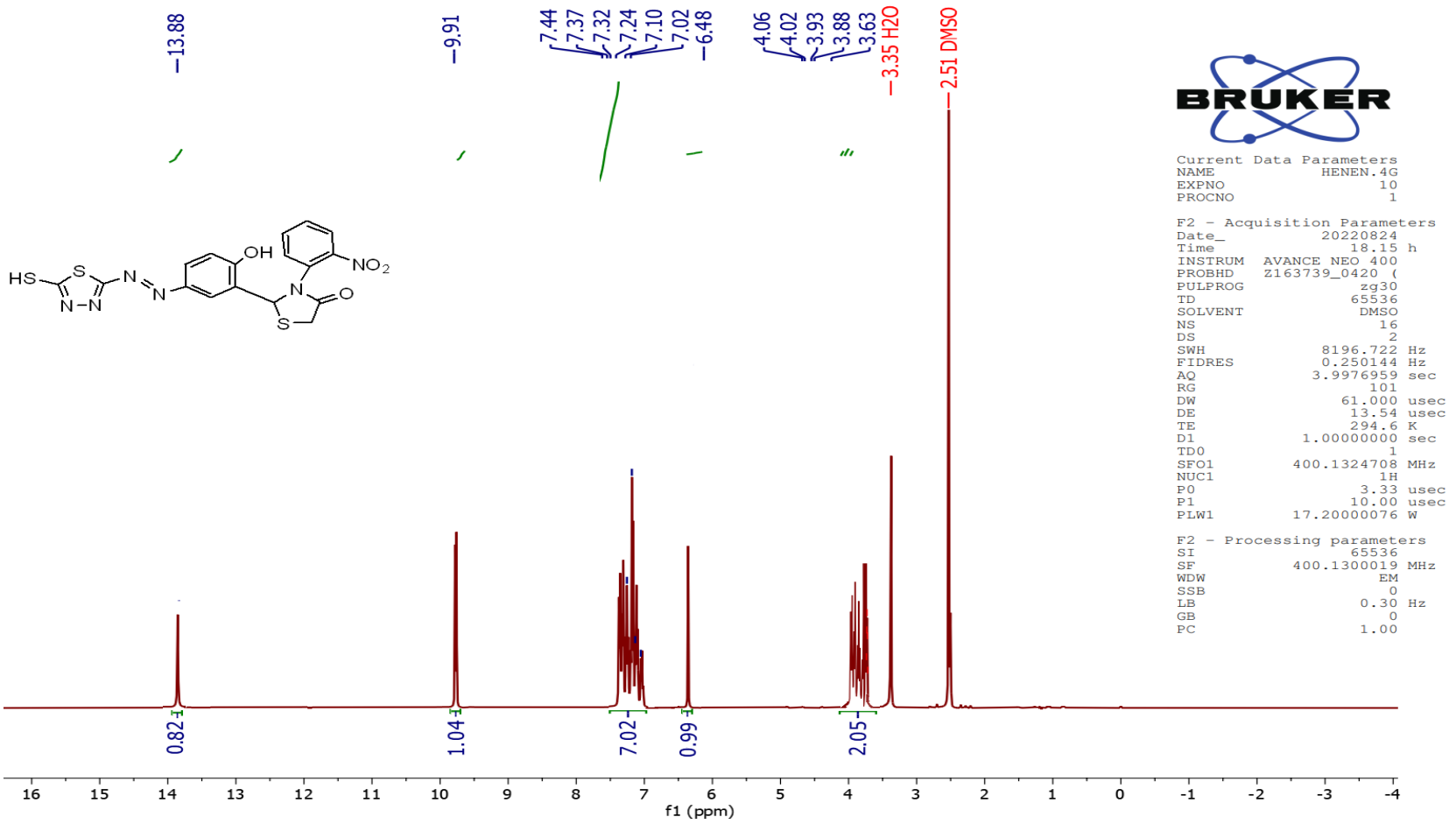


Figure (3-32):^{1}H NMR spectrum of compound (4g)

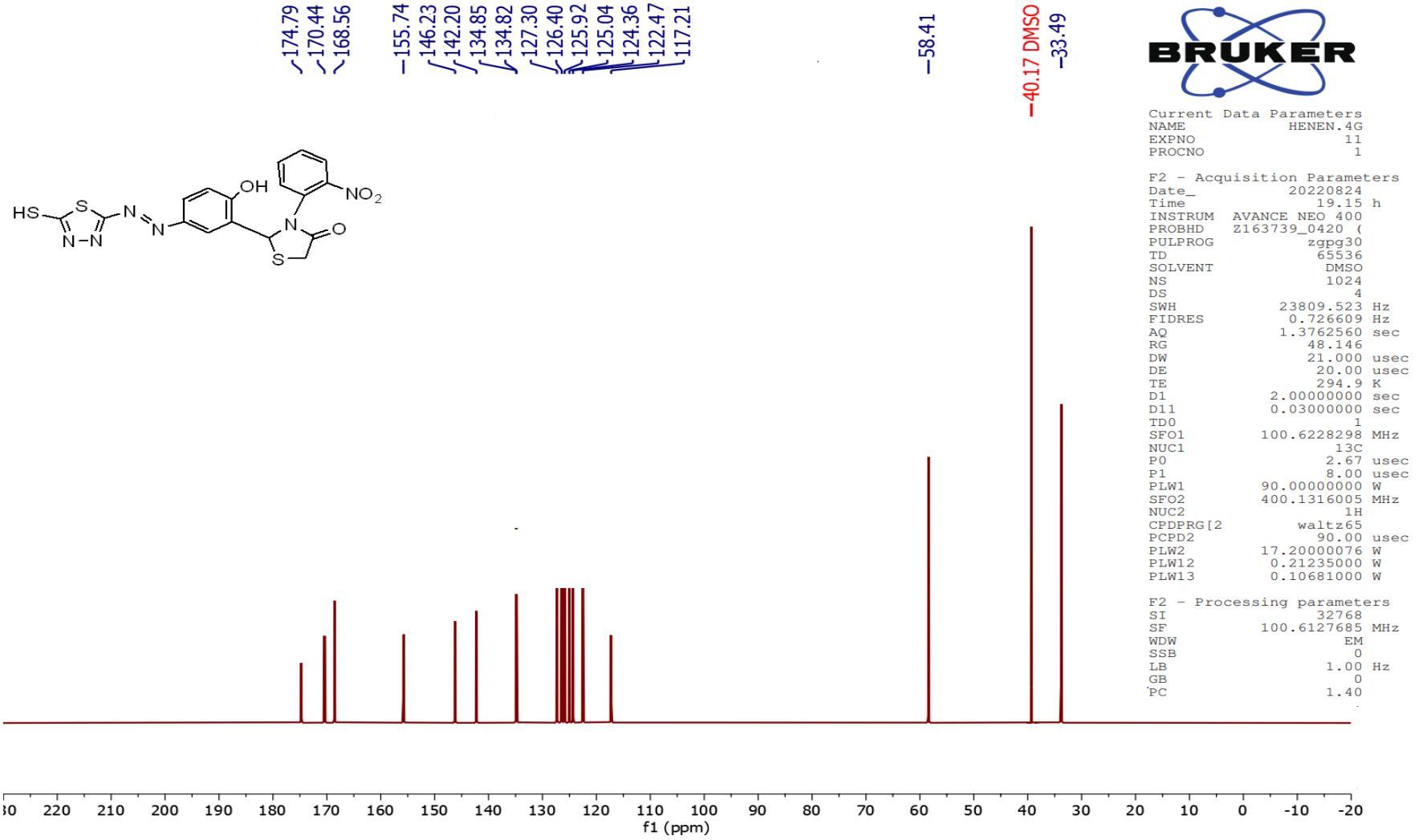


Figure (3-33):^{13}C NMR spectrum of compound (4g)

Infrared spectrum of thiazolidin-4-one (4h) pointed peak of (C=O) stretching of thiazolidinone ring at 1701 cm^{-1}), the peak of (C=N) stretching of thiadiazole was recorded around 1624 cm^{-1}, (table 2).

^{1}H NMR spectrum of compound (4h) showed multiple peak around δ 3.99 ppm assigned to methylene protons of thiazolidinone moiety. The signal of (CH) proton for thiazolidinone unit pointed around δ 6.84 ppm. The multiple signals around δ 6.89–7.32 ppm assigned to (Ar-H) hydrogens. The singlet peaks around δ 9.39 ppm and 9.85 ppm assigned to protons of (O-H) groups. The peak around δ 13.21 ppm attributed to sulfhydryl proton.

^{13}C NMR spectrum of compound (4h) pointed signals of (CH_2) and (CH) carbons of thiazolidinone around δ 33.82 ppm and 57.84 ppm, correspondingly, the signals recorded at the range δ 116.99-155.76 ppm due aromatic carbons, the signal around δ 168.74 ppm for (C-SH) carbon of thiadiazole, the signal of carbonyl carbon of thiazolidinone appered at δ 171.20 ppm, the signal pointed around 174.57 ppm attributed to (C-N=N) carbon of thiadiazole ring.

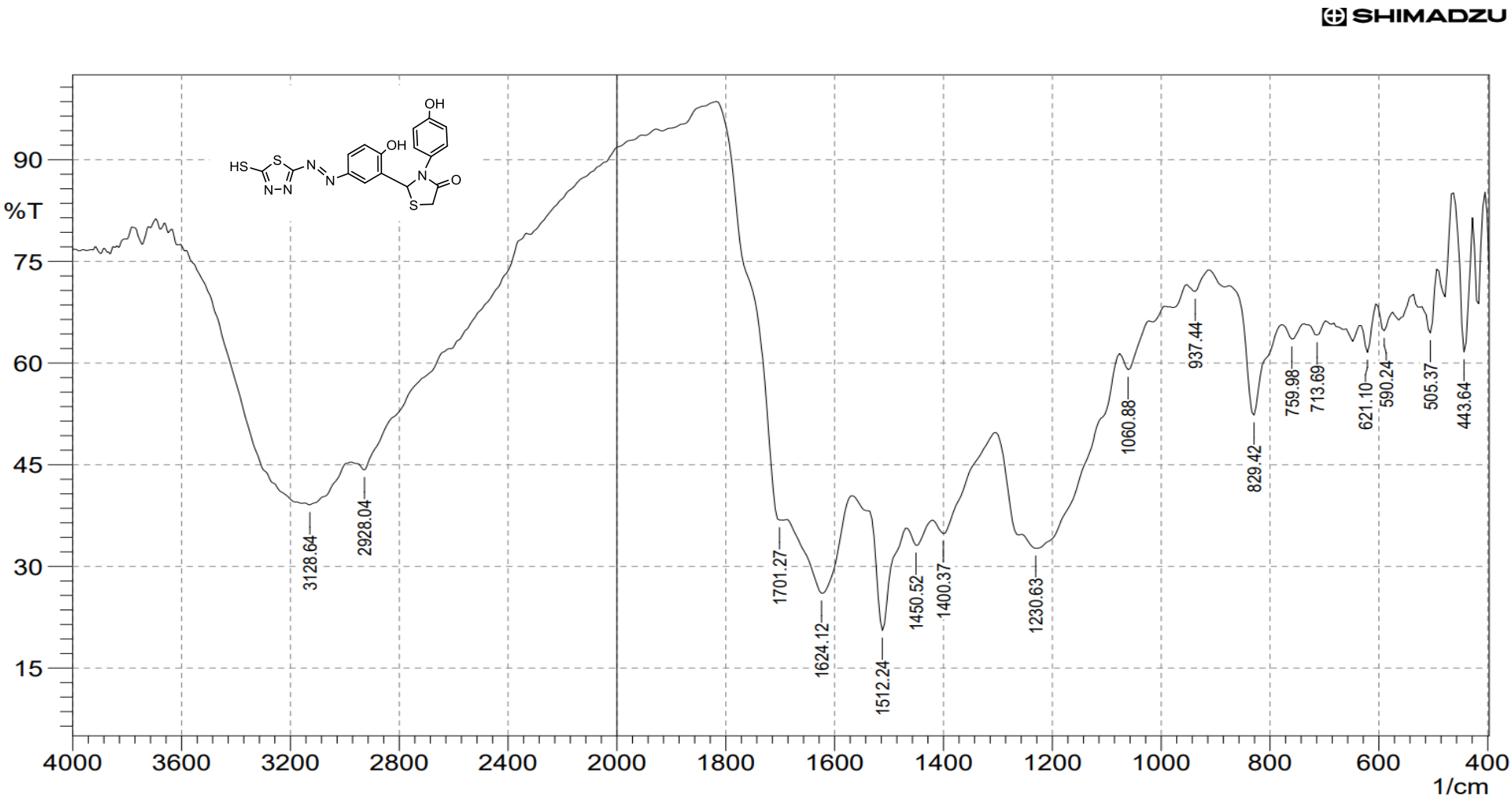


Figure (3-34): FT-IR spectrum of compound (4h)

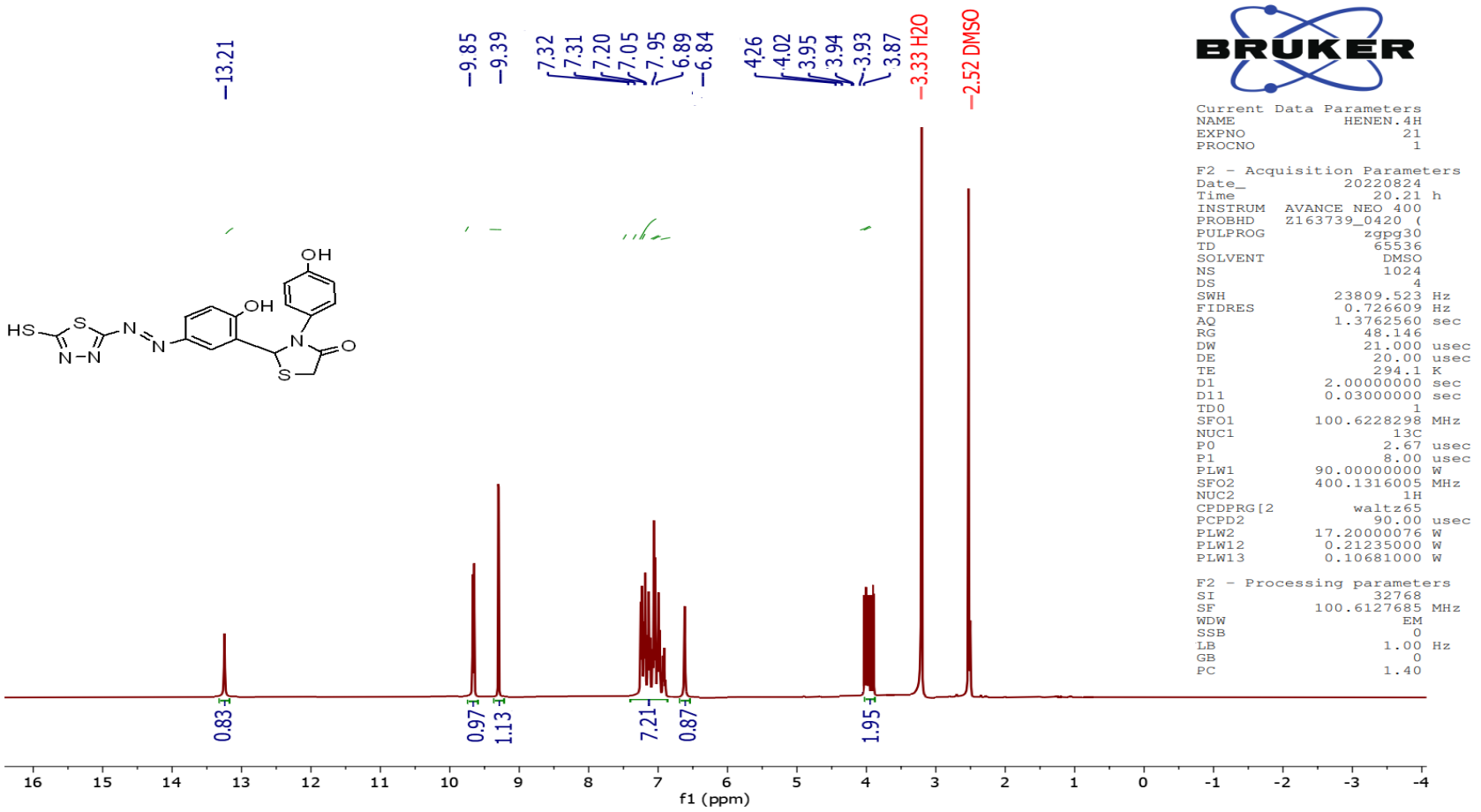


Figure (3-35): ^{1}H NMR spectrum of compound (4h)

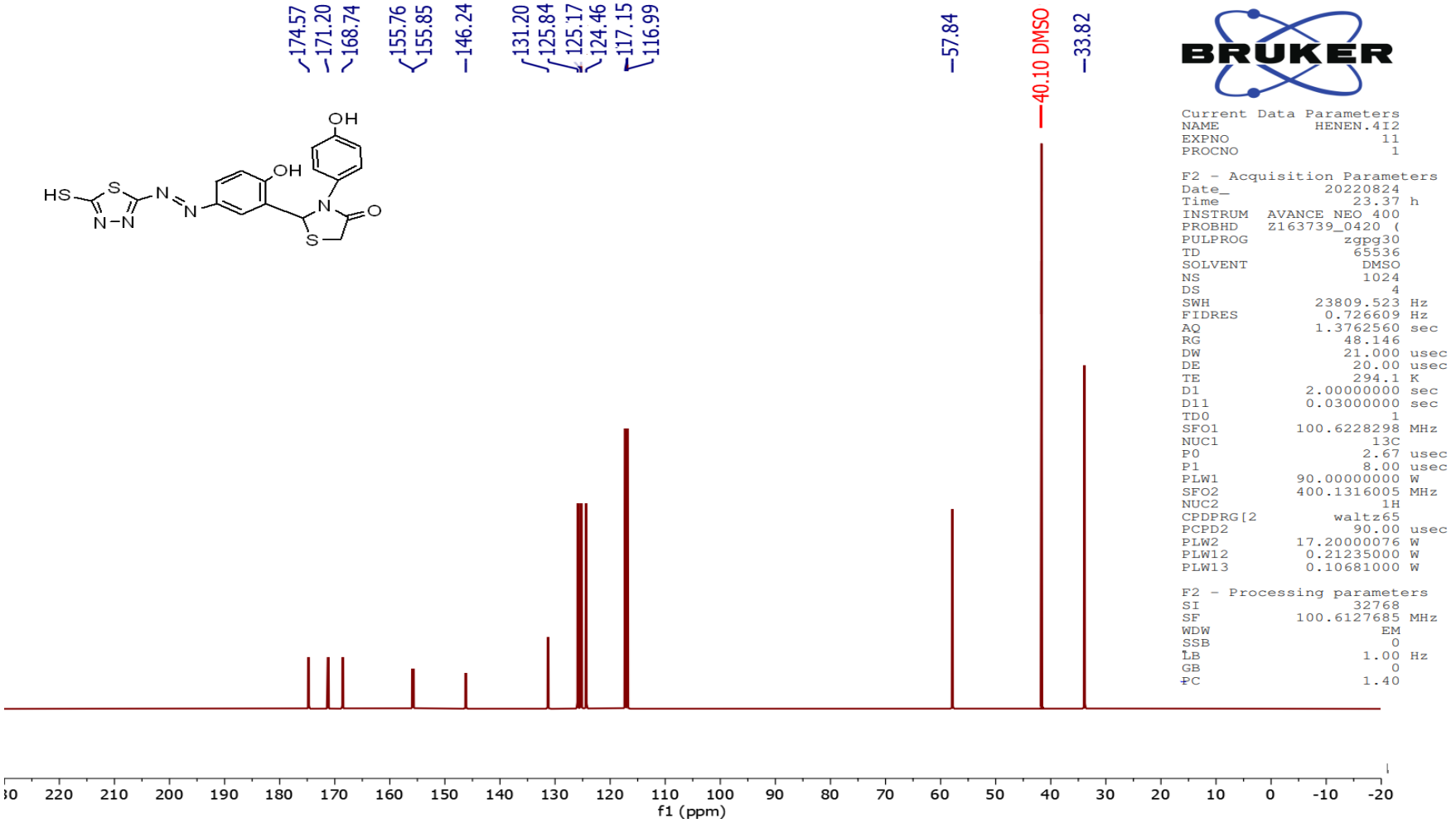


Figure (3-36): ^{13}C NMR spectrum of compound (4h)

Infrared spectrum of thiazolidin-4-one compound (4i) showed band around 1658 cm^{-1} due to (C=O) stretching of thiazolidinone moiety, also the peak at 1616 cm^{-1} attributed to stretching of (C=N) group of thiadiazole unit, table (3-2).

^{1}H NMR spectrum of compound (4i) indicated multiplet signal around 3.99 ppm for (CH_2) protons of thiazolidinone ring. The peak of (CH) proton of thiazolidinone ring appeared as singlet around 6.87 ppm. The (Ar-H) hydrogens appeared as multiplet around δ 6.89–7.39 ppm. The signals of (O-H) groups hydrogens appeared at δ 9.30 ppm and 9.81 ppm. Proton of (S-H) recorded at δ 13.31 ppm.

^{13}C NMR spectrum of compound (4i) appeared two signals for (CH_2) and (CH) carbons of thiazolidinone moiety at δ 33.85 ppm and 57.87 ppm, correspondingly, the signals of aromatic carbons pointed around δ 107.19-158.74 ppm. The signal around δ 168.55 ppm for (C-SH) carbon of thiadiazole, the signal around δ 171.26 ppm assigned to carbonyl carbon of thiazolidinone unit, the signal of (C-N=N) carbon of thiadiazole unit recorded around 174.64 ppm.

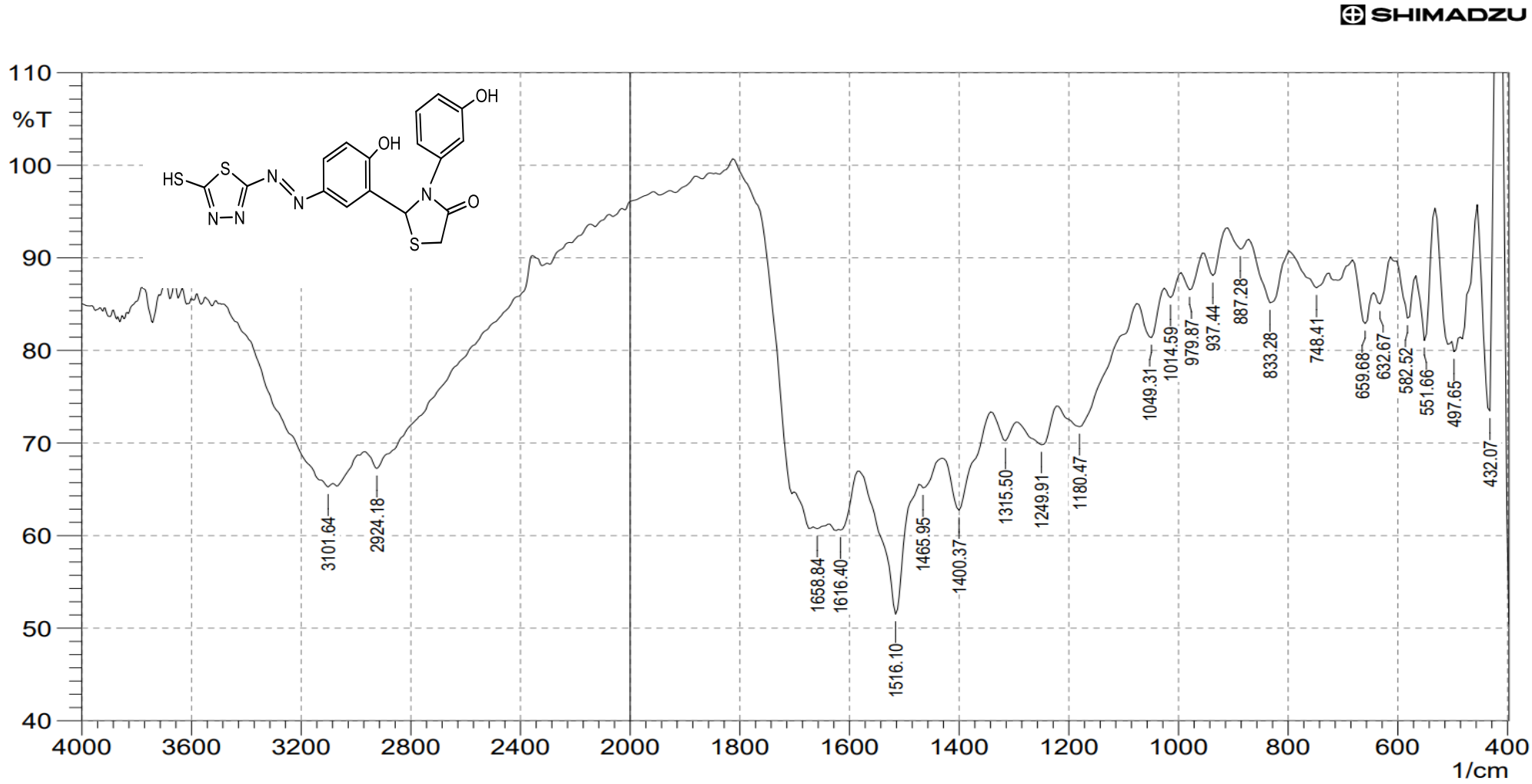


Figure (3-37): FT-IR spectrum of compound (4i)

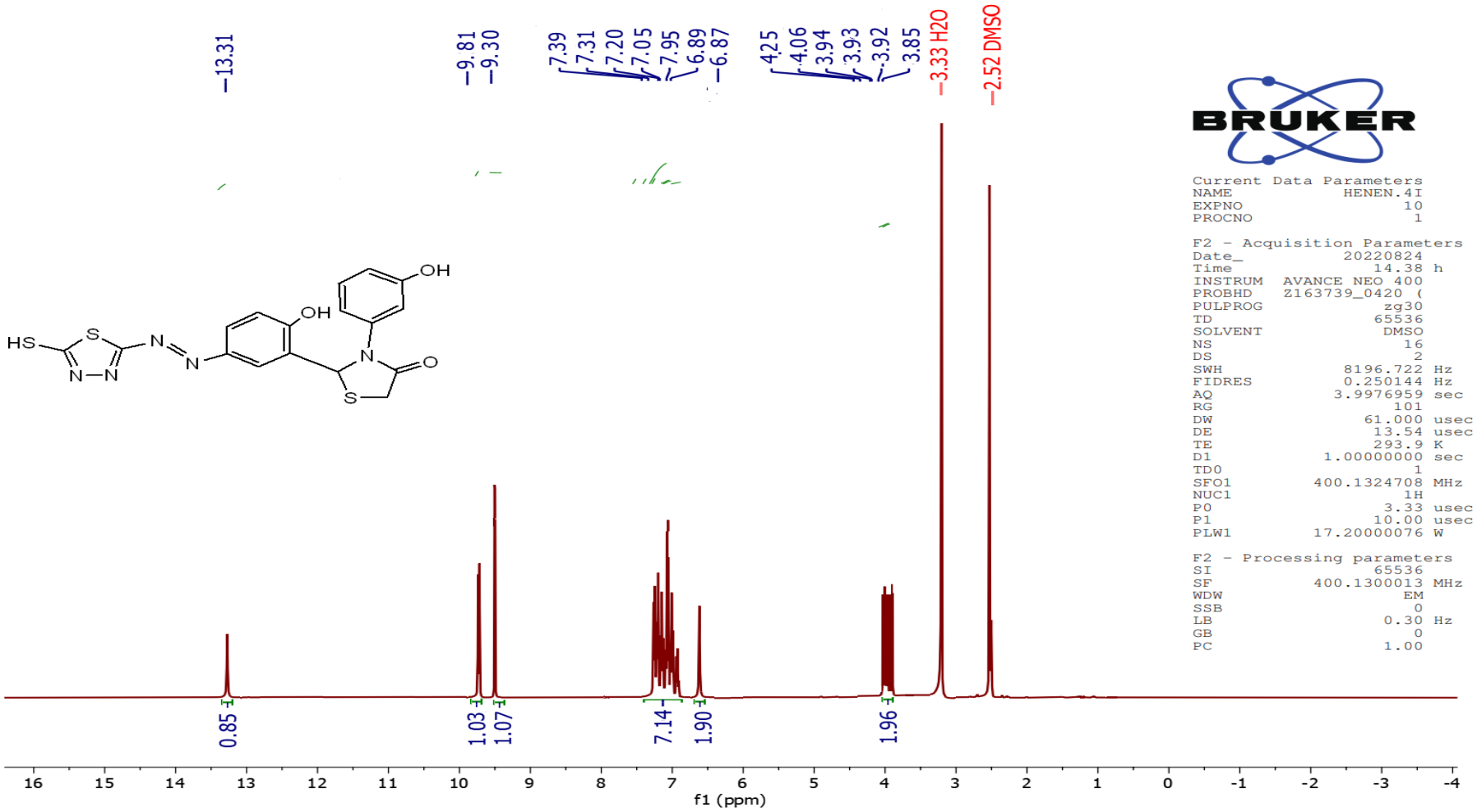


Figure (3-38):^{1}H NMR spectrum of compound (4i)

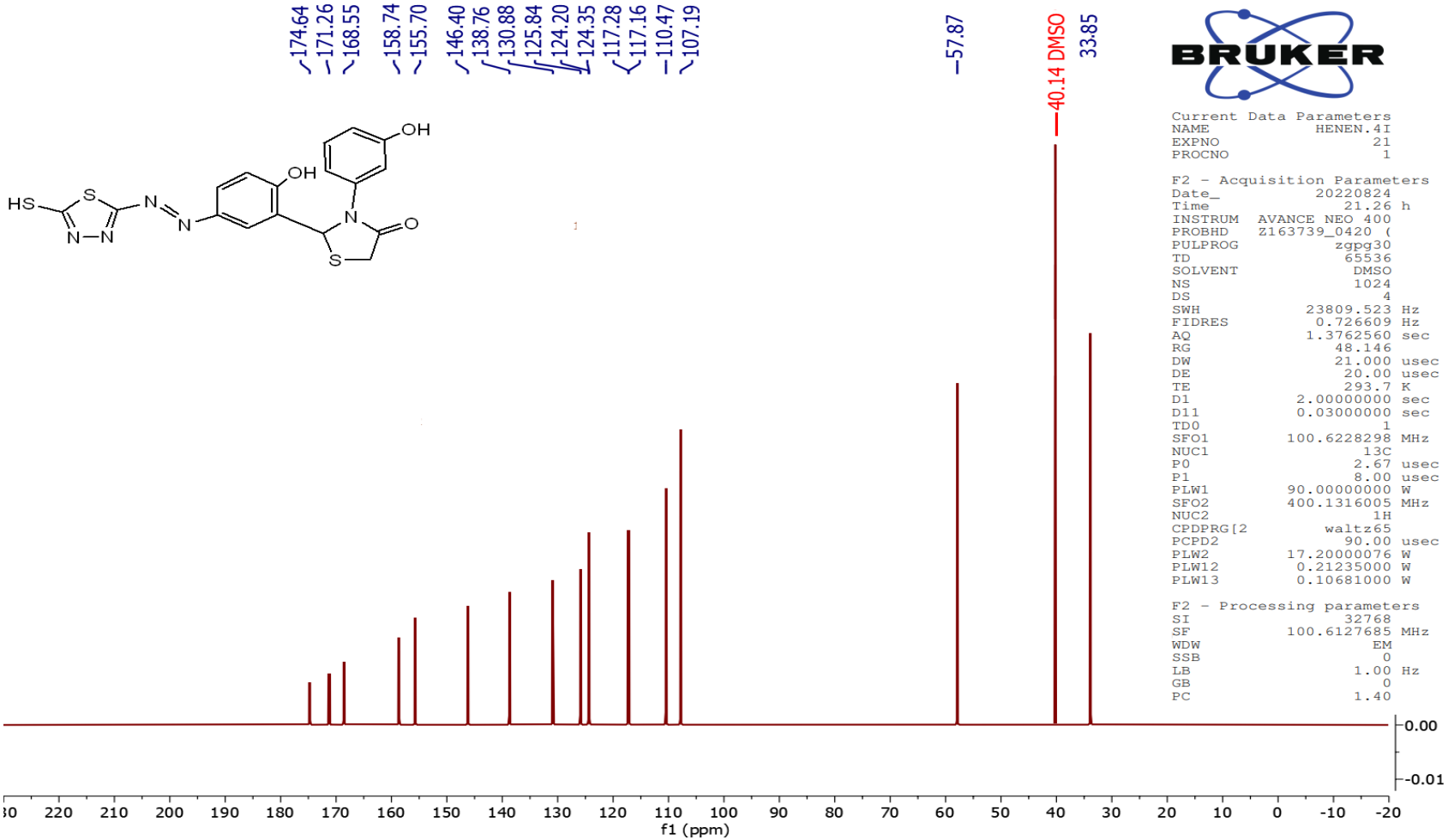


Figure (3-39):^{13}C NMR spectrum of compound (4i)

Infrared of thiazolidin-4-one derivative (4j) showed appearance of peak around 1627 cm^{-1}) for (C=O) stretching of thiazolidinone unit, whereas band around 1585 cm^{-1} assigned to (C=N) group of thiadiazole moiety, (table 2).

^{1}H NMR of derivative (4j) appeared the multiplet signal of (CH_2) protons around δ 3.99 ppm, the (CH) hydrogen appeared around δ 6.80 ppm. (Ar-H) hydrogen as multiplet at δ 6.89-7.36 ppm. The hydroxyl groups protons as two signals around δ 9.35 ppm and 10.33 ppm. The peak around 13.33 ppm for (S-H) hydrogen.

^{13}C NMR of derivatives (4j) appeared two lines around δ 33.57 ppm and 58.63 ppm for (CH_2) and (CH) carbons of thiazolidinone unit, respectively. The signals of aromatic carbons recorded around δ 115.35-155.75 ppm, the signal of (C-SH) carbon of thiadiazole ring pointed around δ 168.55 ppm, the signal of (C=O) carbon of thiazolidinone recorded around δ 170.63 ppm, the signal of (C-N=N) carbon for thiadiazole indicated around 174.89 ppm.

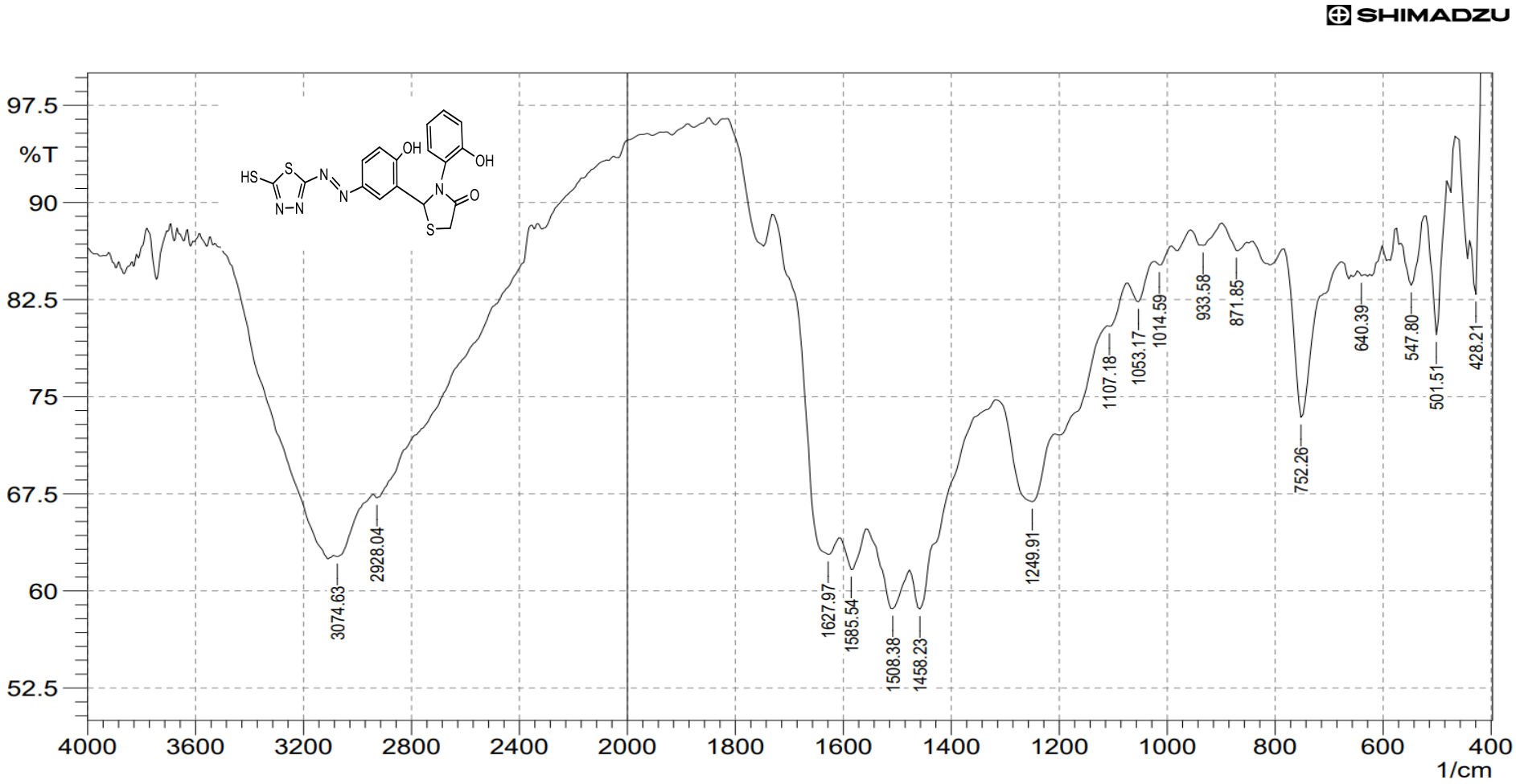


Figure (3-40): FT-IR spectrum of compound (4j)

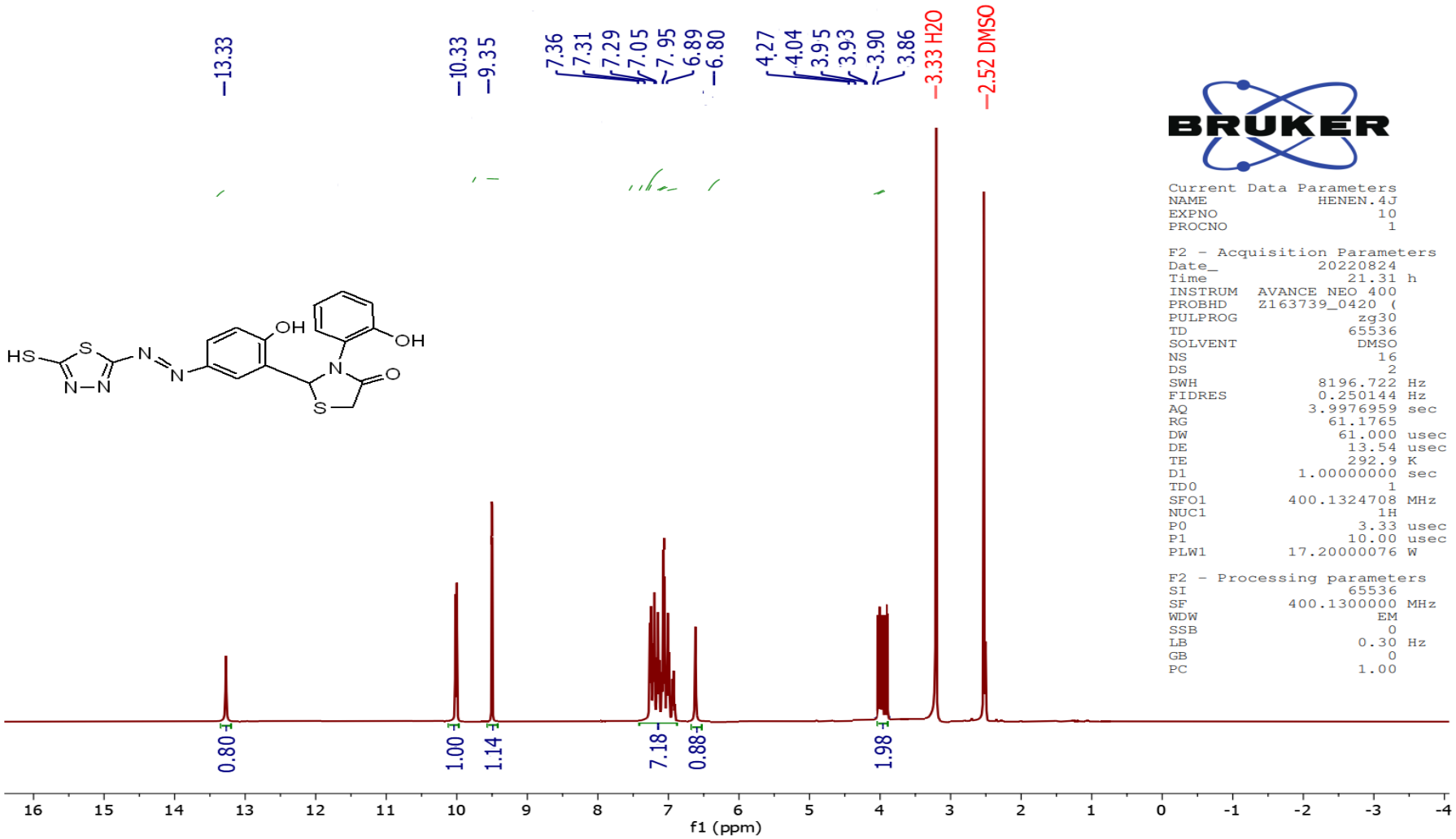


Figure (3-41):^{1}H NMR spectrum of compound (4j)

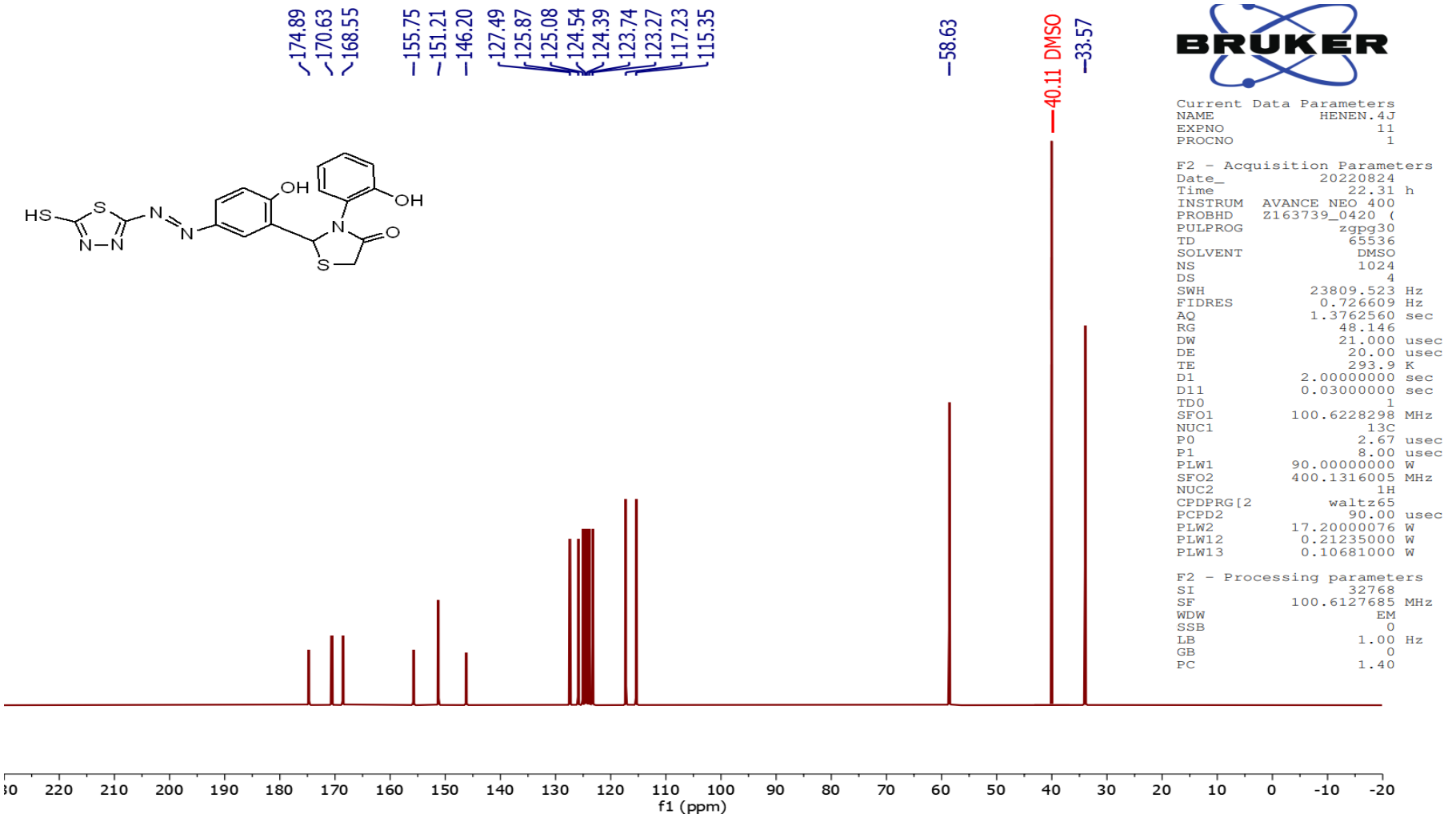


Figure (3-42): ^{13}C NMR spectrum of compound (4j)

Table (3-2): Infrared data of 1,3-thiazolidin-4-ones (4a-j) in cm^{-1}

Comp. NO	(O-H)str	(N-H)str thione form	(C-H)str aroma.	(C=O)str	(C=N) str imine	(C=N)str thiadiazole	(C=C)str benzene	(N=N)str	(C=S)str thione form	Others
4a	3371	3228	3050	1643	-	1612	1516 1462	1420	1060	2900 (C-H) str aliph.
4b	3120	3120 overlapped	3020	1658	-	-	1516 1450	1410	1049	2920.(C-H)str aliph.
4c	3086	3086 overlapped	3086 overlapped	1647	-	1581	1516 1485	1425	1060	2920 (C-H)str thiazolidine 1103 (C-Cl)str
4d	3279	3109	3063	1712	-	1600	1531 1492	-	1091	2931 (C-H)str thiazolidine 1091(C-Cl)str overlapped
4e	3282	3282 overlapped	3051	1670	-	1600	1570 1523	1400	1060	2928 (C-H)str thiazolidine 1516, 1246 (NO_2)str
4f	3325	3115	3059	1674	-	1616	1462	1425	1057	2924 (C-H)str thiazolidine 1523, 1269 (NO_2)str
4g	3124	3124 overlapped	3039	1643	-	1624	1462	1427	1060	2925 (C-H)str thiazolidine 1516, 1261 (NO_2)str
4h	3128	3128 overlapped	3128 overlapped	1701	-	1624	1512 1450	1400	1060	2928(C-H)str thiazolidine
4i	3101	3101 overlapped	3070	1658	-	1616	1516 1465	1400	1049	2924.(C-H)str thiazolidine
4j	3100	3100 overlapped	3074	1627	-	1585	1508 1458	-	1053	2928(C-H)str thiazolidine

Table (3-3): ^{1}H NMR data of 1,3-thiazolidin-4-ones (4a-j) (400 MHz, δ ppm, DMSO-d_6 solvent)

Entry	CH_2 thiazolidinone	C-H Thiazolidinone	Ar-H	O-H	S-H	Others
4a	3.90 (m, 2H)	6.24 (s, 1H)	7.06–7.47 (m, 7H)	9.68 (s, 1H)	13.78 (s, 1H)	3.84 (s, 3H, OCH_3) 2.51 (s, DMSO) 3.39 (m, HOD)
4b	3.73 (m, 2H)	5.95 (s, 1H)	6.89–7.36 (m, 6H)	9.54 (s, 1H)	13.60 (s, 1H)	2.34 (s, 3H, 2-CH_3) 2.67 (s, 3H, 4-CH_3) 2.51 (s, DMSO) 3.30 (m, HOD)
4c	3.93 (m, 2H)	6.16 (s, 1H)	6.93–7.43 (m, 6H)	9.61 (s, 1H)	13.05 (s, 1H)	2.51 (s, DMSO) 3.30 (s, HOD)
4d	3.98 (m, 2H)	6.55 (s, 1H)	6.91–7.48 (m, 7H)	9.15 (s, 1H)	13.52 (s, 1H)	2.51 (s, DMSO) 3.35 (s, HOD)
4e	3.90 (m, 2H)	6.48 (s, 1H)	6.85–7.34 (m, 7H)	9.79 (s, 1H)	13.96 (s, 1H)	2.53 (s, DMSO) 3.30 (s, HOD)
4f	3.99 (m, 2H)	6.29 (s, 1H)	7.88–7.37 (m, 7H)	9.89 (s, 1H)	13.15 (s, 1H)	2.53 (s, DMSO) 3.30 (s, HOD)
4g	3.90 (m, 2H)	6.48 (s, 1H)	7.02–7.44 (m, 7H)	9.91 (s, 1H)	13.88 (s, 1H)	2.51 (s, DMSO) 3.35 (s, HOD)
4h	3.99 (m, 2H)	6.84 (s, 1H)	6.89–7.32 (m, 7H)	9.39, 9.85 (s, s, 2H, 2OH)	13.21 (s, 1H)	2.52 (s, DMSO) 3.33 (s, HOD)
4i	3.99 (m, 2H)	6.87 (s, 1H)	6.89–7.39 (m, 7H)	9.30, 9.81 (s, s, 2H, 2OH)	13.31 (s, 1H)	2.52 (s, DMSO) 3.33 (s, HOD)
4j	3.99 (m, 2H)	6.80 (s, 1H)	6.89–7.36 (m, 7H)	9.35, 10.33 (s, s, 2H, 2OH)	13.33 (s, 1H)	2.52 (s, DMSO) 3.33 (s, HOD)

Table (3-4): ^{13}C NMR data of 1,3-thiazolidin-4-ones (4a-j) (100 MHz, δ ppm, DMSO-d_6 solvent)

Entry	CH_2 thiazolidinone	C-H thiazolidinone	Ar-H	C-SH thiadiazole	C=O thiazolidinone	C-N=N thiadiazole	Others
4a	33.96	58.42	113.57-155.74 (12C)	168.20	170.57	174.76	55.0 (OCH_3)
4b	33.89	58.55	117.20-155.77 (12C)	168.58	170.54	174.72	18.20 (2-CH_3) 20.80 (4-CH_3)
4c	33.72	58.58	117.24-155.69 (12C)	168.54	170.20	174.69	-
4d	33.83	57.88	117.24-155.57 (12C)	168.55	171.74	174.20	-
4e	33.82	57.85	117.24-155.70 (12C)	168.77	171.24	174.64	-
4f	33.85	57.83	116.29 -148.80 (12C)	168.53	171.24	174.71	-
4g	33.49	58.41	117.21-155.74 (12C)	168.56	170.44	174.79	-
4h	33.82	57.84	116.99-155.76 (12C)	168.74	171.20	174.57	-
4i	33.85	57.87	107.19-158.74 (12C)	168.55	171.26	174.64	-
4j	33.57	58.63	115.35-155.75 (12C)	168.55	170.63	174.89	-

(CHNS) Elemental analysis of 1,3-thiazolidin-4-ones 4a-j

The (CHNS) elemental microanalysis measurements of the final 1,3-thiazolidin-4-one compounds showed good agreement between calculated and observed values, table (3-5).

Table (3-5): (CHNS) Elemental analysis of thiazolidin-4-ones (4a–j)

Entry	Calculated %				Found %			
	C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
4a	48.53	3.39	15.72	21.25	48.41	3. 44	15.60	21.11
4b	51.45	3.86	15.79	21.68	51.31	3.89	15.58	21.78
4c	42.15	2.29	14.46	19.86	42.24	2.36	14.53	19.76
4d	45.38	2.69	15.57	21.38	45.22	2.75	15.41	21.47
4e	44.34	2.63	18.25	20.89	44.43	2.70	18.26	21.01
4f	44.34	2.63	18.25	20.89	44.28	2.49	18.10	20.96
4g	44.34	2.63	18.25	20.89	44.21	2.52	18.13	21.03
4h	47.32	3.04	16.23	22.29	47.45	3.16	16.24	.22.41
4i	47.32	3.04	16.23	22.29	47.39	3.13	16.32	22.38
4j	47.32	3.04	16.23	22.29	47.43	2.97	16.15	22.24

3.5. The antibacterial activities

The actions athwart bacteria of the novel 1,3-thiazolidin-4-ones **(4a-j)** have been screened via using method of agar diffusion [131] on Gram negative and Gram positive germs in dimethylsulfoxide as solvent. The novel synthesized 4-thiazolidinone compounds are containing relatively high ratio of nitrogen as well as sulfur that may be caused rise in biological activity. The new thiazolidin-4-one compounds **(4a**, **4d**, **4e**, **4h**, **4i**, and **4j)** showed activities against Gram-positive bacteria greater than Amoxicillin-clavulanate, whereas compounds **(4e**, **4h**, and **4j**)

expressed better action than Amoxicillin-clavulanate against Gram-negative bacteria, table (3-6).

Table (3-6): Antibacterial potency of 4-thiazolidinone derivatives (4a-j)

Bacteria	(Gram-positive) *Staphylococcus aurous*	(Gram-negative) *Escherichia coli*
Comp. no	**Diameter of inhibition zone in (mm)**	
4a	19	15
4b	18	16
4c	15	12
4d	24	11
4e	22	19
4f	0	0
4g	17	14
4h	22	22
4i	26	17
4j	28	22
DMSO	0	0
Amoxicillin-clavulanate	18	18

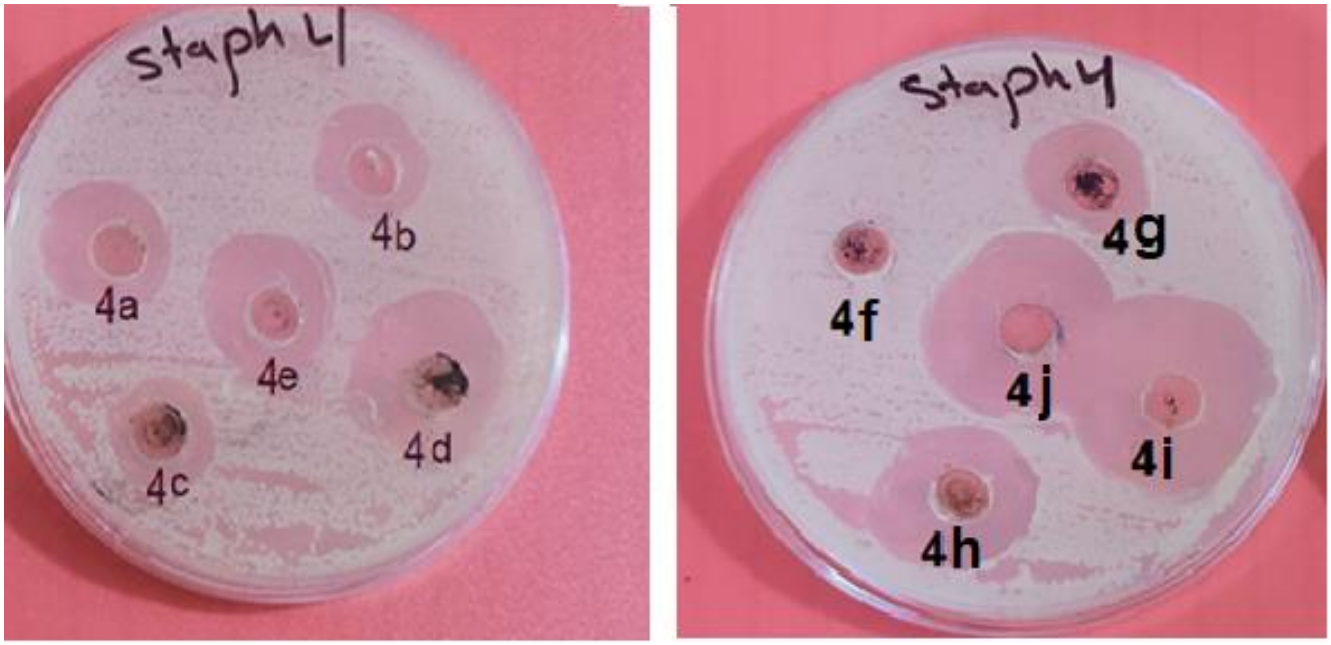


Figure (3-43): Antibacterial photographs of 4-thiazolidinone derivatives (4a-j) against *Staphylococcus aurous* .

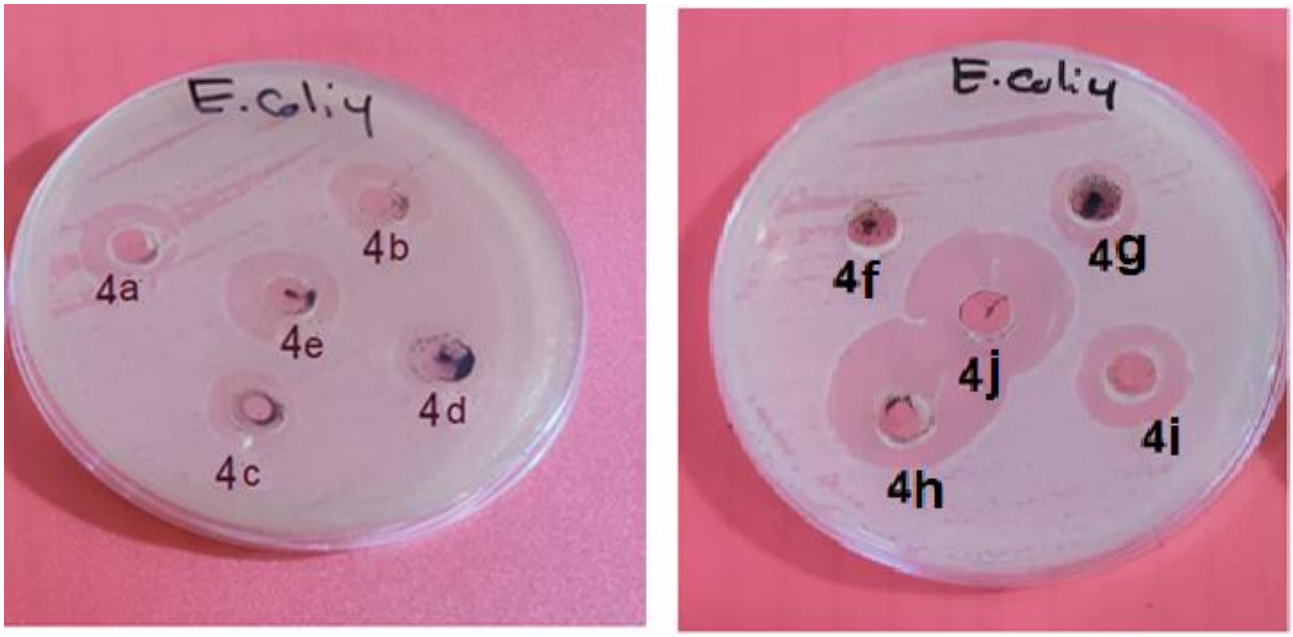


Figure (3-44): Antibacterial photographs of 4-thiazolidinone derivatives (4a-j) against *E. coli.*

Conclusions and Future work

Conclusions

1. Using microwave irradiation method assisted formation of thiazolidin-4-one ring in short reaction time and good yield, as well as green chemistry.
2. The target 4-thiazolidinone compounds have been found in two tautomeric forms (thioenol and thioketone) at part of 1,3,4-thiadiazole moiety.
3. The prepared thiazolidin-4-one derivatives have good solubility in water due to polar substituents like hydroxyl and carbonyl. If phenolic group is converted to analogues phenoxide salt, the solubility will be completed
4. The preliminary antibacterial test of the prepared thiazolidin-4-ones showed promising antibacterial results against both kinds of bacteria. Most compounds appeared activity better than that of standard antibiotic.

Future work

1. Addition of 2-aminobenzoic acid to imines to produce quinazoline compounds.
2. The synthesized imines could be oxidized into the analogues nitrone compounds using hydrogen peroxide in acidic medium.
3. Testing toxicity and minimum-influenced concentration of the synthesized thiazolidinones.
4. Study the biological actions of the prepared thiazolidinones athwart another

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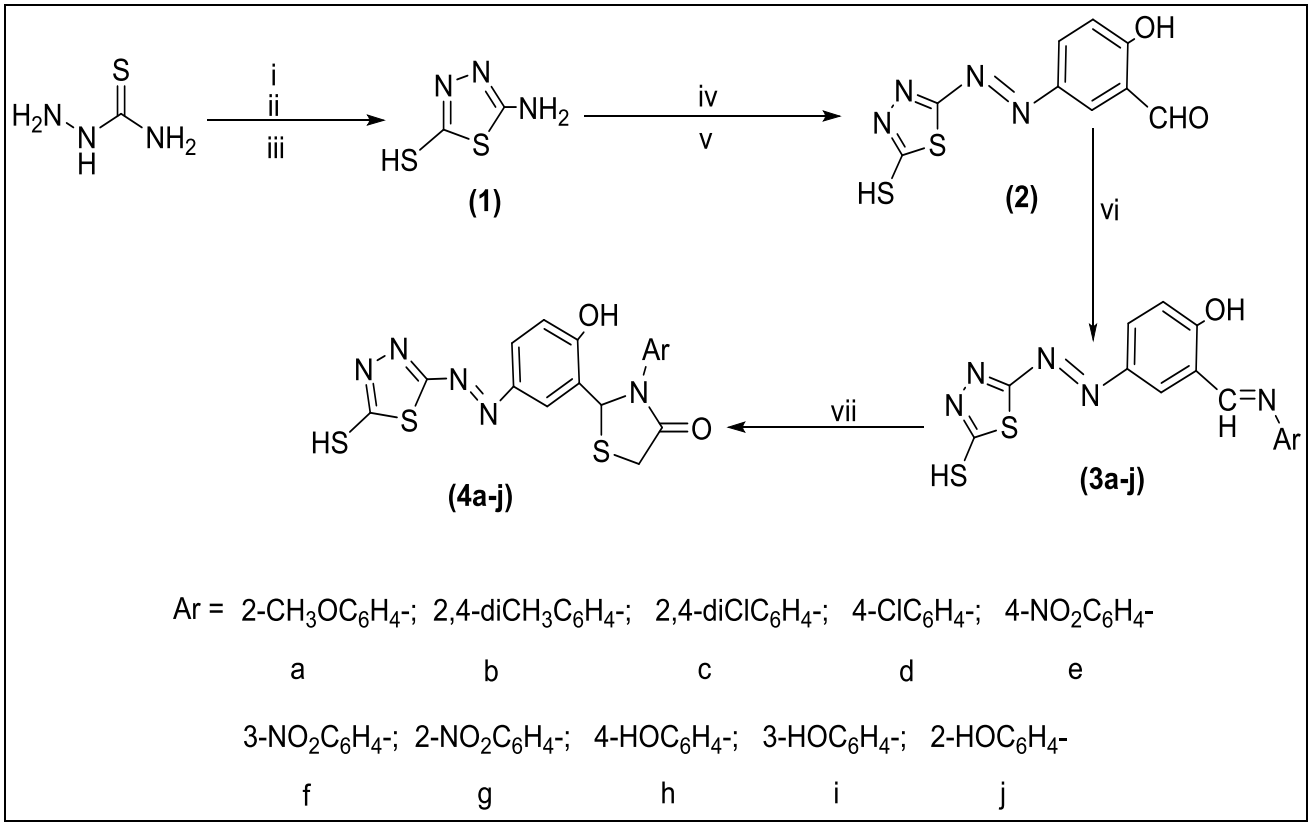
الخلاصة

تم في هذا العمل تحضير مشتقات 3،1-ثيازوليدين-4-اون جديدة حاملة لوحدة-4،3،1-ثياديازول. حضر المركب البادیء 2-امينو-5-مركبتو-4،3،1-ثياديازول بوساطة تصعيد مركب الثايوسميكاربزايد وثنائي كبريتيد الكاربون بوجود كاربونات الصوديوم اللامائية في الكحول الاثيلي المطلق. تم تحويل مركب 2-امينو-5-مركبتو-4،3،1-ثياديازول **(1)** الى ملح كلوريد 2-ثياديازوليل ازو الذي ازوج مع السالسالديهايد من خلال تفاعل ازدواج الازو معطيا مركب الالديهايد الثياديازولي الازوي **(2)**. ان تكاثف مجموعة الالديهايد في مركب **(2)** مع انيلينات متنوعة (2-ميثوكسي انيلين، 4،2-ثنائي مثيل انيلين، 4،2-ثنائي كلوروانيلين، 4-كلوروانيلين، 4-نايترو انيلين، 3-نايترو انيلين، 2-نايتروانيلين، 4-امينوفينول، 3-امينوفينول، 2-امينوفينول) من خلال تقنية المايكروويف انتج مشتقات الايمين **(3a-j)**، على التوالي. تم مفاعلة مركبات الايمين مع α-كلورواسيتايل كلورايد باستعمال طريقة الاثارة بالاشعة المايكروية في مذيب ثنائي مثيل فورماميد لانتاج مشتقات 3،1-ثيازوليدين-4-اون المطلوبة ل 4،3،1-ثياديازول **4a-j)** ،على التتالي، مخطط (I).

تم اثبات صحة التراكيب المقترحة لمركبات 4-ثيازوليدينون المطلوبة بوساطة التقنيات الطيفية المتمثلة بمطيافية الأشعة تحت الحمراء ومطيافية الرنين النووي المغناطسي للبروتون و^{13}C بالاضافة الى قياسات التحليل الكمي الدقيق للعناصر CHN). تمثل مشتقات الثيازوليدين صنف قوي جدا من المركبات الحلقية غير المجانسة في المجال الصيدلاني مما يحث الباحثين على تحضير واختبار ادوية جديدة. اشارت نتائج الدراسة الاولية ضد البكتريا بان غالبية مشتقات الثيازوليدينون الجديدة **(4a, 4d, 4e, 4h, 4i, 4j)** تمتلك تاثيراً اعلى من الدواء المرجعي (الاموكسيلين-كلافولانيت) تجاه البكتريا الموجبة لصبغة كرام (*Staphylococcus aurous*)، بينما اظهرت بعض المركبات **(4e, 4h, 4j)** نشاط افضل من المضاد المرجعي ضد البكتريا السالبة لصبغة كرام (*Escherichia coli*)، الاشكال (44-3)-(43-3).



مخطط **(I):** تحضير مشتقات 1،3-ثيازوليدين-4-ون

Scheme (I): Synthesis of 1,3-thiazolidin-4-one derivatives, Reagents and conditions (i) Na2CO3/ EtOH; (ii) CS2, 65 oC, 24 hrs; (iii) Conc. HCl; (iv) Conc. HCl, NaNO2, 0 oC; (v) 2-hydroxybenzaldehyde, NaOH 10% , 5oC; (vi) Ar-NH2, EtOH, MW (300W), (10 min); (vii) α-mercaptoacetic acid, DMF, MW (300W), (15 min).

جامعة كربلاء

كلية العلوم

قسم الكيمياء

تحضير وتقييم الفعاليات ضد البكتريا لبعض مشتقات الثيازوليدينون الجديدة للثياديازول

رسالة مقدمة إلى

جامعة كربلاء - مجلس كلية العلوم
وهي جزء من متطلبات نيل درجة الماجستيرعلوم في الكيمياء

بواسطة

حنين هادي عباس

بكالوريوس علوم في الكيمياء (2018) جامعة كربلاء

بإشراف

ا.د. زيد حسن عبود الأعرجي

2023 م **1444 هـ**