Republic of Iraq

Ministry of Higher Education & Scientific Research
University of Kerbala, College of Science
Department of Chemistry

Synthesis of Some New Heterocyclic Derivatives and Preliminary Evaluation of Their Antibacterial Activity

A Thesis

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

By

Zainab Salam Merzah
B.Sc. in Chemistry(2019)
University of Kerbala/ College of Science

Supervised by

Prof. Dr. Zeid HassanAbood

1442 A.H **2021A.D**

وَتِلْكَ الْأَمْثَالُ نَضْرِبُهَا لِلنَّاسِ وَمَا يَعْقِلُهَا إِلَّا الْعَالِمُونَ

صَدَقَ اللهُ العَلِيُّ العَظِيم

سورة العنكبوت: (43)

Supervisor Certification

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

Signature:

Name: **Prof. Dr. Zeid Hassan Abood**

Address: **University of Kerbala / College of Science**

Date: **/ /2021**

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

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

Signature:

Name: **Assist. Prof. Dr. Adnan Ibrahim Mohammed**

Address: **University of Kerbala / College of Science**

Date: **/ /2021**

Report of Linguistic Evaluator

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

Signature:

Name:

Address:

Date: **/ /2021**

Report of Scientific Evaluator

I certify that the scientific evaluation of this thesis was carried out by me and it is accepted scientifically.

Signature:

Name:

Address:

Date: **/ /2021**

Examination Committee Certification

We, the examining committee, certify that we have read this thesis "Synthesis of Some New Heterocyclic Derivatives and Preliminary Evaluation of Their Antibacterial Activity" and *examined the student* (Zainab Salam Merzah) *in its contents and that in our opinion, it is adequate as a thesis for the degree of Master of Science in chemistry.*

(Chairman)

Signature:

Name:

Title:

Address:

Date: / / 2021

(Member)

Signature:

Name:

Title:

Address:

Date: / / 2021

(Member)

Signature:

Name:

Title:

Address:

Date: / / 2021

(Member & Supervisor)

Signature:

Name: **Dr. Zeid Hassan Abood**

Title: **Prof.**

Address: **University of Kerbala / College of Science**

Date: **/ / 2021**

Approved by the council of the College of Science in its session No. **in**

/ /2021

Signature:

Name: **Dr. Jasem Hannon Hashim Al-Awadi**

Title: **Assist. Prof.**

Address: **University of Kerbala - Dean of College of Science**

Date: **/ / 2021**

Dedication

To be encouraged to persevere throughout my age, to the most prominent man in my life

(my dear father)

To those who have an increase, and they are based on the heart (My beloved mother)

To the trail and a friend

(Dear husband)

To those who made an effort in my help and they were good

(My brothers and sisters)

To my daughter ....

To everyone who contributed even a letter in my life .....To all these: I give this work, who ask God to accept him pure .

Acknowledgment

First of all, great thanks to **Allah** for the uncountable gifts and for the help to achieve this thesis.

I would like to express my sincere thanks and my appreciation to my supervisor; **Prof. Dr. Zeid Hassan Abood Ala'arajy** for his kindly interest, suggesting the project, encouragement and guidance throughout the course of this work.

Also, I want to thank all faculty members of Department of Chemistry, College of Science, University of Kerbala for their irreplaceable support of the work.

Great thanks for the staff of central health lab., Kerbala city for their assistance in antibacterial potency measurements.

Last, I would like to express my thanks to all those who helped me, in a way or another to fulfillment of this work.

Table of contents

List of tables

List of Figures

Abbreviations

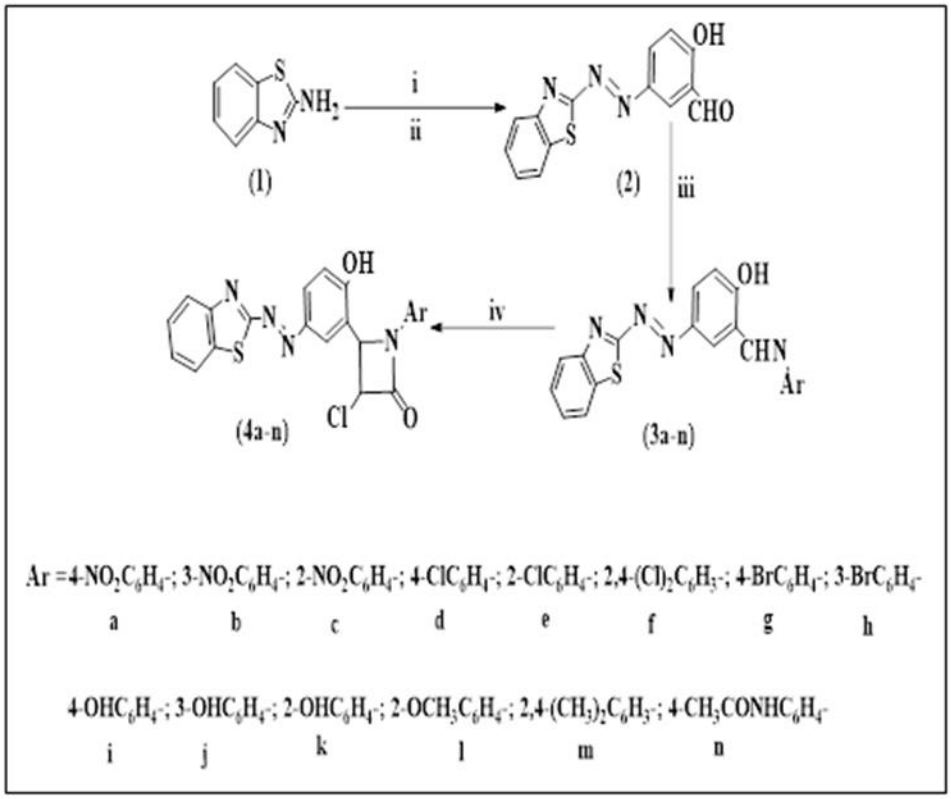
Symbol	Definition
AIDS	acquired immunodeficiency syndrome
CAC	Chloroacetyl chloride
TEA	Triethylamine
MW	Microwave
EWGs	Electron withdrawing groups
ERGs	Electron releasing groups
Et	Ethyl
HCMV	Human cytomegalovirus
µg	Microgram
^{i}Pr	isopropyl
ee	Enantiomeric excess
THF	Tetrahydrofuran
Bmim	1-Butyl-3-methylimidazolium
Cbz	Benzyloxycarbonyl
TOX	Trisoxazolines
TLC	Thin layer chromatography
d	Deutrated
DMSO	Dimethyl sulfoxide
mp	Melting point
W	Watt
n	Normal
EtOAc	Ethyl acetate
M.Wt.	Molecular weight
Min.	minute
R_f	Retention factor
FT-IR	Fourier Transform Infrared
mm	Millimeter
ν	Stretching vibration
Abs.	Absolute
Ar	Aryl
Str.	Stretching
MHz	Megahertz

EtOH	Ethanol
ppm	Part per million
MIC	Minimum influenced concentration
HIU	High intensity ultrasound
^{1}H NMR	Proton Nuclear Magnetic Resonance

Abstract

A coupling reaction of aryl diazonium salt for 2-aminobenzothiazole **(1)** with phenoxide salt for 2-hydroxybenzaldehyde afforded azoaldehyde derivative arometic **(2)** which was undergone in condensation reactions with some primary amines (4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-chloroaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-bromoaniline, 3-bromoaniline, 4-aminoophenol, 3-aminophenol, 2-aminophenol, 2-methoxyaniline, 2,4-dimethylaniline and 4-acetamidoaniline), respectively by microwave irradiation technique to give Schiff bases derivatives **(3a-n)**. The resulting imines were introduced in cyclization reaction with α-chloroacetyl chloride in *N*,*N*-dimethylformamide as solvent using microwave method to yield the target azetidin-2-one derivatives **(4a-n)**, respectively, Scheme (I).

The chemical structures of the target compounds synthesized were deduced from (CHNS) elemental analysis and FT-IR, ^{1}H NMR spectral measurements. Evaluation of activities of final β-lactam compounds **(4a n)** was taken place using two kinds of bacteria. Inhibition zones measurements pointed that azetidinone compounds **(4b**, **4c**, **4i**, **4j**, **4k, 4m** and **4n)** have best impacts to reference antibiotic (amoxicillin-clavulanate) against *E. coli* germs. On the other hand, the β-lactam compounds **(4i**, **4j**, **4k, 4m** and **4n)** indicated better activity athwart *Staphylococcus aurous* germs when compared with that of the standard antibiotic (amoxicillin-clavulanate) Figures (3-45), (3-46).



(I): Synthesis of azetidin-2-ones, Reagents and conditions (i) Conc. H2SO4, NaNO2, 0 oC; (ii) 2-hydroxybenzaldehyde, NaOH 10% , 5oC; (iii) Ar-NH2, EtOH, MW (300W), (40 min); (iv) α-chloroacetyl chloride, DMF, MW (300W), (150 min).

Chapter One

Introduction

1.1. Benzothiazole

Benzothiazole is a heterocyclic aromatic organic compound [1]. It is an important pharmacophore and a privileged structure in a medicinal chemistry, this compound is bycyclic in nature which consists of the fusion of benzene and thiazole [2]. Now a days, is a moiety of choice which posseses manypharma-cological properties. The most important compound in nature vitamin B group possess heterocyclic ring containing nitrogen, One example is vitamin B6. Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole [3]. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter [4]. Thiazole was first described by Hantzsch and Waber in 2015. Popp confirmed its structure in 2017 [5]. The basic structure of 1,3-benzothiazole consist of benzene ring fused with 4,5 position of thiazole [6], Figure (1-1).

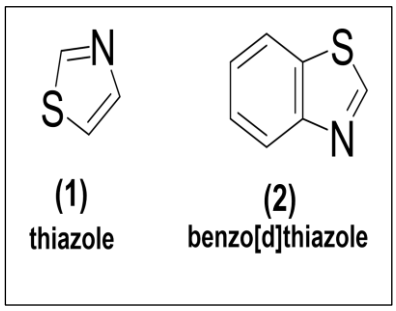


Figure (1-1) structures of thiazole and benzothiazole

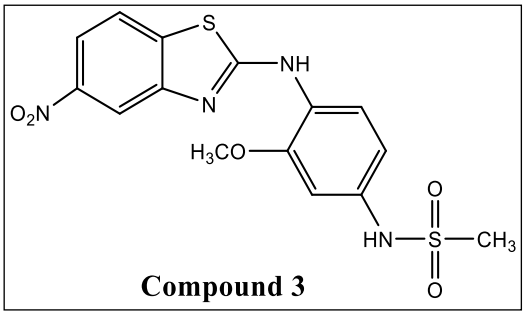
1.2. Biologically active benzothiazole

Benzothizole ring is found to be possessing many pharmacological activities such as antimicrobial [7], antiviral [8], anti bacteria [9], anticancer [10], antidiabietic [11], antiallergic [12] , antifungal [13], anti-inflammatory

[14], anthelmatic [15] and anti-HIV agents [16]. Benzothizole quinazolines show antiviral activity, subsituted 6-nitro and 6-aminobenzothizole show antimicrobial activity [17]. Due to its potent and significant biological activities, benzothiazole haseat pharmaceutical importance, hence, synthesis of this compound is of considerable interest [18]. The small and simple benzothiazole nucleus if present in compounds involved in research aimed at evaluating new products that possess interesting biological activities [19]. In the 1950s, a number of 2-aminobenzothiazoles were intensively studied, as the 2-aminobenzothiazole scaffold is one of privileged structure in medicinal chemistry and reported cytotoxic on cancer cells [20]. It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering, there are important examples of these biotargets [21].

1.2.1. Antidiabetic activity

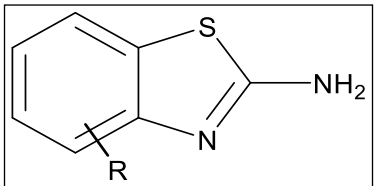
A series of N-(3-methoxy-4-((5-nitrobenzo [d]thiazol-2-yl)amino) phenyl) methane sulfonamide was synthesized and screened for their antidiabetic activity on Albino rat by alloxan induced tail tipping method [22], Compound 3.



Compound 3

1.2.2. Anti-inflammatory

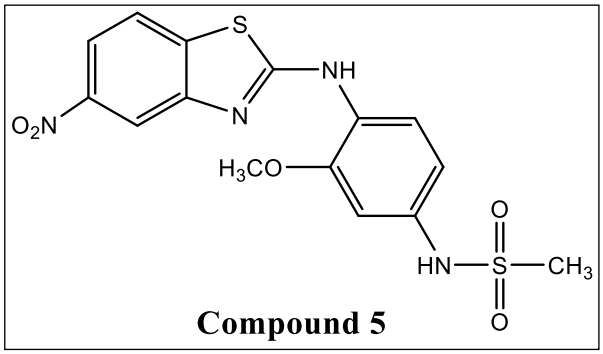
In recent years, large number of benzothiazole based anti-inflammatory agents have been synthesized. Some novel 2-amino benzothiazole derivatives and evaluated them for anti-inflammatory activity[6]. Test compounds showed significant anti-inflammatory activity and it was noted that when the 2-amino benzothiazole is substituted at 4 or 5 positions with electron-withdrawing groups like Cl, NO_2, OCH_3 increase in anti-inflammatory activity was found [23], Compound 4.



Compound 4

1.2.3. Antimalarial activity

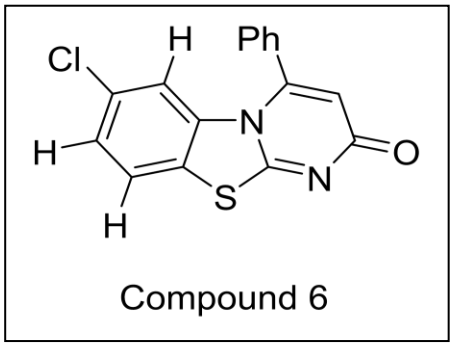
Antimalarial activity of 2- substituted-6- nitro and 6-amino benzothiazoles and their anthranilic acids were carried out on W2 and 3D7 strains of *P. falciparum*. The result srevealed the potency of compounds as the antimalarial agents of clinical and biological research [24], Compound 5.



Compound 5

1.2.4. Antimicrobial activity

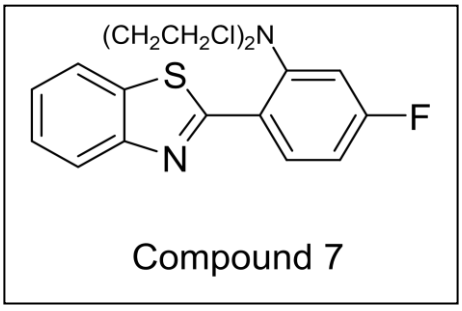
Microbes are causative agents for various types of disease like pneumonia, ameobiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various approaches were made to check the role of benzothiazole moiety as antimicrobial agent from the discovery of molecule to the present scenario [25]. Synthesis of series of pyrimido [2,1-b] benzothiazoles by conjugation addition to imino nitrogen of 2-aminobenzothiazoles to alkyne α-carbon atom of acetylenic acid followed by ring closure and synthesized compounds are studied for antimicrobial activity against *E. coli* and Enterobacter as test organisms at conc 100μg per disc using vancomycine and meropenam as standard drug [26], Compound 6.



Compound 6

1.2.5. Anticancer activity

specific antigen inhibiting activity of 2-azetidinones. A homology derived molecular model of prostate specific antigen (PSA) was created and refined [27], Compound 7.



Compound 7

1.3.*β*-lactams

Azetidin-2-one is a four member cyclic amide which was first synthesized by H. Staüdinger in 2003 [28]. Beta-Lactam antibiotics have proved to be chemotherapeutics of incomparable effectiveness, possessing a broad spectrum of biological activities with low host toxicity [29], did not come to the forefront in organic chemistry until Fleming's landmark discovery of penicillin in 2016 [30]. The resulting recognition of the b-lactam moiety as the key pharmacophoric component of the penam antibiotics initiated a flurry of synthetic activity. Today, thousands of compounds containing β-lactam rings are known, Whether isolated from natural sources or synthesized chemically, penicillins [31], [32] and cephalosporins [33] are marked by high efficacy and safe toxicological profiles and are still the most commonly used antibiotics the world over. Further, the discovery of 7-methoxycephalosporins from "Streptomyces" in 1971, carbapenems [34], thienamycin [35] , clavulanic acid [36], sulbactum [37] as well as the totally synthetic oxapenems [38], oxacephams [39], and other bicyclic β-lactams stimulated the search for novel antibiotics . More recent dedicated efforts to find new active molecules and modify the penicillin and cephalosporin structure have resulted in the discovery of simple monocyclic β-lactams such as norcardicins and monobactams [40] . Yet another dimension has been added to the b-lactam research with the recent discovery of tricyclic β-lactam antibiotics called trinems . Thus, β-lactam antibiotics in general can be classified into several groups based on their structures [41], Figure (1-2).

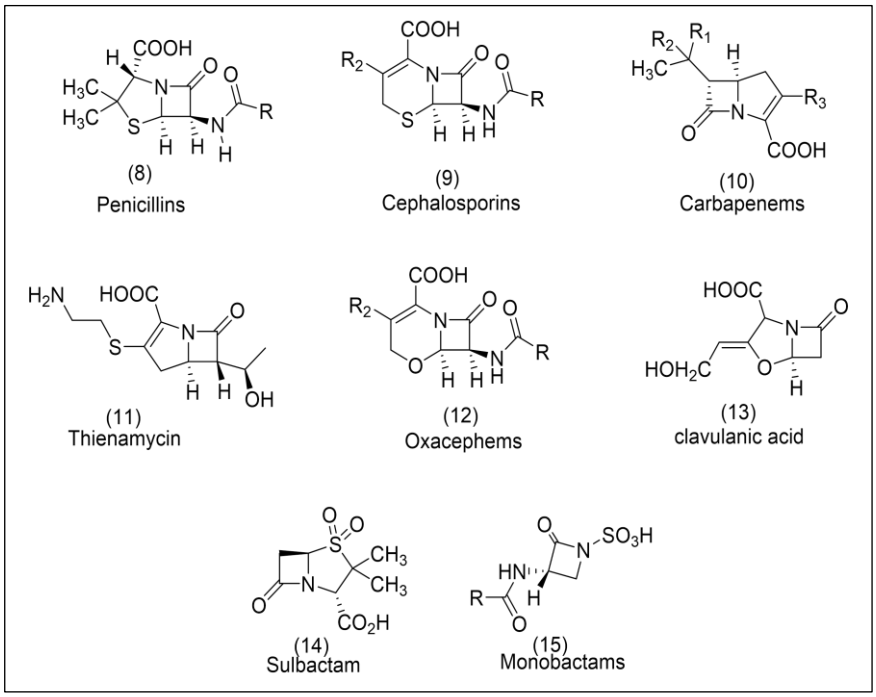


Figure (1-2) some beta-lactam antibiotics

Amongst the two types of azetidinones, more common are those with a β-lactam ring azetidin-2-ones , while the other type, azetidin-3-ones is less known . This is probably because they are not found normally in the nature. A β-lactam (beta-lactam) ring is a four-membered lactam , in which the carbonyl carbon atom is β to the ring nitrogen [42], Figure (1-3).

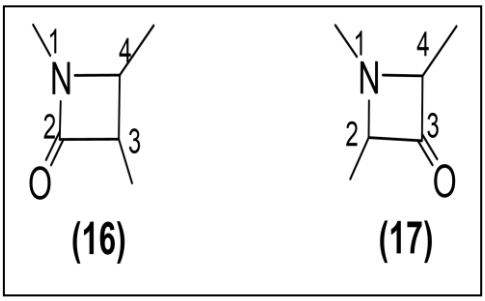


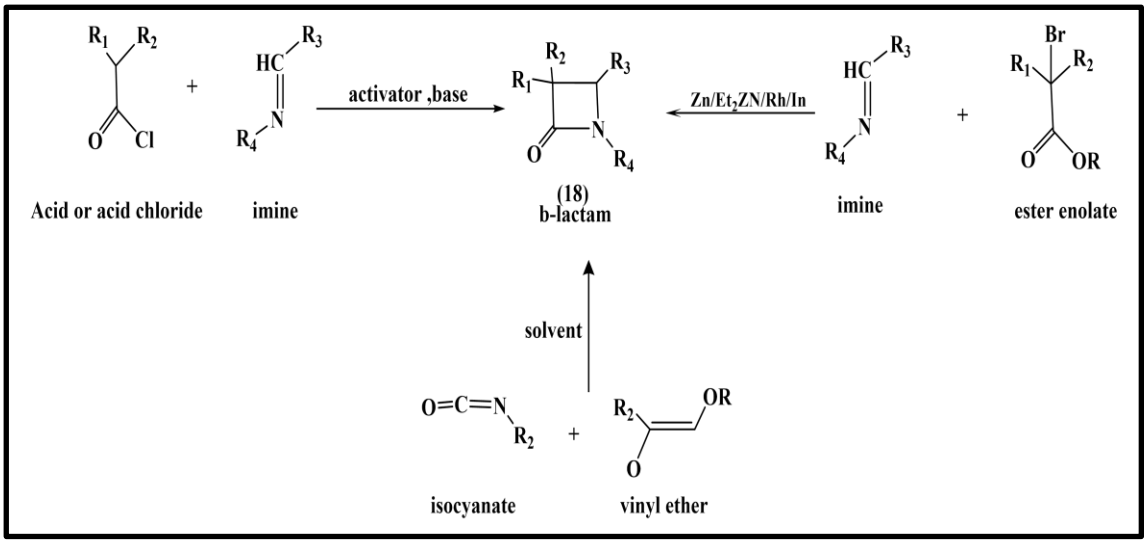
Figure (1-3) the two types of azetidinones

The biological activity of the β-lactam skeleton is generally believed to be associated with the chemical reactivity of the β-lactam ring as well as the substituents especially at the nitrogen of the azetidin-2-one ring [43].

The substituents at the N-1, C-3 and C-4 position may be varied, the continuous increase in the activity spectrum of the β-lactam antibiotics and also the discovery of more types of microorganisms producing them can be attributed to the development of more sensitive screening techniques [44]. This has given impetus to increased interest in synthesis and evaluation of more and more derivatives of β-lactams, Furthermore, the β-lactam ring also serves as a synthon or versatile intermediates for the synthesis of aromatic amino acids derivatives, peptides, polyamines, polyamino alcohols, amino sugars and polyamino ethers as well as for many biologically important classes of organic compounds [45]. Due to this, the investigation into the chemistry of these compounds continues to appeal the synthetic and medicinal organic chemists world over [46].

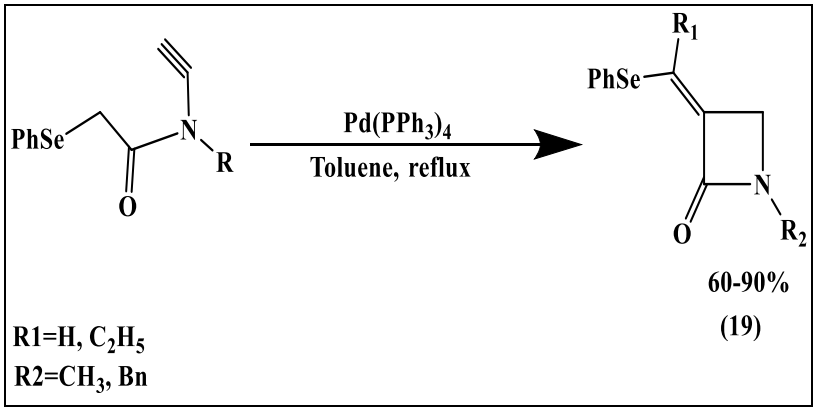
1.3.1. Synthesis of β-lactams

The first successful total synthesis of penicillin-V was carried out by Sheehan and Henry Logan in 1958 by the ring closure of natural penicilloic acid [47]. Transition metal reagents have a role in synthetic approach for preparing 6-aminopenicillanic acid (6-APA). Cycloaddition reaction is one of the most important and useful tool for the construction of β-lactam ring with high efficiency and atom economy. The most popular cycloaddition reactions aimed at β-lactams synthesis are enolate-imine condensation and isocyanates-vinyl ethers condensation [48], Scheme(1-1).



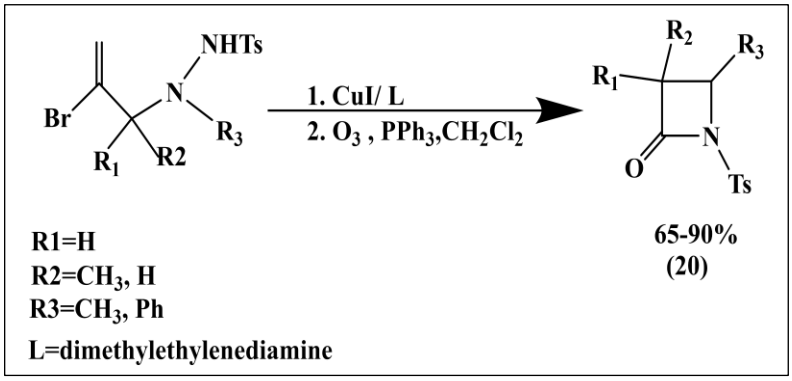
Scheme (1-1) Cycloaddition reactions for the synthesis of beta-lactams

Kambe and co-workers have described the formation of a-alkylidene-β-lactams **(19)** in good yields via intramolecular selenocarbamoylation of alkynes using palladium catalyst. The reaction was found to be highly selective and favours the formation (*Z)* product with (*Z*/*E)* ration of up to 100. Synthesis of conjugated lactams and thio/seleno incorporated cyclobutanones can also be achieved by using this catalytic system. They have also proposed the mechanism involving the role of palladium-alkyne coordination [49], Scheme (1-2).



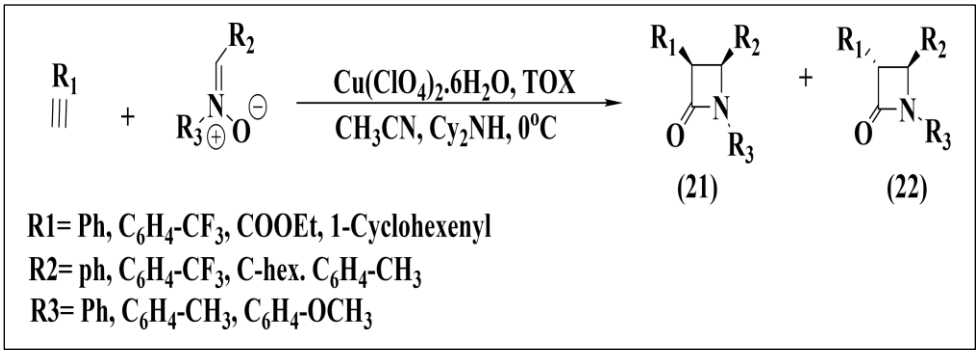
Scheme (1-2) Synthesis of 3-alkylidene-β -lactams via Pd(PPh3)4 catalysed intramolecular cyclization

Li et al. have reported an efficient route for the synthesis of 2-alkylidene azetidines and azetidinones via intramolecular *N*-vinylation of *N*-tosyl-3-halo-3-butenylamines catalysed by copper halide. Appropriate amines underwent Ullmann type coupling in the presence of CuI and *N*,*N*′-dimethylethylenediamine to yield 2-alkylideneazetidines which subsequently oxidised to corresponding 2-azetidinones **(20)** in good yields [50], Scheme(1-3).



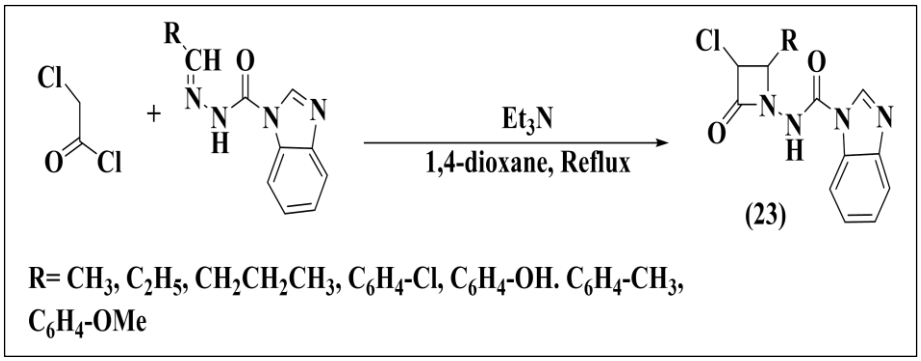
Scheme (1-3) Preparation of β -lactams via copper salt mediated intramolecular N-vinylation

Tang and co-workers have described an efficient methodology for the enantioselective synthesis of β-lactams utilising Cu(II) salts for the first time in Kinugasa reaction. It involves reaction of terminal alkynes with nitrones to afford β-lactams in moderate to good yields. The reaction was catalysed by ^{i}Pr-tris oxazoline/$Cu(ClO_4)_2$ system resulting in high ee (up to 85%). The distereoselectivity was highly dependent upon terminal alkynes. Most of the alkynes afforded cis-β-lactams **(21)** as compared to propiolates which prefers trans product **(22)** . Moreover, secondary base were found to be better in producing higher enantio selectivity [51] , Scheme (1-4).



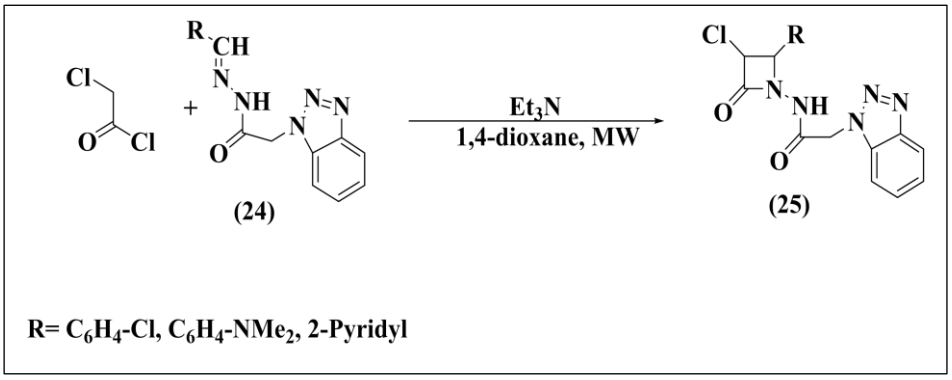
Scheme (1- 4) Enantioselective synthesis of 2-azetidionones via CuClO4/TOX mediated Kinugasa reaction

Lal and Ansari have prepared benzimidazole linked β-lactam derivatives **(23)**. Treatment of CAC with heterocyclic imines afforded target β-lactams, in good yields [52], Scheme (1-5).



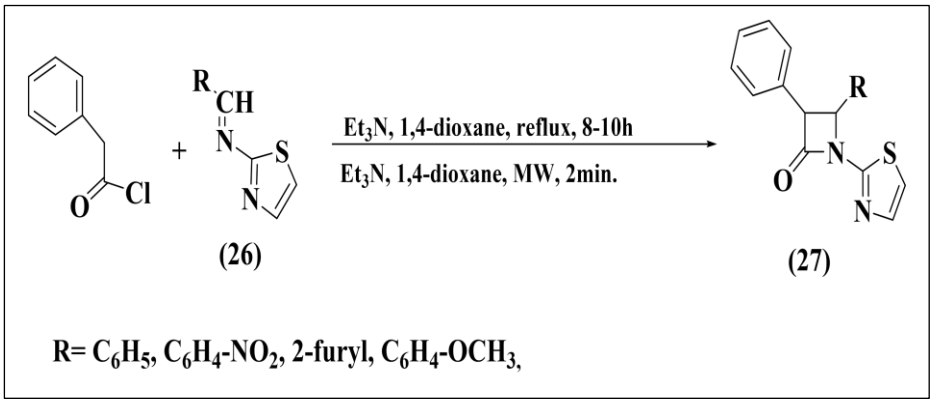
Scheme (1-5) General strategy for the synthesis of benzimidazole anchored beta-lactams

Kulkarni and Kadam have synthesized benzotriazole appended azetidin-2-one derivatives **(25)** via cyclocondensation reaction between chloroacetyl chloride and 2-(1*H*-benzotriazol-1-yl)-*N*- substituted heteroaryl/phenylmethylidene) acetohydrazide **(24)** in the presence of TEA[53] , Scheme(1-6).



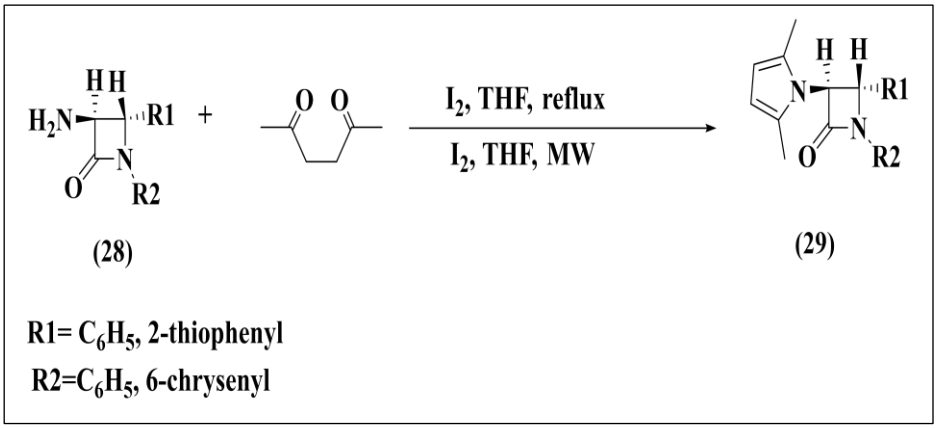
Scheme (1-6) Efficient approach for the synthesis of benzotriazole linked β -lactams

Meshram and co-workers have carried out synthesis of novel *N*-thiazole substituted azetidin-2-one derivatives **(27)** via conventional and non-conventional MW method. These monocyclic β-lactams were obtained from cyclocondensation between phenylacetyl chloride and thiazole substituted imines **(26)**. Out of the two methods, the MW method afforded the product in excellent yields in very less time [54], Scheme(1-7).



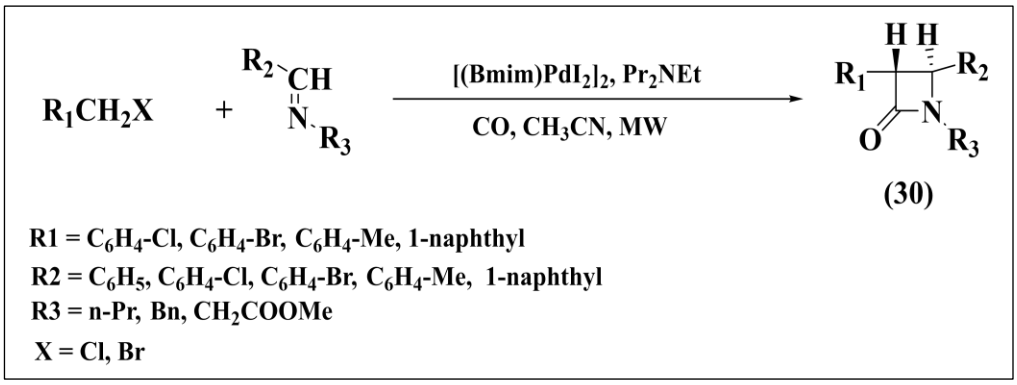
Scheme (1-7) Efficient synthesis of 1-thiazolyl-azetidin-2-ones

Banik has described a novel and efficient synthetic route for the synthesis of pyrrole substituted azetidin-2-one **(29)** in excellent yields. The methodology involves treatment of 3-amino-β-lactams **(28)** with acetonylacetone [55], Scheme(1-8).



Scheme (1-8) Microwave induced synthesis of 3-pyrrole substituted β-lactams

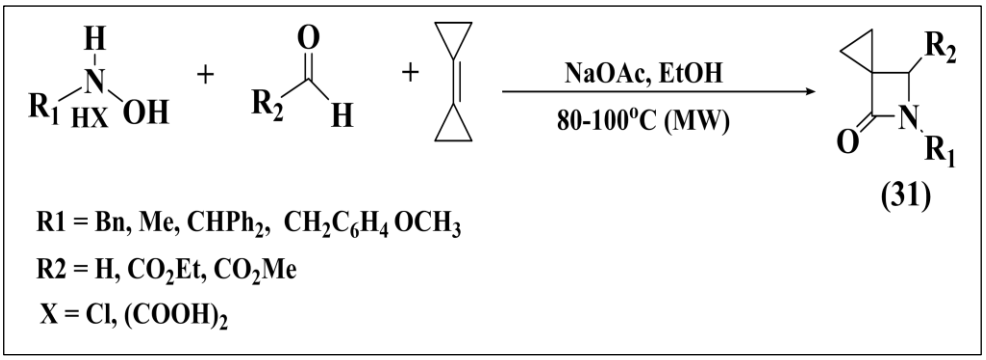
Huang et al. have carried out synthesis of *trans*-β -lactams **(30)** stereoselectively via carbonylative cyclcoaddition reaction catalysed by palladium and *N*-heterocyclic carbene complex. It involves reaction of various imines with benzyl chlorides or allyl derivatives in the presence of carbon monoxide. This methodology provides high efficiency and excellent regioselectivities. Further, reaction under asymmetric environment affords moderate diastereoselectivities [56], Scheme(1-9).



Scheme (1-9) Synthesis of trans-beta-lactams via palladium/NHC catalysed carbonylation and cycloaddition

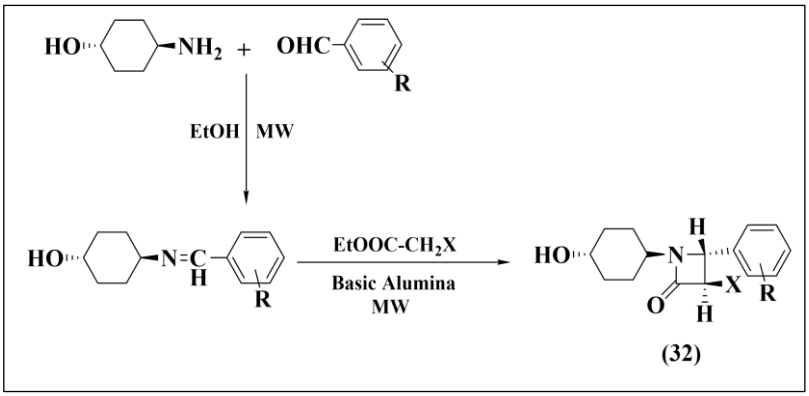
García and Brandi together explored the effect of microwave heating during the 1,3-dipolar cycloaddition of nitrones, generated in situ and bicyclopropylidene for the synthesis of these spiro-β-lactams. The reaction

of *N*-substituted hydroxylamine hydrochlorides, aldehydes, and bicyclopropylidene in the presence of sodium acetate and ethanol under microwave irradiation furnished the desired spiro-b-lactams **(31)** after 30-120 min [57], Scheme(1-10).



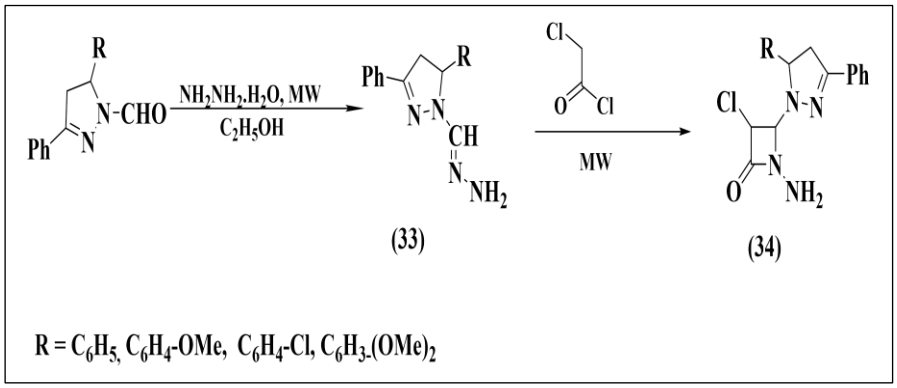
Scheme (1-10) Three components cascade reaction to afford spirocyclo propanated beta-lactams

Kidwai et al. prepared b-lactams via an ester-imine based synthesis under solvent-free microwave irradiation. The *trans*-4-aminocyclohexanol was condensed with different aromatic aldehyde to give the respective Schiff base.to affordrequired β-lactams **(32** [58], Scheme(1-11).



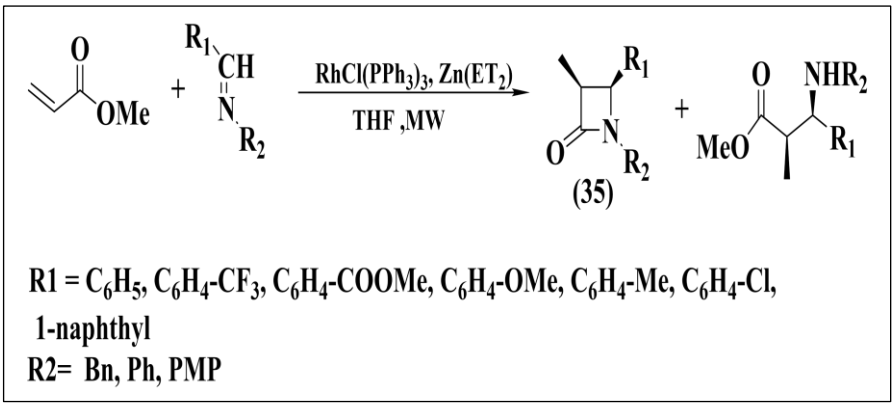
Scheme(1-11) Synthesis of β- lactam on basic alumina surface under microwave irradiation

Synthesis of a novel series of 1-amino-4- (3,5-diaryl-2-pyrazoline-2-yl)azetidin-2-ones **(34)** has been reported by Srivastava et al. via microwave assisted organic synthesis. The dehydrative annulation between diversely substituted pyrazoline hydrazones **(33)** and chloroacetyl chloride as resulted in the target products in very good yields [59], Scheme(1-12).



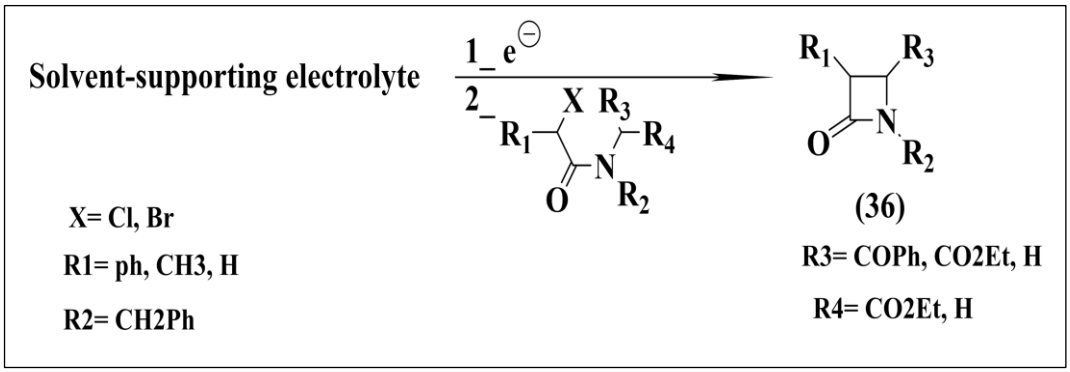
Scheme (1-12) Synthesis of 4-pyrazolyl-b-lactams from chloroacetyl chloride and pyrazolyl imine

Isoda et al. have synthesized *syn*-β-lactams **(35)** diastereoselectively via rhodium catalyzed Mannich-type reduction. The reaction between α,β-unsaturated esters and diversely substituted imines in presence of RhCl $(PPh_3)_3$ and diethyl zinc to afford *syn*-β-lactams in very good yields. The combination of rhodium and zinc reagent produces rhodium hydride complex which actually plays catalytic role. Further, various EWGs and ERGs did not cause any significant change in either yields or diastereomeric ratio [60], Scheme(1-13)



Scheme (1-13) Synthesis of syn-b-lactams via rhodium catalyzed Mannich type reduction

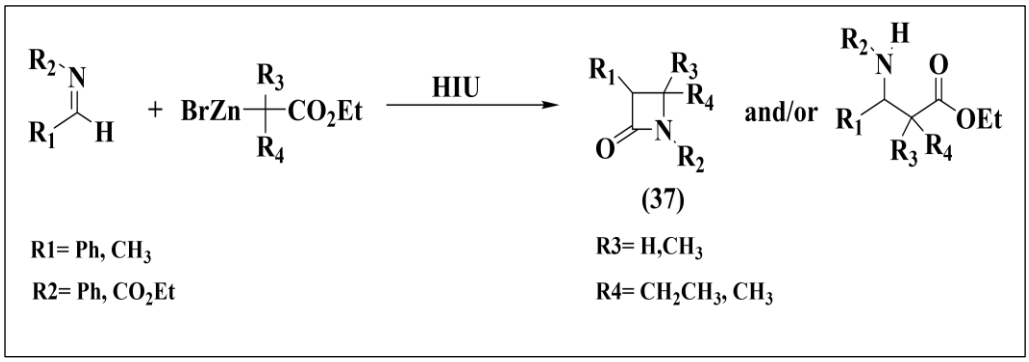
In 2006, electrochemically induced synthesis of β-lactams, by cyclization of haloamides, has been achieved in suitable solvent-supporting electrolyte solutions previously electrolyzed under galvanostatic control. The yields and the stereochemistry of the process were influenced by the nature of the R1 R4 substituents, by the solvent-supporting electrolyte solutions, and by the electrolysis conditions [62], scheme(1-14).



Scheme(1-14). Electrochemical synthesis of β-lactams

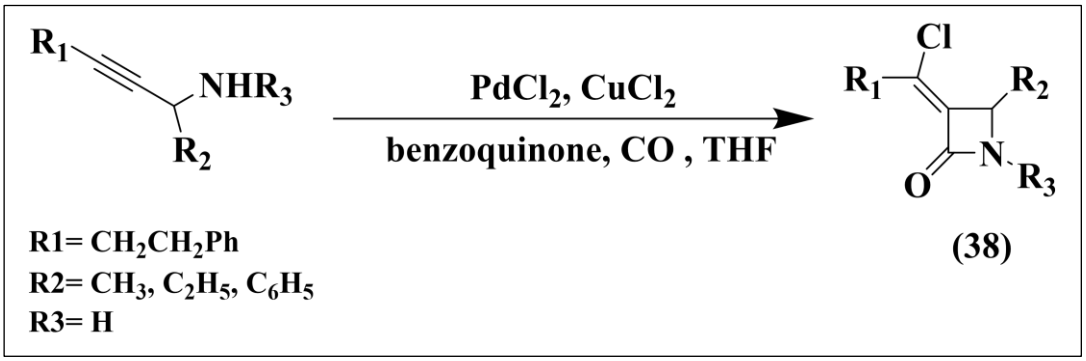
In 2004, the Reformatsky reactions of imine, a-bromoester, zinc dust, and a catalytic amount of iodine in dioxane under high intensity ultrasound (HIU) irradiation have been reported to afford β-lactam and the corresponding b-aminoester. The reactions were performed in short reaction

times and high yields of both products or a mixture of the two products were obtained, depending on the starting imine and on the a-bromoester [63], Scheme (1-15).



Scheme(1-15). Reformatsky reaction of imines and a bromoesters affording b-lactams and β-aminoesters

Ma et al. have carried out the cyclocarbonylation of propargylic amines 3 in the presence of CuCl2 and benzoquinone catalysed by palladium chloride to afford (E)-a-chloroalkylidene-b-lactams 4 in moderate to good yields. The formation of five membered product or (Z)-isomer was not observed at all. Furthermore, the reaction of optically active propargylic amines has resulted in the product formation in moderate yields with high ee (up to 98%) [64], scheme(1-16).



Scheme(1-16). PdCl2 catalysed synthesis of α-alkylidene-β -lactams

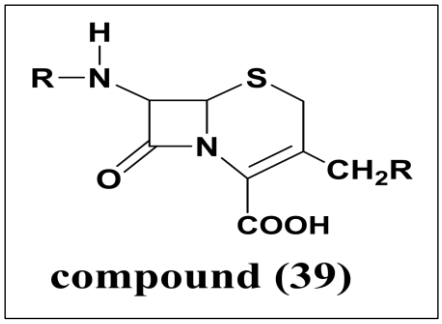
1.4. Biological potency of lactams

The 2-azetidinone (β-lactam) ring has been recognized as the fundamental pharmacophore group for a wide range of bioactive compounds. It is the central core of the most extensively used class of antibiotic agents, such as penicillins, cephalosporins, carbapenems, and monobactams [65]. The ever-increasing bacterial resistance to β-lactam antibiotics, due to their massive use in medicine,represents a serious concern, but at the same time increases the interest in the development of novel azetidinone derivatives. The medicinal application of β-lactams as therapeutic agents for lowering plasma cholesterol levels has been publishe, b-lactams are widely and safely used as antibacterials without significant toxicity [66].

1.4.1. Antibacterial activity

The emergence of pathogenic microorganisms resistant to multiple classes of antibiotics is a serious clinical challenge. Among these classes of antibacterials, β-lactam antibiotics are still the most commonly used, over 50 years after their initial introduction [67]. The most common mechanism for resistance to β-lactam antibiotics is the ability of bacteria to produce b-lactamases, These enzymes hydrolyze the b-lactam moiety in the drugs, inactivating the antibiotics. Studies of amino acid sequence homology have identified four distinct classes of β-lactamase: A, B, C, and D . Among these, classes A and C are currently the most important in human disease [68]. A successful approach to overcoming the adverse action of these enzymes has been the coadministration of β-lactamase inhibitors together with the typical β-lactam antibiotics, such as pennicillins [69].

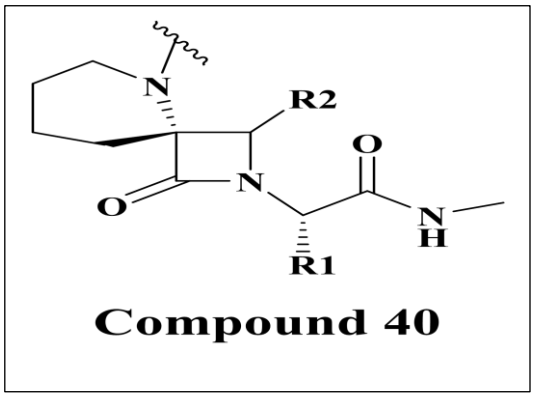
Unfortunately, this approach has been compromised by the discovery of new variants of β-lactamases, resistant to the inhibition afforded by know to withstand inactivation by the ever-increasing diversity of β-lactamases has thus been a continuous and still on-going battle, Several monocyclic β-lactams variously substituted have also been reported to have antibacterial activity against different strains of bacteria and with different mechanisms of actionn inhibitors. Therefore, the development of novel β-lactam inhibitors [70], compound 39.



compound (39)

1.4.2. β-lactams turn mimics

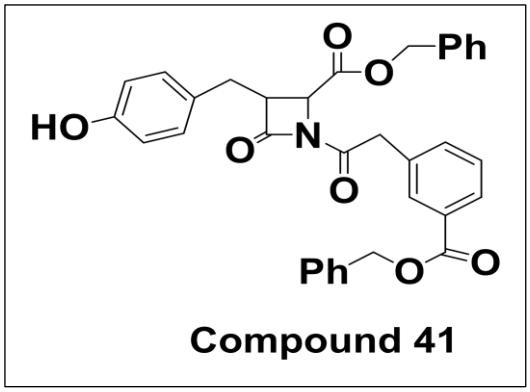
Recently, much attention has been directed toward the synthesis of peptidomimetics. These compounds can replace native peptides in the interaction with receptors. They showed increased metabolic stability, better bioavailability, and longer duration of action than native peptides, thus displaying favorable pharmacological properties. In this sense, the design and synthesis of conformationally restricted peptidomimetics is an important approach toward improving the potency, selectivity, and metabolic stability of peptide based drugs [71], Compound 40.



Compound 40

1.4. 3. Anticancer activity

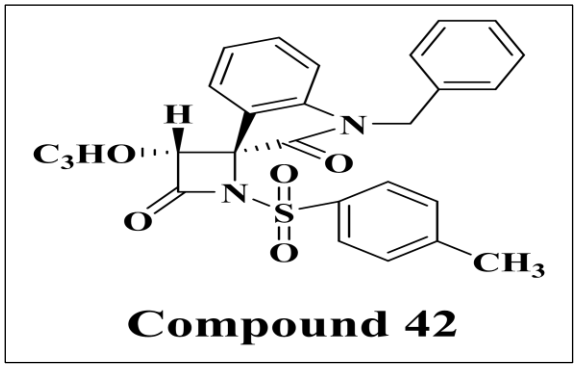
Recently discovered antitumor monocyclic and bicyclic β-lactam systems are, in general, in good agreement with the phenomenon of azetidin-2-one pharmacophore of inexhaustible pharmacological potential on account of the specific ability of its numerous derivatives to inhibit not only bacterial transpeptidase, but also mammalian serin and cystein proteases [72]. As a measure of cytotoxicity, some compounds have been assayed against nine human cancer cell lines. A family of novel β-lactam antibiotics based on 2-azetidinones have also shown the apoptosis-inducing properties against human solid tumor cell lines such as breast, prostate, head-and-neck [73], Compound 41.



Compound 41

1.4.4. Antiviral activity

Human cytomegalovirus (HCMV) is a ubiquitous member of the herpes virus family. Although most infections are asymptomatic, severe manifestations of HCMV can be seen in individuals whose immune system has been weakened by disease such as late-stage cancers and AIDS, or by immunosuppressive therapy following organ transplantation. Due to its critical role in capsid assembly and viral maturation, HCMV serine protease has become an attractive target for the development of anti-HMCV drugs. Among the latter, a series of monocyclic β-lactams have resulted in highly potent inhibitors [74], Compound42.

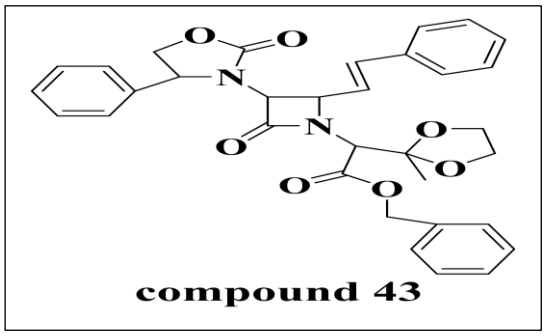


Compound 42

1.4.5. Azetidin-2-ones as vasopressin V1a antagonists

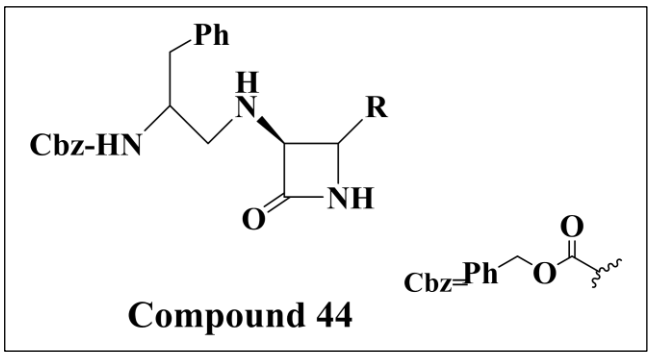
The neurohypophysical hormones vasopressin and oxytocin exert a wide range of physiological effects through binding to specific membrane receptors belonging to the *G* protein-coupled receptor superfamily [75]. To date, three vasopressin receptor subtypes and one oxytocin receptor have been pharmacologically and functionally described. Although vasopressin is perhaps best-known for its role in the cardiovascular system, it also has actions in the central nervous system (CNS). Arginine vasopressin functions as a neurochemical signal in the brain to affect social behavior, There is an expanding literature from animal and human studies showing that

vasopressin, through the vasopressin 1A receptor (V1a), can stimulate aggressive behavior. The β-lactam structure, prepared by different research groups, is the essential scaffold of several antagonists directed to the vasopressin V1a receptor [76], compound43.



1.4.6. Inhibitors of Cysteine Protease

The cysteine proteases cathepsin B, L, K, and S are involved in diseases such as osteoporosis, cancer metastasis, rheumatoid arthritis, and infectious diseases. Thus, the proteases became an important target for developing inhibitors as therapeutic agents. Recently, a series of 4-substituted-3-Cbz-phenyl-β -lactams has been identified as a novel class of cysteine protease inhibitors [78], Compound 44.



1.5. Microwave heating-the fundamentals

Microwaves (MW) are a form of electromagnetic energy located on the electromagnetic spectrum between 300 and 300,000 MHz; a region that lies between infrared and radio frequencies and correspond to wavelengths of 1 cm to 1 m [79]. In order to avoid interference with telecommunications and mobile cellular phone frequencies, most microwave reactors (that are typically used for chemical synthesis reactions) and domestic microwave ovens operate at a frequency of 2.45 GHz or around 900 MHz. Essentially, MW heating is the reverse of conventional heating, where heat is transferred to the surface of a material (from an external heat source) by conduction/convection or radiation and is then transferred towards the cooler interior regions by thermal conduction [80]. MW heating can therefore be described as a form of energy conversion rather than a form of heating; as electromagnetic energy is converted into heat. This unique inverse heating profile mechanism offers many benefits such as an increase in energy transfer efficiency and reductions in process heating time (to achieve a given temperature) [81].

1.5.1. Advent of microwave

The rapid development of microwave syntheses technology is visible in the publications trends of the last decade. A search of the word “microwave” and the phrase “microwave, reaction” in the science irect scientific search engine -eresulted, respectively , inallavailable research fields from 2010 to 2017 [82]. The increasing availability and diversity of microwave equipment have allowed this heating technology to become more and more popular and useful. Abreak through in microwave technology

occurred before1990, with the advent to the development of controlled equipment using a closed pressure vessel reactor (Milestone, ERTEC), Nowadays, there are plenty of well-known companies offering microwave reactors for a wide variety of applications. Microwave heating technology, when applied to chemical reactions, represents a sustainable "green chemistry by utilizing safer solvents and reaction conditions, minimizing the potential for accidents, preventing the waste of products, and minimizing the time of reactions [83]. For instance, in different microwave frequencies, it is possible to efficiently synthesize nanoparticles at much shorter times than when relying on conventional synthesis, without the use of microwaves. The development of the industrial applications of microwave heating, mainly in drying and other thermal treatment processes, was significant, and commercially available on the market from 2019 [84]. Thus, manufacturers quickly found a wide range of applications for microwave technology, thanks to its easy use and low costs. A typical home microwave oven can be easily adapted for use in chemical experiments, and until the 1990s, it was considered the primary model for laboratory equipment manufacturers. 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. Therefore, in recent years, specialized microwave devices designed for laboratories and industries [85].

1.5.2. Basic microwave equipment

The microwave equipment (also frequently called " applicators ") used in chemical processing can be divided into three basic categories: the

multimode, the mono (or single)-mode, and the traveling-wave devices. The multimode applicators are the most widespread ones, with applications starting from domestic ovens up to large-scale industrial dryers [86]. They usually have the form of a rectangular closed metal box a Faraday cage that has at least two dimensions longer than half of the wavelength. Inside the cavity, a large number of resonance modes exist as the microwaves get reflected from the cavity walls. Owing to these reflections, wave interference occurs. Microwave activation and solvent-free conditions in organic synthesis provides clean chemical processes characterized by enhanced reaction rates, higher yields and enhanced ease of manipulation [87], Figure (1-4).

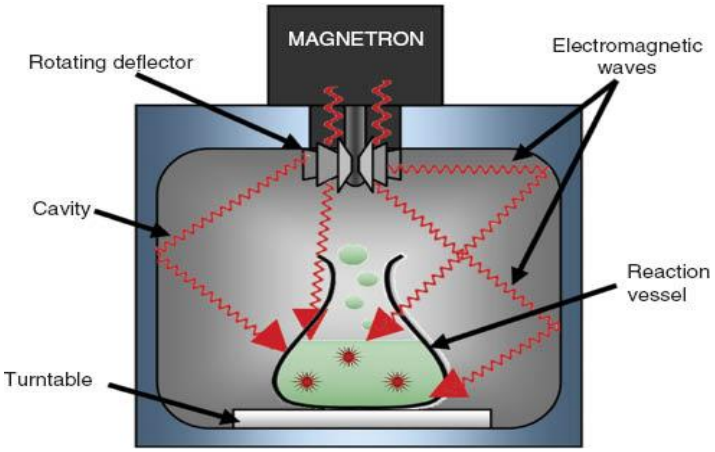


Fig. (1-4): Multimode microwave applicator

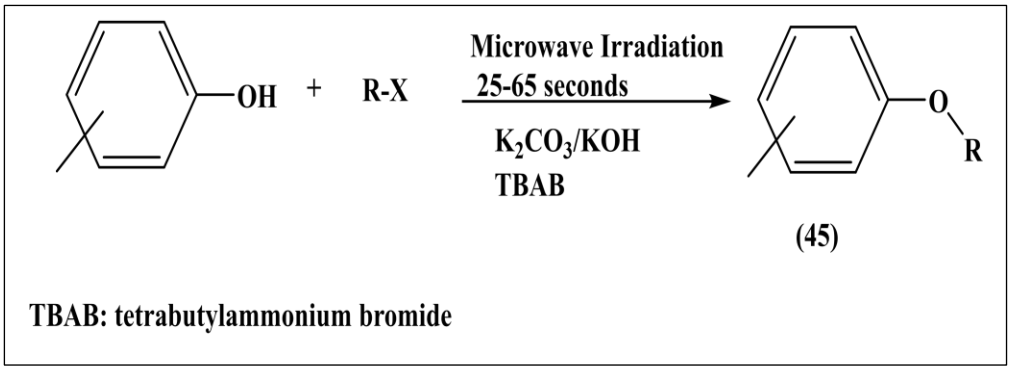
1.5.3. Microwave in organic synthesis

Synthetic method has shown broad applications as a very efficient way to accelerate the course of many organic reactions, producing high yields and higher selectivity, lower quantities of side products and, consequently, easier work-up and purification of the products. Microwave-assisted organic synthesis (MAOS) is considered as an “green” technology, principally since many organic reactions can be carry out in solvent-free

conditions [88]. MAOS has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. (MAOS) is the study of chemical reactions under the effect of microwave radiation. Microwaves radiation have high energy electric fields and will generally heat any substance containing mobile electric charges. Microwave irradiation was found to increase the yields of the desired products and shorten the reaction times [90]. Microwave- assisted organic synthesis has been the one of the most researched applications of microwaves in chemical reactions.Chemists have successfully conducted a large range of. Organic reactions assisted with microwave irradiation such as Diels-Alder reactions between dienes and dienophiles, these reactions have been carried out with and without solid support and by both conventional and MW assisted techniques. Heck reaction, Suzuki reaction, Mannich reaction, hydrogenation of β-lactams, hydrolysis, dehydration, esterification, epoxidation, reductions, condensations and cycloaddition reactions [91],

1.5.3.1. Alkylation

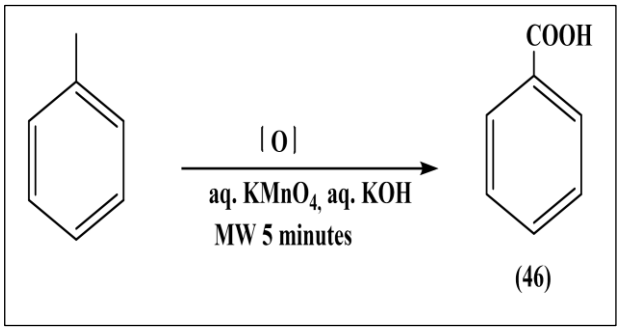
Dariusz et al. used microwave heating under solvent free PTC conditions for alkylation of phenols **(45)**[92], Scheme(1-17).



Scheme(1-17)

1.5.3.2. Oxidation

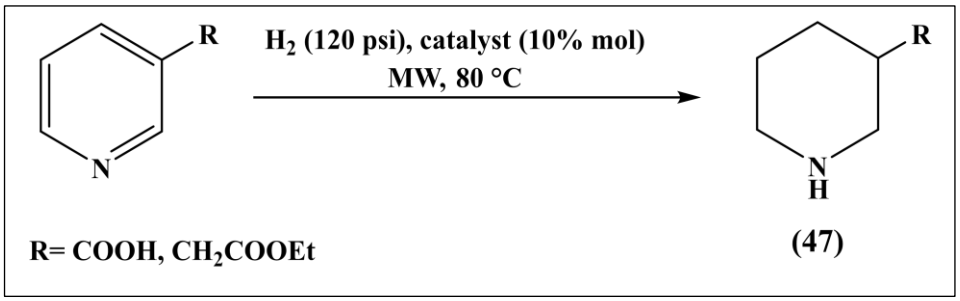
Grewal et al. oxidized toluene to benzoic acid **(46)** with $KMnO_4$ by microwave radiation [93], Scheme(1-18).



Scheme(1-18)

1.5.3.3. Reduction

Piras et al. converted the substituted pyridines into the corresponding piperidines **(47)** optimisation of the procedure for microwave-assisted hydrogenation [94], Scheme(1-19).



Scheme(1-19)

Aims of the study

The present work aims to synthesize series of new azetidin-2-one derivatives containing benzothiazole moiety from Schiff bases using microwave irradiation method and evaluate their antibacterial activity against Gram-positive and Gram-negative bacteria as well as comparing the effects with amoxicillin-clavulanate as standard drug.

Chapter Two

Experimental Part

2.1. Materials

All chemicals, reagents and solvents were supplied from the commercial sources, Table (2-1**).**

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

Chemicals	Molecular formula	M.Wt g/mol	Purity %	Supplied companies
2-Aminobenzothiazole	$C_7H_6N_2S$	150.20	97	Sigma-Aldrich
Ethanol (absolute)	C_2H_6O	46.06	99.9	J.T.Baker, Netherlands
Sulfuric acid (Conc.)	H_2SO_4	98.08	99	Merck, Germany
Sodium nitrite	$NaNO_2$	68.99	99	BDH, England
2-Hydroxy benzaldehyde	$C_7H_6O_2$	122.12	98	S.D,Fine.india
Sodium hydroxide	NaOH	39.99	99	BDH, England
4-Bromoaniline	C_6H_6NBr	172.02	96	BDH, England
3-Bromoaniline	C_6H_6NBr	172.02	96	BDH, England
4-Chloroaniline	C_6H_6NCl	127.57	99	BDH, England
2-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
4-Acetamidoaniline	$C_8H_{10}N_2O$	150.18	99	Fluka

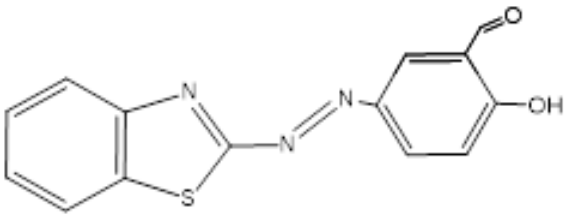
2-Chloroacetyl chloride	$C_2H_2Cl_2O$	112.94	99	Fluka
N,*N*-Dimethylformamide	C_3H_7NO	73.10	99.8	Sigma-Aldrich
Diethyl ether	$C_4H_{10}O$	74.12	99.5	Scharlau, Spain
n-Hexane	C_6H_{14}	86.17	99	Scharlau, Spain
Ethyl acetate	$C_4H_8O_2$	88.10	99	BDH, England
Iodine	I_2	253.80	99.5	GCC, Germany
Dimethyl sulfoxide	C_2H_6OS	78.13	99	BDH, England

2.2. Equipment

1. Silica TLC plates with an aluminum backing (0.2 mm, 60 F_{254}) were used for monitoring reaction. The spots were visualized by iodine vapor.
2. Melting points were measured by an Electro thermal Stuart SMP 30 capillary melting point apparatus, UK.
3. Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide disc at Kerbala University.
4. ^{1}H NMR data were obtained via INOVA 500 MHz varian, USA NMR spectrometer in DMSO-d_6 as solvent and TMS as an internal standard in Tehran University, Iran.
5. Perkin Elmer 300A was used for determining elemental Analyses at Tehran University, Iran.
6. Microwave reactions were done by domestic microwave oven in crucible.
7. Autoclave was used to sterilize agar media, supplied from Prestige Medical-England.
8. Incubator was used to maintain different temperature required for the growth of organism, supplied from Binder - Germany.

2.3. Preparation methods

2.3.1. Preparation of 5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxybenzaldehyde (2)



(2)

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

A solution of 2-aminobenzothiazole **[I]** (8.1 g, 0.054 mol) in H_2SO_4 (15 mL) was cooled to 0°C. To this solution, a cold solution of sodium nitrite (3.726 g, 0.054 mol) dissolved in distilled water (20 mL) was added drop wise with constant stirring. When the addition was completed, the resultant reaction mixture was left in ice-chest for 1h. The ice cold solution of diazonium bisulfate was then added drop wise to the cold solution of 2-hydroxy benzaldehyde (6.588 g, 0.054 mol) dissolved in (45 mL) of (10% w/v) sodium hydroxide with constant shaking. A dark dye resulted which darkened on adding more alkaline solution of phenol derivative. When the addition was completed, the resultant reaction mixture was vigorously stirred. A solid separated out which was allowed to stand at room temperature for 30 min., then filtered off and washed well with distilled water. The precipitated substance was collected and recrystallized from ethanol to yield **[2**] as a dark brown solid, yield (7.9 g, 52%), m.p. 141-143 ^{o}C. The physical properties of compound **(2)** [95] was given in Table (2-2).

2.3.2. General procedure for preparing Schiff bases (3a-n)

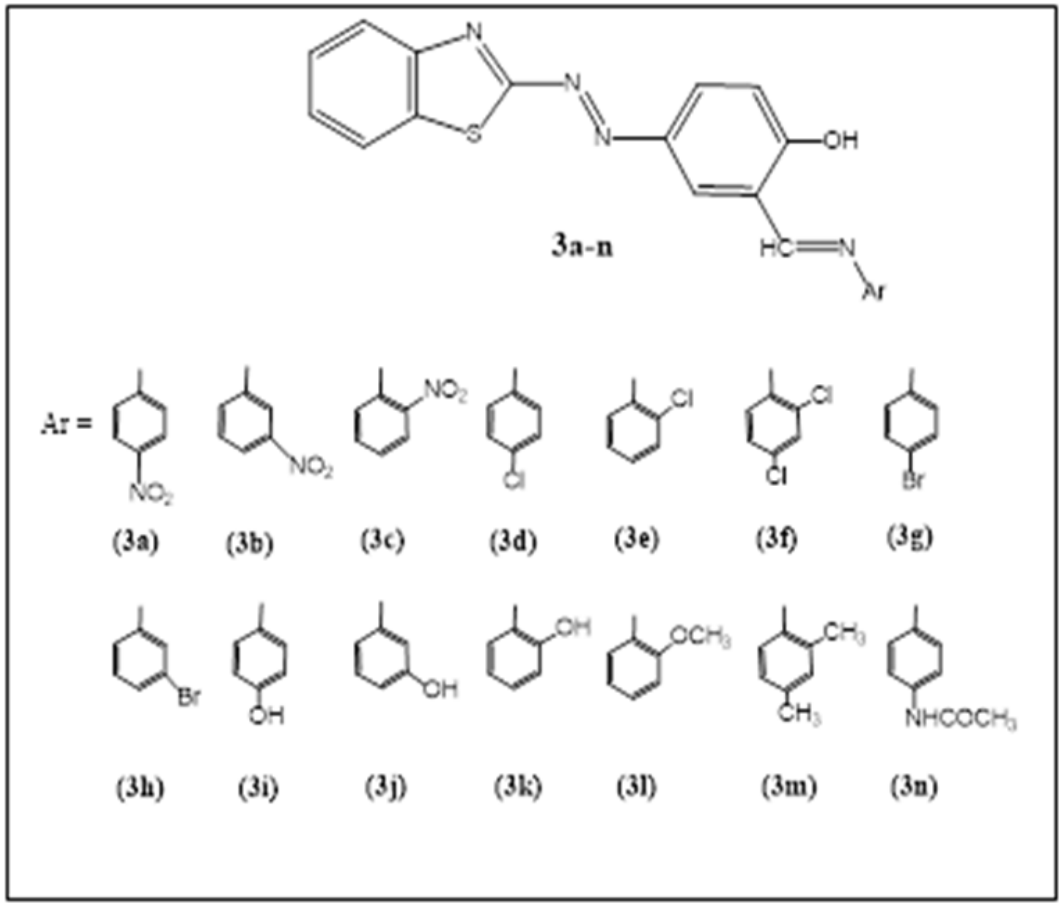
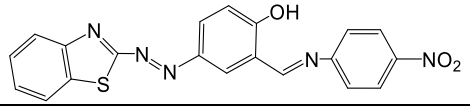
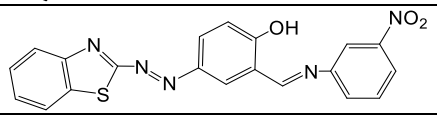


Fig. (2-2): Structures of compounds (3a-n)

The aldehyde derivative **(2)** (0.283 g, 1 mmol), suitable aromatic amines (1 mmol) and absolute ethanol (1 mL) were placed in crucible. The reaction mixture was irradiated in a domestic microwave oven at (300W) for (40 min). TLC (*n*-hexane: EtOAc, 1:2) showed end of reactions. Recrystallization of crude yields was carried out using ethanol, [96].

Table (2-2). shows name and structure for compounds (3a-n).

Name	Structure
4-benzo[d]thiazol-2-yldiazenyl)-2-((4-nitrophenyl)imino)methyl)phenol (3a)	
4-benzo[d]thiazol-2-yldiazenyl)-2-((3-nitrophenyl)imino)methyl)phenol (3b)	

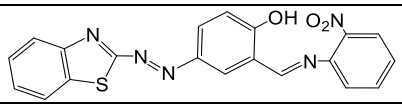
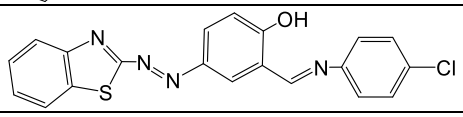
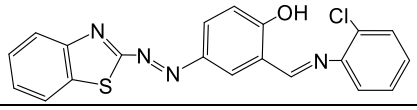
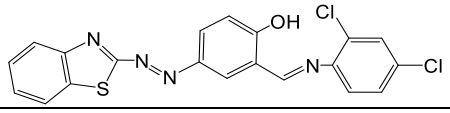
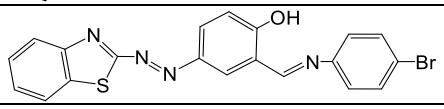
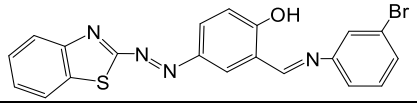
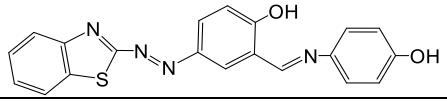
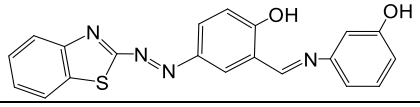
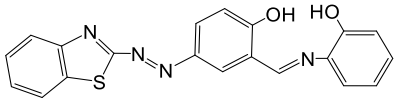
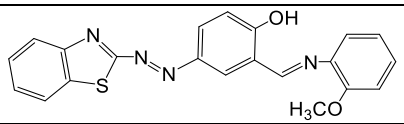
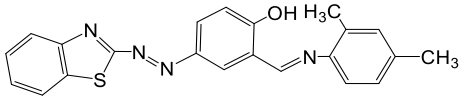
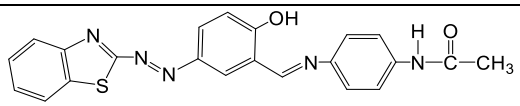
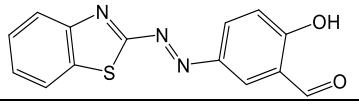
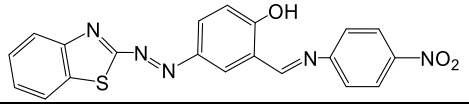
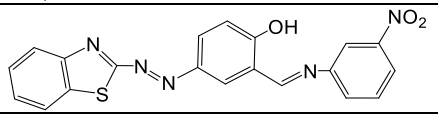
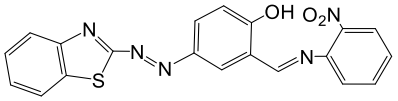
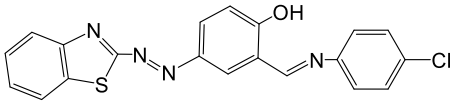
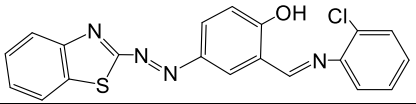
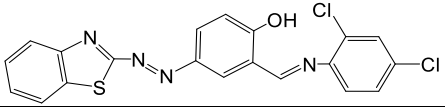
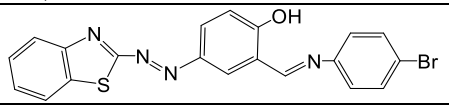
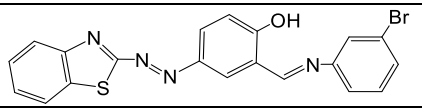
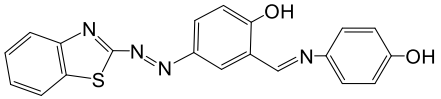
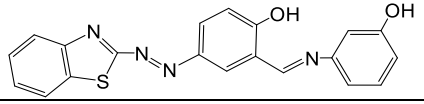
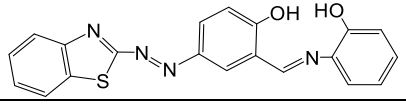
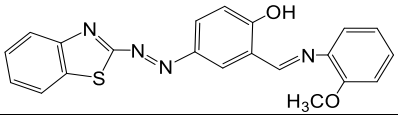
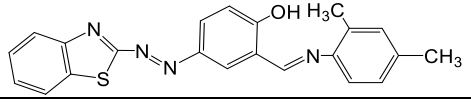
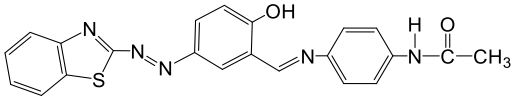
4-benzo[d]thiazol-2-yldiazenyl)-2-((2-nitrophenyl)imino)methyl)phenol (3c)	
4-benzo[d]thiazol-2-yldiazenyl)-2-((4-chlorophenyl)imino)methyl)phenol (3d)	
4-benzo[d]thiazol-2-yldiazenyl)-2-((2-chlorophenyl)imino)methyl)phenol (3e)	
4-benzo[d]thiazol-2-yldiazenyl)-2-2,4-dichlorophenyl)imino)methyl)phenol (3f)	
4-(benzo[d]thiazol-2-yldiazenyl)-2-((4-bromophenyl)imino)methyl)phenol (3g)	
4-(benzo[d]thiazol-2-yldiazenyl)-2-(3-bromophenyl)imino)methyl)phenol (3h)	
4-(benzo[d]thiazol-2-yldiazenyl)-2-((4-hydroxyphenyl)imino)methyl)phenol (3i)	
4-(benzo[d]thiazol-2-yldiazenyl)-2-((3-hydroxyphenyl)imino)methyl)phenol (3j)	
4-((E-benzo[d]thiazol-2-yldiazenyl)-2-((E)-((2-hydroxy phenyl) imino) methyl) phenol (3k)	
4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E)-((2-methoxy phenyl)imino) methyl) phenol (3l)	
4-((E)-benzo[d]thiazol-2-yldiazenyl)-2-((E)-((2,4-dimethylphenyl)imino)methyl) phenol (3m)	
N-(4-((5-benzo[d]thiazol-2-yldiazenyl)-2-hydroxybenzylidene) amino)phenyl) acetamide (3n)	

Table (2-3): Physical properties and other characteristics for compounds (3a-n)

Comp. No	Structure	Formula	M.Wt	Color	M.P. ºC	R_f *n*-hexane : EtOAc 1 : 2	Yield %
2		$C_{14}H_9N_3O_2S$	283.31	Dark brown	141-143	o.68	52
(3a)		$C_{20}H_{13}N_5O_3S$	403.42	Brown	175-177	0.69	86
(3b)		$C_{20}H_{13}N_5O_3S$	403.42	Dark brown	145-147	0.77	75
(3c)		$C_{20}H_{13}N_5O_3S$	403.42	Dark brown	137-139	0.60	82
(3d)		$C_{20}H_{13}N_4OSCl$	392.86	Dark brown	162-164	0.79	77
(3e)		$C_{20}H_{13}N_4OSCl$	392.86	brown	151-153	0.85	71
(3f)		$C_{20}H_{12}N_4OSCl_2$	427.30	Dark brown	125-127	0.81	83
(3g)		$C_{20}H_{13}N_4OSBr$	437.32	brown	171-173	0.82	87

(3h)		$C_{20}H_{13}N_4OSBr$	437.32	Dark brown	131-133	0.85	87
(3i)		$C_{20}H_{14}N_4O_2S$	374.42	Dark brown	158-160	0.71	76
(3j)		$C_{20}H_{14}N_4O_2S$	374.42	Brown	146-148	0.70	75
(3k)		$C_{20}H_{14}N_4O_2S$	374.42	Dark brown	123-125	0.75	72
(3l)		$C_{21}H_{16}N_4O_2S$	388.45	Dark brown	121-123	0.72	75
(3m)		$C_{22}H_{18}N_4OS$	386.47	Brown	139-141	0.60	70
(3n)		$C_{22}H_{17}N_5O_2S$	415.47	Dark brown	184-186	0.83	88

2.3.3. General procedure for preparing azetidin-2-ones

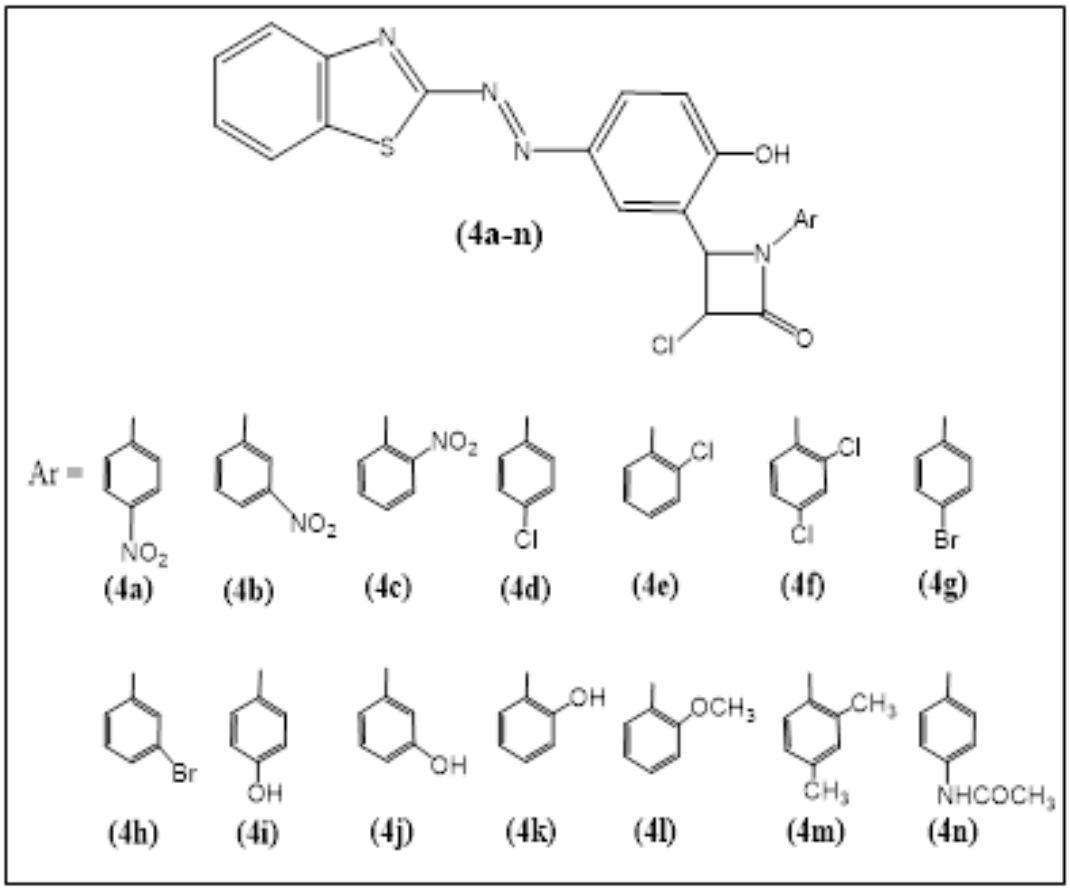
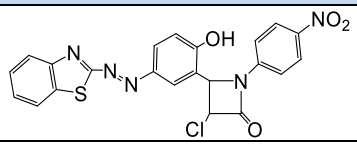
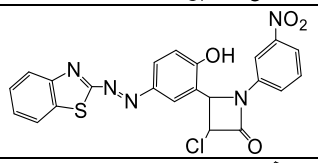
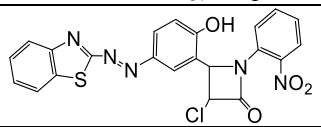


Fig. (2-3): Structures of compounds (4a-n)

(1 mmol) from each Schiff bases **(3a**–**n)** and Chloroacetyl chloride dissolved by (DMF) (1 mL) were irradiated around (300W) about (150 min). End of reactions was carried out by TLC (*n*-hexane: Ethyl acetate, 1:2. The products were recrystallized from ethanol.

Table (2-4). Name and structure of compounds (4a-n)

Name	Structure
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(4-nitrophenyl)azetidin-2-one (4a)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(3-nitrophenyl)azetidin-2-one (4b)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2-nitrophenyl)azetidin-2-one (4c)	

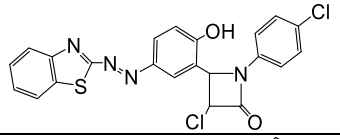
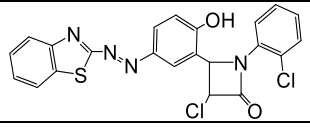
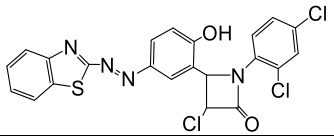
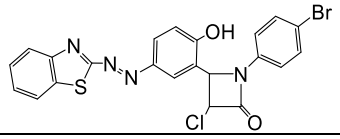
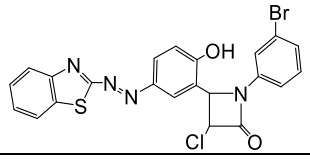
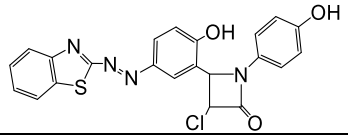
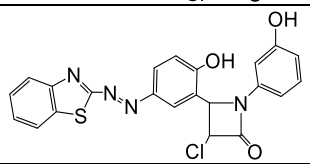
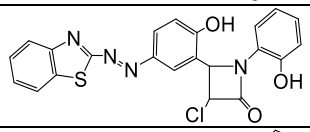
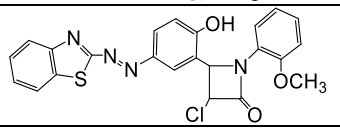
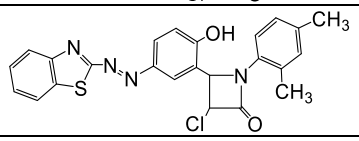
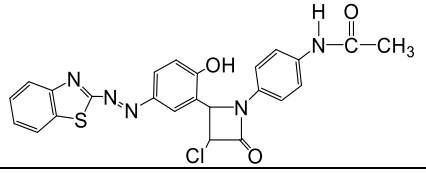
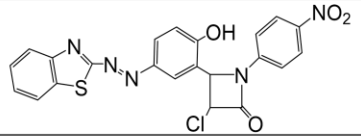
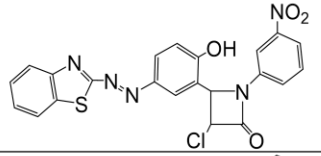
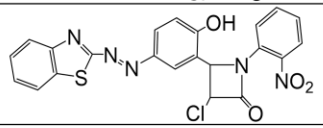
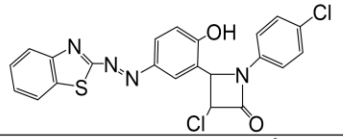
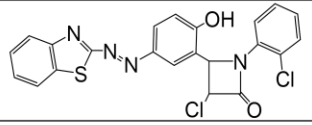
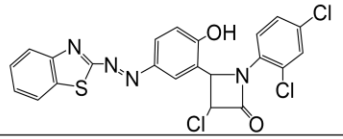
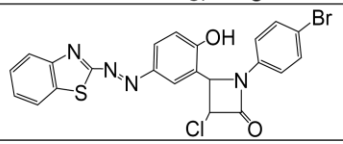
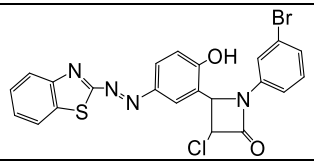
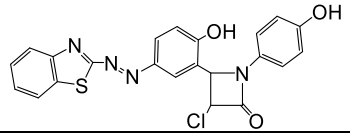
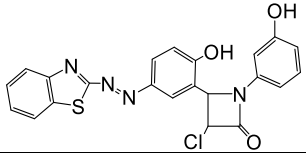
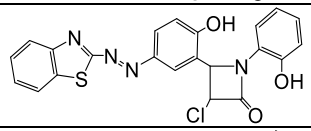
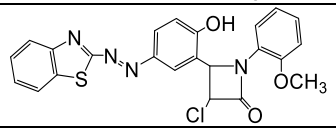
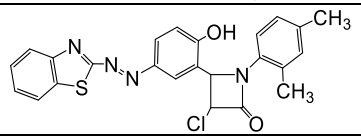
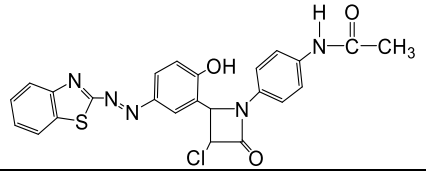
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(4-chlorophenyl)azetidin-2-one (4d)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2-chlorophenyl)azetidin-2-one (4e)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2,4-dichlorophenyl)azetidin-2-one (4f)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-1-(4-bromophenyl)-3-chloroazetidin-2-one (4g)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-1-(3-bromophenyl)-3-chloroazetidin-2-one (4h)	
(E)-4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(4-hydroxyphenyl)azetidin-2-one (4i)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(3-hydroxyphenyl)azetidin-2-one (4j)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2-hydroxyphenyl)azetidin-2-one (4k)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2-methoxyphenyl)azetidin-2-one (4l)	
4-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-1-(2,4-dimethylphenyl)azetidin-2-one (4m)	
N-(4-(2-(5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxyphenyl)-3-chloro-4-oxoazetidin-1-yl)phenyl)acetamid (4n)	

Table (2-5): Physical properties and other characteristics of azetidin-2one compounds (4a-n)

Comp. No	Structure	Formula	M.Wt	Color	M.P. °C	R_f *n*-hexane : EtOAc 1 : 2	Yield %
(4a)		$C_{22}H_{14}N_5O_4SCl$	479.90	Brown	239-241	0.54	90
(4b)		$C_{22}H_{14}N_5O_4SCl$	479.90	Dark Brown	221-223	0.47	83
(4c)		$C_{22}H_{14}N_5O_4SCl$	479.90	Brown	211-213	0.40	87
(4d)		$C_{22}H_{14}N_4O_2SCl_2$	469.34	Brown	199-201	0.39	96
(4e)		$C_{22}H_{14}N_4O_2SCl_2$	469.34	Dark Brown	210-212	0.42	91
(4f)		$C_{22}H_{13}N_4O_2SCl_3$	503.78	Brown	218-220	0.50	80
(4g)		$C_{22}H_{14}N_4O_2SClBr$	513.79	Dark Brown	226-228	0.62	93

4h		$C_{22}H_{14}N_4O_2SClBr$	513.79	Dark Brown	204-206	0.34	76
4i		$C_{22}H_{15}N_4O_3SCl$	450.90	Brown	215-217	0.39	93
4j		$C_{22}H_{15}N_4O_3SCl$	450.90	Brown	209-2	0.48	95
4k		$C_{22}H_{15}N_4O_3SCl$	450.90	Dark Brown	162-164	0.52	92
4l		$C_{23}H_{17}N_4O_3SCl$	464.92	Dark Brown	264-266	0.39	75
4m		$C_{24}H_{19}N_4O_2SCl$	462.95	Brown	177-179	0.45	73
4n		$C_{24}H_{18}N_5O_3SCl$	491.95	Brown	283-285	0.50	96

2.4. Antibacterial tests

2.4.1. Preparation of 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 [97].

2.4.2. Preparation of 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 [98].

2.4.3. Preparation of 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 [99].

2.4.4. Antibacterial tests method

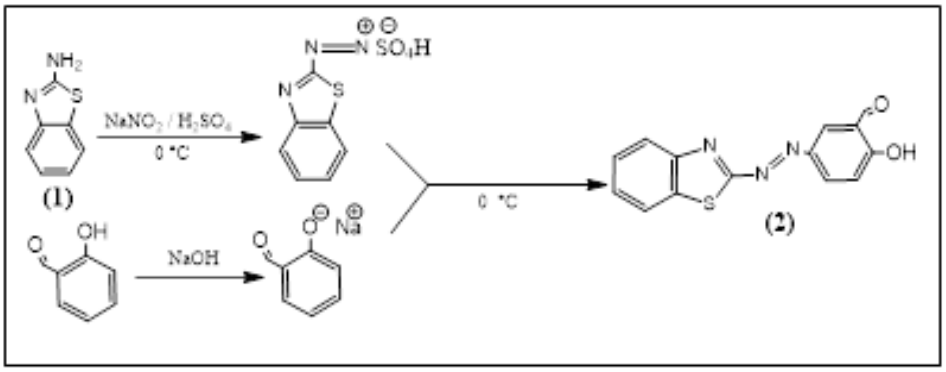
The antibacterial test has been carried out according to the disc diffusion method . All synthesized Azetidin-2-one compounds **(4a-n)** have been examined for their antibacterial activity *in vitro* against one type of Gram-positive bacteria (*Staphylococcus aurous*) and one type of Gram-negative bacteria (*Escherichia coli*). 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. These holes were filled with 40 µL of the prepared compounds (20 mg of the compound dissolved in 1ml of DMSO solvent). These plates have been incubated at 37 ^{o}C for 24 h. for both bacteria. The zones of bacterial growth inhibition around the discs have been measured in (mm), [100].

Chapter Three

Results And Discussion

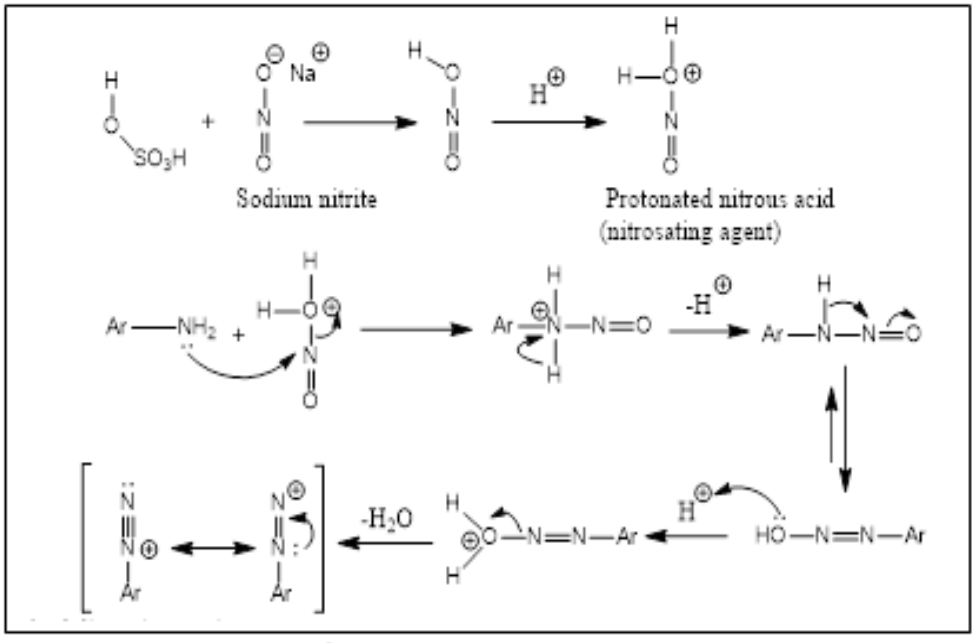
3.1. Synthesis of 5-(benzo[d]thiazol-2-yldiazenyl)-2-hydroxybenzaldehyde 2

Amino function in 2-aminobenzothiazole [I] was diazotized with sodium nitrite and sulfuric acid. The forming diazonium salt was coupled with 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution to yield azo derivative **(2)** involving aldehyde group. Scheme (3-1).

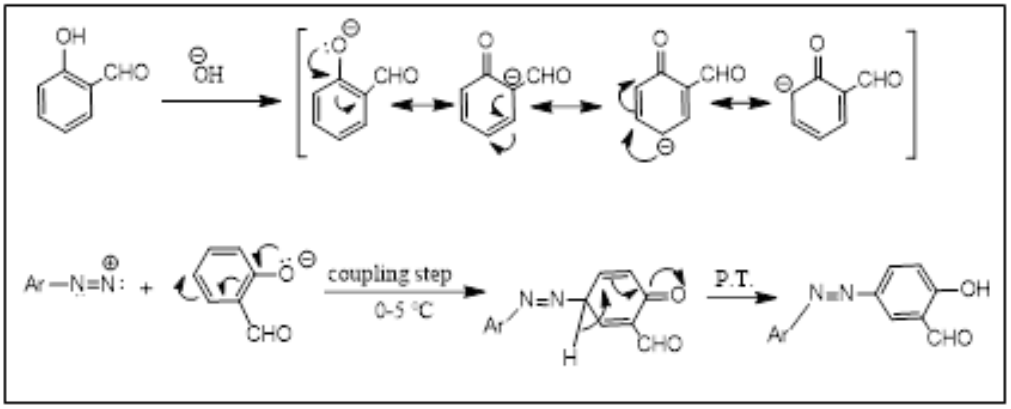


Scheme (3-1): Synthesis of azo compound (2)

The reaction mechanisms were outlined in schemes (3-2) and (3-3), [101].



Scheme (3-2): Mechanism of diazotization of amine



Scheme (3-3): Coupling reaction mechanism

IR spectrum of azoaldehyde compound **(2)** pointed the disappearance of sharp bands at 3402 cm^{-1} and 3273 cm^{-1} for (NH_2)str, also absence of a sharp band belong to (NH_2) bending at 1643 cm^{-1} and appearance of band at 3277 cm^{-1} assigned to (O-H)str, the strong band at 1654 cm^{-1} due to (C=O)str, the weak band at 1435 cm^{-1} attributed to azo group (N=N)str, the benzothiazolic (C=N)str appeared as a weak band at 1587 cm^{-1}. Other bands were listed in Table (3-1).

Table (3-1): (FT-IR) bands of compounds (1a) and (2a)

Comp. NO	**ν(NH_2)** cm^{-1}	**ν(O-H)** cm^{-1}	**ν(C=O)** cm^{-1}	**ν(C=N) benzothiazole** cm^{-1}	**ν(N=N)** cm^{-1}
(1a)	3402 3273	–	–	1587	–
(2a)	1643	3277	1654	-	1435

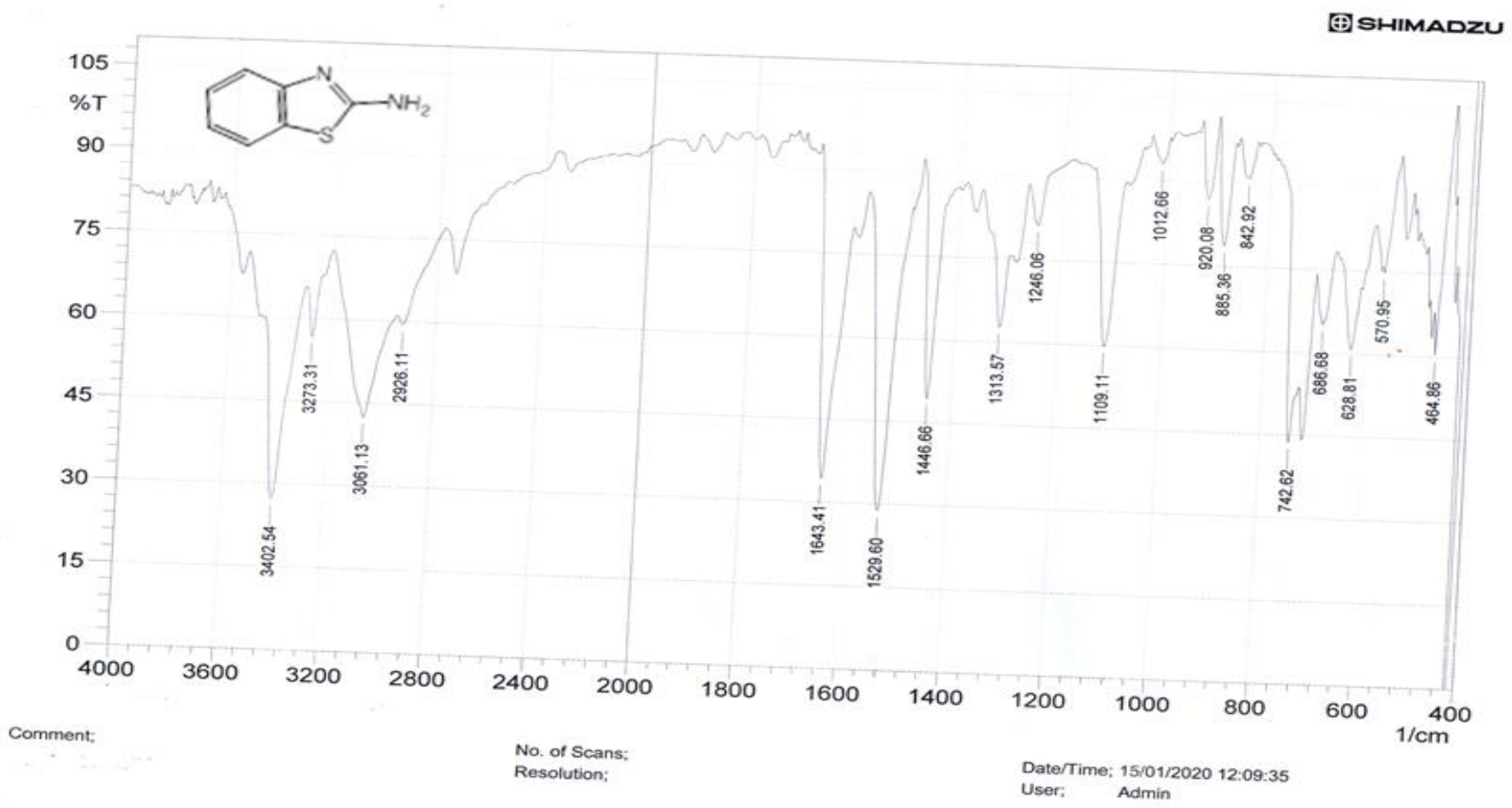


Figure (3-1): FT-IR spectrum of 2-Aminobenzothiazole **(1a)**

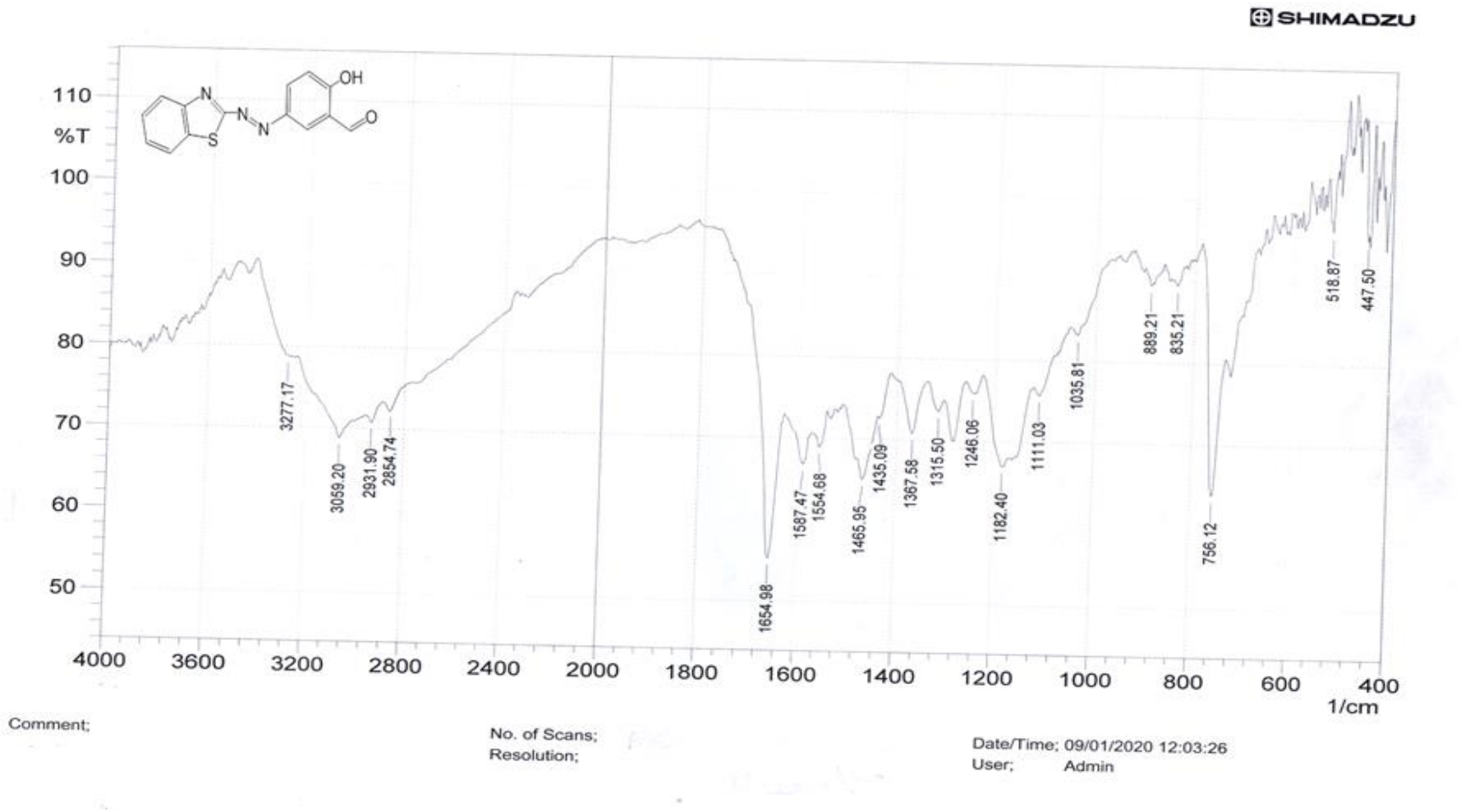
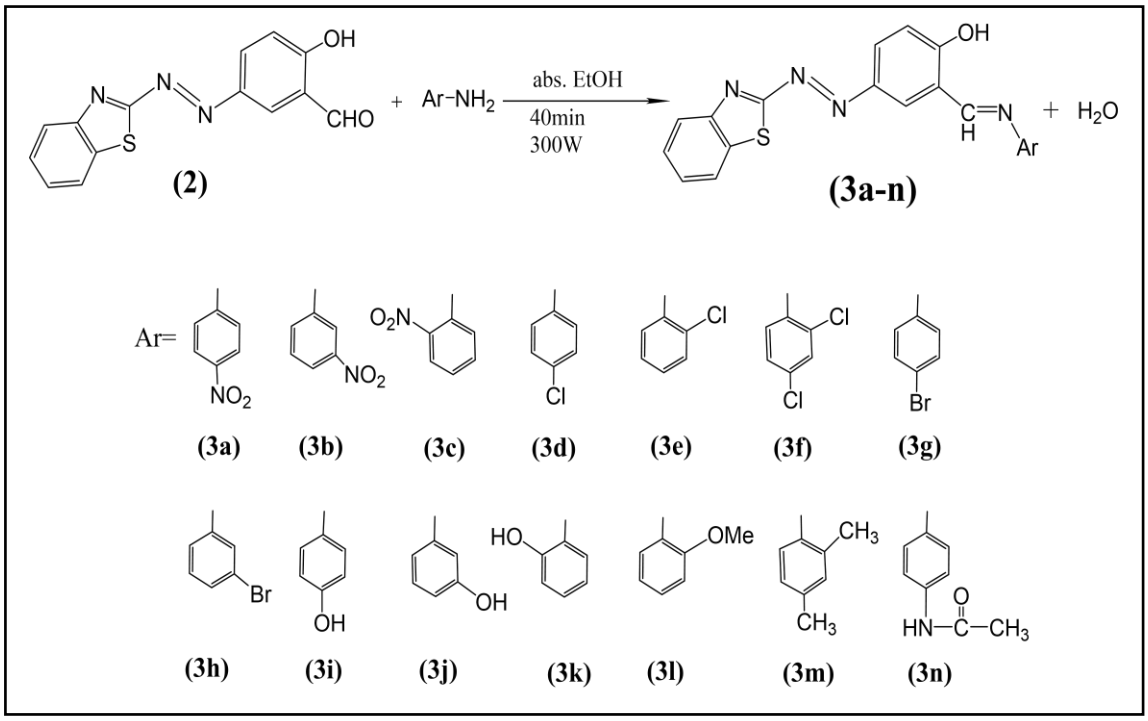


Figure (3-2): FT-IR spectrum of compound **(2a)**

3.2. Synthesis of Schiff bases derivatives (3a-n)

Compound **(2)** was undergone in condensation reactions with some primary anilines derivatives including (4-nitroaniline, 3-nitroaniline, 2-nitroaniline, 4-chloroaniline, 2-chloroaniline, 2,4-dichloroaniline, 4-bromoaniline, 3-bromoaniline, 4-aminoophenol, 3-aminophenol, 2-aminophenol, 2-methoxyaniline, 2,4-dimethylaniline and 4-acetamidoaniline), respectively using microwave irradiation technique in absolute ethanol to give Schiff bases **(3a-n)** as a trivet for this work, Scheme (3-4).



Scheme (3-4): Synthesis of Schiff bases (3a-n)

IR spectra of imines **(3a-n)**, figures showed disappearance of strong band at 1654 cm^{-1} for aldehydic (C=O)str, also disappearing the doublet band for (NH_2)str in the starting amines at the general range (3400-3250) cm^{-1} and appearing a band at the range (1595-1620) cm^{-1} assigned to imine function (C=N)str. Compound (3n) appeared band around 1666 cm^{-1} assigned to amidic (C=O)str. Other characteristic bands were interpreted in Table (3-2).

Table (3-2): FT-IR data of Schiff bases derivatives (3a-n) in cm^{-1}

Comp. NO	ν(O-H)	ν(C-H) aroma.	(νC=N) imine exo	ν(C=N) benzothiazole endo	ν(C=C) benzene	ν(N=N)	Others
(3a)	3362 3219	3064	1595	1595 overlapped	1494	1444	1494 overlapped, 1303 (NO_2)str
(3b)	3350	3072	1614	1614 overlapped	1479	1433	1527 1348 (NO_2)str
(3c)	3473 3381	3063	1620	1620 overlapped	1479	1433	1525 1346 (NO_2)str
(3d)	3257	3057	1614	1614 overlapped	1529 1485	1446	1402 (C-Cl)str.
(3e)	3200	3057	1616	1616 overlapped	1529	1444	1373 (C-Cl)str
(3f)	3282	3063	1614	1614 overlapped	1523 1471	1446	1393 $(C-Cl_2)$str
(3g)	3458	3061	1612	1612 overlapped	1575,1533, 1479	1450	1398 (C-Br)str

(3h)	3294	3063	1616	1587	1529 1475	1437	1309 (C-Br)str.
(3i)	3406	3068	1614	1614 overlapped	1510 1458	-	
(3j)	3369	3064	1620	1620 overlapped	1512 1450	-	
(3k)	3313	3066	1618	1618 overlapped	1518 1464	-	
(3l)	3315 3180	3057	1614	1614 overlapped	1531 1458	-	2943 2831 (CH_3)str
3m	3414	3063	1616	1616 overlapped	1573 1529 1471	1446	2931 (CH_3)str
3n	3300	3059	1610	1616 overlapped	1516	1411	3192 (N-H)str 1666 C=O)str, amide

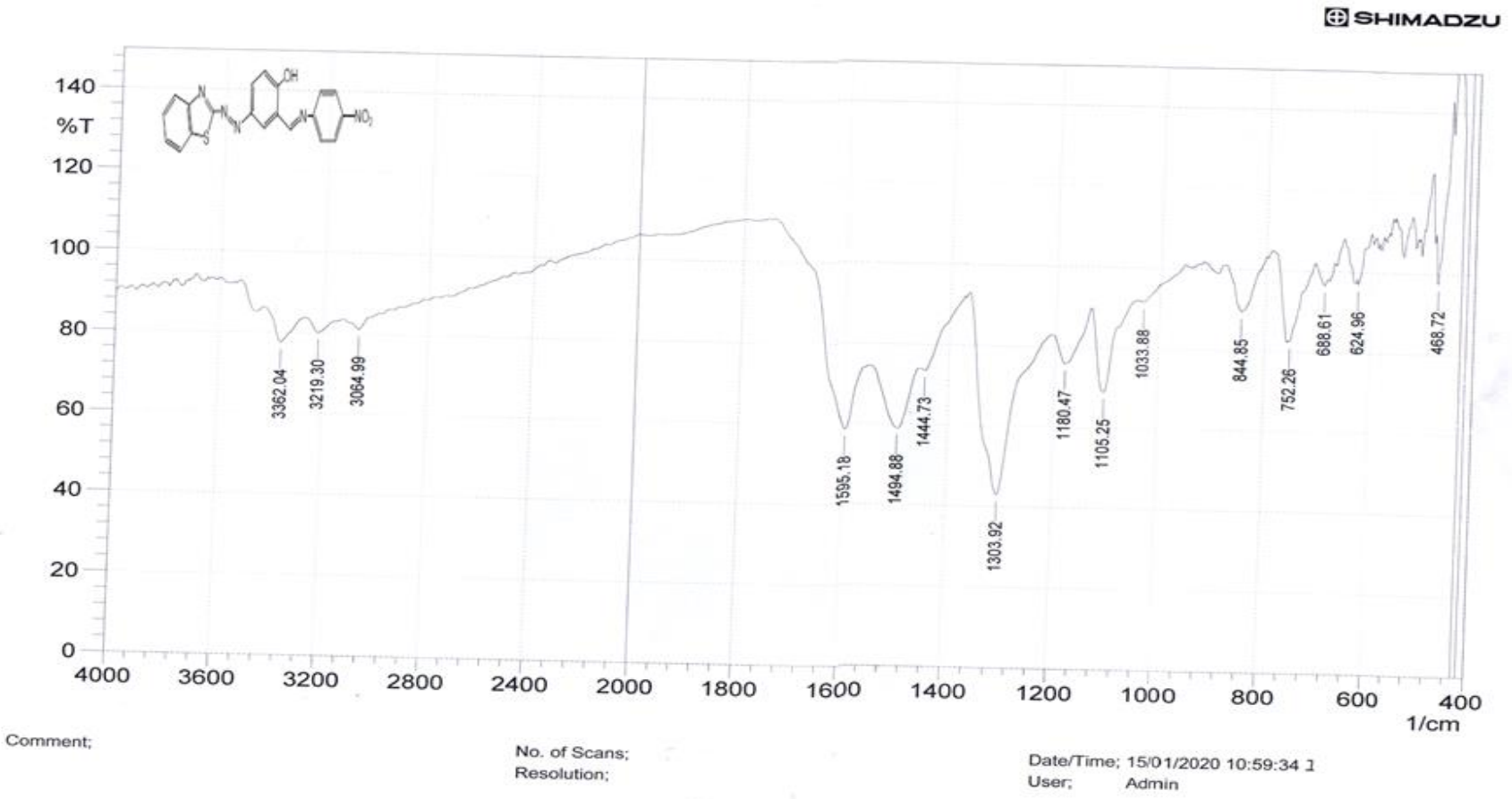


Figure (3-3): FT-IR spectrum of compound (**3a)**

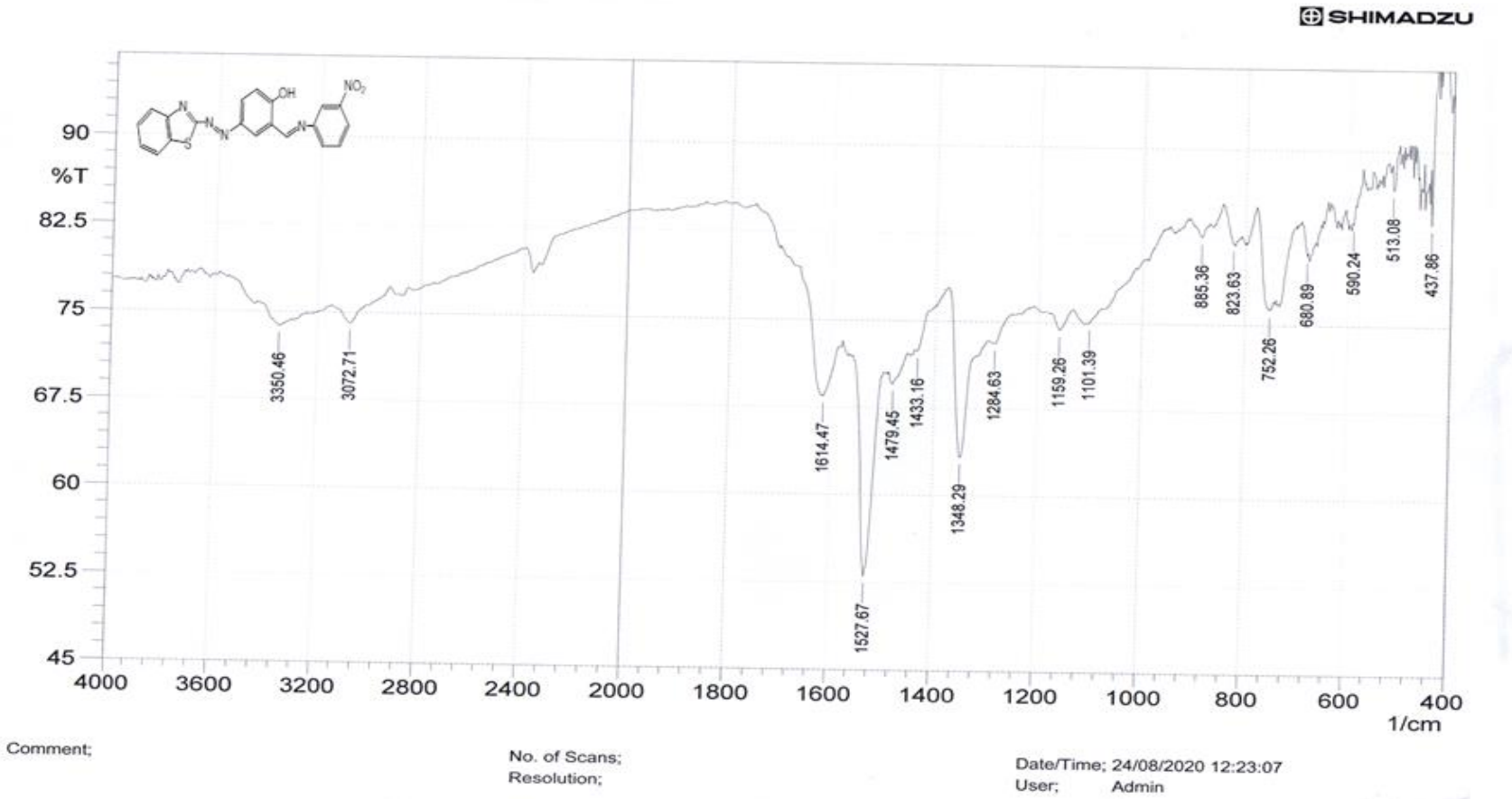


Figure (3-4): FT-IR spectrum of compound **(3b)**

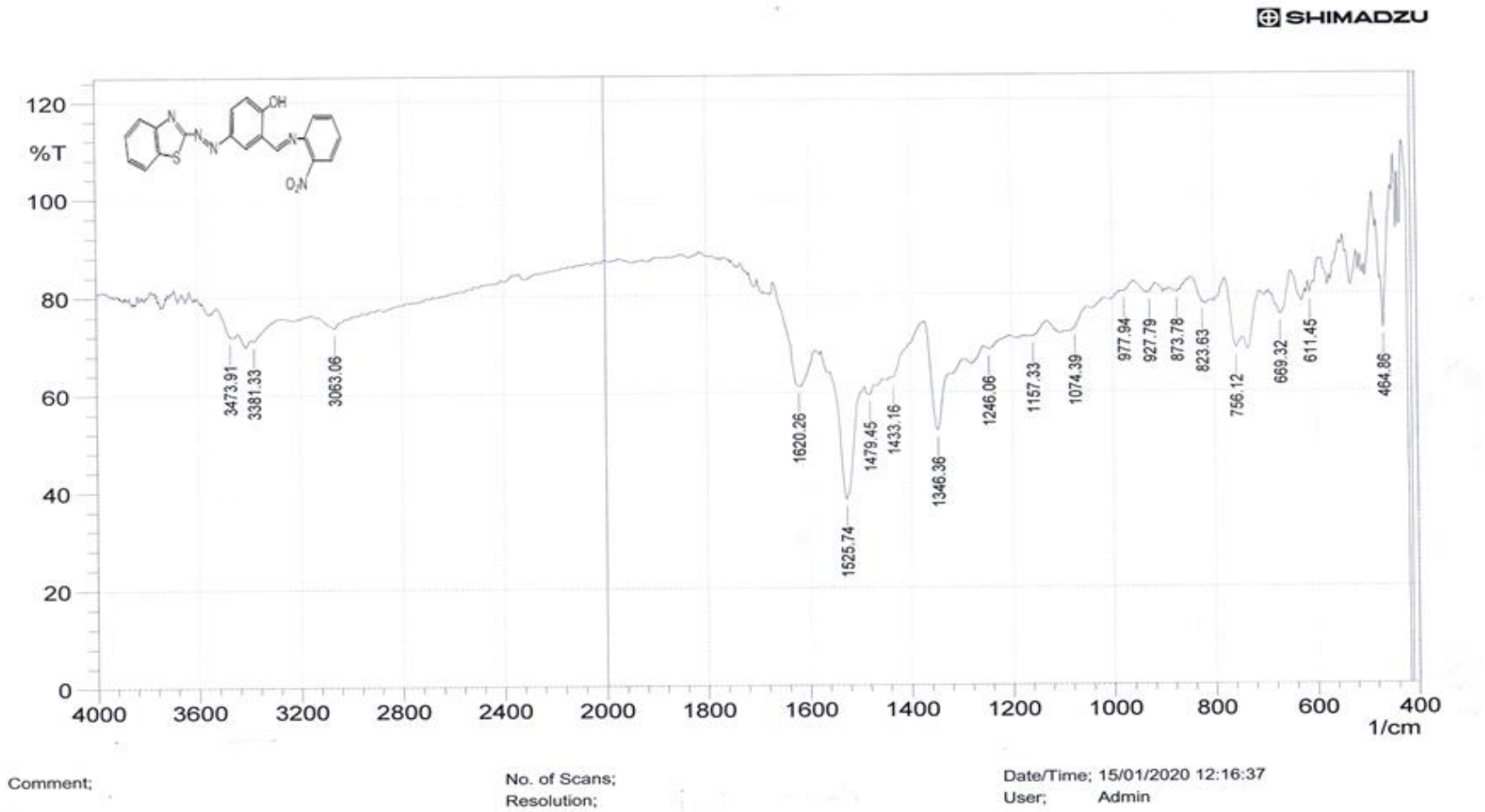


Figure (3-5): FT-IR spectrum of compound **(3c)**

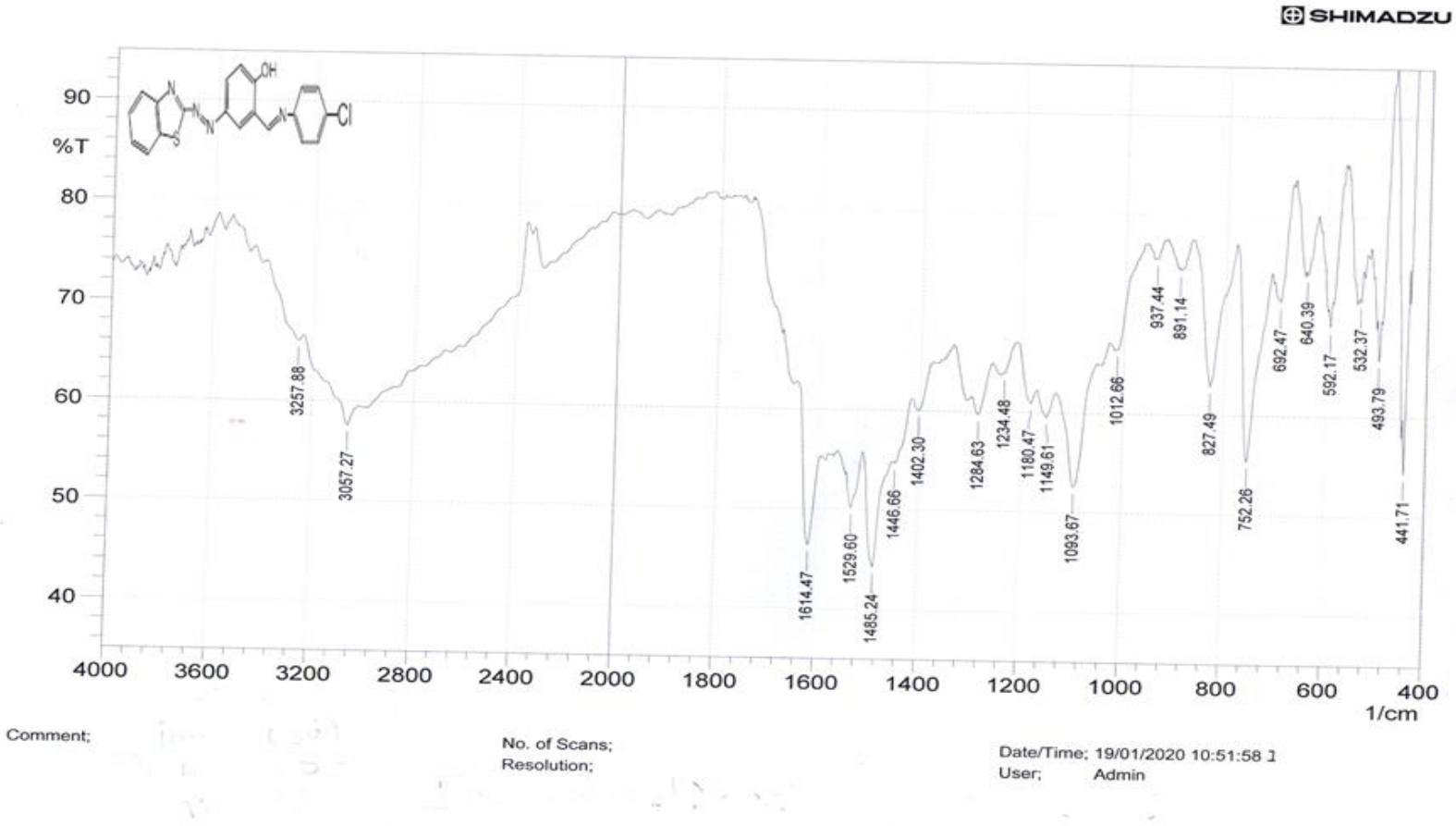


Figure (3-6): FT-IR spectrum of compound **(3d)**

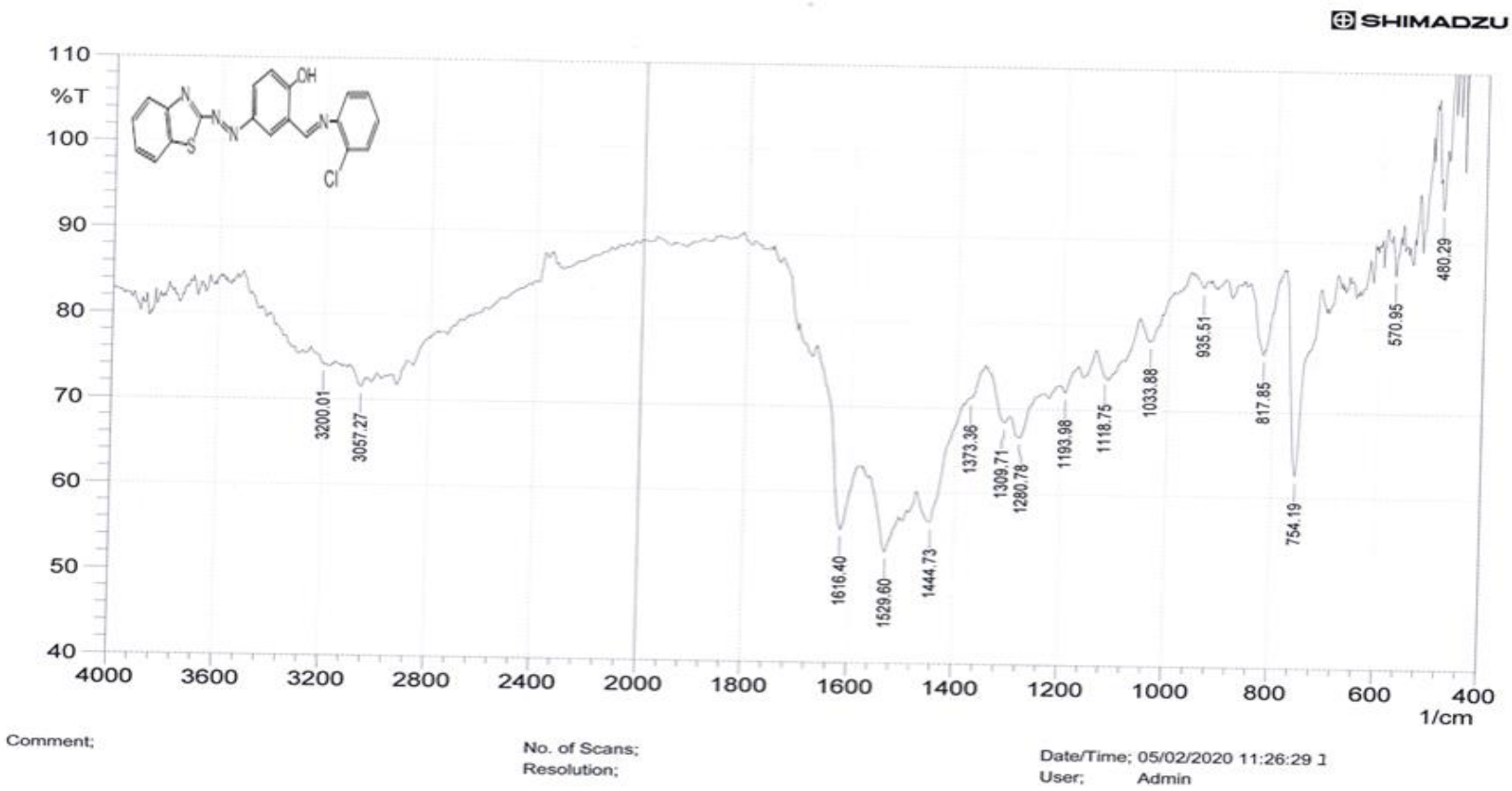


Figure (3-7): FT-IR spectrum of compound (**3e)**

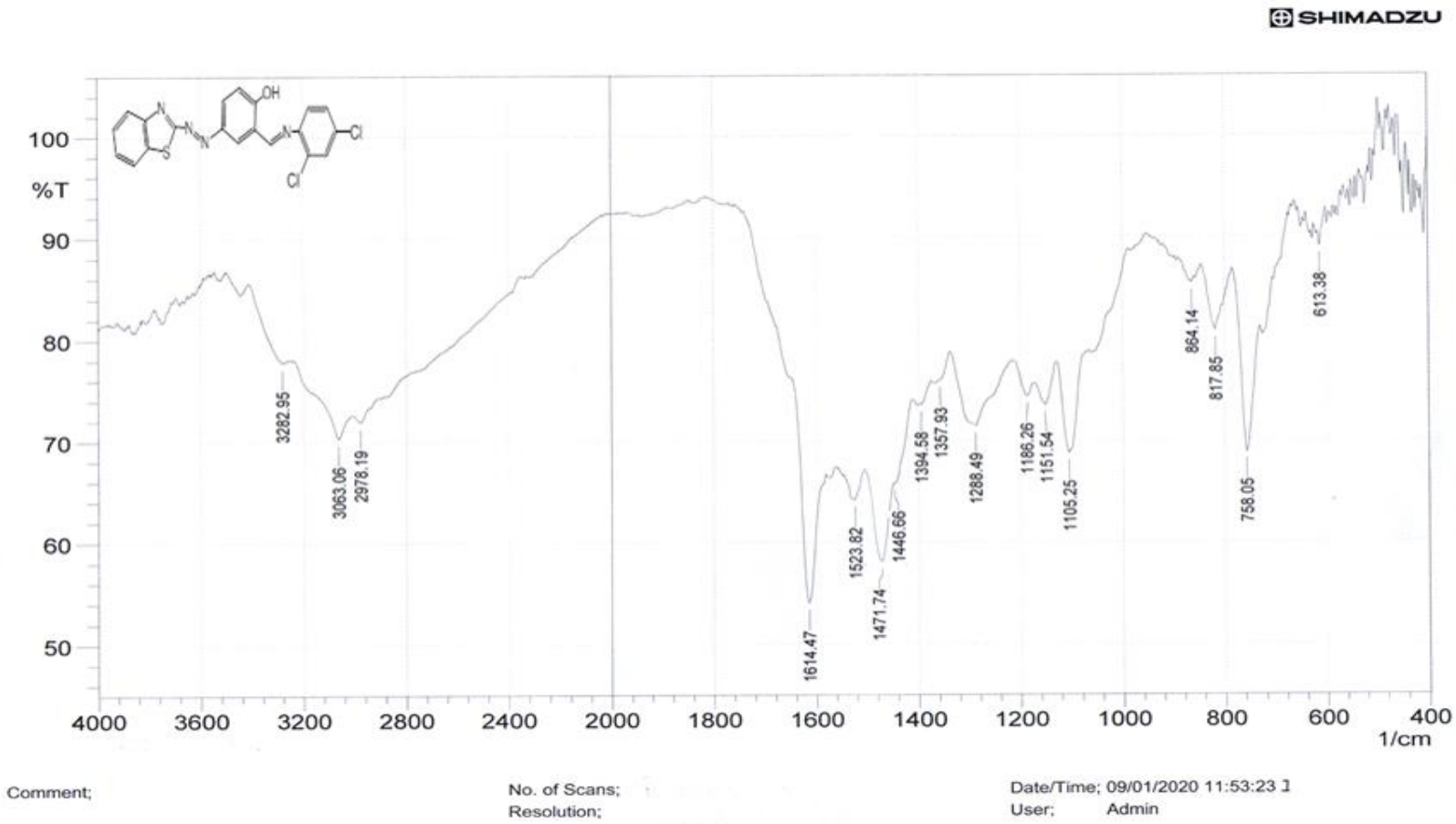


Figure (3-8): FT-IR spectrum of compound **(3f)**

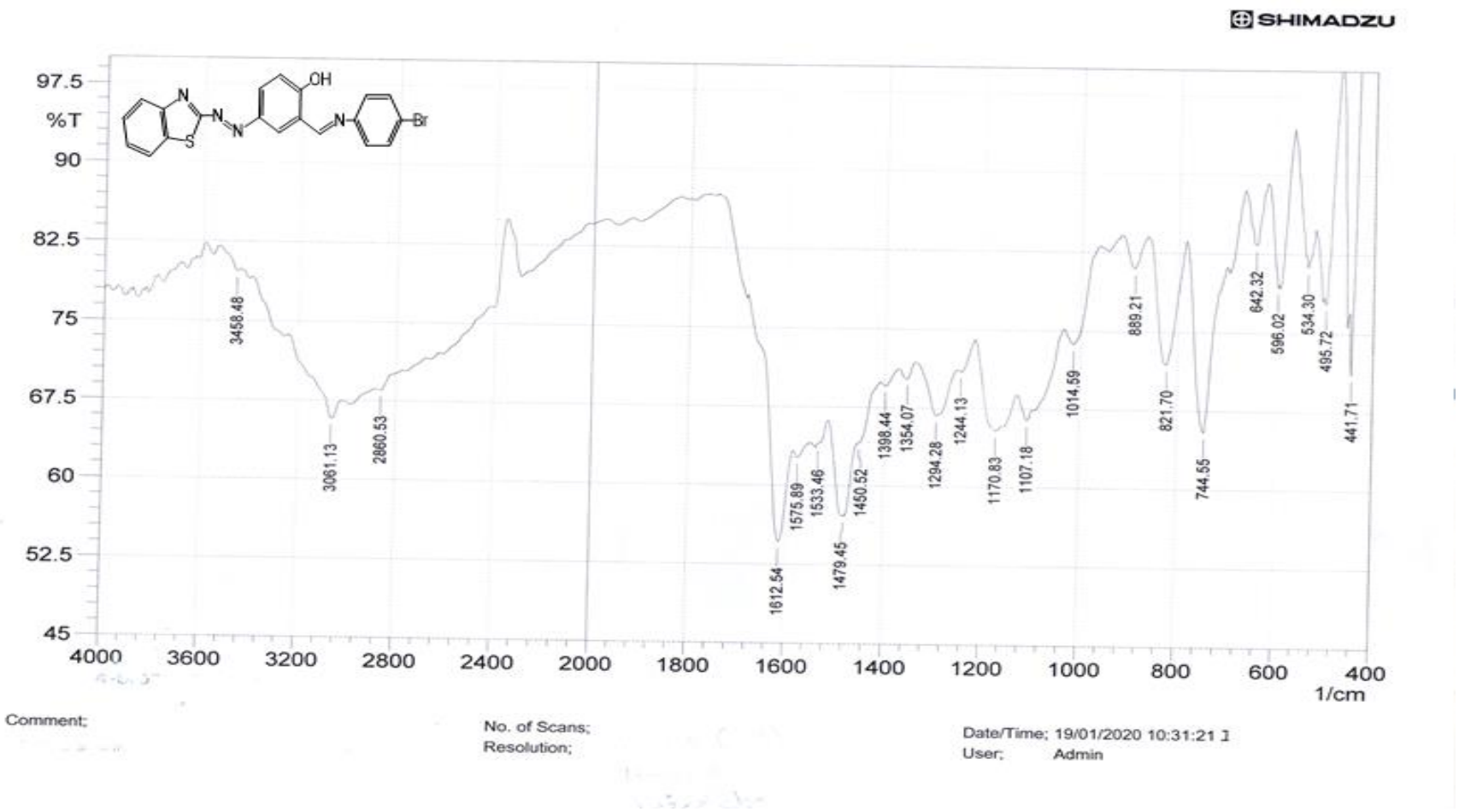


Figure (3-9): FT-IR spectrum of compound (**3g)**

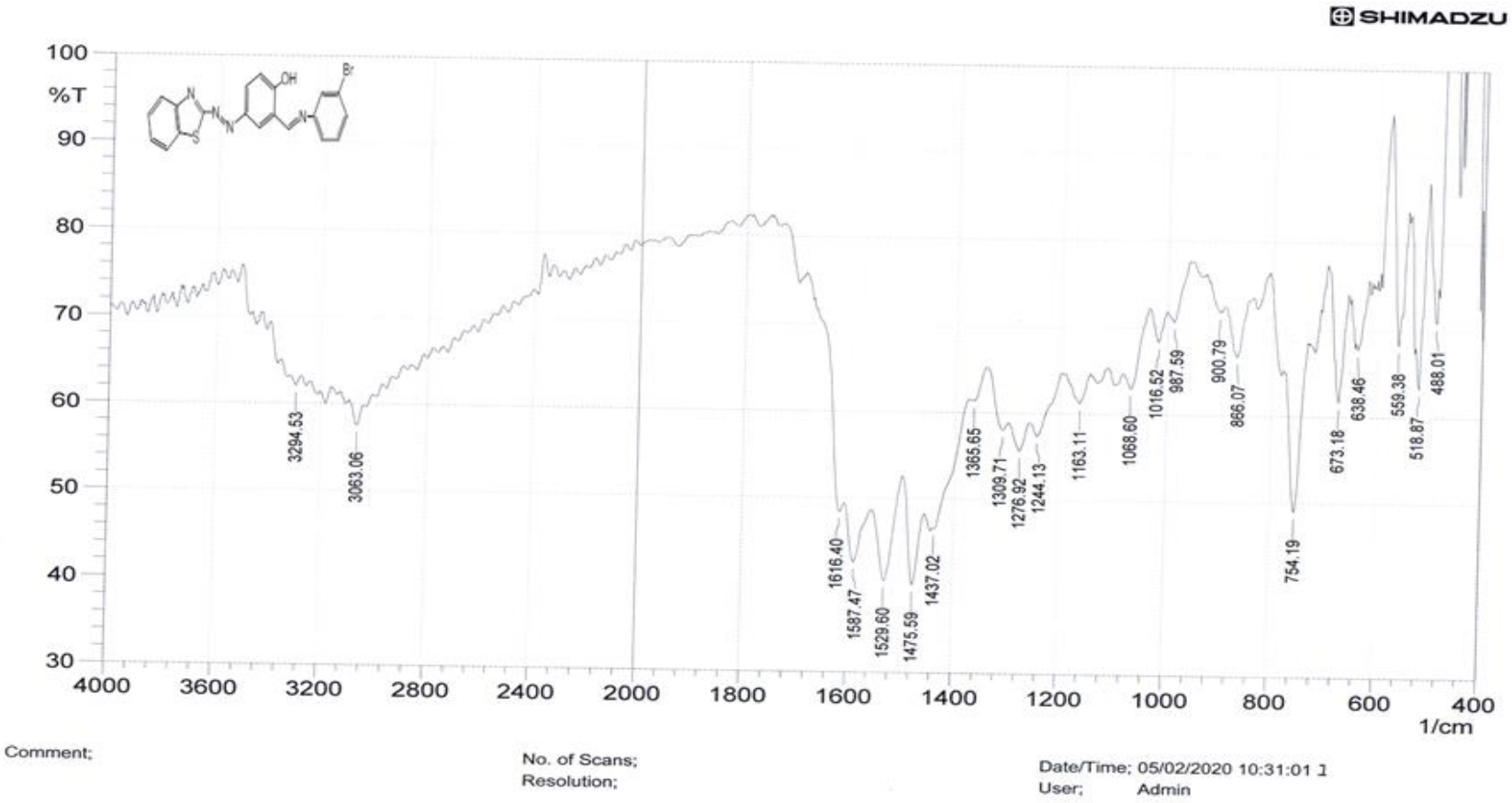


Figure (3-10): FT-IR spectrum of compound (**3h)**

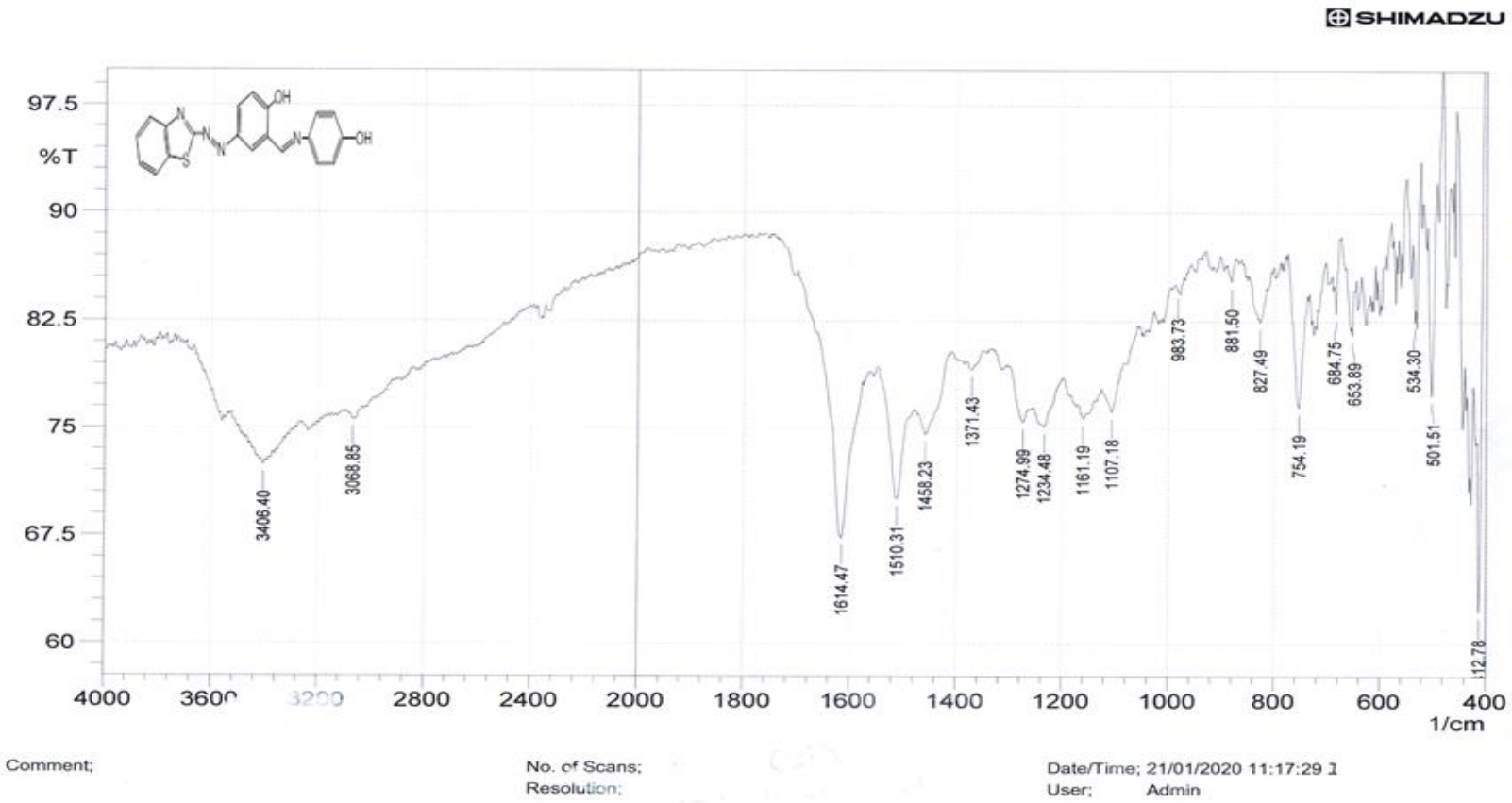


Figure (3-11): FT-IR spectrum of compound (**3i)**

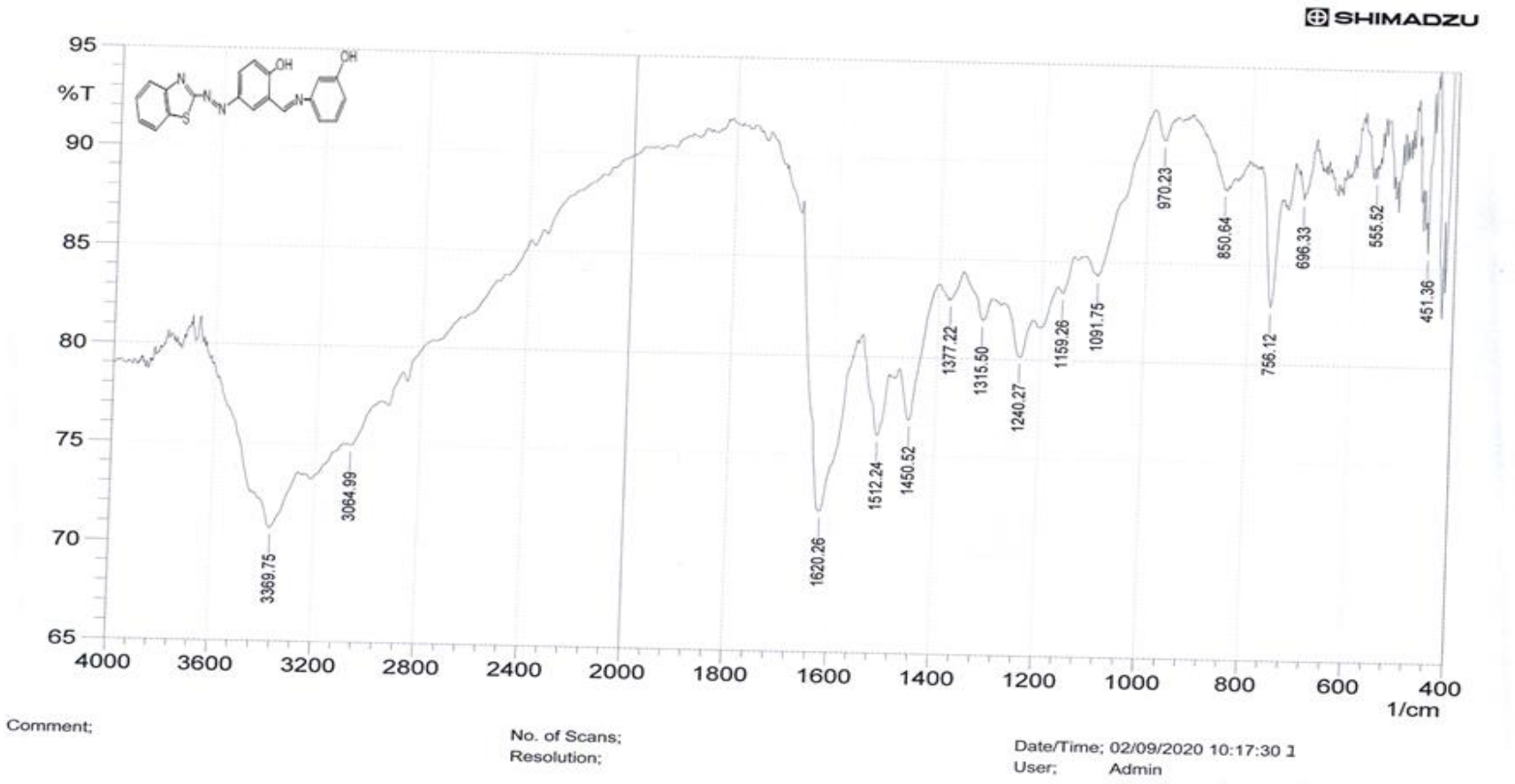


Figure (3-12): FT-IR spectrum of compound (**3j)**

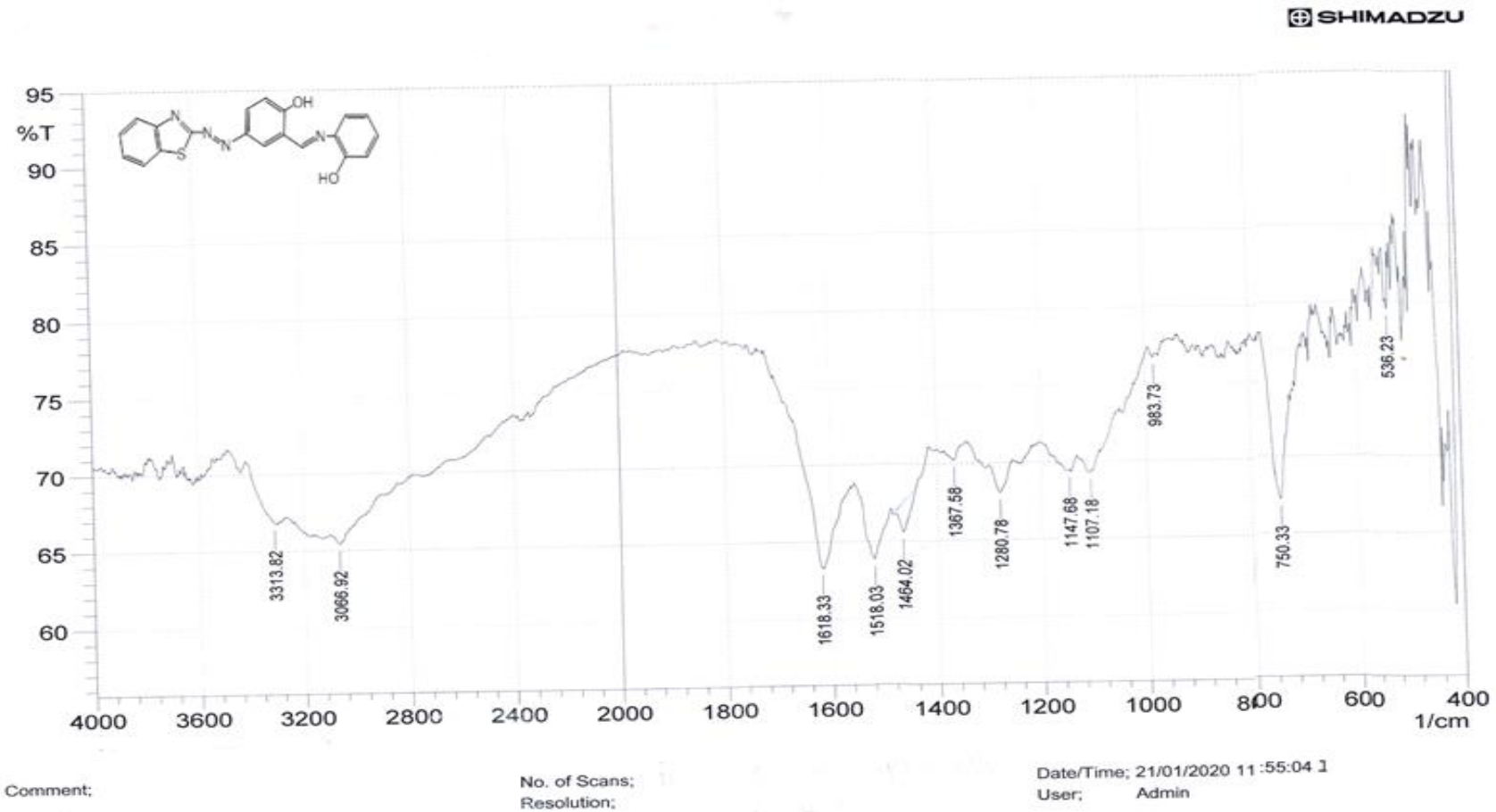


Figure (3-13): FT-IR spectrum of compound (**3k)**

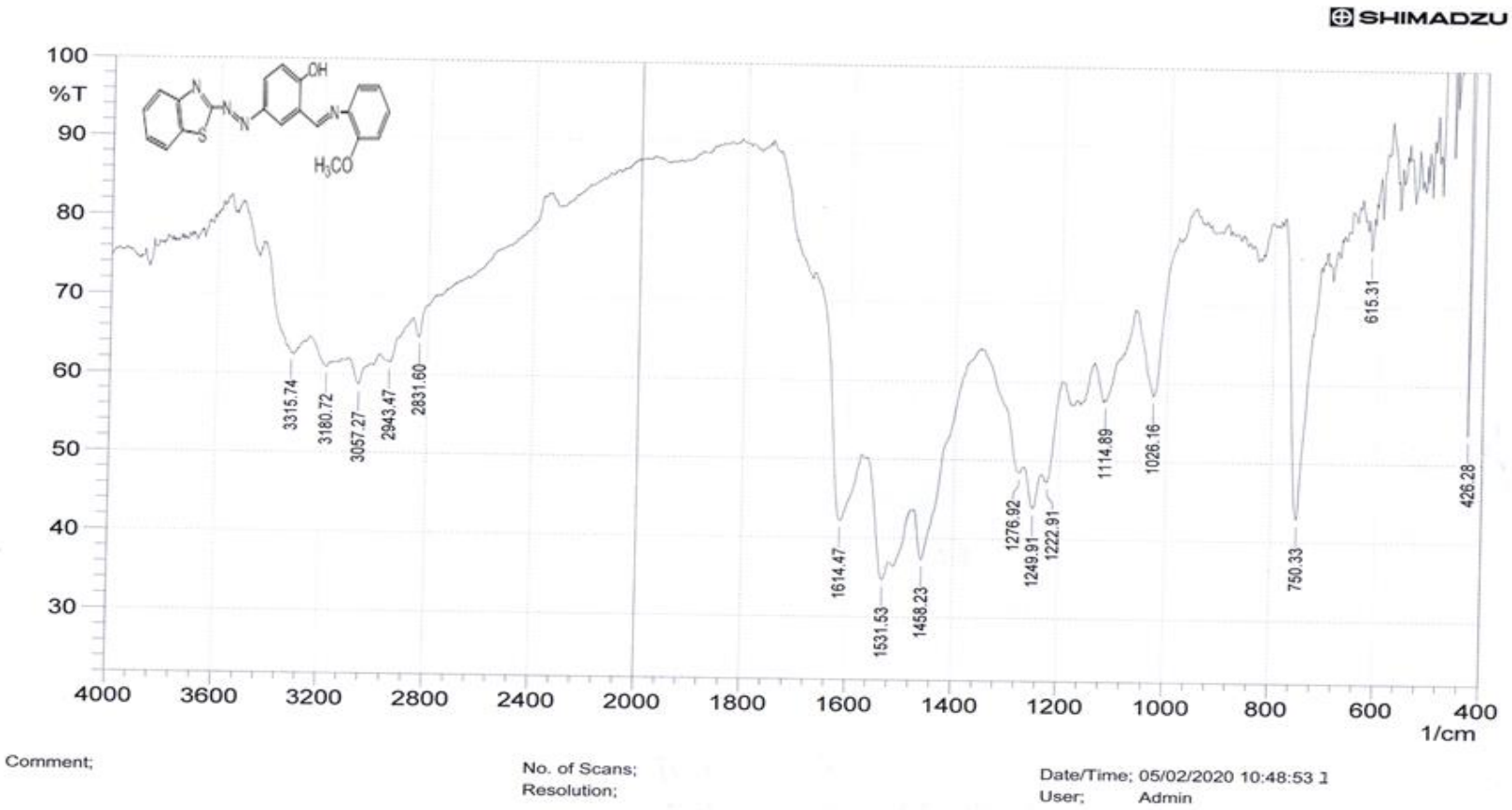


Figure (3-14): FT-IR spectrum of compound (**3l)**

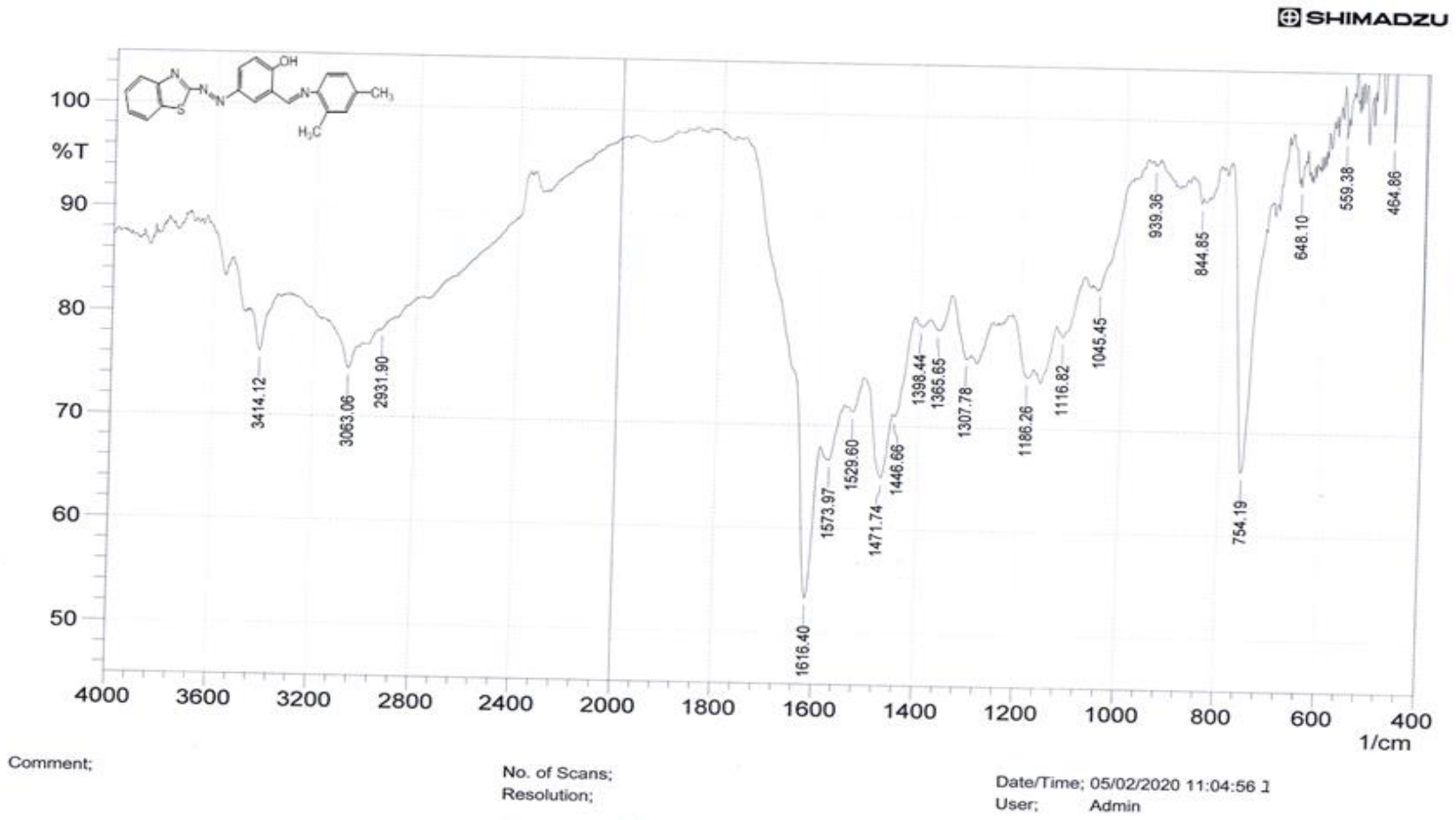


Figure (3-15): FT-IR spectrum of compound (**3m)**

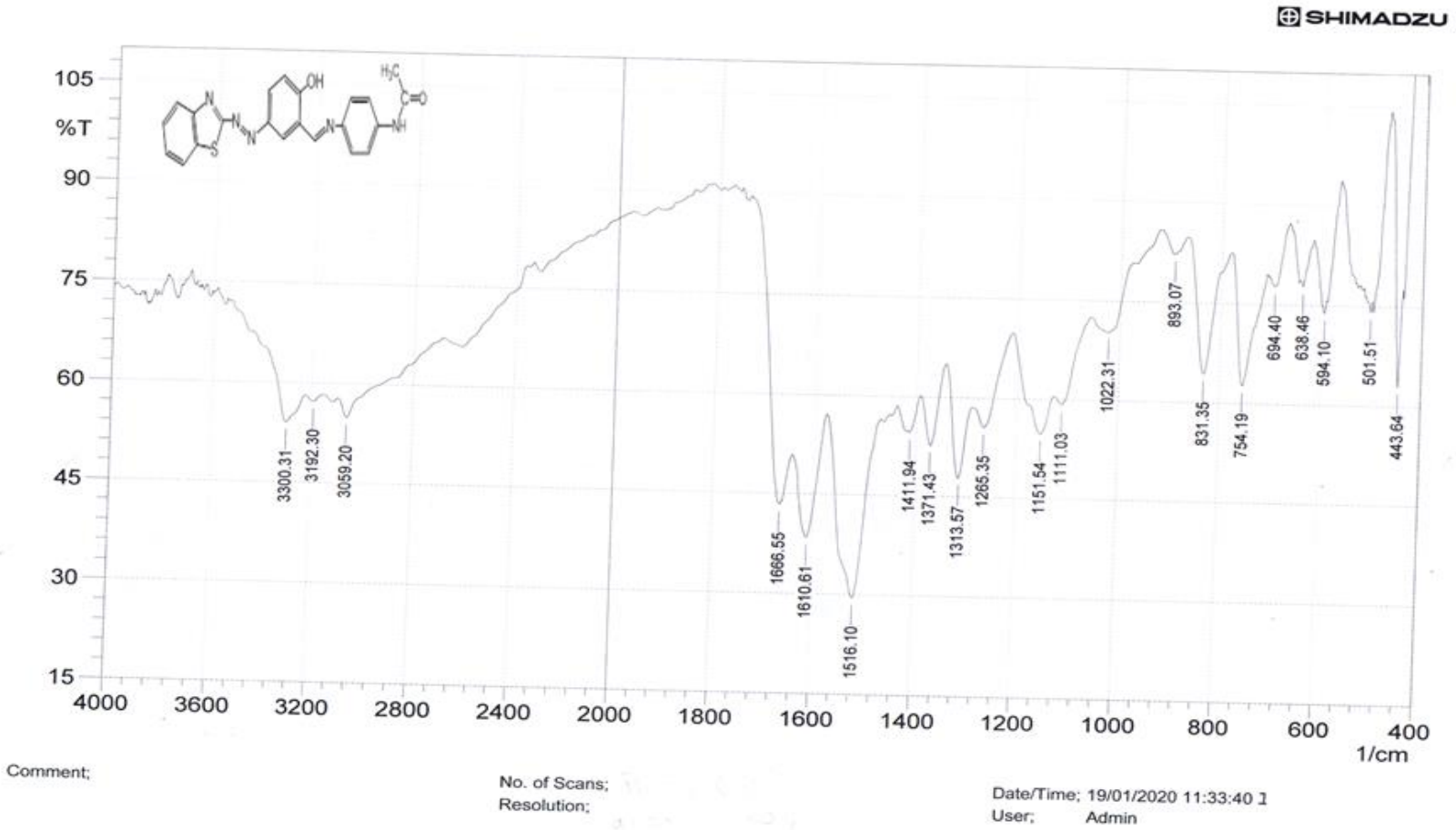
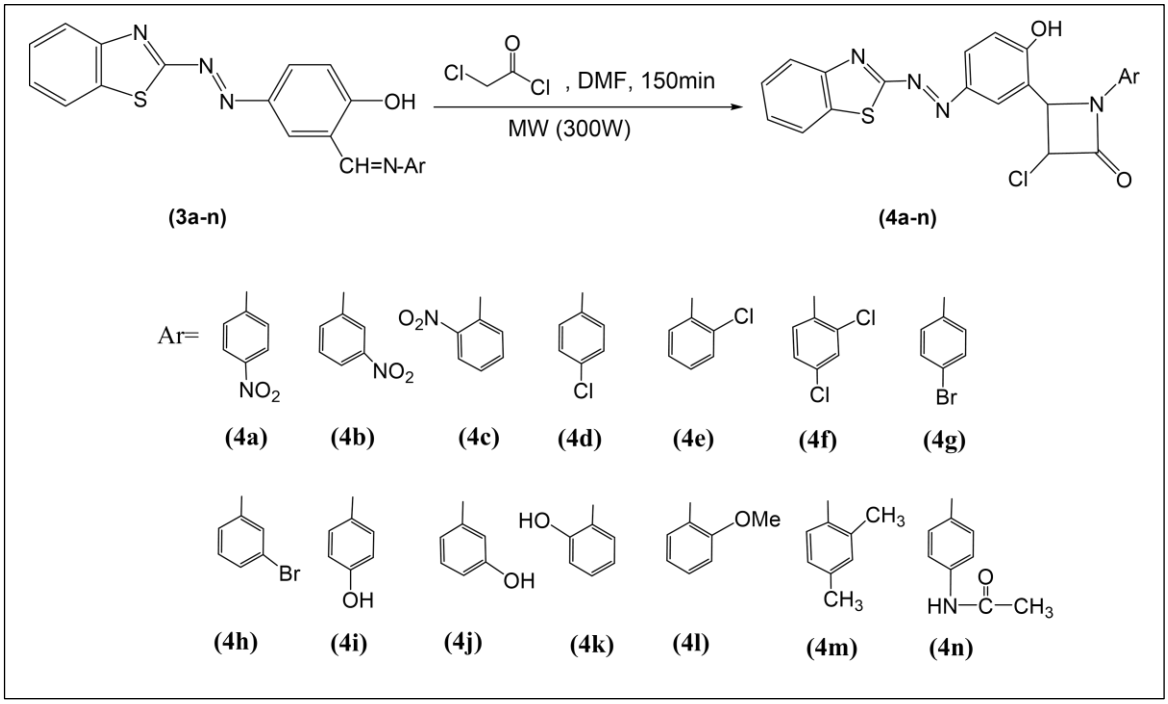


Figure (3-16): FT-IR spectrum of compound (**3n)**

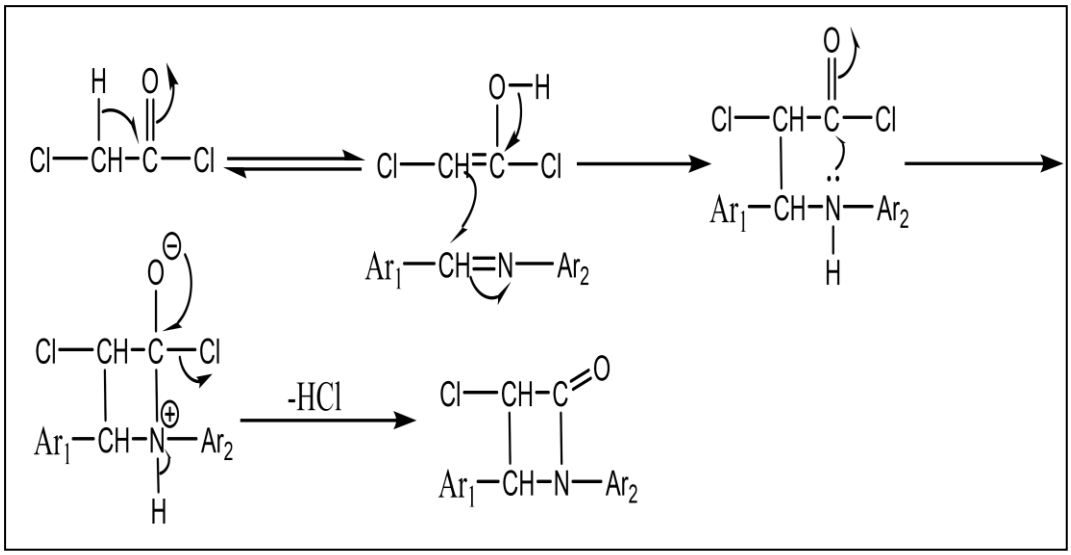
3.3. Synthesis of azetidin-2-ones (4a-n)

The synthesized Schiff bases **(3a-n)** were introduced in cyclization reaction with α-chloroacetyl chloride in *N*,*N*-dimethylformamide as solvent using microwave irradiation method to yield the target azetidin-2-one derivatives, Scheme (3-5).



Scheme (3-5): Synthesis of azetidine-2-ones (4a-n)

The proposed mechanism for cyclization reaction to form azetidine ring was outlined in Scheme (3-5)



Scheme (3-5): Proposed mechanism of cyclization reaction to form β-lactam ring

FT-IR spectra of azetidinone compounds **(4a-n)** present apparent proof that the reactions occurred swimmingly through the appearance of two bands for (C=O) stretching of β-lactam ring, the first at the range (1710-1676 cm^{-1}) while the second at the scope (1678-1643 cm^{-1}) due to field effect between chlorine atom and carbonyl group oxygen atom, the steric orientation of chlorine atom may be up or down of plane of the azetidine ring and thus the π-bond characteristic in carbonyl group (C=O) will be changed. The spectra also appeared the benzothiazolic (C=N)str at the range (1608-1583 cm^{-1}), while (C=N)str of Schiff bases disappeared. Moreover, compound **(4n)** appeared additional band at 1656 cm^{-1} assigned to amidic (C=O)str. Other bands were listed in table (3-3).

Table (3-3): FT-IR data of azetidin-2-one derivatives (4a-n) in cm^{-1}

Comp. NO	ν(O-H)	ν(C-H) aroma.	(νC=O) lactam	ν(C=N) benzothiazole	ν(C=C) benzene	ν(N=N)	Others
(4a)	3412	3063	1685 1649	1606	1469	-	1539 1307 (NO_2)str
(4b)	3346	3061	1676 1645	1600	1465	1435	1531 1309 (NO_2)str
(4c)	3018	3018 overlapped	1689 1649	1599	1518 1464	1431	1546 1311 (NO_2)str

(4d)	3423	3059	1710 1678	1593	1525 1489	1435	1379 (C-Cl)str.
(4e)	3416	3053	1705 1643	1591	1525 1475	-	1302 (C-Cl)str.
(4f)	3387	Overlapped with broad (C-H) aliph. str at 2978	1693 1656	1600	1525 1471	1417	1305 (C-Cl_2)str.
(4g)	3390	3064	1685	1587	1529 1475	1442	1312 (C-Br)str.
(4h)	3057	3057 overlapped	1687 1647	1583	1531 1471	1431	1307 (C-Br)str.
(4i)	3055	3055 overlapped	1693 1647	1608	1546 1512 1462	-	
(4j)	3180	3022	1703 1647	1595	1525 1469	1431	
(4k)	3387	3024	1707 1668	1595	1531 1471	1431	

4l	3379	3063	1687	1604	1521 1464	-	2935, 2839 (CH_3)str
4m	3389	3059	1710 1670	1587	1529 1477	1435	2922 2858 (CH_3)str
4n	3423	3055	1676 1649	1608	1514	1433	3234 (N-H)str 1656 **(C=O)str** amide

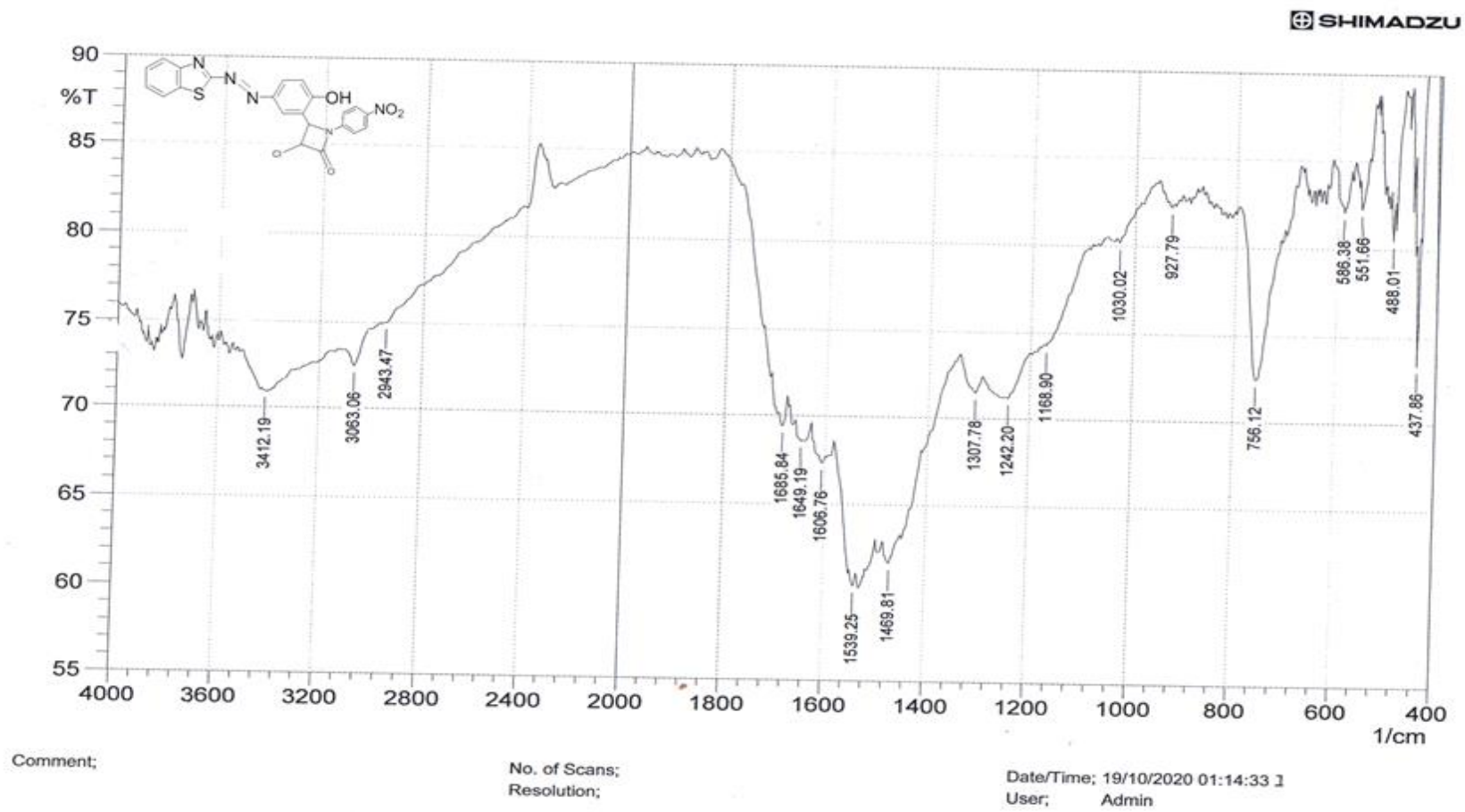


Figure (3-17): FT-IR spectrum of compound (**4a)**

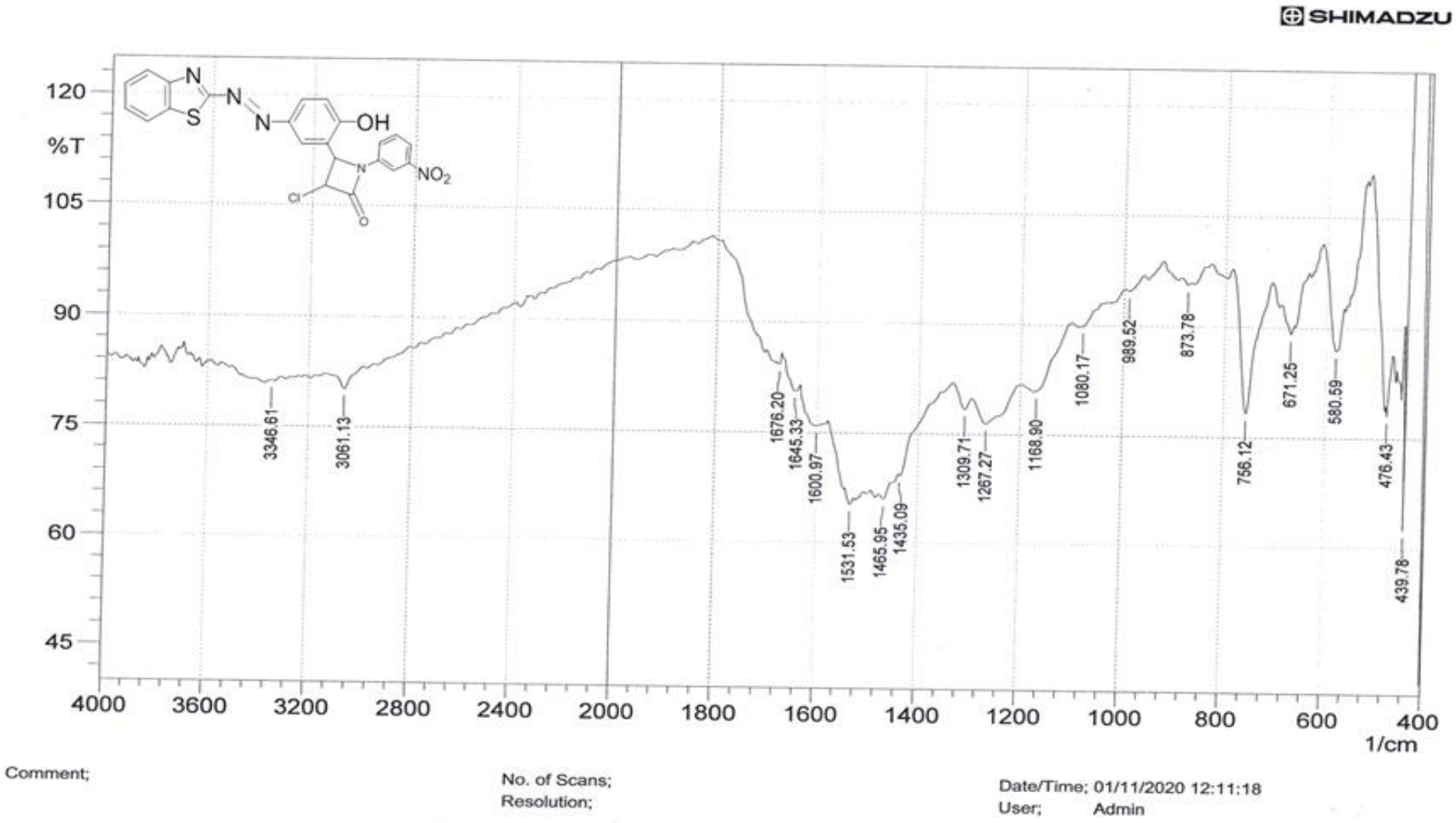


Figure (3-18): FT-IR spectrum of compound (**4b)**

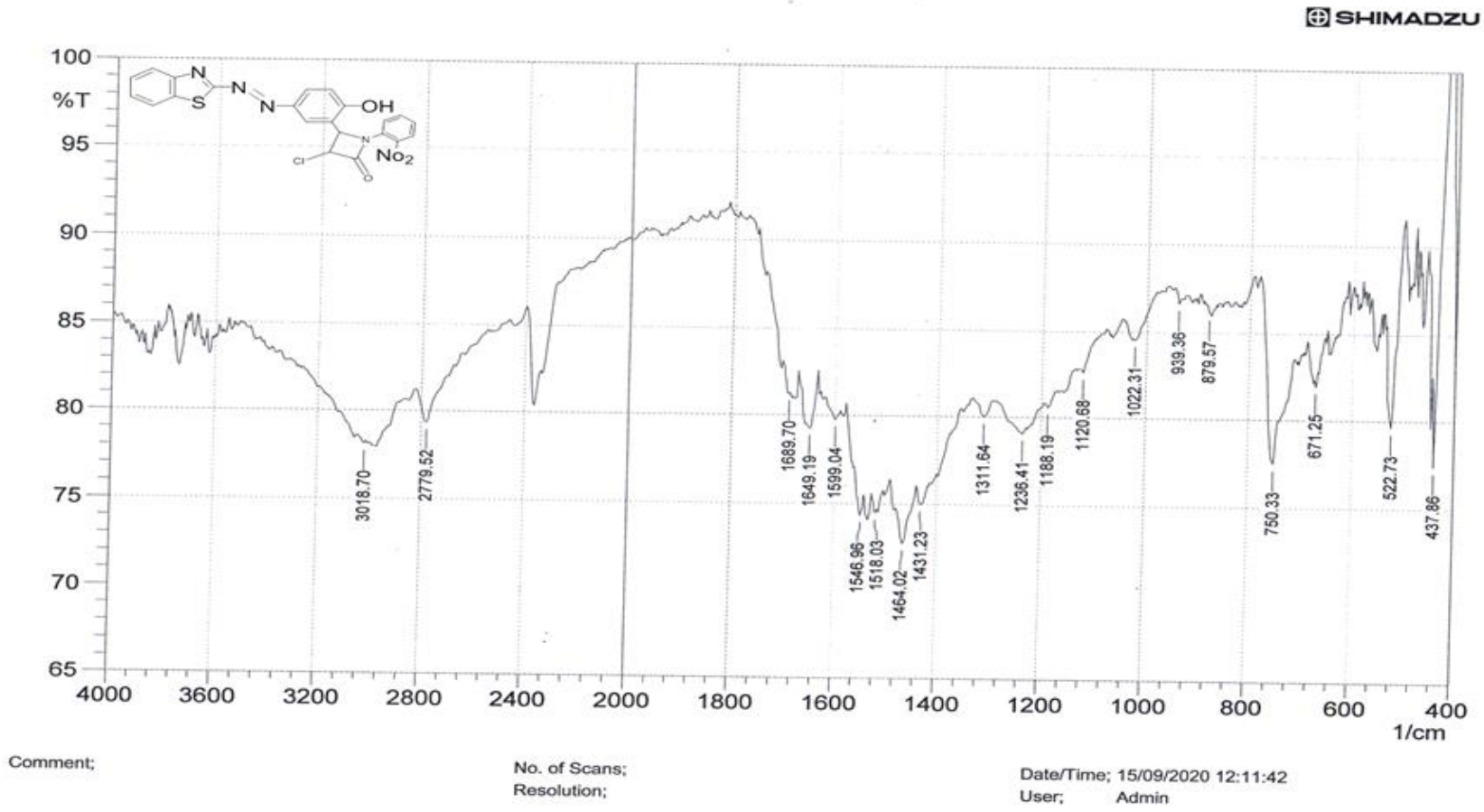


Figure (3-19): FT-IR spectrum of compound (**4c)**

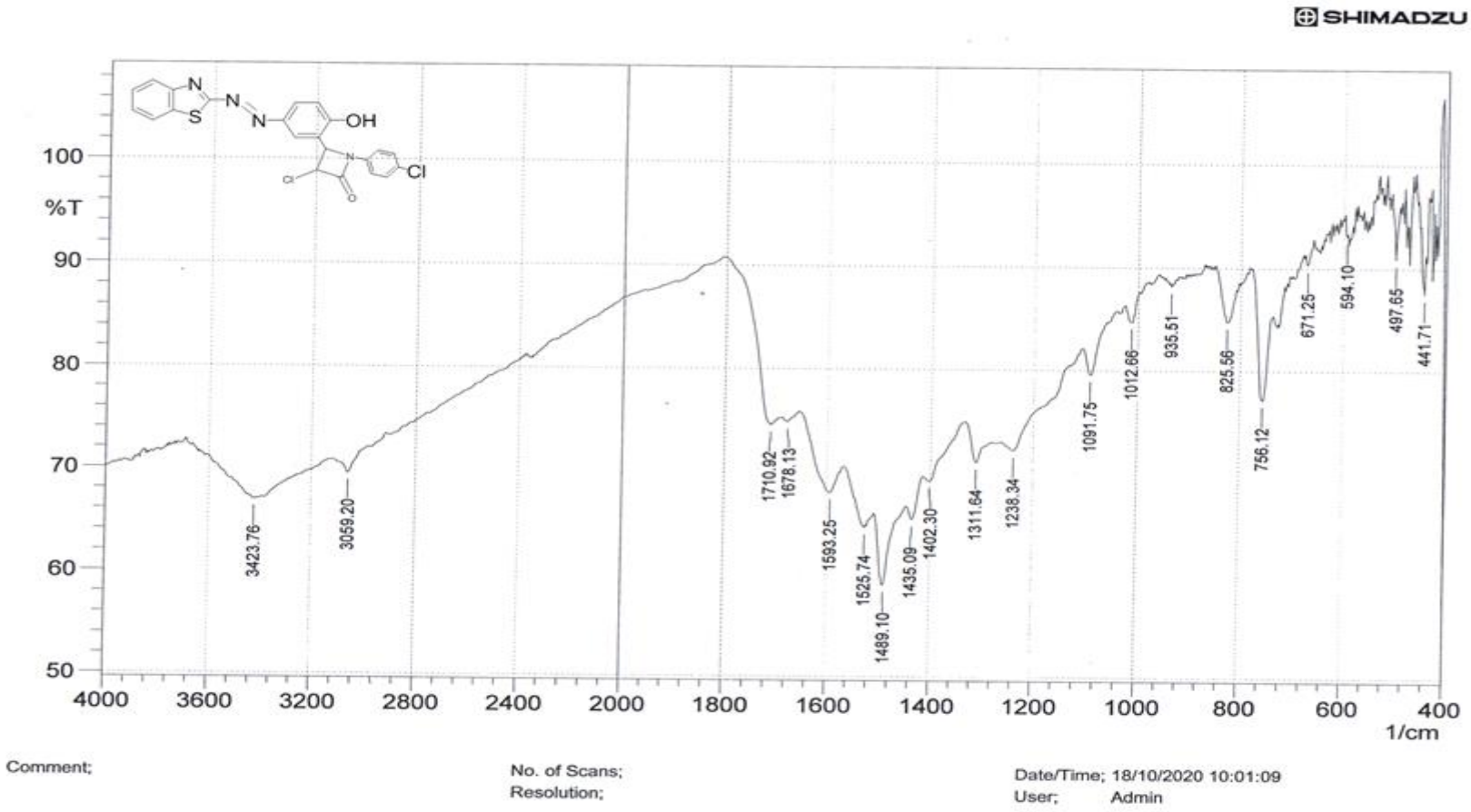


Figure (3-20): FT-IR spectrum of compound (**4d)**

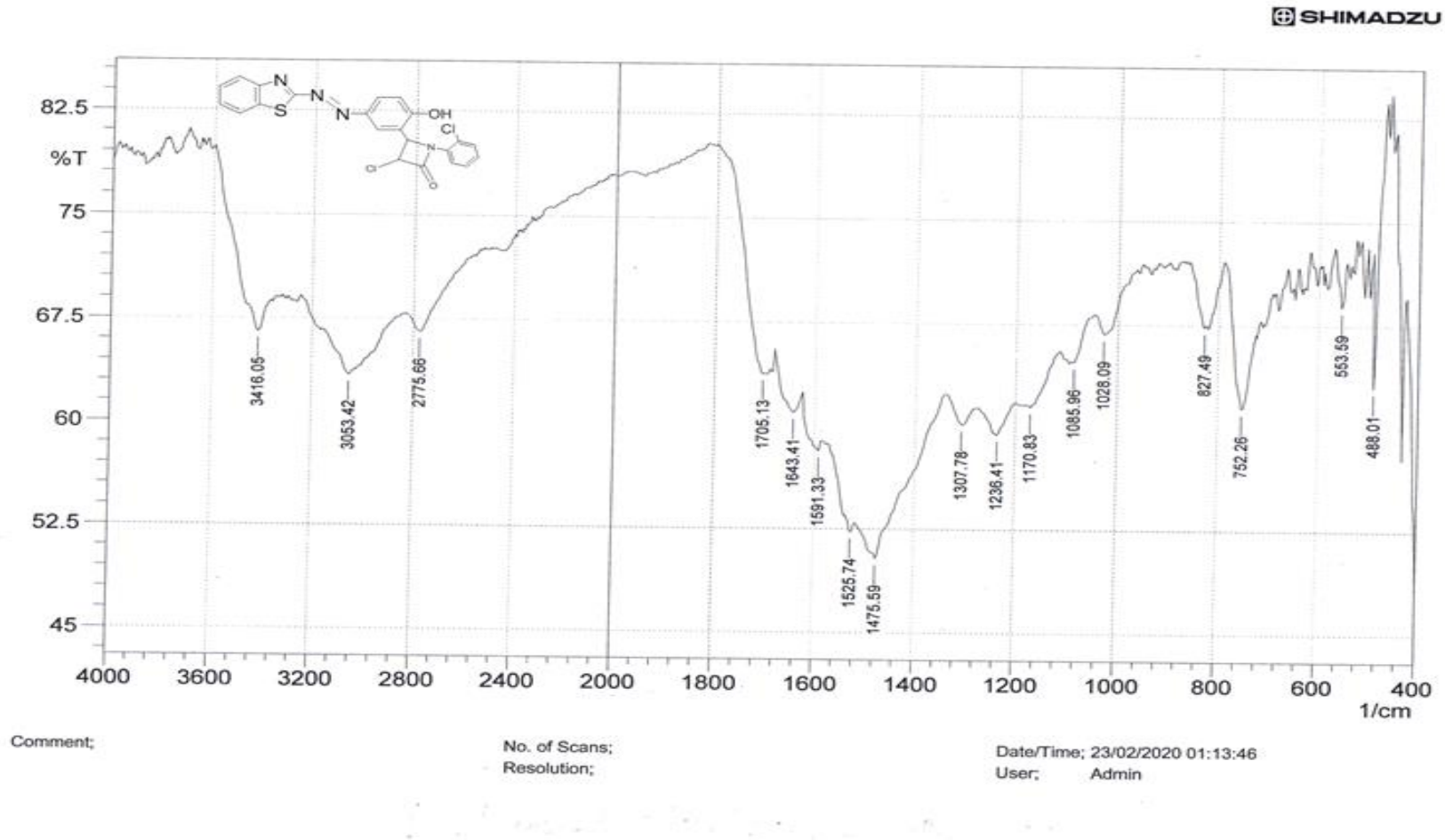


Figure (3-21): FT-IR spectrum of compound (**4e)**

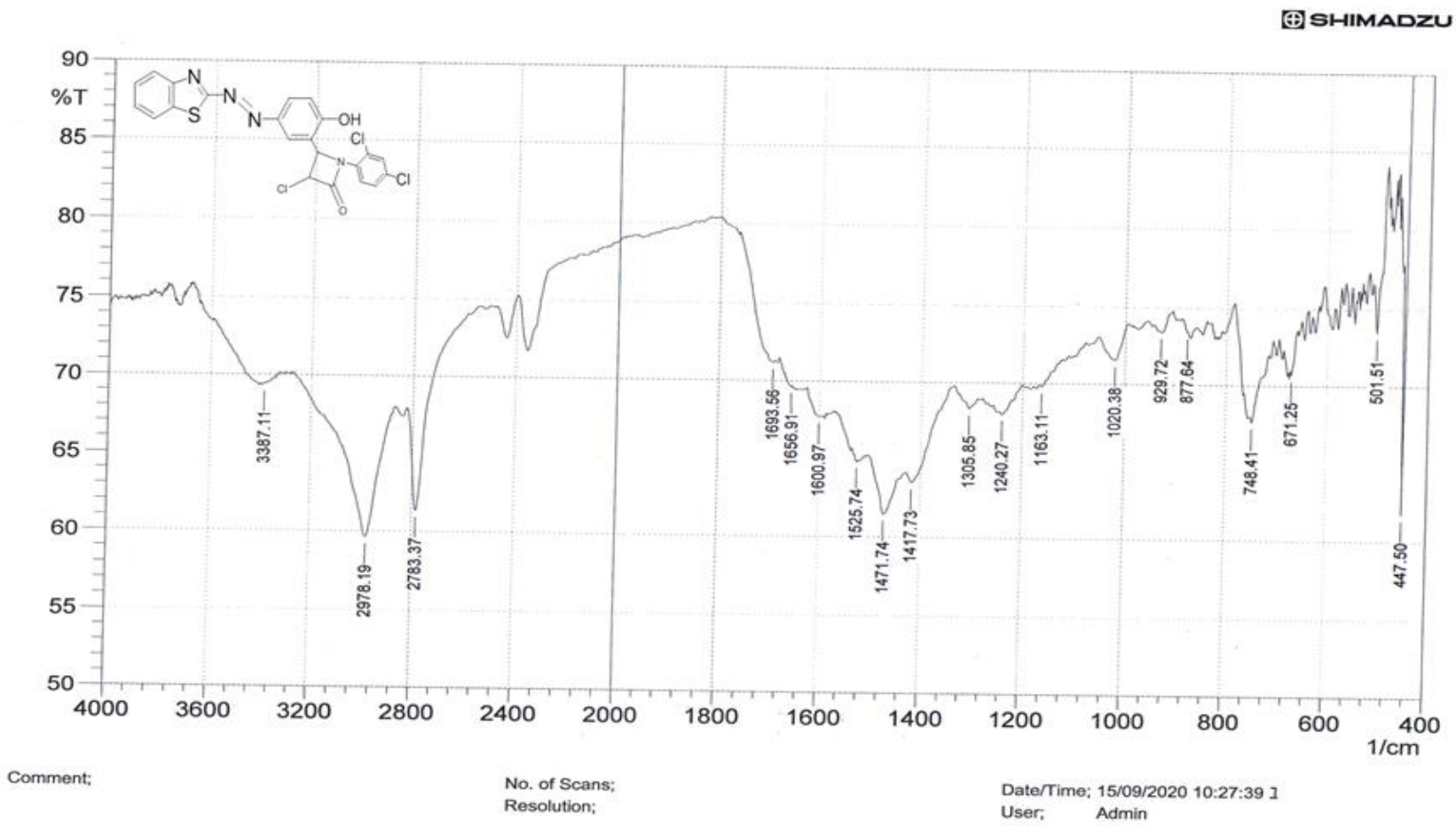


Figure (3-22): FT-IR spectrum of compound (**4f)**

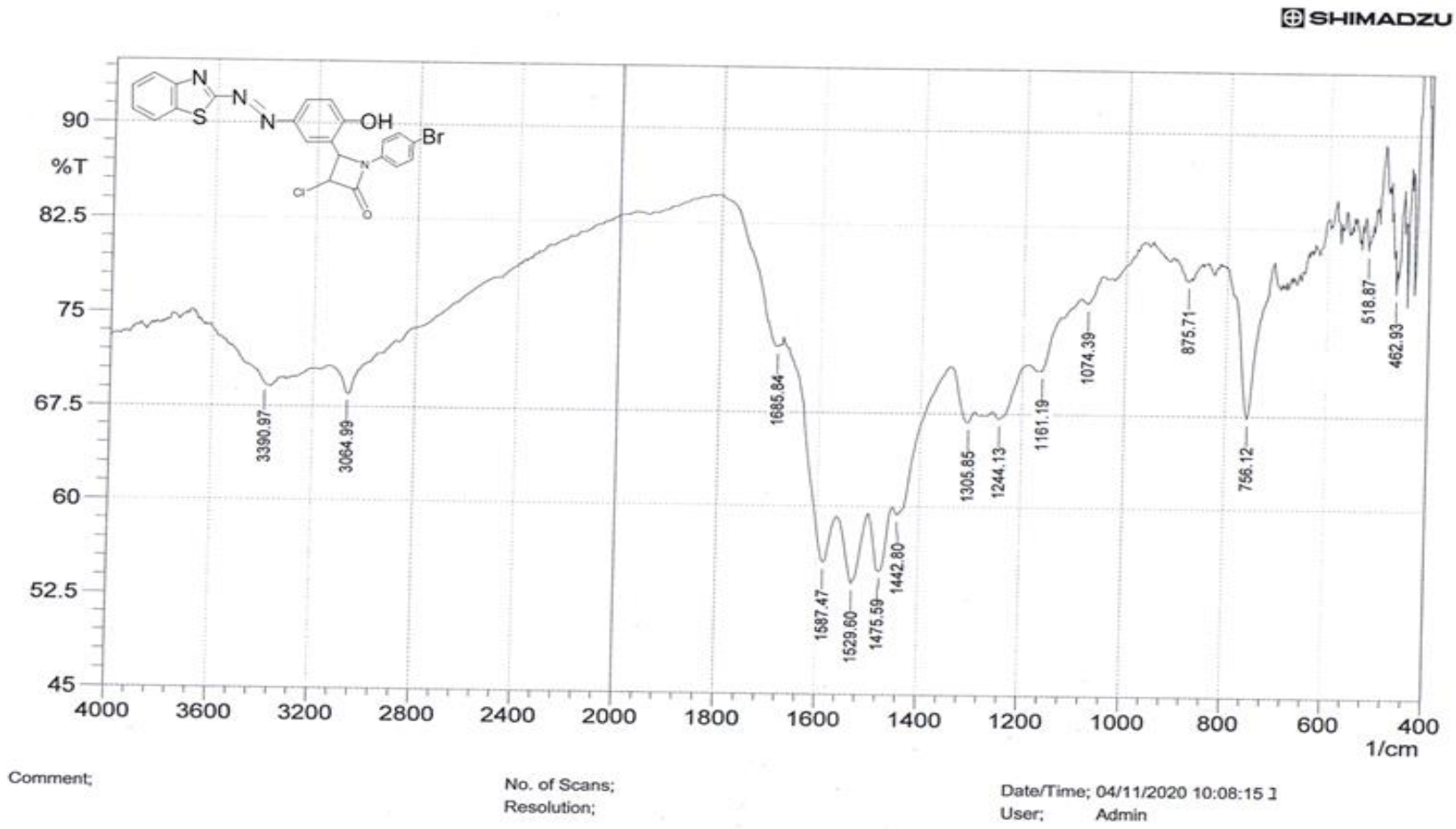


Figure (3-23): FT-IR spectrum of compound (**4g)**

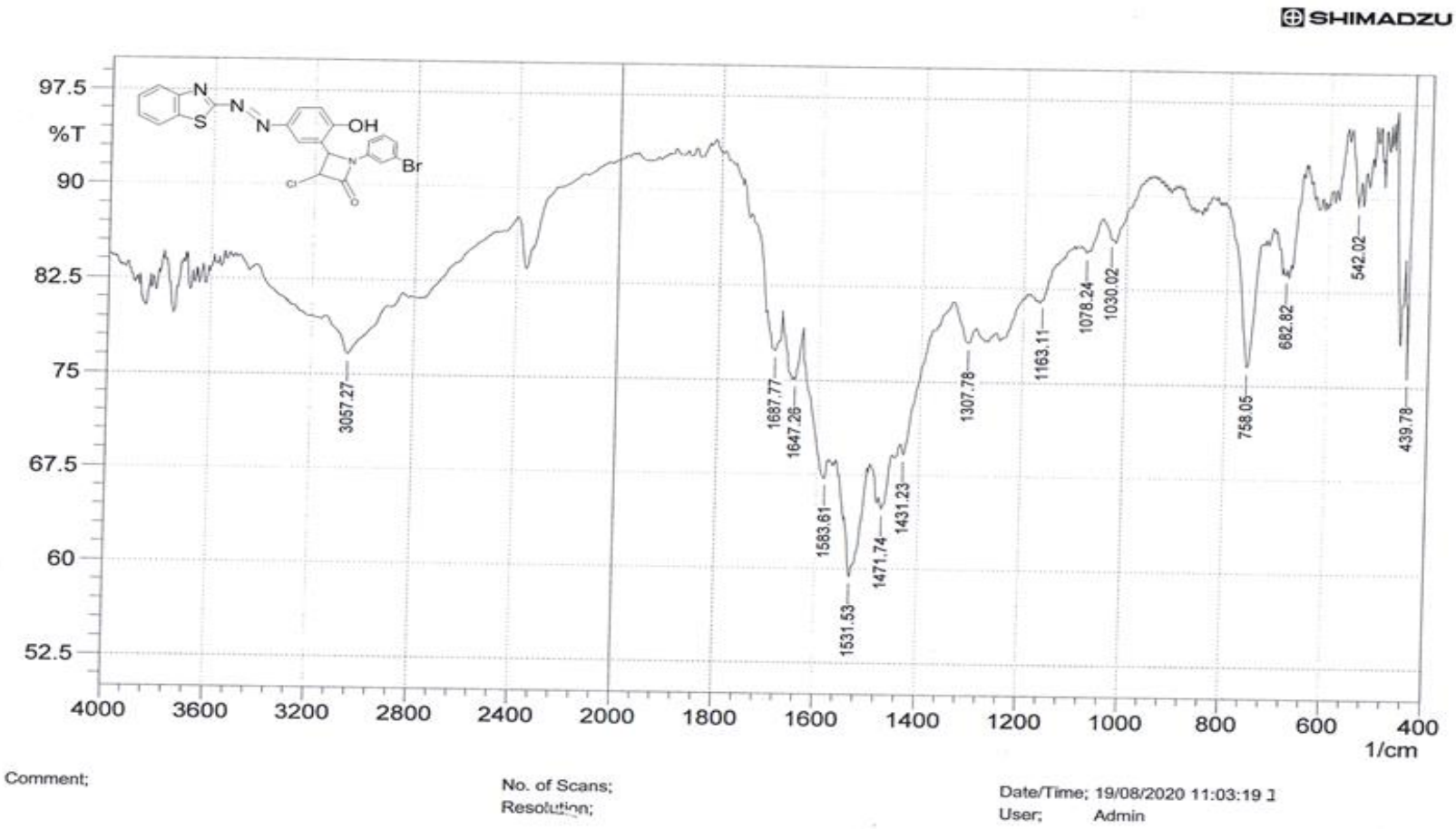


Figure (3-24): FT-IR spectrum of compound (**4h)**

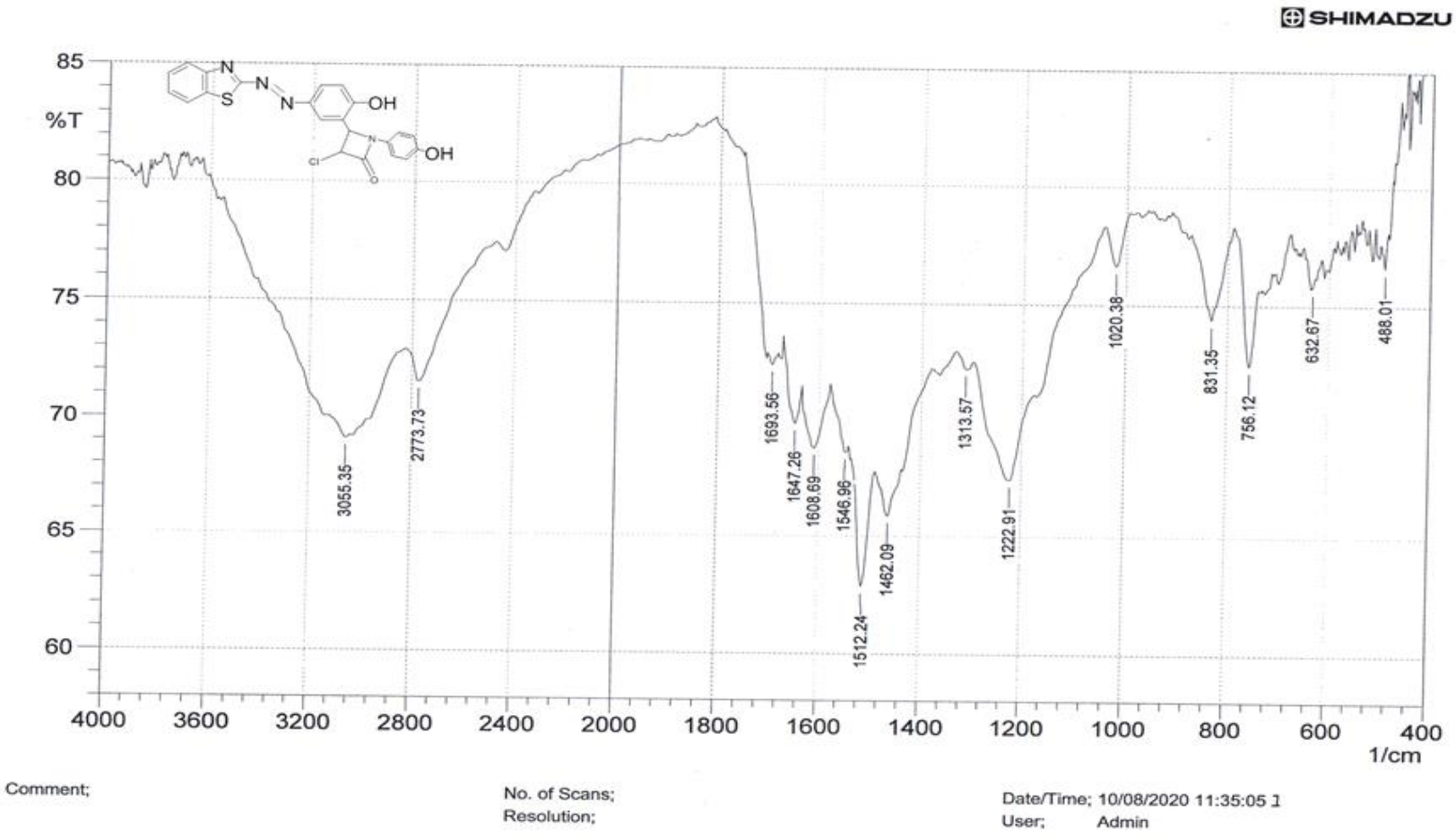


Figure (3-25): FT-IR spectrum of compound (**4i)**

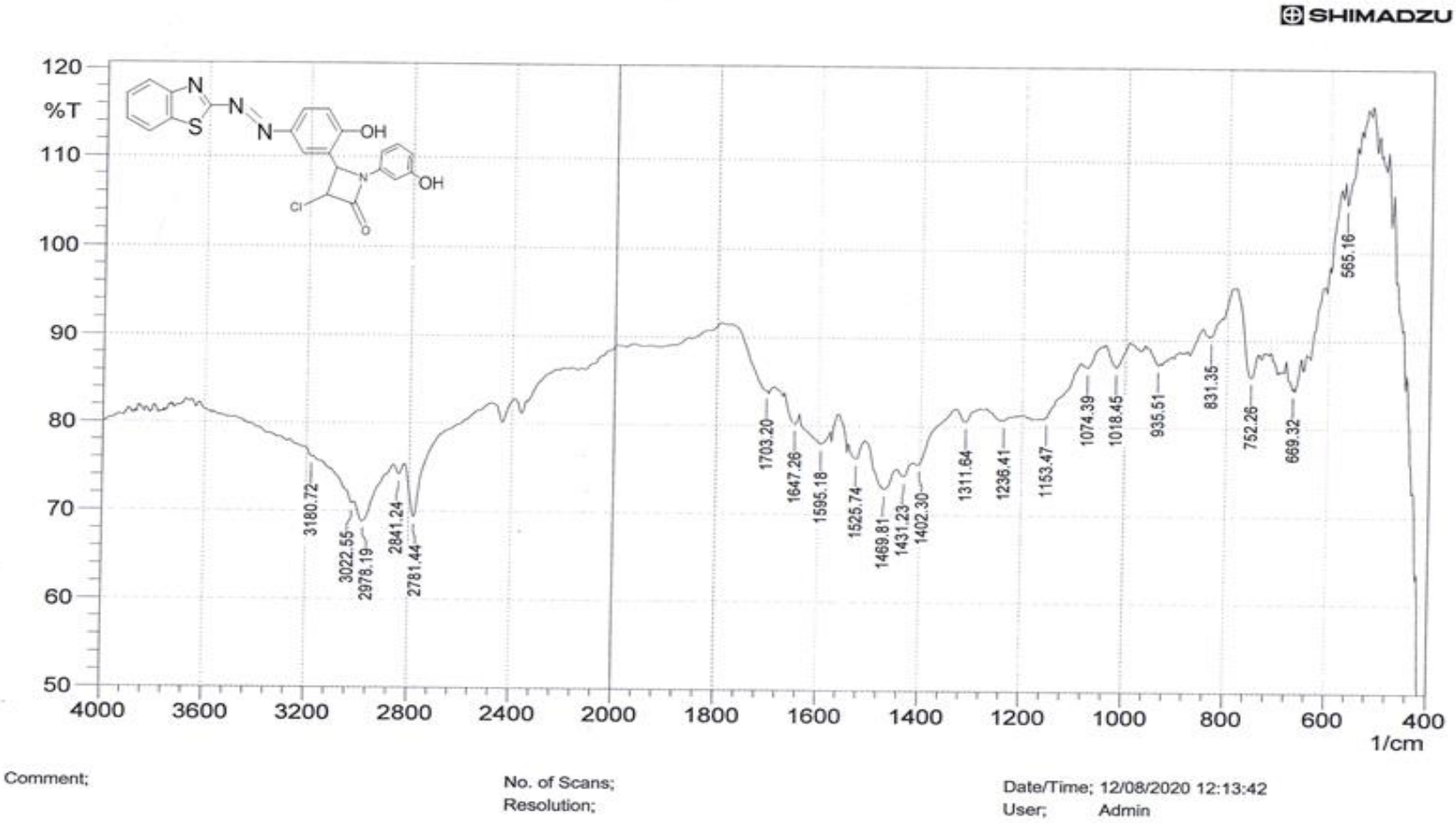


Figure (3-26): FT-IR spectrum of compound (**4j)**

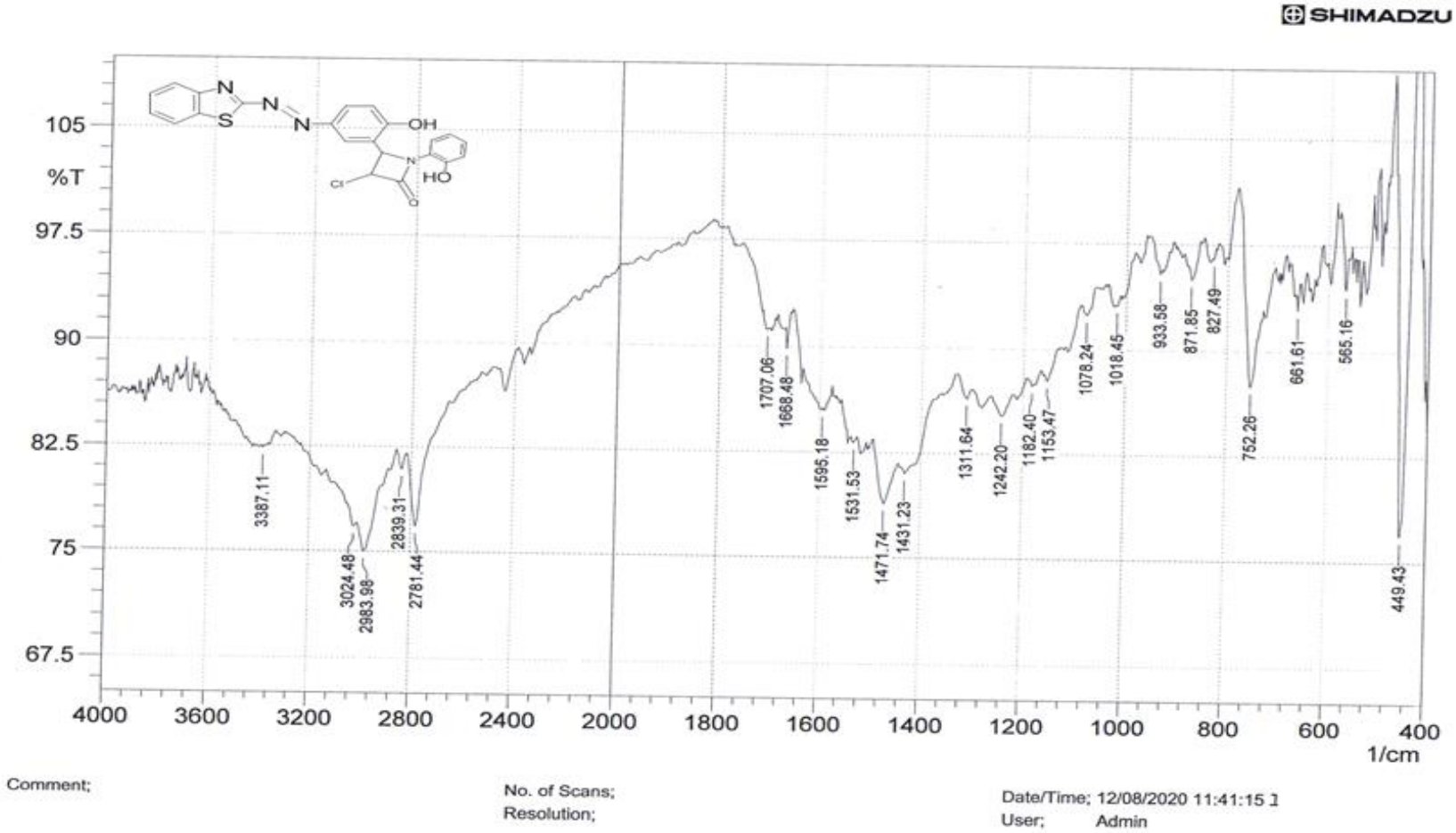


Figure (3-27): FT-IR spectrum of compound (**4k)**

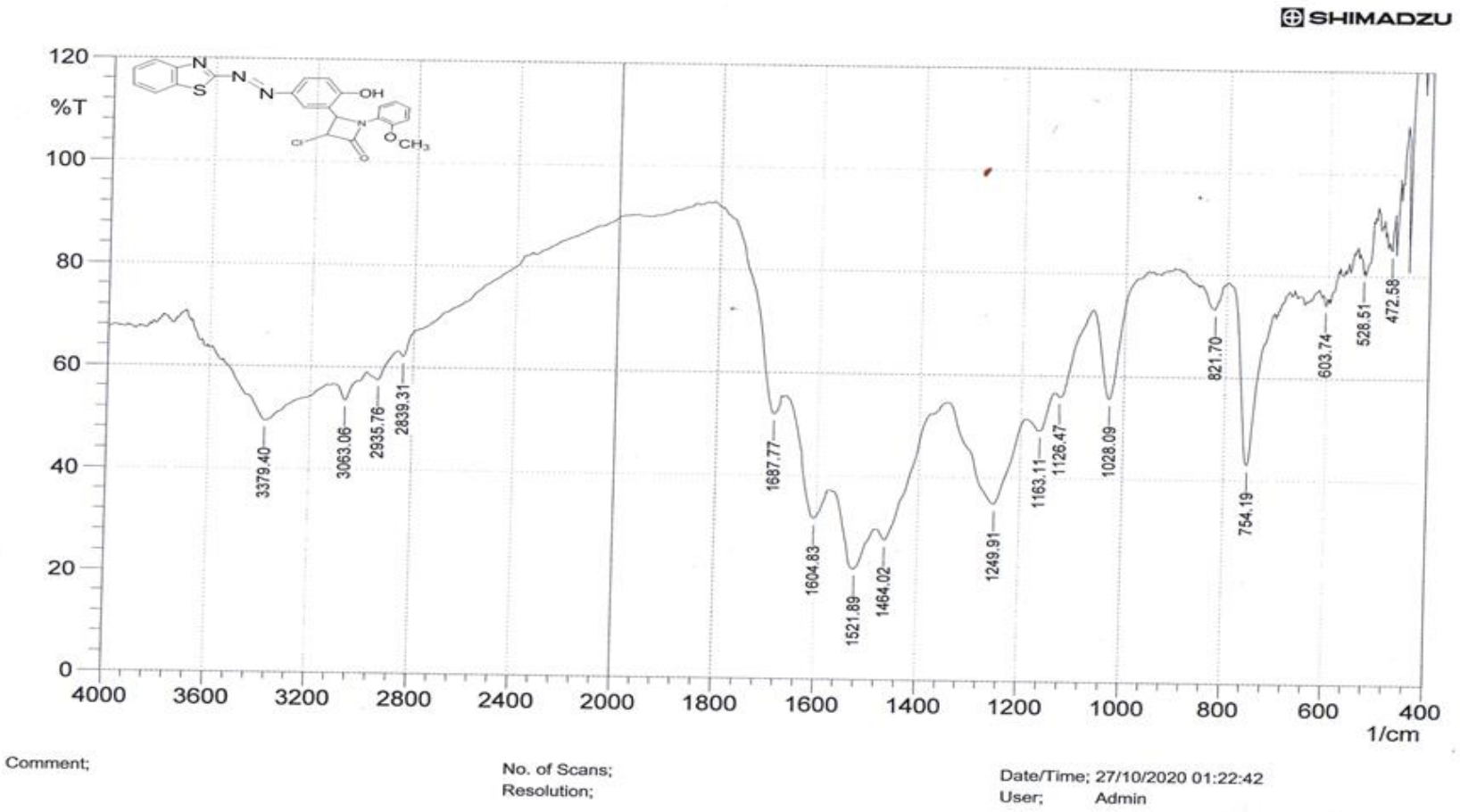


Figure (3-28): FT-IR spectrum of compound (**4l)**

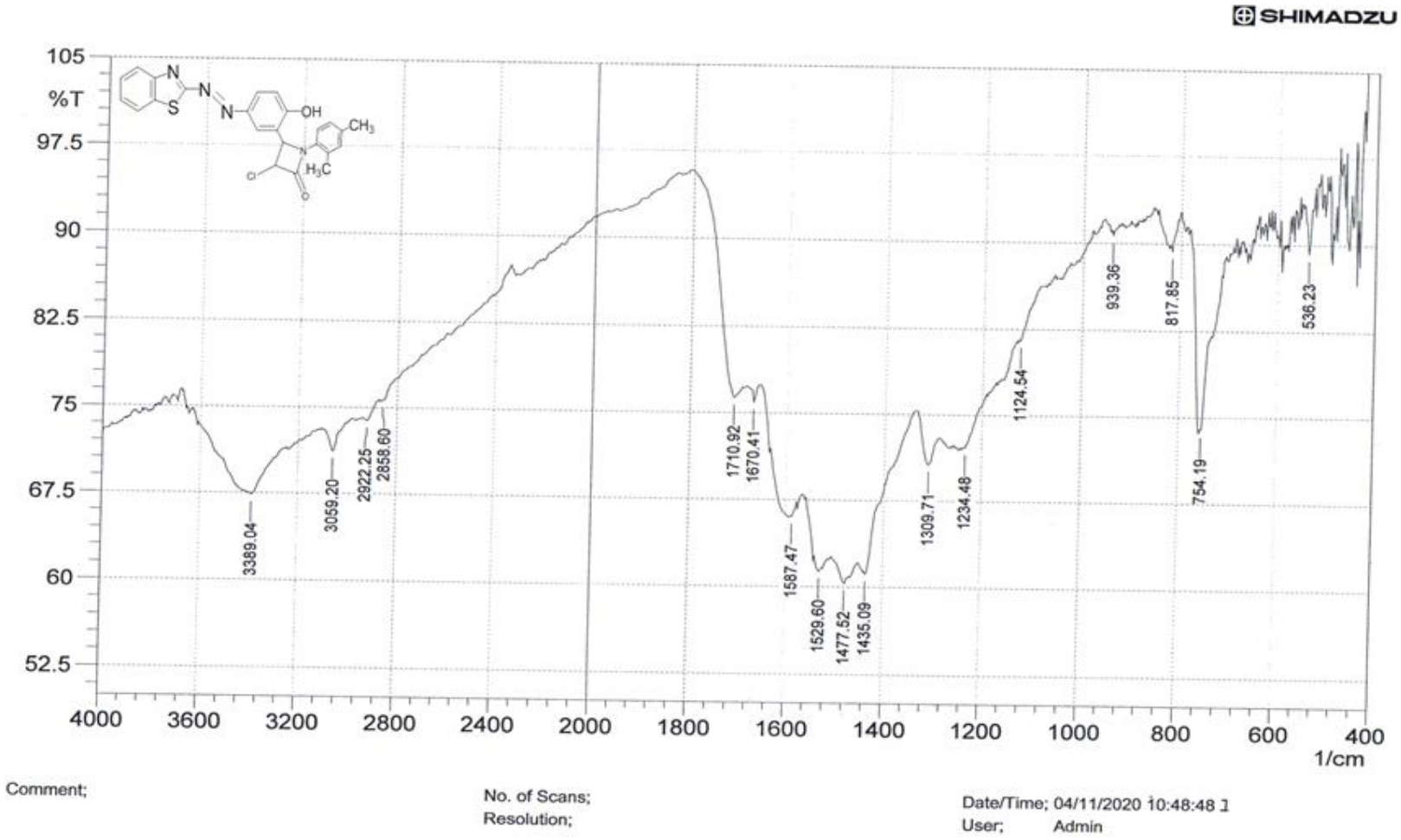


Figure (3-29): FT-IR spectrum of compound (**4m)**

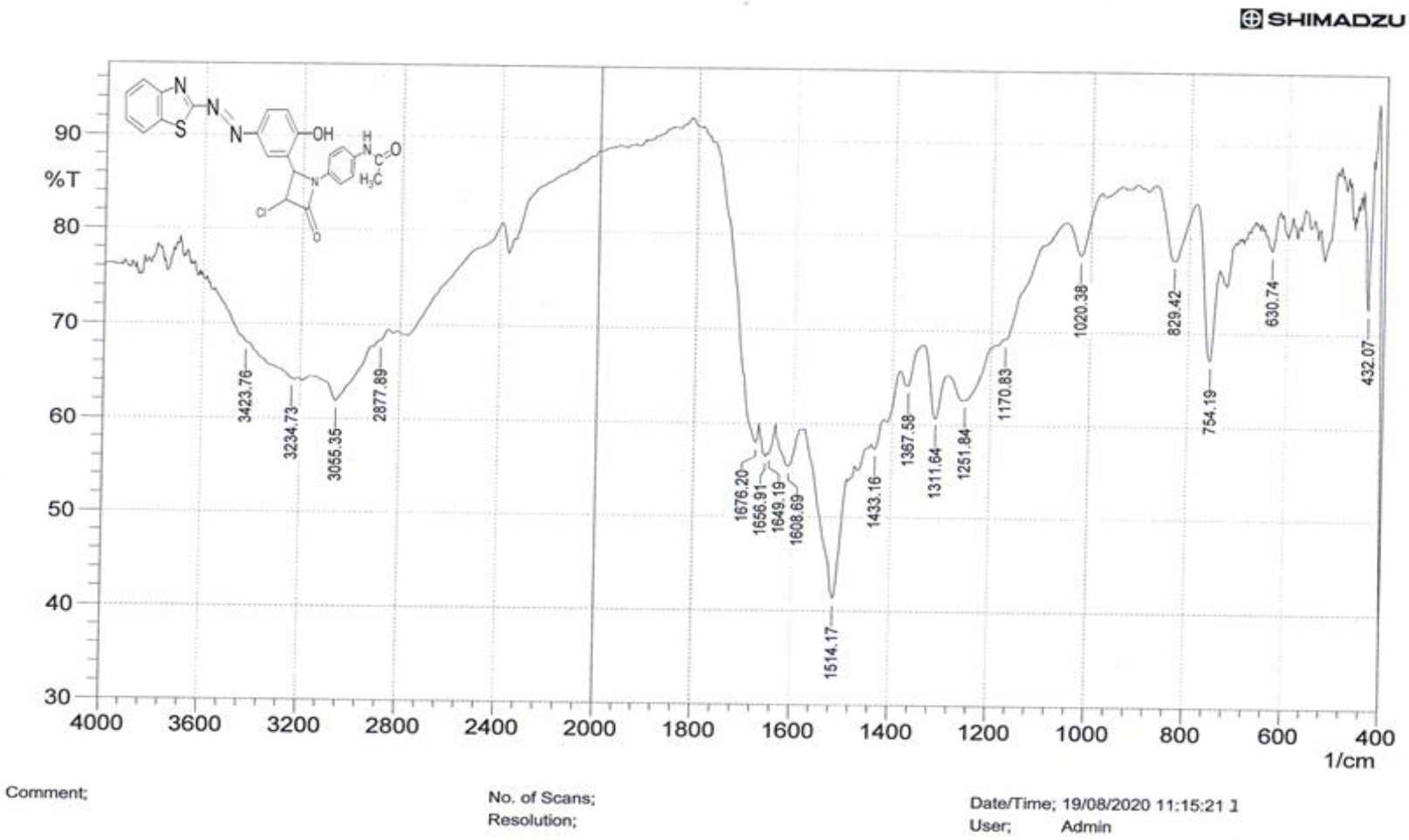


Figure (3-30): FT-IR spectrum of compound (**4n)**

^{1}H NMR spectra of azetidin-2-ones (4a-n)

^{1}H NMR spectra of β-lactams **(4a-n)** (500 MHz, DMSO-d_6) appeared peak of (CH-N) proton of lactam ring at δ 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.72, 2.79, 2.72 and 2.72 ppm, respectively. The peak of (CH-Cl) proton for lactam ring appeared at δ 2.88, 2.88, 2.88, 2.88, 2.88, 2.88, 2.88, 2.87, 2.87, 2.87, 2.88, 2.88, 2.88 and 2.88 ppm, consecutively. Signals of aromatic hydrogens around 6.80–8.78 ppm. Signal of (O-H) hydrogen appeared just in compounds **(4c**, **4e** and **4h)** at δ 10, 10 and 10.40 ppm,respectively, while it is disappeared in spectra of the other compounds due to the fast exchange with acidic impurities in (DMSO) solvent. Compound **(4l)** showed singlet signal of (OCH_3) hydrogens around δ 3.75 ppm. Compound **(4m)** pointed two singlet signals for hydrogens of the two methyl groups around δ 1.91 ppm and 2.08 ppm. Signals of methyl group protons and (N-H) proton of compound **(4n)** were recorded around 2.02 ppm and 9.91 ppm, respectively. The ^{1}H NMR data of compounds **4a-h** were summarized in table (3-4) [109].

Table (3-4): ^{1}H NMR data of β-lactams (4a-n) (500 MHz, δ ppm, DMSO solvent)

Entry	(DMSO)	(HOD)	CH-N	CH-Cl	Ar-H	O-H	Others
4a	2.5	3.38	2.72 (s, 1H, lactam)	2.88 (d, 1H, *J* = 1.2 Hz, lactam)	7.10-8.52 (m, 11H)	-	-
4b	2.50	3.35	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.41-8.02 (m, 11H)	-	-
4c	2.50	3.38	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	6.91-8.50 (m, 11H)	10.00 (s, 1H)	-
4d	2.50	3.35	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.39-7.99 (m, 11H)	-	-
4e	2.50	3.35	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.16-8.69 (m, 11H)	10.00 (s, 1H)	-
4f	2.50	3.46	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.40-8.05 (m, 10H)	-	-

4g	2.50	3.38	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.47-8.11 (m, 11H)	-	-
4h	2.5	3.3	2.72 (s, 1H, lactam)	2.87 (s, 1H, lactam)	7.40-8.42 (m, 11H)	10.40 (s, 1H)	-
4i	2.50	3.37	2.72 (s, 1H, lactam)	2.87 (d, 1H, *J* = 11.5 Hz, lactam)	6.80-8.04 (m, 11H)	-	-
4j	2.50	3.40	2.72 (s, 1H, lactam)	2.87 (s, 1H, lactam)	6.86-7.93 (m, 11H)	-	-
4k	2.50	3.41	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.20-8.78 (m, 11H)	-	-
4l	2.50	3.34	2.79 (s, 1H, lactam)	2.88 (d, 1H, *J* = 3.5 Hz, lactam)	7.00-8.13 (m, 11H)	-	3.75 (s, 3H, OCH_3)
4m	2.50	3.35	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.47-8.09 (m, 10H)	-	1.91 (s, 3H, 2-CH_3), 2.08 (s, 3H, 4-CH_3)
4n	2.50	3.36	2.72 (s, 1H, lactam)	2.88 (s, 1H, lactam)	7.41-8.03 (m, 11H)	-	2.02 (s, 3H, CH_3), 9.91 (s, 1H, NH)

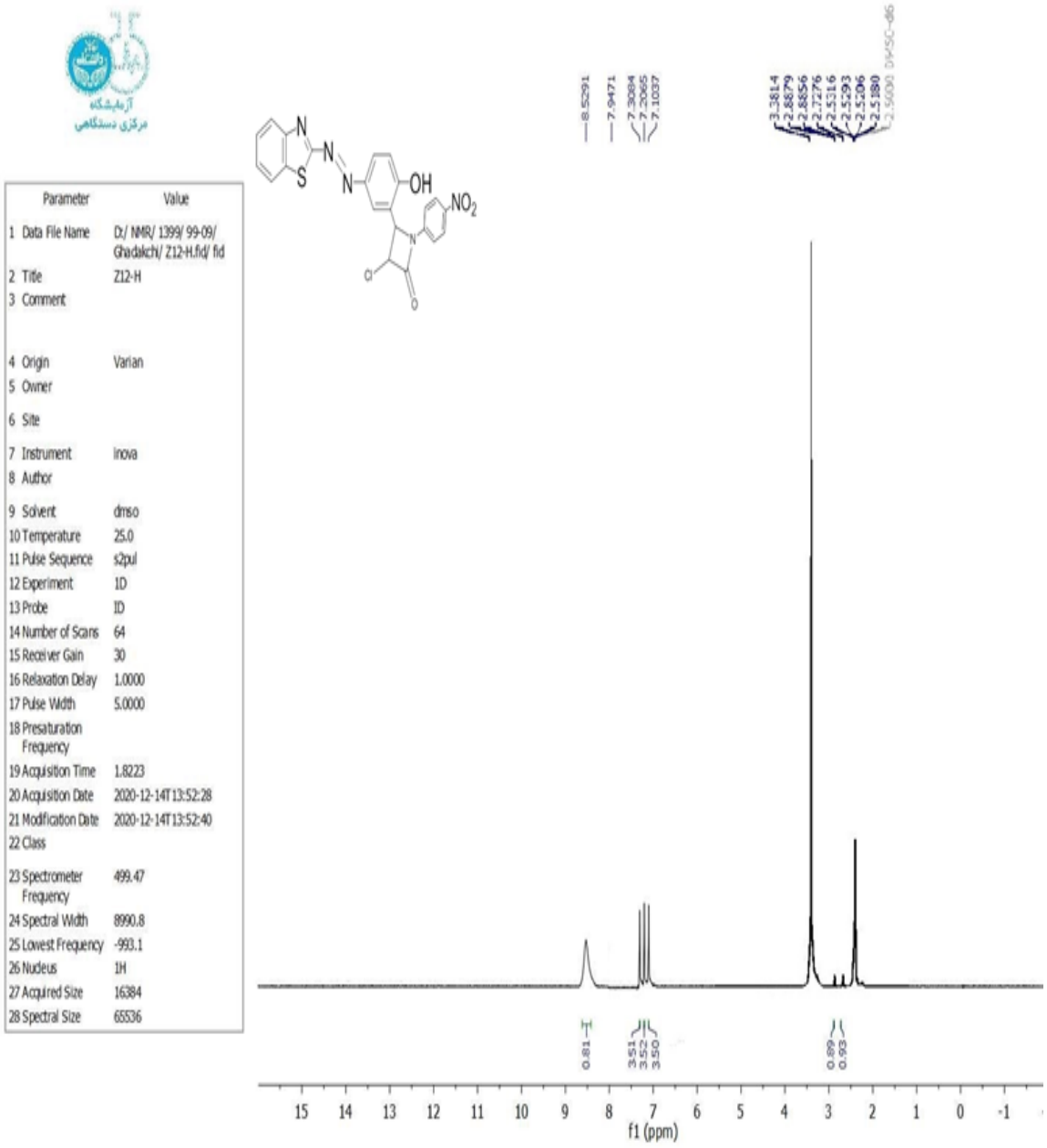


Figure (3-31): ^{1}H NMR spectrum of compound (**4a)**

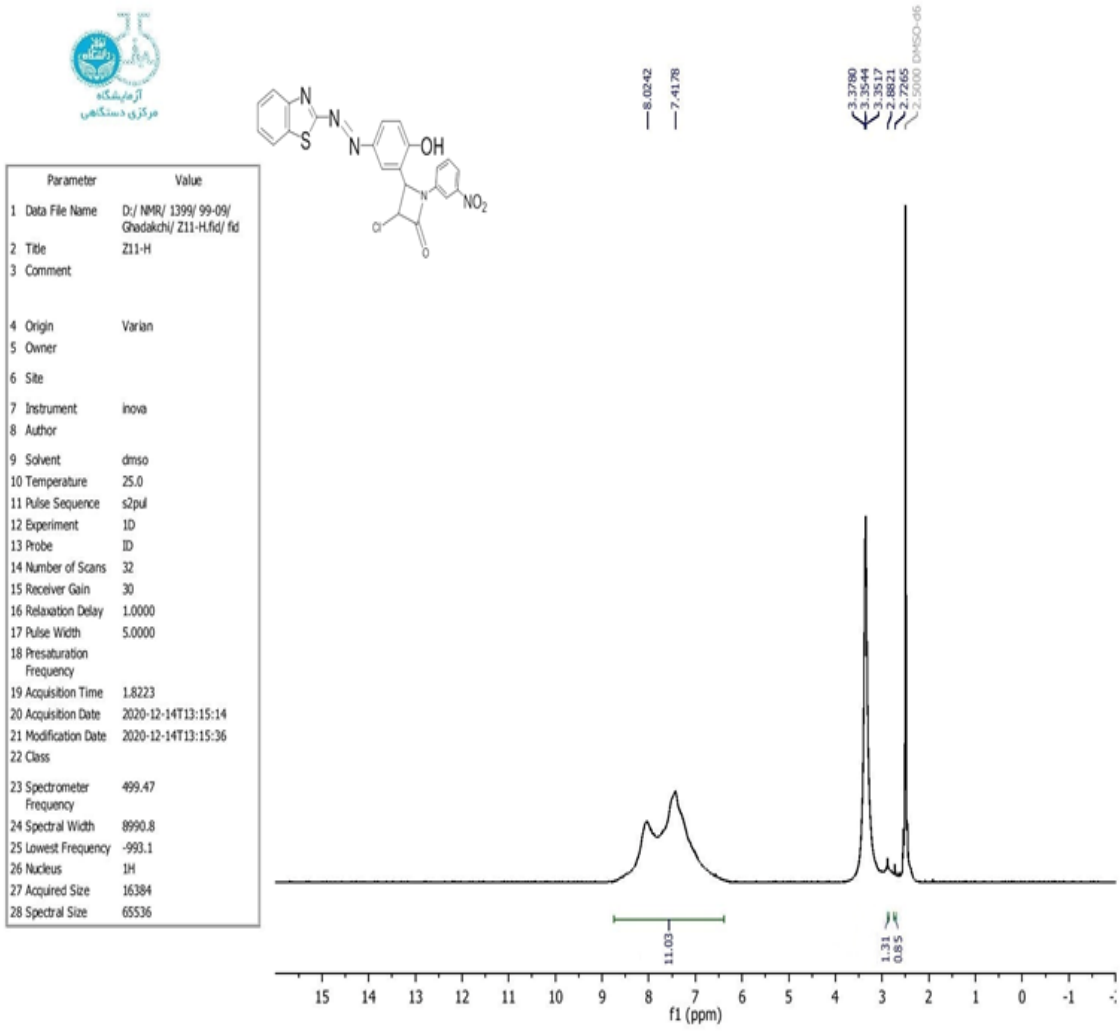


Figure (3-32): ^{1}H NMR spectrum of compound (**4b)**

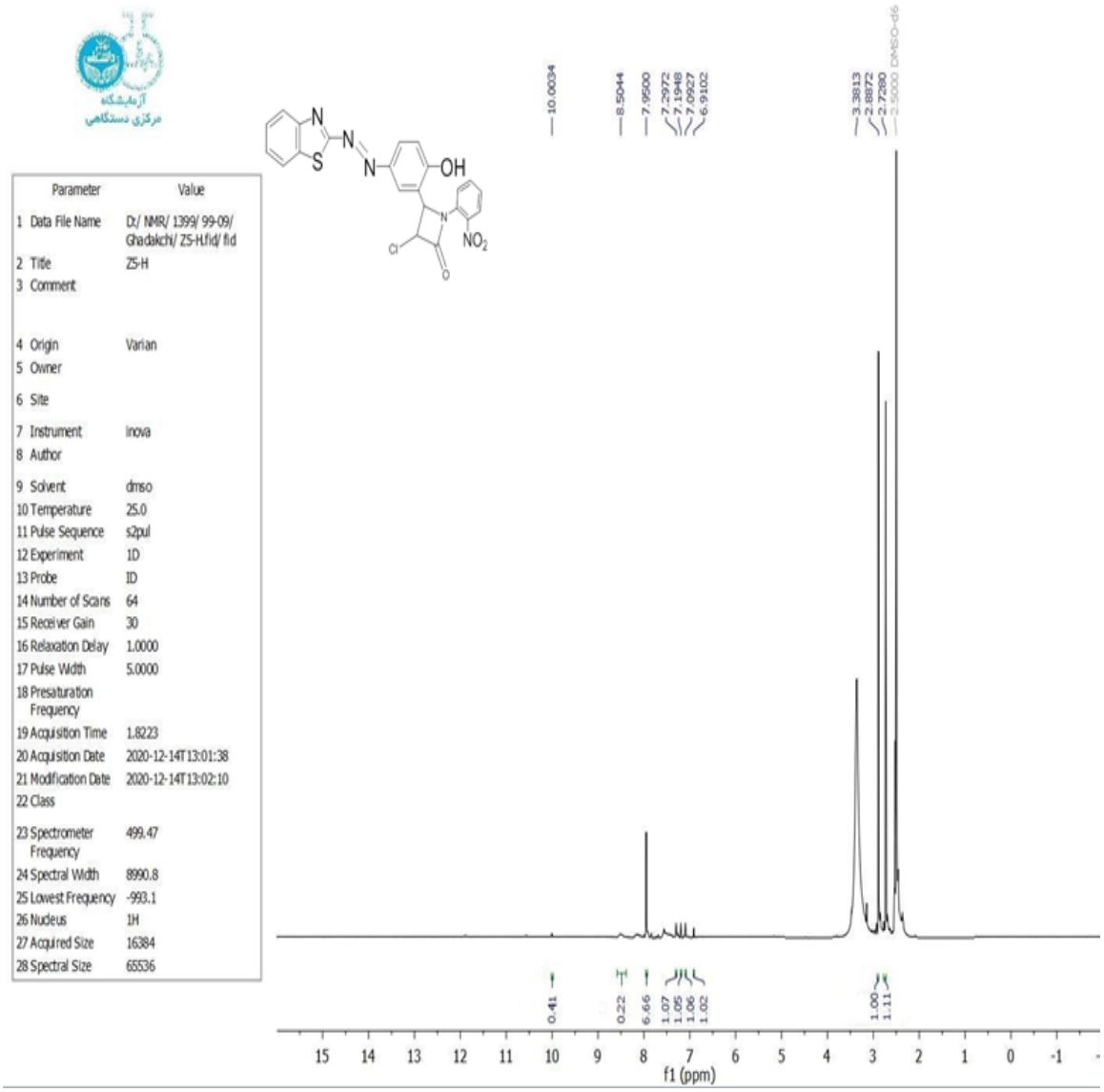


Figure (3-33): ^{1}H NMR spectrum of compound (**4c)**

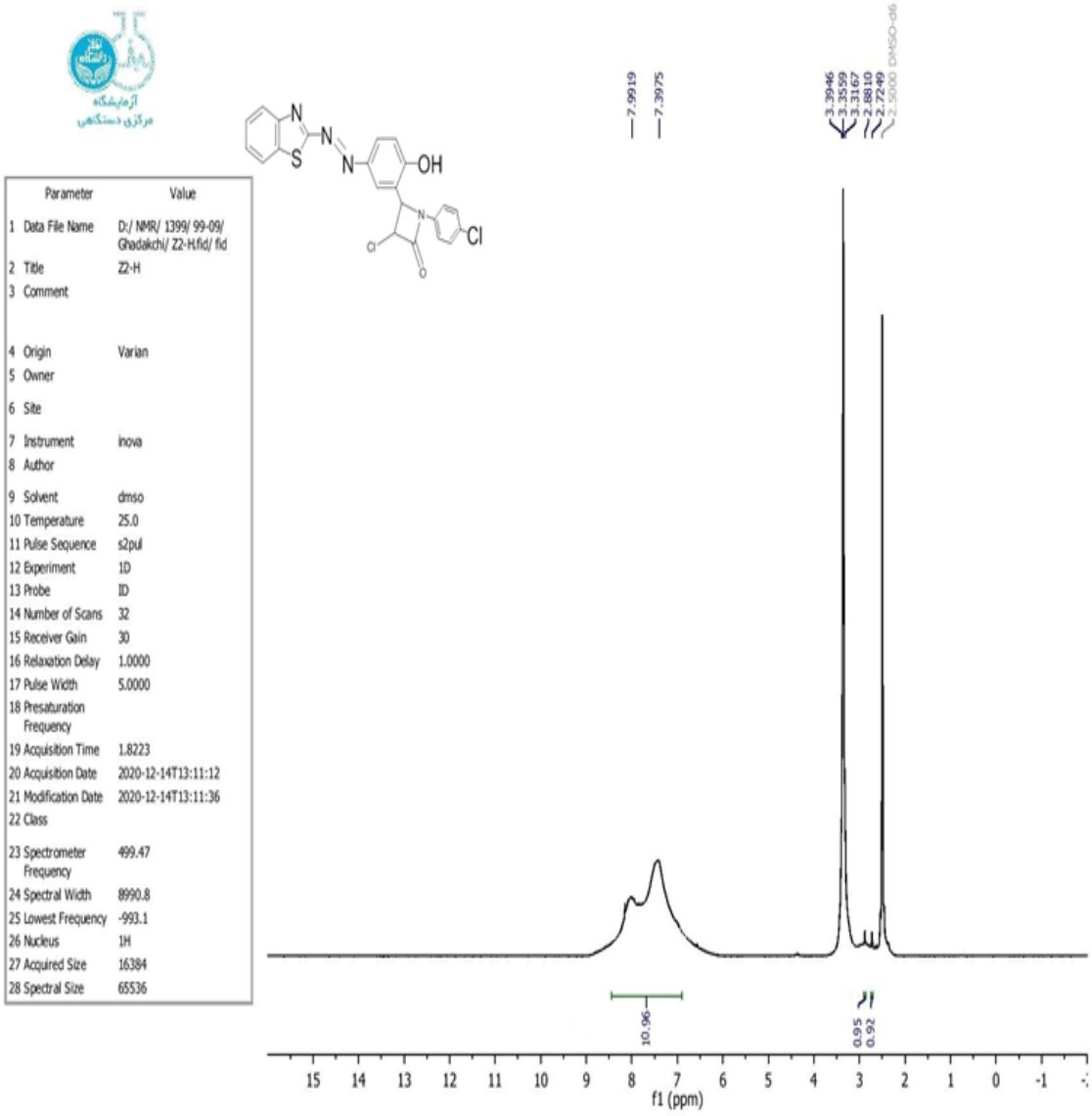


Figure (3-34): ^{1}H NMR spectrum of compound (**4d)**

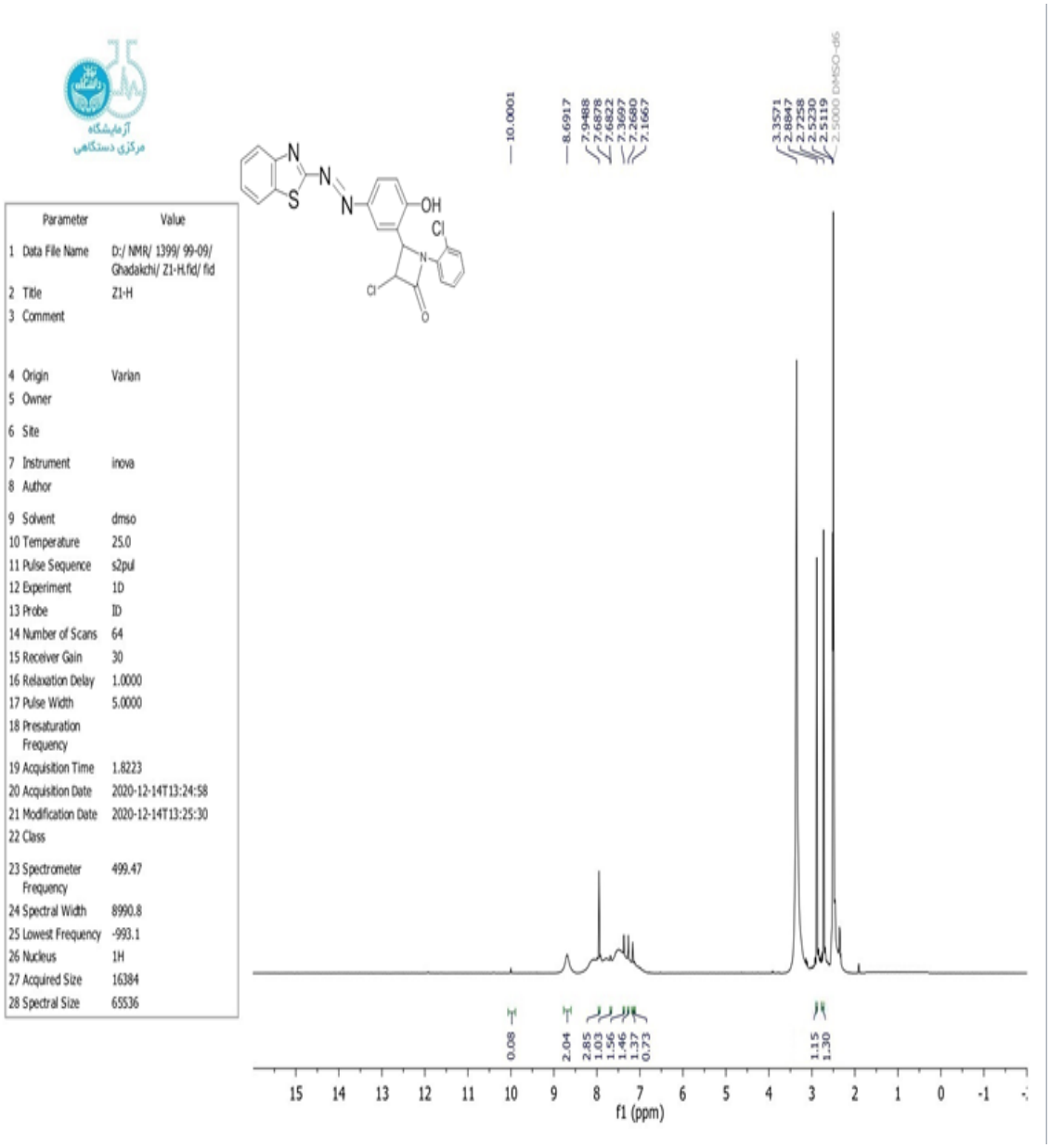


Figure (3-35): ^{1}H NMR spectrum of compound (**4e)**

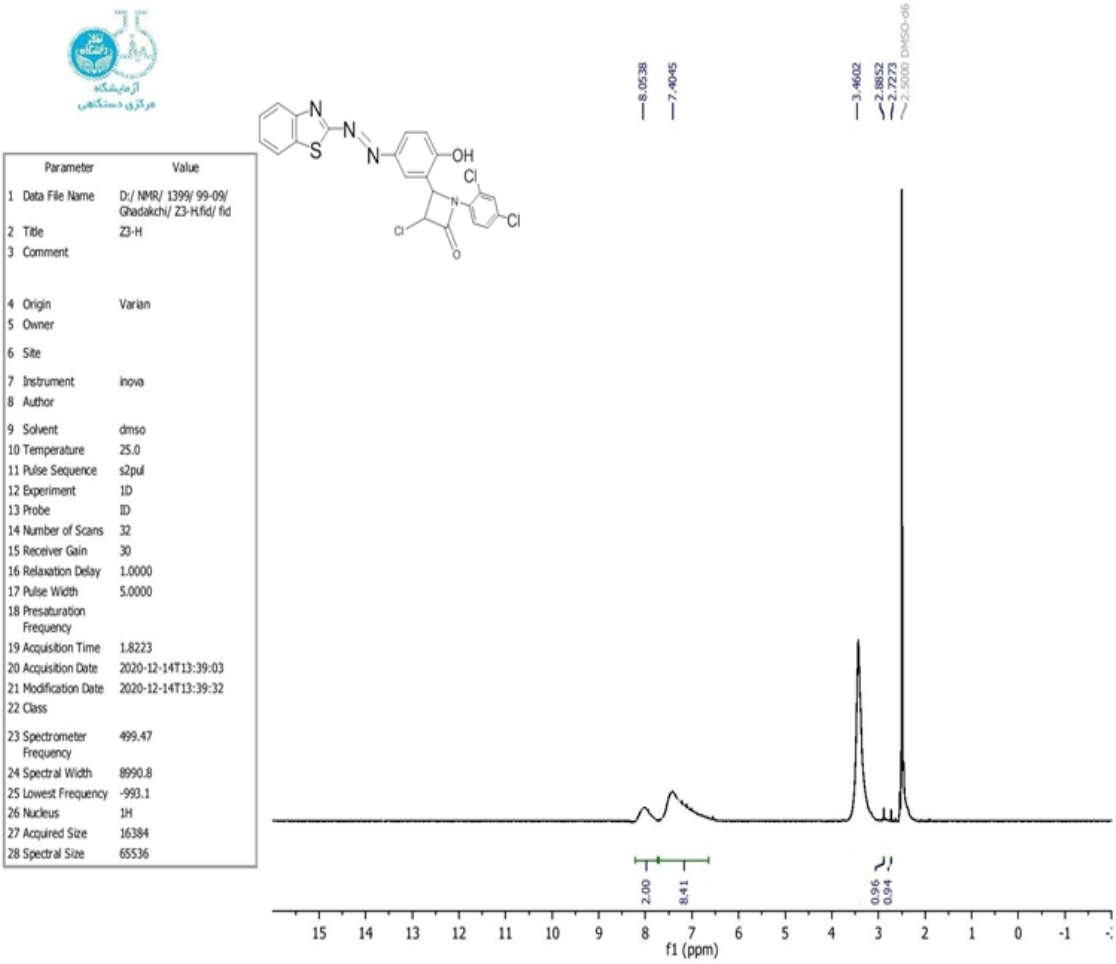


Figure (3-36): ^{1}H NMR spectrum of compound (**4f)**

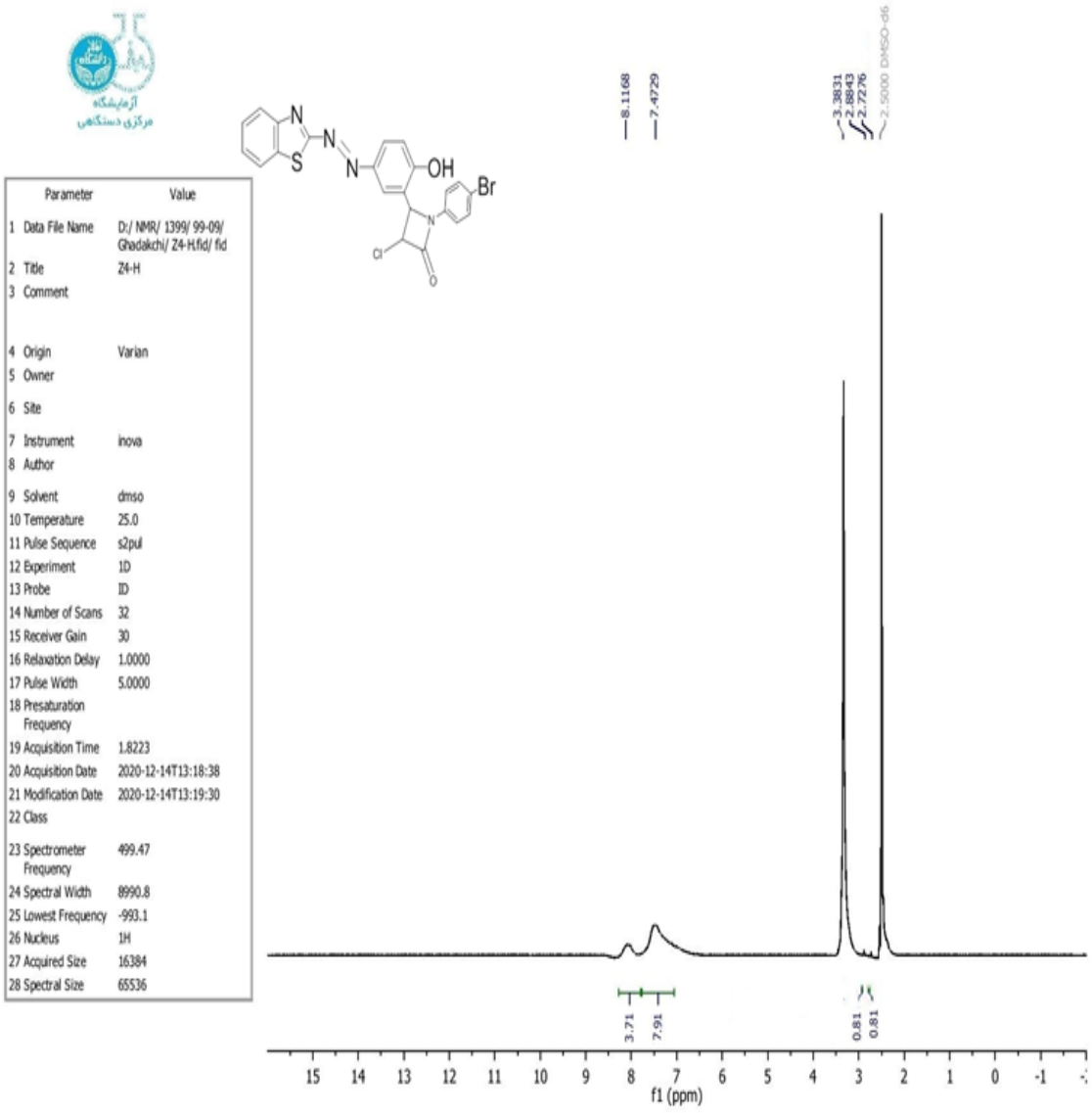


Figure (3-37): ^{1}H NMR spectrum of compound (**4g)**

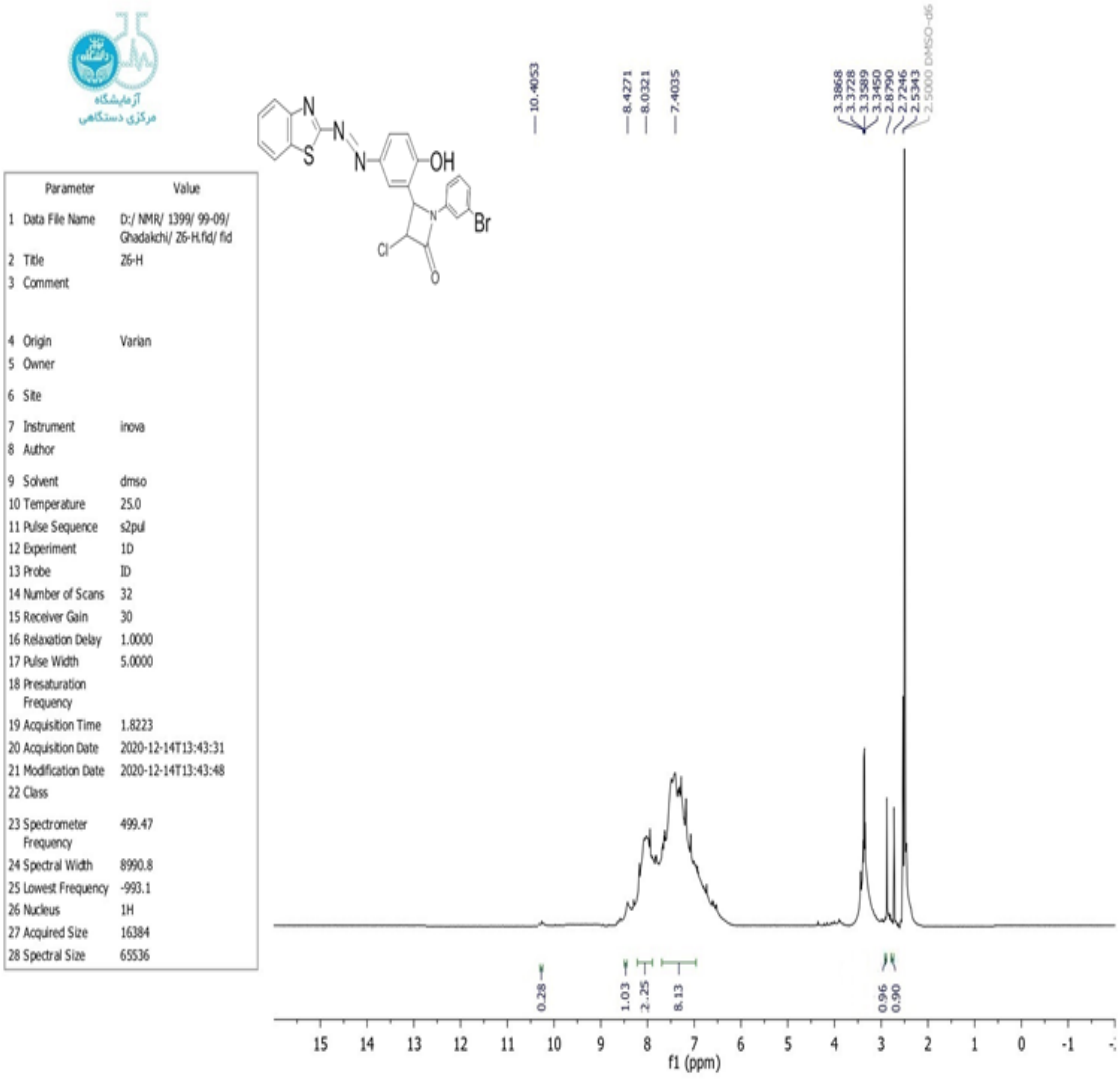


Figure (3-38): ^{1}H NMR spectrum of compound (**4h)**

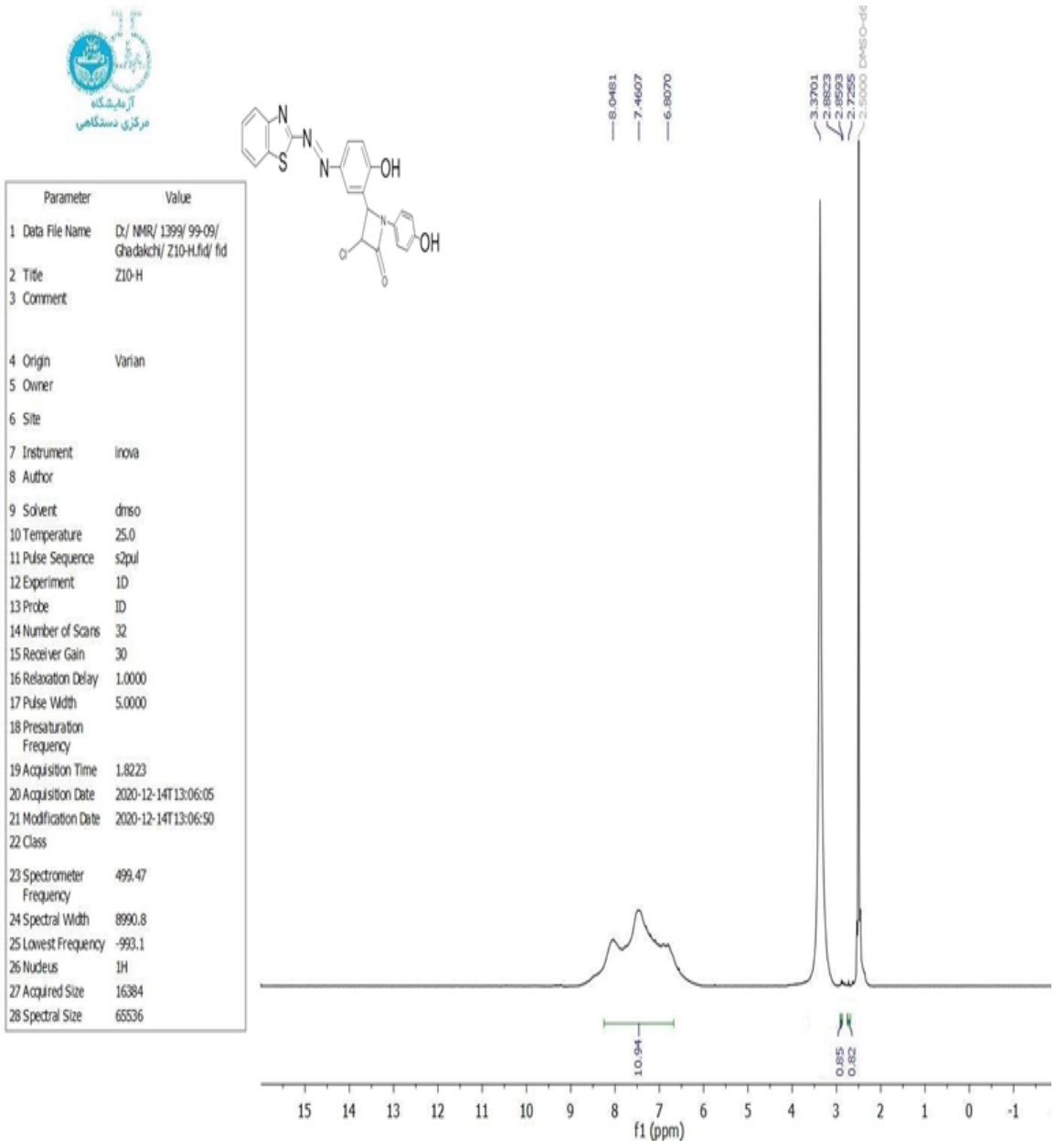


Figure (3-39): ^{1}H NMR spectrum of compound (**4i)**

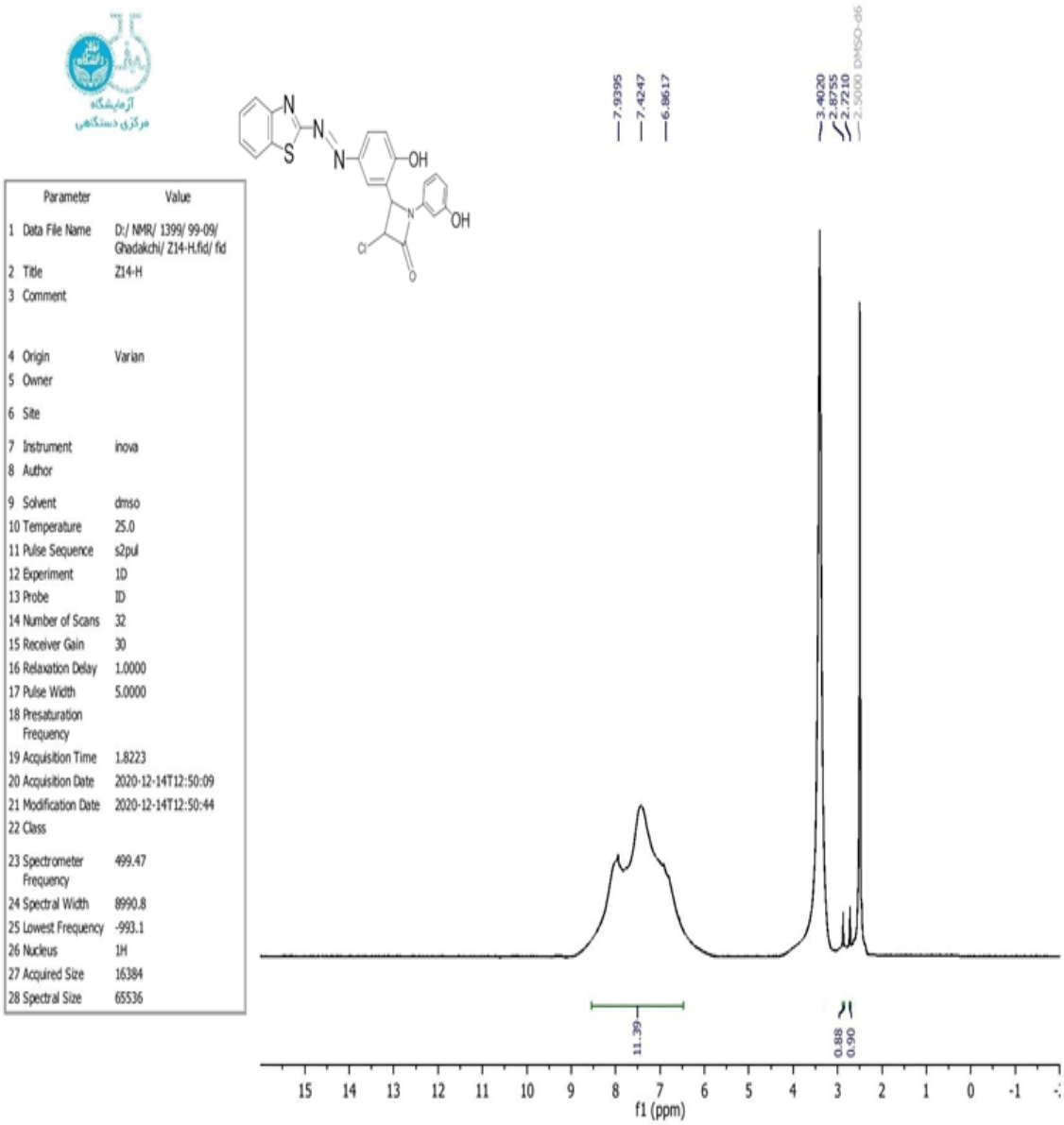
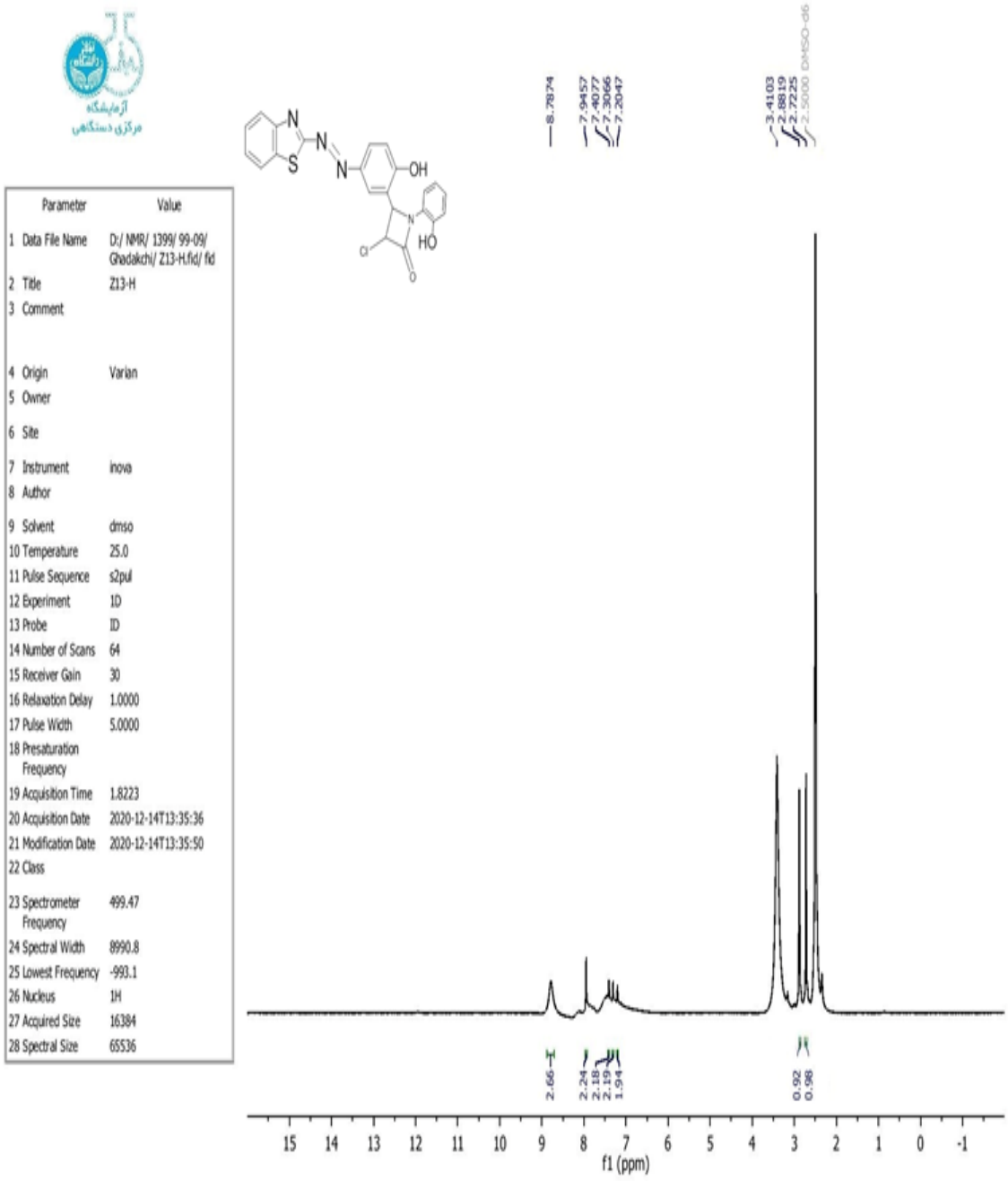


Figure (3-40): ^{1}H NMR spectrum of compound (**4j)**



	Parameter	Value
1	Data File Name	D:/ NMR/ 1399/ 99-09/ Ghadakchi/ Z13-H.fid/ fid
2	Title	Z13-H
3	Comment	
4	Origin	Varian
5	Owner	
6	Site	
7	Instrument	inova
8	Author	
9	Solvent	dmso
10	Temperature	25.0
11	Pulse Sequence	s2pul
12	Experiment	1D
13	Probe	ID
14	Number of Scans	64
15	Receiver Gain	30
16	Relaxation Delay	1.0000
17	Pulse Width	5.0000
18	Presaturation Frequency	
19	Acquisition Time	1.8223
20	Acquisition Date	2020-12-14T13:35:36
21	Modification Date	2020-12-14T13:35:50
22	Class	
23	Spectrometer Frequency	499.47
24	Spectral Width	8990.8
25	Lowest Frequency	-993.1
26	Nucleus	1H
27	Acquired Size	16384
28	Spectral Size	65536

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

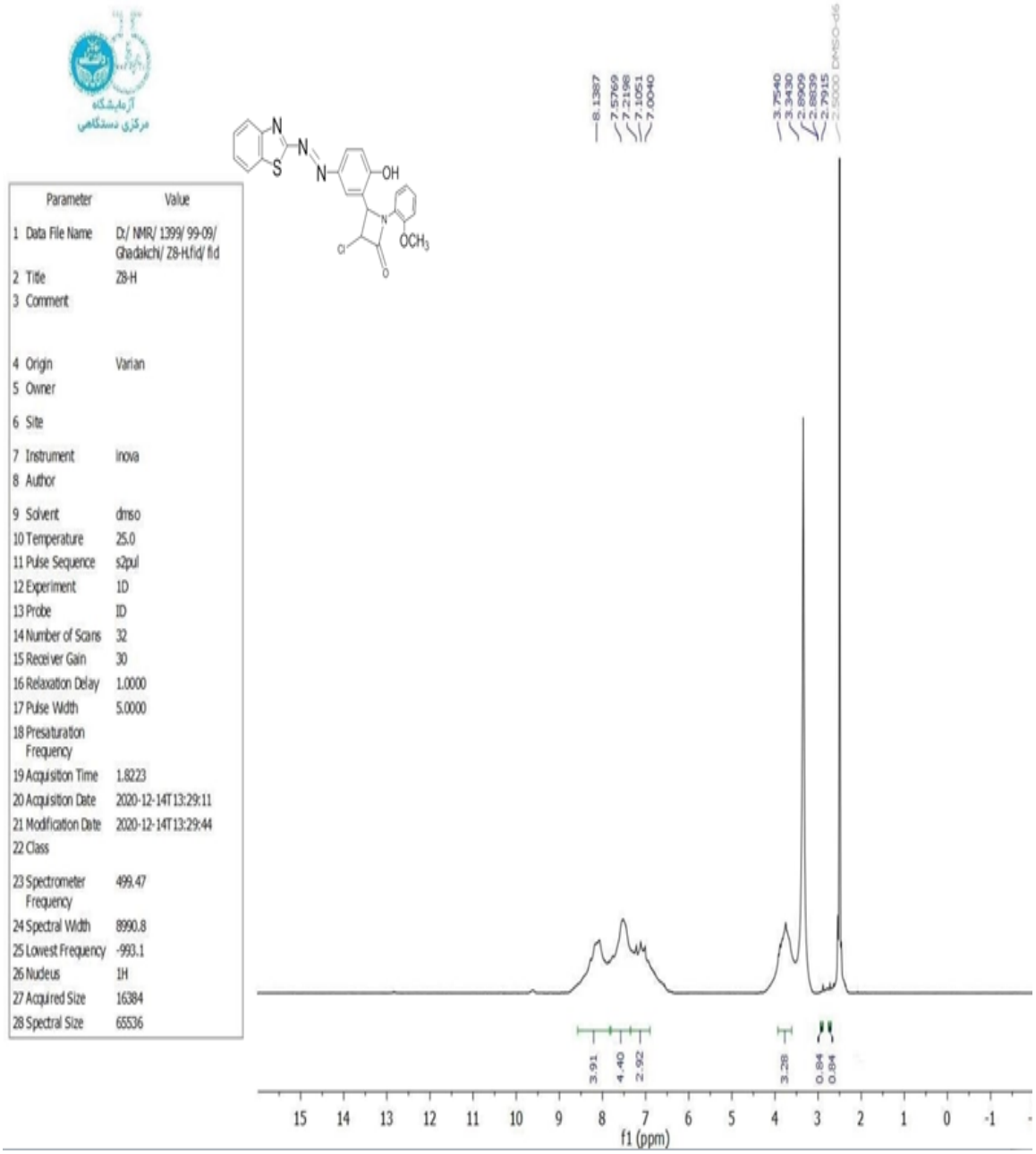


Figure (3-42): ^{1}H NMR spectrum of compound (**4l)**

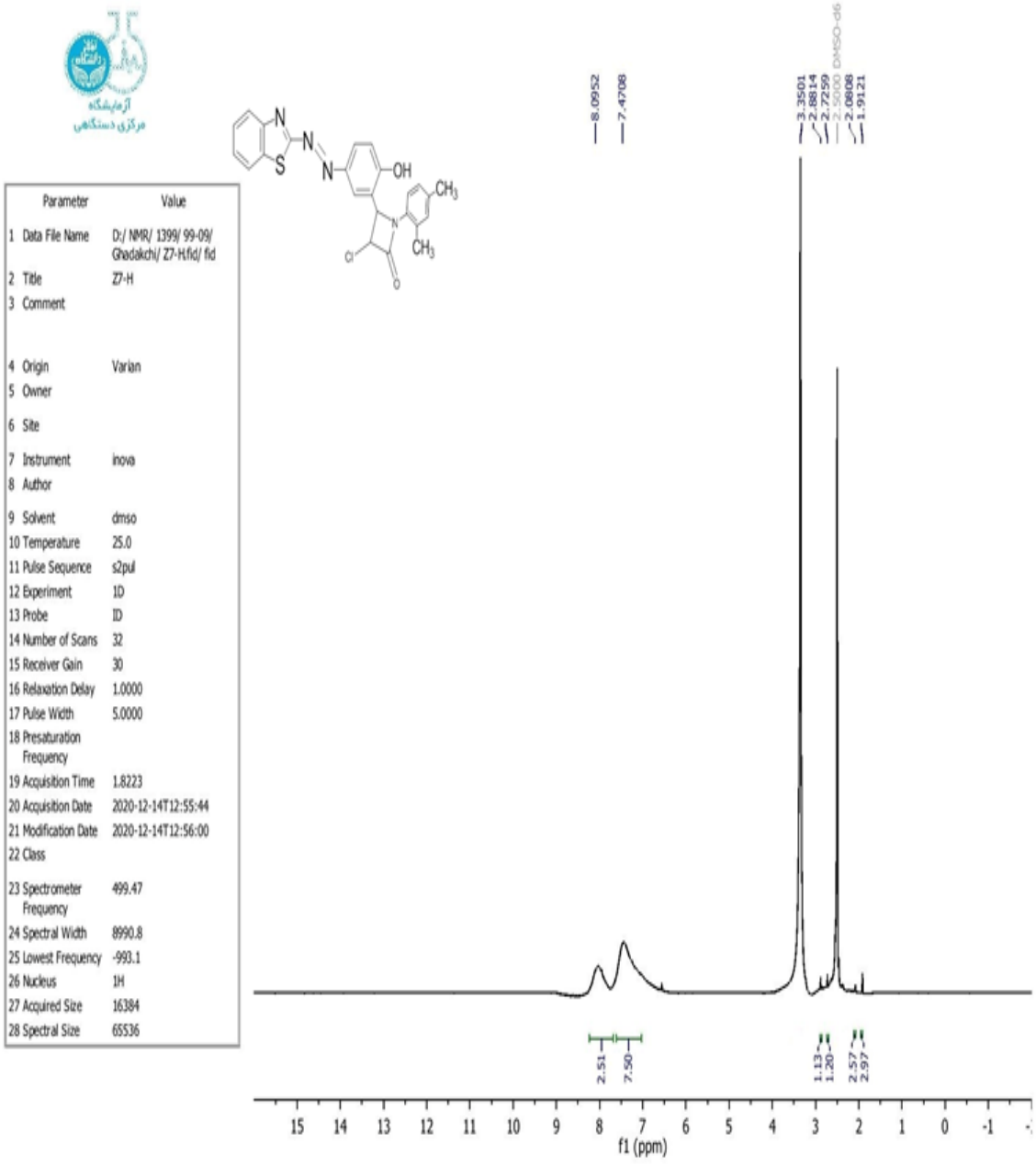


Figure (3-43): ^{1}H NMR spectrum of compound (**4m)**

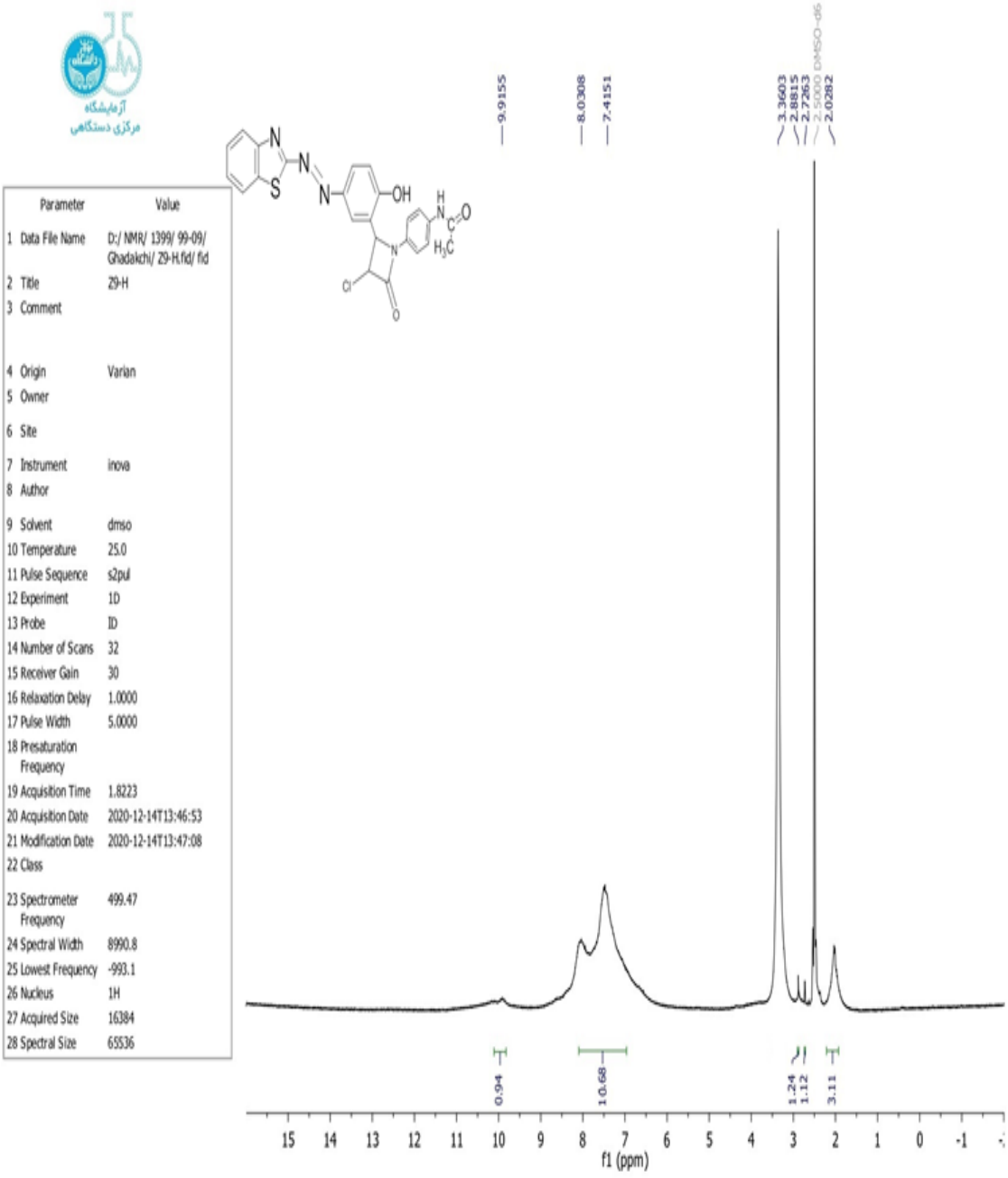


Figure (3-44): ^{1}H NMR spectrum of compound (**4n**)

(CHNS) Elemental analysis of compounds 4a-n

Elemental analysis measurements appeared accorded agreeable to calculated values as shown in Table (3-5).

Table (3-5): (CHNS) Elemental analysis of compounds (4a-n)

Com.no.	Calculated %				Found %			
	C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
4a	55.06	2.94	14.59	6.68	55.42	3.19	14.20	7.05
4b	55.06	2.94	14.59	6.68	55.39	2.84	14.25	7.12
4c	55.06	2.94	14.59	6.68	55.37	3.05	14.32	7.08
4d	56.30	3.01	11.94	6.83	56.08	3.07	11.49	7.17
4e	56.30	3.01	11.94	6.83	56.52	3.04	11.73	7.21
4f	52.45	2.60	11.12	6.36	52.80	2.82	11.27	6.78
4g	51.43	2.75	10.90	6.24	51.65	2.69	10.81	6.59
4h	51.43	2.75	10.90	6.24	51.31	2.47	10.51	6.57
4i	58.60	3.35	12.43	7.11	58.23	3.29	12.03	7.41
4j	58.60	3.35	12.43	7.11	58.67	3.16	12.24	7.46
4k	58.60	3.35	12.43	7.11	58.39	3.31	12.72	7.49
4l	59.42	3.69	12.05	6.90	59.74	3.82	11.89	7.22
4m	62.27	4.14	12.10	6.93	62.53	4.34	12.37	7.25
4n	58.60	3.69	14.24	6.52	58.85	3.50	14.55	6.88

3.4. Antibacterial activity

All target β-lactam compounds **(4a-n)** were screened for their antibacterial action against *Staphylococcus aurous* (Gram-positive) and *Escherichia coli* (Gram-negative). The data of inhibition zones indicated that compounds **(4b**, **4c**, **4i**, **4j**, **4k, 4m** and **4n)** pointed better effects to standard antibiotic (amoxicillin-clavulanate) against *E. coli*. Correspondingly, compounds **(4i**, **4j**, **4k, 4m** and **4n)** recorded better effects against *Staphylococcus aurous* when compared with that of

Table (3-6): Activities of β-lactams (4a-n) as well as amoxicillin-clavulanate as reference drug

Bacteria	*Staphylococcus aurous* (Gram-positive)	*Escherichia coli* (Gram-negative)
Comp. no	**Diameter of inhibition zone in (mm)**	
4a	0	15
4b	0	19
4c	0	20
4d	0	10
4e	0	0
4f	0	0
4g	0	0
4h	0	30
4i	30	28
4j	28	26
4k	30	0
4l	0	27
4m	26	30
4n	25	16
DMSO	0	0
Amoxicillin-clavulanate	18	18

Highly active (inhibition zone > 15 mm) Slightly active (inhibition zone 5-10 mm)

Moderately active (inhibition zone 11-15 mm) Inactive (inhibition zone < 5 mm)

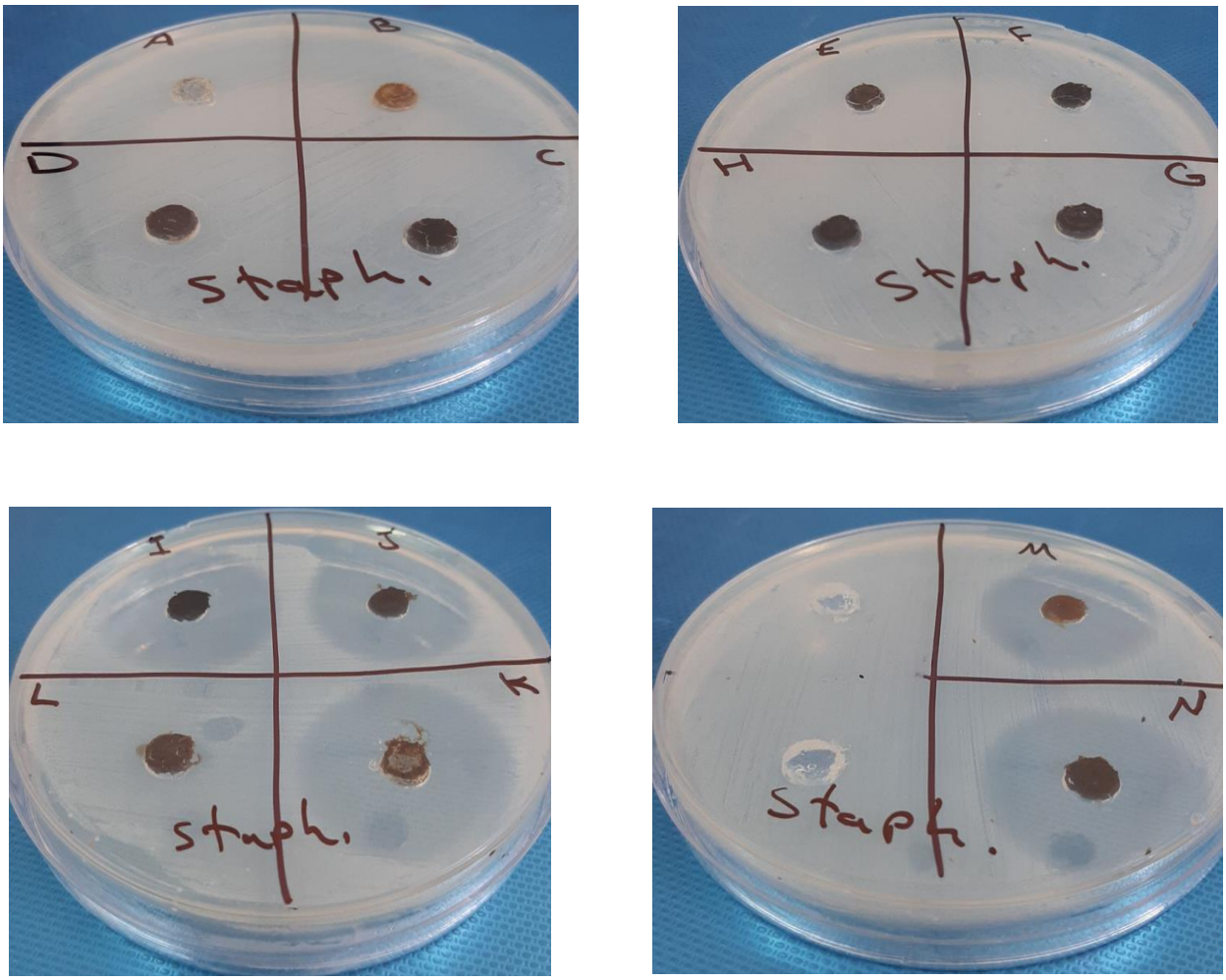


Figure (3-45): Antibacterial photographs of compounds (**4a-n)** against *Staphylococcus aurous*

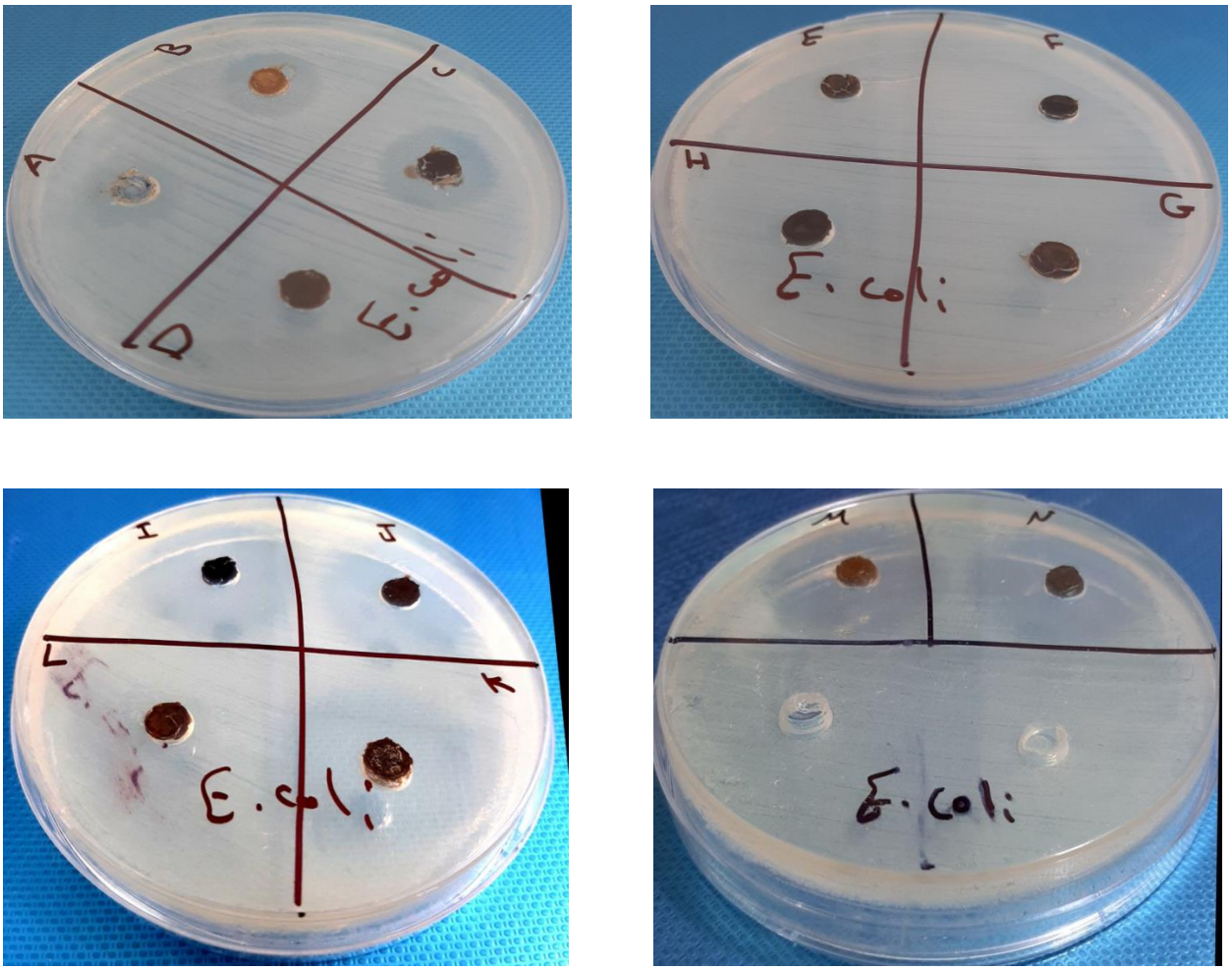


Figure (3-46): Antibacterial photographs of compounds **(4a-g)** against *Escherichia coli*

Conclusions and Future work

Conclusions

1. In spite of using microwave irradiation method, β-lactam ring formation needed relatively long reaction time. The reason may be due to less stability of four-membered ring in comparison with five and six-membered rings.
2. The synthesized β-lactams possess good solubility in water due to presence of polar substituents such as hydroxyl and carbonyl, this solubility could be increased through conversion of phenol group into the phenoxide salt.
3. Some of β-lactam compounds afforded greater influences to the control drug (amoxicillin-clavulanate) against both types of bacteria (Gram-negative and Gram-positive).

Future work

1. Preparing another Schiff bases by reacting the initiator aldehyde with another substituted anilines as precursors for the synthesis of new azetidine-2-ones.
2. Oxidation of imines into the nitrones using hydrogen peroxide could be taken place.
3. Cyclization of imines with mercaptoacetic acid may be undergone to yield thiazolidine compounds.
4. Determining toxicity and minimum-influenced concentration for prepared azetidinones.
5. Determining biological actions of β-lactams athwart another germs and some animal tissues diseases.

References

[1] K. Anand, “Synthesis, Biological Activity and Recent Advancement of Benzothiazoles: a Classical Review,” *World J. Pharm. Pharm. Sci.*, vol. 6, no. 6, pp. 1842–1869, 2017.

[2] P. Mathur, “Review on Different Methods of Synthesis of 2-Amino Substituted Benzothiazole,” *EPRA Int. J. Multidiscip. Res.*, vol. 5, no. 1, pp. 2455–3662, 2019.

[3] G. K. Patil, H. C. Patil, and I. M. Patil, “Benzotriazole – the Molecule of Diverse Biological,” *J. Pharma. Sci.*, vol. 4, no. 05, pp. 532–548, 2015.

[4] F. Yan, J. Sun, Y. Zang, Z. Sun, H. Zhang, and X. Wang, “Benzothiazole applications as fluorescent probes for analyte detection,” *J. Iran. Chem. Soc.*, vol. 17, no. 12, pp. 3179–3203, 2020.

[5] M. . Charde, M. . Shinde, A. . Welankiwar, and K. Jitendra, “Development of analytical and stability testing method for vitamin A palmitate formulation,” *Int. J. Pharm. Chem.*, vol. 5, no. 4, pp. 104–114, 2015.

[6] P. Chander Sharma *et al.*, “New horizons in benzothiazole scaffold for cancer therapy: Advances in bioactivity, functionality, and chemistry,” *Appl. Mater. Today*, vol. 20, 2020.

[7] D. Chauhan, A. A. Siddiqui, R. Kataria, and R. Singh, “Synthesis, characterization and antimicrobial evaluation of some new benzothiazole derivatives,” *Int. J. Pharm. Pharm. Sci.*, vol. 7, no. 10, pp. 316–319, 2015.

[8] C. W. Ghanavatkar, V. R. Mishra, and N. Sekar, “Benzothiazole-pyridone and benzothiazole-pyrazole clubbed emissive azo dyes and dyeing application on polyester fabric: UPF, biological, photophysical and fastness properties with correlative computational assessments,” *Spectrochim. Acta* -

Part A Mol. Biomol. Spectrosc., vol. 230, p. 118064, 2020.

[9] M. Chhabra, S. Sinha, S. Banerjee, and P. Paira, "An efficient green synthesis of 2-arylbenzothiazole analogues as potent antibacterial and anticancer agents," *Bioorganic Med. Chem. Lett.*, vol. 26, no. 1, pp. 213–217, 2016.

[10] A. Ammazzalorso, S. Carradori, R. Amoroso, and I. F. Fernández, "2-substituted benzothiazoles as antiproliferative agents: Novel insights on structure-activity relationships," *Eur. J. Med. Chem.*, vol. 207, 2020.

[11] R. S. Keri, M. R. Patil, S. A. Patil, and S. Budagupi, "A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry," *Eur. J. Med. Chem.*, vol. 89, no. February 2016, pp. 207–251, 2015.

[12] J. Sun, P. Cai, X. Zhang, A. Liang, L. Zhang, and J. Chen, "Synthesis, characterization and device application of a novel blue-emitting copolymer incorporating fluorene and benzothiazole backbone units," *Opt. Mater. (Amst).*, vol. 98, no. September, p. 109443, 2019.

[13] T. Wang, H. Xie, L. Liu, and W. X. Zhao, "N-heterocyclic carbene-palladium(II) complexes with benzoxazole or benzothiazole ligands: Synthesis, characterization, and application to Suzuki-Miyaura cross-coupling reaction," *J. Organomet. Chem.*, vol. 804, no. Ii, pp. 73–79, 2016.

[14] L. Zaffiri, J. Gardner, and L. H. Toledo-Pereyra, "History of antibiotics. from salvarsan to cephalosporins," *J. Investig. Surg.*, vol. 25, no. 2, pp. 67–77, 2012.

[15] S. Harisha, J. Keshavayya, S. M. Prasanna, and H. Joy Hoskeri, "Synthesis,

characterization, pharmacological evaluation and molecular docking studies of benzothiazole azo derivatives," *J. Mol. Struct.*, vol. 1218, p. 128477, 2020.

[16] İ. Şener, N. Şener, and M. Gür, "Synthesis, structural analysis, and absorption properties of disperse benzothiazol-derivative mono-azo dyes," *J. Mol. Struct.*, vol. 1174, pp. 12–17, 2018.

[17] R. S. Keri, C. Quintanova, S. M. Marques, A. R. Esteves, S. M. Cardoso, and M. A. Santos, "Design, synthesis and neuroprotective evaluation of novel tacrine-benzothiazole hybrids as multi-targeted compounds against Alzheimer's disease," *Bioorganic Med. Chem.*, vol. 21, no. 15, pp. 4559–4569, 2013.

[18] P. Sakthivel, K. Sekar, G. Sivaraman, and S. Singaravadivel, "Rhodamine-benzothiazole conjugate as an efficient multimodal sensor for Hg2+ ions and its application to imaging in living cells," *New J. Chem.*, vol. 42, no. 14, pp. 11665–11672, 2018.

[19] J. Guan, Q. Tu, L. Chen, M. Sen Yuan, and J. Wang, "A benzothiazole-rhodol based luminophor: ESIPT-induced AIE and an application for detecting Fe2+ ion," *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.*, vol. 220, p. 117114, 2019.

[20] Y. Yu, H. Xu, W. Zhang, B. Wang, and Y. Jiang, "A novel benzothiazole-based fluorescent probe for cysteine detection and its application on test paper and in living cells," *Talanta*, vol. 176, pp. 151–155, 2018

[21] C. Chang *et al.*, "Benzothiazole-based fluorescent sensor for hypochlorite detection and its application for biological imaging," *Sensors Actuators, B*

Chem., vol. 243, pp. 22–28, 2017.

[22] S. Tariq, P. Kamboj, and M. Amir, "Therapeutic advancement of benzothiazole derivatives in the last decennial period," *Arch. Pharm. (Weinheim).*, vol. 352, no. 1, pp. 1–17, 2019.

[23] R. S. Keri, M. R. Patil, S. A. Patil, and S. Budagupi, "A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry," *Eur. J. Med. Chem.*, vol. 89, pp. 207–251, 2015.

[24] V. R. Mishra, C. W. Ghanavatkar, S. N. Mali, S. I. Qureshi, H. K. Chaudhari, and N. Sekar, "Design, synthesis, antimicrobial activity and computational studies of novel azo linked substituted benzimidazole, benzoxazole and benzothiazole derivatives," *Comput. Biol. Chem.*, vol. 78, no. January, pp. 330–337, 2019.

[25] K. N. Venugopala *et al.*, "Benzothiazole analogs as potential anti-TB agents: computational input and molecular dynamics," *J. Biomol. Struct. Dyn.*, vol. 37, no. 7, pp. 1830–1842, 2019.

[26] N. D. Amnerkar, B. A. Bhongade, and K. P. Bhusari, "Synthesis and biological evaluation of some 4-(6-substituted-1,3-benzothiazol-2-yl)amino-1,3-thiazole-2-amines and their Schiff bases," *Arab. J. Chem.*, vol. 8, no. 4, pp. 545–552, 2015.

[27] D. Osmaniye, S. Levent, A. B. Karaduman, S. Ilgın, Y. Zkay, and Z. A. Kaplancikli, "Synthesis of new benzothiazole acylhydrazones as anticancer agents," *Molecules*, vol. 23, no. 5, pp. 1–14, 2018.

[28] I. Banik, F. F. Becker, and B. K. Banik, "Stereoselective synthesis of β-lactams with polyaromatic imines: Entry to new and novel anticancer

agents," *J. Med. Chem.*, vol. 46, no. 1, pp. 12–15, 2003.

[29] R. Geesala, J. K. Gangasani, M. Budde, S. Balasubramanian, J. R. Vaidya, and A. Das, "2-Azetidinones: Synthesis and biological evaluation as potential anti-breast cancer agents," *Eur. J. Med. Chem.*, vol. 124, pp. 544–558, 2016.

[30] R. Solensky, "Penicillin allergy as a public health measure," *J. Allergy Clin. Immunol.*, vol. 133, no. 3, pp. 797–798, 2014.

[31] B. K. Banik, *Beta-lactams: Novel synthetic pathways and applications*. 2017.

[32] W. F. Marshall and J. E. Blair, "The cephalosporins," *Mayo Clin. Proc.*, vol. 74, no. 2, pp. 187–195, 1999.

[33] J. M. Williamson, E. Inamine, K. E. Wilson, A. W. Douglas, J. M. Liesch, and G. Albers-Schönberg, "Biosynthesis of the β-lactam antibiotic, thienamycin, by Streptomyces cattleya," *J. Biol. Chem.*, vol. 260, no. 8, pp. 4637–4647, 1985.

[34] B. G. Spratt, V. Jobanputra, and W. Zimmermann, "Binding of thienamycin and clavulanic acid to the penicillin binding proteins of Escherichia coli K 12," *Antimicrob. Agents Chemother.*, vol. 12, no. 3, pp. 406–409, 1977.

[35] M.-L. Han *et al.*, "Comparative Metabolomics Reveals Key Pathways Associated With the Synergistic Killing of Colistin and Sulbactam Combination Against Multidrug-Resistant Acinetobacter baumannii," *Front. Pharmacol.*, vol. 10, no. July, 2019.

[36] A. M. Egorov, M. M. Ulyashova, and M. Y. Rubtsova, "Inhibitors of β-Lactamases. New Life of β-Lactam Antibiotics," *Biochem.*, vol. 85, no. 11,

pp. 1292–1309, 2020.

[37] A. H. Dalaf and F. H. Jumaa, “Synthesis , Identification and Assess the Biological and Laser Efficacy of New Compounds of Azetidine Derived from Benzidine,” *MJPS*, vol. 7, no. 2, 2020.

[38] A. Jarrahpour *et al.*, “Synthesis of new β-lactams bearing the biologically important morpholine ring and POM analyses of their antimicrobial and antimalarial activities,” *Iran. J. Pharm. Res.*, vol. 18, no. 1, pp. 34–48, 2019.

[39] S. Stecko, B. Furman, and M. Chmielewski, “Kinugasa reaction: An ‘ugly duckling’ of β-lactam chemistry,” *Tetrahedron*, vol. 70, no. 43, pp. 7817–7844, 2014.

[40] A. Kamath and I. Ojima, “Advances in the chemistry of β-lactam and its medicinal applications,” *Tetrahedron*, vol. 68, no. 52, pp. 10640–10664, 2012.

[41] C. Patel and C. P. Bhasin, “Synthesis and biological evaluation of azitidinone and their derivative as antimicrobial and antifungal agents,” *Rasayan J. Chem.*, vol. 9, no. 1, pp. 84–88, 2016.

[44] M. Drăgan *et al.*, “Biological evaluation of azetidine-2-one derivatives of ferulic acid as promising anti-inflammatory agents,” *Processes*, vol. 8, no. 11, pp. 1–19, 2020.

[42] A. A. Martínez-Gallegos, G. Guerrero-Luna, A. Ortiz-González, M. Cárdenas-García, S. Bernès, and M. G. Hernández-Linares, “Azasteroids from diosgenin: Synthesis and evaluation of their antiproliferative activity,” *Steroids*, vol. 166, no. November 2020, 2021.

[43] S. M. Zachariah, M. Ramkumar, N. George, and M. S. Ashif, “Azetidinones : An overview,” *Int. J. Pharm. Sci. Rev. Res.*, vol. 30, no. 1, pp. 211–218, 2015.

[44] H. D. Thi, T. Van Nguyen, and M. D’hooghe, "Synthesis and reactivity of 4-(trifluoromethyl) azetidin-2-ones," *Monatshefte für Chemie-Chemical Monthly*, vol. 149, no. 4, pp. 687-700, (2018).

[45] M. S. Scholz, L. M. Wingen, S. Brunst, S. K. Wittmann, I. L.Cardoso, L. Weizel, and E. Proschak, "Soluble epoxide hydrolase inhibitors with carboranes as non-natural 3-D pharmacophores," *European journal of medicinal chemistry*, vol. 185, pp. 111766, (2020).

[46] T. Li *et al.*, “TIMER: A web server for comprehensive analysis of tumor-infiltrating immune cells,” *Cancer Res.*, vol. 77, no. 21, pp. e108–e110, 2017.

[47] L. Troisi, E. Pindinelli, V. Strusi, and P. Trinchera, “Stereoselective synthesis of 3,4-diaryl β-lactams,” *Tetrahedron Asymmetry*, vol. 20, no. 3, pp. 368–374, 2019.

[48] K. F. Ansari and C. Lal, “Synthesis and biological activity of some heterocyclic compounds containing benzimidazole and beta-lactam moiety,” *J. Chem. Sci.*, vol. 121, no. 6, pp. 1017–1025, 2019.

[49] M. Genc, B. Inci, Z. K. Genc, C. A. Canbay, and M. Sekerci, “Preparation and investigations of thermal properties of copper oxide, aluminium oxide and graphite based on new organic phase change material for thermal energy storage,” *Bull. Mater. Sci.*, vol. 38, no. 2, pp. 343–350, 2015.

[50] D. Bandyopadhyay, G. Rivera, I. Salinas, H. Aguilar, and B. K. Banik,

"Remarkable iodine-catalyzed synthesis of novel pyrrole- bearing n-polyaromatic β-lactams," *Molecules*, vol. 15, no. 2, pp. 1082–1088, 2010,.

[51] P. Xie, B. Qian, H. Huang, and C. Xia, "Stereoselective synthesis of trans β-lactams via palladium/N- heterocyclic carbene-catalyzed carbonylative [2+2] cycloaddition," *Tetrahedron Lett.*, vol. 53, no. 13, pp. 1613–1616, 2018.

[52] F. M. Cordero and A. Brandi, "Synthesis of β-Lactams and β-Homoprolines by Fragmentative Rearrangement of 5-Spirocyclopropaneisoxazolidines Mediated by Acids," *Chem. Rec.*, vol. 21, no. 2, pp. 284–294, 2021.

[53] M. Kidwai, R. Venkataramanan, and S. Kohli, "Alumina supported synthesis of β-lactams using microwave," *Synth. Commun.*, vol. 30, no. 6, pp. 989–1002, 2018.

[54] F. Blasi, C. Page, G. M. Rossolini, L. Pallecchi, M. G. Matera, P. Rogliani, and M. Cazzola," The effect of N-acetylcysteine on biofilms: Implications for the treatment of respiratory tract infections," *Respiratory medicine*, vol. 117, pp. 190-197, (2016).

[55] A. Roth, and S. E. Denmark," Enantioselective, Lewis Base-Catalyzed, Intermolecular Sulfenoamination of Alkenes," *Journal of the American Chemical Society*, vol. 141, no. 35, pp. 13767-13771, (2019).

[56] H. H. Variya, V. Panchal, and G. R. Patel, "Synthesis and Biological Evolution of Sulfonamide Fused Azitidinone As Antibacterial and Antifungal Agents," vol. 5, no. 1, pp. 1–17, 2019.

[57] M. Feroci, M. Orsini, L.Rossi, G.Sotgiu, & A.Inesi, "An electrochemical alternative strategy to the synthesis of β-lactams: Part 2 [1]. C3C4 bond

formation. Electrochimica acta", vol.51, no. 25, pp. 5540-5547, 2006.

[58] N. A. Ross, R. R.MacGregor , & R. A.Bartsch. "Synthesis of β-lactams and β-aminoesters via high intensity ultrasound-promoted Reformatsky reactions",*Tetrahedron*, vol. 60, no. 9, pp. 2035-2041, 2004.

[59] X. Jiang." PdCl2-catalyzed efficient transformation of propargylic amines to (E)-α-chloroalkylidene-β-lactams". *The Journal of organic chemistry*, vol. 70, no. 7, pp. 2588-2593, 2005.

[60] M. Drăgan, O. Dragostin, A. Iacob, L. Profire, C. D. Stan, and C. Tuchiluş, "Antioxidant and antimicrobial potential of new azetidin-2-one of ferulic acid," *Farmacia*, vol. 67, no. 5, pp. 789–793, 2019.

[61] O. H. R. Al-jeilawi, "Synthesis , Characterization of Organic Derivatives Containing Heterocyclic Rings and Evaluation Their Antibacterial Activity," *J. Pharm. Biol. Sci.*, vol. 13, no. 1, pp. 18–22, 2018.

[62] M. Y.Saleh, "Synthesis and Antibacterial Evaluation of 2-(chloro / ethyl thio / seleno)-1,8-naphthyridine-3-azetidine Derivatives," *Diyala J. Pure Sci.*, vol. 13, no. 3, pp. 104–115, 2017.

[63] D. R. Kerzare, S. S. Menghani, and P. B. Khedekar, "Synthesis, characterization, antidepressant activity and docking studies of some novel indole bearing azetidinone derivatives," *Indian J. Pharm. Educ. Res.*, vol. 52, no. 1, pp. 110–121, 2018.

[64] L. M. Lima, B. N. M. da Silva, G. Barbosa, and E. J. Barreiro, "β-lactam antibiotics: An overview from a medicinal chemistry perspective," *Eur. J. Med. Chem.*, vol. 208, p. 112829, 2020.

[65] F. E. Olazaran, G. Rivera, A. M. Pérez-Vázquez, C. M. Morales-Reyes, A. Segura-Cabrera, and I. Balderas-Rentería, "Biological evaluation in vitro and in silico of azetidin-2-one derivatives as potential anticancer agents," *ACS Med. Chem. Lett.*, vol. 8, no. 1, pp. 32–37, 2017.

[66] S. M. I. Mahboubi Rabbani and A. Zarghi, "Selective COX-2 inhibitors as anticancer agents: a patent review (2014-2018)," *Expert Opin. Ther. Pat.*, vol. 29, no. 6, pp. 407–427, 2019.

[67] P. Sharma and Q. Ain, "Activity of drugs against bacteria, fungi and viruses," *Environ. Conserv. J.*, vol. 19, no. 1&2, pp. 129–133, 2018.

[68] S. T. Odonkor and K. K. Addo, "Review article Bacteria Resistance to Antibiotics : Recent Trends and Challenges," vol. 2, no. 4, pp. 1204–1210, 2011.

[69] G. Bell and C. MacLean, "The Search for 'Evolution-Proof' Antibiotics," *Trends Microbiol.*, vol. 26, no. 6, pp. 471–483, 2018.

[70] J.-K. Cho *et al.*, "Prevalence of antimicrobial resistance and integrons in extended-spectrum β-lactamases producing Escherichia coli isolated from Nakdong and Gumho river," *Korean J. Vet. Serv.*, vol. 37, no. 1, pp. 19–27, 2014.

[71] B. F. Putra, "Analisis hubungan modal sosial terhadap keberdayaan petani karet," *J. Online Mhs. Bid. Pertan.*, vol. 03, no. 01, pp. 1–11, 2016.

[72] H. Feng, H. Y. Wang, and H. Y. Zhao, "Novel random mutagenesis method for directed evolution," *Methods Mol. Biol.*, vol. 1498, pp. 483–490, 2017.

[73] Z. Song, K. E. McCann, J. K. McNeill, T. E. Larkin, K. L. Huhman, and H.

E. Albers, “Oxytocin induces social communication by activating arginine-vasopressin V1a receptors and not oxytocin receptors,” *Psychoneuroendocrinology*, vol. 50, pp. 14–19, 2014.

[74] R. S. Keri and K. M. Hosamani, “A facile and expeditious approach for the synthesis of 2-azetidinone derivatives via a multicomponent reaction,” *Monatshefte fur Chemie*, vol. 141, no. 8, pp. 883–888, 2017.

[75] L. E. García Reyes, “**済無**No Title No Title,” *J. Chem. Inf. Model.*, vol. 53, no. 9, pp. 1689–1699, 2013.

[76] V. Meda, V. Orsat, and V. Raghavan, *Microwave heating and the dielectric properties of foods*, Second Edi. Elsevier Ltd, 2017.

[77] R. R. Mishra and A. K. Sharma, “Microwave-material interaction phenomena: Heating mechanisms, challenges and opportunities in material processing,” *Compos. Part A Appl. Sci. Manuf.*, vol. 81, pp. 78–97, 2016.

[78] K. Guo, A. Baidak, and Z. Yu," Recent advances in green synthesis and modification of inorganic nanomaterials by ionizing and non-ionizing radiation," *Journal of Materials Chemistry A*, vol. 8, no. 44, pp. 23029-23058, (2020).

[79] A. M. Fahim, A. M. Farag, G. A. Nawwar, E. S. M. Yakout, and E. A. Ragab, "Chemistry of terephthalate derivatives: a review," *International Journal of Environment and Waste Management*, vol. 24, no. 3, pp. 273-301, (2019) .

[80] R. Kumar, R. K. Singh, D. P. Singh, R. Savu, and S. A. Moshkalev, “Microwave heating time dependent synthesis of various dimensional graphene oxide supported hierarchical ZnO nanostructures and its

photoluminescence studies," *Mater. Des.*, vol. 111, pp. 291–300, 2016.

[81] H. Nayebzadeh, N. Saghatoleslami, M. Haghighi, and M. Tabasizadeh, "Influence of fuel type on microwave-enhanced fabrication of KOH/Ca12Al14O33 nanocatalyst for biodiesel production via microwave heating," *J. Taiwan Inst. Chem. Eng.*, vol. 75, pp. 148–155, 2017.

[82] E. T. Kostas, D. Beneroso, and J. P. Robinson, "The application of microwave heating in bioenergy: A review on the microwave pre-treatment and upgrading technologies for biomass," *Renew. Sustain. Energy Rev.*, vol. 77, no. March, pp. 12–27, 2017.

[83] N. Patil *et al.*, "Radio Frequency and Microwave Heating of Preceramic Polymer Nanocomposites with Applications in Mold-Free Processing," *Adv. Eng. Mater.*, vol. 1900276, pp. 1–8, 2019.

[84] S. Chudy, A. Makowska, M. Piątek, and M. Krzywdzińska-Bartkowiak, "Application of microwave vacuum drying for snack production: Characteristics of pure cheese puffs," *Int. J. Dairy Technol.*, vol. 72, no. 1, pp. 82–88, 2019.

[85]K. Li *et al.*, "Investigations on the microwave absorption properties and thermal behavior of vanadium slag: Improvement in microwave oxidation roasting for recycling vanadium and chromium," *J. Hazard. Mater.*, vol. 395, no. March, p. 122698, 2020.

[86] M. Ataee, T. Ahmadi-Jouibari, and N. Fattahi, "Application of microwave-assisted dispersive liquid–liquid microextraction and graphite furnace atomic absorption spectrometry for ultra-trace determination of lead and cadmium in cereals and agricultural products," *Int. J. Environ. Anal. Chem.*, vol. 96,

no. 3, pp. 271–283, 2016.

[87] S. N. Mangasuli, K. M. Hosamani, P. Satapute, and S. D. Joshi, “Synthesis, molecular docking studies and biological evaluation of potent coumarin–carbonodithioate hybrids via microwave irradiation,” *Chem. Data Collect.*, vol. 15–16, pp. 115–125, 2018.

[88] M. Kelada, J. M. D. Walsh, R. W. Devine, P. McArdle, and J. C. Stephens, “Synthesis of pyrazolopyrimidinones using a ‘one-pot’ approach under microwave irradiation,” *Beilstein J. Org. Chem.*, vol. 14, pp. 122–1228, 2018.

[89] P. S. Thue *et al.*, “Preparation, characterization and application of microwave-assisted activated carbons from wood chips for removal of phenol from aqueous solution,” *J. Mol. Liq.*, vol. 223, pp. 1067–1080, 2016.

[90] N. M. J. Lavenir, S. Cyrille, N. J. Paul, and C. E. Suh, "Structural Characterization of Outcrop-Scale in Edea and Eseka Area: Evidence for a Complex Polyphase Deformation in the Paleoproterozoic Nyong Serie (Congo craton-South Cameroon)," *IOSR Journal of Applied Geology and Geophysics (IOSR-JAGG)*,vol. 7, no. 5, pp. 01-09, (2019).

[91] M. a. Surat, S. Jauhari, and K. R. Desak, “A brief review : Microwave assisted organic reaction,” Appl. Sci. Res., vol. 4, no. 1, pp. 645–661, 2012.

[92] L. Piras, E. Genesio, C. Ghiron, and M. Taddei, “Microwave-assisted hydrogenation of pyridines,” *Synlett*, no. 8, pp. 1125–1128, 2018.

[93] M. Zare, M. T. Golmakani, and A. Sardarian, “Green synthesis of banana flavor using different catalysts: a comparative study of different methods,” *Green Chem. Lett. Rev.*, vol. 13, no. 2, pp. 82–91, 2020.

[94] D. S. Ermolat, E. V. Van Der Eycken, V. Leu, B.-L. V, and R. V May, “A Divergent Synthesis of Substituted 2-Aminoimidazoles from 2-Aminopyrimidines,” *J. Org. Chem*, vol. 73, no. 17, pp. 6691–6697, 2008.

[95] С. Нанокристалів, L. У. Середовищі, І. Рідини, and З. В. Н. В. Ч. Нагріву, “Фізична хімія,” В.А. Галагуз , 2019.

[96] J. Tan, T. Zheng, K. Xu, and C. Liu, “Aryne triggered [2,3]-sigmatropic rearrangement of allyl and propargyl thioethers,” *Org. Biomol. Chem.*, vol. 15, no. 23, pp. 4946–4950, 2017.

[97] R. U. Ambhure, S. R. Mirgane, D. U. Thombal, R. B. Nawale, R. P. Marathe, and R. P. Pawar, 'Synthesis and antibacterial study of some Schiff bases complexes," *Modern Organic Chemistry Research*, vol. 2, no. 1, pp. 11-16, (2017).

[98] A. R. Katritzky, Y. Zhang, S. K. Singh, and P. J. Steel, “1,3-Dipolar cycloadditions of organic azides to ester orbenzotriazolylcarbonyl activated acetylenic amides,” *Arkivoc*, vol. 2003, no. 15, pp. 47–64, 2015.

[99] T. Weymuth and M. Reiher, “Immersive interactive quantum mechanics for teaching and learning chemistry,” *Chimia (Aarau).*, vol. 75, no. 2, pp. 45–49, 2021.

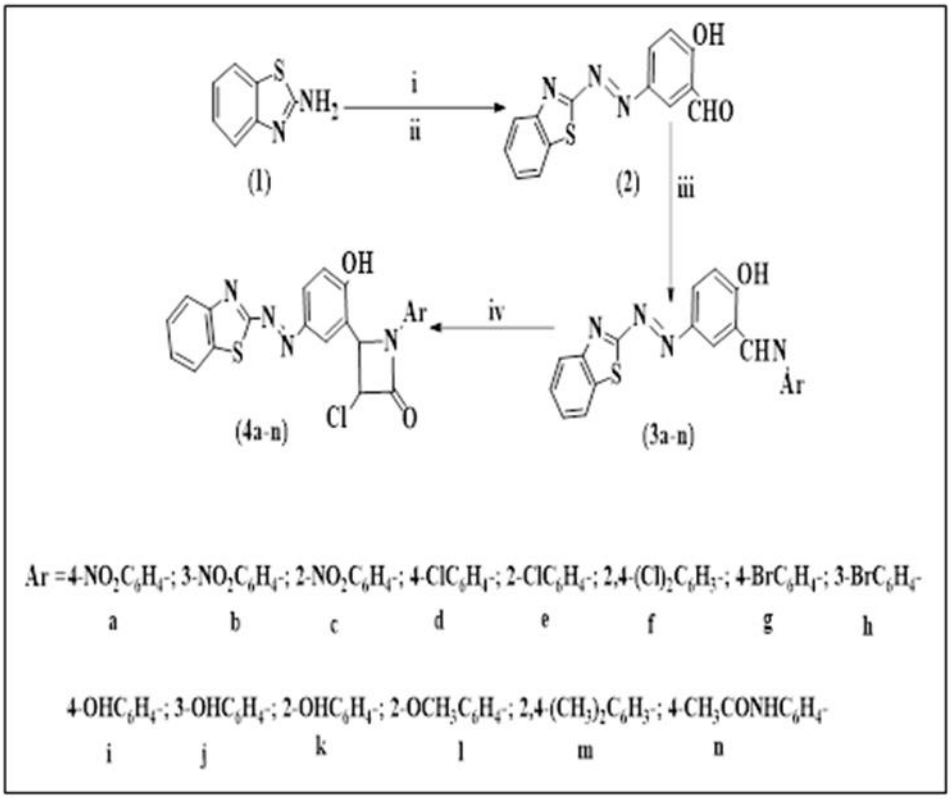
[100] T. Nogueira, P. H. C. David, and J. Pothier, “Antibiotics as both friends and foes of the human gut microbiome: The microbial community approach,” *Drug Dev. Res.*, vol. 80, no. 1, pp. 86–97, 2019.

[101] E. Von Hauff, “Impedance Spectroscopy for Emerging Photovoltaics,” *J. Phys. Chem. C*, vol. 123, no. 18, pp. 11329–11346, 2019.

الخلاصة

تفاعل الازدواج ما بين ملح الديازونيوم لمركب 2-امينوبنزوثيازول **(1)** مع ملح الفينوكسيد لمركب 2-هيدروكسي بنزالديهايد انتج مشتق الازوالديهايد **(2)** والذي ادخل في تفاعلات تكثيفية مع الانلينات الاولية (4-نايتروانيلين، 3-نايتروانيلين، 2-نايتروانيلين، 4-كلوروانيلين، 2-كلورو انيلين، 2،4-ثنائي كلوروانيلين، 4-بروموانيلين، 3-بروموانيلين، 4-امينوفينول، 3- امينوفينول ،2-امينوفينول، 2-ميثوكسي انيلين، 2،4- ثنائي مثيل انيلين، 4-اسيتاميدوانيلين) على التتالي بوساطة تقنية الاثارة بالاشعة المايكروية في الايثانول لإعطاء مشتقات قواعد شف **(3a-n)**. ادخلت الايمينات الناتجة في تفاعل غلق حلقي مع مركب α-كلورواسيتايل كلورايد في مذيب ثنائي مثيل فورماميد باستعمال طريقة الاثارة بالاشعة المايكروية للحصول على مشتقات الازتيدين-2-اون المطلوبة الجديدة **(4a-n)** على التتالي ، مخطط (I).

شخصت تراكيب جميع المركبات الجديدة المحضرة بوساطة التحليل الكمي للعناصر (CHNS) والطرائق الطيفية المتضمنة مطيافية الأشعة تحت الحمراء والرنين النووي المغناطسي للبروتون. تم تقييم الفعالية الحيوية لمركبات β-لاكتام الجديدة ضد نوعين من البكتريا هما (*Staphylococcus aurous*) الموجبة لصبغة كرام و (*Escherichia coli*) السالبة لصبغة كرام، وقد بينت قياسات مناطق التثبيط بان مركبات الازتيدينون المحضرة (**4b**, **4c**, **4i**, **4j**, **4k**, **4m**, **4n**) تمتلك تأثيرا أعظم من المضاد المرجعي(الاموكسيلين- كلافولانيت) تجاه الجراثيم السالبة لصبغة كرام, كما اظهرت مركبات **4i**, **4j**, **4k**, **4m**, **5n**) تاثيرا اعظم من المضاد القياسي تجاه الجراثيم الموجبة لصبغة كرام، الاشكال(45-3),(46 -3).



مخطط **(I)**: تحضير مشتقات الازتيدين-2-اون، الكواشف والظروف:

(i) Conc. H_2SO_4, $NaNO_2$, 0 ^oC; (ii) 2-hydroxybenzaldehyde, NaOH 10% , 5^oC; (iii) Ar-NH_2, EtOH, MW (300W), (40 min); (iv) α-chloroacetyl chloride, DMF, MW (300W), (150 min).

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة كربلاء_كلية العلوم
قسم الكيمياء

تحضير بعض المشتقات الحلقية غير المتجانسة الجديدة وتقييم اولي لفعاليتها ضد البكتريا

رسالة مقدمة الى
مجلس كلية العلوم- جامعة كربلاء
وهي جزء من متطلبات نيل درجة الماجستير
في علوم الكيمياء

من قبل

زينب سلام مرزة
بكلوريوس علوم كيمياء (2019)
جامعة كربلاء\ كلية العلوم

بإشراف

أ.د. زيد حسن عبود

1442هـ 2021م