Sudan University of Science &Technology

College of Graduate Studies

Synthesis of Some Oxazolone and Imidazole derivatives

تخليق بعض مشتقات الاوكسازولون والايميدازول

A thesis Submitted in fulfillment for the Requirement of M.Sc in Chemistry

By

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B.Sc. (Honors) in Chemical Industries

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Dedication

I dedicate this work to my mother and my father's soul

Acknowledgement

Firstly thanks to almighty Allah for given me the strength to complete this research I would like to express my sincere appreciation and gratitude to my supervisor Prof. Dr. Ahmed Elsadig Mohamed Saeed for his unparalled help ,support and his constractive comment throughout this research.

I would like also to acknowledge my gratitude for Dr. Abu baker. M. Osman and Dr. Mohamed S. Eltoum for their value contribution .At last but not least, thanks go to staff of chemistry department at Sudan University of Science and Technology.

Abstract

In this research, seven oxazolone and nine imidazole derivatives were designed and synthesized. The oxazolone derivatives were synthesized using benzoyl chlorides and glycine to produce bezonyl glycine then these bezonyl glycine further were reacted with different aromatic aldehydes in presence of sodium acetate and acetic anhydride to give seven oxazolone derivatives (**I** to **VII**).

The seven synthesized oxazolone derivatives were reacted with 2,4-dinitrophenylhydrazine in the presence of pyridine as solvent to produce seven imidazole derivatives (**VIII** to **XIV).**

Oxazolone derivatives (**I** and **III**) reacted further with hydrazine sulfate in presence of pyridine as a solvent to give two imidazole derivatives (**XV** and **XVI**).

Compounds 1-(2,4-dinitrophenylamino)-2-phenyl-4-(3-phenylallylidene) imidazole-5-one (**IX**), 1-(2,4-dinitrophenylamino)-4-(2-hydroxybenzylidene)-2-phenylimidazole-5-one(**XII**), 1-(2,4-dinitrophenylamino)-4-(hydroxyl-3-methoxy-benzylid-ene)-2-phenyl-5-one(**XIII**) and 1-amino-4-benzylidene-2-phenyl imidazole-5-one (**XIV**) are new and synthesized for the first time.

All the synthesized compounds were identified and characterized using Infrared and ^{1}H NMR spectroscopic techniques.

خلاصة البحث

في هذه الدراسة تم تحضير سبع من مشتقات الاوكسازولون و تسع من مشتقات الايميدازول. مشتقات الاوكسازولون(I الي VII). تم تحضيرها من تفاعل كلوريد البنزوايل مع الجلاسين لتحضير البنزوايل جلاسين التي استخدمت في التفاعل مع الدهيدات العطرية مختلفة في وجود خلات الصوديوم ولامائي حمض الخل.

مشتقات الايميدازول (VIIIالي XIV) تم تحضيرها بتفاعل مشتقات الاوكسازولون المحضرة في الجزء الاول من هذه الدراسة مع 2،4-ثنائي نتروفينايل هيدرازين في وجود البيريدين كمذيب.

أيضا إثنين من مشتقات الاوكسازولون (III,I) تم تفاعلها مع كبريتات الهيدرازين في وجود البيريدين كمذيب لتعطي إثنين من مشتقات الايميدازول (XVI ,XV).

المركبات 1-(2,4-ثنائي نيتروأمين)-2-فينايل-4-(3-فينايل اليليدين) إيميدازول-5-ون(**IX**) , 1-(2,4 – ثنائي نتروامين) – 4- (2 – هيدروكسي بنزاليدين) – 2 – فينايل - ايميدازول – 5 – اون (XII) 1-(2,4 – ثنائي نتروامين) – 4- (هيدروكسي – 3 – ميثوكسي بنزاليدين) – 2 – فينايل – ايميدازول-5-ون (**XIII**) و1-أمين-4-بنزليدين-2-فينايل-إيميدازول-5-ون مركبات جديدة تم تخليقها لأول مرة.

كل المركبات المحضرة في هذه الدراسة تم التعرف عليها عليها بواسطة مطيافيتي الأشعة تحت الحمراء ورنين البروتون النووي المغناطيسي.

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Chapter one

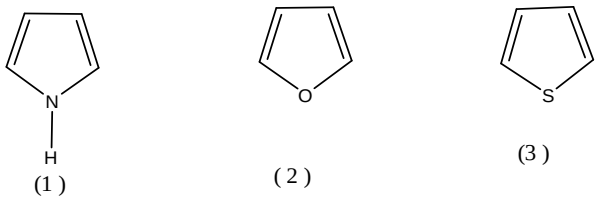
Introduction

1.1. Heterocyclic Compound

Heterocyclic compound are one which possesses a cyclic structure with at least two different kinds of heteroatoms in the ring. Nitrogen, oxygen, and sulfur are the most common heteroatoms (Kuhn and Suflita 1989). Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways (PSYadav, et al., 2011). Most of the sugars and their derivatives, including vitamin C, for instance, exist in the form of five-membered (furan) or six-membered (pyran) rings containing one oxygen atom. Most member of vitamin B group possess heterocyclic ring containing nitrogen. One example is vitamin B6 (pyridoxine), which is a derivative of pyridine, essential in amino acid metabolism (Joule and Mills, 2012).

1.1.1. Five-memeberd rings with one heteroatom

Five-membered aromatic heterocyclic with one heteratoms pyrrole (**1**) furan (2) and thiophene (3) are considered to be derived from cyclopentadienyl anion by replacing CH group by NH, O and S respectively (figure-1.1).



(1) (2) (3)

Figure 1.1 The chemical structure pyrrole, furan and thiophene

These five-membered heterocyclic are therefore expected to possess characteristics of conjugated dienes and acyclic amine and sulfide (Schofide and Kenneth, 2013).

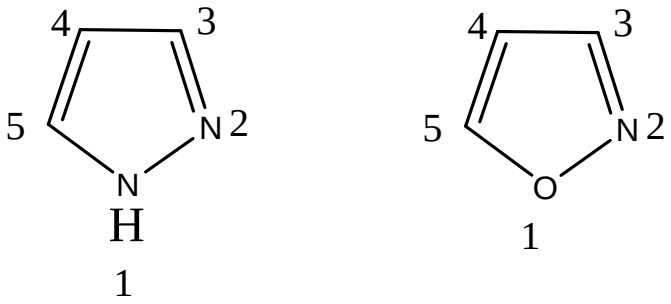
The aromaticity in these heterocycles is attributed to the delocalization of π-electron forming an aromatic sextet in which one electron is contributed by each carbon atom and pair of electrons is contributed by the heteroatom pyrrole, furan

and thiophene are π-excessive and are characterized by their ability to undergo electrophilic substitution reaction (Marcos Mandado, et al., 2006).

1.1.2. Five-membered heterocyclic with two heteroatoms

May be considered to be derived from pyrrole, furan and thiophene by the replacement of -CH= group by sp^2 hybridized azomethane nitrogen (pyridine-type) nitrogen) at the position-2or-3 these heterocycles are termed as azoles and depending on the position of azomethane nitrogen (-N=) are classified as:

(i) 1, 2 azole if the methane is substituted at position -2 (figure -1.2)



Pyrazole isoxazole

Figure .2 The chemical structural pyrazole and isoxazole

(ii) when insertion of azomethane at position -3(figure 1.3) (Li and Gribble, 2006)

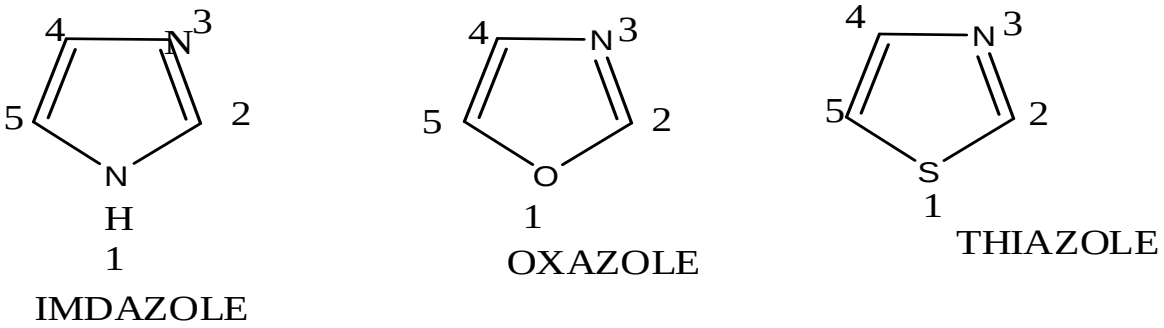


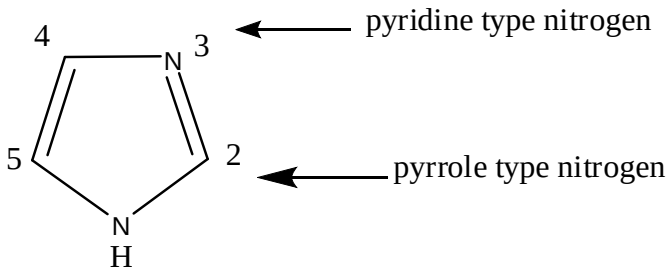
Figure 1.3 the chemical structure of Imidazole, Oxazole and Thiazole

1.2. Imidazole

Imidazole is a white or colourless soild that is soluble in water however they have very much higher boiling point (256-199^{0}C). Which is probably due to dipolar association and in addition in the case of imidazole itself to extended hydrogen bonding (Gilli et al., 1993).The nitrogen atom at position -1 bears a hydrogen atom and regarded as pyrrole –type nitrogen and the second nitrogen-type nitrogen. In its various oxidation states, the imidazole nucleus has proven to be an unusually fertile source of medicinal agents, Nitroimidazoles are very often associated with antimicrobial activity, whereas imidazolines are often present in drugs acting as adrenergic agents (Ernsberger et al., 1992). These considerations suggest, as a working hypothesis, that these particular imidazole derivatives are integral parts of the respective pharmacophores (Kumar, 2010). While nitrofurans are often prepared as antibacterial agents (Pieczonka et al., 2013), nitroimidazole forms the basis for an extensive class of agents used in the treatment of infections by the protozoans (Ghannoum and Rice, 1999). Unlike bacterial infections, protozoal infections are seldom life-threatening. The physical discomfort occasioned by such infections is, however, sufficient importance to provide a useful therapeutic place for antiprotozoal agents. A particularly common set of such conditions are parasitic infections of the genitalia caused by *Trichomonas vaginalis.* These disorders are called trichomonas's (Saudi et al., 2014).

One of the problems complicating the chemistry of the imidazoles needed for preparing these agents is their structural ambiguity. Imidazoles undergo a facile tautomeric equilibrium involving a shift of the proton on nitrogen so that it is sometimes difficult to assign unambiguous structures to unsymmetrically substituted derivatives. Most drugs containing this ring system are alkylated on one of the nitrogen ring, which locks the molecule into a single tautomeric form and removes the source of ambiguity. The ambient character of imidazoles

requires care in selecting those conditions that will lead to alkylation on the desired nitrogen atom (figure1.4).



1

(10)

Figure 1.4 Imidazole reduced form

Imidazole compound [10] exist in three partially reduced forms compound [11], compound[12] and compound[13] was designated as follows depending on the position of double bond, the completely reduced forms of imidazole is known as imidazolidine compound[14] figure 1.5).

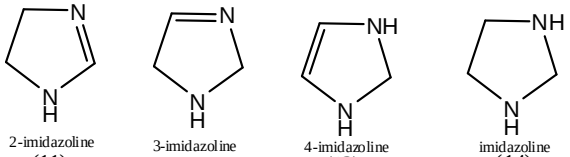
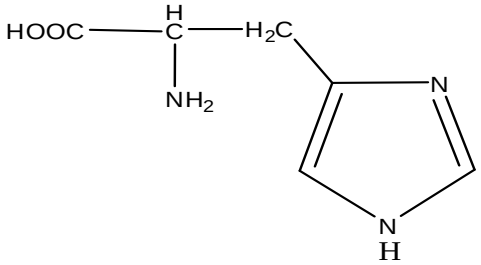


Figure 1.5 Imidazole form according to the position of double bond

Imidazole nucleus is present in number of important naturally occurring products as amino acid e.g. histidine (involved in the biochemical reaction of living systems) compound [15] (figure 1.6).

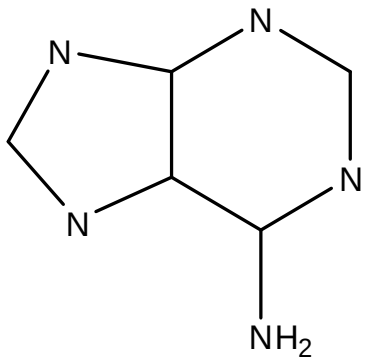


histidine

15

Figure 1.6 The chemical structural of histidine

And purine compound [16] (forming bases of nucleic acid) (figure 1.7)



Adenosine-base

16

Figure 1.7 Adenosine

The imidazole nucleus is a fertile source of biologically important molecules. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes (Gupta et al, 2013; Mohammadi et al., 2012).

1.2.1. Structure of imidazole:

Imidazole is a planar molecule with following structure parameters (Kovacevic and Kokalj, 2011) (figure 1.8).

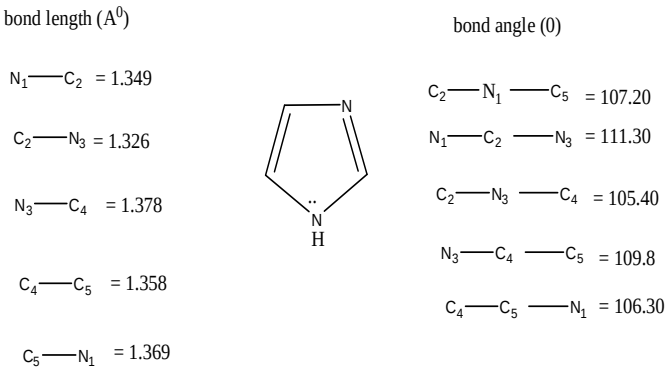


Figure 1.8 Imidazole structure parameter

1.2.2. The hydrogen bonding of imidazole

The boiling point of imidazole is (b.p. 256^0C) relatively higher as compound to boiling points of the other five-membered heterocyclic systems. The higher boiling point of imidazole is attributed probably to the interamolecular hydrogen bonding of the type , if the position -1 of imidazole is substituted ,N-substituted imidazoles ,therefore ,have lower boiling points (1- methylimidazole b.p 198^0C) (Gupta et al., 2013)

1.2.3.Snythesis of Imidazole

1.2.3.1.Reaction of α- diketone, α- hydroxy-, α- halo – α amino ketone with formaldehyde

The formamide synthesis is an extension of the earliest synthetic method which involved the reaction of glyoxal, formaldehyde and ammonia. Modified synthesis involve the reaction of α-diketone, α- hydroxy-, α- halo-or α-amino ketones with formamide. (figure-1.9) (.Gupta et al., 2013)

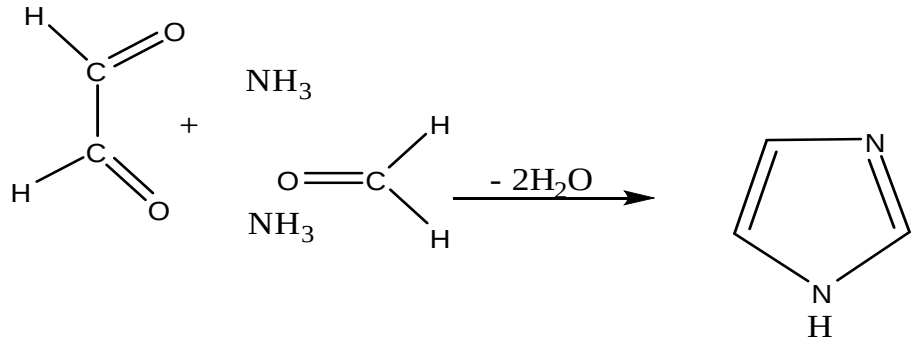


Figure 1.9 Reaction of α-diketone , α-hydroxy , α-halo- α-amino ketone with formaldehyde

1.2.3.2. Reaction of oxamide with phosphorus oxychloride

The reaction of N,N-disubstituted oxamide with phosphorus oxychloride produces chlorine-containing intermediate which on reduction with hydrochloric acid affords 1-substituted imidazole (figure-1.10) (Gupta et al., 2013).

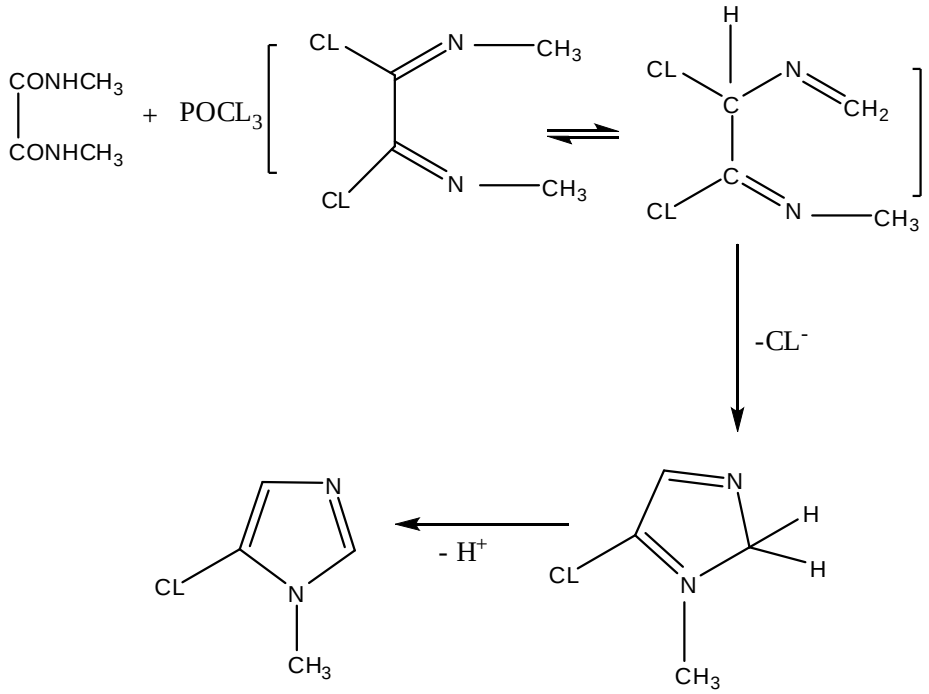


Figure 1.10 Reaction of oxamide with phosphorus oxychloride

1.2.3. Reaction of 1, 2- diaminoalkanes with carboxylic acid and Aldehydes or ketones:

When 1,2-diaminoalkanes are treated with carboxylic acid and aldehyde or ketones at high temperature in the presence of dehydrogenating agent (Pt /Al_2O_3), 2-alkylimidazole are obtained (figure -1.11) (Seregin and Gevorgyan, 2007).

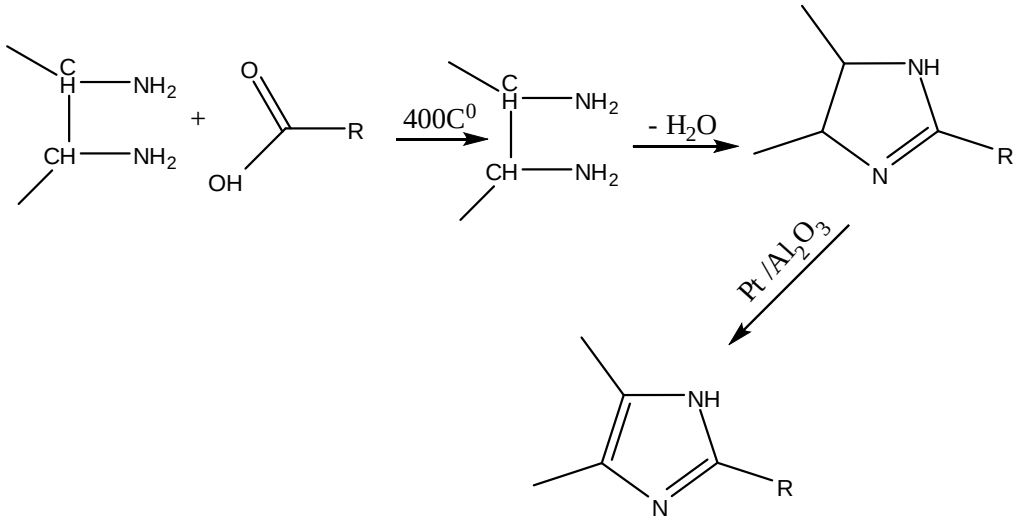


Figure 1.11 Reaction of 1, 2- diaminoalkanes with carboxylic acid and Aldehydes or ketones

1.2.4. Reaction of imidazole:

1.2.4.1. Reactivity of imidazole:

Imidazole is considered to exhibit properties of pyrrole as wellas pyridine type because of the present of pyrrole- type and pyridine – type nitrogens in the imidazole ring system the reactivity of imidazole can be inferred from the structural specificity of imidazole nucleus relating to resonating structures contributing maximum to the imidazole nucleus (Lin, et al., 2007).

1.2.4.2. Reaction with electrophiles

1.2.4.2.1. Electrophilic attack at Nitrogen

Imidazole contain two nitrogen atoms (pyrrole-type and pyridine-type), but the attack of electrophile occurs at pyridine-type containing lone pair in the plane of the ring (figure1.12) (Hamano and Hameka, 1962).

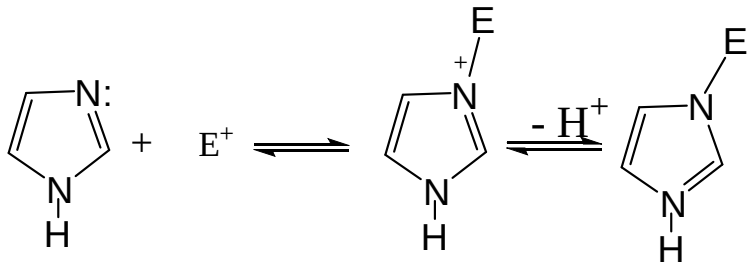


Figure 1.12 Electrophilic attack in imidazole

1.2.4.2.2. N-alkylation

Imidazole substituted at N-1 are alkylated readily at N-3 with formation of quaternary salt, but alkylation of imidazole (with free NH group) produces protonated N-alkyl imidazole which can be deprotonated by a base (imidazole) to provide N-alkyl imidazole (figure-1.13) (Mirzaei et al., 2002).

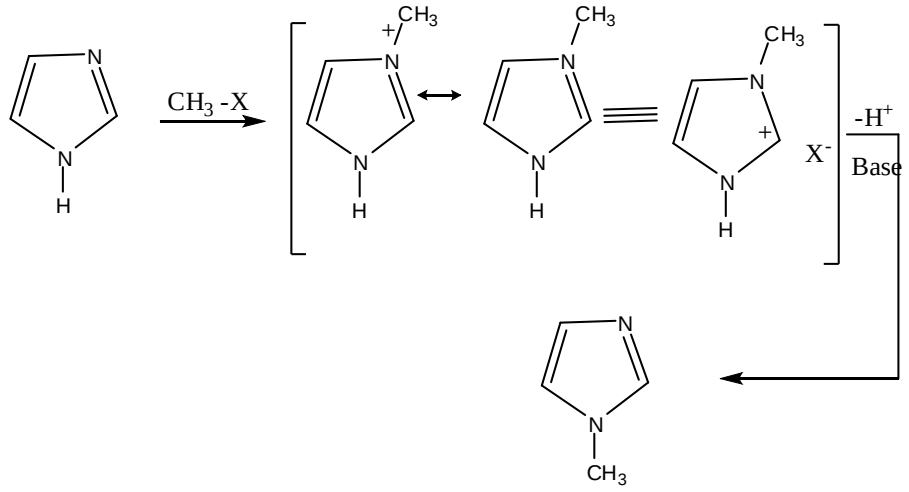


Figure 1.13 N-alkylation of imidazole

1.2.4.2.3. N-acylation:

Imidazole with free NH group can be N-acylated by the reaction with acid chloride (2:1 ratio)in an inert solvent at room temperature with formation of N-acylimidazole via N- 3 acylimidazolium action (figure -1.14) (Kouta et al., 2014).

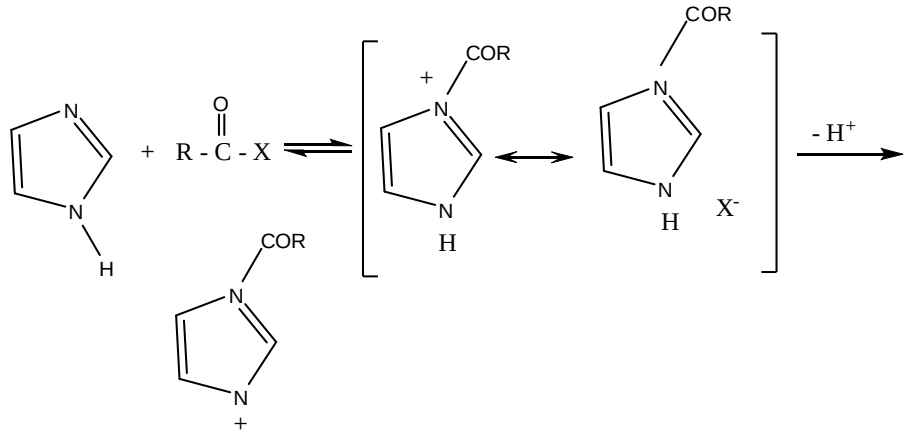


Figure 1.14 N- acylation of imidazole

1.2.4.3. Elecrophilic attack at carbon

The reaction at the carbon atoms in imidazole ring are expected to be similar to those in aromatic heterocyclic which is less reactive than pyrrole and more reactive than pyridine toward electrophiles (Katritzky and Lagowski, 2013).

In imidazole ring system the attack of electrophile occurs at C-5 which is the most activated position for electrophiles attack(Katritzky and Lagowski 2013).

1.2.4.3.1. Nitration of imidazole:

Imidazole is nitrated with a mixture of concentrated nitric acid and sulfuric acid at 160^0C with the formation of 4- nitroimidazole .the reaction proceeds to involve the attack of electrophile (nitronium ion) at the position-4 of the imidazolium cation (figure- 1.15) (Chu et al., 2004).

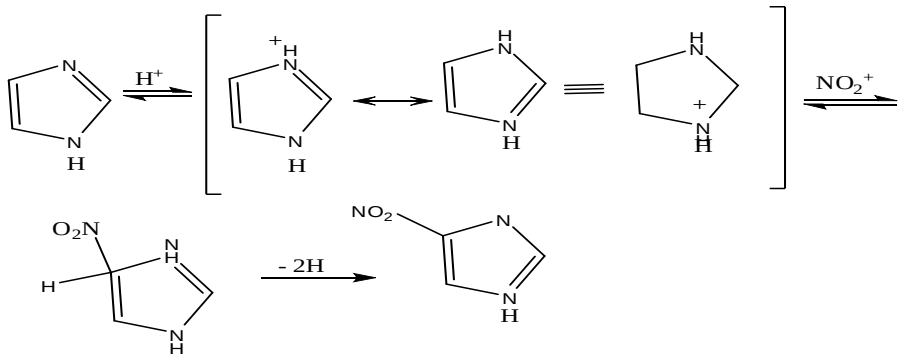


Figure 1.15 Nitration of imidazole

1.2.4.3.2. Sulphonation of imidazole:

When imidazole is treated with 50- 60 % oleum (H_2SO_4 –$SO_{3)}$ at 160^0C the sulphonation occurs at position-4 involving the attack on the imidazolium cation (figure- 1.16) (Duran-Valle et al., 2012).

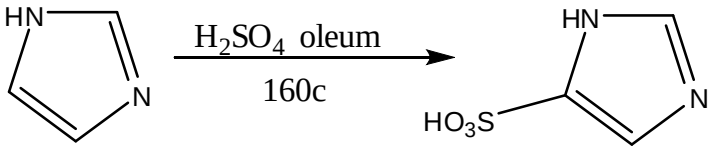


Figure1.16 Sulphonation of imidazole

1.2.4.3.3. Halogenation of imidazole:

Imidazole is brominated very readily by bromine in aqueous solution or organic solvent with the formation at available vacant position providing 2, 4, and 5-tribromoimidazole (figure-1.17) (Wahren, 1973).

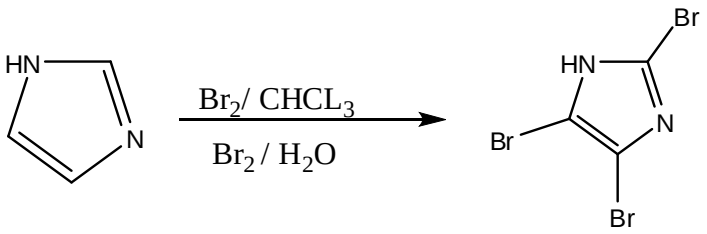


Figure 1.17 Halogenation of imidazole

1.2.4.3.4. Reaction with aldehyde and ketone

Unsubstituted imidazole undergo hydroxymethylation at the position-4 (or-5) when treated with formaldehyde in the presence of dimethyl sulfoxide (DMSO) (figure -1.18) (Siddiqui, et al., 2005).

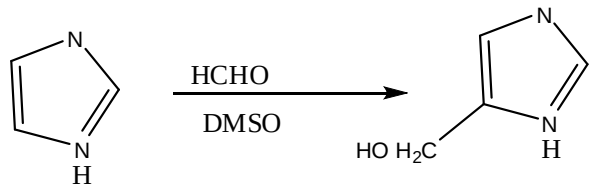


Figure1.18 Reaction of imidazole with aldehyde and ketone

1.2.4.4. Reaction with Nucleophiles

1.2.4.4.1. Nucleophilic attack at carbon

Imidazole undergo nucleophilic substitution reaction very readily with the nucleophilic attack at the position -2 if substituted with electron-withdrawing substituents or quaternized, however the position of electron-withdrawing substituents can modify the site of nucleophilic attack (figure-1.19) (Li and Zhang, 2005).

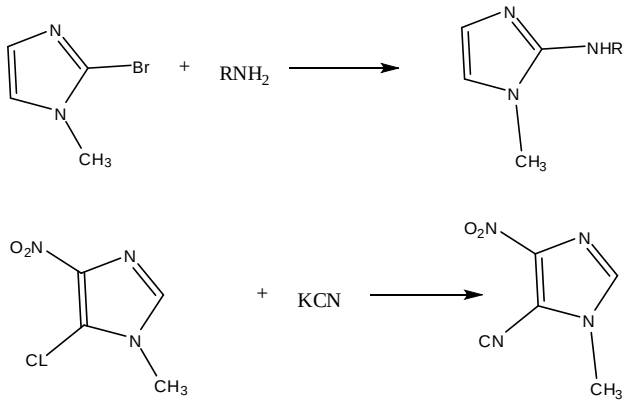


Figure -1.19 Nucleophilic attack at carbon

1.2.4.4.2. Nucleophilic at hydrogen:

1.2.4.4.2.1. Deprotonation of NH (acidity):

The acidic character of imidazole is attributed to the enhanced delocalization in the symmetric imidazyl anion resulting from the deprotonation of NH by a strong base (figure-1.20)(Hofmann, 2009)

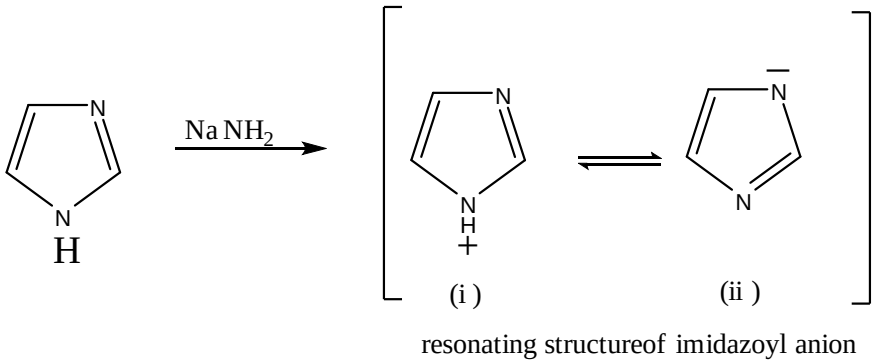


Figure 1.20 Deprotonation of NH (acidity)

1.2.4.4.2.2. Deprotonating of carbon -2

Hydrogen atom attached to C-2 of imidazole and particularly imidazolium ion , is acidic and can be abstracted as a proton by a base with the generation of imidazolium yeilde, the mechanism involves initially N-3 protonation followed by C_2-H deprotonation(Shimba, et al.,1998) (figure-1.21).

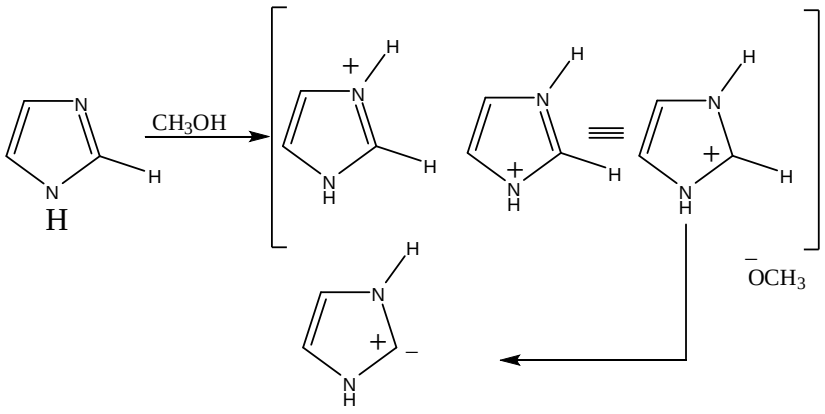


Figure 1.21 Deprotonating of carbon -2

1.3. The chemistry of Oxazole:

Oxazole is considered to be derived from furan by the replacement of the -CH= (methane group) for the position-3 by azomethane nitrogen (-N=), oxzaole ring system is numbered as follows (figure -1.22)

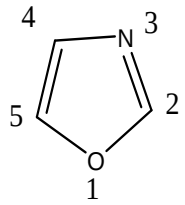


Figure1.22 The structure of Oxazole

The chemistry of oxazole began in 1876 with the synthesis of 2-methyloxazole, although parent oxazole was synthesized in 1947and 1962. The interest in the chemistry of oxazole was developed during the war when penicillin was considered to contain the oxazole ring system, but the discovery of oxazoles as dienes in Diels-alder reaction and in1, 3-dipolar cycloaddition of mesoionic heterocycles gave impetus to the development of oxazole chemistry.

The fusion of benzene ring to the 4, 5-position of the oxazole ring results in benzoxazole (Turchi, 1981) (figure -1.23) and numbered as follows:

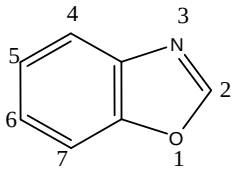
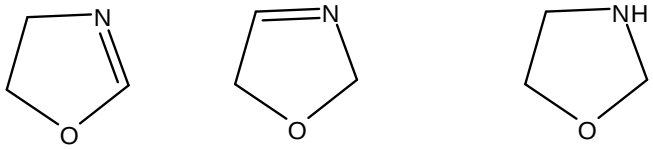


Figure 1.23 benzoxazole

Two partially saturated oxazoles with different position of double bond are possible and are named as 4,5- dihydro oxazole compound[19], 2,5- dihyro

oxazole compound [20] and fully saturated oxazole is named as oxazolidine compound [21](figure1.24).



(19) (20) (21)

Figure 1. 24 Saturated oxazole

The oxazole ring is planar with considerable bond fixation as indicated by the bond length in oxazole (with an appreciable in C_2-N and C_4-N bonds).Oxazole although possesses sextet of π electrons but the complete delocalization is restricted due to the presence of electronegative oxygen atom and up to extent nitrogen atom. The aromaticity order has been observed to be similar as in the five-membered heterocycles with one heteroatom.

The oxazole molecule is considered as the resonance hybrid of the following resonating structures (the predominance of inductively electron-withdrawing effect of the electronegative oxygen over its mesomerically electron-releasing effect (Jorgensen et al., 1998)

Oxazoles are one of the key building elements of natural products, numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities, such as hypoglycemic, analgesic, anti-inflammatory, and antibacterial activities (Xin-Hua Liua at el., 2009).

1.3.1. Synthesis of oxazoles

1.3.1.1. Cyclohydration of α-acyl amino ketone

It involves cyclohydration of α-amino ketone in the presence of dehydrating agents such as H_2SO_4, $POCl_3$ and $SOCl_2$, however, polyphosphoric acid,

phosgene or anhydrous hydrogen fluoride have also recently been used to facilitate the cyclization. The reaction proceed via an intermediate compound[22] with the formation of C_5-O bond and demonstrated O^{18} labelling that the oxygen atom of oxazole ring compound[23] derived from that of the acyl group (figure-1.25) (Wipf, et al., 2004).

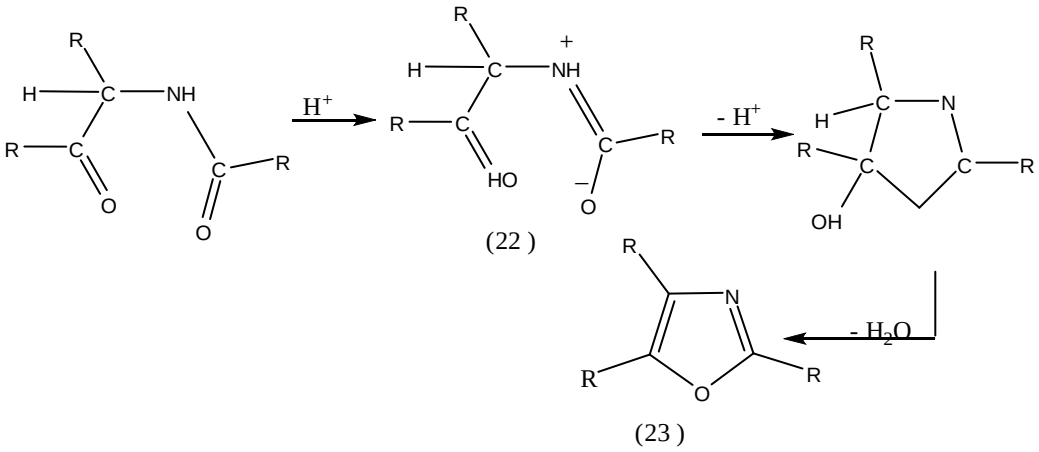


Figure 1.25 Cyclohydration of α-acyl amino ketone

1.3.1.2. Reaction of halo ketone with primary amines

The condensation of α-halo ketones with primary amides lead to the formation of oxazoles. This method is suitable for the oxazole containing one or more aryl groups, however with use of formamide (R=H) 2-substituted oxazole are obtained. This method can also extended to synthesized 2-aminoxazoles involving the use of urea and it is derivatives or cyanamide(Estevez et al.,2010).

1.3.1.3. Reaction of hydroxyaminoaketones with aldehydes

The reaction of hydroxyaminoketones with aldehyde in the presence of sulfuric acid and acetic anhydride provides oxazoles in which C-2 atoms come from aldehyde (figure -1.26).

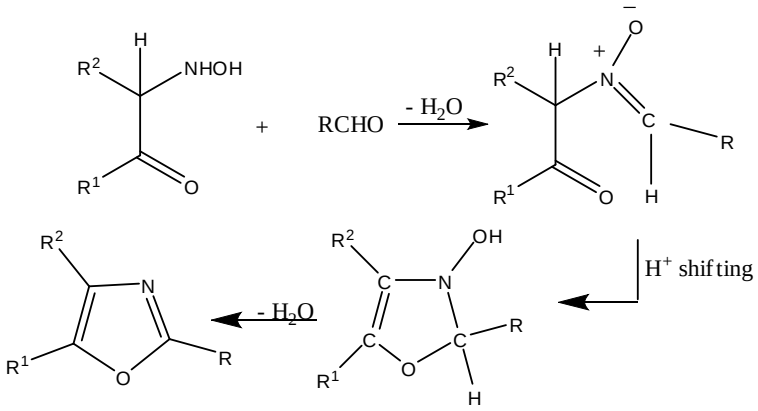


Figure -1.26 Reaction of hydroxyaminoaketones with aldehydes

1.3.2. Reaction of oxazole:

1.3.2.1. Reactivity of oxazole:

Oxazole contains pyridine-type nitrogen at position-3 and furan – type oxygen at the position-1, oxazole is, therefore considered as the hybrid of both the heterocyclic systems and exhibits characteristic properties associated with:

i- Pyridine-type nitrogen protonation, N-alkylation and reactivity of halogen atom at the position-2.

ii- furan-type oxygen ,diene-type characteristic due to bond localization (Ducept, 2000).

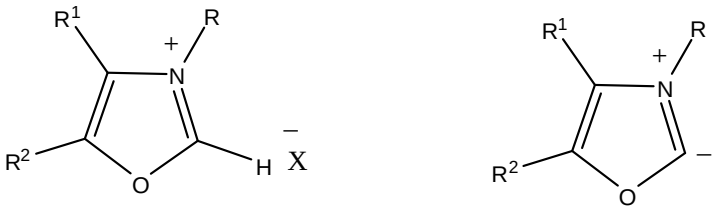
1.3.2.2. Electrophilic attack at nitrogen:

1.3.2.2.1. Protonation of oxazole (basicity):

Oxazole colorless liquid, (b.p =69 – 70^{0}C) is very weak base with pka=0.8 as it forms unstable salts (hydrochlorides and picrate) the weakly basic nature of oxazole is attributed to the balancing effect of the two structural effects operating in the opposite directions due to the presence of electronegative oxygen atom (i) strong inductively electron-withdrawing effect (base-weakening effect) and (ii) weak mesomerically electron-releasing effect *(Eicher et al.,2004)*.

1.3.2.2.2. N-alkylation of oxazole:

Oxazole form quaternary salts with alkylating agents, in alkyoxazolium salts compound [24], the acidic hydrogen at C-2 can undergo $H \rightleftharpoons D$ exchange easily via heterocyclic yield compound [25] generated as the intermediates during the process(Zhu et al., 2006) (figure -1.27).



(24)
quaternary salt

(25)
yeild

Figure -1.27 N-alkylation of oxazole

1.3.2.3. Electrophilic attack of oxazole at carbon

The oxazole ring not undergoes electrophilic substitutions easily unless oxazole ring is substituted with electron-releasing substitutions. The reduced reactivity of the oxazole ring towards electrophile is attributed to its electron deficiency caused by effective inductively electron-withdrawal effect of the both electronegative heteroatoms. The coupled electron-withdrawal effect of the both the heteroatoms, oxygen and nitrogen, affects position-2 most strongly, however ,the position-4 and-5 are also affected by the electron-withdrawal effect of nitrogen and oxygen respectively (Hashmi et al., 2004).

1.4. The oxazolone

The active heterocyclic compounds are one of the main topic of interest for the medicinal chemists and as it displays of pharmacological activities. Nitrogen ,sulfur ,oxygen containing five and six–membered heterocyclic compounds have occupied enormous significance in the field of the medicinal chemistry (Bala, et al., 2011).

Oxazolones are heterocyclic compounds which perform an important role in the synthesis of several organic molecules including amino acids, amino alcohols, thiamine, amides, peptides and polyfuctional compounds. Certain natural and synthetic oxazolone also including benzoxazolone derivatives possess important biological activities such as antimicrobial, anti-inflammatory, anticancer, anti HIV, anti angiogenic, anti convulsant, anti-tumor, sedative and cardio tonic activity (figure 1.28) (Mesaik et al., 2004; Tikdari et al., 2008).

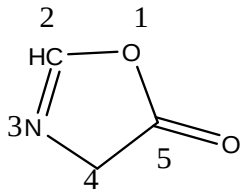


Figure 1.28 Oxazol-5-one

Oxazolones exhibited promising photophysical and photochemical activities (Bourotte et al., 2004; Jung et al., 1996), and also used in semiconductor devices such as electro photographic photoreceptors and in non-linear optical materials (Ozturk et al., 2007; Murthy et al., 2010). Oxazol-5-ones also known as azlactones, are readily prepared from N-protected amino acids by dehydration (Seebach et al., 1997; Gottwald, et al., 1999). Ring opening of oxazolone leading to enriched N-protected phenylalanine ester and peptido-alcohols oxazolone linked to the structure and chemistry of penicillin, Oxazolones show interesting behavior toward polymerization, condensation reagents, herbicides, fungicides, pesticides and agrochemical intermediates (Matsunaga et al.,2005; Abdel-Aty et al., 2009)

1.4.1. The chemistry of oxazolone

Substitution functional group at C-4 and C-2 position plays a vital role in the activity of the oxazolone. Substituted (p-nitro) exocyclic phenyl group at C-4 of

oxazolone moiety greatly influences the immunosuppressive activity. Cinnamoyl residue at C-4 of oxazolone moiety and substitution of functional group at C-4 and C-2 positions of oxazolone are crucial for tyrosinase inhibitory activity. An extension of conjugation through an aliphatic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity(Khan et al., 2006).The rate of the oxazolone ring-opening reaction decreased with an increase of the electron donating properties of the substituted of the phenyl ring at -2position (Betłakowska et al., 2002) Exocyclic double bond can operate a dienophile and N-substituted oxazolone participate in intermolecular Deils- alder reactions(Fearnley et al., 2002).Lewis acid activation of the carbonyl group of unsaturated oxazolone give electrophilic character to the β-carbon(Tandel et al., 2008)

The positive charge of carbon C-2 increase by m- NO_2 group which may be easily attacked by any nucleophile, an alkoxy group at the para position of the phenyl ring decrease the negative effect of the nitro group and the electron-withdrawing effect of this group may support the attack of the C= N group. The bond order of the C=N group decreases by the presence of m- NO_2 group at the benzylidine ring (Bala et al., 2011).

1.4.2. Synthesis of the oxazolone

1.4.2.1. Synthesis of 4-(4-hydroxybenzylidine)-2-substituted oxazol- 5-one using glycine and benzadehyde:

The preparation of 5-oxazolone by Erlenmeyer-polchl reaction, cyclodehydration condensation of the appropriate aldehyde and hippuric acid in dry acetic anhydride and used acetate anion as catalyst. Compound 4-(4-hydroxy benzylidine)-2-substituted oxazol- 5-one compound[28] were synthesized from acetyl glycine compound[26] and p-hydroxybenzaldehyde compound[27](figure-1.29)(Pasha et al.,2007)

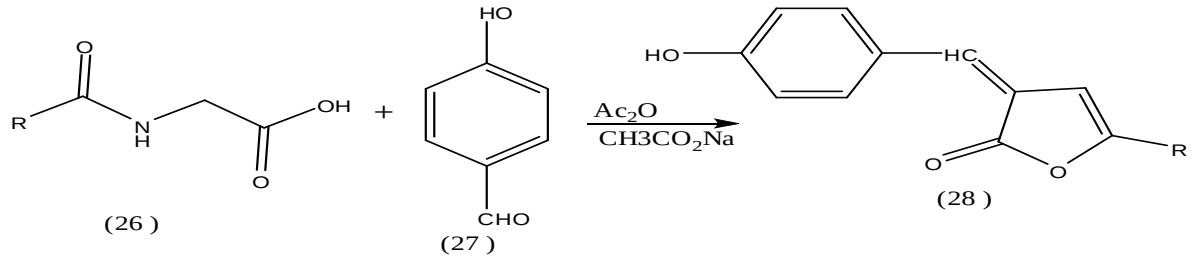


Figure 1.29 Synthesis of 4-(4-hydroxybenzylidine)- 2- substituted oxazol- 5-one using glycine and benzadehyde

1.4.2.2. Synthesis of 4-arylmethylidine-2-aryloxazol-5-one using ZnO as catalyst:

Synthesis of 4-arylmethylidine-2- aryloxazol-5-one compound[31] by stirred suspension of substituted benzaldehyde compound[29] hippuric acid compound[30] and acetic anhydride and used ZnO as catalyst, the reaction was completed at room temperature in short time with good yield (figure-1.30)(Tikdari et al., 2008)

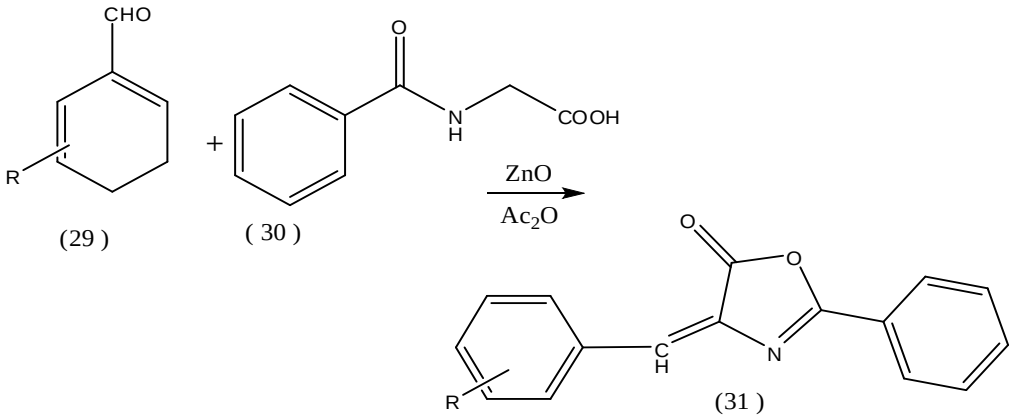


Figure1.30 Synthesis of 4-arylmethylidine-2- aryloxazol-5-one using ZnO as catalyst

1.4.2.3. Synthesis of 2-phenyl 5-oxazolone from dodecatungstophosphoric acid samarium and ruthenium (III) chloride as catalyst

Synthesis of 2-phenyl-5-oxazolone by microwave irradiation from mixture of hippuric acid compound[30] and aldehyde or ketone compound[32] in presence of acetic anhydride and catalyst (dodecatugstophosphoric acid samarium and ruthenium (iii) chloride) of the reaction was very fast and lead to good yield of oxazolone compound[33] (figure– 1.31)(Lykkebergl et al., 1972)

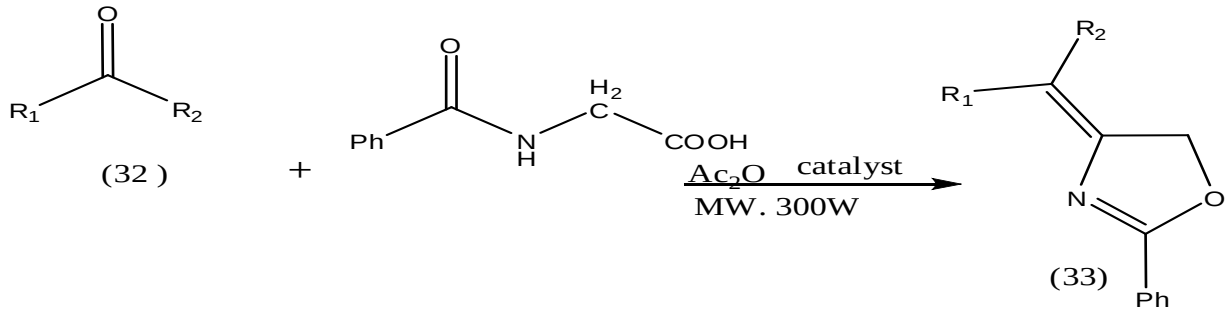


Figure 1.31 Synthesis of 2-phenyl 5-oxazolone from dodecatungstophosphoric acid samarium and ruthenium (III) chloride as catalyst

1.4.2.4. Synthesis of oxazolone using K_3PO_4 as catalyst:

The Erlenmeyer reaction afford oxazolone compound[39] by the reaction of carboxylic acid compund[37] and benzaldehyde compound[38] and potassium phosphate as catalyst instead of sodium acetate underwent condition of aromatic aldehyde by dehydrating agent such as an acetic anhydride (figure-1.32)(Williams et al., 1997).

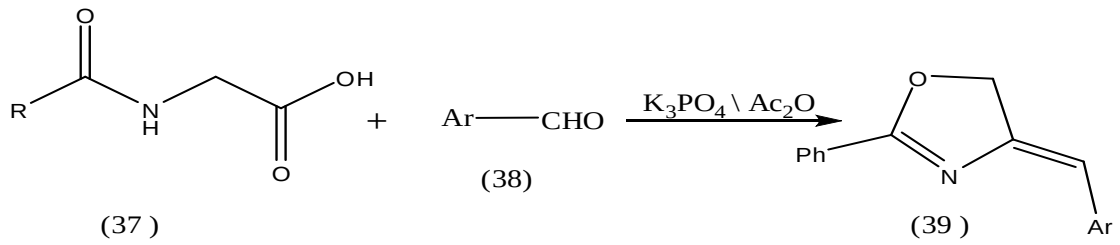


Figure 1.32.synthesisof oxazolone using K_3PO_4 as catalyst

1.4.3. The pharmacological activity of oxazolone

Oxazolone nucleus has various phoarmacological activities, some of which are for exhibitive their potent therapeutics use .mainly substitution at the C-4 position and C-2 position in oxazolone ring may be affect the activity to certain N-substituted oxazolone also used as cinical and therapeutic agents (Bala et al., 2011).

1.5. Aim and objective

The main objective of this research are:

-To estabilished Method of the synthesis of proposed compounds.

-To synthesized the title compounds by appropriate methods.

-To carry out the preliminary test such as physical constant deterimination TLC.

-To confirm the structure of synthesized compounds by IR and ^{1}HNMR.

Chapter two

Experimental

2. Material and Methods

2.1. Materials and Instruments:

2.1.1. Materials:

2.1.1.1. Chemical:

Acetic anhydride (assay = 98 % . UK), Benzoyl Chloride (98.5-100 %), Cenamaldehyde, Salicyaldehyde, Anisaldehyde, Furfural, Vaniline, N-N-di amino benzaldehyde (Loba chemie, India), Benzaldehyde (Techno Pharmchem, India), Sodium acetate (Qualikems, New Deh, India), Glycine (NICE, India), Ethanol (National distillations company, Sudan), Chloroform (loba chemie, India), Hydrochloric acid (Loba Chemie , India), 2, 4-di nitro phenyl hydrazine (Loba Chemie, India).

2.1.1. 2. Thin layer chromatography (TLC)

TLC was carried out using Silica gel (H-Humbai400002India)coated sheets.

2.1. 2. Instruments

2.1.2.1. Infrared spectrophotometer(IR)

Infra-red spectroscopy was recorded on FT-IR-8400 intrument (Shamazu,Japan) using KBr disc and Agilent Cary 630 FTIR spectrometer(USA).

2.1.3. Proton Nuclear Magnetic Resonance Spectrophotometer (^{1}HNMR)

Proton nuclear magnetic resonance Spectrophotometer (^{1}HNMR) was recorded on Ultra shield -500 plus instrument (Bruker, Germany) using DMSO as solvent and operating at 500.13MHz for Protons.

Employing a 5mm high-resolution broad-band TMS gradients probe, the zg30 pluse program was used. Spectra were recorded over a sweep width of (10330.57Hz) at 293.4k temperature and time domain data point giving an acquisition time of 1.00 seconds.

2.1.4. Apparatus and equipment:

- Fume cupboard
- Magnetic stirrer with hot plate model L.M.S 100 volts, 220 volts 50/60 Hz serial No 0401401

- Melting point apparatus (SMP10, biby stuart scientific, UK)

2.1.5. Glassware:

- All of the glasses used were of Pyrextype.

2.2. Methods

2.2.1. Preparation of benzoyl glycine:

In 250ml conical flask were placed 7.5 g of glycine (0.01 mol) in 150 ml distilled water, added 8 g of sodium hydroxide (0.02 mol) with vigorously stirred until to complete the dissolve of glycine and then added 14.17 ml (0.012 mol) of benzoyl chloride in five portion to solution, after that the reaction mixture was neutralized the reactant by adding concentrated hydrochloric acid slowly and stirred until the mixture is acidity and takes it overnight, after that the precipitate was washed with cold water, filtered and recrystallized, the benzoyl glycine by distilled water 28 g m.p 183-184^{0}C.

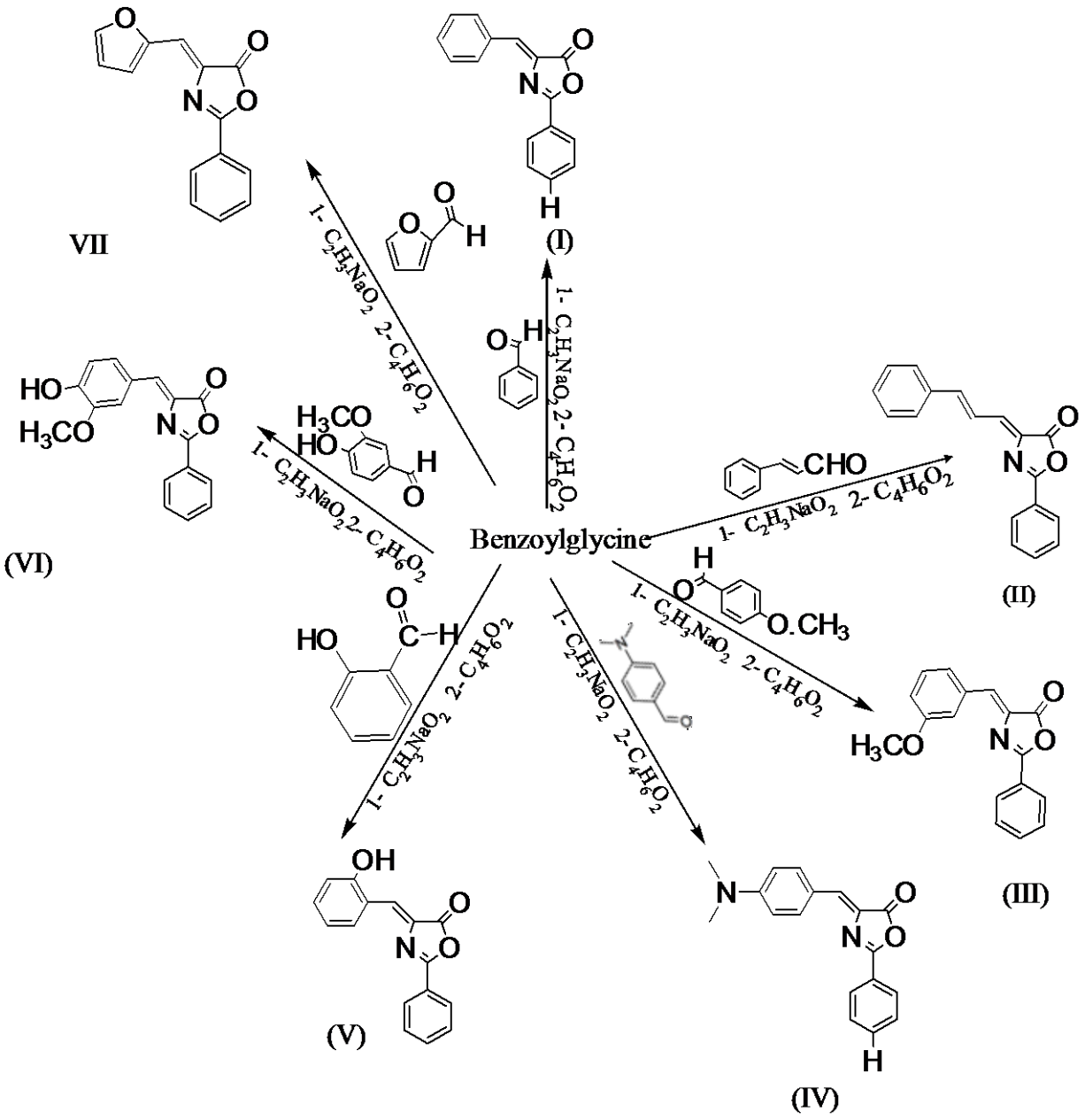
2.2.2. Preparation of oxazolone derivatives I, II, III, IV, V, VI and VII

In round bottom flask 100ml were placed the mixture of aldehyde (0.025 mol), (0.25mol) of benzoylglycine, (0.75mol) of acetic anhydride and (0.25mol) of sodium acetate (equipped with reflux condenser) on a hotplate with vigorous stirring for 1hr then cooled and leaved in a refrigerator overnight, the solid mass of crystal was stirring with 60ml of cold water, filtered and recrytallised with Ethanol.

2.2.3. Preparation of imidazole derivativesVIII, IX, X, XI, XII, XIII, XIV, XV and XVI

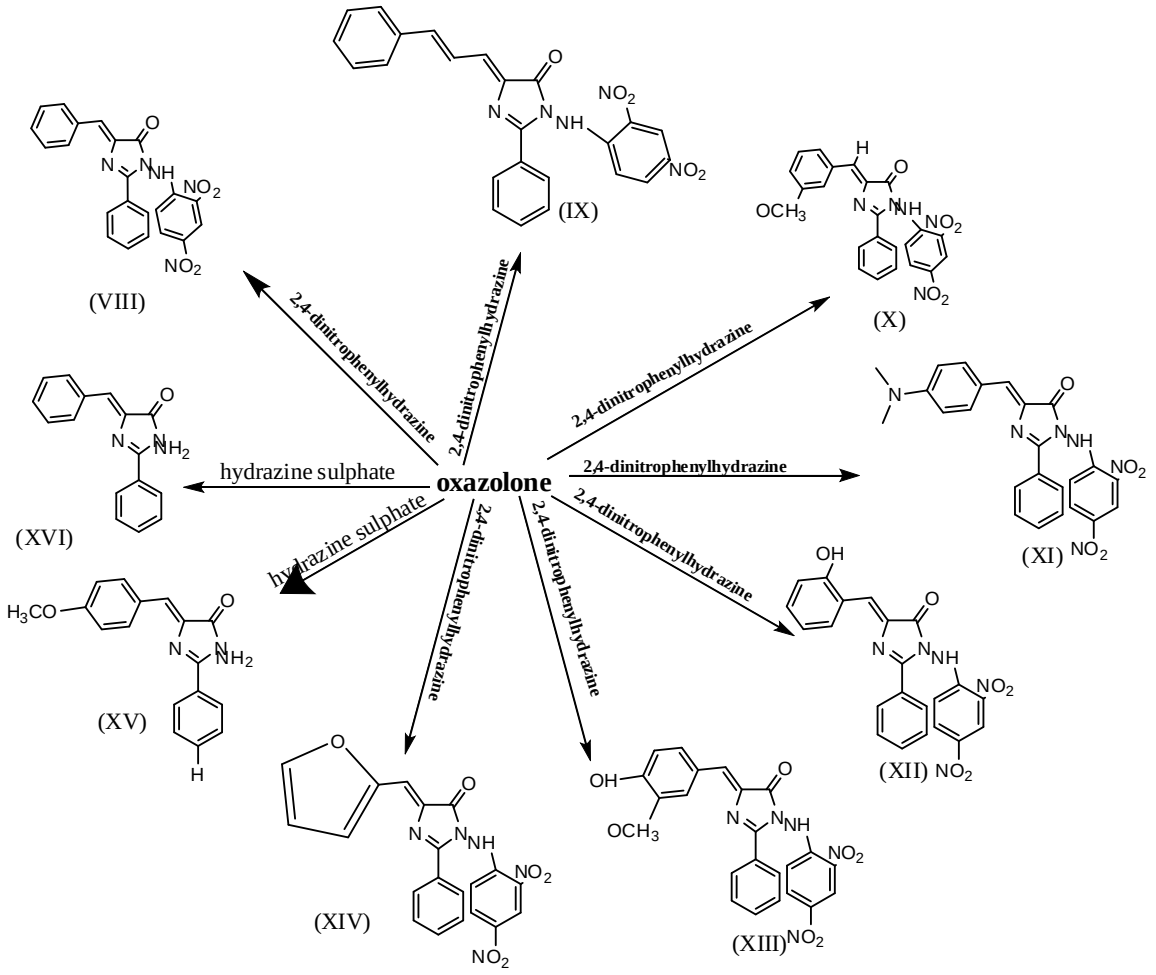
In round bottom flask 100ml were placed mixture of oxazolone derivatives, 2, 4 -dinitrophenyl hydrazine (0.015 mol) and (I, III) oxazolone derivatives with hydrazine sulphate (0.01 mol) reflux for 10hrs in present of dry pyridine, after refluxing complete then reaction mass cooled and reaction mixture was poured into ice-cold water containing HCl conc., filtered, wash by distilled water , dried and recrystallized with acetone.

2.3.1. The scheme of oxazolone:



Scheme 2.1.The preparation of oxazolone derivatives

2.3.2. The scheme of imidazole derivatives

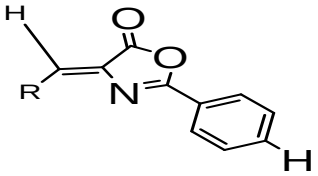


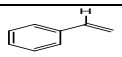
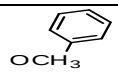
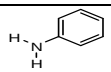
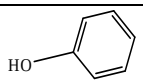
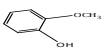
Scheme 2.2. The preparation of imidazole derivatives

2.4. Chemical name of prepared compounds

2.4.1. Chemical name of prepared of oxazolone derivatives

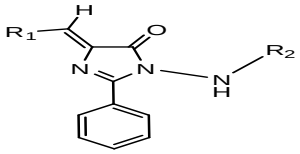
Table (2.1) Chemical name of prepared oxazolone

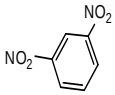
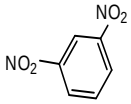
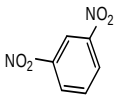
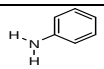
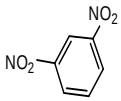
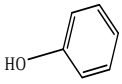
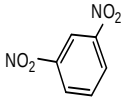
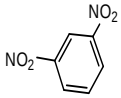
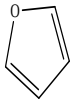
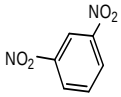
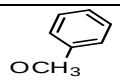


No	R	Chemical name	M.Formula	M.Wt
I		4-benzylidene-2-phenyloxazol-5-one	$C_{16}H_{11}NO_2$	249.26
II		4-phenyl-4-(3-phenylallylidene), oxazol-5-one	$C_{18}H_{13}NO_2$	275
III		4-(3-methoxybenzylidene)-2-phenyloxazol-5-one	$C_{17}H_{13}NO_2$	279
IV		4-(4-dimthylamine)benzylidene)-2-phenyloxazol-5-one	$C_{17}H_{13}N_2O_2$	277
V		4-(2-hydroxybenzylidene)-2-phenyl oxazol-5-one,	$C_{16}H_{11}NO_3$	265
VI		4-(4-hydroxy-3-methoxybenzylidene)-2-phenyloxazol-5-one	$C_{17}H_{13}NO_4$	295
VII		4-(furan-2-ylmethylene)2-phenyloxazol-5-one	$C_{14}H_9NO_3$	239

2.4.2. Chemical name of prepared of imidazole derivatives

Table (2.2) chemical name of prepared imidazole

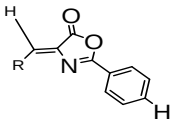


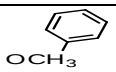
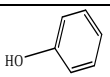
Comp.No	R1	R2	Chemical name	M.Formula	M.Wt
VIII			4-benzylidene-1-(2,4-dinitrophenylamino)-2-phenylimidazole-5-one	$C_{22}H_{15}N_5O_5$	556.29
IX			1-(2,4-dinitrophenylamino)-2-phenyl-4-(3-phenylallylidene) imidazole-5-one	$C_{24}H_{17}N_5O_5$	709.23
X			1-(2,4-dinitrophenylamino)-4-(3-methoxybenzylidene)-2-phenylimidazole-5-one	$C_{23}H_{17}N_5O_6$	840.12
XI			4-(4-dimethylamino)benzylidene)-1-(2,4-dinitrophenylamino)-2-phenylimidazole-5-one	$C_{24}H_{20}N_6O_5$	650.30
XII			1-(2,4-dinitrophenylamino)-4-(2-hydroxybenzylidene)-2-phenylimidazole-5-one	$C_{22}H_{15}N_5O_6$	496.33
XIII			1-(2,4-dinitrophenylamino)-4-(hydroxyl-3-methoxybenzylidene)-2-phenyl-5-one	$C_{23}H_{17}N_5O_7$	653.26
XIV			1-(2,4-dinitrophenylamino)-4-(furan-2-ylmethylene)-2-phenyl imidazole-5-one	$C_{20}H_{13}N_5O_6$	724.10
XV			1-amino-4-benzylidene-2-phenylimidazole-5-one	$C_{17}H_{15}N_3O_2$	293.32
XVI			1-amino-4-(4-methoxybenzylidene)-2-phenylimidazole-5-one	$C_{16}H_{13}N_3O$	263.29

2.5. Reaction condition

2.5.1. Reaction conditions of prepared oxazolone derivatives

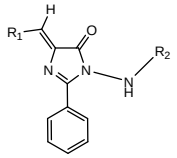
Table (2.3) Reaction conditions of prepared oxazolone derivatives

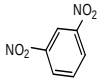
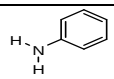
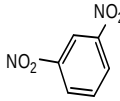
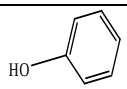
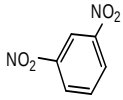
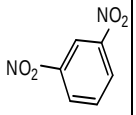
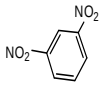
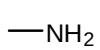


Comp. No	R	Mol ratio	React.Temp./ ċ	Recryst.solvent	m.p/ċ
I		Benzoylglycine: aldehyde (I) [0.25 :0.75]	80 – 100	Ethanol	160-161
II		Benzoylglycine: aldehyde (II) [0.25 :0.75]	80 – 100	Ethanol	148 – 149
III		Benzoylglycine: aldehyde (III) [0.25 :0.75]	80 – 100	Ethanol	158 -159
IV		Benzoylglycine: aldehyde (IV) [0.25 :0.75]	80 – 100	Ethanol	90 -91
V		Benzoylglycine: aldehyde (V) [0.25 :0.75]	80 – 100	Ethanol	177-178
VI		Benzoylglycine: aldehyde (VI) [0.25 :0.75]	80 – 100	Ethanol	134 -135
VII		Benzoylglycine: aldehyde (VII) [0.25 :0.75]	80 – 100	Ethanol	166 -167

2.5.2. Reaction conditions of prepared imidazole derivatives

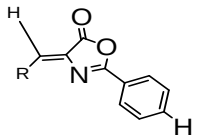
Table (2.4) Reaction condition of prepared imidazole

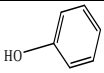
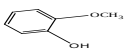


Comp. No	R1	R2	Mol ratio	React. Temp /c	Recryst. solvent	Precent .yield %	m.p/ċ
VIII			Oxazolone(I) : dinitro [0.01:0.015]	60 -80	Acetone	30.98	180 -181
IX			Oxazolone(II) : dinitro [0.01:0.015]	60 -80	Acetone	62	191 -192
X			Oxazolone(III) : dinitro [0.01:0.015]	60 -80	Acetone	50.29	193-194
XI			Oxazolone(IV) : dinitro [0.01:0.015]	60 -80	Acetone	43.29	219 -220
XII			Oxazolone(V) : dinitro [0.01:0.015]	60 -80	Acetone	40	157 -158
XIII			Oxazolone(VI) : dinitro [0.01:0.015]	60 -80	Acetone	90.19	218 -219
XIV			Oxazolone(VII) : dinitro [0.01:0.015]	60 -80	Acetone	94.59	129 -130
XV			Oxazolone(III) : hydrazine sulphate [0.01:0.015]	60 -80	Acetone	35.88	173 -174
XVI			Oxazolone(I) : hydrazine sulphate [0.01:0.015]	60 -80	Acetone	87.99	198 -199

2.5. R_F-Value of prepared Oxazolone derivatives

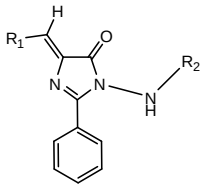
Table 2.5 R_F-Value of prepared Oxazolone derivatives

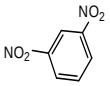
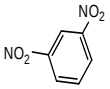
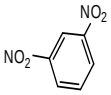
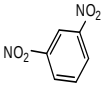
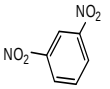
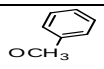


Comp.No	R	Mobile phase (Hexane :Ethyl acetate) 08:02
I		0.78
II		0.77
III		0.75
IV		0.62
V		0.66
VI		0.54
VII		0.56

2.6. R_f –Values of prepared Imidazole derivatives

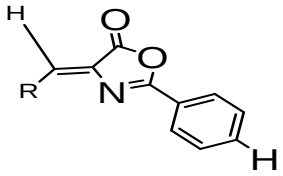
Table 2.6 R_F-Value of prepared Imidazole



Comp.No	R1	R2	Mobile phase (Hexane :Ethyl acetate) 08:02
VIII			0.76
IX			0.71
X			0.68
XI			0.75
XII			0.50
XIII			0.56
XIV			0.55
XV			0.52
XVI			0.70

2.7. IR Results of Oxazolone derivatives

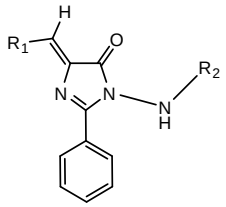
Table 2.7 IR Result of Oxazolone derivatives



Comp.No	C=O cm^{1} st.v.b1740-1690	-C=N cm^{-1} st.v.b1640-1690	-C= C cm^{-1} st.v.b1680-1620	O-H St, H bonding3550- 3200
I	1770	1550	1520	-
II	1760	1580	1530	-
III	1730	1600	1510	-
IV	1595	1525	1500	-
V	1725	1520	1503	-
VI	1700	1560	1510	3350
VII	1770	1630	1520	-

2.8. IR Results of imidazole derivatives

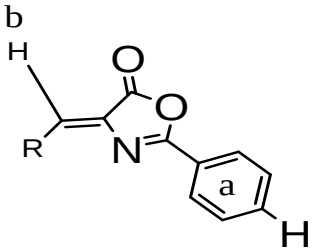
Table 2.8 IR Result of Imidazole derivatives

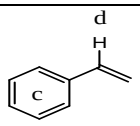
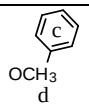
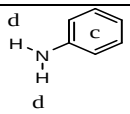
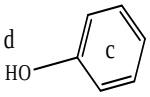
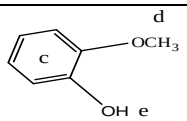
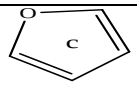


Comp.No	C=O cm^{1} st.v.b1740-1690	-C=N cm^{-1} st.v.b 1640-1690	-C= C cm^{-1} st.v.b1680-1620	N-H St.v.b3500-3300
VIII	1616.24	1589.23	1419.51	3286.48
IX	1647.10	1618.17	1488.94	3319.26
X	1793.68	1652.88	1508.23	3228.62
XI	1789.82	1770.53	1508.23	3253.69
XI	1616.24	1602.74	1508.23	3319.26
XIII	1622.02	1558.38[1]	1515.94	3400.50
XIV	1652.88	1616.24	1488.94 [1]	3325.05
XV	1602.74	1558.38	1413.72	3276.83
XVI	1716.53	1701.10	1668,31	3566.14

2.9. [1]HNMR Spectrophotometer data of prepared Oxazolone derivatives

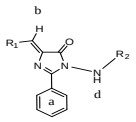
Table 2.9. H[1]NMR Spectrophotometer data of prepared Oxazolone derivatives

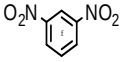
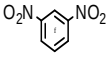
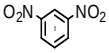
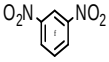


Comp No	R	Chemical shift ppm (intensity, multiplicity, J const)				
		A	B	C	D	E
I		7.63-8.32(5, m)	7.36(1, s)	7.63-8.32(5, m)	-	-
II		7.40-7.95(5, m)	7.51(1, s)	7.40-7.95(5, m)	7.28(1, s)	-
III		7.10-7.59(5, m)	7.61(1, s)	7.10-7.59(5, m)	3.86(3, s)	-
IV		6.77-7.70(5, m)	7.61(1, s)	6.77-7.70(4, dd)	3.07(2, s)	-
V		7.52-7.91(5, m)	8.01(1, s)	7.52-7.91(4, m)	3.84(1, s)	-
VI		7.49-7.96(5, m)	7.59(1, s)	8.13-9.65(3, m)	3.35(3, s)	4.88(1, s)
VII		7.56-7.72(5, m)	7.60(1, s)	6.85-7.72(3, m)	-	-

2.10. [1]HNMR Spectrophotometer data of prepared Imidazole derivatives

Table2.10H[1]NMRSpectrophotometer data of prepared Imidazole



Comp No.	R1	R2	Chemical shift ppm (intensity, multiplicity, J const)					
			a	b	C	D	E	F
VIII			7.63-8.32 (5, m)	7.36 (1, s)	7.54-7.85 (5, m)	4.18 (1, s)	-	8.7-10.16 (3, m)
IX			7.53-7.83 (5, m)	7.34 (1,s)	7.357.60 (5, m)	3.82 (1,s)	-	8.85-10.80 (3, m)
X			7.28-7.88 (5, m)	7.55 (1, s)	7.10-7.88 (5, m)	4.02 (1, s)	-	8.90-10.17 (3, m)
XI			6.77-7.68 (5, m)	7.55 (1, s)	7.57-7.94 (5, m)	3.07 (2, s)	-	8.4-8.86 (3,m)
XII			6.99-7.50 (5, m)	7.92 (1, s)	7.95-8.28 (4, m)	4.06 (1, s)	11.21 (1.s)	8.289.10 (3,m)
XIII			6.96-7.24 (5, m)	7.92 (1, s)	7.95-8.28 (3, m)	4.04 (3, s)	-	8.258.28 (3,m)
XIV			6.96-7.24 (5, m)	7.54 (1, s)	7.93-8.26 (3, m)	-	-	8.268.28 (3,m)
XV			6.79-7.61 (5, m)	7.51 (1, s)	7.52-8.00 (4, m)	5.11 (2, s)	-	-
XVI			7.33-7.60 (5, m)	7.52 (1, s)	7.53-7.82 (5, m)	-	-	-

Chapter three

Results and Discussion

3.1. Back ground

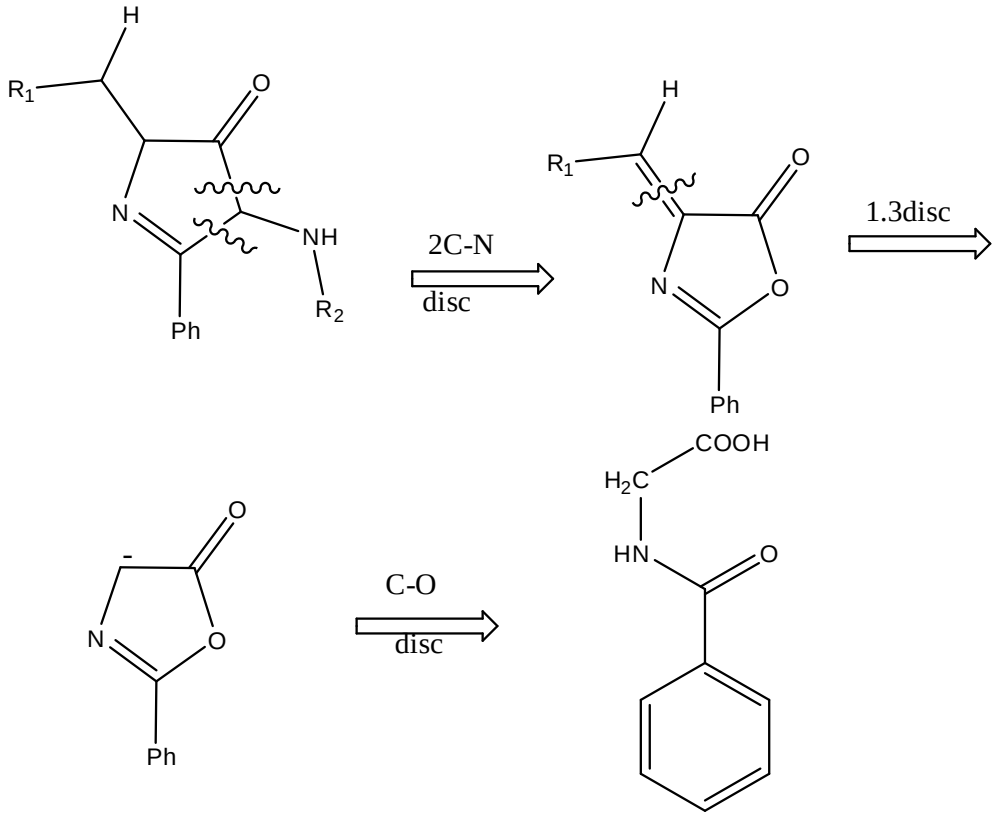
A five-membered imidazole ring is a structural unit found in many biologically active compounds. The strong therapeutic properties of imidazole containing drugs have encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents comprising this entity. Amongst others, imidazole core care structures are found in different carboxypeptidase, hemeoxygenase and lactamase inhibitors, as well as among anti-inflammatory, anticancer, antibacterial, antifungal, antitubercular, antidiabetic and antiviral products(Saudi et al., 2014). The Imidazole compounds exhibited different cytostatic and cytotoxic activities for further developing potential application as anticancer drugs (Chen et al., 2013; Hossain et al., 2013). The compounds of benzofuran and imidazole moieties and their potential antitumor activities (Liu et al., 2013; Martins et al., 2015) benzimidazole derivatives exhibited moderate tuberculostatic activity (Gobis et al., 2015). Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents(Bhatnagar et al., 2011). It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, Imidazole is amphoteric; that is, it can function as both an acid and a base (Chawla et al., 2012)The compound is classified as aromatic due to the presence of a sextet of - electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring(Shalini et al., 2010).

The imidazole and its derivatives had many Pharmacological Activities like antitubercular, antifungal, analgesic, anti-HIV, anticancer and antibacterial (Verma et al., 2013).

3.2. Retrosynthetic analysis of Oxazolone and Imidazole derivatives (RSA)

Retrosynthetic analysis (RSA), help in the establishment of good synthetic scheme in (RSA), key steps are developed by examine important structural element in final product and figuring out how to specific reaction could lead to the product. The procedure is performed it relatively so that complex final molecule is reduced to simpler intermediates. The advantage of such an approach is that greatly simplified planning the synthesis of a complex product and readily leads to convergent synthesis(Golan et al., 2008).

In performing (RSA), it may also be useful to disconnection abond showing the fragment not as real compounds but as an only electrophile and nucleophile(sythons). This may help bring to mind other reaction that can be used to reassemble the fragment (Hornback, 2005).



R1 = benzaldehyde, cennamaldehyde,vanillin.2,4-aminobenzaldehyde, salicylaldehyde,anisaldehyde , furfural.
R2 = 2,4-dinitrophenylhydrazine and hydrazine sulphate

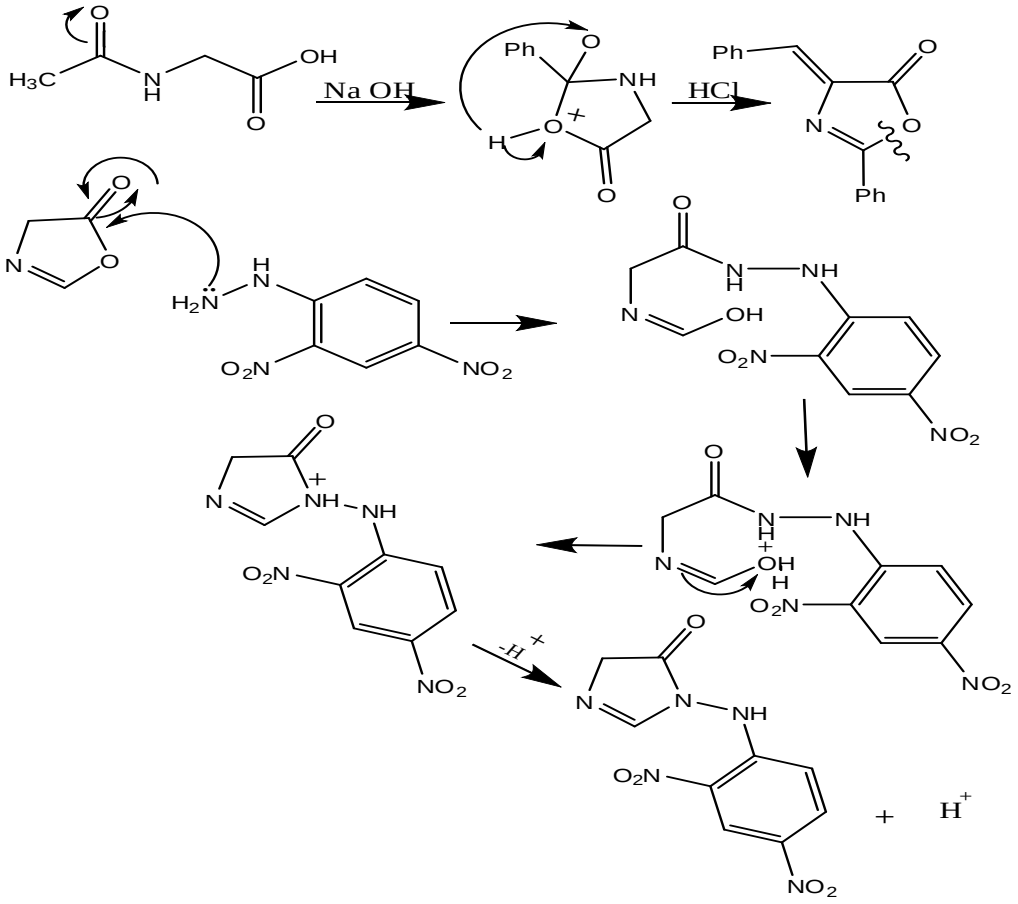
Scheme(1.3.) Retrosynthetic analysis of Oxazolone and Imidazole derivatives(RSA)

3.3. Reaction mechanism of oxazolone and imidazole derivatives

Benzoylchloride can be used to prepare Benzoylglycine by react with glycine in alkali media. Benzoylchloride are very active than glycine and it has a good leaving group chloride, the acyl group is highly polarized and the positive carbon is attacked the nucleophilic amine glycine as anucleophilic pair in amine.

The intermediate is very unstable ion via C-N bond and simultaneously the p-electron pair of the carbonyl bond. The positive centre of carboxylic bond attached to the negative side of carbonyl group then give cyclization.

Finaly the Oxazolone undergo the condensation reaction with hydrazine to give imidazole by the carbonyl group of Oxazolone with amine of hydrazine to give the final product.



Scheme (3.2) Reaction mechanism of oxazolone and imidazole derivatives

3.4.Rf-values

Thin layer chromatography is method for analyzing the purity of the compound and monitoring the reaction progress.

Hexane and Ethyl acetate were used as solvent system, then record Rf- value in table (2.5&2.6).

3.5.1. Spectral data of IR and H^1NMR of Oxazolone derivatives

Infrared spectroscopy is one of the most important tool in structure elucidation it provide an excellent means identification of the different functional groups associated with in molecule. In present work, IR analysis was carried out using FTIR Agilent Cary 630 instrument(USA).The results were tabulated in table (2.7) and the IR spectra of some oxazolone derivatives were show the characteristics peak for oxazolone derivatives were observed for phenyl ring C=O $_{st.vib}$ at (1595- 1770cm^{-1}), C =N $_{st.vib}$ at (1520-1630 cm^{-1})and C=C (1503-1530) $_{st.vib}$ bands

Compound (I) compound showed the appearance of C=O st,vib , C =N st.vib and C=C st.vib bands that confirm correct formation of the product.The appearance of strong absorption at 1770 cm^{-1} and weak absorption at 1550 cm^{-1} .and 1520 cm^{-1} respectively. .

Compound (II) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib bands that confirm correct formation of the product. The appearance of strong absorption at 1760 cm^{-1} and weak absorption at 1580 cm^{-1} and 1530 cm^{-1} respectively.

Compound (III) showed the appearance of C=O st,vib , C =N st.vib and C=C st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1730 cm^{-1} and weak absorption at 1600 cm^{-1} and 1510 cm^{-1} respectively.

Compound(VI) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib bands that confirm correct formation of the product. The appearance of strong absorption at 1595 cm^{-1} and weak absorption at 1525 cm^{-1} and 1500 cm^{-1} respectively.

Compound(V) show the appearance of C=O st,vib, C =N st.vib and C=C st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1725 cm^{-1} and weak absorption at 1520 cm^{-1} and 1503 cm^{-1} respectively.

Compound(VI) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib bands that confirm correct formation of the product.The appearance of strong absorption at 1700 cm^{-1} and weak absorption at 1660 cm^{-1} and 1510 cm^{-1} respectively.

Compound (VII) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1770 cm^{-1} and weak absorption at 1630 cm^{-1} and 1520 cm^{-1} respectively.

Nuclear magnetic resonance (^{1}HNMR) is spectroscopic method that even more important to organic chemist then infrared spectroscopy were IR revel the type of functional group in a molecule, ^{1}HNMR give information about the number of each distant type of nuclei or as obtains information regarding the nature of the immediate environment of each type. The combination of IR and NMR data is often sufficient to determine completely of unknown molecule (Pavia et al., 2001).

H^{1}NMR spectrum data of oxazolone derivatives showed (s, 1) for aliphatic proton at (7.28-8.01ppm), (s, 3) at (3.35 -3.86ppm)and (5, m) for phenyl ring at (7.10 – 8.32ppm).

Compound (I) showed multiplet at 7.63-8.32 ppm (5,m) due to the benzene ring and singlet at 7.36 (1,s).

Compound (II) showed multiplet at 7.40-7.95 ppm (5, m) due to the benzene ring, singlet at 7.51 (1, s) and singlet 7.28 (1, s) .

Compound (III) showed multiplet at 7.10-7.95 ppm (5, m) due to the benzene ring , singlet at 7.61 (1, s) and singlet at 3.86 (3, s).

Compound (IV) showed multiplet at 6.77-7.70 ppm (5,m) due to the benzene ring , singlet at 7.61 (1, s) ,dd at 6.77-7.70 (4, dd) and singlet at 3.07(2, s).

Compound (V) showed multiplet at 7.52-7.91 ppm (5, m) due to the benzene ring , singlet at 8.01 (1, s), multiplet 7.52-7.91 (4, m), and singlet at 3.84(1, s).

Compound (VI) showed multiplet at 7.49 – 7.96ppm (5,m) due to the benzene ring , multiplet at 8.13-9.65(3, m) , singlet at 3.53.(3, s) and singlet at 4.88(1, s).

Compound (VII) showed multiplet at 7.56-7.72 ppm (5, m) due to the benzene ring , singlet at 7.60 (1, s) and multiplet at 6.85-7.72(3, m).

3.5.2. Spectral data of IR and H^1NMR of imidazole derivatives

Infrared spectroscopy is one of the most important tool in structure elucidation it provide an excellent means identification of the different functional groups associated with in molecule. In present work, IR analysis was carried out using FTIR-8400 instrument (Shamazu,Japan) using KBr disc.The results were tabulated in table (2.8) and theIR spectra of some oxazolone derivatives were show the characteristics peak for imidazole derivatives were observed for phenyl ring C=O $_{st.vib}$ at (1602.02- 1793.68cm^{-1}), C =N $_{st.vib}$ at (1558.38-1770.53 cm^{-1}), C=C $_{st.vib}$ (1413.72-1668.31)and N-H (3228.62-3566.14)bands.

Compound (VIII) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1616.24cm^{-1}, weak absorption at1589.23 cm^{-1}, 1419.51 cm^{-1} and 3286.48 cm^{-1}.respectively.

Compound (IX) showed the appearance of C=O st, vib, C =N st.vib and C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1647.10cm^{-1}, weak absorption at 1618.17cm^{-1},1488.94 cm^{-1} and 3319.26 cm^{-1}.respectively.

Compound (X)showed the appearance of C=O st, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1793.68 cm^{-1}, weak absorption at 1652.88 cm^{-1}, 1508.23 cm^{-1} and 3319.26cm^{-1} respectively.

Compound (XI) showed the appearance of C=O st, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1793.68 cm^{-1}, weak absorption at 1652.88cm^{-1}, 1508.23cm^{-1} and 3228.62 cm^{-1} respectively.

Compound (XII) showed the appearance of C=O st, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1789.82 cm^{-1} and weak absorption at 1770.53cm^{-1}, 1508.23cm^{-1} and 3253.69 cm^{-1} respectively.

Compound (XIII)showed the appearance of C=O st, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1616.24 cm^{-1} and weak absorption at 1602.02 cm^{-1},1508.23cm^{-1} and 3319.26 cm^{-1} respectively .

Compound (XIV) showed the appearance of C=O st, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product. The

appearance of strong absorption at 1622.02 cm^{-1}, weak absorption at 1558.38 cm^{-1}, 1515.94 cm^{-1} and 3325.05 cm^{-1} respectively.

Compound (XV) showed the appearance of C=O st, vib, C =N st.vib C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1602.74 cm^{-1}, weak absorption at 1558.38 cm^{-1}, 1413.72cm^{-1} and 3276.83 cm^{-1} respectively.

Compound (XVI) showed the appearance of C=Ost, vib, C =N st.vib, C=C st.vib and N-H st.vib bands that confirm correct formation of the product.

The appearance of strong absorption at 1716.53 cm^{-1}, weak absorption at 1701.10 cm^{-1}, 1668.31 cm^{-1} and 3566.14cm^{-1} respectively.

^{1}HNMR spectrum data of imidazole derivatives showed (s, 1) for aliphatic proton at (7.33-7.92ppm), (m,3) at (7.87 -10.80ppm)and (5,m) for phenyl ring at (6.77 – 7.88ppm)

Compound (VIII) showed multiplet at 7.63-8.32ppm (5, m) due to the benzene ring, singlet at 7.36 (1, s) , multiplet at 7.54- 7.85(5, m), singlet 4.18(1, s)and multiplet at 7.87-10.16(3, m) .

Compound (IX) showed multiplet at 7.53-7.83 ppm (5, m) due to the benzene ring, singlet at 7.34 (1, s), multiplet at 7.35-7.60(5, m), singlet at 3.82(1, s) and multiplet at 8.85-10.80(3, m) .

Compound (X) showed multiplet at 7.28-7.88 ppm (5, m) due to the benzene ring, singlet at 7.55 (1, s), multiplet at 7.10-7.88(5, m) , singlet at 4.02(1,s) and multiplet at 8.90-10.17(3, m)

Compound (XI) showed multiplet at 6.77-7.68 ppm (5, m) due to the benzene ring, singlet at 7.55 (1, s), multiplet at 7.57-7.94(5, m), singlet at 3.07(2, s) and multiplet at 8.40-8.86 (3, m).

Compound (XII) showed multiplet at 6.99-7.50 ppm (5, m) due to the benzene ring, singlet at 7.92 (1, s), multiplet at 7.95-8.28 (4,m), singlet at 4.06(1, s), singlet at 11.21(1, s) and multiplet at 8.28-9.10 (3, m).

Compound (XIII) showed multiplet at 6.96-7.24 ppm (5, m) due to the benzene ring, singlet at 7.92 (1, s), multiplet at 7.95-28(3,m), singlet at 4.04(3, s) and multiplet at 8.25-8.28 (3, m).

Compound (XIV) showed multiplet at 6.96-7.24 ppm (5, m) due to the benzene ring, singlet at 7.54(1, s), multiplet at 7.93-8.26(3, m) and multiplet at 8.26-8.28 (3,m).

Compound (XV) showed multiplet at 6.79-7.61 ppm (5, m) due to the benzene ring, singlet at 7.51(1, s), multiplet at 7.52-8.00(4, m), singlet at 5.11 (2, m).

Compound (XVI) showed multiplet at 7.33-7.60 ppm (5, m) due to the benzene ring, singlet at 7.52(1, s)and multiplet at 7.53-7.82(5,m).

3.6. Conclusion and Recommendation

- The synthesis in this research followed three steps reaction.

- Of the compounds synthesized in this work four of them are new and has been synthesized for the first time.

- The biological activities of these compounds specially the new one should be done to evaluate their medicinal uses(use cancer cell line).

- The microwave synthesis can be used to synthesized these compounds and similar one sine it is friendly environment methods.

- The characterization of these synthesized compounds should be confirm by 2DNMR and High Resolution Mass Spectrometry (HR-MS) in order to complete the spectral data.

Chapter Four

References

4. References

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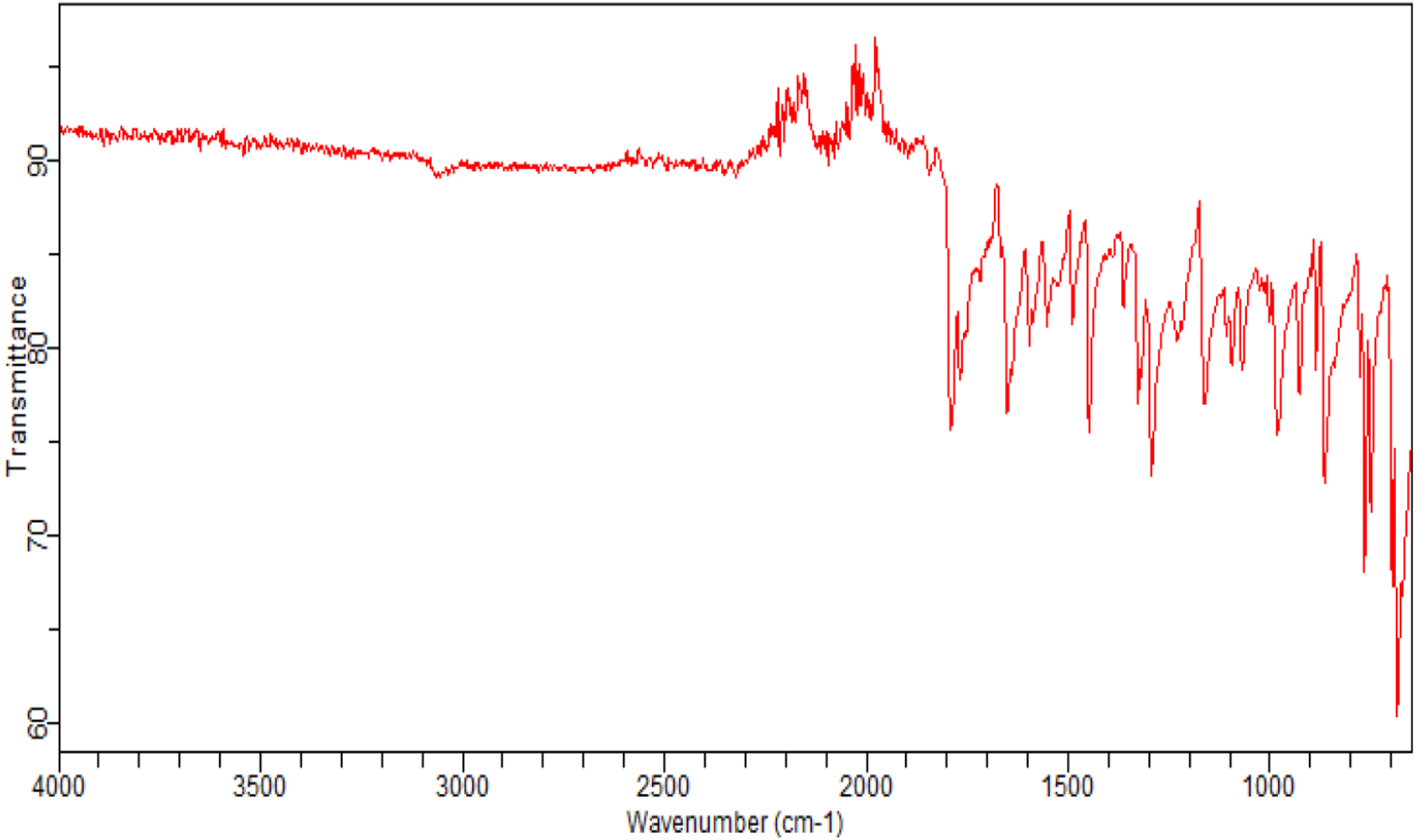

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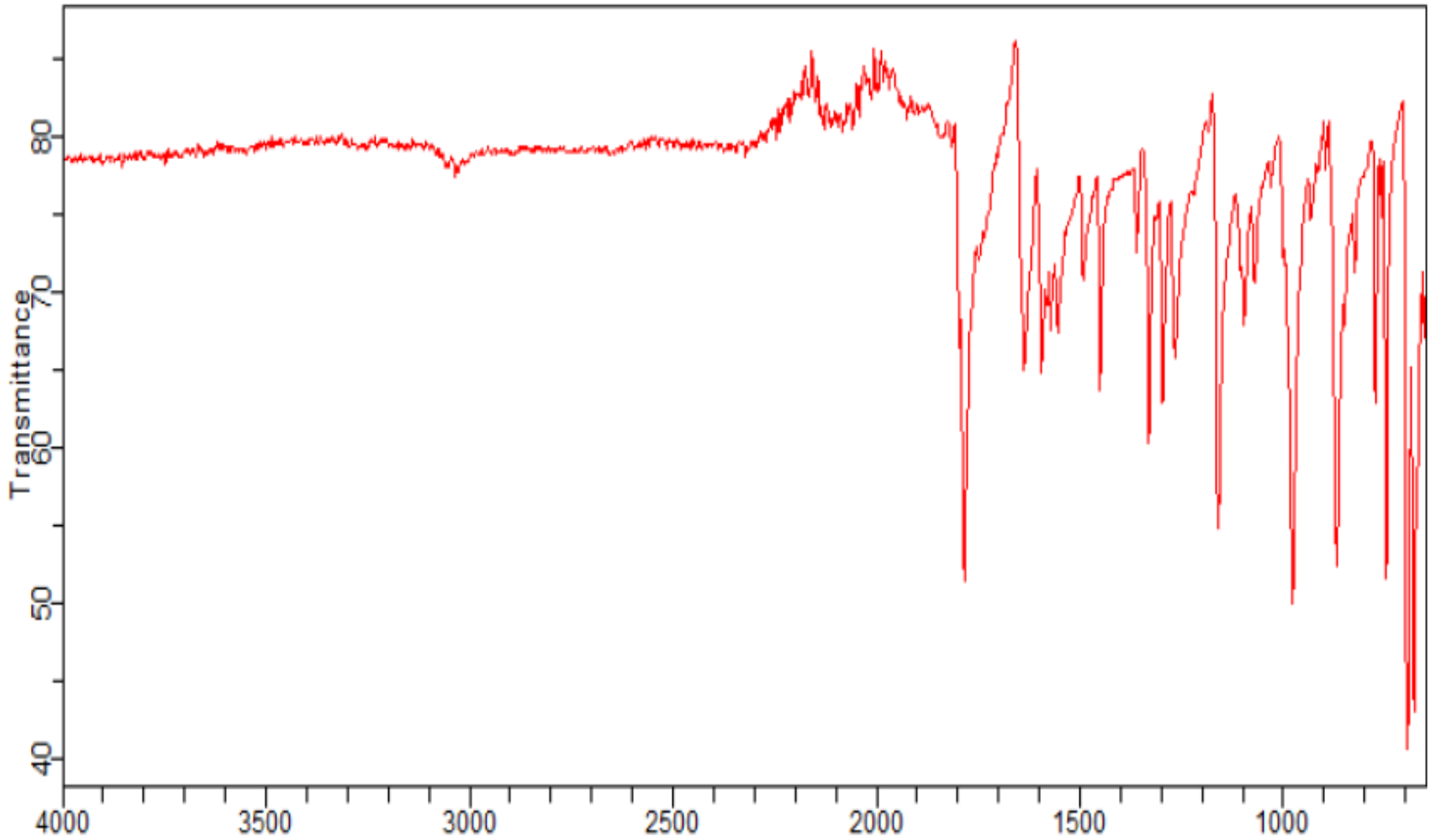

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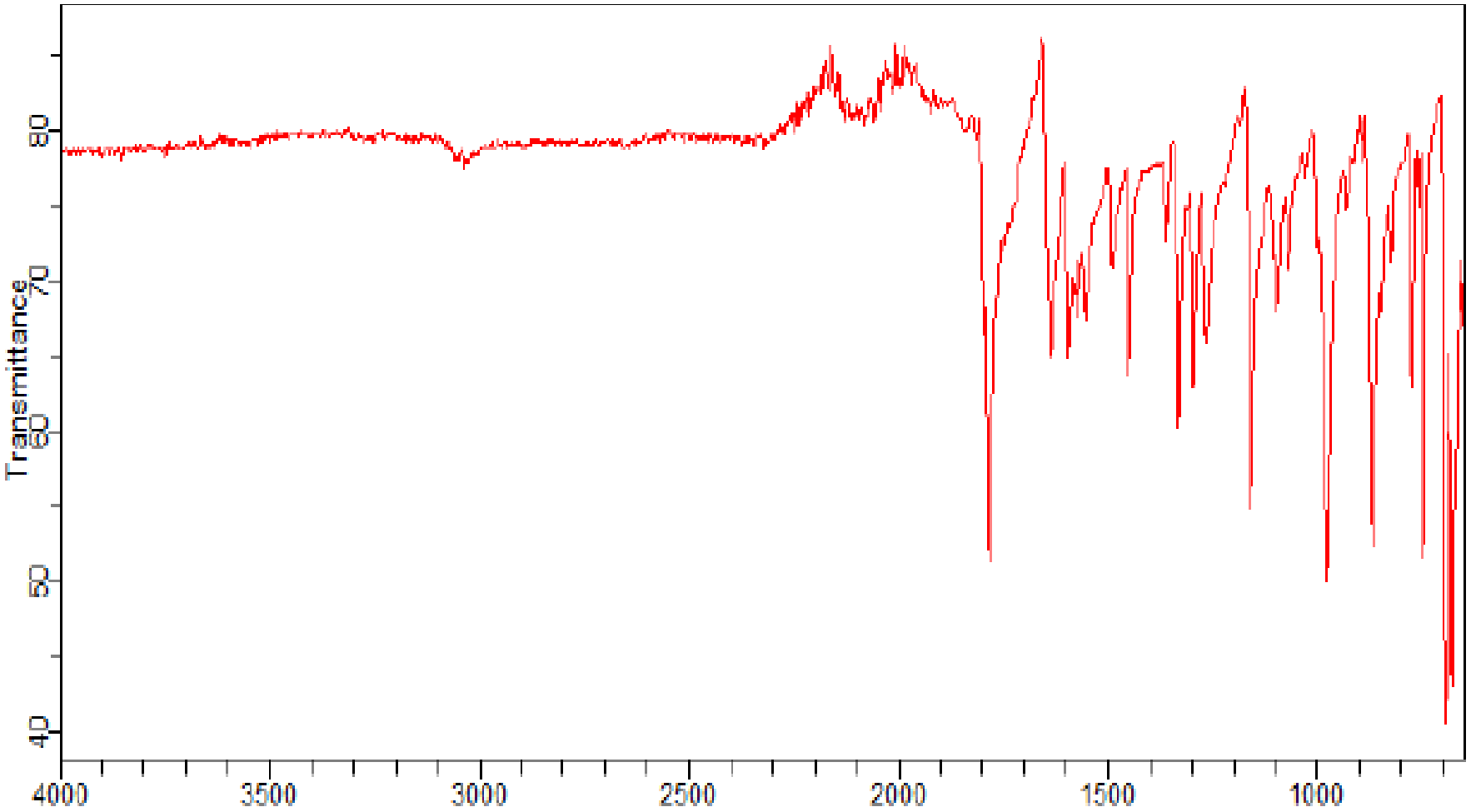

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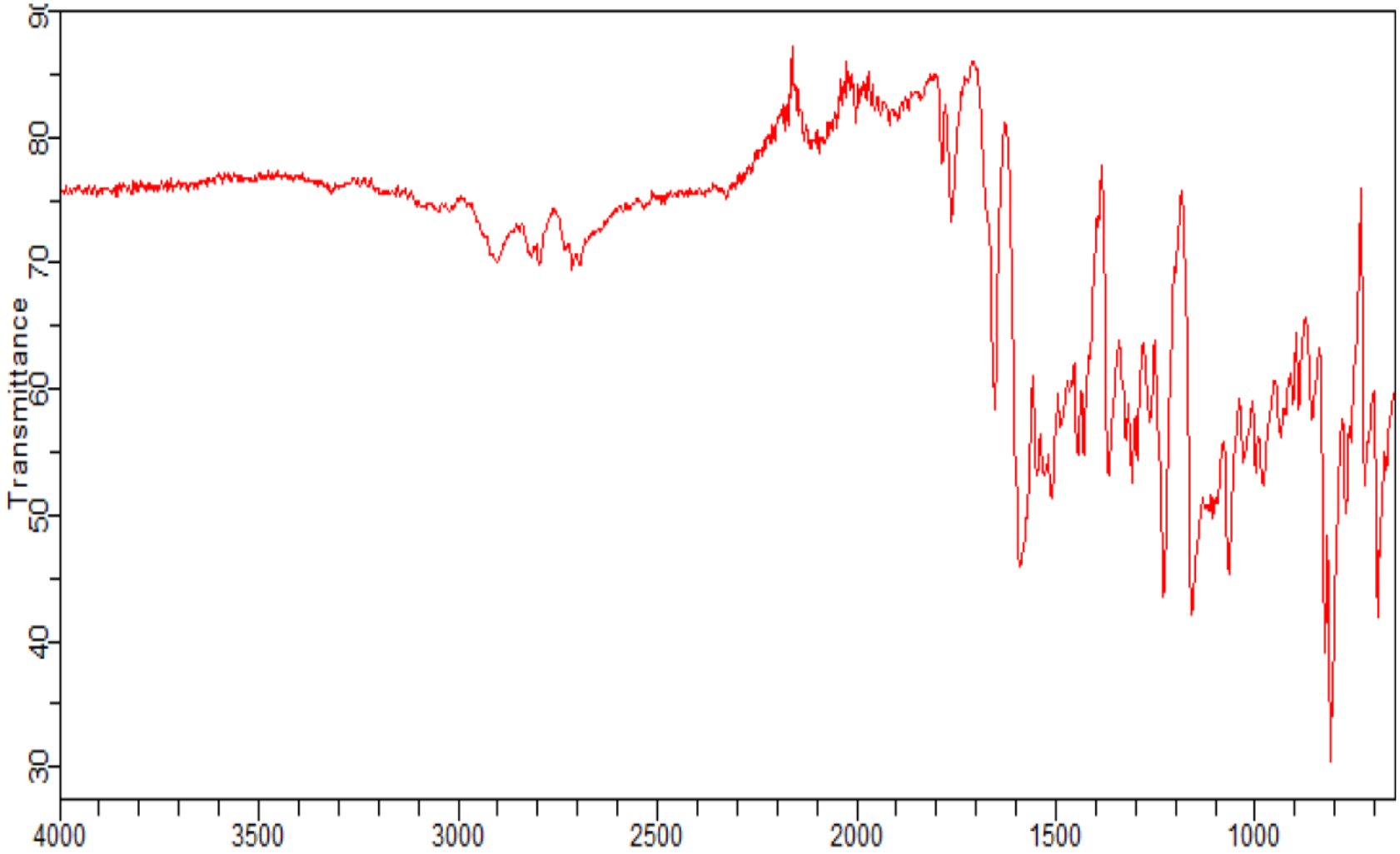

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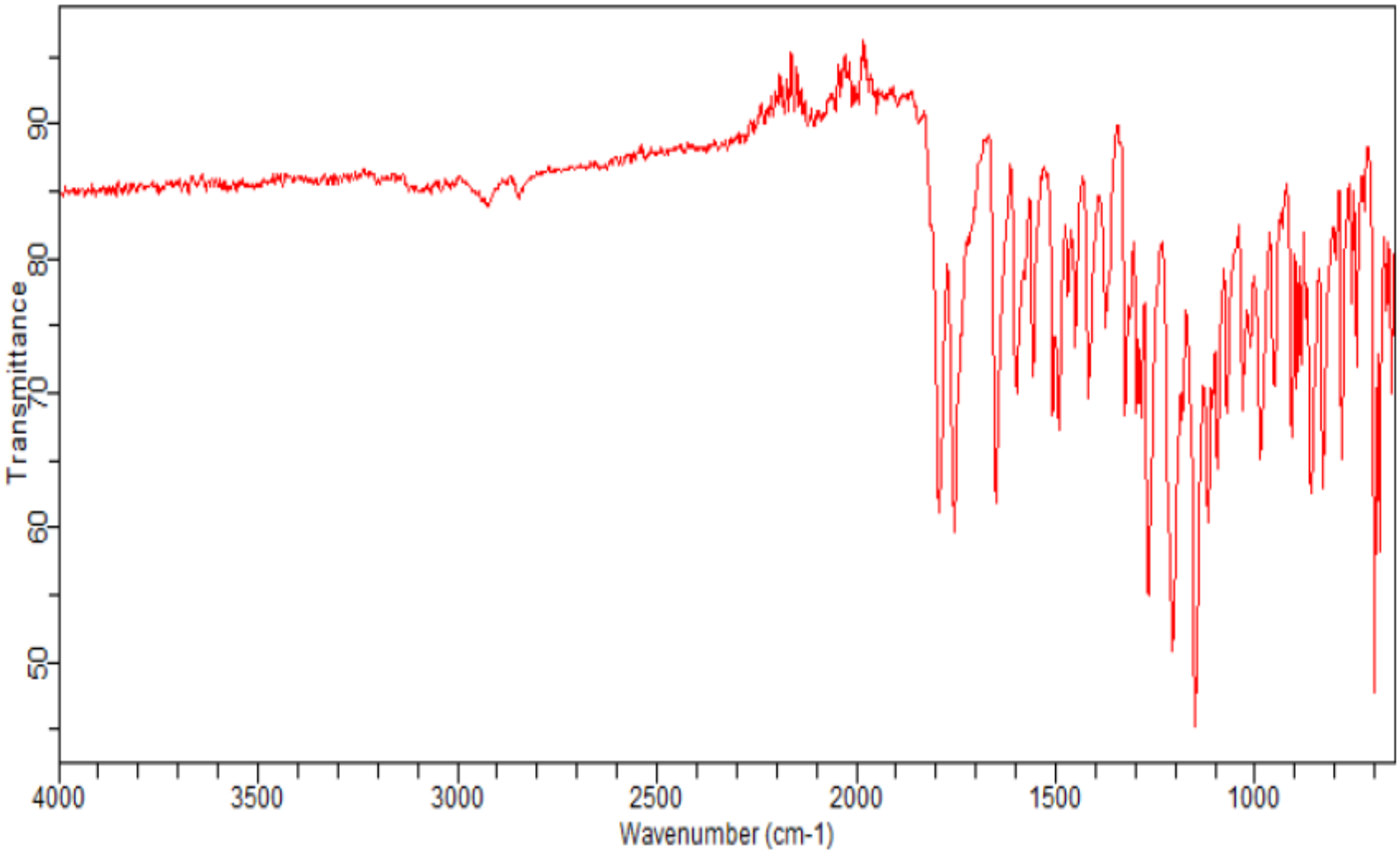

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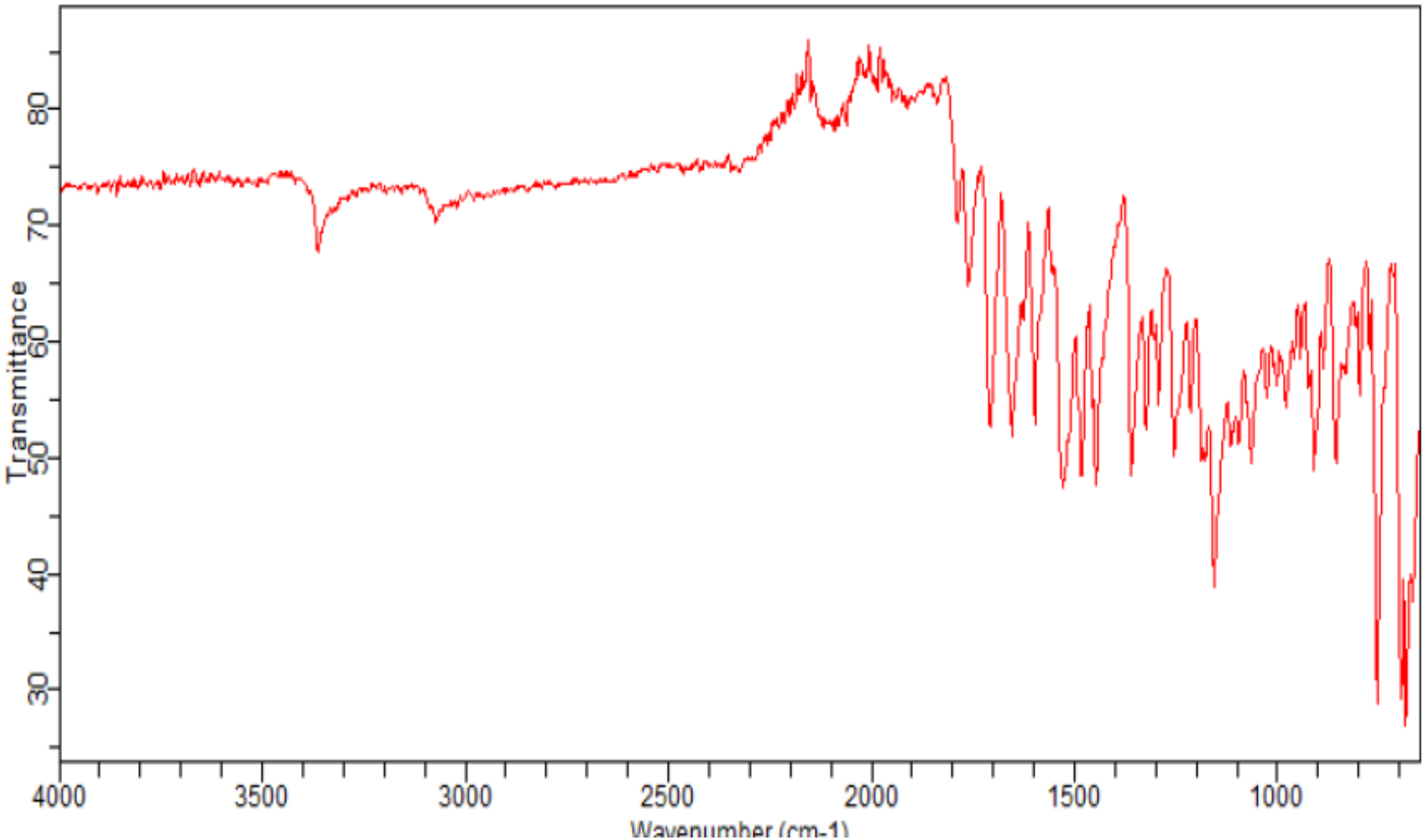

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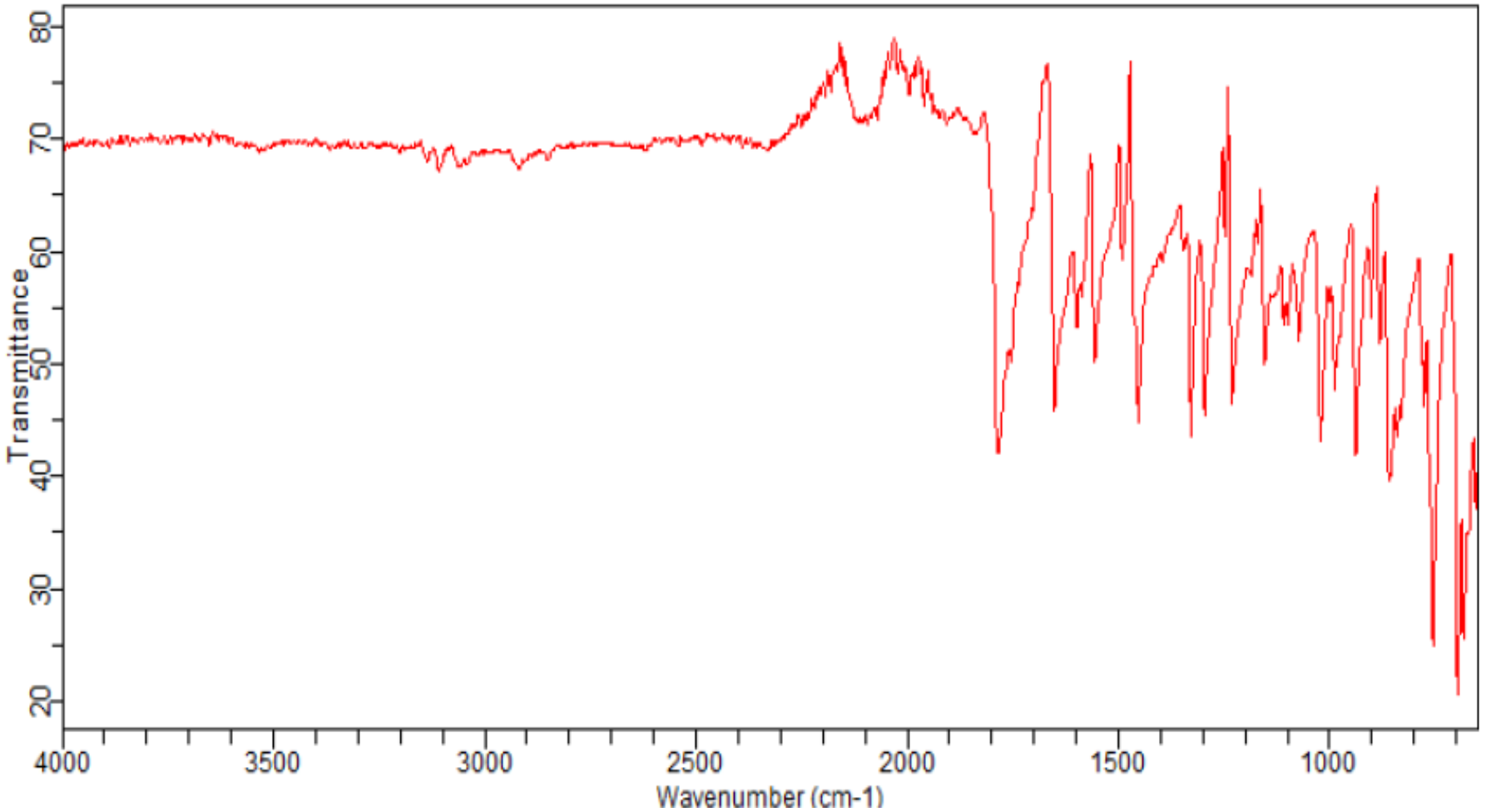

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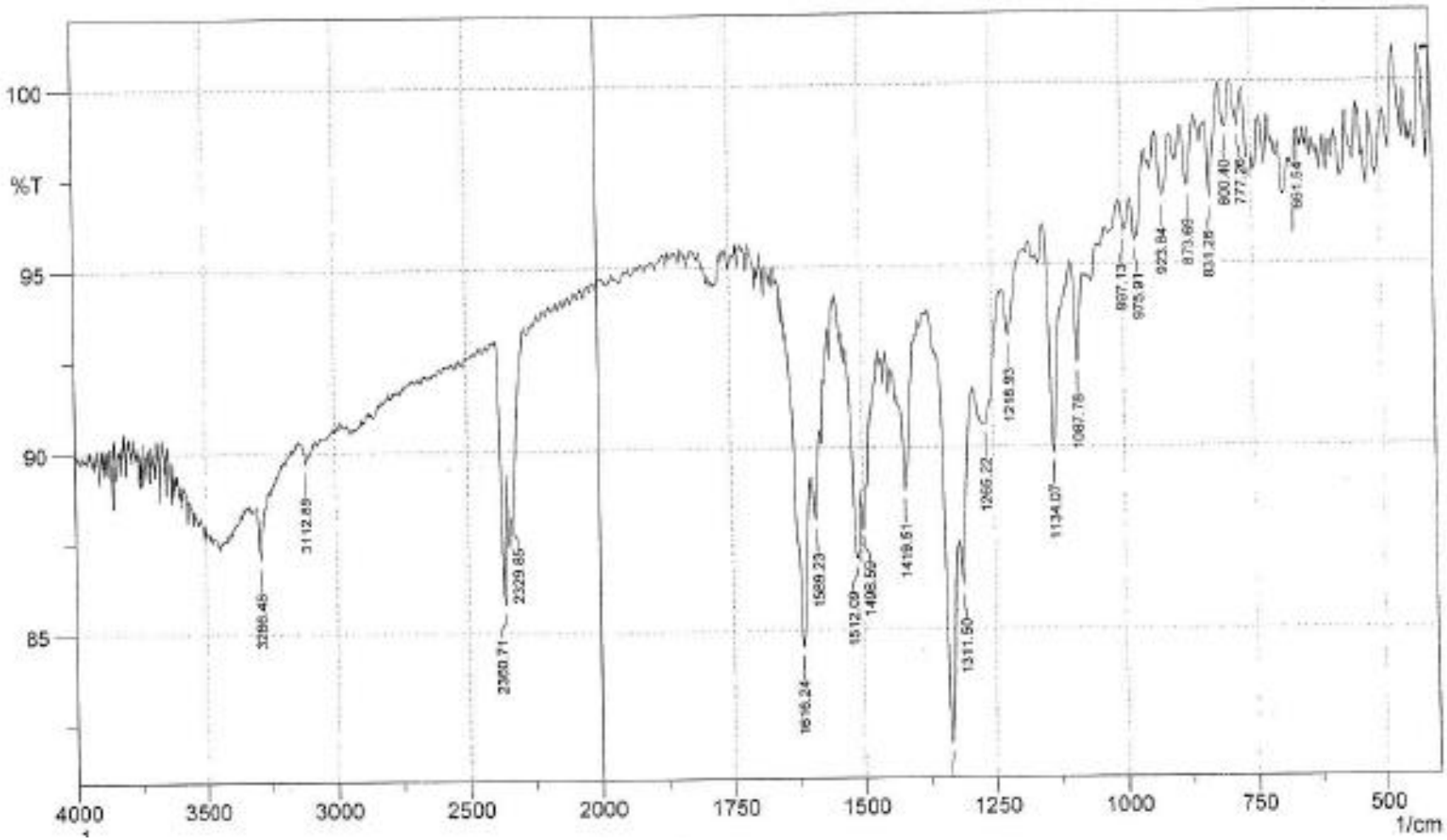

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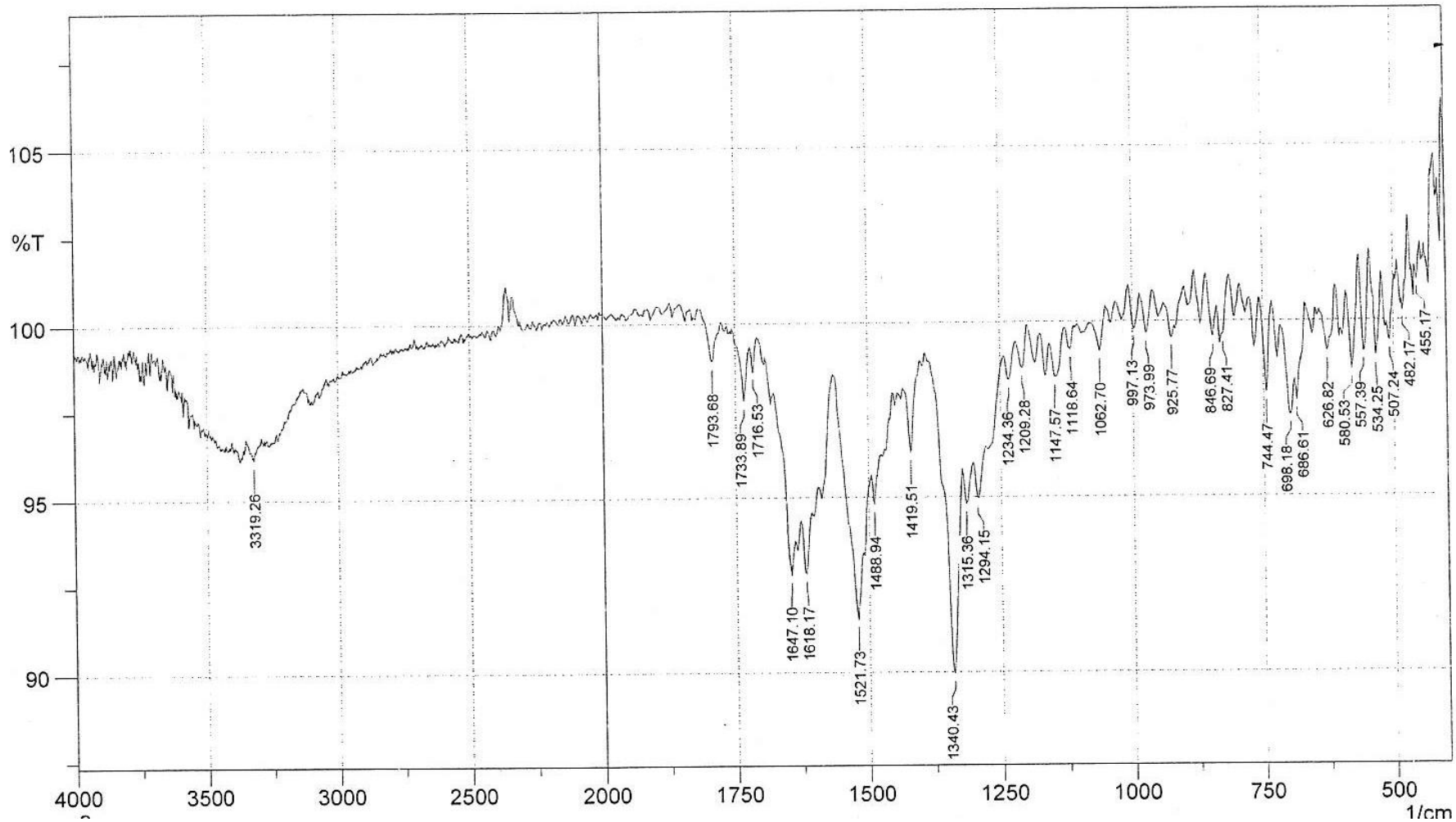

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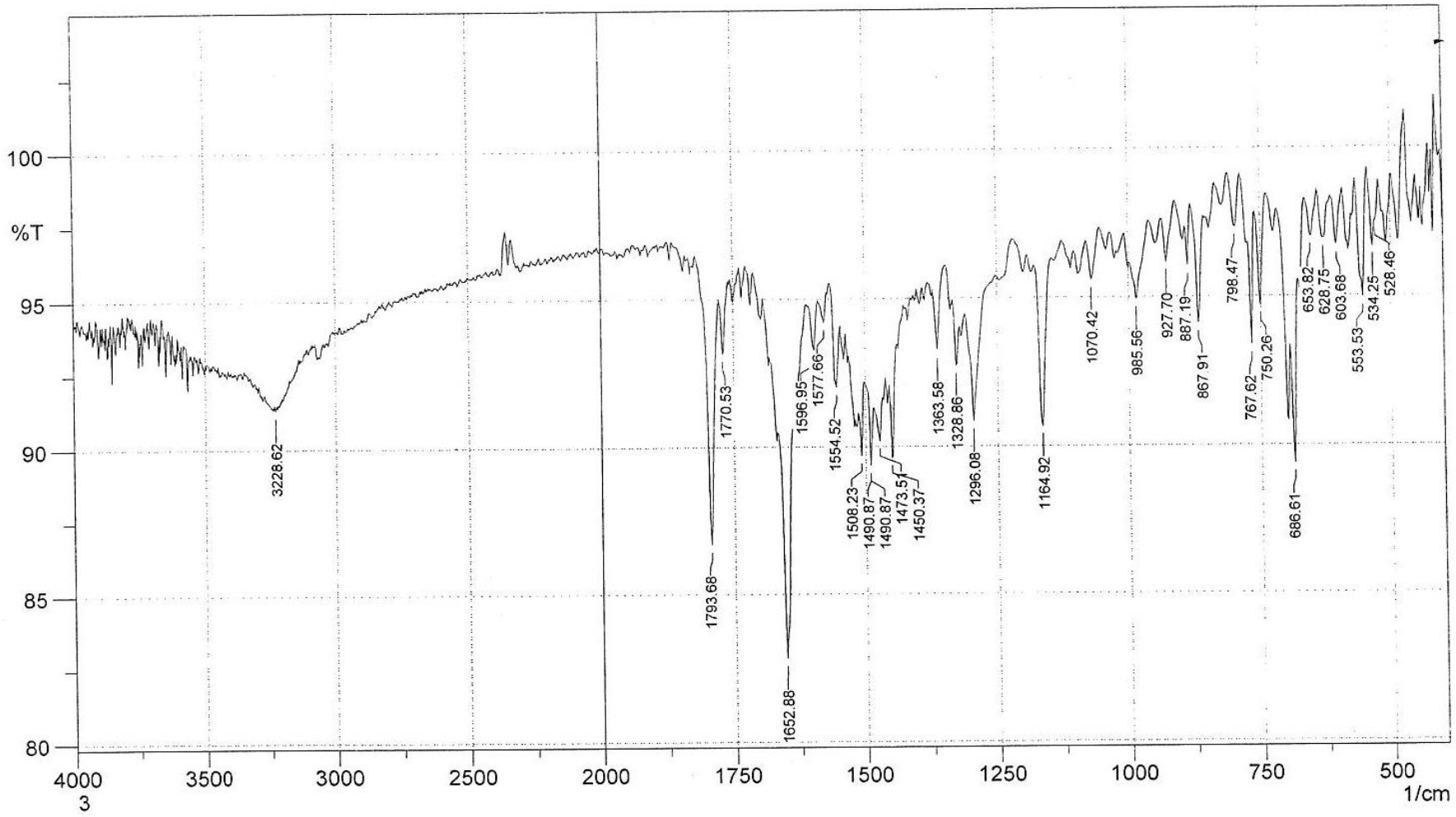
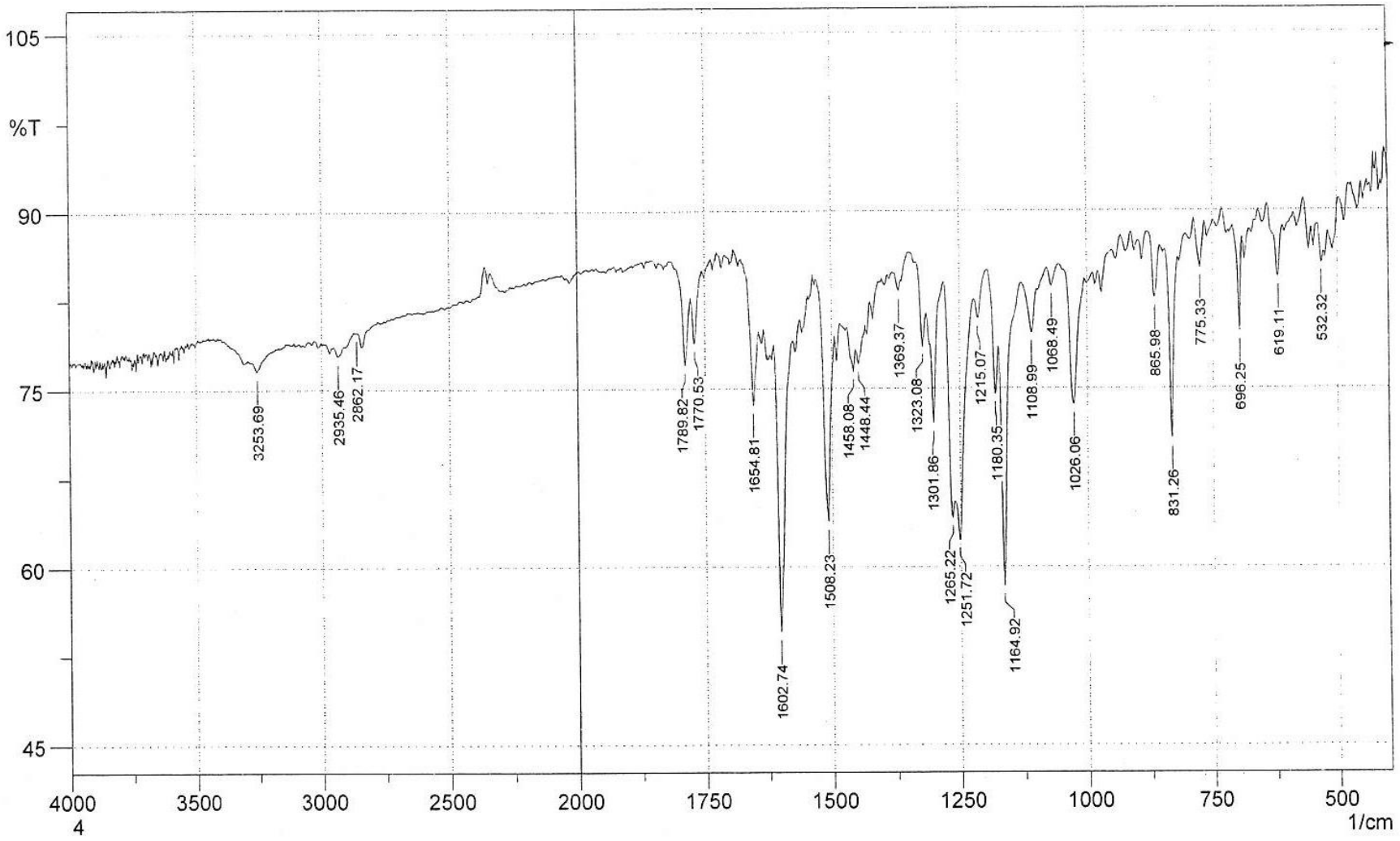
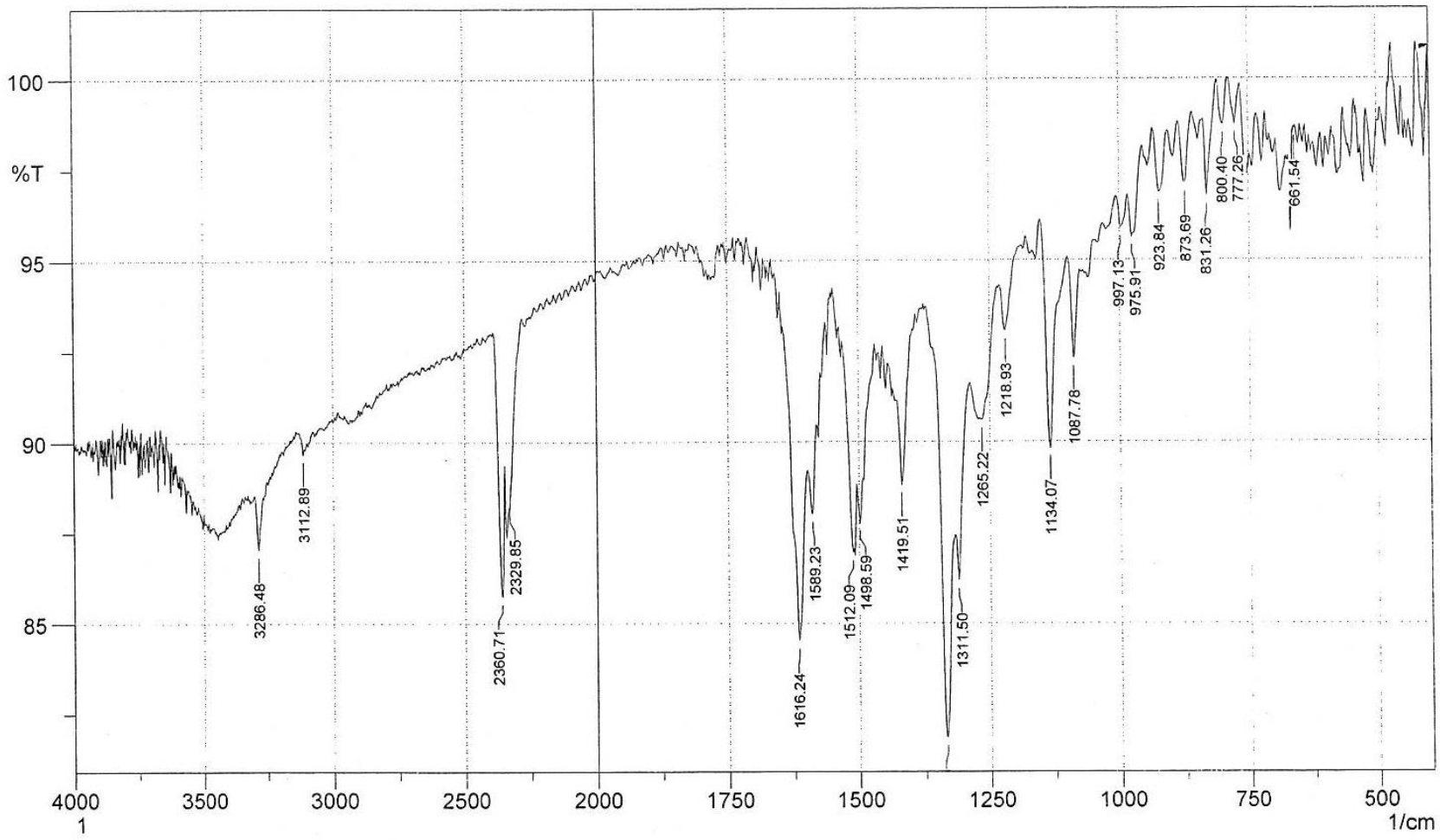


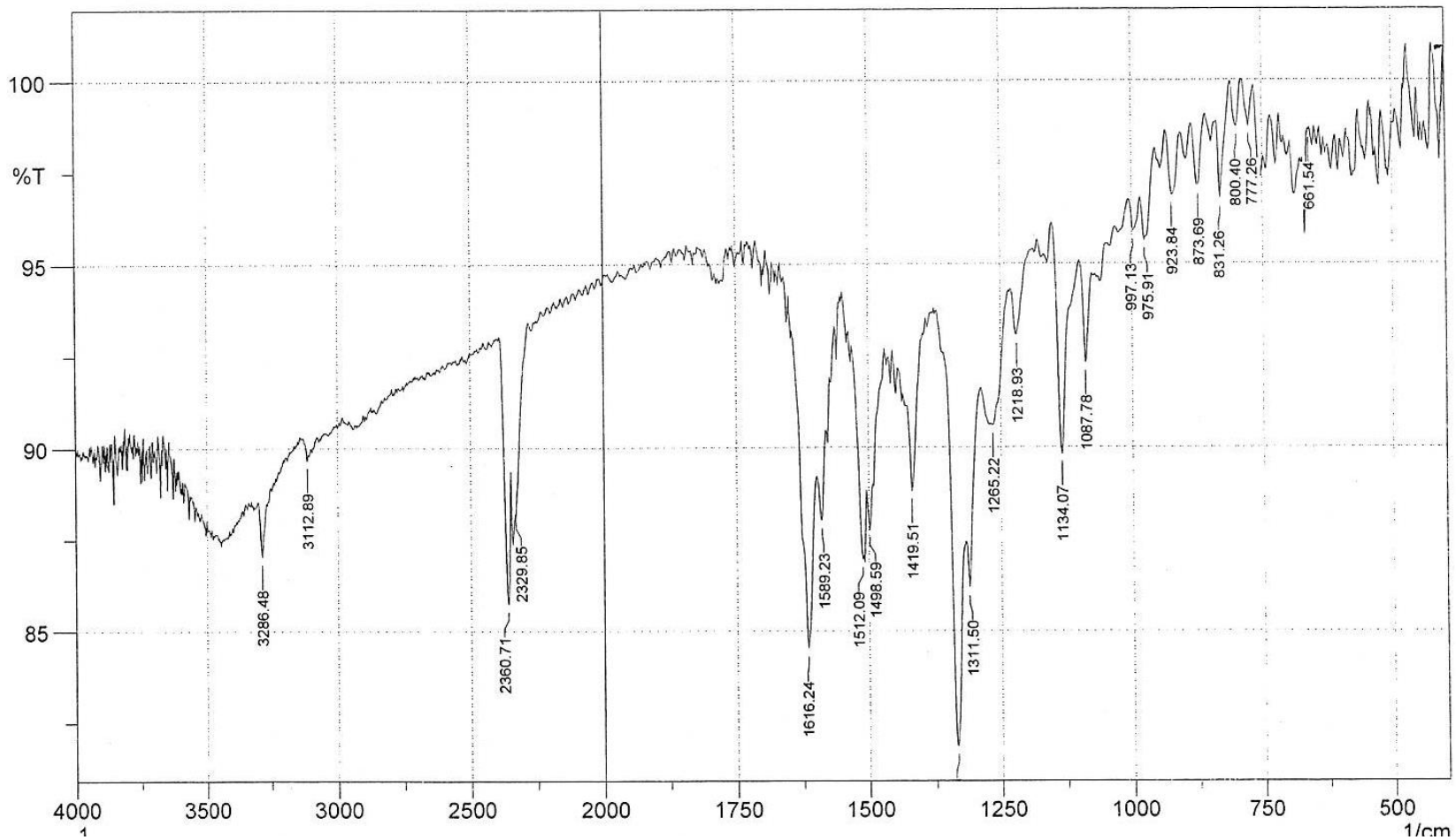
Index (10) 1-(2, 4-dinitrophenylamino)-4-(3-methoxybenzylidene)-2-phenylimidazole-5-one



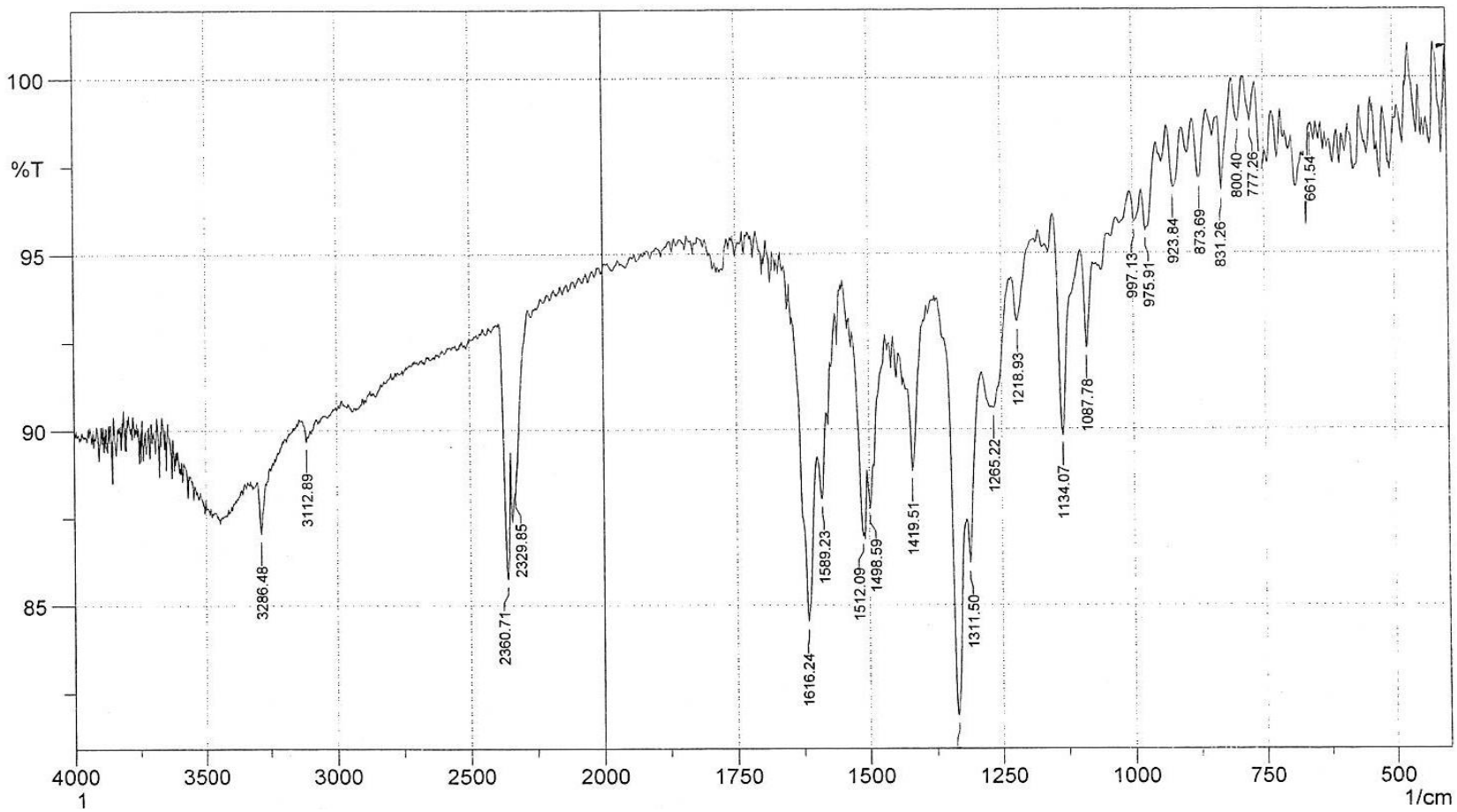
Index (11) 4-(4-dimethylamino) benzylidene)-1-(2, 4-dinitrophenylamino)-2-phenylimidazole-5-one



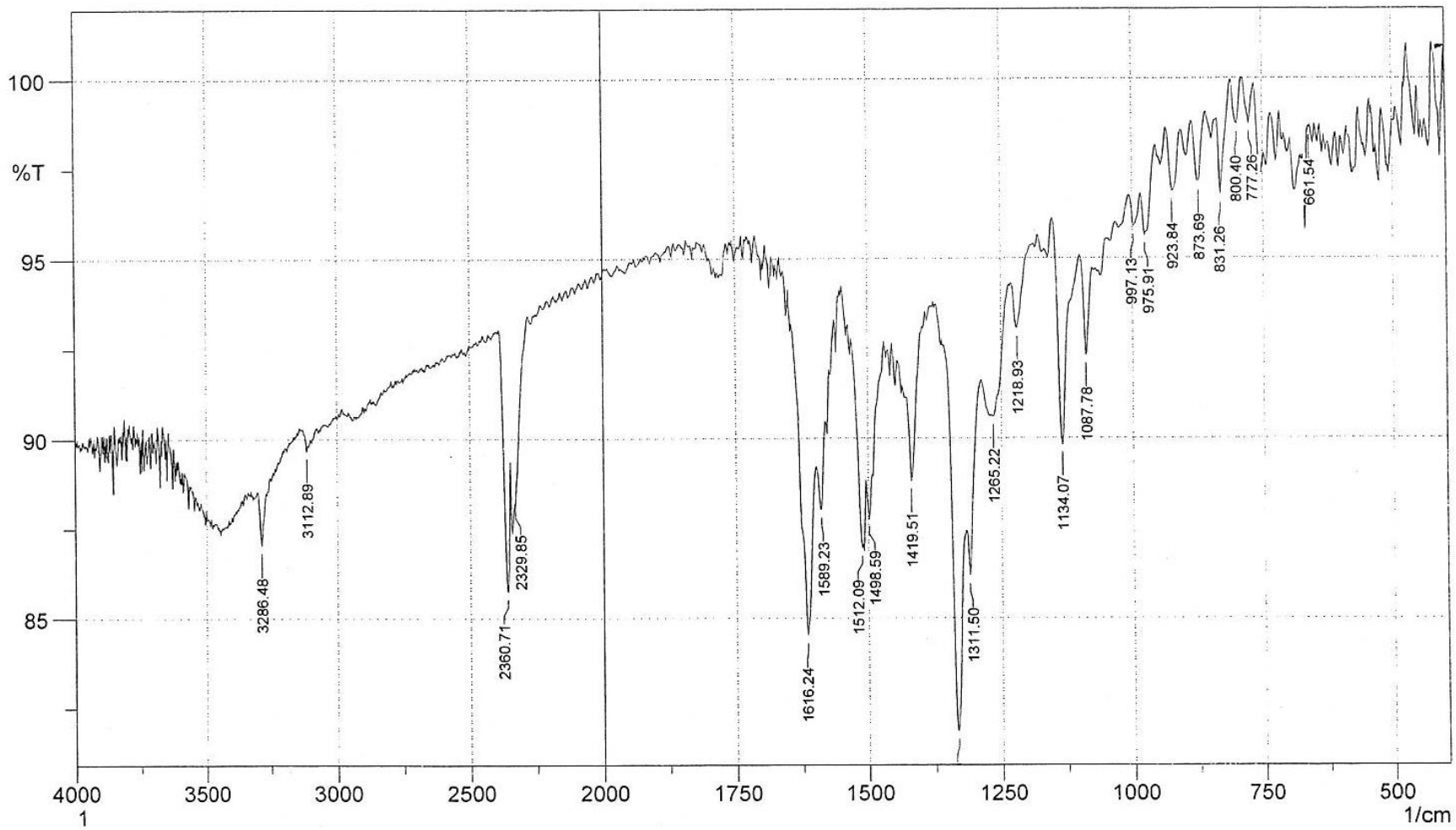
Index (12) 1-(2, 4-dinitrophenylamino)-4-(2-hydroxybenzylidene)-2-phenylimidazole-5-one



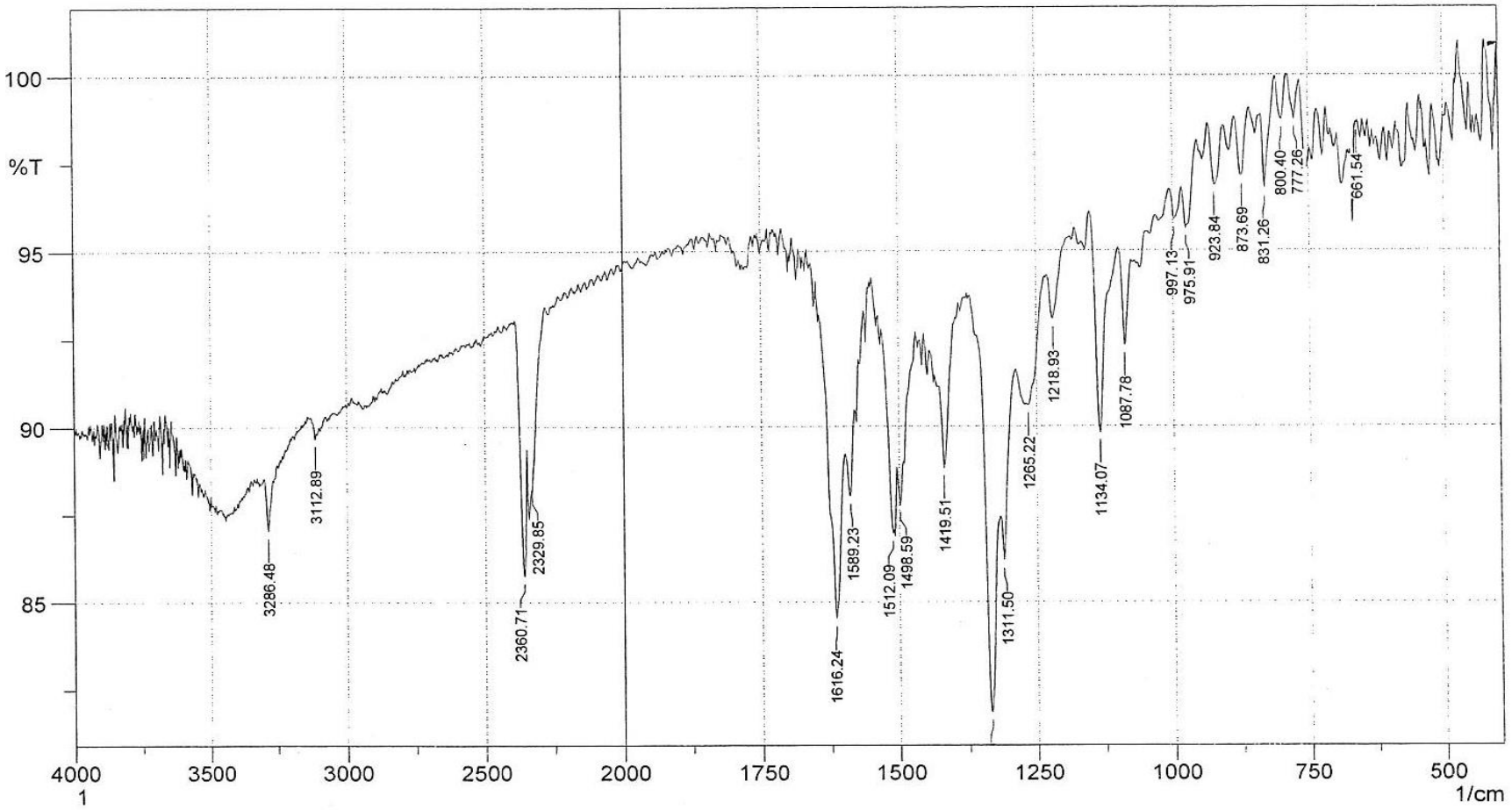
Index (13) 1-(2, 4-dinitrophenylamino)-4-(hydroxyl-3-methoxybenzylidene)-2-phenyl-5-one



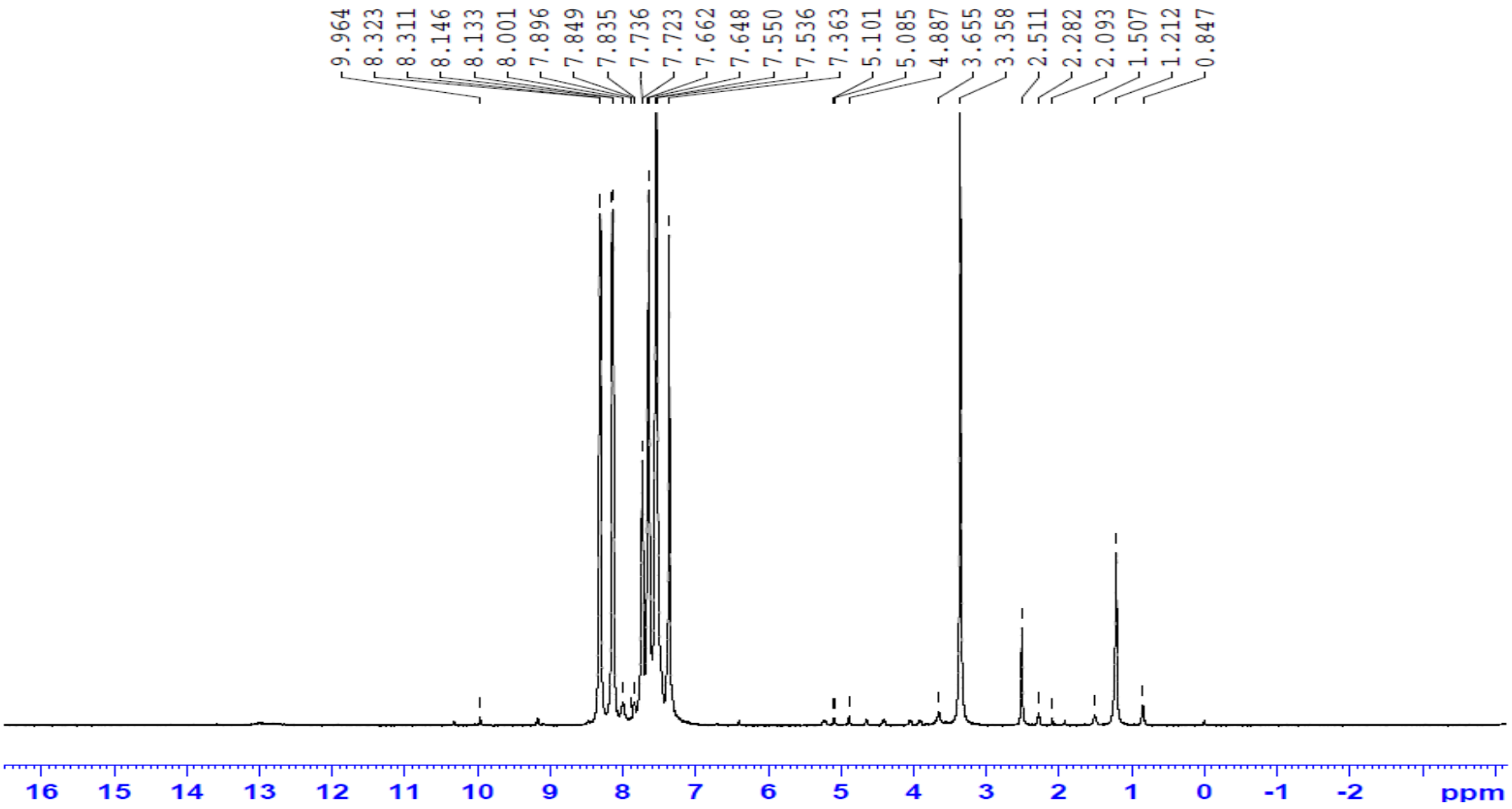
Index (14) 1-(2, 4-dinitrophenylamino)-4-(furan-2-ylmethylene)-2-phenyl imidazole-5-one



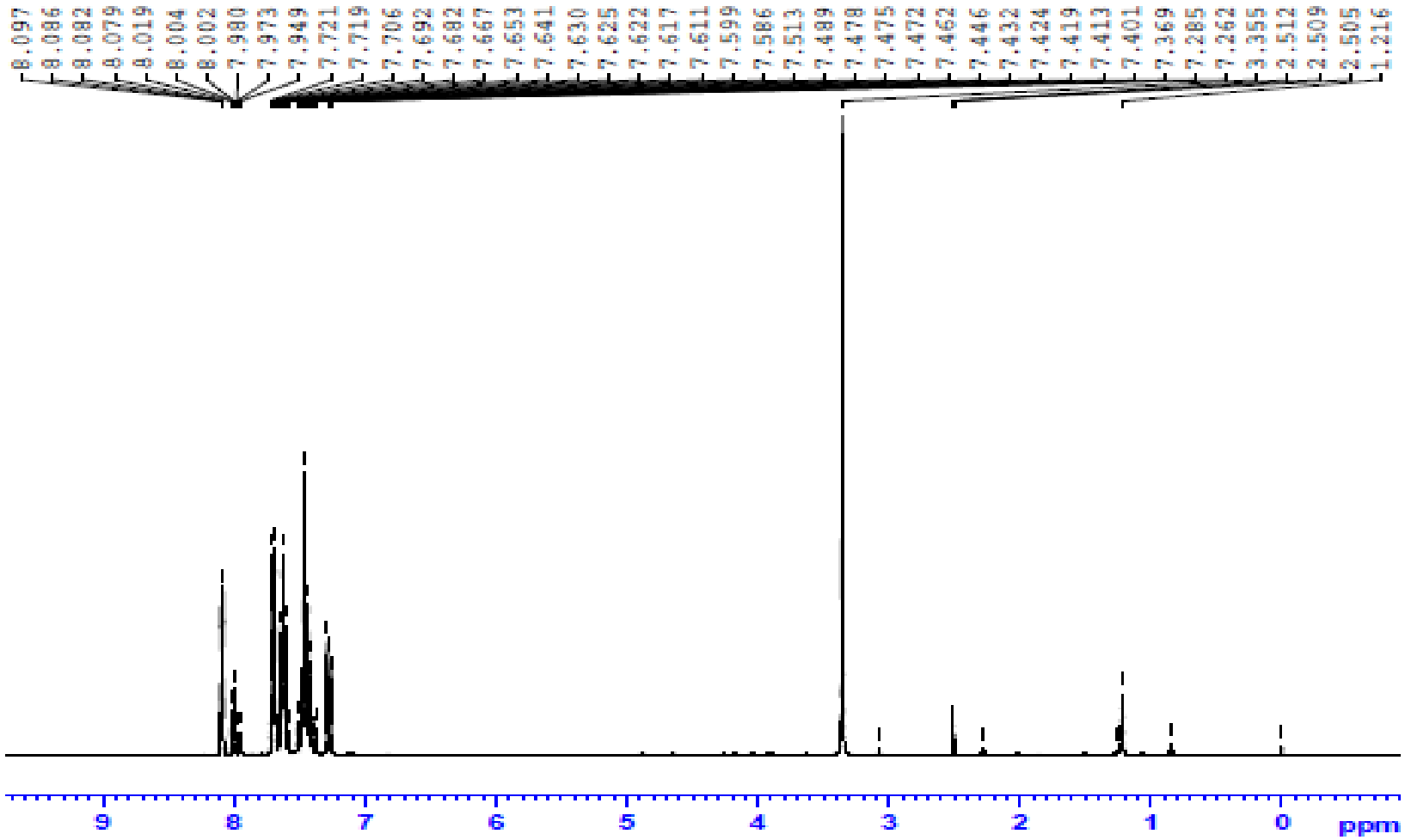
Index (15) 1-amino-4-benzylidene-2-phenylimidazole-5-one



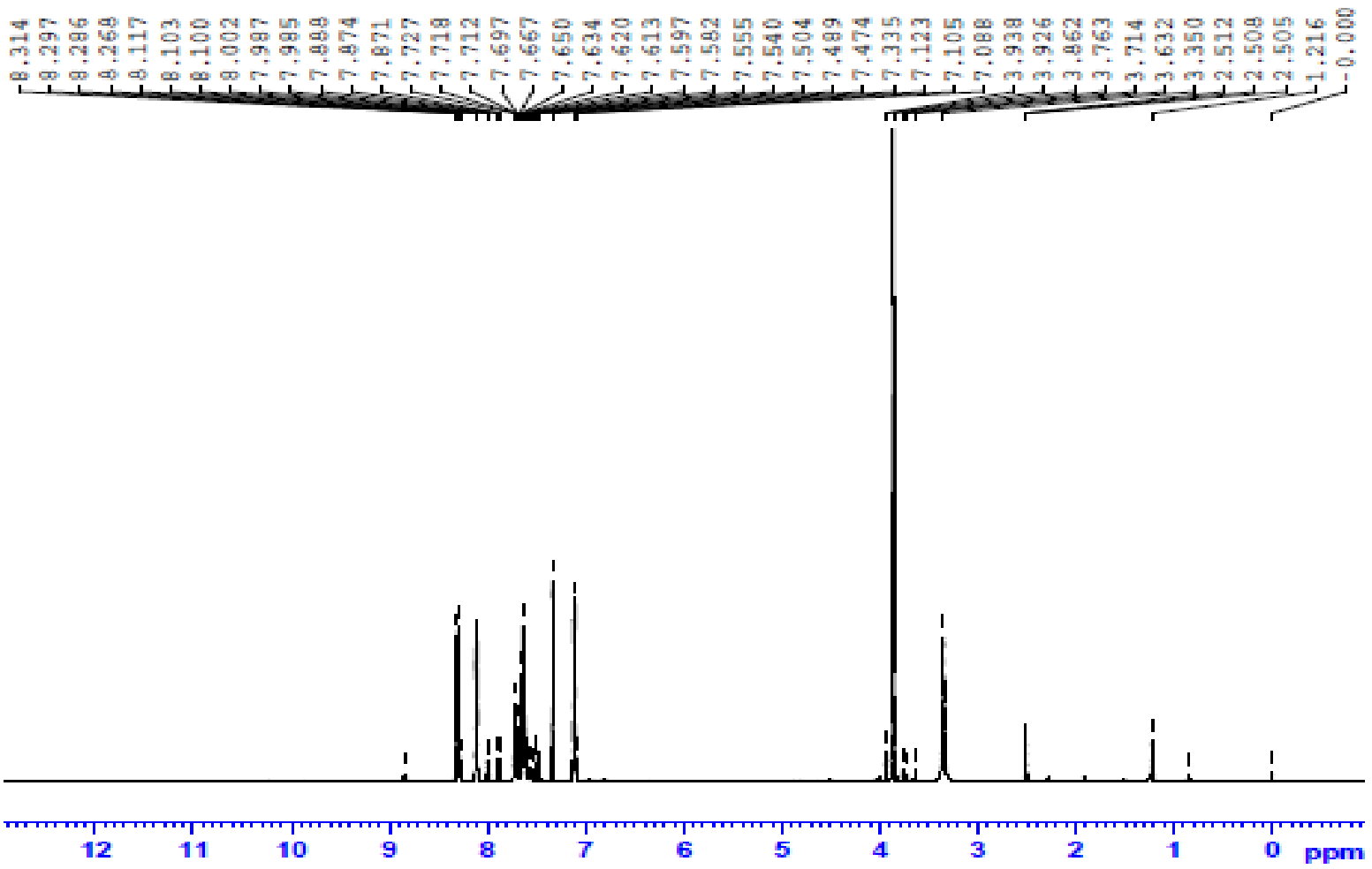
Index (16) 1-amino-4-(4-methoxybenzylidene)-2-phenylimidazole-5-one



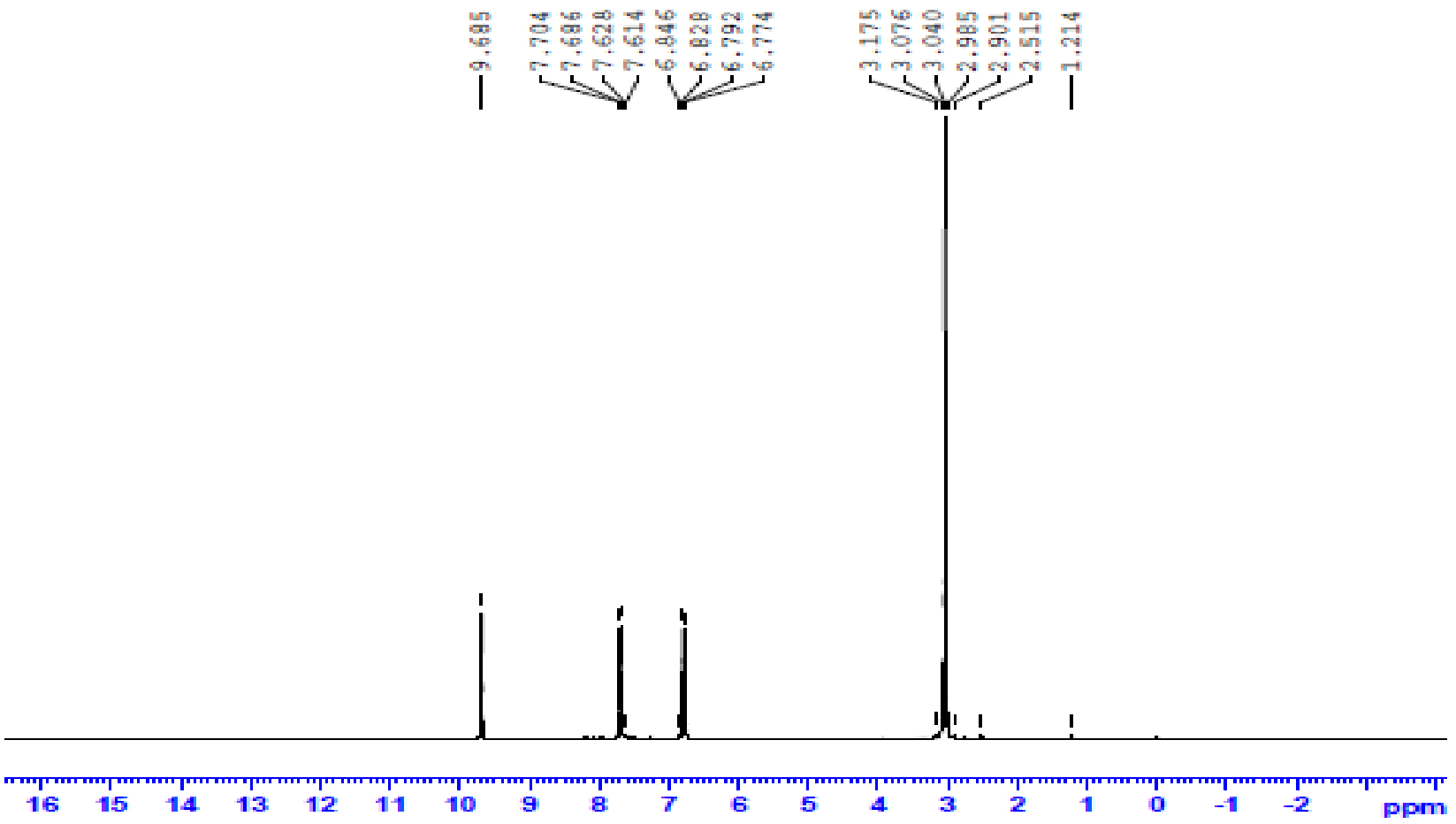
Index(17) ^{1}HNMR of 4-benzylidene-2-phenyloxazol-5-one



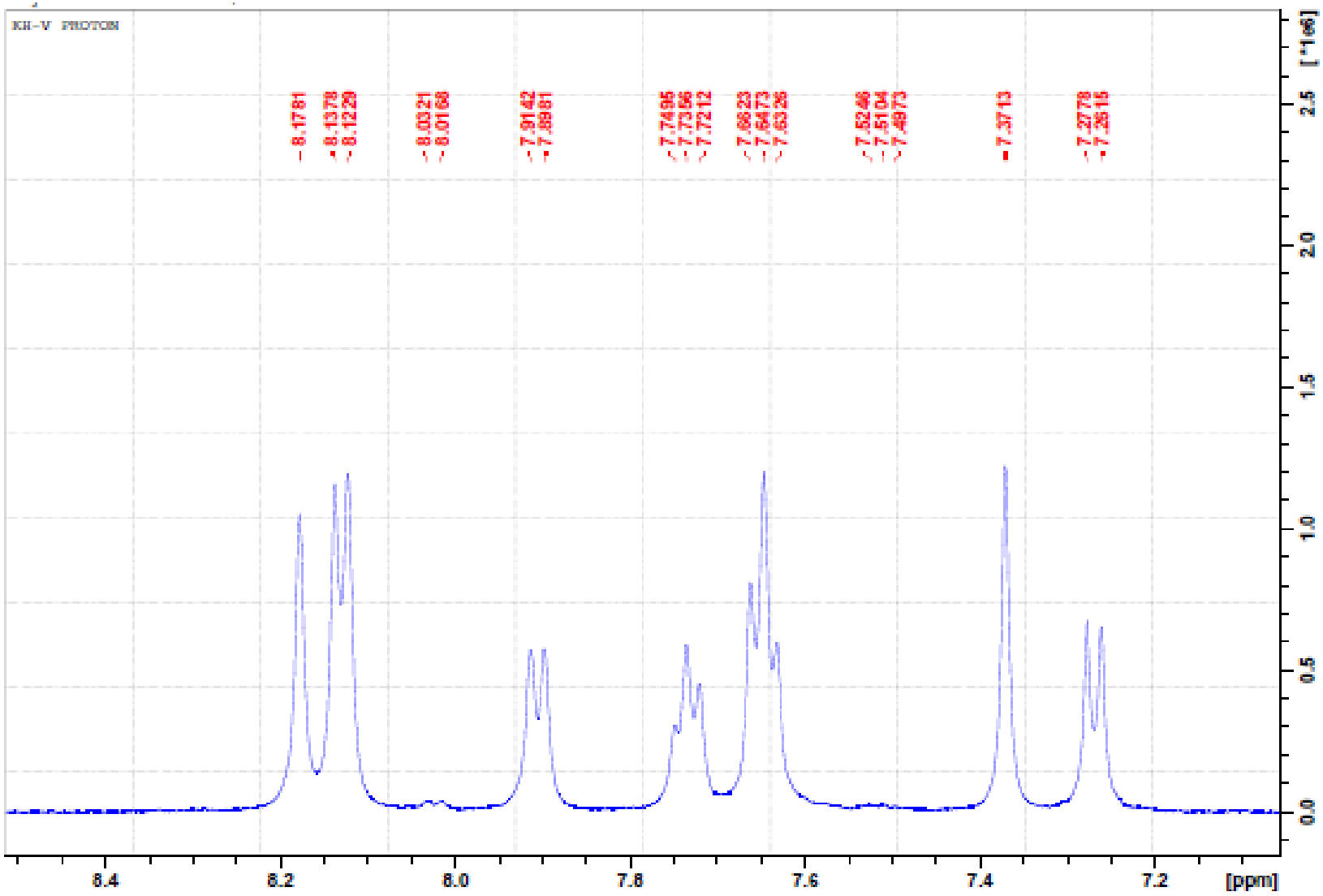
Index (18) ^{1}HNMR of 4-phenyl-4-(3-phenylallylidene), oxazol-5-one



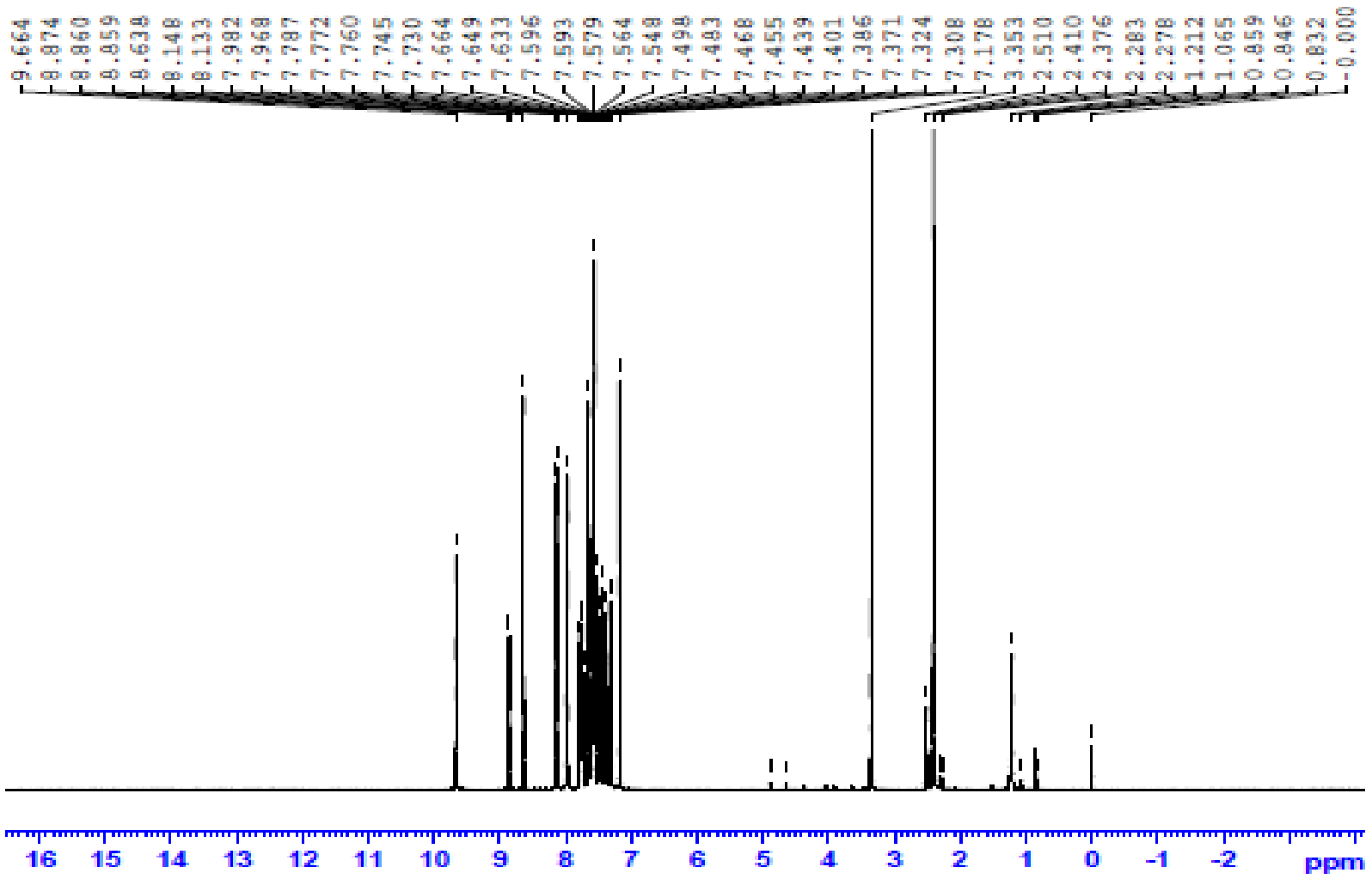
Index (19) ^{1}HNMR of 4-(3-methoxybenzylidene)-2-phenyloxazol-5-one



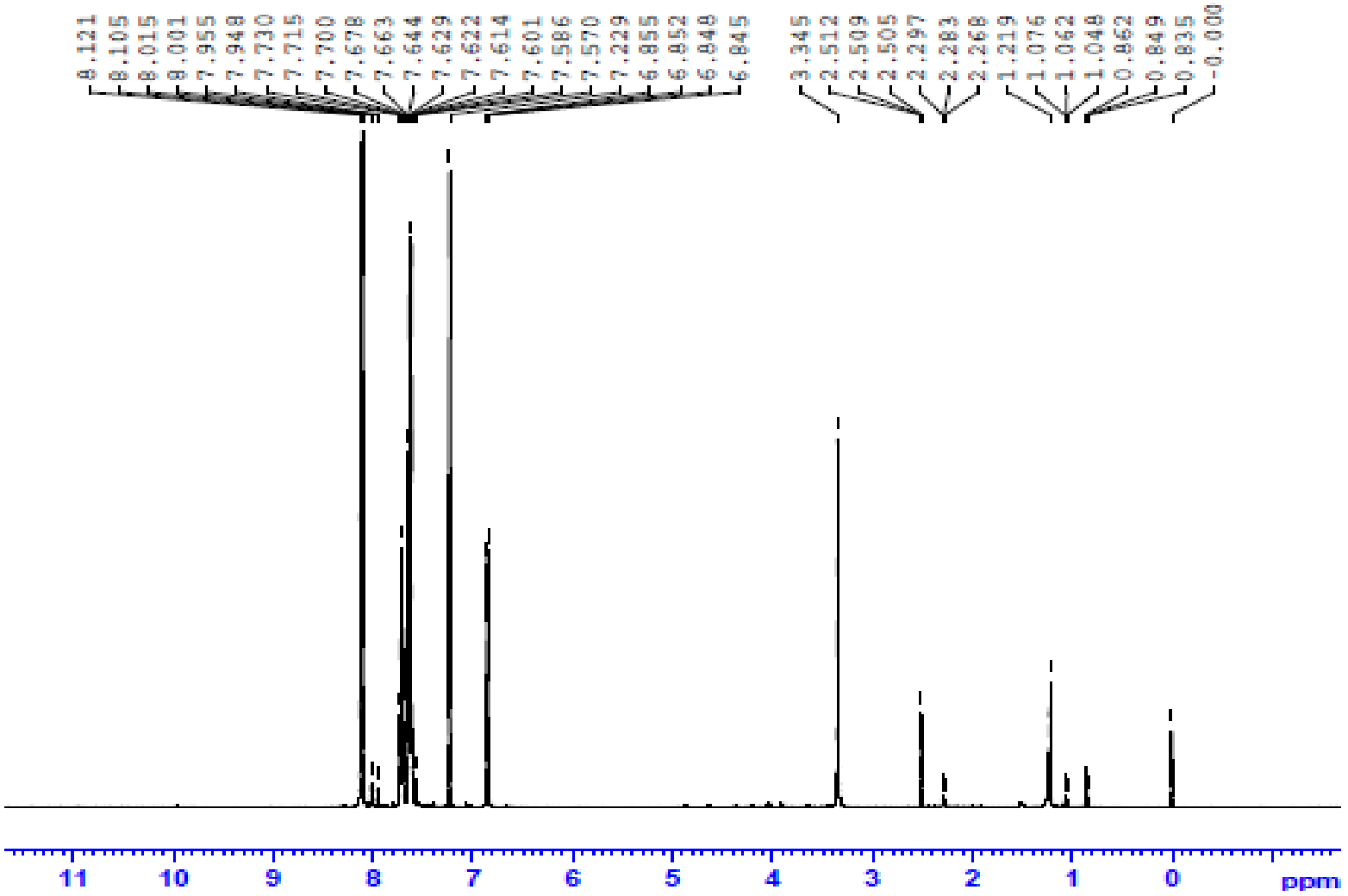
Index (20) 1HNMR of 4-(4-dimthylamine) benzylidene)-2-phenyloxazol-5-one



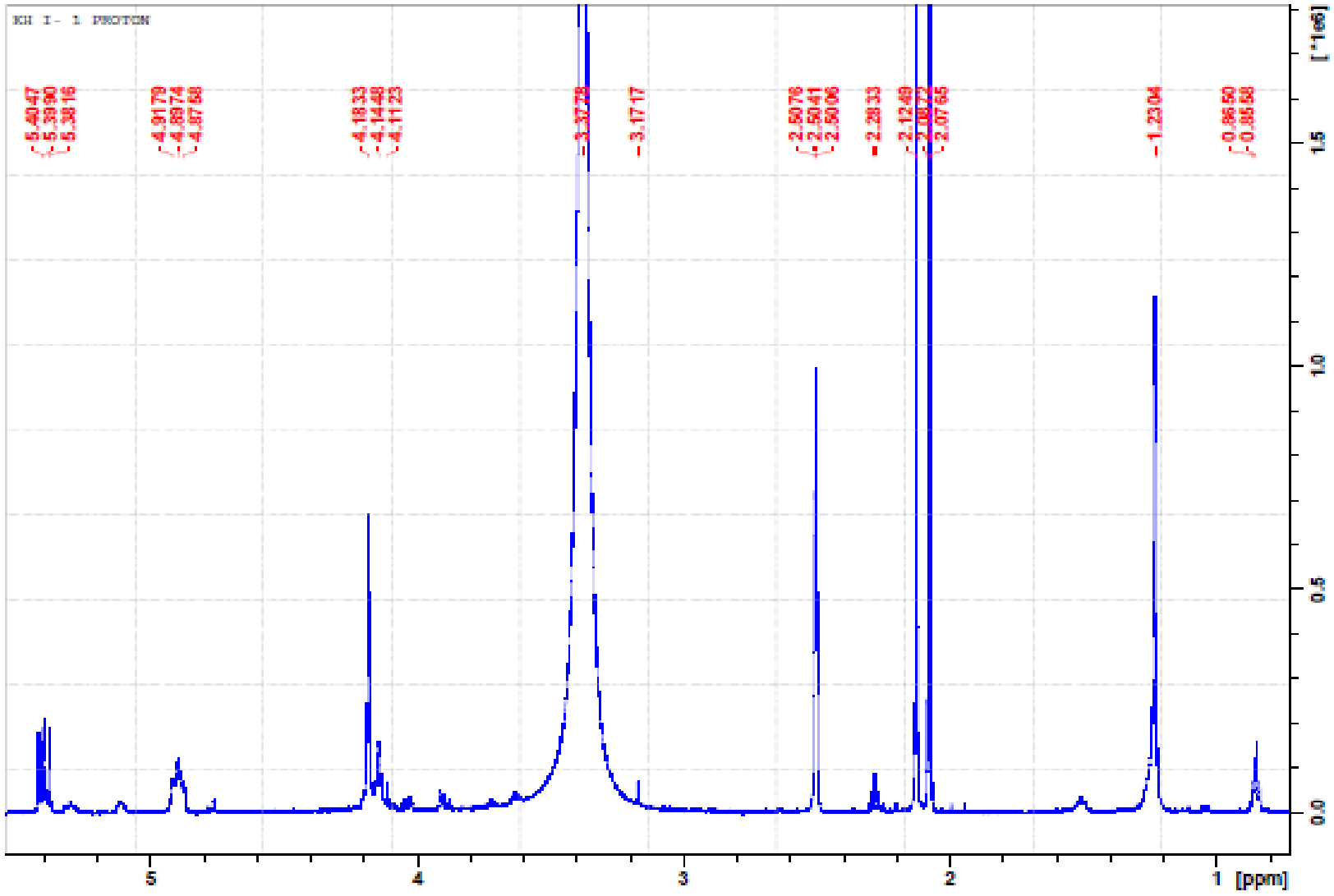
Index (21) 1HNMR of 4-(2-hydroxybenzylidene)-2-phenyl oxazol-5-one



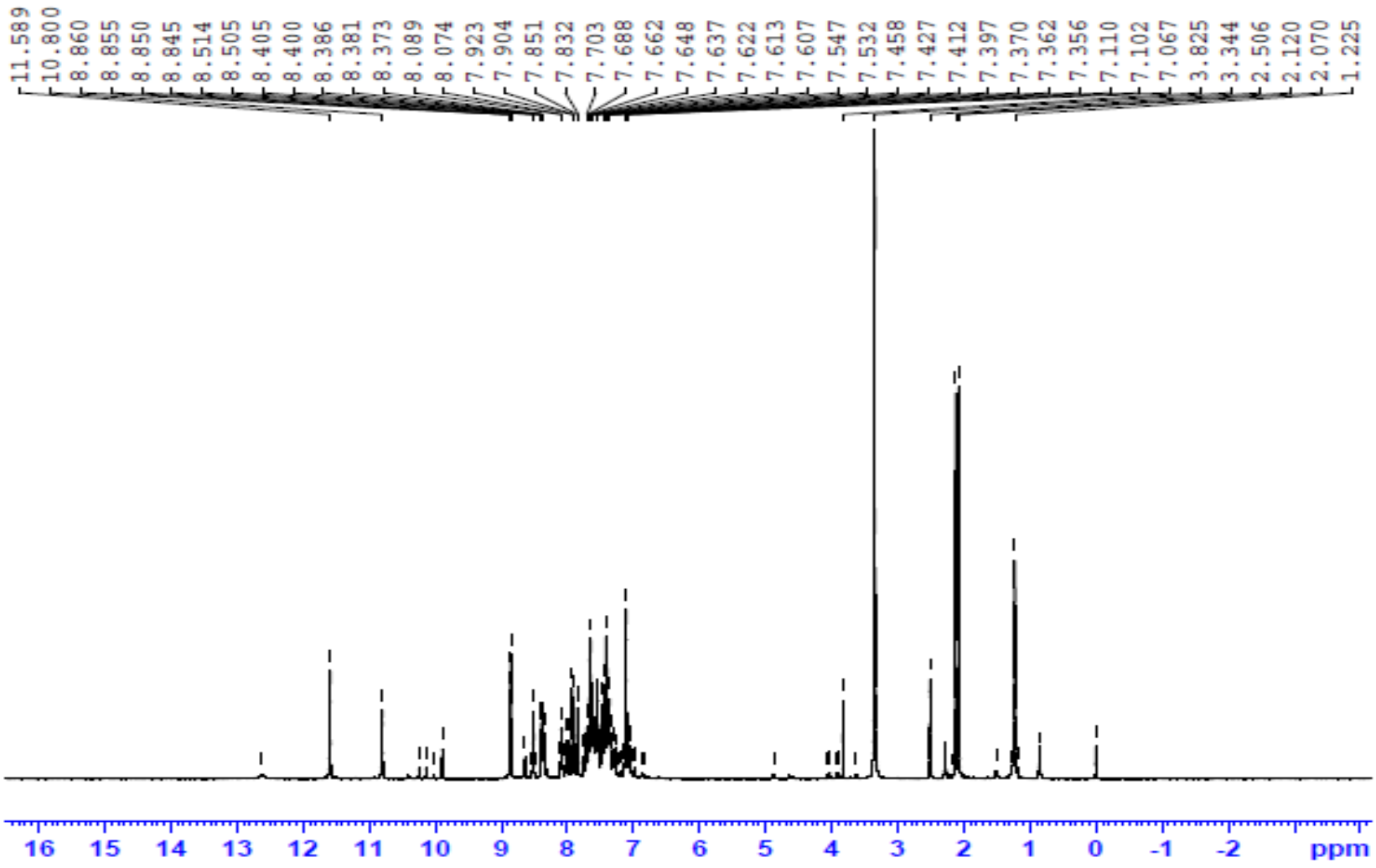
Index (22) ^{1}HNMR of 4-(4-hydroxy-3-methoxybenzylidene)-2-phenyloxazol-5-one



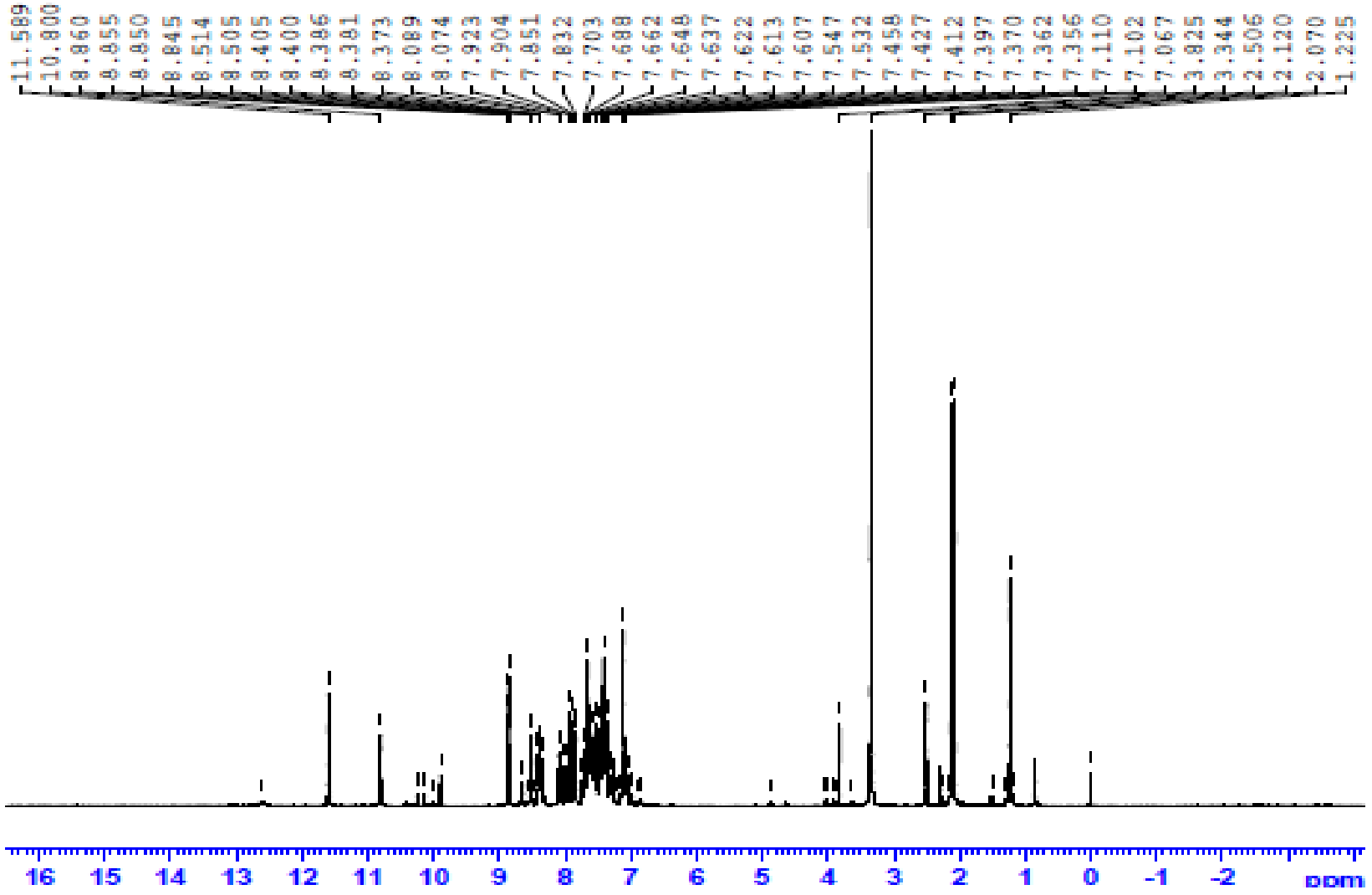
Index (23) [1]HNMR of 4-(furan-2-ylmethylene)2-phenyloxazol-5-one



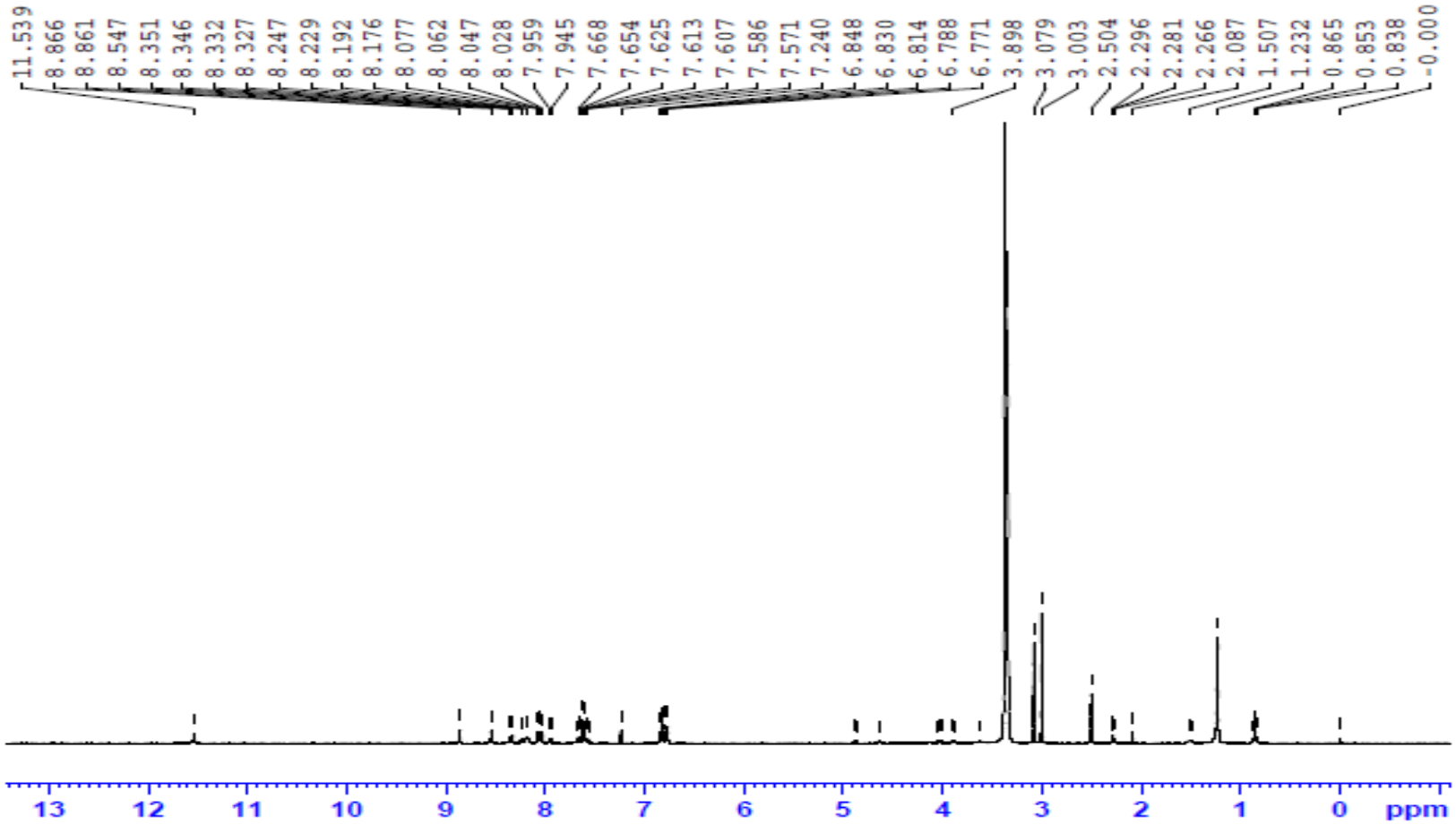
Index (24) [1]HNMR of 4-benzylidene-1-(2, 4-dinitrophenylamino)-2-phenylimidazole-5-one



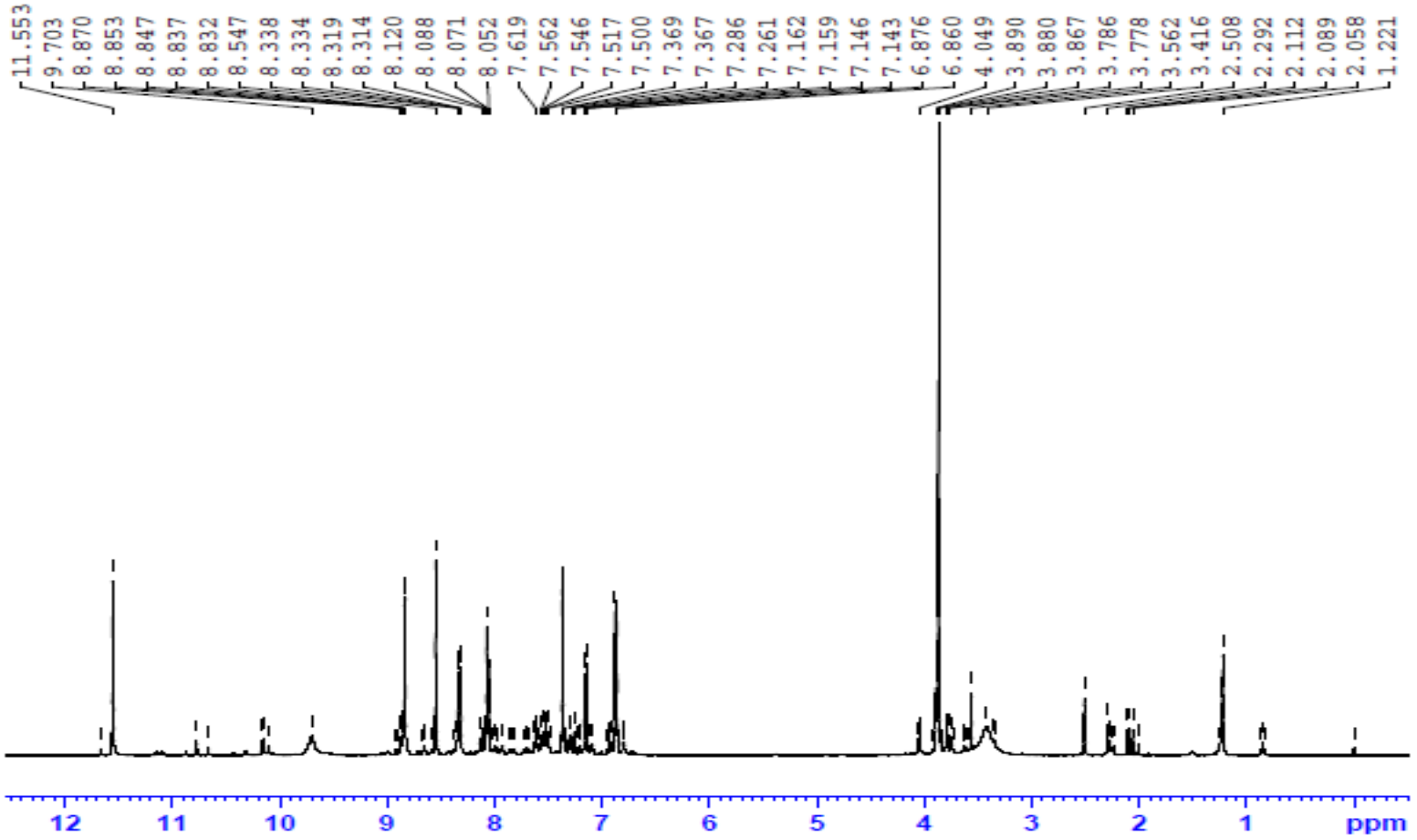
Index (25) ^{1}HNMR of 1-(2, 4-dinitrophenylamino)-2-phenyl-4-(3-phenylallylidene) imidazole-5-one



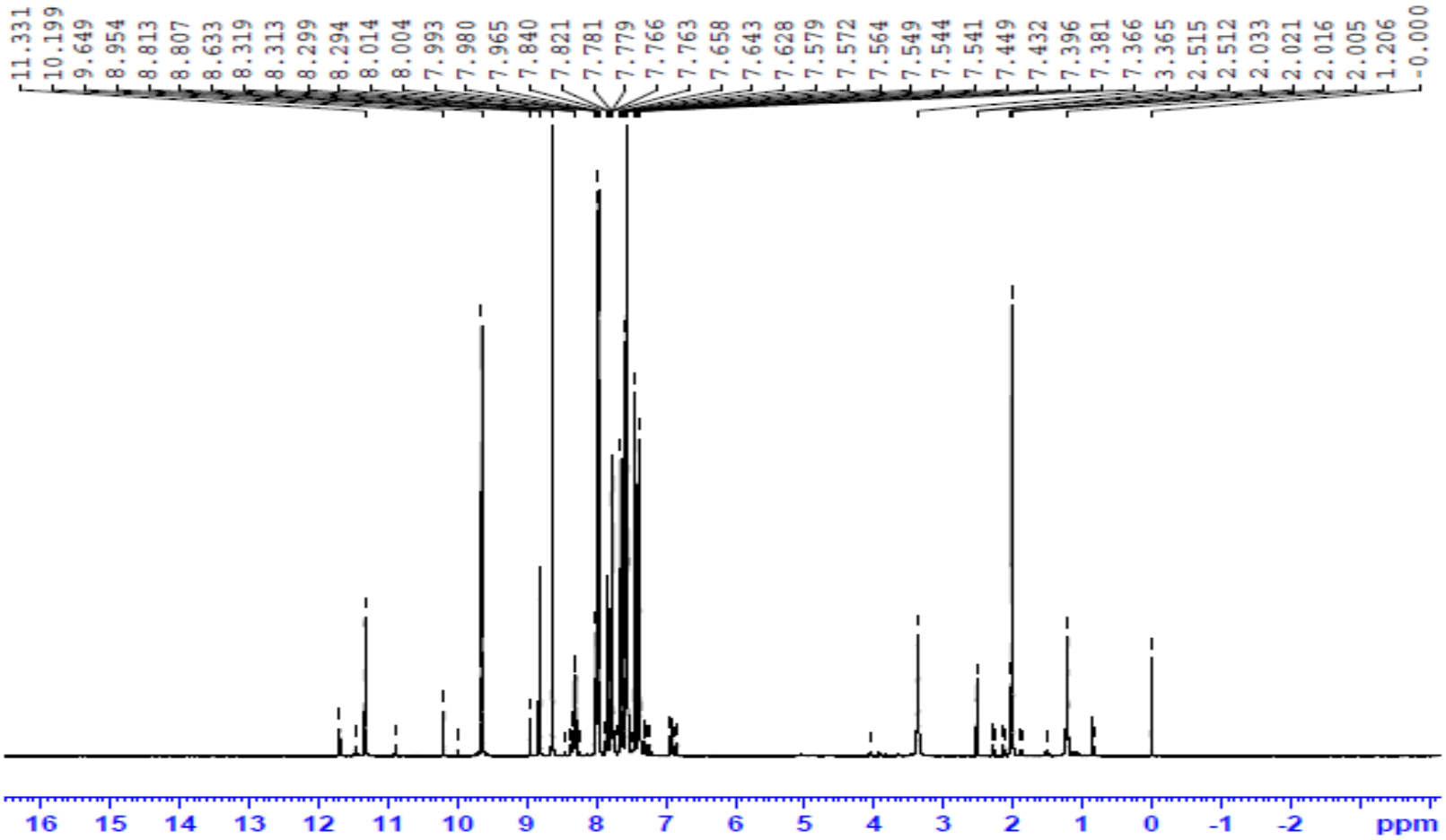
Index (26) ^{1}HNMR of 1-(2, 4-dinitrophenylamino)-4-(3-methoxybenzylidene)-2-phenylimidazole-5-one



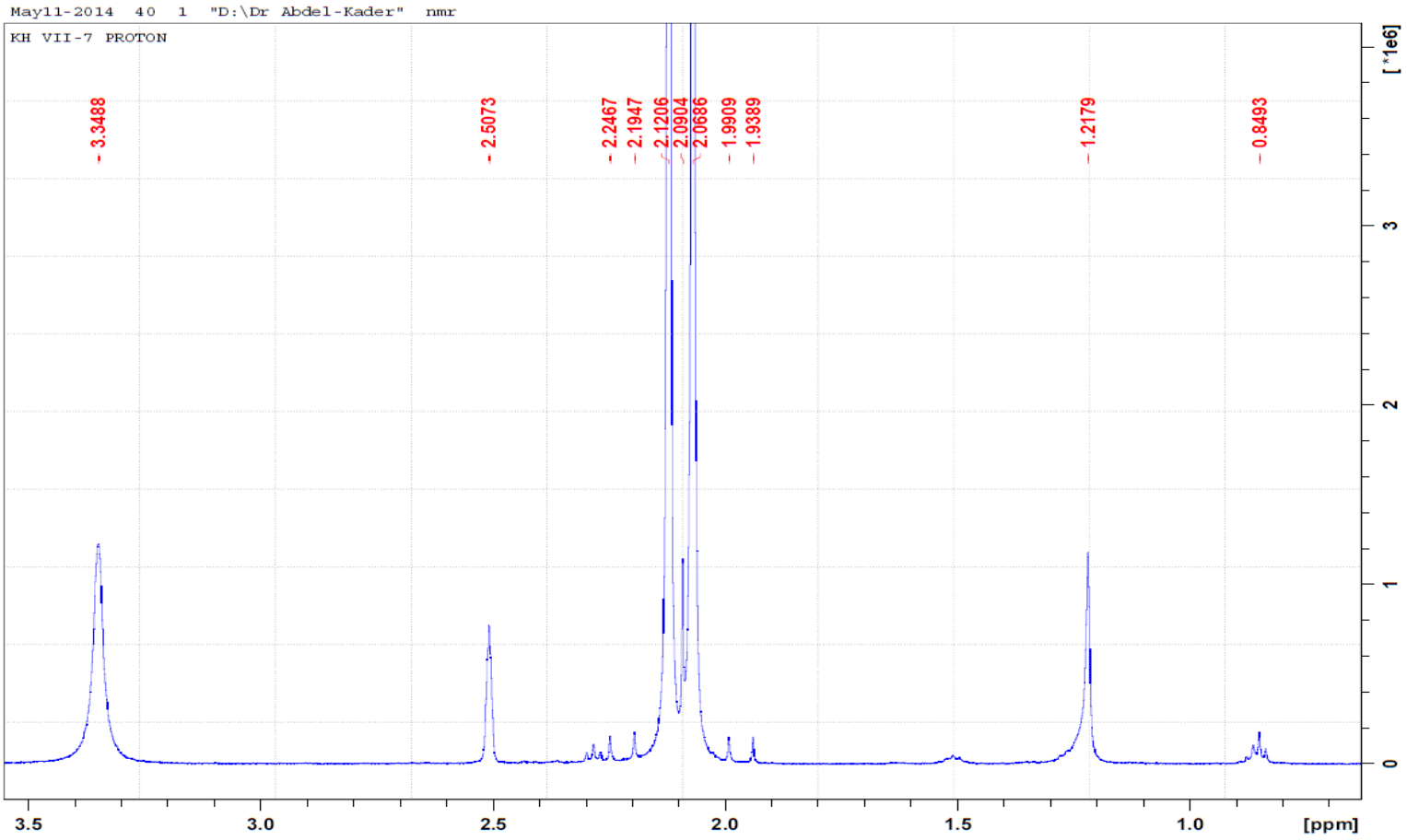
Index (27) [1]HNMR of 4-(4-dimethylamino) benzylidene)-1-(2, 4-dinitrophenylamino)-2-phenylimidazole-5-one



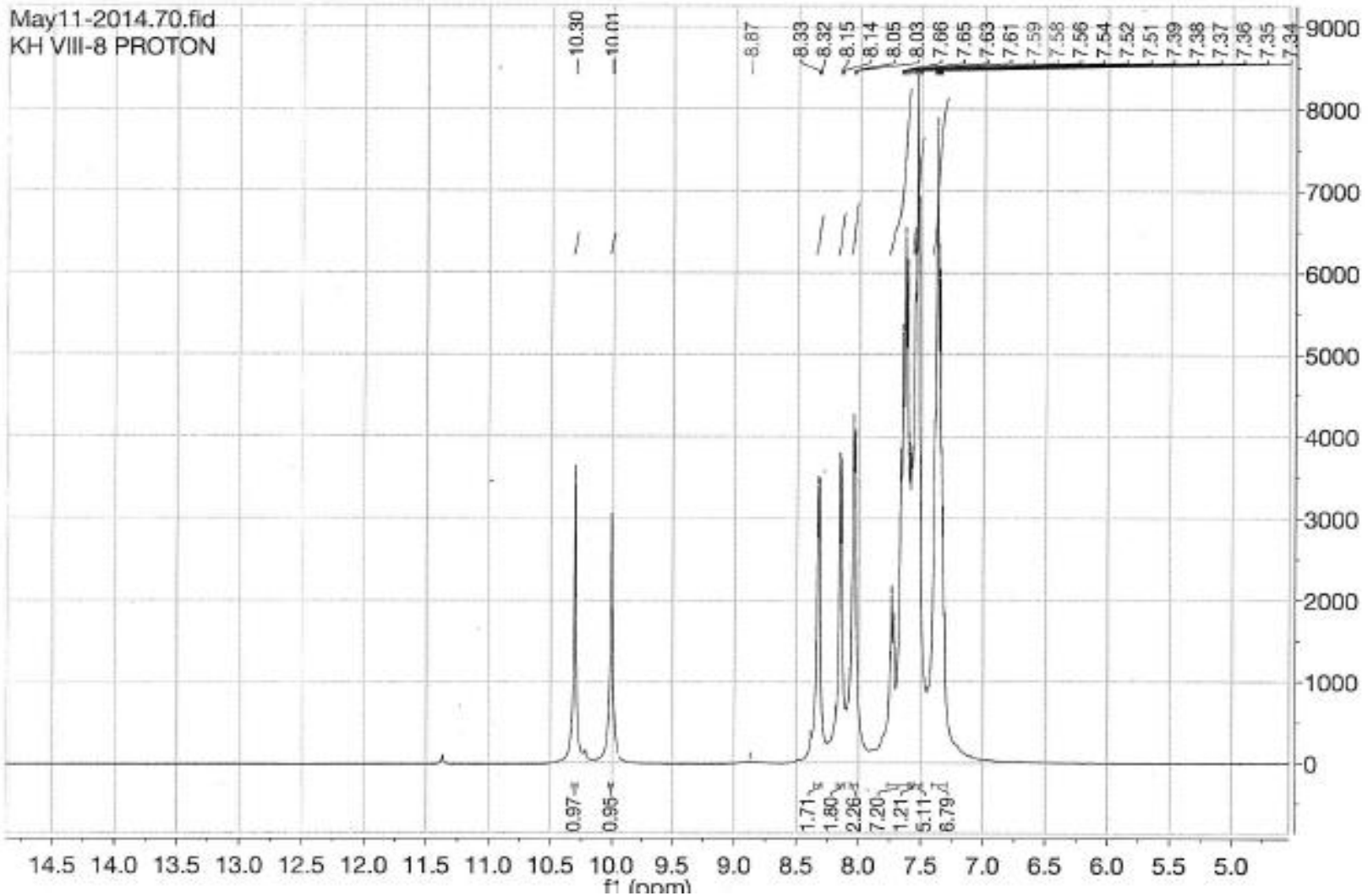
Index (28) ^{1}HNMR of 1-(2, 4-dinitrophenylamino)-4-(2-hydroxybenzylidene)-2-phenylimidazole-5-one



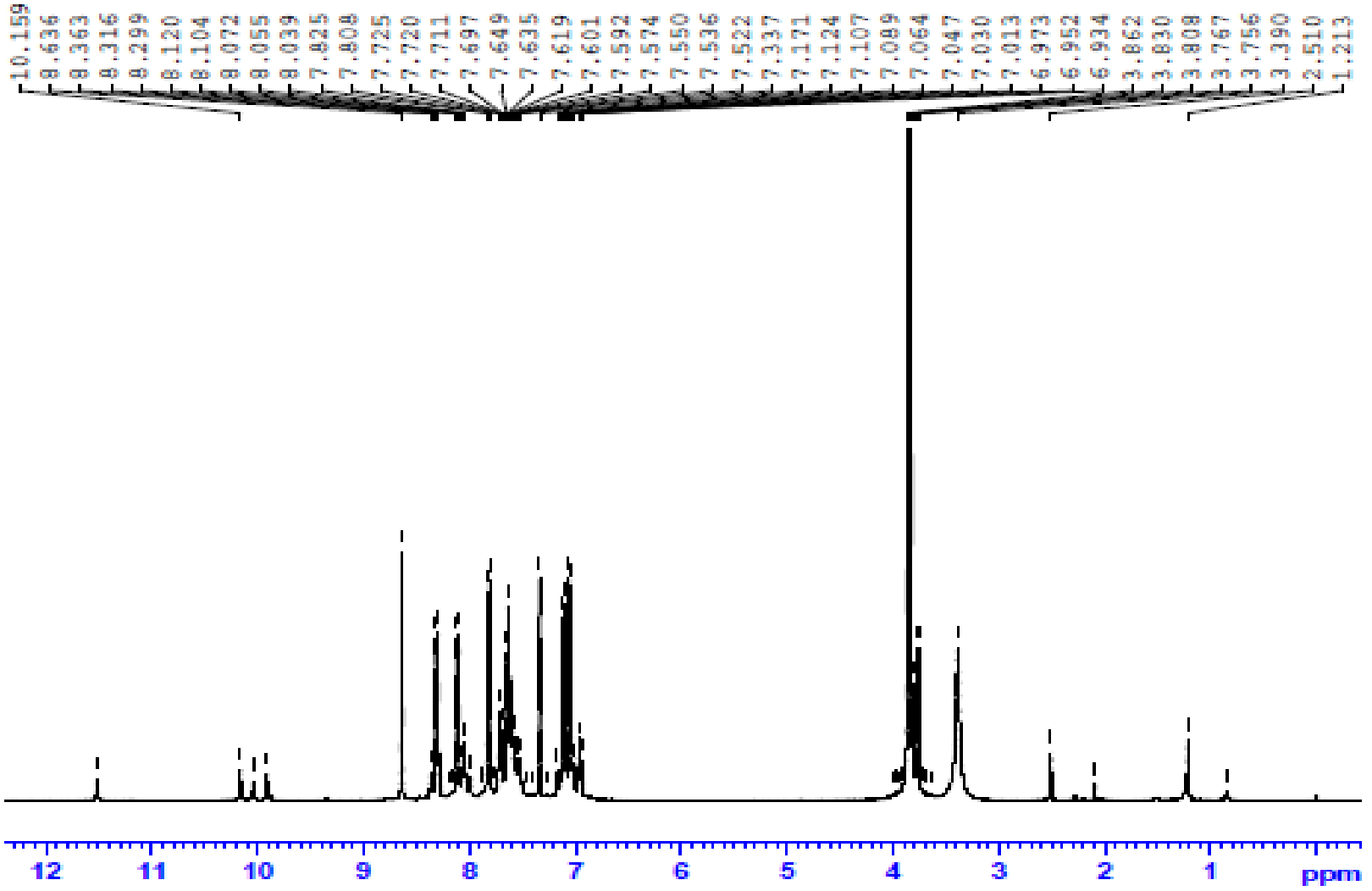
Index (29) ^{1}HNMR of 1-(2, 4-dinitrophenylamino)-4-(hydroxyl-3-methoxybenzylidene)-2-phenyl-5-one



Index (30) ^{1}HNMR of 1-(2, 4-dinitrophenylamino)-4-(furan-2-ylmethylene)-2-phenyl imidazole-5-one



Index (31) [1]HNMR of 1-amino-4-benzylidene-2phenylimidazole-5-one



Index (32) 1HNMR of 1-amino-4-(4-methoxybenzylidene)-2-phenylimidazole-5-one