SYNTHESIS OF IMINES, AMINES AND HALOGENATED IMINES

M. PHIL THESIS

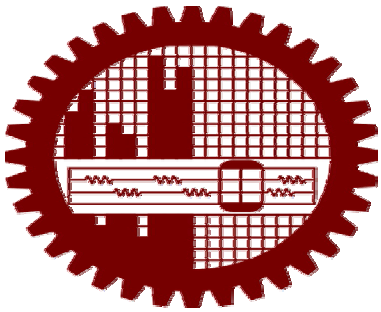
SUBMITTED BY

MD. MAZADUL ISLAM

Student No: 100703106 F

Registration No: 100703106

Session: October 2007



ORGANIC CHEMISTRY RESEARCH LABORATORY

DEPARTMENT OF CHEMISTRY

BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY

DHAKA-1000, BANGLADESH

OCTOBER, 2014

DEDICATED

TO

MY PARENTS AND DAUGHTER

CANDIDATE'S DECLARATION

It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

_____

Signature of the candidate

Md. Mazadul Islam
M. Phil Student
Roll No.: 100703106
Department of Chemistry
BUET, Dhaka,
Bangladesh

Acknowledgement

In the name of almighty Allah to whom all the praises are due for his infinite mercy and kindness.

I am very grateful to my honorable supervisor Prof. Dr. Md. Wahab Khan, Department of Chemistry, BUET, Dhaka for his scholastic supervision, friendly collaboration, valuable suggestions and constructive criticism in the entire period of this research work.

I would like to give thanks to all other respected teachers of the Chemistry Department, BUET for their kind co-operation.

I desire to offer my pleasant thanks to Dr. M. A. Rashid, professor, Department of Pharmacy, University of Dhaka and Mohammad Firoz Khan, Senior Lecturer, State University of Bangladesh for their heartiest cooperation to carry out biological test of various synthesized compounds.

I would like to express my deepest gratitude to the Department of Chemistry, Bangladesh University of Engineering and Technology (BUET) for financial support to carry out my research work.

I also desire to offer my pleasant thanks to Dr. Kazuaki Shimada, Professor, Department of Chemical Engineering, Iwate University, Japan, Md. Ashraful Alam and BCSIR for their kind help for taking NMR spectra of my synthesized compounds.

I am grateful to Geological Survey of Bangladesh, Ministry of Power, Energy and Mineral Resources for giving me permission to continue my thesis. I express my great thanks to Mrs. Meherun Nessa Begum, Director (Chemistry), GSB and all other colleagues who always encourage me to continue my thesis.

I would like to extend thanks to my fellow lab mates for their friendly cooperation in the laboratory. I thank all staffs of the Chemistry Department, BUET for their kind support.

Author

(Md. Mazadul Islam)

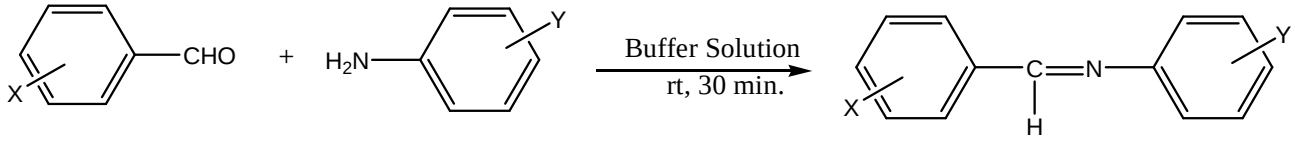
Content

Chapter-3

EXPERIMENTAL

Abstract:

Synthesis of substituted benzylidene benzanamine (imine) derivatives from **11-17** was developed by treating substituted benzaldehyde with substituted aryl amine in presence of acetic acid buffer solution at room temperature for 10-30 minutes as shown in the **Scheme 1.**



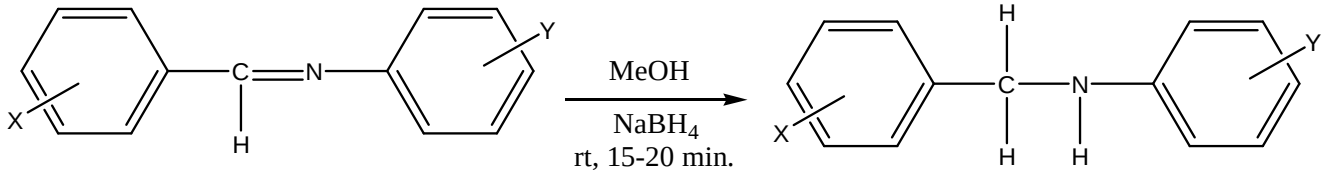
1-4 **5-10** **11-17**

1, 11 X = NO_2-*p*; **2, 12** X = OCH_3-*p*; **3, 13** X = H; **1, 14** X = NO_2-*p*; **1, 15** X = NO_2-*p*; **4, 16** X = CH_3-*p*; 1, 15 X = NO_2-*p*

5, 11 Y = Cl-*p*; **6, 12** Y = CH_3-*p*; **5, 13** Y = Cl-*p*; **7, 14** Y = H; **6, 15** Y = CH_3-*p*; **8, 16** Y = OCH_3-*p*; **9, 17** Y = CH_3-*m*;

Scheme 1

The synthesized imines **13, 16** were reduced to secondary amine **18, 19** by using $NaBH_4$ in methanol at room temperature for 15-20 minutes as shown in the **Scheme 2.**

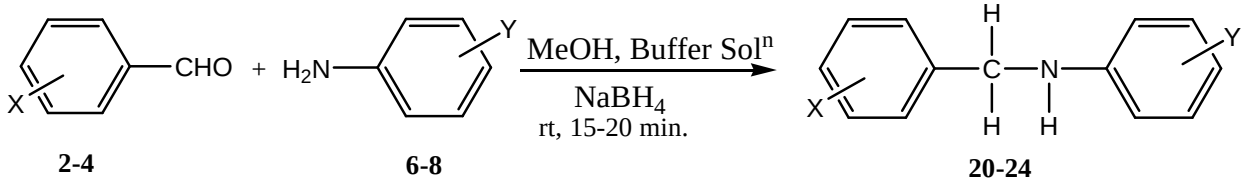


13, 16 **18, 19**

13, 18 X, Y = H, Cl-*p*; **16, 19** X, Y = CH_3-*p*, OCH_3-*p*

Scheme 2

The compounds **20-24** were synthesized by treating aldehyde and aryl amine in presence of acetic acid buffer solution with alcoholic $NaBH_4$ at room temperature for 15-20 minutes **(Scheme 3)**.



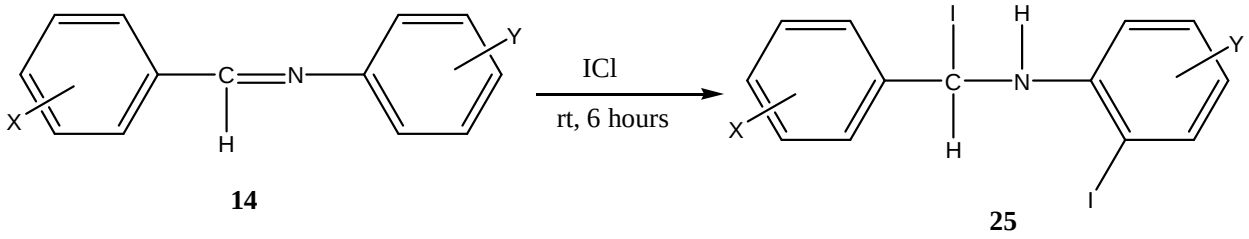
2-4 **6-8** **20-24**

3, 20 X = H; **3, 21** X =H; **4, 22 X =** CH_3-*p*; **3, 23** X = H; **2, 24** X = OCH_3-*p*

7, 20 Y =H; **6, 21** Y = CH_3-*p*; **7, 22** Y = H; **8, 23** Y = OCH_3-*p*; **7, 24** Y = H

Scheme 3

The synthesized imine **14** was iodinated to **25** by monochloro iodine in methanol at room temperature for 6 hours as shown in the **Scheme 4.**



14 **25**

14, 25 X, Y = NO_2-*p*, H

Scheme 4

CHAPTER-1

INTRODUCTION

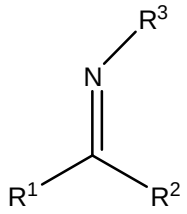
INTRODUCTION

1.1. General:

The condensation of carbonyl compounds with primary amines to produce the corresponding imines was first discovered in 1864 by Hugo Schiff. Hence, imines are often referred to as Schiff bases or azomethines. Many natural products and most biologically interesting compounds (drugs) contain N-atoms. Therefore, development of new methods for C-N bond formation is important. An imine is a functional group or chemical compound containing a carbon–nitrogendouble bond, with the nitrogen attached to a hydrogen atom (H) or an organic group. If this group is not a hydrogen atom, then the compound can sometimes be referred to as a Schiff base .The carbon has two additional single bonds. Imines are typically prepared by the condensation of primary amines and aldehydes and less commonly ketones. In terms of mechanism, such reactions proceed via the nucleophilic addition giving a hemiaminal -C(OH)(NHR)- intermediate, followed by an elimination of water to yield the imine. The equilibrium in this reaction usually favors the carbonyl compound and amine, so that azeotropic distillation or use of a dehydrating agent, such as molecular sieves or magnesium sulfate, is required to push the reaction in favor of imine formation.

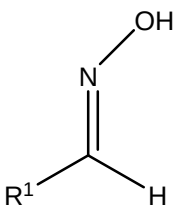
1.2. Nomenclature and classification

Imines are related to ketones and aldehydes by replacement of the oxygen with an NR group. When R = H, the compound is a primary imine, when R is hydrocarbyl, the compound is a secondary imine. Imines exhibit diverse reactivity and are commonly encountered throughout chemistry.[1]

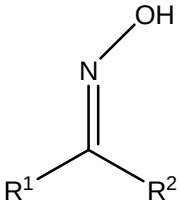


The general structure of an imine

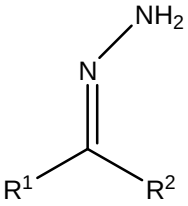
When R^3 is OH, the imine is called an oxime, and when R^3 is NH_2 the imine is called a hydrazone.



Aldoxime

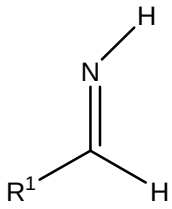


Ketoxime

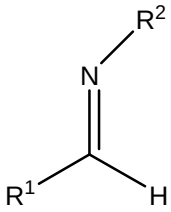


Hydrazone

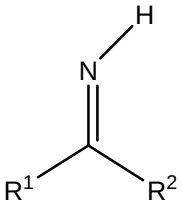
A primary imine in which C is attached to both a hydrocarbyl and a H is called a primary aldimine; a secondary imine with such groups is called a secondary aldimine.[2] A primary imine in which C is attached to two hydrocarbyls is called a primary ketimine; an imine with such groups is called a secondary ketimine.[3]



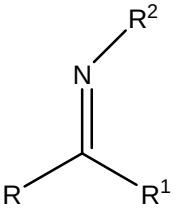
Primary aldimine



Secondary adimine



Primary ketimine



Secondary ketimine

One way of naming aldimines is to take the name of the radical, remove final "e", and add "-imine", for example ethanimine. Alternately, an imine is named as a derivative of a carbonyl, adding the word "imine" to the name of a carbonyl compound whose oxo group is replaced by an imino group, for example sydnone imine and acetone imine (an intermediate in the synthesis of acetone azine).

N-Sulfinyl imines are a special class of imines having a sulfinyl group attached to the nitrogen atom.

1.3. Importance of imines:

a) Schiff base compounds are well known because of their wide applications and are useful intermediates in organic synthesis.[4,5]

b) Imino esters, such as the N-p-methoxyphenyl (N-PMP) α-imino ethyl glyoxalate are important electrophiles that, when reacted with organic nucleophiles; can produce optically α and β-amino acid derivative as well as β-lactams.[6] The amino acid derivatives, containing imine moiety are useful precursors to natural and medicinal products including antibiotic.[7]Physiologically, imines are essential components of many systems, such as vision and a variety of enzymatic reaction. For example, rhodopsin, the biomolecule responsible for vision, is the product of an imine synthesis: the chromophore*cis*- retinal and the protein opsin from rhodopsin through the reaction of the aldehyde group of the retinal and the lysine amino side chain of the opsin. Light induces the isomerization within the imine that ultimately causes an electrical impulse to be transmitted to the brain.[8]

c) The imine formation is one of the most important reactions in organic and medicinal chemistry. Imines have been discovered to have a wide range of biological activities such as lipoxygenase inhibition, anti-inflammatory[9], anti-cancer[10], antibacterial, and antifungal behavior.

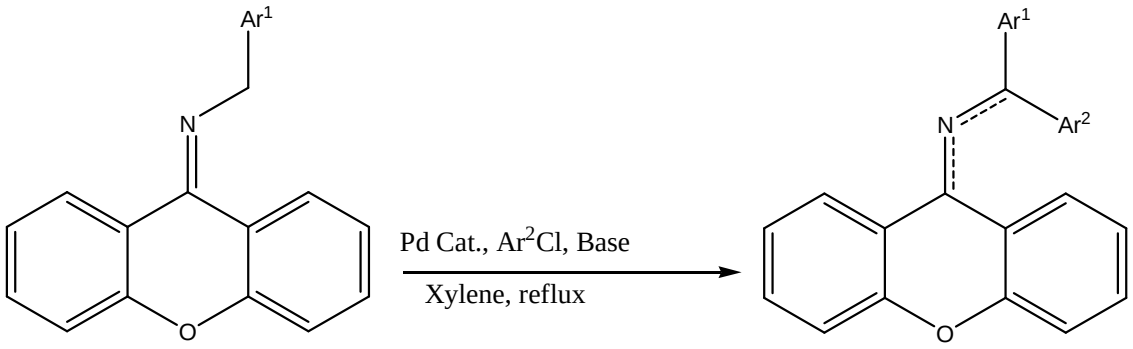
d) The distereoselectiveaza-Diels-Alder reaction between cyclopentadiene chiral glyoxalate – derived imines is used to synthesize chiral ligands and synthetic precursors.[11]

e) Transition–Metal-Catalyzed Imine Metathesis is a valuable reaction. Which reported the identification of a class of imide catalysts that effectively promote C=N bond formation via metathesis of imines.[12] Metal-Catalyzed metathesis is a valuable reaction both in polymer[13] and small molecule synthesis.[14]

f) Imines are used as versatile components in the asymmetric synthesis of α-aminonitriles, preparation of secondary amines by hydrogenation[15], and in cycloaddition reactions.[16]

g) Furthermore, they are used as versatile components in the formation of optically active α-alkyl aldehydes[17], in nucleophilic addition with organometallic reagents.[18]

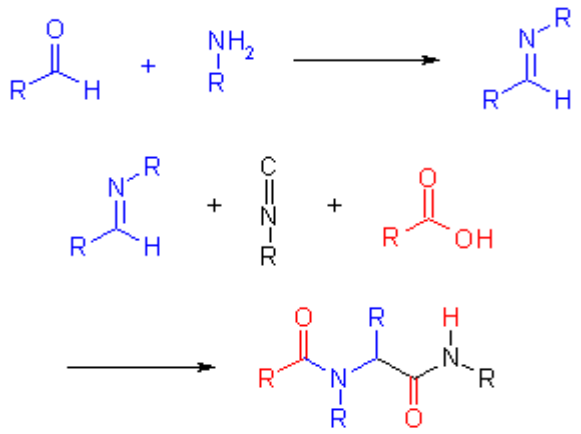
h) The direct benzylicarylation of *N*-benzylxanthone imine with aryl chloride proceeds under palladium catalysis, yielding the corresponding coupling product. The product is readily transformed to benzhydrylamine. Taking into the consideration that the imine is readily available from benzylic amine, the overall transformation represents a formal cross-coupling reaction of aryl halide with α-aminobenzyl metal.[19] **(Scheme 1)**



(Scheme 1)

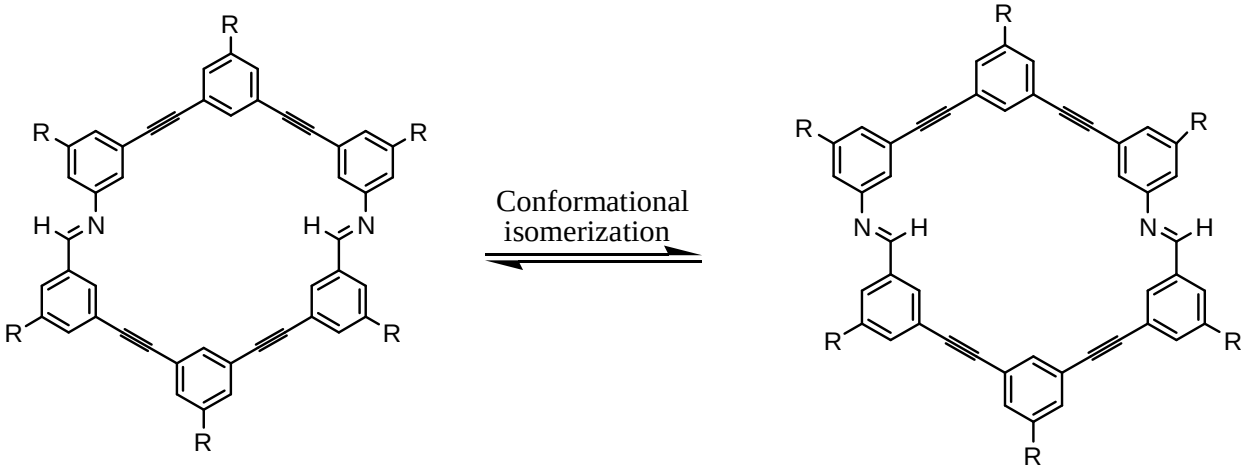
i) Theoretical study of the aldol condensation with imine-type electrophiles has been reported by Fernando Bernardi.[20]

j) The formation of the imine is the initial step in the Ugi reaction. The Ugi reaction is a multi-component reaction in organic chemistry involving a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to form a bis-amide.[21,22,23]The reaction is named after Ivar Karl Ugi, who first published this reaction in 1959. Using the principles of combinatorial chemistry, the Ugi reaction offers the possibility to synthesize a great number of different compounds in one reaction, by the reaction of various ketones (or aldehydes), amines, isocyanides and carboxylic acids. **(Scheme 2)**



(Scheme 2)

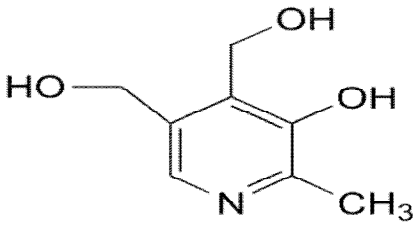
k) Synthesis and Self-Association of an Imine-Containing *m*-PhenyleneEthynyleneMacrocycle: The purpose of this study was to test the suitability of the imine bond as a structural unit within the backbone of phenyleneethynylenemacrocycles and oligomers by determining the ability of *m*-phenyleneethynylenemacrocycle to form π-stacked aggregates in both solution and the solid state.[24] Macrocycle, with two imine bonds was synthesized in high yield from diamine and dialdehyde. The imine bond is more flexible than the ethynylene unit due to its ability to undergo facile *syn- anti* isomerization (Scheme3).[25]



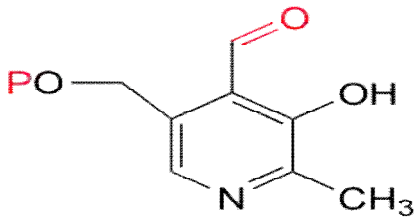
[R = $CO_2(CH_2CH_2O)_3CH_3$]

(Scheme 3)

l) Biochemistry of imines: Imines are common in nature. Schiff base (imine) formation is a very important reaction in biological chemistry. Schiff bases are common enzymatic intermediates where an amine, such as the terminal group of a lysine residue reversibly reacts with an aldehyde or ketone of a cofactor or substrate. One example involves the chemistry of pyridoxal phosphate (PLP), a derivative of pyridoxine, commonly known as vitamin B_6.Vitamin B_6 promotes the domination of amino acids via the formation of imines.

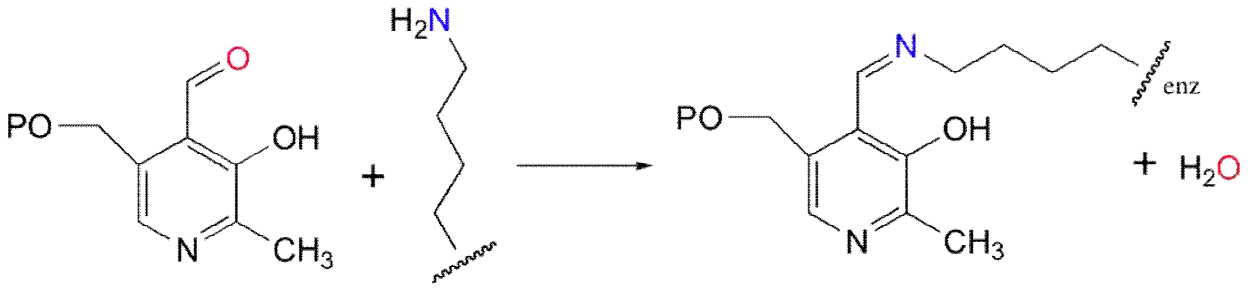


pyridoxine (vitamin B_6)



pyridoxal phosphate (PLP)

The common enzyme cofactor PLP forms a Schiff base with a lysine residue and is transaldiminated to the substrate(s).[26] Similarly, the cofactor retinal forms a Schiff base in rhodopsins, including human rhodopsin (via Lysine 296), which is key in the photoreception mechanism.**(Scheme 4)**



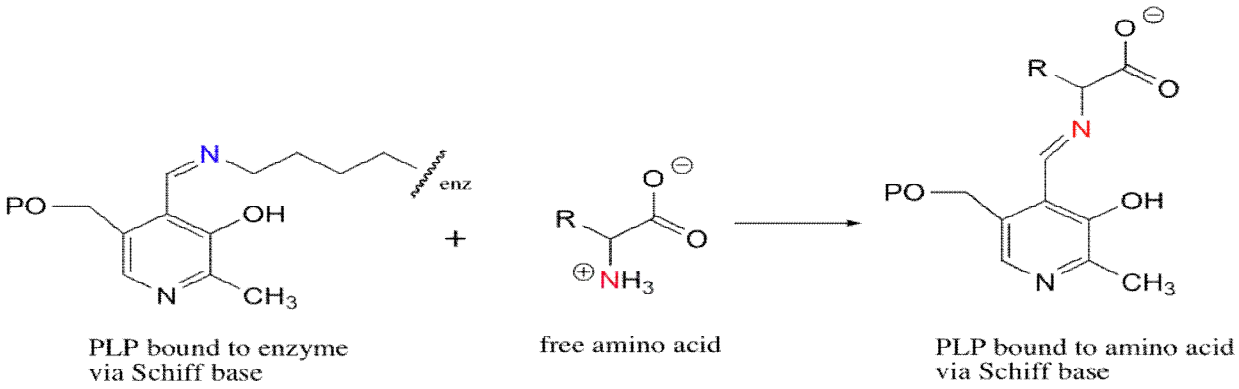
PLP

lysine
(in enzyme)

PLP linked to enzyme
via Schiff base

(Scheme 4)

Often, the next step is what could be called a Schiff base transfer: the PLP is transferred from the enzyme lysine to the nitrogen of the amino acid substrate. **(Scheme 5)**



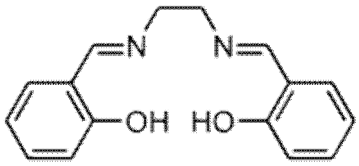
PLP bound to enzyme via Schiff base

free amino acid

PLP bound to amino acid via Schiff base

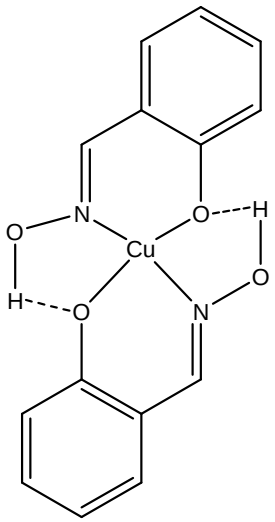
(Scheme 5)

m) Use in Coordination chemistry**:** Schiff bases are common ligands in coordination chemistry. The imine nitrogen is basic and exhibits pi-acceptor properties. The ligands are typically derived from alkyl diamines and aromatic aldehydes.[27] Salenis a common tetradentate ligand, it becomes deprotonated upon complexation.



Structure of Salen

For example, Copper (II) complex of the Schiff base ligand salicylaldoxime.



1.4. Reactions of Imines:

The most important reactions of imines are their hydrolysis to the corresponding amine and carbonyl compound. Otherwise this functional group participates in many other reactions, many of which are analogous to the reactions of aldehydes and ketones.

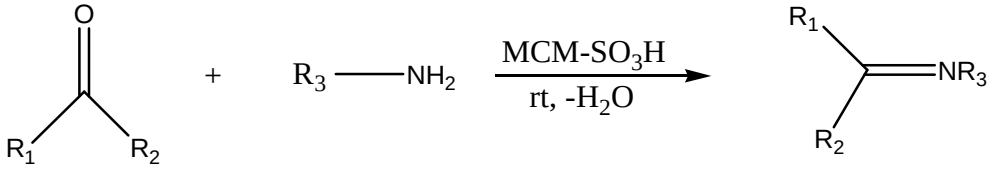
- An imine reacts with an amine to an aminal, for example the synthesis of cucurbituril.
- An imine reacts with dienes in the Aza Diels-Alder reaction to a tetrahydropyridine.
- An imine can be oxidized with meta-chloroperoxybenzoic acid (mCPBA) to give an oxaziridine
- An aromatic imine reacts with an enol ether to a quinoline in the Povarov reaction.
- A tosylimine reacts with an α,β-unsaturated carbonyl compound to an allylicamine in the Aza-Baylis–Hillman reaction.
- Imines are intermediates in the alkylation of amines with formic acid in the Eschweiler-Clarke reaction.
- A rearrangement in carbohydrate chemistry involving an imine is the Amadori rearrangement.
- A methylene transfer reaction of an imine by an unstabilisedsulphoniumylide can give an aziridine system.
- An imine is an intermediate in reductive amination.

1.5. Different arenas of Imines formation:

Many procedures have been introduced for the preparation of imines in the literature since the pioneering work of Hugo Schiff.

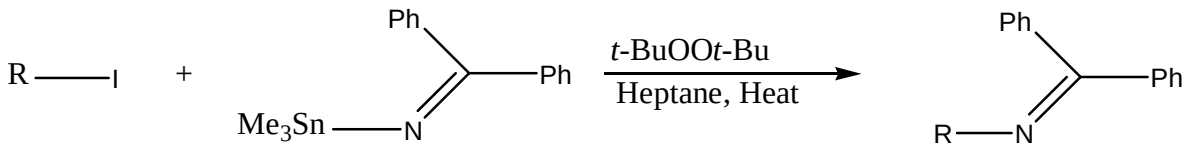
a) Effective synthesis of imines by MCM-41-SO_3H nanocatalyst: Nano-ordered MCM-41 anchored sulfonic acid (MCM-41- SO_3H) was used as an efficient heterogeneous catalyst for the synthesis of Schiff bases by the reaction of different aryl/alkyl aldehydes or ketones with primary amines at room temperature with high to excellent yields. **(Scheme 6)**

In a model reaction, to a mixture of 4-chlorobenzaldehyde (0.140 g, 1 mmol) and aniline (0.093 g, 1 mmol) in 5ml ethanol in around bottom flask, MCM-41-SO_3H (0.005 g) was added slowly, with stirring at room temperature.



(Scheme 6)

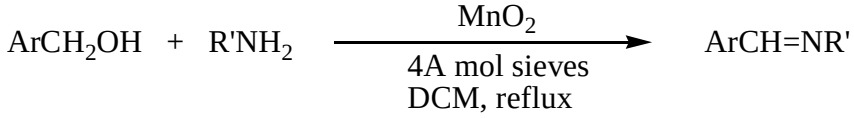
b) **Synthesis of imines by Radical Reaction:** *N*-trimethylstannylatedbenzophenone imine is a novel radical acceptor.The reaction of various primary, secondary and tertiary alkyl radical with *N*-trimethylstannylatedbenzophenone imine to provide corresponding imine.[28]**(Scheme 7)**



(R= *prim, sec* and *tert*-alkyl)

(Scheme 7)

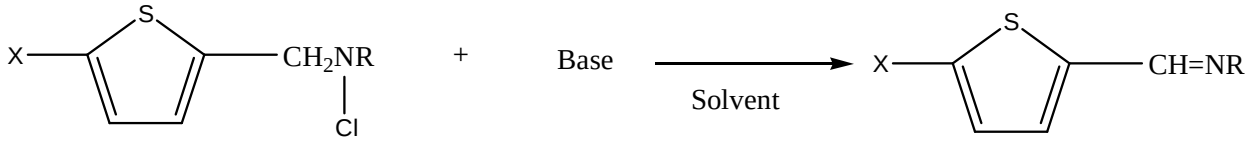
c) **Synthesis of imines by In Situ oxidation:** A new process for the conversion of alcohol into imine was developed. Manganese dioxide is employed as an in situ oxidant for the one-pot conversion of alcohol into imines.[29] **(Scheme 8)**



(Scheme 8)

d) **Synthesis of imines by Elimination reactions of *N*-Alkyl- *N*-chlorothenylamines:** Elimination reactions of *N*-Alkyl- *N*-chlorothenylamines with MeONa-

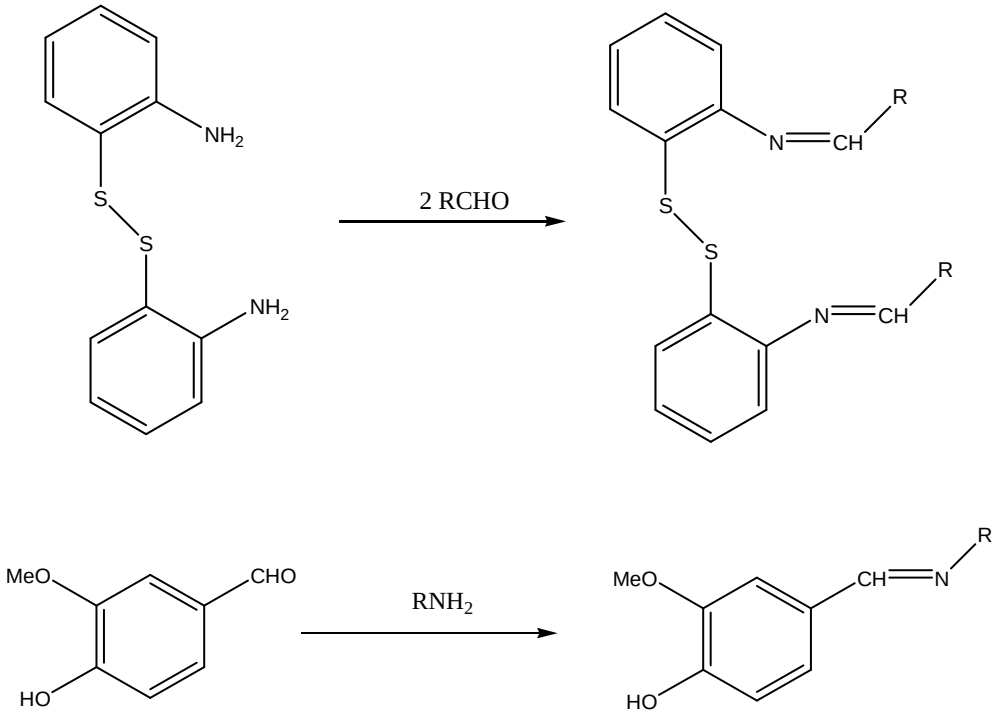
MeOH and Et_2NH-MeCN have been studied kinetically. The elimination reactions are regiospecific, producing only the conjugated imines.[30] **(Scheme 9)**



R= Me; Et; *i*-Pr; *t*-Bu
X= NO_2, Me, H, Br

(Scheme 9)

e) **Solvent less synthesis of imine:** In a typical solventless experiment the aldehyde (2 equiv.) was added to the diphenyldisulphidesdiamine (1 equiv.) and the mixture was grinding in a motor and pestle at room temperature for 5 to 20 min afforded the *bis*-imine product as a paste or a solid. Some of the reaction mixtures after grinding become viscous liquids or paste even where all reagents are solids. Amines and *p*-vanillin also produce imine by this process.[31] **(Scheme 10)**



(Scheme 10)

Several other methods exist for the synthesis of imines.

- Condensation of carbon acids with nitroso compounds.
- The rearrangement of trityl N-haloamines in the Stieglitz rearrangement.
- Dehydration of hemiaminals.[32]
- By reaction of alkenes with hydrazoic acid in the Schmidt reaction.
- By reaction of a nitrile, hydrochloric acid and an arene in the Hoesch reaction.
- Multicomponent synthesis of 3-thiazolines in the Asinger reaction.
- Primaryketimines can be synthesized via a Grignard reaction with a nitrile.[33, 34]

Some another recent methods for the preparation of imines are including polymer-supported[35], catalyzed by different Lewis acids, e.g. $ZnCl_2$[36], Infrared Irradiation[37], P_2O_5/SiO_2 [38], or molecular sieves[39], $MgSO_4$–$Mg(ClO_4)_2$[40], promoted by microwave irradiation[41], ultrasound irradiation[42], and or their combination. These methodologies often require complex procedures, long reaction times, large quantities of organic solvents, high reaction temperatures, huge amounts of costly dehydrating agents or catalysts, etc.

1.6. Amine

The **reduction of imines** is one of the most significant and useful methods for preparation of thecorrespondingamines.[43]Herein we report the results of synthesis of amines and a practical procedure for their preparation.

1.6.1 Importance of amines

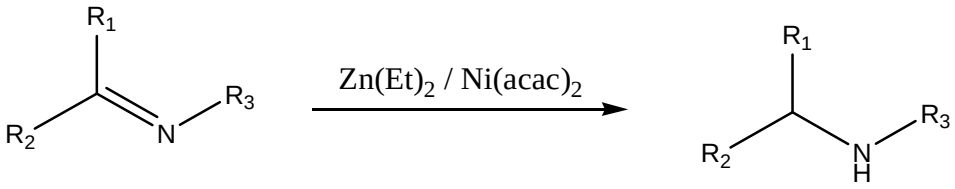
Amines and their derivatives are important functionalities in various natural and synthetic biomolecules. The amine functional group is widely present in bioactive natural products and many pharmaceutically important substances. Due to its unique biological properties the amine moiety plays a central role in chemotherapeutics of numerous diseases.[44]Considering their numerous applications in the fields of medical, bioorganic and synthetic organic chemistry, there has been tremendous interest in synthesis of amines and developing efficient methods for their

derivatives. Derivatives of 2-aminopyrimidine, 6-aminoquinoline, 1-methylpiperazine, morpholine are used as the key organic intermediates for synthesis of biomolecules.[45]For synthetic purposes, we were interested in preparation of some functionalized derivatives of these heterocyclic amines.[46]

1.6.2. Different arenas of Amine formation:

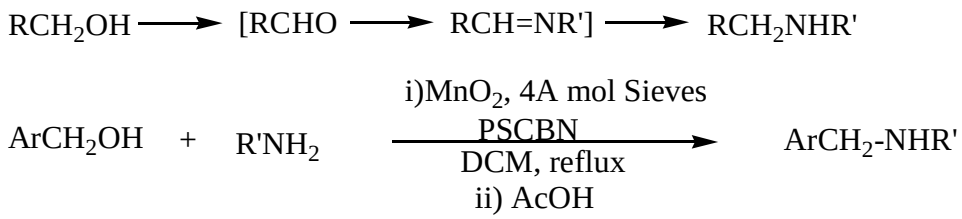
A large number of methods have been developed to prepare amine.

a) Catalytic Reduction of imine: Effective reduction of imines by employing diethylzinc as a reductant in the prsesence of a catalytic amount of $Ni(acac)_2$ as an important complement to imine reduction protocols.[47]**(Scheme 11)**



(Scheme 11)

b) Conversion of alcohol into amine: The conversion of alcohol into amines via an in situ oxidation-imine formation reduction sequence shown in Scheme **(Scheme 12)**.[48]Such a process would extend the well known reductive amination procedure[49] and would have the advantage that the intermediate aldehydes and imines would not require isolation. This method is useful in cases where these intermediates are unstable or otherwise difficult to handle (e.g. toxic, volatile or prone to polymerization).[50]



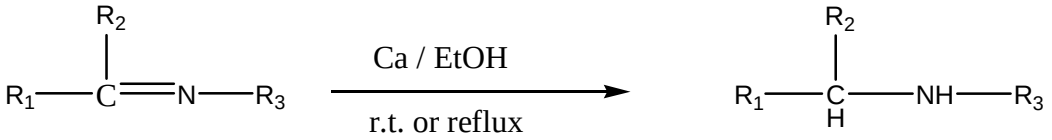
PSCBN- Polymer Supported Cyanoborohydride

(Scheme 12)

Manganese dioxide is employed as an in situ oxidant for the one-pot conversion of alcohols into imines. In combination with Polymer Supported Cyanoborohydride (PSCBN), a one-pot oxidation imine formation-reduction sequence is reported here. This procedure enables alcohols to be converted directly into both secondary and tertiary amines.

c) **Zinc powder in aqueous 5% NaOH solution:** Zinc powder in aqueous 5% NaOH solutionis effective for the reduction of imines to corresponding amines.[51]

d) **Reduction of imines using Ca in EtOH:** The reduction of aromatic and aliphatic imines using metallic calcium in ethanol is a rapid and convenient method for formation of secondary amines in high yields without any undesired by-product, such as reductive coupling or hydrolysis products.[52] **(Scheme 13)**



R_1= *p*-CH_3-C_6H_4-, *m*-CH_3O-C_6H_4-, *p*-F-C_6H_4-, C_5H_{11}-, C_6H_5-

R_2= H, CH_3-, C_6H_5-

R_3= *p*-CH_3-C_6H_4-, *p*-F-C_6H_4-, C_6H_5-CH_2-, C_6H_5-, $(CH_3)_3C$-, C_3H_7-

(Scheme 13): Reduction of imines using calcium in ethanol.

1.7. Iodination of imine:

In numerous transformations, aryl iodides are valuable synthetic intermediate, particularly in metal-catalyzed cross-coupling reaction.[53,54] Electrophilic iodination of aniline, phenols,

provides straightforward access to a wide range of essential iodoarene intermediates[55,56], and it was reported that iodine bonded at the *ortho* position to -NH_2 or –$NHCOCH_3$ makes the molecule a very convenient synthon for further transformation.[57,58] In synthesis of *N*-substituted-3-alkylisoindoline esters[59], isocoumarin[60], and α-(aminocarbonyl)iminly radicals[61], aryl iodides provided evidence of their potential applications. Some iodo aromatic compounds are employed in medicine as drugs or diagnostic aids. For instance, a notable imaging agent (iodo-PK11195) and galanthamine drug synthesized from iodo intermediate are frequently used for testing Alzheimer patients.[62,63] The iodoarenes moiety is also an important structural motif of various bioactive compounds, such as berkelic acid methyl ester.[64] The challenge of introducing iodine is particularly important since iodine is preferred over other aromatic halides for some reactions.

Moreover, halogen (especially Br and I) atoms form halogen bonding analogous to hydrogen bonding and these noncovalent interactions play pivotal roles in biological and chemical systems. In halogen bonding[65-67], X atom can act as an electron deficient (electropositive crown or σ-hole) Lewis acid which in turn attracted by electron rich Lewis bases (such as carbonyl oxygen, amine nitrogen). The halogen bonding phenomena are also widely available in the biological molecules such as proteins in which some halogenated ligands form noncovalent halogen bonding with carbonyl oxygen of amino acids.[68] It is also observed that installing halogen in some drugs can significantly enhance the performance since halogen atom can enter through the hydrophobic regions of integral membrane proteins.[69] That's why the versatility of the C-I bond makes aryl iodides essential buildings block in medicinal chemistry, supramolecular chemistry and material science.

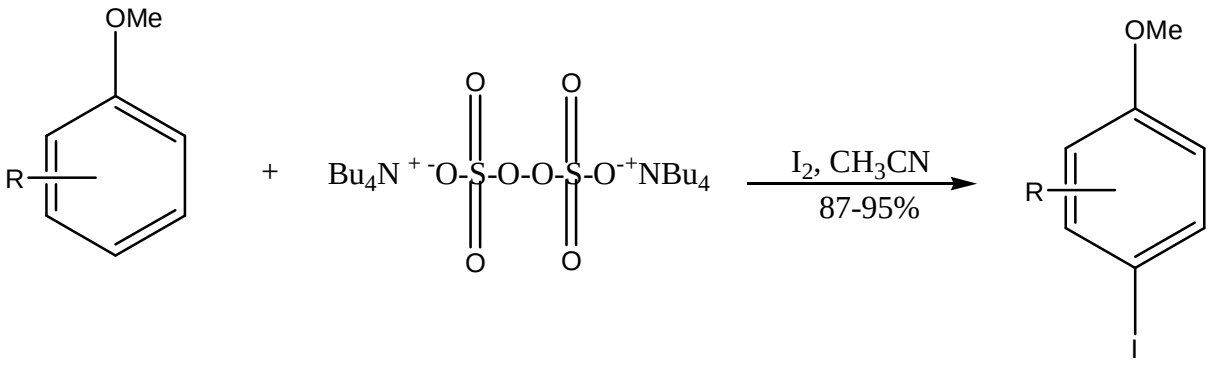
Different methods, direct and indirect, are applied for iodoarene synthesis.[70-72] In direct aromatic iodination, the iodonium species directly forms carbon-iodine bond.[73]However, direct halogenations suffer from some difficulties; firstly, the halogens have incredibly dissimilar reactivity, with iodine generally requiring some technique of activation, whereas others are reactive and hazardous chemicals.[74] Secondly, there is a reducing effect of hydrogen iodide produce in the system.[75] Iodination is carried out under oxidative conditions, where iodine ions formed in reactions are oxidized to molecular iodine. The oxidizing agents can degrade sensitive groups, for this reason it is not always feasible. Several iodination methods have been reported using various reagents, such as-py, ICl, MeOH[76]; I_2, $NaNO_2$, H_2O-MeOH[77]; I_2/CAN[78]; KI or I_2/polyvinylpyrrolodone supported $H_2O_2/H_3PW_{12}O_{40}$ in CH_2Cl_2[79];I_2-HIO_3[80];$NaBO_3.4H_2O/I_2$ in

ionic liquids[81]; NIS(N-Iodosuccinimide), $[Rh(III)CpCl_2]_2AgSbF_6$,Pi-vOH in 1,2-DCE[82]; {[K.18-C-6]ICl_2}$_{n.}$[83] Moreover, Baird and Surridge reported[84] that the iodination of aromatic compounds with iodine and copper(II) halides gave the aryl iodides. It is also indicated that the iodination of less reactive substrates with iodie aluminum (III) and copper (II) clorides[85] provided the corresponding aryl halides. Although numerous methods related to the iodination of aromatic compound for various transformations are available, there is still a vast need finding of trouble-free, nonhazardous and cost effective reagents for the introduction of iodine into an aromatic ring.

1.7.1. Iodination of different Arenas

Iodination of aromatic compounds using $(TBA)_2S_2O_8$ and Iodine: A combination of tetrabutylammoniumperoxydisulfate, $(TBA)_2S_2O_8$and Iodine has been found to be an excellent reagent for the efficient iodination of aromatic compounds such as methoxybenzene, phenol and aniline acetonitrile under mild conditions. This reaction has an advantage to be carried outat 20°C under the neutral condition in acetonitrile.

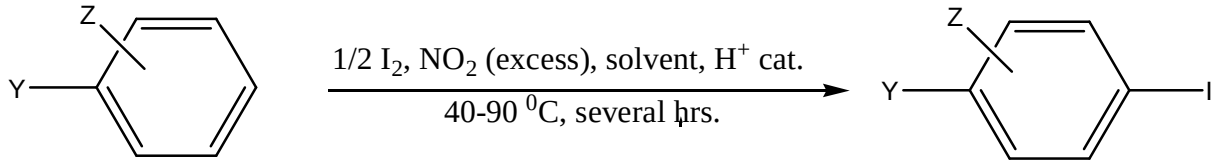
Tetrabutylammoniumperoxydisulfate, $(TBA)_2S_2O_8$ was successfully prepared[87] and turned out to be useful source of tetrabutylammonium sulfate radical, which can be readily converted to sulfate anion by one electron transfer from substrate.[86]**(Scheme 14)**



(Scheme 14)

Direct Aromatic Iodination Using Iodine and Nitrogen Dioxide

The method is based on the *in situ* oxidation of iodine by nitrogen dioxide.[88]The reaction is carried at out simply by bubbling nitrogen oxide, or adding a solution of it, into a mixture of the substrate and an equivalent amount of iodine in an appropriate solvent with a catalytic amount of an acid. **(Scheme 15)**



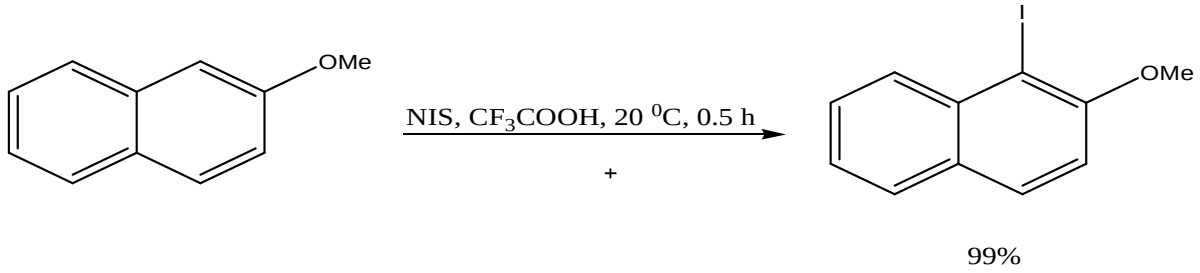
Y,Z= H, alkyl, aryl, alkoxy, aryloxy, arylthio, acetoxy and acetylamino groups.

Y>Z (Electron donating ability)

(Scheme 15)

Regioselective Iodination of Activated Aromatic Compounds

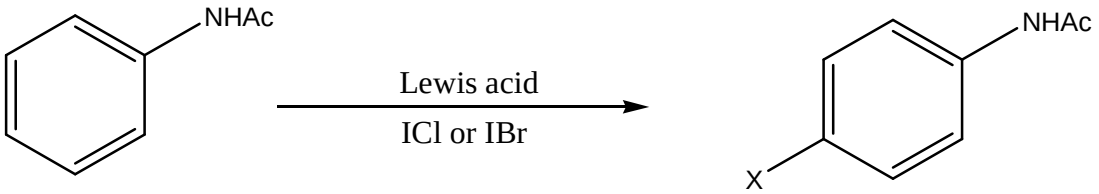
A combination of *N*-iodosuccinamide[89] (1.1 equiv.) and catalytic trifluoroacetic acid (0.3 equiv.) is an excellent reagent for regioselective iodination of activated aromatic compounds. A variety of commercially available methoxy and methyl aromatic derivatives were submitted of the reaction with NIS and cat. CF_3COOH and result are collected that iodination of methoxy aromatic derivatives took place with high yield at a temperature, 20°C with short reaction time.**(Scheme 16)**



(Scheme 16)

Optimization of Aromatic Iodination

The activating properties of various Lewis acids, together with either ICl or IBr, were examined using the halogenations of acetanilide. Acetanilide was treated with inter halogen in the presence of different Lewis acids for 15 minutes at room temperature. The reaction mixtures were then extracted and the crude mixtures were analyzed by NMR in order to estimate reaction conversion of acetanilide into halogenated products.[90] **(Scheme 17)**

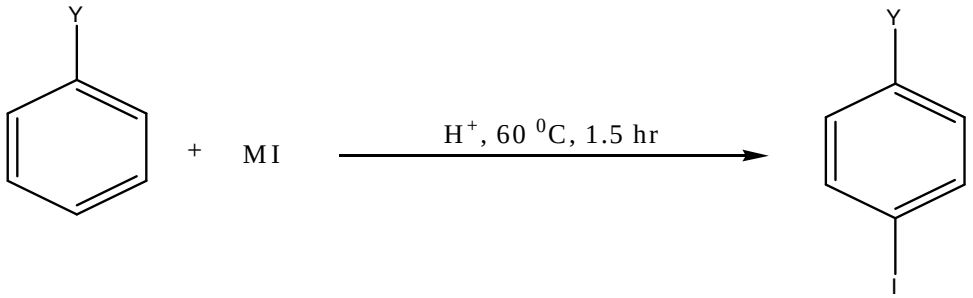


X= I or Br

(Scheme 17)

Acid Catalyzed Selective Mono iodination of Electron-Rich Arenas

The reaction of chlorobenzene and alkali metal iodides (NaI or KI) was carried out at different reaction temperatures (25°C, 40°C, 60°C, 80°C, 100°C and 120°C) in the presence of conc. H_2SO_4. The reaction goes to completion within 1.5 hour at 60°C and *p*-chloroiodobenzene was obtained in high yields.[91] **(Scheme 18)**



Y = CH_3, Cl, OCH_3, OH, NH_2
M = K,Na

(Scheme 18)

2.0. Present work: Synthesis of Imines, Amines and Halogenated Imines.

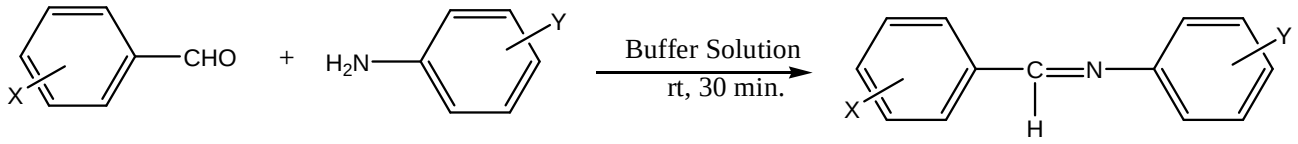
2.1. Rationale:

Imines, known as Schiff bases, are useful molecules both biologically and synthetically. The imines formation is one of the most important reactions in organic and medicinal chemistry. Imines have been discovered to have a wide range of biological activities such as lipoxygenase inhibition, anti-inflammatory, anti-cancer, antibacterial, and antifungal behavior. Imines are used as versatile components in the asymmetric synthesis of α-aminonitriles, preparation of secondary amines by hydrogenation and in cycloaddition reactions. Imino esters, such as the N-p-methoxyphenyl (N-PMP) α-imino ethyl glyoxalate are important electrophiles that, when reacted with organic nucleophiles, can produce optically α and β-amino acid derivative as well as β-lactams. The amino acid derivatives, containing imine moiety are useful precursors to natural and medicinal products including antibiotics. Physiologically, imines are essential components of many systems, such as vision and a variety of enzymatic reactions. Aldimines containing imine moiety have comprised a broad reaction class that occupies a privileged place in asymmetric synthesis. The development of metal-catalyzed imine synthesis may offer important advantages over acid catalyzed imine, exchange, including selectivity, mild reaction condition and varied functional group tolerances. The distereo selective aza-Diels-Alder reaction between cyclopentadiene chiral glyoxalate –derived imines is used to synthesize chiral ligands and synthetic precursors. The imine and amine functional group is widely present in bioactive natural products and many pharmaceutically important substances. Imines can be reduced to the corresponding secondary amine. A few methods have been developed to prepare imine and amines. There still exist many challenges and opportunities for the synthesis of imine and its derivatives. Therefore, it was planned to develop condensation reaction between aldehyde and primary amine to obtain substituted imine and to synthesize halogenated imine derivatives. It was also planned to synthesis amine from synthesized imines. It was expected to develop a facile, economic and green method for construction of imine, amine and halogenated imine derivatives.

2.2. Results and Discussion:

2.2.1 Synthesis of Imines 11-17

The compounds **11-17** were synthesized by treating substituted aldehyde with aryl amine in methanol and in the presence of acetic acid buffer (P^H was fixed at 5.5-5.6) solution at room temperature for 10-30 minutes **(Scheme 1)**. After usual workup, the crude products were purified by column chromatography on silica gel using n-hexane: ethyl acetate (10:1) as eluent and products **11-17** were isolated.



1-4 **5-10** **11-17**

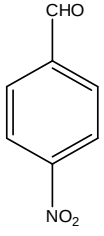
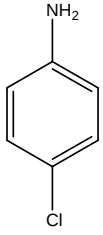
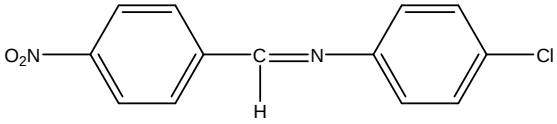
1, 11 X = NO_2-*p*; **2, 12** X = OCH_3-*p*; **3, 13** X = H; **1, 14** X = NO_2-*p*; **1, 15** X = NO_2-*p*; **4, 16** X = CH_3-*p*; 1, 15 X = NO_2-*p*

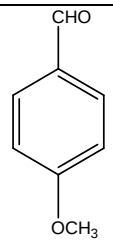
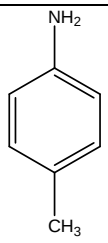
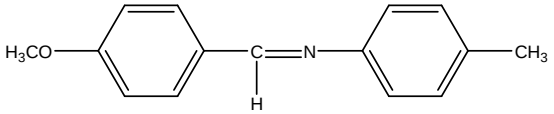
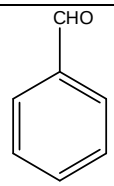
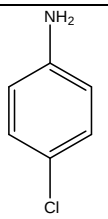
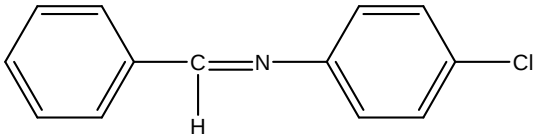
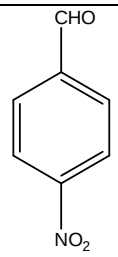
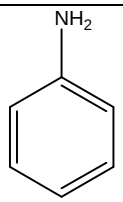
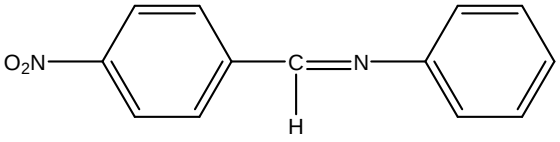
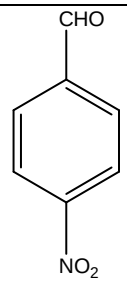
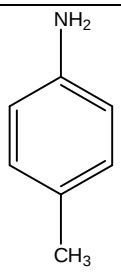
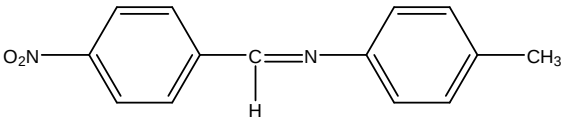
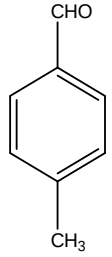
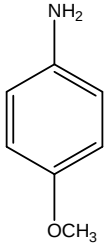
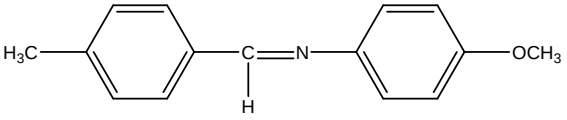
5, 11 Y = Cl-*p*; **6, 12** Y = CH_3-*p*; **5, 13** Y = Cl-*p*; **7, 14** Y = H; **6, 15** Y = CH_3-*p*; **8, 16** Y = OCH_3-*p*; **9, 17** Y = CH_3-*m*;

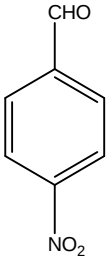
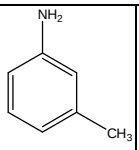
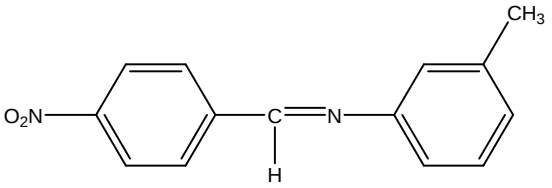
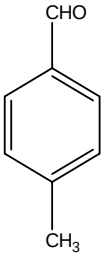
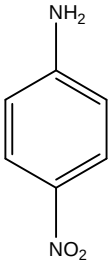
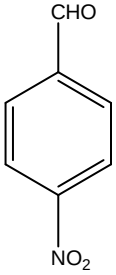
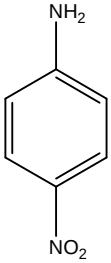
Scheme 1

The results are given in the Table **1**.

Table 1: Synthesis of Imines

Sl. No.	Aldehyde	Amines	Reagent & Condition	Products	Yield (%)
1	 **1**	 **5**	MeOH, Acetic acid Buffer, r.t. 10 min	 **11**	68

2	 **2**	 **6**	MeOH, Acetic acid Buffer, r.t. 10 min	 **12**	73
3	 **3**	 **5**	MeOH, Acetic acid Buffer, r.t. 10 min	 **13**	67
4	 **1**	 **7**	MeOH, Acetic acid Buffer, r.t. 30 min	 **14**	71
5	 **1**	 **6**	MeOH, Acetic acid Buffer, r.t. 30 min	 **15**	68
6	 **4**	 **8**	MeOH, Acetic acid Buffer, r.t. 10 min	 **16**	78

7	 **1**	 **9**	MeOH, Acetic acid Buffer, r.t. 10 min	 **17**	73
8	 **4**	 **10**	MeOH, Acetic acid Buffer, 120° C, 48 hours.	**No Reaction**	
9	 **1**	 **10**	MeOH, Acetic acid Buffer, 120° C, 48 hours.	**No Reaction**	

N.B: Yield % was calculated on the basis of aldehyde.

Substituted aldehydes **1-4** and substituted primary aryl amines **5-10** were used in different ratio (1:1; 1:3; 3:1) for the synthesis of imine derivatives **11-17**. In all the cases un-reactant aldehyde amine were found after work up. The un-reacted aryl primary amines could be removed by using acidic work up. But removal of un-reacted aldehyde was very crucial step. Removal of aldehyde was done by repeated column chromatography. The R_f value of aldehyde and imine was very close. The suitable ratio of aldehyde and primary amine for the synthesis imine might be 1:3.

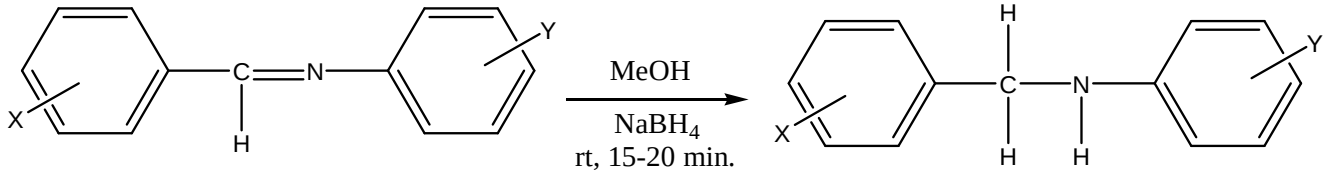
It was observed that the coupling reactions between aldehyde and amine containing electron withdrawing group were negligible at any condition. No desired compounds were isolated (Entry 8, 9; Table 1).

The coupling reactions were performed in different solvents (THF, MeCN, Ethanol and Methanol). Methanol was found as the best solvent for imine formation.

Different acid mediums were used for the preparation of imine from aldehyde amine. Acetic acid buffer (P^H at 5.5-5.6) was found to be the best medium for the coupling reaction. In strong acid medium salt of amines were formed. In basic or neutral medium carbocation did not form.
The coupling reactions were performed at different temperature (25° C, 80° C and 120° C). At higher temperature the yield percent was not increased, and un-reacted aldehyde and primary amine were found. Therefore, room temperature was found to be suitable condition.

2.2.2. Synthesis of Amines 18, 19

The compounds **18, 19** were synthesized by treating imine with alcoholic $NaBH_4$ solution at room temperature for 15-20 minutes **(Scheme 2)**. After usual workup, the crude products were purified by column chromatography on silica gel using n-hexane: ethyl acetate (10:1) as eluent and products **18** and **19** were isolated.



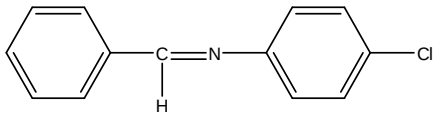
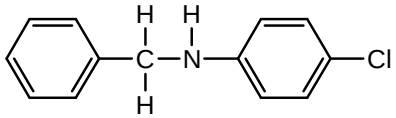
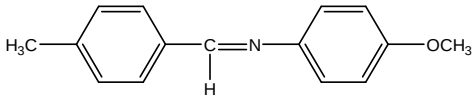
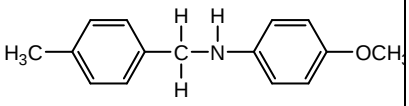
13, 16 **18, 19**

13, 18 X, Y = H, Cl-*p*; **16, 19** X, Y = CH_3-*p*, OCH_3-*p*

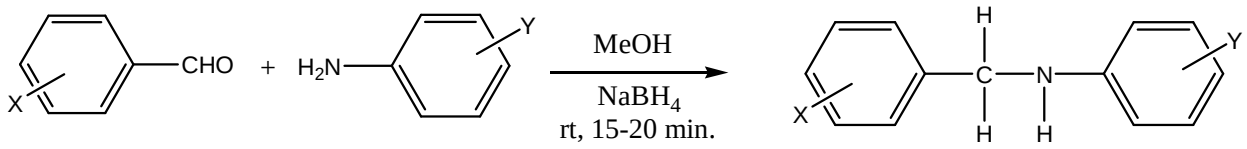
Scheme 2

The results are given in the Table **2**.

Table 2

Sl. No.	Imine	Reagent & Condition	Products	Yield (%)
1	 **13**	Alcoholic $NaBH_4$, r t, 15 min.	 **18**	85
2	 **16**	Alcoholic $NaBH_4$, r t, 20 min.	 **19**	68

2.2.3. Synthesis of Amines 20-24 in one pot reduction: The compounds **20-24** were synthesized by treating aldehyde and aryl amine with alcoholic $NaBH_4$ solution at room temperature for 15-20 minutes **(Scheme 3)**. After usual workup, the crude products were purified by column chromatography on silica gel using n-hexane: ethyl acetate (10:1) as eluant and products **20 -24** were isolated.



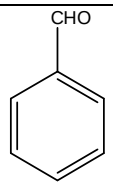
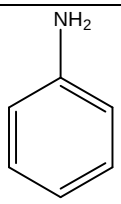
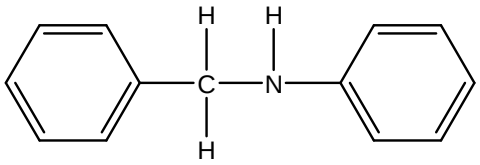
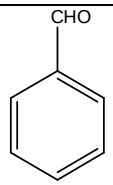
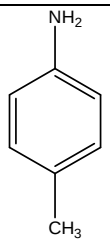
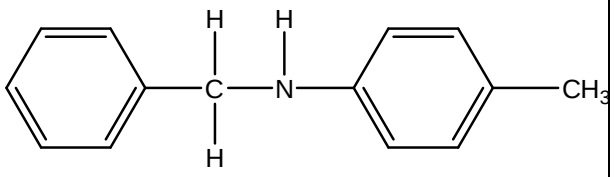
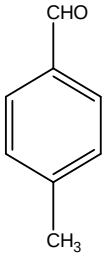
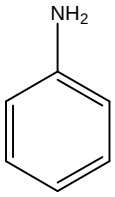
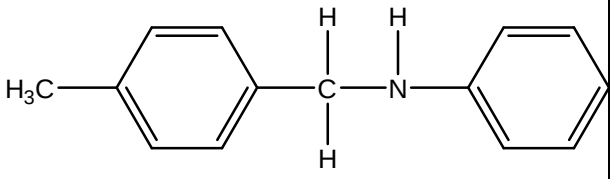
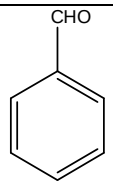
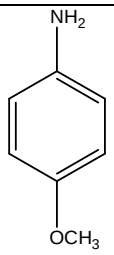
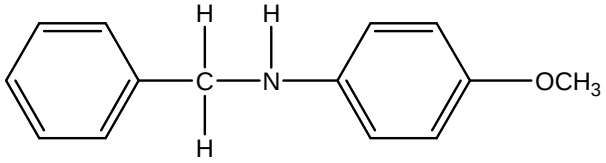
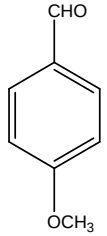
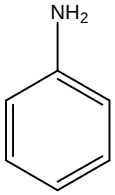
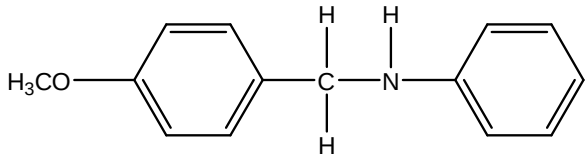
2-4 **6-8** **20-24**

3, 20 X = H; **3, 21** X =H; **4, 22 X =** CH_3-*p*; **3, 23** X = H; **2, 24** X = OCH_3-*p*

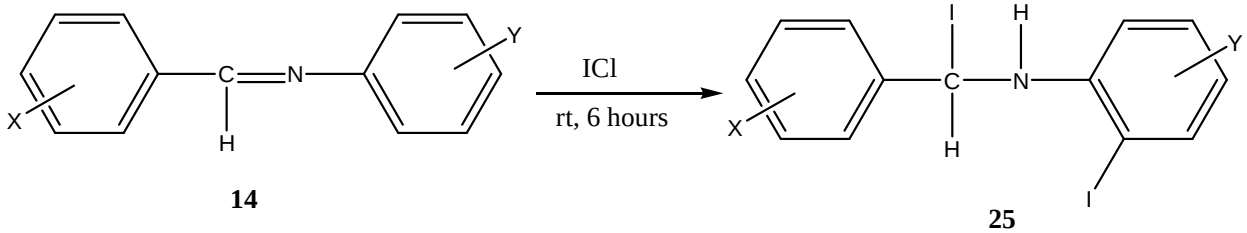
7, 20 Y =H; **6, 21** Y = CH_3-*p*; **7, 22** Y = H; **8, 23** Y = OCH_3-*p*; **7, 24** Y = H

Scheme 3

The results are given in the Table **3**.

Sl. No.	Aldehyde	Amine	Reagent & Condition	Product	Yield (%)
1	 **3**	 **7**	Alcoholic $NaBH_4$, r t, 15 min.	 **20**	61
2	 **3**	 **6**	Alcoholic $NaBH_4$, r t, 15 min.	 **21**	67
3	 **4**	 **7**	Alcoholic $NaBH_4$, r t, 15 min.	 **22**	65
4	 **3**	 **8**	Alcoholic $NaBH_4$, r t, 15 min.	 **23**	72
5	 **2**	 **7**	Alcoholic $NaBH_4$, r t, 15 min.	 **24**	55

2.2.4. Halogenation of Imine: The synthesized imine **14** was iodinated to **25** by monochloro iodine in methanol at room temperature for 6 hours as shown in the **Scheme 4.**



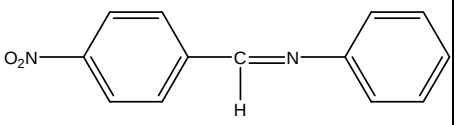
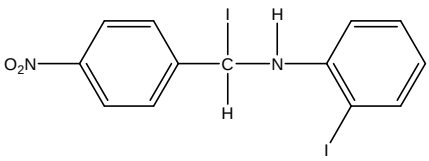
14 **25**

14, 25 X, Y = NO_2-*p*, H

Scheme 4

The results are given in the Table **4**.

Table **4**

Sl. No.	Imine	Reagent & Condition	Products	Yield (%)
1	 **14**	MeOH, ICl, 6 hours	 **25**	58

2.3. Characterization of the compounds:

2.3.1. Characterization of *N*-(4-nitrobenzylidene)-4-chlorobenzenamine 11

Compound **11** was synthesized from 4-nitro benzaldehyde and 4-chloro aniline dissolve in methnol by stirring at room temperature for around 30 minutes in presence of acetic acid buffer solution.

A yellowish crystalline solid, m. p: 136-137° C, odorless and 81 % of yield. The structure of the compound was established by UV, IR and ^{1}H NMR spectral data (Fig. 1A-1D)

The UV spectrum of the compound **11** showed λ_{max} at 345 and 295 nm.

In the FT-IR spectrum of compound **11** the absorption band was found at 3100 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 1595 cm^{-1} represents the C=C stretching vibration in the aromatic ring and imine group (C=N). The absorption band at 1517.9 cm^{-1} appeared due to the stretching vibration of NO_2 group. The bands at 1344.3 cm^{-1} and 752 cm^{-1} were due to C-N asymmetric vibration and C-Cl stretching mode respectively.

The compound **11** can be easily identified from ^1H NMR (400 MHz, $CDCl_3$) spectrum. The compound **11** contains nine hydrogens of five different types. The peak at chemical shift δ_H 8.53 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 8.32 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 8.05 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.37 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 7.18 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′.

On the basis of complete analysis of the UV, IR, ^1H NMR spectra the structure of this compound was accorded as *N*-(4-nitrobenzylidene)-4-chlorobenzenamine.

2.3.2. Characterization of *N*-(4-methoxybenzylidene)-4-methylbenzenamine 12

The UV spectrum of the compound **12** showed λ_{max} at 293 nm. (Fig. 2B)

In the FT-IR spectrum of compound **12** the absorption band was found at 2970.20 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 2844.8 cm-1 indicated the presence of O-CH_3 group. A sharp band at 1640 cm^{-1} represents the imine group (C=N) and band at 1475.0 cm^{-1} represents the C=C stretching vibration in the aromatic ring. The bands at 1450 $cm^{-1}$and 1375 cm^{-1} were due to the bending vibration of CH_3 group. The absorption band appeared at 1247.8 cm^{-1} due to the C-N stretching frequency of the compound. (Fig. 2A)

The compound **12** can be easily identified from ^1H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 2C-2D). The compound **12** contains fifteen hydrogens of seven different types. The peak at chemical shift δ_H 8.38 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 7.83 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at δ_H 7.16 ppm appears as doublet, which is assigned for two aromatic proton H-2′ &

H-6′. The peak at δ_H 7.10 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 6.96 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at chemical shift δ_H 3.86 ppm appears as singlet, which is assigned for three proton of -OCH_3. Peak at δ_H 2.35 ppm appears as singlet, which is assigned for three proton of CH_3 group.

Finally, the compound **12** was identified from ^{13}C NMR spectrum (Fig. 2E). The chemical shift at δ 162.25 and 159.13 found for C-4 and C=N carbon respectively. The peak at δ 149.87 and 135.50 represent the C-1′ and C-4′ carbons of phenyl ring respectively. The chemical shift at δ 130.54 was obtained for the two carbons C-3′ & C-5′. The chemical shift at δ 129.86 was obtained for the two carbons C-2 & C-6, on the other hand chemical shift at δ 129.51 represent the C-1 carbon. The chemical shift at δ 120.91 was obtained for the two carbons C-2′ & C-6′. The chemical shift at δ 114.29 was obtained for the two carbons C-3 & C-5. The peak at δ 55.57 and 21.13 represent the -OCH_3 and CH_3 group carbon respectively.

On the basis of complete analysis of the UV, IR, ^1H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-(4-methoxybenzylidene)-4-methylbenzenamine.

2.3.3. Characterization of *N*-benzylidene-4-chlorobenzenamine 13

The UV spectrum of the compound **13** showed λ_{max} at 294 nm. (Fig. 3B)

In the FT-IR spectrum (Fig. 3A) of compound **13** the absorption band was found at 2921.90 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 1623.9 cm-1 was due to the imine group (C=N). 1450.4 cm^{-1} represents the C=C stretching vibration in the aromatic ring. The absorption band appeared at 1311.5 cm^{-1} due to the C-N stretching frequency of the compound. Bands 819.7 cm^{-1} and 758 cm^{-1} indicated the aromatic C-H out of plane bend and C-Cl respectively.

The compound **13** can be easily identified from ^1H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 3C-3D). The compound **13** contains ten hydrogens of six different types. The peak at chemical shift δ_H 8.42 ppm appears as singlet, which is assigned for one proton -CH=N-. The peak at chemical shift δ_H 7.87 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The

peak at δ_H 7.48 ppm appears as multiplate, which is assigned for three aromatic proton H-3, H-4 & H-5.The peak at δ_H 7.33 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 7.13 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′.

On the basis of complete analysis of the UV, IR and ^{1}H NMR spectra the structure of this compound was accorded as *N*-benzylidene-4-chlorobenzenamine.

2.3.4. Characterization of *N*-(4-nitrobenzylidene)benzenamine 14

The UV spectrum of the compound **14** showed λ_{max} at 296, 279 and 271 nm. (Fig.4B)

In the FT-IR spectrum of compound **14** the absorption band was found at 1640 cm^{-1} due to the imine group (C=N), on the other hand 1595.0 cm^{-1} was due to the C=C stretching vibration in the aromatic ring. The absorption band at 1342.4 cm^{-1} appeared due to the stretching vibration of NO_2 group. (Fig.4A)

The compound **14** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 4C-4D). The compound **14** contains ten hydrogens of six different types. The peak at chemical shift δ_H 8.55 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 8.31ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 8.06 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.40 ppm appears as triplet, which is assigned for one aromatic proton H-4′.The peak at δ_H 7.29 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at chemical shift δ_H 7.24 ppm appears as doublet, which is assigned for two proton H-2′ & H-6′.

Finally, the compound **14** was identified from ^{13}C NMR spectrum (Fig. 4E-4F). The chemical shift at δ 157.52 found for C=N carbon. The peak at δ 151.06 and 149.43 represent the C-1′ and C-4 carbons of phenyl ring respectively. The chemical shift at δ 141.71 was obtained for the C-1 carbon. The chemical shift at δ 129.55 was obtained for the two carbons C-3′ & C-5′, on the other hand chemical shift at δ 129.49 represent the C-2 & C-6 carbon. The chemical shift at δ

127.23 was obtained for the C-4′ carbon. The chemical shift at δ 124.17 was obtained for the two carbons C-2′ & C-6′. The peak at 121.11 represents C-3 & C-5 carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-(4-nitrobenzylidene)benzenamine.

2.3.5. Characterization of *N*-(4-nitrobenzylidene)-4-methylbenzenamine 15

The UV spectrum of the compound **15** showed λ_{max} at 350, 318 and 302 nm. (Fig.5B)

In the FT-IR spectrum of compound **15** the absorption band was found at 3100 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 1610 cm^{-1} indicated the C=C stretching vibration in the aromatic ring. A sharp band at 1595.0 cm^{-1} represents the imine group (C=N). The absorption band appeared at 1338.5 cm^{-1} due to the C-N stretching frequency of the compound. 1338.5 cm^{-1} and 690 cm^{-1} indicated the CH_3 group and aromatic C-H out of plane bend respectively. (Fig.5A)

The compound **15** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 5C-5D). The compound **15** contains twelve hydrogens of six different types. The peak at chemical shift δ_H 8.55 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 8.29 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 8.04 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 7.21 ppm appears as doublet, which is assigned for two aromatic proton H-2′ & 6′. The peak at δ_H 7.17 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at chemical shift δ_H 2.38 ppm appears as singlet, which is assigned for three protons of CH_3 group.

Finally, the compound **15** was identified from ^{13}C NMR spectrum (Fig. 5E). The chemical shift at δ 156.50 was found for C-H carbon. The peak at δ 149.29 and 148.39 represent the C-4 and C-1′ carbon of phenyl ring respectively. The chemical shift at δ 141.91 and δ 137.39 was obtained for the C-1and C-4′ carbon. The chemical shift at δ 129.89 was obtained for the two carbons C-3′ & C-5′, on the other hand chemical shift at δ 129.42 represent the C-2 & C-6 carbon. The

chemical shift at δ 124.15 was obtained for the two carbons C-2′ & C-6′. The peak at 121.13 represents C-3 & C-5 carbon. The peak at 21.25 represents CH_3 carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-(4-nitrobenzylidene)-4-methylbenzenamine.

2.3.6. Characterization of *N*-(4-methylbenzylidene)-4-methoxylbenzenamine 16

The UV spectrum of the compound **16** showed λ_{max} at 310 and 291.5 nm. (Fig. 6B)

In the FT-IR spectrum of compound **16** the absorption band was found at 2912.3 cm^{-1} due to the -OCH_3 group, whereas the absorption band at 1623.9 cm^{-1} indicated the C=N. The band 1514.0 cm^{-1} represents the C=C stretching vibration in the aromatic ring and 1296 cm^{-1}indicates the bending vibration of CH_3 group. The absorption bands at 1031.0 cm^{-1} and 837.0 cm^{-1} appeared due to the C-N stretching vibration and aromatic C-H out of plane bend respectively. (Fig.6A)

The compound **16** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig.6C). The compound **16** contains fifteen hydrogens of seven different types. The peak at chemical shift δ_H 8.43 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 7.76 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.31 ppm appears as doublet, which is assigned for two aromatic proton H-2′ & H-6′. The peak at δ_H 7.25 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 6.91 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at chemical shift δ_H 3.82 ppm appears as singlet, which is assigned for three protons of -OCH_3 group and peak at chemical shift δ_H 2.37 ppm appears as singlet, which is assigned for three protons of CH_3 group.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-(4-methylbenzylidene)-4-methoxylbenzenamine.

2.3.7. Characterization of *N*-(4-nitrobenzylidene)-3-methylbenzenamine 17

The UV spectrum of the compound **17** showed λ_{max} at 336, 331 and 291 nm. (Fig.7B)

In the FT-IR spectrum of compound **17** the absorption band was found at 3100 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 2931.6 cm-1 indicated the stretching vibration of CH_3 group. A sharp band at 1600.0 cm^{-1} represents the imine group (C=N) and 1342.0 cm^{-1} appeared due to the stretching vibration of NO_2 group. The absorption bands at 1105.1 cm^{-1} and 858.3 cm^{-1} appeared due to the C-N stretching vibration and aromatic C-H out of plane bend respectively. (Fig.7A)

The compound **17** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 7C-7D). The compound **17** contains twelve hydrogens of eight different types. The peak at chemical shift δ_H 8.55 ppm appears as singlet, which is assigned for one proton C-H. The peak at chemical shift δ_H 8.31 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 8.08 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.29 ppm appears as tripilet, which is assigned for one aromatic proton H-5′. The peak at δ_H 7.25 ppm appears as singlet, which is assigned for one aromatic proton H-2′. The peak at chemical shift δ_H 7.08 ppm appears as multiple, which is assigned for two protons H-4′ & H-6′. Peak at chemical shift δ_H 2.35 ppm appears as singlet, which is assigned for three protons of CH_3 group.

Finally, the compound **17** was identified from ^{13}C NMR spectrum (Fig. 7E-7F). The chemical shift at δ 157.28 ppm was found for C-H carbon. The peak at δ 151.05 ppm and 149.36 was found for C-1′ & C-4 carbon respectively. The chemical shift at δ 141.77 and δ 139.37 was obtained for the C-1 and C-3′ carbon respectively. The chemical shift at δ 129.49 was obtained for the two carbons C-2 & C-6. On the other hand chemical shift at δ 129.29 represent the C-5′. The chemical shift at δ 127.99 and 124.45 was obtained for the C-4′ & C-2′ respectively. The chemical shift at δ 124.15 was obtained for C-3 & C-5. The peak at 118.07 represents C-6′. The peak at 21.53 represents CH_3 group carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-(4-nitrobenzylidene)-3-methylbenzenamine.

2.3.8. Characterization of *N*-benzylidene-4-chlorobenzenamine 18

The UV spectrum of the compound **18** showed λ_{max} at 309.50 nm. (Fig. 8B)

In the FT-IR spectrum of compound **18** the absorption band was found at 3037.7 cm^{-1} due to the stretching frequency of aromatic C-H, whereas the absorption band at 1600 cm^{-1} indicated the bending vibration of N-H. The band 1475.0 cm^{-1} represents the C=C stretching vibration in the aromatic ring and -CH_2- group. The absorption bands at 1315 $cm^{-1}$and 819 cm^{-1} appeared due to the C-N stretching vibration and aromatic C-H out of plane bend respectively. Band 758 cm^{-1} indicated the vibration of C-Cl bond. (Fig. 8A)

The compound **18** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 8C-8D). The compound **18** contains twelve hydrogens of six different types. The peak at chemical shift δ_H 7.36 ppm appears as doublet, which is assigned for two proton H-3 & H-5. The peak at chemical shift δ_H 7.31 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.11 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 6.54 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′. The peak at δ_H 4.70 ppm appears as singlet, which is assigned for two proton of -CH_2-. The peak at δ_H 4.30 ppm appears as singlet, which is assigned for one proton of N-H.

Finally, the compound **18** was identified from ^{13}C NMR spectrum (Fig. 8E). The chemical shift at δ 160.90 ppm was found for C-1′carbon. The peak at δ 150.65 ppm and 136.07 ppm was found for C-1 & C-4′ carbon respectively. The chemical shift at δ 131.78 ppm was obtained for C-3′ & C-5′ carbon. The chemical shift at δ 131.61was obtained for the C-4. On the other hand chemical shift at δ 129.38 represent the C-3 & C-5. The chemical shift at δ 129.02 was obtained for the C-2 & C-6. The peak at δ 122.35 represents C-2′ & C-6′. The peak at δ 29.85 represents -CH_2- group carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-benzylidene-4-chlorobenzenamine.

2.3.9. Characterization of *N*-4-(methylbenzylidene)-4-methoxybenzenamine 19

The UV spectrum of the compound **19** showed λ_{max} at 297 nm. (Fig. 9B)

In the FT-IR spectrum of compound **19** the absorption band was found at 2921.6 cm^{-1} due to the stretching frequency of -OCH_3 group, whereas the absorption band at 1623.9 cm^{-1} indicated the bending vibration of N-H bond. The band 1465.8 cm^{-1} represents the -CH_2- group. The absorption bands at 1234.3 $cm^{-}1$ and 825 cm^{-1} appeared due to the C-N stretching vibration and aromatic C-H out of plane bend respectively. (Fig. 9A)

The compound **19** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 9C). Compound **19** contains seventeen hydrogens of eight different types. The peak at chemical shift δ_H 7.185 ppm appears as doublet, which is assigned for two proton H-3 & H-5. The peak at chemical shift δ_H 7.13 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 6.77 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 6.62 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′. The peak at δ_H 4.23 ppm appears as singlet, which is assigned for two proton of -CH_2-. The peak at δ_H 3.83 ppm appears as singlet, which is assigned for one proton of N-H. The peak at chemical shift δ_H 3.74 ppm appears as singlet, which is assigned for three protons of -OCH_3 group and peak at chemical shift δ_H 2.34 ppm appears as singlet, which is assigned for three protons of CH_3 group.

Finally, the compound **19** was identified from ^{13}C NMR spectrum (Fig. 9D). The chemical shift at δ 152.27 ppm was found for C-4′ carbon. The peak at δ 136.95 ppm and 136.71 was found for C-1′ & C-1 carbon respectively. The chemical shift at δ 129.41 was obtained for the C-3 and C-5. The chemical shift at δ 127.69 was obtained for the two carbons C-2 & C-6. The chemical shift at δ 122.28 was found for C-4. On the other hand chemical shift at δ 115.02 represent the C-3′ & C-5′. The chemical shift at δ 114.23 represent the C-2′ & C-6′.The chemical shift at δ 55.95 and 49.14 was obtained for the -OCH_3 and –CH_2- carbon respectively. The peak at 21.25 represents CH_3 group carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-4-(methylbenzylidene)-4-methoxybenzenamine.

2.3.10. Characterization of *N*-benzylbenzenamine 20

The UV spectrum of the compound **20** showed λ_{max} at 297.5 nm. (Fig.10B)

In the FT-IR spectrum of compound **20** the absorption band was found at 3415.7 cm^{-1} due to the N-H stretching frequency, whereas the absorption band at 3037.7 cm^{-1} indicated Ar C-H stretching. The band 1610.4 cm^{-1} represents the aromatic C=C stretching. The absorption bands at 1321.1cm^{-1} and 1450 cm^{-1} appeared due to the C-N stretching vibration and -CH_2- bending respectively. The absorption band at 690 represents Ar C-H out of plane bending. (Fig. 10A)

The compound **20** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 10C-10E). Compound **20** contains thirteen hydrogens of eight different types. The peak at chemical shift δ_H 7.35 ppm appears as multiple, which is assigned for two proton H-3 & H-5. The peak at chemical shift δ_H 7.17 ppm appears as triplet, which is assigned for one aromatic proton H-4. The peak at δ_H 7.14 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 7.09 ppm appears as double doublet, which is assigned for two aromatic proton H-3′& H-5′. The peak at δ_H 6.68 ppm appears as triplet, which is assigned for one proton H-4′. The peak at δ_H 6.62 ppm appears as doublet, which is assigned for two proton H-2′& H-6′. The peak at chemical shift δ_H 4.32 ppm appears as singlet, which is assigned for two protons of -CH_2- group and peak at chemical shift δ_H 3.80 ppm appears as singlet, which is assigned for one proton of –NH- group.

Finally, the compound **20** was identified from ^{13}C NMR spectrum (Fig. 10F). The chemical shift at δ 148.22 ppm was found for C-1′ carbon. The peak at δ 139.51 ppm was found for C-1 carbon. The chemical shift at δ 129.38 was obtained for the C-3′ & C-5′. The chemical shift at δ 128.75 was obtained for the two carbons C-3 & C-5. The chemical shift at δ 127.63 was found for C-2 & C-6. On the other hand chemical shift at δ 127.34 represent the C-4 carbon. Chemical shift at δ 117.69 represent C-4′ carbon. Chemical shift at δ 112.97 represent C-2′ & C-6′ carbon. The chemical shift at δ 48.43 was obtained for –CH_2- carbon.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-benzylbenzenamine.

2.3.11. Characterization of *N*-benzyl-4-methylbenzenamine 21

The UV spectrum of the compound **21** showed λ_{max} at 297.5 nm. (Fig.11B)

In the FT-IR spectrum of compound **21** the absorption band was found at 3037.7 cm^{-1} indicated Ar C-H stretching. The band at 1550.7 cm^{-1} and 1249.8 cm^{-1} were found for N-H bending and C-N stretching respectively. The absorption band at 698 cm^{-1} indicates out of plane bending of Ar C-H. (Fig. 11A)

The compound **21** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 11C-11D). Compound **21** contains fifteen hydrogens of six different types. The peak at chemical shift δ_H 7.33 ppm appears as multiple, which is assigned for three proton H-3, H-4 & H-5. The peak at chemical shift δ_H 7.25 ppm appears as dublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 6.99 ppm appears as doublet, which is assigned for two aromatic proton H-3′& H-5′.The peak at δ_H 6.59 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′. The peak at δ_H 4.31 ppm appears as singlet, which is assigned for two proton of -CH_2- group. The peak at chemical shift δ_H 2.23 ppm appears as singlet, which is assigned for three protons of –CH_3 group.

Finally, the compound **21** was identified from ^{13}C NMR spectrum (Fig. 11E). The chemical shift at δ 143.60 ppm was found for C-1′ carbon. The peak at δ 139.52 ppm was found for C-1 carbon. The chemical shift at δ 129.88 was obtained for the C-3′ & C-5′. The chemical shift at δ 128.73 was obtained for the two carbons C-3 & C-5. The chemical shift at δ 127.71 was found for C-2 & C-6. On the other hand chemical shift at δ 127.33 represent the C-4 carbon. Chemical shift at δ 127.20 represent C-4′ carbon. Chemical shift at δ 113.88 represent C-2′ & C-6′ carbon. The chemical shift at δ 48.43 and 20.54 were obtained for –CH_2- and –CH_3 group carbon respectively.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-benzyl-4-methyllbenzenamine.

2.3.12. Characterization of *N*-4-(methylbenzylidene)-benzenamine 22

The UV spectrum of the compound **22** showed λ_{max} at 297.5 nm. (Fig.12B)

In the FT-IR spectrum of compound **22** the absorption band was found at 3425.3 cm^{-1} for N-H stretching. The absorption band at 3037.7 cm^{-1} indicated Ar C-H stretching. Band at 1604.7 cm^{-1} and 1431.1 cm^{-1} were found for Ar C=C stretching respectively. Band at 1325 cm^{-1} and 694.3 cm^{-1} were found for C-N and Ar C-H out of plane bend respectively. (Fig.12A)

The compound **22** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 12C-12D). Compound **22** contains fifteen hydrogens of seven different types. The peak at chemical shift δ_H 7.24 ppm appears as triplet, which is assigned for two proton H-3′& H-5′. The peak at chemical shift δ_H 7.14 ppm appears as multiple, which is assigned for four aromatic proton H-2, H-3, H-5 & H-6. The peak at δ_H 6.68 ppm appears as multiple, which is assigned for one aromatic proton H-4′.The peak at δ_H 6.61 ppm appears as doublet, which is assigned for two aromatic proton H-2′& H-6′. The peak at δ_H 4.27 ppm appears as singlet, which is assigned for two proton of -CH_2- group. The peak at δ_H 3.76 ppm appears as singlet, which is assigned for one proton of -NH- group. The peak at chemical shift δ_H 2.33 ppm appears as singlet, which is assigned for three protons of –CH_3 group.

Finally, the compound **22** was identified from ^{13}C NMR spectrum (Fig. 12E). The chemical shift at δ 148.32 ppm was found for C-1′ carbon. The peak at δ 136.98 ppm was found for C-1 carbon. The chemical shift at δ 136.45 was obtained for the C-4 carbon. The chemical shift at δ 129.42 was obtained for C-3′ & C-5′ carbon. The chemical shift at δ 129.37 was found for C-3 & C-5. On the other hand chemical shift at δ 127.64 was found for C-2 & C-6. Chemical shift at δ 117.59 represent C-4′ carbon. Chemical shift at δ 112.94 represent C-2′ & C-6′ carbon. The chemical shift at δ 48.12 and 21.23 were obtained for –CH_2- and –CH_3 group carbon respectively.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-4-(methylbenzylidene)-benzenamine.

2.3.13. Characterization of *N*-benzyl-4-methoxybenzenamine 23

The UV spectrum of the compound **23** showed λ_{max} at 297.5 nm. (Fig.13B)

In the FT-IR spectrum of compound **23** the absorption band was found at 3450 cm^{-1} for N-H stretching. The absorption band at 3015 cm^{-1} indicated Ar C-H stretching. Band at 1548.7 cm^{-1} and 1454.2 cm^{-1} were found for Ar C=C stretching and -CH_2- respectively. Band at 1245.9 cm^{-1} and 698.2 cm^{-1} were found for C-N and Ar C-H out of plane bend respectively. (Fig. 13A)

The compound **23** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 13C-13D). Compound **23** contains fifteen hydrogens of eight different types. The peak at chemical shift δ_H 7.54 ppm appears as doublet, which is assigned for two proton H-3 & H-5. The peak at chemical shift δ_H 7.38 ppm appears as multiple, which is assigned for one aromatic proton H-4. The peak at δ_H 6.94 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 6.76 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at δ_H 6.60 ppm appears as doublet, which is assigned for two aromatic proton H-2′ & H-6′. The peak at δ_H 4.28 ppm appears as singlet, which is assigned for two proton of -CH_2- group. The peak at δ_H 3.83 ppm appears as singlet, which is assigned for one proton of -NH- group. The peak at chemical shift δ_H 3.74 ppm appears as singlet, which is assigned for three protons of –OCH_3 group.

Finally, the compound **23** was identified from ^{13}C NMR spectrum (Fig. 13E). The chemical shift at δ 152.34 ppm was found for C-4′ carbon. The peak at δ 142.49 ppm was found for C-1 carbon. The chemical shift at δ 139.74 was obtained for the C-1′ carbon. The chemical shift at δ 128.88 was obtained for C-3 & C-5 carbon. The chemical shift at δ 127.70 was found for C-2 & C-6. On the other hand chemical shift at δ 127.32 was found for C-4. Chemical shift at δ 115.02 represent C-3′ & C-5′ carbon. Chemical shift at δ 114.50 represent C-2′ & C-6′ carbon. The chemical shift at δ 55.94 and 49.41 were obtained for –OCH_3 and –CH_2- group carbon respectively.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-benzyl-4-methoxybenzenamine.

2.3.14. Characterization of *N*-4-methoxybenzylidene-benzenamine 24

The UV spectrum of the compound **24** showed λ_{max} at 296.5 nm. (Fig. 14B)

In the FT-IR spectrum of compound **24** the absorption band was found at 3400 cm^{-1} for N-H stretching. The absorption band at 3000 cm^{-1} indicated Ar C-H stretching. Band at 1604.7 cm^{-1} and 1359.7 cm^{-1} were found for Ar C=C stretching and C-N respectively. Band at 698.2 found for C-N Ar C-H out of plane bend respectively. (Fig. 14A)

The compound **24** can be easily identified from ^{1}H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 14C-14D). Compound **24** contains fifteen hydrogens of eight different types. The peak at chemical shift δ_H 7.26 ppm appears as doublet, which is assigned for two aromatic proton H-3′ & H-5′. The peak at chemical shift δ_H 7.14 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 6.86 ppm appears as doublet, which is assigned for two aromatic proton H-3 & H-5. The peak at δ_H 6.81 ppm appears as doublet, which is assigned for two aromatic proton H-2′ & H-6′. The peak at δ_H 6.65 ppm appears as multiple, which is assigned for one aromatic proton H-4′. The peak at δ_H 4.24 ppm appears as singlet, which is assigned for two proton of -CH_2- group. The peak at δ_H 3.79 ppm appears as singlet, which is assigned for one proton of -NH- group. The peak at chemical shift δ_H 3.78 ppm appears as singlet, which is assigned for three protons of –OCH_3 group.

Finally, the compound **24** was identified from ^{13}C NMR spectrum (Fig. 14E). The chemical shift at δ 158.96 ppm was found for C-4 carbon. The peak at δ 148.32 ppm was found for C-1′ carbon. The chemical shift at δ 147.59 was obtained for the C-1′ carbon. The chemical shift at δ 129.31 was obtained for C-3′ & C-5′ carbon. The chemical shift at δ 128.94 was found for C-2 & C-6. On the other hand chemical shift at δ 117.38 was found for C-4′. Chemical shift at δ 114.13 represent C-3′ & C-5′ carbon. Chemical shift at δ 113.52 represent C-2′ & C-6′ carbon. The chemical shift at δ 55.42 and 47.91 were obtained for –OCH_3 and –CH_2- group carbon respectively.

On the basis of complete analysis of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as *N*-4-methoxybenzylidene-benzenamine.

2.3.15. Characterization of 2-iodo-*N*-(iodo(4-nitophenyl)methyl)benzenamine 25

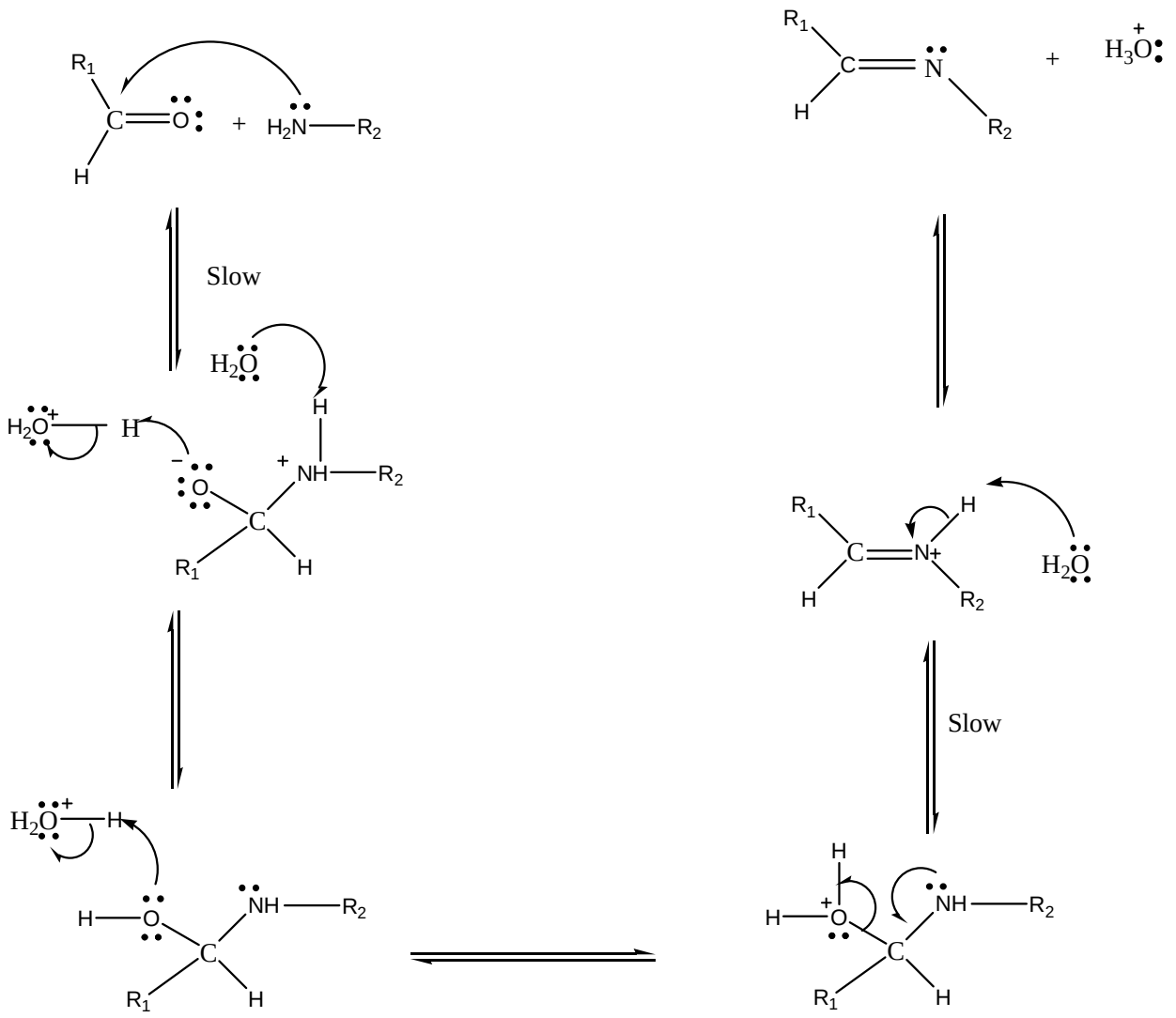
The UV spectrum of the compound **25** showed λ_{max} at 296.50 nm. (Fig. 15B)

In the FT-IR spectrum of compound **25** the absorption band was found at 3350 cm^{-1} for N-H stretching. The absorption band at 1622.0 cm^{-1} indicated N-H bending. Band at 1514 cm^{-1} and 1350.1 cm^{-1} were found for NO_2 and C-N respectively. Band at 814.4 and 694.3 found for aromatic C-H out of plane bending and C-I respectively. (Fig. 15A)

The compound **25** can be easily identified from ^1H NMR (400 MHz, $CDCl_3$) spectrum (Fig. 15C-15D). The compound **25** contains ten hydrogens of seven different types. The peak at chemical shift δ_H 8.15 ppm appears as doublet, which is assigned for two proton H-3 & H-5. The peak at chemical shift δ_H 7.55 ppm appears as doublet, which is assigned for one aromatic proton H-5′. The peak at δ_H 7.12 ppm appears as triplet, which is assigned for one aromatic proton H-3′. The peak at δ_H 7.02 ppm appears as doublet, which is assigned for two aromatic proton H-2 & H-6. The peak at δ_H 6.70 ppm appears as triplet, which is assigned for one proton H-4′. The peak at δ_H 6.47 ppm appears as doublet, which is assigned for one proton H-3′. The peak at chemical shift δ_H 5.44 ppm appears as singlet, which is assigned for one proton of -CHI-. Peak at chemical shift δ_H 4.1 ppm appears as singlet, which is assigned for one proton of-NH-.

Finally, the compound **25** was identified from ^{13}C NMR spectrum (Fig. 15E-15F). The chemical shift at δ 151.0 ppm was found for C-1′ carbon. The peak at δ 146.94 ppm and 146.48 was found for C-1 & C-4 carbon respectively. The chemical shift at δ 129.37 was obtained for the C-5′. The chemical shift at δ 128.95 was obtained for the C-3′. The chemical shift at δ 127.98 was found for C-2 & C-6. On the other hand chemical shift at δ 124.12 represent the C-3 & C-5. The chemical shift at δ 118.30 represents the C-4′. The chemical shift at δ 115.48 and 113.60 were obtained for the C-2′ and C-6′ respectively. The peak at 62.42 represents –CHI- carbon.

2.4. Mechanism of imine formation:



Mechanism of imine formation

EXPERIMENTAL

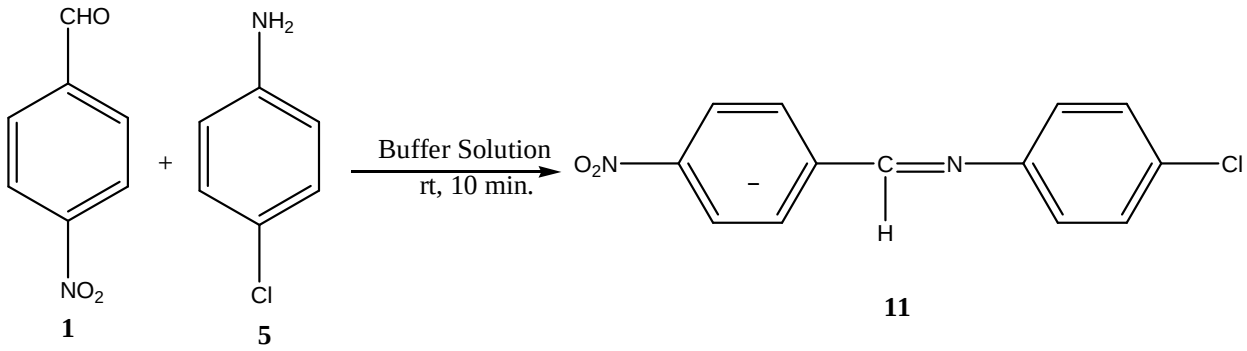
3.0 Instrumentation:

After synthesizing the compounds, melting points were determined in open capillary tubes on BUCHI, B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellets on a SHIMADZU FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER DPX–400 spectrophotometer (400 MHz) using $CDCl_3$ as solvent and tetramethylsilane as an internal reference. Analytical thin-layer chromatography (TLC) was performed on pre coated silica gel 60F-254 (E. Merck) and the spots were visualized with UV light. Column chromatography was performed on silica gel (60-120 mesh).

3.1. Synthesis of imines:

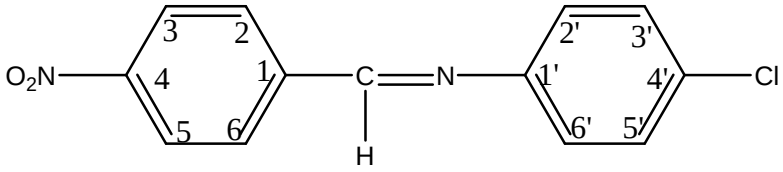
3.1.1. Synthesis of *N*-(4-nitrobenzylidene)-4-chlorobenzenamine 11

In a 50 ml round bottom flask, a mixture of 0.2 g 4-nitro benzaldehyde (1.32 m mol) and 0.507 g (3 equiv.) 4-chloro aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction, the resulting mixture was turned into a light yellowish solution and gradually it turned into yellowish solution. The reaction mixture was treated at room temperature. The progress of the reaction was monitored by TLC (4:1 n-Hexane: Ethyl acetate). After 10 minutes excess of solvent was evaporated at 68-70°C by vacuum distillation and reaction was stopped by adding 20 ml distilled water. Then, the organic layer was extracted with CH_2Cl_2 (3× 25 ml). The extract was washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by column chromatography on silica gel (60-120 mesh) using n-Hexane: Ethyl acetate (8:1) as eluant and compound was isolated.



1 **5** **11**

***N*-(4-nitrobenzylidene)-4-chlorobenzenamine 11**



MF: $C_{13}H_9N_2O_2Cl$

MW: 260.71

R_f Value: 0.71 (4:1; n-hexane: EtOAc)

Physical analysis: Yellowish crystalline solid, m. p: 136-137° C, odorless and 81 % of yield.

Spectra analysis:

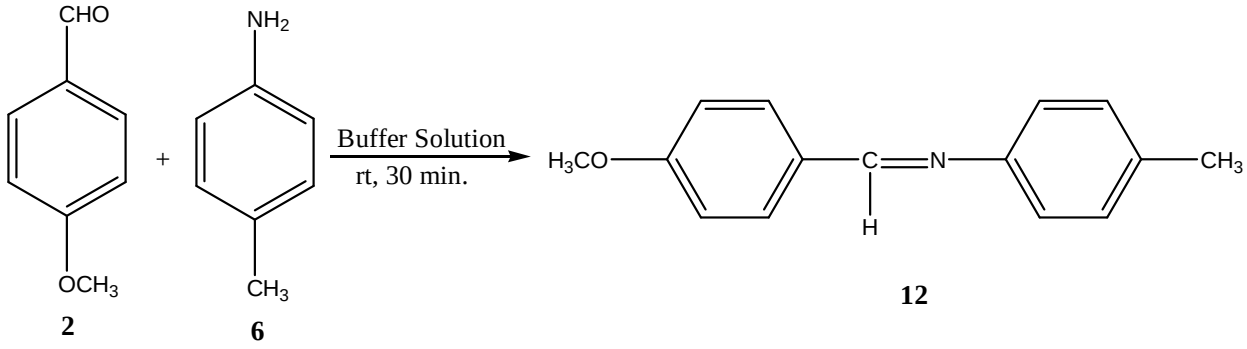
IR (KBr): ν_{max} 3100 (Ar-H stretching), 1595.0 (C=C stretching) & (C =N), 1517.9 (NO_2), 1344.3 (C-N), 752 (C-Cl stretching) cm^{-1}.

UV (EtOH): λ_{max} 295 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.52 (s, 1H, C-H), 8.31 (d, 2H, *J* = 6.8 Hz, H-3, H-5), 8.05 (d, 2H, *J* = 8.8 Hz, H-2, H-6), 7.37 (d, 2H, *J* = 8.4 Hz, H-3′, H-5′), 7.18 (d, 2H, *J* = 8.8 Hz, H-2′,H-6′).

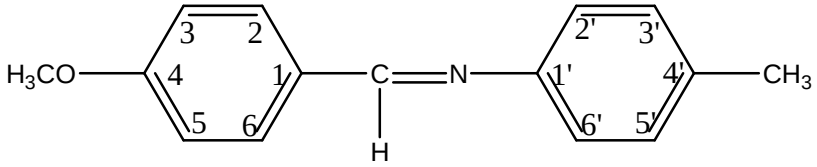
3.1.2. Synthesis of *N*-(4-methoxybenzylidene)-4-methylbenzenamine 12

In a 50 ml round bottom flask, a mixture of 0.2 ml (1.64 m mol) *p*-anisaldehyde and 0.528 g (3 equiv.) *p*-toluidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



2 **6** **12**

***N*-(4-methoxybenzylidene)-4-methylbenzenamine 12**



MF: $C_{15}H_{15}NO$

MW: 225.286

R_f Value: 0.75 (4:1; n-hexane: EtOAc)

Physical analysis: Off white crystalline solid, m. p: 97-98° C, odorless and 73 % of yield

Spectra analysis:

IR (KBr): ν_{max} 2970.2 (Ar C-H stretching), 2844.8 (O-CH_3), 1640 (C=N, sharp), 1475.0 (C=C stretching), 1450 & 1375 (CH_3, bending) & 1247.8 (C-N) cm^{-1}.

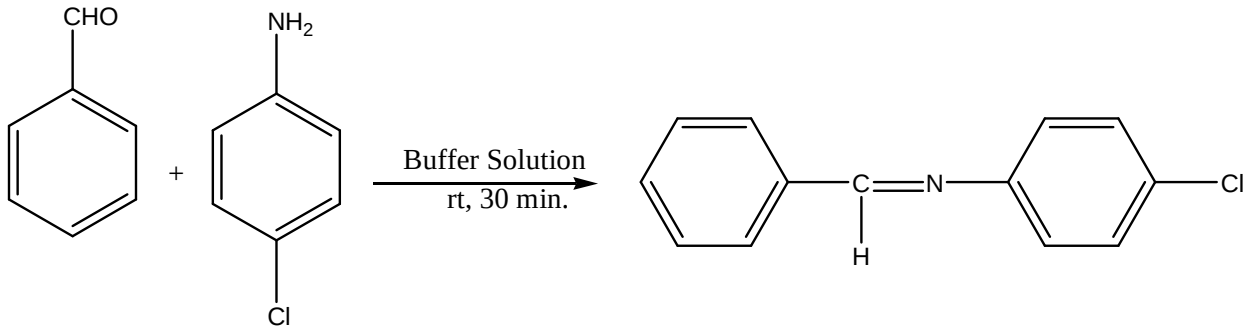
UV (EtOH): λ_{max} 293 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.38 (s, 1H, C-H), 7.83 (d, 2H, *J* = 7.6 Hz, H-2, H-6), 7.16 (d, 2H, *J* = 8.0 Hz, H-2′, H-6′), 7.10 (d, 2H, *J* = 7.6 Hz, H-3′, H-5′), 6.96 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 3.86 (s, 3H, -OCH_3) & 2.35 (s, 3H, -CH_3).

^{13}C NMR: δ 162.25 (C-4), 159.13(C=N), 149.87 (C-1′), 135.50 (C-4′), 130.54 (C-3′, C-5′), 129.86 (C-2, C-6), 129.51(C-1), 120.91(C-2′, C-6′), 114.29 (C-3, C-5), 55.57 (-OCH_3), 21.13 (CH_3).

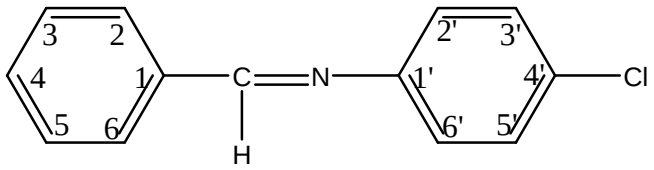
3.1.3. Synthesis of *N*-benzylidene-4-chlorobenzenamine 13

In a 50 ml round bottom flask, a mixture of 0.2 ml (1.97 m mol) benzaldehyde and 0.753 g (3 equiv.) 4-chloro aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



3 **5** **13**

***N*-benzylidene-4-chlorobenzenamine 13**



MF: $C_{13}H_{10}NCl$

MW: 215.725

R_f Value: 0.83 (4:1; n-hexane: EtOAc)

Physical analysis: Cream color solid 63-64 ° C, odorless and 67 % of yield.

Spectra analysis:

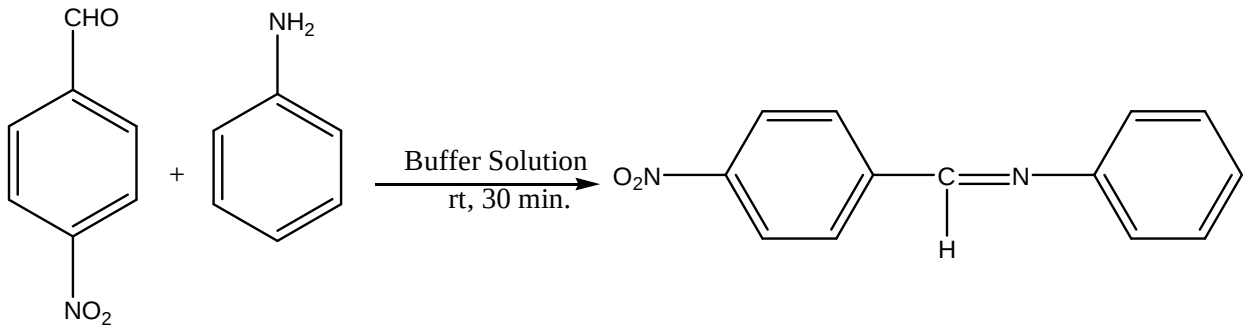
.**IR (KBr):** ν_{max} 2921.9 (Ar C-H stretching), 1623.9 (C=N), 1450.4 (C=C stretching), 1311.5 (C-N stretching), 819 (C-H Ar sharp out of plane bend) & 758 (C-Cl) cm^{-1}.

UV (EtOH): λ_{max} 294 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42 (s, 1H, -HC=N-), 7.87 (d, 2H, *J* = 6.8 Hz, H-2, H-6), 7.48 (m, 3H, H-3, H-4, H-5), 7.33 (d, 2H, *J* = 7.2 Hz, H-3′, H-5′), 7.13 (d, 2H, *J* = 7.2 Hz, H-2′, H-6′).

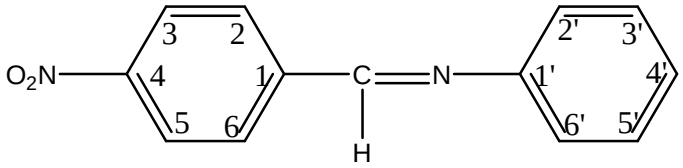
3.1.4. Synthesis of *N*-(4-nitrobenzylidene)benzenamine 14

In a 50 ml round bottom flask, a mixture of 0.2 g (1.32 m mol) 4-nitro benzaldehyde and 0.363 ml (3 equiv.) aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



1 **7** **14**

***N*-(4-nitrobenzylidene)benzenamine 14**



MF: $C_{13}H_{10}N_2O_2$

MW: 226.22

R_f Value: 0.706 (4:1; n-hexane: EtOAc)

Physical analysis: Yellowish crystalline solid, m. p: 94-95° C, odorless and 71 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 1640 (C=N, sharp), 1595.0 (C=C stretching) & 1342.4 (NO_2) cm^{-1}.

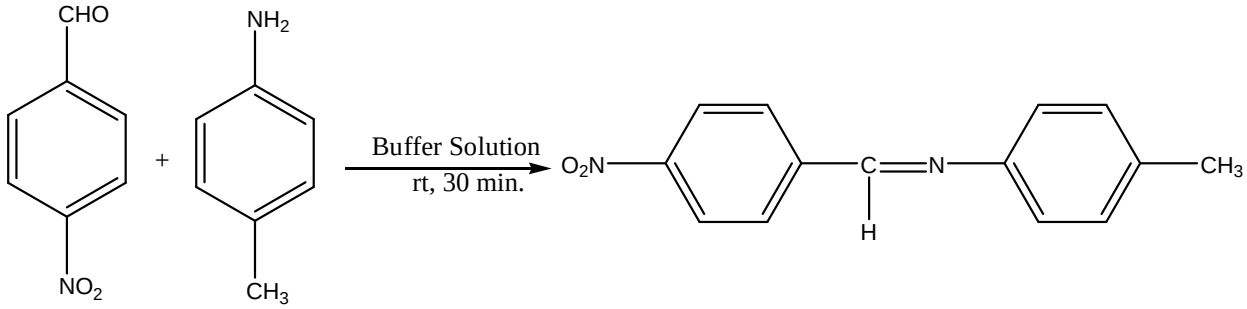
UV (EtOH): λ_{max} 296 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (s, 1H, -HC=N-), 8.31 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 8.06 (d, 2H, *J* = 7.6 Hz, H-2, H-6), 7.40 (t, 1H, H-4′), 7.29 (d, 2H, *J* = 6.8 Hz, H-3′, H-5′) & 7.24 (d, 2H, *J* = 7.2 Hz, H-2′, H-6′).

^{13}C NMR: δ 157.52 (C=N), 151.06 (C-1′), 149.43 (C-4), 141.71(C-1), 129.55 (C-3′, C-5′), 129.49 (C-2, C-6), 127.23 (C-4′), 124.17 (C-2′, C-6′), 121.11 (C-3, C-5).

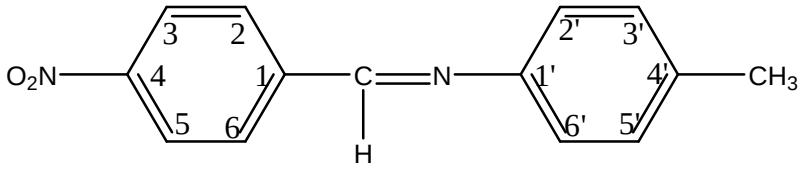
3.1.5 Synthesis of *N*-(4-nitrobenzylidene)-4-methylbenzenamine 15

In a 50 ml round bottom flask, a mixture of 0.2 g (1.32 m mol) 4-nitro benzaldehyde and 0.426 g (3 equiv.) *p*-toluidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



1 **6** **15**

***N*-(4-nitrobenzylidene)-4-methylbenzenamine 15**



MF: $C_{14}H_{12}N_2O_2$

MW: 240.246

R_f Value: 0.79 (3:1; n-hexane: EtOAc)

Physical analysis: Yellowish crystalline solid, m. p: 127-128° C, odorless and 68 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3100 (aromatic C-H stretching), 1610 (C=C stretching), 1595.0 (C=N, sharp), 1338.5 (C-N stretching), 1338.5 (CH_3) & 690 (aromatic C-H out of plane bend) cm^{-1}.

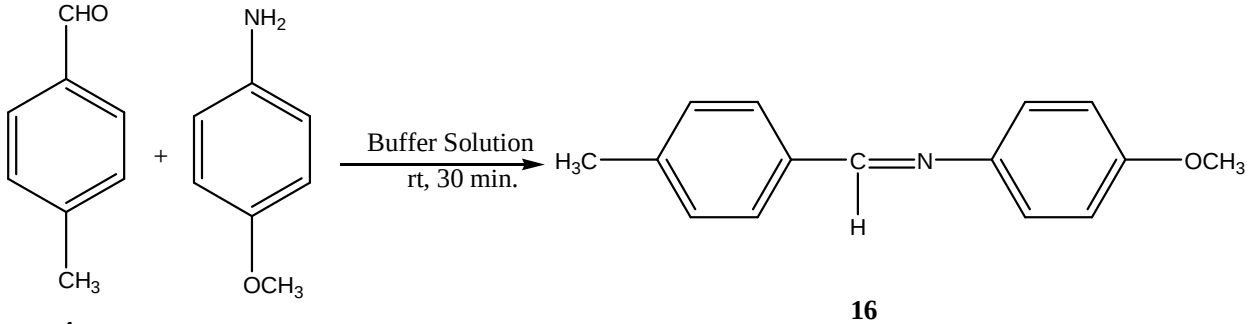
UV (EtOH): λ_{max} 302 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (s, 1H, C-H), 8.29 (d, 2H, *J* = 8.4 Hz, H-2, H-6)), 8.04 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 7.21 (d, 2H, *J* = 8.4 Hz, H-2′, H-6′), 7.17 ((d, 2H, *J* = 8.0 Hz, H-3′, H-5′) & 2.38 (s, 3H, -CH_3).

^{13}C NMR: δ 156.50 (C-H), 149.29 (C-4), 148.39 (C-1′), 141.91 (C-1), 137.39 (C-4′), 129.89 (C-3′, C-5′), 129.42 (C-2, C-6), 124.15 (C-2′, C-6′), 121.13 (C-3, C-5), 21.25 (CH_3).

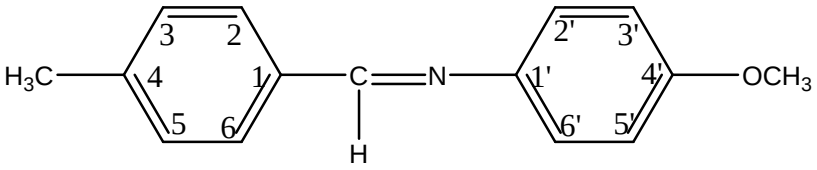
3.1.6. Synthesis of *N*-(4-methylbenzylidene)-4-methoxylbenzenamine 16

In a 50 ml round bottom flask, a mixture of 0.2 ml *p*-tolualdehyde and 0.624 g (3 equiv.) *p*-anisidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



4 **8** **16**

***N*-(4-methylbenzylidene)-4-methoxylbenzenamine 16**



MF: $C_{15}H_{15}NO$

MW: 225.286

R_f Value: 0.86 (3:1; n-hexane: EtOAc)

Physical analysis: Brown color, m. p: 85-86° C, odorless and 78 % of yield.

Spectra analysis:

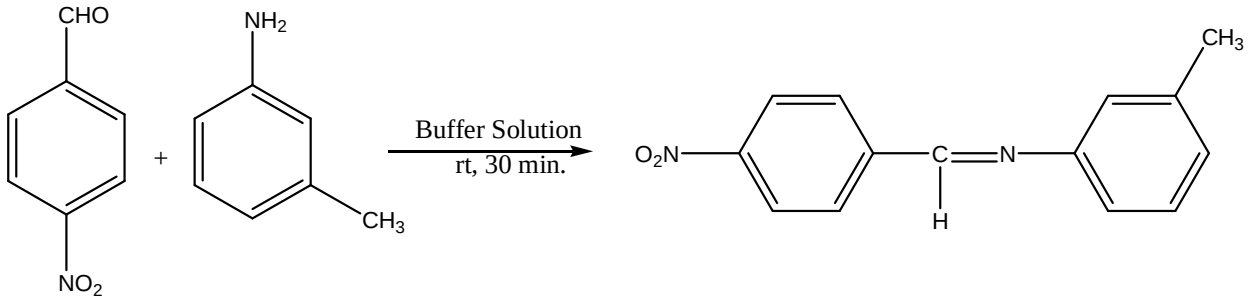
IR (KBr): ν_{max} 2912.3 (O-CH_3), 1623.9 (C=N, sharp), 1514.0 (C=C stretching), 1296 (CH_3, bend), 1031 (C-N stretching) & 837 (Ar C-H out of plane) cm^{-1}.

UV (EtOH): λ_{max} 291.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.43 (s, 1H, C-H), 7.76 (d, 2H, *J* = 7.2 Hz, H-2, H-6), 7.31 (d, 2H, *J* = 7.6 Hz, H-2′, H-6′), 7.25 (d, 2H, *J* = 7.6 Hz, H-3, H-5), 6.91(d, 2H, *J* = 8.8 Hz, H-3′,H-5′), 3.82 (s, 3H, -OCH_3) & 2.37 (s, 3H, -CH_3).

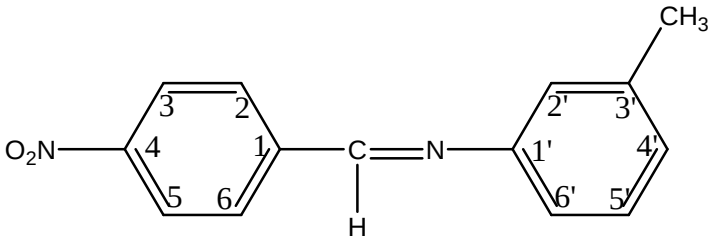
3.1.7. Synthesis of *N*-(4-nitrobenzylidene)-3-methylbenzenamine 17

In a 50 ml round bottom flask, a mixture of 0.2 gm (1.32 m mol) 4-nitro benzaldehyde and 0.42 ml (3 equiv.) *m*-toluidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. This mixture was treated by following the procedure described above for the compound **11**.



1 **9** **17**

***N*-(4-nitrobenzylidene)-3-methylbenzenamine 17**



MF: $C_{14}H_{12}N_2O_2$

MW: 240.246

R_f Value: 0.74 (10:1; n-hexane: EtOAc)

Physical analysis: Brownish yellow crystalline solid, m. p: 89-90° C, odorless and 73 % of yield

Spectra analysis:

IR (KBr): ν_{max} 3100 (C-H stretching), 2931.6 (CH_3 stretch), 1600 (C=N), 1342.0 (NO_2), 1105.1 (C-N), 858.4 & 694 (C-H out of plane bend) cm^{-1}.

UV (EtOH): λ_{max} 296 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.55 (s, 1H, C-H), 8.31(d, 2H, H-3, H-5), 7.29 (t, 1H, H-5′), 7.25 (s, 1H, H-2′), 7.08 (m, 2H, H-4′, H-6′) & 2.35 (s, 3H, CH_3).

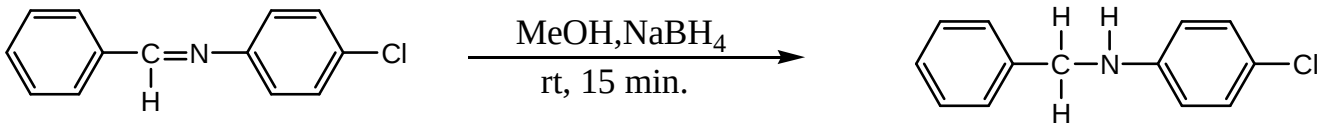
^{13}C NMR: δ 157.28 (C-H), 151.05 (C-1′), 149.36 (C-4), 141.77 (C-1), 139.37 (C-3′), 129.49 (C-2, C-6), 129.29 (C-5′), 127.99 (C-4′), 124.45 (C-2′), 124.15 (C-3, C-5), 118.07 (C-6′), 21.53 (CH_3).

3.2. Synthesis of amine:

3.2.1. Synthesis of *N*-benzylidene-4-chlorobenzenamine 18

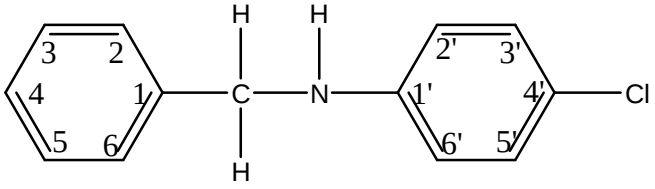
In a 50 ml round bottom flask 0.2 g *N*-benzylidene-4-chlorobenzenamine **13** was dissolve in 10 ml MeOH by magnetic stirring. After that, alcoholic $NaBH_4$ solution was poured into the mixture. At the starting of the reaction, the resulting mixture was turned into a light yellowish solution and gradually it turned into deep yellowish solution. The reaction mixture was treated at

room temperature. The progress of the reaction was monitored by TLC (4:1 n-Hexane: Ethyl acetate). After 15 minutes excess of solvent was evaporated at 68-70°C by vacuum distillation and reaction was stopped by adding 20 ml distilled water. Then, the final product was neutralized by $NaHCO_3$ and extracted with CH_2Cl_2 (3× 25 ml). The extract was washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by column chromatography on silica gel (60-120 mesh) using n-Hexane: Ethyl acetate (8:1) as eluant and compound was isolated.



13 **18**

***N*-benzylidene-4-chlorobenzenamine 18**



MF: $C_{13}H_{12}NCl$

MW: 217.741

R_f Value: 0.51 (4:1; n-hexane: EtOAc)

Physical analysis: Golden yellowish liquid, odorless and 85 % of yield.

Spectra analysis:

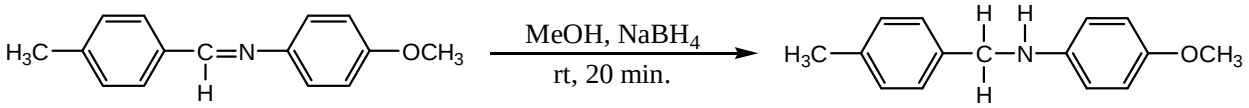
IR (KBr): ν_{max} 3037.7 (Ar C-H stretch), 1600 (N-H), 1475 (C=C stretching), 1315 (C-N stretching) 819 (C-H Ar sharp out of plane bend) & 758 (C-Cl) cm-1.

UV (EtOH): λ_{max} 309.50 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (d, 2H, *J* = 7.2 Hz, H-3, H-5), 7.31 (d, 2H, *J* = 7.2 Hz, H-2, H-6), 7.11(d, 2H, *J* = 7.2 Hz, H-3′, H-5′), 6.54 (d, 2H, *J* = 7.2 Hz, H-2′, 6′), 4.70 (s, 2H, -CH_2-) & 4.30 (s, 1H, N-H).

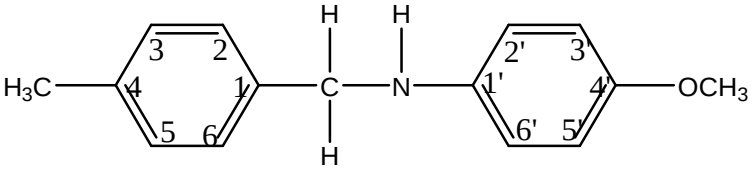
3.2.2. Synthesis of *N*-4-(methylbenzylidene)-4-methoxybenzenamine 19

In a 50 ml round bottom flask 0.2 g *N*-(4-methylbenzylidene)-4-methoxylbenzenamine **16** was dissolve in 10 ml MeOH by magnetic stirring. After that alcoholic $NaBH_4$ solution was poured into the mixture. This mixture was treated by following the procedure described above for the compound **18**.



16 **19**

***N*-4-(methylbenzylidene)-4-methoxybenzenamine 19**



MF: $C_{15}H_{17}NO$

MW: 227.302

R_f Value: 0.77 (3:1; n-hexane: EtOAc)

Physical analysis: Brown color solid, m. p: 70-71 ° C, odorless and 68 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 2912.6 (O-CH_3), 1623.9 (N-H bend), 1465.8 (-CH_2-), 1292.2 (CH_3, bend), 1234.3 (C-N stretching) & 825 (Ar C-H out of plane bend) cm^{-1}.

UV (EtOH): λ_{max} 319 and 297 nm.

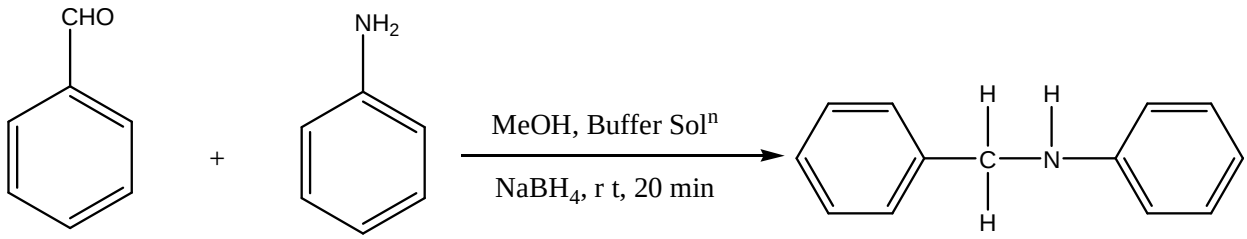
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.185 (d, 2H, H-3, H-5), 7.13 (d, 2H, H-2, H-6), 6.77 (d, 2H, H-3′, H-5′), 6.62 (d, 2H, H-2′, H-6′), 4.23 (s, 2H, -CH_2-), 3.83 (s, 1H, N-H), 3.74 (s, 3H, -OCH_3) & 2.34 (s, 3H, CH_3).

^{13}C NMR: δ 152.27 (C-4′), 136.95 (C-1′), 136.71 (C-1), 129.41 (C-3, C-5), 127.69 (C-2, C-6), 122.28 (C-4), 115.02 (C-3′, C-5′), 114.23 (C-2′, C-6′), 55.95 (-OCH_3), 49.14 (–CH_2-) & 21.25 (CH_3).

3.3. Synthesis of Amines in one pot reduction:

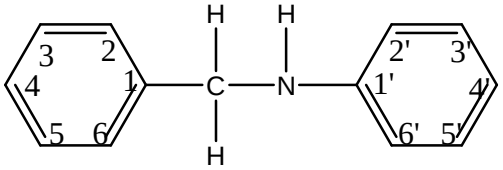
3.3.1. Synthesis of *N*-benzylbenzenamine 20

In a 50 ml round bottom flask, a mixture of 0.2 ml benzaldehyde (1.96 m mol) and 0.55 ml (3 equiv.) aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction alcoholic $NaBH_4$solution was poured into the mixture. The reaction mixture was treated at room temperature. The progress of the reaction was monitored by TLC (4:1 n-Hexane: Ethyl acetate). After 20 minutes excess of solvent was evaporated at 68-70°C by vacuum distillation and reaction was stopped by adding 20 ml distilled water. Then, the organic layer was extracted with CH_2Cl_2 (3× 25 ml). The extract was washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by column chromatography on silica gel (60-120 mesh) using n-Hexane: Ethyl acetate (8:1) as eluant and compound **20** was isolated.



3 **7** **20**

***N*-benzylbenzenamine 20**



MF: $C_{13}H_{13}N$

MW: 183

R_f Value: 0.66 (10:1; n-hexane: EtOAc)

Physical analysis: Yellowish liquid odorless and 61 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3415.7 (N-H stretching), 3037.7 (Ar-H stretching), 1610.4 (C=C stretching), 1321.1 (C-N), 1450 (-CH_2- bending), 690 (Ar C-H out of plane bend)) cm^{-1}.

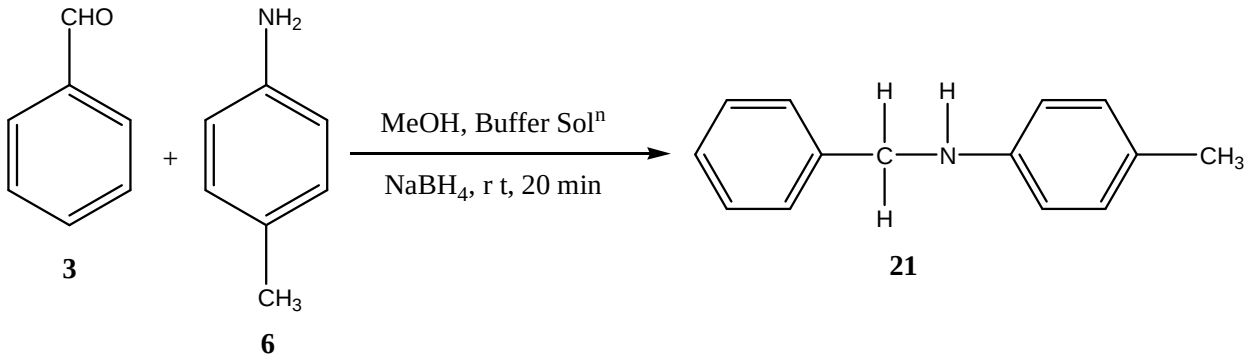
UV (EtOH): λ_{max} 297.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (m, 2H, H-3, H-5), 7.17 (t, 1H, H-4), 7.14 (d, 2H, H-2, H-6), 7.09 (dd, 2H, H-3′, H-5′), 6.68 (t, 1H, H-4′), 6.62 (d, 2H, H-2′, H-6′), 4.32 (s, 2H, -CH_2-), 3.80 (s, 1H, -NH-).

^{13}C NMR: δ 148.22 (C-1′), 139.51 (C-1), 129.38 (C-3′, C-5′), 128.75 (C-3, C-5), 127.63 (C-2, C-6), 127.34 (C-4), 117.69 (C-4′), 112.97 (C-2′, C-6′), 48.43 (–CH_2-).

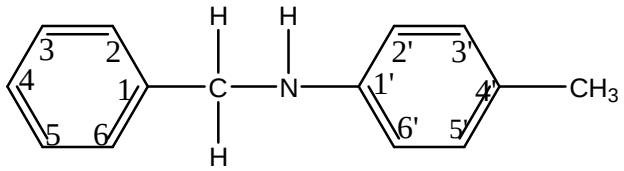
3.3.2. Synthesis of *N*-benzyl-4-methylbenzenamine 21

In a 50 ml round bottom flask, a mixture of 0.2 ml benzaldehyde (1.96 m mol) and 0.633 gm (3 equiv.) *p*-toluidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction alcoholic $NaBH_4$ solution was poured into the mixture. The reaction mixture was treated at room temperature. This mixture was treated by following the procedure described above for the compound **20**.



3 **6** **21**

***N*-benzyl-4-methylbenzenamine 21**



MF: $C_{14}H_{15}N$

MW: 197

R_f Value: 0.85 (3:1; n-hexane: EtOAc)

Physical analysis: Yellowish liquid odorless and 67 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3037.7 (Ar C-H stretching), 1550.7 (N-H bending), 1249.8 (C-N) and 698 (Ar C-H out of plane bend)) cm^{-1}.

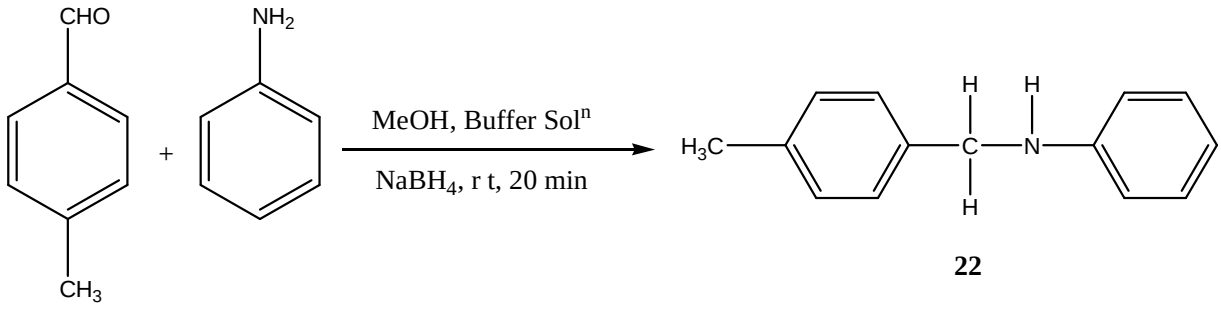
UV (EtOH): λ_{max} 297.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (m, 3H, H-3, H-4, H-5), 7.25 (d, 2H, H-2, H-6), 6.99 (d, 2H, H-3′, H-5′), 6.59 (d, 2H, H-2′, H-6′), 4.31 (s, 2H, -CH_2-), 2.23 (s, 3H, -CH_3).

^{13}C NMR: δ 143.60 (C-1′), 139.52 (C-1), 129.88 (C-3′, C-5′), 128.73 (C-3, C-5), 127.71 (C-2, C-6), 127.33 (C-4), 127.20 (C-4′), 113.88 (C-2′, C-6′), 48.43 (–CH_2-), 20.54 (–CH_3).

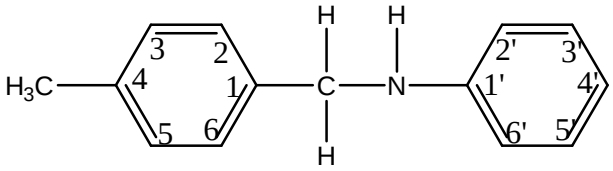
3.3.3. Synthesis of *N*-4-(methylbenzylidene)-benzenamine 22

In a 50 ml round bottom flask, a mixture of 0.2 ml *p*-tolualdehyde (1.69 m mol) and 0.48 ml (3 equiv.) aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction alcoholic $NaBH_4$ solution was poured into the mixture. The reaction mixture was treated at room temperature. This mixture was treated by following the procedure described above for the compound **20**.



4 **7** **22**

***N*-4-(methylbenzylidene)-benzenamine 22**



MF: $C_{14}H_{15}N$

MW: 197

R_f Value: 0.65 (10:1; n-hexane: EtOAc)

Physical analysis: Yellowish liquid odorless and 65 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3425.3 (N-H stretching), 3037.7 (Ar C-H stretching), 1604.7 (N-H bending), 1431.1(Ar C=C stretching), 1325 (C-N) & 694.3 (Ar C-H out of plane bend) cm^{-1}.

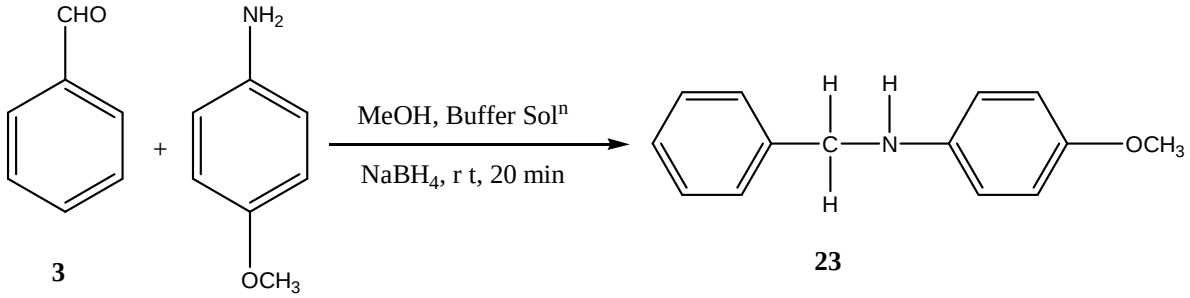
UV (EtOH): λ_{max} 297.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24 (t, 2H, H-3′, H-5′), 7.14 (m, 4H, H-2, H-3, H-5, H-6), 6.68 (m, 1H, H-4′), 6.61 (d, 2H, H-2′, H-6′), 4.27 (s, 2H, -CH_2-), 3.76 (s, 1H, -NH-), 2.23 (s, 3H, -CH_3).

^{13}C NMR: δ 148.32 (C-1′), 136.98 (C-1), 136.45 (C-4), 129.42 (C-3′, C-5′), 129.37 (C-3, C-5), 127.64 (C-2, C-6), 117.59 (C-4′), 112.94 (C-2′, C-6′), 48.12 (–CH_2-), 21.23 (–CH_3).

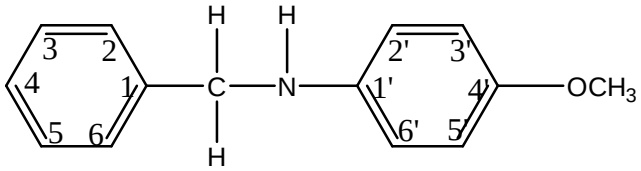
3.3.4 Synthesis of *N*-benzyl-4-methoxybenzenamine 23

In a 50 ml round bottom flask, a mixture of 0.2 ml benzaldehyde (1.96 m mol) and 0.724 gm (3 equiv.) *p*-anisidine was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction alcoholic $NaBH_4$ solution was poured into the mixture. The reaction mixture was treated at roomtemperature. This mixture was treated by following the procedure described above for the compound **20**.



3 **8** **23**

***N*-benzyl-4-methoxybenzenamine 23**



MF: $C_{14}H_{15}NO$

MW: 213

R_f Value: 0.65 (3:1; n-hexane: EtOAc)

Physical analysis: Yellowish liquid odorless and 72 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3450 (N-H stretching), 3015 (Ar C-H stretching), 1548.7 (Ar C=C stretching), 1454.2 (-CH_2- bend), 1245.9 (C-N) & 698.2 (Ar C-H out of plane bend) cm^{-1}.

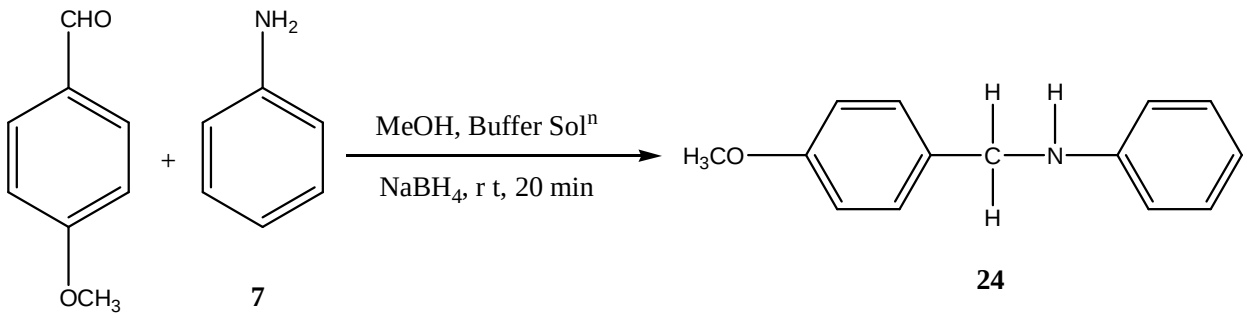
UV (EtOH): λ_{max} 297.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (d, 2H, H-3, H-5), 7.38 (m, 1H, H-4), 6.94 (d, 2H, H-2, H-6), 6.76 (d, 2H, H-3′, H-5′), 6.60 (d, 2H, H-2′, H-6′), 4.28 (s, 2H, -CH_2-), 3.83 (s, 1H, -NH-), 3.74 (s, 3H, -OCH_3).

^{13}C NMR: δ 152.34 (C-4′), 142.49 (C-1), 139.74 (C-1′), 128.88 (C-3, C-5), 127.70 (C-2, C-6), 127.32 (C-4), 115.09 (C-3′, C-5′), 114.50 (C-2′, C-6′), 55.94 (–OCH_3), 49.41 (–CH_2-).

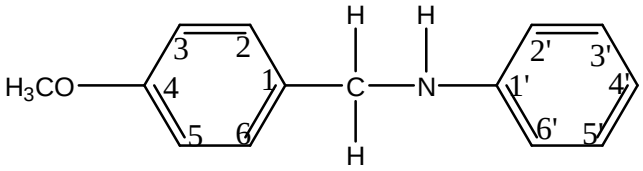
3.3.5. Synthesis of *N*-4-methoxybenzylidene-benzenamine 24

In a 50 ml round bottom flask, a mixture of 0.2 ml *p*-anisaldehyde (1.64 m mol) and 0.46 ml (3 equiv.) aniline was dissolve in 10 ml MeOH by magnetic stirring. After then, few drops acetic acid buffer solution was poured into the mixture and P^H was fixed at 5.5-5.6. At the starting of the reaction alcoholic $NaBH_4$ solution was poured into the mixture. The reaction mixture was treated at room temperature. This mixture was treated by following the procedure described above for the compound **20**.



2 **7** **24**

***N*-4-methoxybenzylidene-benzenamine 24**



MF: $C_{14}H_{15}NO$

MW: 213

R_f Value: 0.82 (3:1; n-hexane: EtOAc)

Physical analysis: Yellowish liquid odorless and 55 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3400 (N-H stretching), 3000 (Ar C-H stretching), 1604.7 (Ar C=C stretching), 1359.7 (C-N) & 698.2 (Ar C-H out of plane bend) cm^{-1}.

UV (EtOH): λ_{max} 296.5 nm.

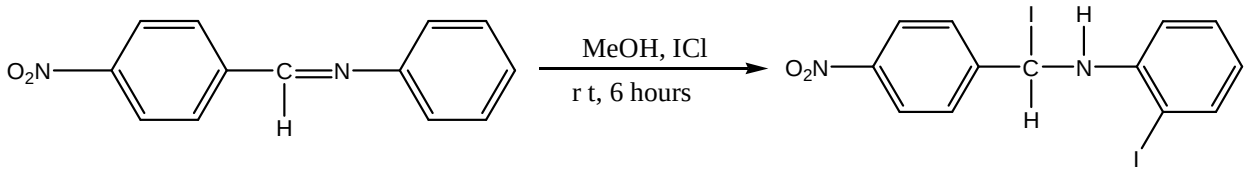
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (d, 2H, H-3′, H-5′), 7.14 (d, 2H, H-2, H-6), 6.86 (d, 2H, H-3, H-5), 6.81 (d, 2H, H-2′, H-6′), 6.65 (m, 1H, H-4′), 4.24 (s, 2H, -CH_2-), 3.79 (s, 1H, -NH-), 3.78 (s, 3H, -OCH_3).

^{13}C NMR: δ 158.96 (C-4), 148.32 (C-1), 147.59 (C-1′), 129.31 (C-3′, C-5′), 128.94 (C-2, C-6), 117.38 (C-4′), 114.13 (C-3′, C-5′), 113.52 (C-2′, C-6′), 55.42 (–OCH_3), 47.91 (–CH_2-).

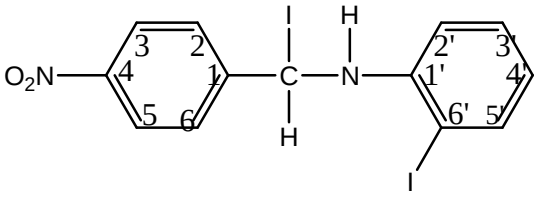
3.4. Halogenation of Imine:

3.4.1. Synthesis of 2-iodo-*N*-(iodo(4-nitophenyl)methyl)benzenamine 25

In a 50 ml round bottom flask 0.2 g synthesized *N*-(4-nitrobenzylidene)benzenamine **14** was dissolved in 8 ml methanol and 0.15 ml monochloro iodine was added in the mixture. Then the mixture was stirred at room temperature for 6 hours. The progress of the reaction was monitored by TLC (4:1 n-Hexane: Ethyl acetate). After 6 hours excess of solvent was evaporated at 68-70°C by vacuum distillation and reaction was stopped by adding 20 ml distilled water. Excess of I_2 was removed by adding aqueous $Na_2S_2O_3$ solution. Then, the organic layer was extracted with CH_2Cl_2 (3× 25 ml). The extract was washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by column chromatography on silica gel (60-120 mesh) using n-Hexane: Ethyl acetate (8:1) as eluant and compound **25** was isolated.



2-iodo-*N*-(iodo(4-nitophenyl)methyl)benzenamine 25



MF: $C_{13}H_{10}N_2O_2I_2$

MW: 532.219

R_f Value: 0.75 (1:1; n-hexane: EtOAc)

Physical analysis: Brown color solid, m. p: 144-145° C, odorless and 58 % of yield.

Spectra analysis:

IR (KBr): ν_{max} 3350 (N-H stretching), 1622.0 (N-H bending), 1514 (NO_2), 1350.1 (C-N), 814.4 (aromatic C-H out of plane bend) & 694.3 (C-I) cm^{-1}.

UV (EtOH): λ_{max} 296.5 and 268 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.15 (d, 2H, H-3, H-5), 7.55 (d,1H, H-5′), 7.12 (t, 1H, H-3′), 7.02 (d, 2H, H-2, H-6), 6.70 (t, 1H, H-4′), 6.47 (d, 1H, H-2′), 5.44 (s, 1H, -CHI-) & 4.1 (s, 1H, -NH-).

^{13}C NMR: δ 151 (C-1′), 146.94 (C-1), 146.48 (C-4), 129.37 (C-5′), 128.95 (C-3′), 127.98 (C-2, C-6), 124.12 (C-3, C-5), 118.30 (C-4′), 115.48 (C-2′), 113.60 (C-6′) & 62.42 (-CHI-).

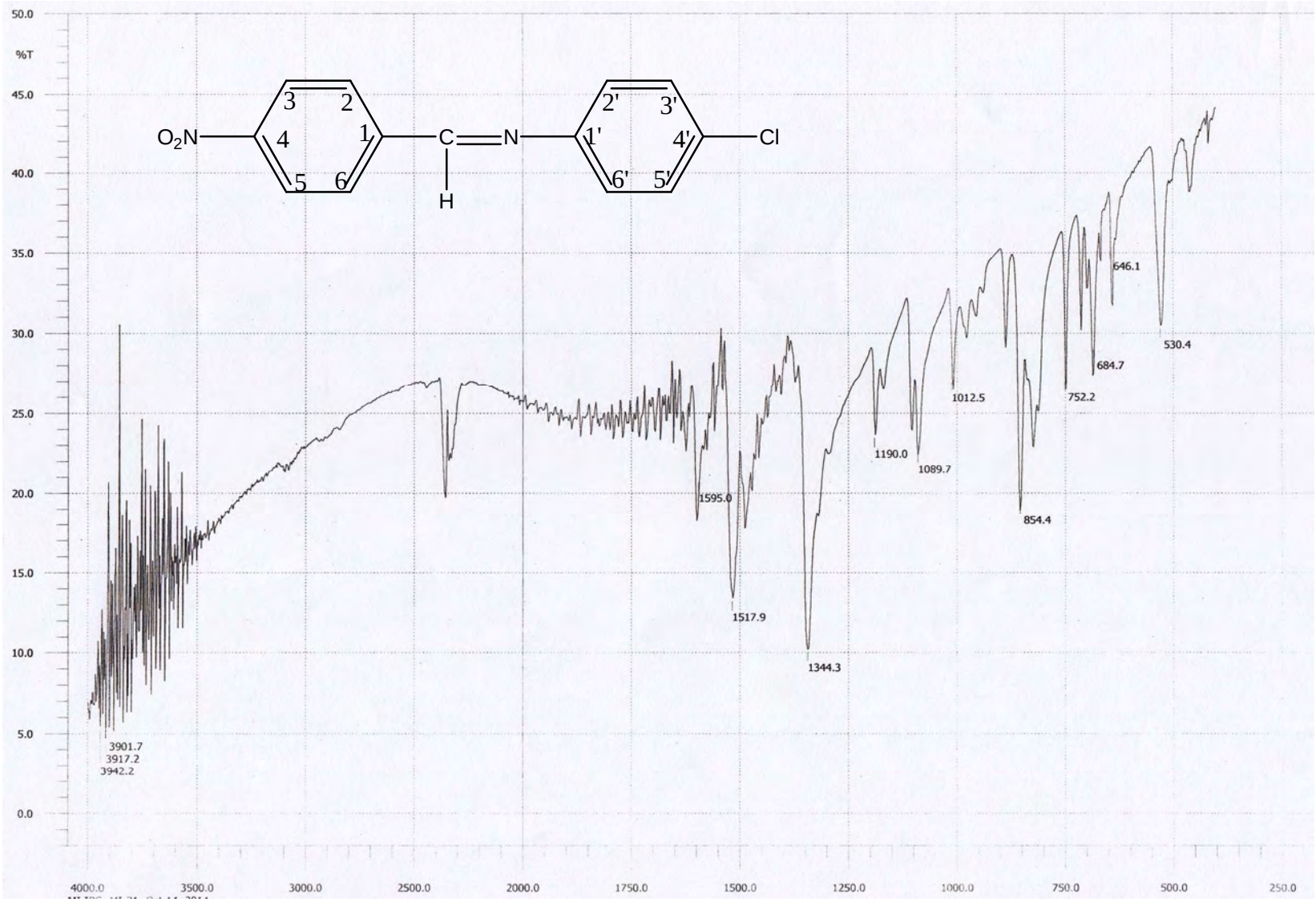
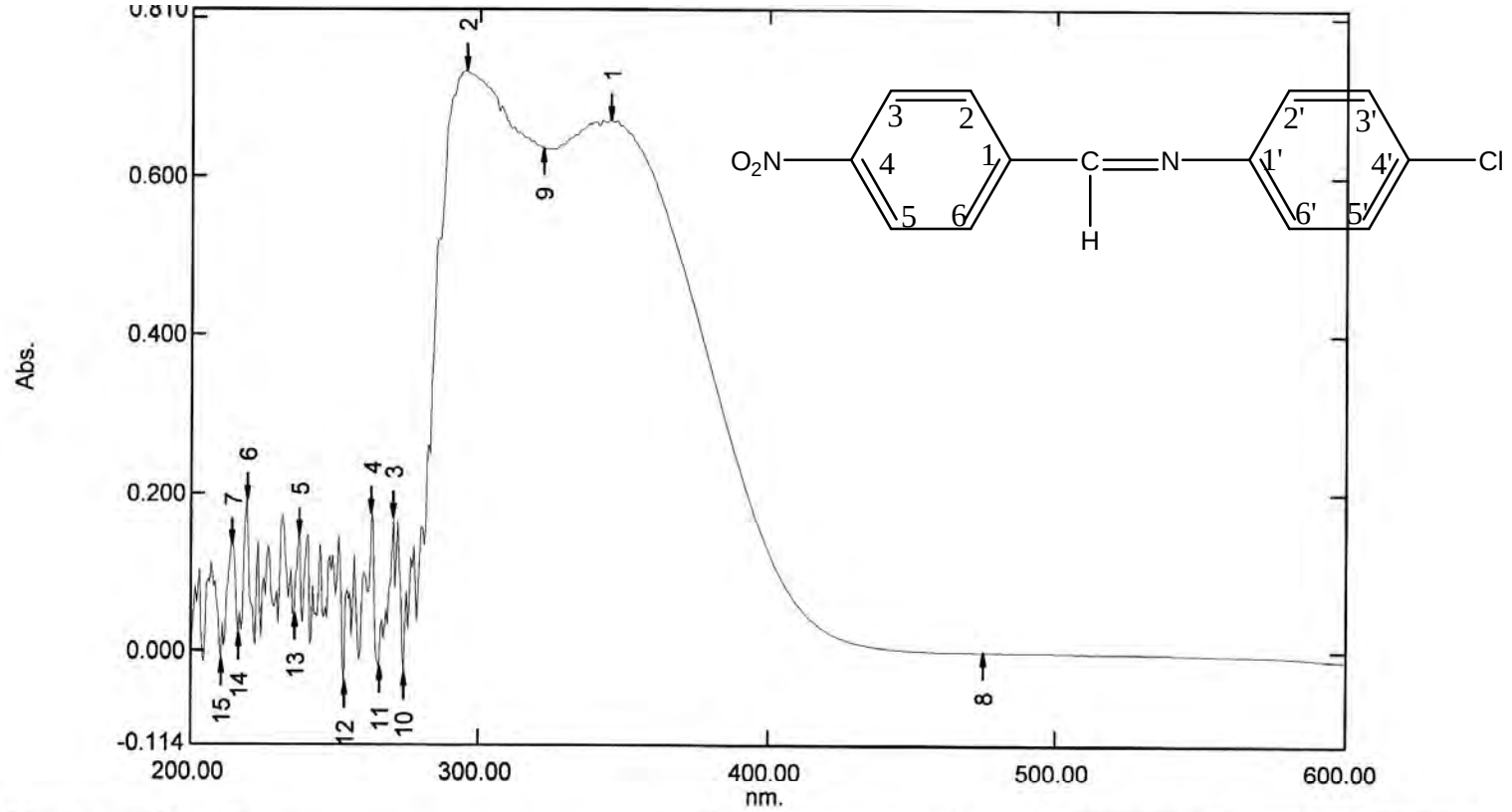


Fig. 1A: IR spectra of compound **11**.



Measurement Properties

Wavelength Range (nm.):	200.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Enabled
Scan Mode:	Single

Sample Preparation Properties

No.	P/V	Wavelength	Abs.	Description
1	↑	345.00	0.672	
2	↑	295.00	0.733	
3	↑	270.50	0.171	
4	↑	263.00	0.177	
5	↑	238.00	0.148	
6	↑	219.50	0.193	

Fig. 1B: UV spectra of compound **11**.

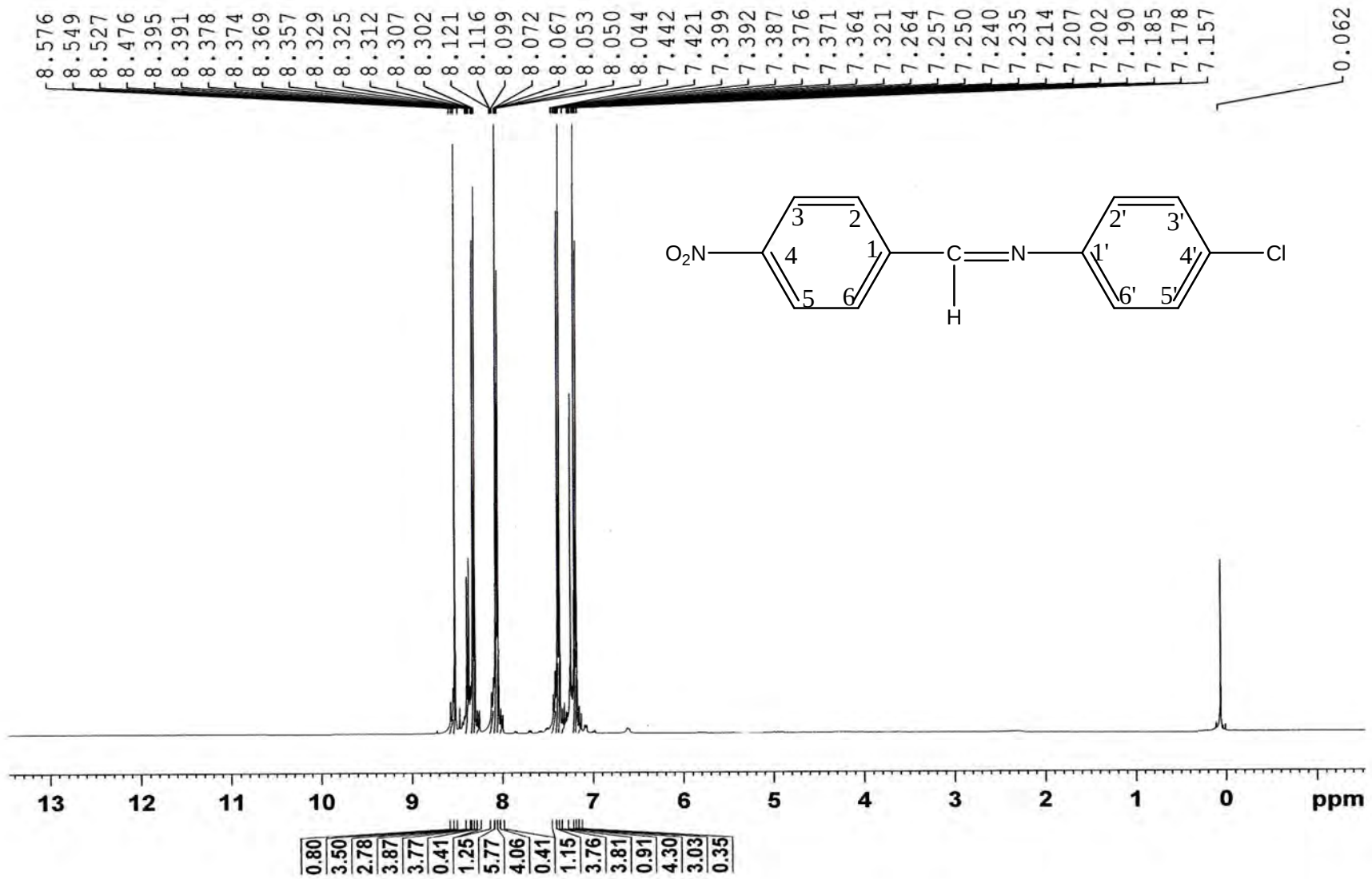


Fig. 1C: ^{1}H NMR spectra of compound **11**.

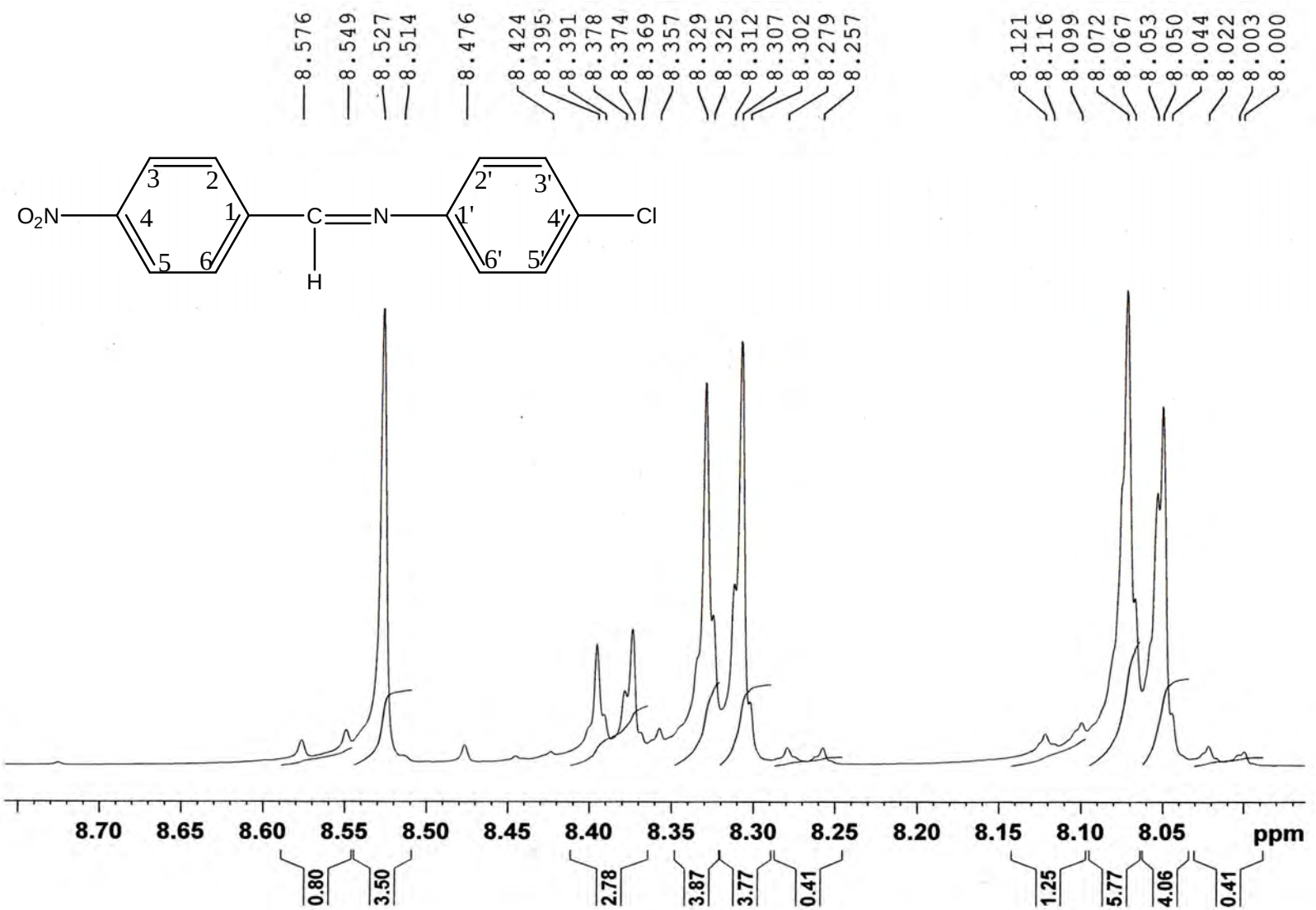


Fig. 1D: ^{1}H NMR spectra of compound **11** (expanded).

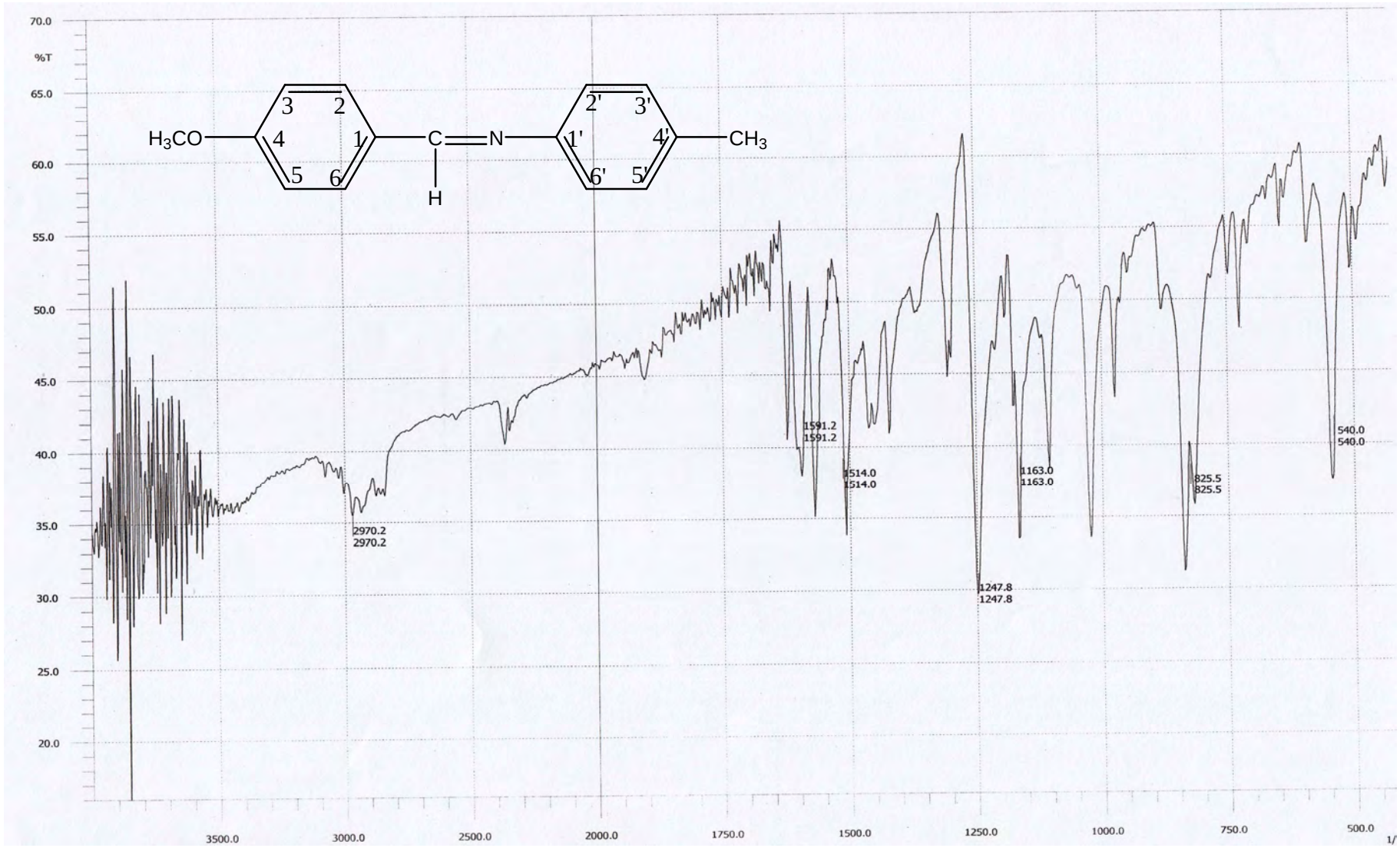
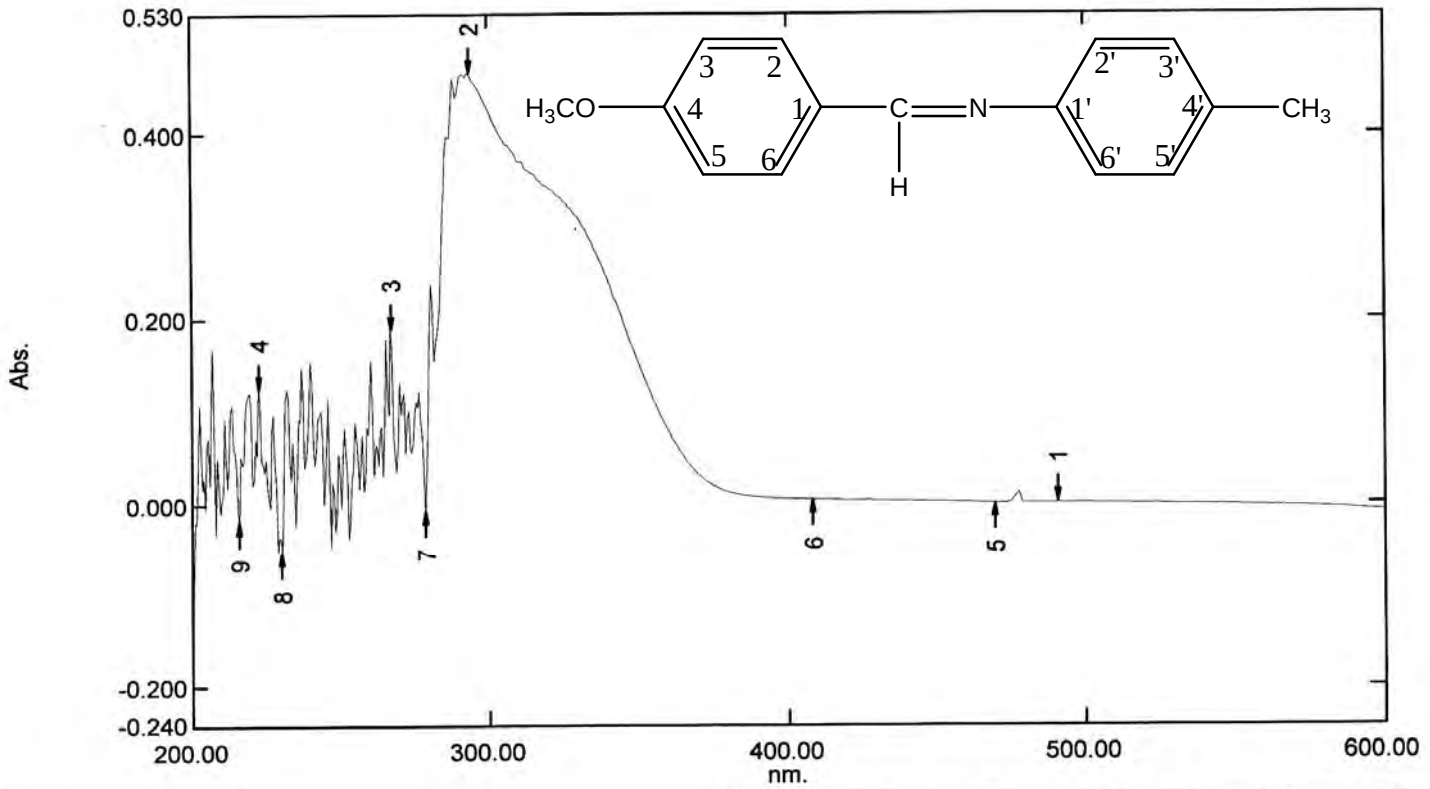


Fig. 2A: FT-IR Spectra of compound **12**



Measurement Properties

Wavelength Range (nm.):	200.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Enabled
Scan Mode:	Single

Sample Preparation Properties

Weight:	
Volume:	
Dilution:	
Path Length:	

No.	P/V	Wavelength	Abs.	Description
1	↑	491.00	0.001	
2	↑	293.50	0.466	
3	↑	267.00	0.189	
4	↑	222.50	0.125	
5	↓	470.00	-0.000	
6	↓	409.00	0.004	
7	↓	278.50	-0.008	
8	↓	230.50	-0.054	
9	↓	216.00	-0.019	

Fig 2B: UV Spectra of compound **12**

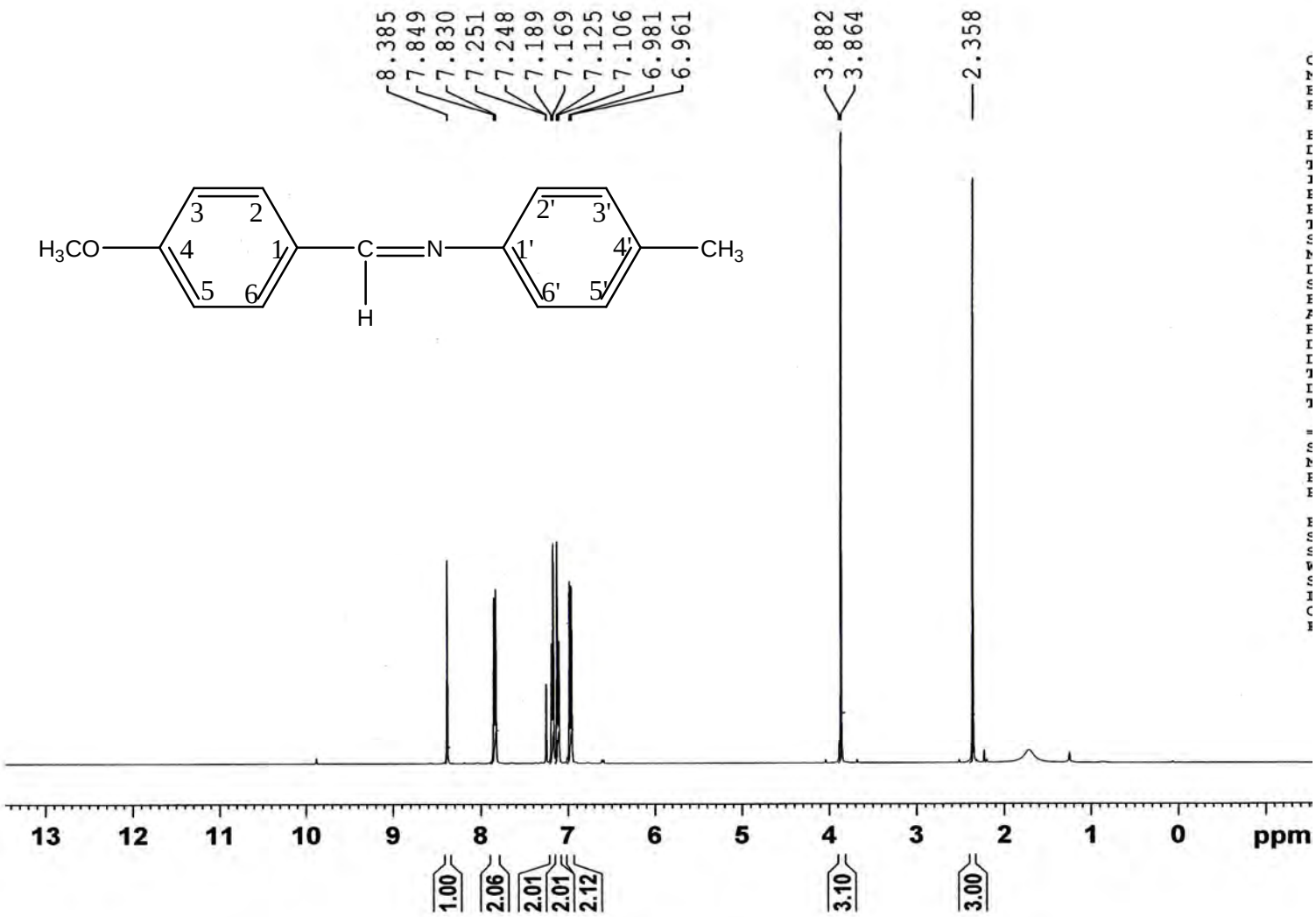


Fig 2C: ^{1}H NMR Spectra of compound **12** (total plot)

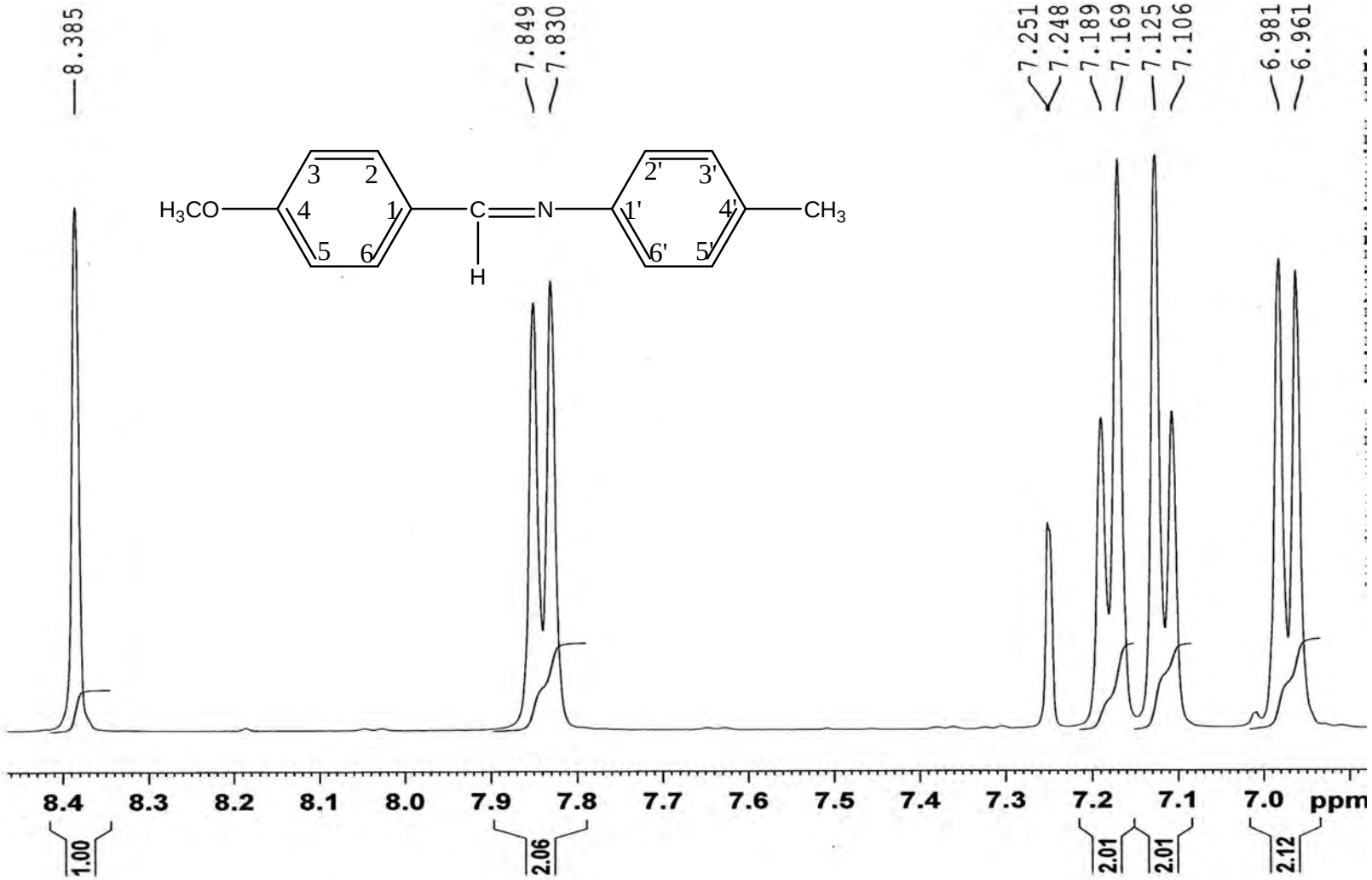


Fig 2D: ^{1}H NMR Spectra of compound **12** (expanded plot)

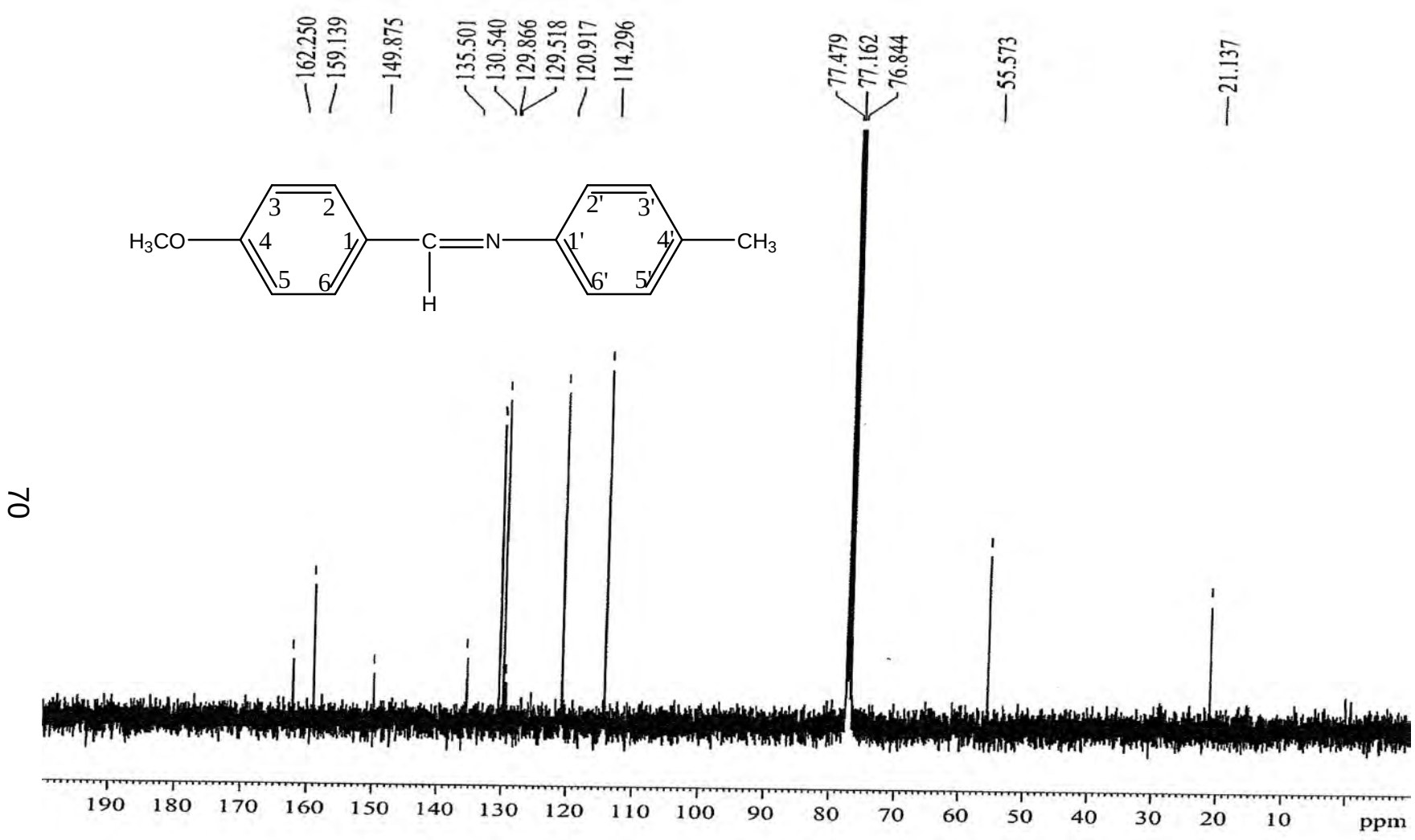


Fig 2E: ^{13}C NMR Spectra of compound **12**

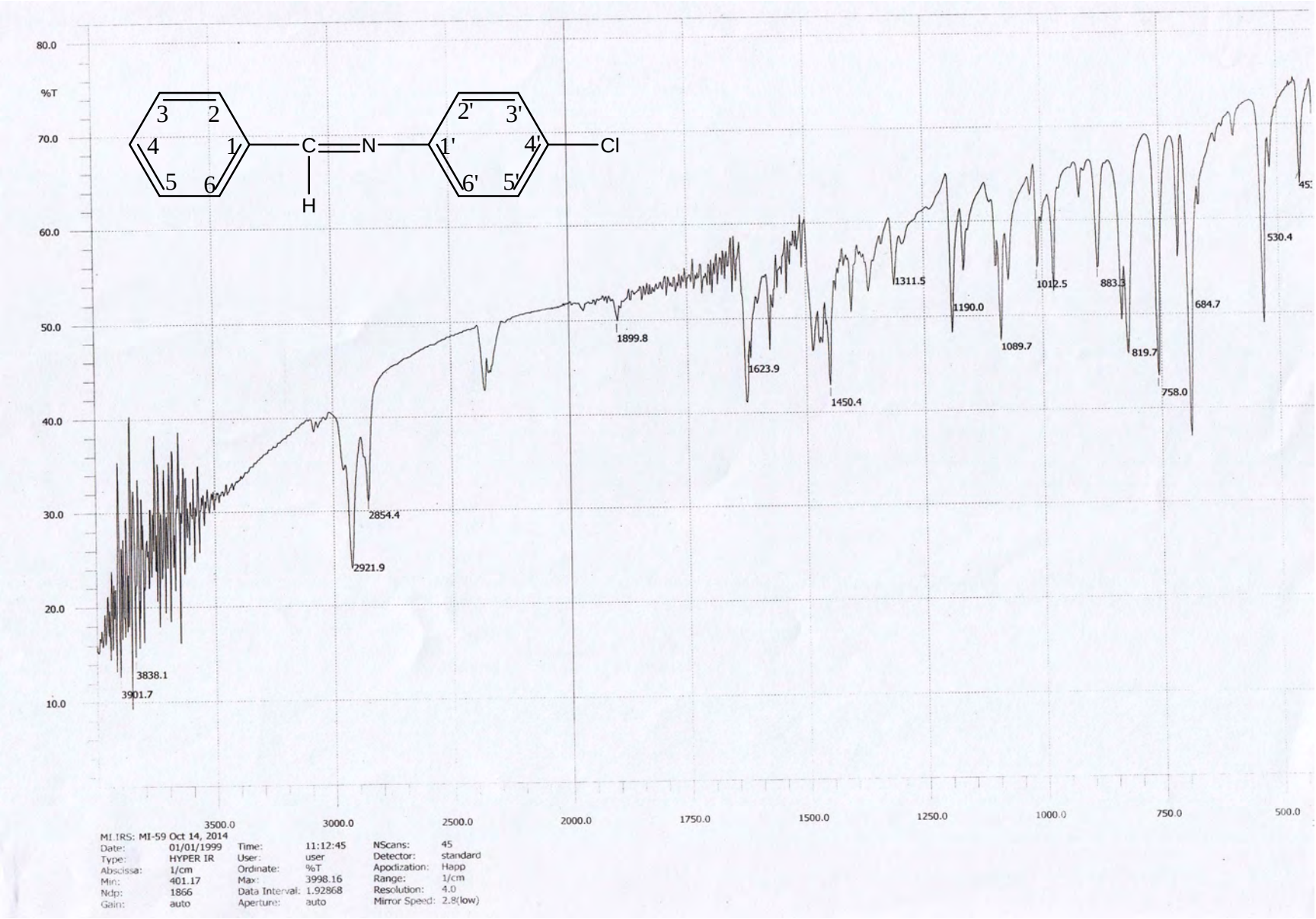
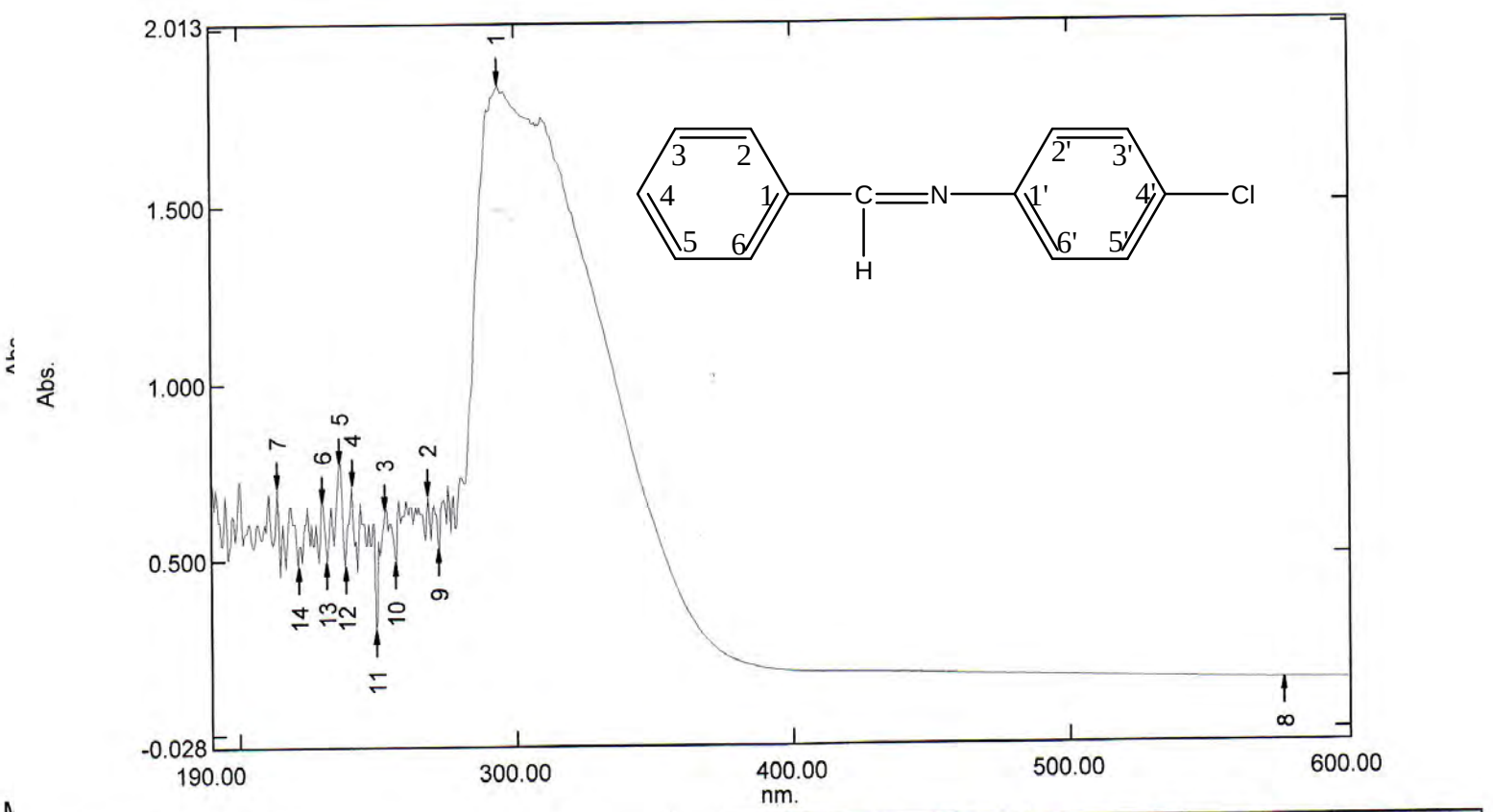


Fig. 3A: FT-IR Spectra of compound **13**



Measurement Properties

Wavelength Range (nm.):	190.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

No.	P/V	Wavelength	Abs.	Description
1	↑	294.00	1.843	
2	↑	268.50	0.682	
3	↑	253.00	0.644	
4	↑	241.00	0.713	
5	↑	236.50	0.776	
6	↑	230.00	0.664	
7	↑	214.00	0.711	

Fig. 3B: UV-Spectra of compound **13**

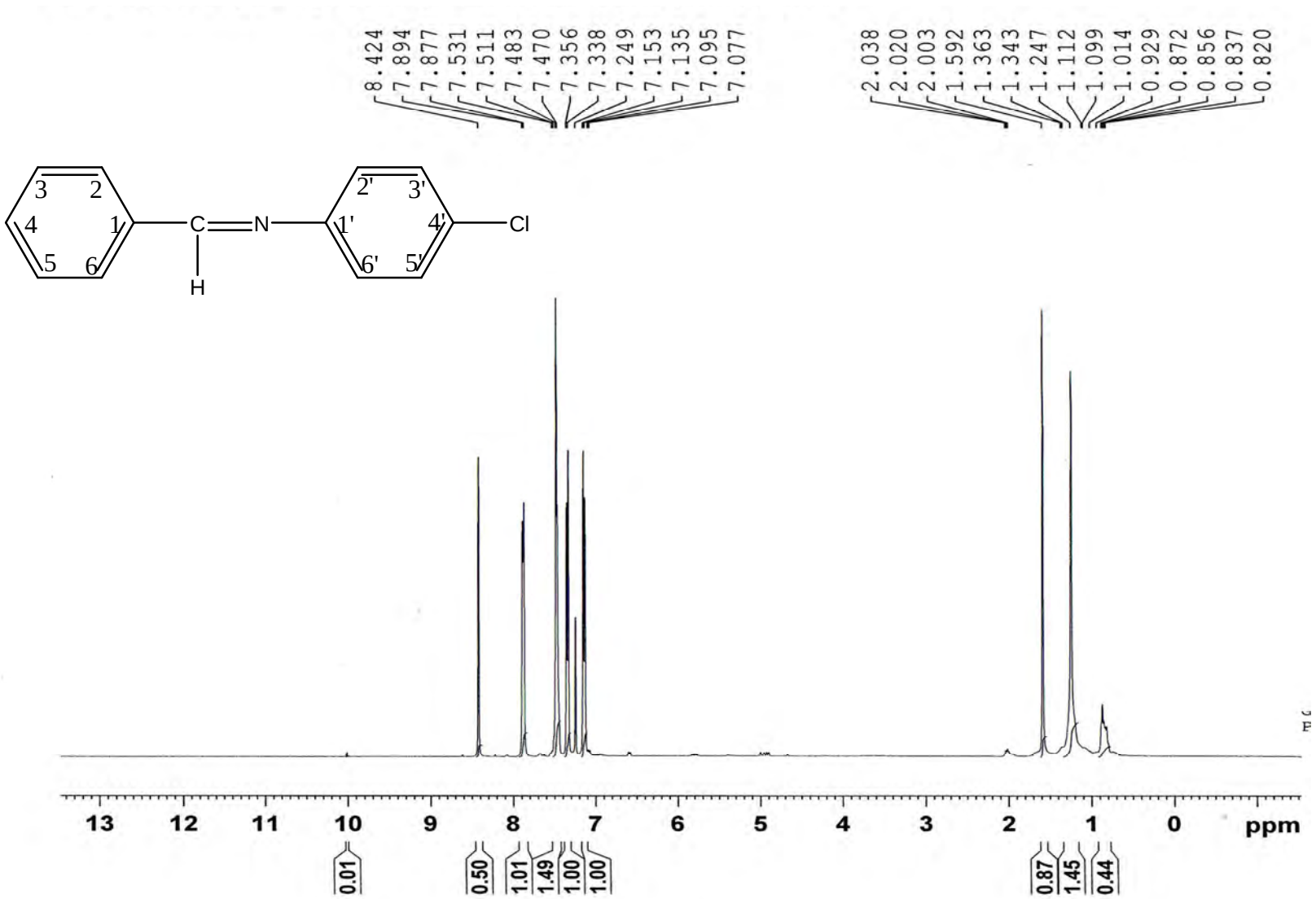


Fig. 3C: ^{1}H NMR Spectra of compound **13** (total plot).

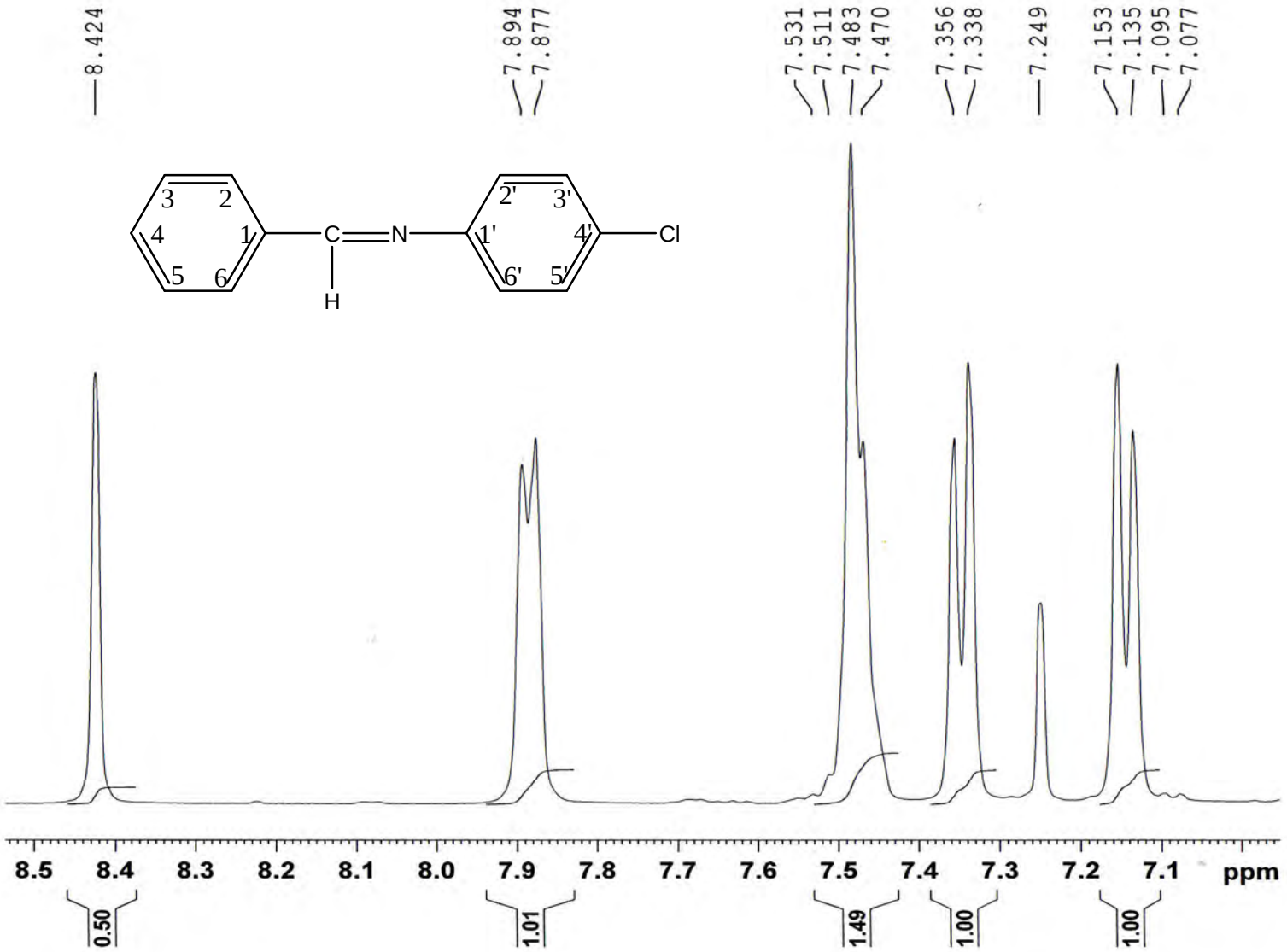


Fig. 3D: ^{1}H NMR-Spectra of compound **13** (Expanded).

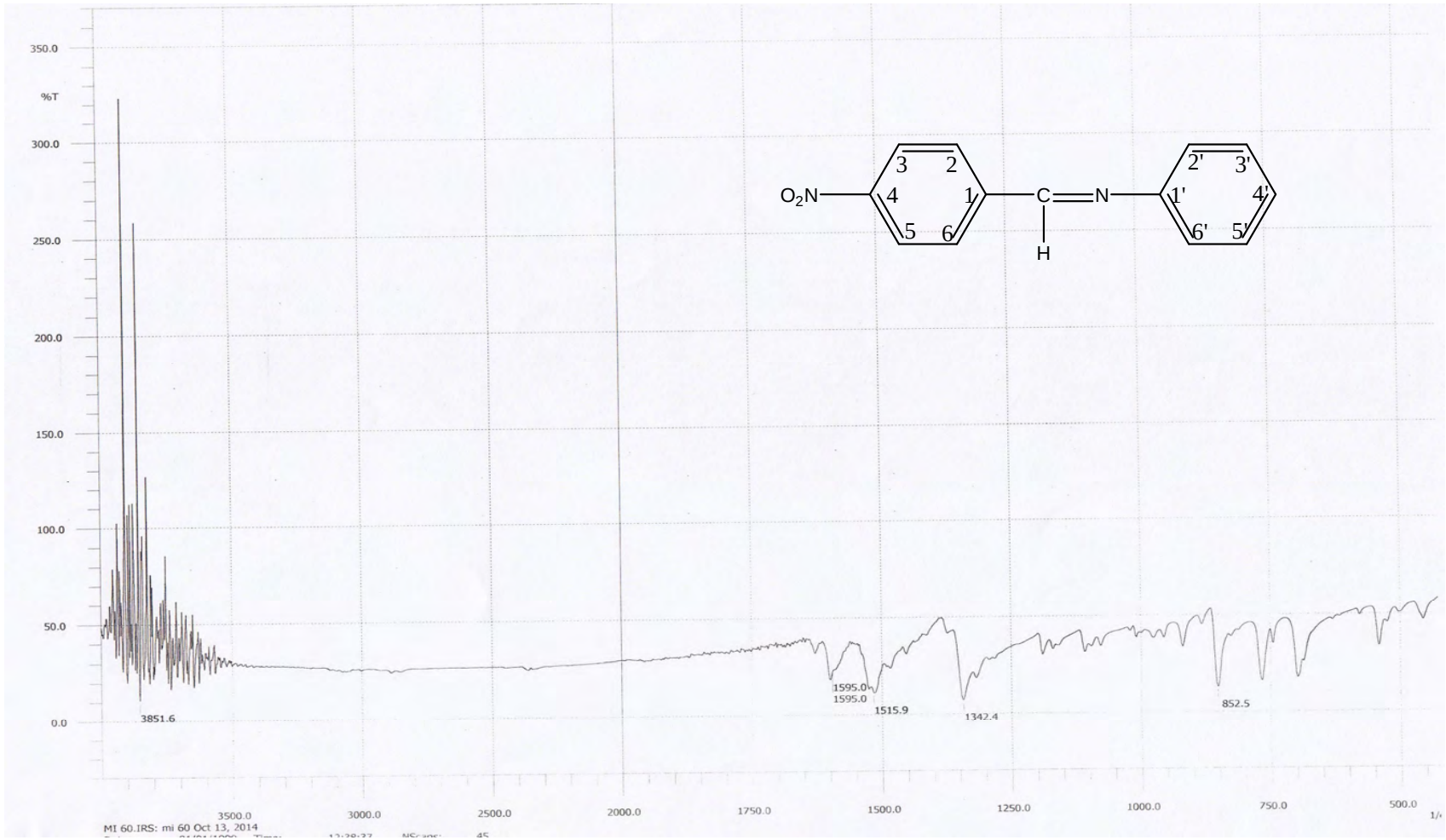
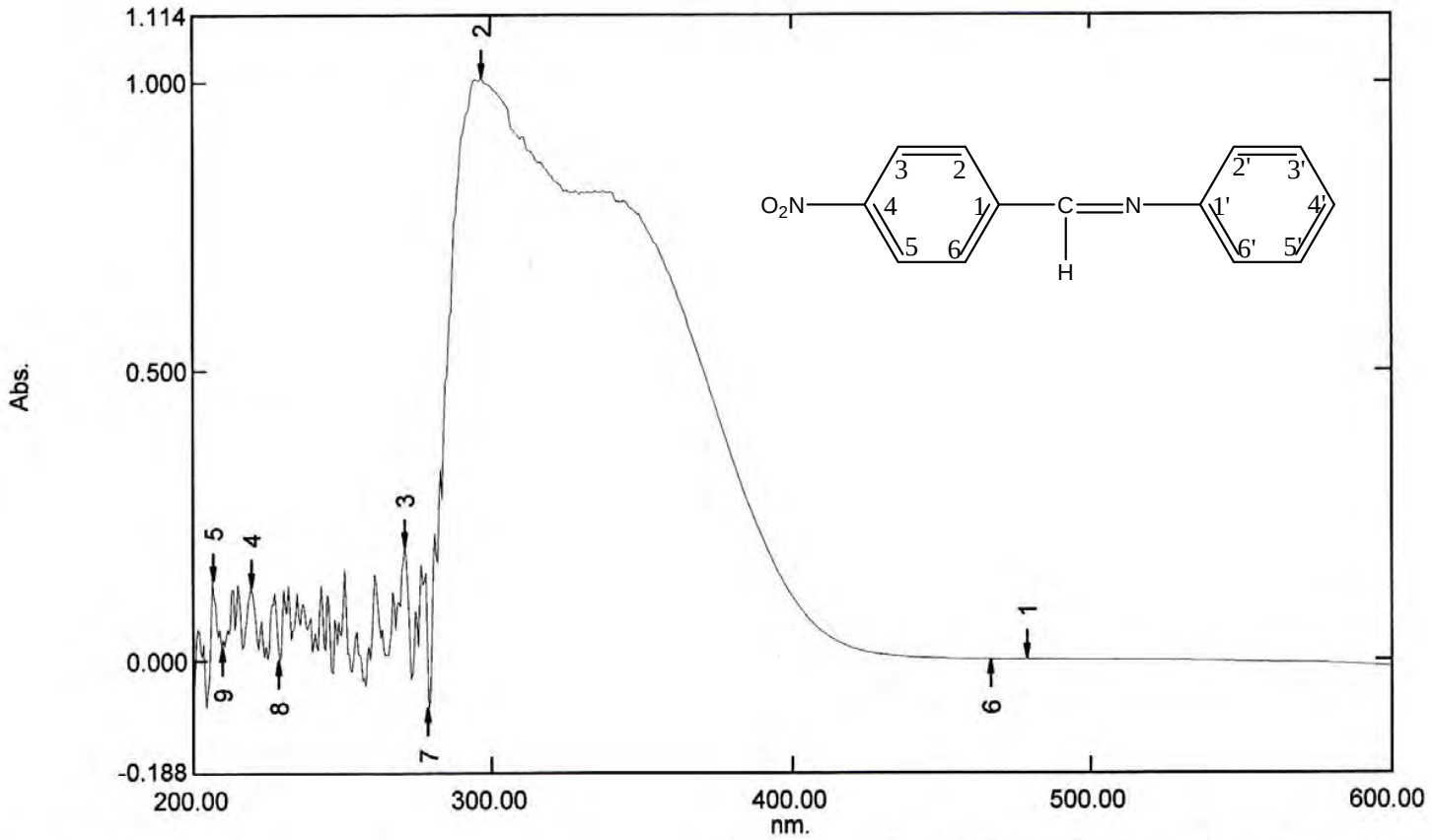


Fig. 4A: FT-IR Spectra of compound **14.**



Measurement Properties

Wavelength Range (nm.):	200.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Enabled
Scan Mode:	Single

No.	P/V	Wavelength	Abs.	Description
1	↑	479.00	0.003	
2	↑	296.50	1.005	
3	↑	271.00	0.198	
4	↑	219.50	0.127	
5	↑	206.50	0.140	

Fig. 4B: UV Spectra of compound **14.**

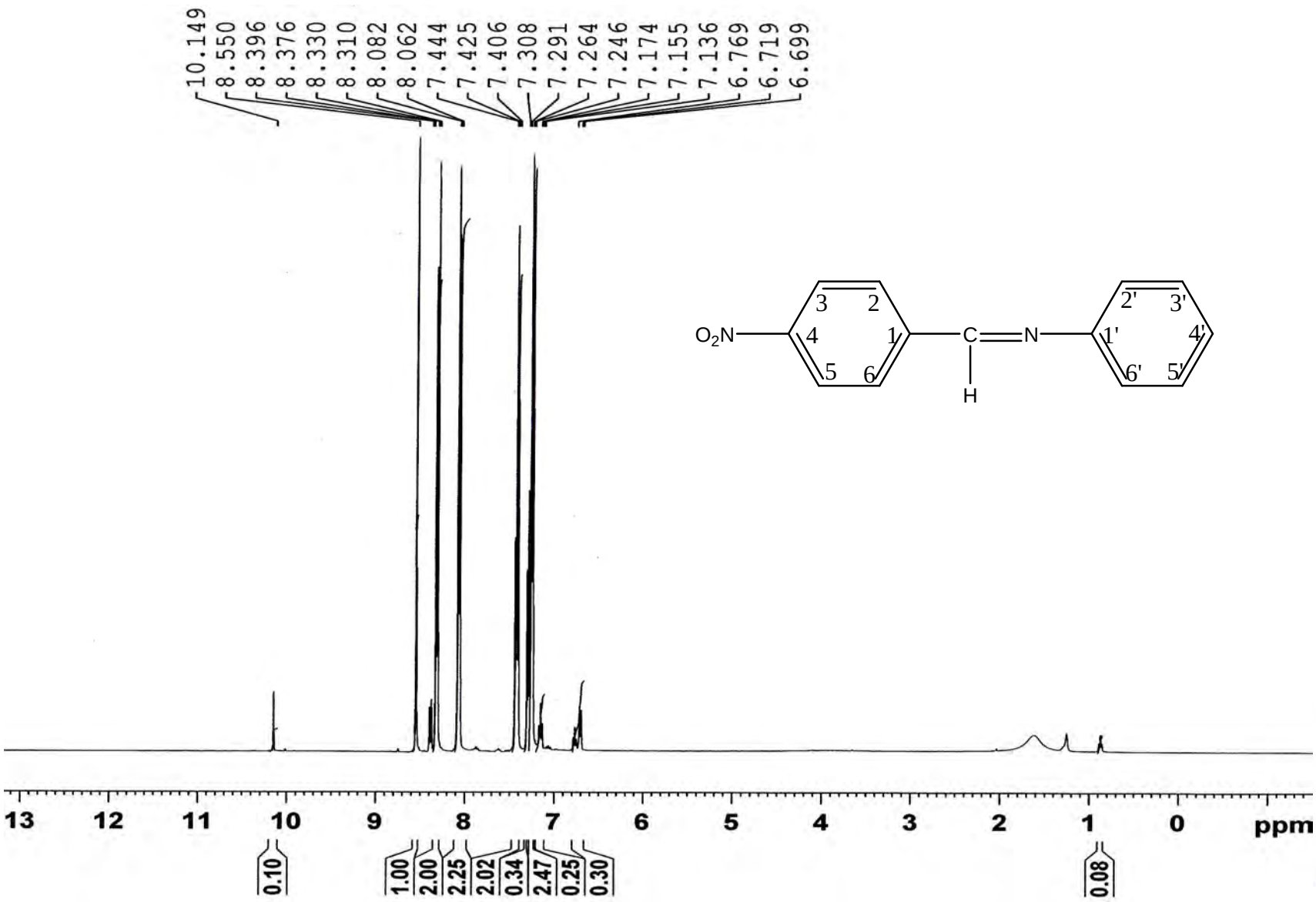


Fig. 4C: ^{1}H NMR Spectra of compound **14** (total).

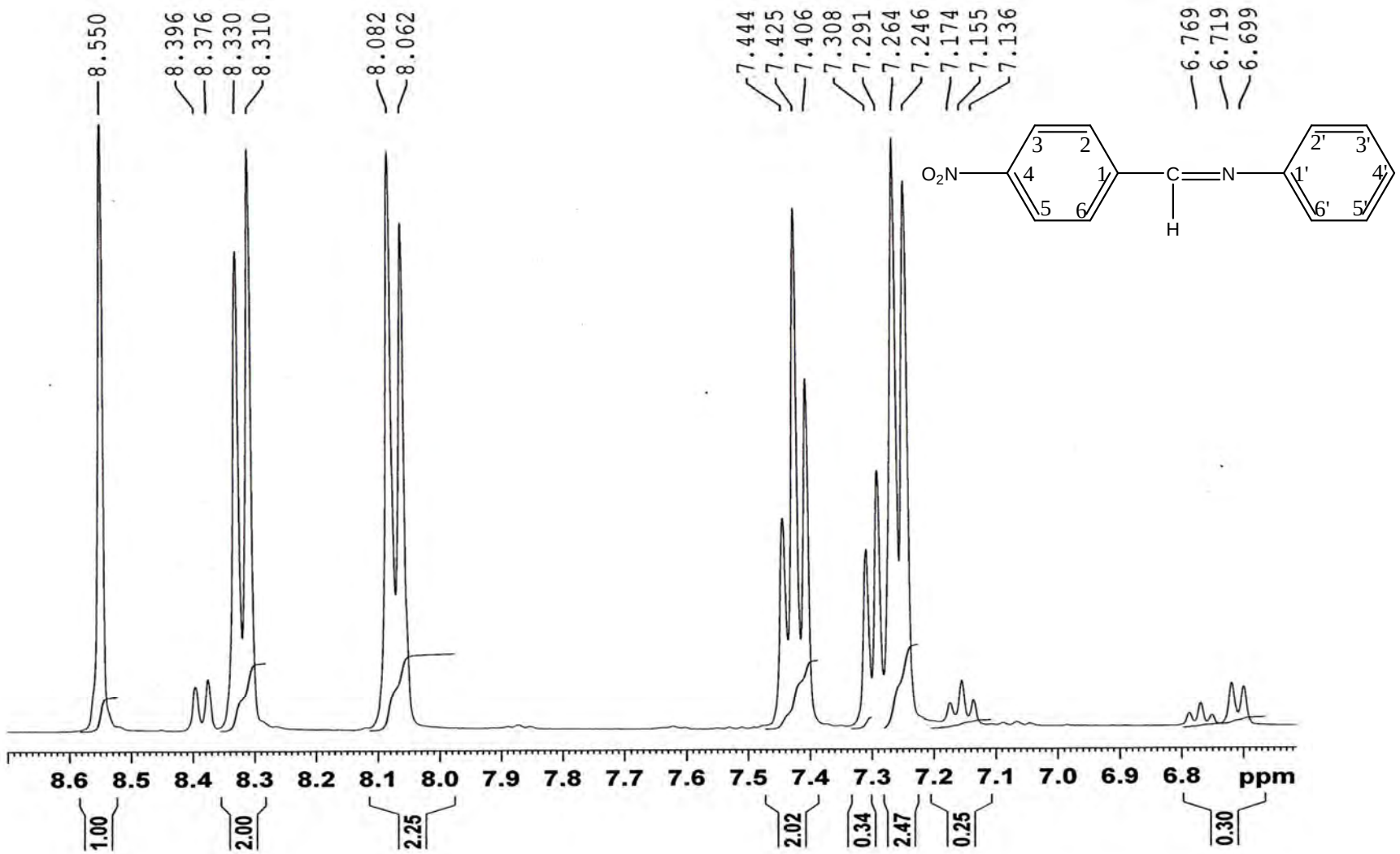


Fig. 4D: ^{1}H NMR Spectra of compound **14**

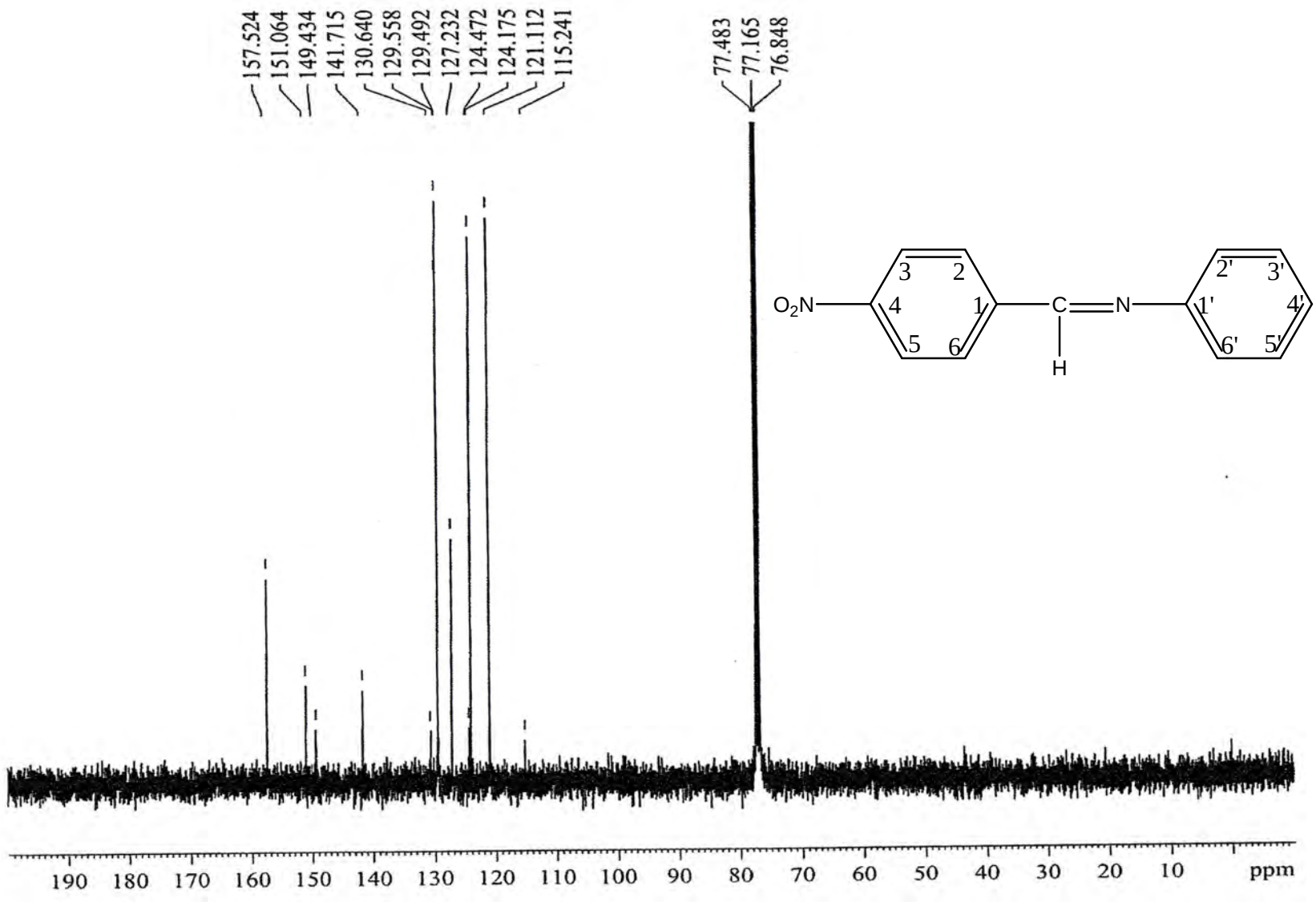


Fig. 4E: ^{13}C NMR Spectra of compound **14** (total).

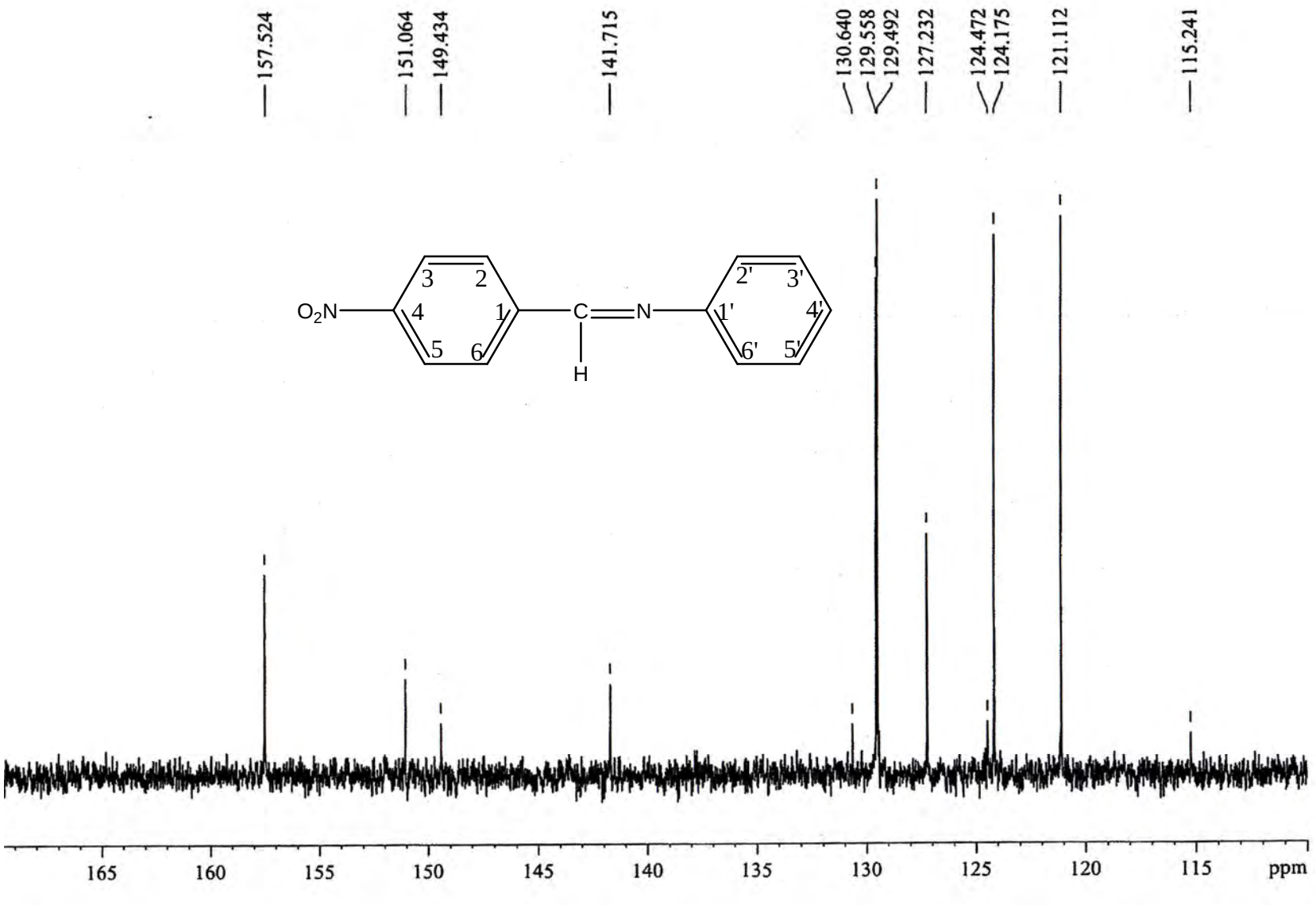


Fig. 4F: ^{13}C NMR Spectra of compound **14** (expanded).

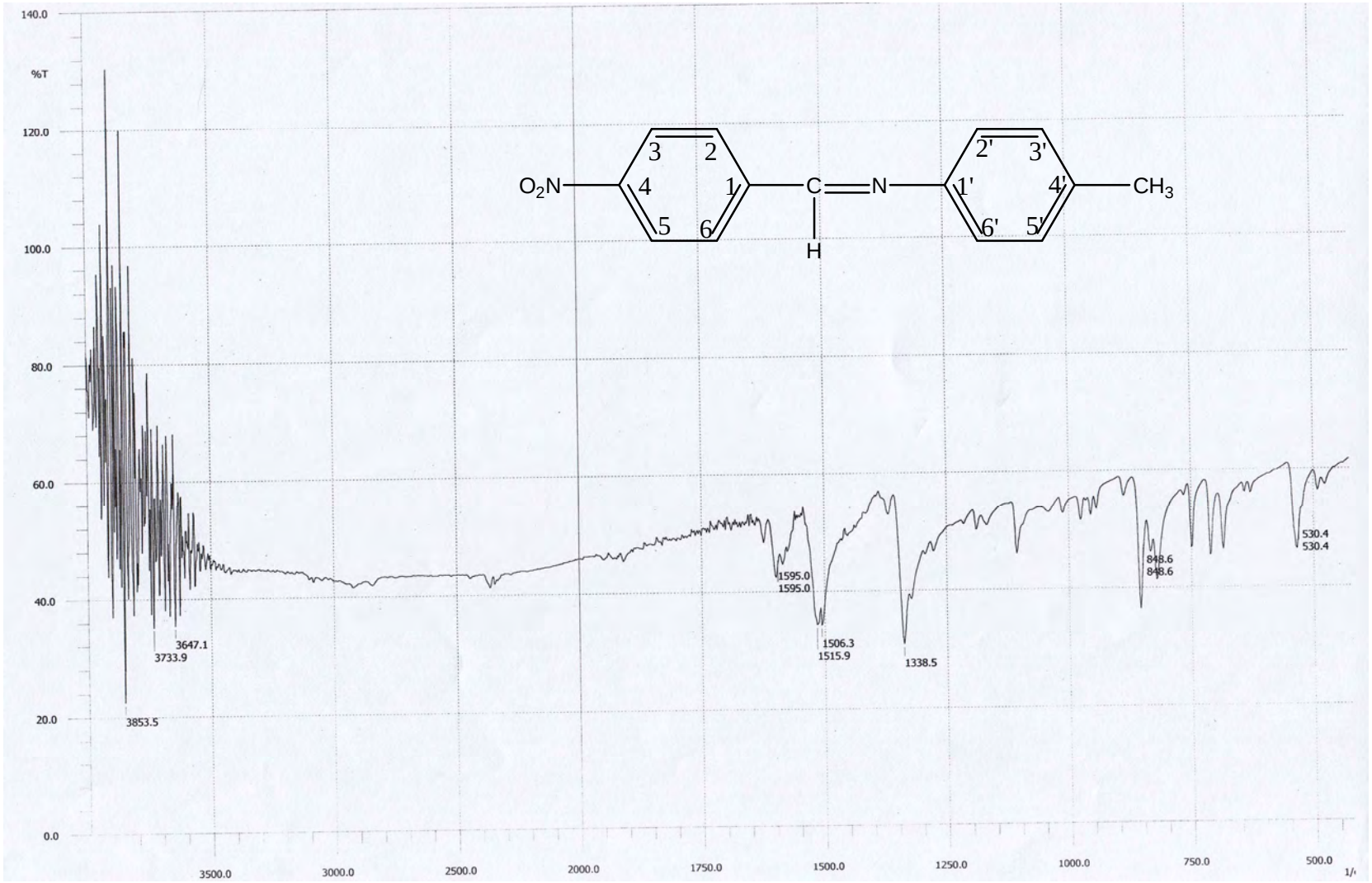
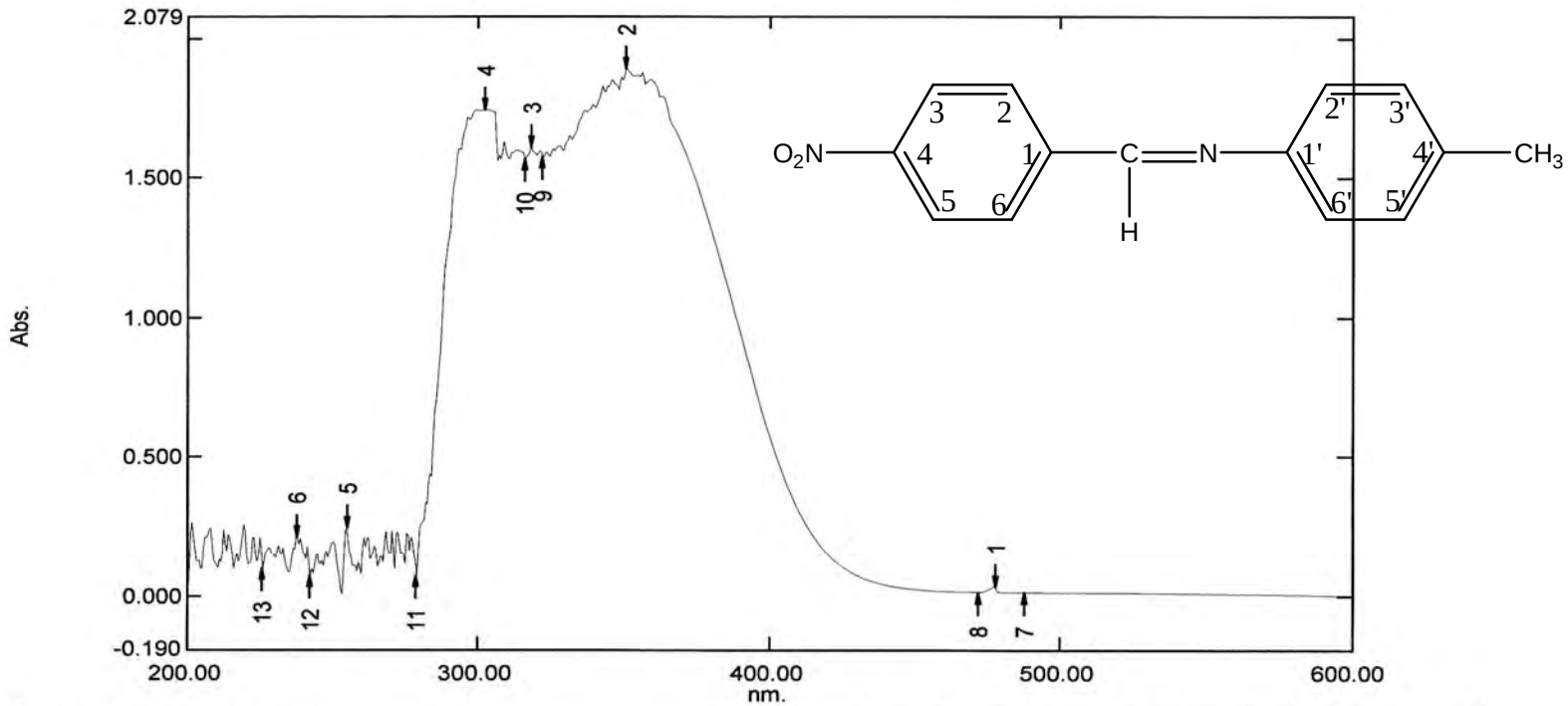


Fig. 5A: FT-IR Spectra of compound **15**



Measurement Properties	
Wavelength Range (nm.):	200.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Enabled
Scan Mode:	Single
Sample Preparation Properties	
Weight:	
Volume:	
Dilution:	
Path Length:	
Additional Information:	
Instrument Properties	
Instrument Type:	UV-1600 Series
Measuring Mode:	Absorbance

No.	P/V	Wavelength	Abs.	Description
1	↑	478.00	0.035	
2	↑	350.50	1.890	
3	↑	318.00	1.612	
4	↑	302.00	1.747	
5	↑	255.00	0.248	
6	↑	238.00	0.213	
7	↓	488.00	0.013	
8	↓	472.00	0.014	
9	↓	322.00	1.573	
10	↓	316.00	1.568	
11	↓	279.00	0.075	
12	↓	242.50	0.074	
13	↓	226.00	0.096	

Fig. 5B: UV Spectra of compound **15**

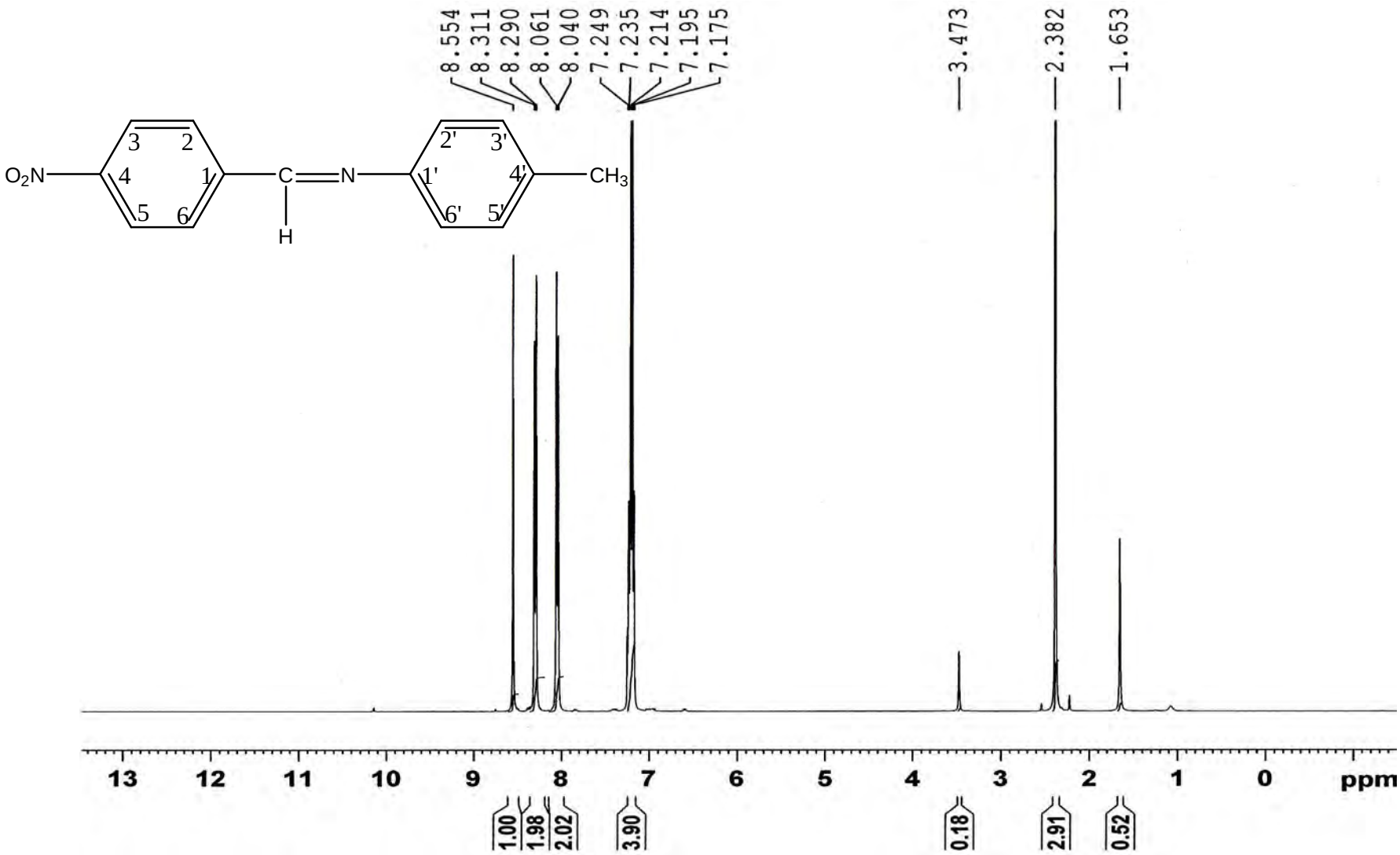


Fig. 5C: ^{1}H NMR Spectra of compound **15**

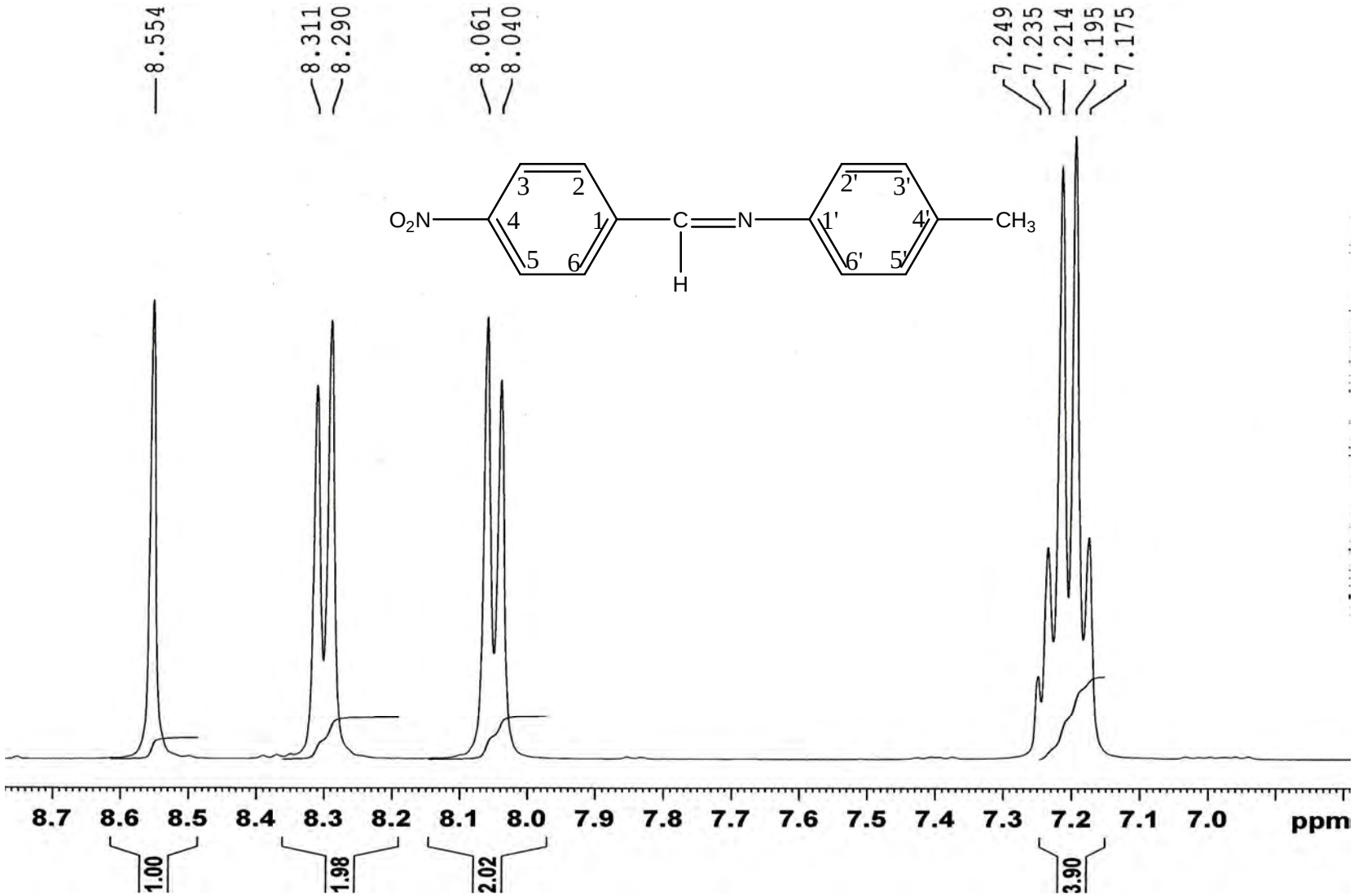


Fig. 5D: ^{1}H NMR Spectra of compound **15** (expanded)

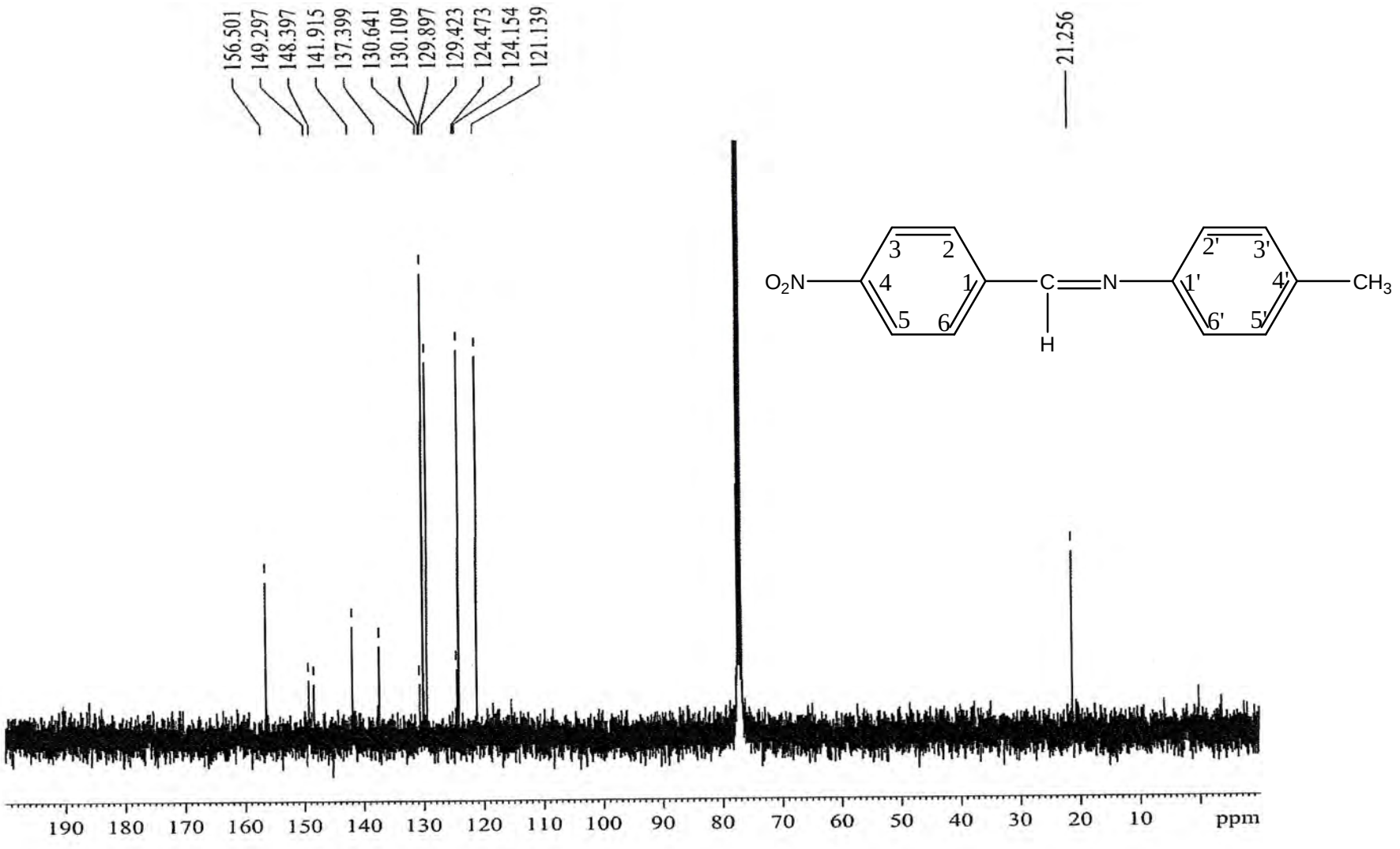


Fig. 5E: ^{13}C NMR Spectra of compound **15**

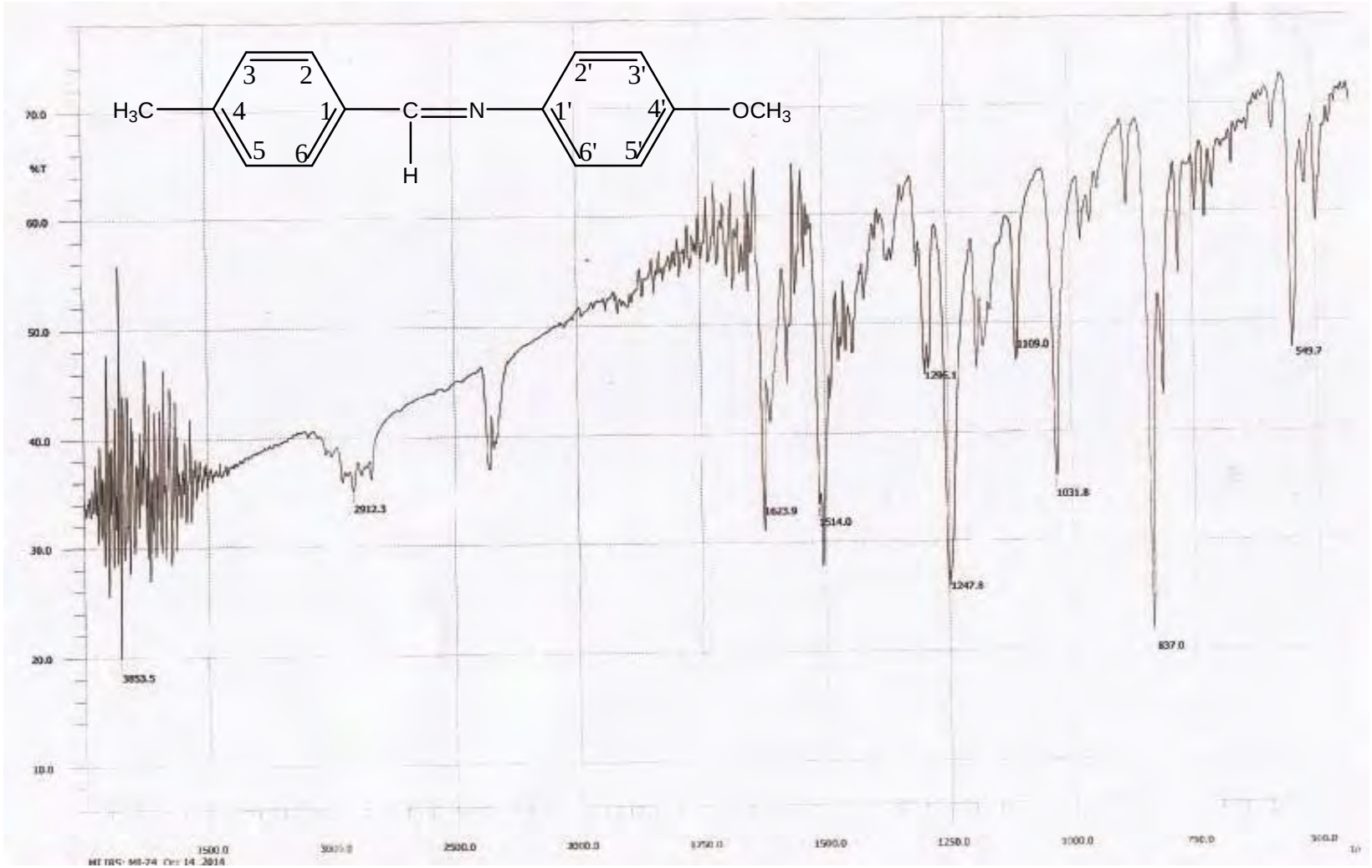
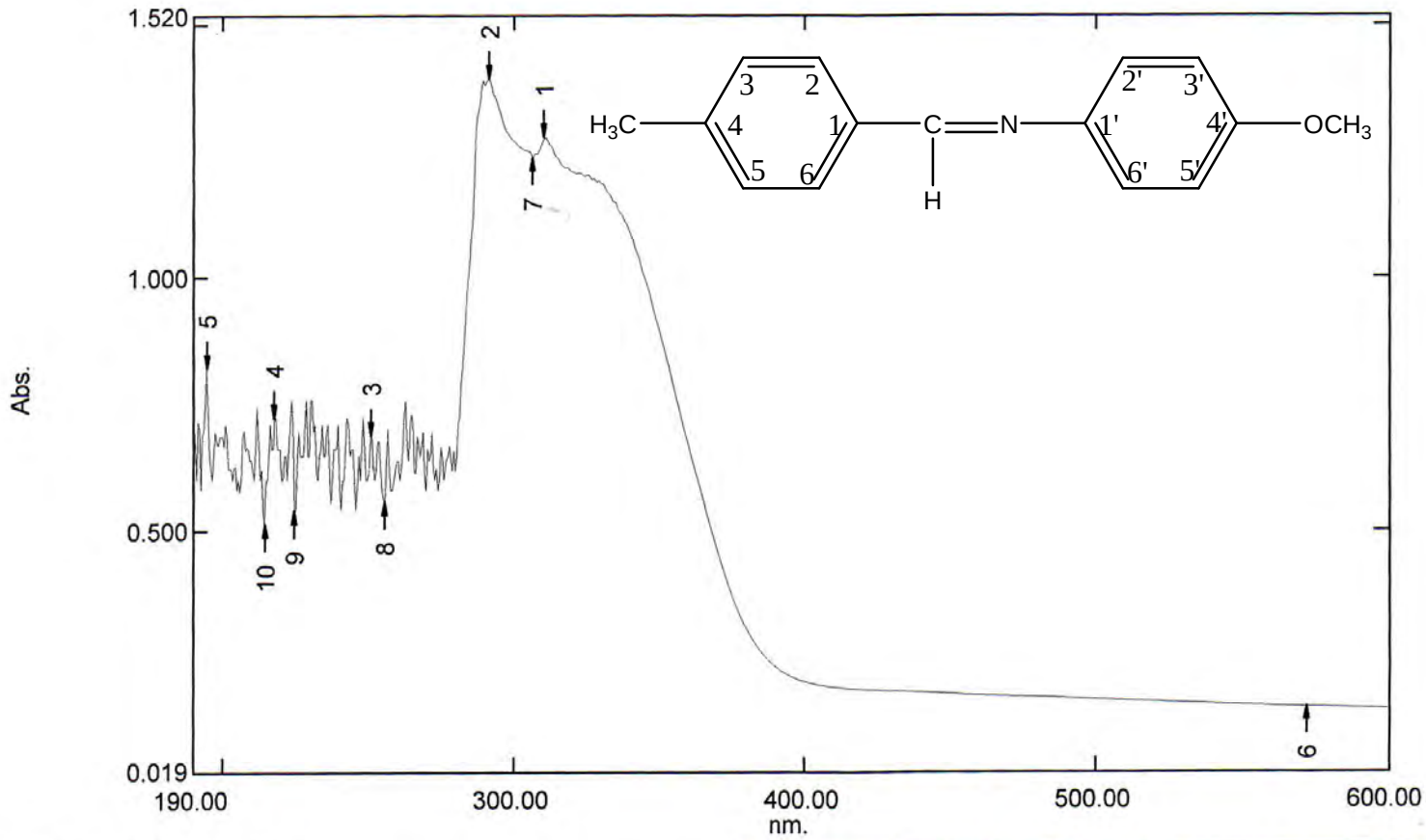


Fig 6A: FT IR spectra of compound **16**.



Measurement Properties

Wavelength Range (nm.):	190.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

No.	P/V	Wavelength	Abs.	Description
1	↑	310.50	1.279	
2	↑	291.50	1.395	
3	↑	251.50	0.690	
4	↑	218.00	0.727	

Fig 6B: UV spectra of compound **16**.

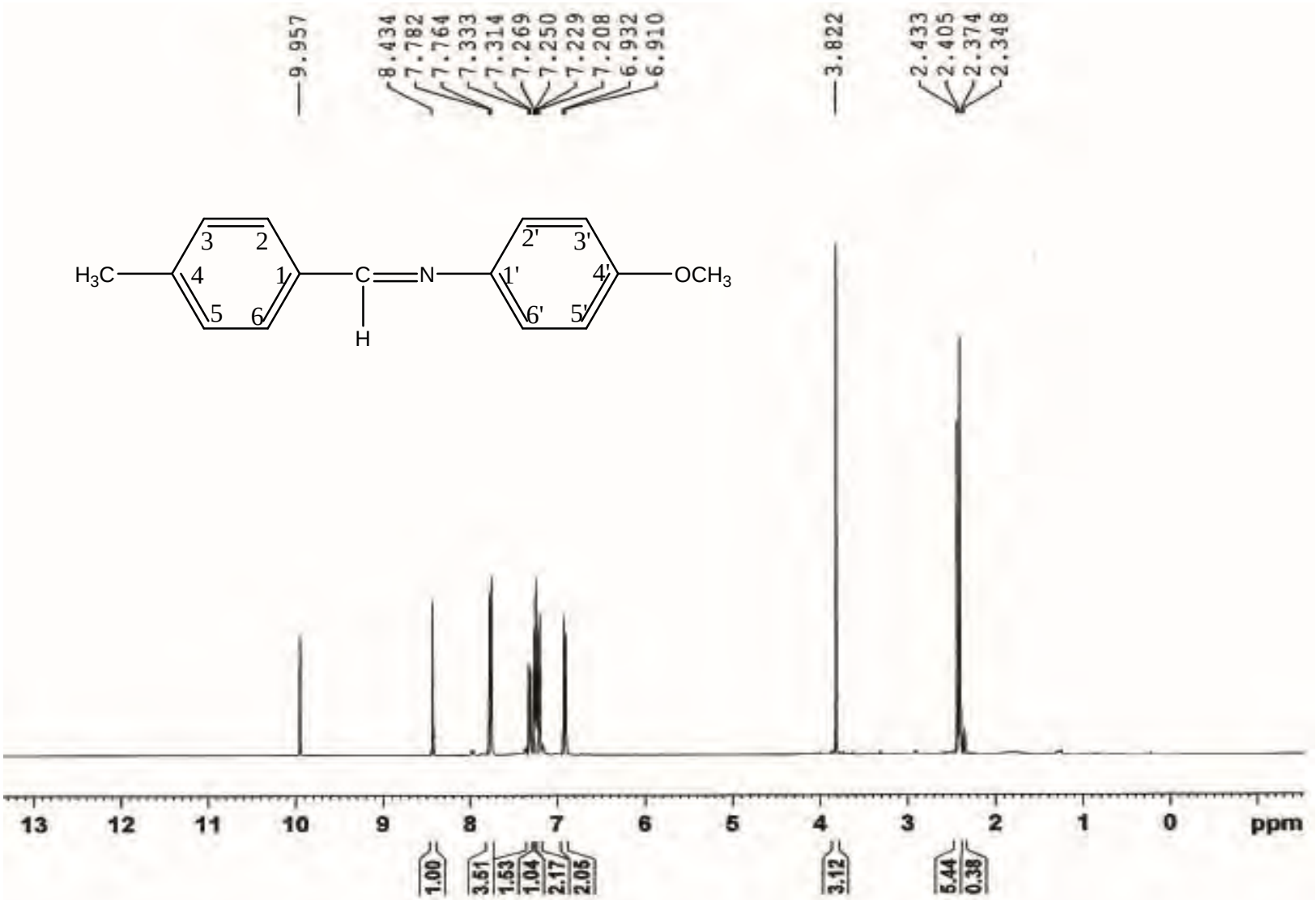


Fig 6C: ^{1}H NMR spectra of compound **16**.

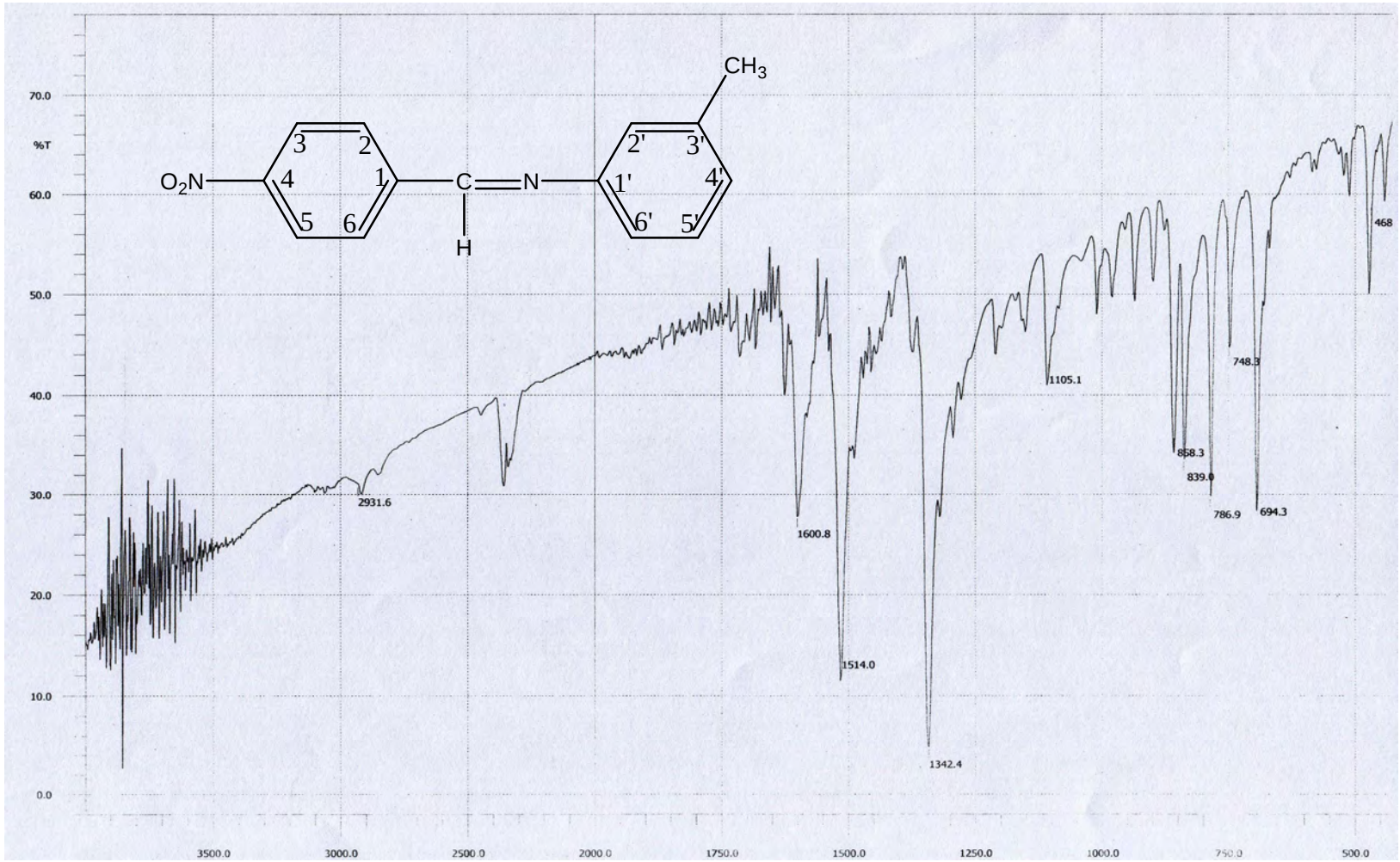
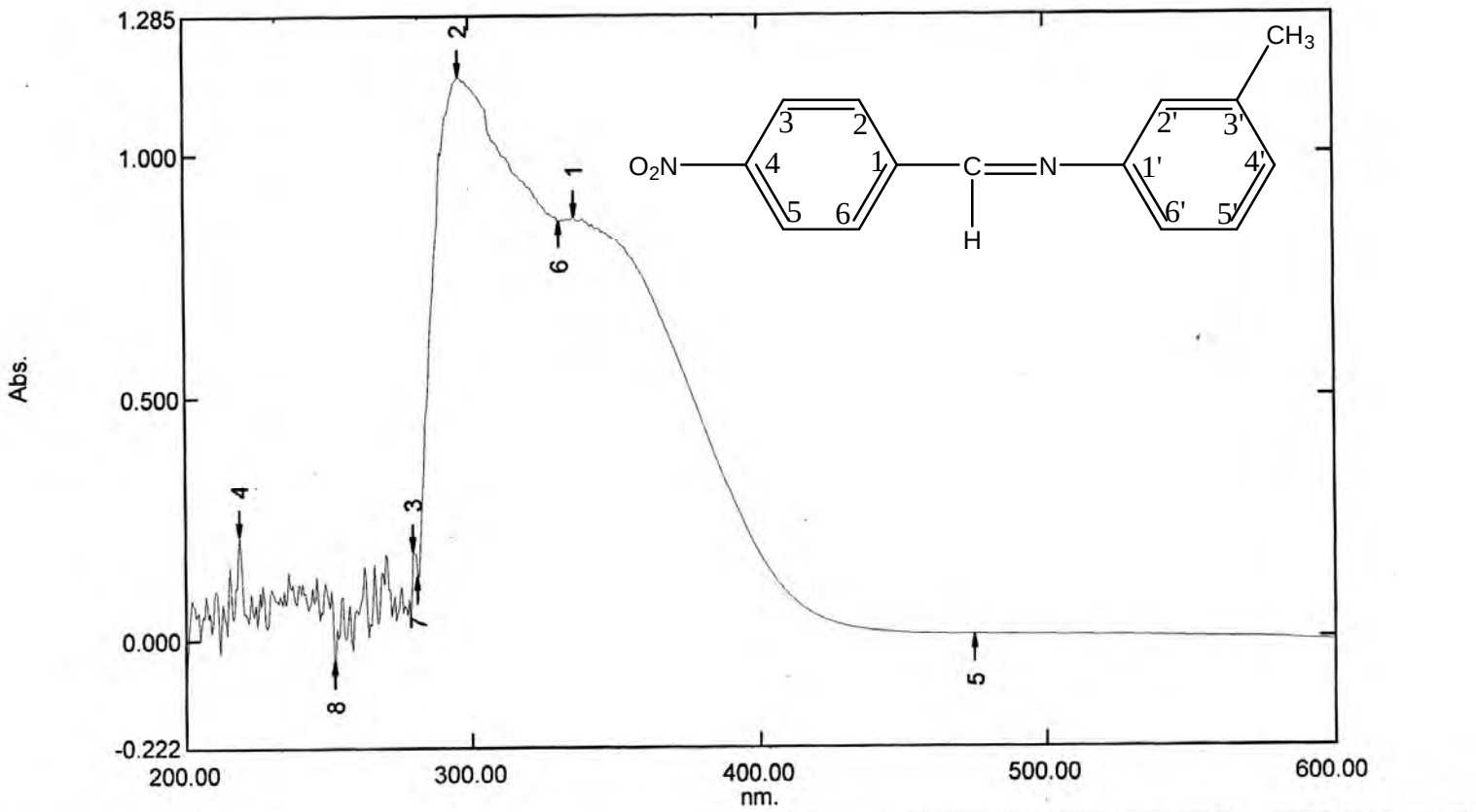


Fig 7A: FT IR spectra of compound **17**.



Measurement Properties

Wavelength Range (nm.):	200.00 to 600.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Enabled
Scan Mode:	Single

No.	P/V	Wavelength	Abs.	Description
1	↑	336.00	0.870	
2	↑	296.00	1.160	
3	↑	279.50	0.184	
4	↑	219.00	0.215	

Fig 7B: UV spectra of compound **17**.

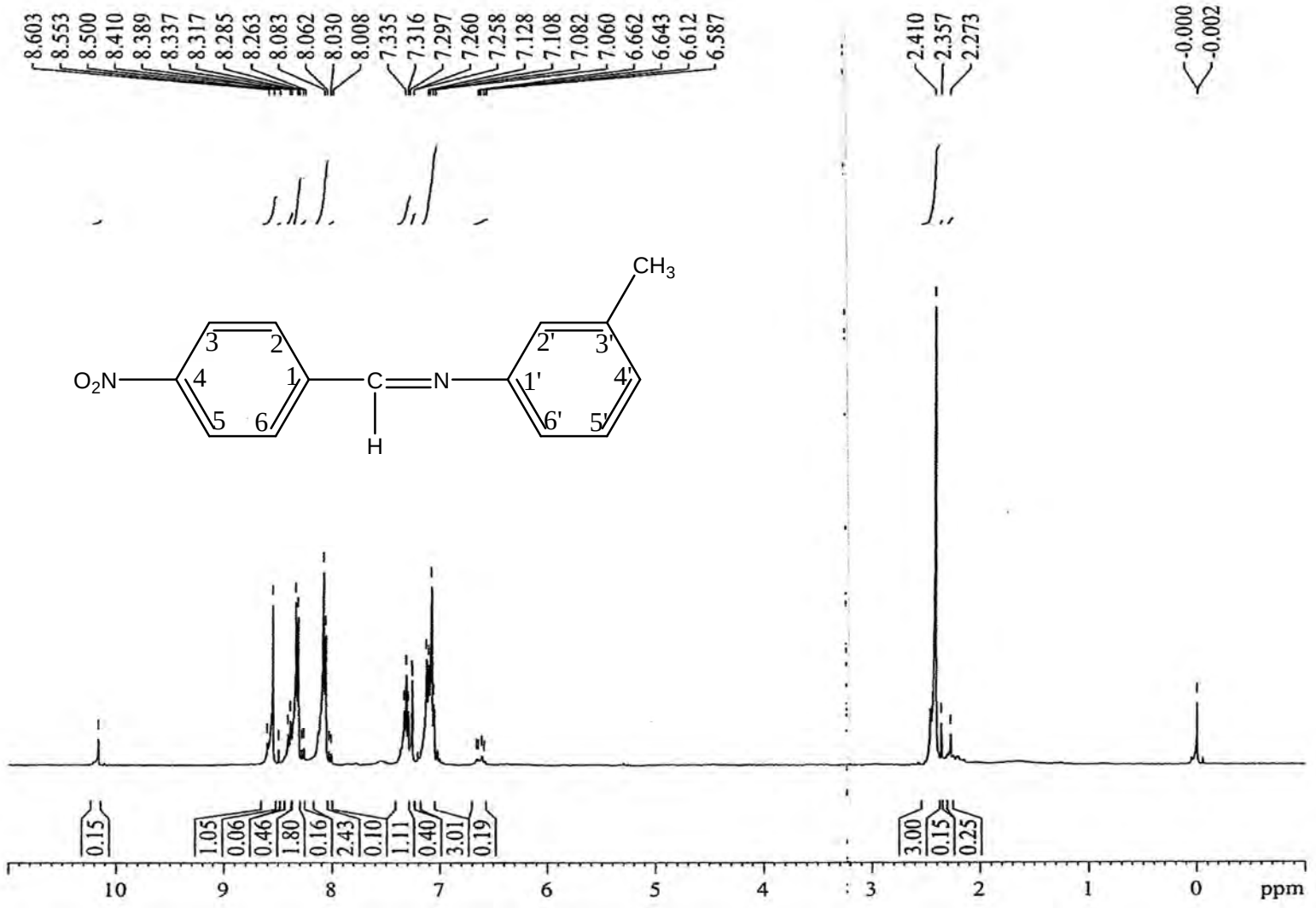


Fig 7C: ^{1}H NMR spectra of compound **17**.

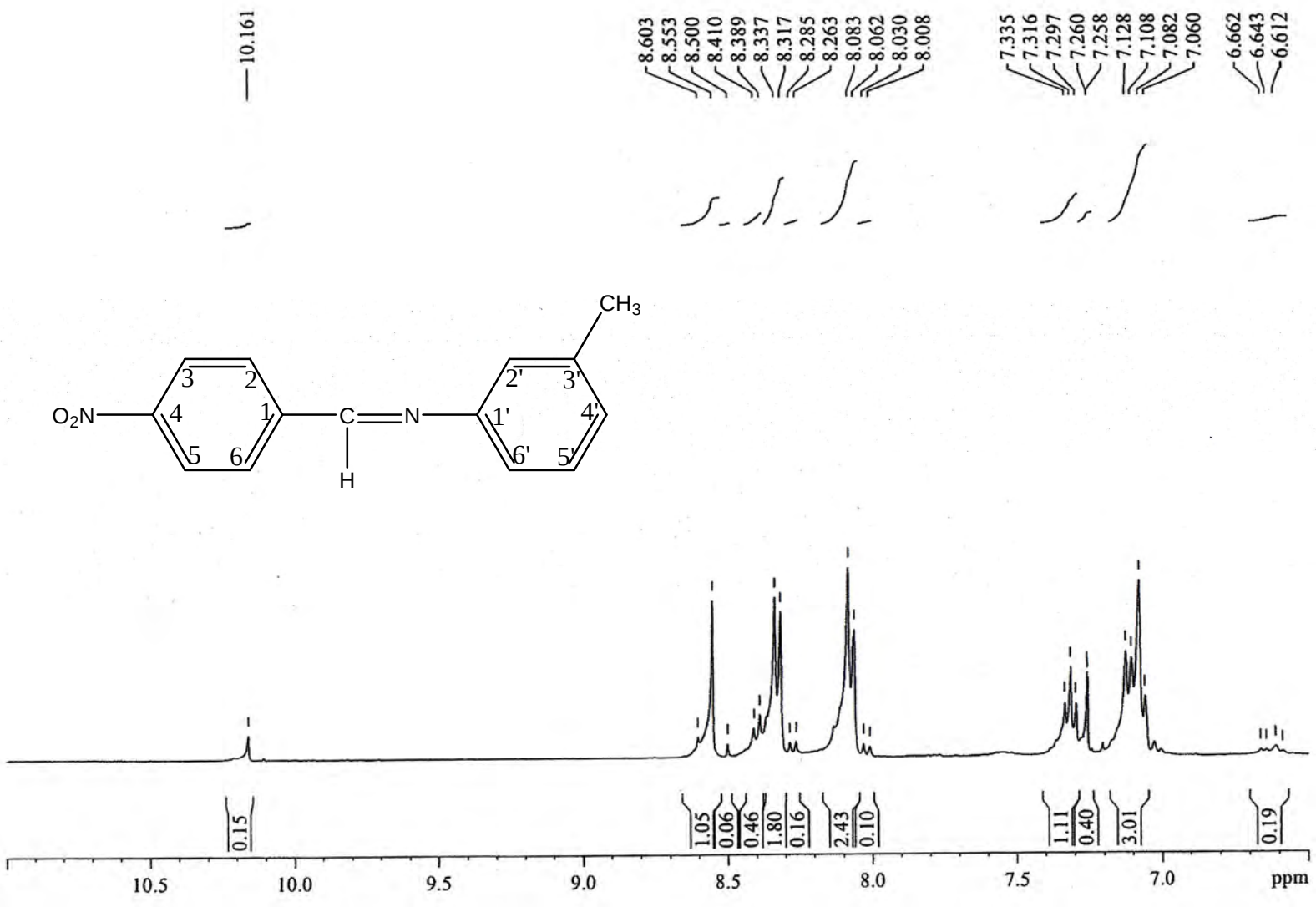


Fig 7D: ^{1}H NMR spectra of compound **17** (expanded).

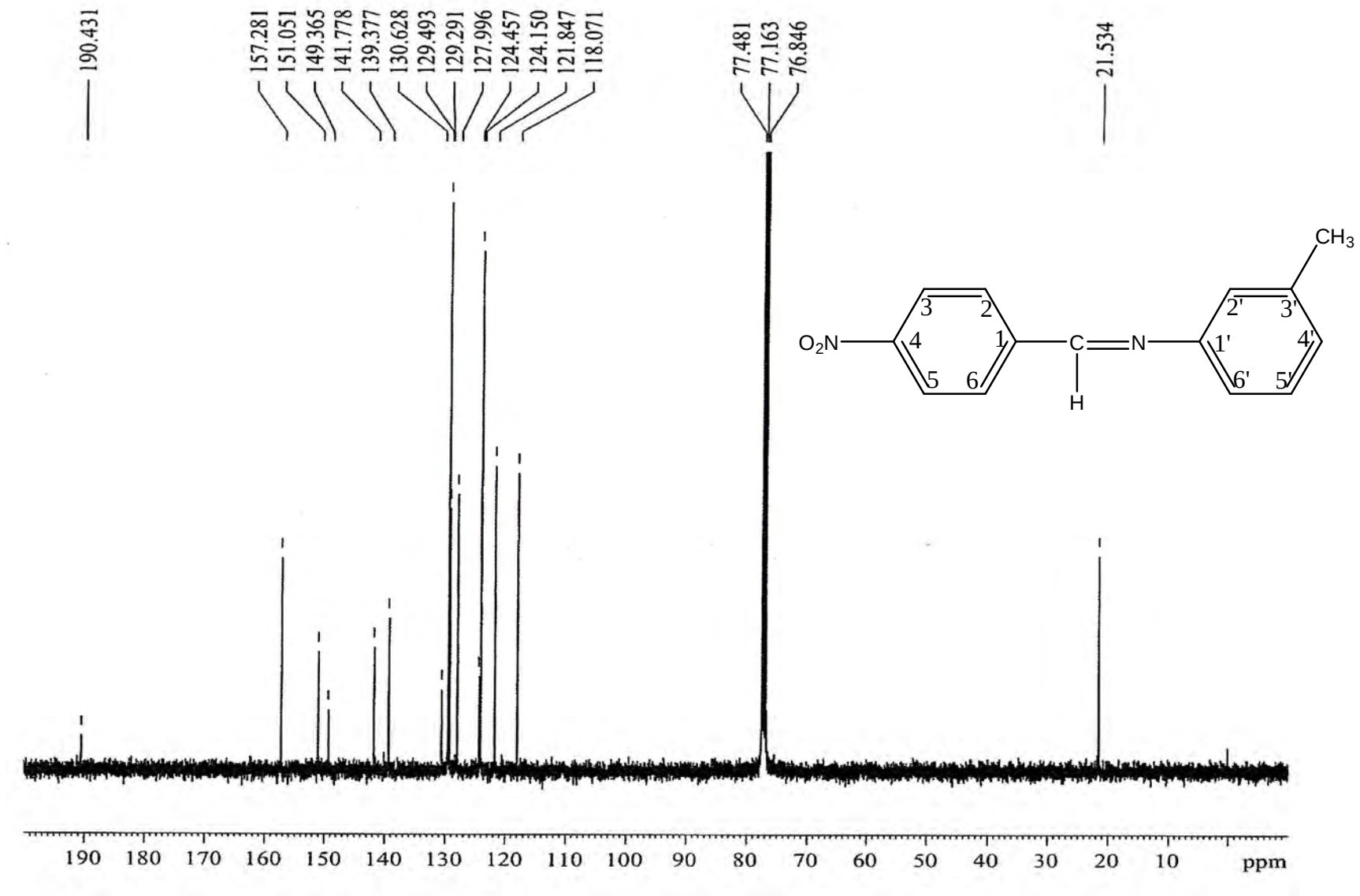


Fig 7E: ^{13}C NMR spectra of compound **17**.

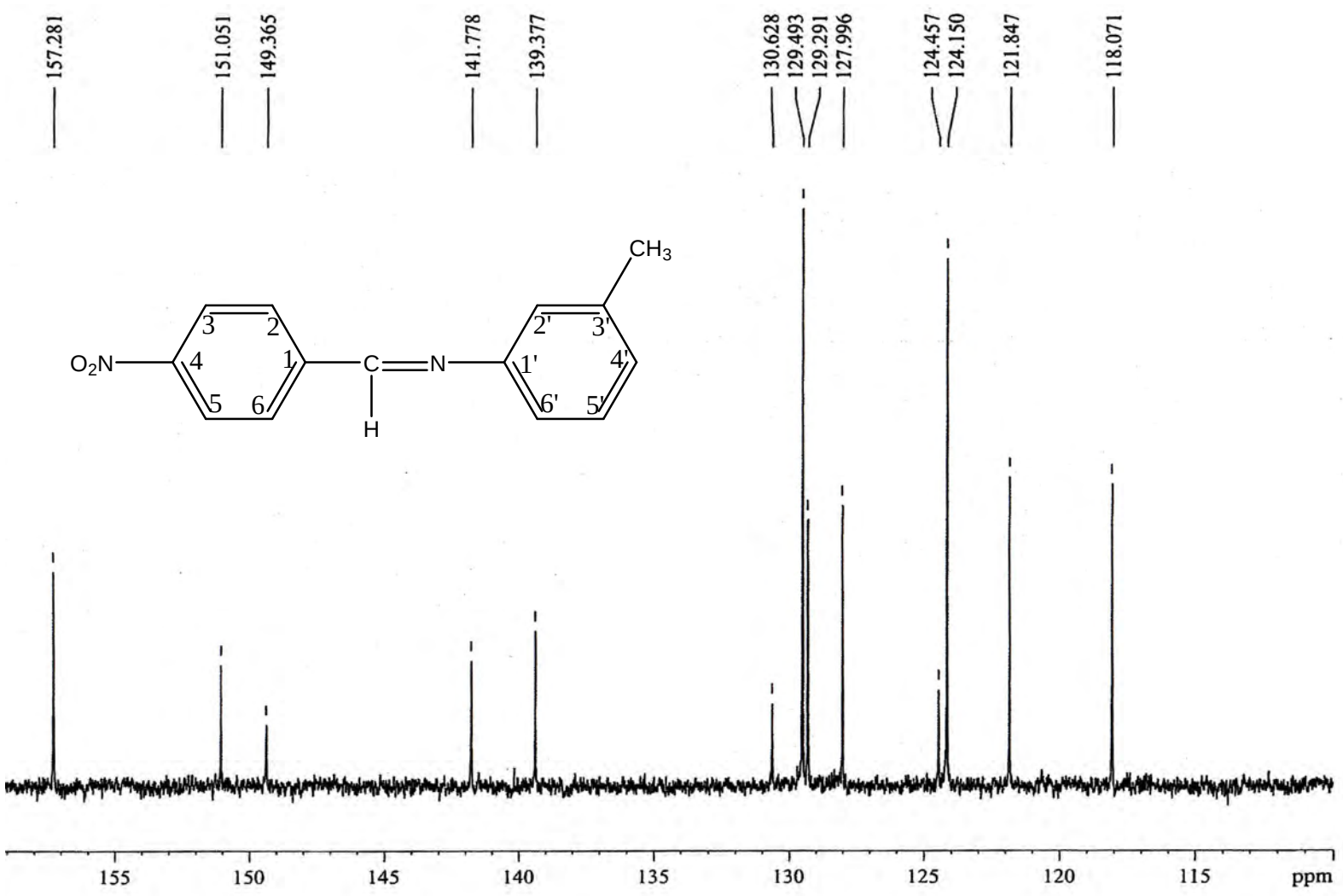


Fig 7F: ^{13}C NMR spectra of compound **17** (expanded).

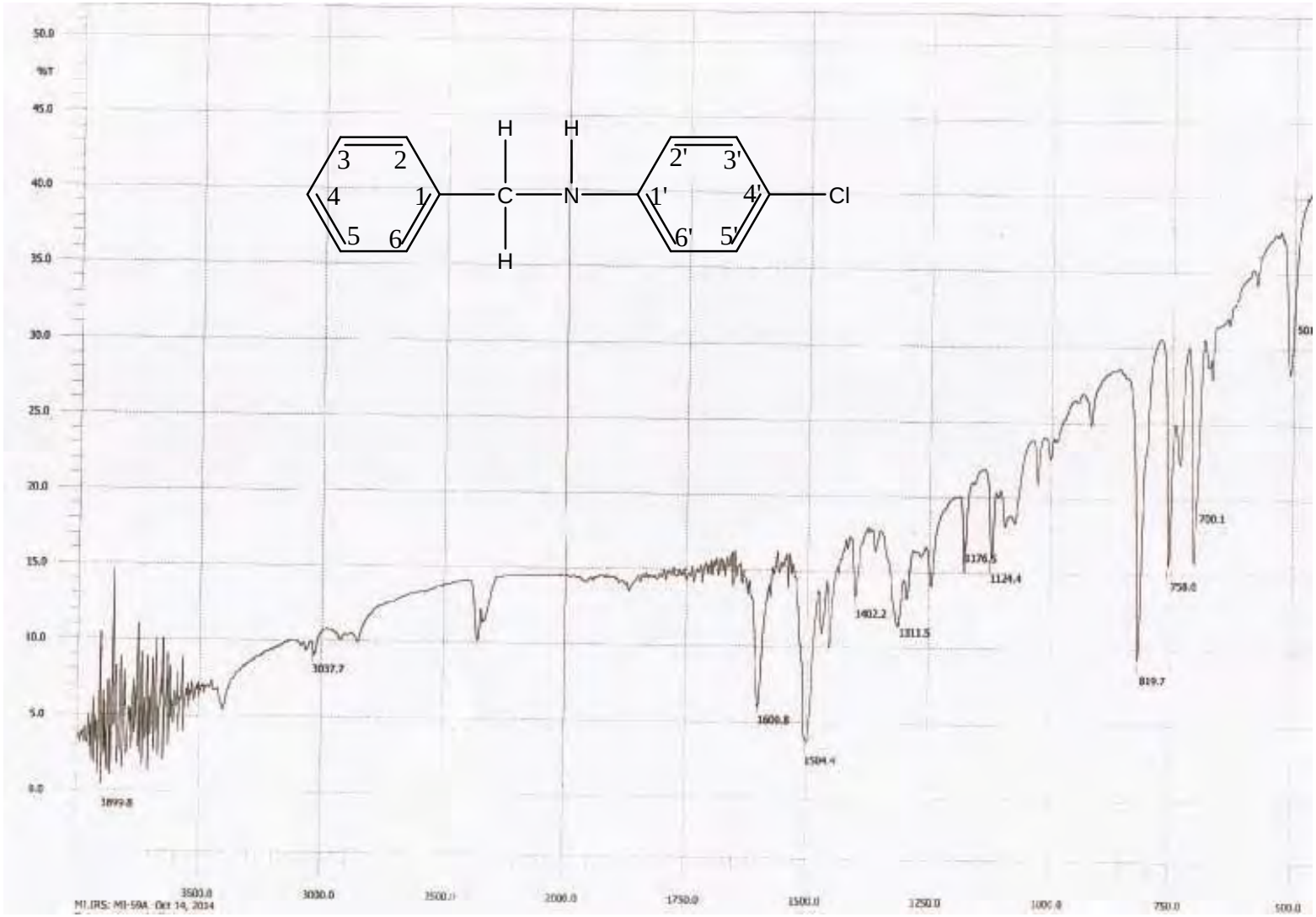


Fig 8A: IR spectra of compound **18.**

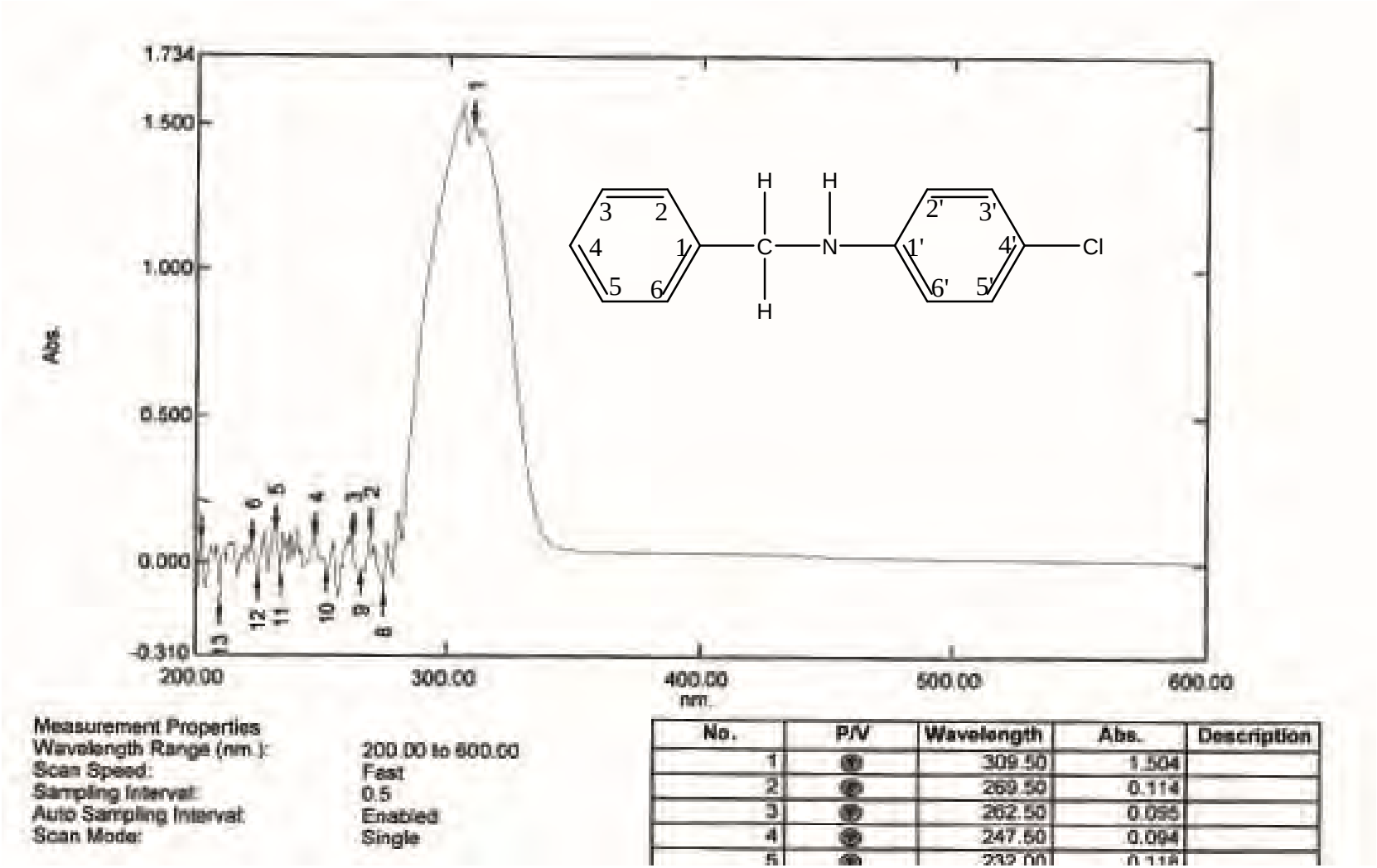


Fig 8B: UV spectra of compound **18.**

Fig 8C: ^{1}H NMR spectra of compound **18.**

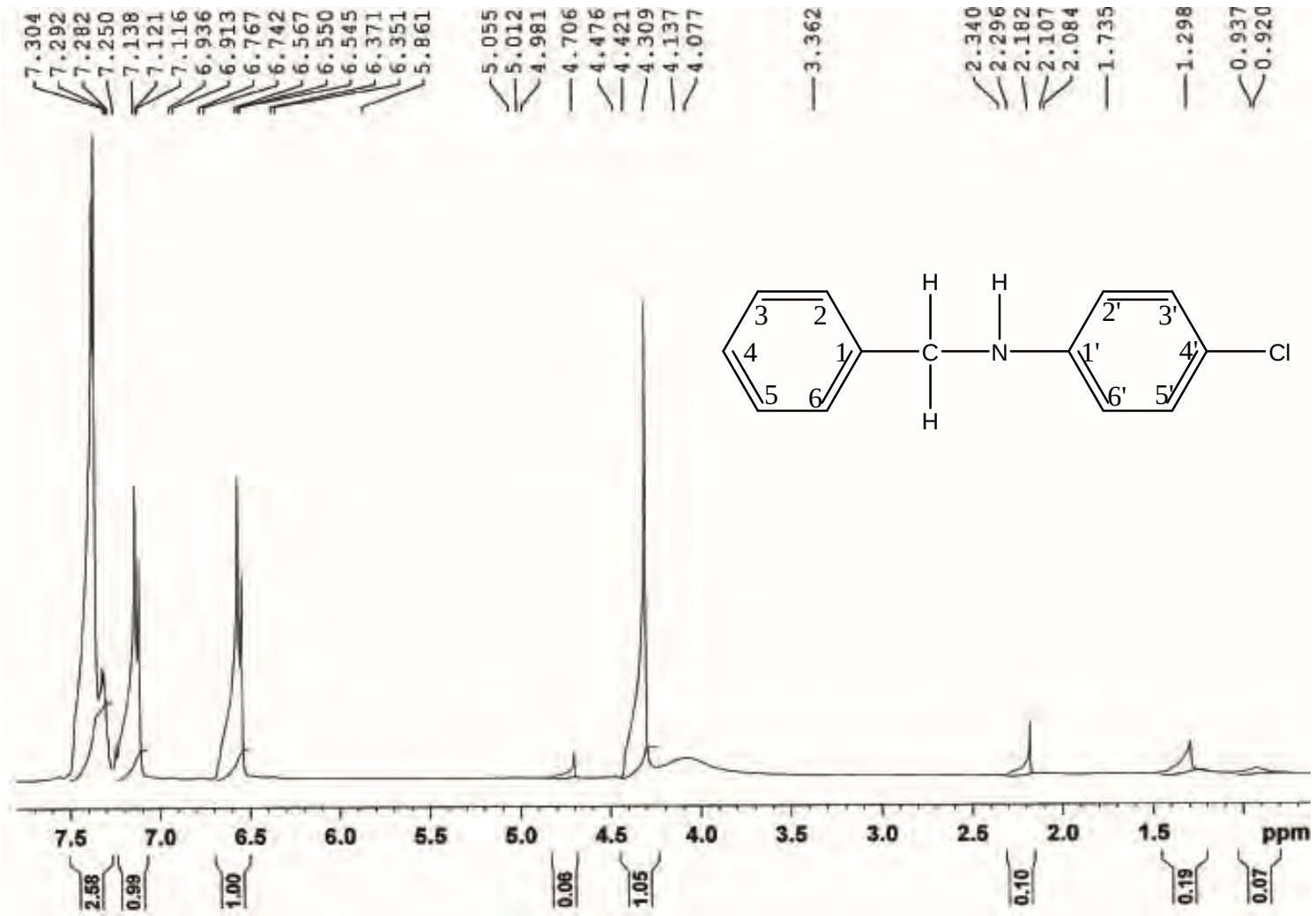


Fig 8D: ^{1}H NMR spectra of compound **18** (expanded)**.**

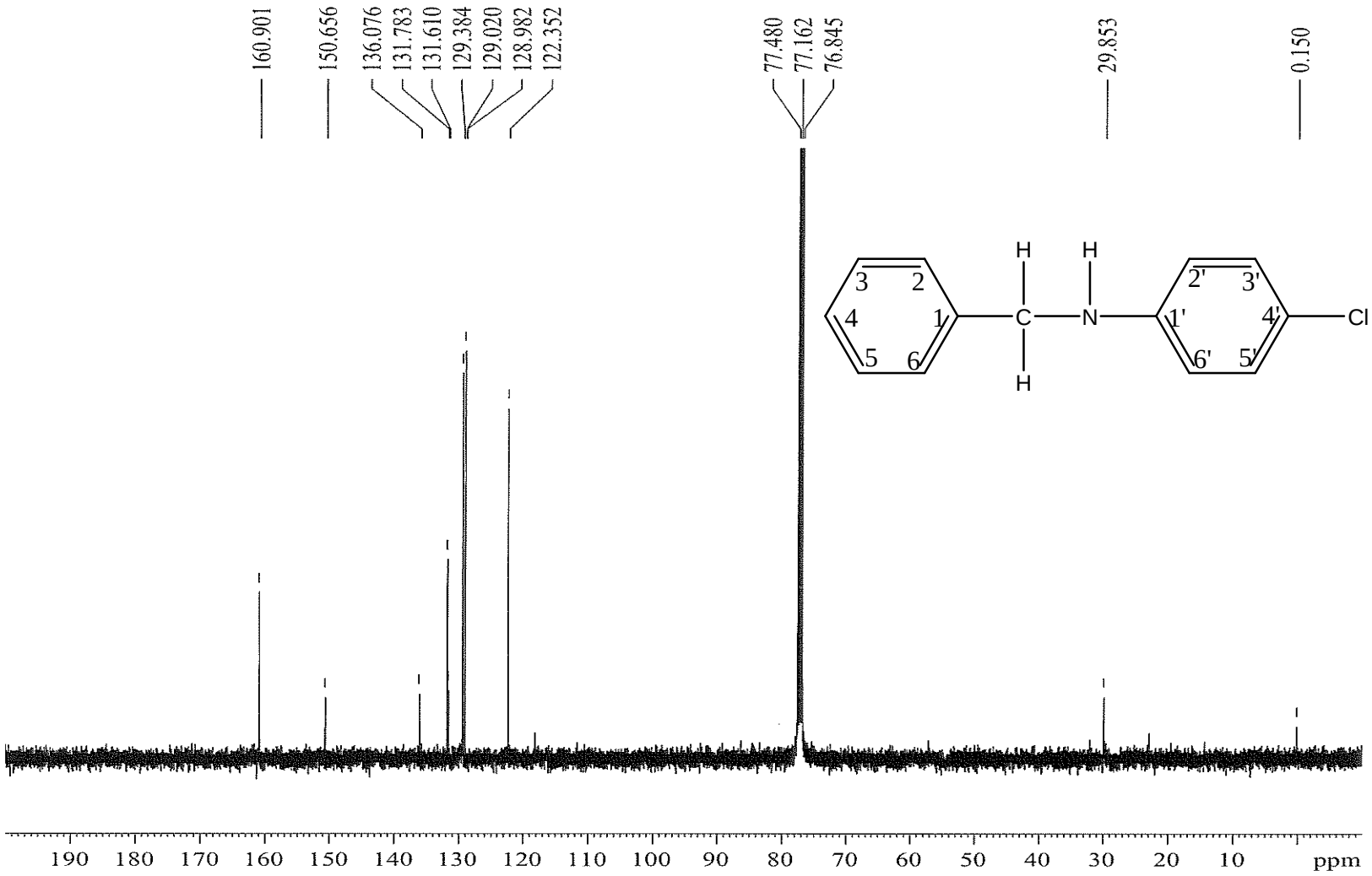


Fig 8E: ^{13}C NMR spectra of compound **18.**

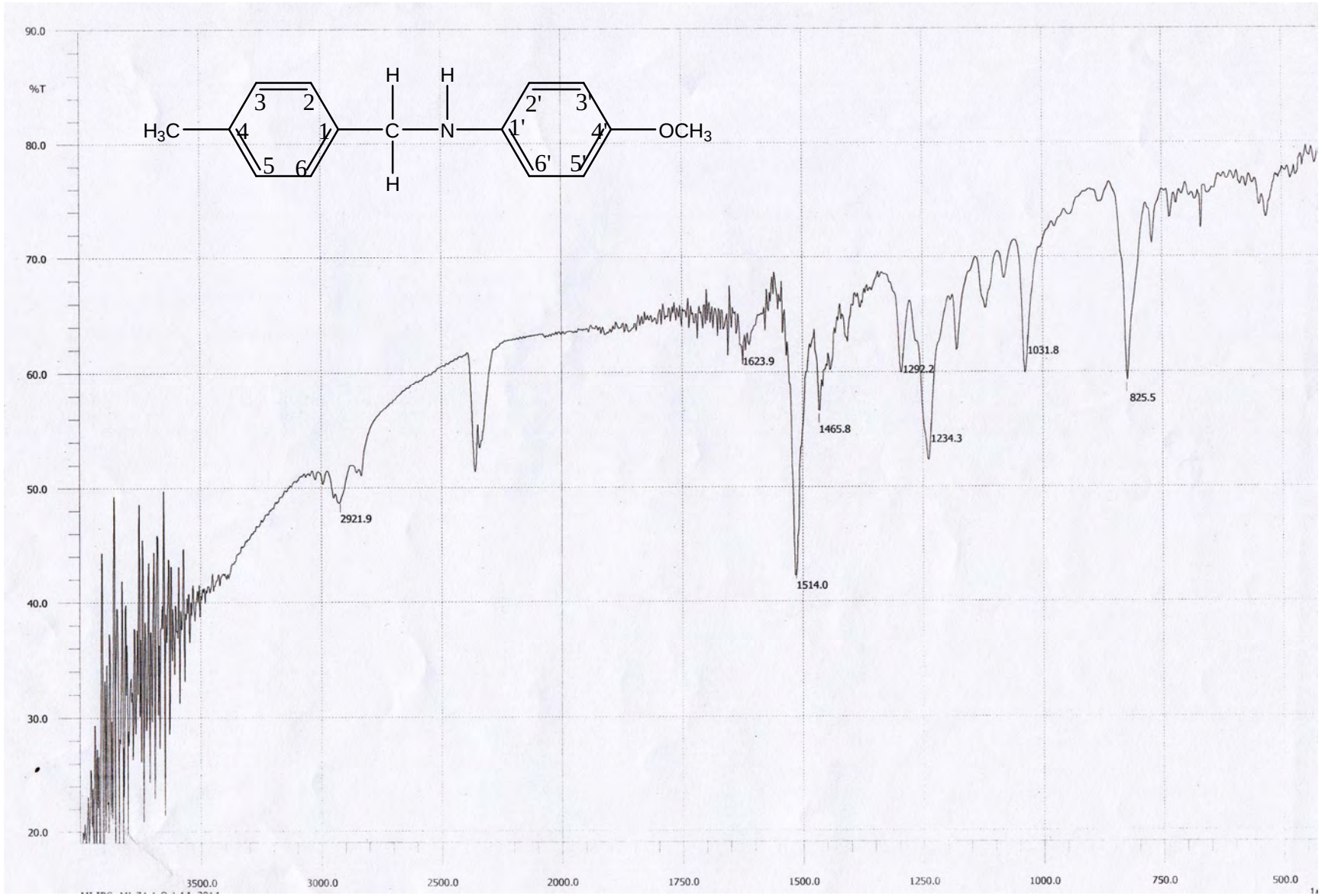
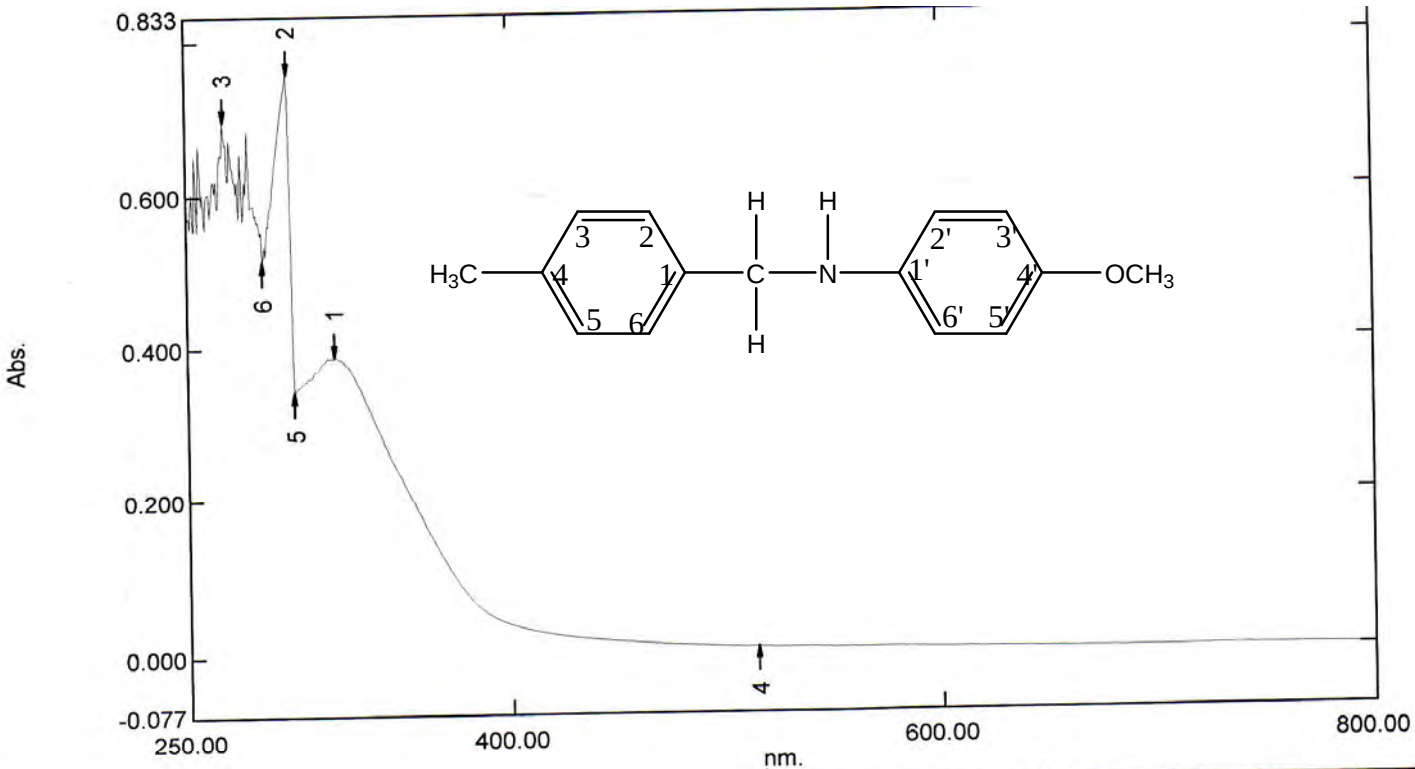


Fig 9A: FT IR spectra of compound **19**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

No.	P/V	Wavelength	Abs.	Description
1	↑	319.00	0.387	
2	↑	297.50	0.757	
3	↑	267.50	0.696	
4	↓	514.00	0.006	
5	↓	300.00	0.342	
6	↓	285.50	0.514	

Fig 9B: UV spectra of compound **19.**

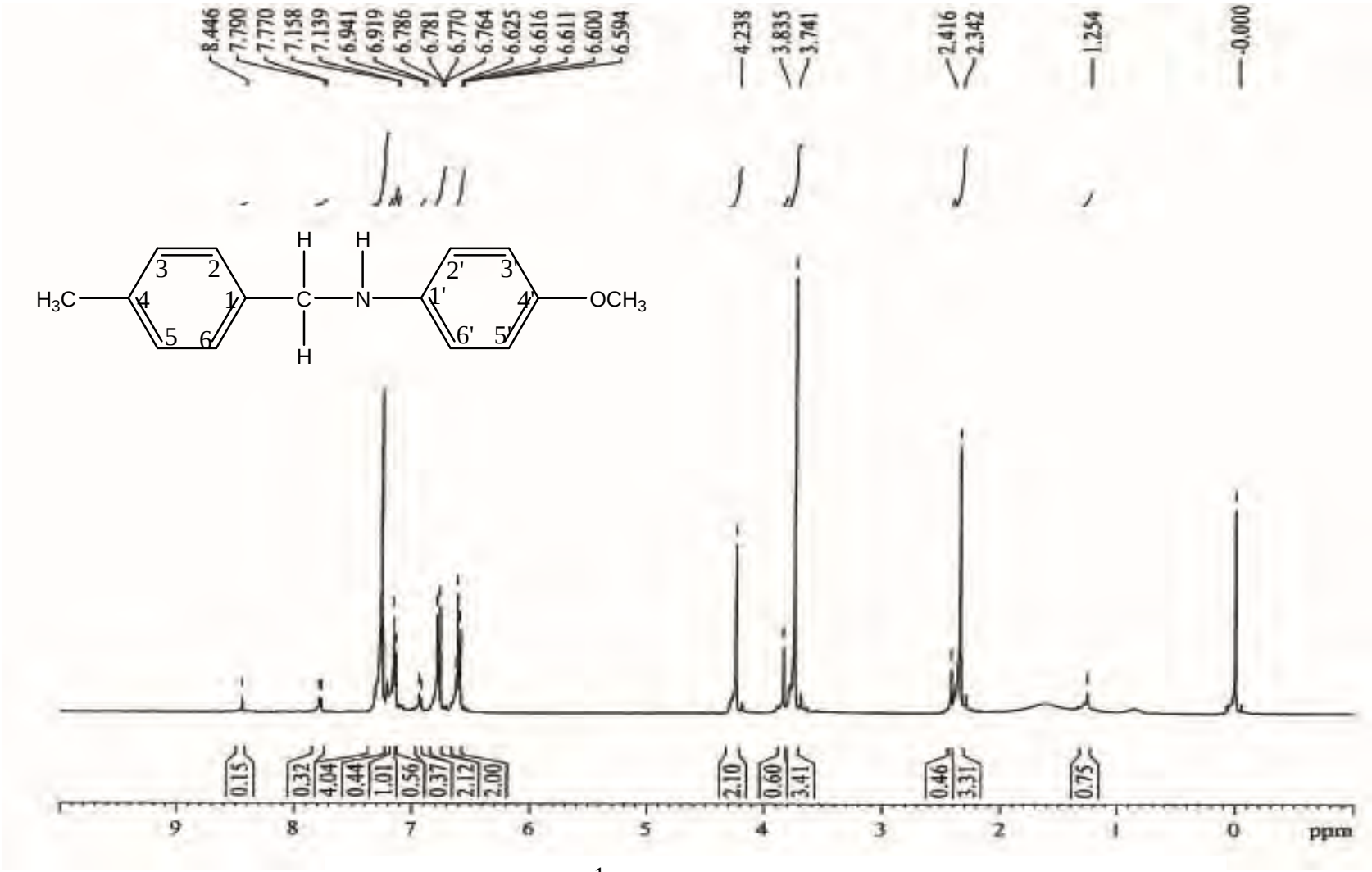


Fig 9C: ^{1}H NMR spectra of compound **19.**

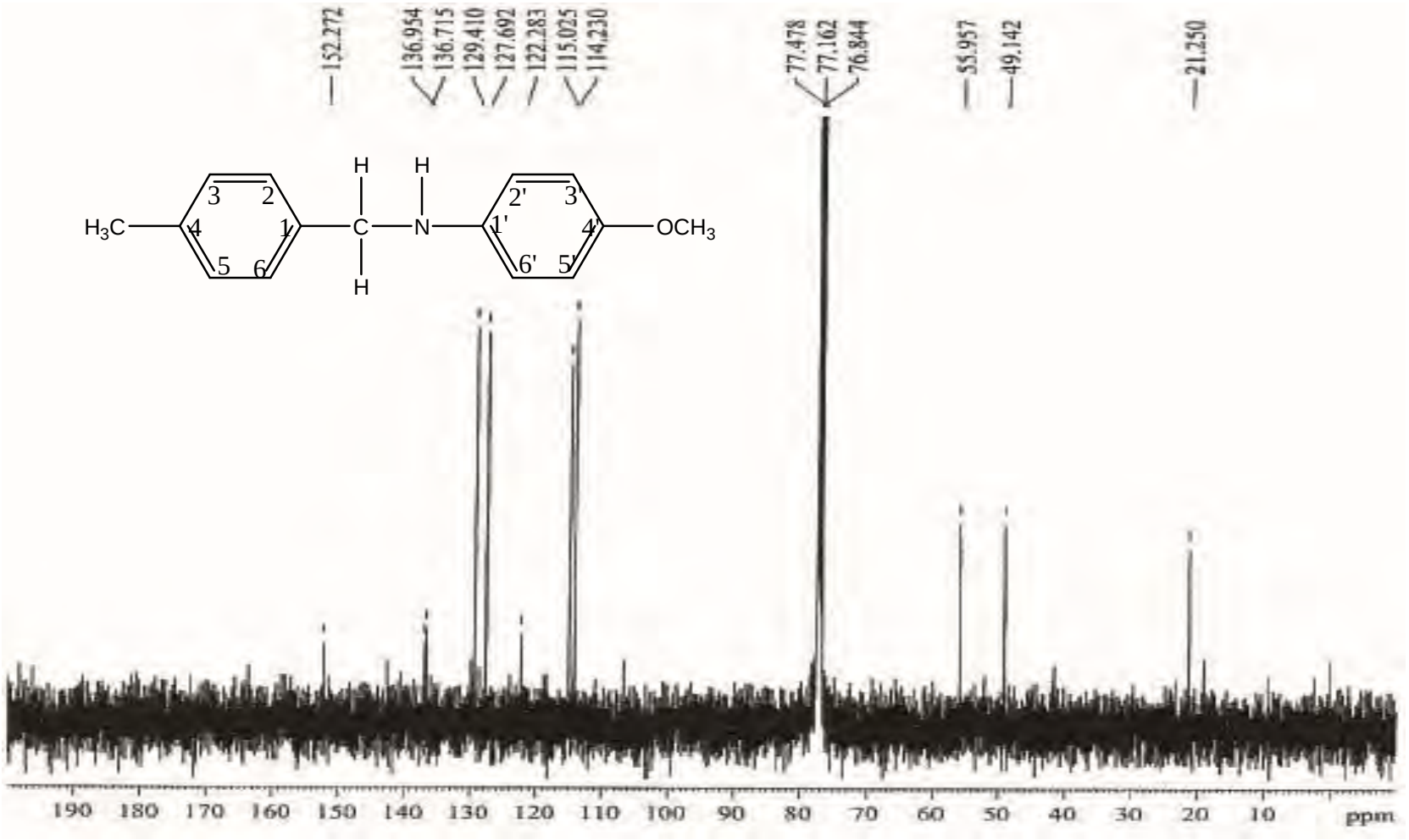


Fig 9D: ^{13}C NMR spectra of compound **19.**

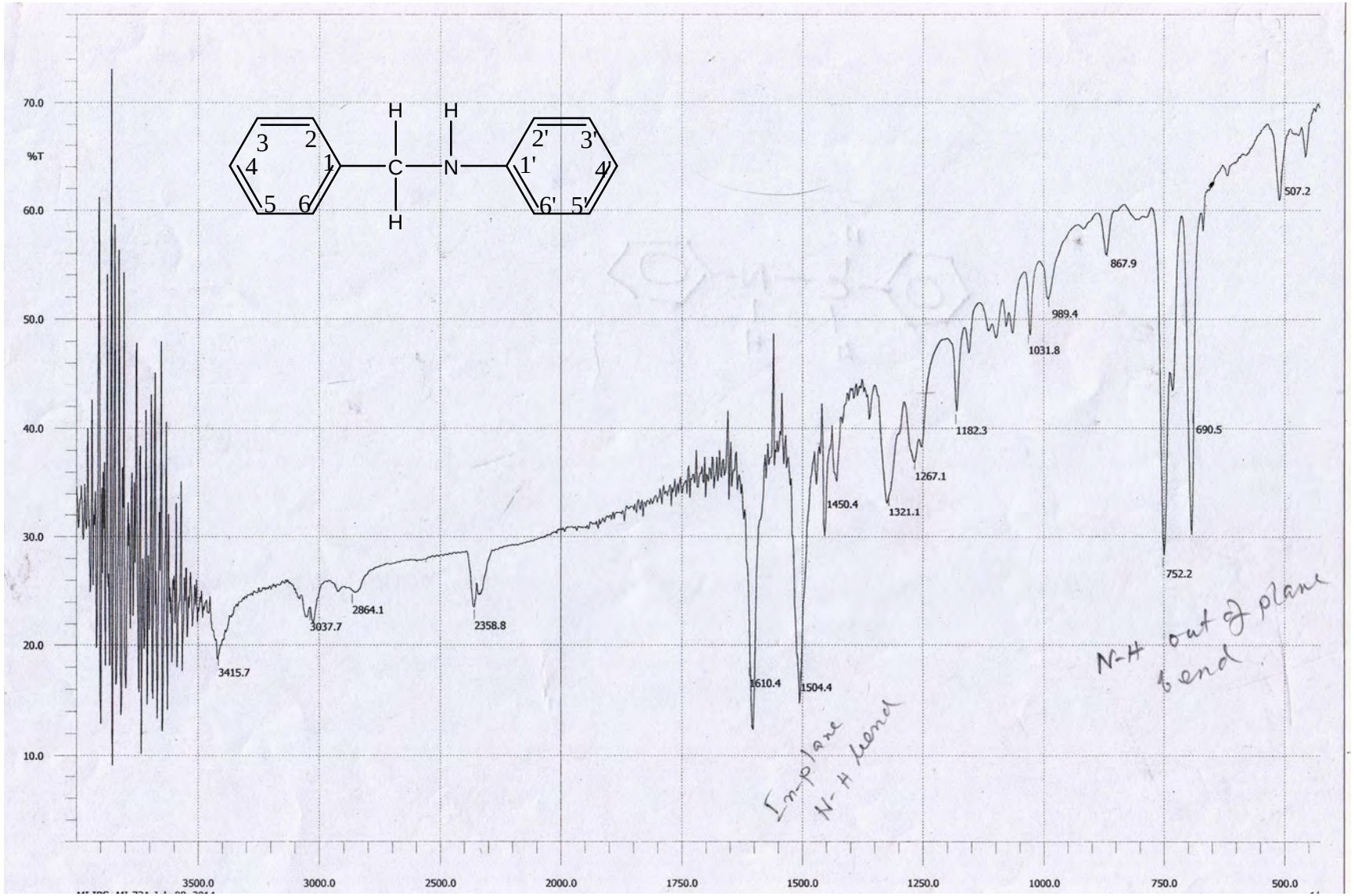
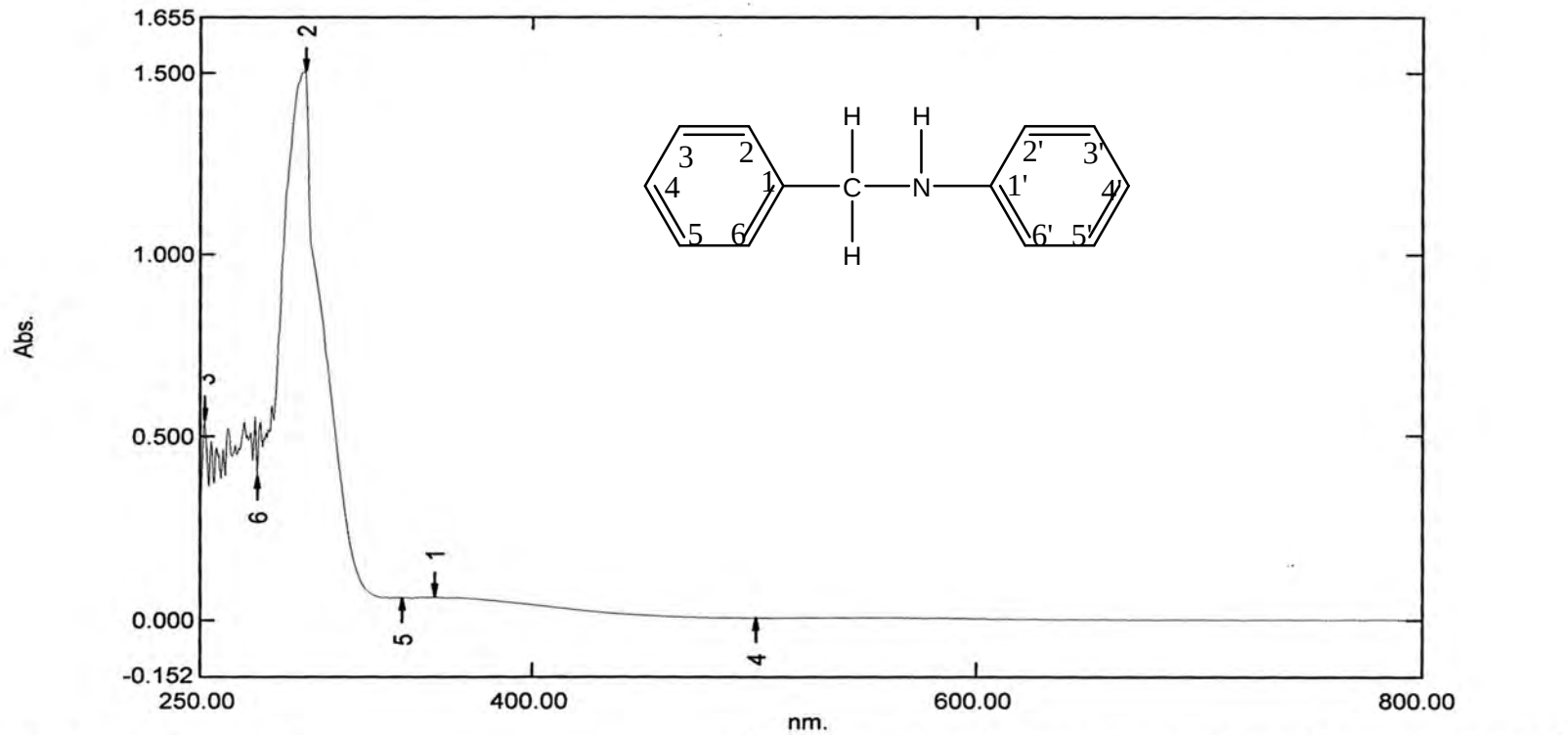


Fig 10A: FT IR spectra of compound **20**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

Weight:

No.	P/V	Wavelength	Abs.	Description
1	↑	356.00	0.060	
2	↑	297.50	1.504	
3	↑	252.00	0.543	
4	↓	500.50	0.004	
5	↓	341.00	0.057	
6	↓	276.00	0.387	

Fig 10B: UV spectra of compound **20**.

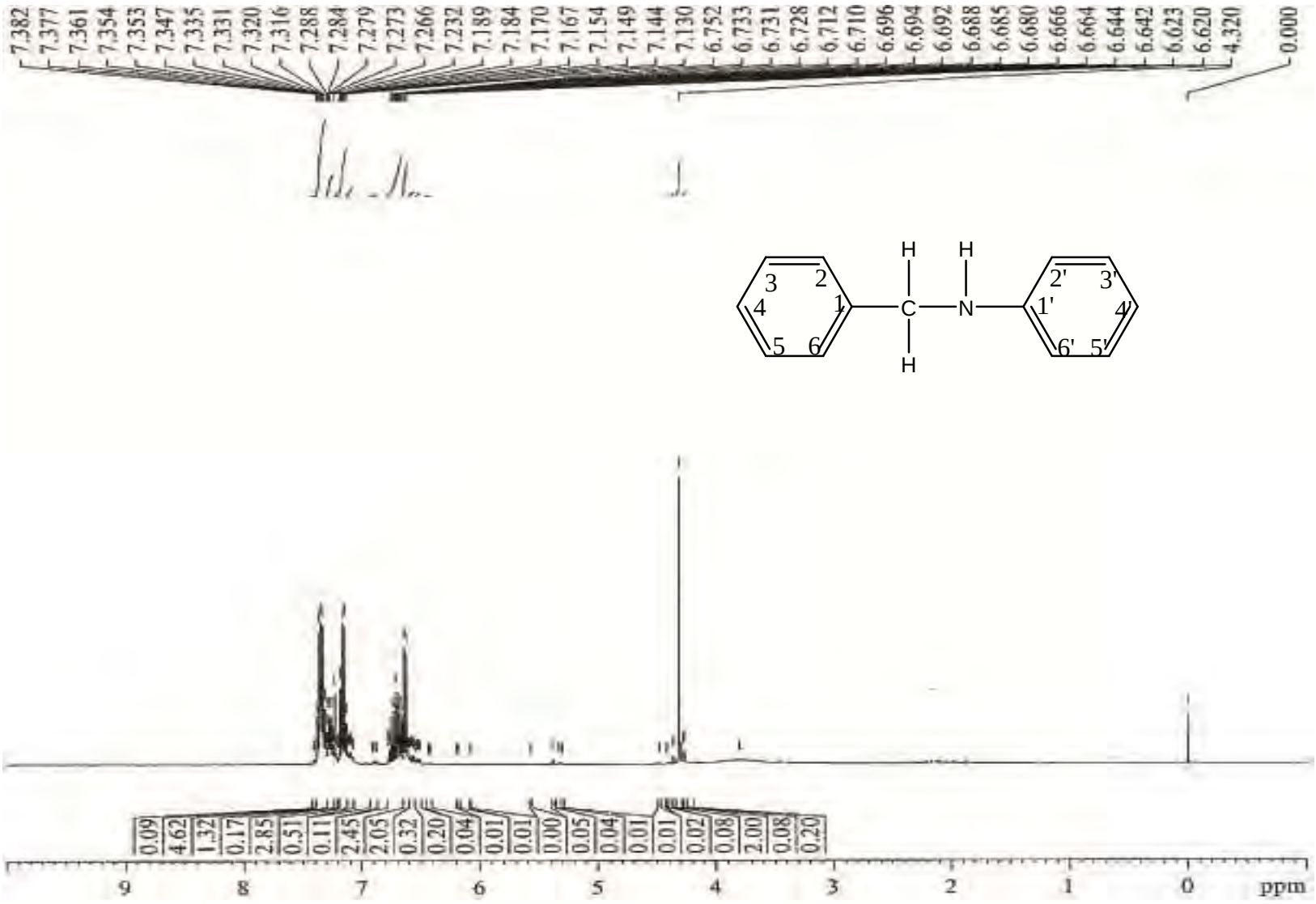


Fig 10C: ^{1}H NMR spectra of compound **20**.

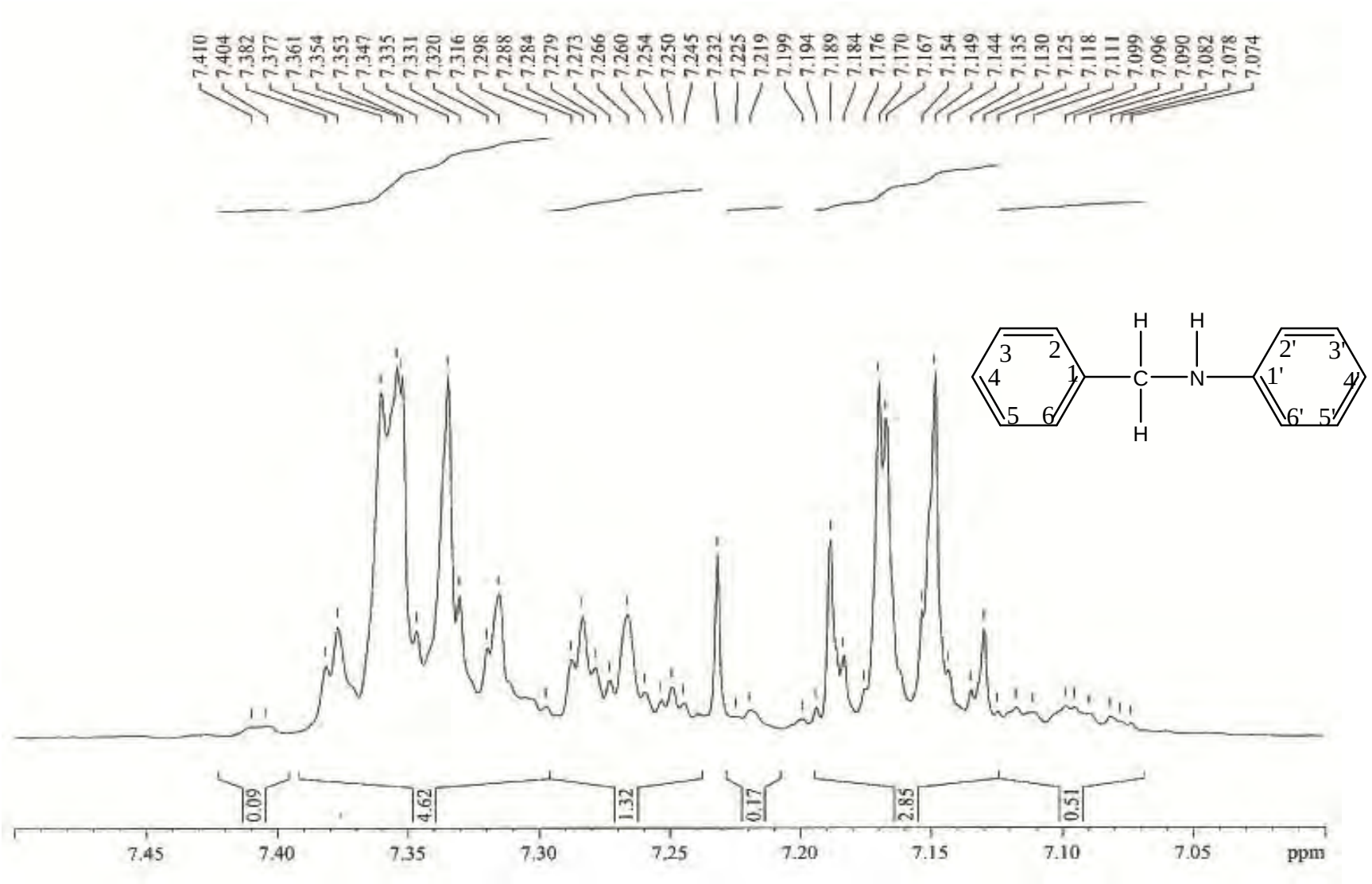


Fig 10D: ^{1}H NMR spectra of compound **20** (Expanded).

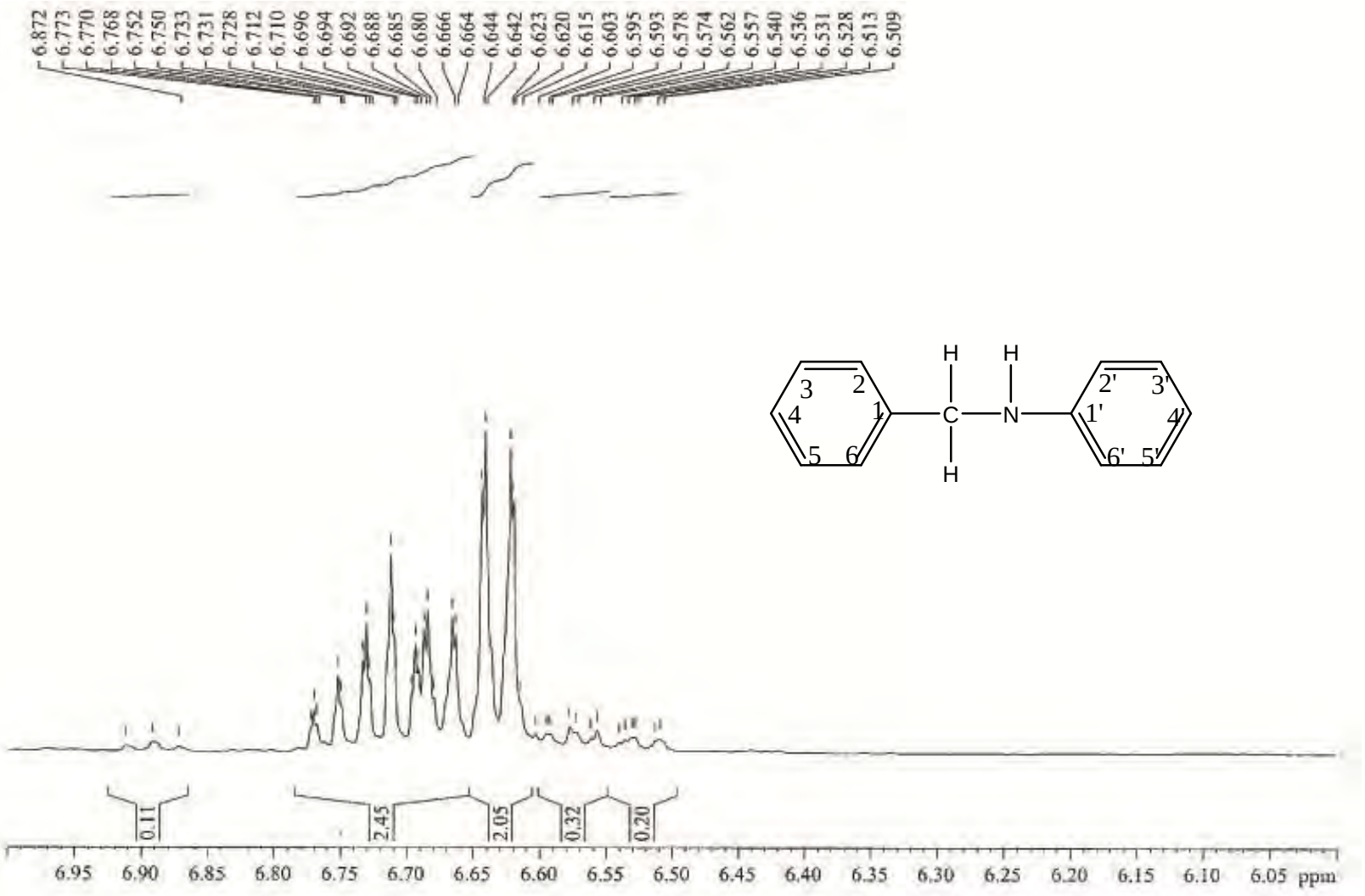


Fig 10E: ^{1}H NMR spectra of compound **20** (Expanded).

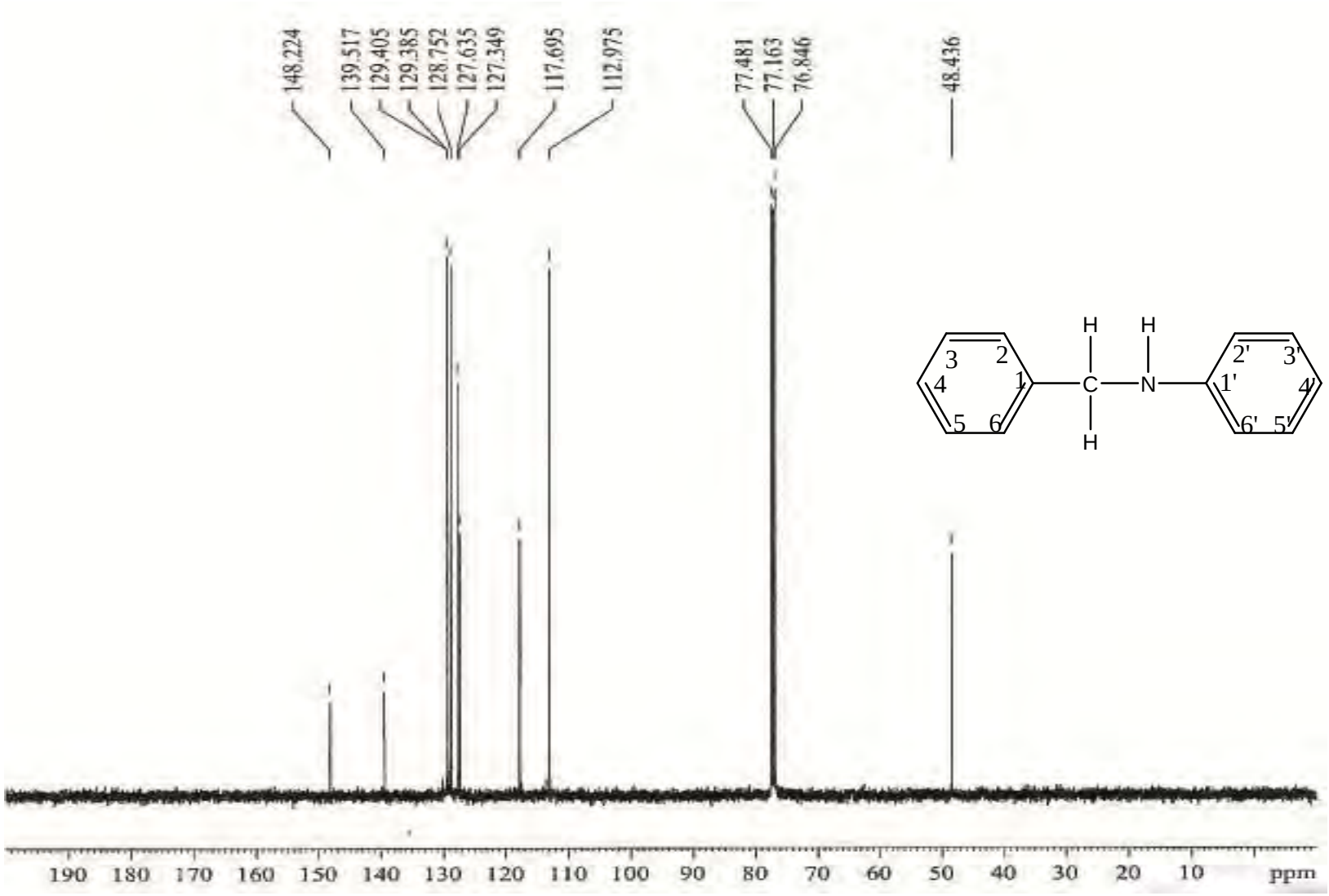


Fig 10F: ^{13}C NMR spectra of compound **20**.

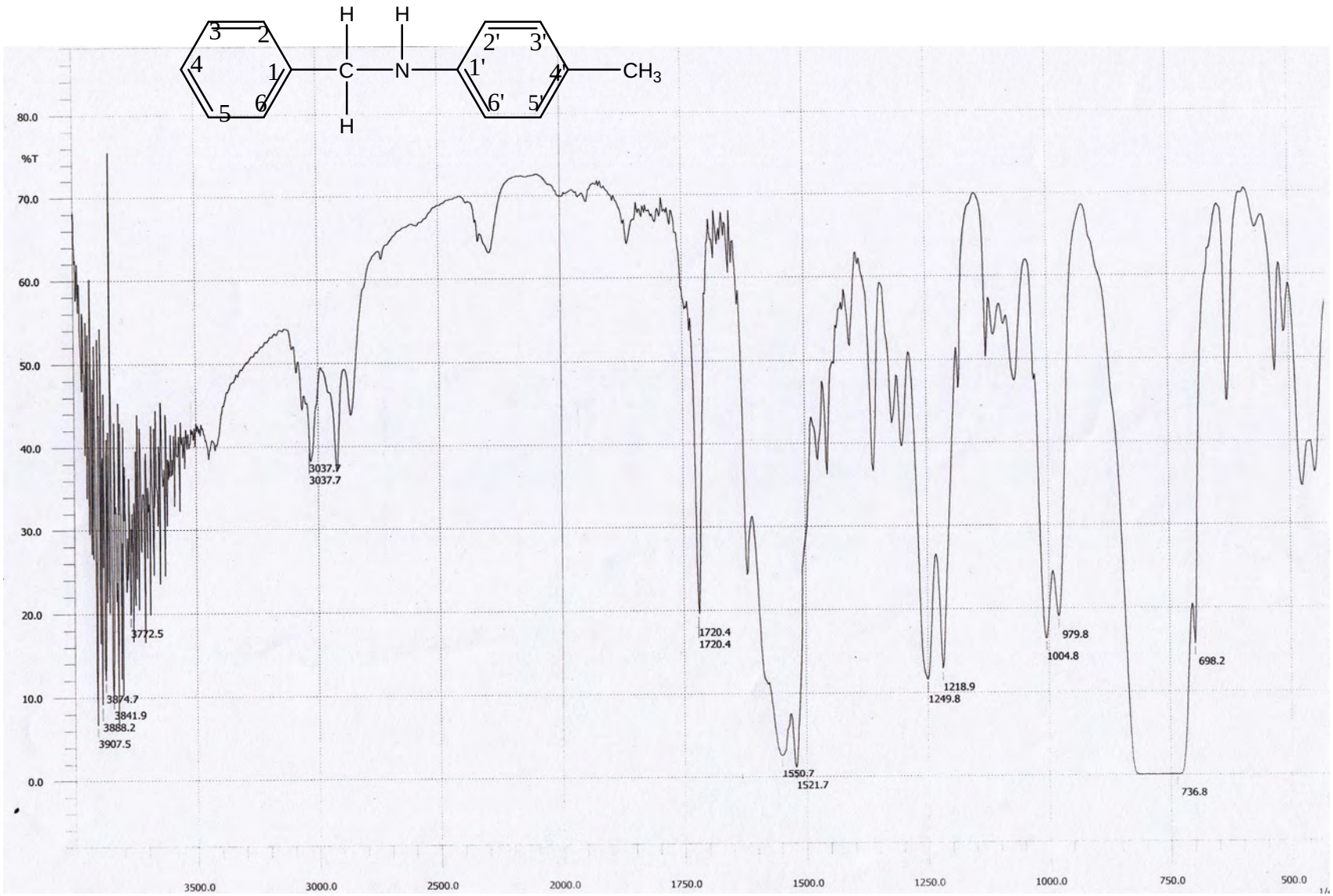
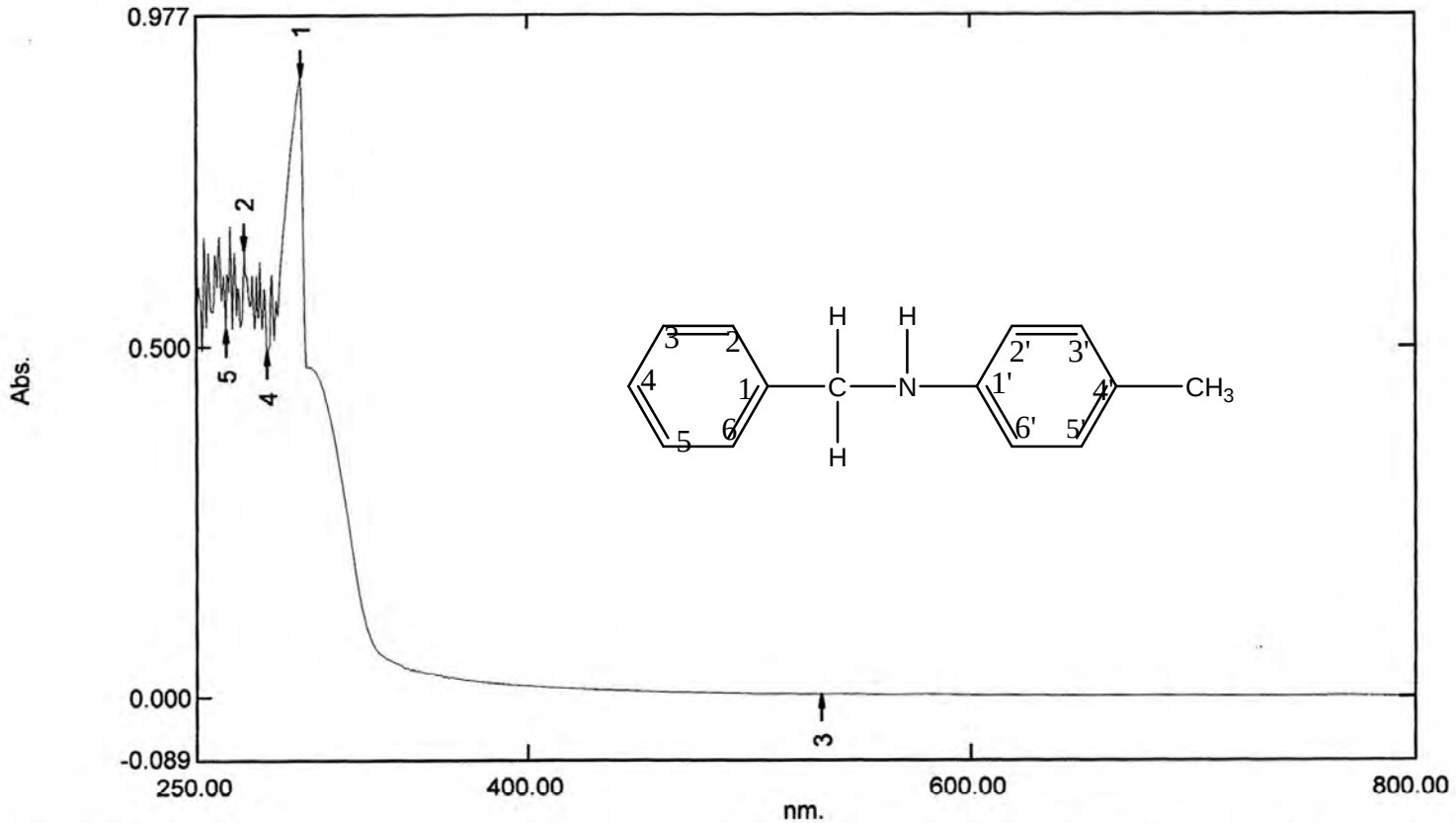


Fig 11A: FT IR spectra of compound **21**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

No.	P/V	Wavelength	Abs.	Description
1	▲	297.50	0.888	
2	▲	272.00	0.640	
3	▼	532.50	0.003	
4	▼	282.00	0.493	
5	▼	263.50	0.527	

Fig 11B: UV spectra of compound **21**.

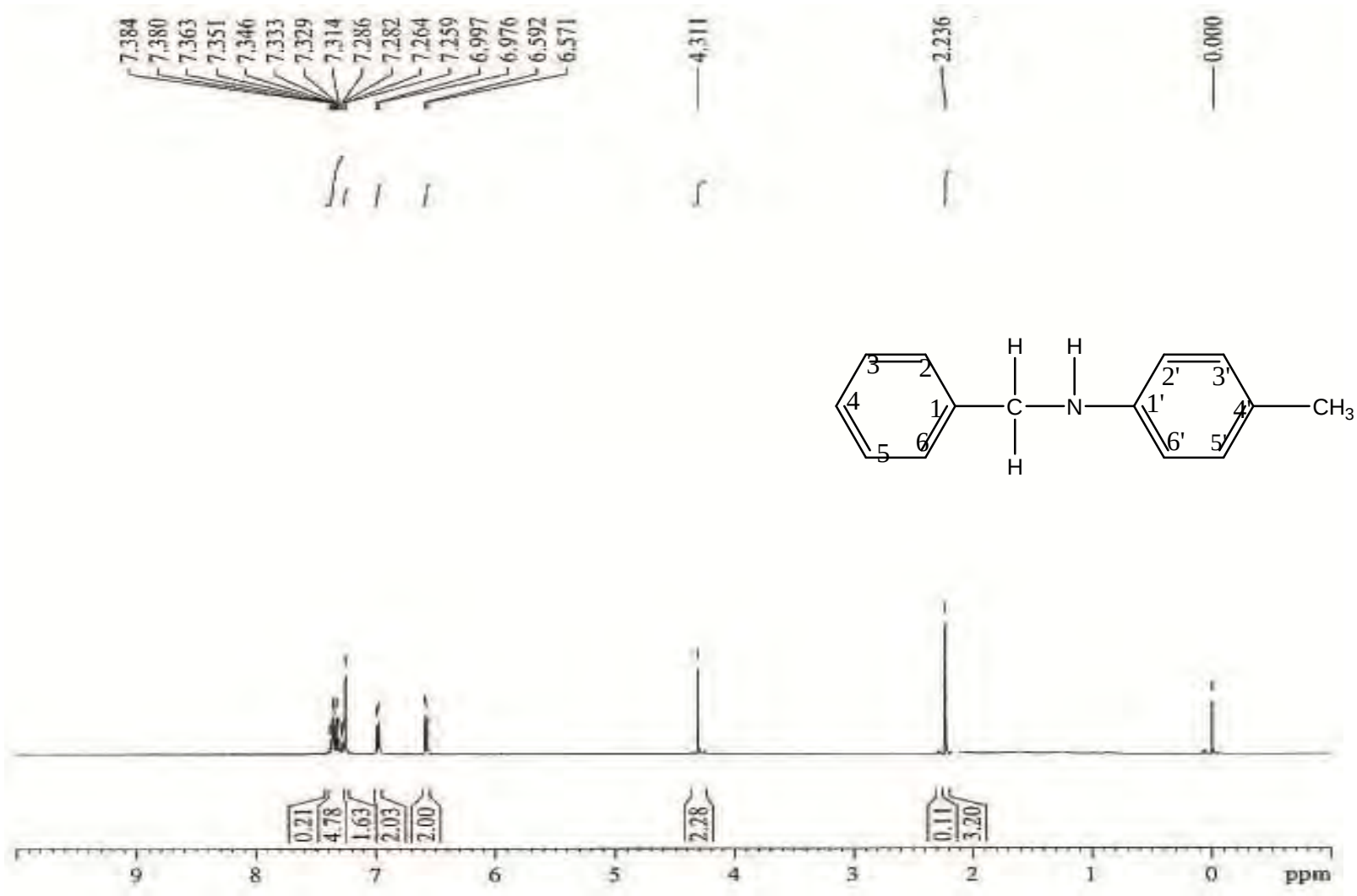


Fig 11C: ^{1}H NMR spectra of compound **21**.

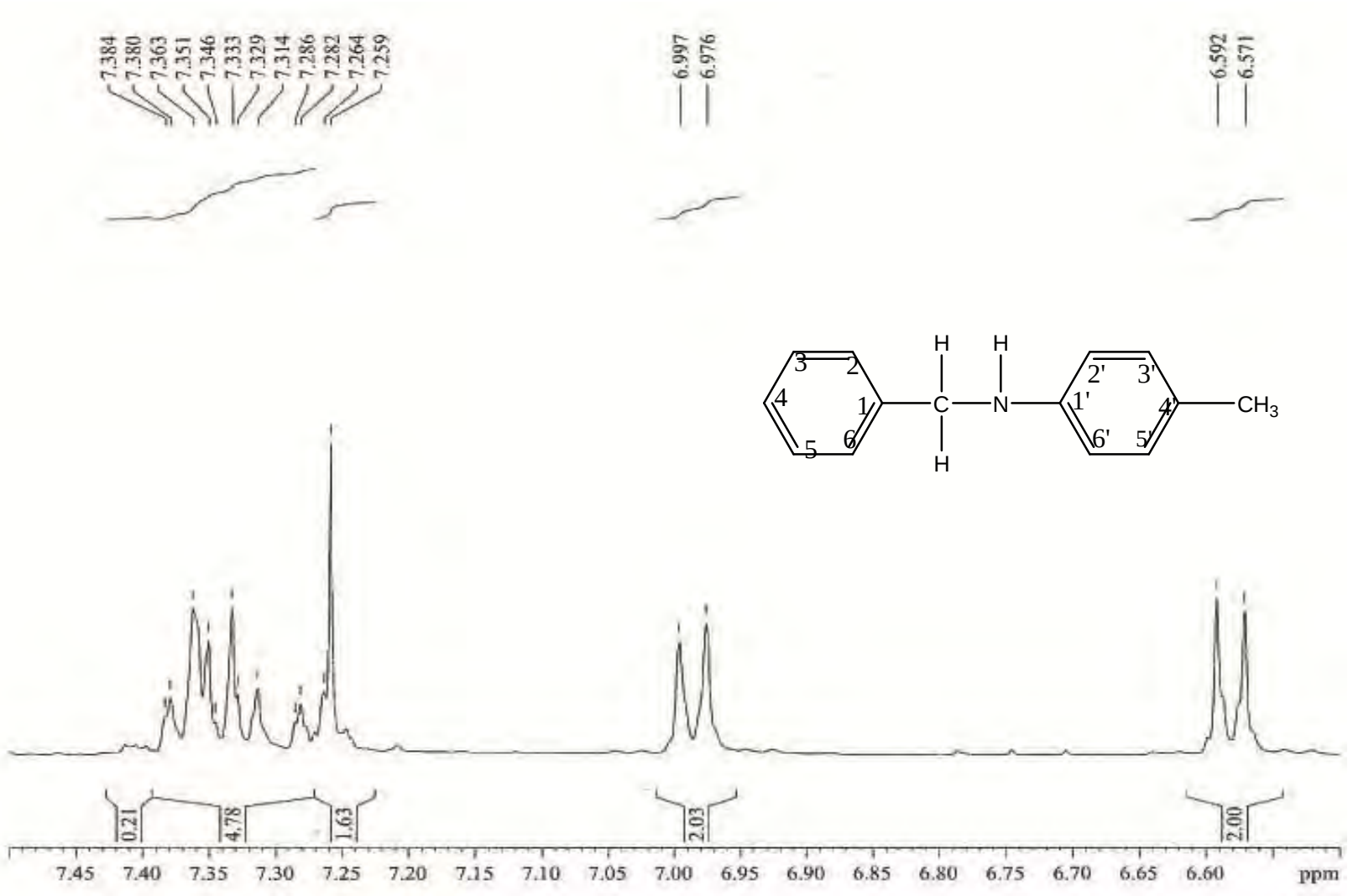


Fig 11D: ^{1}H NMR spectra of compound **21** (Expanded).

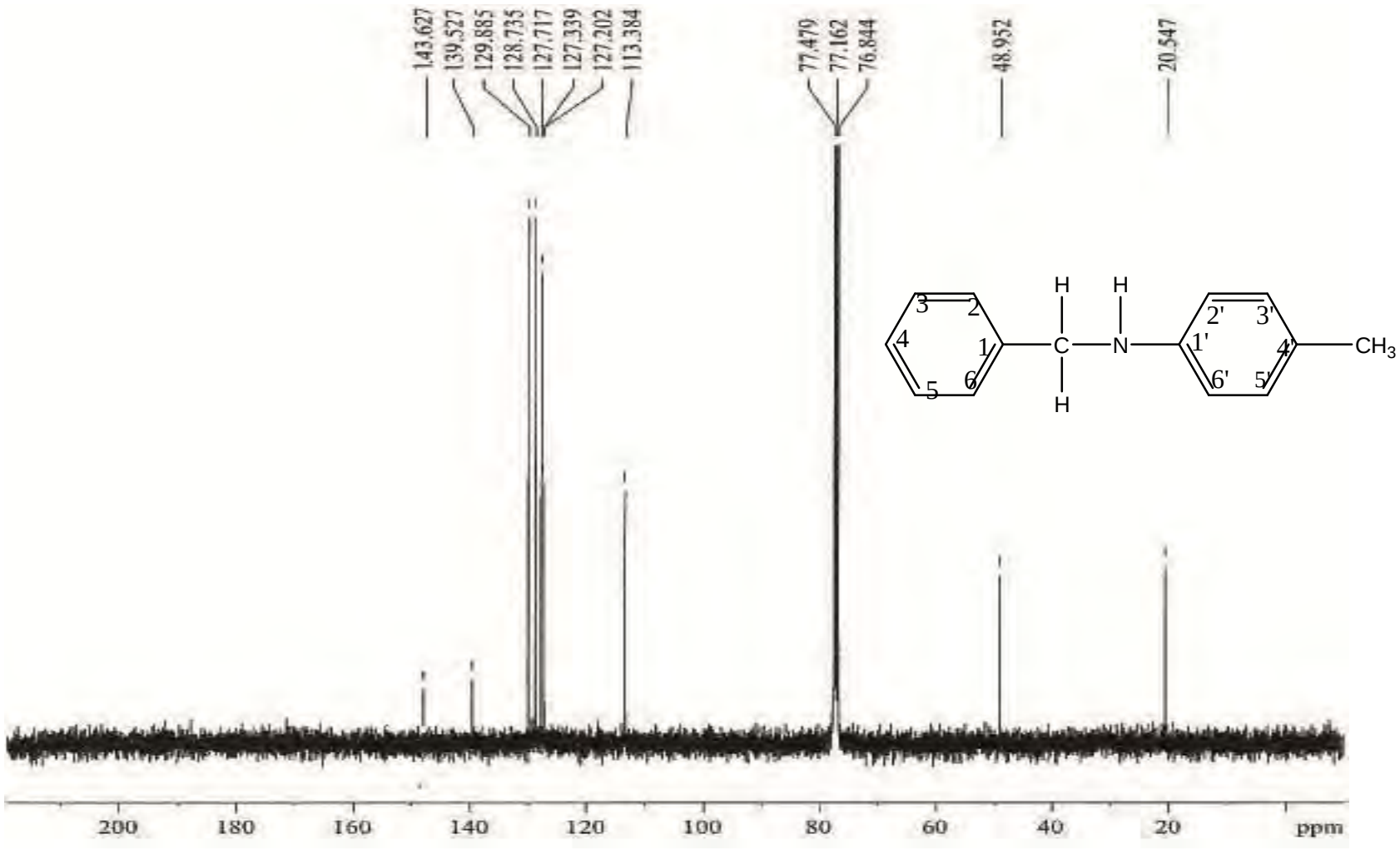


Fig 11E: ^{13}C NMR spectra of compound **21**.

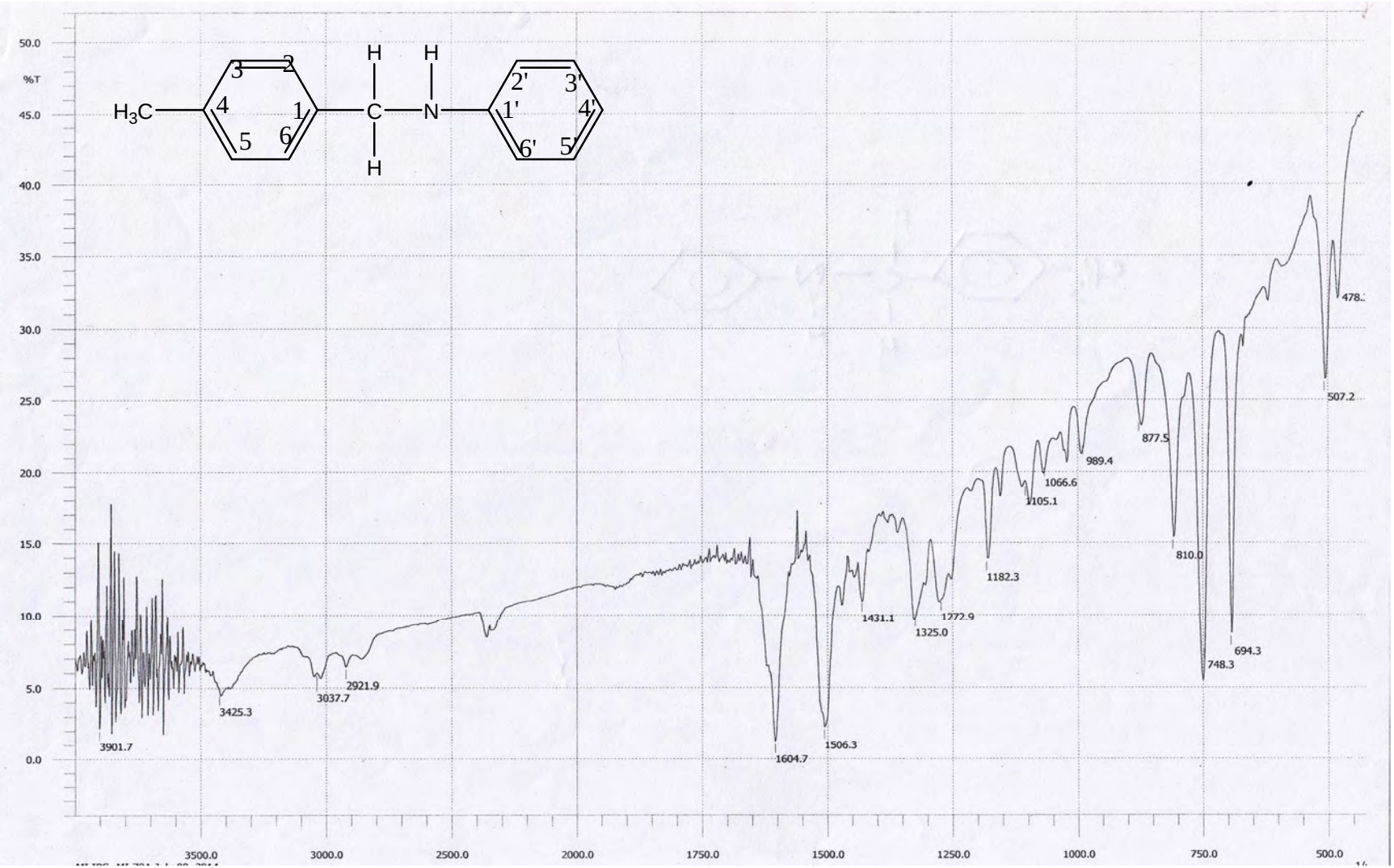
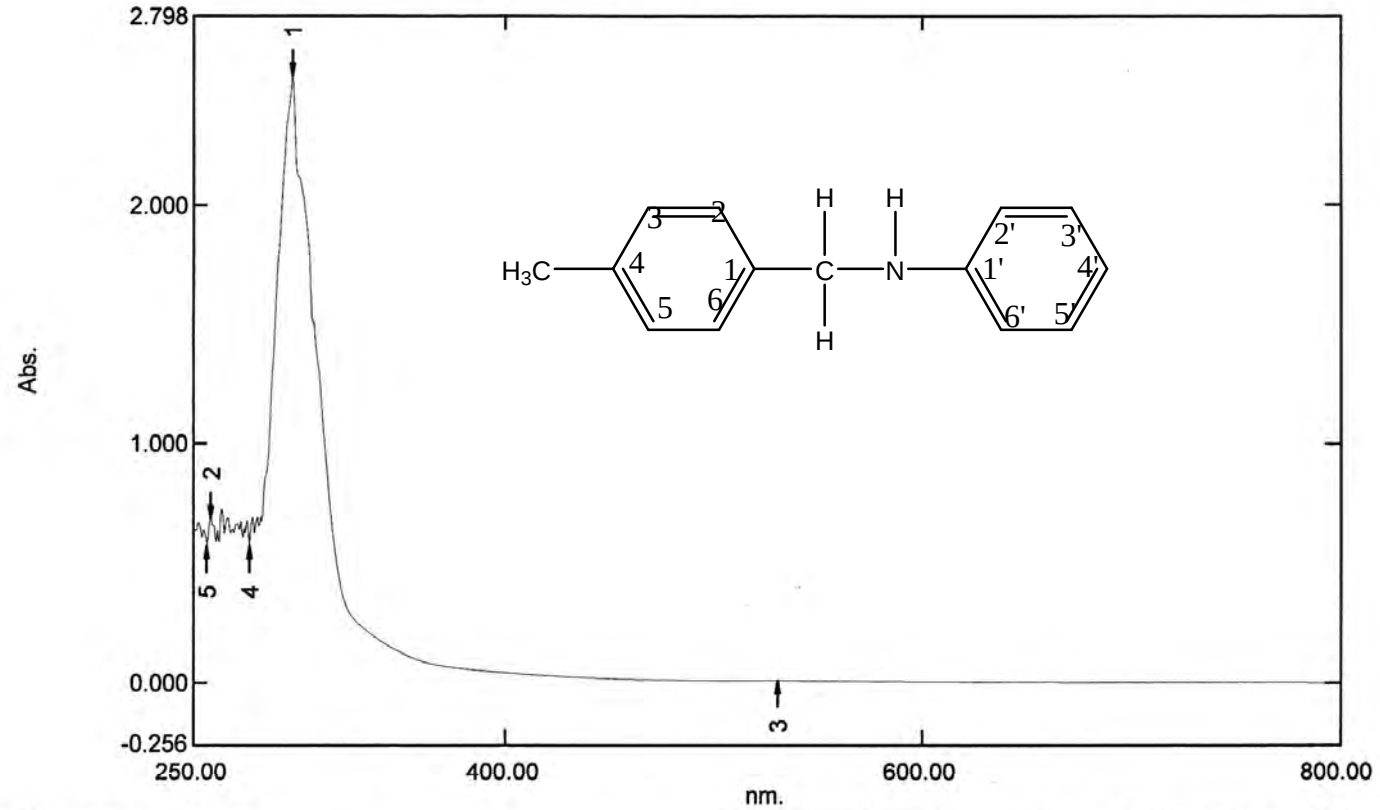


Fig 12A: FT IR spectra of compound **22**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

No.	P/V	Wavelength	Abs.	Description
1	▲	297.50	2.543	
2	▲	258.50	0.687	
3	▼	530.50	0.007	
4	▼	277.00	0.569	
5	▼	256.50	0.570	

Fig 12B: UV spectra of compound **22**.

Fig 12C: ^{1}H NMR spectra of compound **22**.

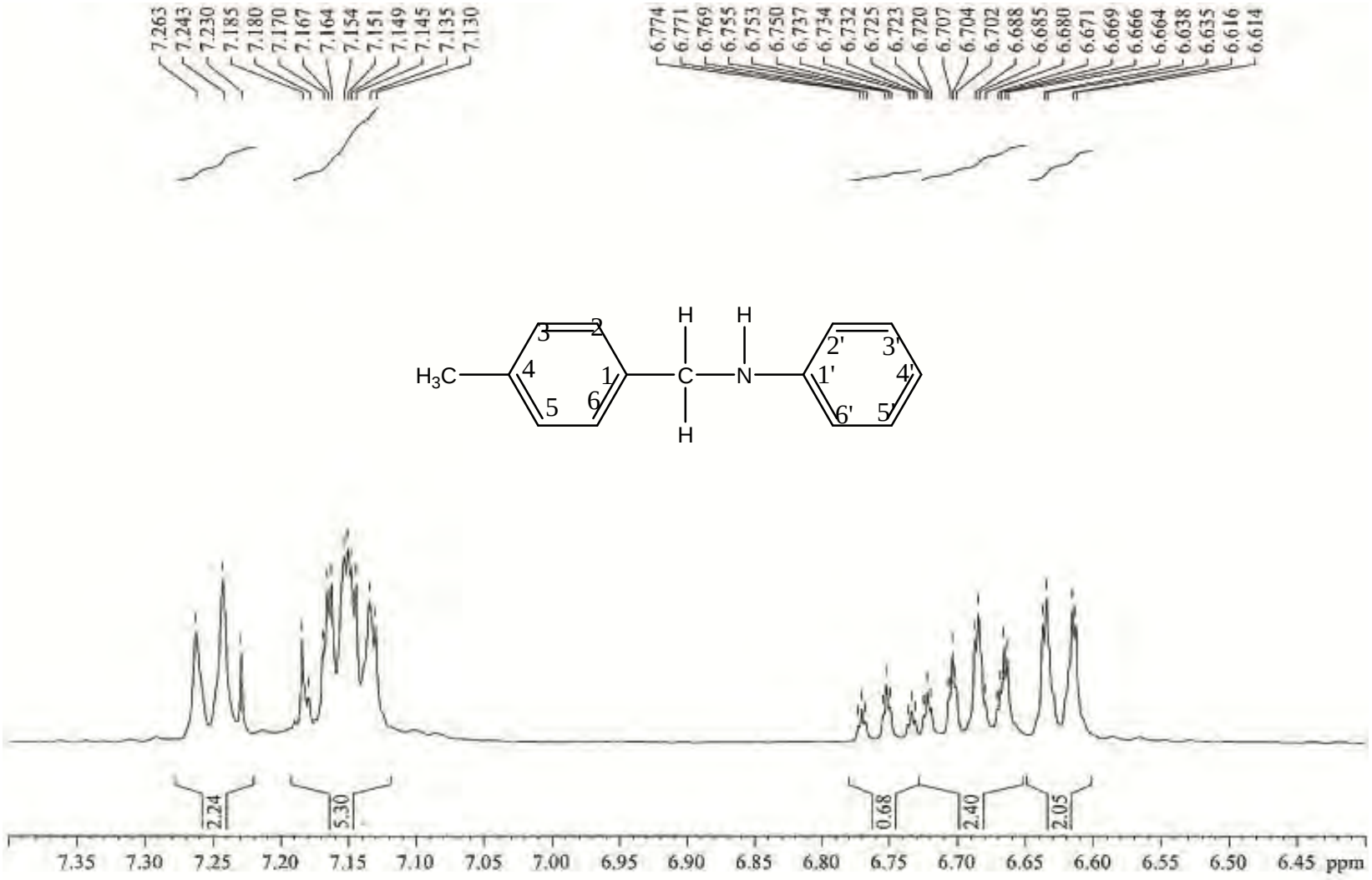


Fig 12D: ^{1}H NMR spectra of compound **22** (Expanded).

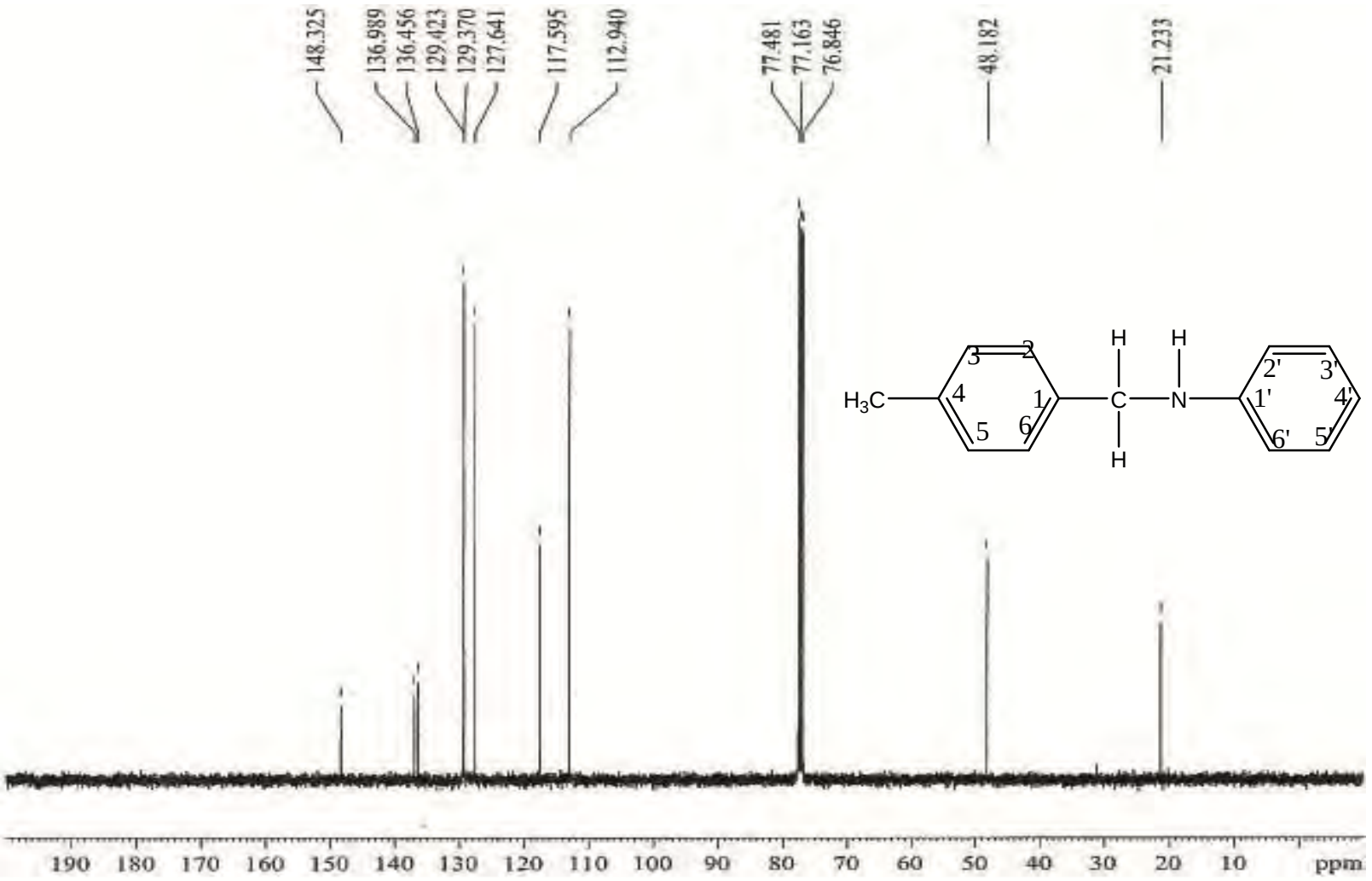


Fig 12E: ^{13}C NMR spectra of compound **22**.

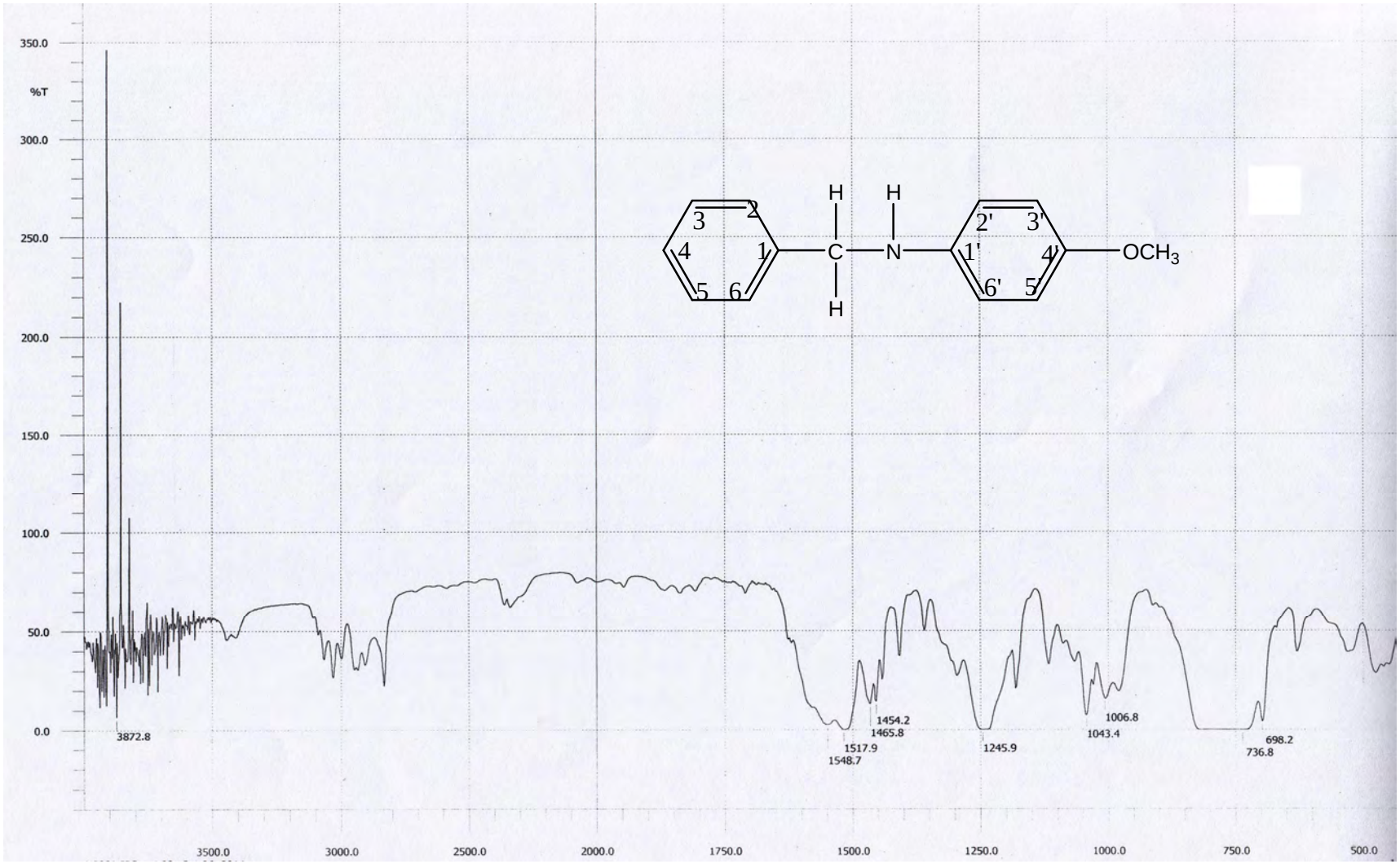
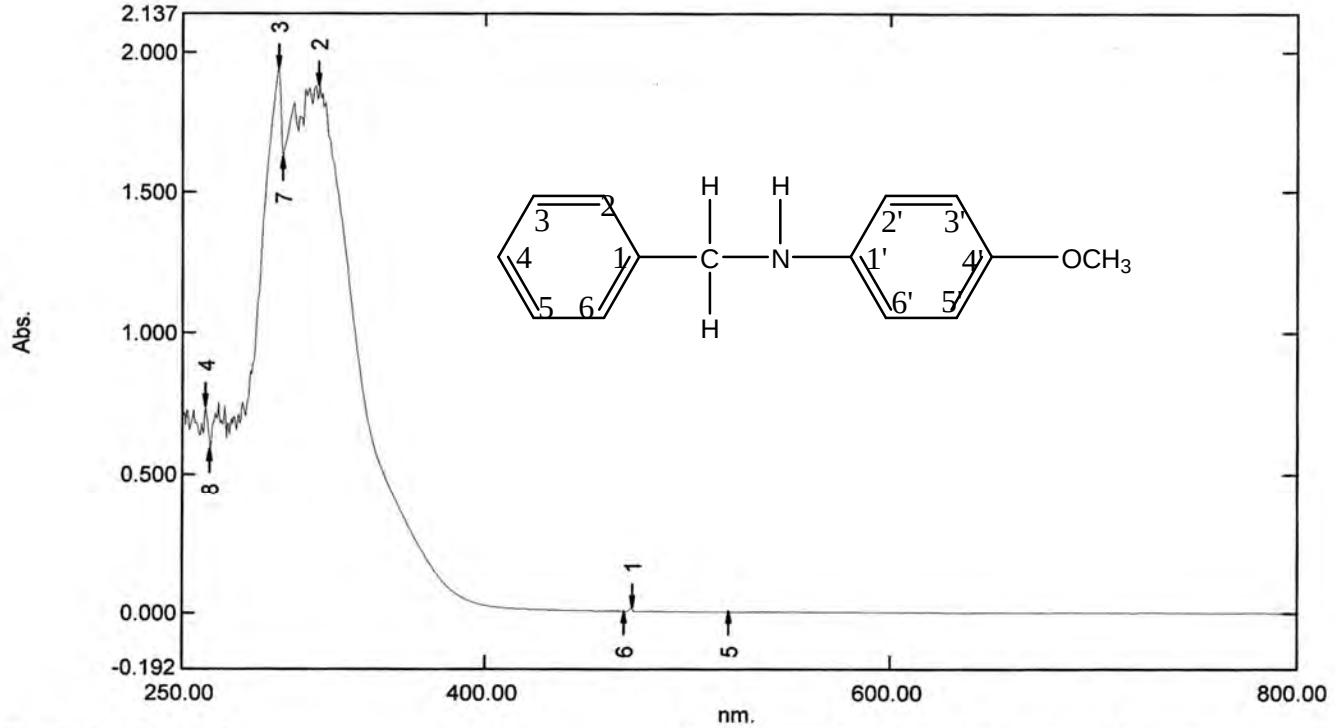


Fig 13A: FT IR spectra of compound **23**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

Weight:	
Volume:	
Dilution:	

No.	P/V	Wavelength	Abs.	Description
1	↑	472.00	0.022	
2	↑	318.00	1.882	
3	↑	297.50	1.943	
4	↑	261.50	0.737	
5	↓	520.00	0.007	
6	↓	468.50	0.009	
7	↓	300.00	1.630	
8	↓	264.00	0.585	

Fig 13B: UV spectra of compound **23**.

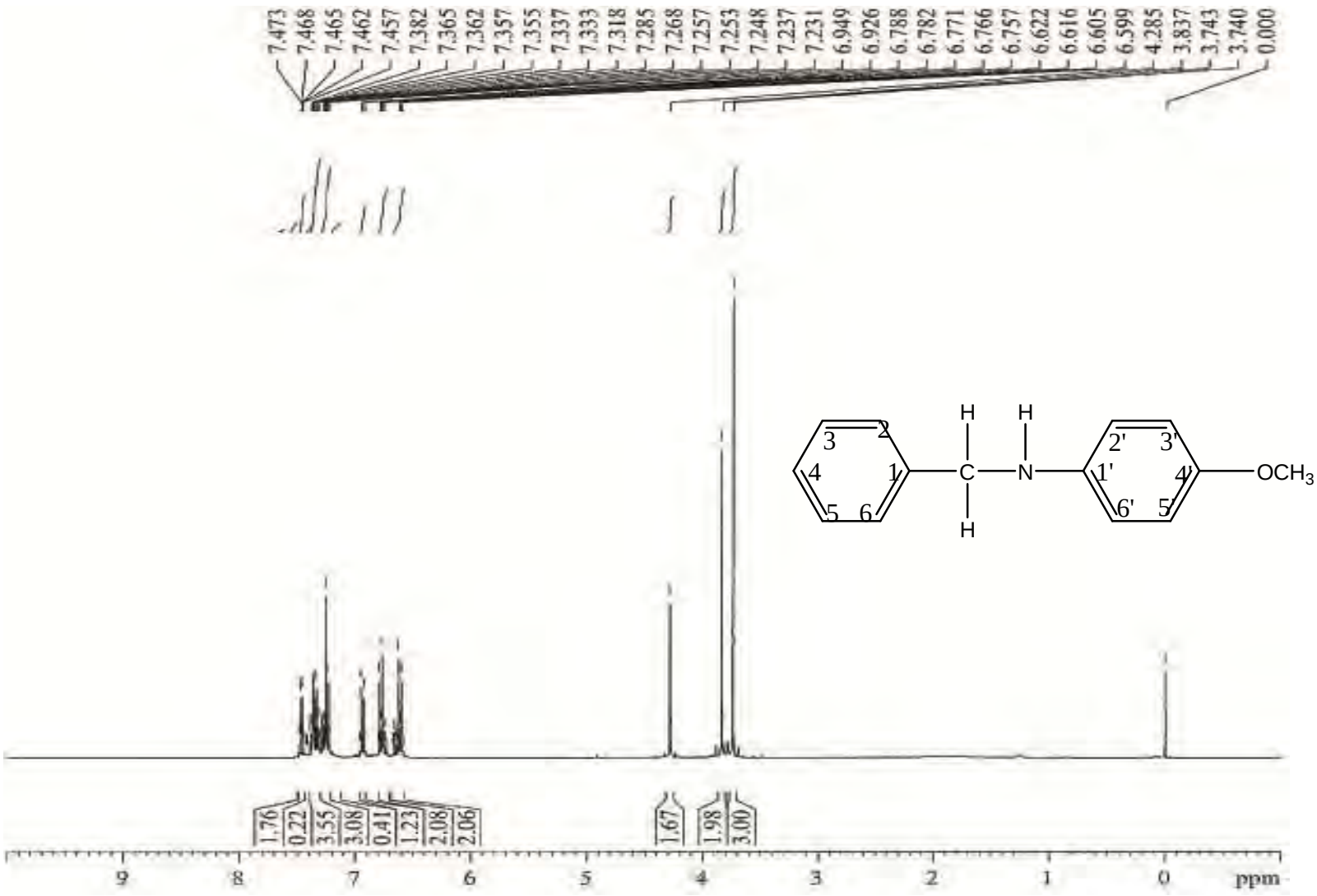


Fig 13C: ^{1}H NMR spectra of compound **23**.

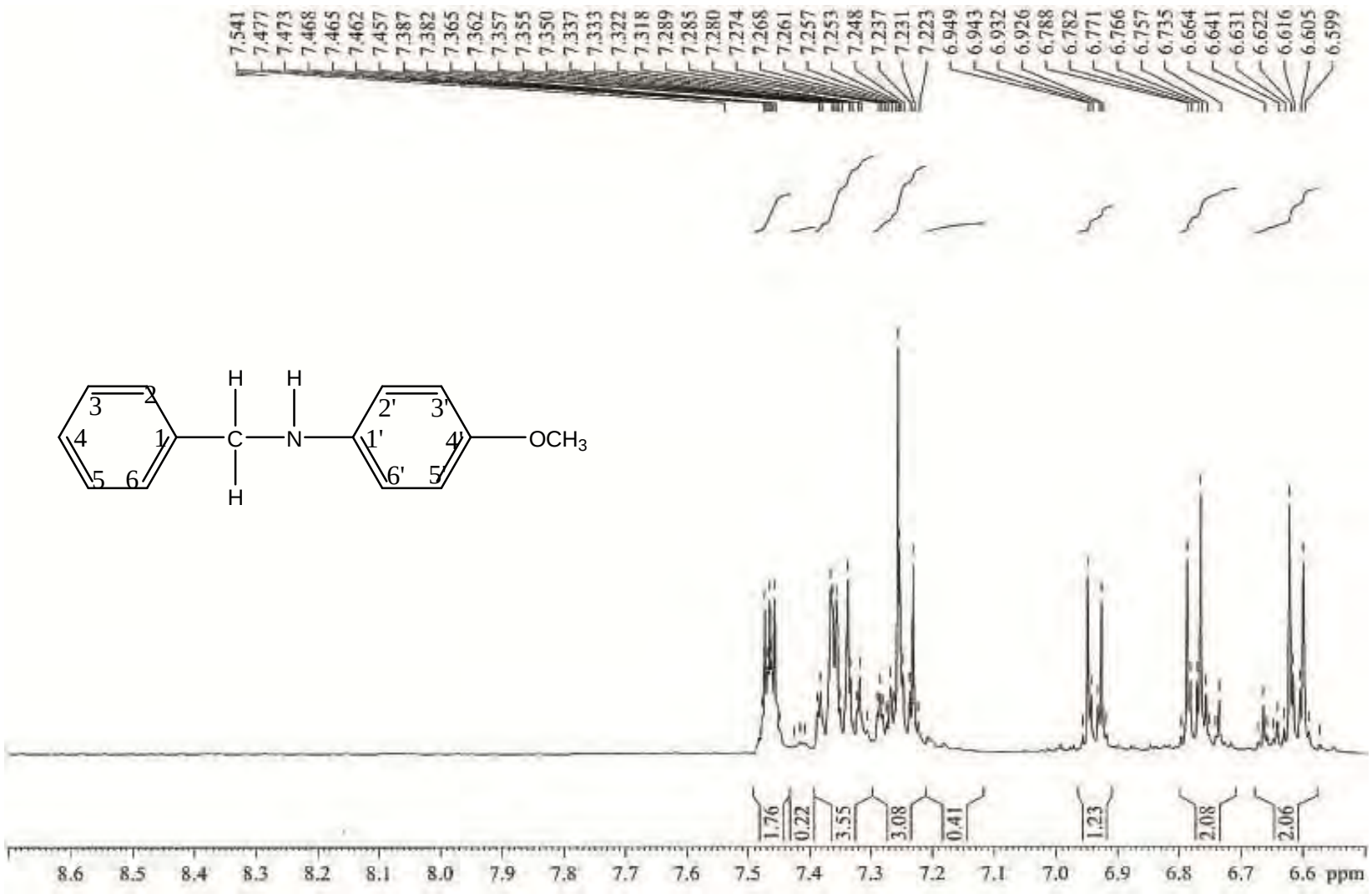


Fig 13D: ^{1}H NMR spectra of compound **23** (Expanded).

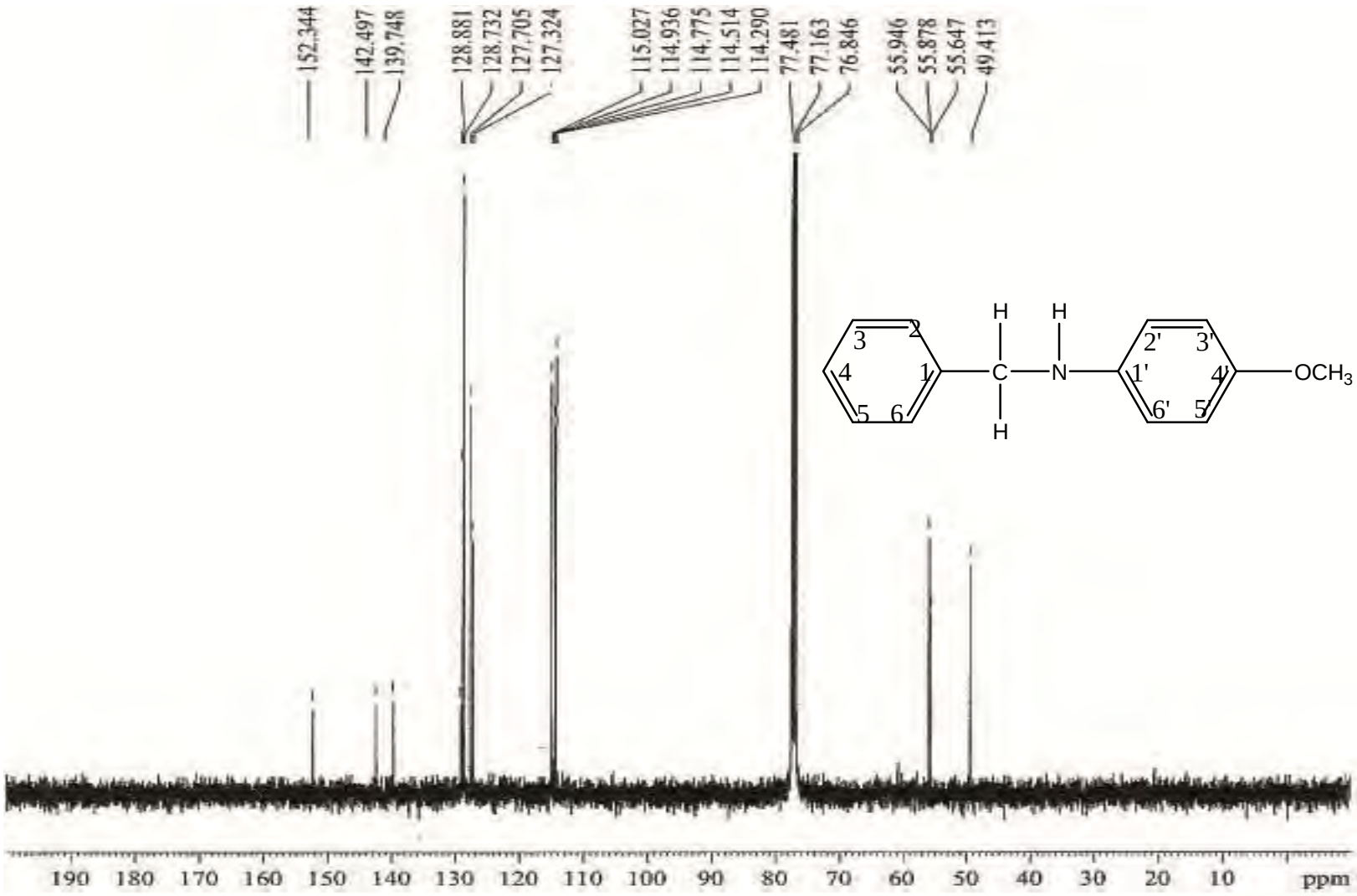


Fig 13E: ^{13}C NMR spectra of compound **23**.

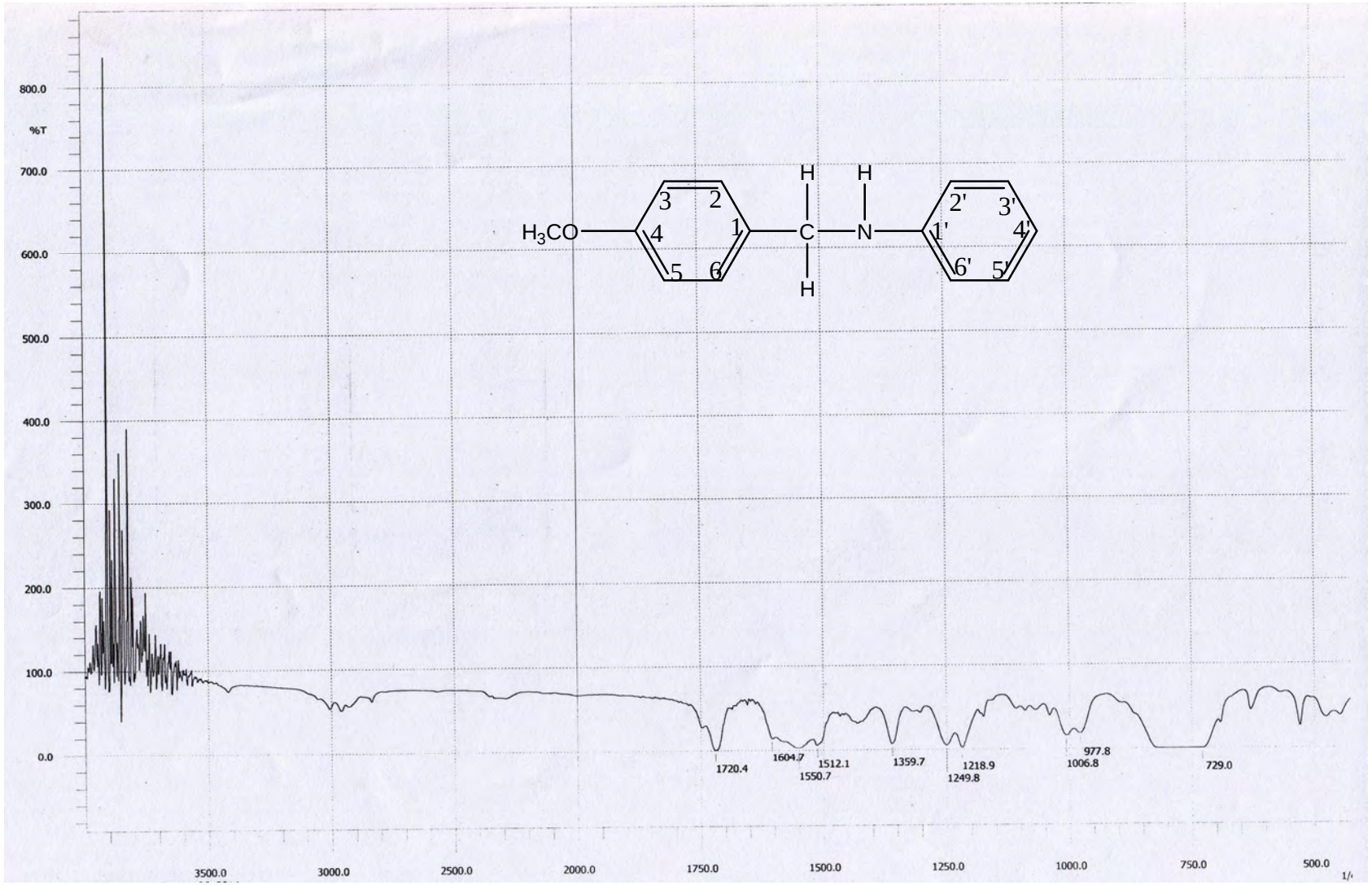
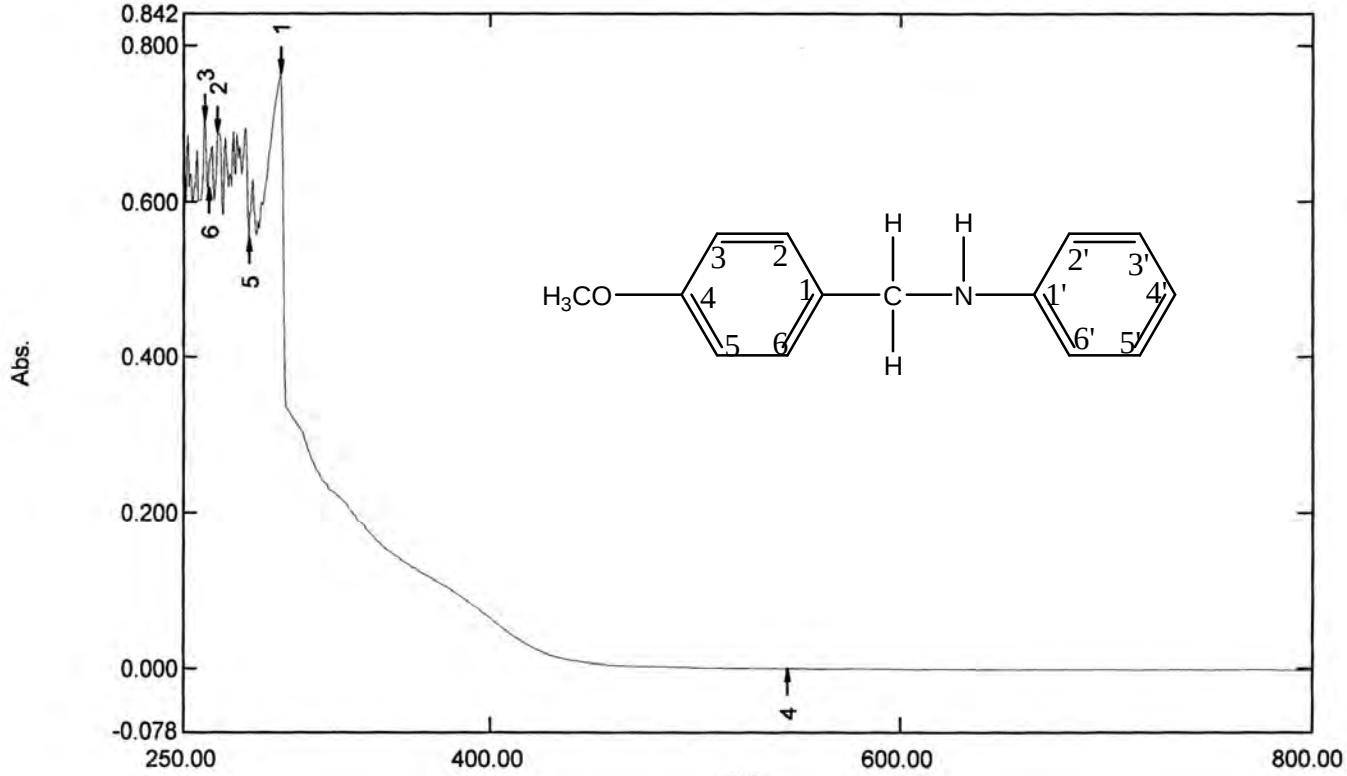


Fig 14A: FT IR spectra of compound **24**.



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

Weight:	
Volume:	

No.	P/V	Wavelength	Abs.	Description
1	↑	297.50	0.766	
2	↑	266.50	0.688	
3	↑	260.00	0.706	
4	↓	545.50	0.002	
5	↓	282.00	0.553	
6	↓	262.00	0.618	

Fig 14B: UV spectra of compound **24**.

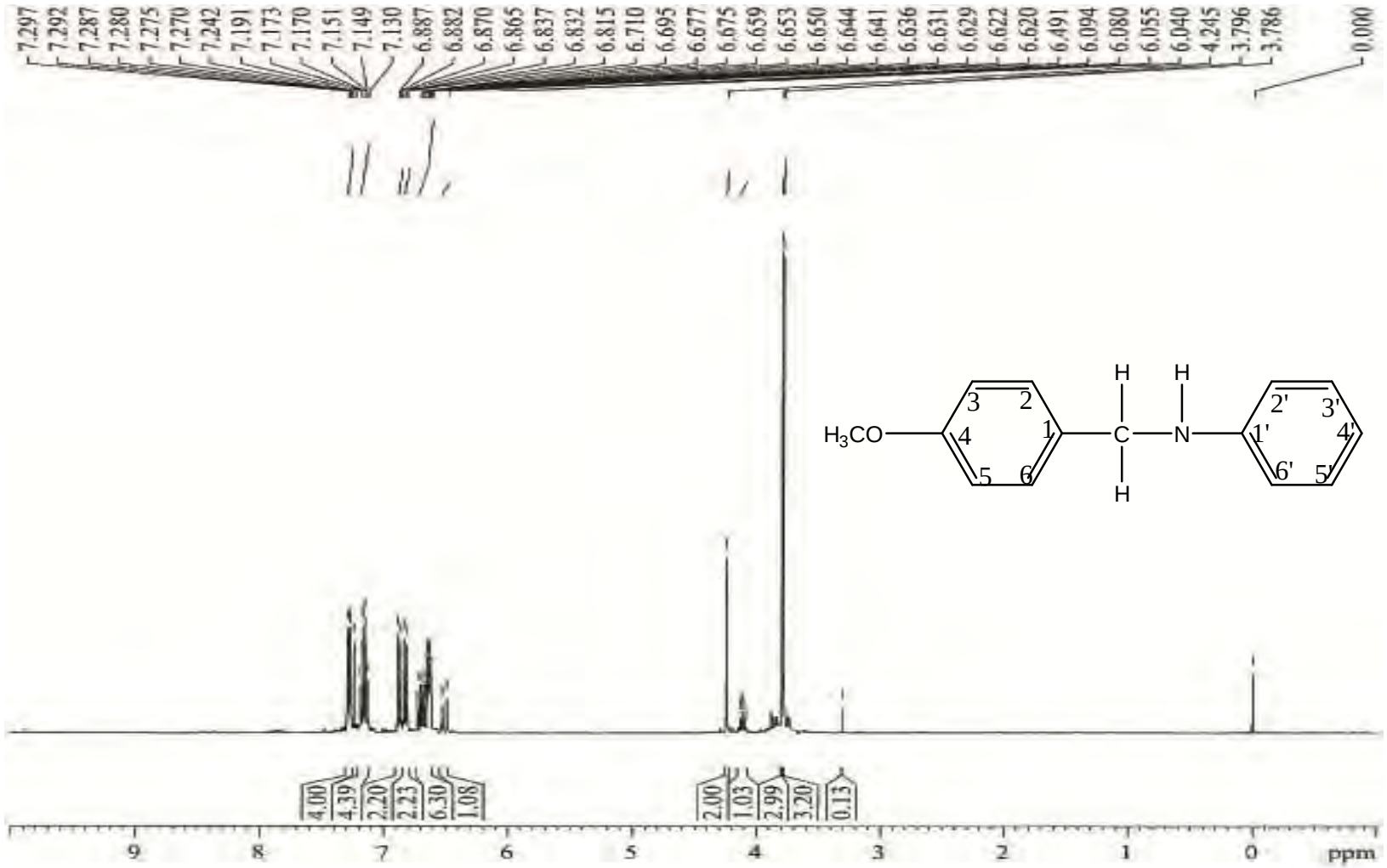


Fig 14C: ^{1}H NMR spectra of compound **24**.

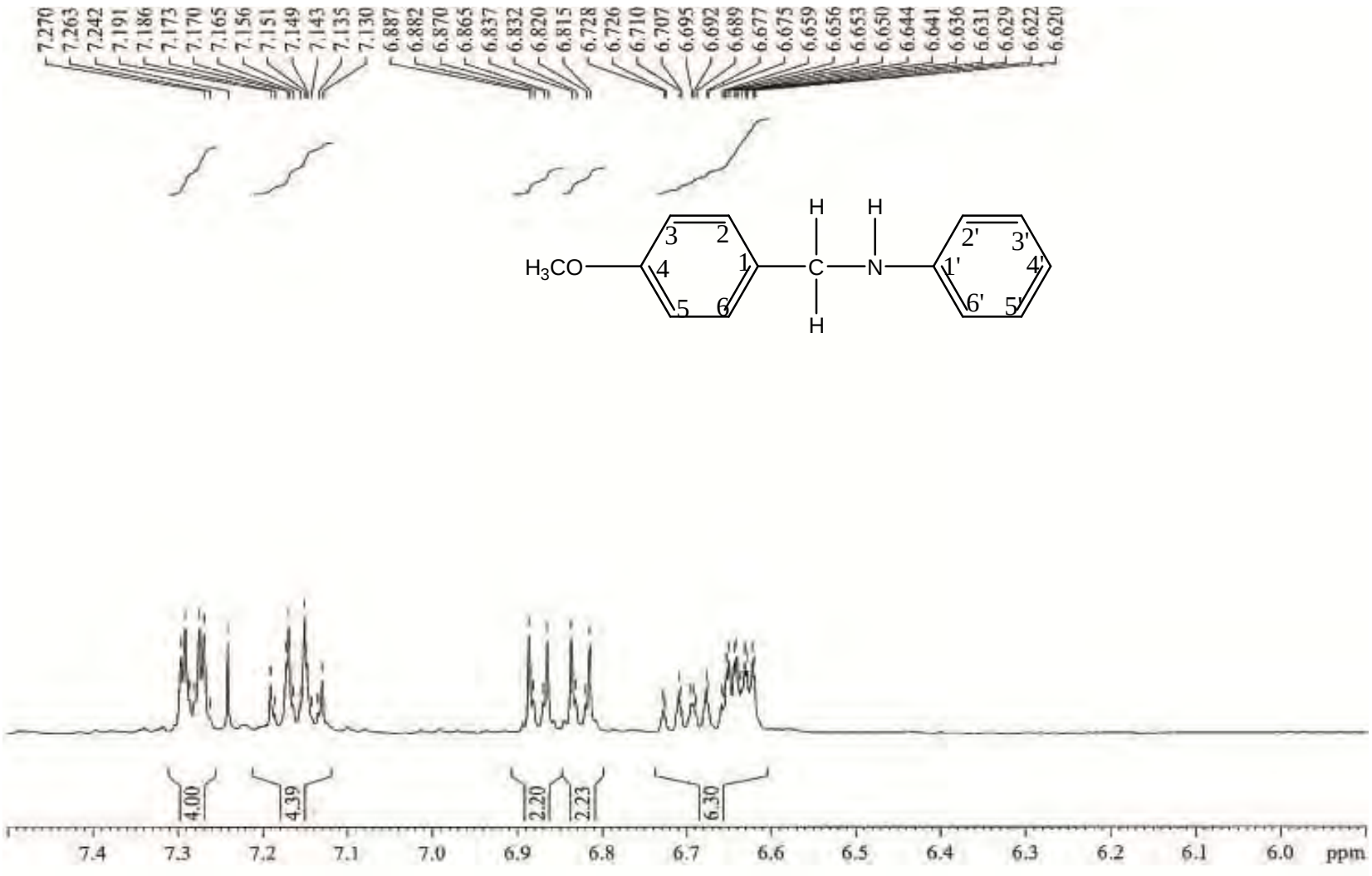


Fig 14D: ^{1}H NMR spectra of compound **24** (Expanded).

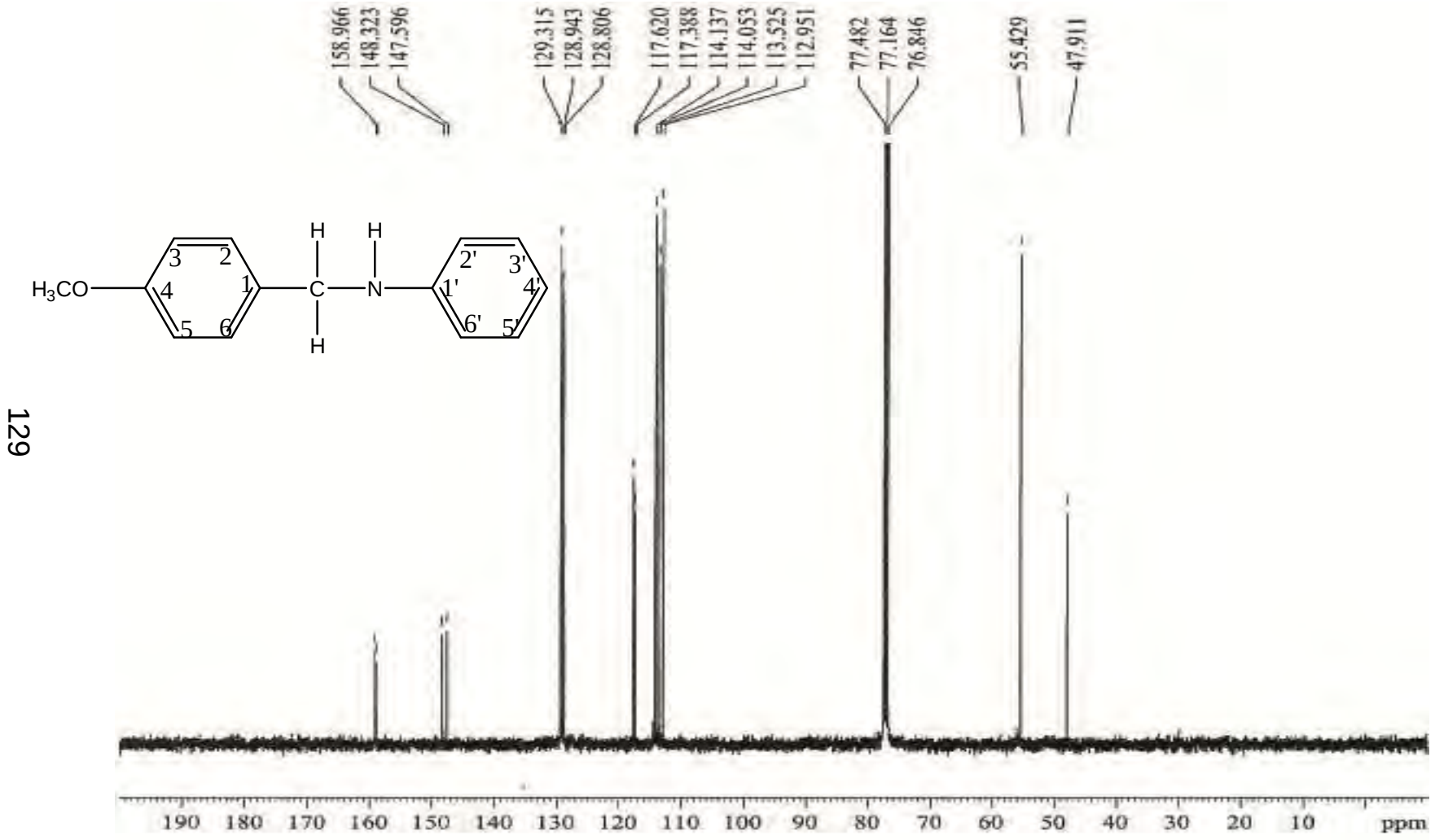


Fig 14E: ^{13}C NMR spectra of compound **24**.

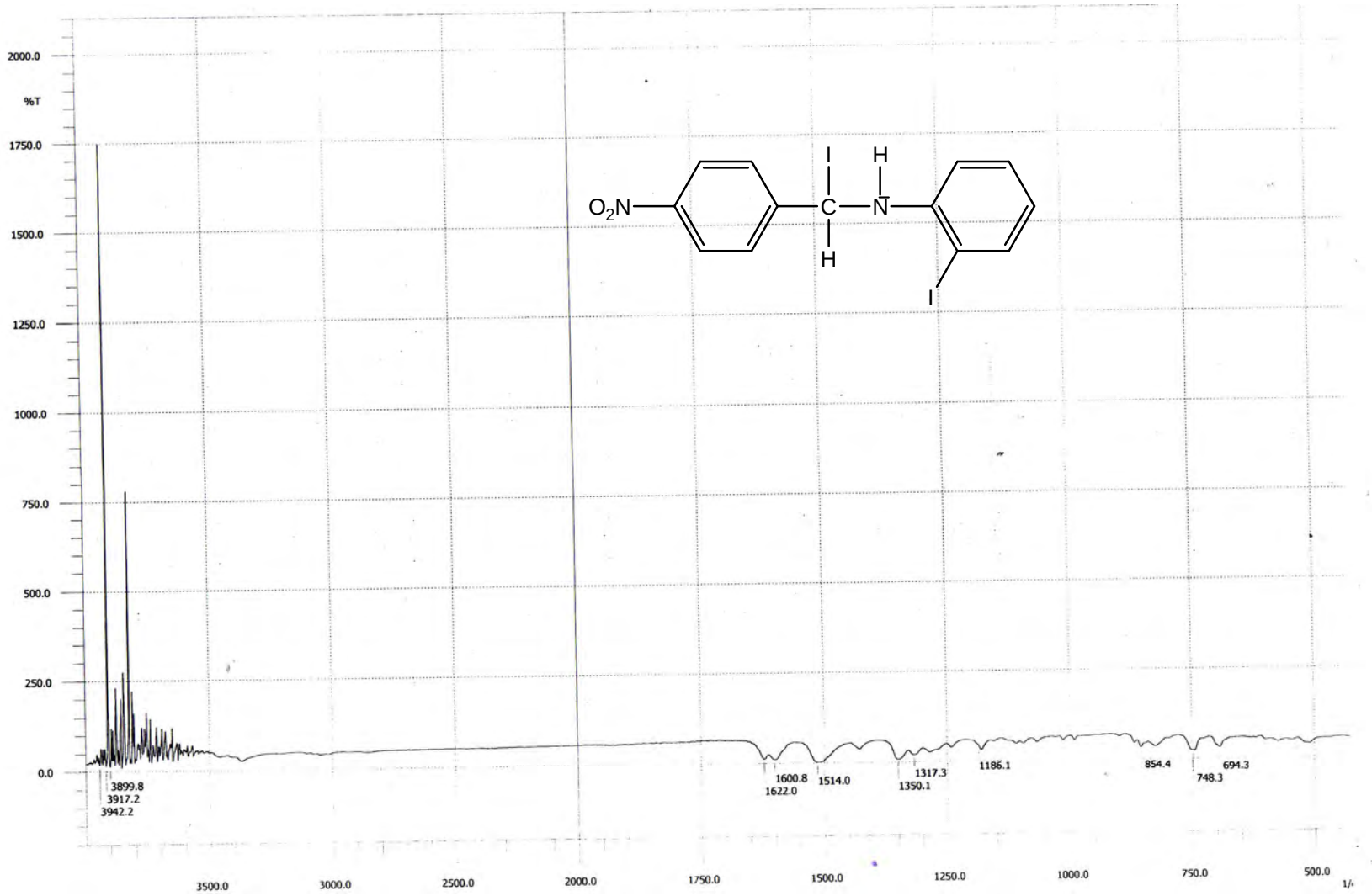
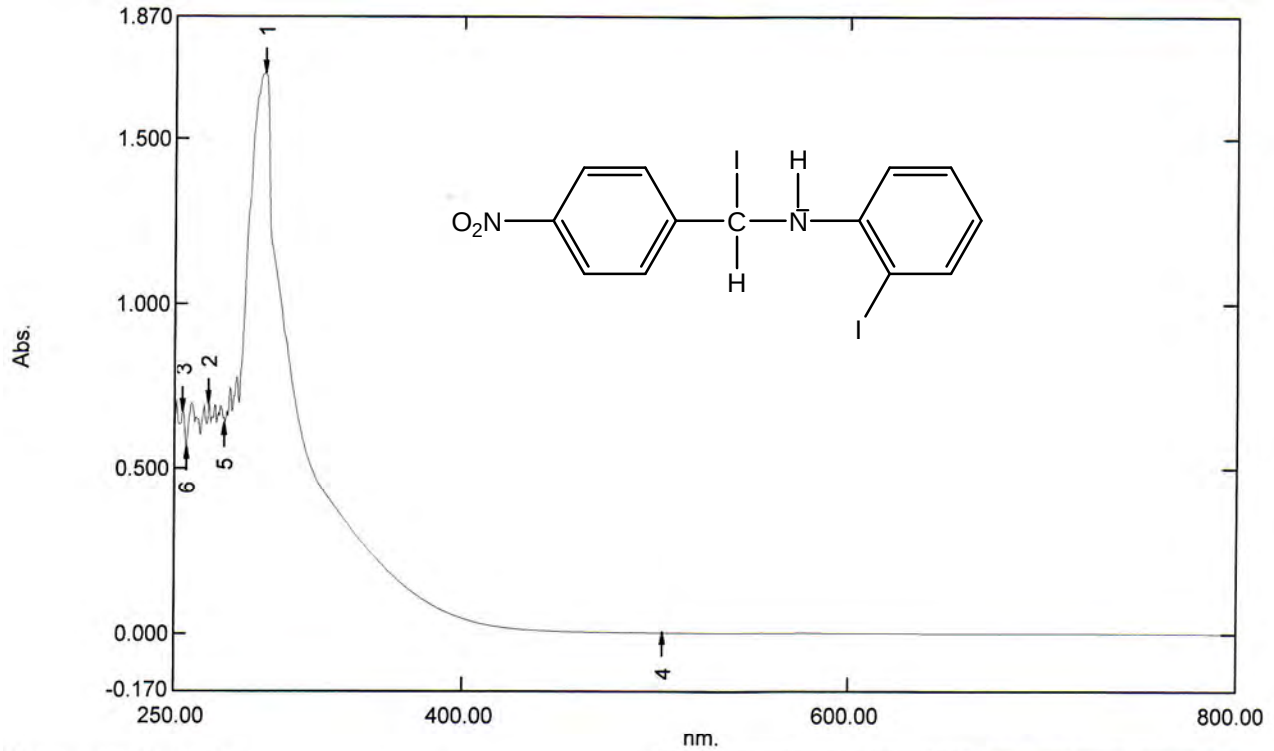


Fig 15A: IR spectra of compound **25.**



Measurement Properties

Wavelength Range (nm.):	250.00 to 800.00
Scan Speed:	Fast
Sampling Interval:	0.5
Auto Sampling Interval:	Disabled
Scan Mode:	Single

Sample Preparation Properties

Weight:

No.	P/V	Wavelength	Abs.	Description
1	↑	296.50	1.700	
2	↑	268.00	0.701	
3	↑	254.00	0.675	
4	↓	504.00	0.002	
5	↓	276.50	0.639	
6	↓	256.00	0.568	

Fig 15B: UV spectra of compound **25.**

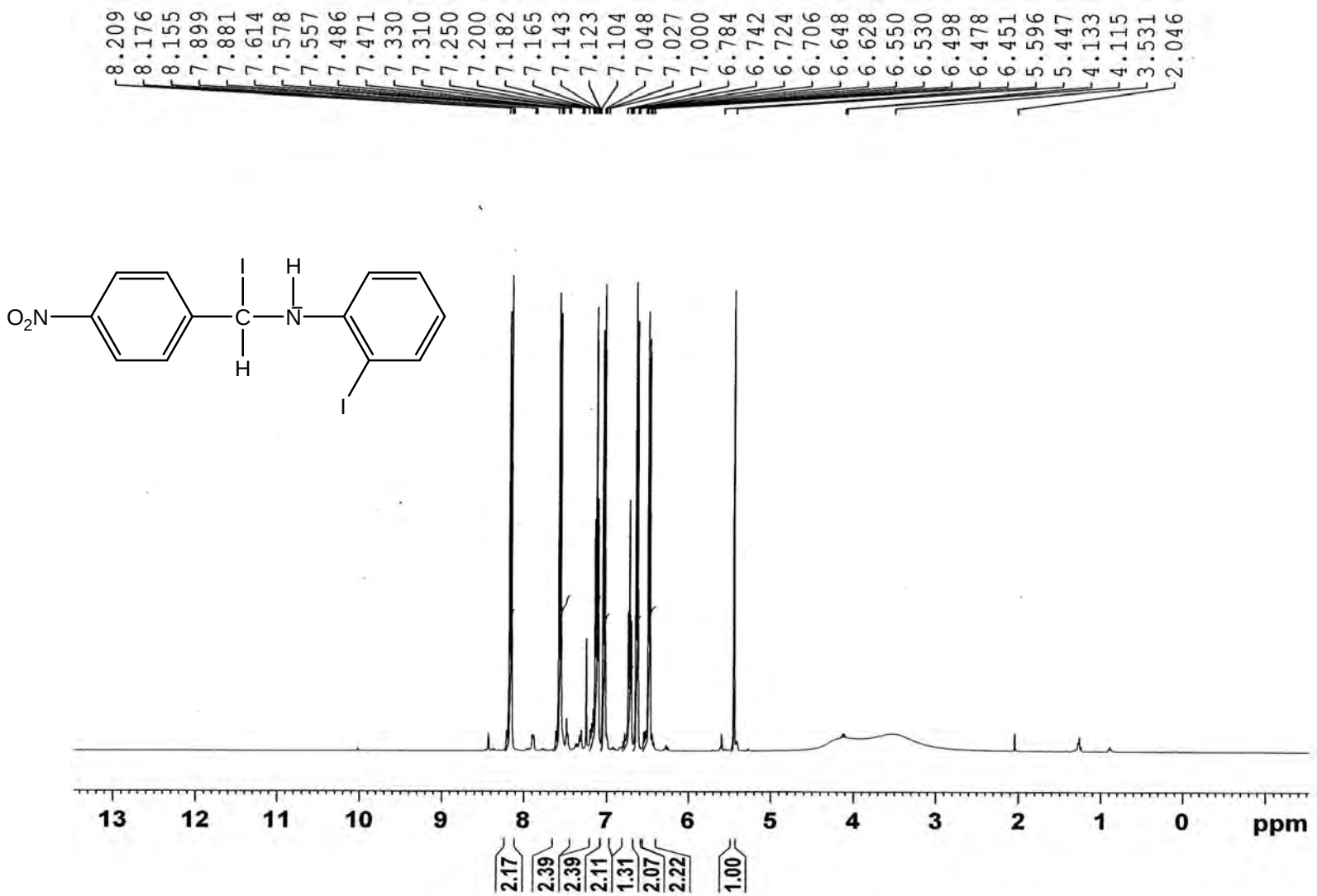


Fig 15C: ^{1}H NMR spectra of compound **25.**

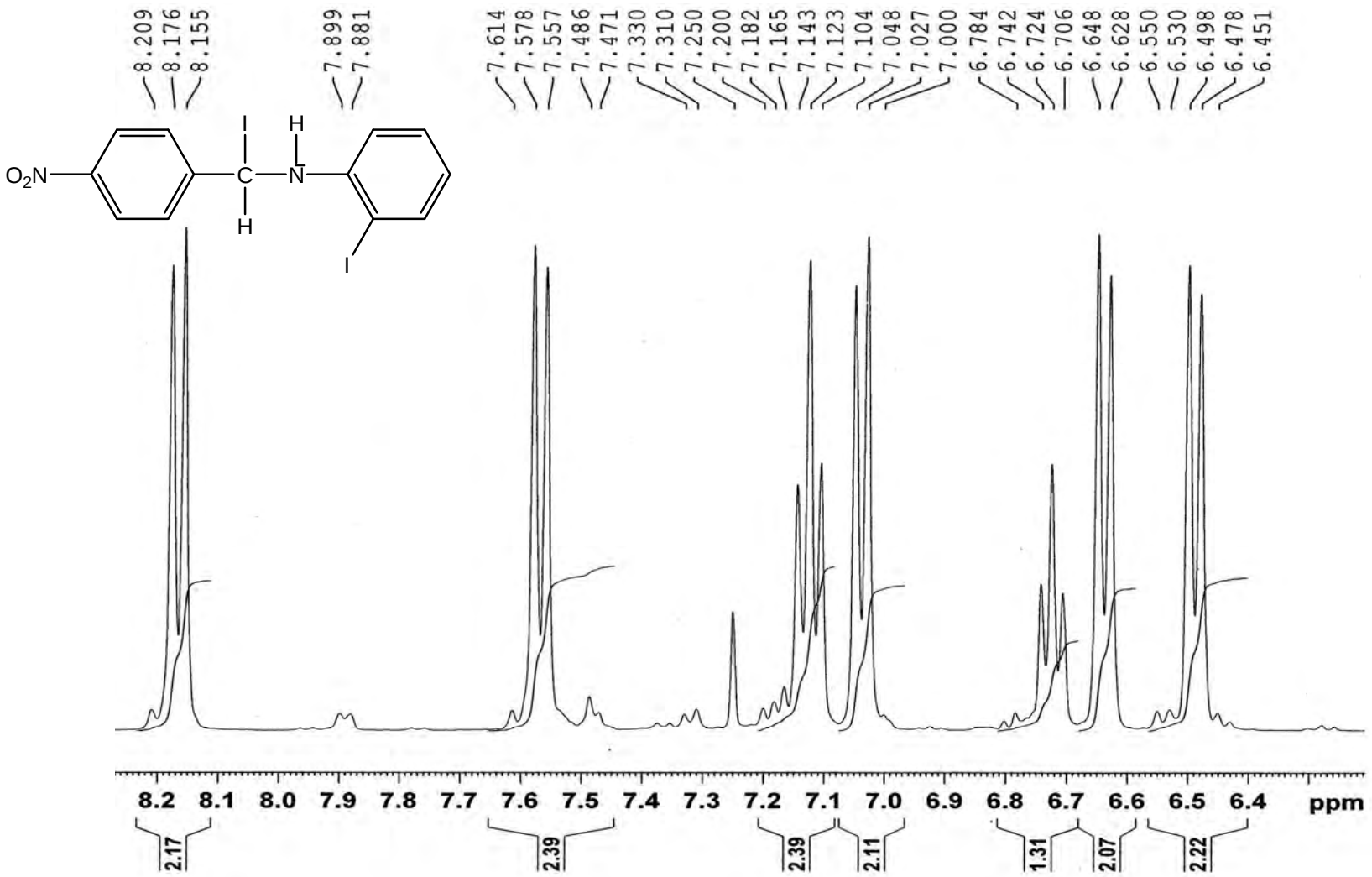


Fig 15D: ^{1}H NMR spectra of compound **25.**

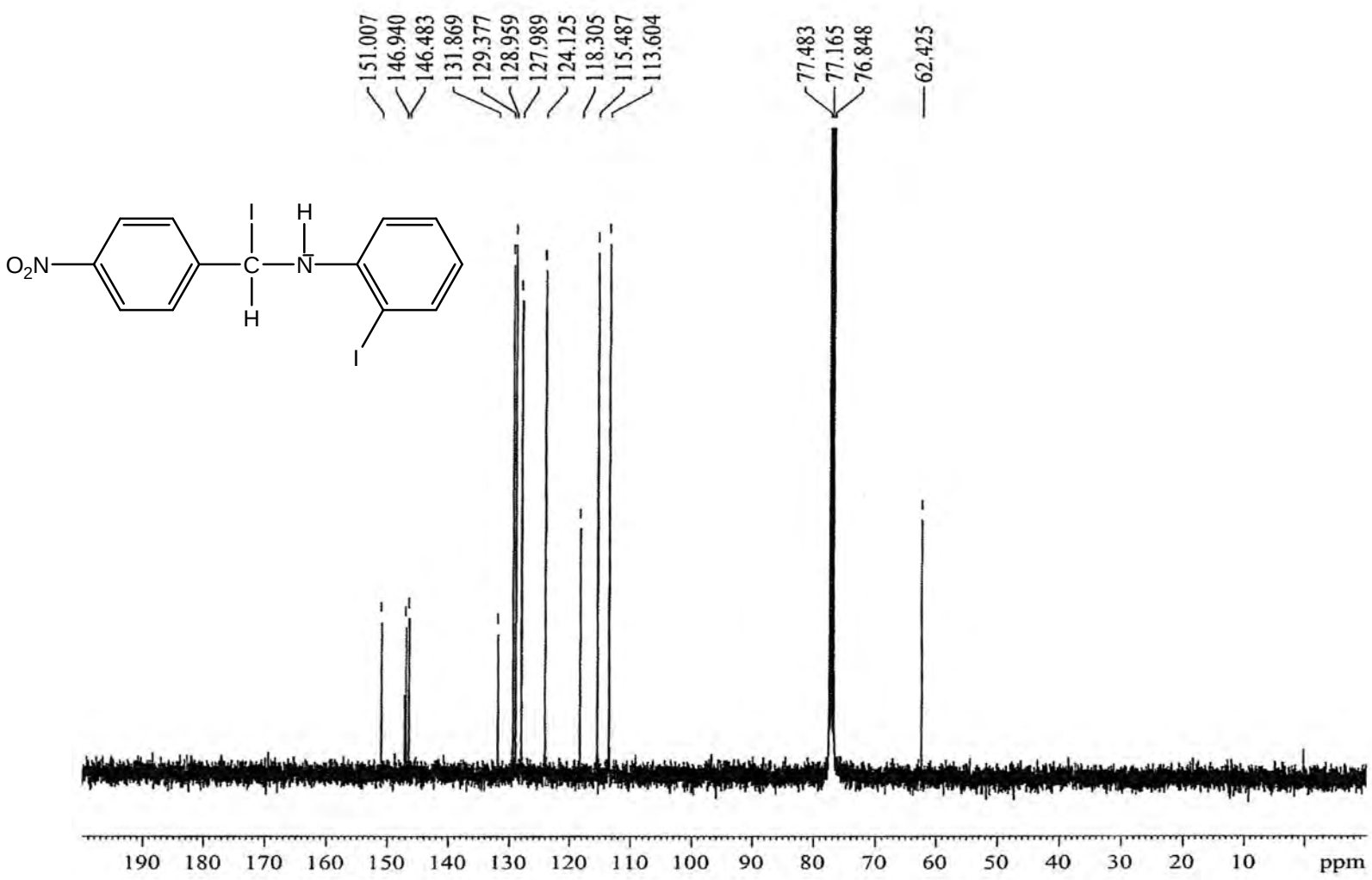


Fig 15E: ^{13}C NMR spectra of compound **25.**

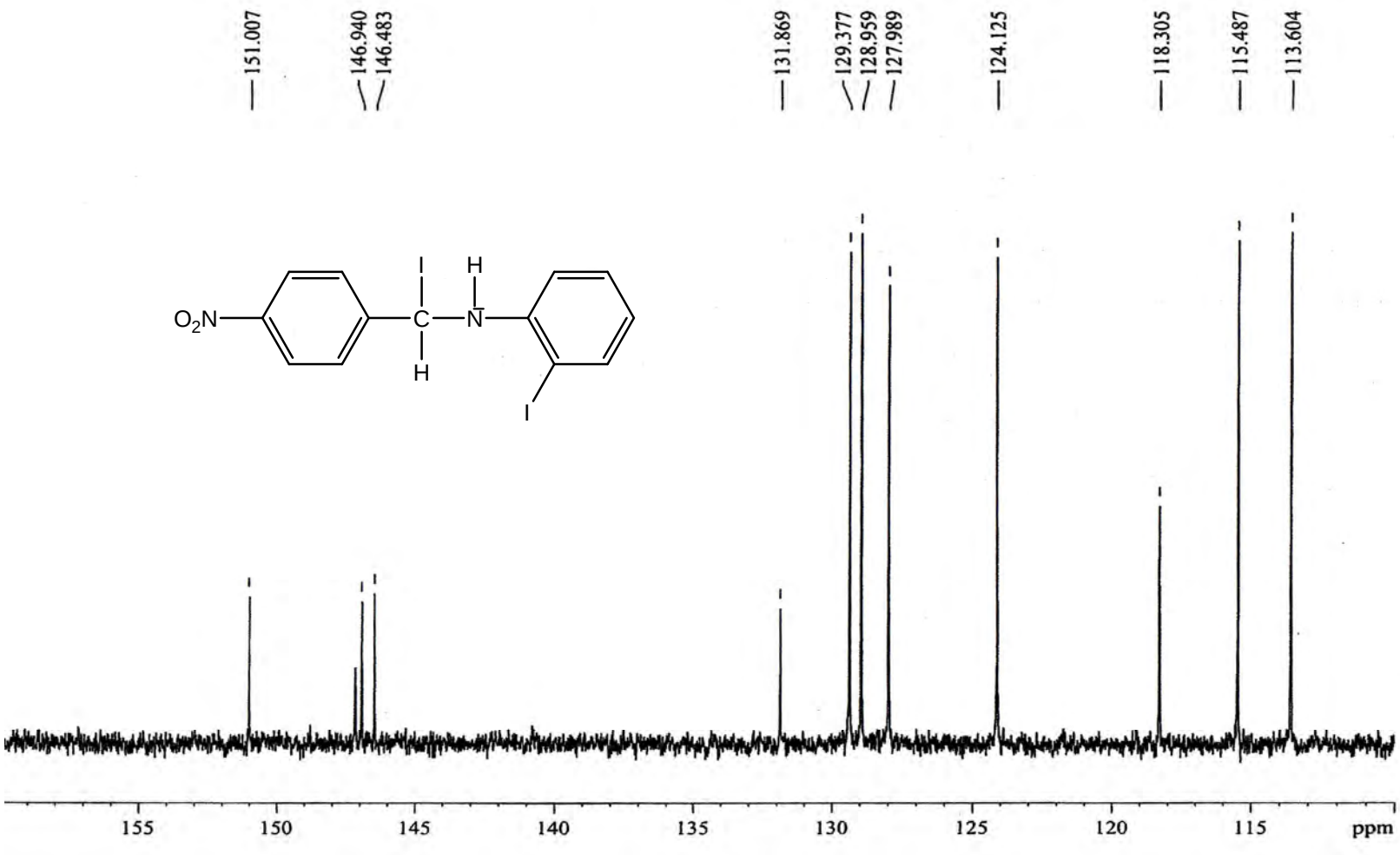


Fig 15E: ^{13}C NMR spectra of compound **25.**

5.1. Introduction

Worldwide, infectious disease is one of main causes of death accounting for approximately one-half of all deaths in tropical countries. Perhaps it is not surprising to see these statistics in developing nations, but what may be remarkable is that infectious disease mortality rates are actually increasing in developed countries, such as the United States. Death from infectious disease, ranked 5th in 1981, has become the 3rd leading cause of death in 1992; an increase of 58% .It is estimated that infectious disease is the underlying cause of death in 8% of the deaths occurring in the US (Middleton, 1996). This is alarming given that it was once believed that we would eliminate infectious diseases by the end of the millennium. The increases are attributed to increases in respiratory tract infections and HIV/AIDS. Other contributing factors are an increase in antibiotic resistance in nosicomial and community acquired infections. Furthermore, the most dramatic increases are occurring in the 25-44 year old age group.[1]

These negative health trends call for a renewed interest in infectious disease in the medical and public health communities and renewed strategies on treatment and prevention. It is this last solution that would encompass the development of new antimicrobials.[2]

The antimicrobial screening which is the first stage of antimicrobial drug research is performed to ascertain the susceptibility of various fungi and bacteria to any agent. This test measures the ability of each test sample to inhibit the *in vitro* fungal and bacterial growth. This ability may be estimated by any of the following three methods.

- ✓ Disc diffusion method.
- ✓ Serial dilution method.
- ✓ Bio-autographic method.

But there is no standardized method for expressing the results of antimicrobial screening. Some investigators use the diameter of zone of inhibition and/or the minimum weight of extract to inhibit the growth of microorganisms. However, a great number of factors viz.,

the extraction methods, inoculums volume, culture medium composition[3], p^H, and incubation temperature can influence the results.

Among the above mentioned techniques the disc diffusion[4] is a widely accepted in vitro investigation for preliminary screening of test agents which may possess antimicrobial activity. It is essentially a quantitative or qualitative test indicating the sensitivity or resistance of the microorganisms to the test materials. However, no distinction between bacteriostatic and bactericidal activity can be made by this method.[5]

5.2. Principle of disc diffusion method

In this classical method, antibiotics diffuse from a confined source through the nutrient agar gel and create a concentration gradient. Dried and sterilized filter paper discs (6 mm diameter) containing the test samples of known amounts are placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard antibiotic (Ciprofloxacillin) discs and blank discs are used as positive and negative control. These plates are kept at low temperature (4°C) for 24 hours to allow maximum diffusion of the test materials to the surrounding media (Brumitt W, 1984). The plates are then inverted and incubated at 37°C for 24 hours for optimum growth of the organisms. The test materials having antimicrobial property inhibit microbial growth in the media surrounding the discs and thereby yield a clear, distinct area defined as zone of inhibition.[6] Antimicrobial activity of the test agent is then determined by measuring the diameter of zone of inhibition expressed in millimeter.

In the present study the crude extracts as well as fractions were tested for antimicrobial activity by disc diffusion method. The experiment is carried out more than once and the mean of the readings is required.

5.3. Experimental description

5.3.1. Apparatus and reagents

- ✓ Filter paper discs
- ✓ Nutrient Agar Medium
- ✓ Petridishes
- ✓ Sterile cotton
- ✓ Micropipette
- ✓ Inoculating loop
- ✓ Sterile forceps
- ✓ Screw cap test tubes
- ✓ Autoclave
- ✓ Laminar air flow hood
- ✓ Spirit burner
- ✓ Refrigerator
- ✓ Incubator
- ✓ Chloroform
- ✓ Ethanol
- ✓ Nose mask and Hand gloves

5.3. 2. Test organisms

The bacterial and fungal strains used for the experiment were collected from State University of Bangladesh. Both gram positive and gram-negative organisms were taken for the test and they are listed in the

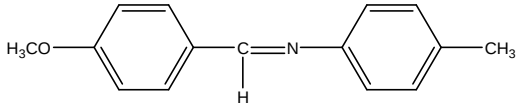
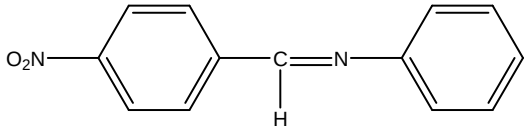
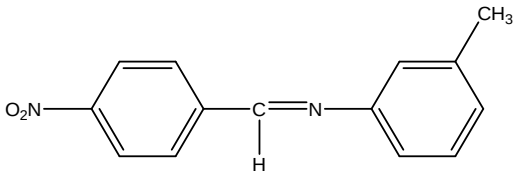
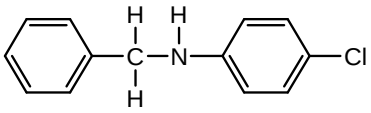
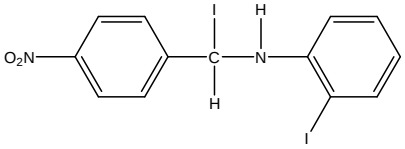
Table 5.1: Gram positive and gram-negative organisms

Gram positive bacteria	Gram negative bacteria
➢ Bacillus cereus	➢ Escherichia coli
➢ Bacillus megaterium	➢ Salmonella paratyphi
➢ Bacillus subtilis	➢ Salmonella typhi
➢ Sarcina lutea	➢ Shigella boydii
➢ Staphylococcus aureus	➢ Shigella dysenteriae
	➢ Pseudomonas aeruginosa
	➢ Vibrio mimicus
	➢ Vibrio parahemolyticus

5.3.3. Test materials

The synthesized compounds for the antimicrobial test are numbered as **12, 14, 17, 18** and **25**. The structure of the test samples are shown in **Table 5.3.**

Table 5.3: Table of test samples/ compounds

Sl. No	Structure of Compounds
1	 **12**
2	 **14**
3	 **17**
4	 **18**
5	 **25**

5.3.4. Composition of culture medium

The following media was used normally to demonstrate the antimicrobial activity and to make subculture of the test organisms.[7]

a) Nutrient agar medium

Ingredients	Amount
Bacto peptone	0.5 gm
Sodium chloride	0.5 gm
Bacto yeast extract	1.0 gm
Bacto agar	2.0 gm
Distilled water q.s.	100 ml
pH	7.2 + 0.1 at 25^{o} C

b) Nutrient broth medium

Ingredients	Amount
Bacto beef extract	0.3 gm
Bacto peptone	0.5 gm
Distilled water q.s.	100 ml
pH	7.2 + 0.1 at 25^{o} C

c) Muller – Hunton medium

Ingredients	Amount
Beef infusion	30 gm
Casamino acid	1.75 gm
Starch	0.15 gm
Bacto agar	1.70 gm
Distilled water q.s.	100 ml
pH	7.3 + 0.2 at 25^{o} C

d) Tryptic soya broth medium (TSB)

Ingredients	**Amount**
Bacto tryptone	1.70 gm
Bacto soytone	0.30 gm
Bacto dextrose	0.25 gm
Sodium chloride	0.50 gm
Di potassium hydrogen Phosphate	0.25 gm
Distilled water q.s	100 ml
pH	7.3 + 0.2 at 25^{o} C

Nutrient agar medium is the most frequently used and also used in the present study for testing the sensitivity of the organisms to the test materials and to prepare fresh cultures.

5.3.5. Preparation of the medium

To prepare required volume of this medium, calculated amount of each of the constituents was taken in a conical flask and distilled water was added to it to make the required volume. The contents were heated in a water bath to make a clear solution. The pH (at 25^{0}C) was adjusted at 7.2-7.6 using NaOH or HCl. 10 ml and 5 ml of the medium was then transferred in screw cap test tubes to prepare plates and slants respectively. The test tubes were then capped and sterilized by autoclaving at 15-lbs. pressure at 121^{0}C for 20 minutes. The slants were used for making fresh culture of bacteria and fungi that were in turn used for sensitivity study.

5.3.6. Sterilization procedure

In order to avoid any type of contamination and cross contamination by the test organisms the antimicrobial screening was done in Laminar Hood and all types of precautions were highly maintained. UV light was switched on one hour before working in the Laminar Hood. Petri dishes and other glassware were sterilized by autoclaving at a temperature of 121^{0}C and a pressure of 15-lbs/sq. inch for 20 minutes. Micropipette tips, cotton, forceps, blank discs etc. were also sterilized by UV light (John Turnidge & Jan Bell, 1994).

5.3.7. Preparation of subculture

In an aseptic condition under laminar air cabinet, the test organisms were transferred from the pure cultures to the agar slants with the help of a transfer loop to have fresh pure cultures. The inoculated strains were then incubated for 24 hours at 37^0C for their optimum growth. These fresh cultures were used for the sensitivity test.

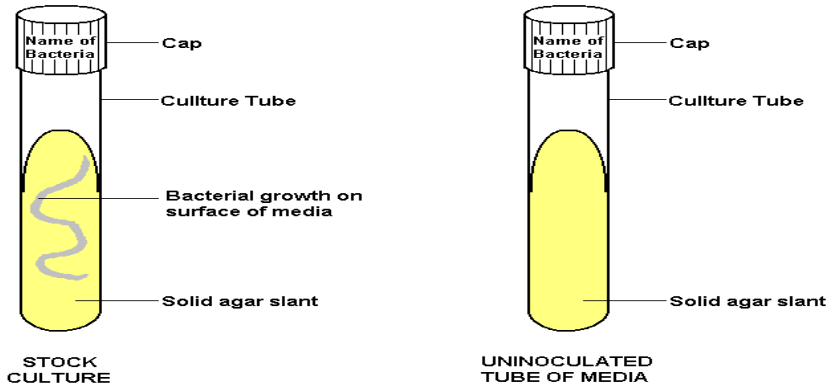
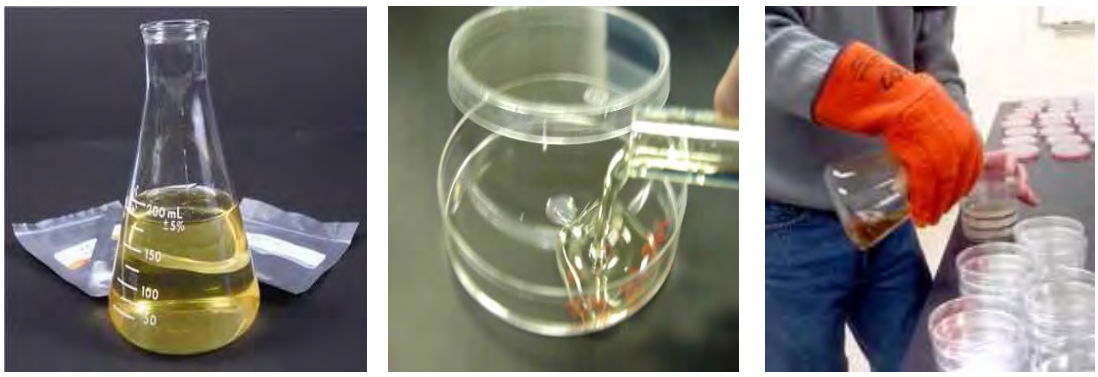


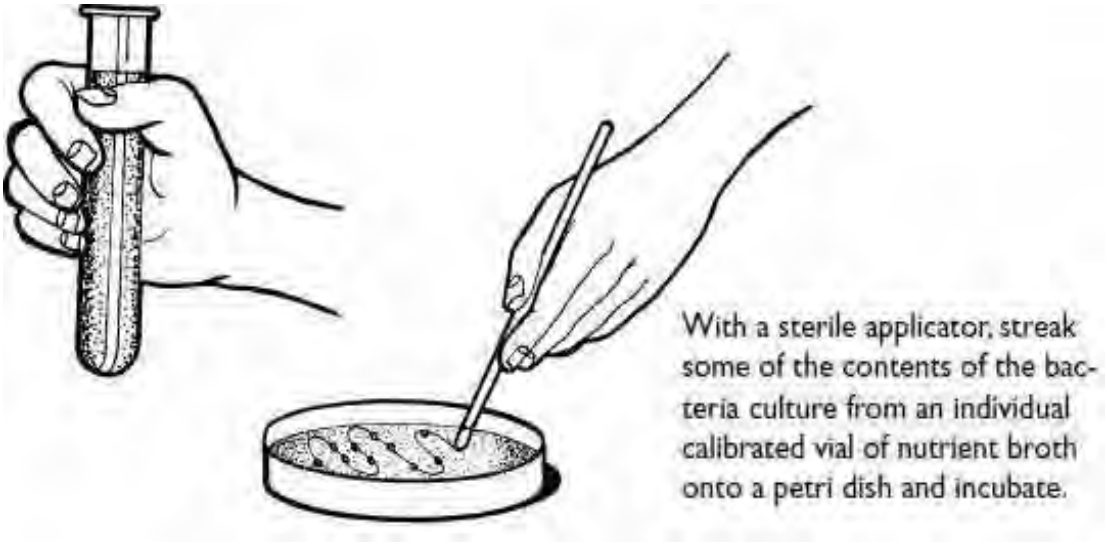
Figure:5.1: Preparation of subculture.

5.3.8. Preparation of the test plate

The test organisms were transferred from the subculture to the test tubes containing about 10 ml of melted and sterilized agar medium with the help of a sterilized transfer loop in an aseptic area. The test tubes were shaken by rotation to get a uniform suspension of the organisms. The bacterial and fungal suspension was immediately transferred to the sterilized Petri dishes. The Petri dishes were rotated several times clockwise and anticlockwise to assure homogenous distribution of the test organisms in the media.



(a) (b) (C)



(d)

Figure: 5.2: (a) Preparation of the test plates (b) Freshly prepared culture medium, (c) Pouring culture medium to petridishes, (d) Transfer of bacterial and fungal suspension to the petridishes.

5.3.9. Preparation of discs

Measured amount of each test sample (specified in table 5.3) was dissolved in specific volume of solvent (Chloroform or methanol) to obtain the desired concentrations in an aseptic condition. Sterilized metrical (BBL, Cocksville, USA) filter paper discs were taken in a blank Petri dish under the laminar hood. Then discs were soaked with solutions of test samples and dried.

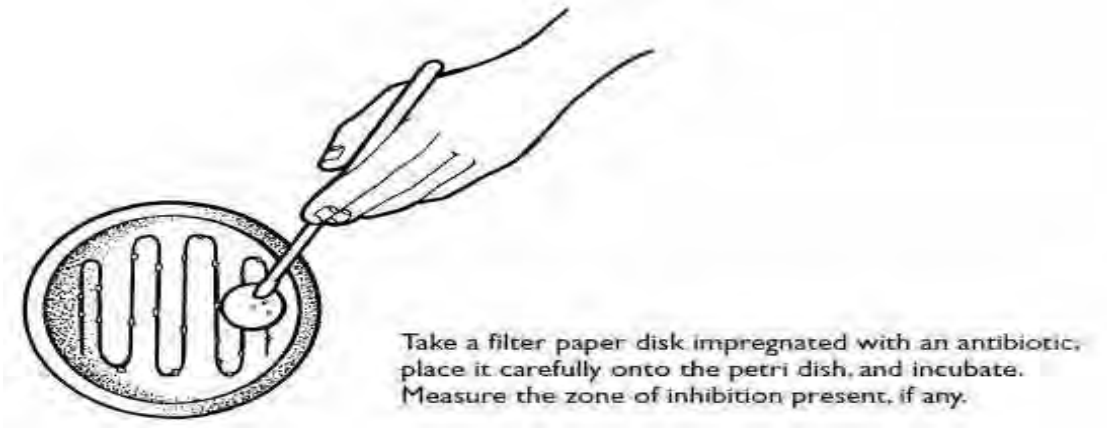


Figure 5.3: Preparation of filter paper discs.

Table 5.3: Preparation of sample Discs

Plant part	Test sample	Dose (µg/disc)	Required amount for 20 disc (mg)
Leaves of *Aganosma dichotoma*	Methanolic extract	400	8.0
	Petroleum ether partitionate	400	8.0
	Carbontetrachloride soluble partitionate	400	8.0
	Chloroform soluble partitionate	400	8.0
	Aqueous soluble partitionate	400	8.0

Standard Ciprofloxacillin (30 µg/disc) discs were used as positive control to ensure the activity of standard antibiotic against the test organisms as well as for comparison of the response produced by the known antimicrobial agent with that of produced by the test sample.

Blank discs were used as negative controls which ensure that the residual solvents (left over the discs even after air-drying) and the filter paper were not active themselves.

5.3.10. Diffusion and incubation

The sample discs, the standard antibiotic discs and the control discs were placed gently on the previously marked zones in the agar plates pre-inoculated with test bacteria and fungi. The plates were then kept in a refrigerator at 4^0C for about 24 hours upside down to allow sufficient diffusion of the materials from the discs to the surrounding agar medium. The plates were then inverted and kept in an incubator at 37^0C for 24 hours.

5.3.11. Determination of the zone of inhibition

The antimicrobial potency of the test agents are measured by their activity to prevent the growth of the microorganisms surrounding the discs which gives clear zone of inhibition. After incubation, the Antimicrobial activities of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with a transparent scale.[8]

Figure 5.4: Clear zone of inhibition.

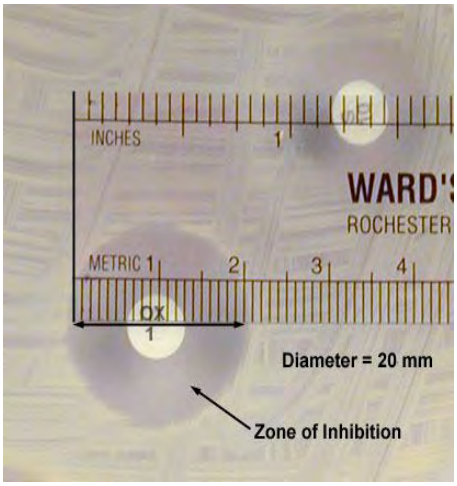


Figure 5.5: Determination of clear zone of inhibition.

5.4. Results and discussion

Ten synthesized compounds **12, 14, 17, 18** and **25** were tested for antibacterial activity against a number of both gram positive and gram negative bacteria (13 bacteria and 3 fungi). Standard disc of Kanamycin (30µg/disc) was used for comparison purpose.

All the synthesized compounds were tested at 200 µg/disc concentration and they exhibited mostly prominent for mild activity against most of the test bacteria which is shown below (**table 5.4)**. The synthesized compounds **8, 10, 12, 13, 14, 15** and **16** were found to be more active compare to other compounds.

Table 5.4: Antibacterial and antifungal activity of synthesized compounds (12, 14, 17, 18 and **25)**

Table 5.4: Antimicrobial activity of test samples

Test microorganisms	**Diameter of zone of inhibition**					
	18	**12**	**25**	**17**	**14**	**Ciprofloxacin**
Gram Positive Bacteria						
Bacillus cereus	7	-	-	-	-	47
Bacillus megaterium	9	-	-	-	10	49
Bacillus subtilis	11	-	-	-	8	50
Sarcina lutea	10	-	-	-	8	44
Staphylococcus aureus	8	-	-	-	-	45
Gram Negative Bacteria						
Escherichia coli	9	-	-	8	7	41
Salmonella paratyphi	9	-	-	-	-	41
Salmonella typhi	9	-	-	-	11	43
Shigella boydii	8	-	-	-	9	43
Shigella dysenteriae	8	-	-	-	7	45
Pseudomonas aeruginosa	8	-	-	-	-	40
Vibrio mimicus	8	-	-	-	7	40
Vibrio parahemolyticus	9	-	-	-	-	29
Fungi						
Saccharomyces cerevacae	8	-	-	-	9	40
Candida albicans	8	-	-	-	9	40
Aspergillus niger	8	-	-	-	-	42

N.B.: “---” Indicates no sensitivity/activity

5.5. References

1. Middleton, J.E. Biological properties of Plant flavonoids: An Overview, Int. J. Pharmacognosy, **1996**, *34*, 344-348.
2. Anthony S. Fauci, Braunwald Eugene, Stephen L Hauser, M.D. Harrison's principles of internal medicine, **1998**, *2*, 2754- 2008.
3. Bayer, A.W.; Kirby. W.M.M,; Sherris, J.C.; Turck. M., Antibiotic susceptibility testing by a standardized single disc method, Am. J. Clin. Pathol, **1966**, *45*, 493-496.
4. Brumitt, W.; Hamilton-Miller, M.T.; Gooding, A. Importance of methodology in determining bactericidal and bacteriostatic activities of **Azlocillin and ticarcillin against *Pseudomonas aeruginosa*,** J. medical microboil, **1984**, *17*, 37-44.
5. Ronald, R.; Hoffman, F.; La Roche & Basle, Co.; *Antibiotics, An Introduction*, Switzerland, **1982**, 70-71.
6. Uta-Christina Hipler, Peter Elsner , Antimicrobial activity, Biofunctional textiles and the skin, **2006**,119.
7. Jian Wang, James D. MacNeil, Jack F. Kay, Chemical Analysis of Antibiotic Residues in Food, Am J Med, **2011**, 7, 119-130.
8. Patrick, R.; Murray, Ellen Jo Baron, Manual of clinical microbiology, American Society for Microbiology, **2003**, *1*, 258, 1112.

5.5. References

1. Middleton, J.E. Biological properties of Plant flavonoids: An Overview, Int. J. Pharmacognosy, **1996**, *34*, 344-348.
2. Anthony S. Fauci, Braunwald Eugene, Stephen L Hauser, M.D. Harrison's principles of internal medicine, **1998**, *2*, 2754- 2008.
3. Bayer, A.W.; Kirby. W.M.M,; Sherris, J.C.; Turck. M., Antibiotic susceptibility testing by a standardized single disc method, Am. J. Clin. Pathol, 1966, *45*, 493-496.
4. Brumitt, W.; Hamilton-Miller, M.T.; Gooding, A. Importance of methodology in determining bactericidal and bacteriostatic activities of Azlocillin and ticarcillin against *Pseudomonas aeruginosa*, J. medical microboil, **1984**, *17*, 37-44.
5. Ronald, R.; Hoffman, F.; La Roche & Basle, Co.; *Antibiotics, An Introduction,* Switzerland, **1982**, 70-71.
6. Uta-Christina Hipler, Peter Elsner , Antimicrobial activity, Biofunctional textiles and the skin, **2006**,119.
7. Jian Wang, James D. MacNeil, Jack F. Kay, Chemical Analysis of Antibiotic Residues in Food, Am J Med, **2011**, 7, 119-130.
8. Patrick, R.; Murray, Ellen Jo Baron, Manual of clinical microbiology, American Society for Microbiology, **2003**, *1*, 258, 1112.

Conclusion:

1. The synthesis of substituted imines from substituted aldehydes and primary aryl amine was developed under mild condition.
2. No toxic and hazardous compounds were produced during the synthesis of the compounds.
3. The most important feature of these methods was that the readily available inexpensive starting materials were used under relatively mild conditions got relatively higher yields.
4. The synthesized substituted imines were reduced to their corresponding amine under mild reaction condition.
5. The synthesized imines were iodinated by different methods but iodination of imine was found to be unsuitable.
6. Antimicrobial activity of some synthesized imines and amine were test and imine **14** and amine **18** was found to be moderately active against gram positive and gram negative bacteria.

References:

1. Fletcher, Dermer, Fox, *Nomenclature of Organic Compounds* (1974) doi:10.1021/ba-1974-0126.ch023.
2. IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006–) "aldimines".
3. IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006–) "ketimines".
4. Hou, X. L.; Wu, J., Fan, R. H.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett.,* **2006**, 181-193.
5. Silveira, C. C.; Vieira, A. S.; Braga, A. *Tetrahedron,* **2005,** *61*, 9312-9318.
6. Manhas, M. S.; Ghosh, M.; Bose, K. *J. Org. Chem.* **1990**, 55.
7. Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**,124.
8. Nelson, D.L.; Cox, M.M. Lehninger Principles of Bio-chemistry; worth pub: NY, **2000**.
9. Hadjipavlou-litina, D. J.; Geronikaki, A. A. *Drug Design Discov.* **1996,** *15*, 199.
10. Vicini, P.; Geronikaki, A.; Incerti, M.; Busonera, B.; Poni, G.; Cabras, C. A.; Colla, P. L. *Bioorg. Med. Chem.***2003**, *11*, 4785.
11. Hedbery, C.; Pinho, P.; Roth, P.; Andersson, P.G. "Diels-Alder Reaction of Heterocyclic imine Dienophiles" *J. Org. Chem.* **2000**,*65*, 2810-2812.
12. Cantrell, G.K.; Meyer, T.Y. "Transition-metal-catalyzed Imine Metathesis", organometalics, *J. Am. Chem. Soc.* **1997**, *16*,5381-5383.
13. Amass, A. J. In *New Methods of Polymer Synthesis*; Ebdon, J. R., Ed.; Chapman and Hall: New York, **1991**; p 76.
14. Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**,*116*, 10801-10802.
15. Schellenberg, K. A.; *J. Org. Chem.* **1963**, *28*, 3259.
16. Tsuge, O.; Kanemasa, R. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.
17. Bergbreiter, D. E.; Newcombe, M. *Asymmetric Synthesis*, *Vol. 2A*, J. D. Morrison (Ed.), p. 243. Academic Press, Orlando, FL(1983).
18. Kuznetsov, V. V.; Pal'ma, A. R.; Aliev, A. E.; Varlamov, A. V.; Prostakov, S. *Zh. Org. Khim.* **1991,** *127*, 1579.

19. Niwa, T.; Yorimitsu, H.; Oshima, K.; *Org. Lett.* **2008**, Vol. 10, No. 20, 4689-4691.
20. Bernardi, F.; Bongini, A.; Cainelli, G.; Robb, M. A.; Valli, G. S. *J. Org. Chem.* **1993**,*58*,750-755.
21. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. (1959). "Versuche mit Isonitrilen". *Angew. Chem.* **71** (11): 386. doi:10.1002/ange.19590711110.
22. Ugi, I; Steinbrückner, C. (1960). "Über ein neues Kondensations-Prinzip". *Angew. Chem.* **72** (7–8): 267–268. doi:10.1002/ange.19600720709.
23. Ugi, I. (1962). "The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions". *Angewandte Chemie International Edition in English* **1** (1): 8–21. doi:10.1002/anie.196200081.
24. Zhao, D.; Moore, J. S. *J. Org. Chem.* **2002**, 67, 3548-3554.
25. (a) Padwa, A. *Chem. Rev*. **1997**, *77*, 37. (b) Layer, R. W. *Chem. Rev*. **1963**, *63*,489.
26. Eliot, A. C.; Kirsch, J. F. "PYRIDOXAL PHOSPHATE ENZYMES: Mechanistic, Structural, and Evolutionary Considerations". *Annual Review of Biochemistry* **2004**, *73*, 383–415.
27. Hernández-Molina, R.; Mederos, A. "Acyclic and Macrocyclic Schiff Base Ligands" in Comprehensive Coordination Chemistry II **2003,** 411–446. doi:10.1016/B0-08-043748-6/01070-7.
28. Lamas, M.C.; Vaillard, S. E.; Wibbelling, B.; Studer, A. *Org. Lett.* **2010**, Vol. 12, No. 9, 2072-2075.
29. Blackburn, L.; Taylor, J. K. *Org. Lett.* **2001**, Vol. 3, No.11, 1637-1639.
30. Pyun, S. Y.; Lee, D. C.; Seung, Y. J.; Cho, B. R. *J. Org. Chem.* **2005**,*70*,5327-5330.
31. Uppiah, D. J.; Bhowon, M. G.; Laulloo, S. J. *E-Journal of Chemistry*, **2009**, *6*, 195-200.
32. Middleton, W. J.; H. D. Carlson, H. D. *Hexafluoroacetone imine*, *Org. Synth.*; *Coll.* **1988,** *6*, 664.
33. Koos, M.; Mosher, H. S. "α-Amino-α-trifluoromethyl-phenylacetonitrile: A potential reagent for NMR determination of enantiomeric purity of acids". *Tetrahedron* **1993,** *49 (8)*, 1541–1546. doi:10.1016/S0040-4020(01)80341-0.
34. Moureu, C.; Mignonac, G.; "Les Cetimines". *Annales de chimie* **1920, *9*** (13), 322–359. Retrieved 18 June 2014.
35. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem*. **2002**, 1184.

36. Billman, J. H.; Tai, K. M. *J. Org. Chem*. **1958**, *23*, 535–539.

37. Miguel A ´ Va´zquez, Miguel Landa, Leonor Reyes, Rene´ Miranda, Joaquı´n Tamariz, and Delgado, Francisco. *Synthetic communications.***2004**, *34*, 2705-2718.

38. Naeimi, H.; Sharghi, H.; Salimi, F.; Khadijeh, R. *Heteroatom Chemistry* **2008**, *19*, 44-47.

39. Taguchi, K.; Westheimer, F. H. *J. Org. Chem*. **1971**, *36*, 1570-1572.

40. Chakraborti, A. K.; Bhagat, S.; Rudrawar, S. *Tetrahedron Letters* **2004**, *45*, 7641–7644.

41. Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Res. Chem. Intermed.* **2007**, *33*, 541–548.

42. Karla, P. Guzen, Alexandre S. Guarezemini, Aline T. G. rf O, Rodrigo Cella, Claudio M. P. Pereira and H lio A. Stefani, *Tetrahedron Letters*. **2007**, *48*,1845–1848.

43. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069-1094 (b) Hutchins, R. O.; Hutchins, M. K. "Comprehensive Organic Synthesis", vol. 8, B.M. Trost, I. Fleming (Eds), Pergamon Press, New York, **1991**, 25-78 (c) Johansson, A. *Contemp. Org. Synth.***1995**, *2*, 393-407 (d) James, B. R. *Chem. Ind. (Dekker)*,**1995**, *62*, 167-180.

44. (a) Reits, A. B.; Bennett, D. J.; Blum, P. S.; Codd, E. E.; Maryanoff, C. A.; Ortegon, M. E.; Renzi, M. J.; Ascott, M. K.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1994**, *37*, 1060. (b) Zhuang, Z.-P; Kung, M. P.; Kung, H. P. *J. Med .Chem.* **1994**, *37*, 1406. (c) Szakacs, Z.; Beni, S.; Vagra, Z.; Orfi, L.; Keri, G.; Noszal, B. *J. Med. Chem.* **2005,** *48*, 249. (d) Arasasinghan, P. N.; Fotsch, C.; Ouyang, X.; Norman, M. H.; Kelly, M. B.; Staerk, K. L.; Karbon, B.; Hale, C.; Baumgart, J. V.; Zambrano, M.; Cheetham, J.; Tamago, N. A. *J. Med. Chem.* **2003**, *46***,** 9. (e) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 901.

45. (a) Venable, J. D.; Chai, W.; Dvorak, C. A.; Grice, C. A.; Jablonowski, J.; Shah, A. C. R.; Kwok, A. K.; Ly, K. S.; Pio, B.; Wei, J.; Desai, P. J.; Jiang, W.; Nguyen, S.; Ling, P.; Wilson, S. J.; Dunford, P.J.; Thurmond, R. L.; Lovenberg, T. W.; Karlsson, L.; Carruthers, N. I.; Edwards, J. P. *J. Med. Chem*. **2005**, *48*, 8289. (b) Andersen, K.; Lifjefors, T.; Gundetoffe K.; Perreguard, J.; Bogeso, K. P. *J. Med. Chem.* **1994**, *37*, 950. (c) Enguehard-Gueiffier, C.; Hübner, H.; Hakmaoui, Ah.; Allouchi, H.; Gmeiner, P.; Argiolas, A.; Melis, M. R.; Gueiffier, A. *J. Med. Chem.* **2006**, *49*, 3938. (d) Romero, D. L.; Busso, M.; Tan, C-K.; Reusser, F.; Palmer, Aristoff, P. A.; So, A. G.; Resnick, L.; Tarplay, W. G. *Proc. Natl. Acad. Sci .U.S.A.* **1991**, *88*, 8806. (e) Leopoldo, M.; de

Giorgio, P.; Berardi, F.; Lacivita, E.; Colabuto, N.A.; Perrone, R.; Tortorella, V. *J. Med. Chem.* **2002**, *45*, 5727.

46. (a) Kozlov, N. G.; Gusak, K. N.; Tkachev, A. A. *Khim. Geterotsyklich. Soed.* **2007**,877. (b)Kozlov, N. G.; Koroleva, E. V.; Ignatovich, J. V.; Gusak, K. N; Kadutskii, A. P. *Zh. Org. Khim.* **2007**,*43*, 902. (c) Kozlov, N. G.; Tereshko, A. B.; Gusak, K. N. *Zh. Org. Khim.* **2006**, *42*,281. (d) Kozlov, N. G.; Pashkovskii, F. S.; Gusak, K. N.; Koroleva, E. V.; Tereshko, A. B.; Lokot, I. P. *Zh. Org. Khim.* **2004**, *40*,584. (e) Kadutskii, A.; Kozlov, N. *Synlett* **2006**, 1349. (f) Koroleva, E. V.; Ignatovich, J. V.; Gusak, K. N. The Second International Symposium on Structure and Function of Biomolecules, Minsk, Belarus, October 3-4, 2006: Abstract No.PR-65.
47. Xiao, X.; Wang, H.; Huang, Z.; Yang, J.; Bian, X.; Qin, Y. *Org. Lett.* **2006**, Vol. 8, No.1, 139-142.
48. (a) Ohtani, B.; Nakagawa, K.; Nishimoto, S.; Kagiya, T. *Chem. Lett*. **1986**, 1917-1920. (b) Murahashi, S.; Kondo, K.; Hakata, T. *Tetrahedron Lett*. **1982**, *23*, 229-232.
49. Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev*. **1999**, *68*, 55-72.
50. Blackburn, L.; Taylor, J. K. *Org. Lett.* **2001**, Vol. 3, No.11,
51. Tsukinoki, T.; Mitoma, Y.; Nagashima, S.; Kawaji, T.; Hashimoto, I.; Tashiro, M. *Tetrahedron Lett*. **1998**, *39*, 8873-8876.
52. Mitoma, Y.; Egashira, N.; Simion, C.; Tashiro, M. *Revue Roumaine de Chimie*, **2006**, *57*(7-8), 839-842.
53. Diederich, F.; Stang, P.J. Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH, New York, **1998**.
54. Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937.
55. Stavber, S.; Jereb, M.; Zupan, M. Synthesis, **2008**, 1487.
56. Hanson, J.R.; *J. Chem. Res.* **2006**, 277.
57. L.S. Hegedus, Angew. Chem. Int. Ed. Engl. **1988**, *27*, 1113P.
58. Kabalka, G.W.; Wang, L.; Pagni, R.M. *Tetrahedron* **2001,***57*,8017.
59. Khan, M.W.; Masud R, A.F.G. *Tetrahedron*, **2005**, *61*, 11204.
60. Kavala, V.; Wang, C.C.; Barange, D.K.; Kuo, C.W.; Lei, P.M.; Yao, C.F. *J. Org. Chem.* **2012**,*77*,5022.

61. Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem*. **2008**, *73*, 4721.
62. Cant, A.A.; Rajiv, B.; Pimlott, S.L.; Sutherland, A. *Chem. Commun*.**2012**, *48*, 2016.
63. Chang, J.H.; Kang, H.U.; Jung, I.H.; Cho, C.G. *Org. Lett.* **2012**, *48*, 3993.
64. Buchgraber, P.; Snaddon, T.N.; Wirtz, C.; Mynott, R.; Goddard, R.; Furstner, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8450.
65. Beale, T.M.; Chudzinski, M.G.; Sarwar, M.G.; Taylor, M.S. *Chem. Soc. Rev.* **2013**, *42*, 1667.
66. Wilcken, R.; Zimmermann, M.O.; Lange, A.; Joerger, A.C.; Boeckler, F.M. *J. Med. Chem*. **2013**, *56*, 1363.
67. Sarwar, M.G.; Dragisic, B.; Salsberg, L.J.; Gouliaras, C.; Taylor, M.S. *J. Am. Chem. Soc*. **2010**, *132*, 1646.
68. Scholfield, M.R.; Vander Zanden, C.M.; Carter, M.; Ho, P.S. *Protein Sci.* **2013**, *22*, 139.
69. Metrangolo, P.; Resnati, G. *Science*,**2008**, *321*,918.
70. Roeding, A. in: Houben-Weyl, Methoden der organischen Chemie, Thieme: Stuttgart **1960**, *4*, 517.
71. March, J. Advanced Organic Chemistry, fourth ed., Reactions, Mechanisms and Structure, Wiley, New York, **1992**. pp. 501-507.
72. March, J. Advanced Organic Chemistry, fourth ed., Reactions, Mechanisms and Structure, Wiley, New York, **1992**. pp. 533-534.
73. Murkushew, E.B. Synthesis **1988**,923.
74. Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem. Int. Ed*. **2009**, *48*, 8424.
75. Firouzabadi, H.; Iranpoor, N.; M. Shiri, M. *Tetrahedron Lett*. **2003**, *44*, 8781.
76. Gonzalez Gomez, J.A.; Green, J.; Vollhardt, K.P.C. *Synlett* **2011**, 805.
77. Kiran, Y.B.; Konakahara, T.; Shakai, N. *Synthesis* **2008**, 2327.
78. Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V.S. *Tetrahedron Lett*. **2007**, *48*, 81.
79. Pourali, A.R.; Ghanei, M. *Chin. J. Chem.* **2006**, *24*, 1077.
80. Junne, S.B.; Vibhute, A.Y.; Vibhute, Y.B.; Gurav, V.M. *Int. J. Chem. Tech. Res.* **2009**, *1*, 1005.
81. Bhilare, S.V.; Deorukhkar, A.R.; Darvatkar, N.B.; Salunkhe, M.M. *Synth. Commun*. **2008**, *38*, 2881.

82. Nils, S.; Joanna, W.D.; Frank, G. *J. Am. Chem. Soc.* **2012**, *134*, 8298.

83. Hannah, W.M.; Olbelina, A.U.; Daniel, P.K.; D.I. Christopher, D.I.; C.B. Shawn, C.B. *Org. Biomol. Chem.* **2011**, *9*, 2987.

84. Baird, C.W.; Surridge, J.H. *J. Org. Chem.***1970**, *35*, 3436.

85. Sugita, T.; Iddei, M.; Ishibashi, Y.; Takegami, Y. *Chem. Let.* **1982**, *9*, 1481.

86. a) Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett.*, **1993**, *34*, 3581-3584 b) Choi, H. C.; Jung, J. C.; Cho, K. I.; Kim, Y. H. *Heteroatom Chem.*, **1995**, *6*, 333-338 c) Choi, H. C.; Cho, K. I.; Kim, Y. H. *Synlett*, **1995,** 207-208.

87. Linus Pauling, *General Chemistry*. Dover Publications, ISBN 0-486-65622-5 (**1988**).

88. Davy, H. "Sur la nouvelle substance decouverte par M. Courtois, dans le sel de Vareck". *Annales de chemie* **1813**, *88*, 322.

89. Castanet, A.S.; Colobert, F.; Broutin, P.E., *Tetrahedron Lett*.**2002**, *43*, 5047-5048.

90. Johnsson, R.; Meizer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657-11663.

91. Pasha, M.A.; Myint, Y. Y. *Synthetic Cmmunications* **2004,** Vol 34, No 15, pp. 2829-2833.