SYNTHESIS OF SUBSTITUTED INDOLES BY METAL MEDIATED REACTIONS

A DISSERTATION SUBMITTED IN THE PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF PHILOSOPHY (M.PHIL) IN CHEMISTRY

SUBMITTED

BY

MOHAMMAD ISMAIL HOSSAIN

STUDENT NO.100603125 F

REGISTRATION NO. 100603125

SESSION: OCTOBER- 2006

ORGANIC RESEARCH LABORATORY
DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET),
DHAKA-1000, BANGLADESH

August, 2009

BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY

(BUET), DHAKA-1000, BANGLADESH.

DEPARTMENT OF CHEMISTRY

THESIS ACCEPTANCE LETTER

The thesis titled "Synthesis of substituted indoles by metal mediated reactions" submitted by Mohammad Ismail Hossain, Roll No. 100603125 F, Registration No. 100603125, Session October- 2006 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Master of Philosophy (M.Phil) in chemistry on August 23, 2009.

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Professor,
Department of Chemistry,
Dhaka University, Dhaka.

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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

(Mohamad Ismail Hossain)

Date: August 23, 2009.

Acknowledgment

All praise and admiration for almighty Allah, the most kind and merciful who has enabled me in carrying out the research work presented in this dissertation.

I am extremely delighted to express my deepest gratitude and sincere thank to my advisor and supervisor, Prof. Dr. Md. Wahab Khan, for his helpful advice, keen interest, thoughtful invaluable suggestions and encouragement offered throughout the progress of my research work.

I am highly grateful to all my respected teachers of this department, particularly Dr. Enamul Huq, Dr. A. K. M. Matlor Rahman, Dr. Md. Rafique Ullah, Dr. Md. Abdur Rashid, Dr, Md. Monimul Haque, Dr, Md. Manwarul Islam, Dr. Al-Nakib chowdhury, Dr. Nazrul Islam, Dr. Md. Nazrul Islam, Dr. Shakila Rahman, and Mrs Tahera Saad for their helpful suggestions at different stages of studies in chemistry.

I am thankful to Dr Kazuaki Shimada, professor, Department of chemical Engineering, Iwate University, Japan for taking ^{1}HNMR and ^{13}CNMR spectra of my synthesized compounds.

I am also grateful to Masud Reza, Ph.D student, Institute for molecular science, Japan for taking ^{1}HNMR and ^{13}CNMR spectra of my some synthesized compounds.

I would like to thanks Md. Younus Ahamed, Md Abdul Bari, Md Abu Bakkar siddique, Md. Mizanur Rahman, Md. Mazaharul Islam, Md. Enamul Haque, Tania, Fatema, Fahmida, Md. Humayon Kabir, and Fayez Ahamed for their generous technical help and co-operation in the laboratory.

I acknowledge to the University of Engineering and Technology (BUET), Dhaka and Ministry of National science Information and Communication Technology (NSICT), Bangladesh for giving me the financial support to carry out my research work and I am also grateful to the Department of Chemistry to give me opportunity to do M.Phil program.

I convey thanks to all staffs in the Department of Chemistry, BUET for their kind co-operations.

Last of all, I wish to express my thankful gratitude to the member of my family for their encouragement, sincere co-operation and sacrifice during the tenure of this work. In times of uncertainty, their love and guidance always steered me in the right direction.

Author

(Mohammad Ismail Hossain)

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Chapter 2

Section- II

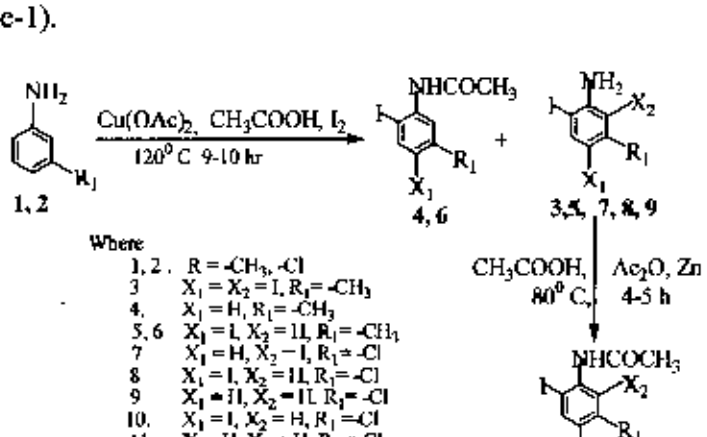
LIST OF ABBREVIATIONS

Ac	acetyl, acetate
aq.	aqueous
bp	boiling point
br	broad
d	doublet
dec.	decomposition
DMF	*N*, *N*-dimethylformamide
Equiv.	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hour
HPLC	high performance liquid chromatography
hν	light
Hz	hertz
IR	infrared (spectrum)
J	coupling constant
m	multiplet or medium
M	mass or metal
min	minutes
mmol	millimole
mol	mole
mol%	mole percent
mp	melting point
NMR	nuclear magnetic resonance
OAc	acetate
Ph	phenyl
PhH	benzene
ppm	parts per million

rt	room temperature
s	singlet, strong, or second
sec	seconds
t	triplet
T	temperature
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultra violet
w	weak
Δ	heat at reflux
δ	chemical shift
λ_{max}	ultraviolet absorption in nm
ν_{max}	infrared absorption in per centimeter

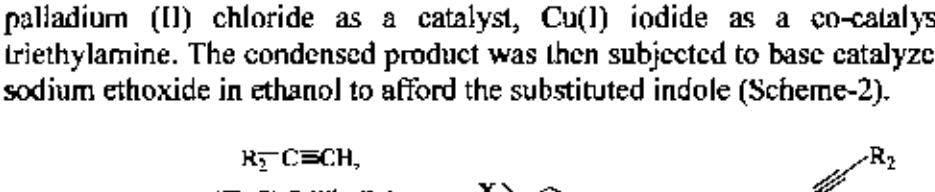
ABSTRACT

In view of the extensive natural occurrence and biological importance of the indole nucleus containing heterocyclic compounds a general and facile method for the synthesis of indole derivatives through palladium catalyzed reaction using terminal alkyne followed by base catalyzed reactions is reported. In this purpose different 2-iodo acetanilide compounds were synthesized from m-substituted aryl amines by iodination reaction (Scheme-1).

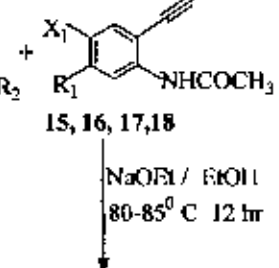


Scheme-1

The heteroannulation reaction was carried out by stirring a mixture of 2-iodo substituted acetanilide and different terminal alkynes in presence of bis(triphenylphosphine) palladium (II) chloride as a catalyst, Cu(I) iodide as a co-catalyst and a base triethylamine. The condensed product was then subjected to base catalyzed reaction with sodium ethoxide in ethanol to afford the substituted indole (Scheme-2).



X	R_1	R_2	Comp. No.
H	$-CH_3$	-Ph	**12**
H	$-CH_3$	$-C(CH_2)_2CH_3$	**13**
I	$-CH_3$	-Ph	**15, 20**
I	$-CH_3$	$-C(CH_2)_2CH_3$	**16**
I	$-CH_3$	$-C(CH_2)_3CH_3$	**17**
I	-Cl	-Ph	**18, 21**



Scheme-2

All the synthesized compounds were characterized by using analytical data obtained from M.P, UV, IR, ^{1}H NMR and ^{13}C NMR.

SUMMARY

Investigation incorporated in this dissertation titled, "Synthesis of substituted indoles by metal mediated reactions" have been presented in two chapters. The first chapter is the introductory section, in which the background, biological action and the important synthesis are presented. Chapter 2 is divided into two sections. Section one deal with the rationale, results and discussion and conclusion of the synthesis of substituted indole. Section 2 deals with the detailed methodologies and experimental procedures for the synthesis of 2,6- disubstituted indole derivatives, spectra and references.

Chapter-I

It represents the importance and synthesis of indole derivatives. Indoles are a class of fused heterocycles that are of increasing interest in synthetic and pharmaceutical chemistry. In spite of their scarce presence in nature, indole derivatives have proved considerable interest due to their pharmacological activities. Various methods are known for the synthesis of indole derivatives but palladium catalyzed procedures for the synthesis of indole derivatives are limited in number.

Chapter-II

Section –1

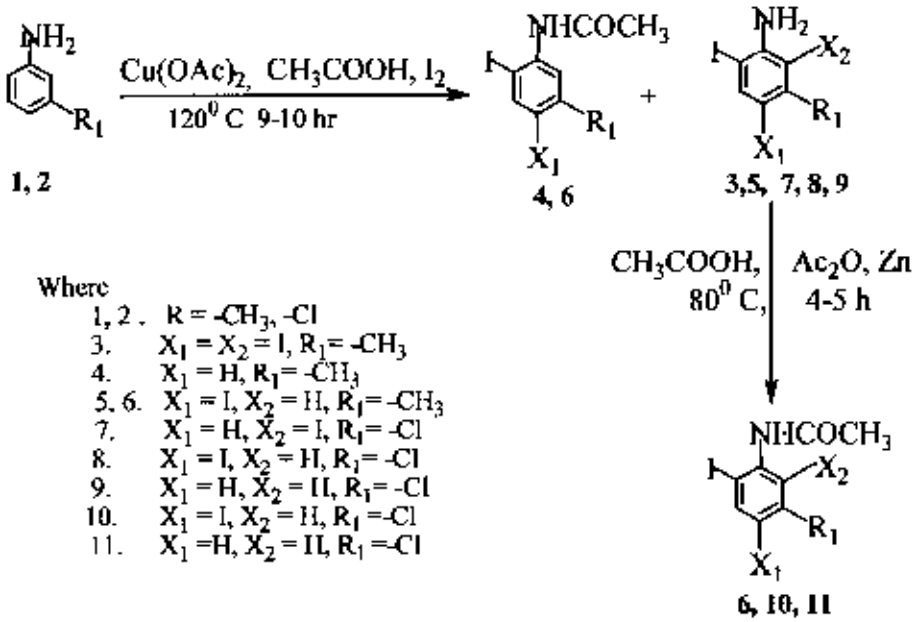
In this section results and discussion are presented. Here a strategy for the synthesis of indole derivatives is reported through the palladium catalyzed reaction of substituted 2-iodoacetanilide and terminal alkynes.

In one pot reaction indole derivatives were obtained in few cases e.g with phenyl acetylene but with hexyne and heptyne condensed products were produced. Then these condensed products were cyclized to the indole derivatives by base catalyzed reaction.

The yield of substituted indole in the case of phenyl acetylene (yield 52 %) with various acetanilides was greater than that of the n- Hexyne (43 %) or 1-Heptyne.Similarly the yield of substituted indoe in the case of m-toluidine (yield 65%) was better than that of m-chloroaniline (yield 42 %).

Section –II

In this section the general procedure for the synthesis of indole is described. For this purpose first of all different substituted iodo compounds were synthesized from m-substituted aniline by iodination reaction (Scheme-1).

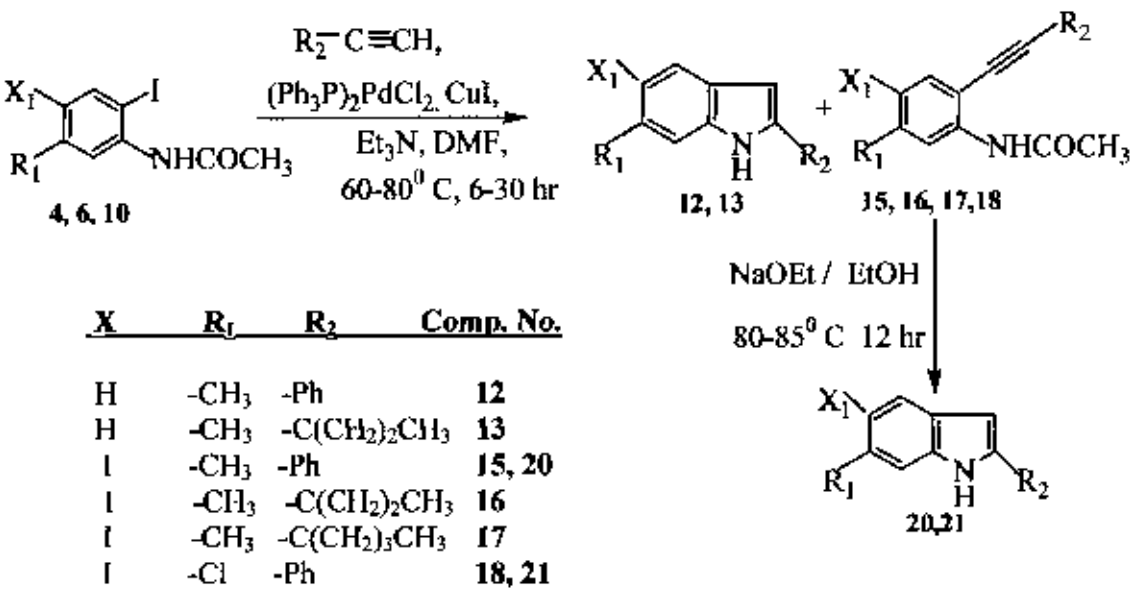


Where
1, 2 . R = -CH_3, -Cl
3. $X_1 = X_2 = I$, $R_1 = -CH_3$
4. $X_1 = H$, $R_1 = -CH_3$
5, 6. $X_1 = I$, $X_2 = H$, $R_1 = -CH_3$
7. $X_1 = H$, $X_2 = I$, $R_1 = -Cl$
8. $X_1 = I$, $X_2 = H$, $R_1 = -Cl$
9. $X_1 = H$, $X_2 = I$, $R_1 = -Cl$
10. $X_1 = I$, $X_2 = H$, $R_1 = -Cl$
11. $X_1 = H$, $X_2 = I$, $R_1 = -Cl$

Scheme-1

The palladium-catalyzed reaction was carried out by stirring of 2-iodo or 2, 4-diiodo-5 methyl or chloro acetanilides in DMF (3.5 equiv.), in which Bis-(triphenyl phosphine) palladium (II) chloride (3.5 mol %), CuI (8 mol %), Et_3N (4 equiv.) were added at 0^0 C (Scheme-2). Then terminal alkyne was added under N_2 atmosphere. Then the reaction mixture was stirred for 6-30 hours. After usual workup the crude products were purified by column chromatography using silica gel and pure substitute 2- alkynyl acetanilide **15, 16, 17, 18** were obtained.

Substituted 2-alkynyl acetanilide was subjected to base catalyzed cyclization reaction for the formation of substituted indoles. 2- Alkynyl acetanilide was added to sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml) and the mixture was stirred under a nitrogen atmosphere for 10-12 hr at 80-85^0 C. After usual workup and purification by column chromatography substituted indoles **12, 13, 20, 21** were obtained in moderate to good yields.



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I	$-CH_3$	$-C(CH_2)_3CH_3$	**17**
I	-Cl	-Ph	**18, 21**

Scheme-2

All the synthesized compounds were characterized by using analytical data obtained from M.P, UV, IR, ^{1}H NMR and ^{13}C NMR. The spectra of all the compounds and related references are given here.

Prefatory Note

All the solvents for reaction separation, extraction and recrystalization were purified and the test was used as available commercially.

Analytical or laboratory grade solvents and chemicals were used in all experiments and these were procured from E. Merk (Germany) and Fluka (Switzerland). Reagent grade of chloroform, n-hexane, ethylacetate, ethanol, acetone etc. were purified by distillation at the boiling point of the respective solvent. The following methods were used for the purification and drying of the solvents.

1. Purification of solvents and reagents

a) Dry ethanol (EtOH)

About 2 gm of clean and dry magnesium turnings and 0.125 gm of iodine were placed in a dry 500 ml round bottom flask containing 30-40 ml of reagent grade ethanol. The flask was then fitted with a double surface condenser carrying a calcium chloride guard tube on the top. The mixture was warmed until the iodine disappeared, if a lively evolution of hydrogen did not set in a further little amount of iodine was added. Heating was continued until all the magnesium was covered into pasty mass ethanolate. About 230 ml of commercial grade ethanol was then added to the flask and refluxed the mixture for an additional hour. The resulting mixture was distilled off and the first 10-15 ml of distillate was discarded. Then the dry ethanol was collected into a receiving flask from which it was stored into a quick fit bottle.

b) Ethyl acetate

Ethyl acetate from E. Mark (Germany) was used directly as it was bought commercially.

2. Melting point

Melting points were determined on Gallenkamp (England) melting point apparatus and paraffin oil bath were uncorrected.

3. Infra-red (IR) spectra

The Infra-red spectra were recorded on KBr pellet for films with a Shimadzu FTIR spectrophotometer from the Department of Chemistry, BUET, Dhaka, Bangladesh.

4. Ultra-violet spectra

The UV spectra were recorded in dry EtOH with a Shimadzu UV spectrophotometer from the Orion pharmaceuticals Co. Ltd, Dhaka, Bangladesh.

5. Nuclear Magnetic Resonance (NMR) spectra

The NMR spectroscopy is very widely used for the detailed investigation of an unknown compound. With the help of this spectroscopy the structure or pattern of an unknown compound can be set up. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in deuteriochloroform ($CDCl_3$) with a Bruker DPX-400 spectrophotometer using tetramethylsilane (TMS) as internal standard at the Bangladesh Council of Scientific and Industrial Research laboratories (*BCSIR*), Dhaka, Bangladesh and Department of Chemical Engineering, Iwate University, Japan. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra of some of my compounds were recorded in deuteriochloroform ($CDCl_3$) with a Jeol spectrophotometer using tetramethylsilane (TMS) as internal standard at the Institute for Molecular Science laboratory, Okazaki, Japan.

6. Drying

All organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before concentration.

7. Evaporation

All evaporation were carried out under reduced pressure in Buchi rotatory evaporator (W. Germany) with a bath temperature below 40^{0} C.

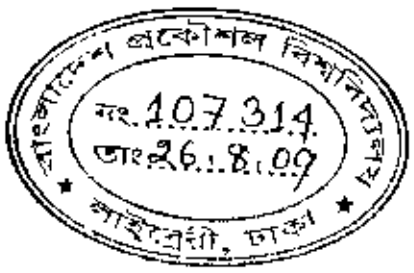
8. Column chromatography

Column chromatography has been successfully applied to separate the individual components (having different R_f values) of mixture obtained from the reaction. This technique was also employed for purification of the product.

A long cylindrical column (70 cm long and 2 cm in diameter usually a burette type is used) made of glass drowns out at one end and packed with glass wool. To the lower constricted end of the column a stop cork was fitted in order to control the flow of the eluant. A seperatory funnel fitted with a specially made quick fit stopper and fitted with the eluant was placed at the top of the column and this served as a store of eluant.

Adjusting the stop cork controlled the flow of the eluant. The column was prepared by slurry method, silica gel being used as the stationary phase; the column was made half filled with various types of solvents as light petroleum, ethyl acetate, chloroform, n-hexane etc. and slurry of silica gel in the chosen solvent was poured into it, so that the packing was compact and uniform.

Making the column as quickly as possible and allowing the solvent to fall drop by drop through the stop cork of the column removed air bubble. The mixture of the components was then placed on the upper surface of the slurry of the silica gel and the mixture was covered in limited area by some amount of dry silica gel. Then the solvent mixture was passed through the column. The fractions were collected in the test tubes about 20 to 30 ml in each at a regular interval of time and respective fractions were detected by TLC. The solvent used for elution was chromatographically pure.



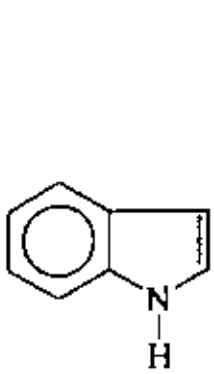
CHAPTER-I

INTRODUCTION

INTRODUCTION

1.1 General remarks

The indole **1** moiety is common to a large number and wide variety of biologically active natural and synthetic compounds[1]. The presence of the indole nucleus in biologically active compounds has led to the development of numerous approaches to its synthesis for over one hundred years[2]. Among the many more recent synthetic targets containing indole moeity, the pharmacologically active Ergot[3] alkaloids **2**, the antitumor agent Ellipticine[4] **3**, Reserpine[5] as a tranquillizer and Vincristine[6] in the treatment of leukemia have been widely known as effective drugs.



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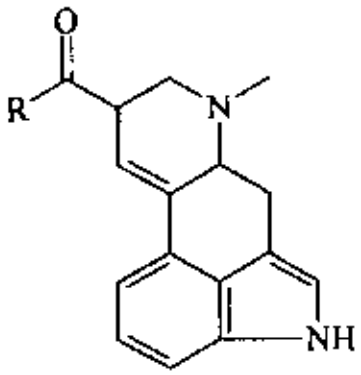

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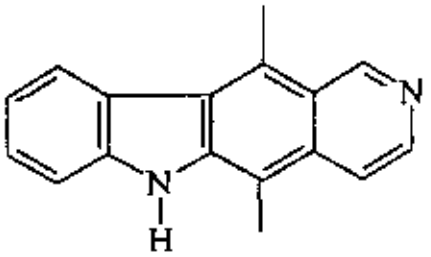
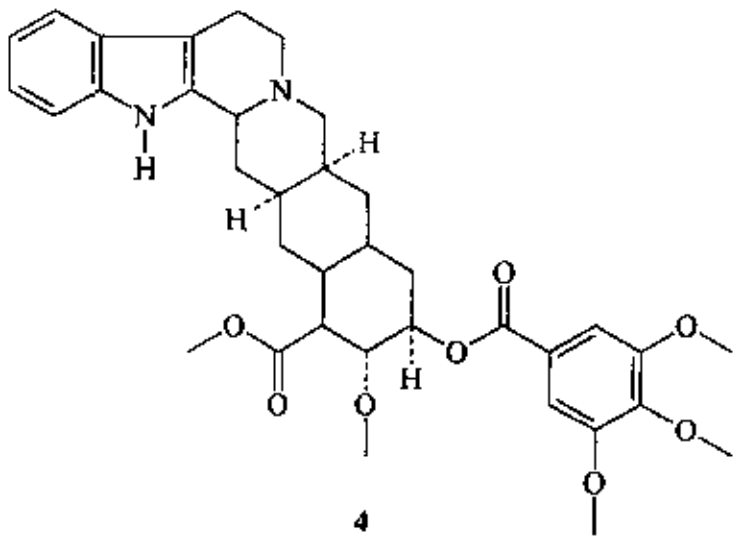


3

The indole skeleton containing Tryptophan[7] **4** is an essential amino acid and as such is a constituent of most protein. Among the synthetic chemotherapeutics the β-indolyl acetic acid derivatives **5**, indomethacin **6**, are of value in the treatment of rheumatoid arthritis[7].



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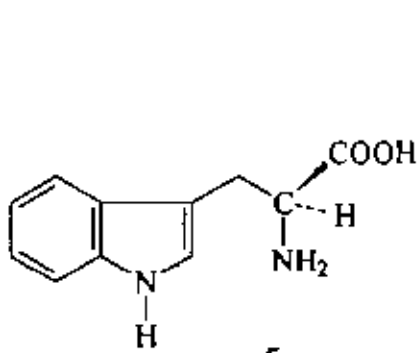

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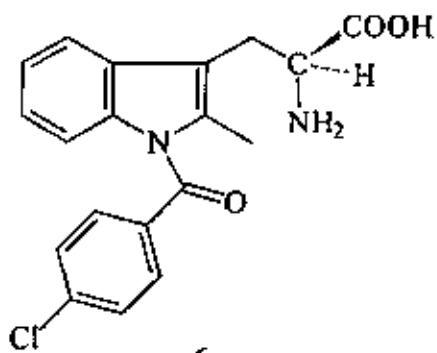


6

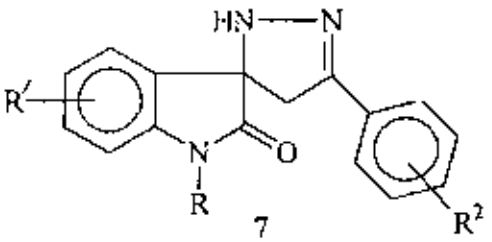
1.2 Importance of indole derivatives

1.2.1 As Acemotherapeutic and pharmacological agents

Indole nucleus has raised great interest in recent years due to their biological activities[1, 8] and pharmacological studies[9]. Indole derivatives have many fold uses. Some of them are mentioned below:

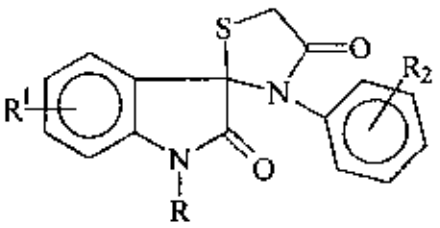
a) As antibacterial agents

Johsi *et al*[10, 11] reported the antibacterial activity of the following compounds **7**, **8** and **9**.



7

R	R^1	R^2
H	H	F
	F	Cl
Me	Cl	F.Cl



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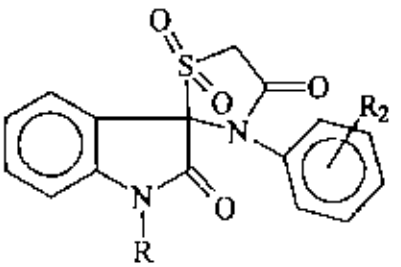

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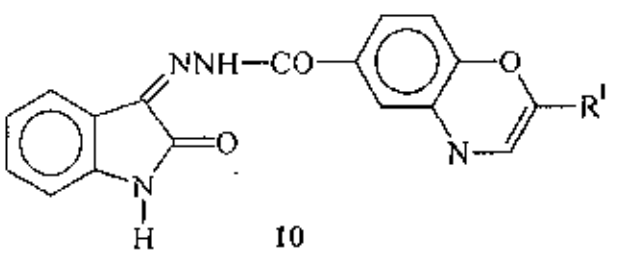
Recently Pani *et al*[12] and Shailaza Rani *et al*[13] also found anti bacterial activity in the compounds **10** and **11** respectively.



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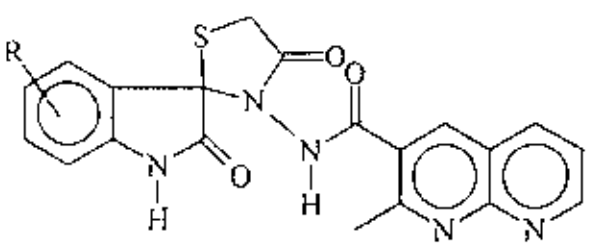
R = H, 5 - Me, 7 - Me, 5 - Br, 7 - Cl,
R^1 = H, Me, Et.

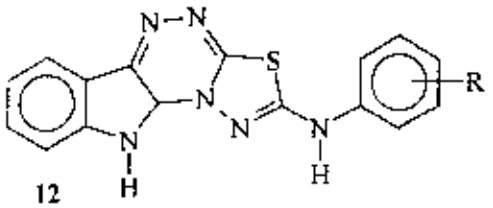


11

R = H, 7-Cl, 5 - Br

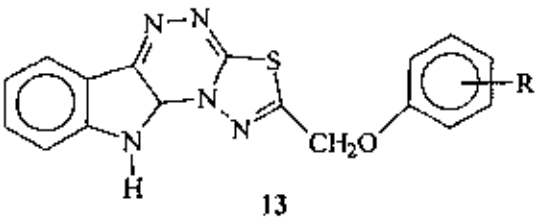
b) As antifungal agents

Sailendra *et al*[14] prepared some important compounds **12-13** from isatin and heterocyclic aromatic hydrazines which showed tremendous antifungal activity.



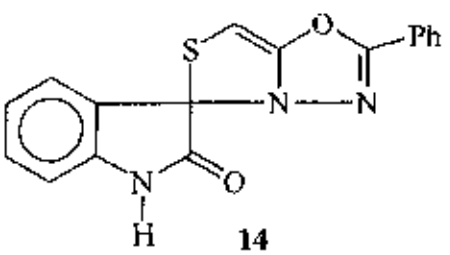
12

R = Cl, CH_3, NO_2, OCH_3



13

Sing *et al*[15] synthesized **14** and **15** have potential antifungal activity.



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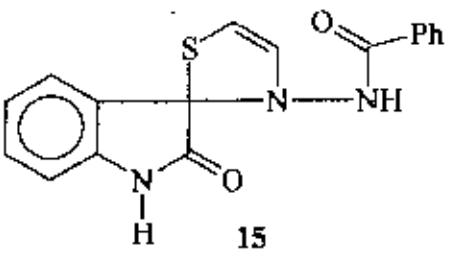

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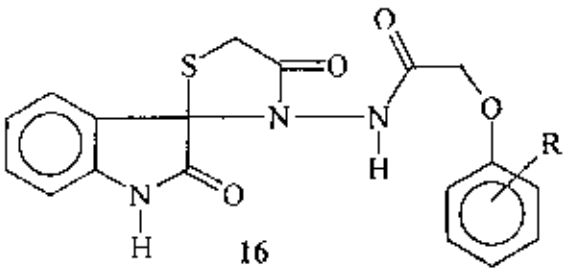
Nizamuddin *et al*[16] Puzari *et al*[17] and Mahmood *et al*[18] also prepared some isatin derivatives which were reported as antifungal agents.



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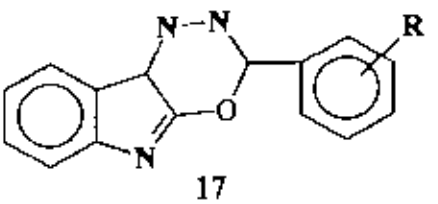

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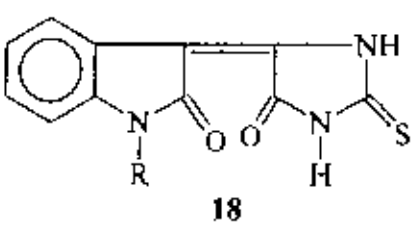
c) As anticancer agents

The immuno-suppressive and anticancerous (carcinoma) activities[19] of some indole derivatives and given below.



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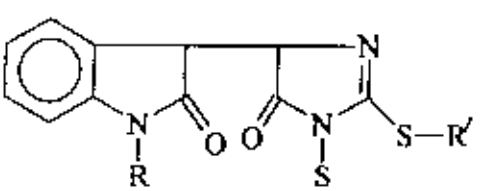
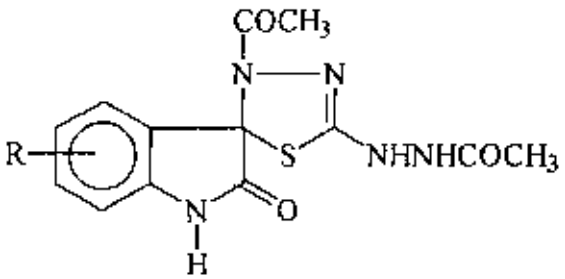


here R = H, Ph **19**

R′ = CH_3, Ch_2Ph, CH_2CO_2Et.

Recently Islam *et al*[20] in collaboration with National cancer Institute (NCI) of USA observed that acylated Δ^2- 1,3, 4- thaidiazoline derivatives of isatin show potential anticancerous activity against a number of cancer cells.

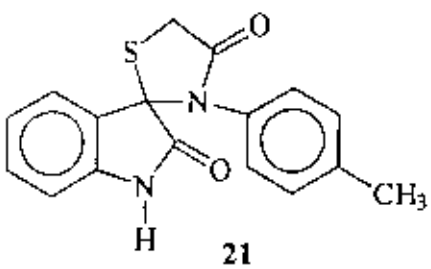


R = Cl, Br, CH_3, NO_2, CO_2H

20

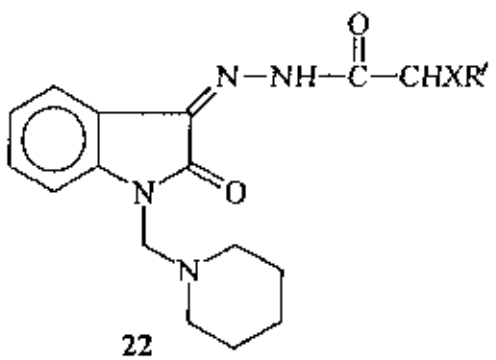
d) As Anticonvulsant agents

El-Gendy *et al*[21] and Gursoy *et al*[22, 23] (1994-19960) prepared the compounds below, showed potential anticonvulsant activities.



21

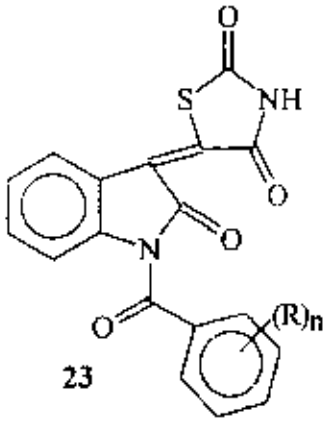
here X = O, S
R = H, Br
R′ = Ph. 3 - MeC_6H_4



22

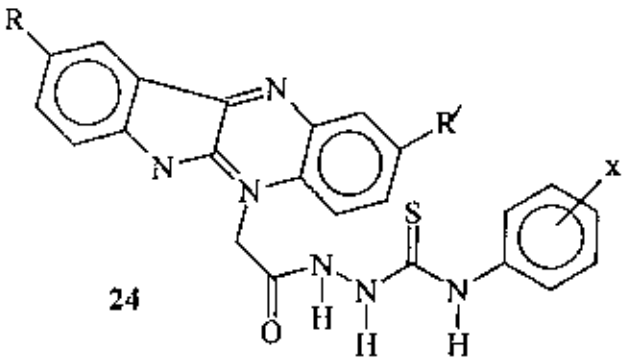
e) As cell migration inhibitors

Nigita *et al*[24] synthesized some compounds from substituted indole which acted as cell migration inhibitors for the treatment of inflammation, atherosclesis etc. The compounds **23-26** were also reported to show significant anti-inflammatory activity[25-29].



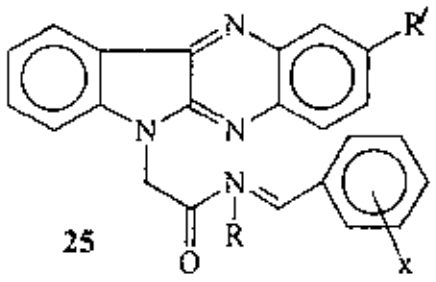
23

R = halogel n = 0 - 5



24

R = halogel n = 0 - 5



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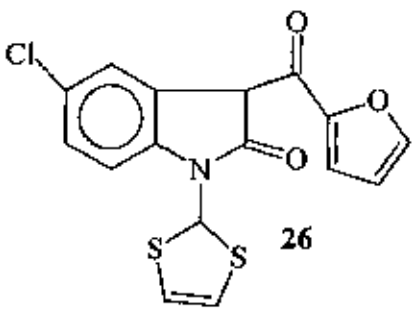
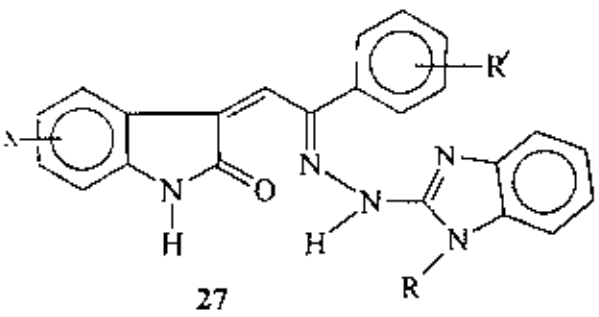


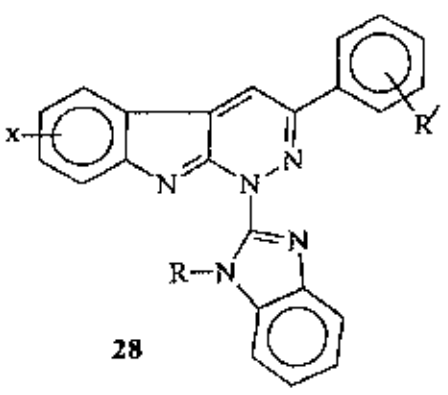
26

f) As insecticidal agent

Sharma *et al*[30] synthesized the following compounds of indole which showed insecticidal activities.



27



28

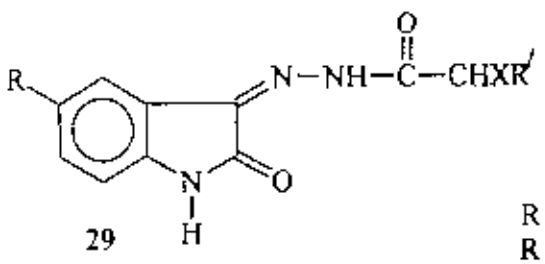
x = H. F.
R = H, Ph.
R′ = halo-C_6H_4, Ph

g) As antimicrobial agents

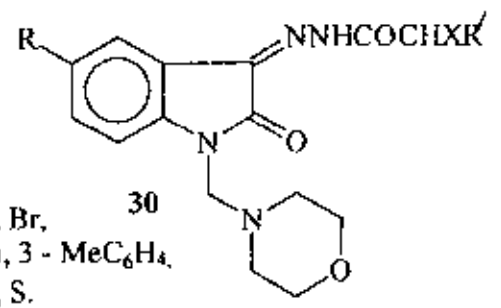
Mohon *et al*[31] in 1989 and 1995 and Patel *et al*[29] synthesized and studied some new heterocycles frnm indole derivatives as potent antimicrobial agent which are designated as **25** and **26.**

h) As antiviral agents

The vivo antiinfluenza[32] virus and antivaccinia[33] virus activity of biologically active compounds were detected. Several drugs dose (DL- nofirmocin), NSC, 72942) were tested against that virus. Isatin β-thiosemicarbazone (NCS 721) also used as reproducible activity against vaccinia virus.



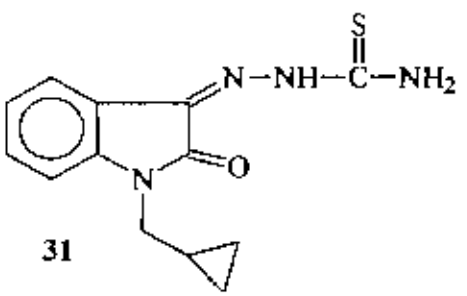
29



30

R = H, Br,
R = Ph, 3 - MeC_6H_4,
X = O, S.

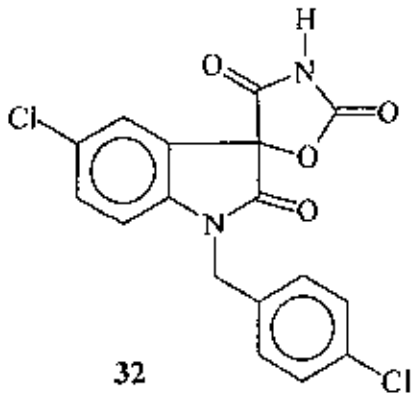
Some *N*-cyclopropane derivatives. **31** of indole and its β-thiosemicarbazones display antiviral activity



31

i) As antidiabetes agents

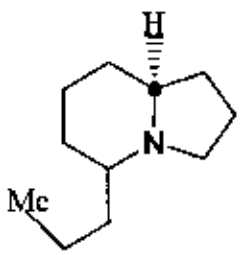
The following spiro compounds **32** can inhibit the enzymatic activity of aldose reductase and hence it is used as antidiabetes[34].



32

j) As antituberculosis agents

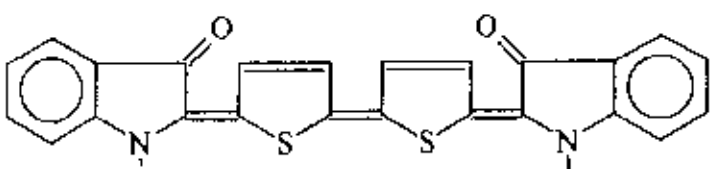
The indolizidine and indolizine **33** frameworks represent a fundamental and important class of heterocycles, which is used as antituberculosis agents, histamine H_3 receptor antagonists, and microtubule inhibitors[35].



33

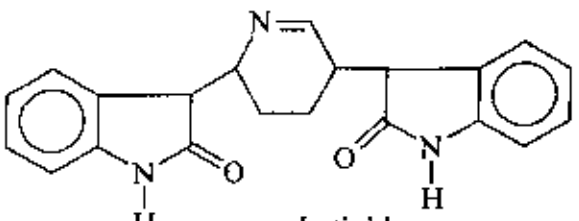
1.2.2 As dying agents

Baeyer[36] obtained a blue dye indophenin **34** by treating isatin with concentrated H_2SO_4 and crude benzene.

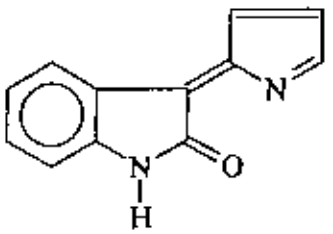


34 indophenin

The isatin blue **34a** and Pyrrole blue **34b** were synthesized from indole derivatives as powerful dying agent.



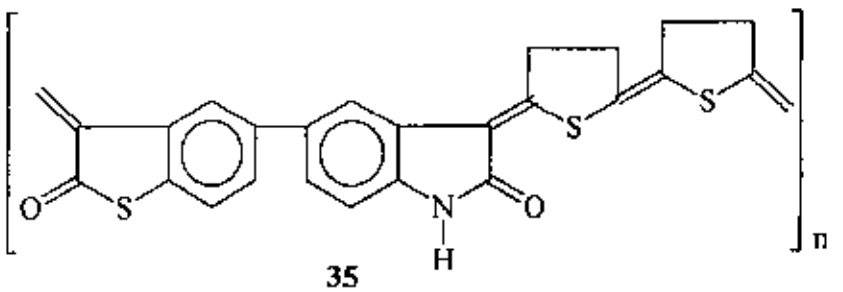
34a Isatin blue



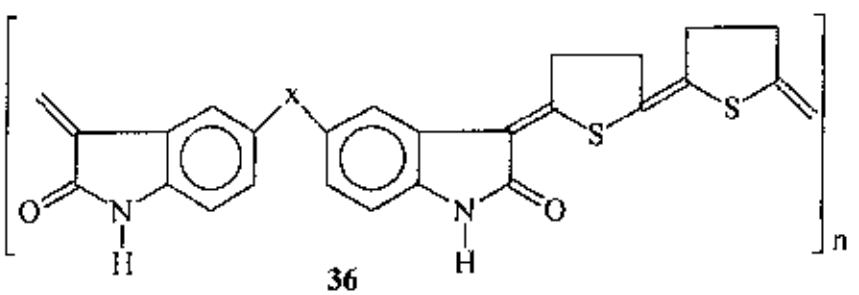
34b Pyrrole blue

1.2.3 As polymeric substance

A series of polyindophenines have been prepared by the reaction of isatin with thiophene under acidic conditions[37].



35



36

These polymers could be reduced into the leuco form and they showed some conductor properties.

1.2.4 As enzymatic agents

In the dehydrogenation of amino acids, isatin possesses an apparent enzyme like activity. When α-amino acid is heated with isatin in aqueous solution, benzaldehyde[38] is produced.

In a series of organic catalysis, Langenbeck[39] reported that certain isatin and oxiindole derivatives possess enzyme like activity particularly in the dehydrogenation of amino acid.

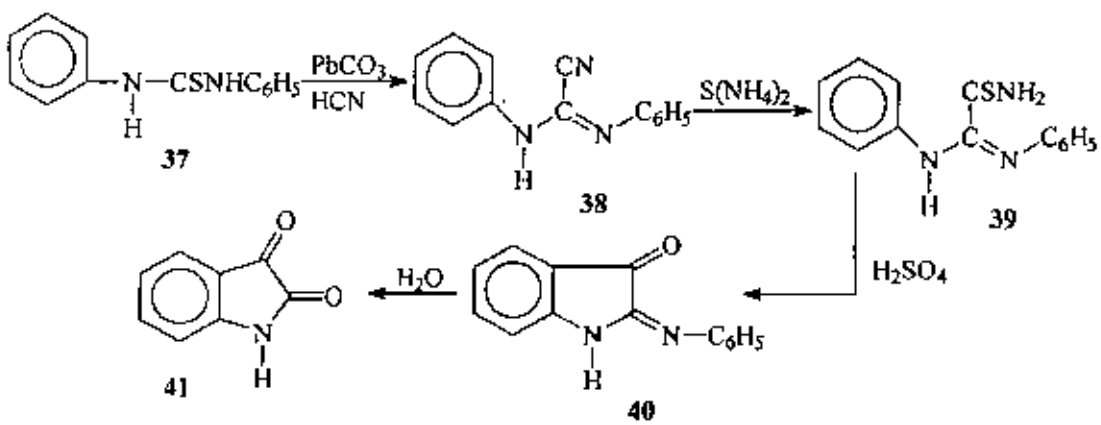
1.3 Synthesis of indole and substituted indole

The presence of the indole nucleus in a wide variety of biologically active compounds has led to the development of the approaches to its synthesis.

A few of the approaches of the synthesis of indole derivatives are mentioned below.

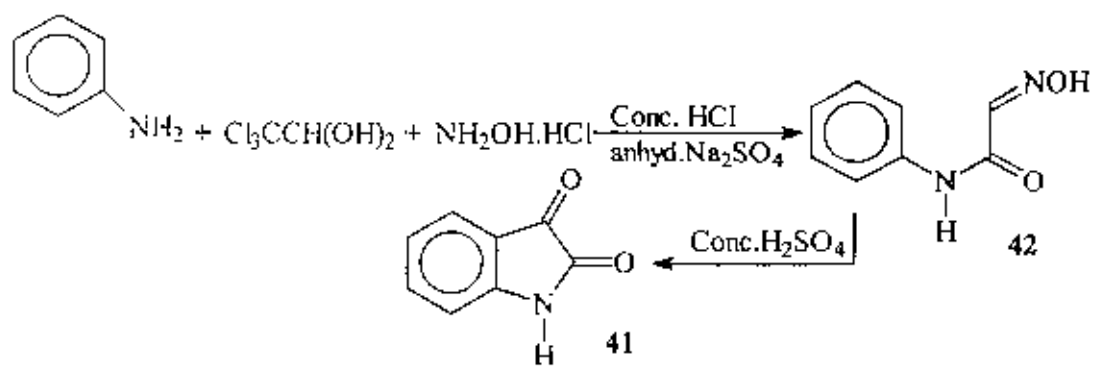
Sandmeyer procedure

The most important and mostly used method was devoled by Sandmeyer. There are two process[40]. In the first process, thiocarbanilide is treated with lead carbonate and hydrogen cyanide and converted into nitrile-anilide. This on treatment with ammonium sulphide yields thioamide. It produces isatin (1) by cyclization[40] with sulfuric acid and subsequent hydrolysis.



Scheme-1

The second method (sendmeyer)[41, 42] involves the formation of a Isonitrosoacetanilide[42] from the condensation of aniline with chloralhydrate and hydroxylarvine hydrochloride in presence of Na_2SO_4. Cyclization of **42** with concentrated Sulfuric acid gives indole derivatives.



Scheme-2

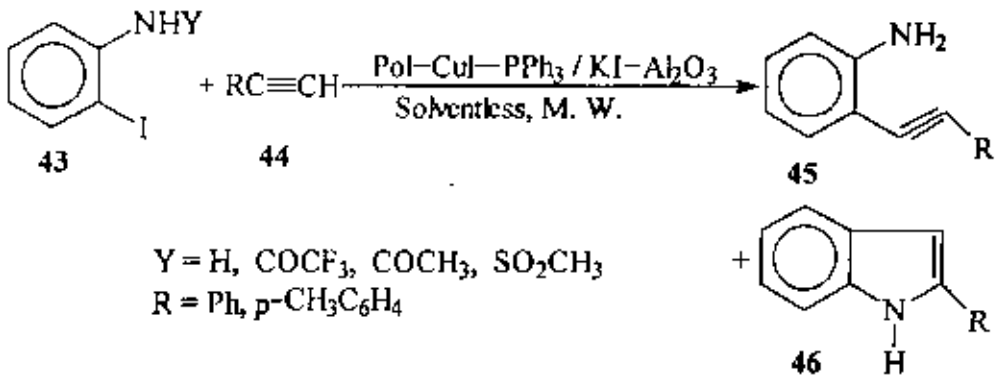
1.3.1 Palladium complexes in the synthesis of indole

Palladium complexes have been used in the synthesis of organic compounds for over twenty years. Palladium exists in two stable oxidation states such as Pd (II) and Pd (0).

Indole can be prepared by many ways through palladium-mediated reaction. Some of them are given below.

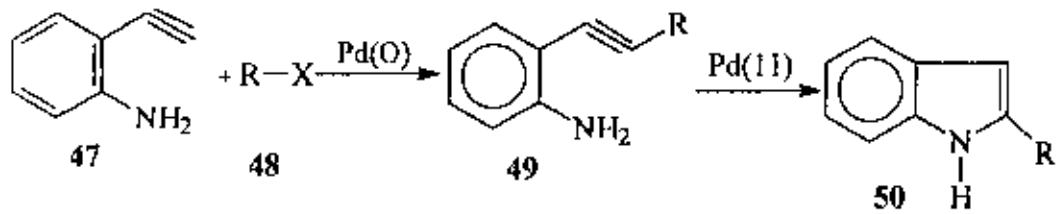
1.3.1.1 Coupling cyclization reaction

Coupling cyclization reaction[43] can be used to the synthesis of indoles. The reactions of *o*-iodoaniline, *o*-iodoacetanilide, *o*-iodo-trifluoroacetanilide, and *N*- (o-iodophenyl)-methanesulfonamide with terminal alkynes were investigated in the presence of Pd-CuI-PPh_3 / KI-Al_2O_3 and under solvent free conditions and microwave irradiation. A mixture of coupling and coupling-cyclization products were obtained when iodoaniline (2 equiv) was allowed to react with phenyl acetylene. When *o*-iodo- acetanilide was used instead of *o*-iodoanilines only indole product formed (41%). The use of (*o*-Iodophenyl)-methane sulfonamide resulted in the exclusive formation of the indole in good yield.



Scheme-3

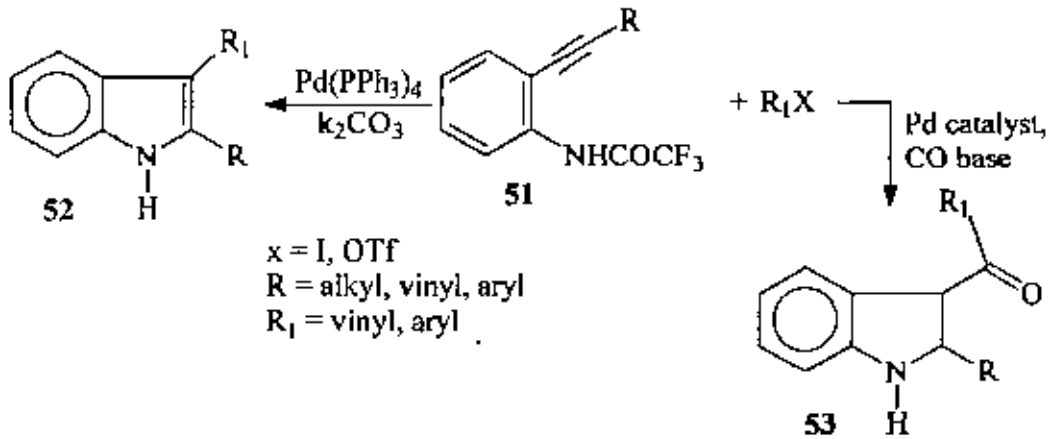
The Palladium (0) catalysed coupling of aryl and vinyl trifluoride or halides with 2-ethynyaniline, followed by palladium (II) catalyzed cyclization step, provides an efficient and very versatile procedure for the synthesis of functionalyzed-substituted indoles[44].



Scheme-4

The use of palladium catalyst in the development of new routes to indole derivatives[45, 46, 47] was investigated as shown in the **scheme-5.**

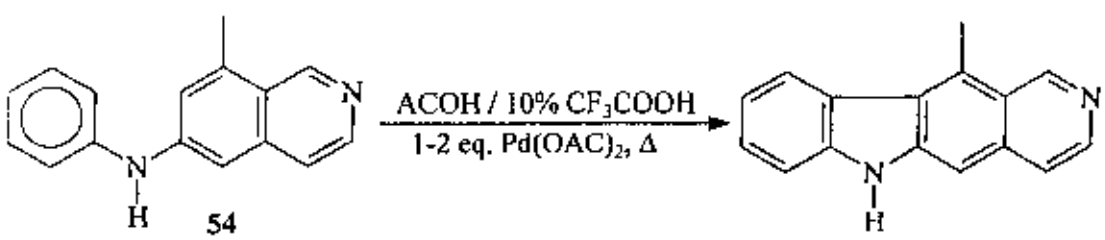
3-Acylindole has been reported to be important therapeutic agents and useful intermediates[48] for the preparation of pyridocarbazole alkaloids.



Scheme-5

1.3.1.2 Coupling of arenes by palladation

Although the coupling of arenes by direct palladation is not an efficient process, it has been used in several cases to synthesize functionalized indole ring system. Ellipticine **3** was made by this process[49].



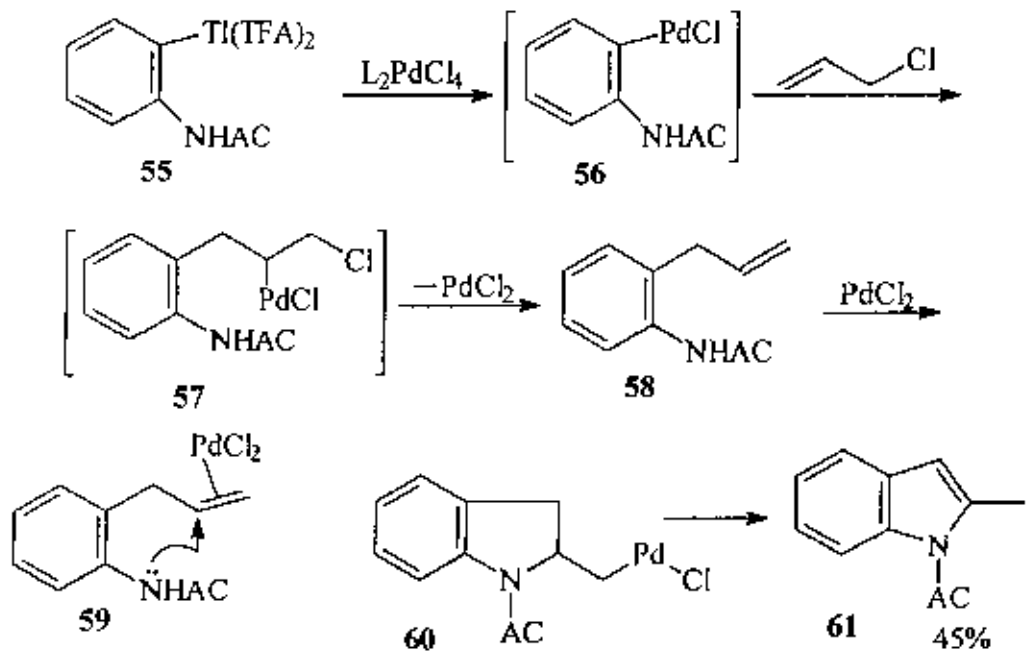
Scheme-6

1.3.1.3 Palladium (II) catalysed amination of olefins

O-Allyl anilines, which contain amine and olefin in the same molecules, were efficiently converted into 2- methyl indoles using palladium (II) catalysis[50, 51]

(Scheme-1). This process was thought to involve co-ordination of the olefin to Pd (II) followed by intramolecular amination.

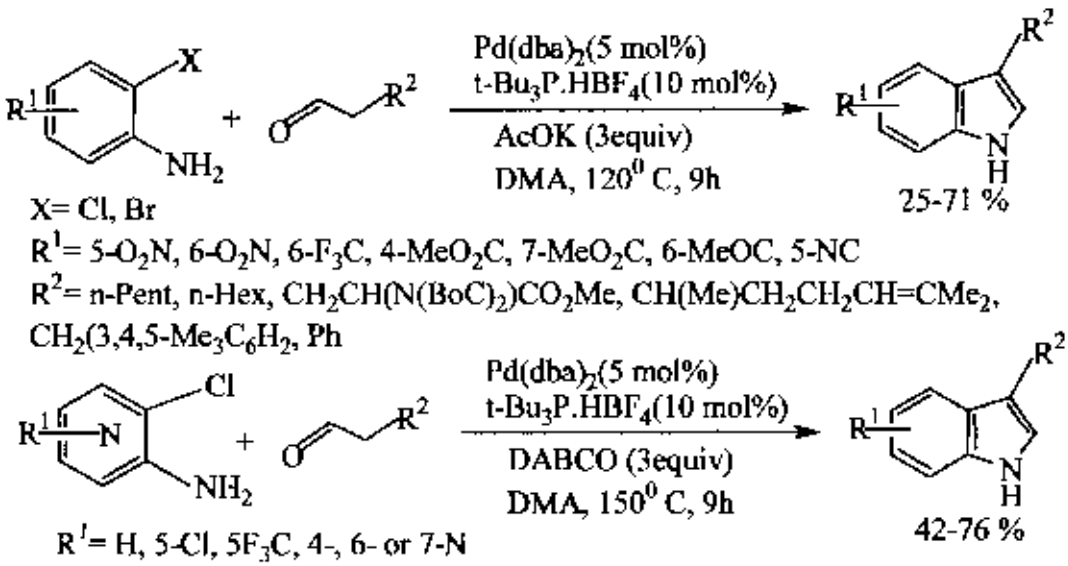
Indoles such as **61** were also produced in a stoichometric reaction including transmetalation, insertion, elimination and amination of olefins[52] in **scheme-7.**



Scheme-7

1.3.1.4 Palladium Catalyzed Synthesis of Indoles by Direct Annulation

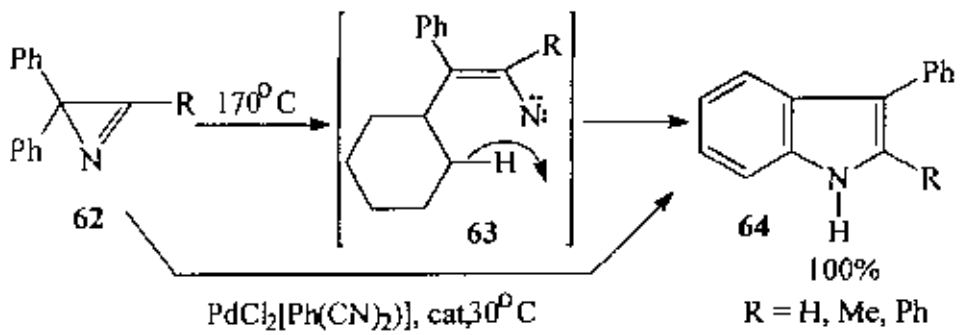
Palladium-Catalyzed Indole and Azaindoles Synthesis by direct annulation of electron-poor *o*-Chloroanilines and *o*-Chloroaminopyridines with Aldehyde was reported[53]. Both chloro- and bromoanilines might be used with equal efficiency. However, low yields wee obtained when ortho-substituted anilines were used.



Scheme-8

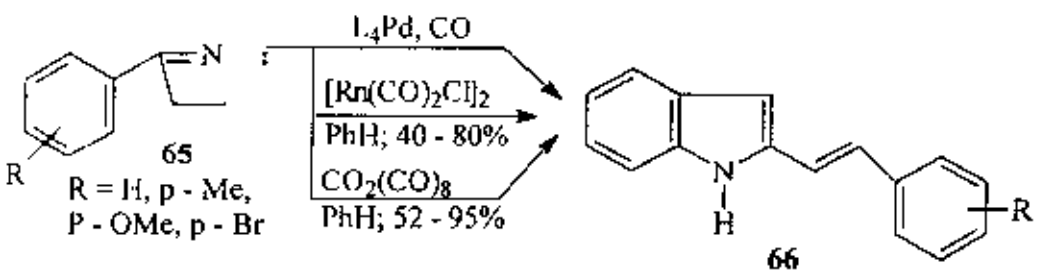
1.3.1.5 Palladium (II)-catalyzed (and other metal catalyzed) Reactions of Azirines

Thermolysis of phenyl azirines **62** at temperature above 170° C produced indoles, via a nitrene intermediate. Palladium (II) chloride was used as catalyst in this process, permitting it to ensure at 30° C[54].



Scheme-9

Rhodium (I), Palladium (0), and Cobalt (0) complexes catalyzed a puzzling dimerization of azirines **65** to produce indoles in variable yields[55-58].

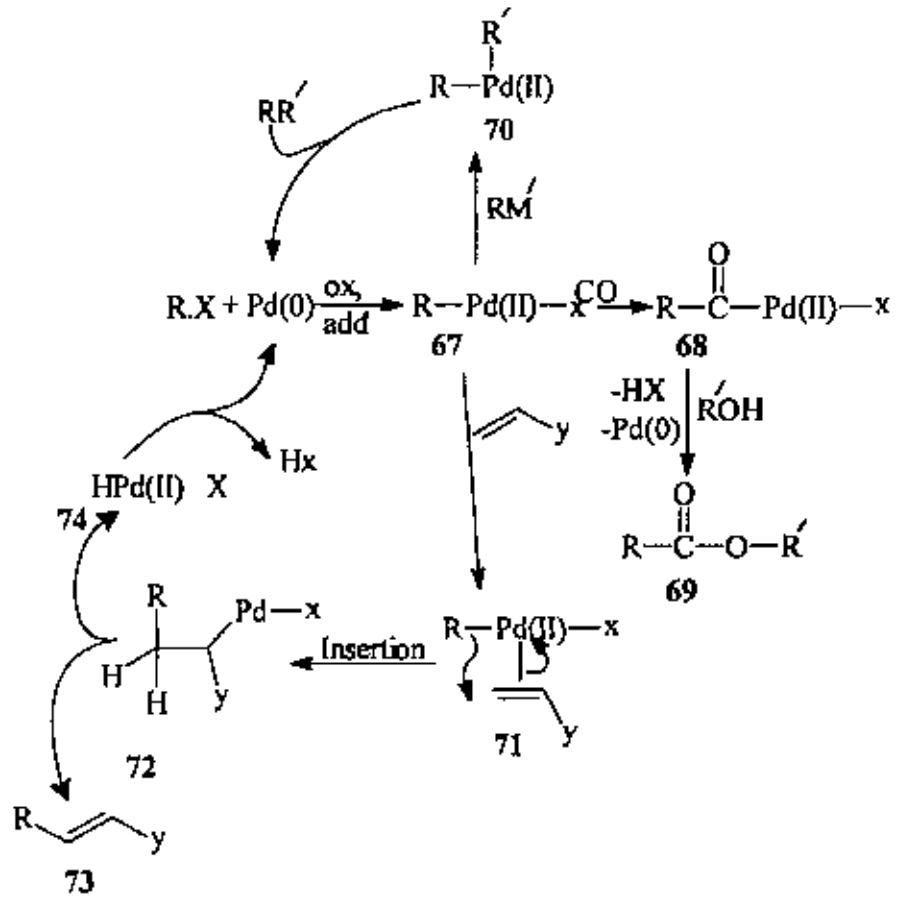


Scheme-10

1.3.2 Palladium (0) and Nickel (0) complex chemistry

While palladium (II) salts are electrophilic reagents, which react with olefins and arenes, palladium (0) complexes are strong nucleophiles and are most reactive toward organic halides. The two most common, commercially available complexes of palladium (0) catalysis are $Pd(PPh_3)_4$ and $Pd(dba)_2$ (dba= dibenzylideneacetone), which is converted into $Pd(PPh_3)_4$,when treated with triphenylphosphate.

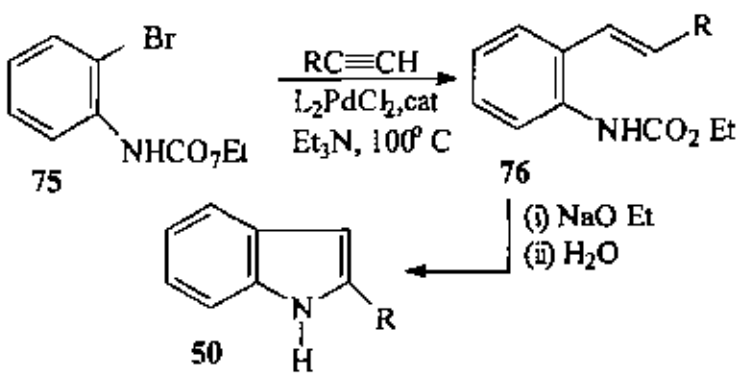
Both of these have been extensively used as catalysts in organic synthesis. However, it is frequently more convenient to generate palladium (0) catalysts insitu by reducing palladium (II) catalysts precursors. Thus, treatment of $Pd(PPh_3)_2Cl_2$ with diisobutylaluminium hydride or with CO or triethyl amine will generate the catalytically active Pd(0) species "Pdl_n".Perhaps the most extensively used palladium (0) catalyst precursor, however in palladium (II) acetate, which is readily reduced insitu by a range of compounds including carbon monoxide, olefins, phosphates and tertiary aliphatic amines such as triethyl of tri-*n*-butylamine[58]. This causes some confusion in the literature, since palladium (0) catalysis is involved but palladium (II) acetate appears in all the equations. Invariably, some reducing agent is present in these systems and palladium (0) catalysis is indeed involved.



Scheme-11

1.3.2.1 Palladium (0)- catalyzed Alkynylation of Bromoanilines

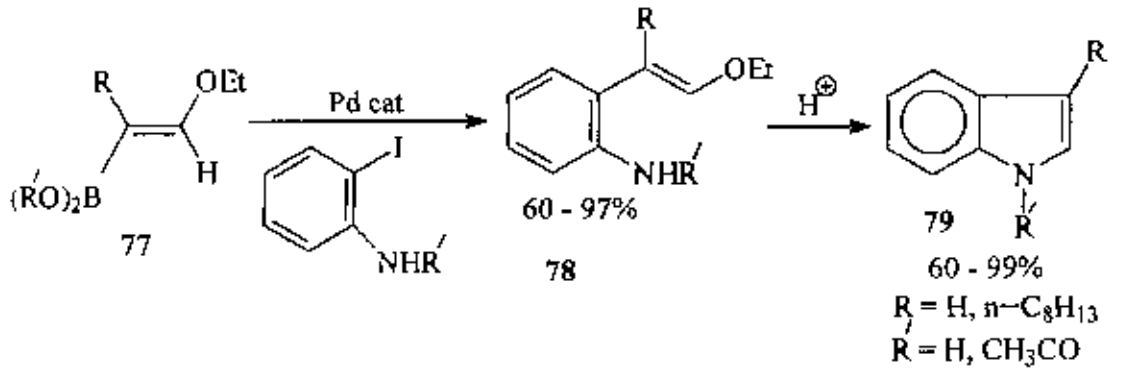
O-Alkynyl anilines such as **76**, made by palladium (0) catalyzed coupling of alkynes with *o*-halo aniline precursors[59-60] were readily cyclized to indoles **50**.



R = H, Bu, Ph, 65 – 93%

Scheme-12

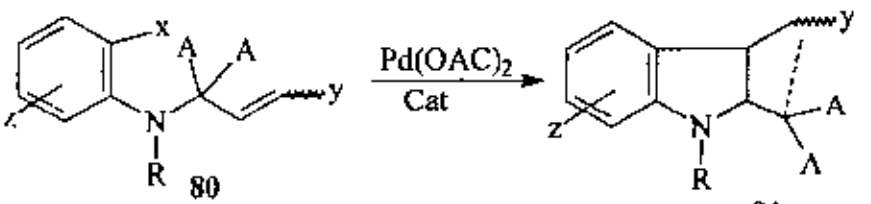
In a related process, hydroboration of ethoxyacetyline gave a vinylborane **77** which under went Pd (0)- catalyzed oxidative addition / transmetalation to produce an indole precurssor[61] **79.**



Scheme-13

1.3.2.2 Palladium (0) catalyzed cyclization of 2- halogenated *N*-allyl-, *N*-vinyl, or *N*-Arylanilines to indoles.

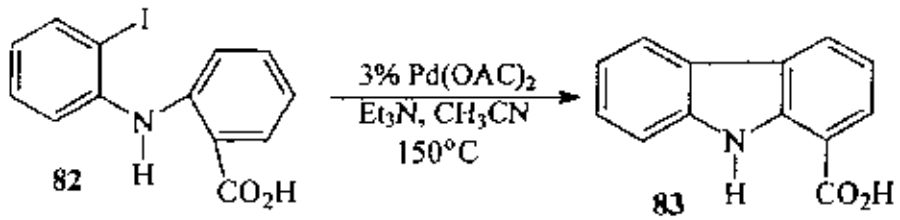
O-Bromoanilines were easily *N*-allylated, producing substrates ideally suited for a Pd (0) catalyzed oxidative addition / olefin insertion approach to the indole ring system. As a conseqnence, this route has been extensively developed. Both activated[62-64] and simple olefines[64] inserted efficiently. The insertion product **80** of simple olefins produces good yielded indoles **81** with catalytic amounts of palladium.



A	R	X	y	z	yields[%]
O	$PhCH_2$	Br	Ph / CO_2Me	H	50–73
H	Ac	Br	CO_2Me	H	73
H	H	I	H	-5—Me,5,6(OMe)$_2$ / 5—CO_2Me,H	50–87

Scheme-14

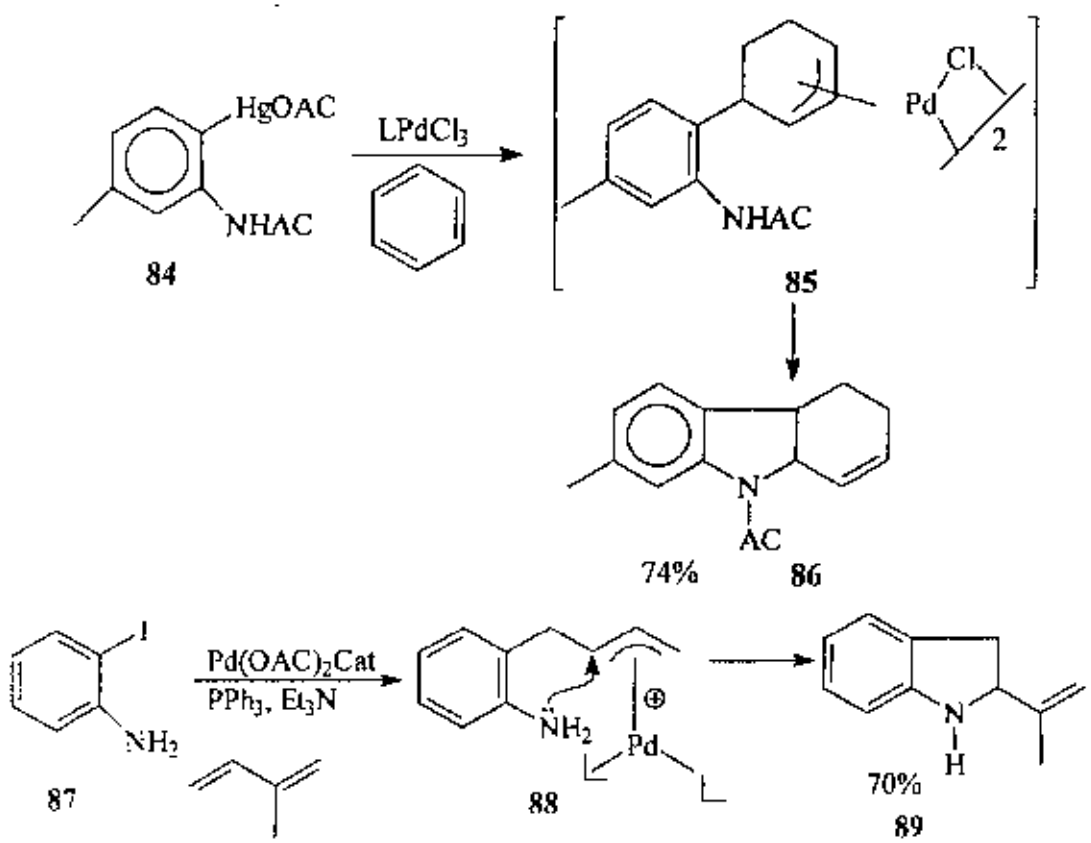
Carbazoles[65] were produced in good yield from diphenylamine such as **83** utilizing oxidative addition / insertion chemistry.



Scheme-15

1.3.3 π- Allyl palladium complexes in the synthesis of indoles

Formation of the indole ring via π- Allyl palladium (II) intermediates[66, 67] e.g. **85** and **88** is relatively uncommon. These two examples involve diene insertion into σ-arrylpalladium (II) species.

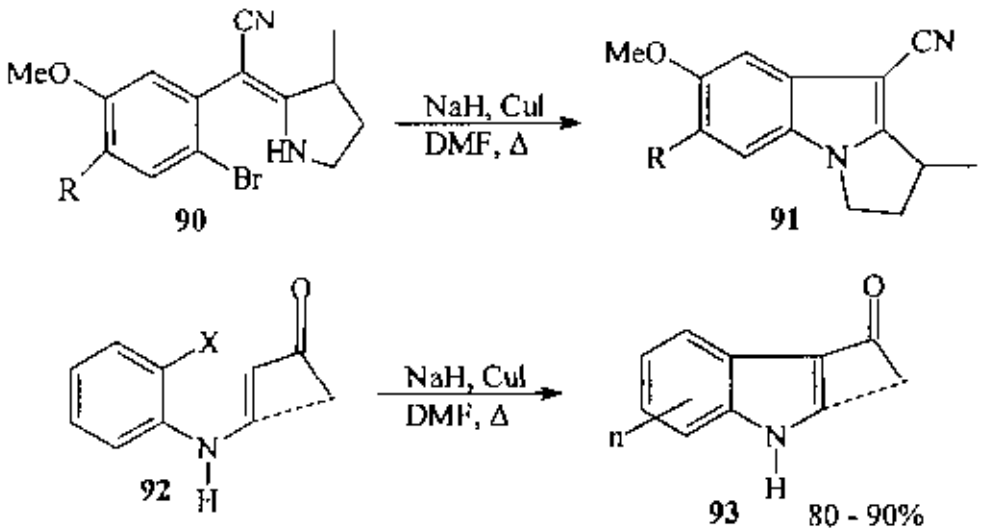


Scheme-16

1.3.4 Other Transition Metals in the Synthesis of indoles

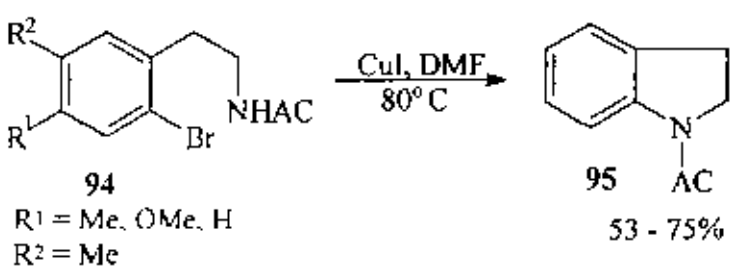
1.3.4.1 copper (I)-catalyzed Cyclization and condensation

Although palladium is by far the most extensively used transition metal for the synthesis and functionalization of indoles, many others have found at least limited use in this regard.



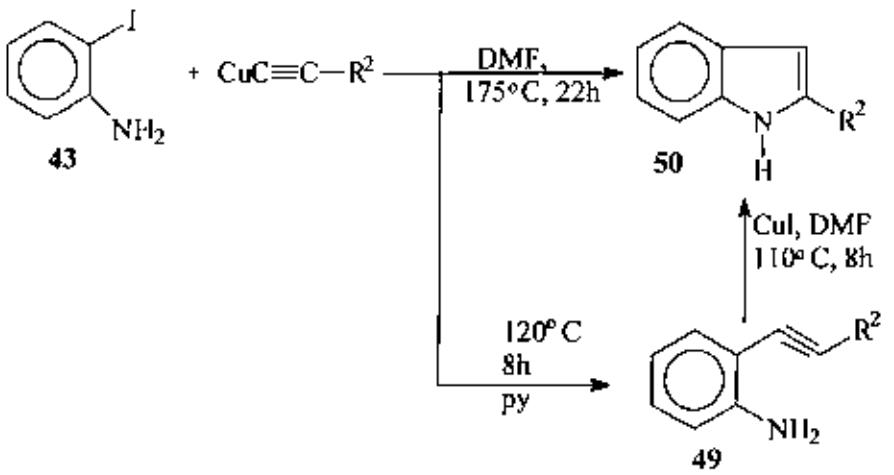
Scheme-17

For instances copper (I) salts have been known to catalyze the reactions of nucleophiles with aromatic halides (e.g. the Hurtly reaction). Thus *O*-haloaryl enamines such as **91,** (R= Me, OMe, H)and **92** cyclized to indoles in the presence of copper (I) iodide in excellent yield[68, 69]. Under similar conditions enolates condensed with o-iodoaniline to produce indoles[70]. *O*-Haloacetamides[71] (e.g. **94**) also cyclized to indole derivatives under these conditions, copper (I) oxide catalyzed the cyclization of *o*-isocyano-phenylacetones to indoles[72].



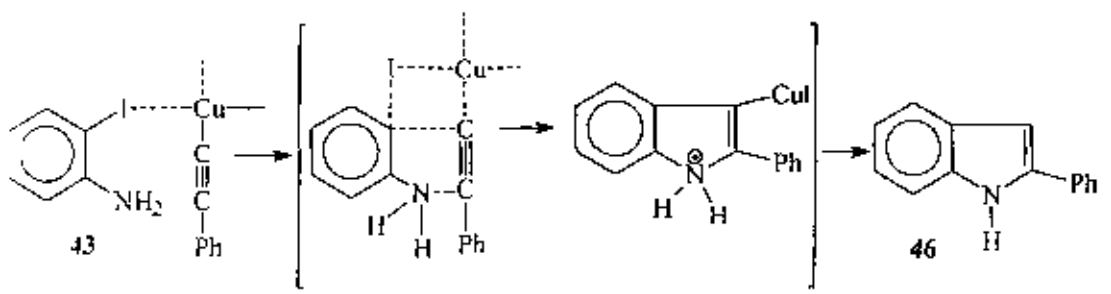
Scheme-18

In fact the reaction between 2- iodoaniline and cuprous phenylacetylide (R^2= ph) was found to be markedly solvent dependent. When DMF was used 2-phenylindole R^2 = ph was obtained in 89% yield. When pyridine was used 2- alkynylaniline was obtained as the exclusive product. However, it could be cyclized to 2- phenylindole by warming with catalytic amount of cuprous iodide in DMF at 110^0 C for 8 hours **(Scheme-19).**



Scheme-19

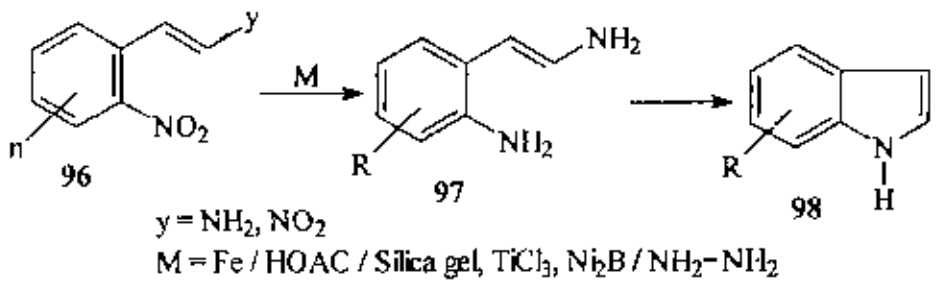
The reactivity of halides was found to be in the order I> Br> Cl. Furthermore the presence of *N*-ethyl piperidine was found to decrease the efficiency of the syntheses, indicating that strong co-ordination of copper could mask the ability of the metal to effect the initial alkylations or to co-ordinates with the acetylene[73]. The substitute of halide and cyclization were thought to occur within the same copper complex[74] **(scheme-20)**.



Scheme-20

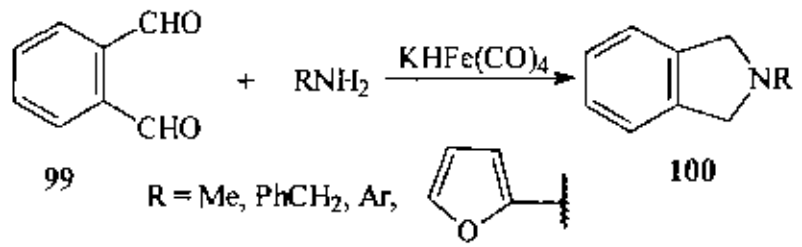
1.3.4.2 Reductive Cyclizations Using Low-Valent Transition-Metal Compounds.

Using low valent transition metals to reduce aromatic nitro groups to amines carried out a number of indole syntheses. Which could then cyclize with electrophilic groups in the ortho position to form indoles. These typically involved o-nitro aryl enamines 96 and reducing agents such as iron[75], titanium (III) chloride[76] and nickel boride[76].



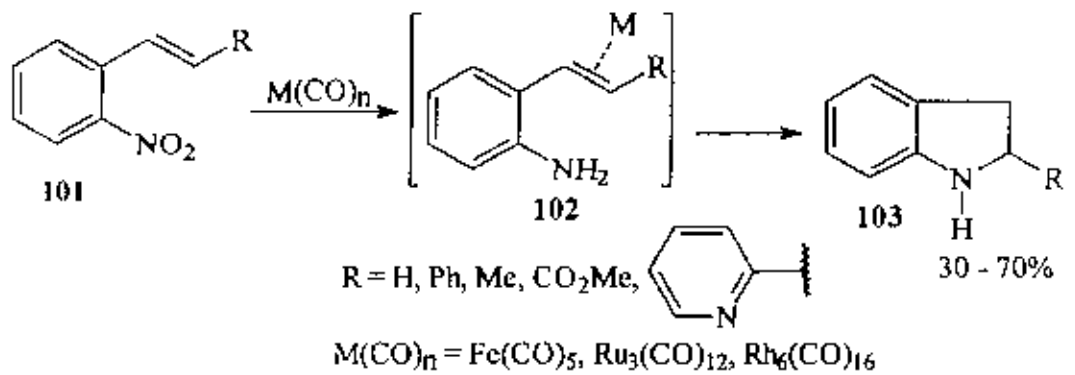
Scheme-21

Dihydroisoindoles **100** were produced in excellent yield by $KHFe(CO)_4^-$ promoted reductive amination of *o*-dialdehydes[77].



Scheme-22

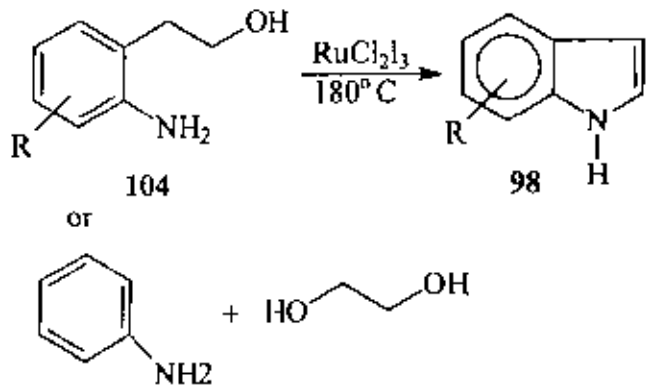
Finally, *o*-nitrostyrenes such as **101** were reductively cyclized to indoles by metal carbonyls, in a process that must involve olefin activation by the metal, as well as nitro group reduction[78].



Scheme-23.

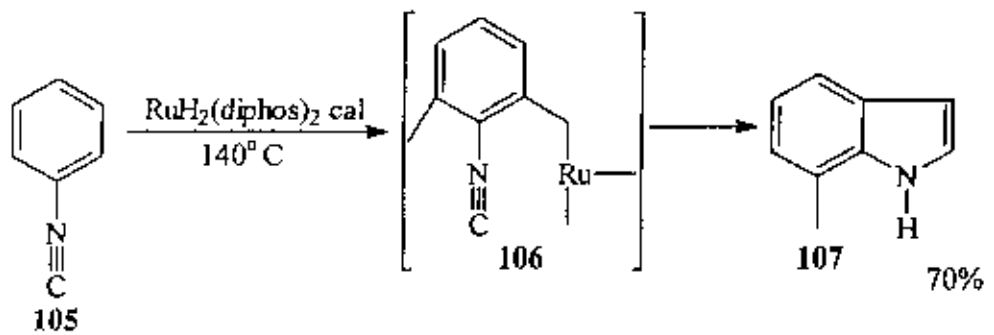
1.3.4.3 Ruthenium (II)-or Palladium catalyzed oxidative cyclization

Ruthenium (II) chloride- catalyzed oxidation of alcohols has been used to indoles in modest yield, although the conditions are somewhat severe[79, 80].



Scheme-24

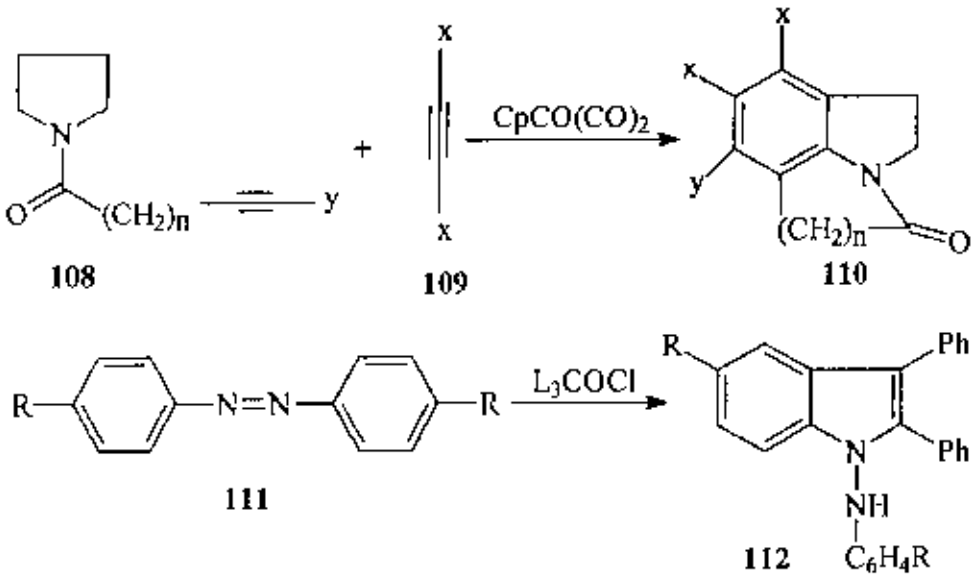
2,6- Dimethyl phenyl / isocyanide was converted in to 7- metyl indole **107** in a process which must have involved C-H activation by the ruthenium (four catalytic cycles per $[RuH_2(diphos)_2]$[81].



Scheme-25

1.3.4.4 Cobalt - Catalyzed Cyclotrimerization Reactions

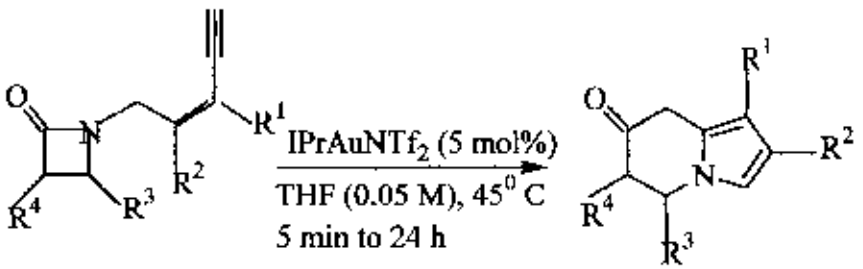
The cobalt catalysed cyclotrimerization of alkynes and cocyclotrimerization of alkynes and alkenes have been extensively developed for use in organic synthesis[82]. The synthesis[83] of compound **110** exemplify the use of the later in the synthesis of indoles. Cobalt (I) complexes also catalyzed the addition of alkynes to diazenes to produce *N*-aminoindoles[84] **112.**



Scheme-26

1.3.4.5 Gold- Catalyzed Synthesis of Indolizin-7-ones

A gold catalyzed synthesis of 5,6- dihydro-8H-indolizin-7-ones from *N*-(Pent-2-en-4-ynyl)-β-lactams has been reported[85].



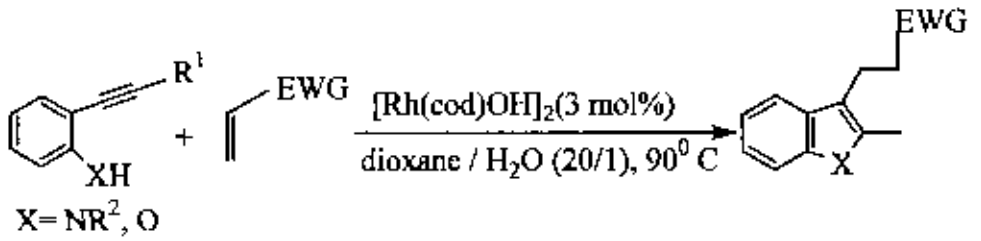
R^1= H, n-Pr, CH_2CH_2OBn, Cy
R^2= H, n-Hex, Ph
R^1-R^2=-$(CH_2)_5$-, -$(CH_2)_6$-
R^3= H, Me, Et, Bn
R^4= H, Me, Et

60-90 % yield

Scheme-27

1.3.4.6 Rhodium (I)- Catalyzed Cyclization Reaction

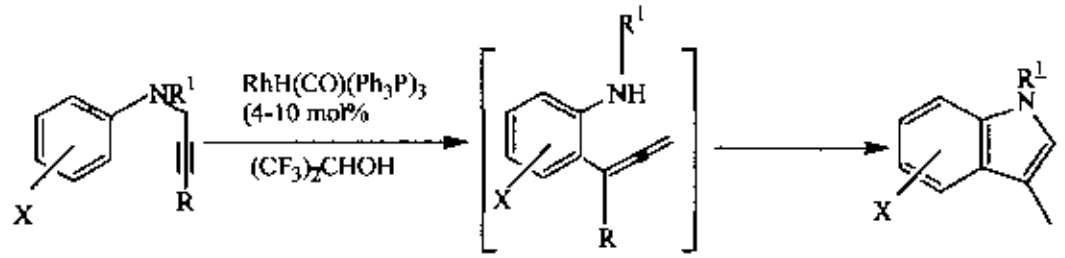
A rhodium- catalyzed cyclization of *O*-alkynylphenols and anilines followed by intermolecular conjugate addition that succeeds with alkyl and aryl alkynes[86]. In this reaction, 2,3- disubstituted benzofurans or indoles are obtained in one pot in good to excellent yields.



Scheme-28

1.3.4.7 Rhodium (I)- Catalyzed Amino-Claisen Rearrangement

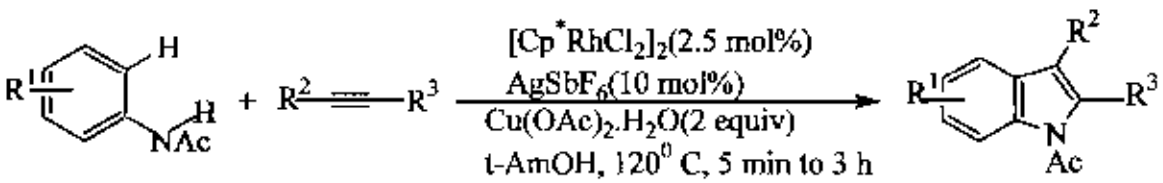
Mild and facile preparations of 2-substituted or 2,3-disubstituted indole compounds were achieved by $RhH(CO)(Ph_3P)_3$(4-10 mol%)- catalyzed reaction of *N*-propargylanilines in hexafluoroisopropyl alcohol(HFIP)[87].



Scheme-29

1.3.4.8 Rhodium (I)- Catalyzed Oxidative coupling Reaction

Indole was syhthesized via rhodium catalyzed oxidative coupling of acetanilides and internal alkynes[88]. The current method takes advantages of a C-H activation event to provide indoles from simple and inexpensive anilines.

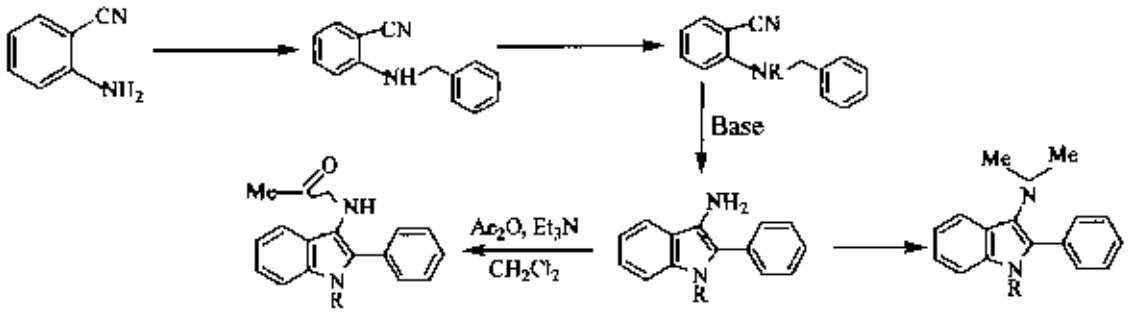


R^1= 4- OMe, 5-OMe, 3,5-di-OMe, 4-F, 4-Cl, 4-CO_2Me, 6-Me
R^2= Me, n-Pr, n-Hex, Ph
R^3= n-Pr, n-Hex, Ph, thiophen-2-yl, N-tosylindol-5-yl

Scheme-30

1.3.4.9 Base mediated intramolecular condensation

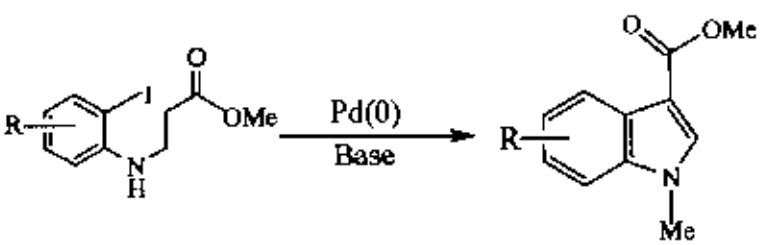
An efficient base-mediated intramolecul;ar condensation of 2-(disubstitnted amino)-benzonitriles to 3- aminoindoles has been reported by Churl Min Seong et al[89]. 3-aminoindoles was obtained from 2-(disubstituted amino)- benzonitriles using NaH as a base in DMF at 80° C.



Scheme-31

1.3.4.10 Pd (0)- Catalyzed Intramolecular Reaction

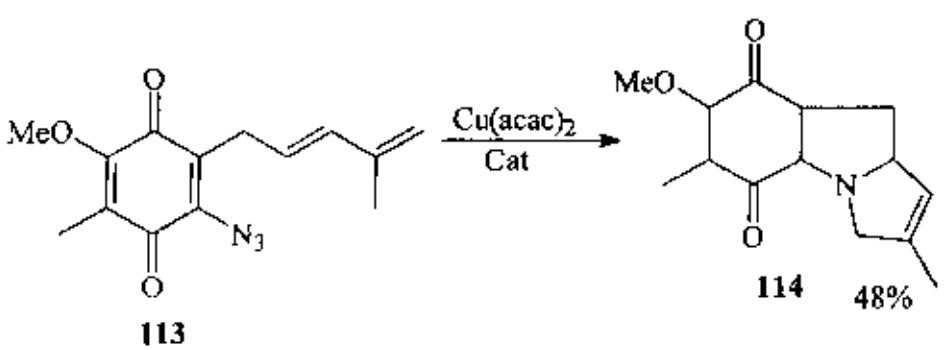
Daniel *et al*[90] synthesized Indole-3-carboxylic acid derivatives by Pd (0)- Catalyzed Intramolecular α-arylation of β-(2-Iodoanilino) esters. β-(2-Iodoanilino) esters undergo intramolecular α-arylation in the presence of $Pd(PPh_3)_4$ and potassium penoxide. The reaction is a useful methodology for the preparation of indole-3- carboxylic acid ester derivatives.



Scheme-32

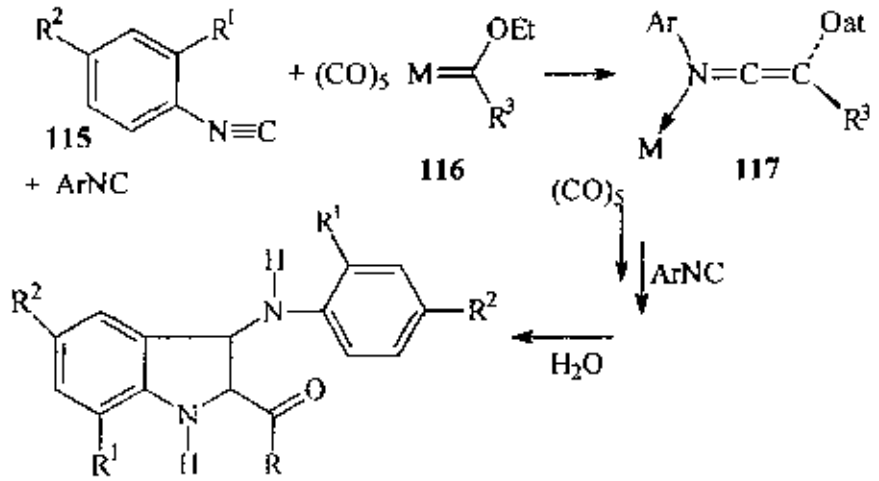
1.3.4.11 Miscellaneous Indole Synthesis

The copper catalyzed decomposition of aryl azides to produce nitrenes has been used to synthesize a number of pyrrolindolequinones[91] **114**



Scheme-33

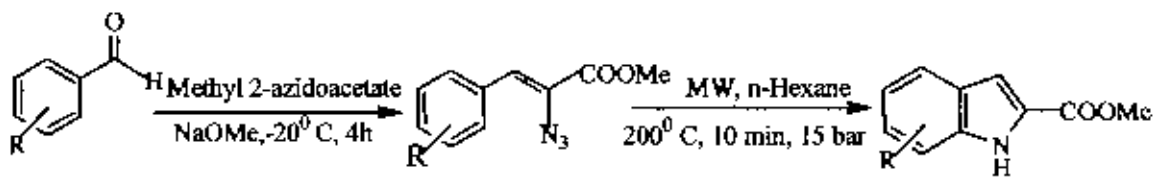
Aryl isocyanides were combined with carbene complexes (M= G, Mo, W) to produce indoles, via kelenimine complexes[92,93]**118.**



Scheme-34

1.3.4.12 Indoles via microwave-assisted Hemetsberger- Knittel synthesis

The Hemetsberger-Knittel indole synthesis involves the condensation between an arylaldehyde and an azidoacetate to provide α-azidocinnamates which upon heating give indoles[94]. The process has been applied using high boiling solvents such as xylene, toluene, and mesitylene and a reaction time of approximately 4 h to obtain the corresponding indoles and a variety of aromatic *N*-heterocycles in yields between 53% and 79%.



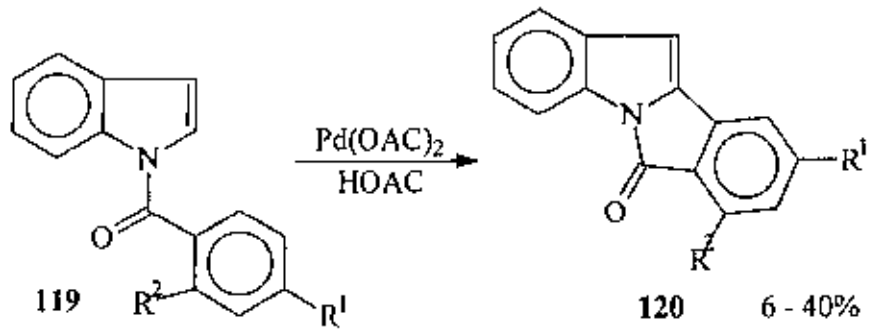
Scheme-35

1.4 Indole reactions

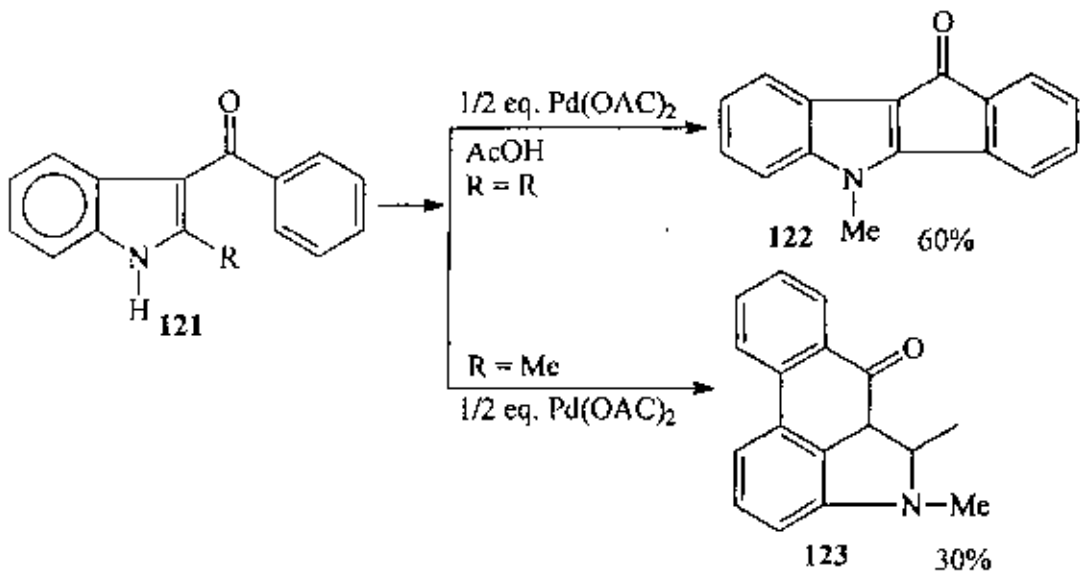
Indole is a π-electron rich system. So, the typical reaction of indole is electrophilic substitution. Some of the important reactions of indole derivatives are cited below.

1.4.1 Functionalization of indole through coupling

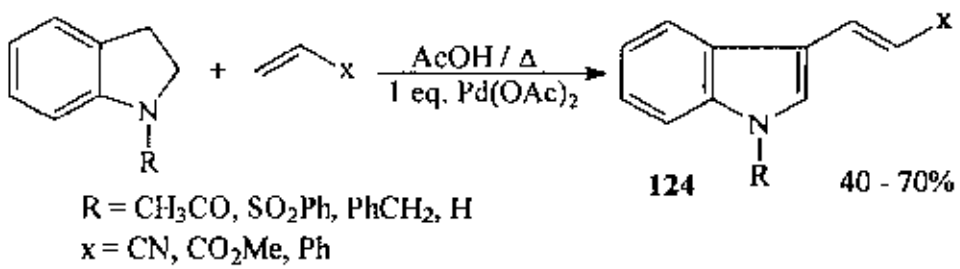
Indole itself undergoes direct palladation of 2- and 3- positions. This has been used to make fused ring indole system e.g.[95, 96] **120,122** and **123** as well as to introduce olefinic side chains at the position **124** or at the 2- position in 3- methyl indole[96-99].



Scheme-36

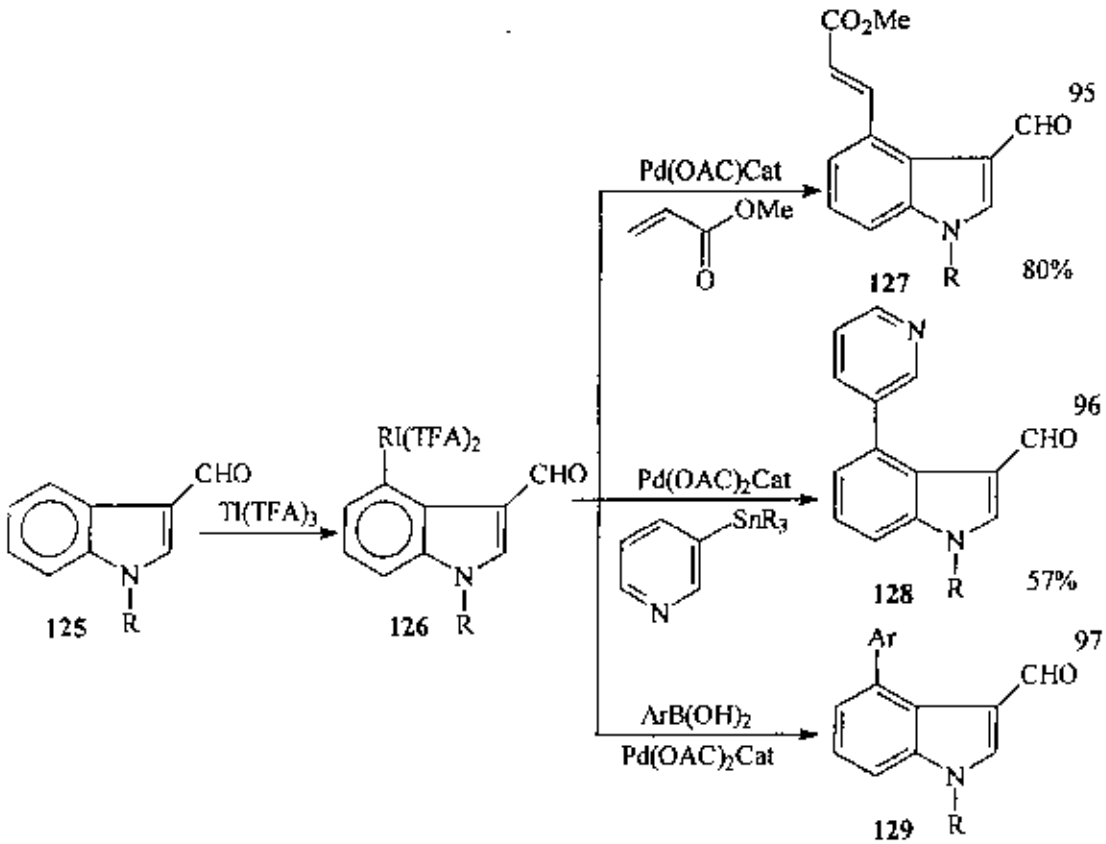


Scheme-37



Scheme-38

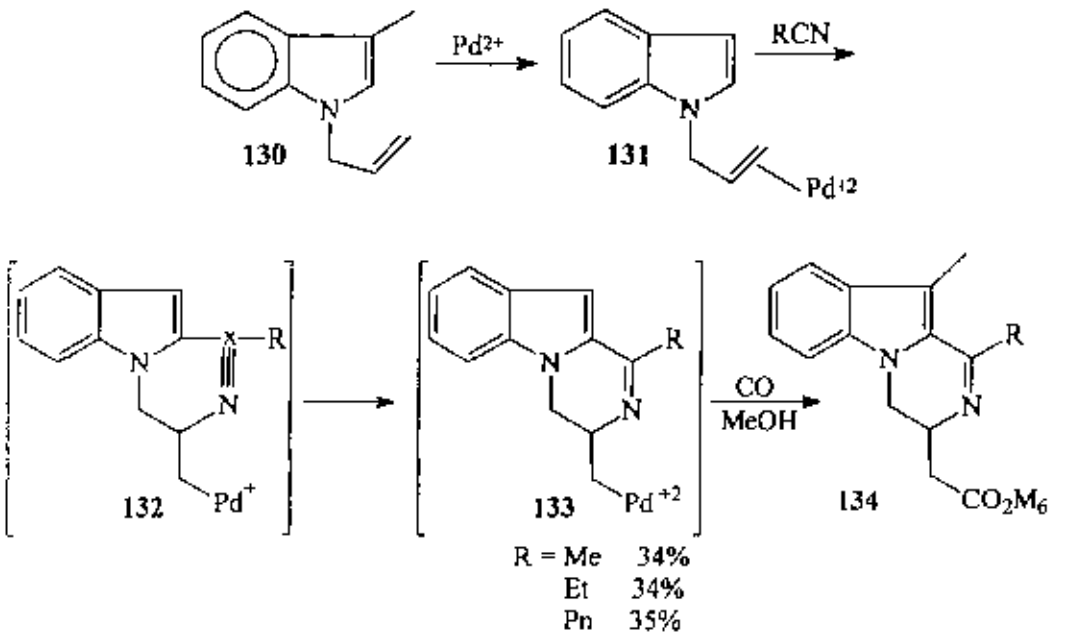
Indole-3- carbohydrate under went thallation primarily at the 4- position **126**. In the presence of a $Pd(OAc)_2$ as catalyst[100-102], transmetalation to palladium, followed by olefin insertion or reductive eliminations, ensured producing 4- alkylated indoles in modest yield(R= CO_2Me, H) Thallium (III) probably serves us the reoxidant for palladium(0).



Scheme-39

1.4.2 Ritter like reactions

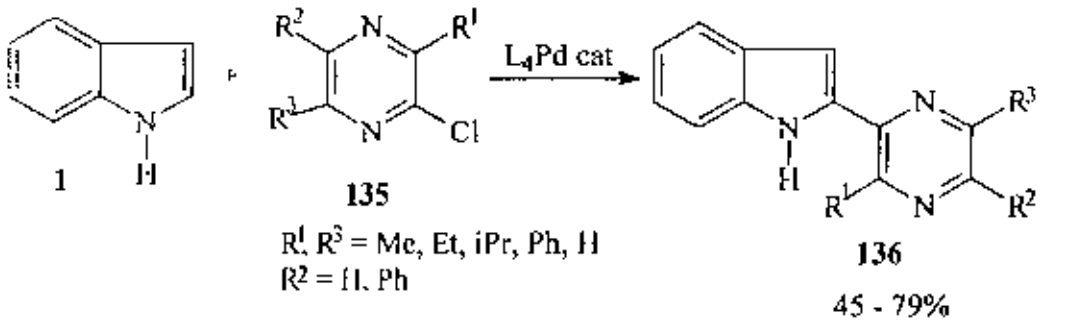
The strongly electrophilic $[Pd(CH_3CN)_4BF_4]_2$ promoted a Ritter like reaction between N-allyl-3-methylindole and nitriles, giving pyrazino [1, 2-a] indoles[103] such as **134.** While interesting, this process was neither efficient nor general.



Scheme-40

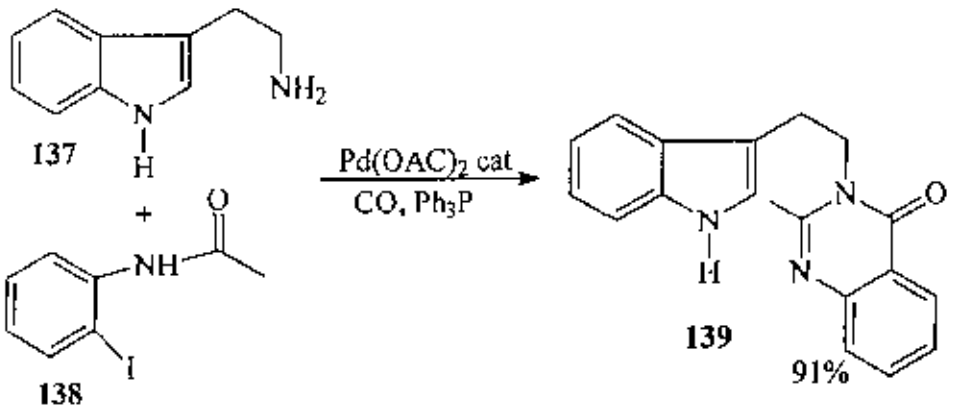
1.4.3 Palladium (0)- Catalyzed Functionalization of Indoles

Palladium (0) catalysis has also been used extensively to functionalize indoles. Chloropyrazines **135** coupled to the 2- position of indole in the presence of Pd(0), probably by an oxidative addition / insertion process[104].



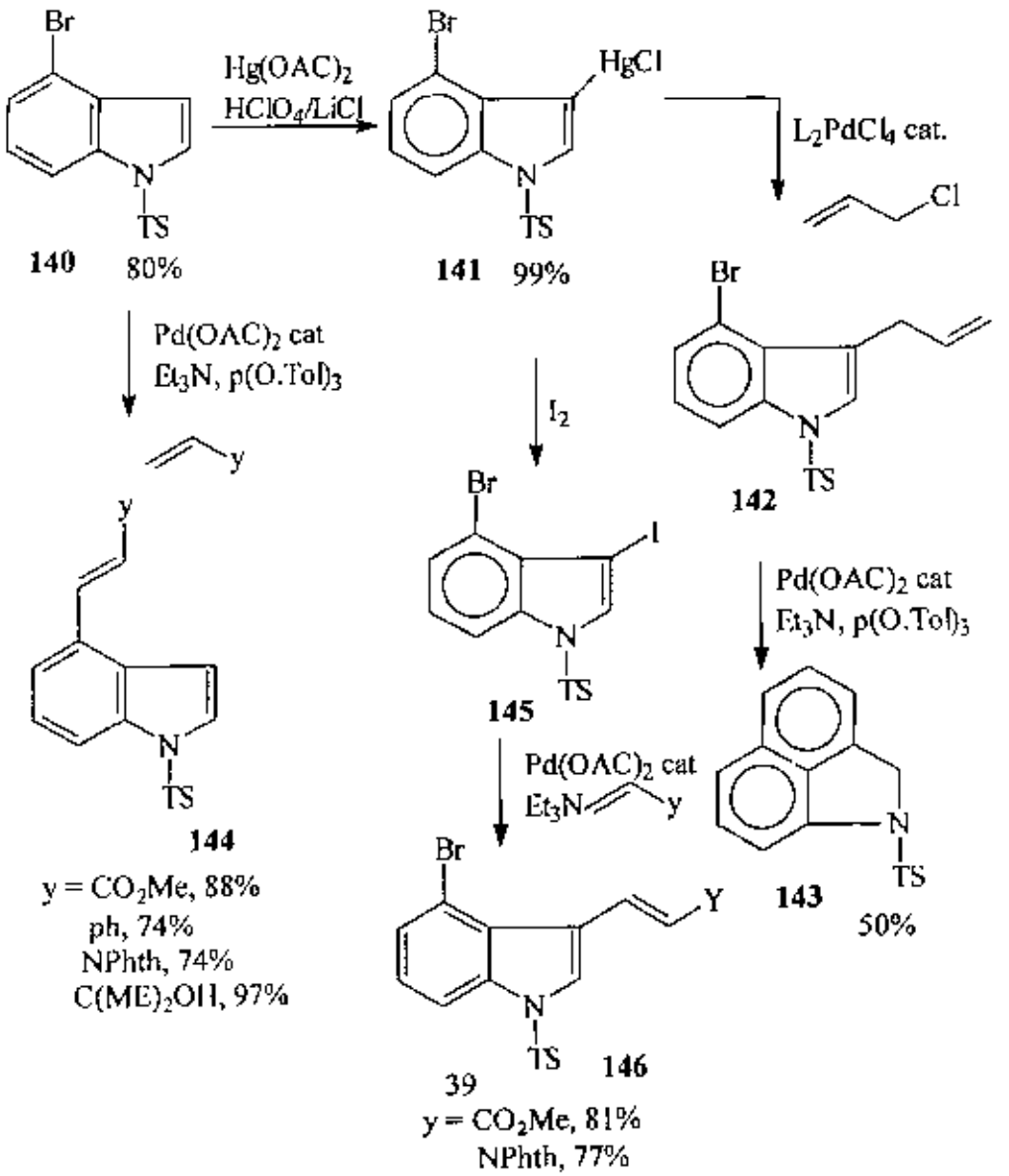
Scheme-41

The 3-amino ethyl side chains of indoles were treated by a Pd(0)-catalyzed carbonylation[105] for example with ring closure to give **139**.



Scheme-42

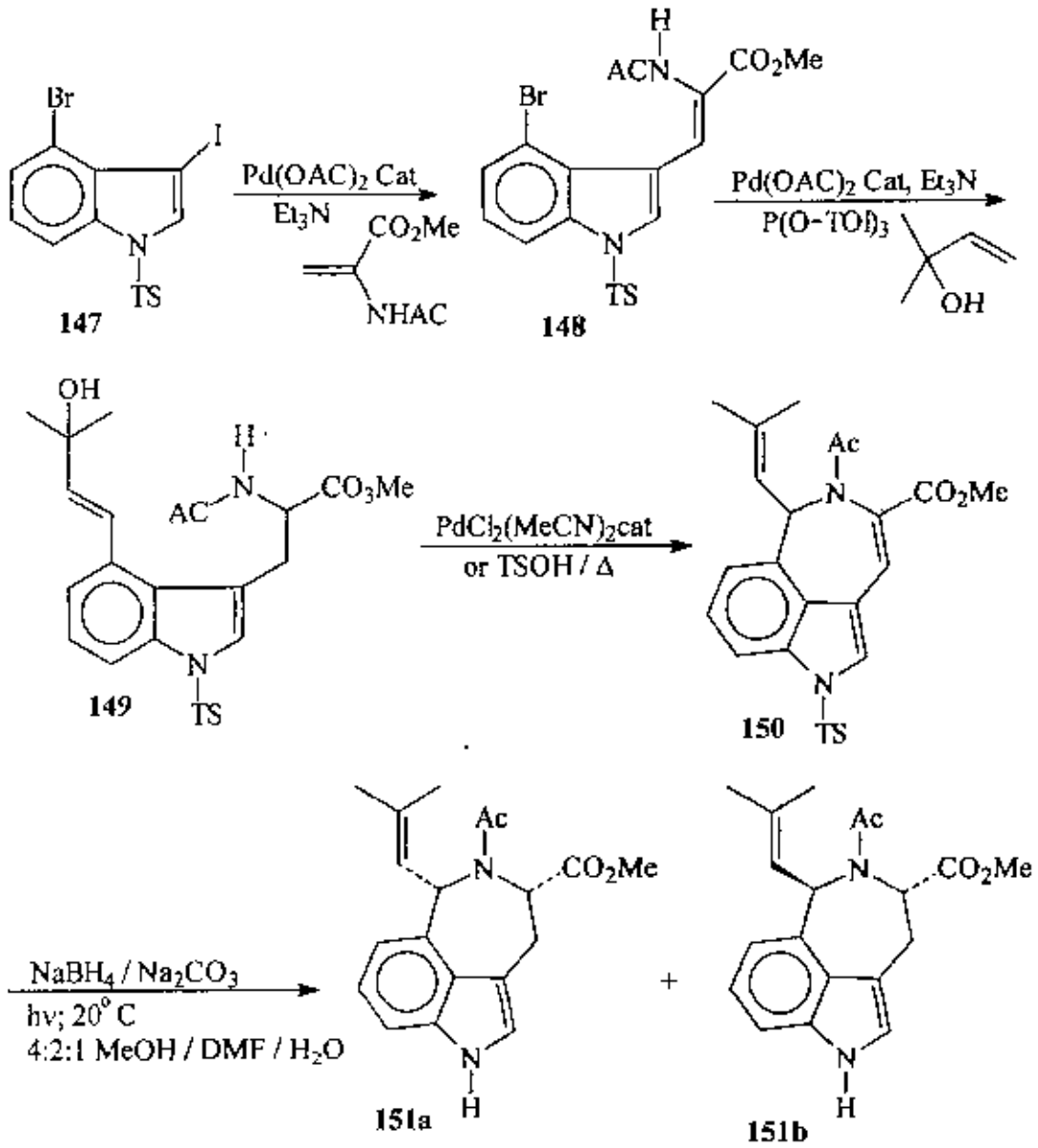
Palladium (0) catalyzed reactions of haloindoles are among the most synthetically useful processes and have been extensively developed for application in the synthesis of 3,4- disubstituted indole ring systems including ergot alkaloids. Introduction of functionality at the 4- position[105] of indole using conventional electrophilic indole chemistry is difficult, since the 1-, 2-, and 3- positions[105] are considerably more reactive.



Scheme-43

1.4.4 Synthesis of Ergot Alkaloids

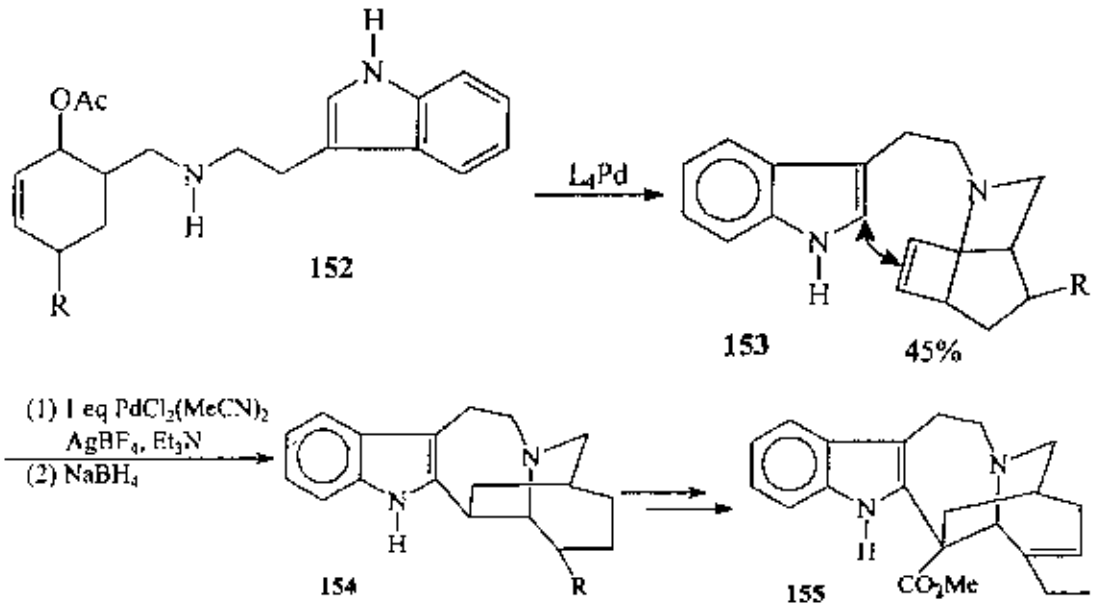
An even more extensive use of palladium catalysis was seen in the total synthesis of the methyl ester of (±)-N-acetylclavicipitic acid[106] **151** which involve as key steps Pd (II)-catalyzed formation of the indole ring, Pd (0)- catalyzed introduction of both C-ring side chain precursors and Pd (II) catalyzed formation of the seven membered ring.



Scheme-44

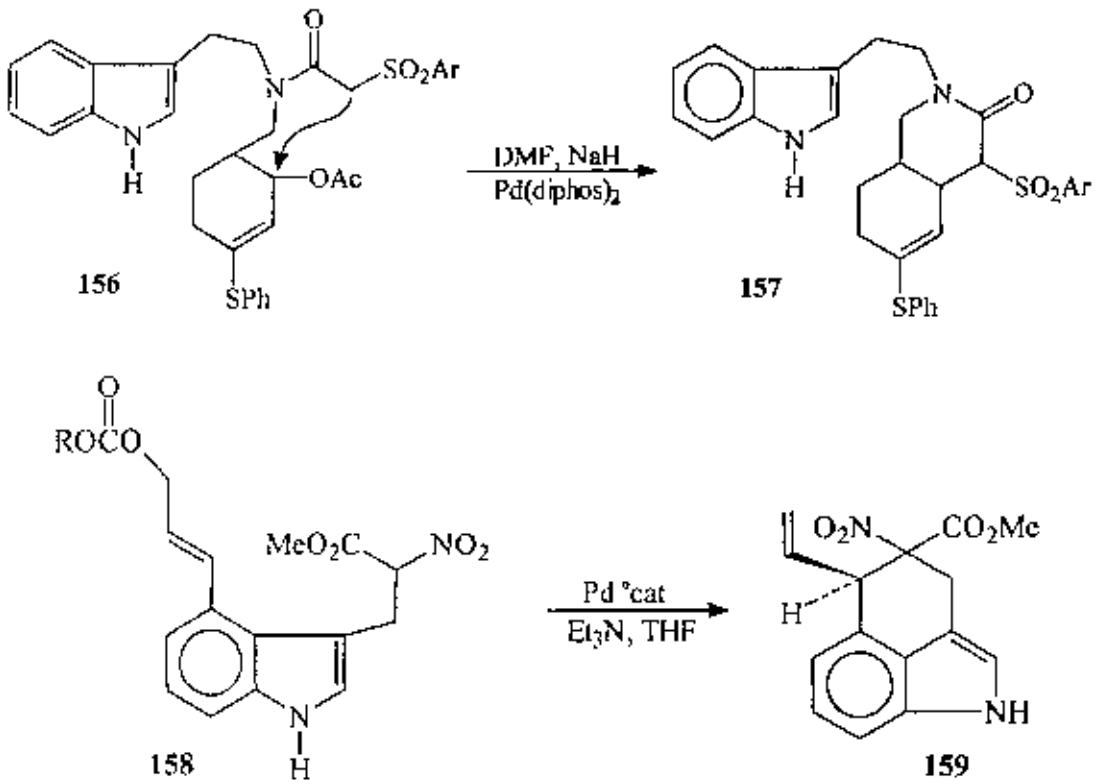
1.4.5 π-Allyl palladium Complexes in the Functionalization of Indole

In scheme-44 π-Allylpalladium (II) chemistry is more commonly used to elaborate existing indole ring systems. The isoquinuclidine ring of ibogamine[107] **154** and cantharanthine[107] **155** were synthesized by Pd (0) catalyzed allylic amination.



Scheme-45

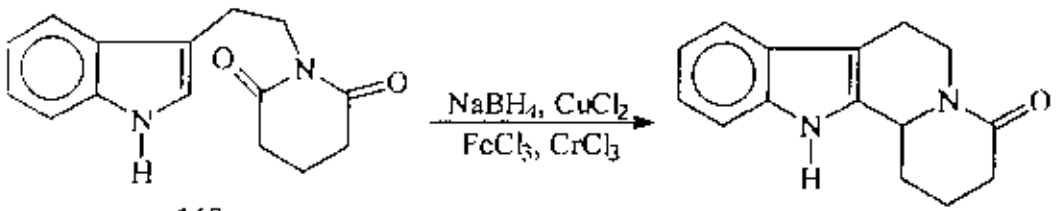
Other indole alkaloid synthesis has used Pd (0)- catalyzed allylic alkylation to elaborate nonindolic heterocyclic rings[rm] such as **157** and **159.**



Scheme-46

1.4.6 Reductive cyclization (using low-valent Transition-metal complex)

Tryptamine derivatives such 160 were reductively cyclized to β-carbolines **161** by $NaBH_4$ and copper (II), Iron (III), or chromium (III) halides[109].

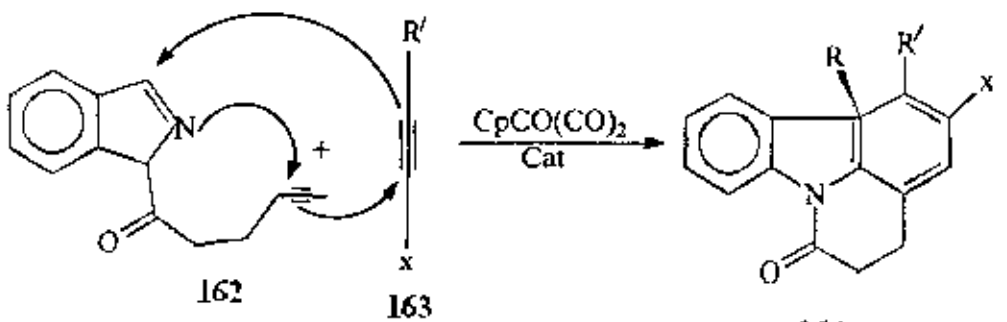


160 **161**

Scheme-47

1.4.7 Cyclotrimerization Reaction

Cyclotrimerization of alkyne and alkene of indole have been extensively developed for use in organic synthesis[110].

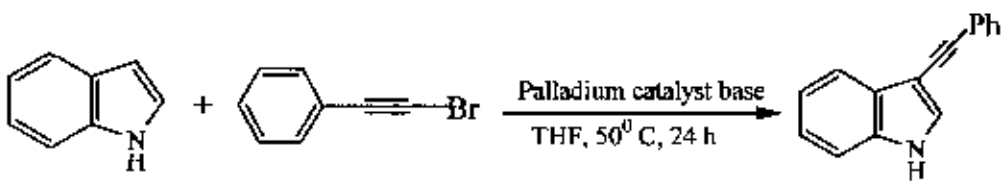


162 **163** **164**

Scheme-48

1.4.8 Direct Palladium catalyzed C-3 alkynylation of indoles

The direct palladium-catalyzed coupling reaction of indoles with alkynyl bromides was described by Yonghong Gu et al[111]. In the presence of catalytic amount of $PdCl_2(PPh_3)_2$ and 2.0 equiv. NaOAc, the coupling reaction of indoles with alkynyl bromides proceeded smoothly at 50^0 C to give the corresponding 3-alkynylindoles with high regioselectivity in good to excellent yields.



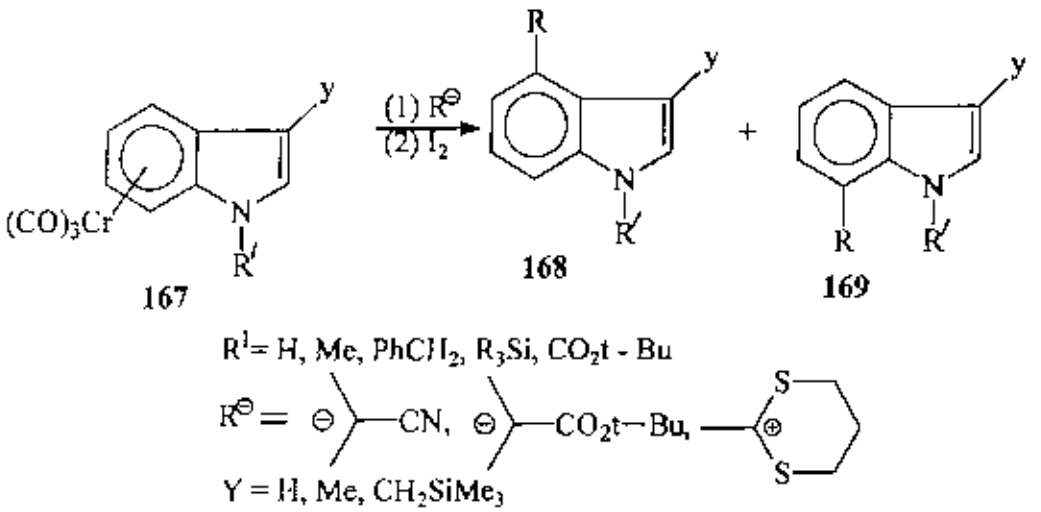
165 **166**

Scheme-49

1.4.9 Nucleophilic aromatic substitution

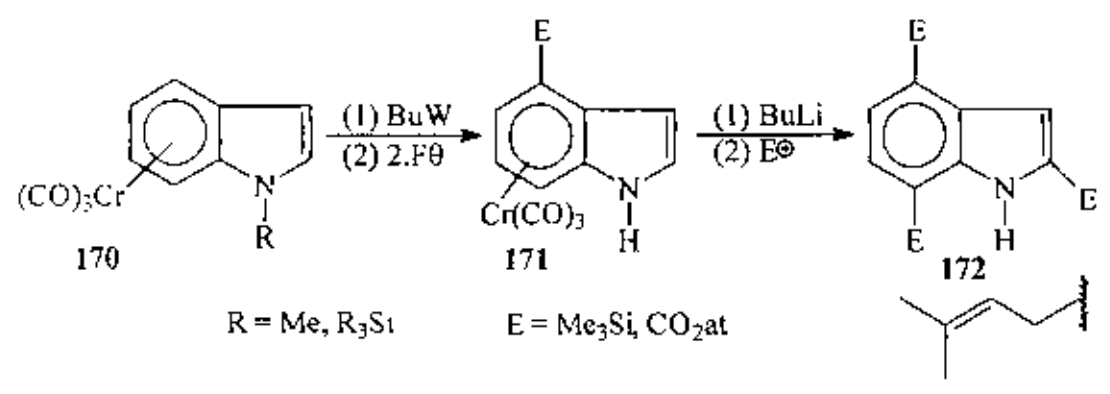
When, chromium tricarbonyl fragment inserted into indoles, it undergo nucleophilic aromatic substitution and lithiation. This feature has been used to introduce functionality at normally unreactive position of the indole ring system.

This chemistry allowed 5- chlorodihydro indoles to be converted into 5- methoxy dihydroindoles by nucleophilic substitution of chloride by methoxide[112] and complexed indoles **167** were alkylated in the 4- and 7- positions (major and minor product respectively) by carbanions[113, 114].



Scheme-50

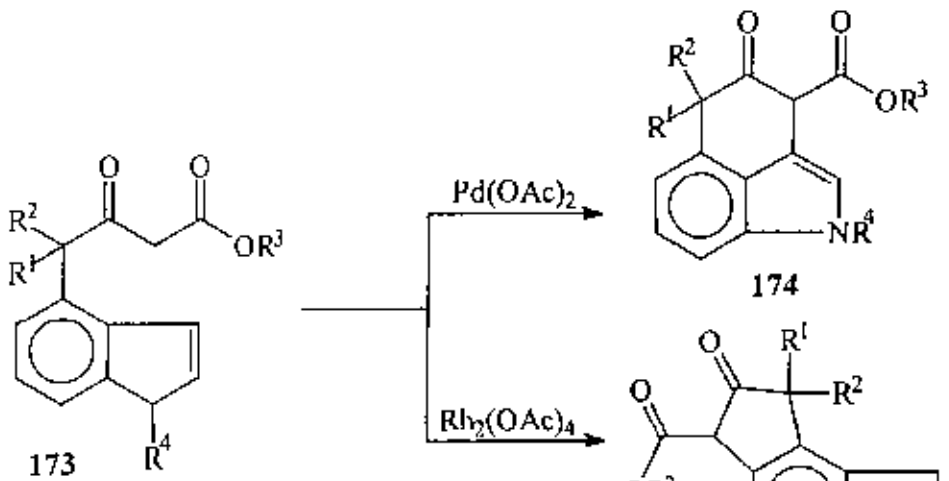
Lithiation of complexed indoles **170** occurred at the 4-position when the *N*-substituent was largely but at the 2-, 4-, and 7- position when it was small[115].



Scheme-51

1.4.10 Insertion of Carbene

The site of insertion of carbons generated by transition-metal-catalyzed decomposition of α-diazoesters such as **173** depended strongly on the catalyst[116].



Scheme-52

CHAPTER-II

Section-I

Results And Discussion

Present work: Synthesis of substituted indoles by metal mediated reactions

2.1 Rationale

Indole nucleus is a class of fused heterocycles, has arose great interest in recent years due to their wide variety of biological activities[117] and pharmacological studies[118] and use as a common building block of a wide variety of alkaloids. Although various methods have been developed previously for the synthesis of indoles but only a few of them were mediated through palladium catalysis.

Palladium catalysed[119] reactions have been extensively utilized for carboannulation[120] and hetero annulation[121] processes. Many research groups have reported the synthesis of various aromatic heterocycles via palladium-catalyzed annulation of internal alkynes[122]. Others have shown the palladium-catalyzed cyclizations to be valuable synthetic tools for the synthesis of a wide variety of heterocycles using vinylic compounds, terminal alkynes, alkenes and other substrates.

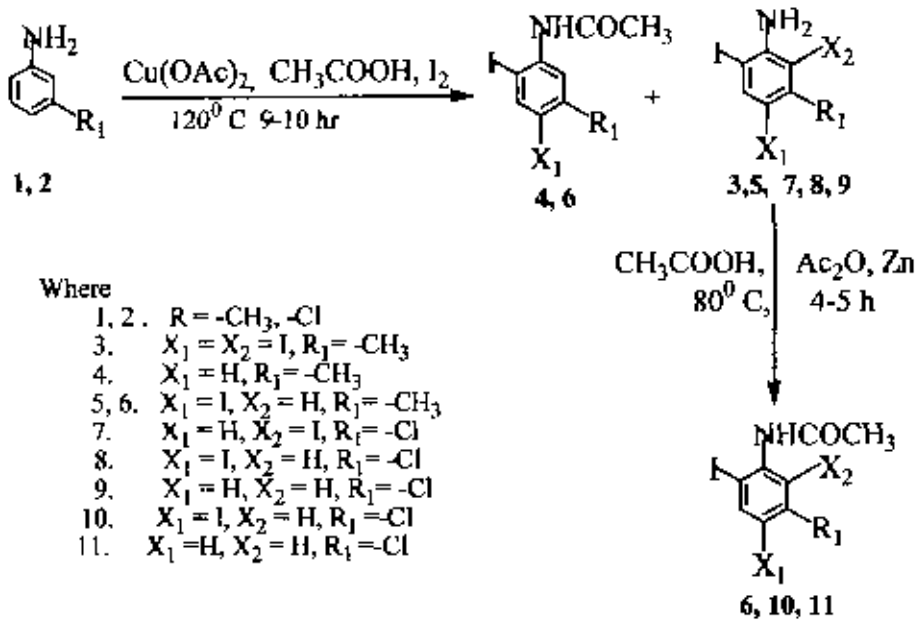
In recent years, our research group has developed methods for the synthesis of various benzofused heterocyclic compounds e.g. benzofurans[123] isoindolinones[124] and isoquinolinone[125] by palladium catalyzed reactions with terminal alkynes and acid chloride.

Due to the natural occurrence and biological importance of the indole derivatives and lack of convenient palladium precursors, we were interested in developing a general and facile method for the synthesis of indole derivatives. We became interested in the synthesis of 2,6-disubstituted indole derivatives through palladium catalyzed and base catalyzed cyclization reactions.

2.2 RESULTS AND DISCUSSION

Here an approach of the synthesis of substituted indoles through palladium-catalyzed reaction followed by base catalyzed cyclization is demonstrated. In this regards different iodo compounds were synthesized from its parent amino compounds by iodination reaction. Among the iodo compounds 2, 4 disubstituted iodo compounds were the major product. Then this substituted iodo compounds were converted to its acetanilide by using acetic acid and acetic anhydride. 2, 4-diiodo-5-methyl aniline **5**, 5-chloro- 2, 4 diiodo-aniline **8** and 5-chloro- 2-iodoaniline **9** were stirred with acetic acid, acetic anhydride (1: 1) and small amount of zinc dust at room temperature for half an hour. Then the reaction

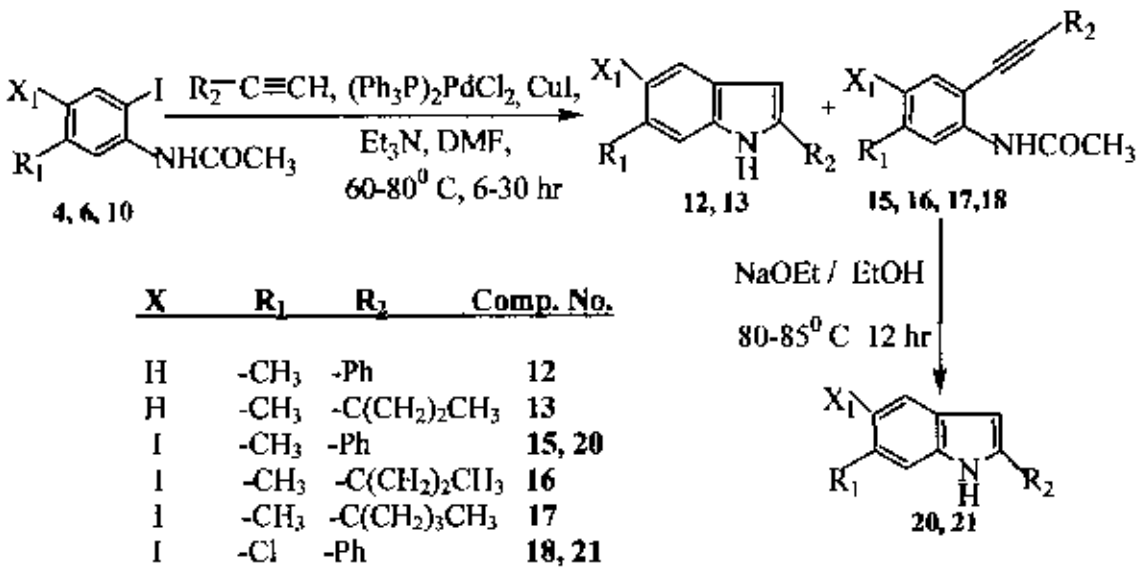
mixture was refluxed for 2-3 hours with constant stirring at 80^0 C giving 2, 4-diiodo-5-methyl acetanilide **6**, 5-chloro- 2,4 diiodo- acetanilide **10** and 5-chloro- 2- iodoacetanilide **11** with 65 %-70 % yield as shown in scheme-1.



Where
1, 2. R = $-CH_3$, -Cl
3. $X_1 = X_2 = I$, $R_1 = -CH_3$
4. $X_1 = H$, $R_1 = -CH_3$
5, 6. $X_1 = I$, $X_2 = H$, $R_1 = -CH_3$
7. $X_1 = H$, $X_2 = I$, $R_1 = -Cl$
8. $X_1 = I$, $X_2 = H$, $R_1 = -Cl$
9. $X_1 = H$, $X_2 = H$, $R_1 = -Cl$
10. $X_1 = I$, $X_2 = H$, $R_1 = -Cl$
11. $X_1 = H$, $X_2 = H$, $R_1 = -Cl$

Scheme-1

2, 4-diiodo-5-methyl acetanilide **6**, 5-chloro- 2,4 diiodo- acetanilide **10** and 5-chloro- 2-iodoacetanilide **11** in DMF underwent facile reaction with terminal alkynes in presence of bis-(triphenyl phosphine) palladium (II) chloride (3.5 mol %) and triethylamine (4 equiv), cupper iodide (8 mol %) under nitrogen atmosphere at room temperature for 1 hour and then at 60-80^0 C for 24 hours giving 2-ethynyl acetanilide with 55- 60 % yield. 2- Ethynyl acetanilide was then subjected to base catalyzed reaction with sodium ethoxide (1.2-1.5 mol%) in ethanol to afford the substituted indoles 5-Iodo-6- methyl – 2- phenyl indole **20** and 6- Chloro – 5- iodo – 2- Phenyl indole **21** in good yield, as shown in scheme-2.

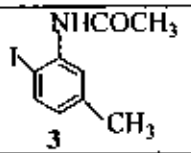
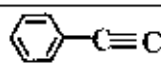
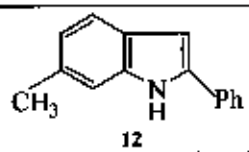
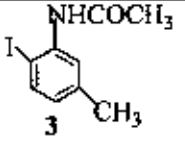
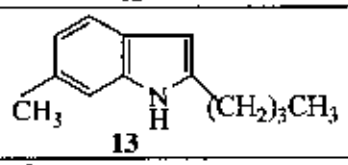
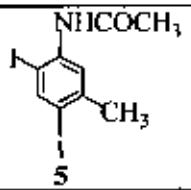
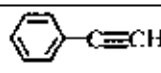
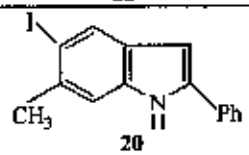
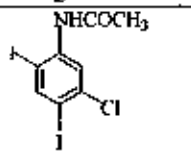
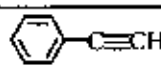
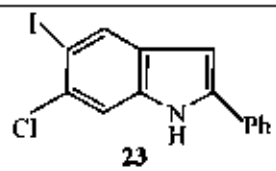


X	R_1	R_2	Comp. No.
H	$-CH_3$	-Ph	**12**
H	$-CH_3$	$-C(CH_2)_2CH_3$	**13**
I	$-CH_3$	-Ph	**15, 20**
I	$-CH_3$	$-C(CH_2)_2CH_3$	**16**
I	$-CH_3$	$-C(CH_2)_3CH_3$	**17**
I	-Cl	-Ph	**18, 21**

Scheme-2

In the case of 2-Iodo-5-methyl acetanilide the desired final indole product **12, 13** were produced in the one pot reaction. But in other cases the condensed product was produced at first then it was cyclized to the indole. 2- Ethynyl acetanilide was added to sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml) and the mixture were stirred under a nitrogen atmosphere for 4-5 hr at 80-85^0 C to yield 2,6- substituted indoles. In this case the yields were 65 % for phenyl acetylene and 40-45 % for n-hexyne or 1-heptyne.

Table- 1: Synthesis of 2, 6-disubstituted indole through palladium catalyzed reaction followed by base catalyzed cyclization.

Entry	Acetanilide	Terminal alkyne	Product	Yield[a] (%)
1	 3		 12	52
2	 3	$HC\equiv C-(CH_2)_3CH_3$	 13	43
3	 5		 20	65
4	 9		 23	42

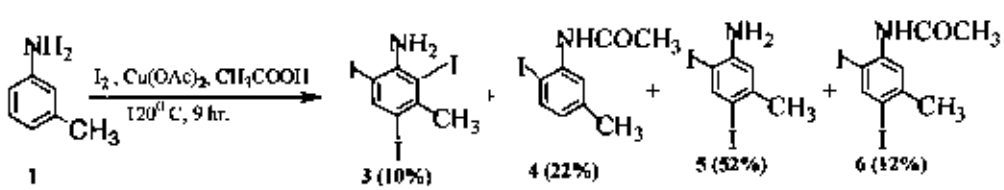
[a]Yield was calculated on the basis of iodo compound 3, 5, 9.

2.3. Synthesis of starting materials

2.3.1 Iodination of 3-substituted aniline

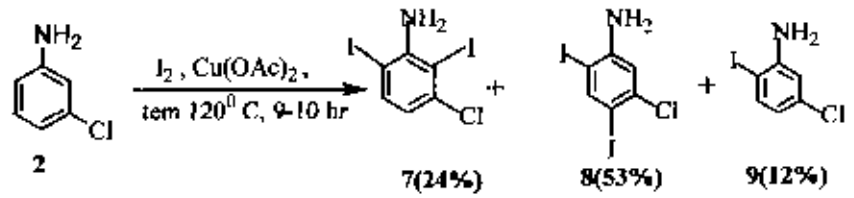
Meta toulidine, **1** and 3-chloro aniline **2** has been used as starting materials because of its easy availability from commercial market. Iodination reaction was done as shown in the following scheme-3 and scheme-4.

After usual workup the crude product was purified by chromatography on column of silica gel with hexane: chloroform. Various types of product were yielded in different ratio.



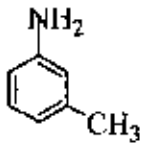
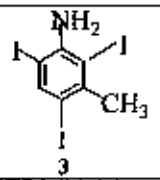
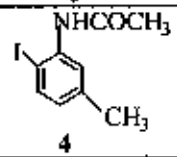
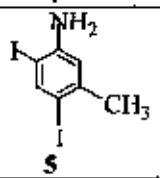
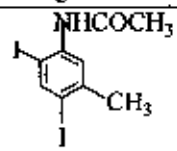
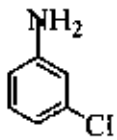
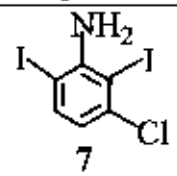
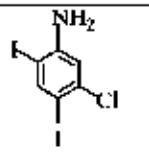
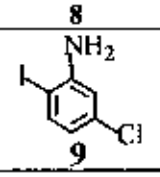
1 3 (10%) 4 (22%) 5 (52%) 6 (12%)

Scheme-3



Scheme-4

Table-2: Synthesis of 2,4-disubstituted iodo aniline or acetanilide.

Entry	Starting Material	Condition	Product	[b]Yield (%)
1		I_2 , $Cu(OAc)_2$ CH_3COOH 120° C, 9 hr.	 **3**	10
			 **4**	22
			 **5**	52
			 **6**	12
2		I_2 , $Cu(OAc)_2$ CH_3COOH 120° C, 9 hr.	 **7**	24
			 **8**	53
			 **9**	12

[b]Yield (%) was calculated on the base of the amount of compound 1and 2

2.3.2 Characterization of starting materials

2.3.2.1 Characterization of 2,4, 6-triiodo-5-methyl aniline 3

The structure was established from the study of IR, ^{1}H NMR and ^{13}C NMR spectrum data. 2,4, 6-Triiodo-5-methyl aniline was white crystal and obtained (yield 10 %), m.p. 136 ^{0}C.

In the **IR spectrum** (fig-1) of the compound **3** the absorption band found at 3313.76 cm^{-1} was due to the ν_{NH} of the amine group. Where as bands at 1599.02 cm^{-1} and 1420.60 cm^{-1} due to the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig-2) of the compound showed, the peaks at δ_H 8.04 (s, 1H,CH) due to the aromatic ring protons. The chemical shift position at δ 4.78 was found in the form of singlet due to the NH_2 proton. The chemical shift position at δ 2.73 (s, 3H, $-CH_3$) was due to the aromatic methyl protons.

The structure of the compound **3** was further confirmed by its **^{13}C NMR** data (Fig-3) at the chemical shift position of δ 86.45, 83.55, 78.35 due to the Ar-I carbon, at δ 146.92 and at 143.96 in favor of C-NH and $C-CH_3$ carbon of the aromatic ring respectively. The chemical shift position at δ 35.98 in favors of $Ar-CH_3$ carbon, the structure was finally established from its DEPT (Fig-4) spectrum due to the presence of only one aromatic carbon in the ring at δ146.84 and one aryl methyl carbon at 35.98.
The position of the carbon in the DEPT spectrum further confirmed from the COSY spectrum (Fig-5).

2.3.2.2 Characterization of 2-iodo-5-methyl acetanilide 4

UV, IR, ^{1}H NMR and ^{13}C NMR spectrum data established the structure of compound **4.**
2-Iodo-5-methyl acetanilide was white crystal and obtained (yield 22%).

In the **IR spectrum** of the compound (fig – 6) the absorption band found at 3315.4 (-NH) cm^{-1} due to the ν_{NH} of the acetanilide group. where as a band at 1668.3 cm^{-1} due to the presence of keto (-C=O) group in the acetanilide.

The **^{1}H NMR spectrum** (fig -7) of the compound showed, the peaks at δ_H 7.67 (d, 1H,CH, J= 8.5 Hz) and δ_H 7.42(d, 1H, CH, J= 1.94 Hz) due to the aromatic ring adjacent protons.

The chemical shift position at δ 7.03 (dd, 1H, CH, J=11.2 Hz) results from long-range coupling of 2,4 protons. The chemical shift position at δ 7.46 was found in the form of broad singlet due to the NH proton.

The structure of the compound **4** was further confirmed by its **^{13}C NMR** data (Fig-8) at the chemical shift position of δ 168.52 due to the presence of (C=O) carbon, at δ 142.03 in favor of C-NH, δ 94.43 designed for Ar-I, δ 28.13 and 24.58 in support of CO-CH_3 carbon and Ar-CH_3 carbon respectively.
From the DEPT (Fig-9) spectrum it is clearly shown that there are three tertiary carbons present at 142.03, 138.11 and 121.11 in the aromatic ring.

2.3.2.3 Characterization of of 2,4-diodo-5-methyl aniline 5

The compound was Brown solid, m.p: 80^{0}C, R_f Value: 0.56, (Hexane: Chloroform = 1:1).
In the **IR spectrum** of the compound (fig –10) the absorption band found at 3413.10 cm^{-1} due to the ν_{NH} of the aniline (-NH_2) group, where as a band at 1599.98 cm^{-1}, 1546.94, 1461.10 cm^{-1} due to the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig – 11) of the compound showed, the peaks at δ_H 7.94 (s, 1H,CH), δ_H 6064 (s, 1H, CH) due to the aromatic ring protons. The chemical shift position at δ 4.03 (s, 2H, NH_2) was found in the form of broad singlet due to the NH_2 protons.

The structure of the compound **5** was further confirmed by its **^{13}C NMR data** (Fig -12) at the chemical shift position of 86.45 and 81.12 due to the presence of (Ar-I) carbon, at δ 146.90 due to the Ar-NH_2, at δ 146.66 and at δ 142.25 due to the C-3 and C-5 respectively, at δ 115.55 designed for C-6 and at δ 27.50 in support of Ar-CH_3 carbon respectively.
The structure of the compound **5** was finally established from its DEPT- 135 (Fig -13) spectrum. Where there are only two aromatic CH carbons at 146.66 and 115.55 are found in the DEPT spectrum. Another carbon at 27.50 represents the aromatic methyl group.
In UV spectrum (Fig -14), the value was found in the range of λ_{max} 252.30 and 232.80 nm

2.3.2.4 Characterization of 2,4-diodo-5-methyl acetanilide 6

The compound was white crystal with m.p. 215^0 C and R_f value: 0.58 (Hexane: Ethylacetate = 1:1).

In the **IR spectrum** (fig - 15) of the compound the absorption band found at 3265.54 cm^{-1} dueto the ν_{NH} of the acetanilide (-NH) group, where as a band at 1659.77 cm^{-1} represents the ν_{co} of the acetanilide. The band at 1554.65 and 1512.22, cm^{-1} represents the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig - 16) of the compound showed, the peaks at δ_H 8.14 (s, 2H,CH) due to the aromatic ring protons. The chemical shift position at , δ_H 7.30 (s, 1H, NH) was found in the form of a singlet due to the NH protons.

The structure of the compound 6 was further confirmed by its **^{13}C NMR** data (Fig – 17) at the chemical shift position of δ 168.09 due to the presence of (C=O) carbon, at δ 142.03 in favor of C-NH, δ 96 and 86 designed for Ar-I, at δ 138.38 designed for C-5, at δ 146.79 and at δ 122.47 due to the C-3 and C-6 respectively, at δ 27.90 and 24.88 in support of -OCH_3 carbon and Ar-CH_3 carbon respectively.

The structure of the compound 6 was confirmed from the DEPT-135 (Fig – 18) spectrum. In the dept spectrum there are two –CH carbons present in the aromatic ring at 122.47 and 146.83.

The position of the carbon found in the Dept spectrum further confirmed from the COSY (Fig – 19) spectrum.

In UV (Fig – 20) spectrum, the value was found in the range of λ_{max} 274 and 226 nm indicated acetanilide group.

2.3.2.5 Characterization of 3-chloro- 2, 6 diiodo-aniline 7

The structure of the compound was characterized by its UV, IR and ^{1}H NMR spectra.

In the **IR spectrum** of the compound *(fig – 21)* the absorption band found at 3312.80 cm^{-1} due to the ν_{NH} of the aniline (-NH_2) group. The band at 1595.16, 1416.74 cm^{-1} represents the double bond in the aromatic ring. A strong band at 873.77 represents the cloro compound.

The **^{1}H NMR spectrum** (fig -22) of the compound showed, the peaks at δ_H 7.53 (d, 1H,CH, J= 8.36 Hz), 6.58 (d, 1H, J=8.37 Hz) due to the two adjacent aromatic protons. The chemical shift position at δ 4.87 (brS, 2H, NH_2) was found in the form of broad singlet due to the NH_2 protons.

In UV (fig -23) spectrum, the value was found in the range of λ_{max} 244 and 234 nm indicated aniline group.

2.3.2.6 Characterization of 5-chloro- 2,4 diiodo-aniline 8

The compound was white crystal, m.p-75^0 C. R_f Value 0.91 (hexane: chloroform =1:1).

In the **IR spectrum** (fig - 24) of the compound the absorption band found at 3333.05 cm^{-1} due to the ν_{NH} of the aniline (-NH_2) group. The band at 1613.48 cm^{-1} and 1454.35 cm^{-1} represent the double bond in the aromatic ring. A strong band at 877.63 represents the cloro compound.

The **^{1}H NMR spectrum** (fig - 25) of the compound showed, the peaks at δ_H 7.98 (s, 1H,CH), 6.83 (s, 1H, CH) due to the two isolated aromatic protons. The chemical shift position at δ 4.27 (br S, 2H, NH_2) was found in the form of broad singlet due to the NH_2 protons.

The structure of the compound **8** was further confirmed by its **^{13}C NMR data** (Fig -26) at the chemical shift position of 82.93 and 82.05 due to the presence of (Ar-I) carbon, at δ 147.90 and at δ 114.38 due to the C-3 and C-6 respectively, at δ 147.79 due to the Ar-NH_2 and at δ 139.13 designed for C-5 carbon respectively.

The structure of the compound **8** was further established from its DEPT (Fig -27) Spectrum, where only two carbons in the aromatic ring at positions 147.80 and 114.38 are Presented.

In UV spectrum (Fig -28), the value was found in the range of λ_{max} 274 and 250 nm.

2.3.2.7 Characterization of 5-chloro- 2-iodoaniline 9

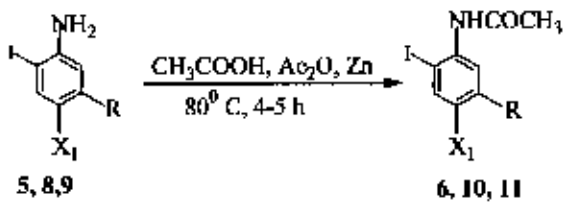
The compound brown solid, m.p- 70^0 C, R_f Value 0.58 Hexane: Chloroform (1:1).

In the **IR spectrum** of the compound (fig -29) the absorption band found at 3421.78 cm^{-1} due to the ν_{NH} of the aniline (-NH_2) group. The band at 1621.20, 1463.03 cm^{-1} represents the double bond in the aromatic ring. A strong band at 854.48 and 817.83 represents the halogen compound.

The **^{1}H NMR spectrum** (fig - 30) of the compound showed, the peaks at δ_H 7.50 (d, 1H,CH, J= 8.16 Hz), 6.30 (d, 1H, J=7.46 Hz) due to the two adjacent aromatic protons. The chemical shift position at δ 3.73 (br S, 2H, NH_2) was found in the form of broad singlet due to the NH_2 protons. A singlet in the position at 6.80 was due to the aromatic isolated proton in the C-6 position.

2.4 Synthesis of 2-Iodo-5-substituted acetanilide derivatives (6, 10, 11) of 2- Iodo-5-substituted aniline (5, 8, 9)

Different 2,4-diodo-5-substituted aniline **5, 8 and 9** was stirred with acetic acid and acetic anhydride (1: 1) and small amount of zinc dust at room temperature for half an hour. Then the reaction mixture was refluxed for 2-5 hours with constant stirring at 80^0 C for the formation of 2, 4-diodo-5-substituted acetanilide. . The hot reaction mixture was poured in a thin stream into a 500 ml beaker containing 200 ml of cold water with constant stirring. Filtered the crude product by using suction pump, washed with a little cold water and dried upon a filter paper in the air. The desired product **6, 10, 11** was purified by crystallization from ethanol.



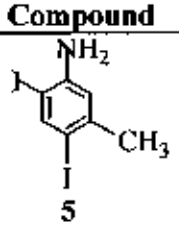
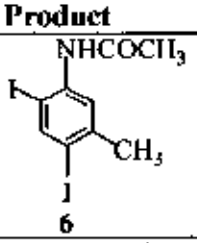
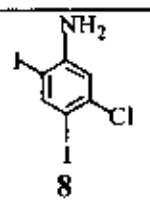
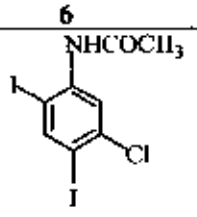
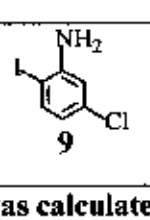
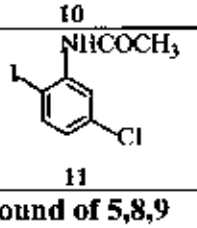
5, 8,9 **6, 10, 11**

Where

5, 6. X_1 = I, R=-CH_3
8, 10. X_1 = I, R=-Cl
9, 11. X_1 =H, R=-Cl

Scheme-5

Table-3: Synthesis of Iodoacetanilide derivatives of 5- substituted aniline,

Entry	Compound	Condition	Product	[c]Yield(%)
1	 5	CH_3COOH, Ac_2O, Zn, 80^0 C, 2-3 h	 6	72
2	 8	CH_3COOH, Ac_2O, Zn, 80^0 C, 4-5 h	 10	68
3	 9	CH_3COOH, Ac_2O, Zn, 80^0 C, 4-5 h	 11	65

[c]**Yield (%) was calculated on the based on the compound of 5,8,9**

2.4.1 (a) Characterization of 2,4-diodo-5-methyl acetanilide 6

The compound was trunsparent crystal; yield 72%, m.p 214-215^0 C. R_f = 0.58, (Hexane: Ethyl acetate = 1:1). The product was characterized by its IR, ^{1}H NMR and ^{13}C NMR spectrum data.

In the **IR spectrum** of the compound (fig- 15) the absorption band found at 3267 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1659.77 cm^{-1} due to the ν_{co} of the acetanilide. The absorption band at 1554.85 and 1510.29 cm^{-1} represents the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig -16) of the compound showed, the peaks at δ_H 8.13 (s, 2H, CH), due to the aromatic protons. The chemical shift position at δ 7 .30 (s, 1H, NH) was found due to the NH proton.

The structure of the compound **6** was further confirmed by its **^{13}C NMR** data (Fig.- 17) at the chemical shift position of δ 168.52 due to the presence of (C=O) carbon, at δ 142.03 in favor of C-NH, at δ 138.39 designated for C-5, at δ 146.77 and at δ 122.47 due to the C-3 and C-6 respectively, at δ 95.65 and at δ 95.65 designed for Ar-I, δ 27.90 and 24.88 in support of CO-CH_3 carbon and Ar-CH_3 carbon respectively.

2.4.1 (b) Characterization of 5-chloro- 2,4 diiodo- acetanilide 10

The compound was white crystal; yield 75%, m.p 158^0 C. R_f = 0.52 (Hexane: Ethyl acetate =1:1).

In the **IR spectrum** of the compound (fig - 31) the absorption band found at 3272 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1658.81 cm^{-1} due to the ν_{co} of the acetanilide grouo. The absorption band at 1568.15 and 1525.72 cm^{-1} represents the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig-32) of the compound showed, the peaks at δ_H 8.30 (s, 1H CH) and at δ_H 7.66 (d, 1H) due to the aromatic protons. The doublet at position 7.66 might be due to the long range coupling in the aromatic ring. The chemical shift position at δ_H 7.37 (s, 1H NH) was found in the form of singlet due to the NH proton.

The structure of the compound further confirmed by its **^{13}C NMR spectrum** (Fig. 33) (100 MHz, $CDCl_3$). It was observed that the chemical shift at δ 168.0 (C=O), 147.68 (C-1), 139.18 (C-5), 139.18 (C-3), 136 (C-6), 121.79 (C-2) and 121.53 for C-4 respectively. The

chemical shift at 24.79 indicated for $-OCH_3$, and so the ^{13}C NMR spectrum indicated the presence of eight carbon atoms in the molecule corresponding to the formation of compound **10**.

2.4.1 (c) Characterization of 5-Chloro- 2- iodoacetanilide 11

The compound was white crystal; yield 65%, m.p 120-122^0 C. R_f = 0.52 (Hexane: Ethyl acetate =1:1).

In the **IR spectrum** of the compound (fig -34) the absorption band found at 3510 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1653.99 cm^{-1} represents the keto group (C=O) of the acetanilide. The absorption band at 1581.66 and 1466.89 cm^{-1} represents the double bond in the aromatic ring.

The **^{1}H NMR spectrum** (fig – 35) of the compound showed, the peaks at δ_H 7.73 (m, 1H, CH), 7.10 (d, 1H. J=8.13), 7.30 (s, 1H, CH) due to the aromatic protons. The multiplate at δ 7.72 was results from the long rage coupling with proton in the C-6 position. The chemical shift position at δ 7.41 was found in the form of singlet due to the NH proton.

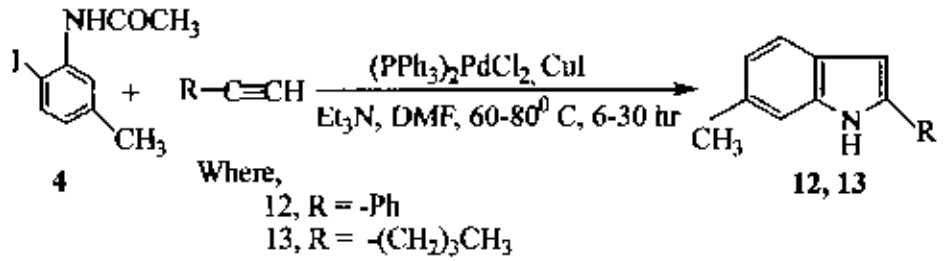
The **^{13}C NMR spectrum** (fig - 36) of the compound showed, the peaks at δ_c 168.45 due to the C=O carbon, at δ 139.12 in favor of Ar-NH, at δ 138.39 designated for C-5, at δ 120.40 and at δ 119.29 due to the C-4 and C-6 respectively, at δ 91.06 designed for Ar-I and at δ 24.62 due to the $-CH_3$ group attached to the C=O bond.

Finally the structure of the compound **11** was confirmed from the data obtained from DEPT spectrum (fig – 37). Where four tertiary carbons vanish out of eight carbons found in the normal ^{13}C NMR spectrum.

2.5 General procedure for synthesis of 2, 6-disubstituted indoles

Bis-(triphenyl phosphine) palladium(II) chloride (3.5 mol %), copper (II) iodide (8 mol %), triethylamine (4 equiv) were added to a solution of 2-iodo-5-methyl acetanilide (1 mol) in DMF (5ml).

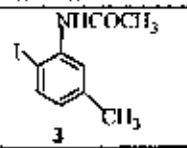
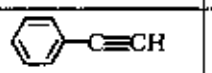
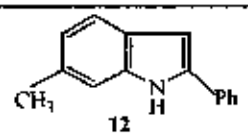
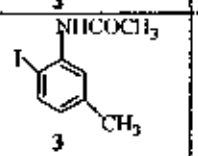
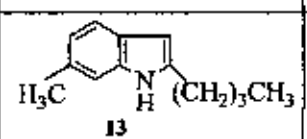
The reaction mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then terminal alkyne (R-C≡CH) (1.2 mol %) was added drop wise to the mixture. The reaction mixture was heated at 80-85^0 C for 24-30 hours with constant stirring as shown in the scheme-6.



Scheme-6

Then it was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform, washed with distilled water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The desired product (**12, 13**) was obtained by column Chromatography on silica gel using n-Hexane: chloroform in different ratio. Reaction of 2-iodo-5-methyl acetanilide with Phenyl acetylene (entry 1) gave product in the highest yield (55 %) in the table 4.The reaction of 2-iodo-5- methyl acetanilide with n-Hexyne took place at lower temperature (60^0 C) but longer time than phenyl acetylene.

Table-4: synthesis of 2, 6-disubstituted indoles of 2-iodo-5-methly acetanilide

Entry	2-iodo-5-methyl acetanilide	Terminal Alkyne	Condition	Product	Yield (%)
1	 3		$80\text{-}85^0$ C, 24 hr	 12	52
2	 3	$H_3C(H_2C)_3C\equiv CH$	60^0 C, 30 hr	 13	43

% Of yield was based on mol% of 2-iodo-5-methyl acetanilide

2.6.1 Characterization 6-methyl-2-phenyl indole 12

The compound **12** (260 mg, 52 %) was yellow solid, m.p-122^0 C, R_f value 0.73 (n-Hexane: Chloroform = 2:1).

In the **IR spectrum** (fig - 37) of the compound the absorption band found at 3420 cm^{-1} due to the ν_{NH} of the indole ring, where as a weak band at 1491.66 cm^{-1} due to the ν_{NH} of the secondary N-H of the indole ring. The absorption band at 1608.66 cm^{-1} and 1453.39cm^{-1}

represents the double bond in the aromatic ring. The absorption band at 1371.41 cm^{-1} might be due to the bending stretching of the $-CH_3$ group.

The **^{1}H NMR spectrum** (fig - 38) of the compound showed, the peaks at δ_H 7.54 (s, 1H, CH), 7.50 (m, 2H, CH) in the aromatic ring, 7.30 (s, 1H, =CH) due to the venylic protons. The multiplate at δ 7.35 was results from the coupling with of the protons in the phenyl ring. The chemical shift position at δ 5.05 was found in the form of singlet due to the NH proton.

The chemical shift position at 2.70 represents the methyl group of the aromatic ring.

The **^{13}C NMR spectrum** (fig -39) of the compound showed, the peaks at δ_c 148.06 and 144.92 due to the adjacent carbon of the indole ring.

The compound shows the absorption in the UV spectrum (fig -40) in the region of 280-300 nm.

2.6.2 Characterization of 2-Hexynyl- 5- methyl indole 13

The compound **13** was white solid, R_f value 0.75 (n-Hexane: Chloroform 3:1).

In the **IR spectrum** of the compound shows the absorption band found at 3420 cm^{-1} due to the ν_{NH} of the indole ring, where as a weak band at 1598.05 cm^{-1} due to the ν_{NH} of the secondary N-H of the indole ring. The absorption band at 1371.41 cm^{-1} due to the $-CH_3$ group.

The **^{1}H NMR spectrum** (fig - 41) of the compound showed, the peaks at δ_H 7.53 (d, 1H, CH) in the aromatic ring, 7.35 (m, 5H, CH) due to the coupling of the protons in the phenyl ring.The chemical shift position at δ 4.80 was found in the form of singlet due to the NH proton. The chemical shift position at 2.56 represents the methyl group of the aromatic ring. The muliplate at 1.48 and 2.41 represents the methylene ($-CH_2$) protons. The chemical shift position at 0.9 represents the methyl group of the hexyne.

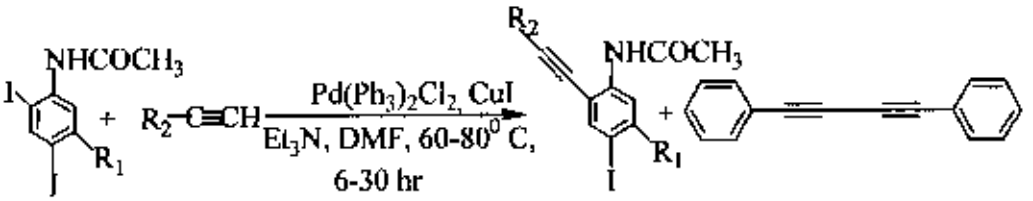
The **^{13}C NMR spectrum** (fig -42) of the compound showed, the peaks at δ_c 148.06 and 144.92 due to the adjacent carbon of the indole ring.

The absorption band found in the UV spectrum (fig -43) in the region of 290- 350 nm.

2.7 General procedure for synthesis of 2-Alkynyl – 4 –iodo- 5- methyl acetanilide

Bis-(triphenyl phosphine) palladium(II) chloride (3.5 mol%), copper (II) iodide (8 mol%), triethylamine (4 equiv) were added to a solution of 2, 4-diiodo-5-methyl acetanilide (1 mol) in DMF (5ml).

The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then terminal alkyne (R-C≡CH) (1.2 mol%) was added drop wise to the mixture. The reaction mixture was heated at 60-80^0 C for 24-30 hours with constant stirring as shown in the scheme-5.



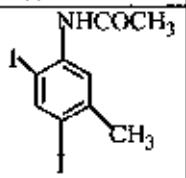
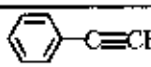
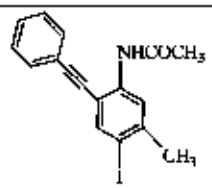
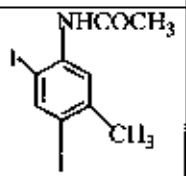
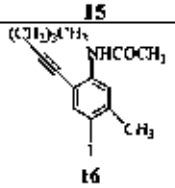
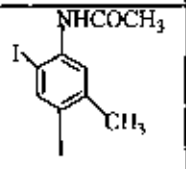
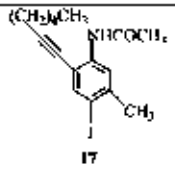
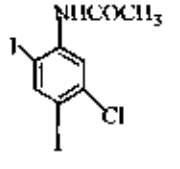
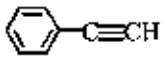
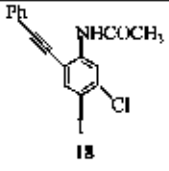
6, 10 15, 16, 17, 18 14

Where,

15. R_1 = -CH_3, R_2 = -Ph
16. R_1 = -CH_3, R_2 = -$C(CH_3)_3CH_3$
17. R_1 = -CH_3, R_2 = -$C(CH_3)_4CH_3$
18. R_1 = -Cl, R_2 = -Ph

Scheme-7

Table-5: Synthesis of 2-Ethynyl – 4 –iodo- 5- methyl and chloro acetanilide of 2-iodo-5-methly or chloro acetanilide

Entry	2-iodo-5-alkyl acetanilide	Terminal Alkyne	Condition	Product	[d]Yield (%)
1			80-85^0 C, 24 hr	 15	62
2		$H_3C(H_2C)_3C\equiv CH$	60^0 C, 30 hr	 16	37
3		$CH_3(CH_2)_4C\equiv CH$	60^0 C, 30 hr	 17	33
4			80-85^0 C, 24 hr	 18	58

Yield[d] (%) was based on the amount (mmol) of 2-iodo-5-methly or chloro acetanilide

2.8 Characterization of 2-Alkynyl – 4 –iodo- 5- methyl and chloro acetanilide

2.8.1 Characterization of Pheny acetylene dimmer 14

During Sonogashira coupling a dimmer of phenyl acetylene **14** was produced. It was separated by hexane with R_f 0.90 (100 % hexane) in the column chromatography. The compound was greenish solid.

In the **IR spectrum**(fig- 44) of the compound the absorption band found at 2148.74 cm^{-1} represent the ν_{cc} of the c≡c bond in the dimmer.

The **^{1}H NMR spectrum** (fig- 45) of the compound showed, the peaks at δ_H 7.52 (d, 4H, CH, J= 6.84 Hz) was due to the similar CH proton of the C-2 and C-6 carbon of the both phenyl ring. The chemical shift position at δ_H 7.3.5 (m, 6H, CH) showed as multiplate due to the long range coupling among the protons (C-3, C-4 and C-5) of the aromatic ring.
The coupling of the adjacent protons are clearly observed from the COSY (fig- 46) spectrum.
The **^{13}C NMR spectrum** (fig -47) of the compound showed, the peaks at δ_c 132.52, 129.27, 128.51 designated for similar carbon at C-2, C-3 and C-4 of the both ring. The chemical shift at 121.89 represents the C-1 carbon of the both aromatic ring. The positions at δ 81.63 and at δ 73.99 represent the acetylenic (C≡C) carbon respectively.

2.8.2 Characterization of 2-Phenylethynyl – 4 – iodo -5- methylacetanilide 15

The compound **15** (yield 60%) was yellow solid with R_f value 0.73 (n-Hexane: Chloroform 2:1). The structure of compound **15** was assigned by spectral data.

In the **IR spectrum** (fig – 48) of the compound the absorption band found at 3293.51 cm^{-1} due to the ν_{NH} of the acetanilide group, the band at 2214.32 cm^{-1} represent the ν_{cc} of the c≡c bond, where as a band at 1663.63 cm^{-1} represents the ν_{co} of the acetanilide group.

The **^{1}H NMR spectrum** (fig - 49) of the compound showed, the peaks at δ_H 8.35 (s, 1H, CH) and at δ_H 7.91 (s, 1H, CH) due to the aromatic protons. The multiplate at δ 7.51 – 7.33 was results from the coupling with proton in the phenyl ring. The chemical shift position at δ 7.85 was found in the form of singlet due to the NH proton.

The **^{13}C NMR spectrum** (fig – 50) of the compound showed, the peaks at δ_c 168.45 due to the C=O carbon, at 143.43 for C-2, at δ 140.92 in favor of Ar-NH, at δ 138.82 designated for C-5, at δ 98.30 and at δ 82.64 due to the acetylenic (C≡C) respectively. The chemical shift position at δ 92.85 designed for Ar-I, at δ 28.53 and at 25.02 due to the O-CH_3 group and aromatic methyl respectively.
In the UV (fig – 51) spectrum the peak was found in the range of 292-250 nm.

Complete analysis of the UV, IR, and 1H NMR spectrum of this compound was agreement with the structure accorded to it as synthesis of **2**-Phenylethynyl – 4 —iodo -5- methyl acetanilide **15**

2.8.3 Characterization of 2-Hexynyl – 4 –iodo- 5- methyl acetanilide 16

In the **IR spectrum** (fig-52) of the compound the absorption band found at 3299.30 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1665.56 cm^{-1} due to the ν_{co} of the acetanilide group and the band at 2230.71 cm^{-1} represent the C≡C bond.
The **^{1}H NMR spectrum** (fig- 53) of the compound showed, the peaks at δ_H 8.30 (s, 1H, CH) and 7.76 (s, 1H, CH) due to the aromatic protons. The chemical shift position at δ 7.80 was found in the form of singlet due to the NH proton. The chemical shift at 2.40 and 2.18 in the form of singlet represent the -OCH_3 and Ar-CH_3 respectively. The chemical shift at 2.48, 1.60 and 1.50 correspondence the –CH_2- group of the hexyne. The chemical shift at 0.96 in the form of triplet represents the alkyl group of the hexyne.
The **^{13}C NMR spectrum** (fig- 54) of the compound showed, the peaks at δ_c 168.13 due to the C=O carbon, at δ 142.52 in favor of Ar-NH, at δ 138.95 designated for C-5, at δ 119.84 due to the C-6 respectively, at δ 76.87 and at δ 98.38 due to the acetylenic(C≡C) respectively, at δ 92.72 designed for Ar-I, and at δ 23.84 and 28.49 due to the –CH_3 and –OCH_3 group respectively.
The structure was further confirmed from its DEPT (fig- 55) spectrum. There are only two carbon in the aromatic ring at 139.84 and 119.84 represent the -CH of the aromatic ring.

2.8.4 Characterization of 2-Heptynyl – 4 –iodo- 5- methyl acetanilide 17

The compound 17 (65 mg, 33%) was brown solid, m.p- 100^0 C and R_f value 0.73 (n-Hexane: Ethylacetate = 1:1).

In the **IR spectrum** of the compound (fig- 56) the absorption band found at 3293.51 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1663.63 cm^{-1} due to the ν_{co} of the acetanilide group and the band at 2224.93 cm^{-1} represent the C≡C bond.

The **^{1}H NMR spectrum** (fig- 57) of the compound showed, the peaks at δ_H 8.31 (s, 1H, CH) and 7.77 (s, 1H, CH) due to the aromatic protons. The chemical shift position at δ 7.81 was found in the form of singlet due to the NH proton. The chemical shift at 2.41 and 2.19 in the form of singlet represent the -OCH_3 and Ar-CH_3 respectively. The chemical shift at 2.48, 1.62 and 1.45, 1.38 correspondence the –CH_2- group of the heptyne. The chemical shift at 0.93 in the form of triplet represents the alkyl group of the heptyne.

The **^{13}C NMR spectrum** (fig- 58) of the compound showed, the peaks at δ_c 168.50 due to the C=O carbon, at δ 142.48 in favor of Ar-NH, at δ 138.95 designated for C-5, at δ 119.73 due to the C-6 respectively, at δ 74.47 and at δ 98.38 due to the acetylenic (C≡C) carbon respectively, at δ 92.72 designed for Ar-I, and at δ 28.40 and 31.14 due to the –CH_3 and –OCH_3 group respectively.
In the UV (fig- 59) spectrum the absorption band of the compound **17** shows in the region 290-320 nm.

2.8.5 Characterization of 3- Chloro- 2-Phenylethynyl – 4 – iodo acetanilide 18

The compound **18** (55 mg, 58%) was white solid, m.p-122^0 C, R_f value 0.73(n-Hexane: Chloroform 2:1).
In the **IR spectrum** of the compound (fig -60) the absorption band found at 3297.37 cm^{-1} due to the ν_{NH} of the acetanilide group, where as a band at 1664.60 cm^{-1} due to the ν_{co} of the acetanilide group and the band at 2217.21 cm^{-1} represent the C≡C bond.

The **^{1}H NMR spectrum** (fig - 61) of the compound showed, the peaks at δ_H 8.50 (s, 1H, CH) and at δ_H 7.94 (d, 1H, CH) due to the aromatic protons. This proton causes the coupling with the nearby proton. The multiplate at δ 7.51 – 7.34 was results from the coupling with proton in the phenyl ring. The chemical shift position at δ 7.68 was found in the form of singlet due to the NH proton.
The **^{13}C NMR spectrum** (fig – 62) of the compound showed, the peaks at δ_c 168.50 due to the C=O carbon, at δ 109.89 and at δ 96.64 due to the acetylenic (C≡C) carbon

respectively. The chemical shift position at δ 98.88 designed for Ar-I, at 24.30 due to the O–CH_3 group.

2.9 Mechanism of palladium catalyzed reactions of 2-iodoacetanilide with terminal alkynes:

Although the detailed mechanism of the reaction is yet to be clarified, it can be perceived that the reactions proceed according to scheme- 8. It was observed that the presence of palladium catalyst and base were very essential for the success of heteroannulation reactions. The key steps of the possible mechanism were based on the following observations.

It could be suggested that Pd (0) must be the intermediate involved in the catalytic process. The reduction of Pd (II) to Pd (0) in the presence of Et_3N and terminal alkynes took place.

In the step-1, terminal alkynes went to react with CuI and Et_3N to the Cu inversion in the alkynes.

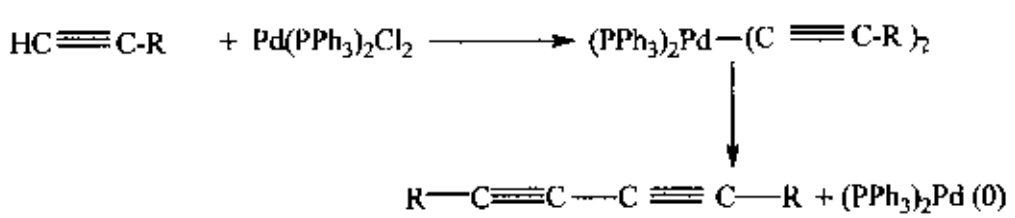
In the step-II, the formation of Pd (0) from the interaction of bis-(triphenylphosphine) palladium (II) chloride and cuprous acetylide was proposed by Hagihara[126].

In step-III, the catalytic cycle substituted acetanilide oxidatively added to bis(triphenylphosphine) palladium(0) to generate a 2-anilide palladim (II) complex A. Then the terminal alkyne could be co-ordinated with palladium (II) complex A (Heek reaction) giving rise to co-ordinated complex B. The alkynyl palladium complex B generated the original bis (triphenyl phosphine) palladium (0) through the reductive elimination of the substituted products to afford the 2-ethynyl acetanilide. Bis(triphenylphosphine) palladium (0) could then continue the catalytic cycle.

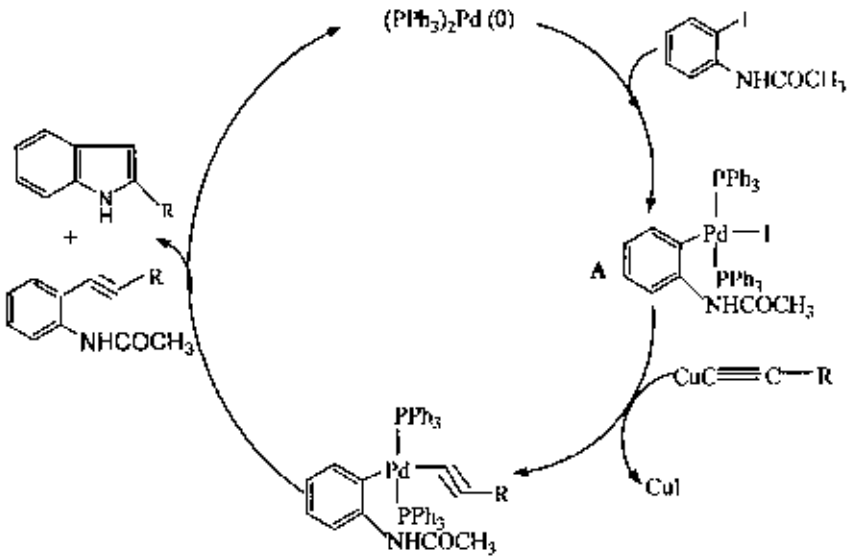
The mechanism of the reaction is given below.

Step-1

Step-II



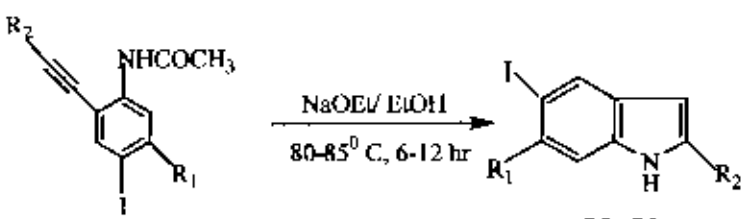
Step-III



Scheme-8

2.10 Base catalyzed reaction with 2-Ethynyl substituted acetanilide

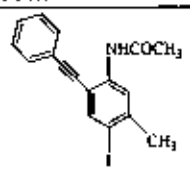
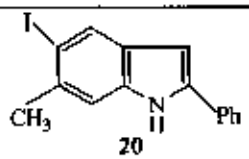
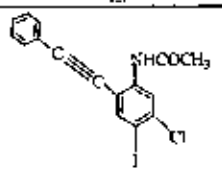
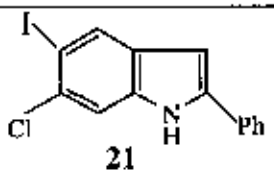
The 2-Ethynyl – 4 –iodo- 5- methyl acetanilide **15** and 2-Ethynyl – 4- iodo- 5- chloro acetanilide **18** was added to sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml) and the mixture was stirred under a nitrogen atmosphere for 6-12 hr at 80-85^0 C. After usual workup the crude product was purified by column Chromatography on silica gel using n-Hexane: Ethyl acetate (1:1) to yield indole **20, 21** as shown in scheme-9.



15, 18 **20, 21**

Scheme-9

Table-6: Synthesis of 4-Iodo –5-methyl or chloro – 2 – phenyl indole

Entry	2-iodo-5-methyl acetanilide	Condition	Product	Yield[c] (%)
1	 15	80-85^0 C, 6 hr	 20	65
2	 18	80-85^0 C, 12 hr	 21	42

Yield[c] (%) calculated on the base of the amount of compound 15 and 18

2.11.1 Characterization 4 - iodo –5 – methyl – 2 – phenylethylaniline 19

The struture of the compound **19** was established by obserbation of the ^{1}H NMR and ^{13} C NMR spectra.

In the ^{1}H NMR (fig-63) spectra the chemical shift was found in the position δ_H 7.75 (s, 1H, CH) and 6.64 (s, 1H, - CH) represent the C11 of the aromatic ring. Where as the chemical shift at the position δ_H 4.22 (s, 1H, -NH_2) represents the proton of the aniline. The multiplate in the region 7.50-7.33 (m, 5H, CH) due to the aromatic phrotons and the δ_H 2.34 (s, 3H, -CH_3) due to the aromatic methyl group.

^{13}C NMR spectrum (fig- 64) reveals the structure of the compound **19** at positions δ_C 147.75, 145.70, 142.72, 141.28, 137.80, 131.40, 128.37, 128.32, 123.00, 115.45, due to the aromatic ring carbons. The chemical shift at positions 107.95, 95.07, represents the acetylenic carbons. The chemical shift at 84.22 due to the Ar-I and 28.07 for aryl methyl respectively.

2.11.2 Characterization of 5-Iodo-6- methyl – 2- phenyl indole 20

The compound **20** was yellow solid and R_f value: 0.59 (hexane: ethyl acetate= 1:1).

The **^{1}H NMR spectrum** (fig- 66) of the compound showed, the peaks at δ_H 7.53-7.48 (m, 2H, CH) of the protons of the m-toluidine ring and 7.33-7.31 (m, 5H, CH) due to the isolated aromatic protons. A distinguish peak at position 6.59 was due to the venylic

proton of the indole ring. The chemical shift position at δ 4.37 was found in the form of singlet due to the NH proton.

The **^{13}C NMR spectrum** (fig- 67) of the compound showed, the peaks at 29.67 due to the aromatic methyl. The peak at 85.38 is due to the Ar-I carbon. The peaks at 135.82 and 128.27 are due to the C-8 and C-9 respectively. The peaks at 115.45 and at 98.38 might be due to the C-2 and C-3 respectively. The peak at 112.01 represents the C-7 carbon.
In the UV spectrum (fig- 68) the peak was found in the range of 266-216 nm.

2.11.2 Characterization of 6- Chloro – 5- iodo – 2- Phenyl indole 21

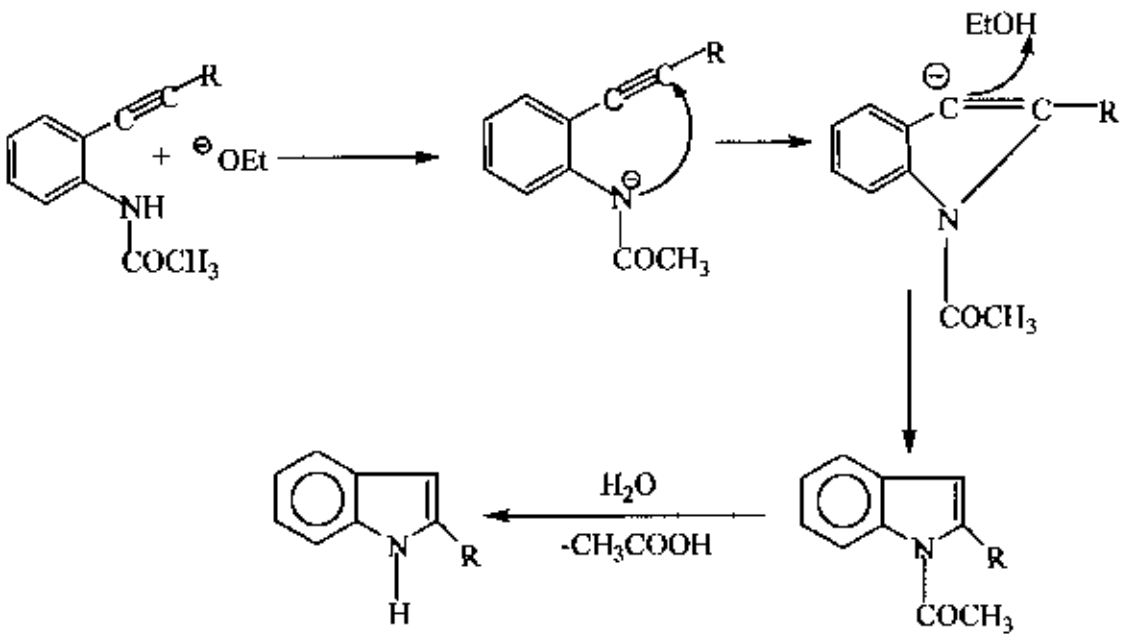
The compound **21** was brown semisolid, R_f value 0.68(n-Hexane: Chloroform 2:1).
The **^{1}H NMR spectrum** (fig- 69) of the compound showed, the peaks at δ_H 7.57-7.52 (m, 2H, CH) of the protons of the m-chloro aromatic ring and 7.33-7.31 (m, 5H, CH) due to the isolated aromatic protons. A distinguish peak at position 6.79 was due to the venylic proton of the indole ring. The chemical shift position at δ 4.49 was found in the form of a singlet due to the NH proton.

The **^{13}C NMR spectrum** (fig-70) of the compound showed, the peaks at 88.20 is due to the Ar-I carbon. The peaks at 137.89 and 128.27 are due to the C-8 and C-9 respectively. The peaks at 125.27 and at 102.89 might be due to the C-2 and C-3 respectively. The peak at 113.67 represents the C-7 carbon.
In the UV spectrum (fig- 71) the peak was found in the range of 366-226 nm.

2.12 Mechanism of the base catalyzed cyclization of indoles

The cyclization reaction of 2-Ethynyl – 4 –iodo- 5- methyl and chloro acetanilide was carried out by sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml).
The plausible mechanism for base catalyzed cyclization of indoles was shown in the scheme- 10.

1. In the first step ethoxide ion extract the proton from nitrogen and nitrogen bears the negative charge.
2. The nitrogen attacks the partially positive carbon of the alkyne and the partially negative carbon attacks the proton of the alcohol available in the solvent system.
3. In the final step CH_3COOH removed by hydrolysis during workup.



Scheme-10

2.13 Conclusion

Here we developed a convenient and facile method for the synthesis of 2, 6-disubstituted-indole derivatives through palladium and base catalyzed reactions. The most important features of the synthesis were that –

- Readily available inexpensive starting materials were used under relatively mild conditions.
- Various Iodoacetanilide compounds were synthesized successfully.
- The approach of synthesis of indole from substituted iodo aniline by palladium-catalyzed reaction was found to be inconvenient.
- The one pot synthesis of 2-Hexynyl- 5- methyl indole by the palladium-catalyzed reaction of 2-iodo-5-methyl acetanilide is developed in mild condition.
- The yield of substituted indole in the case of phenyl acetylene with various acetanilides was greater than that of the n- Hexyne or 1-Heptyne.
- The yield of substituted indoe in the case of m-toluidine was better than that of m-chloroaniline.
- This methodology is also expected to be widely used in synthesis of indole skeleton containing natural products and spiro compounds.
- The synthesized indole derivative might show antibacterial and antifungal activity.

CHAPTER-II

Section-II

Experimental

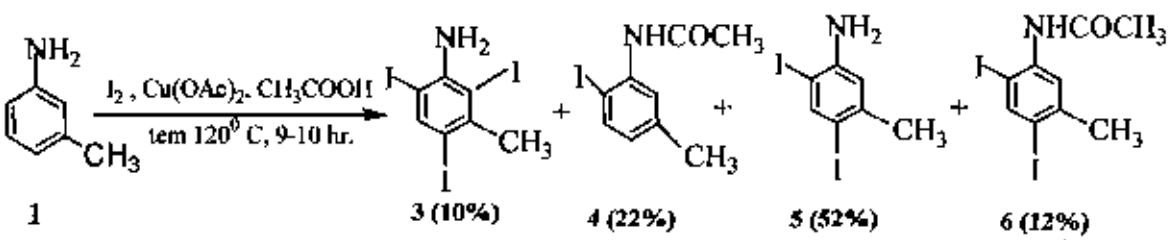
Experimental

3.1 Synthesis of starting materials

3.1.1 Iodination of m-toluidine

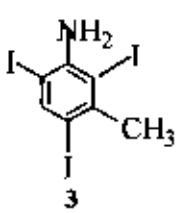
Into a round bottom flask equipped with condenser 5 ml (0.05 mol) of meta toluidine, 11.61 gm (0.05 mol) of granulated iodine and 9.31 gm copper acetate (0.05 mol) were placed . Then 50 ml of acetic acid was poured in to the mixture and was shaken the contents of the flask steadily. Finally the reaction mixture was refluxed for 9-10 hours with constant stirring at 120^0 C. The completion of the reaction was monitored by TLC. After completion of the reaction, acetic acid was evaporated to dryness and was extracted with chloroform. The product was neutralized by saturated solution of sodium hydrogen carbonate ($NaHCO_3$), free iodine was removed by using sodium thiosulfate solution, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude product was purified by column chromatography on silica gel with hexane: chloroform in different ratio. Five compounds were detected but four compounds **(3, 4, 5, 6)** were isolated in different ratio.



Scheme-1

i) Characterization of 2, 4, 6-triiodo-3-methyl aniline 3



Physical state: White crystal

M.P: 136^0 C

R_f Value: 0.72 (Hexane: chloroform = 1:1)

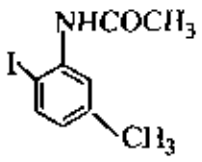
IR (KBr): ν_{max} 3403.45, 3313.76, 3050.47, 1599.02, 1420.60, 1362.73, 1080.16, 868.95.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H 8.04 (s, 1H,CH), 4.78 (s, 2H, NH_2), 2.73(s, 3H, Ar-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.93, 146.84, 143.97, 86.45, 83.55, 78.35, 35.98.

DEPT : 146.84, 35.98

ii) Characterization of 2-iodo-5-methyl acetanilide 4



4

Physical state: White crystal

R_f Value : 0.65 hexane: chloroform (1:1).

UV (EtOH) : λ_{max} 252, 232, 212 nm.

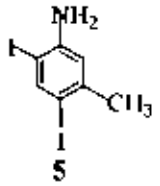
IR (KBr): ν_{max} 3315.4 (-NH), 1668.3 (C=O), 1606.6, 1581.5, 1533.3, 1471.6, 1396.4, 1311.5, 819.7

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (d, 1H,CH, J= 8.5 Hz), 7.46 (s, 1H, NH), 7.42(d, 1H,CH, J= 1.94 Hz), 7.03-(dd, 1H, CH, J=11.2 Hz), 2.36 (s, 3H,-OCH_3), 2.13 (s, 3H, Ar-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.52 (C=O), 142.03, 139.11, 138.11, 121.11, 119.02, 94.43, 28.13, 24.58.

DEPT : 139.09, 121.09, 119.02, 28.13, 24.58.

iii) Characterization of 2,4-diiodo-5-methyl aniline 5



5

Physical state: Brown solid

M.P: 80^0 C

R_f Value: 0.67 (n-Hexane: Chloroform = 1: 1)

UV (EtOH) : λ_{max} 252, 232, 224 nm.

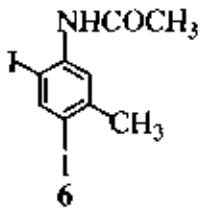
IR (KBr): ν_{max} 3401.53, 3300.26, 2967.53, 2936.67, 1599.02, 1543.08 1459.17, 1257.61, 1021.33, 869.91, 616.27cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.94(s, 1H,CH), 6.64(s, 1H, CH), 4.03(s, 2H, NH_2), 2.27(s, 3H,$ArCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 146.90, 146.66, 142.25, 115.55, 86.45, 81.12, 27.50.

DEPT: 146.66, 115.55, 27.50.

iv) Characterization of 2,4-diiodo-5-methyl acetanilide 6



6

Physical state: White crystal

M.P: 215^{0}C

R_f Value: 0.58 (Hexane: Ethyl acetate = 1:1)

UV (EtOH) : λ_{max} 204, 274, 250, 226 nm.

IR (KBr): ν_{max} 3265.54, 3057.23, 2971.39, 2921.24, 2849.87, 1659.77 (C=O), 1554.65, 1512.22, 1359.84, 1278.83,1032.90, 870.88 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.14 (s, 2H, CH), 7.30 (s, 1H, NH), 2.38 (s, 3H,-OCH_3), 2.21 (s, 3H, Ar-CH_3)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.24 (C=O), 146.83, 143.02, 138.40, 122.23, 95.33, 86.52, 27.97, 24.97.

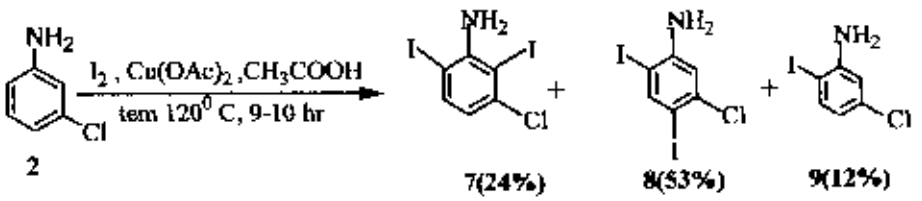
DEPT: 146.83, 122.23

3.1.2 Iodination of 3-Chloro-aniline:

5 ml (0.05 mol) of 3-Chloro-aniline, 12.09 gm (0.05 mol) of granulated iodine and 9.31 gm copper acetate (0.05 mol) were placed one by one into a round bottom flask equipped with condenser. Then 50 ml of acetic acid was poured in to the mixture and was shaken the reaction mixture steadily. Finally the reaction mixture was refluxed for 9-10 hours with constant stirring at 120^0 C. The completion of the reaction was monitored by TLC comparing with starting material. After completion of the reaction, acetic acid was evaporated to dryness and was extracted with chloroform. The product was neutralized by

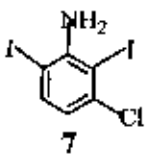
a saturated solution sodium hydrogen carbonate ($NaHCO_3$), free iodine was removed by using sodium thiosulfate solution, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude product was purified by column chromatography on silica gel with hexane: chloroform in different ratio and three compounds were isolated.



Scheme-2

i) Characterization of 3-chloro- 2,6 diiodo-aniline 7



7

Physical state: Yellow Solid

M.P: 148^0 C

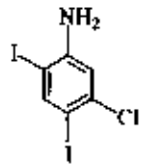
R_f Value : 0.78, hexane: chloroform (5:1).

UV (EtOH) : λ_{max} 244, 234, 210 nm.

IR (KBr): ν_{max} 3447.82, 3403.45, 3312.80, 2925.10, 1595.16, 1416.74, 1355.02, 1256.65, 165.99, 1031.93, 873.77 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (d, 1H,CH, *J*= 8.36 Hz), 6.58 (d, 1H, J=8.37 Hz), 4.87 (br S, 2H, NH_2).

ii) Characterization of 5-chloro- 2, 4 diiodo-aniline 8



8

Physical state: White crystal

M.P: 75^0 C

R_f Value : 0.90 hexane: chloroform (1:1).

UV (EtOH) : λ_{max} 290, 274, 250 nm

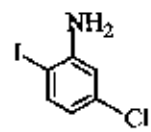
IR (KBr): ν_{max} 3410.50, 3333.05 (N-H_2), 3071.69, 2925.10, 1613.48, 1454.35, 1360.80, 1022.29, 877.63 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.98 (s, 1H,CH), 6.83 (s, 1H, CH), δ 4.27 (br S, 2H, NH_2)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 147.90, 147.79, 139.13, 114.38, 82.93 and 82.05

DEPT: 147.80, 114.38

iii) Characterization of 5-chloro- 2-iodoaniline 9



9

Physical state: brown solid

M.P: 70^0 C

R_f Value: 0.58 Hexane: Chloroform (1:1).

UV (EtOH) : λ_{max} 258, 210 nm

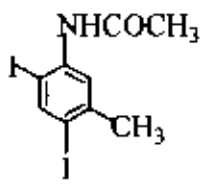
IR (KBr): ν_{max} 3421.78, 3343.66, 2956.93, 2925.10, 2854.70, 1621.20, 1463.03, 1289.44, 101.37, 854.48 and 817.83 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (d, 1H,CH, J= 8.16 Hz), 6.30 (d, 1H,CH, J= 7.46 Hz), 6.80 (s, 1H, CH), 3.73 (br S, 2H, NH_2).

3.2.1 Preparation of 2,4-diiodo-5-methyl acetanilide 6:

2,4-Diiodo-5-methyl aniline **5** was stirred with acetic acid, acetic anhydride (1: 1) and small amount of zinc dust at room temperature for half an hour. Then the reaction mixture was refluxed for 2-3 hours with constant stirring at 80^0 C. The hot reaction mixture was poured in a thin stream into a 500 ml beaker containing 200 ml of cold water with constant stirring. Filtered the crude product by using suction pump, washed with a little cold water and dried upon a filter paper in the air. The desired product **6** was purified by crystallization using ethanol.

The compound was transparent crystal; yield 72%, m.p 214-215^0 C. R_f = 0.58 (Hexane: Ethyl acetate =1:1).



6

IR (KBr): ν_{max} 3266.51, 1659.77 (C=O), 1556.77, 1554.65, 1371.41, 1278.83, 1033.86, 870.88 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.13 (s, 2H,CH), 7.30 (s, 1H, NH), 2.38 (s,3H, OCH_3), 2.20 (s, 3H, Ar-CH_3)

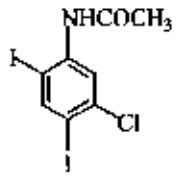
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.75 (C=O), 146.79, 142.96, 138.39, 122.47, 95.65, 87.88, 27.90, 24.88.

DEPT: 146.76, 122.47, 27.88, 24.88

UV (EtOH) : λ_{max} 274, 250, 226 nm

3.2.2 Preparation of 5-chloro- 2,4 diiodo- acetanilide 10

5-Chloro- 2,4-diiodoaniline, **8** was stirred with acetic acid, acetic anhydride (1: 1) and small amount of zinc dust at room temperature for half an hour. Then the reaction mixture was refluxed for 2-3 hours with constant stirring at 80^0 C. After usual workup as it was done before, the product, **10** was purified by crystallization process using ethanol.



10

The compound was white crystal; yield 75%, m.p 158^0 C. R_f = 0.52 (Hexane: Ethyl acetate =1:1).

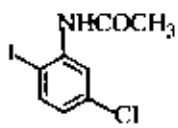
IR (KBr): ν_{max} 3272.29 (N-H), 3084.23, 2923.17, 1658.81 (C=O), 1568.15m, 1525.72, 1397.45, 1280.76, 1089.80, 867.98, 603.73 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.30 (s, 1H, CH), 7.66 (d, 1H, CH), 7.37(s, 1H, NH), 2.23 (s, 3H, -OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.0(C=O), 147.68, 139.18, 136, 125.95, 121.79, 121.53, 24.79.

3.2.3 Preparation of 5-chloro- 2- iodoacetanilide 11

5-Chloro- 2-iodoaniline, 9 was stirred with acetic acid, acetic anhydride (1: 1) and small amount of zinc dust at room temperature for half an hour. Then the reaction mixture was refluxed for 2-3 hours with constant stirring at 80^0 C. After usual workup the product, **11** was washed with water and finally dried, recrystallized from ethanol.



11

The compound was white crystal; yield 65%, m.p 120-122^0 C. R_f = 0.52 (Hexane: Ethyl acetate =1:1).

IR (KBr): ν_{max} 3510, 3395, 3237.57, 3095.80, 1653.99 (C=O), 1581.66, 1466.89, 1375.27, 870.88, 569.97 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.73 (m, 2H,CH), 7.10 (d, 1H, CH), 7.41 (s, 1H, NH)

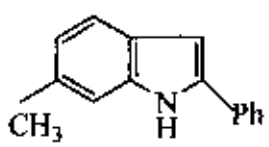
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.45 (C=O), 140.19, 139.12, 138.92, 120.40, 119.29, 91.06, 24.62.

DEPT: 140.166, 120.38, 119.28 and 24.59

3.3 Synthesis of 6-methyl-2-phenyl indole 12

Bis-(triphenyl phosphine) palladium(II) chloride (44.65 mg, 0.0636 mmol), copper (II) iodide (27.77 mg, 0.145 mmol), triethylamine (734.27 mg, 7.27 mmol) were added to a solution of 2-iodo-5-methyl acetanilide (500 mg, 1.818 mmol) in DMF (5ml).

The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then phenylacetylene (222.58 mg, 2.811 mmol) was added drop wise to the mixture. The reaction mixture was heated at 80-85^0 C for 24 hours with constant stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The desired product **12** was purified by column Chromatography on silica gel using n-Hexane: chloroform (3:1).



12

The compound **12** (260 mg, 52%) was yellow solid, m.p-122^0 C, R_f value 0.73 (n-Hexane: Chloroform = 2:1).

IR (KBr): ν_{max} 3420.81, 3320.51, 3057.23, 2208.53, 1608.66, 1491.00, 1453.39, 749.36, 682.81 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (m, 3H, CH), 7.35 (m, 5H, CH) 5.02 (brS, 1H, NH), 2.70 (s, 3H, -CH_3)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.06, 144.93, 135.16, 131.54, 131.33, 128.57, 128.48, 128.35, 127.96, 122.78, 112.49, 104.96, 94.83, 91.29, 84.95, 28.32.

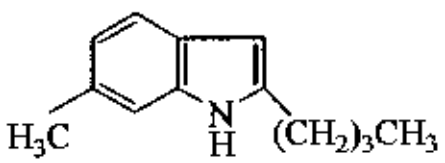
UV (EtOH) : λ_{max} 302, 296, 292, 288, 210 nm.

3.4 Synthesis of 2-Hexynyl- 5- methyl indole 13

Bis-(triphenyl phosphine) palladium(II) chloride(18 mg, 0.025 mmol), copper (II) iodide (11 mg, 0.058 mmol), triethylamine (293.78 mg, 2.908 mmol) were added to a solution of 2-iodo-5-methyl acetanilide (200 mg, 0.727 mmol) in DMF(5ml).

The mixture was stirred for 1 hr under a nitrogen atmosphere at room temperature. Then Hexyne (72.4 mg, 0.8724 mmol) was added drop wise to the mixture. The reaction mixture was heated at 60^0 C for 30 hours with constant stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mass was purified by column Chromatography on silica gel using n-Hexane: chloroform (3:1).

The compound **13** (85 mg, 43 %) was white solid and R_f value 0.75 (n-Hexane: Chloroform 5:1).



13

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (d, 2H, CH), 7.35 (m, 2H, CH) 4.80 (brS, 1H, NH), 2.56 (s, 3H, $-CH_3$) 2.41 (m, 2H, $-CH_2-$), 1.48 (m, 2H, $-CH_2-$), 0.9 (s, 3H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$): 142.42, 140.87, 132.50. 129.20, 128.44, 119. 75, 11.91, 98.29, 28.41, 24.94, 22.05, 19.22, 13.56.

UV (EtOH) : λ_{max} 346, 290, 278, 264, 216 nm.

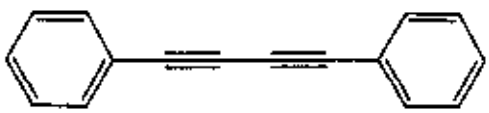
3.5 Synthesis of 2-alkynyl-4- iodo-5- methyl or chloro acetanilide

3.5.1 Synthesis of 2-Phenylethynyl – 4 – iodo -5- methylacetanilide 15

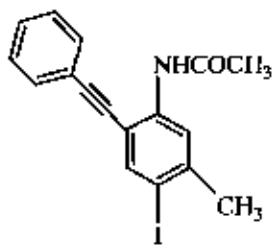
Bis-(triphenyl phosphine) palladium(II) chloride(18 mg, 0.025 mmol), copper (II) iodide (11.30 mg, 0.059 mmol), triethylamine (597 mg, 2.96 mmol) were added to a solution of 2,4-diiodo-5-methyl acetanilide (300 mg, 0.740 mmol) in DMF(5ml).

The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then phenylacetylene (90.72 mg, 0.888 mmol) was added drop wise to the mixture. The reaction

mixture was heated at 80-85^0 C for 24 hours with constant stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mass was purified by column Chromatography on silica gel using n-Hexane: chloroform (3:1).



14



15

During this reaction another product phenyl acetylene dimmer **14** was also isolated using n-Hexane (100 %).

IR (KBr): ν_{max} 3277.11, 3048.55, 2931.85, 2184.74, 1347.30, 1024.22, 915.24, 755.14, 686.67.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.52 (d, 4H,CH), 7.35 (m, 6H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 132.58, 129.28, 128.51, 121.90, 81.63, 73.99.

DEPT : 132.58, 129.27,128.51

The compound **15** (185 mg, 62 %) was yellow crystal and R_f value 0.91(n-Hexane: Ethylacetate = 1: 1).

IR (KBr): ν_{max} 3455.53, 3293.51, 3056.26, 2922.21. 2214.32 (C ≡ C), 1663.63 (C=O), 1554.65, 1507.40, 881.48, 753.22, 689.56 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.35 (s, 1H,CH), 7.91 (s, 1H, CH), 7.85 (s,1H, NH), 7.51- 7.39 (m, 5H, CH), 2.24 (s, 3H, CH_3), 2.0 (s, 3H, -O-CH_3).

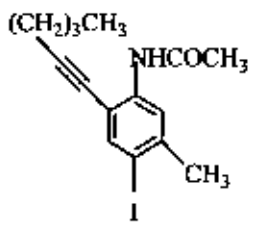
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168, 143.43. 140.92, 138.82, 131.46, 129.06, 128.60, 121.39, 120.07, 98.30, 92.85, 82.64, 28.582, 25.01.

UV (EtOH) : λ_{max} 292, 284, 258, 210 *nm*.

3.5.2 Synthesis of 2-Hexynyl – 4 –iodo- 5- methyl acetanilide 16

Bis-(triphenyl phosphine) palladium(II) chloride(2 mg, 0.0025 mmol), copper (II) iodide (11 mg, 0.059 mmol), triethylamine (298.96 mg, 2.96 mmol) were added to a solution of 2,4-diiodo-5-methyl acetanilide (200 mg, 0.50 mmol) in DMF(5ml).

The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then Hexyne (73.8 mg, 0.888 mmol) was added drop wise to the mixture. The reaction mixture was heated at 60^0 C for 30 hours with constant stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mass was purified by column Chromatography on silica gel using *n*-Hexane: Ethylacetate (1:1).



16

The compound **16** (73 mg, 37 %) was white crystal m.p- 129^0 C and R_f value 0.77 (n-Hexane: Ethylacetate = 1:1)

IR (KBr): ν_{max} 3447.82, 3299.30, 2930.89, 2871.07, 2230.71(C≡C), 1665.56 (C=O), 1560.44, 1464.96, 1288.47, 884.38 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H 8.30 (s, 1H, CH), 7.80 (s, 1H, NH), 7.76 (s, 1H, CH), 2.48(t, 2H, -CH_2), 2.40 (s, 3H, OCH_3), 2.18 (s, 3H, -CH_3), 1.60 (m, 2H, -CH_2), 1.50 (m, 2H, -CH_2), 0.96 (t, 3H, -CH_3).

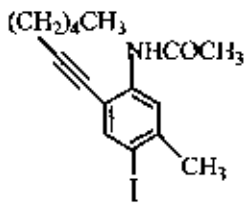
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.64, 19.31, 22.13, 25.01, 28.49, 30.76, 76.87, 92.72, 98.38, 112.01, 119.84, 138.95, 140.97, 142.52. 168.13.

DEPT: 13.64, 19.31, 22.13, 25.01, 28.49, 30.76, 119.84, 140.97,

3.5.3 Synthesis of 2-Heptynyl – 4 –iodo- 5- methyl acetanilide 17

Bis-(triphenyl phosphine) palladium(II) chloride(12 mg, 0.0173 mmol), copper (II) iodide (8 mg, 0.039 mmol), triethylamine (199.576 mg, 1.976 mmol) were added to a solution of 2,4-diiodo-5-methyl acetanilide (200 mg, 0.494 mmol) in DMF(5ml).

The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then Heptyne (56.9 mg, 0.593 mmol) was added drop wise to the mixture. The reaction mixture was heated at 60^0 C for 30 hours with constant stirring. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mass was purified by column Chromatography on silica gel using n-Hexane: Ethylacetate (1:1).



17

The compound **17** (65 mg, 33%) was brown solid, m.p- 100^0 C and R_f value 0.73(n-Hexane: Ethylacetate (1:1).

IR (KBr): ν_{max} 3293.51, 2957.89, 2928.96, 2856.63, 2224.93 (C≡C), 1663.63 (C=O), 1559.47, 1512.22,1465.93, 883.41

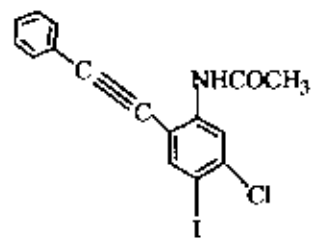
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.31 (s, 1H, CH), 7.81 (s, 1H, NH), 7.77 (s, 1H, CH), 2.48 (t, 2H,-CH_2), 2.41 (s, 3H, -OCH_3), 2.19 (s, 3H, Ar-CH_3), 1.62 (m, 2H, -CH_2), 1.45 (m, 2H, -CH_2), 1.38 (m, 2H, -CH_2), 0.93 (t, 3H, -CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.50 (C=O), 142.48, 140.92, 138.88, 119.73, 111.92, 98.38, 92.72, 74.47, 31.14, 29.68, 28.40, 24.94, 22.19, 19.51, 13.97.

UV (EtOH) : λ_{max} 242, 234, 212 nm.

3.5.4 Synthesis of 3- Chloro- 2-Phenylethynyl – 4 – iodo acetanilide 18

A mixture of 5-chloro 2,4-diiodo acetanilide (100 mg, 0.237 mmol), bis-(triphenyl phosphine) palladium(II) chloride(6 mg, 0.009 mmol), copper (II) iodide (3.62 mg, 0.02 mmol), triethylamine (95 mg, 0.948 mmol) was stirred in DMF (5 ml) under nitrogen atmosphere for 1 hour. Then phenyl acetylene (29 mg, 0.29mmol) was added and heated the reaction mixture with constant stirring at 80^0 C for 24 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue obtained was extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude mass was purified by column Chromatography on silica gel using n-Hexane: Ethyl acetate (1:1).



18

The compound **18** (55 mg, 58%) was white solid, m.p-122^0 C, R_f value 0.73(n-Hexane: Chloroform 2:1).

IR (KBr): ν_{max} 3297.37, 3057.23, 2930.89, 2217.21 (C≡C), 1664.60 (C=O), 1565.26, 1412.88, 1273.04, 752.25 cm^{-1}.

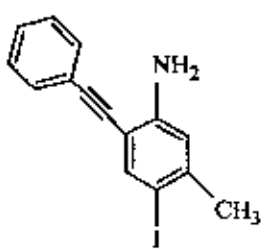
^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.50 (s, 1H, CH), 7.94 (d,1H, CH), 7.68 (s, 1H, NH)7.51- 7.34 (m, 5H, CH), 2.24 (s, 3H, -OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.50 (C=O), 147.68, 139.89, 132.33, 131.70, 131.57, 131.51, 129.15, 128.66, 128.37, 123.55, 119.67, 109.89, 98.88, 96.64, 24.30

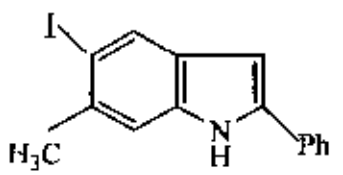
UV (EtOH) : λ_{max} 318, 292, 234 nm.

3.6 Synthesis of 4 - iodo –5 – methyl – 2 – phenylethylaniline 19 and 5-Iodo-6-methyl – 2- phenyl indole 20

The 2-Phenylethynyl – 4 – iodo -5- methylacetanilide (45 mg, 0.119 mmol) was added to sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml) and the mixture was stirred under a nitrogen atmosphere for 4 hr at 80-85^0 C. The reaction the reaction mixture was evaporated to dryness under reduced pressure. Distilled water (200 ml was added to the residue and it was neutralized with dilute 6 N HCl, extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column Chromatography on silica gel using n-Hexane: Ethyl acetate (1:1) to yield pure 4 - iodo –5 – methyl – 2 – phenylethylaniline **19** and 5-iodo-6- methyl – 2- phenyl indole **20.**



19



20

3.6 a) Characterization of 4 - iodo –5 – methyl – 2 – phenylethylaniline 19

IR (KBr): ν_{max} 3420, 2925.10, 2853.73, 1252.79, 756.11cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 (s, 1H, CH), 7.50-7.33 (m, 5H, CH), 6.64 (s, 1H, -CH), 4.22 (s, 1H, -NH_2), 2.34 (s, 3H, -CH_3)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C δ_C 147.75, 145.70, 142.72, 141.28, 137.80, 131.40, 128.37, 128.32, 123.00, 115.45, 107.95, 95.07, 85.09, 84.22, 28.07.

UV (EtOH) : λ_{max} 350, 292, 266, 222 nm.

3.6 b) Characterization of 5-Iodo-6- methyl – 2- phenyl indole 20

R_f Value : 0.59 hexane: ethyl acetate (1:1).

UV (EtOH) : λ_{max} 266, 216, 210 nm.

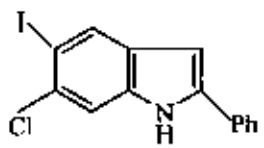
IR (KBr): ν_{max}2925.10, 2852.77, 2204.67, 1616.38, 1594.19, 12555.68, 753.22, 689.56 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 7.53-7.48 (m, 3H, CH), 7.33-7.31(m, 4H, CH), 6.59 (s, 1H, =CH), 4.37 (s, 1H, NH), 2.44 (s. 3H, -CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 137.80, 135.82, 131.42, 131.25, 128.37, 128.27, 115.45, 112.01. 98.38, 85.10, 29.67

3.7 Synthesis of 6- Chloro – 5- iodo – 2- Phenyl indole 21

The 3- Chloro- 2-Phenylethynyl – 4 – iodo acetanilide (35 mg, 0.088 mmol) was added to sodium ethoxide (1.2-1.5 mmol) in ethanol (20 ml) and the mixture was stirred under a nitrogen atmosphere for 4 hr at 80-85^0 C. At the end of the reaction the reaction mixture was evaporated to dryness under reduced pressure. Distilled water (200) ml was added to the residue and it was neutralized with dilute 6N HCl, extracted with chloroform (3×50 ml). The organic extract was washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column Chromatography on silica gel using n-Hexane: Ethyl acetate (1:1) to yield pure 6- Chloro – 5- iodo – 2- Phenyl indole.



21

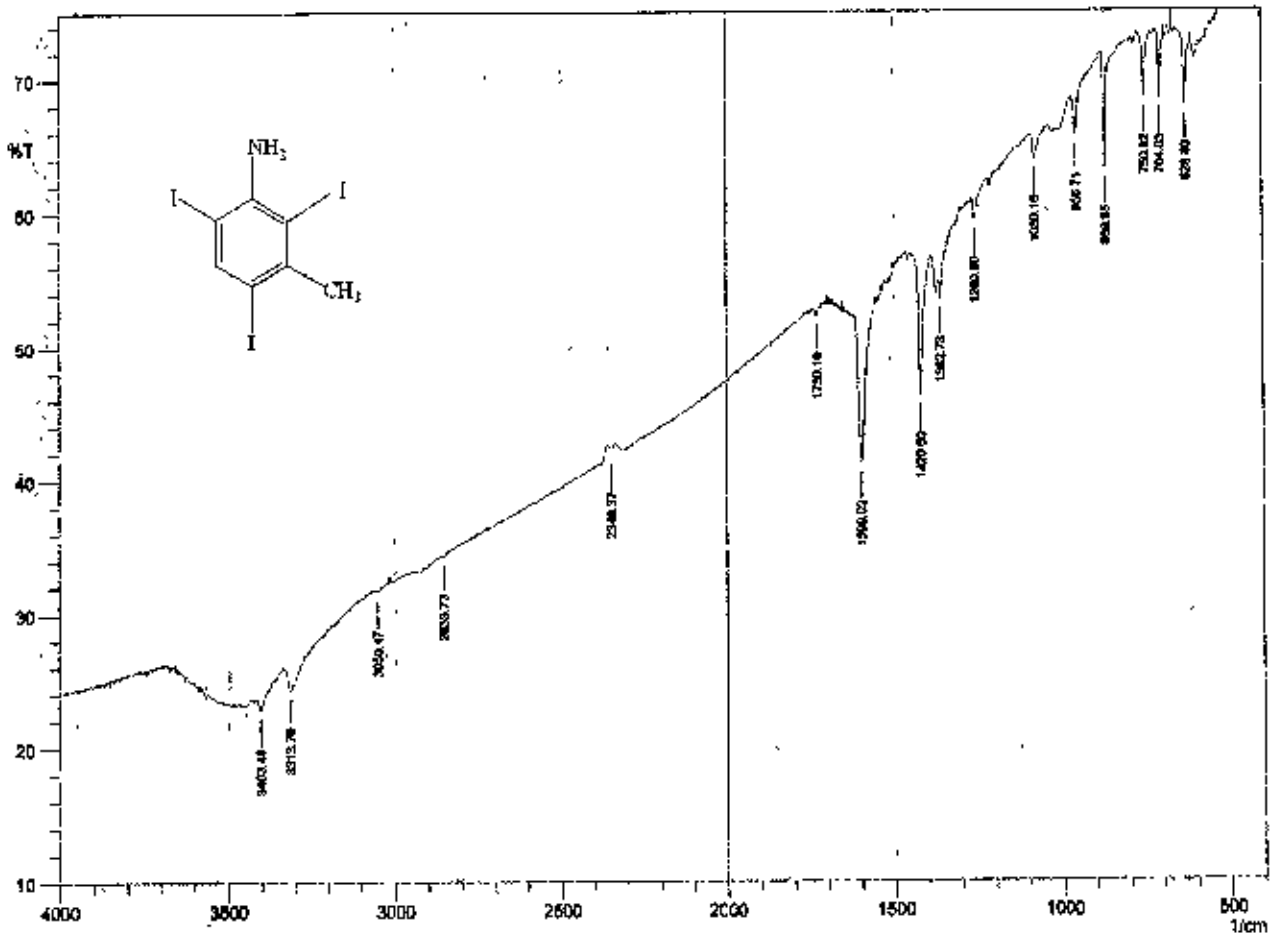
The compound **21** (15 mg, 42 %) was brown semisolid, R_f value 0.68(n-Hexane: Chloroform 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.57-7.52 (m, 2H, CH), 7.35 (m, 5H, CH), 6.79 (s, 1H, =CH) 4.49 (s, 1H, NH)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.68, 137.89, 132.33, 131.70, 131.47, 131.51, 129.15, 128.27, 125.27, 122.55, 113.67, 102.89, 94.18, 88.20

UV (EtOH) : λ_{max} 366, 290, 226, 210 nm.

SPECTRA



	Peak	Intensity
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2	704.03	68.465
3	750.32	68.457
4	868.95	63.19
5	956.71	65.891
6	1060.16	63.946
7	1260.5	58.391
8	1382.73	53.479
9	1420.6	46.266
10	1596.02	41.212
11	1730.16	52.281
12	2348.37	41.916
13	2853.73	34.342
14	3050.47	31.658
15	3313.78	24.383
16	3403.48	22.654

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Analysed By/Date

Fig-1: IR Spectrum of compound 3.

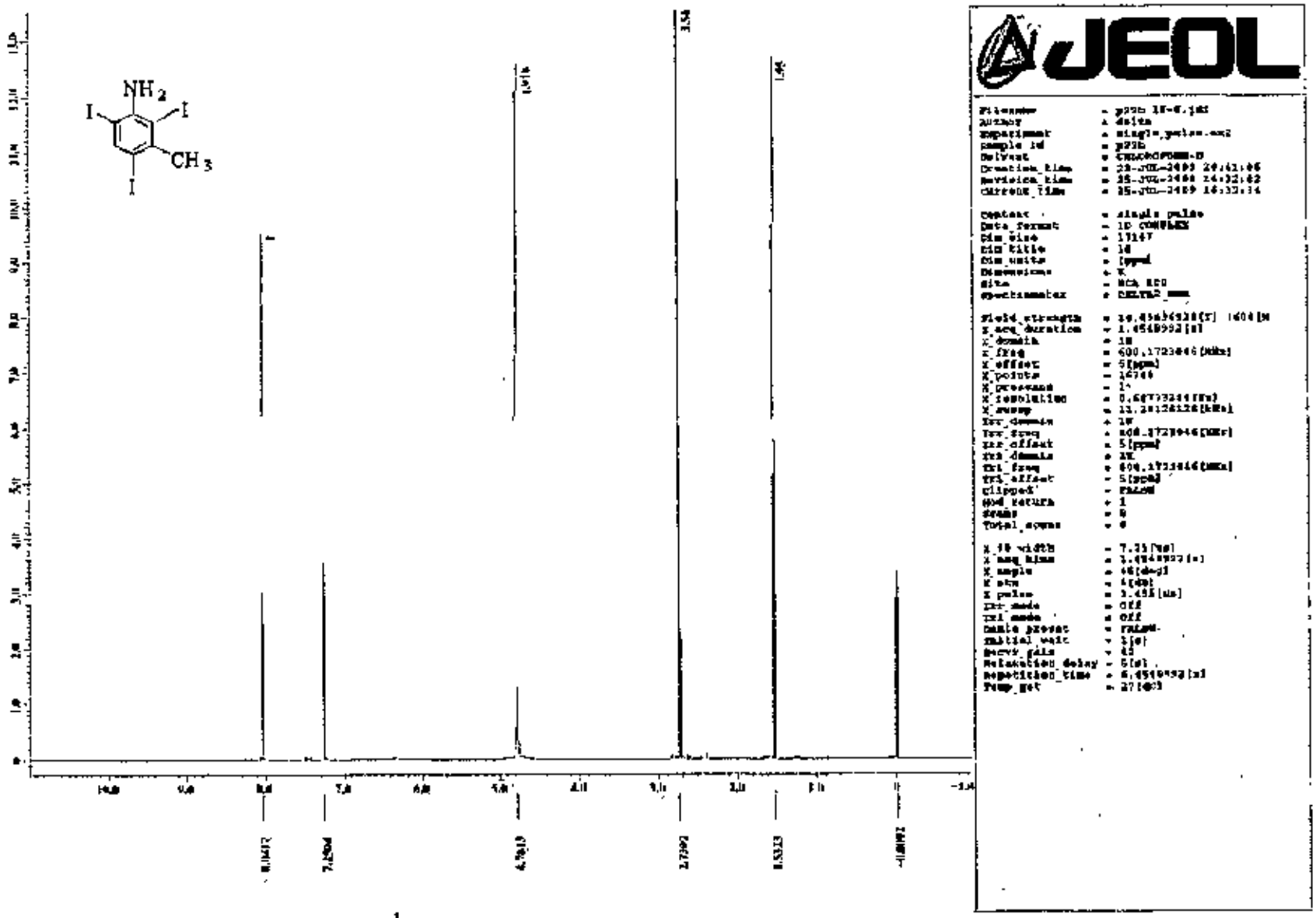


Fig-2: ^{1}H NMR Spectrum of compound **3.**

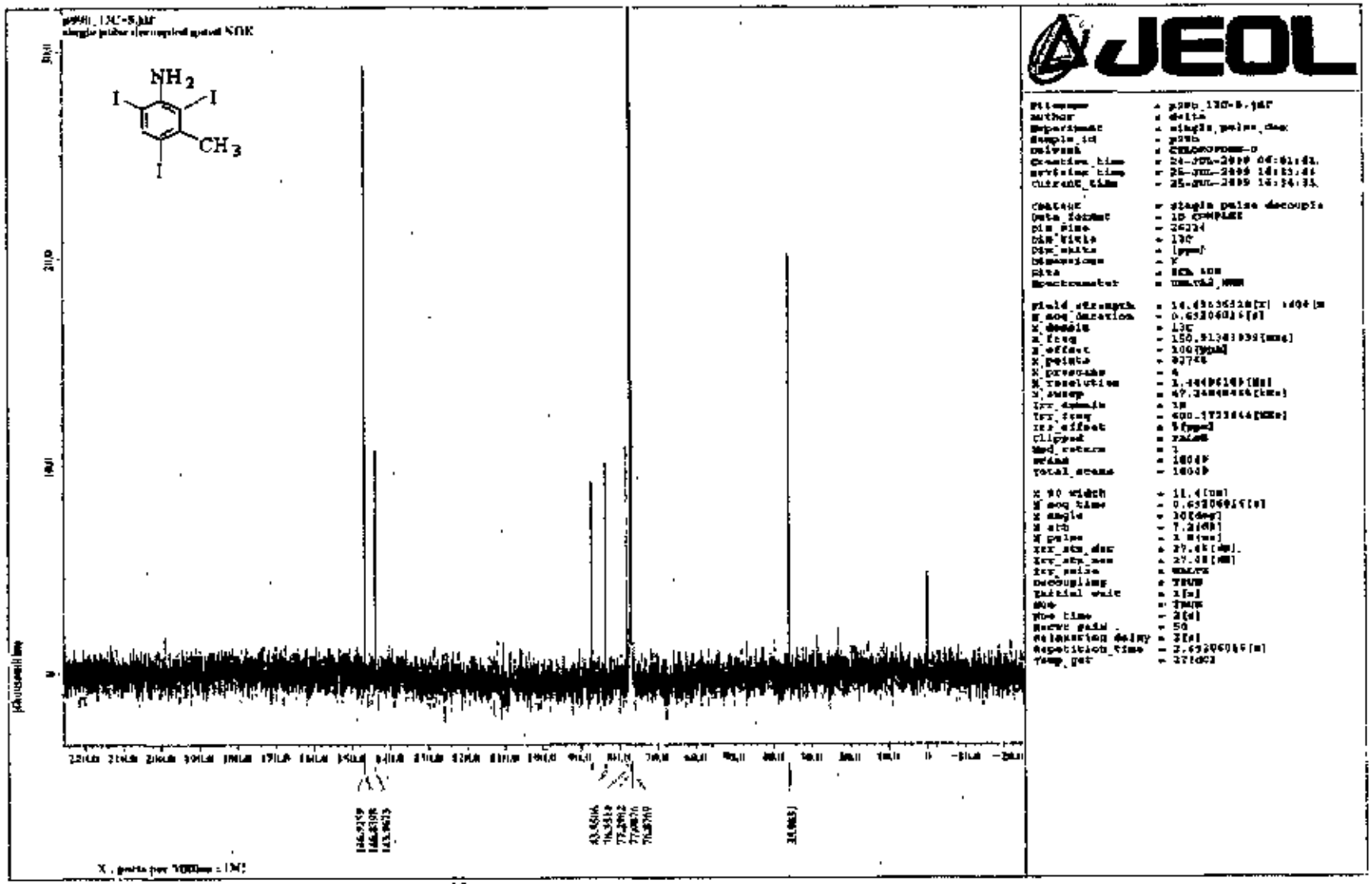


Fig-3: ^{13}C NMR Spectrum of compound **3.**

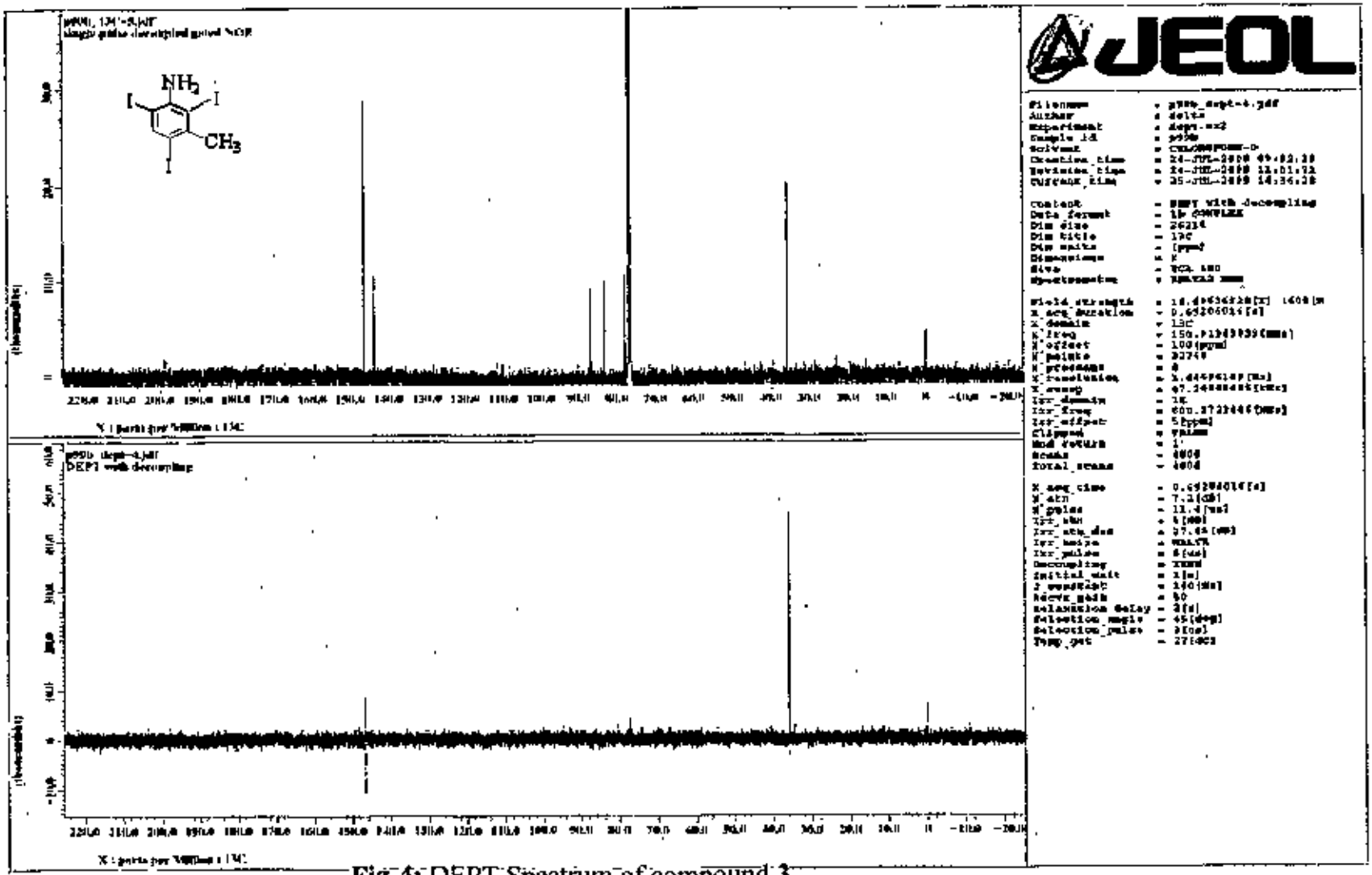


Fig-4: DEPT Spectrum of compound 3.

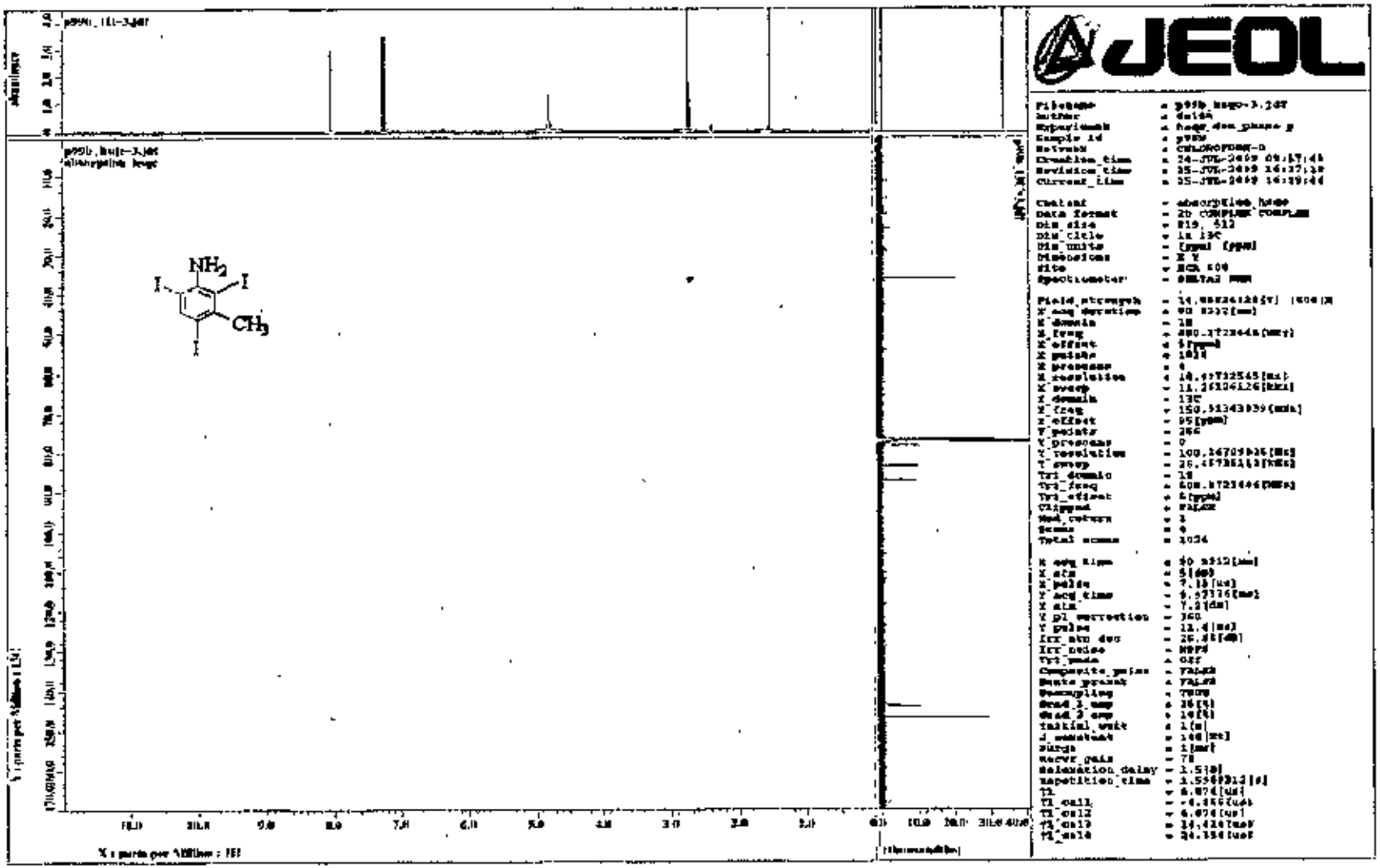


Fig-5: COSY Spectrum of compound **3.**

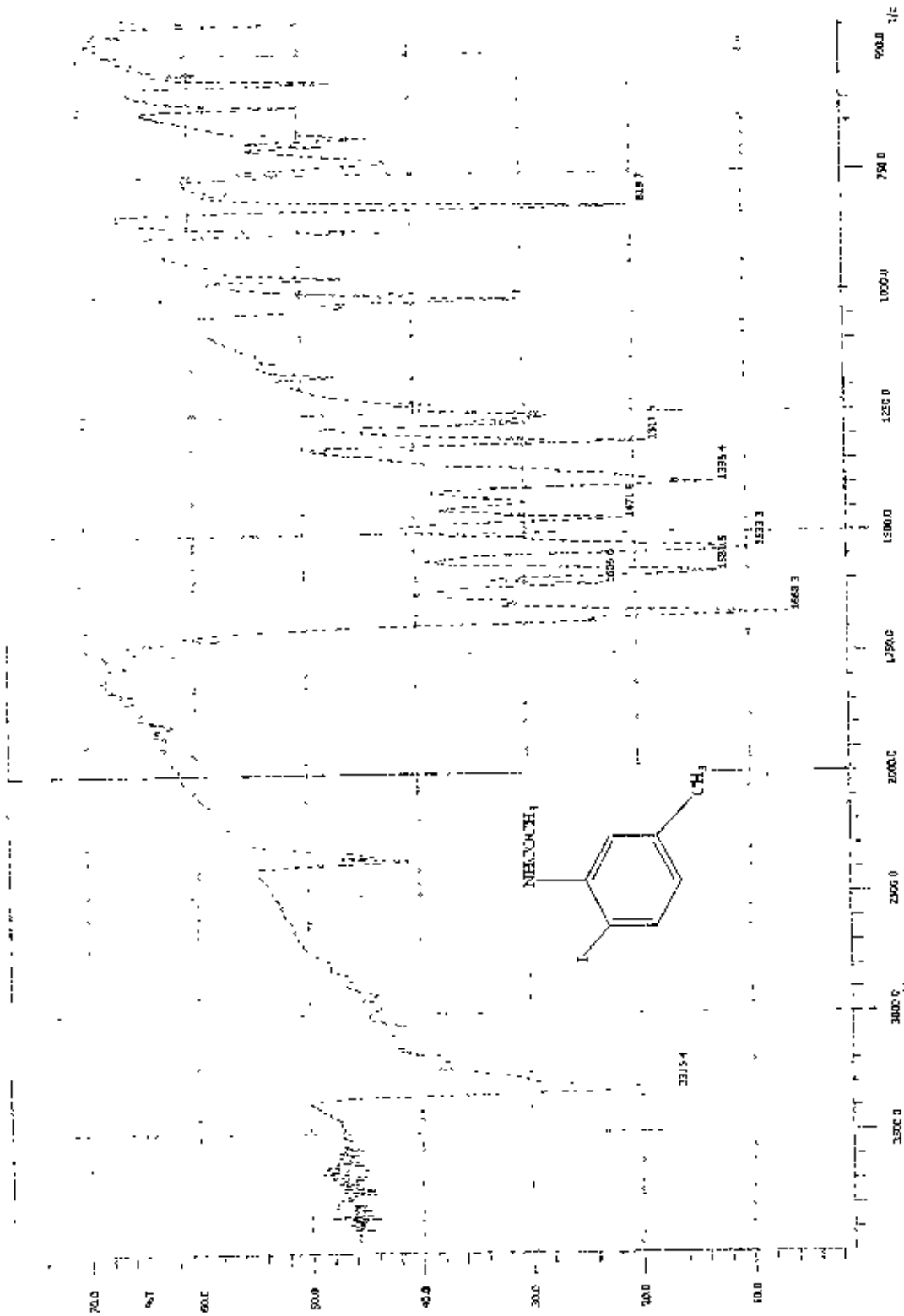


Fig-6: IR Spectrum of compound **4.**

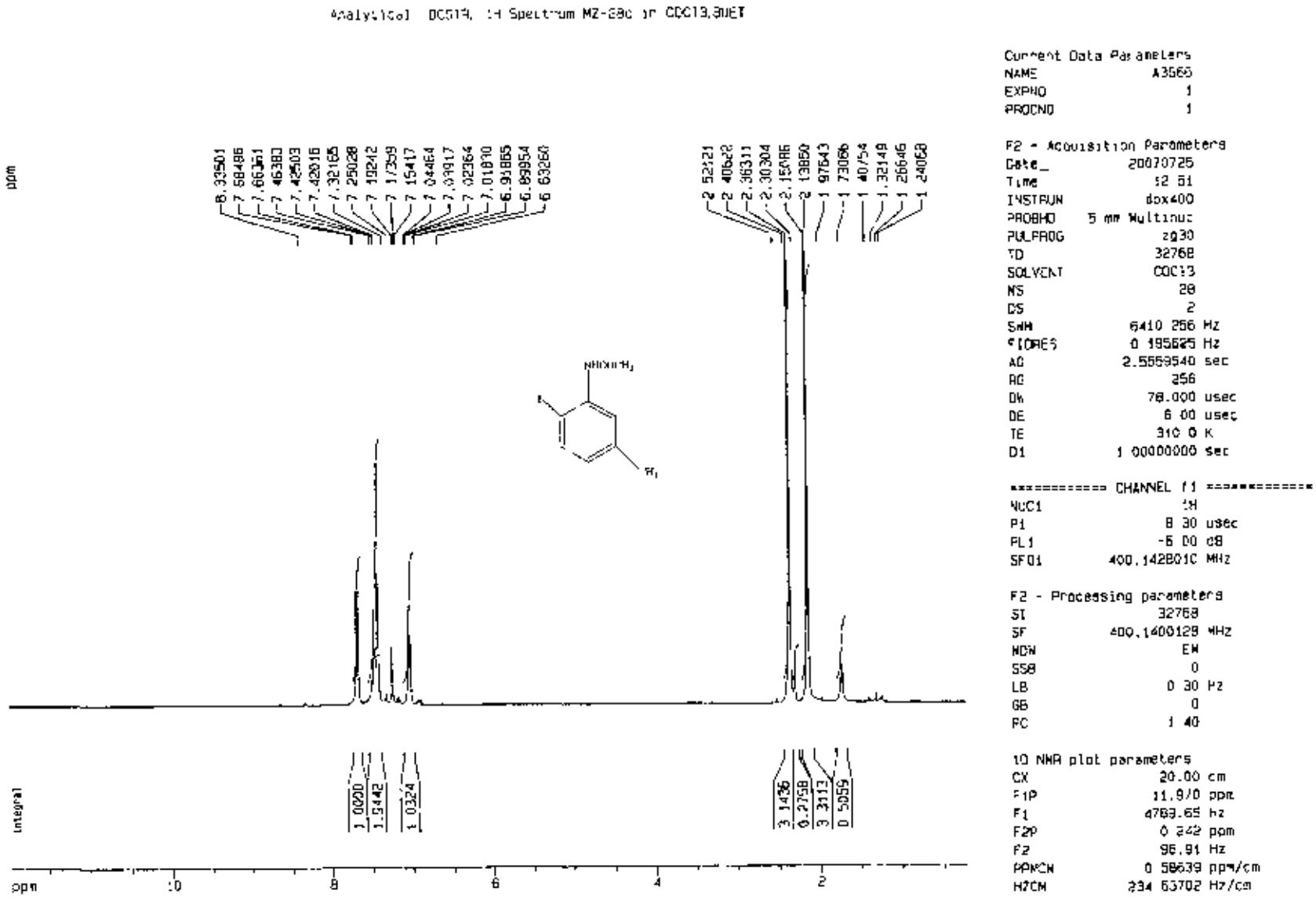
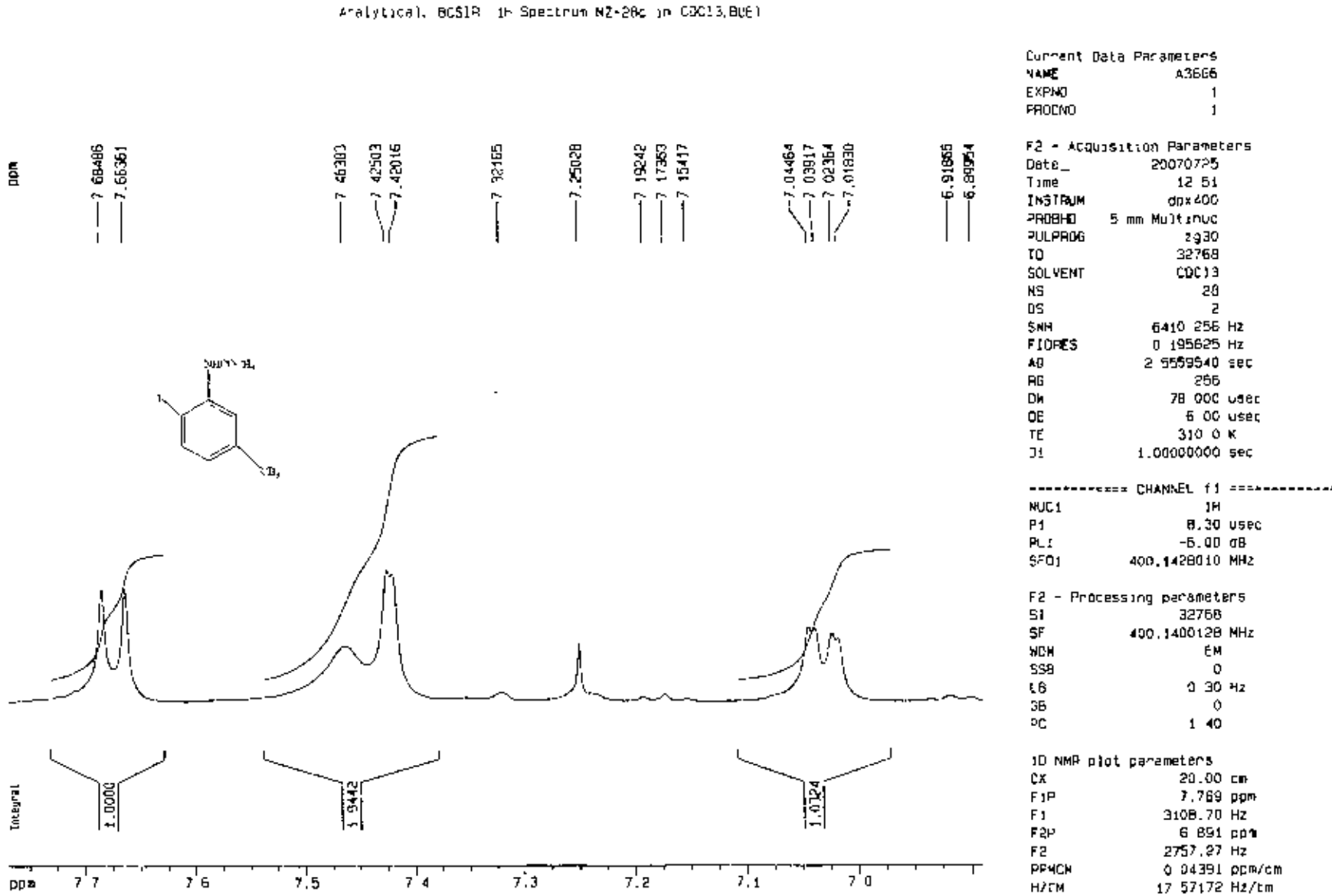


Fig-7: ^{1}H NMR Spectrum of compound **4.**



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PROCNO 1

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Time 12 51
INSTRUM dpx400
PROBHD 5 mm Multinuc
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 28
DS 2
SWH 6410 256 Hz
FIDRES 0 195625 Hz
AQ 2 5559540 sec
RG 256
DW 78 000 usec
DE 6 00 usec
TE 310 0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 8.30 usec
PL1 -6.00 dB
SFO1 400.1428010 MHz

F2 - Processing parameters
SI 32768
SF 400.1400128 MHz
WDW EM
SSB 0
LB 0 30 Hz
GB 0
PC 1 40

1D NMR plot parameters
CX 20.00 cm
F1P 7.769 ppm
F1 3108.70 Hz
F2P 6 891 ppm
F2 2757.27 Hz
PPMCM 0 04391 ppm/cm
HZCM 17 57172 Hz/cm

Fig-7: ^{1}H NMR Spectrum of compound **4.**

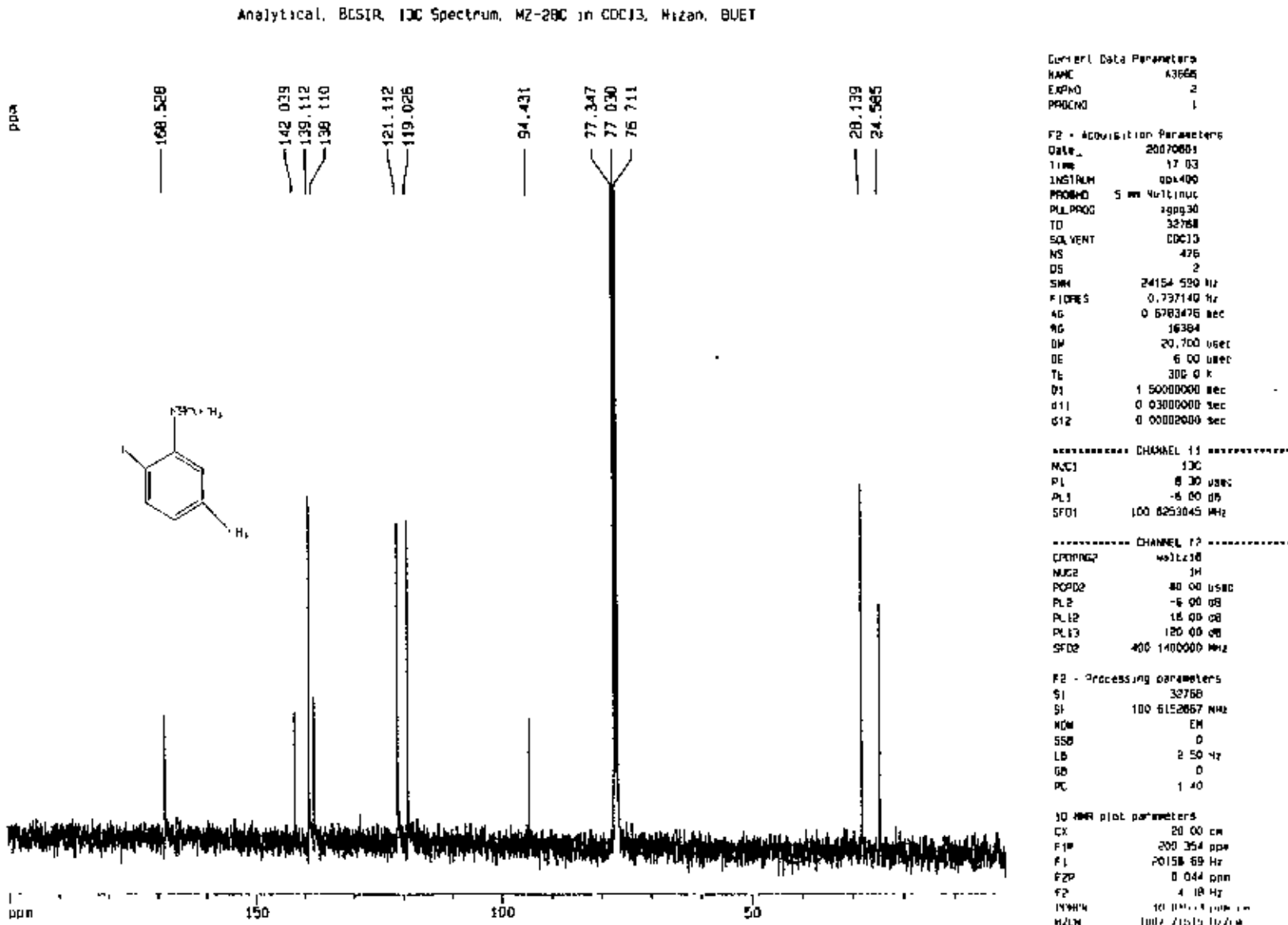


Fig-8: ^{13}C NMR Spectrum of compound **4.**

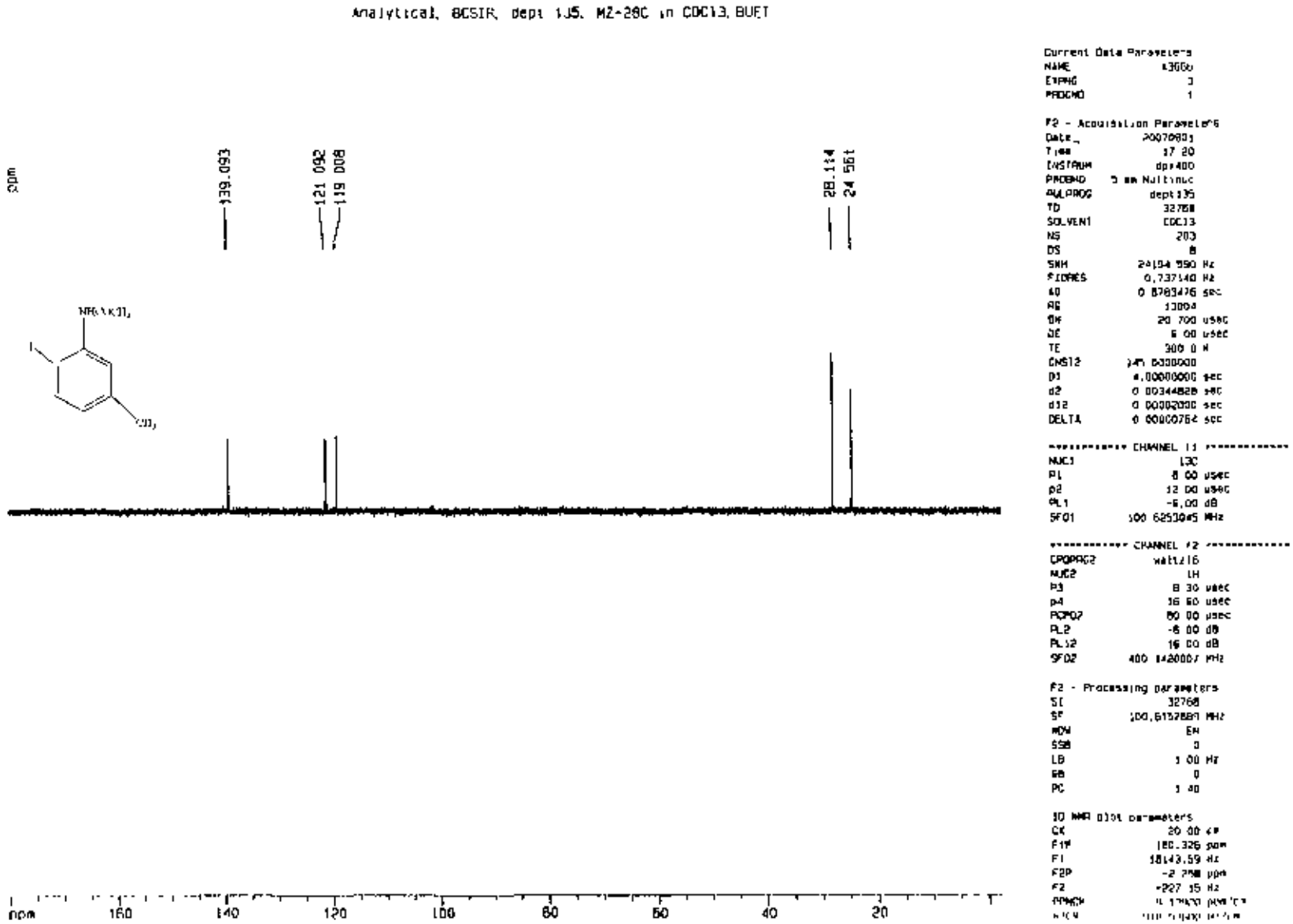
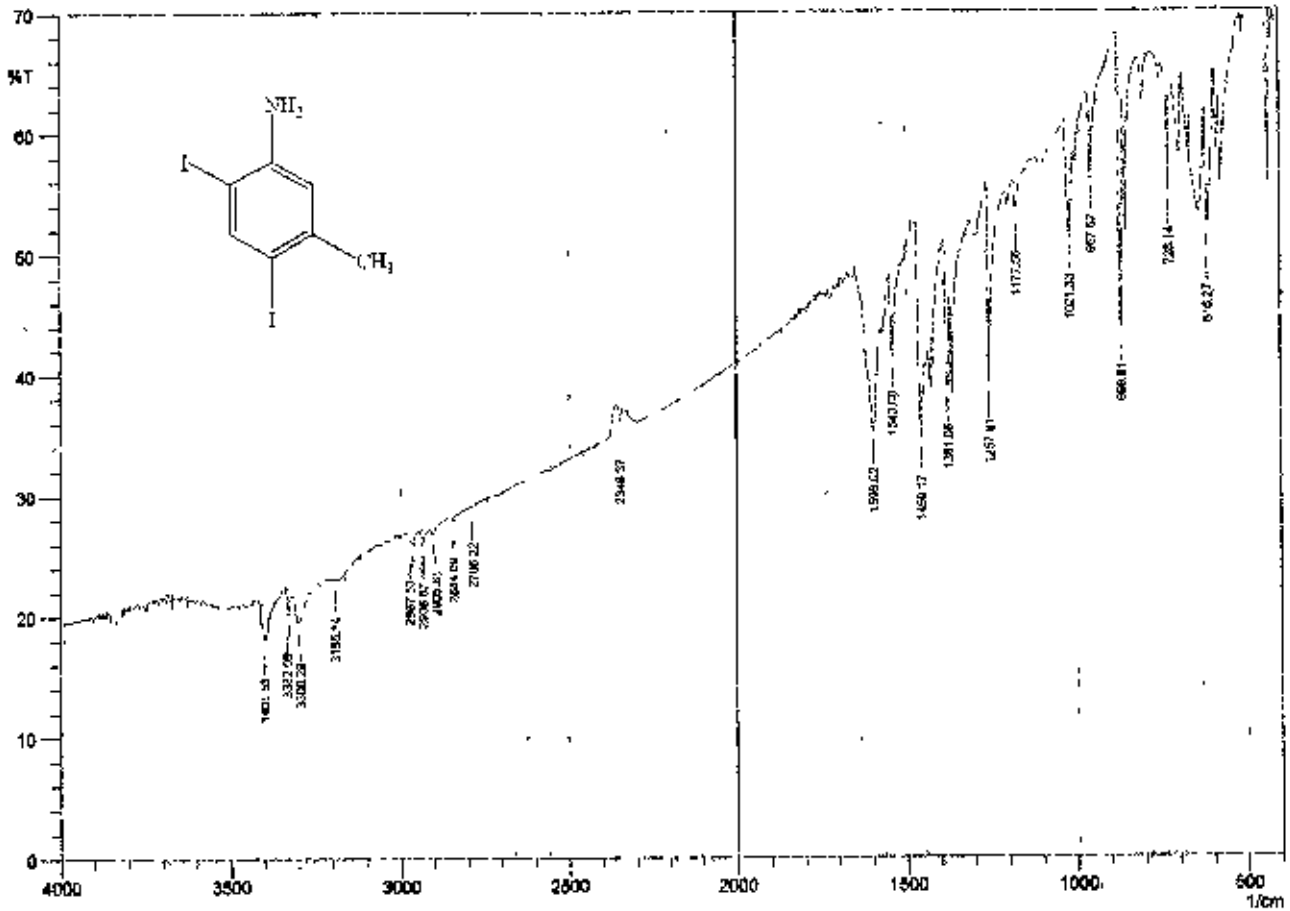


Fig-9: DEPTectrum of compound **4.**



	Peak	Intensity
1	816.27	50.257
2	728.14	55.045
3	669.91	43.779
4	957.67	56.061
5	1021.33	51.158
6	1177.58	53.143
7	1257.61	39.218
8	1361.06	36.807
9	1459.17	34.546
10	1543.08	41.581
11	1599.02	35.23
12	2348.37	36.049
13	2786.22	29.195
14	2844.09	27.942
15	2905.61	28.886
16	2936.67	25.845
17	2967.53	26.066
18	3195.14	23.05
19	3360.28	19.271
20	3332.09	20.117
21	3401.53	18.045

Data File : E:\Research\P_99 (C) final.smf

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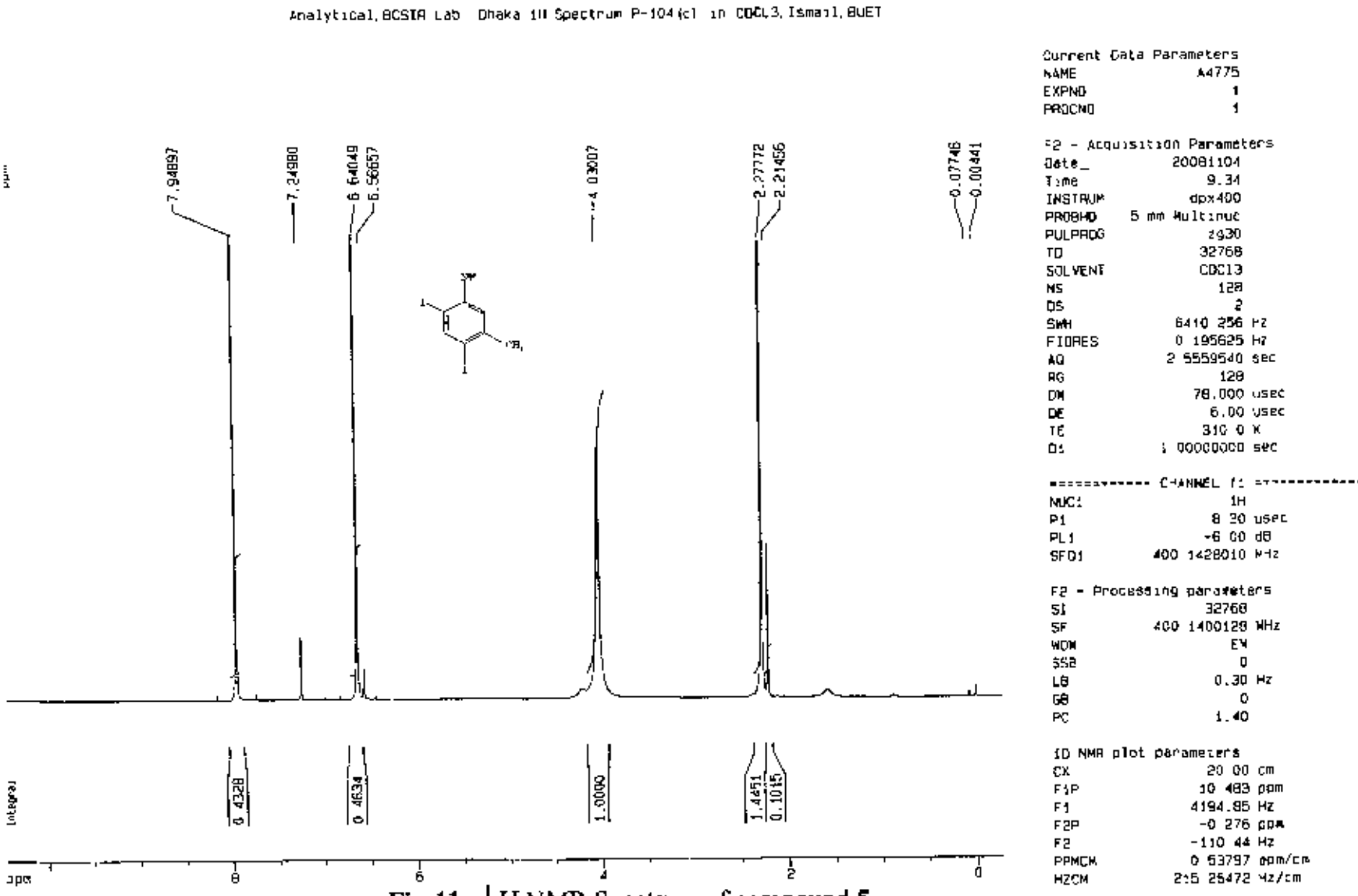
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 08/08/2009 05:37:42 PM
Gain : auto

Analysed By/Date

Fig-10: IR Spectrum of compound **5.**

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EXPNO                     1
PROCNO                    1

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Time                   9.34
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PROBHD     5 mm Multinuc
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                     128
DS                       2
SWH               6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5559540 sec
RG                     128
DW                78.000 usec
DE                 6.00 usec
TE                 310.0 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  8.20 usec
PL1                -6.00 dB
SFO1          400.1428010 MHz

F2 - Processing parameters
SI                   32768
SF          400.1400129 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                10.483 ppm
F1                4194.85 Hz
F2P                -0.276 ppm
F2                -110.44 Hz
PPMCM             0.53797 ppm/cm
HZCM              215.25472 Hz/cm
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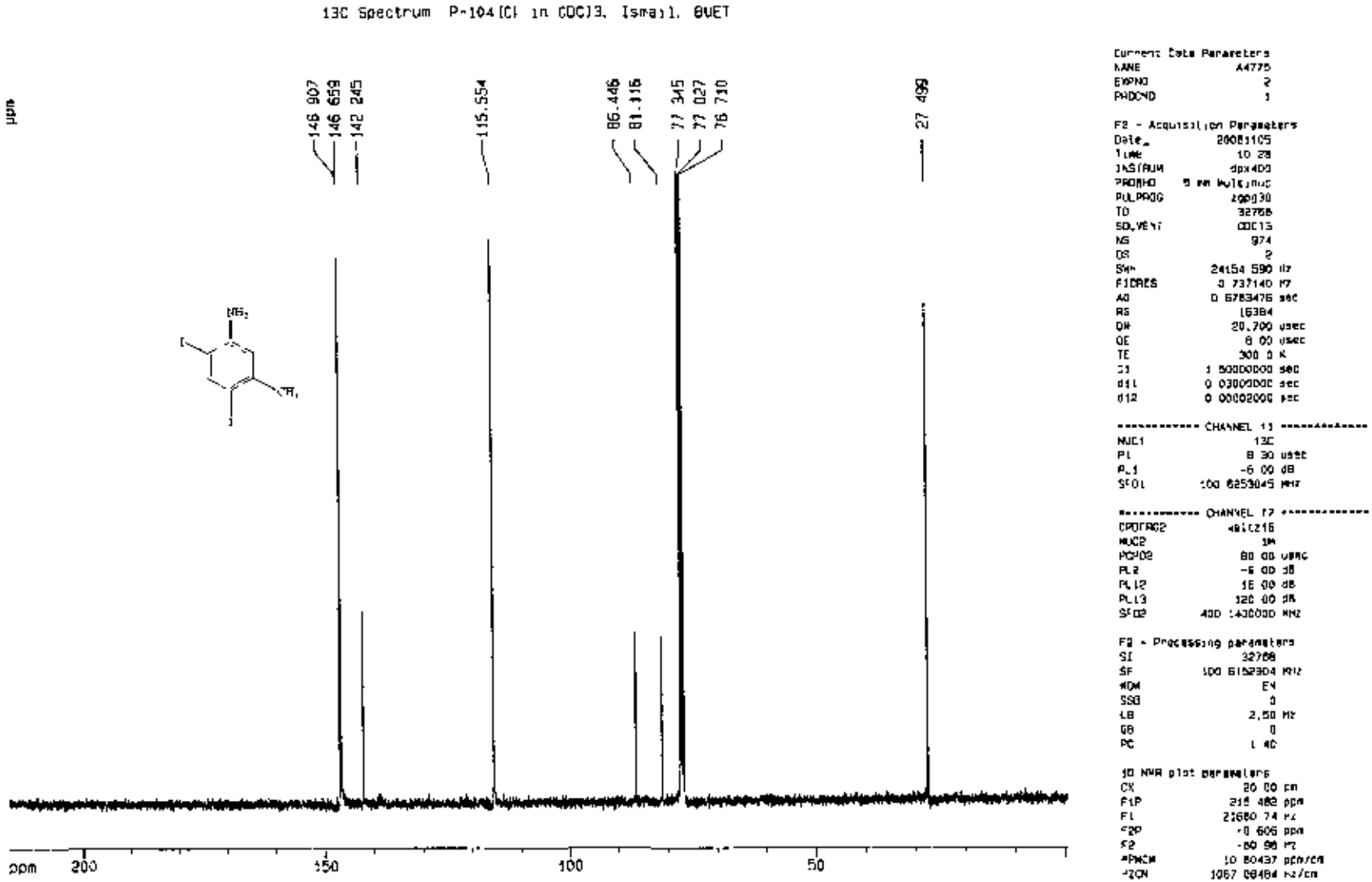
Fig-11: ^{1}H NMR Spectrum of compound **5** .



Current Data Parameters
NAME A4775
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20081105
Time 10 28
INSTRUM dpx400
PROBHD 5 mm Multinuc
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 974
DS 2
SWH 24154.590 Hz
FIDRES 0.737140 Hz
AQ 0.6783476 sec
RG 163B4
DW 20.700 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

------------ CHANNEL f1 ------------
NUC1 13C
P1 8.30 usec
PL1 -6.00 dB
SFO1 100.6253045 MHz

------------ CHANNEL f2 ------------
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 16.00 dB
PL13 120.00 dB
SFO2 400.1400000 MHz

F2 - Processing parameters
SI 32768
SF 100.6152304 MHz
WDW EM
SSB 0
LB 2.50 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 218.482 ppm
F1 21980.74 Hz
F2P -0.606 ppm
F2 -60.96 Hz
PPMCM 10.80437 ppm/cm
HZCM 1087.08484 Hz/cm

Fig-12: ^{13}C NMR Spectrum of compound **5.**

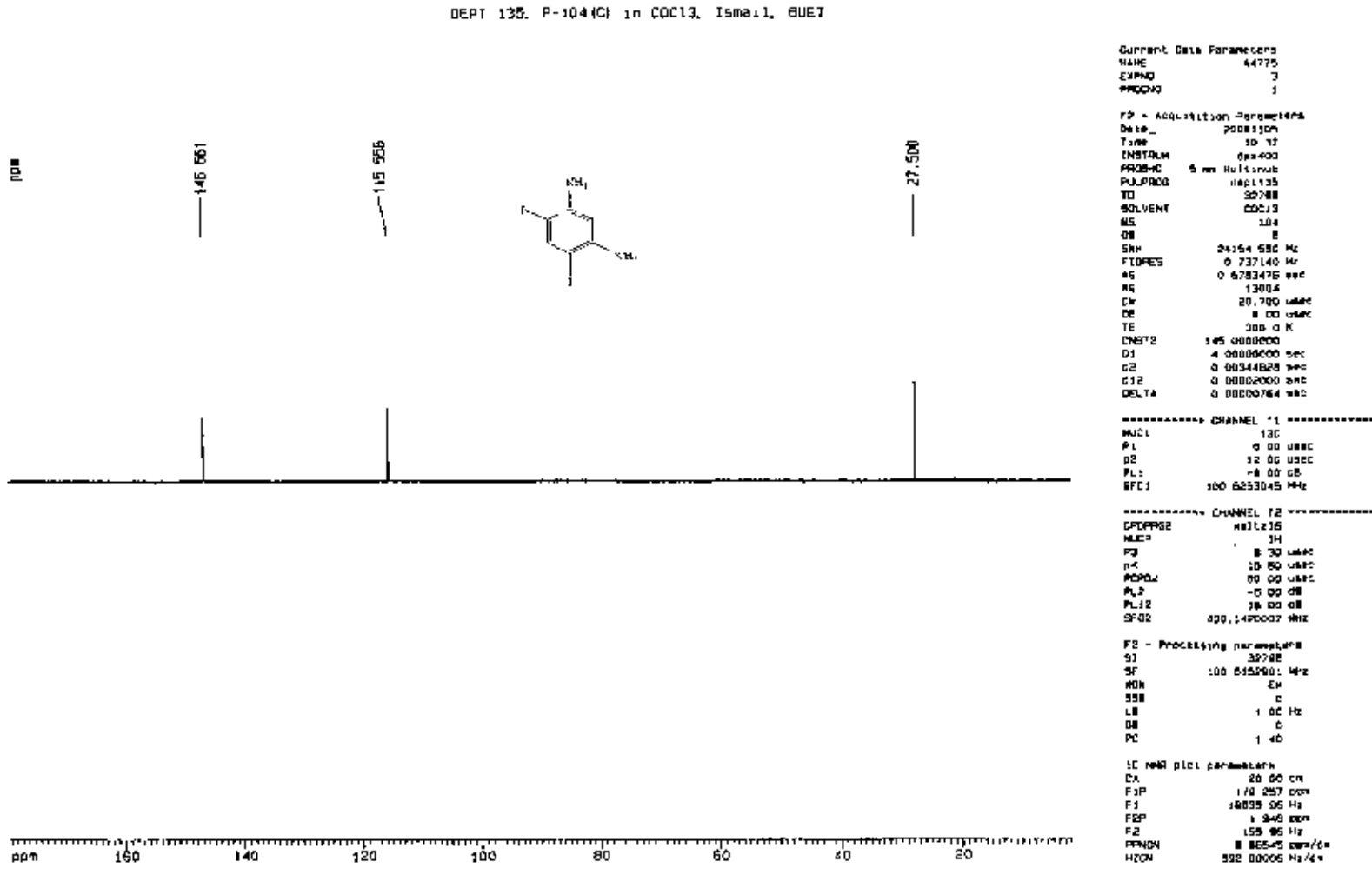
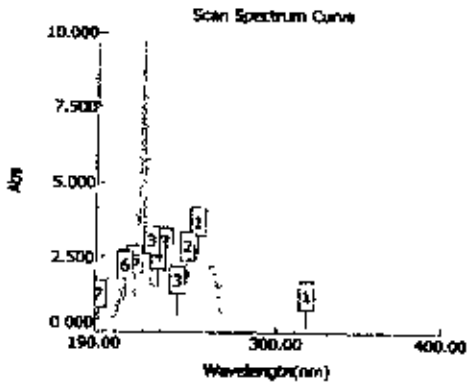


Fig-13: DEPT Spectrum of compound **5.**



1	Peak	252.00	2.440
2	Peak	232.00	1.785
3	Peak	224.00	1.821
1	Valley	318.00	-0.913
2	Valley	246.00	1.630
3	Valley	240.00	0.504
4	Valley	228.00	1.327
5	Valley	214.00	1.173
6	Valley	208.00	0.989
7	Valley	192.00	-1.171

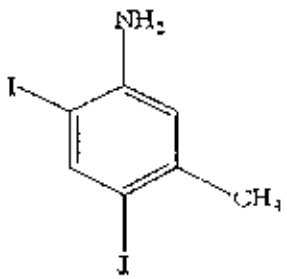
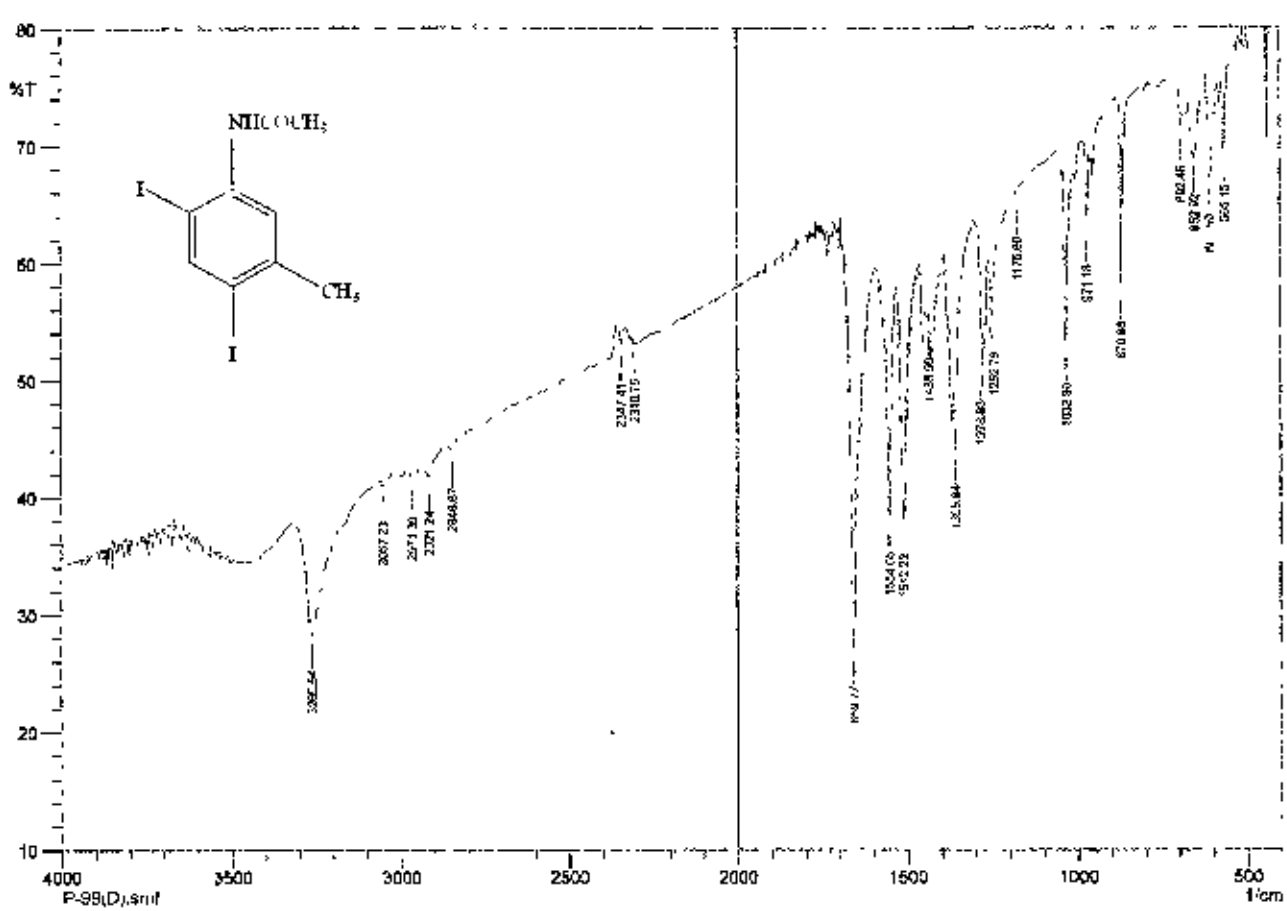


Fig-14: UV Spectrum of compound **5.**



	Peak	Intensity
1	585.15	69.868
2	607.59	67.102
3	652.92	68.895
4	692.46	71.31
5	870.88	57.986
6	971.16	62.823
7	1032.9	52.759
8	1176.8	65.206
9	1252.79	55.431
10	1278.83	51.234
11	1359.84	44.052
12	1438.98	54.9
13	1512.22	38.227
14	1554.65	38.427
15	1659.77	26.971
16	2310.76	58.152
17	2347.41	62.788
18	2849.87	43.874
19	2921.24	41.88
20	2971.39	41.439
21	3057.23	41.006
22	3285.54	26.38

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Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 07/08/2009 05:58:02 PM
Gain : auto

Analysed By/Date

Fig-15: IR Spectrum of compound **6.**

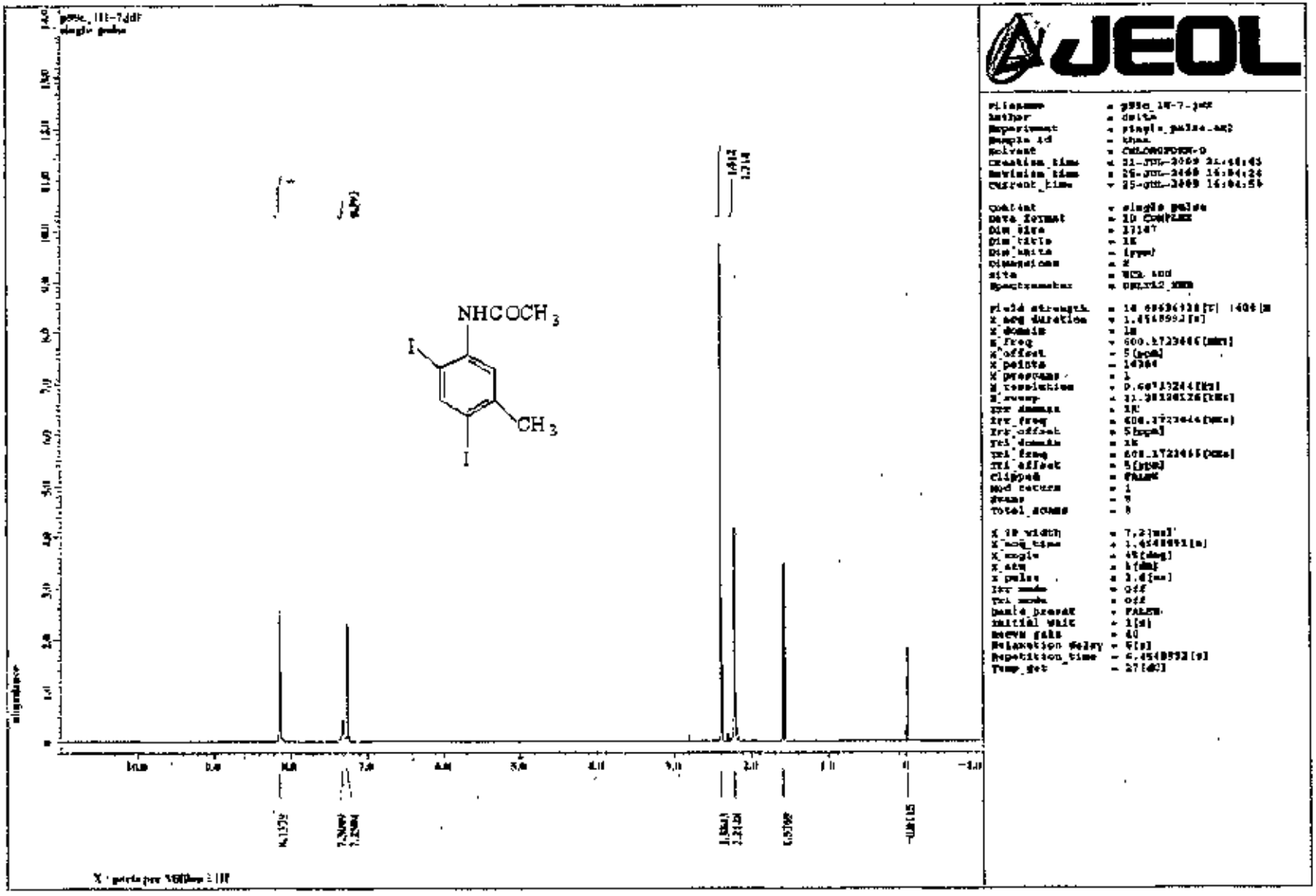


Fig-16: ^{1}H NMR Spectrum of compound **6.**

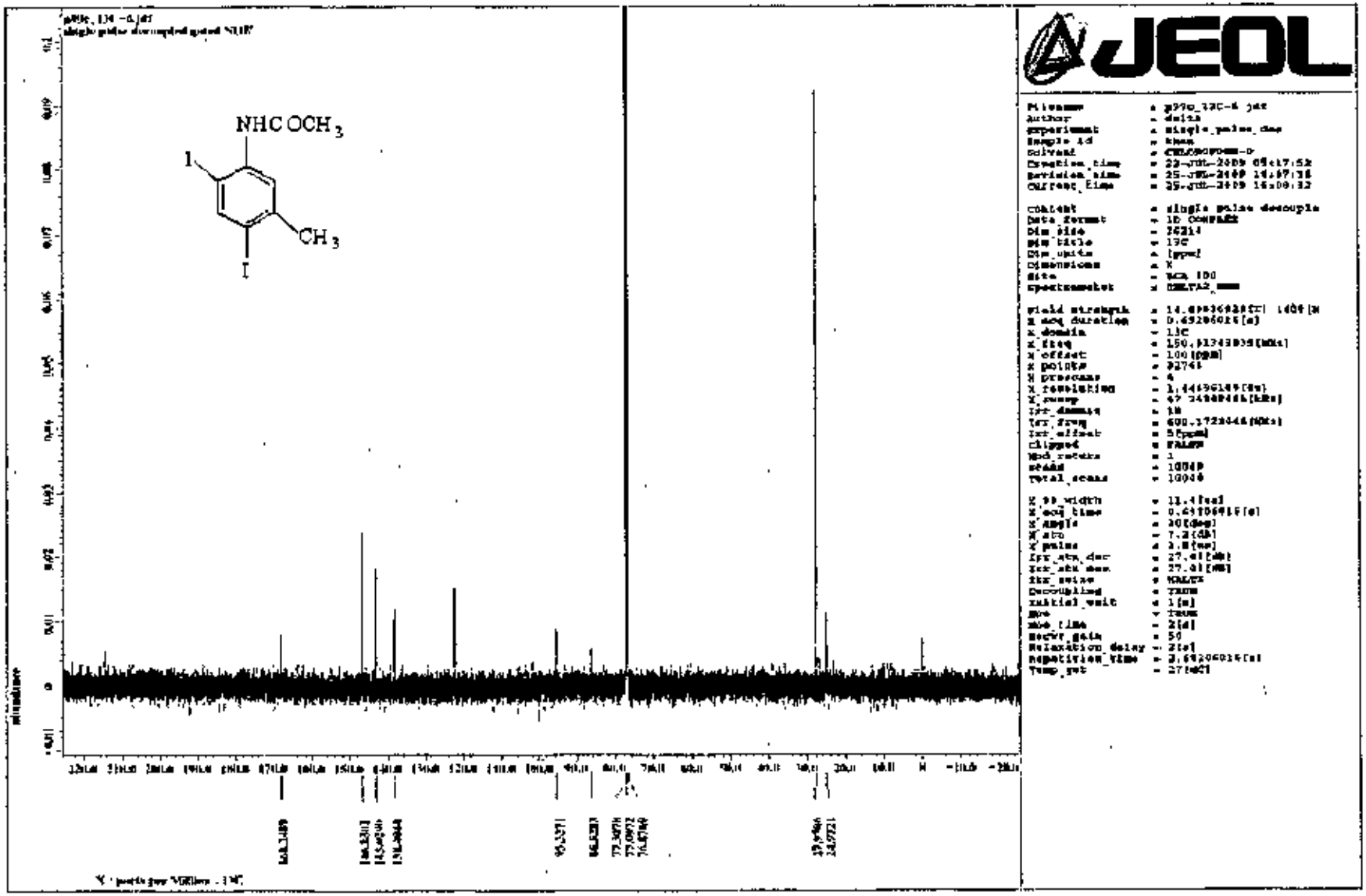


Fig-17: ^{13}C NMR Spectrum of compound **6**

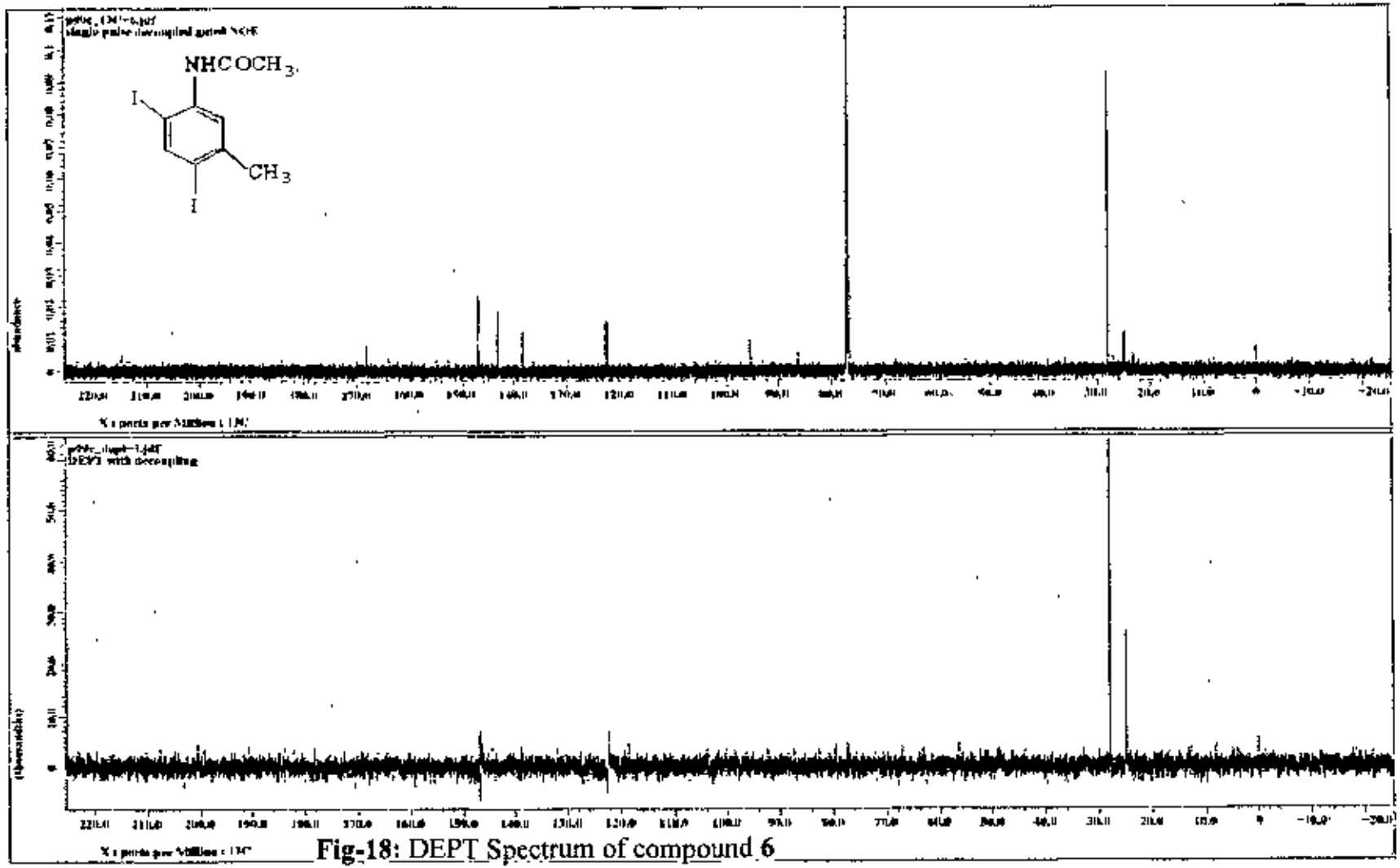


Fig-18: DEPT Spectrum of compound **6**

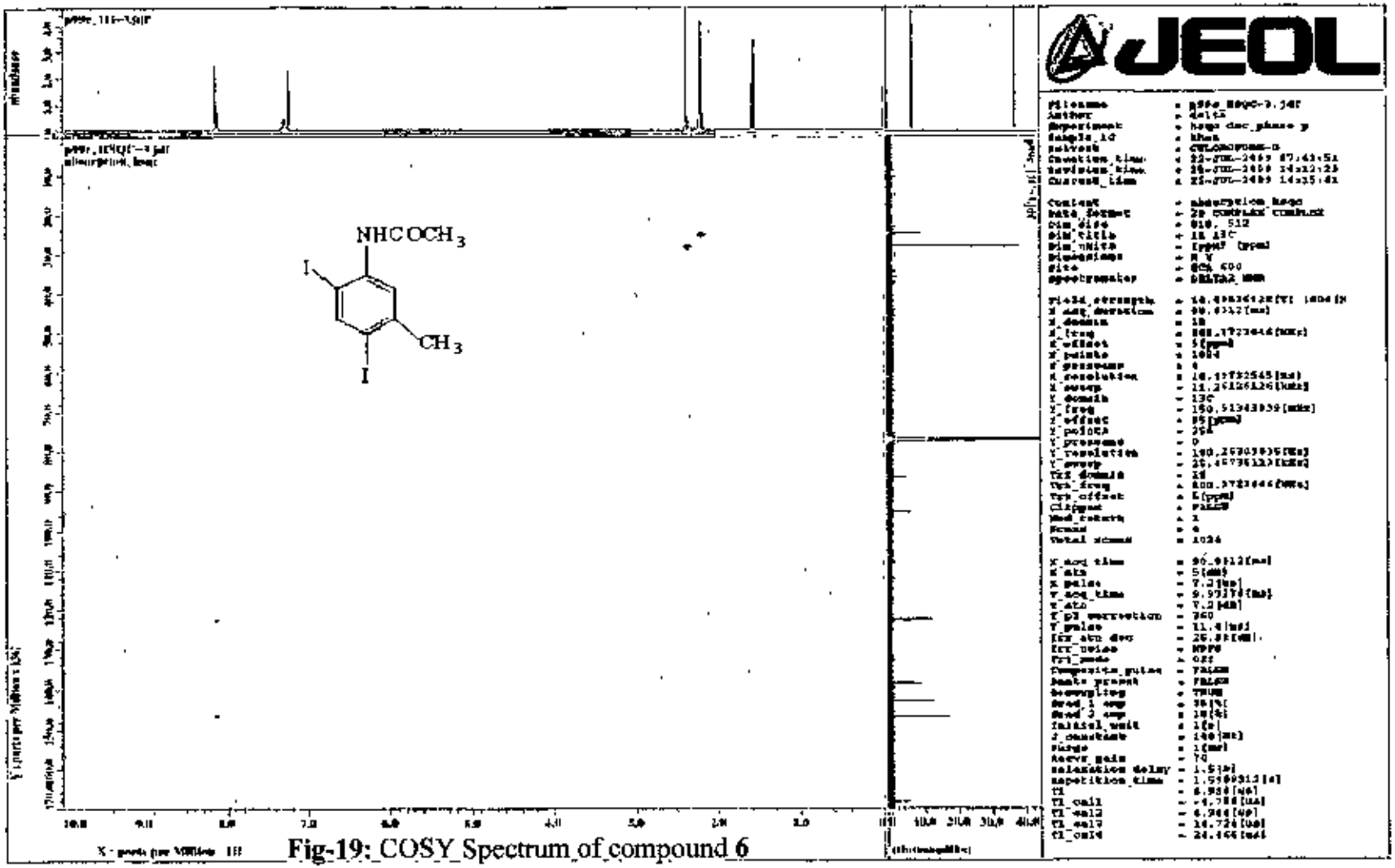
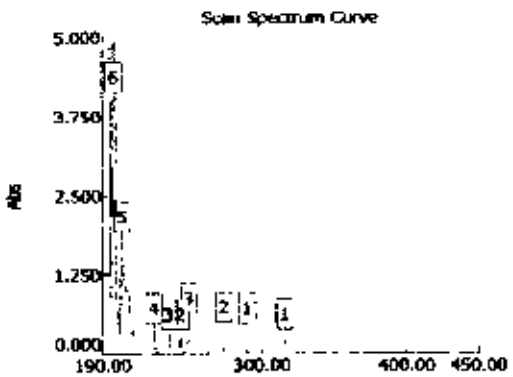


Fig-19: COSY Spectrum of compound 6



1	Peak	290.00	0.098
2	Peak	274.00	0.115
3	Peak	250.00	0.265
4	Peak	226.00	0.097
5	Peak	204.00	1.544
6	Peak	198.00	9.999
1	Valley	316.00	-1.326
2	Valley	244.00	-0.604
3	Valley	236.00	-0.269

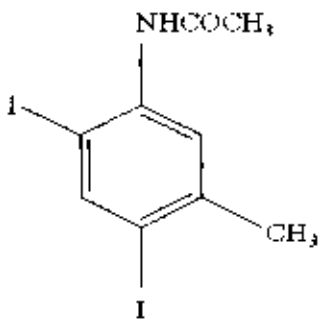
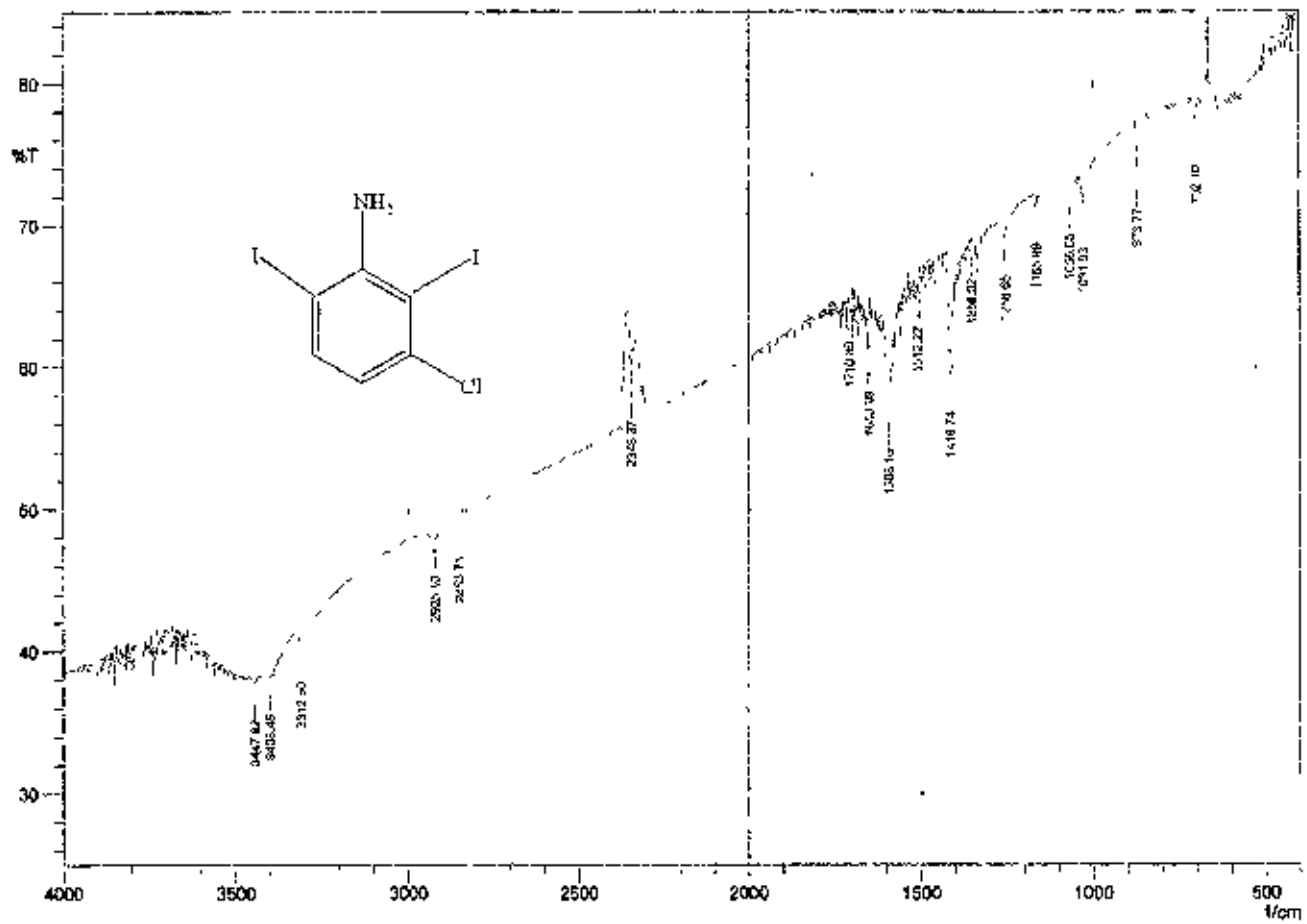


Fig-20: UV Spectrum of compound 6 .



	Peak	Intensity
1	702.1	76.738
2	873.77	73.739
3	1031.93	70.972
4	1066.65	71.945
5	1165.99	71.803
6	1256.65	69.089
7	1355.02	68.81
8	1416.74	58.457
9	1512.22	65.414
10	1595.16	58.766
11	1853.99	60.943
12	1710.89	64.373
13	2348.37	58.824
14	2853.73	49.25
15	2925.1	47.915
16	3312.8	40.455
17	3403.45	38.199
18	3447.82	37.792

Data File : E:\Research\P-91(A).smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 07/08/2009 06.14.40 PM
Gain : auto

Analysed By/Date

Fig-21: IR Spectrum of compound **7**.

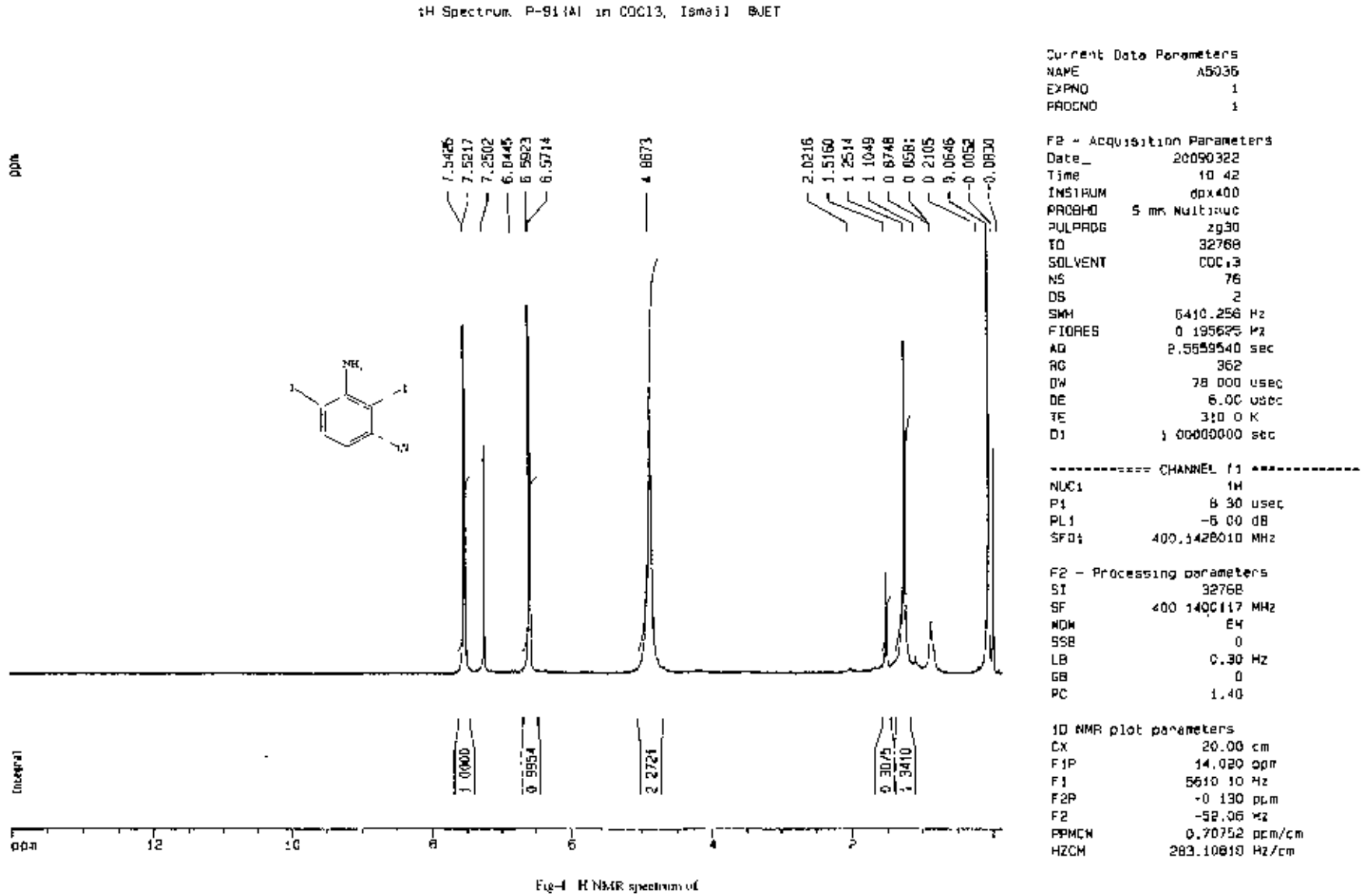
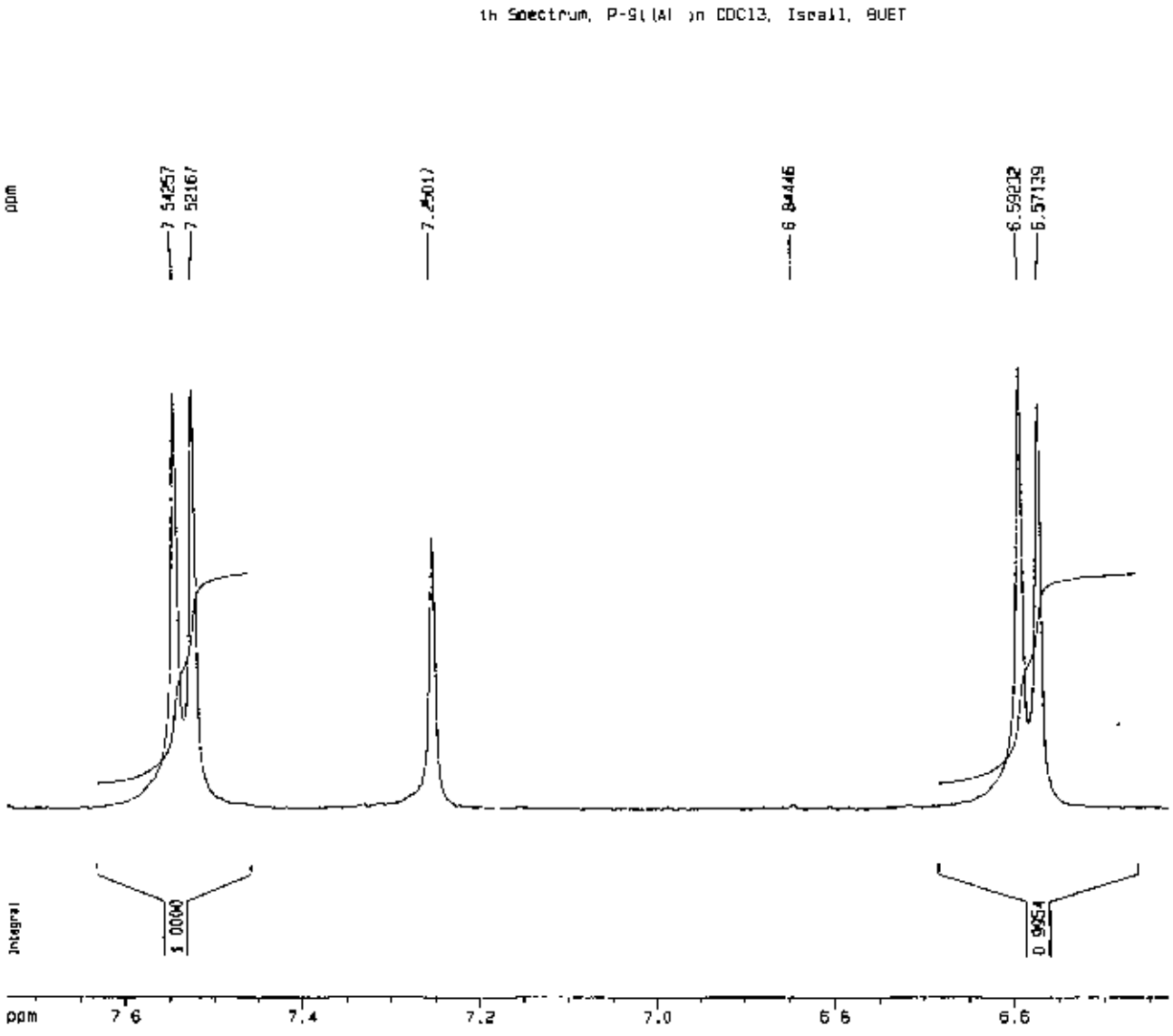


Fig-4 H NMR spectrum of

Fig-22: ^{1}H NMR Spectrum of compound 7.

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PROCNO                    1

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PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5569540 sec
RG                      362
DW                 78.000 usec
DE                  6.00 usec
TE                  310.0 K
D1                1.00000000 sec

============ CHANNEL f1 ============
NUC1                    1H
P1                   8.30 usec
PL1                 -6.00 dB
SFO1           400.1429010 MHz

F2 - Processing parameters
SI                    32768
SF              400.1400117 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                  7.733 ppm
F1                 3094.26 Hz
F2P                  6.430 ppm
F2                 2572.90 Hz
PPMCM              0.06515 ppm/cm
HZCM              26.06778 Hz/cm
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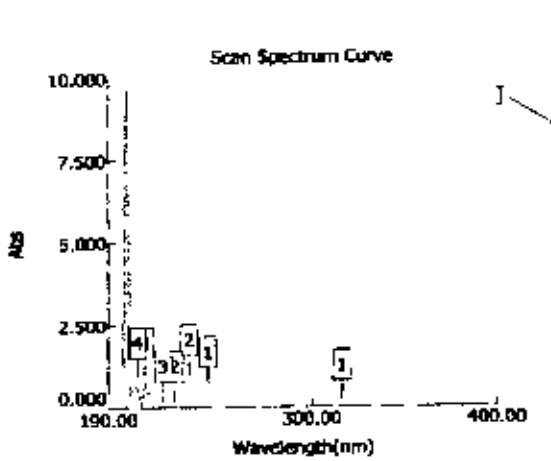
Fig-22: ^{1}H NMR Spectrum of compound **7.**



1	Peak	244.00	0.417
2	Peak	234.00	0.801
3	Peak	210.00	0.714
4	Peak	206.00	0.708
1	Valley	316.00	-1.189
2	Valley	236.00	-0.071
3	Valley	220.00	-0.200

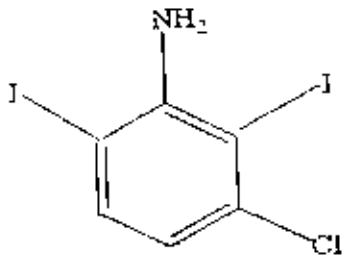
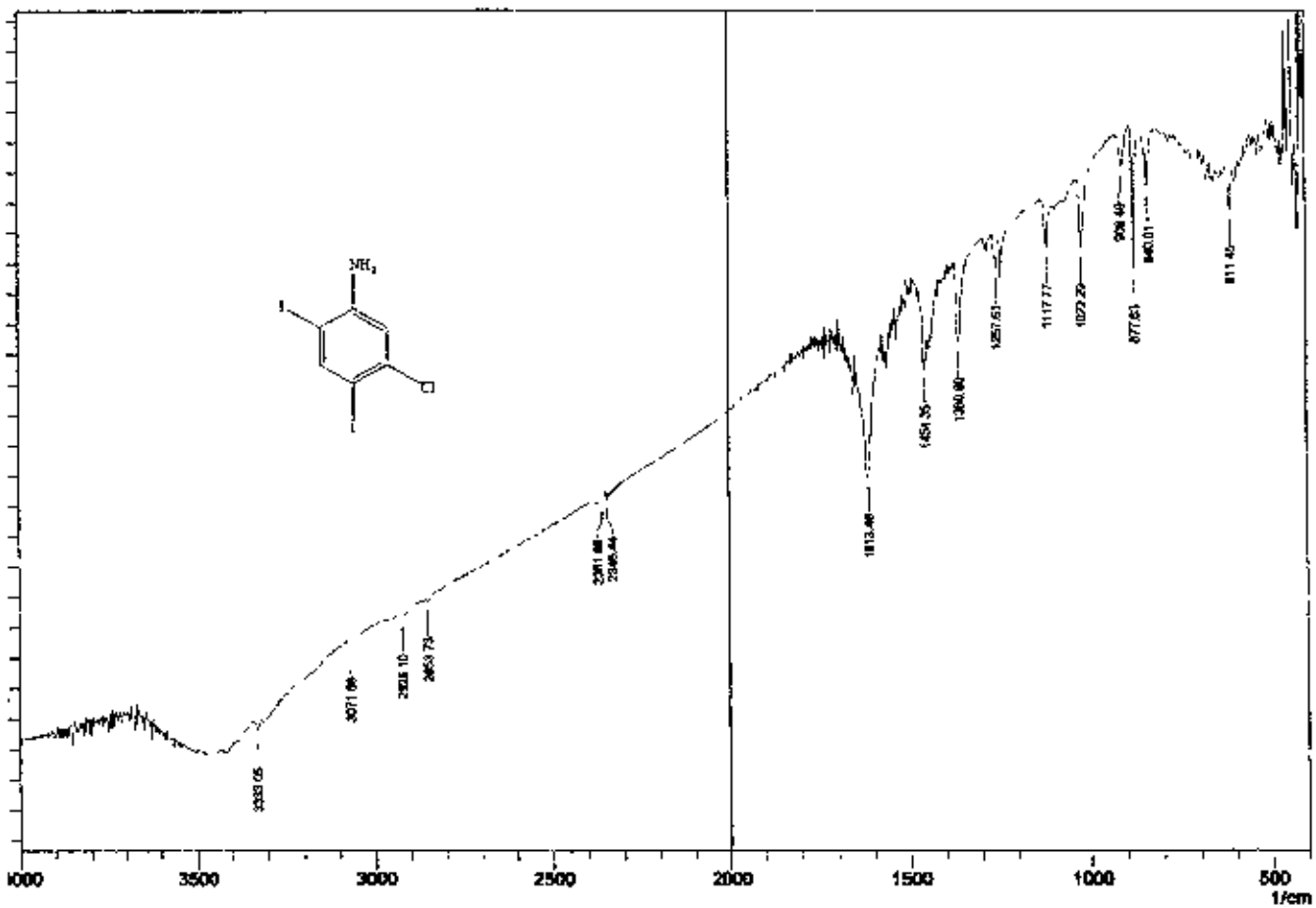


Fig-23: UV Spectrum of compound 7.



	Peak	Intensity
1	811.45	65.36
2	840.01	67.46
3	877.63	59.515
4	908.49	69.594
5	1022.29	61.823
6	1117.77	61.829
7	1257.61	59.545
8	1380.6	52.374
9	1454.35	49.66
10	1813.46	38.863
11	2346.44	38.62
12	2361.88	36.348
13	2853.73	28.693
14	2928.1	24.991
15	3071.66	22.731
16	3333.05	13.869

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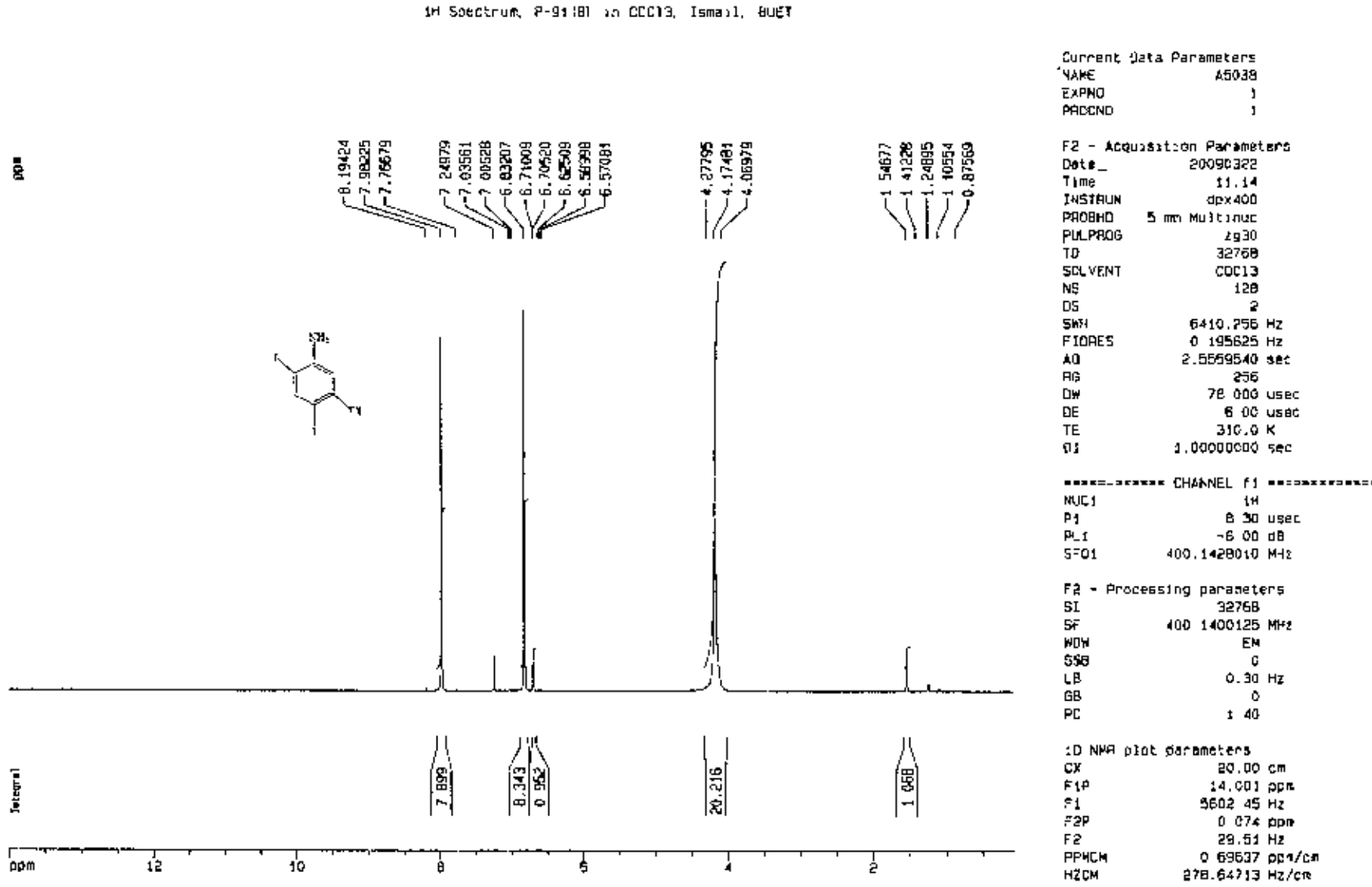
Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 09:42:51 PM
Gain : auto

Analysed By/Date

Fig-24: IR Spectrum of compound **8.**



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NAME A5038
EXPNO 1
PROCNO 1

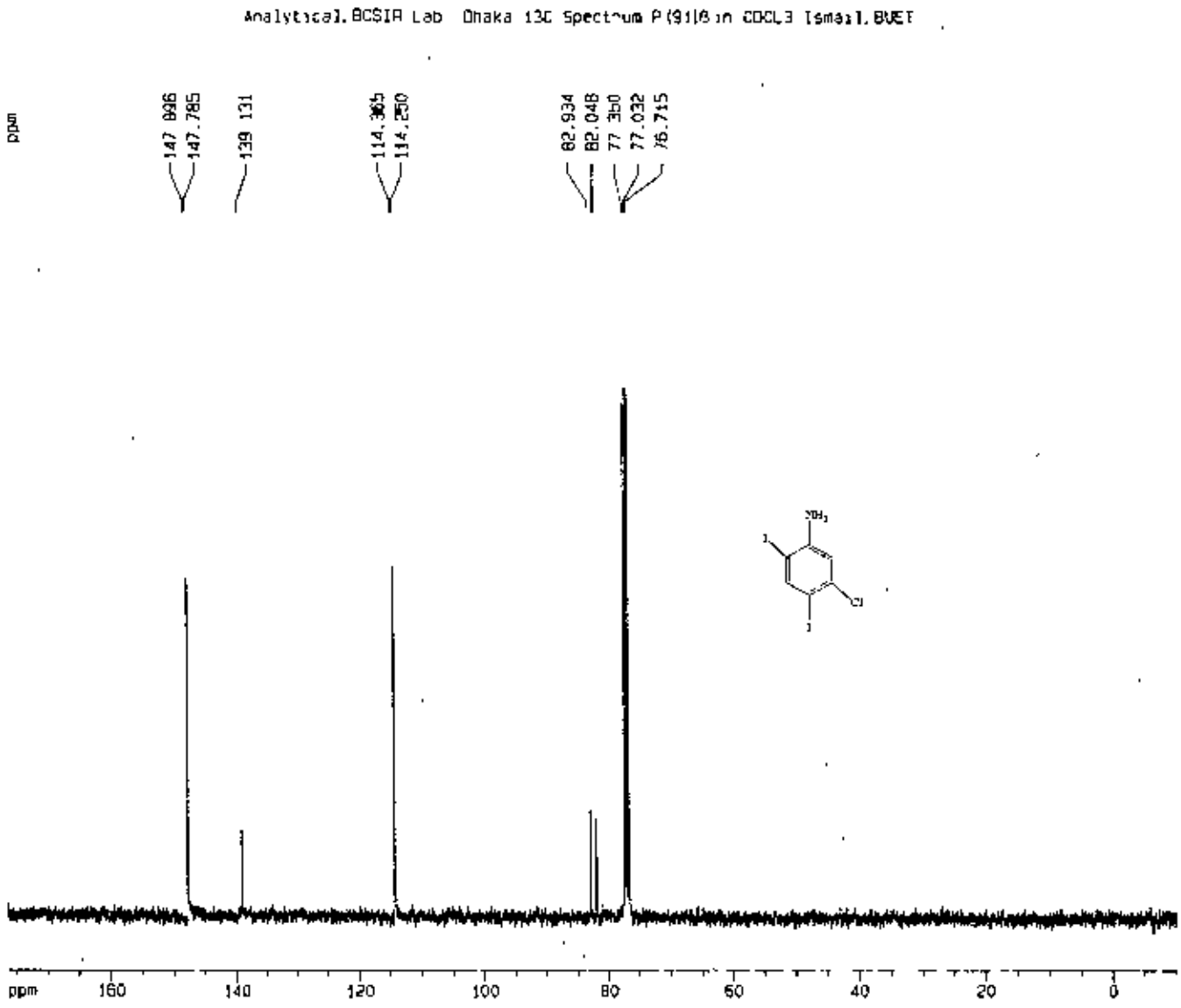
F2 - Acquisition Parameters
Date_ 20090322
Time 11.14
INSTRUM dpx400
PROBHD 5 mm Multinuc
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 128
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 256
DW 78.000 usec
DE 6.00 usec
TE 310.0 K
D1 1.00000000 sec

====== CHANNEL f1 ======
NUC1 1H
P1 8.30 usec
PL1 -6.00 dB
SFO1 400.1428010 MHz

F2 - Processing parameters
SI 32768
SF 400.1400125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 14.001 ppm
F1 5602.45 Hz
F2P 0.074 ppm
F2 29.51 Hz
PPMCM 0.69637 ppm/cm
HZCM 278.64713 Hz/cm

Fig-25: ^{1}H NMR Spectrum of compound **8.**



Current Data Parameters
NAME A5038
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20090408
Time 10 12
INSTRUM dck400
PROBHD 5 mm Multinuc
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 399
DS 2
SWH 24154.590 Hz
FIDRES 0.737140 Hz
AQ 0.6783472 sec
RG 18384
DW 20.700 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

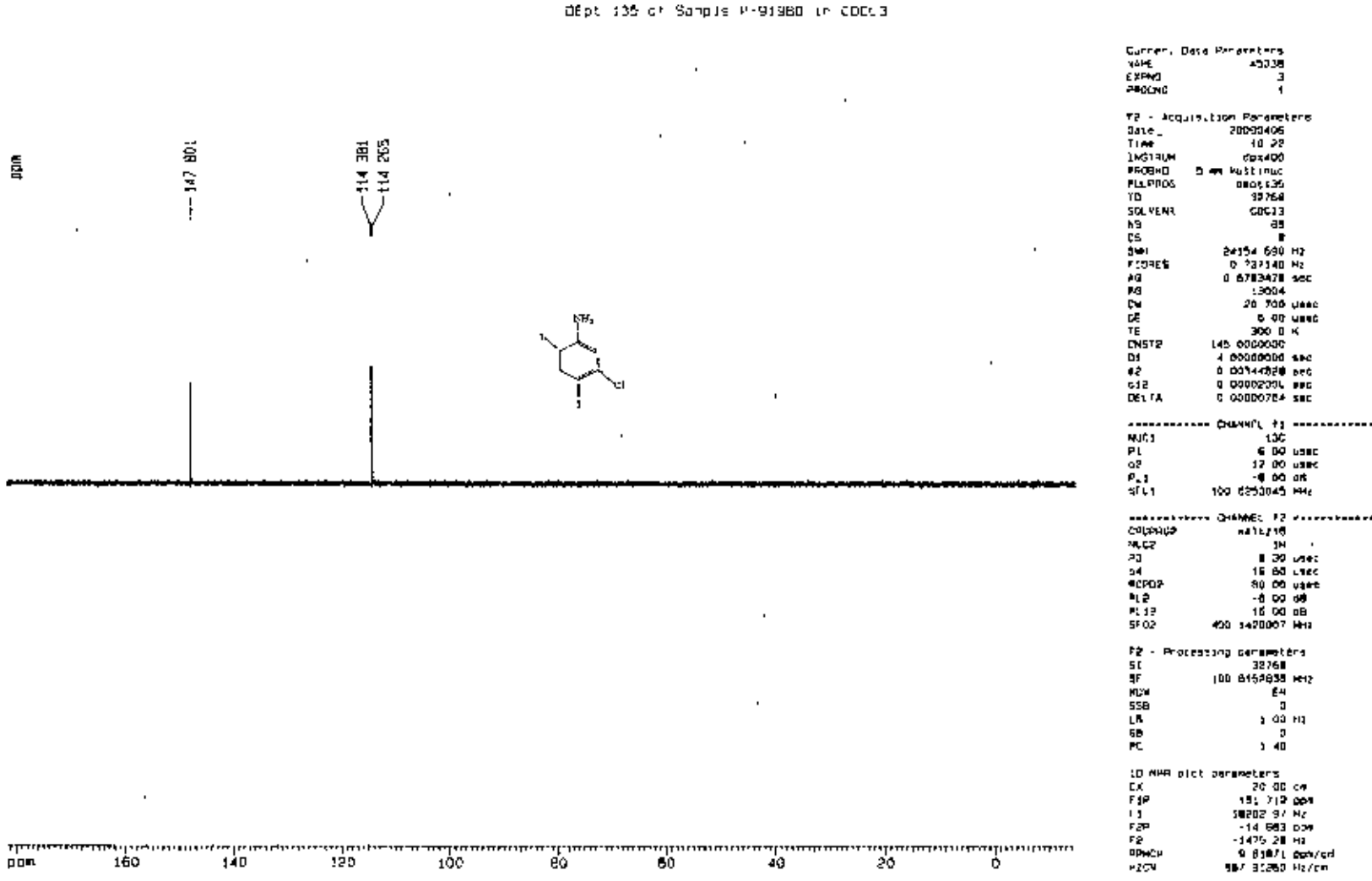
------------ CHANNEL f1 ------------
NUC1 13C
P1 8.30 usec
PL1 -2.00 dB
SFO1 100.6253045 MHz

------------ CHANNEL f2 ------------
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 16.06 dB
PL13 120.00 dB
SFO2 400.1400002 MHz

F2 - Processing parameters
SI 32768
SF 100.6152852 MHz
WDW EM
SSB 0
LB 2.50 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 175.599 ppm
F1 17684.53 Hz
F2P -10.018 ppm
F2 -1007.78 Hz
PPMCM 9.32876 ppm/cm
HZCM 938.81591 Hz/cm

Fig-26: ^{13}C NMR Spectrum of compound **8**.



Current Data Parameters
NAME A5038
EXPNO 3
PROCNO 1

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TIME 10.22
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PROBHD 5 mm PABBI BB/
PULPROG dept135
TD 32768
SOLVENT CDCl3
NS 88
DS 8
SWH 2e154.680 Hz
FIDRES 0.737140 Hz
AQ 0.6783478 sec
RG 13004
DW 20.700 usec
DE 6.00 usec
TE 300.0 K
D0 145.0000000
D1 4.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
DELTA 0.00000784 sec

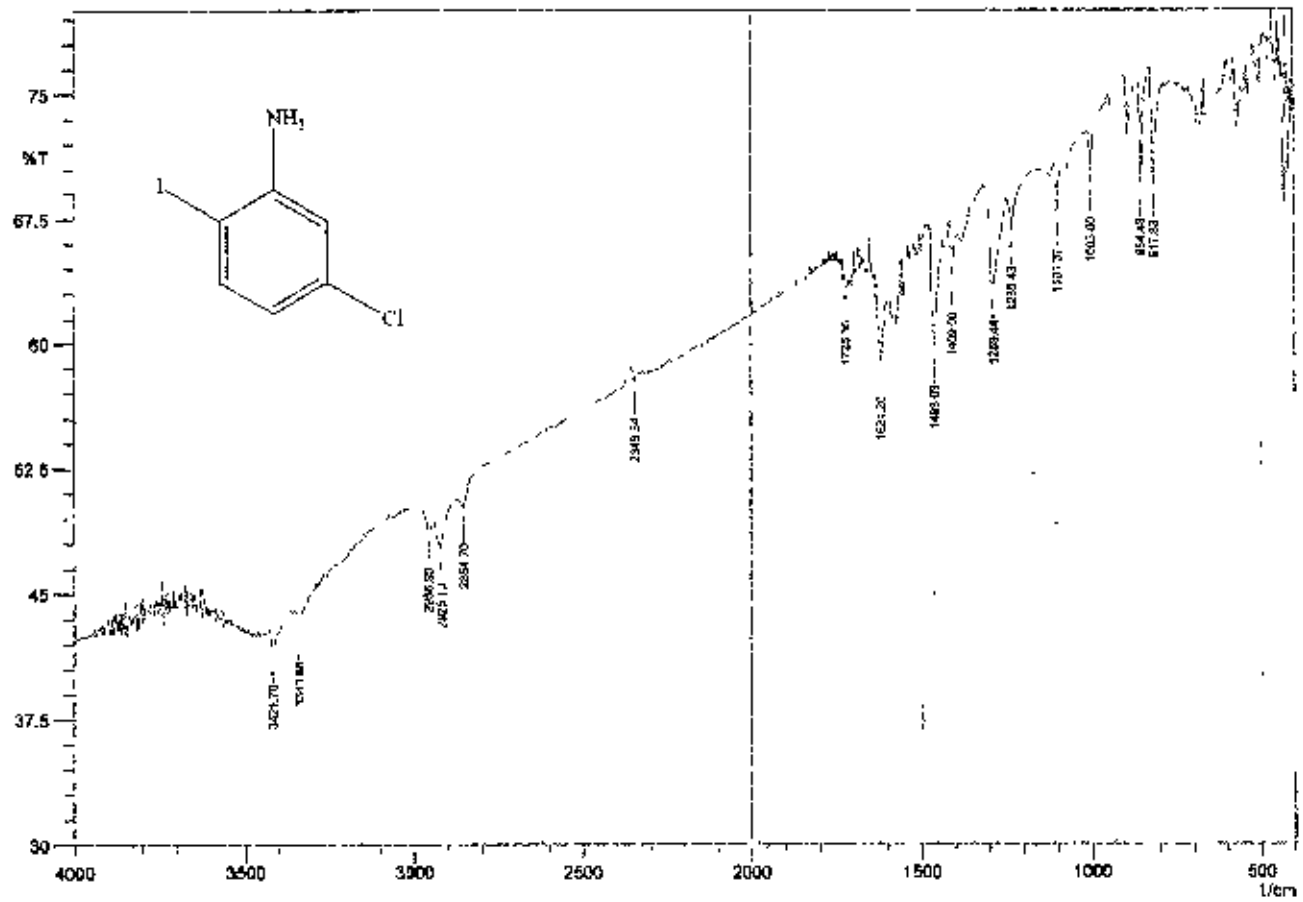
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 12.00 usec
PL1 -0.00 dB
SFO1 100.6253045 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
P3 8.30 usec
P4 16.60 usec
PCPD2 80.00 usec
PL2 -0.00 dB
PL12 16.00 dB
SFO2 400.1320007 MHz

F2 - Processing parameters
SI 32768
SF 100.6150838 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 151.719 ppm
F1 15202.97 Hz
F2P -14.683 ppm
F2 -1476.28 Hz
PPMCM 9.81871 ppm/cm
HZCM 987.81260 Hz/cm

Fig-27: DEPT Spectrum of compound **8**.



	Peak	Intensity
1	817.83	68.52
2	864.48	69.645
3	1003	69.695
4	1101.37	67.632
5	1235.43	66.771
6	1289.44	63.526
7	1409.99	64.029
8	1463.03	69.656
9	1621.2	58.987
10	1725.36	63.506
11	2349.34	57.697
12	2854.7	60.177
13	2925.1	47.808
14	2958.83	48.741
15	3343.66	43.13
16	3421.78	41.786

Fig-29: IR Spectrum of compound 9.

Data File : E:\Research\P-91 (D).smf

Resolution : 2 [1/cm]
No of Scans : 45
Apodization : Happ-Genzel

Date/Time : 07/08/2009 06:43:47 PM
Gain : auto

Analysed By/Date

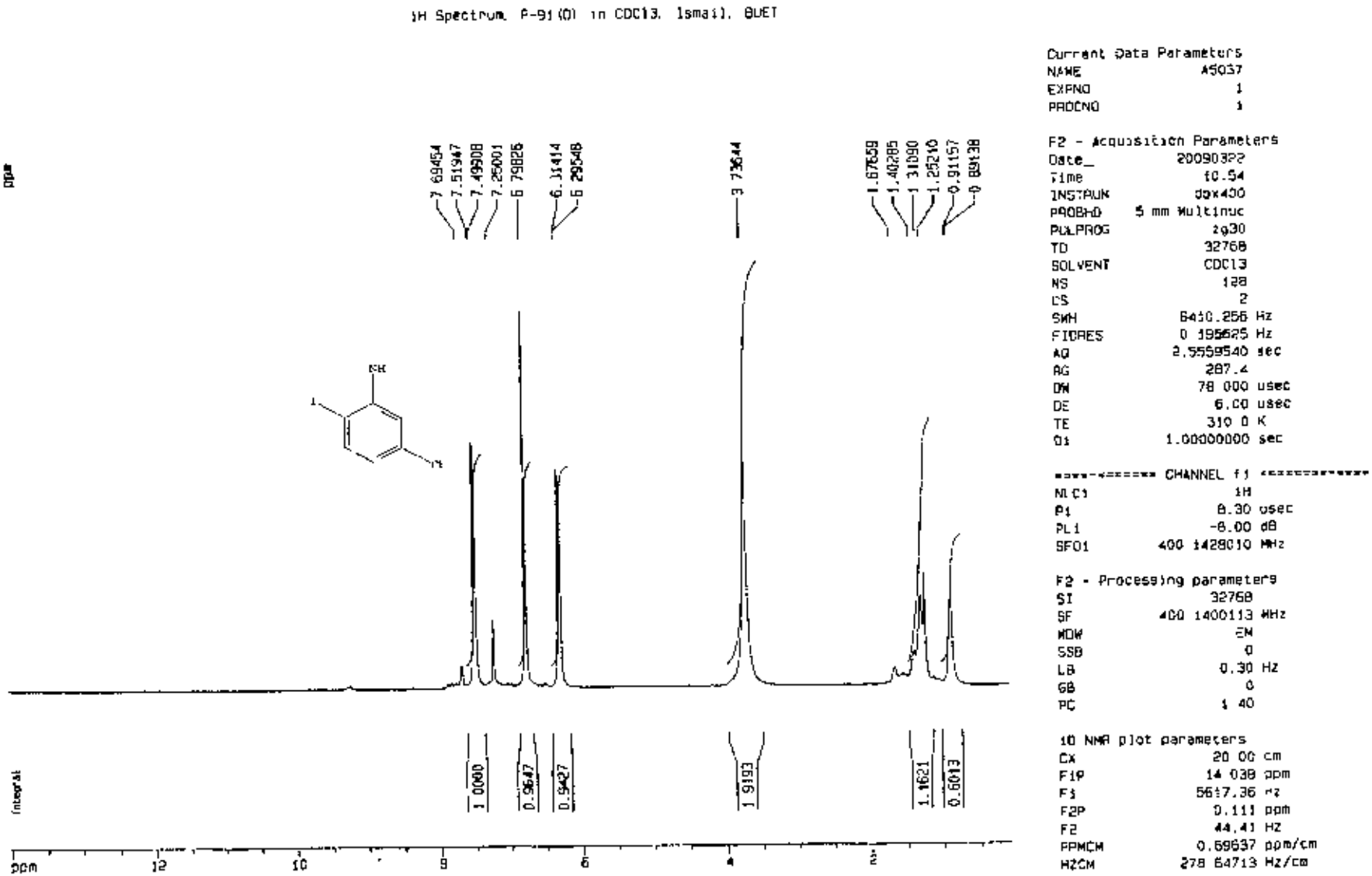


Fig-30: ^{1}H NMR Spectrum of compound **9.**

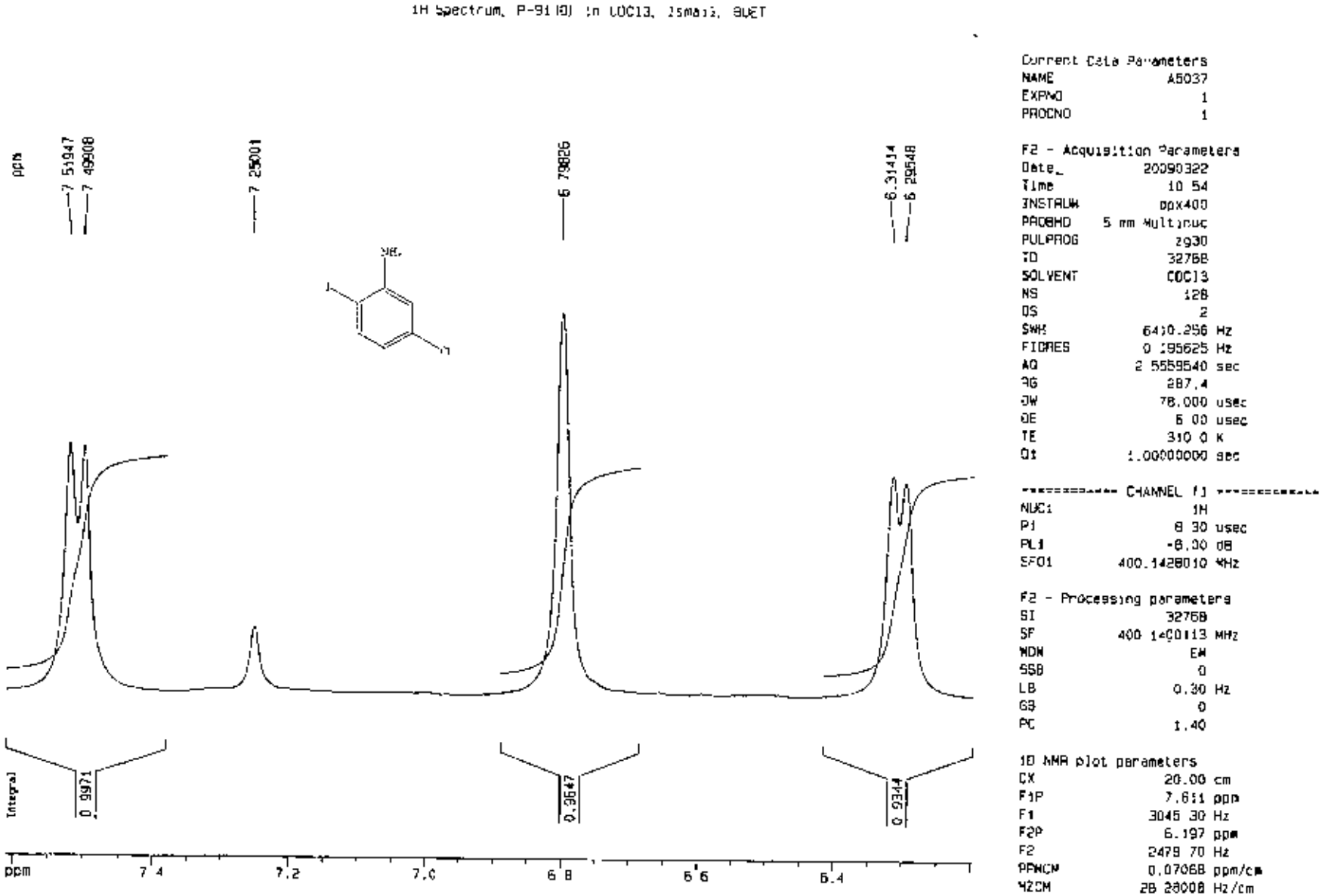
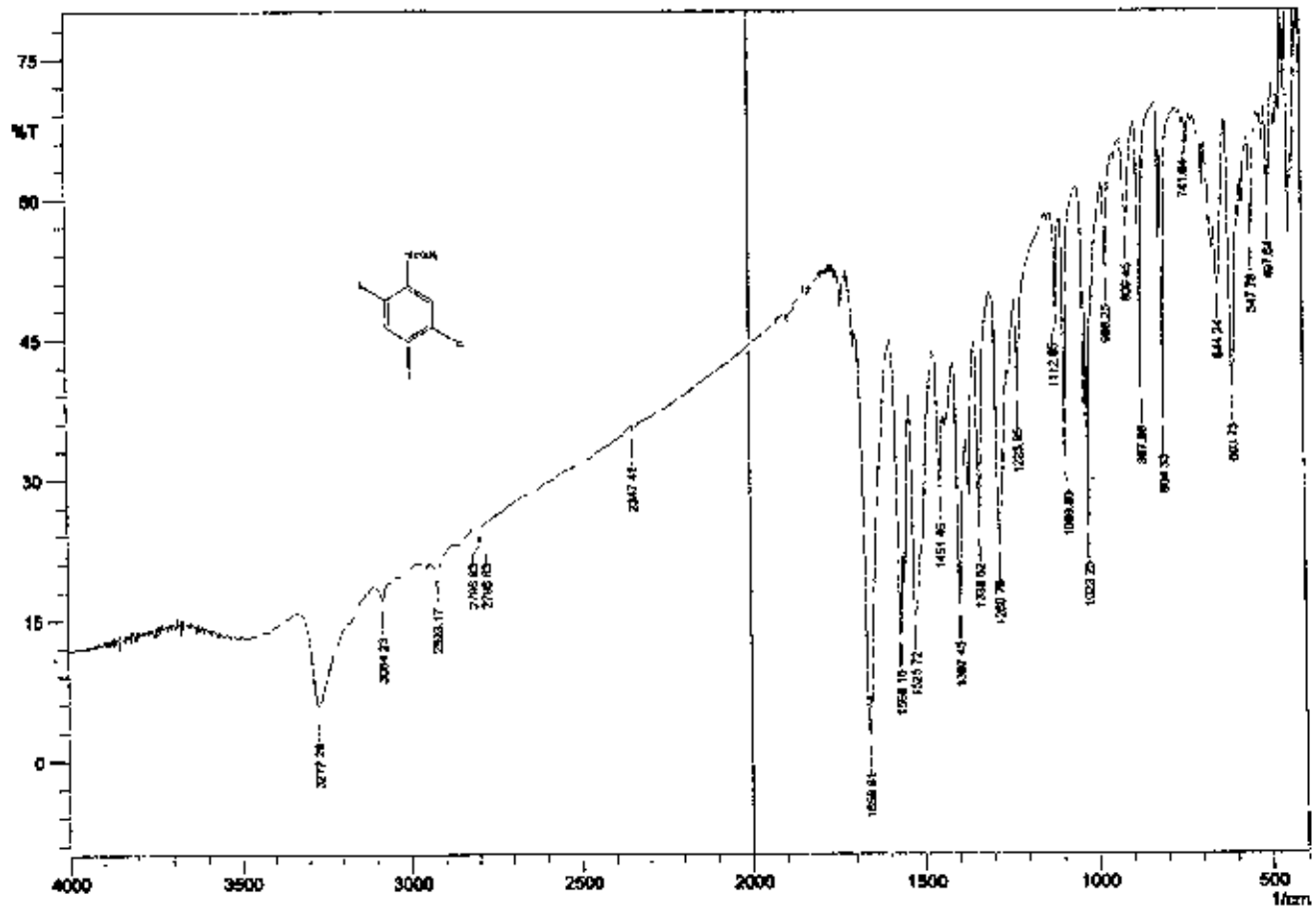


Fig-30: ^{1}H NMR Spectrum of compound **9.**



	Peak	Intensity
1	497.84	59.12
2	547.79	55.59
3	603.73	38.56
4	644.24	50.85
5	741.64	67.87
6	804.33	36.35
7	867.96	36.42
8	909.46	56.8
9	969.25	52.39
10	1023.25	24.96
11	1069.8	32.43
12	1112.95	46.33
13	1223.85	39.22
14	1260.78	22.98
15	1336.62	24.81
16	1397.45	18.43
17	1451.46	29.04
18	1525.72	15.42
19	1568.15	13.43
20	1658.81	2.56
21	2347.41	35.21
22	2796.63	24.97
23	2796.63	24.97
24	2923.17	20.23
25	3064.23	17.06
26	3272.29	5.84

Data File : E:\Research\P-115 (B) amf.smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 09:28:53 PM
Gain : auto

Analysed By/Date

Fig-31: IR Spectrum of compound **10.**

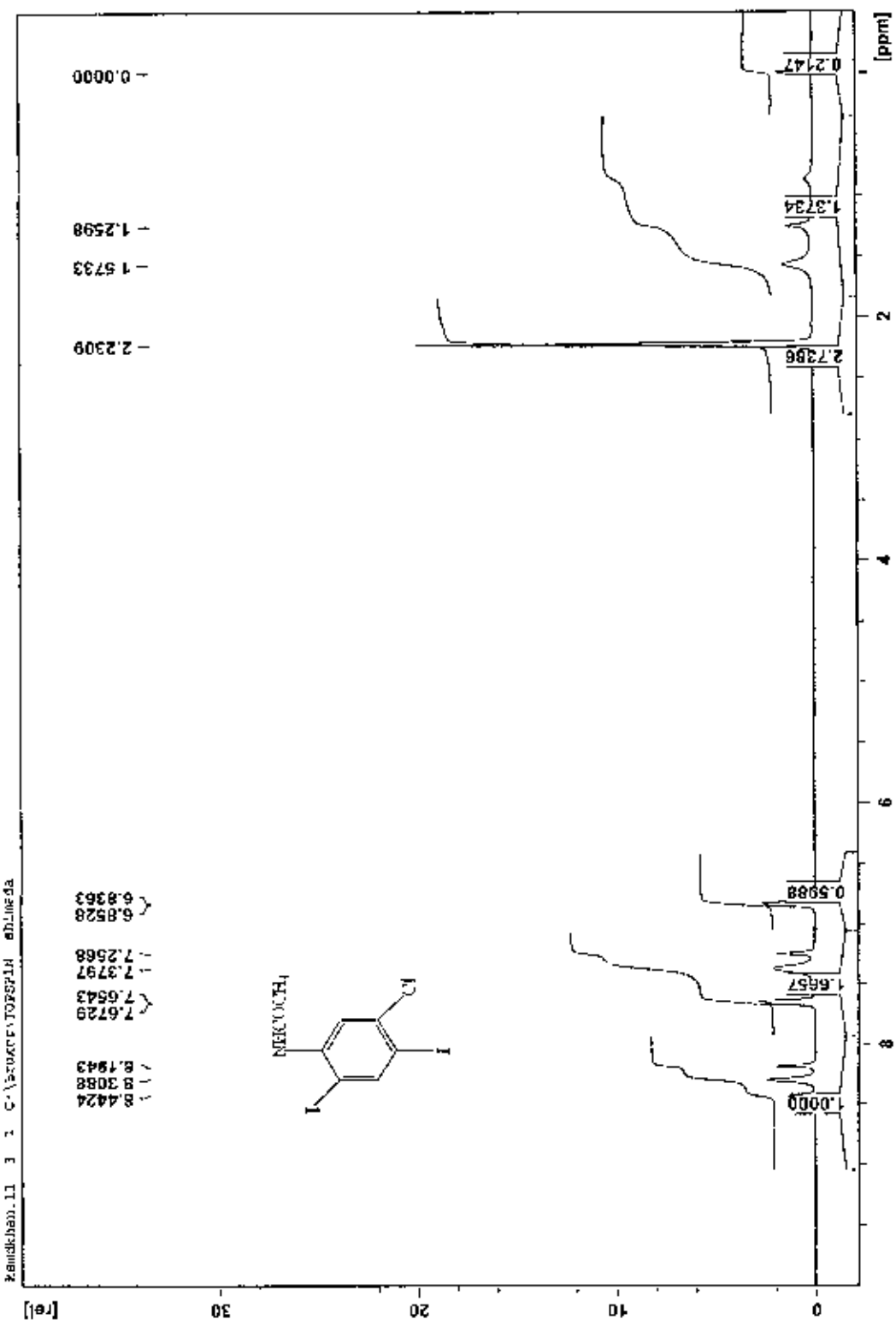


Fig-32: ^{1}H NMR Spectrum of compound **10.**

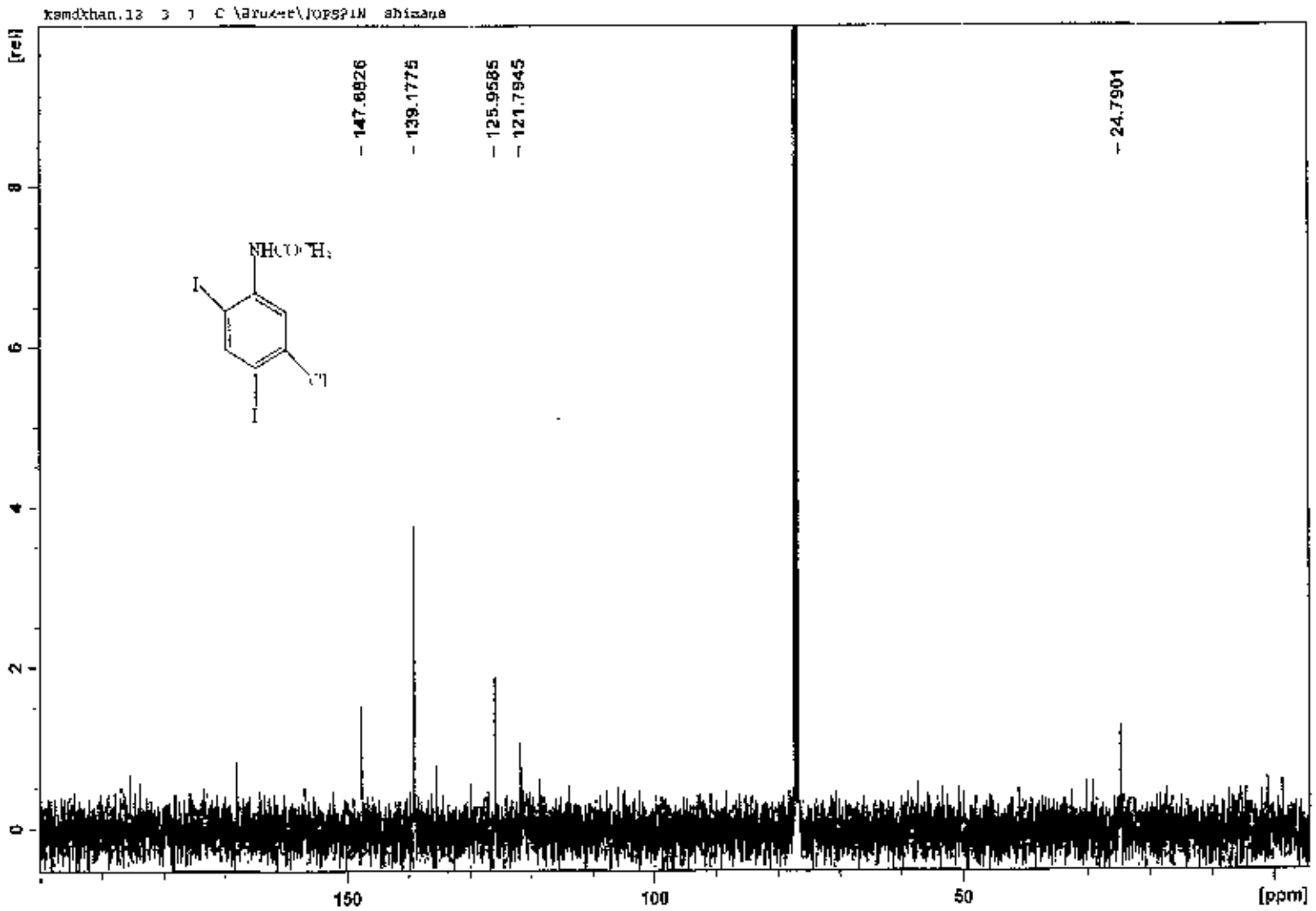
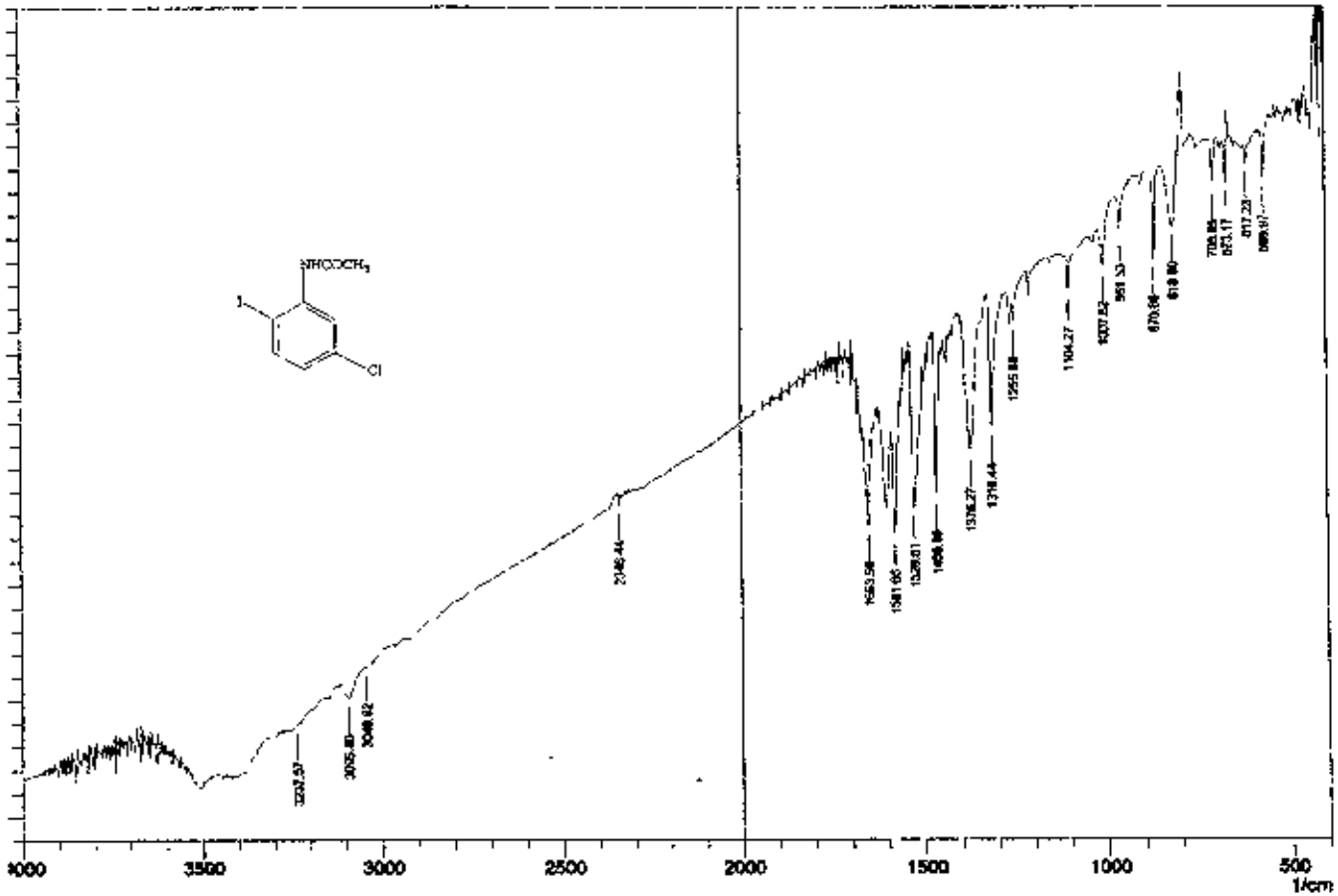


Fig-33: ^{13}C NMR Spectrum of compound **10.**



No.	Peak	Intensity
1	589.97	75.12
2	617.23	76.4
3	673.17	74.6
4	706.65	74.67
5	818.6	71.04
6	870.88	68.17
7	961.53	70.83
8	1007.82	67.63
9	1104.27	65.4
10	1256.66	62.8
11	1316.44	53.59
12	1375.27	51.5
13	1456.89	47.83
14	1525.61	46.71
15	1561.66	44.42
16	1653.99	45.12
17	2346.44	46.95
18	3046.62	32.97
19	3096.8	30.27
20	3257.57	27.92

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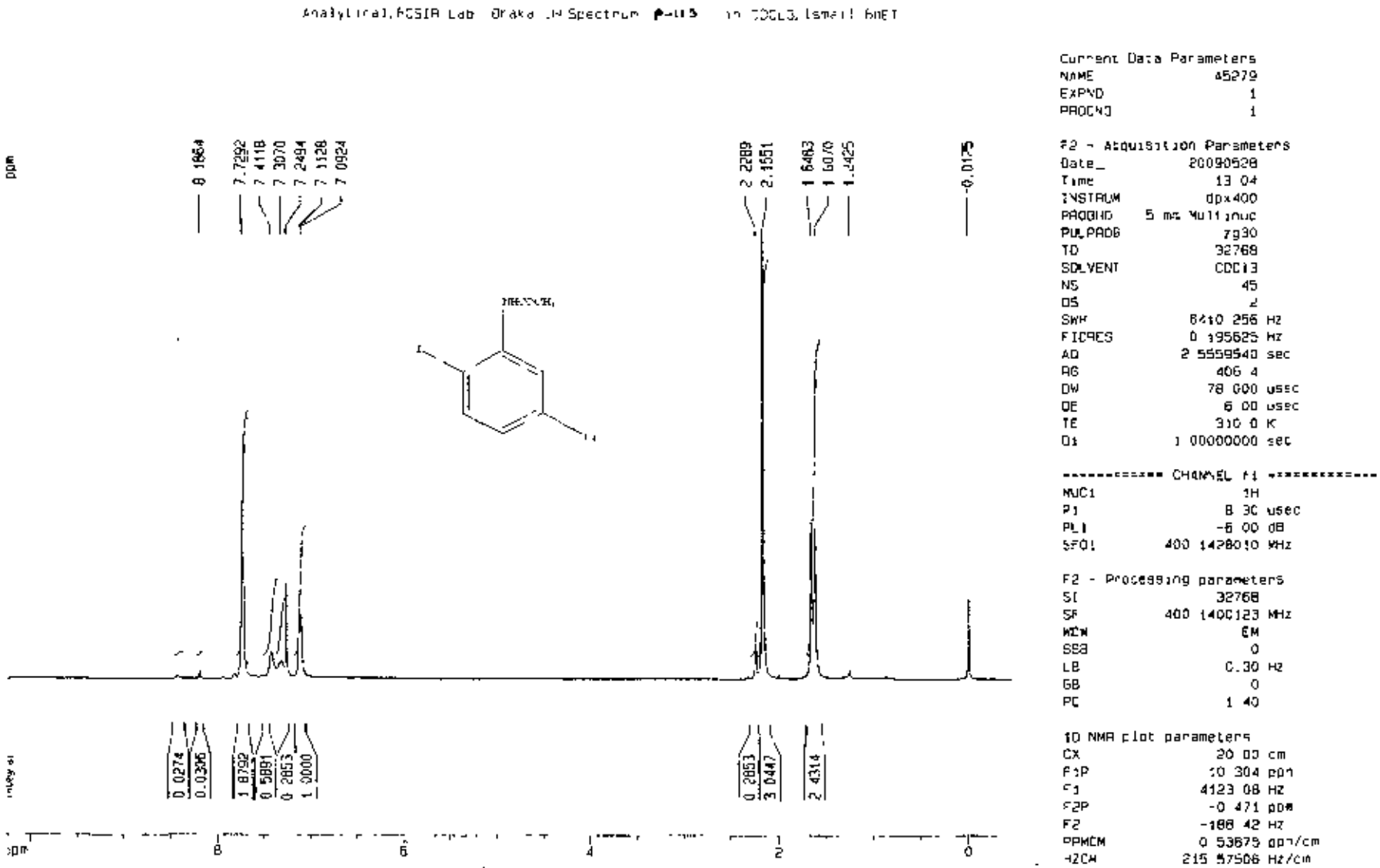
Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 07:56:31 PM
Gain : auto

Analysed By/Date

Fig-34: IR Spectrum of compound **11.**

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PROCNO                    1

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PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      45
DS                       2
SWH              6410 256 Hz
FIDRES           0 195625 Hz
AQ               2 5559540 sec
RG                   406 4
DW                  78 000 usec
DE                   6 00 usec
TE                  310 0 K
D1               1 00000000 sec

========== CHANNEL f1 ==========
NUC1                    1H
P1                   8 30 usec
PL1                 -6 00 dB
SFO1           400 1428010 MHz

F2 - Processing parameters
SI                   32768
SF             400 1400123 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1 40

1D NMR plot parameters
CX                   20 00 cm
F1P                 10 304 ppm
F1                 4123 08 Hz
F2P                 -0 471 ppm
F2                 -188 42 Hz
PPMCM              0 53675 ppm/cm
HZCM             215 57506 Hz/cm
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Fig-35: ^{1}H NMR Spectrum of compound **11.**

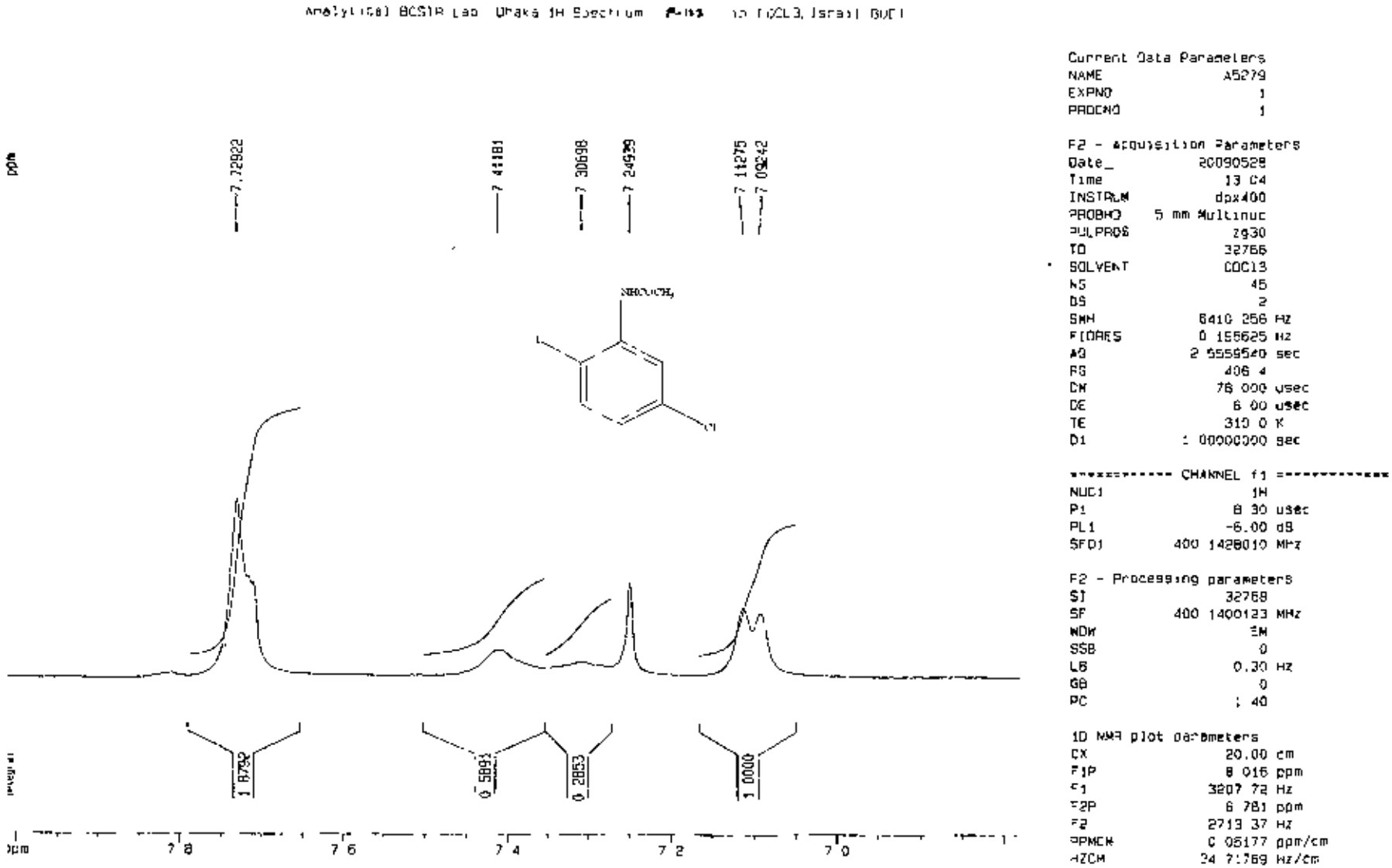


Fig-35: ^{1}H NMR Spectrum of compound **11.**

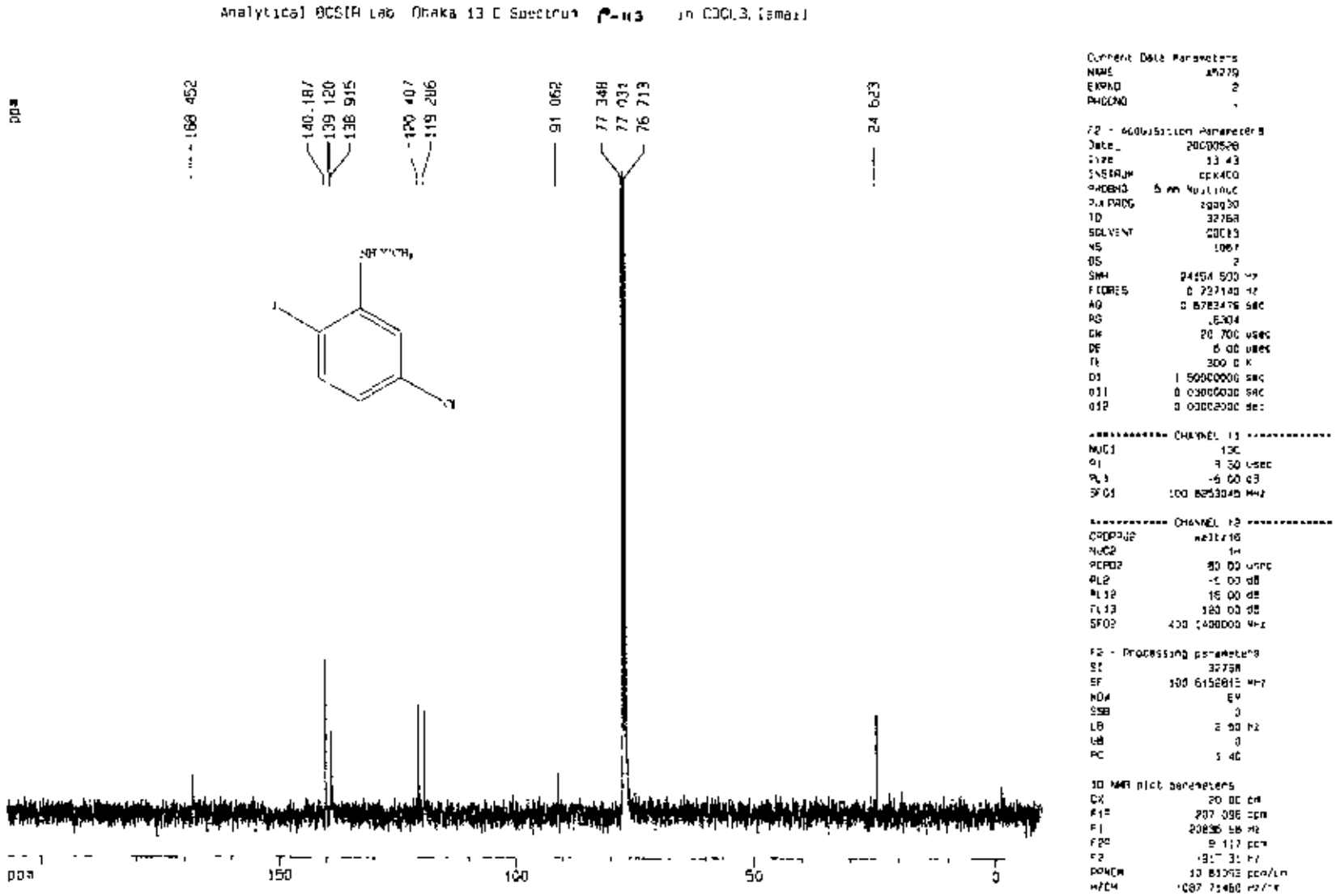


Fig-36: ^{13}C NMR Spectrum of compound **11.**

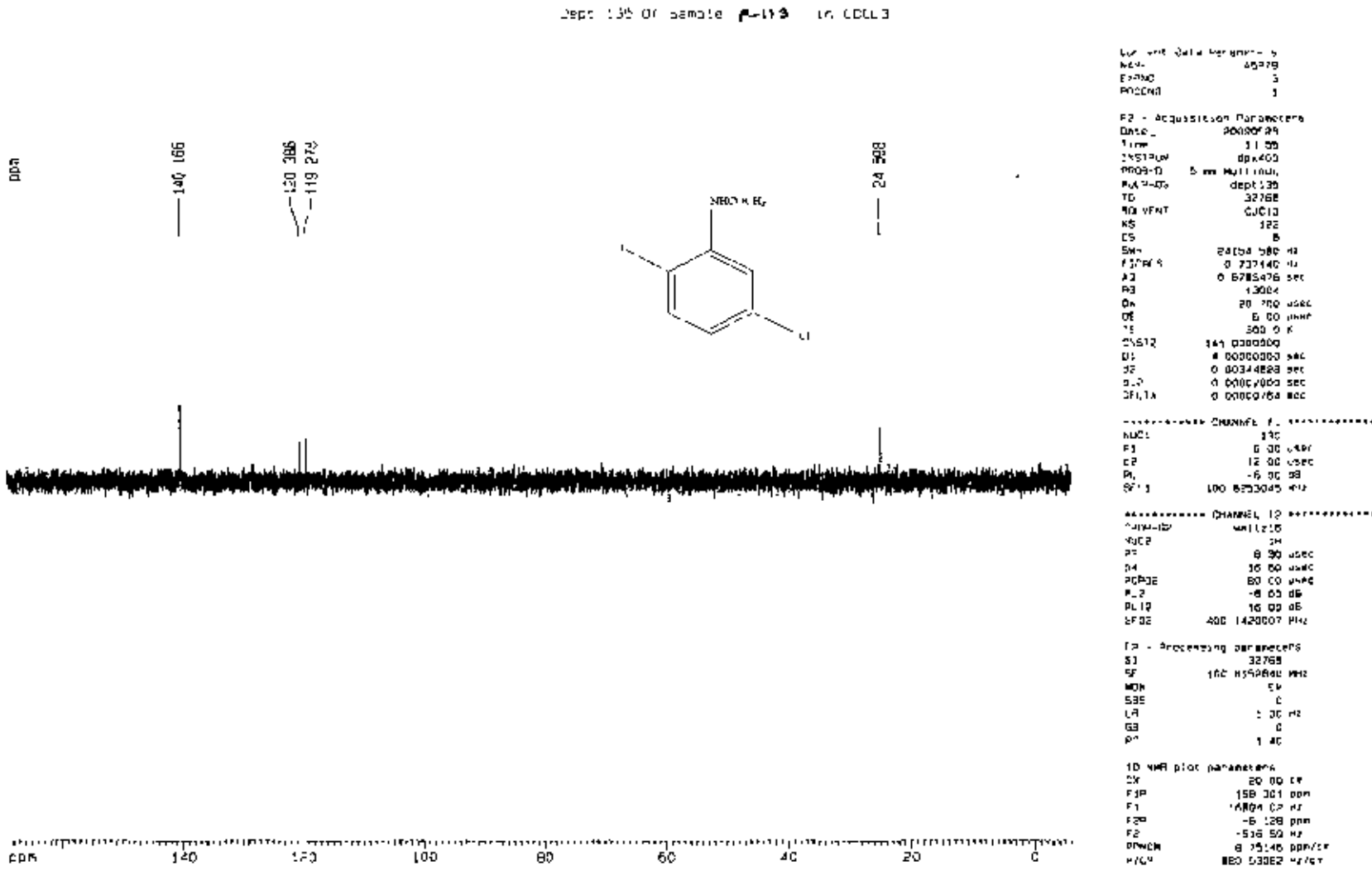
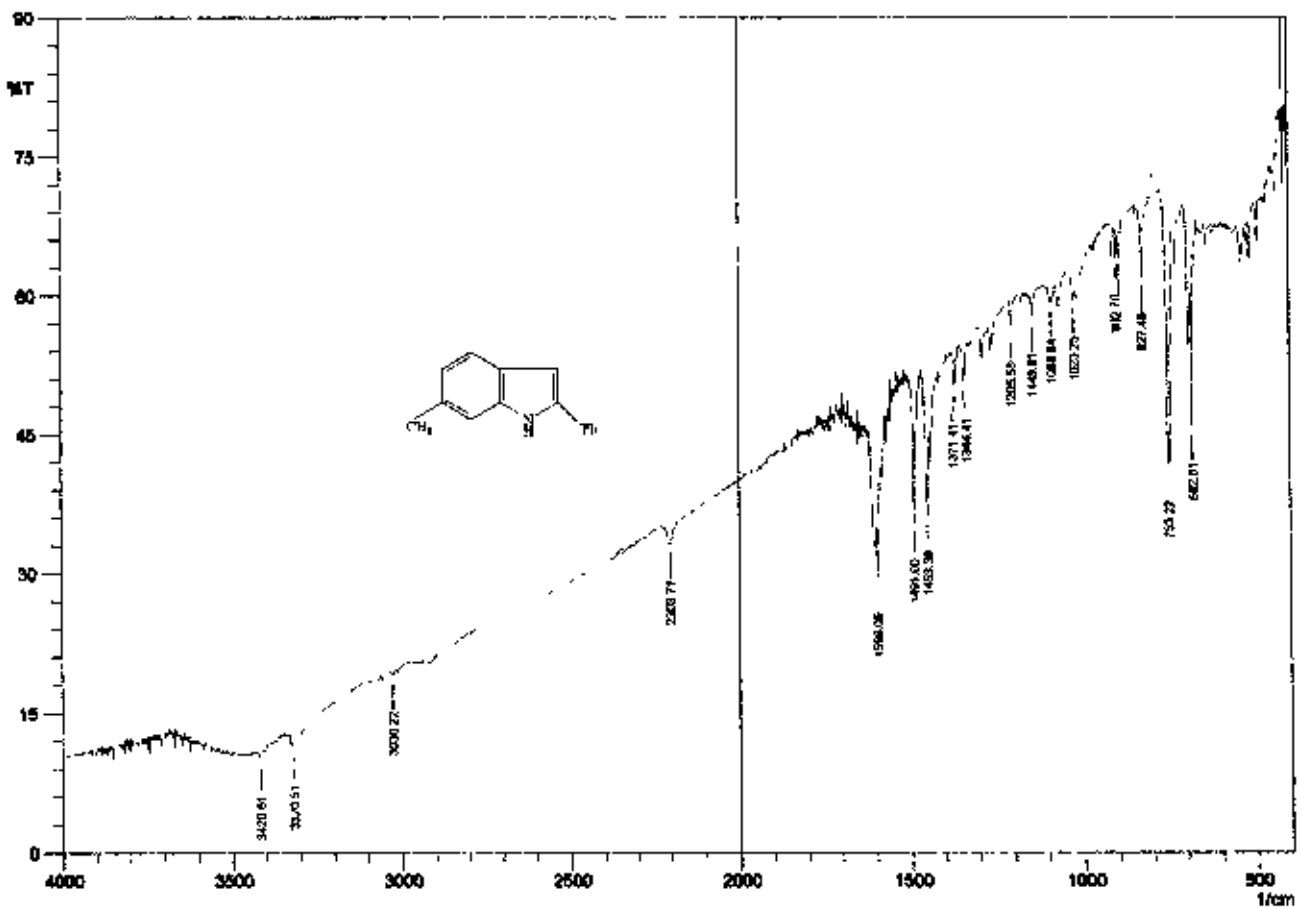


Fig-36: DEPT Spectrum of compound 11.



No.	Peak	Intensity
1	682.61	45.86
2	753.22	41.74
3	827.48	62
4	902.7	64.04
5	1023.25	59.54
6	1088.84	59.22
7	1143.81	57.73
8	1205.53	56.89
9	1344.41	50.71
10	1371.41	50.11
11	1453.39	36.36
12	1491	35.47
13	1596.08	29.65
14	2203.71	33.22
15	3030.22	19.11
16	3320.51	11.23
17	3420.61	10.09

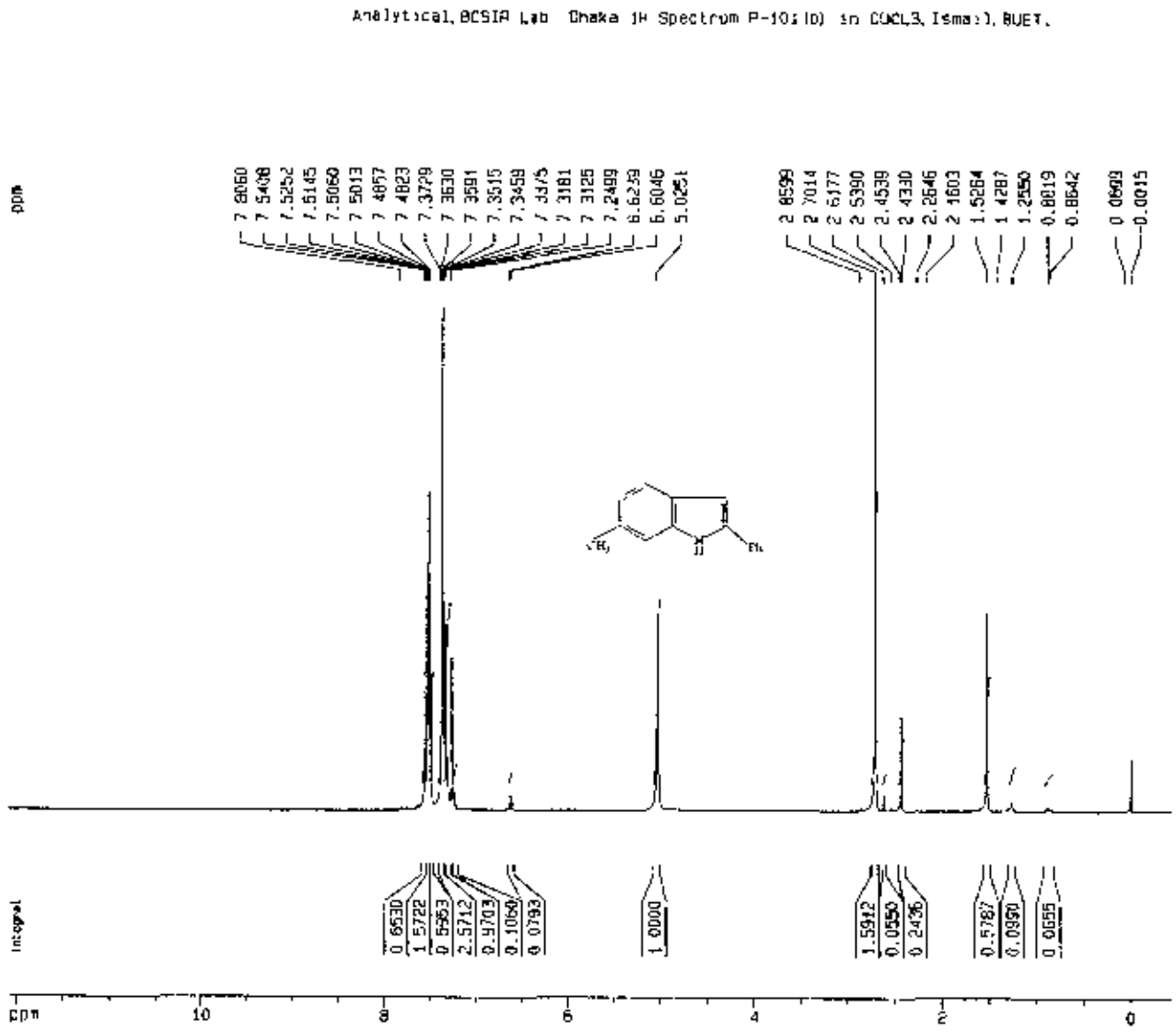
Data File : E:\Research\P-101 (B)smf.smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Hepp-Genzel

Date/Time : 06/23/2009 07:36:10 PM
Gain : auto

Analysed By/Date

Fig-37: IR Spectrum of compound **12.**

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EXPNO                     1
PROCNO                    1

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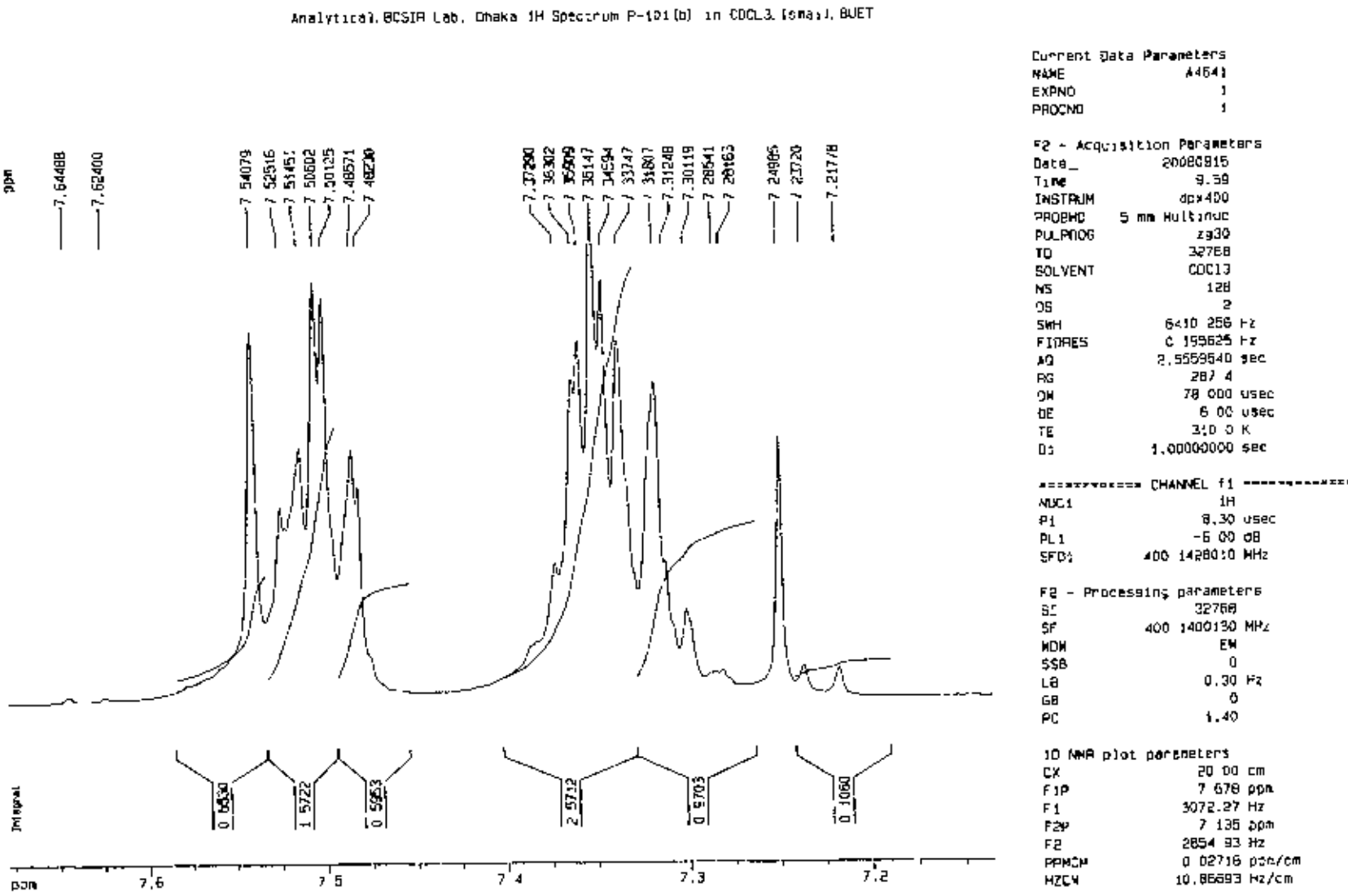
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                      128
DS                        2
SWH               6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5559540 sec
RG                    287.4
DW                   78.000 usec
DE                    6.00 usec
TE                   310.0 K
D1                1.00000000 sec

------------ CHANNEL f1 ------------
NUC1                     1H
P1                    8.30 usec
PL1                  -6.00 dB
SFO1          400.1478010 MHz

F2 - Processing parameters
SI                    32768
SF          400.1400130 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
CX                    20.00 cm
F1P                  12.066 ppm
F1                 4828.19 Hz
F2P                  -0.413 ppm
F2                 -165.13 Hz
PPMCM              0.62395 ppm/cm
HZCM             249.66621 Hz/cm
```

Fig-38: ^{1}H NMR Spectrum of compound **12.**

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Current Data Parameters
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EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
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Time                   9.59
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                     128
DS                       2
SWH               6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5559540 sec
RG                    287.4
DW                  78.000 usec
DE                   6.00 usec
TE                  310.0 K
D1                1.00000000 sec

========== CHANNEL f1 ============
NUC1                    1H
P1                   8.30 usec
PL1                 -6.00 dB
SFO1          400.1428010 MHz

F2 - Processing parameters
SI                   32768
SF          400.1400130 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                  7.678 ppm
F1                3072.27 Hz
F2P                  7.135 ppm
F2                2854.93 Hz
PPMCM             0.02716 ppm/cm
HZCM             10.86693 Hz/cm
```

Fig-38: ^{1}H NMR Spectrum of compound **12** .

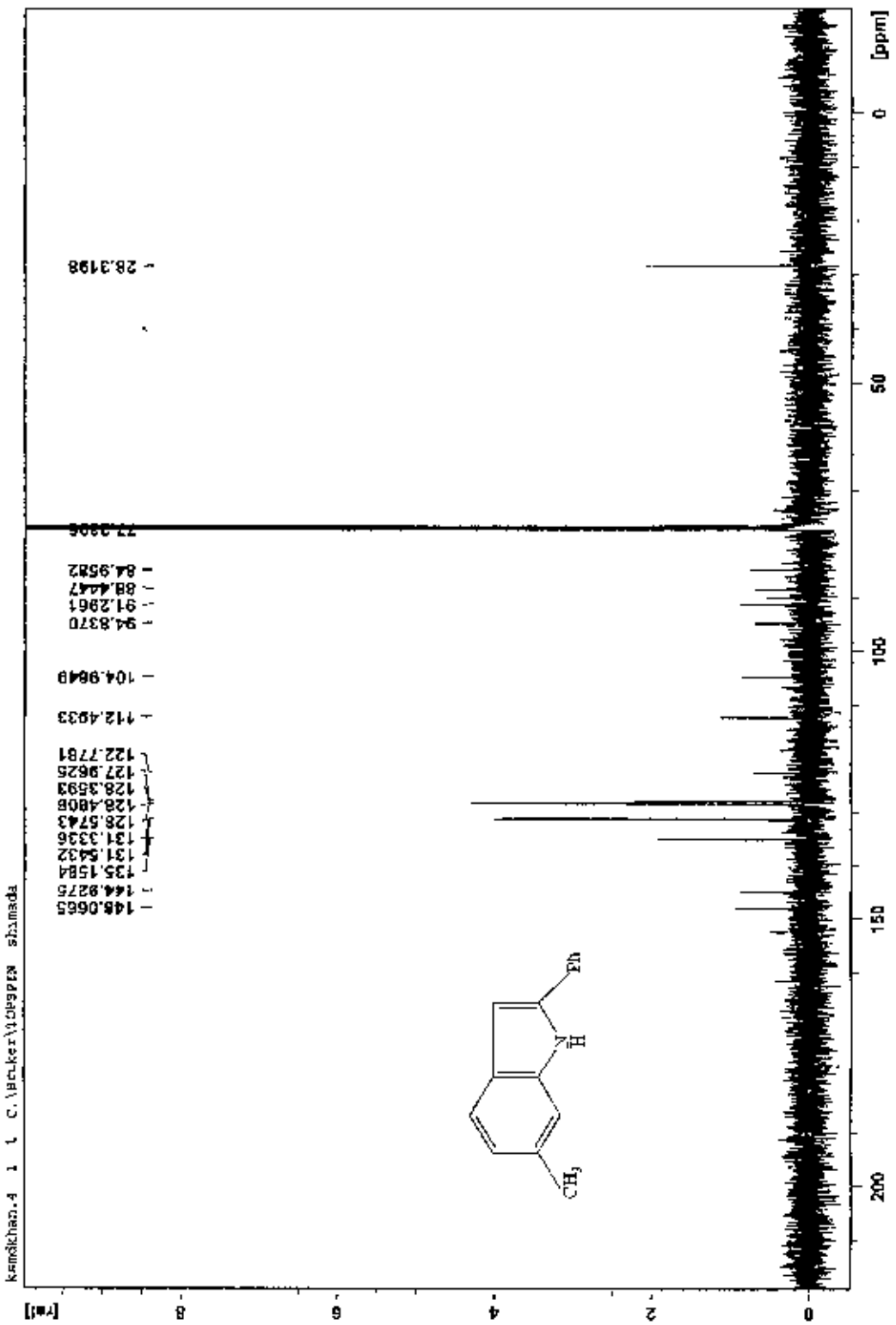
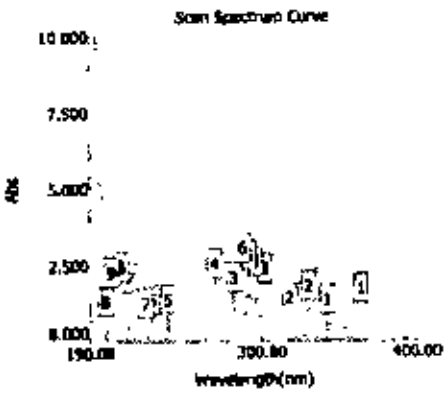


Fig-39: ^{13}C NMR Spectrum of compound **12.**



1	Peak	364.00	0.464
2	Peak	330.00	0.542
3	Peak	302.00	1.127
4	Peak	296.00	1.363
5	Peak	292.00	1.558
6	Peak	288.00	1.795
7	Peak	216.00	0.840
8	Peak	210.00	1.199
9	Peak	204.00	1.824
1	Valley	342.00	0.102
2	Valley	318.00	0.163
3	Valley	282.00	0.829
4	Valley	270.00	1.276
5	Valley	240.00	0.125
6	Valley	220.00	0.124
7	Valley	226.00	-0.066
8	Valley	208.00	0.084

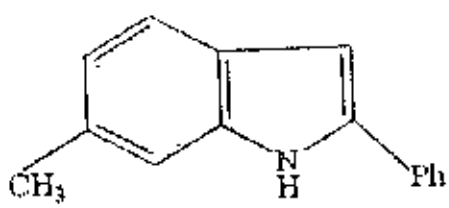


Fig-40: UV Spectrum of compound **12.**

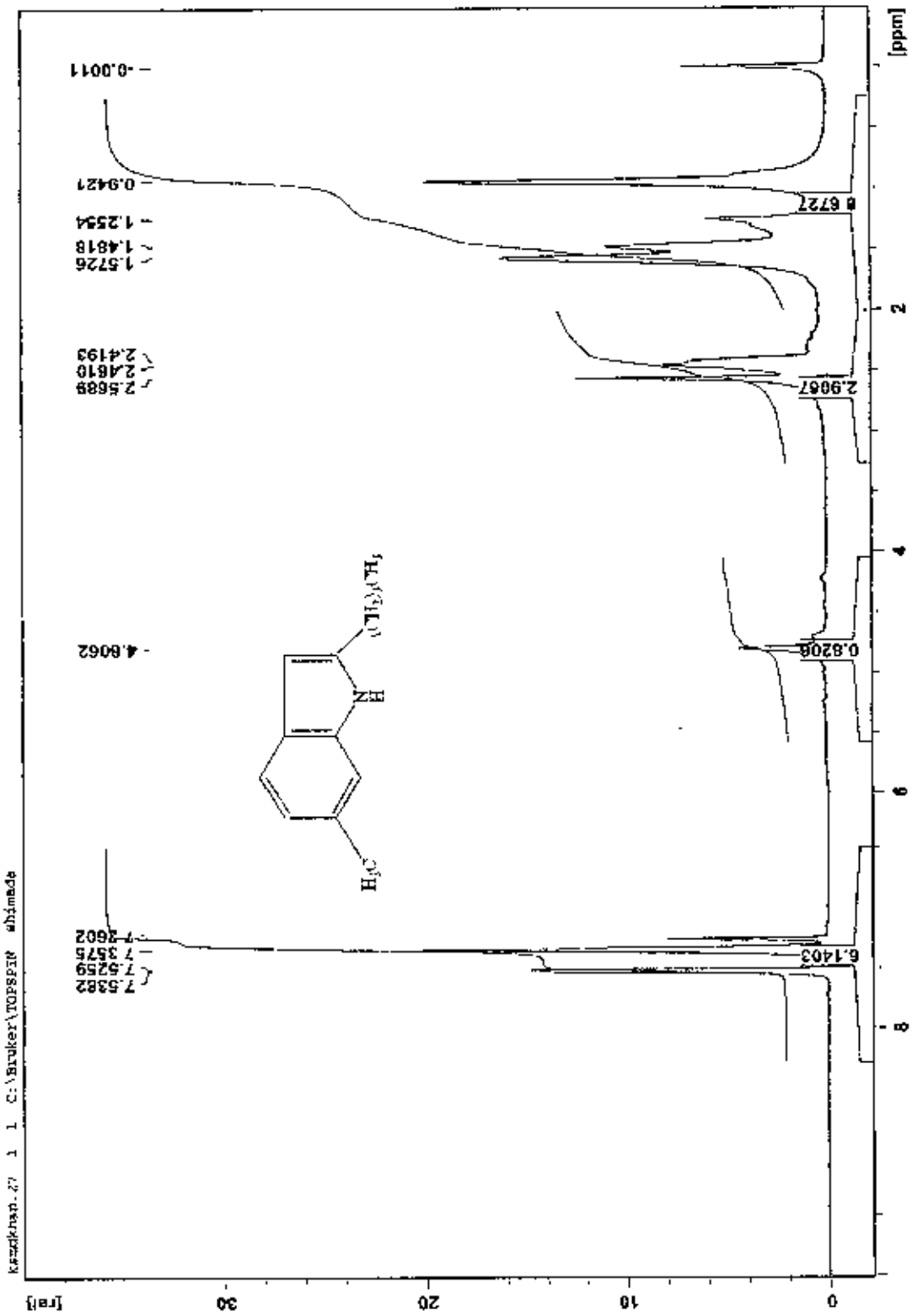


Fig-41: ^{1}H NMR Spectrum of compound **13.**

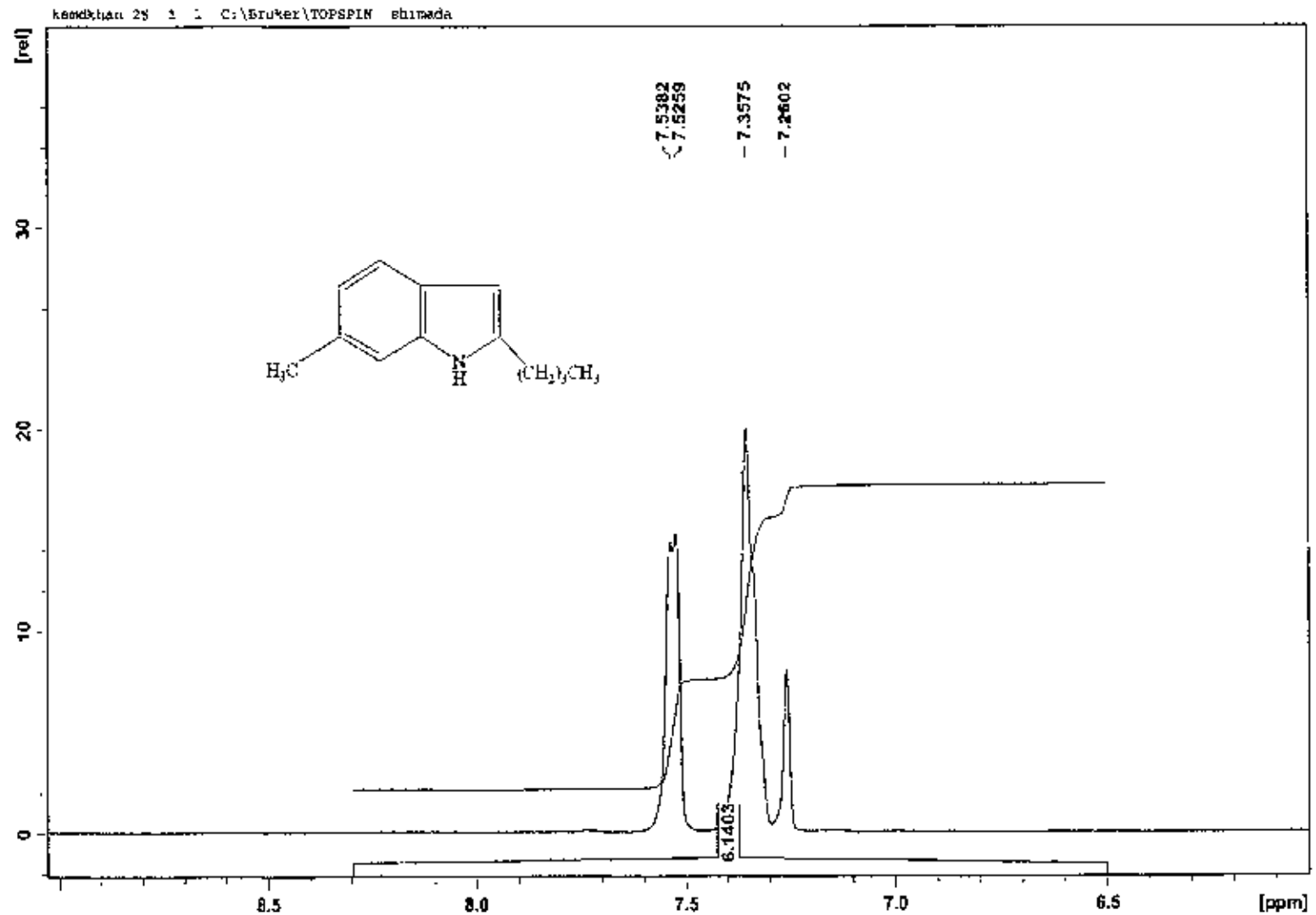


Fig-41: ^{1}H NMR Spectrum of compound **13** .

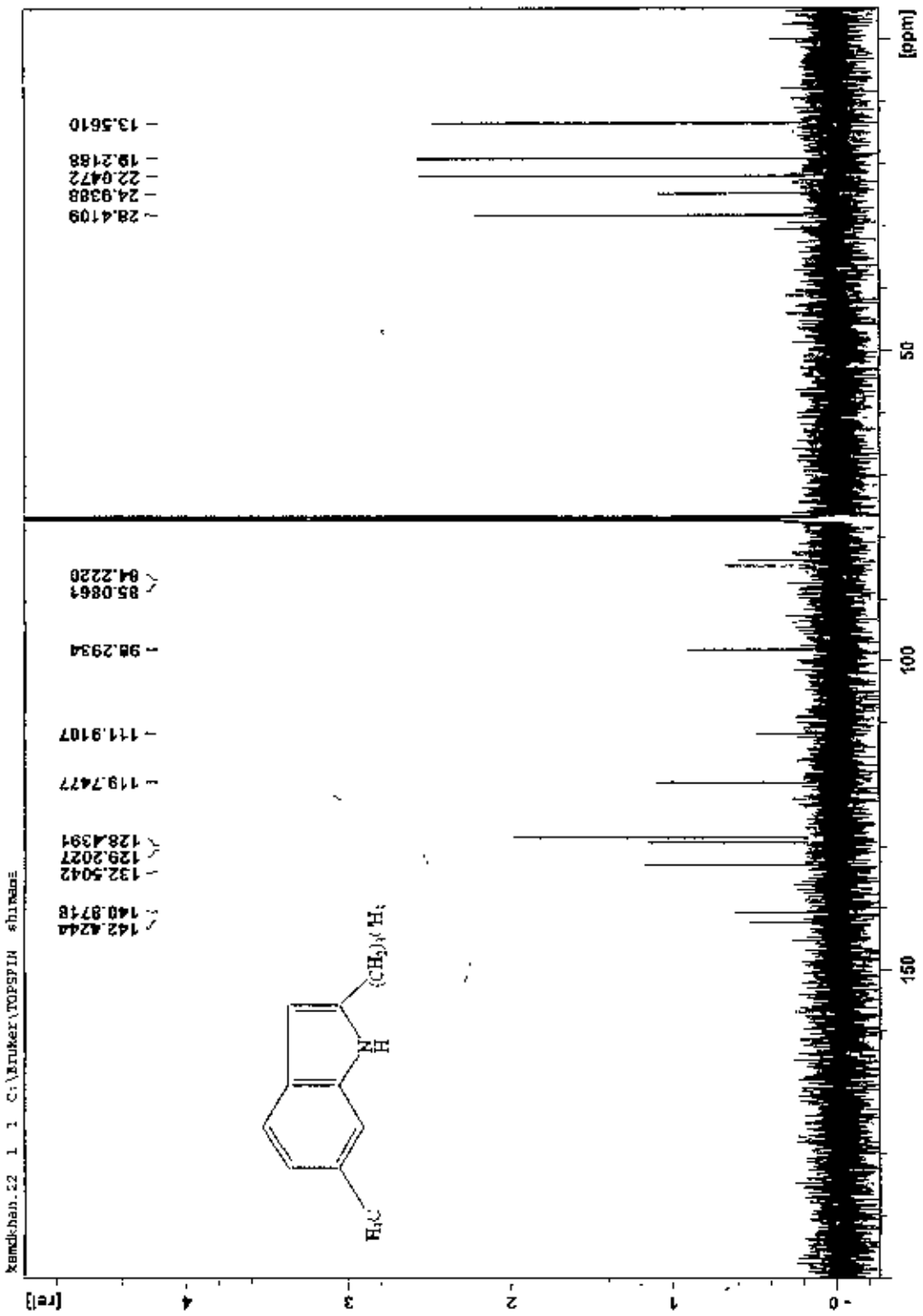
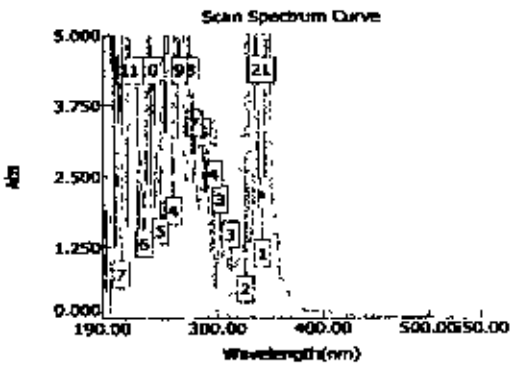


Fig-42: ^{13}C NMR Spectrum of compound **13**.



1	Peak	346.00	9.999
2	Peak	336.00	9.999
3	Peak	302.00	1.460
4	Peak	296.00	1.908
5	Peak	290.00	2.604
6	Peak	286.00	2.649
7	Peak	278.00	2.805
8	Peak	342.00	1.763
9	Peak	326.00	1.135
10	Peak	312.00	0.839
11	Peak	258.00	2.509
1	Valley	246.00	2.160
2	Valley	230.00	1.933
3	Valley	208.00	1.397

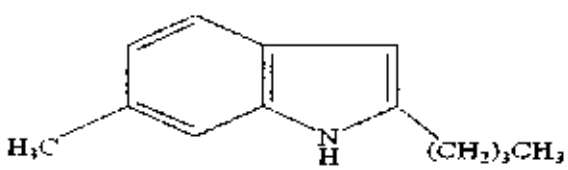


Fig-43: UV Spectrum of compound **13**.

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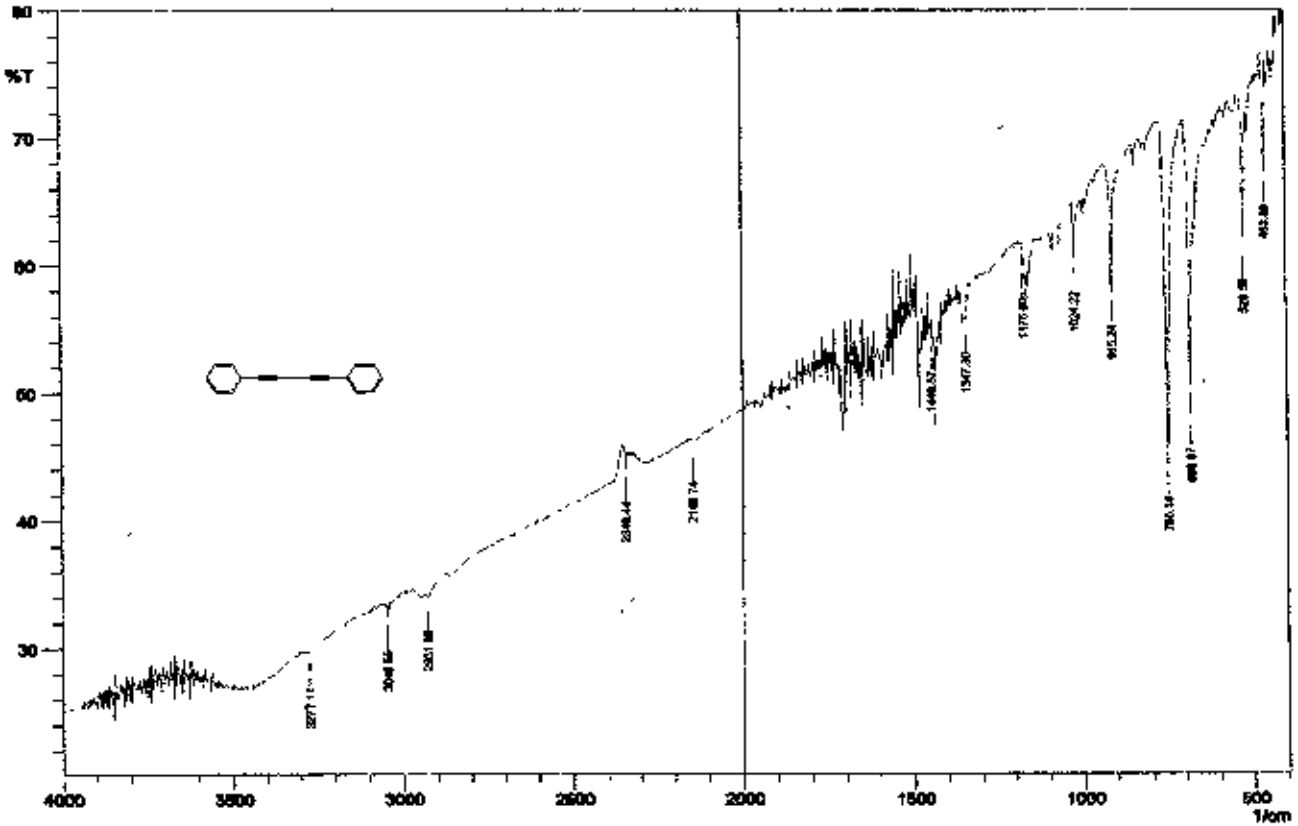
Industrial Operations, Tongi I/A
Quality Control Department



No.	Peak	Intensity
1	463.59	67.327
2	525.59	61.479
3	686.67	48.283
4	758.14	44.423
5	915.24	57.879
6	1024.22	60.823
7	1176.8	60.094
8	1347.3	56.78
9	1448.67	64.274
10	2148.74	48.86
11	2346.44	44.077
12	2851.66	34.075
13	3048.58	37.488
14	3277.11	28.626

Data File : E:\Research\Phenyl acrylene dimer\P-(24(A).smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 11:26:23 AM
Gain : auto

Analysed By/Date

Fig-44: IR Spectrum of compound 14 .

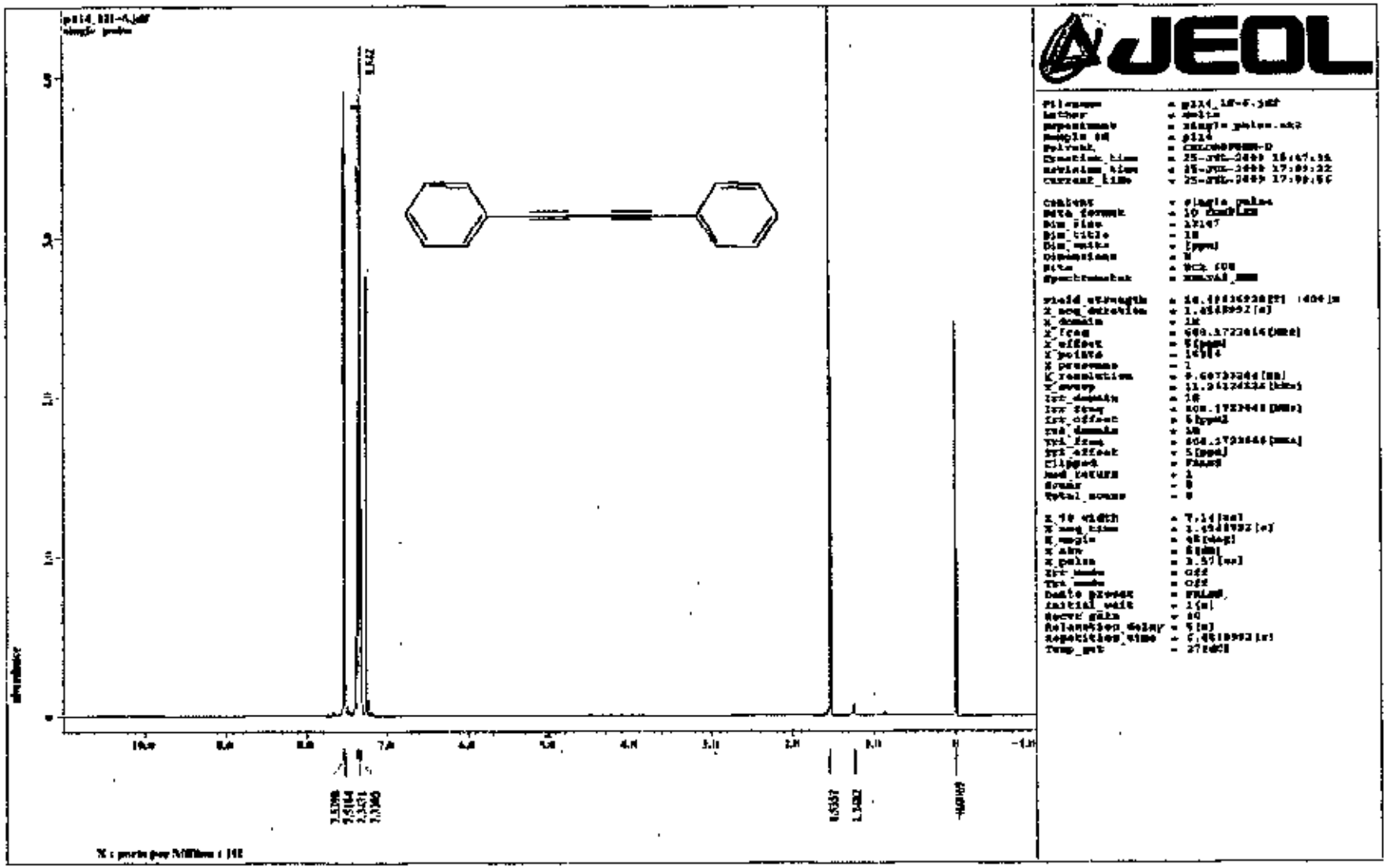


Fig-45: ^{1}H NMR Spectrum of compound **14.**

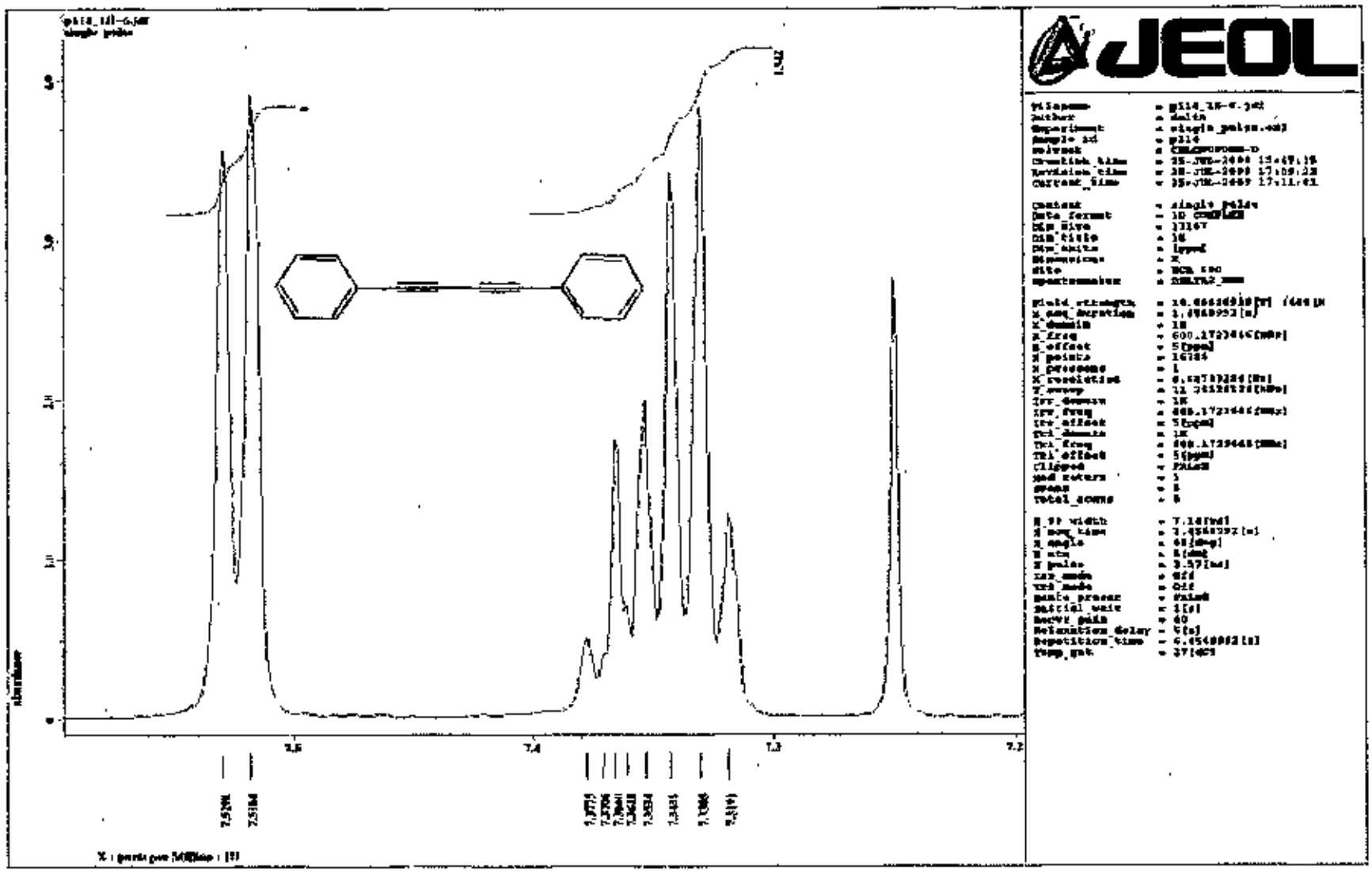


Fig-45: ^{1}H NMR Spectrum of compound **14.**

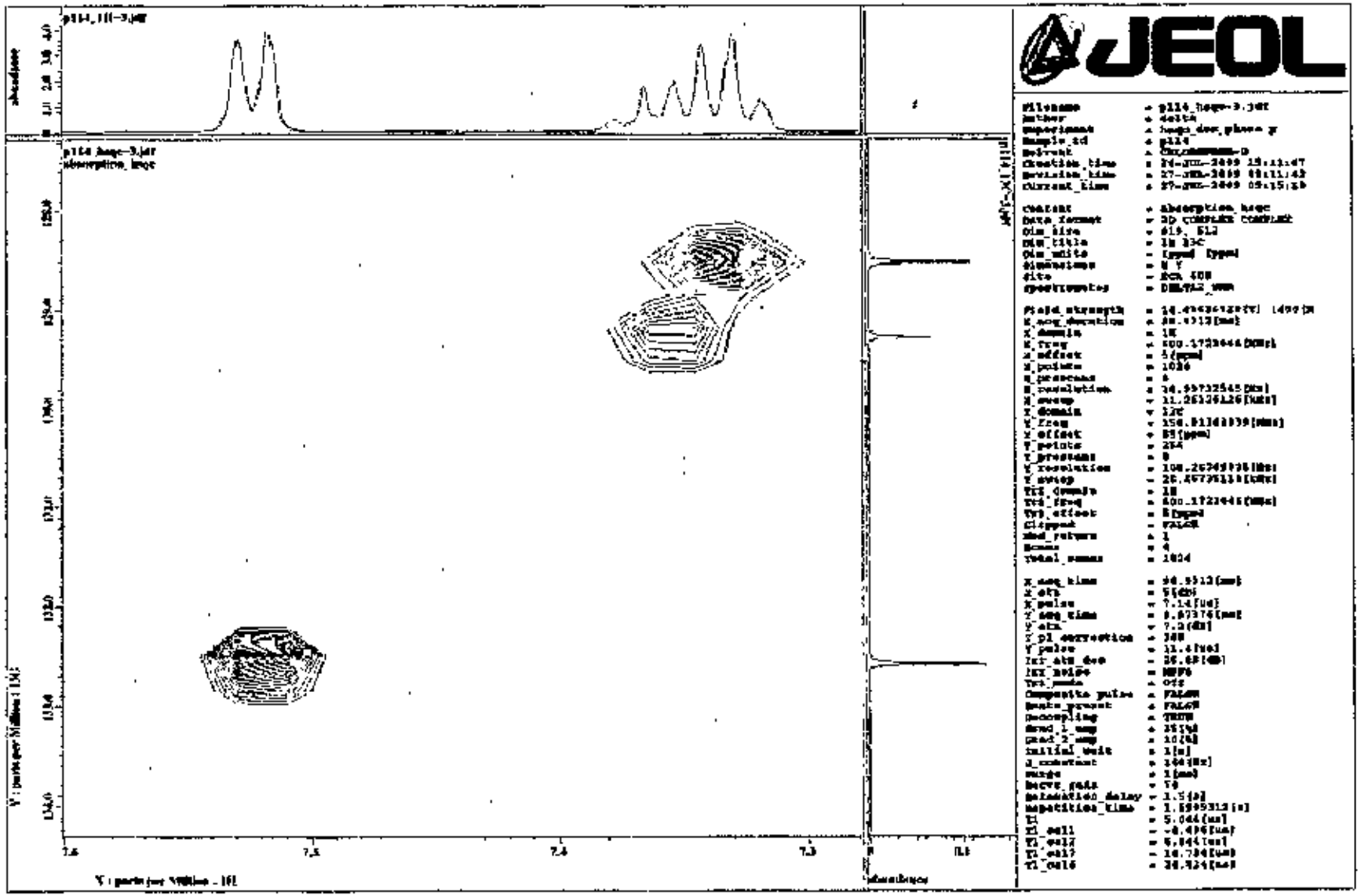


Fig-46: COSY Spectrum of compound **14.**

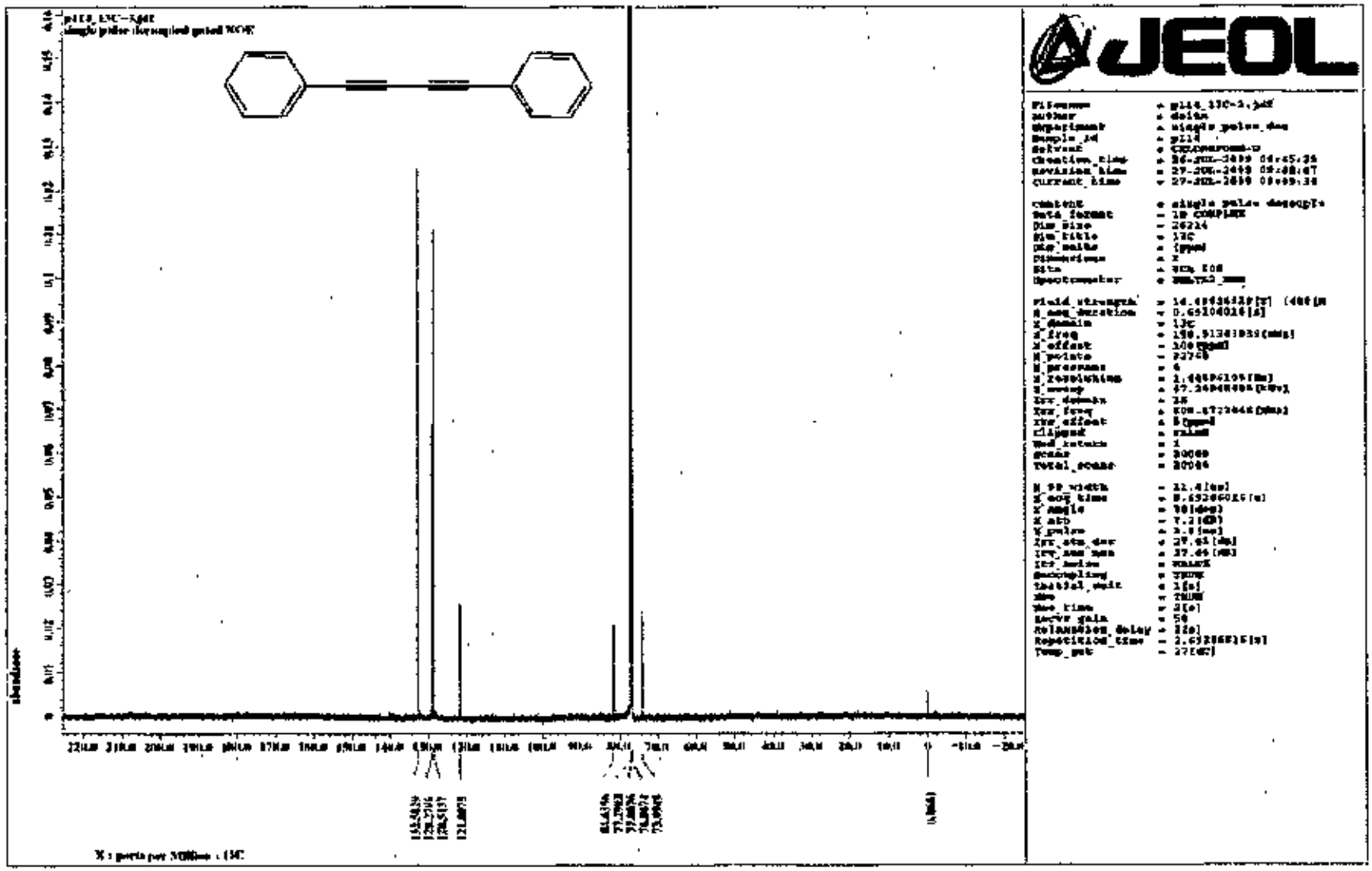
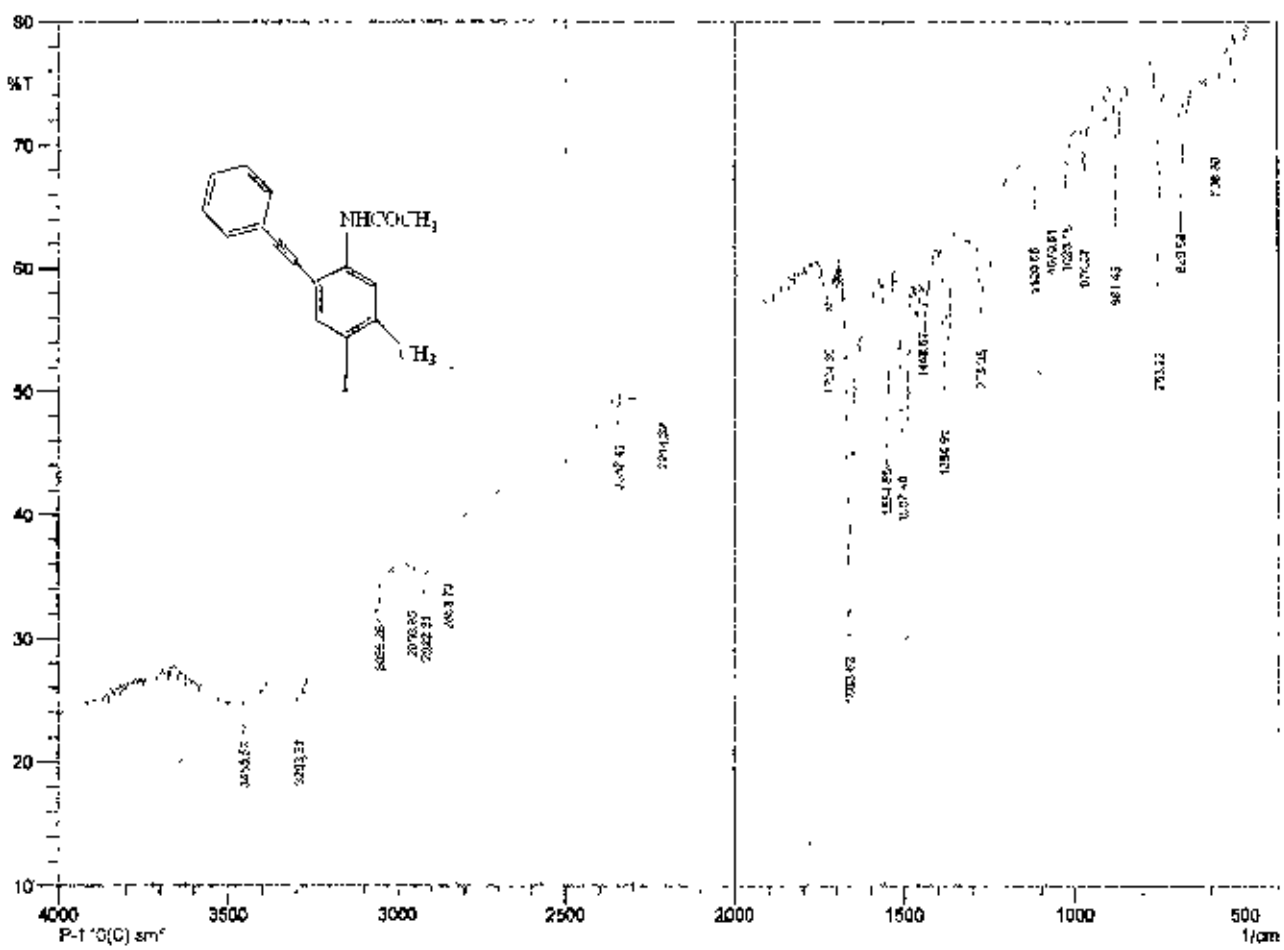


Fig-47: ^{13}C NMR Spectrum of compound 14.



	Peak	Intensity
1	588.3	72.163
2	669.66	66.959
3	753.22	58.377
4	881.48	69.24
5	974.07	84.73
6	1026.15	86.589
7	1070.51	86.374
8	1120.66	84.829
9	1275.93	56.512
10	1384.91	60.021
11	1448.57	57.95
12	1507.4	48.268
13	1554.65	45.798
14	1663.63	31.58
15	1724.39	58.644
16	2214.82	60.538
17	2347.41	48.826
18	2853.73	37.542
19	2922.21	34.982
20	2958.85	35.26
21	3056.26	34.122
22	3293.51	24.865
23	3455.53	24.698

Comments : P-110(C).smf
Data File : E:\Research\P-110(C).smf

Resolution . 2 [1/cm]
No of Scans 45
Apodization . Happ-Genzel

Date/Time . 07/08/2009 05:48:26 PM
Gain : auto

Analysed By/Date

Fig-48: IR Spectrum of compound 15.

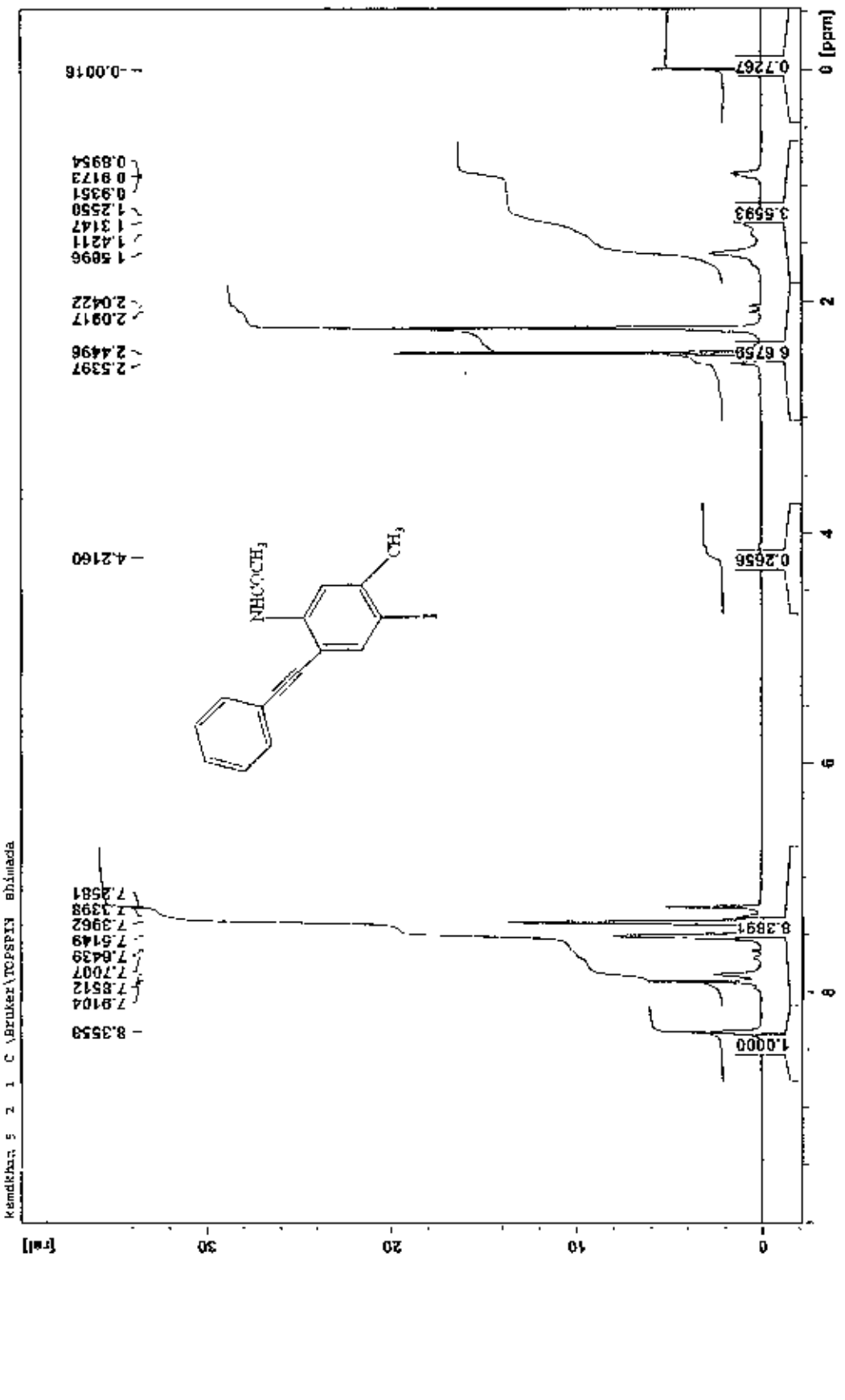


Fig-49: ^{1}H NMR Spectrum of compound **15.**

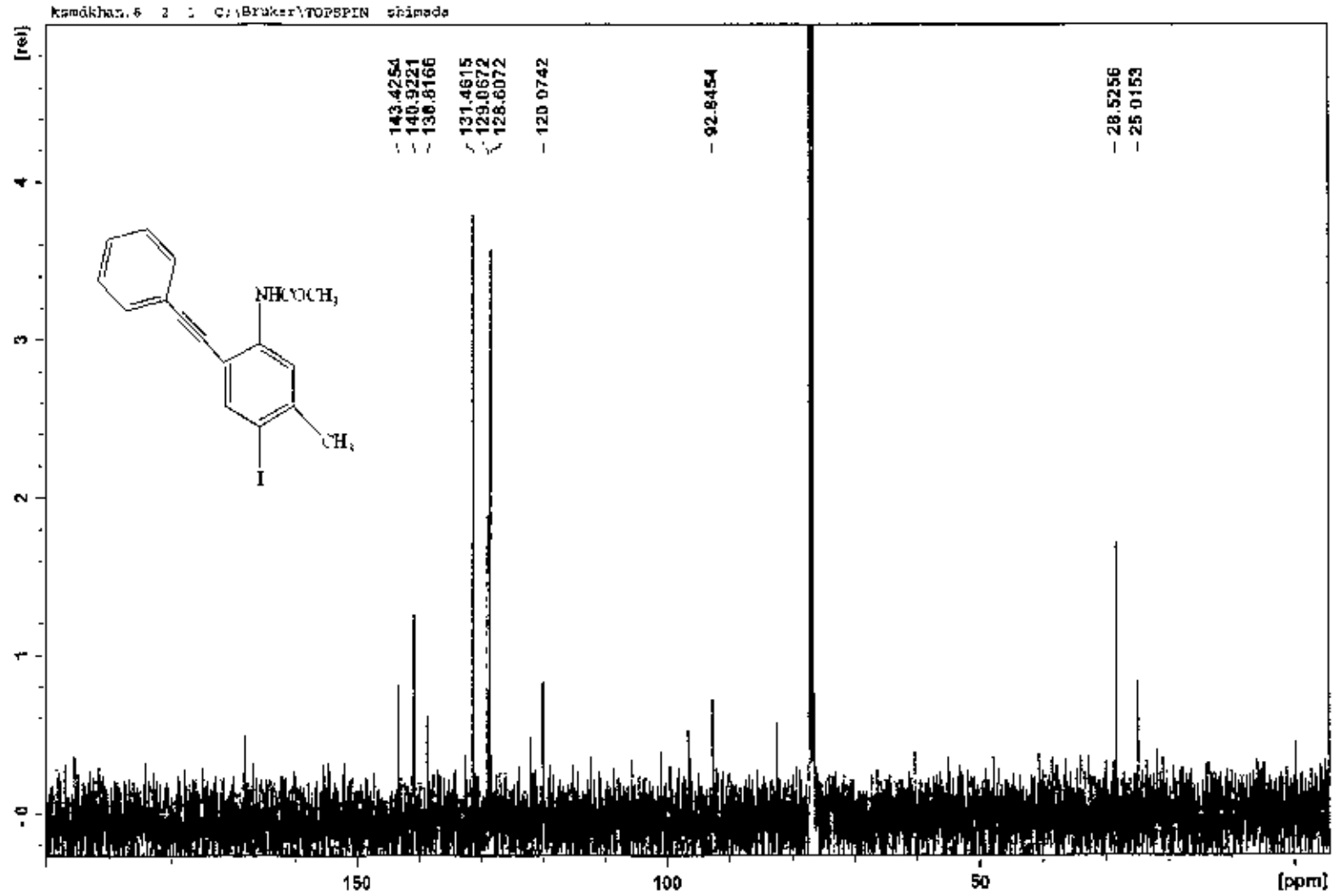
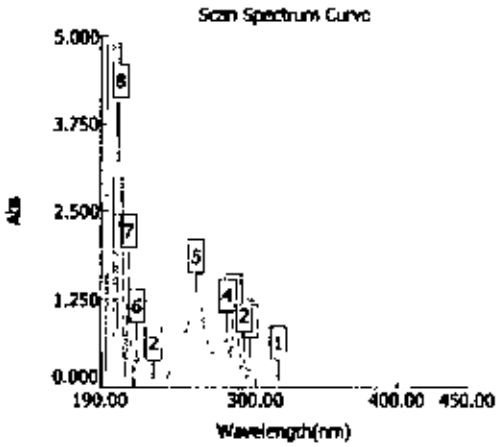


Fig-50: ^{13}C NMR Spectrum of compound **3** .



1	Peak	296.00	0.307
2	Peak	292.00	0.388
3	Peak	284.00	0.751
4	Peak	280.00	0.680
5	Peak	258.00	1.240
6	Peak	216.00	0.534
7	Peak	210.00	1.595
8	Peak	204.00	9.999
1	Valley	316.00	-0.973
2	Valley	226.00	-0.303

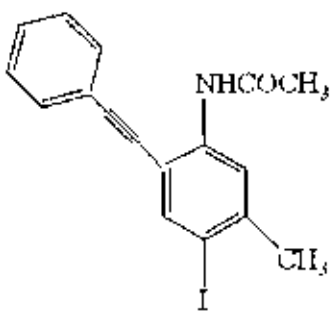
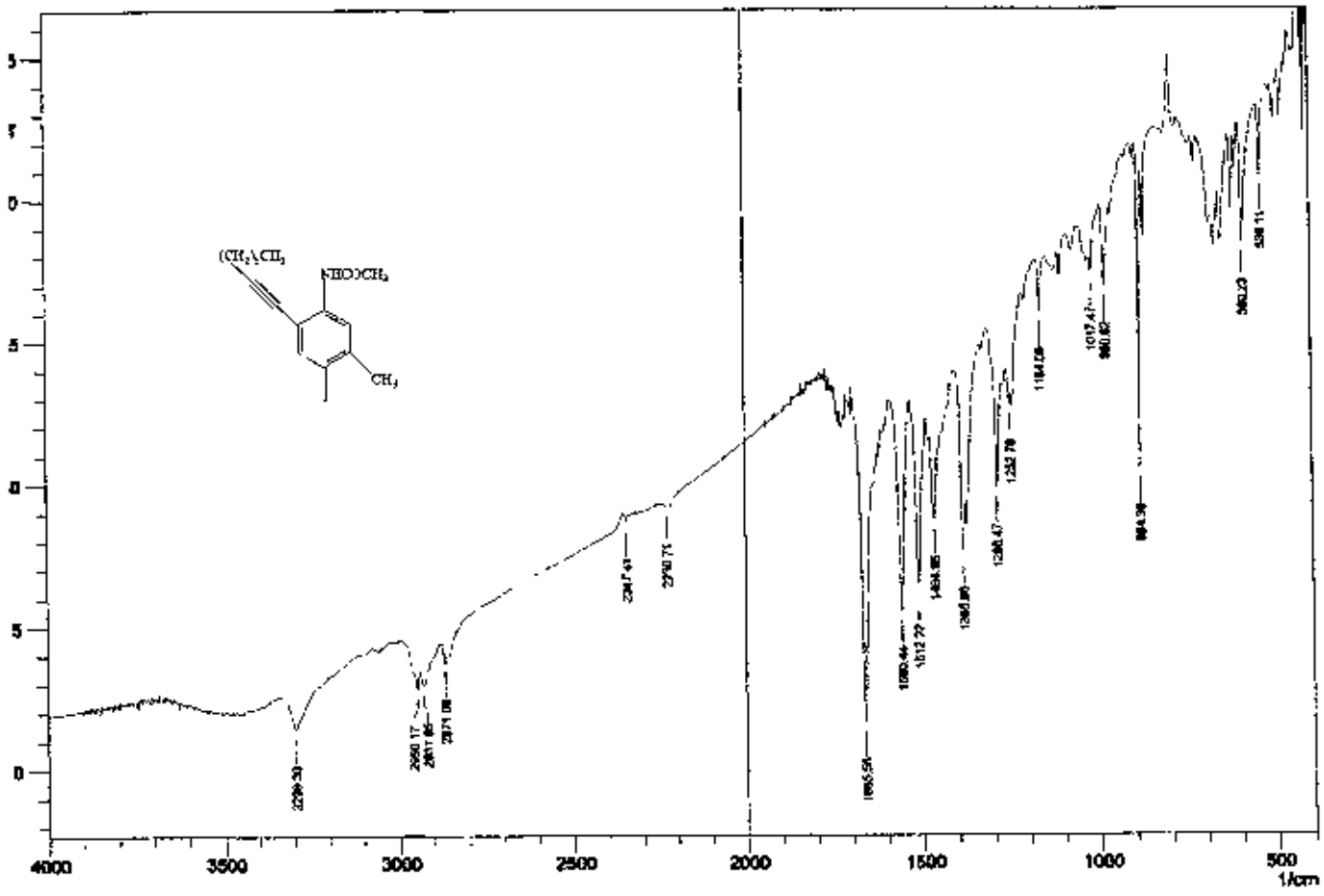


Fig-51: UV Spectrum of compound **15.**



	Peak	Intensity
1	539.11	62.34
2	590.23	55.27
3	984.38	31.42
4	980.82	50.73
5	1017.47	52.32
6	1164.06	48.06
7	1252.79	38.28
8	1288.47	29.45
9	1365.86	22.84
10	1464.96	26.04
11	1512.22	18.94
12	1560.44	18.63
13	1886.56	4.93
14	2230.71	27.56
15	2347.41	26.07
16	2871.09	11.22
17	2931.85	8.76
18	2950.17	8.57
19	3299.3	4.27

Data File : B:\Research\P-119(B) sm.1.smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 09:16:53 PM
Gain : auto

Analysed By/Date

Fig-52: IR Spectrum of compound **16.**

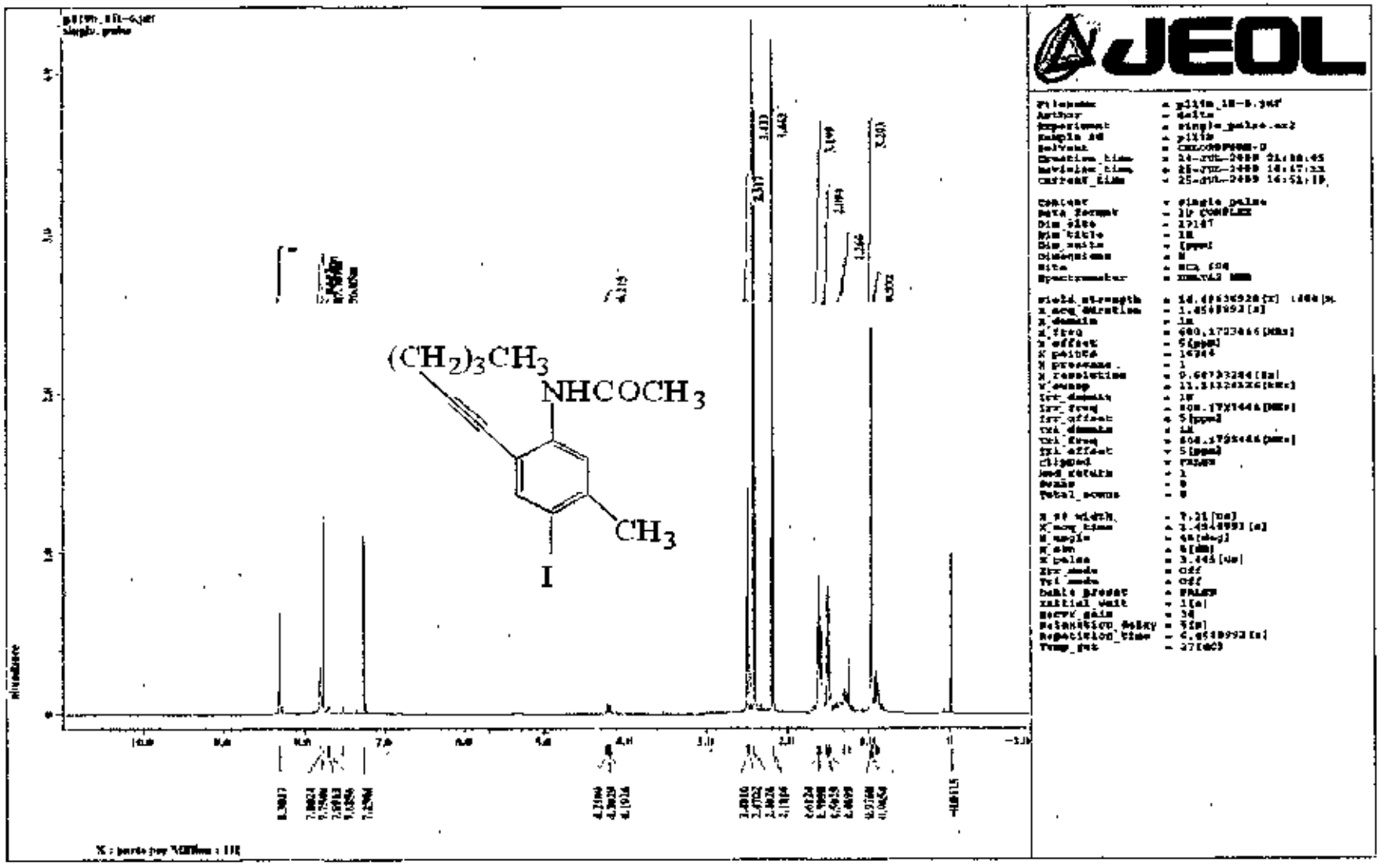


Fig-53: ^{1}H NMR Spectrum of compound **16.**

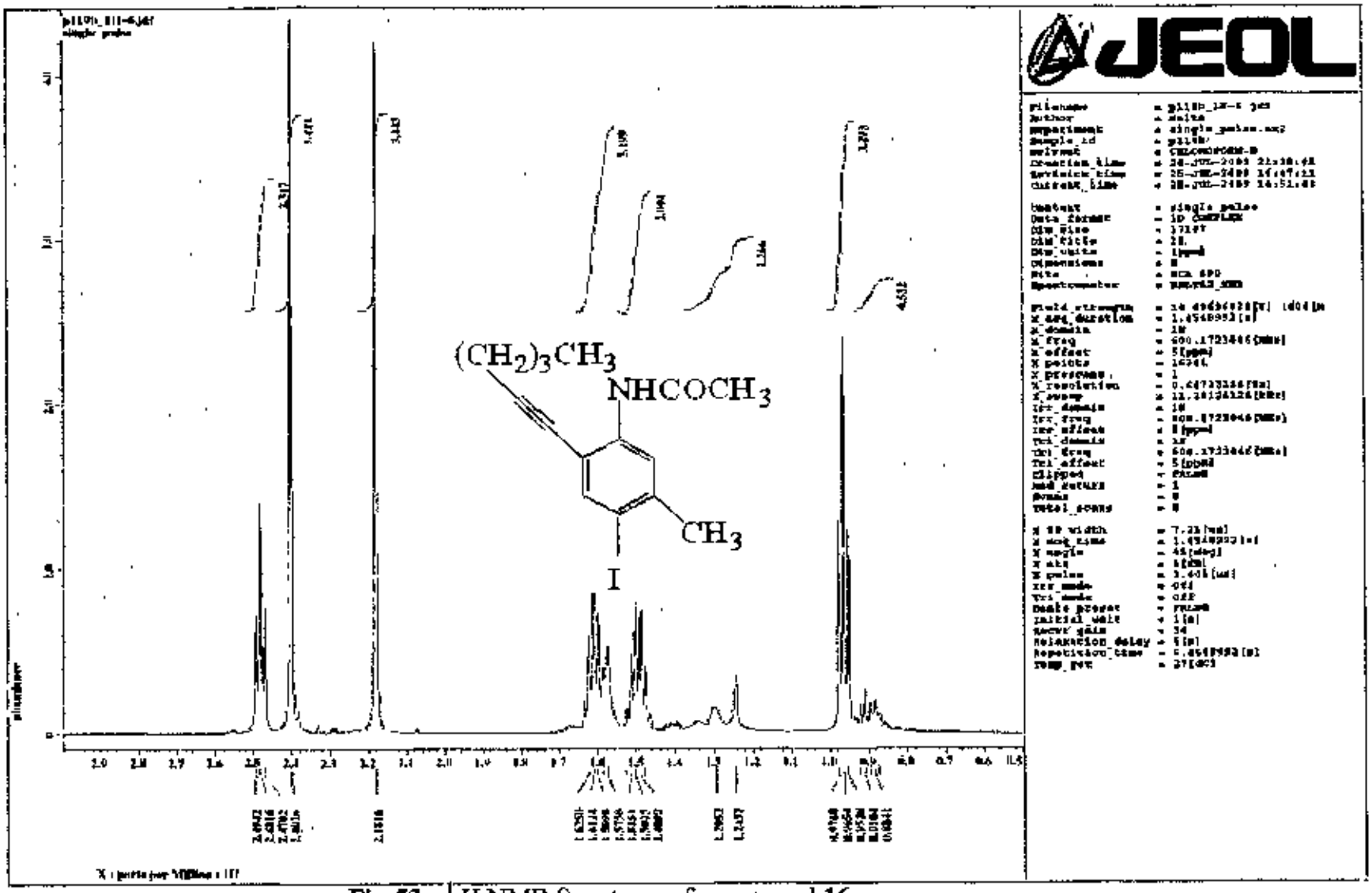


Fig-53: ^{1}H NMR Spectrum of compound **16.**

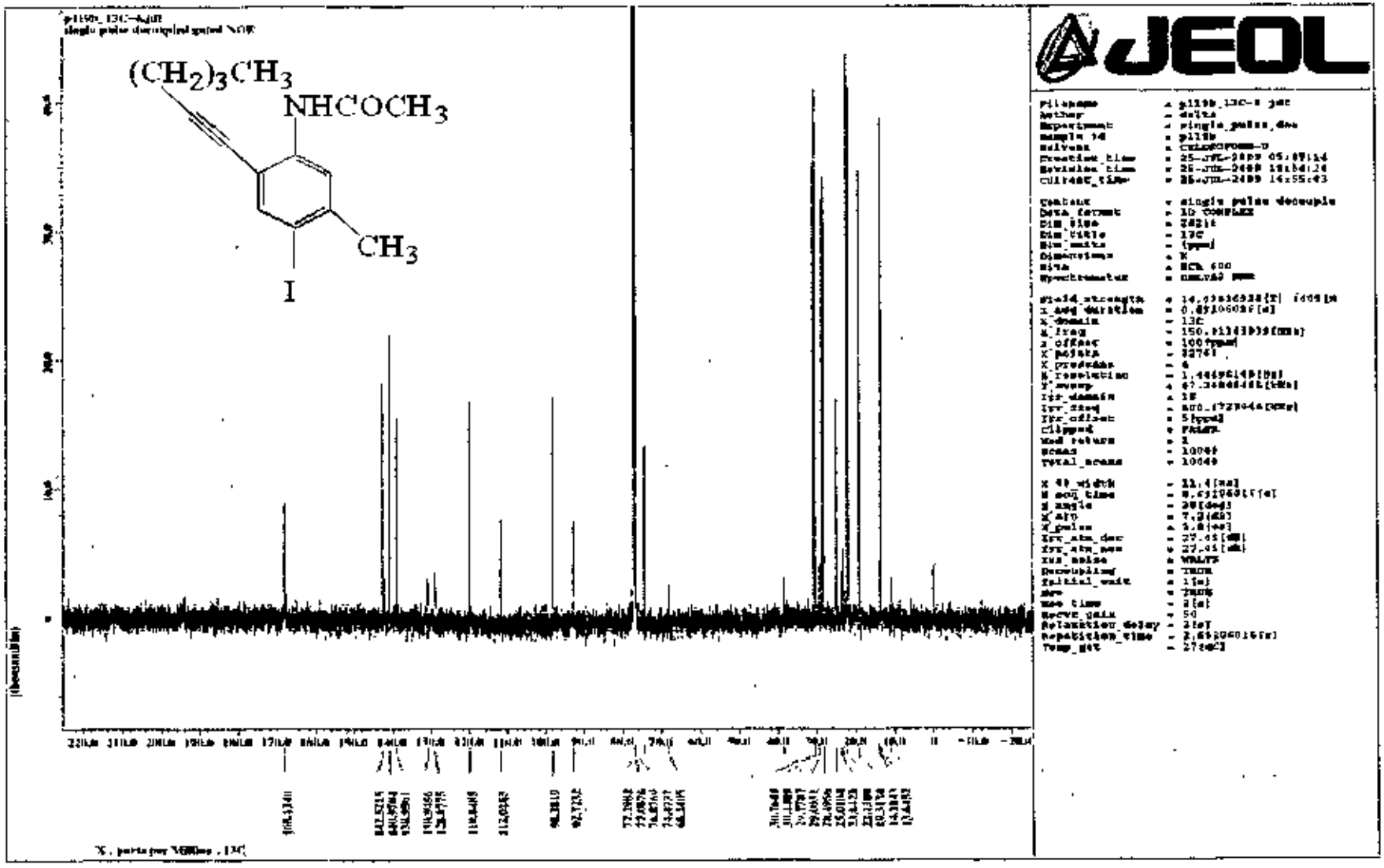


Fig-54: ^{13}C NMR Spectrum of compound **16.**

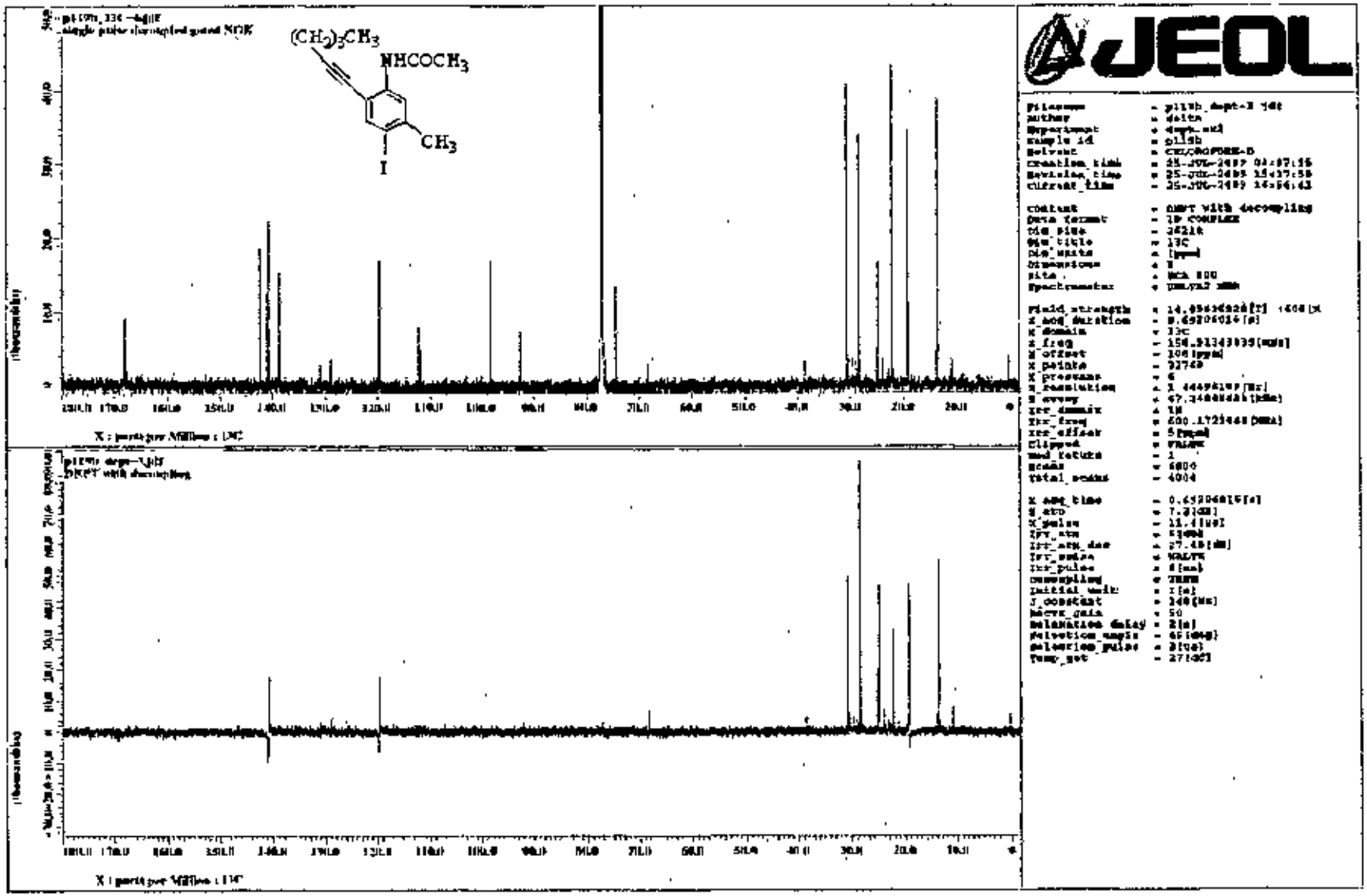


Fig-55 a: DEPT Spectrum of compound **16.**

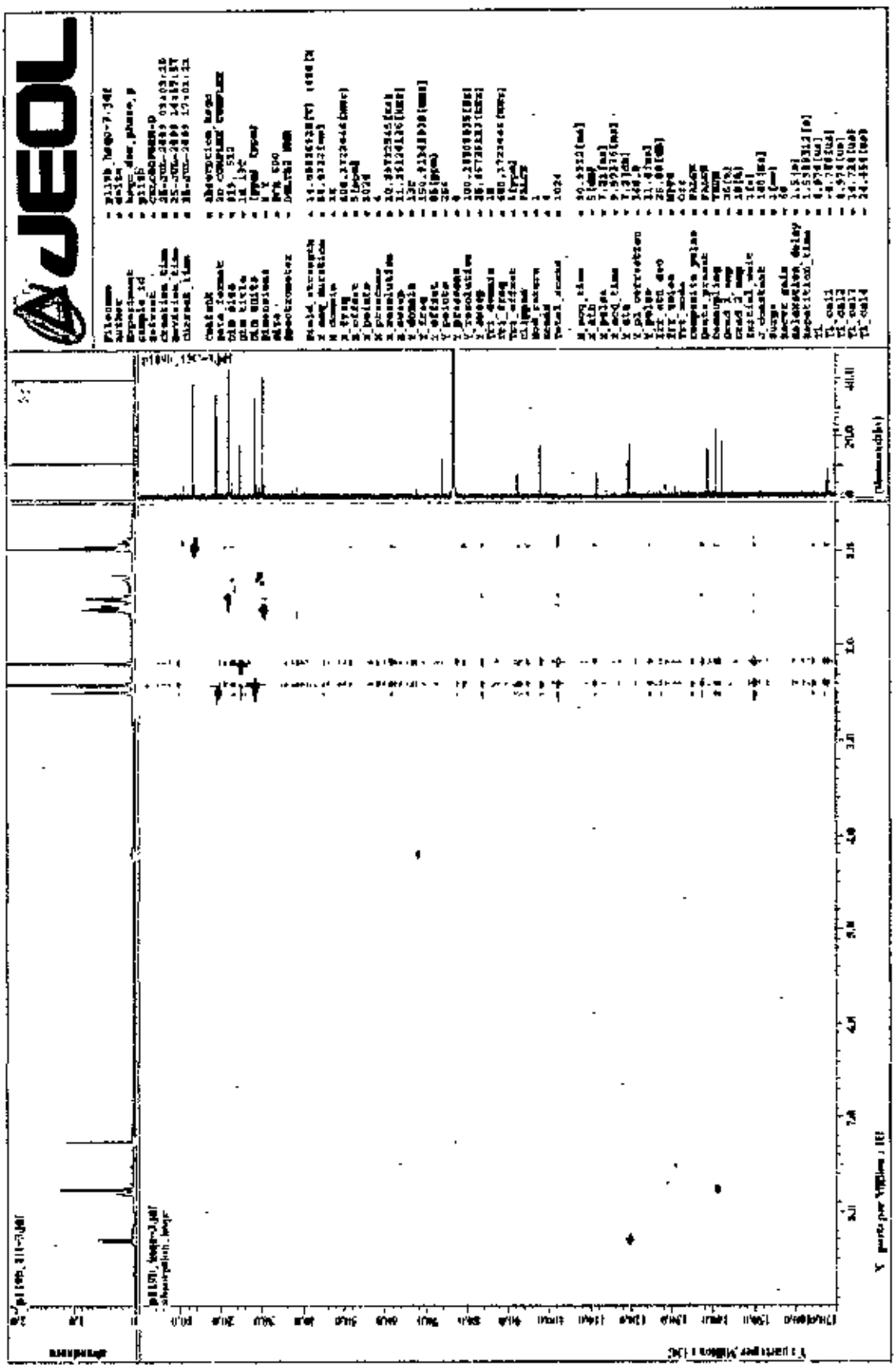
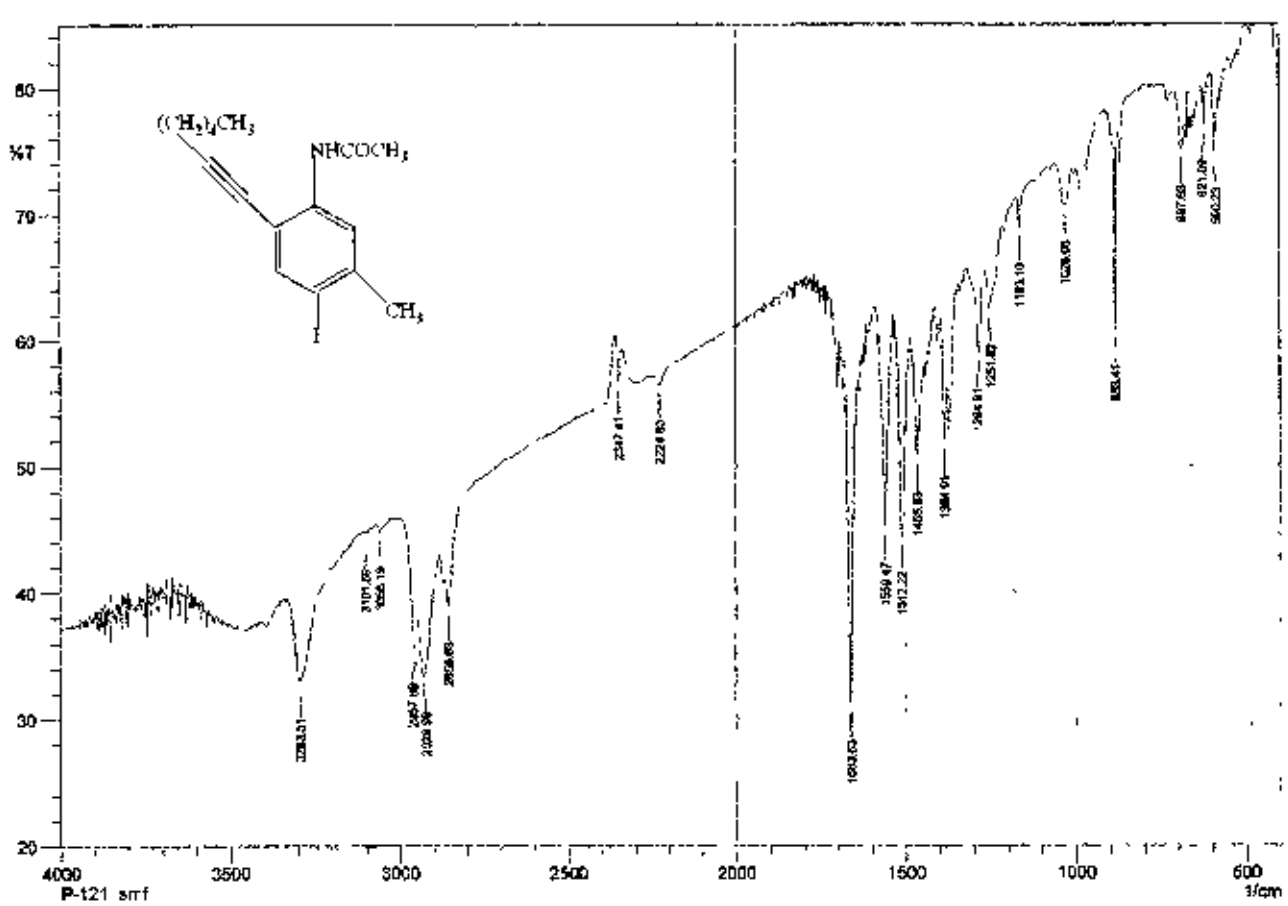


Fig-55 b: COSY Spectrum of compound 16.



	Peak	Intensity
1	590.23	74.886
2	621.09	77.044
3	887.63	76.09
4	883.41	80.884
5	1028.08	70.965
6	1163.1	66.893
7	1251.82	62.501
8	1284.61	58.012
9	1384.91	52.081
10	1465.93	50.786
11	1512.22	44.514
12	1559.47	45.212
13	1663.83	31.177
14	2224.93	58.47
15	2347.41	66.771
16	2866.83	38.932
17	2926.96	33.413
18	2957.89	35.83
19	3058.19	44.879
20	3101.59	44.733
21	3293.51	32.942

Comments : P-121.smf
Data File : E:\Research\P-121.smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 07/08/2009 06:06:40 PM
Gain : auto

Analysed By/Date

Fig- 56: IR Spectrum of compound **17.**

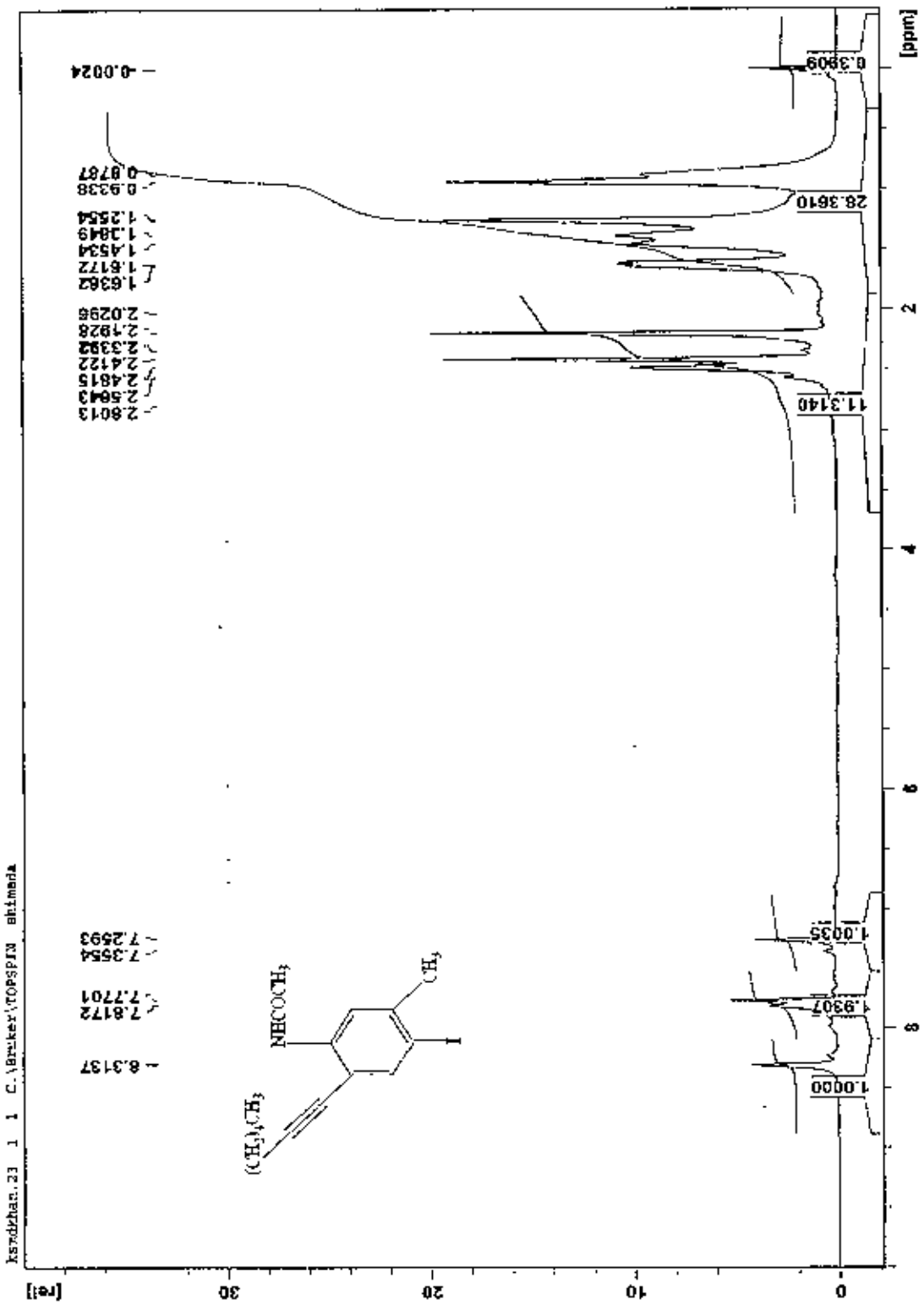


Fig- 57: ^{1}H NMR Spectrum of compound 17.

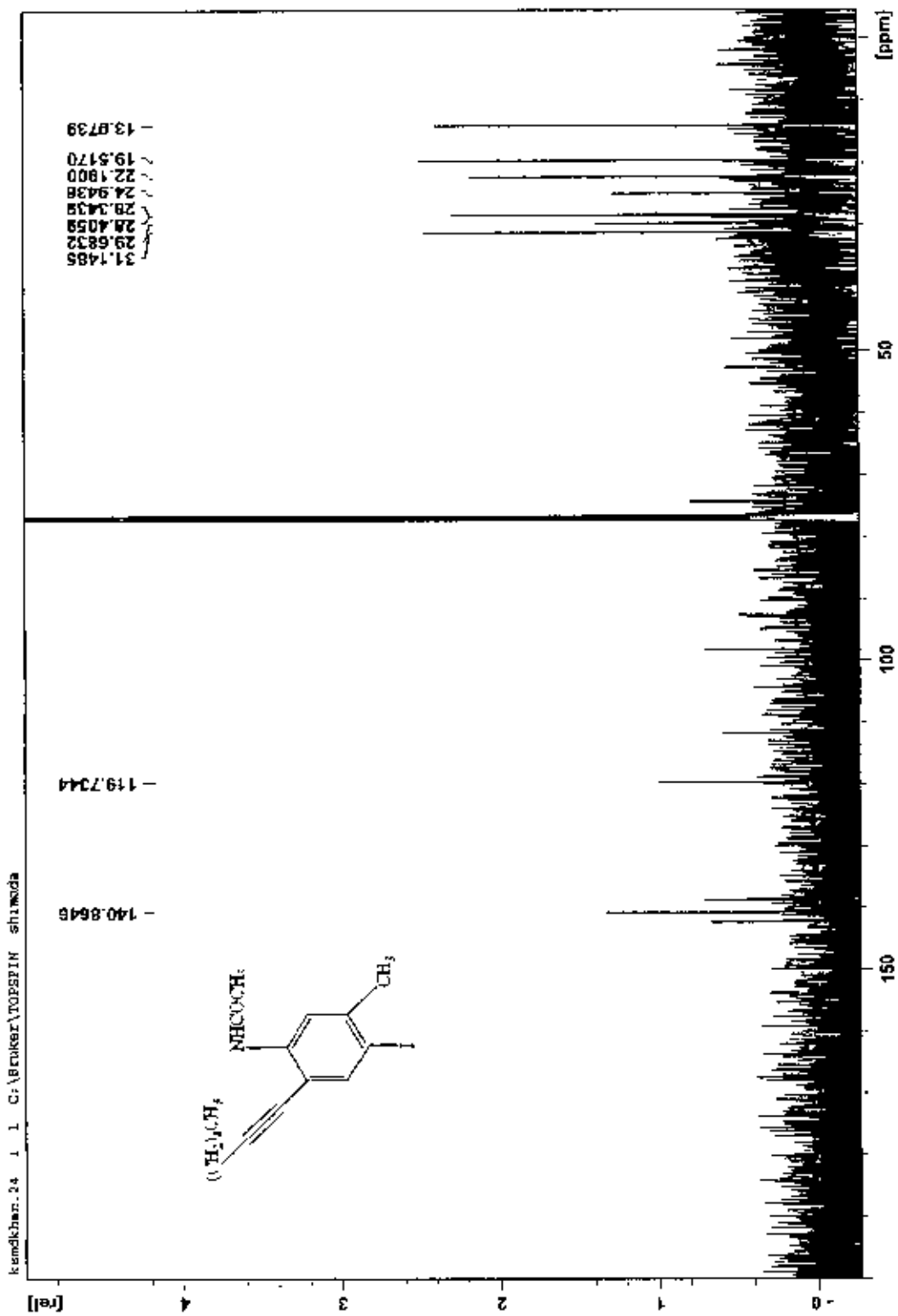
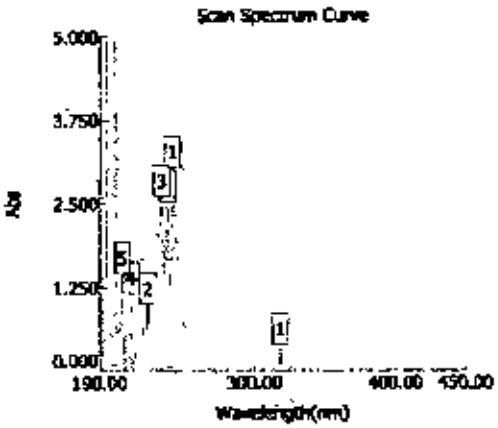


Fig-58: ^{13}C NMR Spectrum of compound 17.



1	Peak	242.00	2.653
2	Peak	238.00	2.138
3	Peak	234.00	2.212
4	Peak	212.00	0.769
5	Peak	206.00	1.065
1	Valley	318.00	-1.247
2	Valley	224.00	0.501

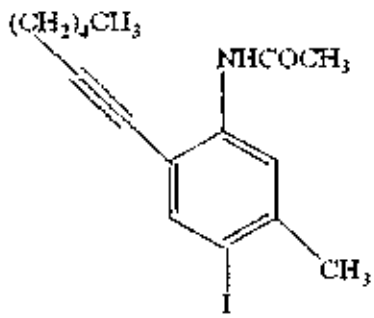
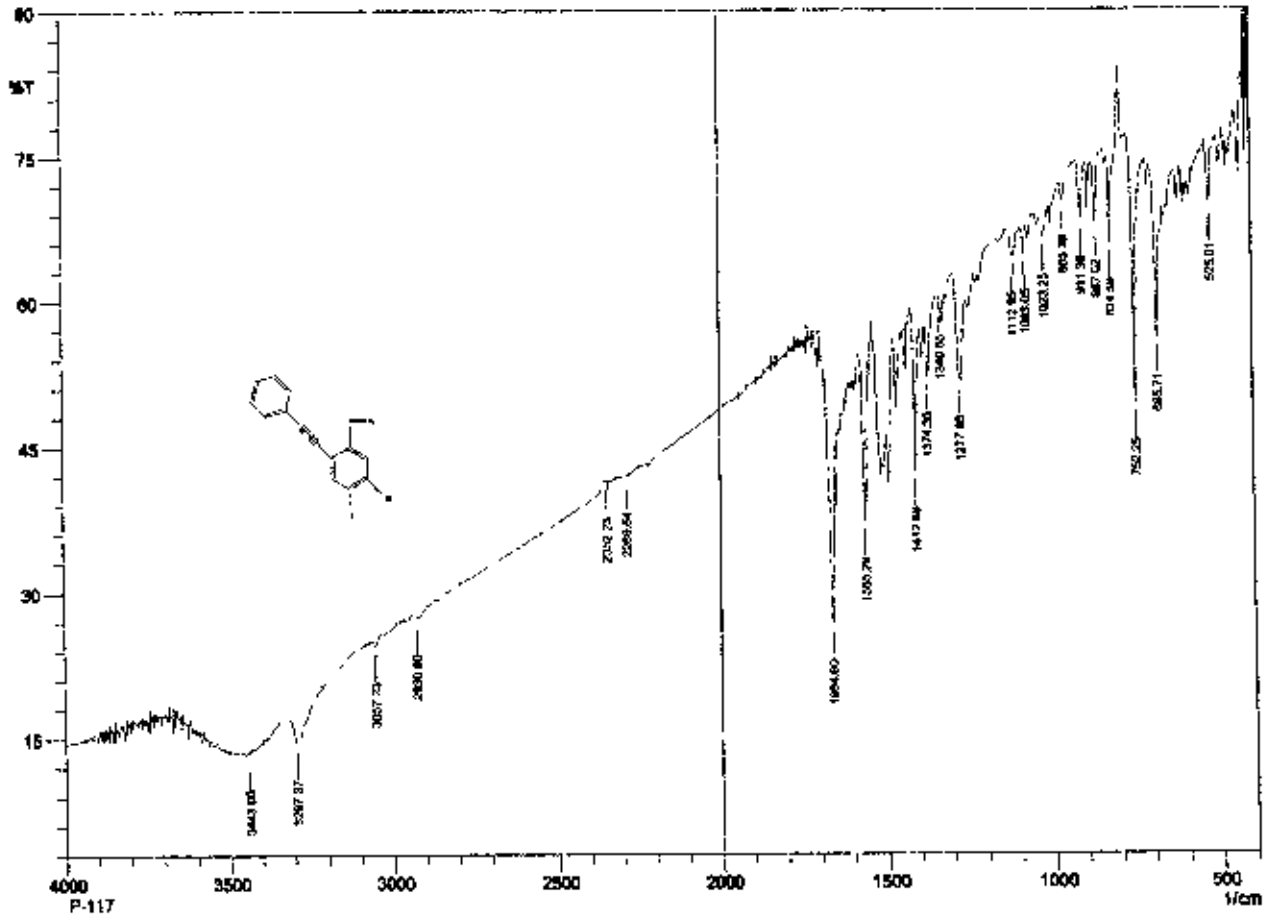


Fig-59: UV Spectrum of compound **17.**



No.	Peak	Intensity
1	526.61	69.55
2	565.71	58.07
3	762.25	49.41
4	824.58	65.92
5	867.02	67.68
6	911.38	68.24
7	965.39	70.42
8	1023.25	66.49
9	1083.05	64.67
10	1112.95	64.83
11	1277.88	61.82
12	1340.55	60.2
13	1374.3	52.19
14	1412.88	42.39
15	1585.26	37.29
16	1664.6	26.69
17	2269.54	42.01
18	2352.23	41.48
19	2930.89	27.43
20	3067.23	24.57
21	3297.37	14.61
22	3443	13.59

Data File : E:\Research\P-117 sm1.smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time . 06/23/2009 09:01:29 PM
Gain : auto

Analysed By/Date

Fig-60: IR Spectrum of compound **18.**

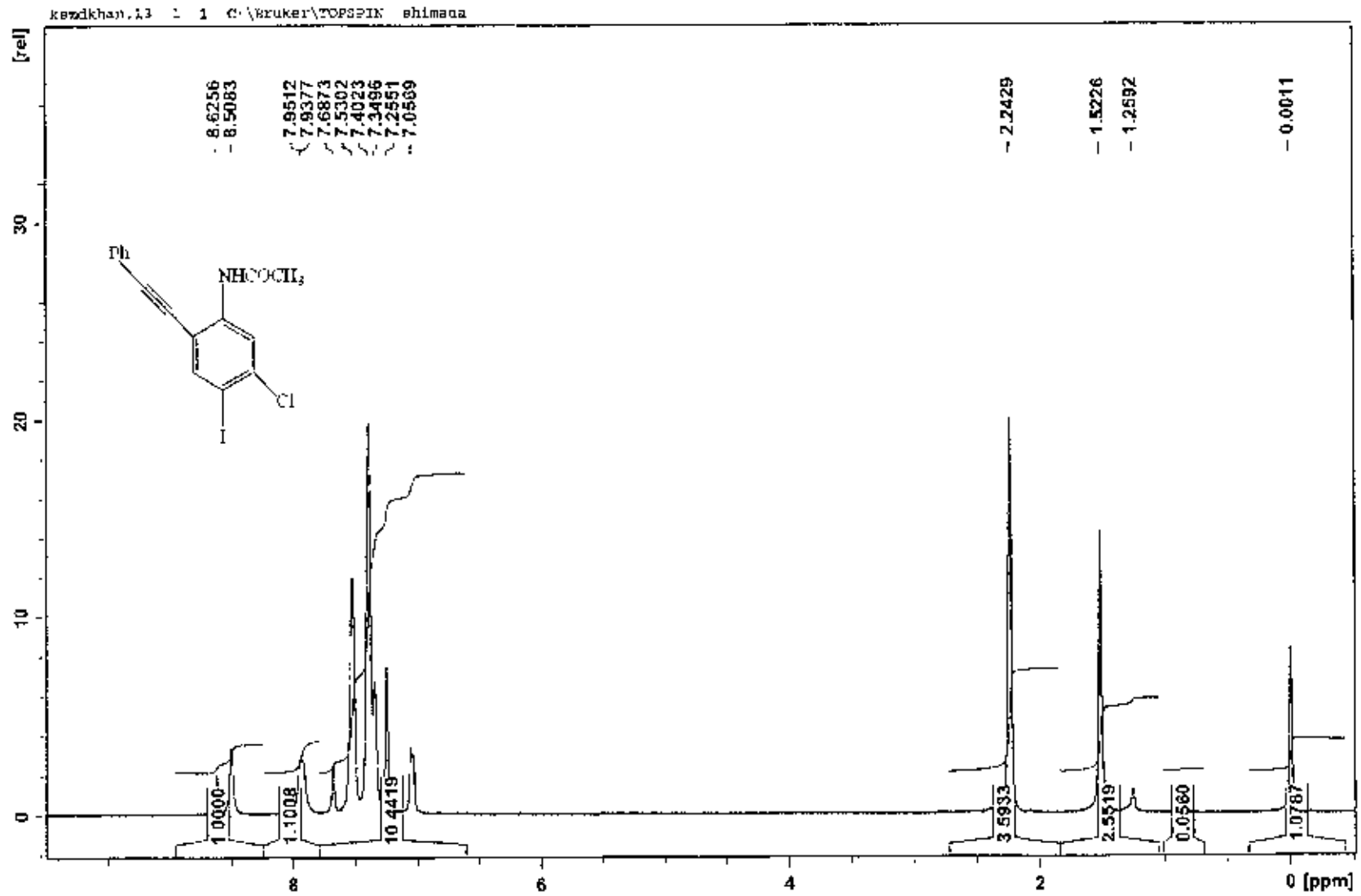


Fig-61: ^{1}H NMR Spectrum of compound **18.**

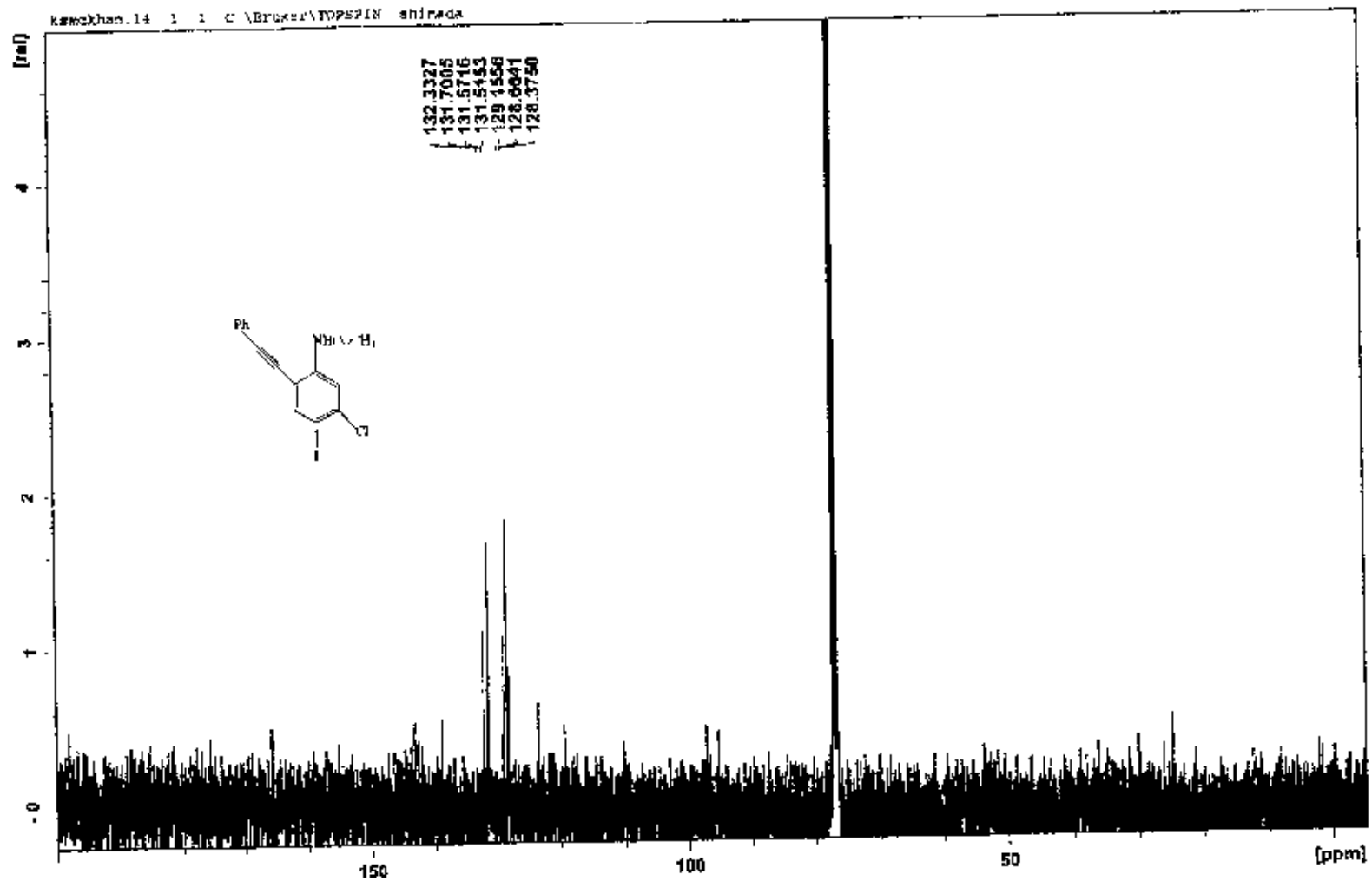


Fig-62: ^{1}H NMR Spectrum of compound **18.**

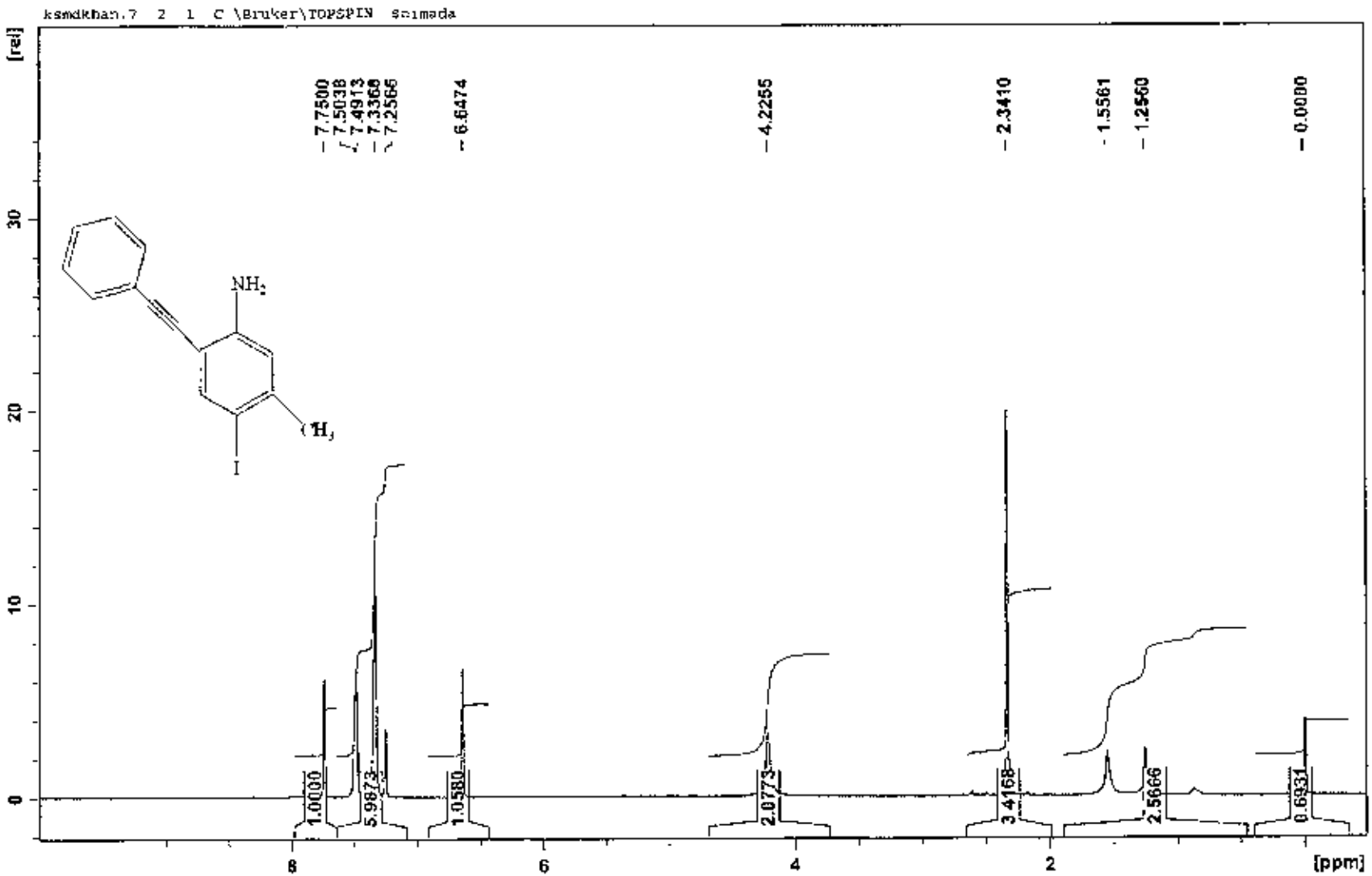


Fig-63: ^{1}H NMR Spectrum of compound **19.**

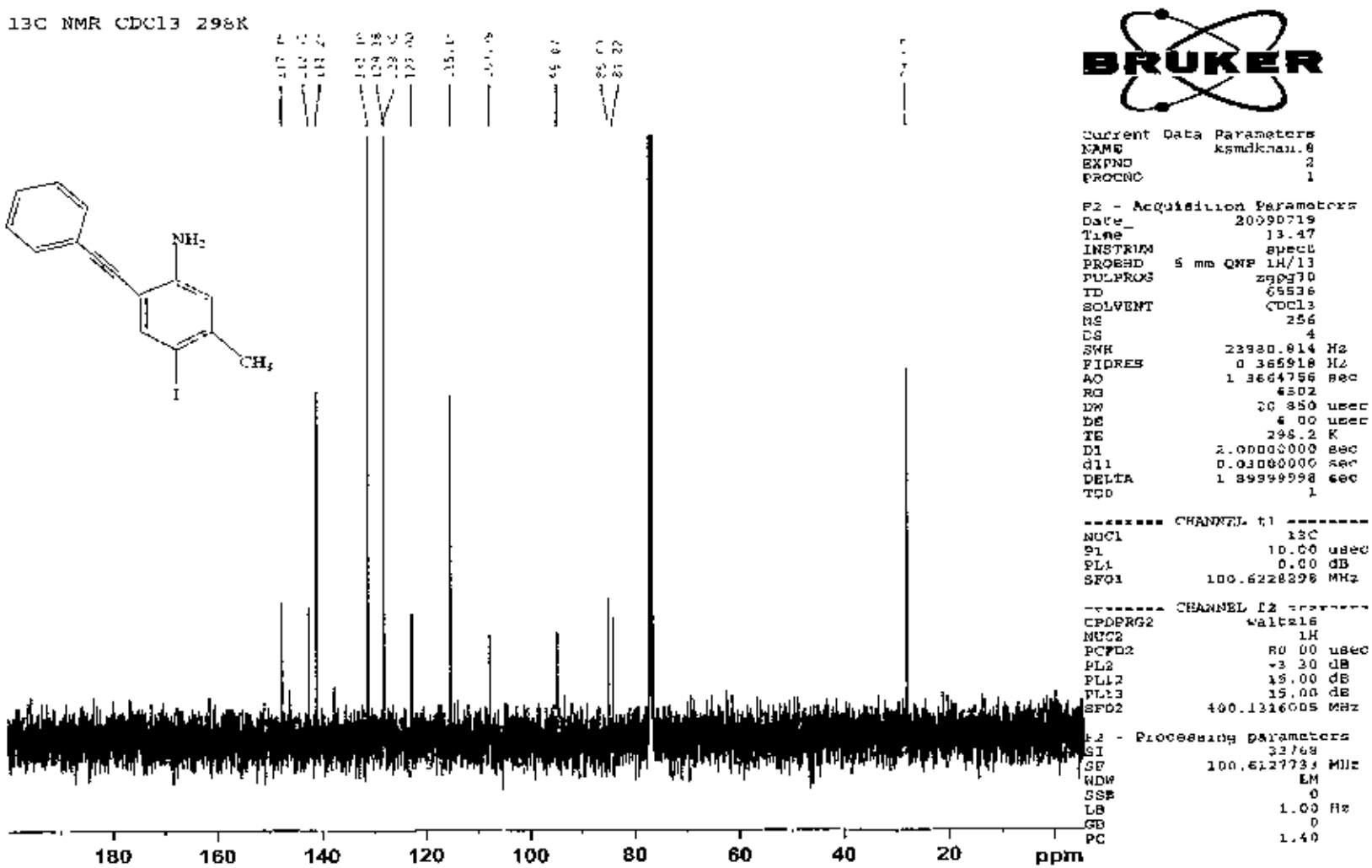
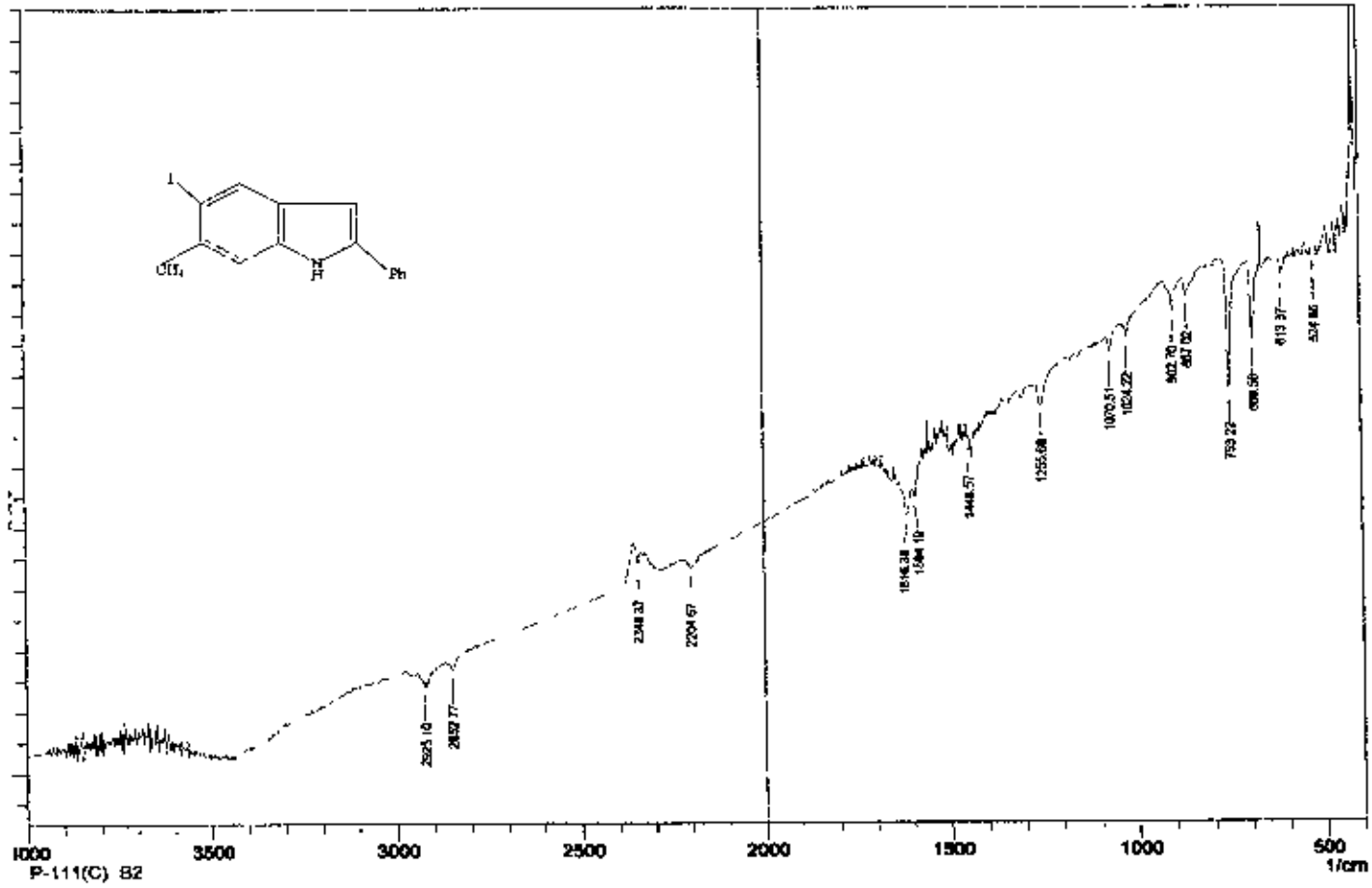


Fig-64: [1] H NMR Spectrum of compound **19.**



No.	Peak	Intensity
1	524.86	63.989
2	613.37	63.744
3	689.66	57.249
4	753.22	52.484
5	857.02	61.548
6	902.7	60.048
7	1024.22	57.458
8	1070.51	58.05
9	1255.68	50.934
10	1448.57	47.488
11	1594.19	41.977
12	1616.38	40.107
13	2204.67	35.034
14	2348.37	35.377
15	2852.77	25.16
16	2925.1	23.368

mments : P-111(C) .B2
ta File : E:\Research\P-111(C) .smf

Resolution : 2 [1/cm]
No. of Scans : 45
Apodization : Happ-Genzel

Date/Time : 06/23/2009 06:08:45 PM
Gain : auto

Analysed By/Date

Fig-65: IR Spectrum of compound **20.**

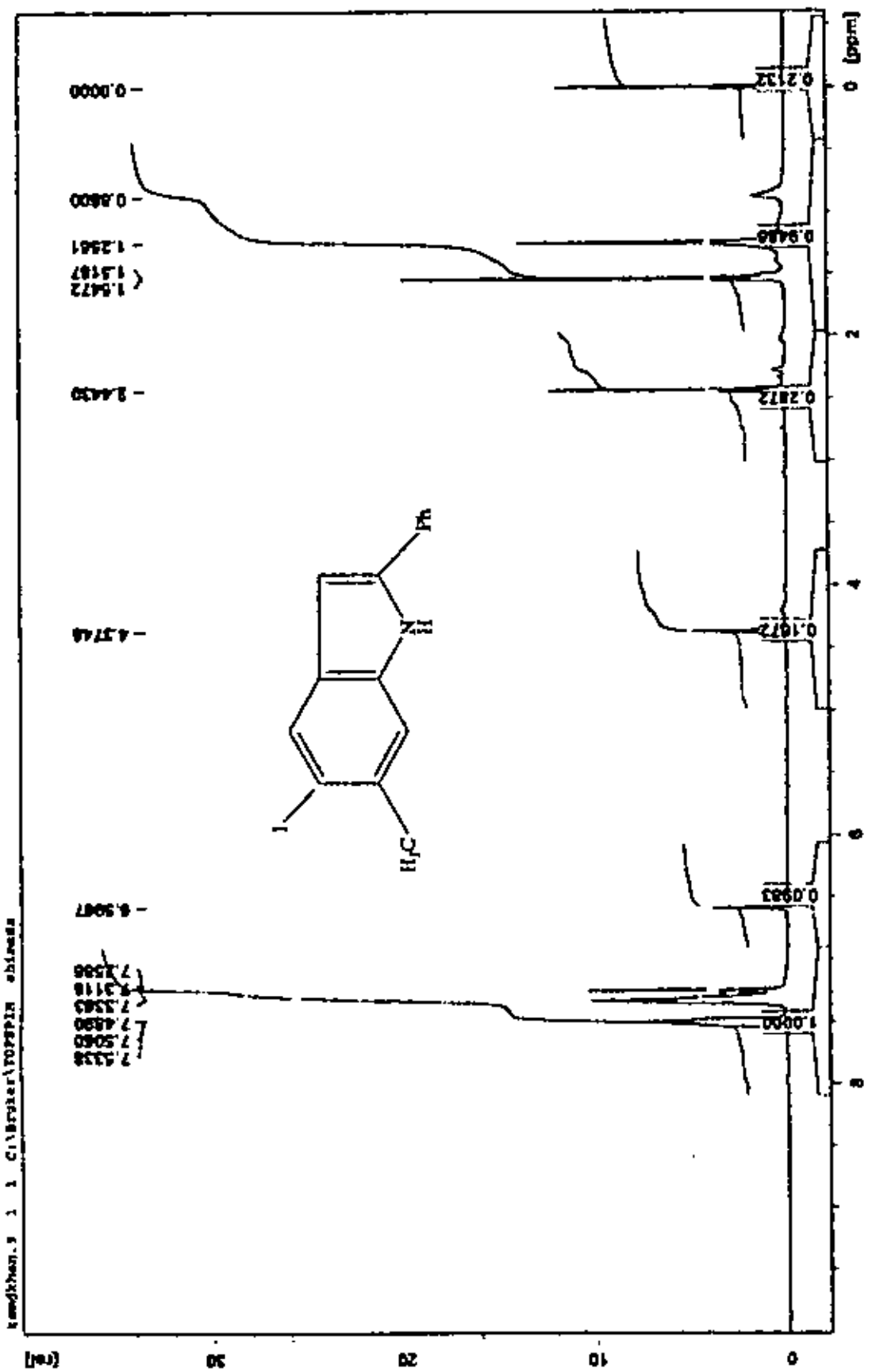


Fig-66: ^{1}H NMR Spectrum of compound 20.

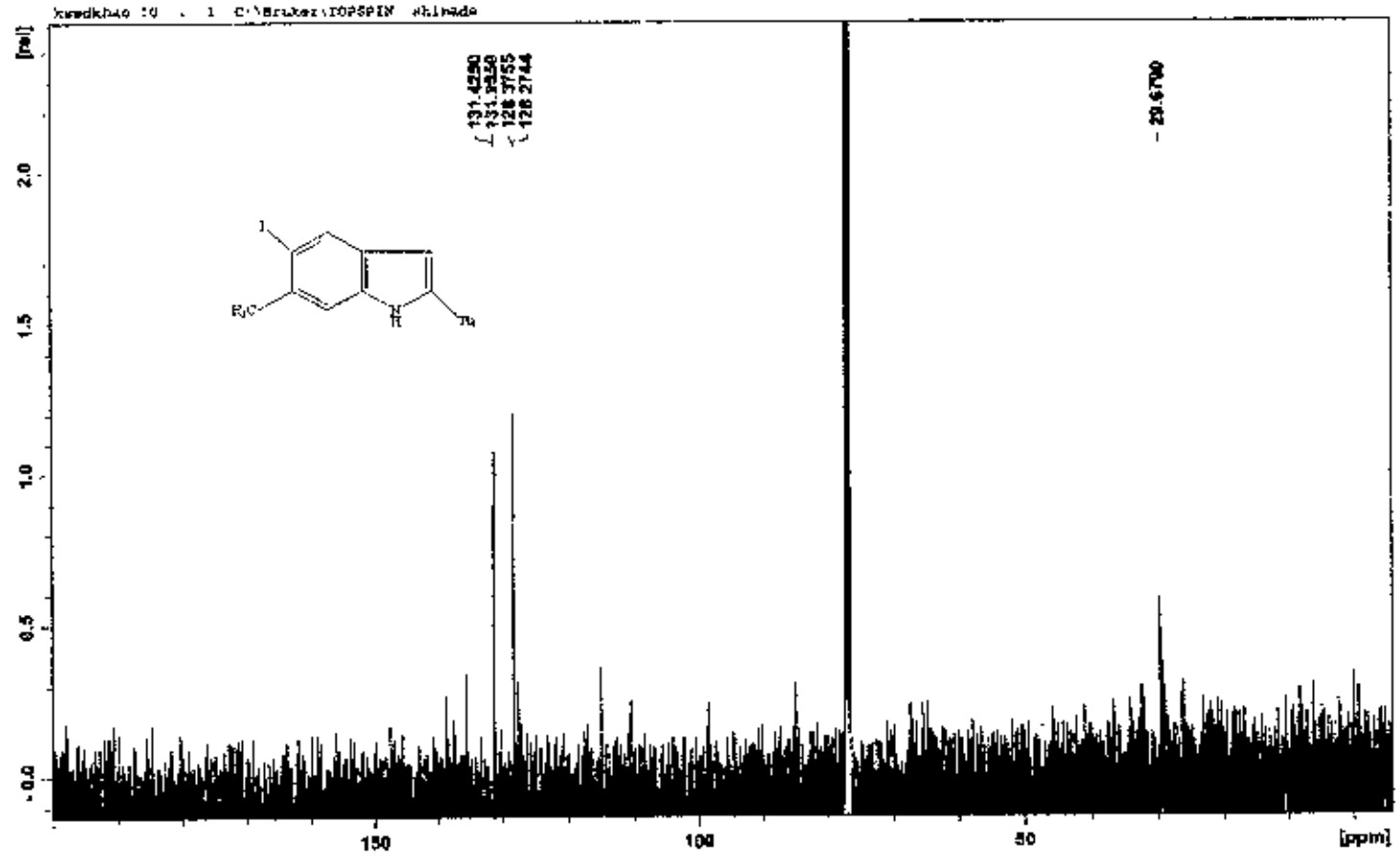
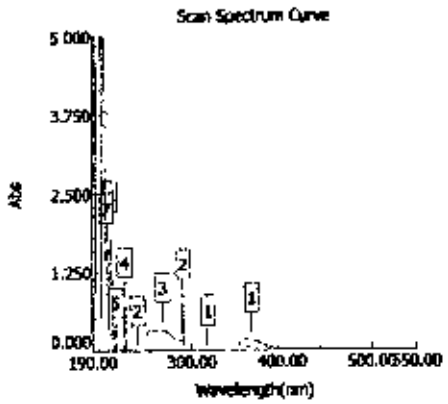


Fig-67: ^{13}C NMR Spectrum of compound **20.**



1	Peak	366.00	0.191
2	Peak	290.00	0.747
3	Peak	268.00	0.364
4	Peak	226.00	0.768
5	Peak	216.00	0.132
6	Peak	210.00	1.836
7	Peak	206.00	1.650
1	Valley	316.00	-0.862
2	Valley	240.00	-0.374

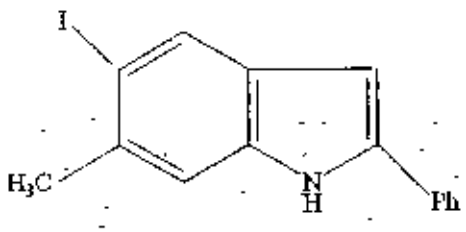


Fig-68: UV Spectrum of compound **20**.

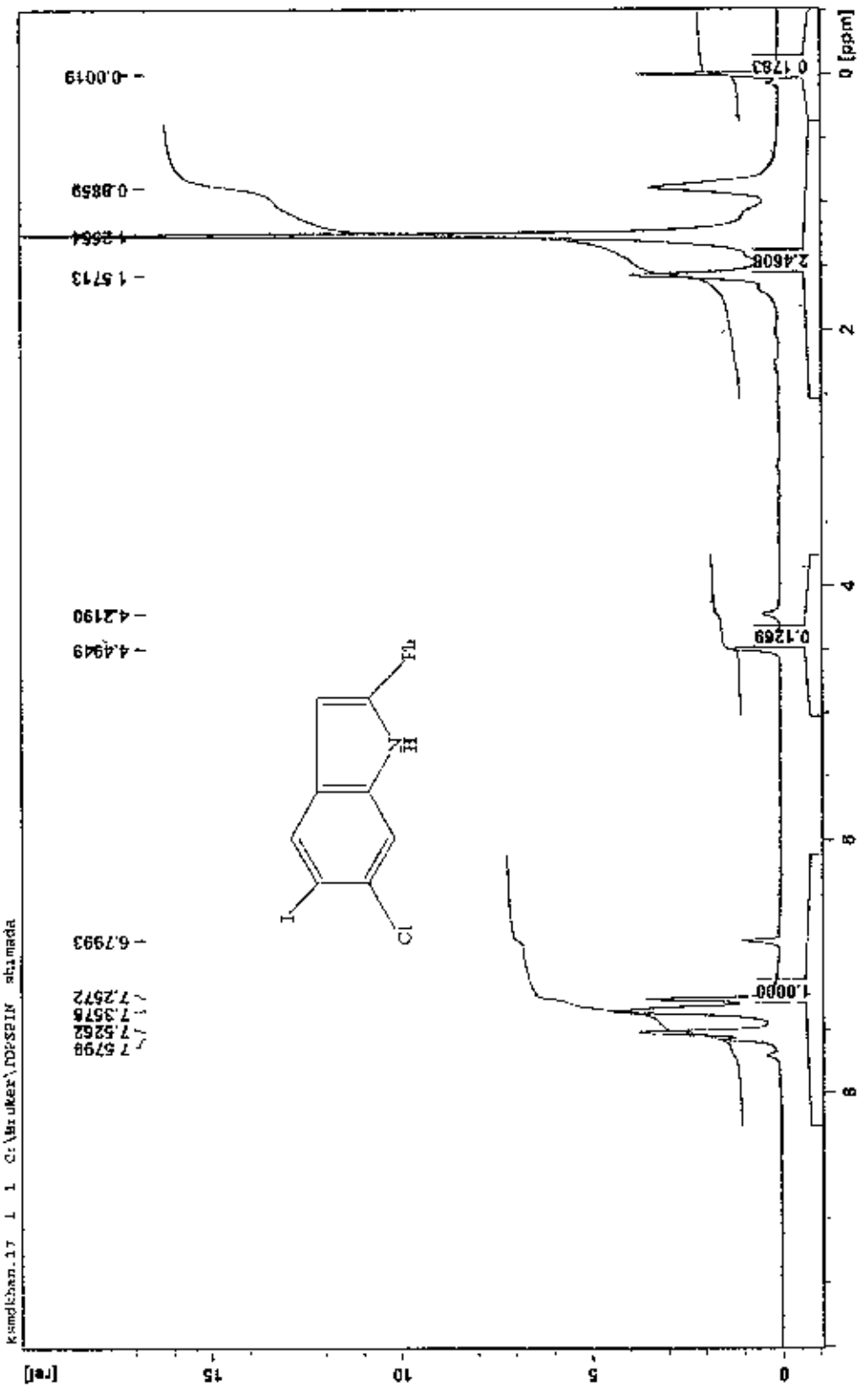


Fig-69: ^{1}H NMR Spectrum of compound **21.**

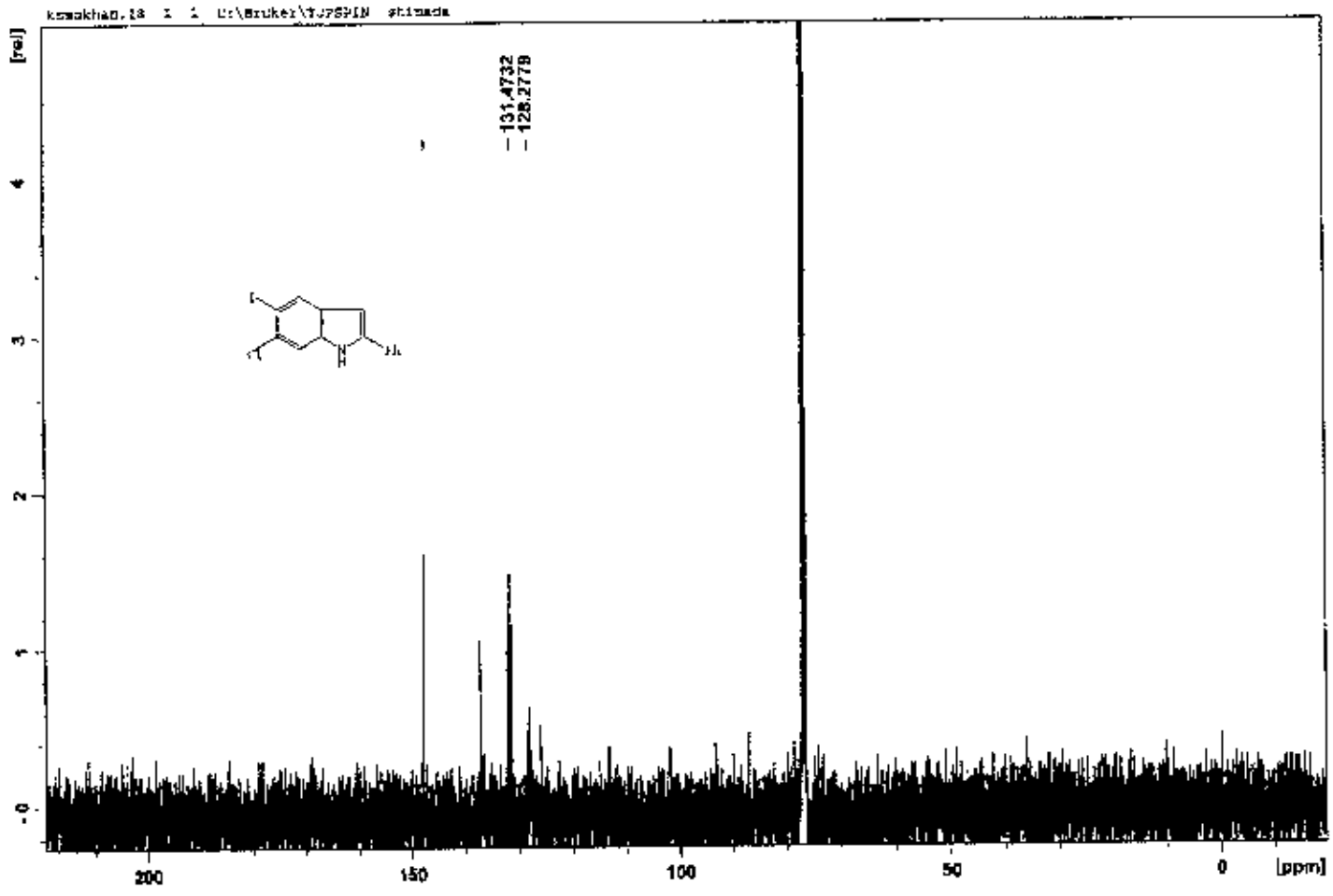
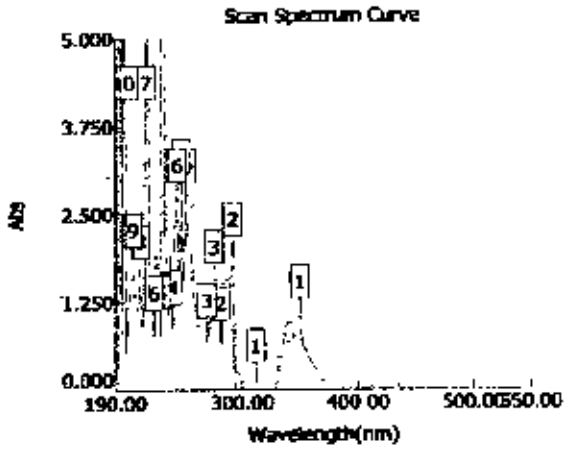


Fig-70: ^{13}C NMR Spectrum of compound **21.**



1	Peak	350.00	0.901
2	Peak	292.00	1.792
3	Peak	278.00	1.482
4	Peak	252.00	2.555
5	Peak	248.00	2.701
6	Peak	244.00	2.565
7	Peak	218.00	9.999
8	Peak	212.00	1.487
9	Peak	206.00	1.650
10	Peak	198.00	9.999
1	Valley	312.00	-0.800
2	Valley	282.00	0.604
3	Valley	270.00	0.642
4	Valley	240.00	0.826
5	Valley	230.00	0.757
6	Valley	224.00	0.751

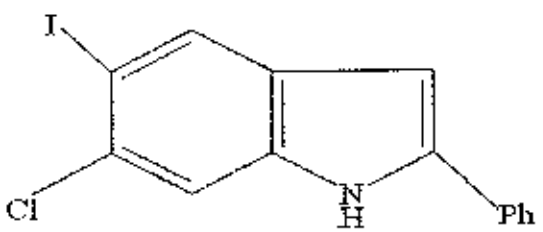


Fig-71: UV Spectrum of compound **21.**

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