SYNTHESIS OF INDOLE DERIVATIVES THROUGH COMBINED PALLADIUM CATALYSED AND FRIEDEL-CRAFTS REACTIONS.

A Dissertation Submitted in Partial fulfillment of the Requirements for the Degree

Of

Master of Philosophy (M. Phil)
in Chemistry

By

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BANGLADESH UNIVERSITY OF ENGINEERING AND TECHONOLOGY, DHAKA, BANGLADESH
DEPARTMENT OF CHEMISTRY

THESIS ACCEPTANCE LETTER

The thesis titled "Synthesis of indole derivatives through combined palladium catalysed and Friedel-Crafts Reaction". Submitted by Arifa Akther, Roll No. 100003103P, Registration No. 001023, Session- October, 2000 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Philosophy (M. Phil) in chemistry on April, 2006.

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CANDIDATE'S DECLATATION

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

Arifa Akther

Arifa Akther
Date: 29/4/2006

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Arifa Akther

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Date: 29.4.06.

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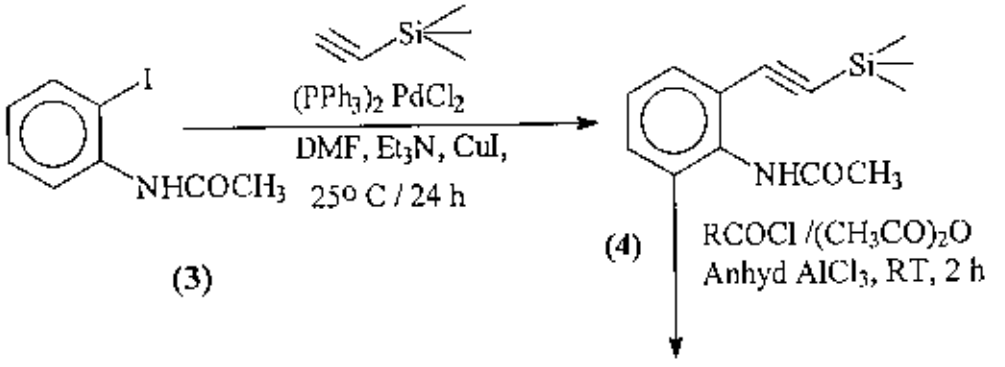
Methodology of the antimicrobial study

Section –III

Thesis title: **"Synthesis of some indole derivatives through combined palladium catalysed and Friedel-Crafts Reaction"**

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 catalysed reaction using trimethyl silylacetylene followed by Friedel-Crafts acylation reactions is reported. The heteroannulation reaction was carried out by stirring a mixture of 2-iodoacetanilide **3** and trimethylsilylacetylene in presence of *bis*(-triphenylphosphene) palladium(II)chloride as a catalyst, Cu(I)iodide as a co-catalyst and a base triethylamine . The condensed product was then subjected to Friedel-Crafts acylation reaction with acid chlorides to afford the *N*-acyl-2-acyl (Aroyl)-indolium chloride **5-8**.



R	Compound
$-CH_3$	5
$-C_6H_4$ MeO-*p*	6
-Ph	7
$-C_6H_4$ Me-*p*	8

In *vitro* antimicrobial activity of *N*-acyl-2-acyl (Aroyl)indolium chloride **5-8** were evaluated. The *N*-acyl-2-acyl (Aroyl)indolium chloride showed more sensitivity against gram-positive and gram-negative bacteria as well as human fungal pathogens.

Varying substitution at the indole moiety and subsequent antimicrobial screening identified the C-2-acetyl functionality as a new structural alternative for optimal antimicrobial property in the indole class of compounds.

SUMMARY

Investigation incorporated in this dissertation entitled, "Synthesis of some indole derivatives through combined palladium catalysed and Friedel-Crafts Reaction" have been presented in two parts. Part –I is divided into two sections, the first section is the introductory section, in which the background, biological action and the important synthesis are presented. Section 2 deals with the detailed methodologies and experimental procedures for the synthesis of 2-substituted indole derivatives and results and discussion of the synthesis.

Part II is for biological studies. This part contain, introduction, results and discussion and experimental of the biological activity of the compound.

Part I:

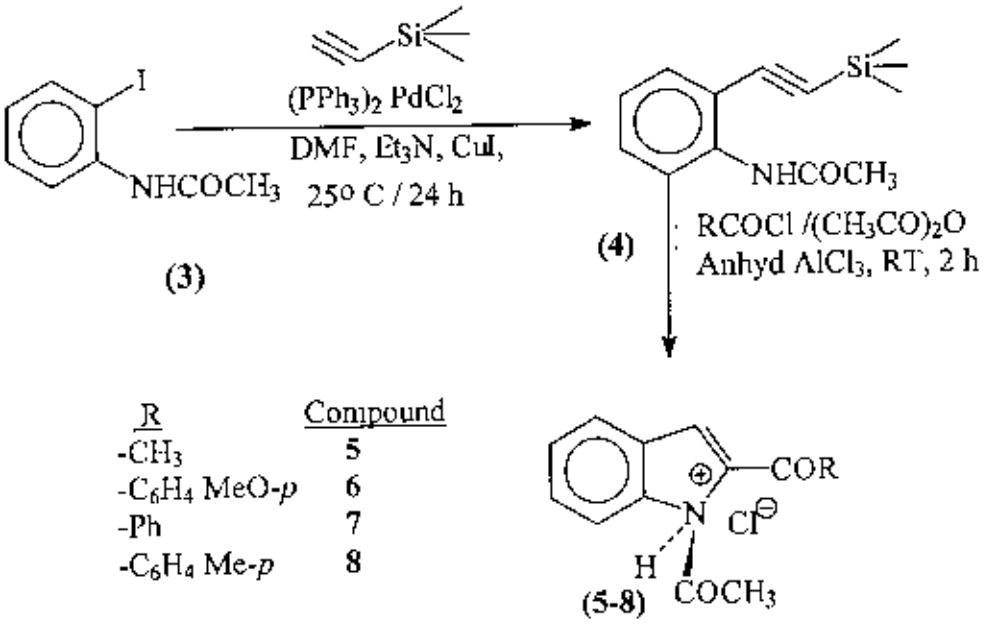
Section -1

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 catalysed procedure for the synthesis of indole derivatives are limited in number.

In section II: We report a new strategy for the regioselective synthesis of indole derivatives **5-8** through combined the palladium catalysed and Friedel-Craft reactions of 2-Iodoacetanilide **3**. The palladium-catalysed reaction was usually carried out by stirring of 2-iodo acetanilide **3** in DMF (3.5 equiv.) in which Bis-(triphenyl phosphine) palladium (II) chloride (3.5 mol%), CuI (8 mol %) Et_3N (4 equiv.) was added at 0 °C. Then trimethylsilylacetylene (2 equiv.) was added under N_2 atmosphere.

2-(Trimethylsilylethynyl)acetanilide **4** was subjected to Friedel-Crafts acylation reaction. 2-(Trimethylsilylethynyl)acetanilide **4** was dissolved in 1,1,2,2-tetrachloroethane and anhydrous aluminium chloride (1 equiv.) was added to the

mixture at 0 °C. Then acyl chloride (1 equiv.) was added to the mixture and continued stirring for 2 h at room temperature. After usual workup and purification by column chromatography 2-acyl(aroyl)*N*-acyl indolium chloride **5-8** were obtained in good yields.



R	Compound
$-CH_3$	5
$-C_6H_4$ MeO-*p*	6
-Ph	7
$-C_6H_4$ Me-*p*	8

Part II: Biological activity

Section I represents the background of biological activity.

Section II represents the biological test, the methodology and results and discussion of the synthesized compounds.

Among the synthesized compounds Indolium chloride **5-8**, exhibited relatively great inhibition of growth of the microorganism. The highest sensitive compound was compound **5**.

Varying substitution at the indole moiety and subsequent antimicrobial screening identified the C-2-acetyl functionality as a new structural alternative for optimal antimicrobial property in the indole class of compounds.

Prefatory Note

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

Analytical or laboratory grade solvents and chemicals were used in all experiments and these were procured from E. Merck (Germany) and Fluka (Switzerland). Reagent grade of chloroform, n-hexane, ethylacetate, methanol, ethanol, acetone etc. were purified by distillation at the boiling point of the respective solvent. Petroleum ether used during this research work had boiling point 40° – 60°C. The following methods were used for the purification and drying of the solvents.

1. Purification of solvents and reagents

a. Dry methanol (MeOH):

About 1.25gm of clean and dry magnesium turnings and 0.125 gm of iodine were placed in a dry 500 ml round bottom flask containing 30 to 40 ml of reagent grade methanol. 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 converted into pasty mass methanolate. About 230 ml of commercial grade methanol was then added to the fluxed 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 methanol was collected into a receiving flask from which it was stored into a quick fit bottle.

b. Dry Ethanol (EtOH):

This solvent was purified in exactly analogous manner as described with methanol.

c. Anhydrous acetone:

The acetone was heated under reflux with successive quantities of potassium permanganate until the violet colour persists. It was then dried by the addition of anhydrous potassium carbonate filtered and distillate. The distillate was collected at 55–56°C as pure solvent.

d Chloroform ($CHCl_3$):

The commercial product was contained up to 1-percent of ethyl alcohol, which was added as a stabilizer. The alcohol was removed by the following procedures.

(i) The chloroform was shaken six times with about half its volume of water then dried over anhydrous calcium chloride for at last 24 hours and distilled.

(ii) The chloroform was shaken three times with a small volume (5 percent) of concentrated sulphuric acid, thoroughly washed with water, dried with anhydrous potassium carbonate and distilled water. Pure chloroform had bp. 61°C / 760 mm the solvent when free from alcohol, was kept in the dark to avoid the photochemical formation of phosgene.

e. Petrolium ether (PE):

The laboratory grade petroleum ether was fractionally distilled and then fractions having the boiling point 40-60°C.

f. Ethyl acetate (EA):

Ethyl acetate from E. Mark (Germany) was fractionated and collected at 78°C/760 nm.

2. Melting point

Melting points were determined on Gallenkamp (England) melting point apparatus (England) 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. The absorption bands were expressed in cm^{-1}.

4. Ultra-Violet spectra

The UV spectra were recorded in dry EtOH with a Shimadzu UV Visible spectrophotometer at the Department of Chemistry, BUET, 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 patten of unknown compound can be set up. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in deuteriochoroform ($CDCl_3$) with a Bruker DPX-400 spectrophotometer (400 MHz) using tetramethylsilane (TMS) as internal standard at the Bangladesh Council of Scientific and Industrial Research laboratories (BCSIR), Dhaka, Bangladesh.

6. Drying

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

7. Evaporation

All evaporatiou werc carried out under reduced pressure in Buchi rotatory evaporator (W. Germany) with a bath temperature below 40°C.

8. Column chromatography

Column chromatography has been successfully applied to separate to individual components (having different R_f values) of the 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 drown 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 separatory 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.]

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

Air bubble was removed by making the column as quickly as possible and allowing the solvent to fall drop by drop through the stop cork of the column. The mixture of the components was then placed on the npper 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 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 élution was chromatographically pure.

PART-I

Section-I

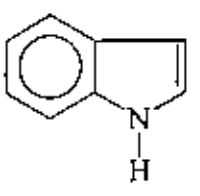
INTRODUCTION

INTRODUCTION

1.1 General remarks

Indole nucleus **1**, is common to a large number and a wide variety of biologically active natural and synthetic compounds[1]. The Synthesis and functionalization of indoles have been the object of research for over one hundred years beginning with synthetic studies of indole based dyes[2]. Among the many more recent synthetic target 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.

The indole skelcton containing Tryptophan[7] **4** is an essential amino acid and as such is a constituent of most protein. Among the synthetic chemothera peutics the β-indolyl acetic acid derivatives **5**, indomethacin **6**, are of value in the treatment of rheumatoid arthitis[7], some of the importance and synthesis of indole derivatives are described below.



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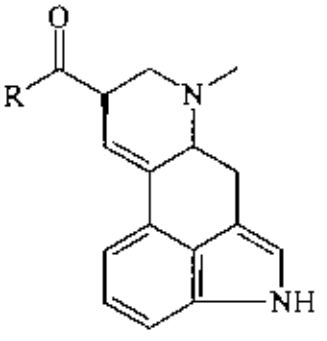

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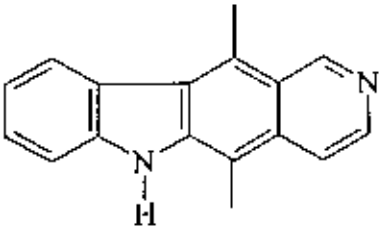

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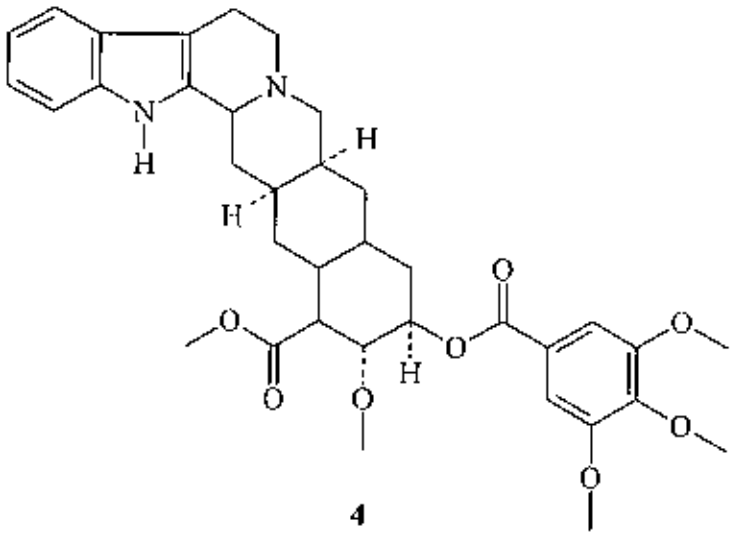

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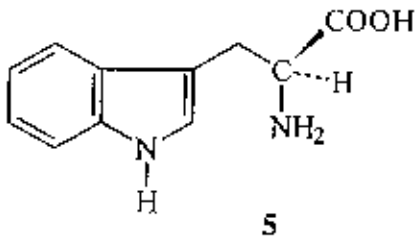

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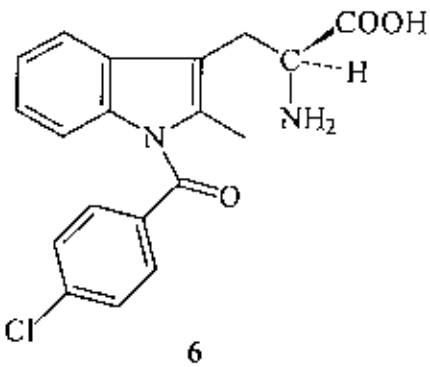


6

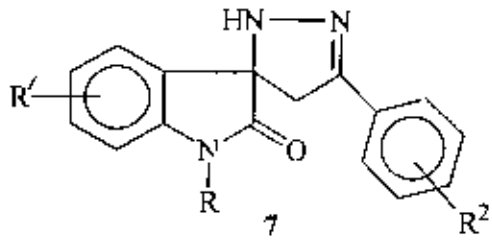
1.2 Importance of indole derivatives

1.2.1 As Chemotherapeutic and pharmacological agents

Indole nucleous has arosed 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:

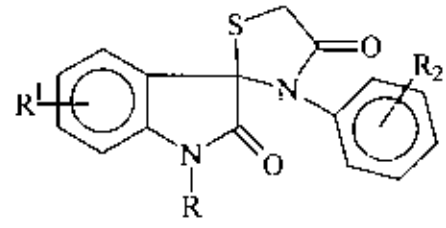
a) As antibacterial agents

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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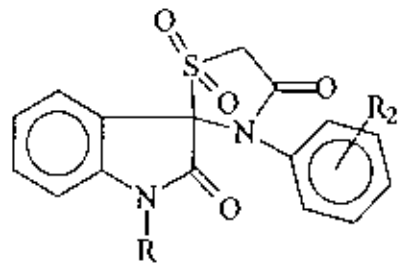

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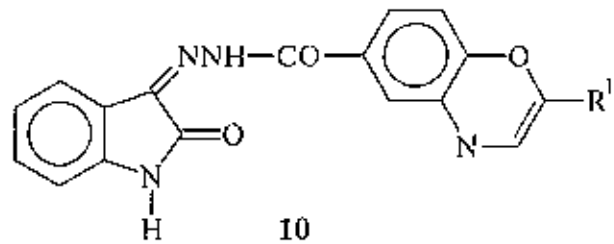
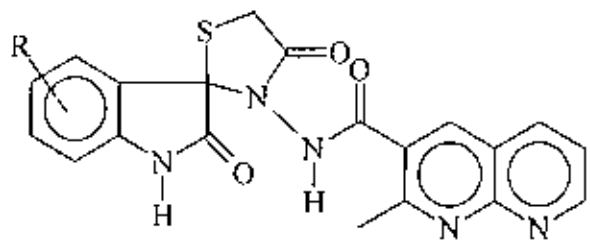
Recently Pani *et al*[12] and Shailaza Rani *et al*[13] also found antibacterial activity in the compounds **10** and **11** respectively.



10

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

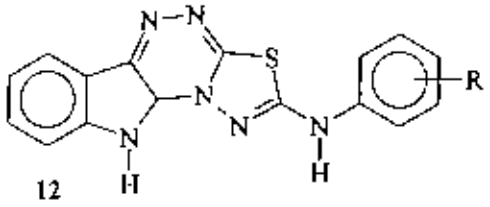


11

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 antifungalactivity.



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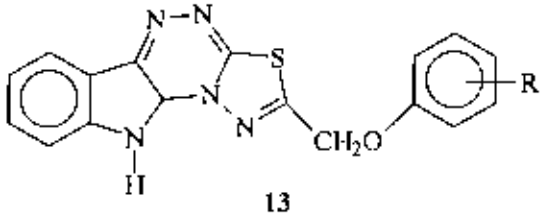
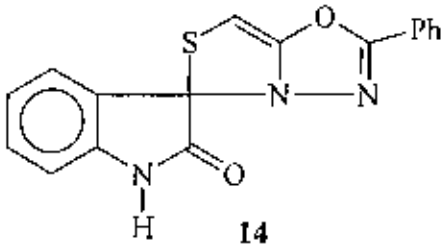
R = Cl, CH_3, NO_2, OCH_3



13

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



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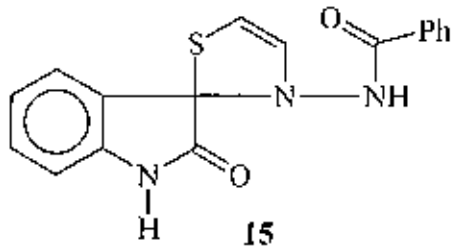
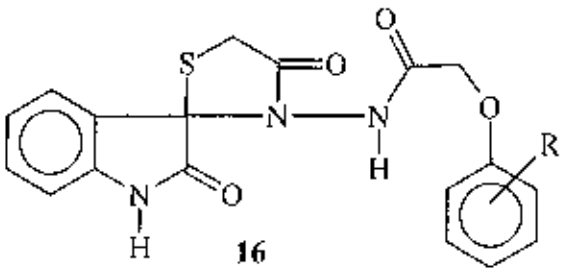


15

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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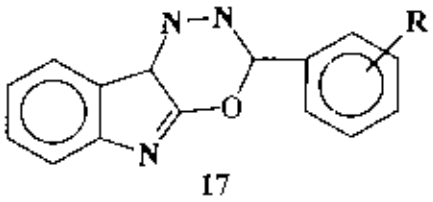

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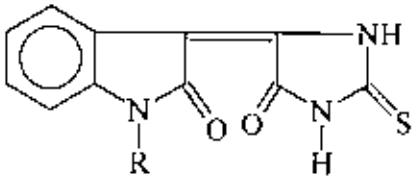
c) As anticancer agents

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



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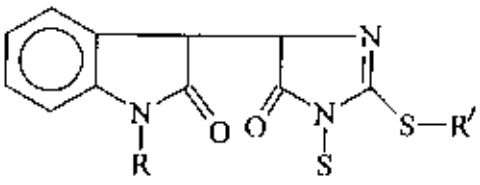
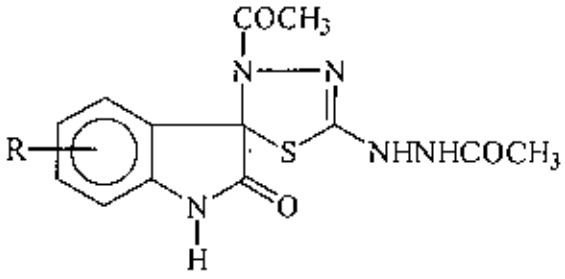


here R = H, Ph 19
R′ = CH_3, Ch_2Ph, CH_2CO_2Et.

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.

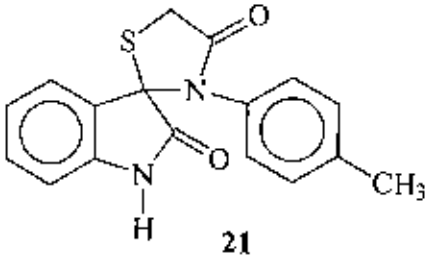


R = Cl, Br, CH_3, NO_2, CO_2H

20

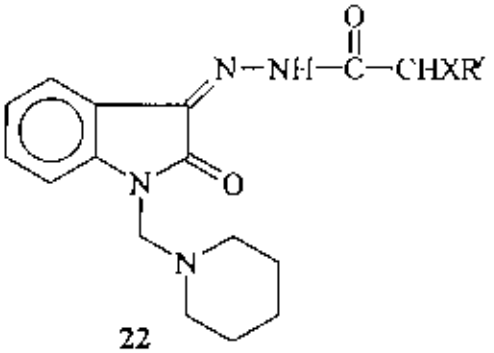
d) Anticonvulsant agents

El-Gendy *et al*[21] and Gursoy *et al*[22 23] (1994–96) prepared the compounds below, showed potential anticonvulsant activities.



21

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



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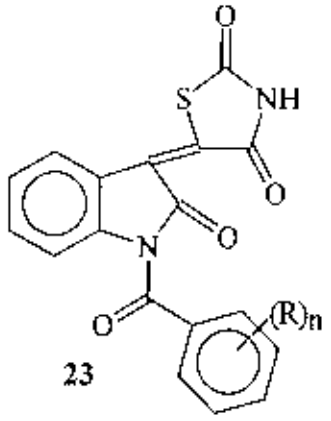
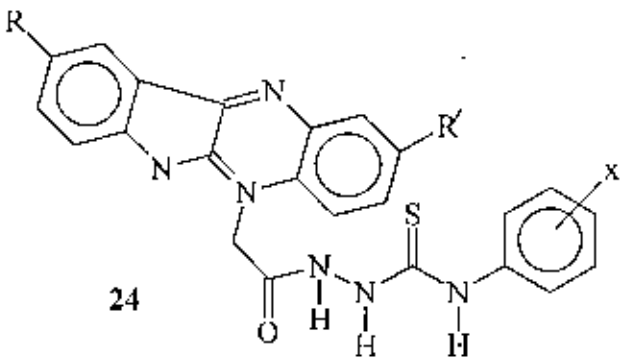
e) As cell migration inhibitors

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



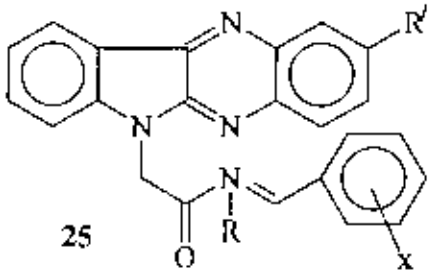
23

R = halogel n = 0 - 5



24

R = halogel n = 0 - 5



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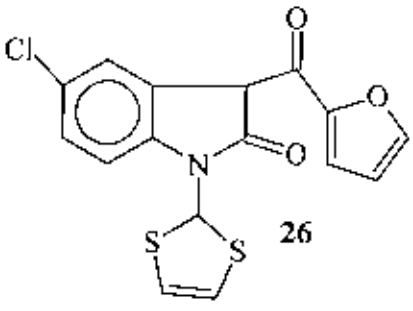
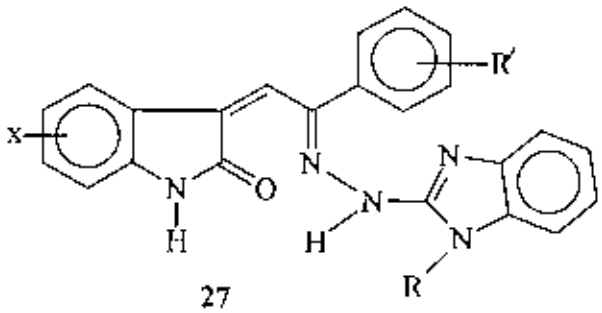


26

f) As insecticidal agent

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



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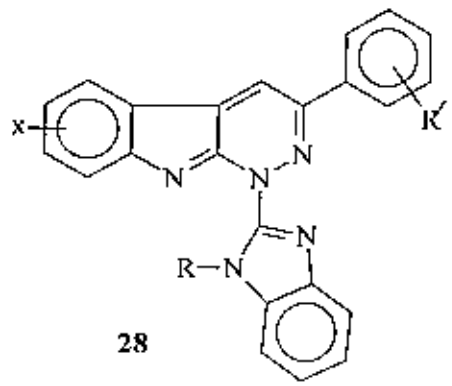


28

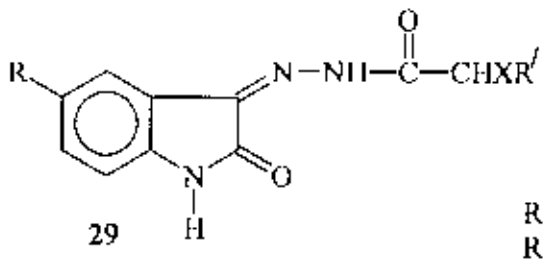
x = H, F.
R = H, Ph.
R′= halo-C_6H_4, Ph

g) As anti microbial agents

Mohon *et al*[32] in 1989 and 1995 and Patel *et al*[29] synthesized and studied some new heterocycles from 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.



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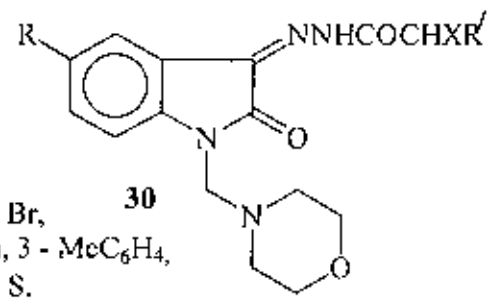
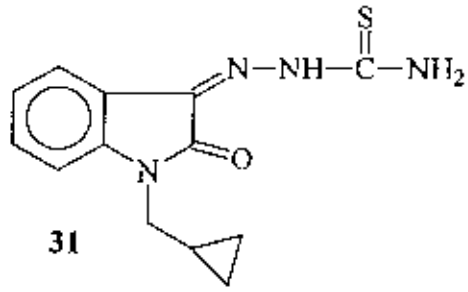


30

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

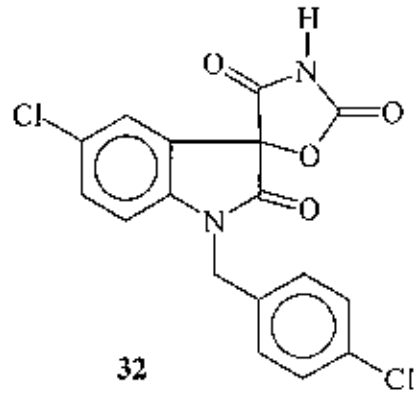
Some *N*-cyclopropane derivatives **31** of indole and its β-thiosemicarbazones display antivirus activity.



31

i) As antidiabetes agents

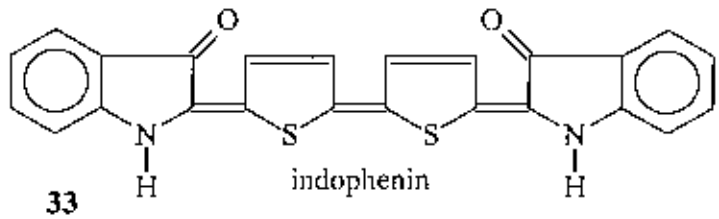
The following spiro compounds **32** can inhibit the enzymetic activity of aldose reductase and hence it is used as antidiabetes[34].



32

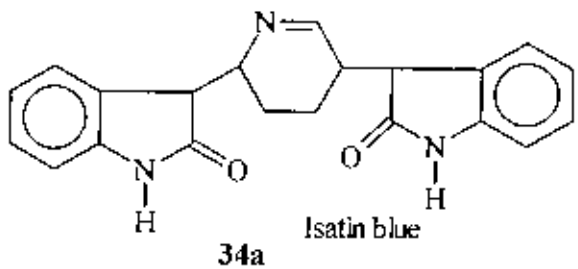
1.2.2 As dying agents

Baeyer[35] obtained a blue dye indophenin **33** by treating isatin with concentrated H_2SO_4 and crude benzene.

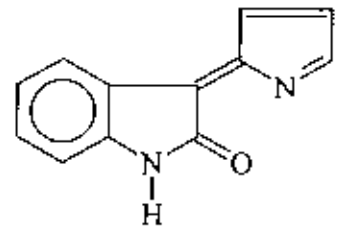


33 indophenin

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



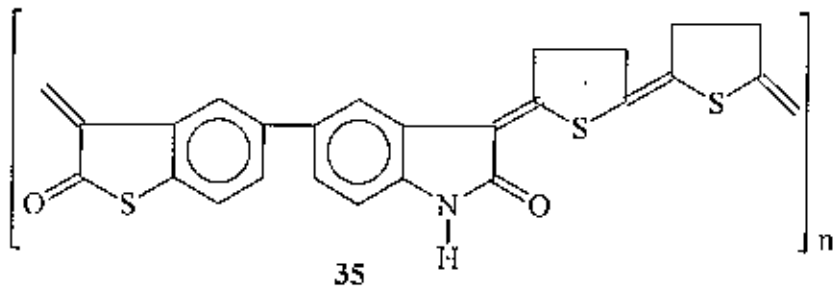
34a Isatin blue



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[38].



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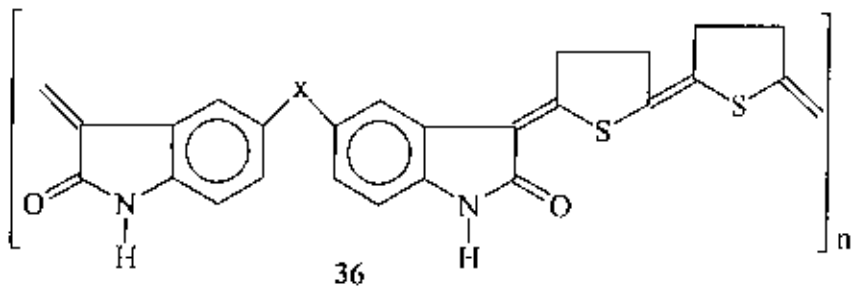


36

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

1.2.4 As enzymatic agents

In the dehydrogenatation of amino acids, isatin possesses an apparent enzyme like activity. When α-amino acid is heated with isatin in aqueous solution, benzaldehyde[39] is produced.

In a series of organic catalysis, Langenbeck[40] reported that certain isatin and oxindole derivatives possess enzyme like activity particularly in the dehydrogenation of amino acid.

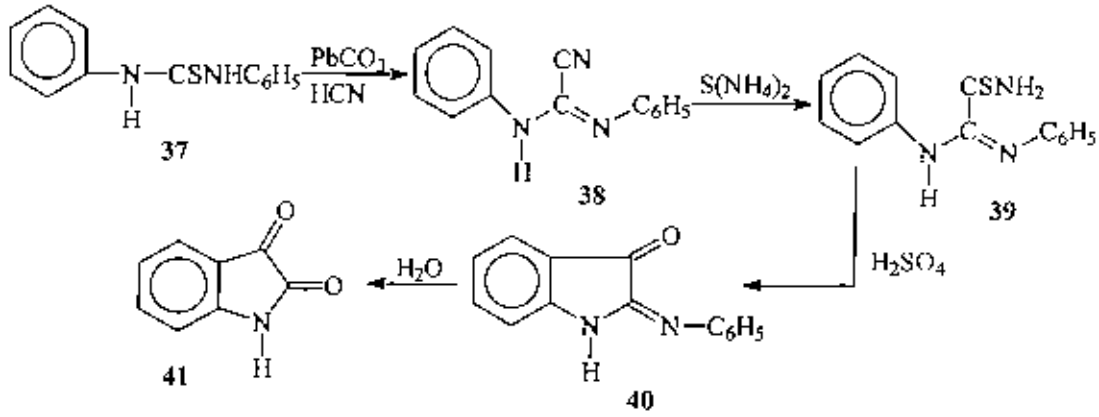
1.3 Synthesis of indole and substituted indole

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.

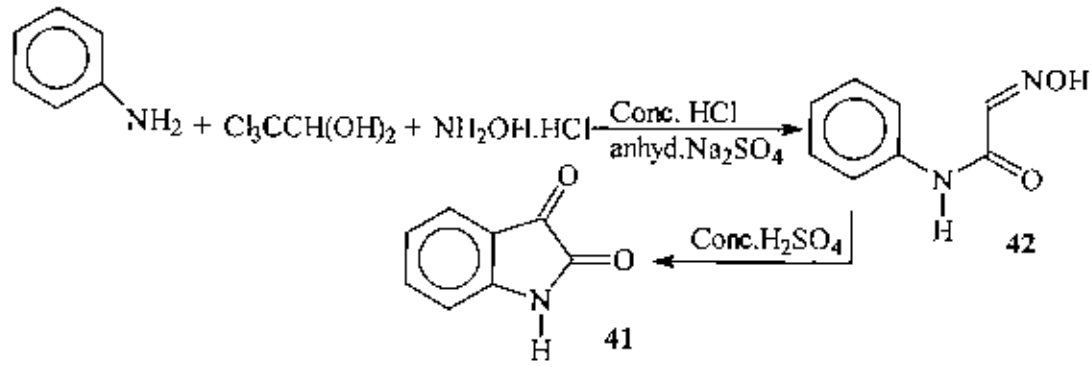
Sandmeyer procedure

The most important and mostly used method was developed by Sandmeyer. There were two process[41]. 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[41] with sulfuric acid and subsequent hydrolysis.



Scheme-1

The second method (Sendmeyer)[42,43] involves the formation of a Isonitroso-acetanilide[43] from the condensation of aniline with chloralhydrate and hydroxyl arvine hydrochloride in presence of Na_2SO_4. Cyclization of **42** with conc. sulfuric acid gives indole derivatives.



Scheme-2

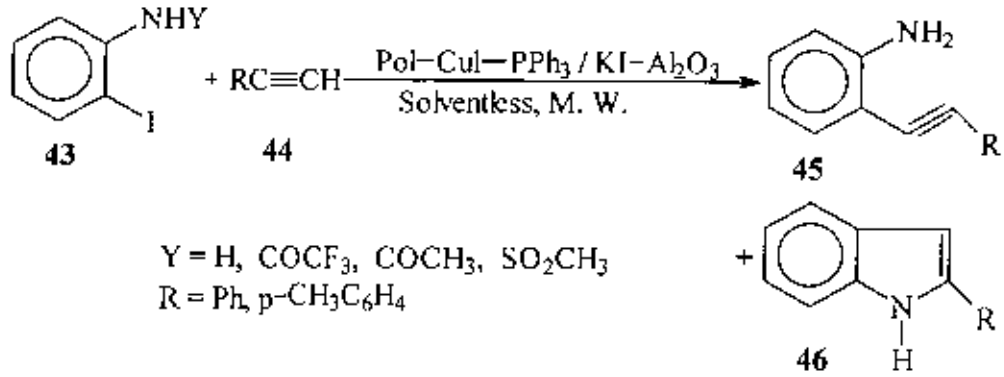
1.3.1 Palladium complexes in the syntheses of indole

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.

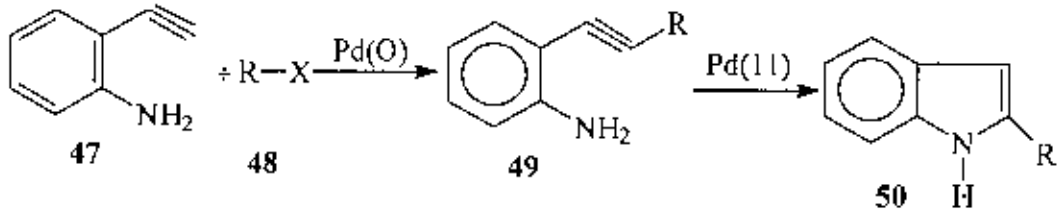
1.3.1.1 Coupling cyclization reaction

Coupling cyclization reaction[44] can be used to the synthesis of indoles. The reactions of o-iodoaniline o-iodocetanilide, 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 plenylacitytene. When o-iodo-acetanilide was used instead of o-iodoanilins 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

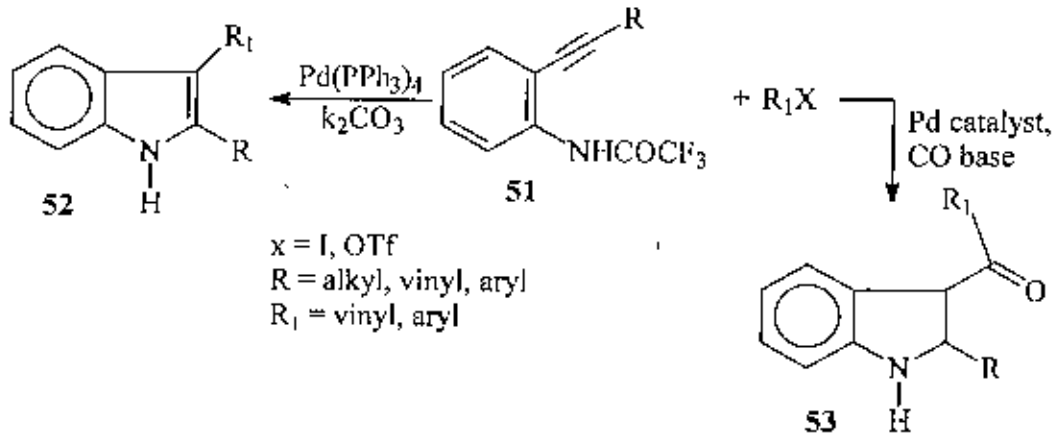
The Palladium (0) catalysed coupling of aryl and vinyl trifluoride or halides with 2-ethynyaniliue, followed by palladium (II) catalysed cyclization step, provides an efficient and very versatile procedure for the synthesis of functionalyzed substituted indoles[45].



Scheme-4

The use of palladium catalysis in the development of uew routes to indole derivatives[46,47,48] was investigated as shown in the scheme –5.

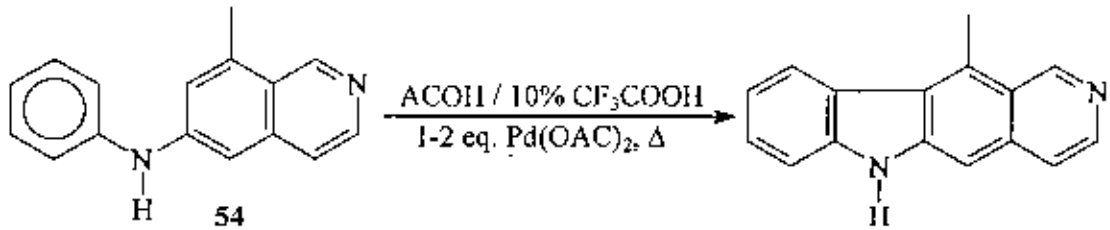
3-Acylindole have been reported to be important therapeutic agents and useful internediates [49] for the preparetion of pyridocarbazole alkaloids.



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[50].

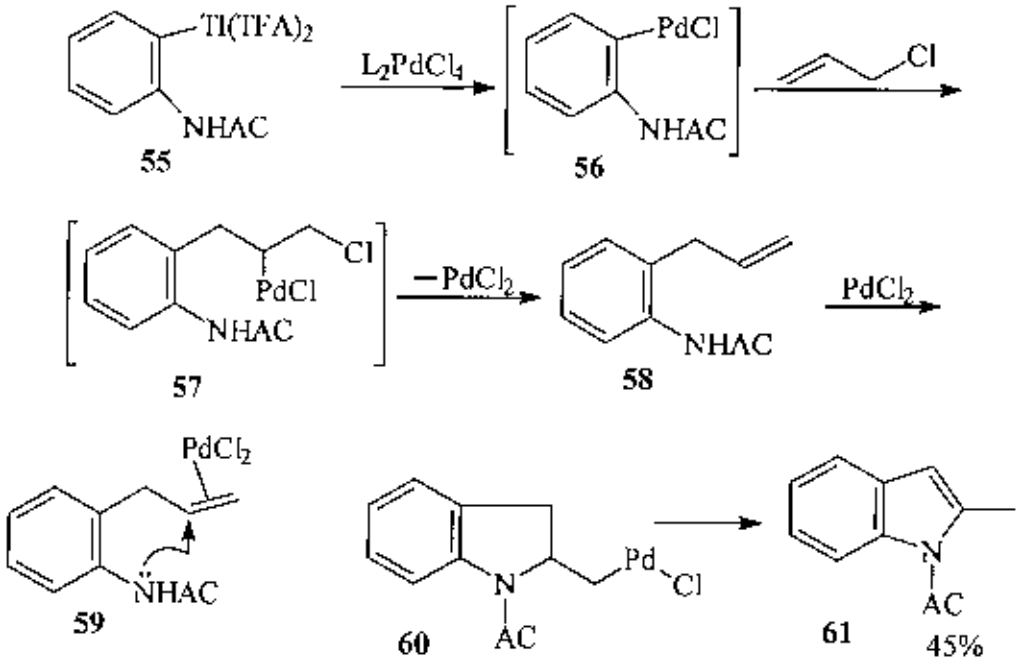


Scheme–6

1.3.1.3 Palladium (II) Catalysed amination of olefins

O-Allyl anilines, which contain amine and olefin in the same molecule. were efficiently converted into 2-methyl indoles using palladium (II) catalysis[51,52] (Scheme-1). This process was thonght to involve co-ordination of the olefin to Pd(II) followed by intramolecular amination.

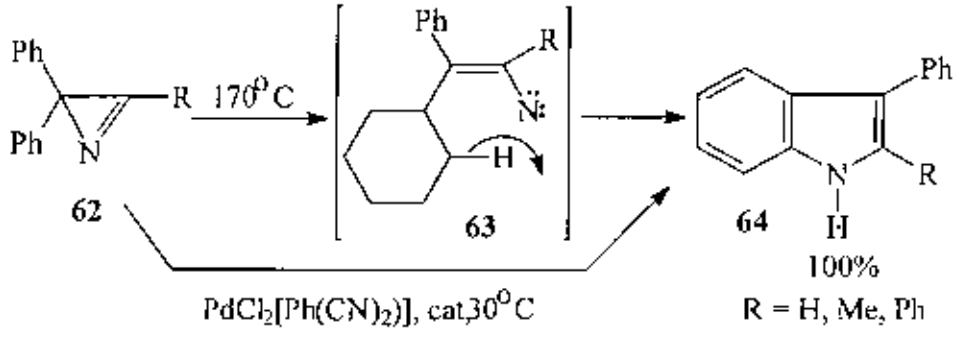
Indoles such as 61 were also produced in a stoaichometric reaction including transmetalation, iusertion, elimination and amination of olefines[52] in scheme-7.



Scheme–7

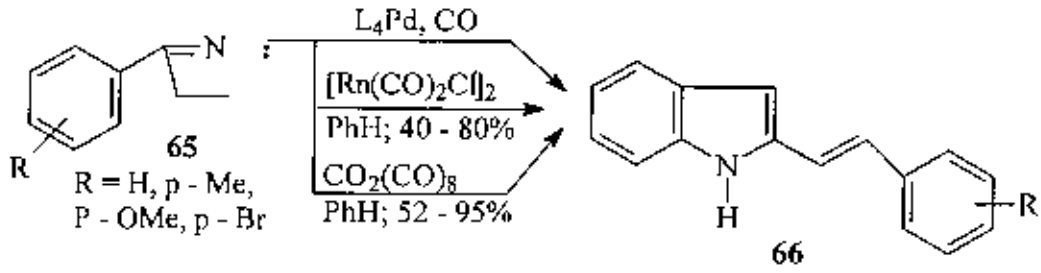
1.3.1.4 Palladium (II)-catalysed (and other metal catalysed) Reactions of Azirines.

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



Scheme–8

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

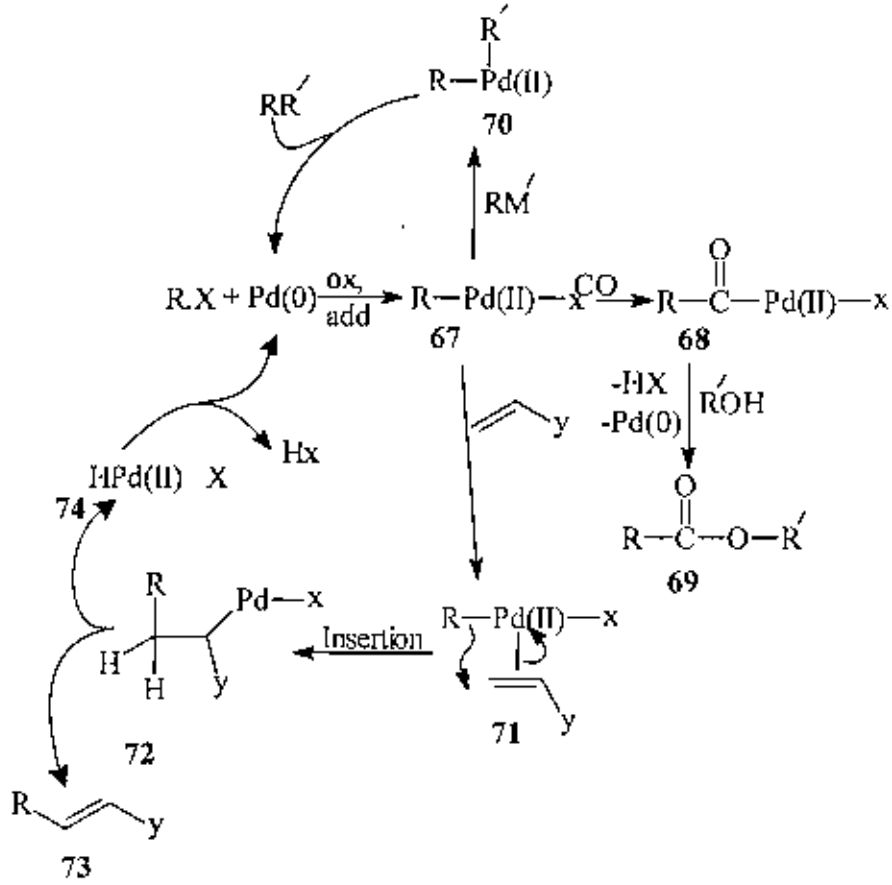


Scheme–9

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

While palladium (II) salts are electrophilic reagents which react with alefines 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 triphenyl phosphane.

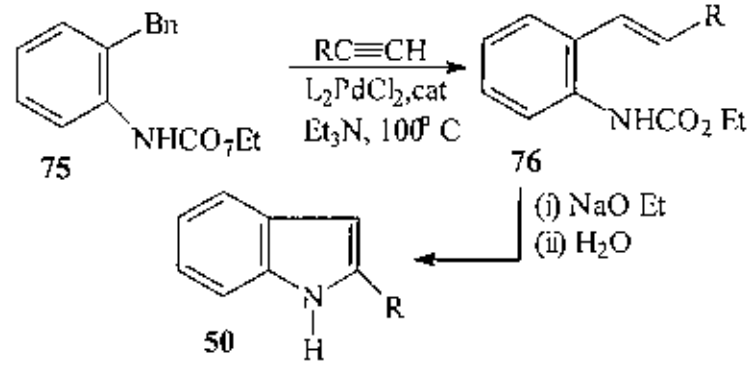
Both of these have been extensively used as catalysts in organic synthesis. However, it is frequently more convenient to generate palladium (0) catalysts insitu by reducing palladium (II) catalyst precursors. Thus, treatment of $Pd(PPh_3)_2Cl_2$ with diisobutylaluminum hydride or with CO or triethyl amine will generale 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 componnds including carbon monoxide, olefins, phosphanes, and tertiary aliphatic amines such as triethyl or 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–10

1.3.2.1 Palladium(0)-catalysed Alkynylation of Bromoanilines

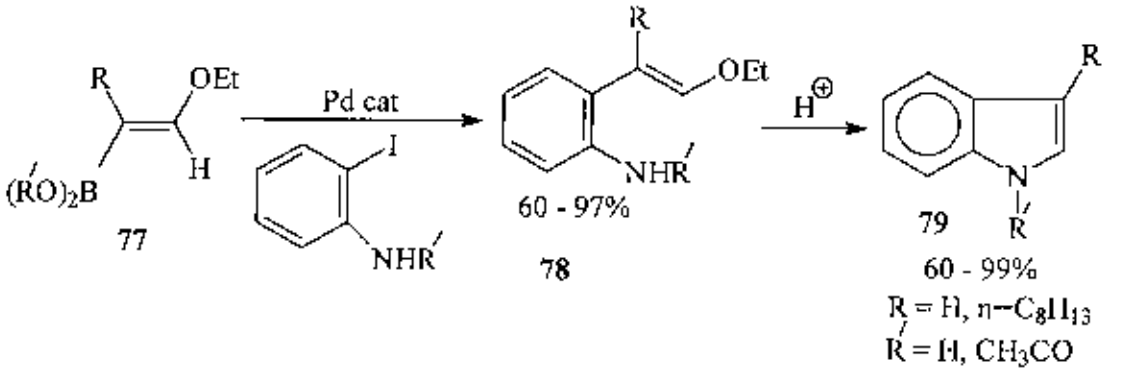
O-Alkynyl anilines such as **76**, made by palladium(0) catalysed coupling of alkynes with o-halo aniline precursons[59–60] were readily cyclized to indoles **50**.



R = H, Bu, Ph, 65 – 93%

Scheme–11

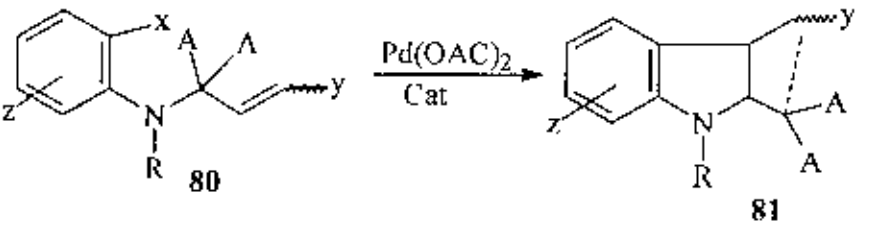
In a releated process, hydroboration of ethoxyacetyline gave a vinylborane 77 which under went Pd(0)-catalysed oxidative addition / transmetalation to produce an indole precussor[61] 79.



Scheme-12

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

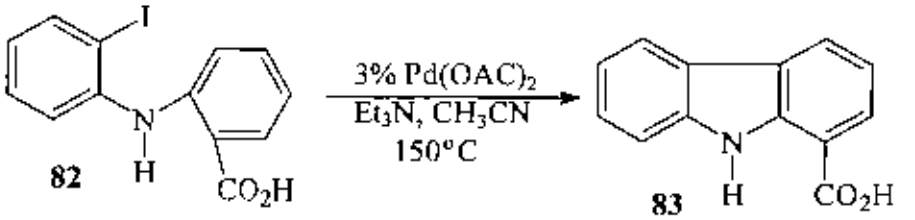
O-Bromoanilines were easily *N*-allylated, producing substrates ideally suited for a Pd(0) catalysed oxidative addition / olefin insertion approach to the indole ring system. As a consequence, this route has been extensively developed. Both activated[62–64] and simple olefines[64] inserted efficieutly.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



A	R	X	y	z	yields[%]
$\frac{1}{2}$O	$PhCH_2$	Br	Ph CO_2Me	H	50–73
H	Ac	Br	CO_2Me	H	73
H_6	H	I	H	-5—Me,5,6(OMe)$_2$ 5—CO_2Me,H	50–87

Scheme–13

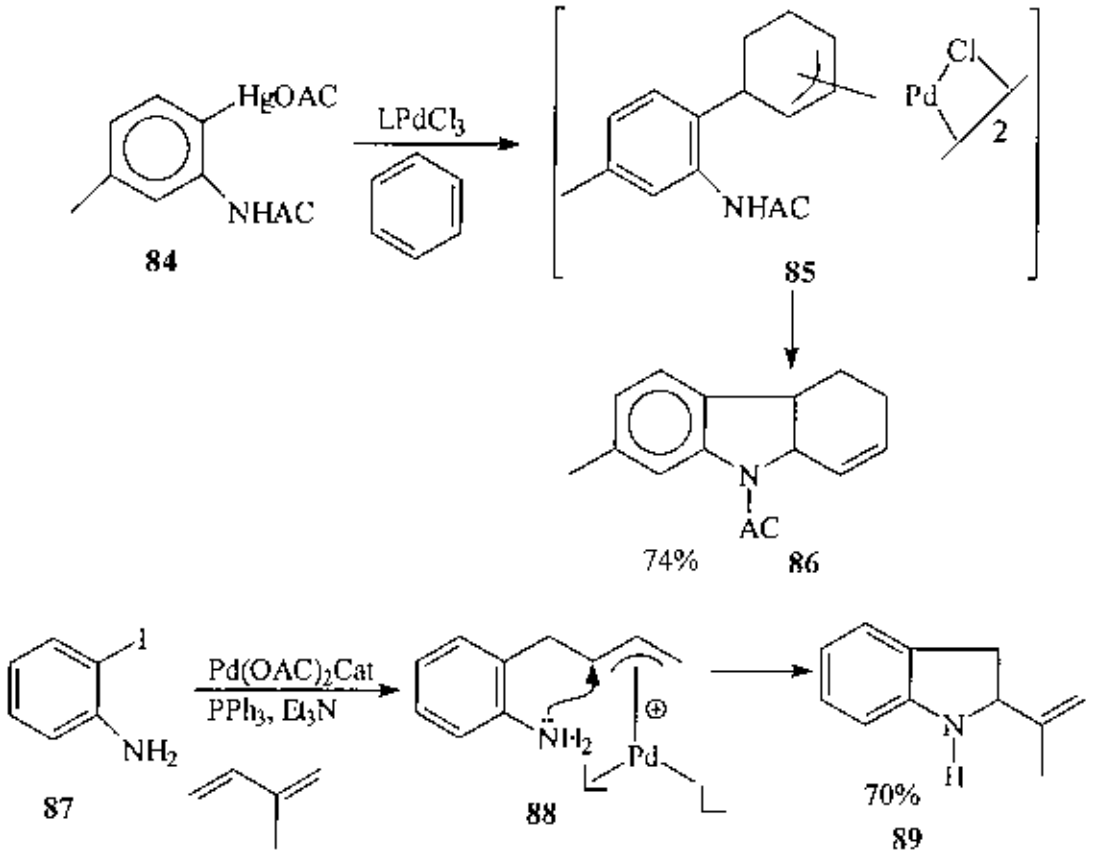
Carbazoles were produced in good yield from diphenylamines such as **83** utilizing oxidative addition / insertion chemistry.



Scheme–14

1.3.3 π-Ally palladium complexes in the synthesis of indoles

Formation of the indole ring via π-allyl palladium (II) intermediates e.g. **85** and **88** is relatively uncommon. These two examples involve diene insertion into σ-arylpalladium (II) species.

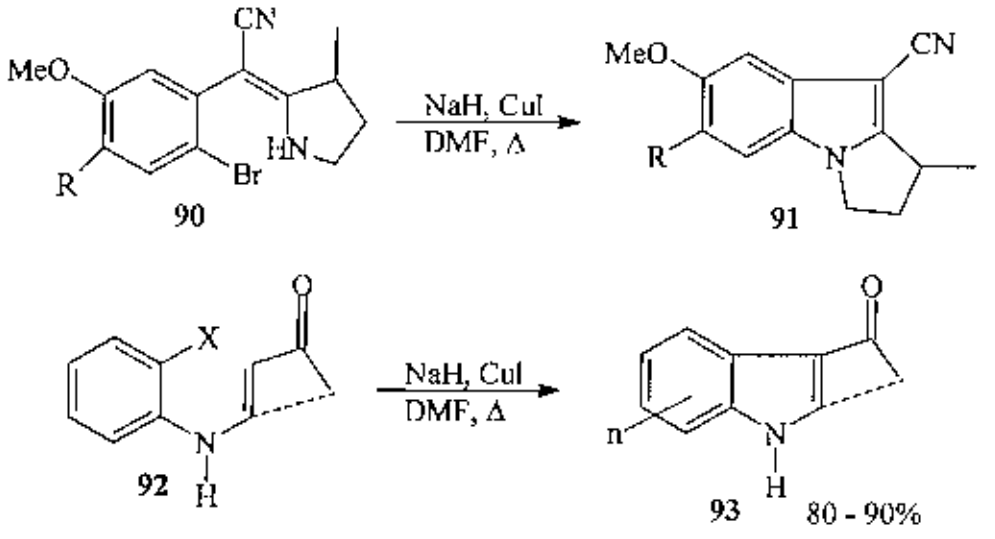


Scheme–15

1.3.3 Other Transition Metals in the Synthesis of indoles.

1.3.3.1 Copper(I)-catalysed Cyclization and condensation

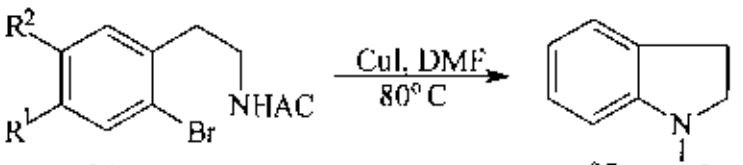
Although palladium is by far the most extensively used transition metal for the synthesis and functionalization of indoles, many others have found at least limited use in this regard.



90 91 92 93

Scheme–16

For instances copper(I) salts have long been known to catalyse 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 catalysed the cyclization of o-isocyano-phenylacetones to indoles[72].

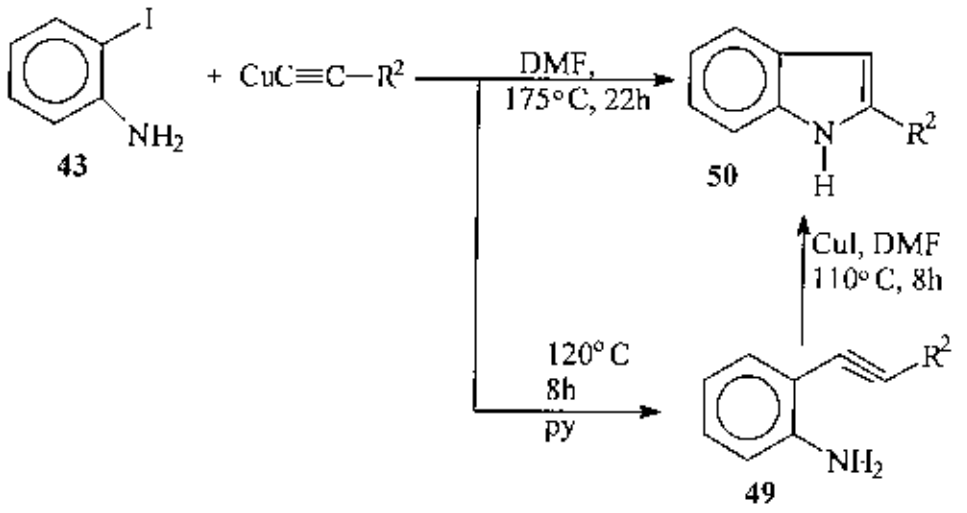


94
R^1 = Me, OMe, H
R^2 = Me

95

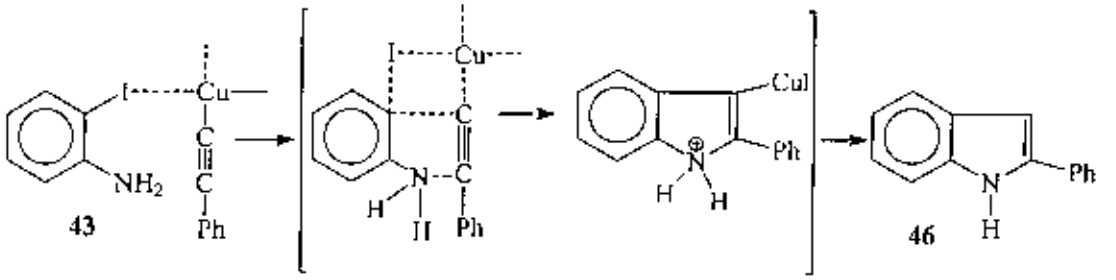
Scheme–17

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°C for 8 hours (Scheme–18)



Scheme–18

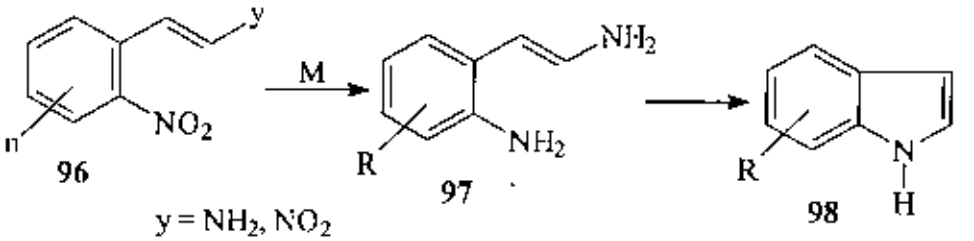
The reactivity of halides was found to be in the order I > Br > Cl. Furthermore the presence of *N*-ethyl piperidine was found to decrease the efficiency of the syntheses, indicating that strong co-ordination of copper could mask the ability of the metal to effect the initial alkylations or to co-ordinate with the acetylene[73]. The substituent of halide and cyclization were thought to occur within the same copper complex[74] (Scheme–19)



Scheme–19

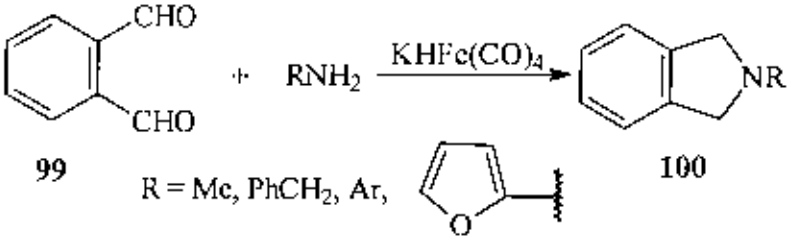
1.3.3.2 Reductive Cyclizations Using Low-Valent Transition-Metal Compounds.

A number of indole syntheses used low valent transition metals to reduce aromatic nitro groups to amines, 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], nickel boride[77].



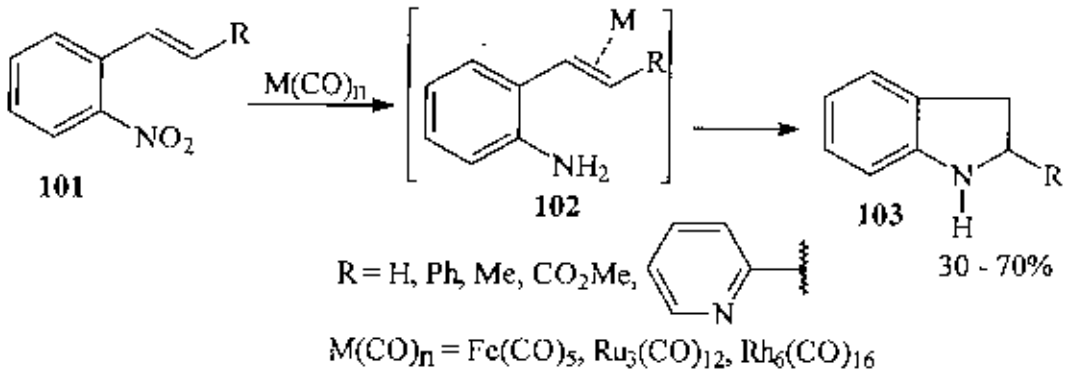
Scheme–20

Dihydroisoindoles **100** were produced in excellent yield by $KHFe(CO)_4^-$ promoted reductive amination of o-dialdehydes[78].



Scheme–21

Finally, o-nitrostyrenes such as **101** were reductively cyclized to indoles by metal carbonyls, in a process which must involve olefin activation by the metal, as well as nitro group reduction[79].

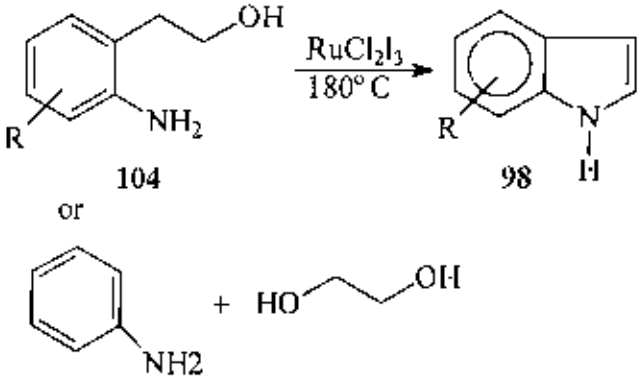


101 102 103 30 - 70%

Scheme–22

1.3.3.3 Ruthenium(II)-Or Palladium-Catalysed Oxidative Cyclization

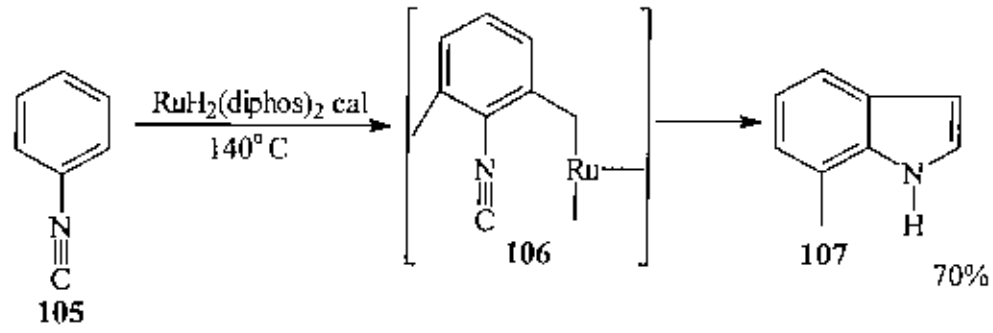
Ruthenium (II) chloride-catalysed oxidation of alcohols has been used to form indoles in modest yield, although the conditions are some what severe[80–82].



104 98

Scheme–23

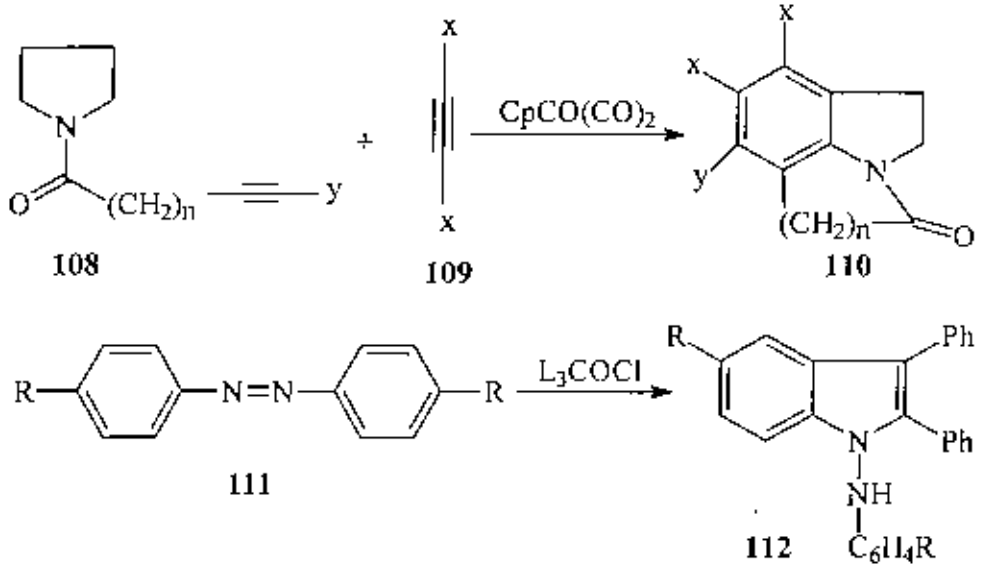
2,6-Dimethyl phenyl / isocyanide was converted into 7-methyl indole **107** in a process which must have involved C–H activation by the ruthenium (four catalytic cycles per $RuH_2(diphos)_2$][83].



Scheme–24

1.3.3.4 Cobalt-Catalysed Cyclotrimerization Reactions

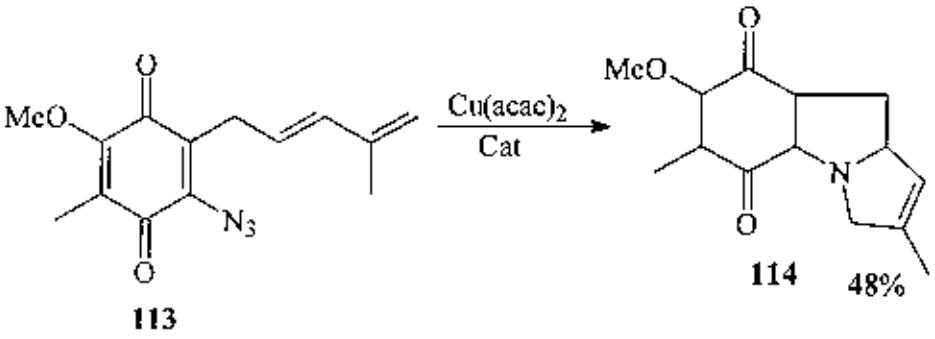
The cobalt catalysed cyclotrimerization of alkynes and cocyclotrimerization of alkynes and alkenes have been extensively developed for use in organic synthesis[84]. The synthesis[85] of compound **110** examplify the use of the later in the synthesis of indoles. Cobalt (I) complexes also catalysed the addition of alkynes to diazenes to produce *N*-aminoindoles[86] **112**.



Scheme–25

1.3.3.5 Miscellaneous Indole Synthesis

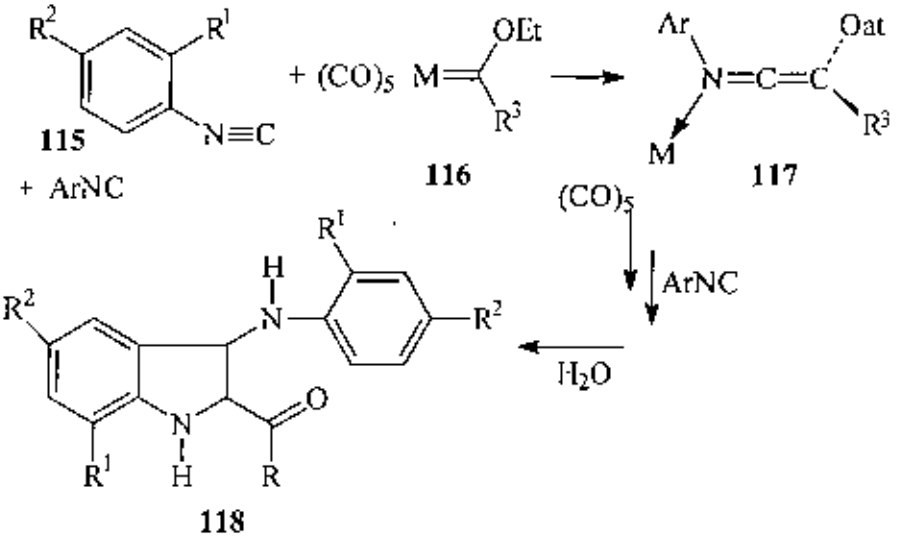
The copper-catalysed decomposition of aryl azides to produce nitrenes has been used to synthesize a number of pyrrolindolequinones[87] **114**.



113 **114** 48%

Scheme–26

Aryl isocyanides were combined with carbene complexes (M = G, Mo, W) to produce indoles, via kelenimine complexes[88–89] **118**.



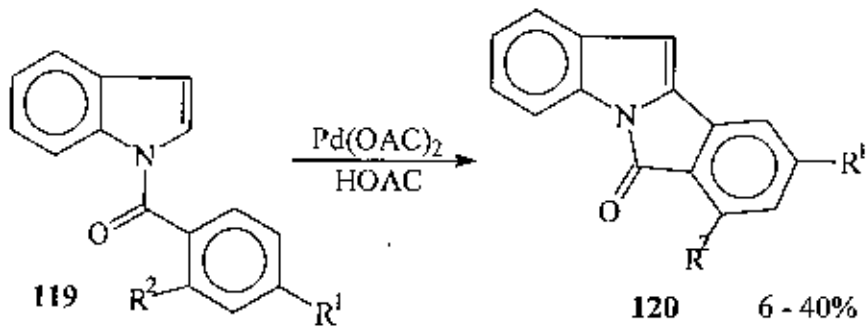
Scheme–27

1.4 Indole reactions

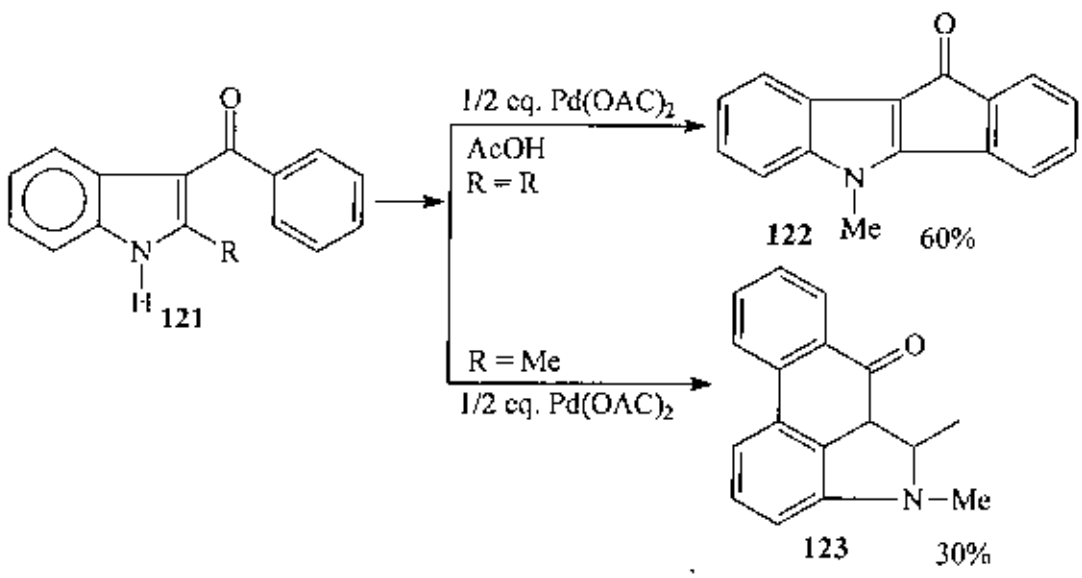
Indole is a π-electron rich system. So, the typical reaction of indole is electrophilic substitution.

1.4.1 Functionalization of indole through coupling

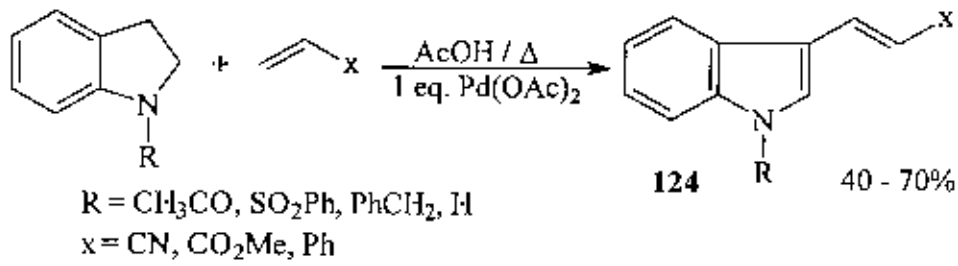
Indoles itself undergoes dirict palladation of 2– and 3– positions. This has been used to make fused ring indole systems e.g. [90, 91] **120, 122** and **123** as well as to introduce olefinic side chains at the 3-position, **124** or at the 2-position in 3-methyl indole [91–94].



Scheme–28

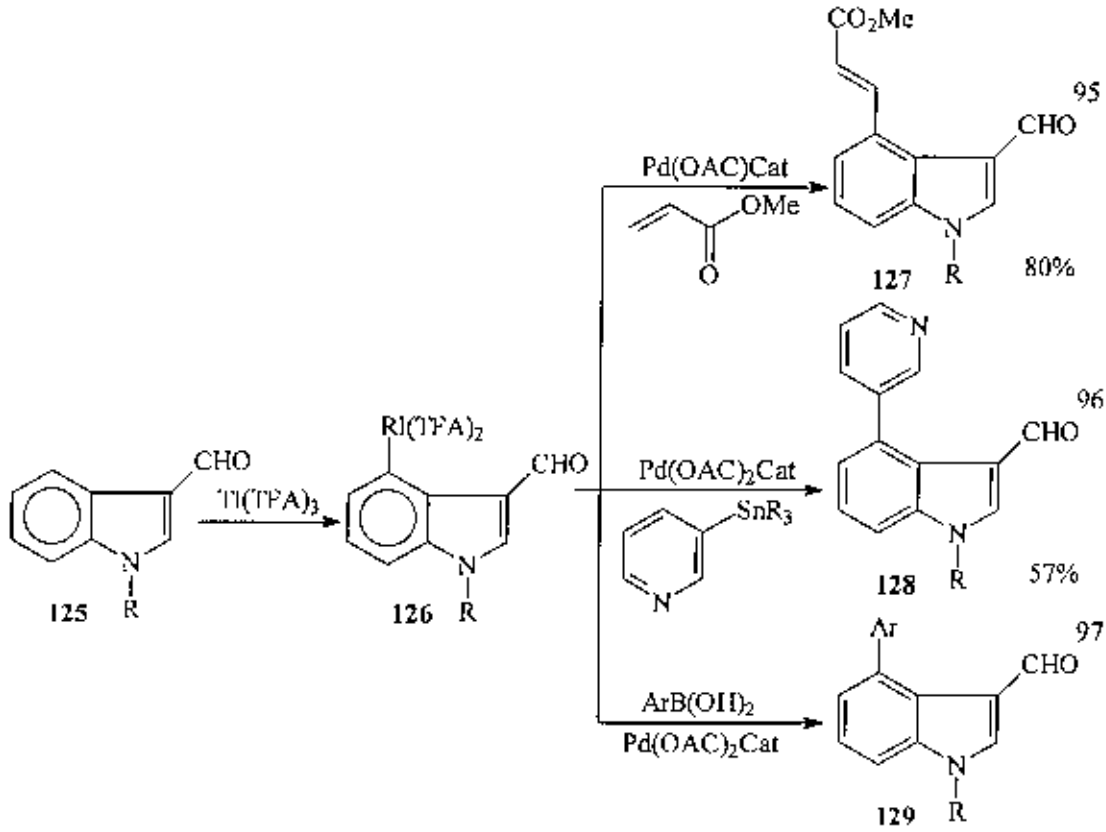


Scheme–29



Scheme–30

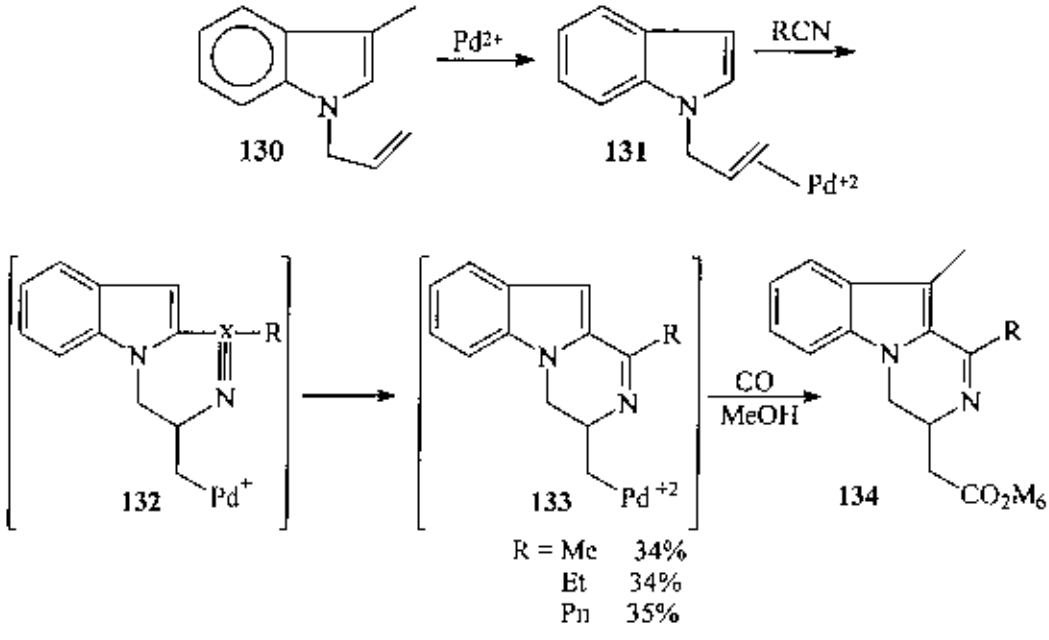
Indole-3-carbohydrate under went Thallation primarily at the 4-position **126**. In the presence of a $Pd(OAC)_2$ as catalyst[95-97], transmetalation to palladium, followed by olefin insertion or reductive eliminations, ensured producing 4-alkylated indoles in modest yield (R = CO_2Me, H) Thallium (III) probably serves as the reoxidant for palladium(0).



Scheme–31

1.4.2 Ritter like reactions

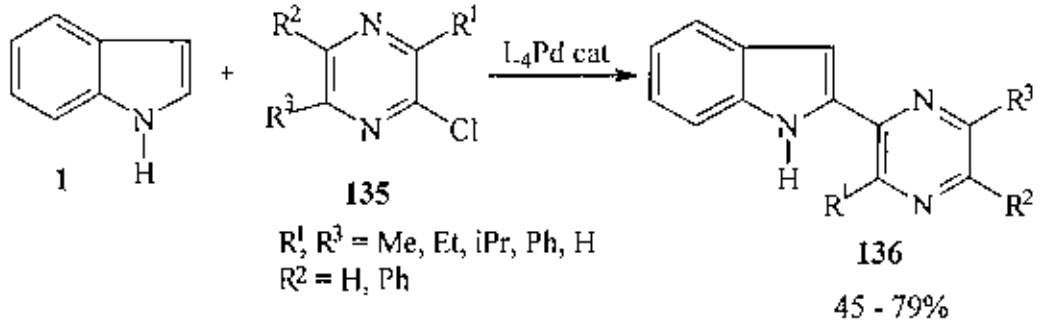
The strongly electrophilic $[Pd(CH_3CN)_4BF_4]_2$ promoted a Ritter like reaction between *N*-allyl-3-methylindole and nitriles, giving pyrazino [1,2-a] indoles[98] such as **134**. While interesting, this process was neither efficient nor general.



Scheme–32

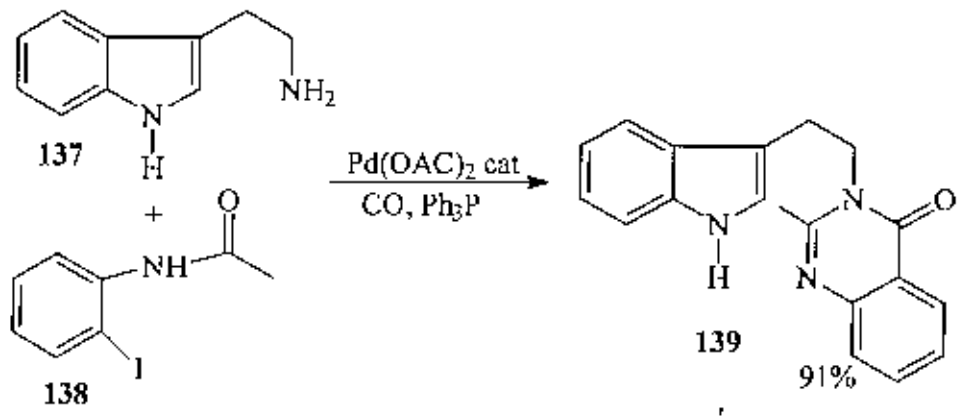
1.4.3 Palladium (0)-Catalysed Functionalization of Indoles

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[99].



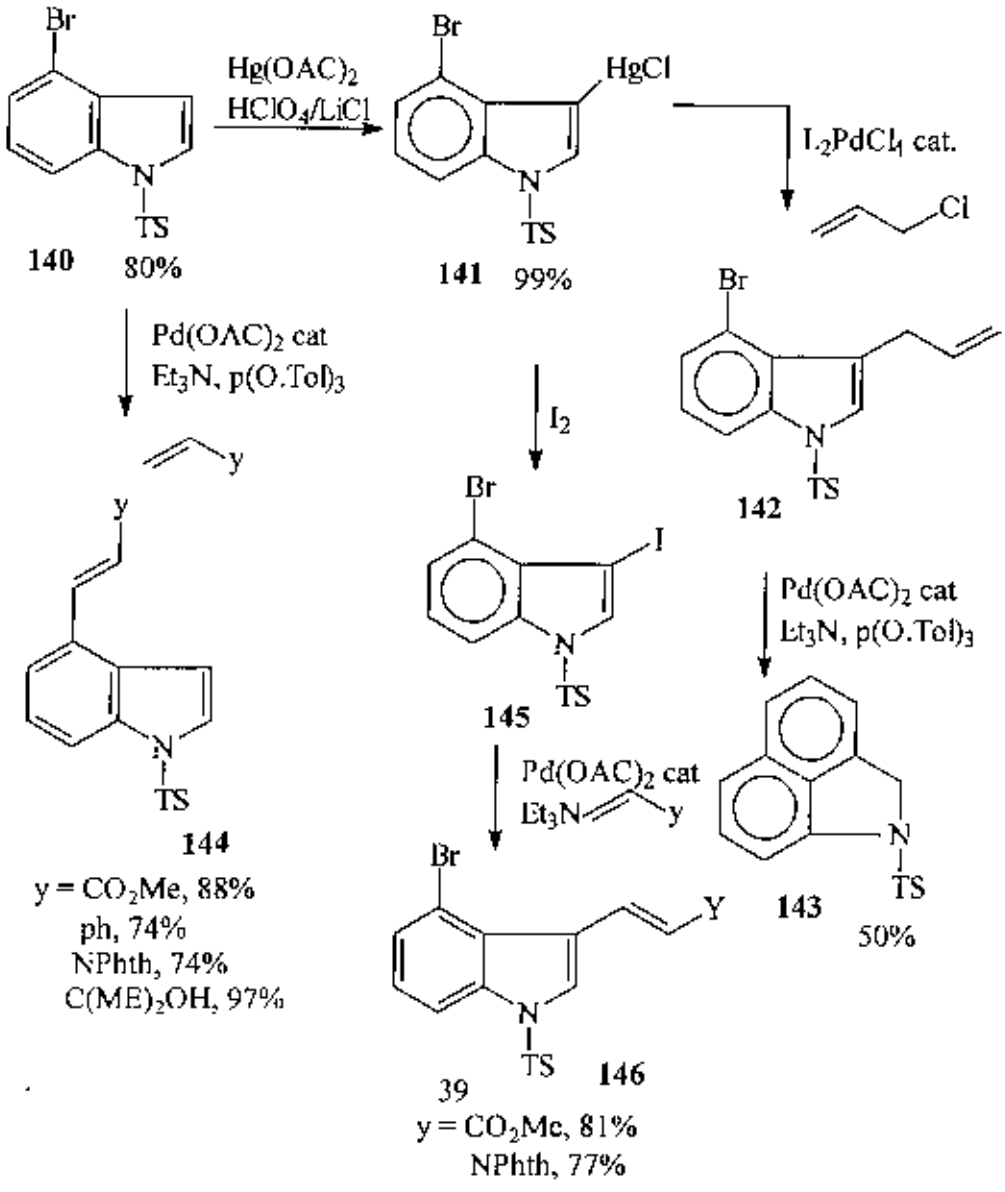
Scheme–33

The 3-amino ethyl side chains of indoles were treated by a Pd(0)-catalysed carbonylation [100] for example with ring closure to give **139**.



Scheme–34

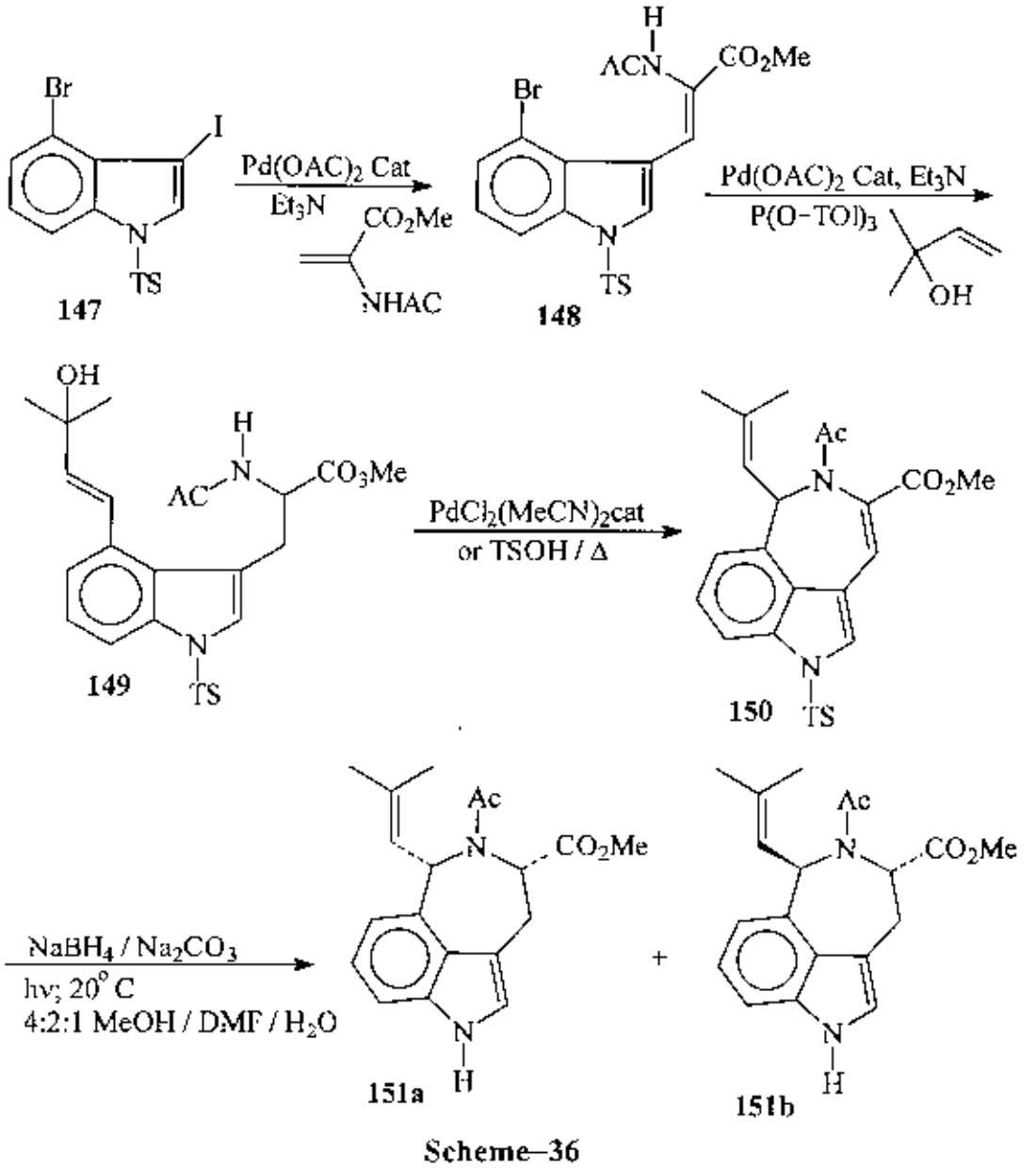
Palladium (0)-catalysed reactions of haloindoles are among the most synthetically useful processes and have been extensively developed for application in the synthesis of 3,4-disubstituted indole ring systems including ergot alkalaids. Introduction of functionality at the 4-position[100] of indole using conventional electrophilic indole chemistry is difficult, since the 1–,2– and 3–positions[100] are considerably more reactive.



Scheme–35

1.4.4 Synthesis of Ergot Alkaloids

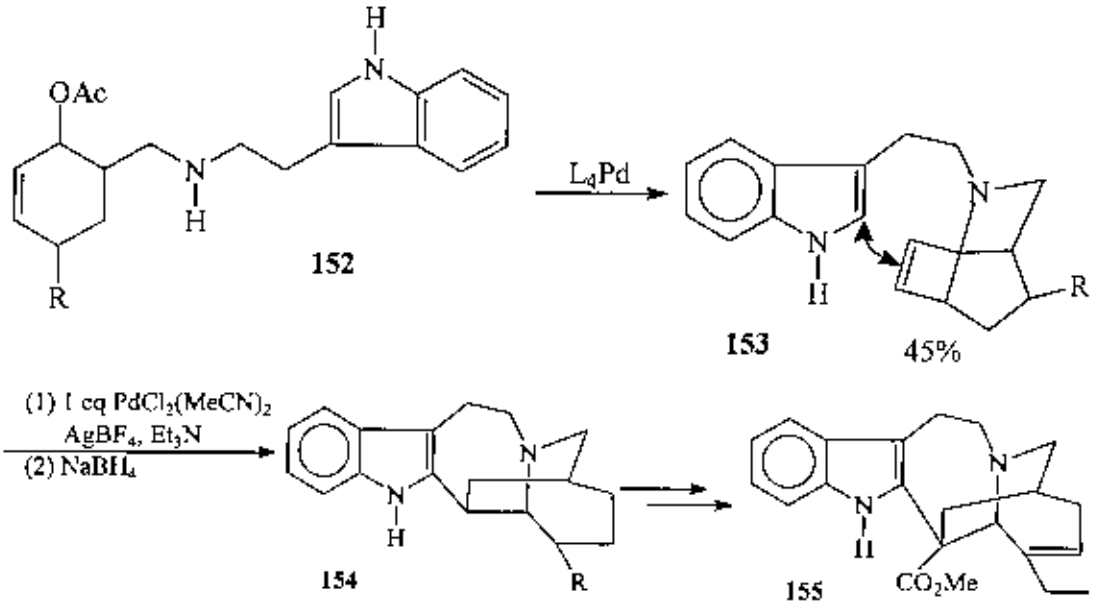
An even more extensive use of palladium catalysis was seen in the total synthesis of the methyl ester of (±)–*N*–acetylclavicipitic acid[101] **151** which involve as key steps Pd(II)-catalysed formation of the indole ring. Pd(0) -catalysed introduction of both C-ring side chain precursors and Pd(II) catalysed formation of the seven membered ring.



Scheme–36

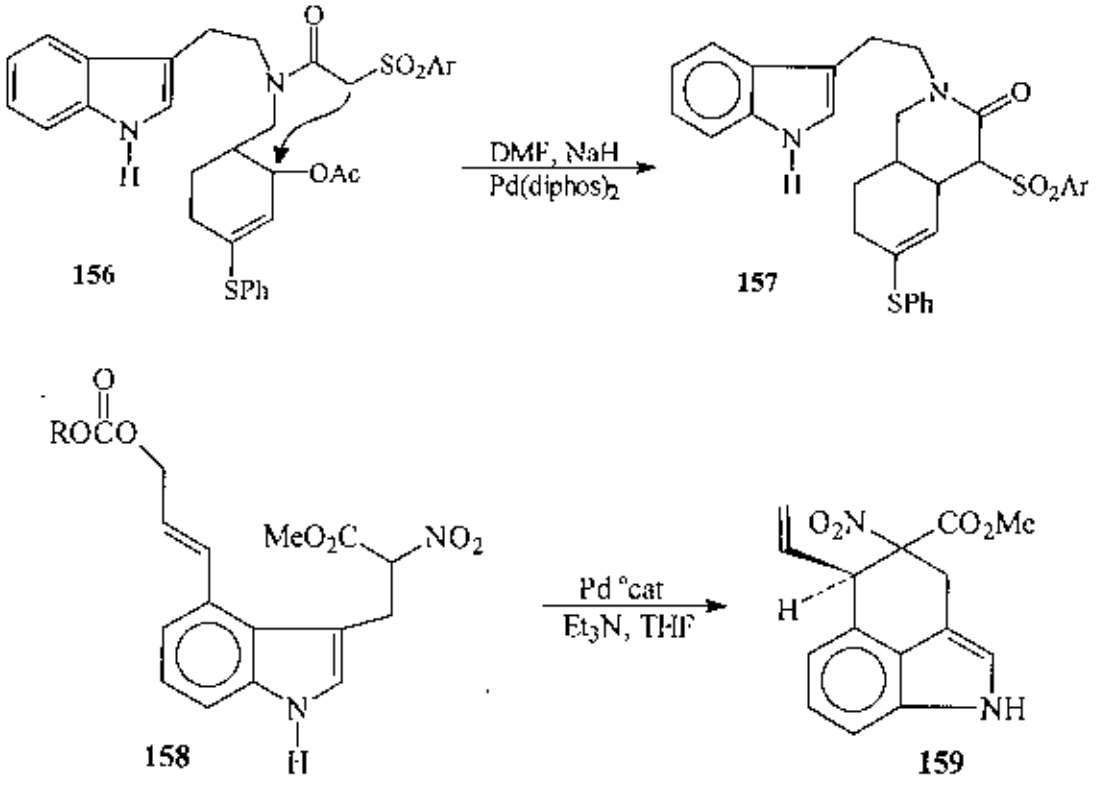
1.4.5 π-Allylpalladium Complexes in the Functionalization of Indole

In scheme–36 π-Allylpalladium (II) chemistry is more commonly used to elaborate existing indole ring systems. The isoquinuclidine ring of ibogamine[102] **154** and cantharanthine[103] **155** were synthesized by a Pd(0)-catalysed allylic amination



Scheme–37

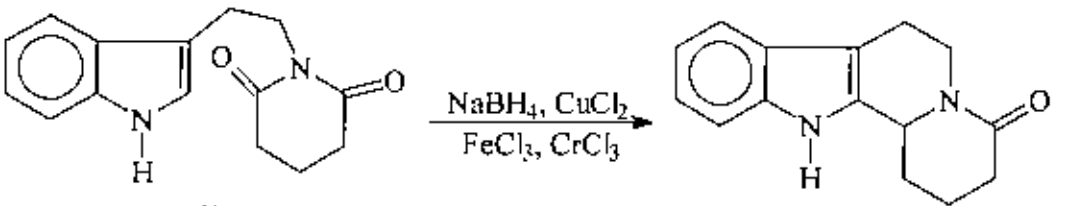
Other indole alkaloid synthesis have used Pd(0)-catalysed allylic alkylation to elaborate nonindolic heterocyclic rings[104] such as **157** and **159**.



Scheme–38

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[105].

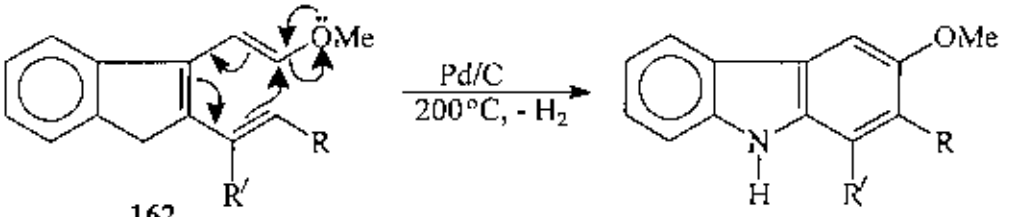


160 **161**

Scheme–39

1.4.7 Oxidative cyclization

Palladium on carbon catalysed oxidative cyclization to 163.

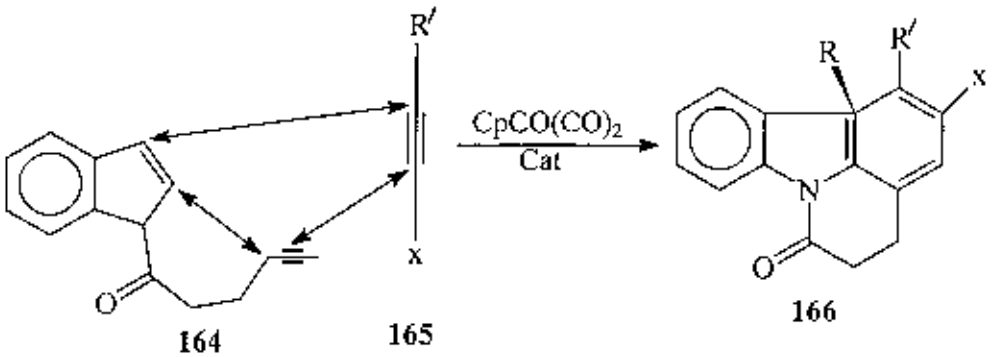


162 **163**

Scheme–40

1.4.8 Cyclotrimerization Reaction

Cyclotrimerization of alkyne and alkene of indole have been extensively developed for use in organic synthesis[106].



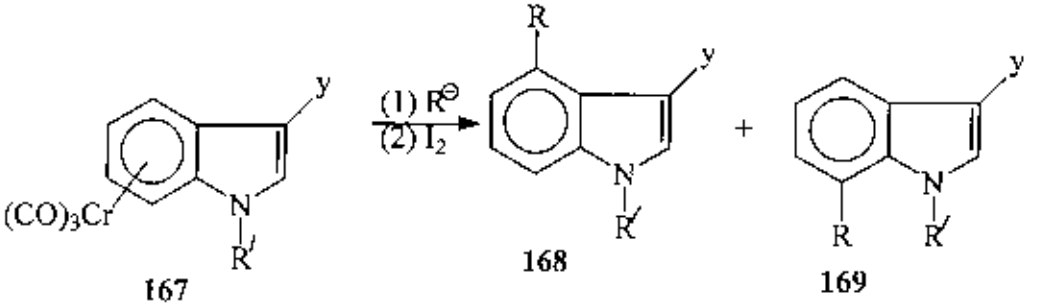
164 **165** **166**

Scheme–41

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[107] and complexed indoles **167** were alkylated in the 4- and 7- positions (major and monor product respectively) by carbanions[108,109].



167 **168** **169**

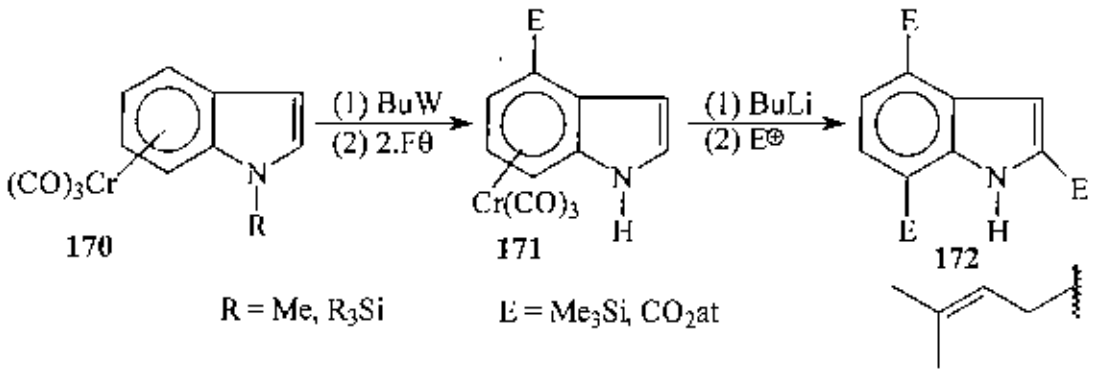
R^1= H, Me, $PhCH_2$, R_3Si, CO_2t - Bu

$R^{\ominus}$ = ⊖—CN, ⊖—CO_2t—Bu, S, ⊕, S

Y = H, Me, CH_2SiMe_3

Scheme–42

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[110,111].



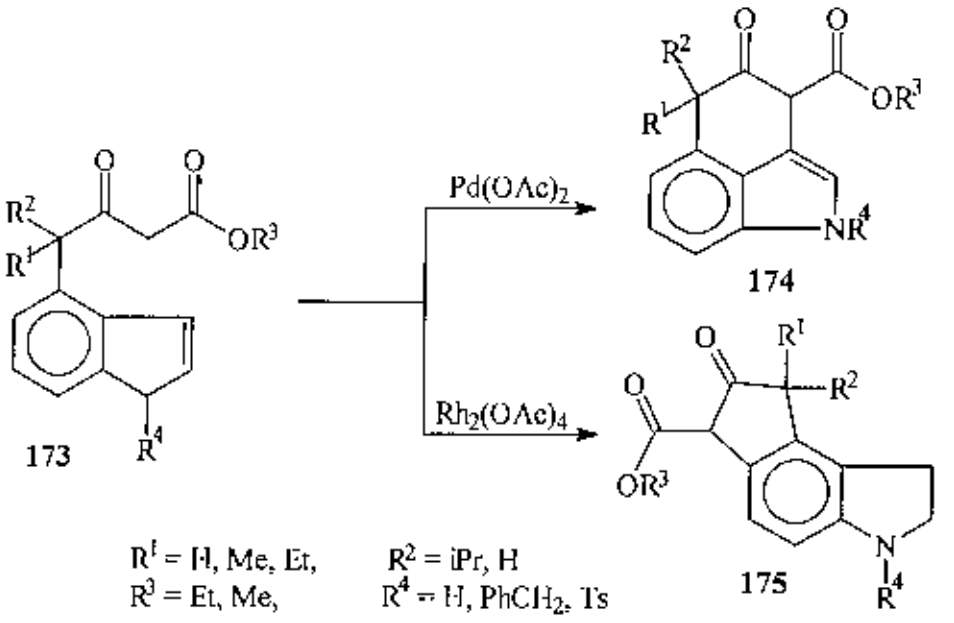
170 **171** **172**

R = Me, R_3Si E = Me_3Si, CO_2at

Scheme–43

1.4.10 Insertion of carbene

The site of insertion of carbones generated by transition-metal-catalysed decomposition of α-diazoesters such as **173** dependend strongly on the catalyst[112].



Scheme–44

PART-I

Section-II

Synthesis of *N*-Acyl-2acyl (aroyl) indole derivatives

Present work: Synthesis of *N*-Acyl-2acyl (aroyl) indole.

1.2.1 Rationale (objectives):

Indole nucleus is a class of fused heterocycles, has arose great interest in recent years due to their wide variety of biological activities [113] and pharmacological studies [114] 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[115] reactions have been extensively utilized for carboannulation [116] and hetero annulation[117] processes. Many research groups have reported the synthesis of various aromatic heterocycles via palladium catalysed annulation of internal alkynes[118]. Others have shown the palladium catalysed cyclizations to be valuable synthetic tools for the synthesis of a wide variety of heterocycles using vinylic compounds, terminal alkynes, allenes and other substrates.

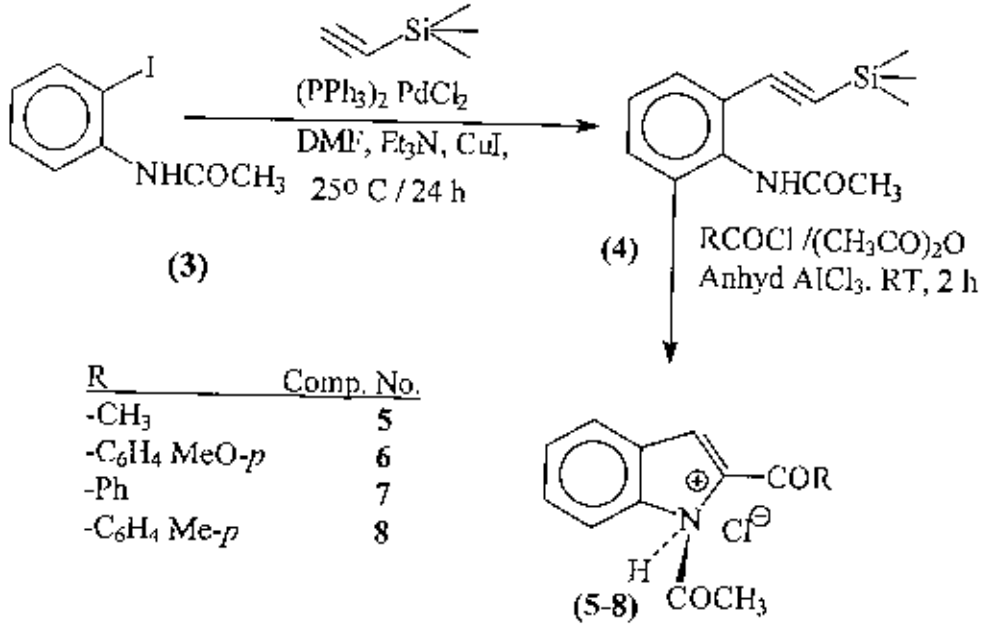
In recent years, our research group has developed methods for the synthesis of various benzofused heterocyclic compounds e.g. benzofurans[120] isoindolinones and isoquinolinone[122] by palladium catalysed reactions with terminal alkynes and acid chloride.

Due to the natural occurrence and biological importance of the indole derivatives and lack of convenient palladium catalysed procedures for their synthesis, we were interested in developing a general and facile method for the synthesis of indole derivatives. We became interested in the synthesis of indole derivatives through combined palladium catalysed and Friedel-Crafts reactions.

1.2.2 Results and Discussion:

Here we demonstrate a novel approach where a regio-selective synthesis of 2-substituted indoles (5-8) through palladium catalysed reaction followed by Friedel-Crafts acylation and simulataneous cyclization. 2-Iodo acetanilide 3 in DMF underwent facile reaction with trimethylsilyl acetylene 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 24 hours giving 2-(trimethylsilyl)ethynyl acetanilide 4 with 63-65% yield. 2-(Trimethylsilyl)ethynyl acetanilide 4 was then subjected to Friedel-Crafts reaction with acid chloride (1 mol equiv.) or acetic anhydride to afford the 2- substituted indoles **5-8** in good yield, as shown in the scheme: 1.



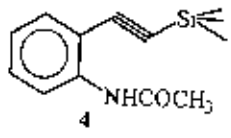
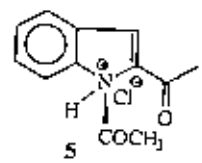
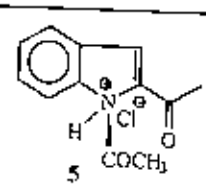
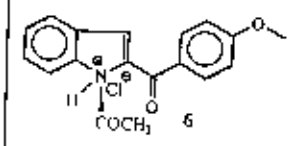
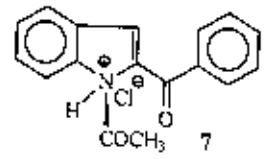
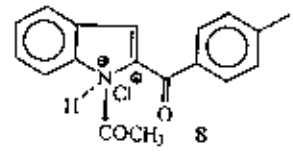
R	Comp. No.
$-CH_3$	**5**
$-C_6H_4$ MeO-*p*	**6**
-Ph	**7**
$-C_6H_4$ Me-*p*	**8**

(5-8)

Scheme-1

An ice cold solution of 2-(trimethylsilylethynyl)acetanilide **4**, anhydrous aluminium chloride (3 mol equiv.) and acid chloride (1 mol equiv.) or acetic anhydride (1mol equiv.) in tetrachloroethane, was stirred at 0-25°C for 2 h to yield 2-acyl indole derivatives **5-8**. In this case yield % is 56-65 for acid chloride and 50-55 for acetic anhydride.

Table-1: Synthesis of *N*-acetyl-2-acyl(aroyl) indolium chloride through Friedel-Crafts acylation reaction.

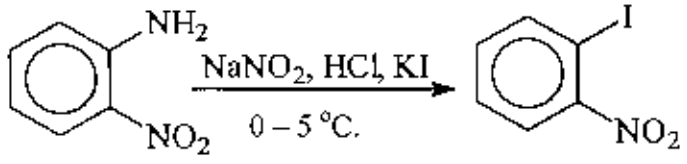
Entry	 4	RCOCl	Compound **5-8**	Yield[a] %
1	4	CH_3COCl	 5	60
2	4	$(CH_3CO)_2O$	 5	55
3	4	CH_3O–C$_6$H$_4$–COCl	 6	61
4	4	C$_6$H$_5$–COCl	 7	60
5	4	CH_3–C$_6$H$_4$–COCl	 8	65

[a]Yield % was calculated on the basis of compound 4.

1.2.2 A Staring materials:

Synthesis of 2-iodinitrobenzene 1:

2-Iodonitrobenzene **1** have been used as staring materials because of their easy availability from 2-nitroaniline. Diazotization of 2– nitroaniline followed by Sandmeyer Iodination with potassium iodide afforded 2-iodonitrobenzene 1 as shown in the scheme-2.



Scheme -2 **1**

The compound was yellow amorphous solid, yield 80.7%, mp 48-49°C. R_f value 0.83 (EA : PF = 1:4).

The product was characterized by its IR, UV, ^{1}H NMR, UV spectroscopy.

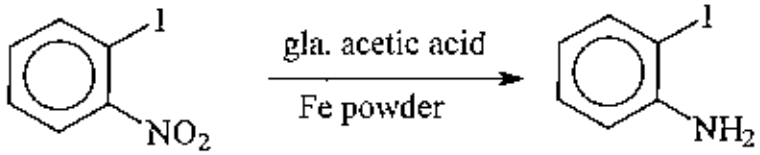
In the **IR spectrum** (Fig-1) of the compound bands at 1581.5 and 1517.9 cm^{-1} was observed due to the benzene υ_{c-c} stretching and bands at 1330 and 1296 cm^{-1} due to υ_{N-O} streaching.

In the **^{1}H NMR spectrum** (Fig 2, 3) of the compound, the peaks were found at δ 8.04 (1H. d, J= 8 Hz, δ 7.85 (1H, d), δ 7.49 (1H, t), δ 7.27 (1H, t).

In the **UV spectrum** (Fig. 4). The λ_{max} value was found in the range of 312.2 and 321.8 nm.

Synthesis of 2-Iodoaniline-2:

2-Iodonitrobenzene was treated with glacial acetic acid in presence of iron powder to afford the 2-iodoaniline. The compound 2 was characterized by their satisfactory spectroscopic (IR, ^{1}HNMR, IR) data.



1 2

Scheme -3

The compound was found as a transparent crystalline solid, yield 68%, mp 59-60°C. R_f value 0.51 (hexane 100%).

The product was characterized by its IR, UV, ^{1}H NMR spectroscopy.

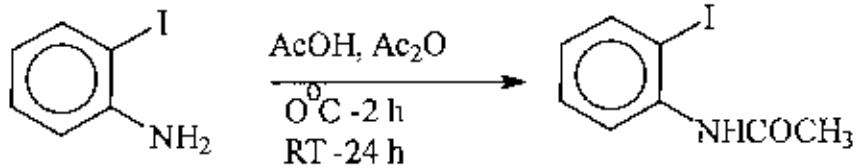
In the **IR spectrum** (Fig-5) of the compound, a band at 3392, 3288 cm^{-1} indicated the presence of NH_2.

In the **^{1}H NMR spectrum** (Fig. 6,7) of the compound, the peaks were found at δ 7.63 (1H, d, J= 8Hz, Ar-H), δ 7.13 (1H, t, J= 8 Hz, Ar-H), δ 6.74 (1H, d, J= 8 Hz, Ar-H), δ 6.47 (1H, t, J= 8 Hz, Ar-H), The broad singlet was found at the δ value of 4.00 for NH_2.

In the **UV spectrum** (Fig. 8) , the peaks were found in the range of 296.00, 238, 219 and 212 nm.

(iii) Synthesis of 2-iodoacetanilide 3

2-iodoaniline **2** was stirred with acetic acid and acetic anhydride at 0°C for two hours and stirred 24 hours at room temperature for the formation of 2-indoacetanilide.



2 3

Scheme -4

The compound was transparent crystalline solid, yield. 72%, mp (108-109°C).

R_f= 0.36 (pet. ether 100%).

The product was characterized by its IR, UV, ^{1}H NMR spectroscopy.

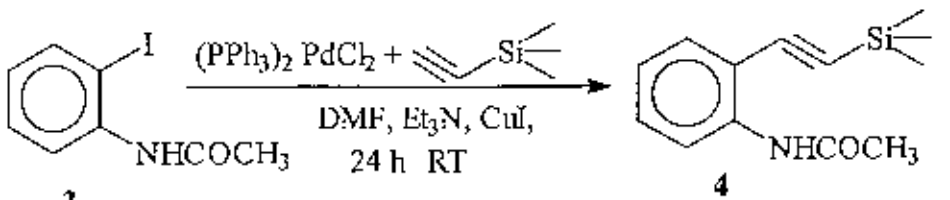
In the **IR spectrum** of the compound (Fig.9) the absorption band found at 3273 cm^{-1} due to υ_{NH} of the anilide group, where as a band at 1660.6 cm^{-1} was due to υ_{co} band of the anilide.

The **^{1}HNMR spectrum** (Fig. 10, 11) of the compound showed, the peaks at δ 8.15 (1H, S), δ 7.75 (1H,d, J=8 Hz), due to the aromatic protons. The chemical shift position at δ 7.42 was found in the form of broad singlet due to the NH proton.

In the **UV spectrum** (Fig. 12) the peak was found in the range of 224.40 nm.

1.2.2.B (i) Synthesis of 2-(Trimethylsilylethynyl) acetanilide 4:

2- (Trimethysilylethynyl) acetanilide 4 was prepared by the palladium catalysed reaction of 2-iodoacetanilide with trimethylsilylacetylene. The crude product on fractionation over column chromatography using pet ether: chloroform (3.1) as solvent system gave pure product.



3 4

Scheme - 5

The compound was transparent, crystalline solid, yield 63-65%, mp 94°C, R_f value 0.44 (PE:$CHCl_3$= 3:1). This componnd was characterized spectoscopically.

In the IR spectrum (KBr) (Fig.13) of the compound, the band in the range of 3327 cm^{-1} indicated the presence of υ_{NH} . The absorption band at 2158 cm^{-1} due to $\upsilon_{c\equiv c}$ where as a band at 1690 cm^{-1} for the characteristic of υ_{co} stretching was observed.

In the **^{1}HNMR spectrum** (400 MHz, $CDCl_3$) (Fig. 14) a singlet at δ 0.30 corresponded to $SiMe_3$ (9H, S). The peak at δ 2.21 was assigned to CH_3 (3H, S). A

broad singlet at δ 7.95-8.03 for NH Proton was observed. The rest of the peaks were found at δ 7.01, 7.32, 7.41, 8.39 for Ar-H which were multiplets.

In the **^{13}C NMR spectra** (100 MHz, $CDCl_3$), δ 0.1 for CH_3 of $SiMe_3$ and 24.7 for CH_3 of $COCH_3$. 168 for CO were observed. The singlet at 100.2 & 102.2 indicated C of C≡C. The rest were 111.5, 118.9, 123.1, 129.9, 131.4, 139.5 for aromatic carbons.

In the **UV Spectrum** (EtOH), (Fig-16) the λ_{max} value were found in the range of 296.2, 250.8, 207.8 nm.

1.2.2. B. (II) Mechanism of palladium-catalysed reactions of 2-iodo-acetanillide 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 - 6. It was observed that the presence of palladium catalyst and base were very essential for the success of the 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_3 N and terminal alkynes took place.

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

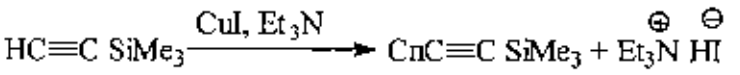
In the step-II, the formation of Pd(0) from the interaction of bis-(triphenyl phosphine) palladium (II) cholorde and cuprous acetylide was proposed by Hagihara[113].

In step-III, the catalytic cycle 2-iodoacetanilide **4** oxidatively added to bis-(triphenylphosphine) palladium (0) to generate a 2- anilide palladium (II) complex A. Then the terminal alkyne could be co-ordinated with palladium (II) complex A (Heck reaction) giving rise to co-ordinated complex B.

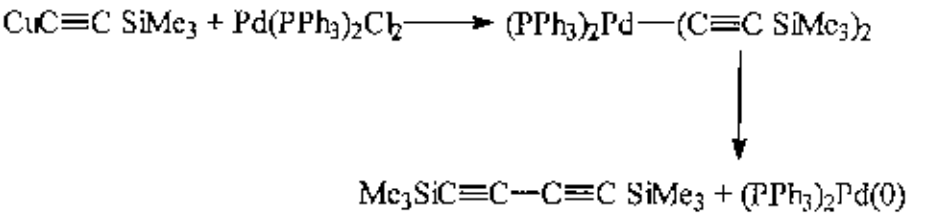
The alknyl palladium complex B generated the original bis (triphenyl phosphine) palladium (0) through the reductive elimination of the substituted products to afford the 2-(trimethylsilylethynyl) acetanilide **4**. *Bis*(triphenyl phosphine) palladium (0) could then continue the catalytic cycle.

The mechanism of the reaction is given below.

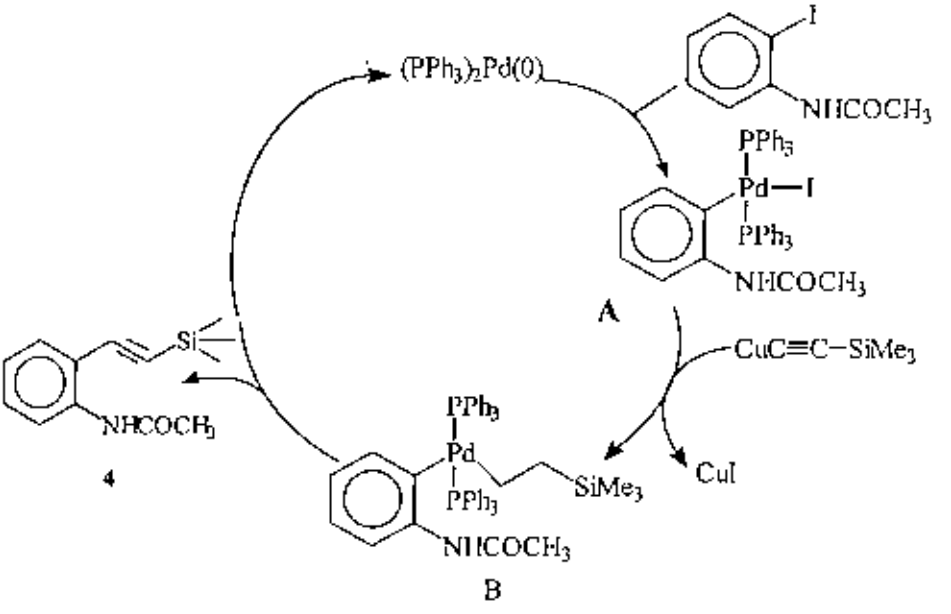
Step-I



Step-II



Step-III

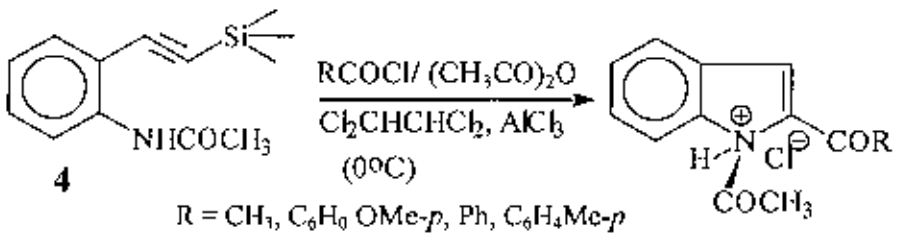


(Scheme- 6)

1.2.2.C (i) Friedel-Crafts acylation reaction:

1.2.2.C (i) Friedel-Crafts acylation reaction:

2-(Trimethylsilylethynyl)acetanilide **4** was subjected to react with acetyl chloride / acetic anhydride/ in presence of tetrachloroethane and anhydrous aluminium chloride at 0°C temperature. The crude product **(5-8)** was purified by chromatography on silica gel using Hexane: Chloroform as a solvent system.



4

R = CH_3, C_6H_0 OMe-*p*, Ph, C_6H_4Me-*p*

Scheme - 7

1.2.2.C. (II) Characterization of the products.

2-Acetyl-*N*-acetyl indolium chloride **5** was obtained form acetyl chloride/acetic anhydride.

This compound **5** was colourless crystalline solid with mp (84-86°C) and R_f value = 0.26 (PE: $CHCl_3$ 2:1).

In the **IR spectrum** (KBr), (Fig.17) of the compound **5**, the band in the range at 3221.9 cm^{-1} due to NH stretching vibration, the baud at 1684 cm^{-1} for $\upsilon_{C=O}$ and 1652 cm^{-1} for $\upsilon_{amide\ CO}$ were observed.

In the **^{1}HNMR spectrum** (400 MHz, $CDCl_3$), (fig-18) a singlet at δ 2.2 corresponded to $COCH_3$ (S.3H). The peak at δ 2.18 due to the three protons of $HNCOCH_3$, a singlet at 6.1 due to the peaks of =C-H and a broad peak at 11.06 for NH proton (bs, 1H) were obtained.

In the **^{13}C NMR spectrum** (100 MHz, $CDCl_3$), (fig-19) the peaks at δ 194 and. 185.3 for the carbon of CO and δ 28.4 & δ 23.15 for carbon of $-CH_3$ group were observed. The rest of the peaks 168.89, 140.15, 133.83, 129.06, 122.41, 122.46, 121.0, 98.02 were obtained for aromatic carbon and double bonded carbons.

In the **UV spectrum** (EtOH) : (Fig.20) of the compound λ_{max} value were found in the range of 334, 305.4, 259.8, 213 and 207.8 nm.

***N*-acetyl-2anisoyl indolium chloride 6**

The compound 6 was white crystalline solid, mp 113°C and R_f value. 0.30 ($CHCl_3$: PE = 2.1)

In the **IR spectrum** (KBr), (Fig21) the stretching vibration of NH at 3327.9 cm^{-1}. and the absorption band at 1683 cm^{-1} due to $\upsilon_{amide\ CO}$ and 1610 cm^{-1} due to υ_{CO} were found.

In the **^{1}H NMR spectrum** (400 MHz, $CDCl_3$), (Fig.22,23) a singlet at δ 2.22 was for $COCH_3$ and another singlet at δ 3.88 due to OCH_3. A peak at δ 6.7 indicated vinylic proton (S, IH, = C-H) A broad band at δ 11.04 indicated NH. The rest of the peaks at δ 6.97 (d,2H, J = 8 Hz) δ 7.12 (d, 1H,J= 8 Hz) δ 7.51 (t, 1H, J= 8Hz), δ 7.77 (d. lH, J = 8Hz) δ 7.91 (d, 2d, J = 8 Hz) δ 8.62 (d, 1H, J= 8Hz) peaks due to aromatic protons were observed.

In the **^{13}C NMR spectrum** (100 MHz, $CDCl_3$) (Fig. 24), the chemical shift position for the carbons of CO at δ 193.46 and δ 180 and C-of CH_3 at 55.53 and 25.48 were observed. The rest of the peaks at δ 168.93, 63.41, 139.83, 133.6, 131.17, 128.995, 126.137, 123.38, 121.46, 114.09, 94.00, 77.34. 76.70 were for aromatic carbons and double bonded carbons.

In the UV spectrum (EtOH) : (Fig. 25) the λ_{max} valne were found in the range of 380.80, 360.6, 238.0 207.80 nm.

N-acetyl-2-benzoyl indolium chloride **7:**

The compound 7 was yellow crystalline solid, mp. 64°C, R_f value 0.17 (PE: $CHCl_3$= 4:1).

In the **IR spectrum** (KBr) (fig. 26), the stretching vibrations were found in the range of 1691.5 and 1606 cm^{-1} for $\upsilon_{C=O}$ and 3320 cm^{-1} for υ_{NH}.

In the **^{1}H NMR spectrum** (400 MHz, $CDCl_3$), (Fig. 27, 28) , a singlet at δ 2.2 due to the proton of $COCH_3$ and another singlet at δ 6.79 due to the proton of =C-H

were observed. Aromatic protons peaks at δ 7.13 (t, 1H), 7.5(m. 4H), 7.81 (d. 1H), 7.94(d, 2H), 8.64 (d, 1H) and a broad singlet 11.8 due NH proton were found.

In the **^{13}C NMR spectrum** (100 MHz, $CDCl_3$)(Fig. 29), the peaks of carbon for CO groups were found in range of δ 194.71 and 179.53. The peaks at 25.49 cm^{-1} was due to CH_3 carbon. The peaks for double bonded carbon and aromatic carbon were in the range of δ value 140.11, 133.99, 133.84, 132.58, 129.15, 128.82, 126.91, 123.13, 122.76, 121.51, 94.99 77.34, 77.03, 76.71.

In the **UV spectrum** (EtOH) : Fig.30), the λ_{max} value were found in the range of 356.6, 236.6, 205.8 nm.

d) *N*-acetyl-2-tolyl indolium chloride **8**.

The compound **8** was white amorphous solid, mp 82-83°C. and R_f value 0.14 with $CHCl_3$: hexane (2:1).

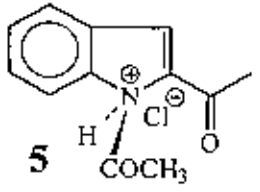
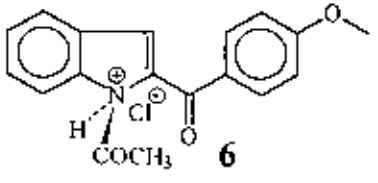
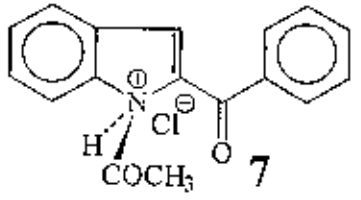
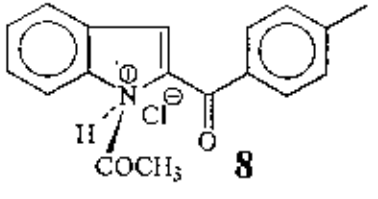
In the **IR spectrum** (KBr) (Fig-31), a band at 3325 cm^{-1} due to υ_{NH} and a band 1687 cm^{-1} due to υ_{CO} and another band 1569 cm^{-1} for υ_{CO} of amide were observed.

In the **^{1}H NMR spectrum** (400 MHz, $CDCl_3$) (Fig- 32, 33), a singlet at δ 2.21 (S, 3H) was due to the protons of CH_3 groups and another singlet at δ 2.41 (s, 3H) due to the proton of $COCH_3$ groups and the peak at δ 6.8 (s, 1H) due to the proton of vinylic proton were found. Chemical shift positions at δ 7.11 (t, 1H), 7.27 (d, 2H), 7.49 (t, 1H), 7.78 (d, 1H), 7.83 (d, 2H), 8.63 (d, 1H) due to aromatic carbon and broad singlet at δ 11.07 (bs, 1H) were observed.

In the **^{13}C NMR spectrum** (100 MHz, $CDCl_3$)(Fig-34), showed the chemical shift position of CO groups in the range of δ 194.21 and δ 179.86. The peaks at 168.89, 143.45, 139.97, 133.74, 130.97, 129.56, 129.04, 126.90, 122.4, 121.4, 77.03 were found due to aromatic and double bonded carbon. The chemical shift position of $-CH_3$ group were found in the range of δ 25.43 and 21 62.

In the **UV spectrum** (EtOH) (Fig 35) the λ_{max} values were found in the range of 361, 256.6 and 206 nm.

Table 2: Comparison of spectra of indole derivatives.

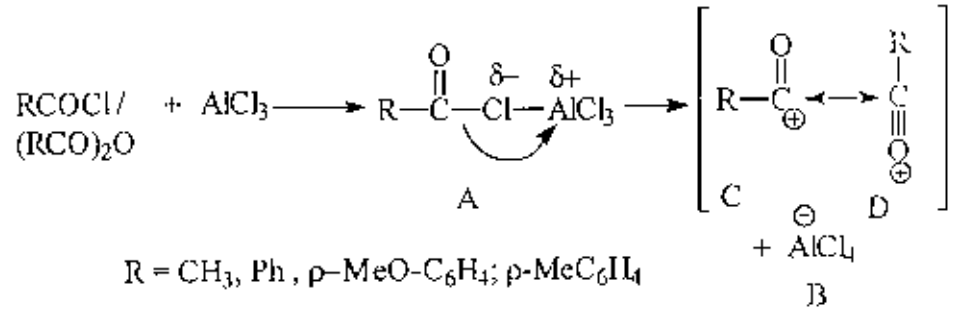
Compound	IR (cm-1)	1H NMR (δ)	13C NMR (δ)	UV nm
 **5**	3221.9 (υ_{NH}) 1684 (υ_{CO}) 1652 (υ_{CO})	2.18 (S, 3H, $COCH_3$) 2.2 (S, 3H,$NCOCH_3$) 6.1 (S, 1H,=C-H) 11.6 (br. S, 1H, NH)	194 (C of $N\underline{C}OCH_3$) 185 (C of $\underline{C}OCH_3$) 25.4 (C of $NCO\underline{C}H_3$) 23.15 (C of $CO\underline{C}H_3$)	207.8 238.8 334.0
 **6**	3327.9 (υ_{NH}) 1683 (υ_{CO}) 1610 (υ_{CO})	2.22 (S, 3H,$COCH_3$) 3.88 (S, 3H,-O-CH3) 6.7 (S, 1H,=C-H) 11.04 (br. S, 1H, NH)	193.4 (C of $N\underline{C}OCH_3$) 180 (C of $\underline{C}OPh$) 25.48 (C of $\underline{C}H3$)	207.8 238.0 360.6
 **7**	3320.0 (υ_{NH}) 1691(υ_{CO}) 1606 (υ_{CO})	2.2(S, 3H,$COCH_3$) 6.79 (S, 1H,=C-H) 11.08 (br. S. 1H,NH)	194.71 (C of $N\underline{C}OCH_3$) 179.53 (C of N $\underline{C}OPh$) 25.49 (C of $\underline{C}H_3$)	205.8 236.0 356.6
 **8**	3325.0 (υ_{NH}) 1687(υ_{CO}) 1569 (υ_{CO})	2.21(S, 3H,$COCH_3$) 2.41(S, 3H,CH_3) 7(S, 1H,=CH) 11.04 (br. S, 1H,NH)	194.2 (CO of $\underline{C}O\underline{C}H_3$) 179.86 (CO of $\underline{C}OPh$) 25.43 (CH_3 of $CO\underline{C}H_3$) 23.15 (CH_3 of $Ph\underline{C}H_3$)	216.0 256.0 361.0

1.2.2.C (iii) Mechanism of Friedel-Crafts acylation reactions

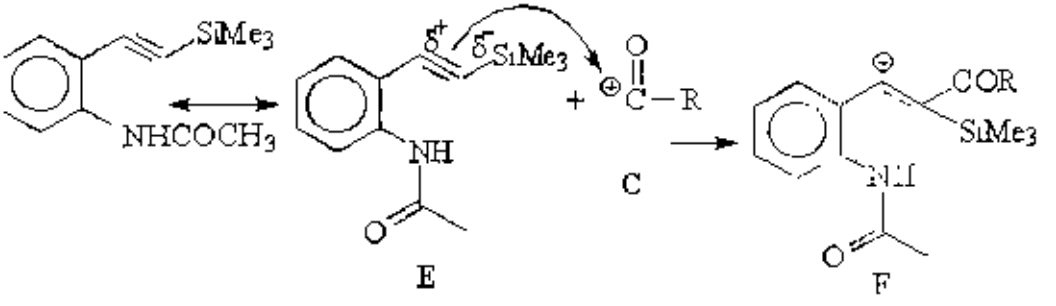
The acylation of 2-(trimethylsilyl)ethylacetanilide 4 was carried out by an acid chloride or acetic anhydride in the presence of a Lewis acid (Anhyd. $AlCl_3$). The most likely mechanism for Friedel-Crafts acylation was shown in the scheme-7.

In the first step Lewis acid catalysed method, an acylium carbocation (C) was formed from complex (A). In the step II trimethylsilyl group acted as an electron donor and partial negative charge was developed on the terminal triple bounded carbon. The generated anion complex (E) was attacked by the acylium ion (C) to form the complex (F) which was a carbocation. In step III the carbonium (F) was attacked by the anion $AlCl_4^-$ (B), furnished the rearrangement and the departure of $SiMe_3$ and finally the formation of indole ring.

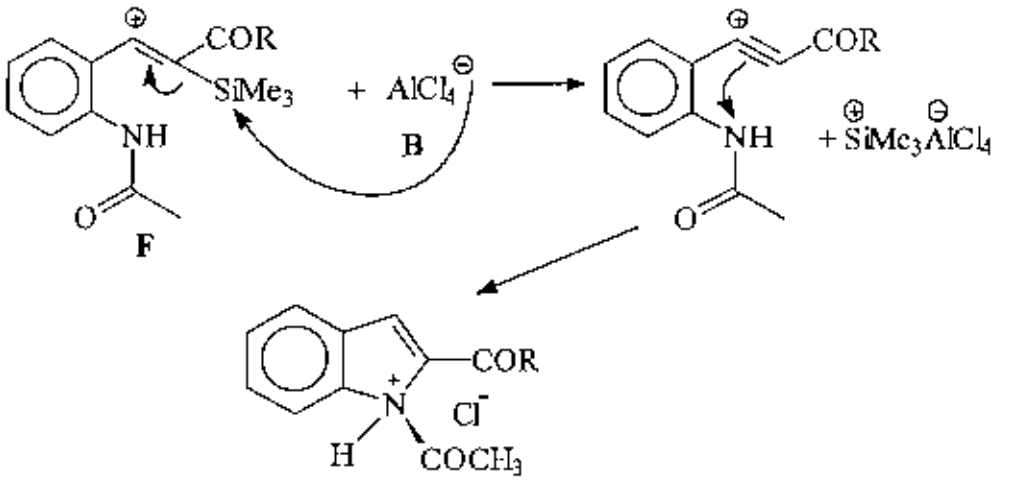
Step-1:



Step- 2:



Step-3:



(Scheme- 7)

1.2.2.D. Conclusion:

For the first time, we have developed a convenient, general and facile method for the synthesis of *N*-acyl-2-Acyl (aroyl) indolium chloride from the reaction of 2-iodoacetanilide with trimethylsilylcetylene by a $(Ph_3P)_2PdCl_2$–Et_3N–CuI system, followed by Friedel-Crafts reaction. The most important features of the synthesis were that readily available inexpensive starting materials were used under relatively mild reaction conditions.

Also, no toxic and hazardous compounds were produced by this procedure. This reaction was highly regioselective in case of palladium-catalysed and Friedel-Crafts reactions. Through this methodology biologically active indole derivatives may easily be synthesized.

1.2.2.E. Experimental

(i) 2-iodonitrobenzene-**1**

5.0 g (0.036 mol) of 2-nitroaniline was stirred with 7.5 gm (4.1 ml) of conc. H_2SO_4 and 40 ml of water for 1 hour. The mixture was cooled in a freezing point (0-5°C) and was stirred mechanically. A solution of 2.5 gm (0.036 mol) of sodium nitrite in 7.5 ml of water was added to the mixture. The filtrate was poured into an ice cold solution of 10 gm (0.06 mol) of potassium iodide in 30 ml water with stirring. The precipitate formed was collected by filtration under reduced pressure and washed with water and finally dried, recystallized from ethanol.

The titled compound 2-iodonitrobenzene 1 (7.25 g, 80%) was found as yellow solid, m.p. 48-49°C. (lit 49-51°C) R_f value = 0.83 (EA: PE = 1:4).

IR (KBr): λ_{max} 1581.5, 1517.9, 1330, 1296, 1020, 779, and 723 cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.04 (1H, d, J = 8 Hz), δ 7.85 (1H, d, J = 8 Hz), δ 7.49 (1H, t, J = 8 Hz). δ 7.27 (1H, t, J = 8 Hz).

UV(EtOH) λ_{max} : 313.2, 231.80 nm.

(ii) 2-iodoaniline **2**

Into a round bottom flask equipped with a reflux condenser, 5 gm (0.02 mol) of 2-iodonitrobenzene and 3.92 gm (0.07) mol of granulated iron was placed. 8.47 gm (8 ml) of glacial acetic acid 48 ml (1.84 mol) ethanol were then poured one by one into the mixture and was shaken the contents of the flask steadily. Finally the mixture was refluxed for 3 hours and diluted with 100 ml of water. Then the mixture was neutralized with dil. NaOH (aq) solution. The product was separated by steam distillation and finally extracted with $CHCl_3$. The organic layer was washed with water, dried over sodium sulfate and dried.

The compound was purified by column chromatography with silica gel using pet ether only. The titled compound **2** (3.03 gm, 68%) was found as a solid, m. p. R_f value 0.51 (cyclo hexane 100%).

IR (KBr): ν_{max} 3392.6, 3288.4, 3184.3, 1622, 1473.5, 1438, 1006.8, 748.3, 644.2 cm^{-1}.

^{1}H NMR (400 MHz. $CDCl_3$): δ 7.63 (1H, d, J = 8 Hz, Ar-H), 7.13 (1H, t, J = 0.8 Hz, Ar-H), 6.74 (1H, d, J = 8 Hz, Ar-H), 6.47 (1H, t, J = 8 Hz, Ar-H). 4.00 (1H, br. s, NH).

UV (EtOH) : λ_{max} 296.00, 238, 219 and 212 nm.

(iii) 2-Iodoacetanilide **3**

2-Iodoaniline **2** (2.2g, 0.01 mole) was stirred with acetic acid (5 ml, 0.08 mole) and acetic anhydride (1.02 gm, 0.01 mol) at 0°C. After two hours stirring at 0°C the reaction mixture was allowed to react at room temperature and stirred over night. The reaction mixture was diluted with water and extracted with chloroform (3×50m), washed with distilled water, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude mass was purified by chromatography on a column of silica gel with eluant pet ether: chloroform, to obtain the titled compound **3** (1.88 gm, 72%) as a white crystalline solid with mp 108 – 109°C , R_f value 0.36 (pet ether 100%).

IR (KBr): 3273.0, 1660.6, 1573.8, 1529.4, 1463.9, 1433.0, 1411.8, 1292.2, 1253.6, 1014.5, 750.3, 663.5 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (1H, s, Ar-H), δ 7.75 (1H, d, J = 8 Hz, Ar-H), 7.31 (1H, t, J = 8 Hz, Ar-H), 6.82 (1H, t, J = 8 Hz) 7.42 (1H. br. s, NH).

UV (EtOH) : λ_{max} 224.40 nm.

(iv) 3-Trimethylsilylethynyl acetanilide **4**

Bis-(triphenyl phosphine) palladium (II) chloride. (47.074 mg, 1.916 m mol), copper II iodide (29.19, 1.9 mol), triethylamine (774.064 mg, 1.916m mol) were added to a solution of 2-iodoacetanilide (500 mg, 1.916 m mol) in DMF (5 ml).

The mixture was stirred for 1 hour under a nitrogen atmosphere at room temperature. Then trimethylsilyl acetylene (375.53 mg, 1.916m mol) was added dropwise to the mixture, stirring continued for 24 hours at room temperature. 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 pet ether: Chloroform (3:1). The compound 4 (292 mg, 63-65%) was a transparent crystalline solid with mp. 94 (R_f value 0.44 PE : $CHCl_3$(2:1).

IR (KBr) ν_{max} 3327, 2158, 1695, 1672, 1576, 1516, 1444 cm^{-1}.

^{1}H NMR (400 MHzCDCl$_3$) δ 0.30 (9H, S), 2.21 (3H, S), 7.01 (1H, br. t, J = 8.0 Hz Ar–H), 7.32 (1H, td, J = 8.3, Hz), 7.41 (1H, dd, J = 8.0, Hz), 7.95 – 8.03 (1H, m), 8.39 (1H, br. d, J = 8.3 Hz).

^{13}CNMR (100 MHz, $CDCl_3$) δ = 0.10(q), 24.7(q), 100.2(s), 102.2(s), 111.5(s), 118.9(d), 123.1(d). 129.9(d), 131.4(d), 139.5(s), 168.0(s).

% of C (67.09), H(7.43), N (6.03).

UV (EtOH) λ_{max} 296.2, 250.8, 207.4 nm.

Anal. Cald. for C13H17S1NO: C,67.48; H, 7.40; N, 6.05. Found: C, 67.09; H, 7.43; N, 6.03.

(v) a. *N*-acetyl-2- acetyl indolium chloride **5**

To the compound 2-trimethylsilylethynyl) acetanilide 4 (200 mg, 0.866m, mol) dissolved in 1,1,2,2-tetrachloroethane (5 ml) anhydrous aluminium chloride

(346.75 mg, 2.59 ml mol) was added at 0°C. Then acetyl chloride (67.9 mg, 0.866 m mol) was added to the cold solution dropwise. The mixture was allowed to warm up to room temperature and stirred further at room temperature (25°C) for two hours. The reaction mixture poured into cold hydrochloric acid solution [5 ml. 12(N) HCl in 250 ml H_2O]. The organic layer was extracted with chloroform (3×50 ml). The combined organic layer was washed with water, sodium bicarbonate solution (10%, 2×50 ml) and water again. It was dried over anhydrous sodium sulphate. After removal of solvent the product was purified by colnmn chromatography (Hexane: Chloroform = 2:1) over silica gel and then crystallized from ethanol. The acylation product **5** (20 mg, 60.00%) was found as colourless crystalline solid with mp (84 – 86°C), R_f value = 0.26 PE : $CHCl_3$(2:1).

IR (KBr): ν_{max} 3221, 1684, 1652. 1608, 1576, 1560, 1502, 1130, cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 11.06 (bs, 1H, NH) 8.59 (d, 1H, J = 8 Hz, Ar – H), 7.46(d, 1H, J = 8 Hz, Arn–H), 7.65(1, 1H, J = 8 Hz, Arn–H), 7.05 (t, 1H, J = 8 Hz, Ar-H), 6.10(s, 1H, =C–H), 2.18(s, 3H, NCO – CH_3), 2.12 (s, 3H, $COCH_3$)

^{13}CNMR (400 MHz, $CDCl_3$): 185.31 (CO), 168.89(O), 140.152. 133.83, 129.06, 122.41, 121.02, 98.02, 55.83, 25.40 (CH_3) 23.15 (CH_3).

UV (EtOH) λ_{max} 334, 305.4, 259.8, 238.4, 213.6, 207.80 nm.

b) *N*-acytyl-2- acetyl indolium chloride **5**

To an ice cold solution of 4 (200 mg, 0.866m, mol) in tetrachloroethane (5 ml) acetic anlydride (7.31, 0.86 m mol) and anhydrous aluminium chloride (346.75mg, 2.597m mol) were added. The mixture was warmed np to room temperature and stirred further for two hours.

Then the mixture was poured into ice-cold solution of dil. HCl [(25 ml 12(N) HCl in 250 ml] and the organic layer was extracted with $CHCl_3$ (3×50 ml). washed with distilled H_2O(2×30 ml), saturated $NaHCO_3$ solution (2×30 ml) and distilled water (2×30 ml) again. After drying over anhydrous Na_2SO_4 and removal of

solvent the residue was obtained. The crude mass was purified by column (Silica gel). Elution with hexane-chloroform (2:1) furnished the product **5** (110 mg, 55%) as a colonrless solid with mp. 84–86°C. R_f value 2:1 (PF : $CHCl_3$)

IR, UV, ^{1}HNMR, ^{13}CNMR spectra of this compound were identical with that of the same compound obtained from acetyl chloride.

c) *N*-acetyl-2- anisoyl indolium chloride **6**

To an ice cold solution of compound **4** (200 mg, 0.866 m mol) in tetrachlorocthane (5 ml), anisoylchloride (0.14 gm, 0.866 m. mol) and anhydrous aluminium chloride (0.35 gm, 2.59m mol) were added. After following the above procedure and workup the crude mass was obtained, which was purified by column chromatography (Silica - gel). Elution with hexane-chloroform 1:2) furnished the desired product **6** (122 mg, 60 %) as a white crystal, mp 112-113°C, R_f value (0.30 $CHCl_3$: PE = 2:1)

IR (KBr) : ν_{max} 3327.9, 1683.7, 1610, 1576.7, 1500, 14.13, 1360, 1175, 1040 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 11.04 (br. s, 1H, NH), 8.62(d, 1H, J = 0.02 Hz, Ar–H) 7.91(d, 2H, J = 0.02 Hz, Ar-H), 7.77(d, 1H, J = 0.02 Hz, Ar – H), 7.51(t, 1H, J = 0.018 Hz. Ar–H), 7.12(d, 1H, J = 0.18 Hz, Ar - H), 6.97(d, 2H, J = 0.02 Hz, ArH), 6.70(s, 1H, = C–H), 3.88(s, 3H, – OCH_3), 2.22 (s, 3H, $COCH_3$)

^{13}CNMR (400 MHz, $CDCl_3$):δ 193.46(CO), 180(CO), 168.93, 163.41, 139.83, 133.6, 131.17, 128.995, 126.137, 123.38, 122.75, 121.46, 114.09, 94.00, 77.34, 76.70, 55.53(CH_3), 25.48 (CH_3).

UV(EtOH) λ_{max} 380.80, 360.6, 238.0, 207.40 nm.

N-Acetyl-2-Benzoyl indolium chloride **7**

To an ice cold solution of compound 4 (200 mg, 0.866 m mol) in tetrachloroethane (5 ml), benzoylchloride (0.12 gm, 0.866 m. mol) and anhydrous aluminium

chloride (0.35 gm, 2.59 m mol) were added. After following the above procedure and usual workup, the crude mass was obtained and purified by column chromatography (Silica- gel). Elution with hexane-chloroform (1:2) afforded product 7 (120 mg. 60.00%) as a white crystalline solid, mp 64-65°C.

IR (KBr): ν_{max} 3320, 1691, 1606, 1560.3, 1521, 14.90, 1442.7 and 1415.7cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 11.08 (br. s, 1H, NH), 8.64 (d, 1H, J = 8 Hz, Ar–H) 7.94(d, 2H, J = 8 Hz, Ar-H), 7.81(d, 1H, J = 8 Hz, Ar – H), 7.5 (m, 4H, J = 7.2 Hz, Ar–H), 7.13(t, 1H, J = 8 Hz, Ar - H), 6.79(S, 1H, =C-H), 6.70(s, 1H, = C–H), 3.88(s, 3H, – OCH_3), 2.2 (s, 3H, CH_3).

^{13}CNMR (100 MHz, $CDCl_3$): δ 194.71(CO), 179.53(CO), 140.11, 133.99, 133.84, 133.58, 131.17, 129.15, 128.82, 126.91, 123.13, 122.76, 121.51, 94.99, 77.03, 76.71, 25.59(CH_3), 25.48 (CH_3).

UV (EtOH) λ_{max} 356.60, 236.6, 205.8 nm.

N-Actyl-2-tolyl indolium chloride **8**

To an ice cold solution of **4** (200 mg, 0.866 m mol) in tetrachloroethane (5 ml), benzoylchloride (0.12 gm, 0.866 m. mol) and anhydrous aluminium chloride (0.35 gm, 2.59 m mol) were added. Under the same reaction condition and usual workup, the crude mass was obtained and purified by column chromatography (Silica- gel). Elution with hexane-chloroform (1:2) gave the desired product **8** (130 mg, 65%) as a white amorphous solid, mp 64-65°C.

IR(KBr): ν_{max} 3325, 1687, 1569, 1508, 1446, 1423, 1365, 1190 and 756 cm^{-1}.

UV(EtOH) λ_{max} 361.4, 256.6 and 216.6 nm.

^{1}H NMR (400 MHz, $CDCl_3$) : 11.07 (br. s, 1H, NH), 8.63 (d, 1H, J = 8 Hz, Ar–H) 7.94(d, 2H, J = 8 Hz, Ar-H), 7.83(d, 2H, J = 8 Hz, Ar – H), 7.78 (d, 1H, J = 8 Hz, Ar–H), 7.49 (t, 1H, J = 7.2 Hz, Ar - H), 7.27(d, 2H, J= 7.2, Ar-H), 7.11(t, 1H, J= 8, Hz, Ar-H), 2.41(s, 3H, $COCH_3$), 2.21 (s, 3H, CH_3).

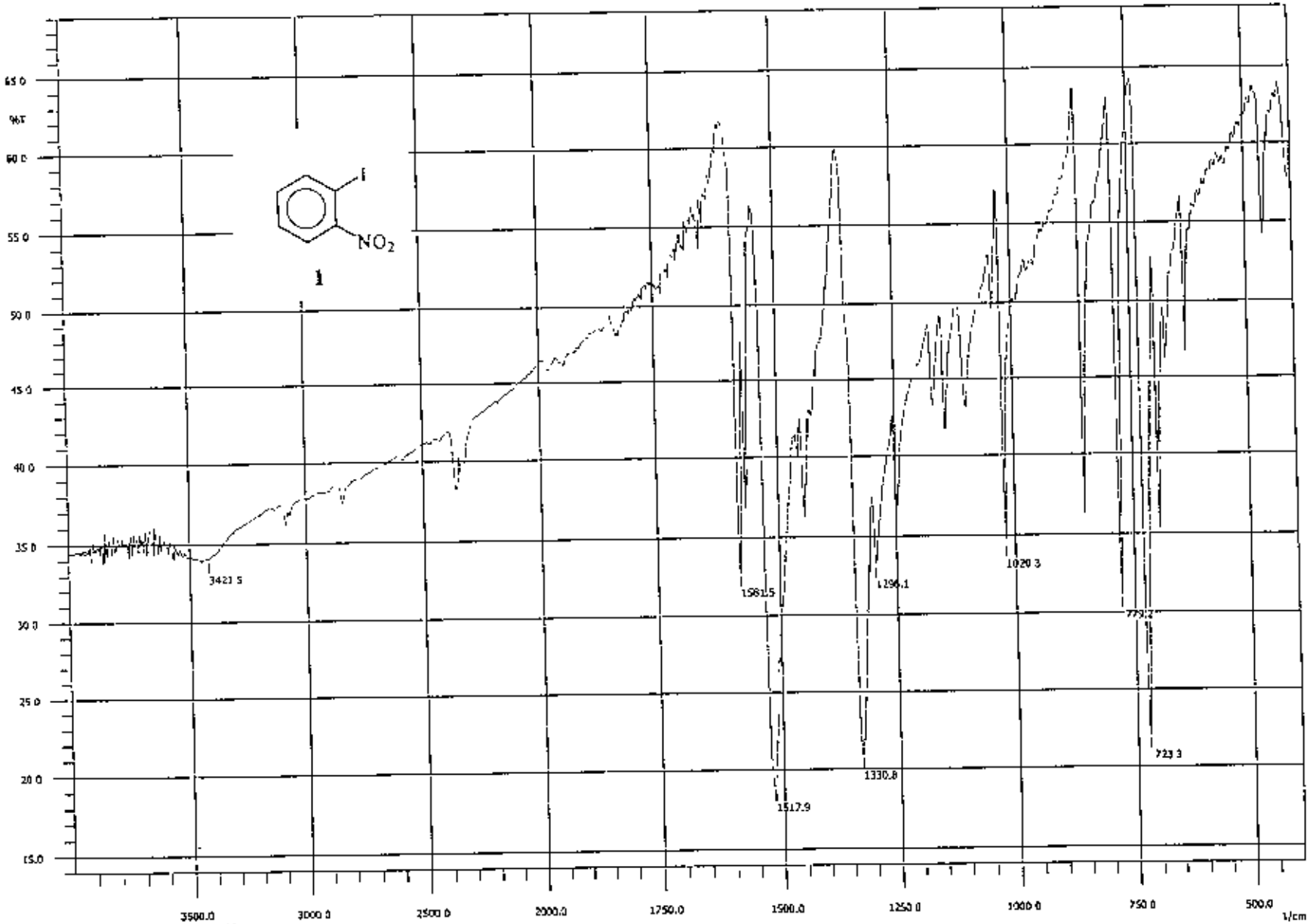
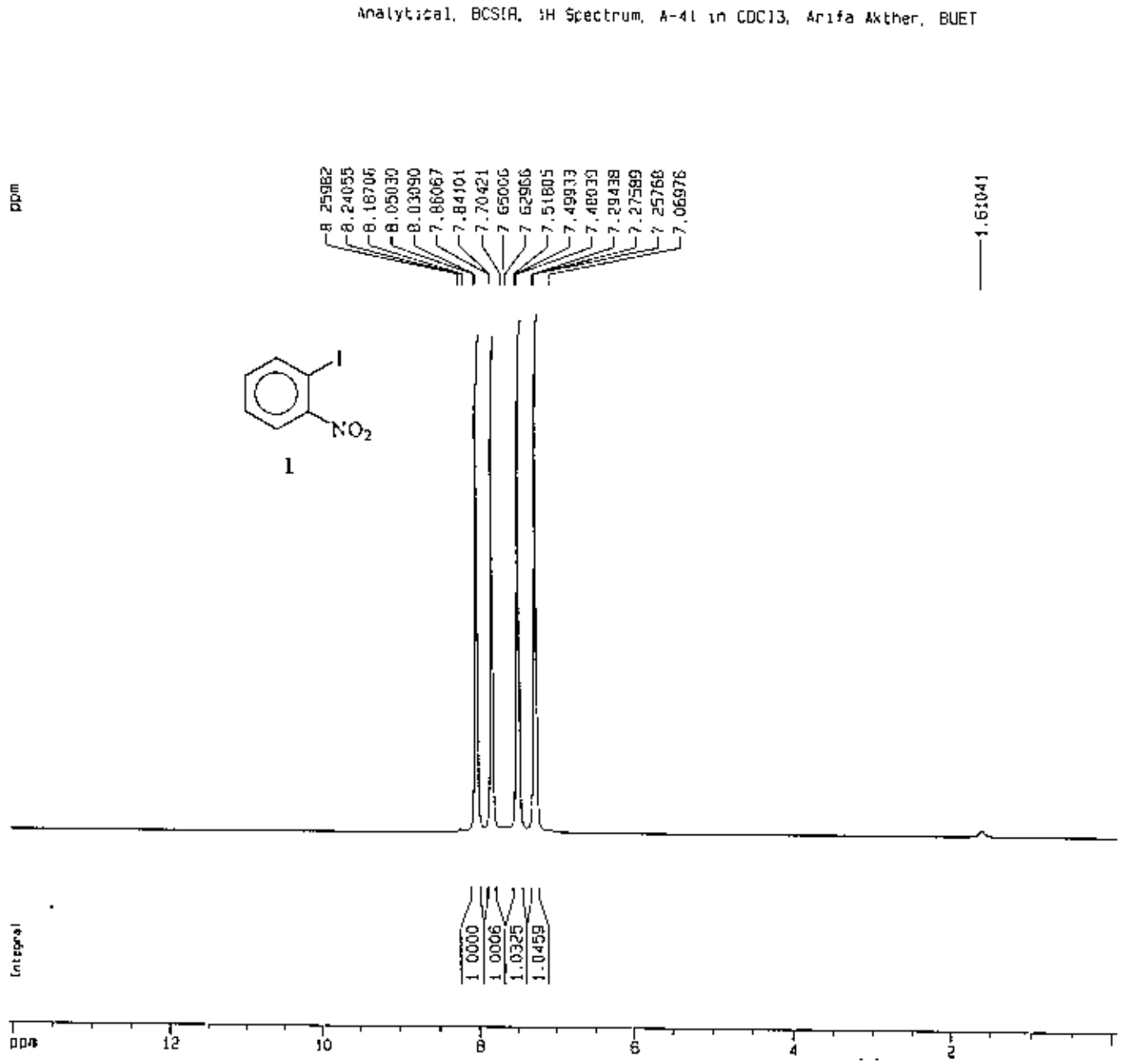


Fig 1: IR spectrum of compound 1.



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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 143 7
DW 78 000 usec
DE 6.00 usec
TE 310.0 K
D1 1 00000000 sec

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PL1 -6.00 dB
SFO1 400.1428010 MHz

F2 - Processing parameters
SI 32768
SF 400 1400024 MHz
WDW EM
SSB 0
LB 0 30 Hz
GB 0
PC 1 40

1D NMR plot parameters
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F1P 14.041 ppm
F1 5618.24 Hz
F2P -0.070 ppm
F2 -27.92 Hz
PPMCM 0 70552 ppm/cm
HZCM 282.30823 Hz/cm

Fig 2: ^{1}H NMR spectrum of compound 1.

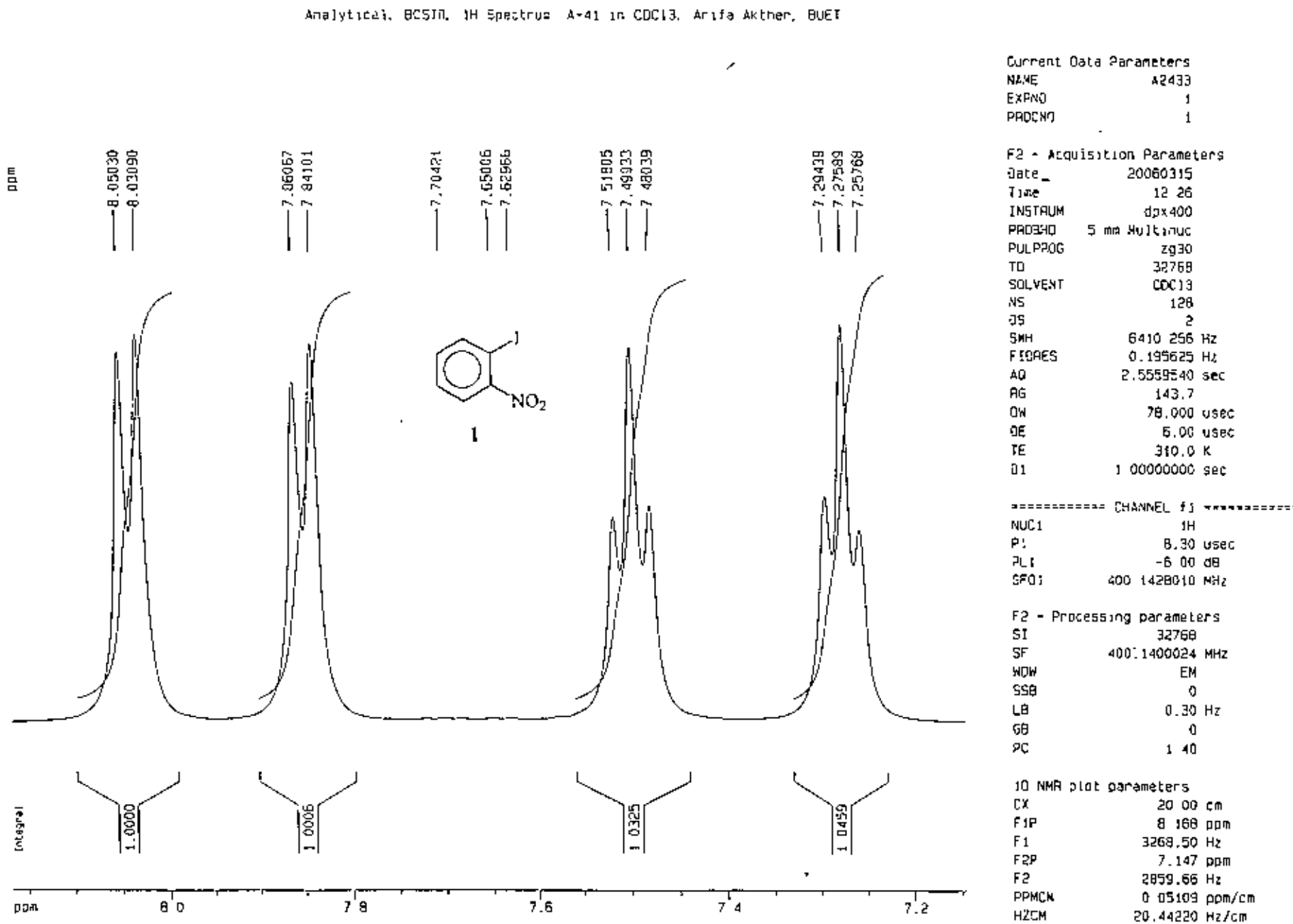
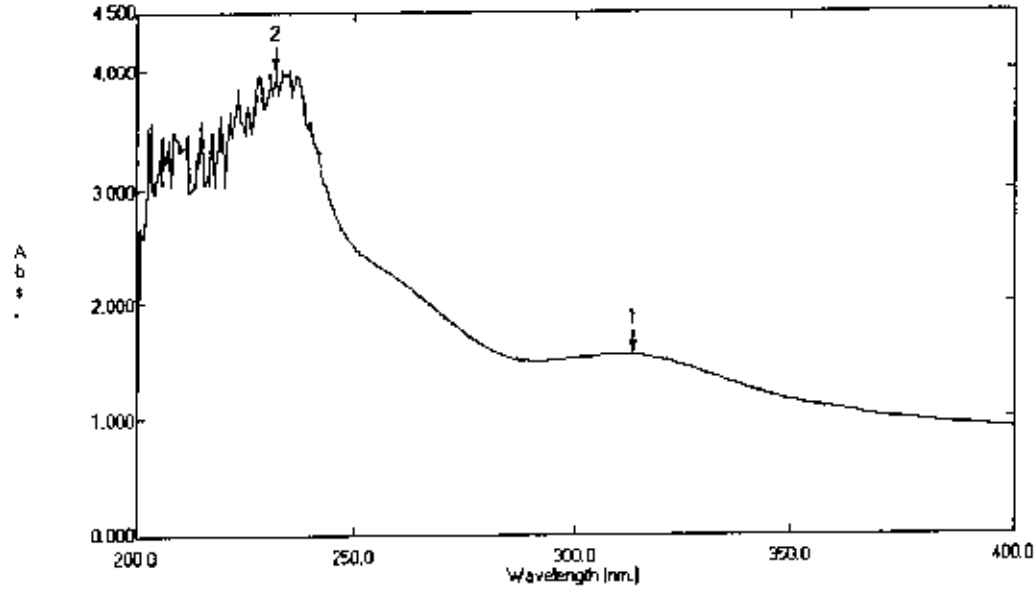


Fig 3: ^{1}H NMR spectrum of compound **1**.



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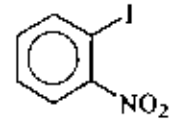
2	231.80	3.9999



I

Fig 4: UV spectrum of compound **1.**

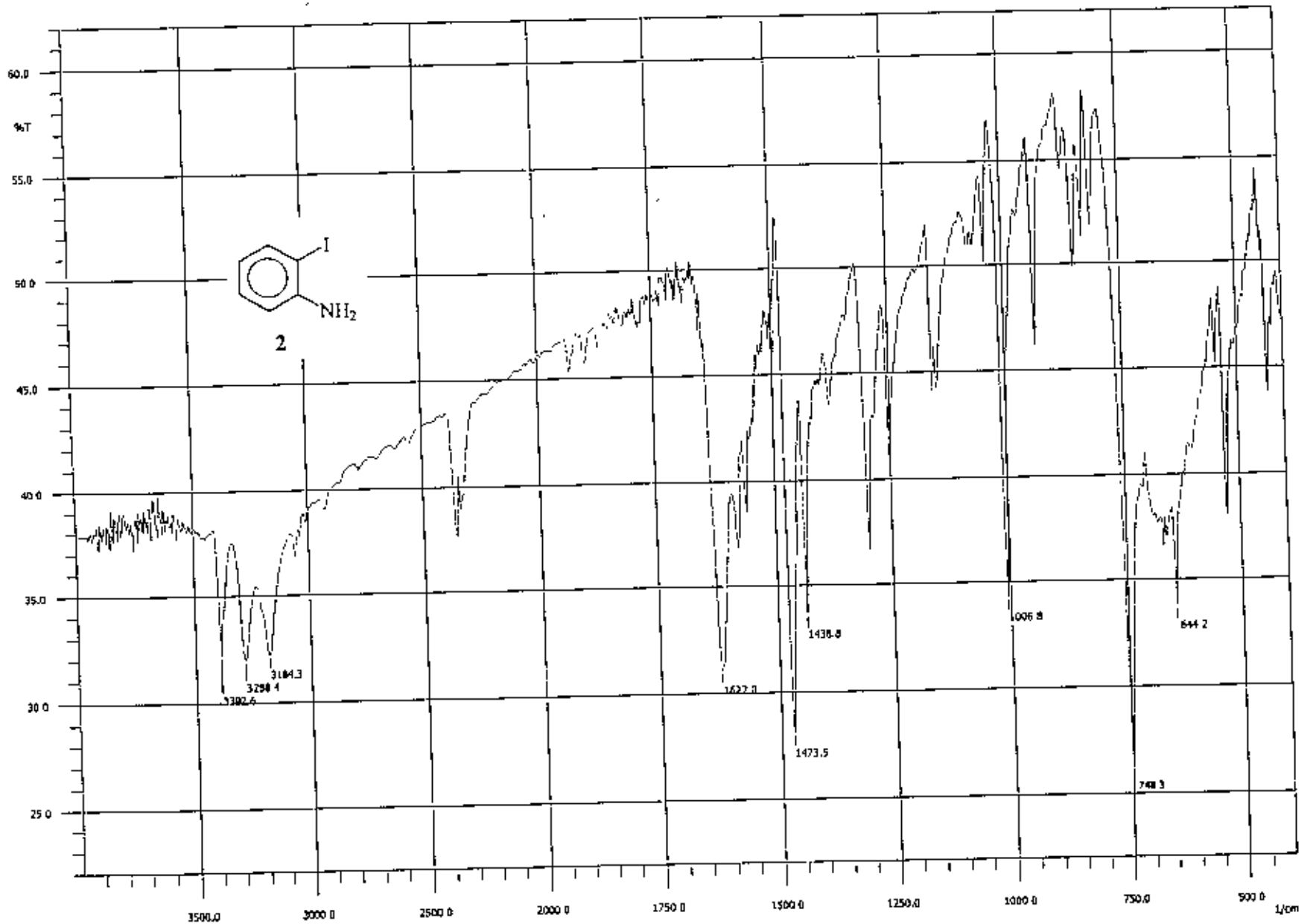


Fig 5: IR spectrum of compound **2**.

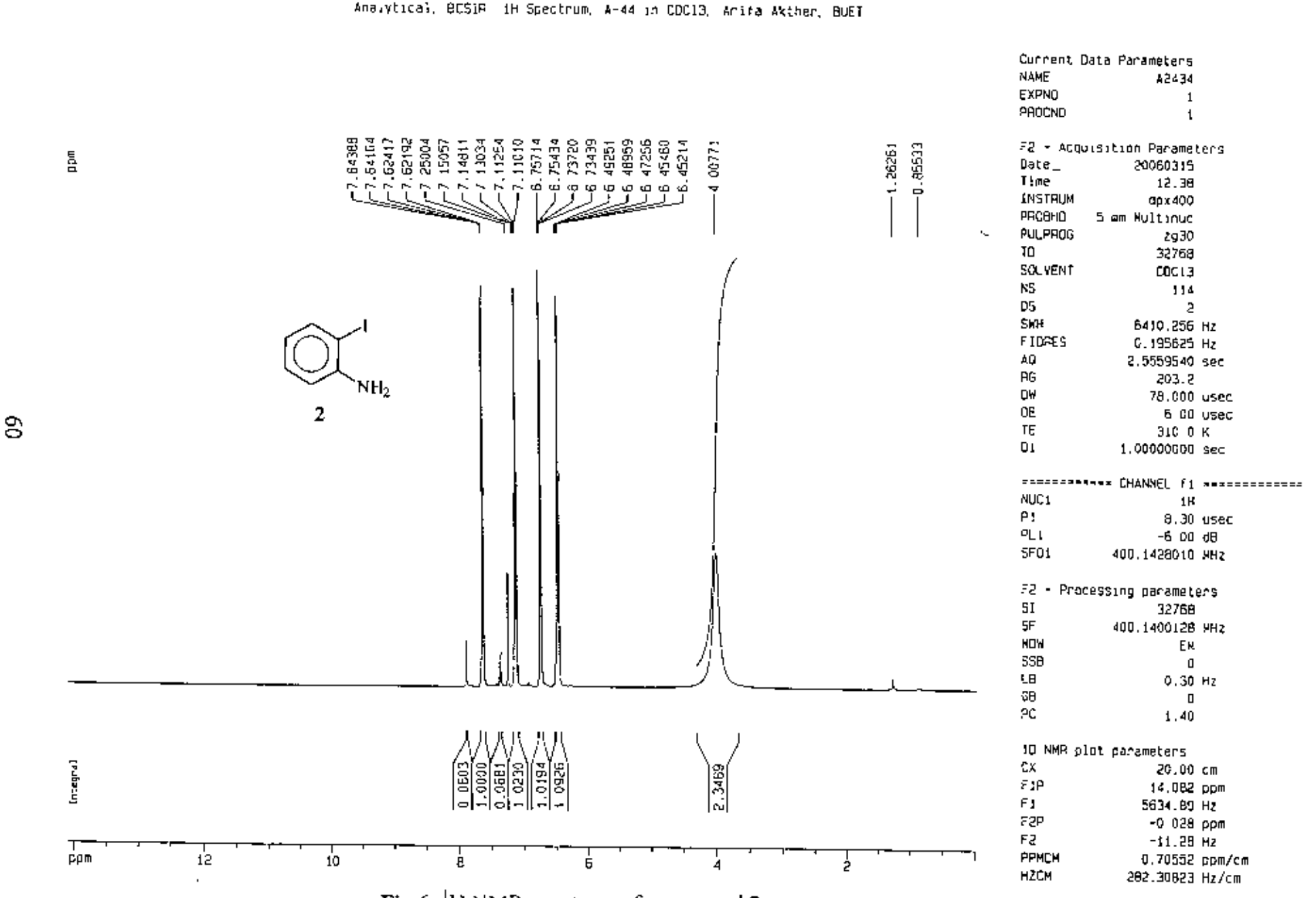


Fig 6: ^{1}H NMR spectrum of compound **2.**

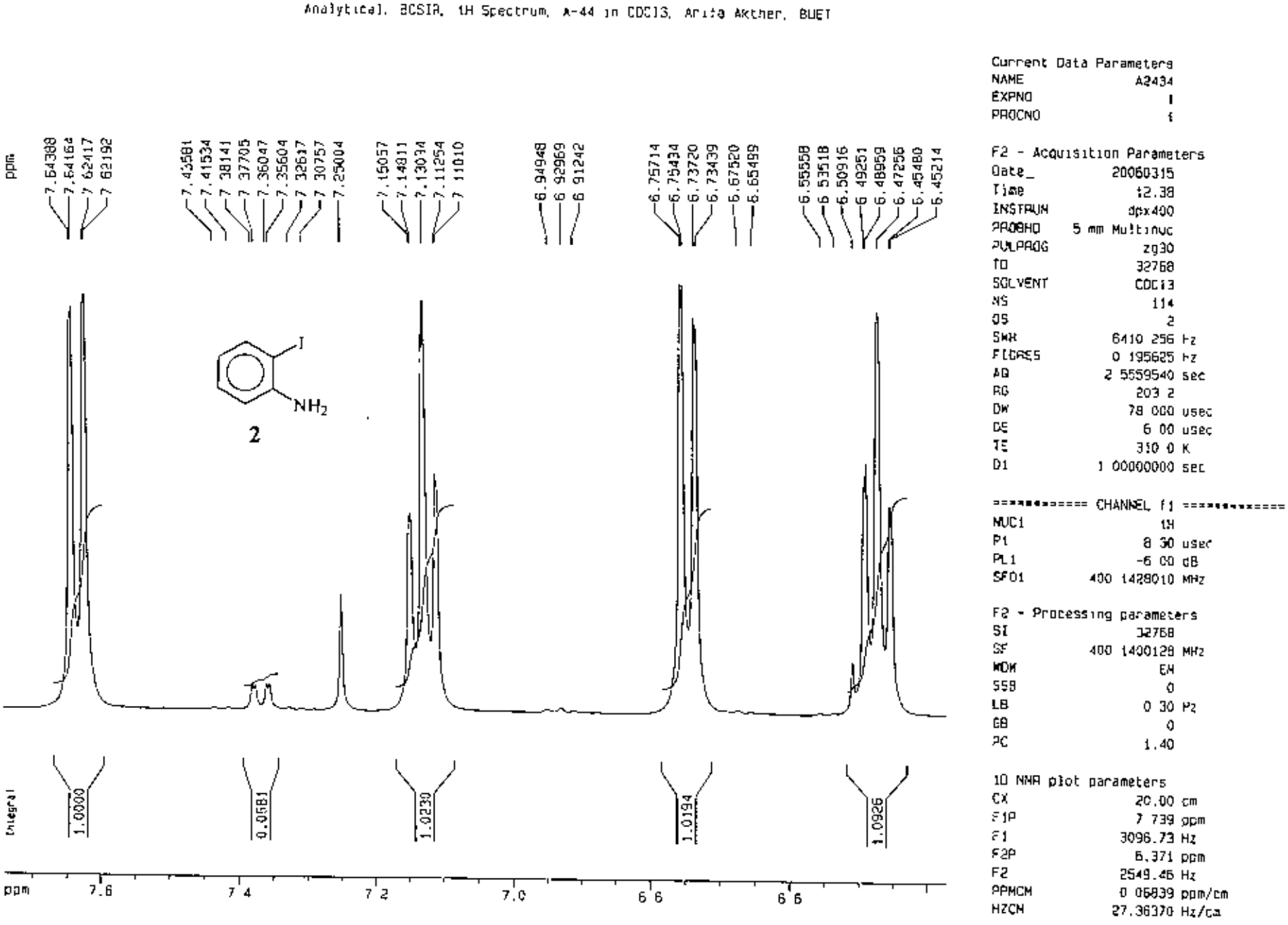
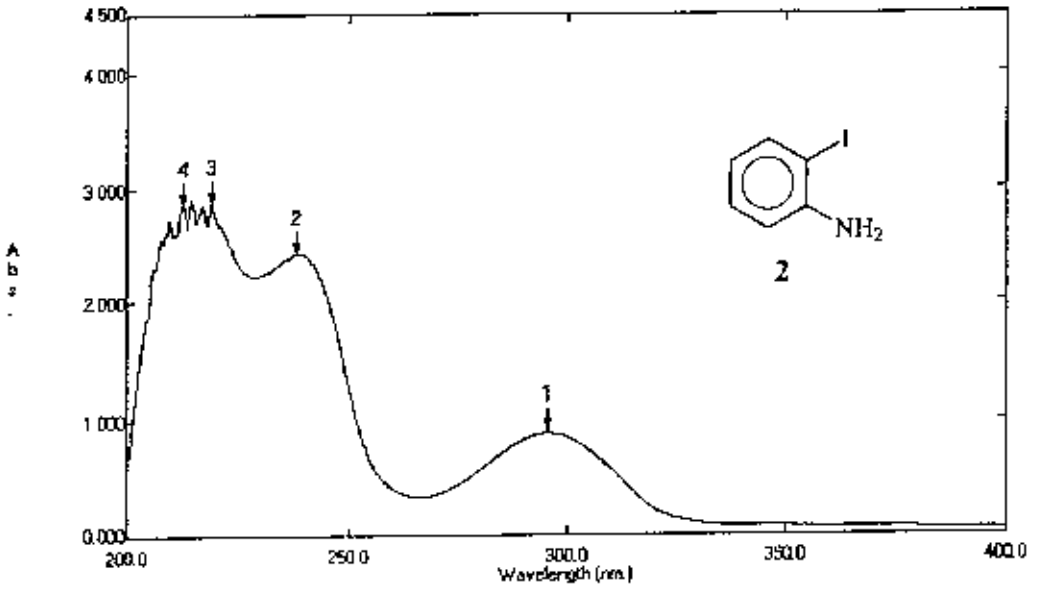


Fig 7: ^{1}H NMR spectrum of compound **2.**



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Data: Original

Measuring Mode: Abs.
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Slit Width: 2.0
Sampling Interval: 0.2

No.	Wavelength (nm.)	Abs.
1	296.00	0.8816
2	238.00	2.4220
3	219.00	2.8696
4	212.80	2.8677

Fig 8: UV spectrum of compound 2.

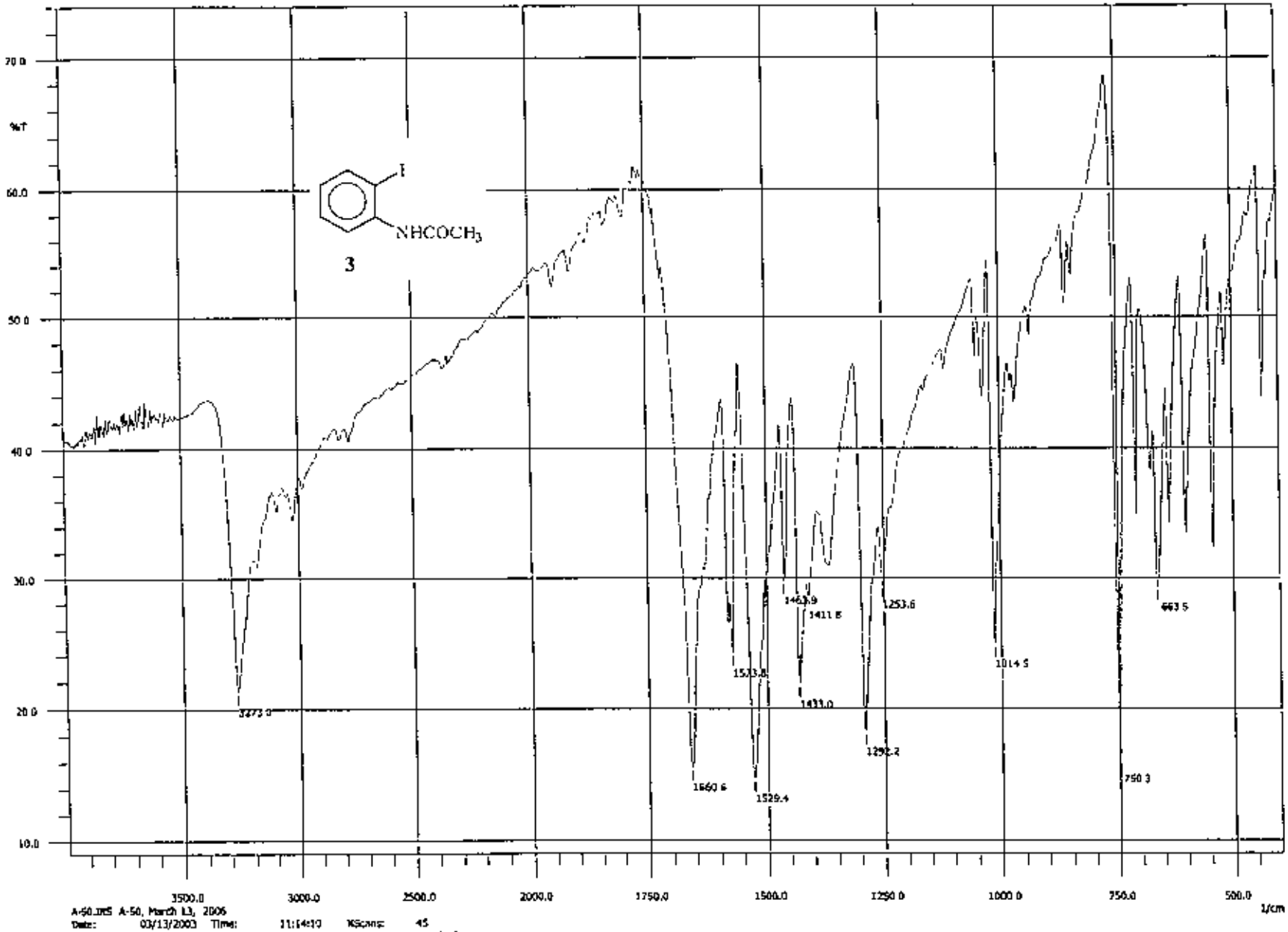


Fig 9: IR spectrum of compound **3.**

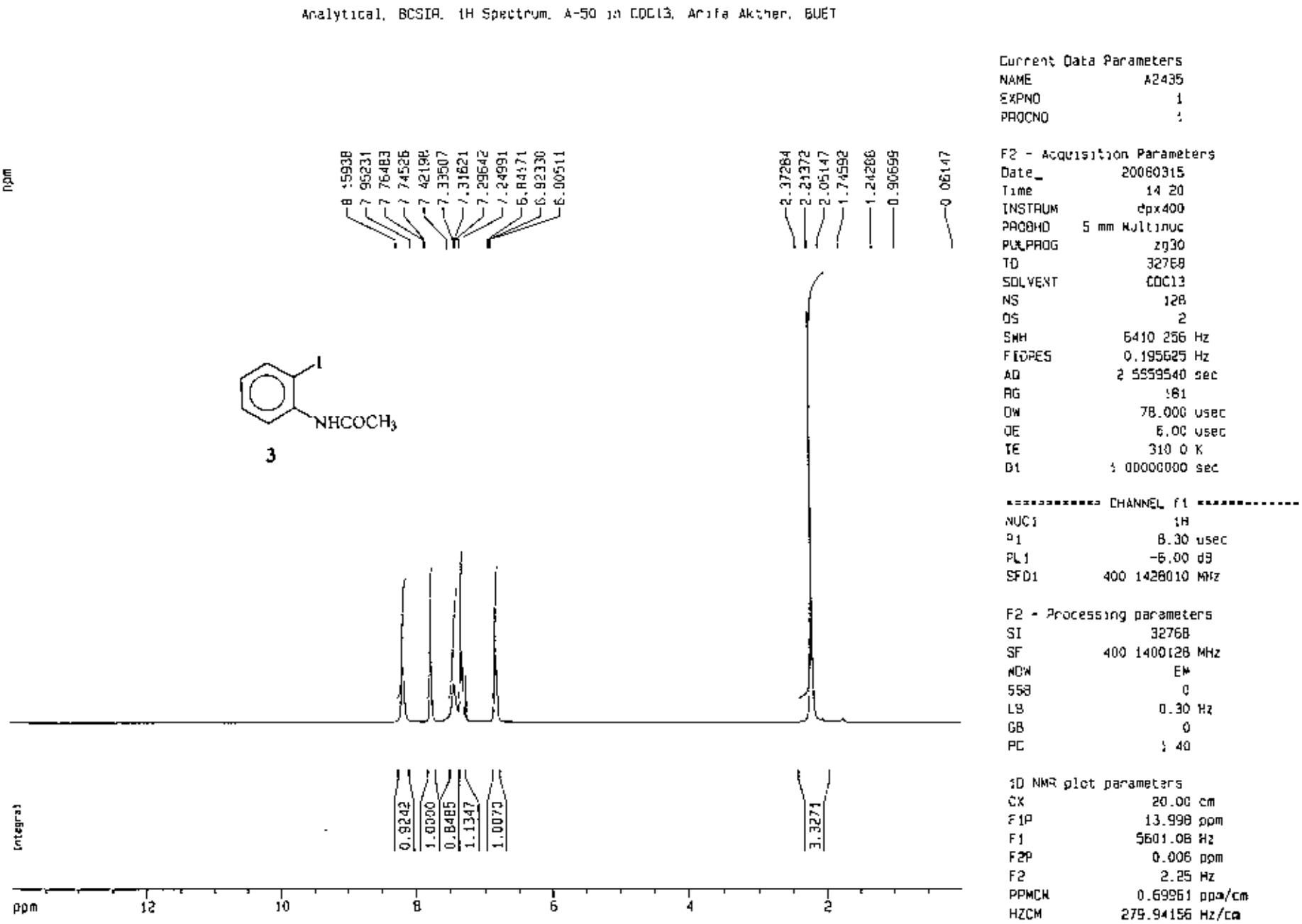


Fig 10: ^{1}H NMR spectrum of compound 3

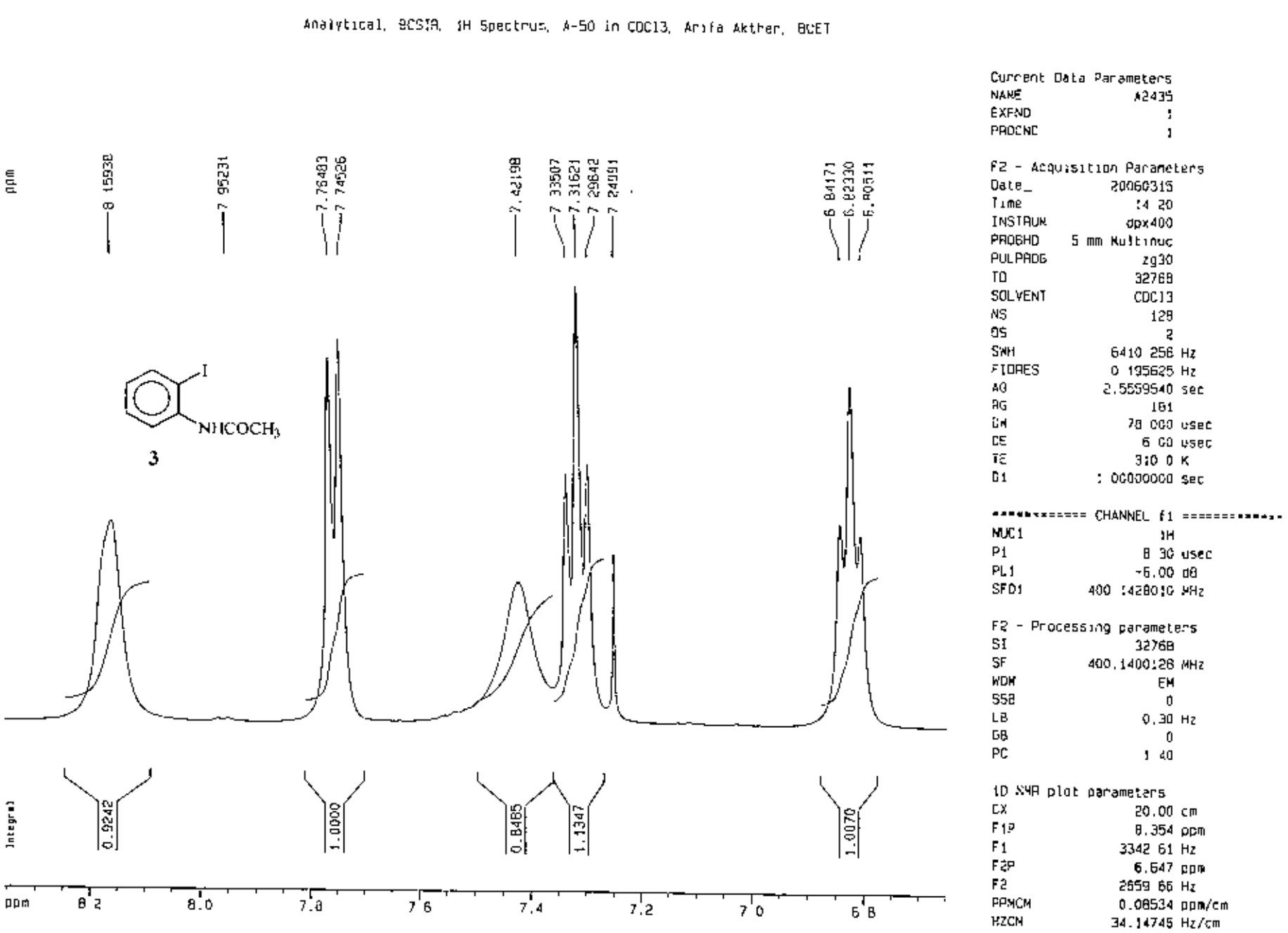
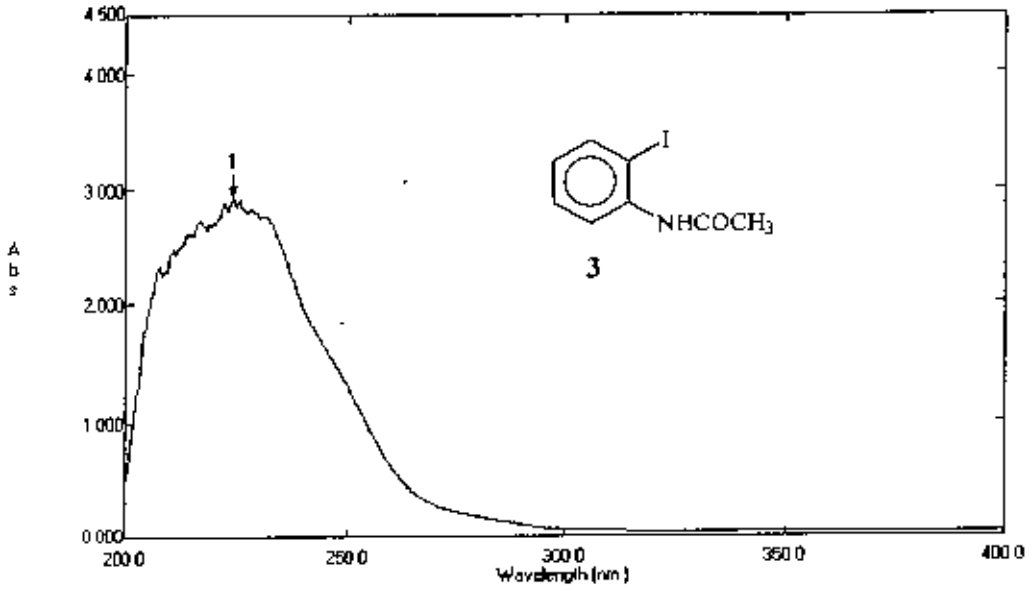


Fig 11: ^{1}H NMR spectrum of compound **3.**



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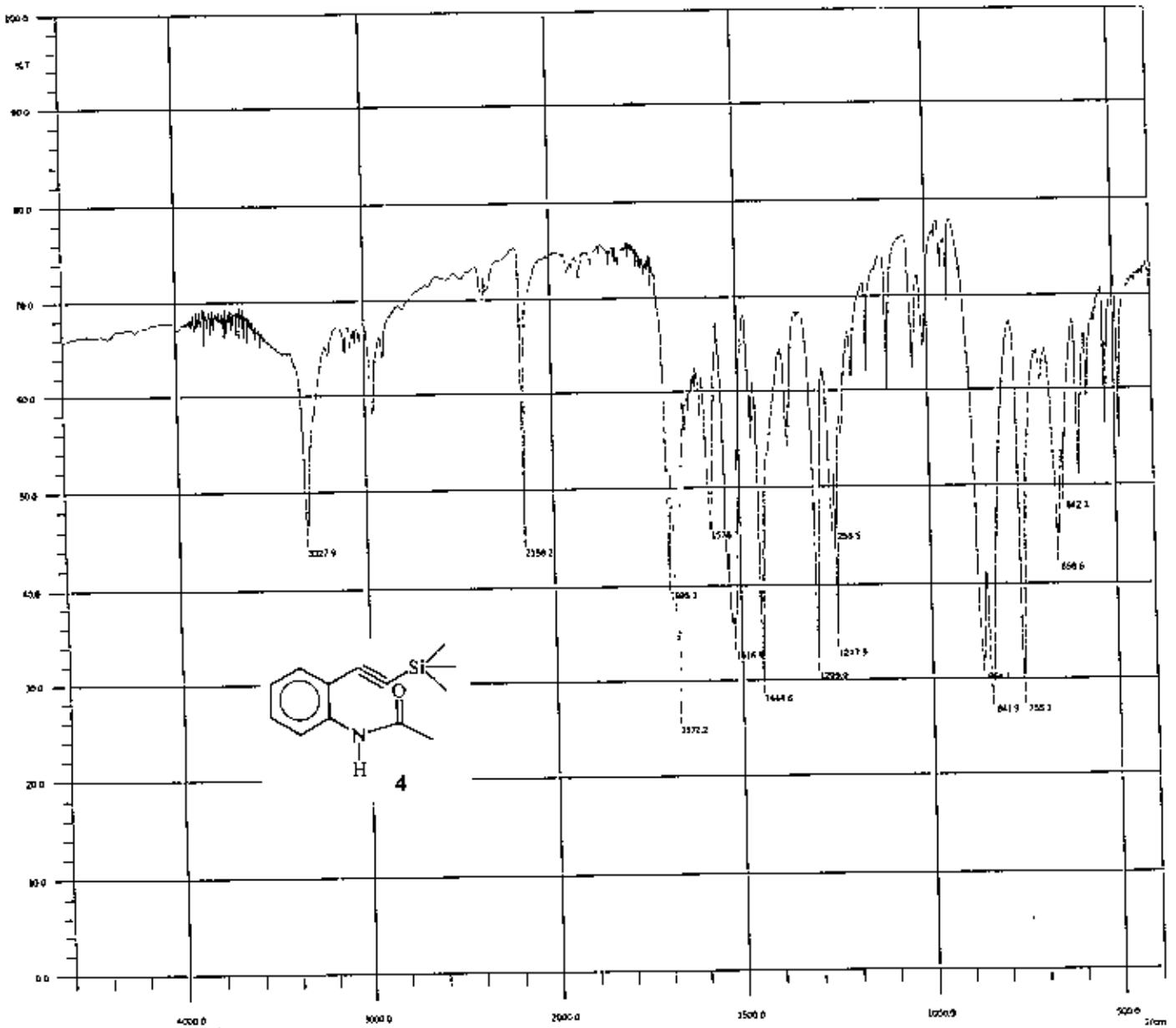
Slit Width: 2.0
Sampling Interval: 0.2

No.	Wavelength (nm.)	Abs.
1	224.40	2.9263

Fig 12: UV spectrum of compound **3.**



Peaktable of ARIFA57.IRS, 15 Peaks
Threshhold 50, Noise. 2, No Range Selection

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1	642.3	49.544
2	638.6	43.323
3	755.1	28.435
4	841.9	28.349
5	864.1	31.823
6	1247.9	34.524
7	1258.5	46.615
8	1299.9	32.082
9	1444.6	29.690
10	1516.9	34.343
11	1576.7	46.817
12	1672.2	26.442
13	1695.3	40.693
14	2158.2	45.272
15	3327.9	45.534

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Fig 13: IR spectrum of compound 4.

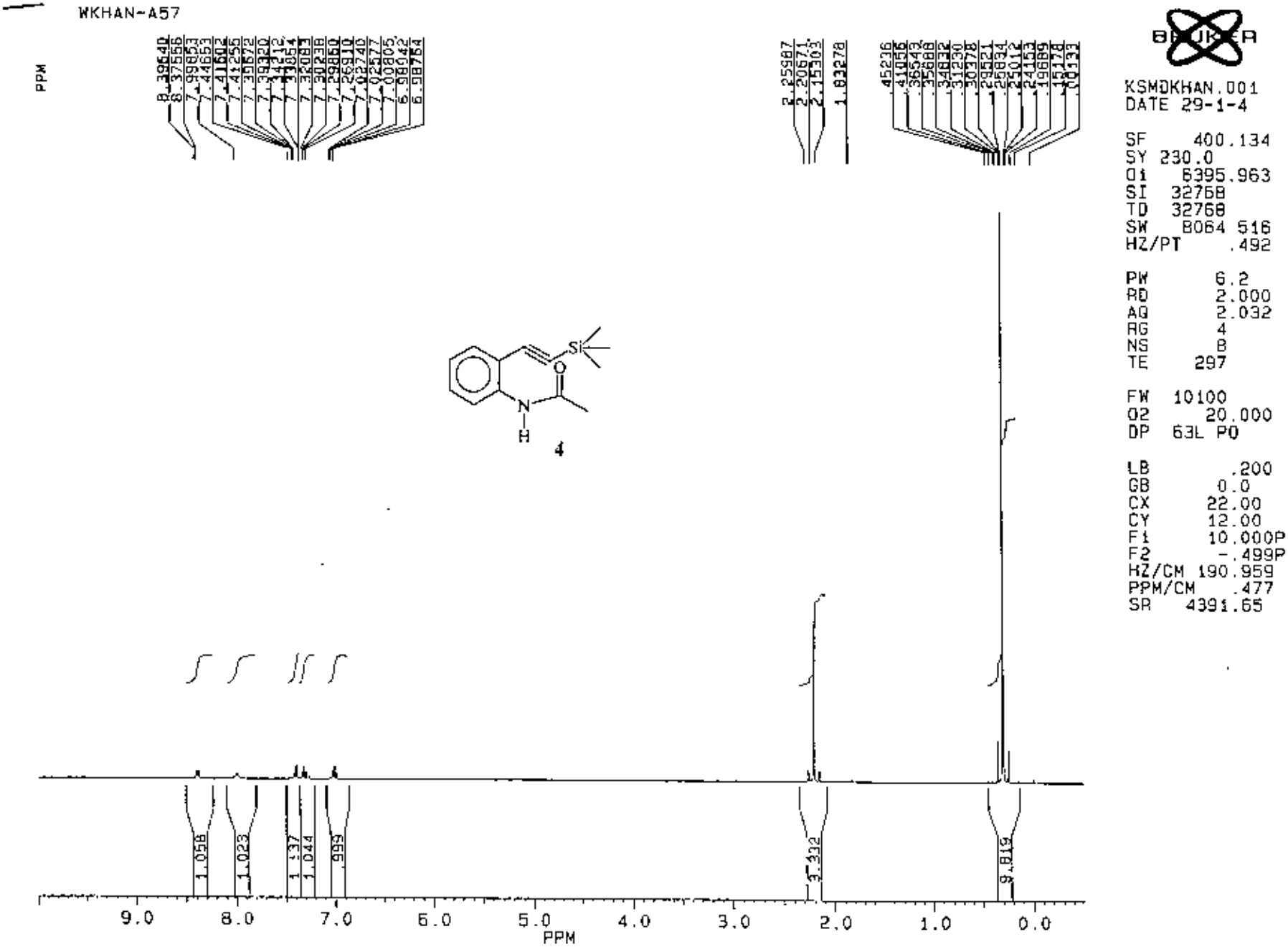


Fig 14: ^{1}H NMR spectrum of compound *4*

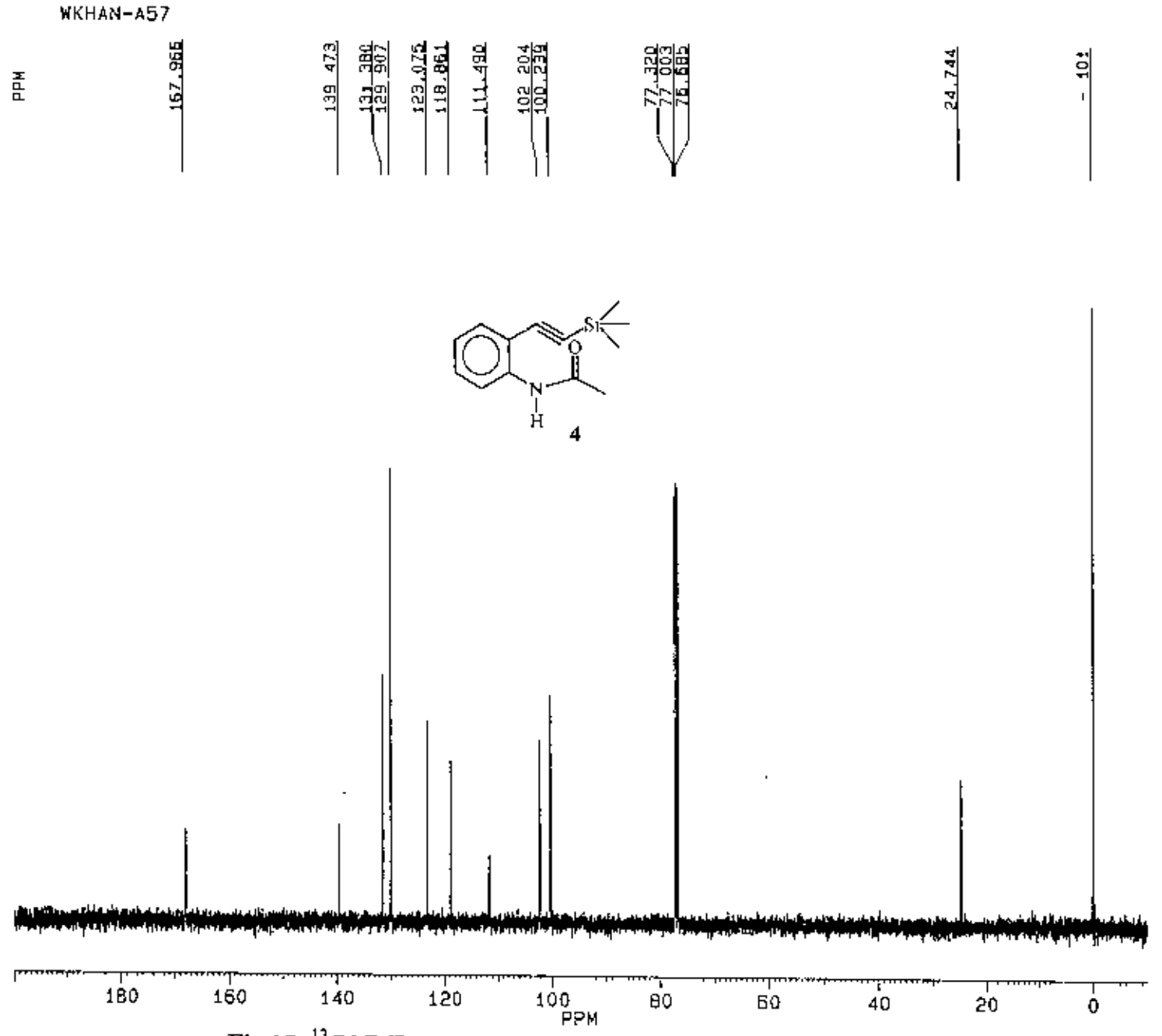
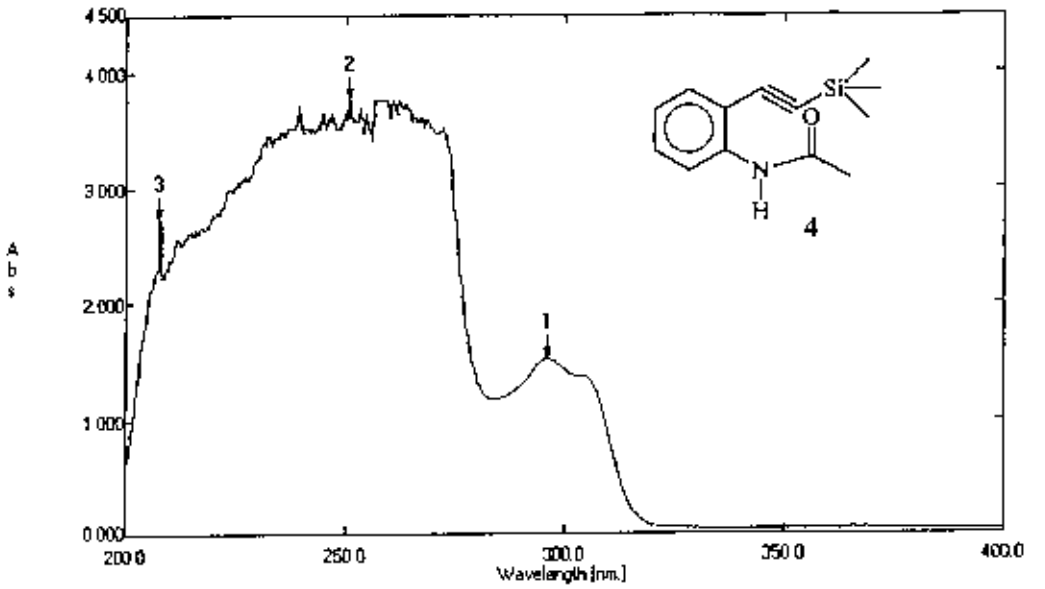


Fig 15: ^{13}C NMR spectrum of compound 4.



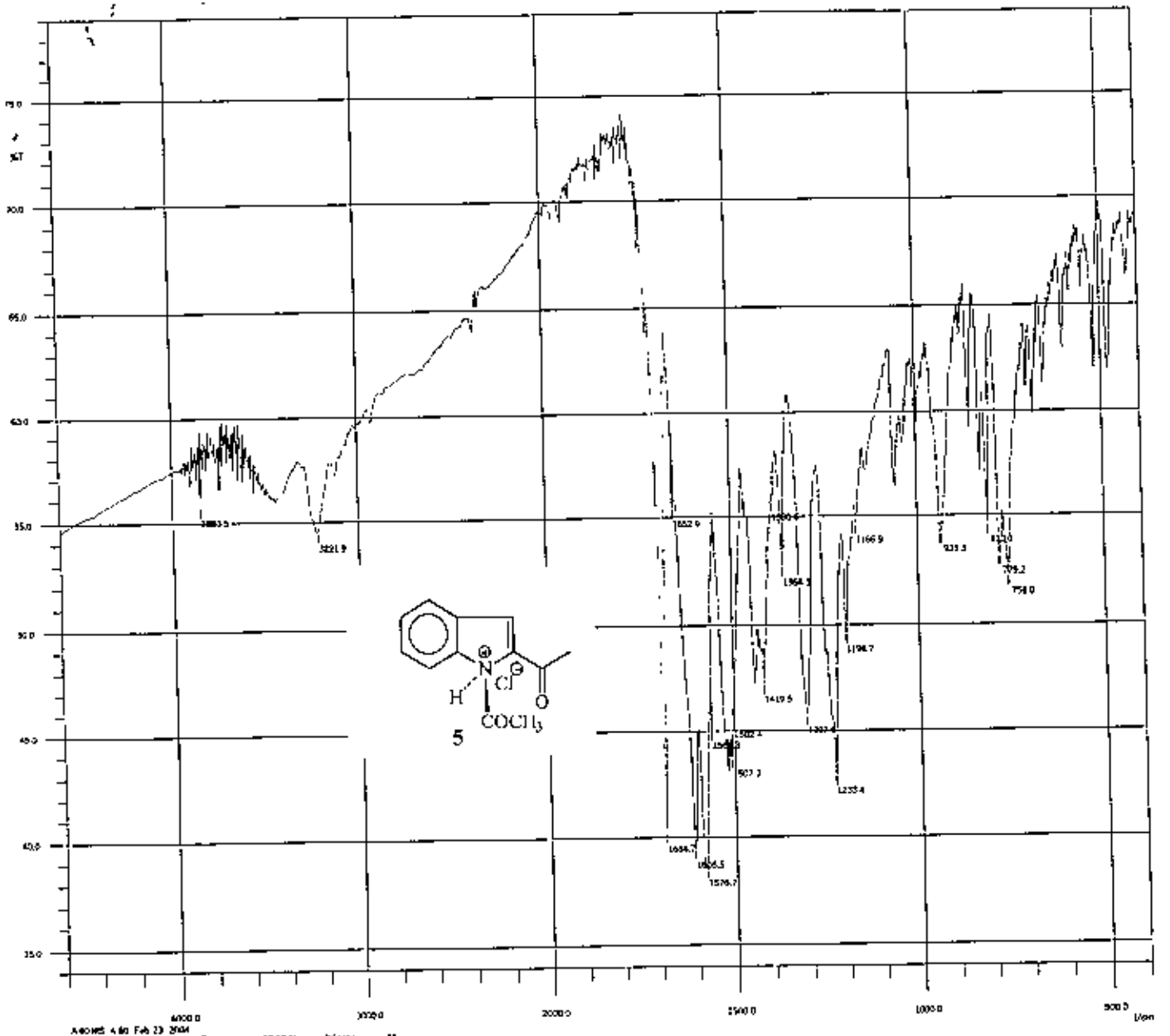
File Name: AFS7

Created: 12:29 12/11/05
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width. 2.0
Sampling Interval: 0.2

No.	Wavelength (nm.)	Abs.
1	296.20	1.5188
2	250.80	3.7628
3	207.80	2.7264

Fig 16: UV spectrum of compound **4.**



Peaktable of A 60 IRS, 20 Peaks
Threshhold. 56, Noise. 2, No Range Selection

No	Pos (1/cm)	Inten. (%T)
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2	779 2	53 161
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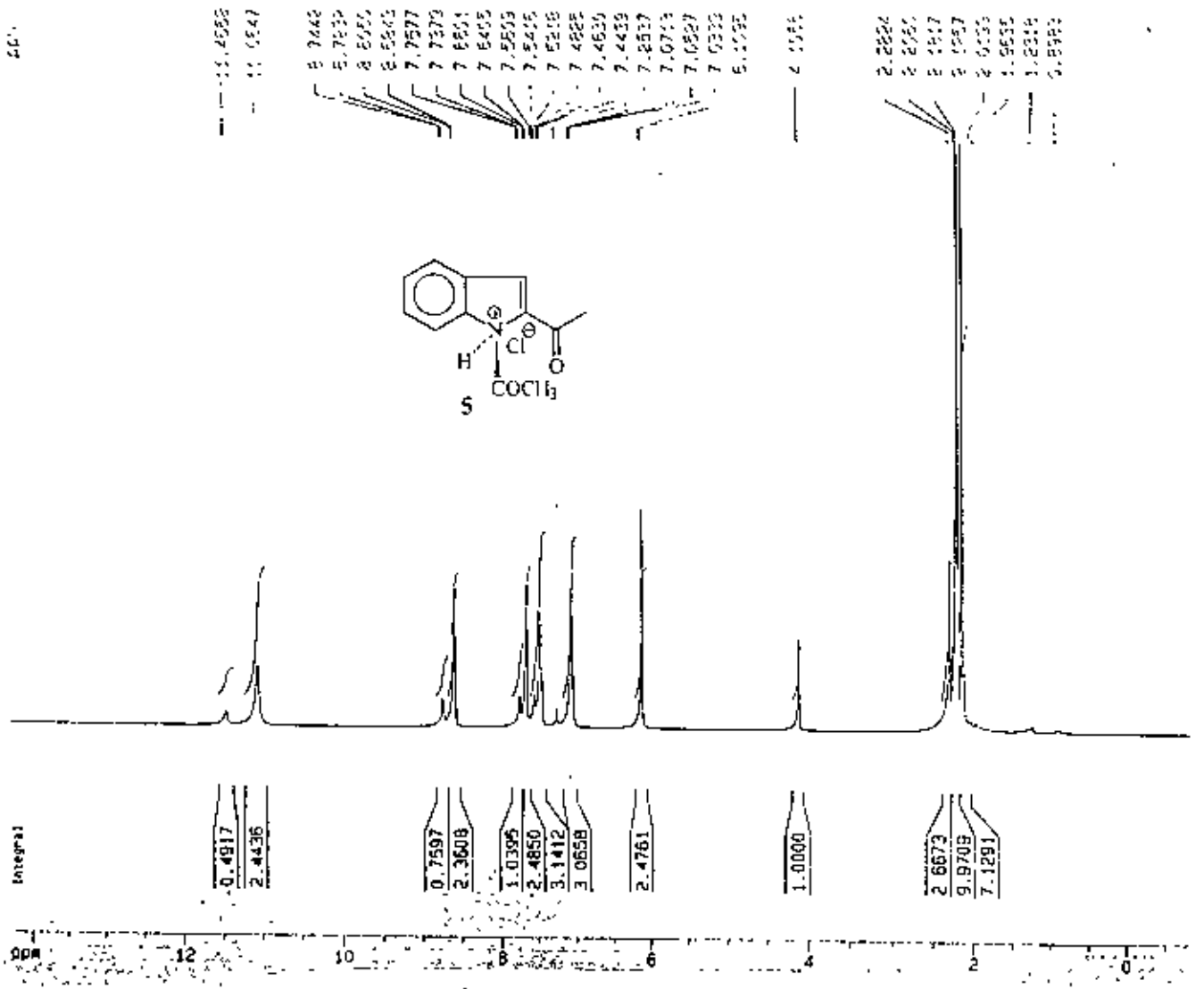
4	938,3	54 207
5	1166 9	54.637
6	1198.7	49 630
7	1233 4	42 905
8	1307 6	45.764
9	1364 5	52,729
10	1390.6	55.717
11	1419 5	47,278
12	1502 4	45.600
13	1507.3	43,744
14	1560 3	45,929
15	1576 7	38.617
16	1608 5	39 455
17	1652.9	55 426
18	1684.7	40,227
19	3221 9	54.537
20	3853 5	55 764

A 60, Feb 23, 2004

Fig 17: IR spectrum of compound 5.



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RG	71.8
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DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

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SF	400.1400107 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

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F1	5718.18 Hz
F2P	-0.834 ppm
F2	-333.70 Hz
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HZCM	302.59387 Hz/cm

Fig 18: ^{1}H NMR spectrum of compound **5.**

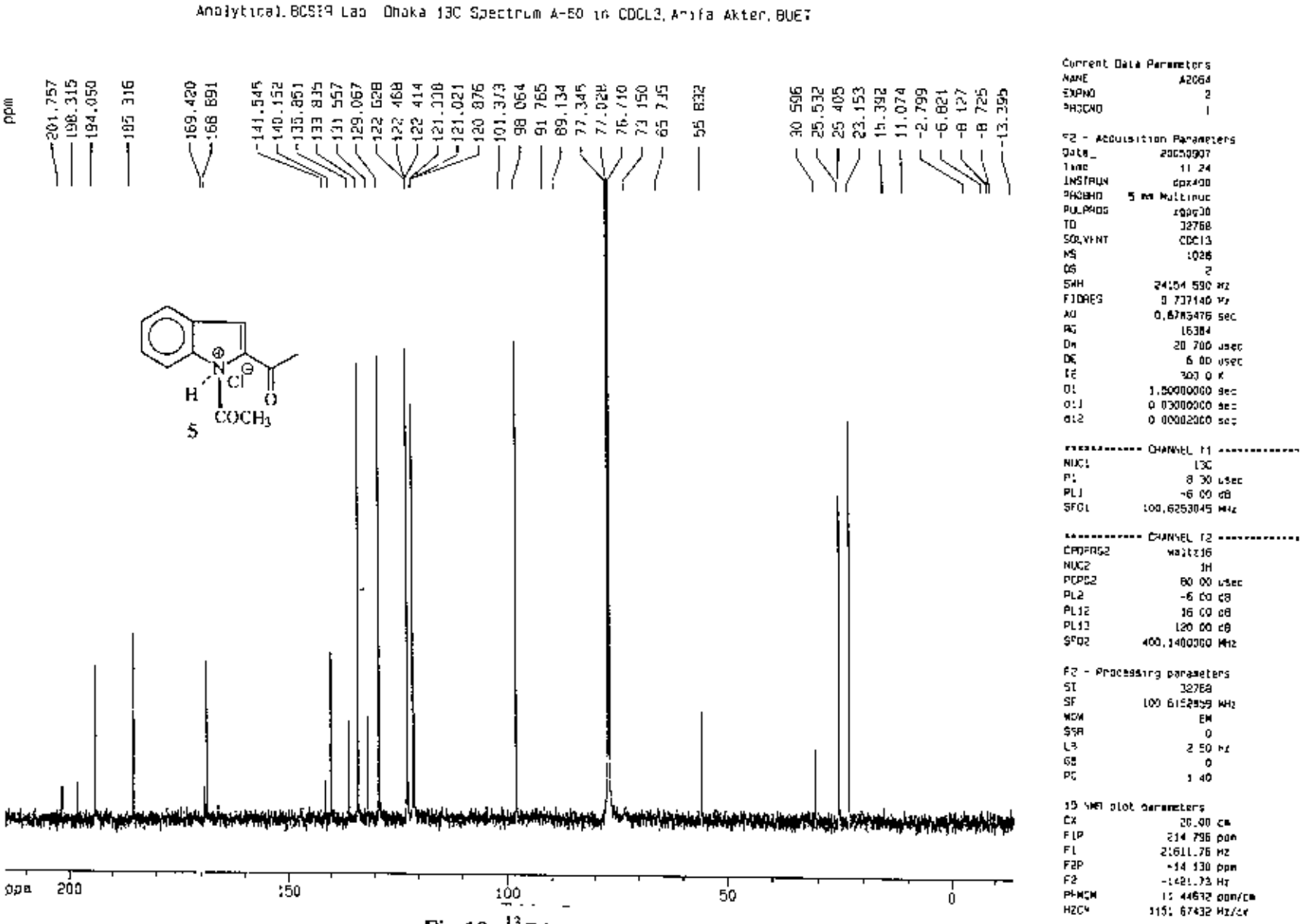
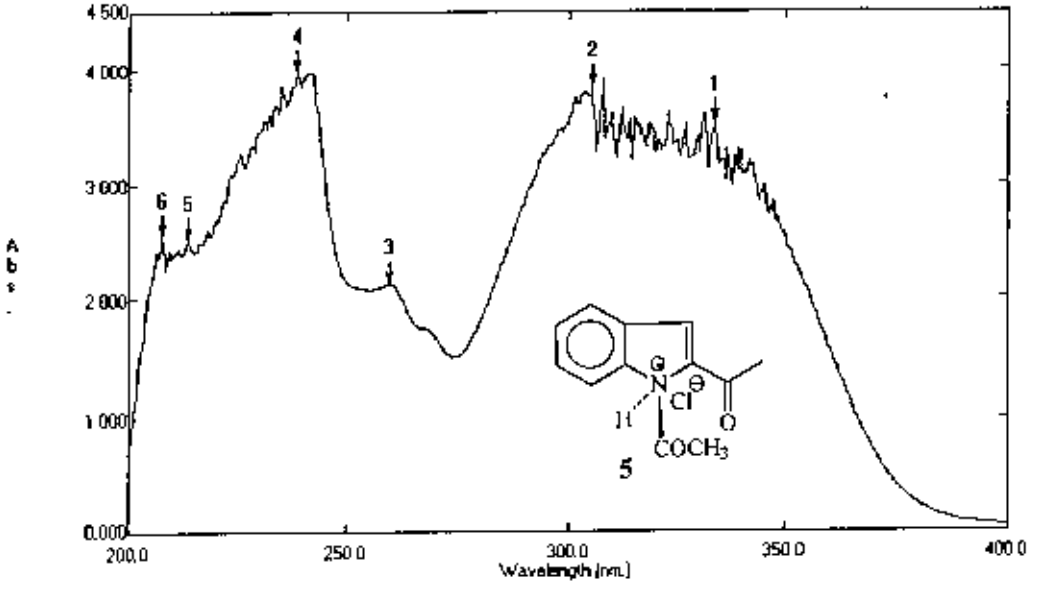


Fig 19: ^{13}C NMR spectrum of compound **5**.



File Name: AF60

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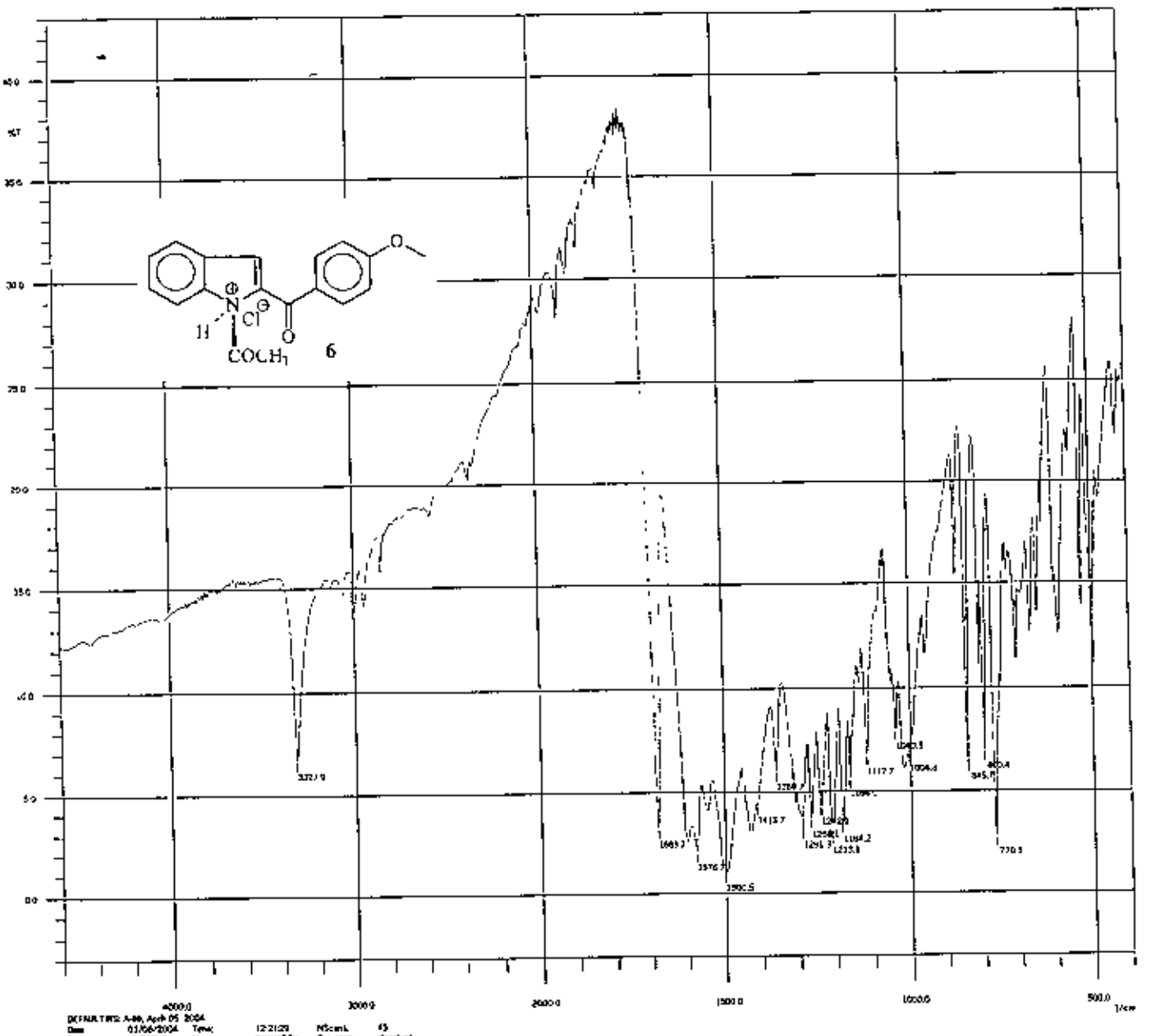
1	334.00	3.5338
2	305.40	3.8380
3	259.80	2.1261
4	238.80	3.9781
5	213.60	2.5186
6	207.80	2.5381

Fig 20: UV spectrum of compound **5.**



Peaktable of DEFAULT IRS, 18 Peaks
Threshhold 10, Noise: 2, No Range Selection

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5	1040 5	7 9658
6	1117.7	6.7332
7	1164 0	5.6811
8	1184 2	3 4212
9	1213 1	2.8869
10	1242 1	4 3106
11	1268.1	3.6643
12	1291 3	3 7397
13	1360 7	6.0469
14	1413 7	4.3739
15	1500.5	1.0512
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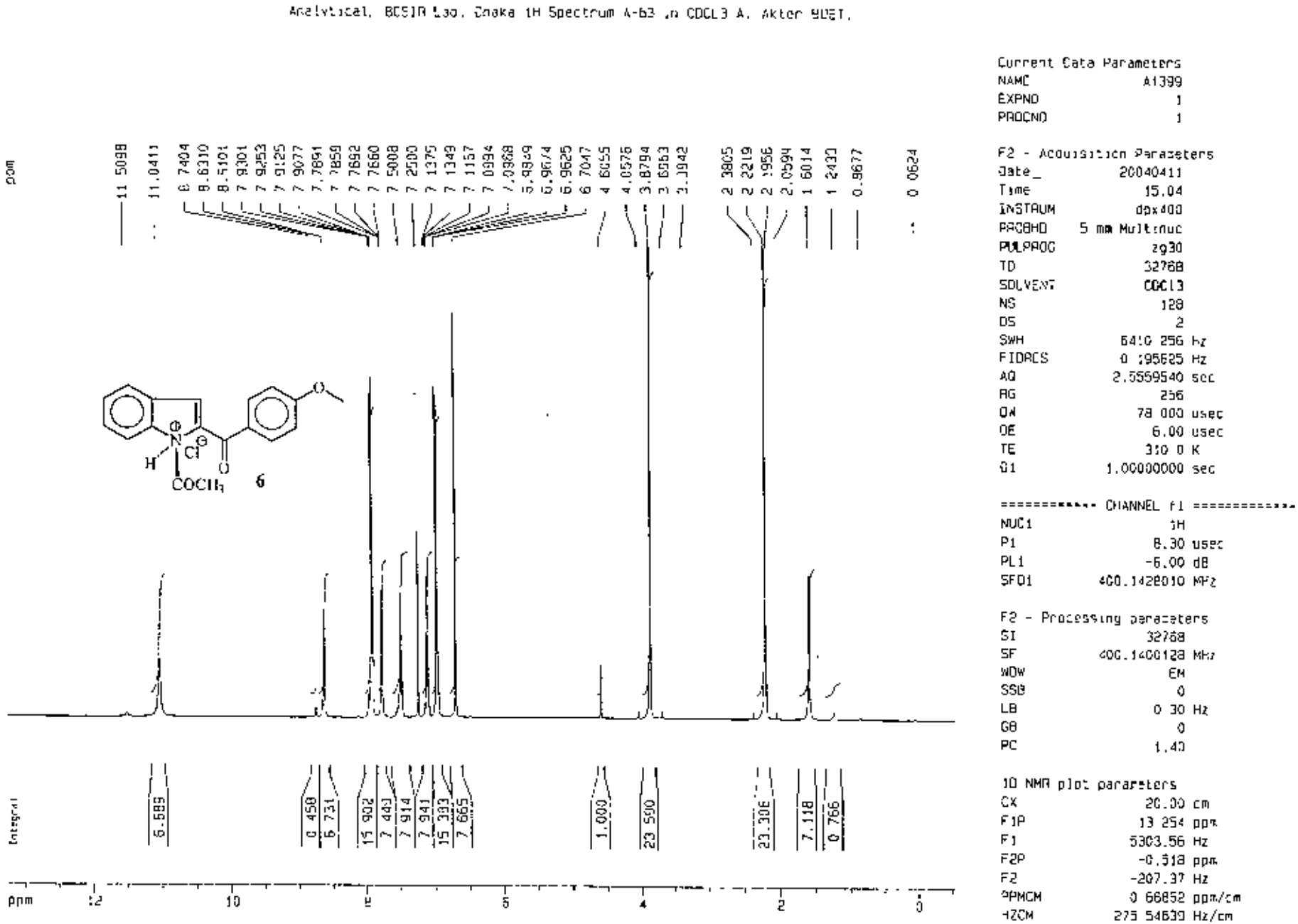
17	1683 7	3 1894
18	3327 9	6 7429

A-69, April 05 2004

Fig 21: IR spectrum of compound 6.

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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 ============
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P1                  8.30 usec
PL1                -6.00 dB
SFO1         400.1428010 MHz

F2 - Processing parameters
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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
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F1                5303.56 Hz
F2P                -0.518 ppm
F2                -207.37 Hz
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HZCM          275.54639 Hz/cm
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Fig 22: ^{1}H NMR spectrum of compound **6.**

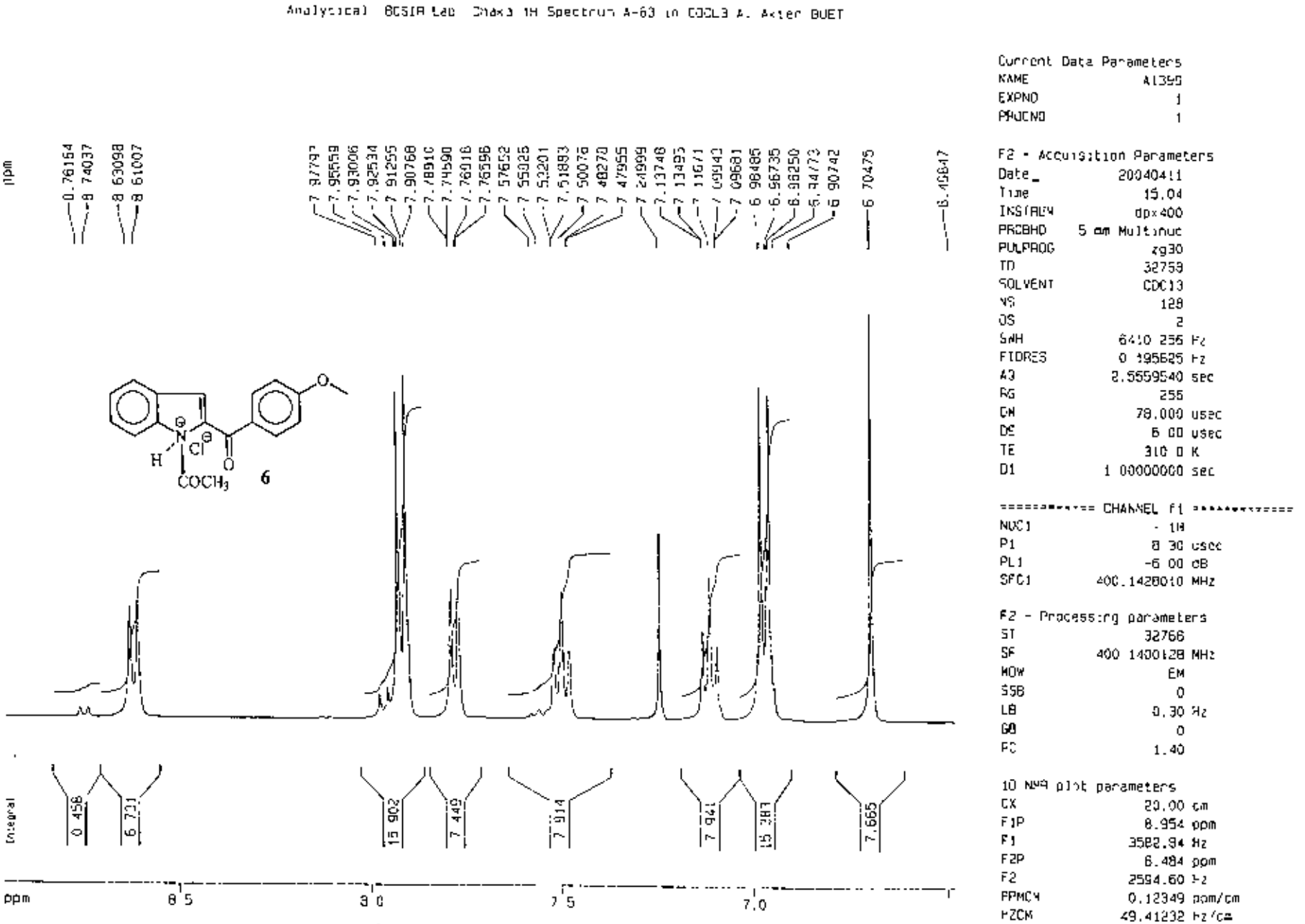
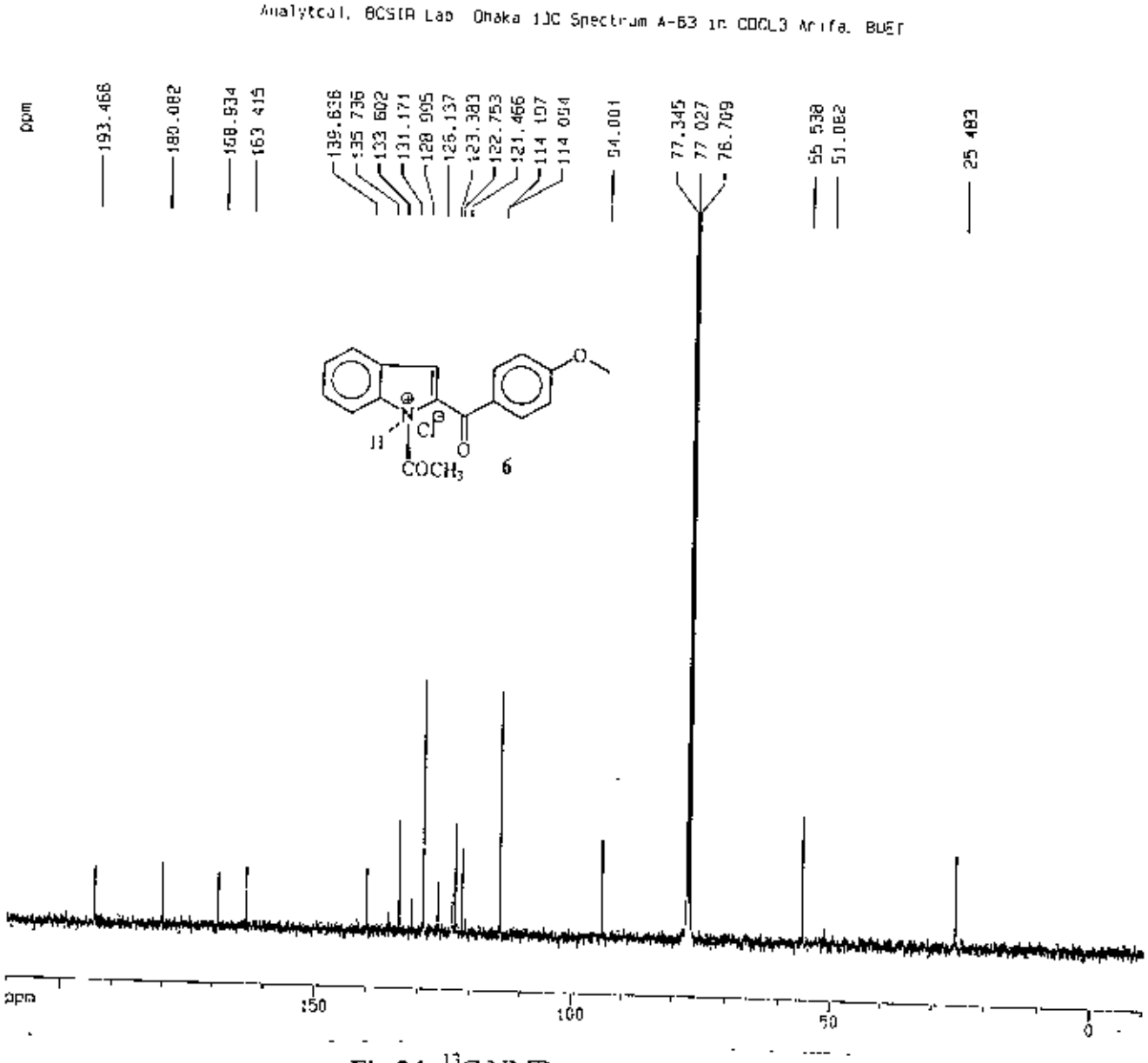


Fig 23: ^{1}H NMR spectrum of compound **6.**



6

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PROCNO 1

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SWH 24154.950 Hz
FIDRES 0.737140 Hz
AQ 0.6778476 sec
RG 4096
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
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PL 8.30 dBm
PL1 -6.00 dB
SFO1 100.5252045 MHz

CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -6.00 dB
PL12 16.00 dB
PL13 120.00 dB
SFO2 400.1400030 MHz

F2 - Processing parameters
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SSB 0
LB 2.50 Hz
GB 0
PC 1.40

1D NMR plot parameters
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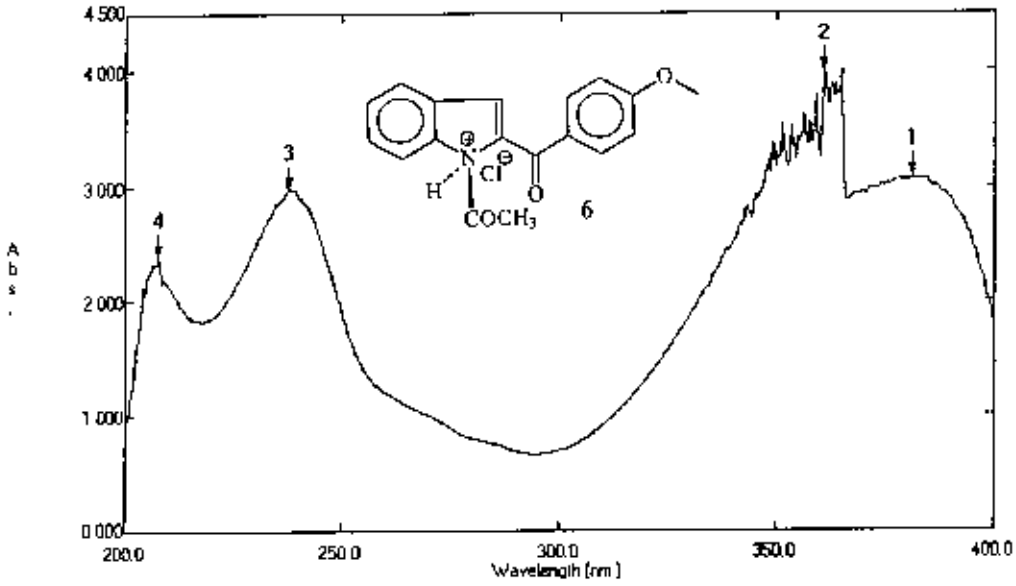
F1 21156.07 Hz
F2P -10.303 ppm
F2 -1035.59 Hz
PPMCM 11.07848 ppm/cm
HZCM 1109.63330 Hz/cm

Fig 24: ^{13}C NMR spectrum of compound **6.**



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No.	Wavelength (nm.)	Abs.
1	380.80	3.0846
2	360.60	3.9999
3	238.00	2.9850
4	207.80	2.3987

Fig 25: UV spectrum of compound **6.**

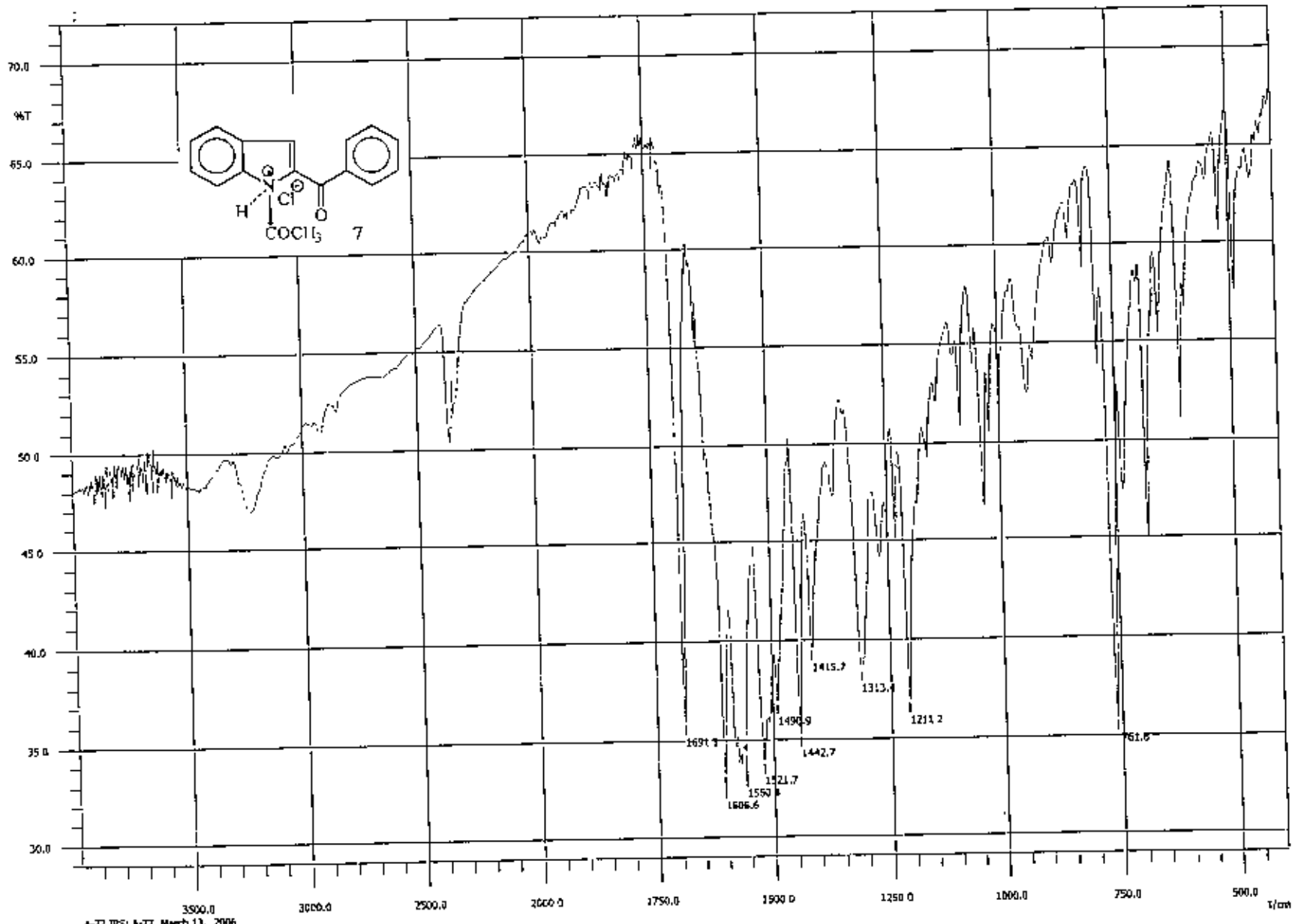
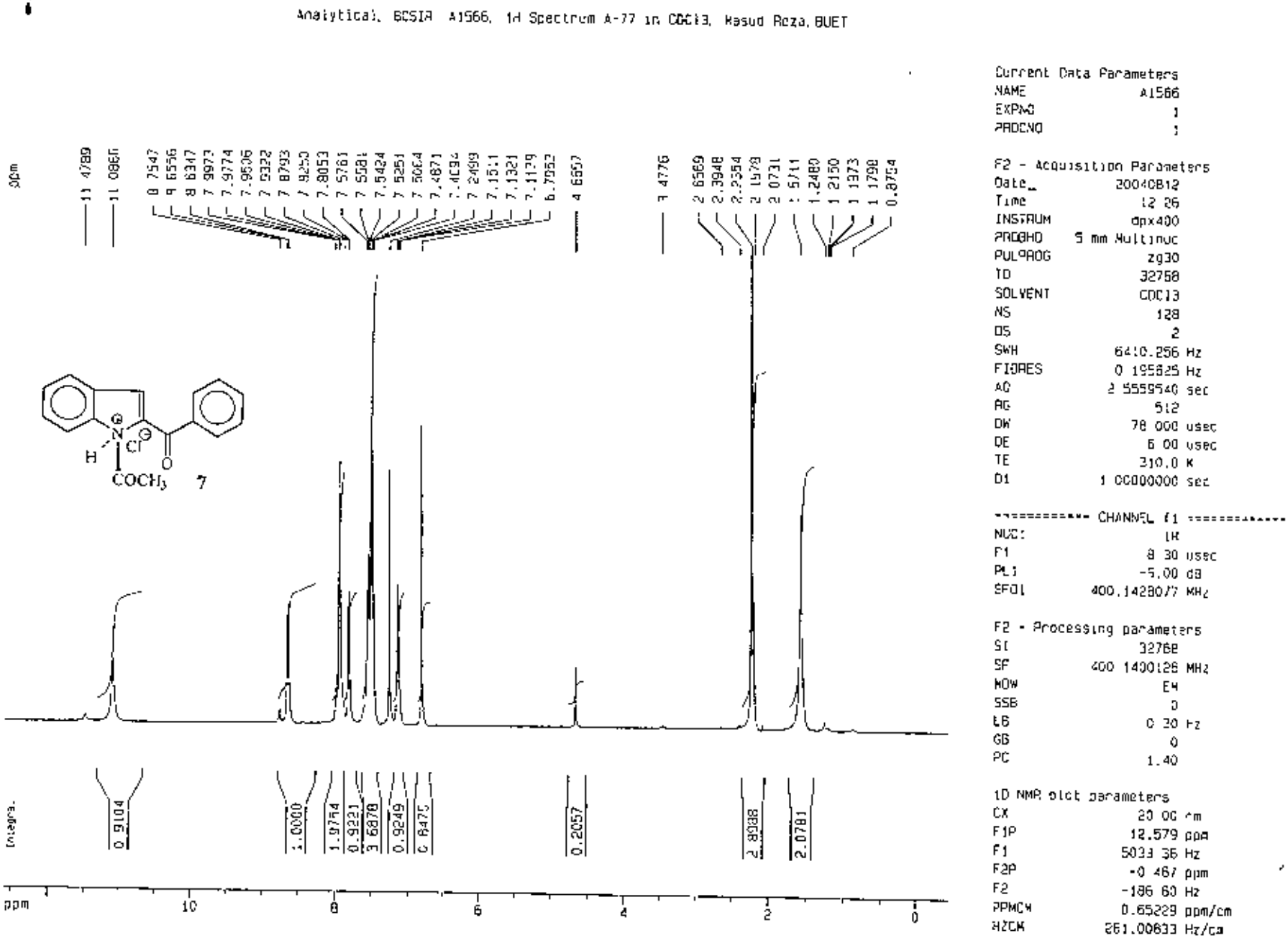


Fig 26: IR spectrum of compound 7.



Current Data Parameters

NAME	A1566
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040812
Time	12 26
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	512
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	-5.00 dB
SFO1	400.1428077 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	12.579 ppm
F1	5033.36 Hz
F2P	-0.467 ppm
F2	-186.60 Hz
PPMCM	0.65229 ppm/cm
HZCM	261.00833 Hz/cm

Fig 27: ^{1}H NMR spectrum of compound 7.

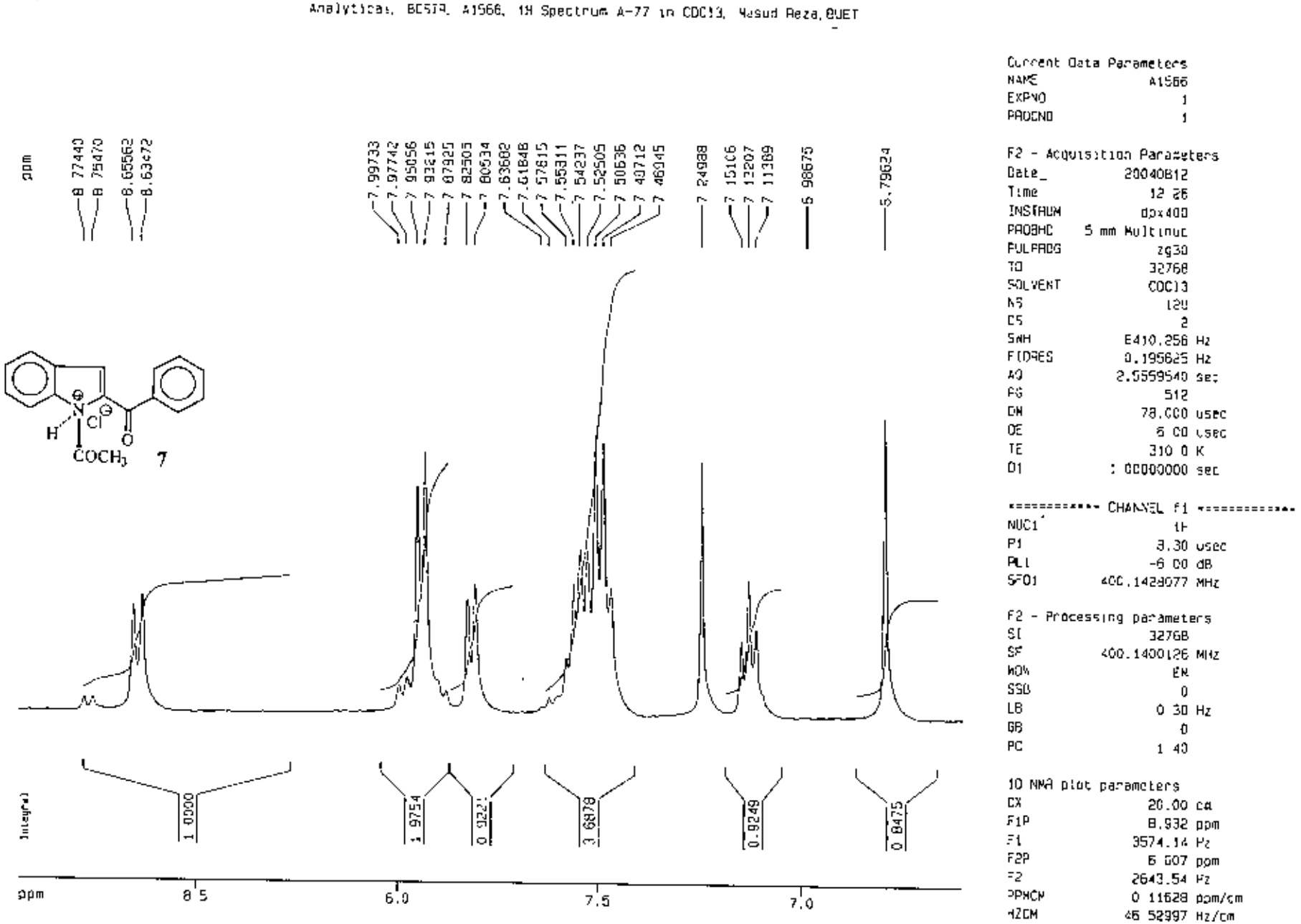


Fig 28: ^{1}H NMR spectrum of compound **7**.

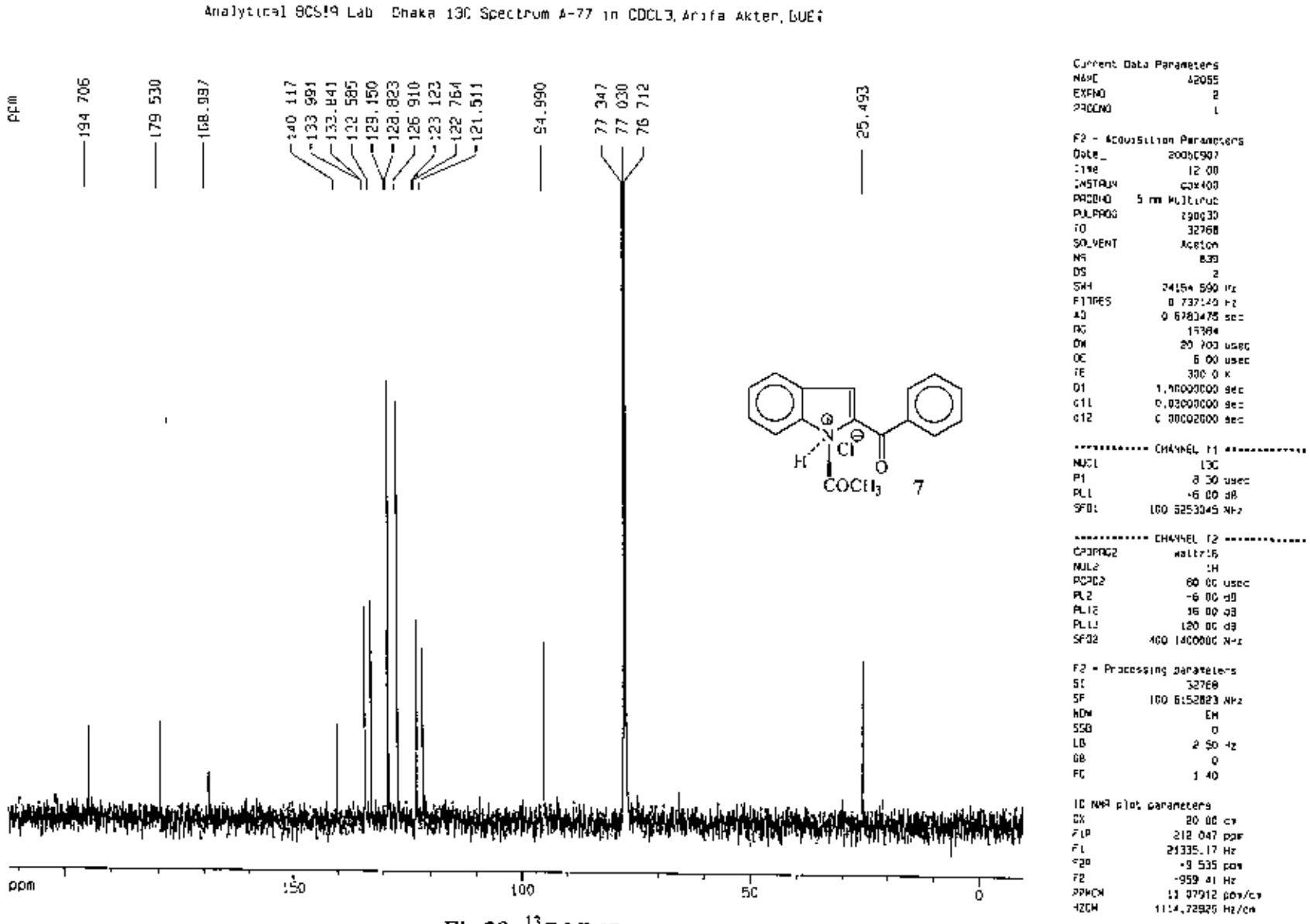
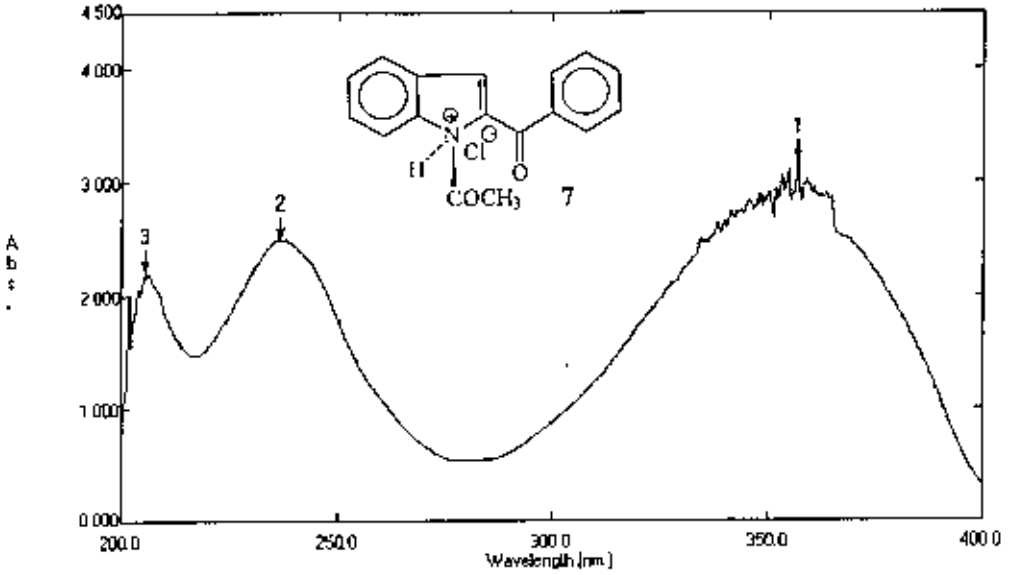


Fig 29: ^{13}C NMR spectrum of compound 7.



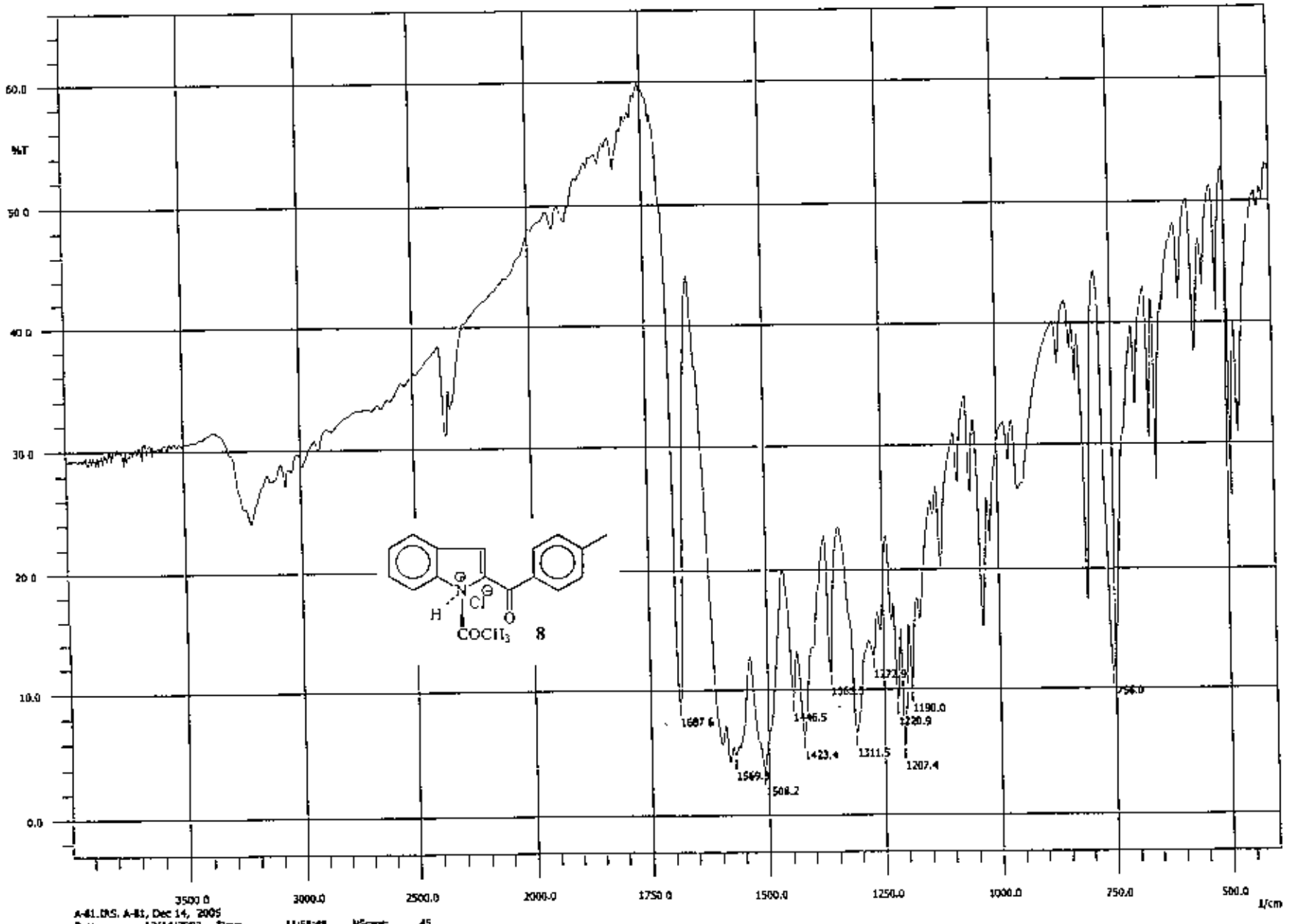
File Name: AJ77

Created: 11:23 12/12/05
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2

No.	Wavelength (nm)	Abs.
1	356.60	3.1597
2	236.60	2.4987
3	205.80	2.2113

Fig 30: UV spectrum of compound 7.



8

Fig 31: IR spectrum of compound **8.**

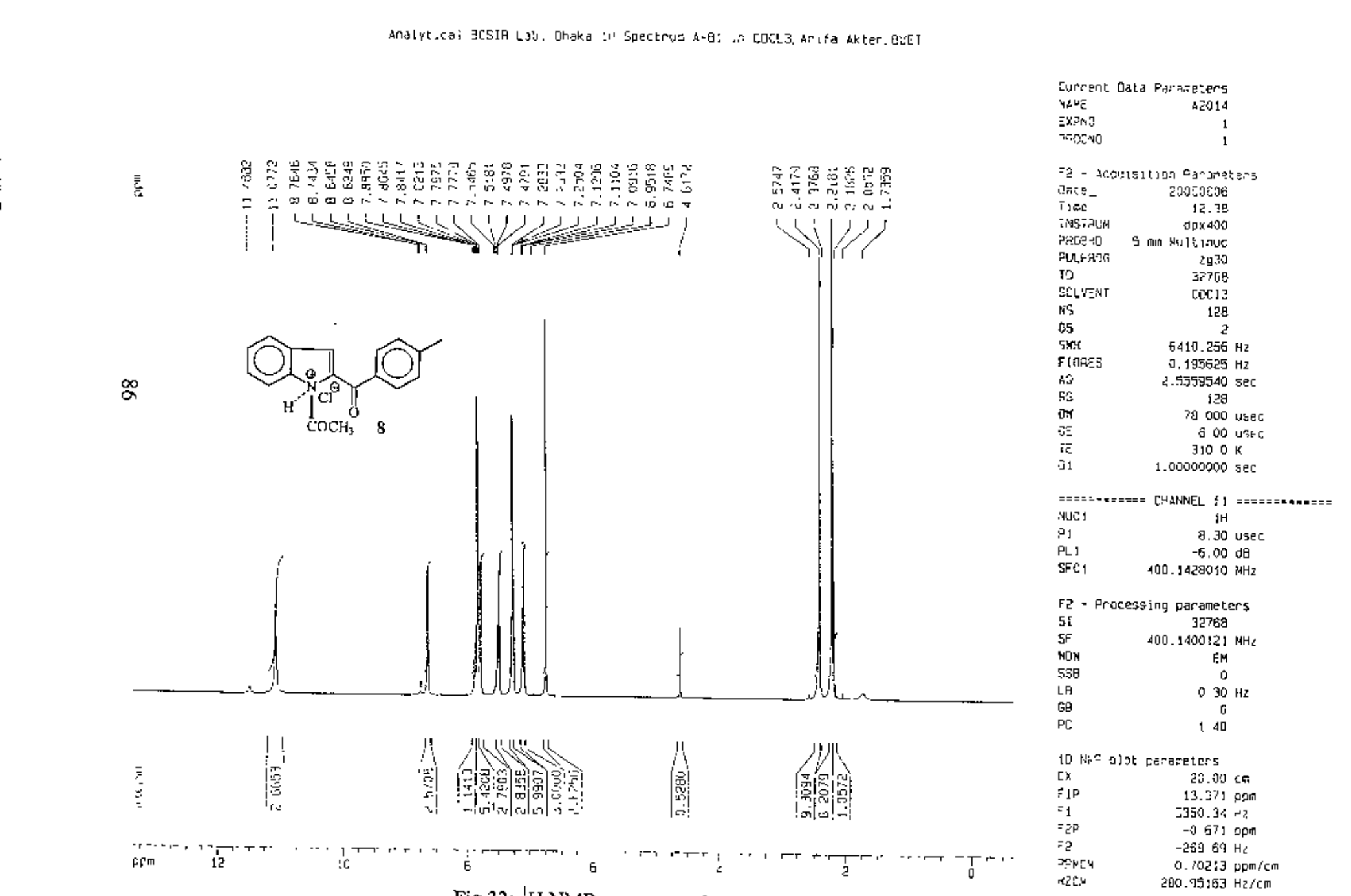


Fig 32: ^{1}H NMR spectrum of compound **8**.

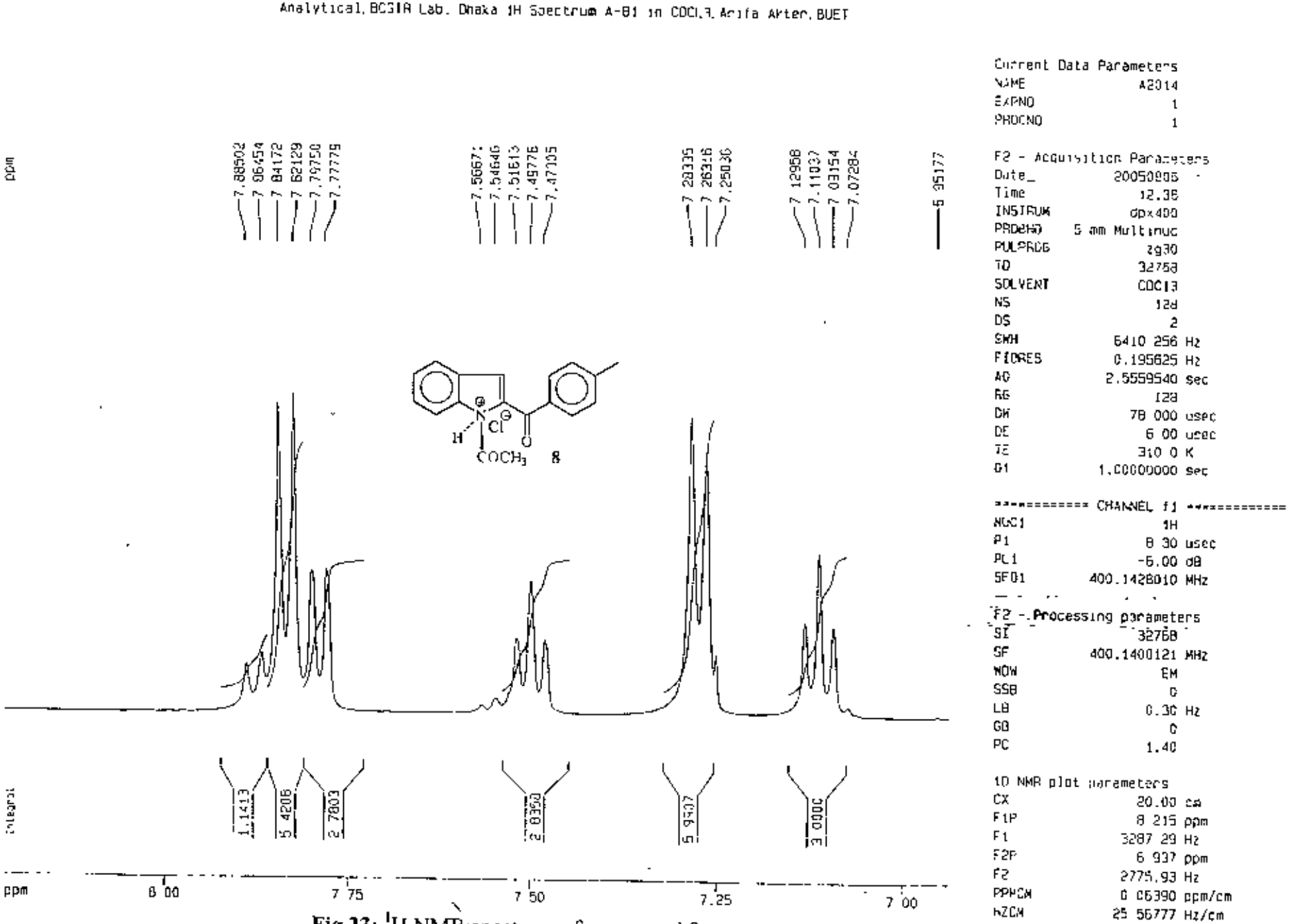
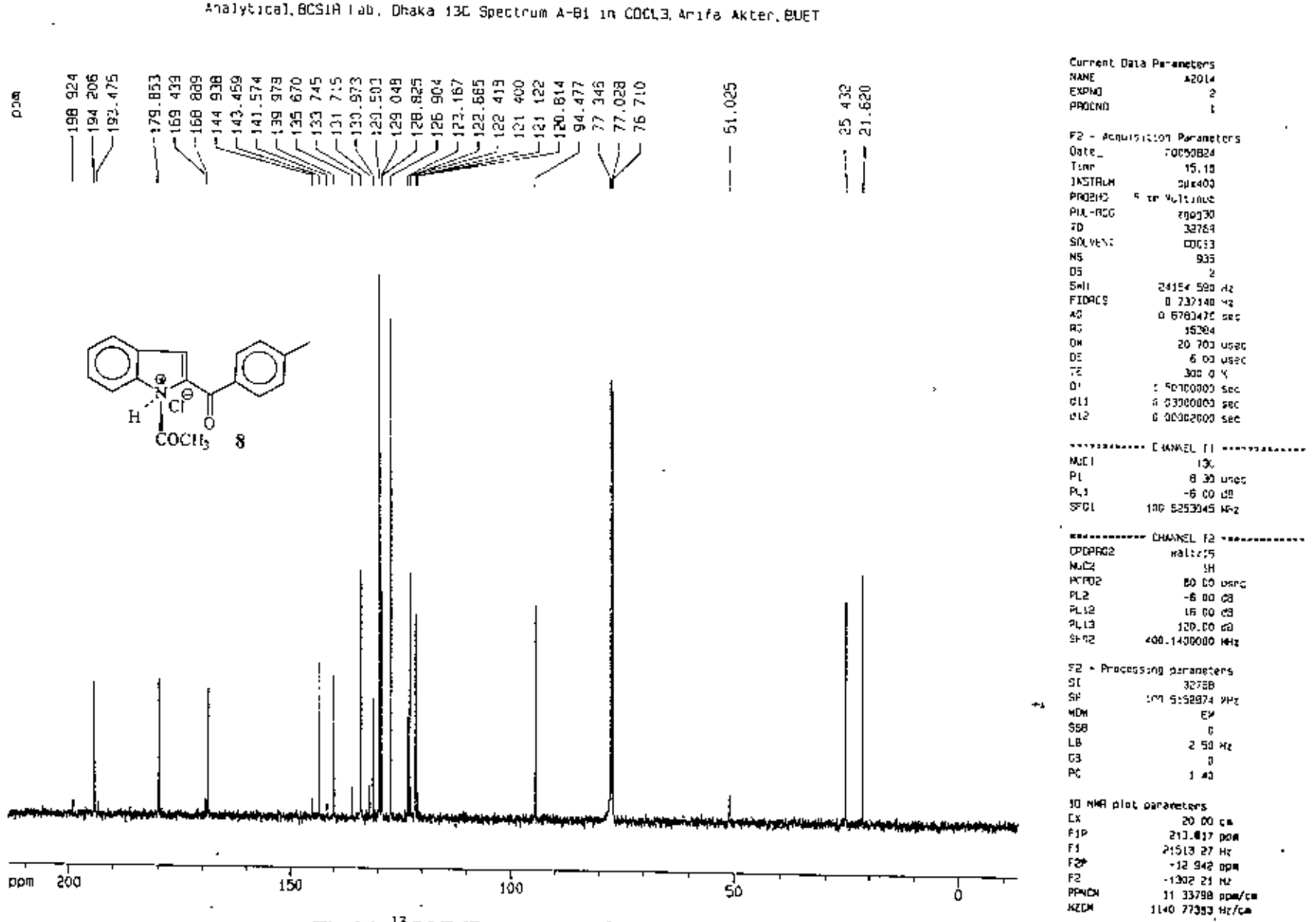


Fig 33: ^{1}H NMR spectrum of compound **8**.



Current Data Parameters
NAME A2014
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 15.18
INSTRUM spe400
PROBHD 5 mm Multinuc
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 935
DS 2
SWH 24154.589 Hz
FIDRES 0.737140 Hz
AQ 0.6783472 sec
RG 15384
DW 20.700 usec
DE 6.00 usec
TE 300.0 K
D1 1.50000000 sec
D11 0.03000000 sec
D12 0.00002000 sec

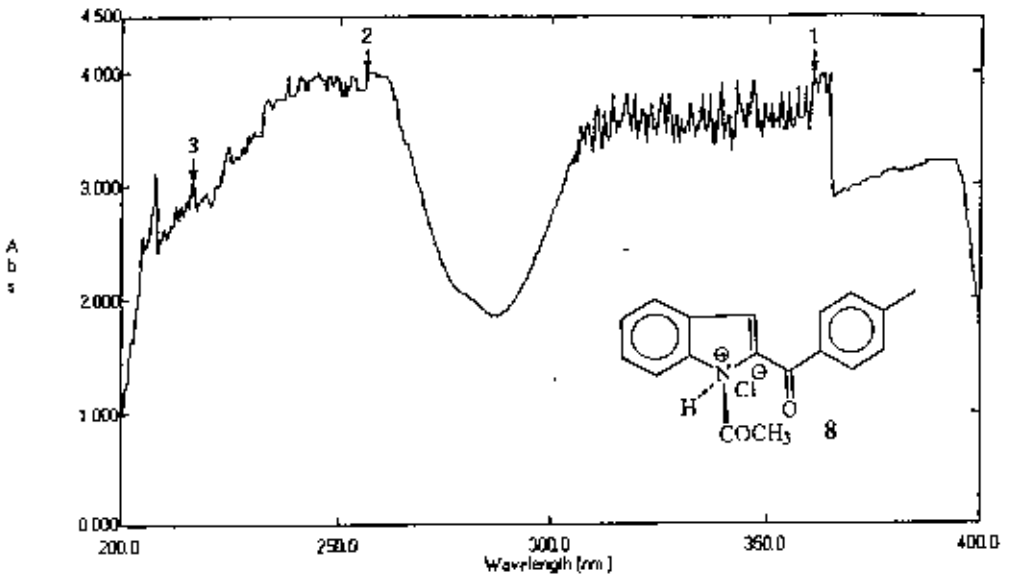
CHANNEL f1
NUC1 13C
P1 8.30 usec
PL1 -6.00 dB
SFO1 100.5253045 MHz

CHANNEL f2
CPDPRG2 waltz65
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 100.5152874 MHz
WDW EM
SSB 0
LB 2.50 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 211.017 ppm
F1 21513.27 Hz
F2P -12.942 ppm
F2 -1302.21 Hz
PPMCM 11.33798 ppm/cm
HZCM 1140.77383 Hz/cm

Fig 34: ^{13}C NMR spectrum of compound 8.



File Name: AF81

Created: 12:17 12/11/05
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2

No.	Wavelength (nm.)	Abs.
1	361.00	3.9781
2	256.60	3.9999
3	216.60	3.0316

Fig 35: UV spectrum of compound **8.**

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PART-II

Section-I

Antimicrobial activities of indole derivatives

2.1 Introduction

Human struggle against the affliction disease, decay and death in eternal. The deterioration of human population due to an enhanced prevalence of infections diseases is becoming a global problem[1]. The contemporary treatment of infection disease involves administration of a multi drug regimen over a long period of time, which has led to the rapid emergence of multi drug resistantstrains plus a high level of patient noncompliance[1]. The prevalence of multi drug resistant superbugs like methicillin- resistant *Staphyli coccus aureus* and *Vancomycin* resistant *Enterococcus faecium centinus* to provide inpetus for the research and discovery to overcome thus resistance problem is to design new and innovative agents with a completely different mode of action, so that, no cross-resistance with the present therapeuticals can occur. Bangladesh is predominantly an agricultural country, depending mainly on crop plants, agriculture and forest products for its economic development. Although crops play a vital role in economy of the country and agroecological conditions are favourable for the production of various crops, the yield of crops is often poor. Plant disease caused by different micro-organism play a sufficient role. Various chemical are used to protect or to kill the pathogenic microorganism. Some chemicals do not kill the microorganisms. They simply inhibit the microbial growth. This phenomenon is called 'stasis'. But some chemicals are called 'pesticides' on the basis of kinds of pathogenic microorganisms. Pesticides may be different types e.g. Fungicides, Viricides etc.

The world bactericide and fungicide have originated from latin words: bacteria, fungus and caedo. The word caedo means 'to kill'. Thus literally speaking a bactericide and fungicide would be any agency, which have the ability to kill a bacteria of fungus. By common usage, the word is restricted to chemicals. Hence the words bactericide and fungicide would mean a chemical capable of killing bacteria and fungus respectively.

A good pesticides should be toxic to the parasite or inhibit the germination of its spores without causing phytotoxicity. A number of chemicals were used to control

the microbial pathogen of human and other animals as medicine. The number of chemicals available for plant diseases control run into hundreds, although all are not equally safe, effective and popular. Also different types of organic, aromatic, inorganic and heterocyclic compounds are employed as antibacterial agents. Salts of toxic metals and organic acids, organic compounds of mercury and sulfur, quinones and heterocyclic nitrogen compounds are the major fungicides in use today.

Many aromatic compounds have significant antimicrobial activity and have been developed into fungicides. Some of these are in commercial use. Examples of this groups of fungicide are Dcoxn (Dimethylaminobenzenediazosodiumsulfonate), Diconil (Tetrachloroisohpthaloutrile) etc. Heterocyclic uitrogen compound used as fungicides included glyodin 2-hepto-decay-2-imidazolin acetate), Oxine (8-hydroxy quinoline) etc.

It was found from the literature that nitrogen and sulfur containing heterocyclic compounds showed marked antimicrobial activities[2-6], when heterocyclic part like imidazoles, nitroimidazole etc. become attached to carbohydrates[7], their efficacy to inhibit fungi of bacteria sharply increased.

It was also found that large number of biologically active componnds possess aromatic and heteroaromatic nucleus. It is also known that, if an active nucleus is linked to another nucleus, the resulting molecule may possess greater potential for biological activity[8]. The benzene and substituted benzene nuclei play an important role as common denominators for various biological activities. It was observed that many a time the combination of two or more nucleus enhanced the biological profile many fold than its parent nuclei. S. M. Shehab[9,10], a post graduate student of Chittagong University laboratory. performed antifungal activities of heterocyclic nitrogen compounds. He used four plant pathogenic fungi such as, *Fusarium equiseti*, *Macrophomina phaseolina*, *Alternaria alternata* and *Curvularia lunata*. He found good inhibition against these tested organisms.

S. Rahman[11], showed that antimicrobial activities of the alkaloids of three plant leaves. The alkaloid fractions were screened against eight pathogenic bacteria. *Viz.* *Shigella dysenteriae*, *Shigella sonnei*, *Salmonella typhi*, *Bacillus oubtilis*, *B. Megaterium*, *B. cereus*, *Staphylococeus aureus*, *Pseudomonas aeruginosa*. The highest zone of inhibition was recorded against *Salmonella typhi*.

S. M. Shehad[12,13]. a former research student of organic laboratory in Chittagong University carried out antifungal activities of a series of acylated D-mannose derivatives, He used four phytopathogenic fungi, such as, *Macrophomma phaseolina*, *Fusarium equiseti*, *Alterneria alternata* and *Curvularia lunata*. Most of the tested chemicals showed good inhibition (more than 50% growth against the above organism).

S. M. Abe Kawasar[14,15] also a former graduate student of the same laboratory carried out in *vitro* antibacterial activities of a series of acylated uridine derivatives. He used ten bacteria such as, *Staphylococcus aureus*, *Bacillus megaterium*, *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Shigella dysenterial*, *Shigella dysenterial INABA-ET (vibrio)* and *Sarcina lutea*. It was observed that most of the acylated compounds exhibited moderate to good antibacterial activity.

M. Fakruddin[16] carried out antifungal activities of fussed pyrimidine. He used five human pathogenic bacteria, viz. *Bacillus subtilies*, *Bacillus megaterium*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and four phytopathogenic fungi Viz *Virticilliu SP*, *Fusariam solanae*, *Aspergilius SP*. *Pencillum SP*. He found that some of the tested chemicals showed very effective antibacterial and antifungal activity.

Recently, our groups synthesized 2-substituted benzofuans[17], isoindolinone and isoquinolinone[18], and tested their anti bacterial and antifungal activities. The synthesized compounds demonstrated mild to significant growth inhibitors against antibiotic –susceptible standard and clinically isolated strains of Gram positive and Gram negative bacteria as well as human fungal pathogens.

PART-II

Section-II

Methodology of the antimicrobial study

2.2.1. Materials and Methods:

Bacteria and fungi were responsible for many infection diseases. The increasing clinical of drug resistant microbial pathogens has lent additional urgency of antimicrobial research. The antimicrobial screening which was the first stage of any agent. This test measures the ability of each antimicrobial agent to inhibit the in *vitro* microbial growth.

The ability may be estimated by either of the following three methods.

i) Disc diffusion method

ii) Serial diffusion method

iii) Bio autographic method.

This disc diffusion technique (Bauer *et al*[19].1966) was widely accepted in *vitro* investigation for preliminary screening of agents which may possess any antimicrobial activity. It was essentially a quantitative of qualitative test indicating the seusitivity or resistance of the microorganisms to the materials. However, no distinction between bacteriostatic of bactericidal activity cau be made by this method. (Roland[20], R, 1982).

2.2.2. Principle of disc diffusion method

Solutions of known concentration (µg/ml) of the test samples were made by dissolving measured amount of the defined volume of solvents. Dried and sterilized filter paper discs (6 cm diameter) were then impregnated with known amounts of the test substance using micropipette. Discs containing the test material were placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard antibiotic dices and blank discs (impregnated with solvent) were used as positive and negative control.

These plates were then kept at low temperature (4°C) for 2 h to allow maxinum diffusion.

During this time dried discs absorb water from the surrounding media and then the test materials were dissolved and diffused out of the media. The physical law

controls the diffusion of molecules through agar gel. As a result there was a gradual change of test materials concentration in the surrounding the discs. The plates were then incubated at 37°C for 24 h to allow maximum growth of the organisms. If the test materials had any antimicrobial activity, it would inhibit the growth of the microorganisms giving a clear, distinct zone called "Zone of Inhibition". The antimicrobial activity of the test agent was determined by measuring the diameter of zone of inhibition expressed in millimeter.

The experiment was carried out more than once and the mean of the reading was required (Bauer *et al*[19] 1966). In the present study some pure compounds were tested for antimicrobial activity by disc diffusion method.

2.2. 3. Experimental

2.2.3.A. Apparatus and reagents

Filter paper discs
Sterile cotton

Micro pipette
Laminar air flow hood
Refrigerator

Chloroform
Patridishes
Sterile forceps

Screw cap test tube
Auto clave

Nutrient Agar Medium
Inoculating loop
Sprit burner

Nose mask and hand gloves
Incubator
Ethanol

2.2.3.B. Test of organisms:

The bacterial stains nsed for the experiment were collected as pure cultures from the Institute of Nutrition and Food Science (INFS), University of Dhaka. Both Germ positive and Gram negative organism and fungi were taken for the test and they were listed below:

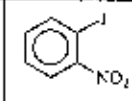
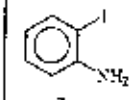
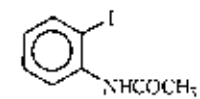
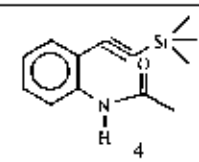
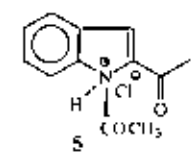
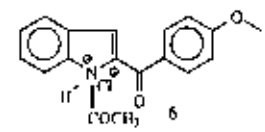
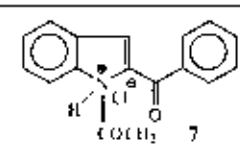
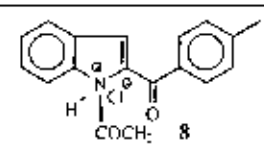
List of Test bacteria

1. Gram positive	2. Germ negative
Bacillus cereus	*Escherichia coli*
Bacillus megaterium	*Salmonella paratyphi*
Bacillus subtilies	*Salmonella typhi*
Staphylo coccus aureus	*Vibrio parahemolyticus*
Sarcina lutea	*Vibrio mimicus*
	Shigella dysenteriae
	P.-aureus

List of Test Fungi

Fungi
Aspergillus niger
Candida albicans
Saccharo myces cerevisiae.

2.2.4. Test of materials:

Compound No.	Name of the Compounds	Structure of the Compounds
1.	2 – Iodonitrobenzene	 1
2.	2 - Iodoamine	 2
3.	2- Iodoacetanilide	 3
4.	2- Trimethylsilylethynylacetanilide	 4
5.	*N*- Acetyl –2– acetyl indolium chloride	 5
6.	*N*- Acetyl –2– anisoylindoliumchloride	 6
7.	*N*- Acetyl –2–benzoylindoliumchloride	 7
8.	*N*- Acetyl –2-tolylindoliumchloride	 8

2.2.5 Culture Medium

Mueller-Hinton (MH) medium and Potato Dextrose Agar (PDA) were used for making plates on which antibacterial and antifungal sensitivity tests were carried out respectively. The antibacterial activity of the metals were detected by disc diffusion method [Bauer *et al*[19], 1966] and antifungal activity of the materials were assessed by food poison. Technique [Miah *et al*[21] 1990 and Groves *et al*,[22] 1962]. This media were also used to prepare fresh cultures.

2.2.6 Medium used:

The medium used were Nutrient Agar (NA) and potato dextrose Agar (PDA). The composition and preparation procedure of NA and PDA were described below.

2.2.6.A. Composition of Nutrient Agar Medium:

Ingredients	Amount (gm/Lit)
Peptone	5.0 gm
Sodium Chloride	5.0 gm
Beef extract	1.5 gm
Yeast extract	1.5 gm
Agar	14.0
pH (at 25°C)	7.2 –7.6

Procedure:

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

2.2.6.B Composition of Potato Dextrose Agar:

Ingredients	Amount (gm/Lit)
Potato	200.0 gm
Dextrose	20.0 gm
Agar	15.0 gm

Procedure:

200 gm of sliced potato was boiled in 500 ml distilled water and extract was decanted after proper boiling. The extract was taken in a 1000 ml beaker and the solution was made up to the mark with distilled water. These solution was taken in a suspense and 20 g dextrose was added slowly in the solution. Then 15 g of agar powder was added in the solution and they were mixed thoroughly with a glass rod. After 10 minutes of boiling the medium was transferred in 250 ml conical flask. Before auto cleaving the conical flask was closed with the cotton plug and rapping with aluminium foil. The medium was autoclaved for 15 minutes at 121°C and 15 lb/sq pressure. After autoclaving the medium was used for culture of different microorganisms.

2.2.7 Sterilization Procedure:

In order to avoid any type of contamination by the test organisms the antibacterial screening was done in laminar Hood and all types of precautions were highly maintained. UV light was switched on an hour before working in the laminar Hood. Petridishes and other glassware were sterilized by autoclaving at a temperature of 121°C and pressure of 15 lb/sq. inch for 20 minutes. Micropipette tips, cotton, forceps discs etc. were also sterilized.

2.2.8 Preparation of subculture

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

2.2.9 Preparation of the test plates

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

2.2.10. Preparation of the Discs:

Three types of disc were used for antibacterial screening. They were:

A. Standard disc

B. Blank Disc and

C. Sample Disc.

The description of these disc were given below:

A. Standard Discs:

These were nsed as positive control to ensure the activity of standard antibiotic against the test organisms as well as for comparison of the response produced by the known antibacterial agent with that of produced by the test sample. In this investigation, kanamycin (30 μg/ disc) standard disc was used as the reference.

B. Blank Discs:

These were used as negative control which ensure that the residual solvent (left over the disc even after air drying) and the filter paper were not active themselves.

C. Sample Discs with Test Sample:

Measured amount of each test sample was dissolved in specific volume of solvent to obtain the desired concentrations in an aseptic condition. Then discs were soaked with solutions of test samples and dried.

2.2.11 Diffusion and Incubation:

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

2.2.12 Determination of Antibacterial Activity by Measuring the Zone of Inhibition:

After incubation the antibacterial activities of the test material were determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale.

PART-II

Section-III

RESULTS AND DISSCUSSION

Antimicrobial Study

2.3.1 Results and Discussion

A total of eight compounds (four starting materials and four indolium chloride derivatives) have been tested for in *vitro* antimicrobial activity against Gram positive and Gram negative bacteria as well as human fungal pathogens. The selected microbes collected as fresh cultures from the Institute of Nutrition and Food Science (INFS), University of Dhaka, Dhaka-1000. No clinically isolated resistant strains were used for the present study. In terms of diameters of zones of inhibitions (mm), the antimicrobial activities were measured. To avoid the experimental and individual errors, all the experiments were performed thrice. The mean value of the diameters of zones of inhibitors (M. DIZ) was taken as in disc for determining antimicrobial spectra. Sensitively test results were interpreted in the table and were compared with a standard antibiotic kanamycin (30 μg/disc).

In the present investigation, the Gram positive as well as Gram negative bacteria were used and were found to be completely resistant against four compounds **3**, **4**, at dose level of 400 μg/ disc.

a. 2-iodonitrobenzene **1**

Showed mild in *vitro* antimicrobial activity against sixteen bacteria. Among them compound 1 causes the mean value of the diameters of zone of inhibition M. DIZ was 7.5 for *B. Cereus*, *B. Migaterium* causes 10 M. DIZ value, *Bacillus sabtilis* causes 9.1 M. DIZ, *S. Lutea* 6.5 M. DIZ, The M. DIZ value for Gram positive bacteria ranges from 7.10 to 10. For Gram negative bacteria *S. paratyphi* have 7.2 M. DIZ (mild) *S. typhi* 14 M. DIZ (intermediate) *V. mimicus* 8 M DIZ (mild), *E. Coli* 7.1 M DIZ (mild), *S. Dysen teriae* 7.5 M. DIZ (mild) *P. aureus* 7.5 M DIZ (mild).

Among the Gram negative bacteria, *S. typhi* caused the intermediate activity and *Shigella boydii* was completely resistant.

The antimicrobial activity towards human fungal pathogens, *S. cerevaceae* have 7.2 M. DIZ (mild), *C. albicans* 8.1 M DIZ (mild) *A. nigar* 10 M. DIZ (mild).

b. 2-Iodoaniline **2**

The average antimicrobial activity was 6.5 M. DIZ which indicated the mild activity. The antimicrobial activities of Gram positive bacteria *B. cereus* 5.1 M. DIZ (mild) , *B. Megaterium* 5.5 M. DIZ (mild) *Bacillus Subtilies* 6.5 M.DIZ (mild), *S. aureus* 6.5 M.DIZ (mild), *S. Lutea* 8 M. DIZ (mild) were observed.

Among the Gram negative Bacteria *S. paratyphi* 6.5 M. DIZ (mild), *S. typhi* 6.5 M. DIZ (mild), *V. parahemolyticus* 6.8 M. DIZ (mild), *V. mimicus* 7 M. DIZ (mild), *E. coli* 6.5 M. DIZ (mild). *S. dysenteriae* 6.5 M. DIZ (mild), *P. aureus* 7.5 M. DIZ (mild), and *Shigella boydii* 6.1 M. DIZ (mild). Were obtained.

For human fungal pathogens *S. cerevaceae* 6.5 M. DIZ (mild), *C. albicans* 6.5 M. DIZ (mild), *A. niger* 6.5 M. DIZ (mild) were obtained.

The antimicrobial activity towards the bacteria and fungus was mild.

c. 2-Iodoacetanilide **3**

This compound was completely resistant against Gram-positive, Gram negative as well as human fungal pathogens.

d. 2-(Trimethylsilylethynyl)acetanilide **4**

Compound 4 was also completely resistant against the tested five Gram positive, eight Gram negative and three fungus organisms.

e. N-Acetyl-2-actylindoliumchloride **5**

This compound was highly reactive towards the selected tested organisms. When the mean value of the diameters of zone of inhibition M. DIZ was greater than eighteen millimeter indicated sensitive for Gram positive bacteria and for Gram negative bacteria it was greater than 16 mm. This compound was tested for

two times at a dose level of 400 µg/disc and 200 µg/disc. For this compound the size of the microbes were higher.

The antimicrobial activity of *N*-Acetyl-2-actylindoliumchloride **5** against 16 bacteria of 400 µg/disc and 200 µg/disc were given as a table: 1.

Table-1: Comparison of different dose of comp **5.**

Sl. No.	Quality	Name of microbes	M. DIZ values for 400 µg/disc (mm)	M. DIZ values 200 µg/disc(mm)
1	G (+)	*B. cereus*	18.2	16.4
2	G (+)	*B. Megaterium*	22	21.9
3	G (+)	*Bacillus sabtilis*	14.5	14.4
4	G (+)	*S. aureus*	17	15.4
5	G (+)	*S. Lutea*	21.0	15.7
6	G (-)	*S. paratyphi*	14.51	16.1
7	G (-)	*S. typhi*	30.1	16.2
8	G (-)	*V. parahemolyticus*	21.0	18.1
9	G (-)	*V. mimicus*	17	14.5
10	G (-)	*E. coli*	20	14.8
11	G (-)	*S. dysenteriae*	16.5	17.4
12	G (-)	*P. aureus*	19.5	14.2
13	G (-)	*Shigella boydii*	16	19.2
14	Fungus	*S. cerevaceae*	17	13.7
15	Fungus	*C. albicans*	17	17.7
16	Fungus	*A. niger*	20	16.9

Among the five Gram positive bacteria the antimicrobial activity against *S. Lulea* was highest 21 M. DIZ , For Gram Negative bacteria, the highest M. DIZ was found for *S. typhi* (30) and Fungal activity was found for *A. nigar* 20 M. DIZ.

f. *N*-Acetyl-2-anisoylindoliumchloride **6**

The antimicrobial sensitivity test for compound **6** gave the M. DIZ value fluctuated from **8** to **9**. The M.DIZ value indicated that the compound **6** was resistant towards the tested bacteria.

The M. DIZ values for Gram positive bacteria at 400 µg/disc were *B. cereus* 9.4 M. DIZ *Bacillus sutlilis* 8.4 M. DIZ, *B. Megaterium* 8.9 M. DIZ, *S. aureus* 9.6 M. DIZ, *S. Lutea*. 7.4 M. DIZ were observed.

For Gram negative bacteria *S. paratyphi* 9.9 M. DIZ., *S. typhi* 9.6 M. DIZ, *V. parahemolitycus* 9.8 M. DIZ, *V. mimicus* 9.5 M. DIZ, *E. coli* 8.7 M. DIZ, *S. dysenteriae* 9.2 M. DIZ, *P. aureus* 8.4 M. DIZand *Shigella boydii* 9.8 M. DIZ were observed.

The activity against human fungal pathogens *S. Cerevaceae* 8.8 M. DIZ *C. albicans* 9.6 M. DIZ, *A. Nigar* 8.6 M. DIZ were observed.

g. *N*-Acetyl-2-benzoylindoliumchloride **7**

The M. DIZ value ranges from 10 to 13, indicated resistant against the sixteen bacteria. Compound 7 showed the second highest activity.

The M. DIZ value for Gram positive bacteria *B. cereus* .10.5 M. DIZ, *B. megaterium* 13.2 M. DIZ, *Bacillus subtilies* 9.9 M. DIZ, *S. aureus* 11.4 M. DIZ *S. Lutea* 11.9 M. DIZ were found.

But for Gram negative bacteria *S. paratyphi* 12.4 M. DIZ, *S. typhi* 11.9 M. DIZ, *V. parahemolyticus* 12.3 M. DIZ, *V. mimicus* 12.5 M. DIZ, *E coli* 9.9 M. DIZ, *S. dysenteriae* 11.8 M. DIZ, *P. aureus* 10.1 M. DIZ and *Shigella boydii* 12.6M. DIZ were afforded.

In the human fungal pathogeus *S. cerevaceae* 15.5 M. DIZ *C. albicans* 11.7 M. DIZ, *A. Nigar* 12.4 M. DIZ were also reported.

h. *N*-Acetyl-2-tolylindoliumchloride **8**

The antimicrobial test against 16 bacteria with compound 8 gave the M. DIZ value ranges from 8.6 to 10, which indicated resistant.

The mean value of the diameter of zone of inhibition against Gram positive bacteria were given below.

B. cereus 8.6 M. DIZ *B. Megaterium* 9.9 M. DIZ, *Bacillus subtilis* 8.3 M. DIZ, *S. aureus* 9.1 M. DIZ, *S. Lutea*. 8.7 M. DIZ were observed.

For Gram negative bacteria *S. paratyphi* 10.2 M. DIZ, *S. typhi* 9.7 M. DIZ, *V. parahemolitycus* 9.7 M. DIZ, *V. mimicus* 10.2 M. DIZ, *E. coli* 9.4 M. DIZ, *S. dysenteriae* 9.8 M. DIZ, *P. aureus* 9.2 M. DIZand *Shigella boydii* 9.1 M. DIZ were also reported.

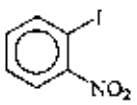
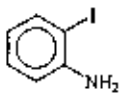
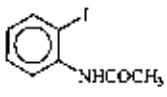
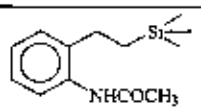
For human fungal pathogens *S. cerevaceae* 9.4. M. DIZ *C. albicans* 10.1 M. DIZ, *A. nigar* 9.8 M. DIZ were found.

The comparison of antimicrobial activity of the starting materials M. DIZ value (mm) was given in table -2.

The comparison of antimicrobial activity of indole compound M. DIZ value (mm) was given in table -3.

Table- 2: In vitro antimicrobial activity of compound **1, 2, 3, 4.**

Potency per disc : 400 µg
Diffusion time : 23 hours
Solvent use : MeOH/ $CHCl_3$
Diameter of zone of inhibition (mm)

Name of the Microorganism	 Comp.-1	 Comp.-2	 Comp.-3	 Comp.-4	Std 20 µg
Gram (+) bacteria					
B. cereus	7.5	5.1	-	-	37.30
B. Megaterium	10	5.5	-	-	43.0
Bacillus sabtilis	9.1	6.5	-	-	38.2
S. aureus	7.32	6.5	-	-	37.2
S. Lutea	6.5	8.0	-	-	32.0
Gram (-) bacteria					
S. paratyphi	7.2	6.5	-	-	30.1
S. typhi	14.0	6.5	-	-	35.0
V. parahemolyticus	8.0	6.3	-	-	41.0
V. mimicus	8.0	7	-	-	17.0
E. coli	7.1	6.5	-	-	37.1
S. dysenteriae	7.5	6.5	-	-	38.0
P. aureus	7.5	7.5	-	-	42.0
Shigella boydii	-	6.1	-	-	31.2
Fungi					
S. cerevaceae	7.2	6.5	-	-	32.1
C. albicans	8.1	6.5	-	-	37.0
A. niger	10	6.5	-	-	35

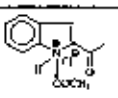
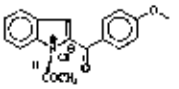
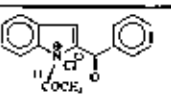
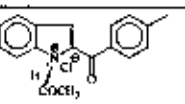
Interpretation of sensitivity test results:

Gram positive bacteria:	Gram negative bacteria:
>18 M. DIZ = sensitive	> 16 mm M. DIZ = sensitive
14-18 mm M. DIZ = intermediate	13-16 mm M. DIZ = intermediate
<14 mm M. DIZ = resistant	> 13 mm M. DIZ = resistant

"–" indicate no sensitivity or zone of inhibition lower than 6 mm.

Table- 3: In vitro antimicrobial activity of indolium chloride compound -**5, 6, 7, 8.**

Diffusion time : 23 hours
Solvent use : MeOH/ $CHCl_3$
Diameter of zone of inhibition (mm)

Name of the Microorganism	 Comp.-**5**		 Comp.-**6**	 Comp.-**7**	 Comp.-**8**	Std 20 µg
Gram (+) bacteria	400µg/ disc	200µg/ disc	400µg/ disc	400µg/ disc	400µg/ disc	
B. cereus	18.2	16.4	9.4	10.5	8.6	35.1
B. Megaterium	22	21.9	8.9	13.2	9.9	37.8
Bacillus sabtilis	14.5	14.4	8.4	9.9	8.3	33.4
S. aureus	17	15.4	9.6	11.4	9.1	36.1
S. Lutea	21.0	15.7	7.4	11.9	8.7	32.2
Gram (–) bacteria						
S paratyphi	14.51	16.1	9.9	12.4	10.2	32.9
S. typhi	30.1	16.2	9.6	11.9	9.7	33.6
V. parahemolyticus	21.0	18.1	9.8	12.3	9.7	37.5
V. mimicus	17	14.5	9.5	12.5	10.2	36.9
E. coli	20	14.8	8.7	9.9	9.4	34.7
S. dysenteria	16.5	17.4	9.2	11.8	9.8	36.3
P. aureus	19.5	14.2	8.4	10.1	9.2	36.9
S. Lutea	21.6	15.7	7.4	11.9	8.7	35.5
Fungi						
S. cerevaceae	17	13.7	8.8	11.5	9.4	31.3
C. albicans	17	17.7	9.6	11.7	10.1	37.2
A. niger	20	16.9	8.6	12.4	9.8	33.3

Interpretation of sensitivity test results:

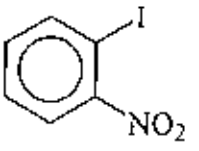
Gram positive bacteria:	Gram negative bacteria:
>18 M. DIZ = sensitive	> 16 mm M. DIZ = sensitive
14-18 mm M. DIZ = intermediate	13-16 mm M. DIZ = intermediate
<14 mm M. DIZ = resistant	> 13 mm M. DIZ = resistant

"–" indicate no sensitivity or zone of inhibition lower than 6 mm .

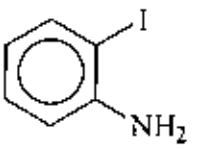
2.3.2 Conclusion:

Eight synthesized compounds have been tested for in antimicrobial activity against five Gram positive and eight Gram negative and three human fungal pathogens. Most of these compound demonstrated mild to moderate antimicrobial activity against most of the test organism. Among tested compounds Indolium chloride salts (**5, 6, 7, 8**) exhibited relatively greater inhibition of growth of the microorganism. But 2-Indonitrobenzene **1** and 2-Iodoaniline **2** show mild activity.

In the case of compound **1** and **2,**



1

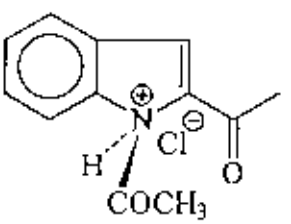


2

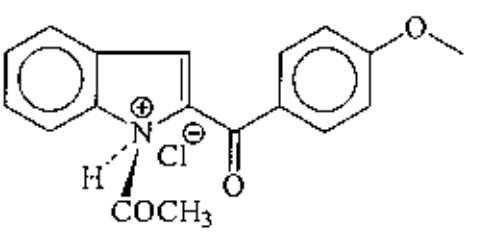
the $-NO_2$ group containing compound causes relatively better antimicrobial growth than $-NH_2$ groups.

We found that, the indolium chloride exhibited relatively higher activity.

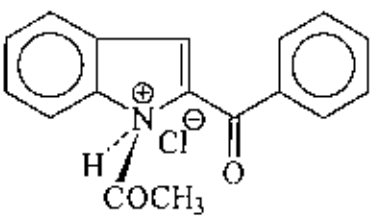
Investigatiou of the S-A-R (structure activity relations) of compounds **5, 6, 7** and & **8** were given below:



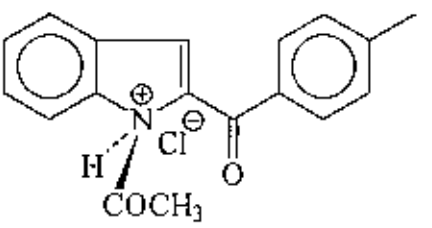
5



6



7



8

From these structure we found that the indole ring causes the better microbial growth. The substituents at 2-position gave different activity.

-COR	highest sensitively
$-COCH_3$	> 18
-COPh	10 ~ 12
$-COC_6H_4\ CH_3$-*p*	9 ~ 10
$-COC_6H_4OCH_3$-*p*	8 ~ 9

The acetyl groups showed highest activity. Varying substitution at the indole moiety and subsequent antibacterial screening identified the 2-acetyl functionality as a new structural alternative for optimal anti microbial property in the indole class of compounds.

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