Palladium Mediated Synthesis of Isoquinolinone Derivatives and Study of Their Biological Activities.

A Dissertation
Submitted in the partial Fulfillment of the requirement
for the Degree of Master of philosophy(M. Phil)
in Chemistry.

Submitted by

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Roll No: 100103112F
Registration No: 0110043
Session : October, 2001

September 12, 2004

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Department of Chemistry
Bangladesh University of Engineering
and Technology (BUET). Dhaka-1000.
Bangladesh.

DEDICATED
To
My Father
And
To The Memory Of

My Mother

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

THESIS ACCEPTANCE LETTER:

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A. F. G. Masud Reza
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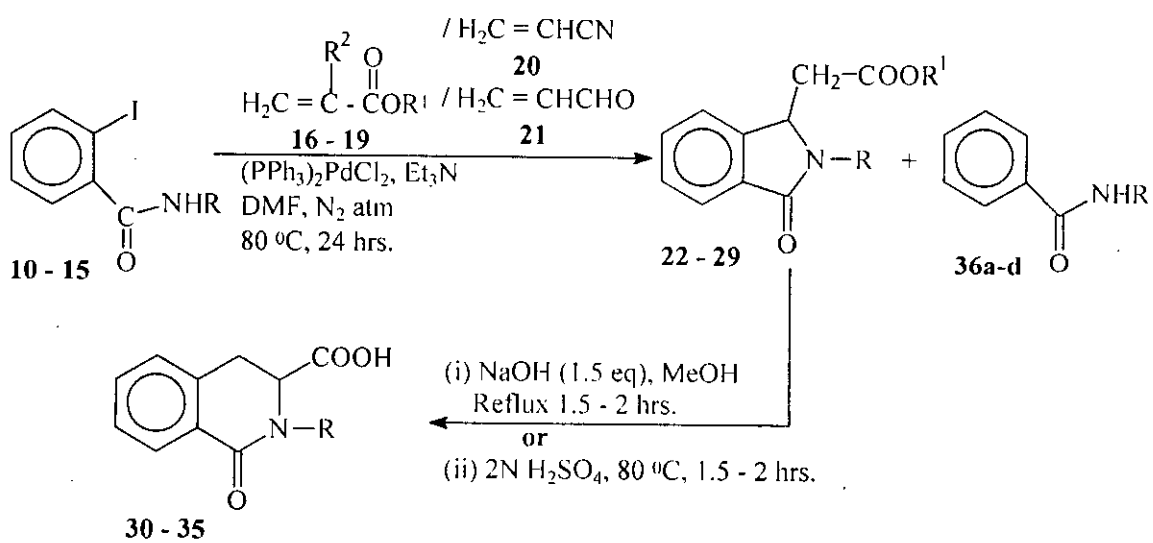
Thesis Title: Palladium Mediated Synthesis of Isoquinolinone Derivatives and Study of Their Biological Activities.

Abstract

Isoquinolinones (1-oxo-1,2-dihydroisoquinoline) are a class of fused heterocycles that are of increasing interest in synthetic and pharmaceutical chemistry. A convenient and facile method for the synthesis of 1,2,3,4-tetrahydro-1-oxoisoquinoline–3-carboxylic acid by palladium-catalyzed reaction of *N*-substituted-2-iodobenzamide with acrylic ester is reported. *N*-(Alky) Aryl-2-iodobenzamides **10-15**, when stirred with acrylate **16-21** in presence of bis (triphenyl phosphine) palladium (II) chloride in DMF and triethylamine at 80 °C for 24 h gave *N*-substituted-3-alkylisoindolin-1-one acetate **22-29** which afforded *N*-substituted-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid **30-35** on base/acid catalyst hydrolysis.



In *Vitro* antimicrobial activity of 3-substituted isoindolinone acetate and isoquinolinone-3-carboxylic acid were evaluated. The compounds demonstrated mild growth inhibition against antibiotic-susceptible standard and clinically isolated strains of Gram positive and Gram-negative bacteria as well as human fungal pathogens.

Summary

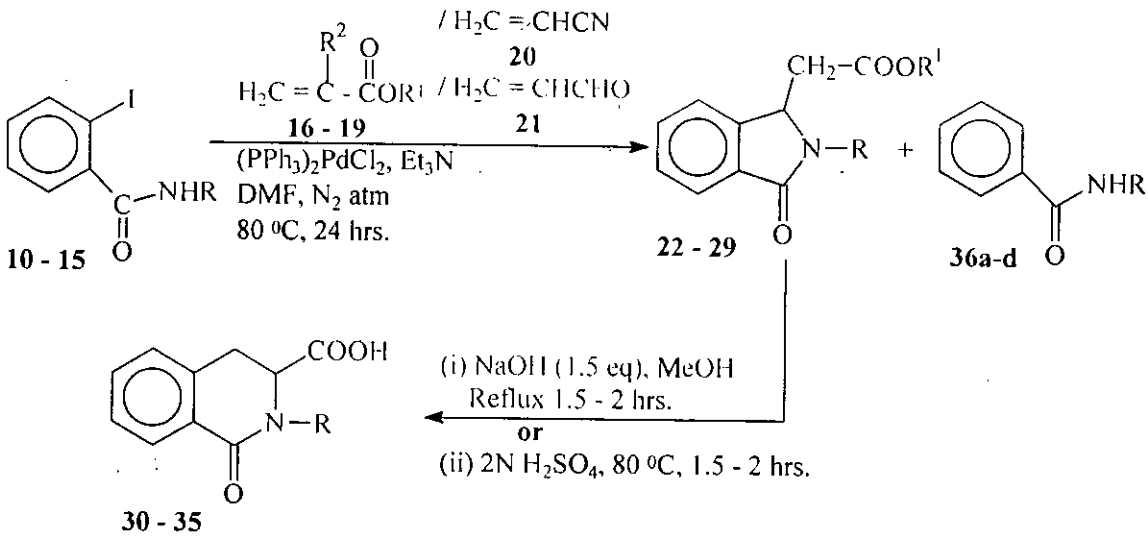
Investigations incorporated in this dissertation entitled "Palladium mediated Synthesis of Isoquinolinone derivatives and Study of their biological activities" have been presented in two parts. Part-I is divided into two sections part-II is divided in three sections. Each part has introductory section-I, in which the background biological action and the important synthetic reactions involved in the synthesis are presented. Section-2 of each part deal with the detailed methodologies and experimental procedures for the synthesis of 3-substituted isoquinolinone and its biological test. Section-2 of part-I and section-3 of part-II represent the results and discussion of the synthesis of the acid of isoquinolinone and their biological test respectively.

Part-I: Synthesis of isoquinolinone.

It represents the importance and synthesis of isoquinolinone derivatives. Isoquinolinones (1-oxo-1, 2-dihydroisoquinoline) are a class of fused heterocycles that are of increasing interest in synthetic and pharmaceutical chemistry. In spite of their scarce presence in nature, isoquinolinone derivatives have provoked considerable interest due to their pharmacological activities. Various methods are known for the synthesis of 1(*2H*)-isoquinolinone and 1,2,3,4-tetrahydro-1(*2H*)-isoquinolinone. However, palladium-catalyzed procedure for the synthesis of isoquinolinone are limited in number.

In section-2, we report a new strategy for the regioselective synthesis of isoquinolinone **30-35** through the palladium-catalyzed condensation of 2-iodo-*N*-substituted benzamides **10-15** with acrylate **16-21** and subsequent cyclization (**scheme-1**). The reactions were usually carried out by heating a mixture of 2-Iodo-*N*-(Alkyl) Aryl benzamides **10-15** (1 mmol) and acrylate **16-21** (3 mmol) in DMF (10 ml) at 80 °C for 24 hrs. under nitrogen atmosphere in the presence of bis (triphenylphosphine) Palladium (II) chloride (3.5 mol %) and triethylanine (4 equiv.) to yield 3-alkyl-*N*-(alkyl) Aryl isoindolin-1-one acetate **22-29**.

The 3-alkyl isoindolinone acetate **22-29** (1 mmol) were subjected to base catalyst hydrolysis using NaOH (1.5 equiv) in MeOH (10 ml) by refluxing the mixture for 1.5 –2 hrs. to alford *N*-(Alkyl) Aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acids **30-35** in good yields. The hydrolysis was also carried out by using 2N H_2SO_4 acid (4 equiv.) in H_2O under heating for 1.5-2 hrs. to yield the same isoquinolinones.



Scheme-1

Compds.		R	Compds.	R^1	R^2	Compds.	R	R^1
10	**34**	CH_3	**16**	C_4H_9	H	**22**	C_6H_5	C_4H_9
11	**35**	$CH_2C_6H_4Cl$–*p*	**17**	C_2H_5	H	**23**	$C_6H_4CH_3$–*p*	C_4H_9
12	**30**	C_6H_5	**18**	CH_3	H	**24**	$C_6H_4OCH_3$–*p*	C_4H_9
13	**31**	$C_6H_4CH_3$–*p*	**19**	CH_3	CH_3	**25**	C_6H_4Cl–*p*	C_4H_9
14	**32**	$C_6H_4OCH_3$–*p*				**26**	$C_6H_4CH_3$–*p*	C_2H_5
15	**33**	C_6H_4Cl–*p*				**27**	$C_6H_4OCH_3$–*p*	C_2H_5
						28	$C_6H_4CH_3$–*p*	CH_3
						29	$C_6H_4OCH_3$–*p*	CH_3

Part-II: Biological Activities.

In Part-II, section-1 the introduction of the biological test is presented. In section-2 and 3 the methodology and results and discussion of the biological test of the ester of isoindolinone and the acid of isoquinolinone are reported respectively.

Six benzamides (**10, 11, 12, 13, 14** and **15**), eight isoindolinone derivatives (**22, 23, 24, 25, 26, 27** and **28**) and six isoquinolinone derivatives (**30, 31, 32, 33, 34** and **35**) have been tested for in antimicrobial activity against five Gram positive and twelve Gram negative bacteria as well as four human fungal pathogens. Most of this compound demonstrated mild to moderate antimicrobial activity against most of the test organism. Among tested compounds isoquinolinone derivatives (**30, 31, 32, 33, 34** and **35**) exhibited relatively greater inhibition of growth of the microorganism as comparative to the benzamides (**10–15**) and isoindolinone (**22–29**) analogus. The higher activity of the compounds (**30–35**) could probably be due to their greater solubility in aqueous medium, which subsequently facilitated the diffusion of the chemical entities through the microbial call wall.

Prefatory Note

Unless otherwise stated the following procedures were used throughout the research work.

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 $CHCl_3$, 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.

1. Purification of solvents and reagents

(a). Dry methanol:

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 flash 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 an airtight bottle.

(b). Dry Ethanol:

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:

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. Pure chloroform had b.p 61°C / 760mm the solvent when free from alcohol, was kept in the dark to avoid the photochemical formation of phosgene. It was not dried with sodium as an expansion occurred.

2. Melting point

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

3. Infra-red (IR) and UV spectra

The Infra-red spectra were recorded on KBr dise for films with a Shimadzu FTIR Spectrophotometer and the UV spectra were recorded in dry EtOH with a Shimadzu UV Visible spectrophotometer at the Department of Chemistry, BUET, Dhaka, Bangladesh.

4. 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.

5. Drying

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

6. Evaporation

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

7. Techniques, preparation and applications of thin-layer chromatography (T.L.C):

Thin layer chromatography is considered to be one of the most useful methods for the separation, purification, progress of the reaction rate and identification of a mixture of organic compounds which involves an absorbent (usually silica gel) as stationary phase and a solvent or solvent mixture as a mobile phase. Due to the differential rate of absorption on the absorbent the compounds of the mixture migrated differently along the T.L.C. plates. In other words, due to the difference in mobility of the components, solvent follows the fact that the more polar compound makes faster the mobility of the components also depends on the polarity of the solvent or solvent mixture.

Procedure for the preparation of T.L.C. platen:

In our laboratory for the preparation of T.L.C. plates usually clinical slide glass plates (1 to 1.5 mm thickness, 1.5 cm breadth and 8 cm length) were used. The plates were cleared with soda water and made completely free from grease. These were then washed with distilled water and then rectified spirit and dried in an electrical oven. Thirty two glass plates of equal thickness were placed on a frame (supplied by quickfit instruments, England). Twelve grams of silica gel was thoroughly mixed with 24 ml of distilled water by swirling in a 250 ml conical flask to yield a homogenous suspension. The spreader was drawn across the plates without applying much force. A uniform layer of adsorbent as obtained. The glass plates thus coated with silica gel (Woelm, TLC) were allowed to stay in position at room temperature until the surface become completely dry. The plates

were then left for about 2 hrs. in an oven at 60 – 65°C for activation as a fine adhering of silica gel with the glass and then these were ready for use.

Procedure for the spotting and development of T.L.C. plates:

The silica gel and alumina coated T.L.C. plates were used. To spot the plates, first a mark was made about 1 cm up from the bottom of each plate and the solution of the compounds were then spotted with thin glass capillaries. More spotting were applied upon the same place to concentrated the component when the first one was completely soaked in. In such a way another spotting was made in a horizonal straight line (base line). The plate was then placed vertically in a suitable solvent in a closed tank, but the spot was not covered by the solvent. The atmosphere inside the tank was saturated with the vapour of the same of the solvent. Development of the chromatogram accused by capillary movement of the solvent up the adsorbent layer. The plates were removed when the solvent front reached half a centimeter apart from a upper edge. The plates were then allowed to dry. If the components of the mixture were coloured, the spots were readily located. If the components were colourless the dried plate was developed with iodine vapour or UV light. For identification of the sample by TLC at least three different solvent were tried and R_f value computed and compared with each case but only the solvent conditions that gave the best results were mentioned. The ratio of the distance traveled by a component to the distance traveled by the solvent front was characteristic of each component and was known as R_f value, i.e.

$$R_f = \frac{\text{Distance traveled by the component front}}{\text{Distance traveled by the solvent front}}$$

True reproducibility in R_f values is however, rarely achieved in practice due to minor changes in a number of variables such as:

i) The particle size of different batches of absorbent.
ii) The solvent composition
iii) Prior activation and storage conditions of the plates
iv) The thickness of absorbent layer.
v) Chamber saturation etc.

Thus when the R_f value for two different components are almost same or hardly distinguishable then to study the different characteristic is the only way to distinguish

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 upper surface of the slurry of the silica gel and the mixture was covered in limited area by some amount of dry silica gel. Then the solvent mixture was passed through the column. The fractions were collected in test tubes about 20 to 30 ml in each at a regular interval of time and respective fractions were detected by TLC. The solvent used for elution was chromatographically pure.

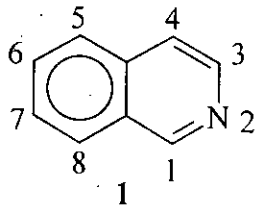
Part – I

Section-1

Background of the Present Work

1.1.A. Introduction:

The isoquinoline **1** and isoquinolinone ring **2** are integral part of many naturally occuring substances[1,2,3]. The importance of isoquinolone derivatives, many of which are pharmacologically active, as intermediates in synthesis of natural products and medicinal chemistry is well documented[4,5,6].



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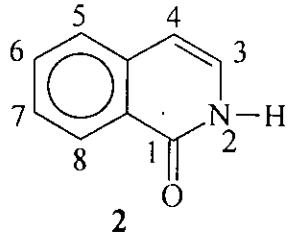


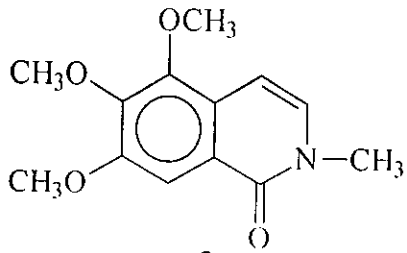
2

Although scarce in nature[7-12], 1(2*H*)-isoquinolones and their perhydro derivatives are constituents of several compounds of medicinal importance. For example 1(2*H*)-isoquinolones have been described as analgesics, antiinflammatory and anticonvulsive agents and tranguilizers. Also, substituted perhydroisoquinoline-3-carboxylic acids have been reported to be potent, systemically active, competitive AMPA receptor antagonists[13].

1.1.B. Naturally Occurring Isoquinolinone:

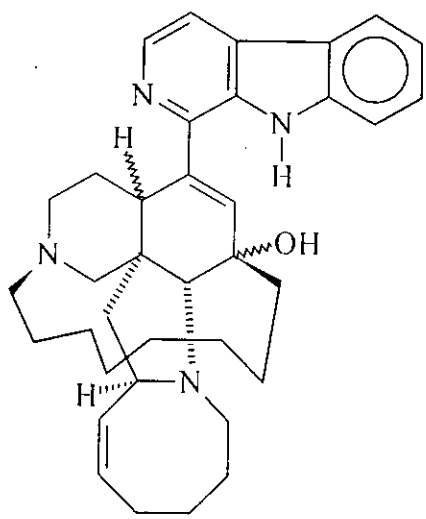
Isoquinoline alkaloids have been a cornerstone in the large collection of naturally occurring substances belonging to the alkaloid family and they figure prominently in the arsenal of pharmacologically active compounds[14].

N. M. Mollove and H. B. Dutschewska isolated[15] a new type of simple isoquinoline alkaloid. Thalactamine, 1-oxo-2-methyl-5,6,7-trimethoxy-1,2-dihydroisoquinoline **3** from the above-ground parts of a Thalictrum minus variety spread near the Black sea coast of Bulgaria.



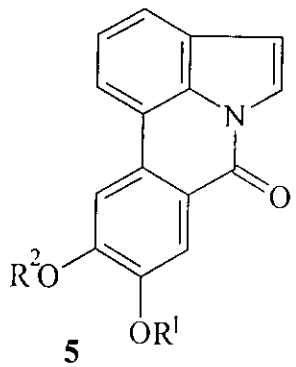
3

The Alkaloid manzamine-A **4**, isolated by Sakai *et at*[16], from Okinawan marine sponge Haliclona SP, exhibits potent antitumour activity (P388. IC_{50} = 0.07 μ/m) . Nakamura and his co-workers[17] have also isolated the same compound from the marine sponge pellina SP.



4

The isoquinolone skeleton containing Hippadine (5a), Pratorimine (5b), Pratorinine (5c), and Pratosinine (5d) comprise a series of Pyrrolophenanthridone alkaloids[18] isolated from the bulbs of several Crinumspecies (Amaryllidaceae). These alkaloids are quite widely distributed in this species and possess significant biological activity. Hippadine (5a) possibly inhibits fertility in male rates with remarkable decrease both in testicular weight and in DNA content[19].

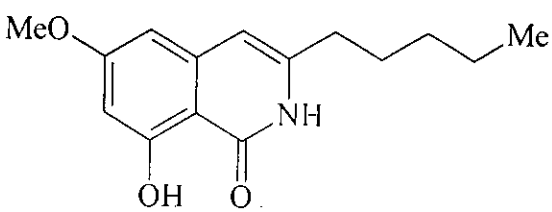


5	R^1	R^2
a	$-CH_2-$	
b	H	Me
c	Me	H
d	Me	Me

5

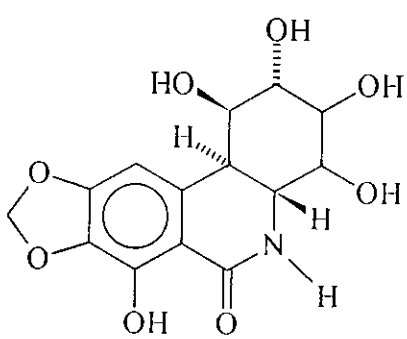
1.1.C. Biologically Important Isoquinolinone:

A new isocarbostyril designated ruprechstyril **6** isolated from Ruprechtia tanagrana exhibited cancer cell and microbial growth inhibition[20].



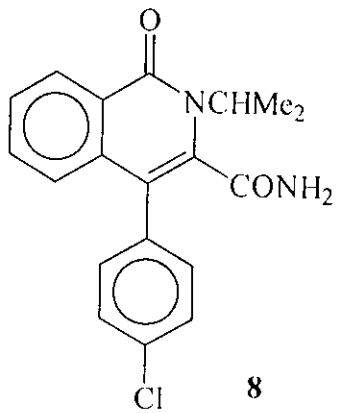
6

The phenanthridone alkaloid pancratistatin **7** [21,22] is of interest because of its antineoplastic activity[23] and synthetically challenging structure which includes a c-ring with six contiguous asymmetric centres.



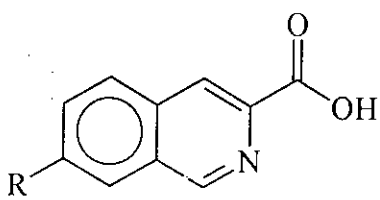
7

3-Carbamide-4-arylisoquinoline-1(2*H*)-ones **8** showed anticonvullsant activity[24] in the max. Electroshock test having an.i.p. ED 50 of 2.1×10^{-4} mol/ kg.

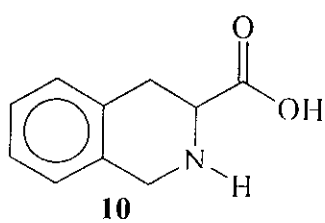


8

Isoquinoline derivatives **9,10,11** are used by medicinal chemists as important conformationaly constrained peptide motifs for phenylalanine and tyrosine inpeptides[25,26]. The replacement phenylalanine in some to statin derived μ-opioid atagonists by 1,2,3, 4- tetrahydroisoquinoline-3-carboxylic acid **10** resulted in one of the most potent and selective μ-opioidreceptor antagonists[27]. Decahydroisoquinoline-3-carboxylic acid **11** is a consituent of saquinavir, the first HIV protease inhibition to reach the market, for use in combination with nucleoside analogues for the treatment of advanced HIV infection[28.29].



9a R = H
9b R = OH
9



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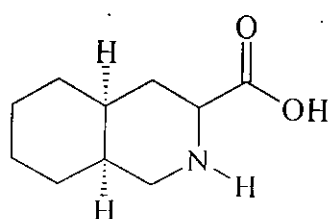
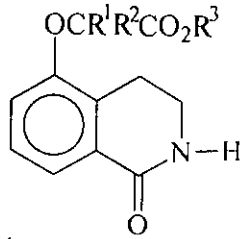


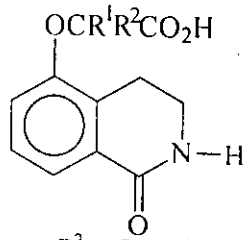
11

5-(Carboxy methoxy)-3,4-dihydro isocarbostyril esters and their corresponding carboxylic acids **12, 13** were found to be anti inflammatory, analgesic, and antithrombosis activities[30].



R^1, R^2 = H, C 1-2 alkyl

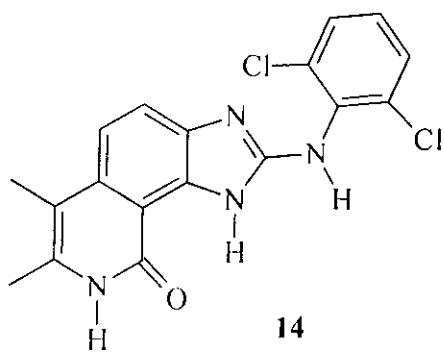
12



$R^3 = C_{1-3}$ alkyl

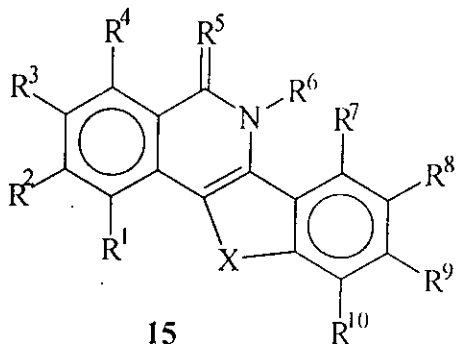
13

Phenylamino imidazo [4,5 -h] isoquinoline-9-one **14** were found to be a potent inhibitors of the tyrosine kinase[31]. These compounds are potentially useful. Therapeutic agents for treating autoimmune diseases.

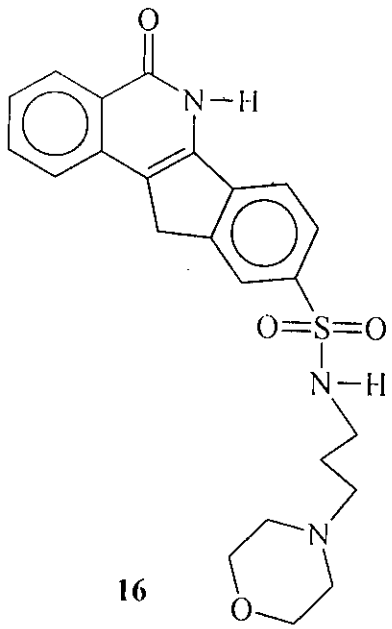


14

Substituted indenol [1,2-c] isoquinoline derivatives **15** were found to be potent for the treatment of inflammatory disease or reperfusion disease[32]. The isoquinolinone dervative **16** was also found to be potent inhibitor of poly (ADP -ribose) synthase 84% at 300 nM.



15



16

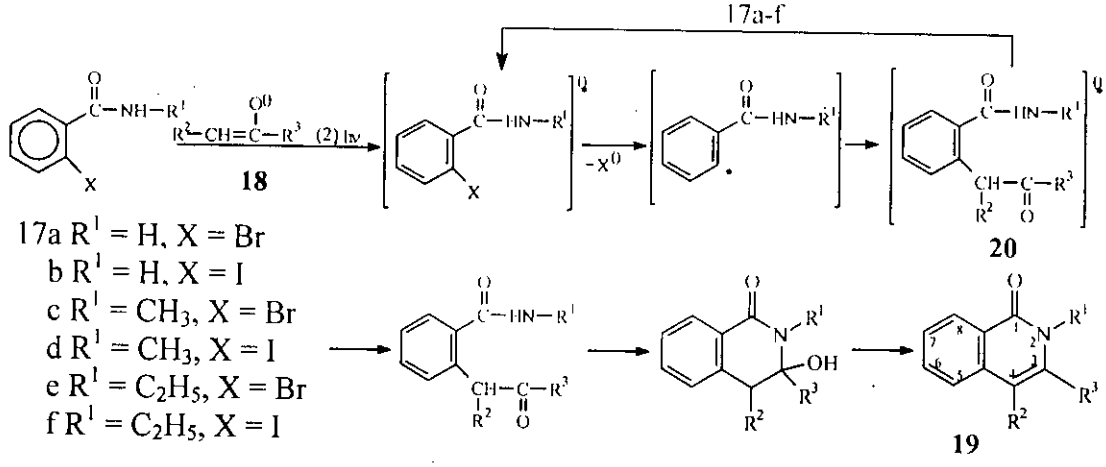
X = CO, CH_2, CH, O, NH, S,

$R^1 - R^4$, $R^7 - R^{10}$ = H, halo, OH, alkoxy, Aryl, NH_2,

R^5= 0, NH, S; R^6 = H, alkyl.

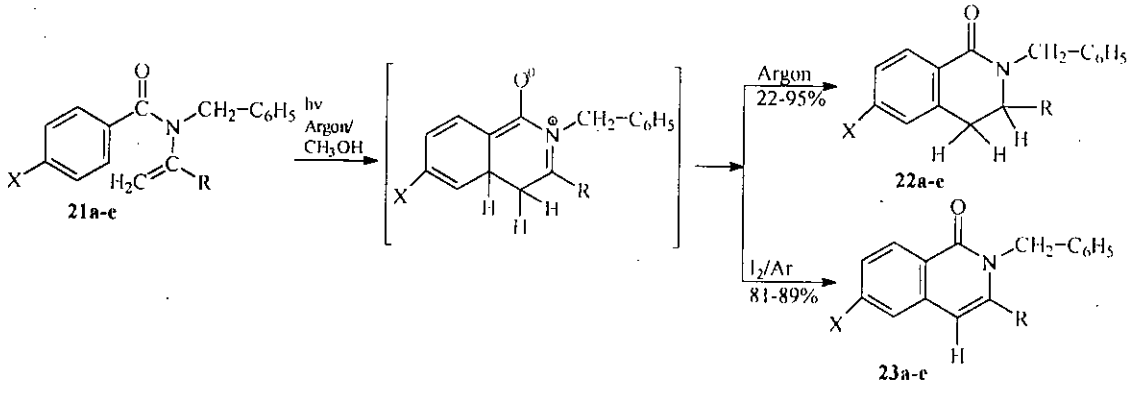
1.1.D. Synthesis of Isoquinolinone Through Classical Methods.

It was reported[33] that treatment of primary **17a,b** or secondary **17c-f** ortho-halobenzamides with various ketone enolates **18** affords the corresponding 3-and 4-substituted 1-Oxo-1,2-dihydro isoquinolines (isocarbostyrils) **19** directly, **Scheme-1**. It was also reported that the lack of regioselectivity for ketones which can produce two enolates leads to a mixture of isocarbostyrils whose ratio depend upon the ratio of the two enolates and of their relative reactivity toward the radical **20**. The yield% was not satisfactory **(Scheme -1)**.



Scheme-1

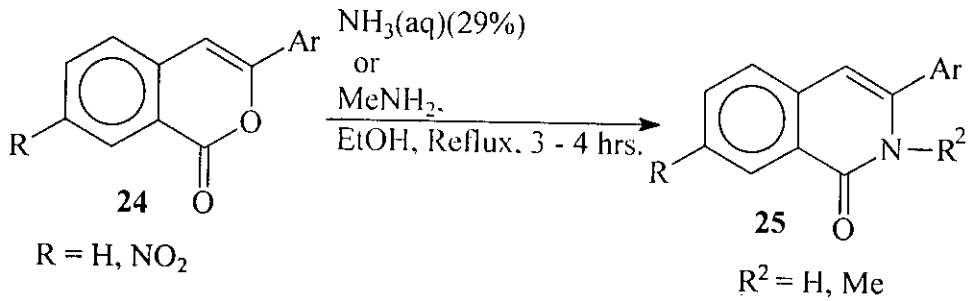
A. Couture *et al*[34] reported irradiation of a carefully degassed methanolic solution of enamides **21a-e** to afford the 3-aryl-2-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinolines **22a-e** which gave the corresponding isocarbostyrils **23a-e** under oxidation reaction. **(Scheme-2).**



Scheme-2

21, 22, 23	R	X
a		H
b	CH_3	H
c	OCH_3	H
d	F	H
e		Cl

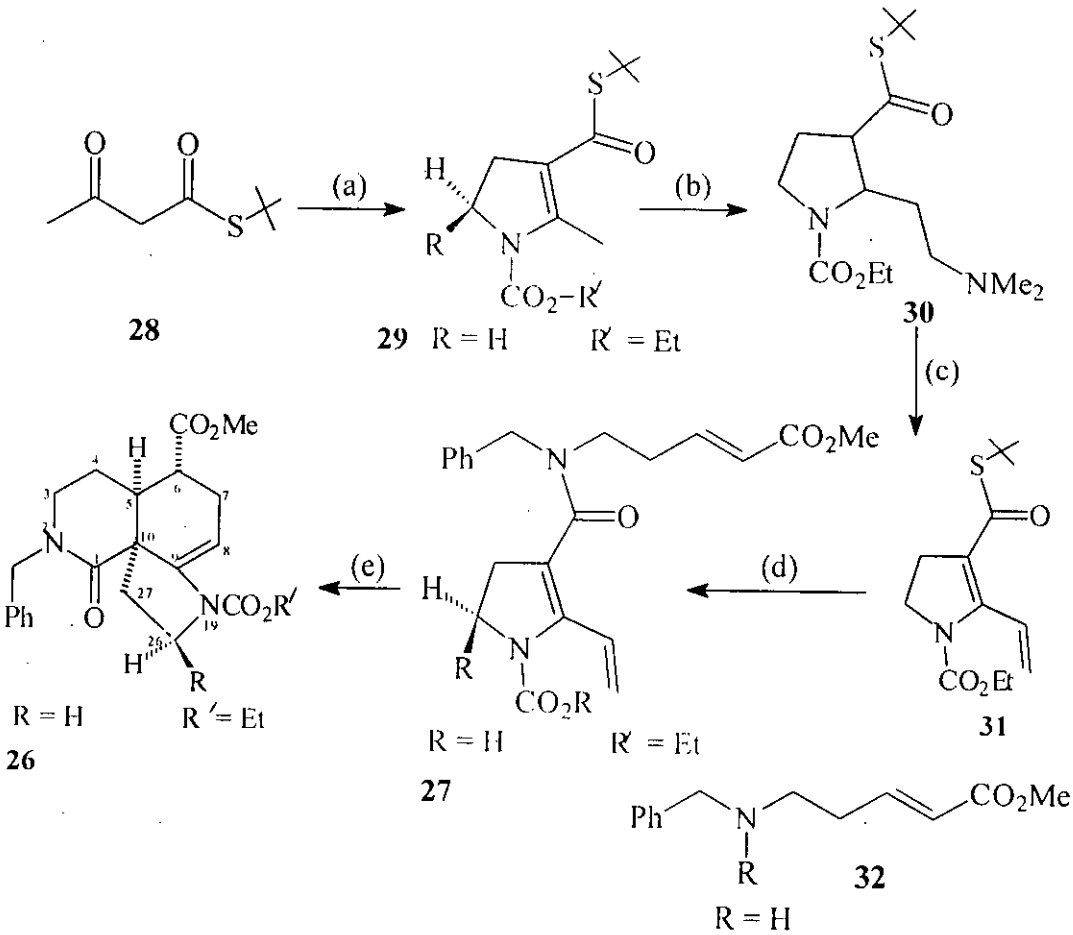
Alain Rose and his co-worker reported[35] the preparation of derivatives of 3-aryl-1,2-dihydro-1-oxoisoquuinoline **25** by the reaction of ammonia or methylamine with a large number of 3 - arylisocoumarins **24 (Schem-3)**.



Ar = 4- Hydroxy phenyl; 4-Methoxy phenyl; 4-Hydroxy-3-methyl phenyl; 2-Hydroxy-4-methyl phenyl.

Scheme - 3

Karel M. J. Brands and his co-workers reported[36] the synthesis of a strategic tricyclic intermediate for the construction of manzamine. The stereoselective synthesis of **26** was visualized by the cyclization of triene **27** in an intermolecular Diels-Alder reaction. Commercially available thiolester **28** was alkylated with $ICH_2CH_2NHCOOEt$ under basic condition and the resulting product cyclized to pyrrolinethiol ester **29**. Subsequently the anion of **29** was subject to monomethylation with the help of Eschenmoser's salt. When the amino group in **30** was further methylated and the quaternary salt induced to undergo a base mediated elimination. The desired product was obtained. Ammonolysis of the thiolester **31** and **32** was carried out in the presence of silver. Triflate and propylethylanine, where upon, the triene **27** was obtained in good yield **(Scheme-4)**.



(a) *i.* NaH, DME, $ICH_2CH_2NHCO_2ET$, r.t-4 hrs. *ii.* TsOH / quinoline, Δ, 30 min. 58%.

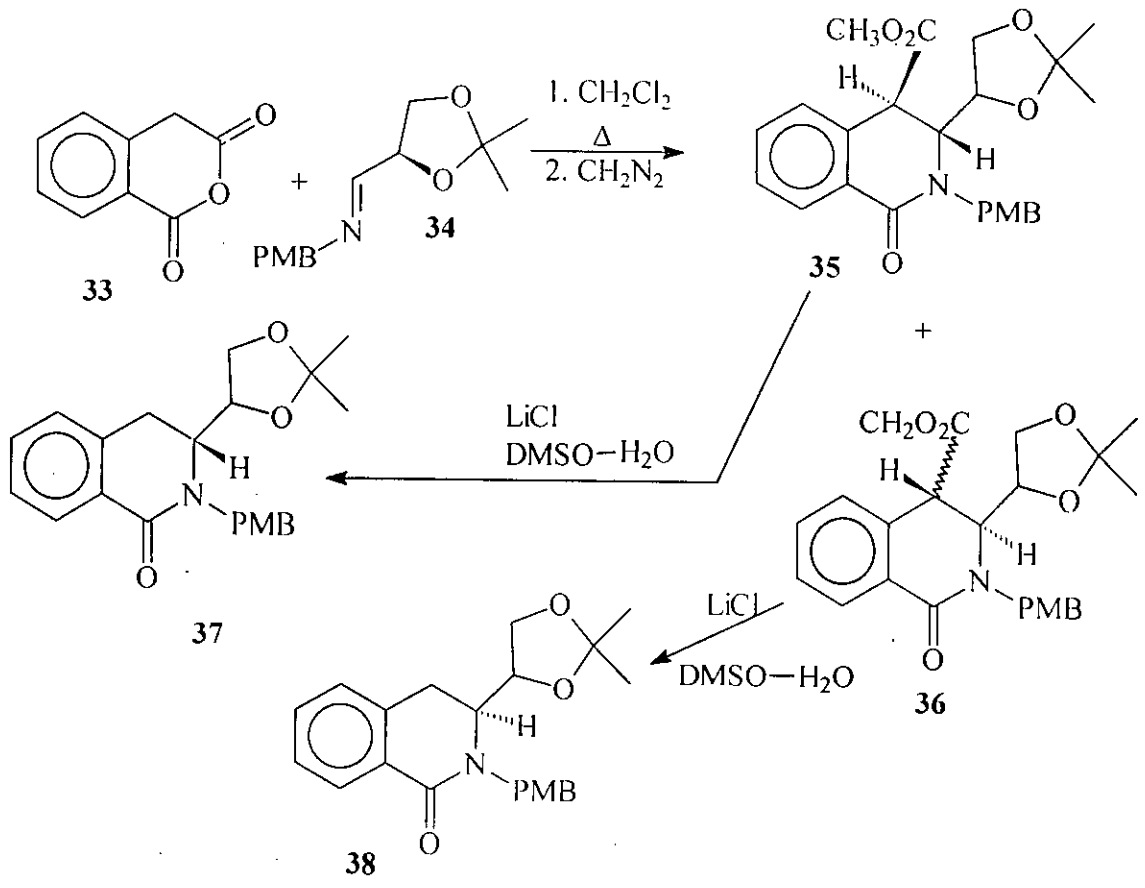
(b) LDA, THE, $CH_2NMe_2^{(+)}I^{(-)}$; 49%; (c) *i.* MeI,CH_3CN,r.t, 16 hrs

ii. DBU; CH_2Cl_2, r.r. 1 hr. 76%.

(d) 5, AgOTf, DiPEA, r.t., 16 hrs., 77%, (e) $PhCH_3$, Δ, 6 hrs.; 96%.

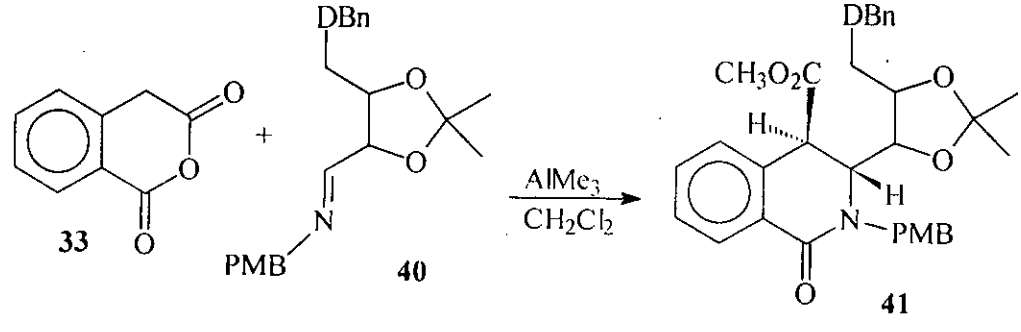
Scheme - 4

R. D. Clark and M. Souchet synthesized[37] Isoquinolinone derivatives **35, 36** by condensation of homopthalic anhydride **33** with *p*-methoxybenzylamine **34** followed by esterification of the crude product with diazomethane which was hydrolyzed to isoquinolinone **37** and **38 (Scheme-5)**.



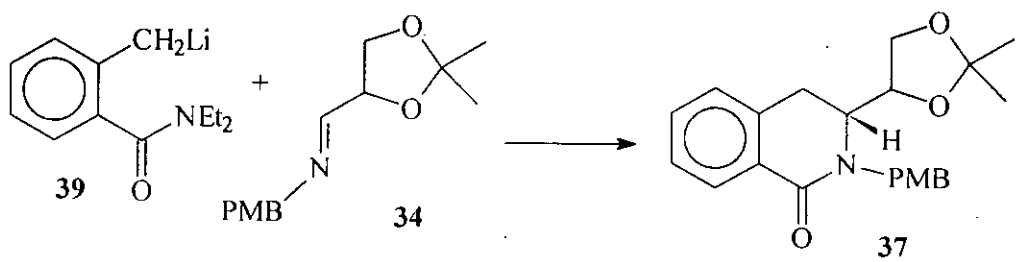
Scheme–5

They also reported the synthesis of isoquinolinone derivative **41** by the trimethylaluminum mediated condensation of homophthalic anhydride **33** and imine (40) **(Scheme-6)**.



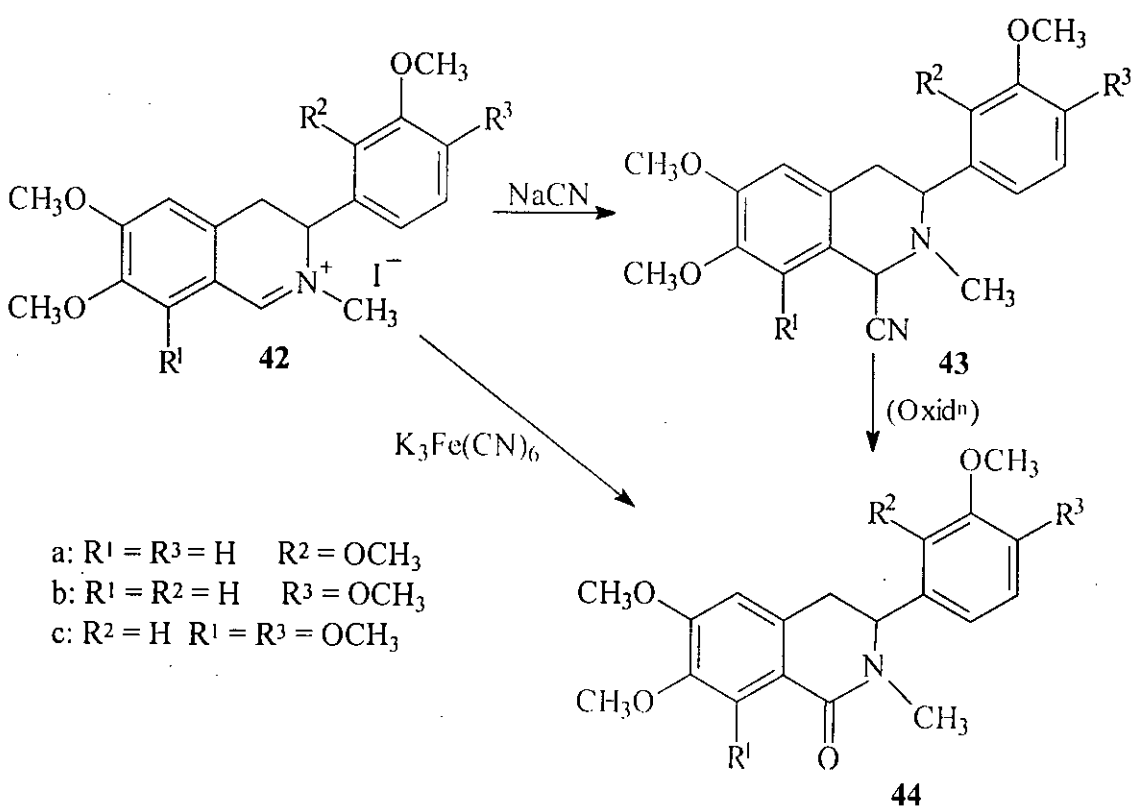
Scheme-6

The synthesis of isoquinolinone derivative **37** had been reported[38] by the same group by condensation of lithiospecies **39** with **34 (Scheme-7)**.



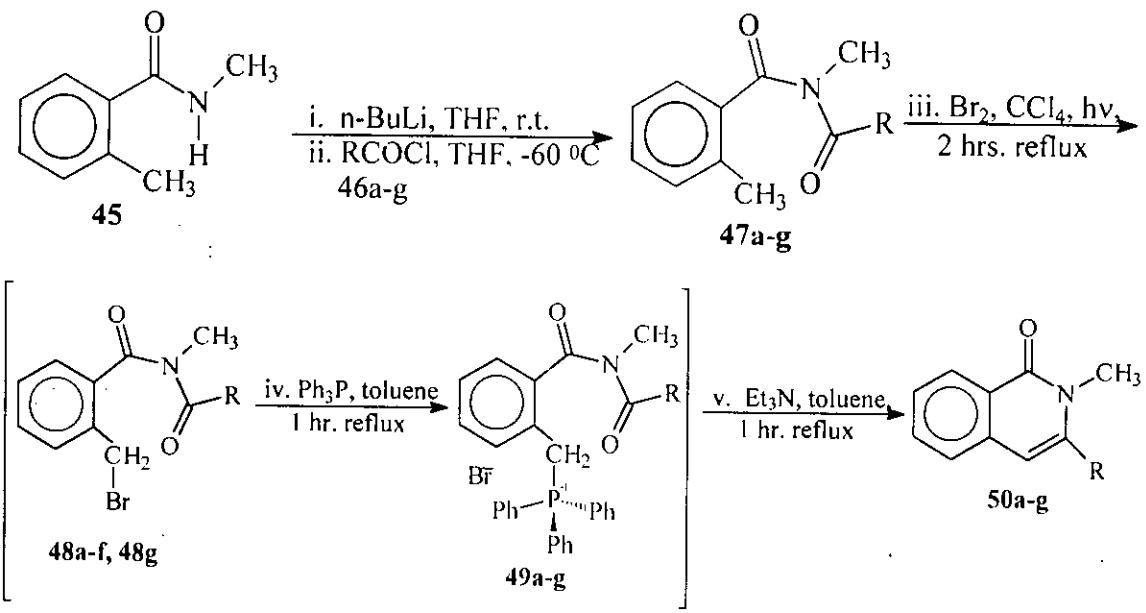
Scheme-7

3-Arylisoquinolinone **44** were synthesized[39] by two new methods of the Oxidation of 3-aryl-3,4-dihydroisoquinolium salt **42 (seheme-8)**. The isoquinolinium derivatives selected as precursors were obtained from the appropriate deoxybenzoins by reductive amination followed by Bischler-Napieralski cyclization and subsequent *N*-methylation[40] **43 (Scheme-8)**.

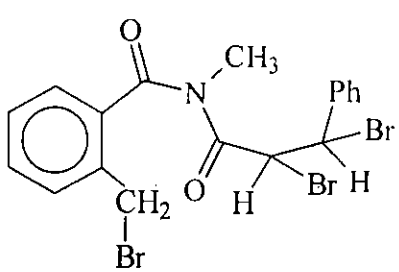


Scheme-8

A new synthetic route to 2-methyl-3-(aryl or alkyl)-1-oxo-1,2-dihydroisoquinoline **50a-g** via an intermolecular Witting reaction from the *N*-acyl-*N*-methyl-o-triphenylphosphoniomethyl benzamide bromides **49a-g** was reported by A. Couture *et al*[41] The *N*-acyl-*N*-methyl-o-toluamides **47a-g** were prepared by reacting the appropriate carboxylic acid chlorides **46a-g** with the anion of *N*-methyl-O-toluamide **45** and air sensitivity of **48a-g (Scheme-9)**.



45 **47a-g** **48a-f, 48g** **49a-g** **50a-g**



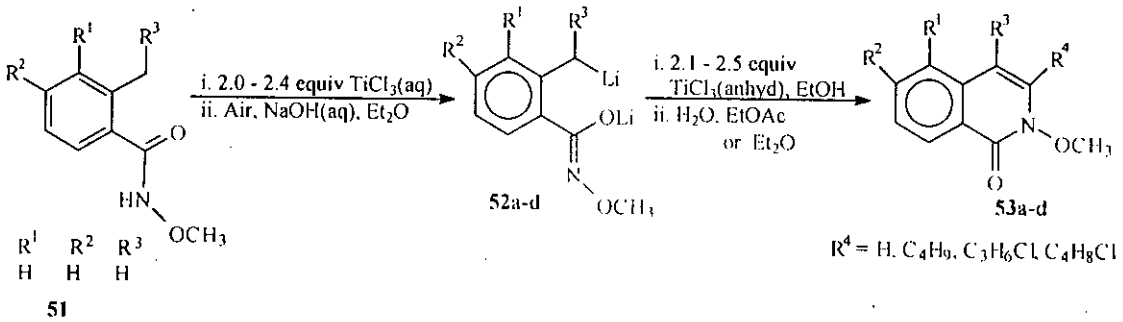
48g

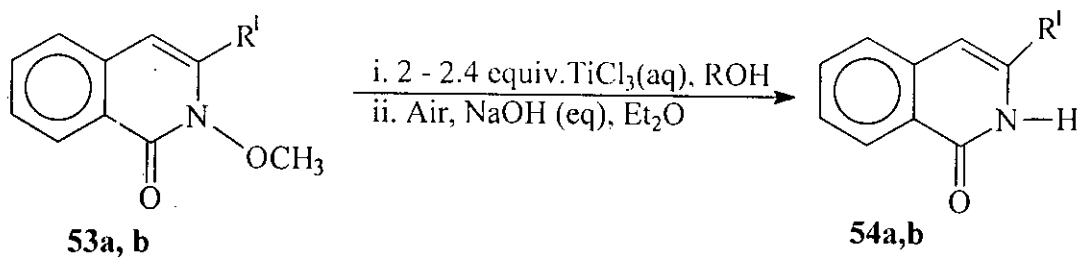
compounds 46, 47, 48, 49, 50	R
a	Ph
b	o -$OMeC_6H_4$
c	p-ClC_6H_4
d	$(OCH_2O)C_6H_3$
e	2—thienyl
f	isopropyl
g	styryl

Scheme-9

Lawrence E. Fisher reported[42] that *o*-methyl 2-methylbenzohydroxamate **51** undergoes regiospecific dilithiation on nitrogen and on the methyl group when treated with secbutyllithium at-70 ^{0}C. These dilithio species react with DMF or "Weinreb type" amides to give condensation products **52a-d** which cyclize to *N*-methoxyisoquinoline-1-(2*H*)-ones **53a-d** under mildly acidic conditions. Removal of the *N*-methoxymoiety under

conditions analogous to those used for *o*-methylbenzohydroxamate provides N-unsubstituted isoquinolin-1(2*H*)-ones **54a-b (Scheme-10)**.

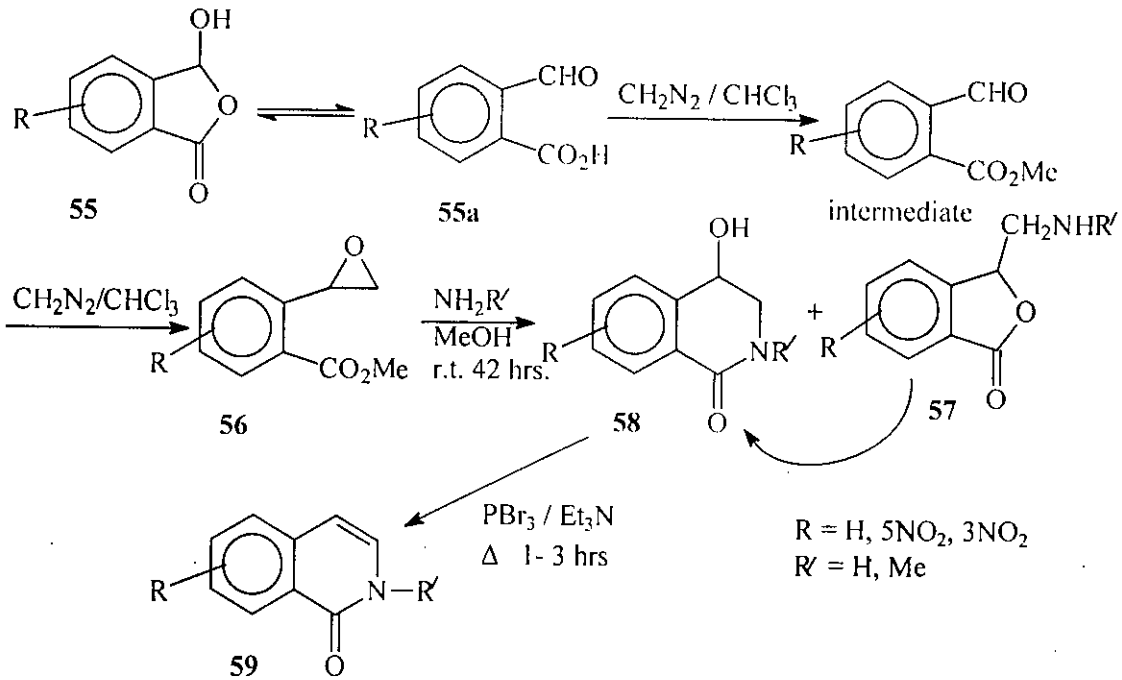




53a, b **54a,b**

Scheme-10

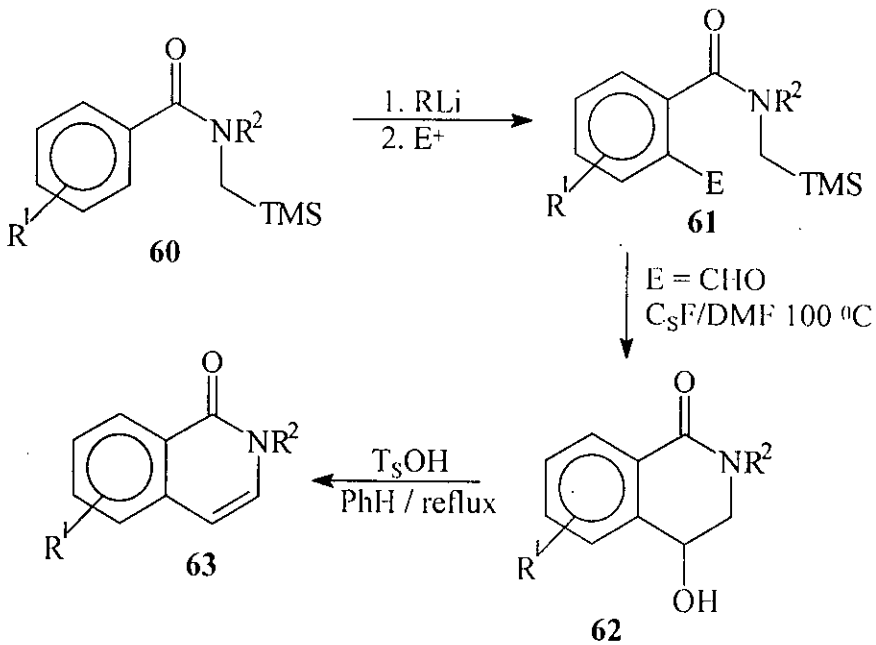
A synthetic route for the conversion of substituted 3-hydroxyphthalides into the corresponding isoquinoline-1(2*H*)-one **55** was established by Akiko Sugimoto *et al*[43] **(Scheme-11)**.



Scheme-11

The styrene oxides **56** derived from 3-hydroxypthalic acid **55** could he converted to *N*-substituted-3,4-dihydroisoquinolones **58** with various added amine. The dehydration of **58** is presumed to lead to the corresponding isoquinolone derivatives **59** using the conventional method.

V. Snieckus and J. C. Cueva reported[44] a synthesis of isoquinolinone derivatives **63** from silylated benzamides **60 (Scheme-12)**.



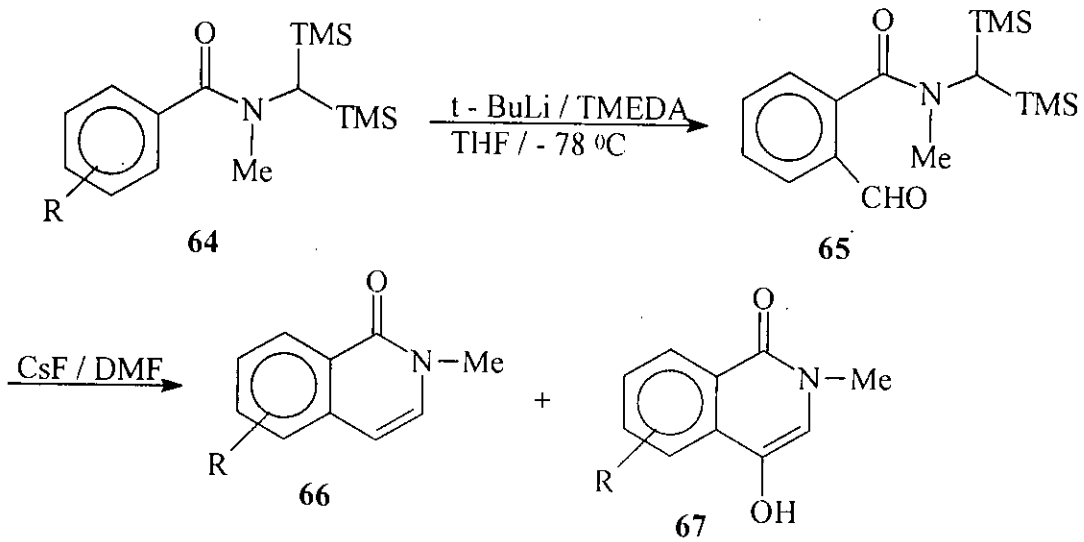
60 R^1 = H, 3–OMe, 4–OMe, 2–Ph, 2–OMe, 2,4–diOMe, 2–Cl ; R^2 = i–Pr, Me

63 R^1 = H, 5–OMe, 6–OMe, 8–Ph, 8–OMe, 6,8–diOMe, 8–Cl; R^2 = i–Pr, Me

Schem-12

Metalation of **60** followed by DMF quenching led only to the self condensation product **61**. Treatment of these products **61** with an hydrous CsF in DMF at 90 ^{0}C afforded the dihydroquinolone **62** which were directly subjected to *p*-toluenesulfonic acid catalyzed dehydration to give the isoquinolone **63**.

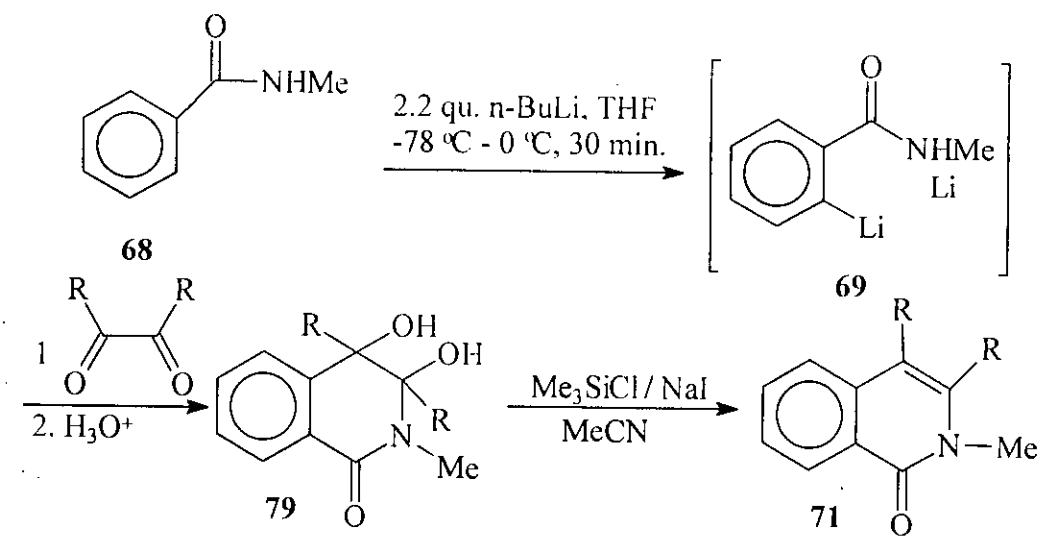
V. Snieckus *et al*[45] developed a synthesis of isoquinolinone derivatives **66** and **67** from α′,α′-disilylated benzamides **64** by intramolecular Peterson **65** olefination reaction as shown in **(Scheme-13)**.



R = H, 4-OMe

Scheme-13

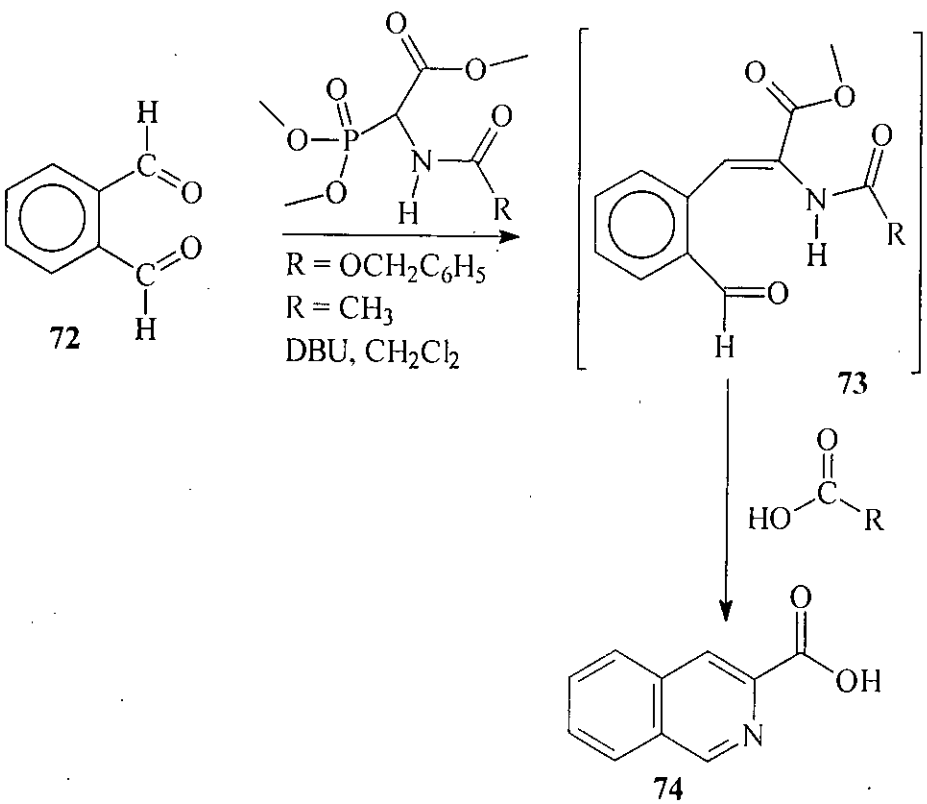
Alexander S. Kiselyov developed[46] a reaction of ortho-lithiated *N*-methylbenzamide **69** with 1,2-diketone to afford diols of *N*-methylisoquinolin-1-one **70** which were converted in to methylisoquinolin-1-ones **71** by treating with the system Me_3SiCl / NaI in dry MeCN, the stating material was *N*-methyl benzamide **68 (Scheme-14)**.



Scheme–14

A new and general[47] synthesis of methyl isoquinoline-3-carboxylate was described starting from aromatic 1,2-dialdehydes **72** by reaction with protected phosphonoglycine

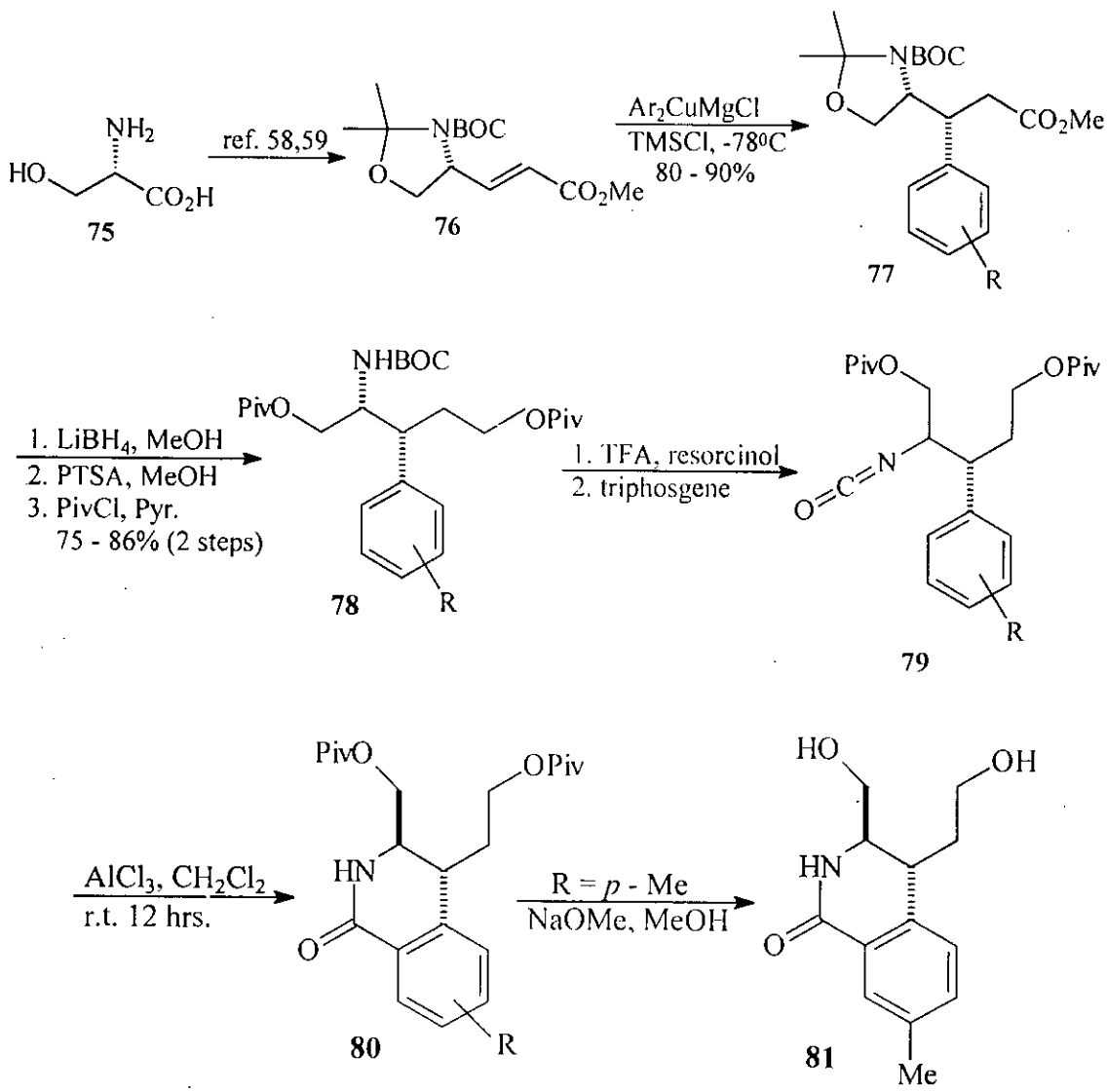
derivatives Methyl-1-oxo-1,2-dihydroisoquinoline-3-carboxylate **74** were obtained from 2-formylbenzoate derivatives **73**. This method allows the preparation of isoquinoline, having withdrawing groups on the benzene ring as shown in **(Scheme-15)**.

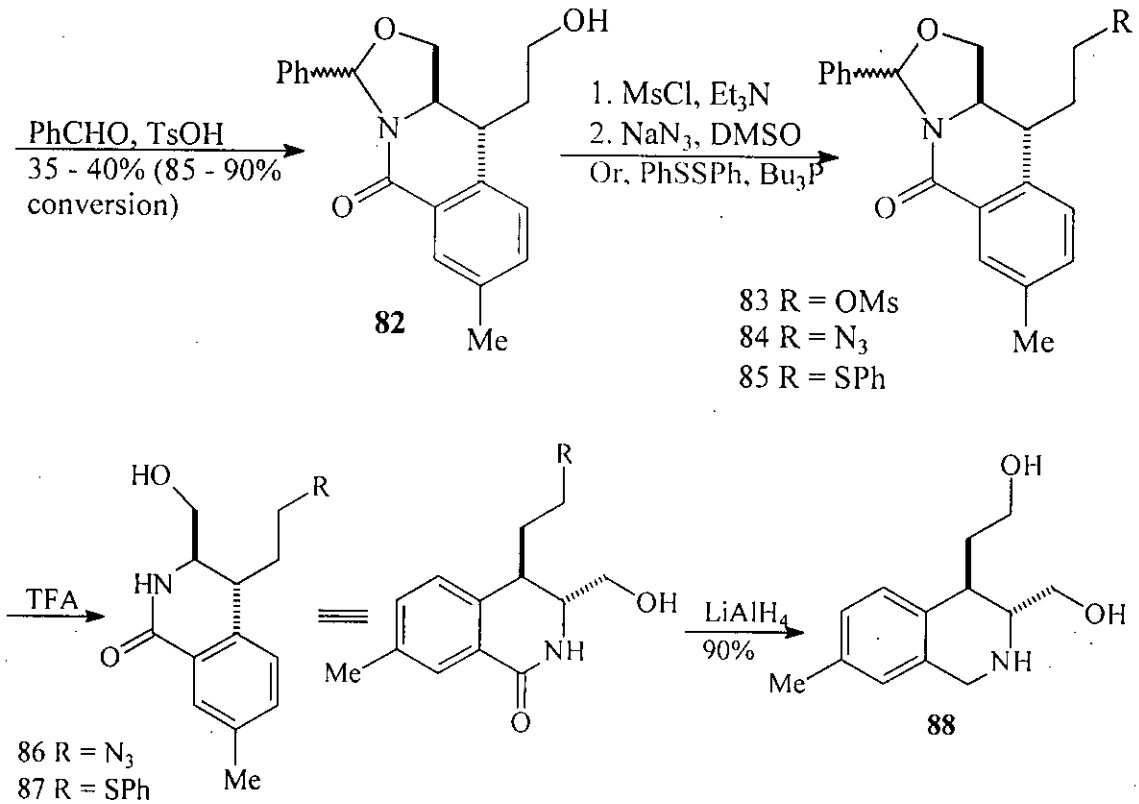


Scheme–15

Stephen Hanessian reported[48] a method for the stereocontrolled synthesis of 3,4-disubstituted tetrahydroisoquinoline-1-one and tetrahydroisoquinoline in enantiopare form starting with L-Serine **75**. The L-Serine was converted to the α, β unsaturated ester **76**, which is known to react with organocuprate reagents in the presence of trimethylsilylchloride to give predominantly syn adducts **(Scheme-16)**. Extension of this reaction to a variety of *o*,*m*, and *p*-substituted diarylmagnesiocuprate led to the corresponding β-aryl adducts **77** in excellent yield. The adducts **77** were transformed to the bis-pivaloyl esters **78** of generic structure in good yields. The removal of the N-BOC group with trifluoroacetic acid in the presence of resorcinol, followed by treatment with triphosgene led to the corresponding isocyanates **79**. Hydrolysis of the pivalate esters gave the corresponding enol **81** which was transformed to a diastereomeric mixture of 2-phenyl-1,3-oxazolidine derivative **80**. The displacement of the mesylate **83** with azide

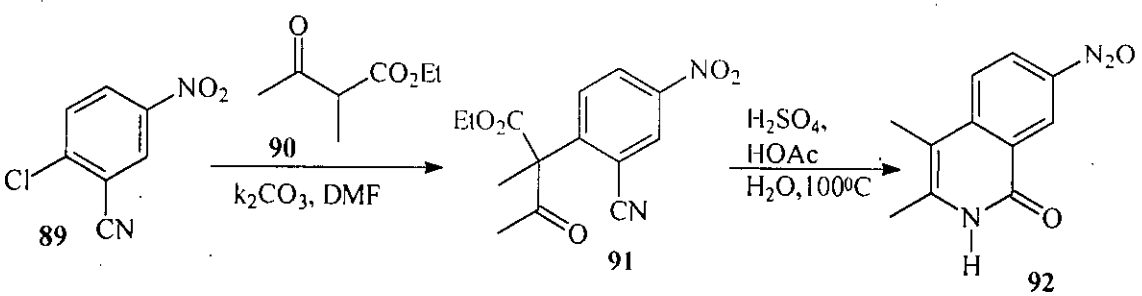
gave the corresponding azido derivative **84**. The phenylthio ether **85** was also prepared from **82**. Acid hydrolysis of **84** and **85** afforded the selectively functionalized azido and phenylthio derivatives **86** and **87** respectively in enantiopure form. A prototypical tetrahydroisoquinoline **88** was prepared by reduction of the enol **81** with $LiAlH_4$ **(Scheme-16)**.





Scheme-16

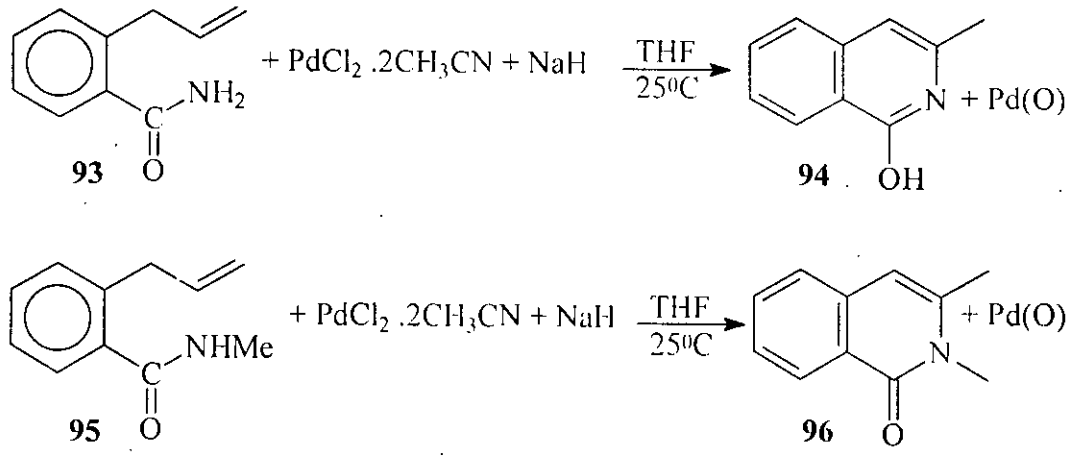
R. J. Show *et al*[49] recently developed an approach to the isoquinolone **92 (Scheme-17)**. which was based on the S_NAr reaction of 2-chlorobenzonitrile **89** with β-keto ester **90** to give **91** followed by cyclization under acid conditions **(Scheme-17)**.



Scheme–17

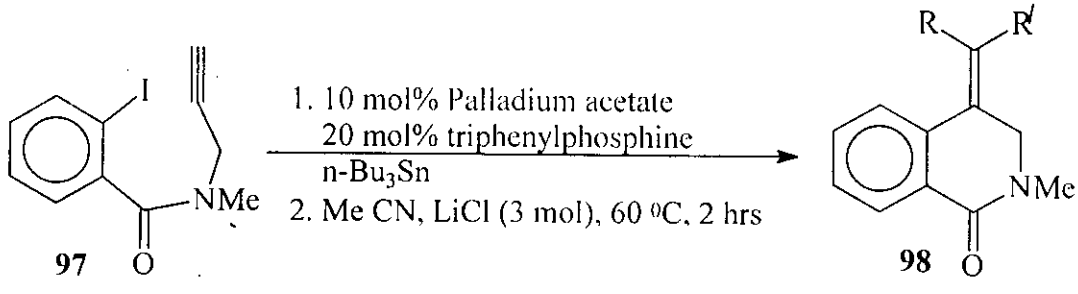
1.1.E. Synthesis of Isoquinolinone Through Palladium Catalysis Reaction.

L. S. Hegedus *et al*[50] converted 2-(2-propenyl) benzamide **93** to 3-methyl isocarbostyril **94** and 2-(2-propenyl)-*N*-methylbenzamide **95** to 3-methyl-*N*-methyl isoquinolone **96** by treatment with $PdCl_2$ and NaH in THF **(Scheme -18)**.



Scheme-18

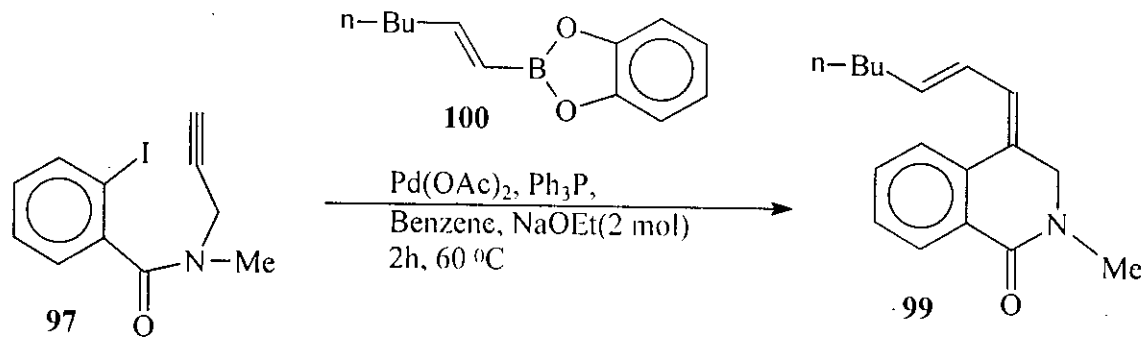
Ronald Grigg *et al*[51,52,53] recently disclosed new synthetic methodolugy involving palladium catalyzed 5-and 6-oxo-triglyclisation onto proximate alkynes, alkenes, or dienes generating intermediate vinil, alkyl, or π-allyl-palladium species which could be intercepted by an anion transfer agent **(Scheme 19, 20, 21)**.



98 a. $R = CH = CH_2$, $R^I = H$
b. $R = H$, $R^I = CH = CH_2$
c. $R = CH_2CH{=}CH_2$, $R^I = H$

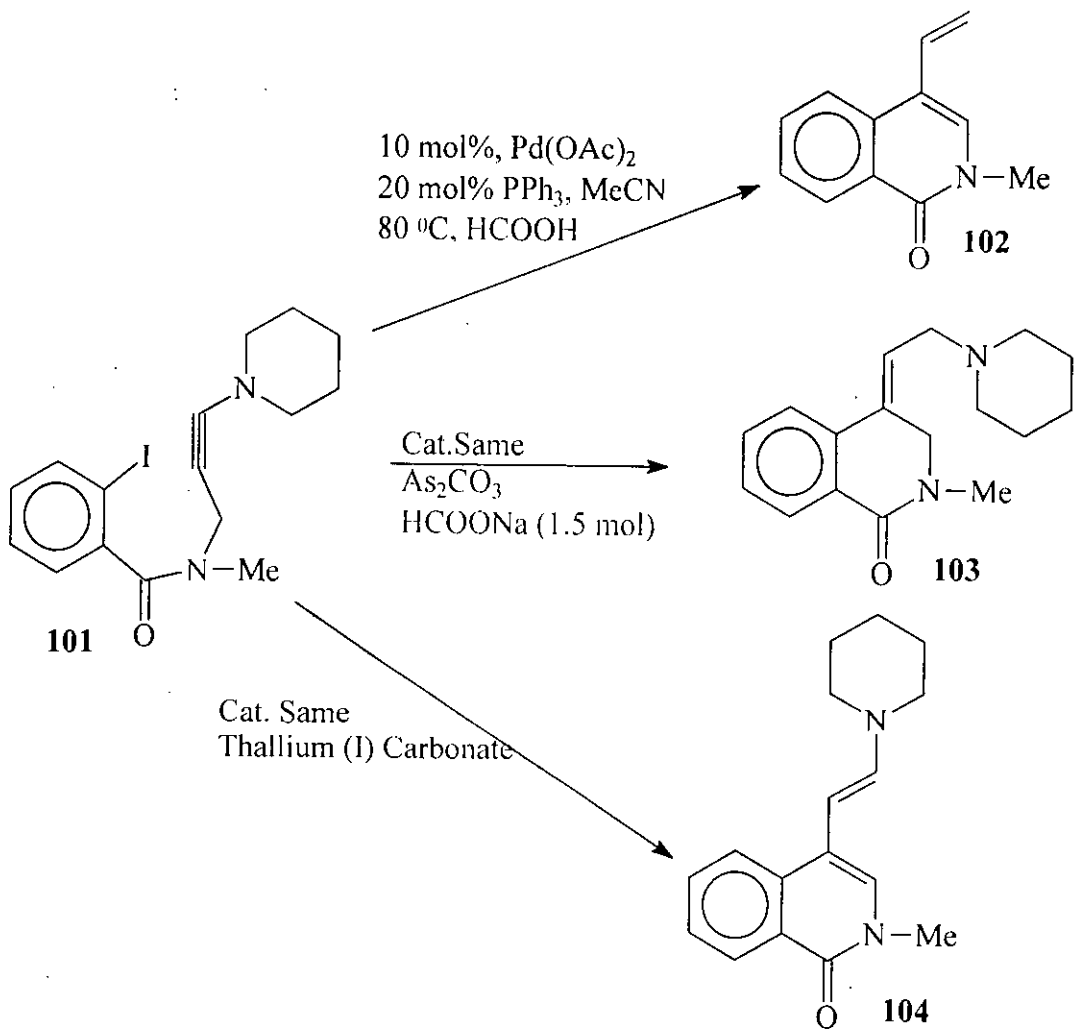
Here oraganotion $Bu_3.SnR$ was used as ion transfer reagent.

Scheme: 19



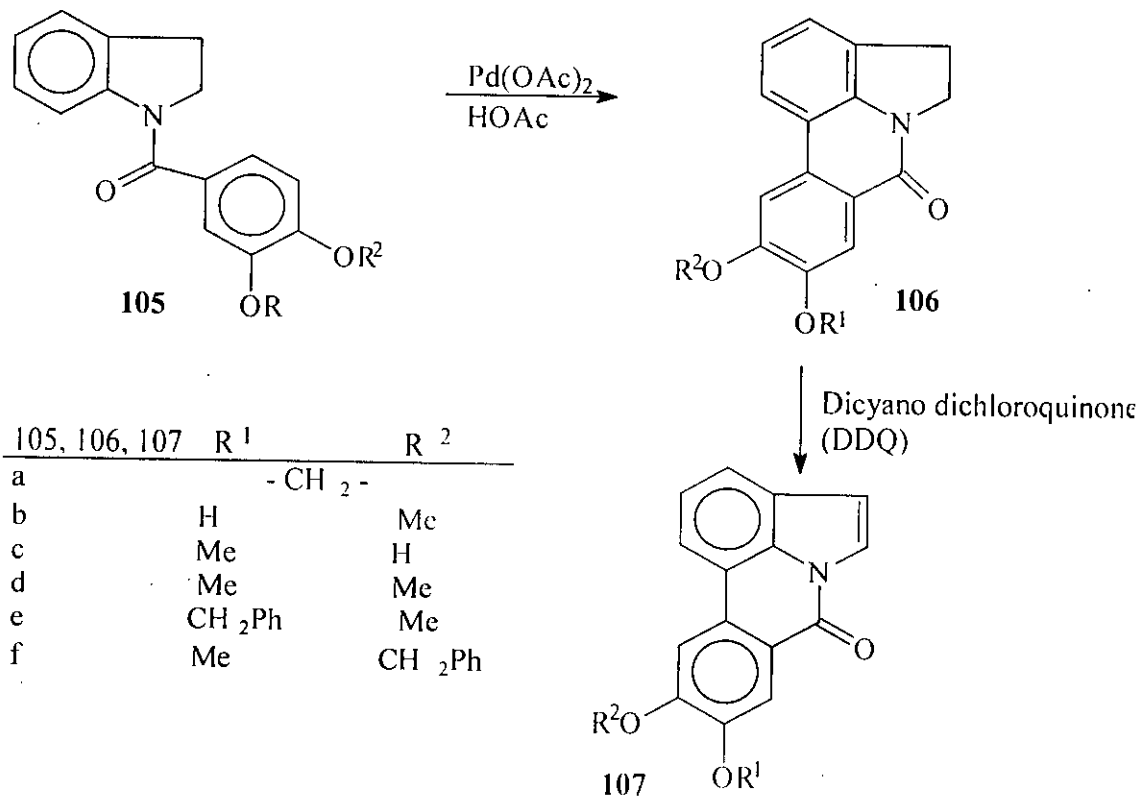
Here Alkenyl borane **100** was used as a transfer reagent.

Scheme-20



Scheme-21

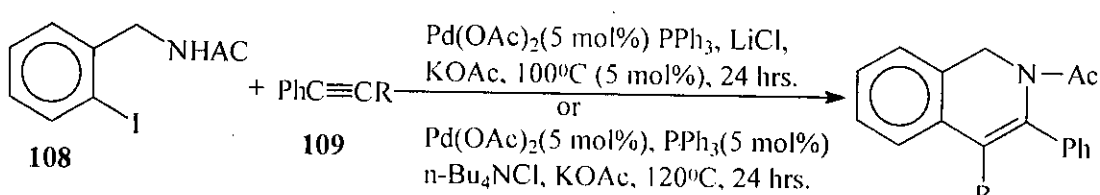
David S. Black reported[54] the synthesis of Pyrrolophenanthridone alkaloids **106, 107** by palladium acetate catalyzed arylation of *N*-acylindolines **105** followed by dehydrogenation **(Scheme-22)**.



105, 106, 107	R 1	R 2
a	- CH 2 -	
b	H	Me
c	Me	H
d	Me	Me
e	CH 2Ph	Me
f	Me	CH 2Ph

Scheme-22

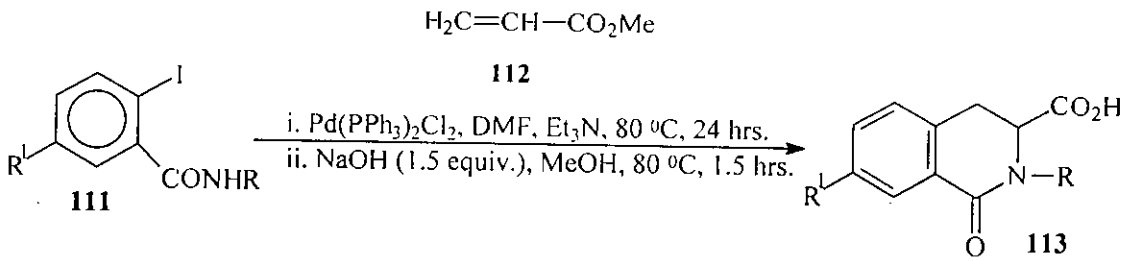
Richard C.Larok and his co-workers[55] developed the synthesis of 1,2-dihydroisoquinoline **110** by the palladium catalyzed hetero annulation of internal alkyne **109** with *o*-iodobenzlamide **108** in the presence of $Pd(OAc)_2$ (5 mol%), KOAc or NaOAc, LiCl or n-Bu_4NCl and occasionally five molar percent Ph_3P in DMF. Alkynes containing aryl or carbonyl containing groups generally gave the best results and proved highly regioselective. The substrate *o*-iodobenzylamine gave poor yields **(Scheme-23)**.



R = -CO_2Et, C_6H_5, CH_3, CHO

Scheme-23

N. G. Kundu *et al*[56] have reported the synthesis of *N*-Aryl -1,2, 3, 4-tetrahydro-1-oxo isoquinoline-3-carboxylic acids **113** by palladium catalyzed olefination **112** of *N*-aryl-2-iodobenzamides **111** followed by hydrolysis with base. They could not separate the ester and deiodinated product as reported **(Scheme-24)**.



Scheme-24

Section-2

Present Work:

Palladium Mediated Synthesis of Isoquinolinone Derivatives and Study of Their Biological Activities.

1.2. Present Work:

Palladium mediated synthesis of isoquinolinone derivatives and study of their biological activities.

1.2.1. Rationale:

Isoquinolinones (1-oxo-1,2-dihydroisoquinoline) are a class of fused heterocycles that are of increasing interest in synthetic and pharmaceutical chemistry[4-6]. Heterocyclic compound containing the isoquinolinone skeleton have generated considerable interest to us because of their pharmacological activities and use as a common building block of a wide variety of alkaloids (as described in section-I). Although various methods have been developed previously for the synthesis of isoquinolinones, only a few of them were mediated through palladium catalysis.

Palladium catalyzed[57] reactions have been extensively utilized for carboannulation[58] and heteroannulation[59] processes. Many research groups have reported the synthesis of various aromatic heterocycles via palladium-catalyzed annulation of internal alkynes[60]. Others have shown the palladium-catalyzed cyclizations to be valuable synthetic tools for the synthesis of a wide variety of heterocycles[61] using vinylic compounds, terminals 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[62] and isoindolinones[63] by palladium-catalyzed reactions with terminal alkynes and acid chloride.

In view of the extensive natural occurrence and biological importance of the isoquinolinone derivatives and lack of convenient palladium catalyzed procedures for their synthesis, we were interested in developing a general and facile method for the synthesis of isoquinolinones. In continuation of the synthesis of various heterocyclic structures through palladium-catalyzed reactions we became interested in the palladium-catalyzed heteroannulation for the synthesis of 3-substituted isoquinolinones using terminal alkene (acrylic esters) and *N*-substituted-2-iodobenzamides.

1.2.2. Results and Discussion:

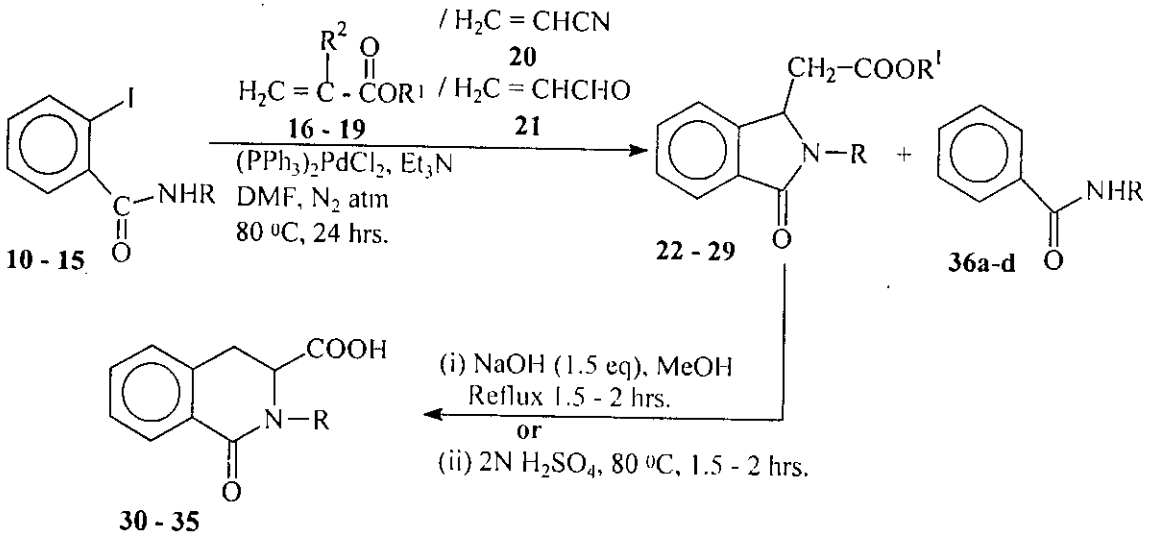
A new strategy for the regio-selective synthesis of 3-substituted isoquinolinones **30–35** through palladium-catalyzed reaction of 2-iodo-*N*-substituted benzamides **10–15** with terminal alkene (acrylic ester) followed by base / acid catalyst hydrolysis is reported. Our results (Table-1, **scheme-1**) demonstrate that a number of 3-alkyl-*N*-substituted isoindolin-1-one acetate **22–29** were formed with small amount of deiodinated benzamide **36a–d**. The ester of isoindolinones gave the corresponding acid of isoquinolinones on hydrolysis.

The reactions were usually carried out by heating a mixture of 2-iodo-*N*-aryl (alkyl) benzamides **10–15** and terminal alkenes (acrylate) **16–21** (3 equiv.) in DMF (10 ml) at 80°C for 2 hrs. in the presence of bis(triphenylphosphine)palladium(II)chloride (3.5 mol%) and triethylamine (4 equiv.) under nitrogen atmosphere. The 3-alkyl isoindolinone acetate **22–29** (1 mmol) were converted to the corresponding acid of isoquinolinone **30–35** by refluxing with NaOH (1.5 equiv.) in MeOH (10 ml) for 1.5–2 hrs. The hydrolysis was also carried out by using 2N H_2SO_4 acid (4 equiv) in H_2O under refluxing for 1.5 – 2 hrs. to afford the corresponding acid of isoquinolinones. The yield % was almost similar in both the cases. The palladium-catalyzed reaction between 2-iodo-*N*-phenylbenzamide and methyl methaacrylate under the same condition afforded a mixture of the ester of isoindolinone and deiodinated products in a lower yield.

We have also carried out an alternative approach towards the synthesis of the acid of isoquinolinone utilizing palladium-catalyzed olefination with acrylonitrile, a mixture of the ester of isoindolinone and deiodinated product in a lower yield has ben obtained (entry 12). In case of acrolein only deiodinated benzamide has been isolated.

It is observed that the vinylic group needing to be activated by conjugation with an ester or a nitrile group for the palladium-catalyzed reaction to take place to afford the desired product. Conjugated aldehyde (acrolein) led only to deiodinated products and methyl methaacrylate gave a mixture of the ester of isoindolinone and the deiodinated product which were not easily separable by column chromatography. It is also investigated that

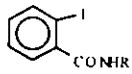
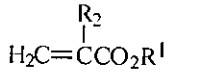
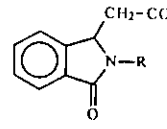
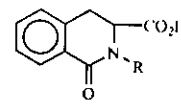
the yield of the ester of isoindolinone and the acid of isoquinolinone was found higher and easily separable when butyl acrylate was used as the terminal alkene.



Scheme-1

Compds.	R	Compds.	R^1	R^2	Compds.	R	R^1
10 **34**	CH_3	**16**	C_4H_9	H	**22**	C_6H_5	C_4H_9
11 **35**	$CH_2C_6H_4Cl$–*p*	**17**	C_2H_5	H	**23**	$C_6H_4CH_3$–*p*	C_4H_9
12 **30**	C_6H_5	**18**	CH_3	H	**24**	$C_6H_4OCH_3$–*p*	C_4H_9
13 **31**	$C_6H_4CH_3$–*p*	**19**	CH_3	CH_3	**25**	C_6H_4Cl–*p*	C_4H_9
14 **32**	$C_6H_4OCH_3$–*p*				**26**	$C_6H_4CH_3$–*p*	C_2H_5
15 **33**	C_6H_4Cl–*p*				**27**	$C_6H_4OCH_3$–*p*	C_2H_5
					28	$C_6H_4CH_3$–*p*	CH_3
					29	$C_6H_4OCH_3$–*p*	CH_3

Table–1: Synthesis of Isoindolinone and Isoquinolinone.

Entry	 2-Iodo-*N*-substituted benzamide (10–15) R	 16–19 R^1 R^2	 22 – 29 Isoindolinone	 30 – 35 Isoquinolinone	Yield[a] %
1	**12** C_6H_5	**16** butyl H	**22**	**30**	(75) 54
2	**13** $C_6H_4CH_3$-*p*	**16** butyl H	**23**	**31**	(76) 68
3	**14** $C_6H_4OCH_3$-*p*	**16** butyl H	**24**	**32**	(80) 72
4	**15** C_6H_4Cl-*p*	**16** butyl H	**25**	**33**	(77) 69
5	**10** CH_3	**16** butyl H	–	**34**	(–) 60
6	**11** $CH_2C_6H_4Cl$-*p*	**16** butyl H	–	**35**	(–) 65
7	**13** $C_6H_4CH_3$-*p*	**17** ethyl H	**26**	**31**	(70) 64
8	**14** $C_6H_4OCH_3$-*p*	**17** ethyl H	**27**	**32**	(72) 66
9	**13** $C_6H_4CH_3$-*p*	**18** methyl H	**28**	**31**	(65) 58
10	**14** $C_6H_4OCH_3$-*p*	**18** methyl H	**29**	**32**	(67) 61
11[b]	**12** C_6H_5	**19** methyl methyl	–	–	–
12[c]	**13** $C_6H_4CH_3$-*p*	**20** Acrylonitrile H_2C=CHCN	–	–	–
13[d]	**14** $C_6H_4OCH_3$-*p*	**21** Acrolein H_2C = CHCHO	–	**36c**	–

Note: [a]yield% inside the bracket is the yield of isoindolinone and outside the bracket is of isoquinolinone based on 2-iodo-*N*-substituted benzamides.

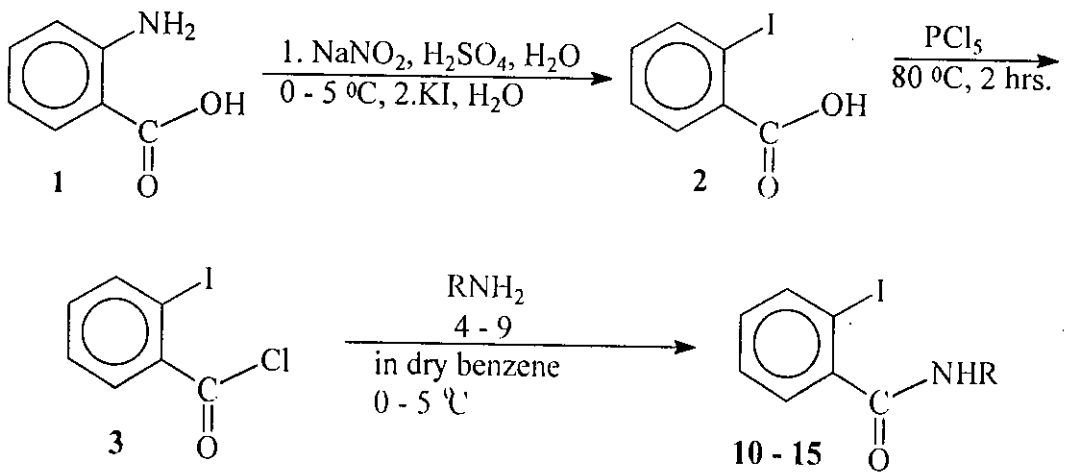
[b,c] The entry 11, 12 afforded mixture of deiodinated and cyclic product.

[d]The entry 13 afforded only deiodinated product **36c**.

1.2.2.A. Starting Materials:

Synthesis of 2-Iodo-*N*-substituted benzamides 10–15

2-Iodo-*N*-substituted benzamides **10–15** have been used as starting materials because of their easy availability from anthranilic acid. Diazotization of anthranilic acid (2-amino benzoic acid) followed by Sandmeyer iodination with potassium iodide afforded 2-Iodobenzoic acid as shown in **scheme-2.**



Scheme-2

4, 10 R = CH_3

5,11 R = $CH_2C_6H_4Cl$–*p*

6, 12 R = C_6H_5

7, 13 R = $C_6H_4CH_3$– *p*

8, 14 R = $C_6H_4OCH_3$– *p*

9, 15 R = C_6H_4Cl– *p*

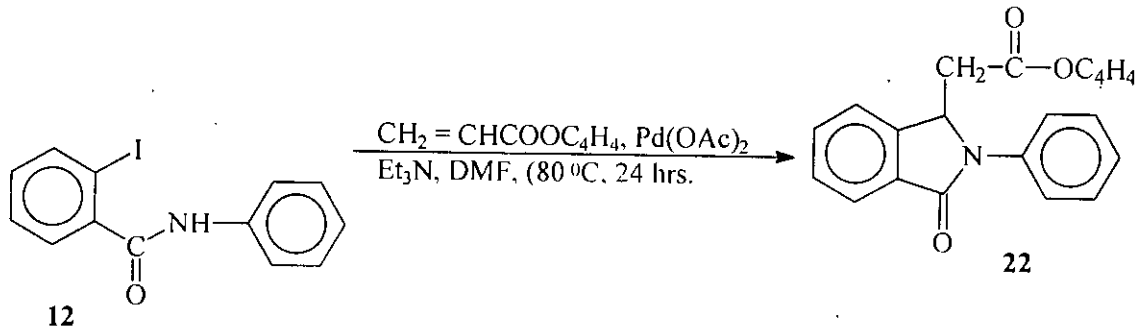
2-Iodobenzoic acid was converted to 2-Iodobenzoyl chloride by heating with PCl_5 at 80 °C for 2 hrs. 2-Iodobenzoyl chloride (1 mmol) was treated with a solution of the primary amine **4-9** (2.02 equiv.) in dry benzene to obtain 2-Iodo-*N*-substituted benzamides as shown in **Scheme-2.**

The products were characterized by its UV, IR, and ^1H NMR. The ^1H NMR and IR spectra of the compounds **10–15** exhibited an NH proton signal in their ^1H NMR spectra

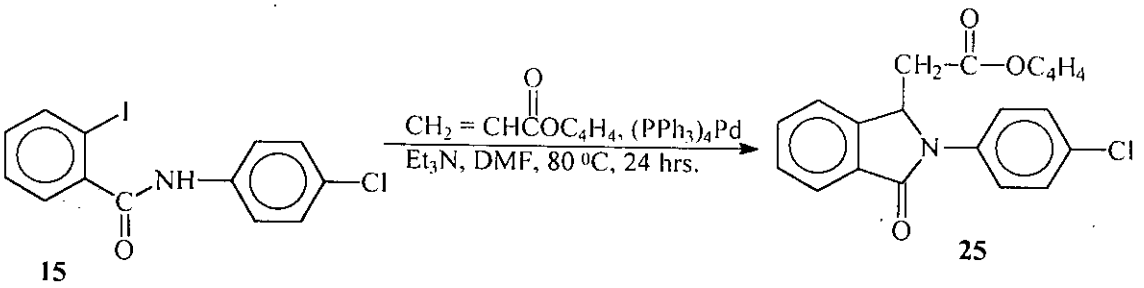
at δ5.76–7.09 (brs); in the IR spectra NH stretching vibration appeared at 3230–3362 cm^{-1} and C=O stretching vibration at 1634–1653 cm^{-1}; UV absorption was found in the region λmax 223–272 nm. All spectral data of the compound **4**, **6**, **8**, were identical to the reported data[64].

1.2.2.B. Role of Catalysts:

In general for the palladium catalyzed reaction of 2-iodo-*N*-substituted benzamides with alkenes, bis (triphenyl phosphine) palladium (II) chloride (3.5 mol%) was used as a catalyst. Bis (triphenyl phosphine) palladium (II) chloride was found to be the catalyst of choice. The palladium-catalyzed reactions of 2-iodo-*N*-phenyl benzamide **12** with alkene **16** was carried out in the presence of $Pd(OAc)_2$ (8 mol %) under the same condition and isoindolinone **22** in 33% yield was obtained. 2-iodo-*N*-*p*-chlorophenyl bezamide **15** with alkene **16** was carried out in the presence of $(PPh_3)_4$ Pd (3.66 mol %) under the same condition, isoindolinone **25** in 40% yield was obtained (**Scheme-3,4**).



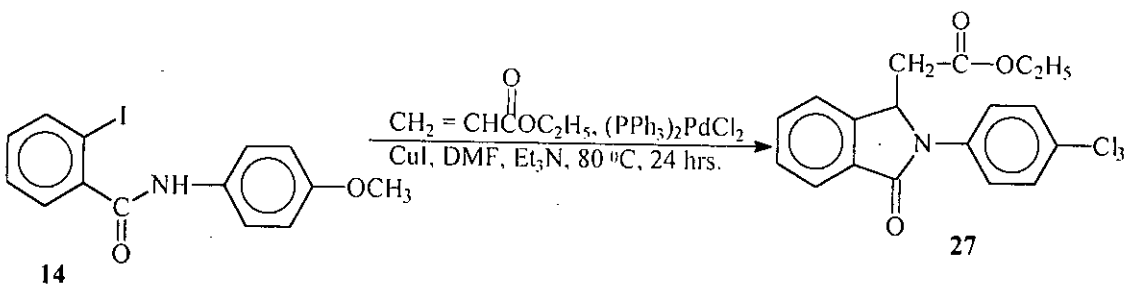
Scheme–3



Scheme–4

1.2.2.C. Role of Co-catalysts:

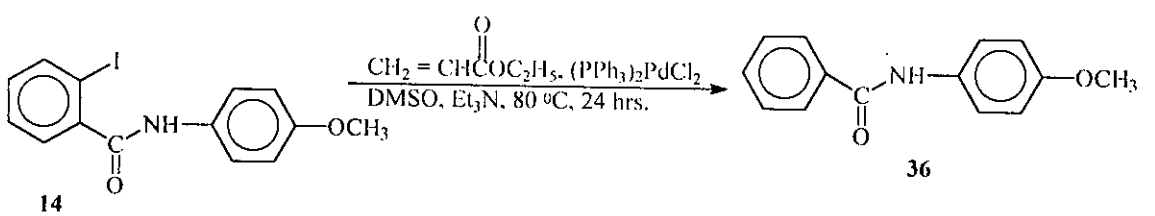
Capper (I) iodide was used as a co-catalyst. The addition of copper (I) iodide was found not to be essential for the success of the reaction. 2-iodo-*N*-*p*-methoxy phenyl benzamide **14** with alkene **17** was carried out in the presence of CuI (6 mol %) under the same condition, isoindolinone compound **27** in 38% yield was obtained (**Scheme-5**).



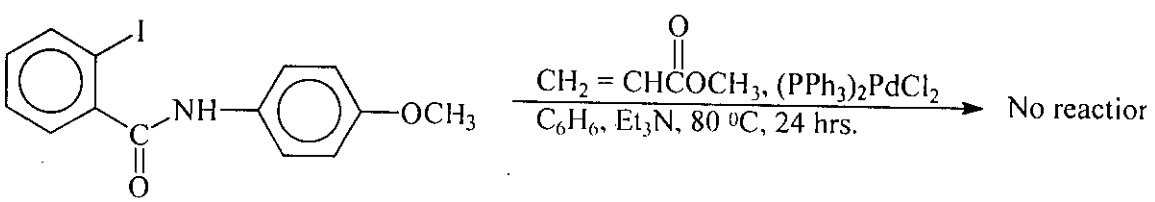
Scheme–5

1.2.2.D. Role of Solvent:

Dimethyl formamide (DMF) was found to be the best solvent for the reaction, Dimethyl sulfoxide giving deiodinated product (60%) along with starting material (**Scheme-6**). No reaction occurred in benzene (**Scheme-6, 7**)



Scheme-6



Scheme–7

1.2.2.E. Role of Base:

Triethyl amine was the base of our choice as was observed by the previous works.

1.2.2.F. Effects of Temperature:

Studying the effect of temperature on the course of the reaction, we found that at 50°C only partial deiodination occurred, where as at 60°C trace amounts of the isoindolinone esters could be identifind (^{1}H NMR). The obtimum temperature appeared to be 80°C, product yields not increasing at higher temperature.

1.2.3. Characterization of products:

The heteroannulation of 2-iodo-*N*-substituted benzamides with terminal alkenes (acrylic ester) in the presence of $(Ph_3P)_2PdCl_2$ and Et_3N in DMF afforded 3-alkyl isoindolinone acetate which were later hydrolyzed with NaOH in MeOH or 2N H_2SO_4 solution to yield the corresponding acid of isoquinolinone exclusively. All the isoindolinones and isoquinolinones were well characterized by their satisfactory spectroscopic (IR, UV, ^{1}H NMR and ^{13}C NMR) and analytical data. The formation of the ester of isoindolinone and the acid of isoquinolinone was established on the basis of the following observations.

The isoindolinones showed characteristic γ-lactam IR absorption at 1678–1711 cm^{-1} and C=O stretching vibration of ester group at 1728 – 1739 cm^{-1}. The ^{1}H NMR spectra of the ester of isoindolinones exhibited characteristic chemical shift positions for the C_3H proton at δ5.5 – 5.6 as doublet with coupling constant 3-4 Hz and 8.0–8.5 Hz. Methylene of ester showed characteristic exo-methylene double doublets at δ 2.50–2.52 and 2.88–2.92 with coupling constant 8 Hz, 16 and 4 Hz approximately.

The ^{13}C NMR spectra to the ester of isoindolinone showed the chemical shift position for the C–3 and for the methylene carbon at δ 57–58 and δ 64 – 65 respectively the chemical shift positions of the carbon at γ-lactam and the C = O of the ester were obtained at δ 166–167 and 170–171 respectively.

The isoquinolinones showed characteristic IR absorption at 1650–1660 cm^{-1} for δ-lactam ring and at 1718–1730 cm^{-1} for C = O of carboxylic group. In the ^1H NMR spectra the presence of an ABX patern corresponding to the part of the ring was clearly H_2C 4–HC 3 exhibited establishing the formation of the six-membered 1,2,3,4-tetrahydroisoquinoline moiety. The isoquinolinone showed the ^1H NMR signals for H–3 at δ 5.56–5.72 as double doublet with coupling constant 4 and 7–8 Hz approximately and the chemical shift positions for H-4ax at δ 2.54 – 2.68 as double doublet and for H-4 eq. at δ 2.85–2.97 as double doublet with a coupling constant 4. 7–8 and 16 Hz approximately. The ^{13}C NMR spectra of the isoquinolinones showed the chemical shift position for C–3 and C–4 at δ 57 and 36 respectively and for the ∂ lactam carbon and C = O of carboxylic group at δ 166 and 170–171 respectively. The key information to distinguish isoindolinones and isoquinolinones was obtained from IR spectra. The pattern of the UV absorption spectra of the two group of compounds were also different. Our observations were also compatible with those reported by other workers.

Table-2: Comparison of Isoindolinone ester and Isoquinolinone acid.

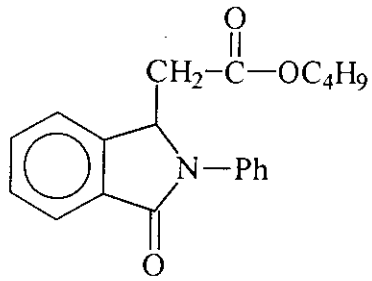
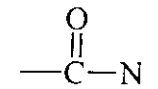
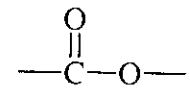
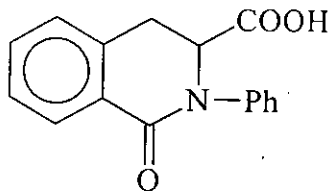
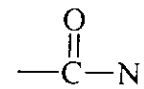
Compounds	^{1}H NMR	^{13}C NMR	IR	M.P.
	2.51 (dd, 1H, J = 8.45, 16.05 Hz, H–2′) 2.95 (dd, H, J = 3.87, 16.08 Hz, H–2′) 5.60 (dd, 1H, J = 3.94, 8.34 Hz, H–3)	 166.90  170.49	γ-lactam, 1678.0 C = O (ester), 1740.6	90–91°C
	2.60(dd, 1H, J = 8.00, 16.00 Hz, H – 4 ax) 2.92 (dd, 1H, J = 4.00, 16.00 Hz, H – 4 eq.) 5.72 (dd, 1H, J = 4.00, 8.00 Hz, H – 3)	 167.00 –COOH 171.810	δ-lactam, 1650.0 C = O (acid) 1730	184 – 185°C

Table-3: Comparison of Isoindolinone ester and Isoquinolinone acid.

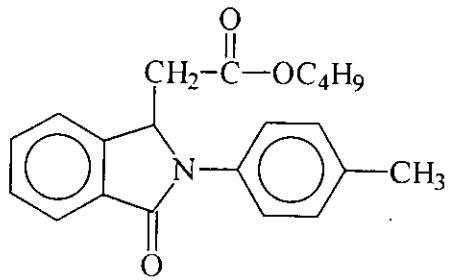
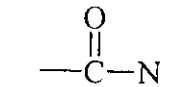
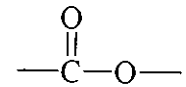
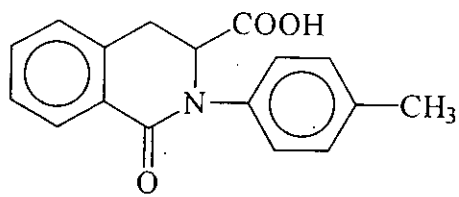
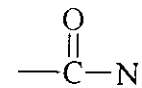
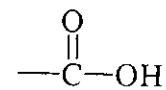
Compounds	^{1}H NMR	^{13}C NMR	IR	M.P.
	2.51 (dd, 1H, J = 8.45, 16.05 Hz, H–2′) 2.94 (dd, 1H, J = 4.09, 16.08 Hz, H–2′) 5.54 (dd, 1H, J = 4.07, 8.34 Hz, H–3)	 166.84  170.53	γ-lactam, 1707.8 C = 0 (ester), 1734.9	liquid
	2.54(dd, 1H, J = 7.30, 16.33 Hz, H – 4 ax) 2.88 (dd, 1H, J = 3.77, 16.34 Hz, H – 4 eq.) 5.61 (dd, 1H, J = 3.70, 7.08 Hz, H – 3)	 166.10  170.95	δ-lactam, 1651.9 C = 0 (acid), 1718	193 – 194°C

Table-4: Comparison of Isoindolinone ester and Isoquinolinone acid.

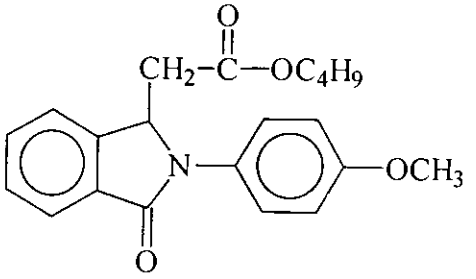
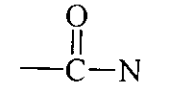
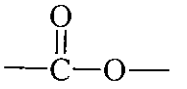
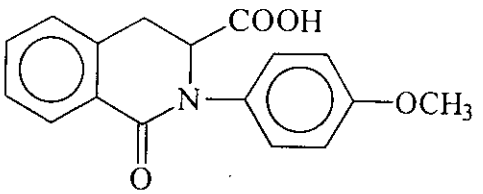
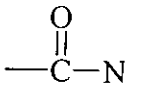
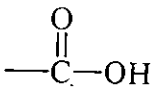
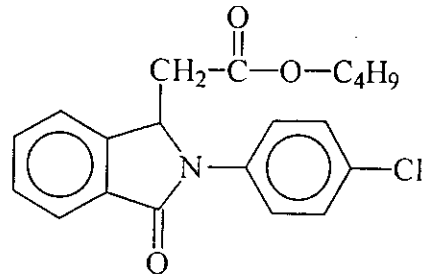
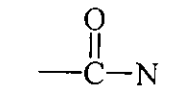
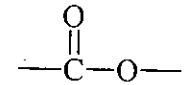
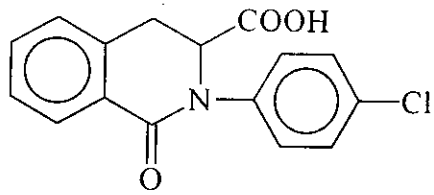
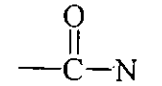
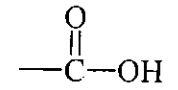
Compounds	^{1}H NMR	^{13}C NMR	IR	M.P.
	2.51 (dd, 1H, J = 8.22, 16.03 Hz, H–2′) 2.89 (dd, 1H, J = 4.39, 16.05 Hz, H–2′) 5.47 (dd, 1H, J = 4.35,8.09 Hz, H–3)	 166.94  170.49	γ-lactam, 17.07 C = O (ester), 1734.9	liquid
	2.54(dd, 1H, J = 7.20, 16.42 Hz, H – 4 ax) 2.85 (dd, 1H, J = 3.98, 16.38 Hz, H – 4 eq.) 5.56 (dd, 1H, J = 3.99, 6.87 Hz, H – 3)	 166.12  171.03	δ-lactam, 1653.8 C = O (acid), 1718.5	216 – 217°C

Table-5: Comparison of Isoindolinone ester and Isoquinolinone acid.

Compounds	^{1}H NMR	^{13}C NMR	IR	M.P.
	2.51 (dd, 1H, J = 8.24, 16.10 Hz, H–2′) 2.92 (dd, 1H, J = 4.04, 16.10 Hz, H–2′) 5.56 (dd, 1H, J = 3.98, 8.11 Hz, H–3)	 166.82  170.28	γ-lactam, 1711.7 C = 0 (ester), 1732.9	liquid
	2.61(dd, 1H, J = 6.96, 16.32 Hz, H – 4 ax) 2.91 (dd, 1H, J = 3.71, 16.34 Hz, H – 4 eq.) 5.69 (dd, 1H, J = 3.746.56 Hz, H – 3)	 166.27  170.86	δ-lactam, 1664.2 C = 0 (acid), 1724.2	183 – 184°C

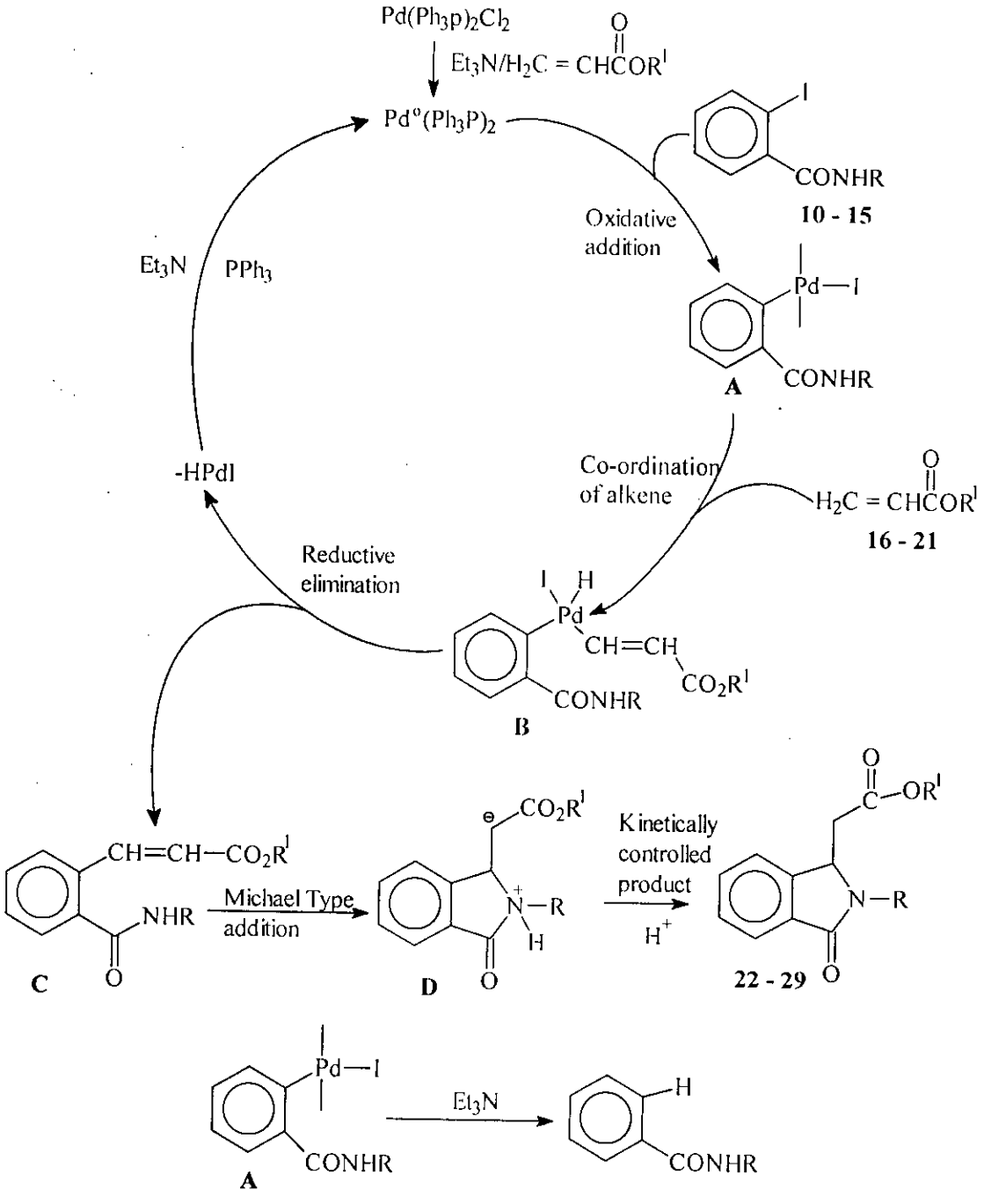
1.2.4. Mechanism of palladium-catalyzed reactions of 2-iodo-*N*-substituted benzamides with terminal alkenes (acrylates):

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

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

In the catalytic cycle 2-Iodo-*N*-substituted benzamides **10–15** oxidatively added to bis (triphenyl phosphine) palladium(0) to generate a 6-aryl palladium (II) complex A. Then the terminal alkene (acrylate) could be co-ordinates with palladium (II) complex A (Heck reaction) giving rise to co-ordinated complex **B**.

The alkenyl palladium complex B generated HPdI through the reductive elimination of the substituted products to afford the 2-alkenyl benzamides **C**. HPdI complex regenerated bis(triphenylphosphine) palladium(0) in presence of Et_3N (which could then continue the catalytic cycle). Then the 2-alkenyl benzamides **C** underwent the Michael type addition followed by protonation to afford the kinetically controlled five membered isoindolinone products **21–29(Scheme-8)**.

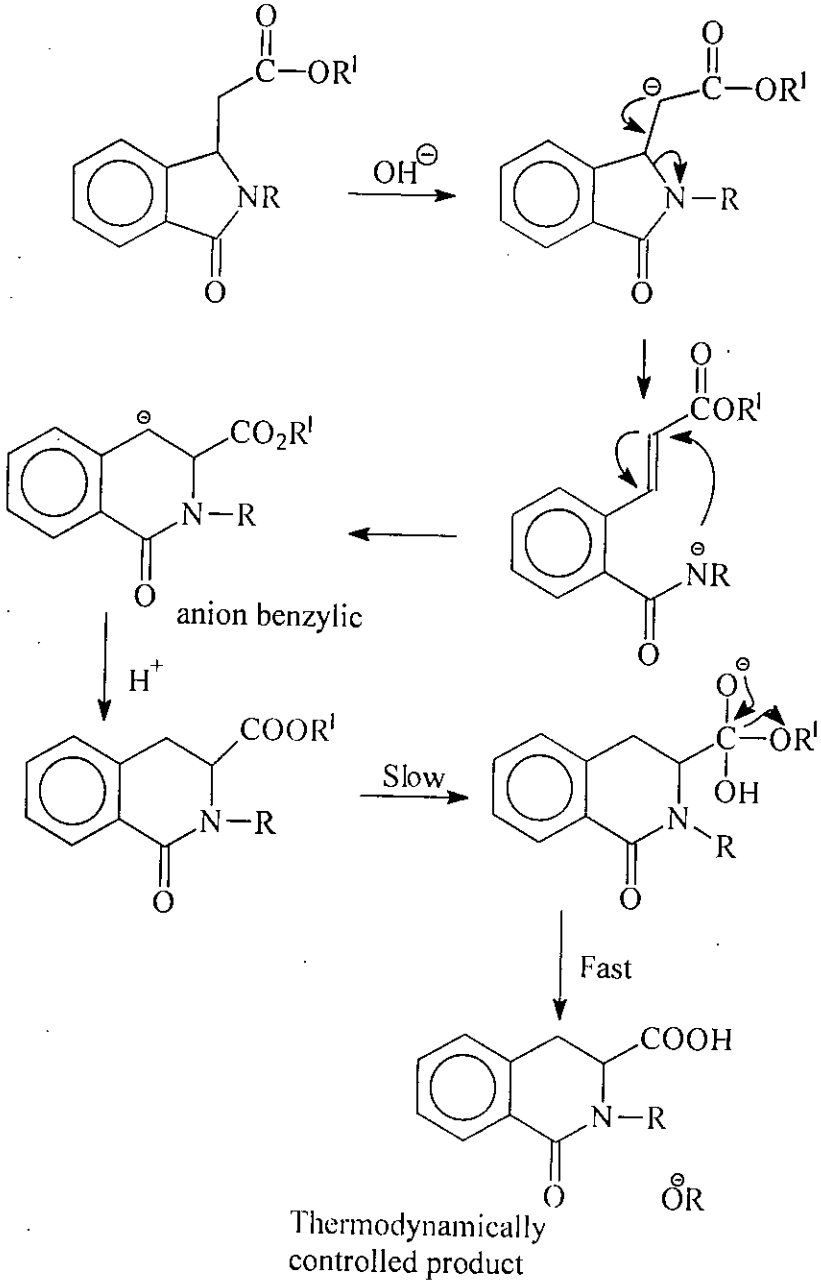


Scheme-8

1.2.5. Mechanism of Alkaline Hydrolysis of the ester of Isoindolinones 22–29.

Hydrolysis of the ester of isoindolinone in base is an irreversible reaction. The reaction involved the nucleophilic attack of hydroxyl OH^- group to the carbonyl group of the ester

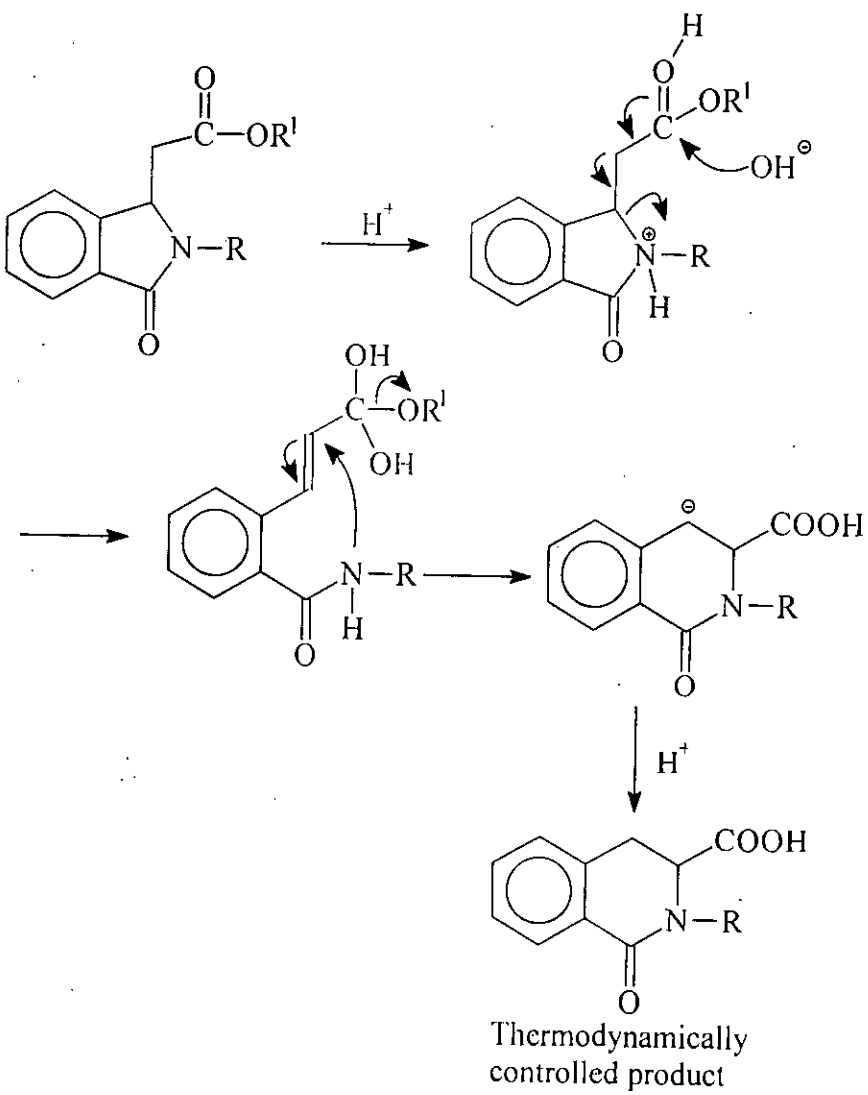
followed by rapid elimination of alkoxy group. The base initiated the opening of the ring by extracting the proton of the methylene carbon. Then Michael type addition reaction occurred to yield the six-membered isoquinolinone followed by protonation as shown in **scheme-9**. The six-membered compound isoquinolinone is the thermodynamically controlled product **(Scheme-9)**.



Scheme-9

1.2.6. Mechanism of Acid Hydrolysis of the ester of Isoindolinone 22–29.

In acidic solution, the carbonyl oxygen of the ester might be protonated. The partially positive carbon could then the attacked by weak nucleophile such as water. At the same time proton (H^+) attracked the nitrogen atom and instigated the opening the ring of isoindolinone. Then Michael type addition reaction occurred to yield six-membered compound isoquinolinones **30–35** followed by protonation which are thermodynamic controlled product **(Scheme-10)**.



Scheme-10

1.2.7. Conclusion:

We have demonstrated for the first time a convenient, general and faile method for the synthesis of *N*-(alkyl)aryl-3-alkyl isoindolinone acetate from the reaction of 2-iodo-*N*-substituted benzamides with acrylic esters by a $(Ph_3P)_2PdCl_2 - Et_3N$ system. The ester of isoindolinones was converted to *N*-aryl (alkyl) isoquinolinone-3-carboxylic acid by base/ acid hydrolysis. The most important features of the synthesis are that readily available inexpensive starting materials are used under relatively mild reaction conditions. Also, no toxic and hazardous compounds are produced by this procedure. The reaction is highly regioselective in case of palladium-catalyzed and hydrolysis reactions. A variety of functional groups can be introduced at the 2-and 3-positions of the isoquinolinones moiety by this procedure. Through this methodology biologically important derivatives may easily be synthesized isoquinolinone

1.2.8. Experimental:

Preparation of 2-Iodobenzoic acid 2:

28g (0.20 mol) of anthranilic acid 1 was dissolved in 200 ml of distrilled water containing 28 ml of concentrated sulphuric acid in a large flask. The mixture was cooled to 5 °C–0 °C and was stirred mechanically. The resulting mixture was diazotised by gradual addition of a cold solution of sodium nitrite (13.8g, 0.2 mol) in water (25 ml). A solution of potassium iodide (53.1g, 0.32 mole) in 1M sulphuric acid (100 ml) was added to the resultant clear solution. Then the mixture was heated to boiling for 10 minutes and cooled. The residue obtained by filtration was crystallized from hot water to yield 2-Iodobenzoic acid 2 (26.0g, 92.8%), Melting point 161–162 °C, lit m.p. 162 °C.

Preparation of 2-Iodobenzoyl chloride 3:

A mixture of 2-Iodobenzoic acid **2** (20g, 80.08 mmol) and PCl_5 (16.8g, 80.57 mmol) was stirred mechanically and heated at 80 °C for 2h. HCl and $POCl_3$ were removed from the reaction mixture under reduced pressure. Then the pure 2-Iodobenzoyl chloride 3 was obtained by vaccum distillation in excellent yield.

1.2.8.A. Synthesis of 2-Iodo-*N*-Substituted Benzamides

Preparation of 2-Iodo-*N*-methyl benzamide 10:

2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) was dissolved in dry benzene (30 ml) under nitrogen atmosphere and cooled under ice bath. To the resulting solution was added a solution of methyl amine **4** (0.74g, 2.02 equiv.) in dry benzene (10 ml) slowly with stirring. The residue obtain by filtration was washed with dilute HCl (3×50 ml), saturated $NaHCO_3$ solution (3×50 ml) and distilled water (3×50 ml) and finally the residue was washed with ether (2×25 ml). The crystallized from ethanol to yield 2-Iodo-*N*-methyl benzamide **10** as a courless amorphous powder m.p. 145 – 146 °C.

IR: ν_{max} (KBr) 3285.5, 1628.8, 1585.4, 1406.0, 1311.5, 1258.5 and 761.8 cm^{-1}.

UV(EtOH): λ_{max} 228.60 and 201.2 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (d, 3H, *J* = 4.92 Hz, $-CH_3$), 5.75 (brs, 1H, –NH), 7.09 (d.d, 1H, *J* = 6.52 Hz, *J* = 8.86 Hz, Ar–H), 7.34 – 7.39 (m, 2H, Ar – H) and 7.86 (d, 1H, *J* = 7.96 Hz, Ar – H).

Preparation of 2-Iodo-*N*-*p*-Chlorobenzyl benzamide 11:

The compound **11** was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and *p*-chlorobenzylamine **5** (3.38g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **10**. After usual work up, the title compound **11** (3g, 88.75%) was obtained as a gum. It was crystallized from ethanol to obtain a white crystal, m.p. 164 – 165 °C.

IR : ν_{max} (KBr) 3276.8, 3059.9, 3029.0, 2921.0, 2845, 1647.1, 1584.4, 1488.9, 1468.8, 1428.2, 1419.5, 1407.9, 1323.1, 1298, 1265.2, 1086.8, 1012.6, 994.2, 827.4, 790.8, 746.4, 716.5 and 618.40 cm^{-1}.

UV (EtOH): λ_{max} 326.4, 305.2, 275.4, 227.6 and 208.0 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (d, 2H, *J* = 4.08 Hz, $-CH_2$), 6.16 (brs, 1H – NH), 7.10 (d, 1H, *J* = 7.09 Hz, Ar – H), 7.26 – 7.37 (m, 6H, Ar – H) and 7.85 (d, 1H, *J* = 7.49, Ar – H).

Preparation of 2-Iodo-*N*-phenyl benzamide 12:

The compound **12** was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and aniline **6** (2.22g, 2.02 equiv.) in dry benzene (30 ml) by following the procedure described above for the compound **10**. It was crystallized from ethanol to yield colourless compound **12** (3.10g, 98.4%) m.p. 144 – 145 °C.

IR : ν_{max} (KBr) 3230.50, 1647.1, 1596.9, 1541.0, 1488.9, 1442.7, 1328.9, 754.1 and 696.3 cm^{-1}.

UV (EtOH): λ_{max} 233.0 and 211.4 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 – 7.92 (m, 9H).

Preparation of 2-Iodo-*N*-*p*-Methylphenyl benzamide 13:

The compound **13** was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and *p*-methylaniline **7** (2.55g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **10**. After usual work up, the title compound **13** (3.10g, 98.41%) was obtained as a colourless gum. It was crystallized from ethanol to obtain a colourless compound **13** m.p 155 – 156 °C.

IR : ν_{max} (KBr) 3235.4, 1653.8, 1600, 1534.3, 1507.3, 1400 and 1327.9 cm^{-1}.

UV (EtOH): λ_{max} 234.80 (log ε 3.774) and 211.60 (log ε 3.754) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H, Ar–CH_3), 7.09 – 7.17 (m, 3H, Ar–H), 7.24 (brs, 1H, NH) and 7.37 – 7.88 (m, 5H, Ar–H)

Preparation of 2-Iodo-*N*-*p*-methoxy phenyl benzamide 14:

The title compound **14** was synthesized from 2-Iodobenzoyl chloride **3**(3.15g, 11.82 mmol) and *p*-methoxy aniline **8** (2.94g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **10** to obtain the compound as a bluish gummy solid. It was crystallized from ethanol to obtain a bluish colour compound **14** (2.95g, 93.65%) m.p. 74–175 °C.

IR : ν_{max} (KBr) : 3308, 1651, 1597, 1512, 1462, 1414, 1315, 1299, 1248, 1232, 1028, 825 and 741 cm^{-1}.

UV (EtOH): λ_{max} 271.0, 262.0, 253.4, 236.8 and 218.40 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 3H, .OCH_3), 7.27 – 7.93 (m, 8H, Ar–H) and 8.28 (d, 1H, J = 7.91 Hz, NH).

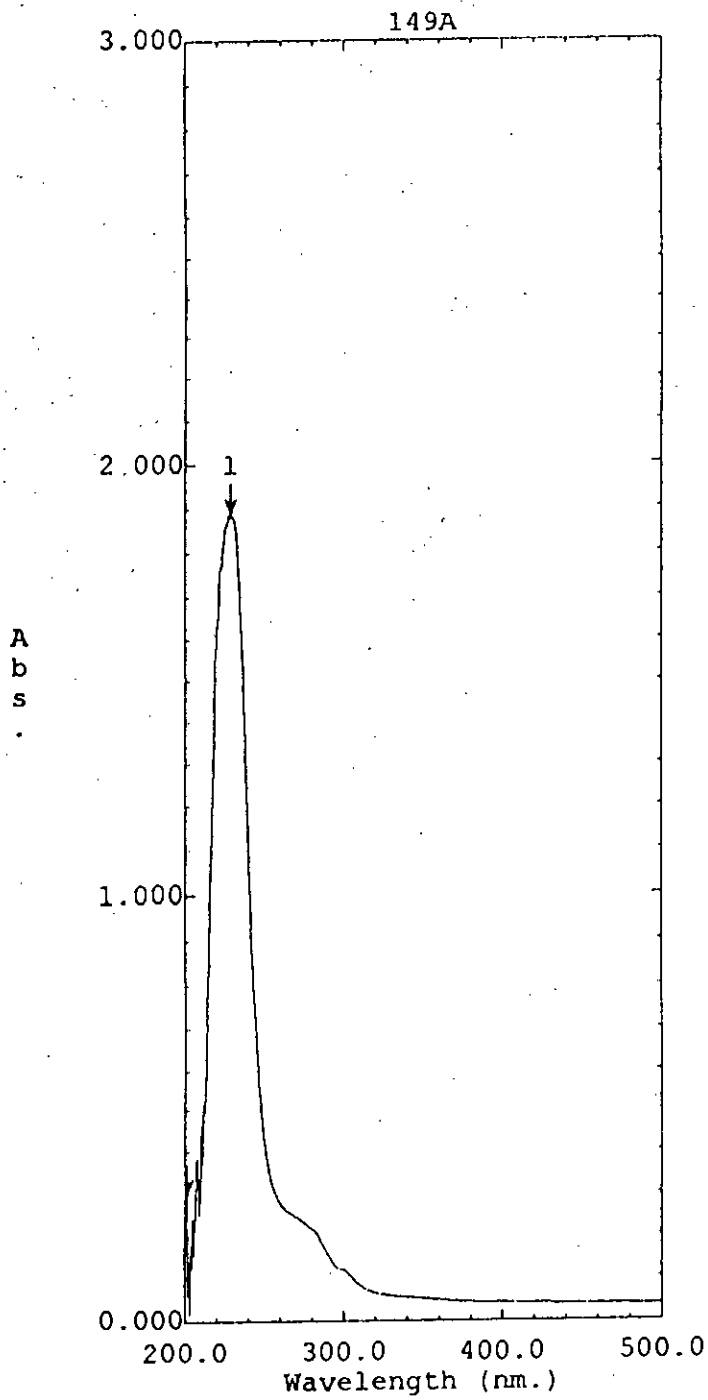
Preparation of 2-Iodo-*N*-*p*-chlorophenyl benzamide 15:

This was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and *p*-chloroamiline **9** (3.04g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **10**. After usual work up, the title compound **15** (2.5g, 79.4%) was obtained as a gummy solid. It was crystallized from ethanol to obtain a colourless needles. m.p. 141–142 °C.

IR : ν_{max} (KBr) 3351.1, 1653.8, 1595.0, 1516.9, 1493.8, 1398.3, 1314.4, 1092.6, 824.5, 717.5, 689.5 and 511.1 cm^{-1}.

UV (EtOH): λ_{max} 272 and 223.8 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 – 7.93 (m, 9H).



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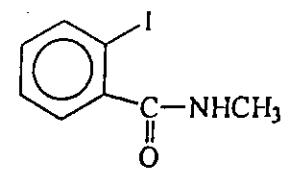

2-Iodo-*N*-methyl benzamide 10

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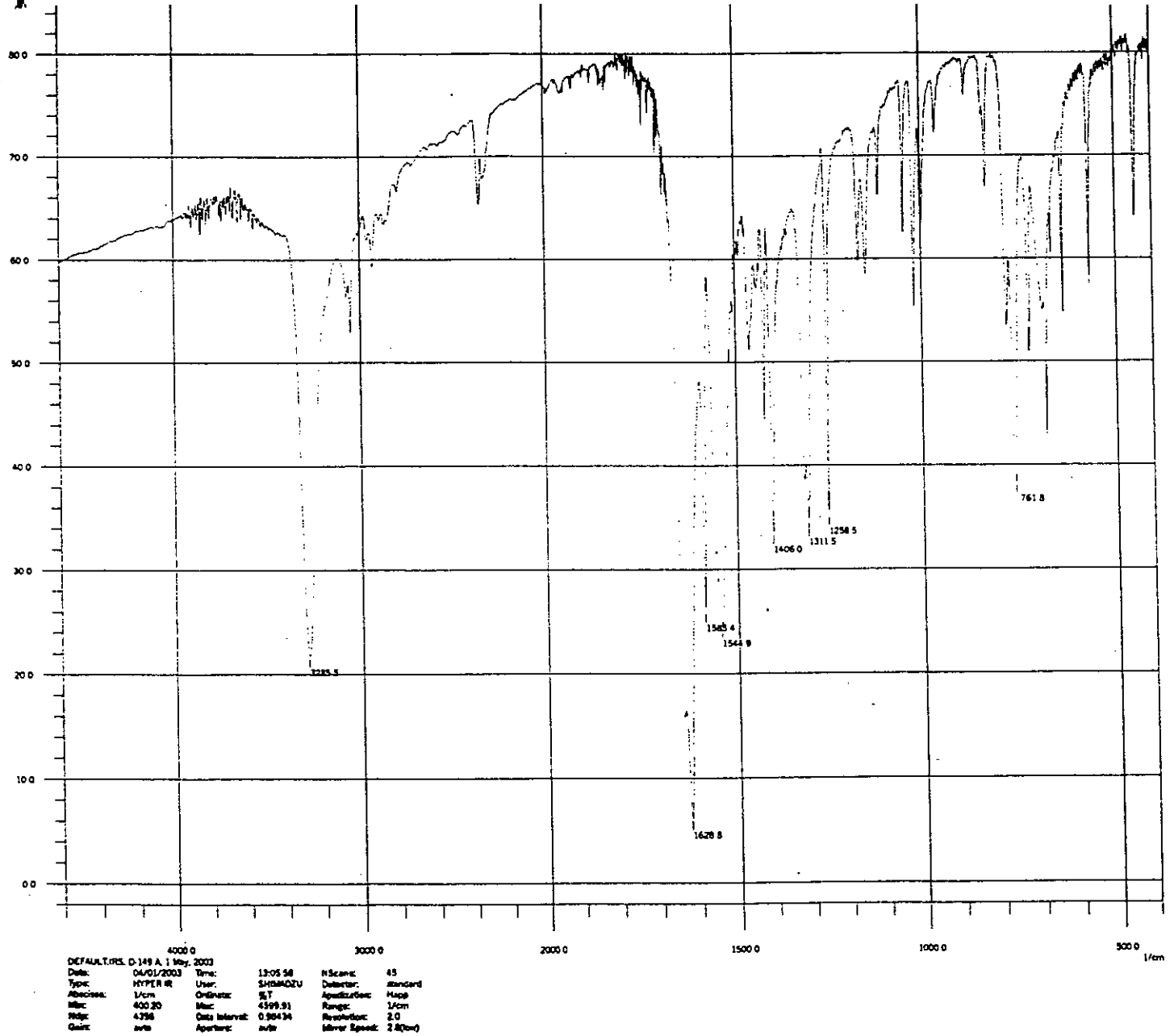

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6	1585.4	25.955
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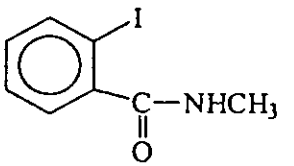
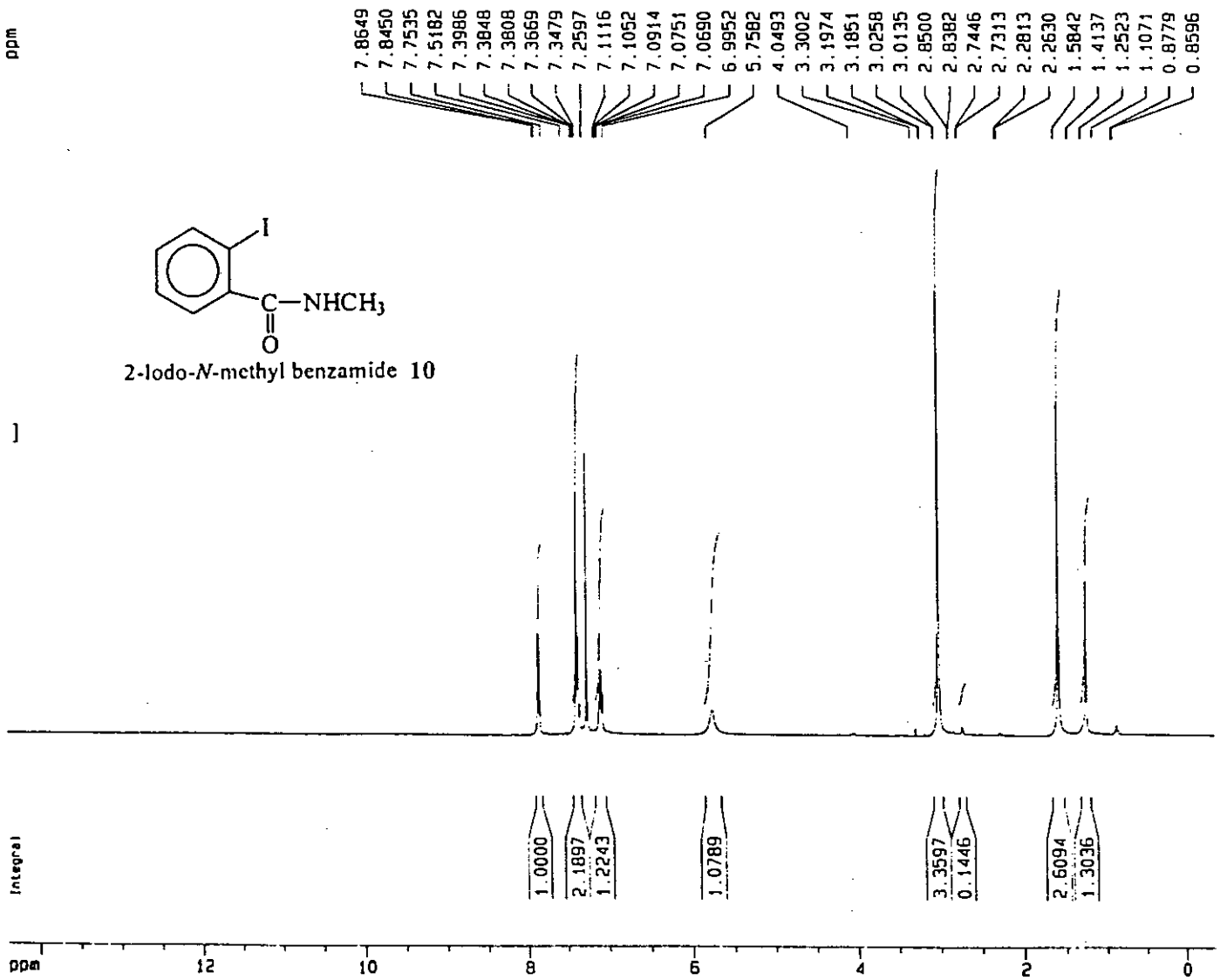
8	3285.5	21.737

D-149 A, 1 May, 2003



2-Iodo-*N*-methyl benzamide **10**

Analytical, BCSIR Lab. Dhaka 1H Spectrum 149A in CDCL3 Delwar BUET.



2-Iodo-*N*-methyl benzamide 10

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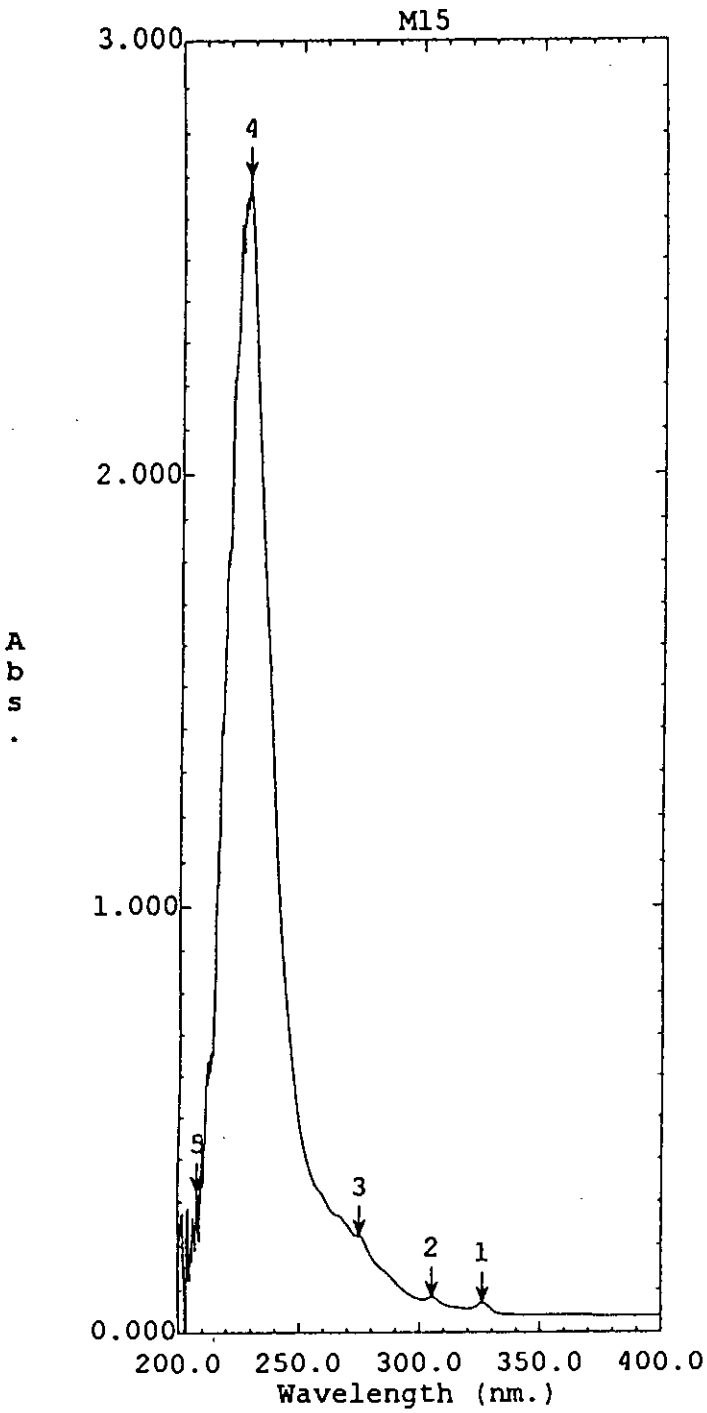

Peak Pick

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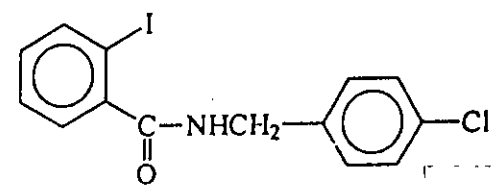

2-Iodo-*N*-*p*-Chlorobenzyl benzamide 11

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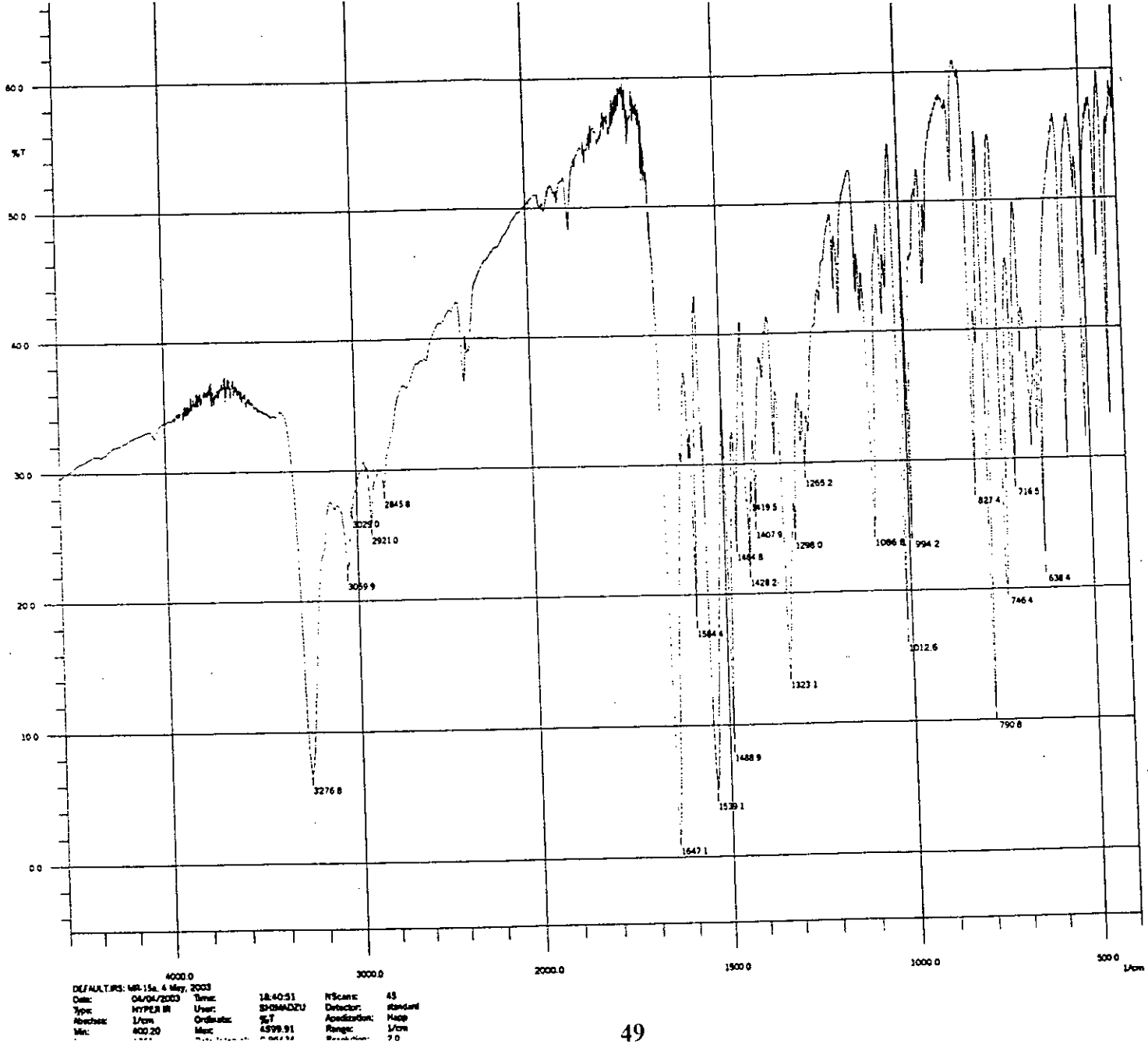

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Selection

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7	1012.6	16.802
8	1086.8	24.915
9	1265.2	29.593
10	1298.0	24.829
11	1323.1	14.171
12	1407.9	25.723
13	1419.5	27.842
14	1428.2	22.066
15	1464.8	24.028
16	1488.9	8.679
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18	1584.4	18.202
19	1647.1	1.650
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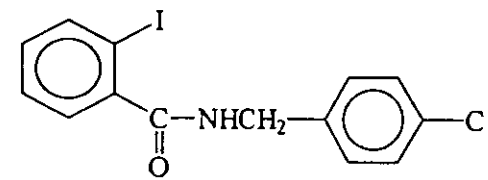
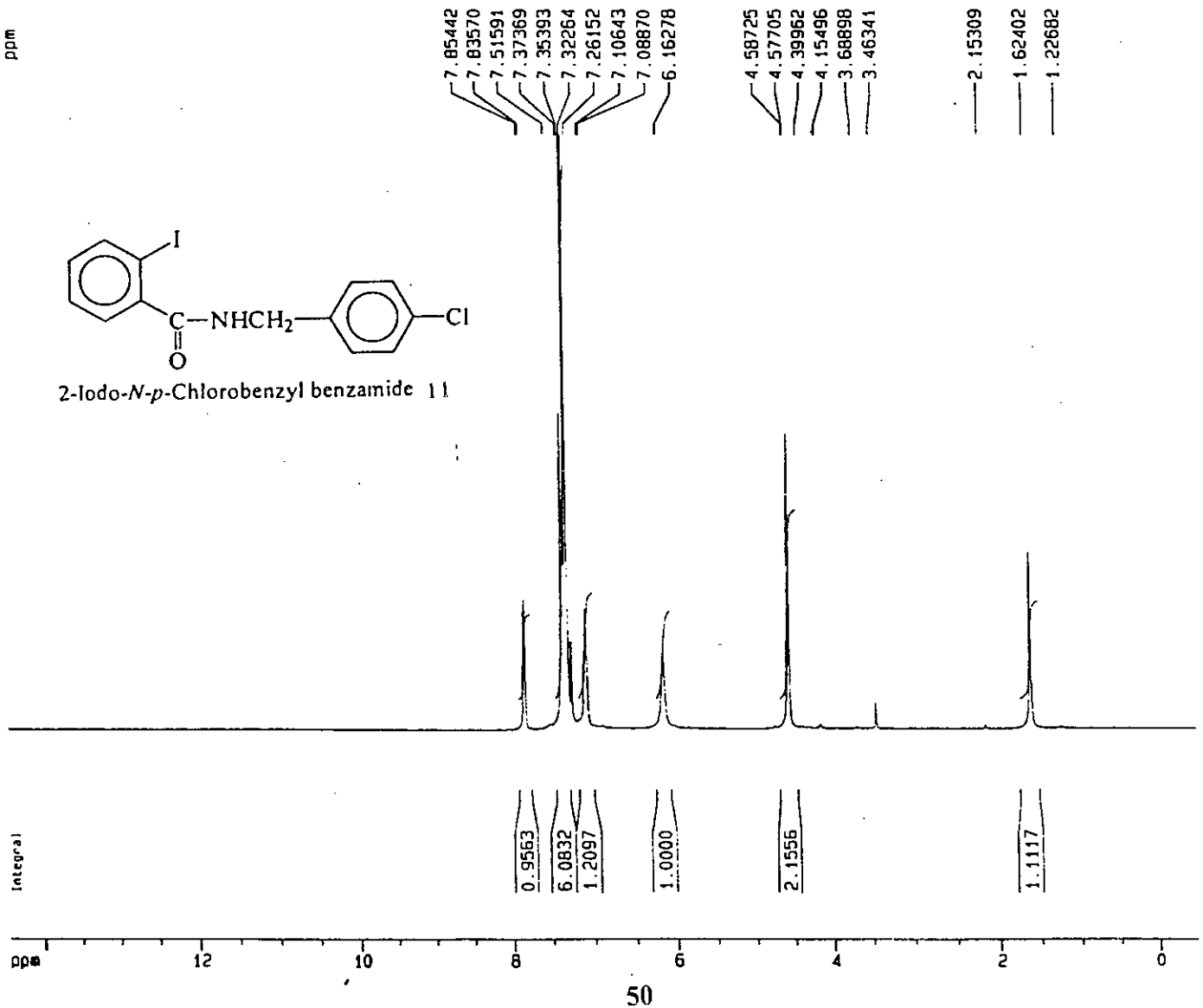
MR-15a, 4 May, 2003



2-Iodo-*N*-*p*-Chlorobenzyl benzamide **11**

Analytical, BCSIR Lab.Dhaka 1H Spectrum M-15a in COCL3 Delwar BUET.



2-Iodo-*N*-*p*-Chlorobenzyl benzamide 11

Current Data Parameters

NAME	A1097
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20030618
Time	19.15
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	COCl3
NS	128
DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	362
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

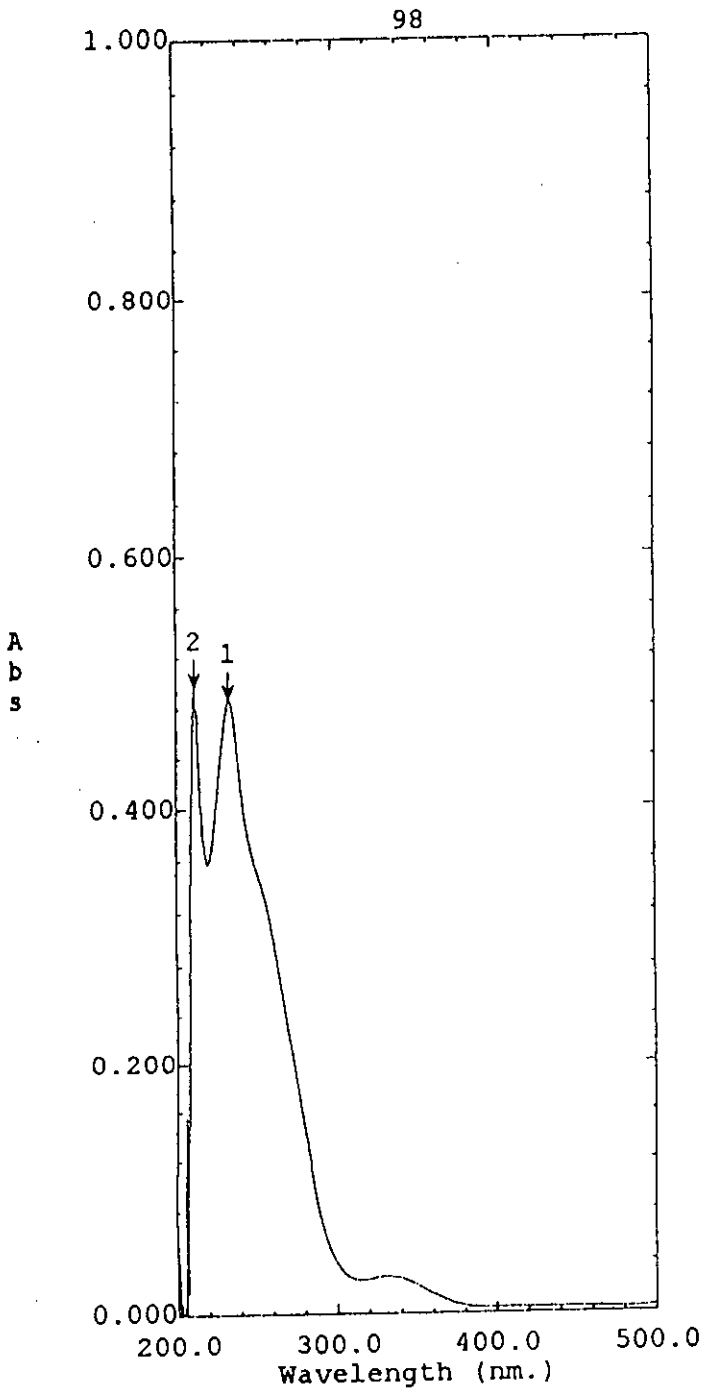
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SF01	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400086 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

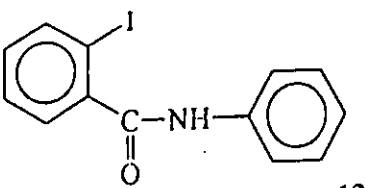
1D NMR plot parameters

CX	20.00 cm
F1P	14.469 ppm
F1	5789.63 Hz
F2P	-0.481 ppm
F2	-192.52 Hz
PPMCM	0.74751 ppm/cm
HZCM	299.10730 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
1	233.00	0.4866
2	211.40	0.4965

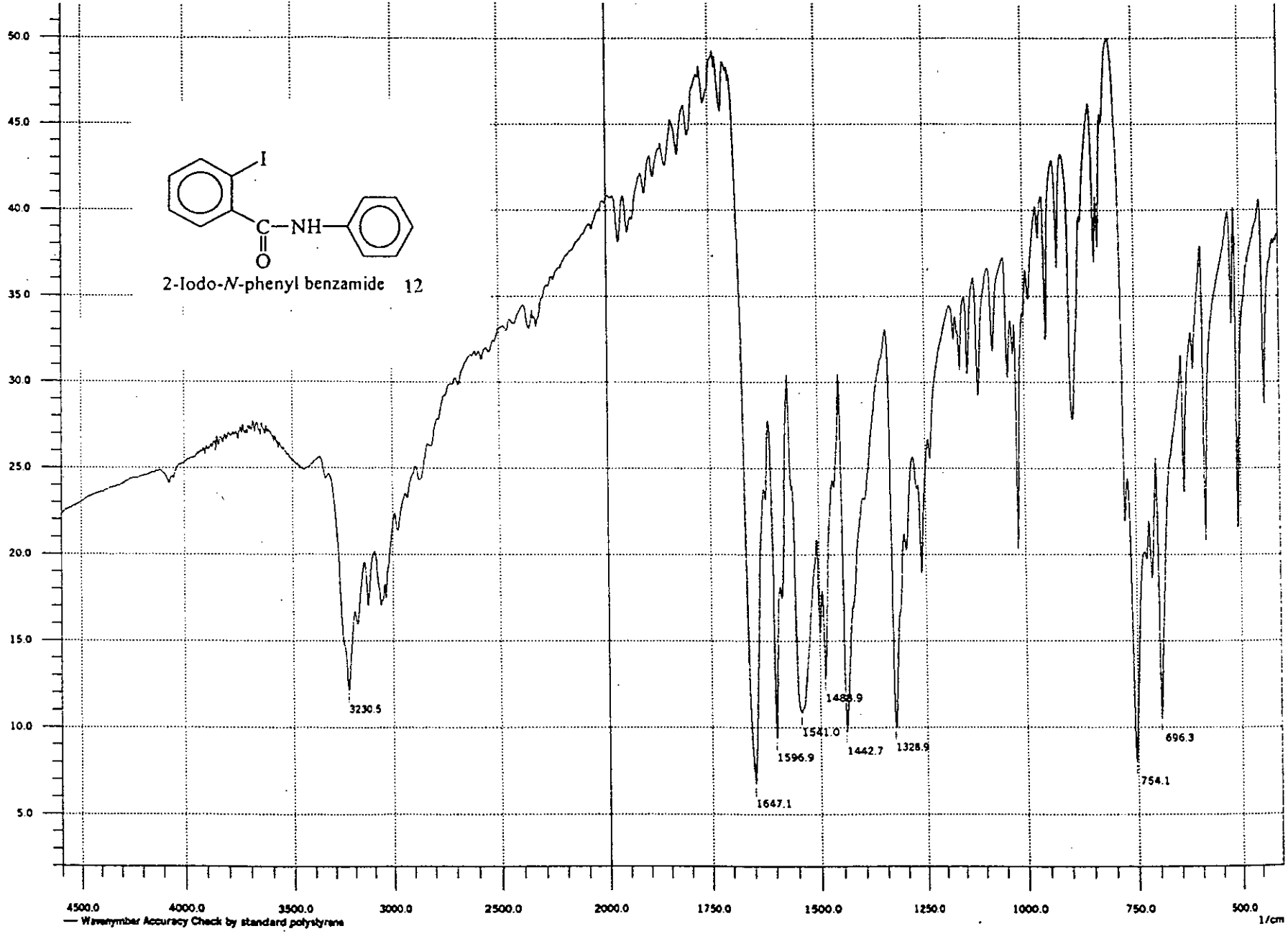


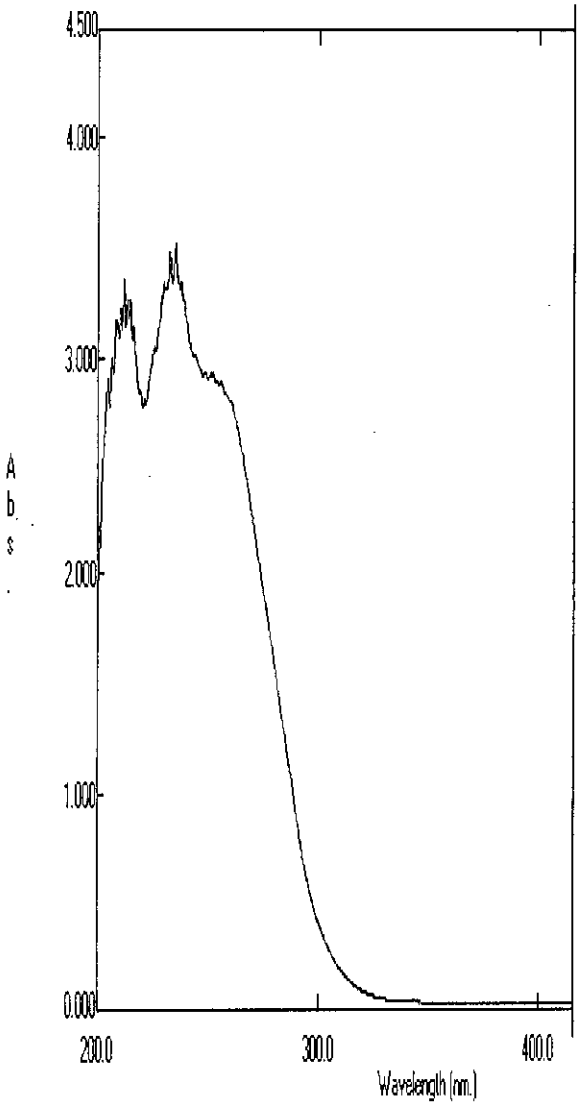
2-Iodo-*N*-phenyl benzamide 12

File Name: 98

Created: 16:44 06/02/03
Data: Original

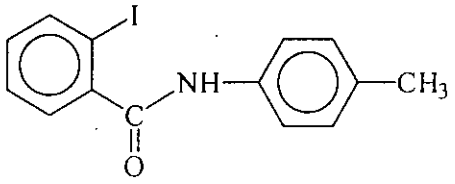
Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2


I
C—NH
O
2-Iodo-N-phenyl benzamide 12
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
3230.5
1647.1
1596.9
1541.0
1488.9
1442.7
1328.9
754.1
696.3
4500.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
— Wavenumber Accuracy Check by standard polystyrene



Peak Pick

No.	Wavelength (nm.)	Abs.
1	234.80	3.5242
2	211.60	3.3608



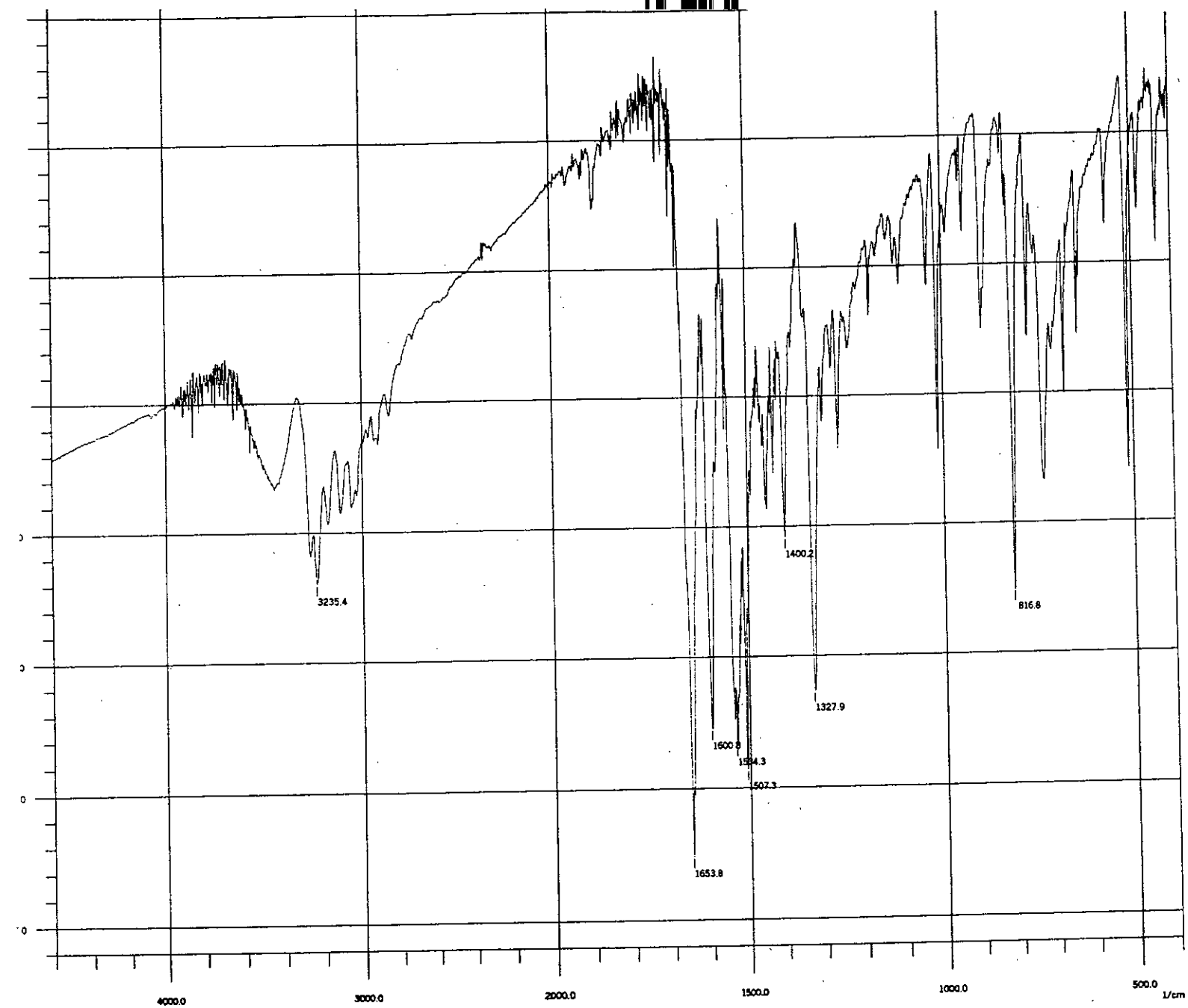
2-Iodo-*N*-*p*-methyl phenyl benzamide

13

File Name: MR88

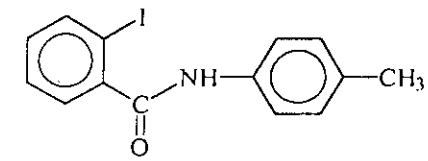
Created: 10:40 08/10/04
Data: Original

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



No.	Pos. (1/cm)	Inten. (%T)
1	816.8	57.398
2	1327.9	53.662
3	1400.2	59.559
4	1507.3	50.703
5	1534.3	51.626
6	1600.8	52.266
7	1653.8	47.405
8	3235.4	57.995

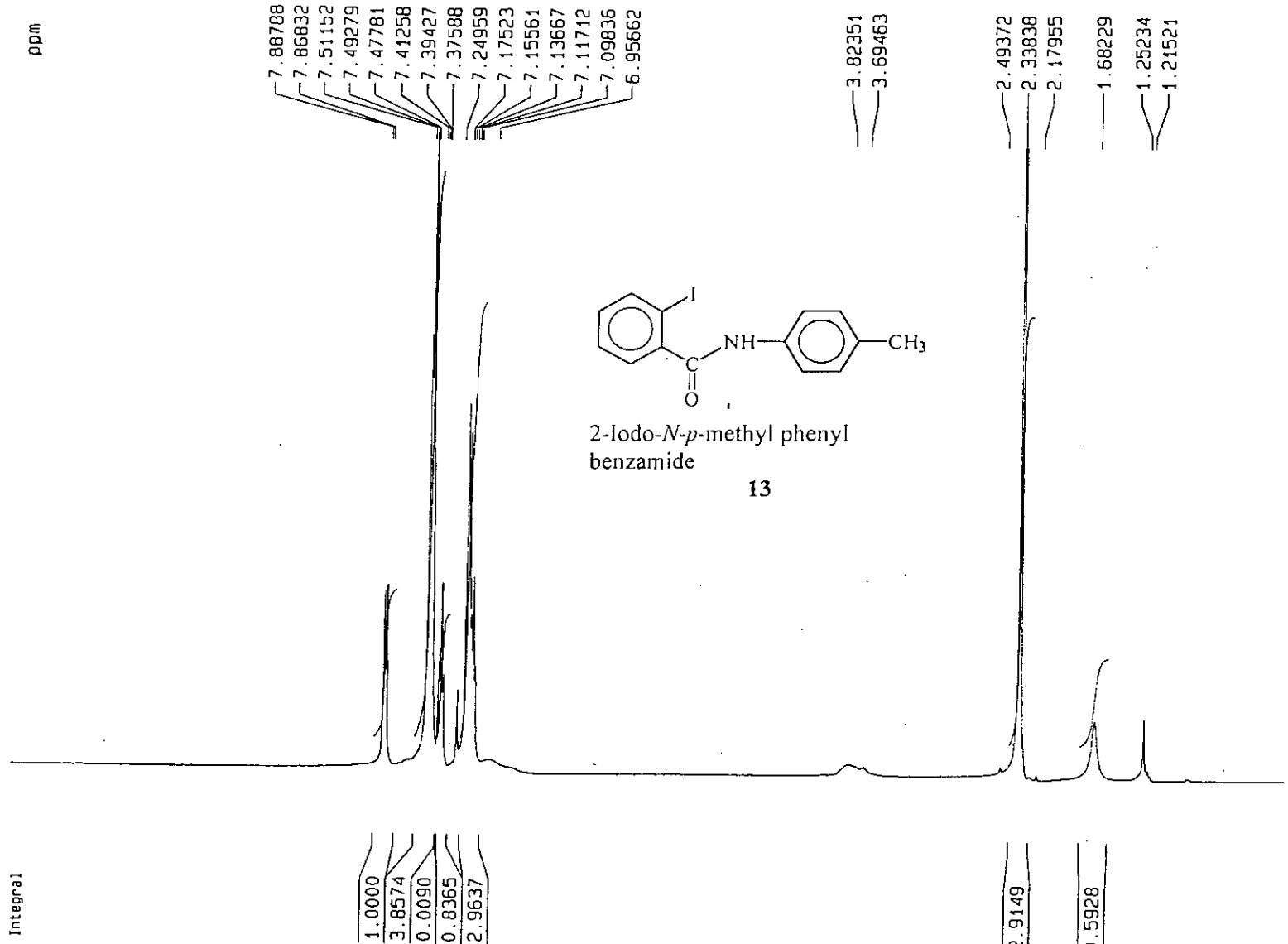
MRta, May21. 2004



2-Iodo-*N*-*p*-methyl phenyl benzamide

13

MRTA.IRS: MRta, May21. 2004					
Date:	04/21/2004	Time:	11:41:08	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.964434	Resolution:	2.0
Coln:	auto	Aperture:	auto	Mirror Speed:	2.80cm/



2-Iodo-*N*-*p*-methyl phenyl benzamide

13

Current Data Parameters

NAME	A1564
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040812
Time	11.59
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

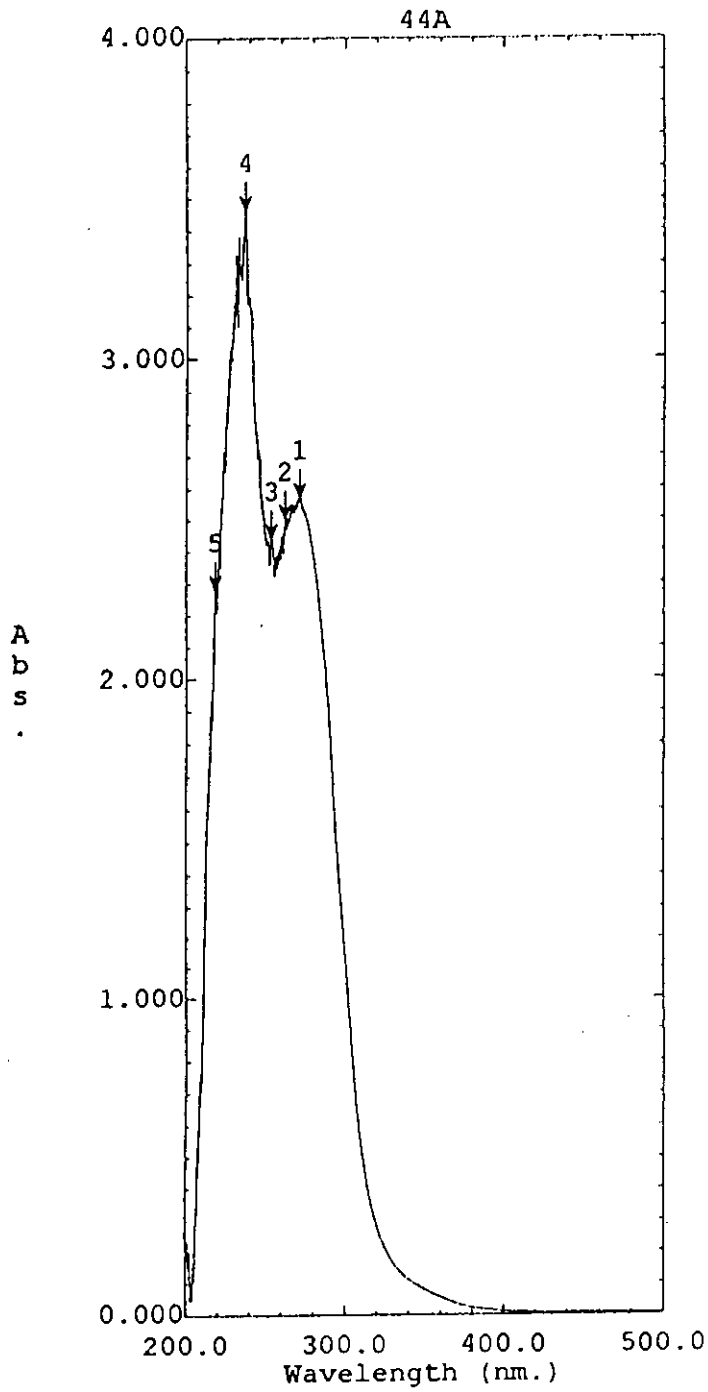
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

SI	32768
SF	400.1400122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	11.160 ppm
F1	4465.75 Hz
F2P	0.007 ppm
F2	2.92 Hz
PPMCM	0.55766 ppm/cm
HZCM	223.14183 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
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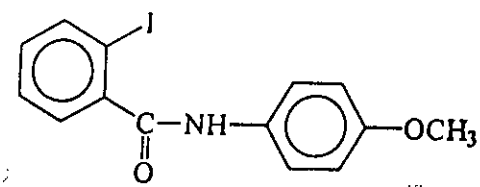
2	262.00	2.5002
3	253.40	2.4393
4	236.80	3.4618
5	218.40	2.2762

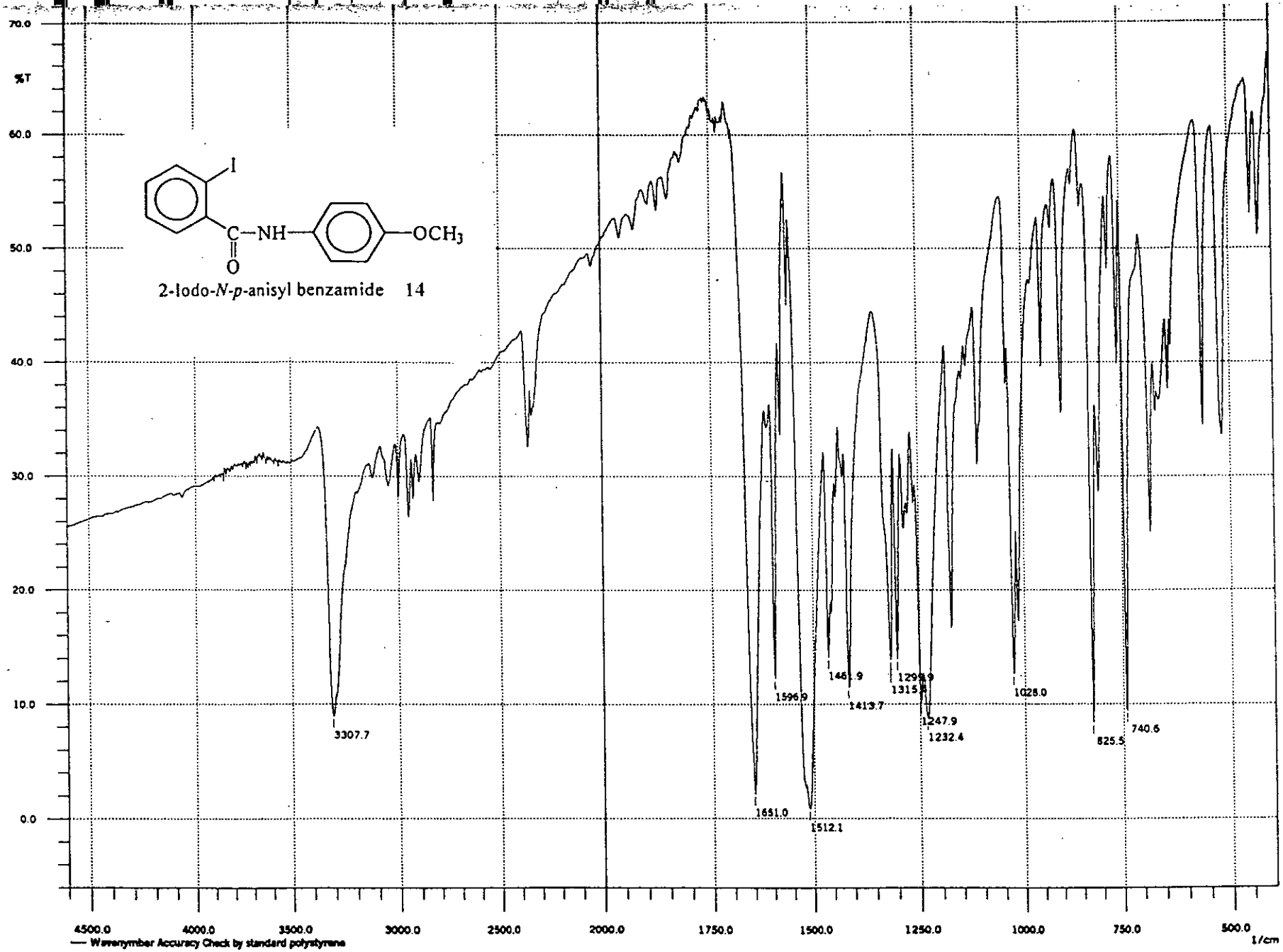


2-Iodo-*N*-*p*-anisyl benzamide 14

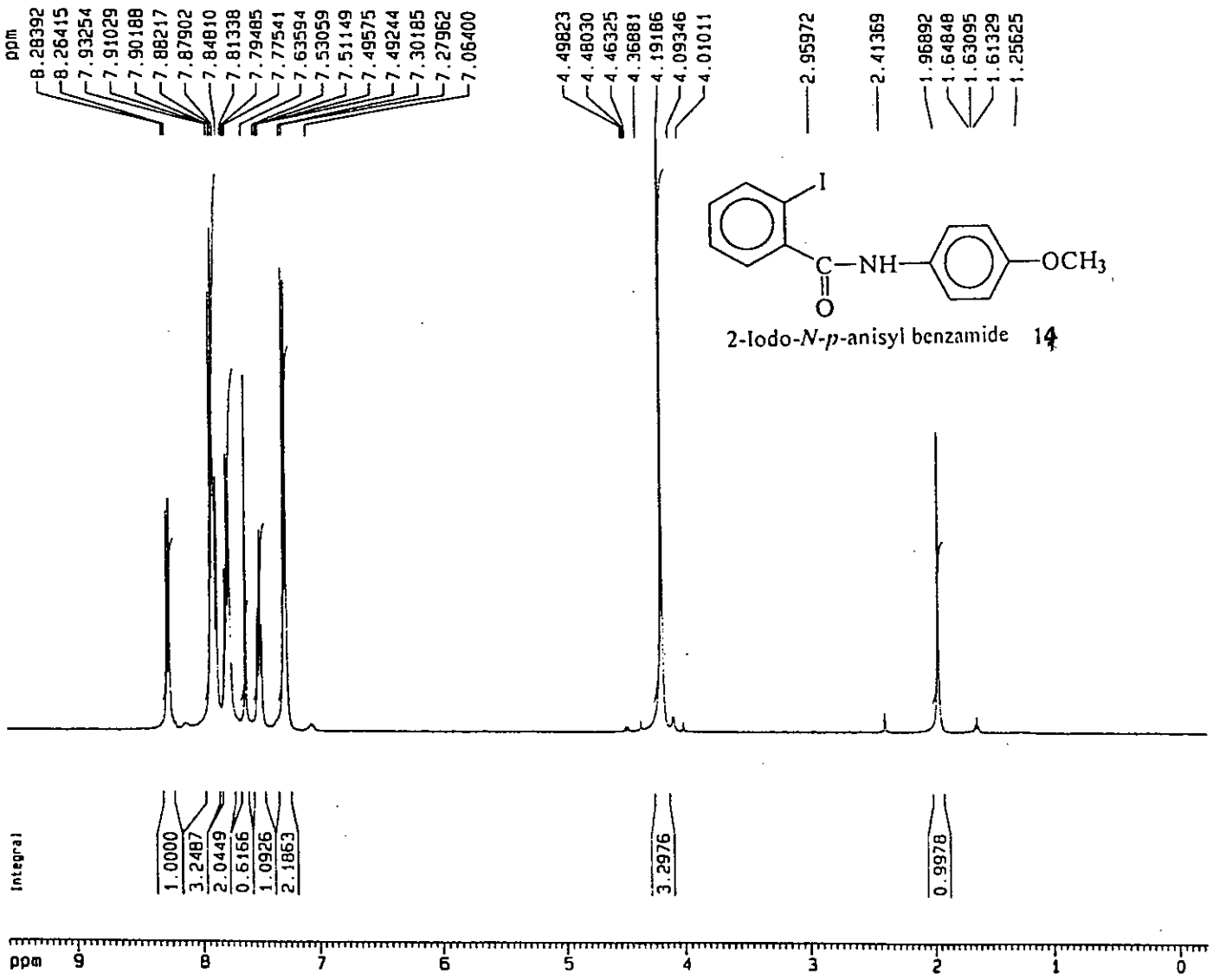
File Name: 44A

Created: 16:54 06/02/03
Data: Original

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


%T
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
I
C—NH—OCH3
O
2-Iodo-N-p-anisyl benzamide 14
3307.7
1651.0
1596.9
1512.1
1461.9
1413.7
1315.8
1298.9
1247.9
1232.4
1028.0
825.5
740.6
4500.0
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
— Wavenumber Accuracy Check by standard polystyrene

Analytical, BCSIR Lab. Dhaka. 1H Spectrum 02A6 in COCl3 Delwar BUET.



2-Iodo-*N*-*p*-anisyl benzamide **14**

Current Data Parameters

NAME	A588
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020430
Time	13.55
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	'Aceton
NS	128
DS	0
SWH	6410.256 Hz
FIORES	0.195625 Hz
AQ	2.5559540 sec
RG	362
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

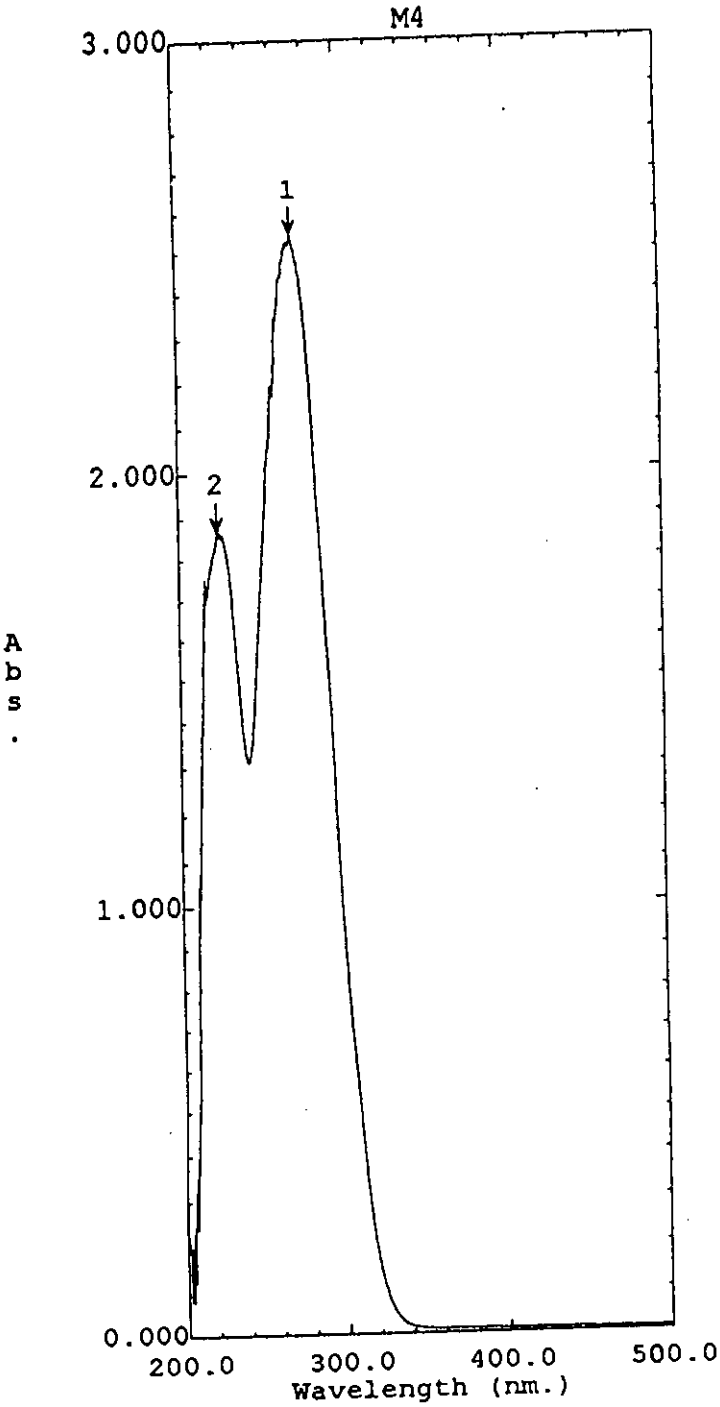
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1398584 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

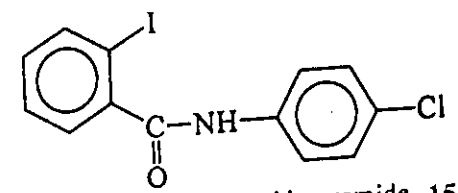
1D NMR plot parameters

CX	20.00 cm
F1P	9.555 ppm
F1	3823.16 Hz
F2P	-0.226 ppm
F2	-90.40 Hz
PPMCM	0.48902 ppm/cm
HZCM	195.67813 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
1	272.00	2.5474
2	223.80	1.8669

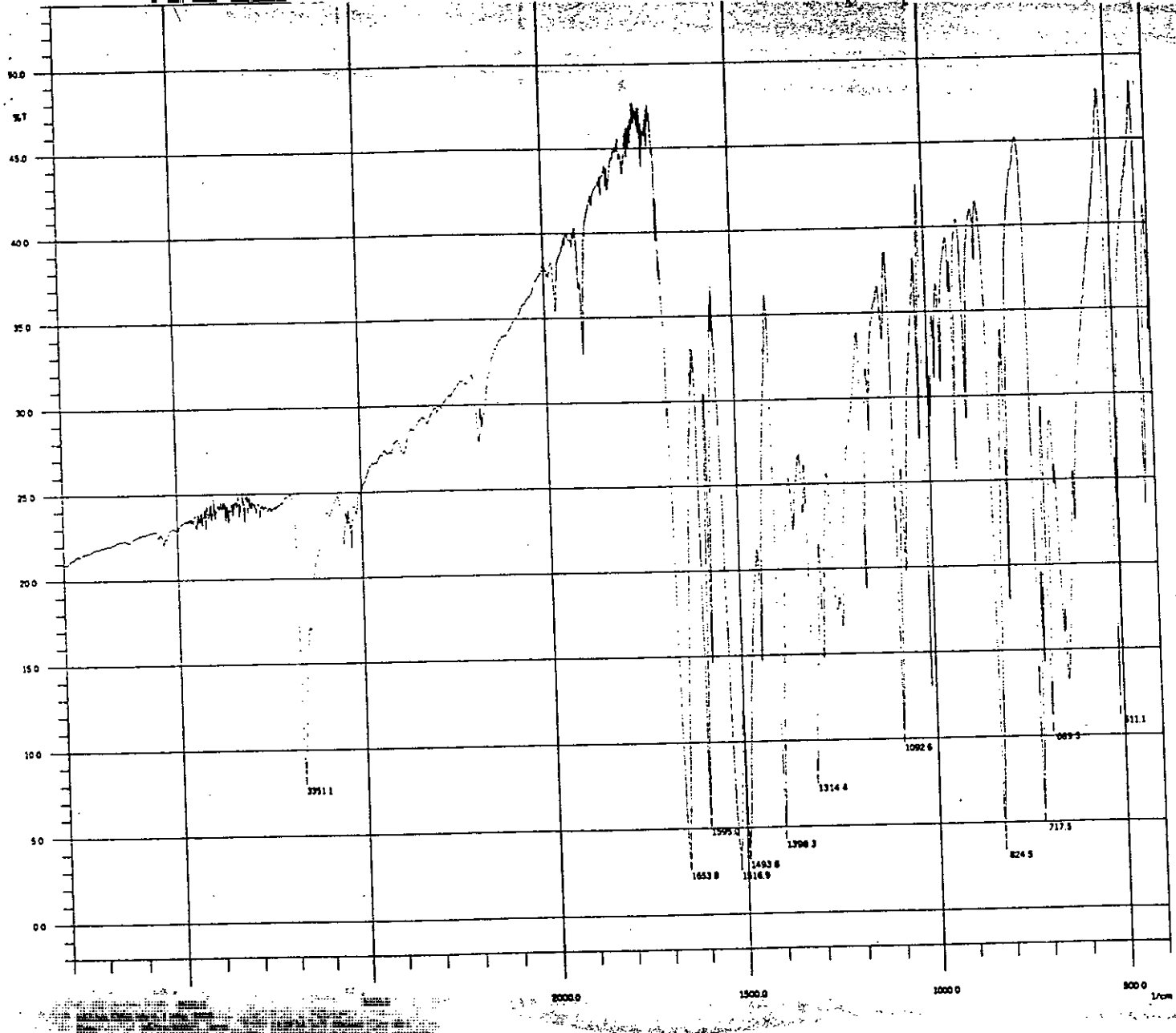


2-Iodo-*N*-*p*-chlorophenyl benzamide 15

File Name: M4

Created: 16:19 06/02/03
Data: Original

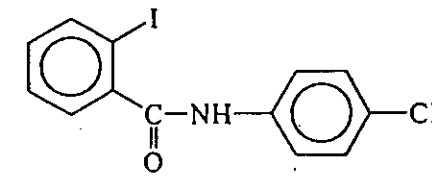
Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2



Selection

No.	Pos. (1/cm)	Inten. (%T)
1	511.1	11.765
2	689.5	10.865
3	717.5	5.589
4	824.5	4.038
5	1092.6	10.406
6	1314.4	8.158
7	1398.3	4.925
8	1493.8	3.786
9	1516.9	3.611
10	1595.0	5.732
11	1653.8	3.213
12	3351.1	8.570

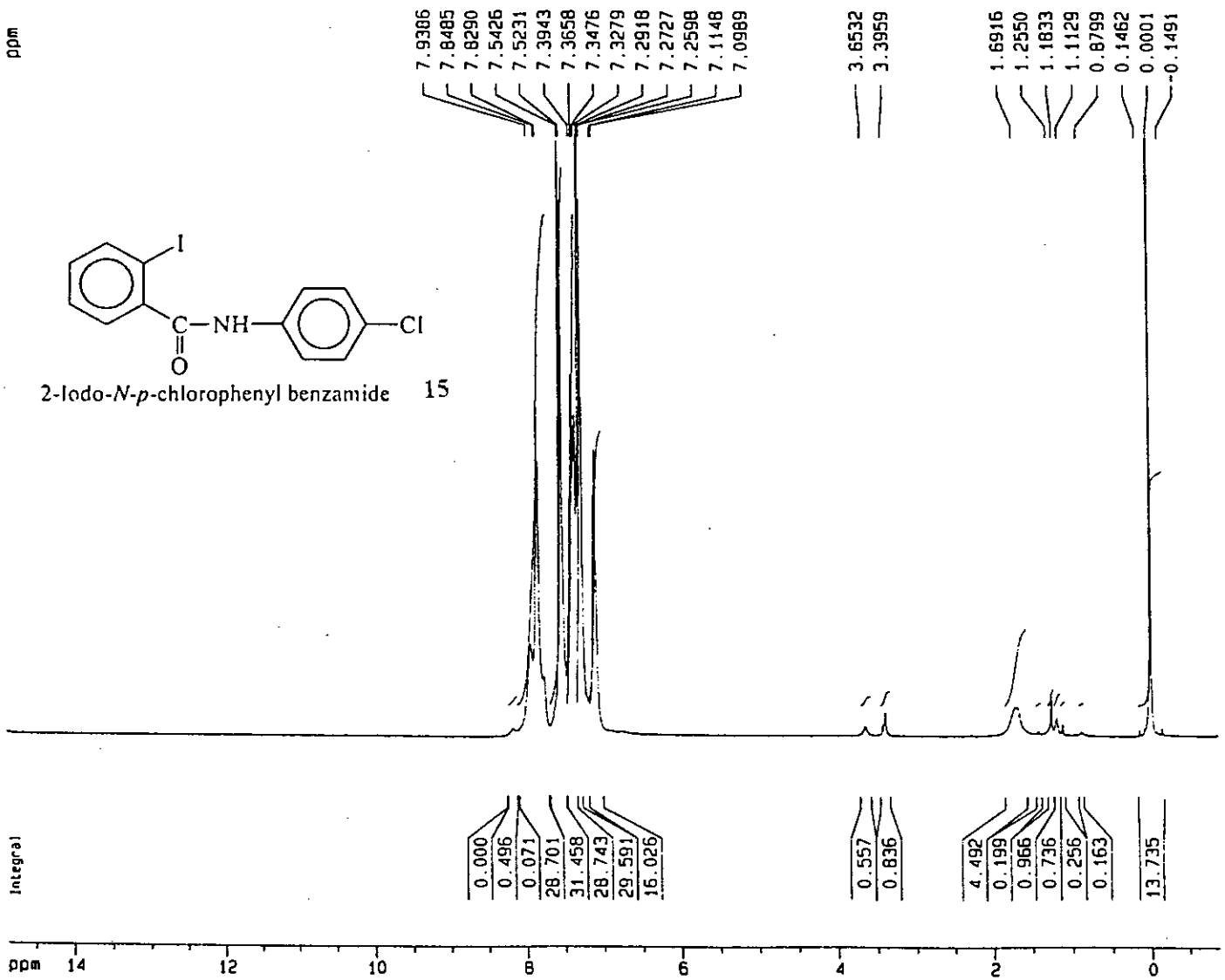
Ma-4, 1 May, 2003



2-Iodo-*N*-*p*-chlorophenyl benzamide

15

60



2-Iodo-*N*-*p*-chlorophenyl benzamide 15

```
Current Data Parameters
NAME                  A766
EXPNO                    1
PROCNO                   1

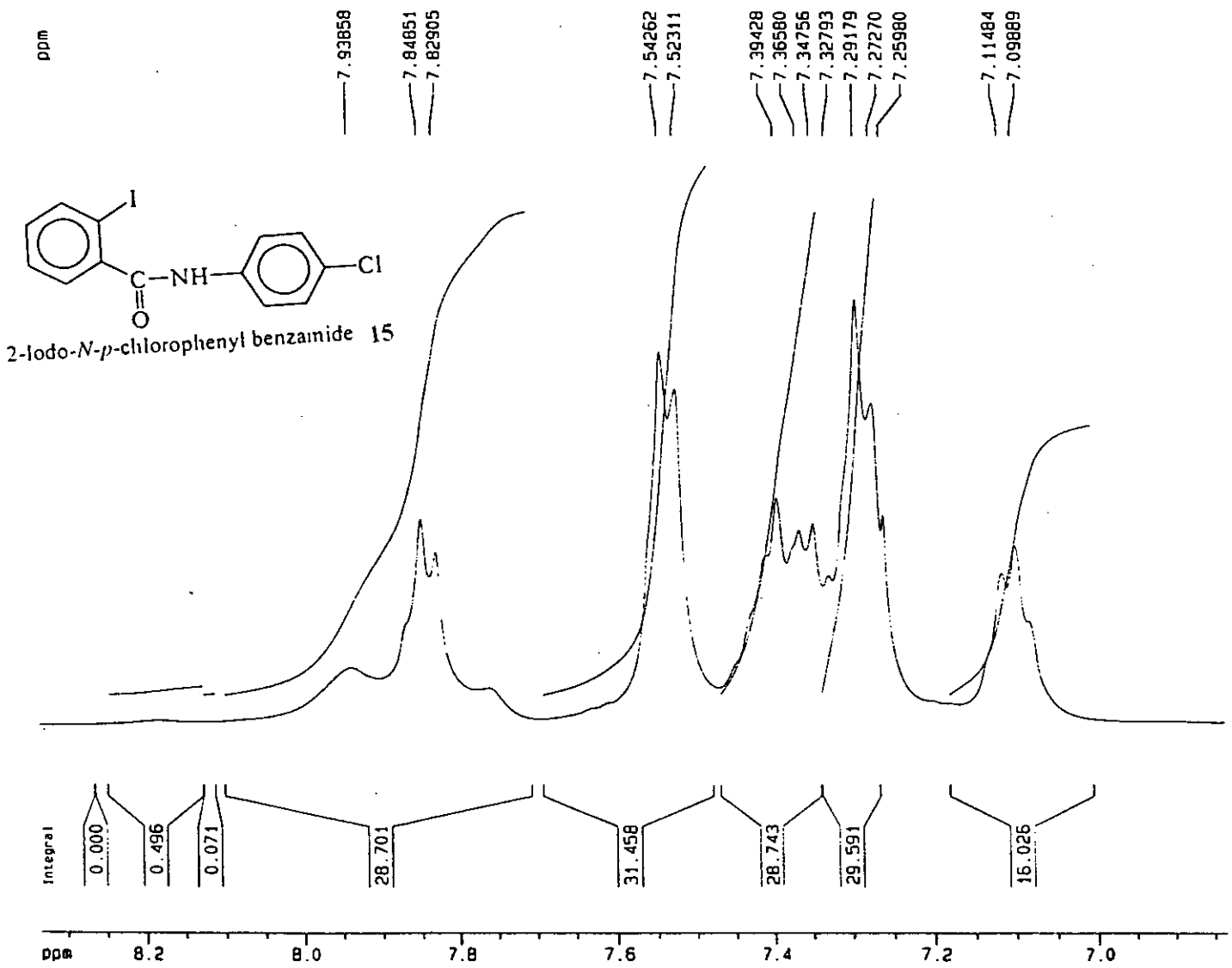
F2 - Acquisition Parameters
Date_              20020904
Time                 12.21
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT           · CDCl3
NS                     128
DS                       0
SWH             6410.256 Hz
FIDRES          0.195625 Hz
AQ              2.5559540 sec
RG                      64
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1              1.00000000 sec

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

F2 - Processing parameters
SI                   32768
SF            400.1400096 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                 14.864 ppm
F1                 5947.71 Hz
F2P                 -0.895 ppm
F2                 -358.03 Hz
PPMCM              0.78794 ppm/cm
HZCM             315.28708 Hz/cm
```

Analytical, BCSIR Lab. Dhaka 1H Spectrum M-3 in CDCl3 Masud BUET.



Current Data Parameters

NAME	A766
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020904
Time	12.21
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	64
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

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

F2 - Processing parameters

SI	32768
SF	400.1400096 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	8.336 ppm
F1	3335.47 Hz
F2P	6.835 ppm
F2	2735.15 Hz
PPMCM	0.07501 ppm/cm
HZCM	30.01613 Hz/cm

1.2.8.B. Synthesis of *N*-Substituted-3-Alkyl Isoindolinone esters:

Synthesis of *N*-phenyl-3-butyl isoindolin-1-one acetate 22:

A mixture of 2-Iodo-*N*-phenyl benzamide **12** (0.5g, 1.55 mmol), bis (triphenyl phosphine)palladium(II) chloride (0.038g, 3.5 mol%) and triethyl amine (0.625g, 4 equiv) was stirred in DMF (10ml) under nitrogen atmosphere for 1 hr. Then Butyl acrylate **16** (0.57g, 3 equiv.) was added to the reaction mixture. The solution was heated at 80 ^{0}C for 23 hrs. The progress of the reaction was monitored by TLC(n-hexane-chloroform 1:1). After completion of the reaction, the mixture was then evaporated to dryness under reduced pressure and the residue was extracted with chloroform (3×50 ml). The combined chloroform extracts washed with distilled water (3×50ml) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain reddish gum. The latter was purified by chromatography on a column of silica gel (60-120 mesh) with n-hexane-chloroform (1:3) and chloroform. The n-hexane-chloroform fraction and the chloroform fraction a small amount of deiodinated product **36a**. The compound **22** was crystallized by n-hexane-ethylacetate to obtain a colourless solid (0.375g, 75%) m.p 90 – 91 °C.

IR: ν_{max} (KBr) 1740.6, 1678.0, 1597.9, 1493.8, 1464.8, 1391.5 and 1301.9 cm^{-1}.

UV(EtOH): λ_{max} 273.00 (log ε 3.810), 236.60, (log ε 3.766), 229.60 (log ε 3.697) and 211.60 (log ε 3.664) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.26 Hz, *J* = 14.66 Hz, $-CH_3$), 1.30 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2$), 2.51 (dd, 1H, *J* = 8.45 Hz, *J* = 16.05 Hz, H–2′), 2.95 (dd, 1H, *J* = 3.87 Hz, *J* = 16.08 Hz, H–2′), 4.05 (m, 2H, $-OCH_2$), 5.60 (dd, 1H, *J* = 3.94 Hz, *J* = 8.34 Hz, H–3), 7.23 – 7.60 (m, 8H, Ar–H), and 7.91 (d, 1H, *J* = 7.80 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.63 (CH_3), 19.03 ($-CH_2-$), 30.47 ($-CH_2-$), 37.75 (C – 2′), 57.58 (C – 3), 64.97 ($-O-CH_2$), 122.57, 123.89, 124.29, 125.95, 128.90, 129.30, 131.96, 132.30, 136.50, 144.28, (Ar – C), 166.90 (CON) and 170.49 ($-CO_2-$).

Synthesis of *N*-*p*-methyl phenyl-3-butyl isoindolin-1-one acetate 23:

The title compound **23** was synthesized from 2--Iodo-*N*-*p*-methyl phenyl benzamid **13** (0.50g, 1.48 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.0365g, 3.5 mol%), triethyl amine (0.599g, 4eqiv.) and butyl acrylate **16** (0.57g, 3equiv.) in DMF (10ml) by following the procedure described above for the compound **22**. After usual work up and column chromatography, *n*-hexane-chloroform fraction the compound **23** was obtained as oil liquid (0.38g, 76%) and chloroform fraction, a small amount of deiodinated product **36b**.

IR: ν_{max} (CCl_4) 1734.9, 1707.8, 1550.7, 1515.0, 1467.7, 1376.1 and 1306.7 cm^{-1}.

UV(EtOH): λ_{max} 243.60 (log ε 3.828) and 208.40 (log ε 3.664) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.33 Hz, *J* = 14.70 Hz, $-CH_3$), 1.27 (m, 2H, $-CH_2$), 1.47 (m, 2H, $-CH_2$), 2.35 (s, 3H, Ar–CH_3), 2.51 (dd, 1H, *J* = 8.45 Hz, *J* = 16.05 Hz, H–2′), 2.94 (dd, 1H, *J* = 4.09 Hz, *J* = 16.08 Hz, H–2′), 4.03 (m, 2H, $-OCH_2$), 5.54 (dd, 1H, *J* = 4.07 Hz, *J* = 8.34 Hz, H–3), 7.24 (t, 1H, *J* = 2.38 Hz, *J* = 8.05 Hz, Ar–H), 7.42 (d, 2H, *J* = 8.24 Hz, Ar–H), 7.49 – 7.58 (m, 4H, Ar–H), and 7.92 (d, 1H, *J* = 7.74 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.63 (CH_3), 19.09 ($-CH_2-$), 21.02 (Ar–CH_3) 30.47 ($-CH_2-$), 37.76 (C–2′), 57.75 (C–3), 64.93 (O–CH_2), 122.55, 124.07, 124.26, 124.22, 129.89, 132.07, 132.15, 133.82, 135.88, 144.31, (Ar–C), 166.84 (CON) and 170.53 ($-CO_2-$).

Synthesis of *N*-*p*-methoxy phenyl-3-butyl isoindolin-1-one acetate 24:

This was synthesized from 2-Iodo-*N*-*p*-methoxy phenyl benzamide **14** (0;50g, 1.426 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.035g, 3.5mol%), triethyl amine (0.57g, 4 equiv.) and butyl acrylate **16** (0.545g, 3 equiv.) in DMF (10ml) by following the procedure described above for the compound **22**. After usual work up, and column chromatography, the compound **24** was obtained as a liquid (0.40g, 80%) and

another fraction, a small amount of deiodinated product **36c** was crystallized from n-hexane-ethyl acetate to obtained a colourless solid compound. (0.05g, 10%) m. p. 166-167 ^{0}C.

IR: ν_{max} (CCl_4) 1734.9, 1706.9, 1549.7, 1514.0, 1249.8, 1217.0 and 1106.1 cm^{-1}.

UV(EtOH): λ_{max} 234.60 (log ε 3.848) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (m, 3H, CH_3), 1.29 (m, 2H, $-CH_2$), 1.51 (m, 2H, $-CH_2$), 2.51 (dd, 1H, *J* = 8.22 Hz, *J* = 16.03 Hz, H–2′), 2.89 (dd, 1H, *J* = 4.39 Hz, *J* = 16.05 Hz, H–2′), 3.81 (s, 3H, $ArOCH_3$), 4.03 (m, 2H, $-OCH_2$), 5.47 (dd, 1H, *J* = 4.35 Hz, *J* = 8.09 Hz, H–3). 6.97 (d, 2H, *J* = 8.90 Hz, Ar–H), 7.40 – 7.58 (m, 5H, Ar–H) and 7.91 (d, 1H, *J* = 7.20 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.62 (CH_3), 19.02 ($-CH_2-$), 30.45 ($-CH_3-$) 37.79 (C–2′), 55.50 ($Ar-OCH_3$), 58.17 (C–3), 64.92 ($O-CH_2$), 114.58, 122.53, 124.16, 126.05, 128.81, 129.18, 132.02, 132.08, 144.27, 157.90, (Ar–C), 166.94 (CON) and 170.49 ($-CO_2-$).

N-p-methoxy phenyl benzamide 36c :

IR: ν_{max} (KBr) 3236.3, 1653.7, 1593.1, 1533.3, 1488.9, 1396.4, and 1321.1 cm^{-1}.

UV(EtOH): λ_{max} 279.80 (log ε 3.115), 225.00 (log ε 3.198) and 203.40 (log ε 3.456) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H, $Ar-CH_3$), 6.90 (d, 2H, *J* = 8.91 Hz, Ar–H), 7.44–753 (m, 5H, Ar–H), 7.77 (brs, 1H, N–H) and 7.85 (d, 2H, *J* = 7.18 Hz, Ar–H)

Synthesis of *N-p*-chlorophenyl-3-butyl isoindolin-1-one acetate 25:

The title compound **25** was synthesized form 2-Iodo-*N-p*-chlorophenyl benzamide **15** (0.50g, 1.39m mol), bis (triphenyl phosphine) palladium (II) chloride (0.034g, 3.5mol%), triethyl amine (0.56g, 4 equiv.) and butyl acrylate **16** (0.54g, 3 equiv.) in DMF (10ml) by following the procedure described above for the compound **22**. After usual work up, a greenish gum was obtained. It was purified by column chromatography with chloroform in n-hexane to obtain the liquid compound **25**, (0.385g, 77%) and chloroform fraction, small amount of deidionated product **36d**.

IR: ν_{max} (CCl_4) 1732.9, 1711.7, 1550.7, 1494.7, 1373.2, 1253.6, 1217.0 and 1173.6 cm^{-1}.

UV(EtOH): λ_{max} 258.20 (log ε 3.854), 226.40 (log ε 3.696) and 209.60 (log ε 3.684) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, 3H, CH_3), 1.29 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 2.51 (dd, 1H, *J* = 8.24 Hz, *J* = 16.10 Hz, H–2′), 2.92 (dd, 1H, *J* = 4.04 Hz, *J* = 16.10 Hz, H–2′), 5.56 (dd, 1H, *J* = 3.98 Hz, *J* = 8.11 Hz, H–3), 7.41 (d, 2H, *J* = 8.72 Hz, Ar–H), 7.50 – 7.61 (m, 5H, Ar–H), and 7.92 (d, 1H, *J* = 7.19 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.62 (CH_3), 19.02 (CH_2), 30.54 (CH_2), 37.63 (C–2′), 57.46 (C–3), 65.06 (–O–CH_2), 122.57, 124.33, 124.85, 129.00, 129.39, 131.27, 131.63, 132.53, 135.10, 144.10 (Ar–C), 166.82 (CON) and 170.28 (–CO_2–).

Synthesis of *N-p*-methyl Phenyl-3-ethyl isoindolin-1-one acetate 26:

Bis (triphenyl phosophine) palladium (II) chloride (0.036g, 3.5mol%), trielthyl ammine (0.57g, 4 equiv.) and ethyl acrylate **17** (0.45g, 3 equiv.) were added to the solution of 2-Iodo -*N-p*-methyl phenyl benzamide **13** (0.50g, 1.4 mmol) in DMF (10ml) by following the procedure described above for the compound **22**. After usual work up, a greenish gum was obtained. It was purified by column chromatography with n-hexane in chloroform. The compound 26 was crystallized from n-hexane-ethylacetate to obtain a colourless solid (0.35g, 70%) m.p 97 – 98 °C.

IR: ν_{max} (KBr) 1728.1, 1682.8, 1515 and 1370.3 cm^{-1}.

UV(EtOH): λ_{max} 247.80 (log ε 3.791) and 210.00 (log ε 3.642) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, *J* = 7.20 Hz, *J* = 14.40 Hz, –CH_3), 2.36 (s, 3H, Ar–CH_3), 2.52 (dd, 1H, *J* = 8.40 Hz, *J* = 16.41 Hz, H–2′), 2.92 (dd, 1H, *J* = 4.0 Hz, *J* = 16.0 Hz, H–2′), 4.07 (dd, 2H, *J* = 2.0 Hz, *J* = 7.20 Hz, –OCH_2), 5.30 (dd, 1H, *J* = 4.00 Hz, *J* = 8.4 Hz, H–3), 7.23 (d, 2H, *J* = 8.00 Hz, Ar–H), 7.41 (d, 2H, *J* = 8.40 Hz, Ar–H), 7.49–7.59 (m, 3H, Ar–H), and 7.92 (d, 1H, *J* = 6.80 Hz, Ar–H)

Synthesis of *N*-*p*-methoxy phenyl-3-ethyl isoindolin-1-one acetate 27:

The compound **27** was synthesized from 2-Iodo-*N*-*p*-methoxy phenyl benzamide **14** (0.50g, 1.414 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.038g, 3.5 mol%), trielthyl amine (0.57g, 4 equiv.) and ethyl acrylate **17** (0.42g, 3 equiv.) in DMF (10ml) by following the procedure described above for the compound **22**. After usual work up, a greenish gum was obtained. It was purified by colunn chromatography with n-hexane in chloroform to obtain a liquid compound (0.36g, 72%).

IR: ν_{max} (CCl_4) 1735.8, 1707.8, 1548.7, 1513.1 and 1248.8 cm^{-1}.

UV(EtOH): λ_{max} 243.80 (log ε 3.813) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, *J* = 7.13 Hz, *J* = 14.28 Hz, CH_3), 2.50 (dd, 1H, *J* = 8.20 Hz, *J* = 16.14 Hz, H–2′), 2.88 (dd, 1H, *J* = 4.42 Hz, *J* = 16.04 Hz, H–2′), 3.81 (s, 3H, OCH_3), 4.07 (dd, 2H, *J* = 2.08 Hz, *J* = 7.17 Hz, O–CH_2), 5.4 (dd, 1H, *J* = 4.41 Hz, *J* = 8.08 Hz, H–3), 6.97 (d, 2H, *J* = 8.96 Hz, Ar–H), 7.39 – 7.67 (m, 5H, Ar–H) and 7.91 (d, 1H, *J* = 8.18 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.02 (–CH_3), 37.80 (C–2′), 55.50 (OCH_3), 58.16 (C–3), 60.97 (–O–C), 114.56, 122.54, 124.13, 126.06, 128.54, 128.80, 129.18, 132.06, 144.24, 157.89, (Ar–C), 166.92 (CON) and 170.35 (–CO_2–).

Synthesis of *N*-*p*-methyl phenyl-3-methyl isoindolin-1-one acetate 28:

A mixture of 2-Iodo-*N*-*p*-methyl phenyl benzamide **13** (0.5g, 1.4 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), triethyl amine (0.52g 4 equiv.) and methyl acrylate **18** (0.40g, 3 equiv.) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up and column chlormatography, n-hexane in chloroform to obtain a liquid compound **28** (0.325g, 65%).

IR: ν_{max} (CCl_4) 1739.7, 1707.8, 1550.7, 1515.9 and 1380.9 cm^{-1}.

UV(EtOH): λ_{max} 245.80 (log ε 3.771) and 206.20 (log ε 3.631) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, Ar–CH_3), 2.50 (dd, 1H, *J* = 8.52 Hz, *J*=16.06 Hz, H–2′), 2.92 (dd, 1H, *J* = 4.1 Hz, *J* = 16.14 Hz, H–2′), 3.60 (s, 3H, OCH_3), 5.52 (dd, 1H, *J* = 4.02 Hz, *J* = 8.4 Hz, H–3), 7.22 (d, 2H, *J* = 8.9, Ar–H), 7.40 (d, 2H, *J* = 8.16 Hz, Ar–H), 7.47 – 7.58 (m, 3H, Ar–H) and 7.91 (d, 1H, *J* = 7.45 Hz, Ar–H).

Synthesis of *N*-*p*-methoxy phenyl-3-methyl isoindolin-1-one acetate 29:

This was synthesized from 2-Iodo-*N*-*p*-methoxy phenyl benzamide **14** (0.50g, 1.416 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.034g, 3.5 mol%), triethyl amine (0.592g, 4 equiv.) and methyl acrylate **18** (0.365g, 3 equiv.) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up, a greenish gum was obtained. It was purified by column chromatography with n-hexane-ethyl acetate to obtain a liquid compound **29** (0.335g, 67%).

IR: ν_{max} (CCl_4) 1740.6, 1707.8, 1550.7, 1514.0, 1249.8, 1217.8 and 1005.8 cm^{-1}.

UV(EtOH): λ_{max} 273.40 (log ε 3.674), 235.20 (log ε 3.742) and 206.00 (log ε 3.652) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (dd, 1H, *J* = 8.39 Hz, *J* = 16.09 Hz, H–2′), 2.91 (dd, 1H, *J* = 4.46 Hz, *J* = 16.08 Hz, H–2′), 3.60 (s, 3H, $-OCH_3$), 3.81 (s, 3H, Ar–OCH_3), 5.48 (dd, 1H, *J* = 4.42 Hz, *J* = 8.31 Hz, H–3), 6.95 – 7.67 (m, 7H, Ar–H), and 7.90 (d, 1H, *J* = 7.40 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 37.69 (C–2′), 51.96 (C–3), 55.51 (Ar–O–C), 58.11 (O–CH_2), 114.59, 122.50, 124.19, 126.04, 128.86, 129.16, 131.96, 132.12, 144.21, 157.90 (Ar–C), 166.89 (CON) and 170.88 ($-CO_2-$).

Synthesis of *N*-phenyl-3-(2′-methyl)-methyl isoidolin-1-one acetate 37:

A mixture of 2-Iodo-*N*-phenyl benzamide **12** (0.5g, 1.55 mmol), bis (tri-phenyl phosphine) palladium (II) chloride (0.038g, 3.5 mol%), triethyl amine 0.625g,4 equiv.) and methyl methyl acrylate **19** (0.465g, 3 equiv.) in DMF by following the procedure described above for the compound **22**. After usual work up, gave a mixture of cyclic product and the deiodinated product were not easily separable by column chromatography.

Synthesis of *N*-*p*-methyl phenyl-3-ethylnitrile isoindolin-1-one acetate 38:

Bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%),triethyl amine (0.599g, 4 equiv.) and acrylonitrile **20** (0.24g, 3 equiv.) were added to the solution of 2-Iodo-*N*-methyl phenyl benzamide **13** (0.50g, 1.48 mmol) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up, gave a mixture of cyclic product and the deiodinated product were not easily separable by column chromatography.

Synthesis of *N*-*p*-methyl phenyl-3-methyl isoindolin-1-one acetate 28:

The title compound was synthesized from 2-Iodo-*N*-*p*-methyl phenyl benzamide **13** (0.50g, 1.4 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%) triethyl amine (0.52 g, 4 equiv.) and methyl acrylate **18** (0.40g, 3 equiv.) in DMF (10 ml) were heated at 100°C for 24 hrs. by following the procedure described above for the compound **22**. After usual work up and purified by column chromatography with n-hexane in chloroform to obtain a liquid compound **28** (0.265g, 35%).

IR: ν_{max} (CCl_4) 1739.7, 1707.8, 1550.7, 1515.9 and 1380.9 cm^{-1}.

UV(EtOH): λ_{max} 245.80 (log ε 3.771) and 206.20 (log ε 3.631) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, Ar–CH_3), 2.50 (dd, 1H, *J* = 8.52 Hz, *J*=16.06 Hz, H–2′), 2.92 (dd, 1H, *J* = 4.1 Hz, *J* = 16.14 Hz, H–2′), 3.60 (s, 3H, OCH_3), 5.52 (dd, 1H, *J* = 4.02 Hz, *J* = 8.4 Hz, H–3), 7.22 (d, 2H, *J* = 8.9, Ar–H), 7.40 (d, 2H, *J* = 8.16 Hz, Ar–H), 7.47 – 7.58 (m, 3H, Ar–H) and 7.91 (d, 1H, *J* = 7.45 Hz, Ar–H)

Synthesis of *N*-phenyl-3-butyl isoindolin-1-one acetate 22:

This was synthesized from 2-Iodo-*N*-phenyl benzamide **12** (0.50g, 1.55 mmol), palladium acetate (0.028g, 8 mol%), triethyl amine (0.626g, 4 equiv.) and butylacrylate **16** (0.57g,3 equiv.) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up and purified by column chromatography, crystallized from *n*-hexane-ethylacetate to obtain a colourless solid compound **22** (0.165 g, 33%) m.p 90–91 °C.

IR: ν_{max} (KBr) 1740.6, 1678.0, 1597.9, 1493.8, 1464.8, 1391.5 and 1301.9 cm^{-1}.

UV(EtOH): λ_{max} 273.00 (log ε 3.810), 236.60, (log ε 3.766), 229.60 (log ε 3.697) and 211.60 (log ε 3.664) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.26 Hz, *J* = 14.66 Hz, $-CH_3$), 1.30 (m, 2H, $-CH_2$), 1.52 (m, 2H, $-CH_2$), 2.51 (dd, 1H, *J* = 8.45 Hz, *J* = 16.05 Hz, H–2′), 2.95 (dd, 1H, *J* = 3.87 Hz, *J* = 16.08 Hz, H–2′), 4.05 (m, 2H, $-OCH_2$), 5.60 (dd, 1H, *J* = 3.94 Hz, *J* = 8.34 Hz, H–3), 7.23 – 7.60 (m, 8H, Ar–H), and 7.91 (d, 1H, *J* = 7.80 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.63 (CH_3), 19.03 ($-CH_2-$), 30.47 ($-CH_2-$), 37.75 (C – 2′), 57.58 (C – 3), 64.97 ($-O-CH_2$), 122.57, 123.89, 124.29, 125.95, 128.90, 129.30, 131.96, 132.30, 136.50, 144.28, (Ar – C), 166.90 (CON) and 170.49 ($-CO_2-$).

Synthesis of *N*-*p*-chlorophynyl-3-butyl isoindolin-1-one acetate 25:

Tetrakis (triphenyl phosphine) palladium (0) (0.058g, 3.66 mol%), triethyl amine (0.56g, 4 equiv.) and butyl acrylate **16** (0.54g, 3 equiv.) were added to the solution of 2-Iodo-*N*-*p*-chlorophenyl benzamide **15** (0.50g, 1.39m mol) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up and purified by column chromatography with chloroform in n-hexane to obtain the liquid compound **25**. (0.20g, 40%).

IR: ν_{max} (CCl_4) 1732.9, 1711.7, 1550.7, 1494.7, 1373.2, 1253.6, 1217.0 and 1173.6 cm^{-1}.

UV(EtOH): λ_{max} 258.20 (log ε 3.854), 226.40 (log ε 3.696) and 209.60 (log ε 3.684) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, 3H, CH_3), 1.29 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 2.51 (dd, 1H, *J* = 8.24 Hz, *J* = 16.10 Hz, H–2′), 2.92 (dd, 1H, *J* = 4.04 Hz, *J* = 16.10 Hz, H–2′), 5.56 (dd, 1H, *J* = 3.98 Hz, *J* = 8.11 Hz, H–3), 7.41 (d, 2H, *J* = 8.72 Hz, Ar–H), 7.50 – 7.61 (m, 5H, Ar–H), and 7.92 (d, 1H, *J* = 7.19 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.62 (CH_3), 19.02 (CH_2), 30.45 (CH_2), 37.63 (C–2′), 57.46 (C–3), 65.06 ($-O-CH_2$), 122.57, 124.33, 124.85, 129.00, 129.39, 131.27, 131.63, 132.53, 135.10, 144.10 (Ar–C), 166.82 (CON) and 170.28 ($-CO_2-$).

Synthesis of *N*-*p*-methoxy phenyl-3-ethyl isoindolin-1-one acetate 27:

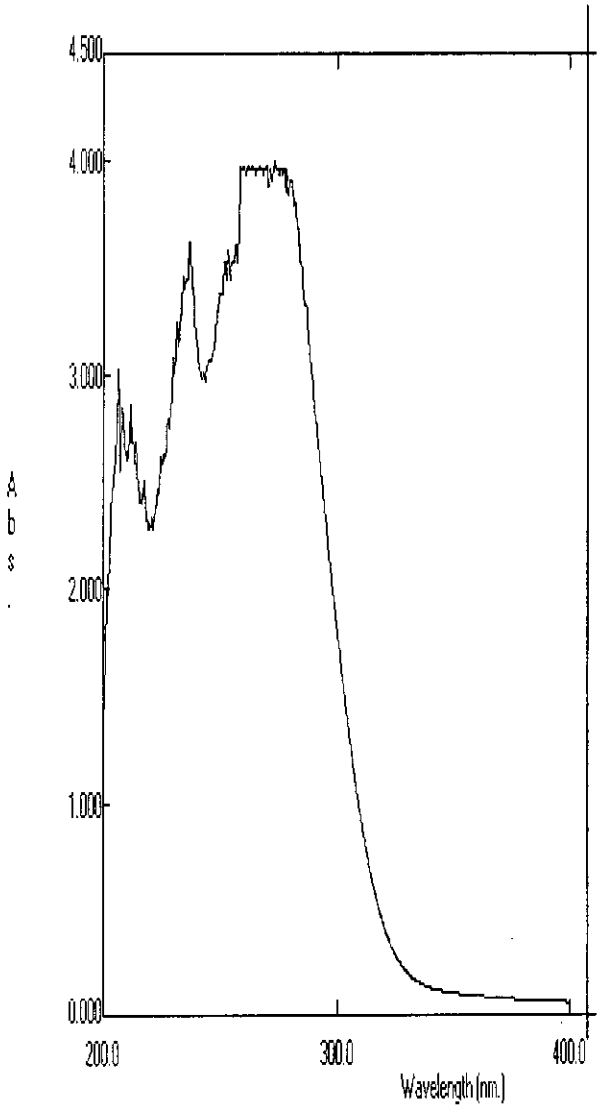
A mixture of 2-Iodo-*N*-*p*-methoxy phenyl benzamide **14** (0.50g, 1.416 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.038g, 3.5 mol%), coppur (I) iodide (0.016g, 6 mol%), triethyl amine (0.57g, 4 equiv.) and ethyl acrylate **17** (0.425g, 3 equiv.) in DMF (10 ml) by following the procedure described above for the compound **22**. After usual work up, a greenish gum was obtained. It was purified by column chromatography with n-hexane in chloroform to obtain a liquid compound **27** (0.19g, 38%).

IR: ν_{max} (CCl_4) 1735.8, 1707.8, 1548.7, 1513.1 and 1248.8 cm^{-1}.

UV(EtOH): λ_{max} 243.80 (log ε 3.813) nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, *J* = 7.13 Hz, *J* = 14.28 Hz, CH_3), 2.50 (dd, 1H, *J* = 8.20 Hz, *J* = 16.14 Hz, H–2′), 2.88 (dd, 1H, *J* = 4.42 Hz, *J* = 16.04 Hz, H–2′), 3.81 (s, 3H, OCH_3), 4.07 (dd, 2H, *J* = 2.08 Hz, *J* = 7.17 Hz, O–CH_2), 5.4 (dd, 1H, *J* = 4.41 Hz, *J* = 8.08 Hz, H–3), 6.97 (d, 2H, *J* = 8.96 Hz, Ar–H), 7.39 – 7.67 (m, 5H, Ar–H) and 7.91 (d, 1H, *J* = 8.18 Hz, Ar–H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.02 (–CH_3), 37.80 (C–2′), 55.50 (OCH_3), 58.16 (C–3), 60.10 (–O–CH_2), 114.57, 122.54, 124.13, 126.06, 128.54, 128.80, 129.18, 132.06, 144.24, 157.89, (Ar–C), 166.92 (CON) and 170.35 (–CO_2–).



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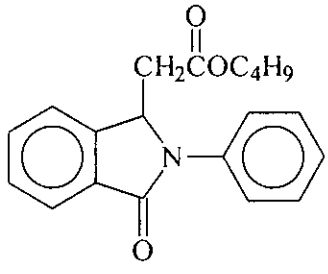

N-phenyl-3-butylisoindolin-1-one acetate

22

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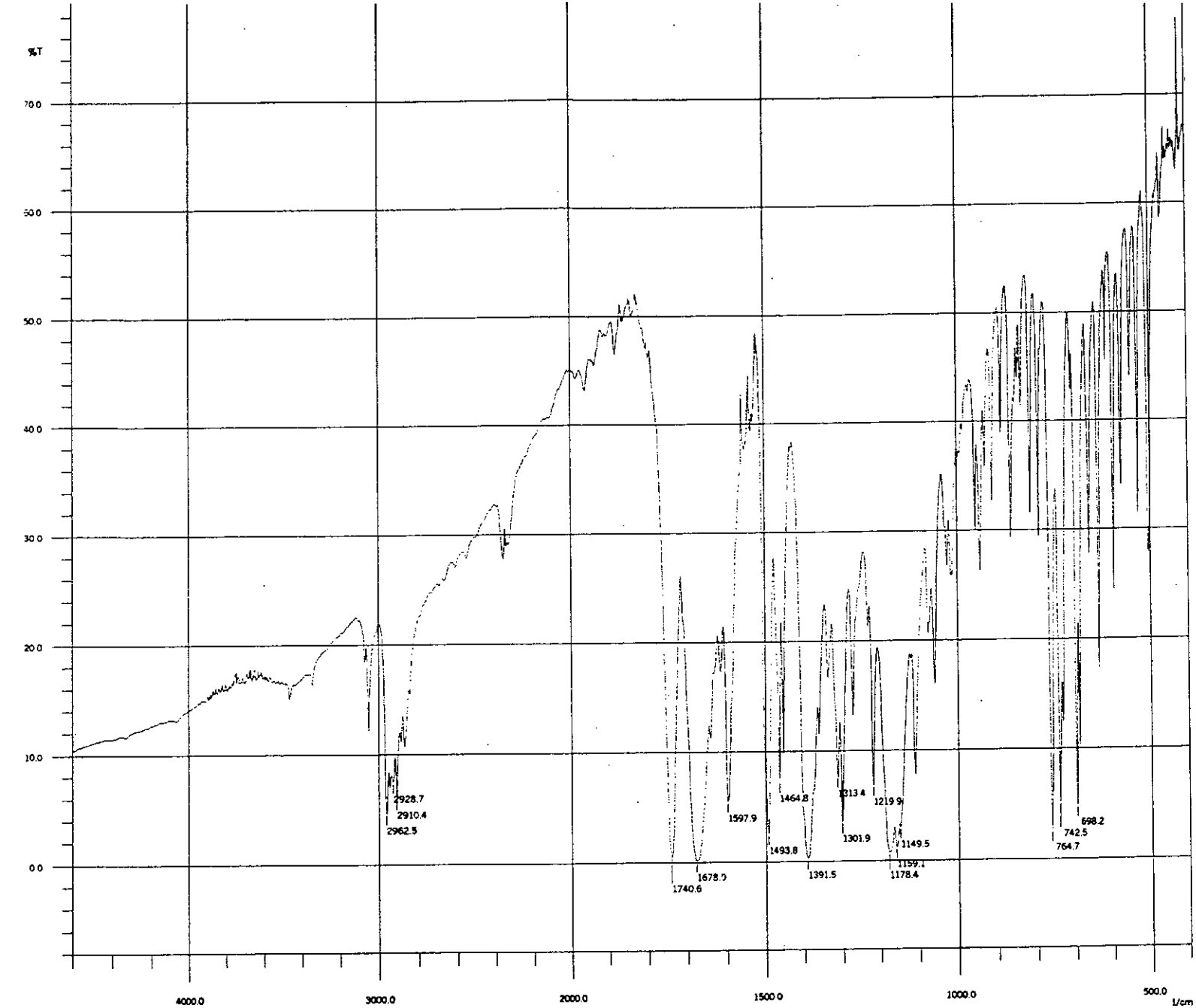

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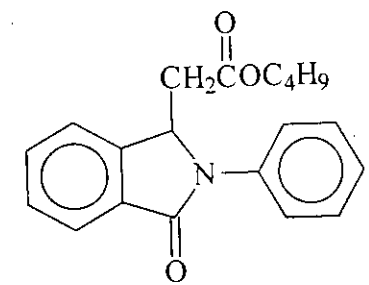
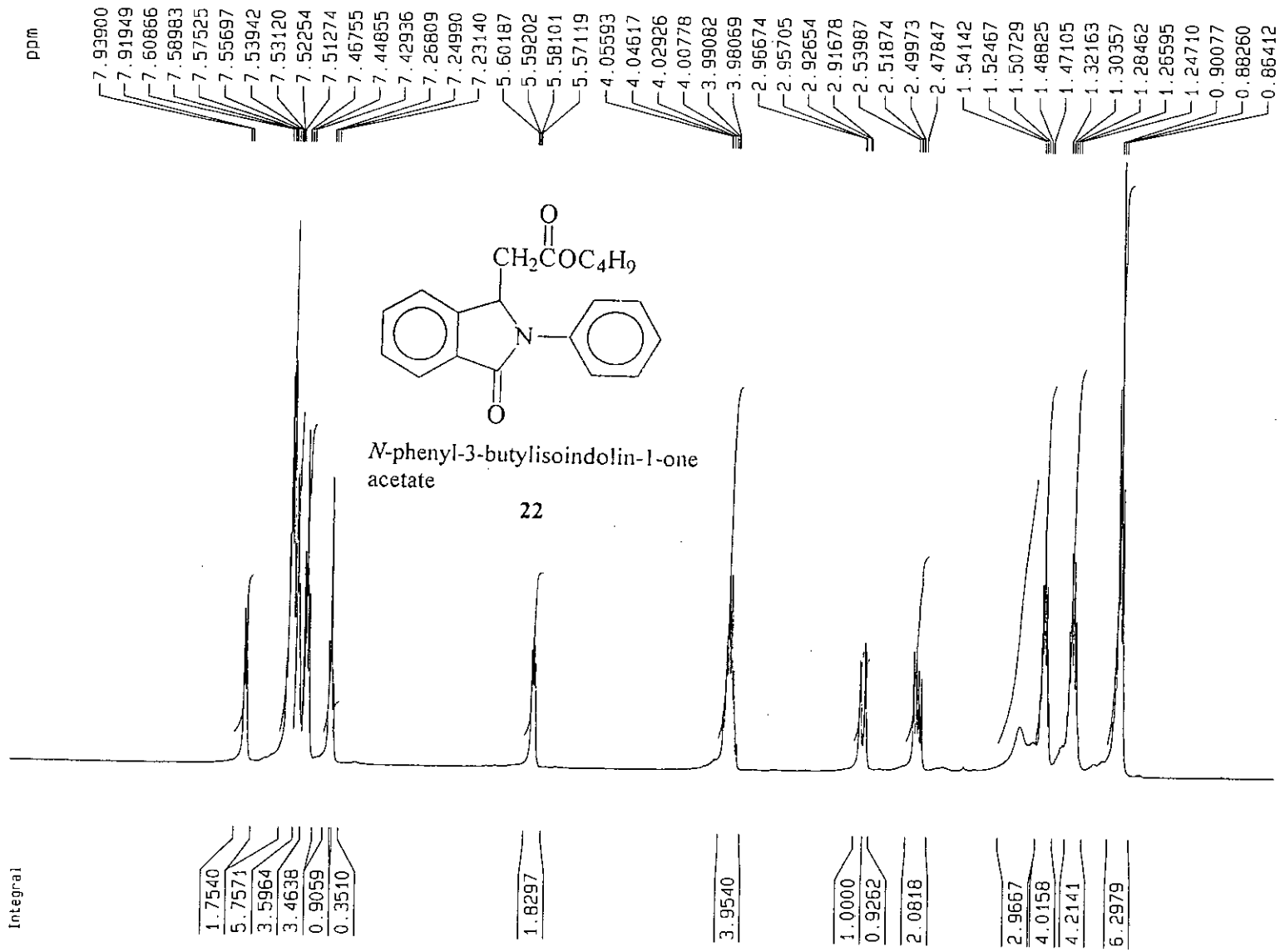
MR-67a1, July 19, 2004



N-phenyl-3-butylisoindolin-1-one acetate

22



N-phenyl-3-butylisoindolin-1-one acetate

22

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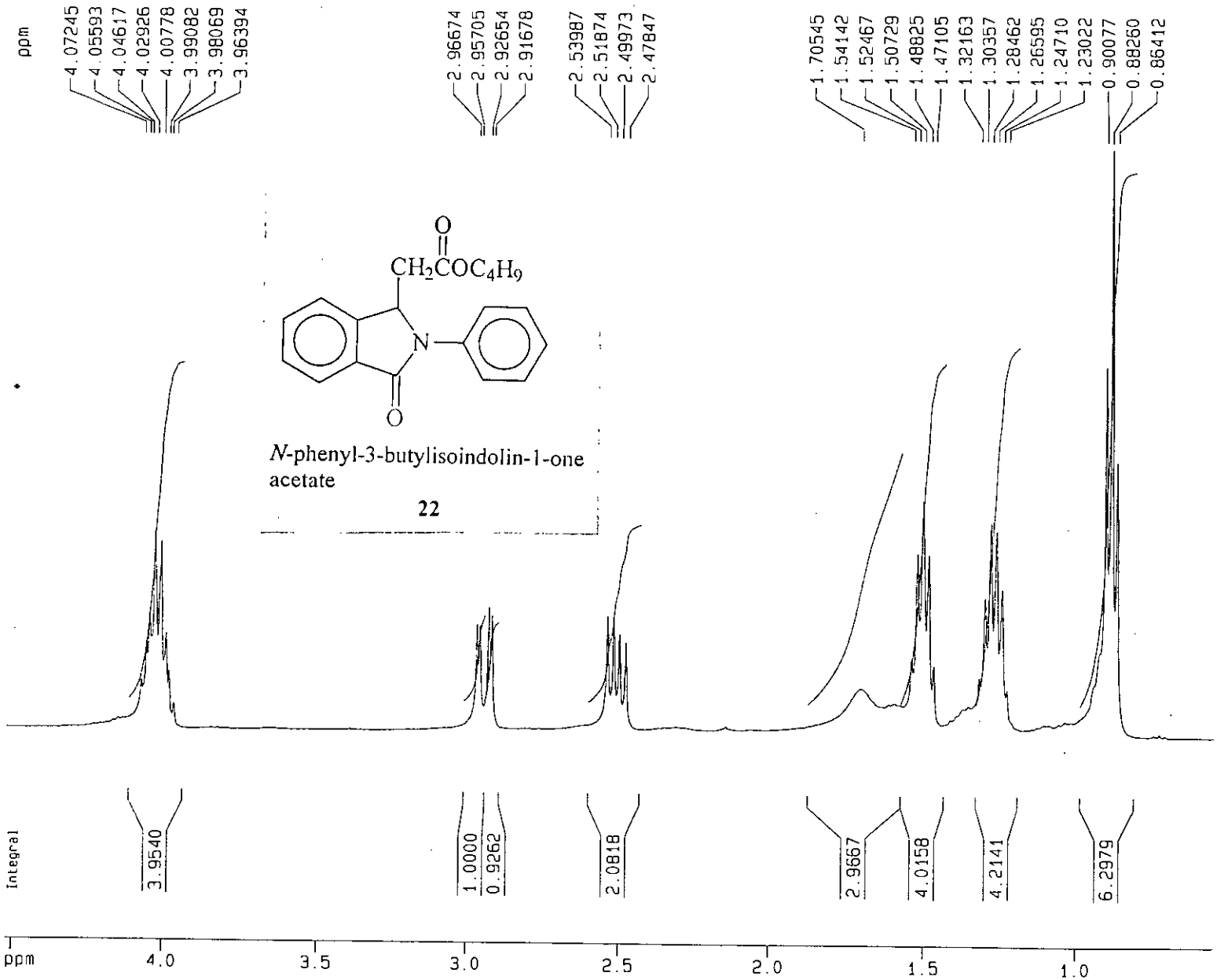

N-phenyl-3-butylisoindolin-1-one acetate

22

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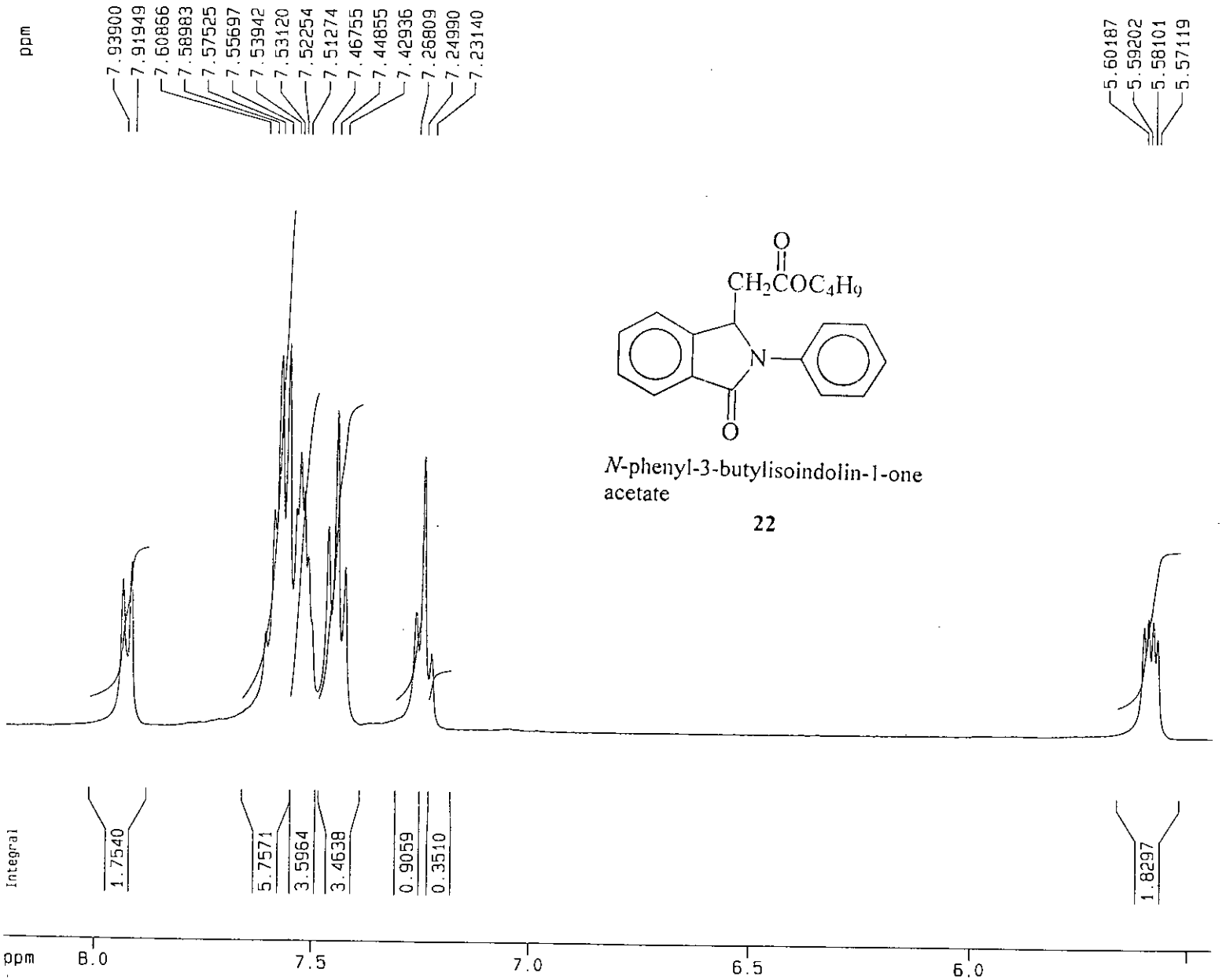


N-phenyl-3-butylisoindolin-1-one acetate

22

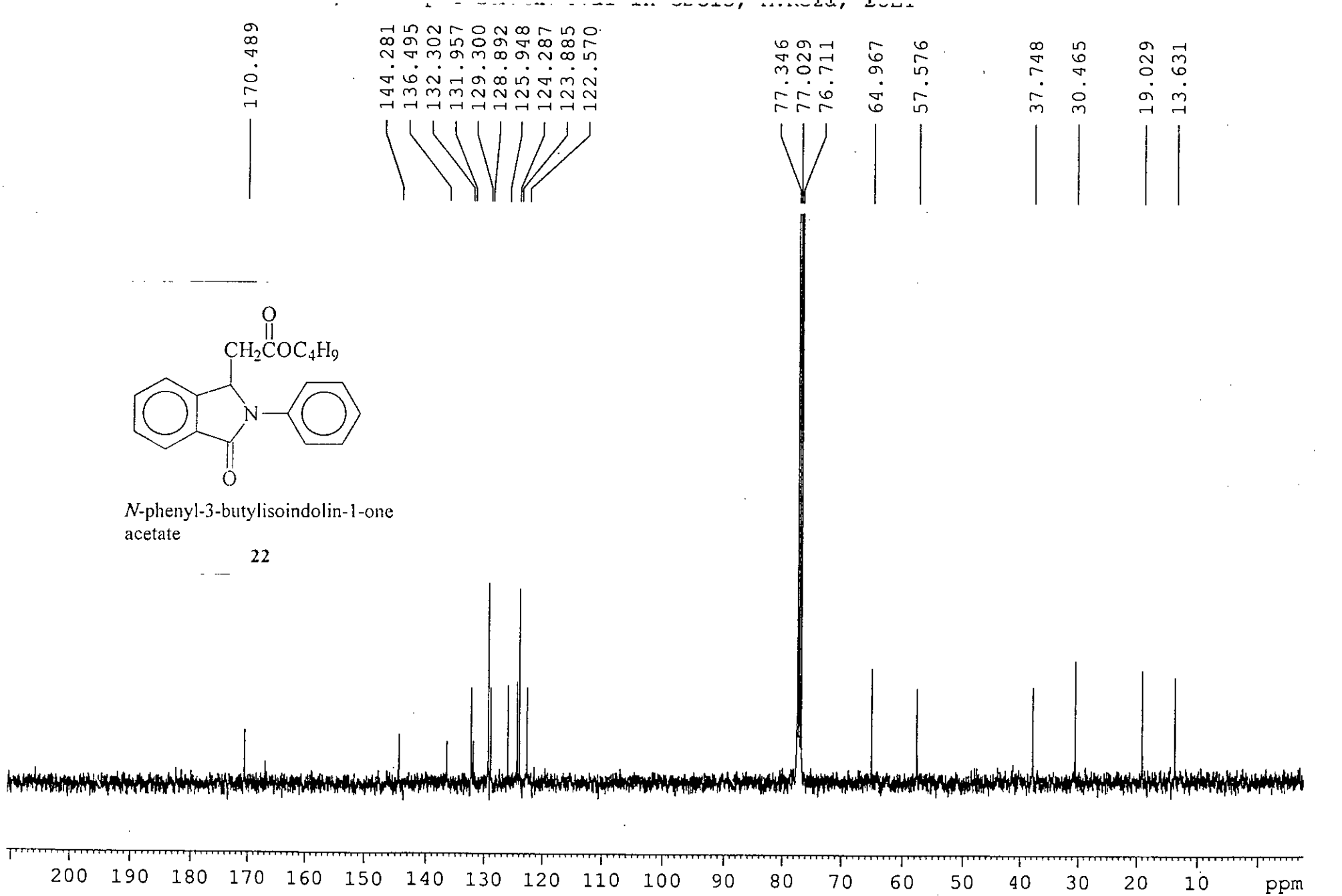
```
Current Data Parameters
NAME                  A1474
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20040626
Time                 14.16
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPRDG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     128
DS                       2
SWH             6410.256 Hz
FIDRES          0.195625 Hz
AQ              2.5559540 sec
RG                     181
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

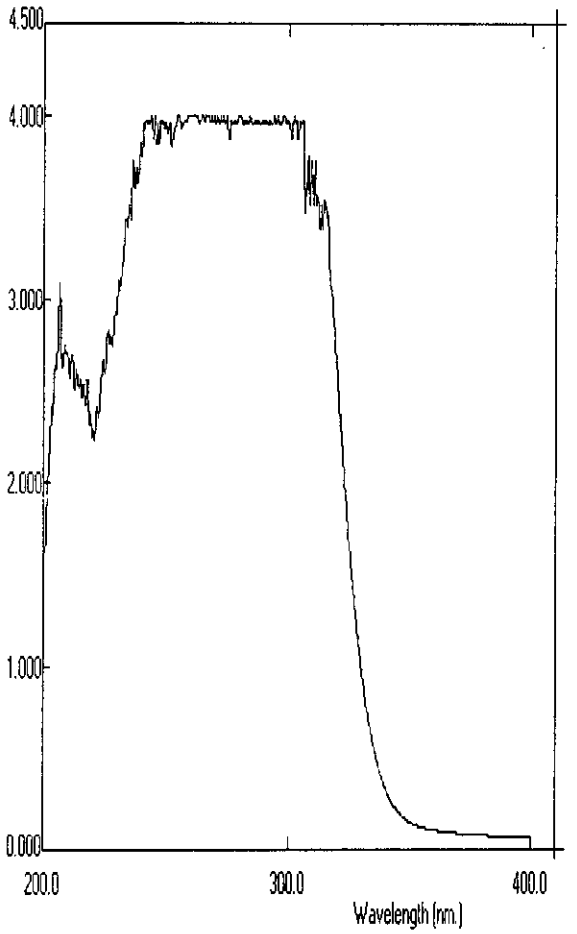
F2 - Processing parameters
SI                  32768
SF            400.1400123 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                20.00 cm
F1P               8.204 ppm
F1              3282.77 Hz
F2P               5.444 ppm
F2              2178.32 Hz
PPMCM          0.13801 ppm/cm
HZCM          55.22268 Hz/cm
```



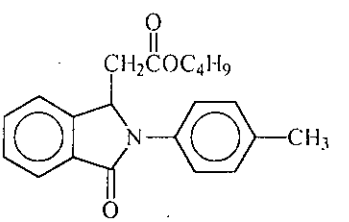
N-phenyl-3-butylisoindolin-1-one acetate

22



Peak Pick

No.	Wavelength (nm.)	Abs.
1	243.60	3.9999
2	208.40	2.7372



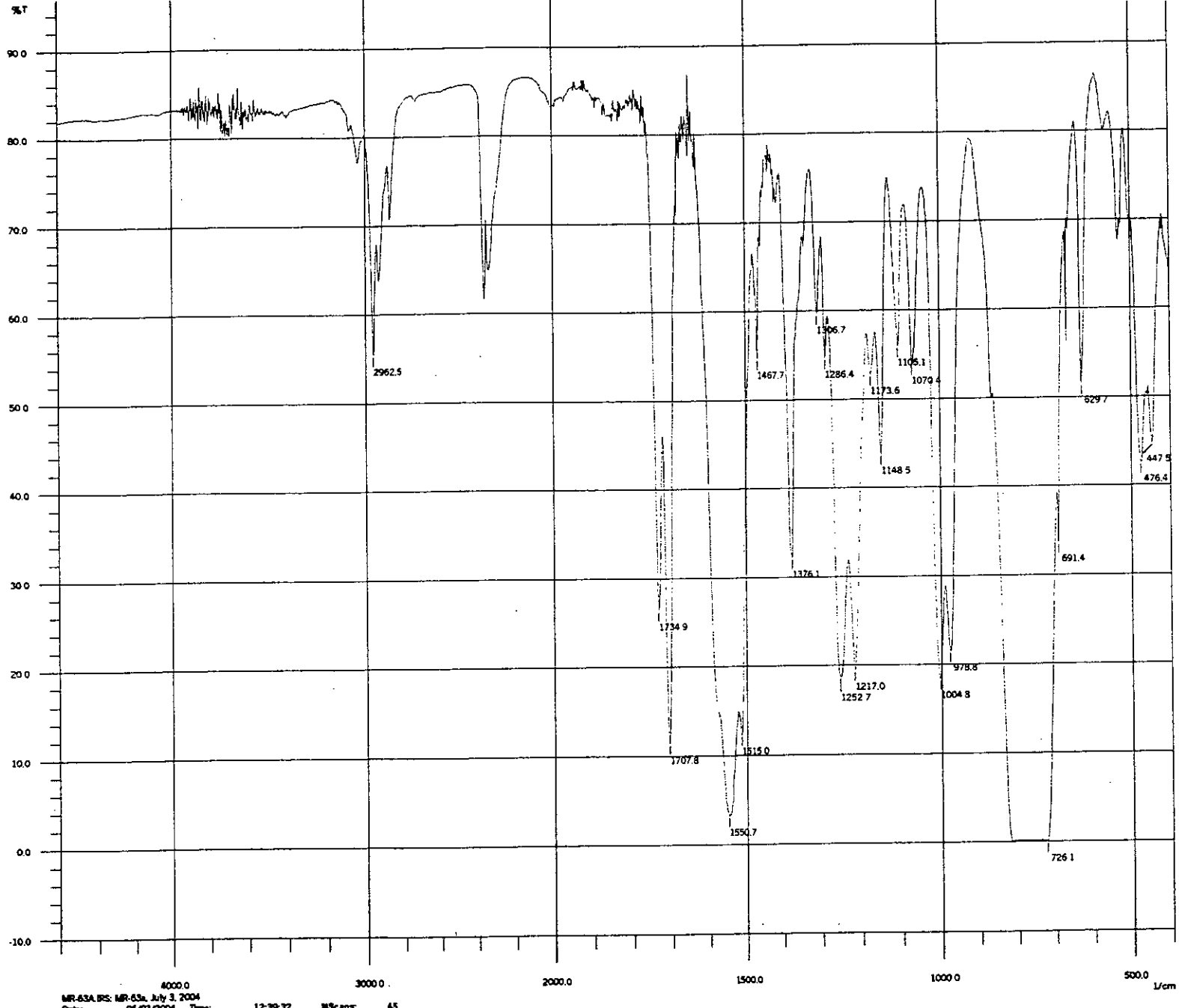
N-p-methylphenyl-3-butylisoindolin-1-one acetate

23

File Name: MR63A1

Created: 11:57 08/09/04
Data: Original

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

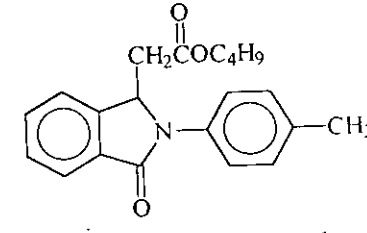


MR-63A.IRS: MR-63a, July 3, 2004

Data:	06/03/2004	Time:	12:39:32	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

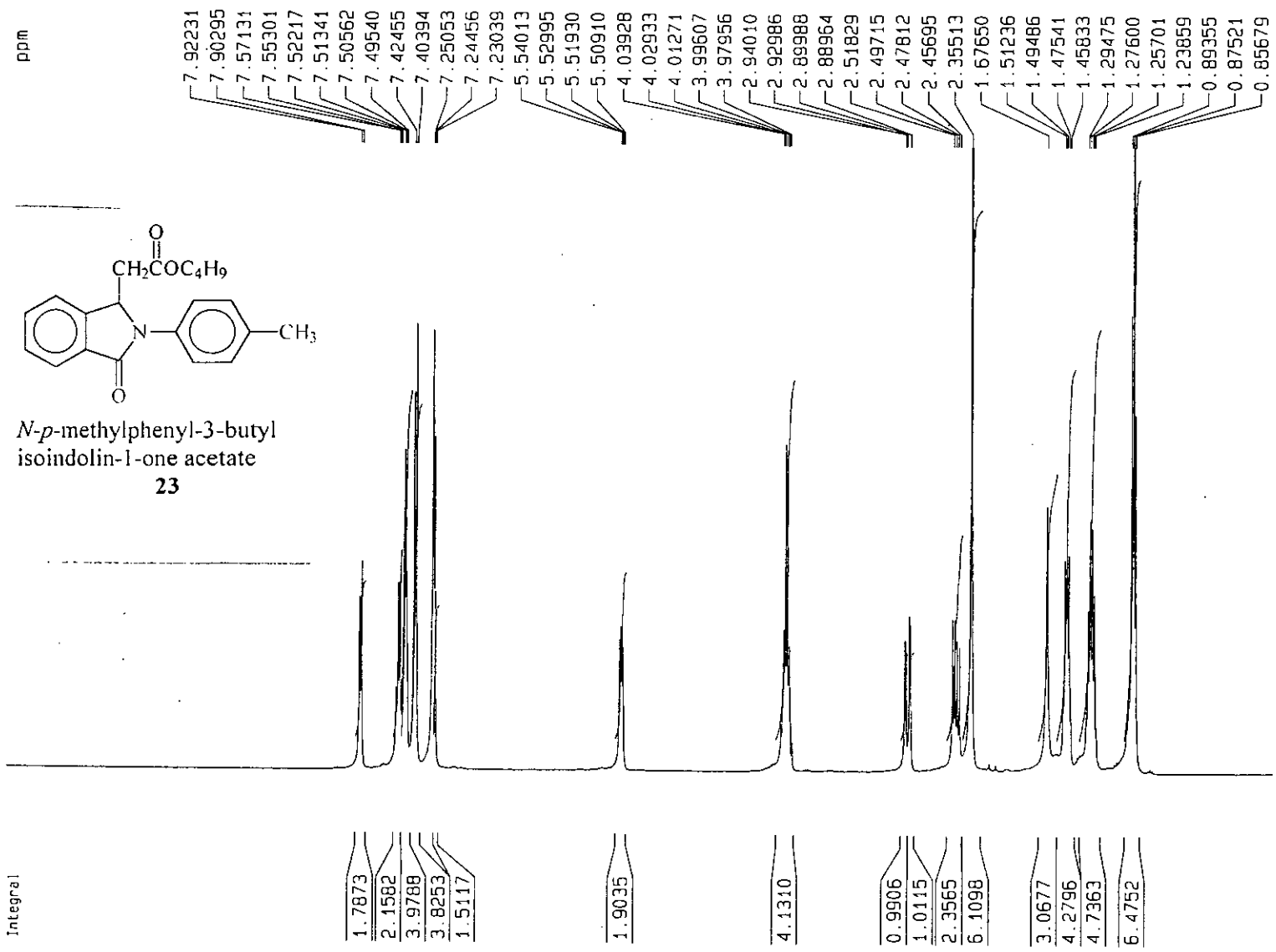
No.	Pos. (1/cm)	Inten. (%T)
1	447.5	44.732
2	476.4	42.574
3	629.7	51.493
4	691.4	33.667
5	726.1	0.030
6	978.8	21.536
7	1004.8	18.439
8	1070.4	53.945
9	1105.1	55.958
10	1148.5	43.762
11	1173.6	52.807
12	1217.0	19.495
13	1252.7	18.712
14	1286.4	54.689
15	1306.7	59.684
16	1376.1	32.220
17	1467.7	54.691
18	1515.0	12.384
19	1550.7	3.264
20	1707.8	11.400
21	1734.9	26.458
22	2962.5	55.426

MR-63a, July 3, 2004



N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23



N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23

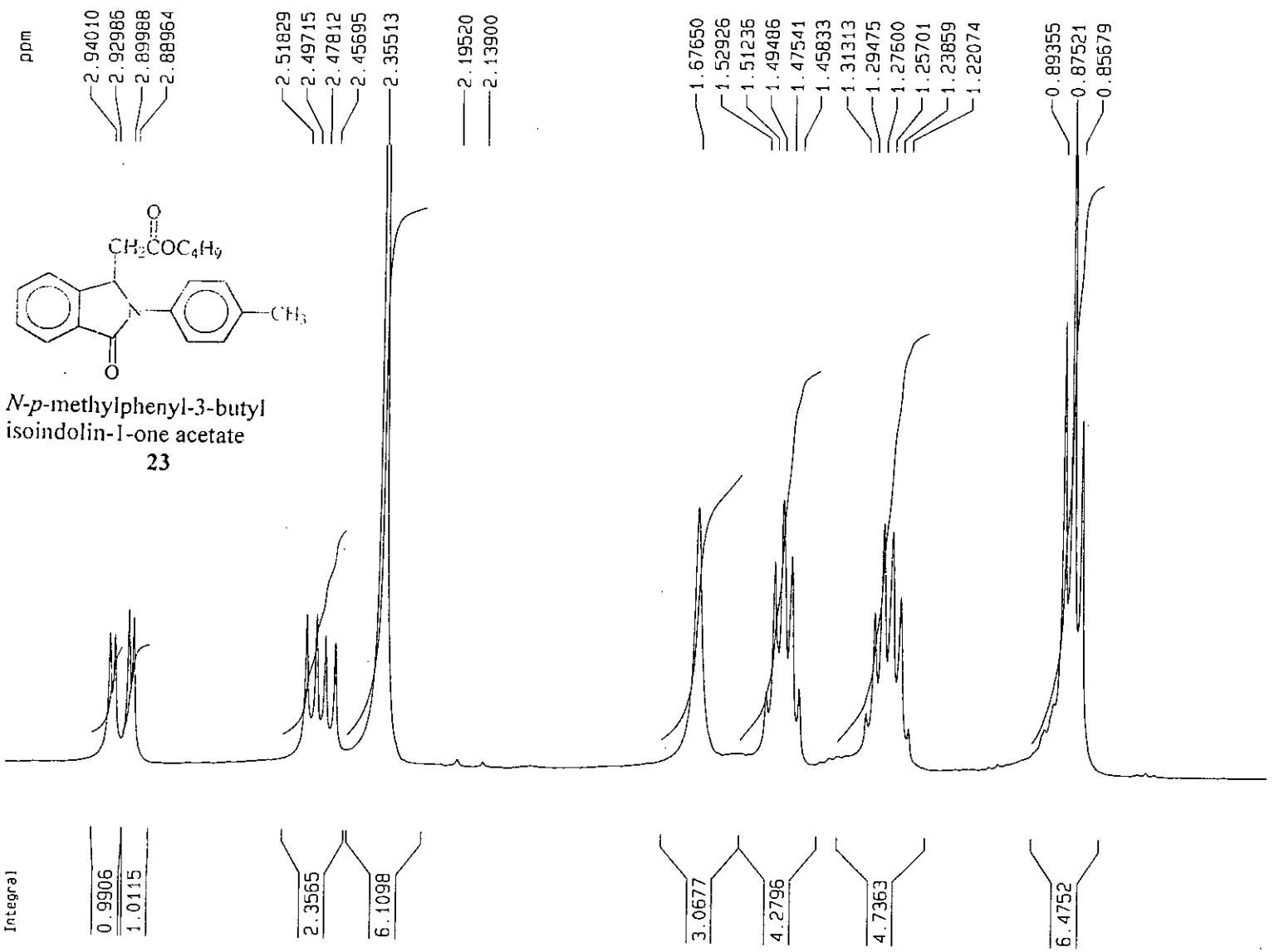
```
Current Data Parameters
NAME                  A1471
EXPNO                    1
PRDCNO                   1

F2 - Acquisition Parameters
Date_              20040626
Time                 13.37
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             Aceton
NS                     128
DS                       2
SWH              6410.256 Hz
FIDRES           0.195625 Hz
AQ               2.5559540 sec
RG                     181
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF            400.1400150 MHz
WDW                    EM
SSB                     0
LB                0.30 Hz
GB                      0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
F1P               11.120 ppm
F1              4449.41 Hz
F2P               -0.372 ppm
F2              -148.66 Hz
PPMCM          0.57456 ppm/cm
HZCM          229.90372 Hz/cm
```



N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23

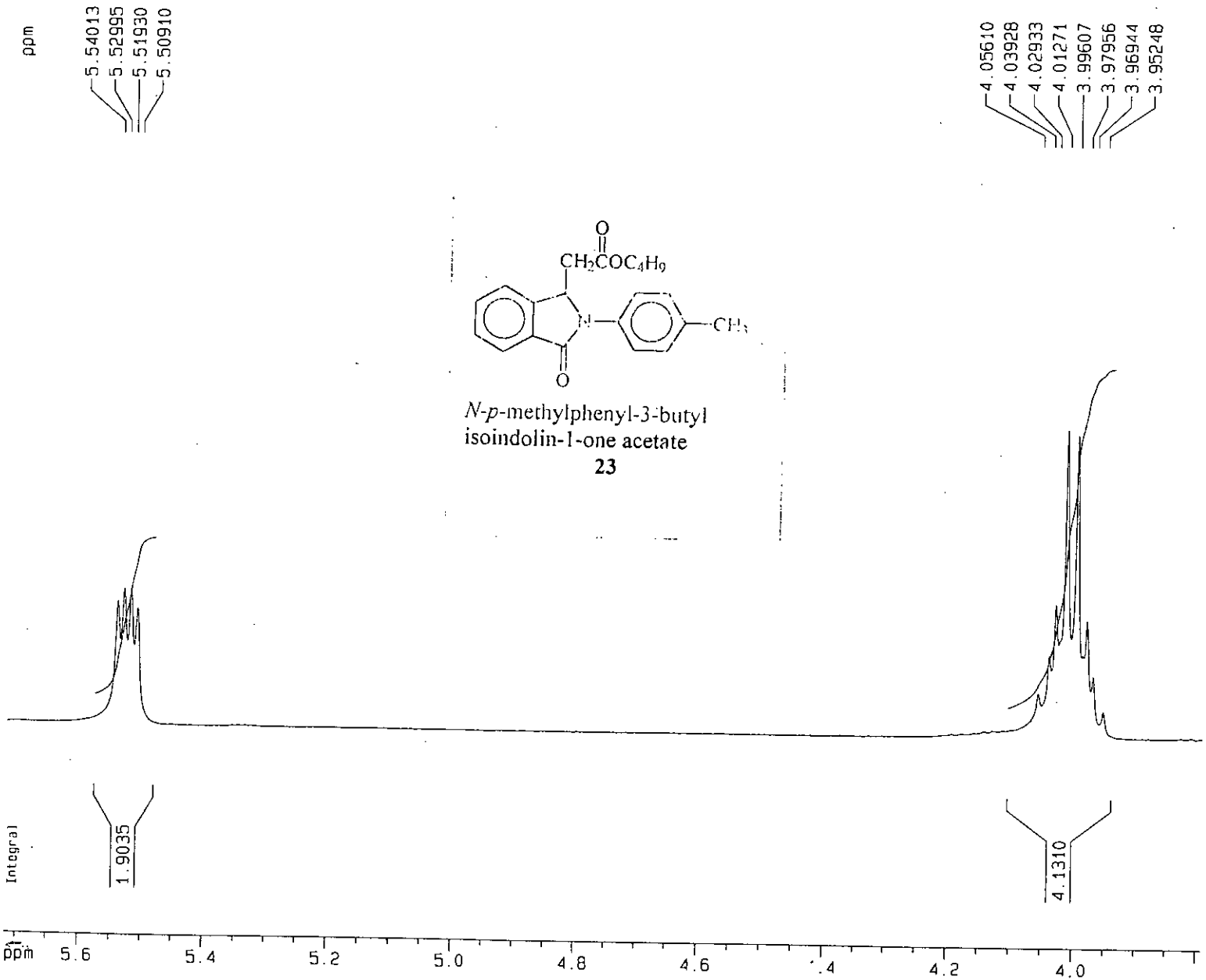
Current Data Parameters	
NAME	A1471
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters	
Date_	20040626
Time	13.37
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	181
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

F2 - Processing parameters	
SI	32768
SF	400.1400150 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters	
CX	20.00 cm
F1P	3.160 ppm
F1	1264.57 Hz
F2P	0.457 ppm
F2	182.67 Hz
PPMCM	0.13519 ppm/cm
HZCM	54.09499 Hz/cm



N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23

Current Data Parameters

NAME	A1471
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040626
Time	13.37
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	181
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

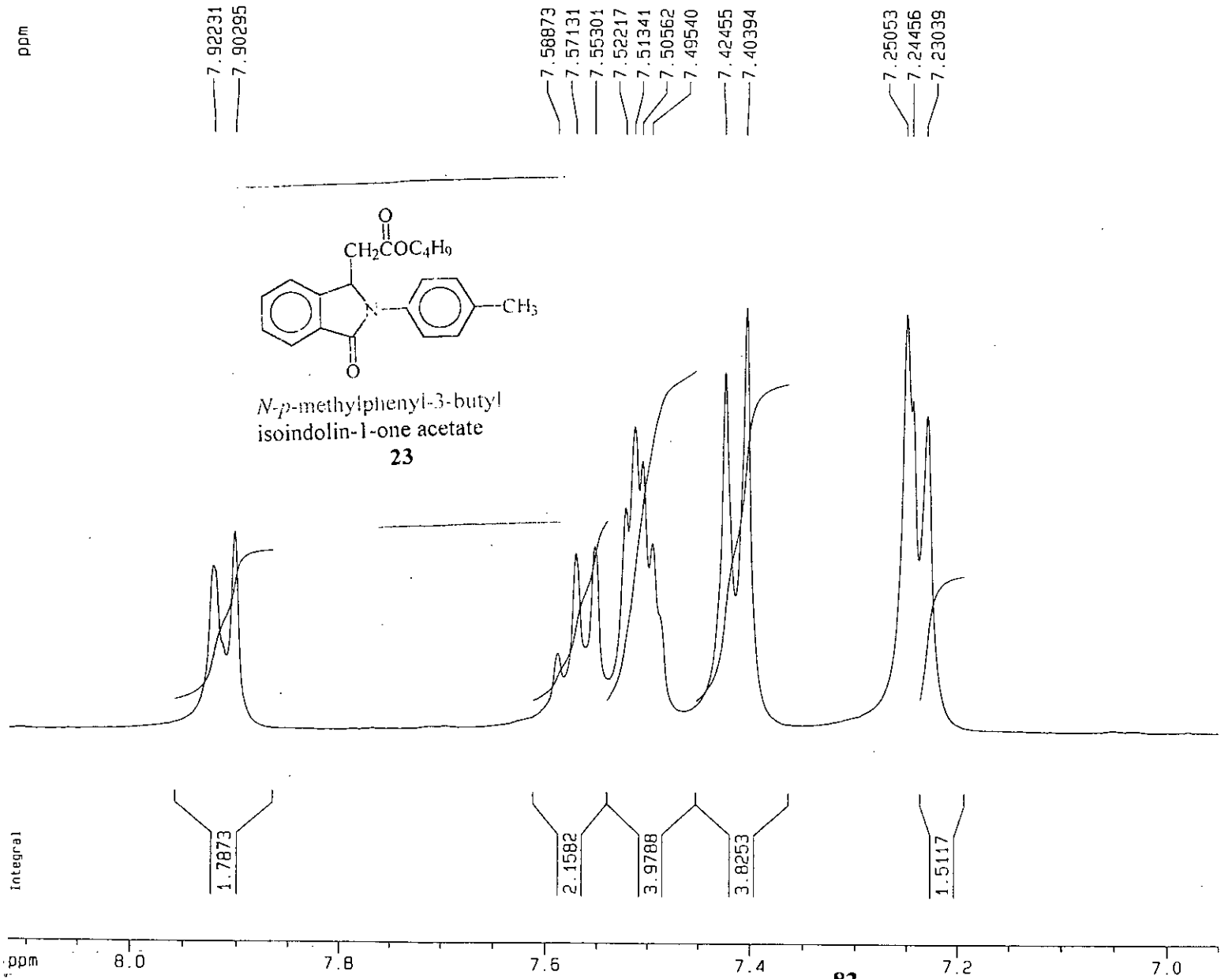
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400150 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	5.717 ppm
F1	2287.46 Hz
F2P	3.791 ppm
F2	1516.84 Hz
PPMCM	0.09629 ppm/cm
HZCM	38.53127 Hz/cm



N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23

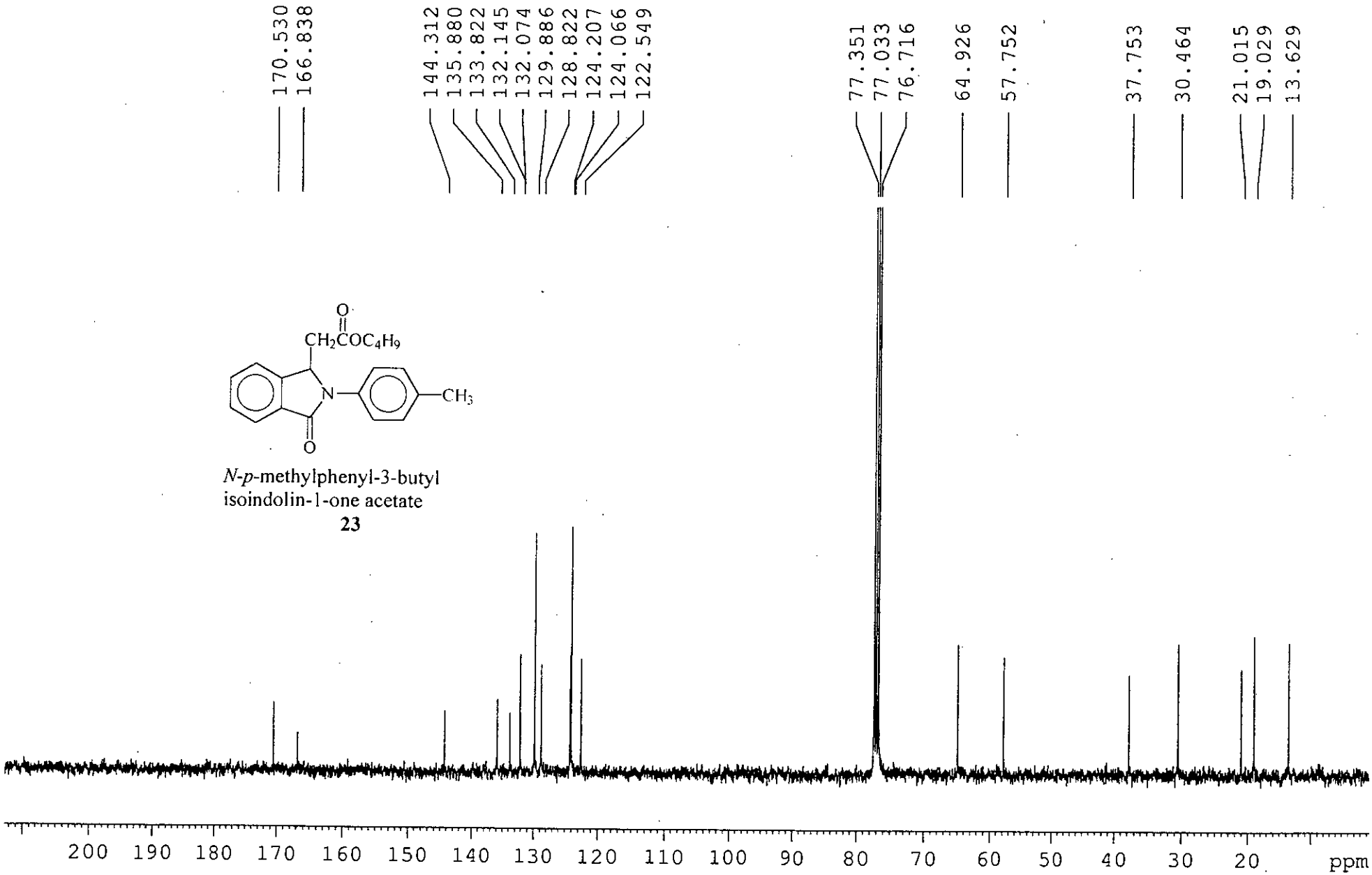
```
Current Data Parameters
NAME                  A1471
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20040626
Time                 13.37
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             Aceton
NS                     128
DS                       2
SWH              6410.256 Hz
FIDRES           0.195625 Hz
AQ               2.5559540 sec
RG                    1B1
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

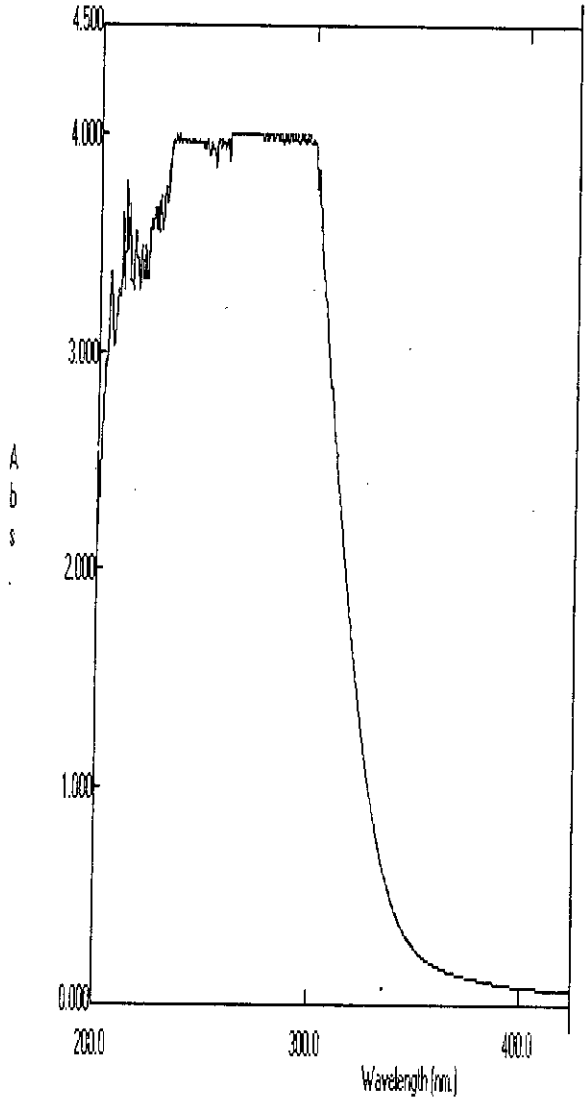
F2 - Processing parameters
SI                   32768
SF            400.1400150 MHz
WDW                    EM
SSB                     0
LB                0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                20.00 cm
F1P                8.118 ppm
F1              3248.31 Hz
F2P                .6.950 ppm
F2              2780.82 Hz
PPMCM          0.05841 ppm/cm
HZCM          23.37411 Hz/cm
```



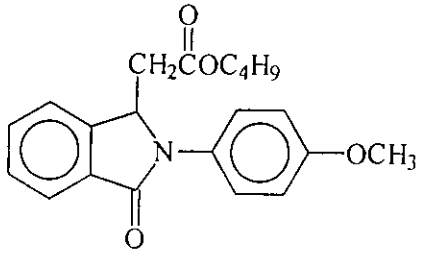
N-p-methylphenyl-3-butyl isoindolin-1-one acetate

23



Peak Pick

No.	Wavelength (nm.)	Abs.
1	234.60	3.9999



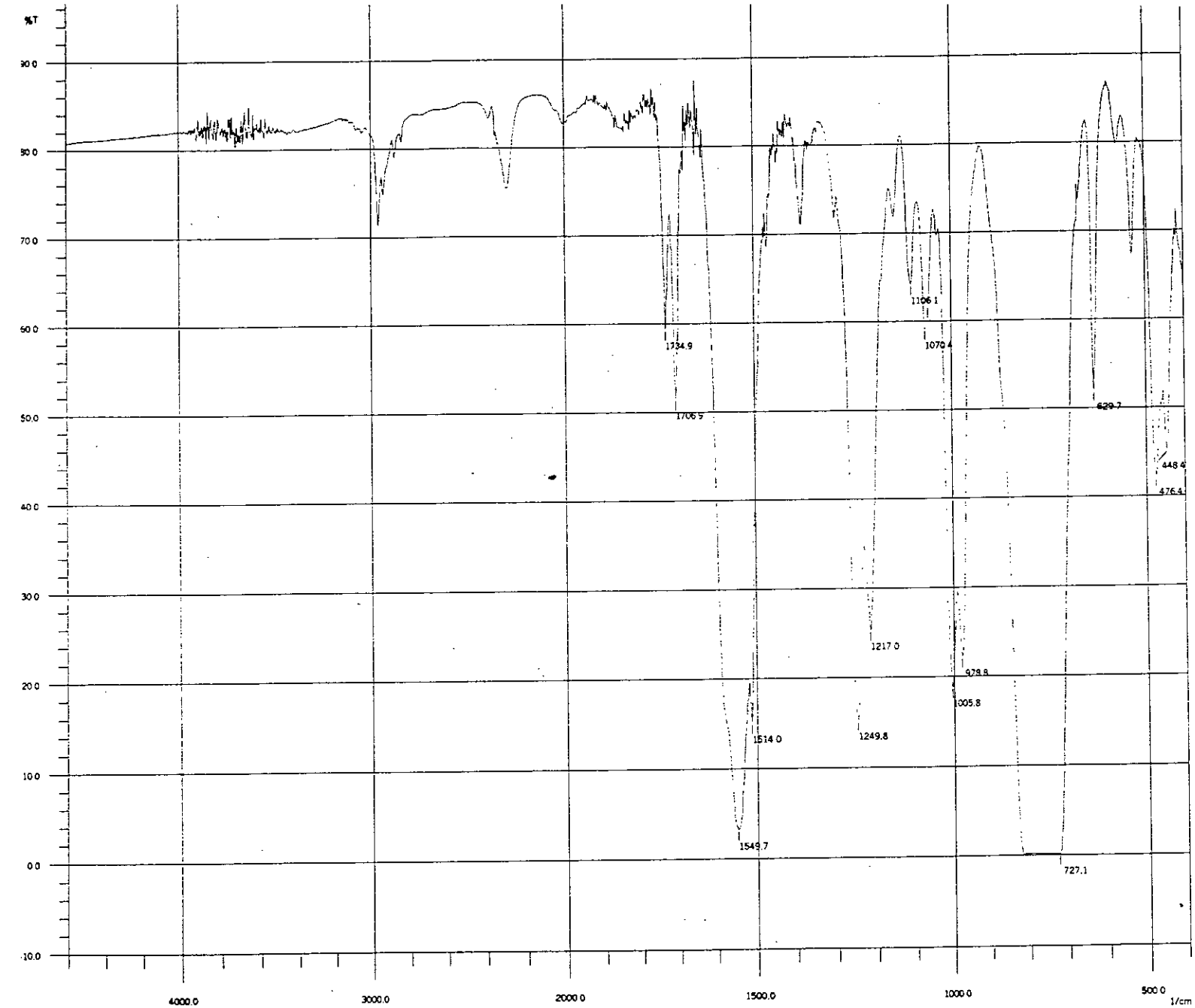
N-p-methoxyphenyl-3-butylisoindolin-1-one acetate

24

File Name: MR64A1

Created: 10:33 08/10/04
Data: Original

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

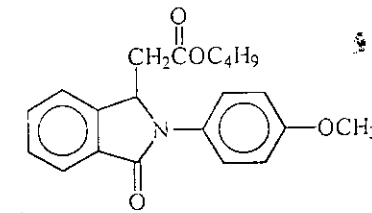


MR-64A.IRS: MR-64a, July 3, 2004

Data:	06/03/2004	Time:	12:27:11	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(cm)

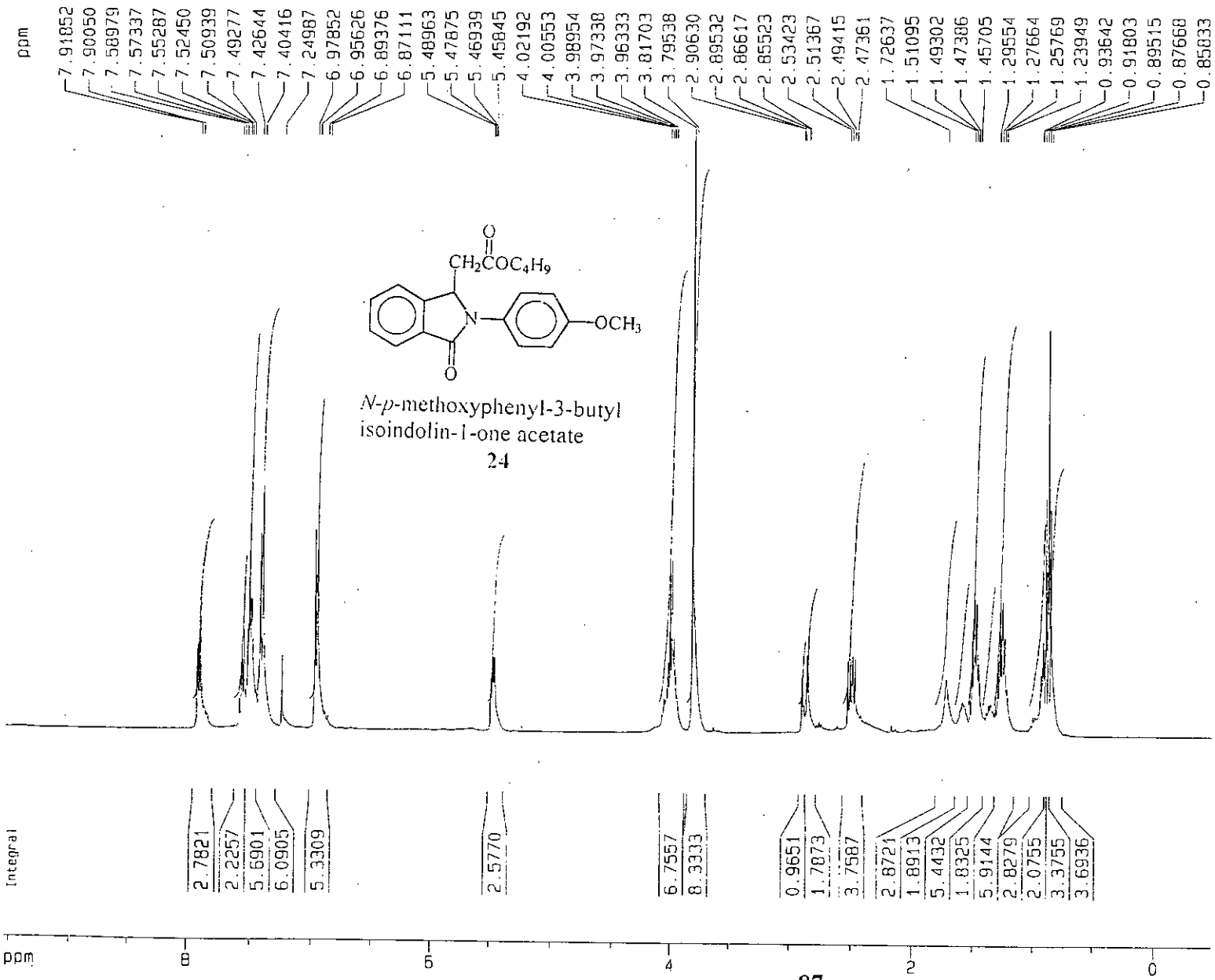
No.	Pos. (1/cm)	Inten. (%T)
1	448.4	45.195
2	476.4	42.302
3	629.7	51.974
4	727.1	0.138
5	978.8	22.227
6	1005.8	18.912
7	1070.4	59.170
8	1106.1	64.233
9	1217.0	25.348
10	1249.8	15.306
11	1514.0	15.101
12	1549.7	3.252
13	1706.9	51.519
14	1734.9	59.377

MR-64a, July 3, 2004



N-*p*-methoxyphenyl-3-butyl isoindolin-1-one acetate

24



N-p-methoxyphenyl-3-butyl isoindolin-1-one acetate

24

Current Data Parameters

NAME	A1440
EXPNO	1
PRDCNO	1

F2 - Acquisition Parameters

Date_	20040610
Time	11.04
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	93
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

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

F2 - Processing parameters

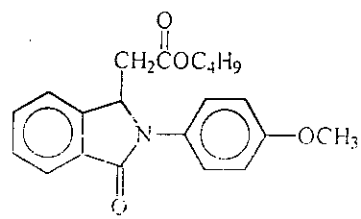
SI	32768
SF	400.1400128 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	9.537 ppm
F1	3815.95 Hz
F2P	-0.468 ppm
F2	-187.08 Hz
PPMCM	0.50020 ppm/cm
HZCM	200.15146 Hz/cm

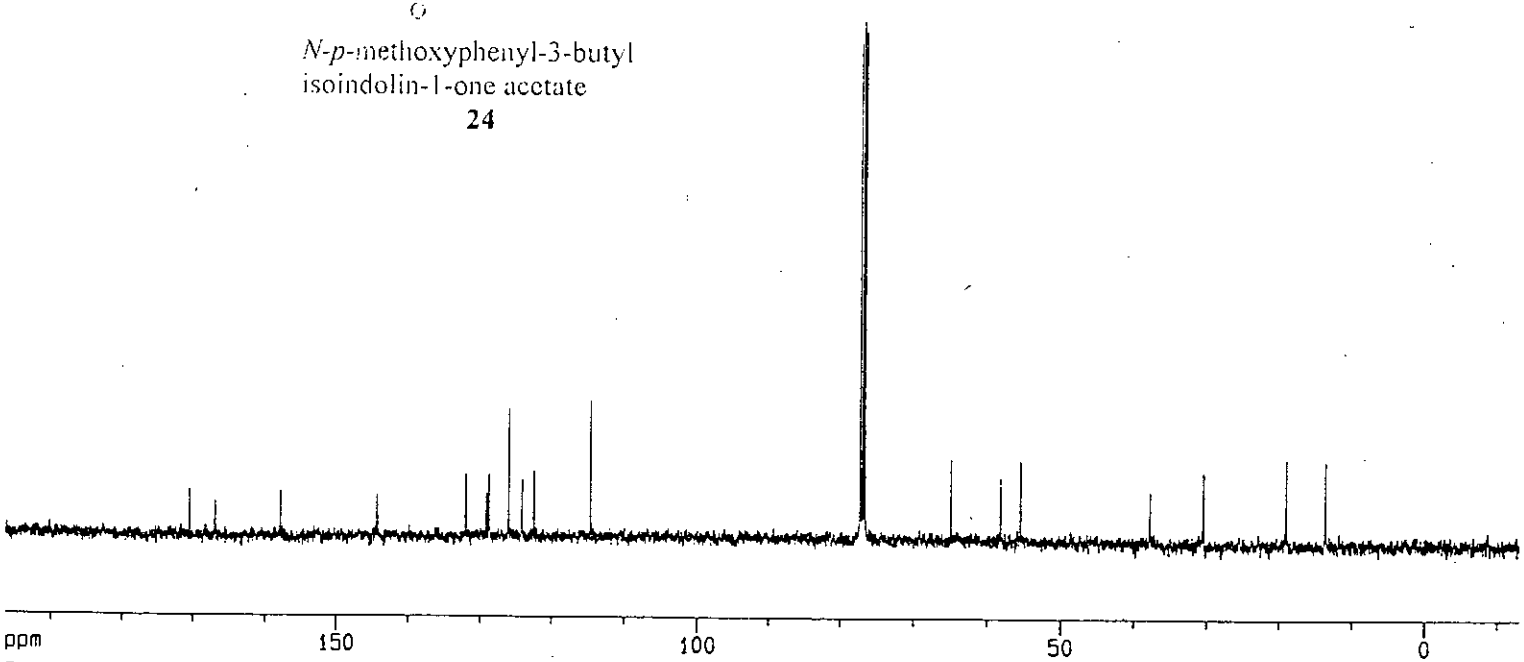
Analytical, BCSIR Lab. Dhaka 13C Spectrum MR-64a1 in CDCL3, Masud, BUET

ppm
190.280
170.486
166.939
157.897
144.270
132.075
132.021
129.179
128.808
126.053
124.159
122.526
114.578
77.350
77.032
76.714
64.921
58.170
55.497
37.787
30.445
19.015
13.618



N-p-methoxyphenyl-3-butyl isoindolin-1-one acetate

24




```
Current Data Parameters
NAME                  A1440
EXPNO                     3
PROCNO                    1

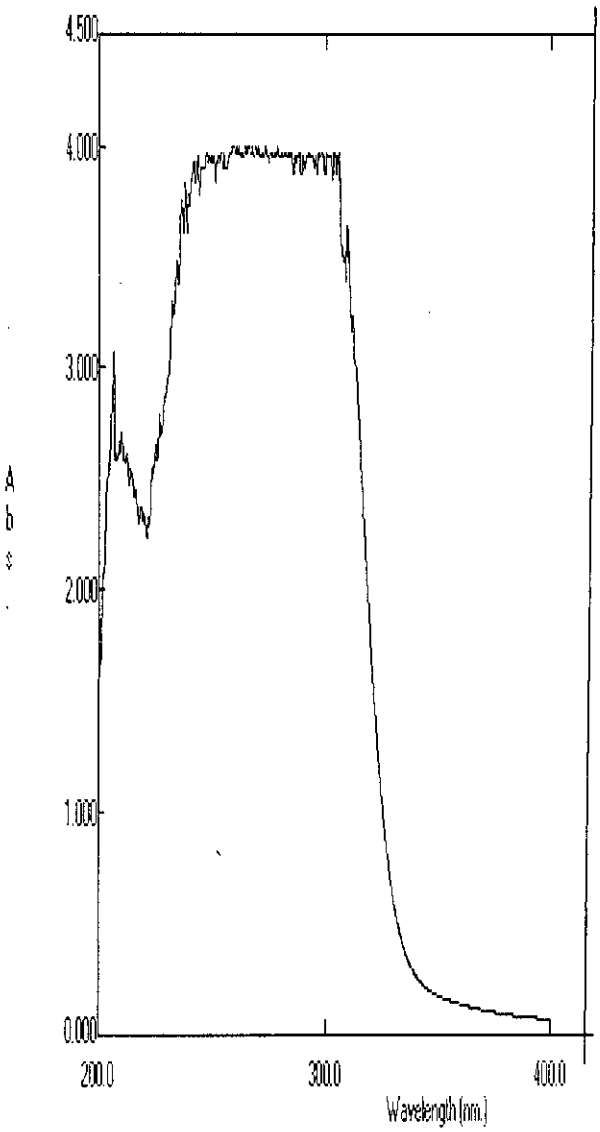
F2 - Acquisition Parameters
Date_              20040626
Time                  14.43
INSTRUM               dpx400
PROBHD     5 mm Multinuc
PULPROG               zgpg30
TD                     32768
SOLVENT                CDCl3
NS                       834
DS                         2
SWH               24154.590 Hz
FIDRES             0.737140 Hz
AQ                 0.5763476 sec
RG                     16384
DW                    20.700 usec
DE                     6.00 usec
TE                    300.0 K
D1                 1.50000000 sec
d11                0.03000000 sec
d12                0.00002000 sec

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

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

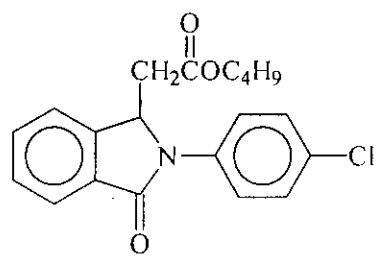
F2 - Processing parameters
SI                       32768
SF                100.6152637 MHz
WDW                         EM
SSB                          0
LB                        2.50 Hz
GB                           0
PC                        1.40

1D NMR plot parameters
CX                       20.00 cm
F1P                     196.585 ppm
F1                    19779.44 Hz
F2P                    -13.095 ppm
F2                    -1317.60 Hz
PPMCM                 10.48402 ppm/cm
HZCM                1054.85229 Hz/cm
```



Peak Pick

No.	Wavelength (nm.)	Abs.
1	258.20	3.9999
2	226.40	2.7820
3	209.60	2.7030



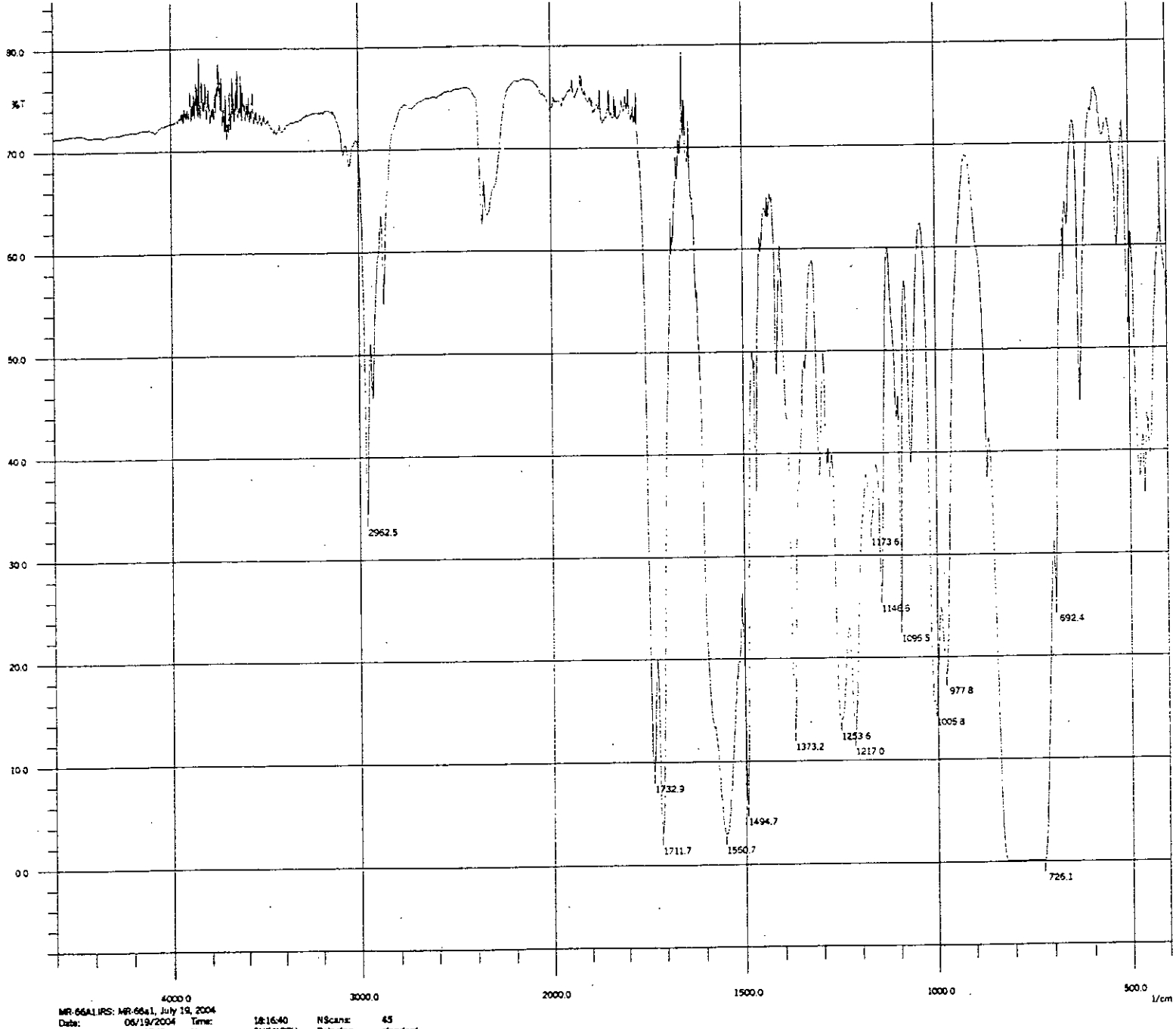
N-p-chlorophenyl-3-butylisoindolin-1-one acetate

25

File Name: MR66A1

Created: 12:00 08/09/04
Data: Original

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



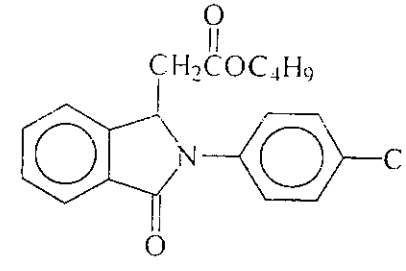
MR-66A1.IRS: MR-66a1, July 19, 2004

Data:	06/19/2004	Time:	18:16:40	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.964.34	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

Selected:

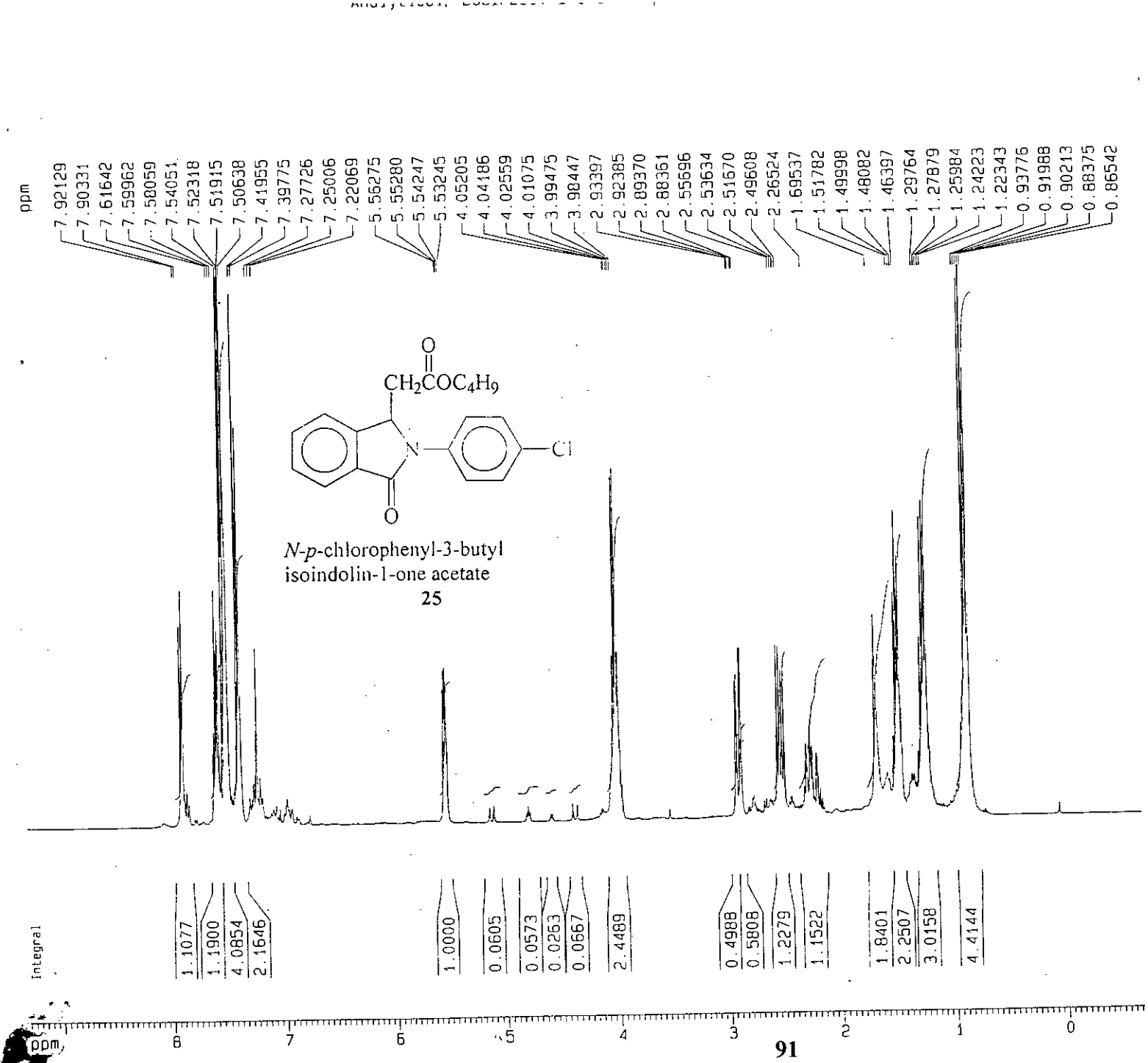
No.	Pos. (1/cm)	Inten. (%T)
1	692.4	25.225
2	726.1	0.063
3	977.8	18.312
4	1005.8	15.294
5	1095.5	23.443
6	1146.6	26.391
7	1173.6	32.869
8	1217.0	12.472
9	1253.6	13.978
10	1373.2	13.014
11	1494.7	5.787
12	1550.7	3.009
13	1711.7	3.028
14	1732.9	9.043
15	2962.5	34.326

MR-66a1, July 19, 2004



N-p-chlorophenyl-3-butyl isoindolin-1-one acetate

25



N-p-chlorophenyl-3-butyl isoindolin-1-one acetate

25

Current Data Parameters

NAME	A1473
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040626
Time	14.03
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	COCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	181
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

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

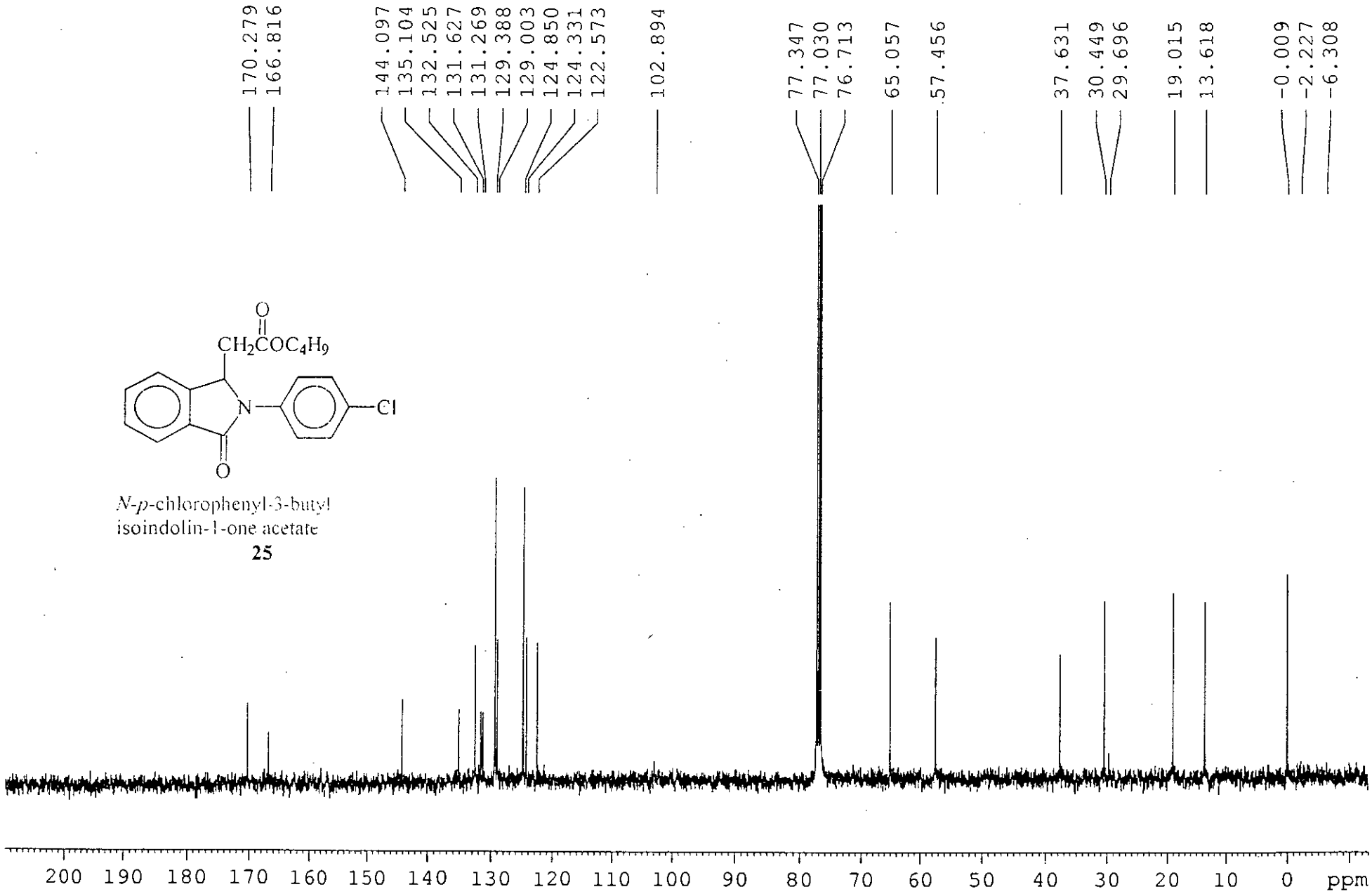
F2 - Processing parameters

SI	32768
SF	400.1400126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

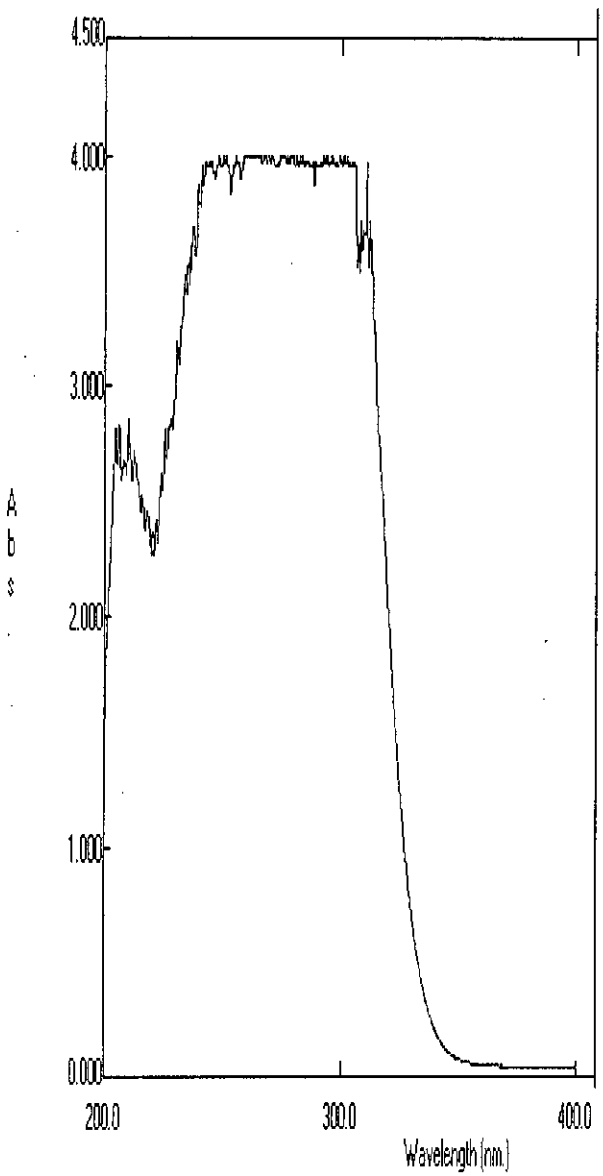
CX	20.00 cm
F1P	9.317 ppm
F1	3728.23 Hz
F2P	-0.670 ppm
F2	-268.03 Hz
PPMCM	0.49936 ppm/cm
HZCM	199.81339 Hz/cm

Analytical, BCSIR, A1473, 13C Spectrum MR-66a1 in CDCl3, M. Reza, BUET



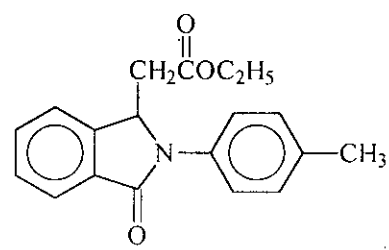
N-p-chlorophenyl-3-butyl isoindolin-1-one acetate

25



Peak Pick

No.	Wavelength (nm.)	Abs.
1	247.80	3.9999
2	210.00	2.8440



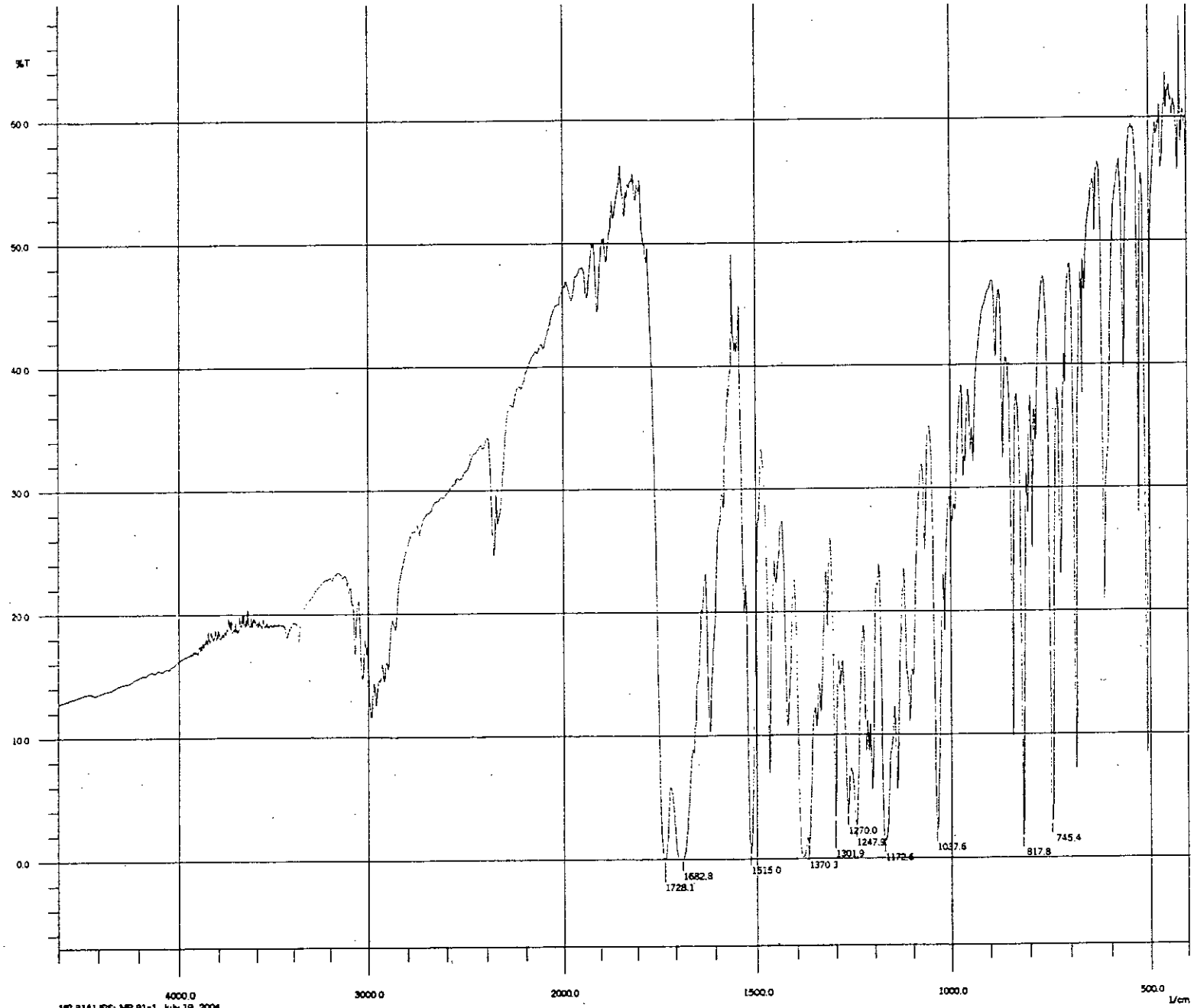
N-p-methylphenyl-3-ethylisoindolin-1-one acetate

26

File Name: MR81A1

Created: 11:00 08/09/04
Data: Original

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

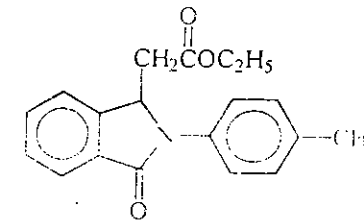


MR-81A1.IRS: MR-81a1, July 19, 2004

Date:	06/19/2004	Time:	18:53:38	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

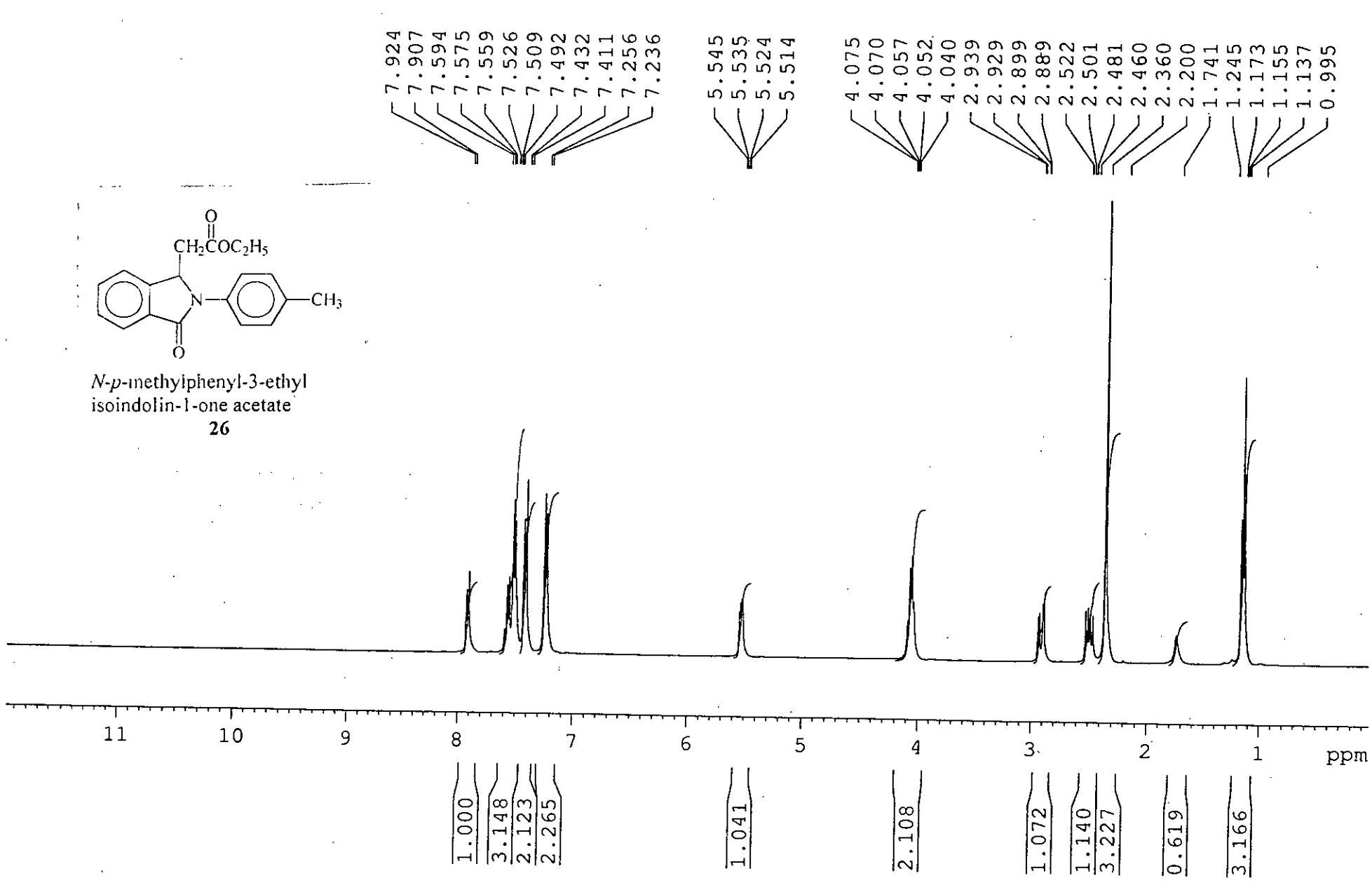
No.	Pos. (1/cm)	Inten. (%T)
1	745.4	2.8836
2	817.8	1.7898
3	1037.6	2.2430
4	1172.6	1.4367
5	1247.9	2.6505
6	1270.0	3.5695
7	1301.9	3.2191
8	1370.3	1.2336
9	1515.0	0.4552
10	1682.8	0.0187
11	1728.1	0.0906

MR-81a1, July 19, 2004



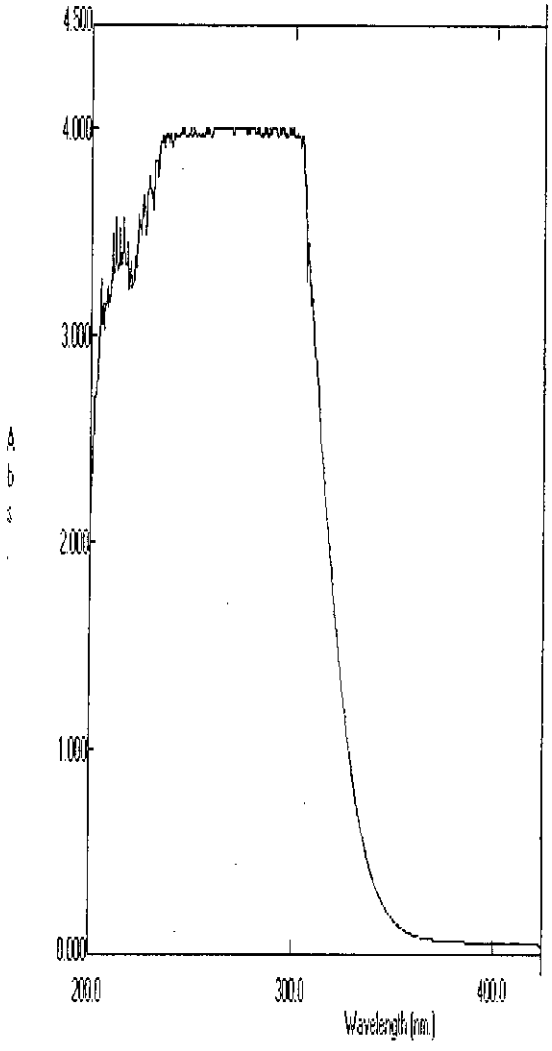
N-p-methylphenyl-3-ethyl isoindolin-1-one acetate

26



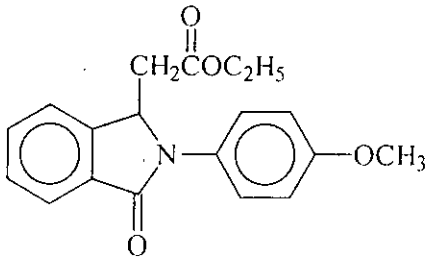
N-p-methylphenyl-3-ethyl isoindolin-1-one acetate

26



Peak Pick

No.	Wavelength (nm.)	Abs.
1	243.80	3.9999



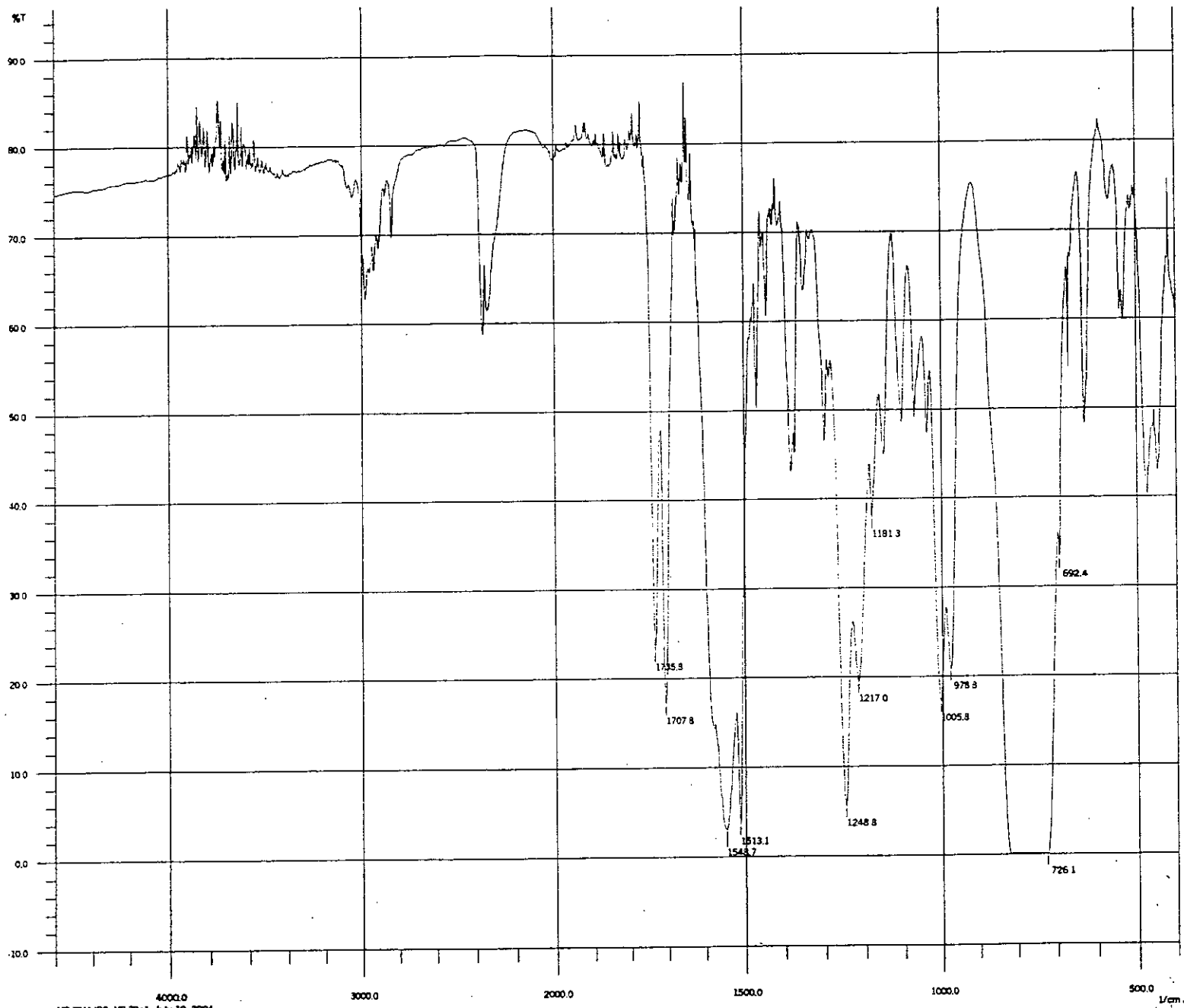
N-p-methoxyphenyl-3-ethylisoindolin-1-one acetate

27

File Name: MR79A1

Created: 10:36 08/10/04
Data: Original

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

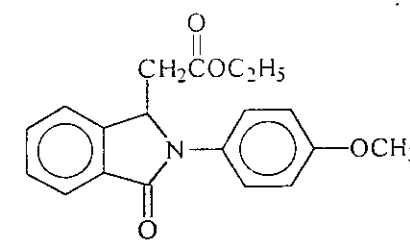


MR-79A1.IRS: MR-79a1, July 19, 2004

Date:	06/19/2004	Time:	18:38:25	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.964434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

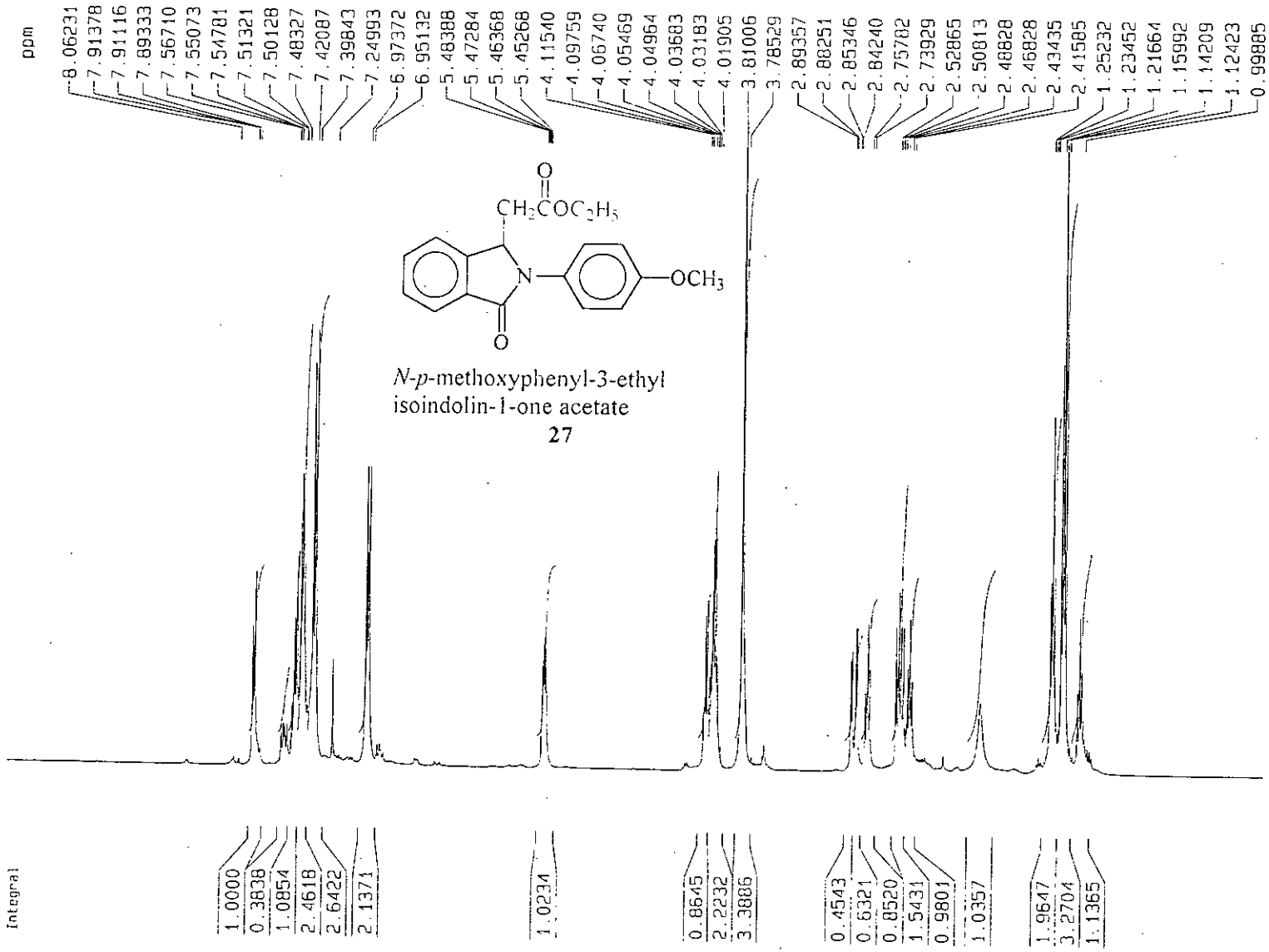
No.	Pos. (1/cm)	Inten. (%T)
1	692.4	33.234
2	726.1	0.026
3	978.8	20.826
4	1005.8	17.294
5	1181.3	37.905
6	1217.0	19.497
7	1248.8	5.553
8	1513.1	3.633
9	1548.7	3.080
10	1707.8	17.147
11	1735.8	23.183

MR-79a1, July 19, 2004



N-p-methoxyphenyl-3-ethyl isoindolin-1-one acetate

27



N-p-methoxyphenyl-3-ethyl isoindolin-1-one acetate

27

```
Current Data Parameters
NAME                  A1516
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20040714
Time                 12.04
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                    90.5
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

========== CHANNEL f1 ============
NUC1                  1H
P1                 8.30 usec
PL1               -6.00 dB
SFO1         400.1428077 MHz

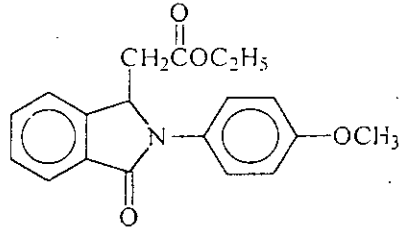
F2 - Processing parameters
SI                  32768
SF           400.1400124 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                20.00 cm
F1P               9.977 ppm
F1              3992.23 Hz
F2P              -0.517 ppm
F2             -206.90 Hz
PPMCM          0.52471 ppm/cm
HZCM         209.95618 Hz/cm
```

Analytical, BCSIR, 13C Spectrum MR-79a1 in CDCl3, M. Reza, BUET

ppm

170.345
166.920
157.893
144.236
132.058
129.184
128.797
128.541
126.062
124.127
122.538
114.564
77.351
77.033
76.715
60.968
60.305
58.164
55.495
48.697
37.795
32.715
14.199
14.020
11.969



N-p-methoxyphenyl-3-ethyl isoindolin-1-one acetate

27

Current Data Parameters

NAME	A1516
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20040812
Time	12.55
INSTRUM	cpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	Aceton
NS	354
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
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	9.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

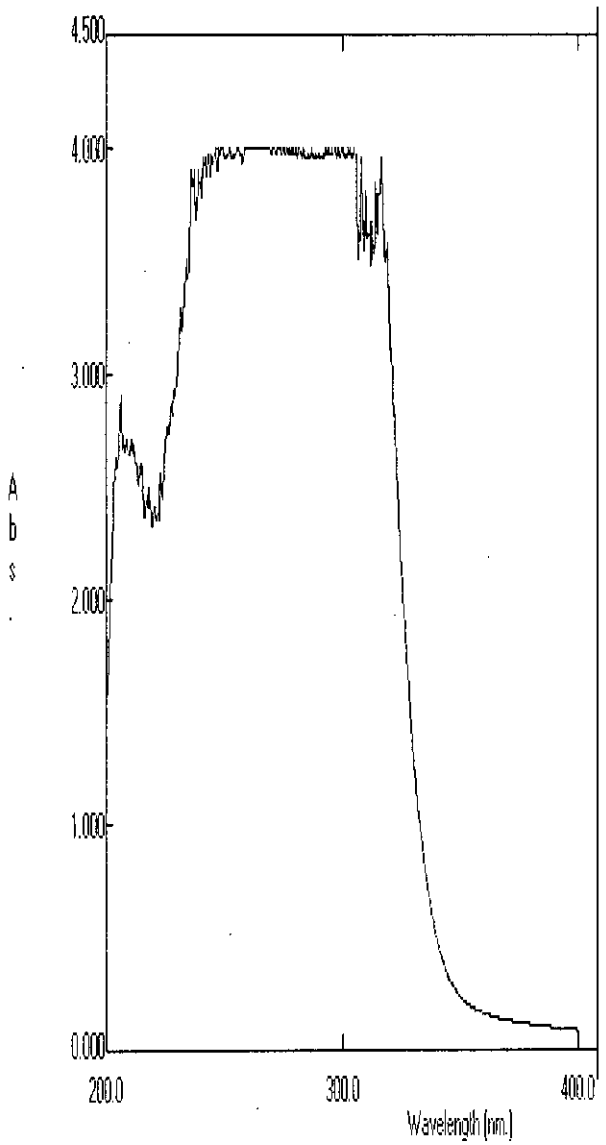
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

F2 - Processing parameters

SI	32768
SF	100.6152845 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

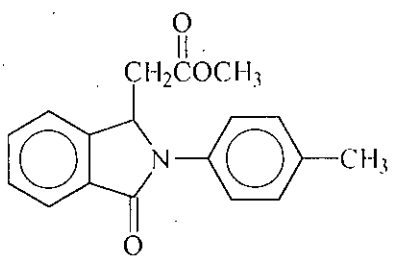
1D NMR plot parameters

CX	20.00 cm
F1P	200.123 ppm
F1	20135.42 Hz
F2P	-3.733 ppm
F2	-375.50 Hz
PPMCM	10.19279 ppm/cm
HZCM	1025.55090 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
1	245.80	3.9999
2	206.20	2.8962



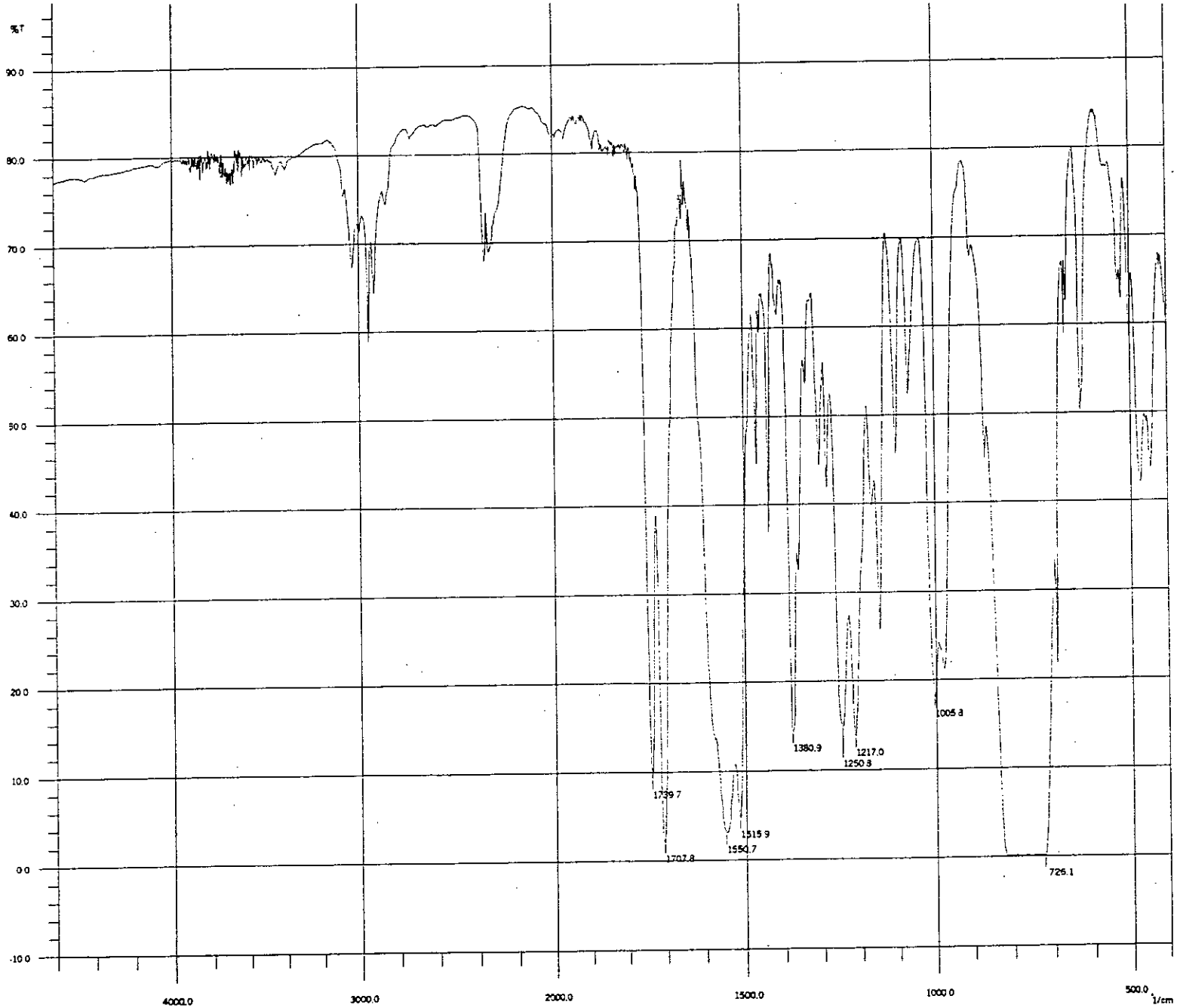
N-p-methylphenyl-3-methylisoindolin-1-one acetate

28

File Name: MR82A1

Created: 10:55 08/09/04
Data: Original

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

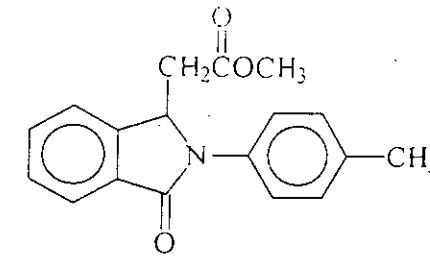


MR-82A1.IRS: MR-82a1, July 20, 2004

Data:	06/20/2004	Time:	18:33:02	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.80(sw)

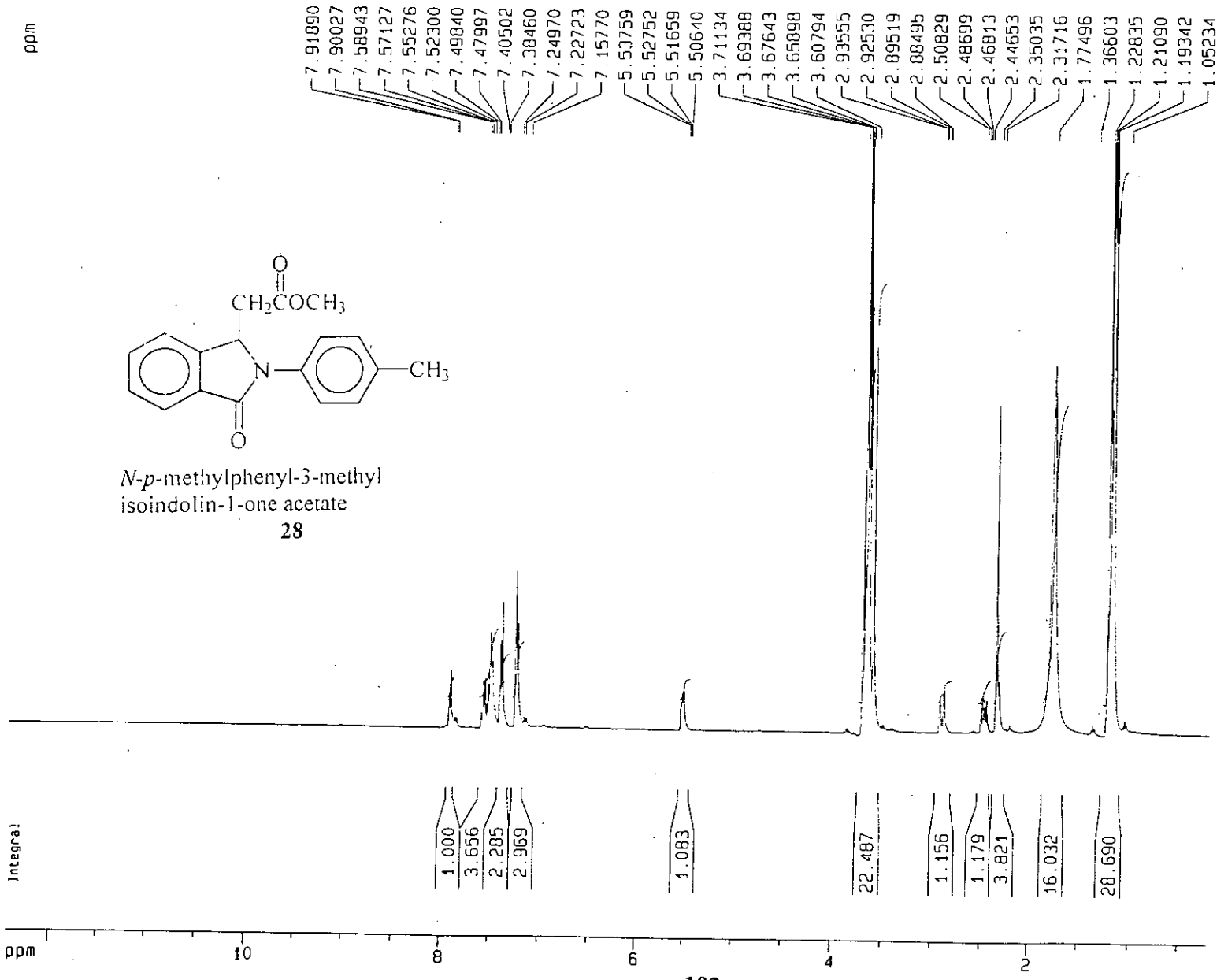
No.	Pos. (1/cm)	Inten. (%T)
1	726.1	0.042
2	1005.8	18.065
3	1217.0	13.808
4	1250.8	14.892
5	1380.9	14.345
6	1515.9	4.785
7	1550.7	3.115
8	1707.8	2.120
9	1739.7	9.340

MR-82a1, July 20, 2004



N-p-methylphenyl-3-methyl isoindolin-1-one acetate

28



CH_2COCH_3

CH_3

N-p-methylphenyl-3-methyl isoindolin-1-one acetate

28

Current Data Parameters

NAME	A1563
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040812
Time	11.42
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	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

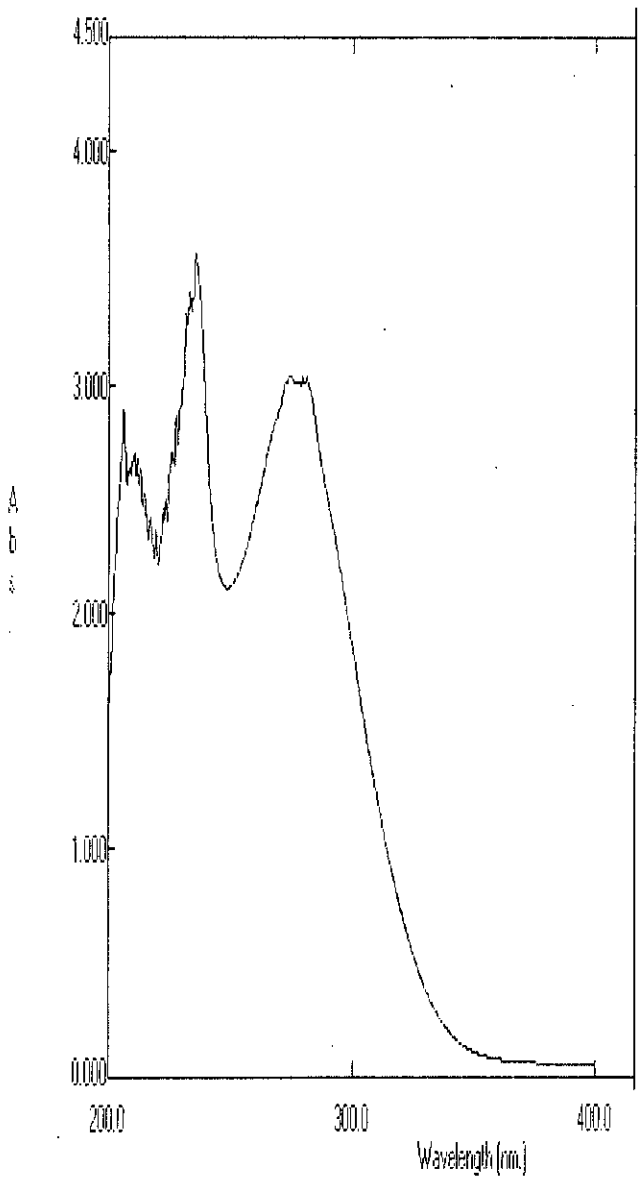
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

SI	32768
SF	400.1400122 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

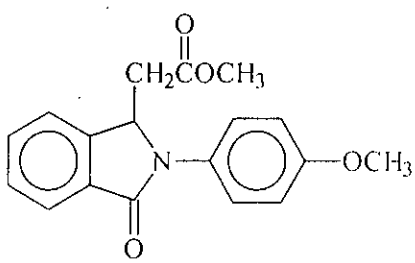
1D NMR plot parameters

CX	20.00 cm
F1P	12.428 ppm
F1	4972.90 Hz
F2P	0.193 ppm
F2	77.30 Hz
PPMCM	0.61174 ppm/cm
HZCM	244.77985 Hz/cm



Peak Pick

No.	Wavelength (nm.)	Abs.
1	273.40	3.0391
2	235.20	3.5554
3	206.00	2.8917



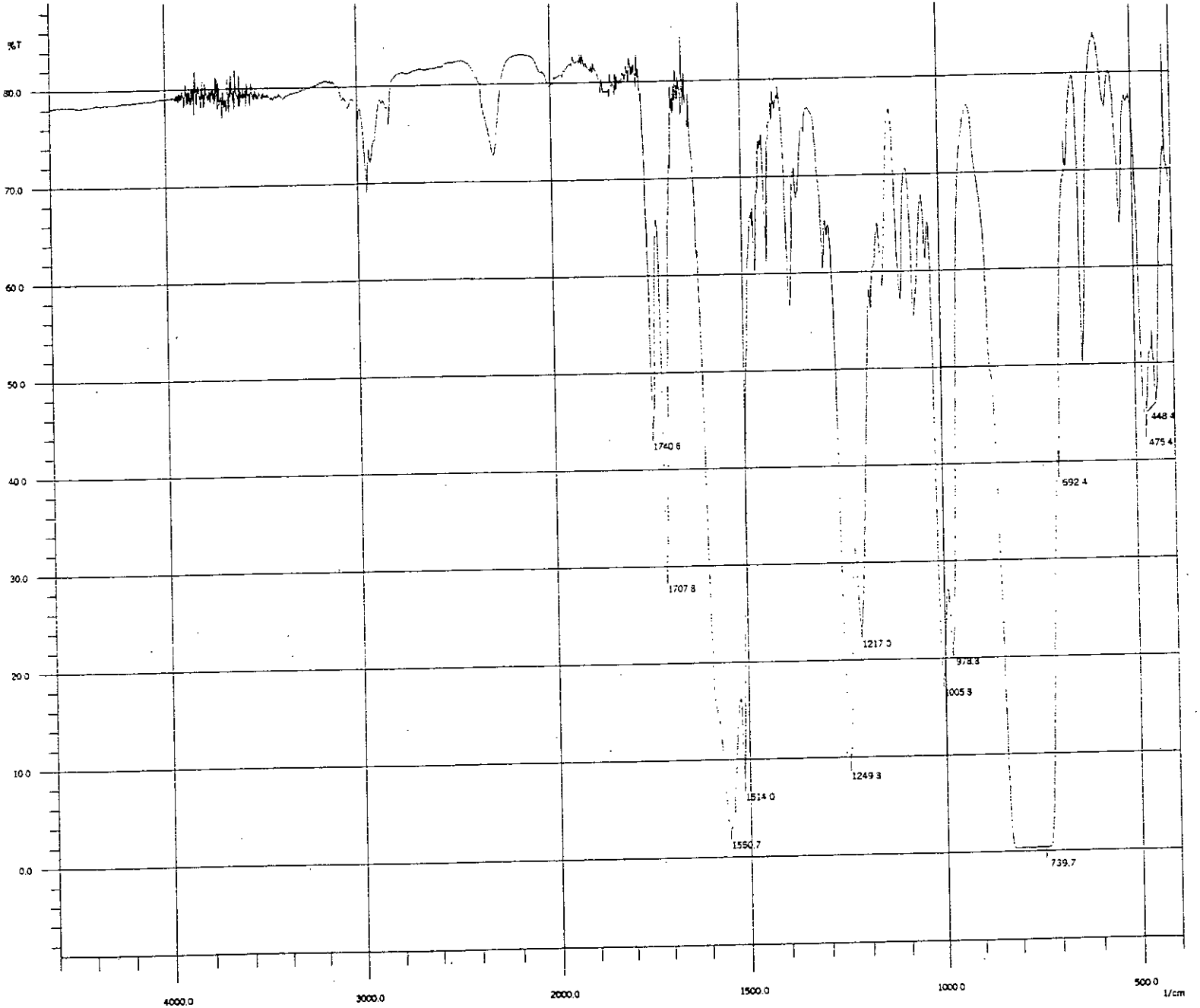
N-p-methoxyphenyl-3-methyl isoindolin-1-one acetate

29

File Name: MR78A1

Created: 11:53 08/09/04
Data: Original

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

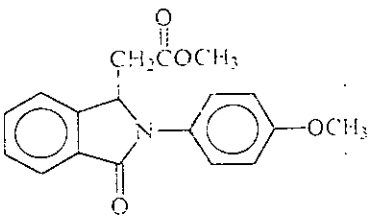


MR-78A1.IRS: MR-78a1, July 20, 2004

Date:	06/20/2004	Time:	18:50:50	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ncp:	4356	Data Interval:	0.964.34	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.80(kw)

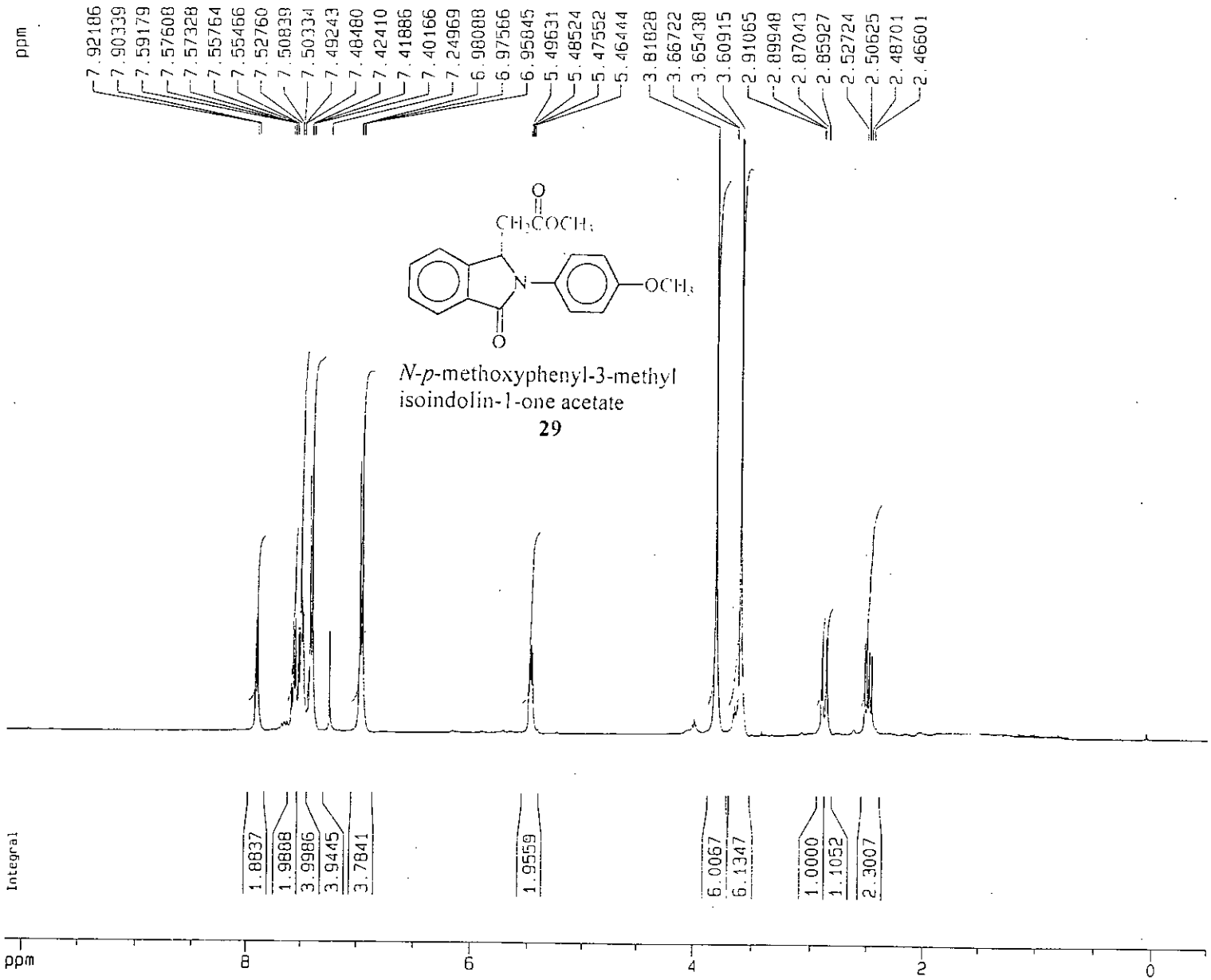
No.	Pos. (1/cm)	Inten. (%T)
1	448.4	46.114
2	475.4	43.462
3	692.4	39.497
4	739.7	0.396
5	978.8	21.351
6	1005.8	18.151
7	1217.0	23.315
8	1249.8	9.733
9	1514.0	7.802
10	1550.7	2.903
11	1707.8	29.390
12	1740.6	44.095

MR-78a1, July 20, 2004



N-p-methoxyphenyl-3-methyl isoindolin-1-one acetate

29



Current Data Parameters

NAME	A1515
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040714
Time	12.30
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	181
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

SI	32768
SF	400.1400128 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

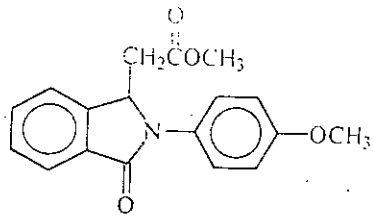
1D NMR plot parameters

CX	20.00 cm
F1P	10.145 ppm
F1	4059.46 Hz
F2P	-0.501 ppm
F2	-200.52 Hz
PPMCM	0.53231 ppm/cm
HZCM	212.99902 Hz/cm

Analytical, BCSIR, 13C Spectrum MR-78a1 in CDCl3, M. reza, BUET

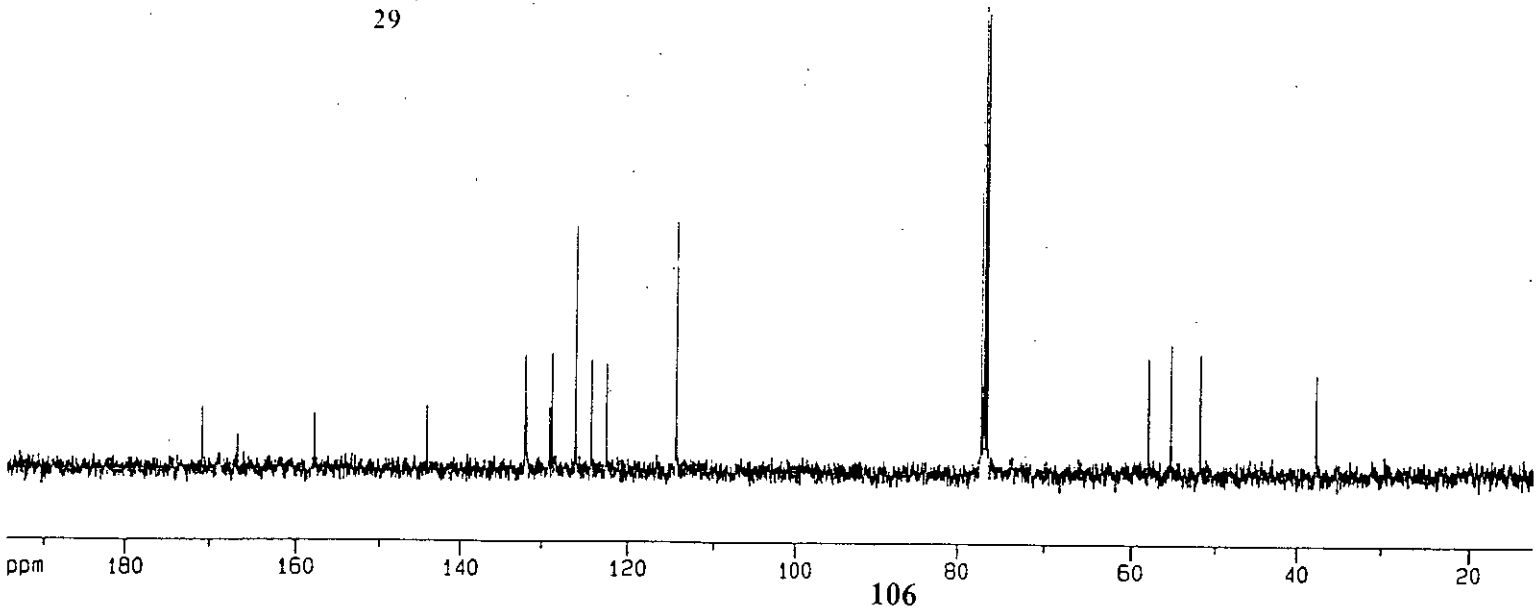
ppm

170.801
166.888
157.904
144.214
132.122
131.964
129.156
128.857
126.035
124.187
122.502
114.591
77.347
77.030
76.712
58.114
55.511
51.955
37.692



N-p-methoxyphenyl-3-methyl isoindolin-1-one acetate

29

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Current Data Parameters
NAME                  A1515
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20040812
Time                  12.38
INSTRUM               qnx400
PROBHD     5 mm Multinuc
PULPROG               zgpg30
TD                     32768
SOLVENT                CDCl3
NS                       256
DS                         2
SWH               24154.590 Hz
FIDRES             0.737140 Hz
AQ                 0.6783478 sec
RG                     16384
DW                  20.700 usec
DE                   6.00 usec
TE                  300.0 K
D1                1.50000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

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

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

F2 - Processing parameters
SI                     32768
SF           100.6152837 MHz
WDW                    EM
SSB                     0
LB                   2.50 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                194.559 ppm
F1                19575.61 Hz
F2P                 12.481 ppm
F2                 1255.83 Hz
PPMCM              9.10387 ppm/cm
HZCM             915.98883 Hz/cm
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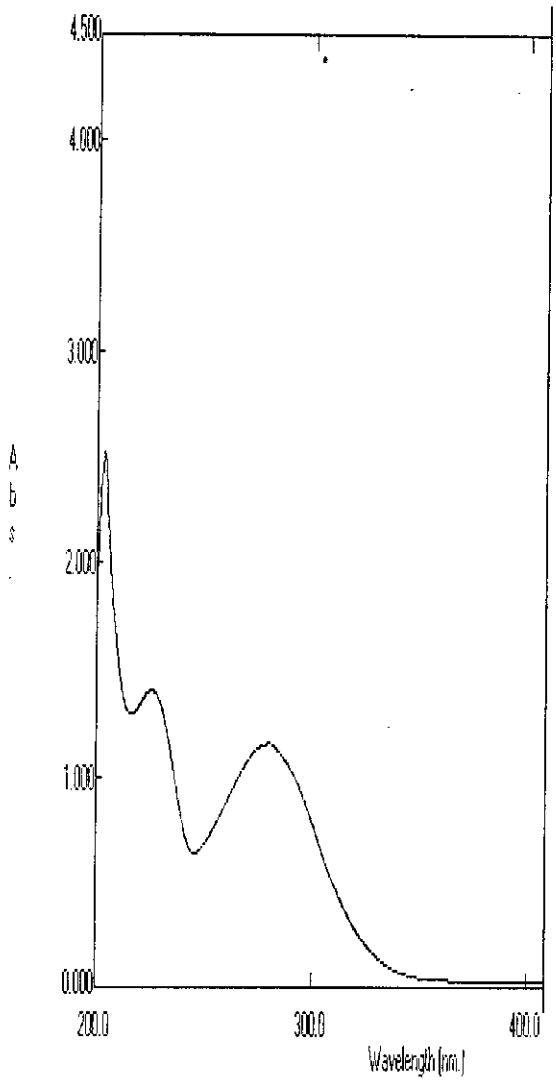
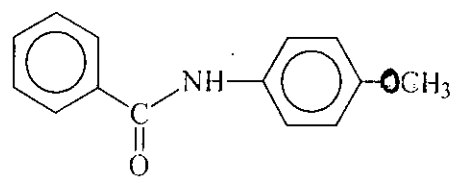


Peak Pick

No.	Wavelength (nm.)	Abs.
1	279.80	1.1499
2	225.00	1.3928
3	203.40	2.5206



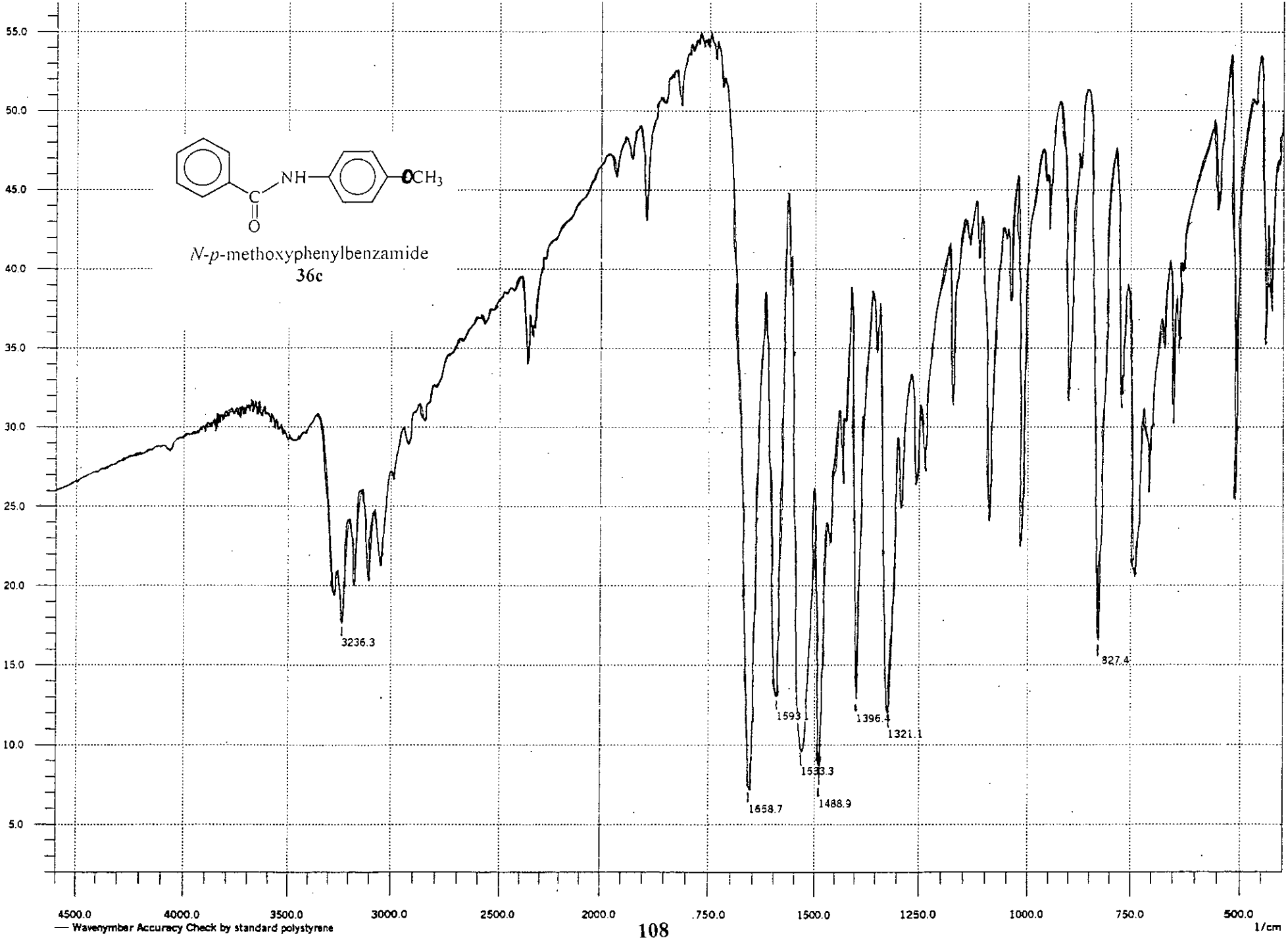
N-*p*-methoxyphenylbenzamide

36c

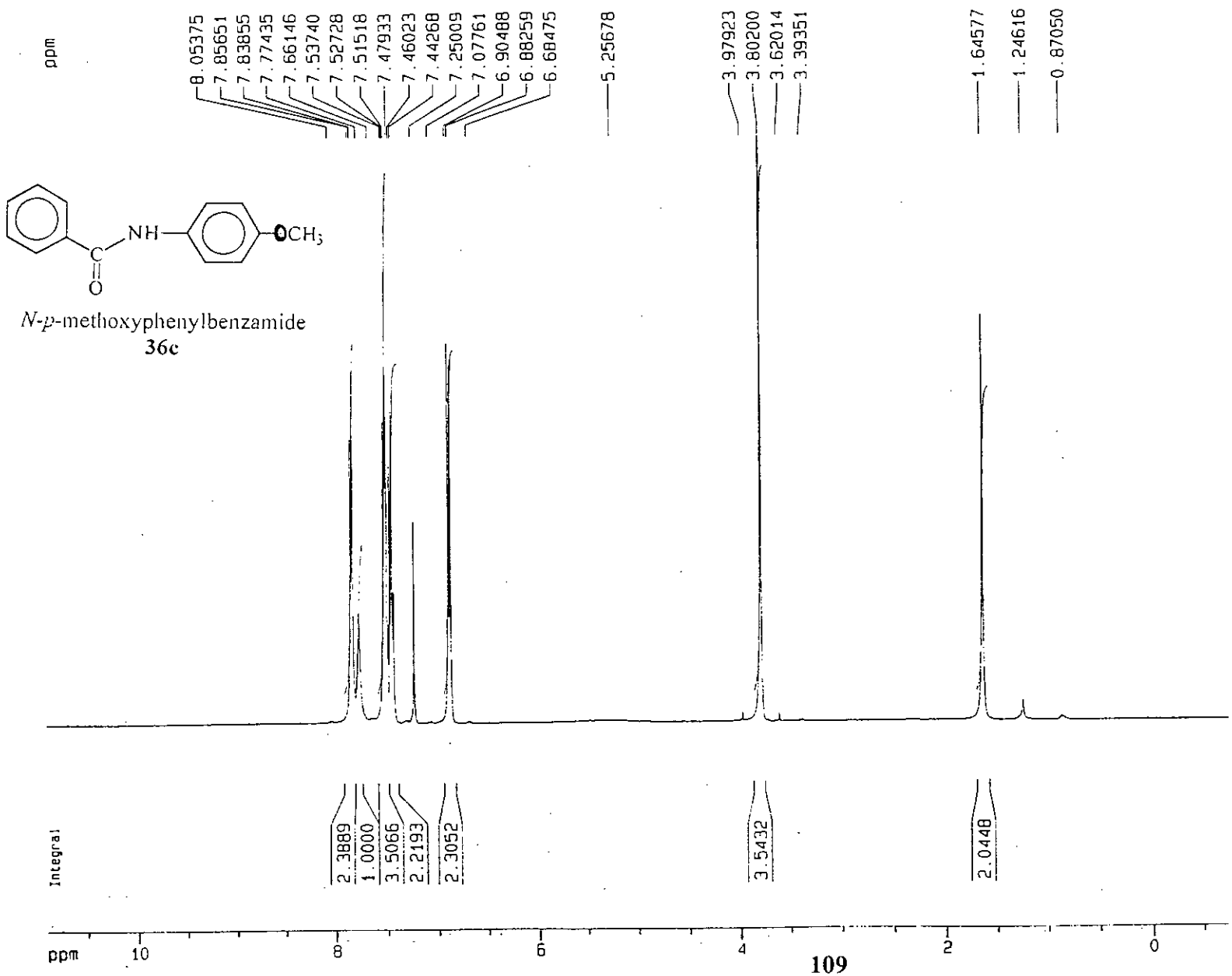
File Name: MR18DI

Created: 10:44 08/10/04
Data: Original

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



N-p-methoxyphenylbenzamide
36c



N-p-methoxyphenylbenzamide

36c

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EXPNO	1
PROCNO	1

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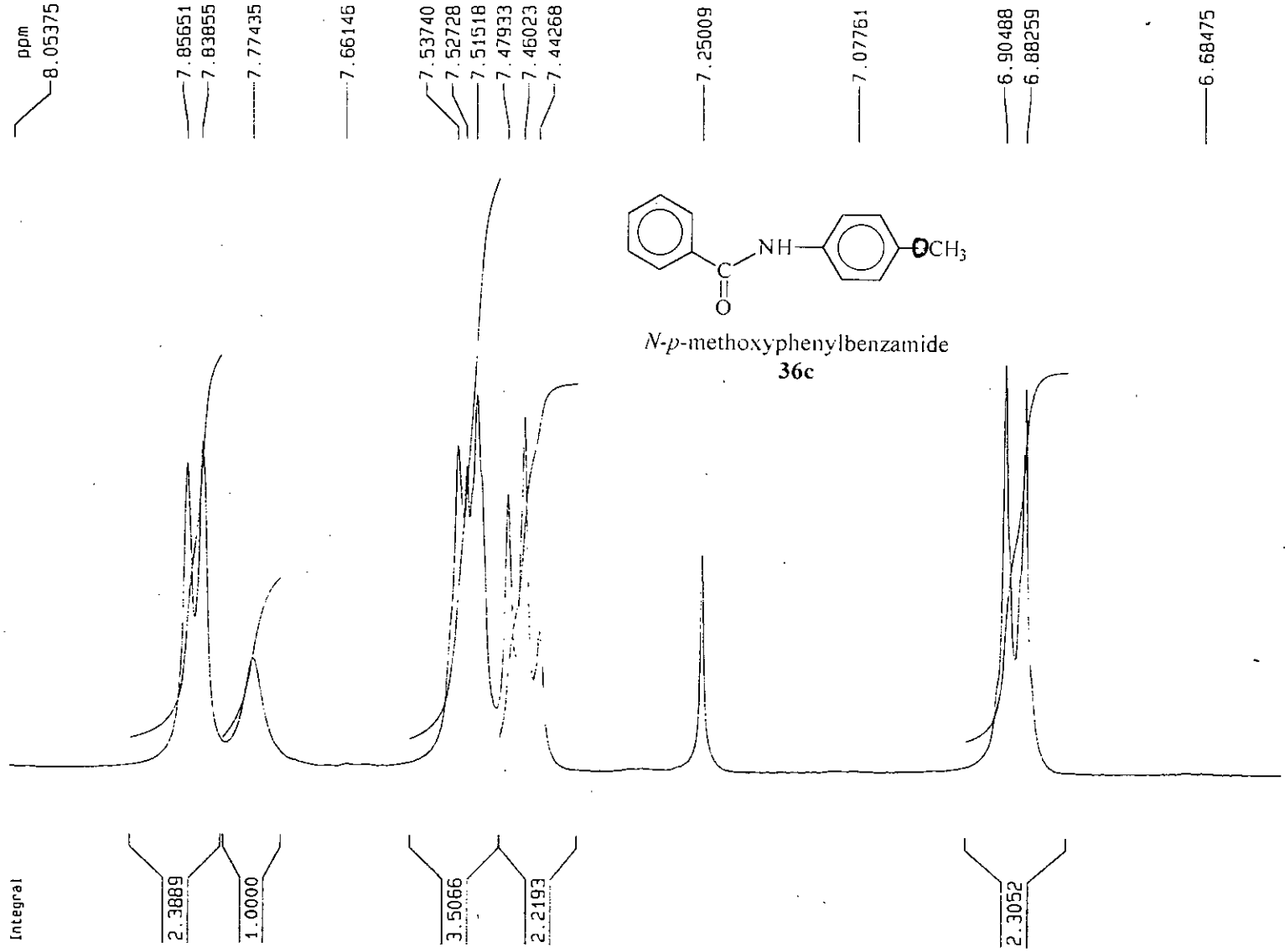

N-p-methoxyphenylbenzamide

36c

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Current Data Parameters
NAME                  A1429
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20040525
Time                  13.41
INSTRUM               dpx400
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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                    322.5
DW                 78.000 usec
DE                  6.00 usec
TE                  310.0 K
D1                1.00000000 sec

============ CHANNEL f1 ============
NUC1                      1H
P1                   8.30 usec
PL1                 -6.00 dB
SFO1           400.1428077 MHz

F2 - Processing parameters
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SF             400.1400126 MHz
WDW                      EM
SSB                       0
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GB                        0
PC                     1.40

1D NMR plot parameters
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F2                2637.20 Hz
PPMCM          0.07332 ppm/cm
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```

1.2.8.C. Synthesis of *N*-Substituted-1,2,3,4-Tetrahydro-1-Oxo isoquinolinoe-3-Carboxylic Acids:

Synthesis of *N*-phenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 30.

The mixture of *N*-Phenyl-3-butyl isoindolin-1-one acetate **22** (200mg, 0.668 mmol) and NaOH (1.5 equiv.) in MeOH (10 ml) was heated under refluxing condition for 1.5 hrs. After removal of solvent from the mixture, the residue was diluted with water (25 ml) and filtered. The filtrate upon neutralization with dilute HCl acid and extracted with chloroform (3×50 ml) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and crystalization from n-hexane-ethyl acetate to obtain a colourless solid compound **30** (108 mg, 54%). m.p. 184–185°C.

IR : ν_{max} (KBr) 1730, 1650, 1600, 1500 and 1420 cm^{-1}.

UV (EtOH): λ_{max} 274.8 (log ε 4.01) and 228.6 (log ε 4.12).

^{1}H NMR (400 MHz, d_6 – DMSO): 2.60 (dd, 1H, *J* = 8.00 Hz, *J* = 16.00 Hz, H–4ax), 2.92 (dd, 1H, *J* = 4.00 Hz, *J* = 16.00 Hz, H–4 eq), 5.72 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, H–3), 7.16–8.12(m, 9H, Ar–H) and 12.40 (brs, 1H, CO_2H)

^{13}C NMR (100 MHz, d_6 – DMSO): 36.82 (C–4), 57.91 (C–3), 123.79, 124.08, 124.76, 126.32, 129.42, 129.79, 132.55, 133.13, 137.50, 145.57 (Ar–C), 167.01, (CON) and 171.82 (CO_2H)

Anal. Calculated for: $C_{16}H_{13}NO_3$; C, 71.90; H, 4.90; N, 5.24%.

Found: C, 71.77; H, 5.03; N, 5.36%.

Synthesis of *N*-*p*-methyl phenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 31.

A mixture of *N*-*p*-methyl phenyl-3-butyl isoindolin-1-one acetate **23** (200 mg, 0.593m mol) and NaOH (1.5 equiv.) in MeOH (10 ml) was heated by following the procedure described above for the compound **30**. After usual work up, crystallization from n-hexane-ethylacetate to obtain a needless colourless solid compound **31**. (136 mg, 68%) m. p-193 -194 ^{0}C. This title compound **31** was also synthesis from *N*-*p*-methyl phenyl-3-

ethyl isoindolin-1-one acetate **26** and *N-p*-methyl phenyl-3-methyl isoindolin-1-one acetate **28**.

IR: ν_{max} (KBr) 1718.5, 1651.9, 1617.2, 1603.7, 1516.9, 1427.2 and 1404.1 cm^{-1}.

UV(EtOH): λ_{max} 257.20 (log ε 3.747), 240.00 (log ε 3.719) and 205.80 (log ε 3.574) nm.

^{1}H NMR (400 MHz, d_6 – DMSO): δ 2.32 (s, 3H, Ar–CH_3), 2.55 (dd, 1H, *J* = 7.30 Hz, *J* = 16.33 Hz, H–4 ax), 2.88 (dd, 1H, *J* = 3.77 Hz, *J* = 16.34 Hz, H–4 eq), 5.61 (dd, 1H, *J* = 3.71 Hz, *J* = 7.08 Hz, H–3) and 7.24 – 7.77 (m, 8H, Ar–H)

^{13}C NMR (100 MHz, d_6 – DMSO) : δ 20.58 (Ar–CH_3), 36.08 (C–4) 57.23 (C–3), 122.90, 123.14, 124.03, 128.52, 129.40, 131.79, 132.13, 134.06, 134.83, 144.72 (Ar–C), 166.10 (CON) and 170.95 (CO_2H).

Anal. Calculated for: $C_{17}H_{15}NO_3$; C = 72.58; H = 5.38, N = 4.9%.

Found: C = 72.59; H = 5.63; N = 5.26%.

Synthesis of *N-p*-methoxy phenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid 32.

The title compound **32** was synthesized from *N-p*-methoxy phenyl-3-butyl isoindolin-1-one acetate **24** (200mg, 0.56m mol) and NaOH (1.5 equiv) in MeOH (10 ml) by following the procedure described above for the compound **30**. After usual work up, crystallized from n-hexane-ethylacetate to obtain a colourless compound **32** (144 mg, 72%) mp. 216 – 217^{0}C. The title compound **32** was also synthesis from *N-p*-methoxy phenyl-3-ethyl isoindolin-1-one acetate **27** and *N-p*-methoxy phenyl-3-methyl isoindolin-1-one acetate **29**. It was also synthesis by hydrolysis with 2N H_2SO_4 (4 equiv.) in H_2O.

IR: ν_{max} (KBr) 1718.5, 1653.8, 1517.9, 1419.5 and 1402 cm^{-1}.

UV(EtOH): λ_{max} 280.60 (log ε 3.033), 275.00 (log ε 3.027), 226.80 (log ε 3.264) and 204.80 (log ε 3.536) nm.

^{1}H NMR (400 MHz, d_6 – DMSO): δ 2.54 (dd, 1H, *J* = 7.20 Hz, *J* = 16.42 Hz, H–4ax), 2.85 (dd, 1H, *J* = 3.98 Hz, *J* = 16.38 Hz, H–4 eq), 3.78 (s, 3H, $ArOCH_3$), 5.56 (dd, 1H, *J* = 3.99 Hz, *J* = 6.87 Hz, H–3), 7.01 (d, 2H, *J* = 8.78 Hz, Ar–H) and 7.43 – 7.76 (m, 6H, Ar–H).

^{13}C NMR (100 MHz, d_6 – DMSO) : δ 36.23 (C–4) 55.29 (OCH_3), 57.69 (C–3), 114.17, 122.90, 123.08, 126.15, 128.49, 129.35, 131.81, 132.02, 144.77, 157.18, (Ar–C), 166.12 (CON) and 171.03 (CO_2H).

Anal. Calculated for: $C_{17}H_{15}NO_3$; C = 68.67; H = 5.08; N = 4.71%.

Found: C = 68.35; H = 5.25; N = 4.69%.

Synthesis of *N*-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid 33.

A mixture of *N*-*p*-chlorophenyl-3-ethyl isoindolin-1-one acetate **25** (200 mg. 0.679 mmol) and NaOH (1.5 equiv.) in MeOH (10 ml) was heated by following the procedure described above for the compound **30**. After usual work up, crystallized from n-hexane-ethyl acetate to obtain a needless brown colour compound **33**. (138 mg, 69%) m.p. 183–184 °C.

IR: ν_{max} (KBr) 1724.2, 1664.5, 1617.2, 1595.0, 1496.2, 1470.6 and 1390.6 cm^{-1}.

UV(EtOH): λ_{max} 274.40 (log ε 3.553), 231.00 (log ε 3.556) and 208.00 (log ε 3.598) nm.

^{1}H NMR (400 MHz, d_6 – DMSO): δ 2.61 (dd, 1H, *J* = 6.96 Hz, *J* = 16.32 Hz, H–4ax), 2.91 (dd, 1H, *J* = 3.71 Hz, *J* = 16.34 Hz, H–4 eq), 5.69 (dd, 1H, *J* = 3.74 Hz, *J* = 6.56 Hz, H–3), and 7.51–7.79 (m, 8H, Ar–H)

^{13}C NMR (100 MHz, d_6 – DMSO) : δ 35.97 (C–4), 57.13 (C–3), 122.97, 123.29, 125.46, 128.62, 128.87, 129.52, 131.41, 132.45, 135.64, 144.67 (Ar–C) 166.27 (CON) and 170.86 (CO_2H).

Anal. Calculated for: $C_{16}H_{12}ClNO_3$, C = 63.69; H = 4.01; N = 4.64%.

Found: C = 63.52; H = 4.27, N = 4.70%.

Synthesis of *N*-Methyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 34.

Bis (triphenyl phosphine) palladium (II) chloride (0.047g, 3.5 mol%), triethyl amine (0.77g, 4 equiv.) and butyl acrylate **16** (0.74g, 3 equiv.) were added to the solution of 2-iodo-*N*-methyl benzamide **10** (0.50g, 1.915 mmol) in DMF (10 ml) by following the

procedure described above for the compound **22** and then hydrolysis with NaOH (1.5 equiv.) in MeOH by following the procedure described above for the compound **30**. After usual work up, crystallized from n-hexane-ethylacetate to obtain **34**. (60%), m. p. 165-166 ^{0}C.

IR: ν_{max} (KBr): 1700. 1660. 1450 and 1400 cm^{-1}

UV: λ_{max} (EtOH): 279.2 (log ε 3.24) and 239.8 (log ε 3.82) nm.

^{1}H NMR (400 MHz, d_6 – DMSO): 2.71 (dd, 1H, *J* = 8.00 Hz, *J* = 16.30 Hz, H–4ax), 2.87 (dd, 1H, *J* = 4.20 Hz, *J* = 16.00 Hz, H–4eq), 3.13 (s, 3H, N-CH_3), 4.83 (dd, 1H, *J* = 4 Hz, *J* = 8.00 Hz, H–3) and 7.53 – 7.73 (m, 4H, Ar–H)

Found: $C_{11}H_{11}NO_3$; C = 64.37; H = 5.40; N = 6.83%

Found: C = 64.05; H = 5.44; N = 6.88%.

Synthesis of *N-p*-chlorobenzyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid: 35.

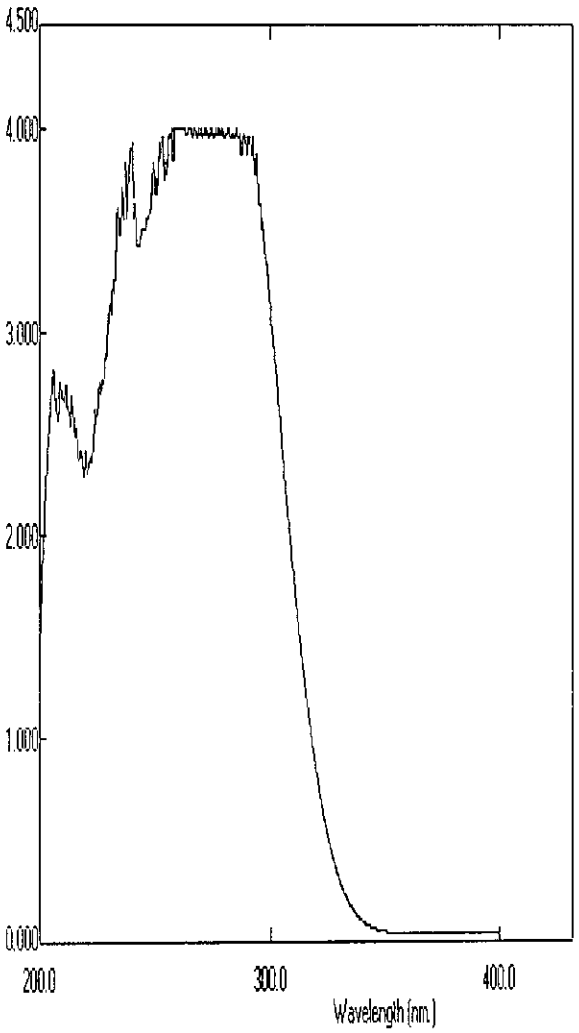
The title compound **35** was synthesized from 2-Iodo-*N-p*-chlorobenzyl benzamide **11** (0.50g, 1.346 mmol), bis (triphenyl phosphine). palladium (II) chloride (0.033g, 3.5 mol%), triethyl amine (0.54g, 4 equiv.) and butyl acrylate **16** (0.518g, 3 equiv.) in DMF (10 ml) by following the procedure described above for the compound **22** and hydrolysis with a refluxing solution of NaOH (1.5 equiv.) in MeOH during a period of 1.5 hrs by following the procedure described above for the compound **30**. After usual work up. It was crystallized from n-hexane ethyl acetate to obtain a white compound **35** (65%) m. p. 163–164 °C.

IR: ν_{max} (KBr) 1721.3, 1648.1, 1618.2, 1497, 1440.7, 1420.5, and 1409.9 cm^{-1}.

UV(EtOH): λ_{max} 223.60 (log ε 3.522) and 206.20 (log ε 3.630) nm.

^{1}H NMR (400 MHz, d_6 – DMSO): δ 2.68 (dd, 1H, *J* = 6.87 Hz, *J* = 16.42 Hz, H–4x), 2.97 (dd, 1H, *J* = 4.86 Hz, *J* = 16.43 Hz. H–4 eq), 4.46 (d, 1H, *J* = 15.69 Hz, NCH_2) 4.74 (dd, 1H, *J* = 6.01 Hz. *J* = 11.49 Hz. H–3). 5.01 (d. 1H. *J* = 15.69 Hz. –NCH_2) and 7.28–7.738 (m, 8H, Ar–H)

^{13}C NMR (100 MHz, d_6 – DMSO) : δ 20.59 (N–CH_2), 36.08 (C–4), 57.24 (C–3) 122.90, 123.15, 124.04, 128.52, 129.41, 131.80, 132.14. 134.07, 134.83, 144.72 (Ar–C), 166.11 (CON) and 170.98 (CO_2H).



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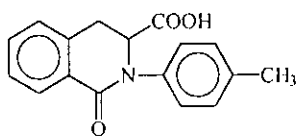

N-*p*-methylphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

31

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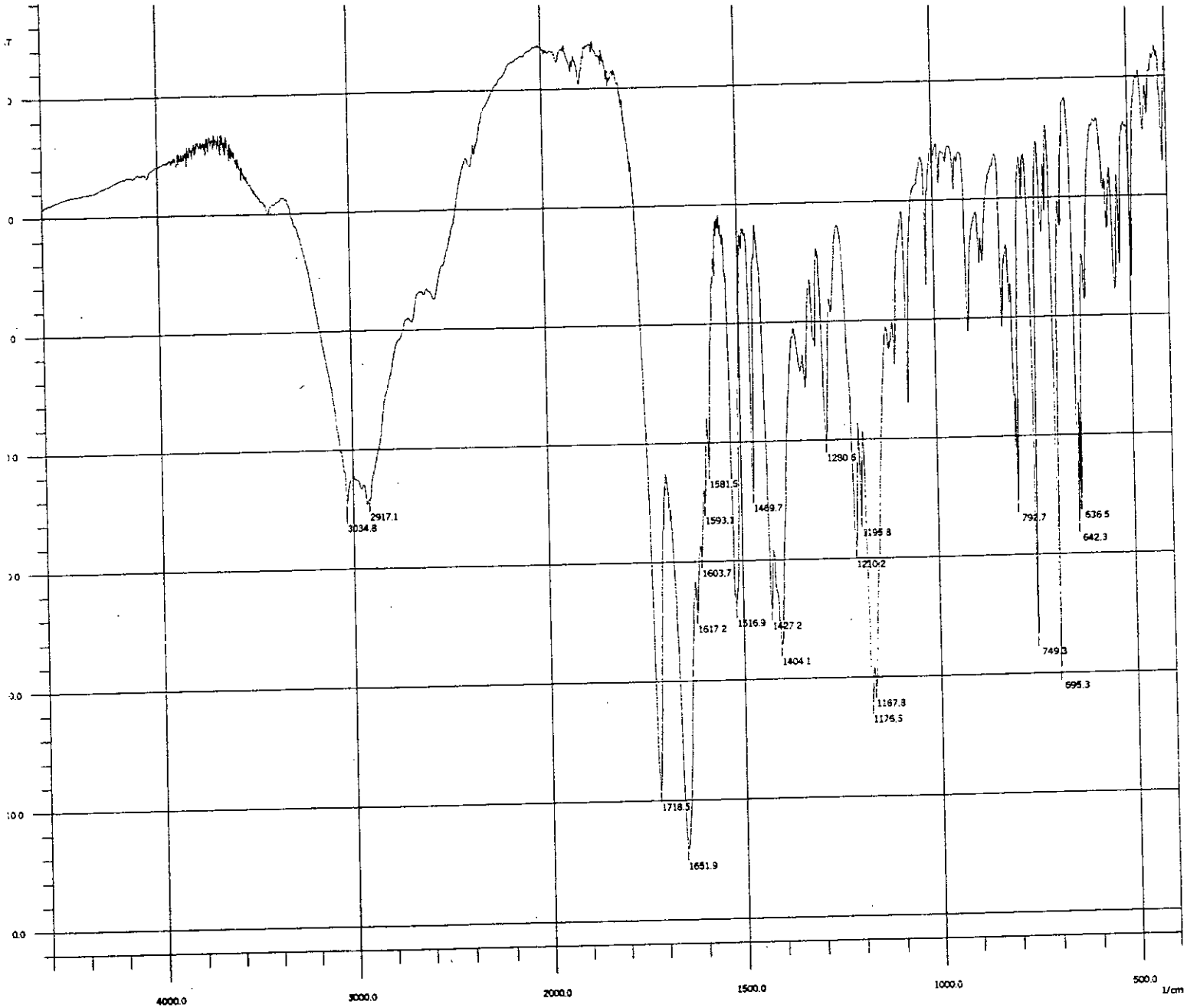

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8	1195.8	33.550
9	1210.2	30.910
10	1280.6	39.892
11	1404.1	22.859
12	1427.2	25.837
13	1469.7	35.780
14	1516.9	26.149
15	1581.5	37.896
16	1593.1	34.827
17	1603.7	30.417
18	1617.2	25.725
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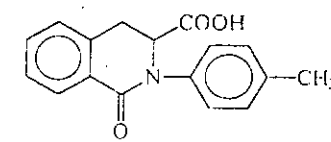
Masud-62b, May21. 2004



N-p-methylphenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

31

NONAME.IRS: Masud-62b, May21. 2004

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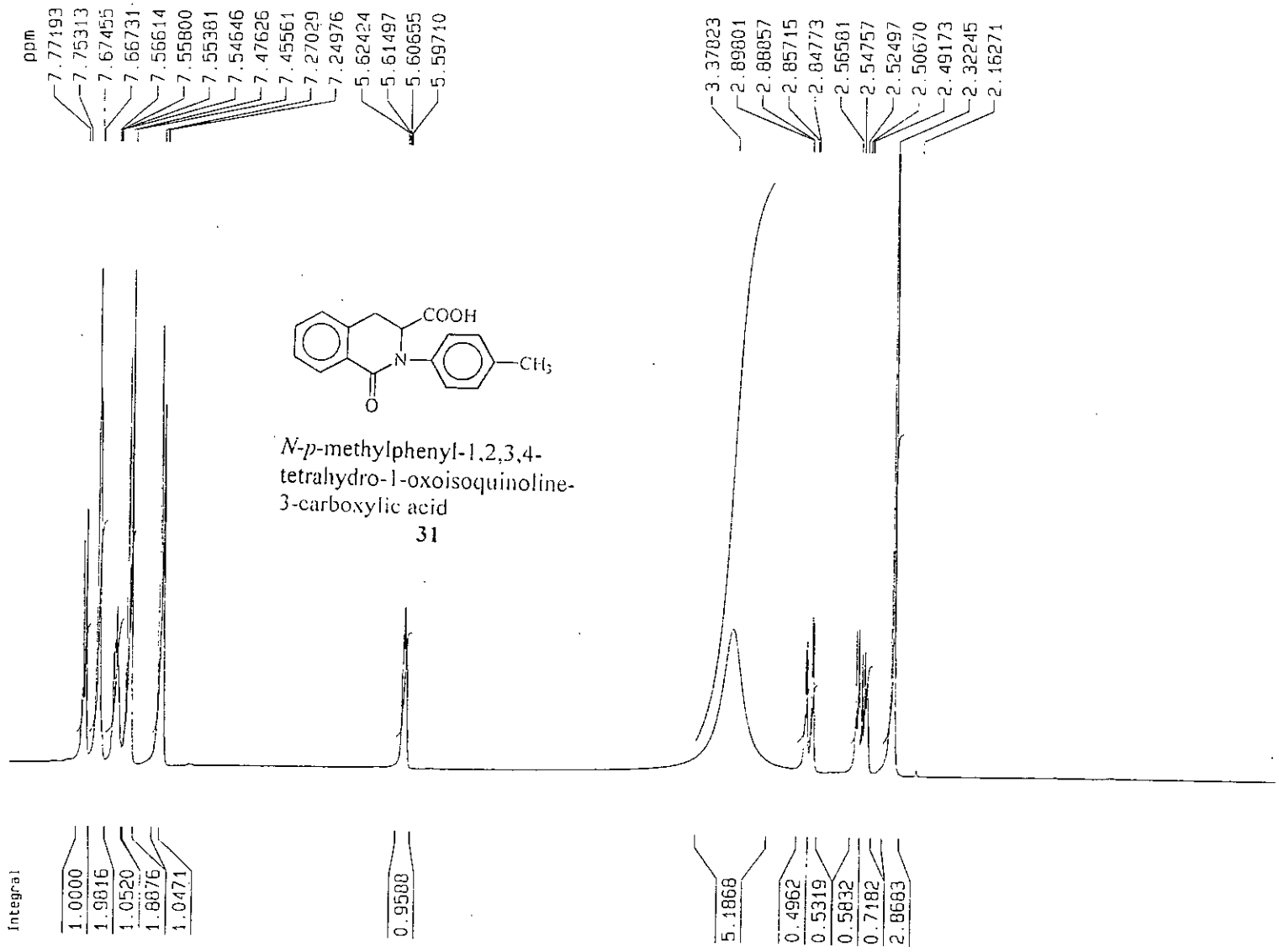
115A



N-p-methylphenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

31

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========== CHANNEL f1 ==========

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F2 - Processing parameters

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1D NMR plot parameters

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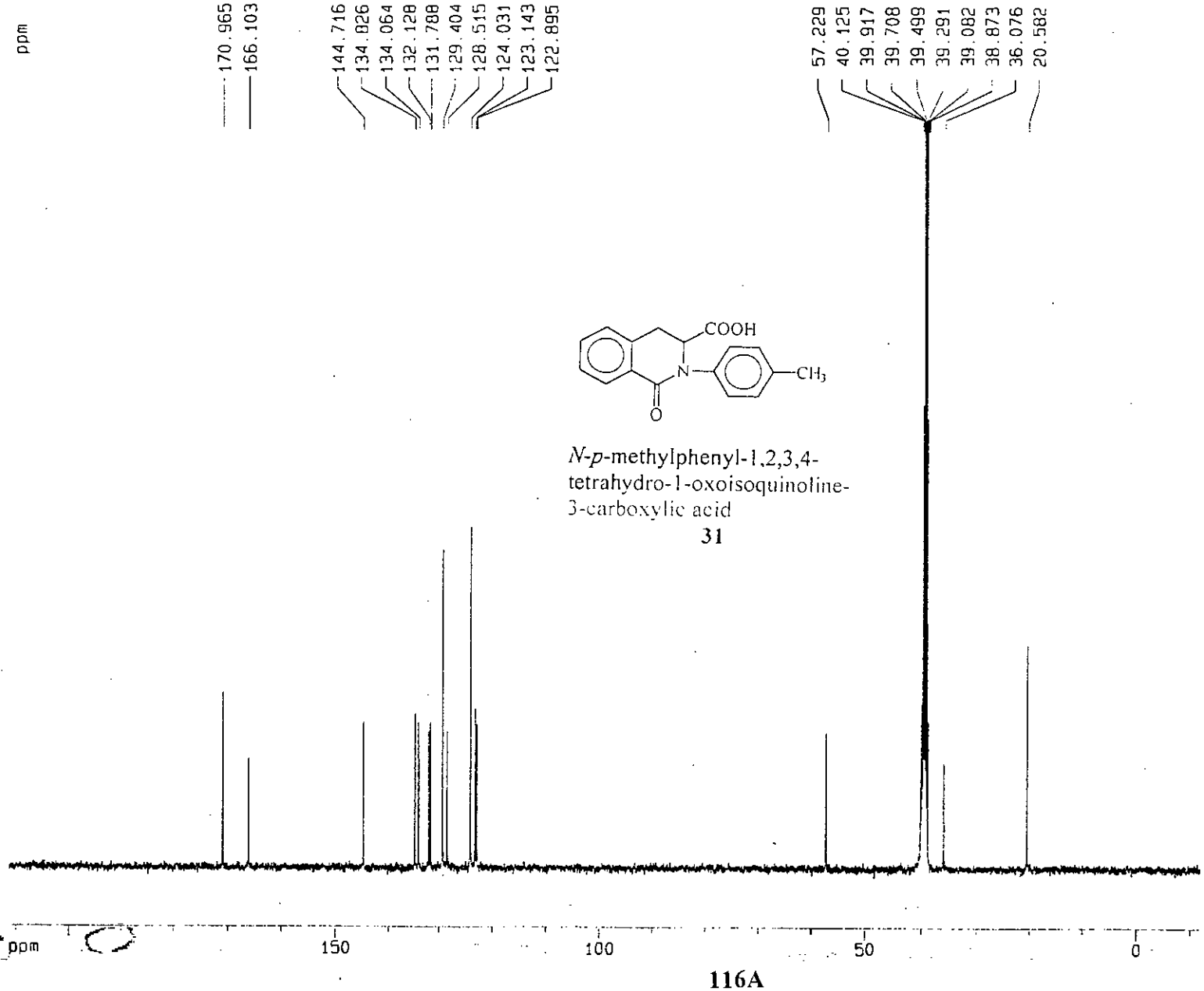
Analytical, BCSIR Lab. Dhaka 13C Spectrum MR-62b in DMSO, M.Reza BUET.



N-p-methylphenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

31

116A

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1D NMR plot parameters
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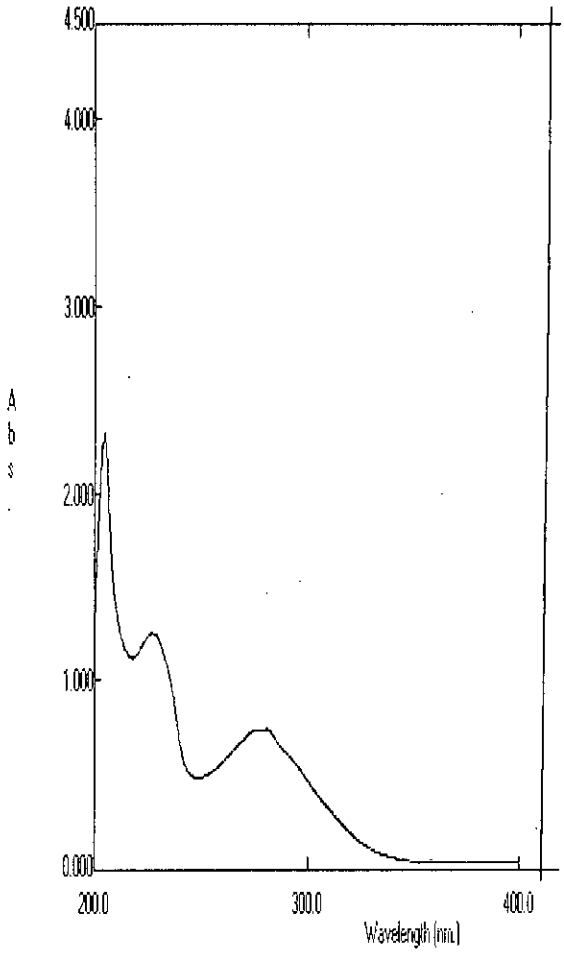

Peak Pick

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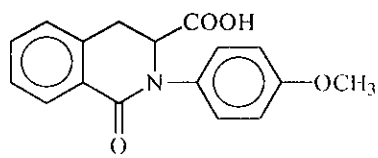

N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

32

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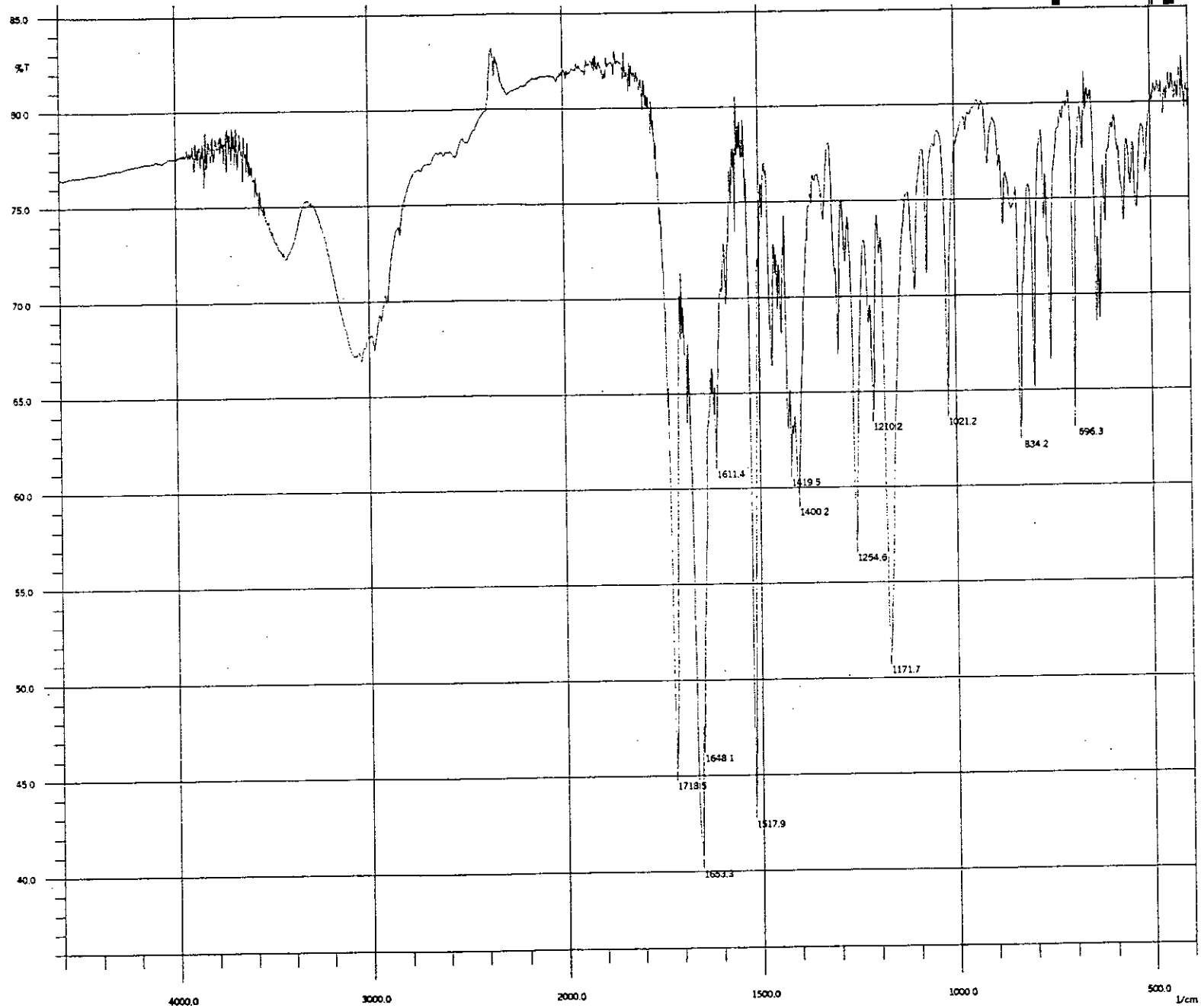

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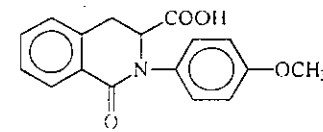
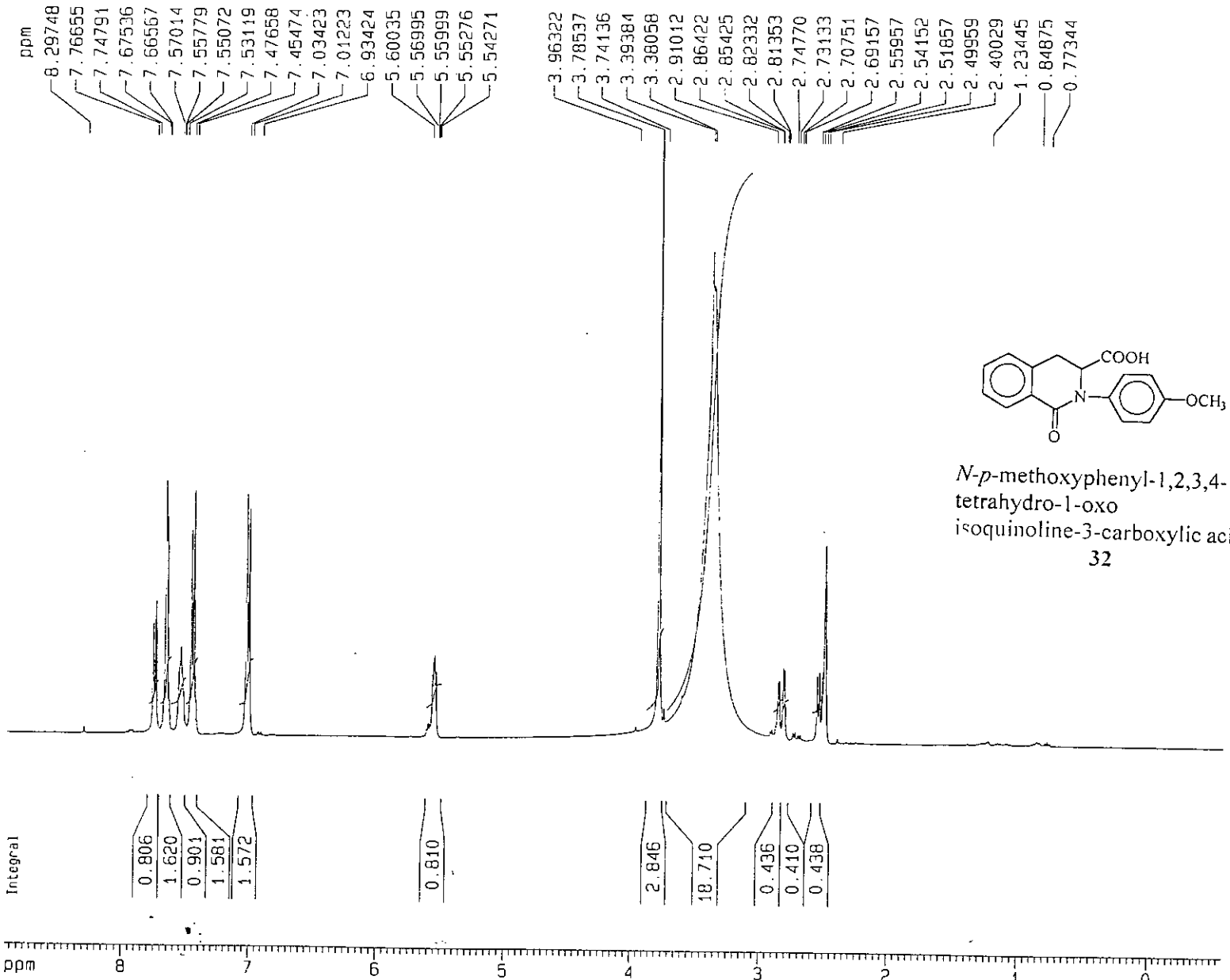
MR-64b, June 26. 2004



N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

32



117B

N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

32

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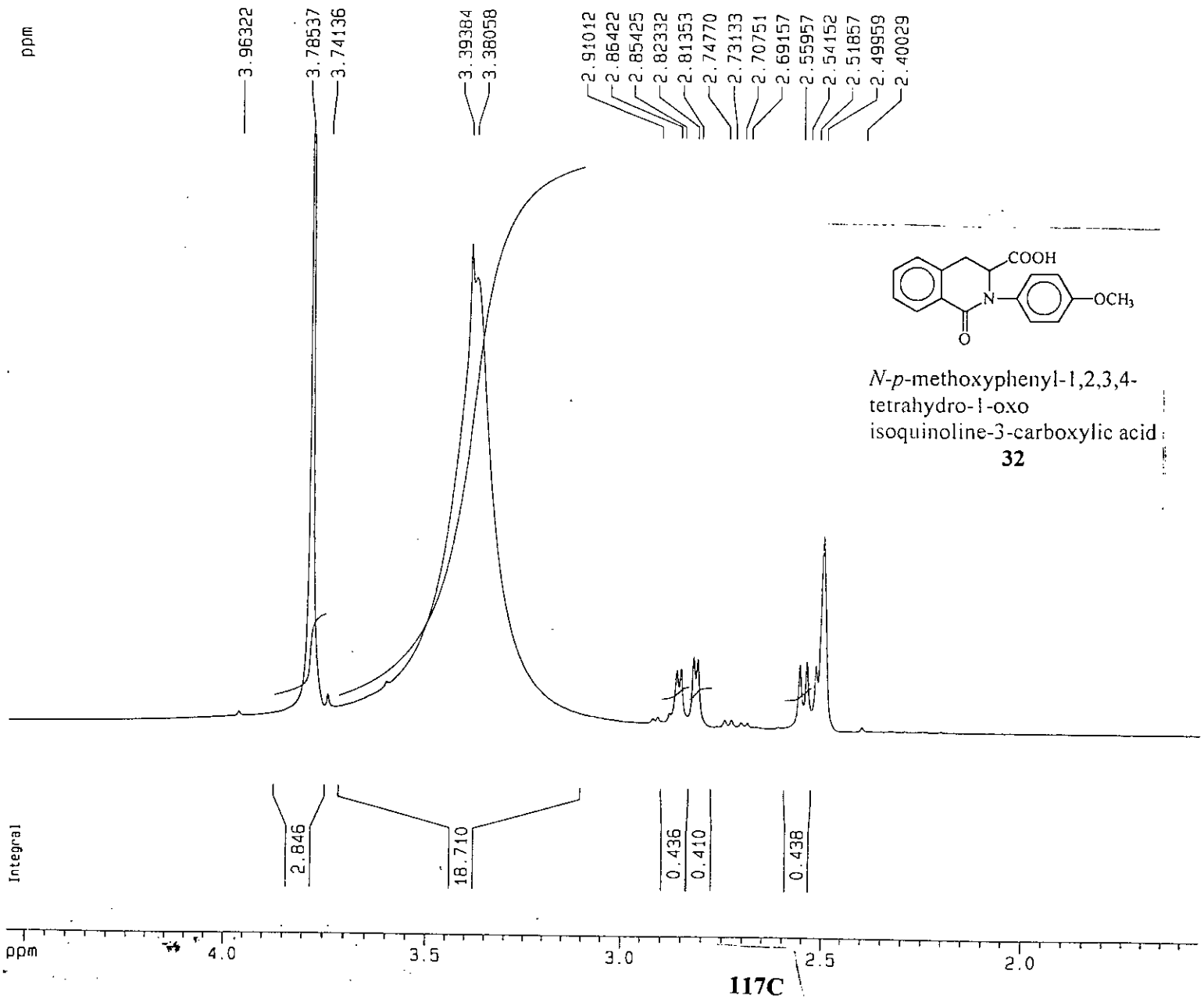
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	114
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========	
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters	
SI	32768
SF	400.1400027 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters	
CX	20.00 cm
F1P	8.886 ppm
F1	3555.56 Hz
F2P	-0.594 ppm
F2	-237.85 Hz
PPMCM	0.47401 ppm/cm
HZCM	189.67058 Hz/cm



N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

32

117C

Current Data Parameters

NAME	A1475
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040626
Time	16.43
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	114
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

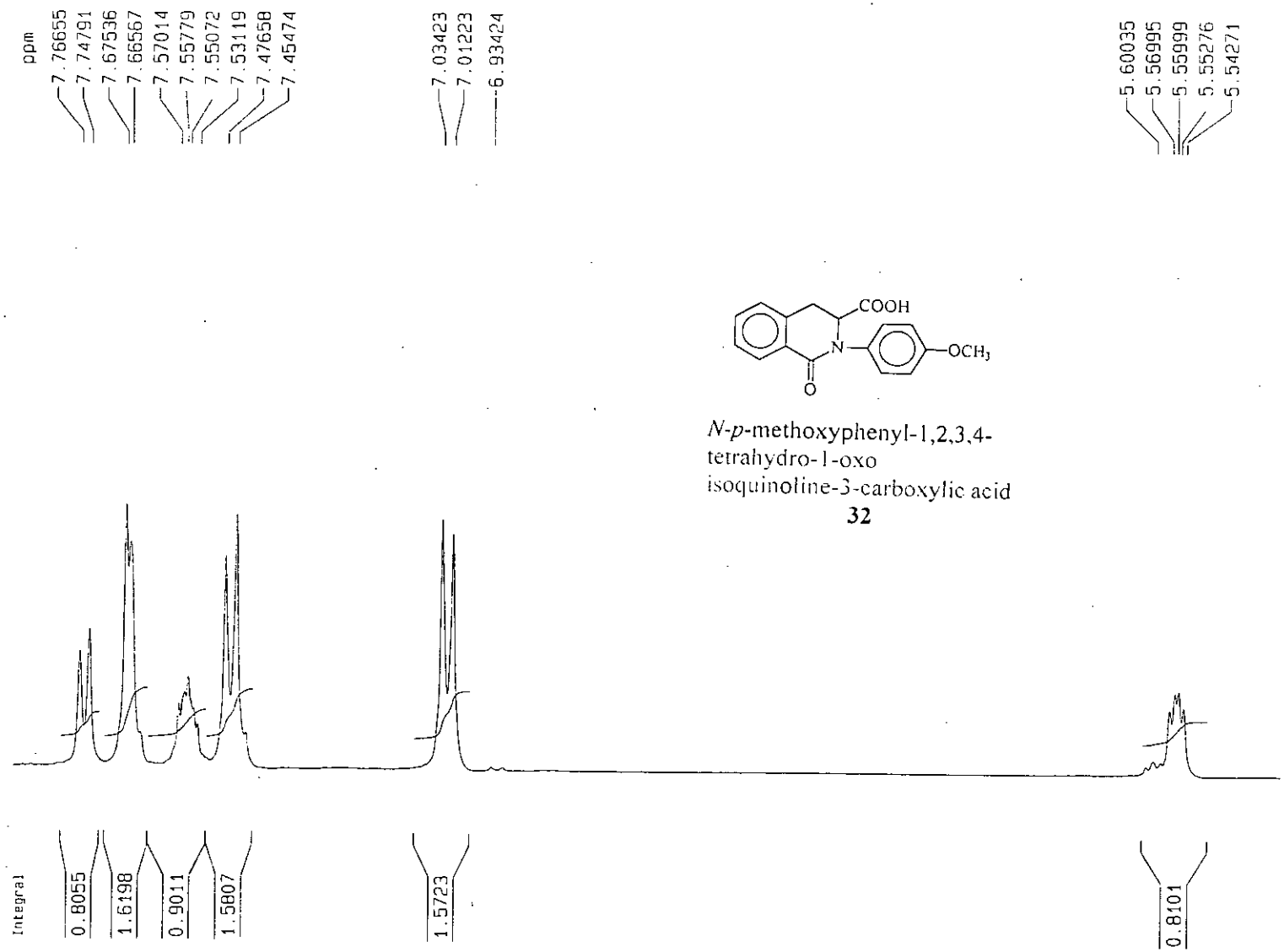
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

SI	32768
SF	400.1400027 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	4.543 ppm
F1	1817.76 Hz
F2P	1.552 ppm
F2	620.91 Hz
PPMCM	0.14955 ppm/cm
HZCM	59.84258 Hz/cm



N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

32

Current Data Parameters

NAME	A1475
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040626
Time	16.43
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	114
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

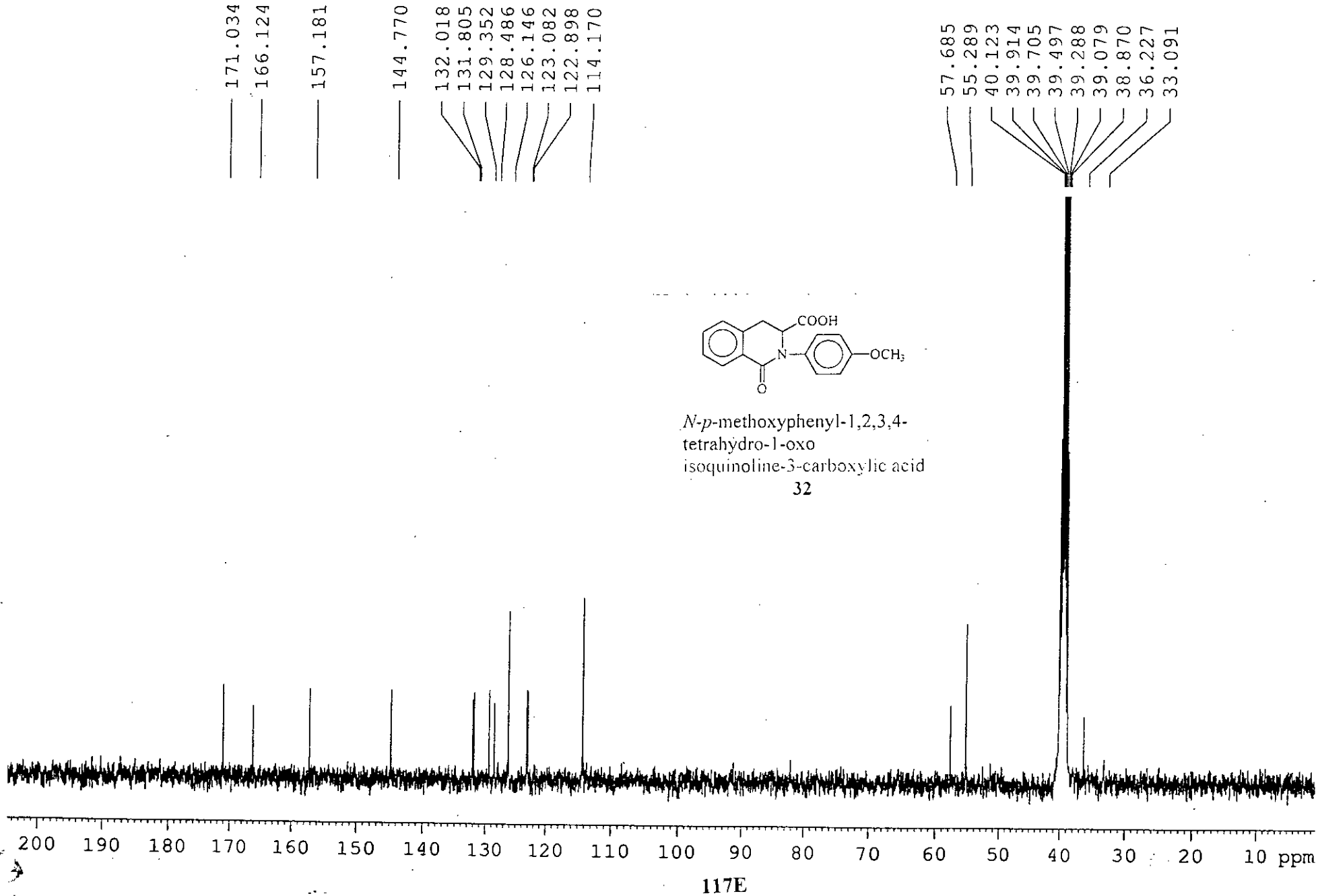
SI	32768
SF	400.1400027 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	7.905 ppm
F1	3163.29 Hz
F2P	5.346 ppm
F2	2139.08 Hz
PPMCM	0.12798 ppm/cm
HZCM	51.21049 Hz/cm

117D

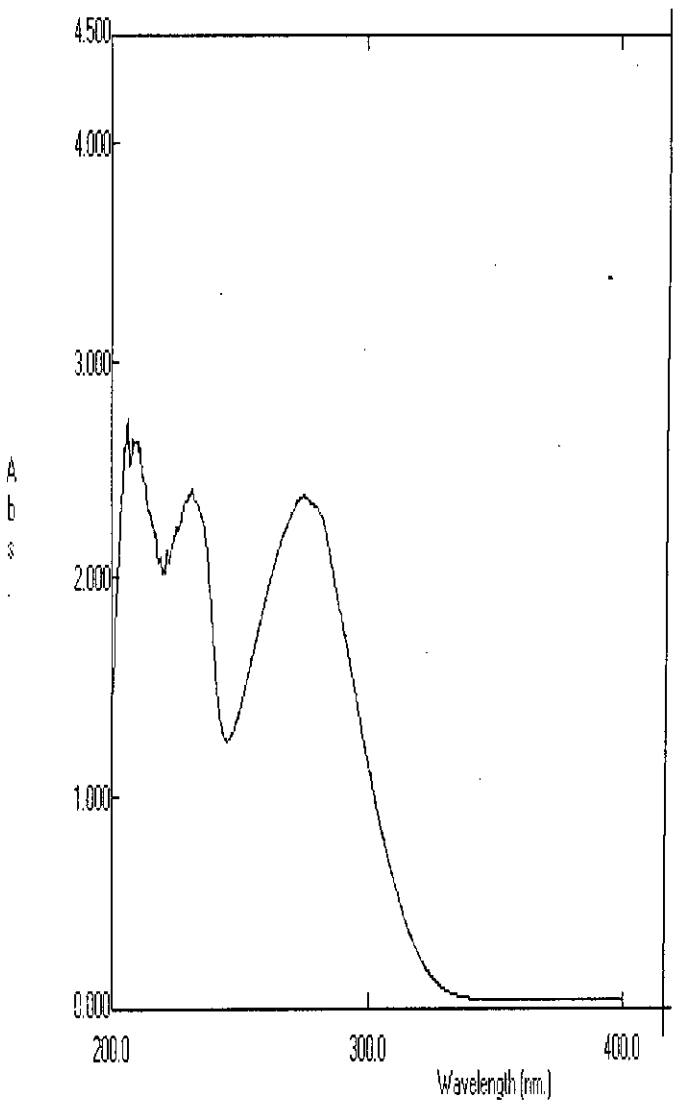
Analytical, BCSIR, A1475, 13C Spectrum MR-64b in DMSO-d6, M.Reza, BUET



N-p-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

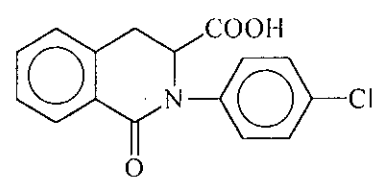
32

117E



Peak Pick

No.	Wavelength (nm.)	Abs.
1	274.40	2.3730
2	231.00	2.3988
3	208.00	2.6351



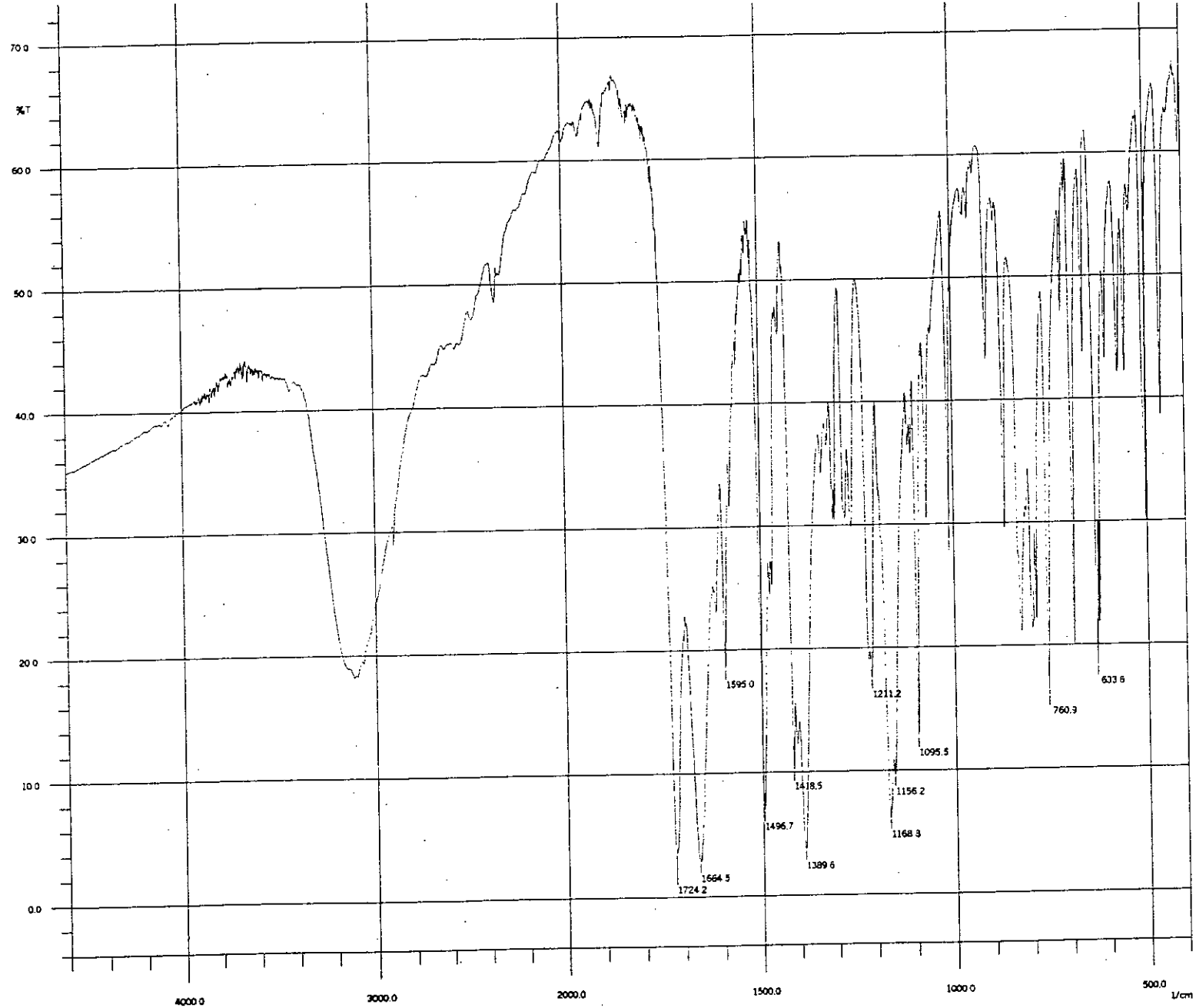
N-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

33

File Name: MR66B

Created: 11:48 08/09/04
Data: Original

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

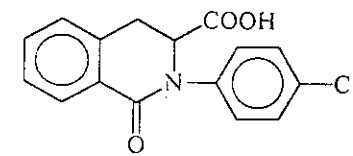


MR-668 IRS: MR-66b, June 26, 2004

Data:	05/27/2004	Time:	18:15:37	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

No.	Pos. (1/cm)	Inten. (%T)
1	633.6	18.382
2	760.9	15.982
3	1095.5	12.775
4	1156.2	9.622
5	1168.8	6.196
6	1211.2	17.543
7	1389.6	3.778
8	1418.5	10.195
9	1496.7	6.965
10	1595.0	18.543
11	1664.5	2.879
12	1724.2	3.578

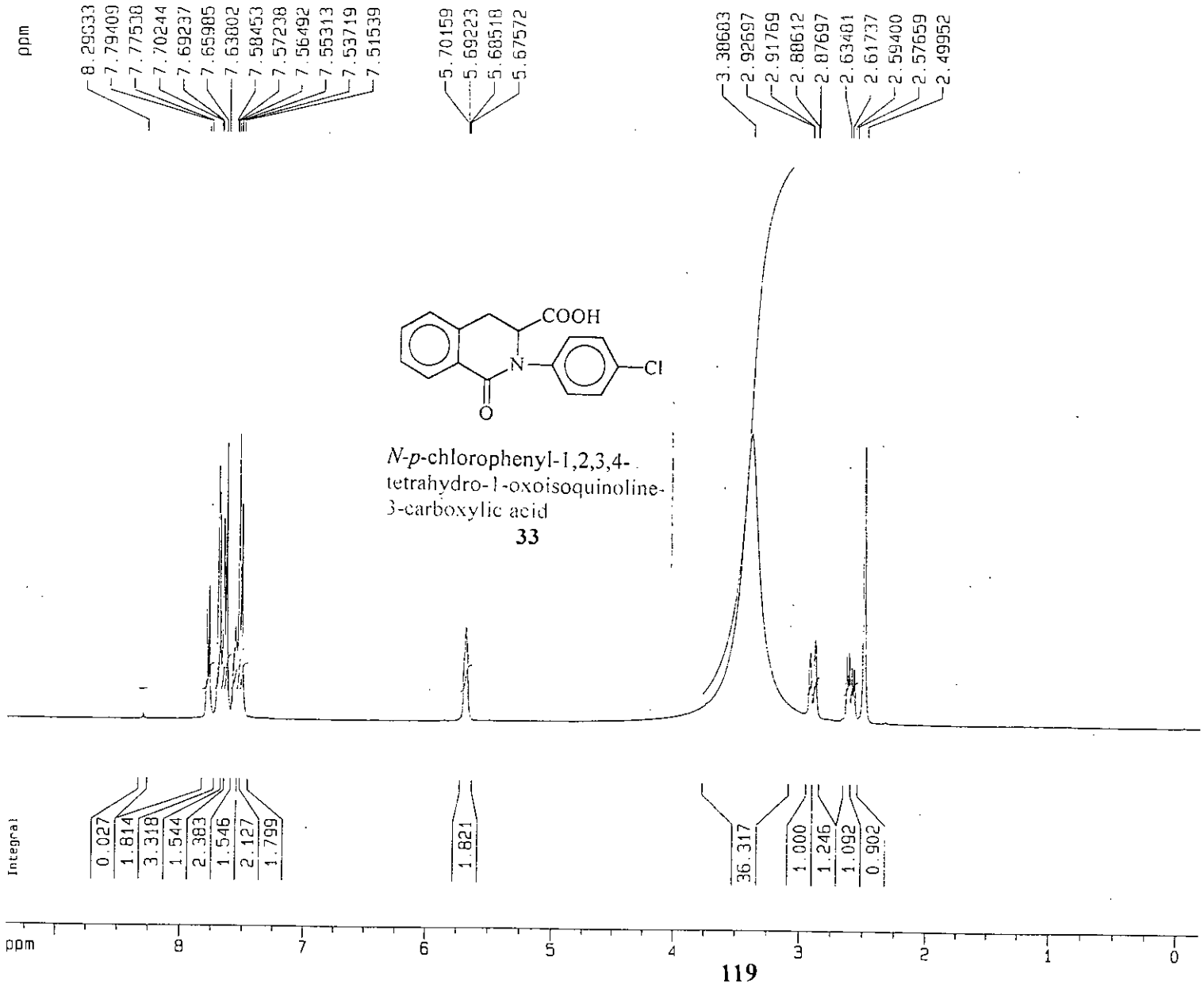
MR-66b, June 26. 2004



N-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

33

118A



N-p-chlorophenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

33

Current Data Parameters

NAME	A1476
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040626
Time	16.57
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	114
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

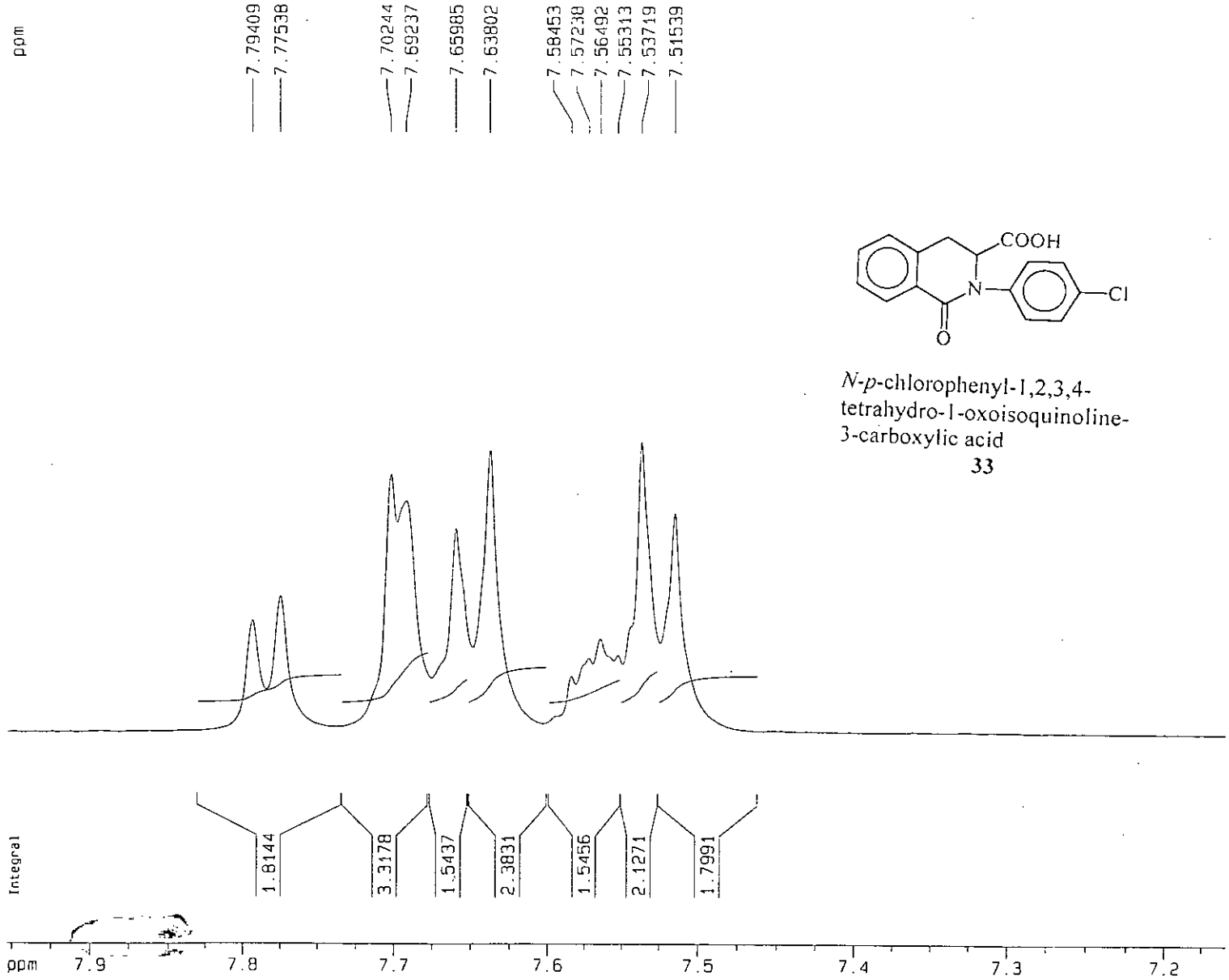
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

SI	32768
SF	400.1400026 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	9.410 ppm
F1	3765.38 Hz
F2P	-0.188 ppm
F2	-75.37 Hz
PPMCM	0.47993 ppm/cm
HZCM	192.03722 Hz/cm



N-p-chlorophenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

33

119A

```
Current Data Parameters
NAME                  A1476
EXPNO                    1
PROCNO                   1

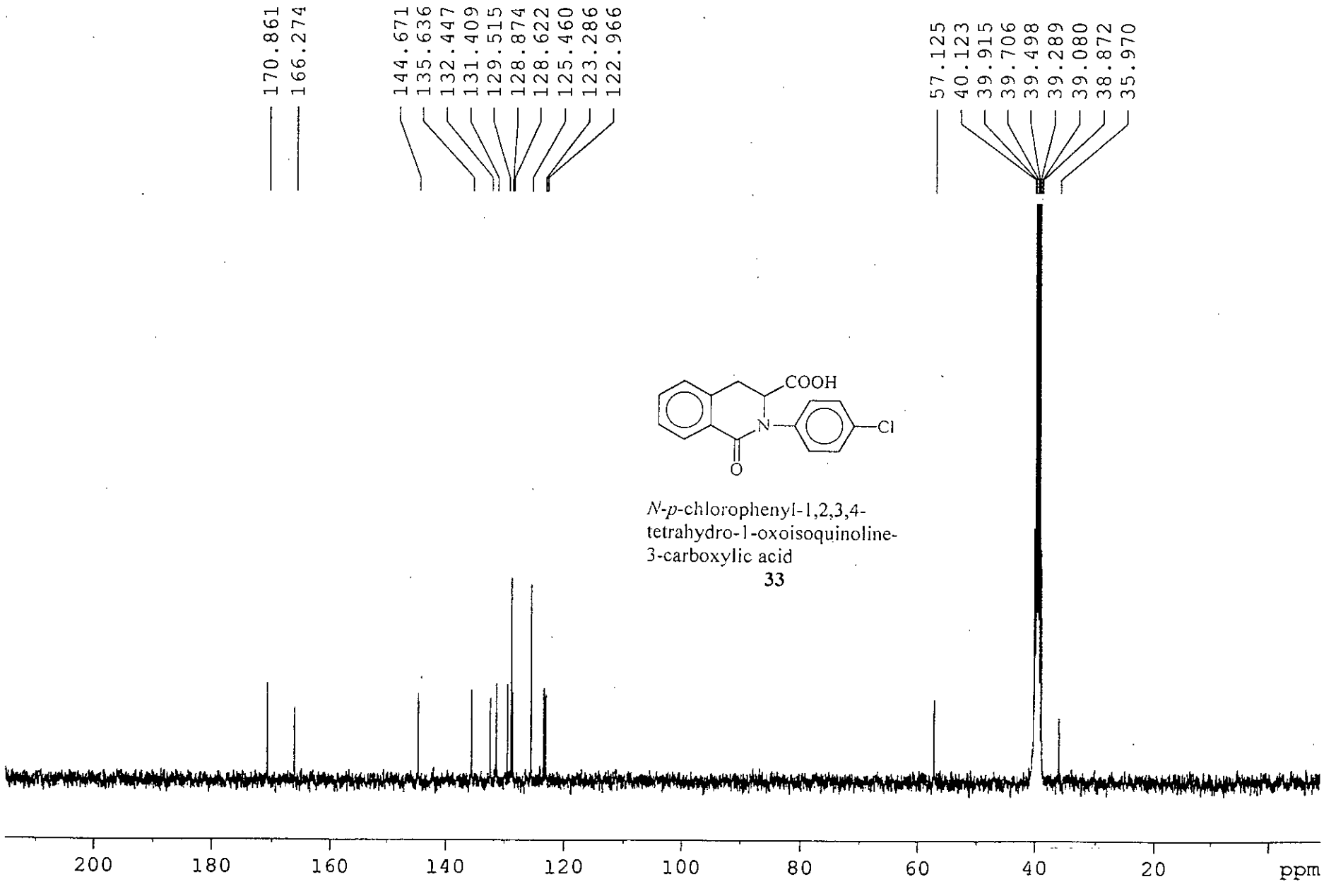
F2 - Acquisition Parameters
Date_              20040626
Time                 16.57
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             Aceton
NS                     128
DS                       2
SWH               6410.256 Hz
FIORES            0.195625 Hz
AQ                2.5559540 sec
RG                     114
DW                 78.000 usec
DE                  6.00 usec
TE                  310.0 K
D1                1.00000000 sec

============ CHANNEL f1 =============
NUC1                    1H
P1                   8.30 usec
PL1                 -6.00 dB
SFO1          400.1428077 MHz

F2 - Processing parameters
SI                   32768
SF            400.1400026 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40

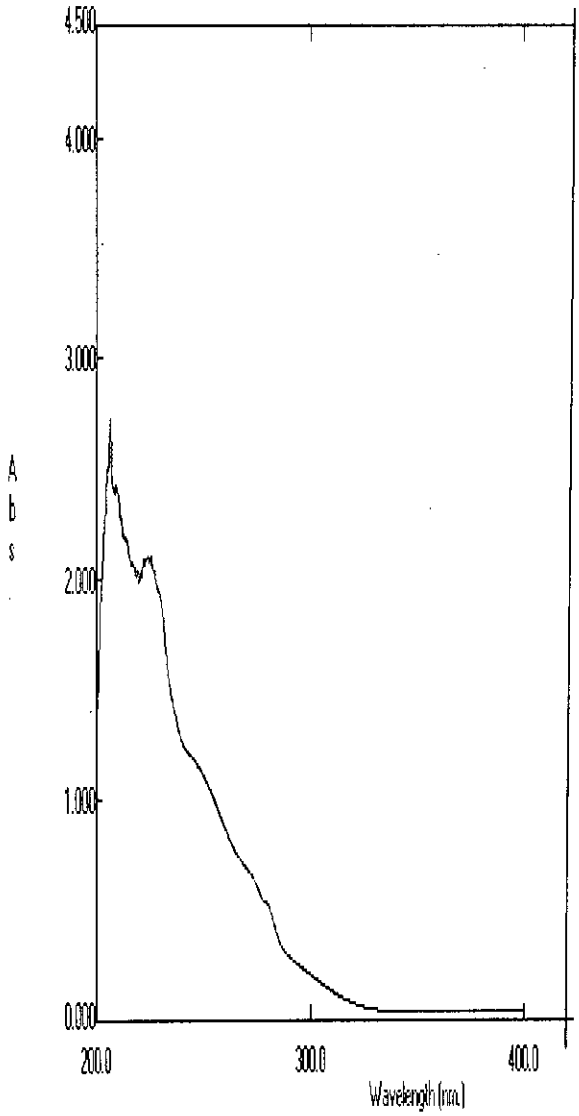
1D NMR plot parameters
CX                   20.00 cm
F1P                 7.953 ppm
F1                3182.39 Hz
F2P                 7.158 ppm
F2                2864.24 Hz
PPMCM             0.03975 ppm/cm
HZCM             15.90752 Hz/cm
```

Analytical, BCSIR, A1476, 13C Spectrum MR-66b in DMSO-d6, M.Reza, BUET



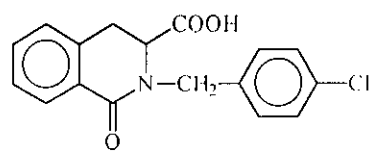
N-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

33



Peak Pick

No.	Wavelength (nm.)	Abs.
1	223.60	2.1117
2	206.20	2.7103



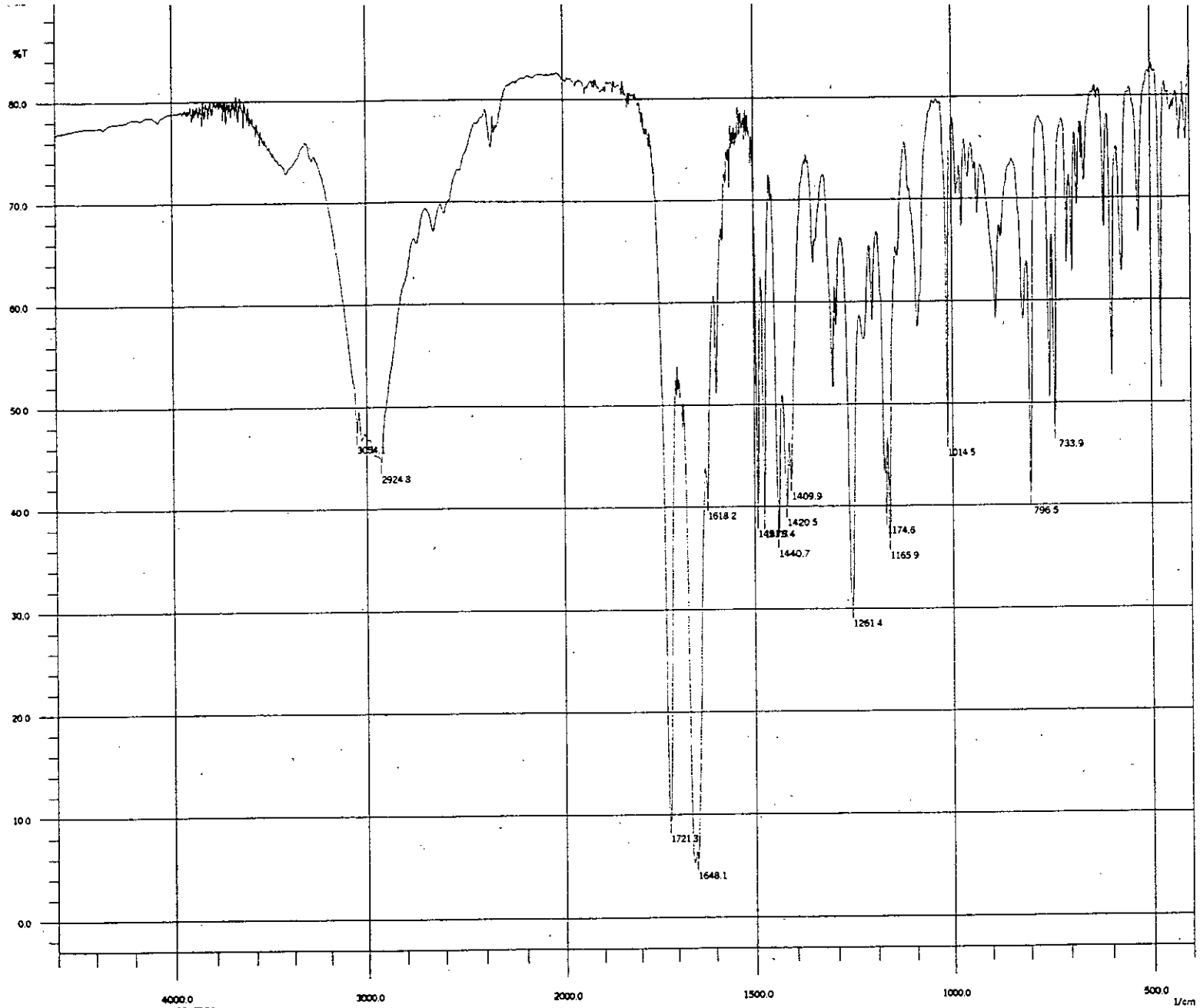
N-p-chlorobenzyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

35

File Name: MR65B

Created: 11:09 08/09/04
Data: Original

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

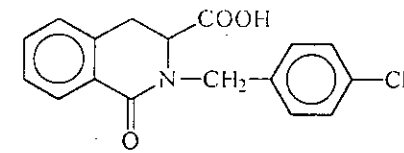


MR-65B.IRS: MR-65b, June 01, 2004

Data:	05/02/2004	Time:	12:30:15	NScans:	45
Type:	HYPER IR	User:	SHIMADZU	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	400.20	Max:	4599.91	Range:	1/cm
Ndp:	4356	Data Interval:	0.96434	Resolution:	2.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(cm)

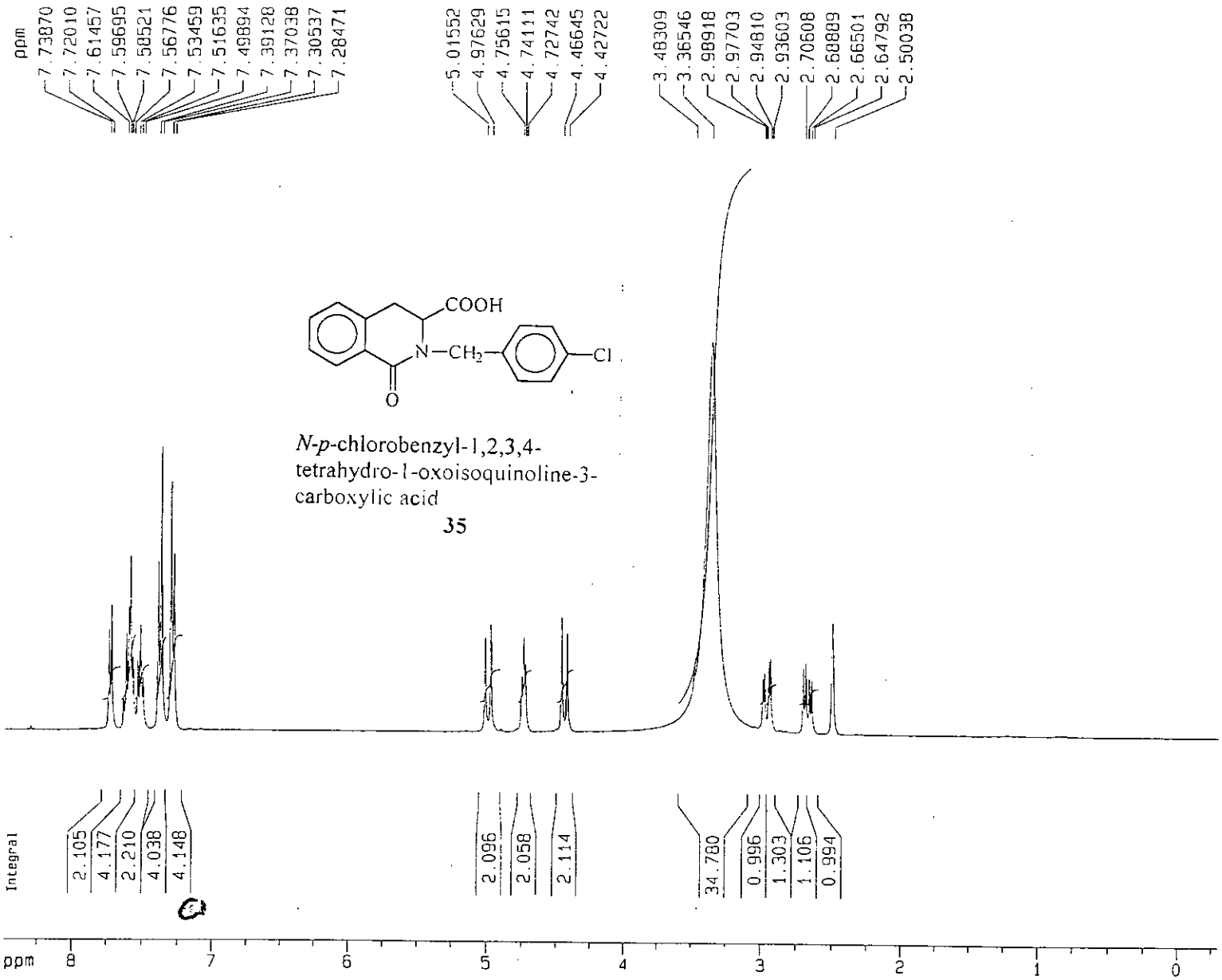
No.	Pos. (1/cm)	Inten. (%T)
1	733.9	47.563
2	796.5	41.072
3	1014.5	46.792
4	1165.9	36.794
5	1174.6	39.227
6	1261.4	30.150
7	1409.9	42.613
8	1420.5	40.071
9	1440.7	37.025
10	1475.4	38.901
11	1491.8	40.286
12	1618.2	40.783
13	1648.1	5.701
14	1721.3	9.328
15	2924.8	44.556
16	3054.1	47.478

MR-65b, June 01. 2004



N-p-chlorobenzyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

35



N-p-chlorobenzyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

35

```
Current Data Parameters
NAME                  A1443
EXPNO                     1
PROCNO                    1

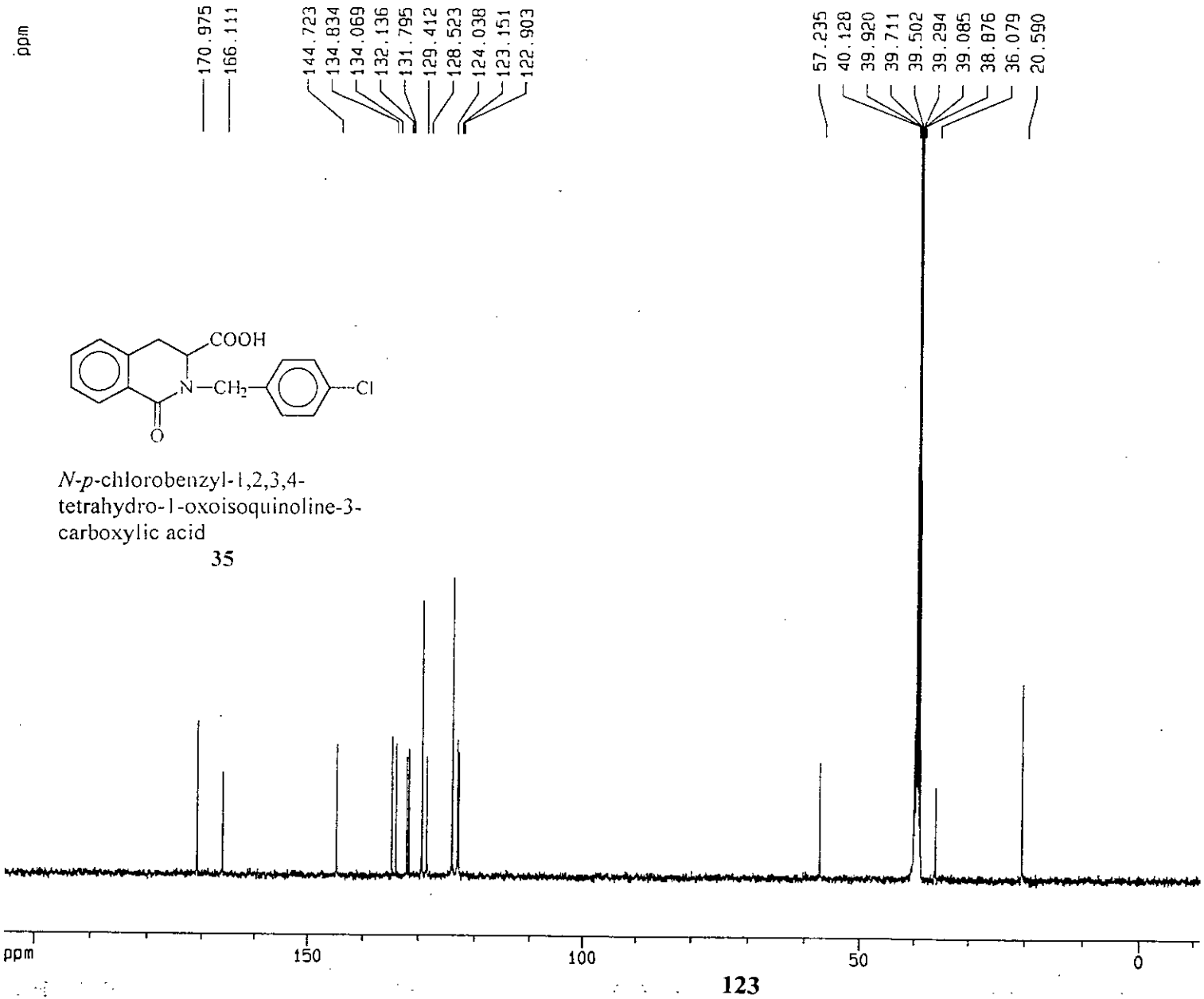
F2 - Acquisition Parameters
Date_              20040610
Time                  11.55
INSTRUM               dpx400
PROBHD     5 mm Multinuc
PULPROG                zg30
TD                    32768
SOLVENT               Aceton
NS                       128
DS                         2
SWH                4816.956 Hz
FIDRES            0.147002 Hz
AQ                3.4013684 sec
RG                       128
DW                 103.800 usec
DE                   6.00 usec
TE                   310.0 K
D1                1.00000000 sec

============ CHANNEL f1 ============
NUC1                      1H
P1                     8.30 usec
PL1                   -6.00 dB
SFO1           400.1421679 MHz

F2 - Processing parameters
SI                    32768
SF             400.1400018 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
CX                    20.00 cm
F1P                   8.486 ppm
F1                 3395.72 Hz
F2P                  -0.301 ppm
F2                 -120.45 Hz
PPMCM             0.43937 ppm/cm
HZCM             175.80872 Hz/cm
```

Analytical, BCSIR Lab. Dhaka 13C Spectrum MA-65b in DMSO, Masud, BUET.



N-p-chlorobenzyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid

35

123

```
Current Data Parameters
NAME                  A1443
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20040613
Time                  11.10
INSTRUM               dpx400
PROBHD     5 mm Multinuc
PULPROG               zgpg30
TD                     32768
SOLVENT                DMSO
NS                      970
DS                        2
SWH               24154.590 Hz
FIDRES            0.737140 Hz
AQ                0.6783476 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 ============
NUC1                     13C
P1                    8.30 usec
PL1                  -6.00 dB
SFO1            100.6253045 MHz

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

F2 - Processing parameters
SI                     32768
SF              100.6153292 MHz
WDW                       EM
SSB                        0
LB                    2.50 Hz
GB                         0
PC                     1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                205.503 ppm
F1                 20676.76 Hz
F2P                -11.258 ppm
F2                 -1133.71 Hz
PPMCM              10.83854 ppm/cm
HZCM             1090.52356 Hz/cm
```

REFERENCES

REFERENCES

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Part – II

Biological Part

Antimicrobial activities of some isoquinolinone derivatives.

Section-1

Introduction

INTRODUCTION

From the time immemorial when the man needed medicine, most probably when the men realized about the cause of disease, they have been tried to discover any preventive agent against disease, from that time. It is a universal truth that disease, decay and death have always co-existed with human life. The study of disease and their treatment must also have been come together with human intellect, when the man occupied sufficient knowledge of chemistry to able to synthesize compounds. Bangladesh is predominantly an agricultural country, depending mainly on crop plants, agricultural 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-organisms play a significant role. Various chemicals 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, Bactericides, Viricides etc.

The word 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 or 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 are used to control the microbial pathogen of human and other animals as medicine. The number of chemicals available for plant disease 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 Dexon (dimethylaminobenzendiazo sodium sulphonate), Diconil (tetrachloro isohpthaloutrile) etc. Heterocyclic nitrogen 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[1-5], when heterocyclic part like imidazoles, nitroimidazole etc. become attached to carbohydrates[6], their efficacy to inhibit fungi or bacteria sharply increased.

It was also found that large number of biologically active compounds 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[7]. 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 enhances the biological profile many fold than its parent nuclei. S. M. Shehab[8,9], a post graduate student of Chittagong University laboratory, performed antifugal 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[10] 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. Shehed[11,12] a former research student of organic laboratory in Chittagong University carried out antifungal activities of a series of acylated D-mannore derivatives. He used four phytophathogenic fungi, such as *Macrophomma phaseolina*, *Fusarium equiseti*, *Alternaria alternata and Curvularia lunata*. Most of the tested chemicals showed good inhibition (more than 50% grouth against the above organism).

S. M. Abe Kawasar[13,14] also a former post 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 cercus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Shigella dysenterial*, *Shigella dysernterial INABA-ET (vibrio) and Sarcina lutea*. It was observed that most of the acylated compounds exihibited moderate to good antibacterial activity. Amongest the acylated compounds exhibit moderate to good antibacterial activity.

M. Fakruddin[15] carried out antifungal actives of fused pyrimidine. He used five human pathogenic bacteria, viz. *Bacillus subtilis*, *Bacillus megaterium*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and four phytopathogenic fungi, *Viz Verticillum SP*, *Fusarium solanae*, *Aspergilius SP. Penicillum SP*. He found that some of the tested chemicals showed very effective antibacterial and antifungal activity.

Section-2

Methodology of the Biological Work

2.2.1. Materials and Methods:

Bacteria and fungi are responsible for many infections diseases. The increasing clinical importance of drug resistant microbial pathogens has lent additional urgency to antimicrobial research. The antimicrobial screening which is the first stage of antimicrobial research is performed to ascertain the susceplibility of various microbes to any agent. This test measures the ability of each antimicrobial agent to inhibit the in *vitro* microbial growth.

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

i) Disc diffusion method

ii) Serial dilution method

iii) Bioautographic method.

The disc diffusion technique (Bauer et al[16], 1966) is a widely accepted in *vitro* investigation for preliminary screening of agents which may possess any antibacterial activity. It is essentially a quantitative or qualitative test indicating the sensitivity or resistance of the microorganisms to the test materials. However, no distinction between baceriostatic or bactericidal activity can be made by this methode. (Roland[17], R, 1982).

2.2.2. Principle of Disc Diffusion method:

Solutions of known concentratoin (μg/mL) of the test samples are made by dissolving measured amount of the samples in definite volume of solvents. Dried and sterilized filter paper discs (6 mm diameter) are then impregnated with known amounts of the test substances using micropipette. Discs containing the test material are placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard antibiotic discs and blank discs (impregnated with solvents) are used as positive and negative control. These plates are then kept at low temperature (4°C) for 2h h to allow maximum diffusion. During this time dried discs absorb water from the surrounding media and then the test materials are dissolved and diffused out of the media. The diffusion according to the physical law that controls the diffusion of molecules through agar gel. As a result there is a gradual change of test materials concentration in the media surrounding the discs. The

plates are then incubated at 37°C for 24h to allow maximum growth of the organisms. If the test materials have any antibacterial activity, it will inhibit the growth of the microorganisms giving a clear, distinct zone called "Zone of Inhibition". The antibacterial activity of the test agent is determined by measuring the diameter of zone of inhibition expressed in millimeter.

The experiment is carried out more than once and the mean of the readings is required (Bauer *et al*[16], 1966). In the present study some pure compounds were tested for antibacterial activity by disc diffusion method.

2.2.3. Experimental:

2.2.3.A. Apparatus and Reagents:

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

2.2.3.B. Test of Organisms:

The bacterial strains used for the experiment were collected as pure cultures from the Institute of Nutrition and Food Science (INFS). University of Dhaka. Both Gram positive and Gram negative organisms and fungi were taken for the test and they are listed in the table–6 and 7.

Table-6 : List of Test Bacteria

Gram positive	Gram negative
Bacillus cereus	*Aeromonus hydrophilia*
Bacillus megaterium	*Escherichia coli*
Bacillus subtilis	*klebsiella SP.*
staphylococcus aureus	*Pscudomonas aeruginosa*
Sarcina lutea	*Salmonella paratyphi* A
	Salmonella paratyphi C
	Salmonella paratyphi SPP
	Sheigella boydii
	Shigella dysenteri
	Shigella flexneriae
	Shigella sonnei
	Vibrio mimicus
	Vibrio parahemolyticus

Table-7 : List of Test Fungi.

Fugi
Aspergillus niger
Candida albicans
Rhizopus oryzae
Saccharo myces cerevisiae

2.2.4. Test of Materials:

Table-8 : List of Test Materials.

Compounds No.	Name of test materials
10	2-Iodo-*N*-methyl benzamide
11	2-Iodo-*N*-*p*-chloro benzyl benzamide
12	2-Iodo-*N*-phenyl benzamide
13	2-Iodo-*N*-*p*-methyl phenyl benzamide
14	2-Iodo-*N*-*p*-methoxy phenyl benzamide
15	2-Iodo-*N*-*p*-chloro phenyl benzamide
22	*N*-phenyl-3-butyl isoindolin-1-one acetate
23	*N*-*p*-methylphenyl-3-butyl isoindolin-1-one acetate
24	*N*-*p*-methoxyphenyl-3-butyl isoindolin-1-one acetate
25	*N*-*p*-chlorophenyl-3-butyl isoindolin-1-one acetate
26	*N*-*p*-methylphenyl-3-ethyl isoindolin-1-one acetate
27	*N*-*p*-methoxyphenyl-3-ethyl isoindolin-1-one acetate
28	*N*-*p*-methylphenyl-3-methyl isoindolin-1-one acetate
29	*N*-*p*-methoxyphenyl-3-methyl isoindolin-1-one acetate
30	*N*-phenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid
31	*N*-*p*-methylphenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid
32	*N*-*p*-methoxyphenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid
33	*N*-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid
34	*N*-methyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid
35	*N*-*p*-chlorobenzyl-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acid

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 materials were detected by disc diffusion method [Bauer *et al*[16], 1966] and antifungal activity of the materials were assessed by food poison technique [Miah *et al*[18], 1990 and Grover *et al*[19], 1962]. This media were also used to prepare fresh cultures.

2.2.6. Medium Used:

Nutrient Agar (NA) and potato Dextrose Agar (PDA) were used through out the work. The composition and preparation procedure of NA and PDA are described below.

2.2.6.A. Composition of Nutrient Agar Medium:

Ingredients	Amounts (gm/lit)
Peptone	5.0
Sodium chloride	5.0
Beef extract	1.5
Yeast extract	1.5
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 constituents was taken in a conical flask and distilled water was added to it to make the required volume. The contents were heated in a water bath to make a clear solution. The pH (at 25°C) was adjusted at 7.2–7.6 using NaOH or HCl. 10ml 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 auto calving at 15 – 1bs/sq, pressure at

121°C for 20 minutes. 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	Amounts (gm/lit)
Potato	200.0
Dextrose	20.0
Agar	15.0 g

Procedure:

200g 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 20g dextrose was added slowly in the solution. Then 15g of agar powder was added in the solution and they were mixed throughly with a glassrod. After 10 minutes of boiling the medium was transferred in 250 ml conical flash. Before autoclaving 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 15–1bs/sq pressure. After autoclaving the medium was used for culture of different microorganisms.

2.2.7. Sterilization Procedures:

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 15–1 bs/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 cabinet, 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 24h 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 suspension was immediately transferred to the sterilized petridishes. The petridishes were rotated several times clockwise and anticlockwise to assure homogenous distribution of the best organisms in the media.

2.2.10. Preparation of Discs:

Three types of discs were used for antibacterial screening.

2.2.10.A. Standard Discs:

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

2.2.10.B. Blank Discs:

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

2.2.10.C. Preparation of 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 discs, the standard antibiotic discs and the control discs were placed gently on the previously marked zones in the agar plates pre-inoculated with test bacteria. The plates were then kept in a refrigerator at 4°C for about 24h 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 24h.

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

After incubation, the antibacterial actives of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale.

Section-3

Results and Discussion

2.3.1. RESULTS AND DISCUSSION

A total of six benzamides (**10, 11, 12, 13, 14** and **15**), eight isoindolinone derivatives (**22, 23, 24, 25, 26, 27, 28** and **29**) and six isoquinolinone derivatives (**30, 31, 32, 33, 34** and **35**) have been tested for in vitro antimicrobial activity against five Gram positive and twelve Gram negative bacteria as well as four human fungal pathogens. The selected microbes were 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. The antimicrobial activities were measured in terms of diameters of zone of inhibition (mm). All the experiments were performed thrice to minimize the experimental plus individual errors. The mean value of the diameters of zone of inhibition (M.DIZ) were taken as indisc for determining antimicrobial spectra. Sensitivity test results are interpreted in (tables 9, 10, 11) and were compared with a standard antibiotic kanamycin (30 μg/dise).

The Gram positive as well as Gram negative bacteria used in the present investigation, were found to be completely resistant against six benzamide derivatives (**10, 11, 12, 13, 14,** and **15**), at a dose level of 200 μg/dise (table-9), compounds **10, 13**, and **15** showed mild in *Vitro* antimicrobial activity, especially against the fungi, *Candida albicans* **10** (M.DIZ 10), **13**(M.DIZ 10), **15**(M.DIZ 12) and *Saccharomyces cerevaceae* **15** (M.DIZ 8). *Aspergillus niger* and *Rhizobus oryzae* were, however, resistant to the compound (Table-9). The compounds **11, 14**, and **15** showed mild in vitro antimicrobial activity especially against the Gram positive *Bacillus cereus* **11**(M.DIZ 9), **15**(M.DIZ 7), *Bacillus megaterium* **14**(M.DIZ 7) and *Staphylococcus aureus* **11**(M.DIZ 11) and **15**(M.DIZ 7). Compound **15** showed only in vitro antimicrobial activity, especially against the Gram negative *Salmonella paratyphi* A (M.DIZ 9). This study can therefore, confer that substitution at the amido nitrogen reduces antimicrobial activity through it does not conclude that the amido group is essential for such microbial group inhibition.

In the arsenal of isoindolinone derivatives, there appears to be no effective warhead to combat the selected organisms. The screening of eight isoinodolinone derivatives (**22, 23, 24, 25, 26, 27, 28** and **29**) demonstrated only mild inhibitory activity with zones of

inhibitions ranging from **6** to **11** mm. (table-10). Among the tested compounds **23** and **25** were found to be completely resistant against the tested organisms. Therefore, it is not possible to determine the essential structural features for antimicrobial action of this series of compounds.

The six insoquinolinone derivatives (**30, 31, 32, 33, 34,** and **35**) exhibited mild to moderate degrees of bacterial group inhibition at 200 μg/disc dose level (Table-11). Among the selected microbes, *Bacillus organisms, salmonella paratyphi* A, *Vibrio minicus*, *Salmonella paratyphi* C and *Saccharomyces cerevaceae* were found to be sensitive towards these size carboxylic acid (**30, 31, 32, 33, 34**, and **35**). It appears that the cyclic moiety of *N*-substiuted-1,2,3,4-tetralyotro-1-oxoisoquinoline-3-carboxylic acids are necessary for antimicrobial action since the corresponding open chain benzamides (**10, 11, 12, 13, 14** and **15**) (Table-9) and *N*-substituted-3-alkyl isoindolinone-1-one acctate (**22, 23, 24, 25, 26, 27, 28** and **29**) (Table-10) were completely resistant to these bacteria (Tables- 9, 10 and 11). In the present investigation, the decarboxylated derivatives of (**30, 31, 32, 33, 34** and **35**) were not synthesized and not tested for their inhibitory activity. Therefore, it is not possible to conclude that the carboxylic acid group is required for antimicrobial action although its presence increases hydrophilicity.

2.3.2. Conclusion:

Six benzamides (**10, 11, 12, 13, 14** and **15**), eight isoinolinone derivatives (**22, 23, 24, 25, 26, 27** and **28**) and six isoquinolinone derivatives (**30, 31, 32, 33, 34** and **35**) have been tested for in antimicrobial activity against five Gram positive and twelve Gram negative bacteria as well as four human fungal pathogens. Most of this compound demonstrated mild to moderate antimicrobial activity against most of the test organism. Among tested compounds isoquinolinone derivatives (**30, 31, 32, 33, 34** and **35**) exhibited relatively greater inhibition of growth of the microorganism as comparative to the benzamides (**10–15**) and isoindolinone (**22–29**) analogus. The higher activity of the compounds (**30–35**) could probably be due to their greater solubility in aqueous medium, which

subsequently facilitated the diffusion of the chemical entities through the microbial call wall.

Substitution of Hydrogen of the ring nitrogen, with bulkier aromatic group increase in the antimicrobial activity of the compounds **30–33** and **35** while methyl substitution at the same place produce weakly active compound **34**.

However, substitution at para-position of the bulky phenyl group with (*p*-chlorophenyl functionality) **33** or (*p*-chlorobenzyl residue) **35** revealed better microbial growth inhibition then such substitution with only **33**.

Table-9: In *Vitro* Antimicrobial activity of 2-Iodo-*N*-subustituted benzamides.

Diameter of Zone of Inhibition (mm)							
Done	200	200	200	200	200	200	30
Microorganism	**10**	**11**	**12**	**13**	**14**	**15**	Kan
Gram positive							
Bacillus cereus	-	9	-	-	-	7	22
Bacillus megaterium	-	-	-	-	7	-	24
Bacillus subtilis	-	-	-	-	-	-	23
Sarcina lutea	NT	NT	NT	NT	NT	NT	24
Staphylococcus aureus	-	11	-	-	-	7	23
Gram negative							
Aeromonas hydrophilia	NT	NT	NT	NT	NT	NT	20
Escherichia coli	-	-	-	-	-	-	22
Pseudomonas aepuginosa	-	-	-	-	-	-	31
Salmonella paratyphi spp							24
Salmonella paratyphi A	-	-	-	-	-	9	21
Salmonella paratyphi C	NT	NT	NT	NT	NT	NT	23
Shigella boydii	NT	NT	NT	NT	NT	NT	23
Shigella dysenteriae	-	-	-	-	-	-	23
Shigella flexneri	-	-	-	-	-	-	23
Shigella sonnei	NT	NT	NT	NT	NT	NT	25
Vibrio mimicus	-	-	-	-	-	-	22
Vibrio parahemolyticus	-	-	-	-	-	-	22
Fungi							
Aspergillus niger	-	-	-	-	-	-	22
Candida albicans	10	-	-	10	-	12	19
Rhizopus oryzae	-	-	-	-	-	-	24
Saccharo myces cerevaceae	-	-	-	-	-	8	24

Interpretation of sensitivity test results:

Gram (+) bacteria;
> 18 mm (M.DIZ) = sensitive;
14-18 mm (M.DIZ) = intermediate;
< 14 mm (M.DIZ) = resistant;

Gram (-) bacteria
> 16 mm (M.DIZ) = sensitive;
13 – 16 mm (M.DIZ) = intermediate;
< 13mm (M.DIZ) = resistant.

'-' indicates no sensitivity or zone of inhibition lower than 6 mm and NT refers to "Not Tested"

Table-10: In *Vitro* Antimicobial activity of *N*-subtituted-3-alkyl isoindolin-1-one acetates.

Diameter of Zone of Inhibition (mm)									
Done	200	200	200	200	200	200	200	200	30
Microorganism	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	Kan
Gram positive									
Bacillus cereus	7	-	10	6	8	8	9	7	22
Bacillus megaterium	9	-	9	-	8	10	8	-	24
Bacillus subtilis	8	-	10	-	7	9	9	-	23
Sarcina lutea	7	-	7	-	6	8	9	-	24
Staphylococcus aureus	10	-	9	7	9	9	9	-	23
Gram negative									
Aeromonas hydrophilia	9	-	9	-	7	8	8	-	20
Escherichia coli	8	-	8	-	6	9	9	-	22
Pseudomonas aepuginosa	6	6	9	-	7	7	8	-	23
Salmonella paratyphi spp	8	6	9	6	6	9	8	-	24
Salmonella paratyphi A	10	-	7	6	7	8	8	-	21
Salmonella paratyphi C	8	-	9	6	7	9	10	9	23
Shigella boydii	6	7	10	7	7	8	8	-	23
Shigella dysenteriae	8	6	9	6	6	6	9	-	23
Shigella flexneri	7	-	9	7	6	7	9	-	23
Shigella sonnei	9	9	9	7	9	8	11	7	25
Vibrio mimicus	9	6	10	7	6	9	8	6	22
Vibrio parahemolyticus	9	-	7	7	6	9	7	8	22
Fungi									
Aspergillus niger	NT	NT	NT	NT	NT	NT	NT	NT	22
Candida albicans	6	NT	NT	-	-	-	-	-	19
Rhizopus oryzae	8	6	8	8	7	8	7	-	24
Saccharo myces cerevaceae	-	-	-	-	-	-	-	-	24

Interpretation of sensitivity test results:

Gram (+) bacteria;
> 18 mm (M.DIZ) = sensitive;
14-18 mm (M.DIZ) = intermediate;
< 14 mm (M.DIZ) = resistant;

Gram (-) bacteria
> 16 mm (M.DIZ) = sensitive;
13 – 16 mm (M.DIZ) = intermediate;
< 13mm (M.DIZ) = resistant.

'-' indicates no sensitivity or zone of inhibition lower than 6 mm and NT refers to "Not Tested"

Table-11: In *Vitro* Antimicrobial activity of 2-Iodo-*N*-subustituted- 1, 2, 3, 4-tetrahydro-1-oxo isoquinoline-3-carboxylic acids.

Diameter of Zone of Inhibition (mm)							
Done	200	200	200	200	200	200	30
Microorganism	**30**	**31**	**32**	**33**	**34**	**35**	Kan
Gram positive							
Bacillus cereus	11	14	15	13	9	14	26
Bacillus megaterium	11	10	16	13	10	14	21
Bacillus subtilis	9	8	13	13	7	12	23
Sarcina lutea	NT	NT	NT	NT	NT	NT	24
Staphylococcus aureus	-	-	12	11	-	13	22
Gram negative							
Aeromonas hydrophilia	NT	NT	NT	NT	NT	NT	20
Escherichia coli	-	-	9	-	-	7	20
Pseudomonas aepuginosa	8	8	7	7	8	7	23
Salmonella paraty phi spp	NT	NT	NT	NT	NT	NT	24
Salmonella paratyphi A	8	8	12	10	10	12	21
Salmonella paratyphi C	12	12	13	-	12	-	23
Shigella boyd ii	-	-	-	-	-	-	23
Shigella dysenteriae	-	-	-	-	-	-	23
Shigella flexniri	-	-	-	-	-	-	23
Shigella sonnei	-	-	-	-	-	-	25
Vibrio mimicus	12	-	-	-	12	10	22
Vibrio parahemolyticus	-	10	-	-	-	-	22
Fungi							
Aspergillus niger	7	10	7	9	8	10	22
Condida albicans	-	8	10	8	-	12	19
Rhizopus oryzae	-	-	-	-	-	9	24
Saccharo myces cerevaceae	6	7	12	12	6	12	24

Interpretation of sensitivity test results:

Gram (+) bacteria;
> 18 mm (M.DIZ) = sensitive;
14-18 mm (M.DIZ) = intermediate;
< 14 mm (M.DIZ) = resistant;

Gram (-) bacteria
> 16 mm (M.DIZ) = sensitive;
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'-' indicates no sensitivity or zone of inhibition lower than 6 mm and NT refers to "Not Tested"

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