SYNTHESIS OF ISOINDOLINES AND ISOINDOLINONES BY PALLADIUM CATALYZED REACTIONS

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

Submitted by

Md. Delwar Hossain
Roll No.# 9603101P
Registration No.# 961801
Session: 1995-96-97

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

August, 2003

DEDICATED
TO
MY PARENTS

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

THESIS ACCEPTANCE LETTER

The thesis titled **"Synthesis of Isoindolines and Isoindolinones by Palladium Catalyzed Reactions"** Submitted by **Md. Delwar Hossain.** Roll No. 9603101P, Registration No. 961801 Session 1995-96-97 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Master of Philosophy (M. Phil.) on August 2003.

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

Signature of the Candidate

Md. Delwar Hossain

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Author

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Thesis Title: "Synthesis of Isoindolines and Isoindolinones by palladium catalyzed Reactions."

Abstract

Isoindolin-1-ones (or 2,3-dihydro-*1H*-isoindol-1-one (phthalimidine) and Isoindoline (2,3-dihydro-*1H*-isoindole) moieties are integral parts of some natural products and have generated considerable interest in recent years for their biological and medicinal properties. A number of 2-substituted isoindolin-1-one was synthesized and their in *vitro* antimicrobial activity was evaluated. A highly regio-and stereoselective method for the synthesis of (Z)-3-aryl(alkyl)idene isoindolinones through palladium-copper catalysis is described. The reactions were carried out by heating a mixture of 2-iodobenzamides and its *N*-substituted derivatives and alkynes in DMF/THF at 80–85 °C / room temperature for 16 h / 24 h in presence of bis(triphenyl phosphine) palladium (II) chloride, copper (I) iodide and triethylamine to yield 2-alkynyl benzamide which could then be cyclized with NaOEt in EtOH to the 3-aryl(alkyl)idene isoindolinones. In certain cases, the isoindolinones could be directly obtained by the palladium-copper catalyzed reaction. It was attempted to synthesize 3-substituted isoindoline from 2-iodobenzamides and also from 3-substituted isoindolin-1-ones but failed. The synthesized compounds showed poor growth inhibition against antibiotic-susceptible standard and clinically isolated strains of gram-positive and gram-negative bacterial as well as human fungal pathogens.

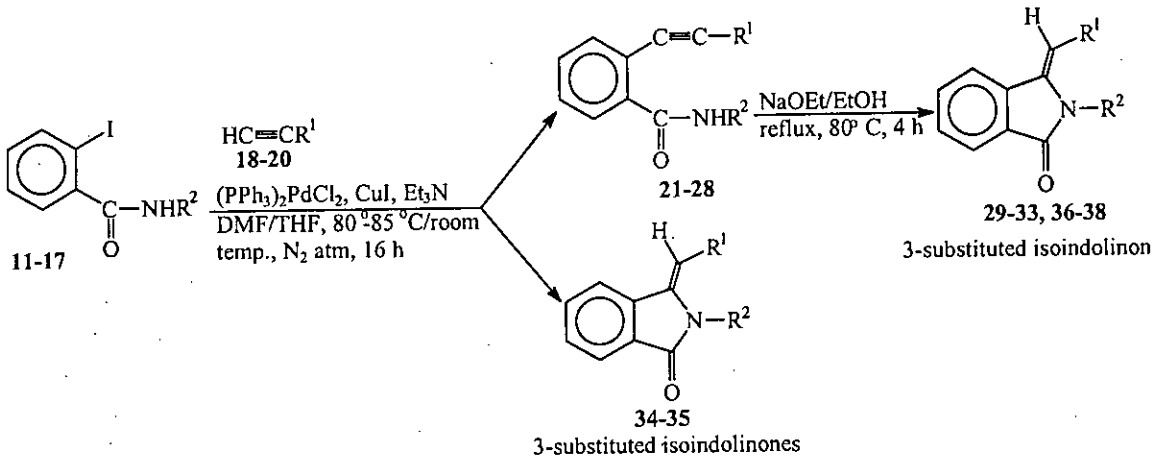
Summary

Investigations incorporated in this dissertation entitled "**Synthesis of isoindolines and isoindolinones by palladium catalyzed reactions**" have been presented in four sections. In section-1 background of biological importance and the important synthetic reactions involved in the syntheses are presented. Section-2 & 4 deal with the detailed methodologoy and experimental procedures for the synthesis of 3-substituted isoindolinones and isoindolines respectively. Section-3 deals with the detailed biological importance of 3-substituted isoindolin-1 ones.

Section–1 represents the importance and synthesis of isoindolinone derivatives. Heterocyclic compounds containing the isoindolinones moiety are of great interest because of their occurrence in nature and their fascinating pharmaceutical and medicinal activities. Although various methods have been developed previously for the synthesis of isoindolinones, only a few of them were mediated through palladium catalysis.

In section-2, the syntheses of 3-substituted isoindolin-1 ones **29–38** through the palladium catalyzed reactions from 2-Iodobenzamides **11–17** are presented. The reactions were usually carried out by heating a mixture of 2-Iodobenzamide or its *N*-substituted derivatives **16, 17** and alkyne **18** in DMF / THF at 80 – 85 °C for 16 h in the presence of bis (triphenyl phosphine) palladium (II) chloride, copper (I) iodide, triethylamine to yield 3-substituterd isoindolin-1-ones 34, 35 directly in excellent yields. 2-Iodobenzamide **11–15** afforded 2-alkynyl benzamide **22-25** through the same reaction with phenylacetylene **18**. 2-Alkynyl benzamides **21–25** were cyclized with sodium ethoxide with ethanol at 80 °C for 4 h to afford the 3-substituted isoindolin-1-ones **29–33**. In the case of (trimethylsilyl) acetylene **19** and n-hexyne **20**, the palladium catalyzed reactions were performed at room temperature for 24 h to yield 2-alkynyl benzamides **26–28** which were cyclized to form 3-substituted isoindolin-1-ones **36–38** as shown in **Scheme 1**.

The starting materials 2-Iodo benzamides **11–17** were prepared from 2-Iodobenzoic acids which were synthesized from anthranilic acids via sandmeyer iodination with potassium iodide according to the known literature procedure.



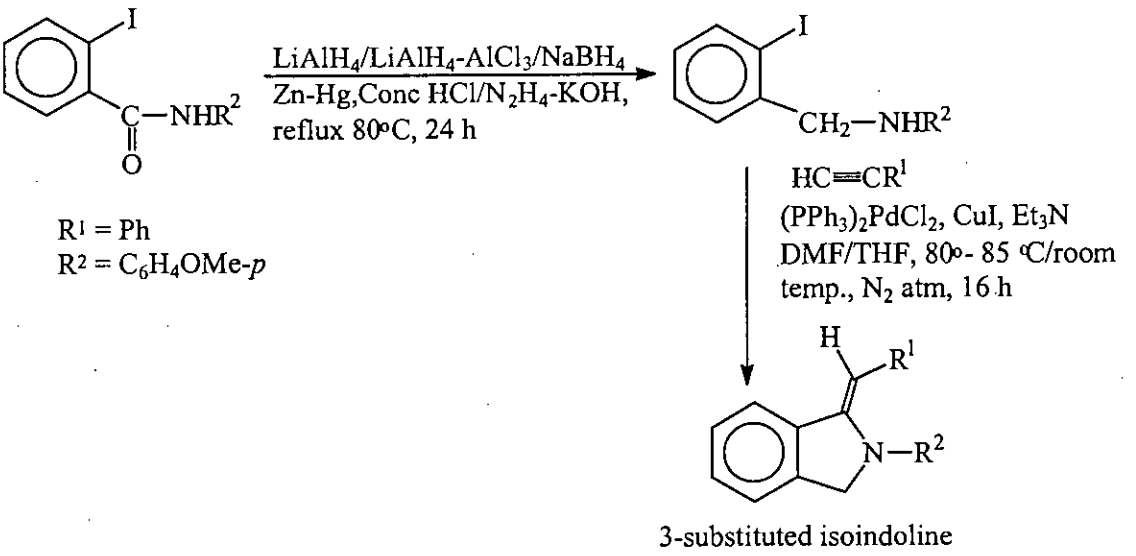
Scheme-1

Compounds	R^1	R^2
11 18 21 29	Ph	C_6H_4Cl-*p*
12 22 30	Ph	$CH_2C_6H_4Cl$-*p*
13 23 31	Ph	H
14 24 32	Ph	CH_3
15 25 33	Ph	CH_2Ph
16 34	Ph	C_6H_4OMe-*p*
17 35	Ph	Ph
17 19 26	$SiMe_3$	Ph
16 27	$SiMe_3$	C_6H_4OMe-*p*
16 20 28 38	$(CH_2)_3CH_3$	C_6H_4OMe-*p*
36	H	Ph
37	H	C_6H_4OMe-*p*

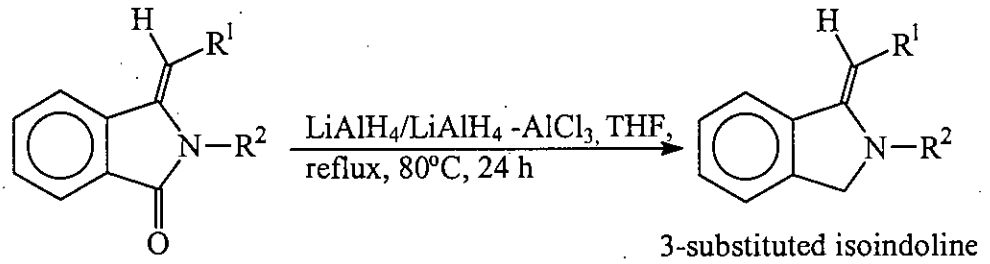
In section-3, the test for the antibacterial and antifungal activity of the compounds 16, 21, 22, 29, 30, 31, 32, 34, 35 through antimicrobial screening are reported. Sixteen bacterial strains and four fungi strains were used to study the antibacterial and antifungal activity of the compounds at the higher concentration 200 μg/disc. The compound 16 showed moderate activity (17 mm) against *Rhizopus oryzae* (fungi). On the other hand rest of the compounds exhibited very poor activity (Table-4 in section-3).

In section-4, a new strategy of the synthesis of 3-substituted isoindolines is presented. At first we attempted to prepare 2-Iodo–*N*-substituted benzylamine by heating a mixture of 2-Iodo-*N*-*p*-anisyl benzamide and $LiAlH_4$ / $LiAlH_4$–$AlCl_3$/$NaBH_4$/ Na–Hg in conc HCl/N_2H_4–KOH in THF/dioxane (scheme 2) at 80 °C for 24 h to obtain a bluish coloured needles. In all cases, spectral data were found to be identical with that of starting

materials and small amount of starting materials were decomposed. So we did not carry out further palladium catalyzed reactions.



Scheme-2



Scheme-3

We also attempted to synthesize 3-Benzylidene-*N*-*p*-anisyl isoindoline (**Scheme 3**) from 3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one by the reaction of $LiAlH_4$ in THF at 80 °C for 24 h to afford a light yellowish needles. Starting materials also came back and small amount of the starting materials were decomposed.

Prefatory Note

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

Analytical or laboratory grade solvents and chemicals were used in all experiments and these were procured from E. Merck (Germany) and Fluka (Switzerland). Commercial grade of $CHCl_3$, n-hexane, ethylacetate, methanol, acetone etc. were purified by distillation at the boiling point of the respective solvent. Petroleum ether used during this research work had boiling point $40^0 - 60^0$C.

Melting Point:

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

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.

Nuclear magnetic resonance (NMR) spectra:

The ^{1}H NMR spectra were recorded in $CDCl_3$ with a Ultra shield (Bruker) Spectrophotometer (400 MHz) at BCSIR, Dhaka, Bangladesh.

Techniques and application 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 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 components 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 horizontal 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 the 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 the absorbent layer.

v) Chamber saturation etc.

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

Column Chromatography:

Column chromatography has been successfully applied to separate the 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 was 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 etc. and slurry of silica gel in the chosen solvent was poured into it, so that the packing was compact and uniform.

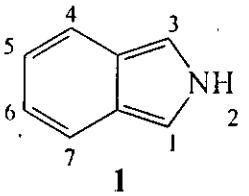
Air bubble was removed by making the column as quickly as possible and allowing the solvent to fall drop by drop through the stop cork of the column. The mixture of the components was then placed on the upper surface of the slurry of the silica gel and the mixture was covered in limited area by some 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 the respective fractions were detected by TLC. The solvent used for elution was chromatographically pure.

Section-1

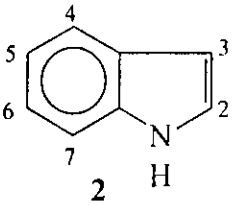
Isoindolinones (Phthalimidines)
Back ground of the present work

I. Introduction

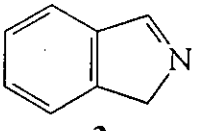
Isoindole **1** is isomeric with indole **2** which comprises a benzene ring fused with a pyrrole nucleus[1a]. The parent compound and the 2-unsubstituted derivatives can tautomerize with the 1H isomer, i.e.isoindolenine or (1H-isoindole)**3**[1a,b]. Isoindole is much more unstable compared with indole and undergoes rapid oxidation in air to form polymers[1a]. Isoindole is thermodynamically more stable than its isoindolenine isomer at room temperature[1a]. The next stable reduction state of isoindole is isoindoline **4**. Isoindolinone (phthalimidine) **5** is the more stable derivative of isoindole.



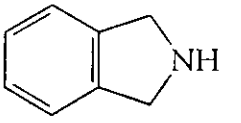
1
Isoindole



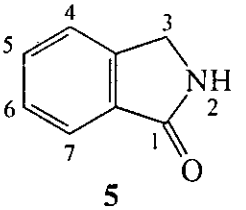
2
Indole



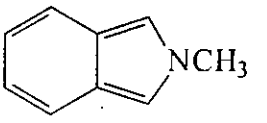
3
1H-Isoindole
(Isoindolenine



4
Isoindoline



5
Isoindolin-1-one/Phthalimidin
2,3-Dihydroisoindol-1-one



6
N-Methyl isoindole

To generate isoindole, phthalimidine ring requires nucleophilic addition or reduction at the carbonyl group followed by elimination of water[1c]. The chemical instability of isoindole **1** is well documented[1b] which prevented its isolation and detailed characterization until 1972[3]. The preparation of the first isoindole derivative, i.e. *N*-methylisoindole **6** in 1951[2] and and the unsubstituted parent isoindole **1** in 1972[3a,b] demonstrated that the ring system was stable enough for isolation.

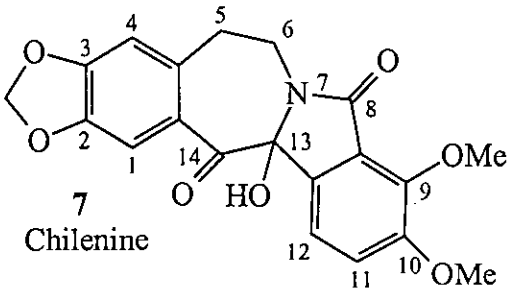
II. Structure of isoindole

Isoindole **1** is a bicyclic 10π electron array and complies with the Hückel ($4n + 2$) rule for aromatic stabilization[4]. There have been several calculations of the electronic structure of isoindoles[5–8]. The distribution of charge density around the isoindole nucleus was

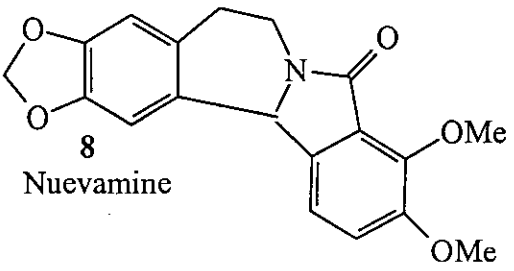
calculated based on the LACO-MO method or the 'frontier electron concept', and the relatively high electron density found at position 1. Therefore, the expectation is that electrophilic substitution on carbon will occur most readily at this position. The semiempirical calculations of Dewar[5] and Polansky *et al.*[8] estimate a substantial degree of resonance stabilization for isoindole with a value of about 56 kcal mol^{-1} which is significantly larger than the value of pyrrole and is close to that ascribed for indole. Isoindole **1** should be favored over its tautomer, isoindolenine **3** by about 8 kcal mol^{-1} according to a molecular orbital calculation of Veber and Lwowski[9]. Theoretical studies by Dewar *et al.*[10] are consistent with structure **1**.

III. Naturally occurring isoindole and isoindolinone (phthalimidine) derivatives

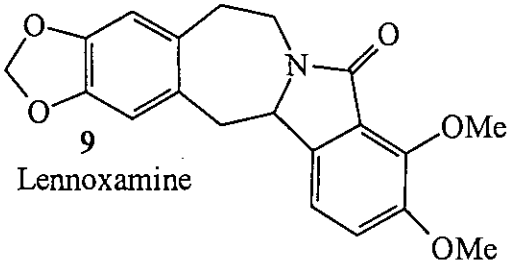
The first isoindolobenzazepine alkaloid (±)-chilenine **7** has been found in *Berberis empetrifalia* Lam. (Berberidaceae) by Fajardo *et al.*[11]; Valuencia *et al.*[12] isolated nuevamine **8**, the first known isoindoloisoquinoline alkaloid and lennoxamine **9**, an isoindolobenzazepine structurally related to (±)-chilenine **7** from *Berberis darwinii* Hook (Berberidaceae).



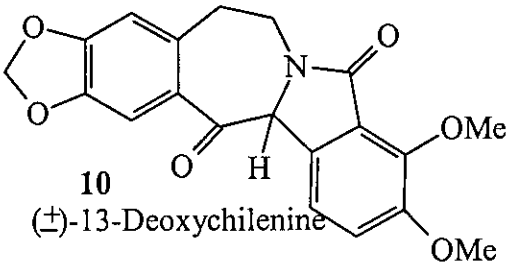
7
Chilenine



8
Nuevamine



9
Lennoxamine



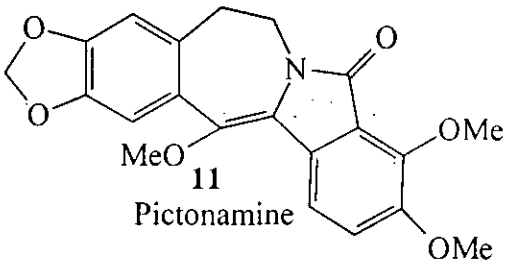
10
(±)-13-Deoxychilenine

Valencia *et al.*[13] also isolated a series of novel isoindolobenzazepines including (±)-13-deoxychilenine **10**, pictonamine **11**, chileninone **12**, (±)-chilenamine **13**, and (±)-

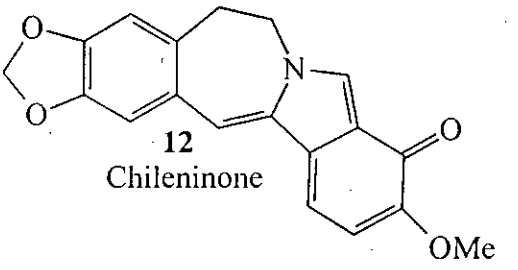
palmanine **14** from three Chilean *Berberis* species, namely, *B. Actinacantha* Mart. ex Schult, *B. darwinii* Hook and *B. valdiviana* Phil. The isolation of the first known isoindolobenzazocine alkaloid magallanesine **15** from *Berberis darwinii* Hook was also achieved by Valencia *et al.*[14].

Staurosporine **16** containing an isoindolinone moiety was isolated from Saccharothrix Sp. AM–2282[15], and has very interesting biological activities, such as antimicrobial[16a], hypotensive[16b], cytotoxic[16c] activities. It is also an inhibitor of protein kinase[16c], and platelet aggregation[16d].

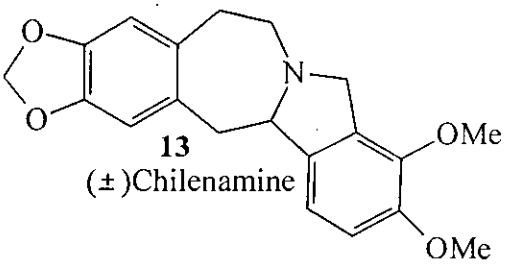
The naturally occurring isoindole(2,5-dimethyl-6-methoxy-4,7-dihydroisoindole-4,7-dione) **17** was isolated from sponge *Reniera* Sp.[17].



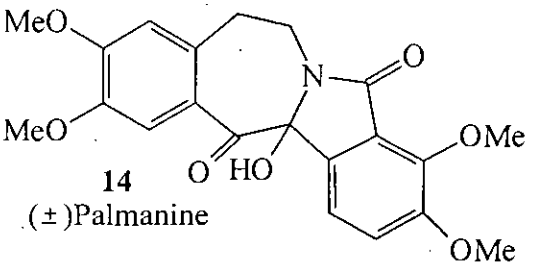
11
Pictonamine



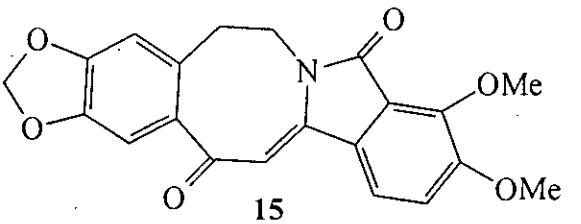
12
Chileninone



13
(±)Chilenamine

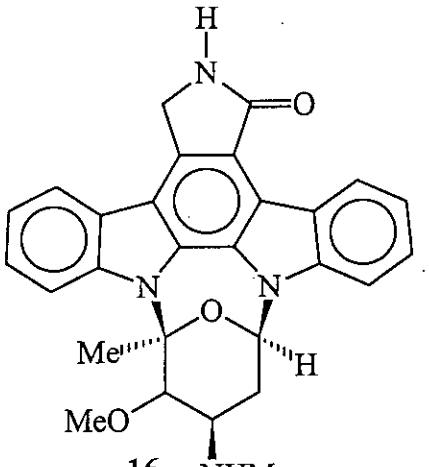


14
(±)Palmanine

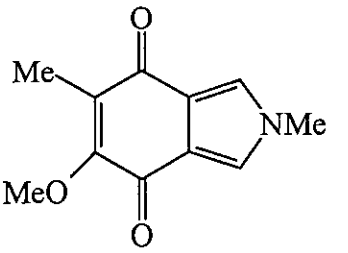


15
Megallanesine

A series of cytostatically active metabolites have been isolated from microorganisms in which a highly substituted hydrogenated isoindolone unit is fused to an 11-to 14-membered macrocycle.

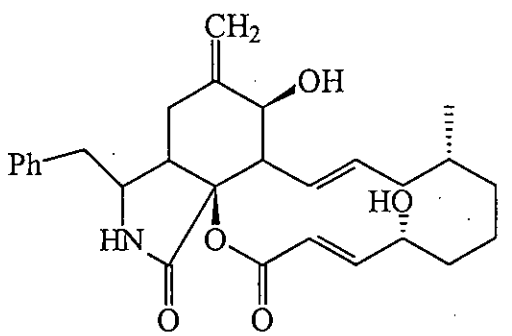


16 NHMe
Staurosporine

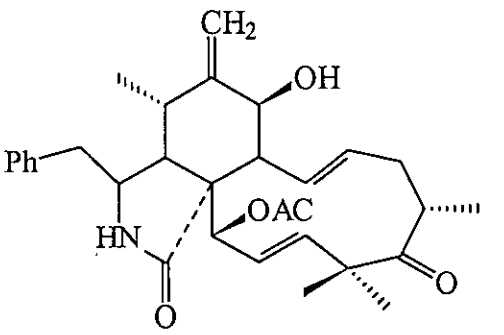


17

The isolation of the first two substances (cytochalasin B **18** and cytochalasin D **19**) of the cytochalasin series was achieved by Rothweiler[18] and Aldridge *et al.*[19]. The cytochalasins are a group of about two dozen structurally related fungal metabolites having a wide range of biological activities[20a,b].



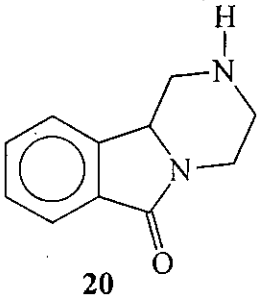
18
Cytochalasin B



19
Cytochalasin D

IV. Biologically important isoindole and isoindolinone (phthalimidine) derivatives

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeleton have outstanding biological and physicochemical activities, few of these are being cited here. The 1,2,3,4-tetrahydropyrazino[2,1-a]isoindol-



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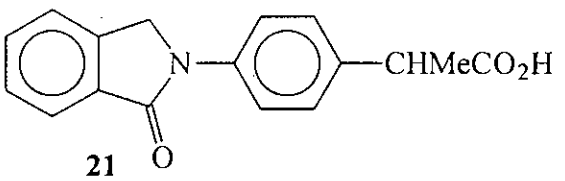
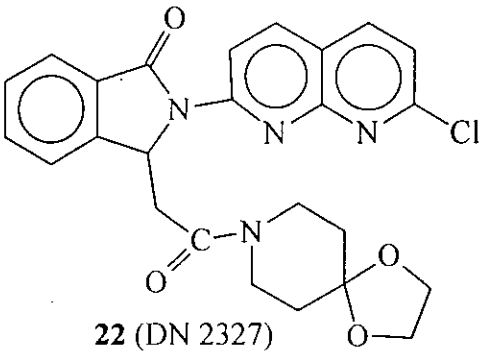


21

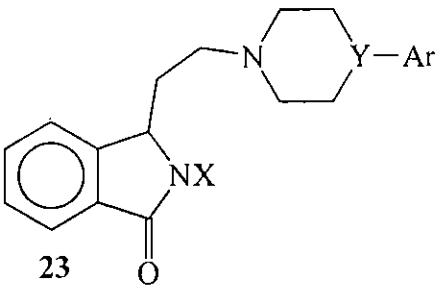


22 (DN 2327)

6-one **20** was found to lower blood pressure in spontaneously hypertensive rats[21]. A new nonsteroidal antiinflammatory agent indoprofen **21** was synthesized by Li *et al.*[22].

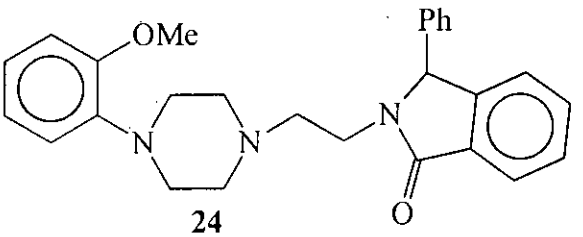
A novel promising anxiolytic drug is DN-2327, a non-benzodiazepine isoindoline derivative **22**, which has sown in animals to have anxiolytic, taming, antiaggressive and anticonvulsive effects without relevant sedative properties, or signs of dependence[23]. DN-2327 showed a higher affinity for the BZ1-GABA receptor in comparison to diazepam or flunitrazepam.

Bellioti *et al.*[24] discovered a series of isoindolinone derivatives **23** having affinity for the dopamine D_4 receptor. Compounds containing substituents in 3- and 4-positions of the phenyl ring have the highest D_4 receptor affinity.



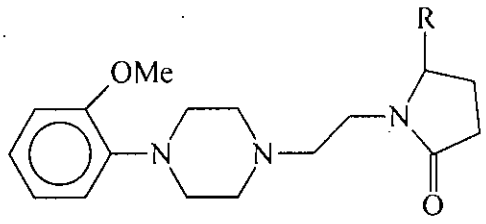
23

X = H or Me
Y = N or CH
Ar = C_6H_5 etc.



24

The synthesis of a group of cyclic amide analogs, e.g. **24** and **25** of 4-(2′-methoxiphenyl)-1-[2′-[*N*-(2″-pyridyl)-*p*-iodobenzamido]ethyl]piperazine (*p*-MPPI **26**) as 5-HT_{1A} receptor ligands was achieved by Zhuang *et al.*[25]. Some of these compounds displayed very high in *vitro* binding affinity for 5-HT_{1A} receptors, comparable to or exceeding that of the parent compound **26**.



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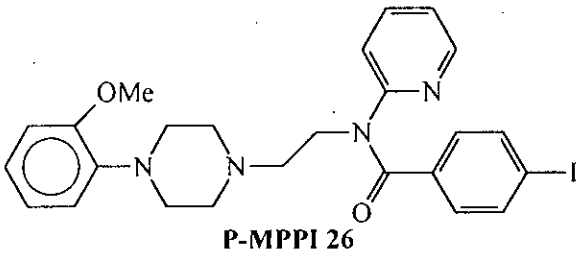
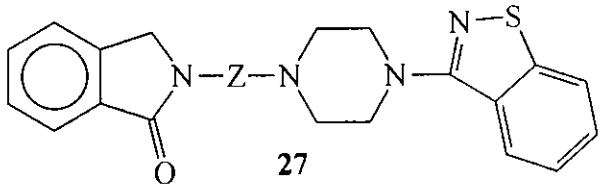
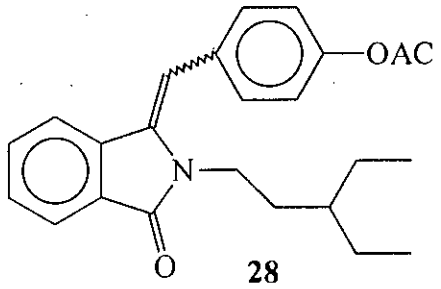


P-MPPI 26

Norman *et al.*[26] prepared a series of isoindolinone derivatives **27** bridged to 4-(1,2-benzisothiazol-3-yl)-1–piperazinyl moiety with a variety of different bridging units. The compounds 5-HT_{1a} and 5-HT_2 receptors and *in vivo* for their ability to antagonize the apomorphine-induced climbing response in mice and found as potential antipsychotic agents. A four-carbon spacer provided optimal activity within the homologous series.



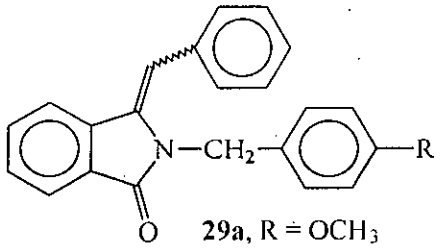
27



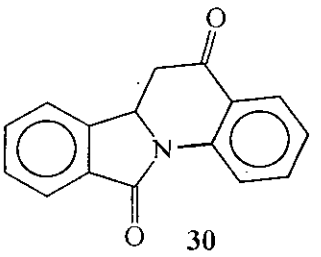
28

Z = – $(CH_2)_2$, – $(CH_2)_3$ etc.

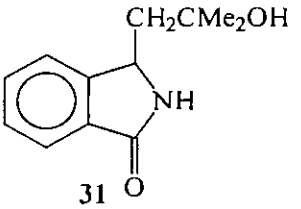
3-(4-Acetoxyphenyl)methylene-2-(2-diethylamino)ethyl-2,3-dihydro-1*H*-isoindol-1-one **28** was found to exhibit local anesthetic activity superior to that of procaine[27]. Achinami *et al.*[28] prepared alkylidene isoindolinone derivatives **29** as vasodilators which exhibited IC_{50} of 5.6 μM in inhibition of 40 mMK^+-induced coronary contraction *in vitro* and inhibitory effect to the thromboxan A_2 analog (U-46619)-induced vasoconstriction. The isoindolo[2,1-a]quinolines of type **30** showed protective effect against N_2 induced hypoxia[29]. Lippmann[30] prepared 1,3-dihydro-3-(2-hydroxy-2-methylpropyl]-2*H*-isoidol-1-one **31** and found it to be useful in the treatment of ulcers.



29a, R = OCH_3
29b, R = OH

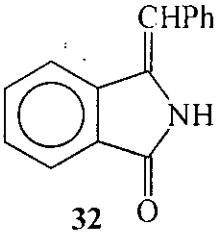


30



31

The study of cytotoxic effects[31] of isoindol-1-one derivatives **32** and **33** on leukemia P388 cells showed that nearly half of the compounds inhibited uridine incorporation, but only three compounds affected incorporation of thymidine and L-valine. The cytotoxic effects of the compounds could be related not only to the types and position of the substituents but to stereoisomerism as well.



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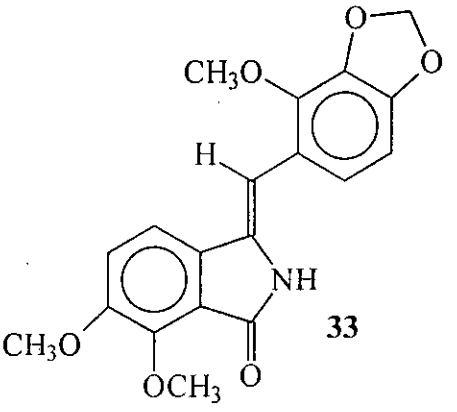


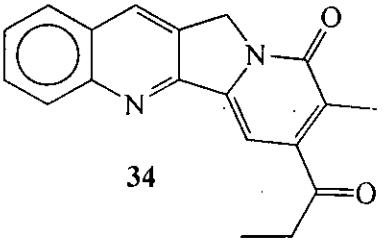
33

Mappicine ketone (MPK) **34**, an analog of mappicine **35**, a naturally derived alkaloid isolated from *Mapia foetida* Miers. (Olacaceae)[32a] has been identified as an antiviral lead compound with selective activity against herpes viruses HSV-1, HSV-2 and human cytomegalovirus (HCMV), MPK appears to be herpes virus selective in that it does not inhibit other DNA or RNA viruses[32b].

Dihydrothiazoloisoindolones **36** were found to be potent non-nucleosidic HIV reverse transcriptase inhibitors[33].

Taylor *et al.*[34] synthesized a conformationally constrained analog **37b** of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) **37a**, in which the glutamate moiety is tied back to the benzoyl ring through an isoindolinone moiety. The preliminary biological

evaluation of **37b** revealed that it was an excellent inhibitor of human CCRF-CEM lymphoblastic leukemic cells and a non-competitive inhibitor of mammalian glycinamide ribonucleotide formyltransferase.



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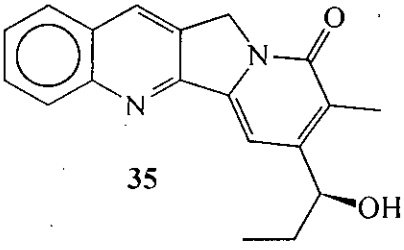

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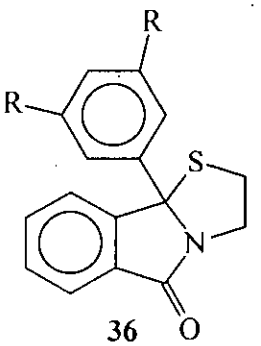
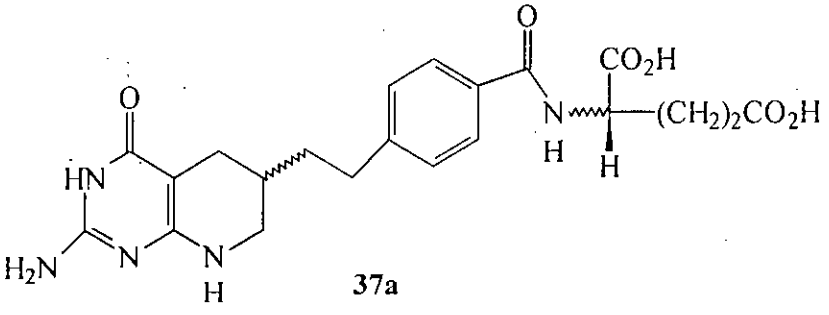


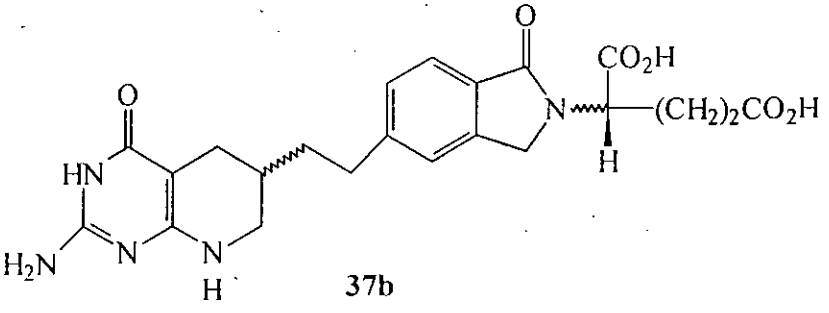
36

R = H, CH_3

Hexahydroisoindole **38** was found to be a potent herbicidal[35]. Kim and Ryu[36] developed a synthetic method for the herbicidal 2,3-dihydro-3-methylene-2-substituted-phenyl-1*H*-isoindol-1-one derivatives. Compound **39** showed good herbicidal activity against various weed species.

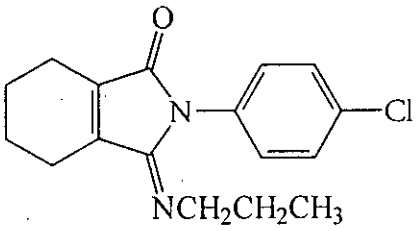


37a

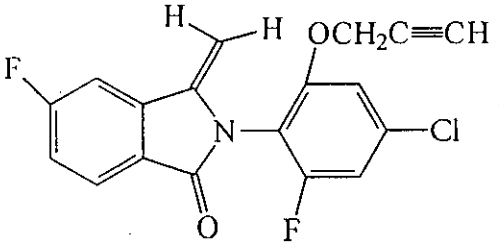


37b

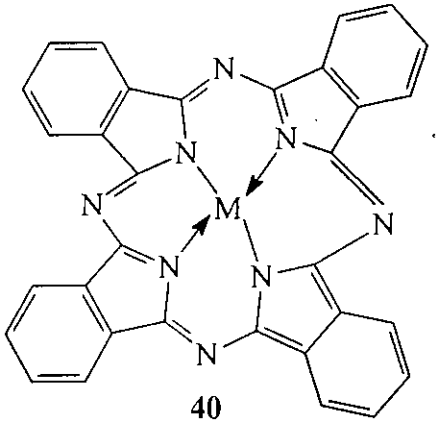
Other important derivatives of isoindole are the metal complexes **40** of phthalocyanines, used as dyes and pigments[37a,b].



38



39



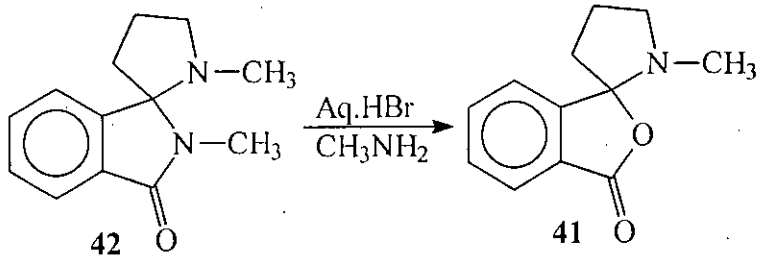
40

M = Cu

M = Mg

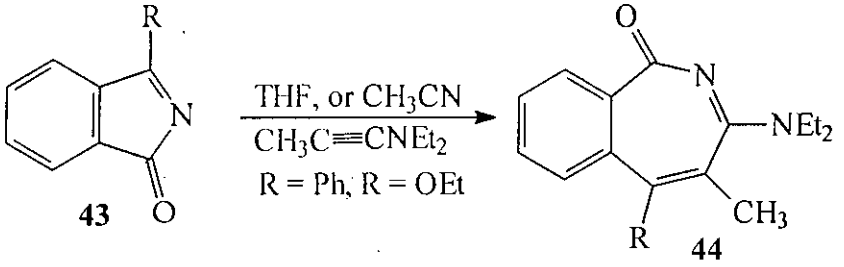
V. Isoindolinone in the synthesis of drugs

Isoindolinones (phthalimidines) have been widely used as intermediates for the synthesis of various important drugs. Shihunine, a popular Chinese drug, sold in Hong Kong, was isolated about 30 years ago by Inubushi *et al.*[38] from *Dendrobium iohonense* as a phthalide pyrrolidine alkaloid which they named shihunine as it was a component of ShiHu. Breuer and Zbaida[39] synthesized shihunine **41** from the lactam, spiro[(1-methylpyrrolidine)-2,3′-(2′-methyl-1′-isoindolinone)] **42** (Scheme 1).



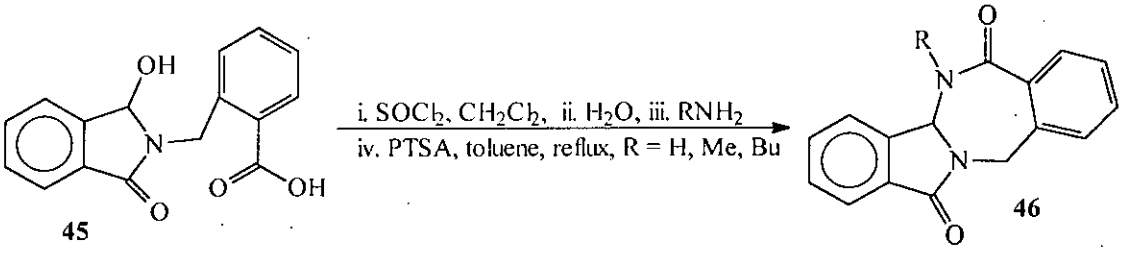
Scheme 1

Abramovitch *et al.*[40] obtained the ring expanded 2-benzazepin-1-one **44** through the reaction of 3-substituted-(1*H*)-1-isoindones **43** (Scheme 2).



Scheme 2

Recently, Pigeon and Decroix[41] developed a new approach to isoindole[2,1-b] benzodiazepines **46** though an intramolecular cyclization of a *N*-substituted-3-hydroxy-isoindolinone **45** (Scheme 3).

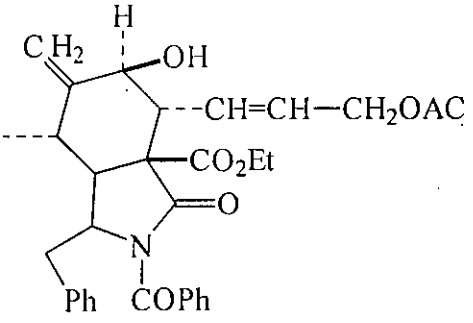


Scheme 3

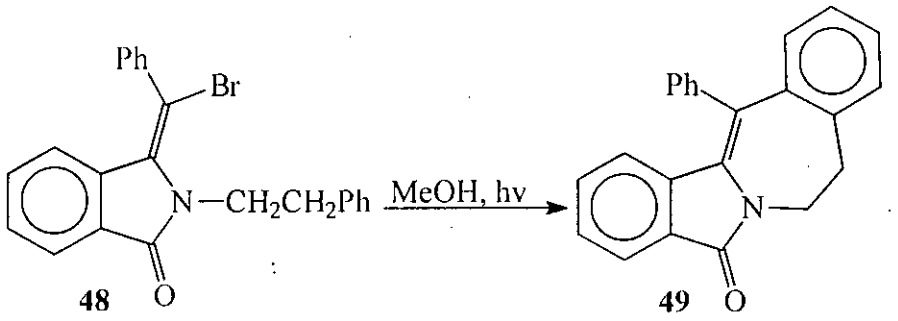
VI. Isoindolinones in the synthesis of natural products

Vedejs *et al.*[42] reported the synthesis of isoindolone **47** having part of the structure of cytochalasin D **19**.

Marsili *et al.*[43] synthesized isoindolobenzazepinone derivative **49** which are structurally related to the alkaloid pictonamine **11**, from isoindolinone **48** (Scheme–4).



47

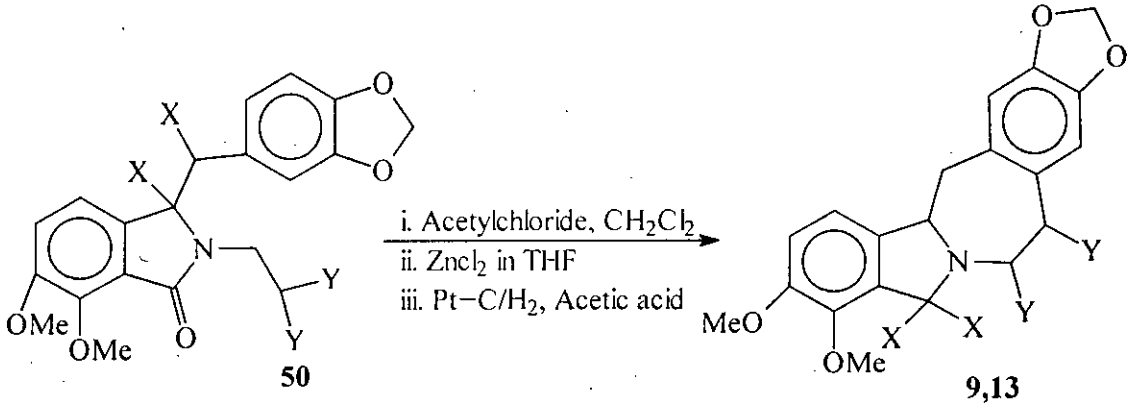


48 49

Scheme 4

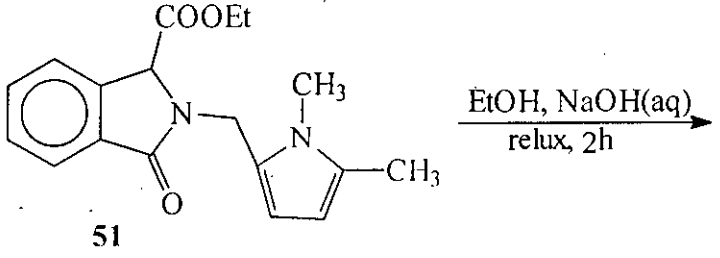
From isoindolinone derivatives **50** Napolitano *et al.*[44] synthesized the isoindolobenzazepine alkaloids lennoxamine **9** and chilenamine **13** (Scheme 5).

Recently, Othman and Decroix[45] reported a synthesis of benzo[a]pyrrolo[2,3-*f*]indolizine **52**, a new heterocyclic analog of chilenine alkaloid **7**, from the isoindolinone derivative **51** (Scheme 6).

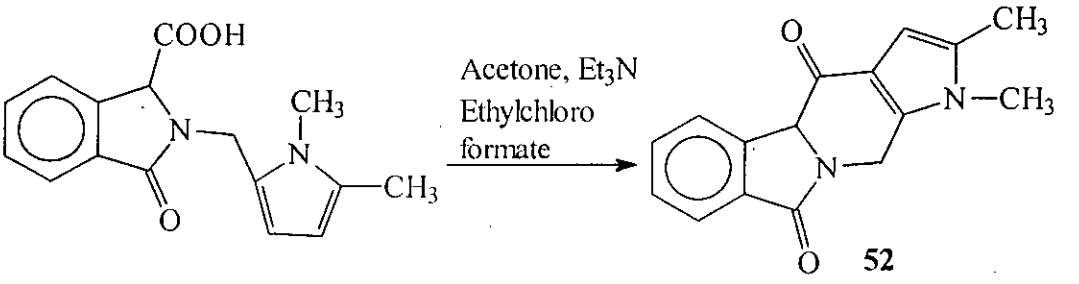


50 **9,13**

Scheme 5

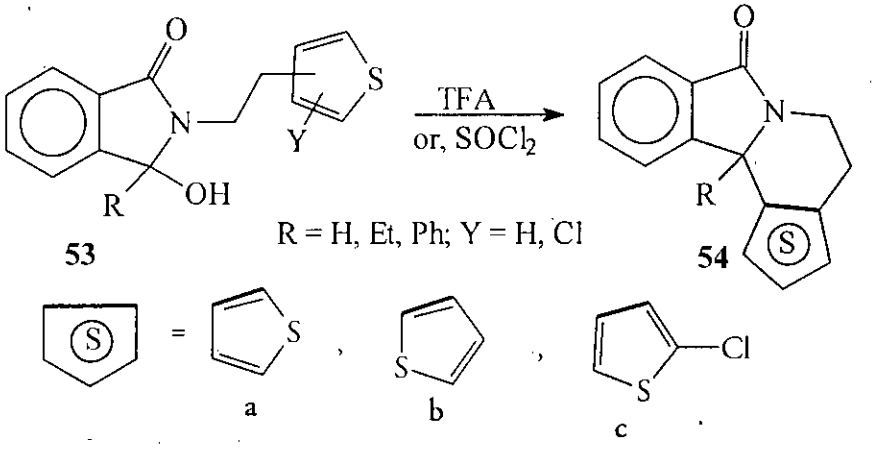


51



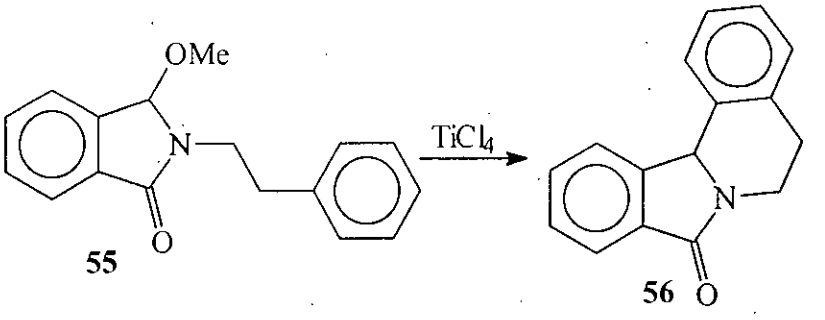
Scheme 6

Othman *et al.*[46] also developed a synthesis of benzo[a]thieno[g]indolizinones **54**, polycyclic compounds analogous to the alkaloid nuevamine **8**, via an intramolecular α-amidoalkylation reaction of isoindolinone derivative **53** with thionyl chloride (Scheme 7a).



Scheme 7a

Recently, Heaney and Shuhaibar[47] reported a synthesis of the alkaloid nuevamine skeleton, e.g. isoindoloisoquinoline derivative **56** from an α-methoxyisoindolone derivative **55** (Scheme 7b).

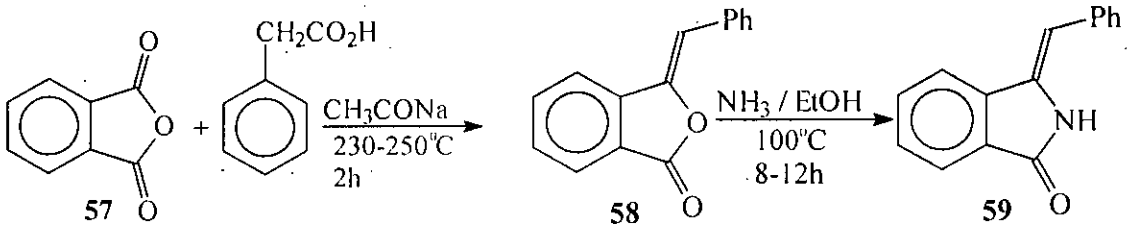


Scheme 7b

VIIA. Classical methods

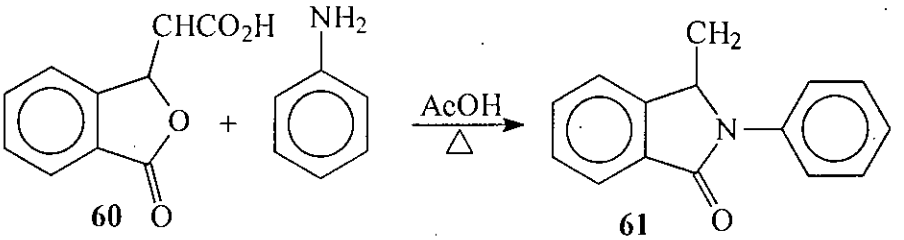
VIIA.1. Synthesis of isoindolinones (phthalimidines) through Gabriel's procedure

In 1885 Gabriel developed[48] a general method for the synthesis of ylidenephthalides by condensation of phthalic anhydride **57** with arylacetic acid in the presence of sodium or potassium acetate at 230–250^0 (a type of Perkin reaction). He also reported that benzylidene phthalide **58** on treatment with ammonia in alcohol at 100^0 for 8–10 h yielded benzylidene phthalimidine **59** (Scheme 8).



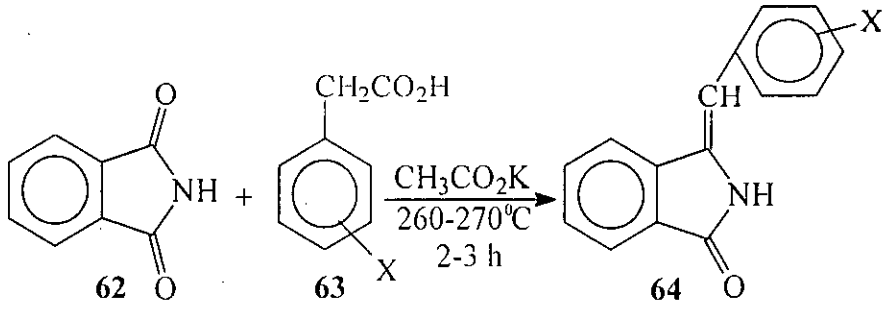
Scheme 8

Honzl[49] reported the synthesis of methylene isoindolinone **61** by heating aniline and phthalylidene acetic acid **60** in acetic acid (Scheme 9).



Scheme 9

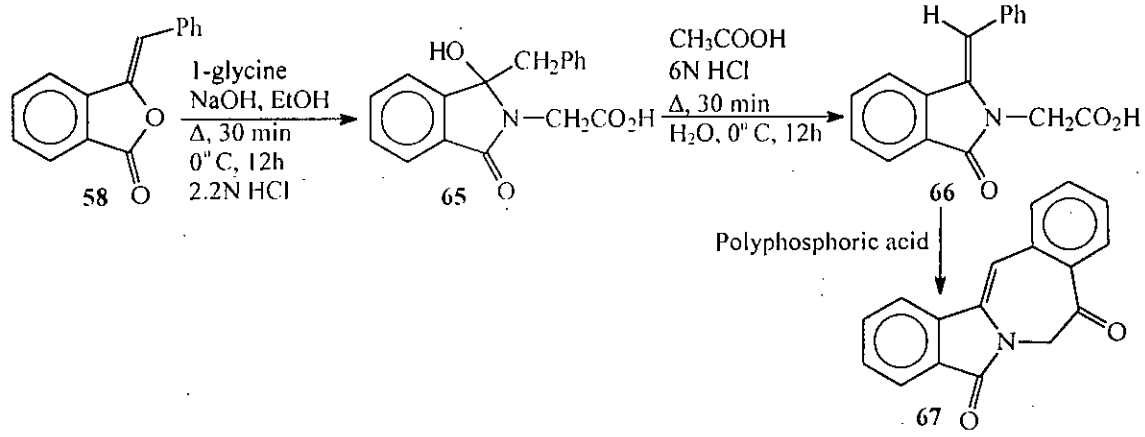
Perjessy *et al.*[50] reported the synthesis of 3-arylmethylene phthalimidines **64** through a Gabriel modification of Perkin condensation where phthalimide **62** was reacted with the corresponding arylacetic acids **63** (Scheme 10).



X = 4-NO_2, 4-OCH_3, 3-CH_3, 4-F, 3-OCH_3, 4-I, 4-Cl, 4-Br, 3-F, 3-I, 4-NH_2

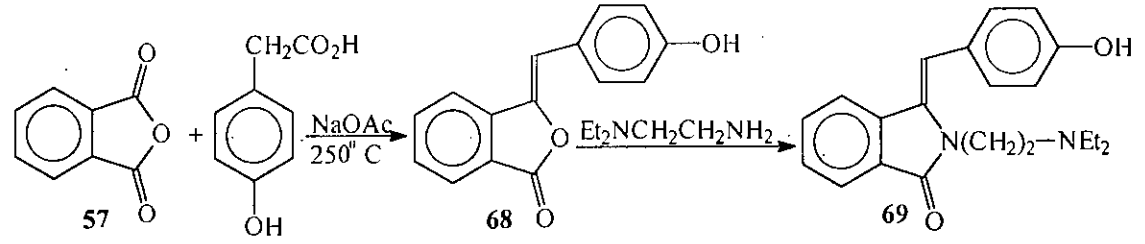
Scheme 10

Scartoni *et al.*[51] reported the synthesis of 3-benzyl-3-hydroxyphthalimidin-2-ylacetic acid **65** which yielded 3-benzylidene phthalimidin-2-ylacetic acid **66**. This was subsequently converted to isoindolobenzazepine **67** (**Scheme 11**).



Scheme 11

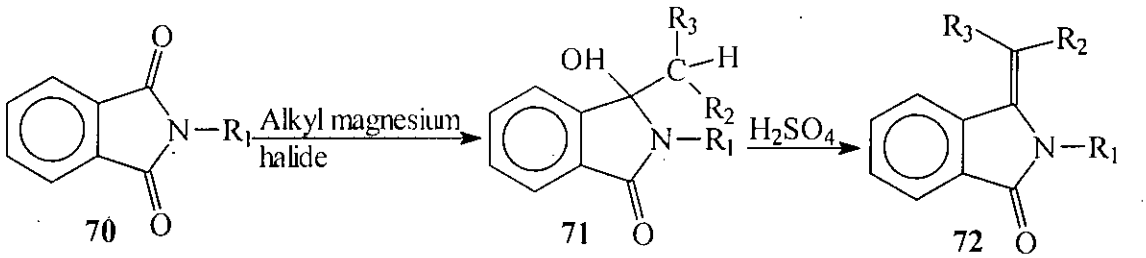
A series of benzylidenes phthalimidines **69** were prepared starting from phthalic anhydride[27] **57**. A typical example is given in (**Scheme 12**).



Scheme 12

VIIA.2. Alkylidene isoindolinones through Grignard procedure

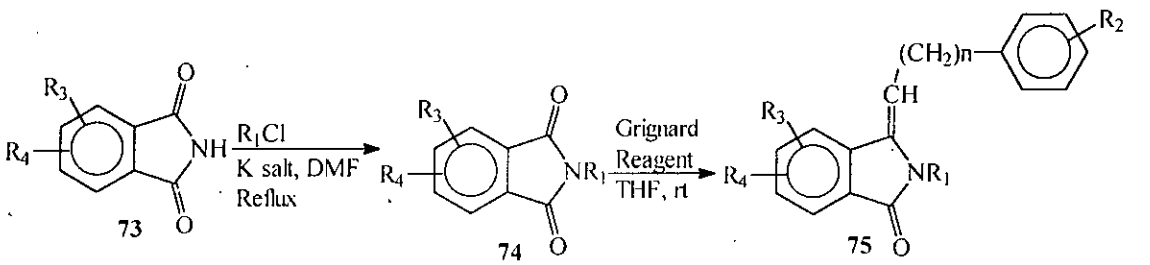
Alkylidene isoindolinones (alkylidenephthalimidines) were synthesized by the action of a Grignard reagent on a *N*-substituted-phthalimide and subsequent dehydration[52]. Ang and Halton[53] applied the Gridnard procedure reported by Heidenbluth *et al.*[52]. to prepare 2-substituted 3-alkyl-3-hydroxyphthalimidines **71** through the reaction of alkyl magnesium halide in ether on phthalimide **70** in benzene at 55^0 for 3 h. Dehydration of the alcohols **71** in concentrated sulfuric acid afforded the alkylidenephthalimidines **72** in good yields (**Scheme 13**).



$R_1(R_2)R_3$ = H(CO_2Et or H) H or CO_2Et; Me(CO_2Et or H) H or CO_2Et; Ph (Me or H) H or Me; Ph (Me) Me; Ph(H)H; Me(Me or H) H or Me; Me(Me) Me; Me(H)H; H(Me or H) H or Me.

Scheme 13

Recently, Achinami *et al.*[28] reported the synthesis of a series of alkylideneisoindolinone derivatives **75** by following the above Grignard procedure (**Scheme 14**).

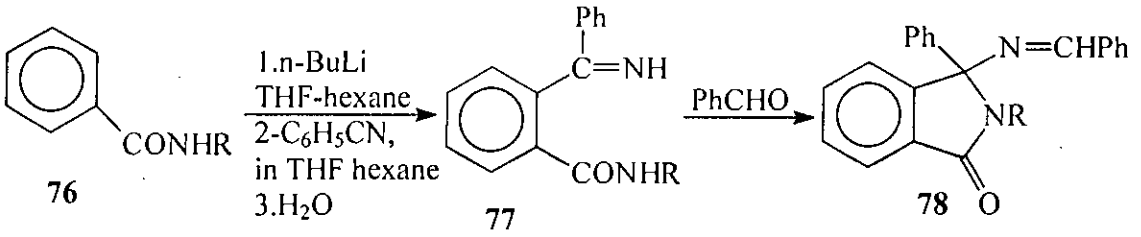


R_1 = (substituted)alkyl,Ph, $PhSO_4$; R_2 = H, alkoxy, OH, halo, (substituted)alkyl, acyl; R_3, R_4 = H, alkyl,aryl, alkoxy, OH; n = 0, 1, 2.

Scheme 14

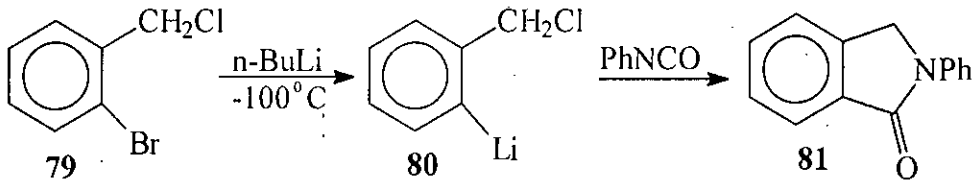
VIIA.3. Synthesis of isoindolinones through lithiation procedures

Watanabe *et al.*[54] reported a synthesis of 3-substituted-phthalimidines **78** from benzanilide**76** through lithiation with *n*-butyllithium and subsequent reaction with benzonitrile (**Scheme 15**).



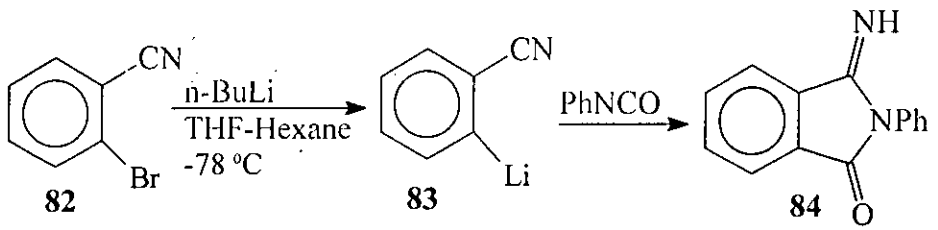
Scheme 15

Parham *et al.*[55] prepared *N*-phenylphthalimidine **81** by selective halogen-lithium exchange in bromophenyl-alkylhalides **79** with *n*-butyllithium followed by treatment with phenyl isocyanate (Scheme 16)



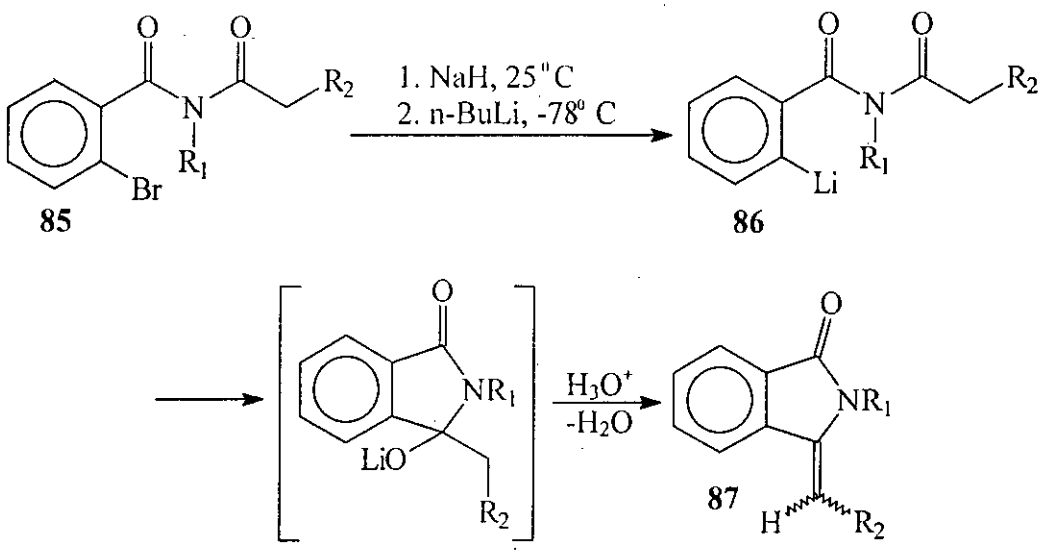
Scheme 16

Parham and Jones[56] also synthesized *N*-phenylphtha-limidine derivative **84** from 2-bromobenzonitrile **82** and *n*-butyllithium at-78^0 followed by the reaction with phenyl isocyanate (Scheme 17).



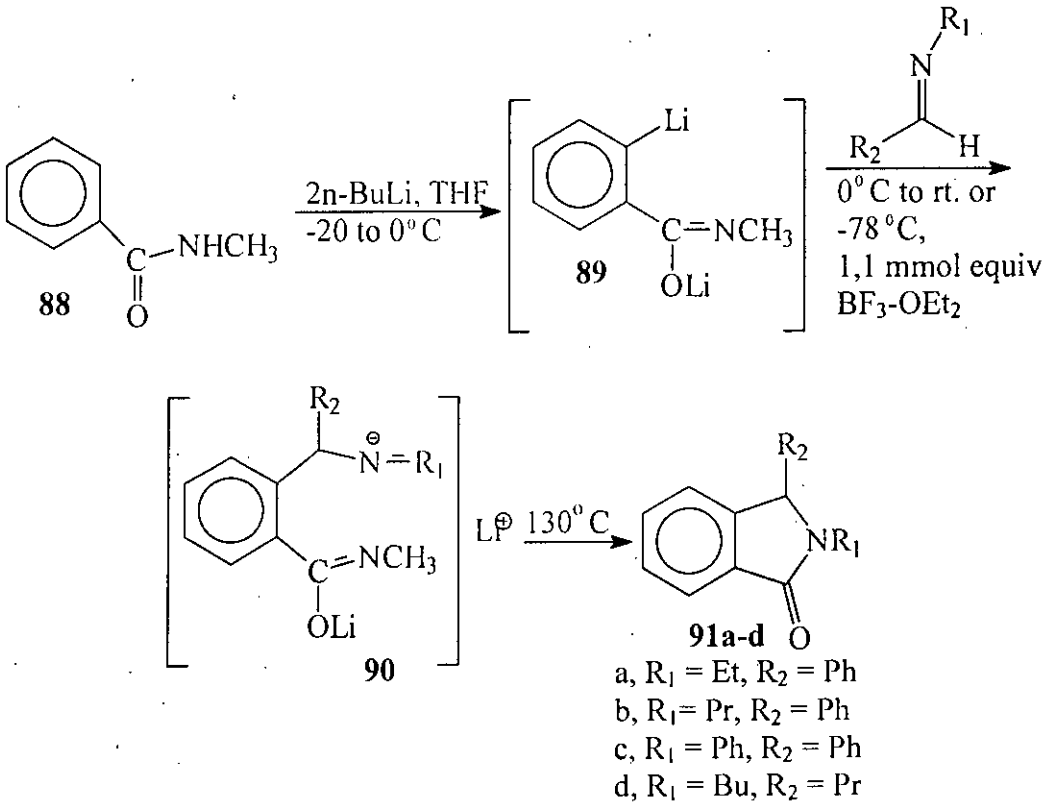
Scheme 17

Hendi *et al.*[57] reported a parham-type cyclization[58] in which *N*-acyl-2-bromobenzamides **85** participated in metal-halogen exchange with *n*-BuLi to form *N*-Acyl-2-lithioben-zamides **86.** The resulting ortho-lithio intermediates **86** then underwent cyclization to afford 3-alkylidenephthalimidines **87** (Scheme 18).



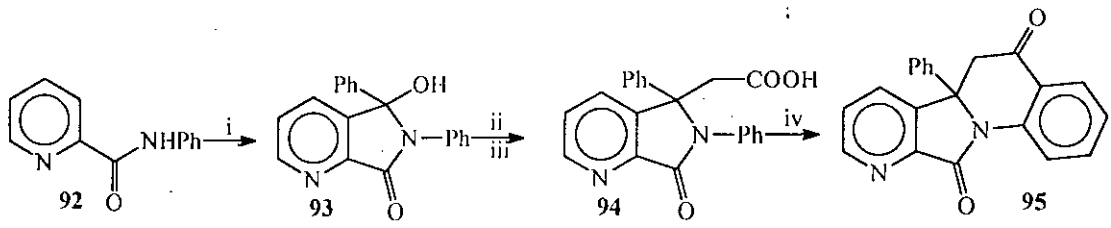
Scheme 18

Campbell *et al.*[59] developed a synthesis of isoindolilnones **91** through a lithiation procedure (Scheme 19).



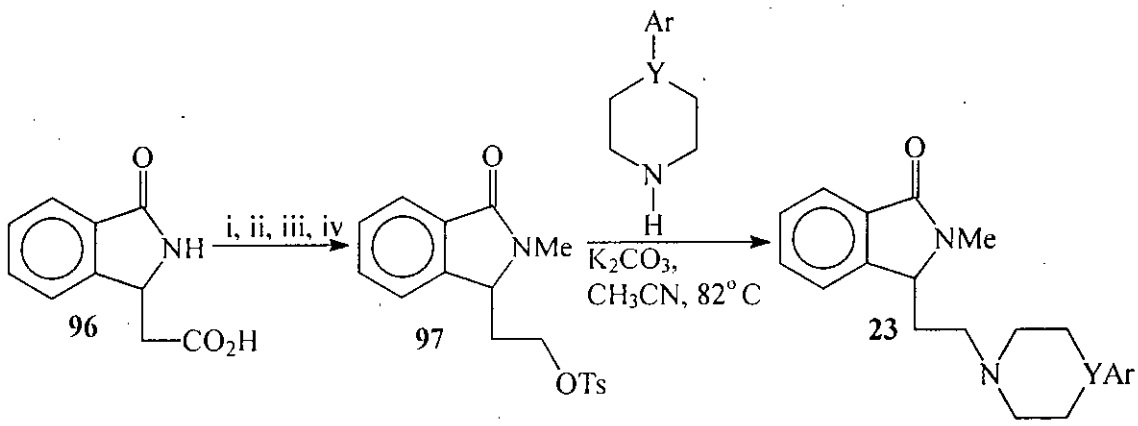
Scheme 19

Recently, Jozwiak and Sadokierska[60] reported the synthesis of hydroxyazaisoindolinones and their successful conversion to azaisoindoleacetic acids as effective precursors for the corresponding 4b-phenyldihydroazaisoindol [2,1-a] quinolinediones **95** (Scheme 20).



Scheme 20. *Reaggents and conditions:* (i) 1. BuLi, THF, -78 to O^0; 2-methyl benzoate, in THF, -78^0 to RT; (ii) diethylmalonate, methanesulfonic acid, $(AcO)_2$, 100^0, (iii) 20% HCl solution, heated upto boiling; (iv) 1. oxalylchloride, $C_2H_4Cl_2$, reflux, 0, 2 h; 2. $AlCl_3$, $C_2H_4Cl_2$, reflux, 2 h.

A series of 3-substituted-isoindolinones **23** having affinity for the dopamine D_4 receptor was prepared by Belliotti *et al.*[24] starting from isoindolinoneacetic acid **96** (Scheme 21).

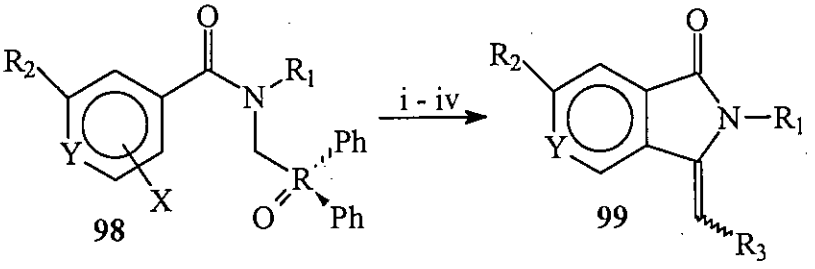


Y = N, CH

Ar = 3,4-dimethylphenyl, 2-naphthyl, 4-methylphenyl, 4,5-dimethyl-2-thiazolyl, phenyl, 4-methyl-2-pyridyl, 4-chlorophenyl and 4-methoxyphenyl.

Scheme 21. *Reagents:* (i) NaH, DMF; (ii) MeI; (iii) $NaBH_4$. MeOH; (iv) P-TsCl, TEA in CH_2Cl_2.

Couture *et al.*[61] developed the synthesis of a series of 3-(alkyl and ary)methylene -2,3-dihydro-1 *H*-isoindol-1-one derivatives. Treatment of phosphorylated amides **98** with KHMDS (2.2 equiv.) in THF at 78^0 followed quenching with selected aromatic and aliphatic carboxaldehydes affords a mixture of *E*-and *Z*-isomers of 2-alkyl-3-(aryl and alkyl) methylene-2,3-dihydro-1 *H*-isoindol-1-ones **99** (Scheme 22).



R_1 = 4-$OMeC_6H_4CH_2$, Me. X = 2– or 3– Cl, Br, F

R_2 = H, OPr.

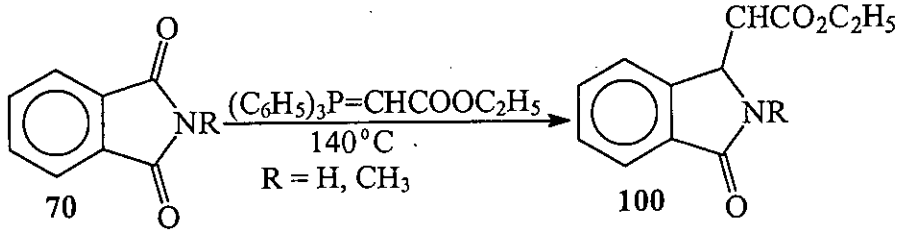
Y = CH, N.

R_1 = Bn, Ph, i-Pr.

Scheme 22. *Reagent and conditions*: (i) KHMDS (2. 2 equiv.). THF, -78^0 to RT 2 h; (ii) R_3CHO, THF, -30^0, (iii) -30^0 to RT 0.5 h; (iv) aqueous HCl.

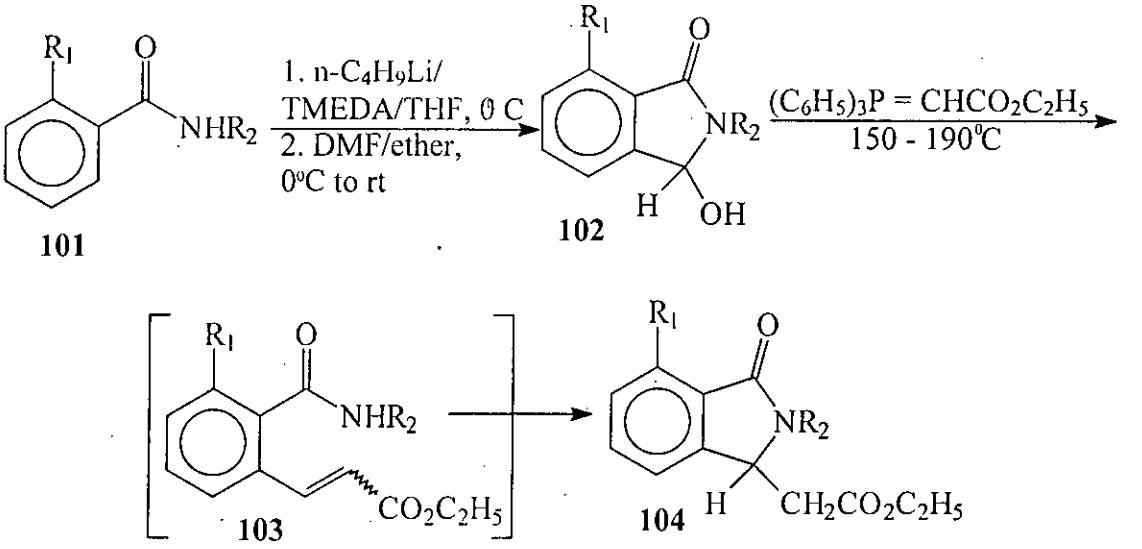
VIIA. 4. 3-Alkylidene sioindolinones through wittig reaction.

Flitsch and Peters[62] synthesized 3-ethoxycarbonyl-methyleneisoindolin-1-ones (phthalimidines) **100** from the reaction of phthalimides **70** with Wittig reagents at 140^0 (Scheme 23).



Scheme 23

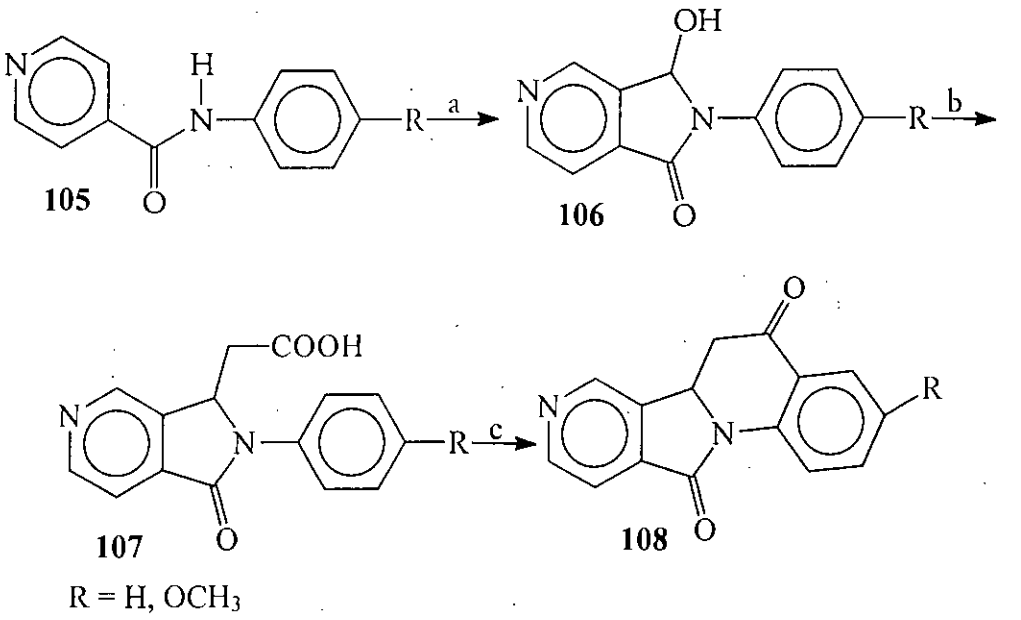
Mali and Yeoa[63] described a novel synthesis of *N*-substituted-3-carbethoxymethylphthalimidines **104** from secondary benzamides through a combination of lithiation and Wittig reaction (Scheme 24)



101–104a–e) R_1 = H, f) R_1 = OCH_3; a) R_2 = CH_3; b) R_2 = Ph, c) R_2 = C_6H_4OMe-*o*, d) R_2 = C_6H_4OMe-m, e) R_2 = C_6H_4OMe-*p*, f) R_2 = Ph)

Scheme 24

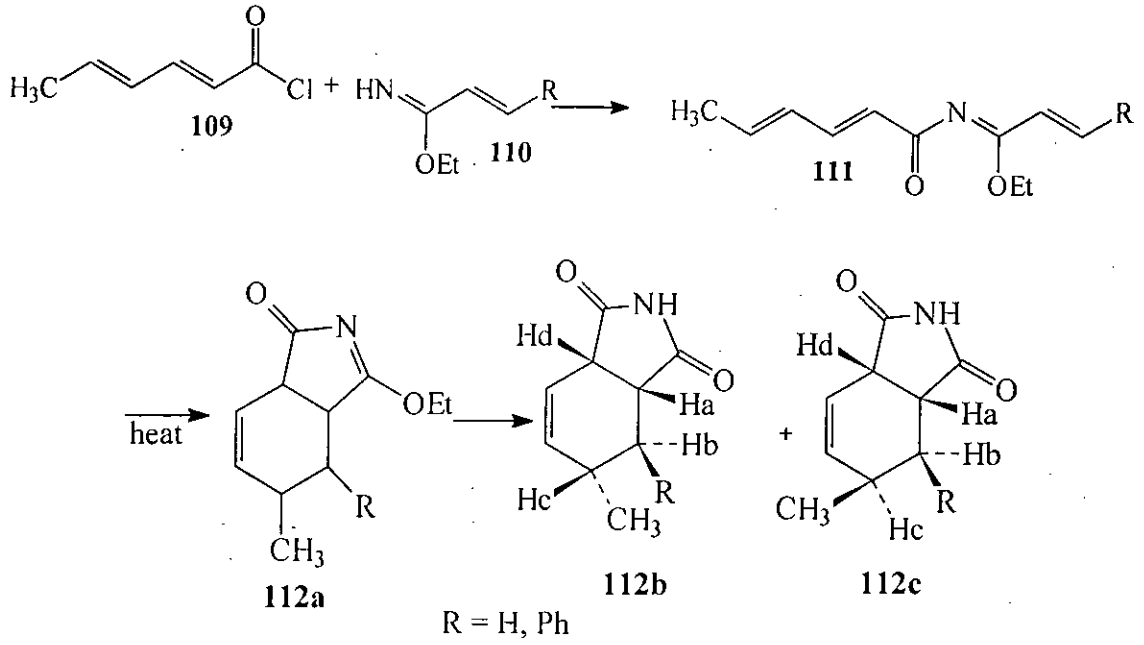
Epsztajn *et al.*[64] described the synthesis of the 3-hydroxy-5-azaisoindolin-1-ones **106** and their conversion to 2-aryl-2,3-dihydro-3-oxo-1*H*-azaisoindole-1-acetic acids **107** and subsequent cyclization to the corresponding dihydroazaisoindolo[2,1-a]quinolinediones **108** (Scheme 25).



Scheme 25. *Reagents and conditions:* (a) i. Buli, THF, –78 to 0^0; ii. DMF, –78 to 0^0; (b) Wittig reagent, 170^0, 0.7 h; (c) i. oxalyl chloride, $Cl_2C_2H_4$; ii. $AlCl_3$, $Cl_2C_2H_4$.

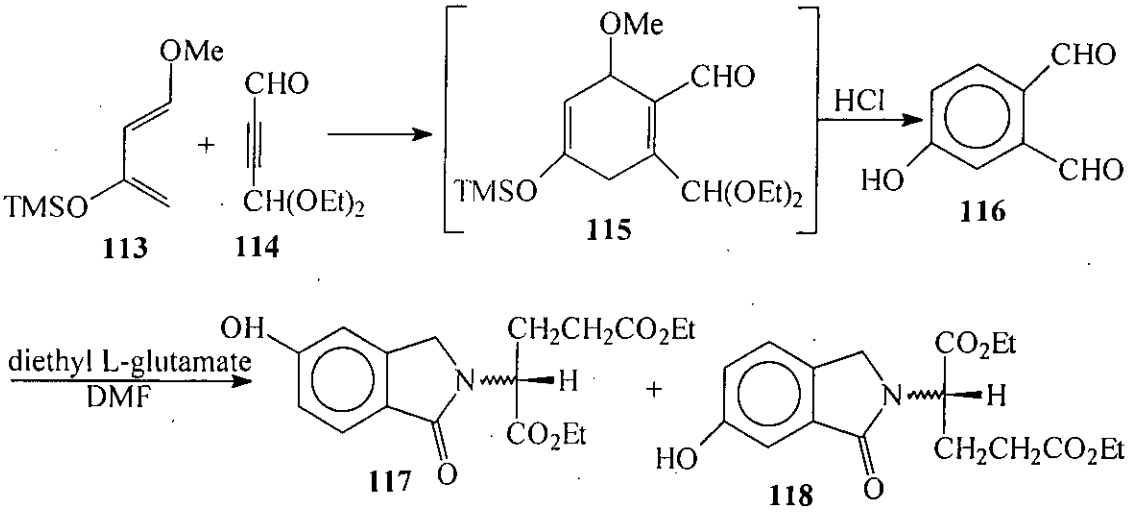
VIIA.5. Synthesis of isoindolinones through Diels-Alder reaction

An efficient approach for the synthesis of hexahydroisoindolones **112** was reported by Gutierrez *et al.*[65] (Scheme 26)



Scheme 26

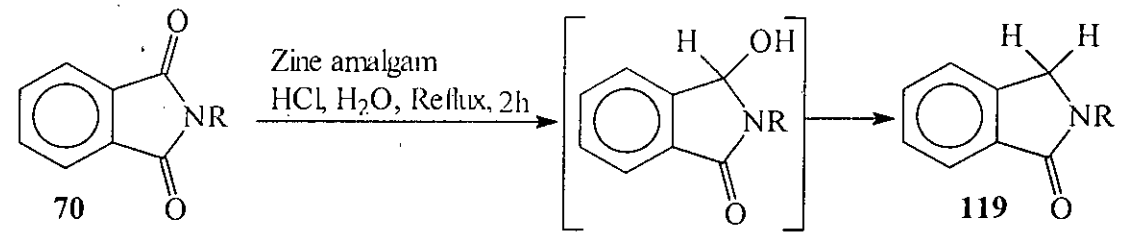
An isoindolinone ring was Synthesized through a series of steps which started with a Diels–Alder reaction of the Danishefsky diene **113** with 4,4-diethoxybut-2-ynal **114** by Taylor *et al.*[34] (Scheme 27)



Scheme 27

VIIA.6. Synthesis of isoindolinones through reduction processes

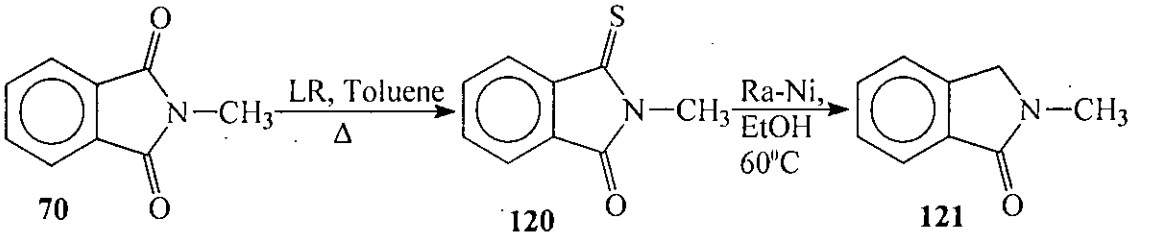
Brewster *et al.*[66] reduced *N*-alkylphthalimides **70** to phthalimidines **119** under Clemmensen condition (Scheme 28).



$R = CH_3, C_2H_5, CH_2Ph$

Scheme 28

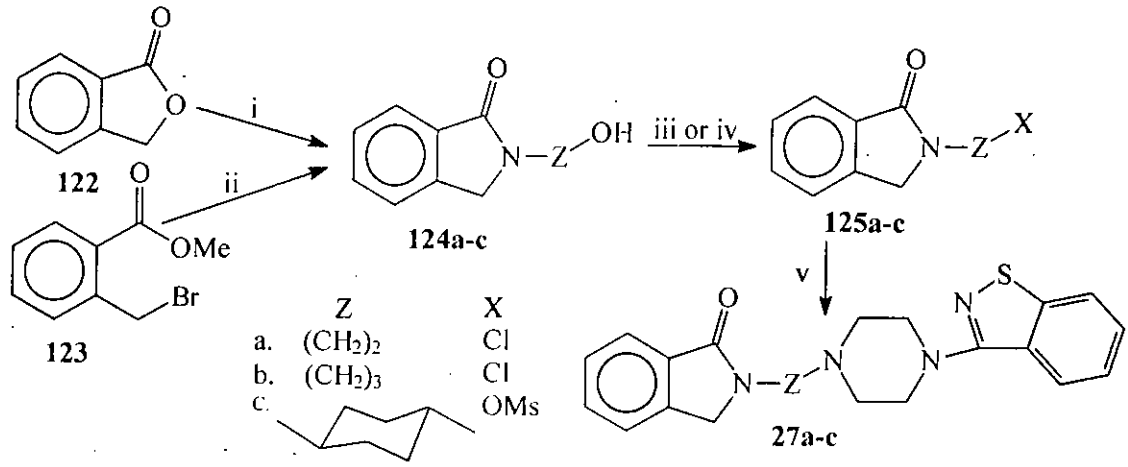
Melewska *et al.*[67] reported a synthesis of *N*-methyl-isoindolinones **121** by regioselective reduction of **70** using Lawesson's reagent (LR) to yield monothioimides **120** followed by desulfurisation of **120** with Raney nickel (Scheme 29)



LR = *p*-$MeOC_6H_4$–P(S)(S)–P(S)(S)–C_6H_4OMe-*p*

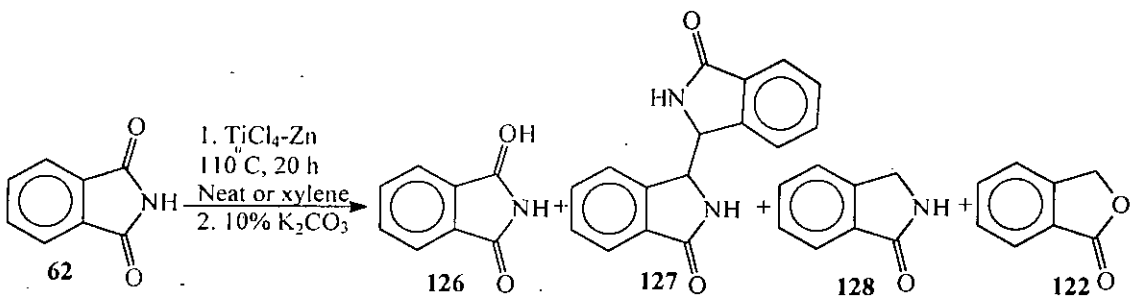
Scheme 29

A series of isoindolinone derivatives[26] **27a–c** attached to the 4-(1,2-benzisothiazol-3-yl)-1-piperazinyl moiety were prepared by a variety of methods (Scheme 30).



Scheme 30. *Reagents:* (i) Ethanolamine or 3-amino-1-propanol, 205–210^0; (ii) *trans*-4-aminocyclohexanol hydrochloride, K_2CO_3, toluene, H_2O reflux; (iii) $SOCl_2$, toluene, 60^0; (iv) Et_3N, CH_2Cl_2, MsCl, 0^0; (v) 3-(1-piperazinyl)-1,2-benzisothiazole, Et_3N, CH_3CN, reflux.

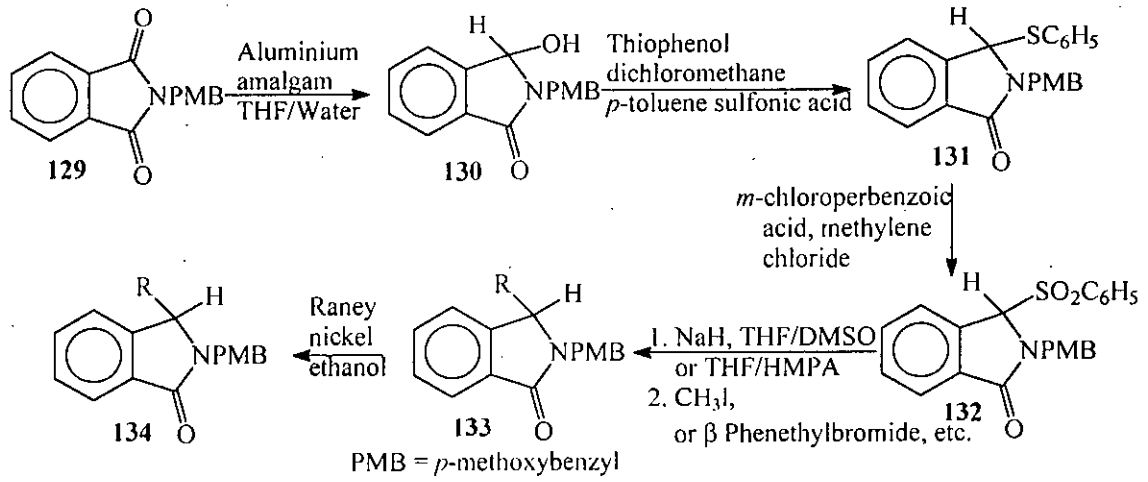
A method for the reduction of phthalimide to the 3-hydroxyisoindolinone **126** and a coupled product **127** was performed[68] by a low-valent-titanium reagent in an aromatic solvent or in the absence of solvent (Scheme 31).



Scheme 31

The coupled product **127** (23%) and phthalimidine **128** (44%) were obtained in the absence of solvent. In *p*-xylene, three monomolecular reductive products were produced (phthalimidine **128** 24%, 3-hydroxyisoindolinone **126** 19% and phthalide **122** 11%); no coupling product was isolated.

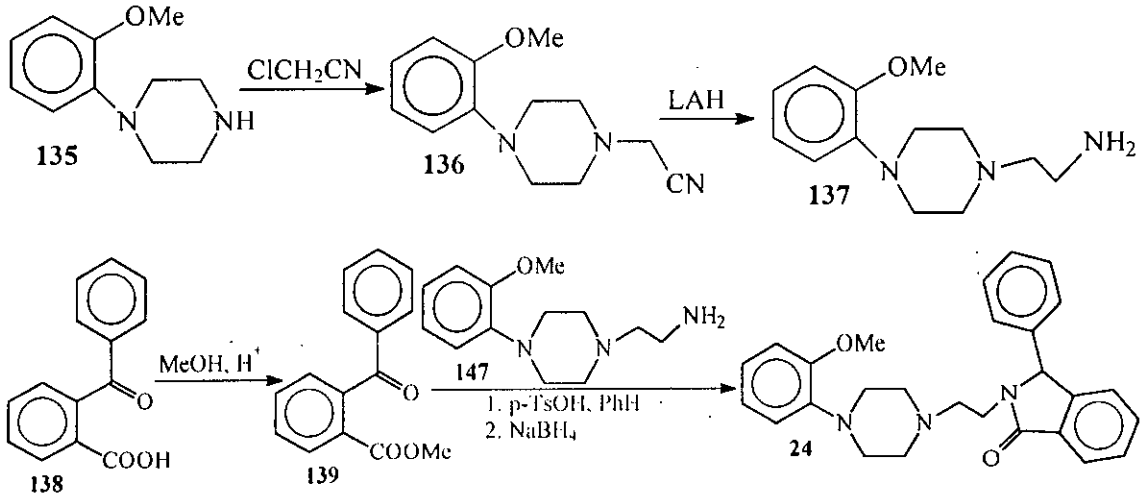
Luzzio and Zacherl[69] described the synthesis of isoindolinone (Scheme 32).



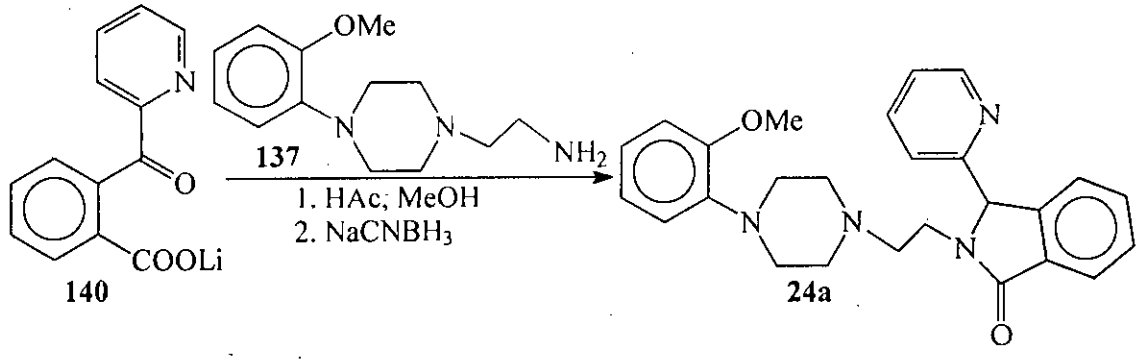
R = CH_3, $CH_2CH_2C_6H_5$, $CH_2CH_2COCH_3$, $CH_2CH_2COOCH_3$

Scheme 32

Zhuang *et al.*[25] developed the synthesis of a group of isoindol-1-ones **24**, cyclic amide analogs of *p*-MPPI **26** as 5-HT_{1A} receptor ligands (Schemes 33 and 34).



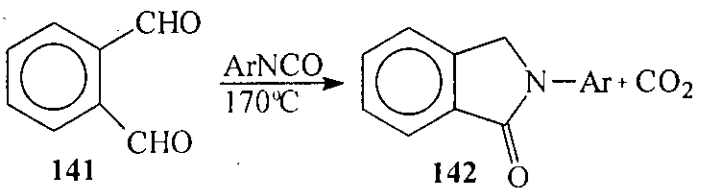
Scheme 33



Scheme 34

VIIA.7. Synthesis of isoindolinones through condensation reactions using phthalaldehyde as starting material

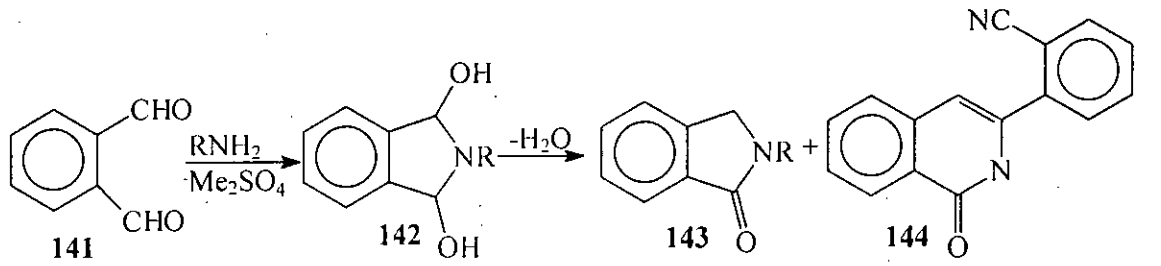
Yamamoto showed[70] that an equimolar mixture of phenyl isocyanate and phthalaldehyde **141** on heating at 170^0 for 4 h afforded *N*-phenylphthalimidine **142** (Scheme 35).



141 142

Scheme 35

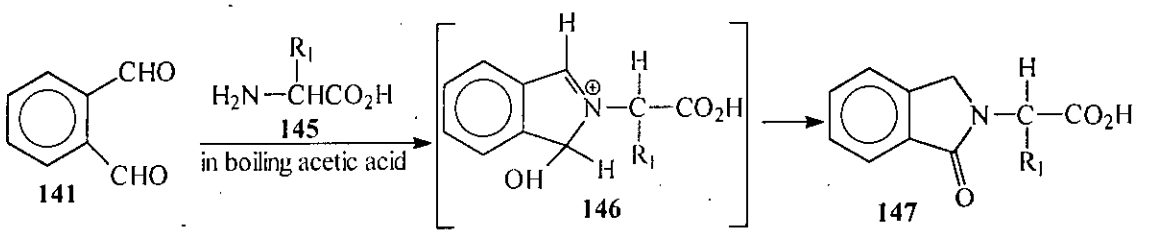
DoMinh *et al.*[71] described a reaction of phthalaldehyde **141** with ammonia and amines in Me_2SO_4 (Scheme–36). Major products were phthalimidines **143** and 3-(2-cyanophenyl)isoquinoline **144**.



141 142 143 144

Scheme 36

Grigg *et al.*[72] investigated the reaction of *o*-phthalaldehyde **141** with α-amino acids **145** in boiling acetic acid and observed that a rapid reaction (5–10 min) accurred to give the *N*-substituted-isoindolin-1-ones **147** (Scheme 37) in good yield.

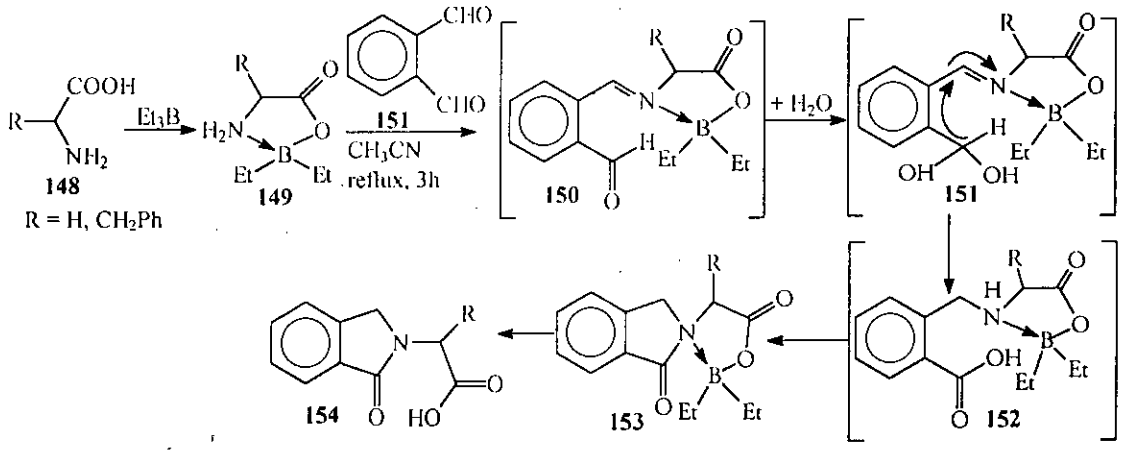


141 146 147

R_1 = H, Ph, Me, iPr, CH_2Ph, CH_2OH

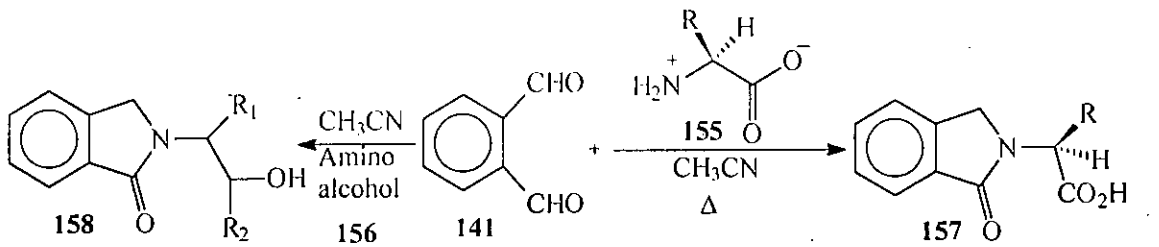
Scheme 37

A new route to isoindolinone derivatives was developed by Nefkens and Zwanenburg[73] as outlined in Scheme 38.



Scheme 38

Allin *et al.*[74] subsequently discovered that the reaction of α-amino acids **155** and amino alcohol **156** with *o*-phthalaldehyde **141** produced the corresponding phthalimidines **157** and **158,** respectively, in good yields (Scheme 39).

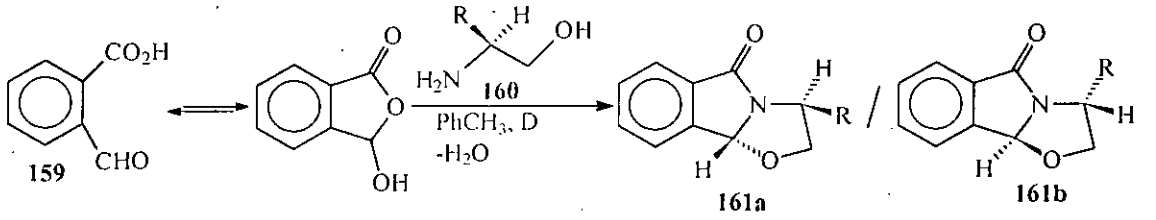


155: L-valine, L-alamine, L-phenylalanine, L-serine, DL-leucine, DL-isoleucine; **157** : R = $CH(CH_3)_2$, CH_3, CH_2Ph, CH_2OH, $CH_2CH(CH_3)_2$, $CHCH_3CH_2CH_3$ respectively; **156** : 2-amino-3-methybutanol, 2-amino-1-butanol, 2-amino-1-phenylpropanol, 2-amino-1-propanol; **158** : R_1/R_2 = $CH(CH_3)_2$/H, CH_2CH_3/H, CH_3/Ph, CH_3/H respectively.

Scheme 39

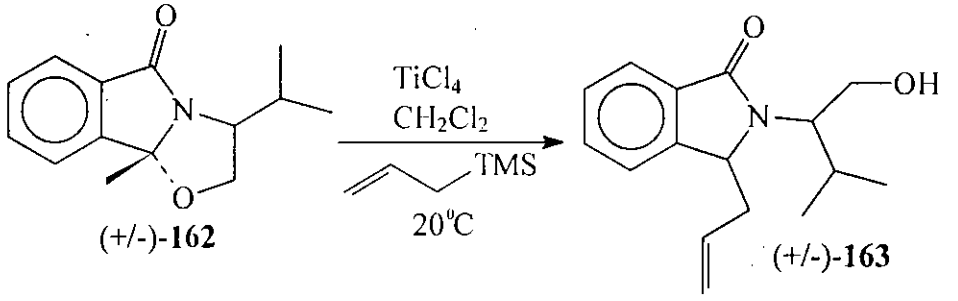
Recently, Allin *et al.*[75] have studied the reaction of α-amino alcohols **160** with 2-formylbenzoic acid **159** as part of an on-going investigation into the preparation and reactivity of the isoindolinone ring system. They have reported the extremely high diastereoselectivity of the reaction to produce the tricyclic γ-lactam products **161** (Scheme 40) through condensation of α-amino alcohols **160** with 2-formylbenzoic acid **159**. This class of heterocycles can act a *N*-acyliminium ion precursors in the synthesis of substituted-isoindolinone derivatives **163** (Scheme 41). The treatment of the (+/–)-

valinol derived tricyclic lactam **162** with titanium tetrachloride at room temperature in dichloromethane prior to addition of allyl trimethylsilane afforded the desired substituted-isoindolinone **163** in 96% isolated yield.



160: (+/-) valinol, (*S*) phenylglycinol, (*R*) phenylglycinol, (*S*) phenylalaninol, (*R*) phenylalaninol; **161a**: R = Ph, CH_2Ph; **161b** : R = Ph, CH_2Ph;

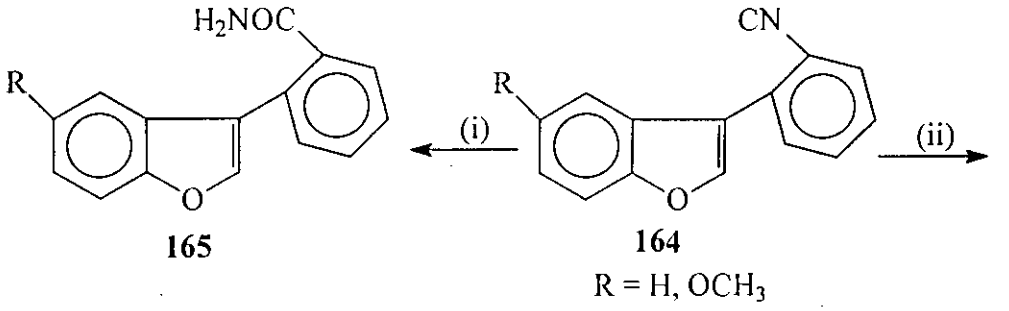
Scheme 40

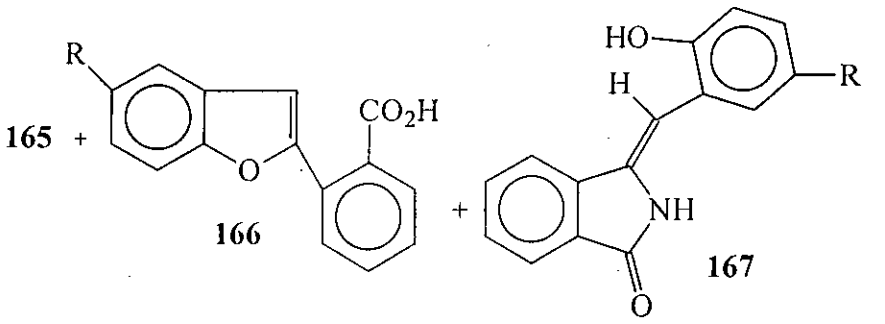


Scheme 41

VIIA.8. Synthesis of isoindolinones through rearrangement reactions

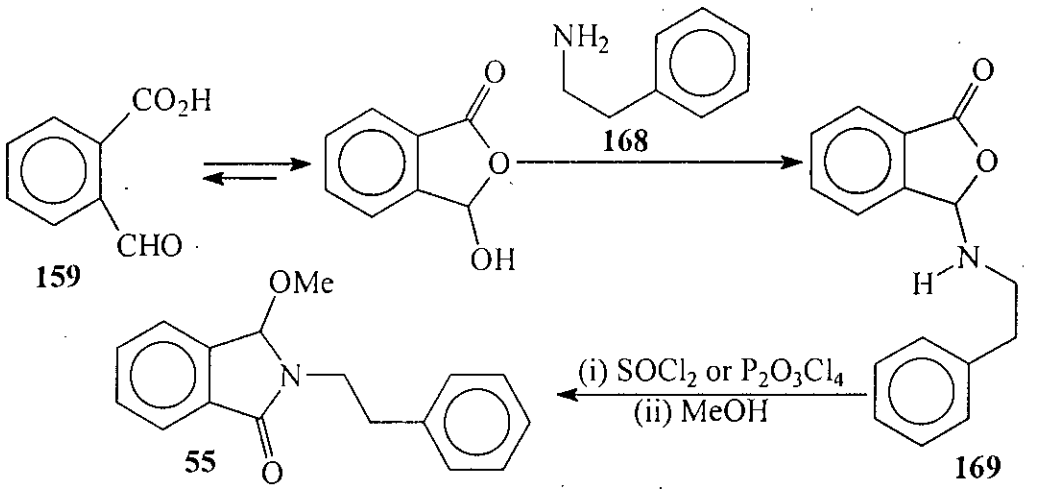
A new route to phenylmethyleneisoindolinones was reported by Guillaumel *et al.*[76]. The alkaline hydrolysis of 2-(2-benzofuranyl)benzonitriles **164** led to Z-2,3-dihydro-3-(2-hydroxyphenylmethylene)-(1*H*)-isoindolin-1-ones **167** by rearrangement (Scheme 42). The formation of the amide **165** or the acid **166** depended on the solvent used.





Scheme 42. *Reagents and conditions:* (i) KOH (3.2 equiv.), ethanol, relux; (ii) KOH (3,2 equiv.), ethyleneglycol or methoxyethanol, reflux.

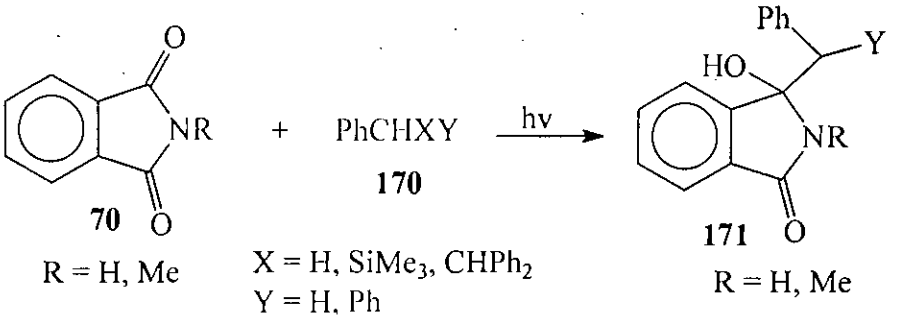
Heaney and Shuhaibar[47] developed a route 3-methoxy-2phenylethylisoindolin-1-one **55** which function as a precursor to synthetically useful acyliminium ions (scheme 43).



Scheme 43

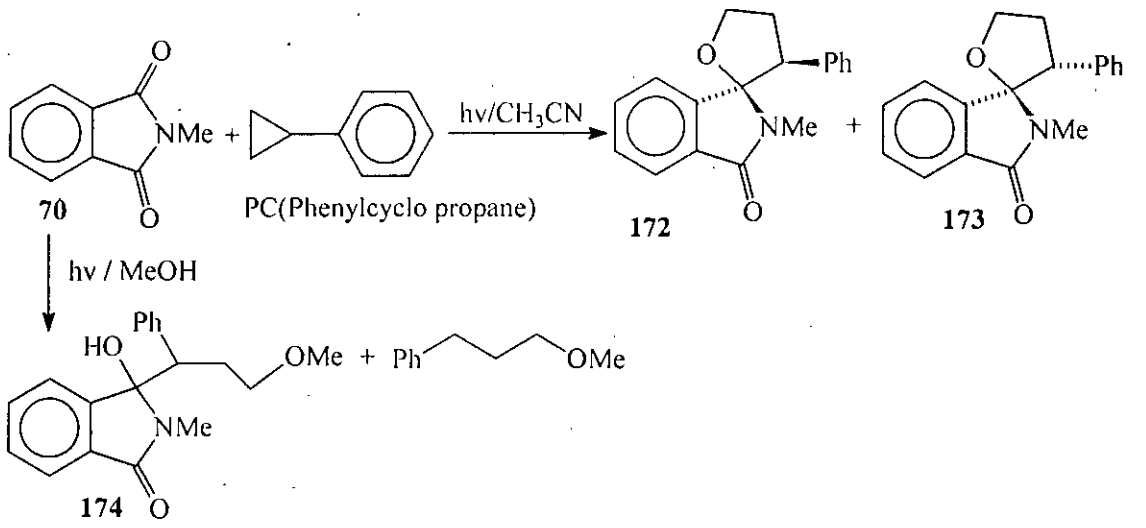
VIIA.9. Synthesis of isoindolinones through photochemical reaction

Freccero *et al.*[77] reported a synthesis of 3-hydroxyisoindolinones **171** by photochemical reactions of phthalimides **70** (Scheme 44)



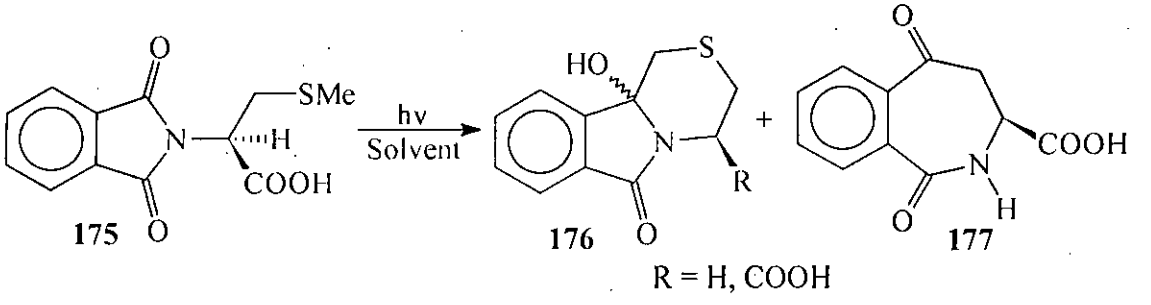
Scheme 44

Weidner-Wells *et al.*[78] showed that *N*-methylphathalimide (NMP) **70** undergoes a photolysis reaction with phenylcyclopropane in acetonitrile to give isomeric spirotetrahy drofuranyl lactams (**172** and **173**). When the reaction was caried out in the nucleophilic solvent MeOH, hydroxylactam **174** and 1-methoxy-3-phenylpropane were obtained (Scheme 45).



Scheme 45

Griesbeck *et al.*[79] photochemically transformed *N*-phthaloylcysteine derivative **175** by elimination, decarboxylation and via electron transfer cyclization to isoindolone derivatives **176** (Scheme 46). The excited singlets were prone to elimination and γ-H abstractions to yield compound **177** whereas the triplets on cyclization afforded 1, 3, 4, 10*b*-tetrahydro-10*b*-hydroxy-6*H*-[1,4]thiazino [3, 4-*a*] isoindol-6-ones **176**.



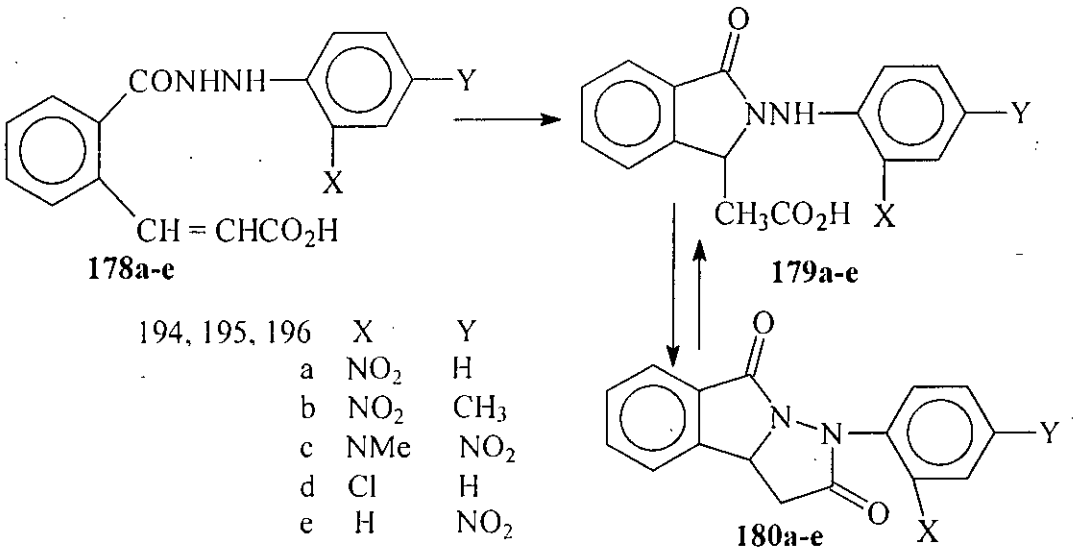
Scheme 46

VIIA.10. Synthesis of isoindolinoes through miscellaneous processes.

Rowe *et al.*[80] reported that the treatment of benzo-2-nitrophenylhydrazide-2-acrylic acid **178a** with boiling dilute Na_2CO_3 solution, H_2O or nitrobenzene afforded 2-(2-nitrophenylamino) isoindolinone-3-acetic acid **179a**. When isoindolinone derivative **179a** was boiled with acetic anhydride with or without addition of pyridine or refluxed with toluene in the presence of phosphorus trichloride, 1 molecule of water was eliminated, yielding 2,5-diketo-3-(2′-nitrophenyl)isoindolinopyrazolidocoline **180a** which was readily hydrolyzed to **179a** preferably by acids (Scheme 47). Similarly, other compounds **179b-e** and **180b-e** were synthesized.

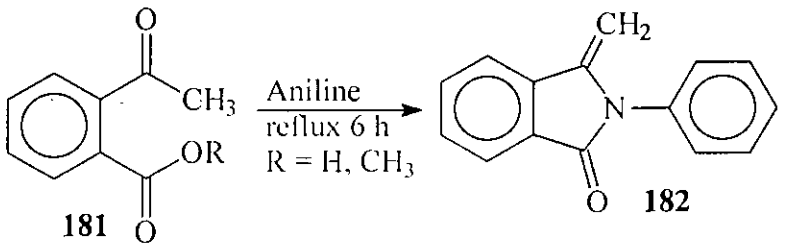
Pojer *et al.*[81] prepared methyleneisoindolinone **182** by refluxing acetylbenzoic acid or its methyl ester **181** with aniline (Scheme 48)

An interesting approach to isoindolinone **184** was published



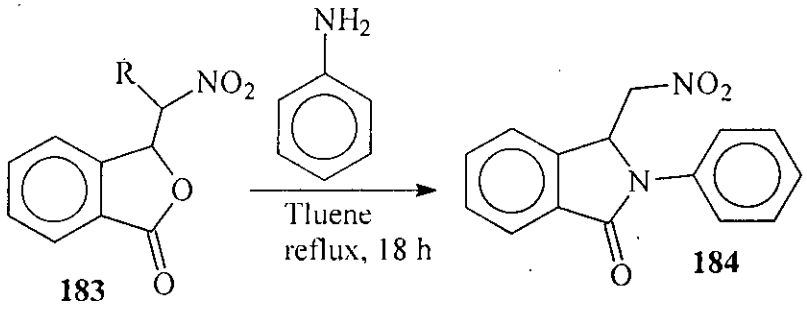
194, 195, 196	X	Y
a	NO_2	H
b	NO_2	CH_3
c	NMe	NO_2
d	Cl	H
e	H	NO_2

Scheme 47



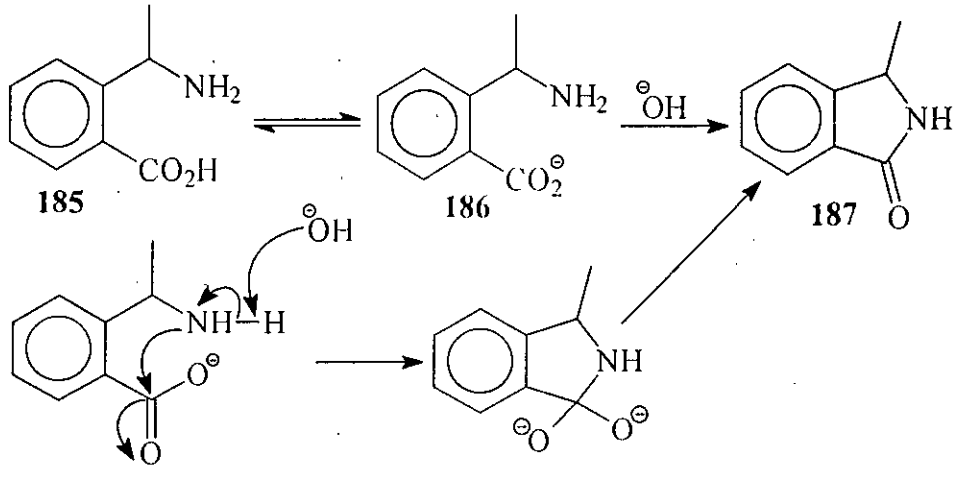
Scheme 48

by Whelton and Huitric[82] involving the reaction of the nitrolactone **183** with bases. The reaction of **183** with aniline led to the phthalimidine **184** (Scheme 49).



Scheme 49

Camileri and Cassola[83] repoted a reaction in which the 2-(1-aminoethyl)benzoate anion cyclized to the lactam 3-methylisoindoline **187** at high pH. 2-(1-Aminoethyl)benzoic acid **185** (prepared by catalytic hydrogenation of the oxime of 2-acetyl benzoic acid) was cyclized in presence of 0.1 *M*-NaOH to yield lactam **187**. They proposed the mechanism shown in Scheme 50.

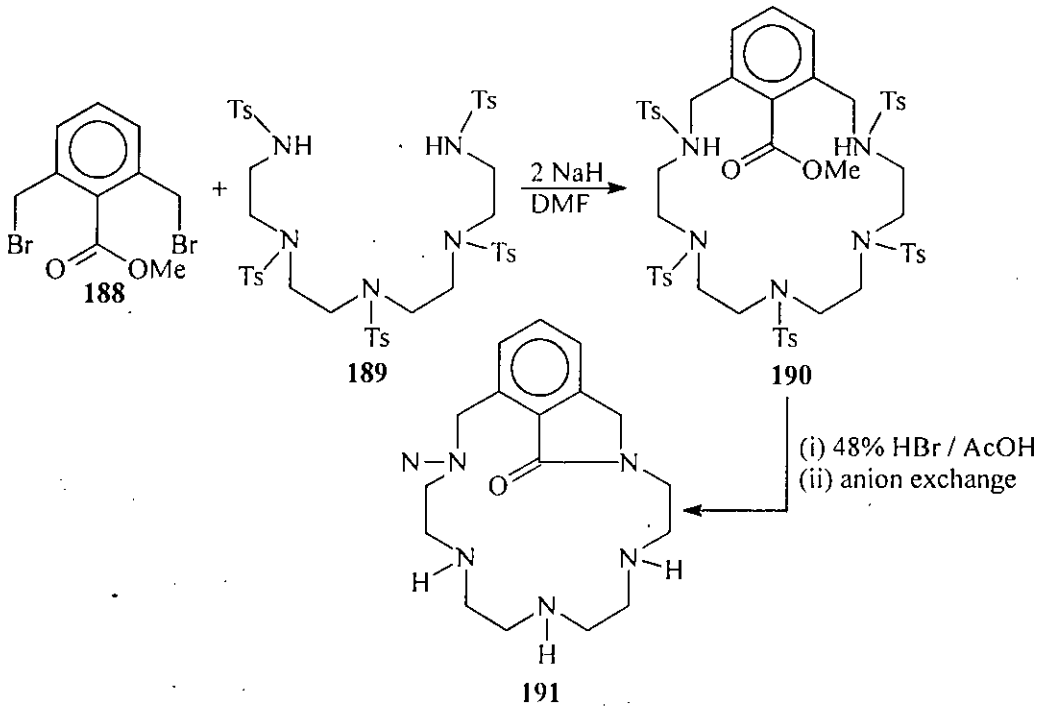


Scheme 50

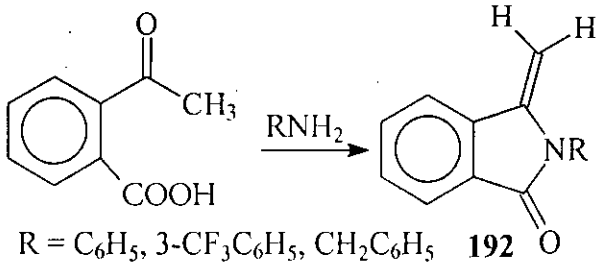
Kimura *et al.*[84] synthesized a new macrocyclic polyamine **191** containing a phthalimidine ring (Scheme 51).

A general procedure for 2,3-dihydro-3-methylene-2-substituted-1 *H*-isoindol-1-ones (3-methylenephthalimidines) **192** was developed by Howe and Shelton[85] (Scheme 52).

An improved method for the synthesis of phthalimidine

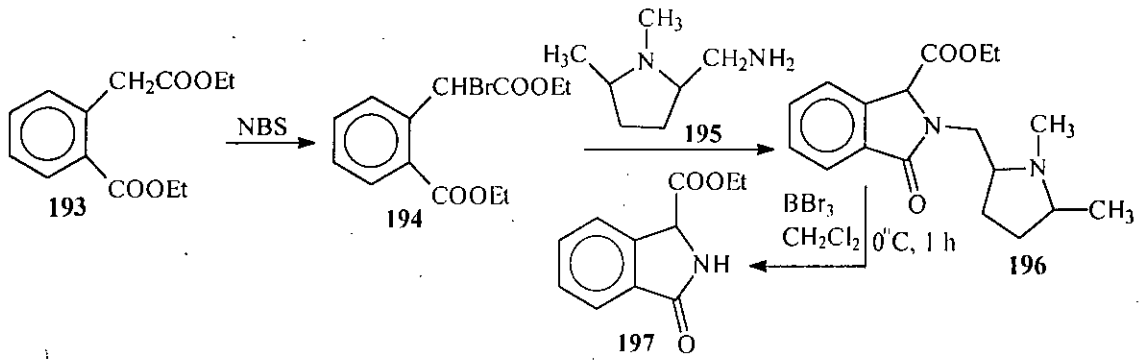


Scheme 51



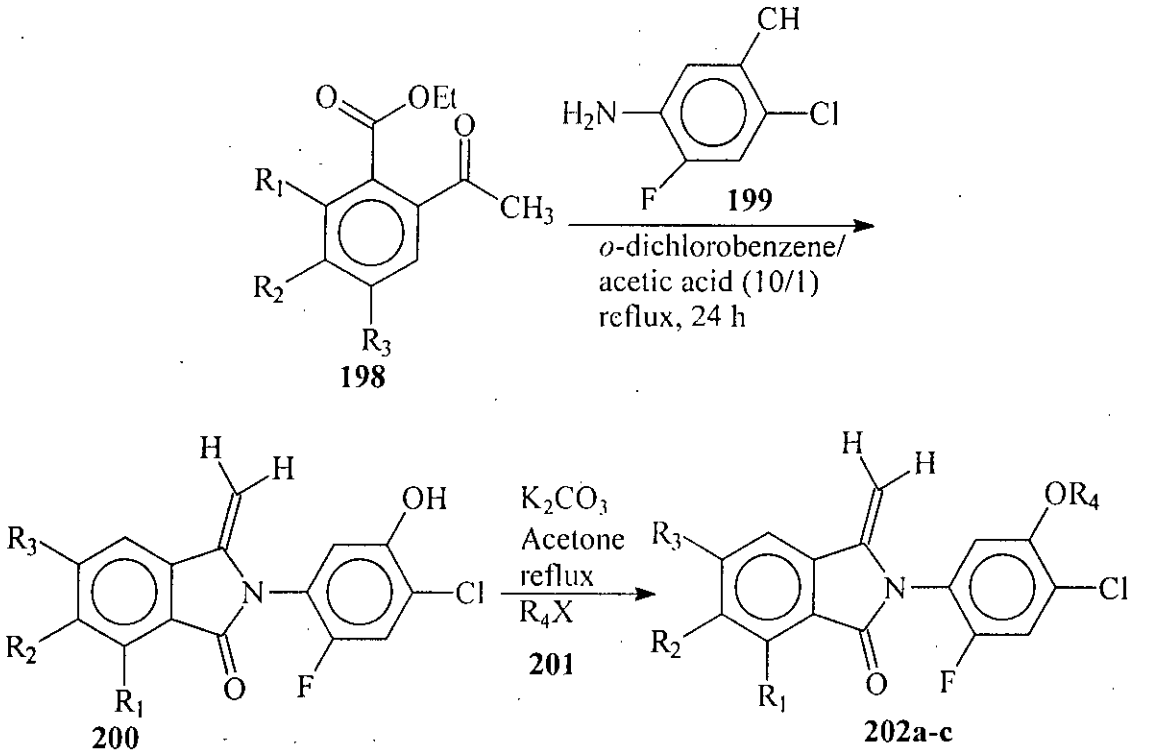
Scheme 52

3-carboxylate was reported by Othman and Decroix[45], (Scheme 53).



Scheme 53

A facile synthetic method for the herbicidal 2,3-dihydro-3-methylene-2-aryl-1*H*-isoindol-1-one system **202a-c** was described by Kim and Ryu[36] (Scheme 54).



198, 200, 202	R_1	R_2	R_3
a	H	H	F
b	H	H	Cl
c	H	OCH_3	H
d	H	CH_3	CH_3
e	Cl	H	Cl

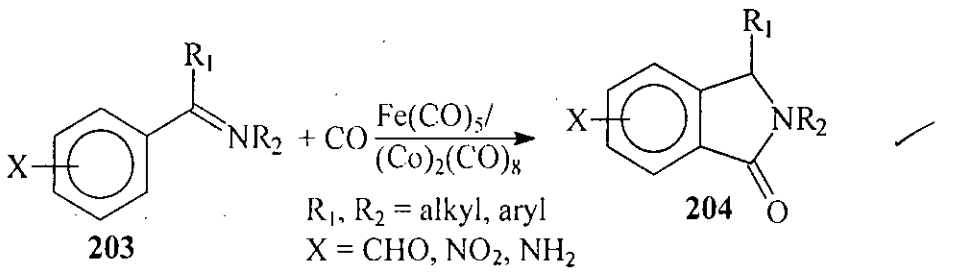
201, R_4X: a) propargyl bromide, b) ethyl iodide, c) 2-chloropropionitrile

Scheme 54

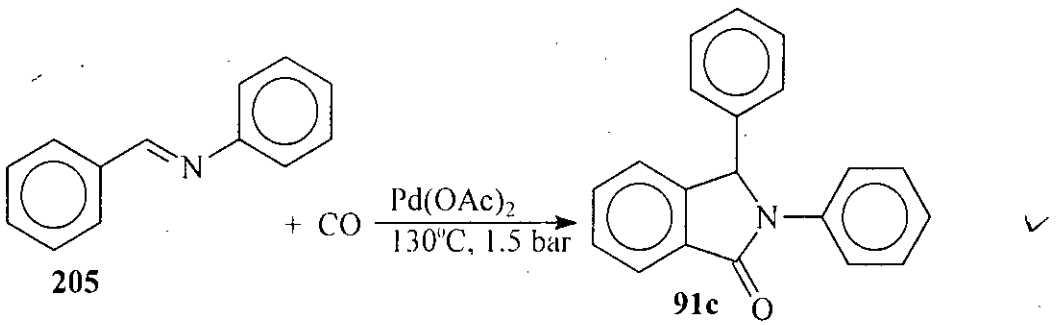
VIIB. Synthesis of isoindolinones through metal mediated reactions

Several methods of synthesis of isoindolinones (phthalimidines) under metal catalysis were discussed by Wilkinson *et al.*[86] where various starting compounds including Schiff bases, aromatic nitrites, ketoximes, phenylhydrazones, semicarbazones and azines have been carbonylated. A series of isoindolinones **204** were produced by the carbonylation of Schiff bases **203** of aromatic and aliphatic amines[87,88]. The reaction was catalyzed by metal carbonyls like pentacarbonyl iron and octacarbonyl dicobalt. The best results were

obtained from cobalt-catalyzed carabonylation which was performed in the temperature range 200-230^0 under a CO pressure of 100-200 bar (Scheme 55). The reaction was also catalyzed by Pd(II)-acetate under milder condition (Scheme 56). Polar solvents were found to inhibit the reaction.

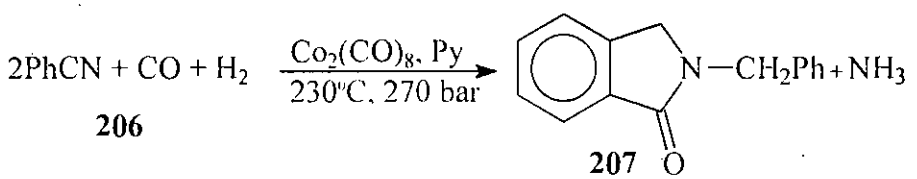


Scheme 55



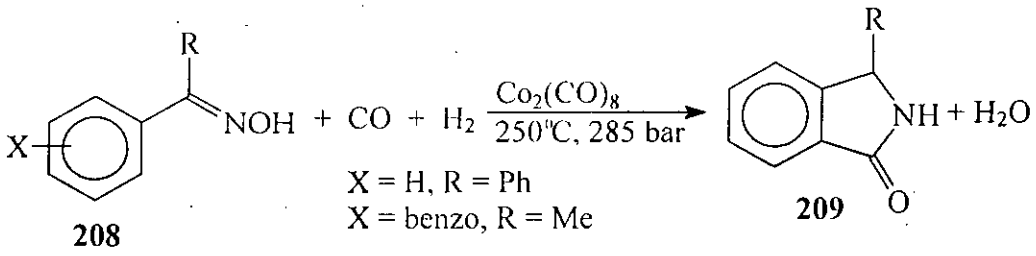
Scheme 56

Phthalimidine derivative **207** was synthesized from the carbonylation of aromatic nitrile **206** under a pressure of CO containing variable amounts of hydrogen in the presence of a cobalt catalyst; the best yields were observed when a small quantity of pyridine was added to the reaction[89] (Scheme 57).



Scheme 57

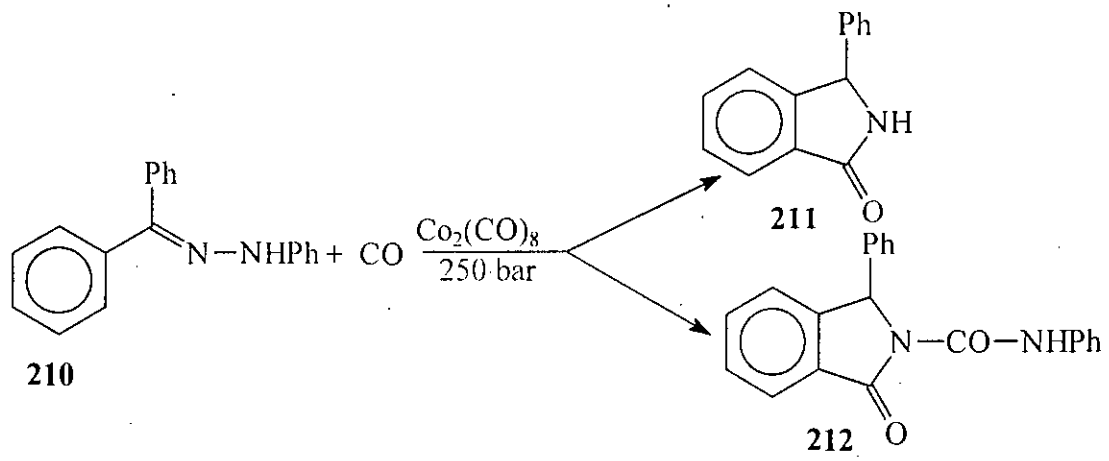
3-Substituted-phthamidines **209** were prepared from the carbonylation of aromatic ketoximes **208** in the presence of hydrogen and the catalyst octacarbonyl dicobalt. The reaction was more selective with diaryl ketoximes than with arylalkyl ketoximes[89] (Scheme 58).



Scheme 58

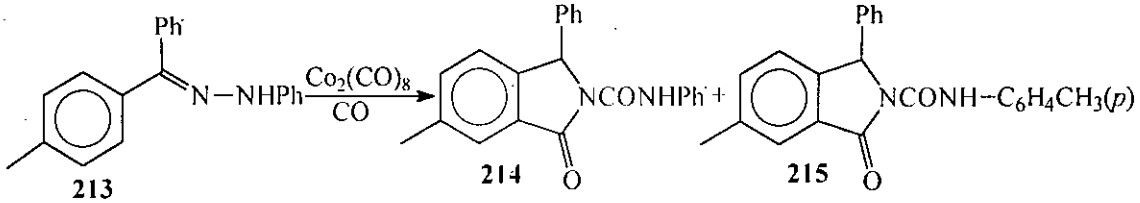
The same reaction applied to the *o*-methyl ether of benzophenone oxime resulted in 3-phenylphthalimidines.

It was reported that benzophenone phenyl hydrazones **210** gave rise to 3-phenylphthalimidine **211** in the presence of octacarbonyl di-cobalt without hydrogen gas at 190-200^0, but at higher temperature (230–240^0) 3-phenyl-*N*-(*N'*-phenylcarbamoyl)phthalimicine **212** was obtained via insertion of CO into the nitrogen-nitrogen bond[88,90] (Scheme 59).



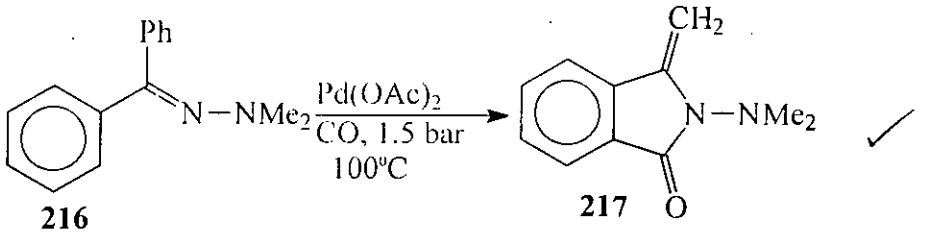
Scheme 59

In the case of unsymmetrically substituted diaryl ketone phenyl hydrazones, e.g. **213**, a mixture of isomeric phthalimidines **214** and **214** were obtained (Scheme 60).



Scheme 60

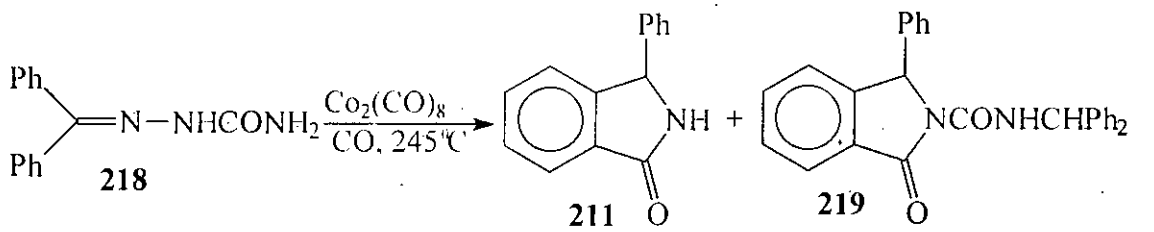
Phthalimidine **217** was also prepared from acetophenone-1,1-dimethylhydrazone **216** through carbonylation reaction mediated by Pd (II)-acetate under much milder conditions[90] (Scheme 61).



216 **217**

Scheme 61

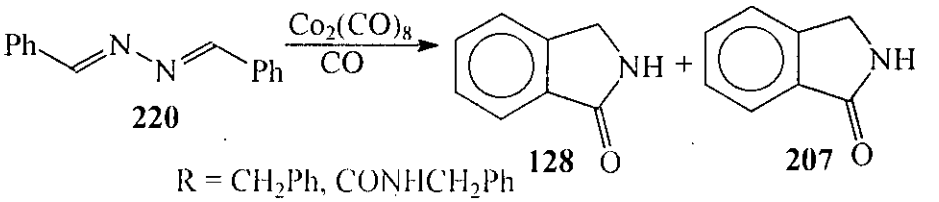
3-Phenylphthalimidines **211** and **219** were obtained when benzophenone semicarbazone **218** reacted with CO in the presence of cobalt catalyst at higher temperature (245^0)[89,90] (Scheme 62).



218 **211** **219**

Scheme 62

Benzaldehyde azine **220** also gave different *N*-substituted-phthalimidines **128** and **207** under the reaction with CO in the presence of cobalt-catalyst (Scheme 63).

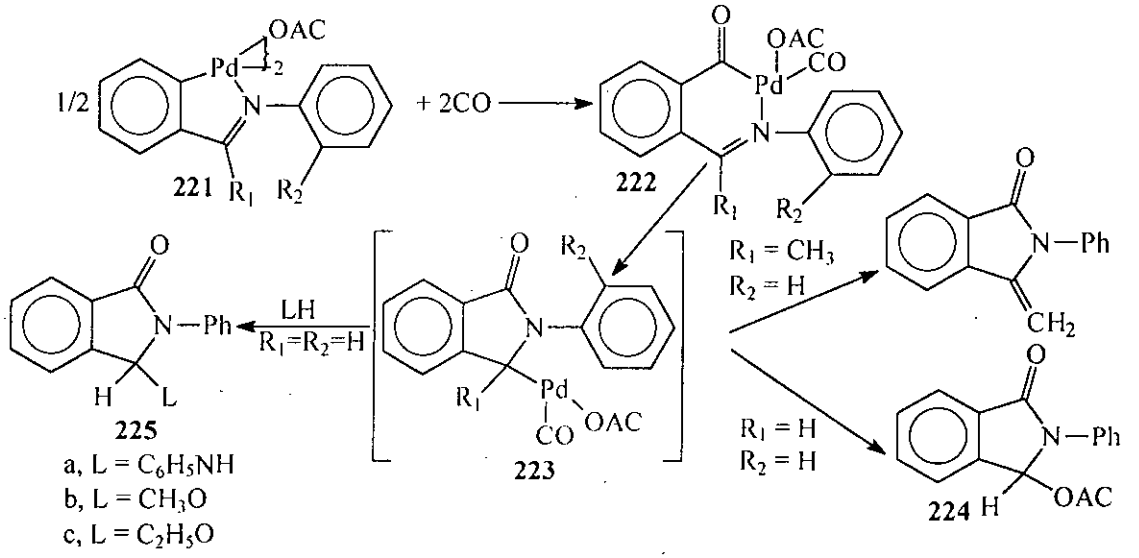


220 **128** **207**

R = CH_2Ph, $CONHCH_2Ph$

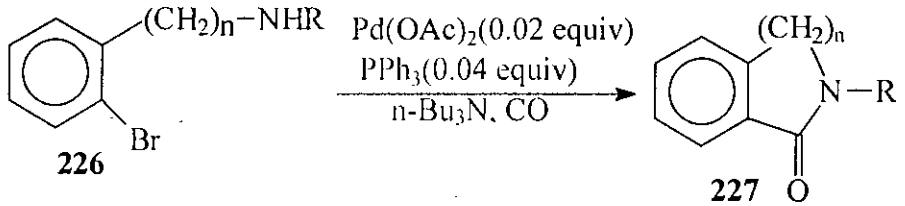
Scheme 63

Thompson and Heek[91] described the carbonylation of the palladium acetate complex **221** to yield 3-acetoxy-2-phenylphthalimidine **224**. The carbonylation of **221** in presence of a nucleophile, e.g. aniline, led to 3-anilino-2-phenylphthalimidines **225** rather than the acetate (Scheme 64).



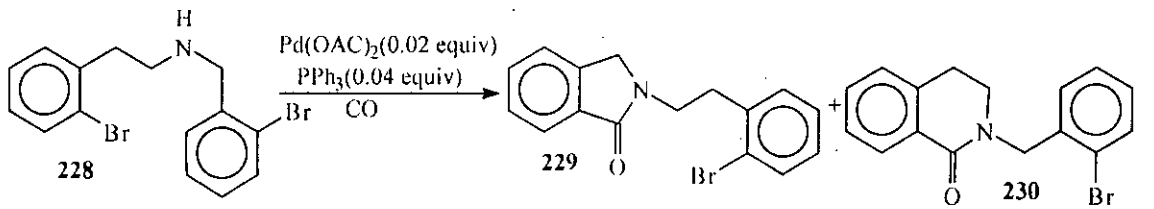
Scheme 64

Mori *et al.*[92] developed a synthesis of benzolactams, i.e. isoindolinone, isoquinoline and benzazepinone derivatives by palladium catalyzed amidation. In a typical example, *N*-benzyl-*o*-bromobenzylamine **226** was treated with *n*-Bu_3N, PPh_3 and a catalytic amount of $Pd(OAc)_2$ in presence of CO at 100^0 for 26 h to afford *N*-benzylisoindolin-l-one **227** (Scheme 65).



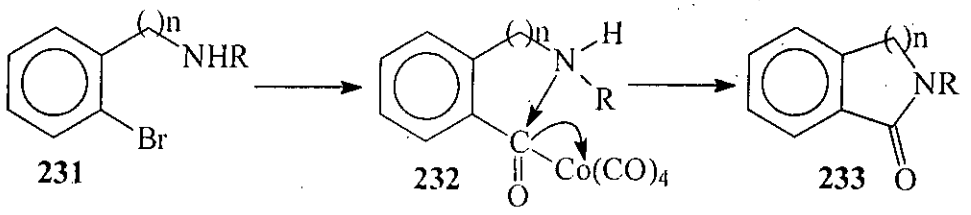
Scheme 65

However, *o*-bromo-*N*-(*o*'-bromobenzyl)phenylethylamine **228**, was cyclized to yield isoindolinone **229** and isoquinolinone **230** in a 2.6 : 1 ratio under the same conditions (Scheme 66).



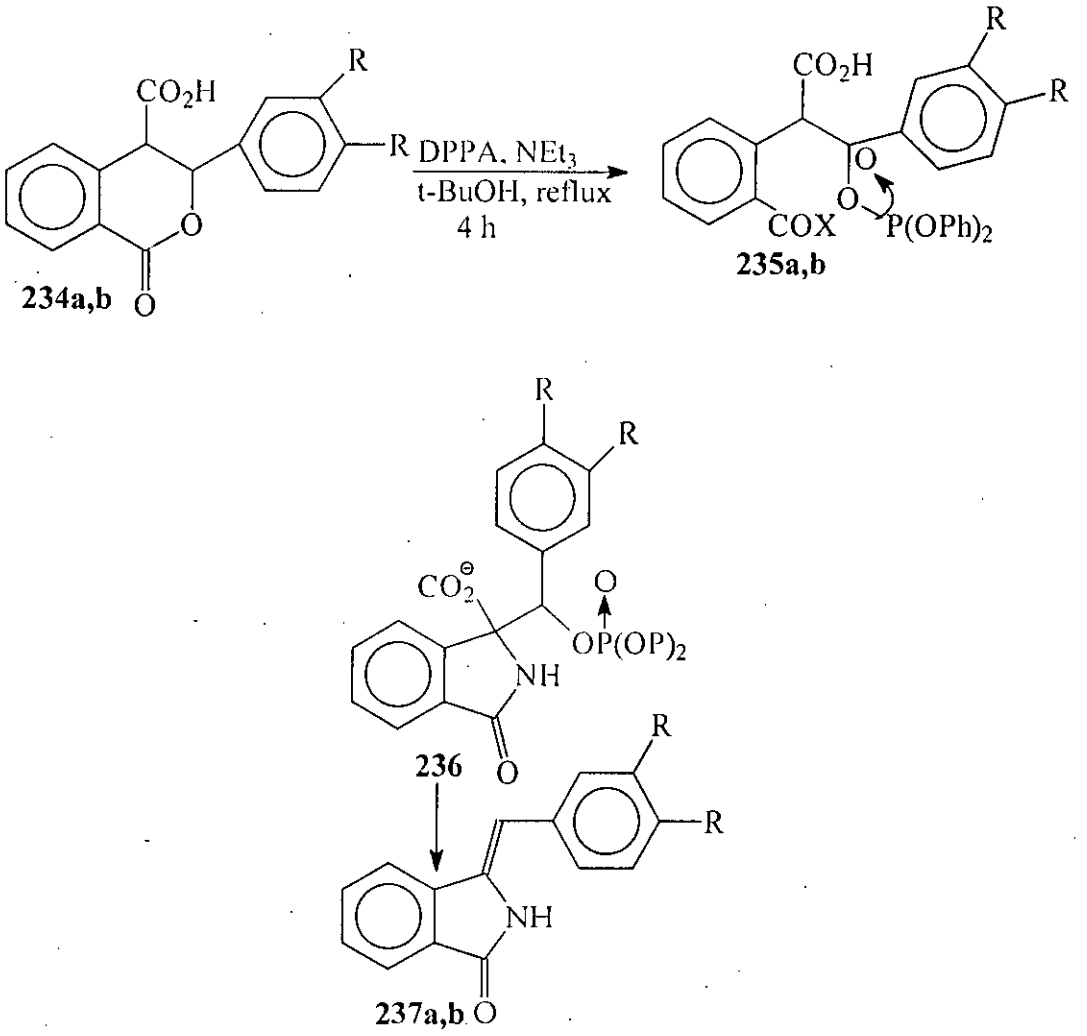
Scheme 66

Brunet *et al.*[93] developed cobalt carbonyl catalyzed carbonylation of arylhalides **231** under phase-transfer-catalysis conditions for the synthesis of benzolactam **233** (Scheme 67).



Scheme 67

Dikshit[94] reported a novel reaction of 3-(3',4'-dimethoxyphenyl)-3,4-dihydro-i-oxo-1*H*-2-benzopyran-4-carboxylic acid **234a** and 3-phenyl-3,4-dihydro-l-oxo-1*H*-2-benzopyran-4-carboxylic acid **234b** to yield 2,3-dihydro-3-arylmethylene-1*H*-isoindol-1-ones **237a,b** (Scheme 68).



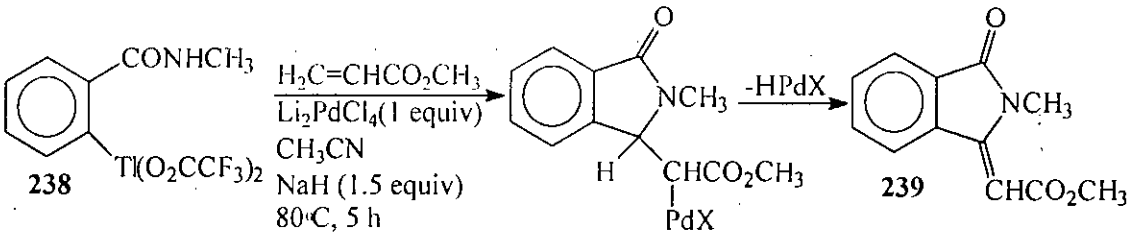
234a R = OMe
b R = H

235a X = N_3
b X = N

237a R = CH_3
b R = H

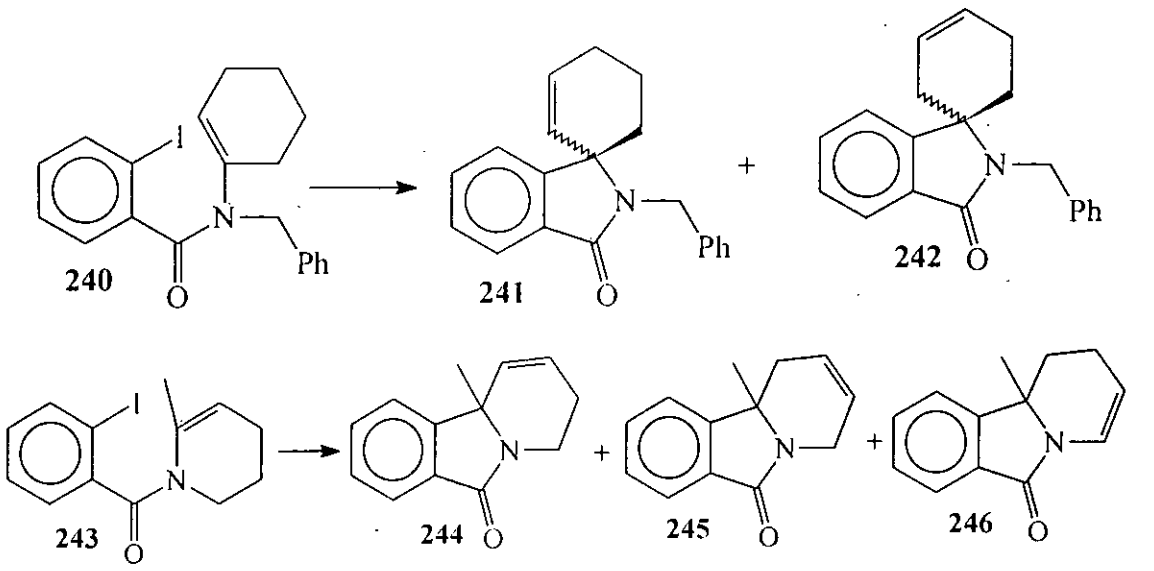
Scheme 68

Larock *et al.*[95] carried palladium-promoted olefination reaction of thallated *N*-methylbenzamide **238** with methyl acrylate to yield an isoindolinone **239** (Scheme 69).



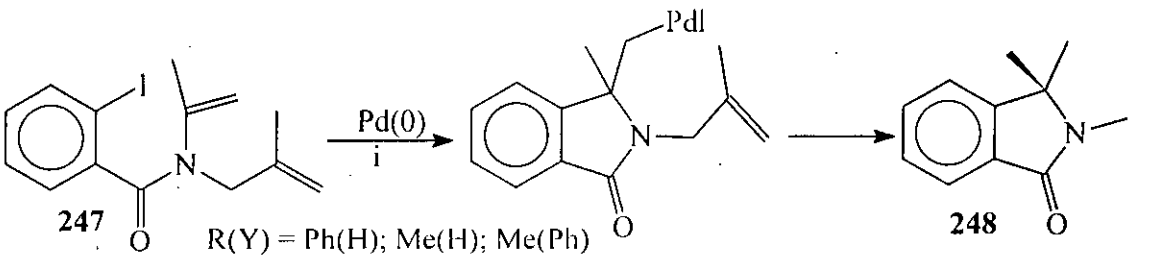
Scheme 69

Grigg *et al.*[96] reported intramolecular Heck reactions for the preparation of isoindolinone derivatives **241, 242, 244-246** (Scheme 70).



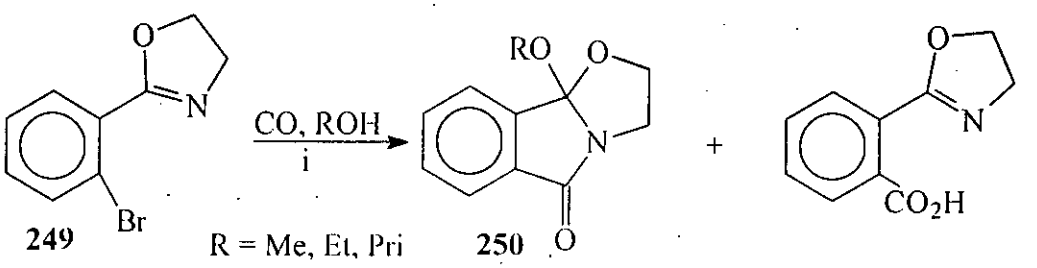
Scheme-70

Burns *et al.*[97] developed a palladium-catalyzed tandem cyclization-anion capture process. They reported that enamide **247** undergoes regiospecific5-exo trig-biscyclization (DMF, 80^0) followed by hydride capture to afford the tricyclic products **248** (Scheme 71).



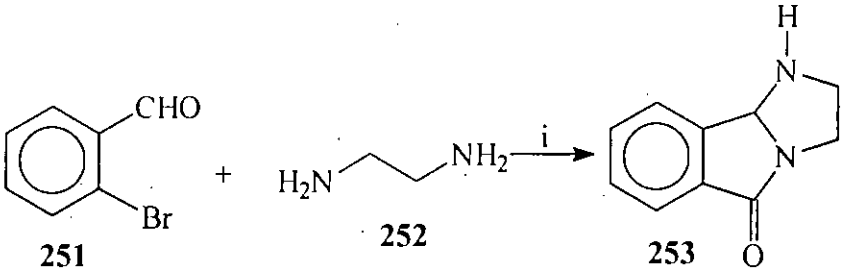
Scheme 71. *Reagents and conditions*: (i) $Pd(OAc)_2$, PPh_3, Bu_4NCl, sodium formate, DMF or CH_3CN, $80^0/100^0$, 6/16 h.

Cho *et al.*[98] synthesised isoindolinones **250** via carbonylative cyclization of 2-(2-bromophenyl)-2-oxazolines **249** by a bimetallic palladium nickel catalyst system with carbon monoxide (3 atm) in alcohol as shown in Scheme 72.



Scheme 72. *Reagents and conditions* $PdCl_2(PPh_3)_2$, $NiCl_2.6H_20$, PPh_3, Et_3N, 3 atm, 100^0.

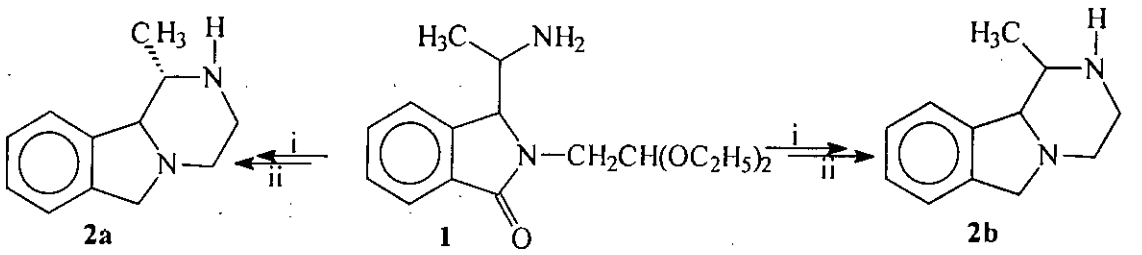
A synthesis of tricyclic isoindolinone **253** by the palladium-catalyzed carbonylative cyclization of 2-bromobenzal dehyde **251** with diamines **252** was carried out by Cho *et al.*[99] (Scheme 73).



Scheme 73. *Reagents and conditions*: (i) 2-Bromobenzaldehyde(2 mmol), ethylenediamine(3 mmol), $(PPh_3)_2PdCl_2$ (0.03 mmol), PPh_3(0.08 mmol), Et_3N(5 mmol), CH_3CN(10 ml), CO (13 atm), 100^0, 20 h.

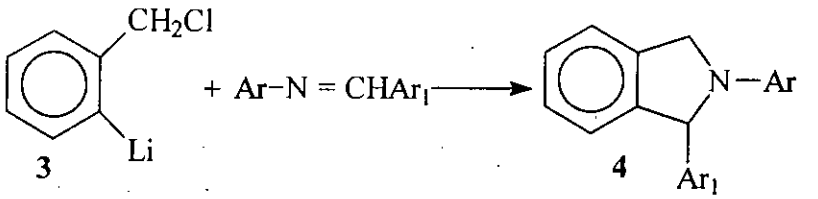
VIII. Synthesis of Isoindolines

A synthesis of pyrazino [2,1-a]isoindole derivative **2** via isoindolinone **1** was developed by Ferland *et al.*[21] (**Scheme 1**). The analogue, e.g. 1,2,3,4-tetrahydropyrazino [2,1-a]isoindol-6-one was found to lower blood pressure in spontaneously hypertensive rats.



Scheme 1. *Reagents*: (i) MeOH, 1N HCl, H_2, Pd/C; (ii) THF, 1M diborane in THF.

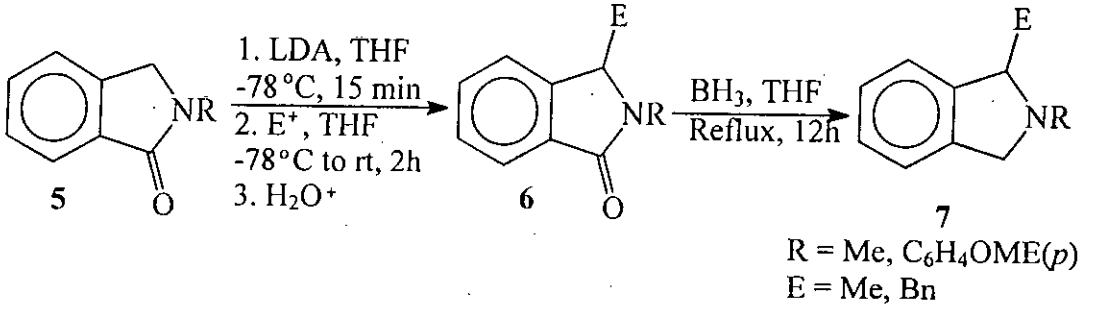
An effective reaction of Schiff bases with certain functionlized organolithium reagents was described by Bradsher and Hunt[100] for the synthesis of 1, 2-diarylisoindolines **4** (**Scheme 2**).



4 : a) Ar = Ar_1 = Ph; b) Ar = 4-BrC_6H_4, Ar_1 = Ph; c) Ar = 2-$BrMeC_6H_4$, Ar_1 = Ph; d) Ar = Ph, Ar_1 = 3,4-$(OCH_3)_2C_6H_3$.

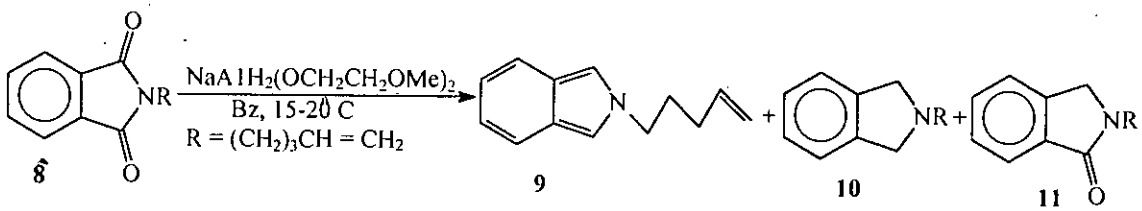
Scheme 2

Couture *et al.*[101], recently reported that 2-alkyl-2,3-dihydroisoindol-1-ones **5** are easily and regioselectively deprotonated at the 3-position of the heterocyclic nucleus with LDA, thus providing ready access to 3-substituted and / or functionalized isoindolinones **6** and consequently to the corresponding isoindolines **7** (Scheme 3).



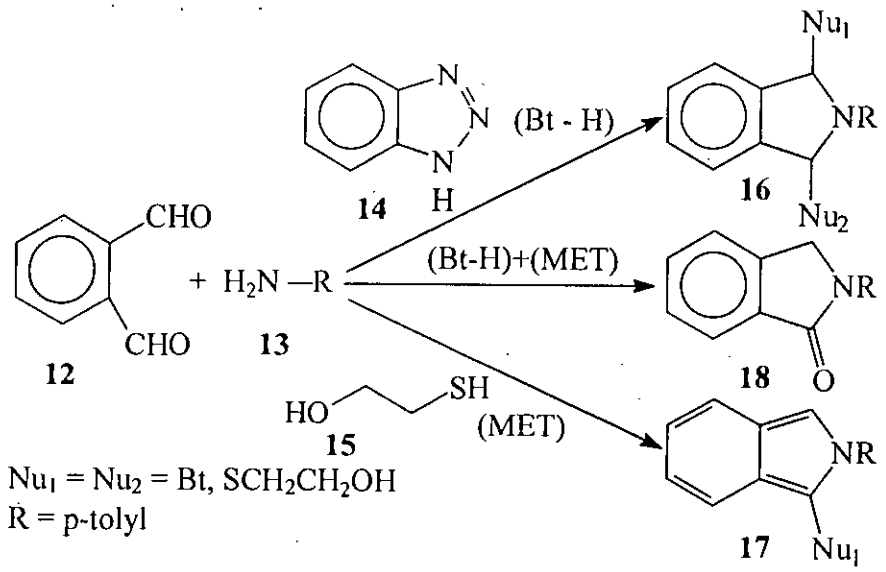
Scheme 3

Ciganek[102] prepared a mixture of *N*-4-pentenylisoindole **9**, isoindoline **10** and isoindolinone **11** by the reduction of *N*-4-pentenylphthalimide **8** with sodium bis(2-methoxyethoxy)aluminium hydride; *N*-4-pentenylisoindole **9** was the major product **(Scheme 4)**.



Scheme 4

Simons, Stobaugh and Takahashi, reported the quantitative formation of 2*H*-isoindole derivatives **16–18** (Scheme 5)[103-107].



Scheme 5

Section-2

Present work :
A Highly Regio- and Stereoselective Synthesis of (*Z*)-3- Aryl (alkyl)idene isoindolin-1- ones by Palladium – catalyzed Annulation of Terminal Alkynes

2.1 Rationale for present work

Heterocyclic compounds containing the isoindolinone skeleton have generated considerable interest in recent years as reflected by recent articles dealing with their synthesis and emphasizing their biological and medicinal properties. Our interest in isoindolinones stemmed from their fascinating chemistry, pharmaceutical and medicinal properties (as described in section–1). Naturally occurring and synthetic isoindolin-1-ones have a range of biological activities[20] including antihypertensive[21], antiinflammatory[22], antipsychotic[23–26], anesthetic[27], vasodilatory[28], antiulcer[30], antiviral[32–33] and antileukemic[34] properties. A number of isoindolin-1-ones have been found to be potent herbicides[36]. Isoindolin-1-ones have also been extensively used for the synthesis of various drugs[39,38] and naturally occurring compounds[43,45–46].

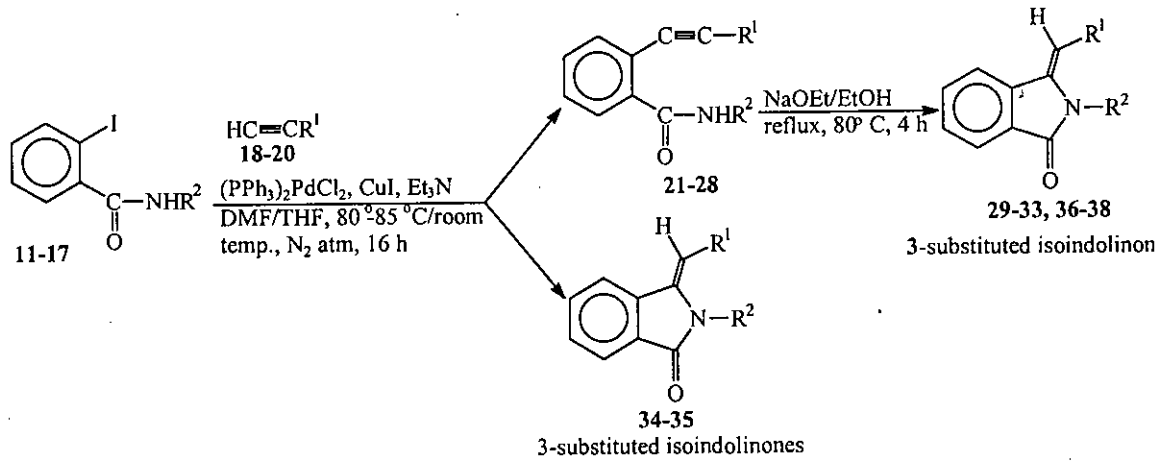
A number of methods have been developed for the synthesis of isoindolines and isoindolinones (phthalimidines). They fall under the following catagories: (i) high temperature procedures based on Gabriel's method[48] for the synthesis of phthalides and phthalimidines, involving the reaction of phthalides with substituted amines[49] or the reaction of phthalimides with aryl acetic acids[50], (ii) a Grignard procedure[52], (iii) Lithiation procedures[54-55,57,61,101], (iv) Wittig reactions on phthalimides or benzamides[62-64], (v) Diels-Alder reactions[34,65], (vi) reduction[66] of *N*-substituted phthalimides to the corresponding phthalimidines; (vii) Condensation of phthalaldehyde with phenyl isocyanate, amines, α-aminoacids[70-72,107], boroxazolidene[73], or iminophosphoranes[108]; (viii) rearrangement reactions of benzofurans or phthalides[46,76], (ix) phtochemical reactions[77-78] and (x) miscellaneous procedures[80,81-82,85]. Besides the above classical methods, several metal (e.g. cobalt or rhodium carbonyl complexes) mediated synthesis of isoindolinones have also been reported[86], but few examples of palladium catalysis[92,95,97-98] have appeared.

Palladium-catalyzed reactions[109] have been extensively utilized for carboannulation[110] and heteroannulation[111]. Aromatic heterocycles can be accessed via palladium catalyzed cyclizatons allow synthesis of a wide variety of heterocycles[112] using vinylic compounds, terminal alkynes and allenes.

In view of the extensive natural occurrence and biological importance of isoindolin-1-one derivatives we planned to develop a general and facile method for the synthesis of isoindolin-1-ones. We became interested in the palladium catalyzed heteroannulation for the synthesis of isoindolinones.

2.2 Results and discussion

We now report a new strategy for the synthesis of isoindolinones **29–38** by the palladium-catalyzed condensation of 2-Iodobenzamides **11–17** with terminal alkynes **18–20** and subsequent cyclization (**Scheme-1**)



Scheme - 1

Compounds	R^1	R^2
11 18 21 29	Ph	C_6H_4Cl-*p*
12 22 30	Ph	$CH_2C_6H_4Cl$-*p*
13 23 31	Ph	H
14 24 32	Ph	CH_3
15 25 33	Ph	CH_2Ph
16 34	Ph	C_6H_4OMe-*p*
17 35	Ph	Ph
17 19 26	$SiMe_3$	Ph
16 27	$SiMe_3$	C_6H_4OMe-*p*
16 20 28 38	$(CH_2)_3CH_3$	C_6H_4OMe-*p*
36	H	Ph
37	H	C_6H_4OMe-*p*

Our results (Table-1) demonstrate that a number of 3-Aryl(alkyl)idene isoindolin-1-ones were formed without any formation of the corresponding Isoquinolinones.

Table –1: Palladium-catalysed reactions of 2-iodobenzamides (11–17) with terminal alkynes (18–20) leading to isoindolinones 29–38 (Scheme 1, page 42)

Entry	2-iodobenzamide (R^2)	Alkynes (R^1)	Conditions	2-Alkynyl bezamides [%][a]	Conditions	isoindolinones [%][b]
1.	11 (C_6H_4Cl-*p*)	18 (Ph)	A	21 [80]	C	29 [80]
2.	12 ($CH_2C_6H_4Cl$-*p*)	18 (Ph)	A	22 [84]	C	30 [75]
3.	13 (H)	18 (Ph)	A	23 [78]	C	31 [60]
4.	14 (CH_3)	18 (Ph)	A	24 [70]	C	32 [62]
5.	15 (CH_2Ph)	18 (Ph)	A	25 [76]	C	33 [60]
6.	16 (C_6H_4OMe-*p*)	18 (Ph)	A	-	-	34 [80][a]
7.	17 (Ph)	18 (Ph)	A	-	-	35 [80][a]
8.	17 (Ph)	19 ($SiMe_3$)	B	26 [70]	C	36 [65]
9.	16 (C_6H_4OMe-*p*)	19 ($SiMe_3$)	B	27 [70]	C	37 [75]
10.	16 (C_6H_4OMe-*p*)	20 [$(CH_2)_3CH_3$]	B	28 [90]	C	38 [60]
11.	11 (C_6H_4Cl-*p*)	18 (Ph)	D	21 [60]	C	29 [70]
12[c].	16 (C_6H_4OMe-*p*)	18 (Ph)	E	-	-	-
13.	11 (C_6H_4Cl-*p*)	18 (Ph)	F	21 [75]	C	29 [72]
14.	12 ($CH_2C_6H_4Cl$-*p*)	18 (Ph)	G	22 [45]	C	30 [70]
15.	11 (C_6H_4Cl-*p*)	18 (Ph)	A	21 [80]	H	29 [50]

[a]yields are based on 2-iodobenzamides.
[b]yields are based on 2-alkynyl benzamides.
[c]the entry **12** afforded only deiodinated product **39**.

The reaction were usually carried out by heating a mixture of 2-Iodobenzamide or its *N*-substituted derivatives **11–17** (1 mmol) and alkyne **18** (1.2 equiv.) in DMF/THF (10 ml) at 80–85 °C for 16/24 h in the presence of bis(triphenyl phosphine) palladium (II) chloride (3.5 mol%), copper (I) iodide (8 mol%) and triethylamine (4 equiv.) [entries 1–7, condition A].

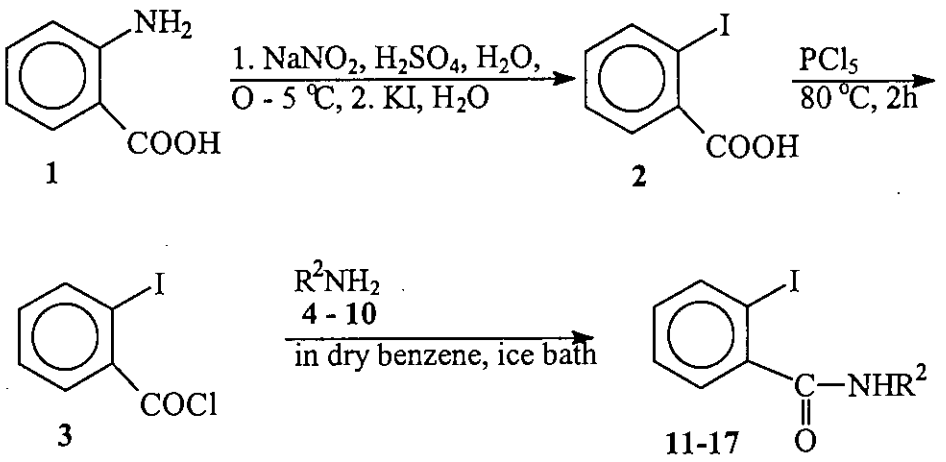
However with (trimethylsilyl)acetylene **19**, and n-hexyne **20**, 1.2 equiv. of the alkynes were used and the reactions were performed at room temperature for 24 h (entries 8–10, condition B). In the case of entries 6–7 the cyclized products, e.g. the isoindolinones **34–35** were obtained directly usually in excellent yields. But in other cases (all entries except 6–7) the open chain condensation products **21–28** were the major products which were cyclized in the same pot, after removal of solvent, by refluxing with sodium ethoxide in ethanol (condition C) for 4 h to afford the isoindolinones **29–33, 36–38** respectively in good yields. The cyclization was also carried out with pure open chain products which were isolated and characterized completely. The yields of the cyclized products were almost the same in both cases.
When trimethylsilyl acetylene **19** was used as the alkyne (entries 8–9), the trimethylsilyl group was completely removed under the cyclization condition C to afford 3-methylene isoindolinones **36, 37**.

It was observed that the alkyne (phenylacetylene) underwent considerable dimerization[116] during the heteroannulation reaction which led to somewhat reduction in yields of the desired products.

2.2.1 Starting materials

Synthesis of 2-Iodobenzamides 11–17

2-Iodobenzamides **11–17** have been used as starting materials because of their easy availability from anthranilic acid. Diazotization of anthranilic acid (2-aminobenzoic acid) followed by sandmeyer iodination with potassium iodide afforded 2-Iodobenzoic acid shown in **Scheme 2 (page 45)**.



Scheme 2

4, 11 $R^2 = C_6H_4Cl$–*p*

5, 12 $R^2 = CH_2C_6H_4Cl$–*p*

6, 13 $R^2 = H$

7, 14 $R^2 = CH_3$

8, 15 $R^2 = CH_2Ph$

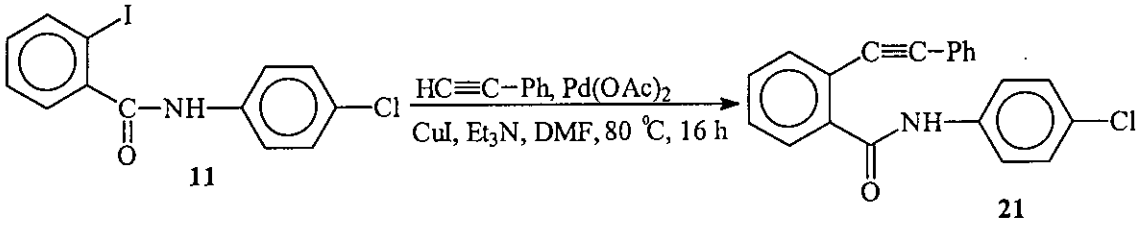
9, 16 $R^2 = C_6H_4OMe$–*p*

10, 17 $R^2 = Ph$

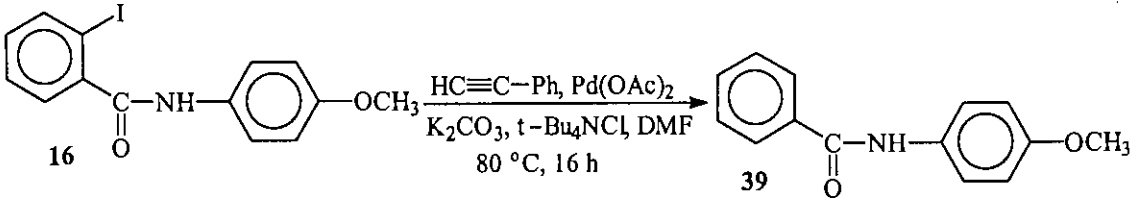
2-Iodobenzoic acid was converted to 2-Iodobenzoyl chloride by heating with PCl_5 at 80 ^0C for 2 h. 2-Iodobenzoyl chloride (1 mmol) was treated with a solution of the primary amine **4–10** (2.02 equiv.) in benzene to obtain 2-iodobenzamides **11–17** shown in **Scheme 2**. The products were characterized by its UV, IR and ^1H NMR. The ^1H NMR and IR spectra of the compounds **11–17** (Fig. 27–31, page 94–100; Fig. 14–19, page 81-86) showed absence of NH_2 group except compound **13** (Fig. 29, page 97; Fig. 16, page 83). **11–12** (Fig. 27–28, page 94–96; Fig. 14-15, page 81–82) and **14–17** (Fig. 30–31, page 99–100; Fig. 17–19, page 84–86)) exhibited an NH proton signal in their ^1H NMR spectra at δ5.76 – 7.09 (br **S**); in the IR spectra NH stretching vibration appeared at 3230 – 3362 cm^{-1} and C = 0 stretching vibration at 1634 – 1653 cm^{-1}; UV absorption was found in the region λ_{max} 223–272 nm (Fig. 1–6, page 68–73). In ^1H NMR spectrum of the compound **13** (Fig. 29, page 97) the chemical shift δ 5.85 (singlet) for NH_2 proton was observed. All spectral data of the compound **13–17** were identical to the reported data[113].

2.2.2 Role of catalysts

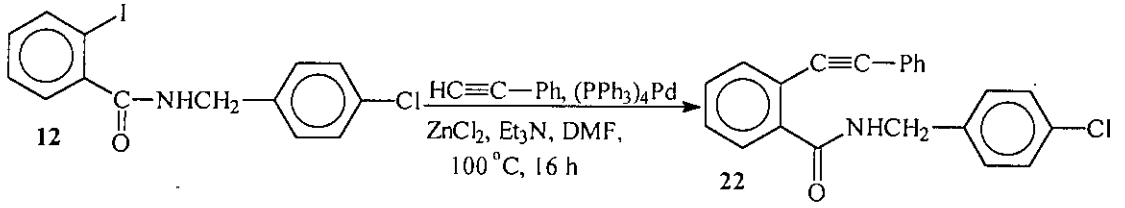
In general for the palladium catalyzed reaction of 2-iodobenzamides with alkynes bis(triphenyl phosphine) palladium (II) chloride (3.5 mol%) was used as a catalyst and cupprous iodide (8 mol%) was used as a co-catalyst. Bis(triphenyl phosphine) palladium (II) chloride along with copper (I) Iodide was found to be the catalyst of choice. The palladium-catalyzed reactions of 2-Iodo-*N*-*p*-chlorophenyl benzamide **11** with the alkynes **18** was carried out in the presence of $Pd(OAc)_2$ (5 mol%) and copper (I) iodide (5 mol%) under the same reaction condition, the substituted alkynyl compound 21 in 60% yield (**Scheme 3, Table 1**, entry 11) was obtained. We have attempted phase transfer catalyst reactions[114] of 2-Iodo benzamides **16** with the alkynes **18** (condition E) in the presence of $Pd(OAc_2)$ (5 mol%) K_2CO_3 tetra butylammonium chloride (1 equiv.) and DMF (10 ml) at 80 °C for **16** h (**Scheme 4, Table-1**, entry 12) and deiodinated product **39** was obtained. We have also carried out the palladium catalyzed reactions of 2-iodo benzamides with terminal alkyne in the presence of tetrakis(triphenyl phosphine) palladium (0), Et_3N and $ZnCl_2$ in DMF at 100 °C (**Scheme 5, page 47**) according to the conditions of Liao and Cheng[115] (condition G) to yield 2-alkynylated product **22**. Usually, the yield of the 2-alkynylated product **22** was higher from the reaction with $(PPh_3)_2PdCl_2$ and CuI than with $(PPh_3)_4Pd$ and $ZnCl_2$ procedure (**Table 1**, entry 2 and entry 14)



Scheme 3



Scheme 4

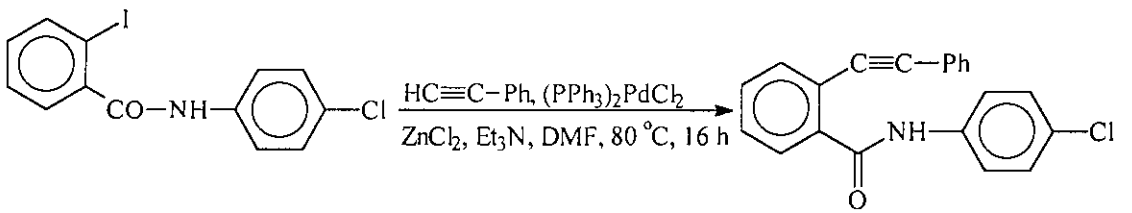


Scheme 5

From the observations shown in **Table-1**, it is revealed that the catalyst system e.g $Pd(PPh_3)_4$ with $ZnCl_2$ and $Pd(OAc)_2$ with CuI can also be used for heteroannulation reaction of 2-iodobenzamides. Howerver, from all considerations the bis(triphenyl phosphine) palladium (II) chloride-copper (I) iodide catalyst system was found better for the heteroannulation processes.

2.2.3 Role of Co-Catalysts

The yield of 2-alkynylated benzamides was covered by the reaction in the presence of $(PPh_3)_2PdCl_2$ as a catalyst and in the absence of CuI as a Co-catalyst. The yield of 2-alkynylated benzamides was also dropped by the use of $ZnCl_2$ instead of CuI as Co-catalyst (**Table 1**, entry 1, 13)



Scheme 6

It was found that the alkynylation of the 2-iodobenzamides could be done with palladium catalyst alone; however, the yields improved significantly when CuI was used as a Co-catalyst.

2.2.4 Role of Solvent

Although many palladium-catalyzed reactions have been reported to be carried out in triethylamine as a solvent and a base, we have found that 2-Iodobenzamides and 2-Iodo-substituted benzamides were sparingly soluble in Et_3N and did not undergo reaction in it. 2-Iodo benzamides were highly soluble in tetrahydrofurane (THF) and dimethyl

formamide (DMF) and underwent the complete reaction in it. In our cases THF was found to be the solvent of choice where maximum yields (60-90%) were obtained.

2.2.5 Role of Base

Triethylamine was the base of our choice as was observed by the previous works[116]. The use of $NaHCO_3$ instead of Et_3N under the same reaction conditions afforded a poorer yield in the presence of K_2CO_3 no reaction occurred under the same reaction condition A.

2.2.6 Effects of Temperature and Time

The reaction at 80 °C for **16** h was found to be the optimum condition for the alkynes **18** with aromatic substituent. Further increase in temperature did not lead to any noticeable change in the product yields. In the case of nonaromatic alkynes e.g trimethylsilyl acetylene **19** and n-hexyne **20**, the reactions at higher temperature gave poorer yields due to the higher volatility of the alkynes. The reactions at room temperature for a longer period (24 h) afforded the maximum yields.

2.3 Characterization of products

The isoindolinones and open chain condensation products gave satisfactory spectroscopic (IR, UV and ^{1}H NMR) data. The structures of the cyclized products (isoindolinones) and acyclic products (2-alkynyl benzamides) were established on the basis of the following observations:

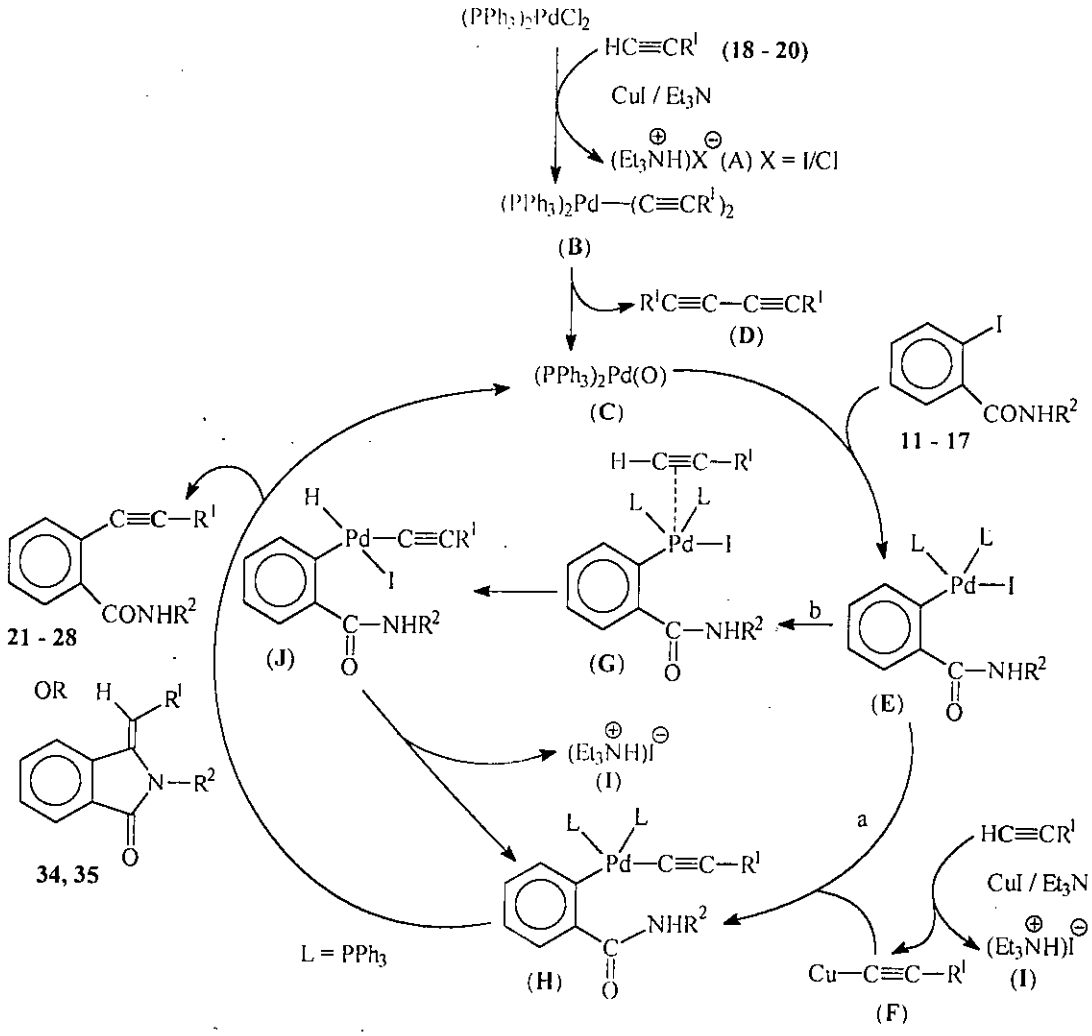
(i) 2-Phenylethynyl-*N*-substituted benzamides **21–25** (Fig. 32, 34 page 101, 104) and 2-Hexynyl-*N*-*p*-anisyl benzamide **28** exhibited an NH proton signal in their ^{1}H NMR spectra at δ7.79 – 9.25 (br.S) and no olefinic proton signal. Appearance of two dublet at δ4.65 and δ2.93 in the ^{1}H NMR spectra were assigned to be 2-H, 3-H of products **22** (Fig. 34, page 104) and **24** respectively. In the IR spectra, products **21-28** (Fig. 20,22 page 87,89) exhibited C ≡ C stretching frequencies appeared at 2205 – 2215 cm^{-1}, NH stretching vibration at 3242–3500 cm^{-1} and C = 0 stretching vibration at 1636–1653 cm^{-1}; UV absorption was found in the region λ_{max} 283.6 – 284.4 nm and 293.5–301.2 nm (Fig. 7,9 page 74,76). In the case of 2-alkynyl benzamides **21–25** (Fig. 32, 34 page 101, 104), **28** the ^{1}H NMR spectra showed chemical shift positions at aromatic zone (δ7.18 – 8.14).

(ii) 2-trimethylsilylethynyl-*N*-substituted benzamides **26–27** displayed the following data: ^{1}H NMR spectra HN proton signal at δ8.9 – 9.2 (br S), TMS – H proton signal at δ0.15 – 0.3, Ar-H proton signal at δ6.8–8.2 and no olefinic proton signal. The ^{1}H NMR spectra of the compound 2-(2′-trimethylsilylethynyl)-*N*-*p*-anisyl benzamide **27** showed singlet at δ3.5 for Ar-OCH_3 proton. In the IR spectra C ≡ C stretching frequency at 2150 – 2160 cm^{-1}, C = O stretching vibration at 1660 cm^{-1} and NH stretching vibration at 3330 cm^{-1} and UV absorption in the region 248.6–249.8 nm. The above data were absent in case of the corresponding cyclized products **29–33** (Fig. 35, 36 page 106, 108; Fig. 23-24, page 90-91), exhibited characteristic vinylic proton signals in the ^{1}H NMR at δ6.58–6.87. Cyclized products **34–35** (Fig. 37–38, page 110–112) exhibited characteristic vinylic proton signals in the ^{1}H NMR at δ6.84 – 6.87. The ^{1}H NMR spectra of the compounds **36 – 37** gave exomethylenic proton signals as double doublets at δ4.76-5.2 and δ4.72–5.16. 3-Pentylidene-*N*-*p*-anisyl isoindolinone **38** gave vinylic proton signal at δ5.18 and characteristic γ-lactam IR absorption at 1700 – 1714.6 cm^{-1} (Fig. 23–26, page 90–93).

The heteroannulation reaction of 2-Iodobenzamides with alkyne in the presence of palladium-catalyst and copper (I) Iodide showed regio- and stereoselectivity. We have established that all the isoindolinones have the (Z)-configuration by comparing them with known compounds[113] **31, 33–35**.

2.4 Mechanism of Palladium-catalyzed Reactions of 2-Iodobenzamides with Terminal Alkynes

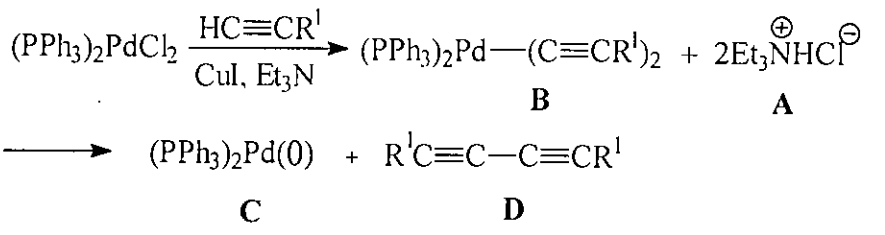
Although the detailed mechanism of the reaction is yet to be clarified, it can be perceived that the reaction proceed according to **scheme** 7 (page 50). From our observations it was clear that the presence of palladium catalyst and copper (I) Iodide was very essential for the success of the heteroannulation reactions. The key steps of the plausible mechanism were based on the following observation.



Scheme 7

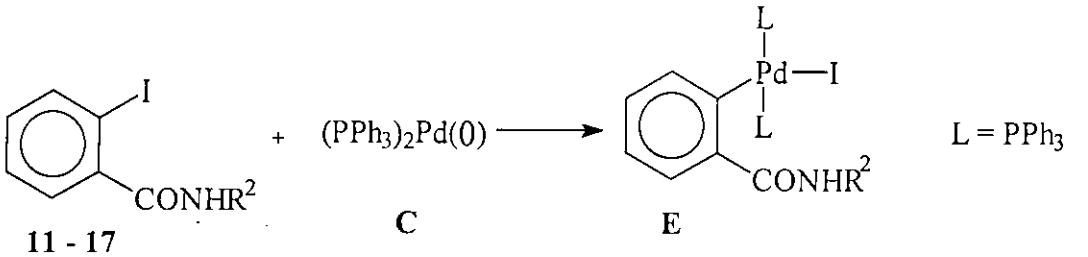
(i) Formation of Pd(0)

The formation of 2 -alkynyl benzamide derivatives **21-28** was catalyzed by $(PPh_3)_2PdCl_2$ in the presence of CuI. It could be suggested that Pd(0) must be intermediate involved in the catalytic process, as originally proposed by sonogashira *et al.*[117] in the arylation of terminal alkynes **18-20**. The reduction of Pd(II) to Pd(0) in the presence of Et_3N, CuI and alkynes took place. The formation of the dimers[118] of the alkynes (R^1-C≡C-C≡C-R^1) under the reaction conditions supports the above action.



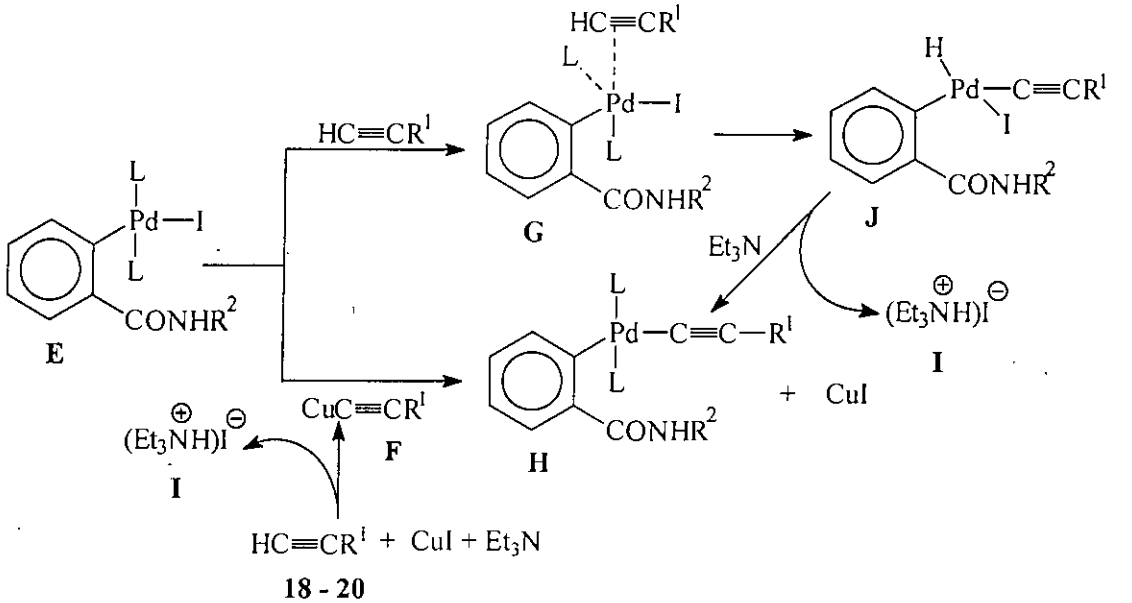
Scheme 8

(ii) In the catalytic cycle 2-iodobenzamides **11-17** oxidatively added to bis(triphenylphosphine) palladium (0) **C** to generate a σ-aryl palladium (II) complex **E**.



Scheme 9

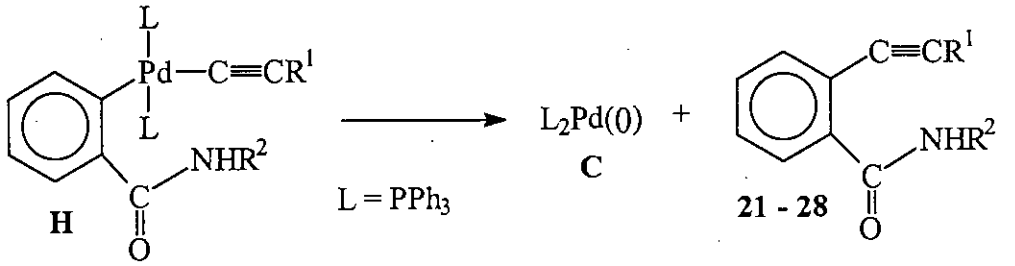
(iii) Then the terminal alkynes through the copper salts Cu-C≡ C-R^1 (**F**) (formed as intermediates with CuI) underwent the transmetallation reaction with the σ-aryl palladium complexes to give σ-alkynyl palladium complexes **H** (path a.) In the absence



Scheme 10

of cuprous iodide, the aryl or alkynyl palladium complexes **H** could also be generated from palladium complexes **J** which could be formed through the co-ordination of the alkynes **18-20** with palladium complexes **E** giving rise to the coordinated complex **G** and then **J** by subsequent insertion of the palladium into the C-H bond of the alkynes and elimination of HI in the presence of Et_3N (path b). The co-ordination of alkynes with palladium complex has been suggested by several investigators[119].

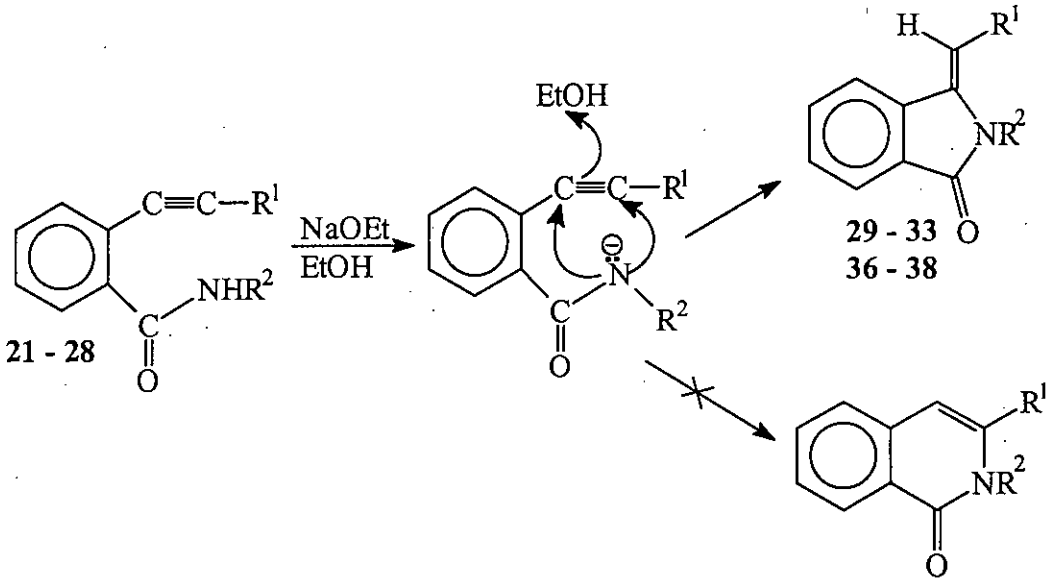
(iv) The alkynyl palladium complex **H** regenerated the original bis(triphenylphosphine) palladium (0) **C** (which could then continue the catalytic cycle) through the reductive elimination of the substituted products to afford the 2-alkynyl benzamides **21–28**.



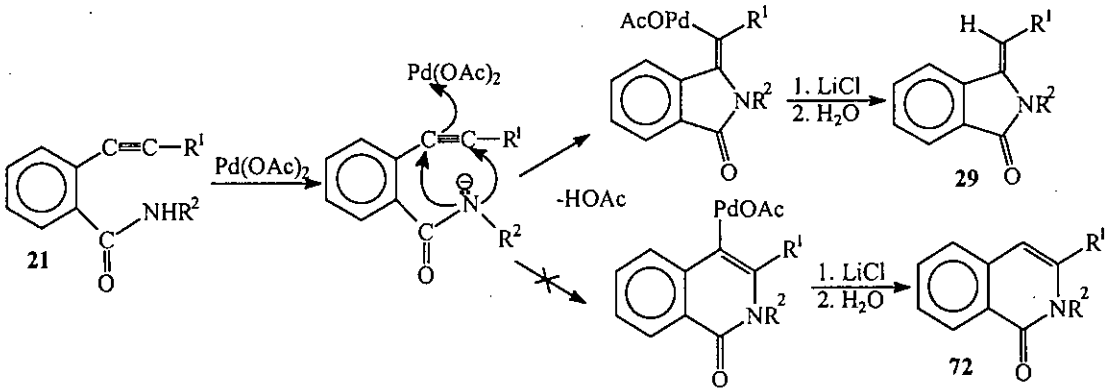
Scheme 11

Cyclization of Acyclic Products 21-28

Usually the cyclization of the acyclic products **21–28** was performed with sodium in ethanol under reflux for 4 h. Some of the cyclizations were also carried out with $Pd(OAc)_2$, LiCl, K_2CO_3 in DMF at 100 ^{0}C for **16** h (condition H)[95] with considerable yields (entry 15). From our observations it was obvious that the 5-exo-dig attack was dominant over the 6-endo-dig attack. In all cases we obtained the isoindolinones exclusively. The proposed mechanism is given in Scheme 12 and 13 9 (page 53).



Scheme 12



Scheme 13

2.5 Conclusion

We have demonstrated a convenient, general and facile method for the synthesis of 3-substituted isoindolin-1-ones from the reaction of 2-Iodobenzamides with terminal alkynes by a $(PPh_3)_2PdCl_2$–CuI–Et_3N system. We have used THF as a solvent in the palladium catalyzed reaction. The most important features of the synthesis are that readily available, inexpensive starting materials are used under relatively mild reaction conditions and relatively good yields. Also no toxic and hazardous compounds are produced by this procedure. We hope this will be of interest to many organic and

medicinal chemists active in this area and stimulate more activities in this promising area. The reaction is highly regio- and stereoselective in case of the aromatic alkynes. A variety of functional groups can be introduced at the **2** and **3** positions of the isoindolinone derivatives by this procedure. Thus biologically and medicinally important isoindolinones could be synthesized in a facile manner through proper choice of terminal alkynes and *N*-substituted 2-Iodobenzamides utilizing $(PPh_3)_2PdCl_2$–CuI–Et_3N system.

2.6 Experimental

Preparation of 2-Iodobenzoic acid

28g (0.20 mol) of anthranilic acid **1** was dissolved in 200 ml of distilled 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** (26.0 g, 92.8%), Melting point 161 – 162 °C, Lit m. p. 162 °C.

Preparation of 2-Iodobenzoyl chloride

A mixture of 2-Iodobenzoic acid (20g, 80.68 mmol) and PCl_5 (16.8g, 80.57 mmol) was stirred mechanically and heated at 80^0C for 2 h. HCl and $POCl_3$ were removed from the reaction mixture under reduced pressure. Then the pure 2-Iodobenzoyl chloride **3** was obtained by vacuum distillation in excellent yield.

Preparation of 2-Iodo-*N*-*p*-chlorophenyl benzamide 11

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 *p*-chloroniline **4** (3.04g, 2.02 equiv.) in benzene (10 ml) slowly with stirring. The residue obtained 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 crystalline powder obtained was crystallized from

ethanol to yield 2-Iodo-*N*-*p*-chlorophenyl benzamide **11** (2.5g, 79.4%) as 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, 511.1 cm^{-1}.

UV(EtOH): λ_{max} 272, 223.8 nm

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

Preparation of 2-Iodo-*N*-*p*-Chlorobenzyl benzamide 12

The compound **12** was synthesised 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 **11**. After usual work up, the title compound **12** (3g, 88.75%) was obtained as a gum. It was crystallized from ethanol to obtain a brown coloured 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, 1419.5, 1428.2, 1407.9, 1323.1, 1298, 1265.2, 1086.8, 1012.6, 994.2, 827.4, 790.8, 746.4, 716.5, 638.40 cm^{-1}.

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

^{1}HNMR (400 MHz, $CDCl_3$): δ 4.58(d, 2H, J = 4.08 Hz), 6.16 (brS, 1H–NH), 7.10(t, 1H, J = 7.09 Hz, Ar–H), 7.26 - 7.37 (m, 6H, Ar–H), 7,84 (d, 1H, J = 7.49, Ar-H).

Preparation of 2-Iodobenzamide 13

The title compound **13** was synthesized from 2-Iodo benzoyl chloride **3** (3.15g, 11.82 mmol) and ammonia solution 6 (0.41g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **11**. After usual work up, a light yellowish gum was obtained and it was crystallized from ethanol to yield, 2-Iodobenzamide **13** (2.8g, 88.89%) as a white needles, m.p. 186–187^{0}C.

IR: ν_{max}(KBr) 3361.7, 3180.4, 1624.0, 1583.4, 1396.0, 661.5, 628.8 cm^{-1}.

UV(EtOH) : λ_{max} 229.4, 217.6, 211.20 nm.

^{1}HNMR (400 MHz, $CDCl_3$): 5.85 (S, 2H, $-CONH_2$), 7.12 (t, 1H, Ar-H, J = 6.92 Hz), 7.39 (t, 1H, Ar-H, J = 7.44 Hz), 7.48 (d, 1H,Ar-H, J = 6.26 Hz), δ7.89 (d, 1H, Ar-H, J = 7.93 Hz)

Preparation of 2-Iodo-*N*-methyl benzamide 14

This was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and methyl amine 7 (0.74g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **11**. After usual work up, the title compound **14** (2.7g, 85.70%) was obtained as a gummy solid. It was crystallized from ethanol to obtain a colourless amorphous powder, m. p. 145 – 146 °C.

IR: ν_{max}(KBr) 3285.5, 1628.8, 1585.4, 1544.9, 1406.0, 1311.5, 1258.5, 761.8 cm^{-1}.

UV (FtOH): λ_{max} 228.60, 201.2 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (d, 3H, $-CH_3$, J = 4.9 Hz), 5.76 (brs, –NH, 1H), 7.09 (d.d, 1H, Ar-H), J = 6.01 Hz), 7.34 - 7.40 (m, 2H, Ar-H), 7.85(d, 1H, Ar-H, J = 7.94 Hz).

Preparation of 2-Iodo-*N*-benzyl benzamide 15

The compound **15** was synthesized from 2-Iodo benzoyl chloride **3** (3.15g, 11.82 mmol) and benzylamine **8** (2.55g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **11**. After usual work up, the title compound **15** (3.10g, 98.41%) was obtained as a colourless gum. It was crystallized from ethanol to obtain a colourless needles, m.p. 124-125 °C.

IR : ν_{max}(KBr) 3275, 1640, 1585, 1550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60(d, 2H, J = 5 Hz), 6.28 (br S, 1H), 6-97-7.52 (m, 8H), 7.95 (m, 1H).

Preparation of 2-Iodo-*N*-*p*-anisyl benzamide 16

The title compound **16** was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and anisidine **9** (2.94g, 2.02 equiv.) in dry benzene by following the procedure described above for the compound **11** to obtain the compound as a bluish gummy solid. It was crystallized from ethanol to obtain a bluish coloured needles **16** (2.95g, 93.65%), m.p. 174 – 175 °C.

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

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

^{1}H NMR (400 MHz, $CDCl_3$): 4.19 (S, 3H, -OCH_3), 7.27- 7.93 (m, 8H), 8.27 (d, 1H, J = 7.91 Hz)

Preparation of 2-Iodo-*N*-phenyl benzamide 17

The compound **17** was synthesized from 2-Iodobenzoyl chloride **3** (3.15g, 11.82 mmol) and Aniline **10** (2.22g, 2.02 equiv.) in dry benzene (30 ml) by following the procedure described above for the compound **11**. The crystalline colourless powder obtained from ethanol to yield colourless needles (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, 696.3 cm^{-1}.

UV(EtOH): λ_{max} 233.0, 211.4 nm.

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

Synthesis of 2-(2′-Phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide 21

A mixture of 2-Iodo-*N*-*p*-chlorophenyl benzamide **11** (0.5g, 1.399 mmol), bis (triphenyl-phosphine) palladium (II) chloride (0.034g, 3.5 mol %), copper (I) iodide (0.021g, 8 mol%) and triethyl amine (0.56g, 4 equiv.) was stirred in THF (10 ml) under nitrogen atmosphere for 1 h. Then phenylacetylene **18** (0.17g, 1.2 equiv.) was added to the reaction mixture. The solution was heated at 80 – 85 °C for 16 h. 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 (3×50 ml), 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 and n-hexane-chloroform (1:1). The n-hexane fraction afforded dimer 124 of phenyl acetylene and n-hexane-chloroform fraction yielded the compound **21**. Both the faction were crystallized from n-hexane-ethylacetate to afford a greenish crystal compound **21** (0.40g, 80%), m.p. 160–161 °C and colourless needles of dimer of Phenylacetylene[116] (30 mg) m. p. 85–86 °C.

Compound 21

IR: ν_{max}(KBr) 3242.10, 3171.7, 2205.0, 1653.8, 1589.2, 1512.1, 1493.8, 1397.3, 1312.5, 1093.6, 818.7, 756.0, 685.8, 505.3 cm^{-1}.

UV(EtOH): λ_{max} 301.0, 281.6, 265.2, 217.2, 208.2, 201.4 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.67(m, 12H, Ar-H), 8.14 (t, 1H, Ar-H, J = 5.22 Hz), 9.25 (brS, 1H, NH).

Dimer of phenylacetylene

IR: ν_{max}(KBr) 1592.1, 1569, 1511.1, 1484.1, 1438.8, 1176.5, 1157.2, 1067.5, 1024.1, 987.5, 915.2, 847.7.

UV(EtOH): λ_{max} 293.2, 242.6, 20.8, 203.0 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.57 (m, 10H, Ar–H).

Synthesis of 2-(2′-Phenyl ethynyl)-*N*-*p* -chlorobenzyl benzamide 22

The title compound **22** was synthesized from 2-Iodo-*N*-*p* -chlorobenzyl benzamide **12** (0.50g, 1.488 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.023g, 4 mol %), triethylamine (0.69, 4 equiv.) and phenyl acetylene **18** (0.18g, 1.2 equiv.) in THF (10 ml) by following the procedure described above for the compound **21**. After usual work up and column chromatography, the compound was obtained as a gum. It was crystallized from n-hexane-ethylacetate to obtain greenish white solid (0.42g, 84%), m.p. 110–111 °C.

IR: ν_{max}(KBr) 3279.7, 2210, 1636.5, 1592.1, 1539.1, 1490.9, 1442.7, 1432.0, 1300.9, 801.4, 756.0, 691.4, 541.0 cm^{-1}.

UV(EtOH): λ_{max} 301.0, 284.0, 237.00 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65(d, 2H, J = 5.42 Hz), 7.12–7.60 (m, 12H, Ar-H), 7.79 (brS, 1H, NH), 8.13 (t, 1H, Ar-H, J = 5.05 Hz).

Synthesis of 2-(2′-Phenyl ethynyl)benzamide 23

The compound **23** was synthesized from 2-Iodobenzamide **13** (0.50g, 2.024 mmol), bis (triphenylphosphine) palladium (II) chloride (0.05g, 3.5 mol %), copper (I) iodide (0.031g, 8 mol %), triethyl amine (0.82g, 4 equiv.) and phenylacetylene **18** (0.25g, 1.2

equiv.) in DMF (5 ml) by following the procedure described above for the compound **21**. After usual work up and column chromatography, the compound was obtained as a gum. It was crystallized from n-hexane-ethyl acetate to obtain a colourless amorphous powder (0.39g, 78%), m.p. 159 – 160 °C.

IR: ν_{max}(KBr) 3500, 3200, 2210, 1650, 1620, 1490, 1400, 1110, 760, 690 cm^{-1}.

UV (EtOH): λ_{max} 301.2, 284.4 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30–8.02 (m, 9H, Ar-H), 8.20 (brS, NH_2)

Synthesis of 2-(2′-Phenyl ethynyl)-*N*-methyl benzamide 24

This was synthesized from 2-Iodo-N-methyl benzamide **14** (0.50g, 1.916 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.047g, 3.5 mol%), copper (I) iodide (0.027g, 4 mol %), triethyl amine (0.77g, 4 equiv.) and phenyl acetylene **18** (0.23g, 1.2 equiv.) in DMF (5 ml) by following the procedure described above for the compound **21**.After usual work up, a greenish gum was obtained. It was purified by column chromatography with 5% ethyl acetate in n-hexane to obtain the colourless amorphous powder compound (0.35g, 70%), m.p. 103 – 104 °C.

IR: ν_{max}(KBr) 3300, 3000, 2215, 1650, 1540, 1410, 1320, 760, 690 cm^{-1}.

UV (EtOH): λ_{max} 301.2, 283.6 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93(d, 3H, J = 5 Hz, CH_3), 7.18 – 7.94 (m, 9H, Ar-H and 1H, NH).

Synthesis of 2-(2′-Phenyl ethynyl)-*N*-benzyl benzamide 25

The title compound **25** was synthesized from 2-Iodo-*N*-benzyl benzamide **15** (0.50g, 1.484 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.023g, 8 mol %), triethylamine (0.609, 4 equiv.) and phenyl acetylene **18** (0.18g, 1.2 equiv.) in DMF (10 ml) by following the procedure described above for the compound **21**. After usual work up and column chromatography, the compound as a gum. It was crystallized from n-hexane-ethylacetate to obtain colourless needles (0.380g, 76%).

Synthesis of 2-(2′-Trimethylsilyl ethynyl)-*N*-phenyl benzamide 26

Bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.023g, 8 mol %), triethyl amine (0.62g, 4 equiv.) were added to a solution of 2-Iodo-*N*-phenyl benzamide **17** (0.5g, 1.548 mmol) in DMF (10 ml). The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then trimethyl silyl acetylene **19** (0.18g, 1.2 equiv.) was added dropwise to the mixture, stirring continued for 24 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue extracted with chloroform (3×50 ml), the organic extracts washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford colourless small needles compound **26** (0.35g, 70%), m.p. 95 – 96 °C.

IR: ν_{max}(KBr) 3300, 2160, 1660 cm^{-1}.

UV (EtOH): λ_{max} 248.6 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.15, (S, 9H, TMS–H), 6.90 – 8.20 (m, 9H, Ar-H), 9.00 – 9.20(br 5, 1H, NH).

Synthesis of 2-(2′-Trimethyl silyl ethynyl)-*N*-*p* -anisyl benzamide 27

The title compound **27** was synthesized from 2-Iodo-*N*-*p*-anisyl benzamide **16** (0.5g, 1.475 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.022g, 8 mol %), triethylamine (0.69g, 4 equiv.) and trimethyl silyl acetylene **19** (0.17g, 1.2 equiv.) in DMF (10 ml) by following the procedure described above for the compound **26**. After column chromatography, the compound was obtained as a gum. It was crystallized from n-hexane-ethyl acetate to obtain colourless small needles (0.35g, 70%), m.p. 116–117 °C.

IR: ν_{max}(KBr) 3330, 3000, 2150, 1660 cm^{-1}.

UV(EtOH): λ_{max} 249.8 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.3 (S, 9H, TMS–H), 3.50 (S, 3H, OCH_3), 6.80–8.00 (m, 8H, Ar-H), 8.90 (brS, 1H, NH).

Synthesis of 2-Hexynyl-*N*-*p*-anisyl benzamide 28

This was synthesized from 2-Iodo-*N*-*p*-anisyl benzamide **16** (0.5g, 1.475 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.022g, 8 mol %), triethyl amine (0.59g, 4 equiv.) 1-hexyne **20** (0.15g, 1.2 equiv.) in DMF (10 ml) by following the procedure described above for the compound **26**. After column chromatography the compound was obtained as a gum. It was crystallized from n-hexane-ethyl acetate to afford colourless needles (0.45g, 90%).

Synthesis of 3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one 29 (Conditoin C)

A mixture of 2-(2'-phenylethynyl)-*N*-*p*-chlorophenyl benzamide **21** (0.20gm. 0.603 mmol), and sodium ethoxide (0.069g, 1.5 equiv.) in dry ethanol (20 ml) was stired under nitrogen atmosphere for 4 h at 80 °C (bath temperature). The progress of the reaction was monitored by TLC (n-hexane-chloroform 1:1). At the end of the reaction the mixture was evaporated to dryness under reduced pressure to give a residue. Distilled water (200 ml) was added to the residue and it was neutralised with dilute 6N HCl solution, extracted with chloroform (3×50 ml), the organic layer washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, a gummy greenish residue was obtained. The residue was purified by column chromatography on silica gel. Elution with n-hexane-chloroform (1:1) furnished the major product **29** (0.16 mg, 80%) as a greenish solid m.p. 135 – 136 °C.

IR: ν_{max}(KBr) 3050, 1702.1, 1644.2, 1489.9, 1472.5, 1383.8, 1131.2, 1086.8, 1014.5, 819.7, 761.8, 726.1, 694.3 cm^{-1}.

UV(EtOH): λ_{max} 331.5, 273.5, 237.5 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (d, 2H, Ar-H), 6.87 (S, 1H, = CH-), 6.96 - 7.06(m, 7H, Ar-H), 7.54 (t, 1H, Ar-H), J = 7.48 Hz), 7.68 (t, 1H, Ar-H, J = 7.54 Hz), 7.86 (d, 1H, Ar-H, J = 7.71 Hz), 7.95 (d, 1H, Ar-H, J = 7.46 Hz).

Synthesis of 3-Benzylidene-*N*-*p*-chlorobenzyl isoindolin-1-one 30

This was synthesized from 2-(2′-phenylethynyl)-*N*-*p*-chlorobenzyl beznamide **22** (0.20 mg, 0.58 mmol) and sodium ethoxide (0.066g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29**. After usual work up, a greenish gum was obtained. It was purified by chromatography on a column of silica gel with 5% ethyl acetate in n-hexane to obtain the title compound **30** (0.15g, 75%), as a greenish white solid. It was crystallized from n-hexane-ethylacetate, m. p. 127 – 128 °C.

IR: ν_{max}(KBr) 3047.3, 1711.7, 1657.7, 1618.2, 1488.9, 1470.6, 1427.2, 1395.4, 1344.3, 1299.9, 1287.4, 1109.0, 1093.6, 1014.5, 979.8, 959.5, 936.4, 792.7, 758.0, 702.0, 690.5, 622.0, 476.4 cm^{-1}.

UV(EtOH): λ_{max} 323.5, 277.0, 233.0 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (S, 2H, N-CH_2), 6.44 (dd, 2H, J = 7.78 Hz, Ar-H), 6.73 (S, 1H, = CH-), 7.01 (dd, 2H, J = 7.72 Hz, Ar - H), 7.07 (dd, 2H, J = 5.64 Hz, Ar-H), 7.29 (dt, 3H, J = 11.0 Hz, Ar-H), 7.54 (t, 1H, J = 7.09 Hz, Ar-H), 7.63 (t, 1H, J = 7.37 Hz, Ar - H), 7.74 (d, 1H, J = 7.54 Hz, Ar-H), 7.91 (t, 1H, J = 8.93 Hz, Ar - H)

Synthesis of 3-Benzylidene isoindolin-1-one 31

The title compound **31** was synthesized from 2-(2′-phenyl ethynyl) benzamide **23** (0.20g, 0.90 mmol), and sodium ethoxide (0.102g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29** to obtain as a colourless gum. It was crystallized from n-hexane-ethylacetate to obtain a colourless small needles (0.12g, 60%), m.p. 184 –185 °C.

IR: ν_{max}(KBr) 3250, 3020, 1710, 1640, 1610, 1450, 1310, 1150, 770, 700, 640 cm^{-1}.

UV(EtOH): λ_{max} 339.2, 241.4 nm.

^{1}HNMR (400 MHz, $CDCl_3$): δ6.58, (S, 1H, = CH–), 7.3–8.05 (m, 9H, Ar-H), 9.15 (br S, 1H, NH).

Synthesis of 3-Benzylidene-*N*-methyl isoindolin-1-one 32

This was synthesized from 2-(2′-phenyl ethynyl)-*N*-methyl benzamide **24** (0.20g, 0.85 mmol) and sodium ethoxide (0.097g, 1.5 equiv.) in dry ethanol (20 ml) by following the

procedure described above for the compound **29**. After column chromatography the compound **32** was obtained as a colourless gum. It was crystallized from n-hexane-ethyl acetate to obtain a colourless small needles (0.125g, 62.5%), m.p. 108–109 °C.

IR: ν_{max}(KBr) 3000, 1700, 1640, 1610, 1470, 1430, 1345, 1330, 1100, 1030, 1010, 770, 760, 720, 690 cm^{-1}.

UV(EtOH): 324.8, 272.4 221.8 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (S, 3H, N–CH_3), 6.78(S, 1H, = CH –), 7.25–8.00 (m, 9H, Ar-H).

Synthesis of 3-Benzylidene-*N*-benzyl isoindolin-1-one 33

This was synthesized from 2-(2′-phenyl ethynyl)-*N*-benzyl benzamide **25** (0.20g, 0.64 mmol) and sodium ethoxide (0.065g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29**. After usual workup, a light yellowish gum was obtained. It was purified by chromatography on a column of silica gel with 5% ethyl acetate in n-hexane to obtain the title compound **33** (0.12g, 60%) as a colourless needles. It was crystallized from n-hexane-ethyl acetate m.p. 122–123 °C.

IR: ν_{max}(KBr) 3020, 1705, 1655, 1495, 1450, 1400, 1350, 1120, 950, 760, 700, 630 cm^{-1}.

UV(EtOH): λ_{max} 323.8 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (S, 2H, N–CH_2), 6.52(dd, 2H, Ar–H), 6.73 (S, 1H, = CH–), 7.05 – 7.09 (m, 5H), 7.25–7.29 (m, 3H), 7.53 (td, 1H) 7.94 (d, 1H, J = 7.5 Hz, Ar-H).

Synthesis of 3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one 34

The title compound **34** was synthesized from 2-Iodo-*N*-*p*-anisyl benzamide **16** (0.5g, 1.475 mmol) bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol %), copper (I) iodide (0.022g, 8 mol %), triethyl amine (0.59g, 4 equiv.) and phenyl acetylene **18** (0.18g, 1.2 equiv.) in DMF (10 ml) by following the procedure described above for the compound **21**. After column chromatography, the compound was obtained as a yellowish gum. It was crystallized from n-hexane-ethyl acetate to obtain a light yellowish needles (0.40g, 80%), m. p. 171 –172 °C.

IR: ν_{max}(KBr) 3050, 3020 1714.6, 1676, 1608.5, 1504.4, 1471.6, 1442.7, 1245.9, 1164.9, 1024.1, 1008, 763.8 cm^{-1}.

UV(EtOH): λ_{max} 330.6, 276.6, 237.4, 220.2 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (S, 3H, $-OCH_3$), 6.82 (d, 2H, J = 7.02 Hz, Ar–H), 6.87 (S, 1H, = CH–), 6.96 (m, 6H, Ar–H), 7.66 (t, 1H, J = 7.51 Hz, Ar–H), 7.72 (d, 1H, J = 8.16 Hz, Ar–H), 7.85 (t, 2H, Ar–H), 7.94(d, 1H, J = 7.54 Hz, Ar–H)

Synthesis of 3-Benzylidene-*N*-phenyl isoindolin-1-one 35

This was synthesized from 2-Iodo-*N*-phenyl benzamide **17** (0.5g, 1.548 mmol) bis (triphenyl phosphine) palladium (II) chloride (0.036g, 3.5 mol%), copper (I) iodide (0.023g, 8 mol%), triethylamine (0.62g, 4 equiv.) and phenylacetylene **18** (0.19g, 1.2 equiv.) in DMF (10 ml) by following the procedure described above for the compound **21**. After chromatography on a column of silica gel with 10% ethyl acetate in chloroform as eluant, the colourless gummy compound was obtained. It was crystallized from n-hexane-ethyl acetate to obtain a colourless small needles (0.4g, 80%), m.p. 197–198 °C.

IR: ν_{max}(KBr) 3050, 1703, 1651, 1595, 1575.7, 1488, 1469, 1444, 1388, 1319, 1298, 1186, 1124, 1068, 931.6, 759.9, 694, 638, 627, 513 cm^{-1}.

UV(EtOH): λ_{max} 323.2, 277, 232.8, 214.6, 209.6 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (S, 1H, = CH–), 6.85–7.08(m, 10H, Ar–H), 7.55 (t, 1H, J = 7.37 Hz, Ar–H), 7.68 (t, 1H, J = 7.48 Hz, Ar–H), 7.86 (d, 1H, J = 7.54 Hz, Ar–H), 7.96 (d, 1H, J = 7.42 Hz, Ar–H).

Synthesis of 3-Methyline--*N*-phenyl isoindolin-1-one 36

The title compound **36** was synthesized from 2-(2′-Trimethylsilyl ethynyl)-*N*-phenyl benzamide **26** (0.20g, 0.68 mmol) and sodium ethoxide (.069g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29** to obtain colourless small needles (0.13g, 65%), m. p. 98 –99 °C.

IR: ν_{max}(KBr) 3000, 1700, 1650, 1595, 1495, 1390, 1180, 890, 760, 720, 700 cm^{-1}.

UV(EtOH): λ_{max} 309.4, 255.2, 223.4 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76, 1H, J = 2Hz, = CH_2), 5.20 (d, 1H, J = 2Hz, = CH_2), 7.35–7.98 (m, 9H, Ar–H).

Synthesis of 3-Methylene-*N*-*p*-anisyl isoindolin-1-one 37

This was synthesized from 2-(2′-trimethylsilyl ethynyl)-*N*-*p*-anisyl bezamide **27** (0.2g, 0.62 mmol) and sodium ethoxide (0.063g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29** and obtain colourless powder (0.15g, 75%).

IR: ν_{max}(KBr) 3000, 1710, 1640, 1510, 1390, 1300, 1260, 1140, 1030, 830, 780, 700 cm^{-1}.

UV(EtOH): λ_{max} 310.6, 255.6, 225.2 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (S, 3H, Ar–OCH_3), 4.72 (d, 1H, J = 2Hz, = CH_2), 5.16 (d, 1H, J = 2 Hz, = CH_2), 6.90–8.00 (m, 8H, Ar–H)

Synthesis of 3-Pentylidene-*N*-*p*-anisyl isoindolin-1-one 38

The title compound **38** was synthesized from 2-hexynyl-*N*-*p*-anisyl benzamide **28** (0.20g, 0.65 mmol) and sodium ethoxide (0.066g, 1.5 equiv.) in dry ethanol (20 ml) by following the procedure described above for the compound **29** to obtain colourless amorphous powder (0.12g, 60%), m. p. 159 –160 °C.

IR: ν_{max}(KBr) 2985, 1705, 1640, 1610, 1590, 1510, 1400, 1250, 1040, 830, 780, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 – 1.12 (m, 3H, CH_3), 1.18–1.66 (m, 4H, –$(CH_2)_2$–), 2.32–2.90 (m, 2H, -CH_2-), 3.82(S, 3H, OCH_3), 5.18 (t, 1H, J = 8 Hz, = CH–), 6.78–7.98 (m, 8H, Ar–H).

Synthesis of 2-(2′-phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide 21

(condition D)

A mixture of 2-Iodo-*N*-*p*-chlorophenyl-benzamide **11** (0.5g, 1.399 mmol), palladium acetate $Pd(OAc)_2$ (0.015g, 5 mol %), copper (I) iodide (0.021g, 5 mol%) and triethyl amine (0.56g, 4 equiv.) and phenyl acetylene (0.18g, 1.2 equiv.) in DMF (5ml) under nitrogen atmosphere for one h. The solution was heated at 80 °C for 16 h. After usual workup and column chromatography, the compound was obtained as a reddish gum. It was crystallized from n-hexane-ethylacetate to afford a greenish crystal **21** (0.39, 60%),

m.p. 160–161 °C. This compound **21** was further cyclized by condition C to obtained the compound **29** (0.14g, 70%) as a greenish solid, m.p. 135–136 °C.

Synthesis of *N-p*-Anisyl benzamide 39 (Condition E)

The title compound **39** was synthesized from 2-Iodo-*N-p*-anisyl benzamide **16** (0.5g, 1.475 mmol), potassium carbonate (0.51g, 2.5 equiv.), tetrabutyl ammonium chloride (0.41g, 1 equiv.), palladium acetate (0.016g, 5 mol%) and phenyl acetylene **18** (0.19g, 1.3 equiv.) in DMF (10 ml) under nitrogen atmosphere. The solution was heated at 85 °C for 16 h. 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 (3×50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After column chromatography, the compound was obtained as a greenish gum. It was crystallized from n-hexane-ethyl acetate to obtain colourless small needles (0.25g, 50%), m. p. 166–167 °C.

IR: ν_{max}(KBr) 3269, 1639.4, 1598.9 1654.8, 1550.7, 1500.5, 1438.8, 1330.8 756.0 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.3(s, 2H, OCH_3), 7.07-7.93 (m, 9H), 8.27 (s, 1H, NH, J=7.92 Hz).

Synthesis of 2-(2′-Phenyl ethynyl)-*N-p*-chlorophenyl benzamide 21 (condition F).

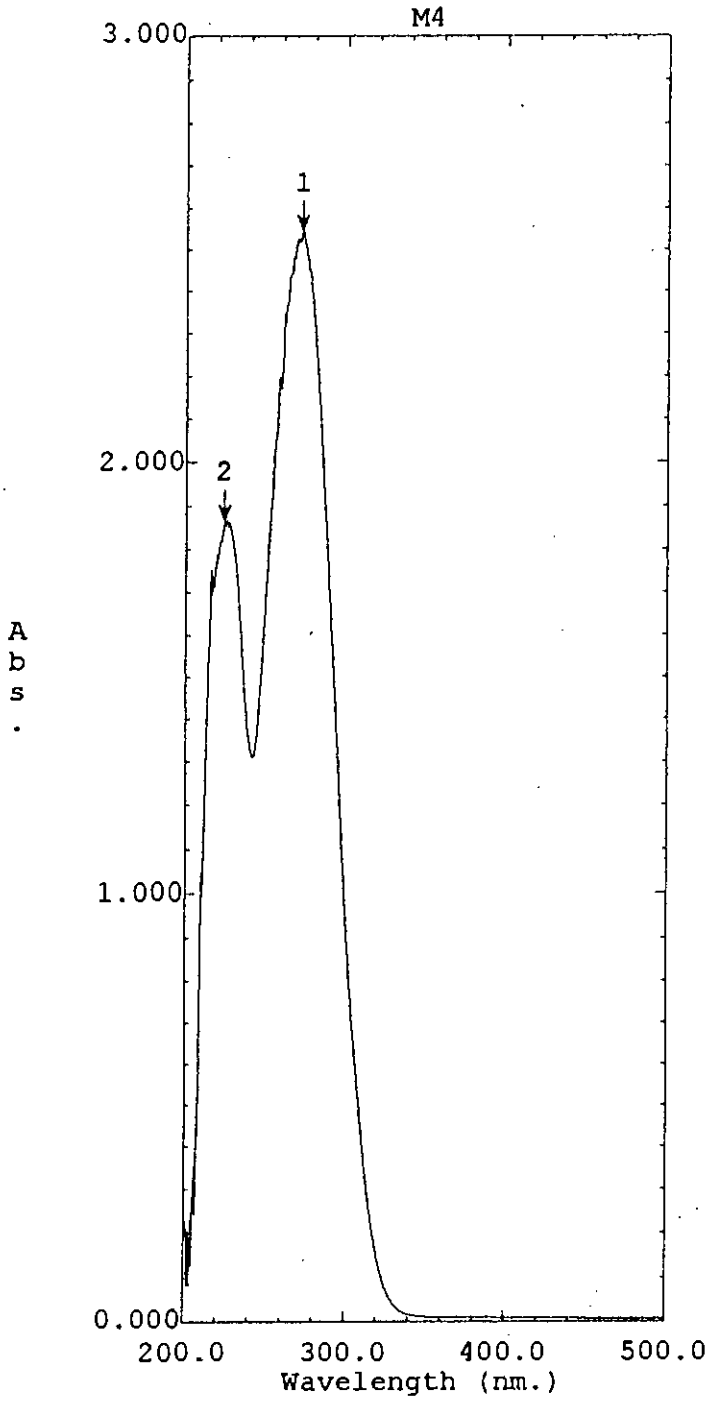
A mixture of 2-Iodo-*N-p*-chlorophenyl benzamide **11** (0.5g, 1.399 mmol), bis (triphenyl phosphine) palladium (II) chloride (0.034g, 3.5 mol%), Zinc chloride (0.015g, 8 mol%), triethylamine (0.56g, 4 equiv.) and phenyl acetylene (0.17g, 1.2 equiv.) in DMF (5 ml) by following the procedure described above for the compound 21 (condition A). After usual workup, a reddish gum was obtained. It was purified by column chromatography with n-hexane-chloroform (1:1) to afford a greenish crystal (0.375g, 75%), m.p. 160 – 161 °C. The title compound **21** was cyclized by condition C to afford greenish solid compound **29** m. p. 135–136 °C.

Synthesis of 2-(2′-Phenyl ethynyl)-*N*-*p*-chlorobenzyl benzamide 22 (condition G)

The title compound **22** was synthesized from 2-Iodo-*N*-*p*-chlorobenzyl benzamide **12** (0.50g, 1.488 mmol), tetrakis (triphenyl phosphine) palladium (0) (0.033g, 3.5 mol%), triethyl amine (0.6g, 4 equiv.), $ZnCl_2$ (0.016g, 8 mol%) and phenyl acetylene **18** (0.18g, 1.2 equiv.) in DMF (5 ml) at 100 °C for 16 h. After usual work up and column chromatography, the compound was obtained as a gum. It was crystallized from n-hexane-ethyl acetate to obtain greenish white solid (0.225g, 45%), m. p. 110 –111 °C. The above compound **22** was then cyclized by condition C to obtain a greenish white solid **30**, m.p. 127–128 °C.

Synthesis of 3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one 29 (condition H) from 21 (condition A).

Palladium (II) acetate (0.007g, 5 mol %), LiCl (0.025g, 1 equiv.) and K_2CO_3 (0.21g, 2.5 mmol) were added to a solution of 2-(2′-phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide (0.20g, 0.603 mmol) **21** in DMF (5 ml), and the mixture was stirred for over night at 100 °C (bath temperature). The reaction mixture was evaporated under reduced pressure, the residue extracted with chloroform (3×50 ml), the combined organic extracts washed with distilled water (3×50 ml), dried over anhydrous Na_2SO_4 and filtered. The residue obtained after removal of solvent was purified by column chromatography on silica gel to yield colourless crystal **29** (0.100g, 50%), 135–136 °C.



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

Peak Pick

No.	Wavelength (nm.)	Abs.
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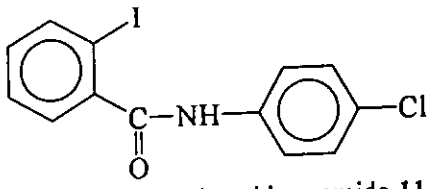
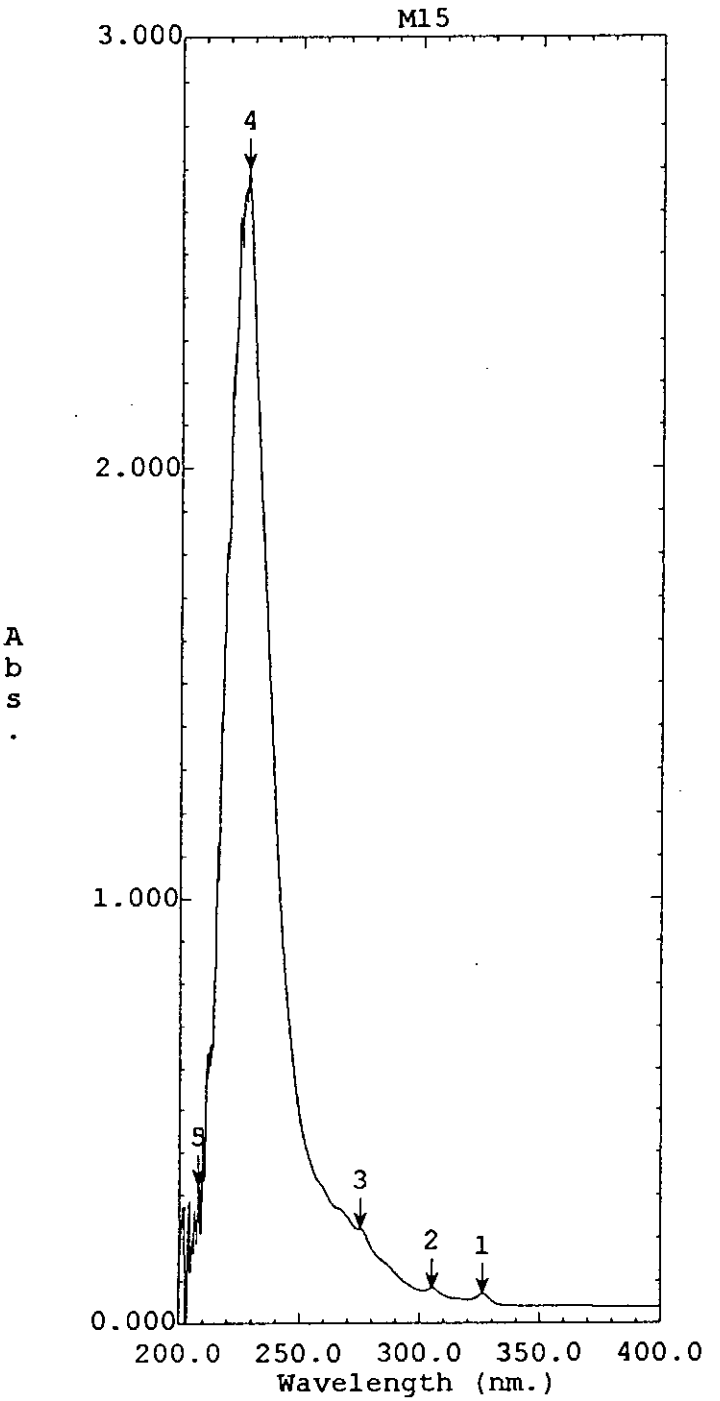
2	223.80	1.8669



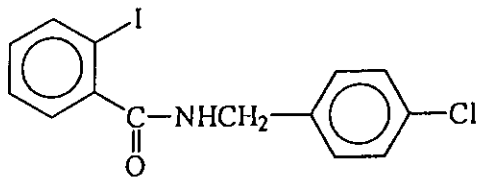
2-Iodo-*N*-*p*-chlorophenyl benzamide **11**

Fig. 1: UV spectrum of compound **11**



Peak Pick

No.	Wavelength (nm.)	Abs.
1	326.40	0.0685
2	305.20	0.0813
3	275.40	0.2208
4	227.60	2.6986
5	208.00	0.3243



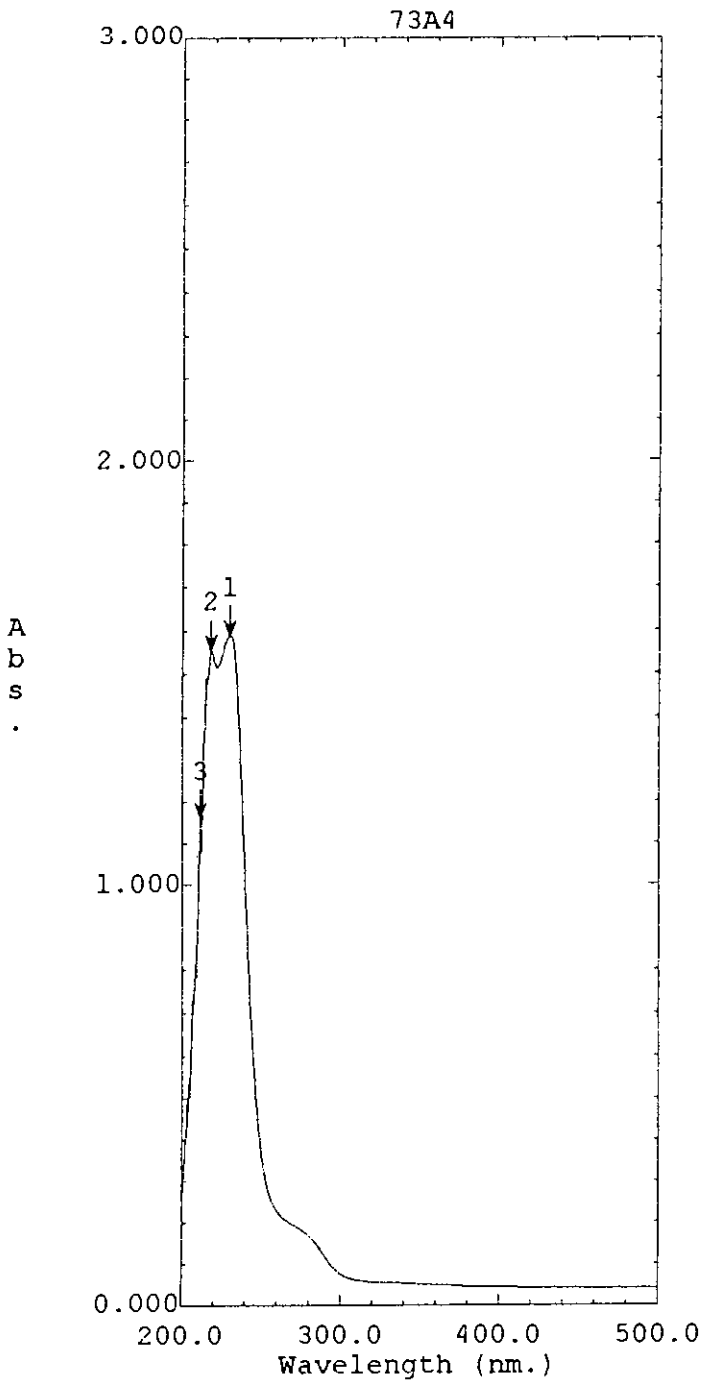
2-Iodo-*N*-*p*-Chlorobenzyl benzamide **12**

Fig. 2: UV spectrum of compound **12**

File Name: M15

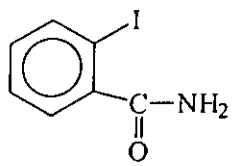
Created: 13:25 07/22/03
Data: Original

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



Peak Pick

No.	Wavelength (nm.)	Abs.
1	229.40	1.5872
2	217.60	1.5541
3	211.20	1.1605



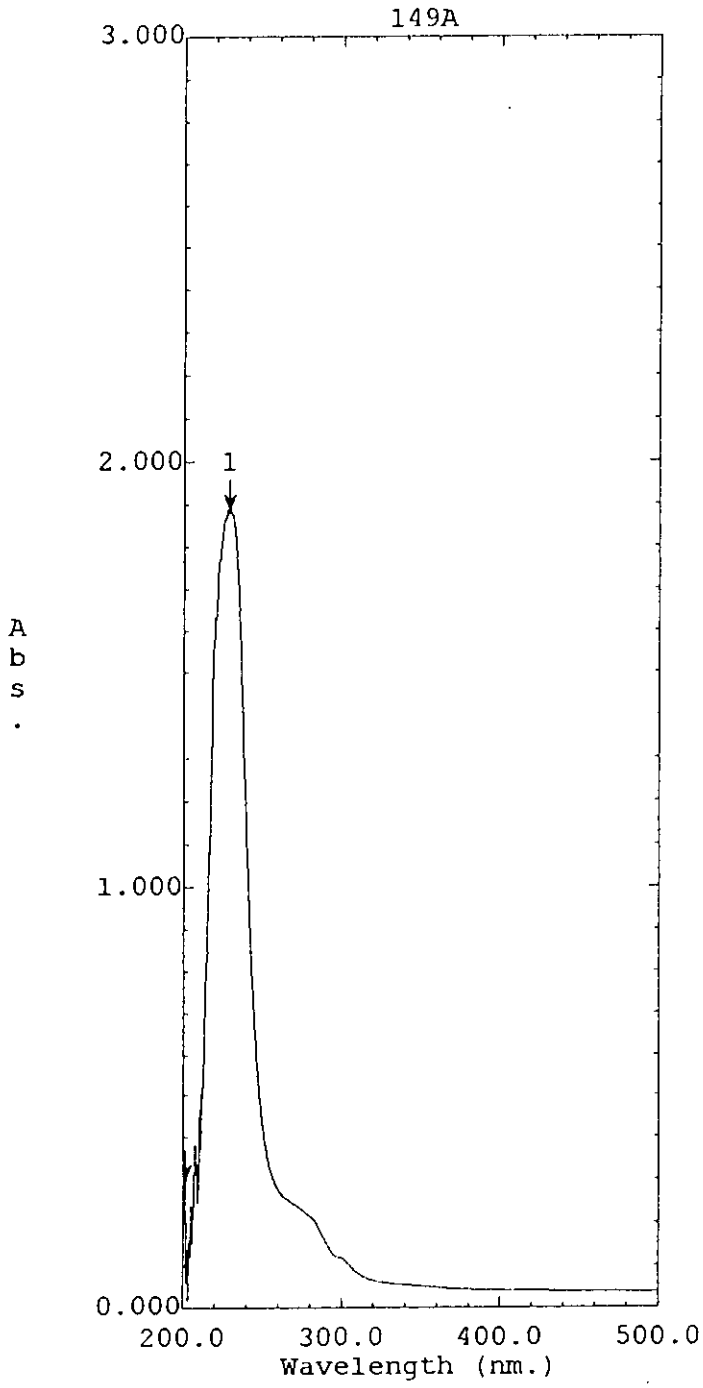
2-Iodobenzamide **13**

Fig. 3: UV spectrum of compound **13**

File Name: 73A4

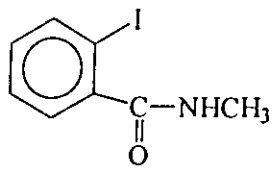
Created: 13:32 07/23/03
Data: Original

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



Peak Pick

No.	Wavelength (nm.)	Abs.
1	228.60	1.8877
2	201.20	0.2987



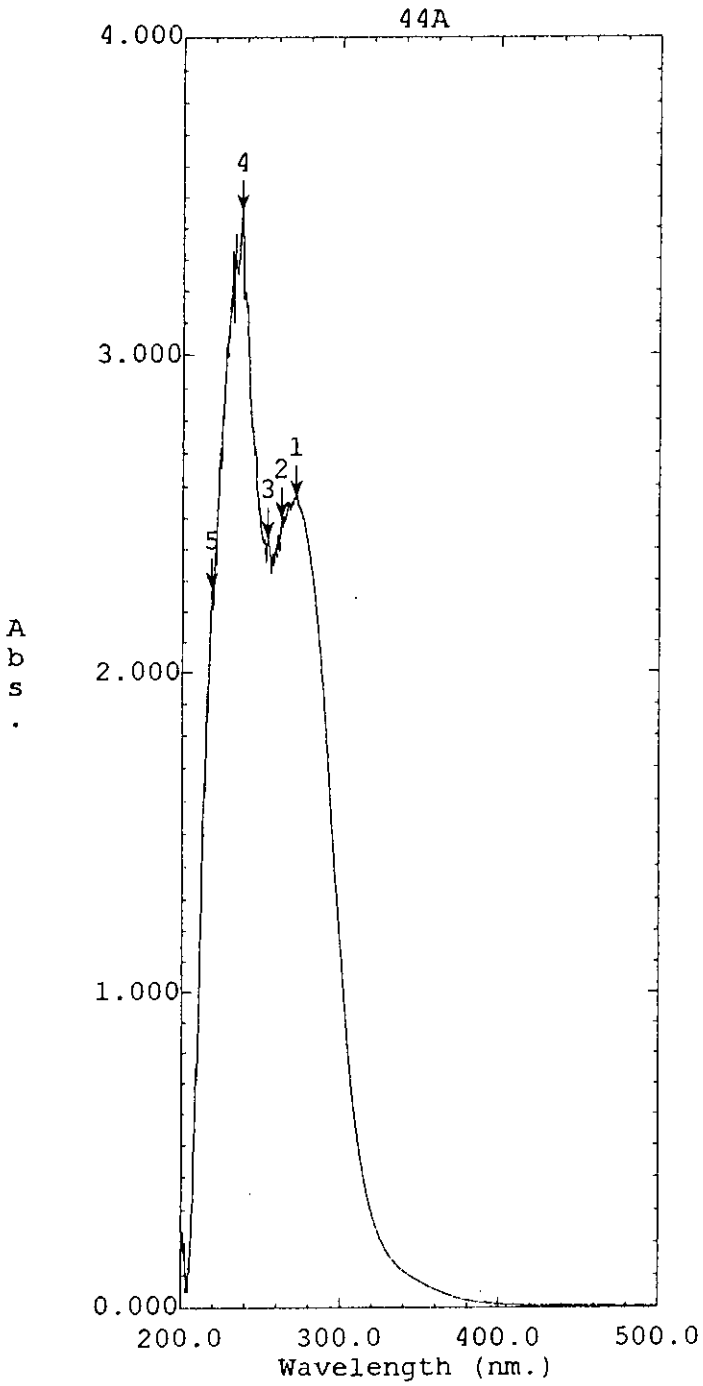
2-Iodo-*N*-methyl benzamide **14**

Fig. 4: UV spectrum of compound **14**

File Name: 149A

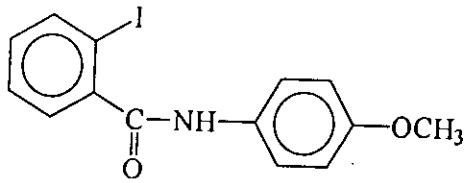
Created: 13:10 07/22/03
Data: Original

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



Peak Pick

No.	Wavelength (nm.)	Abs.
1	271.00	2.5664
2	262.00	2.5002
3	253.40	2.4393
4	236.80	3.4618
5	218.40	2.2762



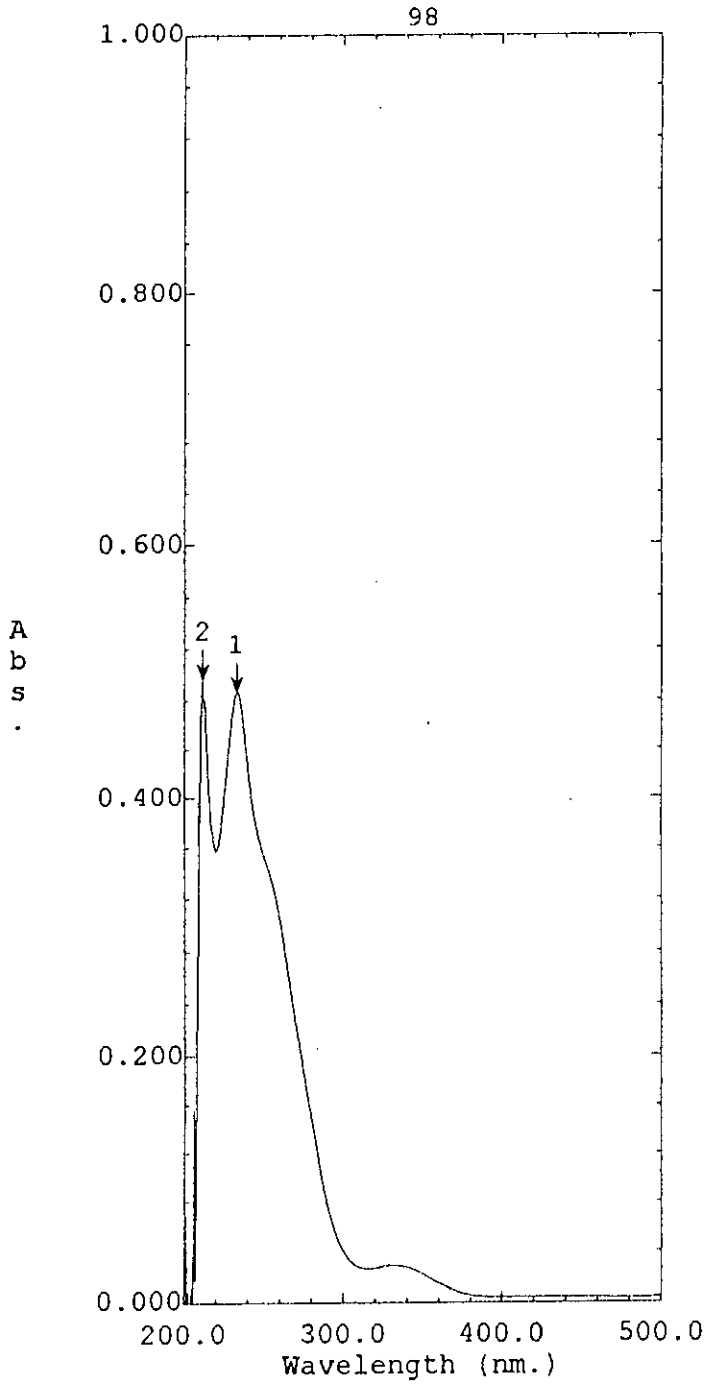
2-Iodo-*N*-*p*-anisyl benzamide **16**

Fig. 5: UV spectrum of compound **16**

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



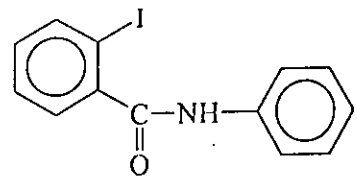
File Name: 98

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

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

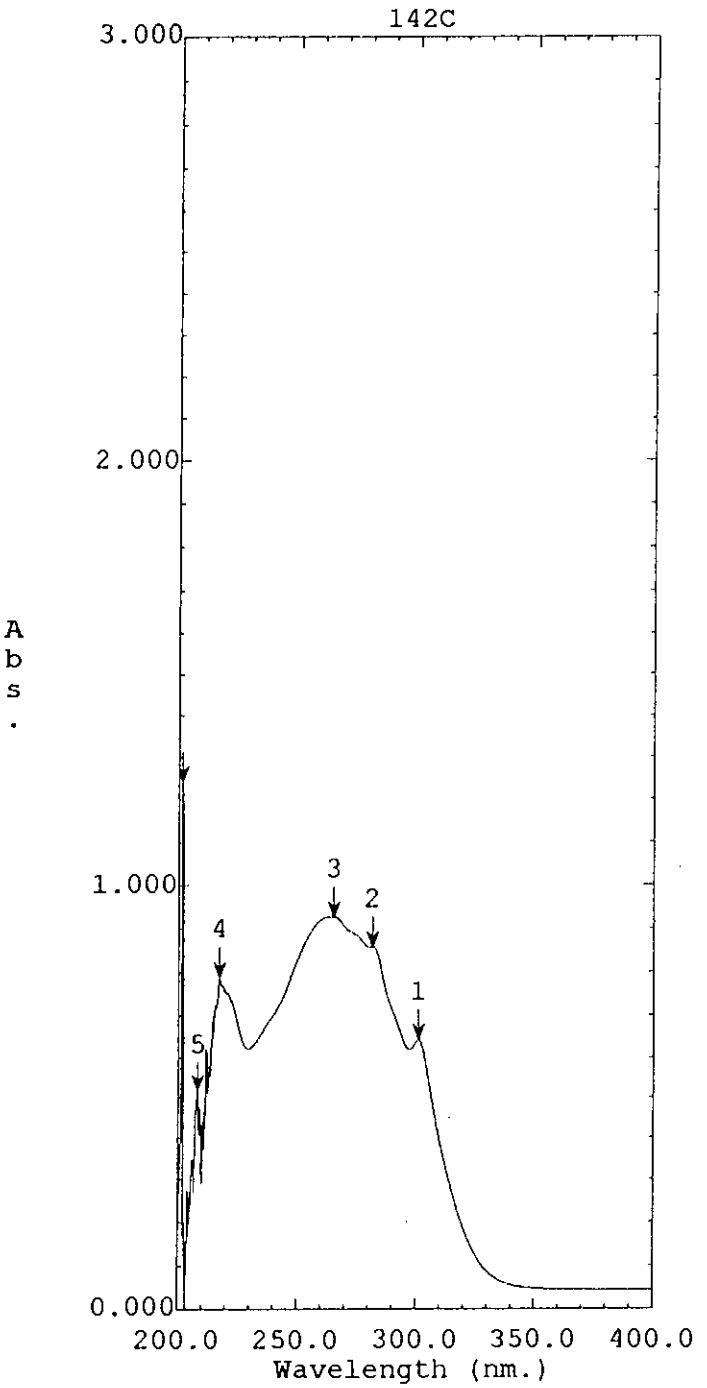
Peak Pick

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



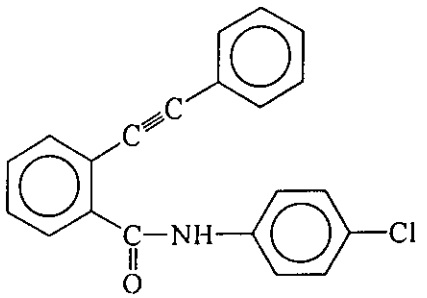
2-Iodo-*N*-phenyl benzamide **17**

Fig. 6: UV spectrum of compound **17**



Peak Pick

No.	Wavelength (nm.)	Abs.
1	301.00	0.6416
2	281.60	0.8567
3	265.20	0.9264
4	217.20	0.7875
5	208.20	0.5187
6	201.40	1.2416



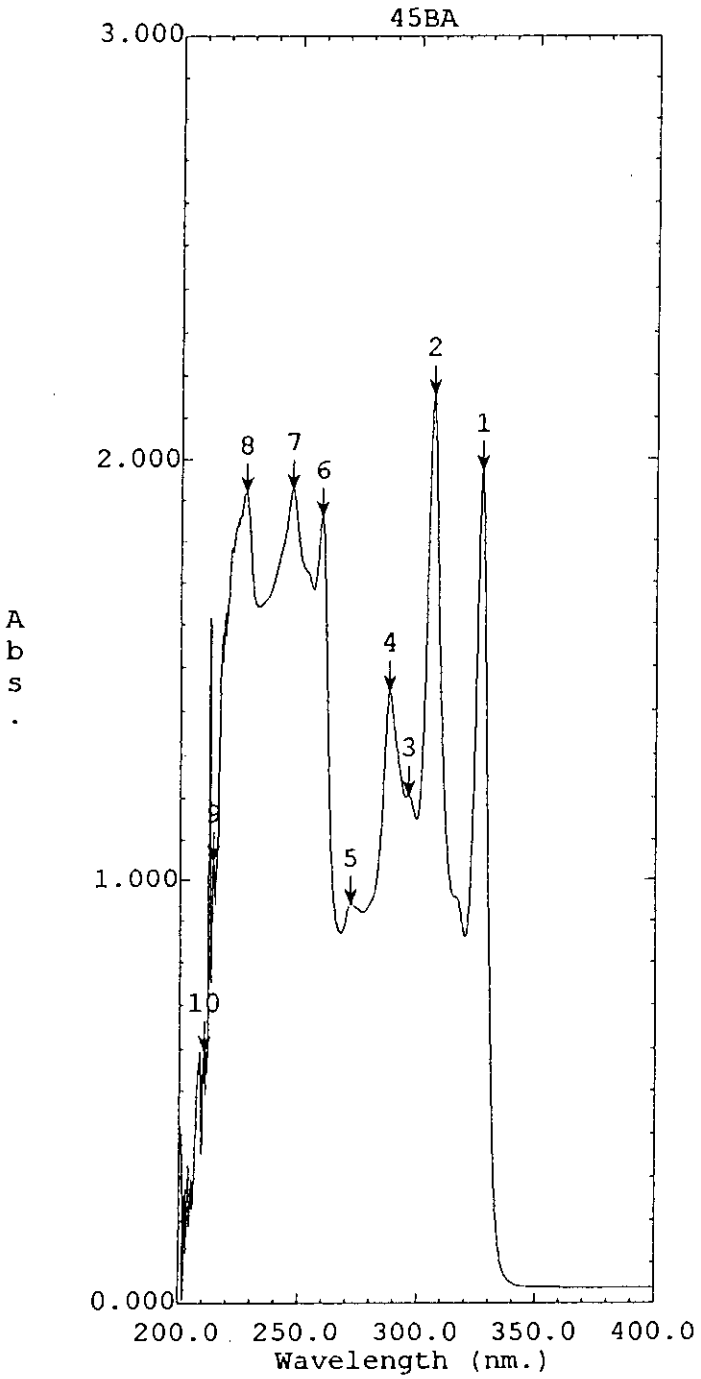
2-(2'-Phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide **21**

Fig. 7: UV spectrum of compound **21**

File Name: 142C

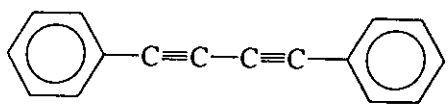
Created: 13:14 07/22/03
Data: Original

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



Peak Pick

No.	Wavelength (nm.)	Abs.
1	326.60	1.9729
2	306.20	2.1523
3	295.80	1.2024
4	287.80	1.4434
5	271.60	0.9397
6	259.20	1.8600
7	246.60	1.9265
8	227.20	1.9200
9	214.00	1.0491
10	210.20	0.5922



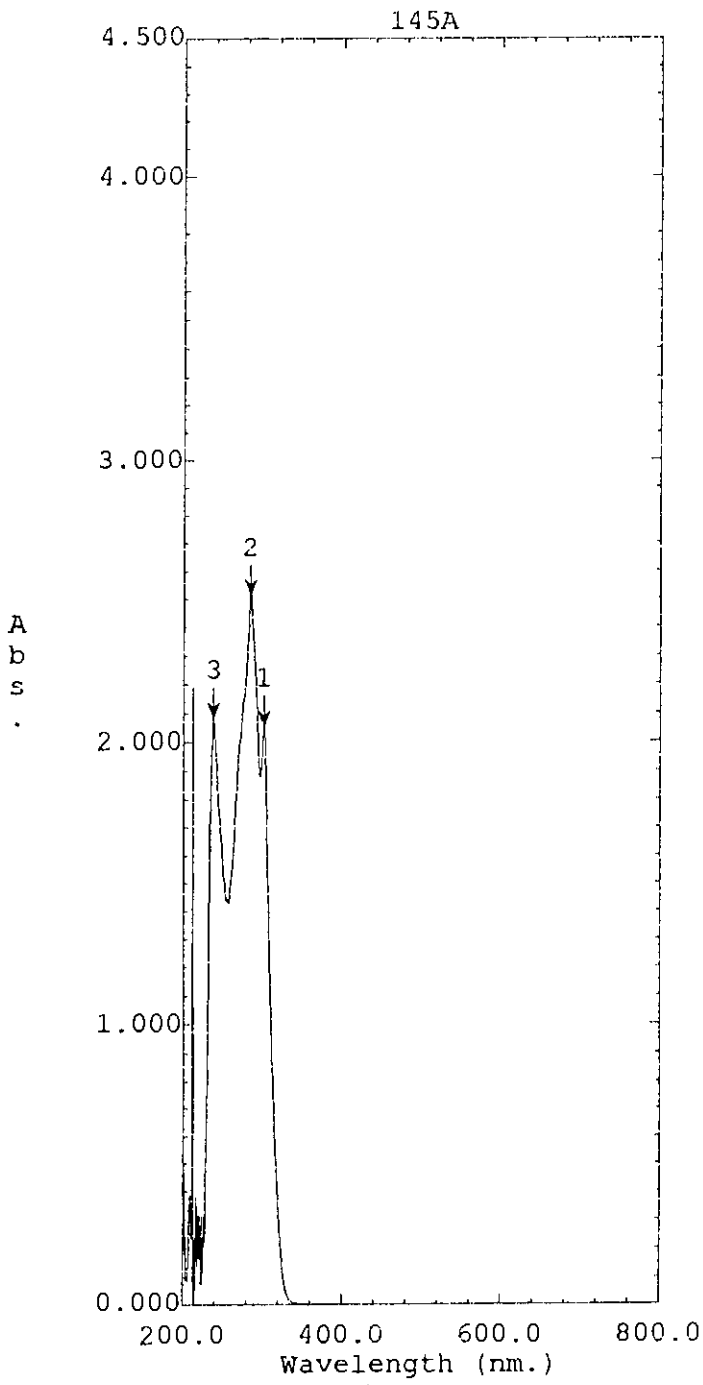
Dimer of Phenylacetylene

Fig. 8: UV spectrum of dimer

File Name: 45BA

Created: 13:22 07/22/03
Data: Original

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



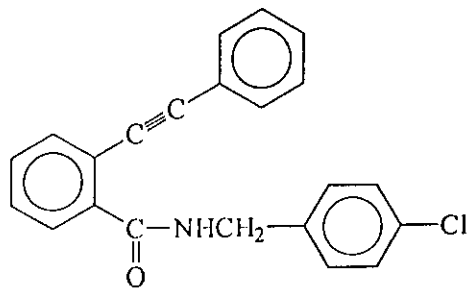
File Name: 145A

Created: 16:36 05/26/03
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

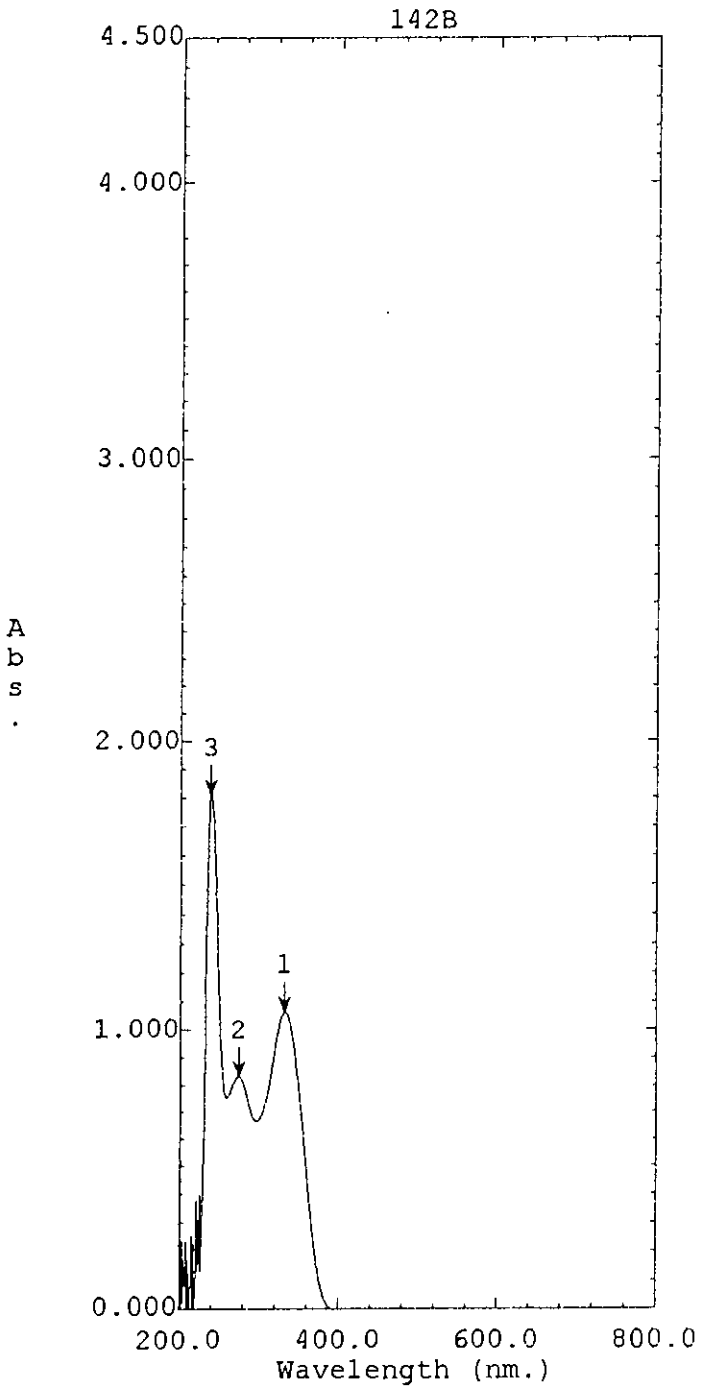
Peak Pick

No.	Wavelength (nm.)	Abs.
1	301.00	2.0565
2	284.00	2.5167
3	237.00	2.0845



2-(2'-Phenyl ethynyl)-*N*-*p* -chlorobenzyl benzamide **22**

Fig. 9: UV spectrum of compound **22**



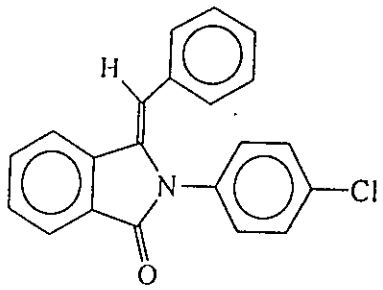
File Name: 142B

Created: 16:31 05/26/03
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5

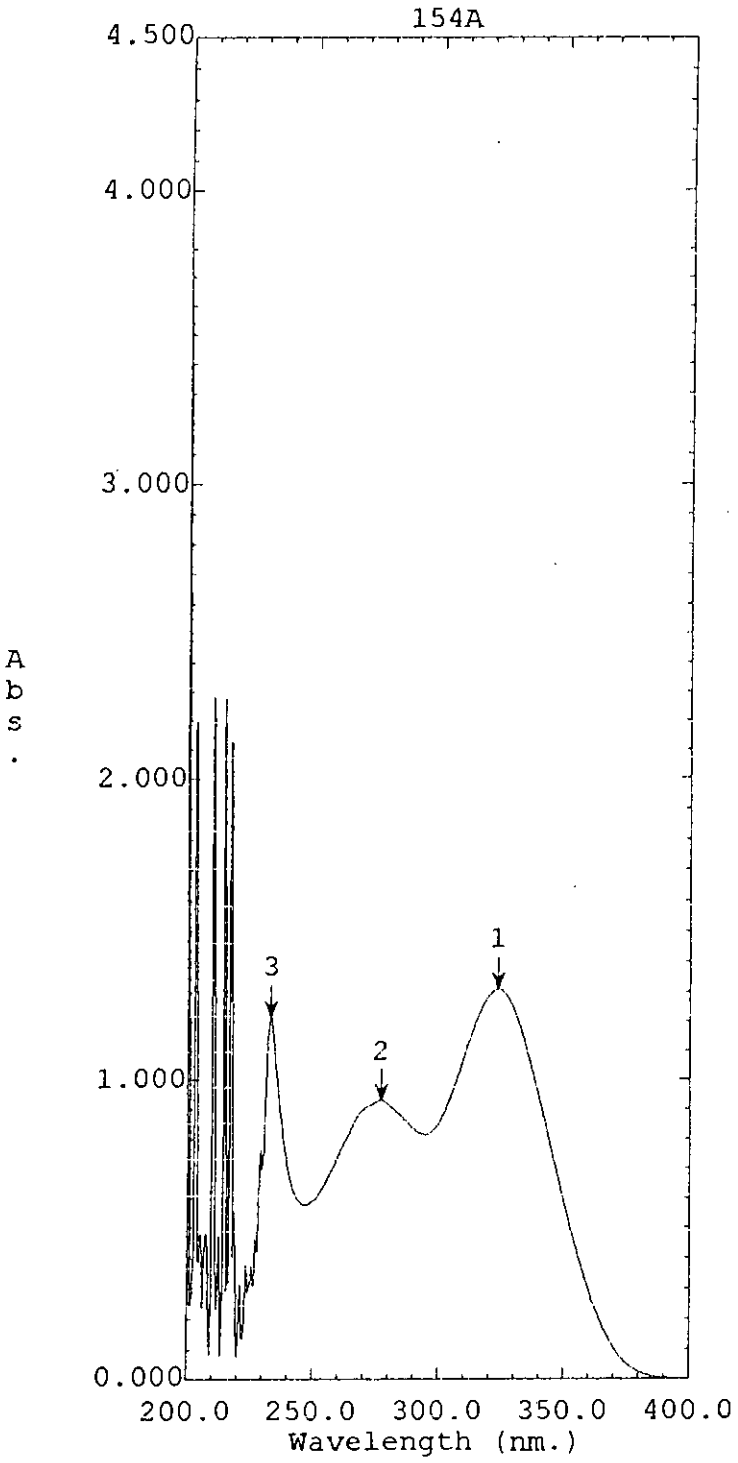
Peak Pick

No.	Wavelength (nm.)	Abs.
1	331.50	1.0621
2	273.50	0.8298
3	237.50	1.8080



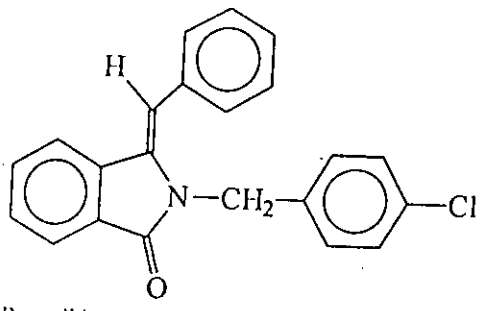
3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one **29**

Fig. 10: UV spectrum of compound **29**



Peak Pick

No.	Wavelength (nm.)	Abs.
1	323.50	1.3073
2	277.00	0.9291
3	233.00	1.2142



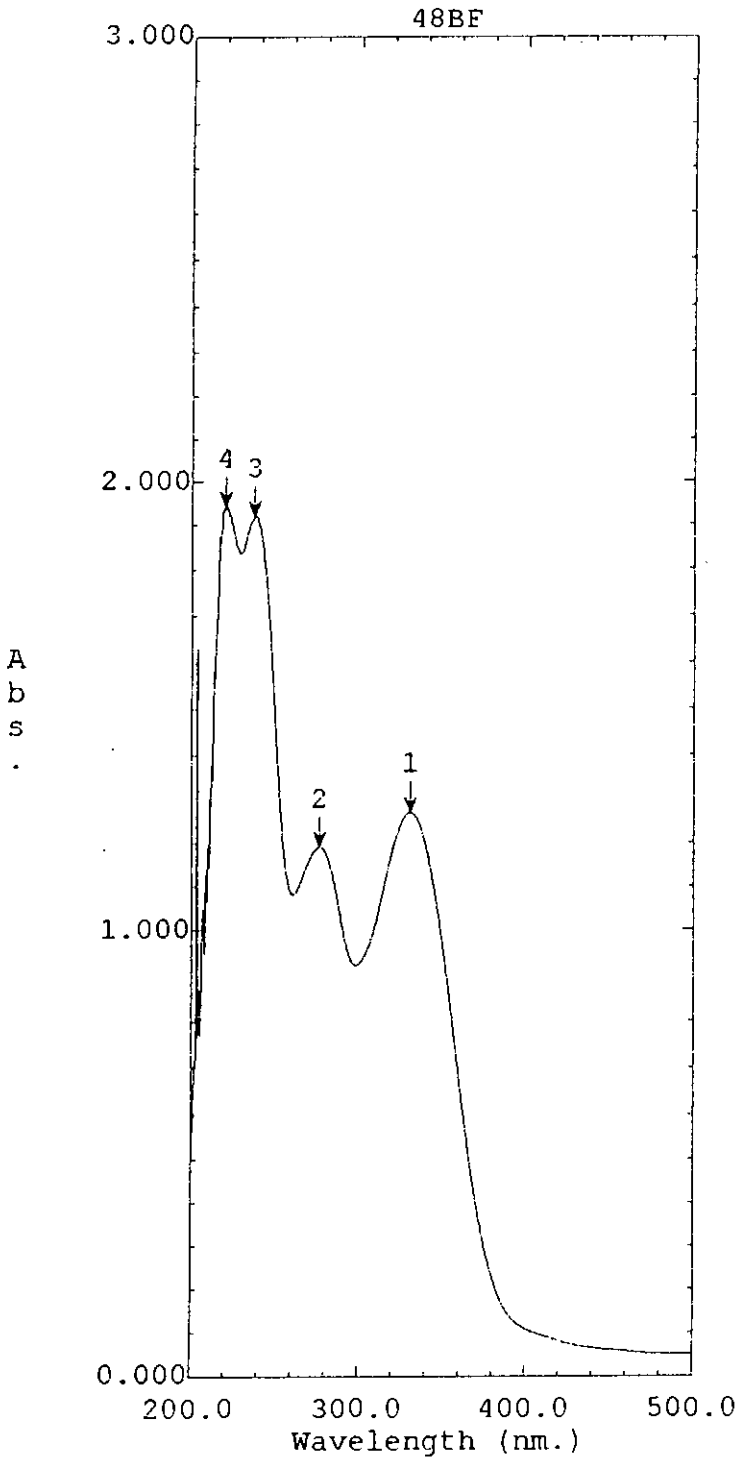
3-Benzylidene-*N*-*p*-chlorobenzyl isoindolin-1-one **30**

Fig. 11: UV spectrum of compound **30**

File Name: 154A

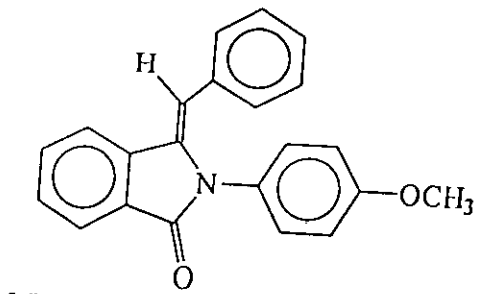
Created: 16:49 05/26/03
Data: Original

Measuring Mode: Abs.
Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.5



Peak Pick

No.	Wavelength (nm.)	Abs.
1	330.60	1.2708
2	276.60	1.1898
3	237.40	1.9186
4	220.20	1.9415



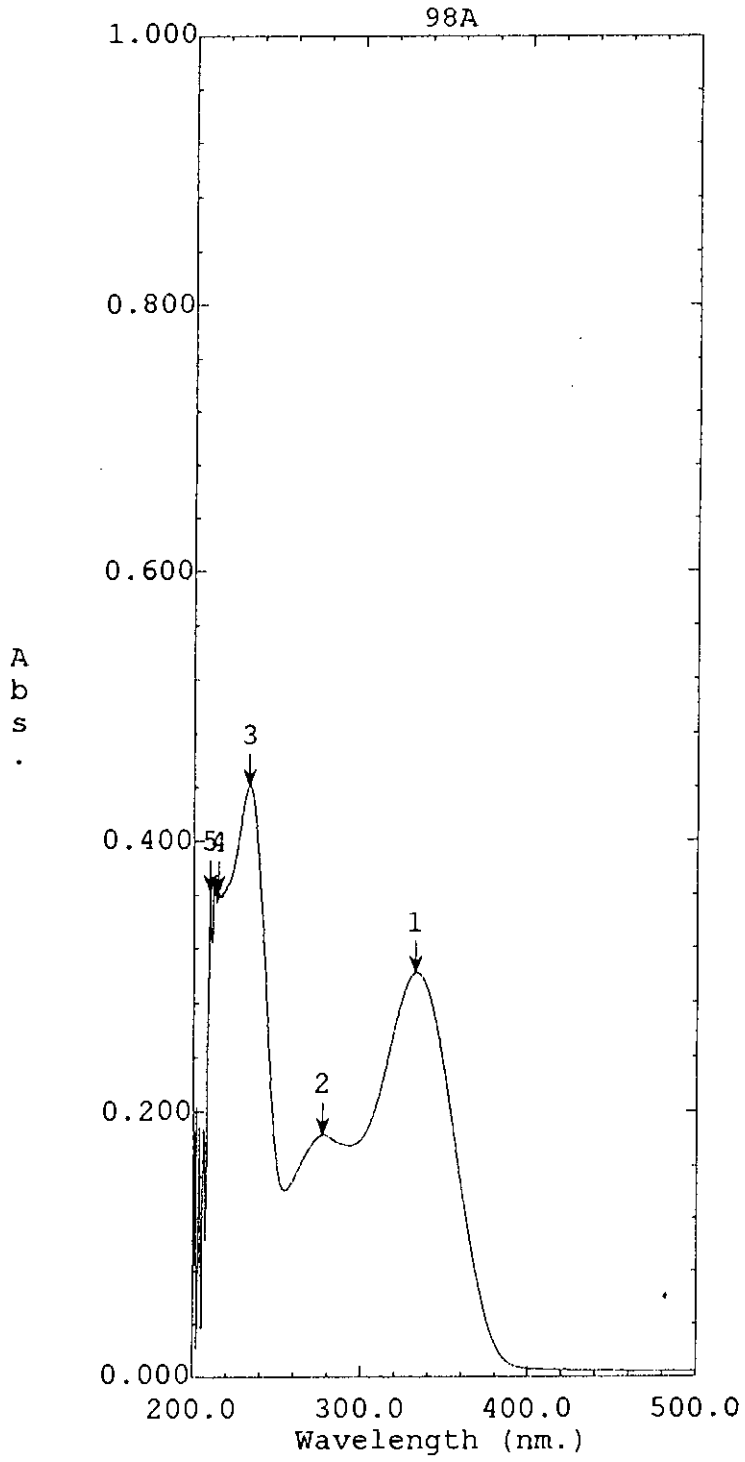
3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one **34**

Fig. 12: UV spectrum of compound **34**

File Name: 48BF

Created: 13:22 07/23/03
Data: Original

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



Peak Pick

No.	Wavelength (nm.)	Abs.
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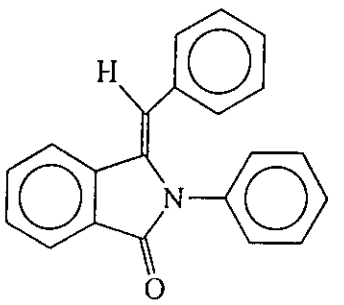
3	232.80	0.4412
4	214.60	0.3619
5	209.60	0.3625



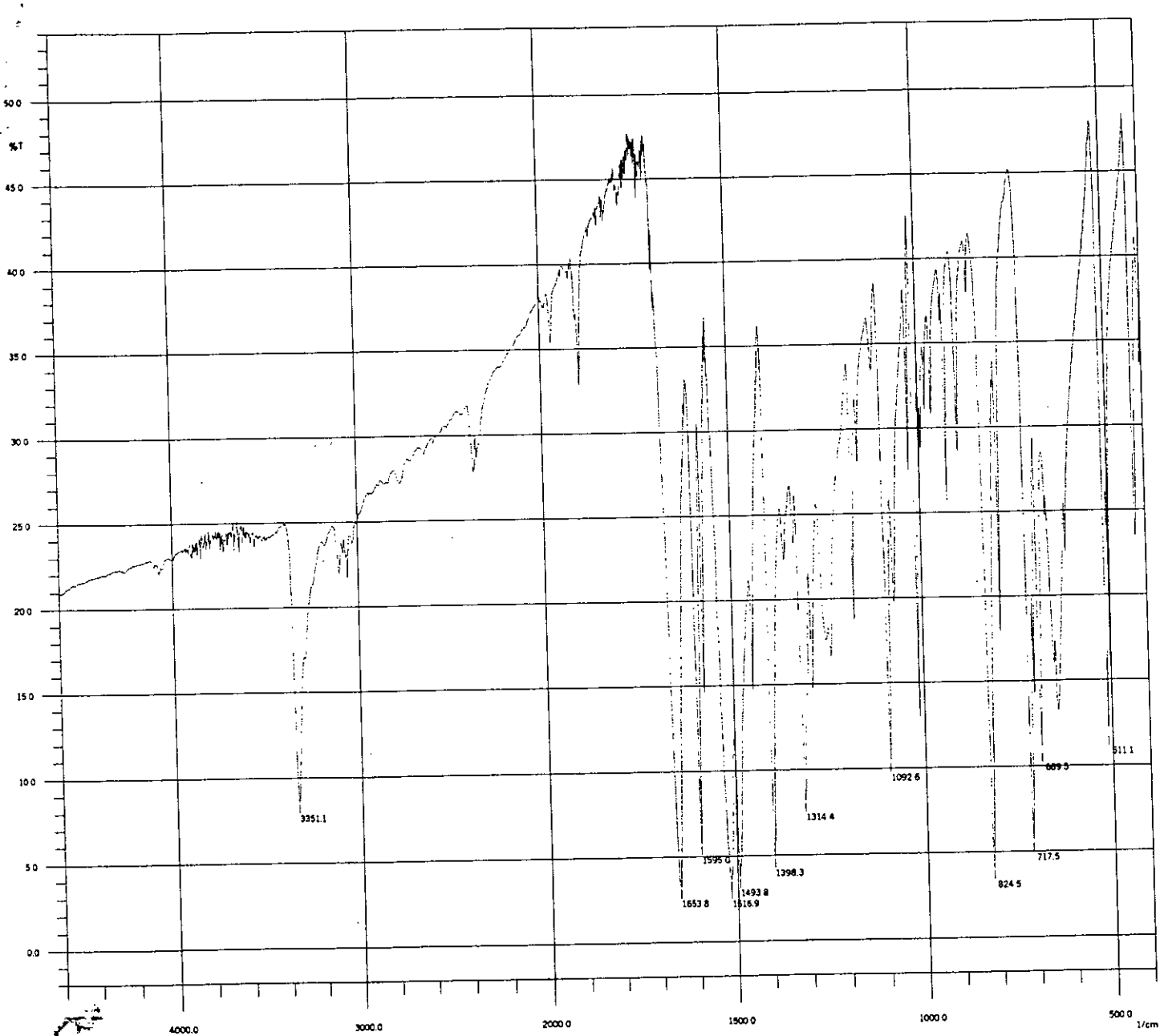
3-Benzylidene-*N*-phenyl isoindolin-1-one **35**

Fig. 13: UV spectrum of compound **35**

File Name: 98A

Created: 16:40 06/02/03
Data: Original

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



Peaktable of DEFAULT.IRS, 12 Peaks
Threshhold: 12, Noise: 2, No Range Selection

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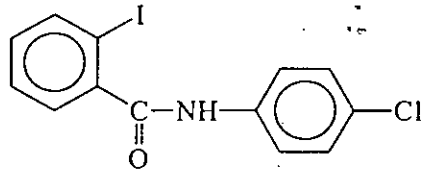
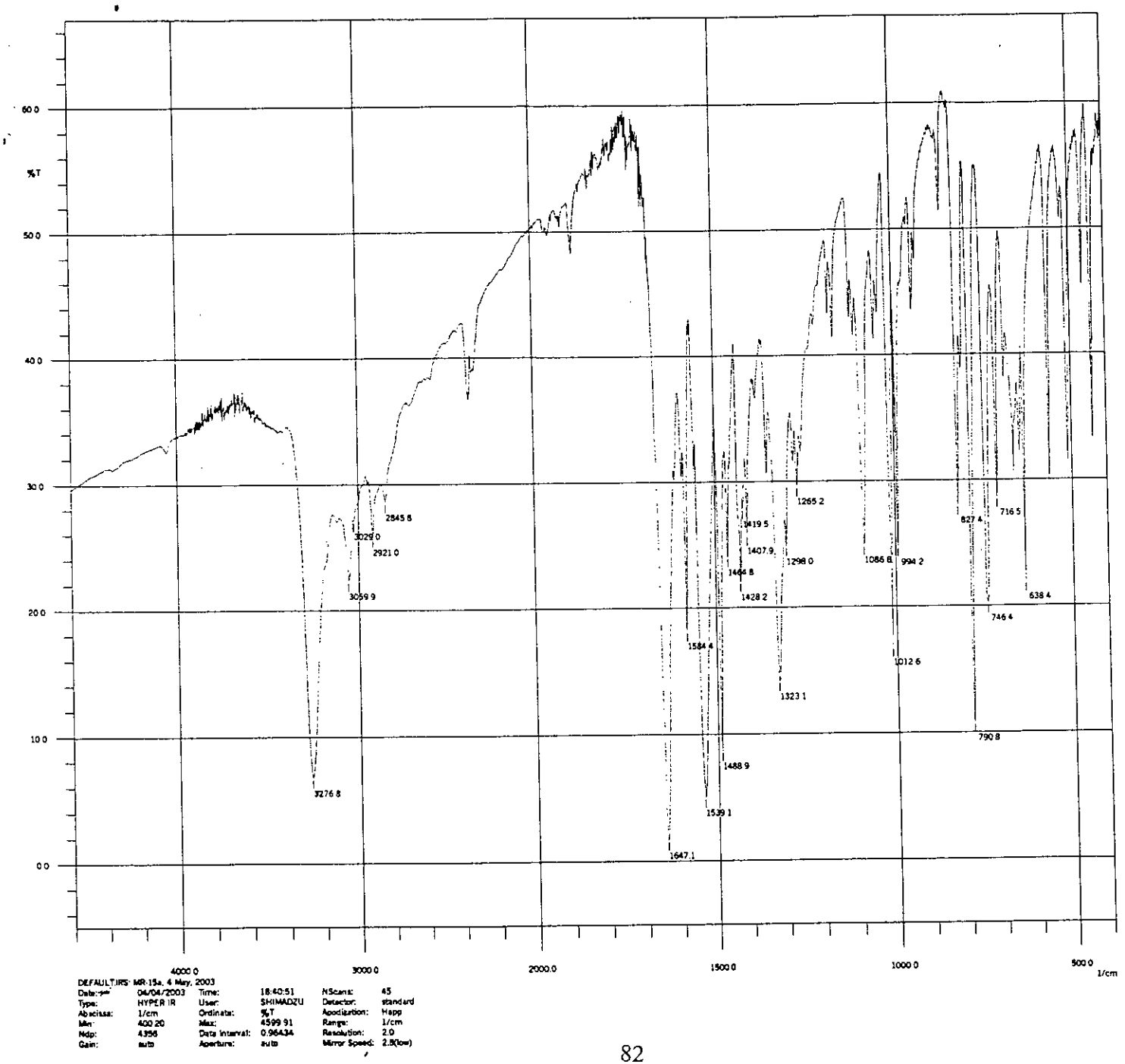
1	511.1	11.765
2	689.5	10.865
3	717.5	5.589
4	824.5	4.038
5	1092.6	10.406
6	1314.4	8.158
7	1398.3	4.925
8	1493.8	3.786
9	1516.9	3.611
10	1595.0	5.732
11	1653.8	3.213
12	3351.1	8.570

Ma-4, 1 May, 2003



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

Fig. 14: IR spectrum of compound **11**



Peaktable of DEFAULT.IRS, 24 Peaks
Threshhold: 30, Noise: 2, No Range Selection

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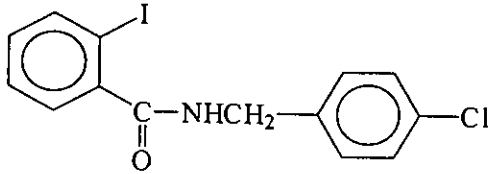
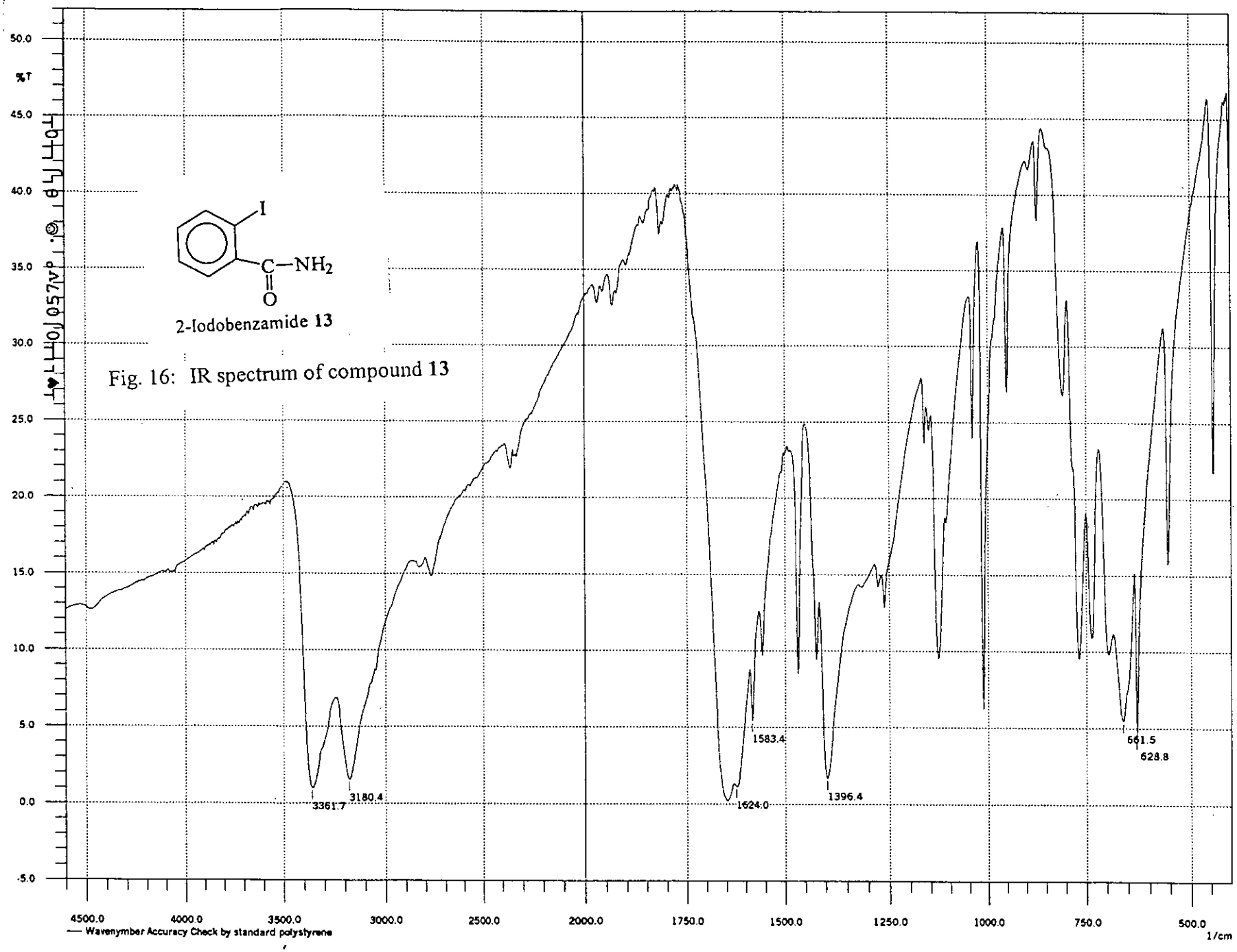
2	716.5	28.629
3	746.4	20.261
4	790.8	10.751
5	827.4	28.010
6	994.2	24.724
7	1012.6	16.802
8	1086.8	24.915
9	1265.2	29.593
10	1298.0	24.829
11	1323.1	14.171
12	1407.9	25.723
13	1419.5	27.842
14	1428.2	22.066
15	1464.8	24.028
16	1488.9	8.679
17	1539.1	5.025
18	1584.4	18.202
19	1647.1	1.650
20	2845.8	28.581
21	2921.0	25.837
22	3029.0	27.105
23	3059.9	22.348
24	3276.8	6.790

MR-15a, 4 May, 2003



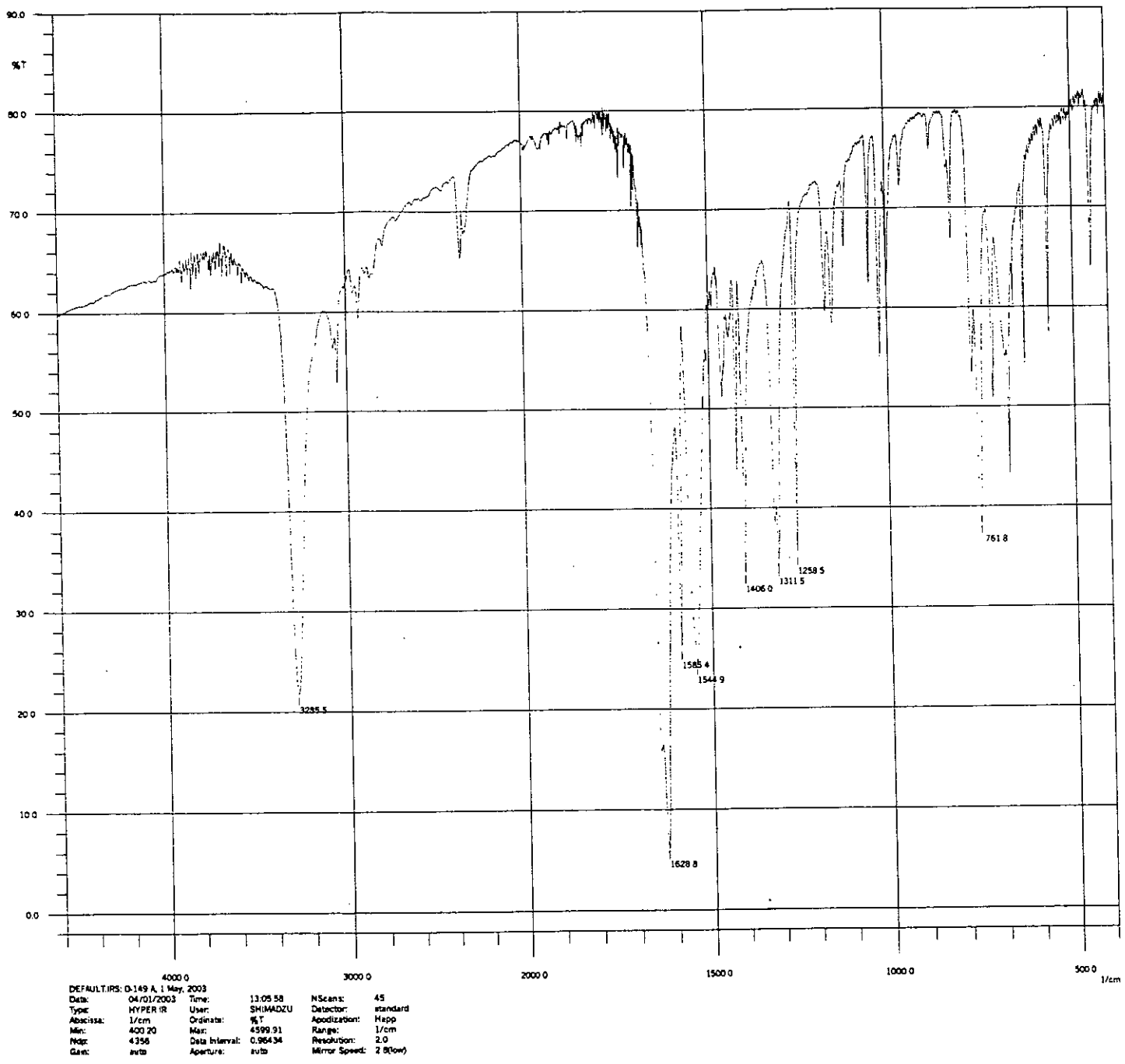
2-Iodo-*N*-*p*-Chlorobenzyl benzamide **12**

Fig. 15: IR spectrum of compound **12**



2-Iodobenzamide **13**

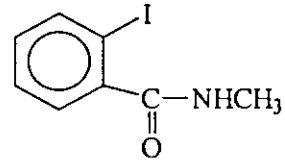
Fig. 16: IR spectrum of compound **13**



Peaktable of DEFAULT.IRS, 8 Peaks
Threshhold: 40, Noise: 2, No Range Selection

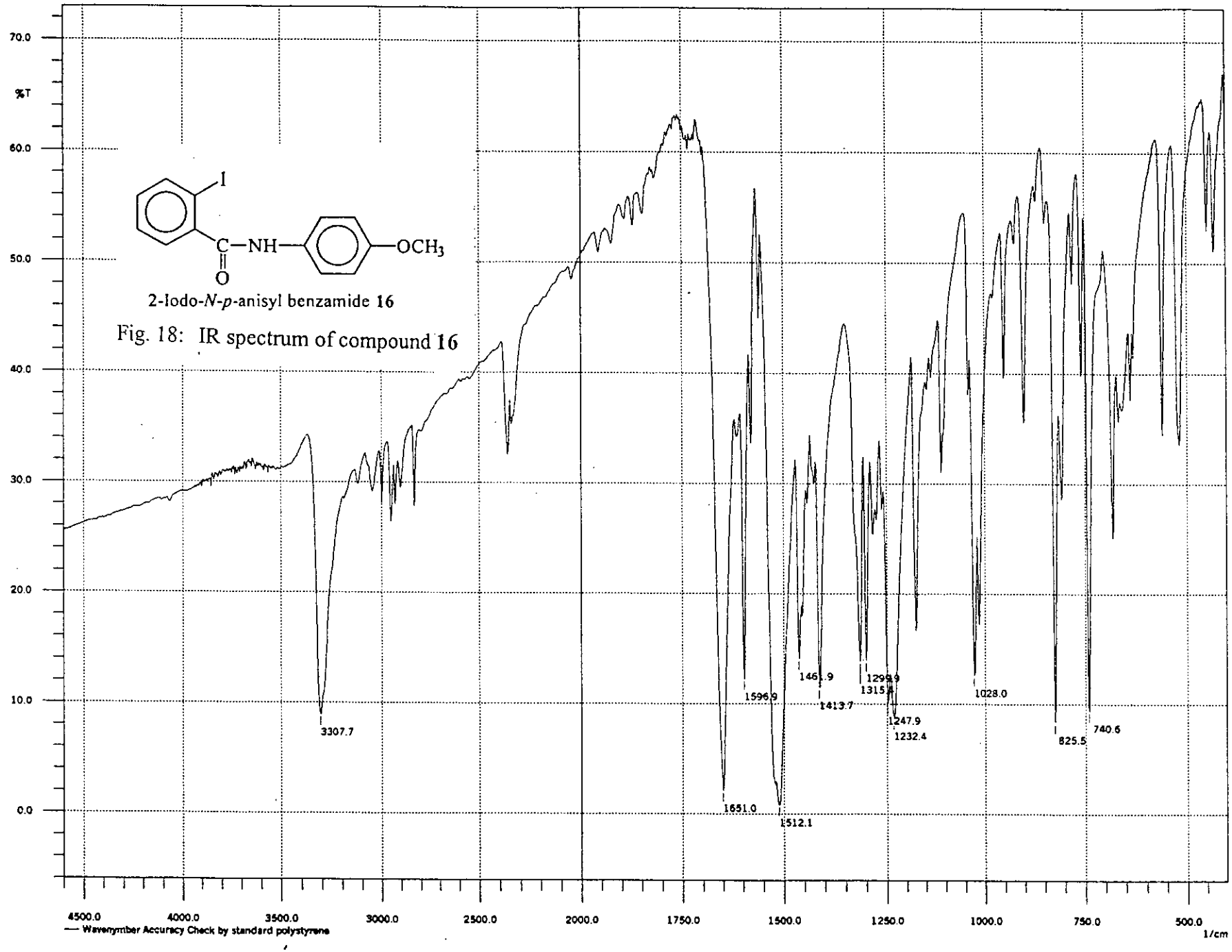
No.	Pos. (1/cm)	Inten. (%T)
1	761.8	38.314
2	1258.5	35.240
3	1311.5	34.659
4	1406.0	33.458
5	1544.9	24.465
6	1585.4	25.955
7	1628.8	6.095
8	3285.5	21.737

D-149 A, 1 May, 2003



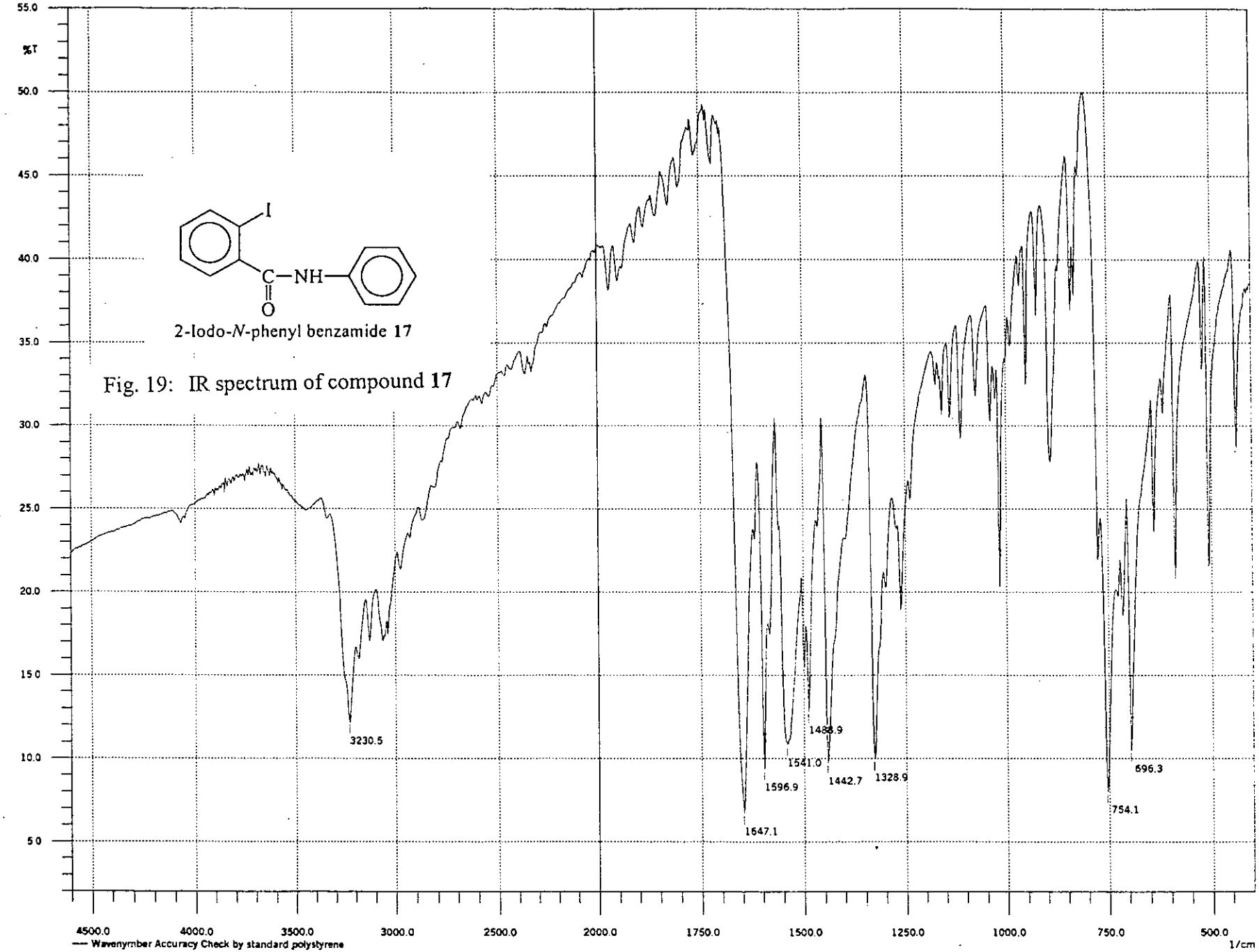
2-Iodo-*N*-methyl benzamide **14**

Fig. 17: IR spectrum of compound **14**



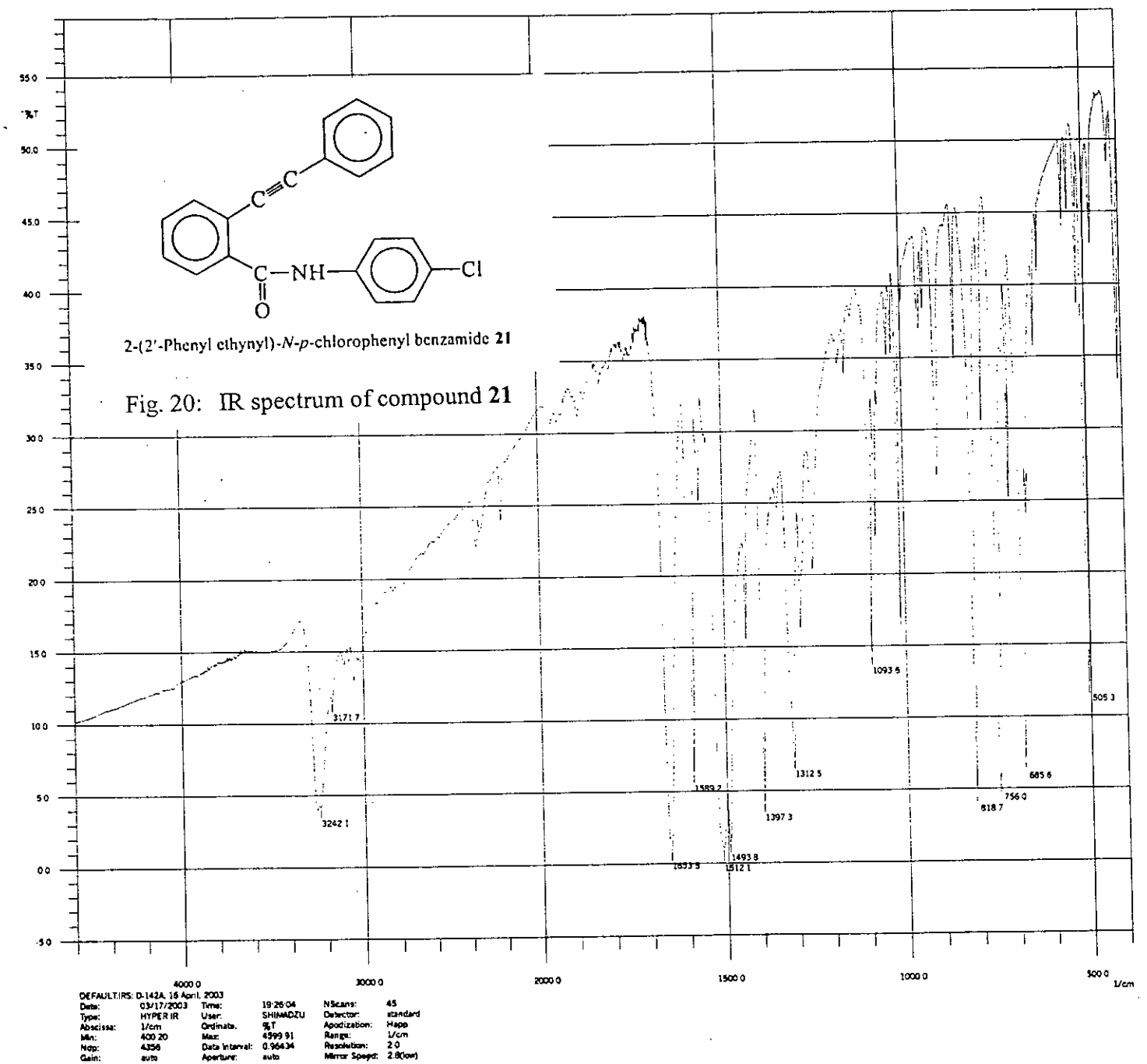
2-Iodo-*N*-*p*-anisyl benzamide **16**

Fig. 18: IR spectrum of compound **16**



2-Iodo-*N*-phenyl benzamide **17**

Fig. 19: IR spectrum of compound **17**



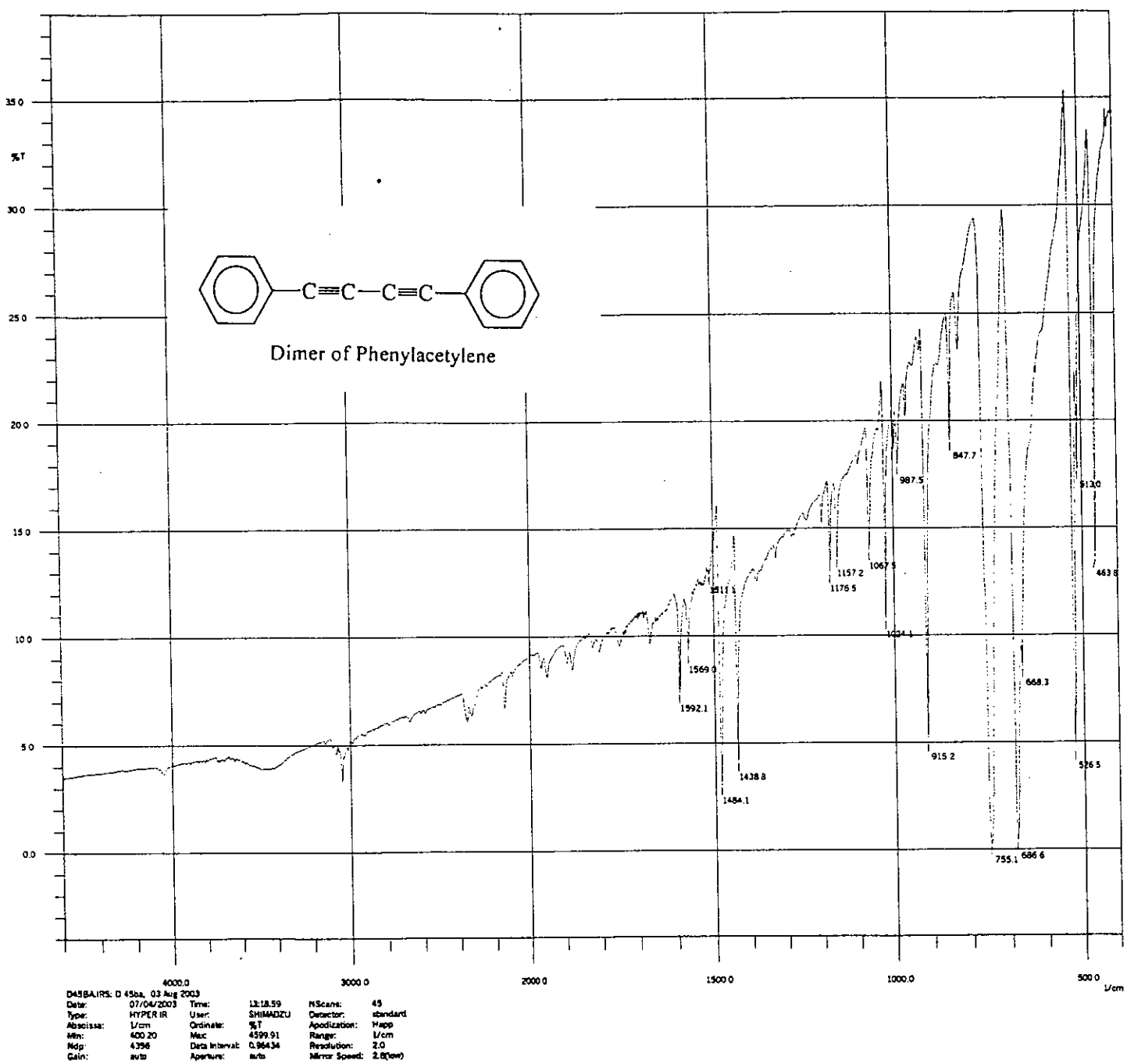
2-(2'-Phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide **21**

Fig. 20: IR spectrum of compound **21**

Peaktable of DEFAULT.IRS, 13 Peaks
Threshhold: 15, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	505.3	12.291
2	685.6	6.933
3	756.0	5.471
4	818.7	4.717
5	1093.6	14.391
6	1312.5	7.245
7	1397.3	4.222
8	1493.8	1.450
9	1512.1	1.091
10	1589.2	6.288
11	1653.8	0.928
12	3171.7	11.508
13	3242.1	4.152

D-142A, 16 April, 2003

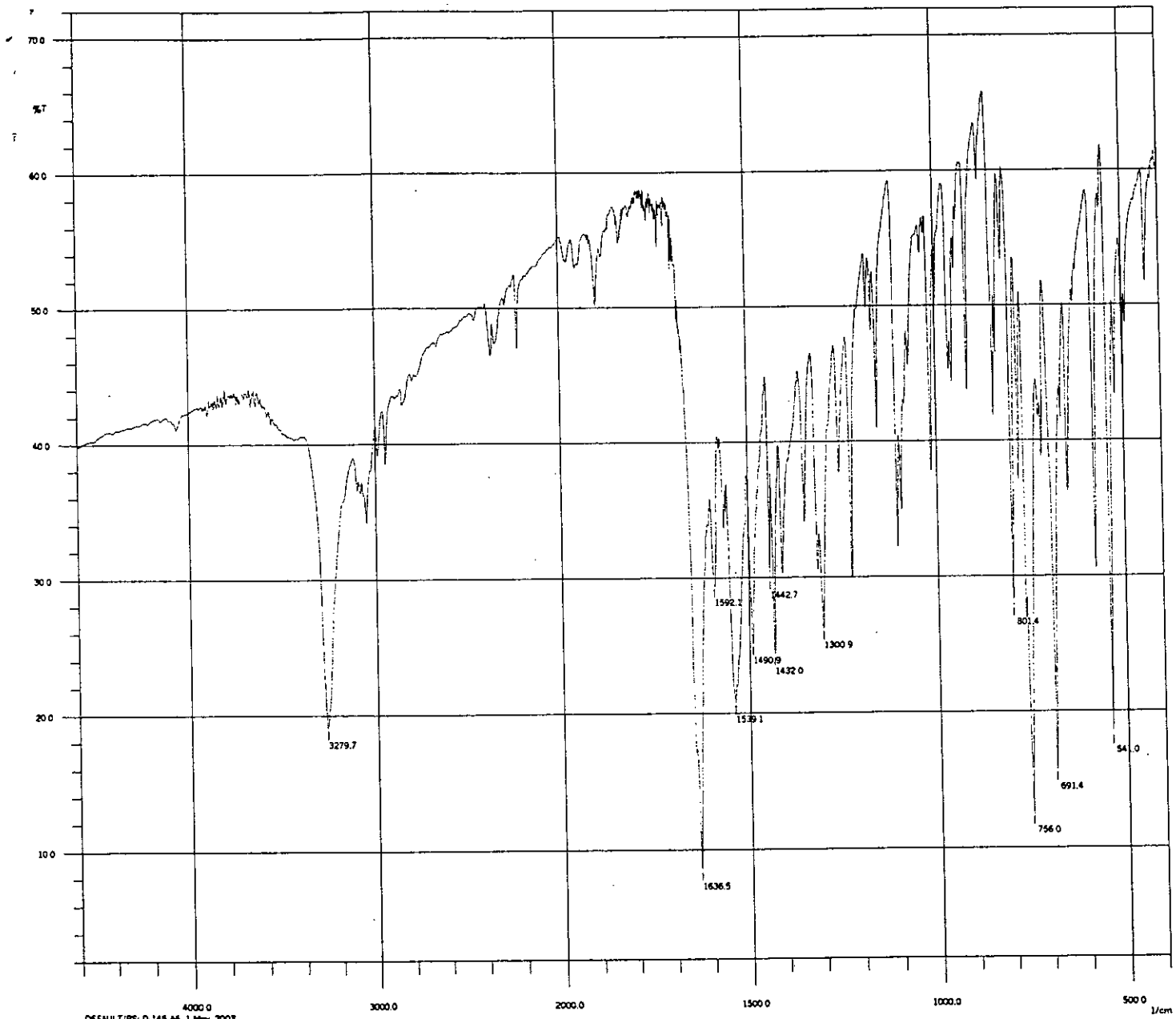


Peaktable of D45BA.IRS, 18 Peaks
Threshhold: 20, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	463.8	13.568
2	513.0	17.697
3	526.5	4.608
4	668.3	8.491
5	686.6	0.429
6	755.1	0.232
7	847.7	19.085
8	915.2	5.052
9	987.5	17.946
10	1024.1	10.786
11	1067.5	13.969
12	1157.2	13.632
13	1176.5	12.908
14	1438.8	4.150
15	1484.1	3.067
16	1511.1	12.881
17	1569.0	9.171
18	1592.1	7.362

D 45ba, 03 Aug 2003

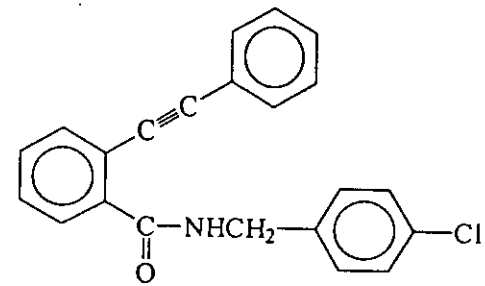
Fig. 21: IR spectrum of dimer



Peaktable of DEFAULT.IRS, 12 Peaks
Threshhold: 30, Noise: 2, No Range Selection

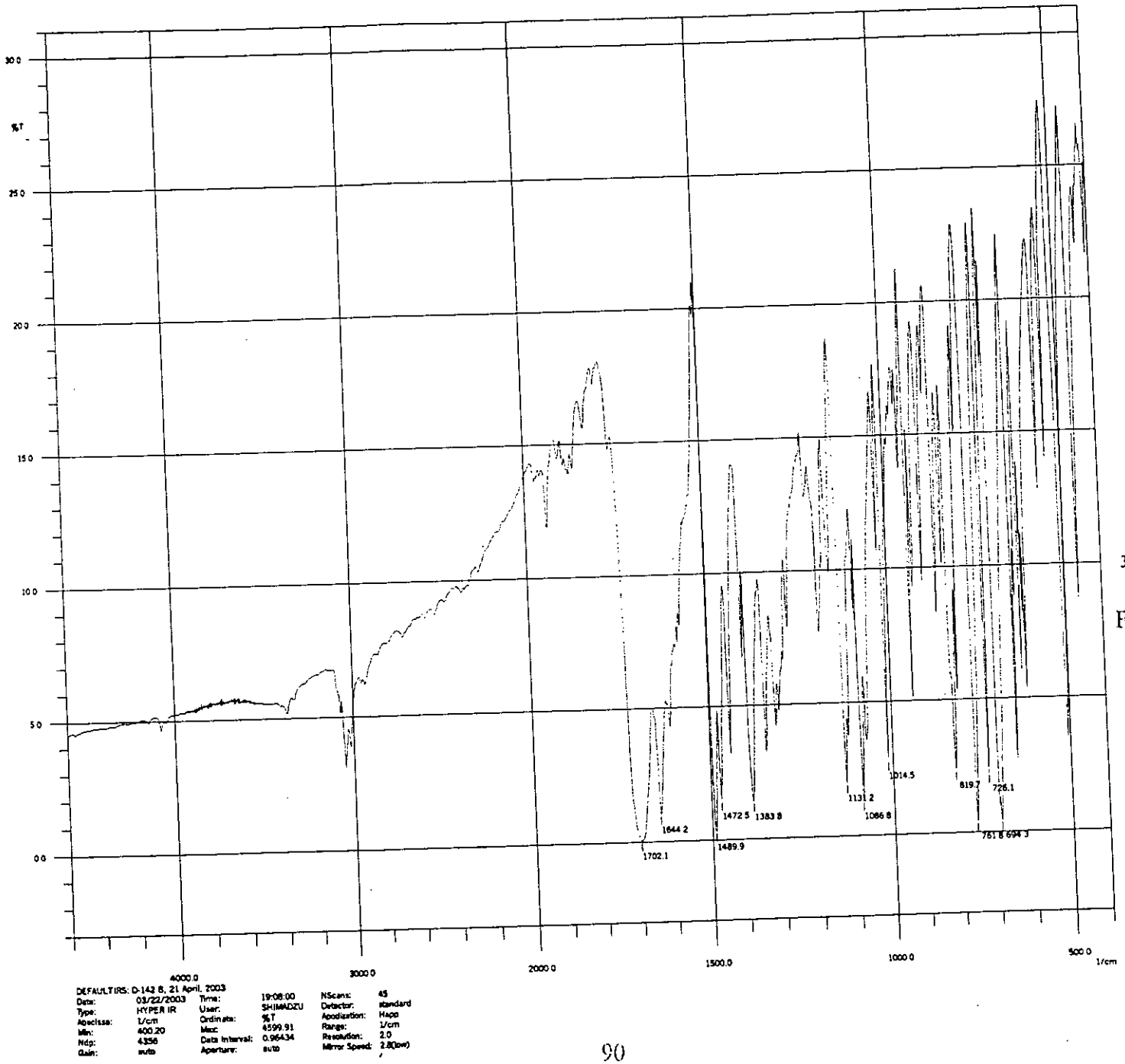
No.	Pos. (1/cm)	Inten. (%T)
1	541.0	18.340
2	691.4	15.633
3	756.0	12.472
4	801.4	27.795
5	1300.9	26.176
6	1432.0	24.279
7	1442.7	29.873
8	1490.9	25.081
9	1539.1	20.776
10	1592.1	29.361
11	1636.5	8.506
12	3279.7	19.045

D-145 A6, 1 May, 2003



2-(2′-Phenyl ethynyl)-*N*-*p* -chlorobenzyl benzamide **22**

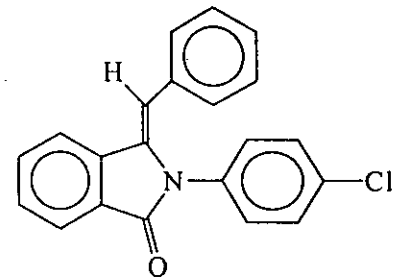
Fig. 22: IR spectrum of compound **22**



Peaktable of DEFAULT.IRS, 12 Peaks
Threshhold: 3, Noise: 2, No Range Selection

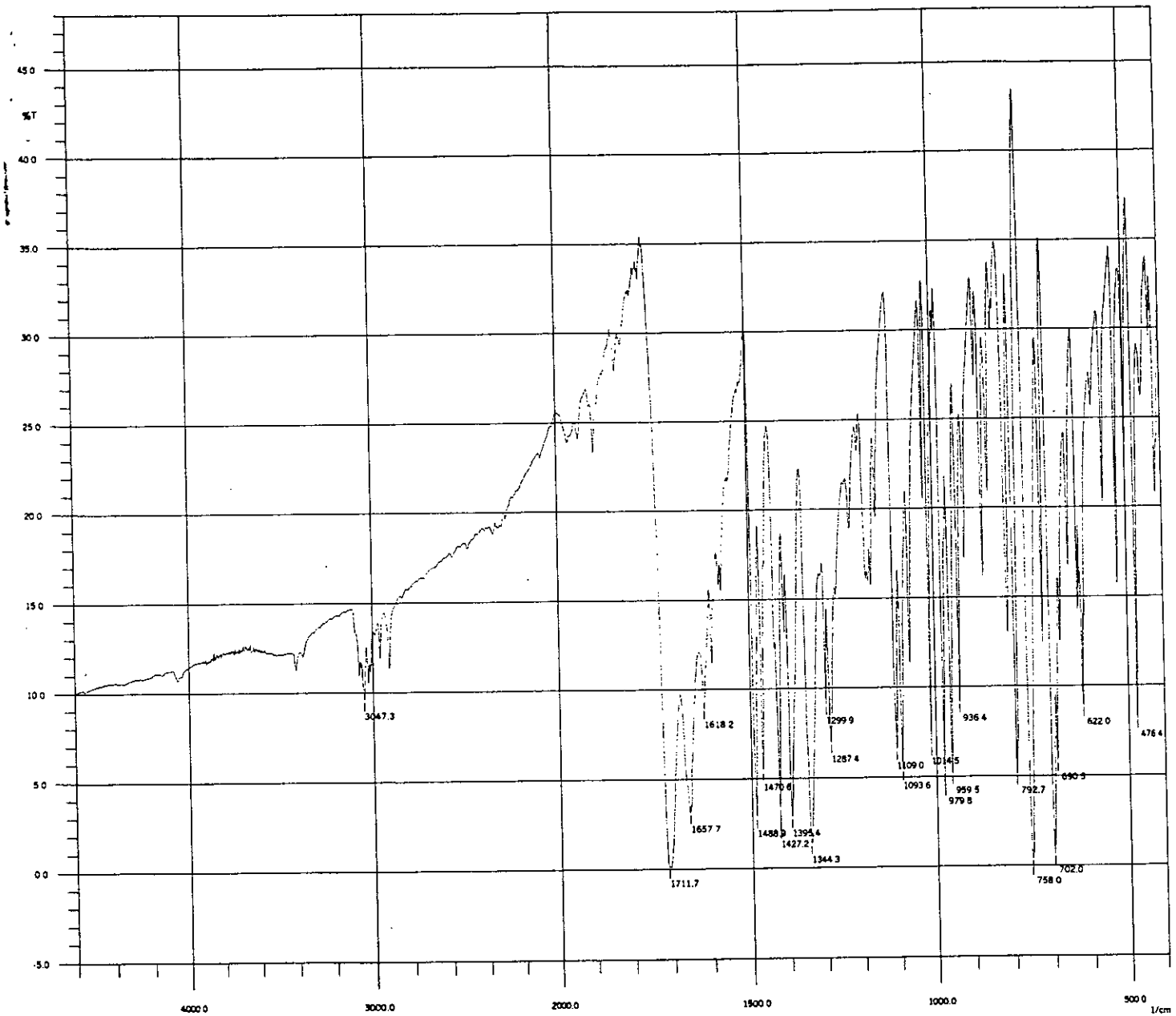
No.	Pos. (1/cm)	Inten. (%T)
1	694.3	0.4267
2	726.1	2.1947
3	761.8	0.4098
4	819.7	2.3520
5	1014.5	2.7819
6	1086.8	1.3034
7	1131.2	1.9752
8	1383.8	1.3931
9	1472.5	1.4694
10	1489.9	0.3172
11	1644.2	1.0108
12	1702.1	0.0464

D-142 B, 21 April, 2003



3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one **29**

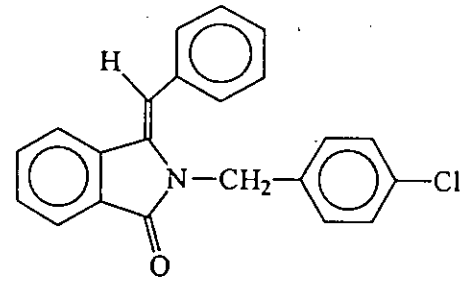
Fig. 23: IR spectrum of compound **29**



Peaktable of DEFAULT.IRS, 23 Peaks
Threshhold: 10, Noise: 2, No Range Selection

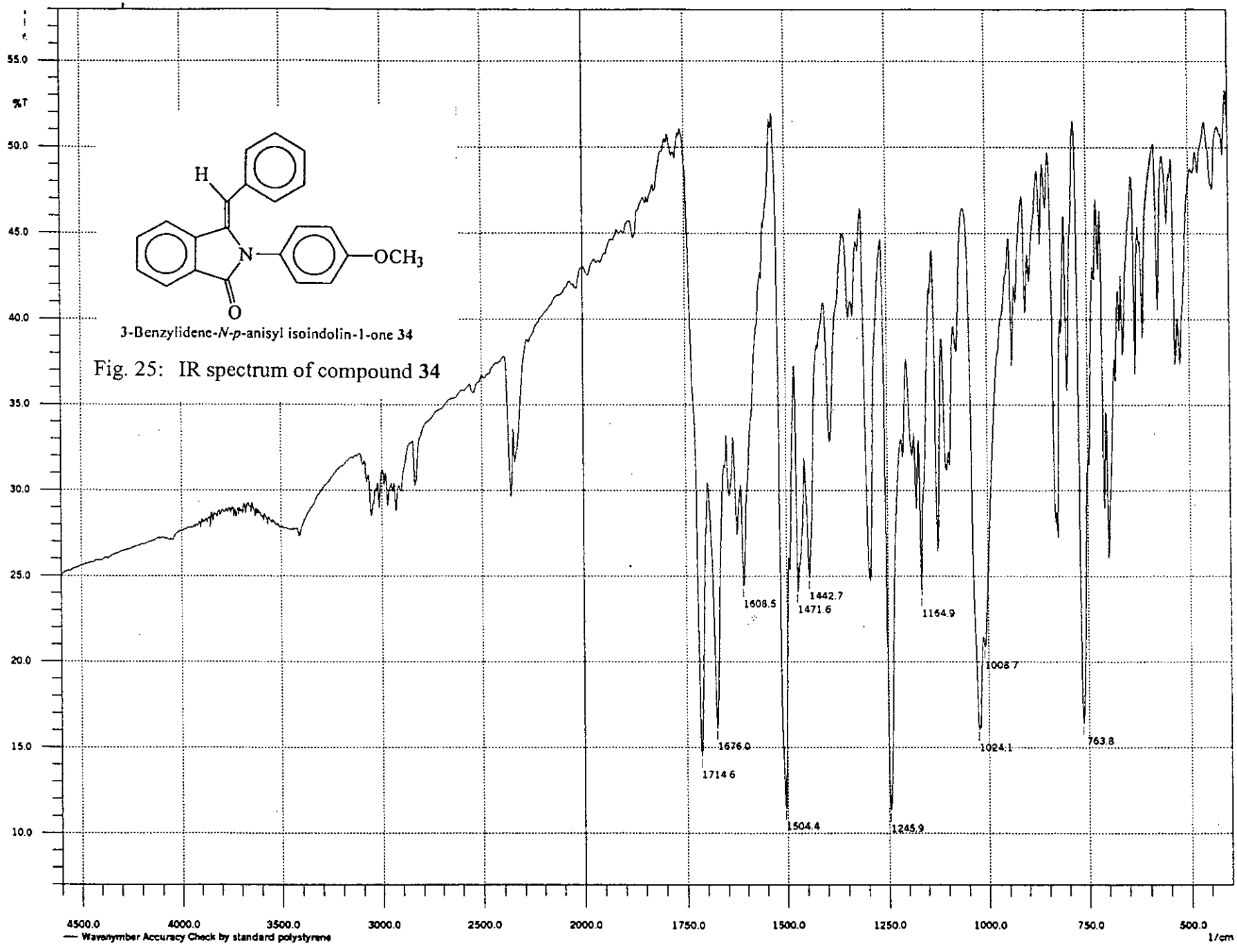
No.	Pos. (1/cm)	Inten. (%T)
1	476.4	8.1766
2	622.0	8.8843
3	690.5	5.8213
4	702.0	0.6573
5	758.0	0.3833
6	792.7	5.0894
7	936.4	9.1481
8	959.5	5.1152
9	979.8	5.2876
10	1014.5	6.7677
11	1093.6	5.4154
12	1109.0	6.5262
13	1287.4	6.9336
14	1299.9	9.1005
15	1344.3	1.3688
16	1395.4	2.8393
17	1427.2	3.3890
18	1470.6	5.4235
19	1488.9	2.8386
20	1618.2	8.9362
21	1657.7	3.1334
22	1711.7	0.1156
23	3047.3	9.5964

D-146B, 4 May, 2003



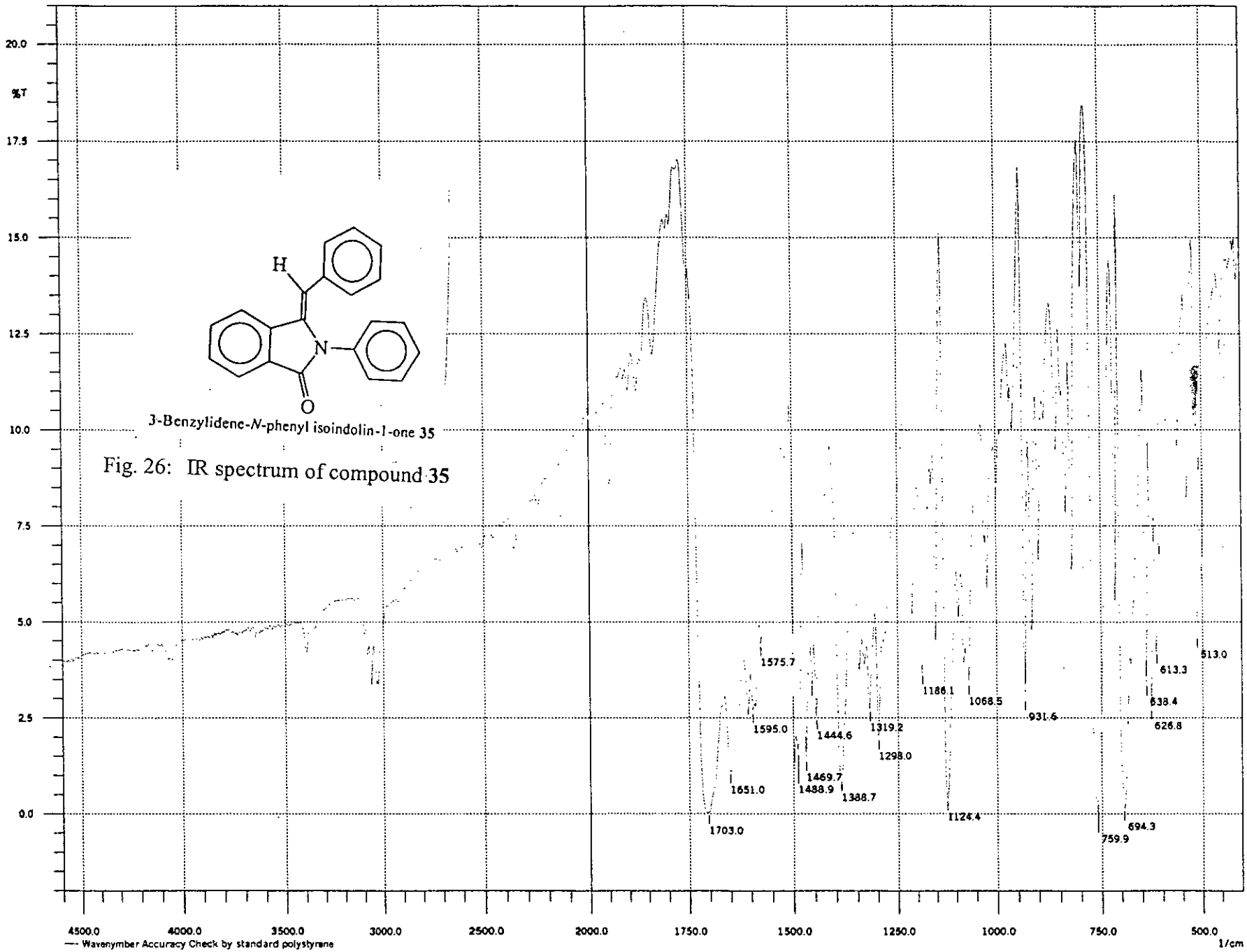
3-Benzylidene-*N*-*p*-chlorobenzyl isoindolin-1-one **30**

Fig. 24: IR spectrum of compound **30**



3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one **34**

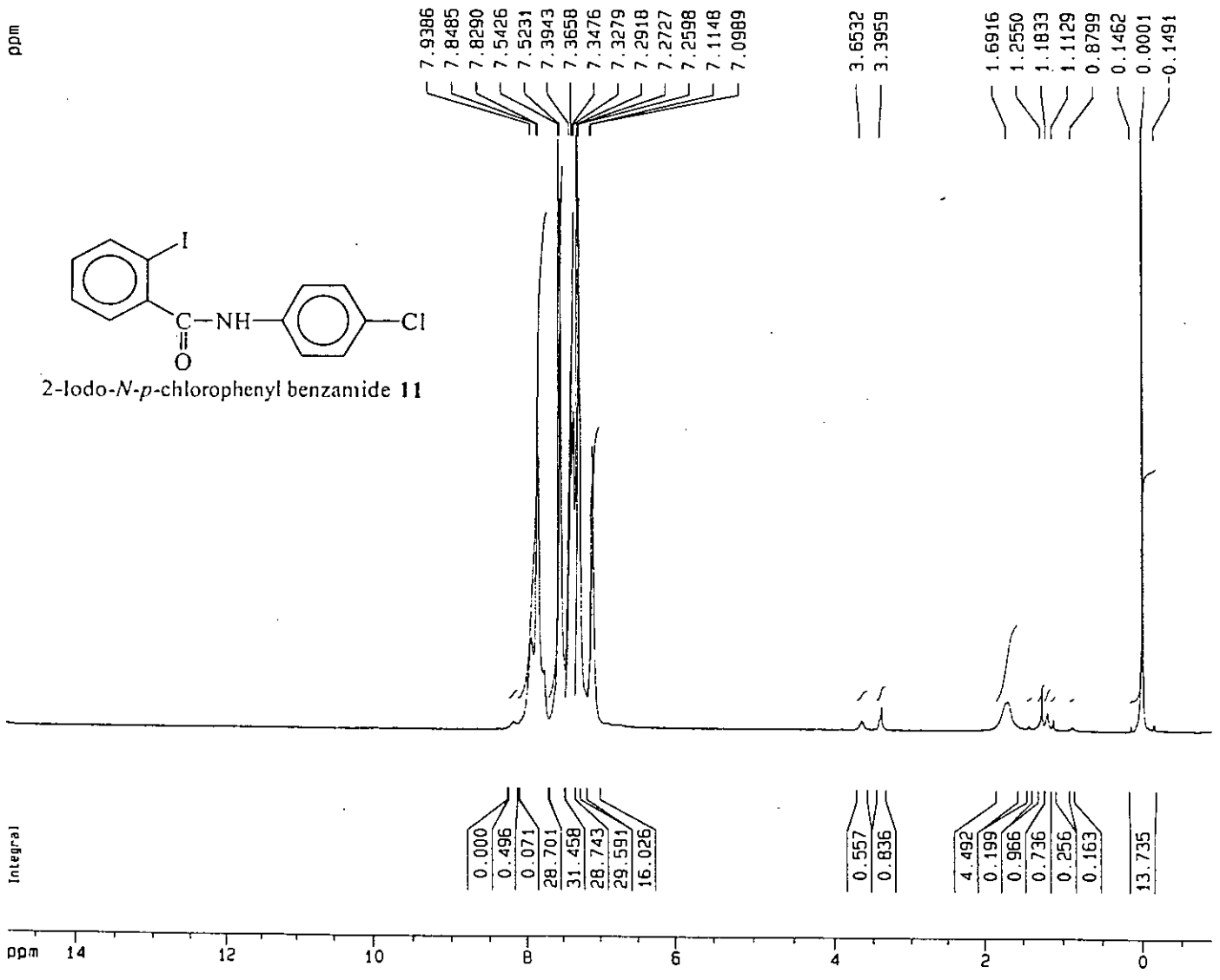
Fig. 25: IR spectrum of compound **34**



3-Benzylidene-*N*-phenyl isoindolin-1-one **35**

Fig. 26: IR spectrum of compound **35**

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



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

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 ==========

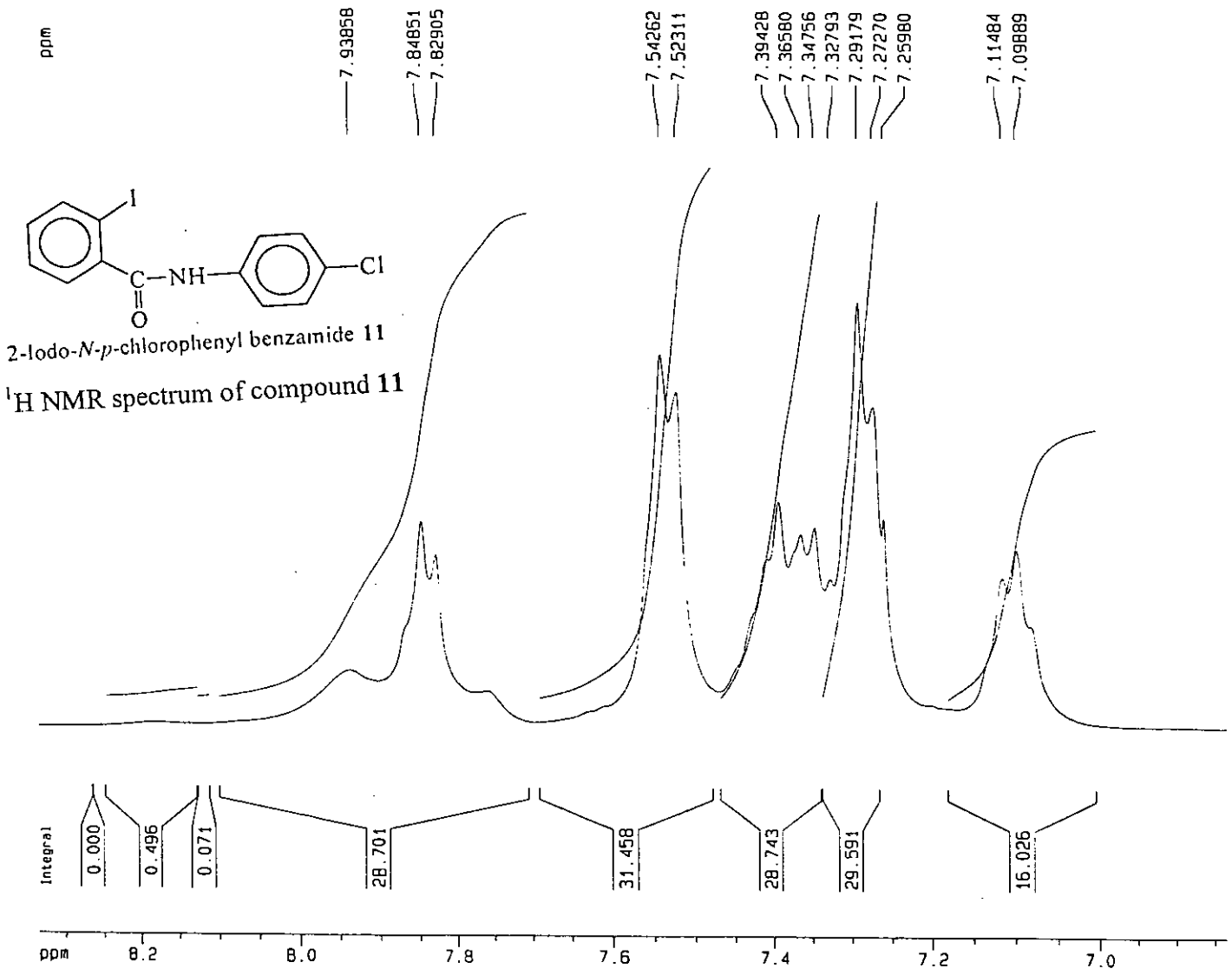
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

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



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

Fig. 27: ^{1}H NMR spectrum of compound **11**

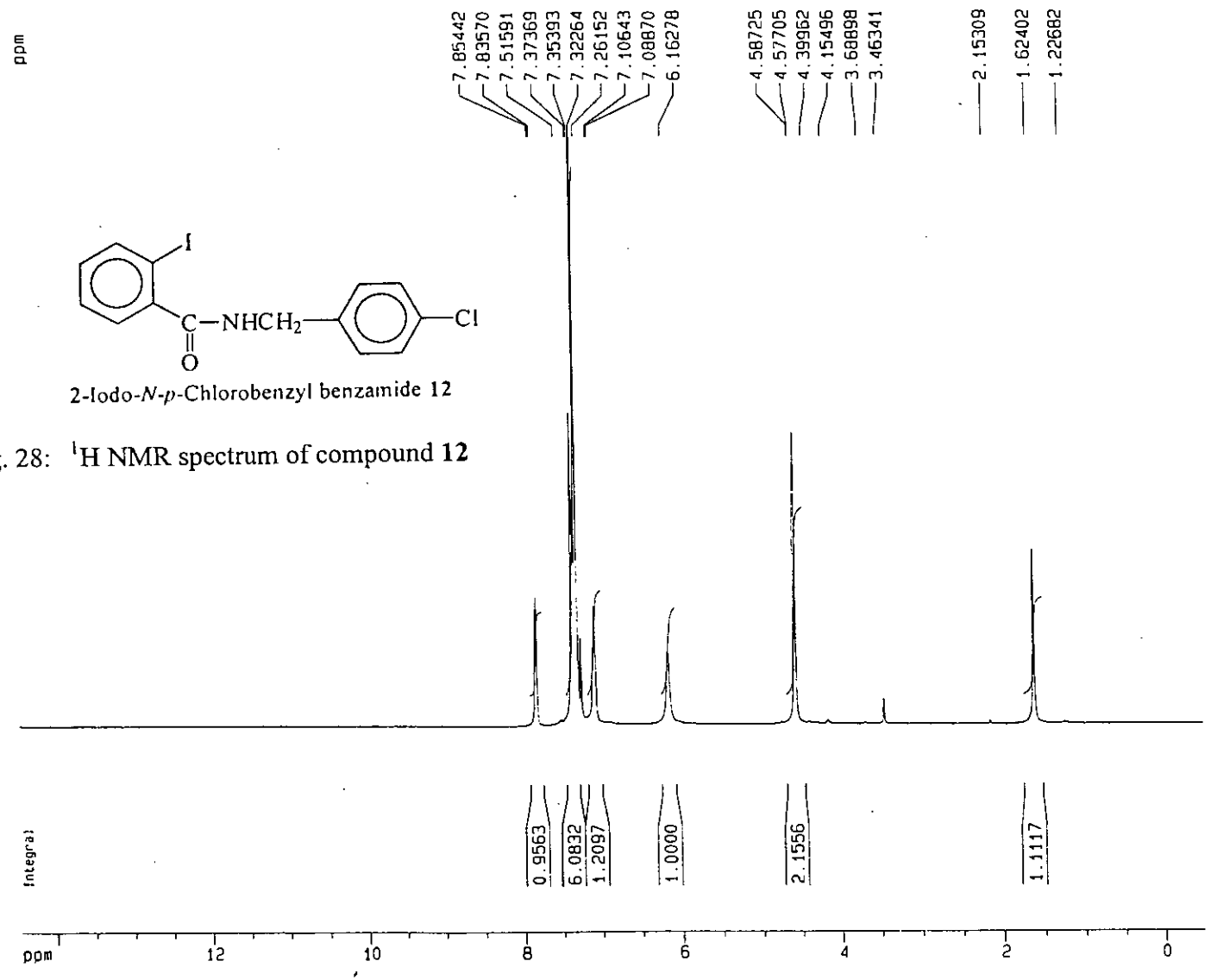
```
Current Data Parameters
NAME                  A766
EXPNO                    1
PROCNO                   1

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
```



2-Iodo-*N*-*p*-Chlorobenzyl benzamide **12**

Fig. 28: ^{1}H NMR spectrum of compound **12**

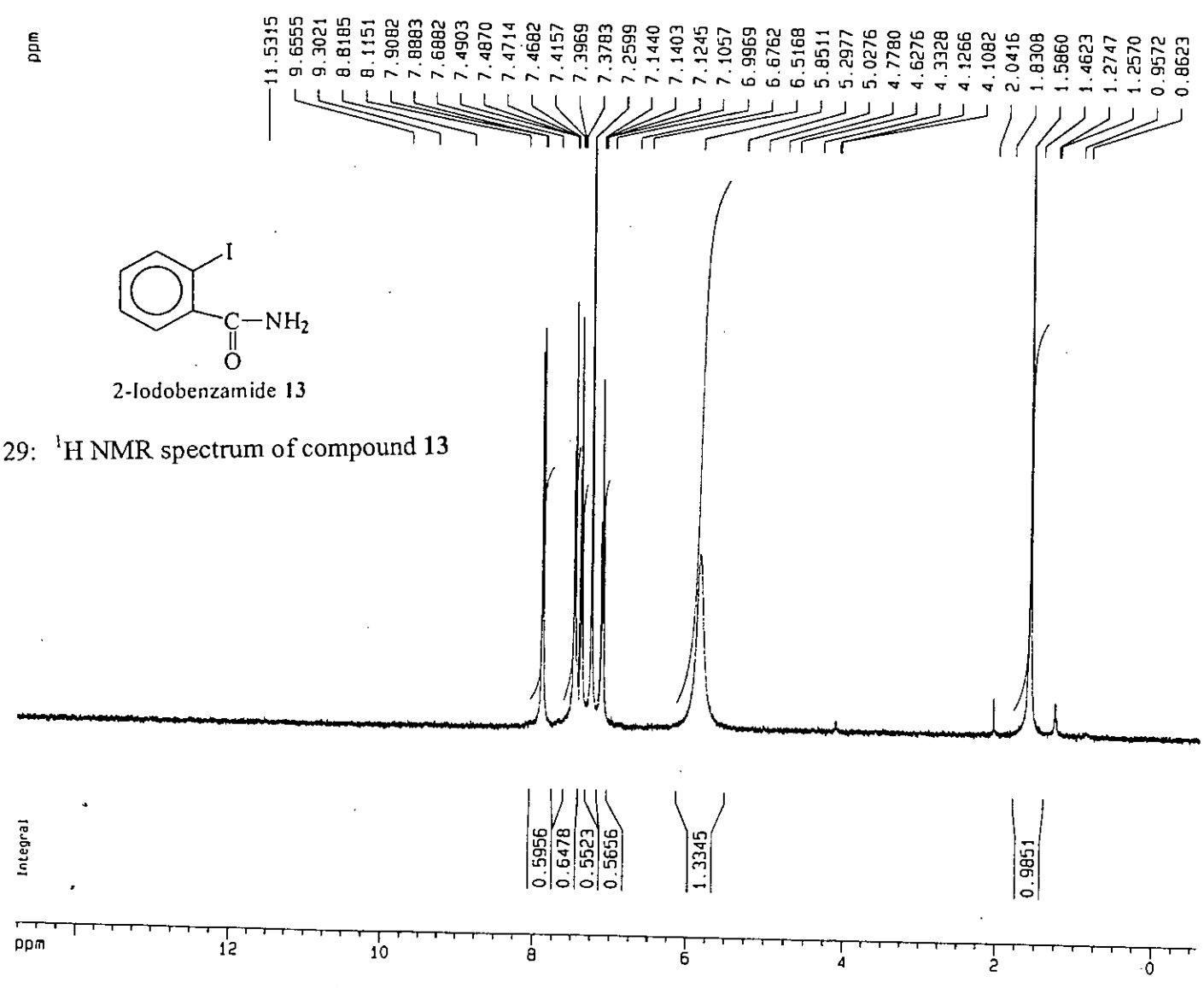
```
Current Data Parameters
NAME                  A1097
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030618
Time                 19.15
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
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
01              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          400.1400086 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
```



2-Iodobenzamide **13**

Fig. 29: ^{1}H NMR spectrum of compound **13**

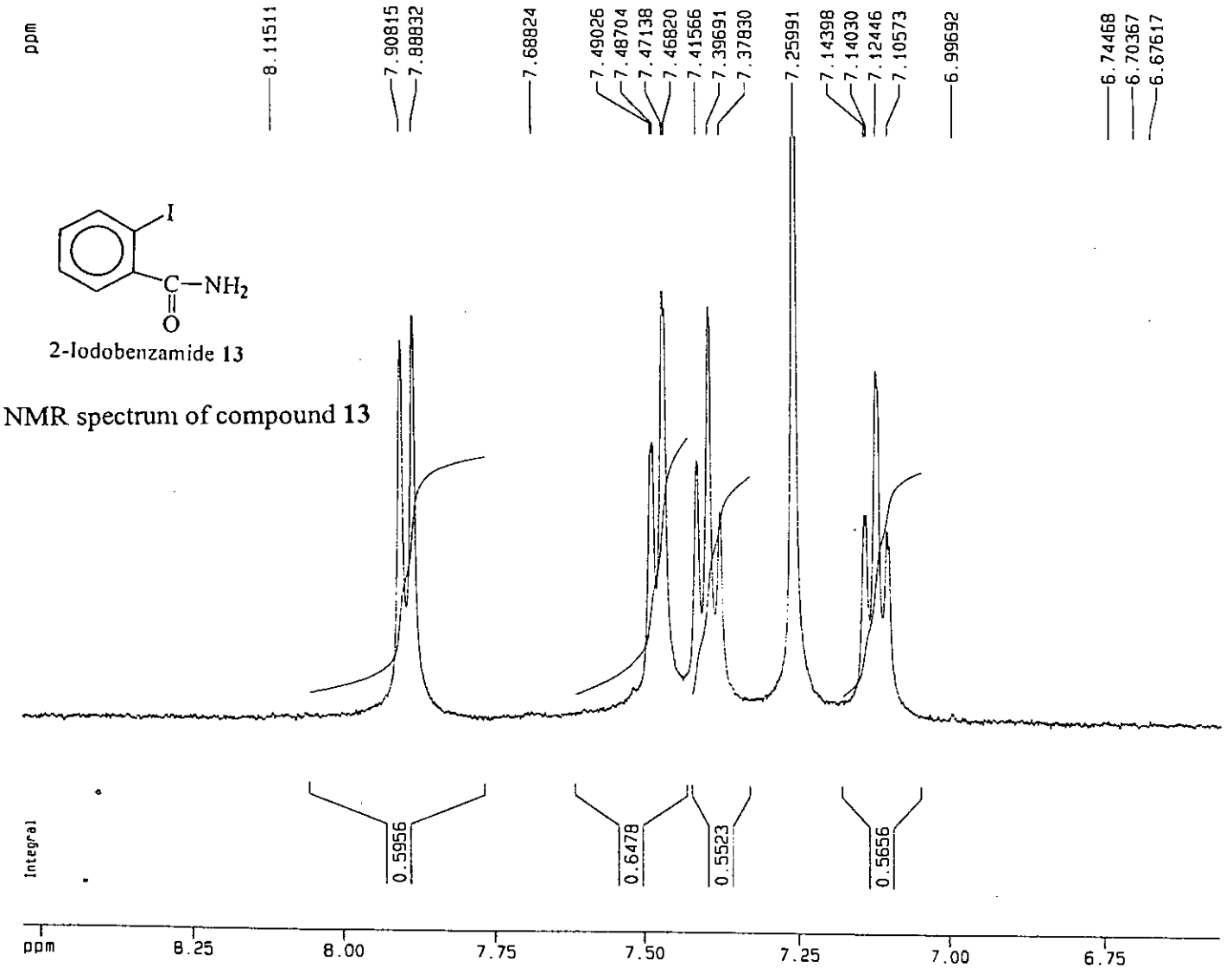
```
Current Data Parameters
NAME                  A552
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020413
Time                  15.10
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG               zg30
TD                   32768
SOLVENT              Aceton
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             400.1400086 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                 14.779 ppm
F1                5913.85 Hz
F2P                -0.596 ppm
F2                -238.60 Hz
PPMCM             0.76879 ppm/cm
HZCM           307.62265 Hz/cm
```



2-Iodobenzamide **13**

Fig. 29: ^{1}H NMR spectrum of compound **13**

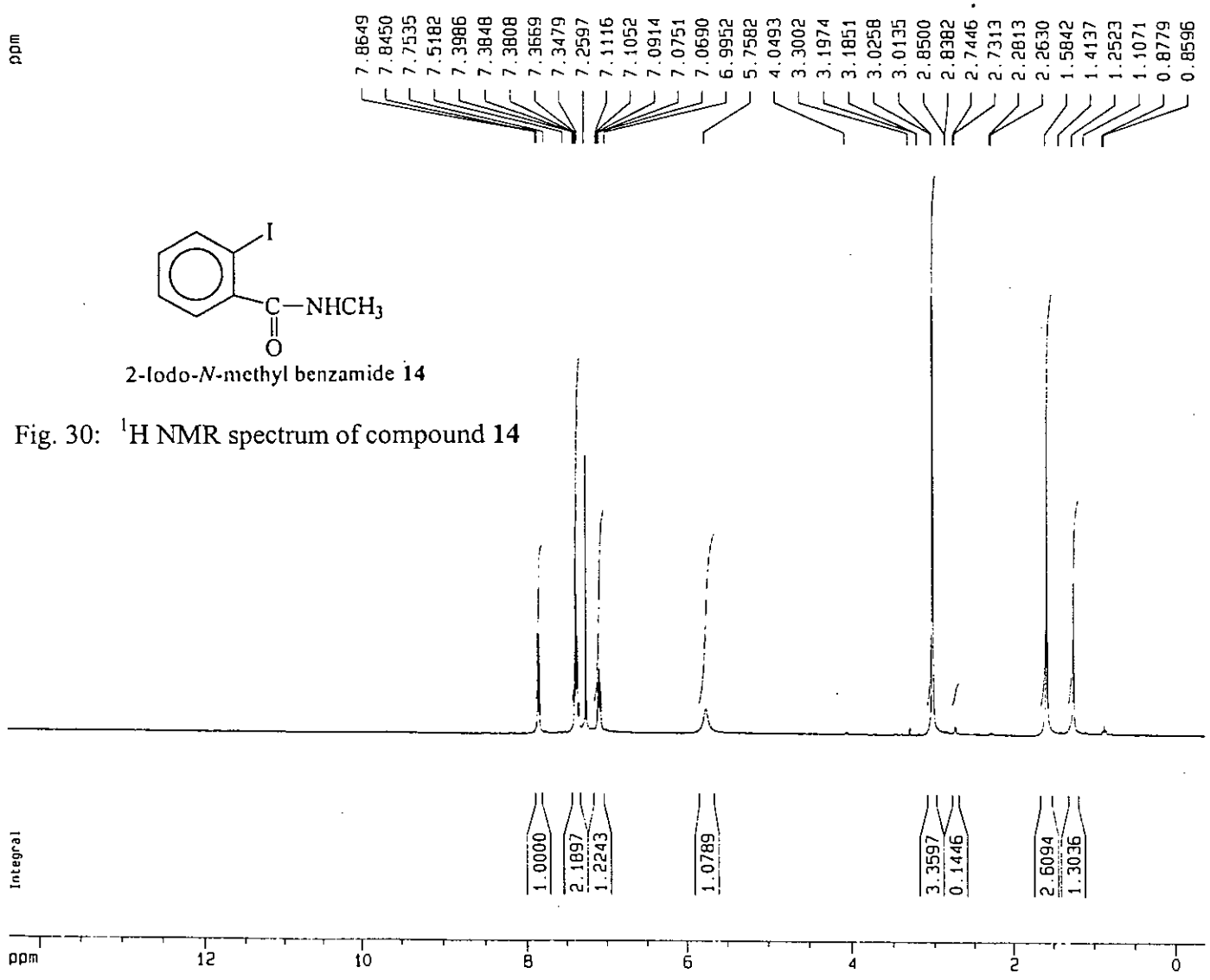
```
Current Data Parameters
NAME                  A552
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020413
Time                 15.10
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                      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           400.1400086 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                20.00 cm
F1P                8.529 ppm
F1               3412.74 Hz
F2P                6.557 ppm
F2               2623.63 Hz
PPMCM            0.09861 ppm/cm
HZCM            39.45594 Hz/cm
```



2-Iodo-*N*-methyl benzamide **14**

Fig. 30: ^{1}H NMR spectrum of compound **14**

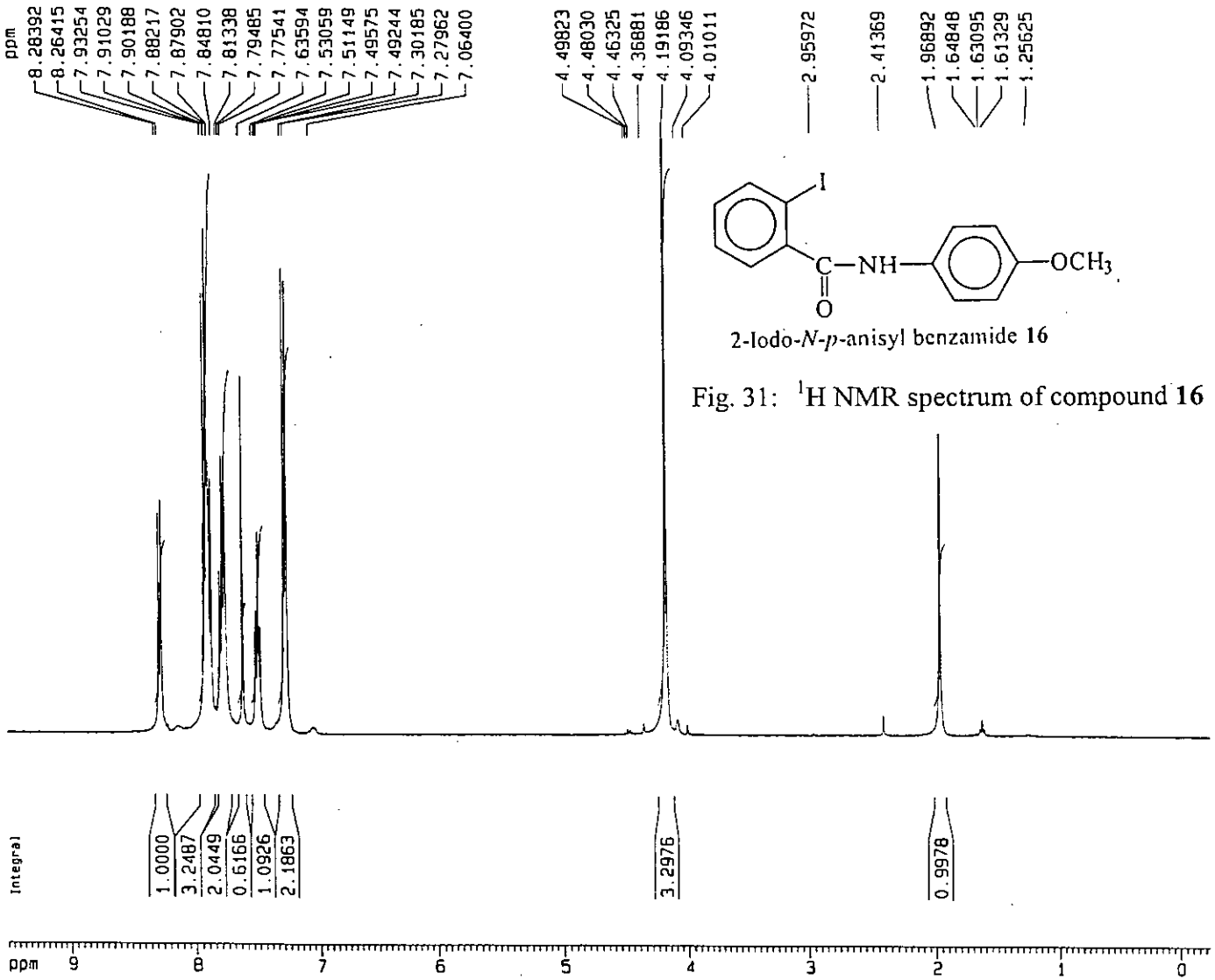
```
Current Data Parameters
NAME                  A10B5
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20030507
Time                  13.48
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG               zg30
TD                   32768
SOLVENT              Aceton
NS                      128
DS                        0
SWH                6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5559540 sec
RG                    574.7
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             400.1400086 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                  14.404 ppm
F1                 5763.73 Hz
F2P                  -0.360 ppm
F2                 -144.23 Hz
PPMCM             0.73824 ppm/cm
HZCM            295.39798 Hz/cm
```



2-Iodo-*N*-*p*-anisyl benzamide **16**

Fig. 31: ^{1}H NMR spectrum of compound **16**

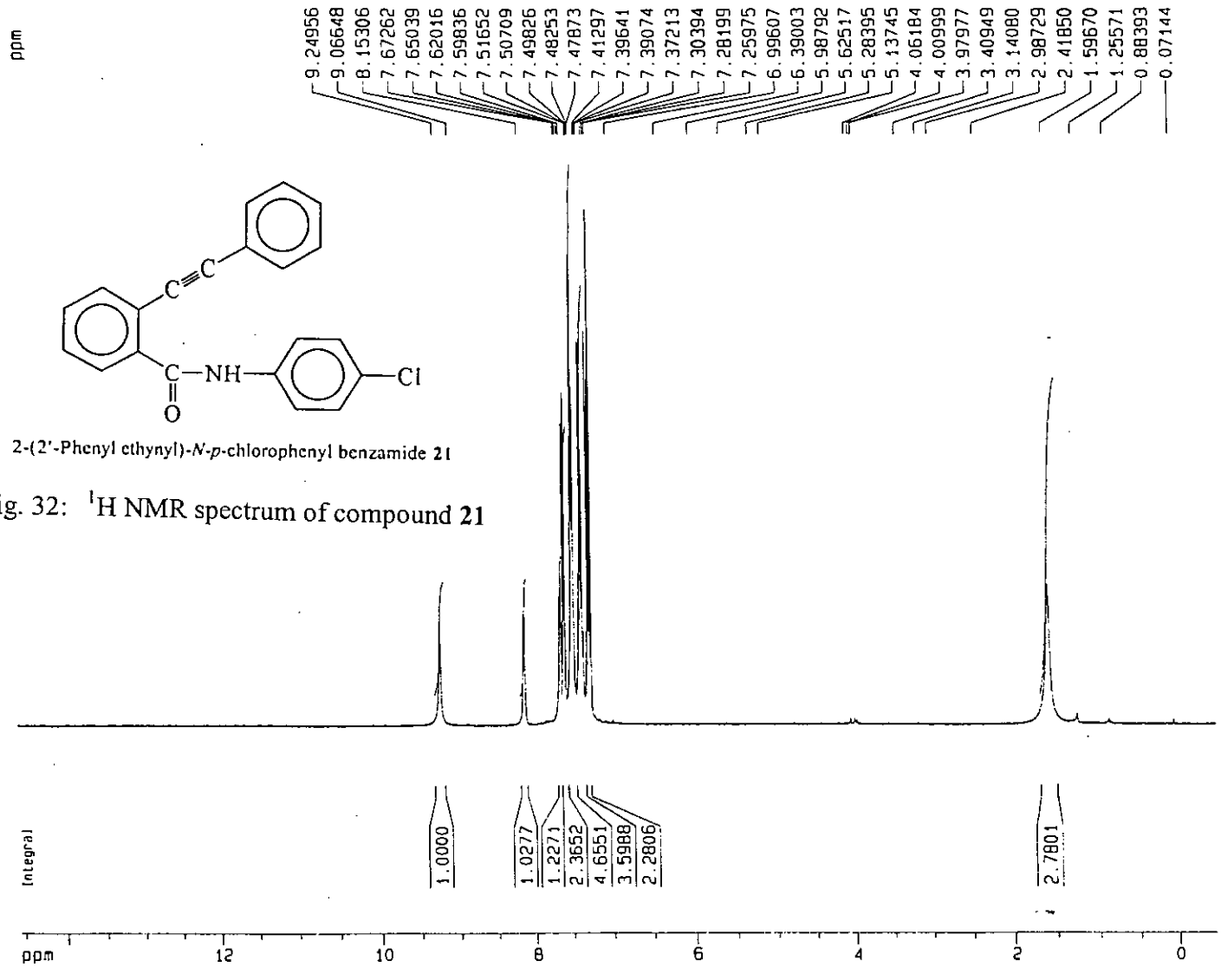
```
Current Data Parameters
NAME                  A588
EXPNO                    1
PROCNO                   1

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
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
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
```



2-(2'-Phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide **21**

Fig. 32: ^{1}H NMR spectrum of compound **21**

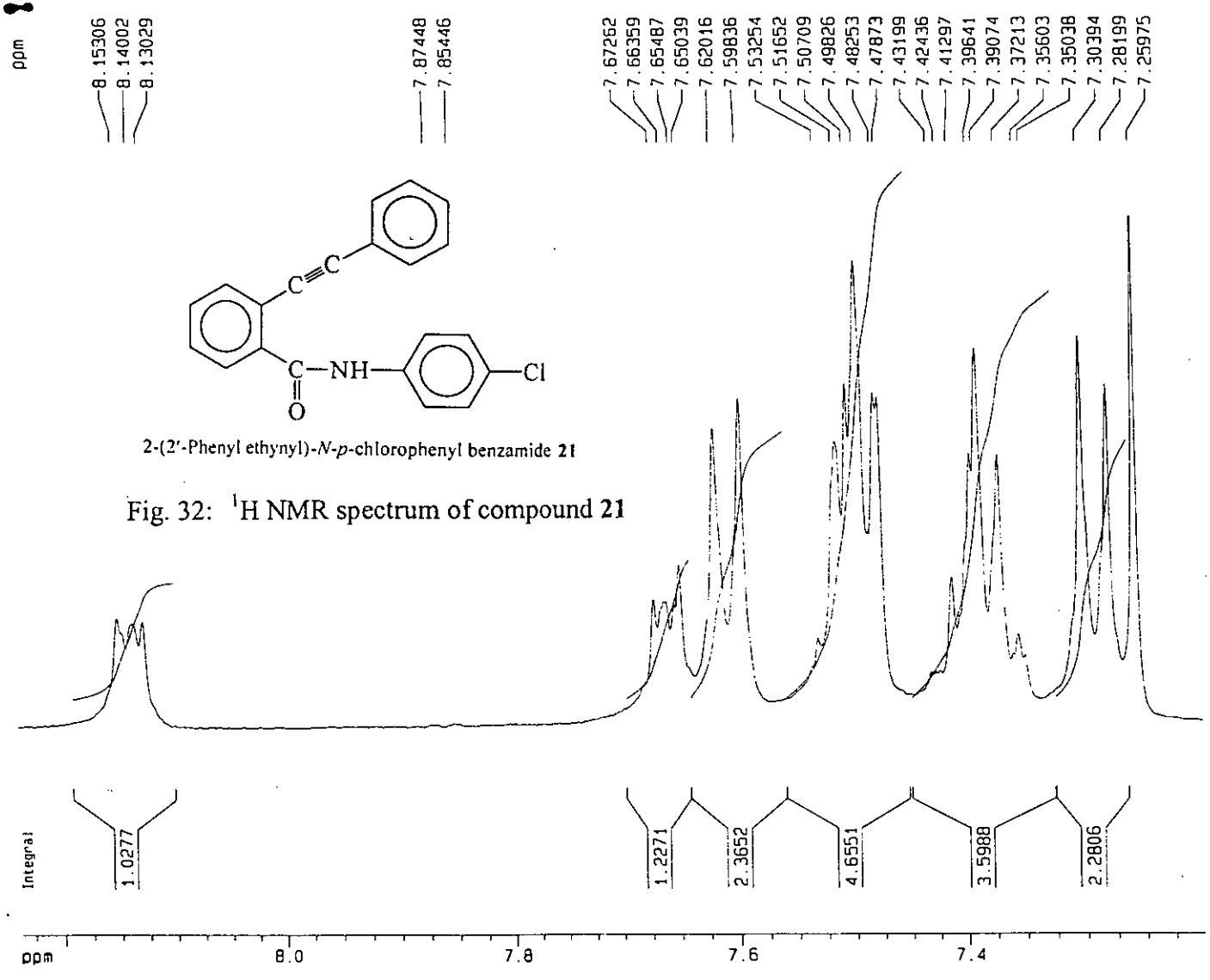
```
Current Data Parameters
NAME                  A1082
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030507
Time                  11.37
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                      512
DW                  78.000 usec
DE                   6.00 usec
TE                   310.0 K
D1                1.00000000 sec

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

F2 - Processing parameters
SI                    32768
SF             400.1400088 MHz
WDW                     EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                 14.573 ppm
F1                 5831.12 Hz
F2P                 -0.479 ppm
F2                 -191.71 Hz
PPMCM              0.75259 ppm/cm
HZCM              301.14136 Hz/cm
```



2-(2′-Phenyl ethynyl)-*N*-*p*-chlorophenyl benzamide **21**

Fig. 32: ^{1}H NMR spectrum of compound **21**

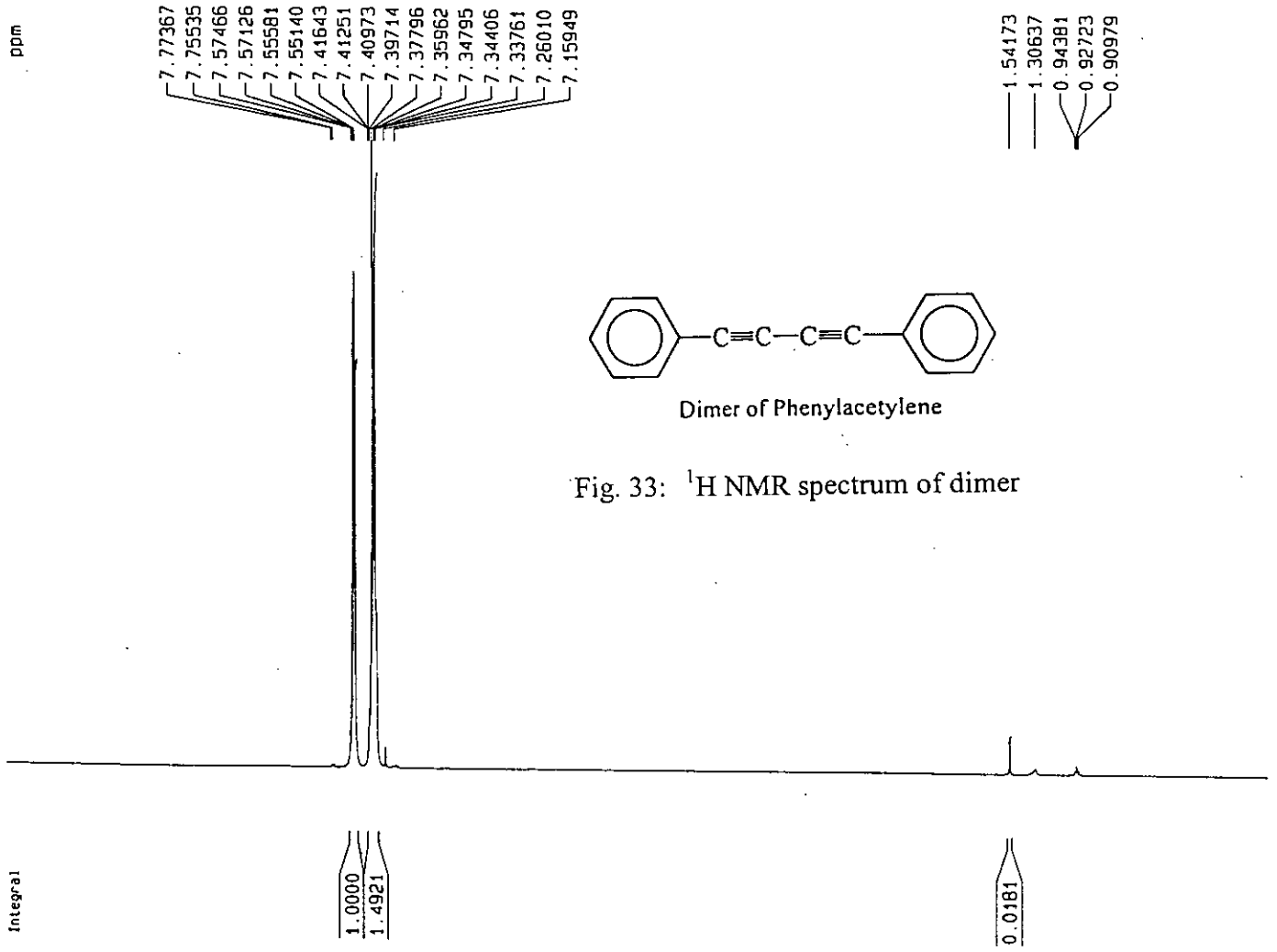
```
Current Data Parameters
NAME                  A1082
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030507
Time                 11.37
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                     512
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1              1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF            400.1400088 MHz
WDW                    EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
F1P                8.239 ppm
F1                 3296.57 Hz
F2P                7.200 ppm
F2                 2881.21 Hz
PPMCM           0.05190 ppm/cm
HZCM           20.76801 Hz/cm
```



Dimer of Phenylacetylene

Fig. 33: ^{1}H NMR spectrum of dimer

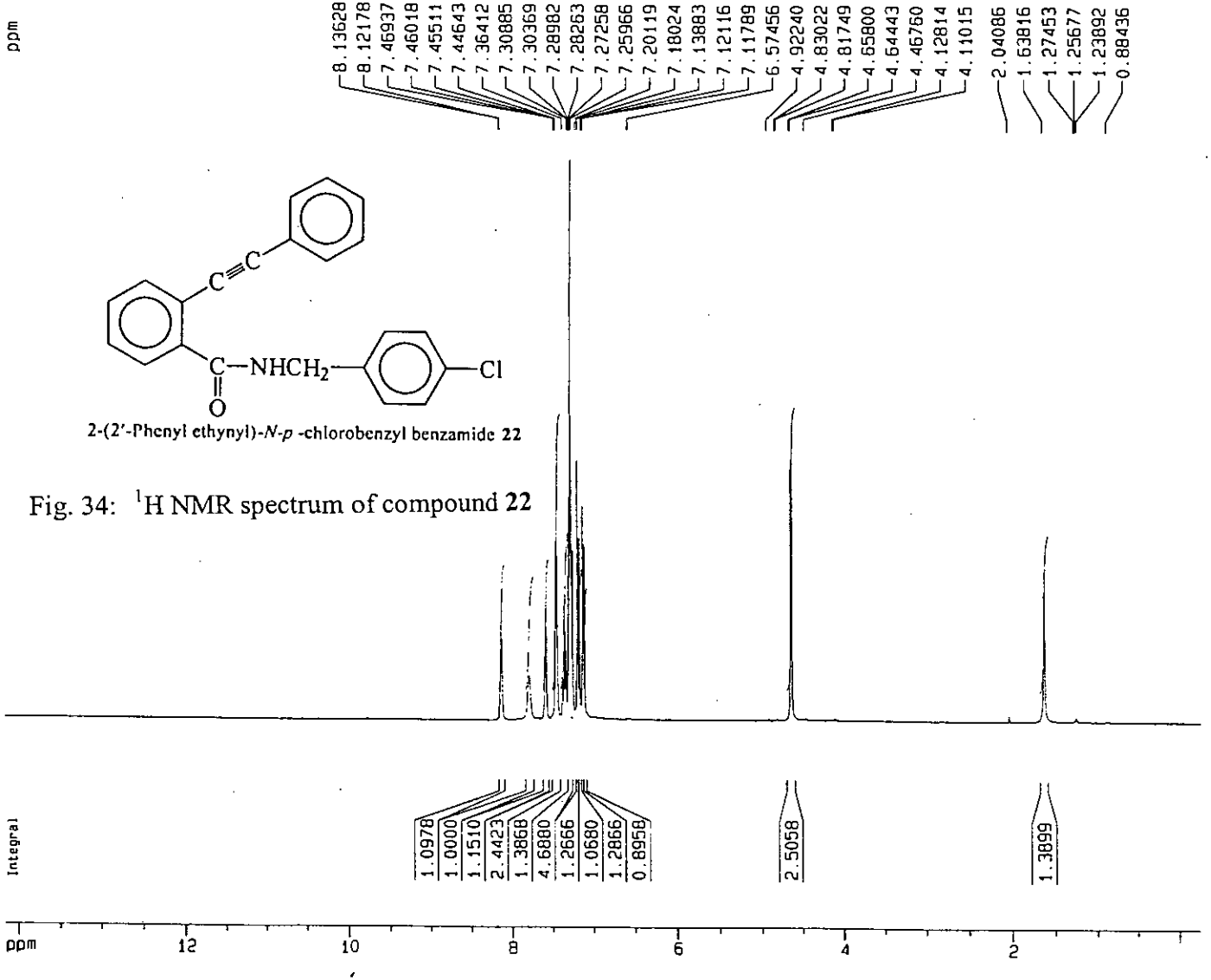
```
Current Data Parameters
NAME                  A429
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020128
Time                 14.57
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     64
DS                      0
SWH               4789.272 Hz
FIDRES            0.146157 Hz
AQ                3.4210291 sec
RG                     64
DW                 104.400 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          400.1420007 MHz

F2 - Processing parameters
SI                  32768
SF            400.1400092 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 10.772 ppm
F1                4310.41 Hz
F2P                -0.832 ppm
F2                -332.75 Hz
PPMCM             0.58019 ppm/cm
HZCM             232.15794 Hz/cm
```



2-(2'-Phenyl ethynyl)-*N*-*p* -chlorobenzyl benzamide **22**

Fig. 34: ^{1}H NMR spectrum of compound **22**

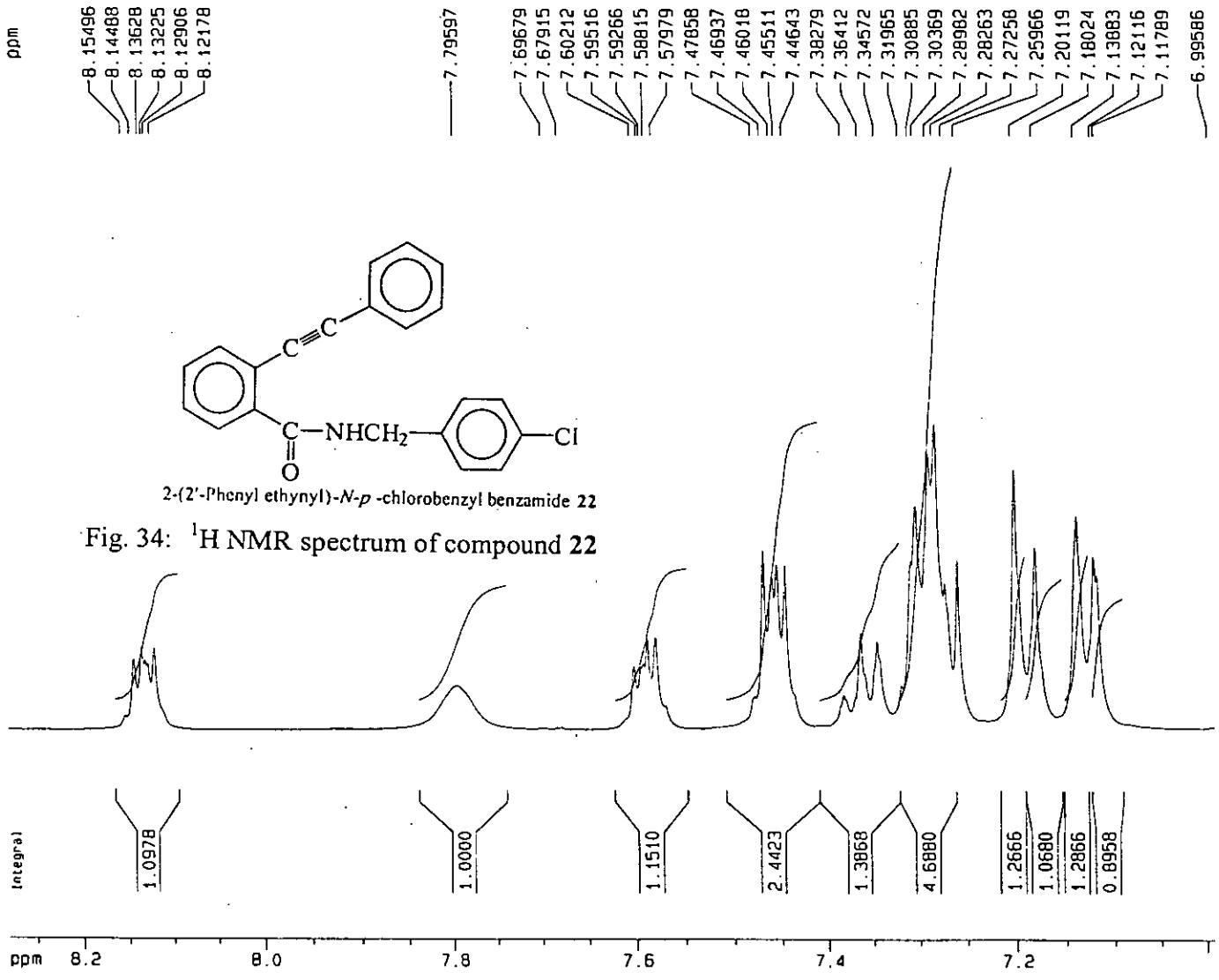
Current Data Parameters	
NAME	A1084
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters	
Date_	20030507
Time	12.14
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	128
DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	256
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

F2 - Processing parameters	
SI	32768
SF	400.1400090 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters	
CX	20.00 cm
F1P	14.165 ppm
F1	5667.94 Hz
F2P	-0.243 ppm
F2	-97.10 Hz
PPMCM	0.72038 ppm/cm
HZCM	288.25192 Hz/cm



2-(2'-Phenyl ethynyl)-*N*-*p* -chlorobenzyl benzamide **22**

Fig. 34: ^{1}H NMR spectrum of compound **22**

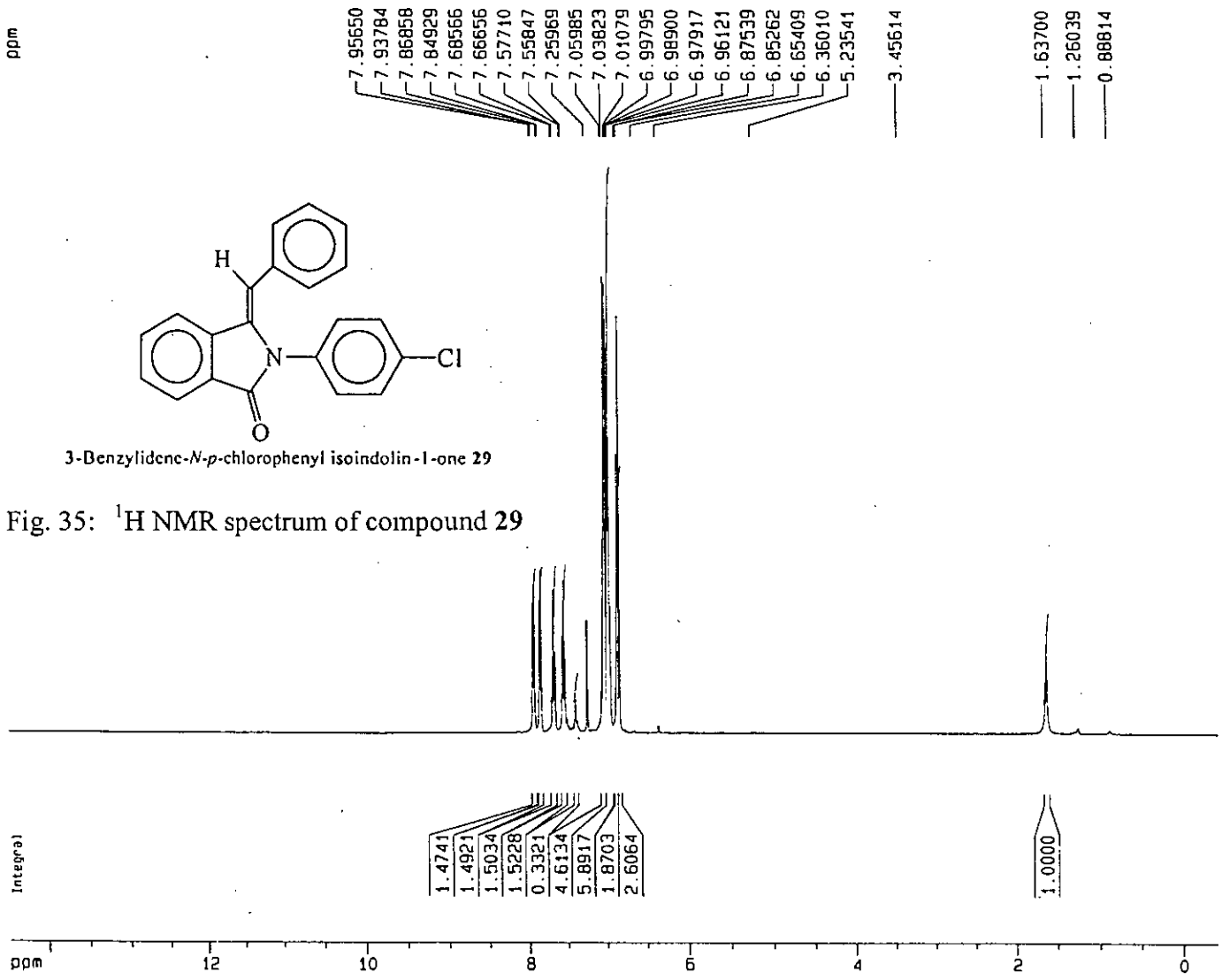
```
Current Data Parameters
NAME                  A1084
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030507
Time                 12.14
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT            -Aceton
NS                     128
OS                       0
SWH           6410.256 Hz
FIORES        0.195625 Hz
AQ            2.5559540 sec
RG                     256
DW              78.000 usec
DE               6.00 usec
TE               310.0 K
D1            1.00000000 sec

========== CHANNEL f1 ============
NUC1                   1H
P1                  8.30 usec
PL1                -6.00 dB
SF01          400.1428010 MHz

F2 - Processing parameters
SI                  32768
SF            400.1400090 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 8.280 ppm
F1                3313.25 Hz
F2P                 6.992 ppm
F2                2797.74 Hz
PPMCM             0.06442 ppm/cm
HZCM             25.77557 Hz/cm
```



3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one **29**

Fig. 35: ^{1}H NMR spectrum of compound **29**

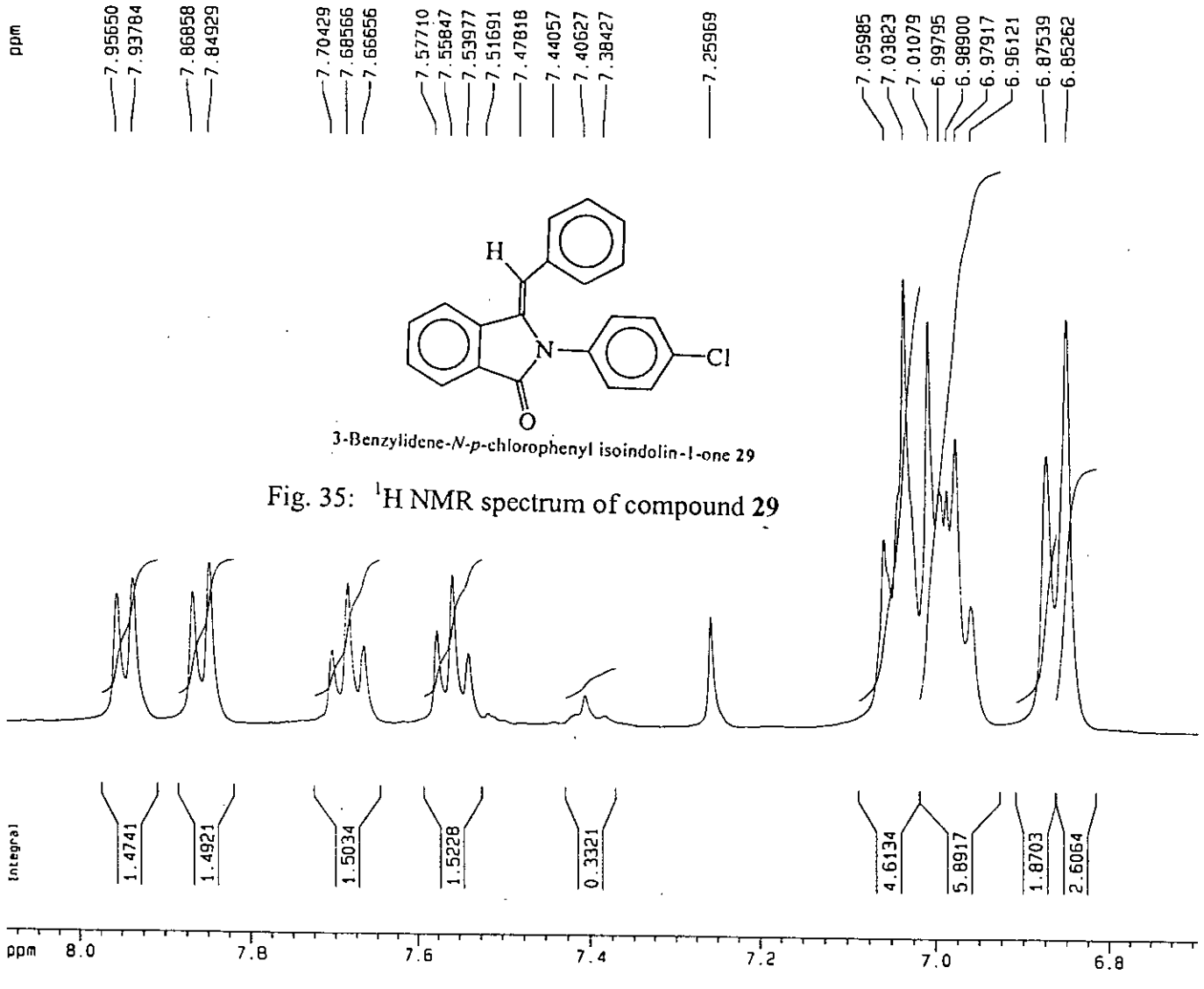
```
Current Data Parameters
NAME                  A1083
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030507
Time                 11.54
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                    256
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF            400.1400092 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                 20.00 cm
F1P                14.485 ppm
F1                 5796.22 Hz
F2P                -0.430 ppm
F2                 -172.07 Hz
PPMCM              0.74578 ppm/cm
HZCM             298.41443 Hz/cm
```



3-Benzylidene-*N*-*p*-chlorophenyl isoindolin-1-one **29**

Fig. 35: ^{1}H NMR spectrum of compound **29**

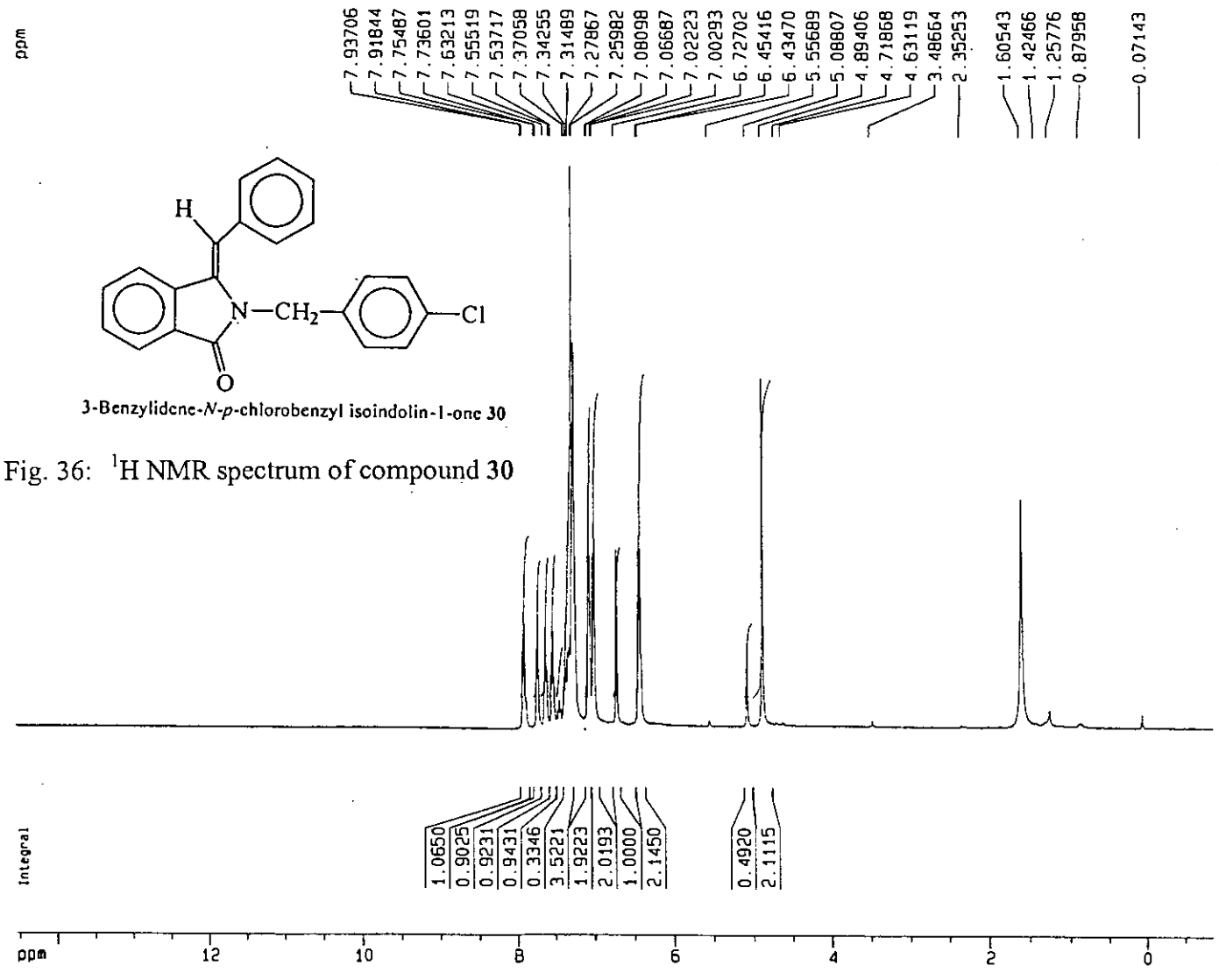
```
Current Data Parameters
NAME                  A1083
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030507
Time                 11.54
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                     256
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF            400.1400092 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 8.089 ppm
F1                3236.74 Hz
F2P                 6.694 ppm
F2                2678.62 Hz
PPMCM            0.06974 ppm/cm
HZCM            27.90596 Hz/cm
```



3-Benzylidene-*N*-*p*-chlorobenzyl isoindolin-1-one **30**

Fig. 36: ^{1}H NMR spectrum of compound **30**

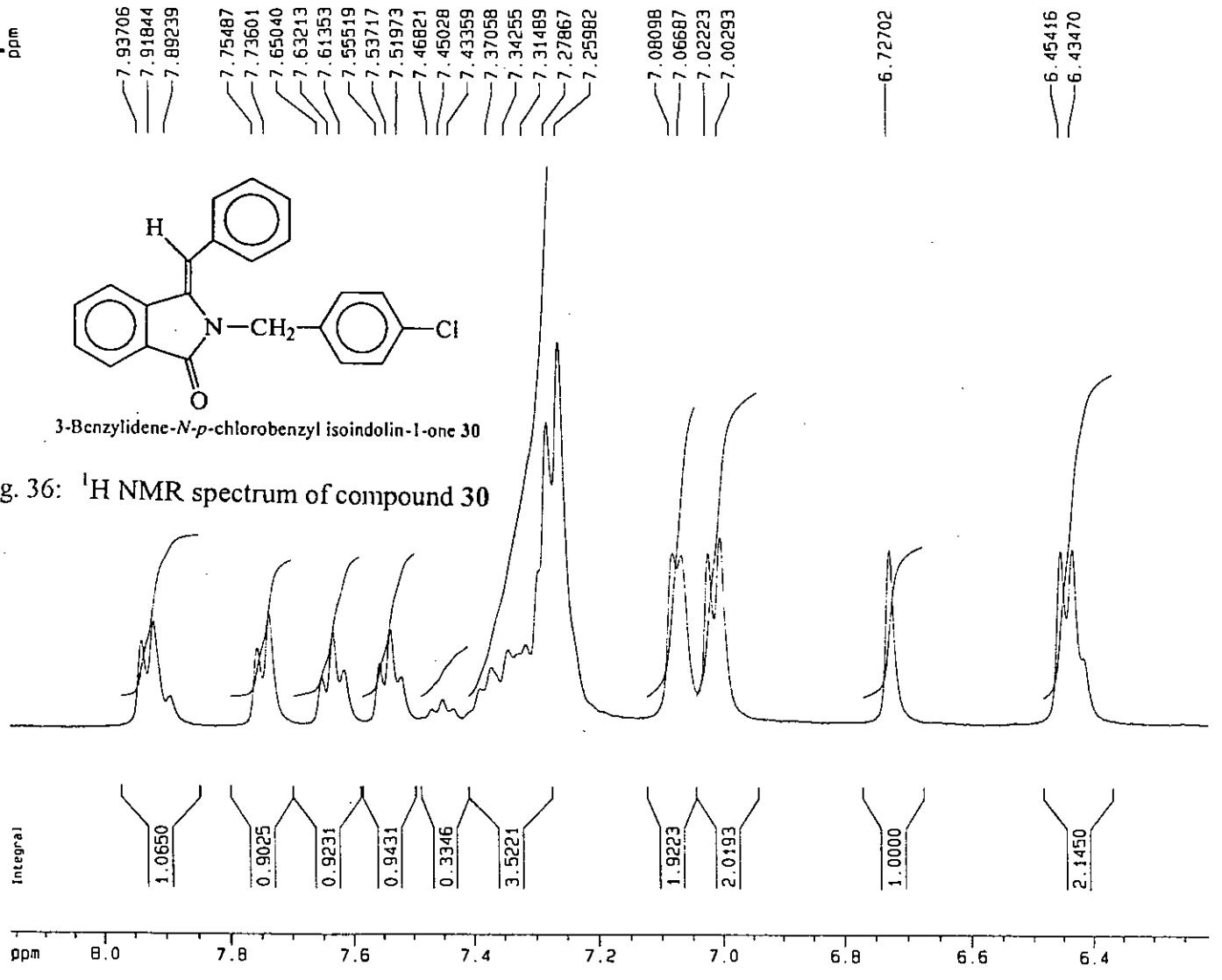
```
Current Data Parameters
NAME                  A1162
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030618
Time                 19.01
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                   406.4
DW                  78.000 usec
DE                    6.00 usec
TE                   310.0 K
D1                1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF             400.1400092 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                  14.548 ppm
F1                 5821.35 Hz
F2P                  -0.858 ppm
F2                 -343.17 Hz
PPMCM              0.77030 ppm/cm
HZCM             308.22592 Hz/cm
```



3-Benzylidene-*N*-*p*-chlorobenzyl isoindolin-1-one **30**

Fig. 36: ^{1}H NMR spectrum of compound **30**

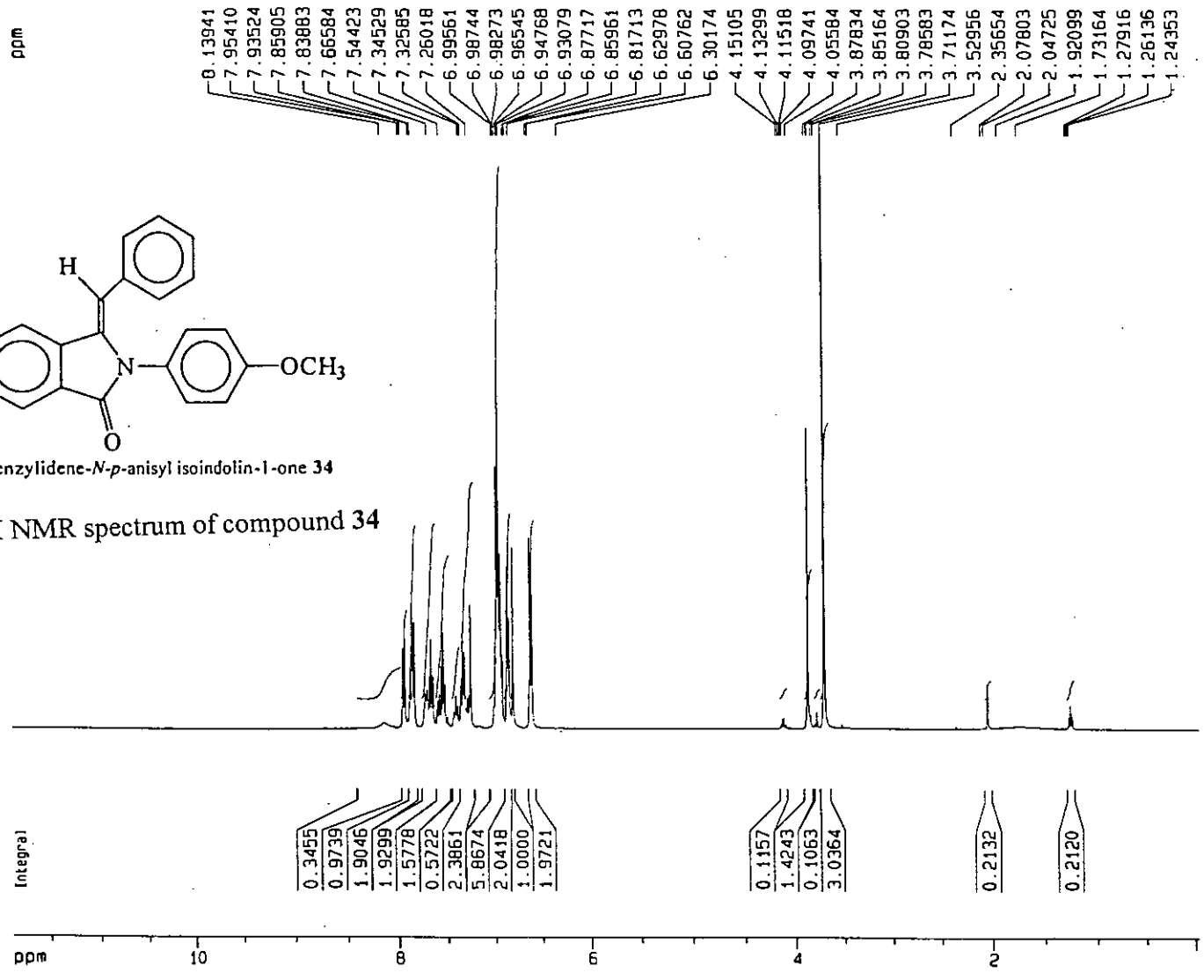
```
Current Data Parameters
NAME                  A1162
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20030618
Time                 19.01
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                   406.4
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

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

F2 - Processing parameters
SI                  32768
SF            400.1400092 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 8.160 ppm
F1                3265.32 Hz
F2P                 6.212 ppm
F2                2485.58 Hz
PPMCM            0.09743 ppm/cm
HZCM            38.98671 Hz/cm
```



3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one **34**

Fig. 37: ^{1}H NMR spectrum of compound **34**

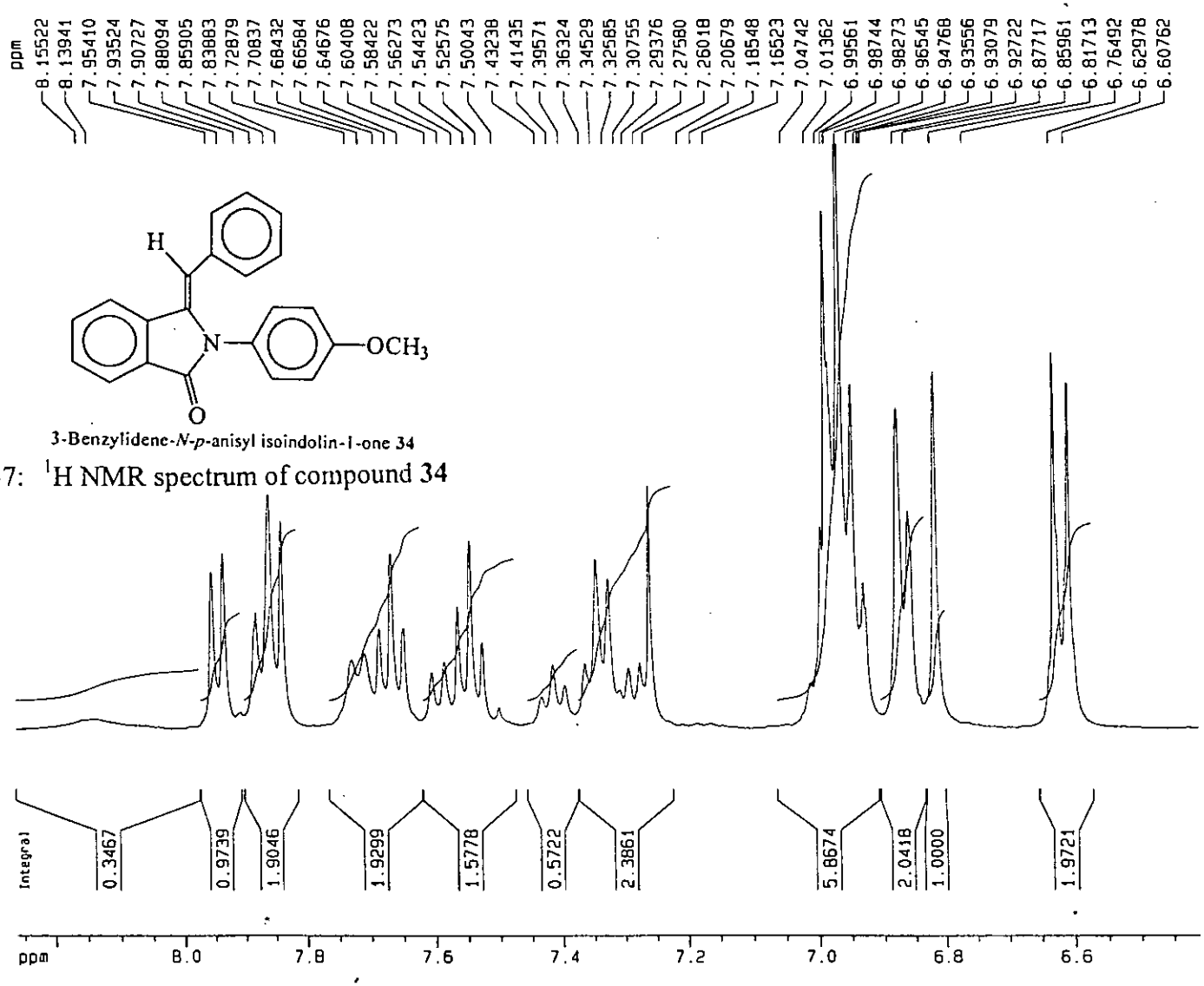
```
Current Data Parameters
NAME                  A477
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020217
Time                 16.23
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
O1              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             400.1400088 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 11.862 ppm
F1                4746.32 Hz
F2P                -0.035 ppm
F2                 -14.04 Hz
PPMCM             0.59484 ppm/cm
HZCM            238.01794 Hz/cm
```



3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one 34

Fig. 37: ^{1}H NMR spectrum of compound **34**

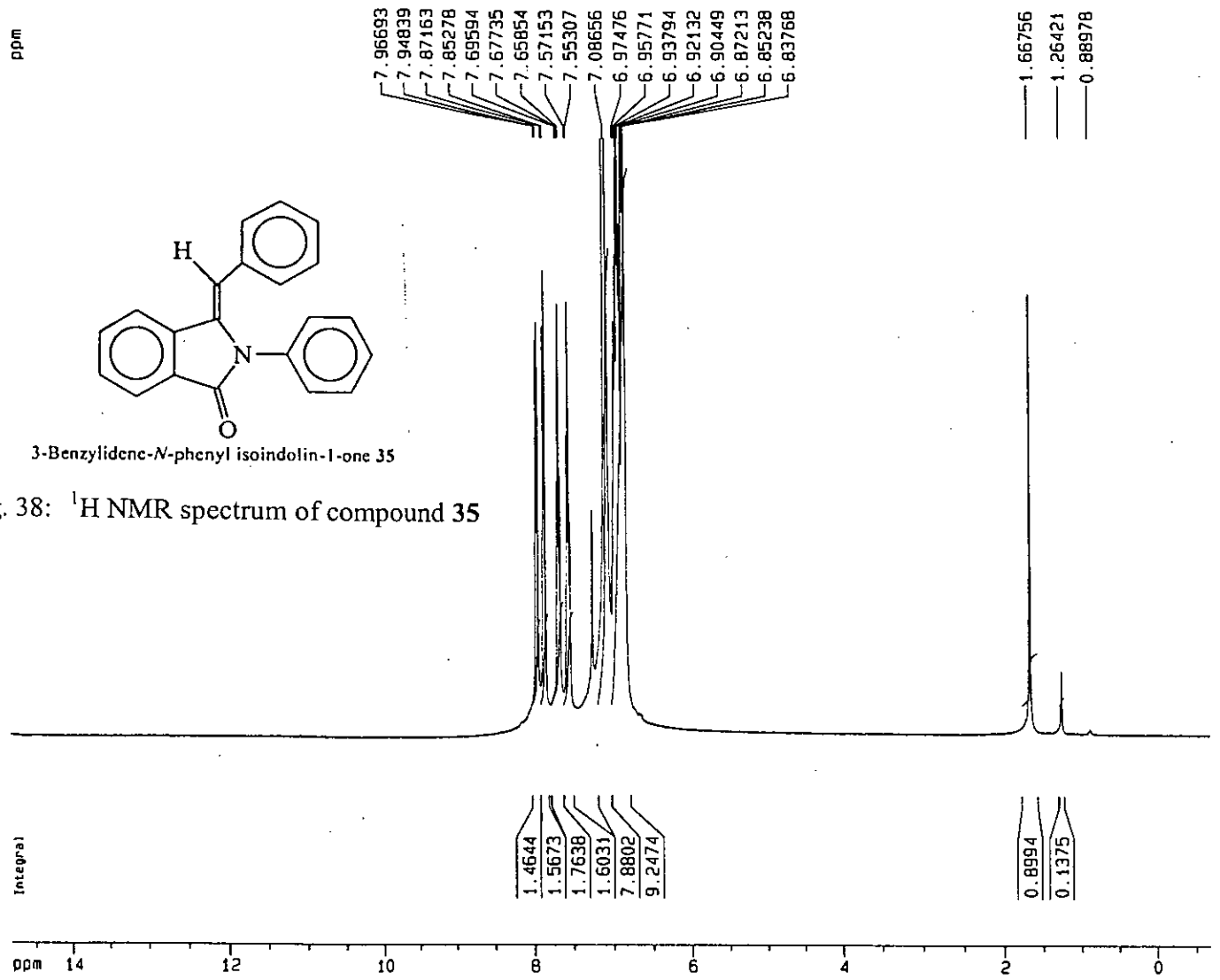
```
Current Data Parameters
NAME                  A477
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020217
Time                 16.23
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              400.1400088 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 8.262 ppm
F1                3306.02 Hz
F2P                 6.411 ppm
F2                2565.11 Hz
PPMCM             0.09258 ppm/cm
HZCM             37.04557 Hz/cm
```



3-Benzylidene-*N*-phenyl isoindolin-1-one **35**

Fig. 38: ^{1}H NMR spectrum of compound **35**

```
Current Data Parameters
NAME                  A641
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20020519
Time                  15.46
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            400.1400086 MHz
WDW                     EM
SSB                      0
LB                0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                 20.00 cm
F1P                14.832 ppm
F1                5934.76 Hz
F2P                -0.666 ppm
F2                -266.47 Hz
PPMCM             0.77488 ppm/cm
HZCM            310.06131 Hz/cm
```

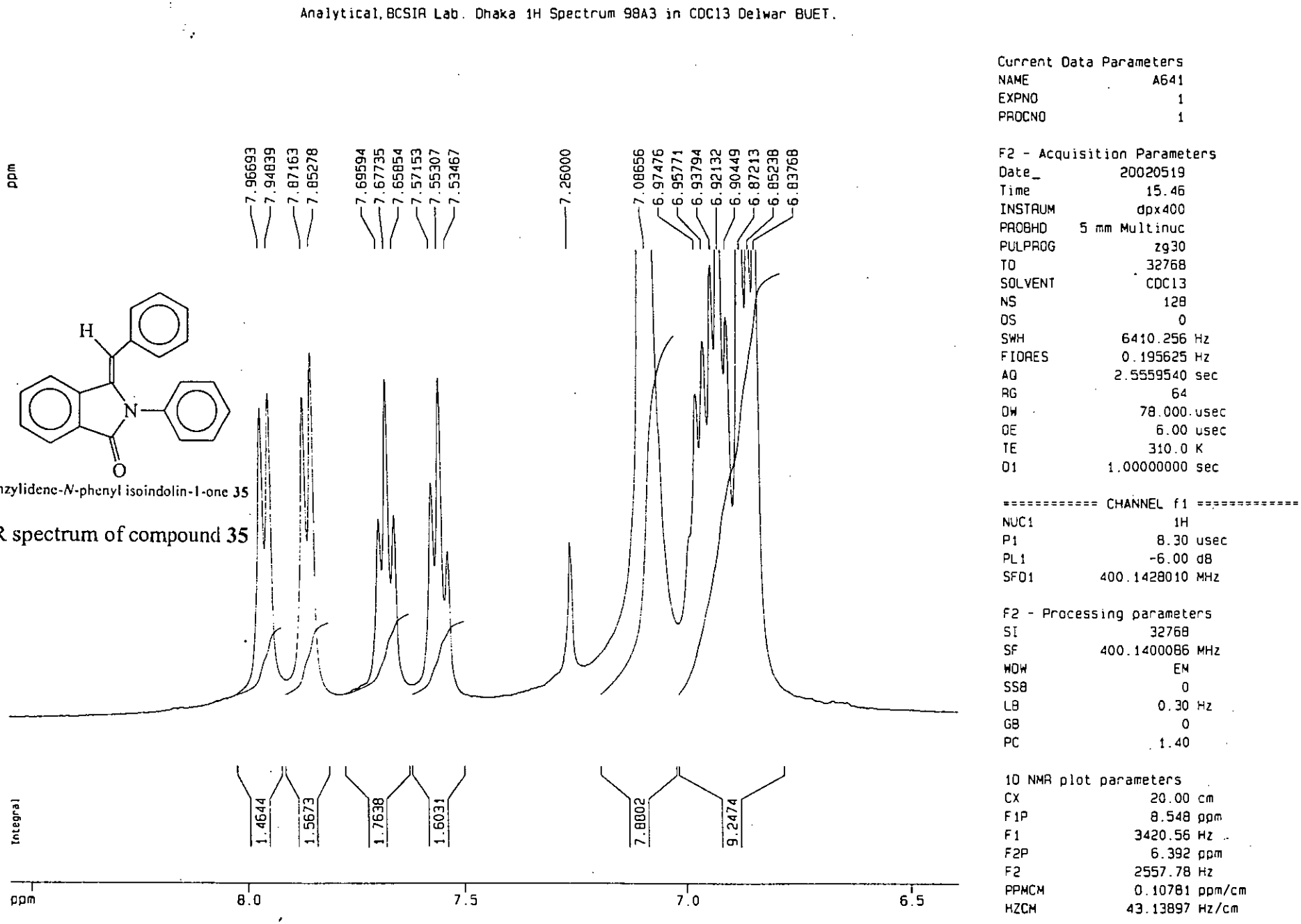


Fig. 38: ^{1}H NMR spectrum of compound **35**

Section-3

Biological Test
Biological Activities of 3-Aryl (alkyl)idene isoindolin-1-ones

Antimicrobial Screening

3.1. Introduction

Bacteria and fungi are responsible for many infectious 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 susceptibility 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.*[120], 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 method (Roland[121], R., 1982).

3.2 Principle of Disc Diffusion Method

Solutions of known concentration (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 24 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 occurs 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 24 h 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.*[120], 1966).

In the present study some pure compounds were tested for antibacterial activity by disc diffusion method.

3.3 Experimental

3.3.1 Apparatus and Reagents

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

3.3.2 Test 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 were taken for the test and they are listed in the Table 2.

Table 2: List of Test Bacteria

Gram positive	Gram negative
Bacillus cereus	*Aeromonus hydrophilia*
Bacillus megaterium	*Escherichia coli*
Bacillus subtilis	*Klebsiella* sp.
Staphylococcus aureus	*Pseudomonas aeruginosa*
Sarcina lutea	*Salmonella paratyphi A*
	Salmonella paratyphi B
	Salmonella typhi
	Shigella boydii
	Shigella dysenteriae
	Shigella flexneriae
	Shigella sonnei
	Vibrio cholerae
	Vibrio mimicus
	Vibrio parahemolyticus

Table 3: List of Test Fungi

Fungi
Aspergillus fumigatus
Candida albicans
Rhizopus oryzae
Saccharomyces cerevisiae

3.3.3 Test materials

Compounds 16, 21, 22, 29, 30, 31, 32, 34, 35.

3.3.4 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. This media were also used to prepare fresh cultures.

3.3.4.1 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	15.0
P^H (at 25°C)	7.2-7.6

3.3.4.2 Preparation of medium

To prepare required volume of this medium, calculated amount of each of the constituents was taken in a conical flask and distilled water was added to it to make the required volume. The contents were heated in a water bath to make a clear solution. The p^H (at 25 °C) was adjusted at 7.2-7.6 using NaOH or HCl. 10 ml and 5 ml of the medium was then transferred in screw cap test tubes to prepare plates and slants respectively. The test tubes were then capped and sterilized by autoclaving at 15-lbs. 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.

3.3.5 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 a pressure of 15-lbs./sq. inch for 20 minutes. Micropipette tips, cotton, forceps, blank discs etc. were also sterilized.

3.3.6 Preparation of subculture

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

3.3.7 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 test organisms in the media.

3.3.8 Preparation of discs

Three types of discs were used for antibacterial screening.

3.3.8.1 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 (30μg/disc) standard disc was used as the reference.

3.3.8.2 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.

3.3.8.3 Preparation of sample discs with test samples

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.

3.3.9 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 24 h to allow sufficient diffusion of the materials from the discs to the surrounding agar medium. The plates were then inverted and kept in an incubator at 37 °C for 24 h.

3.3.10 Determination of antibacterial activity by measuring the Zone of Inhibition.

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

3.4 Results and Discussion of *in vitro* Antibacterial Screening

Some pure compounds were tested for antibacterial activity against a number of both gram positive and gram negative bacteria. Standard disc of kanamycin (30 μg/disc) was used for comparison purpose.

Sixteen bacterial strains and four fungi strains were taken to study the antibacterial and antifungal activity of the compounds (16, 21, 22, 29, 30, 31, 32, 34, 35) at the higher concentration (200 μg/disc).

The zone of inhibition produced by the compound 16 was found to be 17 mm at 200 μg/disc (Table 4). This compound 16 showed moderate activity against *Rhizopus oryzae*. On the other hand rest of the compounds exhibited very poor activity against sixteen bacteria and four fungi (Table 4).

Table 4: Antibacterial activity

Test Organism	Diameter of Zone of Inhibition (mm)									
	16	21	22	29	30	31	32	34	35	Kan
	200	200	200	200	200	200	200	200	200	30
Gram Positive										
Bacillus cereus	–	–	–	–	–	–	–	–	–	09
Bacillus megaterium	–	–	–	–	–	–	–	–	–	22
Bacillus subtilis	–	–	–	–	–	–	–	–	–	11
Staphylococcus aureus	–	–	–	–	–	–	–	–	–	10
Sarcina lutea	–	–	–	–	–	–	–	–	–	15
Gram Negative										
Aeromonus hydrophilia	–	–	–	–	–	–	–	–	–	09
Escherichia coli	–	–	–	–	–	–	–	–	–	12
Pseudomonas aeruginosa	–	–	–	–	–	–	–	–	–	10
Salmonella paratyphi A	–	–	–	–	–	–	–	–	–	36
Salmonella paratyphi B	–	–	–	–	–	–	–	–	–	–
Salmonella typhi	–	–	–	–	–	–	–	–	–	19
Shigella boydii	–	–	–	–	–	–	–	–	–	11
Shigella dysenteriae	–	–	–	–	–	–	–	–	–	–
Shigella sonnei	–	–	–	–	–	–	–	–	–	–
Vibrio mimicus	–	–	–	–	–	–	–	–	–	11
Vibrio parahemolyticus	NT	NT	NT	NT	–	NT	NT	–	–	25
Fungi										
Aspergillus fumigatus	–	–	–	–	–	–	–	–	–	–
Candida albicans	–	–	–	–	–	–	–	–	–	–
Rhizopus oryzae	17	–	–	–	–	–	–	–	–	–
Saccharomyces cerevisiae	NT	NT	NT	NT	–	NT	NT	–	–	22

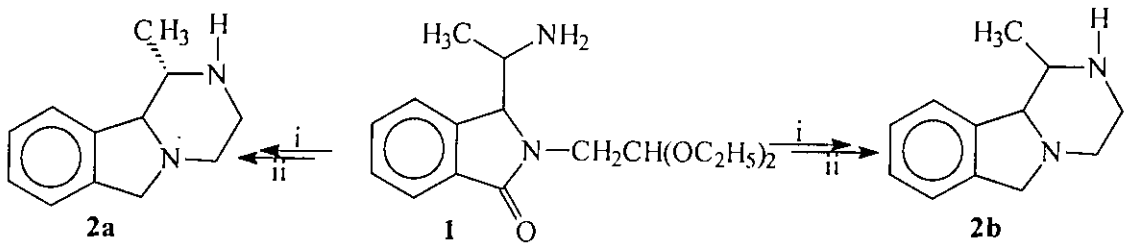
"-" Indicates no sensitivity
"NT" Indicates 'Not tested'

Section-4

Present work
Synthesis of 3-substituted isoindolines

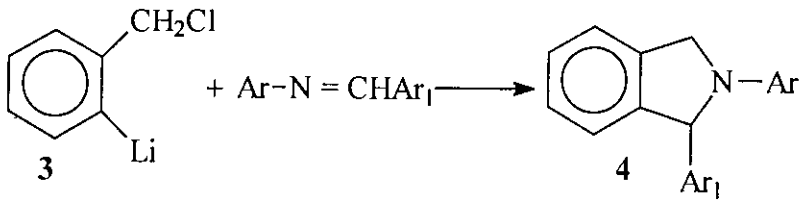
4.1 Introduction

A synthesis of pyrazino [2,1-a]isoindole derivative **2** via isoindolinone **1** was developed by Ferland *et al.*[21] (**Scheme 1**). The analogue, e.g. 1,2,3,4-tetrahydropyrazino [2,1-a]isoindol-6-one was found to lower blood pressure in spontaneously hypertensive rats.



Scheme 1. *Reagents*: (i) MeOH, 1N HCl, H_2, Pd/C; (ii) THF, 1M diborane in THF.

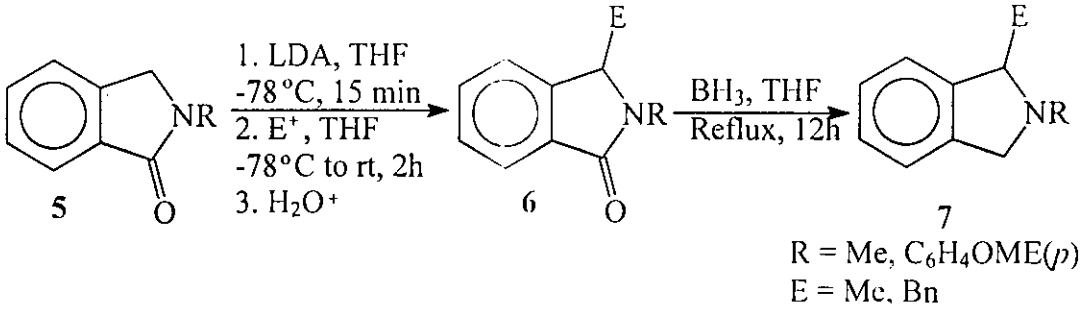
An effective reaction of Schiff bases with certain functionlized organolithium reagents was described by Bradsher and Hunt[100] for the synthesis of 1, 2-diarylisoindolines **4** (**Scheme 2**).



4 : a) Ar = Ar_1 = Ph; b) Ar = 4-BrC_6H_4, Ar_1 = Ph; c) Ar = 2-$BrMeC_6H_4$, Ar_1 = Ph; d) Ar = Ph, Ar_1 = 3,4-$(OCH_3)_2C_6H_3$.

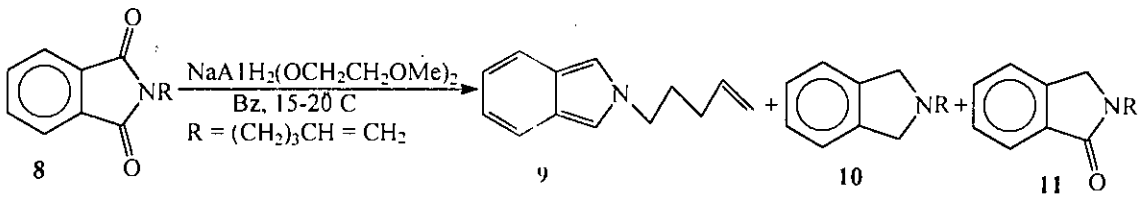
Scheme 2

Couture *et al.*[101], recently reported that 2-alkyl-2,3-dihydroisoindol-1-ones **5** are easily and regioselectively deprotonated at the 3-position of the heterocyclic nucleus with LDA, thus providing ready access to 3-substituted and / or functionalized isoindolinones **6** and consequently to the corresponding isoindolines **7** (Scheme 3).



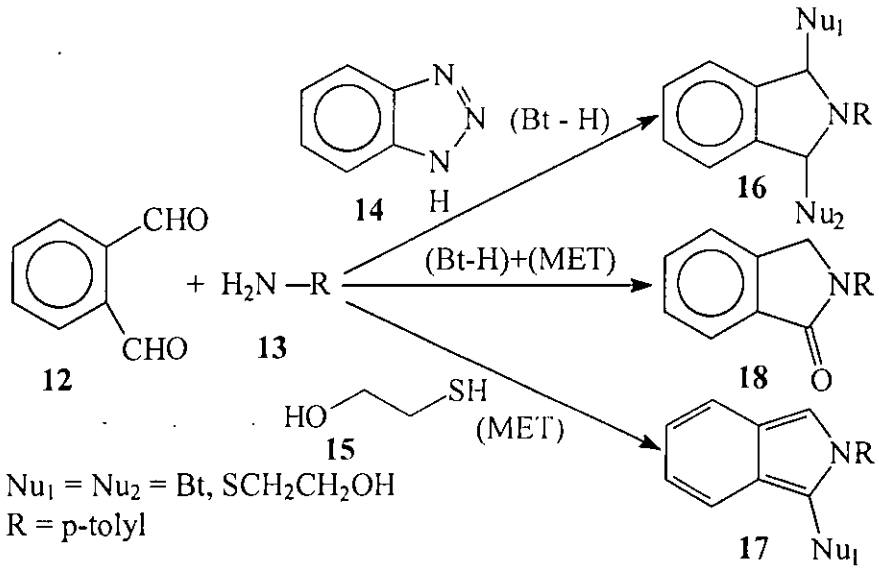
Scheme 3

Ciganek[102] prepared a mixture of *N*-4-pentenylisoindole **9**, isoindoline **10** and isoindolinone **11** by the reduction of *N*-4-pentenylphthalimide **8** with sodium bis(2-methoxyethoxy)aluminium hydride; *N*-4-pentenylisoindole **9** was the major product (**Scheme 4**).



Scheme 4

Simons, Stobaugh and Takahashi, reported the quantitative formation of 2*H*-isoindole derivatives **16–18** (Scheme 5)[103-107].



Scheme 5

Present work
Synthesis of 3- substituted isoindolines by Palladium catalized reactions.

4.2 Rationale for present work

Isoindolines have been used as synthetic intermediates in the preparation of drugs and natural products. Some isoindoline derivatives display interesting biological activities which have been described in Section-1. It was found from the Literature review that a few general procedures for the synthesis of isoindolines have been reported.

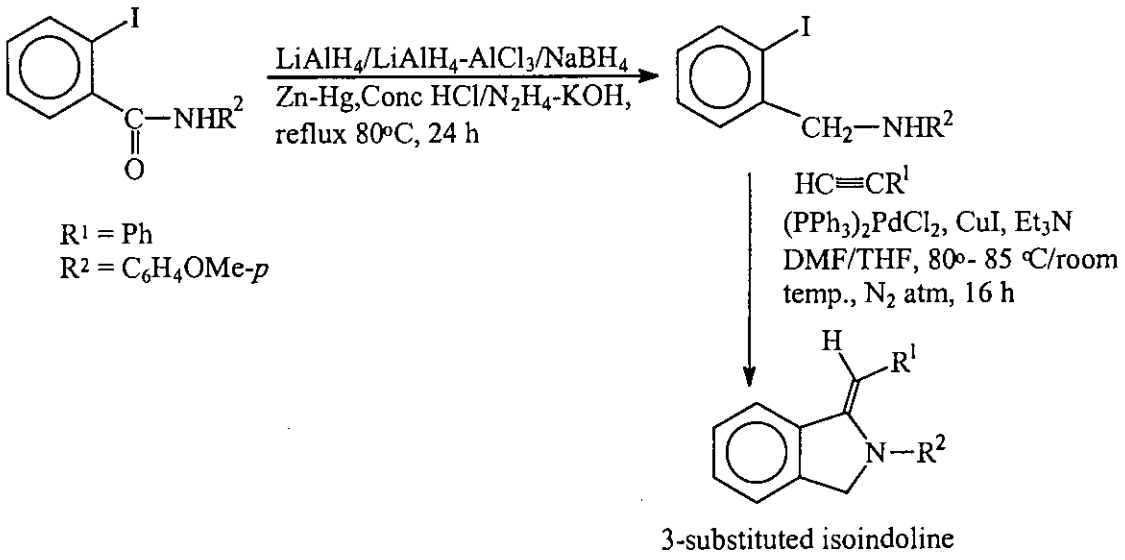
In Section-2 , a strategy for the synthesis of (Z)- 3- Aryl(alkyl)idene isoindolin-1-ones by Palladium catalized reactions of 2-Iodo benzamides with terminal alkynes followed by cyclization in a highly regio and stereoselective manner has been demonstrated. In continuation of our preceding work and in view of the natural occurrence and biological importance of the isoindoline derivatives and lack of convenient general procedures for their synthesis, we were interested in developing a general and facile method for the synthesis of 3- substituted isoindoline derivatives.

4.3 Results and Discussion

4.3.1 Starting Materials

Synthesis of 2-Iodo-benzyl amine

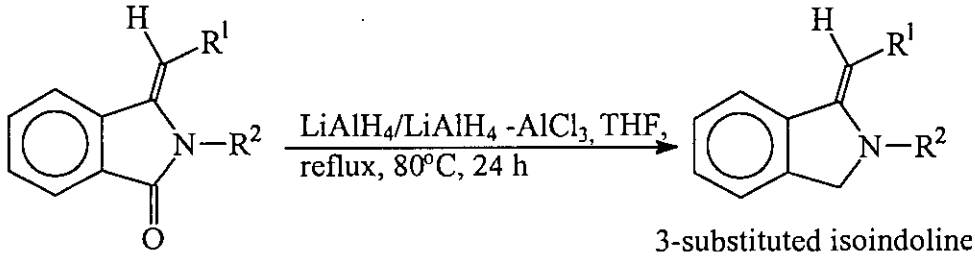
At first we attempted for the synthesis of 2-Iodo-*N-p-* anisyl benzyl amine (**Scheme 6, page 124**) from 2-Iodo-*N-p*-anisyl benzamide with different methods. The reactions were usually carried out by heating a mixture of 2-Iodo-*N- p-* anisyl benzamide and $LiAlH_4/LiAlH_4$–$AlCl_3/NaBH_4$/Na-Hg in conc. HCl/N_2H_4-KOH in THF at 80 °C for 24 h to afford a bluish coloured needles. The products were characterized from their Melting point, H^1 NMR, UV and IR spectra. IR spectra showed the presence of carbonyl group at 1650 cm^{-1}. H^1 NMR spectra indicated the presence of O=C(I)-NH- group at δ 7.9. The spectral data of the compound obtained from the above reactions were identical with that of starting materials. So we did not carry out further Palladium catalyzed reactions.



Scheme 6

4.3.2 Synthesis of 3-Benzylidene-*N*- *p*- anisyl isoindoline

Secondly, we attempted to reduce 3-substituted Isoindolinones to their corresponding Isoindolines. Then 3-Benzylidene-*N*-*p*- anisyl isoindolin-1-one was subjected to reduction reaction with $LiAlH_4/LiAlH_4$-$AlCl_3$ in THF under reflux at 80 °C for 24 h to



Scheme 7

yield a light yellowish needles (**Scheme 7**). The products were characterized by their satisfactory spectroscopic (UV, IR and H^1 NMR) data. The IR spectra showed carbonyl stretching vibration at 1714.0 cm^{-1}. The H^1 NMR spectra showed chemical shift at δ6.87-7.94 for 13H aromatic proton. All spectral data were found to be identical with that of starting materials. Finally, we could not synthesize 3-substituted isoindolines from 3-substituted isoindolinones by this methodology. We do hope that this scheme will be successful if highly reactive $LiAlH_4$ can be used.

4.4 Experimental

Synthesis of 2-Iodo-*N*-*p*-anisyl benzylamine

2-Iodo-*N*-*p*-anisyl benzamide was subjected to prepare 2-Iodo-*N*-*p*-anisyl benzylamine by the following Methods.

Method A (Reduction by $LiAlH_4$)

A mixture of 2-Iodo-*N*-*p*-anisyl benzamide (0.5g, 1.475 mmol) and $LiAlH_4$ (0.17g, 3 equiv.) in THF (10 ml), reflux at 80 °C for 24 h. The mixture was filtered through celite and then evaporated to dryness under reduced pressure, excess reagent was decomposed with water and the solution extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a bluish gummy solid. It was crystallized from ethanol to afford a bluish coloured needles (0.4g, 80%) m.p. 172 – 173 °C.

IR: ν_{max}(KBr): 3306, 1650, 1594, 1512, 1462, 1412, 1315, 1299, 1248, 1232, 1028, 825, 741 cm^{-1}.

UV(EtOH): λ_{max} 270.0, 260.0, 252.4, 236.8, 218.40 nm.

^{1}H NMR (400 MHz, $CDCl_3$): 4.16 (S, 3H, $-OCH_3$), 7.20- 7.90 (m, 8H), 8.25 (d, 1H, J = 7.91 Hz)

Method B (Reduction by $LiAlH_4$-$AlCl_3$)

A mixture of 2-Iodo-*N*-*p*-anisyl benzamide (0.5g, 1.475 mmol) and $LiAlH_4$ (0.17g, 3 equiv.), $AlCl_3$ (0.19g, 1 equiv.) in THF (10 ml), reflux at 80 °C for 24 h. The mixture was filtered through celite and then evaporated to dryness under reduced pressure, excess reagent was decomposed with water and the solution extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to obtain a bluish gummy solid. It was crystallized from ethanol to afford a bluish coloured needles (0.35g, 70%) which was same as starting material.

Method C (Reduction with $NaBH_4$)

To a stirred suspension of $NaBH_4$ (0.28g, 5 equiv.) and 2-Iodo-*N*-*p*-anisyl benzamide (0.5g, 1.475 mmol) in dioxane (20 ml) was added acetic acid (0.44g, 5 equiv.) in dioxane (10 ml) over a period of 10 minutes at 10 °C. Then the reaction mixture was stirred under reflux for 2 h. After usual workup, a bluish gummy solid was obtained. It was purified by column chromatography with 5% ethyl acetate in n-hexane to obtain the bluish coloured needles (0.45g, 90%) which was found to be identical with the starting material.

Method D (Clemmensen method)

2-Iodo-*N*-*p*-anisyl benzamide (0.5g, 1.475 mmol) was stirred with amalgamated zinc (1.1g) and conc HCl (10 ml) in dioxane (20 ml) at 80 °C for 24 h. After usual workup, a bluish gummy solid was obtained. It was crystallized from ethanol to obtain a bluish coloured needles (0.35g, 70%). In this case starting materials also came back and small amount of starting materials were decomposed.

Method E (Huang-Minlon modification of the Wolff-kishner reduction)

2-Iodo-*N*-*p*-anisyl benzamide (0.5g, 1.475 mmol) was stirred with 4.20 ml of diethylene glycol, 0.42 ml of 90% hydrazine and 0.55g of potassium hydroxide pellets. The mixture was boiled gently on a boiling water bath until most of the KOH was dissolved and then it was heated under reflux for 1h. At the end of the reaction the mixture was evaporated to dryness under reduced pressure to give a residue and then extracted with ether (3×20 ml). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a bluish gummy solid mass. It was crystallized from ethanol to obtain a bluish colourd needles (0.3g 60%). Whose spectral data were found to be identical with that of starting materials.

Synthesis of 3-Benzylidene-*N*-*p*-anisyl isoindoline

To prepare 3-Benzylidene-*N*-*p*-anisyl isoindoline from 3-Benzylidene-*N*-*p*-anisyl isoindolinone was attempted by the following method (Reduction by $LiAlH_4$)

A mixture of 3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one **34** (0.3g, 0.917mmol) and $LiAlH_4$ (0.10g, 3 equiv.) in THF (10 ml) was refluxed at 80 °C for 24 h. After usual workup, the compound was obtained as a gum. It was crystallized from n-hexane-ethyl acetate to obtain a light yellowish needles (0.2g, 0.66%) m. p. 170 –171 °C.

IR: ν_{max}(KBr) 3040, 3010, 1712.6, 1670, 1602.5, 1500.4, 1471.6, 1442.7, 1245.9, 1164.9, 1024.1, 1008, 763.8 cm^{-1}.

UV(EtOH): λ_{max} 330.0; 276.0, 237.4, 220.0 nm.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (S, 3H, $-OCH_3$), 6.80 (S, 1H, = CH–), 6.82 (d, 2H, J = 7.02 Hz, Ar–H), 6.90 (m, 6H, Ar–H), 7.60 (t, 1H, J = 7.51 Hz, Ar–H), 7.70 (d, 1H, J = 816 Hz, Ar–H), 7.82 (t, 2H, Ar–H), 7.94(d, 1H, J = 7.54 Hz, Ar–H).

Section-5

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