Synthetic Approaches toward Benzannulated *N*-Heterocycles and Related Natural Products through Metal Catalyzed Domino Electrophilic Cyclization Reactions

A thesis submitted for the partial fulfilment of

the degree of Doctor of Philosophy

by

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Dedicated To

My parents & Wife

…for their immortal support, love

& encouragement

DECLARATION

The work presented in this thesis titled ***"Synthetic Approaches toward Benzannulated N-Heterocycles and Related Natural Products through Metal Catalyzed Domino Electrophilic Cyclization Reactions"*** has been carried out by me under the supervision of **Dr. R. Vijaya Anand** in the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Punjab, India.

This work has not been submitted in part or full for a degree, diploma or a fellowship to any other university or institute.

Whenever contributions of others are involved, every effort is made to indicate this clearly with due acknowledgements of collaborative work and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

VIRSINHA VENKAT REDDY

Date:

Place: IISER Mohali

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. R. Vijaya Anand

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Date:

Place: IISER Mohali

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Abstract

The research work carried out is mainly focused on the synthesis of benzannulated *N*-heterocycles *via* the domino cyclization reaction catalyzed by transition metals (Pd, Ag, Cu & Zn).

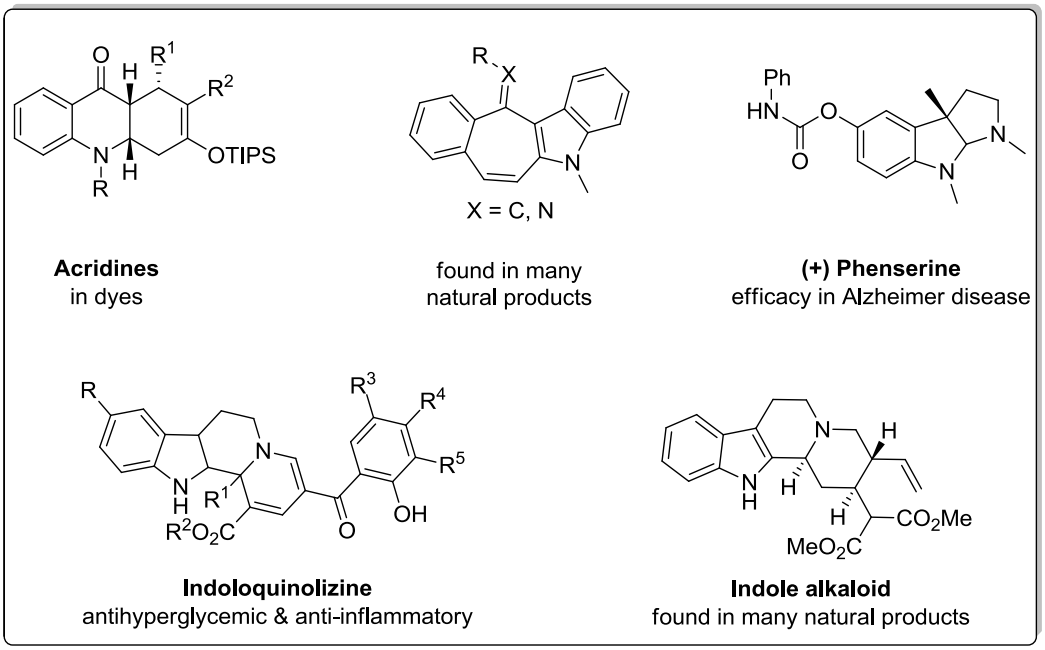
This thesis has been divided into **three chapters**:

Chapter 1:

Pd-catalyzed facile approach toward the unsymmetrical diarylindolylmethanes

It has been realized that the domino annulation approach is an extremely powerful tool for the rapid construction of multiple bonds in a single reaction flask, which leads to a complex carbocycles or heterocycles (Figure 1). Especially, benzannulated *N*-heterocyclic core found in many natural products, active pharmaceutical ingredients (API) and medicinally significant compounds (Figure 1).

Figure 1: Representative bioactive molecules synthesized by domino annulation

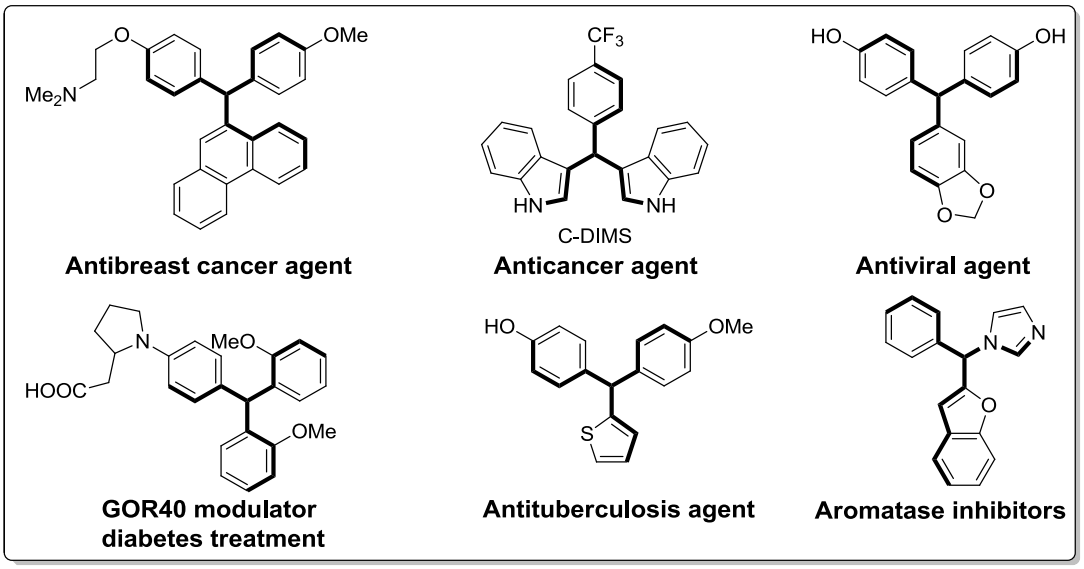


Due to their biological activities, the demand for the one-pot synthesis of benzannulated *N*-heterocycles is increasing rapidly. The major advantages of domino annulation reactions are the minimization of by-products, (generally) provide high atom economy, reduction in the number of synthetic steps and, cost and time efficiency.

Palladium has been used staggeringly for the construction of a wide range of carbon-carbon and carbon-heteroatom bonds. In the last two decades, metal-catalyzed one-pot annulation of *o*-alkynyl anilines followed by electrophilic trapping with suitable electrophiles has become a fascinating research area for the synthesis of heavily substituted indole derivatives. Due to their biological importance, the synthesis and derivatization of indole is an exciting research area in the field of organic chemistry.

Triarylmethanes are considered to be a valuable synthetic target in organic synthesis due to their significant contribution to the dye industry and medicinal chemistry. Although the synthesis of symmetrical triarylmethanes is well-explored in the literature, the synthesis of unsymmetrical triarylmethane remains as a relatively demanding task. Few of the biologically active triarylmethanes are shown in Fig. 2.

Figure 2: Representative bioactive triarylmethane derivatives

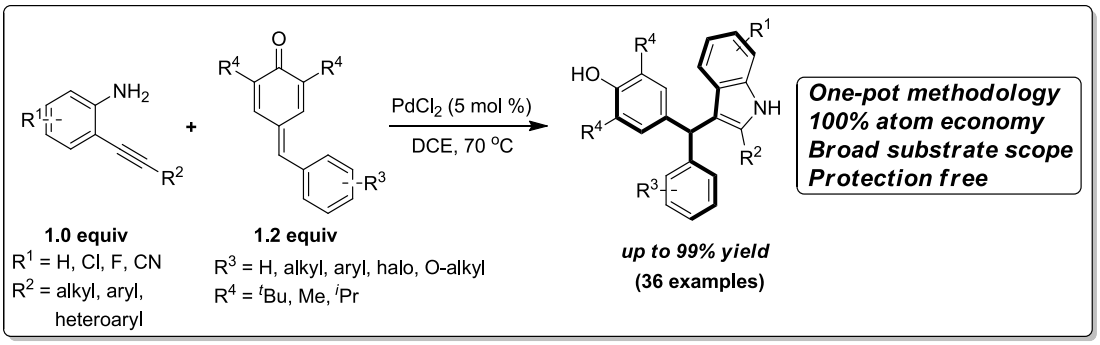


Quinone methides (QMs) are considered as a highly reactive intermediate and an excellent Michael acceptor when compared to the traditional acceptors (enones) in organic synthesis. These are of two types, *ortho*-quinone methides (*o*-QMs) and *para*-quinone methides (*p*-QMs) and usually, they undergo 1,4 and 1,6-conjugate addition reactions respectively.

Inspired by the metal-catalyzed one-pot annulation reactions, we conceived that diarylindolylmethanes could be accessed through a metal-catalyzed annulation of *o*-alkynyl

anilines followed by trapping with *para*-quinone methides (*p*-QMs). Astoundingly, this protocol has not been reported so far. Herein we disclose the palladium-catalyzed highly efficient and atom-economical one-pot annulation of *o*-alkynyl anilines followed by 1,6-conjugate addition to *para*-quinone methides to access valuable unsymmetrical diarylindolylmethanes under relatively mild conditions (Scheme 1). With the optimized reaction conditions in hand, we investigated the substrate scope using a wide range of substituted *para*-quinone methides and *o*-alkynyl anilines. In all the cases, the respected unsymmetrical diarylindolylmethanes were obtained in good to excellent yields. The prominent features of this one-pot annulation protocol are broad substrate scope, and 100% atom economy.

Scheme 1: The Pd-catalyzed synthesis of unsymmetrical diarylindolylmethanes

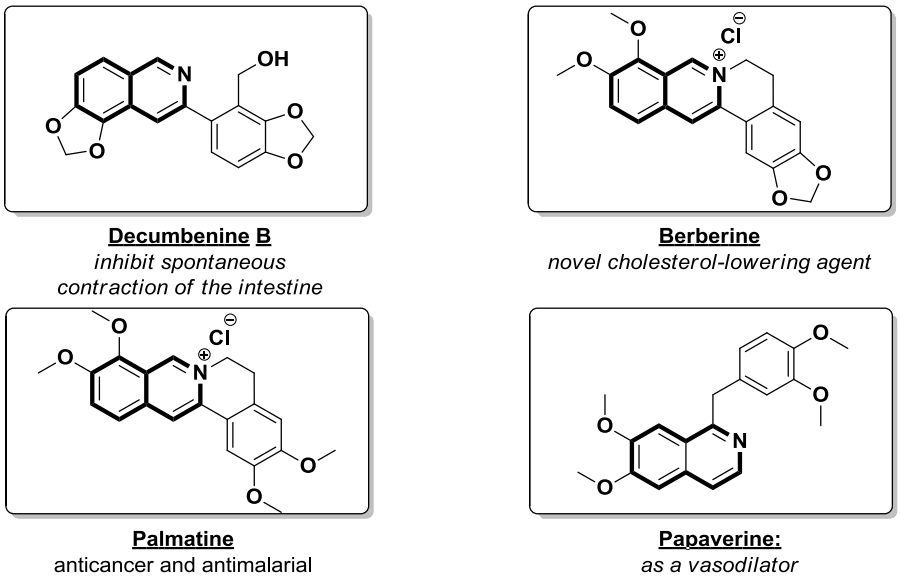


Chapter 2:

Ag(I)-catalyzed synthesis of isoquinolines at room-temperature: Elaboration to berberine and palmatine

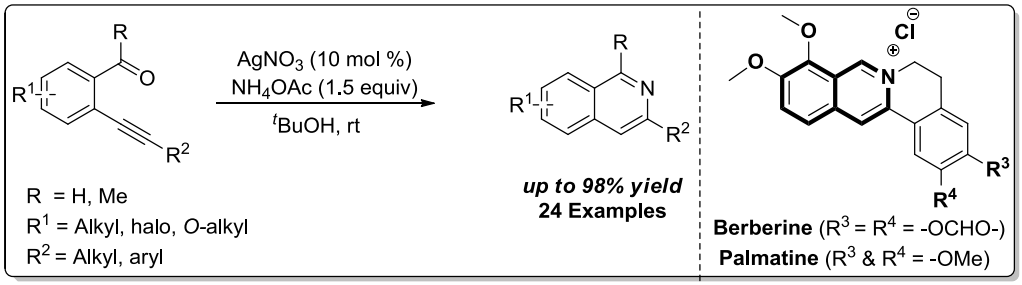
The isoquinoline nucleus is an important and integral part of many natural products and active pharmaceutical ingredients (API) (Figure 3). These natural products exhibit remarkable biological activities and possess structural diversity. The classical approaches for the synthesis of isoquinoline ring systems include the Pomeranz–Fritsch, Bischler-Napieralski and Pictet Spengler reactions. The literature survey reveals that many strategies are known for the synthesis of isoquinolines. However; the methods reported so far were carried out either at higher/elevated temperatures or under microwave irradiation. Various research groups are redirecting efforts toward the development of mild, simple and efficient methods for the synthesis of such kind of rigid molecules.

Figure 3: Isoquinoline scaffold containing biologically active molecules



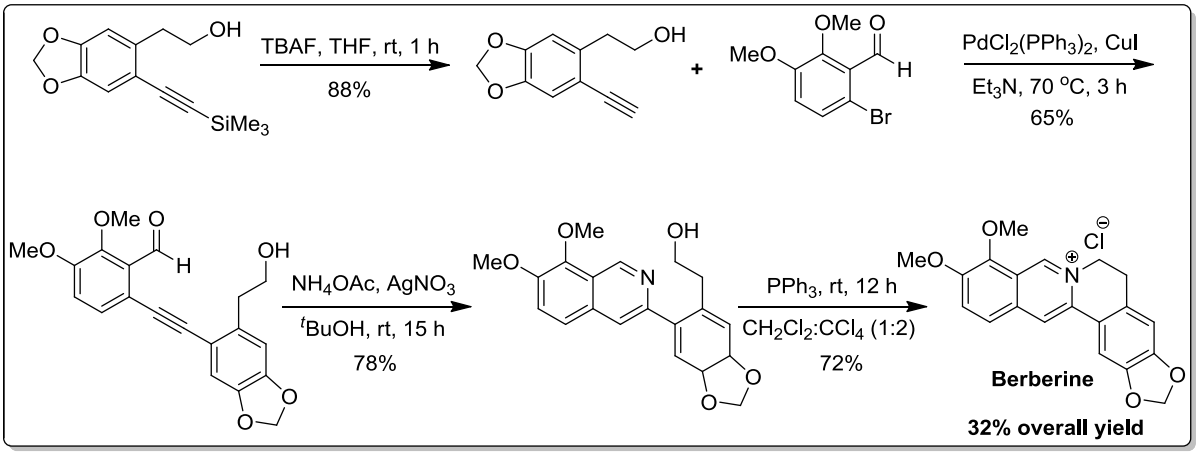
However, to the best of our knowledge, the one-pot synthesis of isoquinolines at *room temperature* from *o*-alkynyl benzaldehyde has not been reported so far. Keeping this point in mind, we have developed a silver-catalyzed mild protocol for the synthesis of isoquinolines through the domino cyclization of *o*-alkynyl benzaldehyde or ketone at *room temperature*. Utilizing the standard reaction condition, we have synthesized a variety of 3-substituted isoquinoline derivatives in moderate to excellent yields (Scheme 2).

Scheme 2: Silver-catalyzed synthesis of isoquinoline derivatives



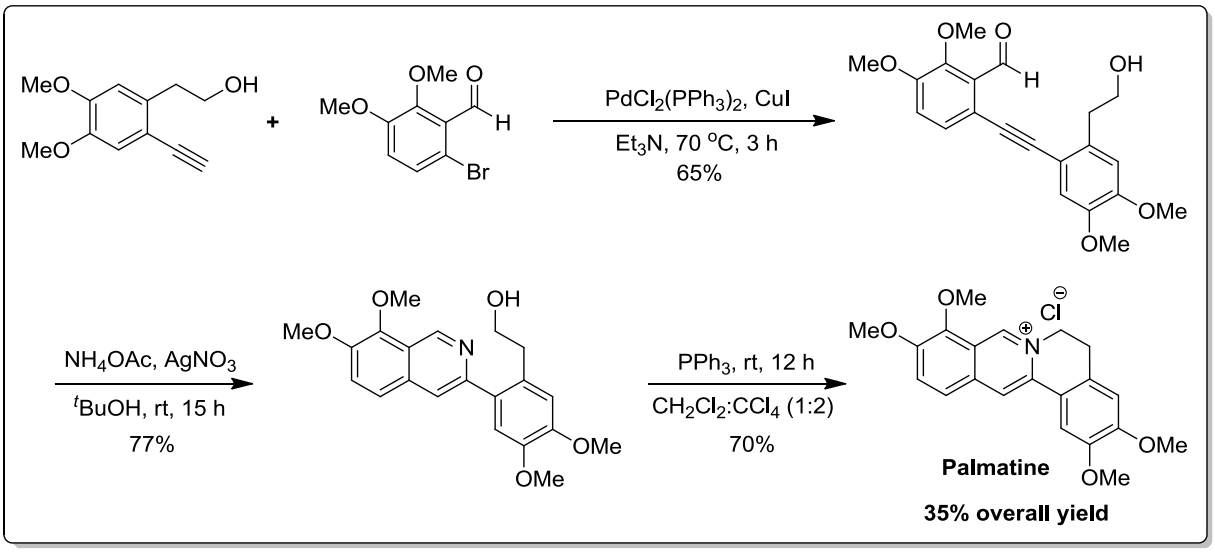
To demonstrate the synthetic application of this protocol, we elaborated this annulation approach in the total synthesis of berberine and palmatine, which are very important protoberberine alkaloids. The total synthesis of berberine was achieved in only four steps with 32% overall yield (Scheme 3).

Scheme 3: Total synthesis of berberine



A similar strategy has also been applied to the total synthesis of palmatine with 35% overall yield (Scheme 4).

Scheme 4: Total synthesis of palmatine



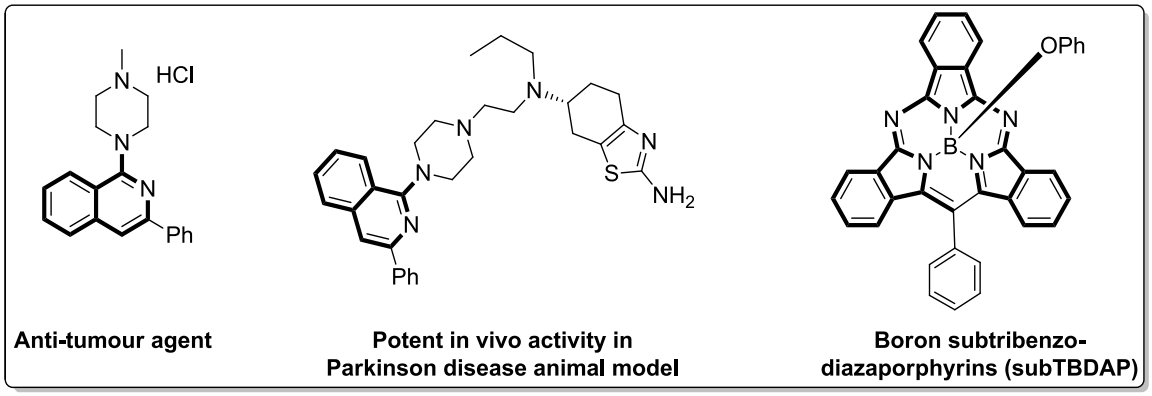
Chapter 3:

Catalyst-controlled regioselective approach to 1-aminoisoquinolines and/or 1-aminoisoindolines under solvent free condition

In continuation of the synthesis of privileged heterocyclic scaffolds and related natural products, we believed that 1-amino isoquinolines could be synthesized from *o*-alkynyl benzonitrile and amine in the presence of metal catalysts through aminative domino cyclization reaction. In the isoquinoline family, 1-aminoisoquinoline is a leading class of

compounds possessing staggering biological activities, such as antitumor, antimalarial, antimicrobial properties and protein kinase D inhibition. Especially, 1-piperazinyl isoquinolines are extremely useful in medicinal chemistry (Figure 4).

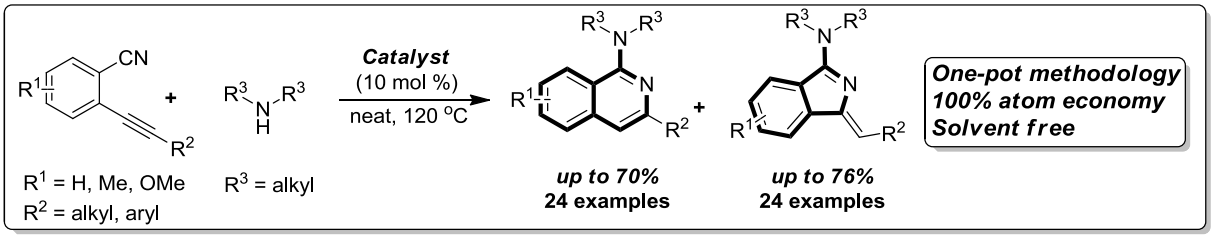
Figure 4: Importance of 1-aminoisoquinolines and 1-aminoisoindolines



Even though 1-aminoisoindolines are rarely useful in medicinal chemistry, they are very useful synthons for the synthesis of BODIPY analogues and modified porphyrins. Few of the 1-aminoisoindolines are also used as ligands in transition metal catalysis (Figure 4). A few reports are available for the synthesis of 1-aminoisoindolines from *o*-alkynyl benzonitriles, but the substrate scope was poor.

So far, there is no report available for the synthesis of 1-aminoisoquinolines from *o*-alkynyl benzonitriles. We herein describe a catalyst controlled regioselective and atom economical approach for the synthesis of 1-aminoisoquinoline as well as 1-aminoisoindoline derivatives from *o*-alkynyl benzonitrile and secondary aliphatic amines under solvent-free conditions (Scheme 5).

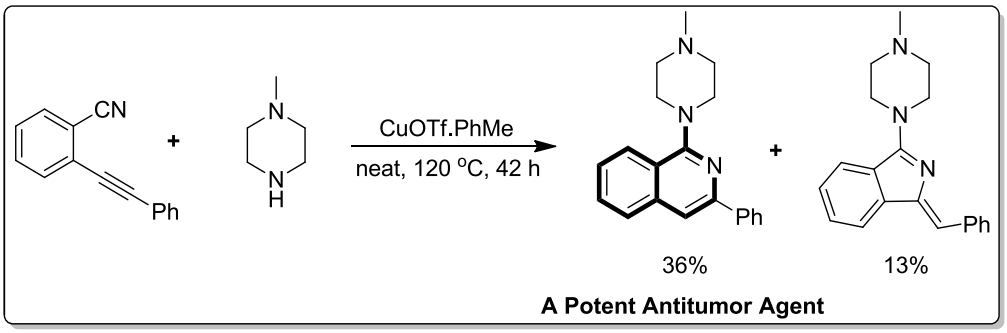
Scheme 5: Synthesis of 1-aminoisoquinoline and 1-aminoisoindoline



The extensive optimization revealed that copper-based catalyst favored the formation of 1-aminoisoquinolines and other metals such as Ag, Zn, Yb, Sc and Ce favored the

formation of 1-aminoisoindolines. We evaluated the substrate scope using a broad range of *o*-alkynyl benzonitriles as well as secondary aliphatic amines under both the optimized conditions. A one-pot domino cyclization, 100% atom economy and solvent free condition are the noticeable features of this protocol. The established protocol was also applied to the concise synthesis of a potent antitumor agent in one-pot (Scheme 6).

Scheme 6: Synthesis of a potent antitumor agent



ABBREVIATIONS

AcOH	Acetic acid
Ac_2O	Acetic anhydride
ACN	Acetonitrile
CD_3CN	Acetonitrile-D_3
Ac	Acetyl
acac	Acetylacetonate
aq	Aqueous
BQ	1,4-Benzoquinone
Bn	Benzyl
JhonPhos	(2-Biphenyl)di-*tert*-butylphosphine
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppo	1,8-Bis(diphenylphosphino)octane
DPPPent	1,5-Bis(diphenylphosphino)pentane)
Amphos	Bis[di-*tert*-butyl(4-dimethylaminophenyl) phosphine]
brs	Broad singlet
NBS	*N*-Bromosuccinimide
PyBroP	Bromotrispyrrolidinophosphonium hexafluorophosphate
CsOAc	Caesium acetate
calcd	Calculated
CSA	Camphorsulfonic acid
CO	Carbon monoxide
Cbz	Benzyloxycarbonyl
cm	Centimeter
δ	Chemical shift
$CDCl_3$	Chloroform-D
J	Coupling constant
Cy	Cyclohexyl
cod	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether

°C	Degree celsius
dr	Diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	Dibenzylidineacetone
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCE	Dichloroethane
DCM	Dichloromethane
SPhos	2-Dicyclohexylphosphino-2,'6'-dimethoxybiphenyl
Et_2O	Diethyl ether
DME	Dimethoxyethane
DMA	Dimethylacetamide
DMF	*N*,*N*'-Dimethyl formamide
DMSO	Dimethyl sulfoxide
d	Doublet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
EWG	Electron withdrawing
ESI	Electrospray ionization
ee	Enantiomeric excess
er	Enantiomeric ratio
EtOH	Ethanol
EtOAc	Ethylacetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
NHC	*N*-Heterocyclic carbene
Hz	Hertz
HRMS	High-resolution Mass Spectrum
h	Hour(s)
i-Pr	*iso*-Propyl
Menthyl	[1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl]
LDA	Lithium diisopropylamide

^{t}BuOLi	Lithium-*tert*-butoxide
m/z	Mass/Charge
MHz	Megahertz
m.p.	Melting point
Mes	Mesityl
MeOH	Methanol
MW	Microwave
mg	Milligram(s)
mL	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
M.S.	Molecular sieves
m	Multiplet
NMR	Nuclear Magnetic Resonance
$POCl_3$	Phosphoryl chloride
Piv	Pivalate
^{t}BuOK	Potassium-*tert*-butoxide
n-Pr	Propyl
Q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
sept	Septet
TPPMS	Sodium triphenylphosphane monosulfonate
tert	Tertiary
^{t}Bu	*tert*-Butyl
Boc	*tert*-Butyloxycarbonyl
TBAF	Tetrabutylammonium fluoride
HBF_4	Tetrafluoroboric acid
THF	Tetrahydrofuran
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Tetramethylsilane
PTSA	*p*-Toluene sulfonic acid
Ts	Tosyl

TFA	Trifluoroacetate
TfOH	Trifluoromethane sulfonic acid
Tf_2O	Trifluoromethane sulfonic anhydride
TIPS	Triisopropylsilyl ether
ttmpp	tris(2,4,6-Trimethoxyphenyl)phosphine
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet

Contents

Chapter 1

Pd-catalyzed Facile Approach toward the Unsymmetrical Diarylindolylmethanes

In this chapter, a palladium catalyzed domino protocol for the synthesis of diarylindolylmethane derivatives has been discussed. This chapter also covers a general introduction on domino reactions, synthesis of triarylmethanes and the reactions of *para*-quinone methides.

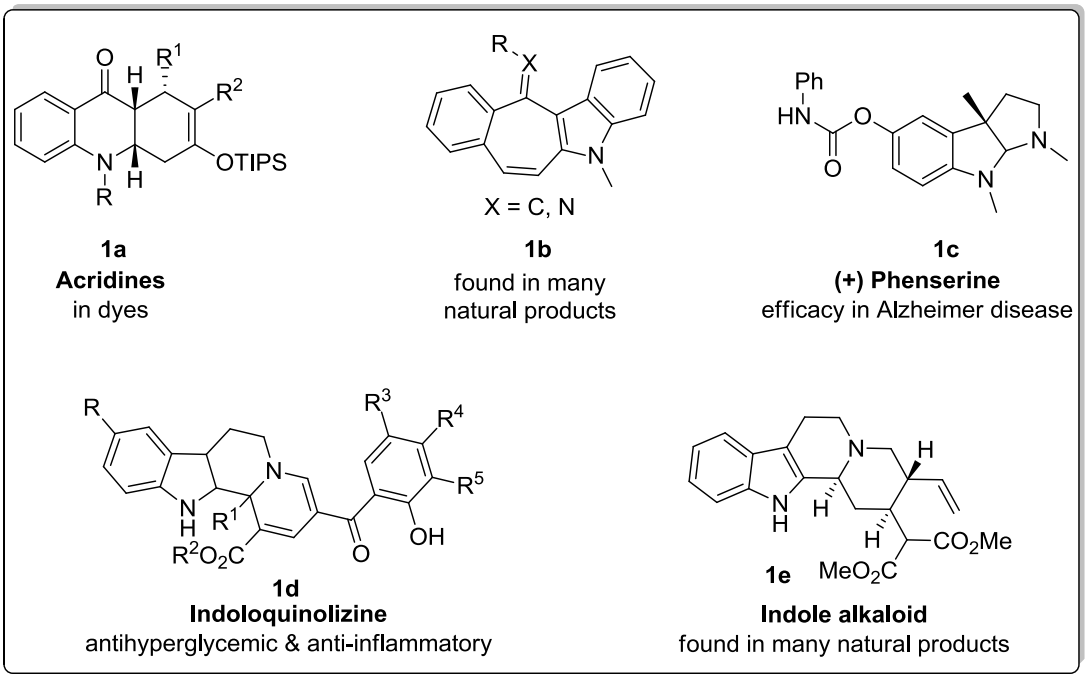
General introduction to domino reactions

Domino annulation approaches are extremely powerful tools for the rapid construction of multiple bonds in a single reaction flask, which leads to complex carbocycles or heterocycles (Figure 1).[1] Tietze beautifully defined the term domino reaction as *'... a process, which involves a formation of inter or intramolecular two or more bonds under the same reaction conditions without addition of any reagents and catalysts, and which gives the structural complexity through the intermediate formed in the initial reaction.*'[1b] Especially, benzannulated *N*-heterocyclic core found in natural products, active pharmaceutical ingredients (API) and medicinally significant compounds (Fig. 1).[2]

Due to their biological activities, the demand for the one-pot synthesis of benzannulated *N*-heterocycles is increasing rapidly. Researchers all over the world are developing a mild, efficient and domino protocol for the synthesis of these *N*-heterocycles.[3] Although, chemistry is a well-recognized subject in the field of science and society, the importance of it is declining due to the environmental issues and health-related problems are associated with waste products generated in the chemical industry. To overcome these problems, one could design a route for the synthesis of a target molecule in one sequence without altering the reaction conditions or isolating the intermediate. These transformations are not only useful from a green chemistry point of view but also regarding production cost.[1b] Such kind of reaction is termed as a domino reaction.

A domino reaction is a broad subclass of one-pot annulation reactions. The major advantages of one-pot annulation reactions are the minimization of by-products, (generally) provide high atom economy and a reduction in the number of synthetic steps as well as time. Among the benzannulated *N*-heterocycles, indoles, isoquinolines, 1-aminoisoquinolnes have drawn an enormous amount of attention from chemists in synthetic organic chemistry due to their applications in medicinal chemistry as well as in dye industry.[4] In recent years, one-pot domino reactions are considered as a promising tool for the synthesis of these privileged scaffolds[5] for drug discovery and material sciences. Domino electrophilic cyclization reaction is the most efficient and multipurpose tool in organic synthesis to achieve a complex framework of vital compounds without purification of any intermediate and with high atom economy. Few of the biologically active molecules have been shown in Figure 1.

Figure 1: Selected biologically active molecules synthesized by domino annulation

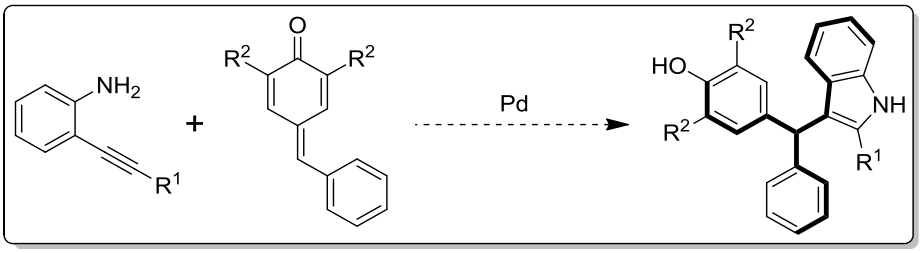


Especially, the indole framework is a privileged building-block present in many natural products such as indole alkaloids, fungal metabolites and marine natural products having biological activities.[6] The word "***Indole***" is the combination of two words "***ind****igo*" and "***ole****um*". Indole was first isolated by the treatment of indigo dye with oleum.[7] The chemistry of indole became interesting in the 1950s when several indole scaffolds were found to possess diverse biological activities. Consequently, the synthesis and derivatization of indole has been an intriguing research area in the field of synthetic organic chemistry.[8]

Transition metals play a crucial role in the synthetic organic chemistry[9] as well as in organometallic chemistry.[10] Palladium has been used outstandingly for the construction of a broad range of carbon-carbon and carbon-heteroatom bonds.[12]

Inspired by the palladium-catalyzed one-pot annulation reactions,[11] we conceived that diarylindolylmethanes could be accessed through metal-catalyzed annulation of *o*-alkynyl anilines followed by trapping with *para*-quinone methides (*p*-QMs), which will be discussed in results and discussion section in detail.

Scheme 1: Proposed scheme for the synthesis of diarylindolylmethane

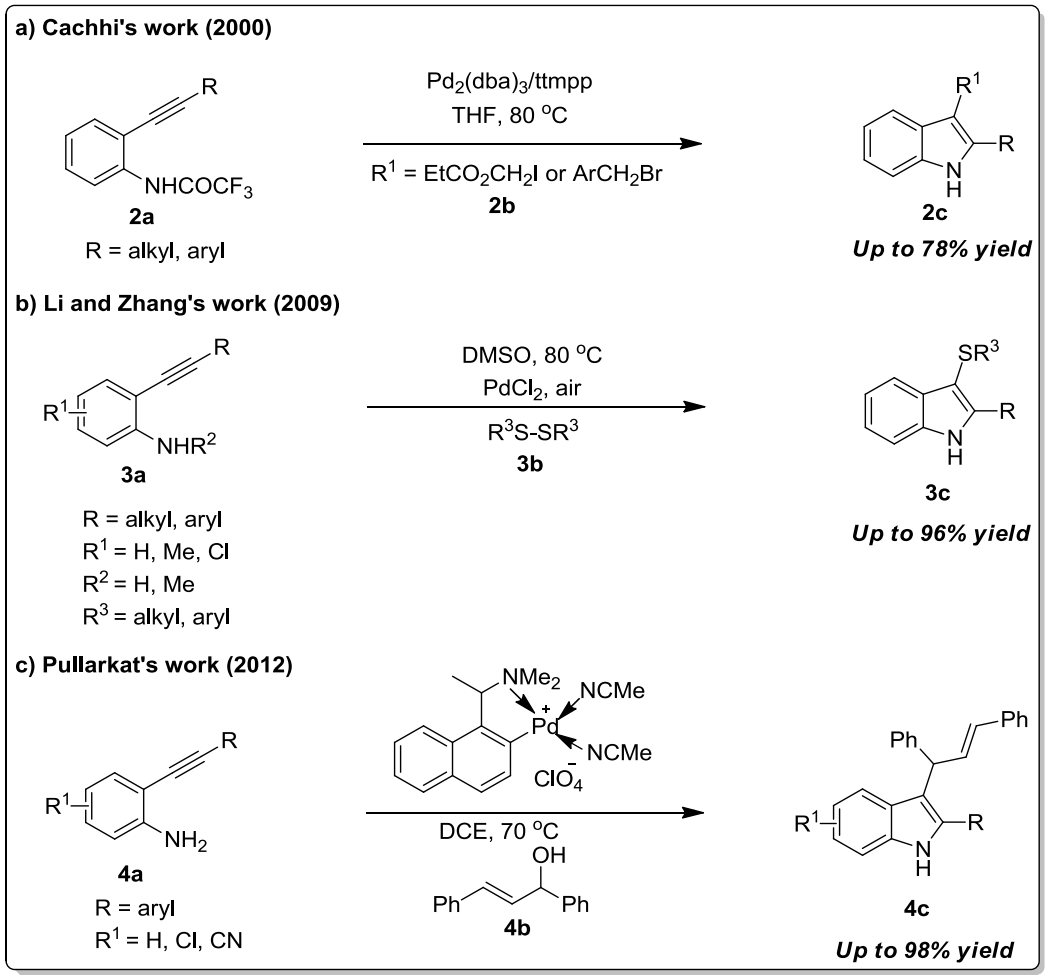


1.2) Literature reports for the synthesis of 2,3-disubstituted indoles from *o*-alkynyl anilines

One-pot annulation of *o*-alkynyl anilines followed by electrophilic trapping with suitable electrophiles has been discussed below to access highly substituted indole derivatives. Pd-catalyzed annulation reactions are summarized in Scheme 1 and 2. In 2000, Cachhi and coworkers developed palladium catalyzed domino cyclization of *o*-alkynyl trifluoracetanilide (**2a**) with activated alkyl halides (**2b**) to access 2,3-disubstituted indole derivatives (**2c**) in good yields. *N*-alkylated products were also observed during the reaction along with 2,3-disubstituted indoles. The optimal result was obtained by the reaction of *o*-alkynyl trifluoracetanilide with alkyl halides in the presence of $Pd_2(dba)_3$ with a bulky ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) (a, Scheme 1).[11a] Li's and Zhang's group reported an efficient protocol for the synthesis of 3-sulfenylindole derivatives **3c** by the annulation of *o*-alkynyl anilines (**3a**) followed by trapping with disulfides (**3b**) under Pd-catalyzed conditions. They have also synthesized new fipronil analogues known to act as pesticides and insecticides (b, Scheme 1).[11b,c] Another palladium catalyzed approach has appeared in the literature by one-pot cyclization of *o*-alkynyl anilines (**4a**) and subsequent

alkylation with allylic alcohols (**4b**) to access 2,3-disubstituted indoles (**4c**). In the case of symmetric compounds such as 1,3-diphenyl-2-propenol, only one isomer was obtained but in the case of unsymmetric alcohols, regiomers have been observed (c, Scheme 1).[11c]

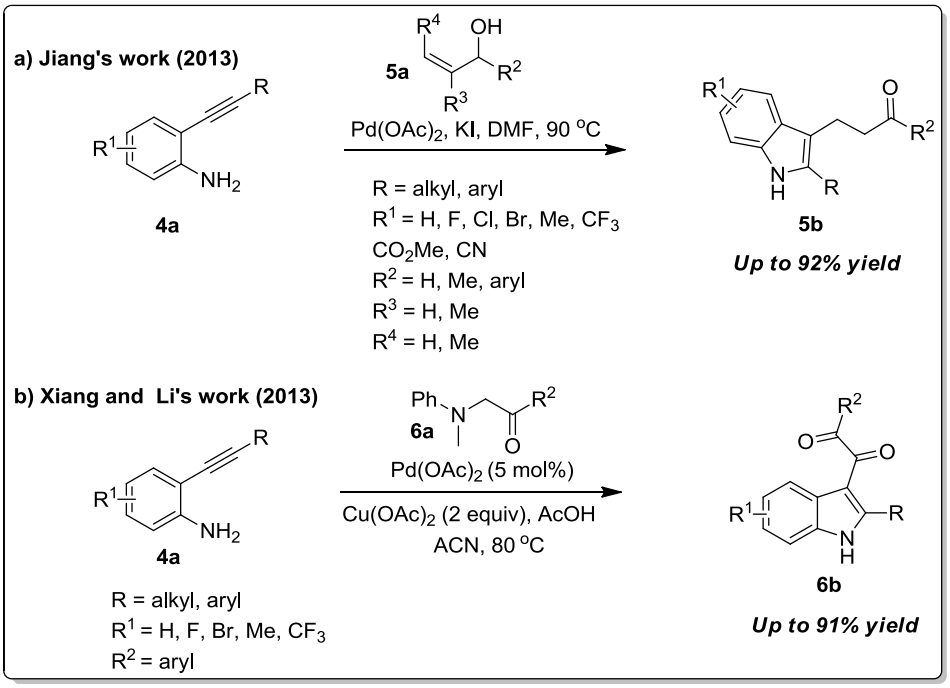
Scheme 1: Pd-catalyzed approaches to the synthesis of 2,3-disubstituted indoles



Recently, a few more approaches have appeared (Scheme 2). Jiang and coworkers reported a one-pot domino cyclization of *o*-alkynyl anilines (**4a**) followed by reaction with allylic alcohols (**5a**) *via* oxidative Pd-catalysis to afford *β*-indolyl ketones (**5b**). A broad substrate scope, high reactivity with readily available starting materials and molecular oxygen as an oxidant are the key feature of this methodology (a, Scheme 2).[13a] Another interesting approach worthy of note is that of Xiang's and Li's group, who reported an efficient method for the synthesis of a library of 3-acylindoles (**6b**). This core is present in a diverse range of natural products and pharmaceutical ingredients. The treatment of indoles with *α*-amino carbonyl (**6a**) compounds under Pd-catalyzed oxidative cross-coupling approach afforded the

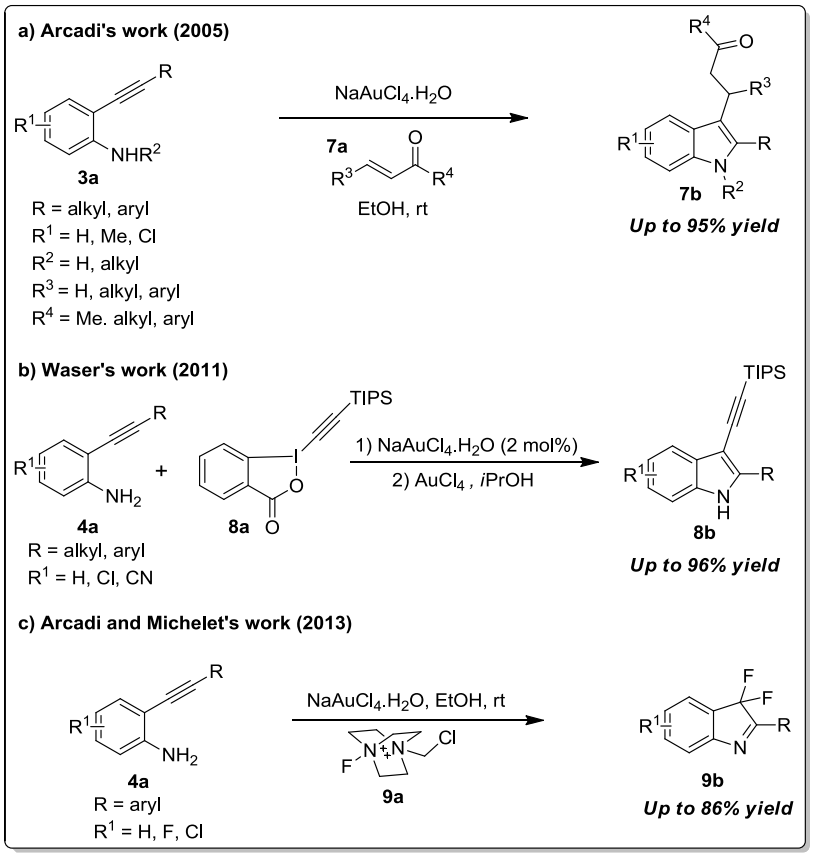
3-acylindole derivatives in moderate to excellent yields. Furthermore, the same methodology also worked smoothly in a one-pot manner for the synthesis of 3-acyl indoles by domino cyclization of *o*-alkynyl anilines (**4a**) followed by trapping with acylating precursors (**6a**) (b, Scheme 2).[13b]

Scheme 2: Pd-catalyzed approaches to the synthesis of 2,3-disubstituted indoles (**5b** & **6b**)



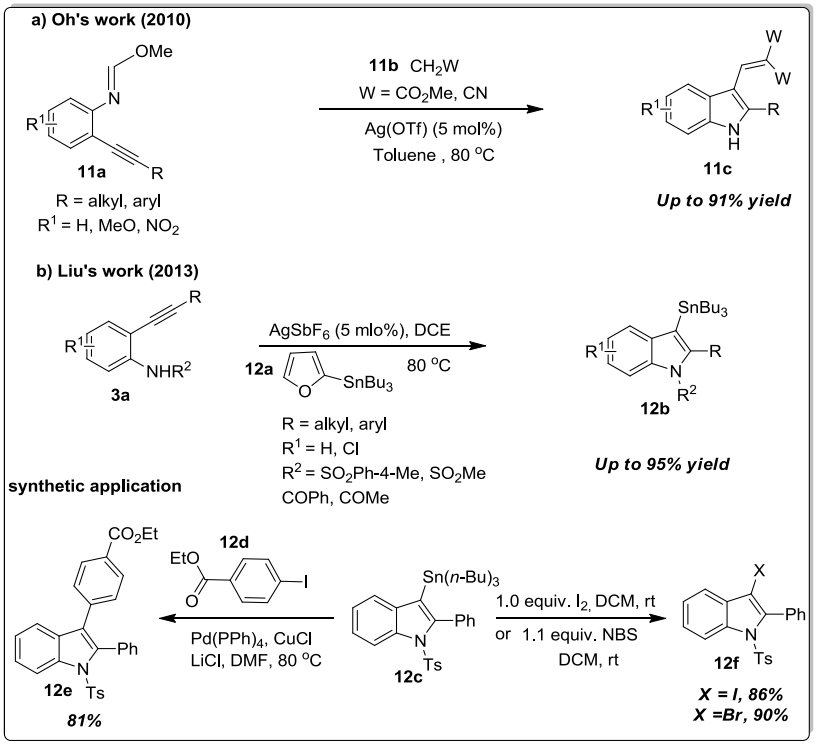
Apart from the Pd-catalyzed approaches, gold catalyzed protocols have also been explored. Arcadi's group reported an efficient method for the synthesis of disubstituted indoles (**7b**) by gold catalyzed annulation of *o*-alkynyl anilines (**3a**) followed by Michael addition to *α,β*-unsaturated carbonyl (**7a**) systems (a, Scheme 3).[14a] Waser and coworkers developed a facile approach for the synthesis of 3-silylethynyl indoles (**8b**) through the combination of Au(III) and Au(I) co-catalyzed cyclization *o*-alkynyl anilines (**4a**) followed by trapping with TIPS.EBX (**8a**) at room temperature (b, Scheme 3).[14c] Fluorinated compounds, especially heterocyclic fluorinated ones are very useful from a medicinal chemistry point of view.[14b] Arcadi and Michelet developed a protocol for the synthesis of 3,3-difluoro-2-substituted-3H-indole (**9b**) *via* gold-catalyzed aminative difluorination of *o*-alkynyl anilines with selectfluor (**9a**) (c, Scheme 3).[14d]

Scheme 3: Gold catalyzed one-pot annulation followed by electrophilic trapping



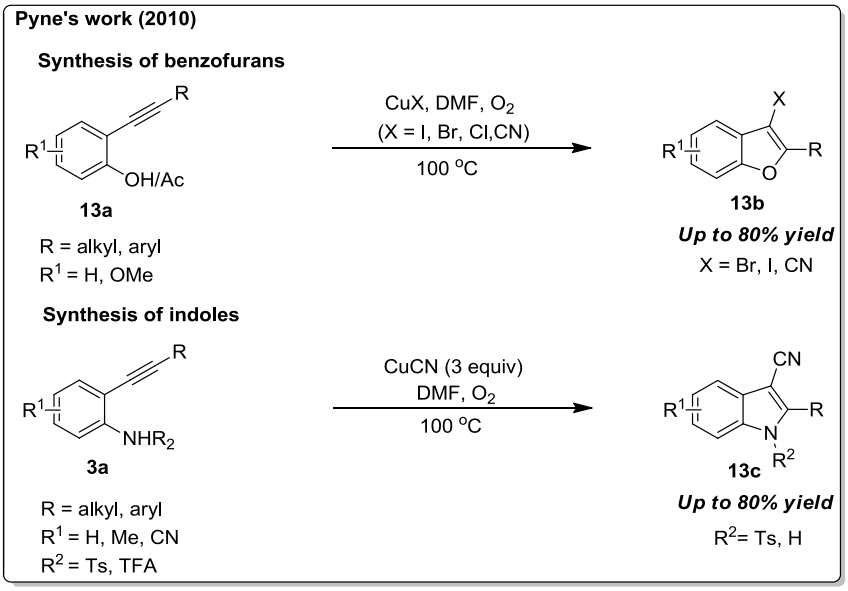
Oh's group has published a beautiful piece of work in 2010. A silver catalyzed domino protocol for the synthesis of 2,3-disubstituted indoles (**11c**) has been developed through cycloisomerization and 1,3 alkenyl shift between the reaction of *N*-arylformimidates (**11a**) and active methylene compounds (**11b**) (a, Scheme 4).[15] Arylstannanes are very useful synthons in Pd-catalyzed cross-coupling reactions as well as in the synthesis of medicinally valuable compounds.[16a] Liu's group was the first to develop silver catalyzed domino cyclization of *o*-alkynyl anilines (**3a**) followed by coupling with 2-tributylstannylfuran (**12a**) (b, Scheme 4). The 2-aryl/alkyl-3-(tributylstannyl)-1H-indole derivatives (**12b**) were obtained in good to excellent yields. To show the synthetic application of this methodology, the products have been employed in a few useful synthetic transformations. In the first case, 3-(tributylstannyl) indole (**12c**) was used in Stille cross-coupling reaction with iodoarene (**12d**) and the coupled product (**12e**) was obtained in 81% yield. In the second case, the reaction between 3-(tributylstannyl) indole with iodine or bromine generates relevant iodinated (86%) or brominated product (90%) (**12f**) in excellent yields (b, Scheme 4).[16b]

Scheme 4: Silver catalyzed one-pot annulation followed by electrophilic trapping



Pyne and coworkers explored a one-pot domino protocol using *o*-alkynyl phenols (**13a**) mediated by different CuX (X = I, Br or CN) salts for the synthesis of 3-halo or cyano substituted benzofuran derivatives (**13b**). The protocol was also extended to different *o*-alkynyl anilines (**3a**) with CuCN and obtained the corresponding 3-cyano indoles (**13c**) in good yields (Scheme 5)[17]

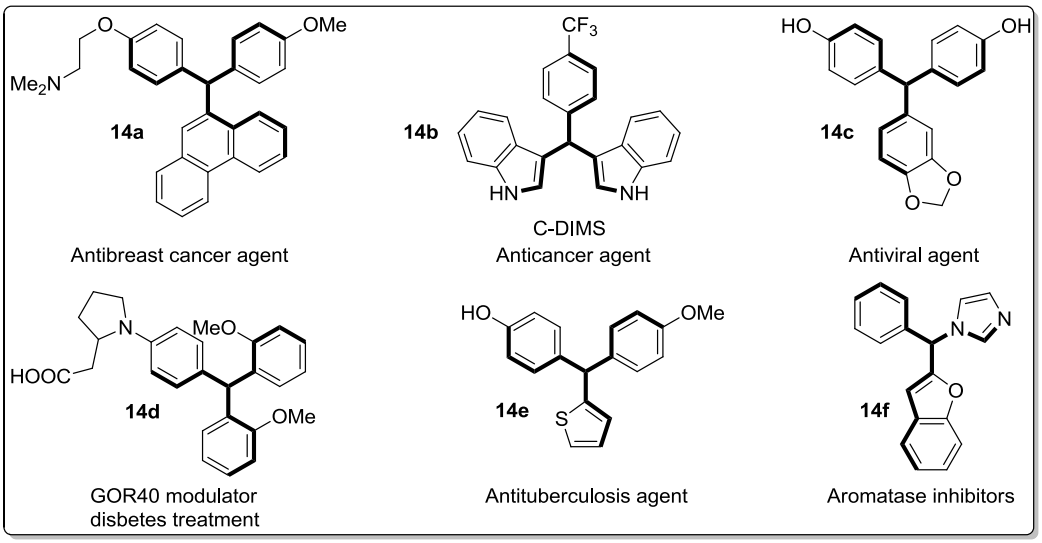
Scheme 5: Copper mediated synthesis benzofurans (**13b**) and indoles (**13c**)



1.3) Literature overview on the synthesis of triarylmethanes

In 1900, Gomberg discovered the triphenyl methyl radical.[18] This discovery is considered a significant breakthrough in the synthesis of triarylmethanes due to its application in organic dyes,[19] fluorescent probes,[20] and metal ion sensors.[21] Moreover, the triarylmethane derivatives are also useful in medicinal chemistry as anticancer, antiviral, anti-tuberculosis and antidiabetic agents (Fig. 2).[19b]

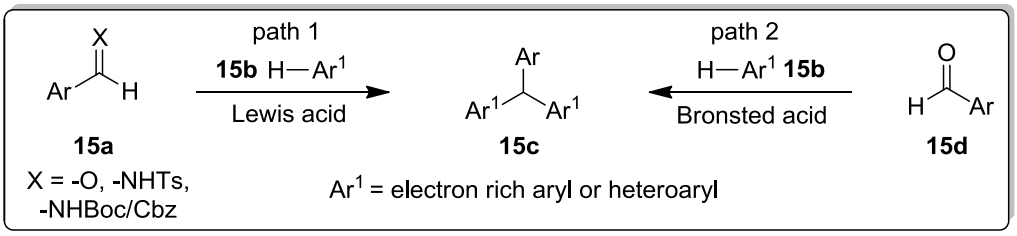
Figure 2: Representative bioactive triarylmethane derivatives



Some of the literature precedents are discussed below for the synthesis of triarylmethanes. Triarylmethanes are mainly classified into two types, "symmetrical triarylmethanes" and "unsymmetrical triarylmethanes." Even though the synthesis of symmetrical triarylmethane is well explored,[22] the synthesis of unsymmetrical triarylmethanes remained a challenging task.[19g]

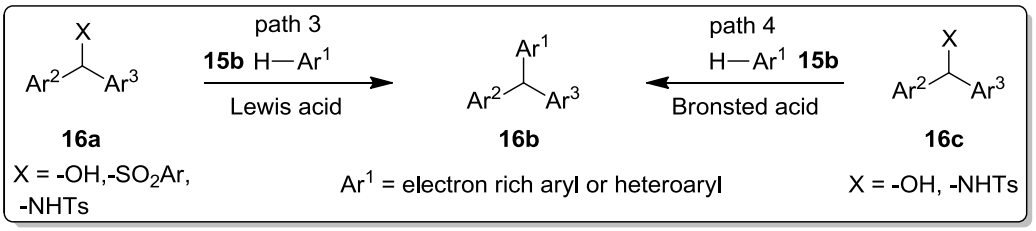
Symmetrical triarylmethanes (**15c**) are achieved either by Lewis acid[22] or Brønsted acid[23] catalyzed condensation of aromatic imines (**15a**) or aldehydes (**15d**) with electron rich arenes or heteroarenes (**15b**) (Scheme 6).

Scheme 6: General route for the synthesis of symmetrical triarylmethanes (**15c**)



The most widely used method for the synthesis of unsymmetrical triarylmethane (**16b**) is Friedel-Crafts dialkylation approach. The Friedel-Crafts approach involves the nucleophilic addition of electron rich arenes or heteroarenes to unsymmetrical diarylmethanols or its derivatives **16a**/**16c** under Lewis[24] or Brønsted acid[25] catalysis (Scheme 7).

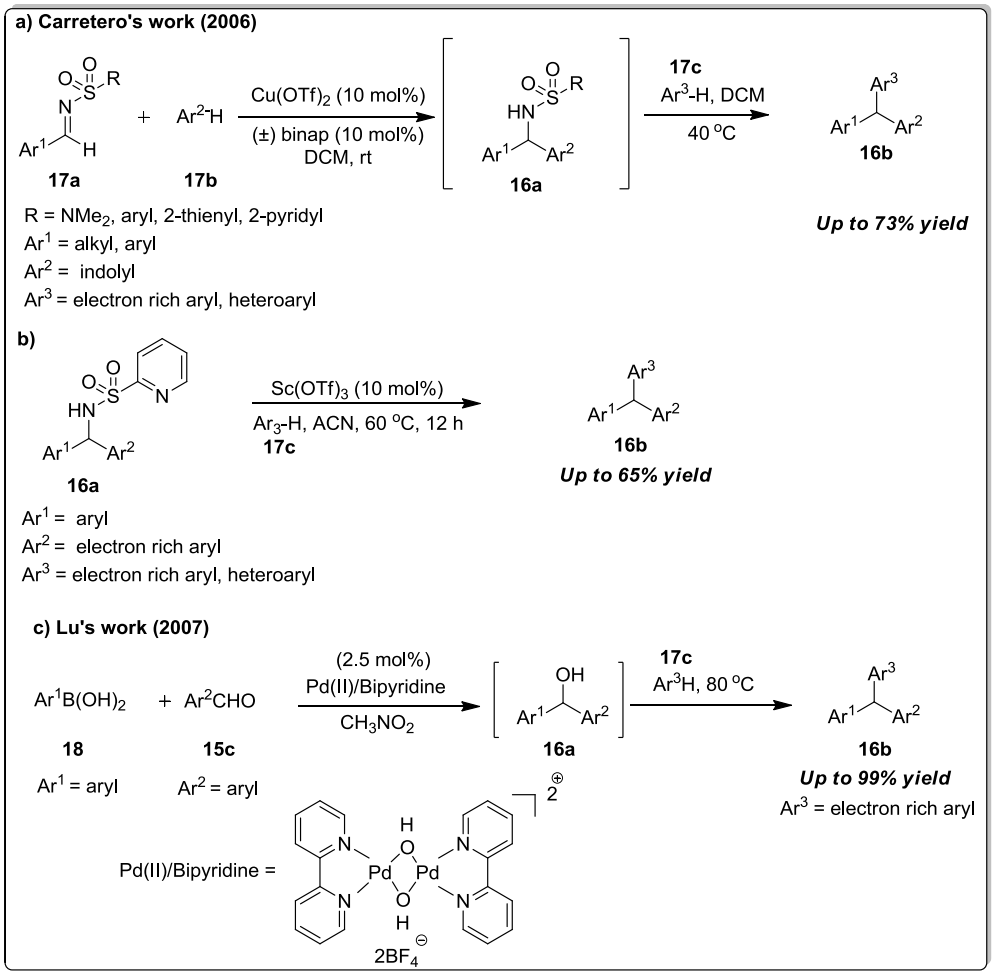
Scheme 7: General route for the synthesis of unsymmetrical triarylmethanes (**16b**)



Some of the literature precedents for the synthesis of unsymmetrical triarylmethanes in the presence of Lewis acids are presented here. Carretero's group reported a copper-catalyzed aza Friedel-Crafts alkylation of *N*-sulfonyl imines (**17a**) with electron rich arenes or heteroarenes (**17b**) to obtain the diarylmethylamines (**16a**). It was found that the 2-pyridylsulfonyl group controls the selectivity in getting diarylmethylamines as a primary product. The present protocol was also used in the synthesis of triarylmethanes (**16b**) in good to excellent yields by dialkylation of *N*-(2-pyridyl) aldimines (**17a**) with electron rich aromatic or heteroaromatic compounds in one-pot. Unfortunately, this Cu-catalyzed one-pot protocol for the synthesis of triarylmethanes applied only to diarylsulfonamide adducts having one of the aromatic rings as indolyl moiety. In the case of diarylsulfonamide (**17d**) adducts lacking any indolyl moiety, $Sc(OTf)_3$ worked well to access the triarylmethanes (**16b**). This second nucleophilic attack was achieved by treatment of electron rich arenes (**17c**) with isolated diarylsulfonamide adducts (**16a**) for to give the triarylmethanes (**16b**) (a & b, Scheme 8).[24a] In 2007, Lu and coworkers developed unique approach to the synthesis of triarylmethanes (**16b**) in one-pot using arylboronic acids (**18**), aromatic aldehydes (**15c**) and

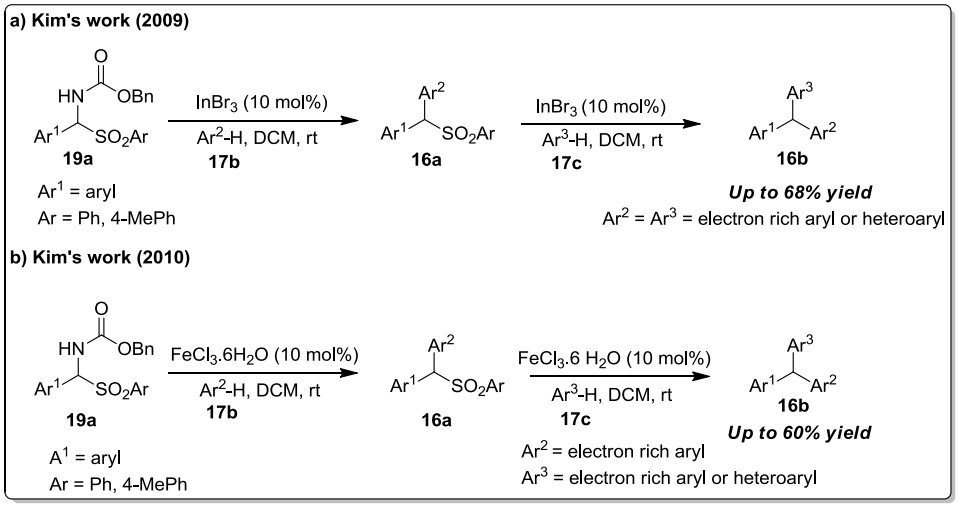
electron rich arenes (**17c**) in the presence of Pd-catalyst. For better selectivity, they have synthesized diarylmethanol derivatives (**16a**) in situ by the treatment of arylboronic acids with aromatic aldehydes. After completion of the reaction, electron rich arenes (**17c**) were added to the reaction mixture and finally triarylmethanes (**16b**) were obtained in moderate to excellent yields (c, Scheme 8).[24b]

Scheme 8: Cu and Pd-catalyzed synthesis of unsymmetrical triarylmethanes (**16b**)



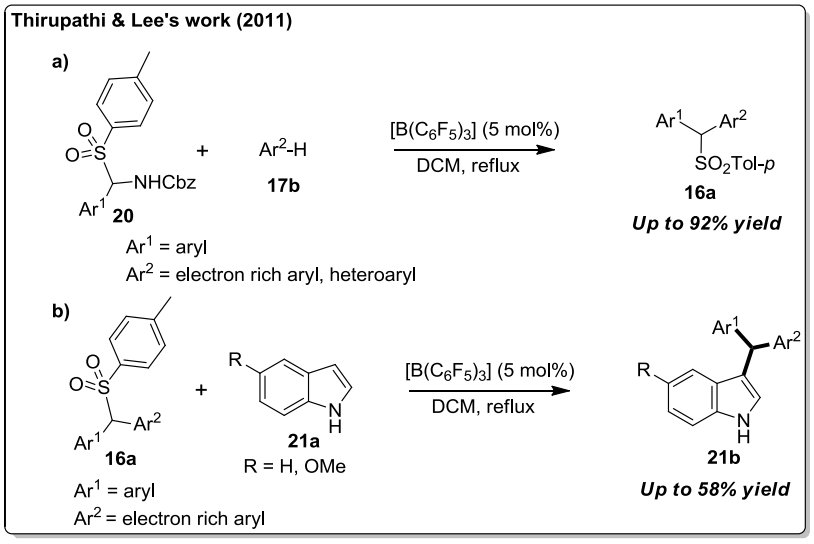
A couple of approaches have been developed separately by Kim and coworkers: indium and iron catalyzed synthesis of diaryl methylsulfones (**16a**) by the treatment of α-amido sulfones (**19a**) with electron rich arenes or heteroarenes (**17b**) (Scheme 9). Furthermore, the diaryl methylsulfone products (**16a**) underwent a second Friedel-Crafts alkylation with electron rich arenes or heteroarenes (**17c**) to afford the unsymmetrical triarylmethanes (**16b**) in good yields.[24c,d]

Scheme 9: Indium and Iron-catalyzed synthesis of diaryl sulfones and unsymmetrical triarylmethanes (**16b**)



In 2011, Lee and coworkers reported a $B(C_6F_5)_3$ catalyzed approach to access the diaryl amidosulfones (**16a)** in moderate to excellent yields, through the treatment of activated arenes and heteroarenes (**17b)** with *α*-amido sulfones (**20)** (Scheme 10). They have also synthesized indole containing triarylmethanes (**21b)** by the addition of indole **21a** to the isolated diaryl amidosulfones (**16a)** in moderate yields.[24e]

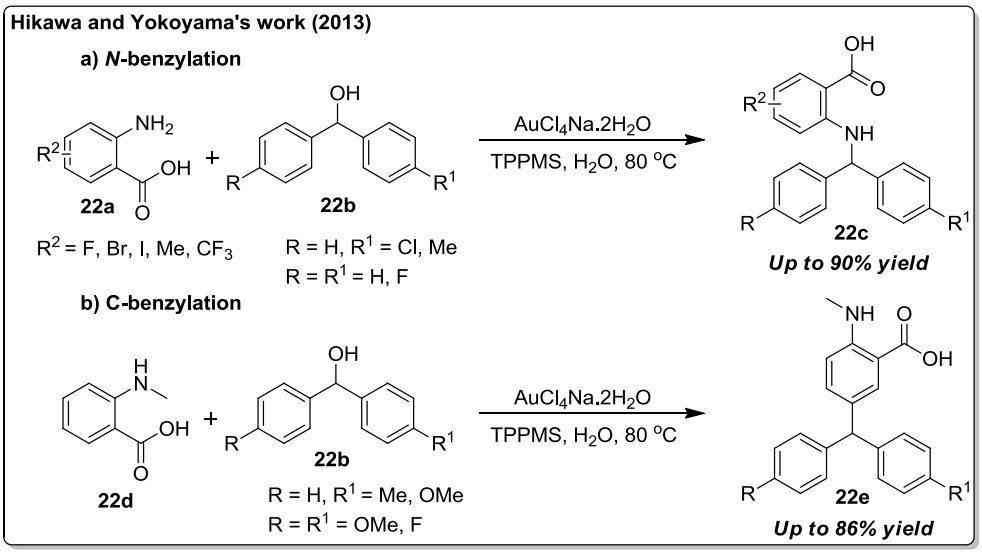
Scheme 10: $B(C_6F_5)_3$ catalyzed synthesis of diarylsulfones and unsymmetrical triarylmethanes (**21b**)



Recently, Hikawa's and Yokoyama's group developed a water-soluble gold-catalyzed chemoselective *N*-benzylation of anthranilic acids (**22a)** with benzhydrols **(22b)** to obtain the

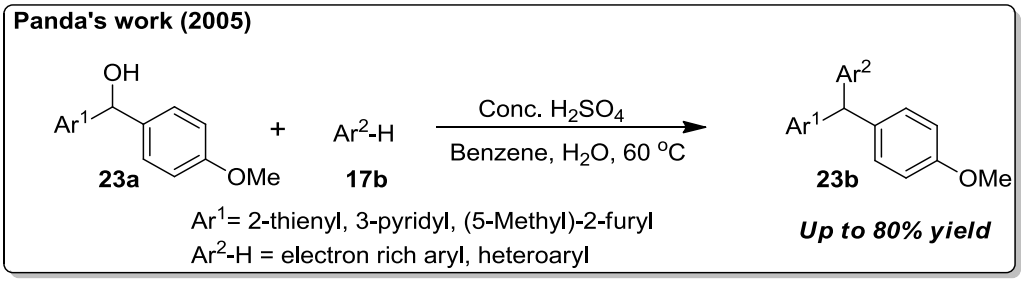
N-dibenzylated products (**22c)** at 80 °C (Scheme 11). Surprisingly, the benzhydryl alcohols, having electron donating as well as electron withdrawing substituents, gave the C-benzylated (triarylmethanes) products using *N*-methyl anthranilic acid (**22d)** under the same reaction conditions.[24f]

Scheme 11: Gold-catalyzed synthesis of unsymmetrical triarylmethanes (**22c** & **22e**)



Furthermore, Brønsted acid catalyzed approaches also appeared in the literature. Panda's group in 2005 developed a novel approach towards the synthesis of unsymmetrical triarylmethanes. The treatment of electron-rich aromatic and heteroaromatic nucleophiles (**17b**) with heteroarylcarbinols (**23a**) in the presence of sulphuric acid afforded the expected products (**23b**) in moderate to good yields (Scheme 12).[25a]

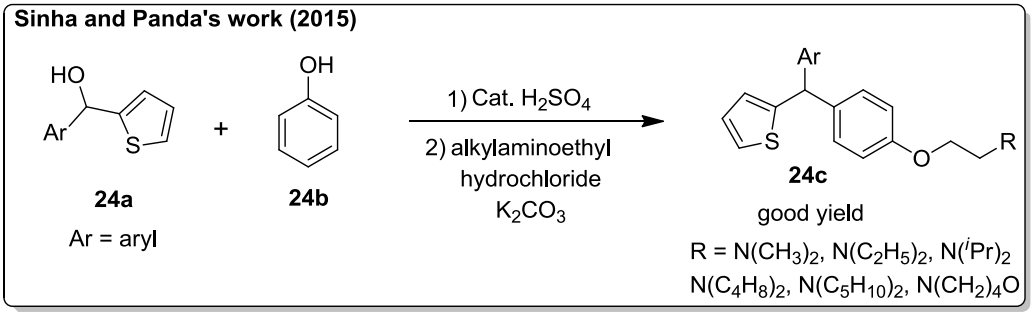
Scheme 12: Brønsted acid catalyzed synthesis of unsymmetrical triarylmethanes



Very recently, the same group developed H_2SO_4 catalyzed synthesis of thiophene-based triarylmethanes (**24c**) by the reaction of phenol (**24b**) with thiophene-based benzhydrol (**24a**) followed by alkylation of phenol with dialkylaminoethyl chloride in the presence of

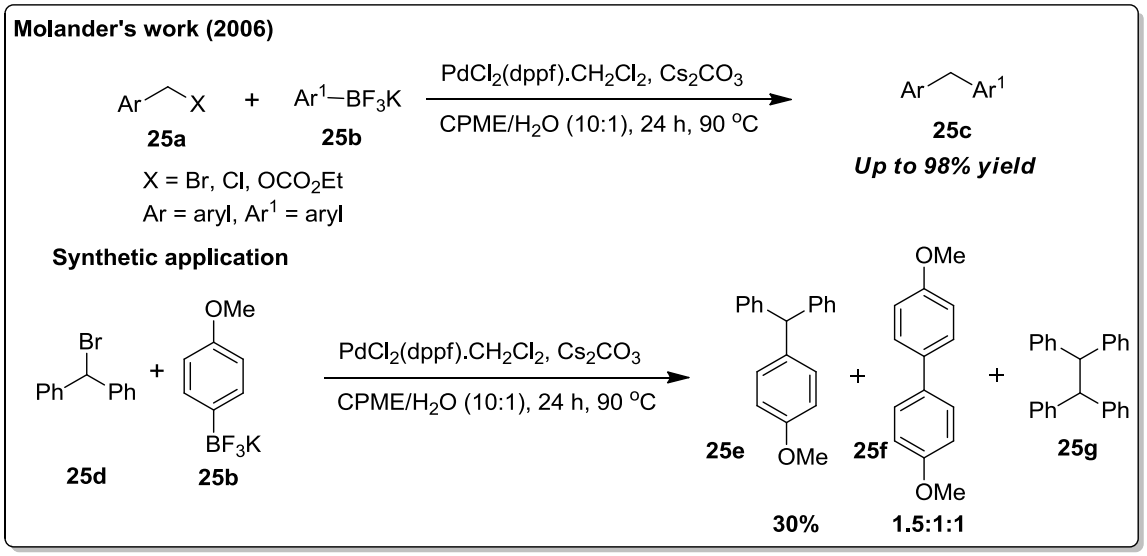
K_2CO_3. The thiophene-based triarylmethanes (**24c**) were found to be useful in the treatment of *Mycobacterium tuberculosis* (Scheme 13).[25b]

Scheme 13: Brønsted acid catalyzed synthesis of thiophene-based triarylmethanes (**24c**)



Although the Friedel-Crafts approach provides a wide substrate scope, it suffers from the generation of undesired regioisomers and is selective only for electron rich arenes or heteroarenes. Apart from the above mentioned Lewis and Brønsted acid catalyzed approaches, a transition metal catalyzed approach has also been developed for the synthesis of unsymmetrical triarylmethanes (**16b**). This approach provides an alternative way to overcome the drawbacks of the Friedel-Crafts approach. The cross-coupling approach for the synthesis of unsymmetrical triarylmethanes (**16b**) became fascinating after the seminal work by Molander's group (Scheme 14). They have described the Pd-catalyzed cross-coupling approach for the synthesis of diarylmethanes (**25c**) by treatment of potassium *p*-MeO-phenyltrifluoroborates (**25b**) with benzyl halides (**25a**).[26] Furthermore, the reaction between

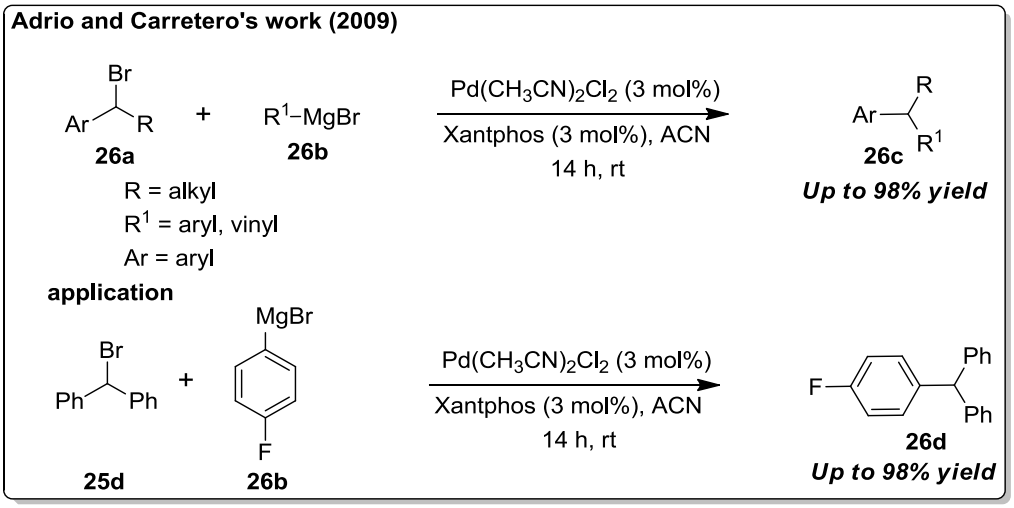
Scheme 14: The synthesis of di- and tri-arylmethanes using organoboron reagents



(bromomethylene) dibenzene (**25d**) and potassium *p*-MeO-phenyltrifluoroborates (**25b**) afforded the symmetrical triarylmethane (**25e**) in 30% yield only along with the dimerized product of diphenyl bromomethane (**25g**) (Scheme 14).[26]

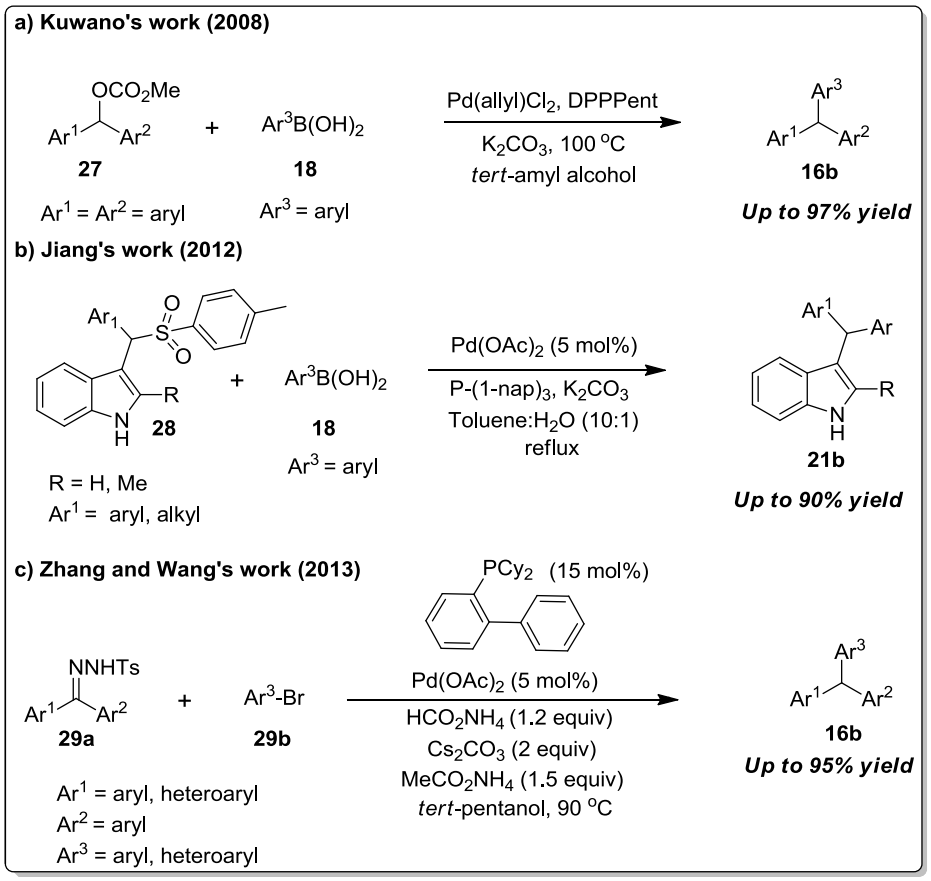
In 2009, Adrio's and Carretero's group reported a Pd-catalyzed protocol using secondary benzylic bromides (**26a**) with aryl and alkenyl Grignard reagents (**26b**) for the synthesis of cross-coupled products (**26c**) in good to excellent yields. Extension of this methodology to other secondary benzyl halides have also been investigated. The treatment of diphenyl bromomethane (**25d**) with Grignard reagent afforded the fluoro substituted triarylmethane (**26d**) in excellent yield in the presence of $Pd(CH_3CN)_2Cl_2$ and Xantphos as a ligand (Scheme 15).[27]

Scheme 15: Pd-catalyzed synthesis of symmetrical and unsymmetrical triarylmethanes



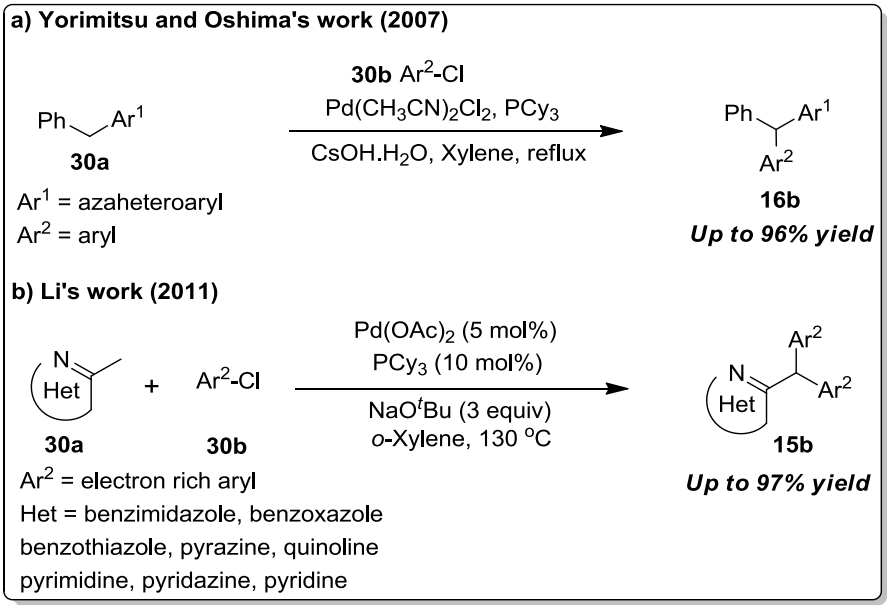
Kuwano and coworkers developed a successful method for the synthesis of unsymmetrical triarylmethanes (**16b**) by using diarylmethyl carbonates (**27**) and arylboronic acids (**18**) *via* Suzuki-Miyaura cross-coupling approach (a, Scheme 16).[28] Jiang's group also reported Pd-catalyzed synthesis of indole-containing triarylmethanes (**21b**) from vinylogous imine precursors (**28**) and arylboronic acids (**18**) in moderate to excellent yields (b, Scheme 16).[29] Apart from the methods developed so far, an interesting approach has been disclosed: a Pd-catalyzed reductive cross-coupling reaction of *N*-tosylhydrazones (**29a**) as a diaryl surrogates with aryl bromides (**29b**) to afford a variety of triarylmethanes (**16b**) (c, Scheme 16).[30]

Scheme 16: Pd-catalyzed synthesis of unsymmetrical triarylmethanes (**16b**)



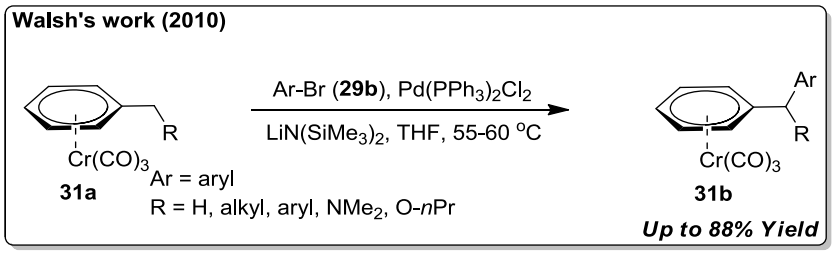
Although Suzuki-Miyaura cross-coupling approach is well explored in the field of organic chemistry, the synthesis of the organometallic reagents and prefunctionlization of the reagents is necessary. To address these issues, a transition metal catalyzed C-H activation approach has been developed.[31] The first report for the synthesis of triarylmethanes by applying C-H activation protocol was carried out by Yorimitsu and Oshima's group in 2007.[32] In this protocol, they have carried out Pd-catalyzed direct arylation of aryl(azaaryl) methanes **30a** (diaryl surrogates) with aryl halides (**30b**), and symmetric as well as unsymmetric triarylmethanes (**16b**) were obtained in excellent yields (a, Scheme 17). Another similar approach has been developed by Li's group: a Pd-catalyzed C-H activation of (2-azaaryl)methanes (**30a**) and successive diarylation with arylchlorides (**30b**) for the synthesis of symmetrical triarylmethanes (**15b**). Variety of heteroaromatic compounds were subjected under the reaction condition and obtained the heteroaromatic containing symmetrical triarylmethanes in good to excellent yields (b, Scheme 17).[33]

Scheme 17: Pd-catalyzed synthesis of symmetrical as well as unsymmetrical triarylmethanes



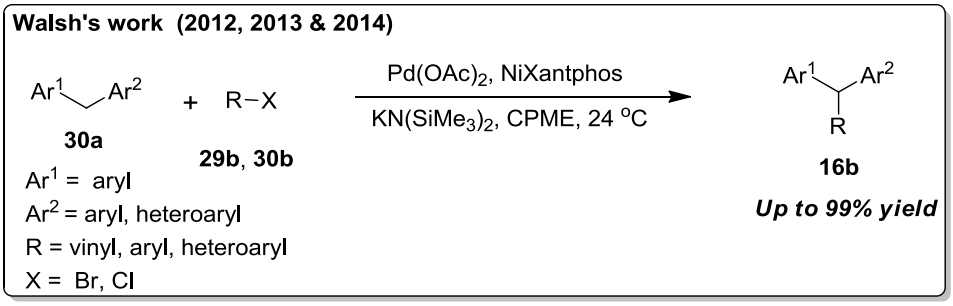
Walsh's group reported the synthesis of di-, tri- and poly-arylated methanes (**31b**) under Pd-catalyzed cross-coupling approach using chromium-activated benzylic derivatives (**31a**) and aryl halides (**29b**) *via* C-H activation strategy (Scheme 18). The products were obtained in moderate to excellent yields.[34]

Scheme 18: Pd-catalyzed synthesis of di- and tri-arylmethanes (**31b**)



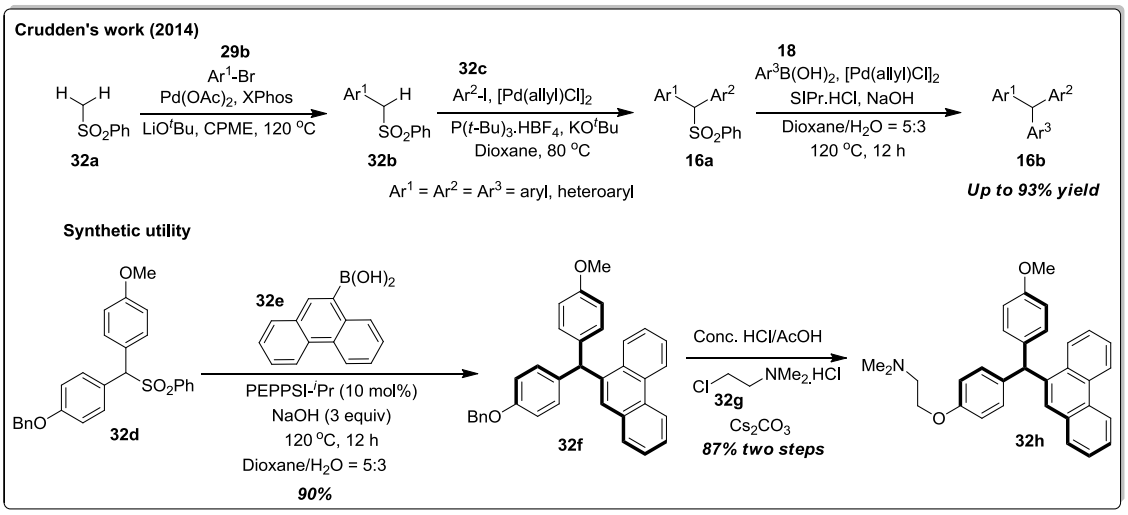
In 2012, a couple of papers from the Walsh's group appeared in the literature describing the Pd-catalyzed cross-coupling approach for the direct arylation of diarylmethane **30a** through C-H activation approach to afford triarylmethanes (**16b**) (Scheme 19).[35] Walsh and coworkers also studied the influence of additives on Pd-catalyzed deprotonative cross-coupling approach (DCCP) in the synthesis of triarylmethanes.[35b]

Scheme 19: Pd-catalyzed synthesis of triarylmethanes



Recently, Crudden and coworkers developed a novel and straightforward sequential arylation approach for the synthesis of unsymmetrical triarylmethanes (**16b)** using readily available (methylsulfonyl) benzene **32a** as a methyl surrogate (Scheme 20).

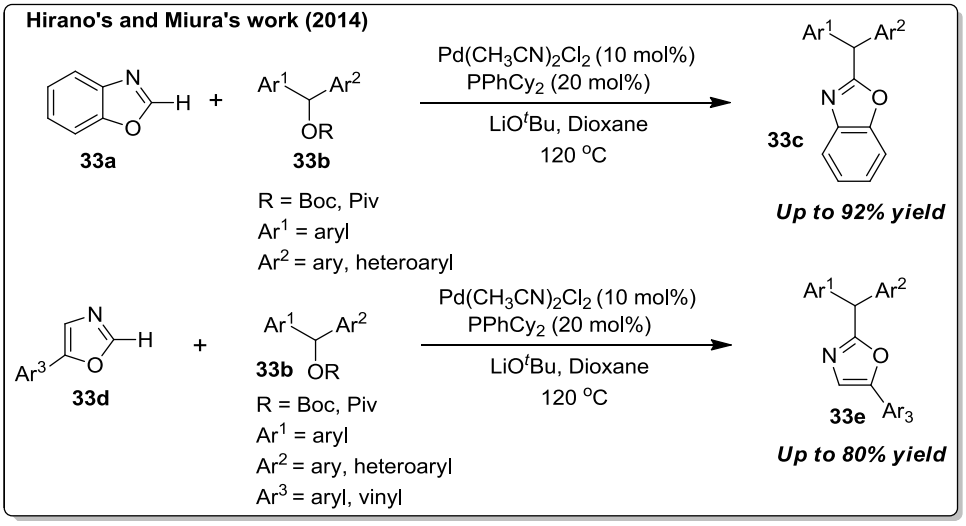
Scheme 20: Pd-catalyzed synthesis of triarylmethanes (**16b**) and its application (**32h**)



They have carried out the Pd-catalyzed C-H monoarylation of methyl phenyl sulfone **32a** with arylbromides (**29b**) and then the second arylation with aryliodides (**32c**) followed by desulfonylative arylation with aryl boronic acids (**18**) to access unsymmetrical triarylmethanes (**16b**) in moderate to excellent yields.[36] Also, they have demonstrated the synthetic application of this methodology through the development of a concise method for the synthesis of anti-breast cancer agent **32h** in five steps. Treatment of phenanthrene boronic acid (**32e**) with diaryl sulfones (**32d**) in the presence of PEPPSI-^{i}Pr afforded a triarylmethane (**32f**) in excellent yield (90%), which followed by deprotection of the benzyl group and subsequent alkylation yielded the anticancer agent **32h** in 36% overall yield (Scheme 20).

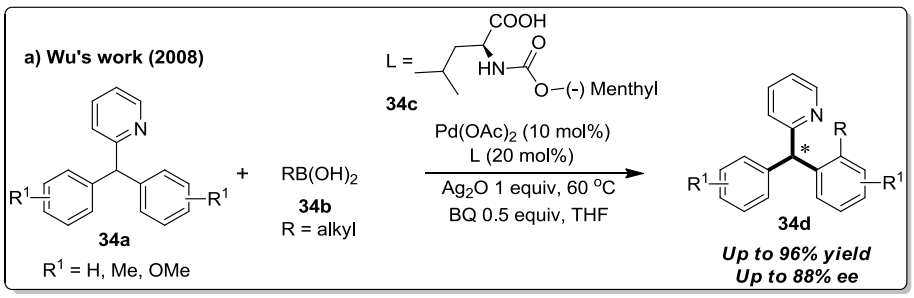
A Pd-catalyzed cross-coupling of dibenzyl carbonates or pivalates (**33b**) (C-O) with benzoxazole (**33a**) and oxazole (**33d**) moieties (C-H) to benzoxazole and oxazole-containing unsymmetrical triarylmethanes (**33c**) & (**33e**) have been reported by Hirano and Miura (Scheme 21).[37]

Scheme 21: Pd-catalyzed cross-coupling approach for the synthesis of triarylmethanes



The transition metal catalyzed synthesis of enantiopure triarylmethanes also became a fascinating research area due to its application in medicinal chemistry. Wu and coworkers developed a Pd-catalyzed efficient protocol for the synthesis of enantiomerically enriched triarylmethane derivatives (**34d**) from its prochiral triarylmethanes **34a**. The chirality has been induced in the product by using monoprotected α-amino acids (**34c**) as a chiral ligand (Scheme 22).[38]

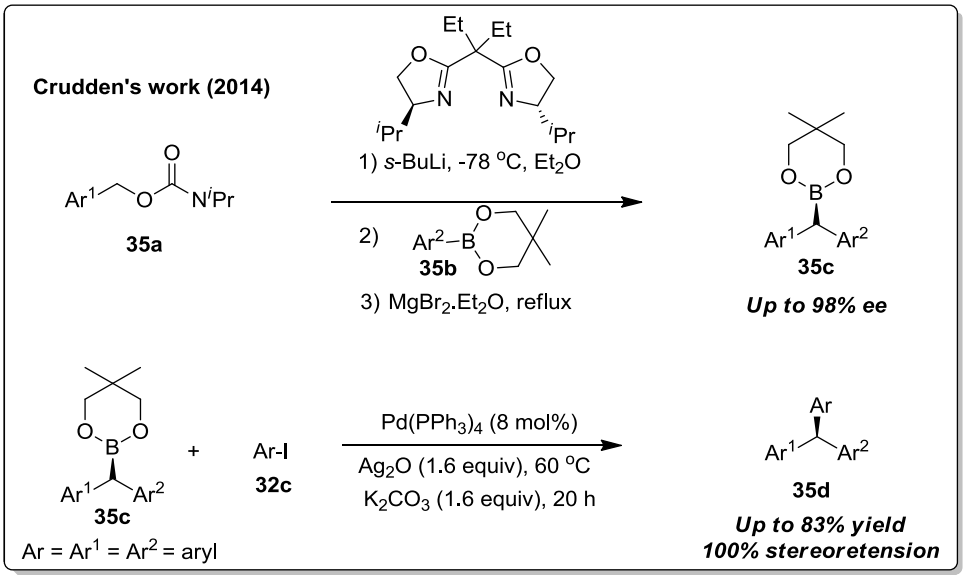
Scheme 22: The Pd-catalyzed synthesis of enantioenriched triarylmethanes (**34c**)



Very recently, Crudden's group developed a Pd-catalyzed facile approach to access the enantiomerically pure dibenzylic boronates (**35c**) with good to excellent enantiomeric

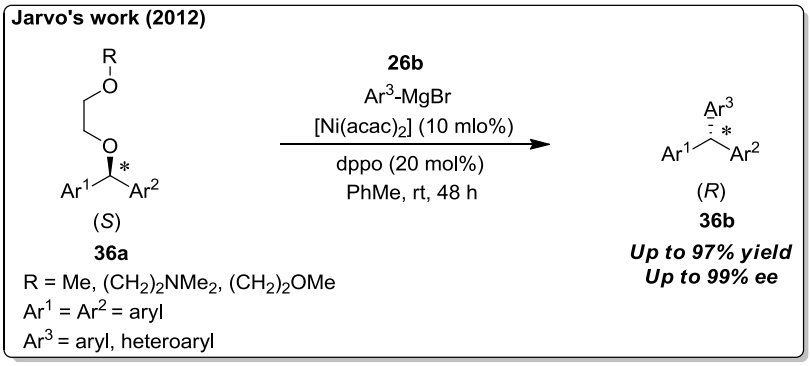
excess. These compounds have been utilized for the synthesis of chiral triarylmethanes **35d** with aryl iodides (**32c)** under Pd-catalyzed cross coupling approach. The enantiopure triarylmethanes (**35d)** were obtained with complete stereoretention (Scheme 23).[39]

Scheme 23: The Pd-catalyzed approach towards the synthesis of chiral triarylmethanes (**35d**)



In 2012, Jarvo and coworkers reported the Nickel-catalyzed stereospecific synthesis of triarylmethanes with excellent enantiomeric excess (ee) (Scheme 24).

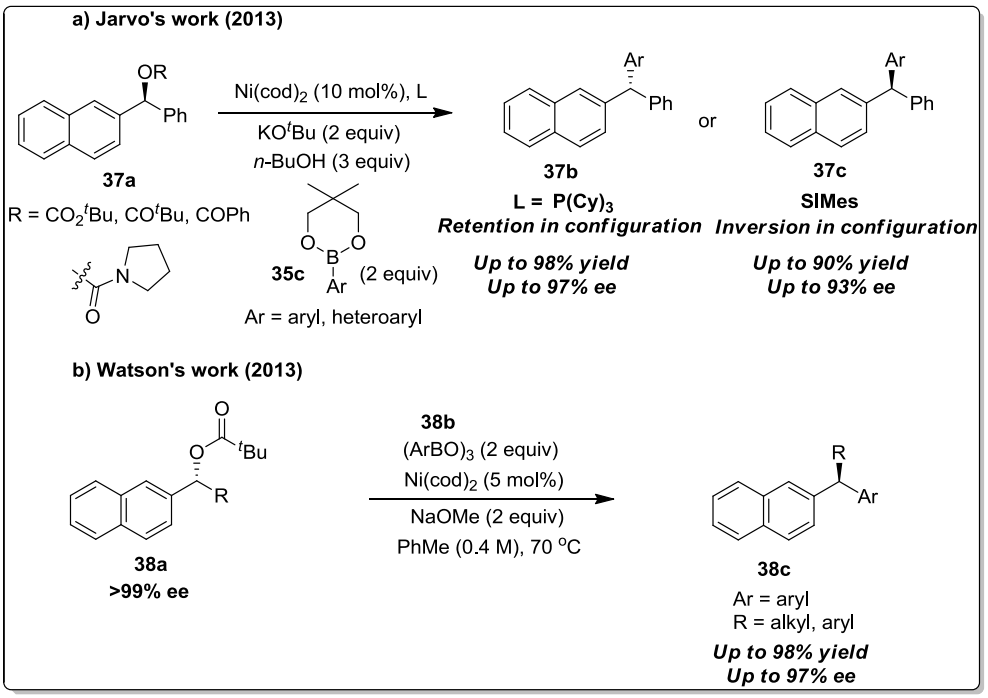
Scheme 24: Ni-catalyzed synthesis of enantiopure triarylmethanes using Grignard reagents



The treatment of enantiopure dibenzylic ethers (**36a**) with aryl Grignard reagents (**26b**) in the presence of Ni-catalyst gave the enantioenriched triarylmethane derivatives (**36b**) in good to excellent yields. They have demonstrated the synthetic application of this method by adopting a short route for the synthesis of anti-breast cancer agent (**32h**).[40]

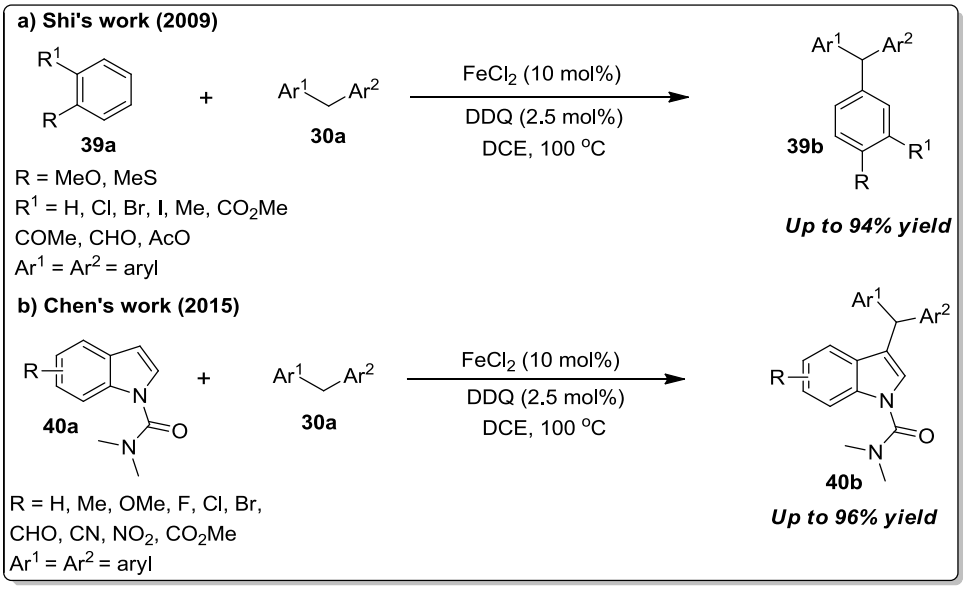
In 2013, another interesting approach was developed by Jarvo's group towards the synthesis of enantiopure triarylmethanes through Ni-catalyzed stereospecific cross-coupling of chiral diaryl carbamates or carbonates (**37a**) with arylboronic esters (**35c**) with inversion (**37b**) or retention (**37c**) of configuration (a, Scheme 25). This retention or inversion solely depends on the nature of the ligands. The use of the phosphine (PCy_3) ligand afforded retention of configuration (**37c**), whereas the NHC based ligand (SIMes) resulted in an inversion of configuration (**37b**). Therefore, it is possible to get both enantiomers from a single enantiomer of starting synthons (a, Scheme 25).[41] Watson and coworkers developed another protocol through Ni-catalyzed cross-coupling reaction of enantiopure secondary benzylic pivalates (**38a**) with arylboronates (**38b**) for the synthesis of enantiomerically enriched library of diarylmethane and triarylmethanes (**38c**) (b, Scheme 25).[42]

Scheme 25: Ni-catalyzed synthesis of enantiopure triarylmethanes



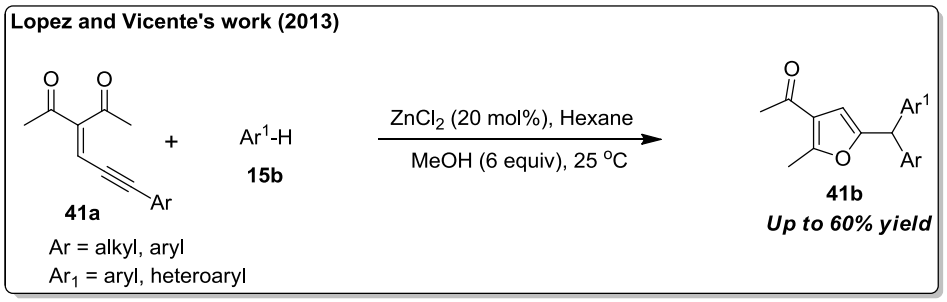
Cross Dehydrogenative Coupling (CDC) approaches[43] also have a potential to synthesize triarylmethanes. This has been proved separately by the groups of Shi and Chen (Scheme 31). In 2009, Shi and coworkers described the formation of triarylmethanes (**39b**) by the treatment of arenes (**39a**) with diarylmethanes (**30a**) under iron-catalyzed oxidative cross dehydrogenative coupling approach (a, Scheme 26).[44] Very recently, the same catalytic system has been applied for the synthesis of indole-containing triarylmethanes (**40b**) by utilizing indole *N*-dimethylcarboxamide (**40a**) and diarylmethanes (**30a**) (b, Scheme 26).[45]

Scheme 26: CDC approaches for the synthesis of triarylmethanes



Lopez and Vicente group developed a Zn-catalyzed mild and efficient route to access functionalized furan derivatives and triarylmethanes (**41b**) (Scheme 27).[46] The treatment of electron rich arenes or heteroarenes (**15b**) with diketoenynone (**41a**) in the presence of Zinc afforded the unsymmetrical triarymethanes (**41b**) in good to moderate yields.

Scheme 27: Different approaches for the synthesis of triarylmethanes (**41b**)

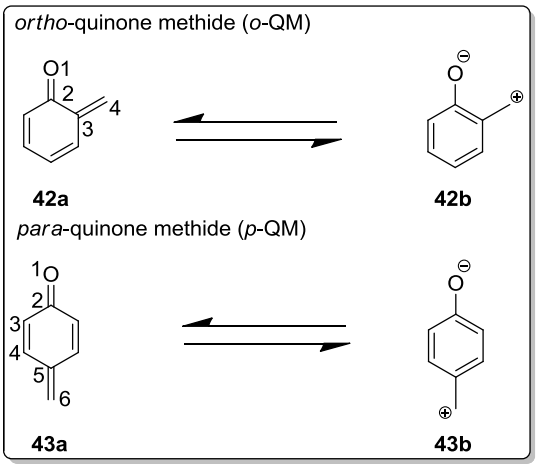


1.4) Literature reports on *para*-Quinone Methides (*p*-QMs)

Quinone methides (QMs) are considered as highly reactive intermediates and an excellent Michael acceptors when compared to the traditional acceptors (enones) in synthetic organic chemistry.[47] These are of two types, *ortho*-quinone methides (*o*-QMs) **42a** and *para*-quinone methides (*p*-QMs) **43a**. Although these compounds are neutral in nature, they can also exist in their resonance stabilized forms **42b** & **43b** respectively. The electron donation

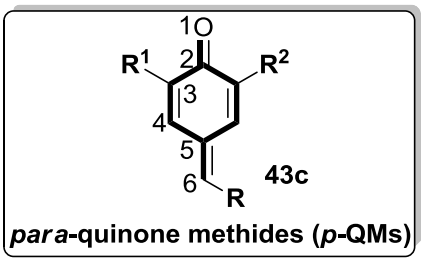
from oxygen to the benzylic carbocation plays a vital role in the kinetic stability as well as enhancement of the reactivity of the compound (Fig. 3).[48]

Figure 3: Types of quinone methides (**42** & **43**)



The *p*-QM scaffold is present in a diverse range of active pharmaceutical ingredients (API) and natural products.[49] The 4-methylene-2,5-cyclohexadienone, a simple quinone methide is highly unstable and difficult to isolate. To increase the stability of *p*-QMs, the C-3 carbon (adjacent to the carbonyl carbon atom) or C-6 carbon (methylene carbon) should be substituted with a bulky or aryl groups respectively. A substituted *p*-QM **43c** is a highly stable intermediate and prefers to undergo 1,6-conjugate addition (Figure 4). The *para*-quinone methides are important not only in synthetic organic chemistry but also in physical organic chemistry.[50]

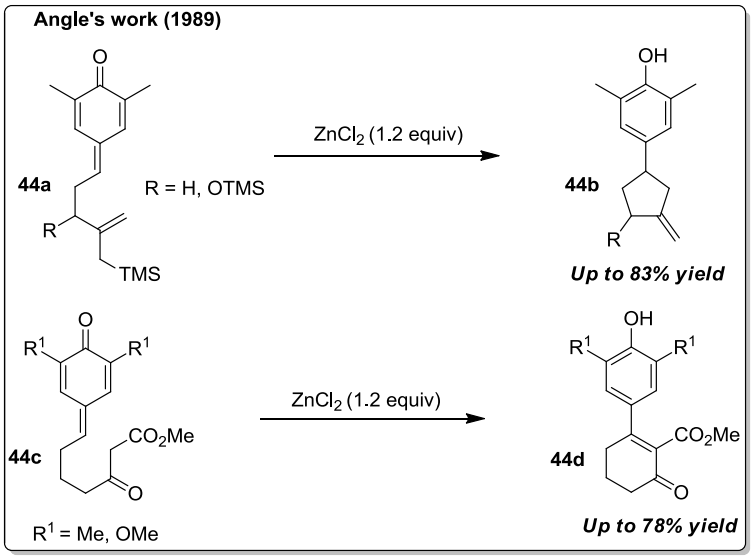
Figure 4: A highly reactive intermediate (*p*-QMs)



Few of the *para*-quinone methide reactions are described below. Angle and coworkers reported a few approaches using *p*-QMs to access the corresponding cyclized products (Scheme 28). The initial report by this group describes the zinc mediated synthesis of

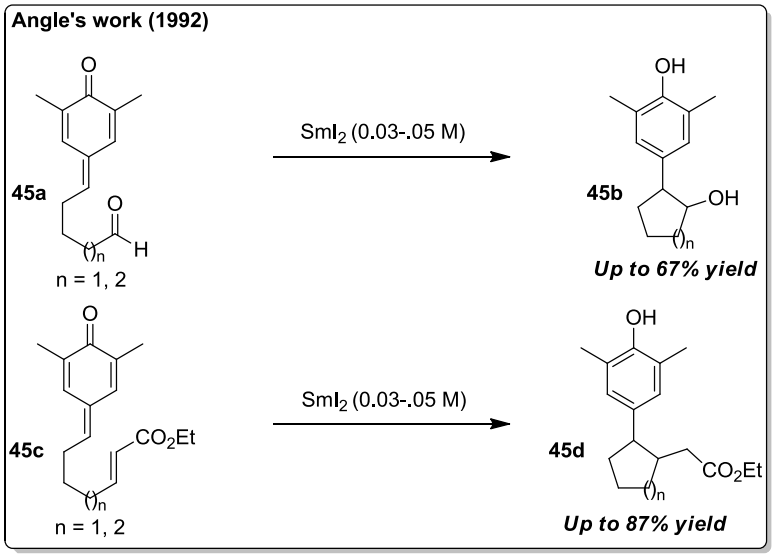
annulated products **44b** & **44d** by intramolecular annulation of allylsilanes (**44a**) or *β*-keto ester (**44c**) to *para*-quinone methide.[51]

Scheme 28: Zn-mediated cyclization reaction



The same group also developed another approach *via* SmI_2 mediated intramolecular reductive annulation of *p*-QMs to prepare the corresponding cyclized products **45b** & **45d** in moderate to good yields (Scheme 29).[52]

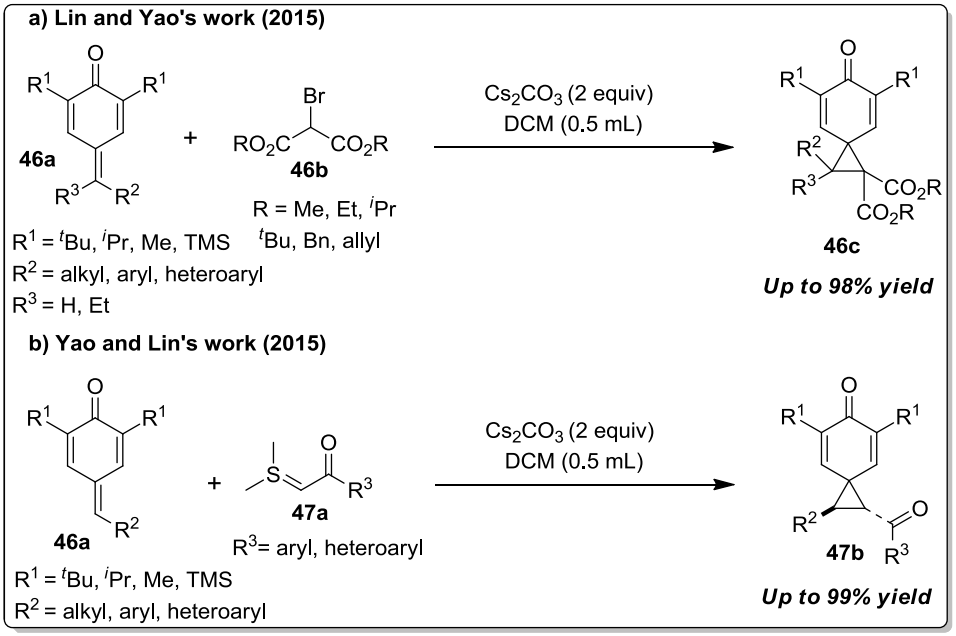
Scheme 29: Reductive cyclization with SmI_2



Very recently, Lin and Yao and coworkers developed two approaches for the synthesis of spiro-octadien-6-one. The method describes the 1,6-conjugate addition of

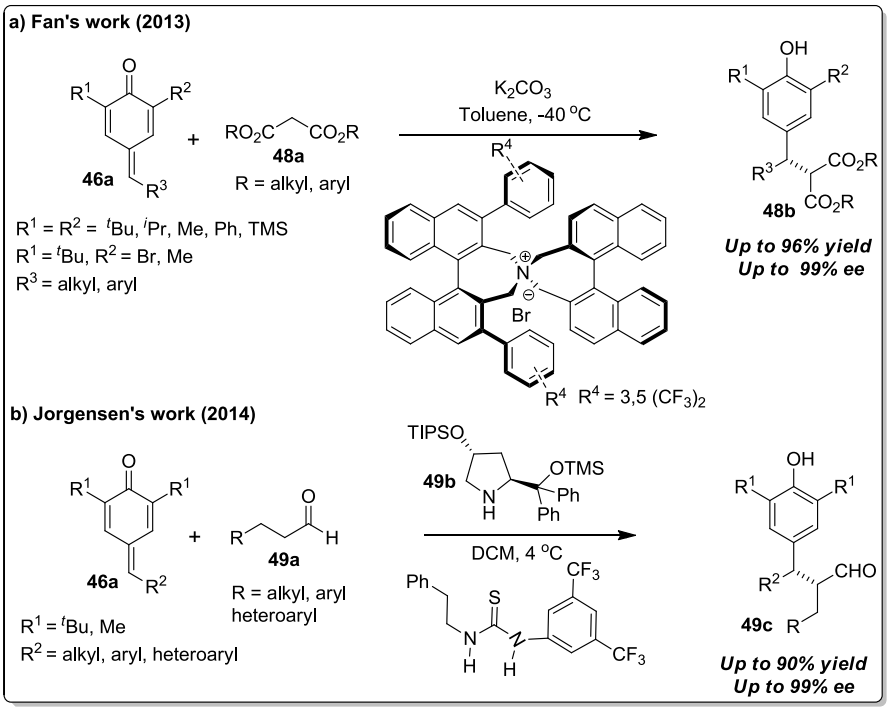
activated bromide (**46b**) to *p*-QMs (**46a**) followed by dearomatization to access the tetrasubstituted spiro compounds (**46c**) (a, Scheme 30).[53a] The same group developed another facile approach utilizing sulfur ylide (**47a**) and *p*-QMs (**46a**), and obtained the spiro derivatives (**47b**) in excellent yields (b, Scheme 30).[53b]

Scheme 30: Synthesis of spiro compounds (**46c** & **47b**) from *p*-QMs (**46a**)



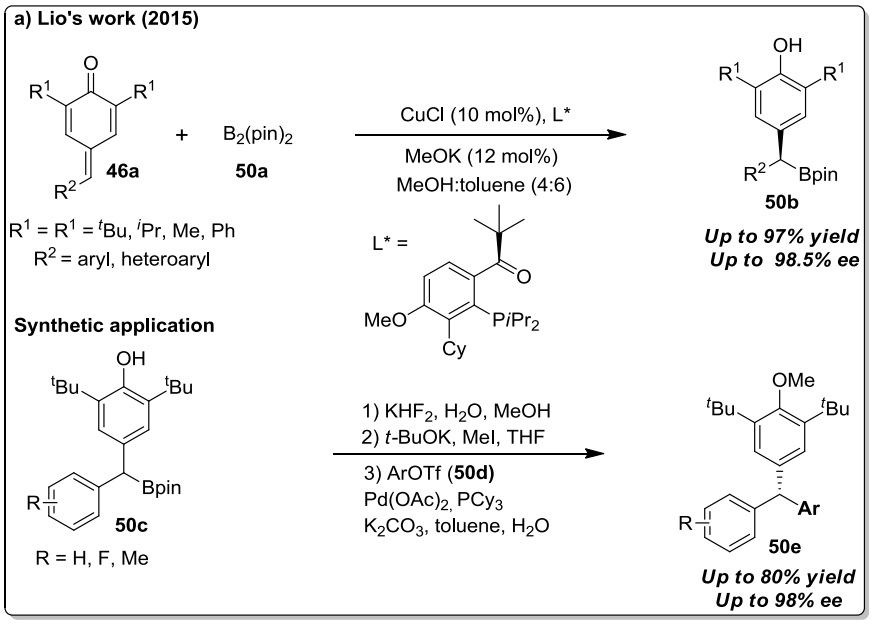
Despite the fact that the chemistry of *o*-quinone methide is very well explored in asymmetric catalysis,[54] only a few stereospecific reports are available for *para*-quinone methides. Recently, Fan and coworkers reported the first approach for the synthesis of enantiopure diarylmethanes **(48b**) through the 1,6-conjugate addition of malonates (**48a**) to *para*-quinone methides (**46a**) using chiral transfer catalysts. The prominent features of this methodology are broad functional group tolerance, and the products were obtained in excellent yields with excellent enantiomeric excess (a, Scheme 31).[55a] Recently, an organocatalytic method has been developed for the stereospecific synthesis of α-alkylated aldehydes (**49c**) with the generation of two adjacent chiral centers using *p*-QMs (**46a**) and aliphatic aldehydes (**49a**). The α-diarylmethine-substituted aldehydes (**49c**) were obtained in good to excellent yields with high diastereoselectivity and enantioselectivity by the use of chiral secondary amine (**49b**) (b, Scheme 31).[55b]

Scheme 31: Synthesis of enantiomerically enriched diarylmethanes (**48b** & **49c**)



The first copper catalyzed enantioenriched synthesis of diarylmethyl boronates (**50b**) has been developed by Liao's group (Scheme 32).[55c] The reaction with bis(pinacolato)diboron (**50a**) and *p*-QMs (**46a**) *via* 1,6-conjugate addition strategy leads to the borylation products (**50b**) in the presence of Cu-catalyst and a chiral ligand.

Scheme 32: Cu-catalyzed enantioselective synthesis of diarylmethylboronates (**50b**) and its application (**50e**)



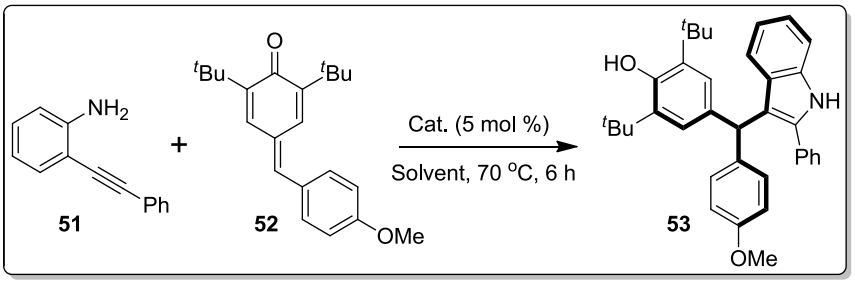
The products have been obtained in very good yields with excellent enantioselectivities. Furthermore, the borylated products were used in the cross-coupling reaction and enantiopure triarylmethanes (**50e**) were obtained in excellent yield without loss of enantioselectivity.

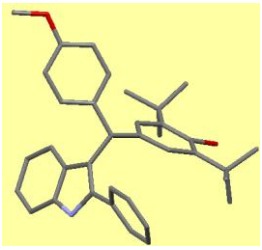
1.5) Results and Discussions

Astoundingly, palladium-catalyzed one-pot annulation of *o*-alkynyl anilines followed by electrophilic trapping with *para*-quinone methides (*p*-QMs) has not been reported to date. Herein we disclose, our findings which explain a highly efficient and atom-economical palladium-catalyzed one-pot annulation of *o*-alkynyl anilines (**51**) followed by 1,6-conjugate addition to *para*-quinone methides (*p*-QMs) (**52**) to access valuable unsymmetrical diarylindolylmethanes (**53**) under relatively mild conditions (Scheme 33).

The optimization studies were carried out using readily available *o*-alkynyl aniline (**51**) and *para*-quinone methide (*p*-QM) (**52**) with different palladium catalysts (Table 1). Our initial studies using catalyst $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ failed to give the expected product in dichloromethane (DCE) at room temperature (entry 1-3, Table 1). Extensive optimization experiments revealed that $Pd(OAc)_2$ and $Pd(TFA)_2$ were found to be effective for this transformation at room temperature and afforded the desired product (**53**) in 20% and 45% yields respectively (entries 4 & 5). Surprisingly, when $PdCl_2$ (5 mol %) was used as a catalyst in DCE, the expected product (**53)** was obtained in 80% yield after 36 h at room temperature (entry 6, Table 1). When the same reaction was carried out at 70 ^oC, **53** was obtained in 99% yield within 6 h (entry 7). Further elaboration of optimization was performed in other solvents at 70 ^oC. But in all those cases (entries 8–10), the yield of **53** was found to be inferior when compared to entry 7. To our great delight, decreasing the catalyst loading (2 mol %) did not decrease the yield (93%) of product (**53**) considerably, but the reaction took longer time (36 h) to complete (entry 11). On the other hand, no desired product was observed in the absence of palladium catalyst at room temperature (entry 12). The structure of **53** was unambiguously confirmed by NMR, HRMS as well as X-ray analysis.

Table 1: Optimization studies[a]



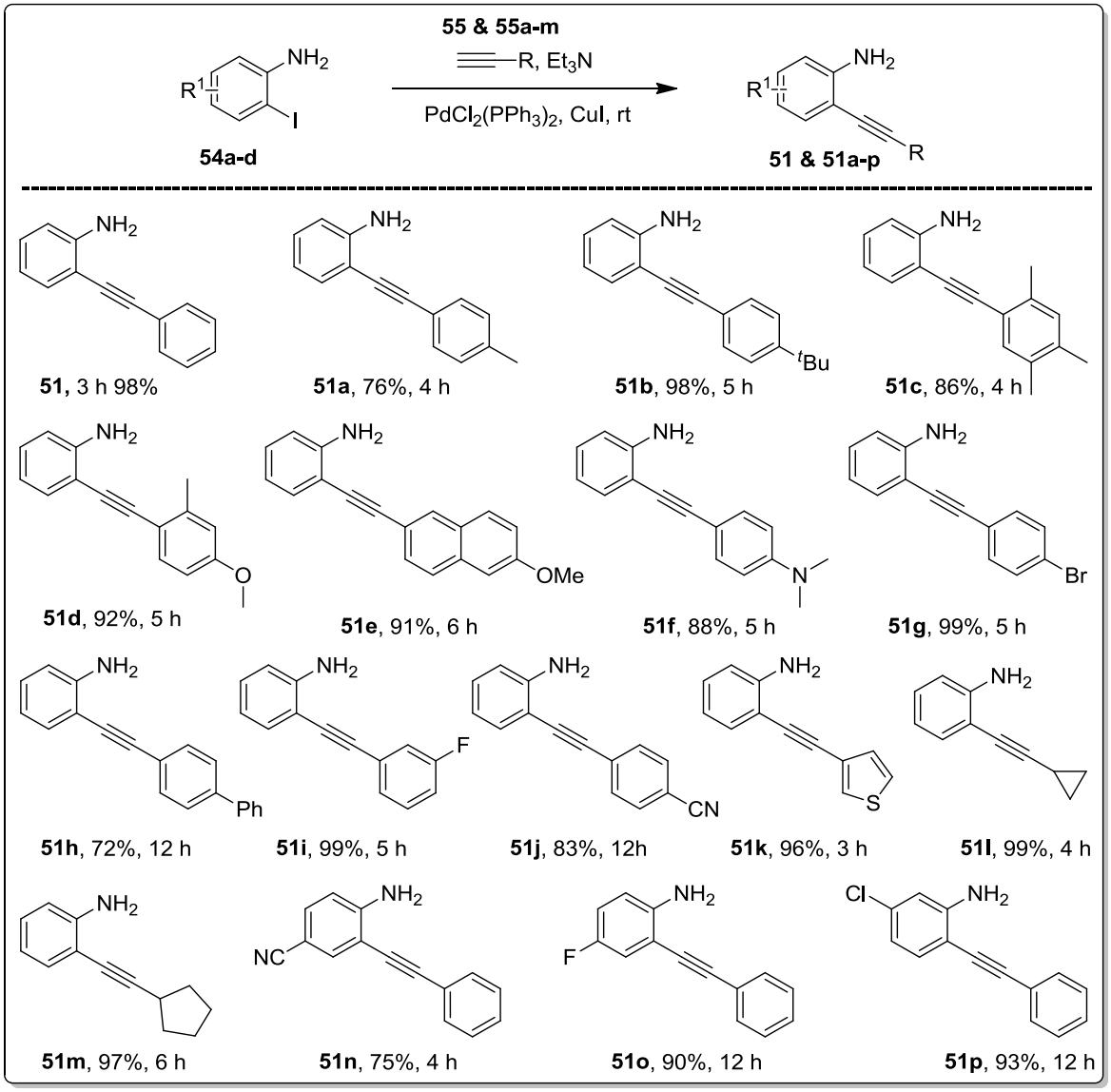


Entry	Catalyst	Solvent	*t* [°C]	Time[h]	Yield[b] [%]
1	$Pd(PPh_3)_4$	DCE	rt	36	0
2	$PdCl_2(PPh_3)_2$	DCE	rt	36	0
3	$Pd_2(dba)_3$	DCE	rt	32	0
4	$Pd(OAc)_2$	DCE	rt	36	20
5	$Pd(TFA)_2$	DCE	rt	36	45
6	$PdCl_2$	DCE	rt	36	80
7	**$PdCl_2$**	**DCE**	**70**	**6**	**99**
8	$PdCl_2$	MeCN	70	6	80
9	$PdCl_2$	THF	70	6	92
10	$PdCl_2$	PhMe	70	6	94
11[c]	$PdCl_2$	DCE	70	36	93
12	-	DCE	rt	36	0

[a]Reaction conditions: 0.04 M solution of **51** in solvent. 5 mol % of Pd catalyst was used. Use of 1.2 equiv of 8 was found to be optimal. [b]Isolated yield. [c]2 mol % of $PdCl_2$ was used. rt = 27–30 °C.

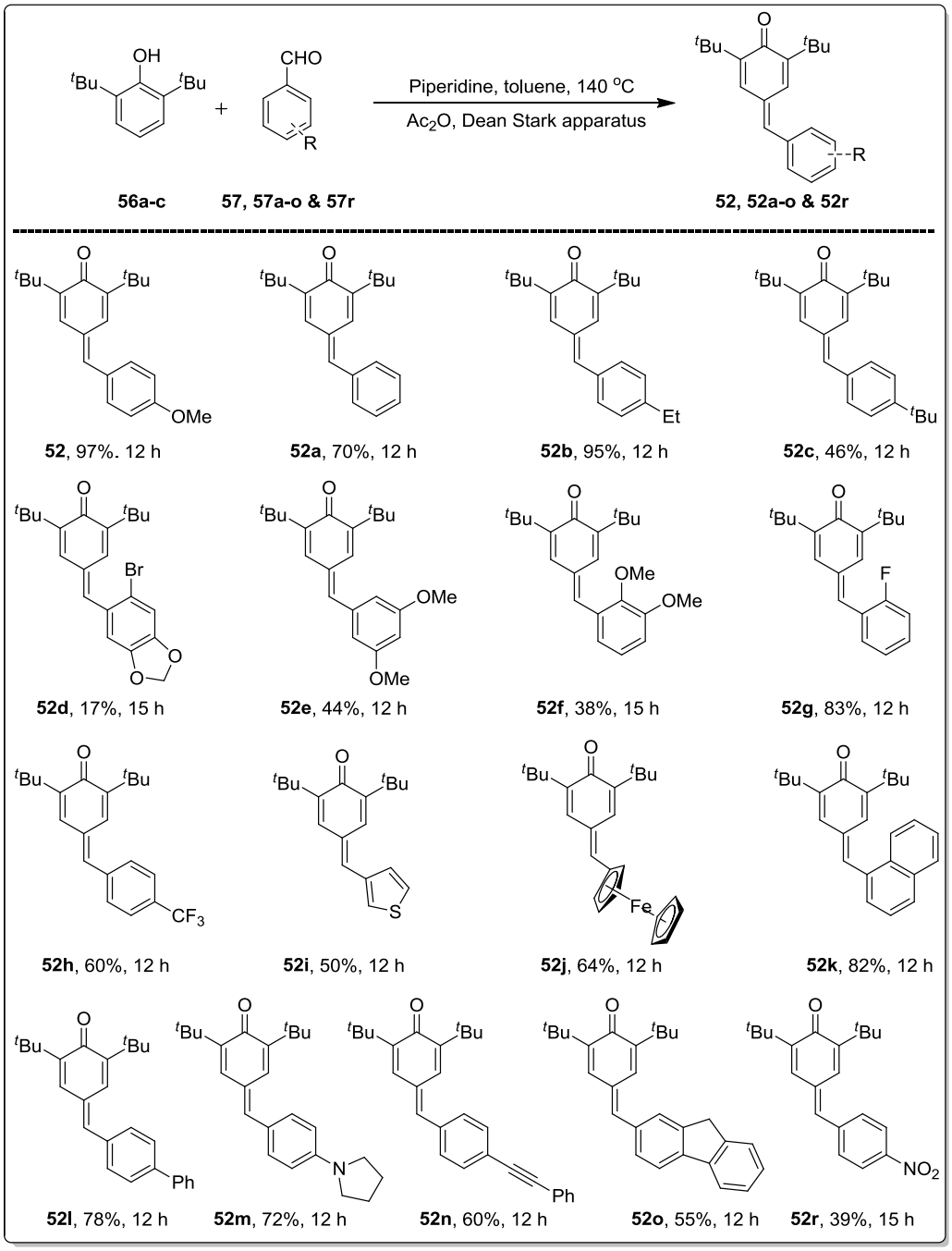
The reaction condition has been optimized, and then we turn our attention towards the synthesis of a variety of *o*-alkynyl anilines (**51** & **51a-p**) (Scheme 33). The *o*-alkynyl anilines (**51** & **51a-p**) were synthesized by Sonogashira coupling between a wide range of *o*-iodo anilines (**54a-d**) and terminal alkynes (**55 & 55a-m**) following a literature procedure.[13b]

Scheme 33: Synthesis of *o*-alkynyl anilines (**51** & **51a-p**)



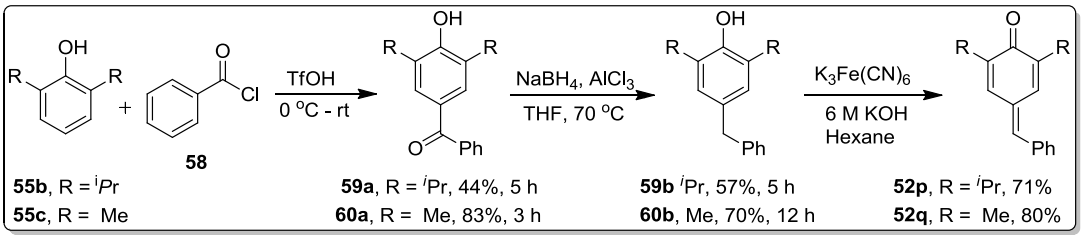
The *para*-quinone methides (**52, 52a-o** & **52r)** were synthesized by refluxing 2,6-disubstituted phenol (**56a-c**), various aromatic aldehydes (**57**, **57a-o** & **57r**) and piperidine in a Dean-Stark apparatus following a literature procedure (Scheme 34).[55a]

Scheme 34: The synthesis of *para*-quinone methides (**52, 52a-o** & **52r)**



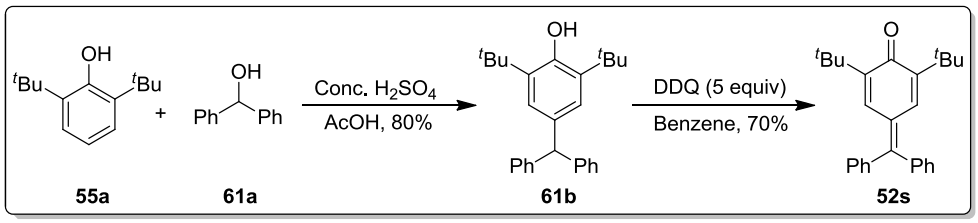
Synthesis of 2,6 diisopropyl (**52p**) and 2,6 dimethyl (**52q**) *p*-QMs were performed using 2,6 diisopropyl (**55b**) and 2,6 dimethylphenols (**55c**). The 4-acylated phenols (**59a** & **60a**) were obtained by the treatment of phenols (**55b** & **55c**) with benzoyl chloride (**58**) in trifluoromethane sulphonic acid (TfOH) as a solvent at 0 °C.[56] The complete reduction of compounds **59a** & **60a** were carried out using sodium borohydride and aluminum trichloride,[57] which followed by oxidation with potassium ferricyanide[58] yielded the expected quinone methides (**52p** & **52q**) in 71 and 80% yields respectively (Scheme 35).

Scheme 35: The synthesis of other *p*-QMs (**52p** & **52q**)



The fuchsone derivative (**52s)** was synthesized in two straightforward steps by following a literature procedure.[59] 2,6 Di-*tert*-butyl phenol (**55a**) treated with dibenzylalcohol (**61a**) in the presence of catalytic amount of conc. H_2SO_4 afforded the triarylmethane (**61b**) in 80% yield. The oxidation of triarylmethane (**61b**) was carried out using DDQ (5 equiv) and fuchsone (**52s**) was achieved in 70% yield (Scheme 36).

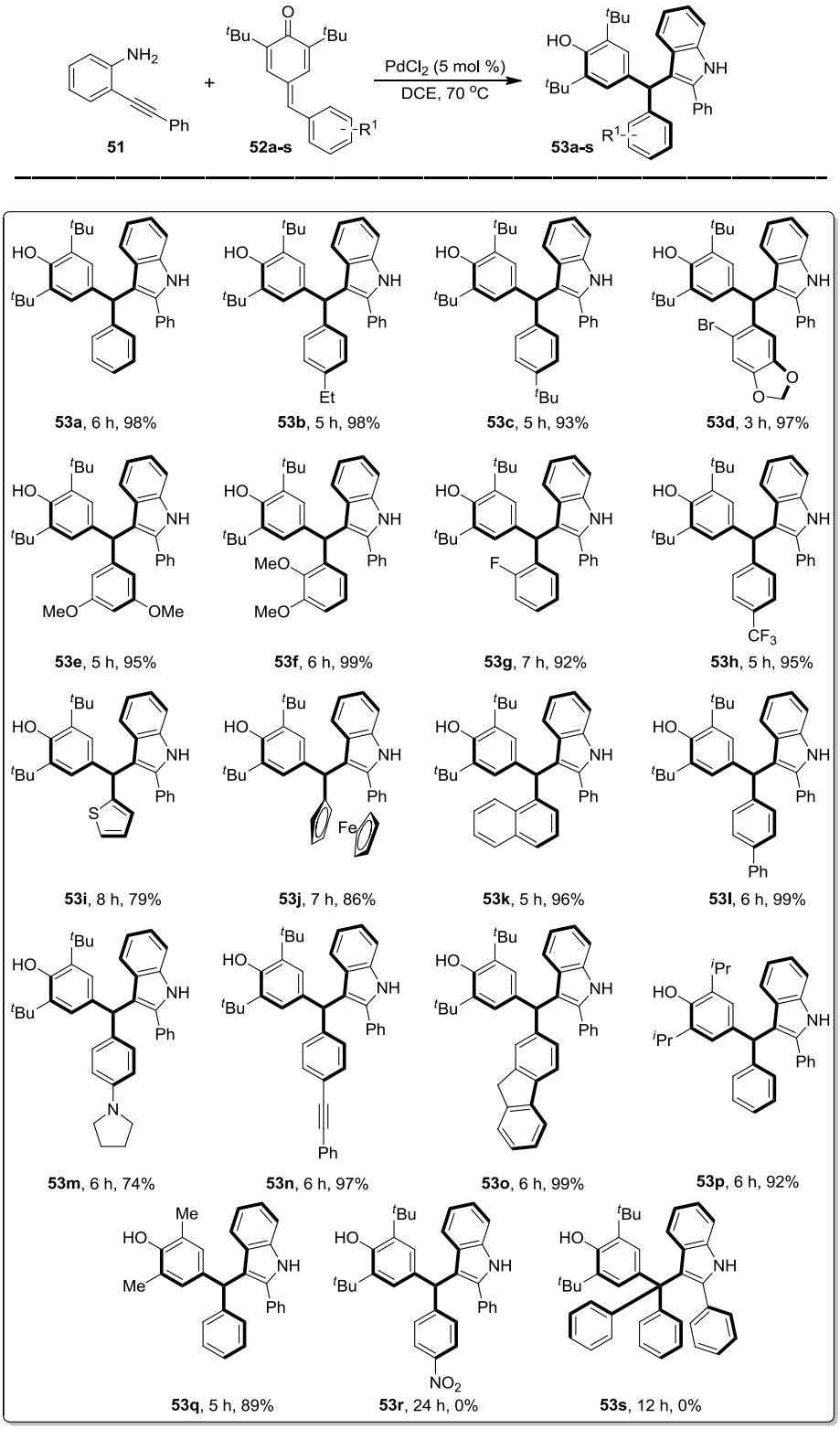
Scheme 36: The synthesis of fuchsone **52s**



With the optimal reaction conditions and *para*-quinone methides **(52** & **52a-s)** in hand, the substrate scope and limitations were examined. Scheme 37 describes the substrate scope for this protocol using substituted *para*-quinone methides. It was found that the reaction worked pretty well in the case of electron donating *p*-QMs (**52a-c**, **52e-f** & **52m)** and moderately electron deficient *p*-QMs (**52g** & **52h**), and provided the expected diarylindolylmethanes (**53a-c, 53e-f**, **53m** & **53g-h**) in excellent yields. Gratifyingly, the reaction also produced the expected products (**53d**) in the case of sterically hindered *p*-QM (**52d**) in excellent yields (97%). The *p*-QMs (**52i & 52j**) derived from corresponding thiophene carboxaldehyde and ferrocene carboxaldehyde also reacted smoothly and furnished the desired products (**53i** & **53j**) in 79% and 86% isolated yields respectively. In the case of *p*-quinone methides **52k** and **52l** gave the expected products in excellent yields (96% & 99% respectively). This transformation was also found to be effective for the synthesis of 4-(2-phenylethynyl) phenyl (**53n)** and 2-fluorene (**53o**) substituted triarylmethane derivatives from

their corresponding *p*-quinone methides. The scope of the methodology was further explored by using other *p*-QMs derived from 2,6 diisopropyl phenol (**52p**) and 2,6 dimethyl phenol

Scheme 37: Substrate scope using different *p*-QMs (**53a-s**)[a]

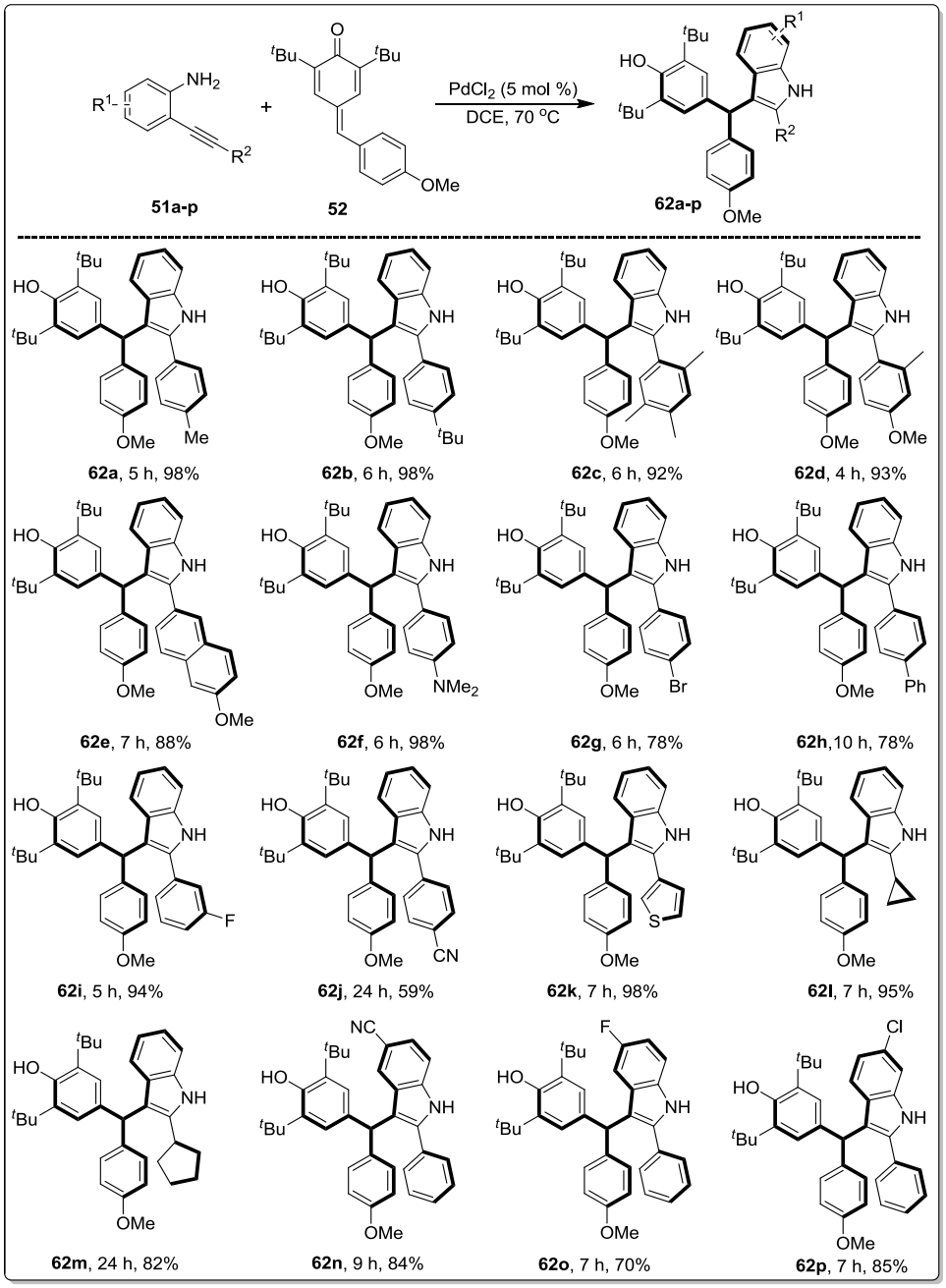


[a]Reaction conditions: 0.04 M solution of **51** in DCE. Yields reported are isolated yields.

(**52q**), and provided the expected products (**53p** & **53q**) in 92% and 89% yields respectively. Unfortunately, the reaction did not work with *para*-quinone methides derived from 4-nitrobenzaldehyde (**52r**) and fuchsone derivatives (**52s**) (Scheme 37).

The substrate scope studies and limitations of this protocol were also carried out using a diverse range of *o*-alkynyl anilines **(51a-p)** and *p*-QMs (**52**) by applying the optimized reaction conditions (Scheme 38).

Scheme 38: Substrate scope using different indole precursors (**62a-p**)[a]

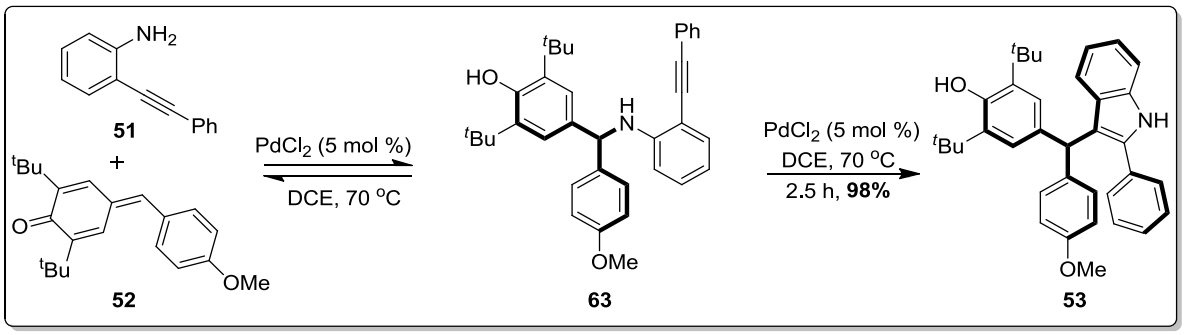


[a]Reaction conditions: 0.04 M solution of **51** in DCE. Yields reported are isolated yields.

The outcome has been disclosed in Scheme 38. Electron donating and withdrawing substituents on *o*-alkynyl anilines afforded the diarylindolylmethane products (**62a-f** & **62i-j**) in moderate to excellent yields. The moderate yield of the products **62g** & **62h** were obtained in the case *o*-alkynyl anilines derived from 4-bromo phenyl acetylene (**51g**) and 4-phenyl phenyl acetylene (**51h**). The indole precursor prepared from 3-ethynyl thiophene (**51k**) was also converted to its corresponding diarylindolylmethane **62k** in excellent yield in 7 h. The reaction worked pretty well in the cases of indole precursors (**51l** and **51m**) derived from ethynyl cyclopropane and ethynyl cyclopentane, and the products **62l** and **62m** were obtained in 95% and 82% yields respectively. We could also synthesize a few other diarylindolylmethanes (**62n**–**p**) in reasonable yields from *p*-quinone methides derived from *o*-alkynyl anilines (**51n**–**51p**) having a substituent in the aniline ring.

Remarkably, we observed that careful monitoring of the reaction between **51** and **52** under standard condition revealed that the amine addition product **63** was also formed in considerable amounts (Scheme 39). But interestingly, the formation of **63** was found to be reversible. TLC analysis of the reaction mixture indicated that the concentration of **63** was gradually decreasing and at the same time, the concentration of **53** was steadily increasing during the reaction. Although **63** was unstable under acidic conditions, we could isolate some amounts of **63** by purification through a short pad neutral alumina column. The amine addition product **63** was also characterized by spectral techniques. To confirm the reversible nature of this reaction, in an independent experiment **63** was treated with $PdCl_2$ under standard conditions and as expected, it was completely converted into **53** in 2.5 h in excellent yields (Scheme 39).

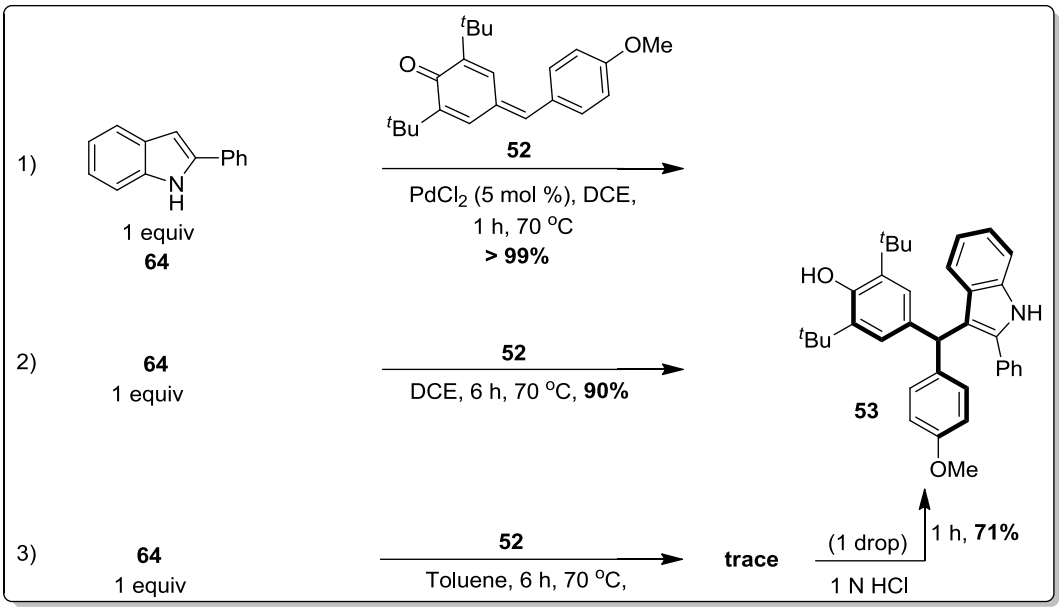
Scheme 39: Reversible nature of amine addition product **63**



In another experiment a solution **63** in dry DCE was heated to 70 ^{o}C for 5 h. in this case, considerable amount of **51** and **52** were obsereved. This is clearly indicates that the formation of **63** is reversible.

At this stage, our attention was shifted to elucidate a reasonable mechanism of this transformation. Initially, we believed that the reaction proceeds *via* 2-substituted indole derivative **64** (through aminopalladation step), which then adds to *p*-QM (**52**) in 1,6-fashion to generate the diarylindolylmethane derivative (**53**). To get a better understanding, a couple of control experiments were performed in which 2-phenylindole (**64**) (1 equiv) was treated with **52** (1.2 equiv) in the presence or absence of Pd-catalyst at 70 ^{o}C in DCE (Scheme 40). In the case of reaction with Pd catalyst, the product **53** was obtained in a quantitative yield within an hour. Unexpectedly, even in the case of reaction without Pd catalyst, **53** was obtained in 90% yield; albeit the reaction time was approximately 6 times more than that of the Pd-catalyzed reaction. Therefore, it is obvious that Pd-catalyst does help in accelerating the reaction. In the case of reaction without Pd-catalyst, we presume that the traces of HCl present in DCE are responsible for effecting this transformation by activating the *p*-QM (**52**) through hydrogen bonding. Another experiment was conducted to confirm the participation of HCl in the reaction, where 2-phenylindole **64** was treated with *p*-QM **52** in toluene instead of DCE at 70 ^{o}C.

Scheme 40: Control experiments

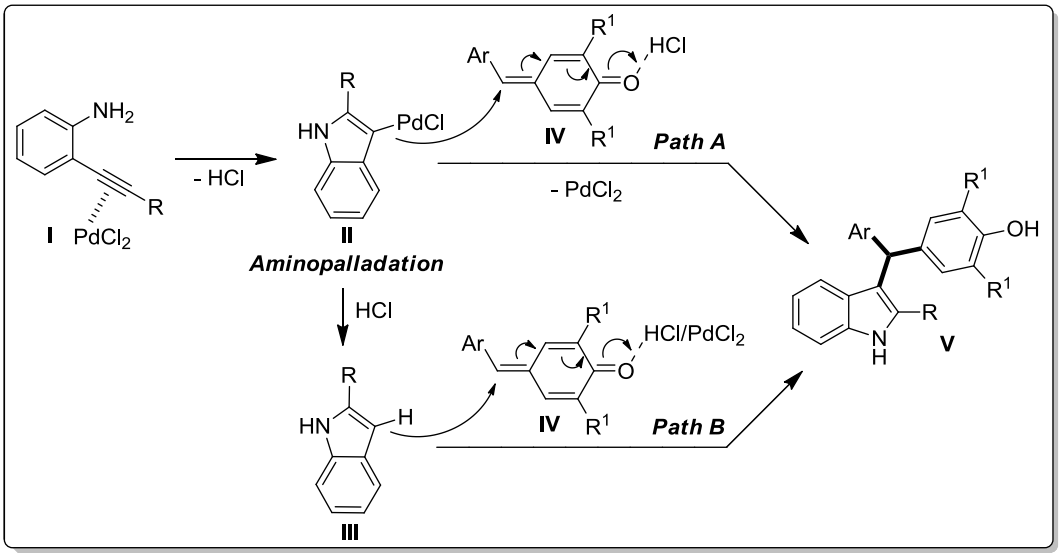


In this case, the product **53** was observed only in trace quantities after 6 h. But interestingly, when one drop of 1N aqueous HCl was added, the reaction was completed in an hour and **53** was obtained in 71% isolated yield. These experimental observations clearly suggest that HCl is playing an important role along with the Pd-catalyst in the 1,6-conjugate addition step to generate the final product. It is also evident that the reaction proceeds through 2-substituted indole intermediate **64**. Based on the above experiments and observations, a plausible mechanism of this transformation has been proposed.

1.6) The Plausible mechanism

The control experiments suggest that the reaction proceeds through the 2-substituted indole derivative (Scheme 41). However, careful monitoring of the standard reaction by ^{1}H NMR spectroscopy revealed that the characteristic peak of a proton in the 3-position of indole was not detectable. One possibility is that 2-arylindole (**III**) formed in the reaction could be a short-lived species under the reaction conditions. Based on these experimental observations and evidence, two plausible mechanisms have been proposed (Scheme 41). In the initial step, *o*-alkynyl aniline (**I**) undergoes aminopalladation with $PdCl_2$ and generates the intermediate **II** along with HCl, which presumably decomposes to 2-arylindole (**III**) under the reaction conditions. 1,6-Addition of 2-arylindole derivative **III** to *p*-QM (IV) presumably activated by HCl or $PdCl_2$, generates the product **V** (Path B).

Scheme 41: The Plausible mechanism



In this case, $PdCl_2$ probably acts as a Lewis acid to activate the *p*-QM. Alternatively, the palladium complex **II** can directly add to **IV** in the presence of HCl to generate the product **V** with the expulsion of Pd-catalyst (Path A).

1.7) Conclusion

An efficient one-pot protocol for the synthesis of heavily substituted unsymmetrical diarylindolylmethane derivatives has been developed through Pd-catalyzed annulation of *o*-alkynyl anilines followed by extended conjugate addition to *p*-quinone methides. Broad substrate scope and 100% atom economy are the key features of this methodology. Unlike most of the reported methods for the synthesis of 2,3-substituted indole derivatives, this protocol does not require any protection of the amino group of the *o*-alkynyl anilines.

1.8) Experimental Section

General Information

All reactions were carried out under an argon atmosphere in an oven dried round bottom flask or reaction vials. Triethylamine and dichloroethane were dried over calcium hydride, distilled and stored over molecular sieves. Melting points were recorded on SMP20 melting point apparatus and are uncorrected. Most of the reagents and starting materials were purchased from commercial sources and used as such. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

Synthesis of *o*-alkynyl anilines

All the *o*-alkynyl anilines (**51** & **51a-p**) were prepared by adapting a literature procedure.[13]

Synthesis of *p*-quinone methides

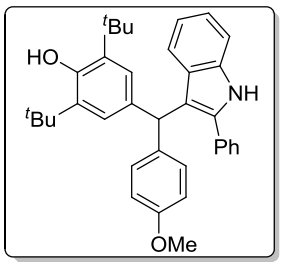
All the *p*-quinone methides (**52, 52a-o & 52r**) were prepared by adapting a literature procedure.[55] The other *p*-quinone methides (**52p** & **52q**) were synthesized following the reported procedure.[56, 57 & 58] The Fuchsone derivative (**52**s) was synthesized following the reported procedure.[59]

General procedure for the synthesis of unsymmetrical diarylindolylmethanes (53a-q & 62a-p)

A mixture of *o*-alkynyl aniline (1 equiv.), *p*-quinone methide (1.2 equiv.) and $PdCl_2$ (0.05 equiv.) in dichloroethane (0.04 M) was heated to 70 °C under an inert atmosphere, and the progress was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was directly loaded on a silica gel column and eluted using 10-20% EtOAc/hexane mixture to obtain pure diarylindolylmethane derivatives.

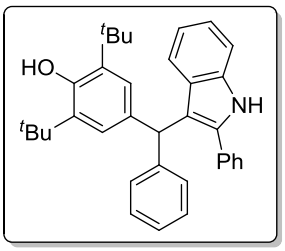
Characterization data for the diarylindolylmethanes (53, 53a-q & 62a-p)

2,6-di-*tert*-butyl-4-[(4-methoxyphenyl)(2-phenyl-1H-indol-3-yl)methyl]phenol (53)



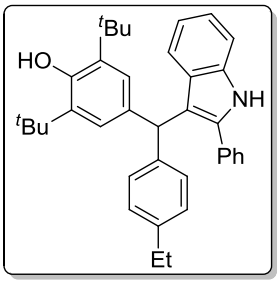
R_f = 0.2 (10% EtOAc in hexane); light yellow solid (40 mg, 99% yield); m.p. = 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.50−7.48 (m, 2H), 7.43−7.39 (m, 2H), 7.37−7.34 (m, 2H), 7.15−7.07 (m, 4H), 7.06 (s, 2H), 6.93−6.89 (m, 1H), 6.77−6.75 (m, 2H), 5.67 (s, 1H), 5.02 (s, 1H), 3.77 (s, 3H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ;157.6, 151.9, 137.2, 136.3, 135.5, 135.4, 134.8, 133.4, 130.1, 128.9, 128.7, 128.4, 127.9, 126.1, 121.9, 121.8, 119.4, 116.5, 113.4, 110.8, 55.3, 47.0, 34.4, 30.5; FT-IR (KBr): 3637, 3407, 2956, 2871, 1509, 1456, 1435, 1246, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}NO_2$ $[M+H]^+$: 518.3059; found: 518.3063.

2,6-di-*tert*-butyl-4-[phenyl(2-phenyl-1H-indol-3-yl)methyl]phenol (53a)



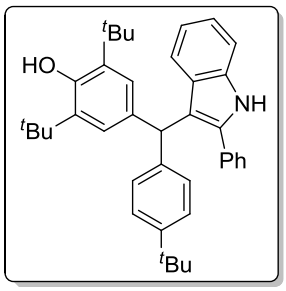
R_f = 0.5 (10% EtOAc in hexane); brown solid (37.2 mg, 98% yield); m.p. = 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.43−7.34 (m, 4H), 7.24−7.10 (m, 7H), 7.07 (s, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 5.03 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 145.1, 136.3, 135.6, 135.4, 134.4, 133.4, 129.1, 128.9, 128.7, 128.4, 128.1, 127.9, 126.2, 125.8, 121.9, 121.8, 119.5, 116.3, 110.8, 47.8, 34.4, 30.5; FT-IR (KBr): 3639, 3410, 2959, 2916, 2873, 1435, 1234, 761 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{35}H_{36}NO$ $[M-H]^+$: 486.2797; found: 486.2800.

2,6-di-*tert*-butyl-4-[(4-ethylphenyl)(2-phenyl-1H-indol-3-yl)methyl]phenol (53b)



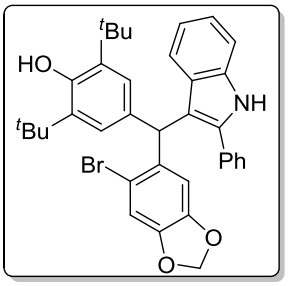
R_f = 0.5 (10% EtOAc in hexane); white solid (39 mg, 97% yield); m.p. = 230−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.52−7.50 (m, 2H), 7.43−7.34 (m, 4H), 7.18−7.04 (m, 6H), 7.08 (s, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 5.71 (s, 1H), 5.03 (s, 1H), 2.61 (q, *J* = 7.6 Hz, 2H) 1.32 (s, 18H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 142.2, 141.6, 136.3, 135.5, 135.4, 134.6, 133.4, 129.0, 128.9, 128.7, 128.5, 127.9, 127.5, 126.2, 122.0, 121.9, 119.4, 116.6, 110.7, 47.4, 34.4, 30.5, 28.5, 15.7; FT-IR (KBr): 3627, 3407, 2963, 2873, 1456, 1435, 761 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{40}NO$ $[M-H]^+$: 514.3110; found: 514.3124.

2,6-di-*tert*-butyl-4-{[4-(*tert*-butyl)phenyl](2-phenyl-1H-indol-3-yl)methyl}phenol (53c)



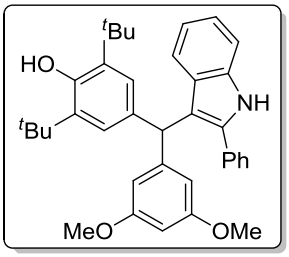
R_f = 0.4 (10% EtOAc in hexane); white solid (39 mg, 92% yield); m.p. = 238−240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.52−7.50 (m, 2H), 7.42−7.34 (m, 4H), 7.24−7.22 (m, 2H), 7.17 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.15−7.07 (m, 5H), 6.92 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.71, (s, 1H), 5.02 (s, 1H), 1.32 (s, 18H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 148.5, 141.9, 136.3, 135.6, 135.4, 134.6, 133.4, 128.9, 128.7, 128.6, 128.5, 127.9, 126.2, 124.9, 122.0, 121.9, 119.4, 116.6, 110.7, 47.3, 34.4, 31.5, 30.5; FT-IR (KBr): 3643, 3412, 2963, 2926, 2869, 1455, 1434, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{44}NO$ $[M-H]^+$: 542.3423; found: 542.3440.

4-{(6-bromobenzo[d][1,3]dioxol-5-yl)(2-phenyl-1H-indol-3-yl)methyl}-2,6-di-*tert*-butyl phenol (53d)



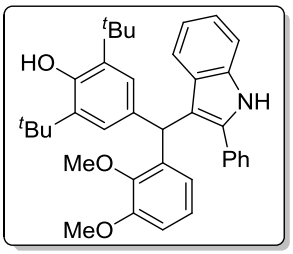
R_f = 0.3 (10% EtOAc in hexane); yellow solid (46 mg, 97% yield); m.p. = 237−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.38−7.33 (m, 6H), 7.15−7.11 (m, *J* = 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.95−6.91 (m, 1H), 6.93 (s, 2H), 6.83 (s, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 5.88 (brs, 1H), 5.05 (s, 1H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 147.1, 146.6, 137.6, 136.2, 136.1, 135.4, 133.4, 133.0, 128.9, 128.6, 128.5, 127.8, 125.8, 121.9, 121.2, 119.7, 115.7, 114.7, 112.9, 111.3, 110.8, 101.6, 47.8, 34.4, 30.5; FT-IR (KBr): 3635, 3409, 2957, 2924, 2856, 1475, 1233, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{35}BrNO_3$ $[M-H]^+$: 608.1800; found: 608.1800.

2,6-di-*tert*-butyl-4-[(3,5-dimethoxyphenyl)(2-phenyl-1H-indol-3-yl)methyl]phenol (53e)



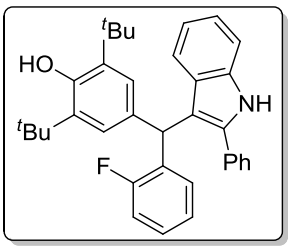
R_f = 0.2 (10% EtOAc in hexane); brown solid (40.5 mg, 95% yield); m.p. = 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.42−7.33 (m, 4H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.07 (s, 2H), 6.92 (t, *J* = 7.5, Hz, 1H), 6.37 (d, *J* = 1.7 Hz, 2H), 6.28 (brs, 1H), 5.65 (s, 1H), 5.02 (s, 1H), 3.65 (s, 6H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 152.0, 147.7, 136.3, 135.6, 135.4, 134.0, 133.4, 128.9, 128.7, 128.5, 127.9, 126.1, 121.9, 121.8, 119.5, 116.0, 110.7, 107.8, 97.8, 55.3, 48.0, 34.4, 30.5; FT-IR (KBr): 3637, 3402, 2956, 2925, 2855, 1456, 1155 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{37}H_{40}NO_3$ $[M-H]^+$: 546.3008; found: 546.3027.

2,6-di-*tert*-butyl-4-[(2,3-dimethoxyphenyl)(2-phenyl-1H-indol-3-yl)methyl]phenol (53f)



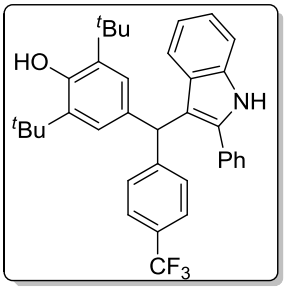
R_f = 0.3 (10% EtOAc in hexane); white solid (42 mg, 98% yield); m.p. = 214−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.50−7.48 (m, 2H), 7.40−7.37 (m, 2H), 7.34−7.31 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.09 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 7.01 (s, 2H), 6.95−6.88 (m, 2H), 6.83 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.08 (s, 1H), 4.99 (s, 1H), 3.80 (s, 3H), 3.22 (s, 3H), 1.30 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 151.9, 147.2, 139.2, 136.1, 135.4, 135.2, 134.3, 133.7, 129.1, 128.8, 128.6, 127.7, 126.1, 123.2, 122.5, 121.7, 121.6, 119.4, 115.8, 110.6, 59.8, 55.8, 42.2, 34.4, 30.5; FT-IR (KBr): 3640, 3401, 2957, 2926, 2871, 1476, 1456, 1435, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{40}NO_3$ $[M-H]^+$: 546.3008; found: 546.3020.

2,6-di-*tert*-butyl-4-[(2-fluorophenyl)(2-phenyl-1H-indol-3-yl)methyl]phenol (53g)



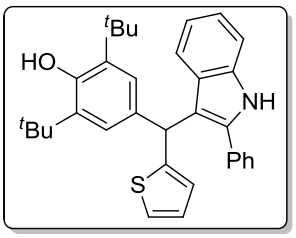
R_f = 0.4 (10% EtOAc in hexane); brown solid (36.1 mg, 92% yield); m.p. = 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.45−7.34 (m, 6H), 7.28−7.24 (m,1H), 7.18−7.11 (m, 3H), 7.05−6.90 (m, 3H), 7.00 (s, 2H), 6.01 (s, 1H), 5,05 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (d, *J* = 245.1 Hz), 152.1, 136.1, 135.7, 135.4, 133.3, 132.9, 132.1 (d, *J* = 13.9 Hz), 130.9, 130.8, 128.8, 128.6, 127.9, 127.8, 125.8, 123.7 (d, *J* = 3.6 Hz), 121.9, 121.2, 119.5, 115.2 (d, *J* = 21.9 Hz), 114.6, 110.8, 41.2 (d, *J* = 2.8 Hz), 34.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.73; FT-IR (KBr): 3638, 3411, 2957, 2925, 2971, 1487, 1456, 1435, 909, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{35}H_{35}FNO$ $[M-H]^+$: 504.2703; found: 504.2719.

2,6-di-*tert*-butyl-4-{(2-phenyl-1H-indol-3-yl)[4-(trifluoromethyl)phenyl]methyl}phenol (53h)



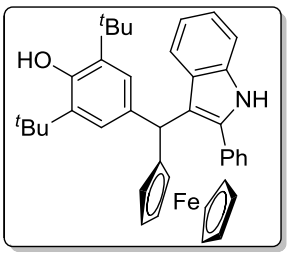
R_f = 0.4 (10% EtOAc in hexane); light pink solid (41 mg, 95% yield); m.p. = 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.48−7.36 (m, 8H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.16−7.12 (m, 1H), 7.1 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 2H), 6.95−6.91 (m, 1H), 5,74 (s, 1H), 5.08 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 149.3 (q, *J* = 1.4 Hz), 136.3, 136.0, 135.8, 133.5, 133.1, 129.4, 128.9, 128.8, 128.2, 128.0, 127.9, 126.1, 125.0 (q, *J* = 3.7 Hz), 124.6 (q, *J* = 270 Hz), 122.2, 121.5, 119.7, 115.3, 110.9, 47.8, 34.5, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.11; FT-IR (KBr): 3647, 3400, 2955, 2924, 2854, 1463, 1378, 1325, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{35}F_3NO$ $[M-H]^+$: 554.2671; found: 554.2658.

2,6-di-*tert*-butyl-4-[(2-phenyl-1H-indol-3-yl)(thiophen-2-yl)methyl]phenol (53i)



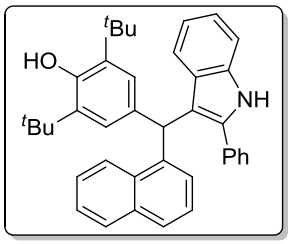
R_f = 0.4 (10% EtOAc in hexane); brown solid (30.2 mg, 79% yield); m.p. = 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.55−7.53 (m, 2H), 7.46−7.43 (m, 2H), 7.41−7.32 (m, 3H), 7.21 (s, 2H), 7.18−7.14 (m, 2H), 7.01−6.97(m, 1H), 6.91 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.75−6.73 (m, 1H), 5.88 (s, 1H), 5.08 (s, 1H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 150.2, 136.2, 135.4, 135.3, 134.3, 133.1, 129.0, 128.8, 128.1, 128.0, 126.4, 125.8, 125.6, 124.1, 122.1, 121.8, 119.6, 116.0, 110.9, 43.6, 34.5, 30.5; FT-IR (KBr): 3636, 3402, 2957, 2871, 1434, 1234, 762, 743, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{34}NOS$ $[M-H]^+$: 492.2361; found: 492.2347.

Cyclopenta-2,4-dien-1-yl{2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-phenyl-1H-indol-3-yl)methyl]cyclopenta-2,4-dien-1-yl}iron (53j)



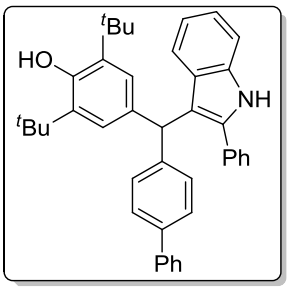
R_f = 0.3 (10% EtOAc in hexane); brown solid (40 mg, 86% yield); m.p. = 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.66−7.64 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.46−7.42 (m, 1H), 7.36−7.32 (m, 2H), 7.33 (s, 2H), 7.15−7.11 (m, 1H), 6.97−6.93 (m, 1H), 5.56 (s, 1H), 5.08 (s, 1H), 4.08−4.02 (m, 4H), 3.95 (s, 5H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 136.2, 135.4, 135.3, 134.3, 133.6, 128.9, 128.8, 128.4, 128.0, 125.6, 122.1, 121.8, 119.3, 117.5, 110.7, 94.0, 69.9, 69.1, 68.7, 67.9, 66.4, 42.9, 34.5, 30.6; FT-IR (KBr): 3638, 3404, 2958, 2924, 2870, 1453, 1435, 736, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{42}FeNO$ $[M+H]^+$: 596.2616; found: 296.2626.

2,6-di-*tert*-butyl-4-[naphthalen-1-yl(2-phenyl-1H-indol-3-yl)methyl]phenol (53k)



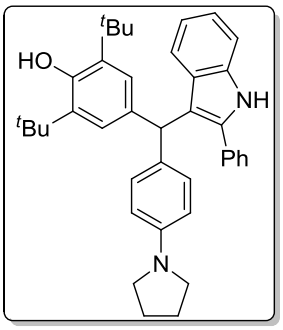
R_f = 0.3 (10% EtOAc in hexane); brown gummy liquid (40 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.82−7.78 (m, 2H), 7.72 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.43−7.40 (m, 2H), 7.38−7.31 (m, 7H), 7.26−7.22 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.09 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.05 (s, 2H), 6.87 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 6.39 (s, 1H), 5.05 (s, 1H), 1.30 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.8, 136.2, 135.4, 135.1, 134.4, 133.9, 133.3, 132.3, 129.2, 128.7, 128.67, 128.62, 127.9, 127.3, 127.1, 126.4, 125.6, 125.3, 125.2, 124.7, 121.8, 121.5, 119.5, 116.0, 110.6, 44.9, 34.4, 30.5; FT-IR (thin film, neat): 3636, 3409, 2957, 2924, 2870,1435, 737 cm-^{1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{38}NO$ $[M-H]^+$: 536.2953; found: 536.2955.

4-{[1,1'-biphenyl]-4-yl(2-phenyl-1H-indol-3-yl)methyl}-2,6-di-*tert*-butylphenol (53l)



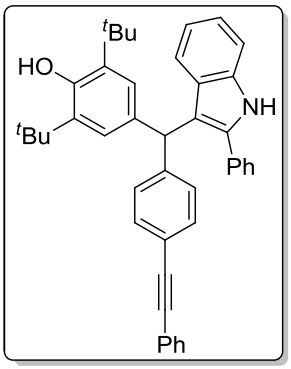
R_f = 0.4 (10% EtOAc in hexane); brown solid (43.3 mg, 99% yield); m.p. = 197−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.48−7.36 (m, 8H), 7.33−7.29 (m, 1H), 7.26−7.20 (m, 3H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.12 (s, 2H), 6.93 (t, *J* = 7.7 Hz, 1H), 5.77, (s, 1H), 5.05 (s, 1H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.3, 141.2, 138.5, 136.3, 135.7, 135.5, 134.3, 133.4, 129.6, 129.0, 128.8, 128.7, 128.4, 128.0, 127.1, 126.7, 126.2, 122.0, 121.9, 119.5, 116.2, 110.8, 47.5, 34.5, 30.5; FT-IR (KBr): 3639, 3407, 2958, 2872, 1486, 1455, 1435, 1227, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{40}NO$ [M-H]$^+$: 562.3110; found: 562.3122.

2,6-di-*tert*-butyl-4-{(2-phenyl-1H-indol-3-yl)[4-(pyrrolidin-1-yl)phenyl]methyl}phenol (53m)



R_f = 0.3 (10% EtOAc in hexane); brown solid (32 mg, 74% yield); m.p. = 225−227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.54−7.52 (m, 2H), 7.44−7.40 (m, 2H), 7.38−7.36 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.13 (s, 2H), 7.12−7.10 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.95−6.91 (m, 1H), 6.48 (d, *J* = 8.6 Hz, 2H), 5.68 (s, 1H), 5,02 (s, 1H), 3.27−3.24 (m, 4H), 1.99−1.96 (m, 4H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 146.2, 136.3, 135.3, 135.2, 134.6, 133.6, 131.8, 129.8, 128.9, 128.64, 128.62, 127.8, 126.1, 122.2, 121.7, 119.4, 117.2, 111.5, 110.6, 47.8, 46.8, 34.4, 30.5, 25.5; FT-IR (KBr): 3639, 3400, 2958, 2925, 2857, 1518, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{43}N_2O$ [M-H]$^+$: 555.3375; found: 555. 3365.

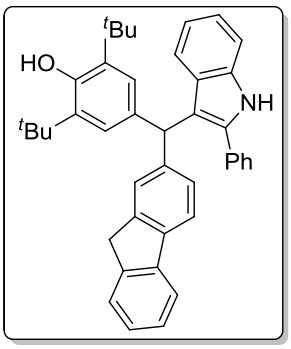
2,6-di-*tert*-butyl-4-{(2-phenyl-1H-indol-3-yl)[4-(phenylethynyl)phenyl]methyl}phenol (53n)



R_f = 0.4 (10% EtOAc in hexane); yellow liquid (44 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.52−7.47 (m, 4H), 7.44−7.31 (m, 9H), 7.17−7.11 (m, 4H), 7.06 (s, 2H), 6.94−6.90 (m, 1H), 5.72 (s, 1H), 5.06 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 145.7, 136.3, 135.8, 135.6, 134.0, 133.3, 131.7, 131.4, 129.2, 128.9, 128.8, 128.4, 128.2, 128.1, 128.0, 126.1, 123.6, 122.0, 121.7, 120.5, 119.6, 115.8, 110.8, 89.9, 89.0, 47.8, 34.5, 30.5;

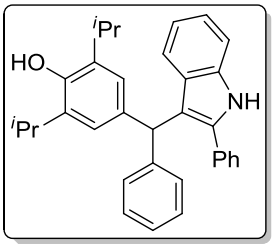
FT-IR (thin film, neat): 3639, 3423, 2957, 2925, 2856, 2218. 1456, 1435, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{40}NO$ $[M-H]^+$: 586.3110; found: 586.3110.

4-[(9H-fluoren-2-yl)(2-phenyl-1H-indol-3-yl)methyl]-2,6-di-*tert*-butylphenol (53o)



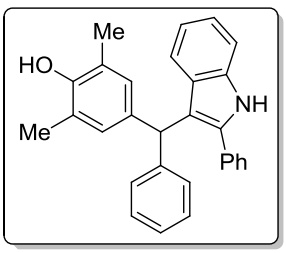
R_f = 0.4 (10% EtOAc in hexane); light brown solid (44 mg, 98% yield); m.p. = 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.54−7.50 (m, 3H), 7.45−7.35 (m, 6H), 7.28 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.26−7.23 (m, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.13 (s, 2H), 6.92 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 5.85 (s, 1H), 5.07 (s, 1H), 3.81 (s, 2H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.0, 143.6, 143.3, 142.0, 139.5, 136.3, 135.6, 135.4, 134.7, 133.4, 128.9, 128.7, 128.5, 127.9, 127.8, 126.7, 126.3, 126.2, 125.8, 125.1, 121.9, 121.90, 119.8, 119.5, 119.4, 116.5, 110.7, 48.0, 37.1, 34.5, 30.5; FT-IR (KBr): 3626, 3414, 2957, 2913, 2872, 1456, 1435, 1234, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{40}NO$ $[M-H]^+$: 574.3110; found: 574. 3123.

2,6-diisopropyl-4-(phenyl(2-phenyl-1H-indol-3-yl)methyl)phenol (53p)



R_f = 0.3 (10% EtOAc in hexane); brown solid (33 mg, 92% yield); m.p. = 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.52−7.50 (m, 2H), 7.45−7.35 (m, 4H), 7.24−7.17 (m, 5H), 7.15−7.11 (m, 2H), 6.97 (s, 2H), 6.94−6.90 (m, 1H), 5.77 (s, 1H), 4.68 (s, 1H), 3.10 (sept, *J* = 6.8 Hz, 2H), 1.16 (d, *J* = 5.6 Hz, 6H), 1.14 (d, *J* = 5.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 145.0, 136.3, 135.9, 135.6, 133.32, 133.29, 129.2, 128.9, 128.8, 128.5, 128.1, 128.0, 125.8, 124.7, 121.9, 121.8, 119.5, 116.1, 110.8, 47.6, 27.4, 22.9, 22.8; FT-IR (KBr): 3573, 3406, 3057, 2961, 2925, 2869, 1490, 1454, 1199, 1151, 741, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}NO$ $[M-H]^+$: 458.2484; found: 458.2488.

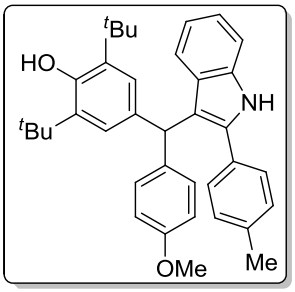
2,6-dimethyl-4-(phenyl(2-phenyl-1H-indol-3-yl)methyl)phenol (53q)



R_f = 0.2 (10% EtOAc in hexane); white solid (28 mg, 89% yield); m.p. = 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.48−7.34 (m, 6H), 7.28−7.19 (m, 5H), 7.17−7.13 (m, 2H), 6.93 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 6.83 (d, *J* = 0.4 Hz, 2H), 5.74 (s, 1H), 4.51 (s, 1H), 2.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 144.8, 136.3, 135.8, 135.6, 133.1, 129.5, 129.3, 128.8, 128.7, 128.6, 128.2, 128.0, 126.0, 122.6, 122.0, 121.8, 119.7, 115.6, 110.9, 47.1, 16.2; FT-IR (KBr): 3563, 3401, 3056, 3024,

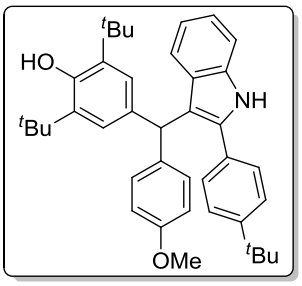
2921, 1487, 1451, 1196, 733, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{24}NO$ $[M-H]^+$: 402.1858; found: 402.1851.

2,6-di-*tert*-butyl-4-{(4-methoxyphenyl)[2-(p-tolyl)-1H-indol-3-yl]methyl}phenol (62a)



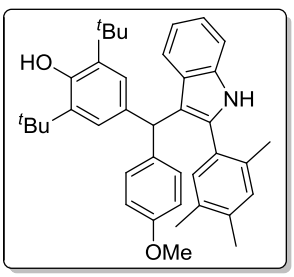
R_f = 0.3 (10% EtOAc in hexane); brown solid (40.5 mg, 98% yield); m.p. = 217−219 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.39−7.37 (m, 2H), 7.35−7.32 (m, 1H), 7.22 (dd, *J* = 8.4, 0.5 Hz, 2H), 7.14−7.07 (m, 3H), 7.07 (s, 3H), 6.90 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.77−6.75 (m, 2H), 5.66 (s, 1H), 5.02 (s, 1H), 3.77 (s, 3H), 2.40 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 137.7, 137.3, 136.2, 135.5, 135.4, 134.8, 130.5, 130.1, 129.4, 128.8, 128.5, 126.1, 121.8, 121.7, 119.4, 116.3, 113.4, 110.7, 55.3, 47.0, 34.4, 30.5, 21.4; FT-IR (KBr): 3622, 3346, 2955, 2922, 2869, 1509, 1436, 1243, 1177, 1033, 825, 745 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{40}NO_2$ $[M-H]^+$: 530.3059; found: 530. 3043.

2,6-di-*tert*-butyl-4-{[2-(4-(tert-butyl)phenyl)-1H-indol-3-yl](4-methoxyphenyl)methyl} phenol (62b)



R_f = 0.3 (5% EtOAc in hexane); brown solid (43.7 mg, 98% yield); m.p. = 187−189 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.43 (s, 4H), 7.36−7.34 (m, 1H), 7.16−7.10 (m, 4H), 7.07 (s, 2H), 6.92 (dd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.80−6.78 (m, 2H), 5.73 (s, 1H), 5.03 (s, 1H), 3.78 (s, 3H), 1.37 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 150.9, 137.2, 136.2, 135.5, 135.3, 134.8, 130.5, 130.1, 128.6, 128.5, 126.1, 125.6, 121.8, 121.7, 119.4, 116.2, 113.4, 110.7, 55.3, 46.9, 43.6, 34.4, 31.4, 30.5*;* FT-IR (KBr): 3641, 3403, 2959, 2870, 1509, 1456, 1435, 1246, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{46}NO_2$ $[M-H]^+$: 572.3529; found: 572.3531.

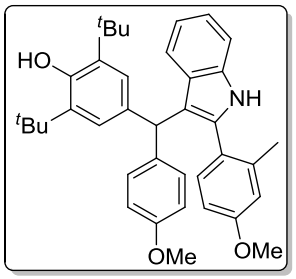
2,6-di-*tert*-butyl-4-{(4-methoxyphenyl)[2-(2,4,5-trimethylphenyl)-1H-indol-3-yl]methyl} phenol (62c)



R_f = 0.3 (5% EtOAc in hexane); yellow gummy liquid (40 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16−7.13 (m, 3H), 7.08 (s, 1H), 7.04 (s, 1H),7.03 (s, 2H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 5.02 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.7, 137.1, 136.8, 136.0, 135.5, 135.4, 135.1, 135.0, 133.5, 132.5, 131.5, 130.1,

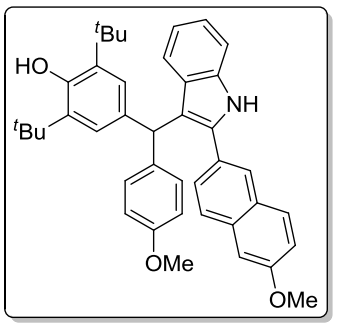
130.0, 127.5, 125.9, 121.6, 121.4, 119.1, 116.9, 113.2, 110.6, 55.3, 47.2, 34.4, 30.4, 19.7, 19.6, 19.4; FT-IR (thin film, neat): 3640, 3404, 2956, 2924, 2858, 1509, 1456, 1436, 1244, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{44}NO_2$ $[M-H]^+$: 558.3372; found: 558.3358.

2,6-di-*tert*-butyl-4-{[2-(4-methoxy-2-methylphenyl)-1H-indol-3-yl](4-methoxyphenyl) methyl}phenol (62d)



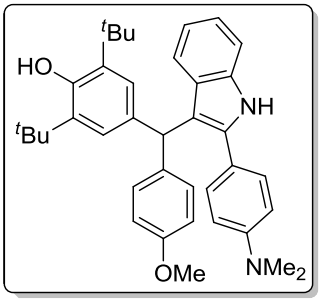
R_f = 0.4 (10% EtOAc in hexane); brown solid (40.6 mg, 93% yield); m.p. = 214−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 6.7 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 4H), 6.98−6.94 (m, 3H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.77−6.72 (m, 3H), 5.30 (s, 1H), 4.98 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.08 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.6, 151.7, 139.9, 136.8, 136.0, 135.2, 135.1, 134.9, 132.6, 130.1, 127.5, 125.9, 125.1, 121.5, 121.4, 119.2, 117.2, 115.5, 113.3, 110.8, 110.6, 55.4, 55.3, 47.3, 34.4, 30.5, 20.5; FT-IR (KBr): 3631 3401, 2956, 2922, 2022, 2854, 1508, 1456, 1436, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{42}NO_3$ $[M-H]^+$: 560.3165; found: 560.3171.

2,6-di-*tert*-butyl-4-{[2-(6-methoxynaphthalen-2-yl)-1H-indol-3-yl](4-methoxyphenyl) methyl}phenol (62e)



R_f = 0.2 (10% EtOAc in hexane); brown solid (40 mg, 86% yield); m.p. = 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.85 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.20−716 (m, 3H), 7.14−7.09 (m, 5H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.75 (s, 1H), 5.05 (s, 1H), 3.95 (s, 3H), 3.77 (s, 3H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.6, 152.0, 137.4, 136.4, 135.6, 135.5, 134.9, 134.0, 130.1, 129.7, 128.8, 128.6, 128.5, 127.8, 127.2, 127.1, 126.1, 121.8, 121.7, 119.5, 119.4, 116.6, 113.4, 110.7, 105.8, 55.5, 55.3, 47.1, 34.4, 30.5; FT-IR (KBr): 3631, 3404, 2956, 2925, 2856, 1508, 1435, 1245, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{42}NO_3$ $[M-H]^+$: 596.3165; found: 596.3146.

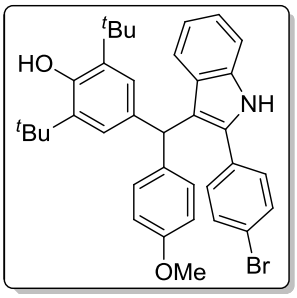
2,6-di-*tert*-butyl-4-{[2-(4-(dimethylamino)phenyl)-1H-indol-3-yl](4methoxyphenyl) methyl}phenol (62f)



R_f = 0.2 (20% EtOAc in hexane); dark brown solid (42.7 mg, 98% yield); m.p. = 216−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7,32 (d, *J* = 8.0 Hz, 1H), 7.11−7.06

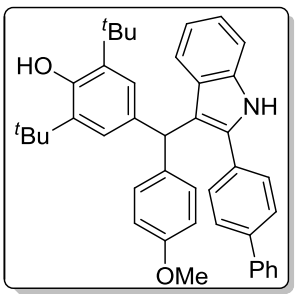
(m, 6H), 6.88 (t, *J* = 7.4, Hz, 1H), 6.78−6.74 (m, 4H), 5.68 (s, 1H), 5.02 (s, 1H), 3.77 (s, 3H), 3.00 (s, 6H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.8, 150.1, 137.6, 136.1, 136.0, 135.3, 135.1, 130.1, 129.7, 128.7, 126.1, 121.5, 121.3, 121.2, 119.2, 115.2, 113.3, 112.4, 110.5, 55.3, 47.0, 40.6, 34.4, 30.5; FT-IR (KBr): 3620, 3354, 2954, 2911, 2871, 1509, 1436, 1243, 1177, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{43}N_2O_2$ $[M-H]^+$: 559.3325; found: 559.3313.

4-{[2-(4-bromophenyl)-1H-indol-3-yl](4-methoxyphenyl)methyl}-2,6-di-*tert*-butylphenol (62g)



R_f = 0.4 (10% EtOAc in hexane); brown solid (36 mg, 78% yield); m.p. = 211−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.52−7.50 (m, 2H), 7.36−7.31 (m, 3H), 7.15−7.11 (m, 2H), 7.07−7.04 (m, 2H), 7.02 (s, 2H), 6.94−6.90 (m, 1H), 6.78−6.75 (m, 2H), 5.63 (s,1H), 5.04 (s, 1H), 3.77 (s, 3H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 137.0, 136.4, 135.5, 134.4, 134.1, 132.3, 131.8, 130.4, 130.1, 128.5, 126.0, 122.2, 122.0, 121.9, 119.7, 117.1, 113.5, 110.8, 55.3, 47.0, 34.4, 30.5; FT-IR (KBr): 3638, 3401, 2956, 2926, 2866, 1509, 1455, 1435, 1245, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{37}BrNO_2$ $[M-H]^+$: 594.2008; found: 594.2027.

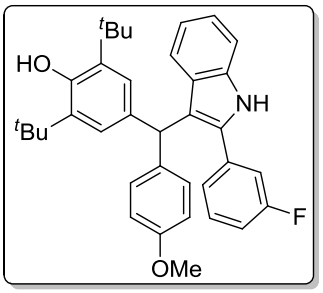
4-{[2-([1,1'-biphenyl]-4-yl)-1H-indol-3-yl](4-methoxyphenyl)methyl}-2,6-di-*tert*-butyl phenol (62h)



R_f = 0.4 (10% EtOAc in hexane); brown solid (36 mg, 78% yield); m.p. = 216−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.66−7.63 (m, 4H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.41−7.36 (m, 2H), 7.18−7.11 (m, 6H), 6.96−6.92 (m, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 1H), 5.05 (s, 1H), 3.78 (s, 3H), 1.34 (s, 18H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 140.7, 140.6, 137.2, 136.4, 135.4, 135.1, 134.7, 132.3, 130.1, 129.2, 129.0, 128.6, 127.6, 127.3, 127.2, 126.1, 122.0, 121.9, 119.5, 116.8, 113.4, 110.8, 55.3, 47.1, 34.4, 30.5; FT-IR (KBr): 3627, 3408, 2957, 2926, 2859, 1509, 1456, 1435, 1245, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{42}NO_2$ $[M-H]^+$: 592.3216; found: 592.3229.

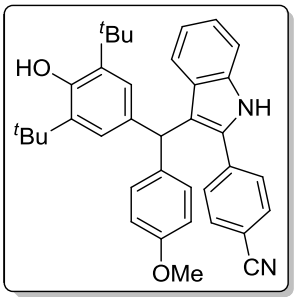
2,6-di-*tert*-butyl-4-{[2-(3-fluorophenyl)-1H-indol-3-yl](4-methoxyphenyl)methyl}phenol (62i)

R_f = 0.3 (5% EtOAc in hexane); brown solid (39 mg, 94% yield); m.p = 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.38−7.34 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 1H),



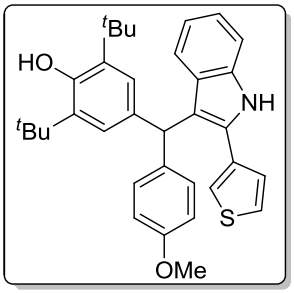
7.22–7.19 (m, 1H), 7.17−7.13 (m, 2H), 7.10 (s, 3H), 7.08−7.03 (m, 2H), 6.94 (t, J = 7.6 Hz, 1H), 6.80−6.78 (m, 2H), 5.69 (s, 1H), 5.07 (s, 1H), 3.78 (s, 3H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J = 244.8 Hz), 157.7, 152.0, 137.0, 136.4, 135.6, 135.5 (d, J = 8.2 Hz), 134.5, 134.0 (d, J = 2.9 Hz), 130.2 (d, J = 8.6 Hz), 130.0, 128.4, 126.1, 124.4 (d, J = 2.8 Hz), 122.3, 122.0, 119.7, 117.4, 115.8 (d, J = 22.5 Hz), 114.7 (d, J = 20.7 Hz), 113.5, 110.8, 55.3, 47.0, 34.4, 30.5; FT-IR (KBr): 3640, 3402, 2957, 2925, 2857, 1509, 1456, 1436, 1246, 739 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.47; HRMS (ESI): *m/z* calcd for $C_{36}H_{37}FNO_2$ $[M-H]^+$: 534.2808; found: 534.2817.

4-{3-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]-1H-indol-2-yl} benzonitrile (62j)



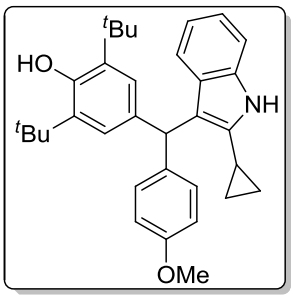
R_f = 0.3 (5% EtOAc in hexane); brown gummy liquid (25 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.19−7.15 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.01 (s, 2H), 6.94 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 6.79−6.77 (m, 2H), 5.66, (s, 1H), 5.07 (s, 1H), 3.77 (s, 3H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 152.1, 138.0, 136.8, 136.6, 135.6, 134.1, 133.1, 132.4, 130.0, 129.2, 128.5, 126.0, 123.0, 122.2, 120.0, 118.9, 118.8, 113.6, 111.02, 111.0, 55.3, 47.1, 34.4, 30.4; FT-IR (thin film, neat): 3636, 3373, 2956, 2926, 2857, 2229, 1509, 1436, 1246, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{37}N_2O_2$ $[M-H]^+$: 541.2855; found: 541.2845.

2,6-di-*tert*-butyl-4-{(4-methoxyphenyl)[2-(thiophen-3-yl)-1H-indol-3-yl]methyl}phenol (62k)



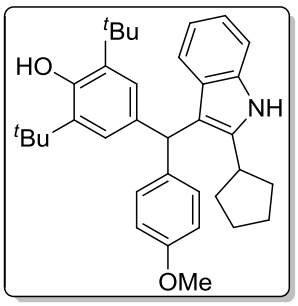
R_f = 0.3 (5% EtOAc in hexane); brown solid (40 mg, 98% yield); m.p. = 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.39 (dd, J = 5.0, 3.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.31 (dd, J = 3.0, 1.3 Hz, 1H), 7.28−7.26 (m, 1H), 7.14−7.10 (m, 3H), 7.07 (s, 2H), 7.06 (d, J = 7.4 Hz, 1H), 6.91 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.81−6.79 (m, 2H), 5.76 (s, 1H), 5.07 (s, 1H), 3.79 (s, 3H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 137.2, 136.1, 135.5, 134.6, 133.9, 130.8, 130.1, 128.6, 127.5, 126.1, 126.0, 122.9, 121.9, 121.6, 119.5, 116.6, 113.5, 110.6, 55.3, 47.0, 34.4, 30.5; FT-IR (KBr): 3637, 3404, 2955, 2925, 2870, 1509, 1457, 1435, 1246, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{36}NO_2S$ $[M-H]^+$: 522.2467; found: 522.2460.

2,6-di-*tert*-butyl-4-[(2-cyclopropyl-1H-indol-3-yl)(4-methoxyphenyl)methyl]phenol (62l)



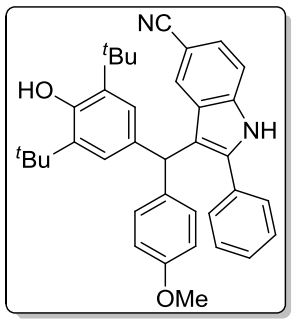
R_f = 0.3 (5% EtOAc in hexane); brown solid (35.5 mg, 95% yield); m.p. = 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.24−7.22 (m, 1H), 7.15−7.13 (m, 2H), 7.11−7.08 (m, 3H), 7.04 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.90 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.80−6.78 (m, 2H), 5.78 (s, 1H), 5.04 (s, 1H), 3.78 (s, 3H), 1.88−1.81 (m, 1H), 1.35 (s, 18H), 0.90−0.85 (m, 2H), 0.71−0.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 137.2, 136.4, 135.3, 134.9, 134.7, 130.1, 128.7, 126.0, 120.9, 120.2, 119.1, 116.7, 113.4, 110.3, 55.3, 46.9, 34.4, 30.5, 8.1, 6.8, 6.7; FT-IR (KBr): 3638, 3410, 2956, 2924, 2857, 1509, 1460, 1436, 1243, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{38}NO_2$ $[M-H]^+$: 480.2903; found: 480.2900.

2,6-di-*tert*-butyl-4-[(2-cyclopentyl-1H-indol-3-yl)(4-methoxyphenyl)methyl]phenol (62m)



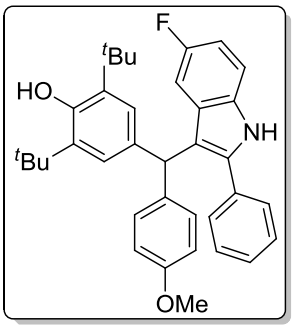
R_f = 0.5 (10% EtOAc in hexane); brown solid (32.5 mg, 82% yield); m.p. = 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.15−7.10 (m, 3H), 7.05 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.04 (s, 2H), 6.90 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.81−6.77 (m, 2H), 5.69 (s, 1H), 5.04 (s, 1H), 3.78 (s, 3H), 3.07−2.98 (m, 1H), 1.90−1.74 (m, 4H), 1.62–1.52 (m, 4H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 151.9, 139.3, 137.0, 135.4, 135.3, 134.9, 130.1, 128.6, 126.0, 120.8, 120.0, 119.0, 114.8, 113.4, 110.2, 55.3, 46.8, 37.1, 34.4, 33.4, 30.5, 25.8; FT-IR (KBr): 3641, 3416, 2956, 2926, 2867, 1509, 1461, 1435, 1244, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{35}H_{42}NO_2$ $[M-H]^+$: 508.3216; found: 508.3218.

3-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl]-2-phenyl-1H-indole-5-carbonitrile (62n)



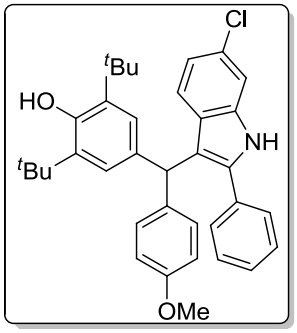
R_f = 0.3 (20% EtOAc in hexane); brown solid (35.5 mg, 84% yield); m.p. = 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.49−7.38 (m, 7H), 7.36−7.33 (m, 1H), 7.04−7.02 (m, 2H), 6.98 (s, 2H), 6.81−6.78 (m, 2H), 5.67 (s, 1H), 5.09 (s, 1H), 3.79 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 152.2, 137.9, 137.5, 136.3, 135.7, 133.9, 132.1, 129.9, 128.9, 128.8, 128.7, 128.3, 127.3, 125.9, 124.9, 121.0, 117.3, 113.7, 111.7, 102.5, 55.3, 46.7, 34.5, 30.4; FT-IR (KBr): 3634, 3311, 2956, 2924, 2855, 2222, 1509, 1468, 1435, 1246, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{39}N_2O_2$ $[M+H]^+$: 543.3012; found: 543.3021.

2,6-di-*tert*-butyl-4-[(5-fluoro-2-phenyl-1H-indol-3-yl)(4-methoxyphenyl)methyl]phenol (62o)



R_f = 0.5 (10% EtOAc in hexane); light yellow solid (29 mg, 70% yield); m.p. = 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.49−7.47 (m, 2H), 7.44−7.37 (m, 3H), 7.24 (dd, *J* = 4.4 Hz, 1H), 7.08−7.06 (m, 2H), 7.04 (s, 2H), 6.89−6.84 (m, 1H), 6.80−6.75 (m, 3H), 5.65 (s, 1H), 5.06 (s, 1H), 3.78 (s, 3H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.5 (d, *J* = 232.6 Hz), 152.0, 137.3, 136.8, 135.5, 134.4, 133.0, 132.8, 130.0, 128.9, 128.8, 128.7, 128.2, 126.0, 116.8 (d, *J* = 4.3 Hz), 113.5, 111.3 (d, *J* = 9.7 Hz), 110. 2 (d, *J* = 26.3 Hz), 106.6 (d, *J* = 24.1 Hz), 55.3, 46.8, 34.4, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −124.41; FT-IR (KBr): 3622, 3346, 2955, 2923, 2869, 1509, 1455, 1436, 1243, 1177, 745 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{37}FNO_2$ $[M-H]^+$: 534.2808; found: 534.2823.

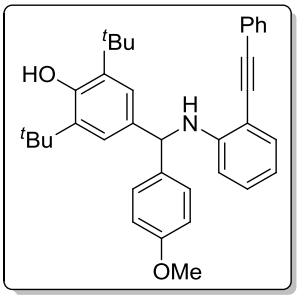
2,6-di-*tert*-butyl-4-[(6-chloro-2-phenyl-1H-indol-3-yl)(4-methoxyphenyl)methyl]phenol (62p)



R_f = 0.5 (10% EtOAc in hexane); light yellow solid (36.6 mg, 85% yield); m.p. = 232−234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.49−7.46 (m, 2H), 7.44−7.37 (m, 3H), 7.33−7.32 (m, 1H), 7.05−7.00 (m, 3H), 7.03 (s, 2H), 6.87 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.78−6.76 (m, 2H), 5.64 (s, 1H), 5.05 (s, 1H), 3.77 (s, 3H), 1.32 (s, 18H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 136.9, 136.7, 136.1, 135.6, 134.4, 132.9, 130.0, 128.8, 128.7, 128.2, 127.7, 127.1, 126.0, 122.7, 120.2, 116.7, 113.5, 110.7, 55.3, 46.8, 34.4, 30.5; FT-IR (KBr): 3637, 3408, 2956, 2925, 2958, 1509, 1437, 1244, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{39}ClNO_2$ $[M+H]^+$: 552.2669; found: 552.2671.

Synthesis and characterization data for compound 63

A mixture of *o*-alkynyl aniline **51** (15 mg, 1 equiv.), *p*-quinone methide **52** (30 mg, 1.2 equiv.) and $PdCl_2$ (0.05 equiv.) in dichloroethane (0.04 M) was stirred at room temperature under inert atmosphere and the progress was monitored by TLC (12 h). Then, solvent was removed under reduced pressure and the residue was directly loaded on a short pad neutral alumina column and eluted using 5-10% EtOAc/hexane mixture to obtain pure compound **63**.



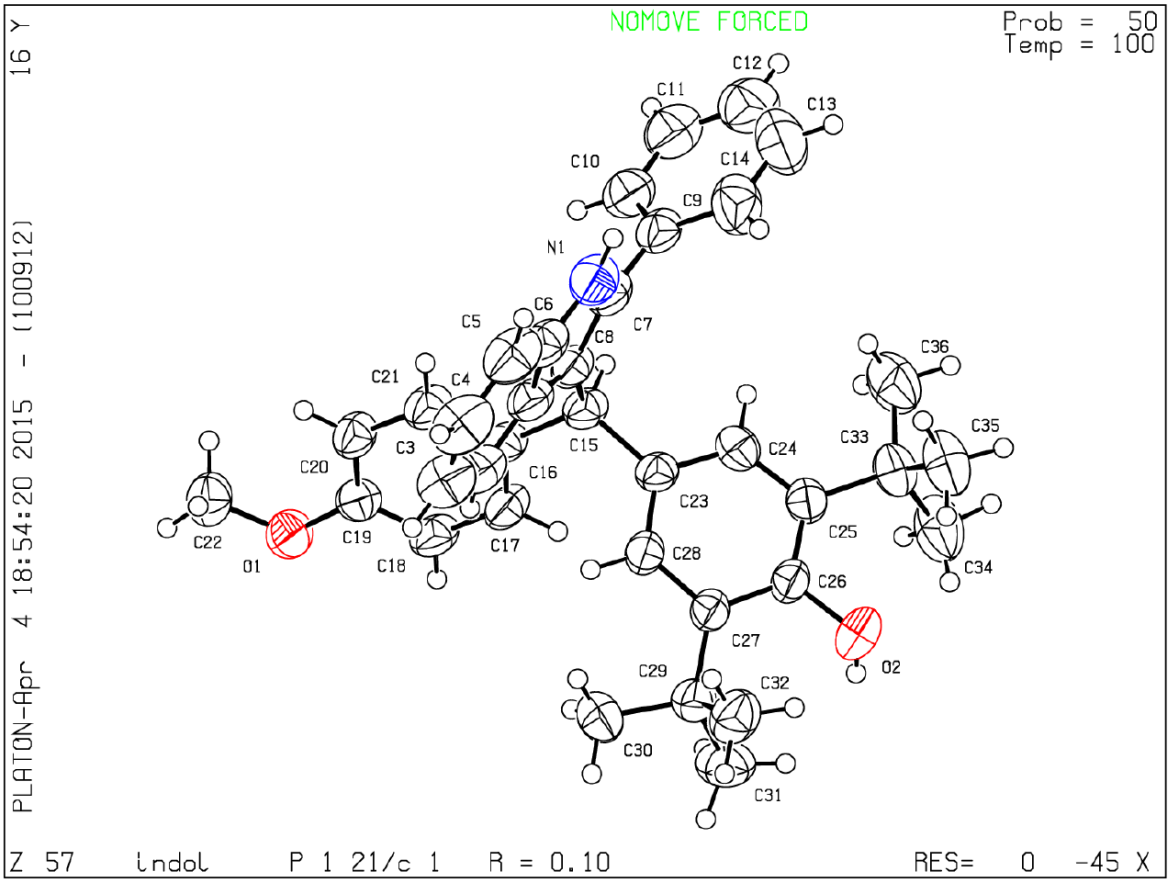
The reaction was performed at 0.078 mmol scale of *o*-alkynyl aniline R_f = 0.5 (5% EtOAc in hexane); yellow gummy liquid; (6 mg, 15%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 7.29−7.27 (m, 3H), 7.13 (s, 2H), 7.09−7.05 (m, 1H), 6.89−6.87 (m, 2H), 6.64 (td, *J* = 7.5, 1.1 Hz, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 4.4 Hz, 1H), 5.30 (d, *J* = 4.4 Hz, 1H), 5.16 (s, 1H), 3.80 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 153.2, 148.6, 136.2, 135.2, 134.4, 131.7, 131.4, 130.0, 128.5, 128.2, 128.1, 124.1, 116.6, 114.6, 114.1, 111.2, 107.8, 95.6, 86.5, 62.4, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{38}NO_2$ $[M-H]^+$: 516.2903; found: 516.2911.

X-Ray crystallographic analysis for compound 53:[60]

Crystal data and structure refinement for compound 53.

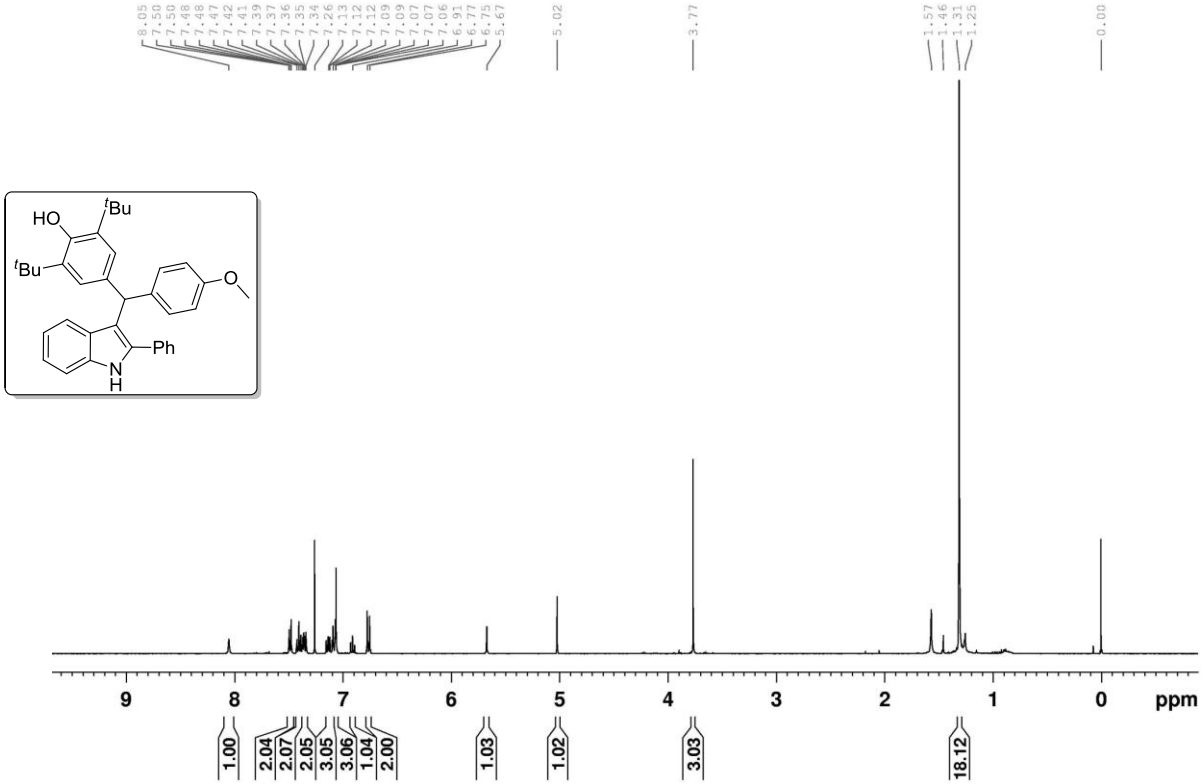
Identification code	**53**
Empirical formula	$C_{36}H_{39}NO_2$
Formula weight	517.68
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.8225(19)
b/Å	11.0736(13)
c/Å	18.657(3)
α/°	90
β/°	100.056(6)
γ/°	90
Volume/Å^3	3015.3(7)
Z	4
ρ_{calc}g/cm^3	1.140
μ/mm^{-1}	0.069
F(000)	1112.0
Crystal size/mm^3	0.2 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	6.056 to 54.976
Index ranges	$-18 \leq h \leq 19$, $-14 \leq k \leq 14$, $-24 \leq l \leq 24$
Reflections collected	19623
Independent reflections	6879 [R_{int} = 0.0840, R_{sigma} = 0.1094]
Data/restraints/parameters	6879/0/359
Goodness-of-fit on F^2	1.088
Final R indexes [I>=2σ (I)]	R_1 = 0.0971, wR_2 = 0.1779
Final R indexes [all data]	R_1 = 0.2069, wR_2 = 0.2350
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.25

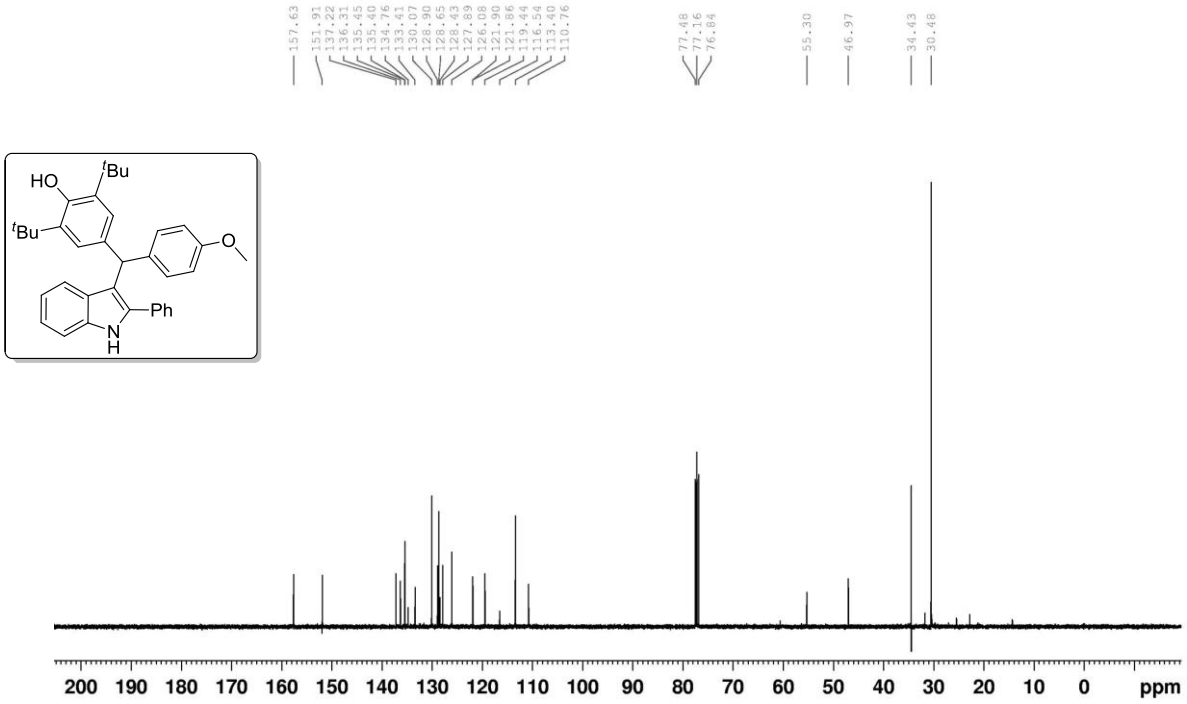


Copies of ^{1}H, ^{13}C & ^{19}F spectra of compounds 53, 53a-q & 62a-p & 63

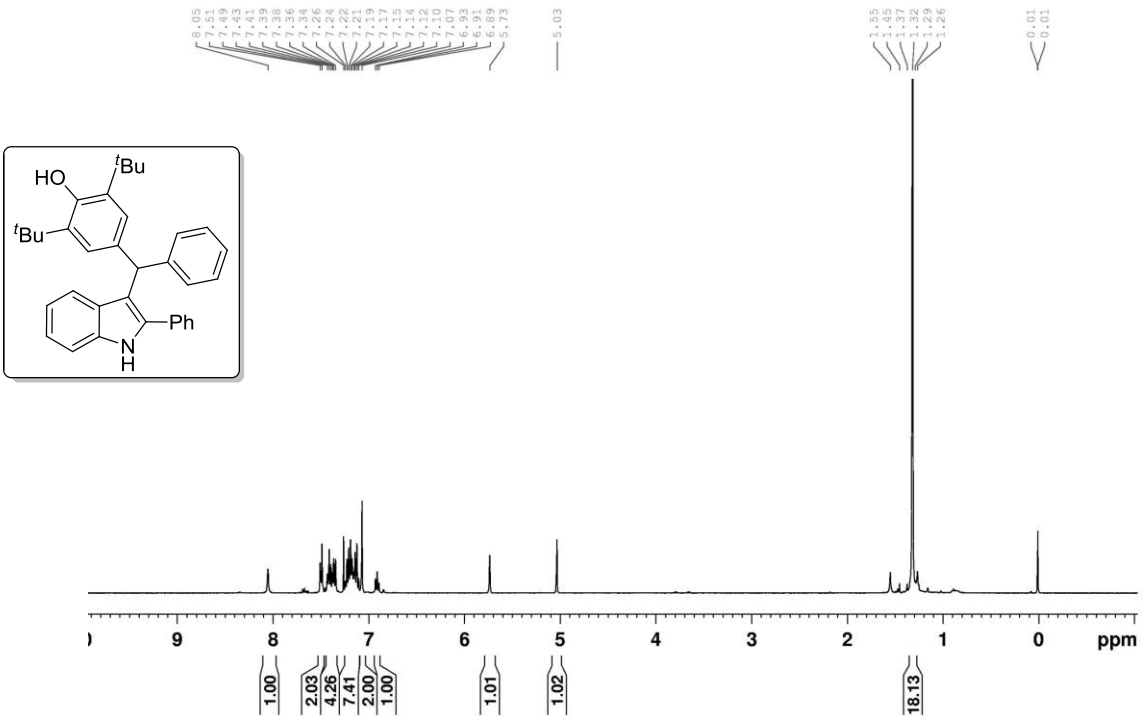
^{1}H NMR spectrum of compound **53**



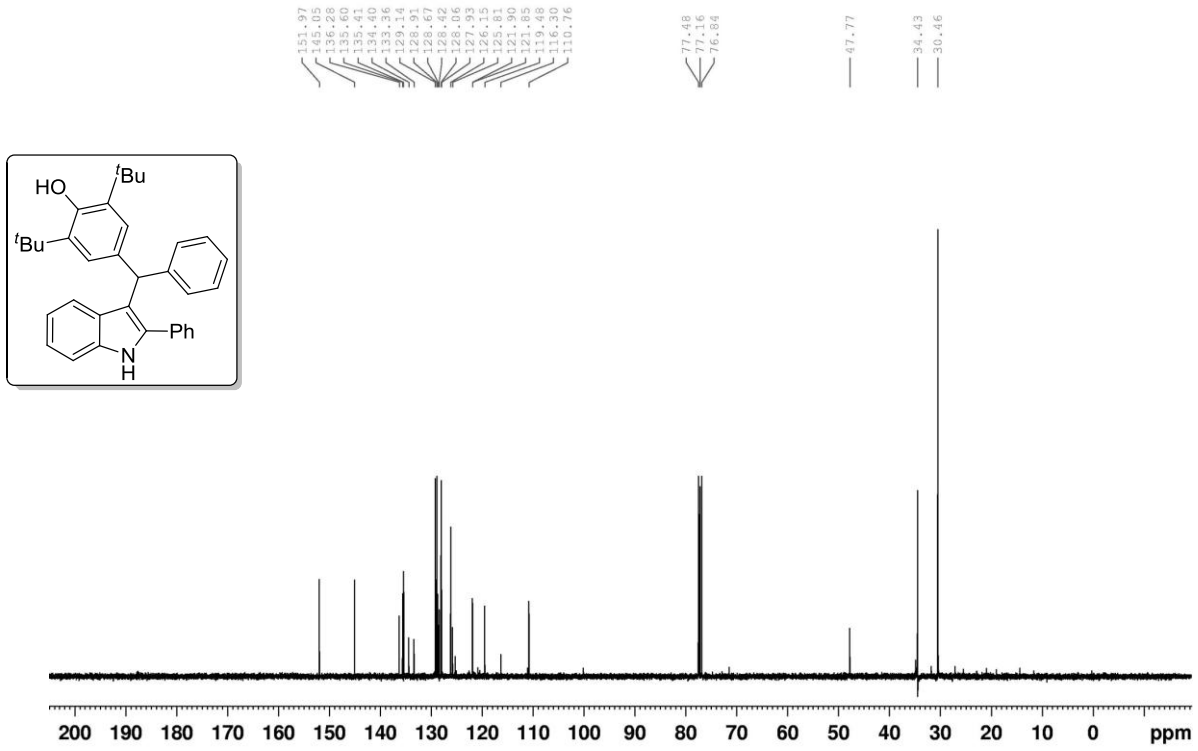
^{13}C NMR spectrum of compound **53**



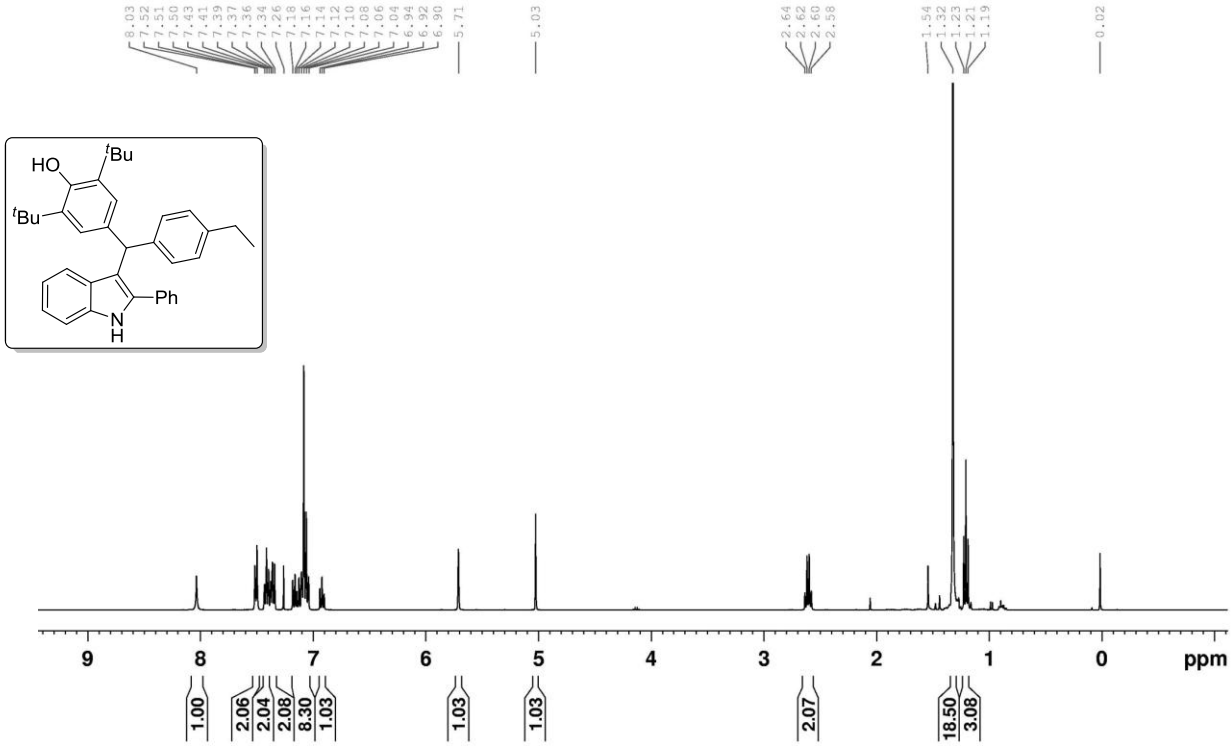
^{1}H NMR spectrum of compound **53a**



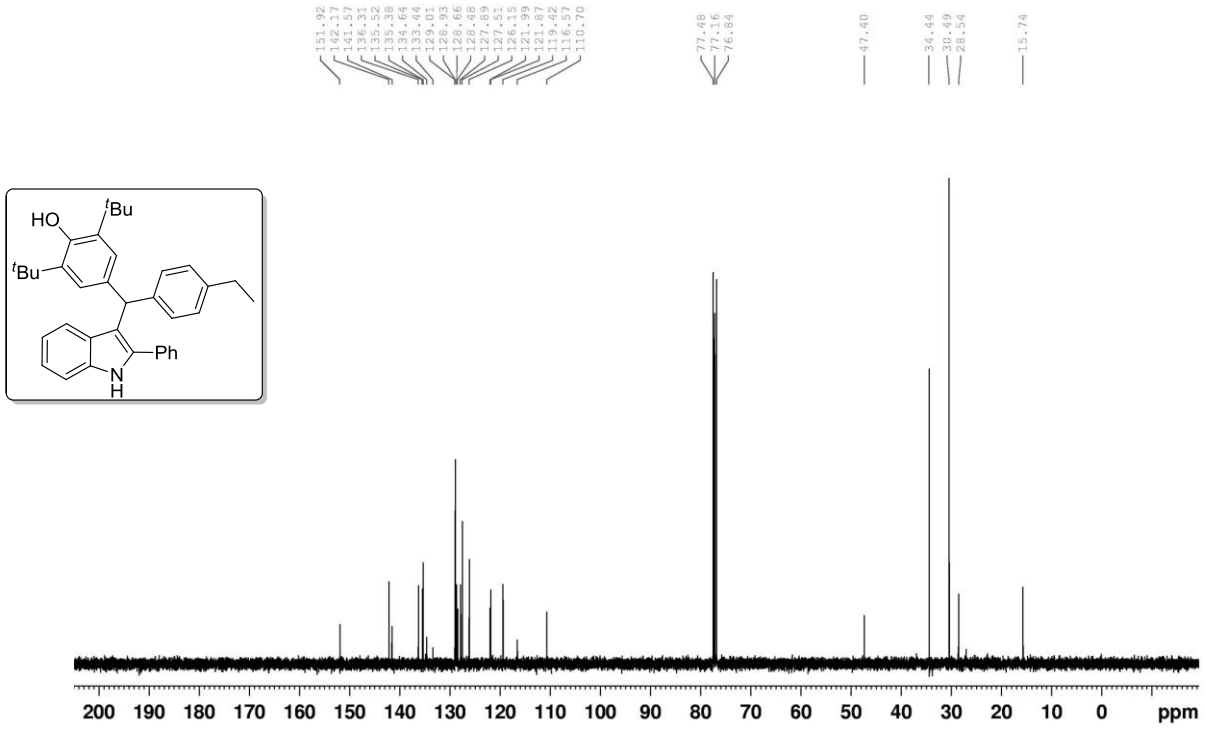
^{13}C NMR spectrum of compound **53a**



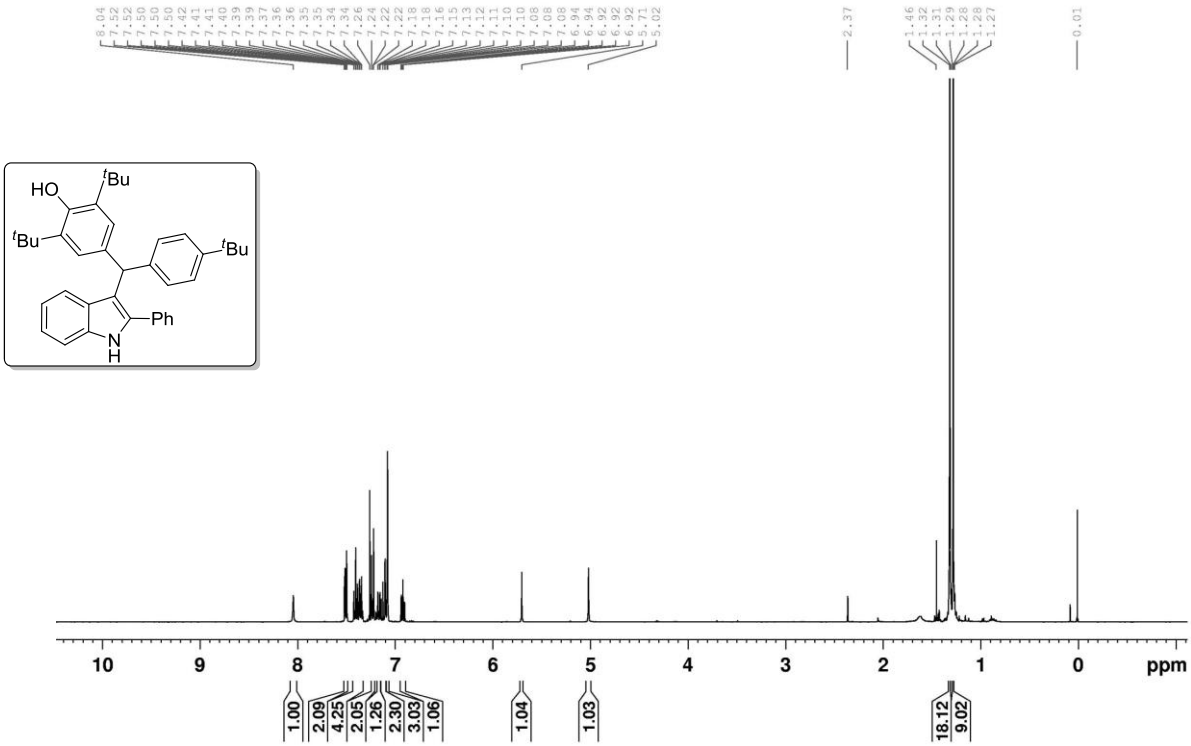
^{1}H NMR spectrum of compound **53b**



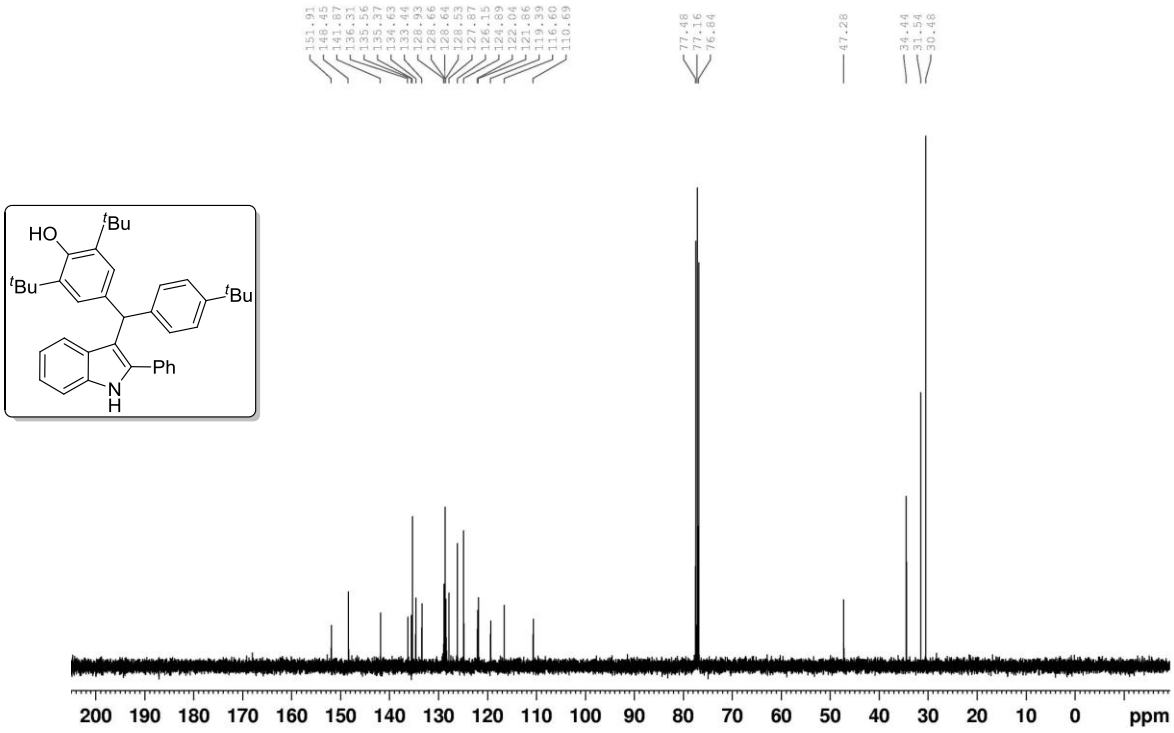
^{13}C NMR spectrum of compound **53b**



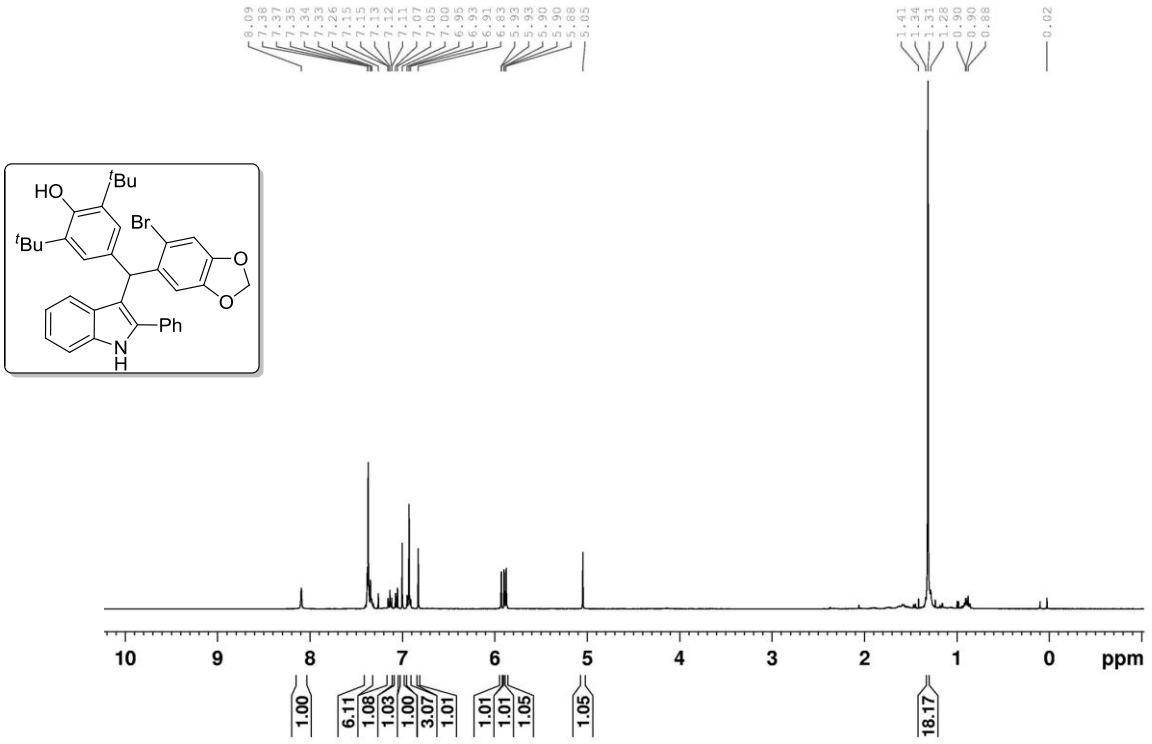
^{1}H NMR spectrum of compound **53c**



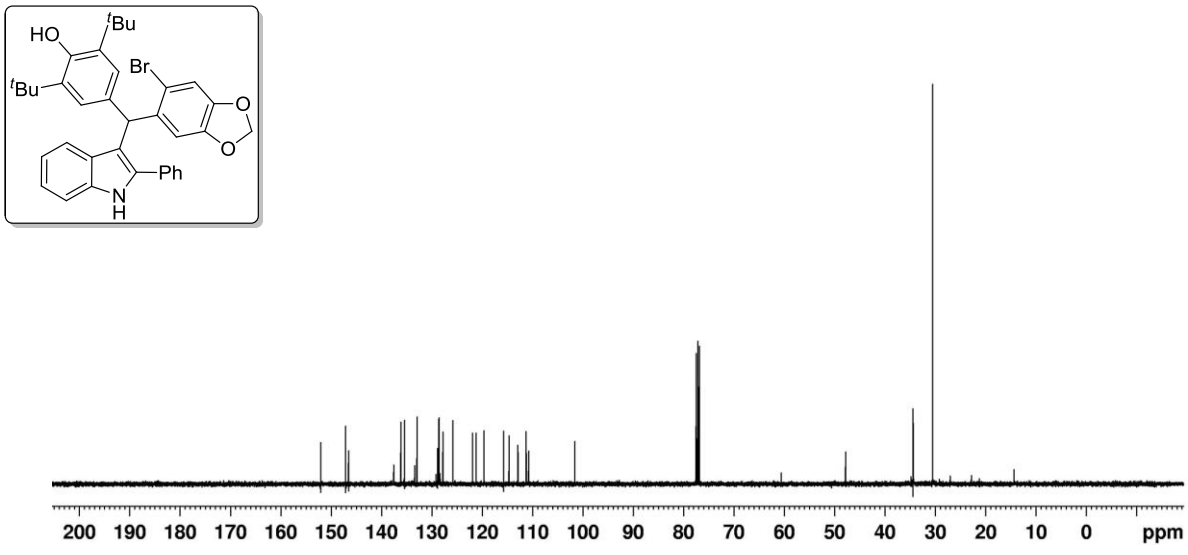
^{13}C NMR spectrum of compound **53c**



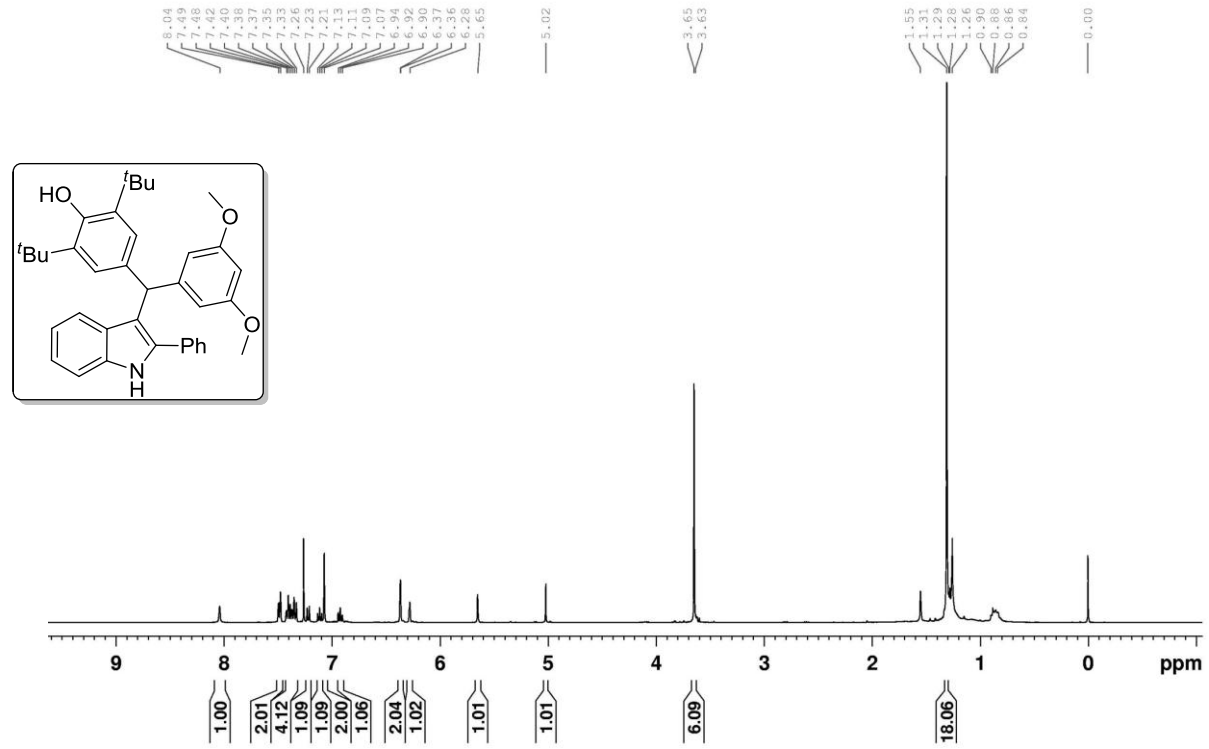
^{1}H NMR spectrum of compound **53d**



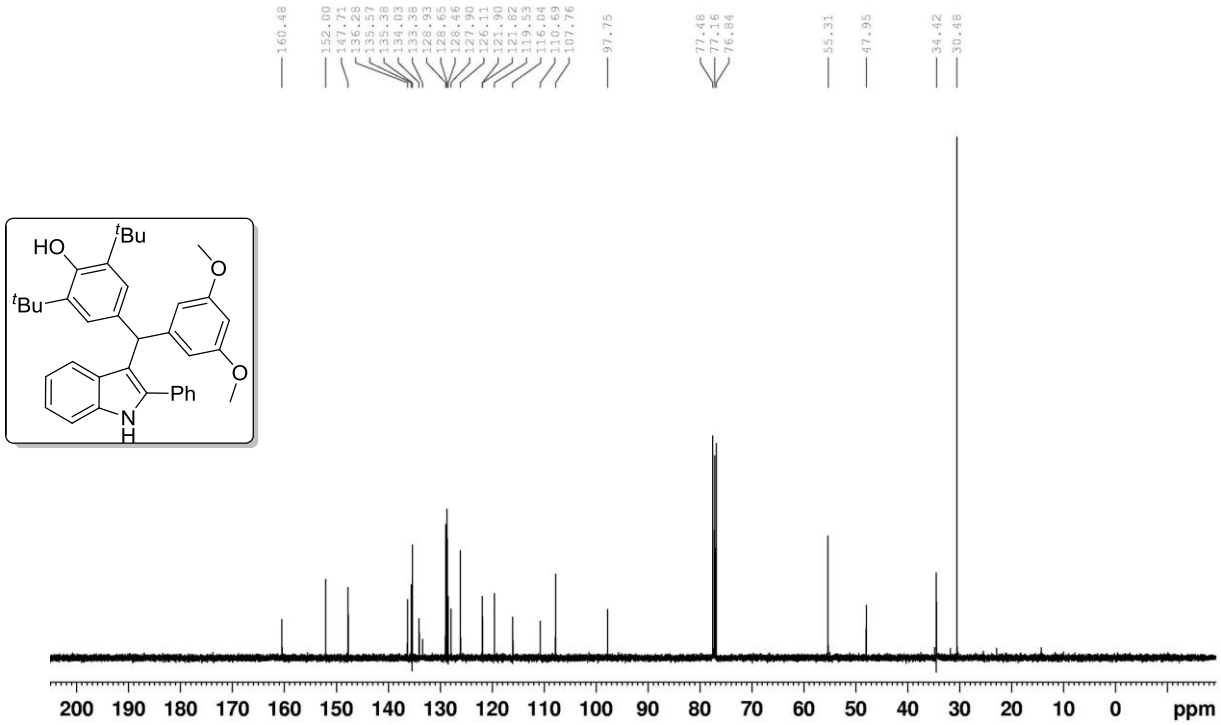
^{13}C NMR spectrum of compound **53d**



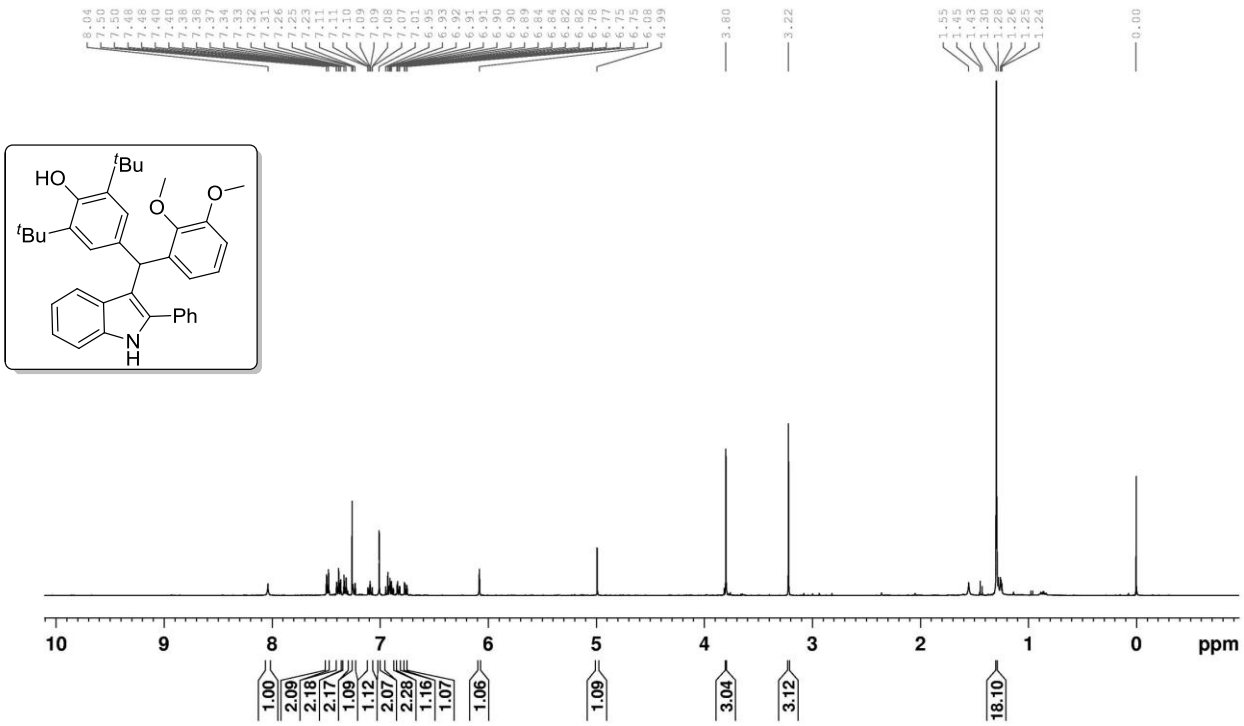
^{1}H NMR spectrum of compound **53e**



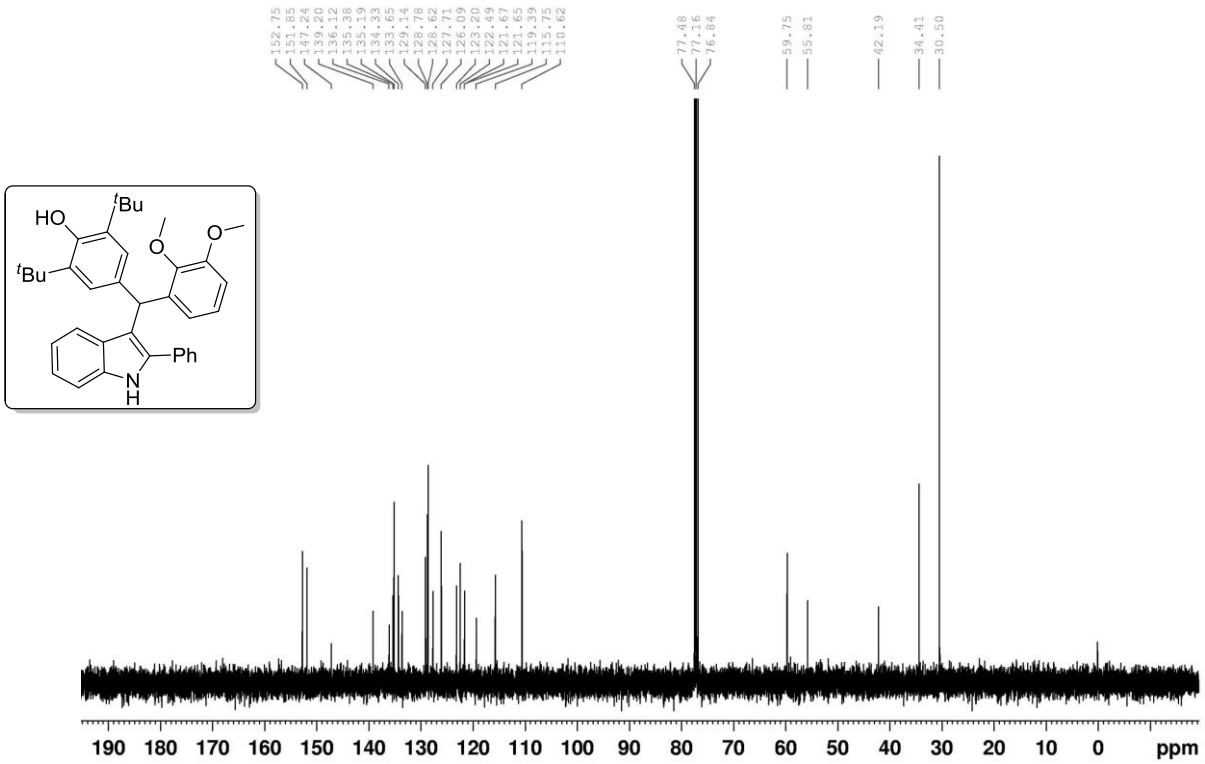
^{13}C NMR spectrum of compound **53e**



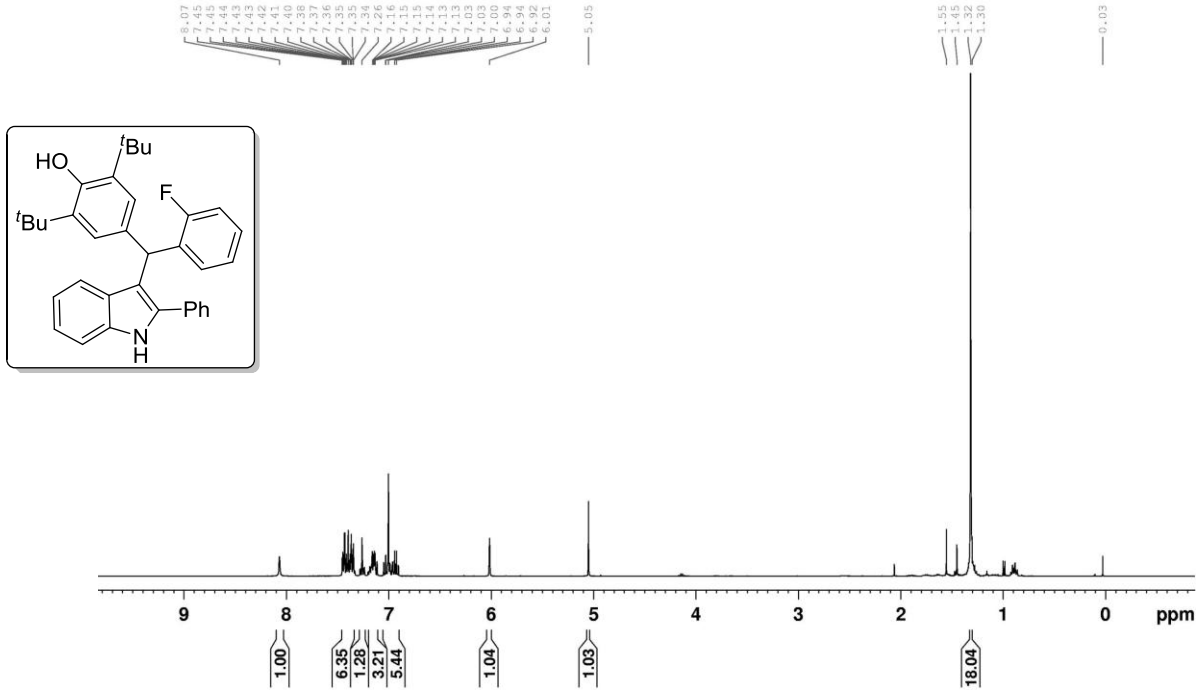
^{1}H NMR spectrum of compound **53f**



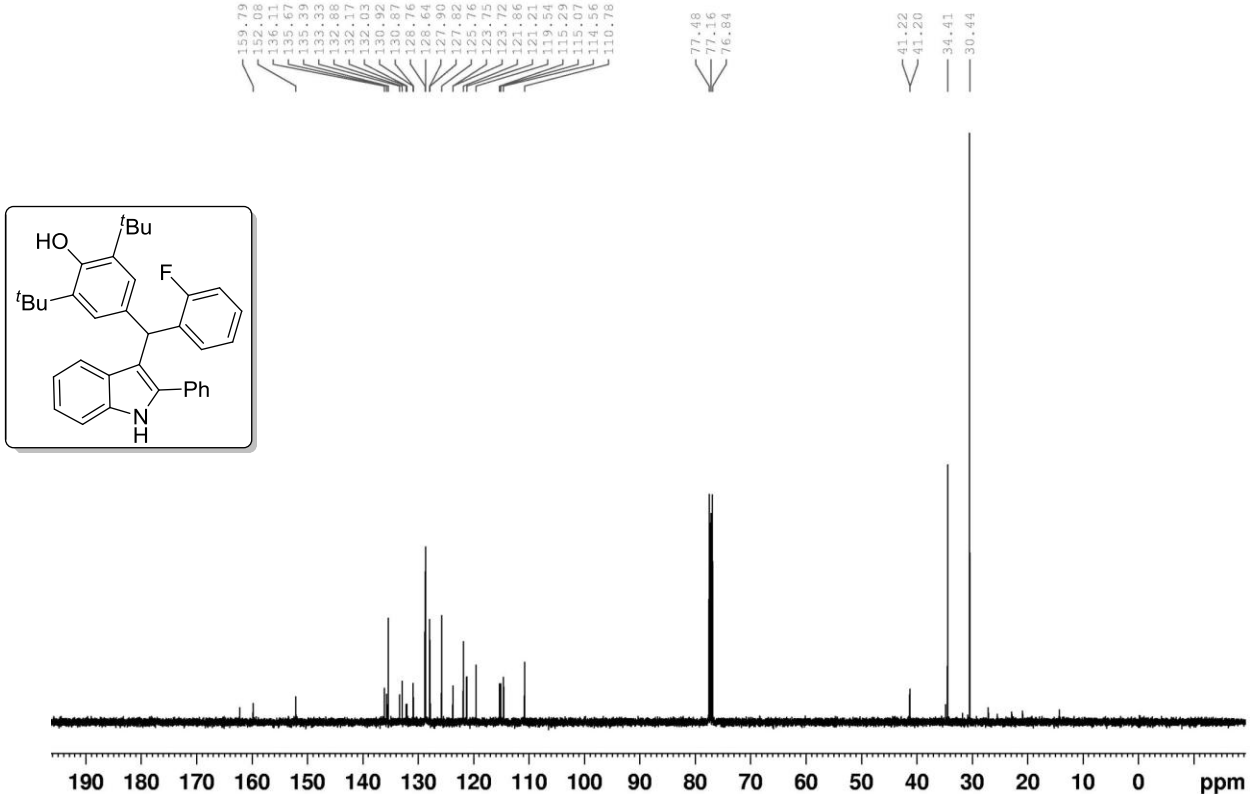
^{13}C NMR spectrum of compound **53f**



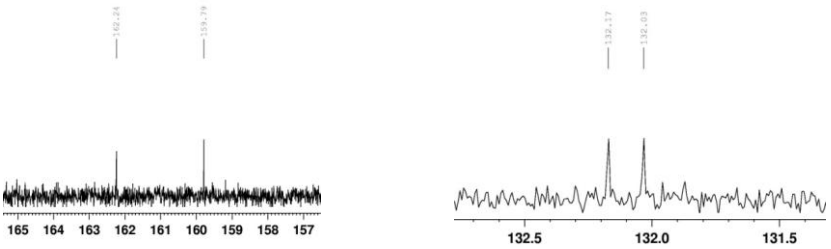
^{1}H NMR spectrum of compound **53g**



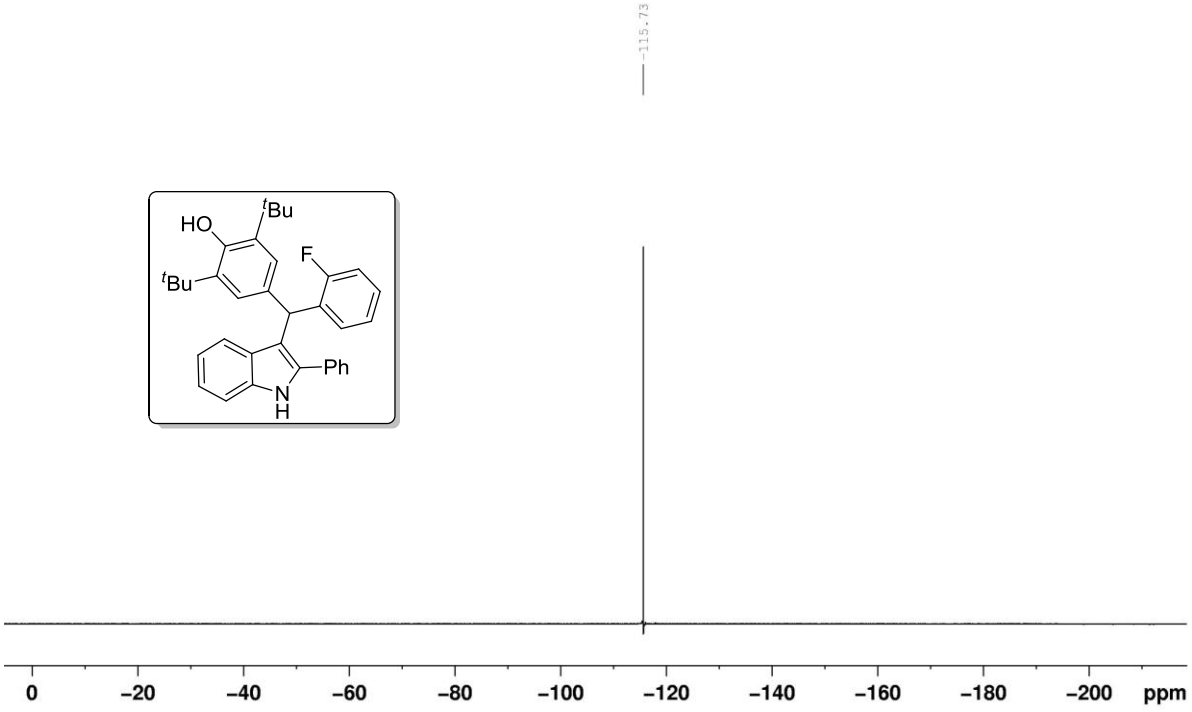
^{13}C NMR spectrum of compound **53g**



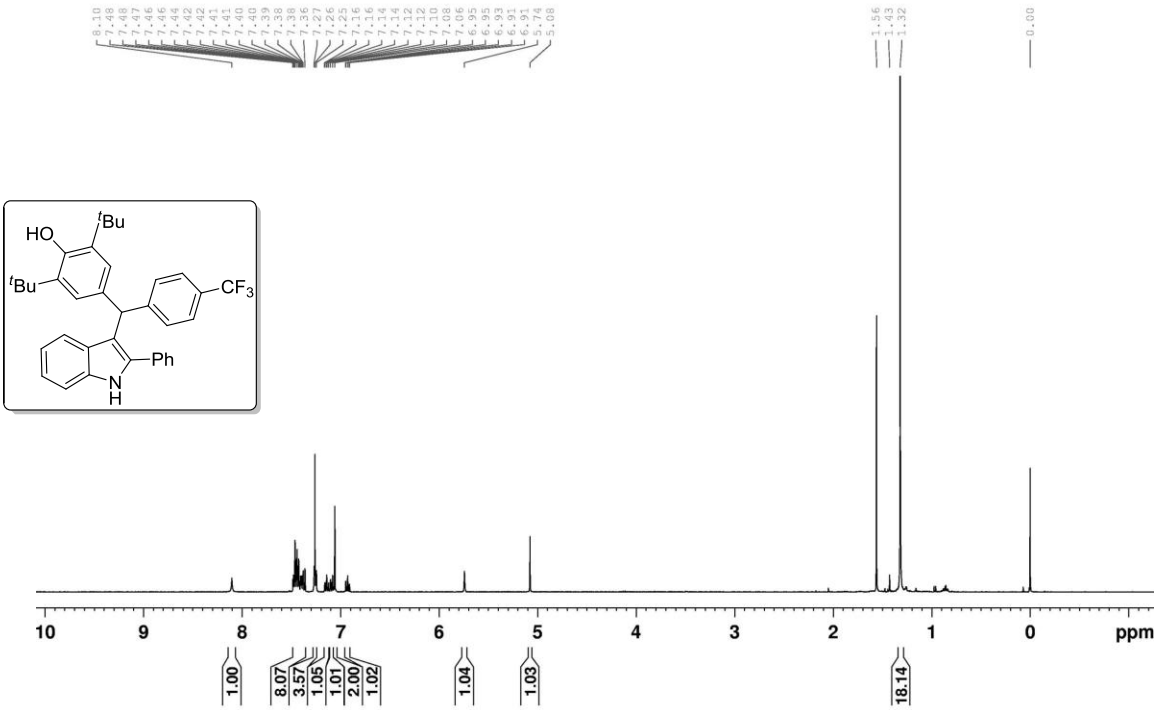
Expansion of ^{13}C spectrum of compound **53g**



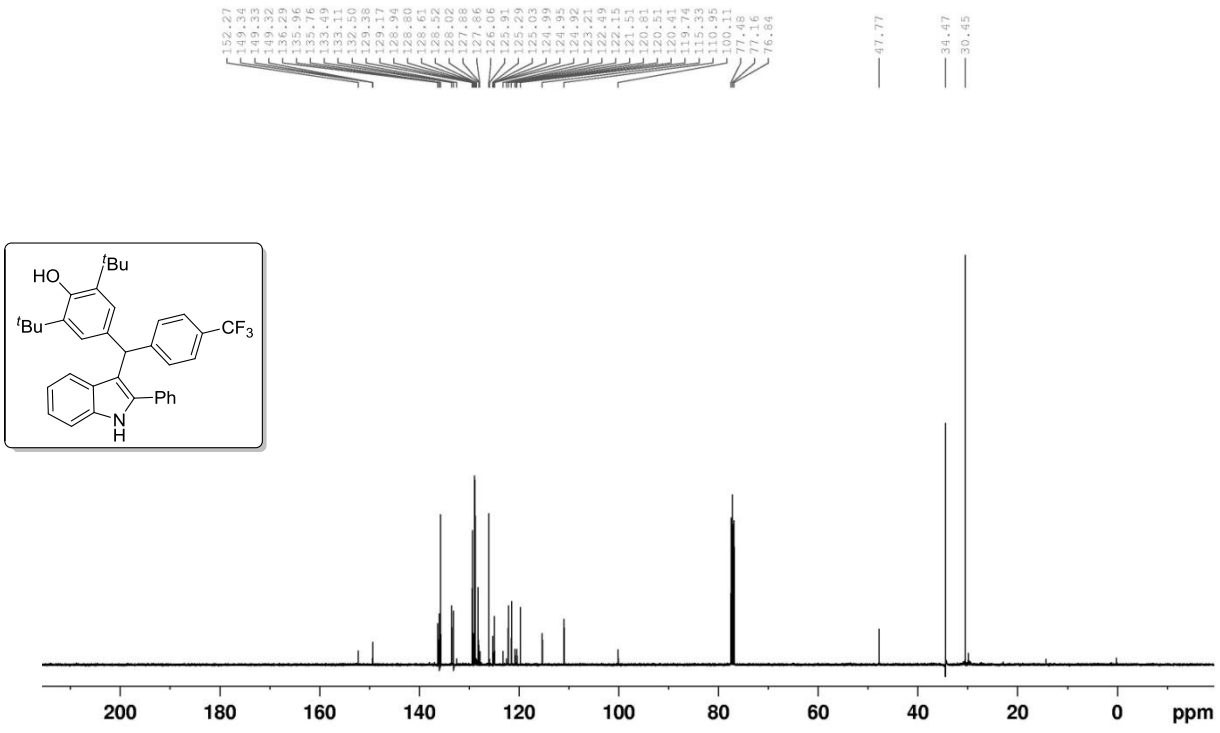
^{19}F NMR spectrum of compound **53g**



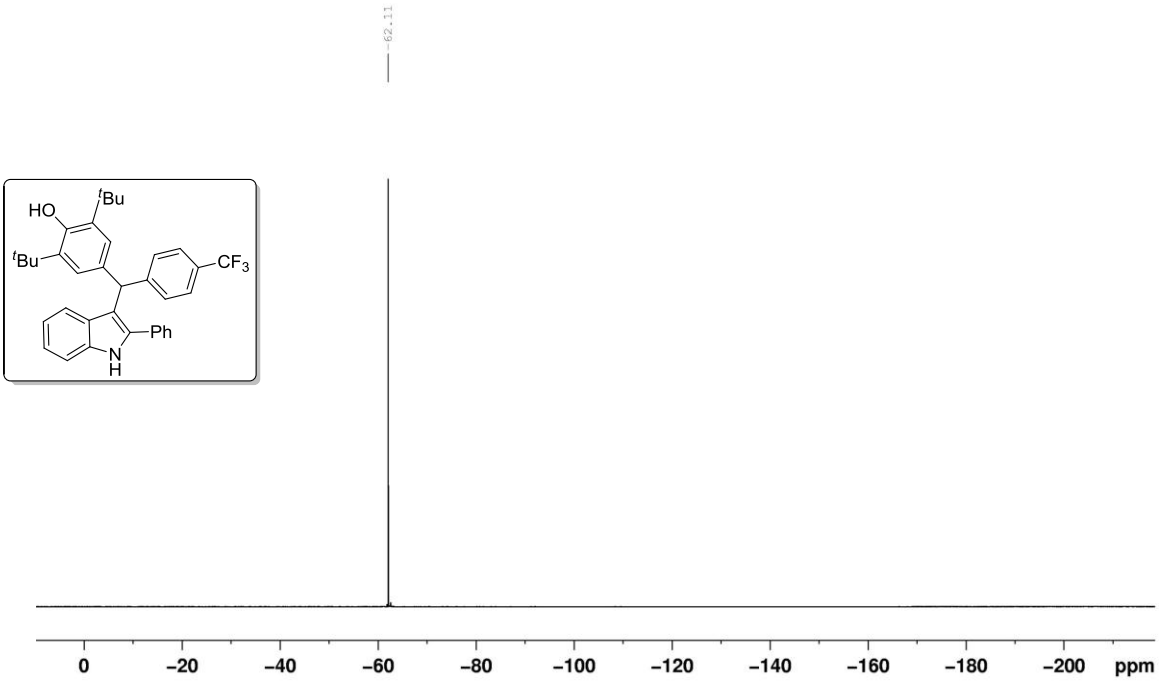
^{1}H NMR spectrum of compound **53h**



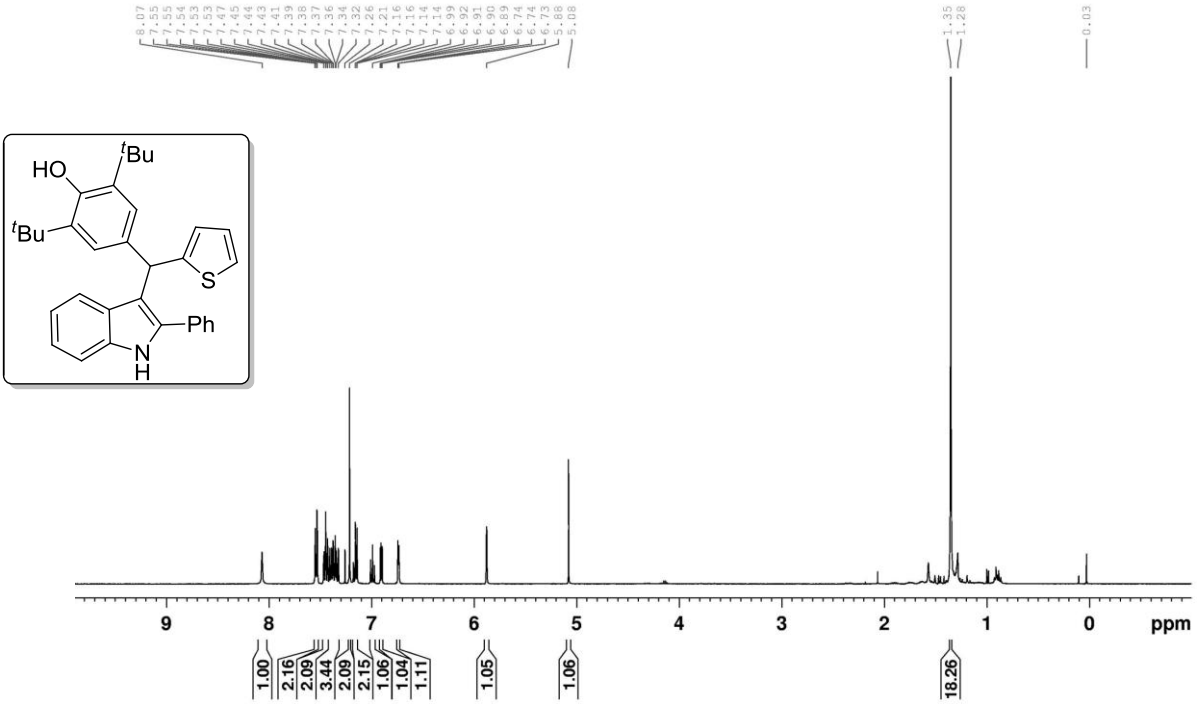
^{13}C NMR spectrum of compound **53h**



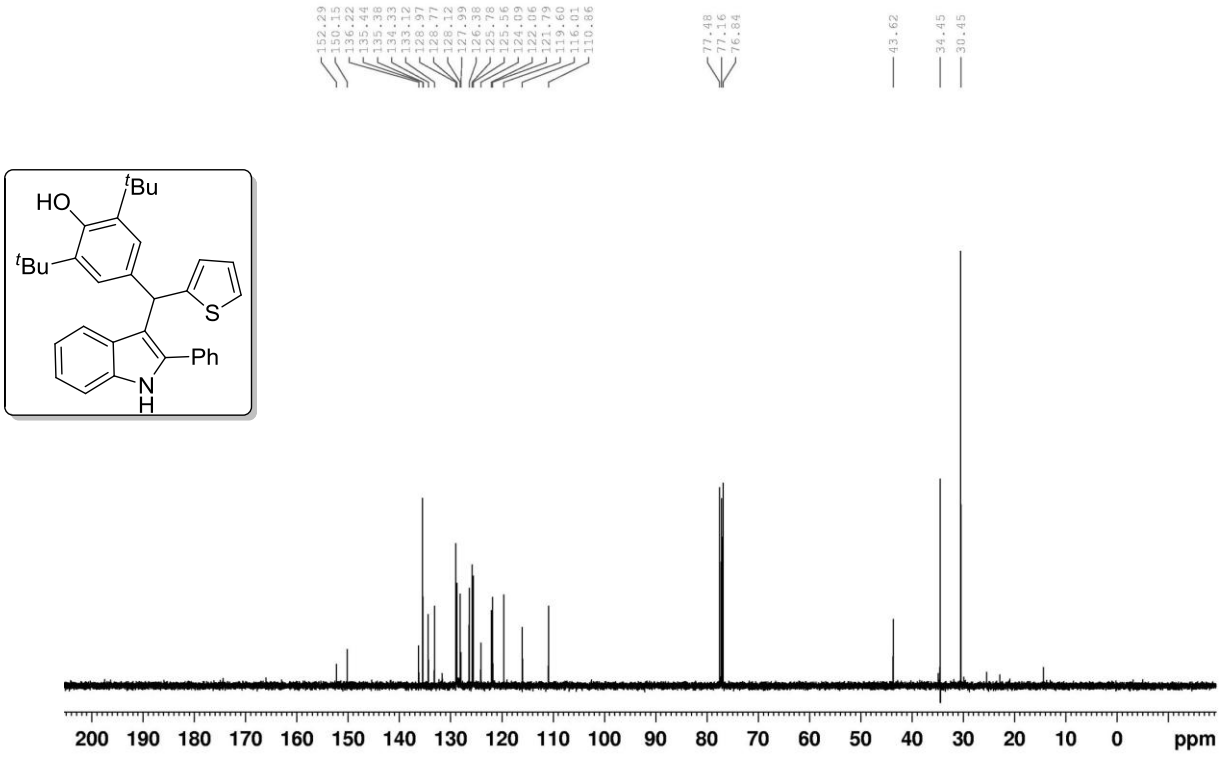
^{19}F NMR spectrum of compound **53h**



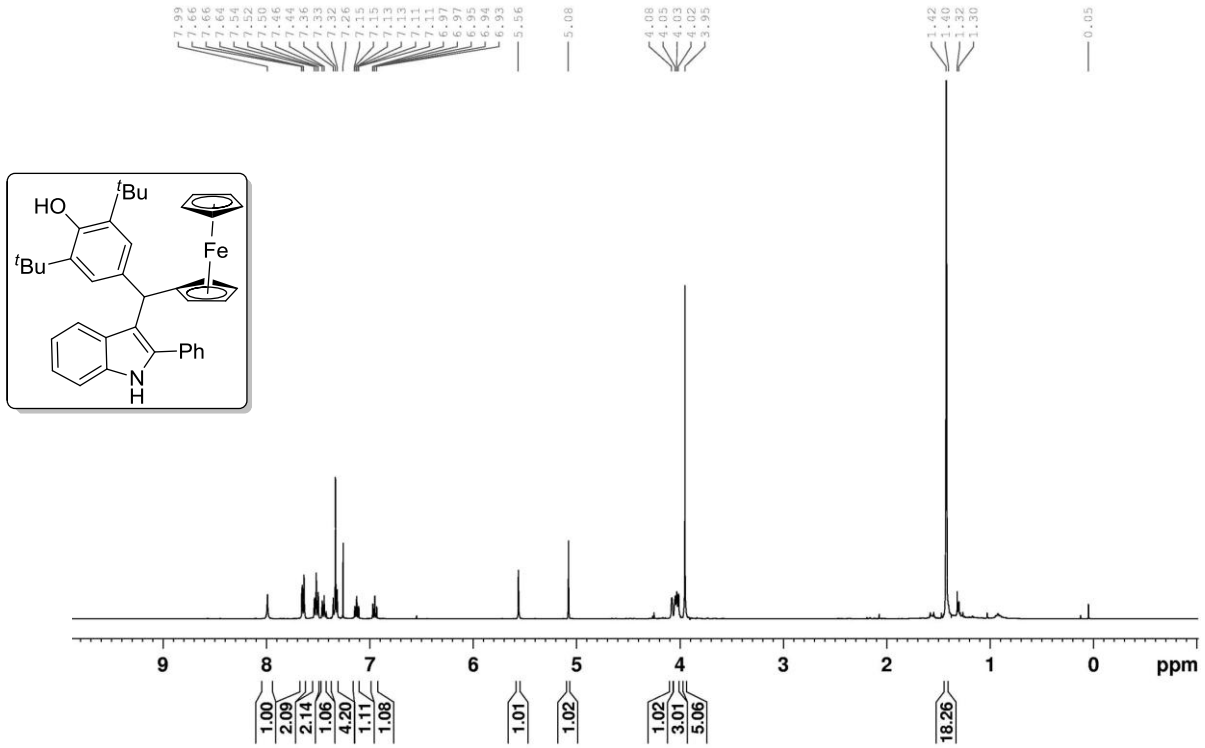
^{1}H NMR spectrum of compound **53i**



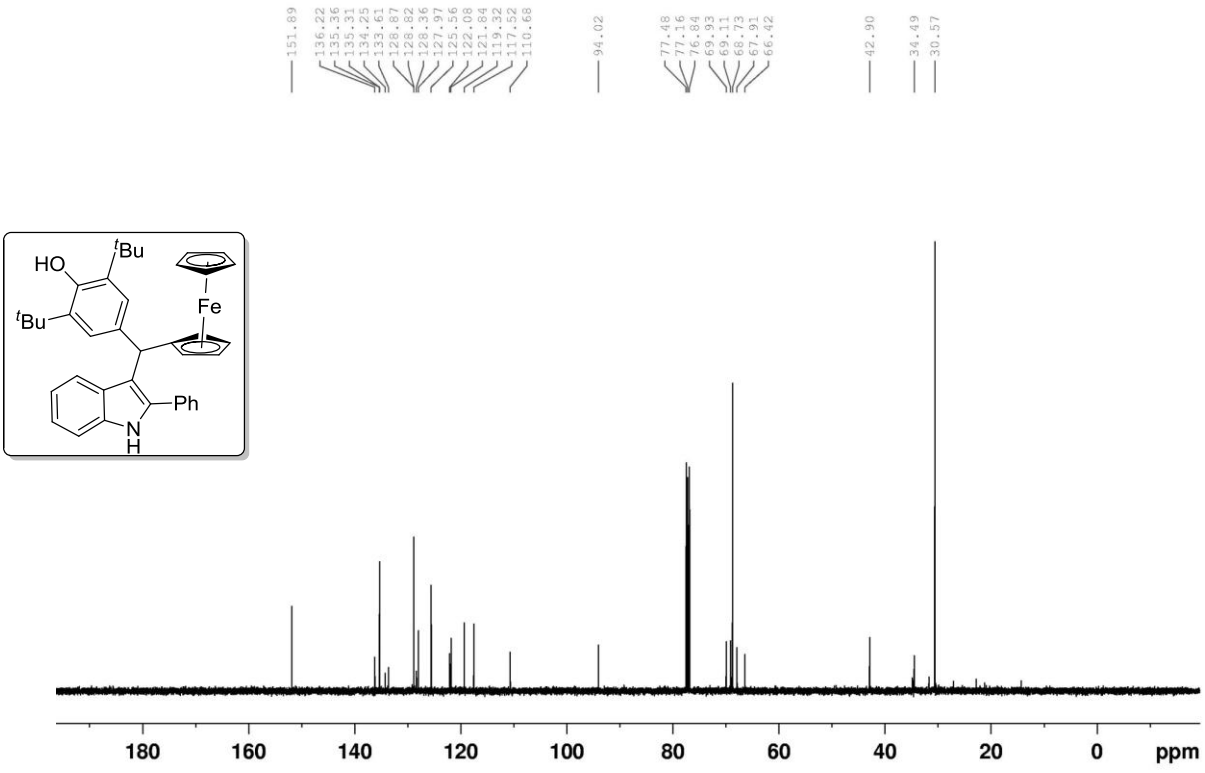
^{13}C NMR spectrum of compound **53i**



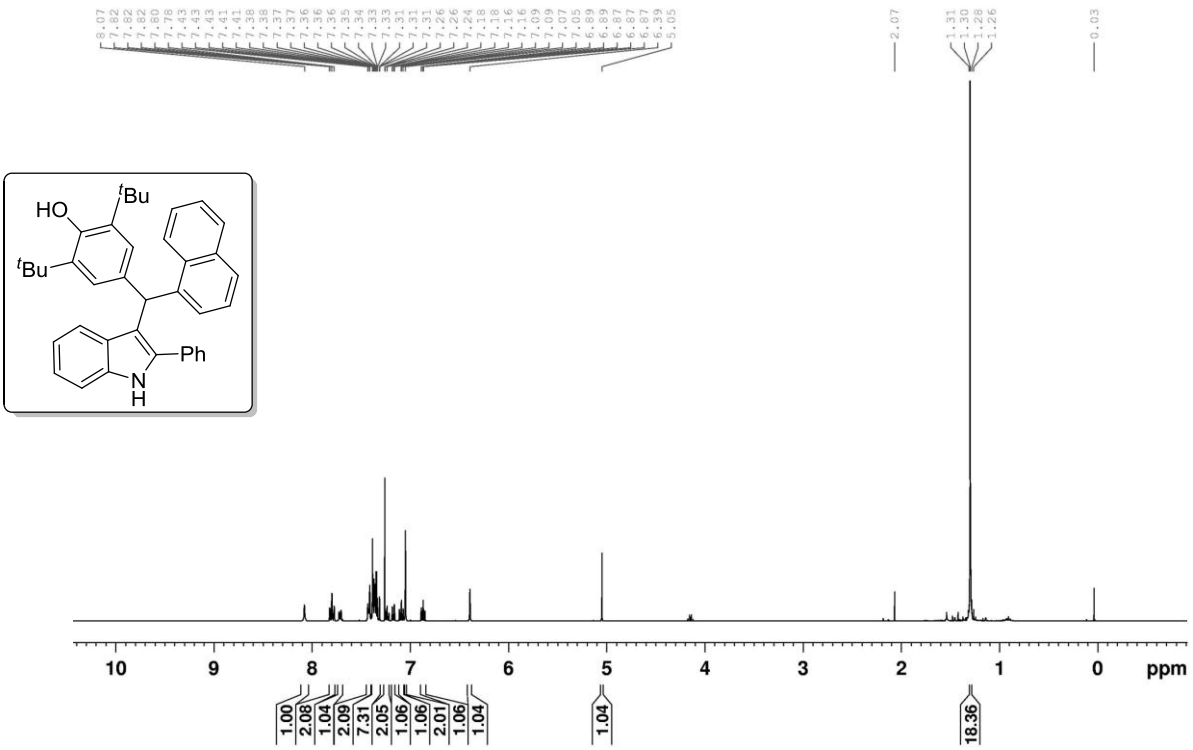
^{1}H NMR spectrum of compound **53j**



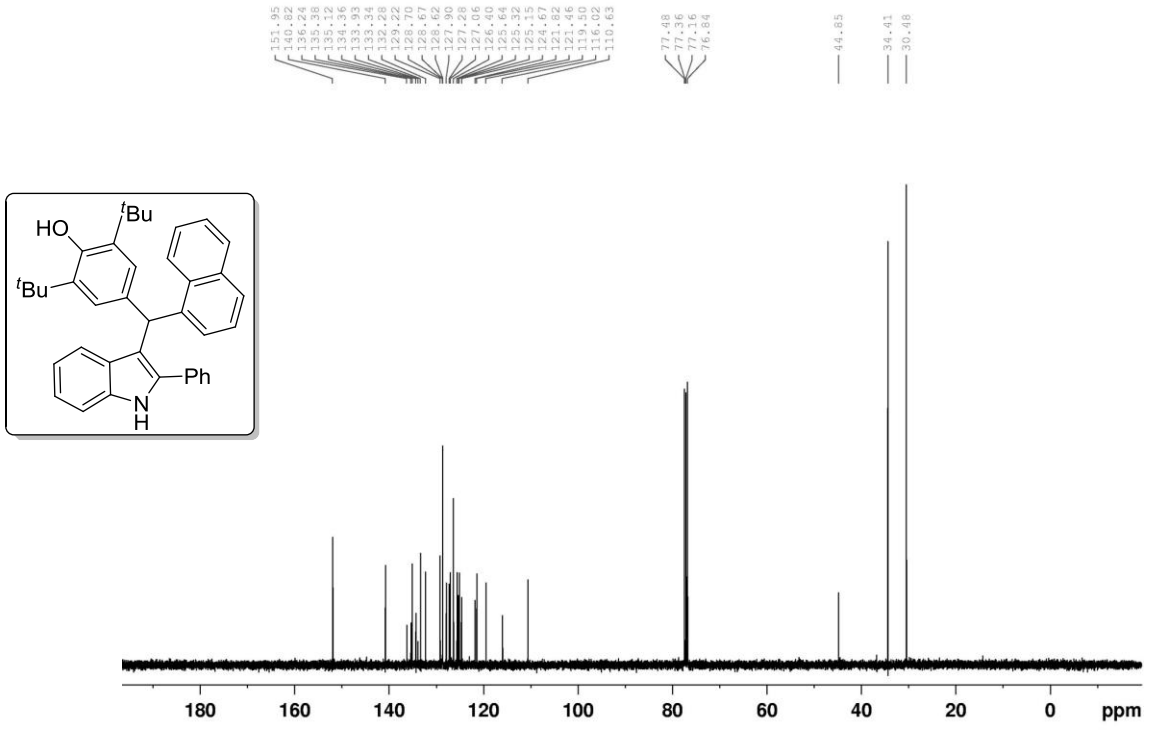
^{13}C NMR spectrum of compound **53j**



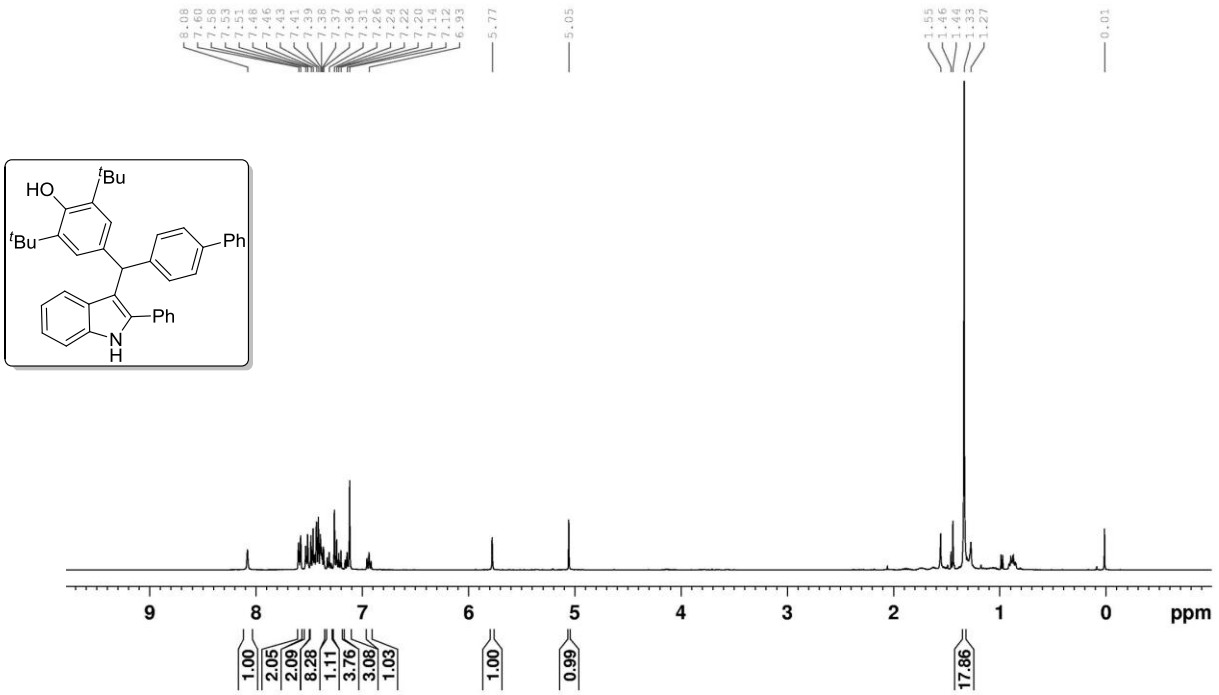
^{1}H NMR spectrum of compound **53k**



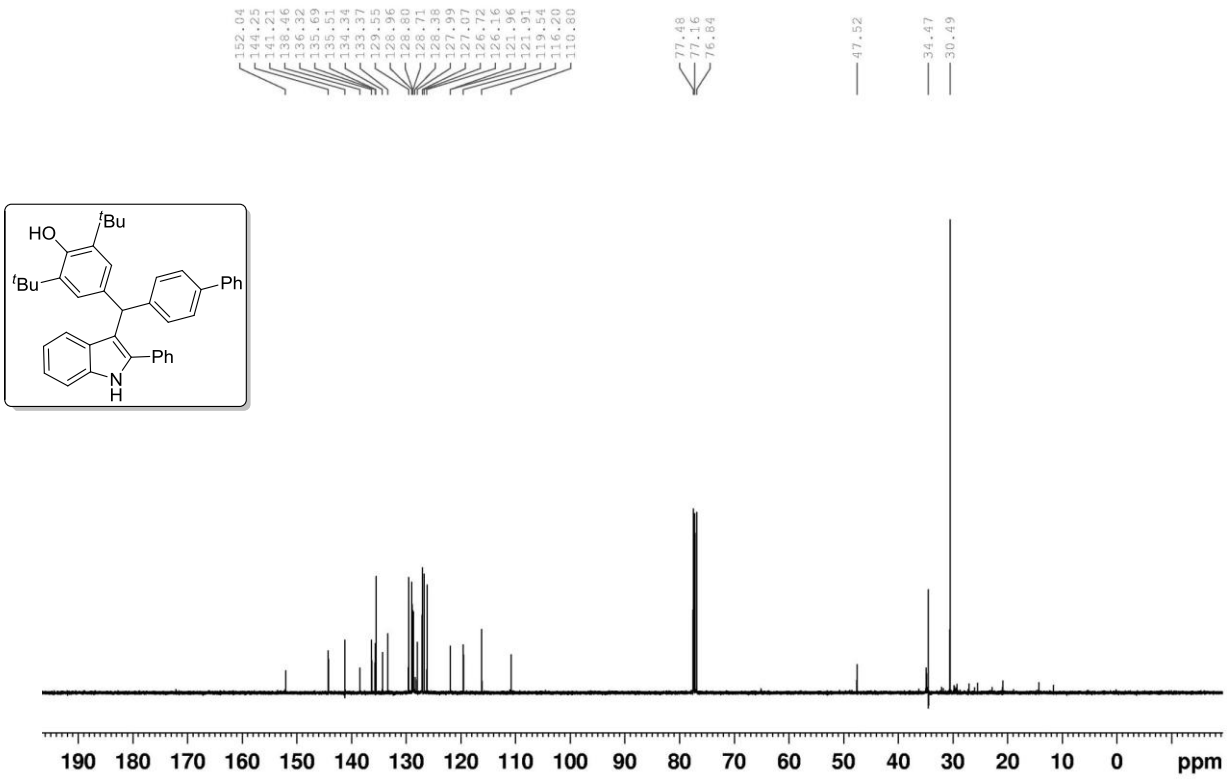
^{13}C NMR spectrum of compound **53k**



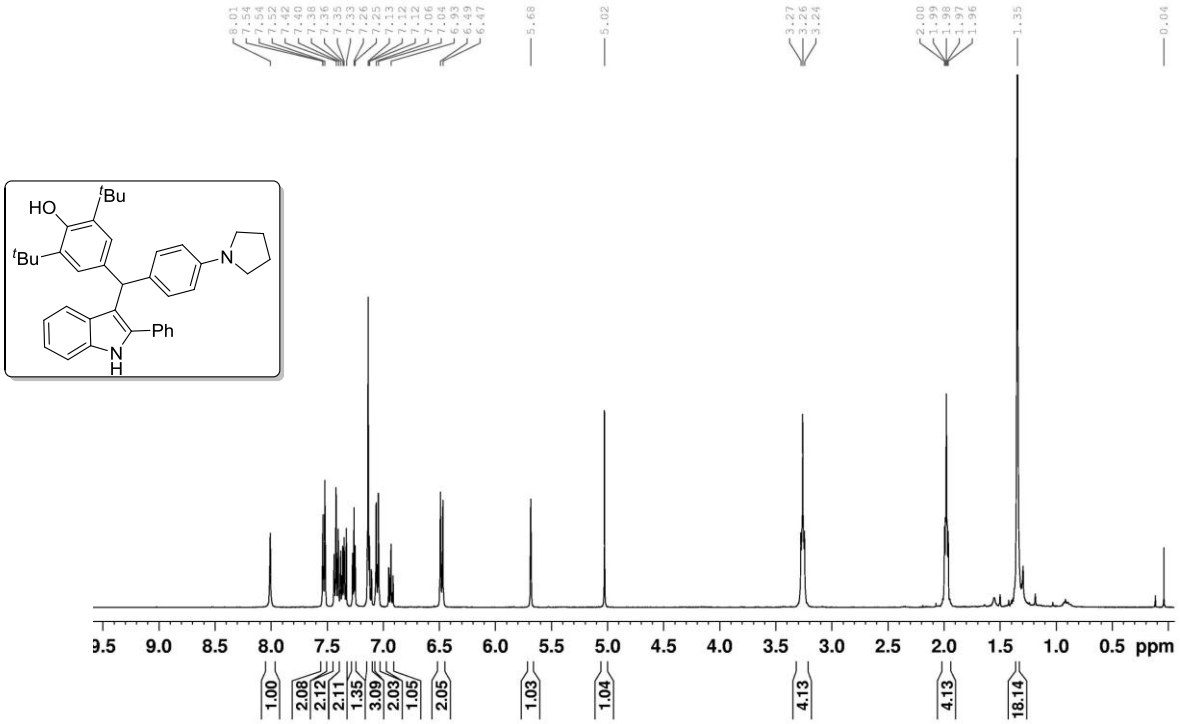
^{1}H NMR spectrum of compound **53l**



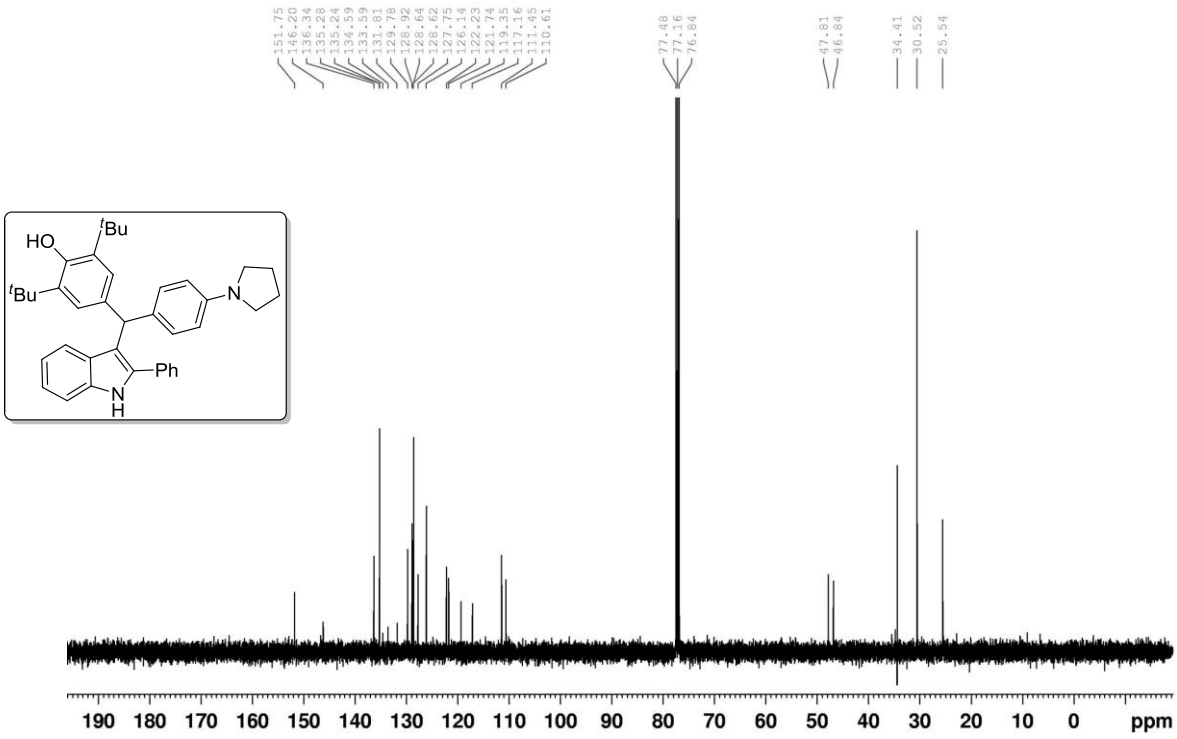
^{13}C NMR spectrum of compound **53l**



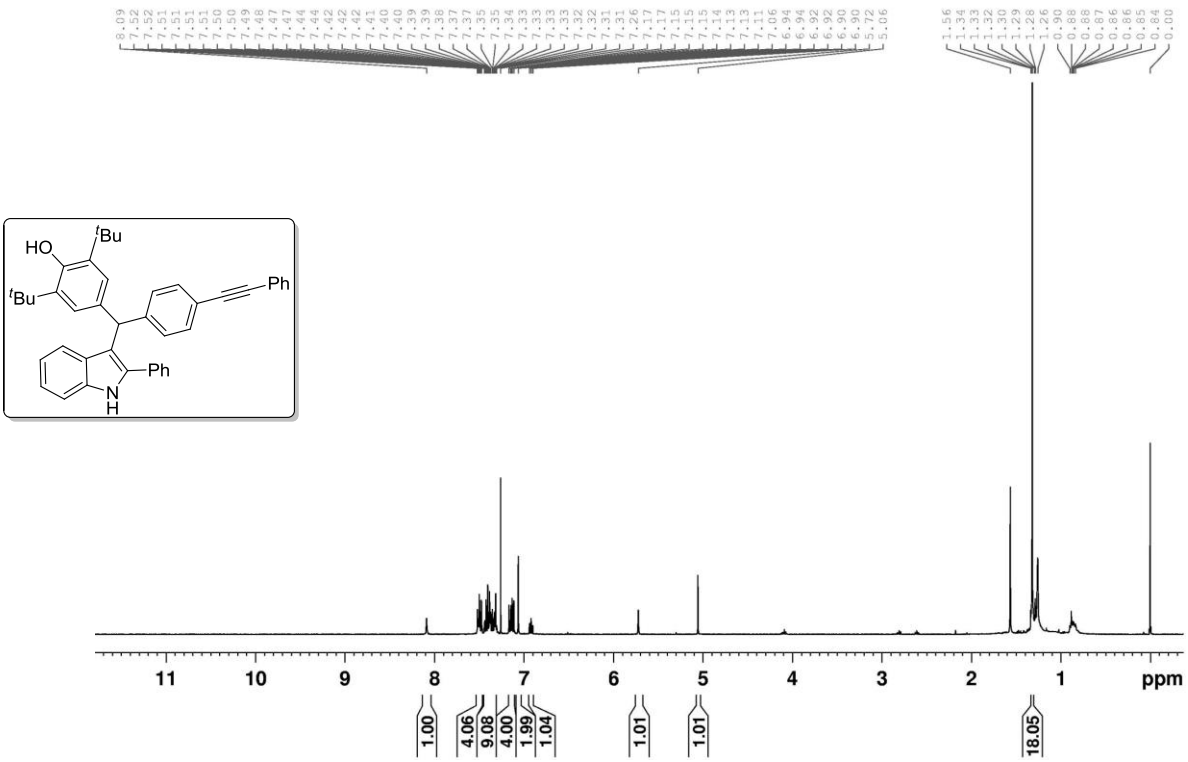
^{1}H NMR spectrum of compound **53m**



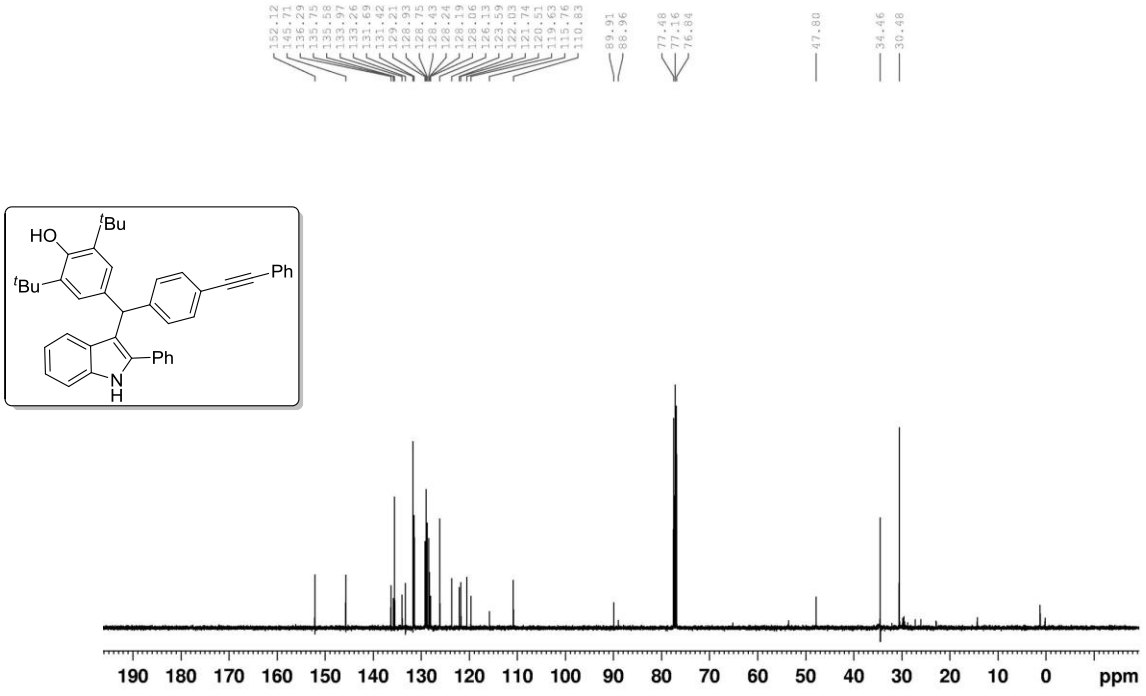
^{13}C NMR spectrum of compound **53m**



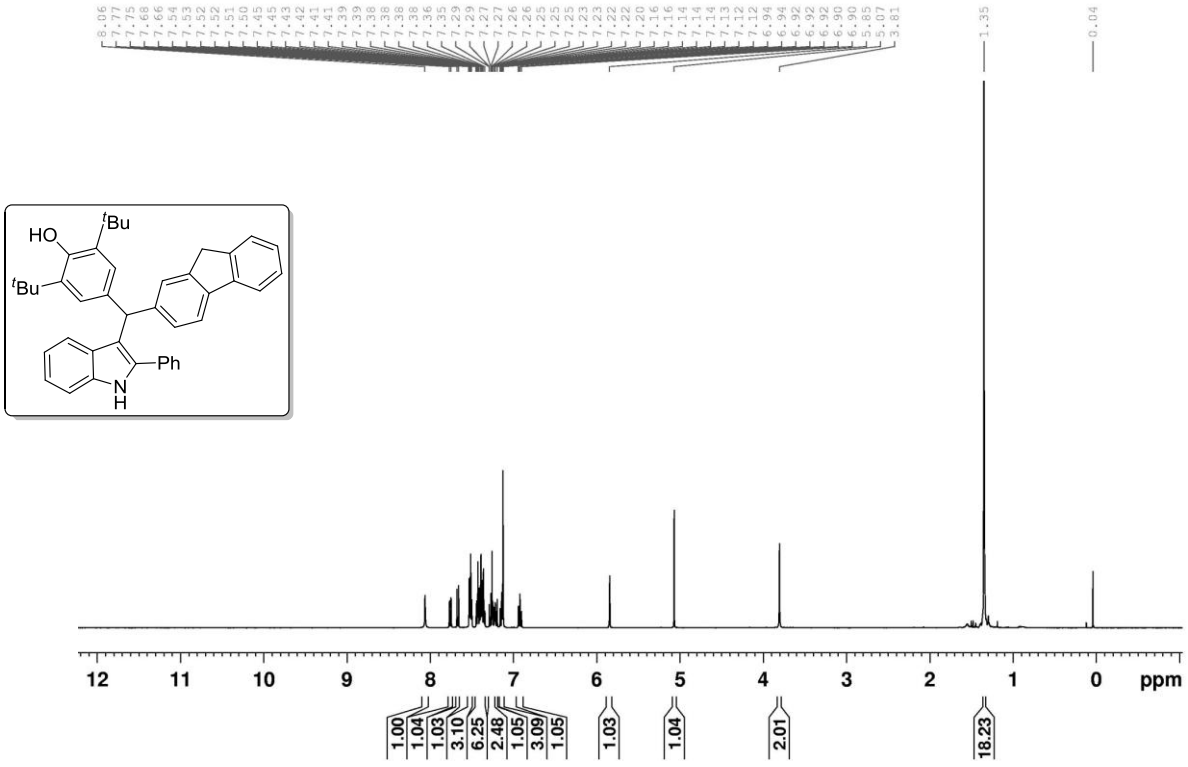
^{1}H NMR spectrum of compound **53n**



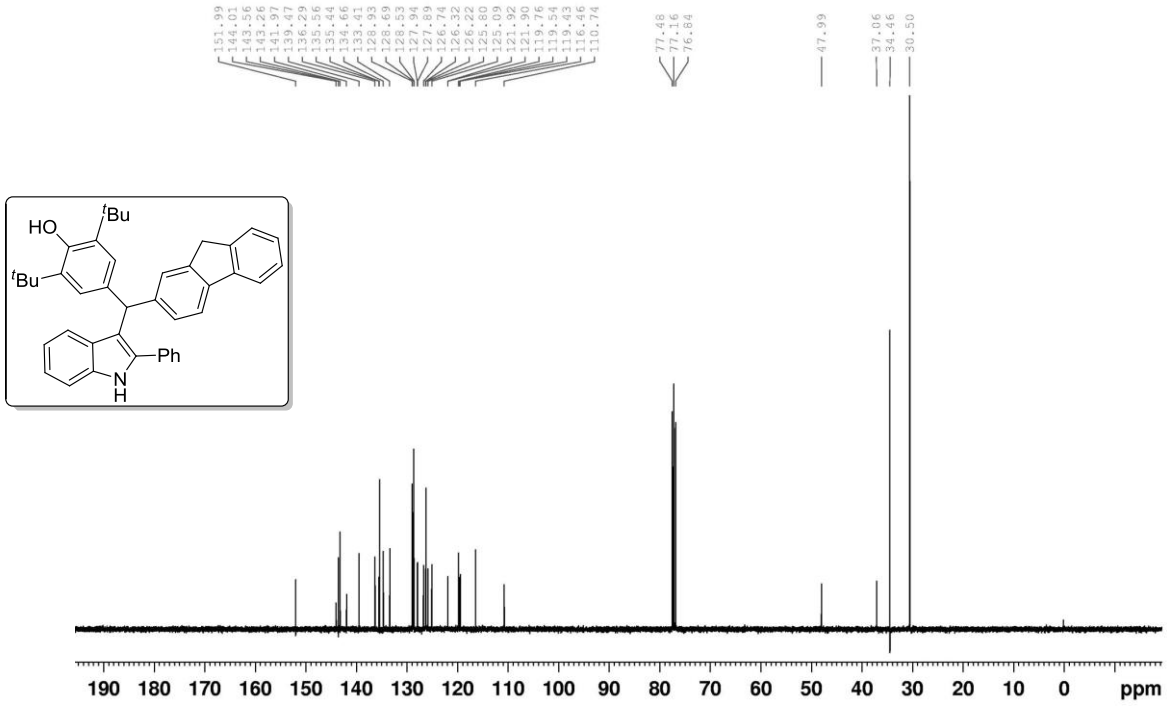
^{13}C NMR spectrum of compound **53n**



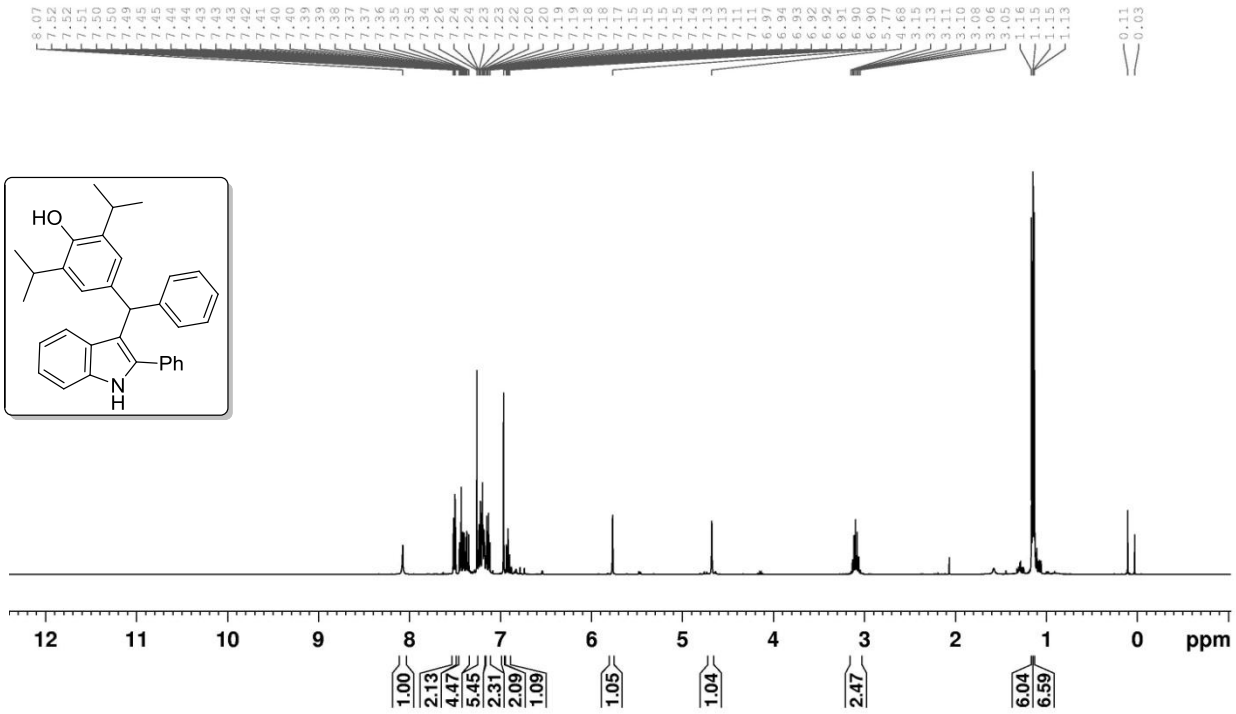
^{1}H NMR spectrum of compound **53o**



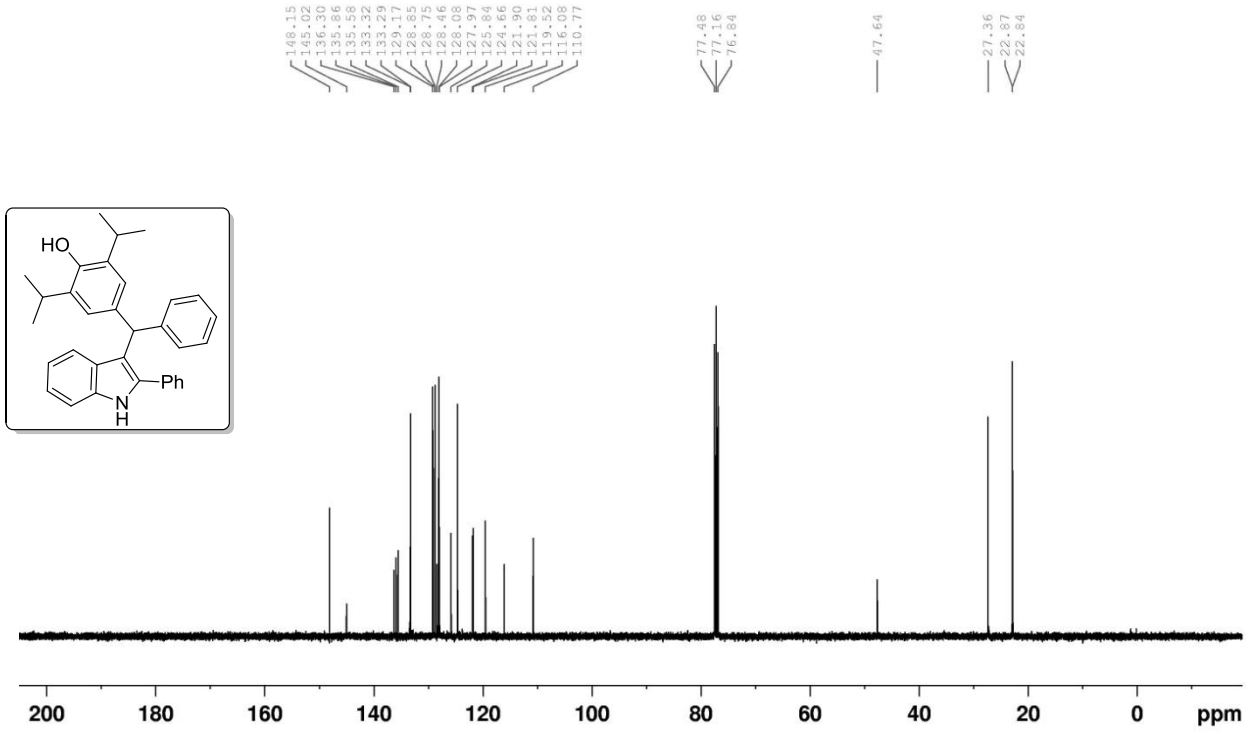
^{13}C NMR spectrum of compound **53o**



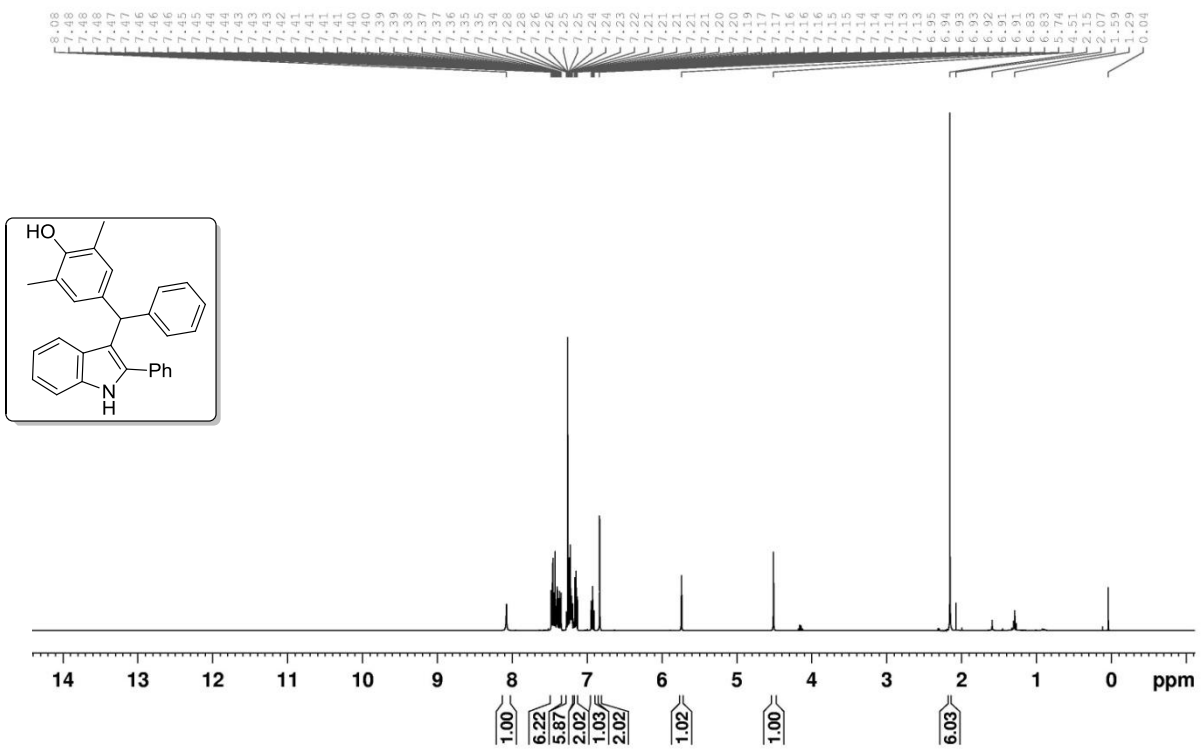
^{1}H NMR spectrum of compound **53p**



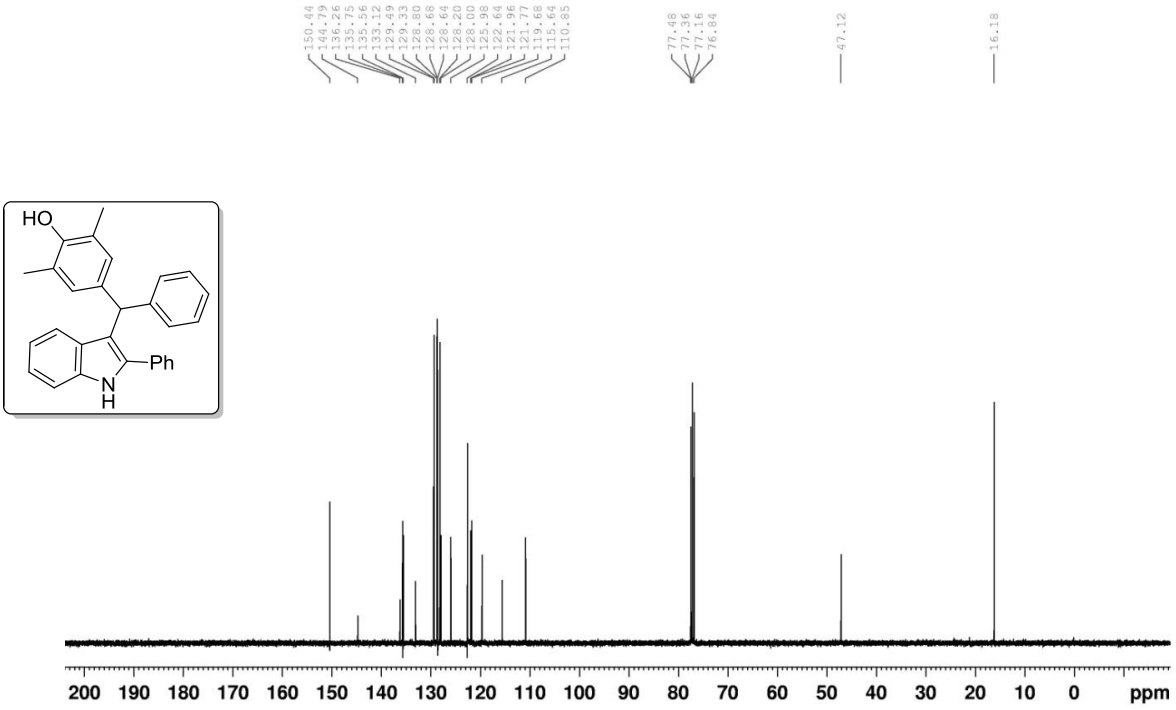
^{13}C NMR spectrum of compound **53p**



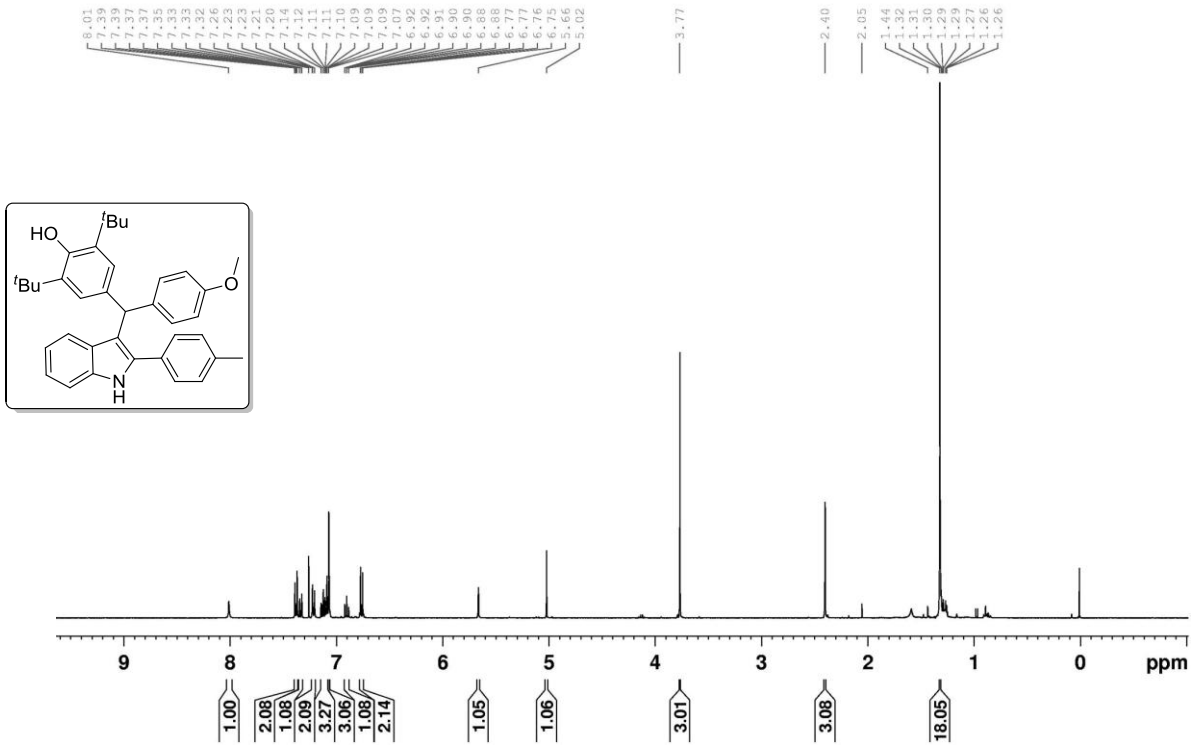
^{1}H NMR spectrum of compound **53q**



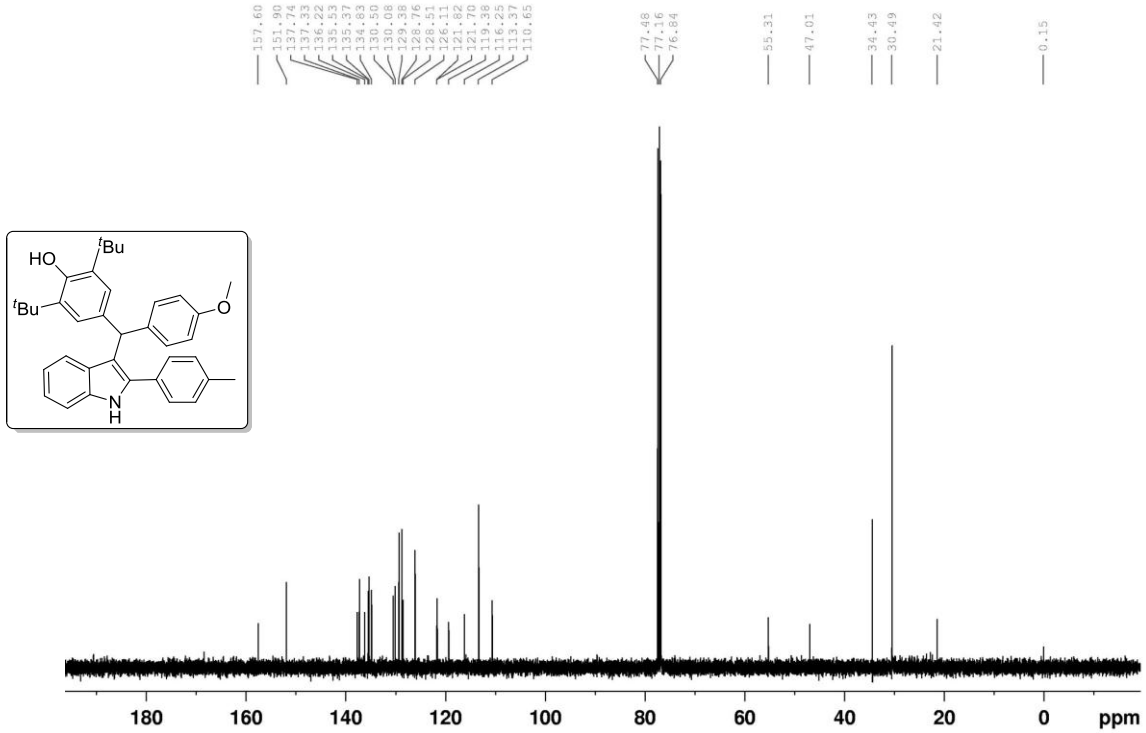
^{13}C NMR spectrum of compound **53q**



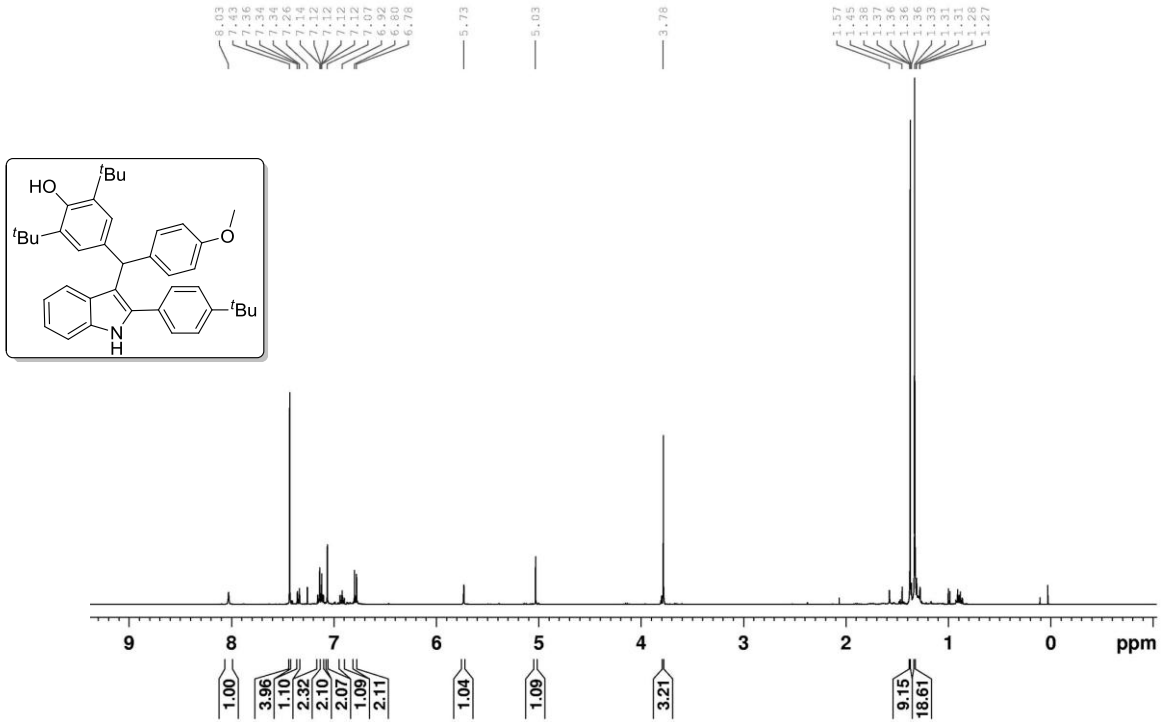
^{1}H NMR spectrum of compound **62a**



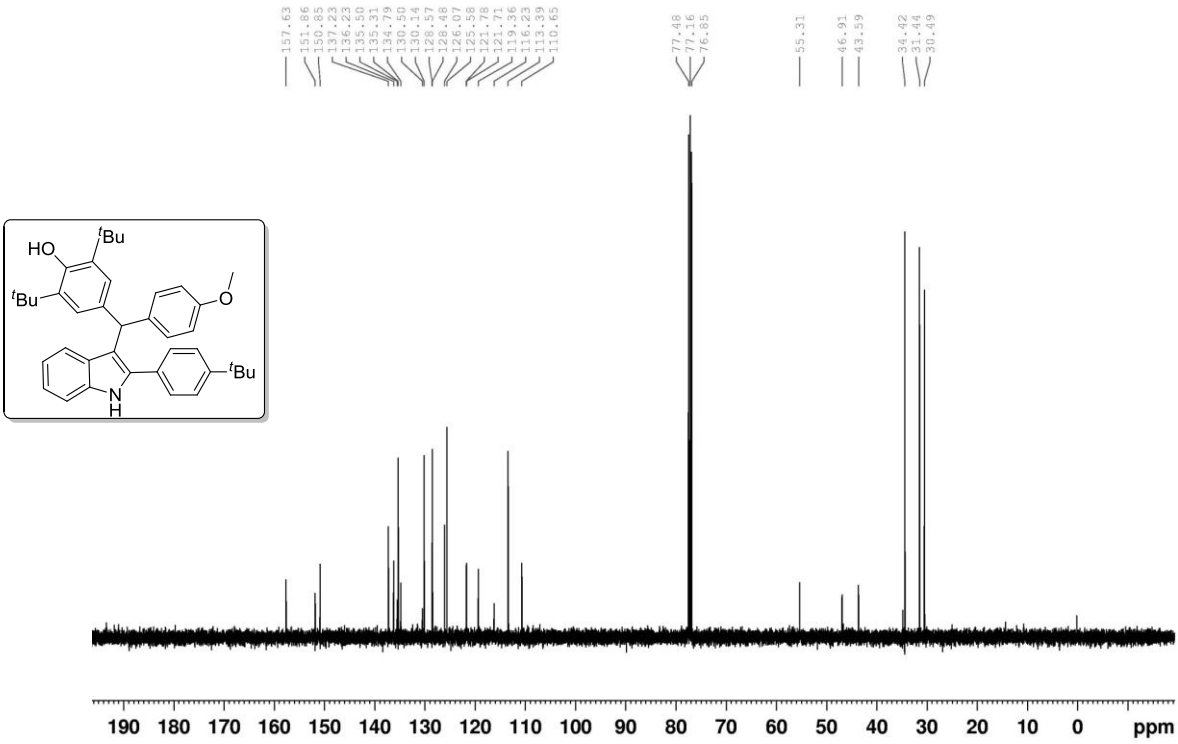
^{13}C NMR spectrum of compound **62a**



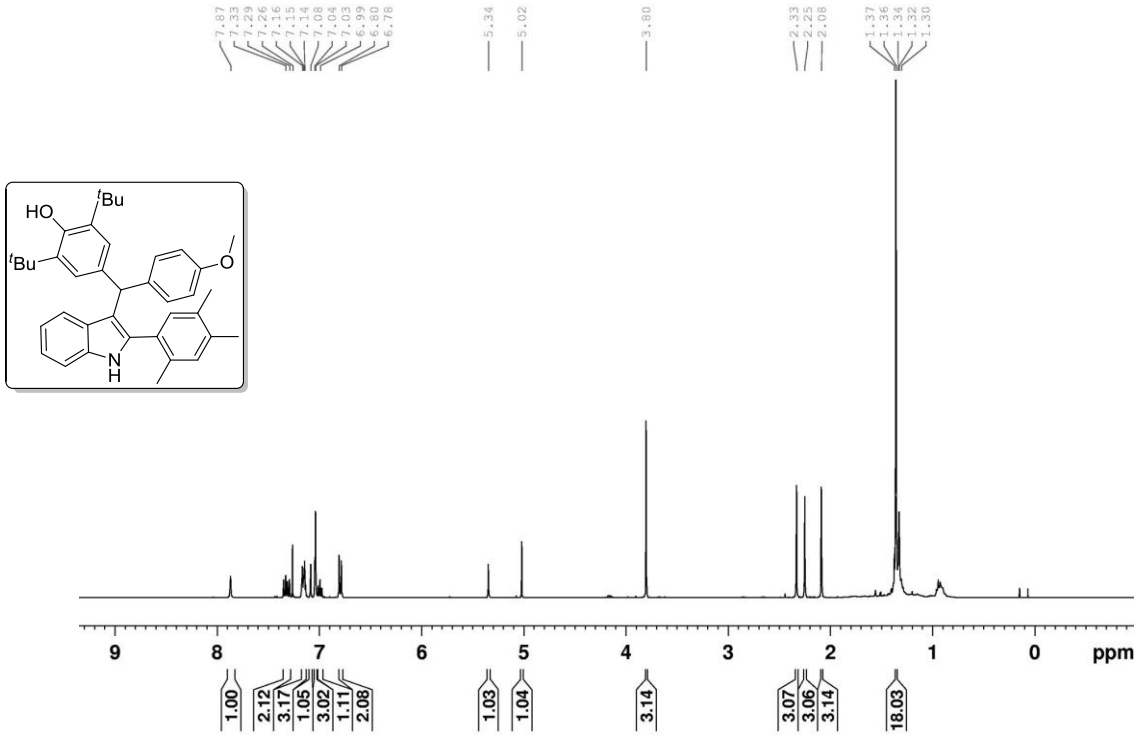
^{1}H NMR spectrum of compound **62b**



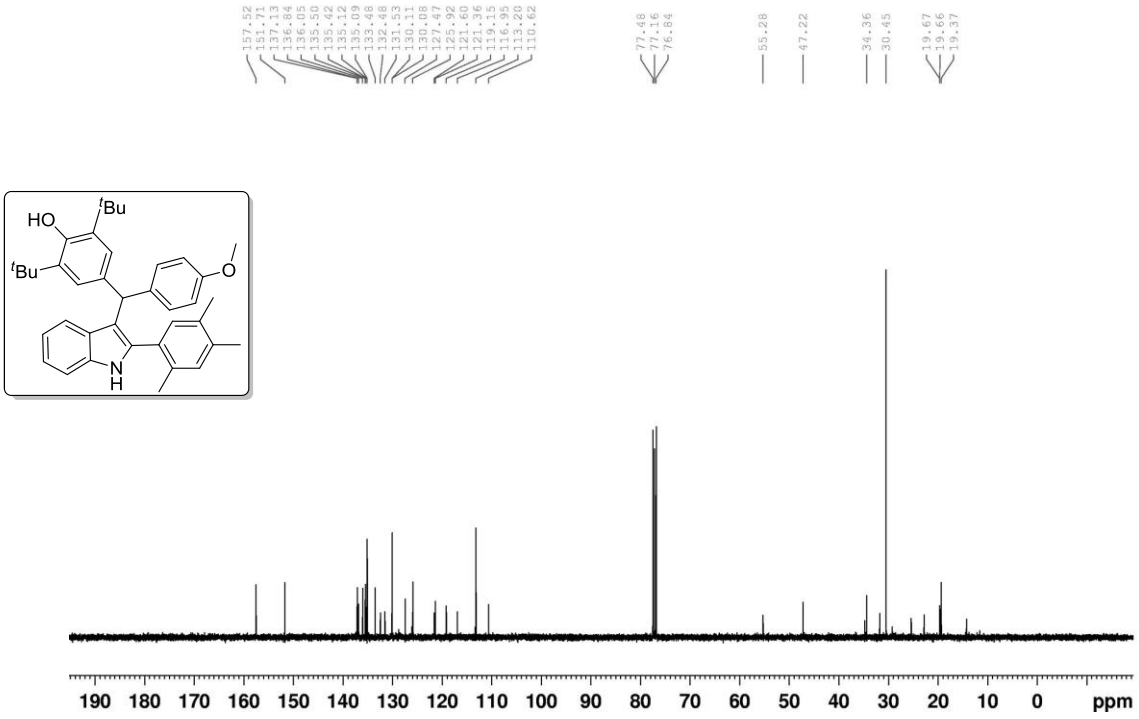
^{13}C NMR spectrum of compound **62b**



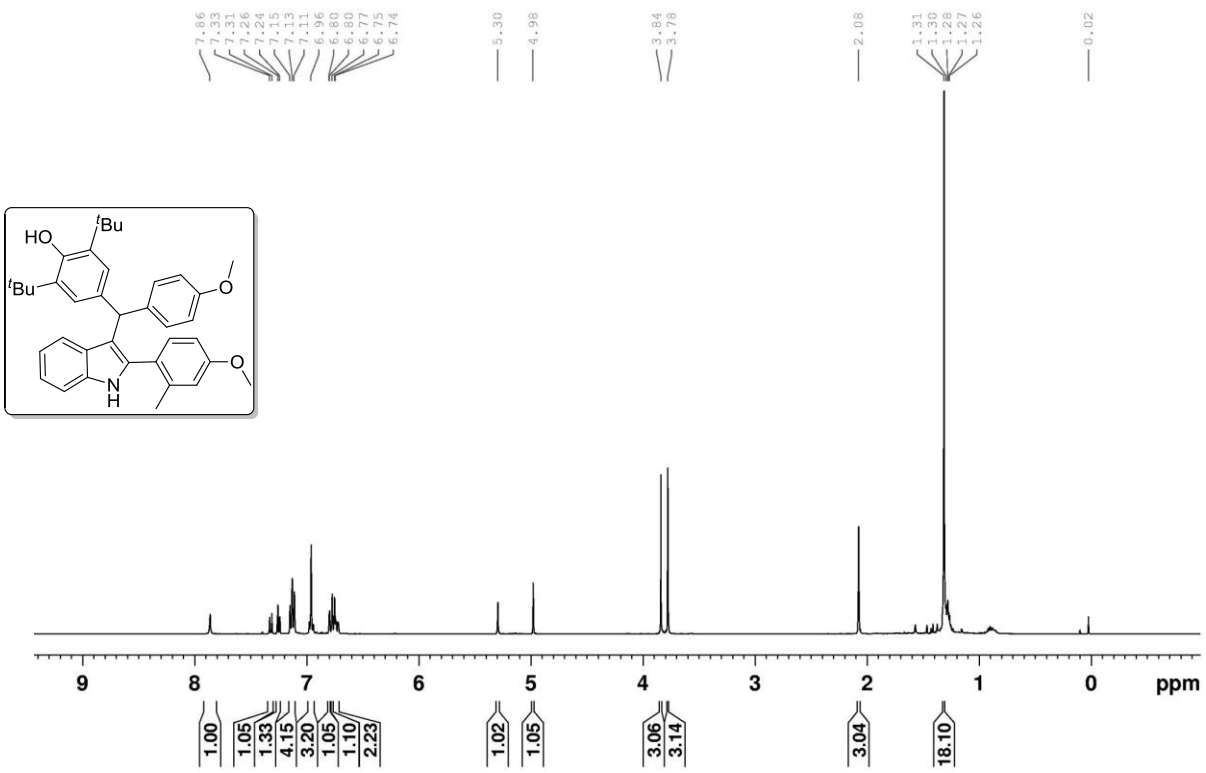
^{1}H NMR spectrum of compound **62c**



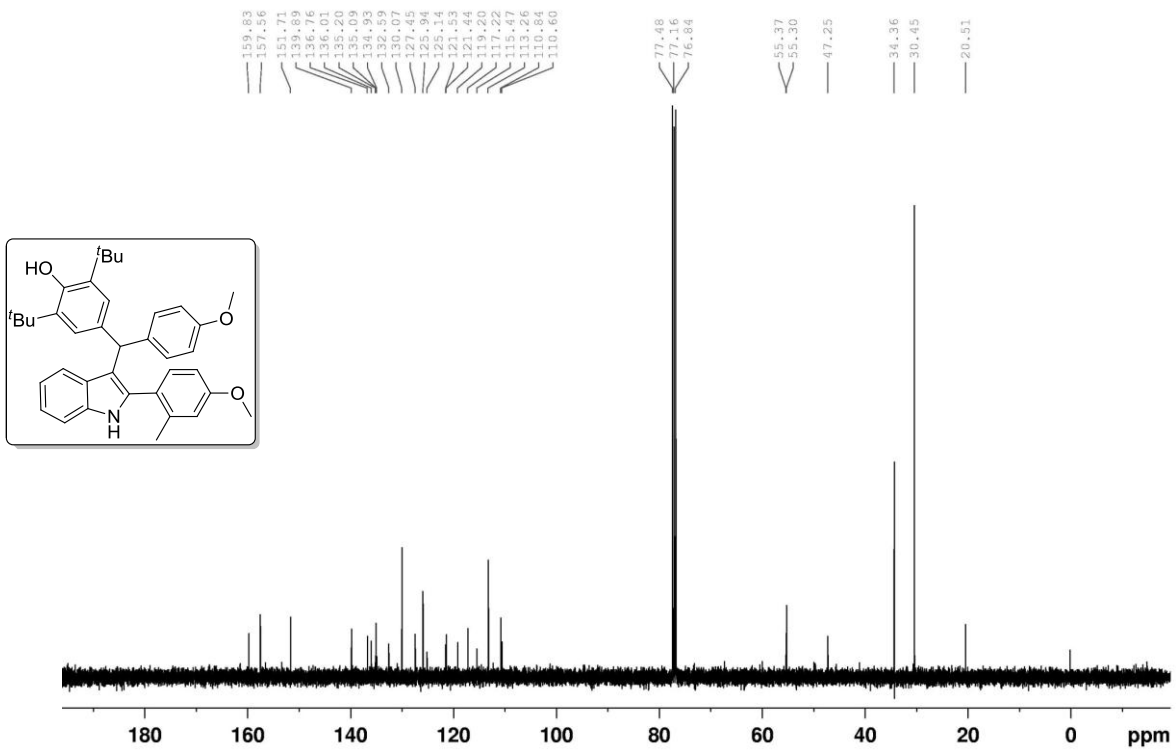
^{13}C NMR spectrum of compound **62c**



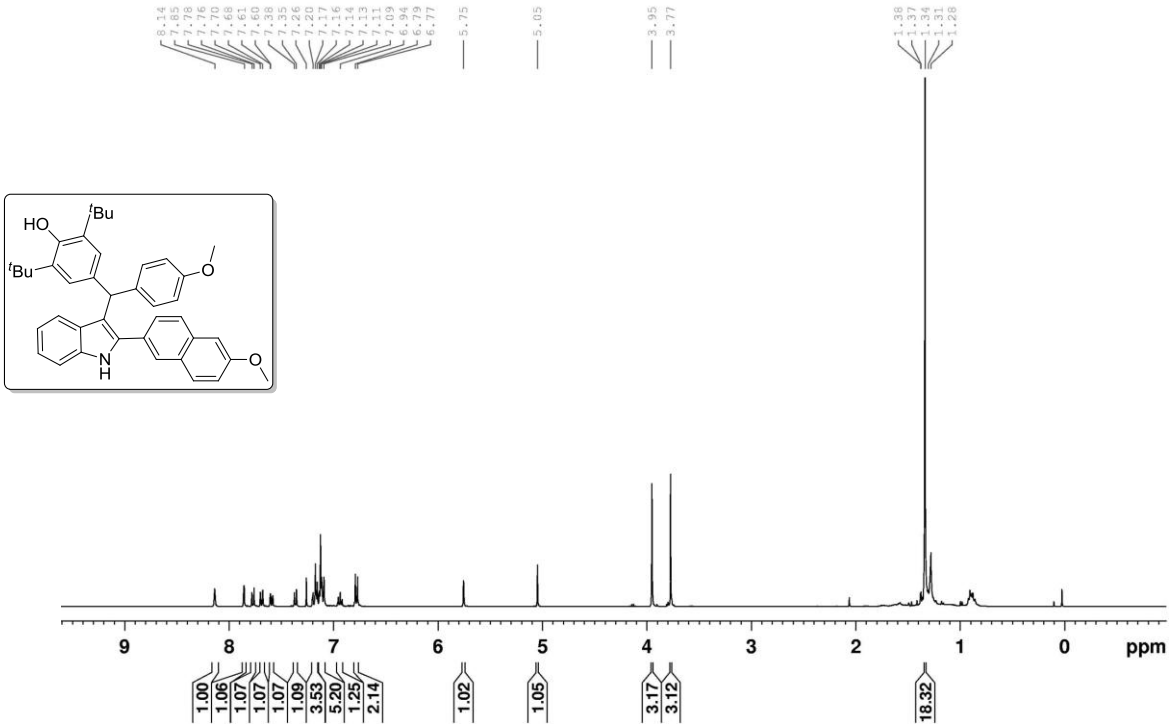
^{1}H NMR spectrum of compound **62d**



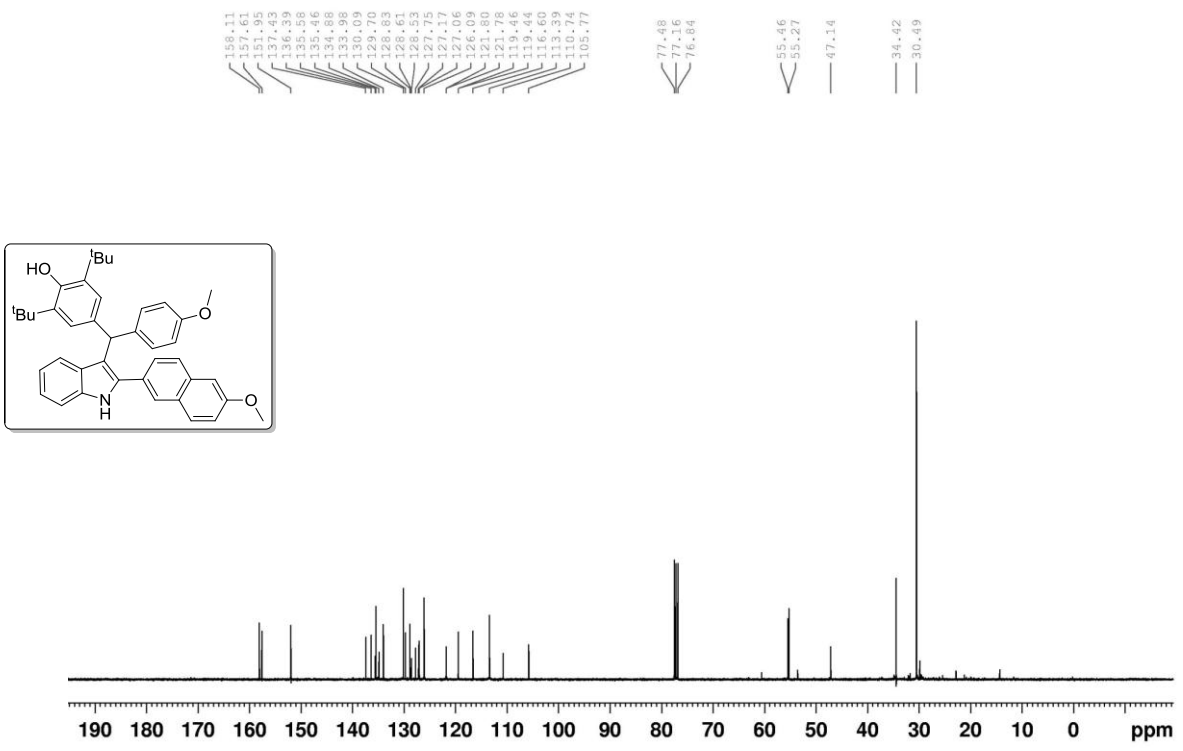
^{13}C NMR spectrum of compound **62d**



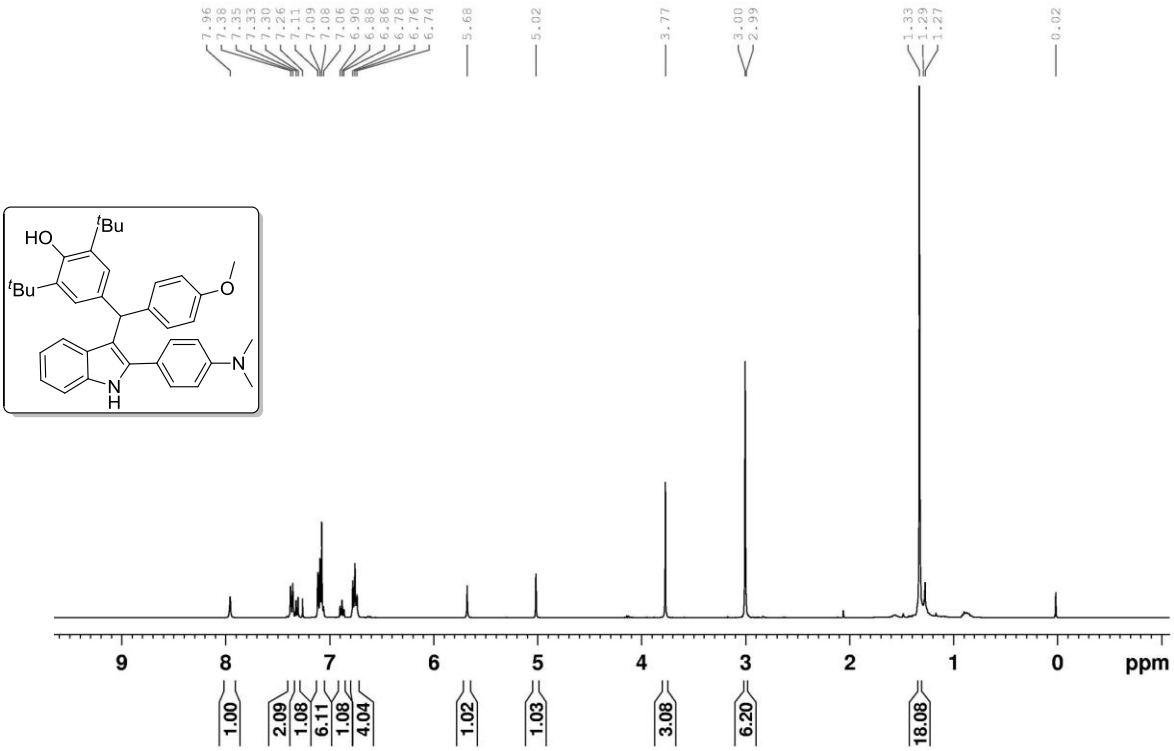
^{1}H NMR spectrum of compound **62e**



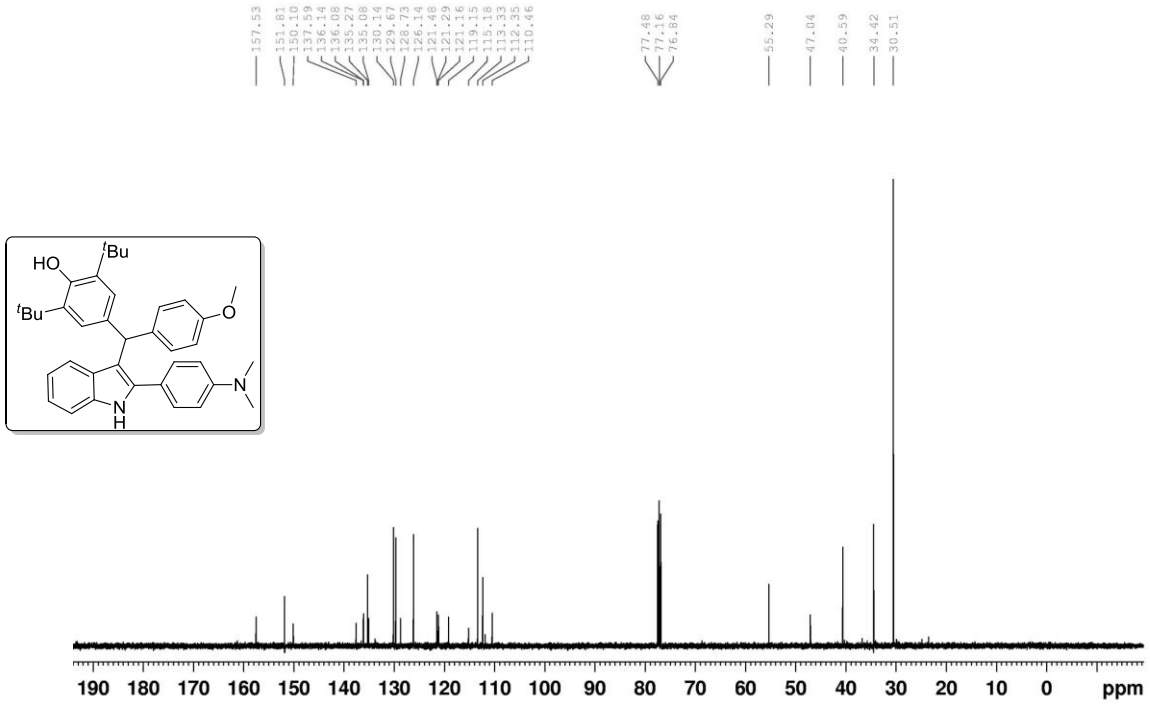
^{13}C NMR spectrum of compound **62e**



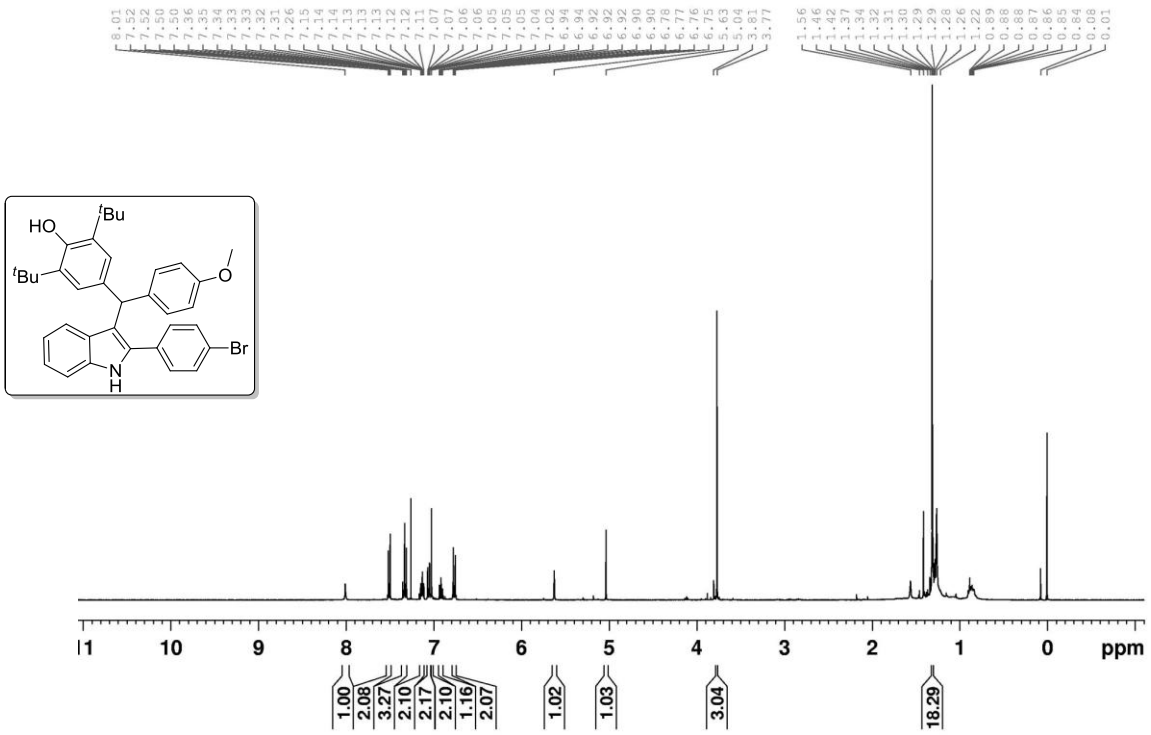
^{1}H NMR spectrum of compound **62f**



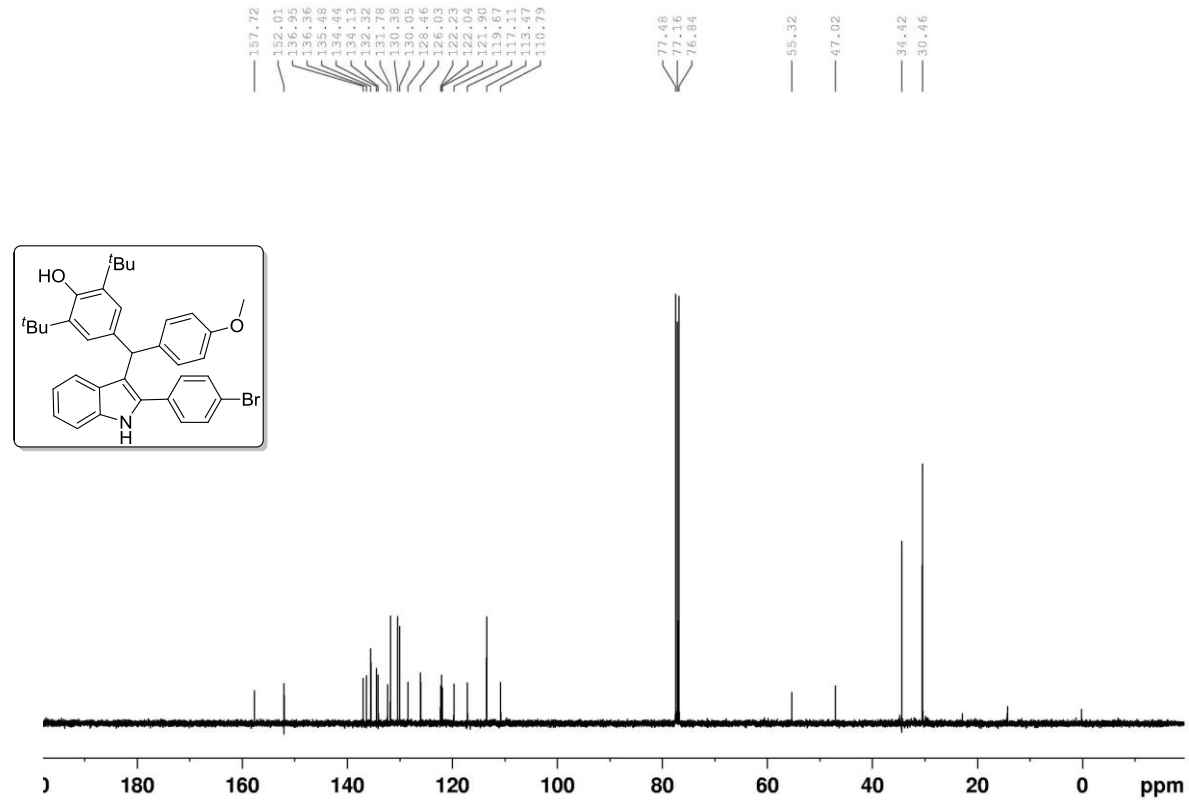
^{13}C NMR spectrum of compound **62f**



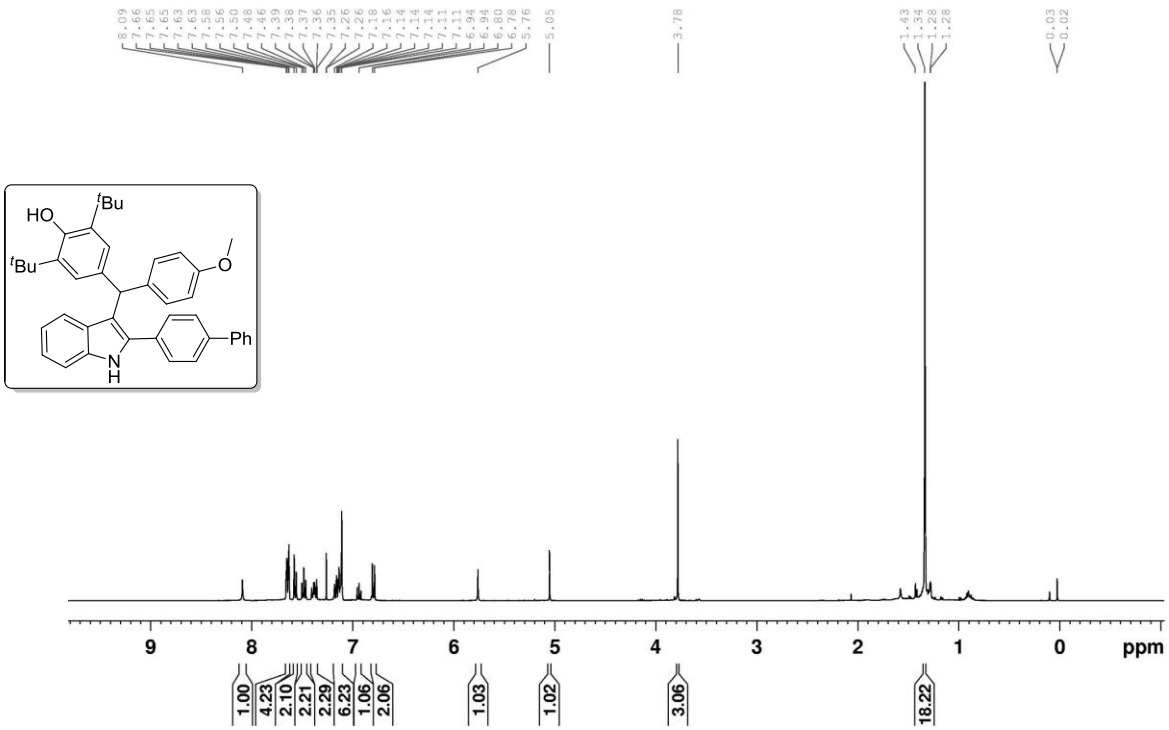
^{1}H NMR spectrum of compound **62g**



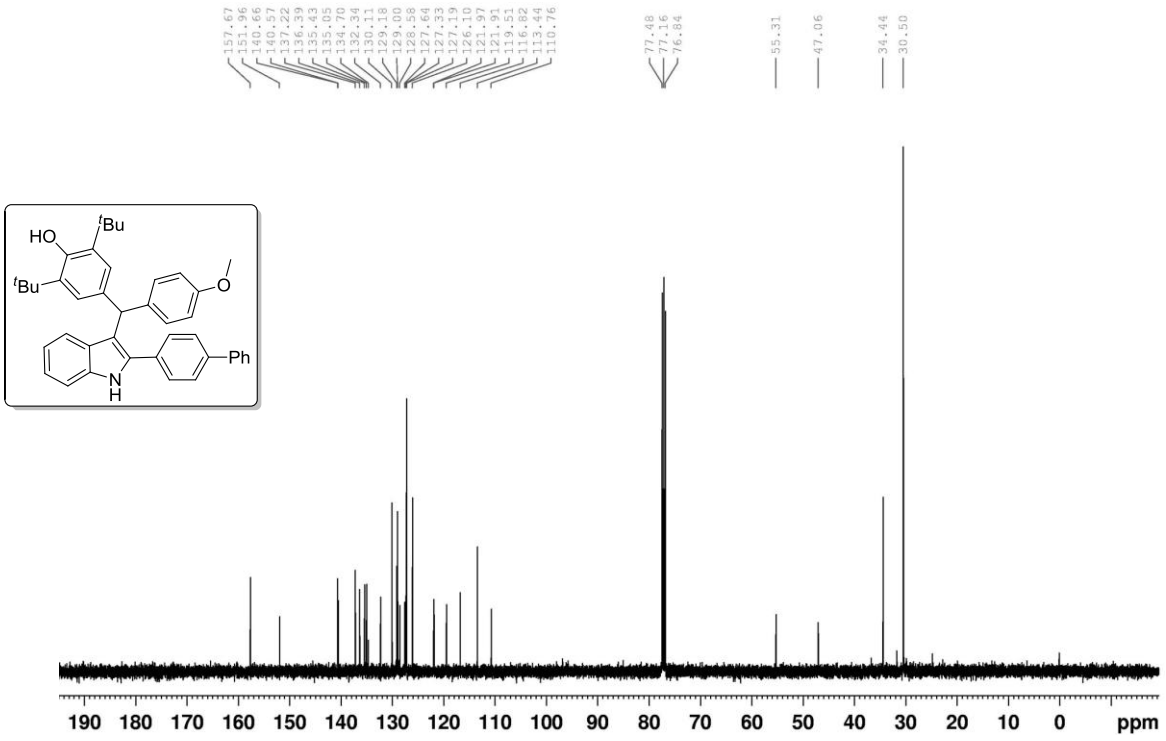
^{13}C NMR spectrum of compound **62g**



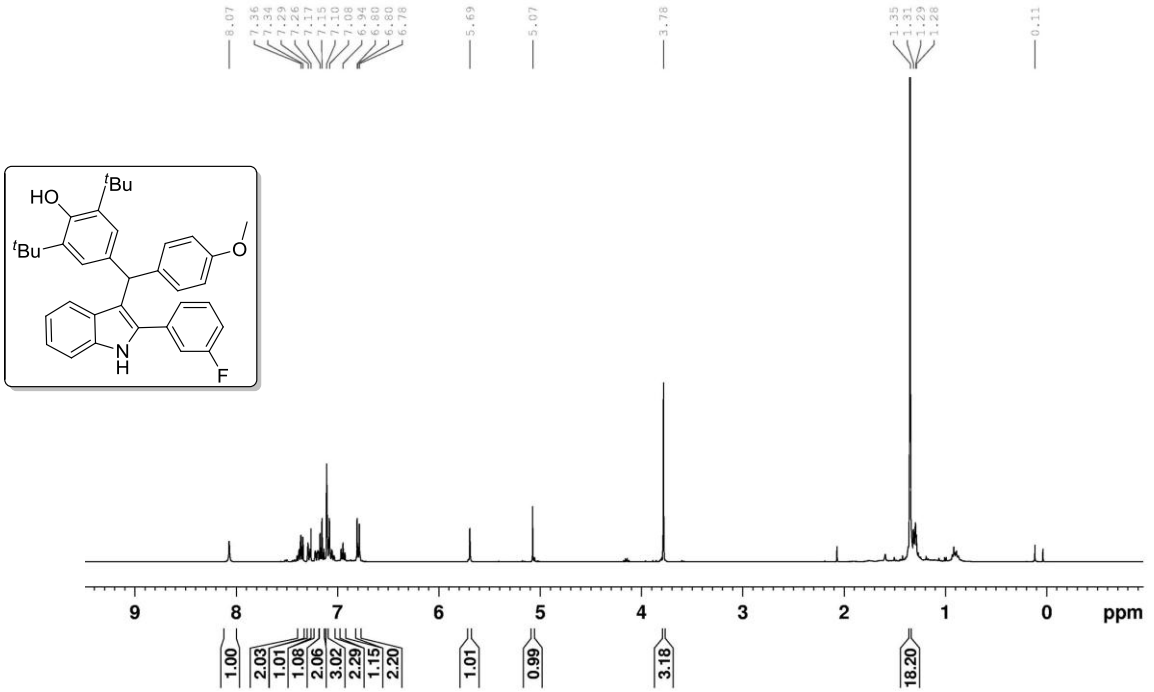
^{1}H NMR spectrum of compound **62h**



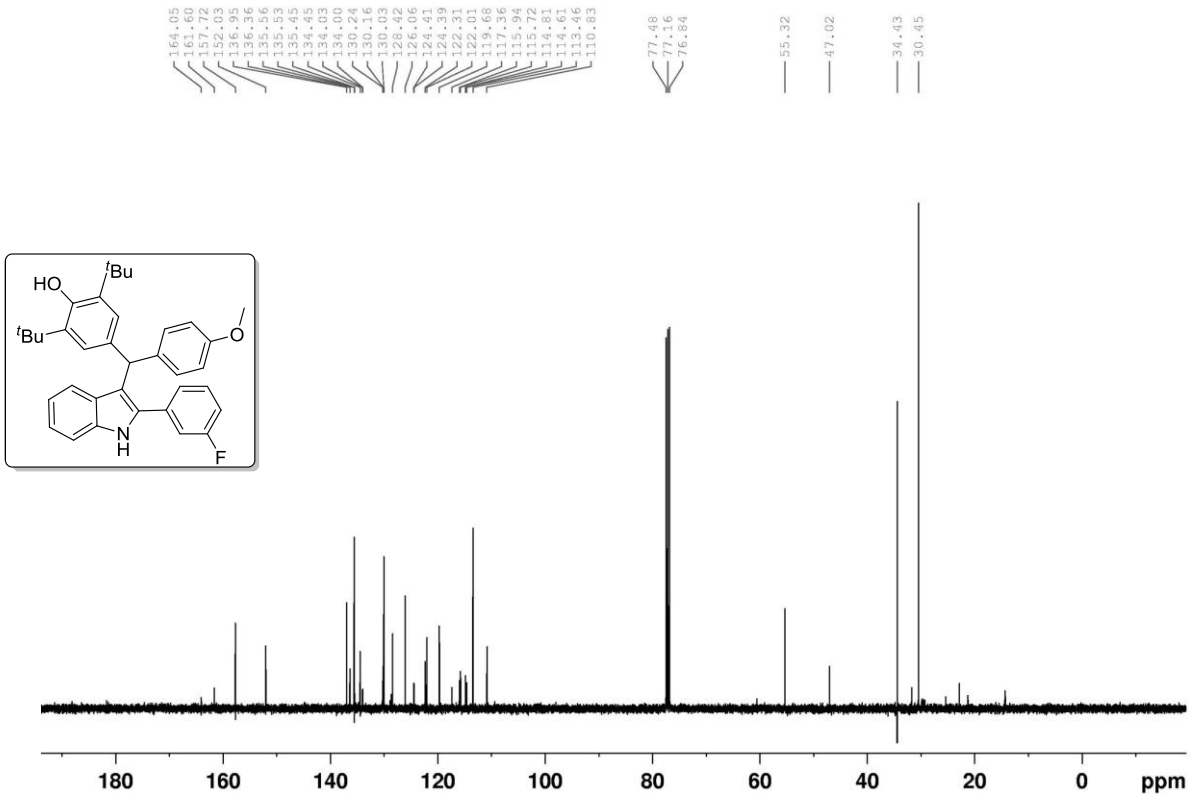
^{13}C NMR spectrum of compound **62h**



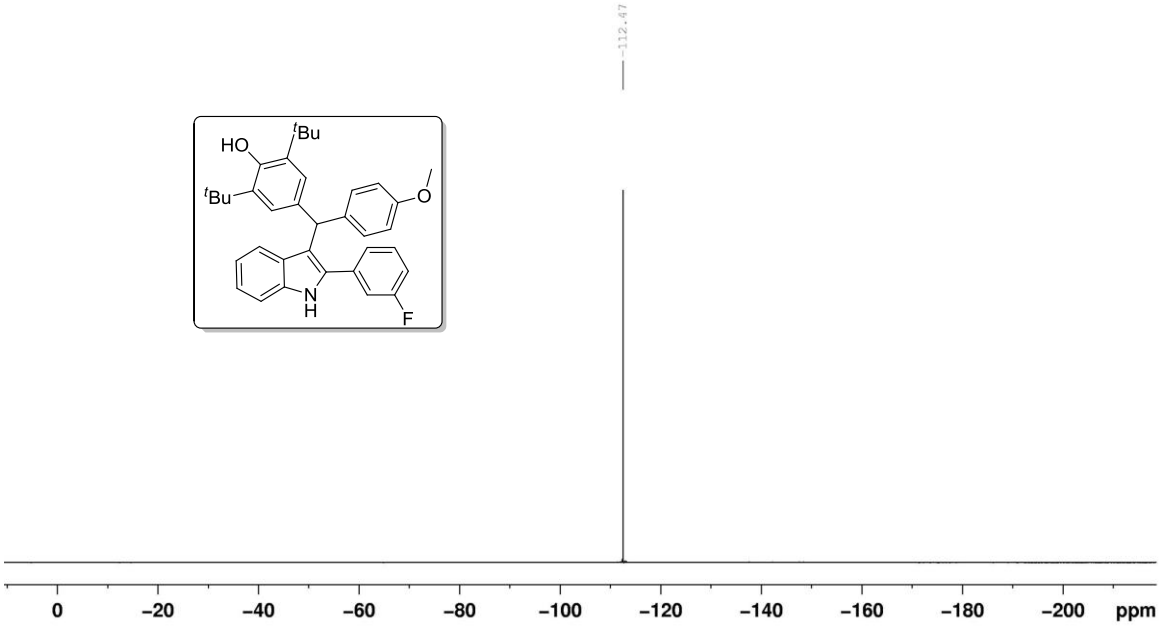
^{1}H NMR spectrum of compound **62i**



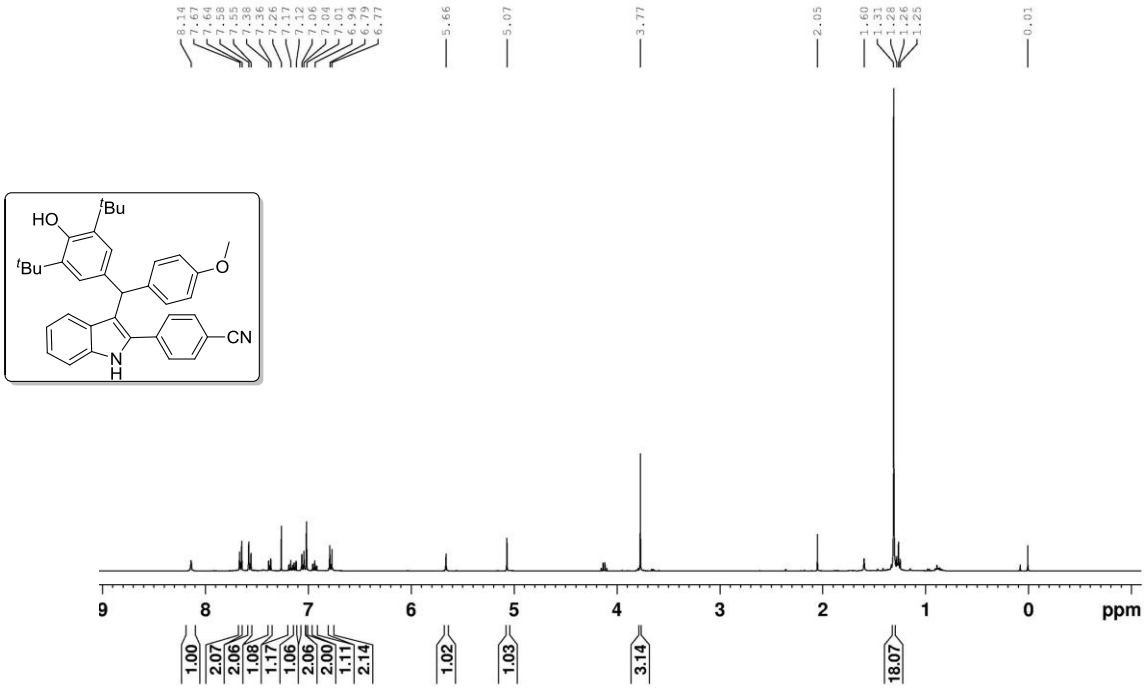
^{13}C NMR spectrum of compound **62i**



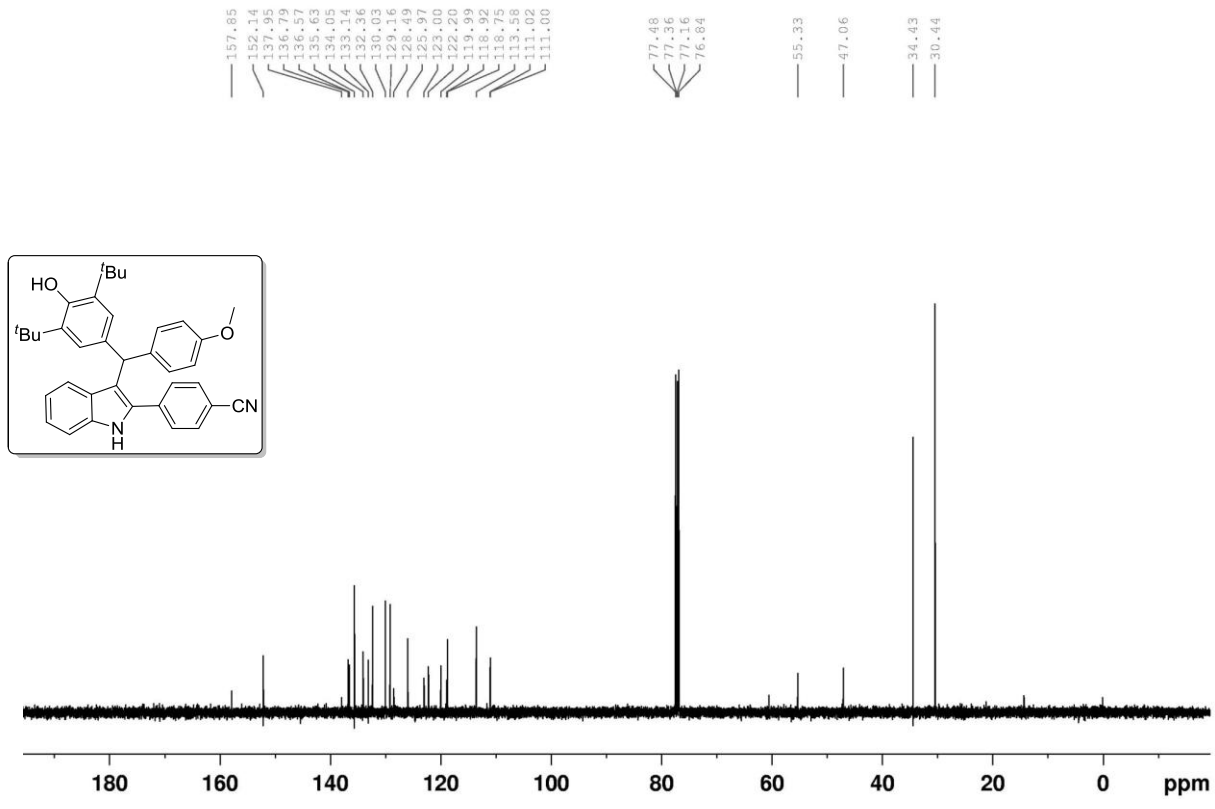
^{19}F NMR spectrum of compound **62i**



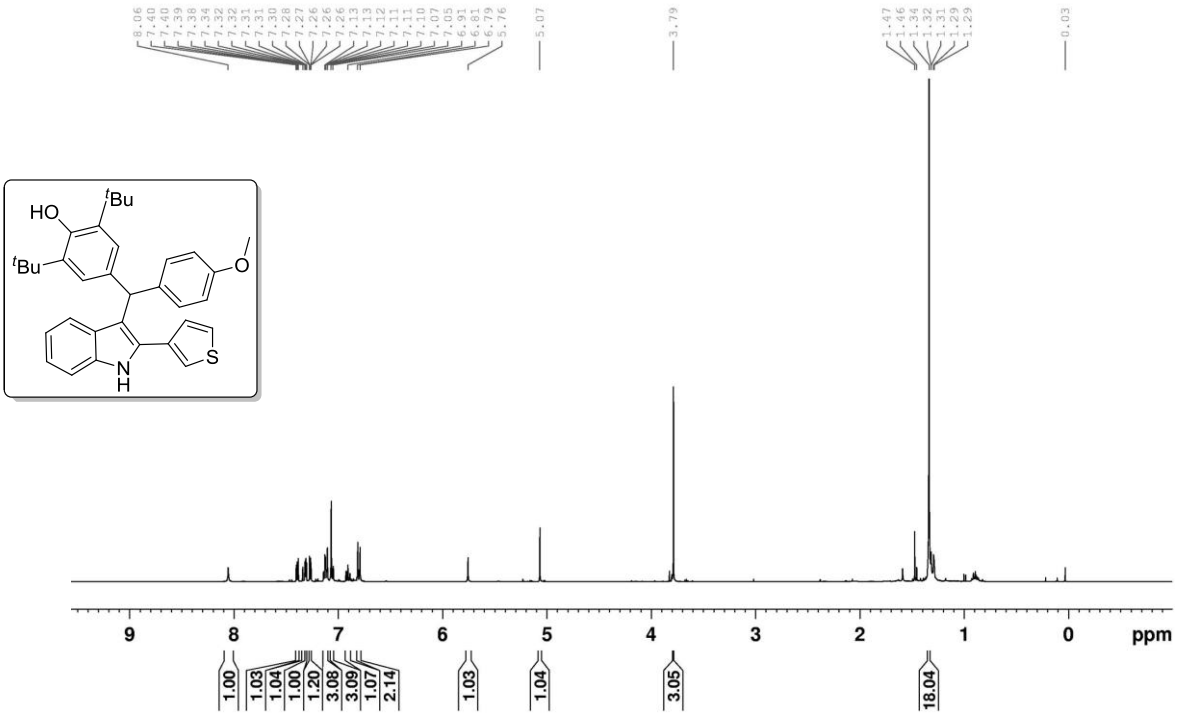
^{1}H NMR spectrum of compound **62j**



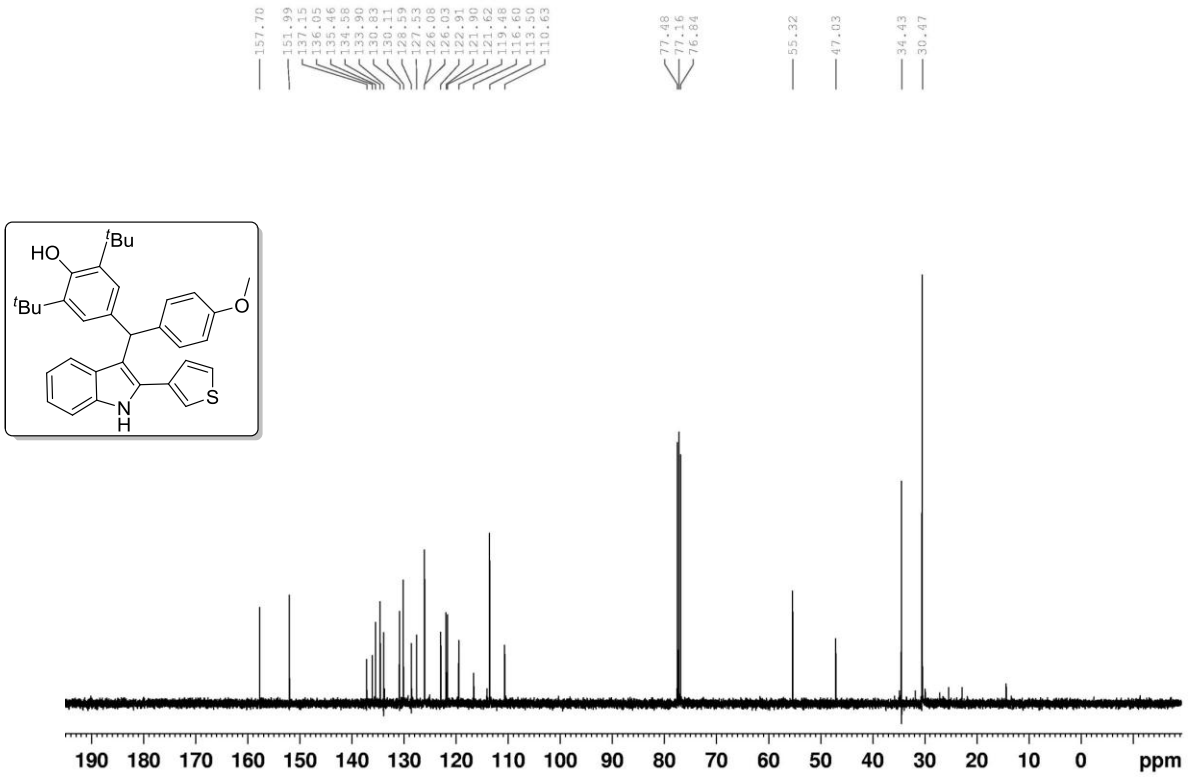
^{13}C NMR spectrum of compound **62j**



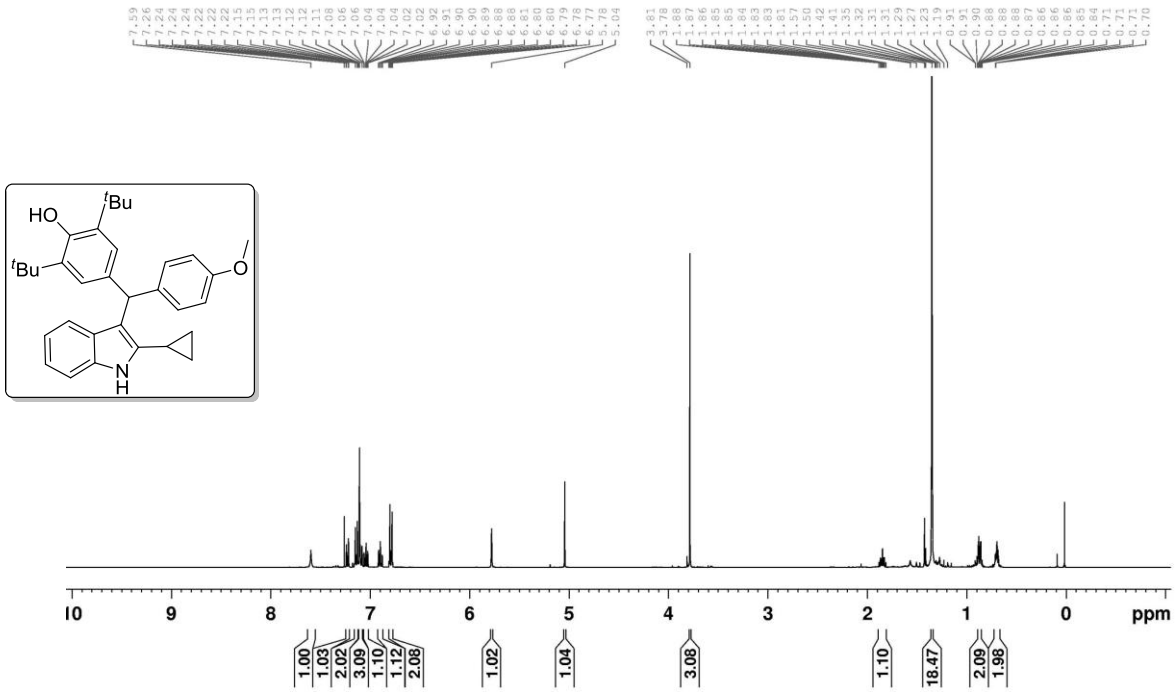
^{1}H NMR spectrum of compound **62k**



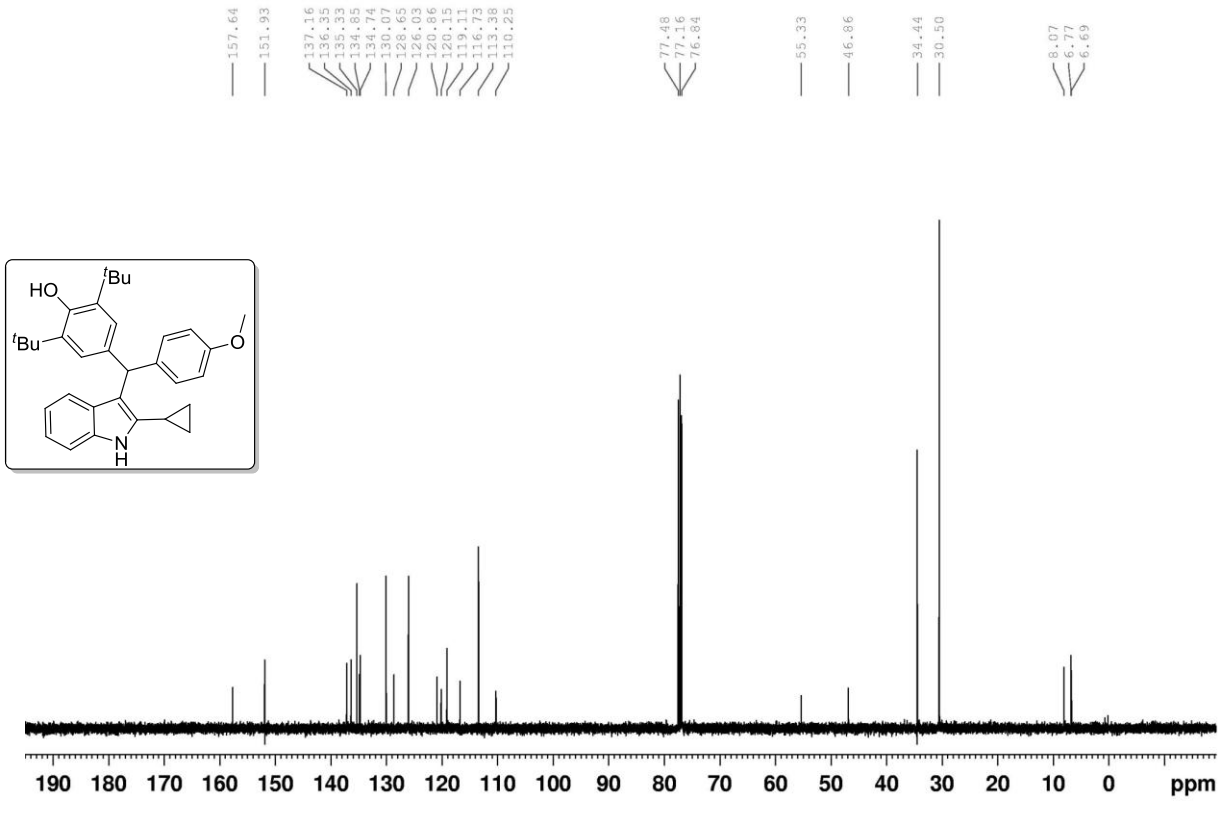
^{13}C NMR spectrum of compound **62k**



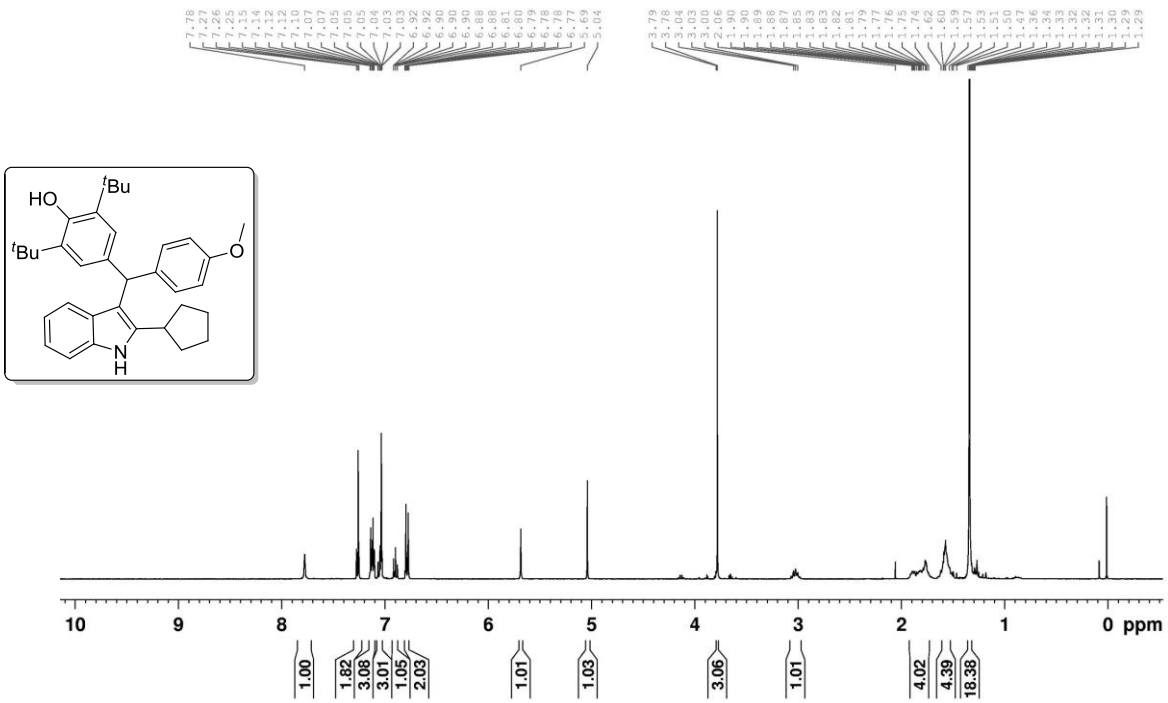
^{1}H NMR spectrum of compound **62l**



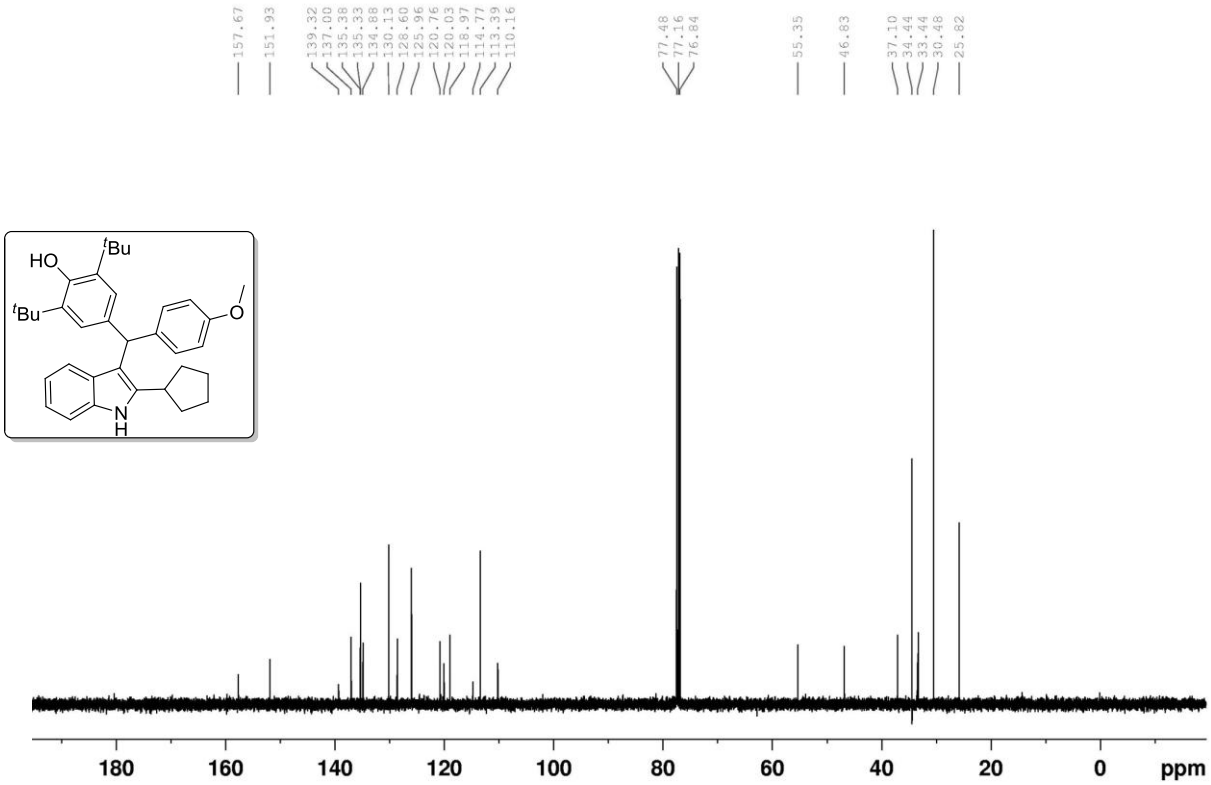
^{13}C NMR spectrum of compound **62l**



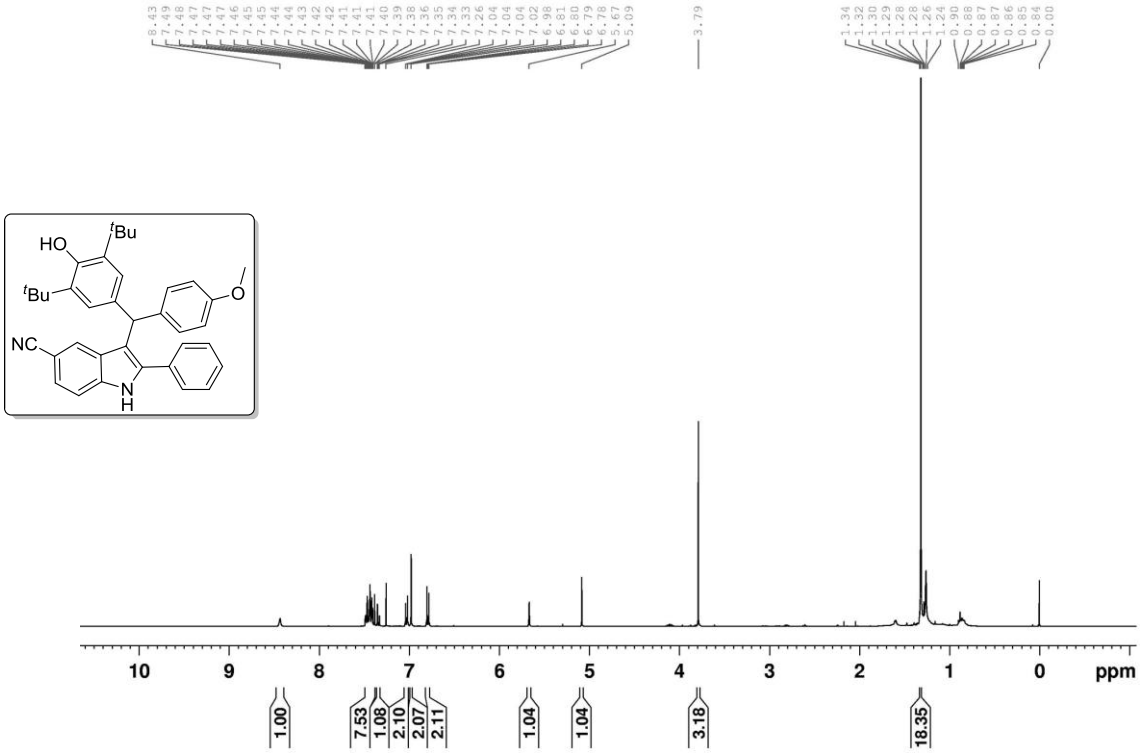
^{1}H NMR spectrum of compound **62m**



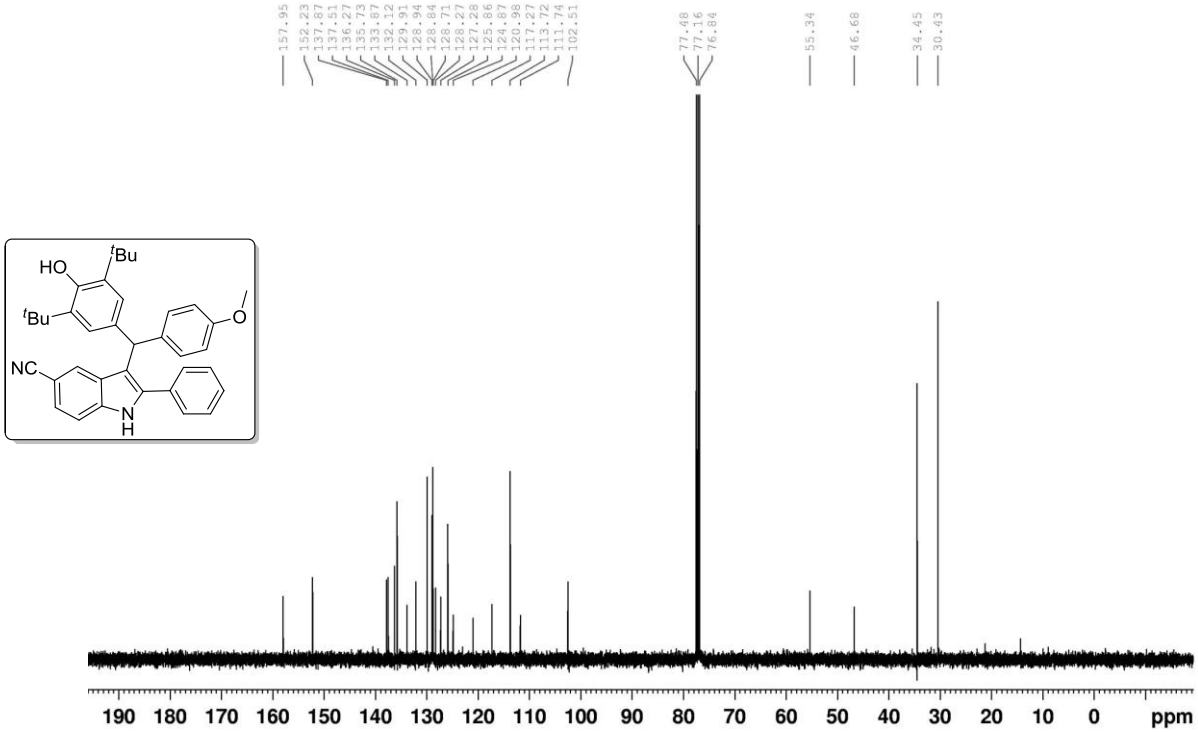
^{13}C NMR spectrum of compound **62m**



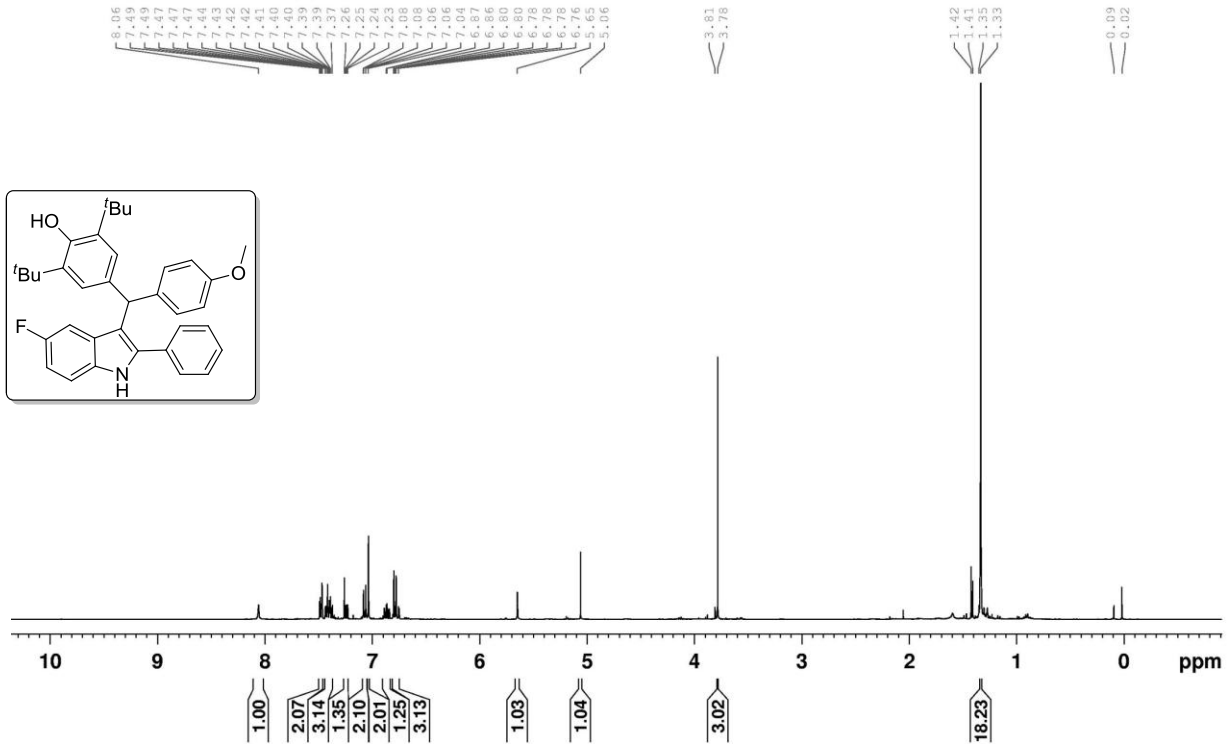
^{1}H NMR spectrum of compound **62n**



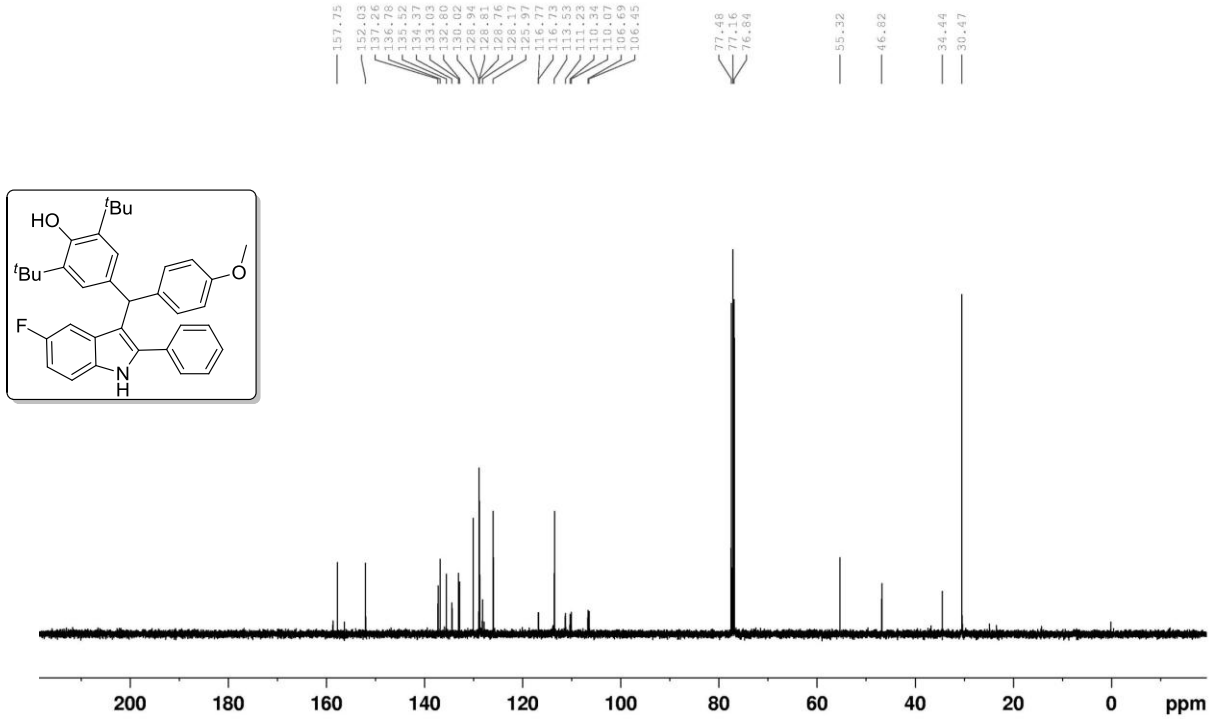
^{13}C NMR spectrum of compound **62n**



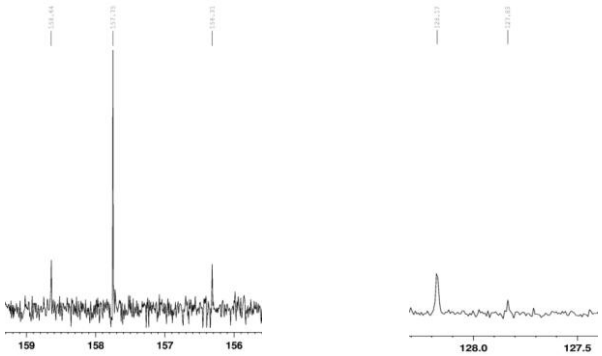
^{1}H NMR spectrum of compound **62o**



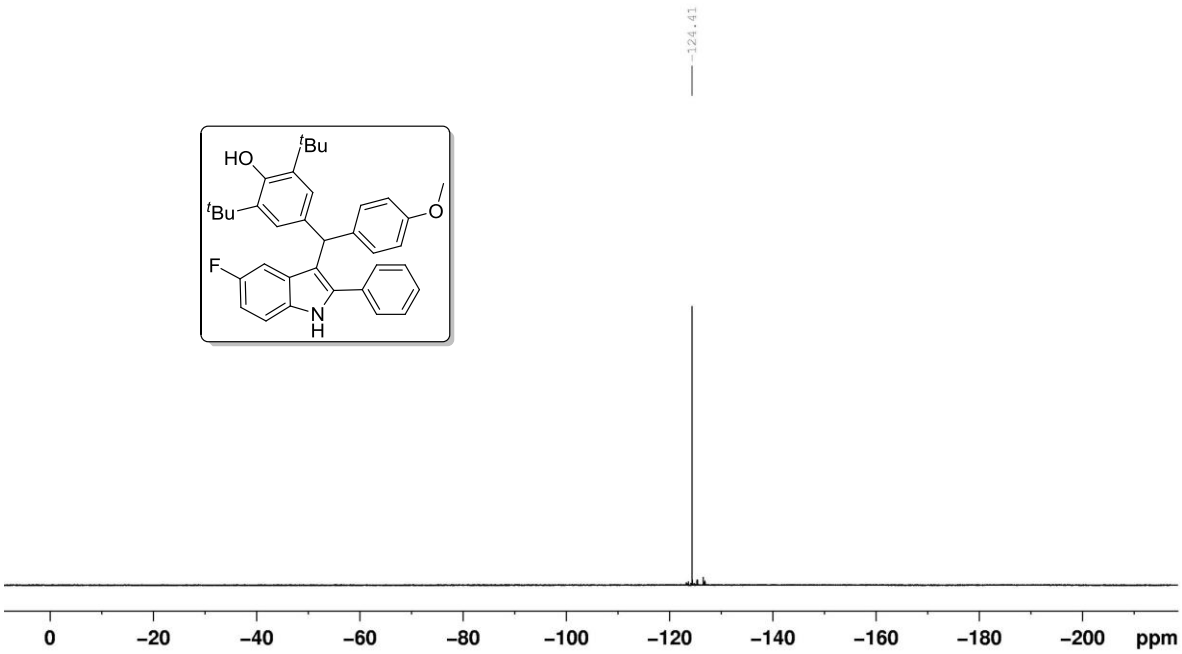
^{13}C NMR spectrum of compound **62o**



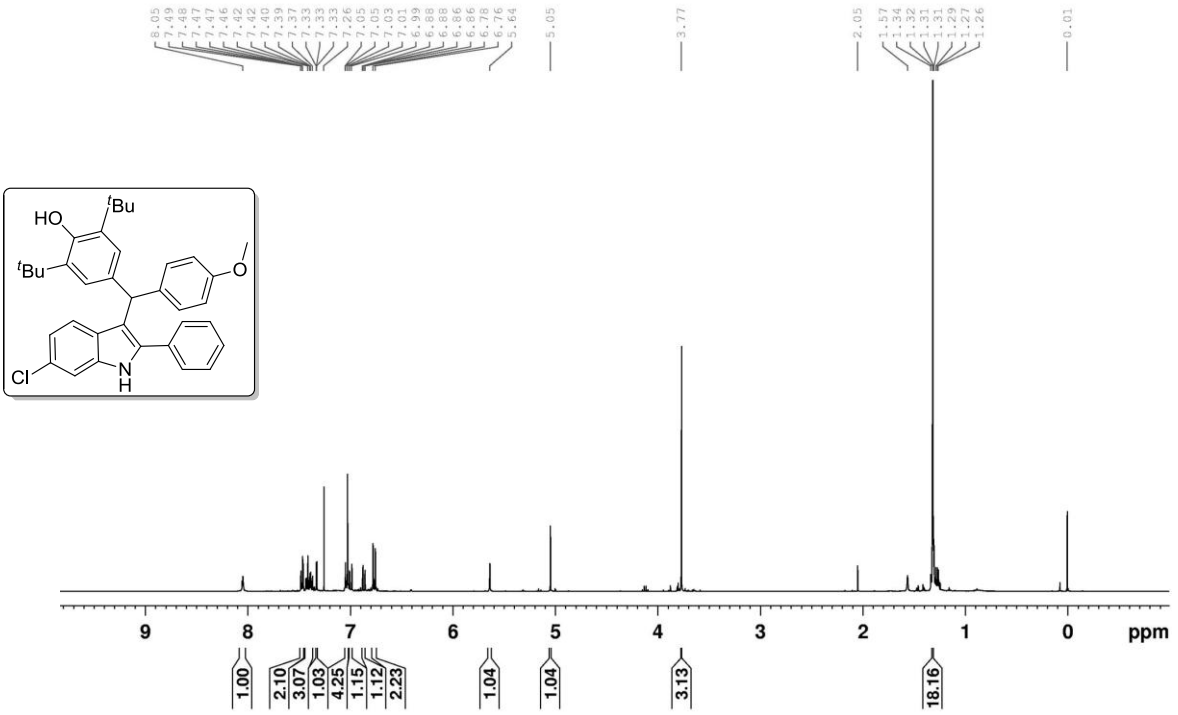
Expansion of ^{13}C spectrum of compound **62o**



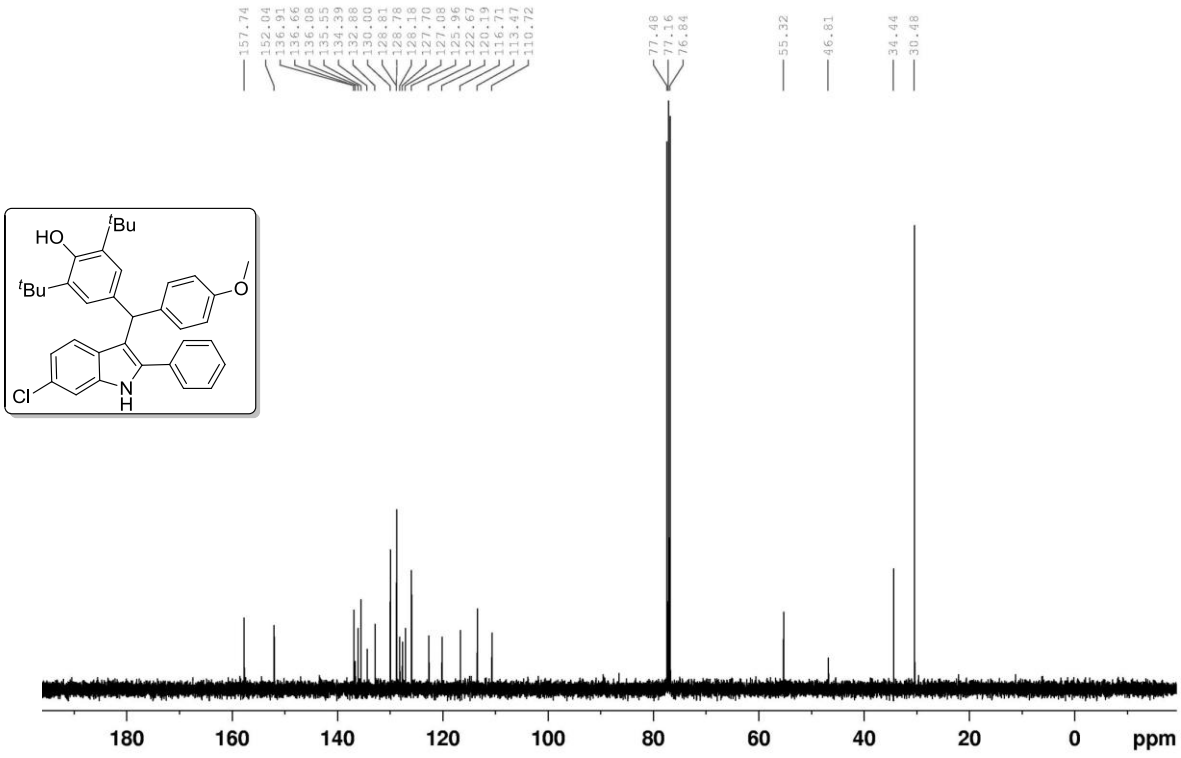
^{19}F NMR spectrum of compound **62o**



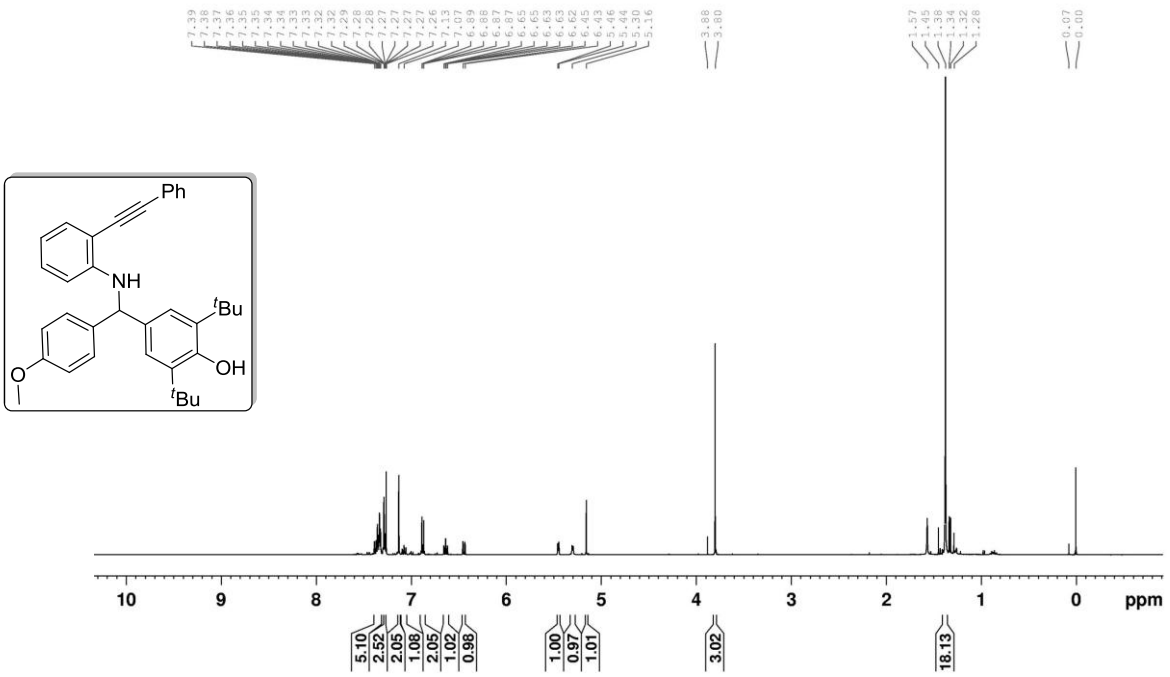
^{1}H NMR spectrum of compound **62p**



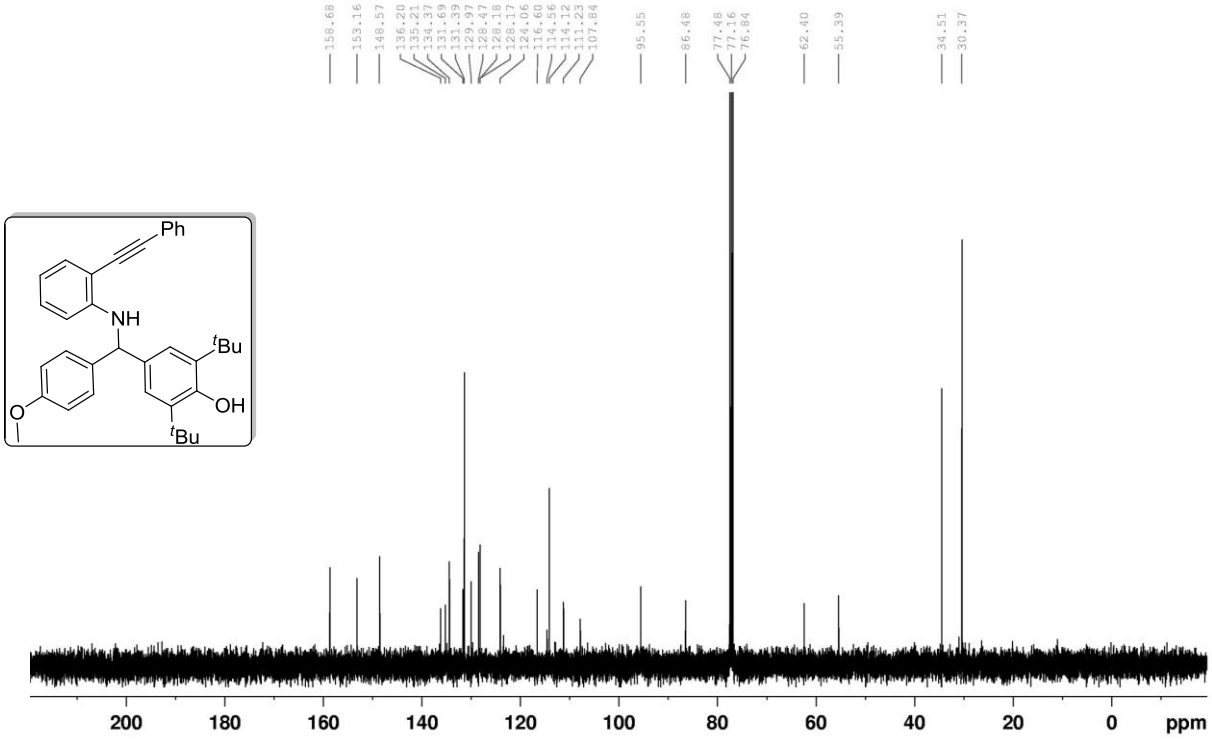
^{13}C NMR spectrum of compound **62p**



^{1}H NMR spectrum of compound **63**



^{13}C NMR spectrum of compound **63**



1.9) References

1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis 1st Edition* 4. Aug. 2006. (d) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365; (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; (f) Franzen, J.; Fisher, A. *Angew. Chem. Int. Ed* **2009,** *48*, 787; (g) Halimehjani, A. Z.; Namboothiri, I. N. N.; Hooshmand, S. E. *RSC. Adv*. **2014**, *4*, 31261; (h) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xia, W. J. *Chem. Rev*. **2015**, *115*, 5301.

2) (a) Taylor, E. C.; Saxton, J. E., *The Chemistry of Heterocyclic Compounds*, Wiley-Interscience, *New York*, **1983**/**1994**; (b) Kreuz, D, M.; Howard, A. L.; Ip, D. *J. Pharm. Biomed. Anal.* **1999**, *19*, 725; (c). Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, Blackwell Science, Oxford, **2000**; (d) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, Wiley-VCH Verlag GmbH & Co, Weinheim, 2nd *edn*, **2003**; (e) Suzen, S. *Top. Heterocycl. Chem.* **2007**, *11*, 145.

3) For a special isuue: (a) *Chem. Rev.* **2004**, *104*, Issue 5; (b) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis*, **2012**, *44*, 817; (c) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res*. **2013**, *46*, 412; (d) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev*. **2014**, *114*, 10829; (e) Yamamoto, Y. *Chem. Soc. Rev*. **2014**, *43*, 1575; (f) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev*. **2014**, *43*, 4633.

4) (a) *The Isoquinoline Alkaloids* (Eds.: K. W. Bentley), Harwood Academic Publishers, Amsterdam, **1998**; (b) Dolle, R. E. *J. Comb. Chem*. **2001**, *3*, 477; (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev*. **2004**, *104*, 3341; (d) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671; (e) Ishikawa, H.; Colby, D. A.; Boge, D. L. *J. Am. Chem. Soc*. **2008**, *130*, 420; (f) Sharma, V.; Kumar, P.; Patha, D. *J. Heterocyclic Chem.* **2010**, *47*, 491; (g) Meredith, E. L.; Ardayfio, O.; Beattie, K.; Dobler, M. R.; Enyedy, I.; Gaul, C.; Hosagrahara, V.; Jewell, C.; Koch, K.; Lee, W.; Lehmann, H. J.; McKinsey, T. A.; Miranda, K.; Pagratis, N.; Pancost, M.; Patnaik, A.; Phan, D.; Plato, C.; Qian, M.; Rajaraman, V.; Rao, C.; Rozhitskaya, O.; Ruppen, T.; Shi, J.; Siska, S. J.; Springer, C.; Eis, M.; Vega, R. B.; Matt, A.; Yang, L.; Yoon, T.; Zhang, J.-H.; Zhu, N.; Monovich, L. G. *J. Med. Chem*. **2010**, *53*, 5400; (h) Ghosh, B.; Antonio, T.; Zhen, J.; Kharkar, P.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2010**, *53*, 1023; (i) Bandgar, B. P.; Sarangdhar, R. J.; Viswakarma, S.; Ahamed, F. A. *J. Med. Chem.* **2011**, *54*, 1191; (j) Zahov, S.; Drews, A.; Hess, M.; Elfringhoff, A. S.; Lehr, M. *ChemMedChem* **2011**, *6*, 544; (k) Hemalatha, K.; Madhumitha, G.; Roopan, S. M. *Che. Sci.*

Rev. Lett. **2013**, *2*, 287; (l) Nagesh, H. N.; Naidu, K. M.; Rao, D. H.; Sridevi, J. P.; Sriram, D.; Yogeeswari, P.; Sekhar, K. V. G. C. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6805; (m) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620; (n) Diaz-Moscoso, A.; Emond, E.; Hughes, D. L.; Tizzard, G. J.; Coles, S. J.; Cammidge, A. N. *J. Org. Chem.* **2014**, *79*, 8932; (o) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421; (p) Remiro-Buenamanana, S.; Diaz-Moscoso, A.; Hughes, D. L.; Bochmann, M.; Tizzard, G. J.; Coles, S. J.; Cammidge, A. N. *Angew. Chem. Int. Ed*. **2015**, *54*, 7510.

5) (a) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev*. **1996**, *96*, 195; (b) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett*. **2007**, *9*, 5255; (c) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem*. **2011**, *76*, 1852; (d) Jiang, B.; Yi, M.-S.; Shi, F.; Tu, S.-J.; Pindi, S.; McDowellb, P.; Li, G. *Chem. Commun*. **2012**, *48*, 808; (e) Sivakumar, S.; Kanchithalaivan, S.; Kumar, R. R. *RSC. Adv*. **2013**, *3*, 13357; (f) Su, X.; Chen, C.; Wang, Y.; Chen, J.; Lou, Z.; Li, M. *Chem. Commun*. **2013**, *49*, 6752; (g) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390; (h) Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11809; (i) Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem. Int. Ed.* **2015**, *54*, 10012; (j) Agasti, S.; Maity, S.;Szabo, K. J.; Maiti, D. *Adv. Synth. Catal.* **2015**, *357*, 2331.

6) (a) Frederich, M.; Tits, M.; Angenot, L. *Tropical Medicine and Hygiene* **2008**, *102*, 11; (b) Barluenga, J.; Rodriguez, F.; Fananas, F. J. *Chem. Asian. J.* **2009**, *4*, 1036; (c) Sanchis, P. R.; Savina, S. A.; Albericio, F.; lvarez, M. *Chem. Eur. J*. **2011**, *17*, 1388.

7) (a) Duxbury, D. F. *Chem. Rev*. **1993**, *93*, 381; (b) Muthyala, R.; Katritzky, A. R.; Lan, X. F. *Dyes Pigm*. **1994**, *25*, 303; (c) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev*. **2003**, *32*, 170.

8) (a) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal*. **2008**, *350*, 2153; (b) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; (c) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195; (d) Vicente, R. *Org. Biomol. Chem*. **2011**, *9*, 6469; (e) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29; (f) Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2011**, *111*, 215; (g) Dalpozzo, R. *Chem. Soc. Rev*. **2015**, *44*, 742.

9) For selected reviews (a) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, *9*, 1399; (b) Shi, Z.; Zhang, C.; Tanga, C.; Jiao, N. *Chem. Soc. Rev*. **2012**, *41*, 3381; (c) Jin, T.; Zhao, J.; Asao, N.; Yamamoto, Y. *Chem. Eur. J*. **2014**, *20*, 3554.

10) (a) Blank, F.; Christoph Janiak, C. *Coord. Chem. Rev.* **2009**, *253*, 827; (b).; Fernandez-Rodriguez, J.-M; Martinez-Viviente, E.; Vicente, J. *Organometallics* **2015**, *34*, 3282; (c) Hering, F.; Radius, U. *Organometallics* **2015**, *34*, 3236.

11) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett*. **2000**, 394; (b) Guo, Y.-J.; Tang, R.-Y.; Li, J.-H.; Zhong, P.; Zhanga, X.-G. *Adv. Synth. Catal*. **2009**, *351*, 2615; (c) Chen, Y.; Cho, C. H.; Larock, R. C. *Org. Lett*. **2009**, *11*, 173; (d) Xu, C.; Murugan, V. K.; Pullarkat, S. A. *Org. Biomol. Chem.* **2012,** *10*, 3875.

12) (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv, Synth. Catal.* **2006**, *348*, 23; (b) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed*. **2009**, *48*, 572; (c) Chernyak, D.; Gevorgyan, V. *Org. Lett*. **2010**, *12*, 5558; (d) Kohn, B. L.; Jarvo, E. R. *Org. Lett*. **2011**, *13*, 4858; (e) Li, Z.; Chernyak, D.; Gevorgyan, V. *Org. Lett*. **2012**, *14*, 6056; (f) Gatland, A. E.; Pilgrim, B. S.; Procopiou P. A.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 14555; (g) Musaev, D. G.; Figg, T. M.; Kaledin, A. L. *Chem. Soc. Rev*. **201**4, *43*, 5009; (h) Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem. Sci.*, **2015**, *6*, 5164; (i) Khan, I.; Chidipudi, S. R.; Lam, H. W. *Chem. Commun*. **2015**, *51*, 2613.

13) (a) Brand, J. P.; Chevalley, C.; Waser, J. *Beilstein J. Org. Chem*. **2011**, *7*, 565; (b) Wang, Q.; Huang, L.; Wu, X.; Jiang, H. *Org. Lett*. **2013**, *15*, 5940; (c) Tang, R.-Y.; Guo, X.-K.; Xiang, J.-N.; Li, J.-H. *J. Org. Chem.* **2013**, *78*, 11163.

14) (a) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem*. **2005**, 70, 2265; (b) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (c) Brand, J. P.; Chevalley, C.; Waser, J. *Beilstein J. Org. Chem.* **2011**, *7*, 565; (d) Arcadi, A.; Pietropaolo, E.; Alvino, A.; Michelet V. *Org. Lett.* **2013**, *15*, 2766.

15) Oh. C. H.; Karmakar, S.; Park, H. S.; Ahn, Y. C.; Kim, J. W. *J. Am. Chem. Soc*. **2010**, *132*, 1792.

16) (a) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508; (b) Liu, J.; Xie, X.; Liu, Y. *Chem. Commun.* **2013**, *49*, 11794.

17) Swamy, N. K.; Yazici, A.; Pyne, S. G. *J. Org. Chem*. **2010**, *75*, 3412.

18) Gomberg, M. J. *J. Am. Chem. Soc*. **1900**, *22*, 757.

19) (a) Ghaisas, V. V.; Kane, B. J.; Nord, F. F. *J. Org. Chem*. **1958**, *23*, 560; (b) Turner, A. B. *Q. Rev. Chem. Soc*. **1964**, *18*, 347; (c) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc*. **1978**, *100*, 1548; (d) Irie, M. *J. Am. Chem. Soc.* **1983**, *105*, 2078.

20) (a) Miura, T.; Urano, Y.; Tanaka, K.; Nagano, T.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 8666; (b) Urano, Y.; Kamiya, M.; Kanada, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc*. **2005**, *127*, 4888.

21) (a) Domaille, D. W.; Que, E. L.; Chang, C. J. *Nat. Chem. Biol*. **2008**, *4*, 168; (b) Chen, X.; Pradham, T.; Wang, F.; Kim, J. S.; Yoon, J. *Chem. Rev*. **2012**, *112*, 1910.

22) (a) Shirakawa, S.; Kobayashi, S. *Org. Lett*. **2006**, *8*, 4939; (b) Kumar, S.; Malik, V.; Kaur, N.; Kaur, K. *Tetrahedron Lett*. **2006**, *47*, 8433; (c) He, Q. L.; Sun, F. L.; Zheng, X. J.; You, S. L. *Synlett* **2009**, *7*, 1111; (d) Wilsdorf, M.; Leichnitz, D.; Reissig, H. U. *Org. Lett*. **2013**, *15*, 2494; (e) Wilsdorf, M.; Leichnitz, D.; Reissig, H. U. *Org. Lett*. **2013**, *15*, 2494.

23) (a) Ungnade, H. E.; Crandall, E. W. *J. Am. Chem. Soc*. **1949**, *71*, 2209; (b) Katrizky, A. R. Toader, D. *J. Org. Chem*. **1997**, *62*, 4137; (c) Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem*. **1997**, *62*, 3575; (d) Yadav, J. S.; Reddy, B. V. S.; Murthy, C. V. S. R.; Kumar, G. M.; Madan, C. *Synthesis* **2001**, 783; (e) Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 1229; (f) Hoffmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem. Int. Ed*. **2004**, *43*, 5402; (g) Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Jiang, Z.-Q.; Loh, T.-P. *Eur. J. Org. Chem*. **2004**, 1584; (h) Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett*. **2005**, *7*, 5857; (i) Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem*. **2007**, *72*, 3100; (j) Periasamy, M.; Kishorebabu, N.; Jayakumar, K. N. *Tetrahedron Lett*. **2007**, *48*, 1955; (k) Liu, C. R.; Li, M. B.; Yang, C. F.; Tian, S. K. *Chem. Commun*. **2008**, 1249; (l) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T,; Olah, G. A. *J. Org. Chem*. **2009**, *74*, 8659; (m) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2010**, *75*, 5240; (n) Thirupathi, P.; Kim, S. S. *Tetrahedron* **2010**, *66*, 2995; (o) Jaratjaroonphong, J.; Tuengpanya, S.; Ruengsangtongkul, S. *J. Org. Chem.* **2015**, *80*, 559; (p) Beltrá, J.; Gimeno, M. C.; Herrera, R. P. *Beilstein J. Org. Chem*. **2014**, *10*, 2206.

24) (a) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed*. **2006**, *45*, 629; (b) Lin, S.; Lu, X. *J. Org. Chem*. **2007**, *72*, 9757; (c) Thirupathi, P.; Kim, S. S. *J. Org. Chem*. **2009**, *74*, 7755; (d) Thirupathi, P.; Kim, S. S. *Eur. J. Org. Chem*. **2010**, 1798; (e) Ponnaboina Thirupathi, P.; Neupane, L. N.; Lee, K.-H. *Tetrahedron* **2011**, *67*, 7301; (f) Hikawa, H.; Suzuki, H.; Yokoyama, Y.; Azumaya, I. *J. Org. Chem*. **2013**, *78*, 6714.

25) (a) Das, S. K.; Shagufta, Panda, G. *Tetrahedron Lett*. **2005**, *46*, 3097; (b) Singh, P.; Mann, S. K.; Jana, A. K.; Saha, T.; Mishra, P.; Bera, S.; Parai, M. K.; Kumar M. S. L.; Mondal, S.; Trivedi, P.; Chaturvedi, V.; Singh, S.; Sinha, S.; Panda, G. *Eur. J. Med. Chem*. **2015**, *95*, 357.

26) Molander, G. A.; Elia, M. D. *J. Org. Chem*. **2006**, *71*, 9198.

27) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *Org. Lett*. **2009**, *11*, 5514.

28) Yu, J.-Y.; Kuwano, R. *Org. Lett*. **2008**, *10*, 973.

29) Cao, L.-L.; Li, X.-N.; Meng, F.-Y.; Jiang, G.-F. *Tetrahedron Lett*. **2012**, *53*, 3873.

30) Xia, Y.; Hu, F.; Liu, Z.; Qu, P.; Ge, R.; Ma, C.; Zhang, Y.; Wang, J. *Org. Lett*. **2013**, *15*, 1784.

31) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2009**, *48*, 5094.

32) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett*. **2007**, *9*, 2373.

33) Song, G.; Su, Y.; Gong, X.; Han, K.; Li, X. Org. Lett. **2011**, *13*, 1968.

34) McGrew, G. I.; Temaismithi, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem. Int. Ed*. **2010**, *49*, 5541.

35) (a) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc*. **2012**, *134*, 13765; (b) Bellomo, A.; Zhang, J.; Trongsiriwat, N.; Walsh, P. *Chem. Sci*. **2013**, *4*, 849; (c) Zhang, J.; Bellomo, A.; Trongsiriwat, N.; Jia, T.; Corroll, P. J.; Dreher, S. D.; Tudge, M. T.; Yin, H.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc*. **2014**, *136*, 6276.

36) Nambo, M.; Crudden C. M. *Angew. Chem. Int. Ed*. **2014**, *53*, 742.

37) Tabuchi, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2014**, *79*, 5401.

38) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2008**, *47*, 4882.

39) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828.

40) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed*. **2012**, *51*, 7790.

41) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

42) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc*. **2013**, *135*, 3307.

43) (a) Li, Z.; Bohle, D. S.; Li, C.-J. *PNAS*, **2006**, *103*, 8928; (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335; (c) Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215.

44) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem. Int. Ed*. **2009**, *48*, 3817.

45) Guo, S.; Li, Y.; Wang, Y.; Guo, X.; Meng, X.; Chen, B. *Adv. Synth. Catal*. **2015**, *357*, 950.

46) Gonzalez, J.; Gonzalez, J.; Perez-Calleja, C.; Lopez, L. A.; Vicente, R.; *Angew. Chem. Int. Ed*. **2013**, *52*, 5853.

47) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015**, *20*, 11733.

48) Richard, J. P.; Toteva, M. M.; Crugeiras, J. *J. Am. Chem. Soc*. **2000**, *122*, 1664.

49) (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc*. **1990**, *112*, 3698; (b) Martin, H. J.; Magauer, T.; Mulzer, J. *Angew. Chem. Int. Ed*. **2010**, *49*, 5614.

50) (a) Angle, S. R.; Arnaiz, D. O.; Boyce, J. P.; Frutos, R. P.; Louie, M. S.; MattsonArnaiz, H. L.; Rainier, J. D.; Turnbull, K. D.; Yang, W. *J. Org. Chem*. **1994**, *59*, 6322; (b) Mondal, S.; Panda G. *RSC. Adv*. **2014**, *4*, 28317.

51) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc*. **1989**, *111*, 1136.

52) Angle, S. T.; Rainier, J. D. *J. Am. Chem. Soc*. **1992**, *57*, 6883.

53) (a) Gai, K.; Fang, X.; Li, X.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Chem. Commun*. 2015, *51*, 15831; (b) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem*. **2015,** *80*, 11123.

54) (a) Amouri, H.; Bras, J. L. *Acc. Chem. Res*. **2002**, *35*, 501; (b) Pathak, T. P.; Sigman, M. S. *J. Org. Chem*. **2011**, *76*, 9210; (c) Willis, N. J.; Bray, C. D. *Chem. Eur. J*. **2012**, *18*, 9160;

55) (a) Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *Angew. Chem. Int. Ed*. **2013**, *52*, 9229; (b) Caruana, L.; Kniep, F.; Johansen, T. K.; Poulsen, P. H.; Jorgensen, K. A. *J. Am. Chem. Soc*. **2014**, *136*, 15929; (c) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 12134.

56) Murashige, R.; Hayashi, Y.; Ohmori, S.; Torii, A.; Aizu, Y.; Muto, Y.; Murai, Y.; Oda, Y.; Hashimoto, M. *Tetrahedron*, **2011**, *67*, 641.

57) Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* **1987**, *8*, 736.

58) Olah, M. G.; Robbins, J. S.; Baker, M. S.; Phillips, S. T. *Macromolecules*, **2013**, *46*, 5924.

59) Nath, N. K.; Nilapwar, S.; Nangia, A. *Cryst. Growth. Des*. **2012**, *12*, 1613.

60) CCDC No: 1057855

Chapter 2

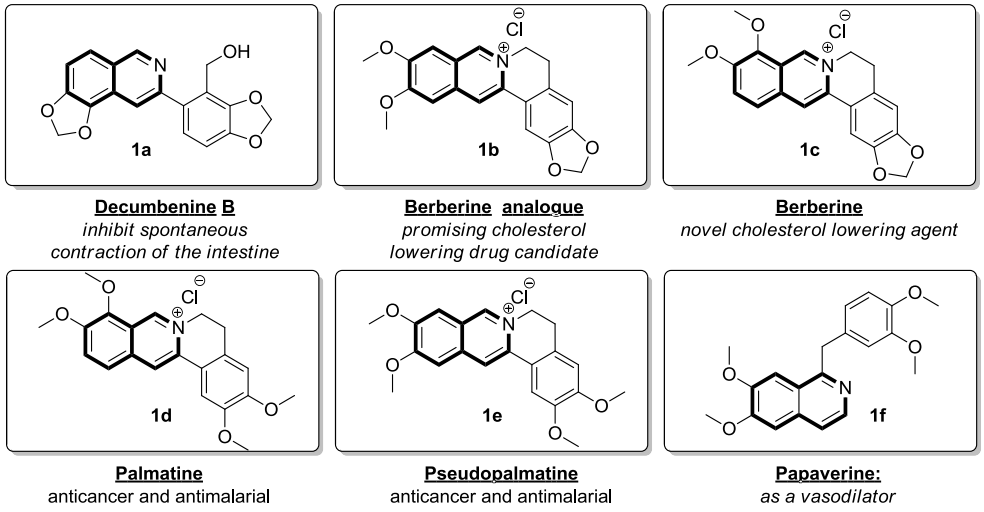
A room-temperature protocol to access isoquinolines through Ag(I)-catalysis: Elaboration to berberine and palmatine

In this chapter, a Ag-catalyzed protocol for synthesis of isquinolines has been discussed. This chapter also covers a general introduction on the synthesis of isoquinolines and related natural products. Finally, the application of this methodology in the synthesis of isoquinoline natural products such as berberine and palmatine has been discussed.

2.1) Introduction

In 1885, Hoogewerf and van Drop isolated isoquinoline from coal tar for the first time. An isoquinoline nucleus is an important and most abundant building block in many natural products and active pharmaceutical ingredients (API). A few of them are shown in Figure 1.[1a] These natural products exhibit remarkable biological activities and possess a structural diversity.[1b] By taking in account this biological importance of isoquinoline alkaloids, various research groups have developed different methods for the synthesis of isoquinolines.

Figure 1: Isoquinoline containing biologically active compounds



Decumbenine B
inhibit spontaneous contraction of the intestine

Berberine analogue
promising cholesterol lowering drug candidate

Berberine
novel cholesterol lowering agent

Palmatine
anticancer and antimalarial

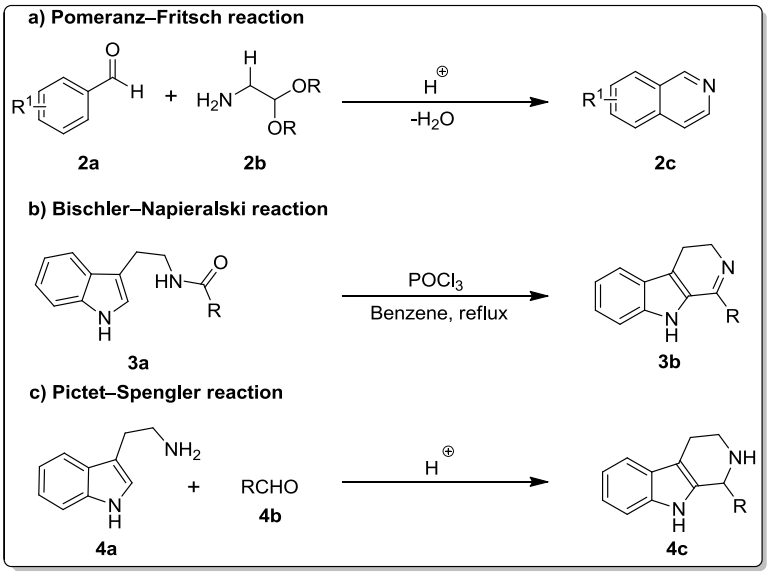
Pseudopalmatine
anticancer and antimalarial

Papaverine:
as a vasodilator

Berberine (**1c**) and Palmatine (**1d**) are a member of protoberberine class of isoquinoline alkaloids.[2] Berberine (**1c**), isolated from *Berberis vulgaris* and known to act as promising cholesterol lowering,[3] anticancer,[4] antiviral,[5] antifungal,[6] antimalarial,[7] antibacterial[8] and antileishmanial[9] agents. Berberine has been used as a drug for the treatment of diarrhea in China for many decades. A recent report shows the potential application of berberine as a complementary therapeutic agent for HIV infection as well.[10] It was found that the cholesterol-lowering activity increased further if **1c** was used in combination with statins.[11] Palmatine, found in *Coptis chinensis* and a structural analogue of berberine, also exhibits remarkable biological activities. Palmatine (**1d**) has been used in the treatment of hypertension, jaundice, dysentery and diseases related to the liver.[12] Its derivatives also possess antimalarial and antimicrobial activities.[13]

The traditional and most useful approaches for the synthesis of isoquinoline ring system include the Pomeranz–Fritsch,[14] Bischler-Napieralski[15] and Pictet Spengler[16] reactions (Scheme 1). These methods are very useful in the total synthesis of isoquinoline core containing natural products. Pomeranz–Fritsch reaction involves the synthesis of isoquinoline (**2c)** through the reaction between aromatic aldehydes (**2a)** and dialkoxyethylamine (**2b)** in the presence of sulphuric acid (a, Scheme 1). Bischler-Napieralski approach describes the intramolecular reaction of *β*-arylethylamides (**3a)** in the presence of highly corrosive phosphoryl chloride to afford the dihydroisoquinolines (**3b)** (b, scheme 1).

Scheme 1: Traditional approaches toward the synthesis of isoquinoline core

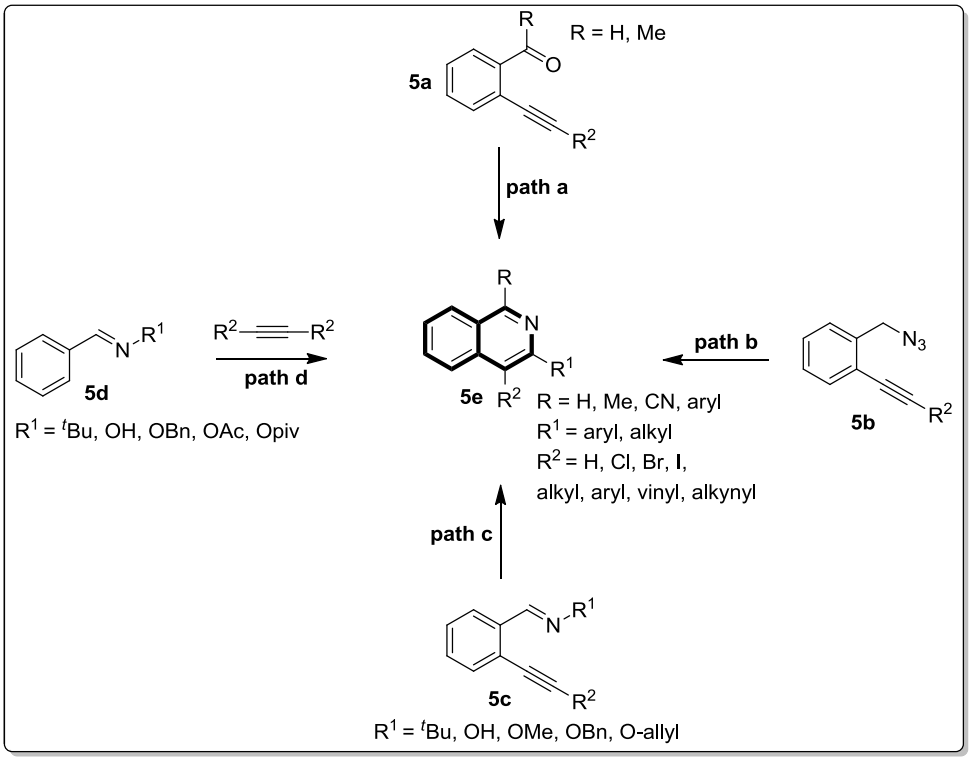


The third approach is Pictet-Spengler reaction which involves the condensation of *β*-arylethylamine (**4a)** with aldehydes (**4b)** in the presence of hydrochloric acid at a higher temperature to access the tetrahydroisoquinolines (**4c)** (c, Scheme 1).

2.2) Literature overview on the synthesis of isoquinoline scaffolds

The traditional methods provide a wide substrate scope however suffer from drawbacks such as harsh reaction conditions, use of highly corrosive chemicals or complicated work-up procedures. To avoid these problems, researchers across the world are redirecting efforts toward developing an efficient method for the synthesis of isoquinoline scaffold. In recent literature, mainly four different strategies have been reported for the synthesis of isoquinolines, path a) from *o*-alkynyl benzaldehydes or ketones (**5a)** with NH_4OAc at higher temperature or microwave irradiation, path b) redctive cyclization of *o*-alkynyl benzyl azides (**5b**), path c) from *o*-alkynyl benzaldimines or aldoximes (**5c**) and path d) from Rhodium-catalyzed intermolecular reaction between benzaldimine or aldoxime derivatives (**5d**) with internal alkynes *via* C-H activation (Scheme 2).

Scheme 2: General classification for the synthesis of isoquinoline core (**5e**)

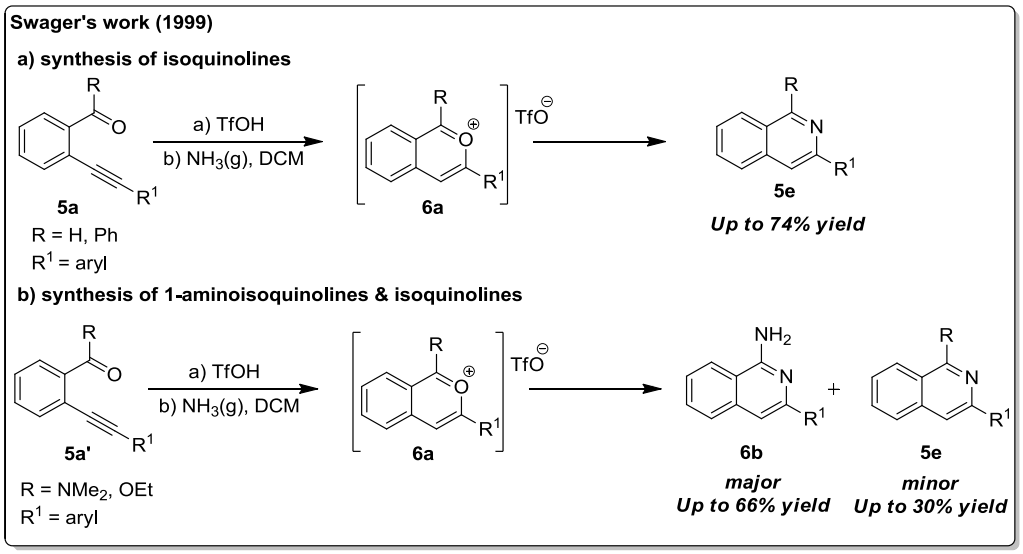


2.2.1) from *o*-alkynyl benzaldehydes or ketones (Path a)

This approach involves three subtypes: Brønsted acid (TfOH)-mediated, under thermal conditions and under microwave irradiation.

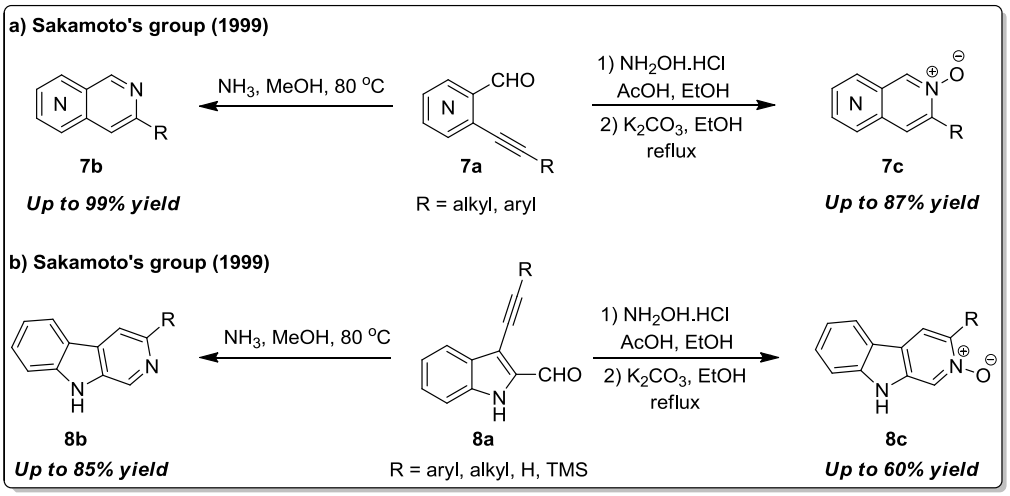
In 1999, Swager and coworkers reported the one-pot synthesis of isoquinolines (**5e**) from *o*-alkynyl benzaldehydes or ketones (**5a**) as shown in scheme 3. The reaction has been carried out between the *o*-alkynyl benzaldehydes or ketones (**5a)** in the presence of triflic acid, which gives the oxo-pyrylium intermediate **6a**. This, followed by treatment with ammonia gas, resulted in the synthesis of isoquinolines (**5e**) for the substrates, where R = H/Ph (**5a**) (a, Scheme 3). In the case of substrates where R = NMe_2 or OEt (**5a'**) 1-aminoisoquinolines (**6b)** was obtained as a major product along with a minor isomer of isoquinolines (**5e)** (b, Scheme 3).[17]

Scheme 3: TfOH mediated synthesis of isoquinolines (**5e**) and 1-aminoisoquinolines (**6b**)



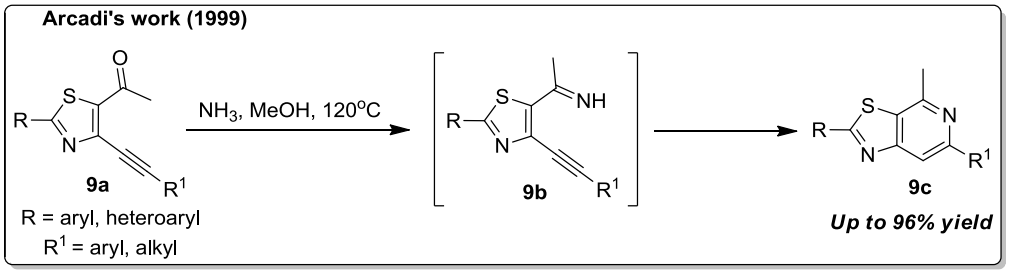
Sakamoto's group reported a few protocols for the synthesis of isoquinoline *N*-oxides. The treatment of *o*-alkynyl pyridine carboxaldehydes (**7a)** with ammonia and hydroxylamine hydrochloride afforded naphthyridines (**7b)** and naphthyridine *N*-oxides (**7c)** respectively in moderate to good yields at a higher temperature (a, Scheme 4).[18a] The same group has developed another protocol for the synthesis of β and γ-carbolines (**8b)** by the reaction of ammonia with 3-ethynyl indole 2-carboxaldehydes (**8a)** and vice-versa. If hydroxylamine hydrochloride is used in place of ammonia, the corresponding *N*-oxides (**8c)** were obtained (b, Scheme 4).[18a-c]

Scheme 4: Synthesis of naphthyridines (**7b**), carbolines (**8b**) and respective *N*-oxides (**7c**, **8c**)



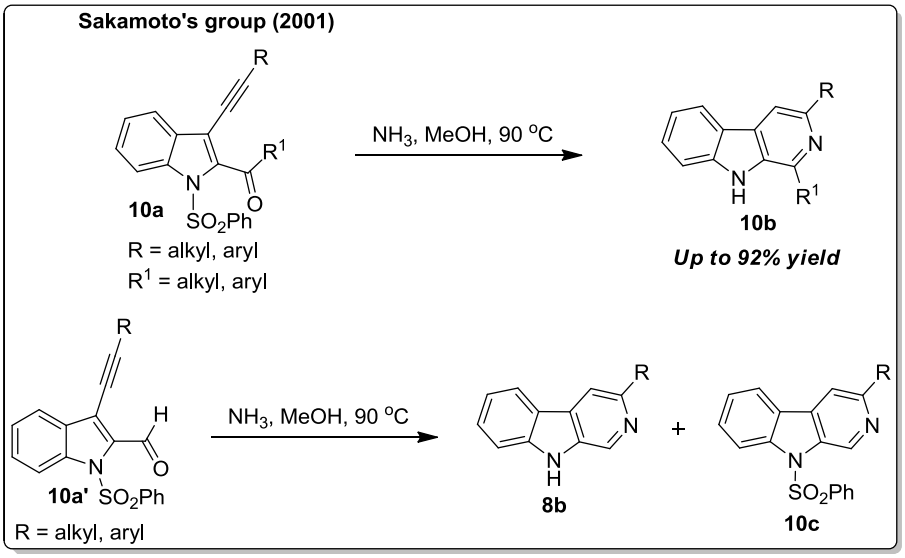
Arcadi and coworkers reported a protocol for the synthesis of thiazole containing 1-methyl isoquinolines (**9c**) by the treatment of ammonia with 2-alkynyl thiazolium ketones (**9a)** at 120 °C (Scheme 5) through imine intermediate **9b.**[18d]

Scheme 5: Synthesis of functionalized pyrido[3,4-c]thiazoles (**9c**)



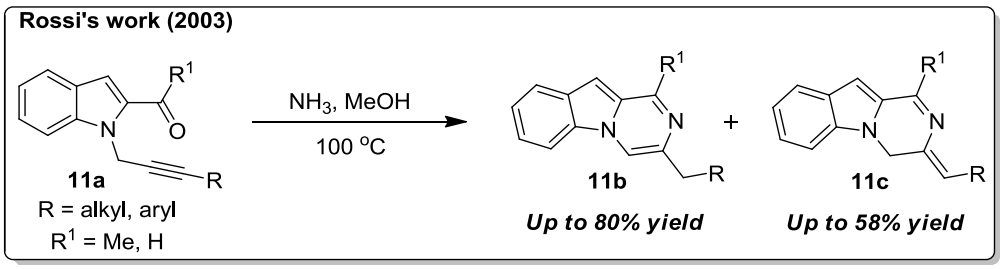
Sakamoto's group has developed another approach for the synthesis of 9H-pyrido[3,4- b]indoles (**10b)**. This reaction with 2-acyl-1-benzenesulfonyl-3-iodo-1H-indoles (**10a)** with ammonia at 90 °C affords the pyridoindole derivatives (**10b)** in moderate to good yields (Scheme 6).[18e] Surprisingly, when the reaction was carried out with an indole, where R^1 = alkyl or aryl (**10a**), deprotection of nitrogen group in the product was observed. But in the case of indoles where R^1 = H (**10a'**), a mixture of *N*-benzenesulfonyl (**10c)** as well as deprotected indole (**8b)** were observed.

Scheme 6: The synthesis of pyridoindole derivatives (**8b** & **10b-c**)



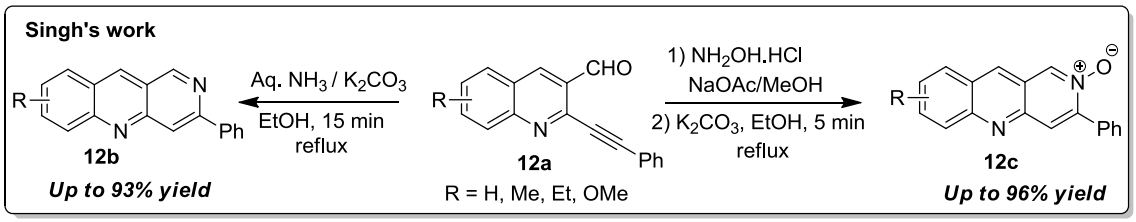
In 2003, Rossi and coworkers reported a method for the synthesis of pyrazino indoles (**11b** & **11c)**. This experiment carried out using 2-acyl-1-propargyl-1H-indole (**11a)** with ammonia at 100 °C, afforded a mixture of isomers of pyrazinoindoles **11b** & **11c** (Scheme 7).[18f]

Scheme 7: Synthesis of pyrazino (**11b**) and dihydropyrazino indoles (**11c**)



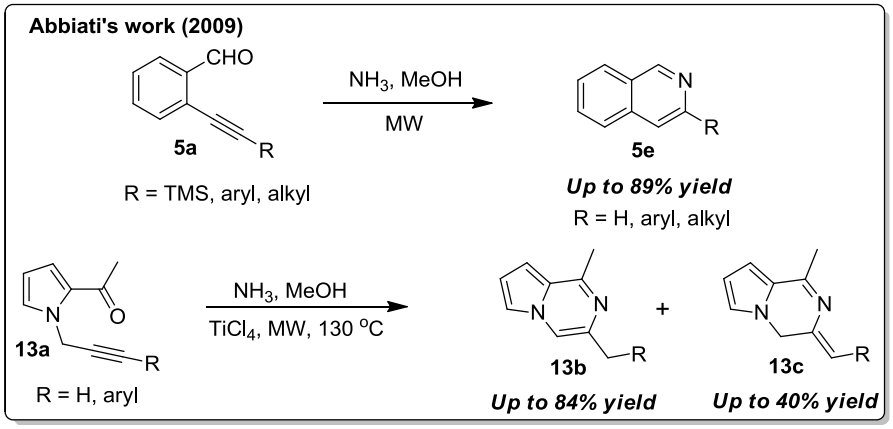
Singh and coworkers reported a copper-free Sonogashira coupling of 2-chloroquinolines with alkynes in 2008. To show the synthetic application of the products (**12a**), they have treated 2-alkynylquinoline carboxaldehyde (**12a**) with ammonia or hydroxylamine hydrochloride to afford benzonaphthyridine (**12b**) or its *N*-oxides (**12c**) at elevated temperature (Scheme 8).[18g]

Scheme 8: Synthesis of benzonaphthyridine (**12b**) or benzonaphthyridine *N*-oxides (**12c**)



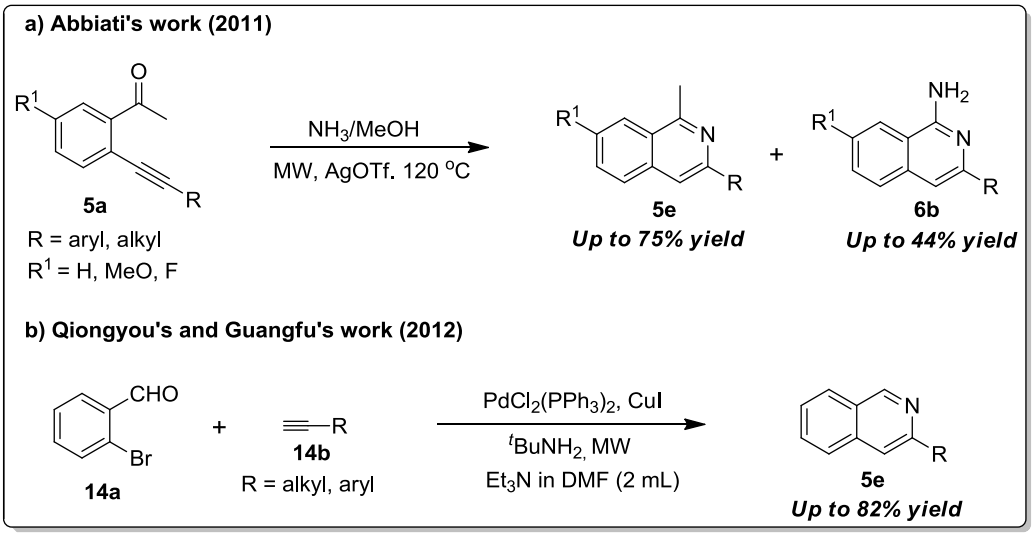
Reactions under microwave irradiations have several advantages over conventional methods in organic synthesis.[19] The main advantage of the microwave technology in synthetic organic chemistry is a decrease in the reaction time and an increase in the rate of reaction. Abbiati and his coworkers developed a microwave-assisted metal-free protocol for the synthesis of isoquinoline (**5e**) derivatives using 2-alkynyl benzaldehydes (**5a**) and NH_3. In the same paper, they also reported a $TiCl_4$ mediated reaction between 2-acetyl-*N*-propargyl pyrrole (**13a**) with NH_3 under microwave irradiation to afford pyrrolo-pyrazines (**13b**) or dihydro pyrrolo-pyrazines (**13c**) products (Scheme 9).[19b]

Scheme 9: $TiCl_4$ mediated synthesis of isoquinoline (**5e**) and pyrazines (**13b** & **13c**) under microwave irradiation



In 2011, Abbiati's group reported one more approach using microwave irradiation. An Ag-catalyzed iminoannulation protocol by the treatment of ammonia with *o*-alkynyl acetophenones (**5a**) resulted in the formation of isoquinolines (**5e**) and 1-amino naphthalenes (**6b**) (a, Scheme 10).[20a] Recently, a straightforward and efficient approach has been developed in one-pot under microwave irradiation by using *o*-bromo-benzaldehydes (**14a**), *tet*-butylamine and terminal alkynes (**14b**) in the presence of Pd/Cu catalysts, affording the isoquinoline derivatives (**5e**) in reasonable yields (b, Scheme 10).[20b]

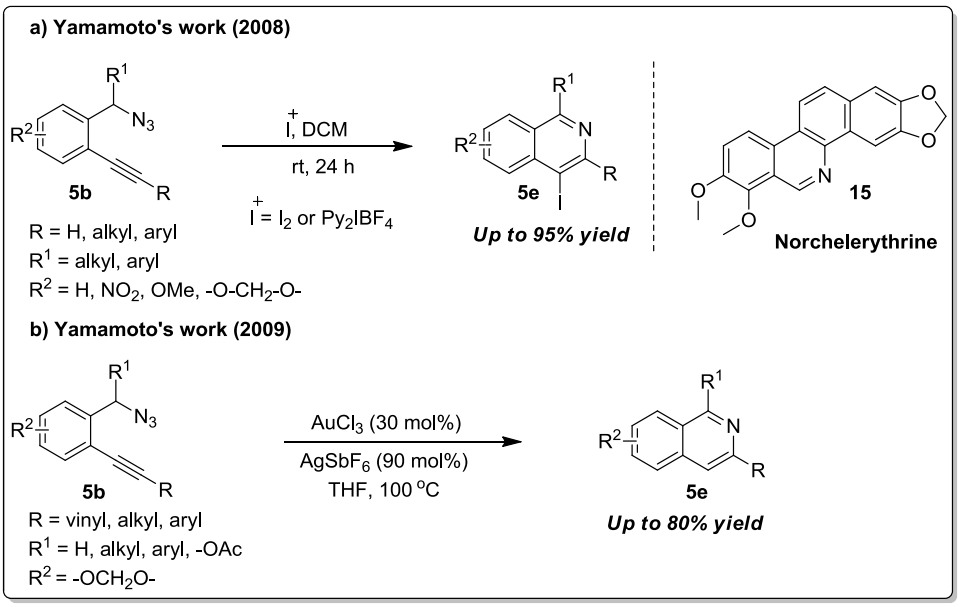
Scheme 10: Microwave-assisted synthesis of isoquinolines and 1-amino isoquinolines (**6b**)



2.2.2) from *o*-alkynyl benzyl azides (Path b)

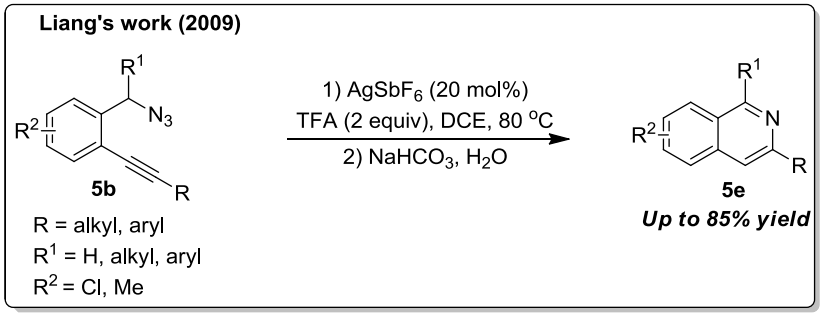
Yamamoto and coworkers reported an efficient metal-free electrophilic tandem approach for the synthesis of iodo-isoquinolines (**5e**) in good yields by the treatment of *o*-alkynyl benzyl azides (**5b**) with iodine surrogates. The synthetic application of this protocol has been shown by the synthesis of norchelerythrine (**15**) isoquinoline alkaloids in a concise manner (Scheme 11).[21a] Later on, the same group developed an Ag/Au-co-catalyzed synthesis of isoquinoline at a higher temperature (b, Scheme 11).[21b]

Scheme 11: Synthesis of 4-iodo-isoquinoline (**5e**) from *o*-alkynyl benzyl azides (**5b**)



In 2009, Liang and coworkers published a paper regarding the Ag-catalyzed synthesis of isoquinoline (**5e**) in moderate to good yields from the reaction of benzyl azide (**5b**) with trifluoroacetic acid. Interestingly, this reaction could not furnish the desired product in the absence of trifluoroacetic acid (Scheme 12).[22]

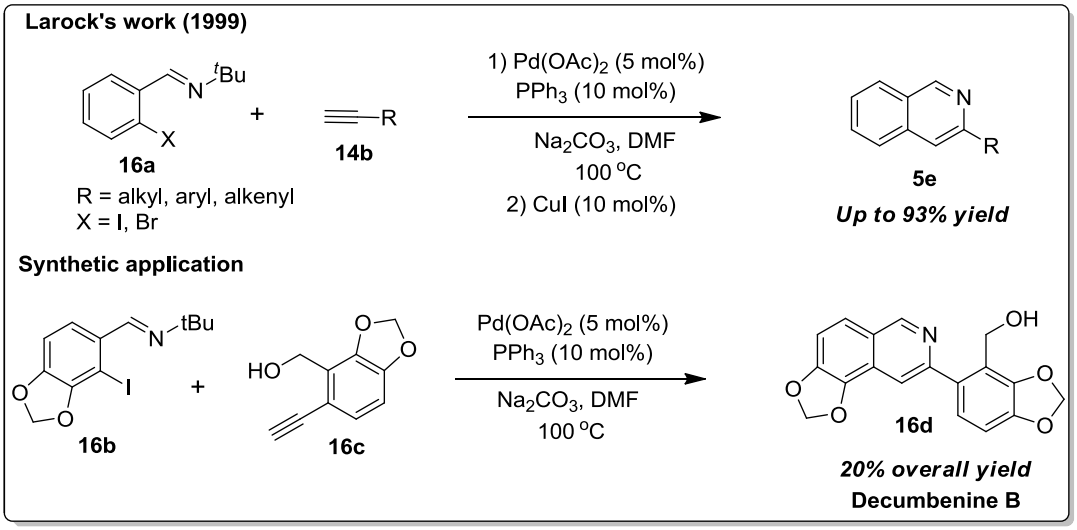
Scheme 12: Synthesis of isoquinoline (**5e**) from *o*-alkynyl benzyl azides (**5b**)



2.2.3) from *o*-alkynyl benzaldimines and aldoximes (Path c)

Larock and coworkers developed a few metal catalyzed methods for the synthesis of isoquinoline derivatives form *o*-alkynyl benzaldimines in one-pot. In 1999, Pd-catalyzed syntheses of isoquinolines (**5e**) and pyridines in moderate to excellent yields have been reported by the reaction between *o*-halobenzaldimines (**16a**) and terminal acetylenes (**14b**) (Scheme 13). Unfortunately, alkyl substituted acetylenes did not afford the desired isoquinolines under Pd-catalyzed condition. The *o*-iminoalkynes prepared from the Pd-

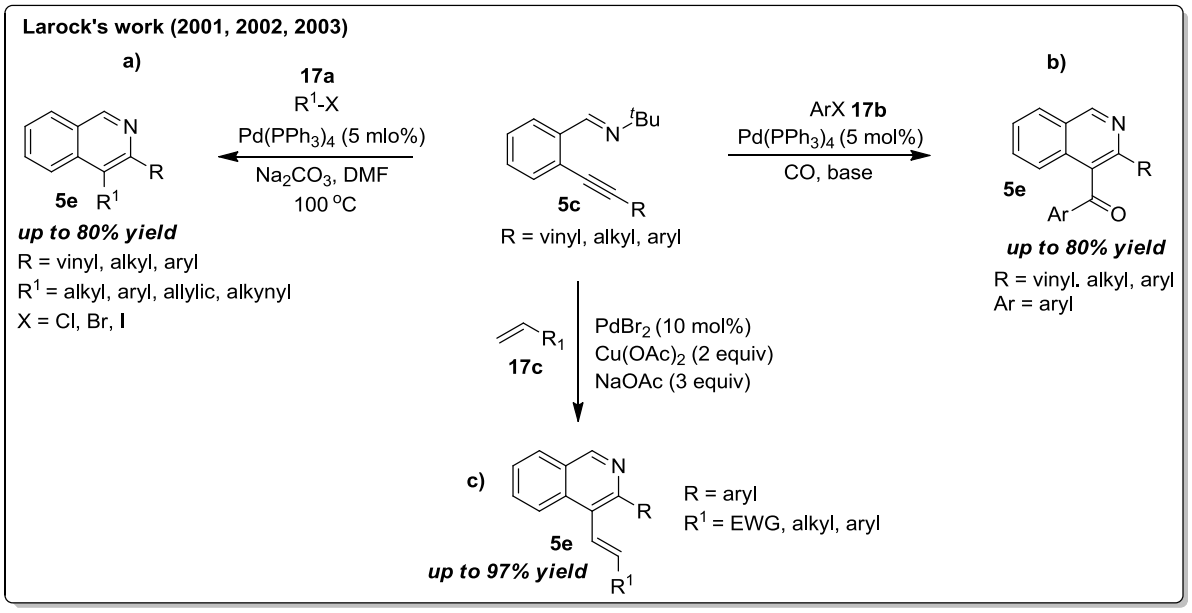
Scheme 13: Pd and Cu-catalyzed synthesis of isoquinolines (**5e**) and Decumbenine B (**16d**)



catalyzed Sonogashira coupling between *o*-halobenzaldimines (**16a**) and the respective alkyl substituted terminal alkynes (**14b**) underwent Cu-catalyzed annulation to provide the isoquinolines (**5e)** in good to excellent yields. They have also synthesized an isoquinoline alkaloid Decumbenine B (**16d**) in seven steps using this iminoannulation protocol between compound **16b** and **16c** in 20% overall yield (Scheme 13).[23a & d]

Larock and coworkers largely contributed to the synthesis of isoquinoline derivatives (**5e**). After developing a successful Pd-Cu catalyzed method for the synthesis of isoquinolines (Scheme 13),[23a] they directed their efforts toward developing cross-coupling approaches using *o*-alkynyl benzaldimines (**5c**) with suitable electrophiles. In 2001, the first cross-coupling approach was developed by the reaction between *o*-alkynyl benzaldimines (**5c**) with aryl, alkyl, allyl or alkynyl halides (**17a**) in the presence of a Pd catalyst and afforded 3,4-disubstituted isoquinoline derivatives (**5e**) in moderate to good yields (a, Scheme 14).[23b] Later on, Pd-catalyzed domino cyclization of *o*-iminoalkynes (**5c**) and consequent trapping with carbon monoxide and aryl halides (**17b**) resulted in the formation of 3-substituted 4-aroyl isoquinolines (**5e**) in good yields. However, this methodology could not afford the desired isoquinolines in the case of allylcarbonates, alkyl chlorides and 1-iodo-1-decyne (b, Scheme 14).[23c & d]

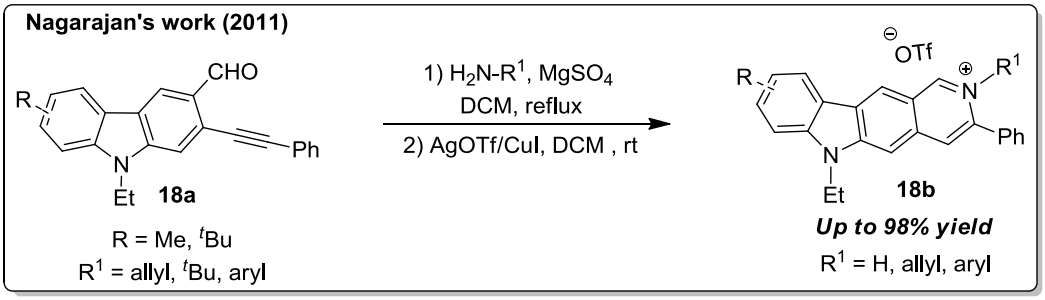
Scheme 14: Pd-catalyzed domino electrophilic cyclization of *o*-alkynyl benzaldimines and subsequent trapping with suitable partners



One more approach has been developed by the same group: Pd-catalyzed electrophilic domino cyclization of *o*-alkynyl benzaldimines (**5c**) with a wide range of olefins (**17c**) to access 3,4-disubstituted isoquinolines (**5e**) in moderate to excellent yields (c, Scheme 14).[23e]

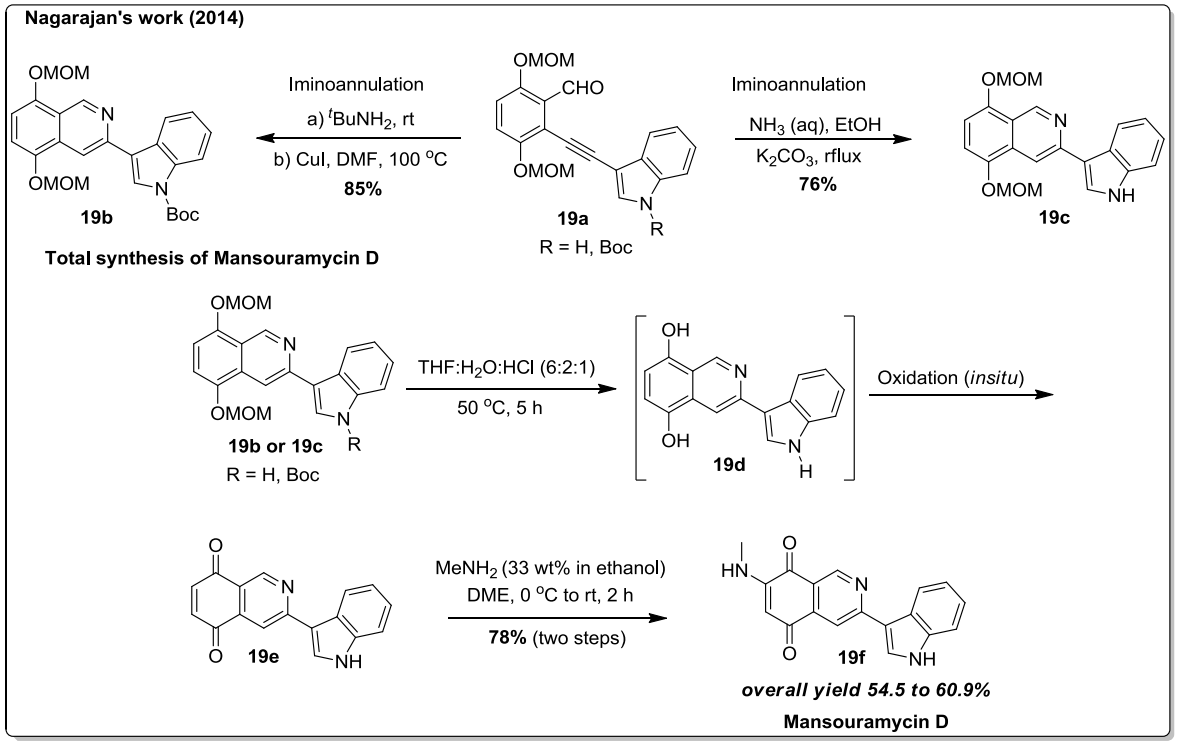
Apart from the above mentioned methods, a couple of other approaches are also known for the synthesis of isoquinolines. In 2012, Nagarajan's group developed a very efficient method to access a diverse range of ellipticinium and ellipticine analogues (**18b**) *via* Ag or Cu-catalyzed domino cyclization of 2-alkynyl-3-carbazole aldehydes (**18a**) with appropriate amines respectively (Scheme 15).[24a]

Scheme 15: Ag- or Cu-catalyzed synthesis of ellipticinium and ellipticine analogues (**18b**)



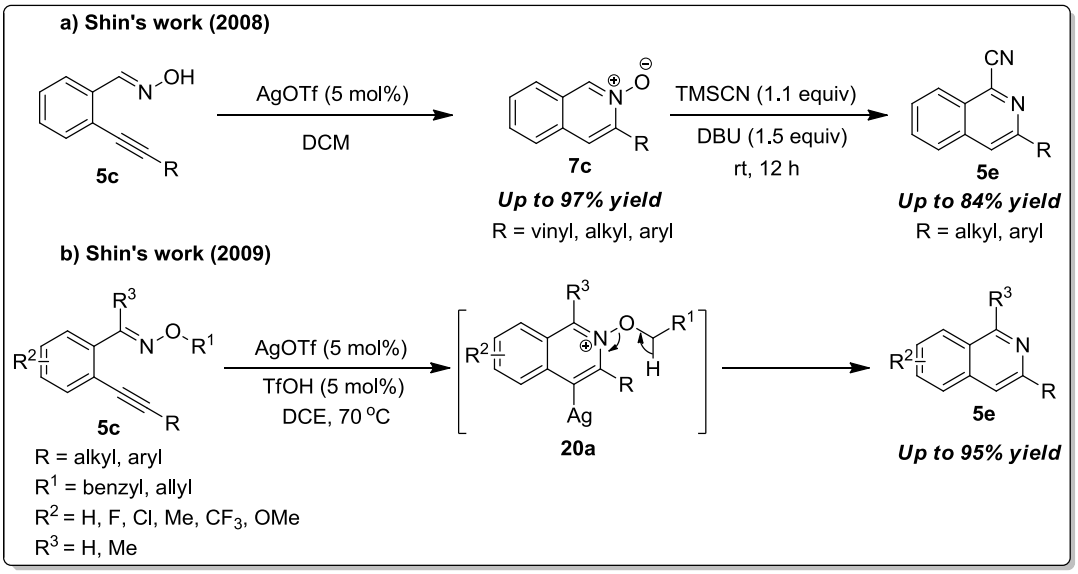
Recently, the same group has reported the first concise total synthesis of marine alkaloid Mansouramycin D (**19f**) in good overall yield (Scheme 16). The report describes the synthesis of the isoquinoline (**19b** or **19c)** framework by applying iminoannulation approach either under metal-free conditions or in the presence of CuI catalyst with *o*-alkynyl benzaldehydes (**19a**) and amine source. With the isoquinoline core (**19b** or **19c**) in hand, the deprotection of MOM as well as Boc group was carried out by THF:H_2O:HCl (6:2:1) mixture. Surprisingly, the deprotected product (**19d**) was oxidized in situ into its quinone form (**19e**) without using oxidizing agents. Aminomethylation was carried out by methylamine (33% ethanolic solution) at 0 ^oC and afforded Mansouramycin D (**19f**) alkaloid in good yields (Scheme 16).[24b]

Scheme 16: Synthesis of marine alkaloids Mansouramycin D (**19f**) *via* iminoannulation approach



In 2008, Shin and coworkers developed a novel metal-catalyzed synthesis of isoquinoline *N*-oxides (**7c**) in moderate to excellent yields by domino cyclization strategy of *o*-alkynyl benzaldoximes (**5c**) (Scheme 17). Furthermore, they have converted these

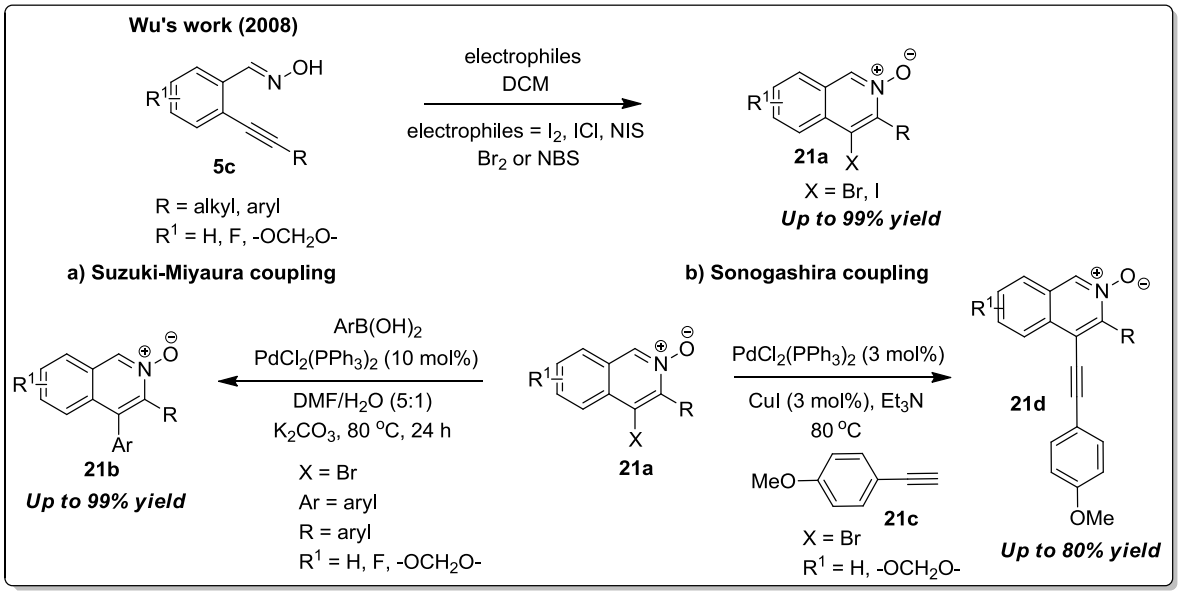
Scheme 17: Ag-catalyzed synthesis of isoquinoline *N*-oxides (**7c**) and isoquinolines (**5e**)



isoquinoline *N*-oxides (**7c**) to 1-cyanoisoquinolines (**5e)** in good yields by the treatment of TMSCN and DBU (a, Scheme 17).[25a] Another approach has been developed by the same group: an Ag-catalyzed synthesis of isoquinoline (**5e**) by annulation reaction of 2-alkynyl O-alkyl benzaldoxime (**5c**) derivatives *via* redox catalysis (b, Scheme 17).[25b]

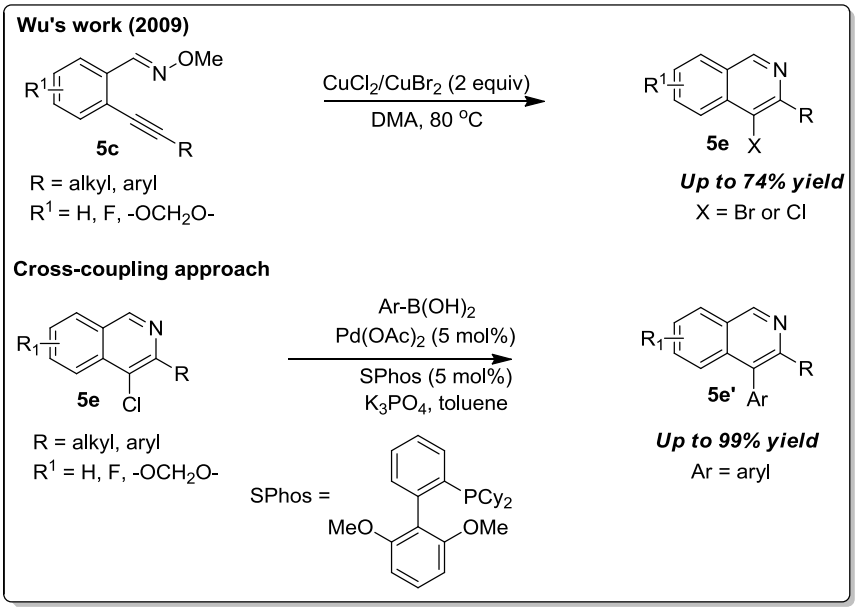
Wu and coworkers reported the metal-free domino electrophilic cyclization of *o*-alkynyl benazladoximes (**5c**) with various electrophiles for the synthesis of 4-iodo/bromo-isoquinoline *N*-oxides (**21a**). They have successfully utilized these 4-iodo/bromo-isoquinoline *N*-oxides (**21a**) in Pd-catalyzed Suzuki-Miyaura and Sonogashira cross-coupling reactions and afforded the desired cross-coupled products **21b** and **21d** in good to excellent yields (Scheme 18).[26]

Scheme 18: Metal-free domino cyclization of *o*-alkynyl benazladoximes (**5c**)



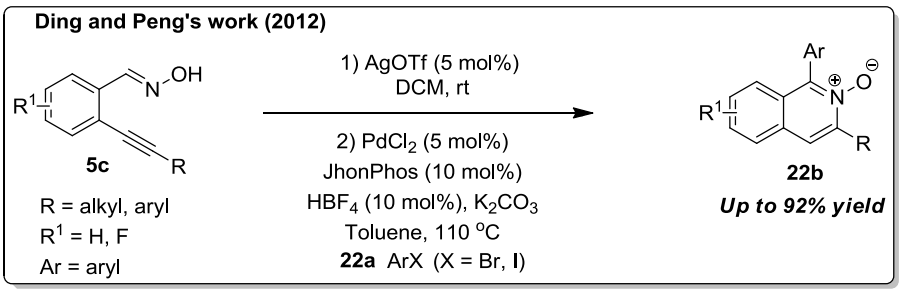
The same group has developed a copper(II)-mediated approach to access 3-substituted 4-halo isoquinolines (**5e)** by the domino electrophilic annulation of *o*-alkynyl O-methyl benzaldoxime derivatives (**5c)** at elevated temperatures. The products have been utilized in Suzuki-Miyuara cross-coupling reaction to access the desired coupled products (**5e'**) (Scheme 19).[27]

Scheme 19: Cu-mediated synthesis of 4-haloisoquinolines (**5e**) and their applications



In 2012, Ding and Peng's group disclosed a one-pot approach for the synthesis of 1-aryl-isoquinoline derivatives (**22b**) in moderate to good yields. They employed an Ag-catalyzed electrophilic domino cyclization to access isoquinoline *N*-oxides and subsequent Pd-catalyzed arylation at 1-position of isoquinoline in one-pot. In the case of alkyl acetylenes, the yields were moderate and in some cases, unfortunately the reaction did not work (Scheme 20).[28]

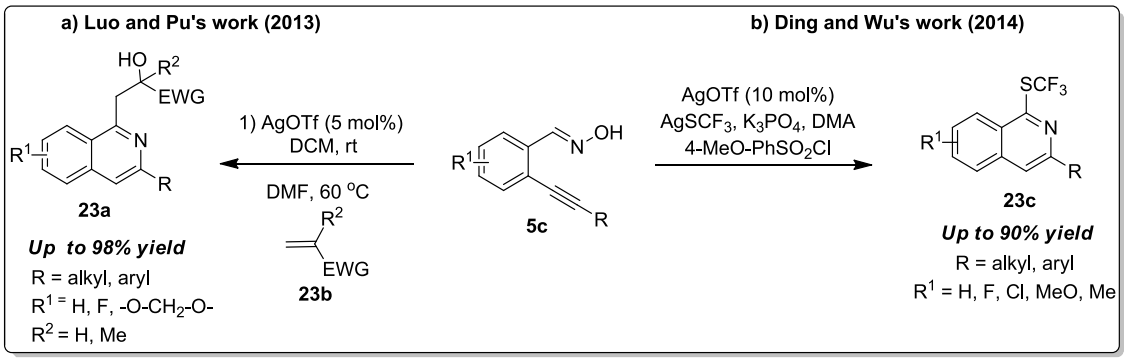
Scheme 20: Ag-catalyzed cyclization and Pd-catalyzed arylation of isoquinolines (**22b**)



It is well documented in the literature that Lewis acid catalyzed domino cyclization of 2-alkynyl benzaldoximes affords isoquinoline *N*-oxides.[25b & 26] Encouraged by these results, Luo and Pu's group developed another approach using aldoximes (**5c**) and *α,β*-unsaturated carbonyl derivatives (**23b**) to access 1-alkyl isoquinolines (**23a**) in moderate to excellent yields (a, Scheme 21).[29a] Ding and Wu also reported the Ag-catalyzed tandem cyclization of

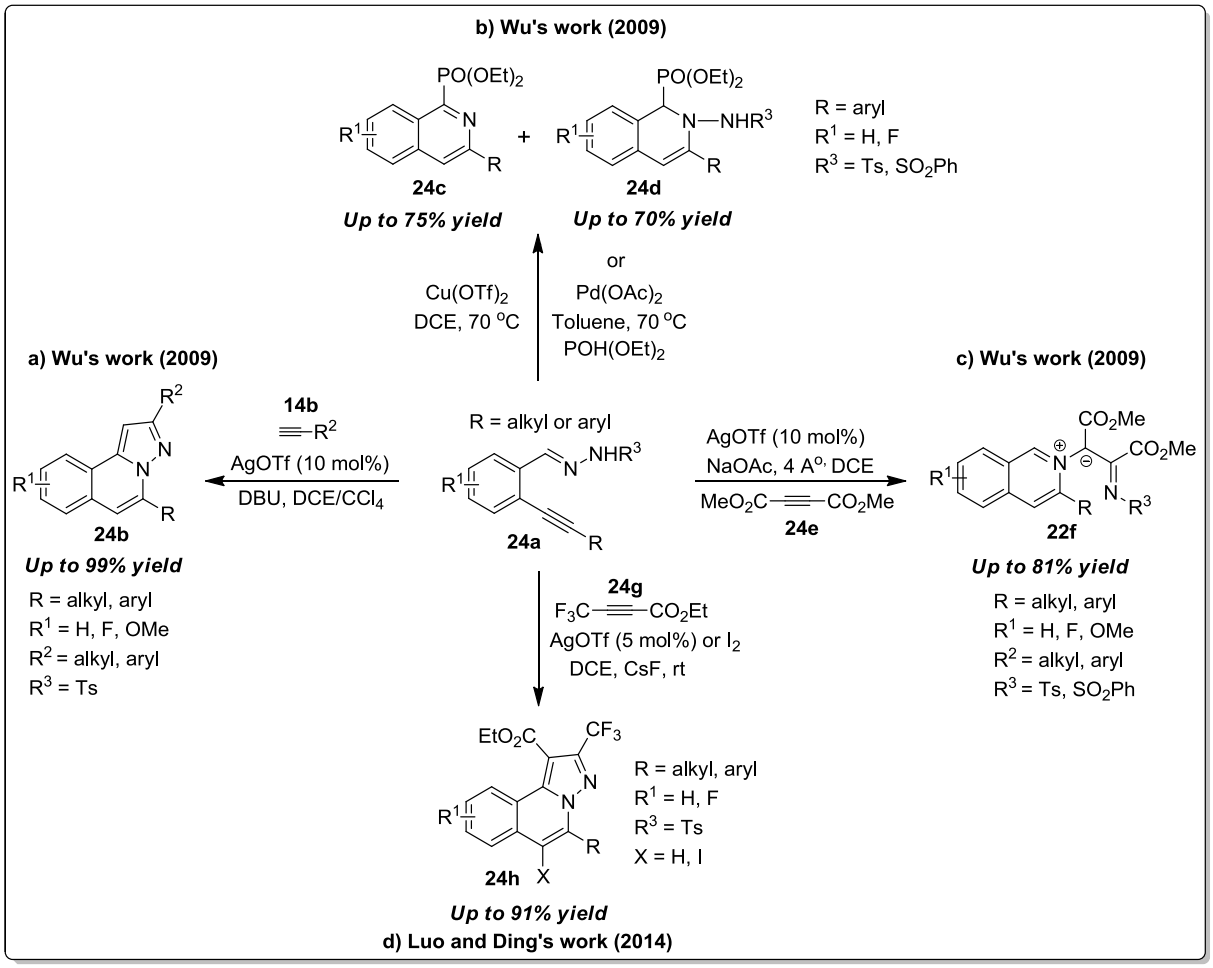
o-alkynyl aldoximes (**5c**) and $AgSCF_3$ under mild reaction conditions to access 1-trifluoromethylthio-isoquinolines (**23c**) (b, Scheme 21).[29b]

Scheme 21: Synthesis of 1-alkyl and 1-trifluoromethylthio isoquinolines (**23a** & **23c**)



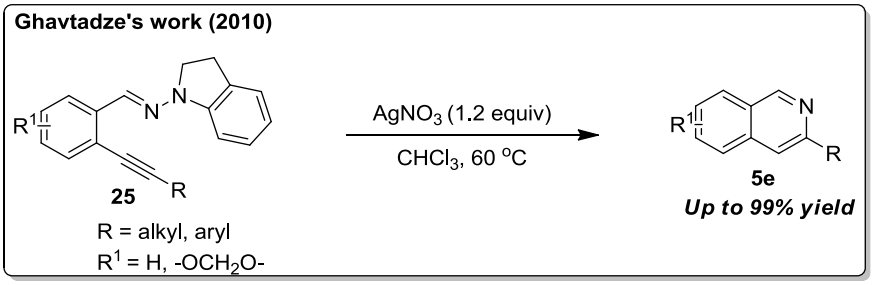
Apart from the afore-mentioned protocols, a few more approaches have been developed through one-pot domino cyclization of *N*-(2-alkynyl benzylidene)hydrazides (**24a**) with different electrophiles resulting in the corresponding products (Scheme 22). In 2009, Wu and coworkers published a couple of papers regarding Ag-catalyzed electrophilic domino cyclization of hydrazide derivatives (**24a**) with terminal alkynes (**14b**) to afford fused 1,2-dihydroisoquinolines (**24b**) (a, Scheme 22).[30a] Another approach has been developed by the same group: a catalyst-dependent synthesis of 1-phopshonate isoquinolines (**24c**) or dihydroisoquinolines (**24d**) by the reaction of *o*-alkynyl hydrazides (**24a**) with diethyl phosphite. Copper catalyst favors the formation of isoquinolines (**24c**) while Pd catalyst favors the formation of dihydroisoquinolines (**24d**) (b, Scheme 22).[30b] They have also developed a tandem annulation between the hydrazide derivatives (**24a**) with dimethyl acetylenedicarboxylate (DMAD) (**24e**) to afford isoquinlines (**22f**) in the presence of AgOTf as a catalyst (c, Scheme 22).[30c] Inspired by Wu's research work (Scheme 18 & 19), Luo and Ding developed a protocol for the synthesis of CF_3-containing pyrazolo isoquinoline derivatives (**24h**) in moderate to excellent yields (d, Scheme 22).[30d]

Scheme 22: Ag-catalyzed annulations of *N*-(2-alkynyl benzylidene)hydrazides (**24a**) with different electrophiles



Ghavtadze and coworkers proposed a new mechanism: They found that even indole can also act like a neutral leaving group from a hydrazone derivatives (**25**). Following their hypothesis, they have carried out the reaction between 1-aminoindoline hydrazones (**25**) and a stoichiometric amount of $AgNO_3$ and afforded the isoquinolines **5e** in good to excellent yields (Scheme 23).[31]

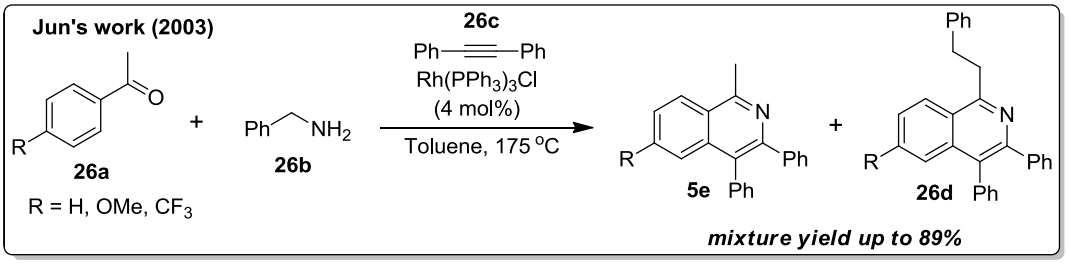
Scheme 23: Ag-mediated synthesis of isoquinolines (**5e**)



2.2.4) Rhodium and Ruthenium catalyzed C-H activation (Path d)

Rhodium and Ruthenium catalyzed synthesis of isoquinolines *via* C-H activation is also well-established. An interesting point about these reactions is that they do not require pre-activation of the reagents.[32] Jun's group has done the fundamental work in the synthesis of isoquinolines (**5e**) *via* Rh-catalyzed C-H activation. They have developed a novel method for the *o*-monoalkenylation of aromatic ketimines with alkynes (**26c**) through Rh-catalyzed C-H activation strategy. Surprisingly, in a few substrates, two different isoquinoline derivatives (**5e** & **26d**) were obtained during the reaction course (Scheme 24).[33]

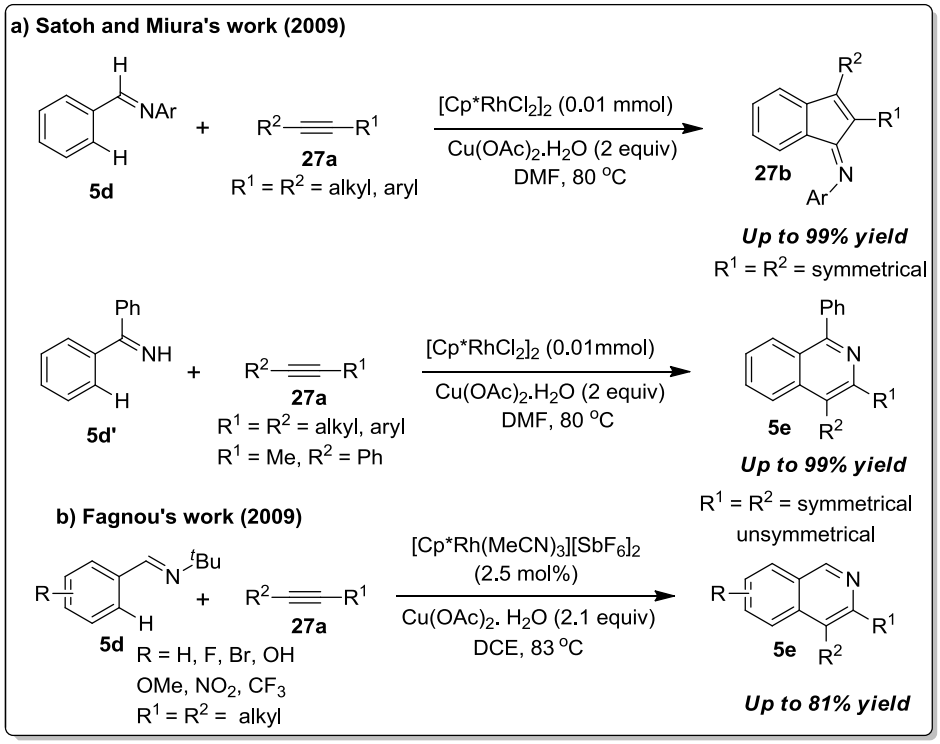
Scheme 24: Rh-catalyzed synthesis of isoquinolines (**5e** & **26d**) *via* C-H activation route



After the influential contribution by Jun's group in the field of Rh-catalyzed synthesis of isoquinolines in one-pot *via* C-H activation approach, many strategies have appeared in the literature. Based on their[34a] and other[33, 34b] literature reports, Satoh and Miura, and Fagnou and coworkers independently postulated that it could be possible to construct the isoquinoline motif by Rh-catalyzed oxidative coupling of aldimines with internal alkynes. In 2009, Satoh and Miura's group explored the synthesis of indenone imines (**27b**) and isoquinolines (**5e**) by the reaction between different benzaldimines (**5d**) with internal alkynes (**27a**) *via* Rh-catalyzed oxidative cross-coupling approach. The reaction between *N*-benzylideneanilines (**5d**) and internal alkyne afforded the indenone imines (**27b**) and benzophenone imines (**5d'**) with internal alkynes (**27a**) generated isoquinolines (**5e**). In the case of unsymmetrical alkynes, the aromatic group preferably placed at the 3-position adjacent to the nitrogen atom in isoquinolines (a, Scheme 25).[34c] In the same year, another approach has been developed by Fagnou's group for the synthesis of isoquinolines (**5e**) with different Rh-catalyst in DCE at elevated temperature from *N-tert*-butylbenzaldimines (**5d**) and internal alkynes (**27a**) (b,

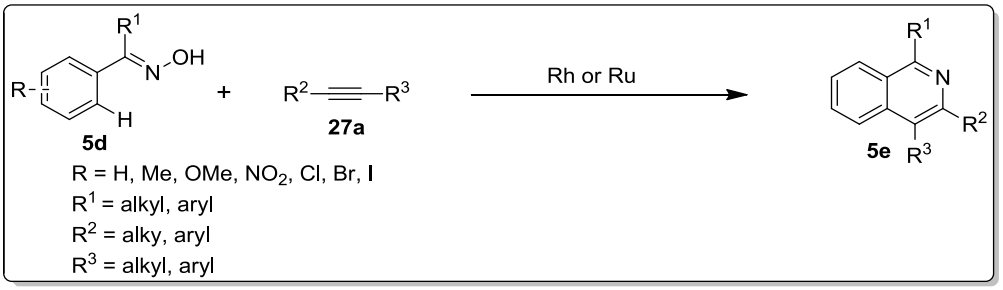
Scheme 25).[34d] In the case of unsymmetrical alkynes, the bulky substituent is preferably located at the 4-position of an isoquinoline.

Scheme 25: Initial reports on Rh-catalyzed synthesis of indenones (**27b**) and isoquinolines (**5e**)



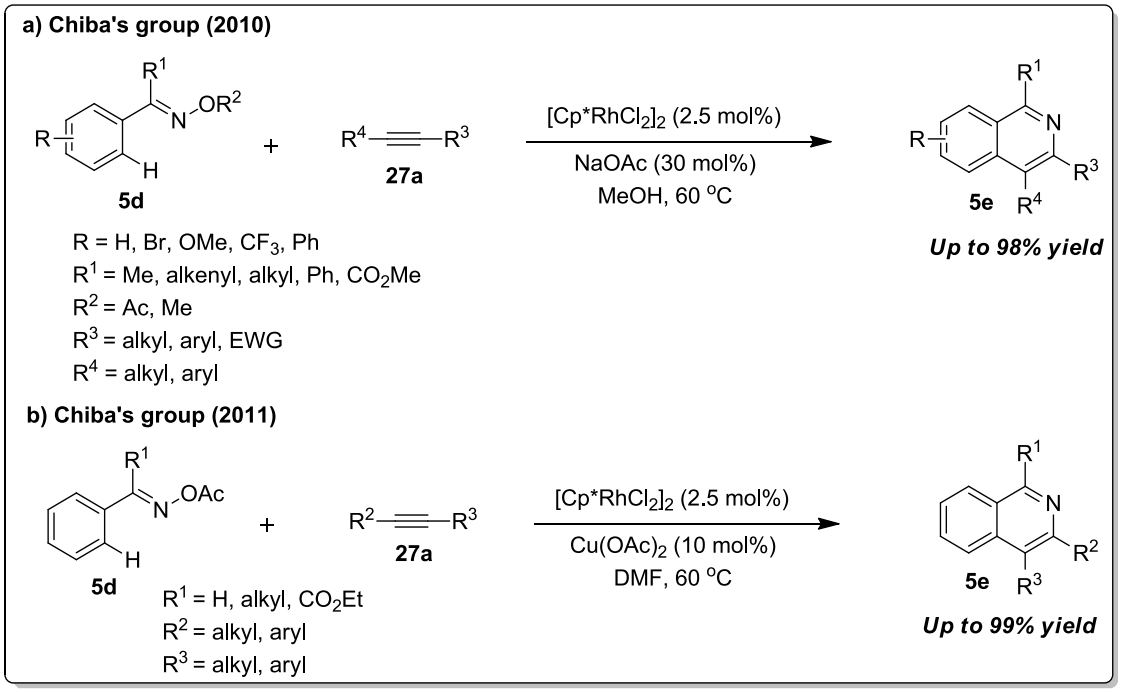
The significance of Rh-catalyzed C-H activation strategy has been increasing due to its application in the synthesis of a wide range of heterocycles in one-pot. Researchers have directed a lot of effort toward the synthesis of isoquinolines (**5e**) from different aromatic aldoximes (**5d**) with internal alkynes (**27a**) *via* Rh[35] and Ru[36]-catalyzed C-H activation (Scheme 26). In the case of unsymmetrical alkynes, the aryl group is located at the 3-position adjacent to the nitrogen atom in an isoquinoline (**5e**).

Scheme 26: Rh or Ru-catalyzed synthesis of isoquinolines (**5e**) using aryl aldoximes (**5d**)



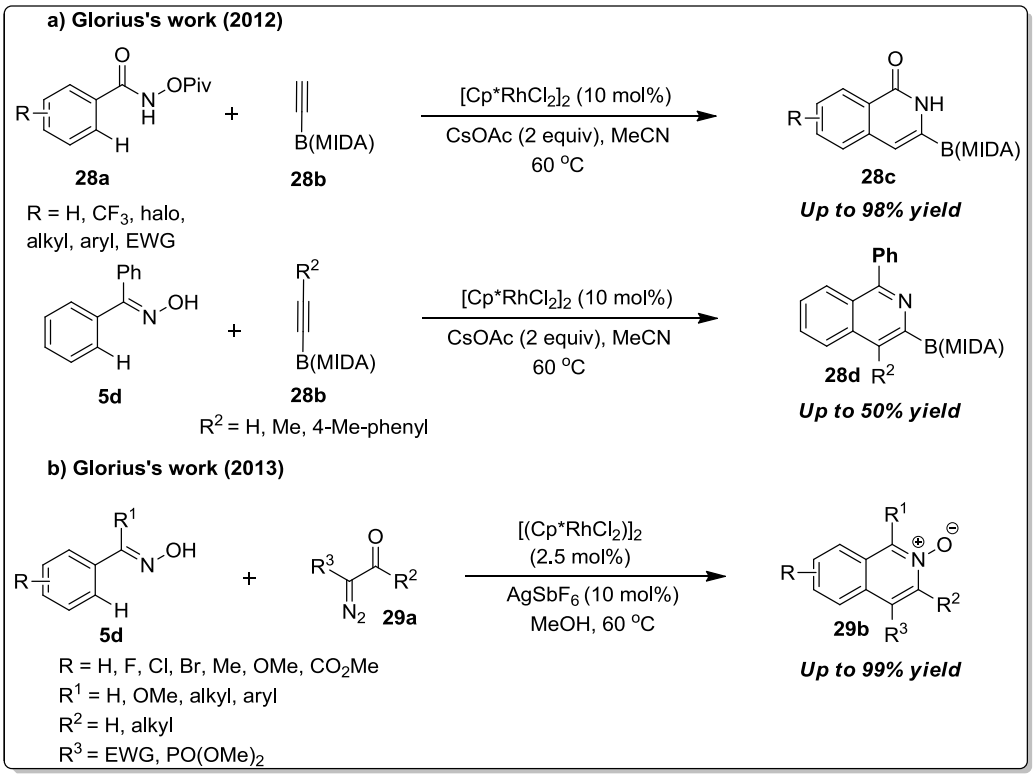
Other approaches were developed including Rh-NaOAc[37a] and Rh/Cu co-catalyzed[37b] syntheses of isoquinolines (**5e**) in excellent yields from aryl or heteroaryl ketone O-acyloximes (**5d**) with internal alkynes (**27a**) from Chiba's group (Scheme 27).

Scheme 27: Rh-catalyzed synthesis of isoquinolines using aryl ketone O-acyloximes (**5d**)



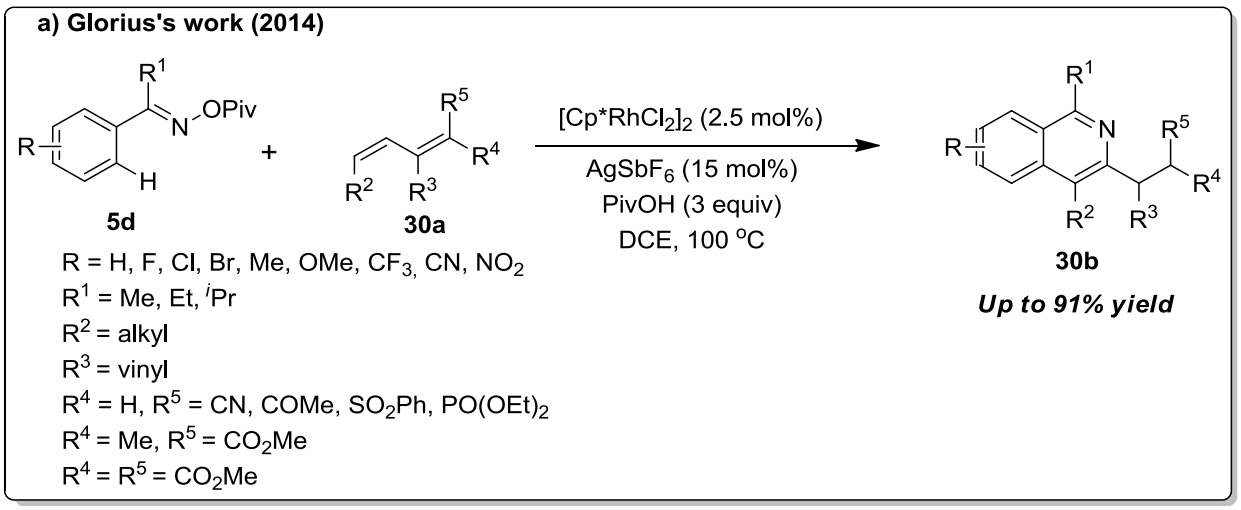
In 2012, due to the vast application of Rh-catalyzed C-H activation protocol, Glorius and coworkers developed a couple of approaches for the synthesis of isoquinolines (Scheme 28). An efficient Rh-catalyzed protocol has been reported for the synthesis of 3-MIDA boronate isoquinolones (**28c**) by the treatment of *N*-O-pivalate benzamides (**28a**) with alkynyl MIDA boronate (**28b**) in one-pot. The 3-MIDA boronate isoquinolones were used in Suzuki-Miyuara cross-coupling reaction and the corresponding products were obtained in good to excellent yields. They also reported the synthesis of borylated isoquinolines (**28d**), indole and pyrrole (a, Scheme 28) from the corresponding precursors.[38] Another interesting approach was developed by the same group by the intermolecular domino cyclization of aldoximes (**5d**) with diazo compounds (**29a**) *via* Rh-catalyzed C-H activation to afford a wide variety of isoquinoline *N*-oxides (**29b**) in good to excellent yields (b, Scheme 28).[38b]

Scheme 28: Diversity oriented Rh-catalyzed synthesis of isoquinolines and *N*-oxides



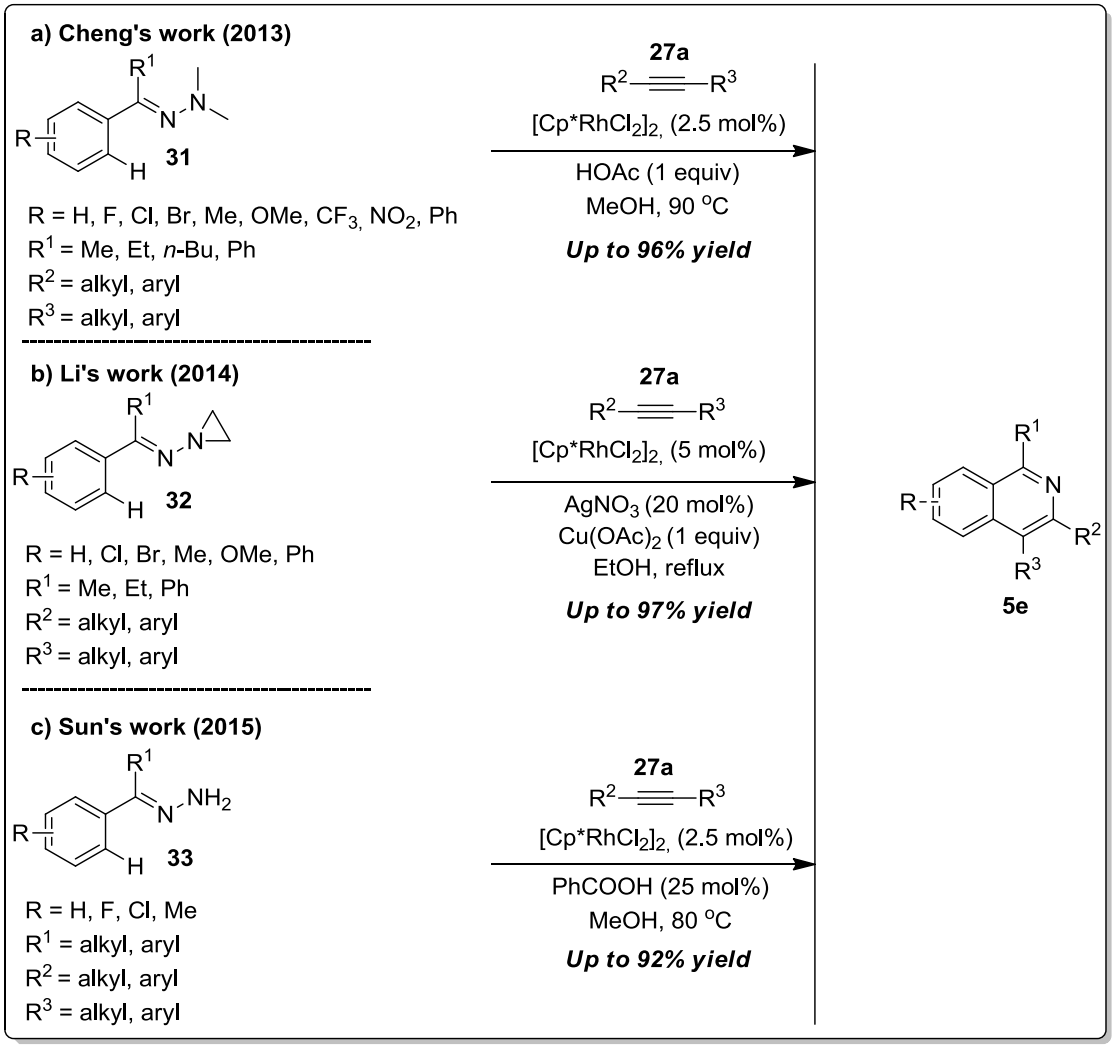
Recently, Glorius and coworkers disclosed another novel work: the Rh-catalyzed redox-neutral C-H/N-H activation followed by domino cyclization of aromatic arylketoximes (**5d**) with a wide range of 1,3-dienes (**30a**) to access functionalized isoquinolines (**30b**) in one-pot (Scheme 29).[39] As a result, the products were obtained in good to excellent yields and with regioselectivity without the use of any external oxidant.

Scheme 29: Rh-catalyzed expedient synthesis of highly substituted isoquinolines (**30b**)



Recently, a few more approaches were reported for the synthesis of isoquinolines (**5e**) by using arylhydrazone derivatives (**31**, **32** & **33**) with internal alkynes (**27a**) *via* Rh-catalyzed C-H activation (a & b, Scheme 30).[40] In the case of unsymmetrical alkynes, the aryl group preferred the 3-position of isoquinolines, similar to literature precedents. Very recently, Sun et. al. published a paper regarding the one-pot synthesis of isoquinolines (**5e**) with a broad substrate scope. In the case of unsymmetrical diaryl alkyne, both regioisomers have been observed in 1:1 ratio (c, Scheme 30).[40c]

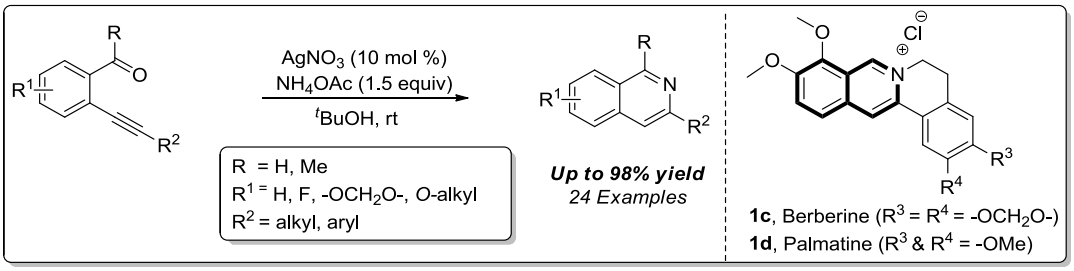
Scheme 30: Rh-catalyzed synthesis of isoquinolines (**5e**) using aryl hydrazones (**31**, **32** & **33**)



2.3) Results and Discussions

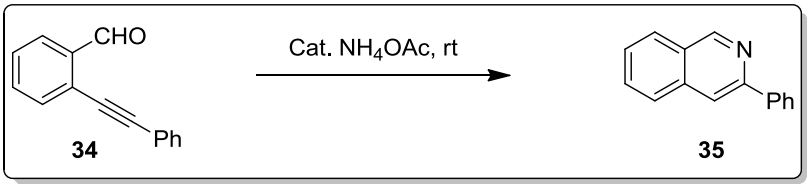
In recent literature, many strategies are known for the synthesis of isoquinolines.[18-27 & 31] The reported methods were carried out either at a elevated temperature or under microwave irradiation. Various research groups all over the world are working toward the development of a mild and efficient method for the synthesis of these rigid molecules. To our surprise, a metal-catalyzed one-pot synthesis of isoquinolines at *room temperature* from *o*-alkynyl benzaldehyde was not reported so far. While working on aromatic annulation reactions, we found an efficient and mild silver-catalyzed protocol for the synthesis isoquinolines at *room temperature* (Scheme 31).

Scheme 31: Silver-catalyzed synthesis of isoquinolines at room temperature



Our initial studies focused on the selection of a suitable reaction condition using a wide range of Lewis acids in ^{t}BuOH at room temperature. The results are summarized in Table 1. The preliminary screening of the catalysts were disappointing as $Bi(OTf)_3$ and $Yb(OTf)_3$ known to activate alkynes,[41] failed to give the desired product **35** even after 12 h at room temperature (entries 1 & 2). Discouraged by these results, we switched to other Lewis acids (Ag salts). Astoundingly, when the reaction was performed using Ag_2O as a catalyst and ammonium acetate as an amine source in ^{t}BuOH, **35** was obtained in 80% yield (entry 3). Following this, a wide range of silver

Table 1: Optimization studies[a]



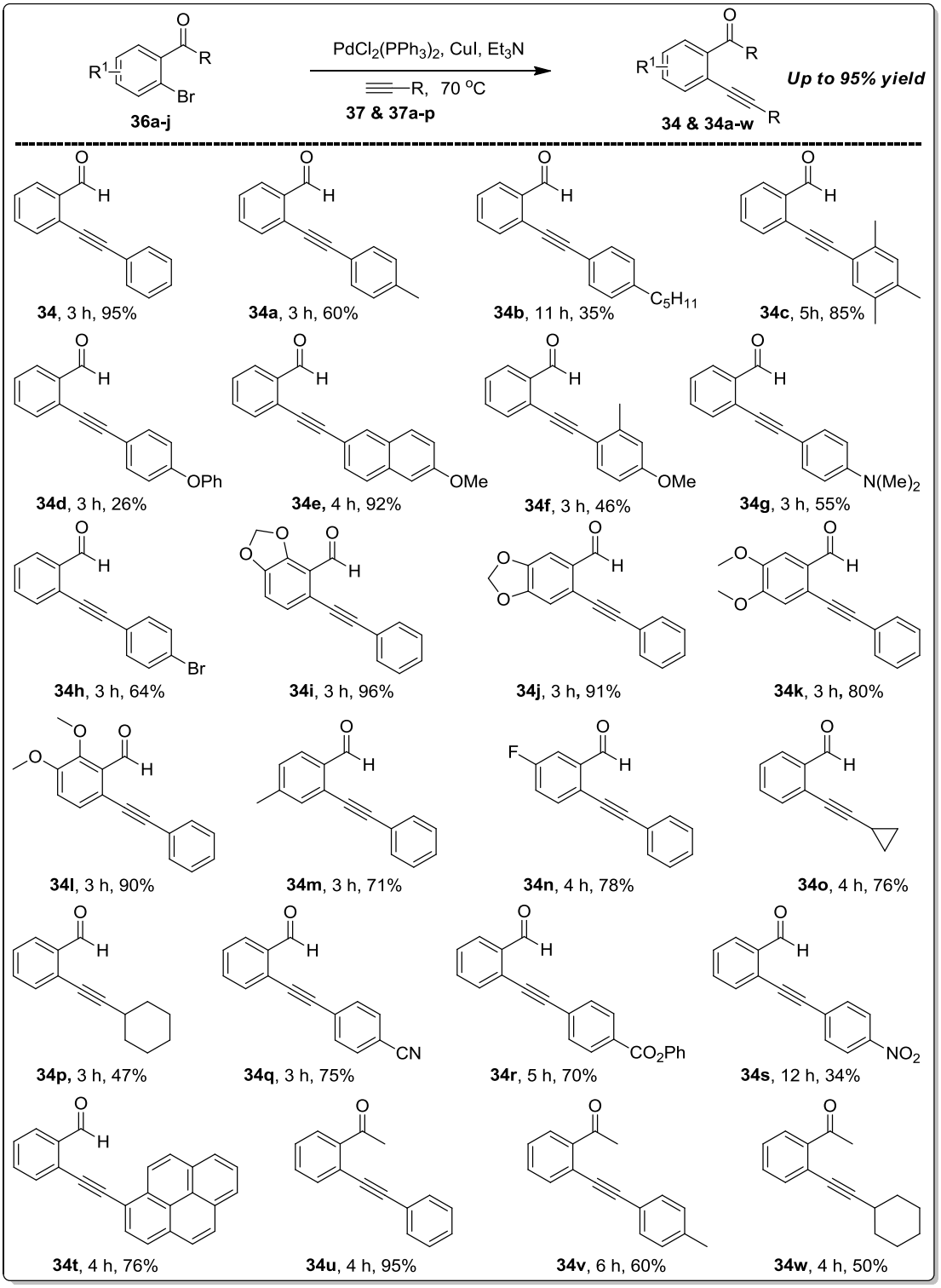
Entry	Catalyst	Nitrogen source[b]	Solvents	Time (h)	Yield[c] (%)
1	$Bi(OTf)_3$	NH_4OAc	^tBuOH	12	-
2	$Yb(OTf)_3$	NH_4OAc	^tBuOH	12	-
3	Ag_2O	NH_4OAc	^tBuOH	8	80
4	$AgClO_4$	NH_4OAc	^tBuOH	8	80
5	$Ag(OCOCF_3)$	NH_4OAc	^tBuOH	8	84
6	**AgOTf**	**NH_4OAc**	**^tBuOH**	**6**	**95**
7	**$AgNO_3$**	**NH_4OAc**	**^tBuOH**	**6**	**95**
8	Ag_2CO_3	NH_4OAc	^tBuOH	8	92
9	$AgSbF_6$	NH_4OAc	^tBuOH	8	92
10	$AgNO_3$	NH_4OAc	CH_2Cl_2	15	57
11	$AgNO_3$	NH_4OAc	CH_3CN	15	45
12	$AgNO_3$	NH_4OAc	THF	15	33
13	$AgNO_3$	NH_4OAc	EtOH	15	65
14	$AgNO_3$	NH_4HCO_3	^tBuOH	9	70
15	$AgNO_3$	NH_4OH	^tBuOH	24	70
16	$AgNO_3$	NH_4Cl	^tBuOH	24	-
17	-	NH_4OAc	^tBuOH	24	>5

[a]*Reaction conditions*: 0.12 M solution of **34** in solvent [b]1.5 equiv. of NH_3 source was used in all the reactions [c]Isolated yields. rt = 27–30 °C

catalysts have been screened at the same reaction condition and the yields were obtained in the range of 80-92% (entries 4-5 & 8-9). Out of all the catalysts tried, AgOTf and $AgNO_3$ (entries 6 & 7) were found to give the best results. Since $AgNO_3$ is inexpensive and less hygroscopic compared to AgOTf, further optimization studies were performed using $AgNO_3$ as a catalyst. A few experiments were also performed using other solvents (entries 10–13) and ammonia sources (entries 14–16) but in all those cases the yield was inferior compared to Entry 7. When the reaction was carried out in the absence of a silver catalyst, **35** was obtained only in <5% yield even after 24 h (entry 17).

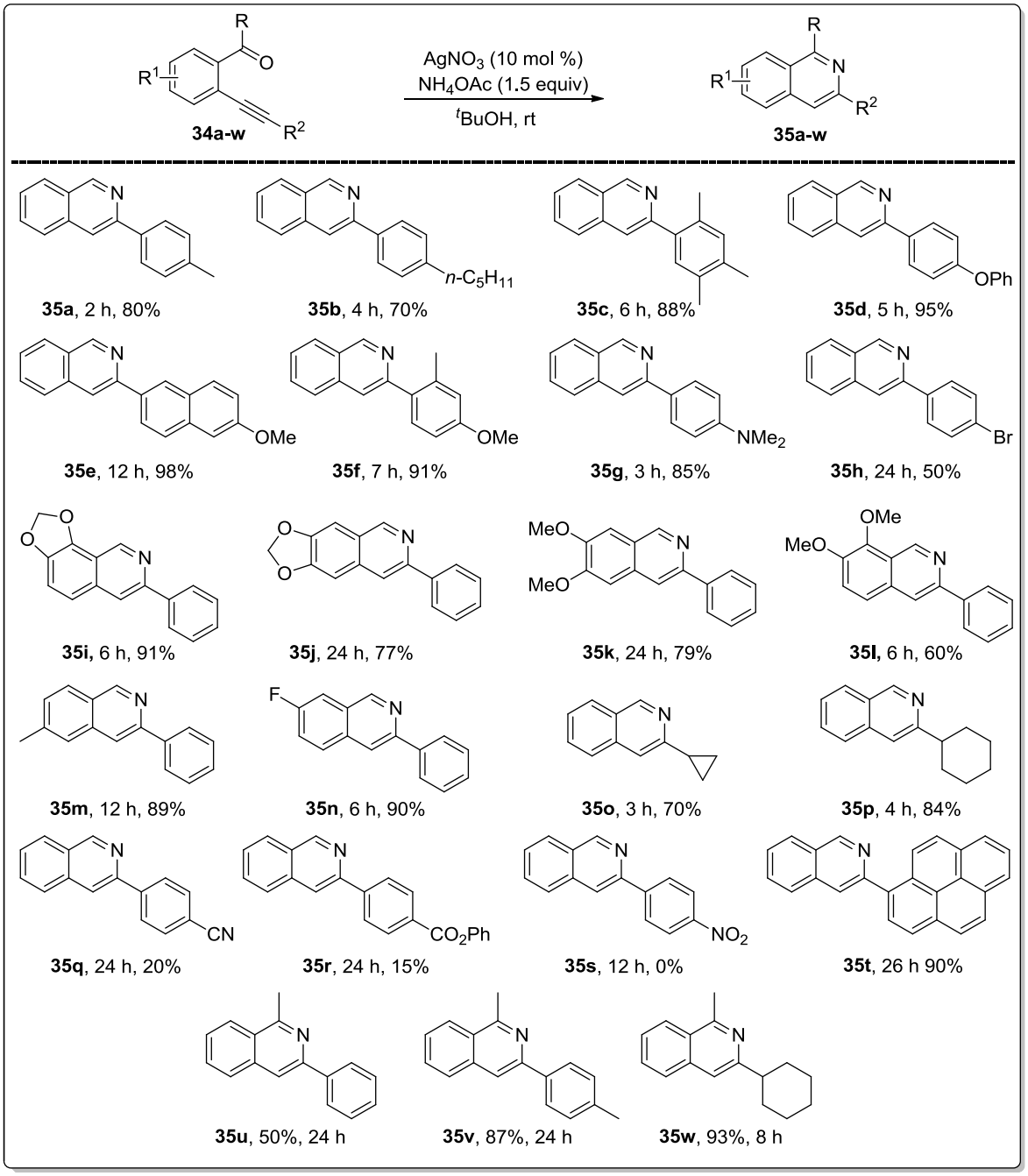
With the optimized reaction condition (entry 7, Table 1) in hand, the substrate scope was now investigated. For this purpose, a wide range of *o*-(1-alkynyl)arylaldehydes and ketones (**34** & **34a-w**) were prepared by Sonogashira coupling between 2-Br-benzaldehyde/2-Br-acetophenone derivatives (**36a-j**) and terminal alkynes (**37** & **37a-p**) (Scheme 32).[42]

Scheme 32: The **s**ynthesis of *o*-alkynyl benzaldehydes (**34** & **34a-w**)



The results obtained under the optimized reaction condition using a wide range of 2-alkynyl benzaldehdyes and ketones (**34** & **34a-w**) are summarized in Scheme 33. It is evident from Scheme 33 that most of the *o*-(1-alkynyl)arylaldehydes were converted to their corresponding isoquinoline derivatives in good to excellent yields. The reaction worked very well in the case of *o*-(1-alkynyl)arylaldehydes derived from alkynes bearing electron rich (**34a-34g)** as well as sterically hindered (**34t**) aryl substituents and afforded the corresponding

Scheme 33: Substrate scope



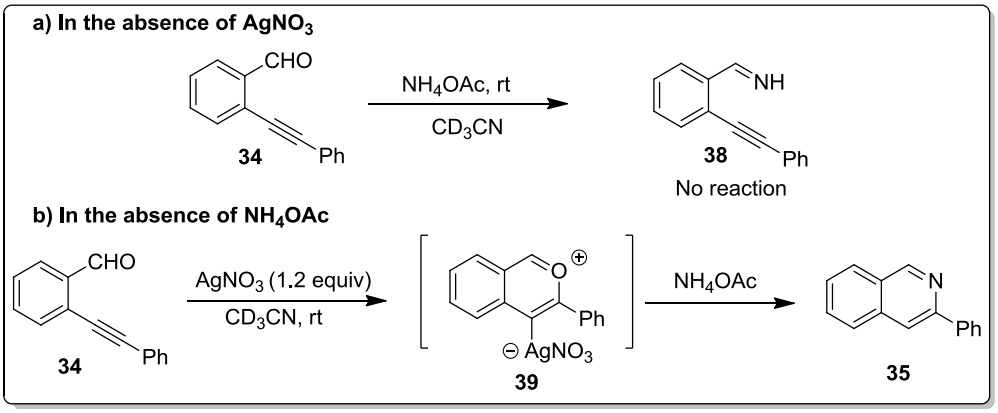
[a]*Reaction conditions*: 0.12 M solution of **34** in ^{t}BuOH. Yields reported are isolated yields. rt = 27–30 °C.

isoquinolines (**35a-35g & 35t**) in good to excellent yields. In the bromo substituted case, the product **35h** was obtained only in 50% yield. For isoquinoline precursors (**34i**–**34n**) derived from other substituted 2-bromo benzaldehydes, the annulation protocol took place capably leading to the products **35i-35n** in good yields. The reaction also worked competently in the cases of isoquinoline precursors **34o** and **34p**, which were derived from alkynes with aliphatic substituents, and the products **35o** and **35p** were obtained in 70% and 84% yields respectively. Unfortunately, this methodology was found to be less effective in the cases of *o*-(1-alkynyl)arylaldehydes with electron poor aryl substituents attached to alkynes (**34q**–**34s**). For example, the aldehydes **34q** and **34r** gave the corresponding isoquinolines **35q** and **35r** in only 15–20% yields. No product (**35s**) was observed in the case of *o*-(4-nitrophenylethynyl)benzaldehyde (**34s**). Gratifyingly, the extension of this methodology to *o*-(1-alkynyl)acetophenones[41] gave fruitful results. As seen in Scheme 33, some of the *o*-(1-alkynyl)acetophenone derivatives (**34u**, **34v & 34w**) underwent 6-*endo*-*dig* cyclization to the respective methyl substituted isoquinoline derivatives **35u, 35v & 35w** in moderate to excellent yields (Scheme 33).

At this stage, we focused our attention on elucidating a reasonable mechanism for this transformation. It is well documented in the literature that the uncatalyzed reaction between **34** and an ammonia source at higher temperature proceeds through imine intermediate **38**, which on cyclization leads to isoquinoline derivative **35**.[18-20] On the other hand, Swager's group found that TfOH promotes the formation of oxo-pyrylium intermediate **6a** (Scheme 3), which on exposure to ammonia gives the isoquinoline derivatives (**5e** & **6b**).[17] To understand whether our methodology proceeds through imine (**38**) or oxo-pyrylium intermediate (**39**), a couple of control experiments were performed (Scheme 34). In one of the experiments, *o*-(1-alkynyl)benzaldehyde **34** was treated with ammonium acetate in the absence of a silver catalyst at room temperature and the progress of the reaction was monitored by ^{1}H NMR spectroscopy (in CD_3CN) (a, scheme 34). In this case, the characteristic peak that corresponds to C*H*=N proton was not observed even after 12 h, and most of the aldehyde **34** remained unreacted. In another experiment, **34** was treated with stoichiometric amounts of $AgNO_3$ in CD_3CN at room temperature and the ^{1}H NMR was recorded after 12 h. In this case, along with the aldehyde peak, a new singlet appeared at 10.01 ppm (b, scheme 34). Although we could not isolate **39**, we presume that the peak at 10.01 ppm corresponds to the C*H*=O proton of the oxo-pyrylium salt (**39**) because this δ value approximately matches with the δ value (10.18 ppm) of the oxo-pyrylium (**39**) C*H*=O proton reported by the Swager's

group though the reaction conditions are different.[17] When ammonium acetate was added to this reaction mixture, the peak at 10.01 disappeared and a new peak at 9.35 ppm, which corresponds to the C*H*=N proton of isoquinoline, appeared after 5 h.

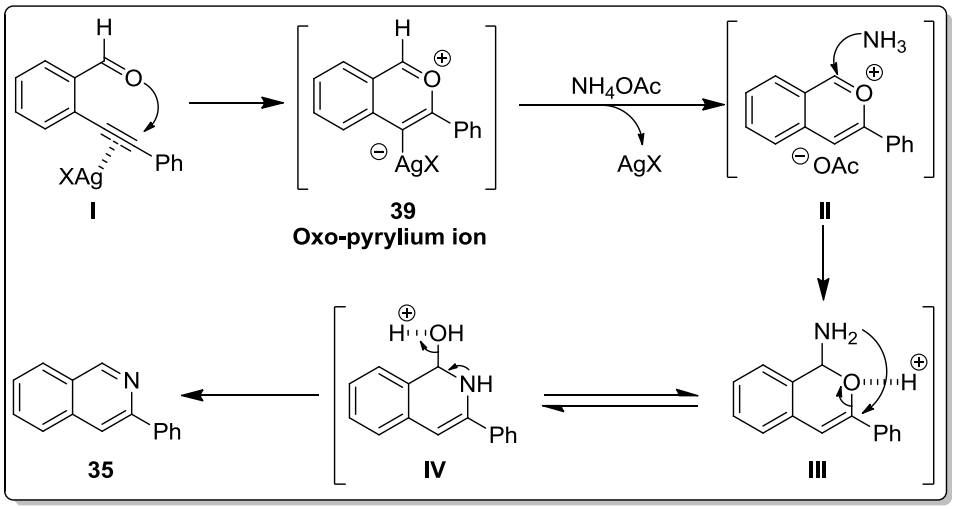
Scheme 34: Control experiments



2.4) Plausible mechanism

The above experiments indicate that our methodology proceeds through oxo-pyrylium intermediate **39** and not through imine intermediate **38**. Based on the above observations, a possible mechanism has been proposed (Scheme 35). In the initial step, $AgNO_3$ coordinates with the alkyne (**I**) and the oxygen of aldehyde group attacks the alkyne in a *6-endo-dig* fashion to give the oxo-pyrylium intermediate **39**, which undergoes protonation with acetic acid (produced during the decomposition of ammonium acetate), giving intermediate **II**.

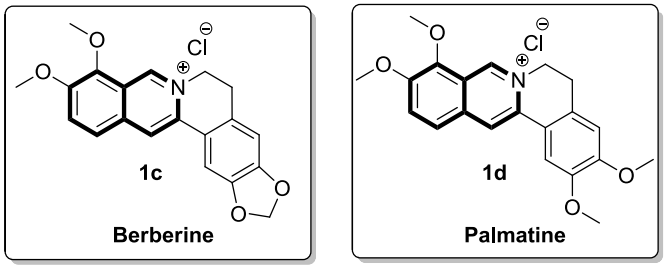
Scheme 35: Plausible mechanism



Nucleophilic addition of ammonia to the oxo-pyrylium C=O leads to the formation of intermediate **III**, which presumably rearranges to hemiaminal **IV** under acidic condition. Finally, hemiaminal **IV** decomposes to isoquinoline **35**.

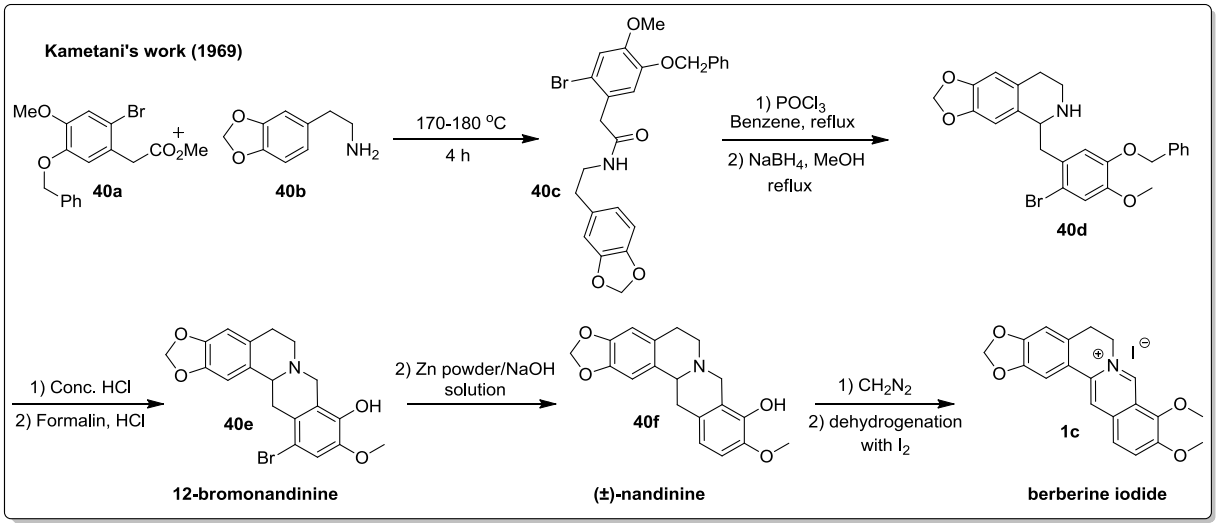
2.5) Our approach towards the synthesis of berberine and palmatine

To demonstrate the synthetic utility of this transformation, the attempted protocol was elaborated to the total synthesis of berberine (**1c**) and palmatine (**1d**).[2 & 43]



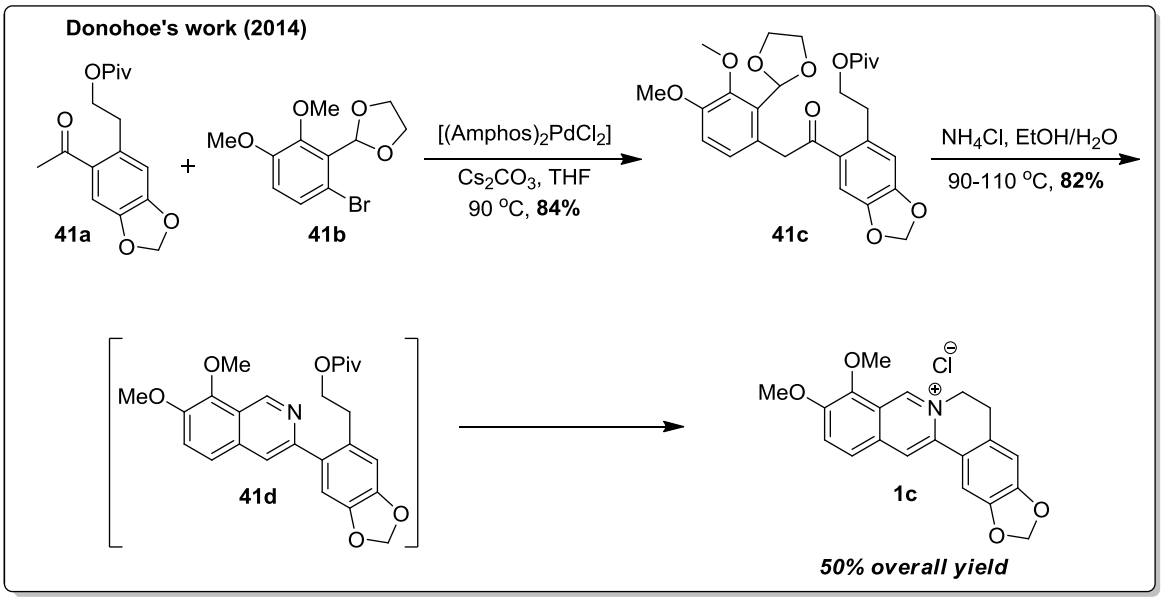
Only two protocols are available in the literature for the total synthesis of berberine (**1c**). Kametani's group reported the first total synthesis of berberine iodide (**1c**) (Scheme 36).[44] The condensation between bromo compound **40a** and amine derivative **40b** afforded the corresponding amide **40c** at 180 °C. The amide **40c** undergoes Bischler-Napieralski cyclization with phosphoryl chloride at reflux temperature to afford dihydroisoquinoline and subsequent reduction with $NaBH_4$ gives the tetrahydroisoquinoline **40d**. Debenzylation of tetrahydroisoquinoline (**40d**) was carried out using conc. HCl followed by Mannich type reaction with formaldehyde in the presence of HCl, obtaining 12-bromonandinine (**40e**). The debromination was carried out with Zn powder in sodium hydroxide solution to access the desired (±)-nandinine product (**40f**). Methylation of nandinine was performed using diazomethane followed by dehydrogenation with iodine, giving the berberine iodide (**1c**) as yellow needles in good yield (Scheme 36).

Scheme 36: First total synthesis of berberine iodide



Very recently, a research article has appeared from Donohoe's group for the synthesis of berberine (**1c**) and palmatine (**1d**) through palladium catalyzed enolate arylation reaction. The Pd-catalyzed *α*-arylation of acetophenone derivatives (**41a)** with aryl bromides (**41b**) afforded the desired compound **41c** and subsequent treatment with ammonium chloride gave the berberine (**1c**) in overall 50% yield through isoquinoline intermediate **41d**. By increasing the temperature from 90 °C to 110 °C, berberine (**1c**) has been obtained in good overall yield (Scheme 37).[45]

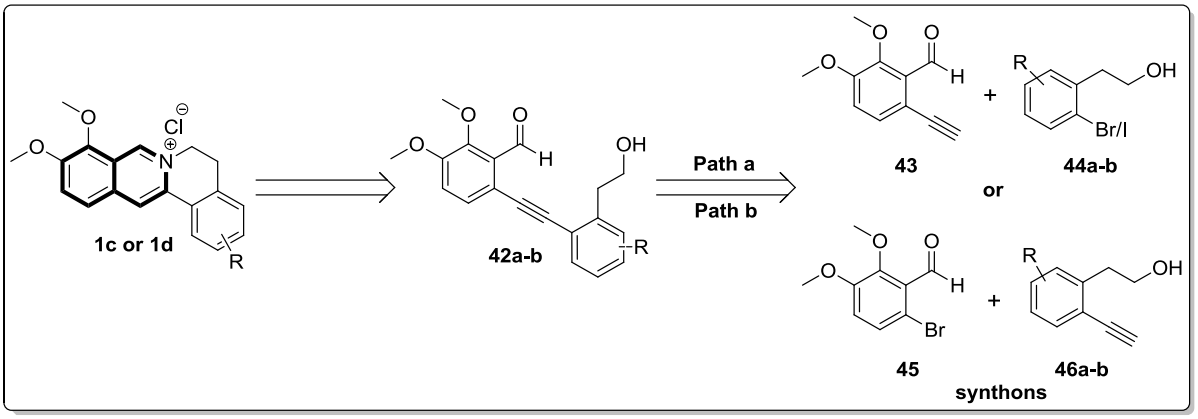
Scheme 37: Donohoe's approach for the synthesis of berberine (**1c**)



2.5.1) Our approach: A general retrosynthetic analysis for the synthesis of berberine and palmatine

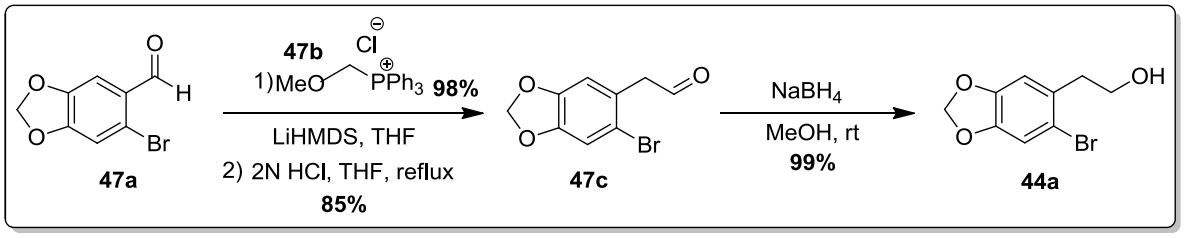
A retrosynthetic analysis for the synthesis of berberine (**1c)** and palmatine (**1d)** is shown in Scheme 38. Compound **42a-b** could be synthesized either from synthons **43** and **44a-b** or **45** and **46a-b** (Scheme 38)

Scheme 38: Retrosynthetic analysis



The Synthesis of berberine has been disscused below. The alcohol **44a** could be achieved in three steps (Scheme 39). 6-bromo 3,4-dimethoxy benzaldehyde **47a** was subjected to the homologation reaction under Wittig reaction condition and subsequent hydrolysis with 2N HCl gave homologated benzaldehyde **47c** in 85% isolated yield. Reduction of aldehyde **47c** with $NaBH_4$ gave the corresponding alcohol **44a** in 86% overall yield (Scheme 39).[46]

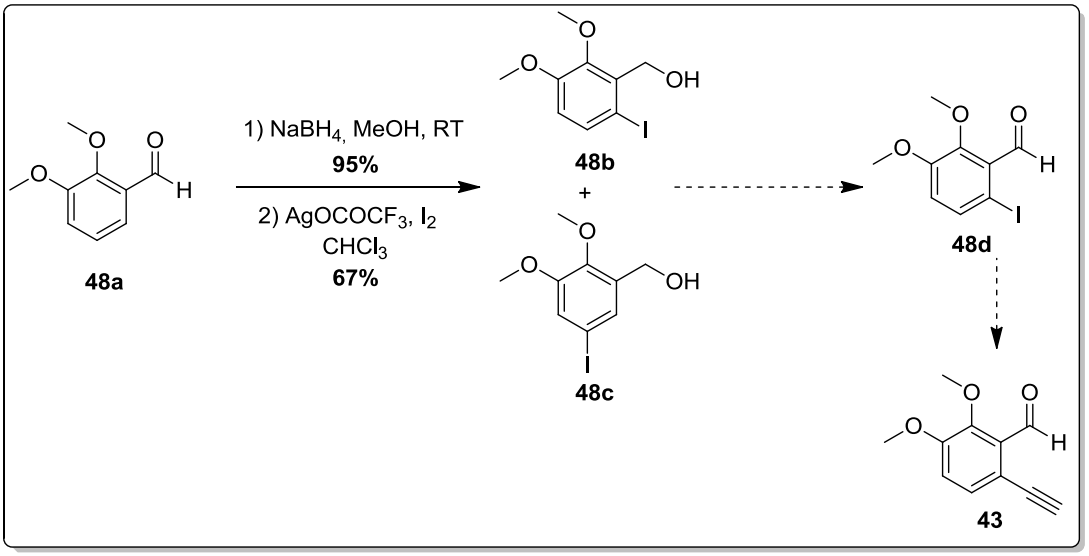
Scheme 39: Synthesis of synthon **44a**



We then turned our attention to the synthesis of *o*-ethynyl benzaldehyde **43**. Initially, it was planned to synthesize *o*-iodo benzaldehyde **48d** from **48b** as shown in Scheme 40. However, reduction of aldehyde **48a** with $NaBH_4$ and subsequent iodination with silver

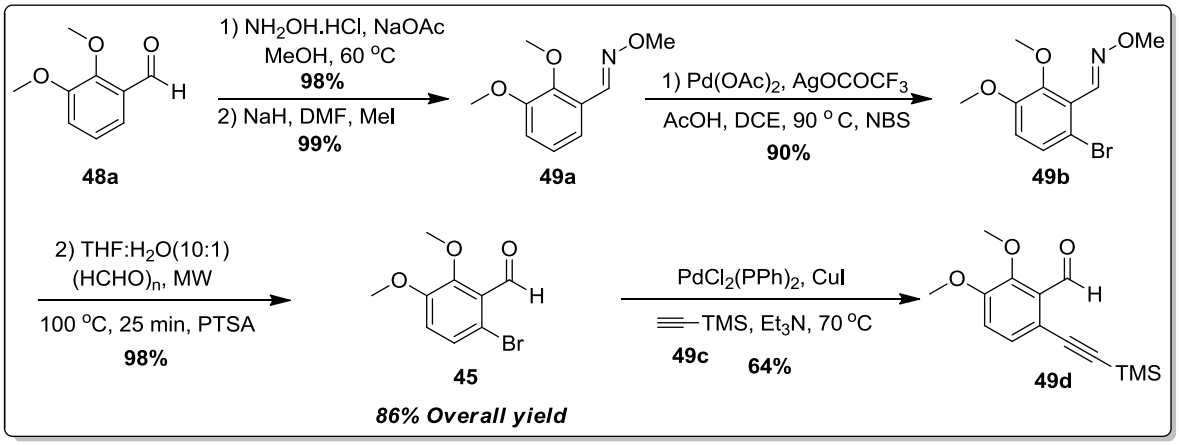
trifluoroacetate (AgOTFA) gave both **48b** and **48c** regioisomers in 67% yields by following the literature procedure,[47] which could be further elaborated to compound **43**. From these regioisomers, the desired compound **48b** was found to be difficult to purify and thus, the scheme was abandoned (Scheme 40).

Scheme 40: Synthesis of 2-iodobenzaldehyde (**48d**)



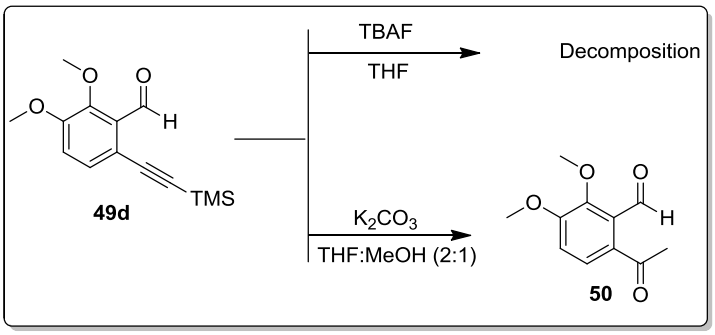
As a result, we set our attention towards the synthesis of *o*-bromo benzaldehydes **45**. This method was successfully achieved in four steps as shown in Scheme 41.[48] Aldoxime **49a** was prepared by the condensation of aldehyde **48a** with hydroxylamine hydrochloride at reflux condition followed by O-methylation with MeI. Subsequently, intermediate **49a** was subjected to Pd-catalyzed *ortho*-bromination with 1.5 equiv. of NBS and afforded brominated aldoxime **49b** in excellent yield. Finally, deprotection of aldoxime **49b** was carried out under microwave irradiation which led to the 2-bromobenzaldehyde **45** in 86% overall yield (Scheme 41). The 6-bromo 2,3-dimethoxy benzaldehyde **45** was subjected to Sonogashira coupling with trimethylsilylacetylene (**49c**) and afforded the desired product (**49d**) in a good yield (Scheme 41).[41]

Scheme 41: Synthesis of *o*-TMS-acetylene benzaldehyde (**49d**)



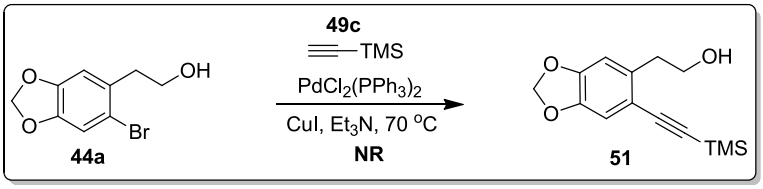
TMS deprotection of compound **49d** has been carried out by two routes. In the first route, compound **49d** was decomposed by the treatment with TBAF in THF; unfortunately, only the decomposition was observed (Scheme 42). Hoever, when the deprotection was carried out using K_2CO_3 in THF:MeOH solvent system, undesired product (**50**) was observed.

Scheme 42: TMS deprotection of compound **49b**



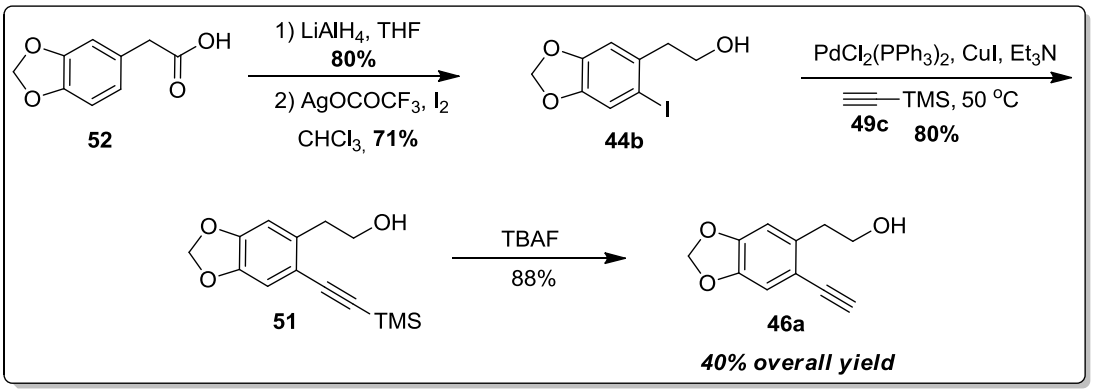
Then we changed our approach, due to the difficulty in the synthesis of synthons **43**. By having the *o*-bromo benzaldehyde **45** in hand, we turn our attention to the synthesis of 2-ethynyl phenylethanol **46a.** However, the Sonogashira coupling of 2-bromo phenylethanol (**44a**) with TMS-acetylene (**49c**) did not afford the alkynylated product (**51**) (Scheme 43).

Scheme 43: The synthesis of 2-ethynyl phenylethanol (**51**)



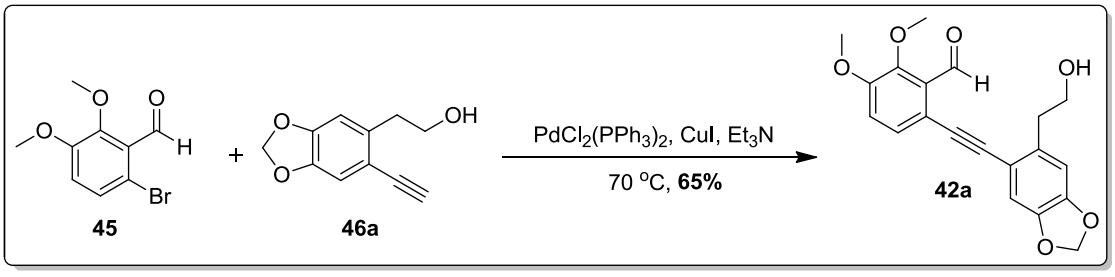
Therefore, we focused our attention on synthesizing 2-iodophenylethanol (**44b**) instead of 2-bromo phenylethanol (**44a**). The compound (**46a**) was achieved in three steps (Scheme 44).[49] The compound **44b** was obtained in 57% overall yield by the reduction of 3,4-methylendioxy phenylacetic acid **52** to the alcohol followed by silver mediated iodination. Sonogashira coupling of **44b** with trimethylsilylacetylene **49c** in the presence of Pd and Cu furnished the product **51**, which on subsequent desilylation with TBAF gave the expected product **46a** in 40% overall yield (Scheme 44).

Scheme 44: The synthesis of 2-ethynyl phenylethanol (**46a**)



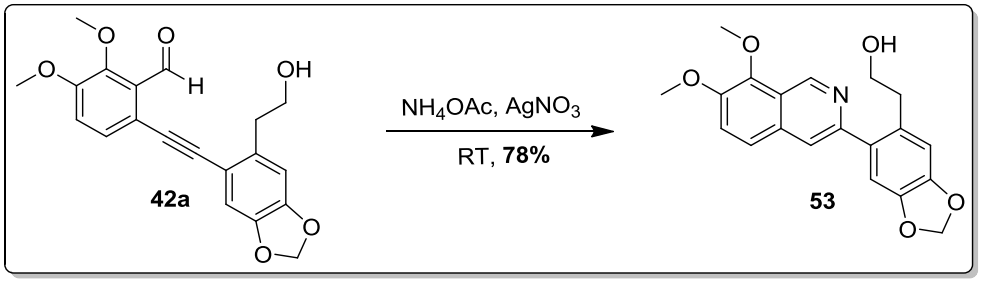
The isoquinoline precursor **42a** was synthesized in 65% yield by the Sonogashira coupling between *o*-bromo benzaldehyde **45** and *o*-alkynyl phenylethanol **46a** in the presence of Pd and Cu catalysts (Scheme 45).

Scheme 45: The synthesis of *o*-alkynyl benzaldehyde **42a**



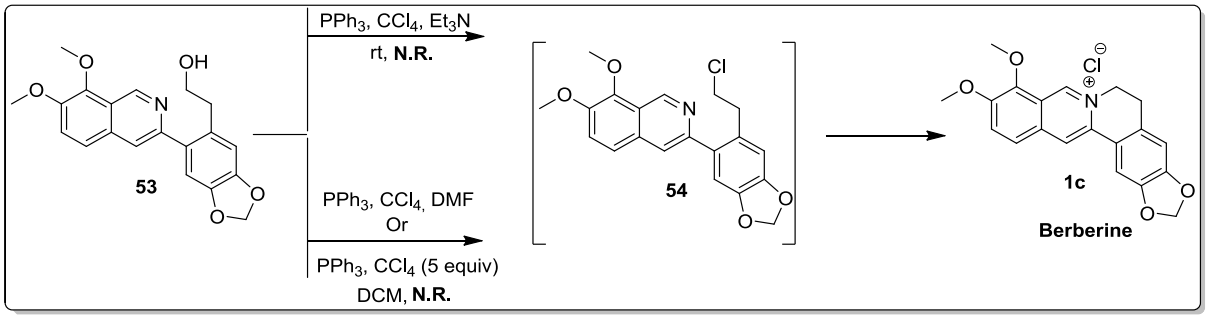
The one-pot annulation of **42a** was carried out under the optimized reaction condition and the isoquinoline derivative **53** was obtained in 78% isolated yield (Scheme 46).

Scheme 46: The synthesis of isoquinoline intermediate **53**



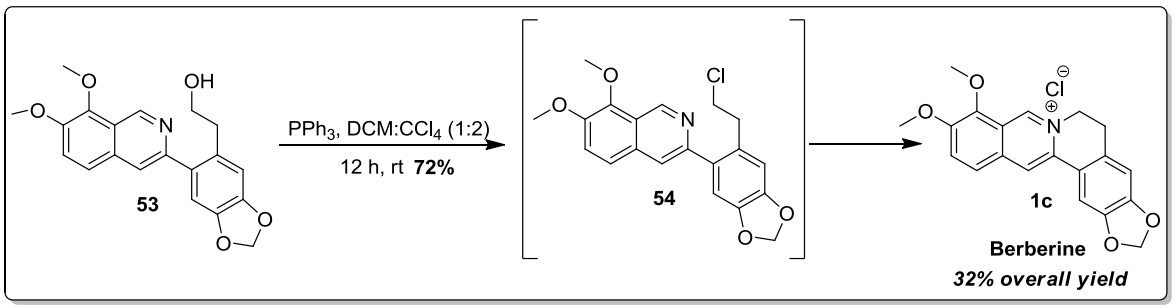
The intermediate **53** was then treated under Appel condition[50] with PPh_3 (1.2 equiv) and CCl_4 (5-7 equiv) in different solvents; however, none of the conditions gave the berberine (**1c**) (Scheme 47).

Scheme 47: Efforts toward the synthesis of berberine (**1c**)



Astoundingly, changing the solvent ratio **$DCM:CCl_4$ (1:2)** in the reaction afforded the expected isoquinoline alkaloid berberine salt (**1c**) in 72% yield through intermediate **54** (32% overall yield from compound **51**) in 12 h at room temperature (Scheme 48).

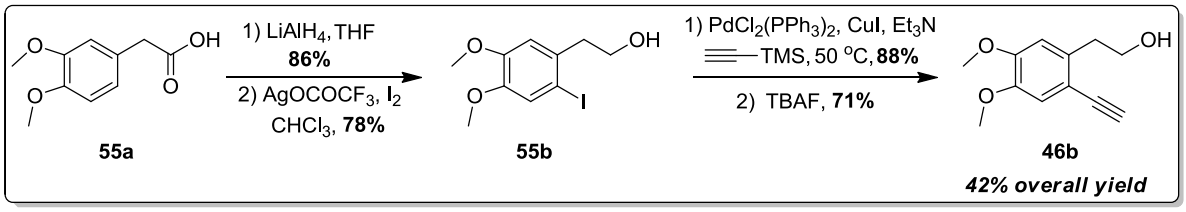
Scheme 48: The successful approach towards the synthesis of berberine **1c**



After the successful synthesis of berberine salt (**1c**), we believed that palmatine (**1d**) could also be prepared in a similar way. The 2-ethynyl phenyl ethanol derivative **46b** was

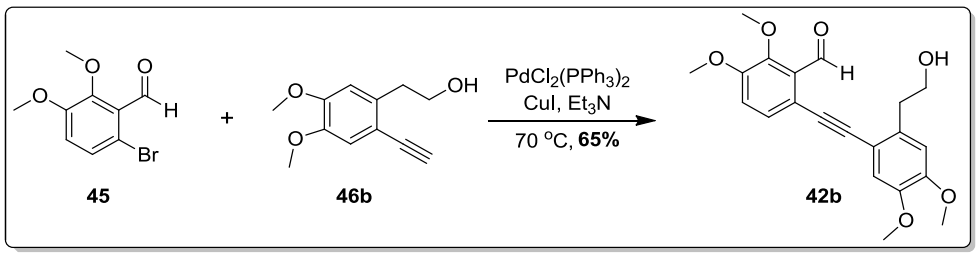
synthesized in four steps as mentioned below (Scheme 49). Reduction of the phenylacetic acid derivatives **55a** with $LiAlH_4$ followed by silver-mediated iodination afforded the *o*-iodophenylethanol **55b**. The Sonogashira coupling of **55b** with TMS acetylene (**49c**) in the presence of Pd and Cu gave the silylated compound and subsequent desilylation with TBAF afforded the 2-ethynyl phenylethanol derivative **46b** in good overall yield (Scheme 49).[51]

Scheme 49: The synthesis of 2-ethynyl phenylethanol (**46b**)



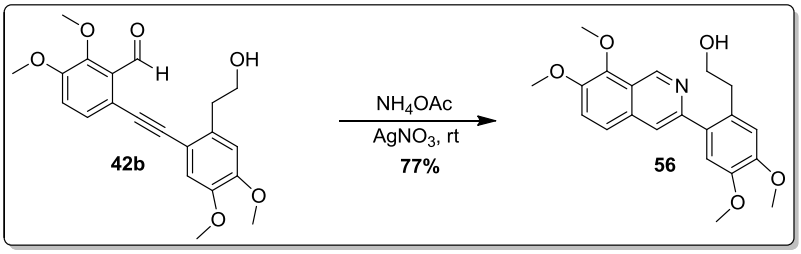
The Sonogashira coupled product **42b** was obtained in 65% yield by the coupling reaction between *o*-Br-benzaldehyde **45** and 2-ethynyl phenylethanol derivative **46b** in the presence of Pd-catalyst (Scheme 50).

Scheme 50: Synthesis of aldehyde **42b**



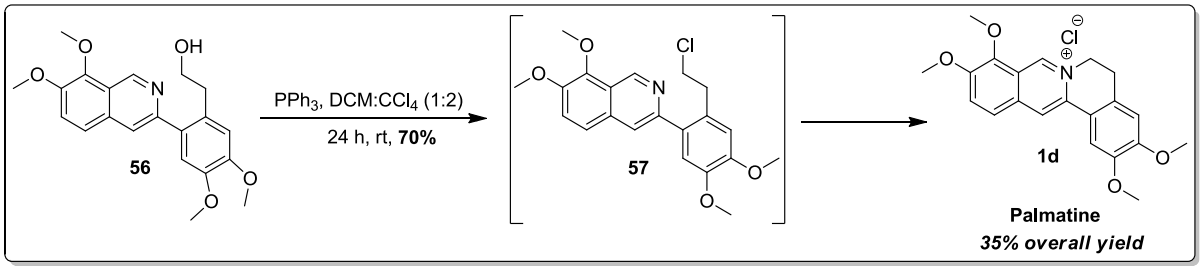
The silver-catalyzed annulation protocol was carried out using aldehyde **42b** and ammonium acetate, and the isoquinoline **56** was isolated in 77% isolated yield (Scheme 51).

Scheme 51: Synthesis of isoquinoline **56**



The isoquinoline **56** was then subjected to Apple reaction to afford palmatine chloride (**1d**) in 70% yield (35% overall yield from **46b**) through chloro-isoquinoline derivatives **57** (Scheme 52).

Scheme 52: Synthesis of palmatine **1d**



2.6) Conclusion

An efficient and mild protocol for the direct construction of aryl- and alkyl-substituted isoquinolines has been realized through silver nitrate catalyzed aromatic annulation of 2-ethynyl arylaldehydes and ketones with ammonium acetate. The salient feature of this methodology is that this annulation could be effected at *room temperature* leading to a wide range of isoquinoline derivatives in good to excellent yields. Additionally, this approach has been employed for the synthesis of biologically important isoquinoline alkaloids such as berberine and palmatine.

2.7) Experimental Section

General information

All reactions were carried out under argon atmosphere in an oven dried round bottom flask. Triethylamine was dried over calcium hydride, distilled and stored over molecular sieves. Melting points were recorded on SMP20 melting point apparatus and are uncorrected. Most of the reagents and starting materials were purchased from commercial sources and used as such. ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 (400, 100 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shifts (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

Synthesis of 2-(ethynyl)arylaldehydes and ketones

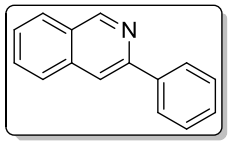
All the 2-ethynyl arylaldehyde or ketone derivatives **34**, **34a-t**[42] & **34u-w**[20, 42b] were synthesised according to the literature procedure.

General procedure for the synthesis of isoquinolines:

^{t}BuOH (1 ml) was added to a mixture of $AgNO_3$ (0.01 mmol, 0.1 equiv.), ammonium acetate (0.18 mmol, 1.5 equiv.) and 2-ethynyl arylaldehyde or ketone (0.12 mmol, 1 equiv.) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (0.48 mmol, 4 equiv.) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (5–10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc in hexane) to get the pure isoquinoline derivative.

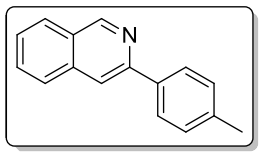
Copies of ^{1}H &^{13}C spectra of compounds 35, 35a-r & 35t-w, 46a-46b, 42a-42b, 51, 53, 56 &1c, 1d

3-Phenyisoquinoline (35)[30b, 31]



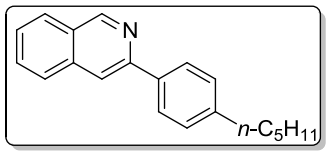
R_f = 0.5 (10% EtOAc in hexane); brown solid (23.5 mg, 95% yield); m.p. = 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.15−8.12 (m, 2H), 8.07 (s, 1H), 7.99 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.59 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.55−7.50 (m, 2H), 7.45−7.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.4, 139.7, 136.8, 130.7, 128.9, 128.6, 127.9, 127.7, 127.2, 127.1, 127.0, 116.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N$ $[M+H]^+$: 206.0970; found: 206.968.

3-(p-Tolyl)isoquinoline (35a)[17]



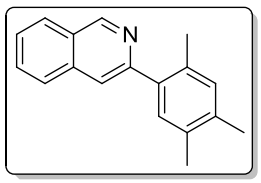
R_f = 0.5 (10% EtOAc in hexane); yellow solid (21 mg, 80% yield); m.p. = 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.04−8.02 (m, 3H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.70−7.66 (m, 1H), 7.59−7.55 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.4, 138.6, 136.9, 136.8, 130.6, 129.7(3C), 127.8, 127.7, 127.0, 116.4, 21.4; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N$ $[M+H]^+$: 220.1126; found: 220.1122.

3-(4-Pentylphenyl)isoquinoline (35b)



R_f = 0.7 (10% EtOAc in hexane); brown solid (23 mg, 70% yield); m.p. = 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (t, *J* = 0.8 Hz, 1H), 8.06−8.03 (m, 3H), 7.98 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.9 1.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.72−1.64 (m, 2H), 1.38−1.33 (m, 4H), 0.93−0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.3, 143.8, 136.9, 136.8, 130.8, 129.1, 127.8, 127.7, 127.1, 127.1, 127.0, 116.3, 35.8, 31.6, 31.3, 22.7, 14.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}N$ $[M+H]^+$: 276.1752; found: 276.1740.

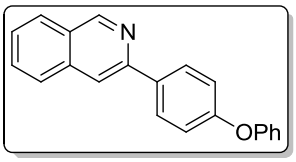
3-(2,4,5-Trimethylphenyl)isoquinoline (35c)



The reaction was performed at 0.11 mmol of 2-[(2,4,5 trimethylphenyl)ethynyl]benzaldehyde (**34c**); R_f = 0.5 (10% EtOAc in hexane); off white solid (24 mg, 88% yield); m.p. = 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.01 (dd, *J* = 8.2, 0.88 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.73−7.68 (m, 2H), 7.61 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.31 (s, 1H), 7.10 (s, 1H), 2.37 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.8,

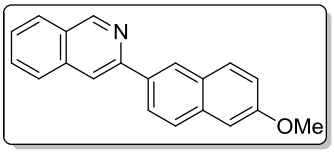
137.9, 136.6, 136.4, 134.1, 133.3, 132.3, 131.5, 130.6, 127.7, 127.2, 127.1, 126.8, 120.2, 20.0, 19.6, 19.4; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N$ $[M+H]^+$: 248.1439; found: 248.1441.

3-(4-Phenoxyphenyl)isoquinoline (35d)



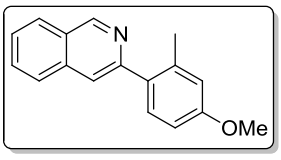
R_f = 0.3 (10% EtOAc in hexane); brown solid (34 mg, 95% yield); m.p. = 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (t, *J* = 0.8 Hz, 1H), 8.12−8.10 (m, 2H), 8.03 (s,1H), 8.0 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.86 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.39−7.35 (m, 2H), 7.16−7.12 (m, 3H), 7.11−7.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.1, 152. 2, 137.0, 131.1, 130.0, 128.7, 127.9, 127.6, 127.3, 127.0, 123.7, 122.0, 119.3, 119.1, 118.9, 116.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1232; found: 298.1231.

3-(6-Methoxynaphthalen-2-yl)isoquinoline (35e)[19b, 20]



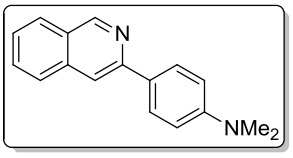
The reaction was performed at 0.07 mmol of 2-((6-methoxynaphthalen-2-yl)ethynyl)benzaldehyde (**34e**); R_f = 0.2 (10% EtOAc in hexane); off white solid (19.6 mg, 98% yield); m.p. = 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 8.21 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.18 (s, 1H), 8.01 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.91−7.86 (m, 3H), 7.72 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.21−7.18 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.5, 151.2, 137.0, 134.9, 134.6, 130.9, 130.4, 129.3, 127.8, 127.7, 127.5, 127.2, 127.1, 126.4, 125.3, 119.3, 116.6, 105.8, 55.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}NO$ $[M+H]^+$: 286.1232; found: 286.1223.

3-(4-Methoxy-2-methylphenyl)isoquinoline (35f)[19b]



R_f = 0.3 (10% EtOAc in hexane); pale yellow gummy solid (27.3 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.03−8.00 (m, 1H), 7.86−7.84 (m, 1H), 7.74−7.70 (m, 2H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.47−7.45 (m, 1H), 6.87−6.84 (m, 2H), 3.86 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.8, 151.7, 137.6, 136.5, 133.2, 131.5, 130.8, 127.8, 127.2, 126.8, 120.3, 116.3, 112.4, 111.4, 55.5, 21.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1232; found: 250.1236.

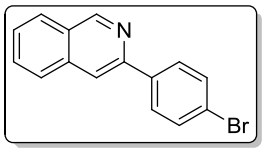
4-(Isoquinolin-3-yl)-N,N-dimethylaniline (35g)[31]



The reaction was performed at 0.1 mmol of 2-[(4-(dimethylamino)phenyl) ethynyl]benzaldehyde (**34g**); R_f = 0.2 (10% EtOAc in hexane); pale yellow solid (21 mg, 85% yield); m.p. =

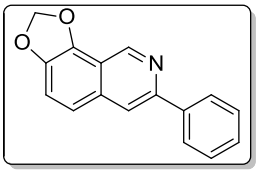
140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.05 (d, J = 9.0 Hz, 2H), 7.97−7.94 (m, 2H), 7.84−7.82 (m, 1H), 7.66 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.52 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.7, 150.9, 137.1, 130.4, 127.9, 127.7, 127.6, 127.3, 126.8, 126.3, 114.4, 112.6, 40.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}N_2$ $[M+H]^+$: 249.1392; found: 249.1404.

3-(4-Bromophenyl)isoquinoline (35h)



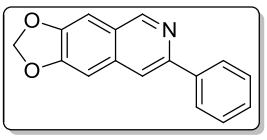
R_f = 0.7 (10% EtOAc in hexane); brown solid (17 mg, 50% yield); m.p. = 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.06 (s, 1H), 8.04−7.99 (m, 3H), 7.88 (dd, J = 8.1, 0.6 Hz, 1H), 7.72 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.66−7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 150.2, 138.6, 136.7, 132.0, 130.9, 128.7, 128.0, 127.8, 127.5, 127.1, 123.0, 116.6; HRMS (ESI): *m/z* calcd for $C_{15}H_{11}BrN$ $[M+H]^+$: 284.0075; found: 284.0067.

7-Phenyl-[1,3]dioxolo[4,5-h]isoquinoline (35i)



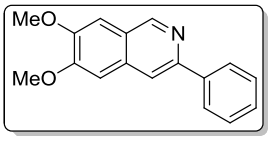
R_f = 0.3 (10% EtOAc in hexane); off white solid (27.3 mg, 91% yield); m.p. = 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.10−8.07 (m, 2H), 7.98 (s, 1H), 7.52−7.48 (m, 2H), 7.43−6.36 (m, 3H), 6.24 (s, 2H); 13C NMR(100 MHz, $CDCl_3$) δ 149.3, 145.7, 144.7, 141.9, 139.7, 132.5, 128.5, 128.4, 126.9, 120.8, 116.9, 115.2, 114.4, 102.6; HRMS (ESI): *m/z* calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868; found: 250.0867.

7-Phenyl-[1,3]dioxolo[4,5-g]isoquinoline (35j)[31]



The reaction was performed at 0.11 mmol of 6-(phenylethynyl)benzo[d][1,3]dioxole-5-carbaldehyde (**34j**); R_f = 0.2 (10% EtOAc in hexane); white solid (21 mg, 77% yield); m.p. = 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.08−8.06 (m, 2H), 7,91 (s, 1H), 7.52−7.47 (m, 2H), 7.42−7.38 (m, 1H), 7.22 (s, 1H), 7.13 (s, 1H), 6.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.6, 150.2, 148.6, 139.6, 135.3, 128.9, 128.5, 126.9, 125.2, 116.6, 103.3, 103.0, 101.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868; found: 250.0868.

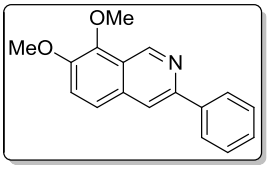
6,7-Dimethoxy-3-phenylisoquinoline (35k)[23f]



The reaction was performed at 0.11 mmol of 4,5-dimethoxy-2-(phenylethynyl)benzaldehyde (**34k**); R_f = 0.1 (10% EtOAc in hexane); brown solid (23 mg, 79% yield); m.p. = 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s,1H), 8.09−8.06 (m, 2H), 7.94 (s, 1H), 7.52−7.47 (m, 2H), 7.42−7.37 (m,1H), 7.23 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

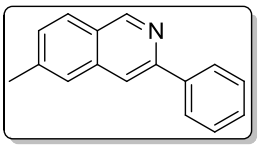
153.3, 150.5, 150.4, 150.0, 140.0, 133.5, 128.9, 128.3, 126.9, 123.9, 115.7, 105.4, 105.1, 56.3, 56.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181; found: 266.1184.

7,8-Dimethoxy-3-phenylisoquinoline (35l)



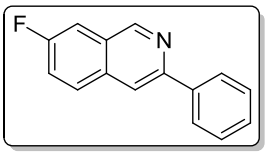
The reaction was performed at 0.11 mmol of 2,3-dimethoxy-6-(phenylethynyl)benzaldehyde (**34l**); R_f = 0.3 (20% EtOAc in hexane); brown solid (17.6 mg, 60% yield); m.p. = 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (t, J = 0.8 Hz, 1H), 8.12−8.10 (m, 2H), 8.0 (d, J = 0.9 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.52−7.48 (m, 3H), 7.42−7.38 (m, 1H), 4.09 (s,3H), 4.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.9, 147.5, 144.1, 139.8, 132.6, 128.9, 128.4, 126.9, 123.3, 123.3, 120.4, 116.1, 61.9, 57.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181; found: 266.1178.

6-Methyl-3-phenylisoquinoline (35m)[52]



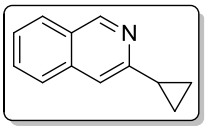
R_f = 0.7 (10% EtOAc in hexane); brown solid (23.4 mg, 89% yield); m.p. = 176−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.13−8.10 (m, 2H), 8.00 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 0.4 Hz, 1H), 7.53−7.49 (m, 2H), 7.44−7.39 (m, 2H). 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.4, 141.1, 139.8, 137.1, 129.6, 128.9, 128.6, 127.5, 127.1, 126.4, 126.0, 116.3, 22.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N$ $[M+H]^+$: 220.1126; found: 220.1121.

7-Fluoro-3-phenylisoquinoline (35n)[25b]



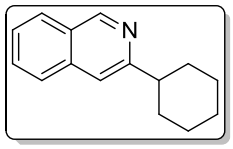
R_f = 0.7 (10% EtOAc in hexane); brown solid (24 mg, 90% yield); m.p. = 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.12−8.09 (m, 2H), 8.06, (s, 1H), 7.88 (dd, J = 9.0, 5.2 Hz, 1H), 7.60 (dd, J = 8.7, 2.6 Hz, 1H), 7.54−7.48 (m, 3H), 7.46−7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (d, J_{CF} = 247.9 Hz), 151.7 (d, J_{CF} = 5.9 Hz), 151.1 (d, J_{CF} = 2.9 Hz), 139.3, 133.9, 129.7 (d, J_{CF} = 7.9 Hz), 129.0, 128.7, 128.4 (d, J_{CF} = 7.9 Hz), 121.3, (d, J_{CF} = 25.3 Hz), 116.4 (d, J_{CF} = 2.0 Hz), 110.8, 110.6; HRMS (ESI): *m/z* calcd for $C_{15}H_{11}FN$ $[M+H]^+$: 224.0876; found: 224.0865.

3-Cyclopropylisoquinoline (35o)[53]



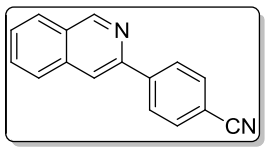
R_f = 0.7 (10% EtOAc in hexane); yellow oil (14.2 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.48−7.45 (m, 2H), 2.20−2.16 (m, 1H), 1.11−1.08 (m, 2H), 1.06−1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.2, 152.2, 136.5, 130.4, 127.7, 127.2, 126.0, 125.9, 116.5, 17.2, 9.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}N$ $[M+H]^+$: 170.0970; found: 170.0973.

3-Cyclohexylisoquinoline (35p)[23d]



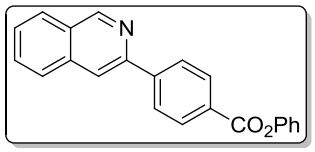
The reaction was performed at 0.13 mmol of 2-(cyclohexylethynyl)benzaldehyde (**34p**); R_f = 0.7 (10% EtOAc in hexane); yellow oil (23 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.92 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.75 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.64 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.46 (s, 1H), 2.85 (tt, *J* = 11.7, 3.3 Hz, 1H), 2.08−2.04 (m, 2H), 1.92−1.87 (m, 2H), 1.81−1.75 (m, 1H), 1.66−1.56 (m, 2H), 1.52−1.41 (m, 2H), 1.37−1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.0, 136.8, 130.3, 127.6, 127.4, 126.5, 126.4, 116.3, 46.3, 33.3, 26.9, 26.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}N$ $[M+H]^+$: 212.1439; found: 212.1442.

4-(Isoquinolin-3-yl)benzonitrile (35q)



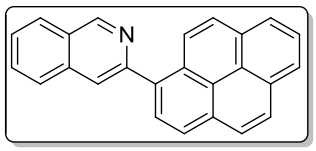
The reaction was performed at 0.11 mmol of 4-[(2-formylphenyl)ethynyl]benzonitrile (**34q**); R_f = 0.2 (10% EtOAc in hexane); brown solid (5.2 mg, 20% yield); m.p. = 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.26 (d, *J* = 7.9 Hz, 2H), 8.13 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7. 75 (t, *J* = 7.1 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 149.1, 143.9, 136.5, 132.7, 131.1, 128.4, 128.2, 127.8, 127.6, 127.3, 119.1, 117.8, 112.0; HRMS (ESI): *m/z* calcd for $C_{16}H_{11}N_2$ $[M+H]^+$: 231.0922; found: 231.0915.

Phenyl 4-(isoquinolin-3-yl)benzoate (35r)



R_f = 0.2 (10% EtOAc in hexane); off white solid (6 mg, 15% yield); m.p. = 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.36−8.33 (m, 2H), 8.31−8.28 (m, 2H), 8.19 (s, 1H), 8.05−8.02 (m, 1H), 7.94−7.92 (m, 1H), 7.75 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.65 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.48−7.44 (m, 2H), 7.32−7.29 (m, 1H), 7.28−7.27 (m,1H), 7.26−7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 152.9, 151.1, 150.0, 144.6, 136.6, 131.0, 130.9, 130.4, 129.7, 129.6, 127.9, 127.8, 127.1, 126.1, 121.9, 121.8, 117.8; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}NO_2$ $[M+H]^+$: 326.1181; found: 326.1189.

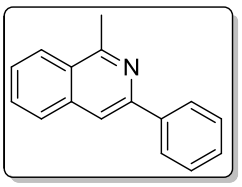
3-(Pyren-1-yl)isoquinoline (35t)



R_f = 0.2 (20% EtOAc in hexane); yellow solid (39 mg, 90% yield); m.p. = 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.46 (d, *J* = 9.0 Hz, 1H), 8.31−8.27 (m, 2H), 8.22 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.19 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.13 (s, 2H), 8.13−8.07 (m, 3H), 8.05−8.01 (m, 1H), 7.95 (dd, *J* = 8.3, 0.7, 1H), 7.78 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.69 (ddd, *J* = 8.1,

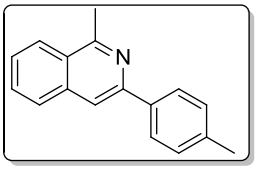
6.9, 1.2 Hz, 1H), 7.26−7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.4, 136.6, 135.6, 131.6, 131.5, 131.13, 131.09, 129.0, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.0, 126.2, 126.0, 125.5, 125.3, 125.2, 125.1, 125.0, 122.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{16}N$ $[M+H]^+$: 330.1283; found: 330.1280.

1-Methyl-3-phenylisoquinoline (35u)



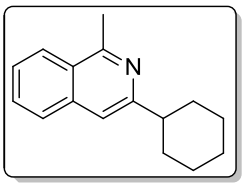
R_f = 0.6 (10% EtOAc in hexane); brown liquid (14 mg, 50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.13 (m, 3H), 7.93 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.68 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.52–7.48 (m, 2H), 7.42–7.38 (m, 1H) 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 150.2, 140.0, 136.9, 130.2, 128.9, 128.4, 127.8, 127.1, 126.9, 126.7, 125.8, 115.4, 22.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N$ $[M+H]^+$: 220.1126; found: 220.1120.

1-Methyl-3-(p-tolyl)isoquinoline (35v)[20]



R_f = 0.7 (10% EtOAc in hexane); brown liquid (24.3 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dq, *J* = 8.3, 0.9 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.85−7.83 (m, 1H), 7.66 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.32−7.30 (m, 2H), 3.04 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.2, 138.3, 137.1, 136.9, 130.1, 129.1, 127.7, 127.0, 126.7, 126.6, 125.8, 114.9, 22.8, 21.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N$ $[M+H]^+$: 234.1283; found: 234.1282.

3-Cyclohexyl-1-methylisoquinoline (35w)[54]

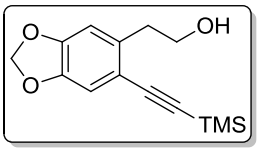


R_f = 0.5 (10% EtOAc in hexane); yellow oil (25 mg, 93% yield); ^{1}NMR (400 MHz, $CDCl_3$) δ 8.08−8.05 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.61 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.50 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.31, (s, 1H), 2.95 (d, *J* = 0.4 Hz, 3H), 2.84−2.77 (m, 1H), 2.10−2.08 (m, 2H), 1.89−1.86 (m, 4H), 1.59−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 136.9, 134.2, 129.8, 127.2, 126.2, 126.1, 125.7, 114.5, 46.2, 33.4, 26.9, 26.4, 22.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N$ $[M+H]^+$: 226.1596; found: 226.1598.

Synthesis of Berberine

2-(6-Iodobenzo[d][1,3]dioxol-5-yl)ethanol (**44b**) [49] and 6-bromo-2,3-dimethoxybenzaldehyde (**45**)[48] were synthesized according to the literature procedure.

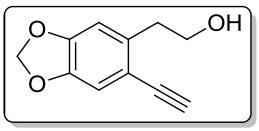
2-{6-[(Trimethylsilyl)ethynyl]benzo[d][1,3]dioxol-5-yl}ethanol (51)[49b]



An oven dried round bottom flask was charged with $PdCl_2(PPh_3)_2$ (15 mg, 0.014 mmol), CuI (2 mg, 0.010 mmol) and 2-(6-iodobenzo[d][1,3]dioxol-5-yl)ethanol (**44b)** (250 mg, 0.87 mmol) in Et_3N (2 ml) under inert atmosphere. After stirring for 2-3 minutes, trimethylsilylacetylene (**49c)** (128 mg, 1.30 mmol) was added at room temperature under inert atmosphere and reaction mixture was heated to 50 °C. After completion of reaction (monitored by TLC) solvent was concentrated under reduced pressure and the residue was diluted with EtOAc (30 mL) and water (15 mL). Organic layer was separated and the aqueous layer was washed two times with EtOAc (20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the pure **51**.

R_f = 0.6 (40% EtOAc in hexane); brown oil (206 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6,71 (s, 1H), 5.94 (s, 2H), 3.86 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 146.0, 136.3, 115.7, 112.0, 110.1, 103.9, 101.5, 96.9, 63.0, 38.0, 0.1; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_3Si$: 263.1103 [M+H]+; found: 263.1116.

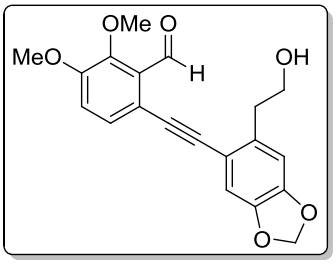
2-(6-Ethynylbenzo[d][1,3]dioxol-5-yl)ethanol (46a)



TBAF solution (1.0 M in THF, 1.26 mL, 1.26 mmol) was added in a drop-wise manner to a stirred solution of **51** (166 mg, 0.63 mmol) in THF (1.3 mL) at rt. Thr reaction mixture immediately turned to dark brown in colour. After completion of the reaction (monitored by TLC), 1M aqueous HCl (15 mL) was added to the reaction mixture and extracted with diethyl ether (20 mL). Aqueous layer was washed two times with diethyl ether (20 mL) and combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through a short pad of silica gel column using EtOAc/hexane as an eluent to obtain pure compound **46a**.

R_f = 0.5 (40% EtOAc in hexane); brown liquid (105 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.73 (s, 1H), 5.95 (s, 2H), 3.85 (t, J = 6.6 Hz, 2H), 3.17 (s, 1H), 2.99 (t, J = 6.6 Hz, 2H); ^{13}C NMR δ (100 MHz, $CDCl_3$) 146.0, 136.4, 112.4, 110.0, 109.5, 101.5, 82.4, 79.7, 63.1, 39.0, 37.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$: 191.0708; found: 191.0704.

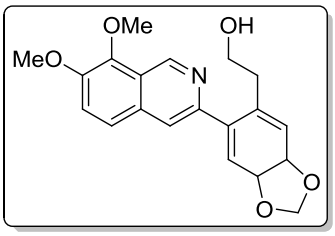
6-{[6-(2-Hydroxyethyl)benzo[d][1,3]dioxol-5-yl]ethynyl}-2,3-dimethoxybenzaldehyde (42a)



Triethylamine (1.2 mL) was added to a mixture of $PdCl_2(PPh_3)_2$ (18 mg, 0.0125 mmol), CuI (1.1 mg, 0.006 mmol), **45** (122 mg, 0.5 mmol) and **46a** (124 mg, 0.65 mmol) under inert atmosphere. The reaction mixture was heated to reflux for 3 h. After completion of the reaction (monitored by TLC), Et_3N was removed under reduced pressure. The residue was then diluted with EtOAc (10 mL) and water (5 mL). Organic layer was separated and aqueous layer was washed two times with EtOAc (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/hexane to obtain pure **42a**.

R_f = 0.5 (60% EtOAc in hexane); pale yellow solid (114 mg, 65% yield); m.p. = 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 6.75 (s, 1H), 5.96 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.87 (t, J = 7.2 Hz, 2H), 3.17 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 152.7, 148.4, 146.1, 136.7, 130.5, 129.7, 117.3, 116.1, 115.4, 112.0, 110.0, 101.5, 92.0, 89.7, 64.1, 62.5, 56.3, 38.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}O_6$ $[M+H]^+$: 355.1182; found: 355.1185.

2-{6-[(7,8-Dimethoxyisoquinolin-3-yl]methyl)benzo[d][1,3]dioxol-5-yl}ethanol (53)

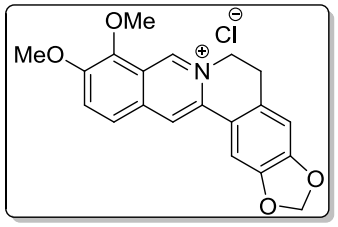


^{t}BuOH (5 mL) was added to a mixture of $AgNO_3$ (9.0 mg, 0.054 mmol), ammonium acetate (62 mg, 0.81 mmol) and **42a** (190, 0.54 mmol) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (180 mg, 2.12 mmol) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc/hexane) to obtain the pure isoquinoline **53**.

R_f = 0.3 (60% EtOAc in hexane); brown solid (149 mg, 78% yield); m.p. = 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (t, J = 0.8 Hz, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.61 (d, J = 9.0, Hz,1H), 7.54 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.0 (s, 2H), 4.09 (s, 3H), 4.03 (s, 3H), 3.99 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5,

149.1, 148.2, 146.2, 145.6, 144.1, 133.6, 132.9, 132.7, 122.9, 122.8, 121.0, 120.2, 110.2, 110.1, 101.4, 64.0, 61.9, 57.2, 35.4; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$: 354.1341; found: 354.1350.

Synthesis of berberine (1c)[45]



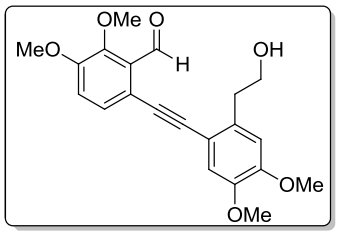
A mixture of isoquinoline derivative **53** (10 mg, 0.028 mmol) and PPh_3 (16 mg, 0.056 mmol) in CH_2Cl_2-CCl_4 mixture (1:2) (0.5 mL) was stirred at room temperature until the starting material got completely consumed (12 h, by TLC). The reaction mixture was carefully filtered and the solid was washed with EtOAc (5 mL x 4) and CH_2Cl_2 (1 mL) to obtain berberine (**1c**).

R_f = 0.3 (10% MeOH in DCM); yellow solid (7.5 mg, 72% yield); m.p. = 204−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.94 (s, 1H), 8,21 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.09 (s, 1H), 6.18 (s, 2H), 4.93 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.4, 149.9, 147.7, 145.5, 143.7, 137.5, 133.0, 130.7, 126.8, 123.6, 121.4, 120.5, 120.2, 108.5, 105.5, 102.1, 62.0, 57.1, 55.2, 26.3; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NO_4$ $[M+H]^+$: 337.1314; found: 337.1323.

Synthesis of Palmatine

The starting material, 2-(2-Ethynyl-4,5-dimethoxyphenyl)ethanol (**46b**), was prepared according to the literature procedure.[51]

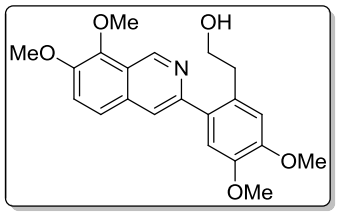
2-{[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]ethynyl}-4,5-dimethoxybenzaldehyde (42b)



Triethylamine (2 mL) was added to a mixture of $PdCl_2(PPh_3)_2$ (9.6 mg, 0.014 mmol), CuI (1.3 mg, 0.007 mmol), **45** (144 mg, 0.71 mmol) and **46b** (135 mg, 0.55 mmol) under inert atmosphere. The reaction mixture was heated to reflux for 3 h. After completion of the reaction (monitored by TLC), solvent was removed under reduced pressure. The residue was then diluted with EtOAc (20 mL) and water (10 mL). Organic layer was separated and aqueous layer was washed with EtOAc (10 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through silica gel column using EtOAc/hexane to obtain the pure compound **42b.**

R_f = 0.5 (60% EtOAc in hexane); yellow gummy solid (132 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (d, J = 0.6 Hz, 1H), 7.38 (dd, J = 8.5, 0.7 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.03, (s, 1H), 6.76 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92−3.91 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.18 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 149.8, 147.3, 135.1, 132.2, 130.4, 129.7, 117.3, 115.6, 115.1, 114.9, 112.5, 92.1, 89.7, 64.1, 62.5, 56.2, 56.1, 56.0, 38.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.1495; found: 371.1491.

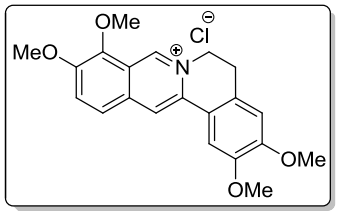
2-[2-(6,7-Dimethoxyisoquinolin-3-yl)-4,5-dimethoxyphenyl]ethanol (56)



^{t}BuOH (2 mL) was added to a mixture of $AgNO_3$ (3.4 mg, 0.02 mmol), ammonium acetate (23 mg, 0.3 mmol) and **42** (76 mg 0.20 mmol) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (83 mg, 1.0 mmol, 4) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc/hexane) to obtain the pure isoquinoline **56**.

R_f = 0.3 (60% EtOAc in hexane); brown solid (55.6 mg, 70% yield); m.p. = 164−166 $^\circ$C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (t, J = 0.9 Hz, 1H), 7.76 (d, J = 0.9 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 4.01 (t, J = 5.8 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 2.86 (t, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 149.6, 149.0, 147.4, 145.6, 144.1, 132.8, 132.6, 131.4, 122.9, 122.7, 121.0, 120.0, 113.4, 113.1, 64.1, 61.9, 57.2, 56.3, 56.1, 35.3; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$: 370.1654; found: 370.1658.

Synthesis of Palmatine (1d)[45]

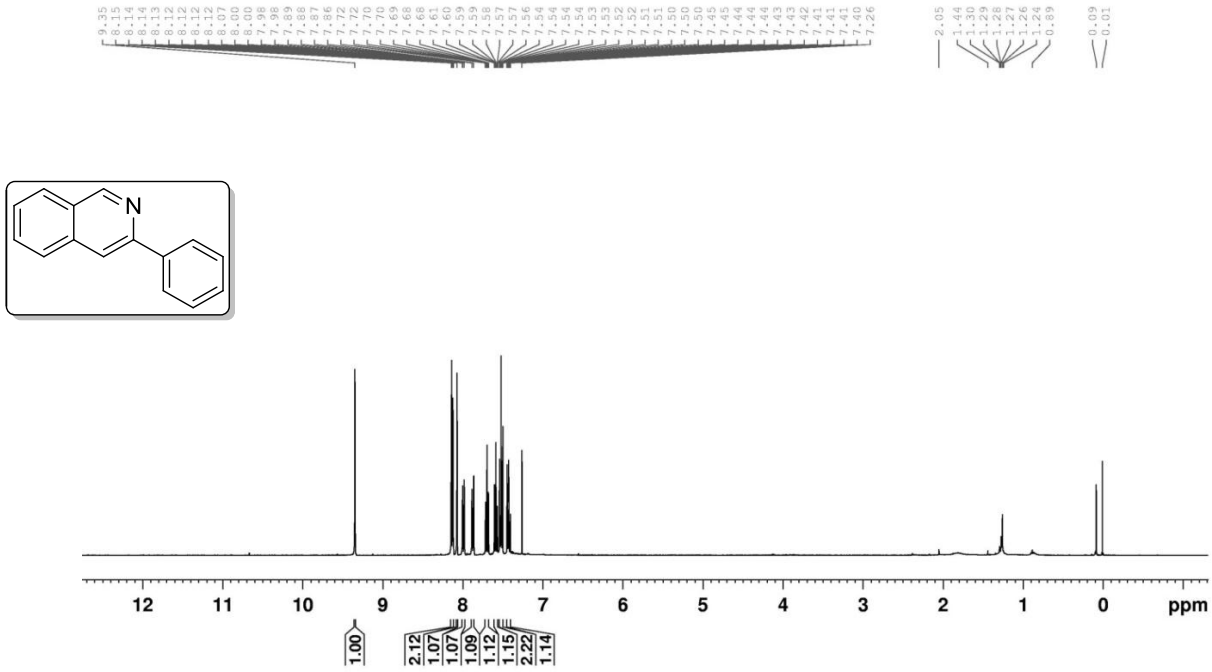


A mixture of isoquinoline derivative **56** (10 mg, 0.027 mmol) and PPh_3 (15 mg, 0.054 mmol) in CH_2Cl_2-CCl_4 mixture (1:2) (0.5 mL) was stirred at room temperature until the starting material got completely consumed (24 h, by TLC). The reaction mixture was carefully filtered and the solid was washed with EtOAc (5 mL x 4) and CH_2Cl_2 (1 mL) to obtain palmatine (**1d**).

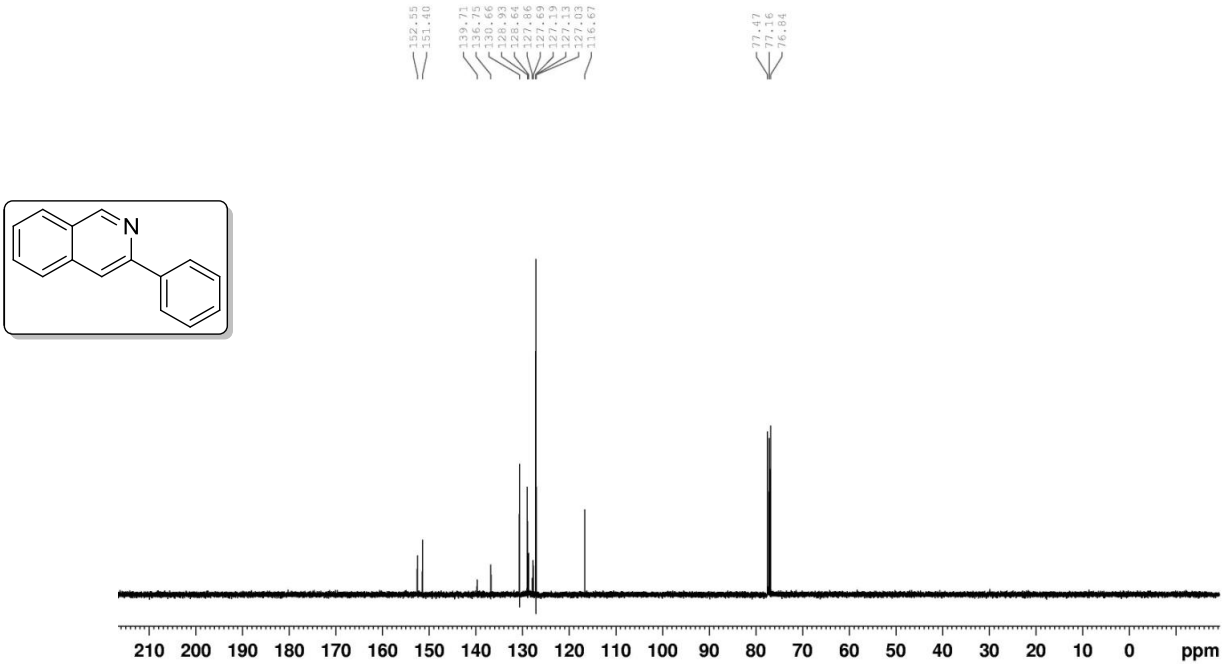
R_f = 0.2 (10% MeOH in DCM); yellow solid (6.6 mg, 70% yield); m.p. = 195−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.06 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.03, (d, J = 9.1 Hz, 1H), 7.72 (s, 1H), 7.10 (s, 1H), 4.95 (t, J = 6.0 Hz, 2H), 4.10 (s, 3H), 4.07 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.23 (t, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.5, 150.3, 148.8, 145.5, 143.7, 137.8, 133.1, 128.7, 126.8, 123.5, 121.4, 119.9, 117.3, 111.3, 108.7, 62.0, 57.1, 56.2, 55.9, 55.4, 26.01; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 353.1627; found: 353.1644.

Copies of ^{1}H &^{13}C spectra of compounds 35, 35a-r & 35t-w, 51, 46a-46b, 42a-42b, 53, 56 &1c, 1d

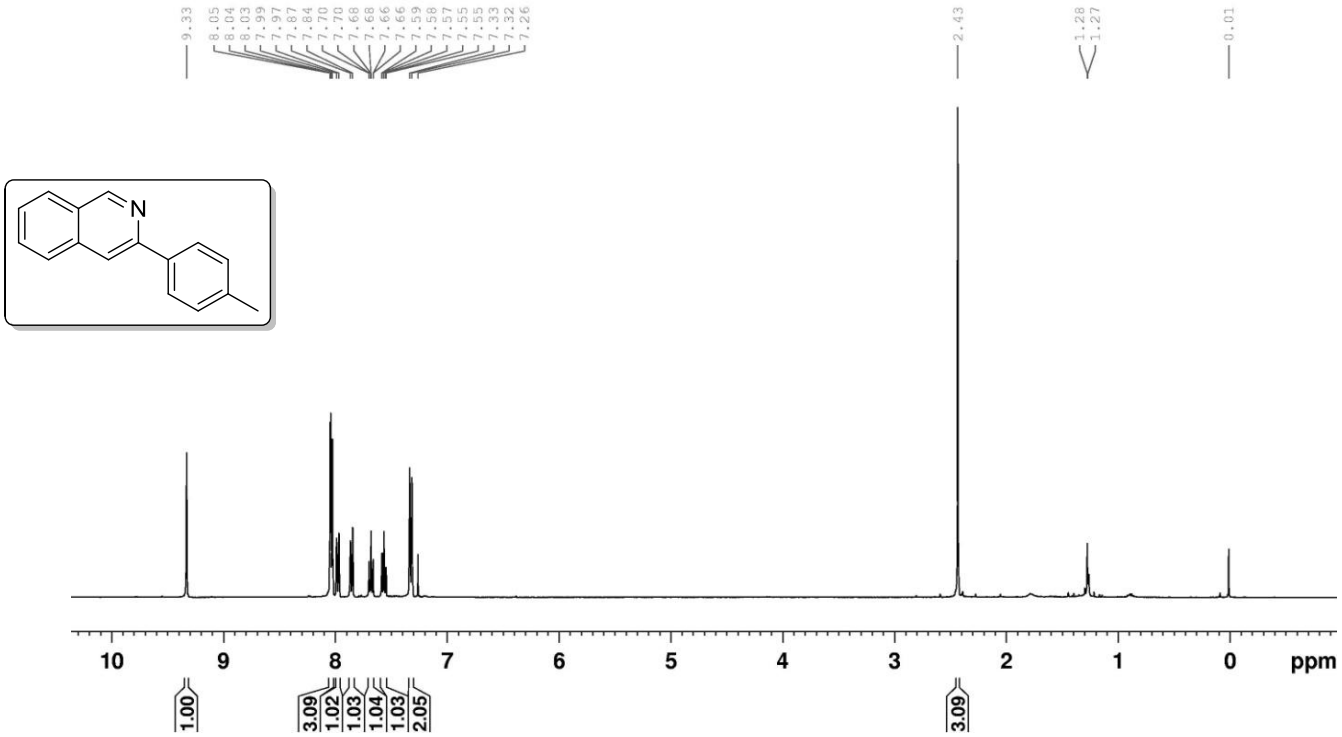
^{1}H NMR Spectrum of compound **35**



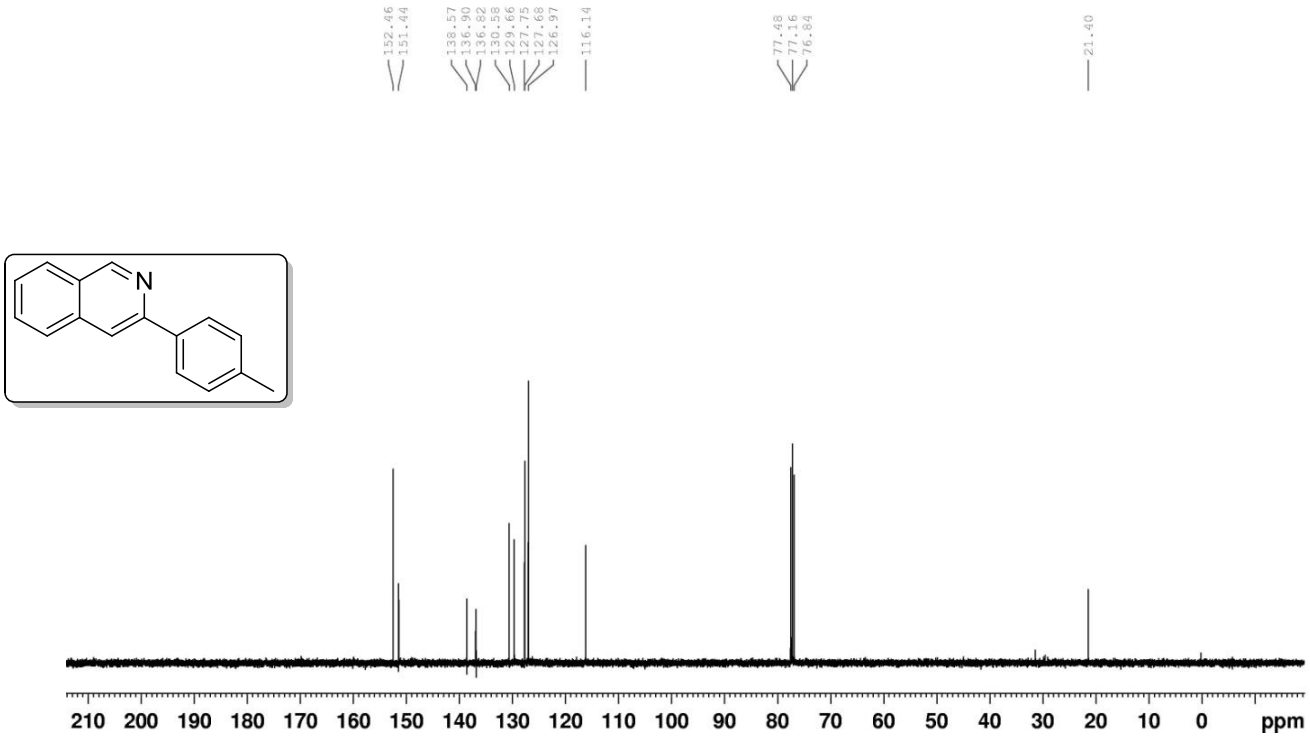
^{13}C NMR Spectrum of compound **35**



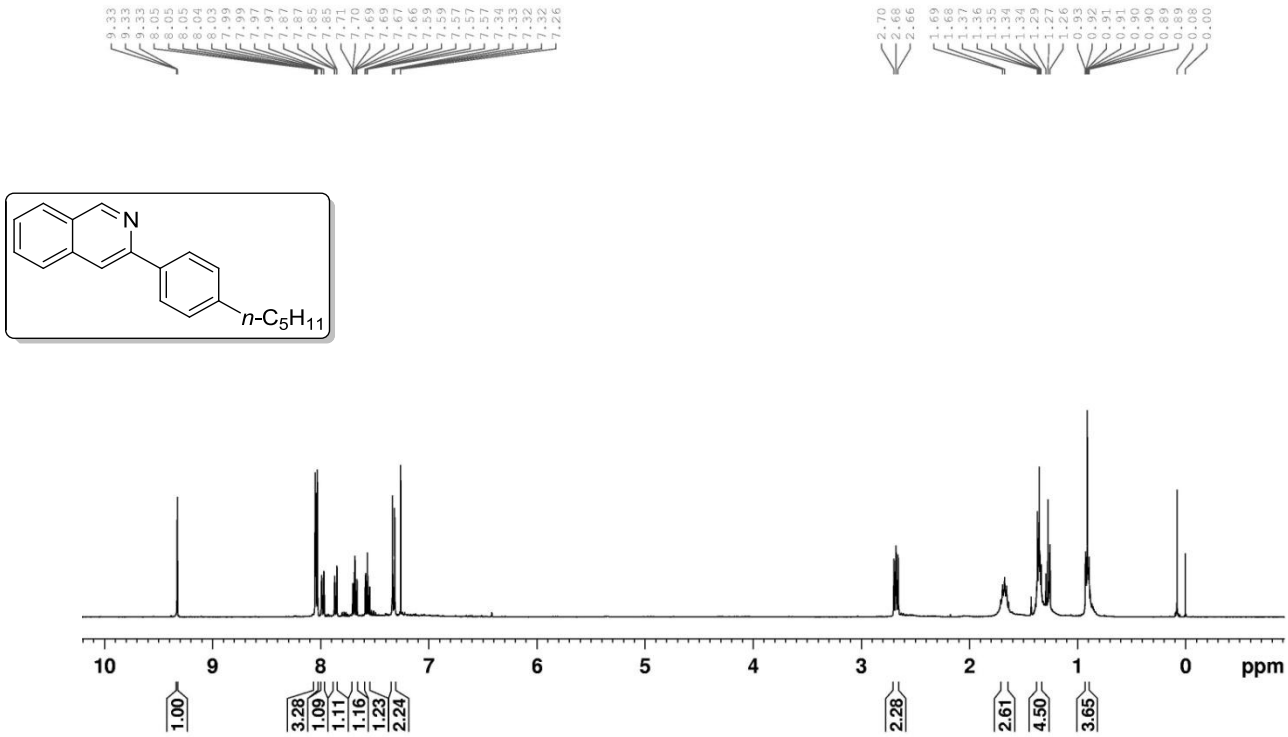
^{1}H NMR Spectrum of compound **35a**



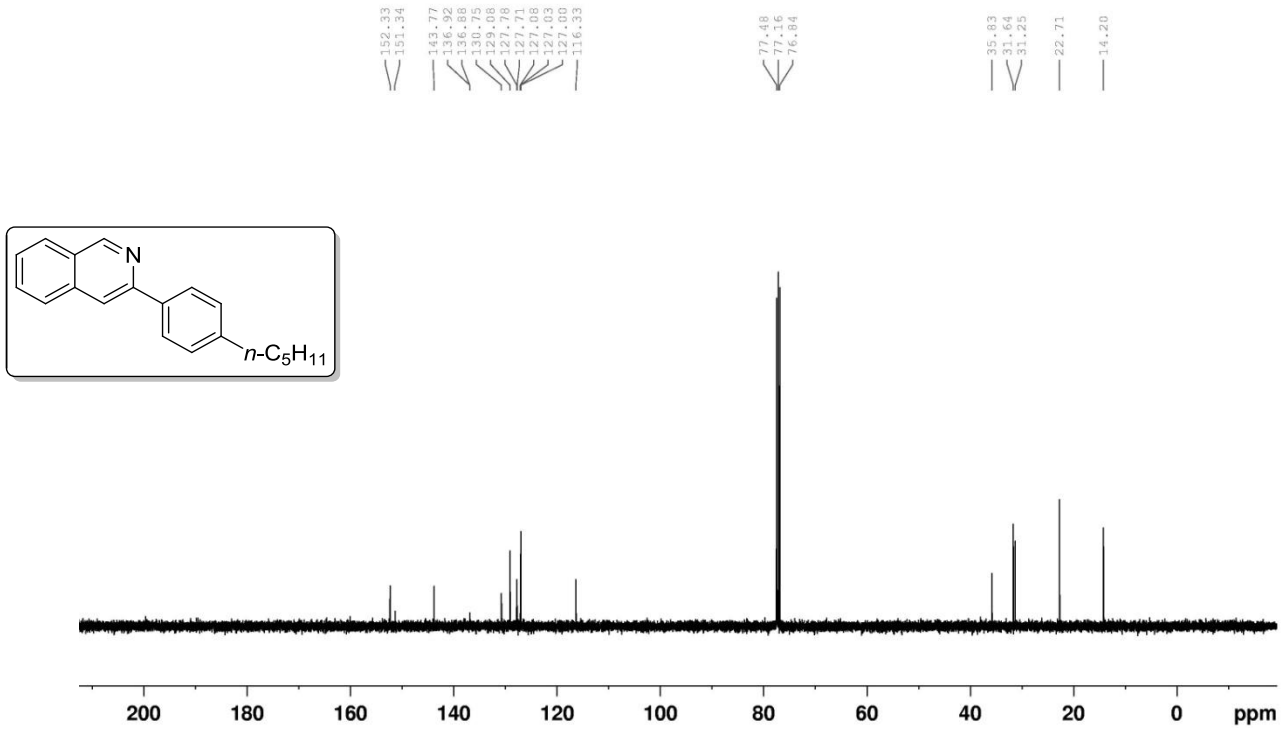
^{13}C NMR Spectrum of compound **35a**



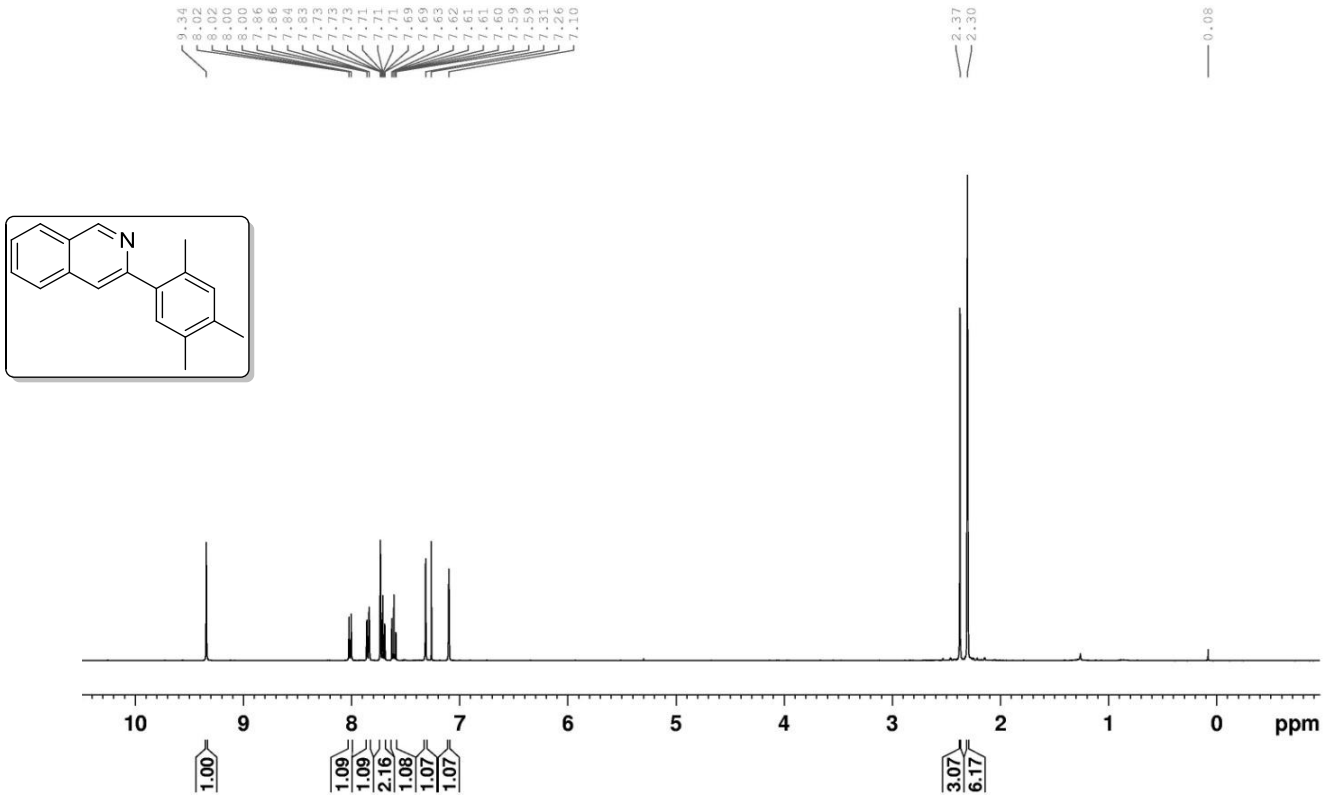
^{1}H NMR Spectrum of compound **35b**



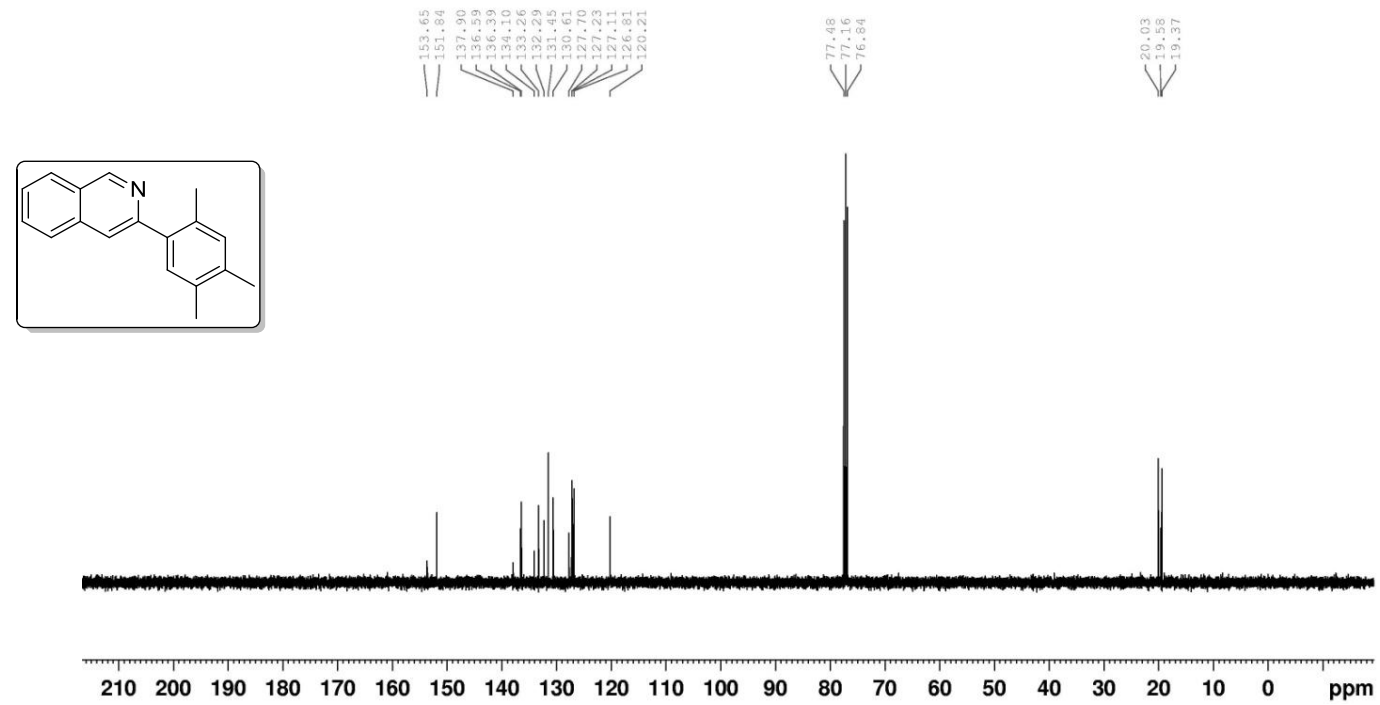
^{13}C NMR Spectrum of compound **35b**



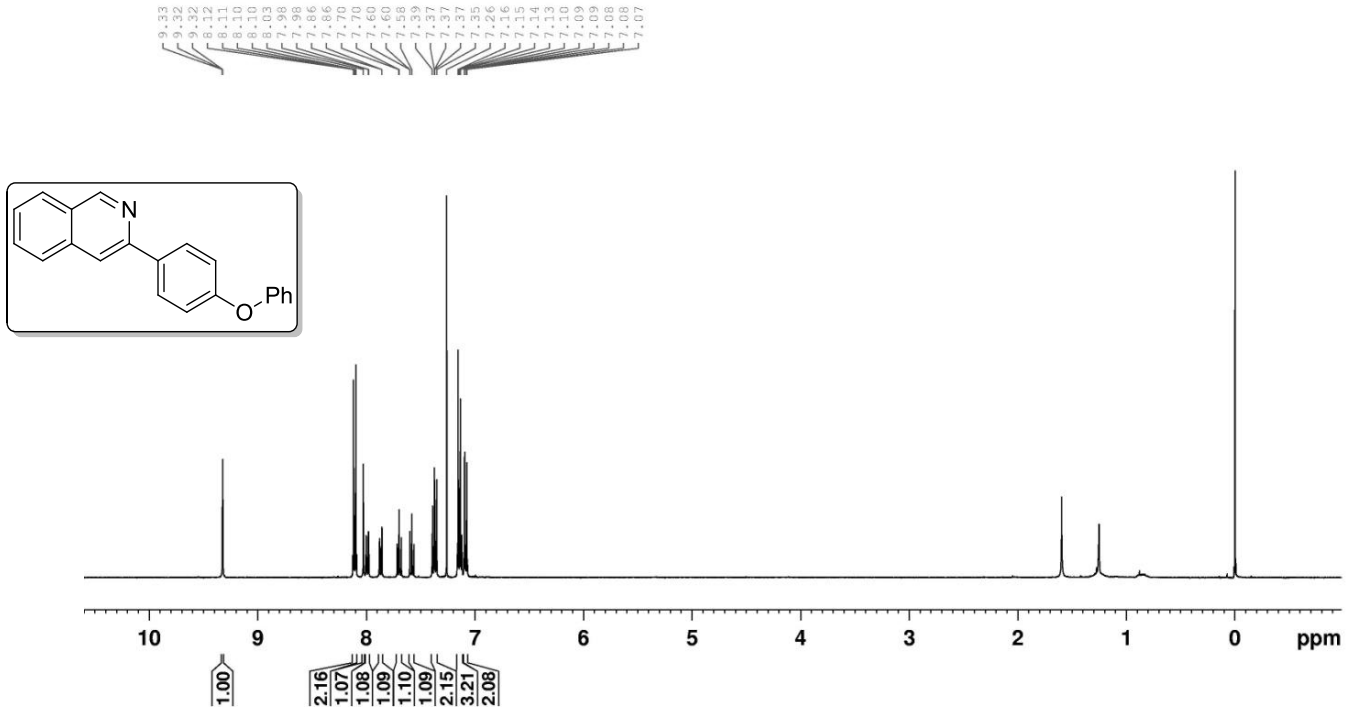
^{1}H NMR Spectrum of compound **35c**



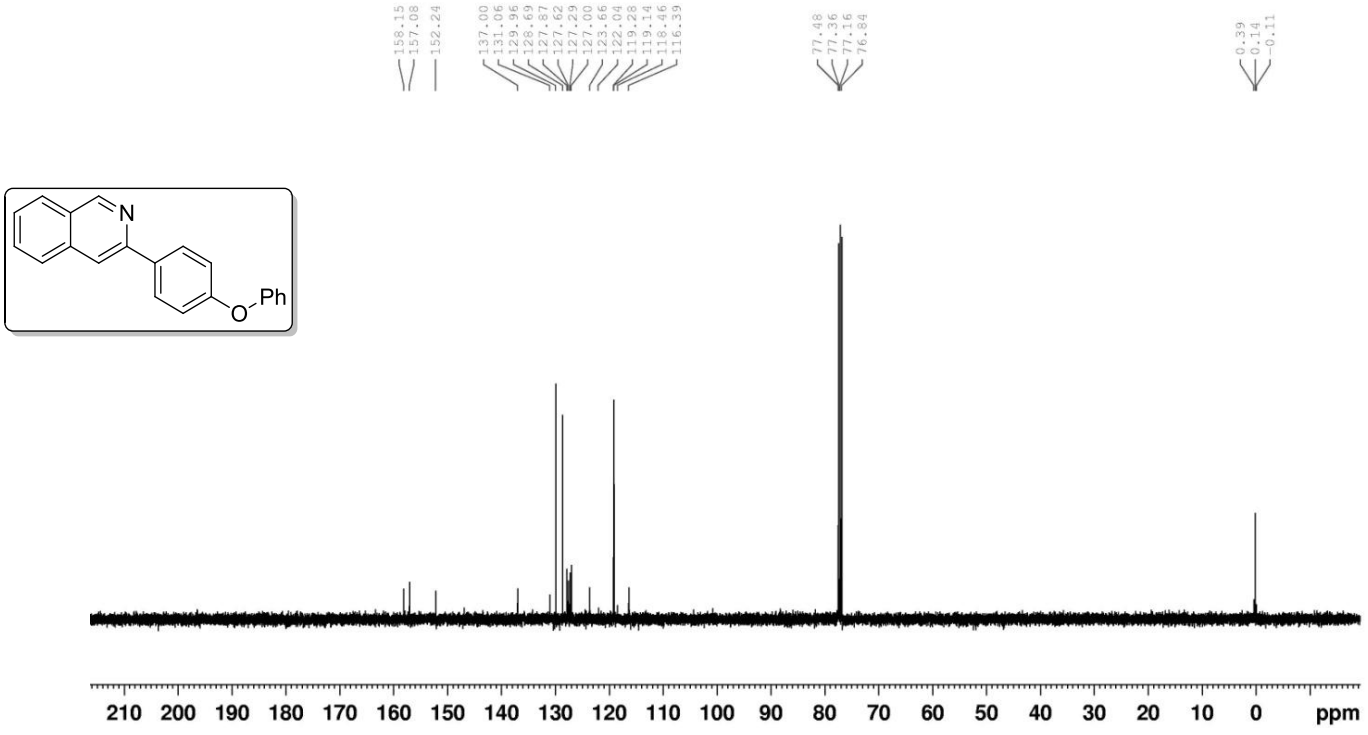
^{13}C NMR Spectrum of compound **35c**



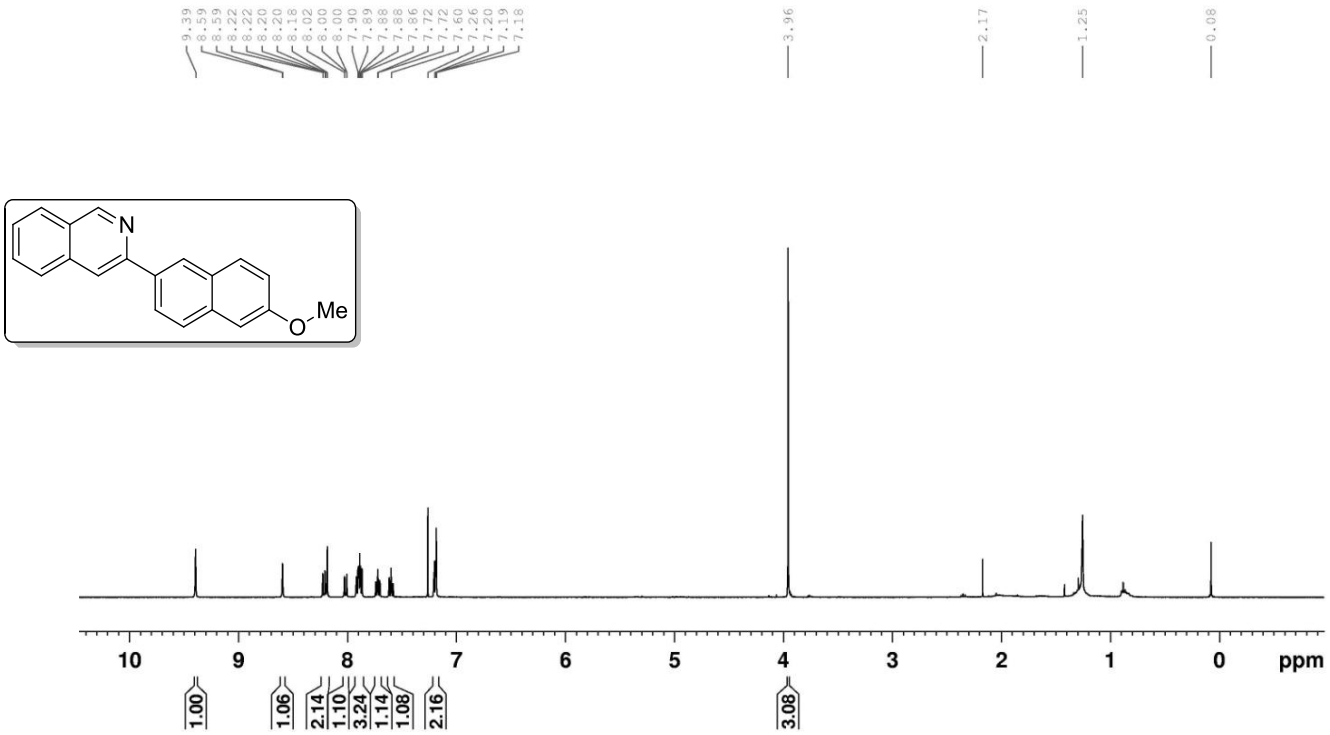
^{1}H NMR Spectrum of compound **35d**



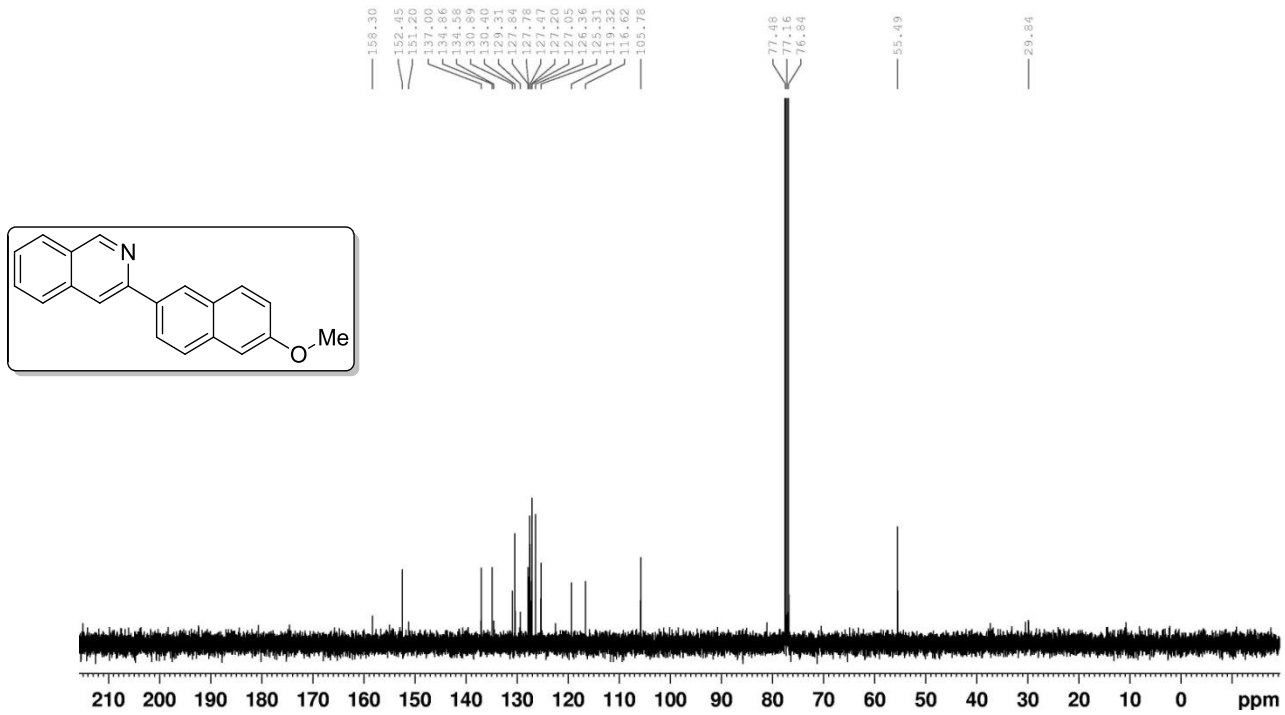
^{13}C NMR Spectrum of compound **35d**



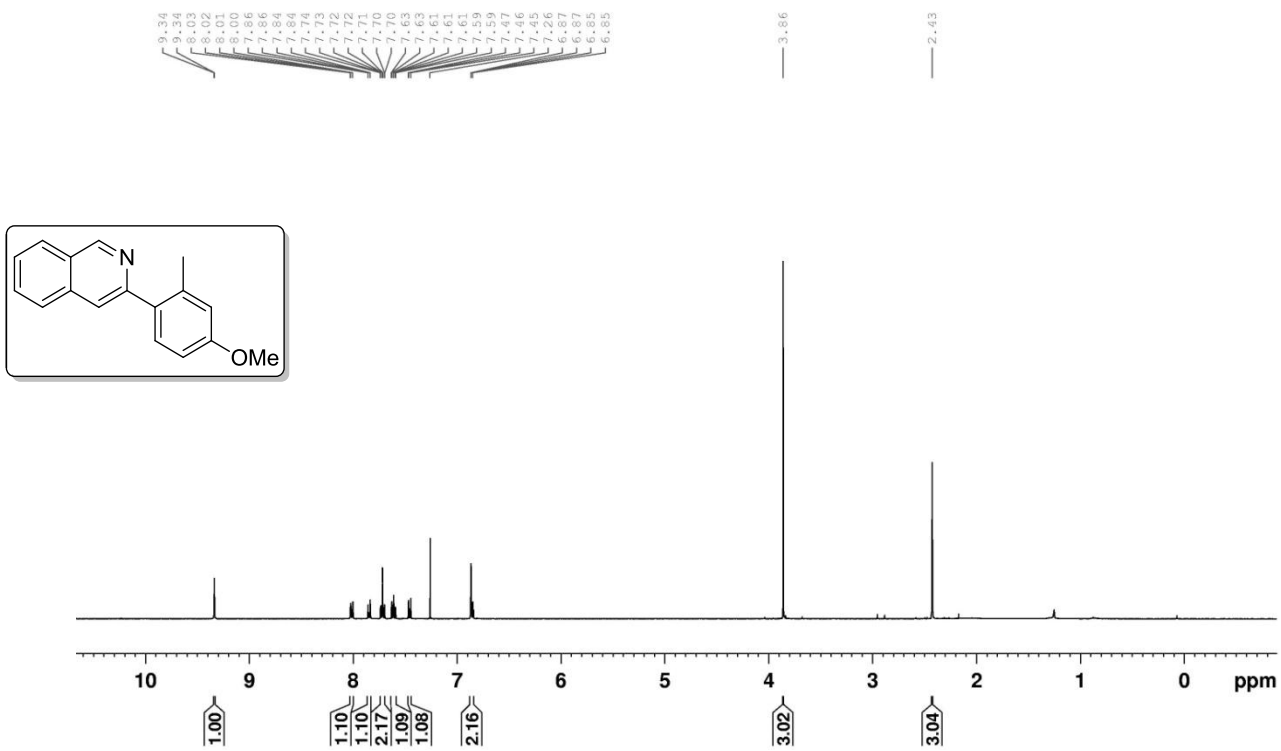
^{1}H NMR of Spectrum of compound **35e**



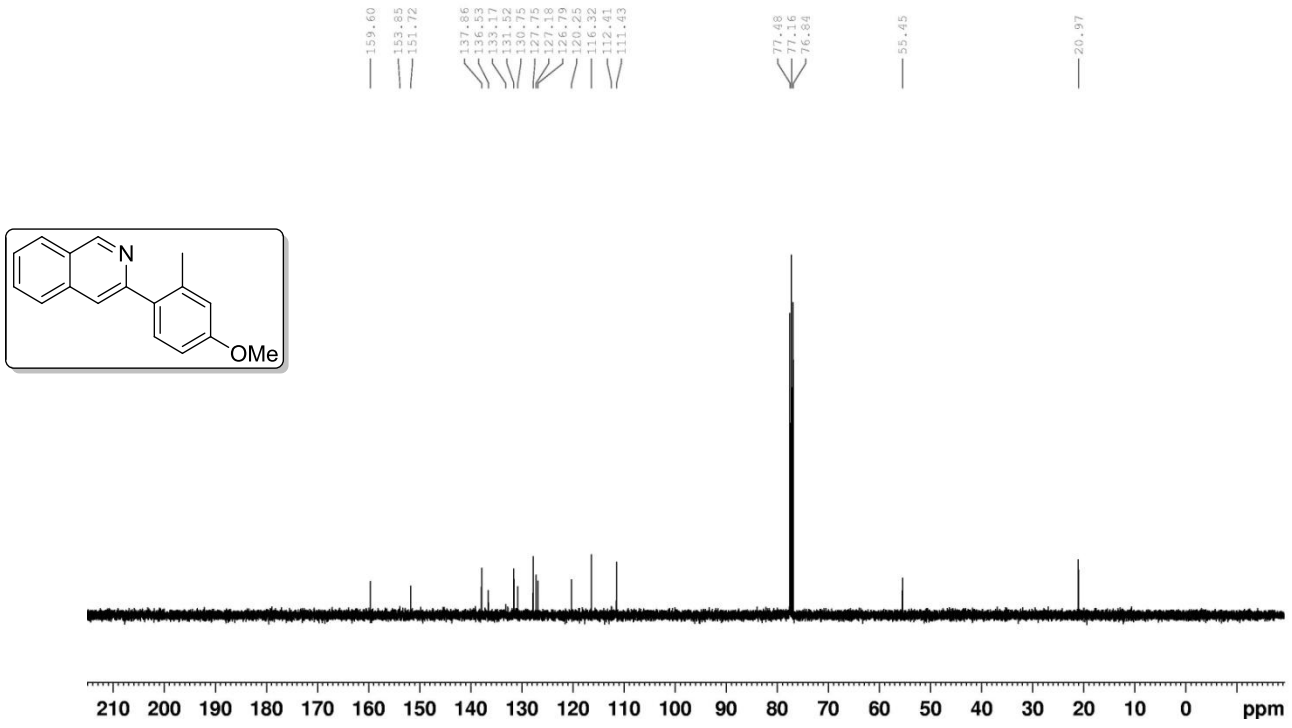
^{13}C NMR of Spectrum of compound **35e**



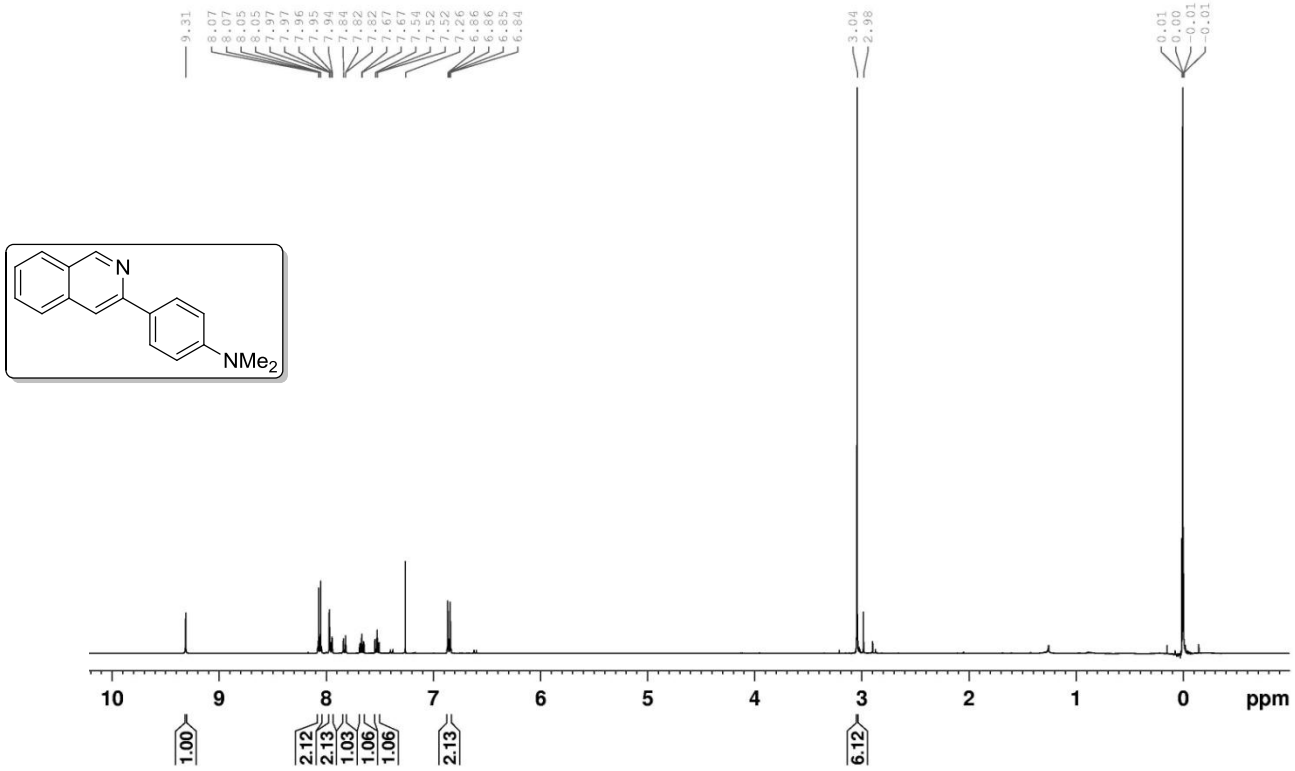
^{1}H NMR Spectrum of compound **35f**



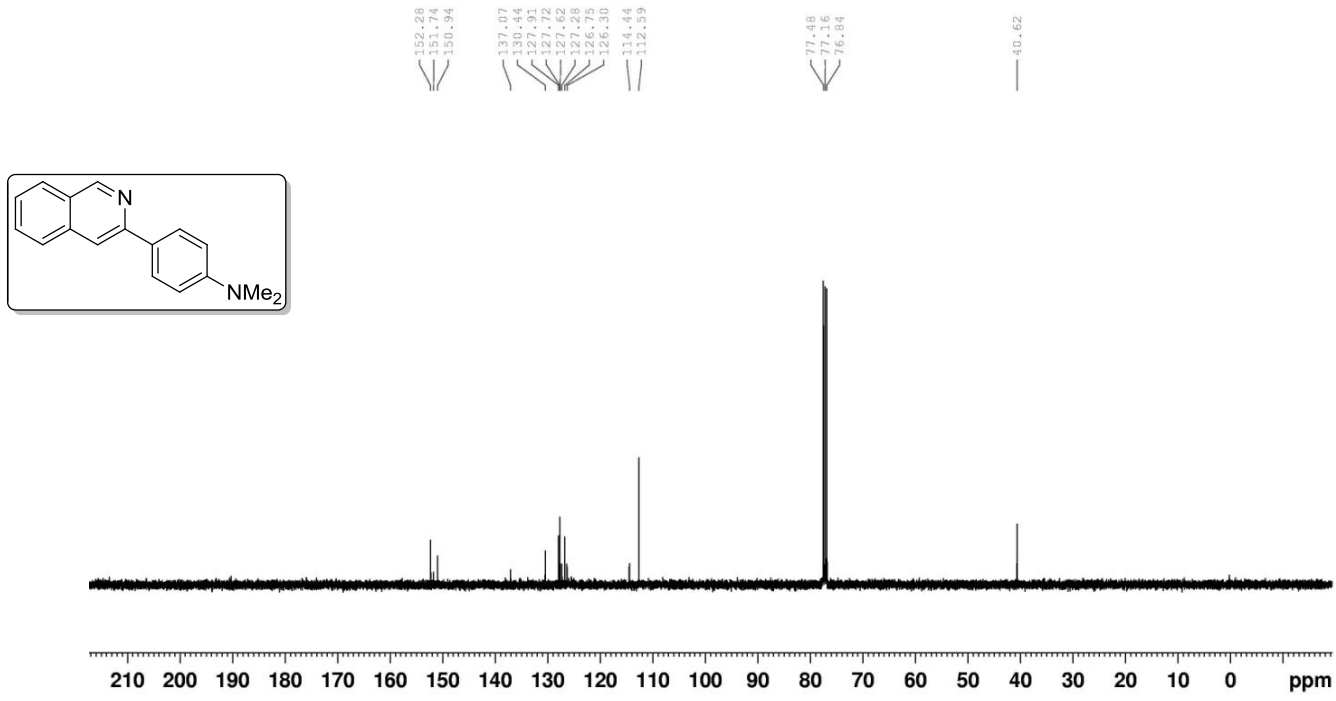
^{13}C NMR Spectrum of compound **35f**



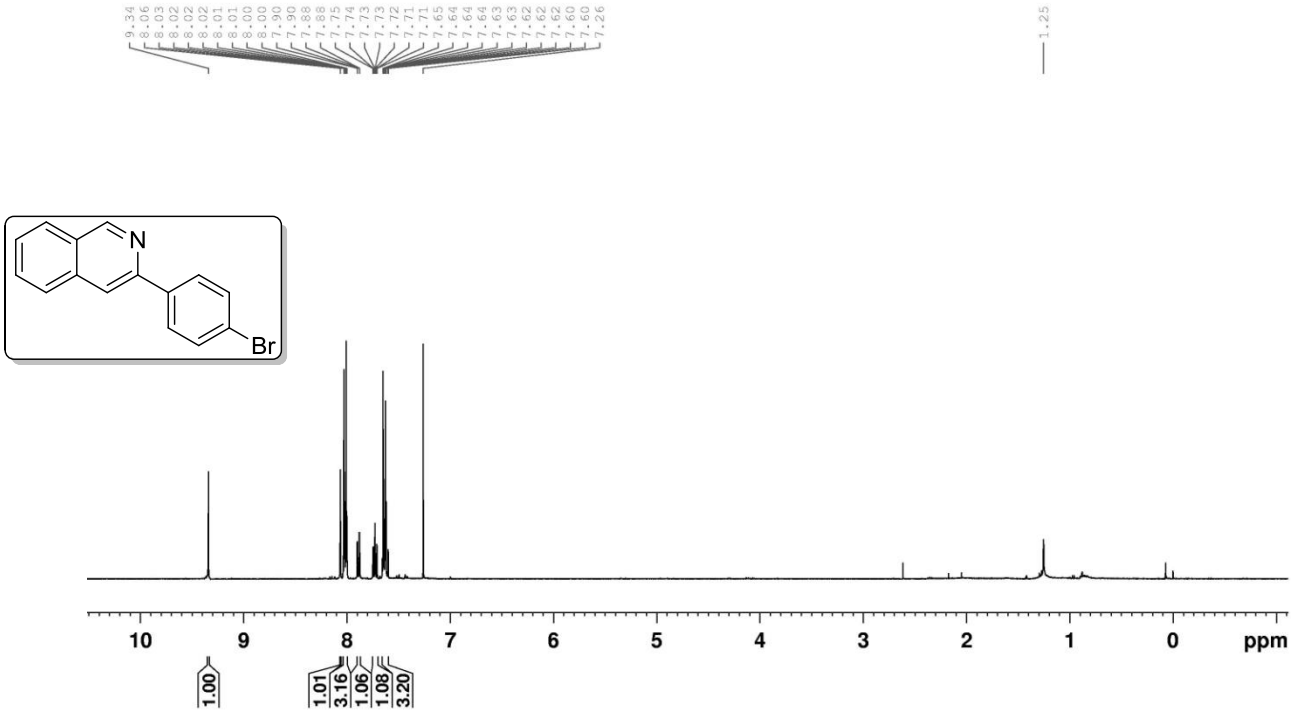
^{1}H NMR Spectrum of compound **35g**



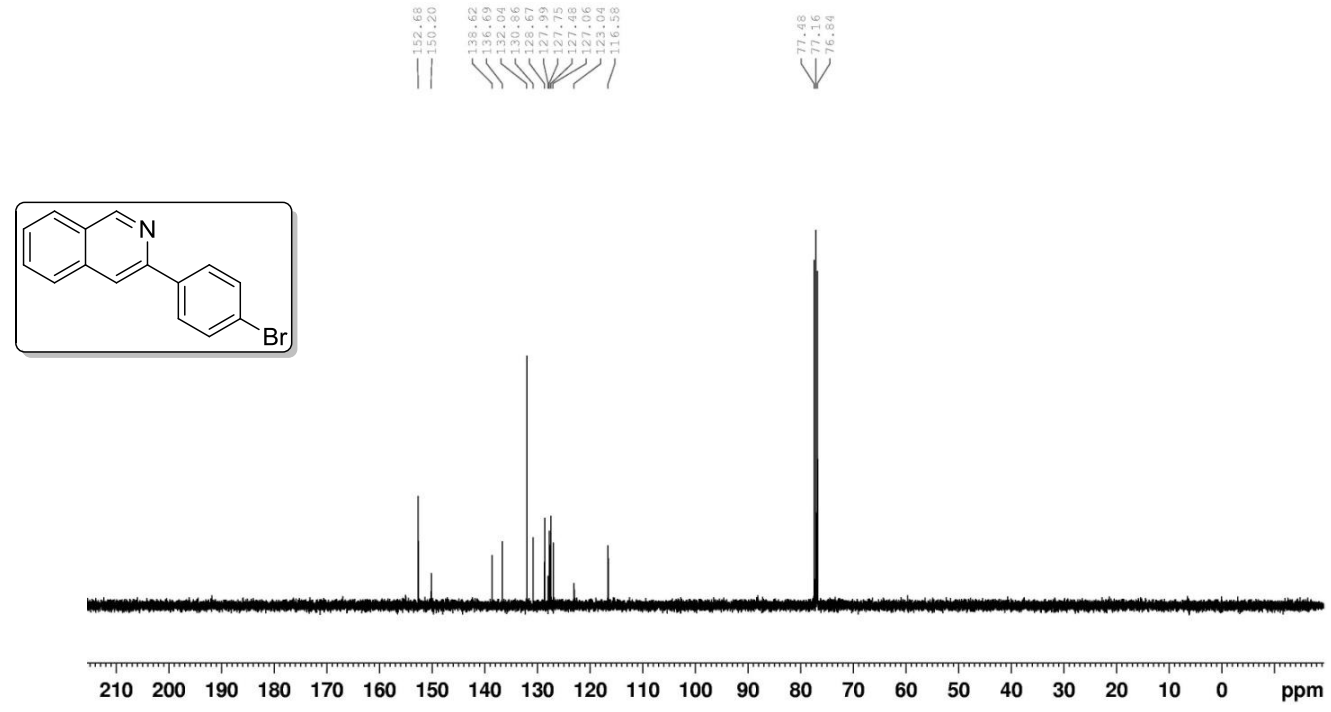
^{13}C NMR Spectrum of compound **35g**



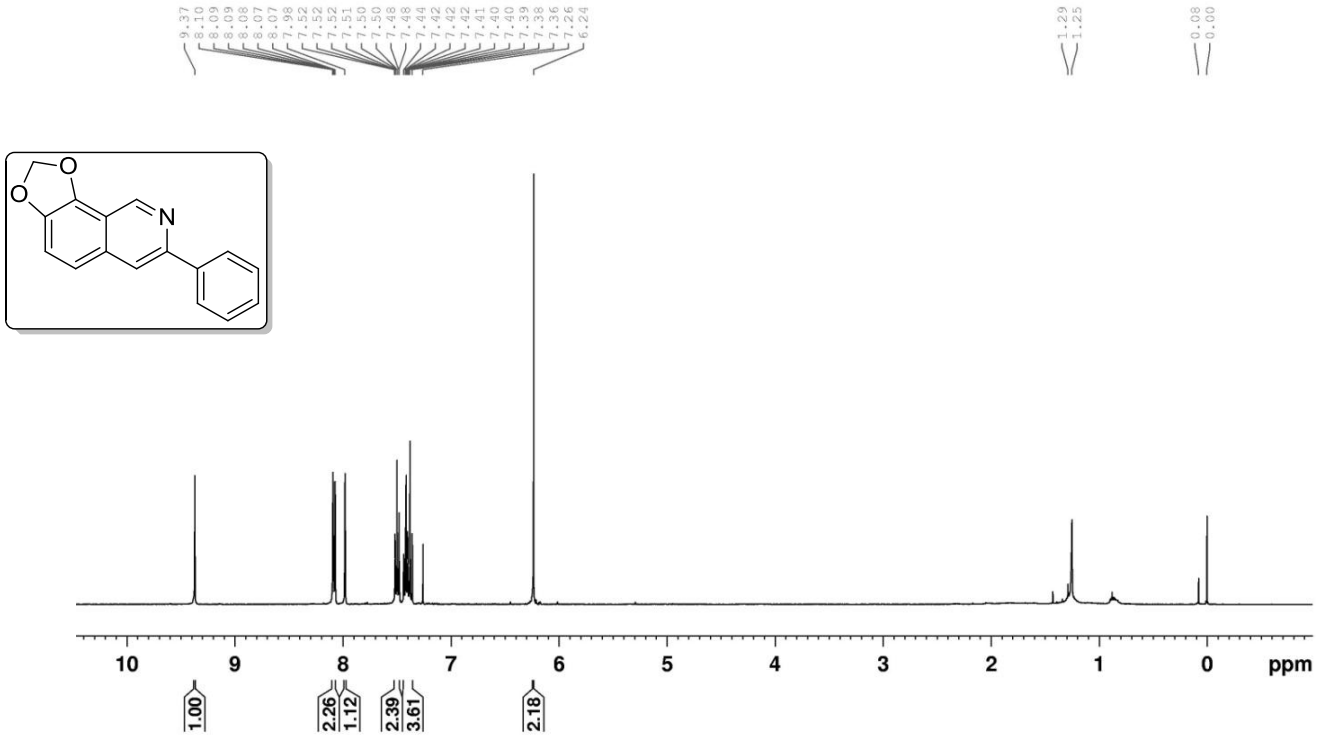
^{1}H NMR Spectrum of compound **35h**



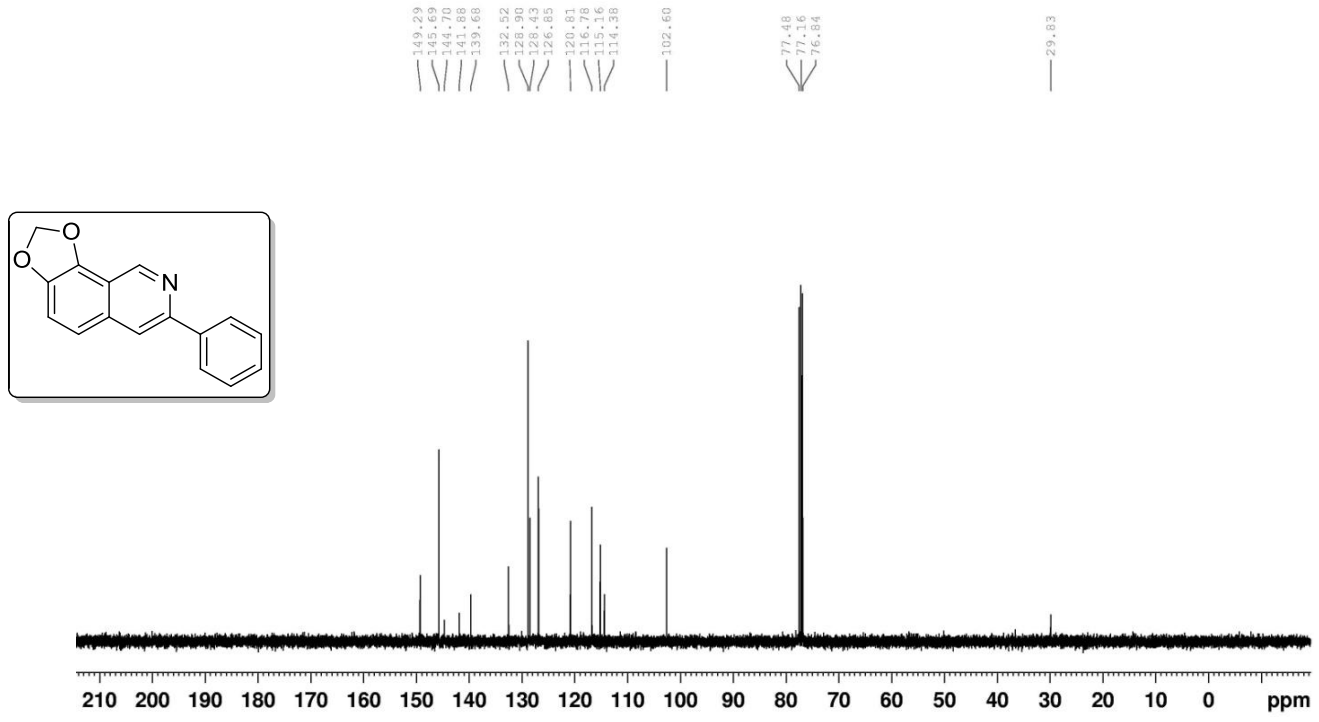
^{13}C NMR Spectrum of compound **35h**



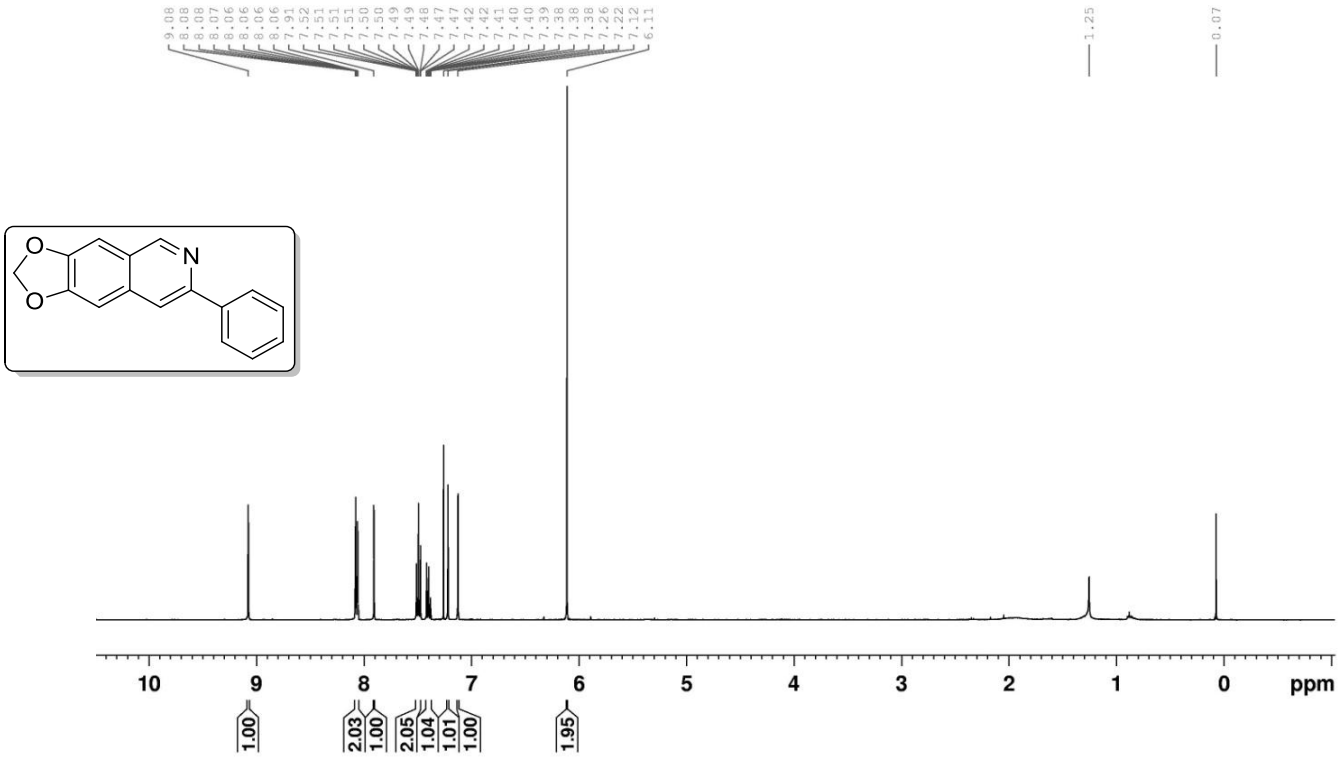
^{1}H NMR Spectrum of compound **35i**



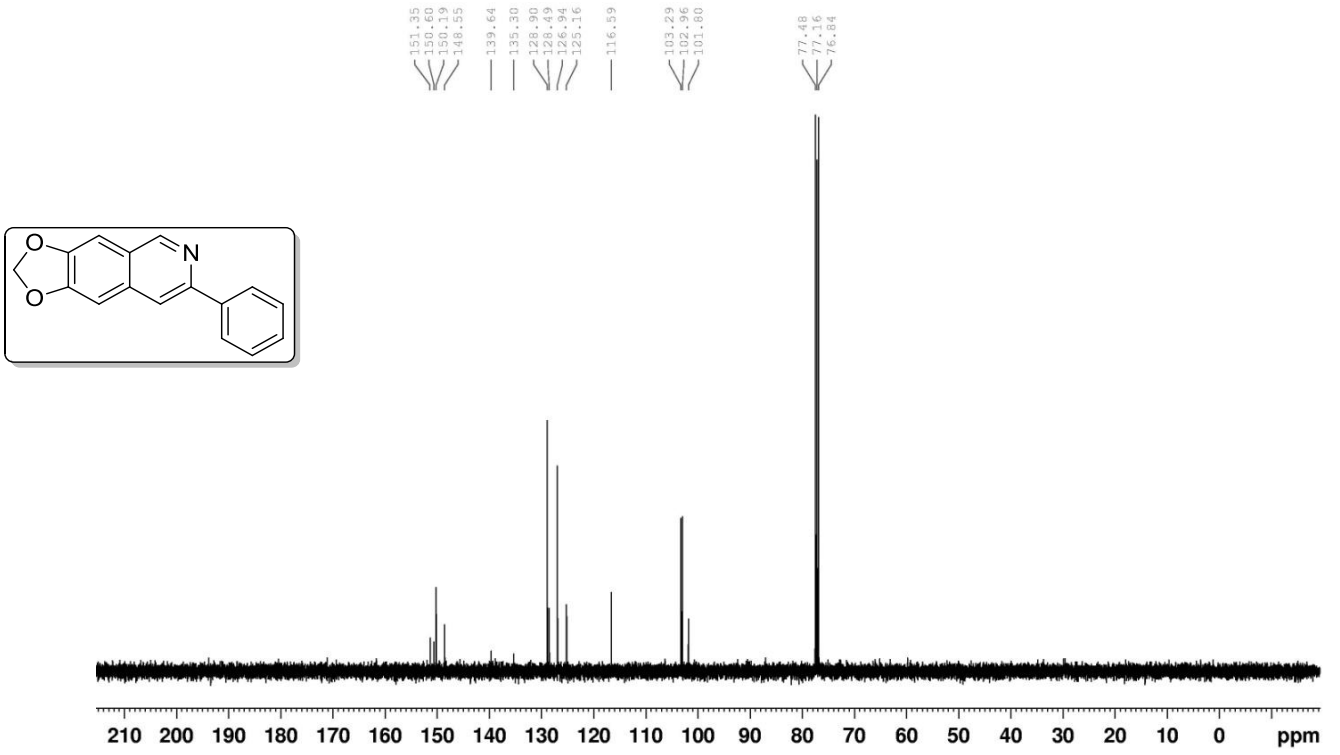
^{13}C NMR Spectrum of compound **35i**



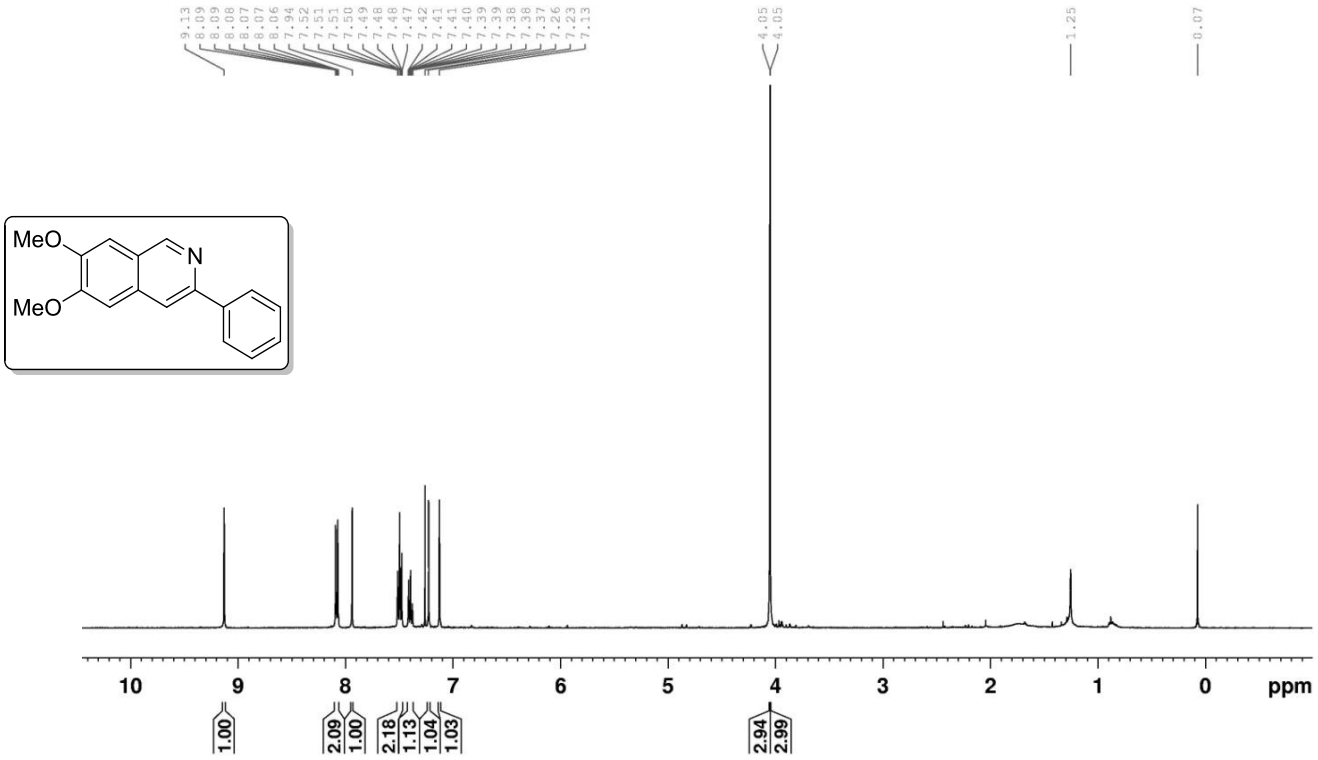
^{1}H NMR Spectrum of compound **35j**



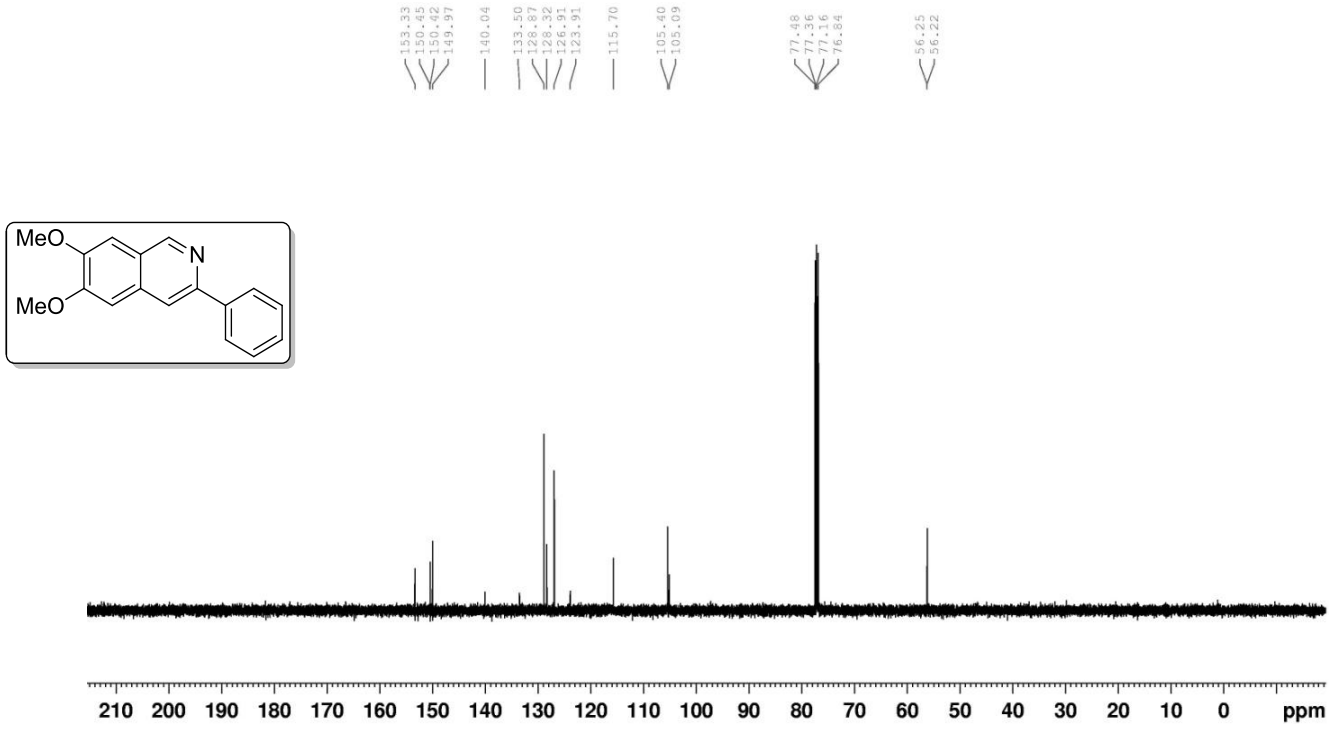
^{13}C NMR Spectrum of compound **35j**



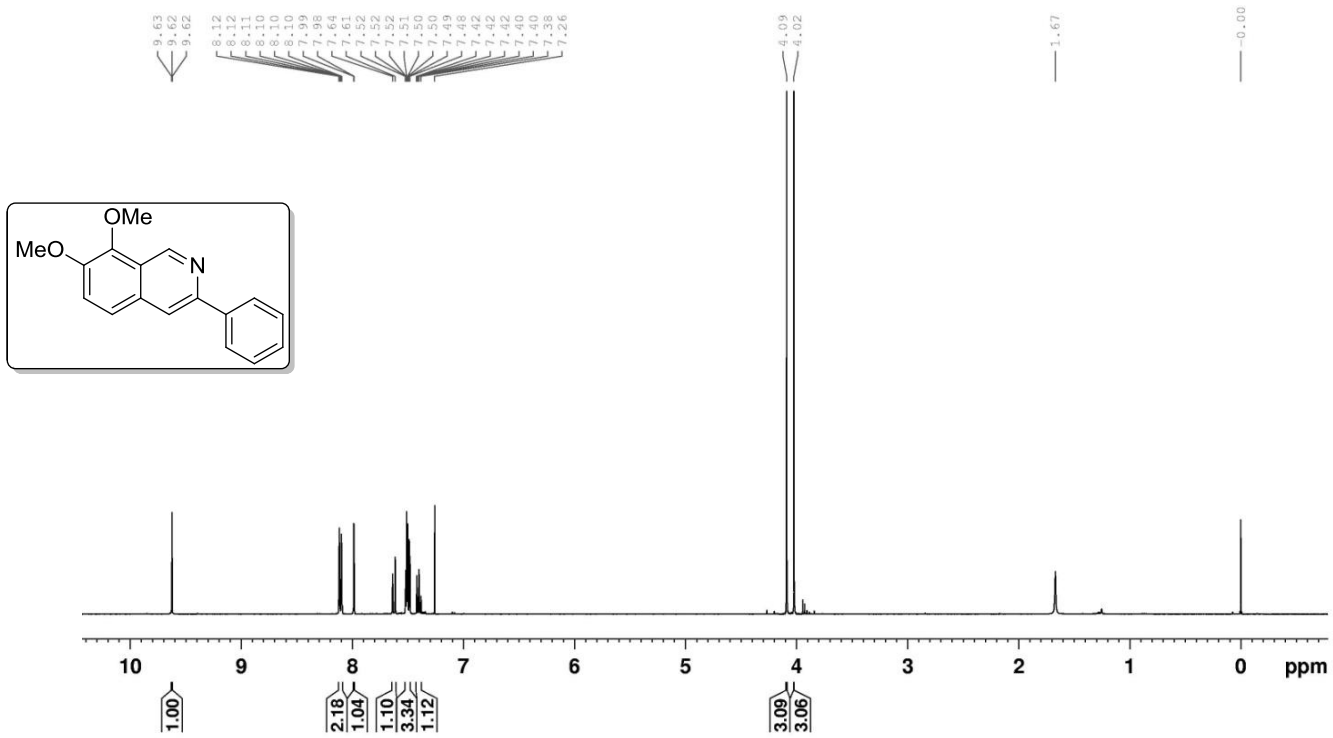
^{1}H NMR Spectrum of compound **35k**



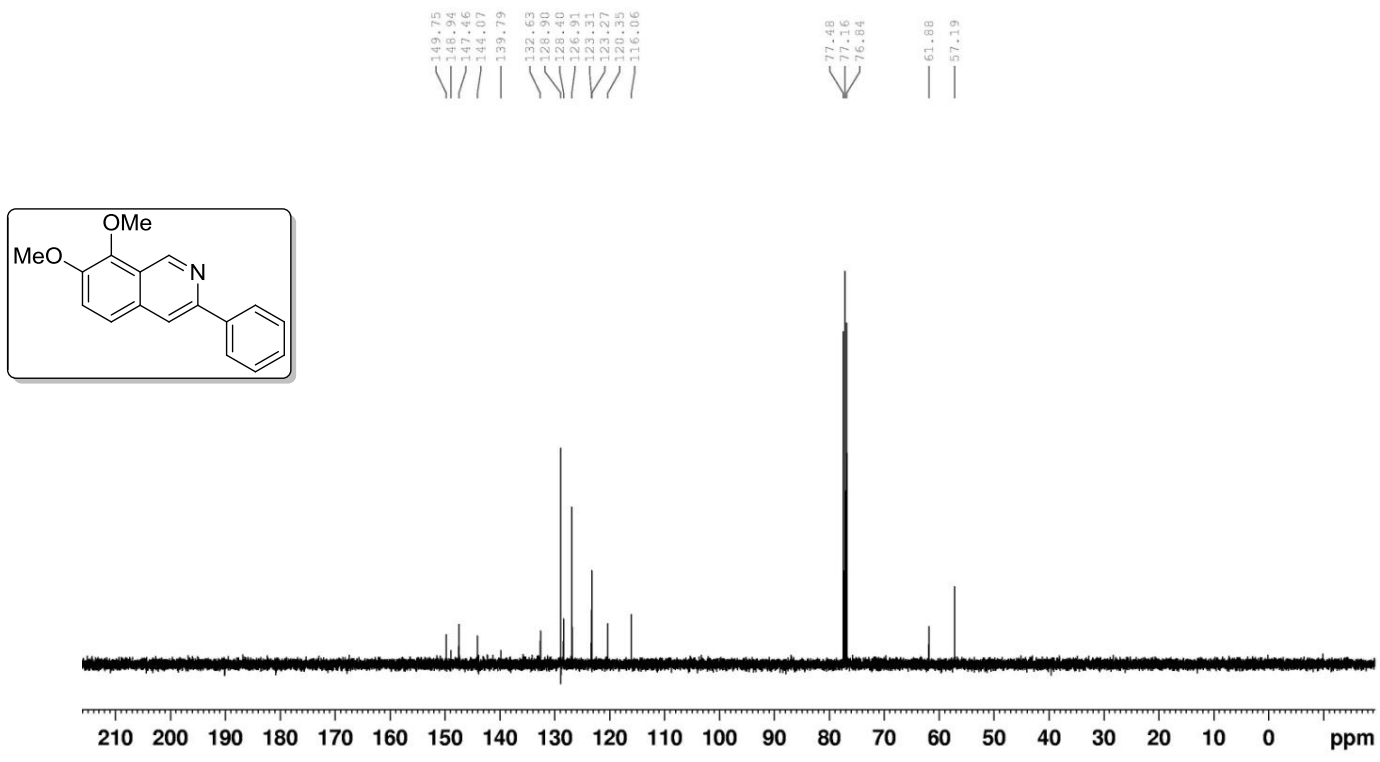
^{13}C NMR Spectrum of compound **35k**



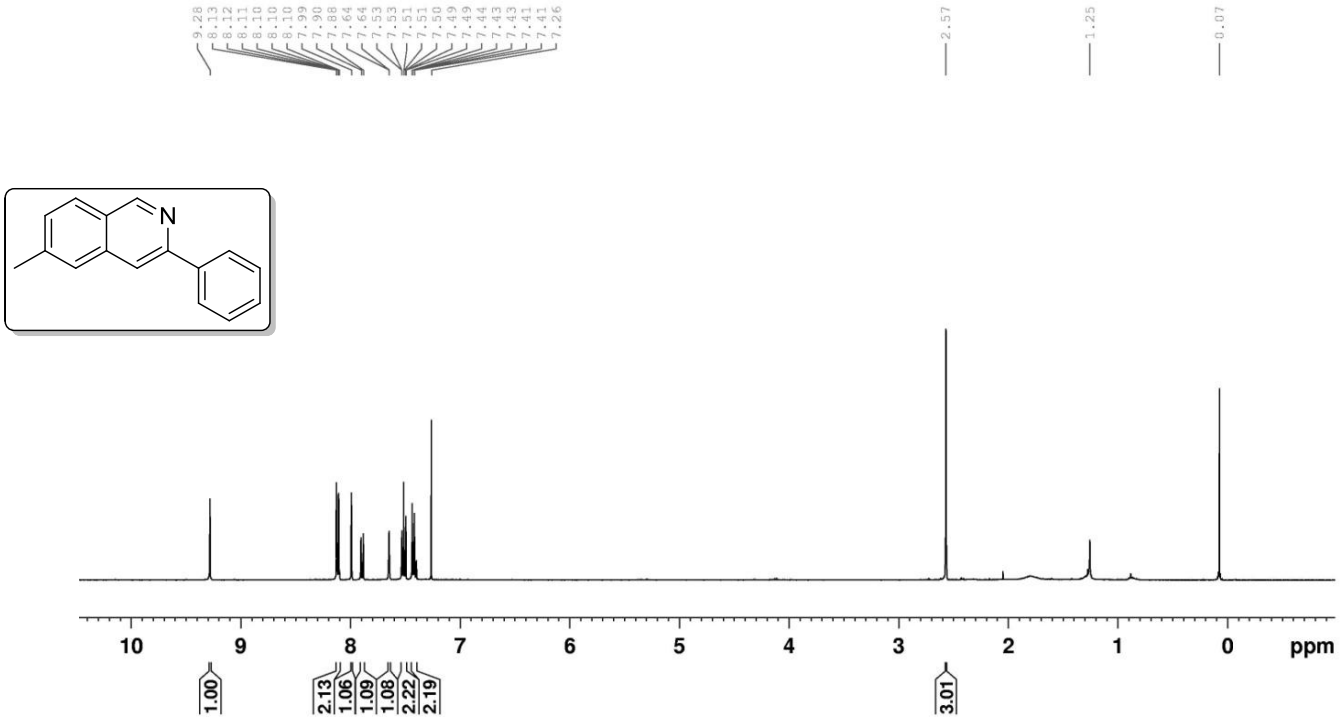
^{1}H NMR Spectrum of compound **35l**



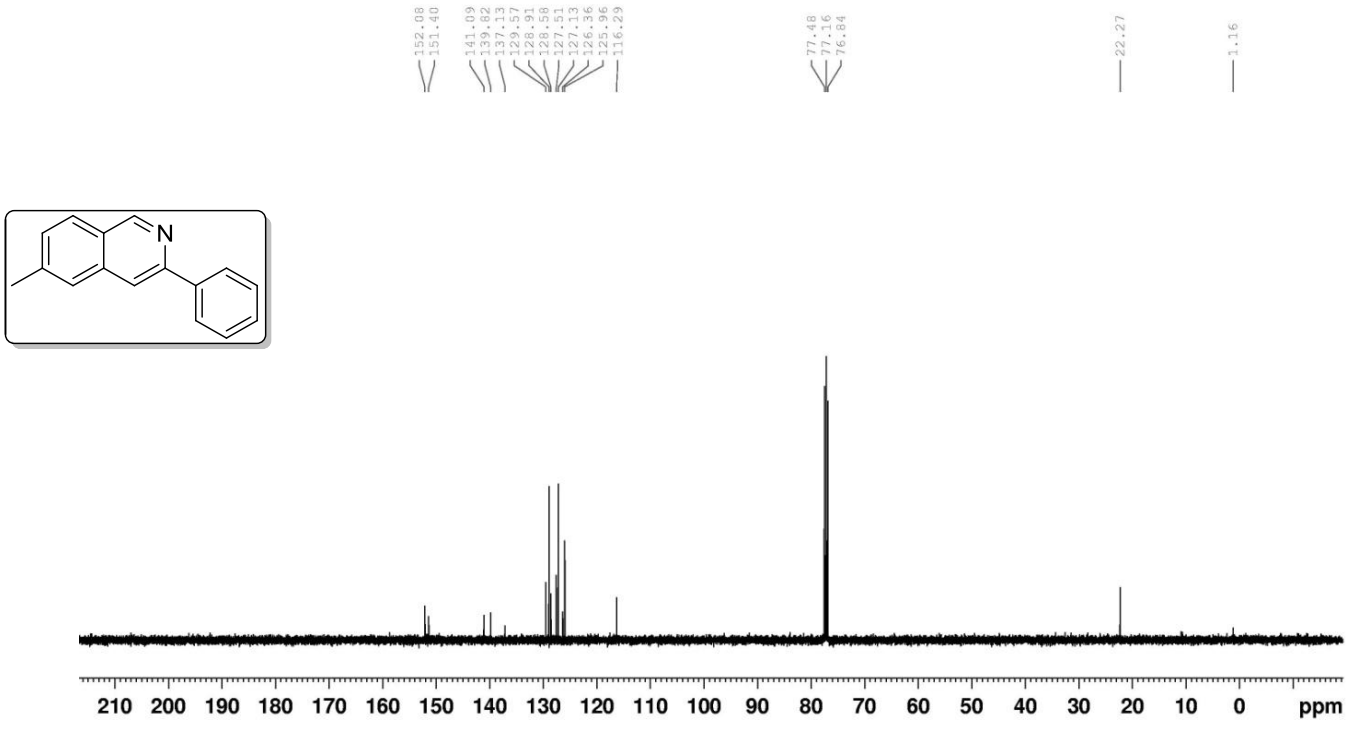
^{13}C NMR Spectrum of compound **35l**



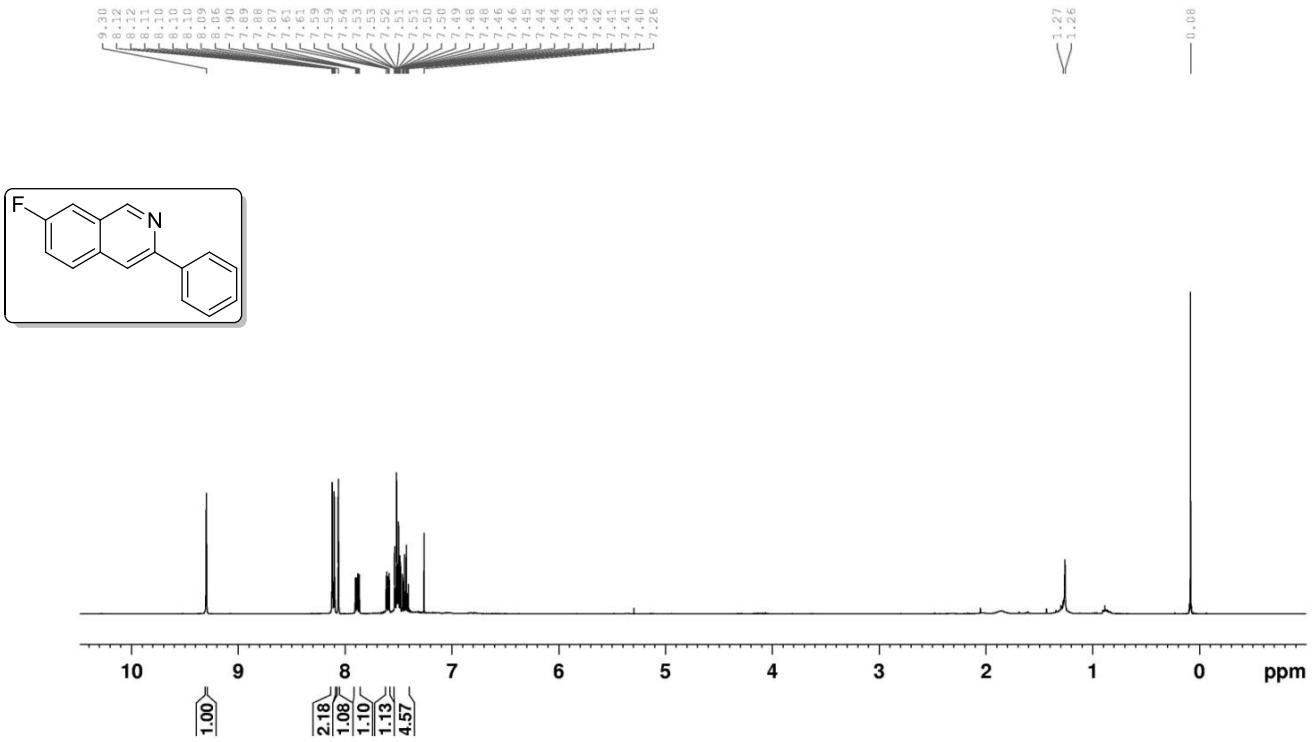
^{1}H NMR Spectrum of compound **35m**



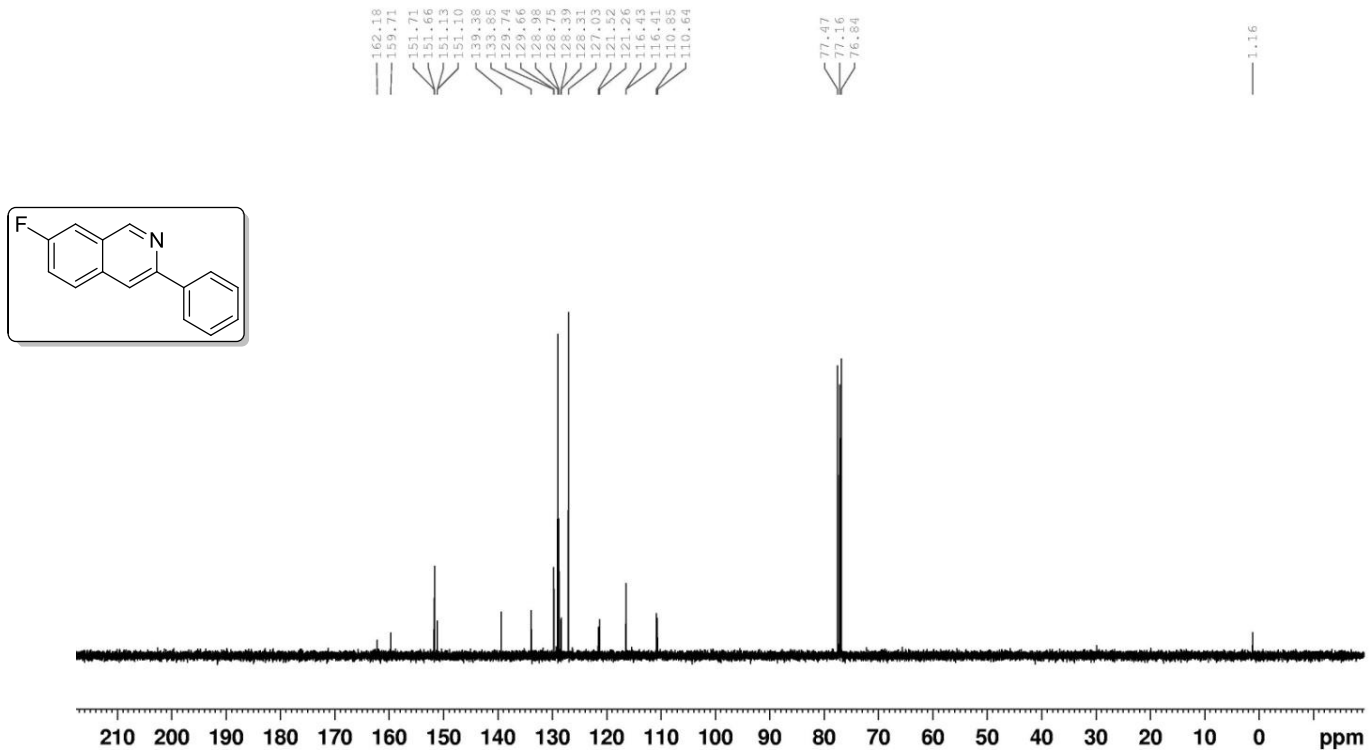
^{13}C NMR Spectrum of compound **35m**



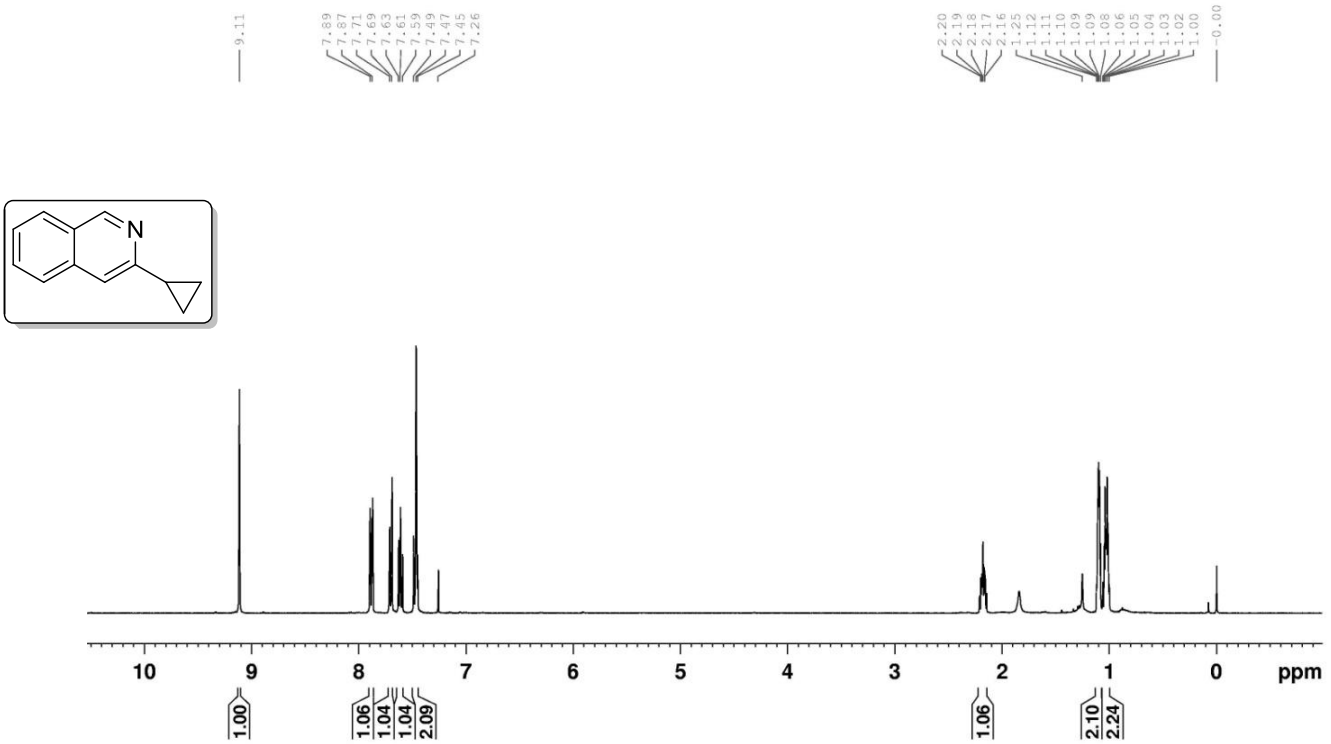
^{1}H NMR Spectrum of compound **35n**



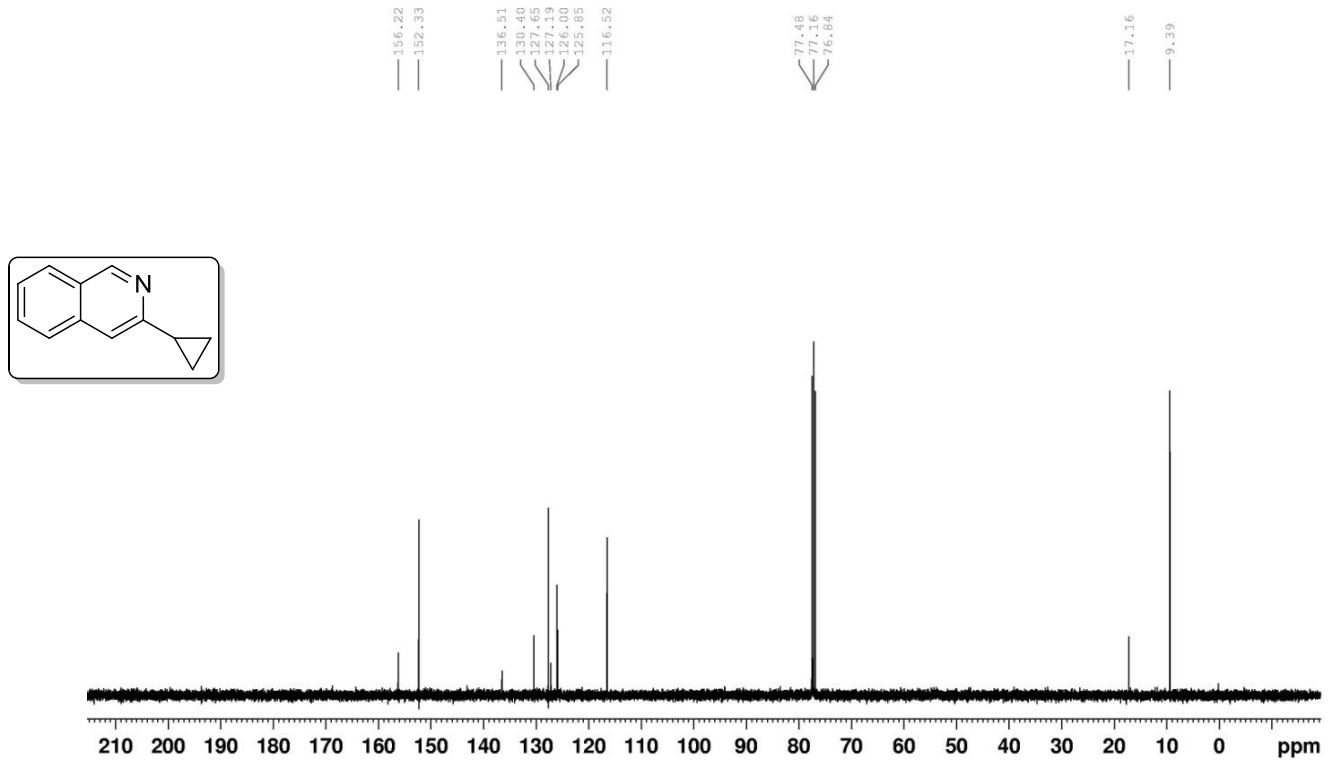
^{13}C NMR Spectrum of compound **35n**



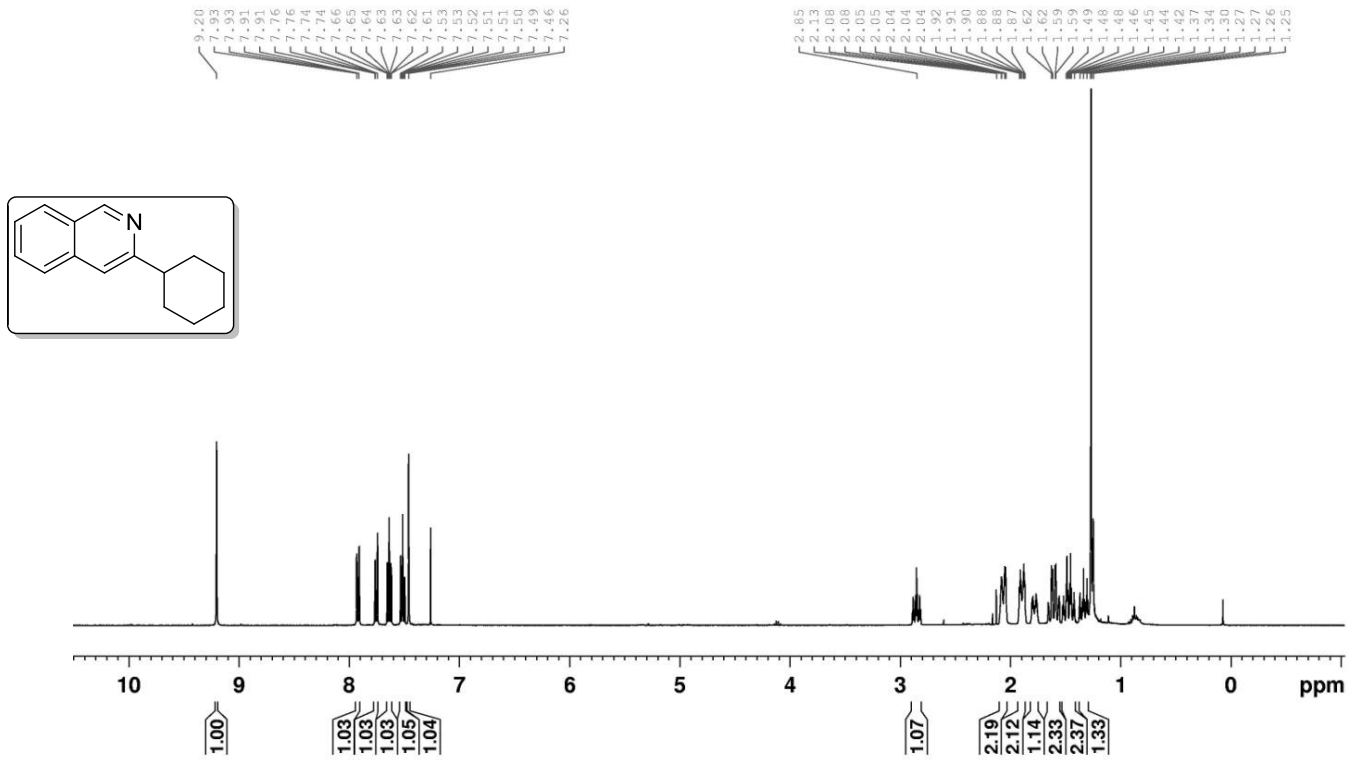
^{1}H NMR Spectrum of compound **35o**



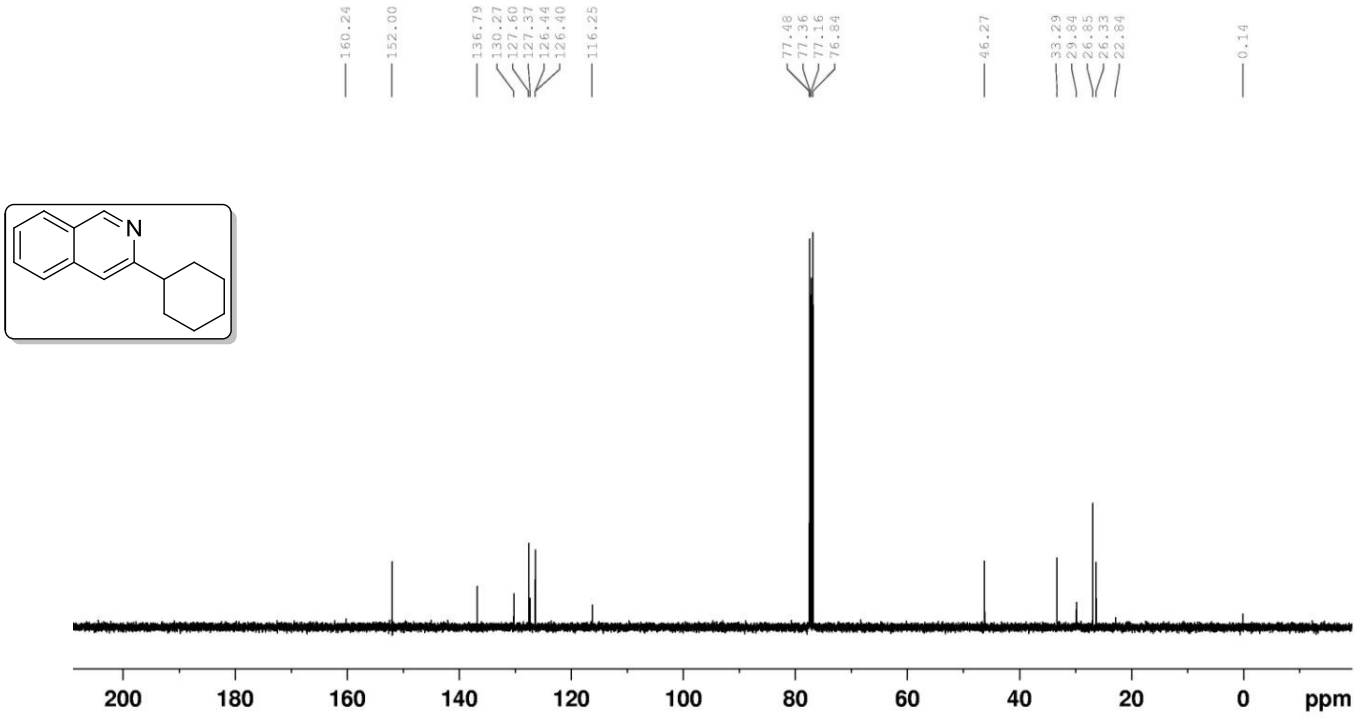
^{13}C NMR Spectrum of compound **35o**



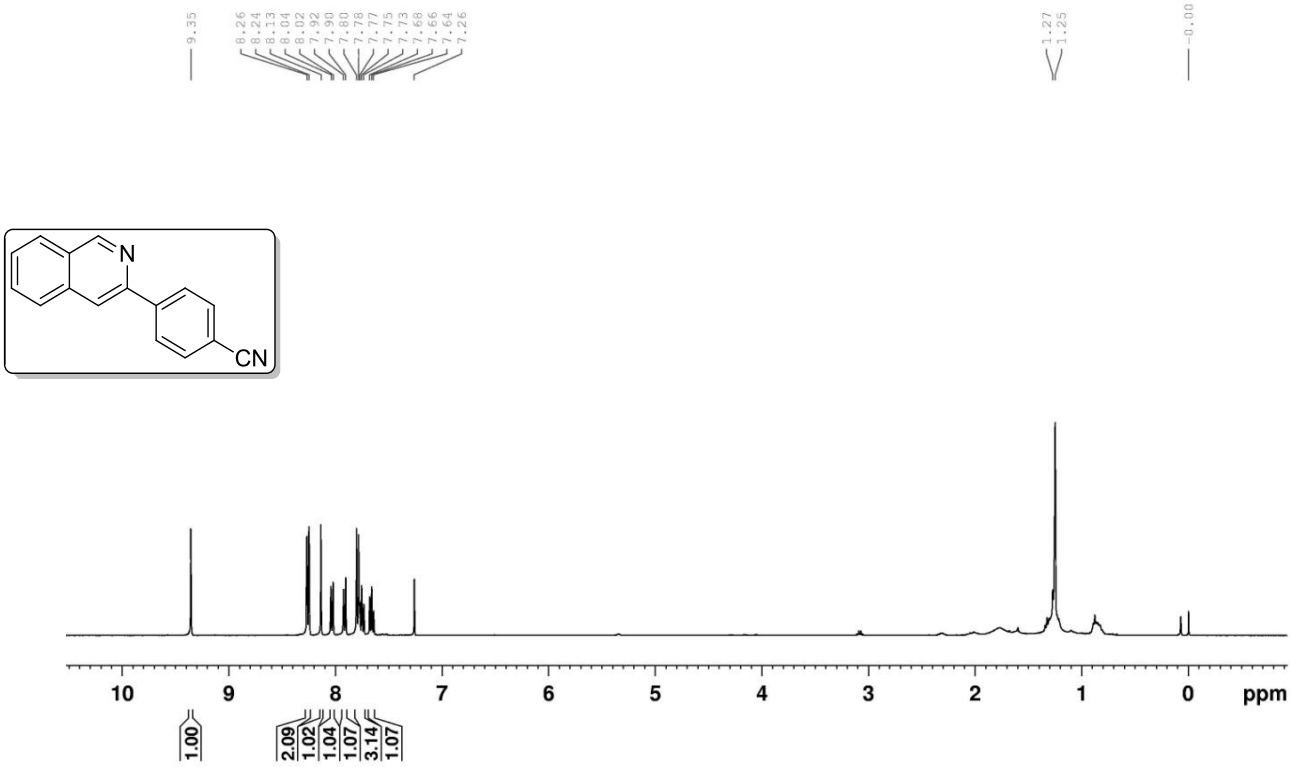
^{1}H NMR Spectrum of compound **35p**



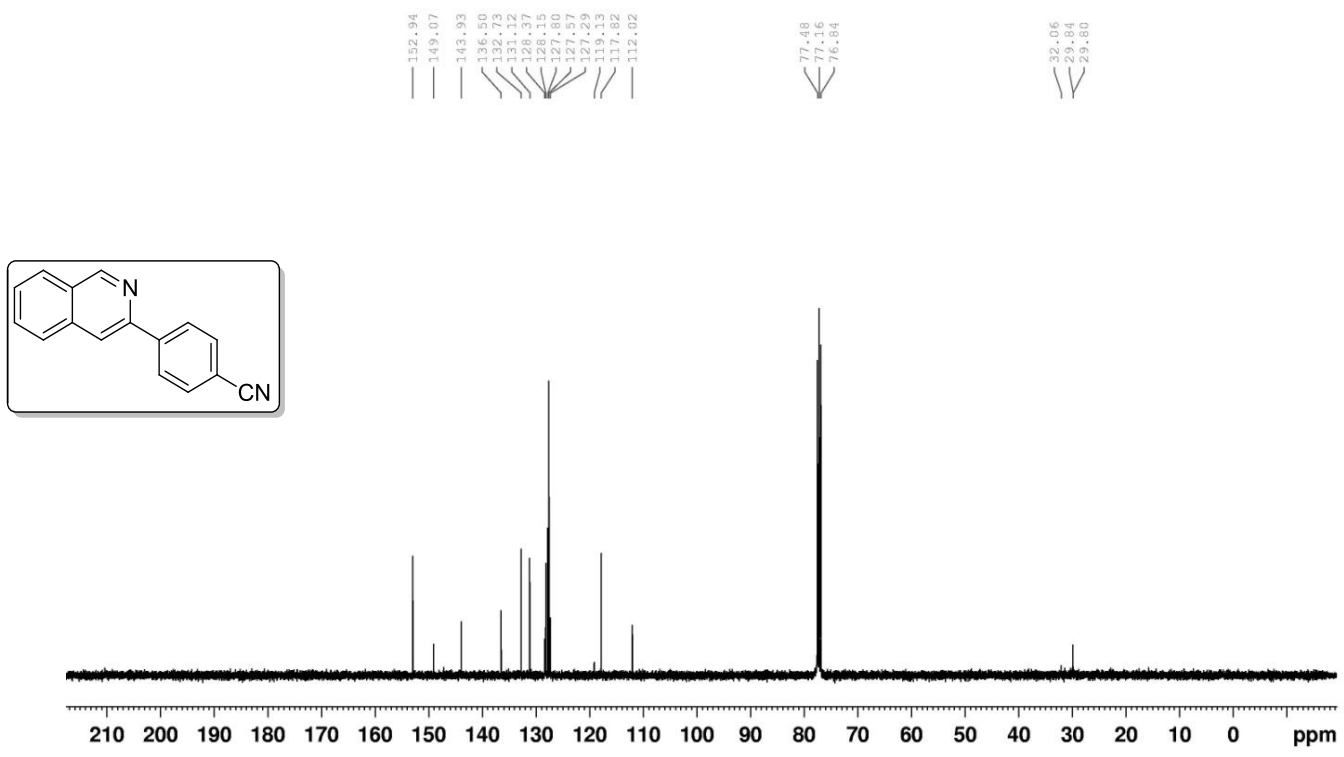
^{13}C NMR Spectrum of compound **35p**



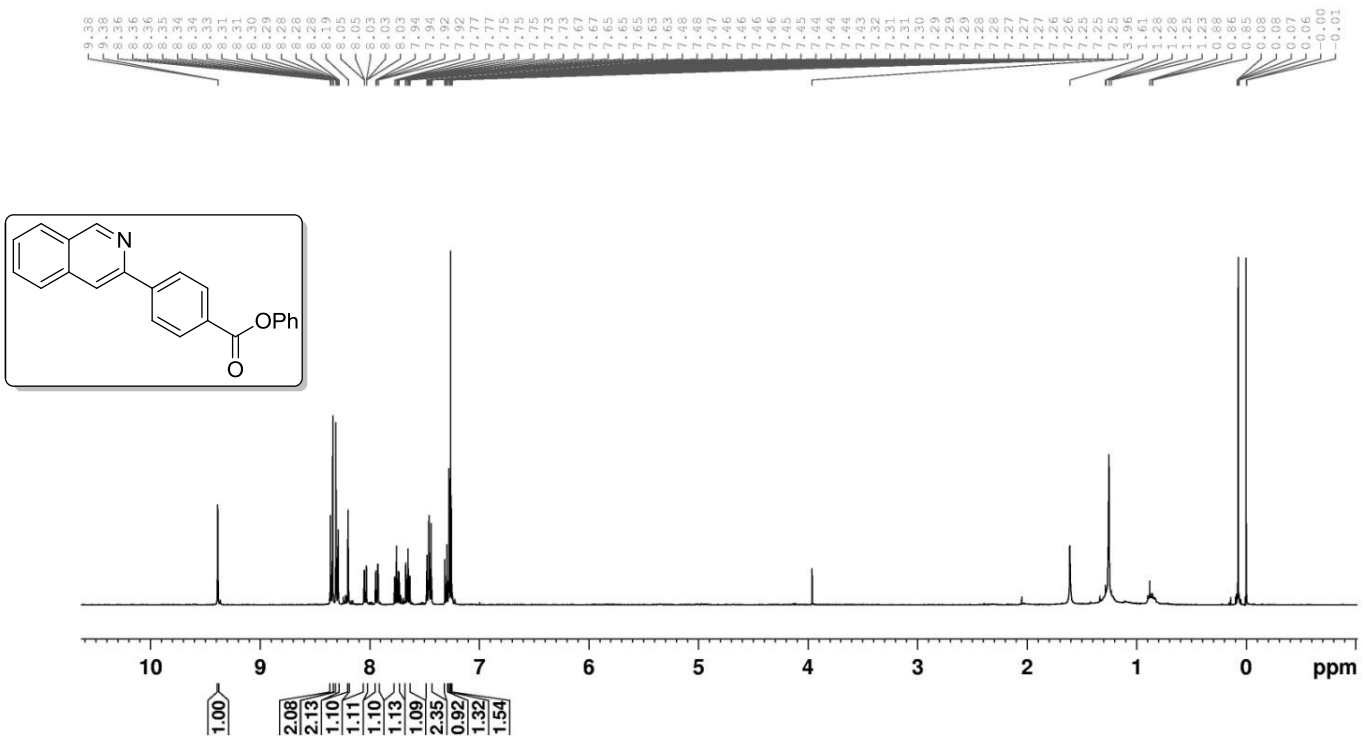
^{1}H NMR Spectrum of compound **35q**



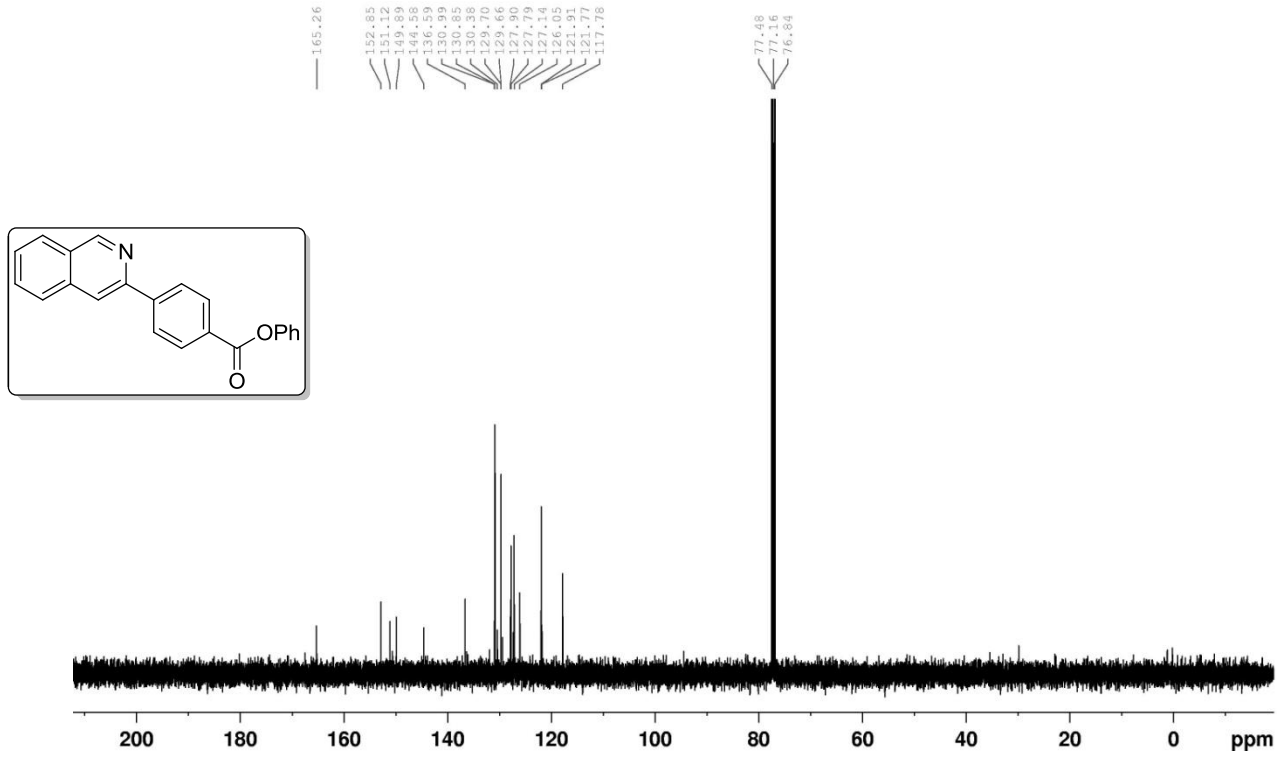
^{13}C NMR Spectrum of compound **35q**



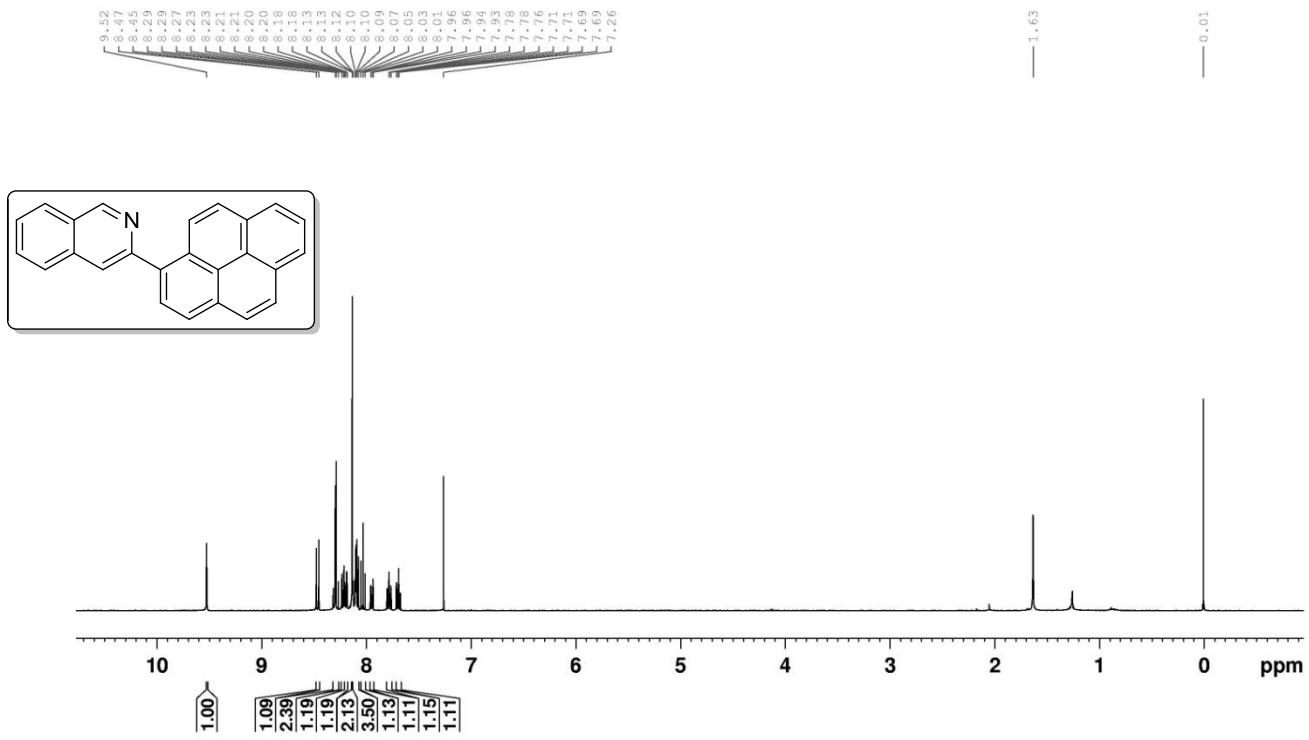
^{1}H NMR Spectrum of compound **35r**



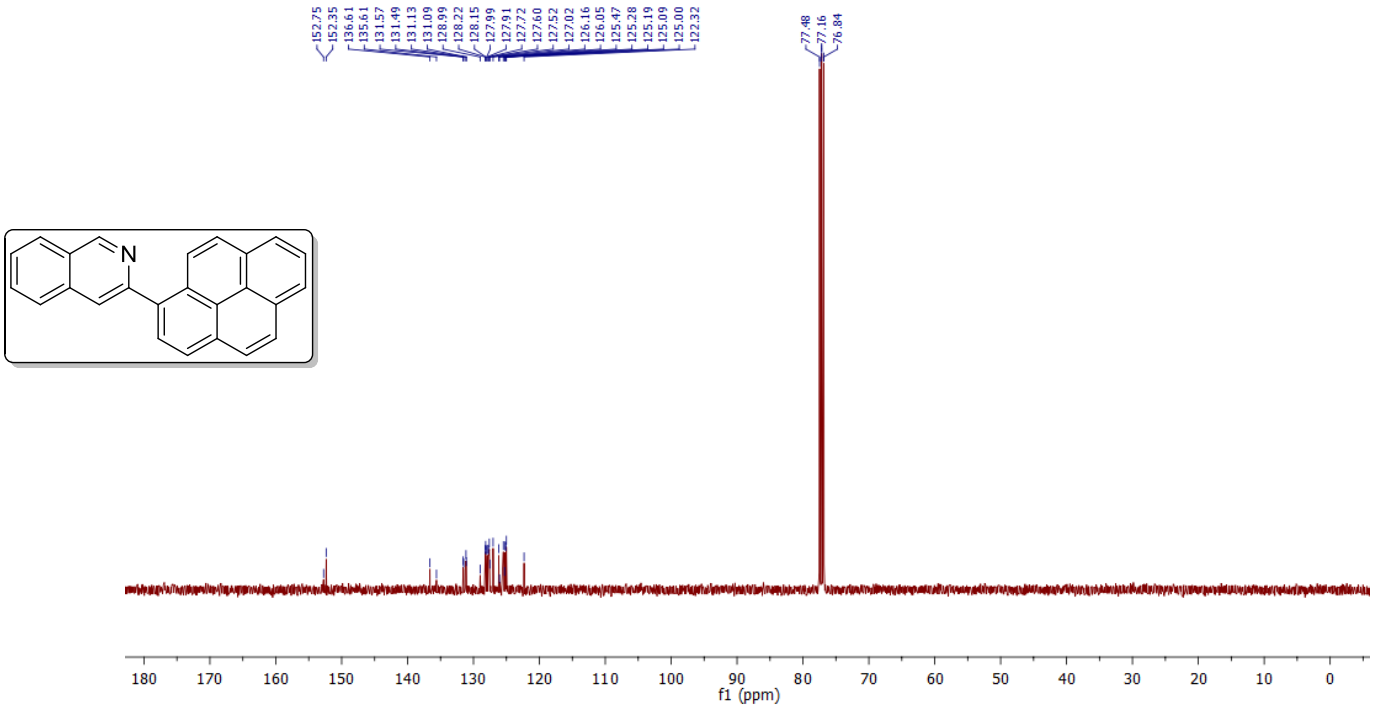
^{13}C NMR Spectrum of compound **35r**



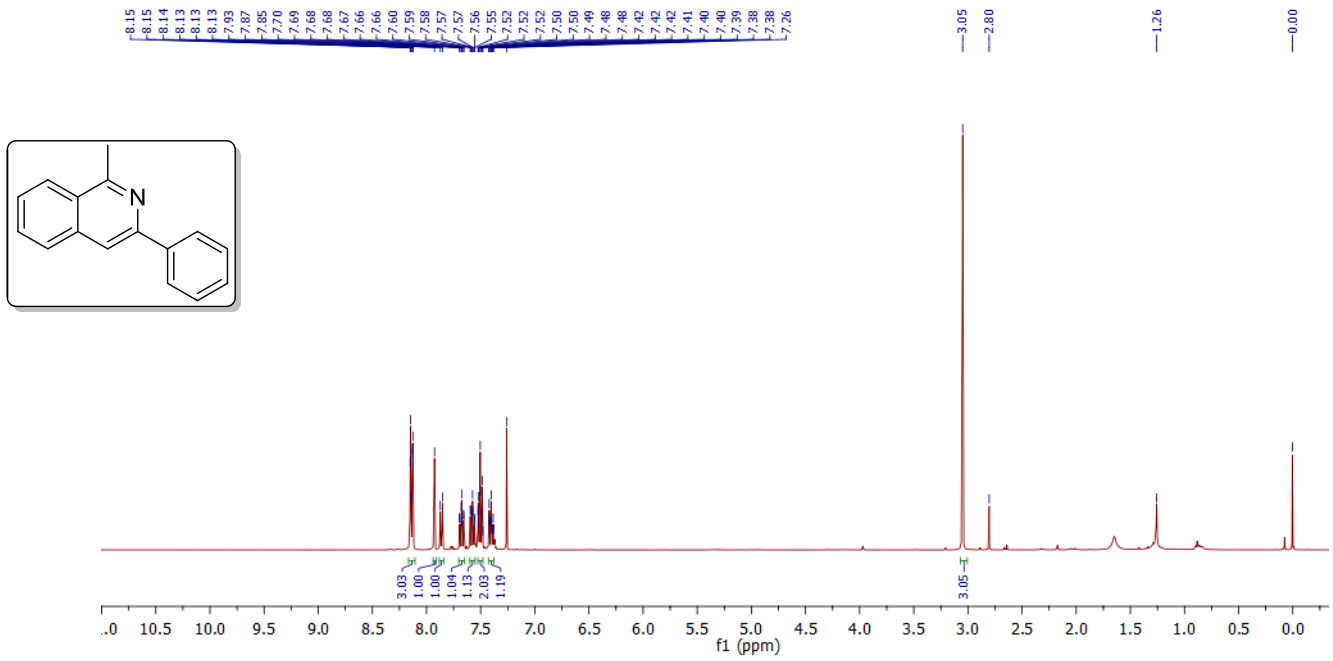
^{1}H NMR Spectrum of compound **35t**



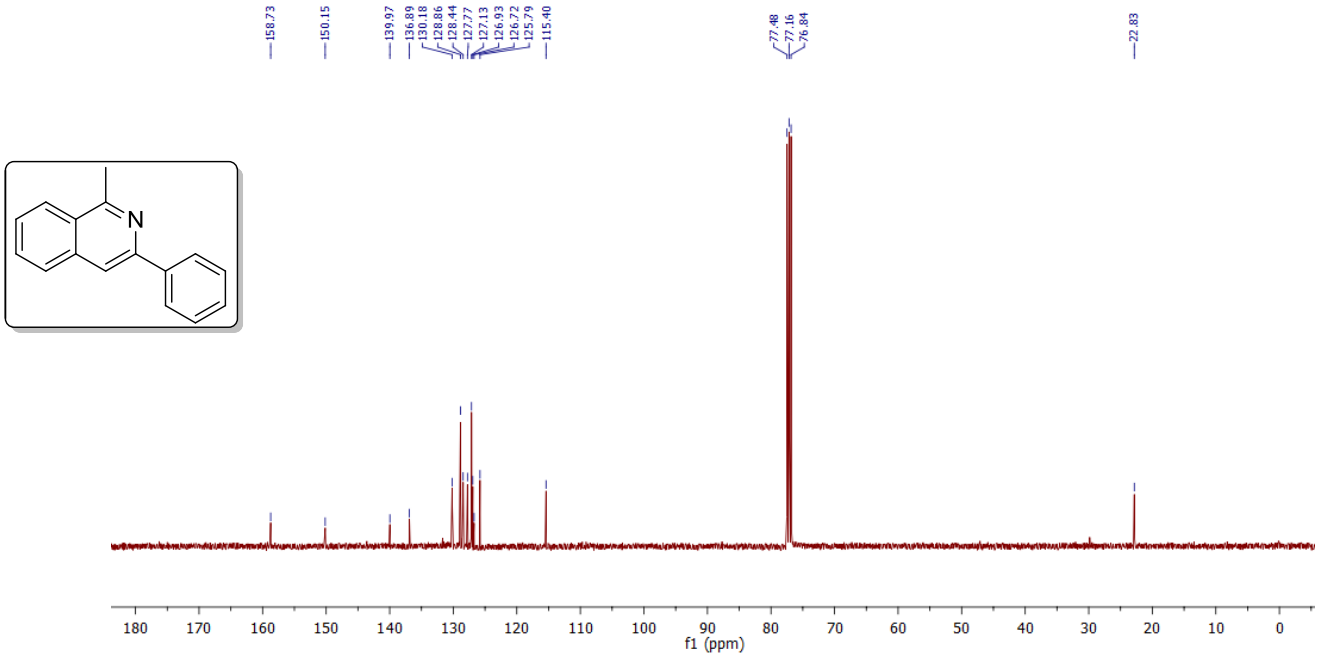
^{13}C NMR Spectrum of compound **35t**



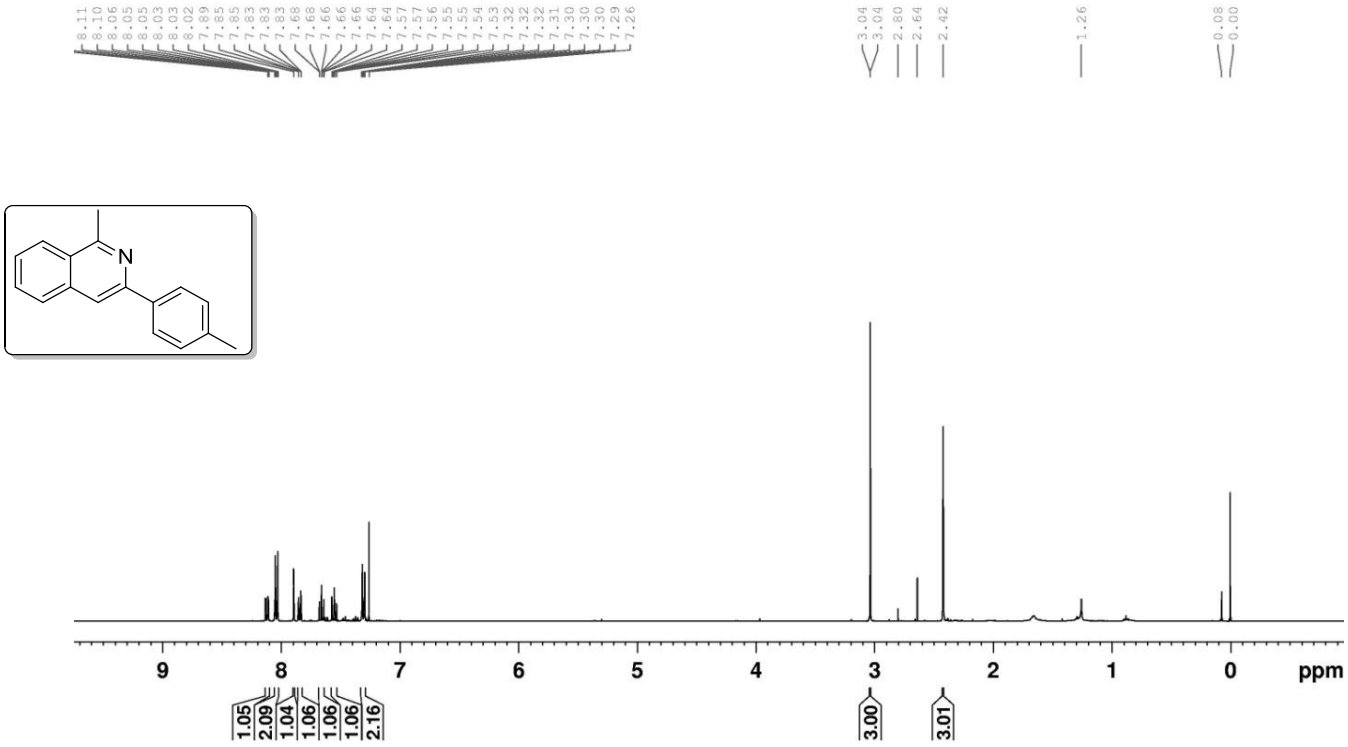
^{1}H NMR Spectrum of compound **35u**



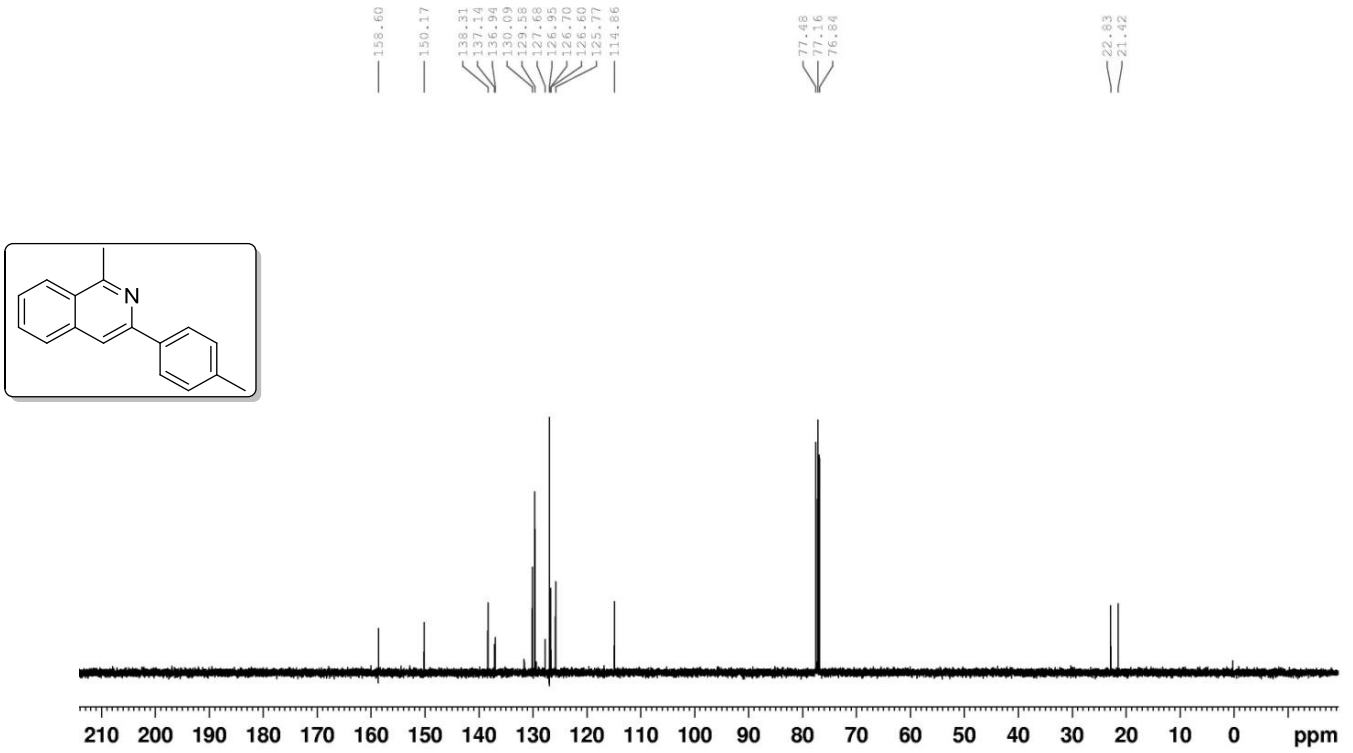
^{13}C NMR Spectrum of compound **35u**



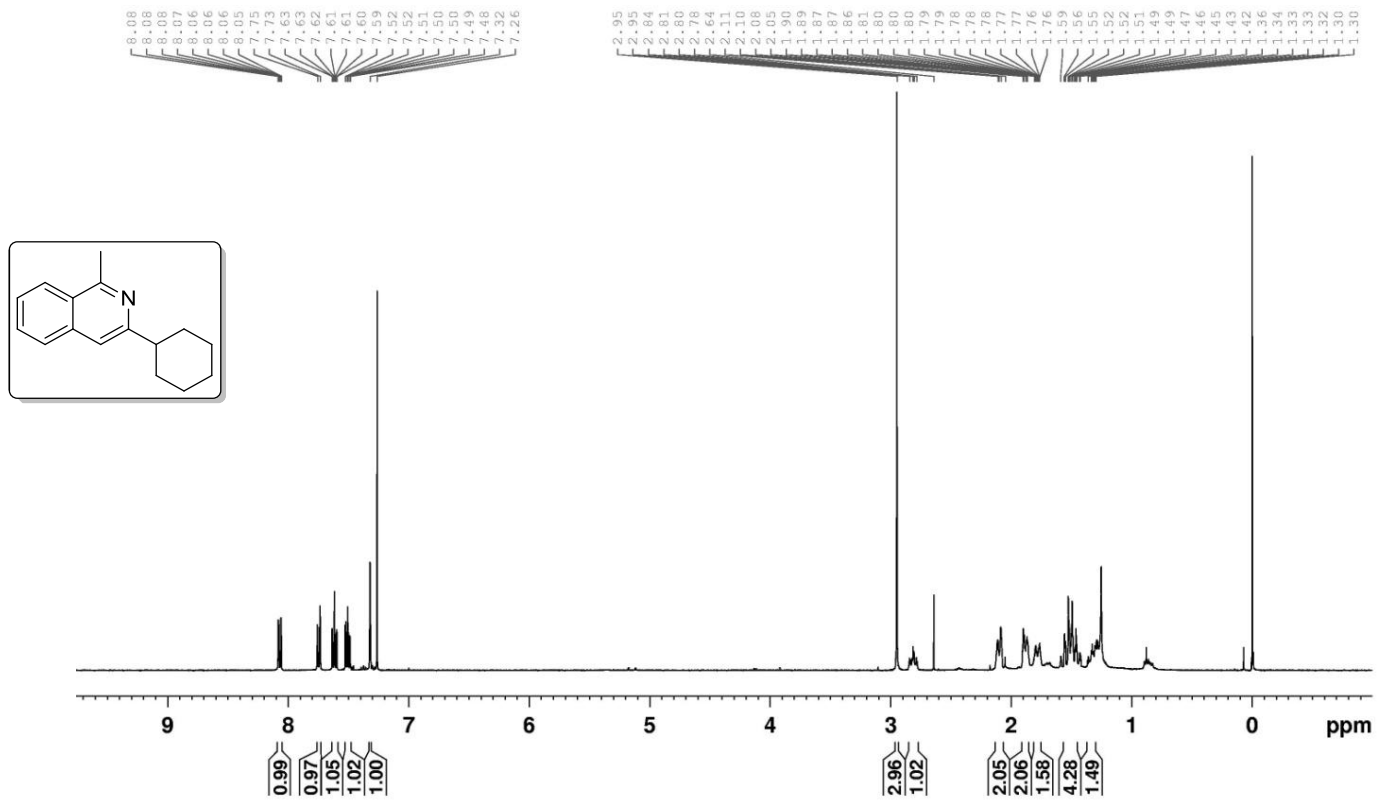
^{1}H NMR Spectrum of compound **35v**



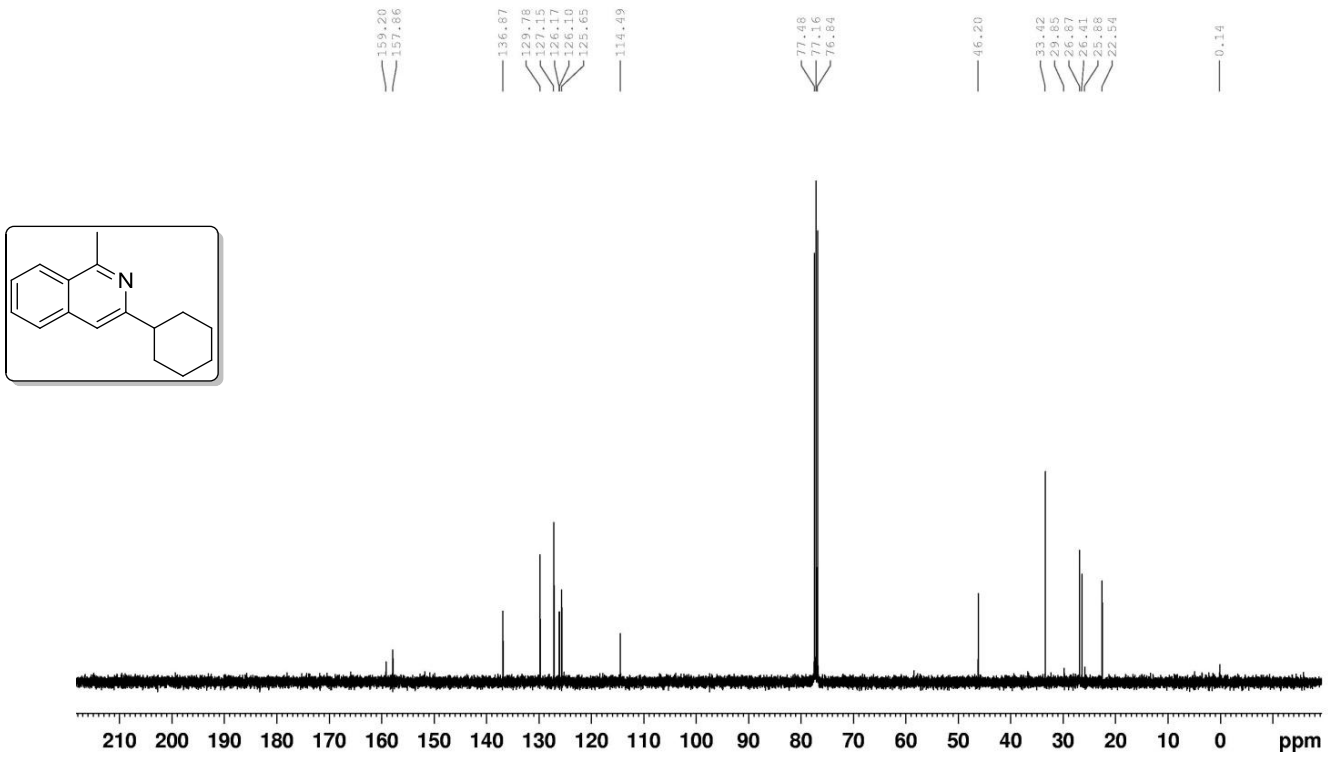
^{13}C NMR Spectrum of compound **35v**



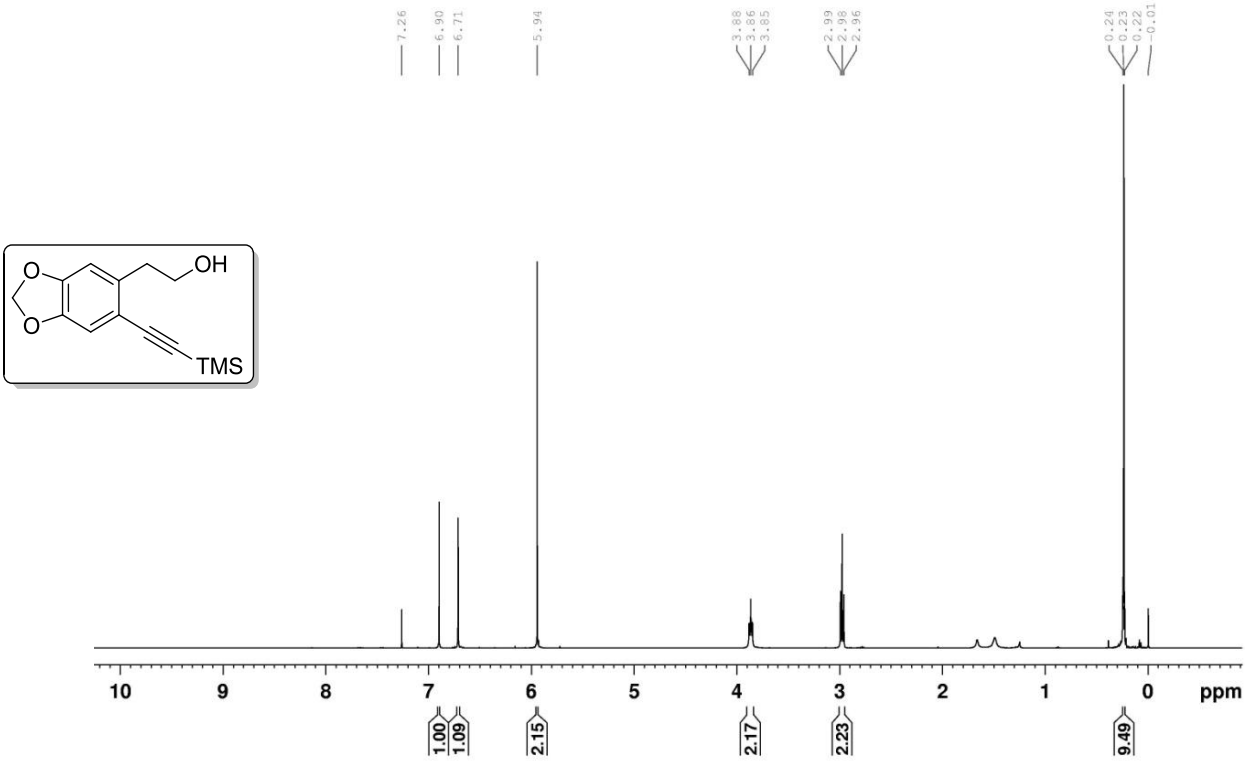
^{1}H NMR Spectrum of compound **35w**



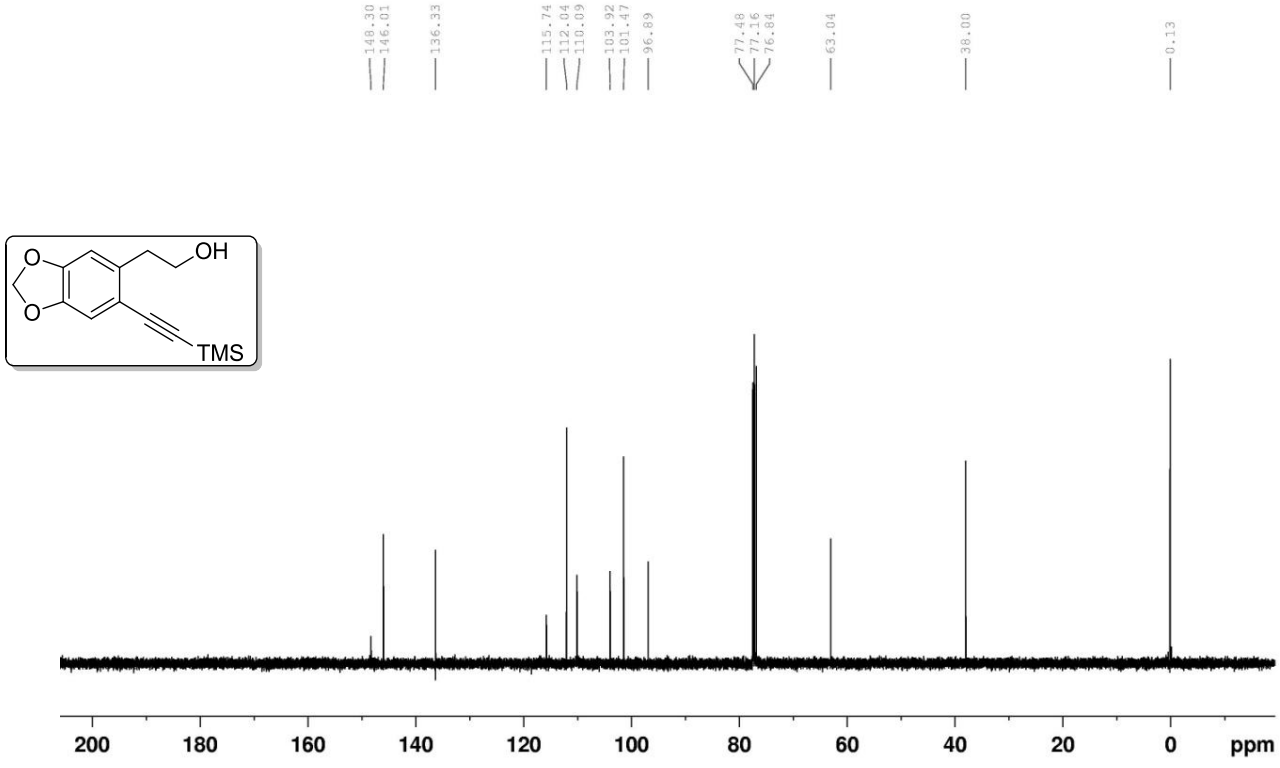
^{13}C NMR Spectrum of compound **35w**



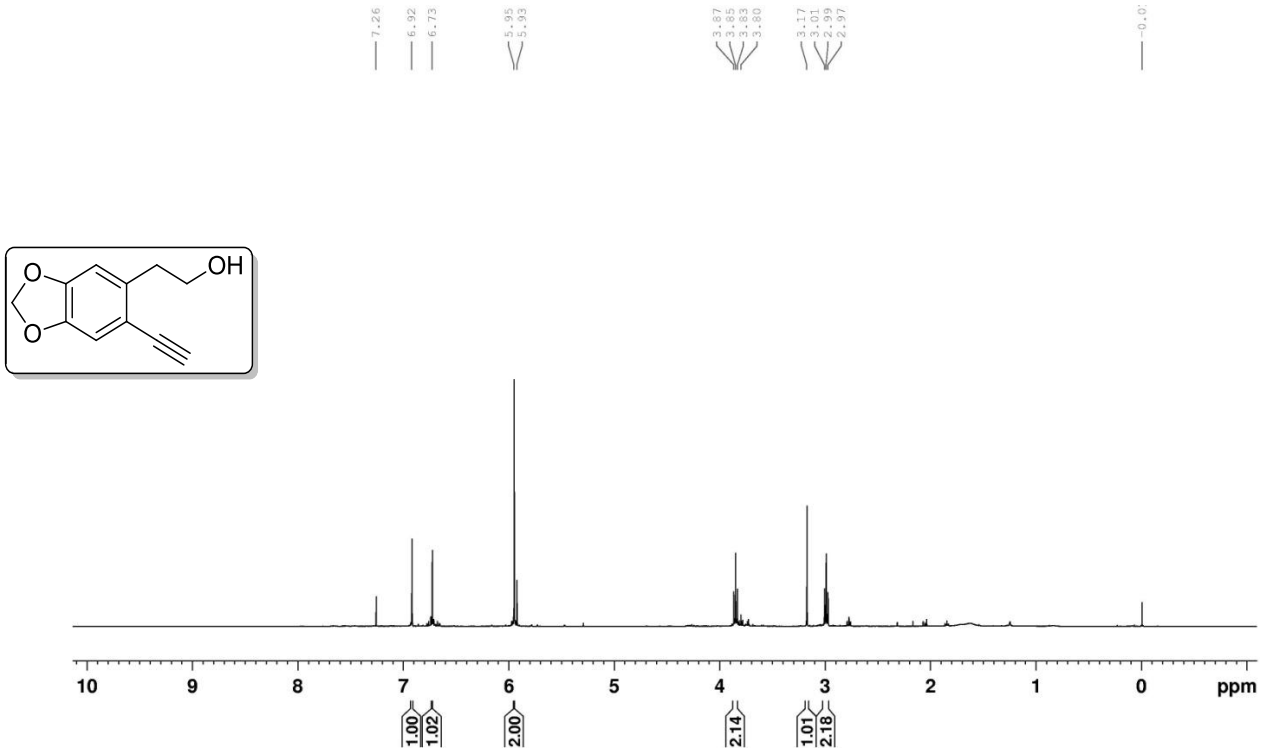
^{1}H NMR Spectrum of compound **51**



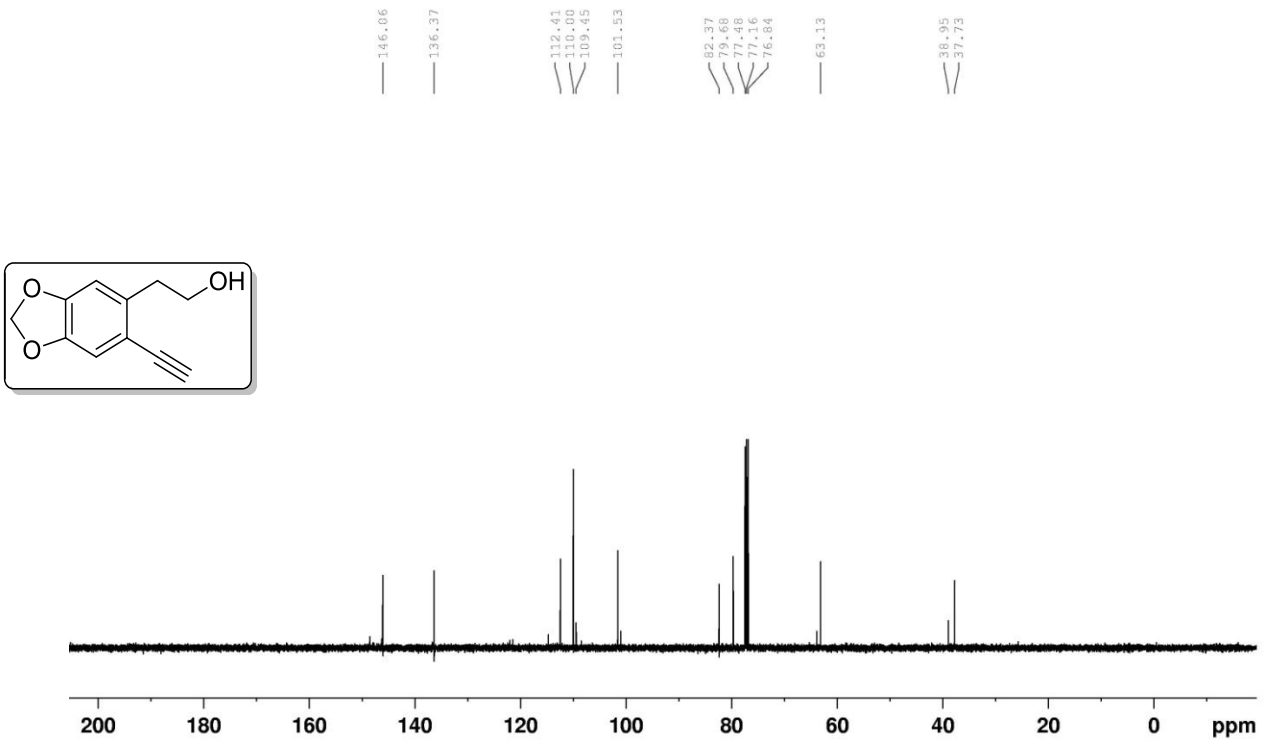
^{13}C NMR Spectrum of compound **51**



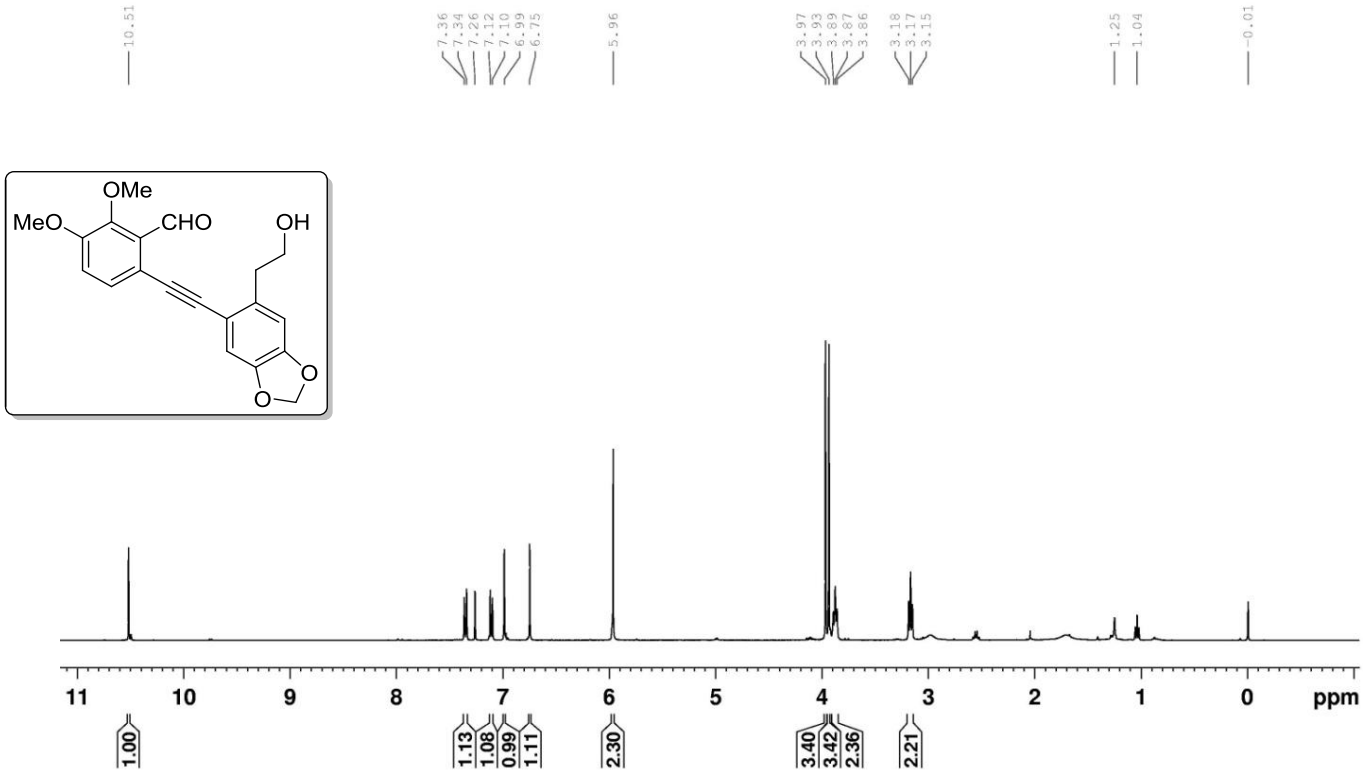
^{1}H NMR Spectrum of compound **46a**



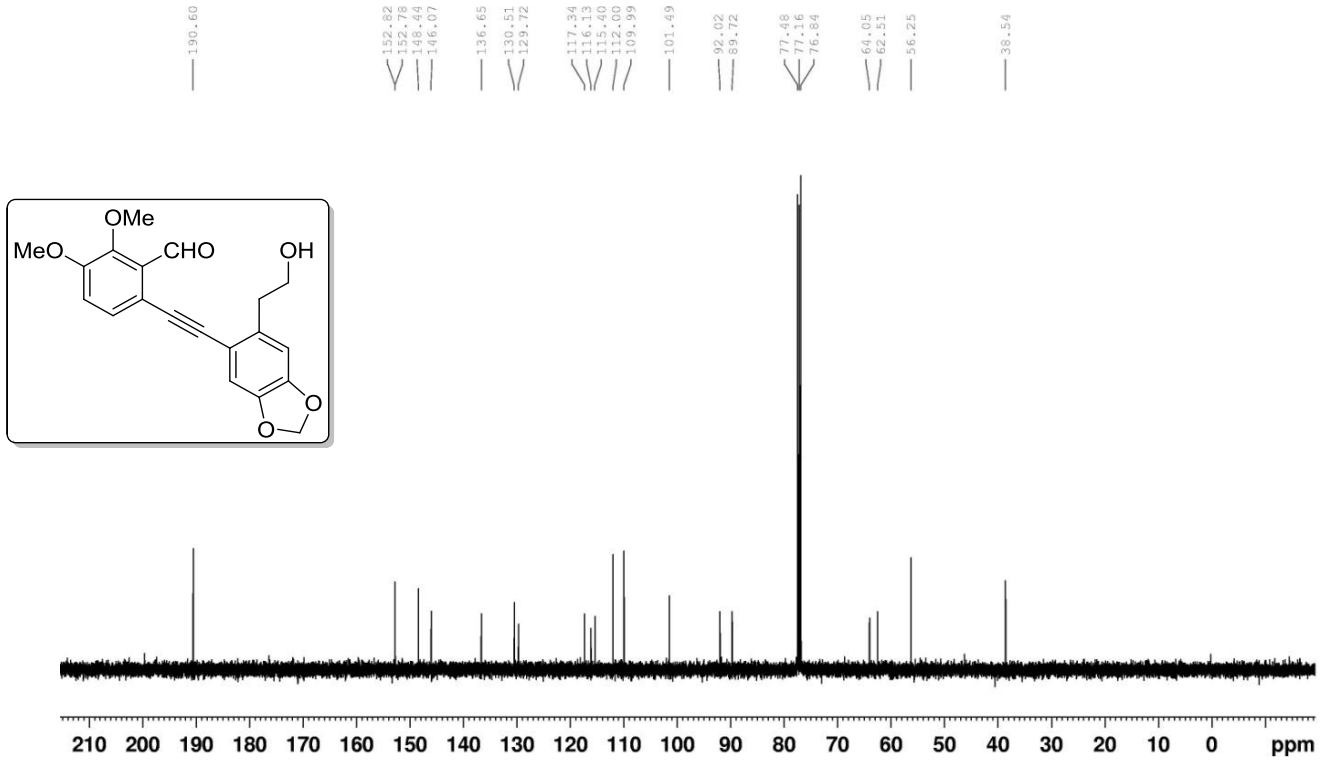
^{13}C NMR Spectrum of compound **46a**



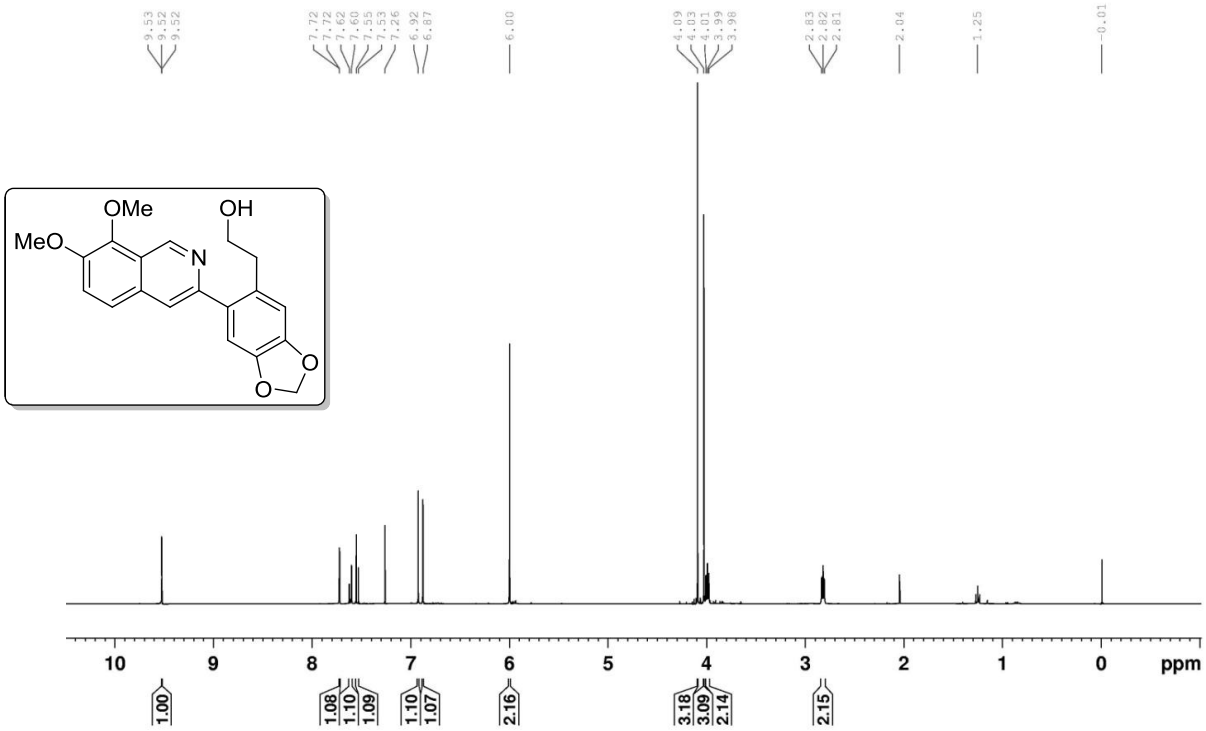
^{1}H NMR Spectrum of compound **42a**



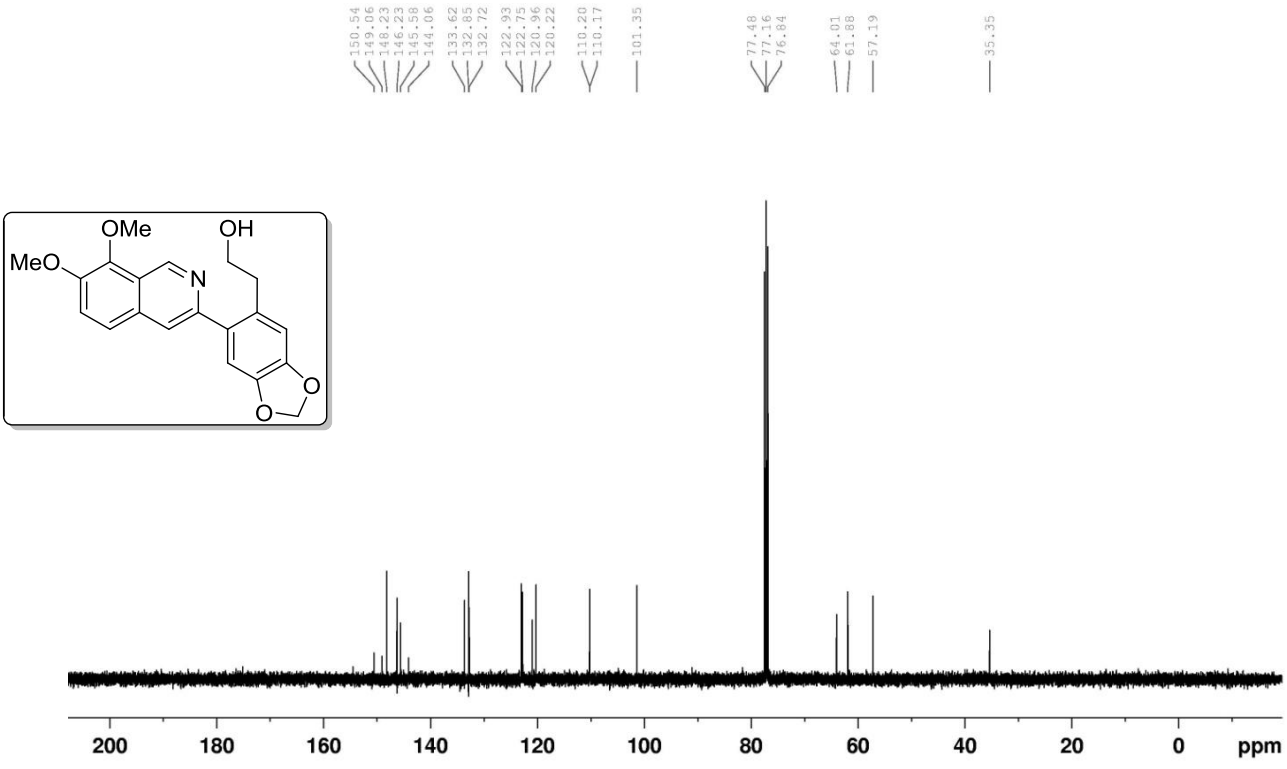
^{13}C NMR Spectrum of compound **42a**



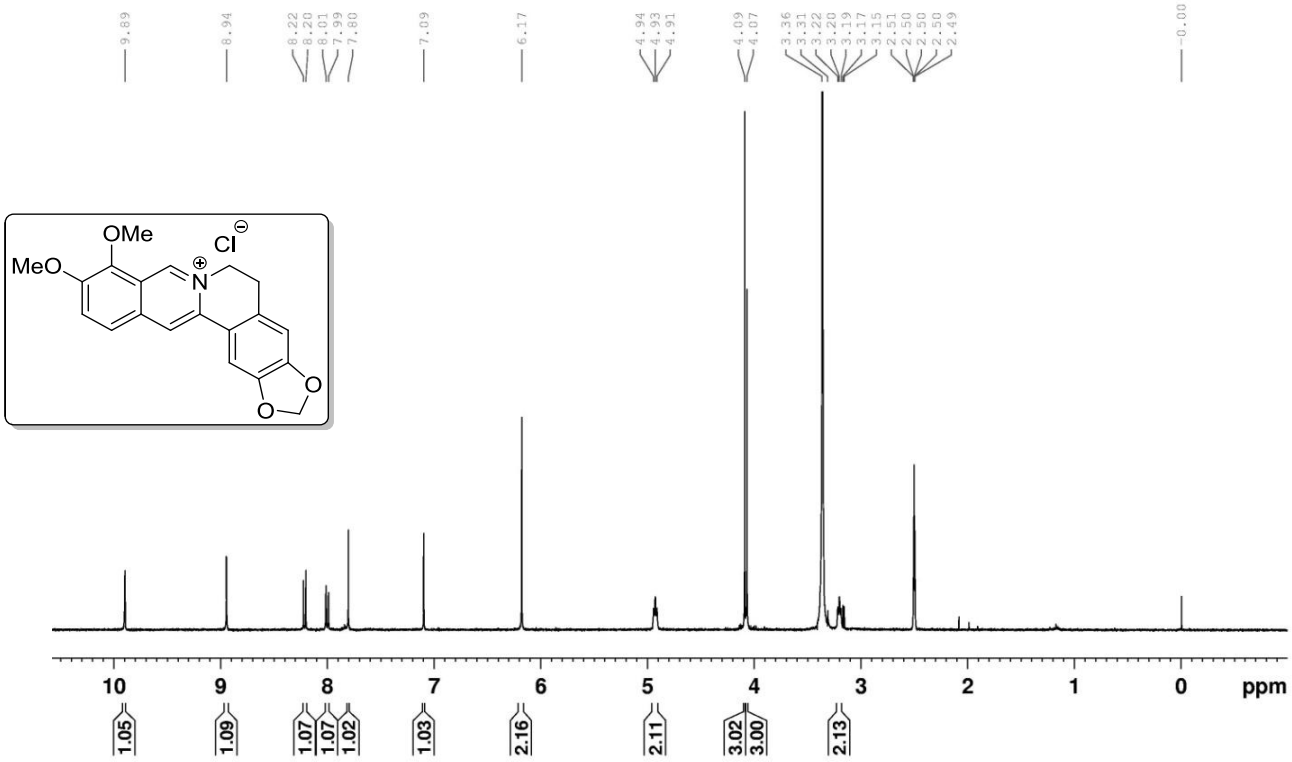
^{1}H NMR Spectrum of compound **53**



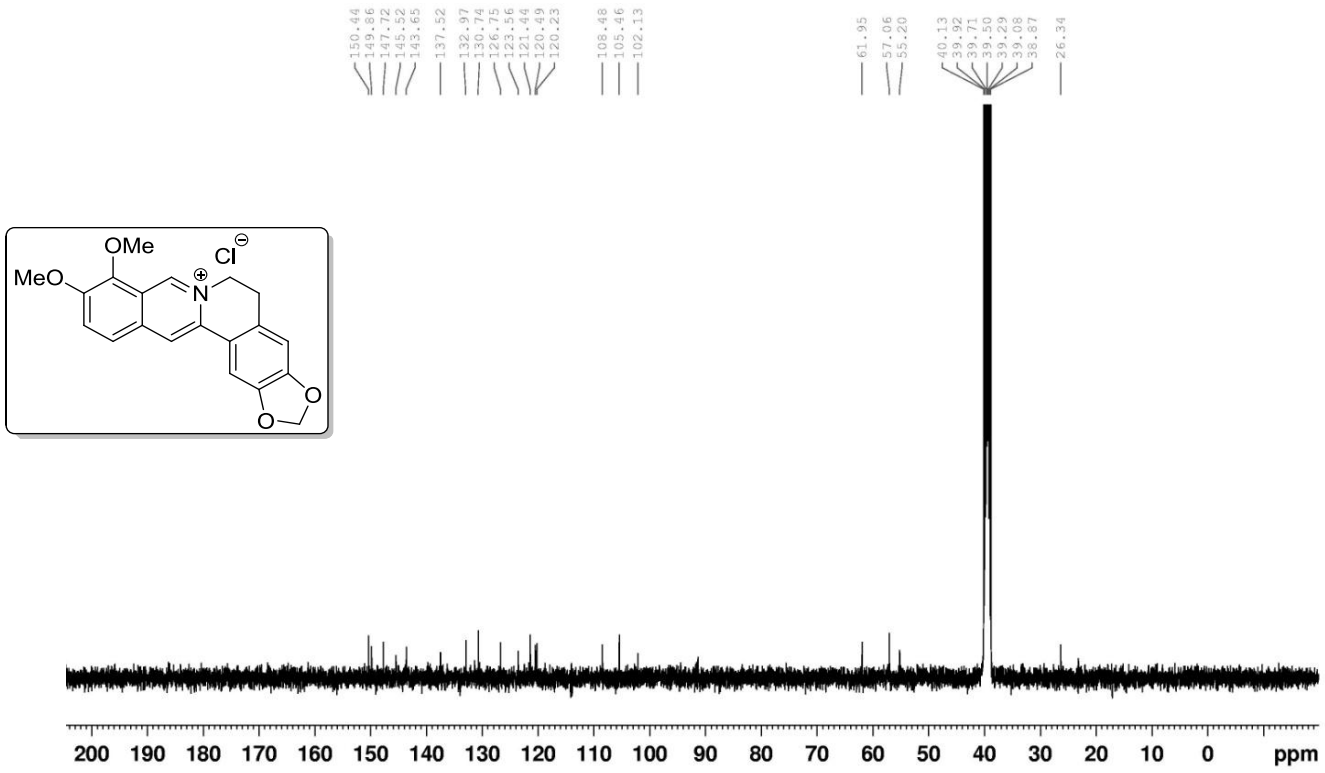
^{13}C NMR Spectrum of compound **53**



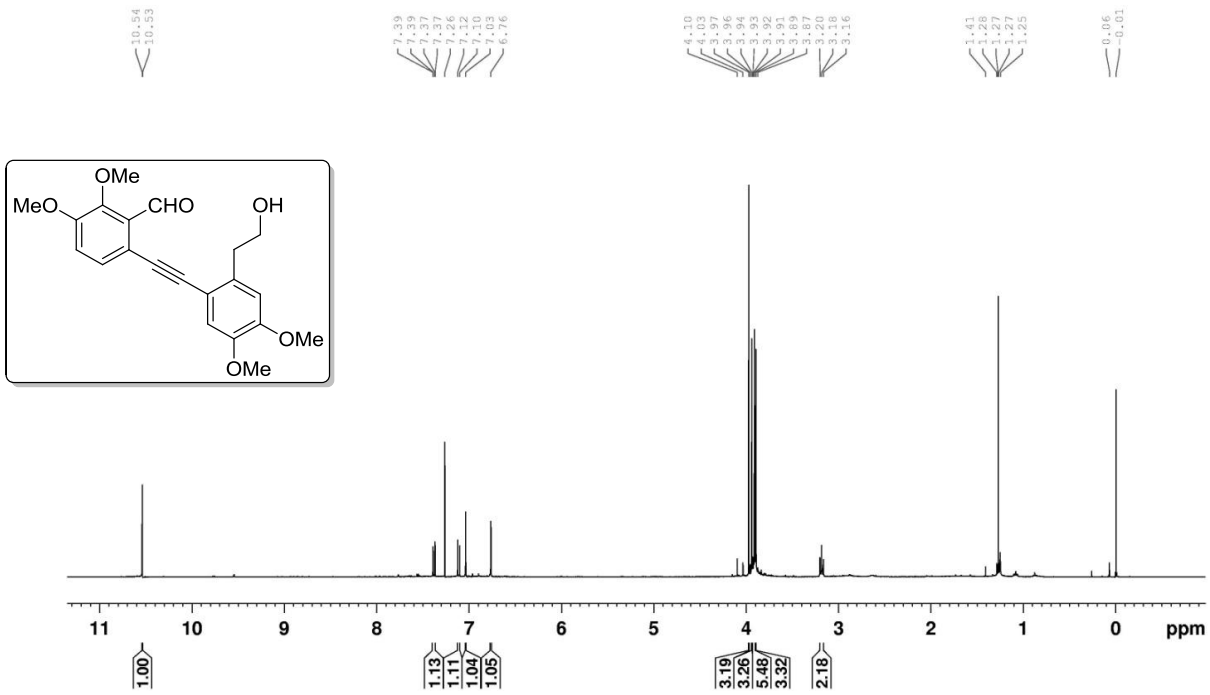
^{1}H NMR Spectrum of compound **1c**



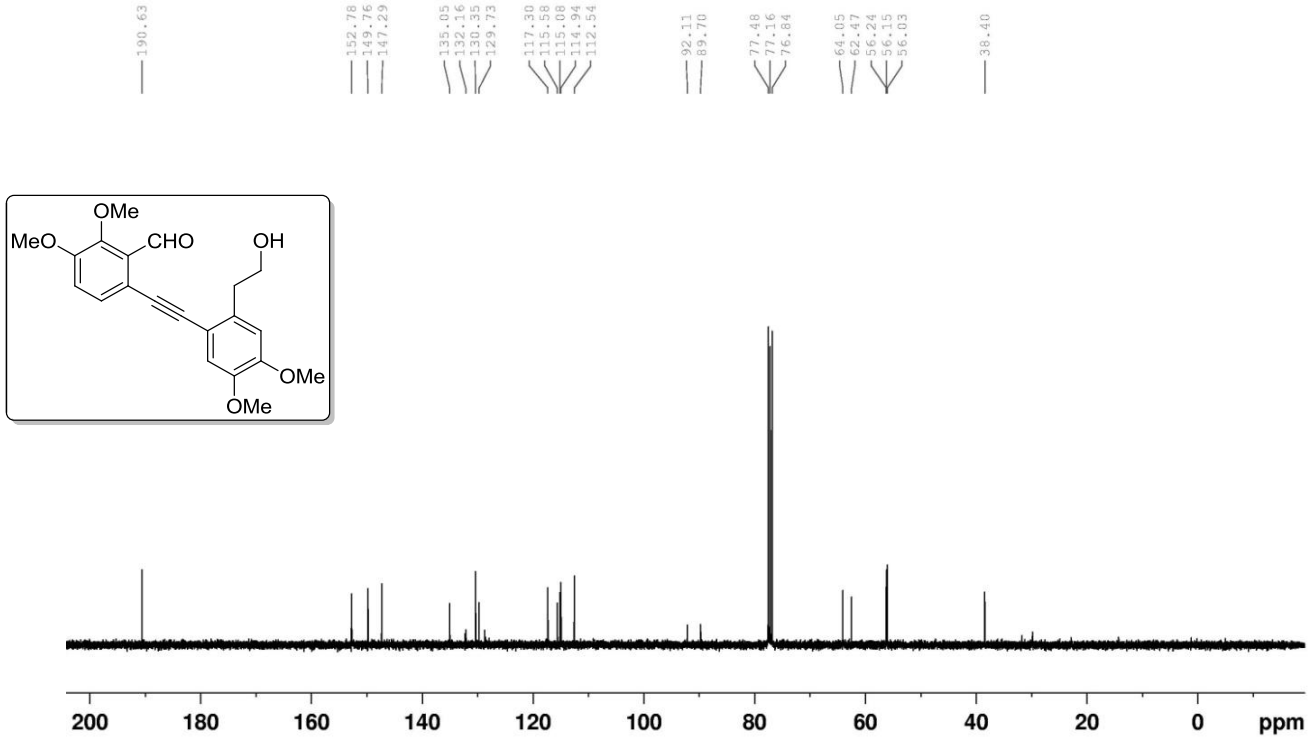
^{13}C NMR Spectrum of compound **1c**



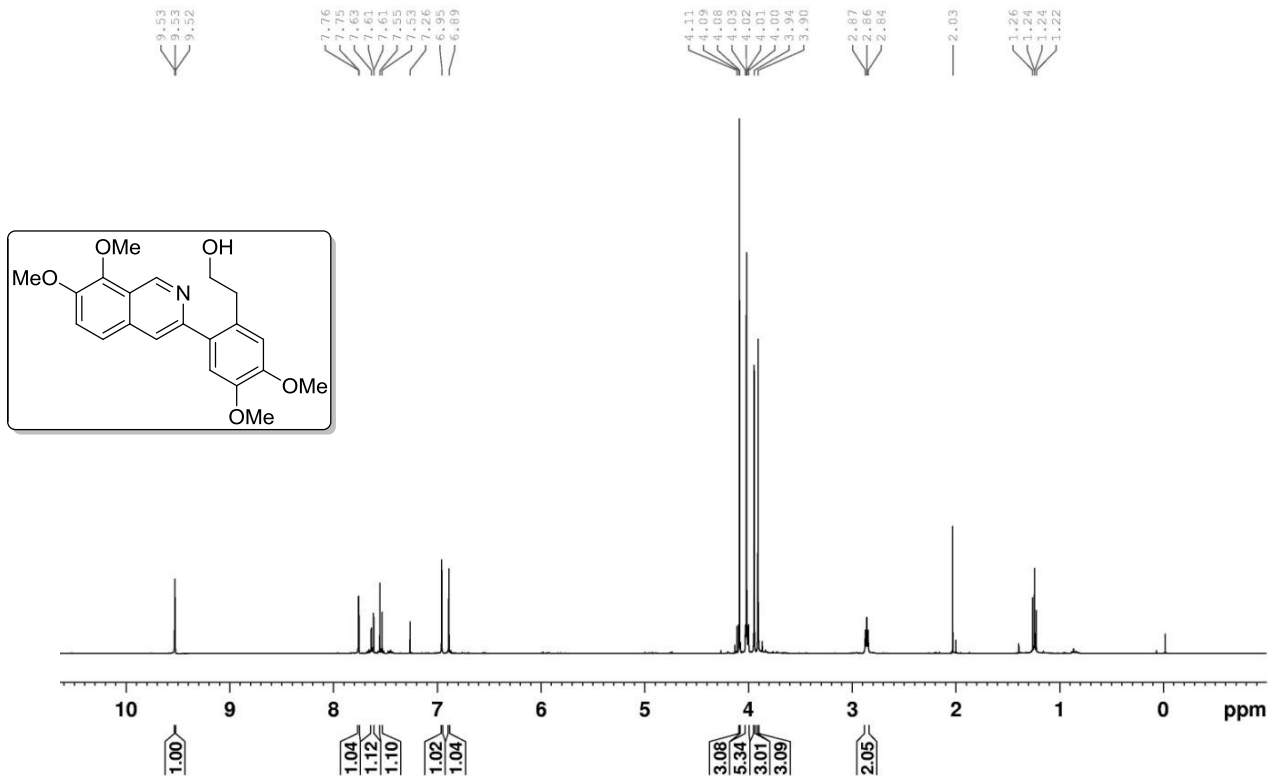
^{1}H NMR Spectrum of compound **42b**



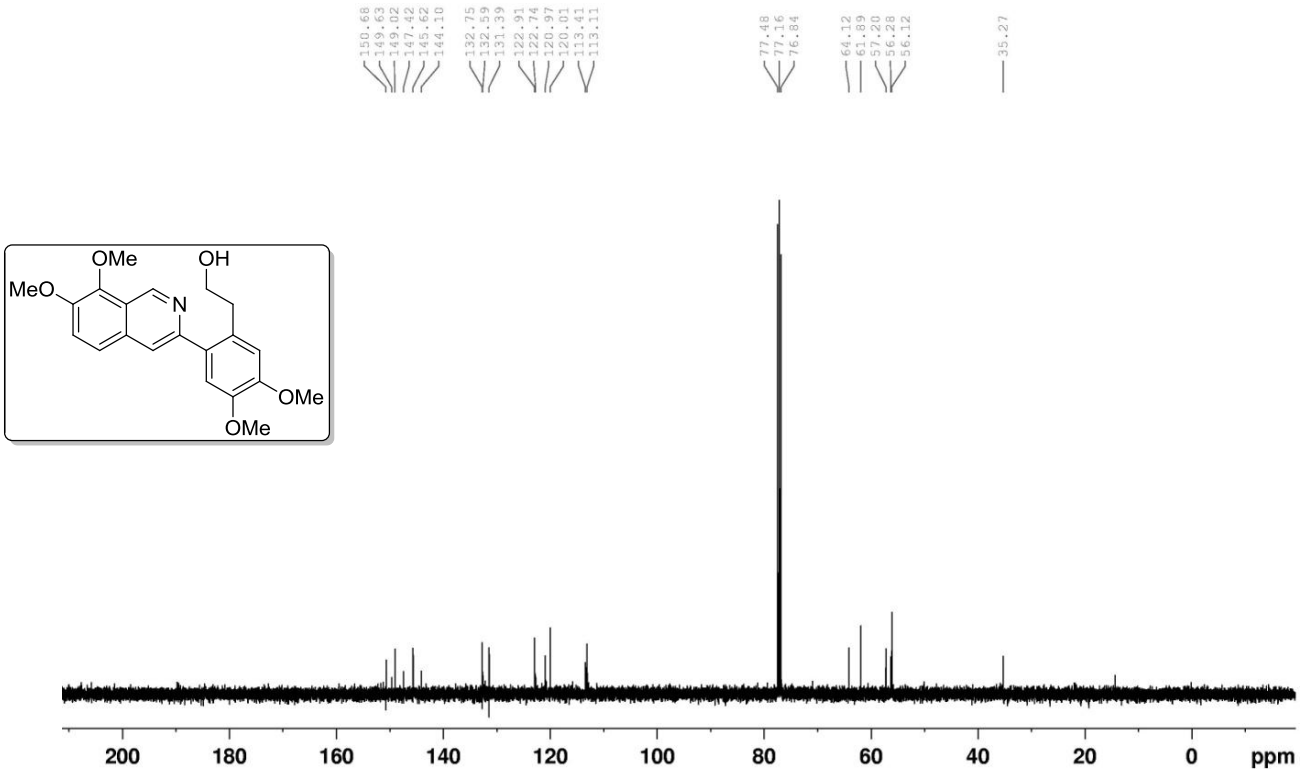
^{13}C NMR Spectrum of compound **42b**



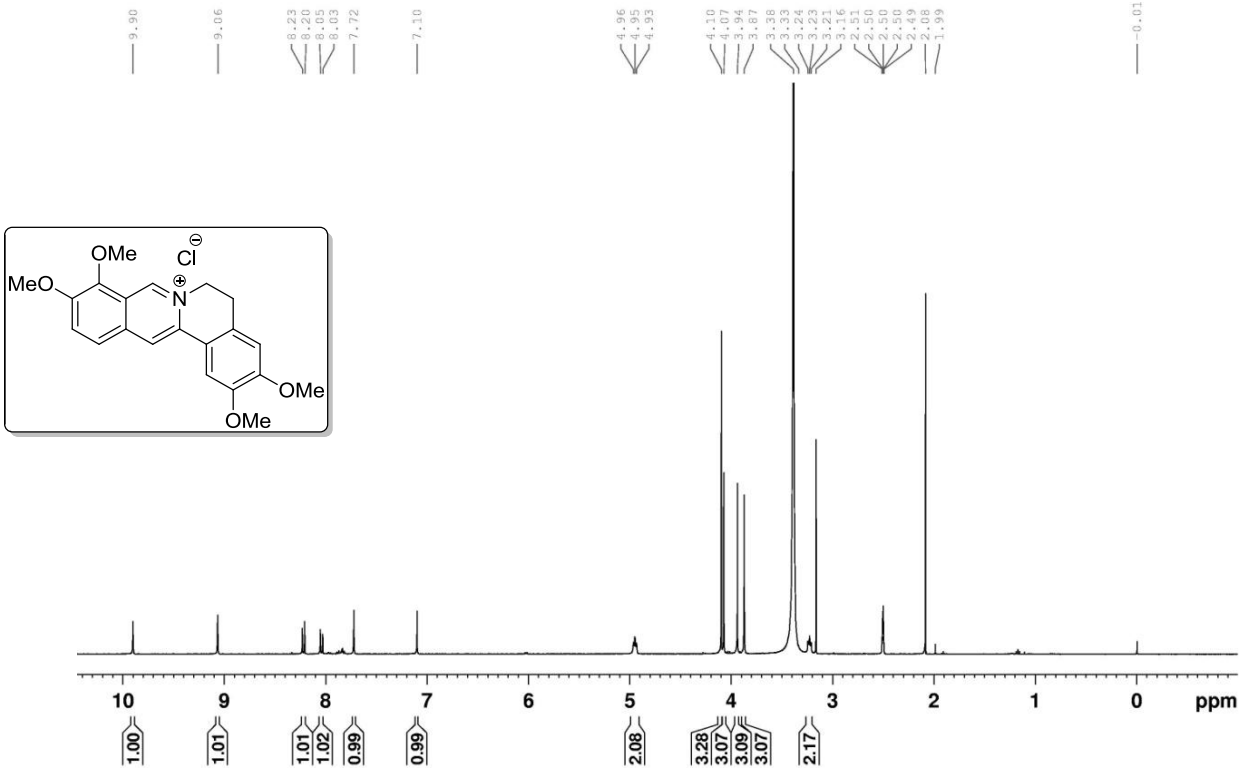
^{1}H NMR Spectrum of compound **56**



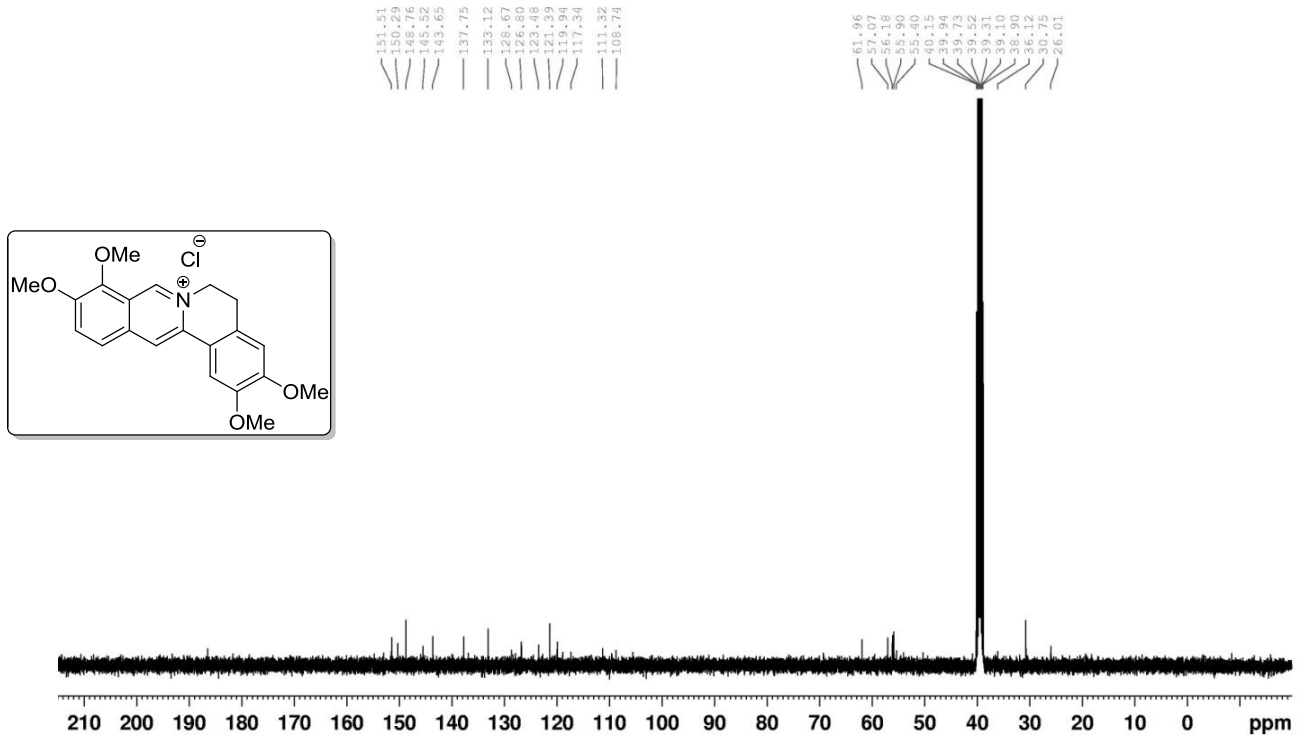
^{13}C NMR Spectrum of compound **56**



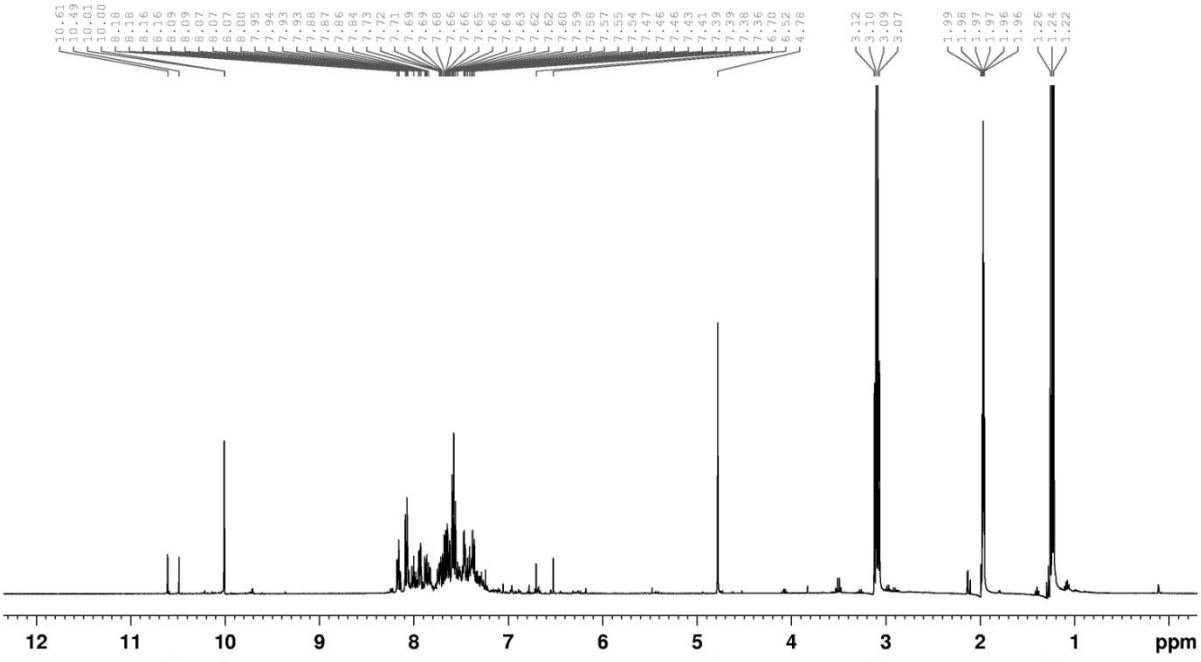
^{1}H NMR Spectrum of compound **1d**



^{13}C NMR Spectrum of compound **1d**



Spectra for the reaction of *o*-alkynyl benzaldehyde (34) with 1 equiv. $AgNO_3$



2.8) References

1) (a) Bentley, K. W. *Nat. Prod. Rep.* **1992**, *9,* 365; (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, **1998**: *Vol. 1*; (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev*. **2004**, *104,* 3341; (d) Kletsas, D.; Li, W.; Han, Z.; Papadopoulos, V. *Biochem. Pharmacol*. **2004**, *67*, 1927.

2) Grycova, L.; Doatal, J.; Marek, R. *Phytochemistry*, **2007**, *68*, 150.

3) (a) Kong, W. J.; Abidi, P.; Lin, M.; Inaba, S.; Li, C.; Wang, Y.; Wang. Z.; Si, S.; Pan, H.; Wang, S.; Wu, J.; Wang, Y.; Li, Z.; Liu, J.; Jiang, J.-D. *Nat. Med*. **2004,** *10*, 1344; (b) Pang, B.; Zhao, L.-H.; Zhou, Q.; Zhao, T.-Y.; Wang, H.; Gu, C.-J.; Tong, X.-L. *Int. J. Endocrinol*. **2015** (doi.org/10.1155/2015/905749).

4) (a) Letasiova, S.; Jantova, S.; Cipak, L.; Muckova, M. *Cancer Lett*. **2006**, *239*, 254; (b) Sun, Y.; Xun, Y.; Wang, Y.; Chen, X. *Anticancer Drugs* **2009**, *20*, 757.

5) Hayashi, K.; Minoda, K.; Nagaoka, Y.; Hayashi, T.; Uesatob, S. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 1562.

6) Park, K. D.; Lee, J. H.; Kim, S. H.; Kang, T. H.; Moon, J. S.; Kim, S. U. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 3913.

7) Iwasa, K.; Kim, H. S.; Wataya, Y.; Lee, D. U. *Eur. J. Med. Chem*. **1998**, *13*, 65.

8) Iwasa, K.; kamigauchi, M.; Ueki, M.; Taniguchi, M. *Eur. J. Med. Chem.* **1996**, *31*, 469.

9) Vennerstrom, J. L.; Lovelace, J. K.; Waits, V. B.; Hanson, W. L.; Klayman, D. L. *Antimicrob. Agents Chemother*, **1990**, *34*, 918.

10) Bodiwala, H. S.; Sabde, S.; Mitra, D.; Bhitani, K. K. *Eur. J. Med. Chem*. **2011**, *46*, 1045.

11) Kong, W. J.; Wei, J.; Zuo, Z. Y.; Wang, Y. M.; Song, D. Q.; You, X. F.; Zhao, L. X.; Pan, H. N.; Jiang, J. D. *Metabolism*, **2008**, *57*, 1029.

12) (a) Chang, Y. L.; Usami, S.; Hsieh, M. T.; Jiang, M. J. *Life Sci.* **1999**, *64*, 597; (b) Bhadra, K.; Kumar G. S. *Med. Res. Rev*. **2010**, 821; (c) Domont, E.; Monari, A. *J. Phys. Chem. B* **2015**, *119*, 410.

13) Vennerstorm, J. L.; Klayman, D. L. *J. Med. Chem*. **1988**, *31*, 1084.

14) (a) Fritsch, P. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 419; (b) Whaley, W. M.; Govindachari, T. R. in *Organic Reactions* (Eds: R. Adams), Wiley: New York, **1951**, *Vol 6*, pp 74.

15) (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903; (b) Sotomayor, N.; Dominguez, E. *J. Org. Chem*. **1996**, *61*, 4062.

16) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030; (b) Youn, S. W. *J. Org. Chem*. **2006**, *71*, 2521.

17) Tovar, J. D.; Swager, T. M. *J. Org. Chem*. **1999**, *64*, 6499.

18) (a) Numata, A.; Kondo, Y.; Sakamoto T. *Synthesis* **1999**, *2*, 306; (b) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull*. 1**999**, *47*, 1740; (c) Sakamoto, T.; Numata, A.; Kondo, Y. *Chem. Pharm. Bull*. **2000**, *48*, 669; (d) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Eur. J. Org. Chem*. **1999**, 3117; (e) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, *16*, 2477; (f) Abbiati, G.; Arcadi, A.; Beccalli, E.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331; (g) Chandra, A.; Singh, B.; Upadhyay, S.; Singh, R. M. *Tetrahedron* **2008**, *64*, 11680; (h) Arbaciauskiene, E.; Martynaitis, V.; Krikstolaityte, S.; Holzer, W.; Sackusa, A. *Arkivoc*, **2011**, (*xi*) 1; (i) Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A.; Sayed El-Ahl, A. A. *Arkivoc*, **2012**, (*i*) 211.

19) (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (b) Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852.

20) (a) Dell'Acqua, M.; Abbiati, G.; Arcadi, A.; Rossi, E. *Org. Biomol. Chem.* **2011**, *9*, 7836; (b) Long, L.; Qiongyou, W.; Shaowei, H.; Guangfu, Y. *Chin. J. Chem.* **2012**, *30*, 1075.

21) (a) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720; (b) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett*. **2009**, *50*, 3651.

22) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem*. **2009**, *74*, 2893.

23) (a) Roesch, K. R.; Larock, R. C. *Org. Lett*. **1999**, *1*, 553; (b) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035; (c) Dai, G.; Larock, R. C. *J. Org. Chem*. **2002**, *67*, 7042; (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86; (e) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003,** *68*, 980; (f) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1061.

24) (a) Chaitanya, T. K.; Nagarajan, R. *Org. Biomol. Chem*. **2011**, *9*, 4662; (b). Prakash, K. S.; Nagarajan, R. *Org. Lett*. **2014**, *16*, 244.

25) (a) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett*. **2008**, 0924; (b) Hwang, S.; Lee, Y.; Lee, P. H.; Shin, S. *Tetrahedron Lett.* **2009**, *50*, 2305.

26) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850.

27) Yu, X.; Wu, J. *J. Comb. Chem*. **2009**, *11*, 895.

28) Ding, Q.; Wang, D.; Sang, X.; Lin, Y.; Peng, Y. *Tetrahedron* **2012**, *68*, 8869.

29) (a) Ding, Q.; Wang, D.; Luo, P.; Liu, M.; Pu, S.; Zhou, L. *Beilstein J. Org. Chem*. **2013**, *9*, 1949; (b) Xiao, Q.; Sheng, J.; Ding, Q.; Wu, J. *Eur. J. Org. Chem*. **2014**, 217.

30) (a) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun*. **2009**, 3469; (b) Yu, X.; Ding, Q.; Chen, Z.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 4279; (c) Chen, Z.; Ding, Q.; Yu, X.; Wu, J. *Adv. Synth. Catal*. **2009**, *351*, 1692; (d) Zhou, X.; Liu, M.; Luo, P.; Lai, Y.; Yang, T.; Ding, Q. *Beilstein J. Org. Chem*. **2014**, *10*, 2286.

31) Ghavtadze, N.; Frohlich, R.; Wurthwein, E.-U. *Eur. J. Org. Chem*. **2010**, 1787.

32) For reviews see: He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang. C. *Tetrahedron Lett*. **2014**, *55*, 5705.

33) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun C.-H. *Org. Lett*. **2003**, *5*, 2759.

34) (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett*. **2007**, *9*, 1407; **(**b) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *130*, 16474; (c) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun*. **2009**, 5141; (d) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc*. **2009**, *131*, 12050.

35) (a) Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem*. **2009**, *74*, 9359; (b) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal*. **2011**, *353*, 719; (c) Hyster, T. K.; Rovis, T. *Chem. Commun*. **2011**, *47*, 11846; (d) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem*. **2012**, *77*, 5794.

36) (a) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan M. *Org. Lett*. **2012**, *14*, 3032; (b) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem*. **2012**, *77*, 9190.

37) (a) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett*. **2010**, *12*, 5688; (b) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem*. **2011**, *76*, 6159.

38) (a) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc*. **2012**, *134*, 19592; (b) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.

39) Zhao, D.; Lied, F.; Glorius, F. *Chem. Sci*. **2014**, *5*, 2869.

40) (a) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett*. **2013**, *15*, 5750; (b) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem*. **2014**, *79*, 1025; (c) Zhang, S.; Huang, D.; Xu, G.; Cao, S.; Wang, R.; Peng, S.; Sun, J. *Org. Biomol. Chem*. **2015,** *13*, 7920.

41) Nishimoto, Y.; Takeuchi, M.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 1051.

42) (a) Park, H. J.; Bhilare S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228; (b) Zhu, S.; Zhang, Z.; Huang, X.; Jiang, H.; Guo, Z. *Chem. Eur. J*. **2013**, *19*, 4695.

43) Bhadra, K.; Kumar, G. S. *Med. Res. Rev*. **2011**, *31*, 821.

44) Kametni, T.; Noguchi, I.; Saito, K.; Kaneda, S. *J. Chem. Soc. C*, **1969**, 2036.

45) Gatland, A. E.; Pilgrim, B. S.; Procopiou, P. A.; Donohoe, T. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 14555.

46) Treu, M.; Jordis, U. *Molecules* **2002**, *7*, 374.

47) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311.

48) Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem*. **2011**, *76*, 6414.

49) (a) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507; (b) Wu, G.; Cederbaum, F. E.; Negishi, E. I. *Tetrahedron, Lett*. **1990**, *31*, 493.

50) Appel, R. *Angew. Chem. Int. Ed*. **1975**, *14*, 801.

51) (a) Varela-Fernandez, A.; Garcia-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saa, *Angew. Chem. Int. Ed*. **2010**, *49*, 4278; (b) Giese, M. W.; Moser, W. H. *J. Org. Chem*. **2005**, *70*, 6222.

52) Dhara, S.; Singha, R.; Nuree, Y.; Ray, J. *Tetrahedron Lett.* **2014**, *55*, 795.

53) Gao, H.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 85.

54) Arambasic, M.; Hooper, J. F.; Willis, M. C. *Org. Lett*. **2013**, *15*, 5162.

Chapter 3

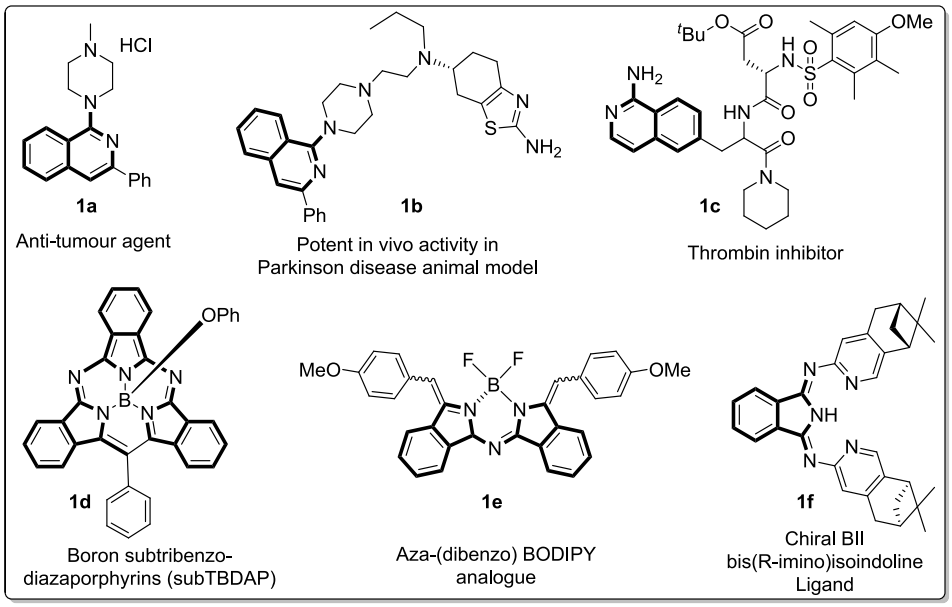
Catalyst-controlled regioselective approach to 1-aminoisoquinolines and/or 1-aminoisoindolines under solvent free condition

In this chapter, the regioselective synthesis of 1-aminoisoquinoline and 1-aminoisoindoline has been discussed**.** This chapter also includes a general introduction on the synthesis of 1-aminoisoquinolines as well as 1-aminoisoindolines.

3.1) Introduction

In the isoquinoline family, 1-aminoisoquinoline is a dominant class of compounds possessing staggering biological and pharmacological activities (Figure 1).[1] Due to their biological importance, compounds having 1-aminoisoquinoline scaffold are potent candidates in medicinal chemistry. The biological activities exhibited include, among others, antitumor cytotoxicity,[2] inhibition of activity towards adenosine A3 receptor,[3] PDE4 inhibition for the treatment of dry eyes,[4] mutant B-Raf enzyme[5] and antimycobacterial activity[6] (Fig. 1).

Figure 1: Importance of 1-aminoisoquinolines and 1-aminoisoindolines

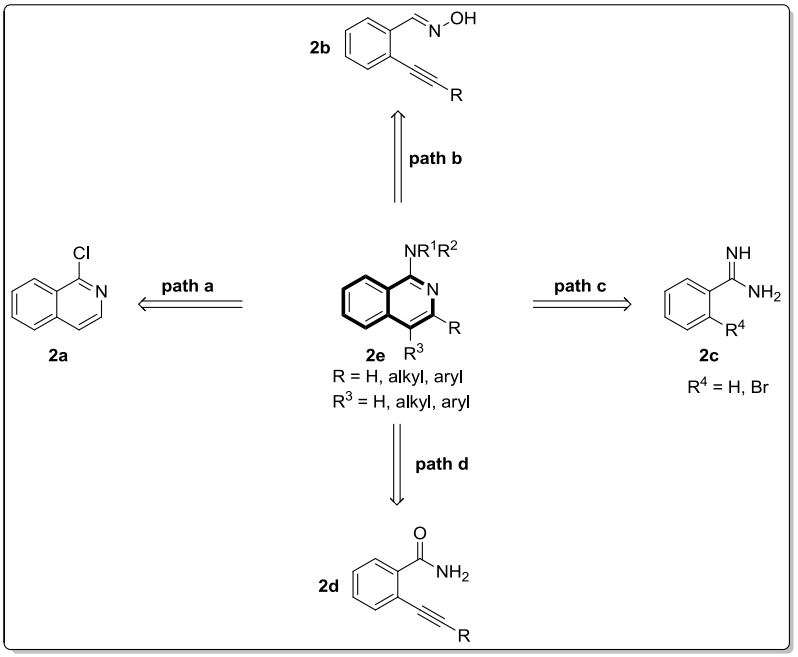


The 1-aminoisoquinoline containing compounds also shows remarkable in vivo activity of Parkinson disease in animals.[7] Especially, 1-piperazinyl isoquinolines or piperazinyl derivatives are extremely useful in medicinal chemistry (Fig. 1).[1a-b, 6, 7] Apart from the above mentioned biological importance, 1-aminoisoquinolines are also considered as efficient synthons for the construction of different heterocycles.[8] Unlike 1-aminoisoquinolines, 1-aminoisoindoles are less effective in medicinal chemistry[9] but they are very useful in the synthesis of hybrid macrocycles[10] and modified aza-BODIPY analogues.[11] Furthermore, 1-aminoisoquinolines also serve as ligands in transition metal catalysis (Fig. 1).[12]

3.2) Literature reports for the synthesis of 1-aminoisoquinoline derivatives

There are four major strategies developed for the synthesis of 1-aminoisoquinolines, which are depicted in Scheme 1.

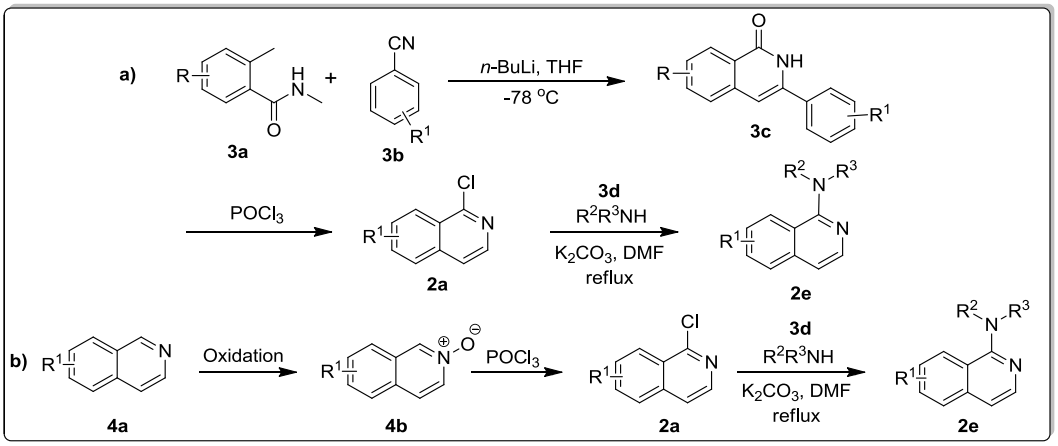
Scheme 1: Major approaches for the synthesis of 1-aminoisoquinolines



Herein we have discussed the related literature reports on the synthesis of 1-aminoisoquinolines and 1-aminoisoindolines respectively. The most accessible and convenient method for the synthesis of 1-aminoisoquinoline is the direct addition of the amine to 1-haloisoquinolines either under a metal-free condition or through a transition metal catalyzed cross coupling reaction **(Scheme 1: Path a)**.

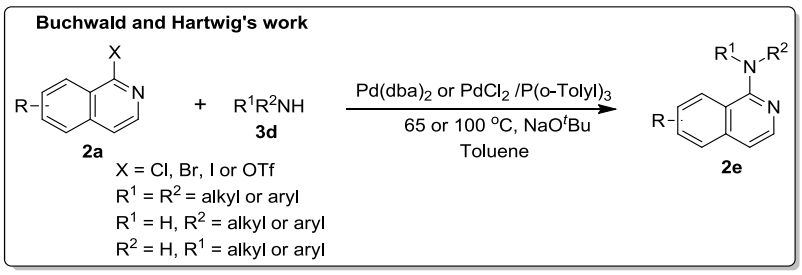
The treatment of *N*-methyl *o*-toluamide (**3a**) with a wide range of benzonitriles (**3b**) in the presence of *n*-BuLi afforded the lactam **3c** and subsequent reaction with phosphoryl chloride gives the 1-chloroisoquinoline (**2a**). Furthermore, the treatment of 1-chloroisoquinoline (**2a**) with different amines (**3d**) in the presence of base at reflux condition generated the 1-aminoisoquinoline (**2e**) in good yields (a, Scheme 2).[2,7,13] Another one, in which the 1-haloisoquinoline (**2a**) could be synthesized is through the oxidation of the corresponding isoquinoline **4a** to its isoquinoline *N*-oxides **4b** followed by the treatment with phosphoryl chloride, which then refluxed with amines to give the 1-aminoisoquinoline (**2e**) in good yields (b, Scheme 2).[14]

Scheme 2: Metal-free synthesis of 1-aminoisoquinolines (**2e**)



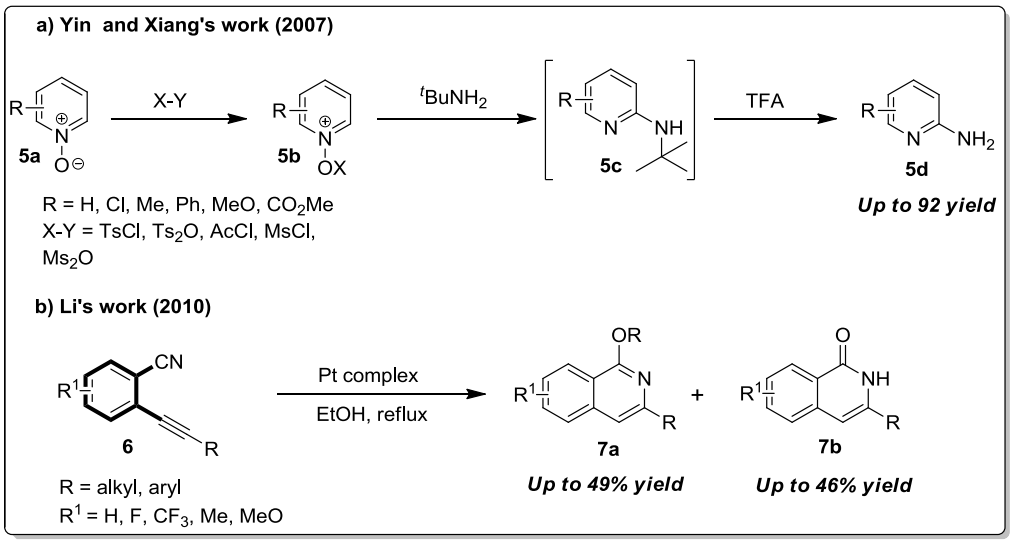
Another interesting approach has been developed by Buchwald and Hartwig, a transition metal catalyzed C-N cross coupling approach between amines (**3d**) and halo-isoquinolines (**2a**) for the synthesis of 1-aminoisoquinolines (**2e**) (Scheme 3).[15] After the ground-breaking work by Buchwald and Hartwig in the field of Pd-catalyzed C-N cross coupling reactions, the field has grown remarkably just by varying the ligands.[16]

Scheme 3: Metal catalyzed C-N cross-coupling



Although the metal-free or transition metal catalyzed synthesis of 1-aminoisoquinolines (**2e**) *via* 1-haloisoquinoline intermediate **2a** was found to be a facile and functional group tolerant protocol, it suffers from drawbacks such as harsh reaction conditions and the generation of 1-chloroisoquinolines (**2a**), which involves the use of highly corrosive reagents ($POCl_3$). Alternative methods have been developed to circumvent these drawbacks. A metal-free protocol has been developed by Yin and Xiang's group. The treatment of *p*-toluenesulfonic anhydride with pyridine *N*-oxides (**5a**) resulted in the formation of O-tosyl pyridine **5b** followed by nucleophilic addition of *tert*-butylamine and in situ deprotection with trifluoroacetic acid gave the respective aminopyridine derivatives (**5d**) in moderate to excellent yields. This protocol was also applied to quinoline and isoquinoline *N*-oxides and obtained the corresponding aminoquinolines or isoquinolines in excellent yields (a, Scheme 4).[17a] In 2010, Li and coworkers reported a synthesis of 1-alkoxy isoquinolines (**7a**) and isoquinolones (**7b**) from the annulation of *o*-alkynyl benzonitriles (**6**) catalyzed by platinum (b, Scheme 4).[17b]

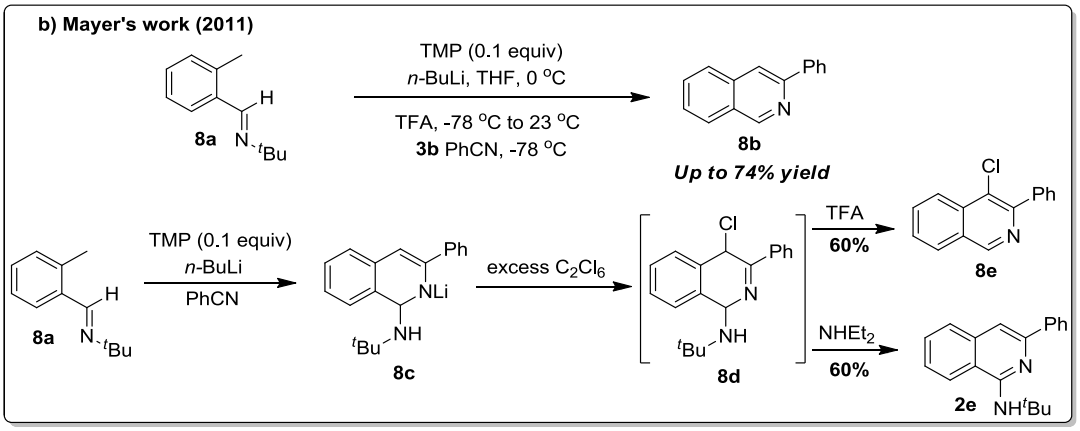
Scheme 4: Alternative approaches for 1-amino isoquinolines and 1-alkoxy isoquinolines



Recently, an interesting approach has been developed for the synthesis of isoquinolines (**8b**) by the reaction of *o*-tolualdehyde *tert*-butylimines (**8a**) with a stoichiometric amount of *n*-BuLi in the presence of benzonitriles (**3b**) and 2,2,6,6-tetramethylpiperidine in THF (Scheme 5). In the same paper, they have also reported the synthesis of 1-*tert*-butyl amino isoquinoline (**2e**) by the treatment of compound **8c** with excess hexachloroethane giving the chloro intermediate **8d**, which then reaction with acid or

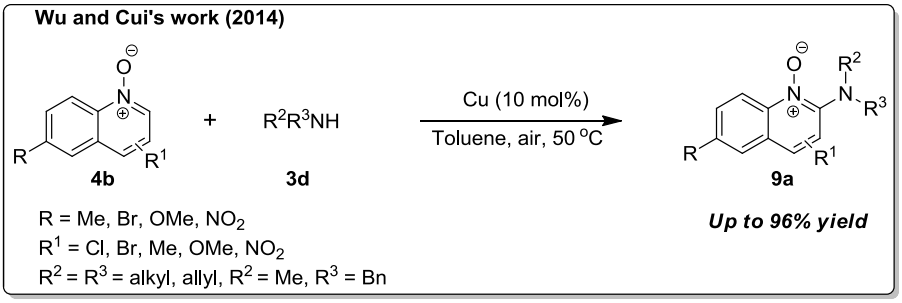
treatment with diethylamine afforded 4-chloroisoquinoline (**8e**) or 1-aminoisoquinoline (**2e**) respectively (Scheme 5).[18]

Scheme 5: The synthesis of 1-aminoisoquinoline (**2e**)



Very recently, Wu and Cui described the Cu-catalyzed efficient and mild synthesis of aminoisoquinoline *N*-oxides (**9a**) in moderate to excellent yields. When further elaborated to isoquinoline, quinoxaline and 1,10-phenanthroline *N*-oxides, desired products were obtained in good to excellent yields (Scheme 6).[19]

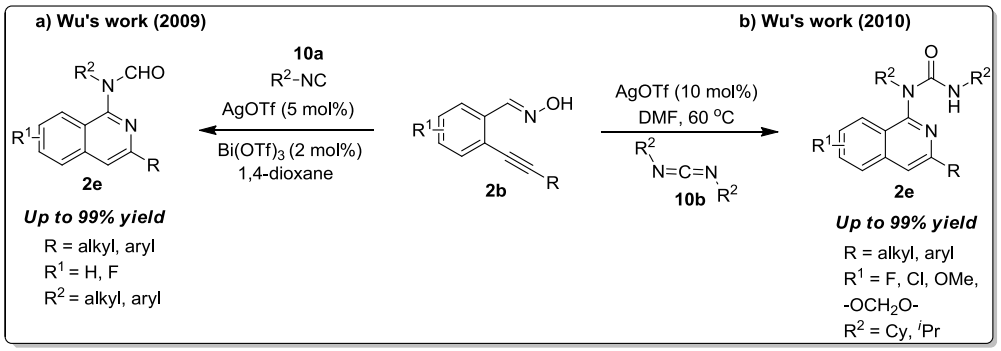
Scheme 6: Cu-catalyzed synthesis of aminoquinoline *N*-oxides (**9a**)



Apart from the above protocols, other approaches have also been reported. The one-pot domino cyclization of *o*-alkynyl benzaldoximes (**2b**) with different electrophiles gave the corresponding 1-amino isoquinolines (**2e**) **(Scheme 1: Path b)**.[20] Based on the literature reports, Wu and other groups started exploring the domino cyclizations of 2-alkynyl benzaldoximes (**2b**) with various coupling partners. Wu has developed the Ag/Bi co-catalyzed new protocol for the synthesis of *N*-(isoquinolin-1-yl)formamides (**2e**) by the domino cyclization of aldoxime derivatives (**2b**) and isocyanides (**10a**) (a, Scheme 7).[21a] The same group has also developed a facile approach to 1-aminoisoquinolines (**2e**) by changing

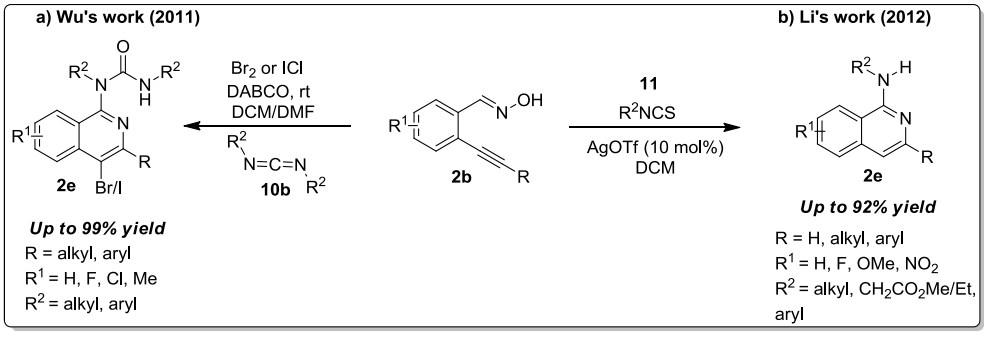
only the coupling partners. A silver-catalyzed synthesis of 1-aminoisoquinoline derivatives (**2e**) by the reaction between benzaldoximes (**2b**) and carbodiimides (**10b**) at elevated temperature has also been developed (b, Scheme 7).[21b]

Scheme 7: Synthesis of 1-aminoisoquinolines (**2e**) *via* annulation of *o*-alkynyl benzaldoximes (**2b**)



A one-pot three-component reaction to access isoquinoline containing urea derivatives has been developed by Wu's group. The reaction has been carried out between 2-alkynyl benzaldoximes (**2b**) and carbodiimides (**10b**) with electrophiles (Br or iodine monochloride) (a, Scheme 8) to access the isoquinoline derivatives (**2e**).[22a] Li and co-workers reported the silver-catalyzed synthesis of 1-aminoisoquinolines (**2e**) in good to excellent yields *via* domino electrophilic cyclization of benzaldoximes (**2b**) with isothiocyanates (**11**) at room temperature (b, Scheme 8).[22b, c]

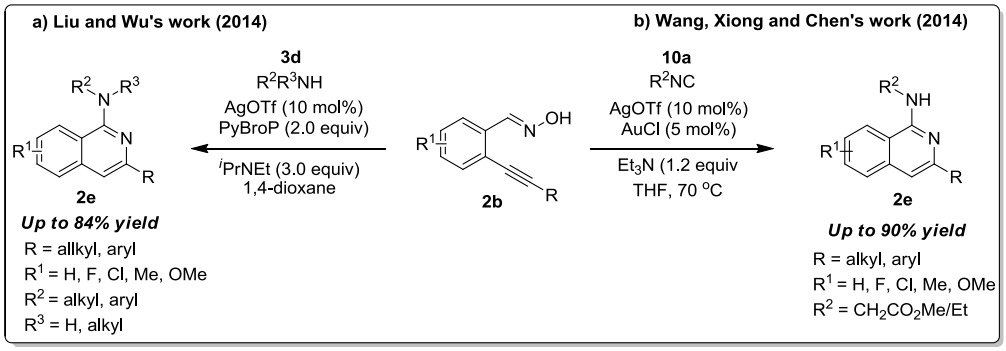
Scheme 8: Synthesis of 1-aminoisoquinolines (**2e**) *via* annulation of *o*-alkynyl aldoximes



In 2014, Liu and Wu's group demonstrated the silver-catalyzed reaction between *o*-alkynyl benzadloximes (**2b**) with amines (**3d**) leading to the formation of 1-aminoisoquinolines (**2e**) in good yields. It was found that the

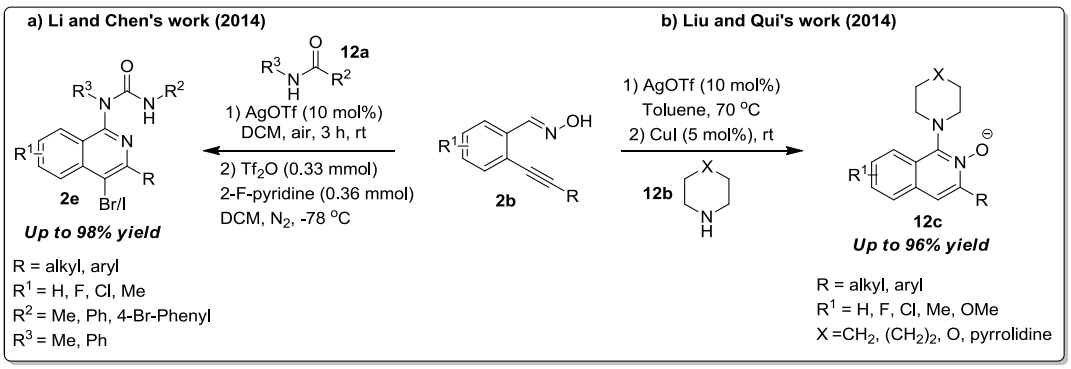
bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP) plays a crucial role in this transformation (a, Scheme 9).[23a] Another approach describes the coinage metal (Ag/Au) co-catalyzed treatment of aldoximes (**2b**) with isocyanoacetates (**10a**) affording 1-aminoisoquinoline (**2e**) in good to excellent yields (b, Scheme 9).[23b]

Scheme 9: Synthesis of 1-aminoisoquinolines (**2e**) *via* annulation of *o*-alkynyl aldoximes (**2b**)



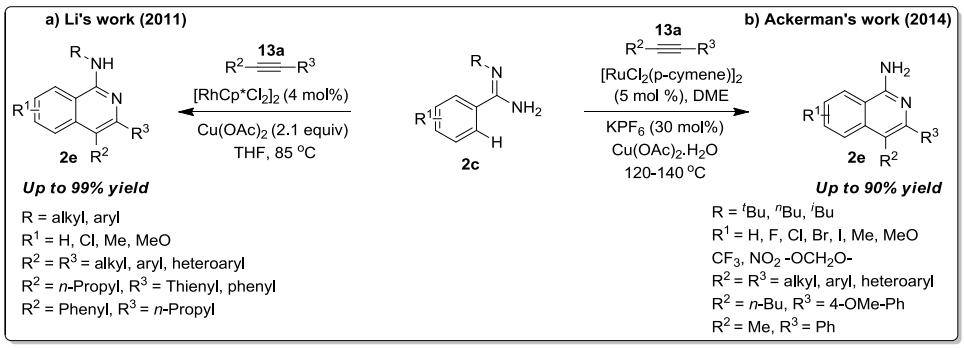
Li and Chen developed a silver triflate catalyzed and trifluoromethane sulfonic anhydride assisted novel protocol for the synthesis 1-(*N*-acyl)-isoquinolines (**2e**) by the electrophilic domino cyclization of *o*-alkynyl aldoximes (**2b**) with amides (**12a**) in good to excellent yields. Unfortunately, in the case of aliphatic alkynes, the reaction either gave traces of product or did not work (a, Scheme 10).[24a] Based on Wu and Cui's work (Scheme 6), Liu and Qui developed a Ag/Cu co-catalyzed mild approach for the synthesis of 1-aminoisoquinoline *N*-oxides (**12c**) through annulation of *o*-alkynyl benzaldoximes (**2b**) with cyclic secondary amines (**12b**) (b, Scheme 10).[24b]

Scheme 10: Synthesis of 1-aminoisoquinolines (**2e**) and *N*-oxides (**12c**) *via* annulations of *o*-alkynyl aldoximes (**2b**)



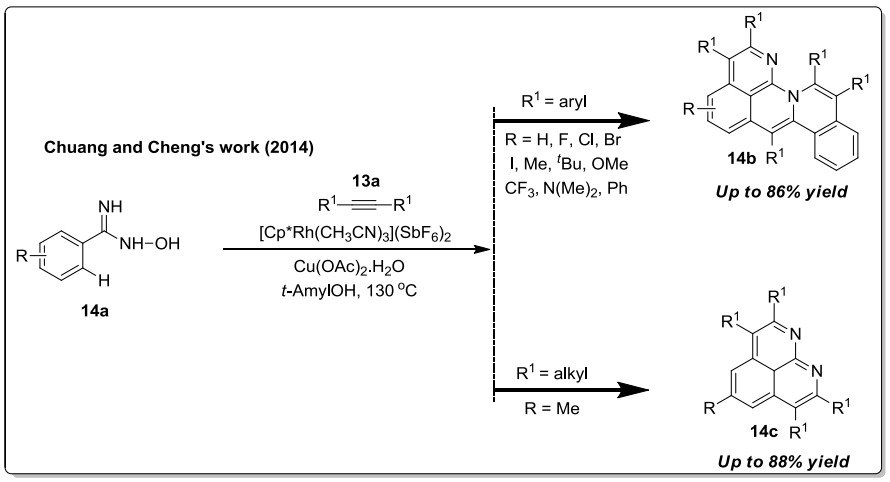
Apart from the above mentioned methods, Rh and Ru-catalyzed synthesis of 1-aminoisoquinolines (**2e**) *via ortho* C-H activation route has also attracted the attention of the scientific world **(Scheme 1: Path c).** In 2011, Li and co-workers envisioned the oxidative Rh-catalyzed synthesis of 1-aminoisoquinolines (**2e**) by the treatment of *N*-alkyl or aryl benzamidines (**2c**) with internal alkynes (**13a**) *via* C-H activation strategy. In the case of unsymmetrical alkynes, pent-1-yn-1-ylbenzene afforded the two regioisomers in 59% yield in a 4:1 ratio but interestingly the case of 2-(pent-1-yn-1-yl)thiophene only got a single isomer in 57% yield. In both the cases, the aryl group was preferably placed at the 3-position of isoquinoline (a, Scheme 11).[25a] Similarly, Ruthenium was also found to be capable of synthesizing the 1-aminoisoquinolines (**2e**) *via* C-H activation. Recently, Ackerman's group described a unique method for the synthesis of pharmaceutically important 1-aminoisoquinolines (**2e**) through Ru-catalyzed C-H bond functionalization of amidines (**2c**) with internal alkynes (**13a**) (b, Scheme 11).[25b] The reaction was found to be highly regioselective in the case of unsymmetrical alkynes as the aryl group was placed at the 3-position of isoquinolines.

Scheme 11: Rh and Ru-catalyzed oxidative C-H functionalization of amidines with alkynes



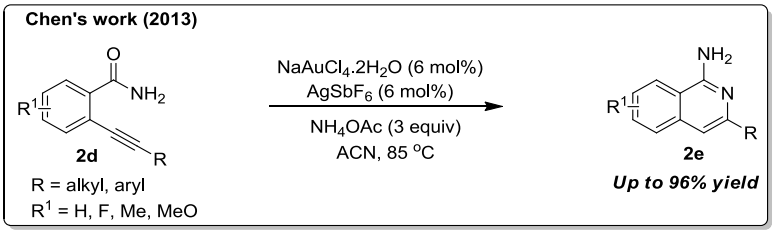
Recently, a novel and facile work has been done by Chuang and Cheng's group for the synthesis of naphthyridine-based polyheteroaromatic (**14b**) systems *via* Rh-catalyzed oxidative C-H activation followed by sequential annulation reaction. The reaction between *N*-hydroxybenzamidines (**14a**) and symmetric diaryl alkynes (**13a**) afforded the benzo(isoquinolino) naphthyridines (**14b**) and symmetric dialkyl alkynes gave the benzonaphthyridines (**14c**). The above mentioned protocol is the first report for the synthesis of benzo(isoquinolino)naphthyridines *via* Rh-catalyzed C-H activation of multiple bonds followed by one-pot annulations (Scheme 12).[26]

Scheme 12: Rh-catalyzed synthesis of polyheteroaromatic compounds *via* C-H activation



A few more approaches are also known for the synthesis of 1-aminoisoquinoline (**2e**) by the domino cyclization of *o*-alkynyl benzamides (**2d**) with suitable reaction partners **(Scheme 1: Path d)**. In 1999, Swager and coworkers reported the TfOH acid mediated synthesis of isoquinoline and 1-aminoisoquinoline by the treatment of *o*-alkynyl benzaldehydes with ammonium acetate *via* pyrylium intermediate (Chapter 2, Scheme 3, ref. no. 17). Chen and coworkers developed a unique protocol for the synthesis of medicinally privileged scaffolds by the cyclization of *o*-alkynyl benzamides (**2d)** with ammonium acetate mediated by the gold (III) catalyst. The aldehydes derived from TMS protected alkyne or terminal alkyne were not compatible under the standard reaction condition (Scheme 13).[27] One-pot domino cyclization with high atom economy, good functional group tolerance, and mild reaction conditions made these protocols more demanding over the conventional methods.

Scheme 13: Gold mediated synthesis of 1-aminoisoquinoline from *o*-alkynyl benzamides

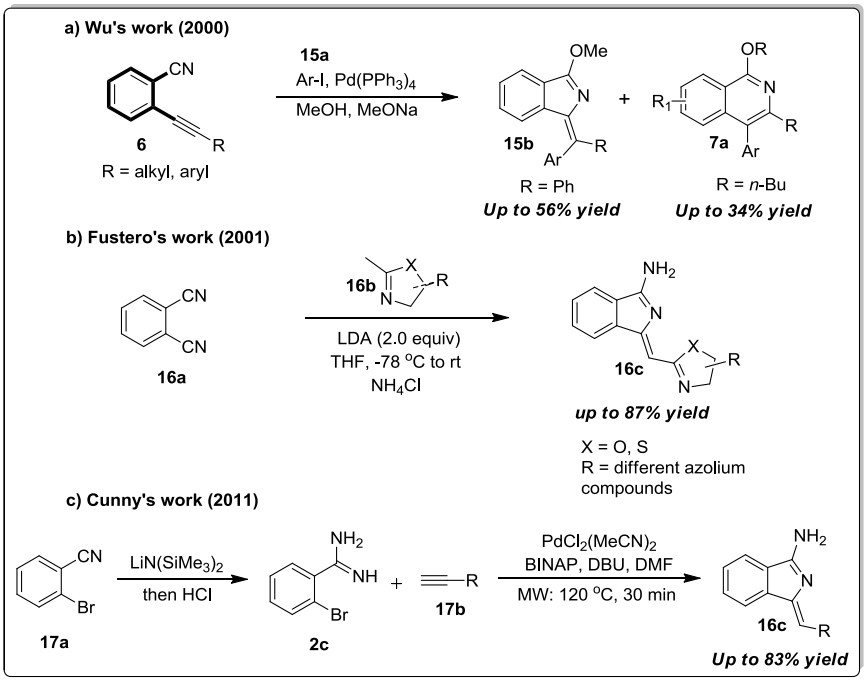


3.3) Literature reports for the synthesis of 1-aminoisoindoline derivatives

In 2000, Wu and coworkers developed a Pd-catalyzed annulation of *o*-alkynyl benzonitriles (**6**) followed by arylation with aryl iodides (**15a**) to access 1-alkoxy 3,4-

disubstituted isoquinolines (**7a**) as well as 1-alkoxy 3-diarylmethylisoindolines (**15b**). In the case of aryl substituted alkynes, only arylated isoindolines (**15b**) were observed. In the case of aliphatic alkynes, a mixture of products was obtained (a, Scheme 14).[28a]

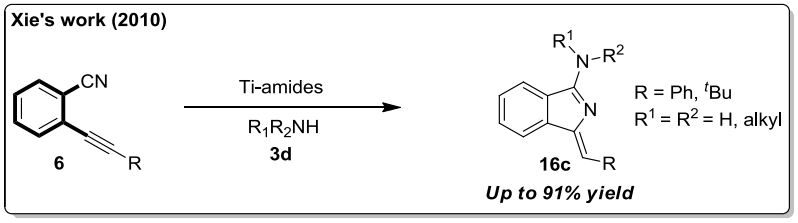
Scheme 14: Conventional approach for the synthesis of 1-aminoisoindolines (**16c**)



Apart from the above mentioned method, a few more traditional approaches are also known, which involves the synthesis of 1-aminoisoindoline (**16c**). Lithium diisopropylamide mediated addition of thiazolium compounds (**16b**) to 1,2-dicyano compounds (**16a**) to afford the corresponding amidines (**16c**) (b, Scheme 14).[28b] Another approach is Pd-catalyzed Sonogashira coupling between amidine **2c** with alkynes (**17b**) to afford the desired 1-aminoisoindolines (**16c**) in good yield under microwave irradiation (c, Scheme 14).[28c, d]

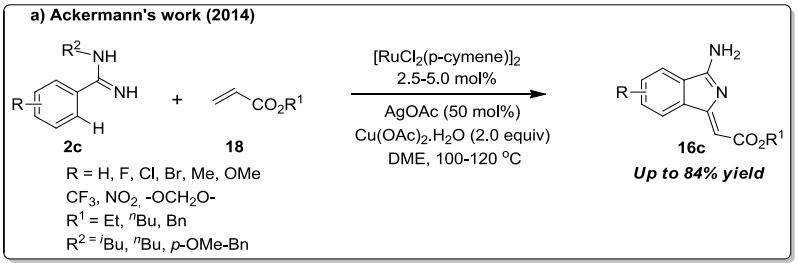
Another interesting approach has been developed by Xie and coworkers. Ti-amide catalyzed atom economical synthesis of nitrogen-containing heterocycles (**16c**) *via* cascade C-N bond formation reaction. They have synthesized 1-aminoisoindolines (**16c**), 3-aminoisoquinolines and substituted imidazoles in excellent yields (Scheme 15).[29]

Scheme 15: Ti-amide catalyzed synthesis of 1-aminoisoindolines (**16c**)



Ackerman group reported a synthesis of 1-aminoisoindolines (**16c**) which involves a reaction between the amidines (**2c**) with *α,β*-unsaturated olefins (**18**) catalyzed by Rhodium *via* oxidative C-H functionalization to afford the desired products (**16c**) in moderate to good yields (Scheme 16).[26b] But the substrate scope is poor in above methods (Scheme 15 & 16).

Scheme 16: Rh-catalyzed synthesis of 1-aminoisoindolines (**16c**)

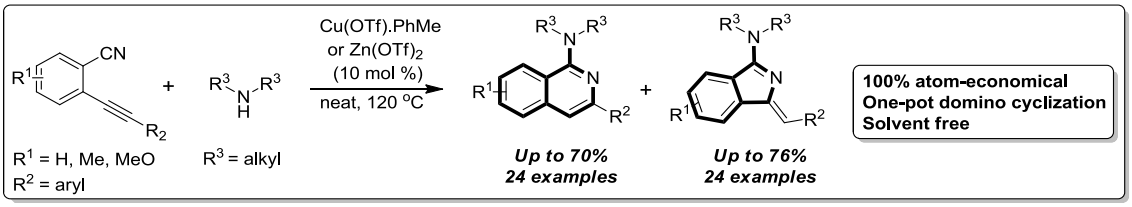


3.4) Results and Discussions

Solvent free reactions are very important from a green chemistry point of view. Literature also reveals that many reactions occur under solvent free conditions.[30] Prof. Paul T. Anastas (Director of the Yale University Center for Green Chemistry and Green Engineering) and Prof. John C. Warner (President of the Warner Babcock Institute for Green Chemistry) presented the "12 Principles of Green Chemistry."[31] These 12 principles pointed out various ways to eliminate environmental and health related issues. The fifth of these asserts: *"the use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used."* Solvent-free reactions firmly adhere to the spirit of this rule. Due to related health problems associated with waste products generated in the chemical industry, chemists are paying increasing amounts of attention towards the development of atom-economical and environmentally benign protocols for the syntheses of compounds. Solvent-free reactions are economical, easy to purify and environmentally benign. On the other hand, it has a couple of drawbacks as in the necessity for homogeneous mixing of the reactants and unfeasibility for solvent-assisted reactions.

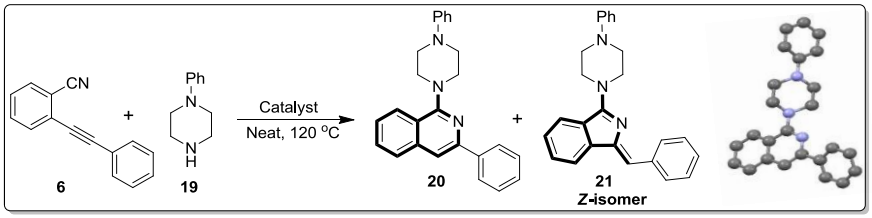
Although 2-alkynylbenzonitriles (**6**) have been utilized for the synthesis of 1-aminonaphthalenes[32] surprisingly, they have not been explored as precursors for the synthesis of 1-aminoisoquinolines (**20**) so far. In our continued efforts toward the synthesis of biologically important heterocyclic systems through annulation reactions,[33] we envisioned that 1-aminoisoquinolines (**20**) or 1-aminoisoindolines (**21**) could be achieved from *o*-alkynyl benzonitrile (**6**) and amine (**19**) in the presence of a metal catalyst. To date, there is no report available for the synthesis of 1-aminoisoquinolines from *o*-alkynyl benzonitrile and amine. Herein we describe a metal catalyzed regioselective approach towards the synthesis of 1-aminoisoquinolines (**20**) and 1-aminoisindolines (**21**) through aminative domino cyclization of 2-alkynyl benzonitrile (**6**) with secondary amine (**19**) under solvent-free conditions. The 1-aminoisoquinolines (**20**) and 1-aminoisoindolines (**21**) were obtained in moderate to good yields (Scheme 17). The salient features of this methodology are 100% atom economy, one-pot domino cyclization under solvent-free condition.

Scheme 17: Synthesis of 1-aminoisoquinolines and 1-aminoisoindolines



We have chosen 2-alkynyl benzonitriles (**6**) as a precursor because it is possible to access both 1-aminoisoquinolines (**20**) and 1-aminoisoindolines (**21**) from this precursor through aminative 6-endo-*dig* and 5-exo-*dig* cyclization respectively by altering the reaction conditions. The optimization studies were carried out using *o*-phenylethynyl benzonitrile (**6**) with *N*-phenyl piperazine (**19**) in the presence of a wide range of metal catalysts. The results are summarized in Table 1. The initial experiments with $Cu(OTf)_2$ as a catalyst in toluene or 1,4-dioxane or DMF did not give any fruitful result as no products (either **20** or **21**) were observed at room temperature or 60 ^oC (entry 1). Even raising the temperature to 120 ^oC did not help in effecting the reaction (entry 2). To our delight, when the same reaction was carried out without a solvent at 120 ^oC, it afforded the 1-aminoisoquinoline **20** and 1-aminoisoindoline

Table 1: Optimization studies[a]



Entry	Catalyst	Time (h)	Ratio (20:21)[b]	Yield (20/21) (%)[c]
1[d]	$Cu(OTf)_2$	24	-	NR
2[e]	$Cu(OTf)_2$	24	-	trace
3	$Cu(OTf)_2$	24	1.7:1	43/28
4	**CuOTf.PhMe**	**24**	**3.3:1**	**62:20**
5	CuBr	40	1.5:1	32/27
6	AgOTf	30	1:4.2	6/50
7	$Bi(OTf)_3$	42	1:5.3	8/52
8	**$Zn(OTf)_2$**	**24**	**1:5.3**	**7/76**
9	$Yb(OTf)_3$	40	1:4.0	6/64
10	$Sc(OTf)_3$	30	1:2.2	7/62
11	$Ce(OTf)_3$	42	1:3.5	14:50
12	-	24	-	NR
13[f]	CuOTf.PhMe	30	1.3:1	39/15
14[f]	$Zn(OTf)_2$	66	1:7.3	2/42

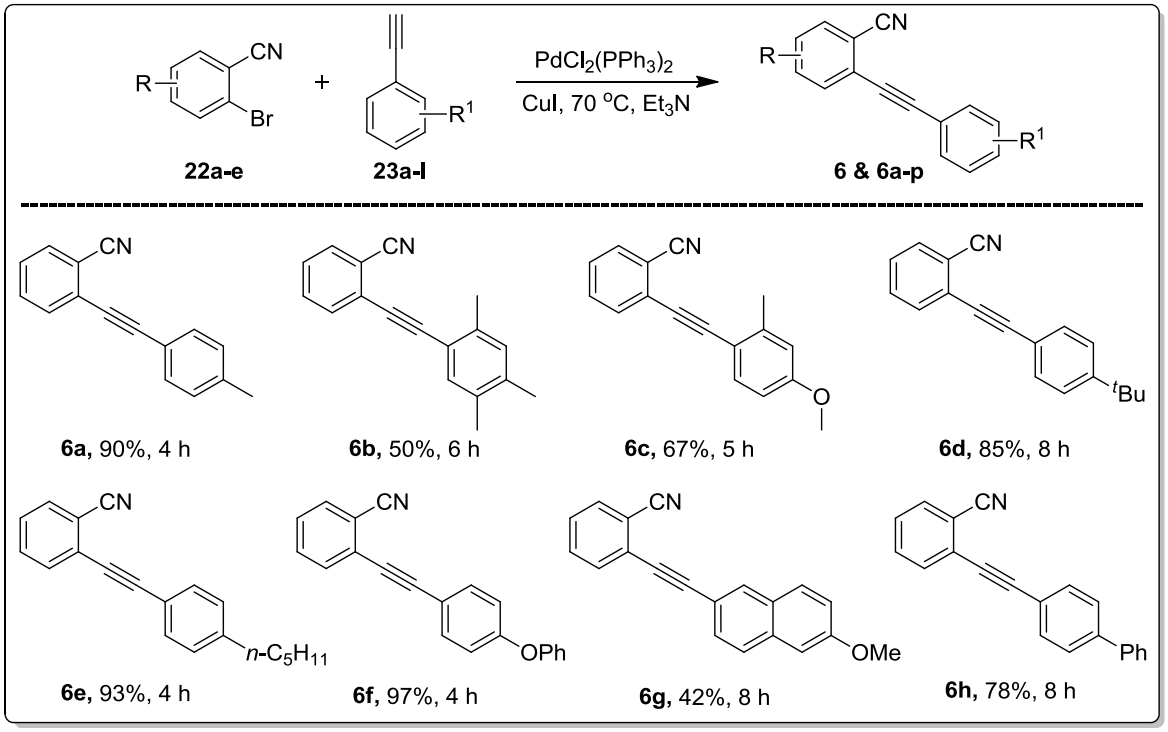
[a]**6** (0.1 mmol), **19** (0.15 mmol), catalyst (0.01 mmol) at 120 °C. [b]Regiomeric ratio was determined by ^{1}H NMR analysis of crude reaction mixture. [c]Isolated yield. [d]Reaction was carried out in toluene or 1,4-dioxane or DMF at rt or 60 °C. [e]Reaction was carried out in toluene or 1,4-dioxane or DMF at 120°C. NR = no reaction. [f]Reaction was carried out at 80°C under neat condition.

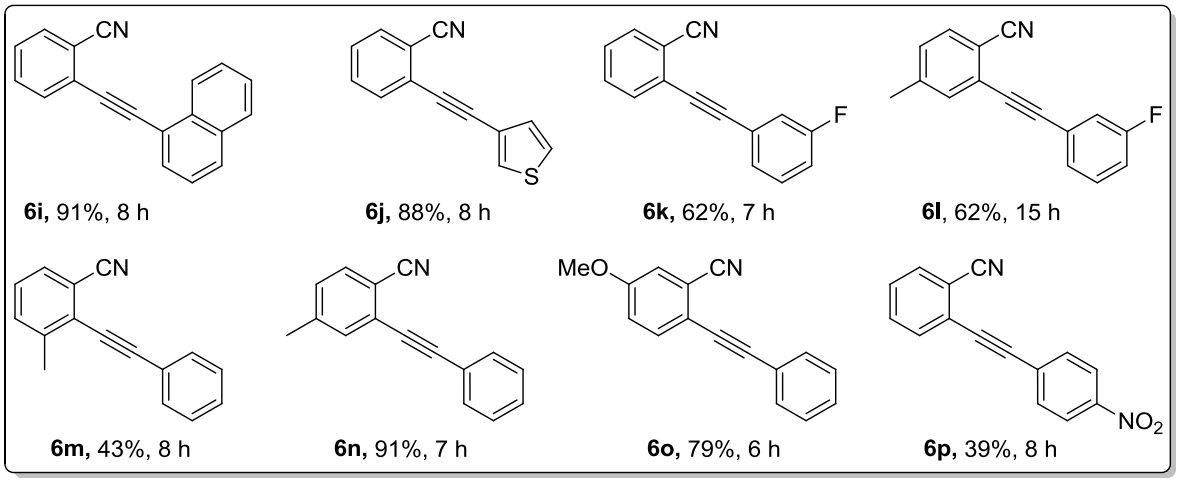
21 in 43% and 28% isolated yields respectively with the ratio of **20**:**21** = 1.7:1 (entry, 3). This result provoked us to carry out further studies in the absence of a solvent. CuOTf.PhMe complex gave the best result, as the yield (62%) as well as the regiomeric ratio (**20**:**21** = 3.3:1) was improved considerably (entry 4). CuBr was found to be inefficient for this transformation as the yield and the regiomeric ratio were found to be lower (entry 5). Gratifyingly, when the reaction was conducted in the presence of AgOTf, the regioselectivity was completely reversed (**20**:**21** = 1:4.2) and the 1-aminoisoindoline **21** was isolated in 50%

along with 1-aminoisoquinoline **20** in 6% yield (entry 6). Encouraged by this result, we screened a few more Lewis acids. $Bi(OTf)_3$ was also found to be helpful in improving the yield of **21** (52%) as well as regioselectivity (**20**:**21** = 1:5.3) (entry 7). Among the Lewis acids screened, $Zn(OTf)_2$ was found to be superior and **21** was isolated in 76% yield with the regiomeric ratio (**20**:**21** = 1:5.3) (entry 8). Other Lewis acids Ytterbium, Scandium, and Cerium triflates were found to be inferior to effect this transformation regarding yield and selectivity when compared to $Zn(OTf)_2$. The isolated yields varied in the range of 50-64% and regioselectivity in the range of **20**:**21** = 1:2.3 - 1:4.0 (entries 9-11). As expected, no product was observed in the absence of any catalyst even after 24 h at 120 ^oC (entry 12). The reaction has been carried out at lower temperatures as well. The reaction with CuOTf.PhMe at 80 ^oC decreases the yield of **20** and regioselectivity (**20**:**21** = 1.3:1) (entry 13). In the case of $Zn(OTf)_2$, the yield of **21** was reduced but the regiomeric ratio was enhanced (**20:21** = 1:7.3) (entry 14).

The optimization studies revealed that copper-based catalyst favored the formation of 1-aminoisoquinoline (**20**) and other metals such as Ag, Zn, Yb, Sc and Ce salts favored the formation of 1-aminoisoindoline (**21**). Variety of *o*-alkynyl benzonitriles (**6** & **6a-p**) were synthesized following the literature procedure (Scheme 18).[32]

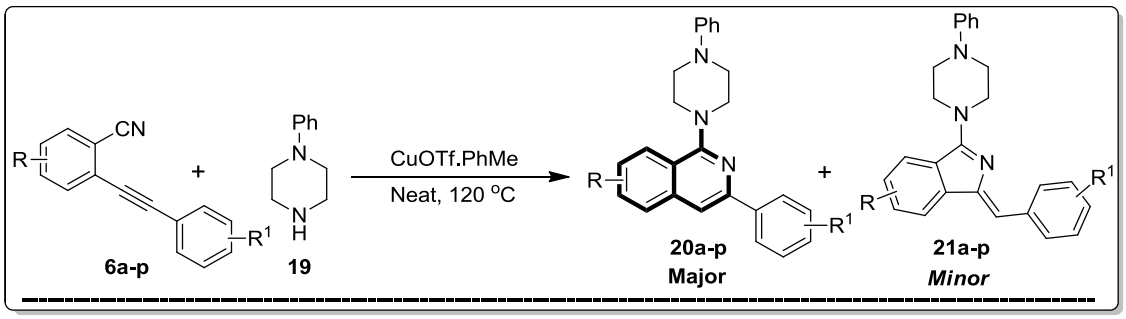
Scheme 18: Synthesis of *o*-alkynyl benzonitriles (**6** & **6a-p**)

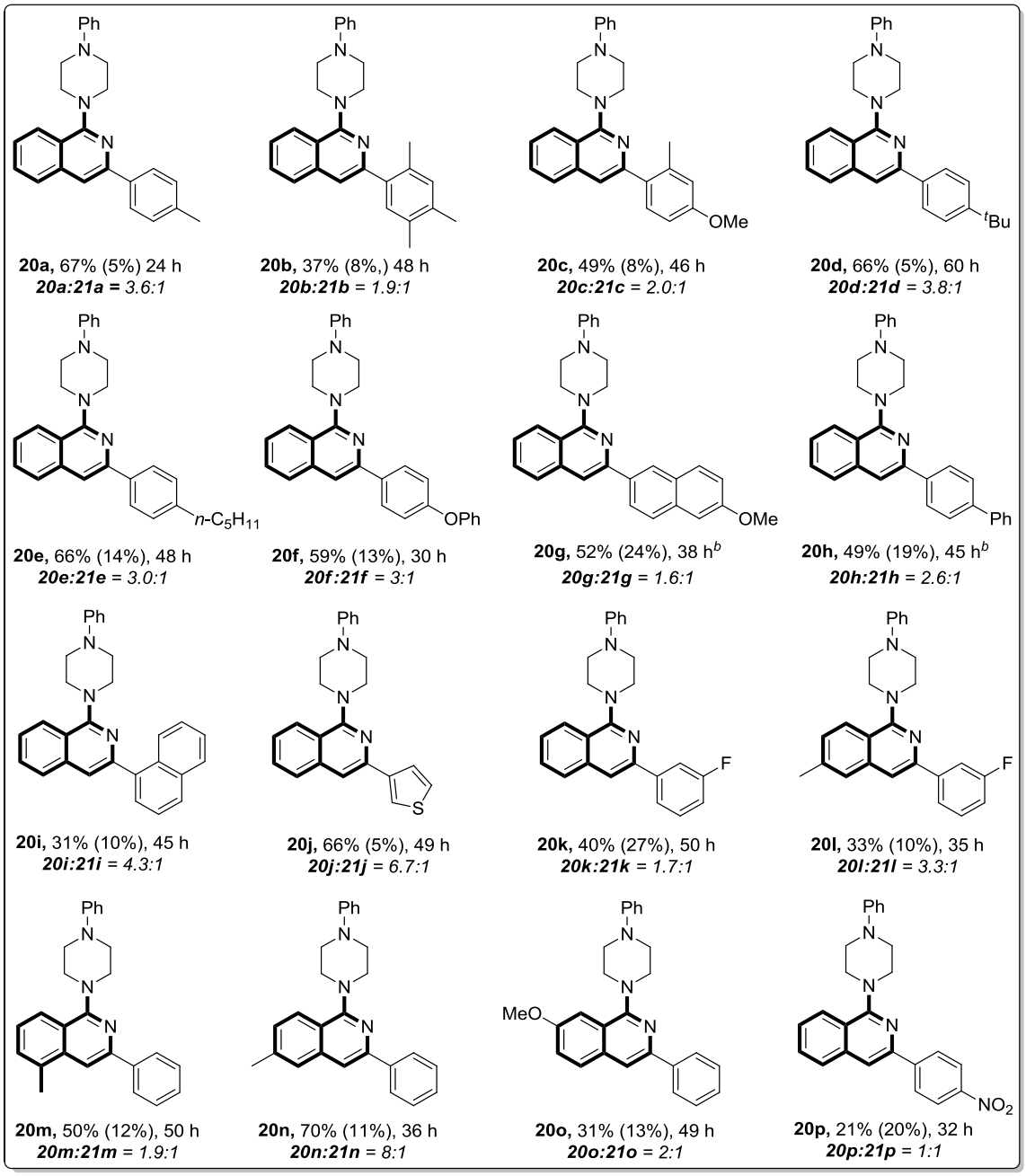




With the optimized reaction conditions in hand for the regioselective synthesis of 1-aminoisquinolines (**20**) (entries 4, Table 1) and 1-aminoisoindolines (**21**) (entries 8, Table 1), a wide range of *o*-alkynyl benzonitriles (**6a-p**) was subjected to the standard reaction condition (Scheme 19 & 20). The results of CuOTf.PhMe catalyzed one-pot domino cyclization of a wide range of *o*-alkynyl benzonitriles (**6a-p**) with *N*-phenyl piperazine (**19**) for the synthesis of 1-aminoisoquinolines (**20**) are summarized in Scheme 19. *o*-Alkynyl benzonitriles derived from alkynes having electron donating, sterically hindered and electronically neutral substituents gave the corresponding 1-aminoisoquinoline as major products (**20a**, **20d-g, 20b-c & 20h-i**) in moderate to good yields. The regioselectivity varied in the range of 1.6:1 to 4.3:1. The *o*-alkynyl benzonitrile obtained from 3-ethynyl thiophene **6j** also reacted smoothly under the reaction condition and obtained the respective 1-aminoisoquinoline (**20j**) in 66% isolated yield with good regioselectivity (**20j**:**21j** = 6.7:1). *o*-Alkynyl benzonitriles with moderately or strongly electron withdrawing groups on the alkyne moiety afforded the expected products (**20k-l** & **20p**) in moderate yields and regioselectivity

Scheme 19: CuOTf.PhMe catalyzed synthesis of 1-aminoisoquinolines (**20a-p**)[a]





20a, 67% (5%) 24 h ***20a:21a =*** *3.6:1*

20b, 37% (8%,) 48 h ***20b:21b*** *= 1.9:1*

20c, 49% (8%), 46 h ***20c:21c*** *= 2.0:1*

20d, 66% (5%), 60 h ***20d:21d*** *= 3.8:1*

20e, 66% (14%), 48 h ***20e:21e*** *= 3.0:1*

20f, 59% (13%), 30 h ***20f:21f*** *= 3:1*

20g, 52% (24%), 38 h[b] ***20g:21g*** *= 1.6:1*

20h, 49% (19%), 45 h[b] ***20h:21h*** *= 2.6:1*

20i, 31% (10%), 45 h ***20i:21i*** *= 4.3:1*

20j, 66% (5%), 49 h ***20j:21j*** *= 6.7:1*

20k, 40% (27%), 50 h ***20k:21k*** *= 1.7:1*

20l, 33% (10%), 35 h ***20l:21l*** *= 3.3:1*

20m, 50% (12%), 50 h ***20m:21m*** *= 1.9:1*

20n, 70% (11%), 36 h ***20n:21n*** *= 8:1*

20o, 31% (13%), 49 h ***20o:21o*** *= 2:1*

20p, 21% (20%), 32 h ***20p:21p*** *= 1:1*

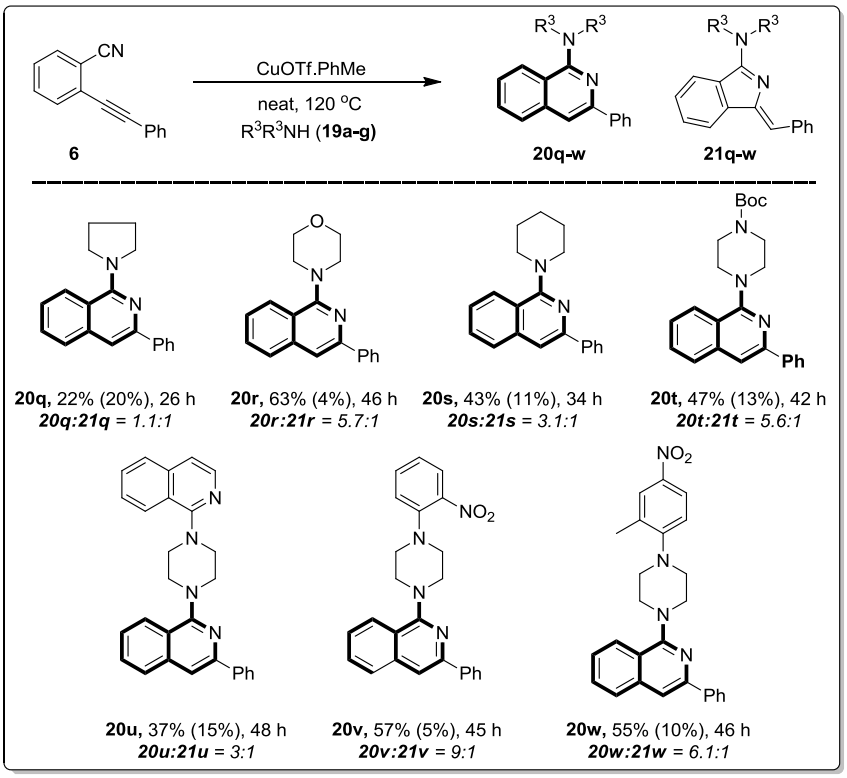
[a]**6** (0.1 mmol), **19** (0.15 mmol), CuOTf.PhMe (0.01 mmol) at 120 °C. [b]3 equivalents of the amine with respect to **6** was used. Regiomeric ratio was determined by ^{1}H NMR analysis of crude reaction mixture.Yields reported are isolated yields of the major product. Yields reported in the parenthesis are isolated yields of the minor product.

changed from 1:1 to 3.3:1. This methodology also worked pretty well in other precursors derived from methyl and methoxy-substituted 2-alkynyl benzonitriles (**6l-o**) and achieved the 1-aminoisoquinolines (**20l-o**) in moderate to good yield with ratios ranging from 1.9:1 to 8:1.

Further substrate scope was explored for the synthesis of 1-aminoisoquinolines (**20q-w**) using different secondary amines (**19a-g**) with *o*-phenylethynyl benzonitrile (**6**) under the

optimized condition. The outcomes are summarized in Scheme 20. The reaction of pyrrolidine **19a** with substrate **6** in the presence of CuOTf.PhMe gave 1-aminoisoquinoline (**20q**) with 1.1:1 regioselectivity. Other amines such as morpholine (**19b**) and piperidine (**19c**) also reacted efficiently and obtained the respective 1-aminoisoquinolines (**20r** & **20s**) in 63% and 43% isolated yields and regioselectivity varied in the range of 3.1:1 to 5.7:1. Apart from the above mentioned amines, a few interesting *N*-substituted piperazine derivatives (**19d-g**) were also used. *N*-Boc piperazine (**19d**) was treated with substrate **6** and the desired product (**20t**) was obtained in 47% isolated yield with 5.6:1 regioselectivity. *N*-aryl piperazine derivatives with electron withdrawing group on aryl moiety were subjected to standard reaction condition and afforded the corresponding 1-aminoisoquinolines (**20u-w**) in moderate yields with regioselectivity varying from 3:1 to 9:1.

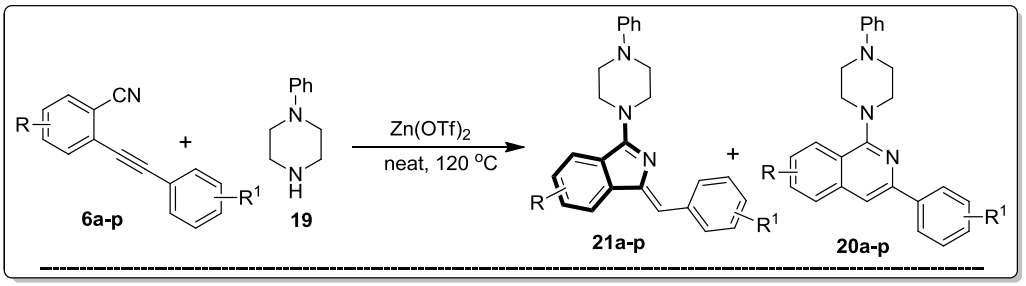
Scheme 20: The synthesis of 1-aminoisoquinoline using different amines (**20q-w**)

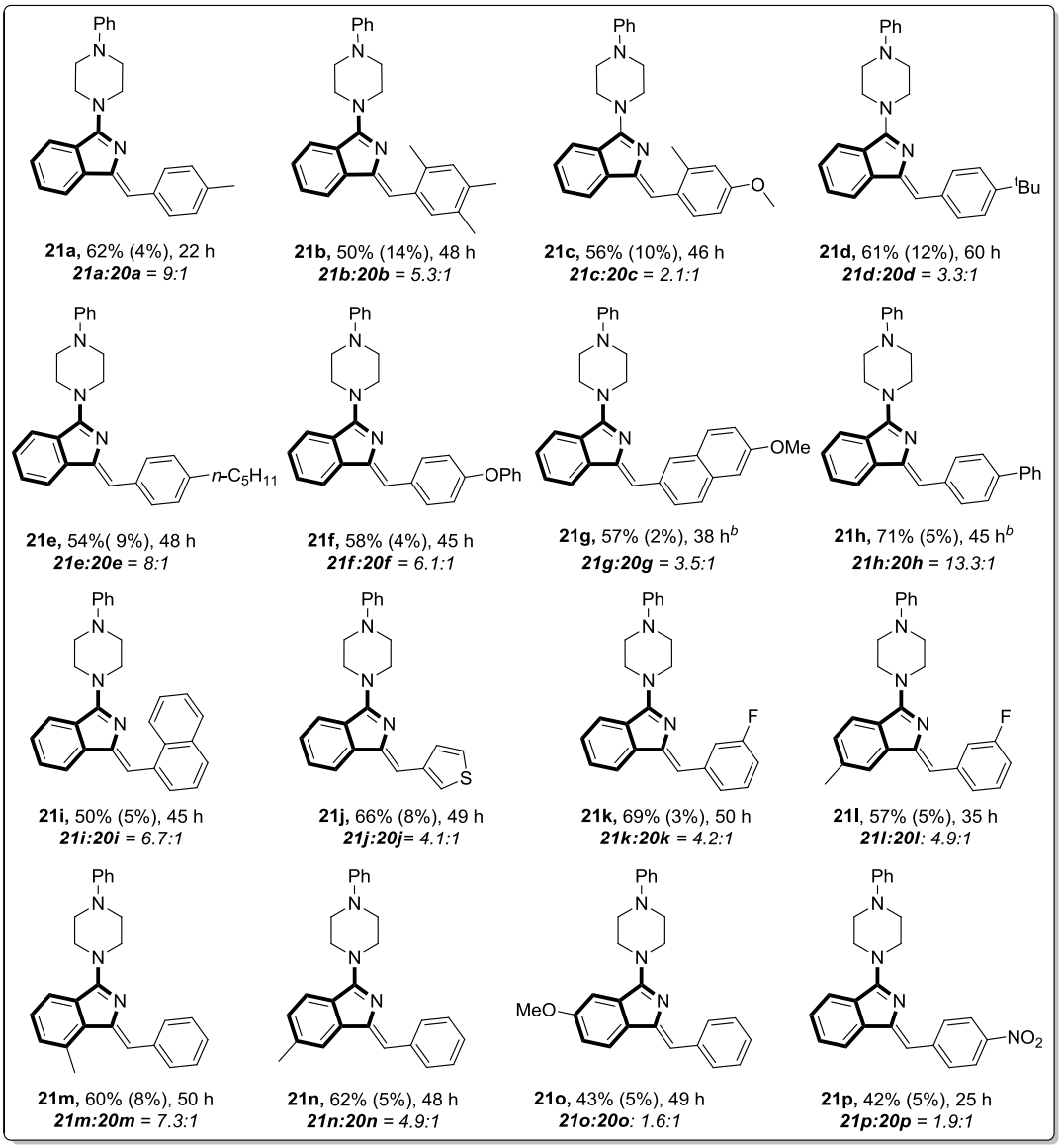


The same set of substrates were investigated under the optimized reaction condition by using $Zn(OTf)_2$ as a catalyst for the synthesis of 1-aminoisoindolines (entry 8, Table 1). The results are summarized in Scheme 21. Electron rich, sterically demanding as well as electronically neutral *o*-alkynyl benzonitriles were reacted smoothly under the optimized reaction condition and afforded the 1-aminoisoindolines (**21a**, **21d-g**, **21b-c** & **21h-i**) in

moderate to good yields. The regioselectivity varied in the range of 2.1:1 to 13.3:1 (scheme 21). The substrate **6j** was also reacted under the optimized reaction condition and obtained

Scheme 21: $Zn(OTf)_2$ catalyzed synthesis of 1-aminoisoindolines (**21a-p**)[a]



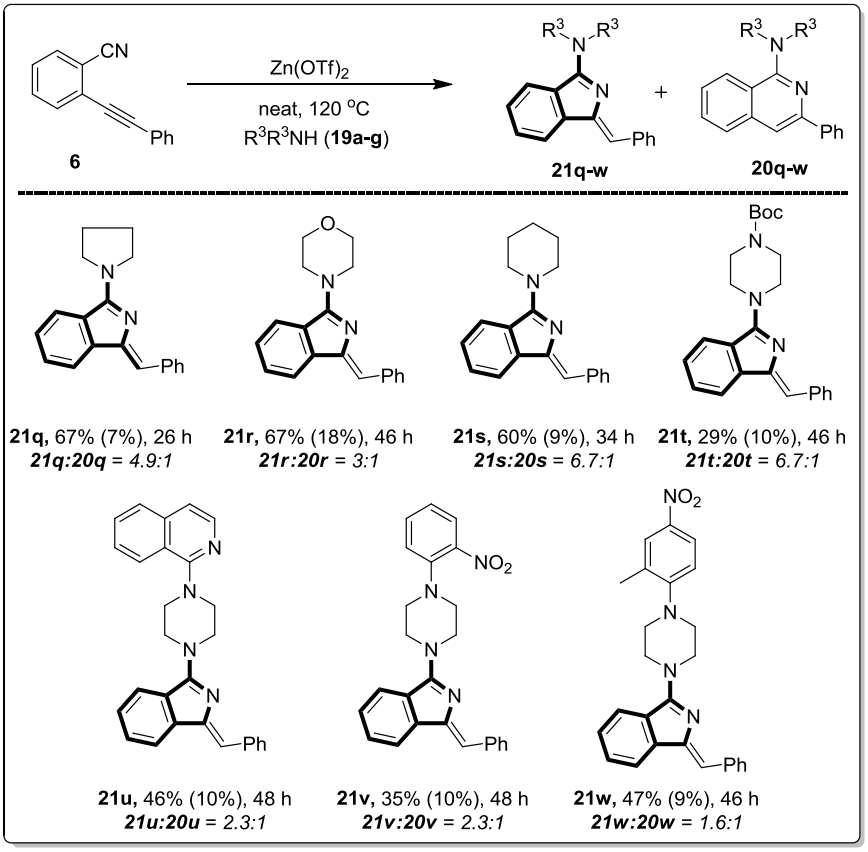


[a]**6** (0.1 mmol), **19** (0.15 mmol), $Zn(OTf)_2$ (0.01 mmol) at 120 °C. [b]3 equivalents of the amine with respect to **6** was used. Regiomeric ratio was determined by ^1H NMR analysis of crude reaction mixture. Yields reported are isolated yields of the major product. Yields reported in the parenthesis are isolated yields of the minor product.

1-aminoisoindoline derivative **21j** in 66% isolated yields with regioselectivity **20j**:**21j** = 4.1:1. The *o*-alkynyl benzonitriles derived from terminal alkynes having electronic withdrawing substituents on aryl group reacted smoothly and afforded the corresponding isoindolines (**21k-l** and **21p**) in good yields with regioselectivity in the range of 1.9:1 to 4.9:1. The other precursors derived from methyl and methoxy-substituted 2-bromo benzonitriles also underwent smooth conversion and afforded the corresponding 1-aminoisoindolines (**21l-o**) in good yields and the range of selectivity was 1.6:1 to 7.3:1.

We carried out the reaction between *o*-phenylethynyl benzonitrile (**6**) and same set of different secondary amines (**19a-g**) for the synthesis of 1-aminoisoindolines (**21q-w**) under the optimized reaction condition using $Zn(OTf)_2$ (Scheme 22).

Scheme 22: The synthesis of 1-aminoisoindolines (**21q-w**) using different amines



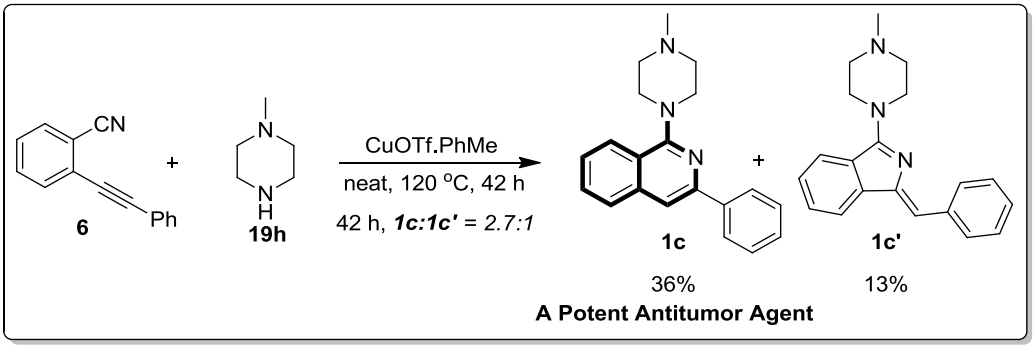
The treatment of pyrrolidine (**19a**), morpholine (**19b**) and piperidine (**19c**) with 2-phenylethynyl benzonitrile (**6**) afforded the expected 1-aminoisoindolines (**21q-s**) in good yields and regioselectivity varied from **21**:**20** = 3:1 to 6.7:1. Apart from the above mentioned amines, different piperazine derivatives (**19d-h**) also reacted smoothly under the standard

condition and obtained the expected products (**21t-w**) in good to moderate yields in a ratio of 1.6 to 6.7.

3.5) The synthesis of antitumor agent

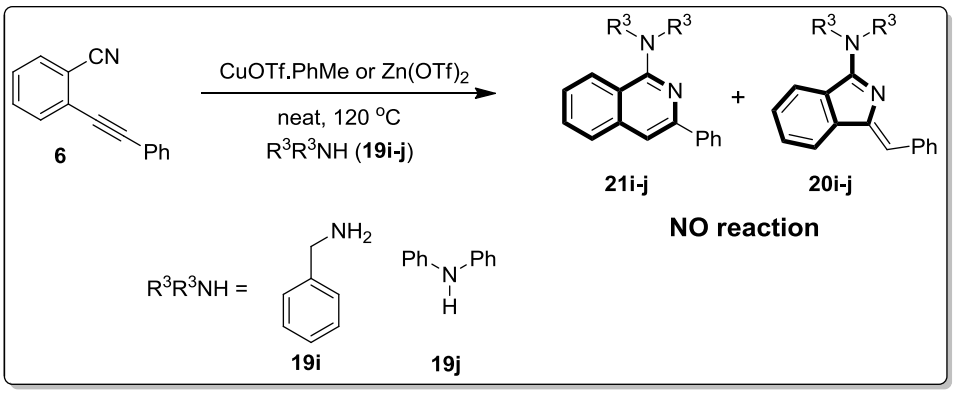
To portray the application potential, this transformation was elaborated for the synthesis of one of the pharmaceutically important 1-aminoisoquinoline derivatives **1c**, which had shown potential antitumor activity (Scheme 23).[2] In this experiment, 2-alkynyl benzonitrile **6** was heated with a little excess of *N*-methyl morpholine (**19h**) in the presence of 10 mol % of CuOTf.PhMe under the standard condition and the products **1c** and **1c'** were obtained in 2.7:1 regiomeric ratio. The required 1-aminoisoquinoline **1c** was obtained in 36% yield after isolation.

Scheme 23: Synthesis of a potent antitumour agent **1c**



Unfortunately, the reaction did not work in the cases of aliphatic primary amines as

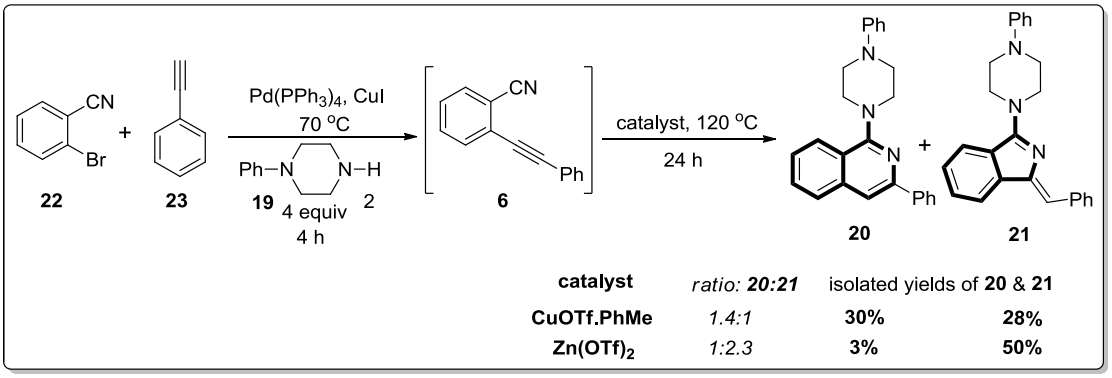
Scheme 24: The reaction with other amines (**19i-j**)



well as aromatic secondary amines such as benzylamine (**19i**) and diphenyl amine (**19j**), as a complex mixture of products was obtained in those cases (Scheme 24).

Finally, we turn our attention to developing a one-pot domino annulation approach for the synthesis of 1-aminoisoquinoline (**20**) and 1-aminoisoindoline (**21**) (Scheme 25). We carried out the Sonogashira coupling reaction between *o*-bromobenzonitrile (**22**) and phenylacetylene (**23**) with 4 equivalent of piperazine (**19**) at 70 ^{o}C for 4 h. Then, Cu(OTf).PhMe complex was added to the same reaction mixture and stirred for 24 h. The 1-aminoisoquinoline (**20**) was obtained in 30% yield. In the case of $Zn(OTf)_2$, the 1-aminoisoindoline (**21**) was obtained in 50% isolated yield and the regiomeric ratio was 2.3:1 (Scheme 25).

Scheme 25: One-pot synthesis of 1-aminoisoquinoline (**20**) and 1-aminoisoindoline (**21**)



3.7) Conclusion

A metal-catalyzed regioselective and atom economic approach has been developed for the synthesis of 1-aminoisoquinolines and/or 1-aminoisindolines through aminative domino cyclization of 2-alkynyl benzonitriles with secondary amines under solvent-free conditions. It was found that the regioselectivity of the reaction was greatly influenced by the choice of the metal catalyst. Copper-based catalysts favored 6-endo-*dig* cyclization leading to 1-aminoisoquinolines, whereas other catalysts such as triflates of Zn, Ag, Bi, Sc and Yb favored the formation of 1-aminoisoindolines through 5-exo-*dig* cyclization. Although the exact role of metal catalyst is not well understood at this point of time, furthure studies to prove the mechanism and regioselectivity through computational calculation are underway.

3.7) Experimental Section

General Information

All reactions were carried out in an oven dried screw cap reaction vials. Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

Synthesis of *o*-alkynyl benzonitriles

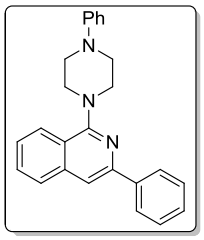
All the 2-alkynyl benzontiriles (**6**, **6a-6p**) were synthesised according to the literature procedure.[32]

General procedure for the synthesis of 1-aminoisoquinolines and/or 1-amino-isoindolines

A mixture of 2-alkynyl benzonitrile **6** (1 equiv, 0.1 mmol), $Zn(OTf)_2$ or CuOTf.PhMe (0.10 equiv, 0.01 mmol) and the secondary amine **19** (1.5 equiv, 0.15 mmol) was heated to 120 $^{\circ}C$ in a closed vial for 24–50 h. After completion, the reaction mixture was diluted with dichloromethane (1 mL) and transferred to a round bottom flask. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using a mixture of EtOAc and hexane as eluent to obtain the pure 1-aminoisoquinoline (**20**) and/or 1-aminoisoindoline (**21**) derivatives.

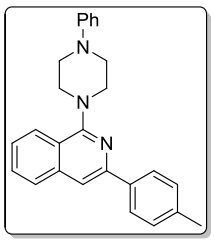
Characterization data for 1-aminoisoquinoline derivatives 20 and 20a-20w & 21, 21a-21w, 1c-1c'

3-phenyl-1-(4-phenylpiperazin-1-yl)isoquinoline (20)



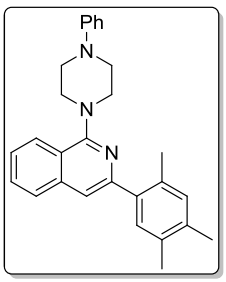
R_f = 0.5 (10% EtOAc in hexane); yellow solid (22.5 mg, 62% yield); m.p. = 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.19 (m, 2H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.76 (s, 1H), 7.63 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.54−7.49 (m, 3H), 7.43−7.39 (m, 1H), 7.37−7.31 (m, 2H), 7.07−7.05 (m, 2H), 6.94−6.90 (m, 1H), 3.73−3.71 (m, 4H), 3.52−3.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 151.6, 148.5, 139.8, 139.3, 129.9, 129.3, 128.8, 128.5, 127.8, 126.8, 126.1, 125.5, 120.8, 119.9, 116.2, 111.6, 51.4, 49.4; FT-IR (KBr): 3053, 2966, 2884, 2831, 1600, 1564, 1499, 1396, 1243, 772, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3$ $[M+H]^+$: 366.1970; found: 366.1976.

1-(4-phenylpiperazin-1-yl)-3-(p-tolyl)isoquinoline (20a)



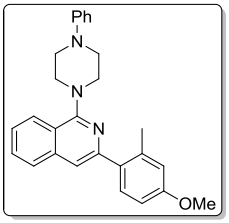
R_f = 0.5 (10% EtOAc in hexane); white solid (25.3 mg, 67% yield); m.p. = 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 1H), 8.11−8.08 (m, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.72 (s, 1H), 7.61 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.35−7.29 (m, 4H), 7.06−7.04 (m, 2H), 6.93−6.89 (m, 1H), 3.72−3.70 (m, 4H), 3.51−3.49 (m, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.6, 148.5, 139.3, 138.3, 137.0, 129.8, 129.5, 129.3, 127.7, 126.7, 125.8, 125.5, 120.7, 119.9, 116.2, 111.1, 51.4, 49.4, 21.4; FT-IR (KBr): 3051, 2918, 2854, 2815, 1594, 1561, 1492, 1412, 1374, 1232, 822, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2143.

1-(4-phenylpiperazin-1-yl)-3-(2,4,5-trimethylphenyl)isoquinoline (20b)



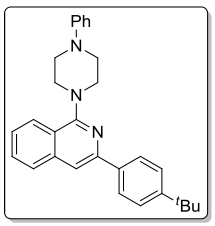
R_f = 0.5 (10% EtOAc in hexane); yellow solid (14.5 mg, 37% yield); m.p. = 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.63 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.34−7.30 (m, 2H), 7.10 (s, 1H), 7.05−7.03 (m, 2H), 6.90 (m, 1H), 3.65−3.62 (m, 4H), 3.50−3.47 (m, 4H), 2.44 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 151.9, 151.6, 138.9, 138.3, 136.4, 133.9, 133.8, 132.5, 131.3, 129.8, 129.3, 127.6, 126.0, 125.5, 120.2, 119.9, 116.2, 115.5, 51.5, 49.5, 20.5, 19.5, 19.4; FT-IR (KBr): 2964, 2919, 2837, 1600, 1561, 1502, 1401, 1372, 1233, 941, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}N_3$ $[M+H]^+$: 408.2440; found: 408.2448.

3-(4-methoxy-2-methylphenyl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20c)



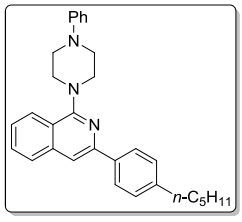
R_f = 0.4 (10% EtOAc in hexane); yellow gummy liquid (20 mg, 49% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.3, 0.8 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.63 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.54−7.50 (m, 2H), 7.38 (d, J = 0.4 Hz, 1H), 7.34−7.30 (m, 2H), 7.05−7.03 (m, 2H), 6.90 (tt, J = 7.3, 1.0 Hz, 1H), 6.86 (s, 1H), 3.86 (d, J = 2.6 Hz, 1H), 3.64−3.62 (m, 4H), 3.49−3.47 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.4, 151.6, 151.4, 138.9, 138.2, 133.6, 131.3, 129.8, 129.3, 127.5, 125.9, 125.4, 120.2, 119.9, 116.5, 116.2, 115.5, 111.3, 55.4, 51.5, 49.5, 21.5; FT-IR (KBr): 2956, 2921, 2833, 1604, 1561, 1504, 1235, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}N_3O$ $[M+H]^+$: 410.2232; found: 410.2243.

3-[4-(*tert*-butyl)phenyl]-1-(4-phenylpiperazin-1-yl)isoquinoline (20d)



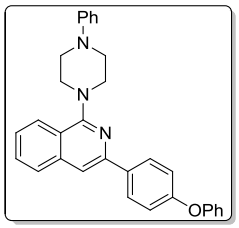
R_f = 0.7 (10% EtOAc in hexane); yellow solid (27.6 mg, 66% yield); m.p. = 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.11 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.55−7.48 (m, 3H), 7.36−7.32 (m, 2H), 7.07−7.05 (m, 2H), 6.94−6.90 (m, 1H), 3.72−3.70 (m, 4H), 3.52−3.49 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 151.6, 151.5, 148.6, 139.3, 137.1, 129.8, 129.3, 127.8, 126.5, 125.9, 125.7, 125.5, 120.7, 119.9, 116.2, 111.3, 51.4, 49.4, 34.8, 31.5; FT-IR (KBr): 2957, 2923, 2852, 1600, 1563, 1492, 1410, 1372, 1229, 837, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_3$ $[M+H]^+$:422.2596; found: 422.2608.

3-(4-*n*-pentylphenyl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20e)



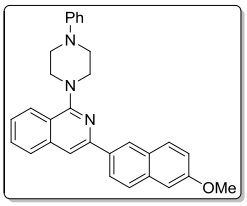
R_f = 0.6 (10% EtOAc in hexane); yellow solid (28.5 mg, 66% yield); m.p. = 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 0.5 Hz, 1H), 8.14−8.10 (m, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.62 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.50 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.36−7.31 (m, 4H), 7.07−7.05 (m, 2H), 6.94−6.90 (m, 1H), 3.73−3.70 (m, 4H), 3.52−3.50 (m, 4H), 2.69 (t, J = 7.5 Hz, 2H), 1.71−1.67 (m, 2H), 1.40−1.36 (m, 4H), 0.95−0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 151.6, 148.6, 143.3, 139.3, 137.2, 129.8, 129.3, 128.9, 127.8, 126.7, 125.8, 125.5, 120.7, 119.9, 116.2, 111.2, 51.4, 49.4, 35.9, 31.6, 31.3, 22.7, 14.2; FT-IR (KBr): 2925, 2847, 1597, 1563, 1503, 1412, 1376, 1238, 755 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}N_3$ $[M+H]^+$: 436.2753; found: 436.2758.

3-(4-phenoxyphenyl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20f)



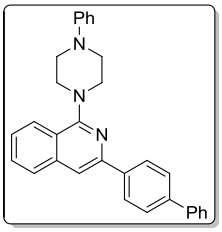
R_f = 0.5 (10% EtOAc in hexane); yellow solid (26.8 mg, 59% yield); m.p. = 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.17 (m, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.62 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.50 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.40−7.32 (m, 4H), 7.16−7.09 (m, 5H), 7.07−7.04 (m, 2H), 6.94−6.90 (m, 1H), 3.72−3.70 (m, 4H), 3.52−3.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 157.7, 157.3, 151.6, 147.9, 139.3, 134.9, 134.5, 129.9, 129.3, 128.3, 127.7, 125.9, 125.5, 123.5, 120.6, 119.9, 119.1, 119.0, 116.2, 111.0, 51.4, 49.4; FT-IR (KBr): 3063, 2831, 1592, 1564, 1505, 1489, 1240, 756, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_3O$ $[M+H]^+$: 458.2232; found: 458.2235.

3-(6-methoxynaphthalen-2-yl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20g)



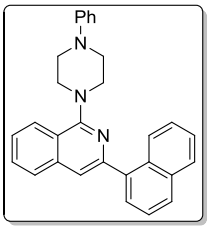
R_f = 0.4 (10% EtOAc in hexane); yellow solid (23 mg, 52% yield); m.p. = 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* =1.3 Hz, 1H), 8.29 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.90−7.84 (m, 4H), 7.63 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.51 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.36−7.32 (m, 2H), 7.21−7.18 (m, 2H), 7.08−7.06 (m, 2H), 6.94−6.90 (m, 1H), 3.96 (s, 3H), 3.76−3.74 (m, 4H), 3.54−3.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.1, 151.6, 148.5, 139.3, 135.0, 134.8, 130.3, 129.9, 129.3, 129.2, 127.8, 127.2, 126.0, 125.8, 125.6, 125.3, 120.7, 119.9, 119.1, 116.3, 111.5, 105.8, 55.5, 51.4, 49.5; FT-IR (KBr): 3057, 2939, 2835, 1598, 1562, 1502, 1484, 1233, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{28}N_3O$ $[M+H]^+$: 446.2232; found: 446.2237.

3-[(1,1'-biphenyl)-4-yl]-1-(4-phenylpiperazin-1-yl)isoquinoline (20h)



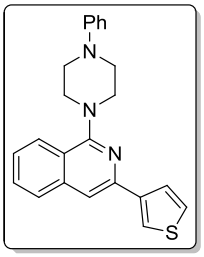
R_f = 0.4 (10% EtOAc in hexane); light yellow solid (21.4 mg, 49% yield); m.p. = 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.27 (m, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 7.76−7.73 (m, 2H), 7.71−7.69 (m, 2H), 7.64 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.51−7.47 (m, 2H), 7.41−7.33 (m, 3H), 7.08−7.06 (m, 2H), 6.95−6.91 (m, 1H), 3.75−3.73 (m, 4H), 3.53−3.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 151.6, 148.1, 141.1, 141.0, 139.2, 138.8, 129.9, 129.3, 128.9, 127.9, 127.48, 127.47, 127.2, 126.1, 125.5, 120.8, 119.9, 116.2, 111.6, 51.4, 49.4; FT-IR (KBr): 2959, 2918, 2826, 1588, 1499, 1457, 1231, 1035, 929, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_3$ $[M+H]^+$: 442.2283; found: 422.2278.

3-(naphthalen-1-yl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20i)



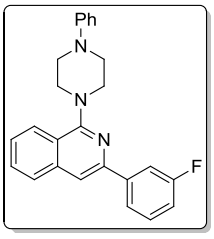
R_f = 0.6 (10% EtOAc in hexane); yellow liquid (12.6 mg, 31% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 7.94−7.92 (m, 1H), 7.91 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 7.1, 1.2 Hz, 1H), 7.67 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.60−7.56 (m, 3H), 7.51 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.46 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.34−7.29 (m, 2H), 7.04−7.01 (m, 2H), 6.92−6.88 (m, 1H), 3.69 (t, J = 4.8 Hz, 4H), 3.49 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.6, 150.8, 139.1, 139.0, 134.2, 132.7, 131.7, 130.0, 129.3, 128.6, 128.4, 127.74, 127.68, 126.5, 126.3, 126.1, 125.8, 125.6, 120.6, 119.9, 116.9, 116.2, 51.5, 49.5; FT-IR (KBr): 3054, 2922, 2840, 1598, 1560, 1494, 1400, 1233, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_3$ $[M+H]^+$: 416.2127; found: 416.2121.

1-(4-phenylpiperazin-1-yl)-3-(thiophen-3-yl)isoquinoline (20j)



R_f = 0.6 (10% EtOAc in hexane); yellow solid (24.3 mg, 66% yield); m.p. = 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.3, 0.8 Hz, 1H), 8.04 (dd, J = 3.1, 1.2 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.74 (dd, J = 5.1, 1.2 Hz, 1H), 7.61 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.58 (s, 1H), 7.48 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.41 (dd, J = 5.0, 3.1 Hz, 1H), 7.35−7.30 (m, 2H), 7.06−7.03 (m, 2H), 6.91 (tt, J = 7.3, 1.0 Hz, 1H), 3.70−3.68 (m, 4H), 3.51−3.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 151.6, 145.0, 142.9, 139.2, 129.9, 129.3, 127.6, 126.2, 126.1, 125.8, 125.6, 123.0, 120.7, 119.9, 116.2, 111.2, 51.3, 49.4; FT-IR (KBr): 2924, 2853, 1596, 1561, 1502, 1490, 1407, 1236, 1011, 802, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{22}N_3S$ $[M+H]^+$: 372.1534; found: 372.1540.

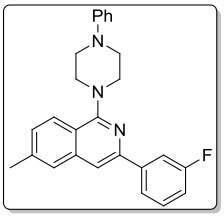
3-(3-fluorophenyl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20k)



R_f = 0.6 (10% EtOAc in hexane); yellow solid (15.3 mg, 40% yield); m.p. = 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.2, 0.6 Hz, 1H), 7.96−7.92 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.74 (s, 1H), 7.64 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.53 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.47−7.41 (m, 1H), 7.35−7.31 (m, 2H), 7.11−7.04 (m, 3H), 6.94−6.90 (m, 1H), 3.72−3.70 (m, 4H), 3.52−3.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, J = 243.4 Hz), 160.8, 151.6, 147.0 (d, J = 2.9 Hz), 142.2 (d, J = 8.1 Hz), 139.1, 130.2, 130.1, 129.3, 127.9, 126.4, 125.6, 122.2, (d, J = 2.9 Hz), 121.1, 120.0, 116.3, 115.2 (d, J = 21.2 Hz), 113.7 (d, J = 22.6 Hz), 111.9, 51.4, 49.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.29; FT-IR (KBr): 3053, 2920,

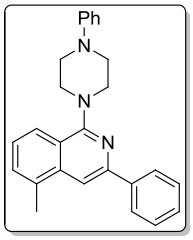
2839, 1602, 1580, 1564, 1500, 1244, 786, 761 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}FN_3$ $[M+H]^+$: 384.1876; found: 384.1870.

3-(3-fluorophenyl)-6-methyl-1-(4-phenylpiperazin-1-yl)isoquinoline (20l)



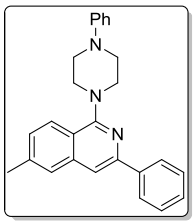
R_f = 0.4 (10% EtOAc in hexane); light brown solid (13 mg, 33% yield); m.p. = 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 1H), 7.94−7.91 (m, 2H), 7.66 (s, 1H), 7.60 (brs, 1H), 7.46−7.40 (m, 1H), 7.36−7.31 (m, 3H), 7.10−7.04 (m, 3H), 6.91 (tt, *J* = 7.3, 1.0 Hz, 1H), 3.70−3.68 (m, 4H), 3.51−3.48 (m, 4H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, *J* = 243.0 Hz), 160.7, 151.6, 147.1 (d, *J* = 2.9 Hz), 142.4 (d, *J* = 8.1 Hz), 140.3, 139.4, 130.1 (d, *J* = 8.2 Hz), 129.3, 128.6, 127.0, 125.4, 122.1, (d, *J* = 2.9 Hz), 119.9, 119.3, 116.3, 115.1 (d, *J* = 21.3 Hz), 113.7 (d, *J* = 22.6 Hz), 111.6, 51.3, 49.4, 22.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.36; FT-IR (KBr): 2952, 2914,2834, 1605, 1570, 1495, 1401, 1240, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}FN_3$ $[M+H]^+$: 398.2033; found: 398.2040.

5-methyl-3-phenyl-1-(4-phenylpiperazin-1-yl)isoquinoline (20m)



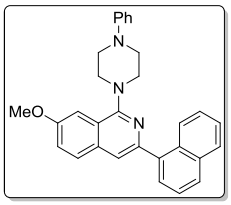
The reaction was performed at 0.05 mmol scale; R_f = 0.6 (10% EtOAc in hexane); yellow solid (9.4 mg, 50% yield); m.p. = 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.19 (m, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 0.8 Hz, 1H), 7.52−7.45 (m, 3H), 7.42−7.37 (m, 2H), 7.34−7.30 (m, 2H), 7.06−7.03 (m, 2H), 6.92−6.88 (m, 1H), 3.71−3.68 (m, 4H), 3.51−3.48 (m, 4H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 151.6, 148.5, 138.5, 134.6, 132.1, 130.4, 129.3, 128.8, 128.4, 126.9, 125.5, 123.6, 120.7, 119.9, 116.2, 108.2, 51.5, 49.5, 19.5; FT-IR (KBr): 2964, 2922, 2832, 1597, 1562, 1500, 1442, 1397, 1234, 755 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2125.

6-methyl-3-phenyl-1-(4-phenylpiperazin-1-yl)isoquinoline (20n)



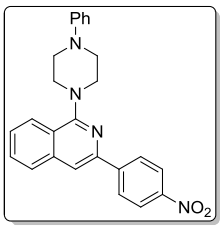
R_f = 0.5 (10% EtOAc in hexane); yellow solid (26.4 mg, 70% yield); m.p. = 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.19 (m, 2H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.42−7.38 (m, 1H), 7.36−7.32 (m, 3H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 3.72−3.69 (m, 4H), 3.51−3.49 (m, 4H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 151.6, 148.5, 140.0, 139.9, 139.6, 129.3, 128.7, 128.4, 128.2, 126.9, 126.8, 125.4, 119.9, 119.1, 116.2, 111.3, 51.3, 49.4, 22.0; FT-IR (KBr): 2916, 2837, 1601, 1569, 1494, 1401, 1245, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2141.

7-methoxy-3-phenyl-1-(4-phenylpiperazin-1-yl)isoquinoline (20o)



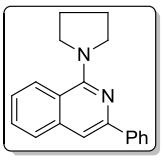
R_f = 0.4 (10% EtOAc in hexane); yellow solid (12 mg, 31% yield); m.p. = 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.16 (m, 2H), 7.76 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 0.3 Hz, 1H), 7.50−7.44 (m, 3H), 7.39−7.29 (m, 4H), 7.06 (d, J = 7.8 Hz, 2H), 6.93−6.89 (m, 1H), 3.96 (s, 3H), 3.68 (t, J = 4.8 Hz, 4H), 3.51 (t, J = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.9, 151.6, 146.8, 139.9, 134.4, 129.4, 129.3, 128.7, 128.2, 126.6, 122.2, 122.0, 119.9, 116.2, 111.8, 104.0, 55.5, 51.1, 49.5; FT-IR (KBr): 2925, 2852, 2824, 1598, 1504, 1241, 1217 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3O$ $[M+H]^+$: 396.2076; found: 396.2086.

3-(4-nitrophenyl)-1-(4-phenylpiperazin-1-yl)isoquinoline (20p)



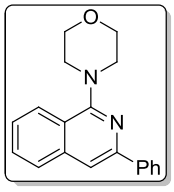
R_f = 0.6 (20% EtOAc in hexane); yellow solid (8.5 mg, 21% yield); m.p. = 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37−8.32 (m, 2H), 8.34 (d, J = 0.5 Hz, 2H), 8.17 (d, J = 8.2 Hz, 1H), 7.88 (dd, J = 8.6, 0.4 Hz, 1H), 7.85 (s, 1H), 7.68 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.58 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.35−7.31 (m, 2H), 7.06−7.04 (m, 2H), 6.94−6.90 (m, 1H), 3.74−3.71 (m, 4H), 3.52−3.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 147.7, 145.9, 145.8, 138.9, 135.5, 130.4, 129.4, 128.2, 127.3, 127.2, 125.7, 124.1, 121.4, 120.1, 116.3, 113.4, 51.4, 49.4; FT-IR (KBr): 2922, 2847, 1595, 1567, 1522, 1499, 1338, 1244, 1108, 846, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_4O_2$ $[M+H]^+$: 411.1821; found: 411.1825.

3-phenyl-1-(pyrrolidin-1-yl)isoquinoline (20q)



R_f = 0.8 (10% EtOAc in hexane); yellow solid (6 mg, 22% yield); m.p. = 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 8.5, 0.8 Hz, 1H), 8.20−8.18 (m, 2H), 7.74−7.72 (m, 1H), 7.53 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 7.49−7.45 (m, 3H), 7.39−7.34 (m, 2H), 3.97−3.94 (m, 4H), 2.05−2.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 148.4, 140.3, 139.9, 129.2, 128.6, 128.2, 127.4, 126.8, 126.2, 124.3, 119.5, 107.5, 51.5, 26.2; FT-IR (KBr): 3052, 2959, 2864, 1550, 1504, 1445, 1430, 770 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2$ $[M+H]^+$: 275.1548; found: 275.1539.

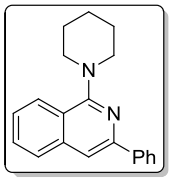
4-(3-phenylisoquinolin-1-yl)morpholine (20r)



R_f = 0.3 (10% EtOAc in hexane); brown solid (18.3 mg, 63% yield); m.p. = 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 8.09 (dd, J = 8.4, 0.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 7.61 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.51−7.47 (m, 3H), 7.41−7.37 (m, 1H), 4.03−4.01 (m, 4H), 3.56−3.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 148.4, 139.7, 139.3, 129.9, 128.8, 128.5, 127.9, 126.8, 126.1, 125.4, 120.7, 111.8, 67.3, 52.0; FT-IR (KBr): 3069, 2960, 2846,

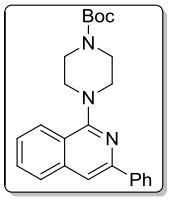
2829, 1563, 1501, 1413, 1399, 1262, 1113, 773 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O$ $[M+H]^+$: 291.1497; found: 291.1487.

3-phenyl-1-(piperidin-1-yl)isoquinoline (20s)



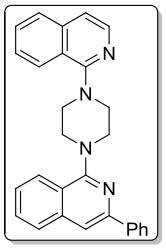
R_f = 0.7 (10% EtOAc in hexane); brown solid (12.3 mg, 43% yield); m.p. = 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.17 (m, 2H), 8.09 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.80−7.78 (m, 1H), 7.69 (s, 1H), 7.58 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.50−7.45 (m, 3H), 7.40−7.35 (m, 1H), 3.49 (t, *J* = 5.2 Hz, 4H), 1.90−1.85 (m, 4H), 1.76−1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 148.4, 140.1, 139.2, 129.7, 128.7, 128.3, 127.7, 126.8, 125.9, 125.7, 121.1, 111.0, 52.8, 26.4, 25.1; FT-IR (KBr): 3055, 2978, 2932, 2816, 1560, 1499, 1416, 1106, 848, 770 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}N_2$ $[M+H]^+$: 289.1705; found: 289.1699.

***tert*-butyl 4-(3-phenylisoquinolin-1-yl)piperazine-1-carboxylate (20t)**



R_f = 0.3 (10% EtOAc in hexane); yellow solid (18.3 mg, 47% yield); m.p. = 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 8.08 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.83−7.81 (m, 1H), 7.75 (d, *J* = 0.3 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.52−7.46 (m, 3H), 7.41−7.36 (m, 1H), 3.75−3.72 (m, 4H), 3.51−3.48 (m, 4H) 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.1, 148.4, 139.7, 139.3, 129.9, 128.8, 128.5, 127.9, 126.8, 126.2, 125.4, 120.8, 111.8, 80.0, 51.2, 44.3 (d, *J* = 90.9 Hz), 28.6; FT-IR (KBr): 3066, 2976, 2838, 1698, 1561, 1414, 1249, 1171, 773 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}N_3O_2$ $[M+H]^+$: 390.2182; found: 390.2176.

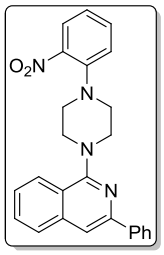
1-[4-(isoquinolin-1-yl)piperazin-1-yl]-3-phenylisoquinoline (20u)



R_f = 0.3 (10% EtOAc in hexane); yellow solid (15.2 mg, 37% yield); m.p. = 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.19 (m, 5H), 8.85−7.83 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 7.67−7.48 (m, 6H), 7.42−7.38 (m, 1H), 7.31 (d, *J* = 5.8 Hz, 1H), 3.84−3.82 (m, 4H), 3.75−3.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.0, 148.5, 147.1, 140.9, 139.9, 139.3, 138.3, 129.9, 128.8, 128.4, 127.8, 127.3, 126.8, 126.4, 126.1, 125.8, 125.6, 122.1, 121.0, 116.3, 111.7, 51.7, 51.6; FT-IR (KBr): 3059, 2988, 2920, 2884, 2835, 1559, 1499, 1404, 1364, 1264, 1012, 810, 771 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{25}N_4$ $[M+H]^+$: 417.2079; found: 417.2079.

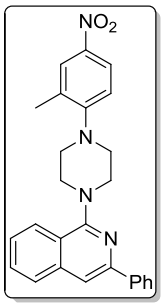
1-[4-(2-nitrophenyl)piperazin-1-yl]-3-phenylisoquinoline (20v)

R_f = 0.4 (10% EtOAc in hexane); gummy brown solid (23 mg, 57% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.19 (m, 2H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.84−7.80 (m, 2H), 7.75 (s, 1H), 7.61 (td, *J* = 6.9, 1.0 Hz, 1H), 7.54−7.48 (m, 4H), 7.41−7.38 (m, 1H), 7.26−7.24 (m, 1H),



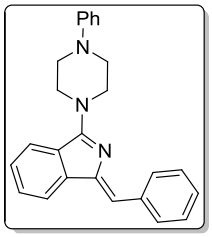
7.09−7.05 (m, 1H), 3.74−3.71 (m, 4H), 3.39−3.37 (m, 4H);. ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 148.4, 146.2, 143.5, 139.6, 139.3, 133.6, 129.9, 128.8, 128.5, 127.9, 126.8, 126.1, 126.0 125.4, 121.9, 121.3, 120.7, 111.6, 51.8, 51.3; FT-IR (KBr): 3059, 2919, 2841, 1604, 1562, 1519, 1368, 1229, 773 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_4O_2$ $[M+H]^+$: 411.1821; found: 411.1810.

1-[4-(2-methyl-4-nitrophenyl)piperazin-1-yl]-3-phenylisoquinoline (20w)



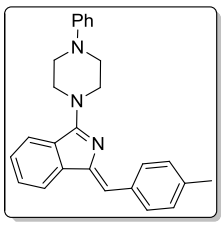
R_f = 0.5 (10% EtOAc in hexane); brown solid (23 mg, 55% yield); m.p. = 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (m, 2H), 8.14 (dd, *J* = 8.2, 0.7 Hz, 1H), 8.10−8.08 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 1H), 7.64 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.54−7.48 (m, 3H), 7.42−7.38 (m, 1H), 7.13−7.11 (m, 1H), 3.74−3.71 (m, 4H), 3.36−3.33 (m, 4H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 157.6, 148.5, 142.6, 139.7, 139.3, 132.6, 130.0, 128.8, 128.5, 127.9, 126.9, 126.8, 126.2, 125.4, 122.9, 120.8, 118.6, 111.9, 51.5, 51.4, 19.1; FT-IR (KBr): 2962, 2920, 2833, 1561, 1503, 1397, 1331, 1231, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}N_4O_2$ $[M+H]^+$: 425.1978; found: 425.1967.

(*Z*)-1-benzylidene-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21)



R_f = 0.2 (10% EtOAc in hexane); yellow solid (27.6 mg, 76% yield); m.p. = 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (m, 2H), 7.85−7.83 (m, 1H), 7.77−7.74 (m, 1H), 7.46−7.30 (m, 6H), 7.25 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.02−6.99 (m, 2H), 6.93 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.73 (s, 1H), 4.21 (t, *J* = 5.2 Hz, 4H), 3.43 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.2, 147.3, 145.2, 137.3, 131.4, 130.7, 129.4, 128.53, 128.48, 127.2, 127.1, 122.4, 120.4, 120.1, 116.5, 114.7, 49.4, 47.1; FT-IR (KBr): 3063, 2924, 2811, 1547, 1353, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}N_3$ $[M+H]^+$: 366.1970; found: 366.1967.

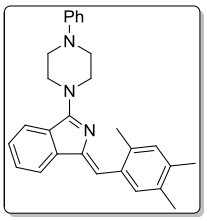
(*Z*)-1-(4-methylbenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21a)



R_f = 0.3 (10% EtOAc in hexane); yellow solid (23.4 mg, 62% yield); m.p. = 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.44−7.40 (m, 1H), 7.35−7.30 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.01 (dd, *J* = 8.8, 0.9 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.72 (s, 1H), 4.20 (t, *J* = 5.1 Hz, 4H), 3.43 (t, *J* = 5.1 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 151.2, 146.6, 145.2, 137.2, 134.5, 131.3, 130.7, 129.4, 129.3, 128.4, 126.9, 122.4, 120.4, 120.0, 116.5, 115.1,

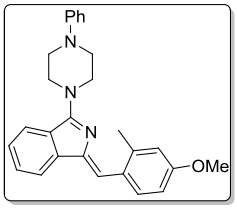
49.4, 47.2, 21.6; FT-IR (KBr): 2923, 2854, 2820, 1600, 1536, 1448, 1351, 1231, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2115.

(*Z*)-3-(4-phenylpiperazin-1-yl)-1-(2,4,5-trimethylbenzylidene)-1H-isoindole (21b)



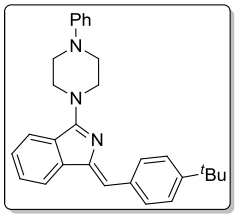
R_f = 0.3 (10% EtOAc in hexane); brown solid (20 mg, 50% yield); m.p. = 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.45−7.42 (m, 1H), 7.37 (m, 3H), 7.04−7.00 (m, 2H), 7.00−6.91 (m, 3H), 4.19 (t, *J* = 5.1 Hz, 4H), 3.43 (t, *J* = 5.1 Hz, 4H), 2.46 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 151.2, 146.2, 145.3, 136.0, 134.6, 134.0, 132.8, 132.7, 131.6, 131.3, 129.4, 128.2, 126.9, 122.3, 120.3, 120.0, 116.5, 112.0, 49.4, 47.2, 20.0, 19.8, 19.7; FT-IR (KBr): 2918, 2853, 1600, 1537, 1502, 1447, 1231, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}N_3$ $[M+H]^+$: 408.2440; found: 408.2451.

(*Z*)-1-(4-methoxy-2-methylbenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21c)



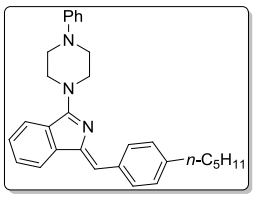
R_f = 0.2 (10% EtOAc in hexane); yellow solid (22.7 mg, 56% yield); m.p. = 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.42 (td, *J* = 7.4, 0.9 Hz, 1H), 7.35−7.30 (m, 3H), 7.01−7.00 (m, 2H), 6.94−6.90 (m, 1H), 6.92 (s, 1H), 6.88 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.75 (d, *J* = 2.7 Hz, 1H), 4.18 (t, *J* = 5.1 Hz, 4H), 3.84 (s, 3H), 3.42 (t, *J* = 5.1 Hz, 4H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 158.8, 151.2, 145.5, 145.3, 138.9, 133.1, 131.1, 129.4, 128.4, 128.2, 126.7, 122.3, 120.4, 119.9, 116.5, 115.7, 111.8, 111.5, 55.3, 49.4, 47.2, 20.7; FT-IR (KBr): 2908, 2812, 1599, 1543, 1497, 1257, 1238, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}N_3O$ $[M+H]^+$: 410.2232; found: 410.2238.

(*Z*)-1-[4-(tert-butyl)benzylidene]-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21d)



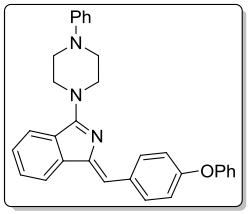
R_f = 0.5 (10% EtOAc in hexane); yellow solid (25.5 mg, 61% yield); m.p. = 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.17 (m, 2H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.47−7.41 (m, 3H), 7.36−7.31 (m, 3H), 7.02−7.00 (m, 2H), 6.96−6.91 (m, 1H), 6.74 (s, 1H), 4.20 (t, *J* = 5.1 Hz, 4H), 3.43 (t, *J* = 5.1 Hz, 4H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 151.2, 150.3, 146.7, 145.2, 134.4, 131.3, 130.5, 129.4, 128.3, 126.9, 125.5, 122.3, 120.4, 120.1, 116.5, 114.9, 49.4, 47.1, 34.8, 31.4; FT-IR (KBr): 2957, 2925, 2854, 1601, 1531, 1503, 1445, 1233, 928, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}N_3$ $[M+H]^+$: 422.2596; found: 422.2586.

(*Z*)-1-(4-*n*-pentylbenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21e)



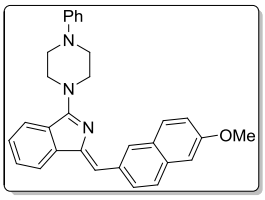
R_f = 0.2 (10% EtOAc in hexane); brown gummy liquid (23.3 mg, 54% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.4, 0.9 Hz, 1H), 7.37−7.30 (m, 3H), 7.23 (d, J = 8.2 Hz, 2H), 7.02−6.99 (m, 2H), 6.93 (tt, J = 7.4, 1.0 Hz, 1H), 6.73 (s, 1H), 4.20 (t, J = 5.1 Hz, 4H), 3.43 (t, J = 5.1 Hz, 4H), 2.64 (t, J = 7.4 Hz, 2H), 1.65 (qui, J = 7.5 Hz, 2H), 1.38−1.30 (m, 4H), 0.93−0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 151.2, 146.6, 145.2, 142.3, 134.7, 131.3, 130.7, 129.4, 128.7, 128.3, 126.9, 122.4, 120.4, 120.0, 116.5, 115.1, 49.4, 47.2, 36.0, 31.6, 31.2, 22.7, 14.2; FT-IR (neat): 2923, 2852, 2822, 1598, 1527, 1505, 1444, 1348, 1233, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}N_3$ $[M+H]^+$: 436.2753; found: 436.2758.

(*Z*)-1-(4-phenoxybenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21f)



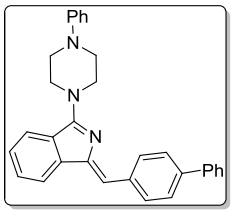
R_f = 0.3 (10% EtOAc in hexane); brown yellow solid (26.3 mg, 58% yield); m.p. = 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.25 (m, 2H), 7.84 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.44 (td, J = 7.4, 0.8 Hz, 1H), 7.39−7.31 (m, 5H), 7.15−7.11 (m, 1H), 7.10−7.05 (m, 4H), 7.00 (dd, J = 8.8, 1.0 Hz, 2H), 6.95−6.91 (m, 1H), 6.73 (s, 1H), 4.19 (t, J = 5.1 Hz, 4H), 3.42 (t, J = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.3, 156.5, 151.2, 146.5, 145.1, 132.6, 132.2, 131.2, 129.9, 129.4, 128.4, 127.0, 123.4, 122.4, 120.4, 120.0, 119.2, 118.9, 116.5, 114.1, 49.3, 47.1; FT-IR (KBr): 2922, 2850, 2811, 1587, 1542, 1501, 1448, 1232 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_3O$ $[M+H]^+$: 458.2232; found: 458.2227.

(*Z*)-1-[(6-methoxynaphthalen-2-yl)methylene]-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21g)



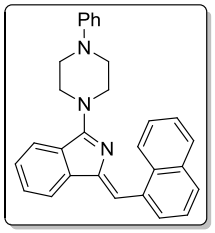
R_f = 0.1 (10% EtOAc in hexane); yellow solid (25.2 mg, 57% yield); m.p. = 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, J = 8.7, 1.7, Hz, 1H), 8.47 (d, J = 0.1 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.80−7.75 (m, 3H), 7.45 (td, J = 7.4, 0.9 Hz, 1H), 7.37−7.31 (m, 3H), 7.16 (d, J = 2.6 Hz, 1H), 7.13 (s, 1H) 7.03−7.00 (m, 2H), 6.94 (tt, J = 7.4, 1.0 Hz, 1H), 6.88 (s, 1H), 4.24 (t, J = 5.1 Hz, 4H), 3.95 (s, 3H), 3.45 (t, J = 5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 158.0, 151.2, 146.9, 145.2, 134.0, 133.0, 131.2, 130.1, 130.0, 129.4, 129.3, 129.1, 128.4, 127.0, 126.9, 122.4, 120.4, 120.1, 118.8, 116.5, 115.2, 105.9, 55.4, 49.4, 47.2; FT-IR (KBr): 3062, 2922, 2851, 2811, 1599, 1542, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{28}N_3O$ $[M+H]^+$: 446.2232; found: 446.2242.

(*Z*)-1-{[1,1'-biphenyl]-4-ylmethylene}-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21h)



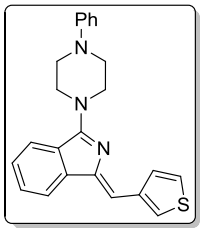
R_f = 0.1 (10% EtOAc in hexane); pale yellow solid (31.2 mg, 71% yield); m.p. = 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35−8.33 (m, 2H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70−7.67 (m, 4H), 7.49−7.43 (m, 3H), 7.38−7.32 (m, 4H), 7.02 (dd, *J* = 8.8, 1.0 Hz, 2H), 6.96−6.92 (m, 1H), 6.77 (s, 1H), 4.32 (t, *J* = 5.1 Hz, 4H), 3.44 (t, *J* = 5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.2, 147.5, 145.1, 141.1, 139.6, 136.5, 131.4, 131.1, 129.4, 128.9, 128.5, 127.3, 127.2, 127.1, 127.0, 122.5, 120.4, 120.2, 116.5, 114.2, 49.4, 47.2; FT-IR (KBr): 3028, 2923, 2853, 2799, 1600, 1555, 1541, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_3$ $[M+H]^+$: 442.2283; found: 442.2275.

(*Z*)-1-(naphthalen-1-ylmethylene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21i)



R_f = 0.2 (10% EtOAc in hexane); brown solid (19.5 mg, 50% yield); m.p. = 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (dd, *J* = 7.4, 0.8 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.89−7.86 (m, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.63−7.55 (m, 3H), 7.52−7.47 (m, 2H), 7.41−7.37 (m, 1H), 7.35−7.31 (m, 2H), 7.01−6.99 (m, 2H), 6.95−6.91 (m, 1H), 4.23 (t, *J* = 5.1 Hz, 4H), 3.43 (t, *J* = 5.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.2, 148.1, 145.3, 134.0, 132.3, 131.6, 130.1, 129.41, 128.38, 129.0, 128.6, 127.7, 127.3, 126.1, 126.0, 125.5, 123.6, 122.5, 120.4, 120.2, 116.5, 109.8, 49.4, 47.2; FT-IR (KBr): 3040, 2922, 2852, 2815, 1600, 1532, 1504, 1446, 1232, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_3$ $[M+H]^+$: 416.2127; found: 416.2116.

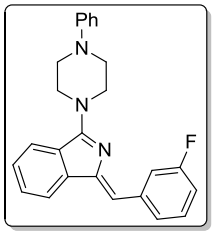
(*Z*)-3-(4-phenylpiperazin-1-yl)-1-(thiophen-3-ylmethylene)-1H-isoindole (21j)



R_f = 0.3 (10% EtOAc in hexane); brown solid (24.3 mg, 66% yield); m.p. = 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 3.0, 1.0, 0.6 Hz, 1H), 7.91 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.80 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.74 (dt, *J* = 7.7, 0.7 Hz, 1H), 7.42 (td, *J* = 7.3, 0.9 Hz, 1H), 7.36−7.30 (m, 4H), 7.01−6.99 (m, 2H), 6.93 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.81 (s, 1H), 4.19 (t, *J* = 5.1 Hz, 4H), 3.42 (t, *J* = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 151.2, 146.2, 144.7, 138.7, 131.7, 129.9, 129.4, 128.4, 127.0, 125.7, 125.1, 122.5, 120.4, 120.0, 116.5, 109.2, 49.3, 47.2; FT-IR (KBr): 2923, 2853, 1597, 1539, 1443, 1339, 1230, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{22}N_3S$ $[M+H]^+$: 372.1534; found: 372.1528.

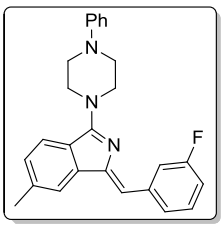
(*Z*)-1-(3-fluorobenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21k)

R_f = 0.4 (10% EtOAc in hexane); yellow solid (26.3 mg, 69% yield); m.p. = 197−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (ddd, *J* = 11.3, 2.6, 1.5 Hz, 1H), 7.82 (dt, *J* = 7.5, 0.8 Hz,



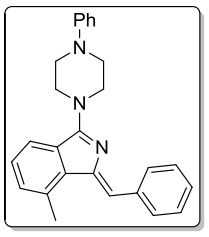
1H), 7.77−7.74 (m, 2H), 7.45 (td, *J* = 7.4, 1.0 Hz, 1H), 7.39−7.30 (m, 4H), 7.02−6.99 (m, 2H), 6.96−6.91 (m, 2H), 6.66 (s, 1H), 4.22 (t, *J* = 5.2 Hz, 4H), 3.43 (t, *J* = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.1 (d, *J* = 242.0 Hz), 151.1, 148.4, 145.0, 139.5 (d, *J* = 8.8 Hz), 131.5, 129.6 (d, *J* = 8.2 Hz), 129.4, 128.7, 127.5, 126.4 (d, *J* = 2.4 Hz), 122.6, 120.3 (d, *J* = 21.8 Hz), 116.8 (d, *J* = 23.0 Hz), 116.5, 113.9 (d, *J* = 21.4 Hz), 112.9, 112.8, 49.3, 47.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.49; FT-IR (KBr): 3065, 2902, 2812, 1572, 1544, 1353, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}FN_3$ $[M+H]^+$: 384.1876; found: 384.1867.

(*Z*)-1-(3-fluorobenzylidene)-6-methyl-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21l)



R_f = 0.2 (10% EtOAc in hexane); yellow solid (22 mg, 57% yield); m.p. = 200−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (ddd, *J* = 11.3, 2.5, 1.5 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.63−7.61 (m, 2H), 7.35−7.30 (m, 3H), 7.18−7.16 (m, 1H), 7.01−7.00 (m, 2H), 6.95−6.90 (m, 2H), 6.62 (s, 1H), 4.21 (t, *J* = 5.2 Hz, 4H), 3.42 (t, *J* = 5.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.1 (d, *J* = 241.3 Hz), 151.1, 148.5, 145.5, 139.7 (d, *J* = 8.7 Hz), 139.1, 129.6 (d, *J* = 8.7 Hz), 129.4, 129.2, 128.5, 126.3 (d, *J* = 2.3 Hz), 122.4, 120.8, 120.4, 116.7 (d, *J* = 23.0 Hz), 116.5, 113.7 (d, *J* = 21.9 Hz), 112.2 (d, *J* = 3.3 Hz), 49.3, 47.0, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.56; FT-IR (KBr): 3067, 2904, 2809, 1577, 1643, 689 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}FN_3$ $[M+H]^+$: 298.2033; found: 398.2042.

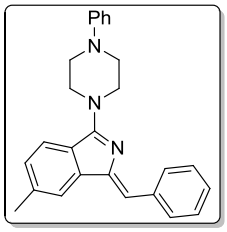
(*Z*)-1-benzylidene-7-methyl-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21m)



R_f = 0.3 (10% EtOAc in hexane); yellow solid (22.6 mg, 60% yield); m.p. = 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.27 (m, 2H), 7.65−7.63 (m, 1H), 7.44−7.40 (m, 2H), 7.35−7.31 (m, 2H), 7.28−7.22 (m, 3H), 7.02−6.99 (m, 2H), 6.93 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.89 (s, 1H), 4.16 (t, *J* = 5.1 Hz, 4H), 3.43 (t, *J* = 5.1 Hz, 4H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.2, 149.1, 141.9, 137.9, 133.3, 132.3, 131.8, 131.3, 129.4, 128.5, 127.3, 126.7, 120.5, 120.3, 120.2, 116.4, 49.3, 47.4; 21.7; FT-IR (KBr): 3064, 3012, 2814, 1540, 1445, 1354, 1328, 1234, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2121.

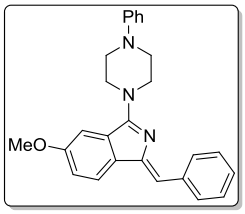
(*Z*)-1-benzylidene-6-methyl-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21n)

R_f = 0.3 (10% EtOAc in hexane); yellow solid (23.4 mg, 62% yield); m.p. = 181−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.23 (m, 2H), 7.64 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34−7.30 (m, 2H), 7.26−7.22 (m, 1H), 7.16 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.00 (dd, *J* = 8.8, 1.0 Hz, 2H), 6.95−6.91 (m, 1H), 6.69 (s, 1H), 4.20 (t, *J* = 5.1 Hz, 4H), 3.42 (t, *J*



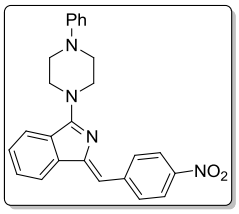
= 5.1 Hz, 4H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.2, 147.4, 145.7, 138.8, 137.4, 130.6, 129.4, 129.1, 128.5, 128.2, 127.1, 122.2, 120.7, 120.4, 116.5, 114.1, 49.4, 47.0; 21.8; FT-IR (KBr): 2902, 2811, 1549, 1444, 1352, 1233 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3$ $[M+H]^+$: 380.2127; found: 380.2121.

(*Z*)-1-benzylidene-5-methoxy-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21o)



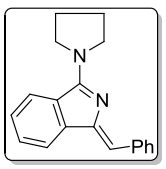
R_f = 0. 2 (10% EtOAc in hexane); yellow solid (16.5 mg, 43% yield); m.p. = 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.21 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.42−7.38 (m, 2H), 7.35−7.31 (m, 2H), 7.25−7.21 (m, 2H), 7.02−7.00 (m, 3H), 6.95−6.91 (m, 1H), 6.61 (s, 1H), 4.17 (t, *J* = 5.1 Hz, 4H), 3.90 (s, 3H), 3.42 (t, *J* = 5.2 Hz, 4H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 159.3, 151.2, 147.0, 138.0, 137.4, 132.7, 130.5, 129.4, 128.5, 127.0, 120.7, 120.0, 116.5, 114.1, 113.8, 108.5, 56.0, 49.3, 47.1; FT-IR (KBr): 3059, 2910, 2833, 1600, 1537, 1229 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3O$ $[M+H]^+$: 396.2076; found: 396.2083.

(*Z*)-1-(4-nitrobenzylidene)-3-(4-phenylpiperazin-1-yl)-1H-isoindole (21p)



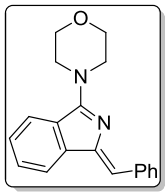
R_f = 0.3 (20% EtOAc in hexane); brown solid (17 mg, 42% yield); m.p. = 237−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37−8.34 (m, 2H), 8.25−8.22 (m, 2H), 7.85−7.82 (m, 1H), 7.79 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.48 (td, *J* = 7.4, 0.9 Hz, 1H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.35−7.31 (m, 2H), 7.02−6.99 (m, 2H), 6.94 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.65 (s, 1H), 4.28 (t, *J* = 5.1 Hz, 4H), 3.46 (t, *J* = 5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.2, 150.9, 145.6, 144.9, 144.4, 131.7, 130.6, 129.5, 129.3, 128.2, 123.9, 123.0, 120.7, 120.6, 116.6, 110.8, 49.4, 47.2; FT-IR (KBr): 2922, 2855, 1591, 1538, 1505, 1321, 1106, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_4O_2$ $[M+H]^+$: 411.1821; found: 411.1819.

(*Z*)-1-benzylidene-3-(pyrrolidin-1-yl)-1H-isoindole (21q)[29]



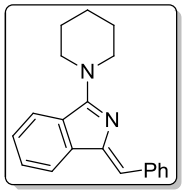
R_f = 0.2 (10% EtOAc in hexane); brown solid (18 mg, 67% yield); m.p. = 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.3, 0.4 Hz, 2H), 7.80 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.41 (td, *J* = 7.4, 1.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H) 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 7.22−7.18 (m, 1H), 6.61 (s, 1H), 4.01 (s, 4H), 2.06 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 148.5, 145.1, 138.3, 137.8, 132.1, 130.5, 128.4, 127.0, 126.6, 122.2, 120.0, 112.4, 49.8, 48.4, 26.9, 24.5; FT-IR (KBr): 3052, 2963, 2874, 1570, 1551, 1321, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2$ $[M+H]^+$: 275.1548; found: 275.1541.

(*Z*)-4-(1-benzylidene-1H-isoindol-3-yl)morpholine (21r)[29]



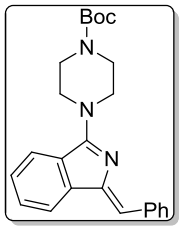
R_f = 0.1 (10% EtOAc in hexane); brown solid (19.3 mg, 67% yield); m.p. = 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23−8.20 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.44−7.36 (m, 3H), 7.33 (td, J = 7.8, 1.0 Hz, 1H), 7.26−7.22 (m, 1H), 6.72 (s, 1H), 4.04 (t, J = 4.5 Hz, 4H), 3.92 (t, J = 4.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.2, 145.2, 137.2, 131.3, 130.8, 128.53, 128.52, 127.3, 127.1, 122.4, 120.2, 114.9, 66.9, 47.5; FT-IR (KBr): 3056, 2953, 2853, 1543, 1347, 1281, 1119, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O$ $[M+H]^+$: 291.1497; found: 291.1492.

(*Z*)-1-benzylidene-3-(piperidin-1-yl)-1H-isoindole (21s)[29]



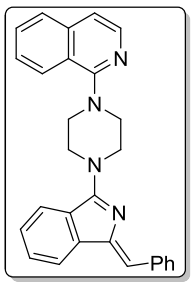
R_f = 0.4 (10% EtOAc in hexane); brown solid (17.2 mg, 60% yield); m.p. = 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.23 (m, 2H), 7.82 (dt, J = 7.6, 0.8 Hz, 1H), 7.73 (dt, J = 7.8, 0.8 Hz, 1H), 7.43−7.37 (m, 3H), 7.32 (td, J = 7.8, 1.1 Hz, 1H), 7.24−7.20 (m, 1H), 6.65 (s, 1H), 3.99−3.98 (m, 4H), 1.83−1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 147.7, 145.3, 137.6, 131.8, 130.5, 128.5, 128.2, 127.0, 126.8, 122.7, 120.0, 113.2; 48.6, 26.2, 24.8; FT-IR (KBr): 3062, 2932, 2849, 1537, 1446, 1280, 766 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}N_2$ $[M+H]^+$: 289.1705; found: 289.1698.

(*Z*)-*tert*-butyl 4-(1-benzylidene-1H-isoindol-3-yl)piperazine-1-carboxylate (21t)



R_f = 0.4 (20% EtOAc in hexane); yellow solid (11.4 mg, 29% yield); m.p. = 177–179 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.44−7.37 (m, 3H), 7.33 (t, J = 7.5 Hz, 1H), 7.26−7.22 (m, 1H), 6.72 (s, 1H), 4.03− 4.00 (m, 4H), 3.69−3.66 (m, 4H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 154.9, 147.2, 145.1, 137.1, 131.3, 130.7, 129.4, 128.5, 127.3, 127.1, 122.3, 120.1, 115.0, 80.3, 47.0, 43.4, (d, J = 118.3 Hz) 28.5; FT-IR (KBr): 3062, 2982, 2926, 2855, 1691, 1520, 1446, 1410, 1248, 1166, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}N_3O_2$ $[M+H]^+$: 390.2182; found: 390.2172.

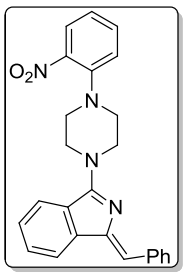
(*Z*)-1-[4-(1-benzylidene-1H-isoindol-3-yl)piperazin-1-yl]isoquinoline (21u)



R_f = 0.1 (10% EtOAc in hexane); brown solid (19 mg, 46% yield); m.p. = 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (m, 2H), 8.21−8.18 (m, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.81−7.78 (m, 2H), 7.66 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.58 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.46−7.34 (m, 4H), 7.32 (dd, J = 5.8, 0.4 Hz, 1H), 7.25−7.21 (m, 1H), 6.73 (s, 1H), 4.33−4.30

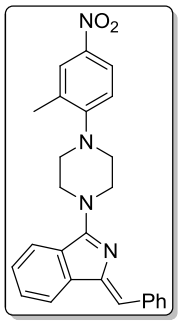
(m, 4H), 3.68−3.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.2, 147.4, 145.2, 140.8, 138.3, 137.3, 131.6, 130.8, 130.0, 128.53, 128.48, 127.4, 127.21, 127.18, 126.6, 125.5, 122.6, 121.8, 120.1, 116.5, 114.7, 51.4, 47.4; FT-IR (KBr): 2910, 2854, 2808, 1545, 1400, 1285, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{25}N_4$ $[M+H]^+$: 417.2079; found: 417.2083.

(*Z*)-1-benzylidene-3-[4-(2-nitrophenyl)piperazin-1-yl]-1H-isoindole (21v)



R_f = 0.1 (10% EtOAc in hexane); yellow solid (14 mg, 35% yield); m.p. = 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.4 Hz, 2H), 7.85−7.82 (m, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.54−7.50 (m, 1H), 7.45−7.32 (m, 4H), 7.24−7.18 (m, 2H), 7.14−7.09 (m, 1H), 6.72 (s, 1H), 4.21 (t, *J* = 4.9 Hz, 4H), 3.30 (t, *J* = 5.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 147.2, 145.9, 145.2, 143.8, 137.2, 133.8, 131.3, 130.8, 128.54, 128.52, 127.3, 127.2, 126.1, 122.7, 122.4, 121.3, 120.2, 114.8, 51.8, 47.3; FT-IR (KBr): 2957, 2924, 2853, 1538, 1533, 1449, 1410, 1247, 1122, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{23}N_4O_2$ $M+H]^+$: 411.1821; found: 411.1816.

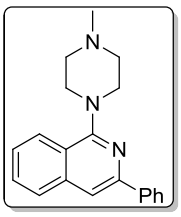
(*Z*)-1-benzylidene-3-[4-(2-methyl-4-nitrophenyl)piperazin-1-yl]-1H-isoindole (21w)



R_f = 0.6 (10% EtOAc in hexane); brown solid (19.5 mg, 47% yield); m.p. = 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.22 (m, 2H), 8.11−8.05 (m, 2H), 7.86−7.84 (m, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.44 (td, *J* = 7.4, 0.9 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.35 (td, *J* = 7.8, 1.1 Hz, 1H), 7.27−7.23 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.75 (s, 1H), 4.21 (t, *J* = 4.9 Hz, 4H), 3.24 (t, *J* = 5.0 Hz, 4H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.1, 147.1, 145.2, 143.0, 137.1, 132.7, 131.3, 130.8, 128.59, 128.56, 127.4, 127.2, 126.9, 122.9, 122.4, 120.2, 118.7, 115.2, 51.2, 47.4, 18.9; FT-IR (KBr): 3061, 3019, 2956, 2921, 2851, 1536, 1584, 1445, 1335, 1230, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}N_4O_2$ $M+H]^+$: 425.1978; found: 425.1978.

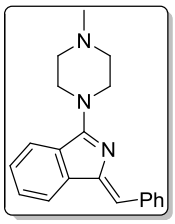
Procedure for the synthesis of a potent anti-tumour agent 1-(4-methylpiperazin-1-yl)-3-phenylisoquinoline (1c) and its characterization data

A mixture of 2-(phenylethynyl)benzonitrile **6** (1 equiv, 0.1 mmol), CuOTf.PhMe (0.10 equiv, 0.01 mmol) and *N*-methyl piperazine **19h** (1.5 equiv, 0.15 mmol) was heated to 120 °C in a closed vial for 42 h. After completion, the reaction mixture was diluted with dichloromethane (1 ml) and transferred to a round bottom flask. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using 5% MeOH in DCM as eluent to obtain the pure 1-(4-methylpiperazin-1-yl)-3-phenylisoquinoline **(1c)**.



R_f = 0.3 (5% MeOH in DCM); brown solid (22 mg, 36% yield); m.p. = 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 8.07 (dd, J = 8.3, 0.9 Hz, 1H), 7.80 (dd, J = 7.6, 0.5 Hz, 1H), 7.71 (d, J = 0.4 Hz, 1H), 7.59 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.50−7.45 (m, 3H), 7.40−7.36 (m, 1H), 3.60 (brs, 4H), 2.75 (brs, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 148.4, 139.8, 139.2, 129.8, 128.7, 128.4, 127.8, 126.8, 125.9, 125.6, 120.7, 111.3, 55.4, 51.2, 46.4; FT-IR (KBr): 3060, 2927, 2849, 2793, 1563, 1499, 1413, 1365, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}N_3$ $[M+H]^+$: 304.1814; found: 304.1825.

(*Z*)-1-benzylidene-3-(4-methylpiperazin-1-yl)-1H-isoindole (1c')

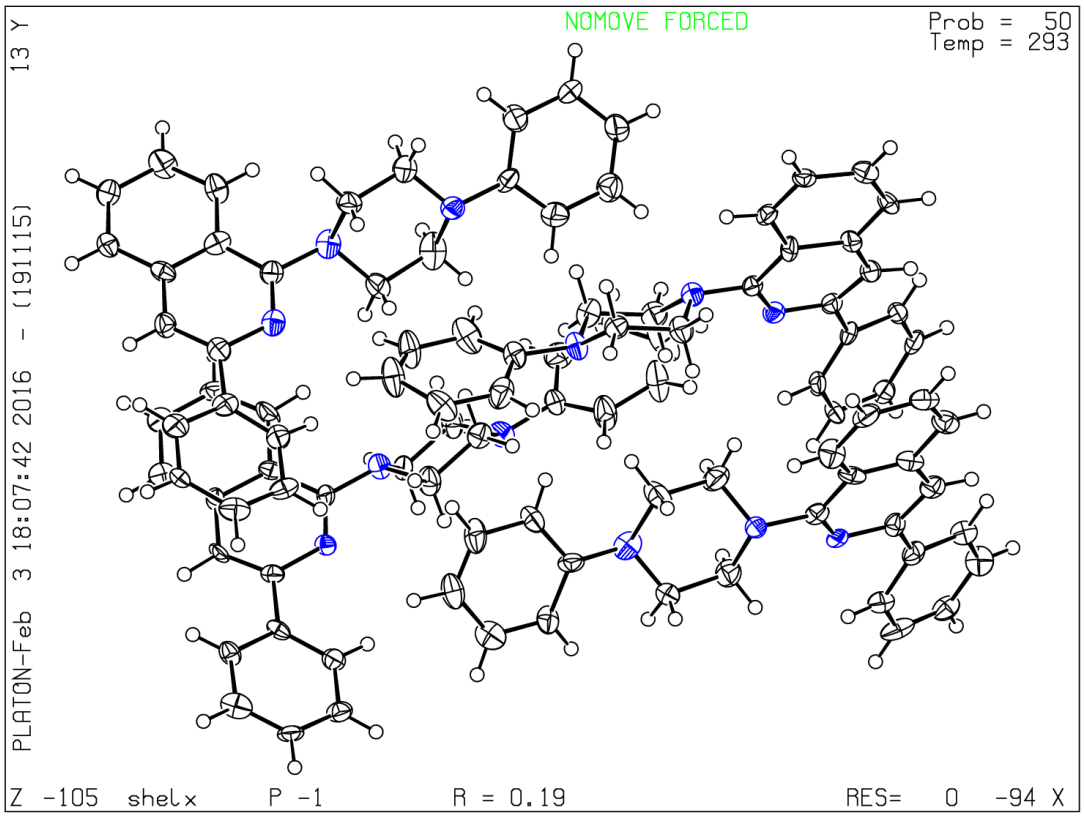


R_f = 0.4 (5% MeOH in DCM); brown solid (8 mg, 13% yield); m.p. = 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.42−7.37 (m, 3H), 7.32 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 6.69 (s, 1H), 4.07 (t, J = 5.0 Hz, 4H), 2.63 (t, J = 5.1 Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 147.3, 145.2, 137.3, 131.4, 130.6, 128.5, 128.4, 127.1, 127.0, 122.5, 120.0, 114.2, 55.0, 47.1, 46.3; FT-IR (KBr): 3059, 2943, 2932, 2838, 2788, 1526, 1448, 1271, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}N_3$ $[M+H]^+$: 304.1814; found: 304.1804.

X-Ray crystallographic analysis for compound 20 & 21q:

Crystal data and structure refinement for 20[34]

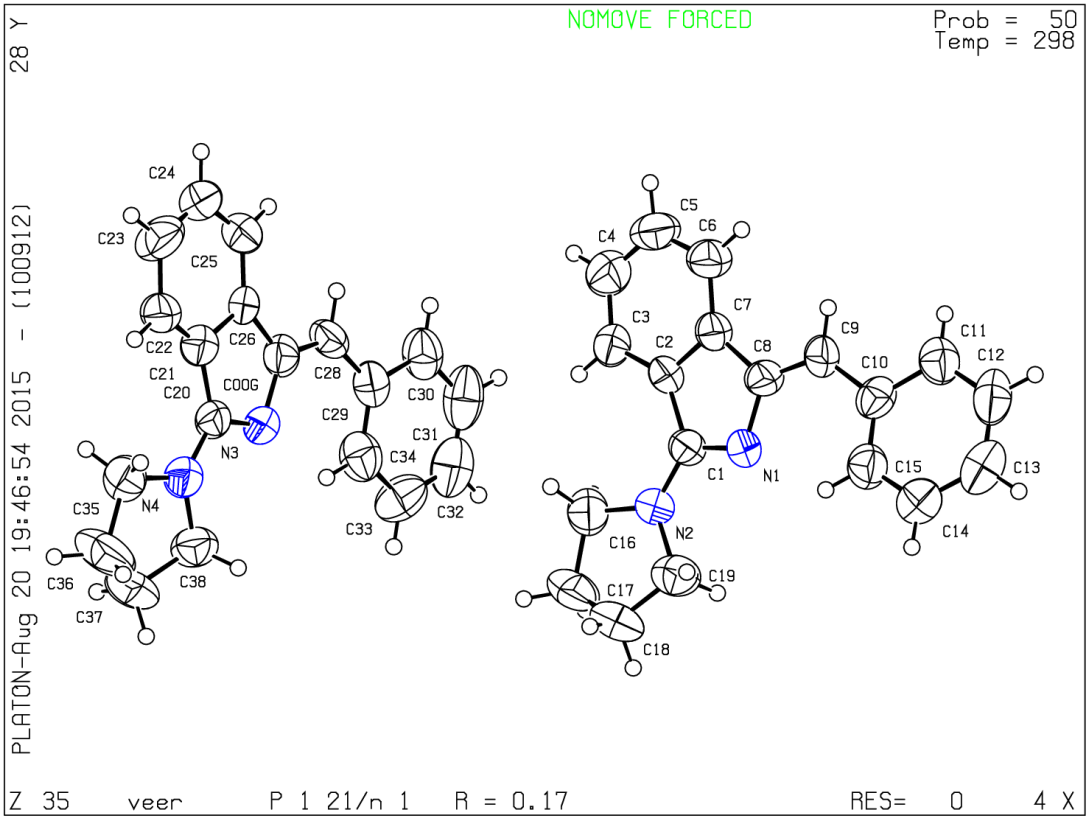
Identification code	**20**
Empirical formula	$C_{25}H_{23}N_3$
Formula weight	365.46
Temperature/K	293
Crystal system	triclinic
Space group	P-1
a/Å	10.409(3)
b/Å	18.311(6)
c/Å	20.951(7)
α/°	104.940(13)
β/°	104.204(8)
γ/°	90.057(9)
Volume/Å^3	3731(2)
Z	8
ρ_{calc}g/cm^3	1.301
μ/mm^{-1}	0.077
F(000)	1552.0
Crystal size/mm^3	0.2 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.052 to 50.7
Index ranges	$-12 \leq h \leq 12$, $-22 \leq k \leq 22$, $-25 \leq l \leq 25$
Reflections collected	34237
Independent reflections	13625 [R_{int} = 0.0882, R_{sigma} = 0.1190]
Data/restraints/parameters	13625/0/1010
Goodness-of-fit on F^2	1.071
Final R indexes [I>=2σ (I)]	R_1 = 0.1910, wR_2 = 0.4649
Final R indexes [all data]	R_1 = 0.2399, wR_2 = 0.4954
Largest diff. peak/hole / e Å^{-3}	1.16/-0.65



Crystal data and structure refinement for compound 21q[35]

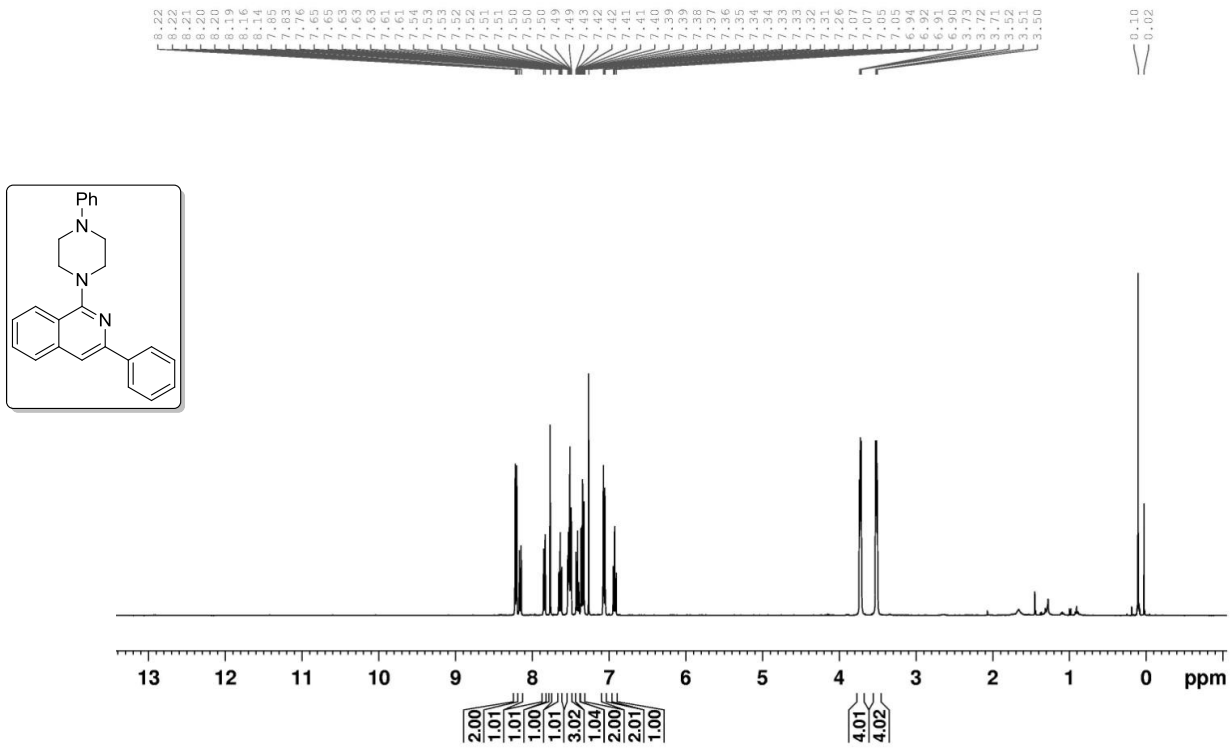
Identification code	**21q**
Empirical formula	$C_{19}H_{18}N_2$
Formula weight	274.35
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	18.099(5)
b/Å	9.777(3)
c/Å	18.228(5)
α/°	90
β/°	113.477(10)
γ/°	90
Volume/Å^3	2958.4(14)
Z	8

$\rho_{calc}g/cm^3$	1.232
μ/mm^{-1}	0.073
F(000)	1168.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.132 to 54.964
Index ranges	-23 ≤ h ≤ 23, -12 ≤ k ≤ 12, -23 ≤ l ≤ 23
Reflections collected	25252
Independent reflections	6764 [R_{int} = 0.1147, R_{sigma} = 0.0860]
Data/restraints/parameters	6764/0/379
Goodness-of-fit on F^2	1.604
Final R indexes [I>=2σ (I)]	R_1 = 0.1720, wR_2 = 0.4955
Final R indexes [all data]	R_1 = 0.2354, wR_2 = 0.5209
Largest diff. peak/hole / e $Å^{-3}$	0.39/-0.35

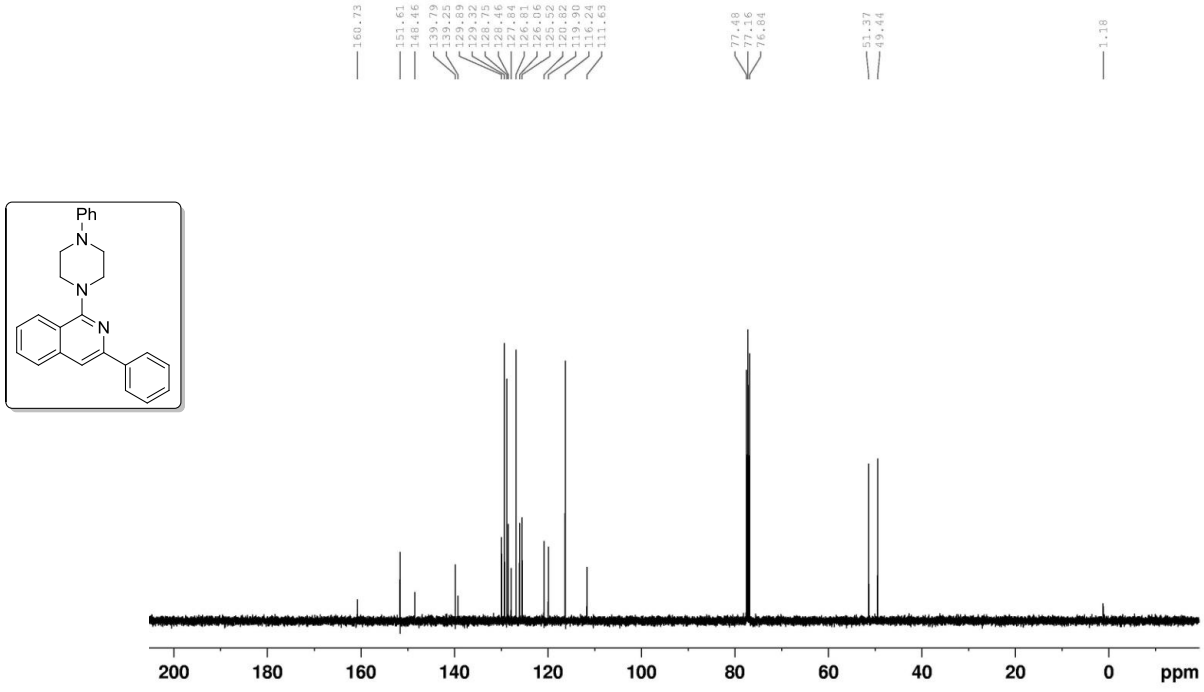


Copies of ^{1}H, ^{13}C & ^{19}F spectra of compounds 20, 20a-20w, 21, 21a-21w & 1c, 1c'

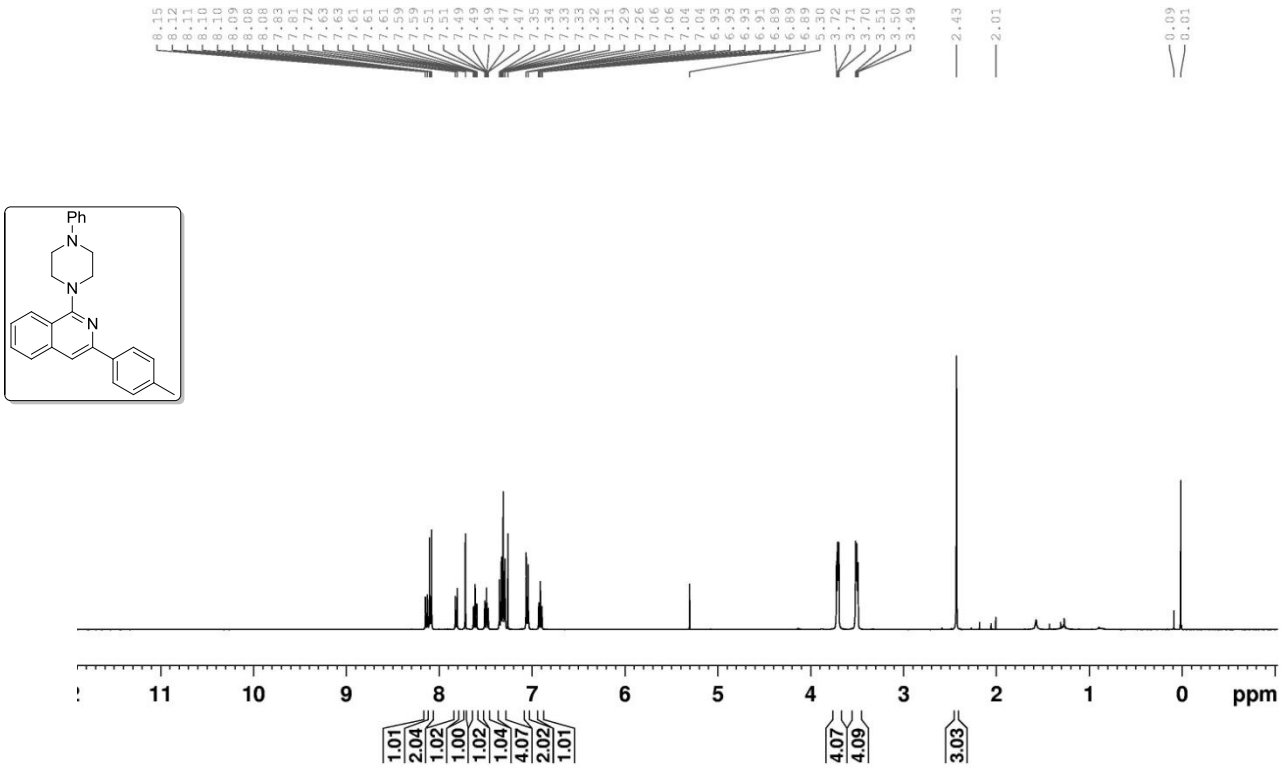
^{1}H NMR spectrum of compound **20**



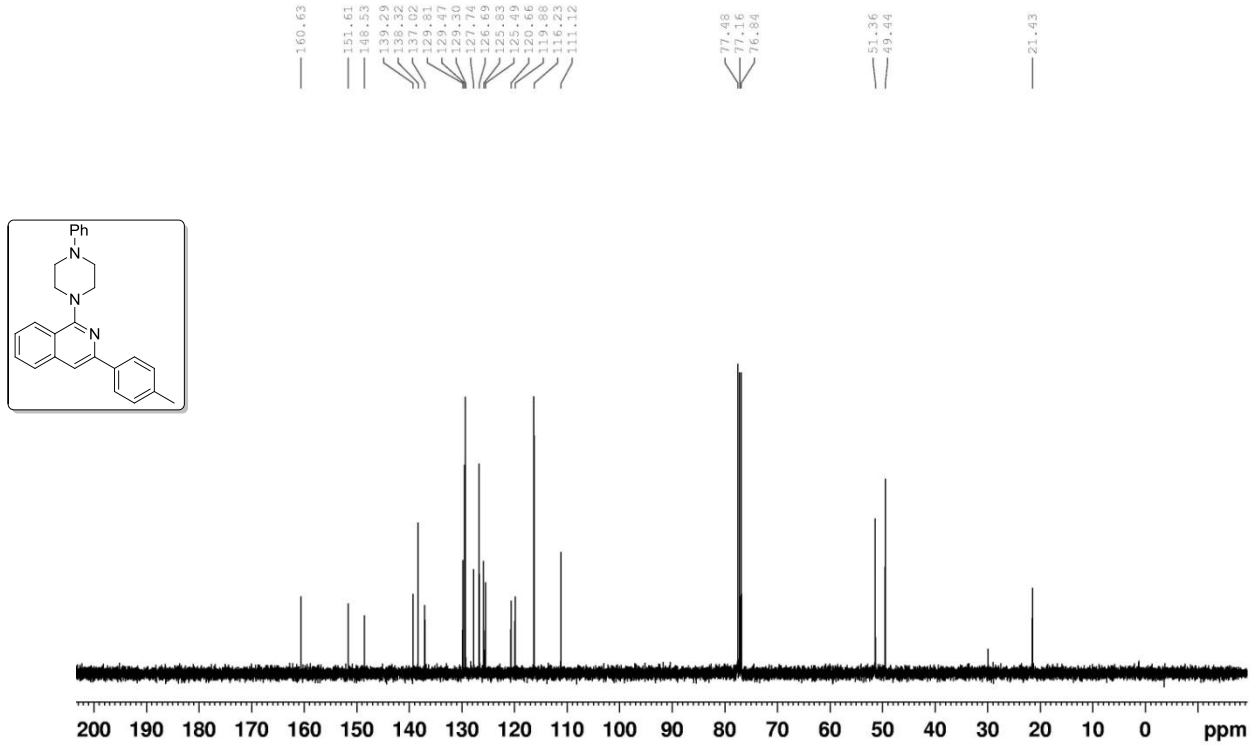
^{13}C NMR spectrum of compound **20**



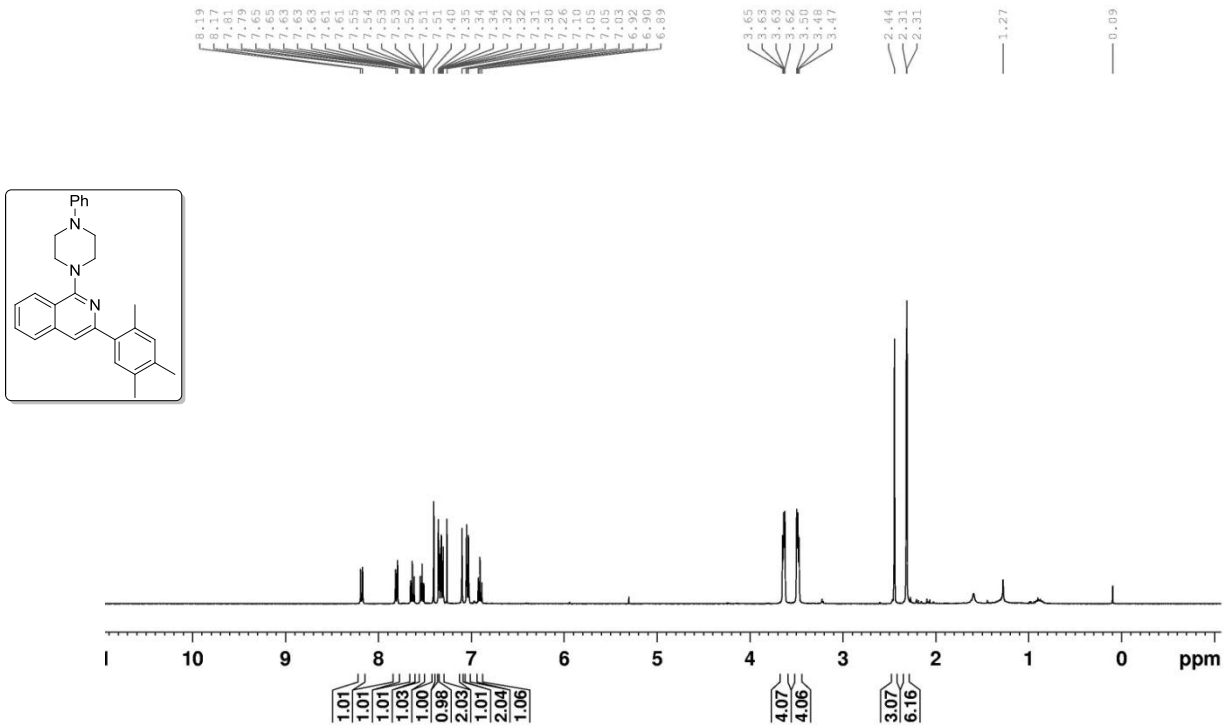
^{1}H NMR spectrum of compound **20a**



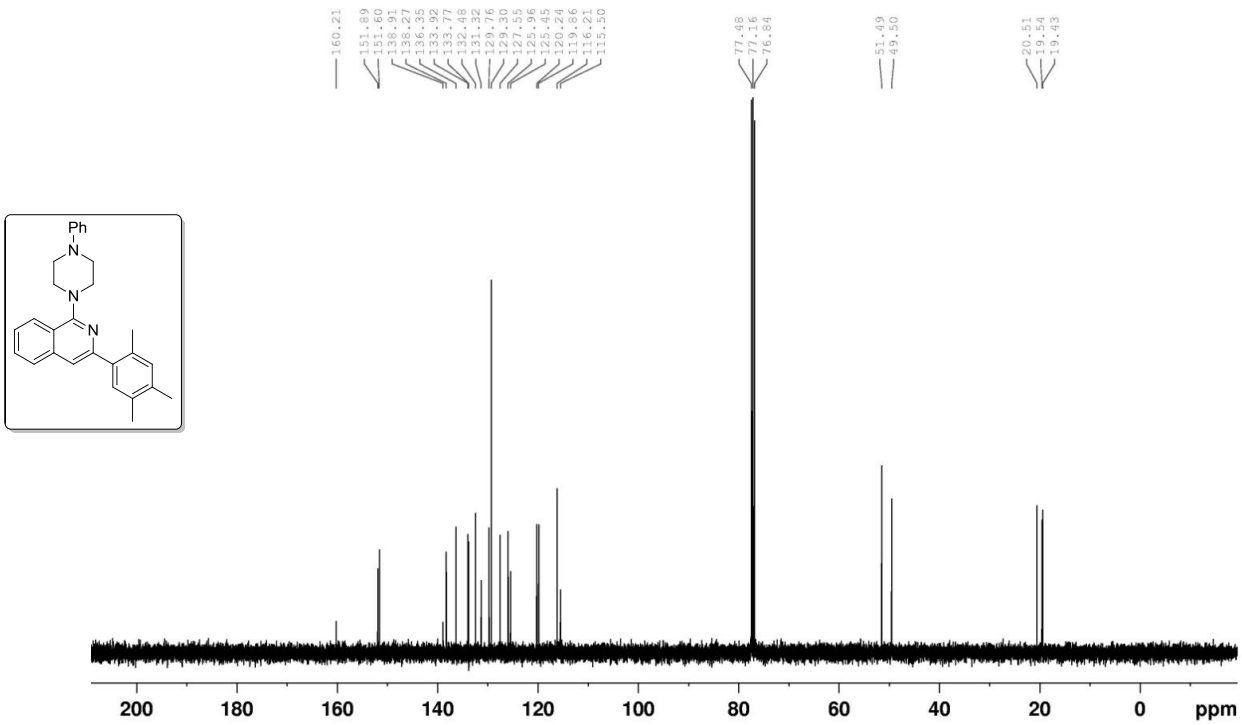
^{13}C NMR spectrum of compound **20a**



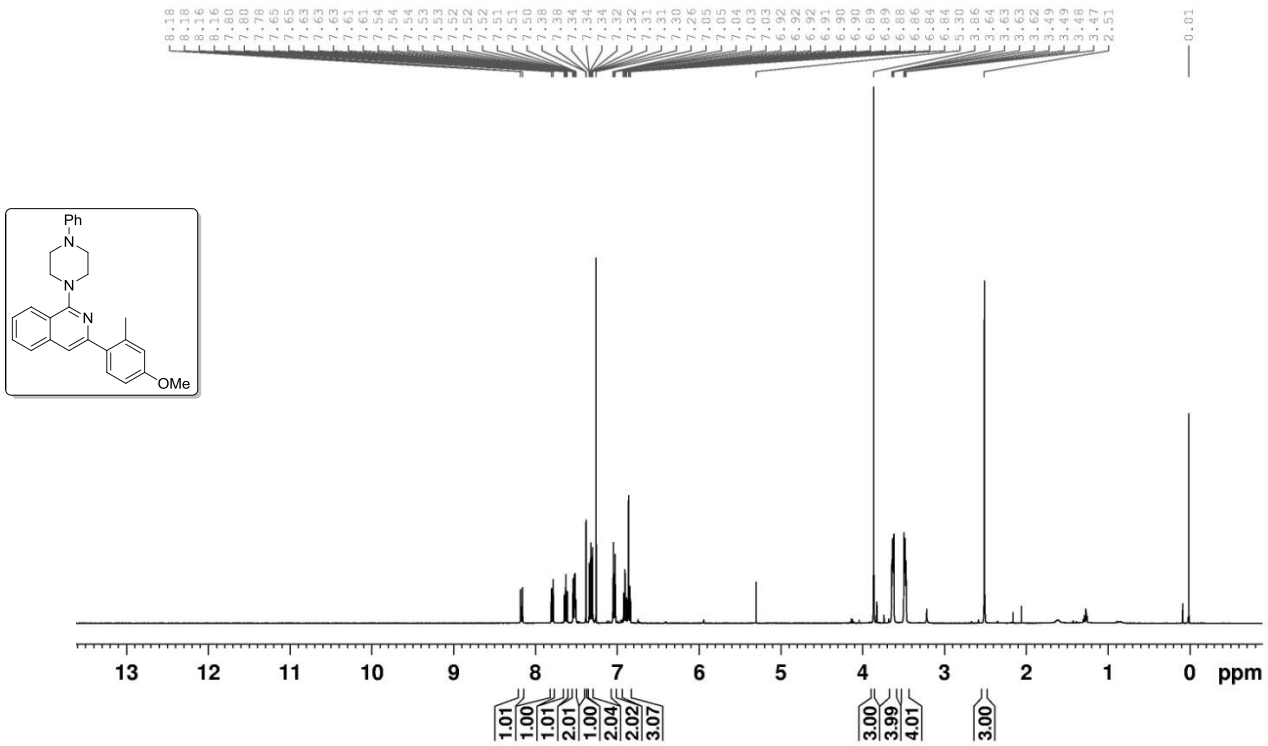
^{1}H NMR spectrum of compound **20b**



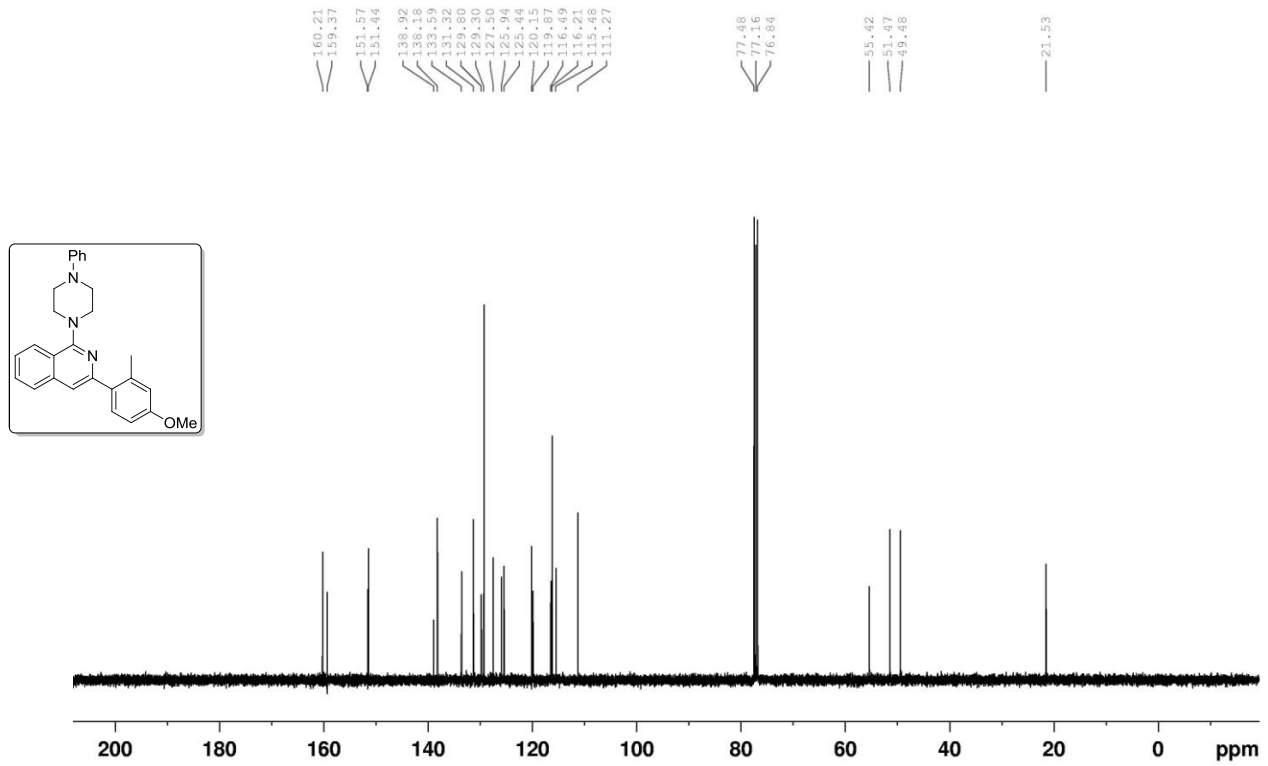
^{13}C NMR spectrum of compound **20b**



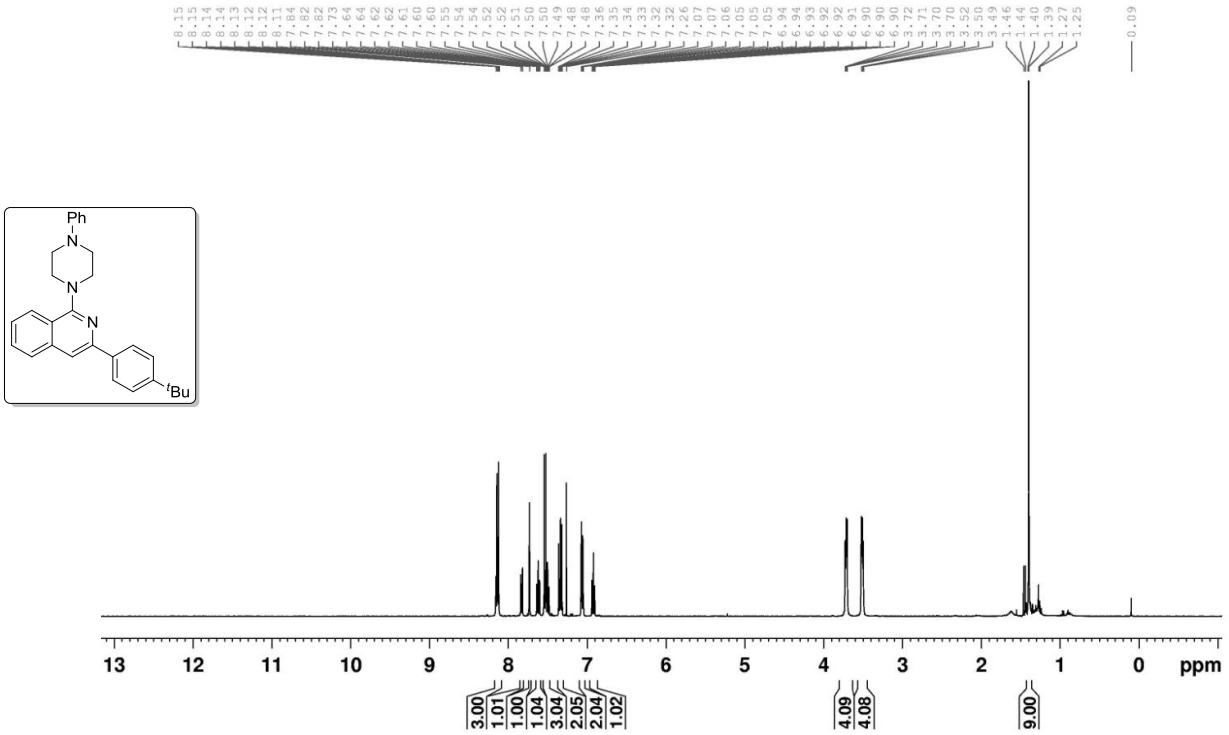
^{1}H NMR spectrum of compound **20c**



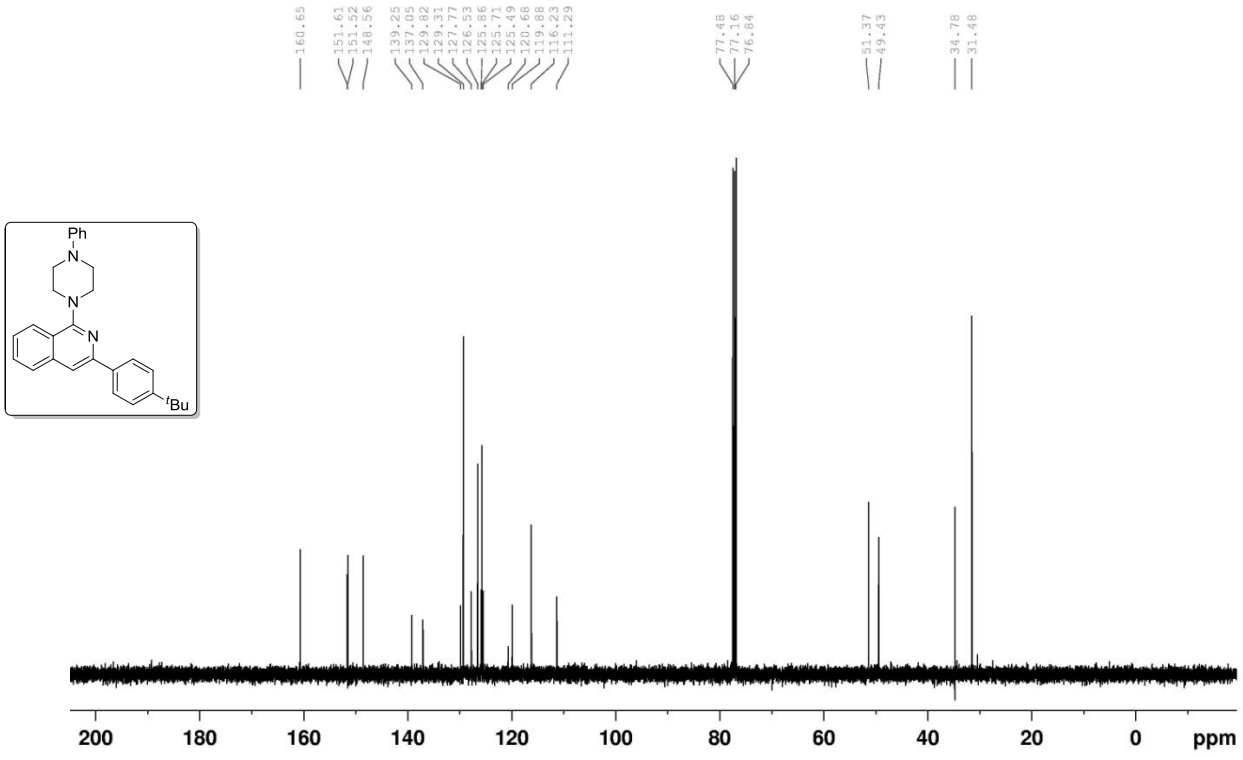
^{13}C NMR spectrum of compound **20c**



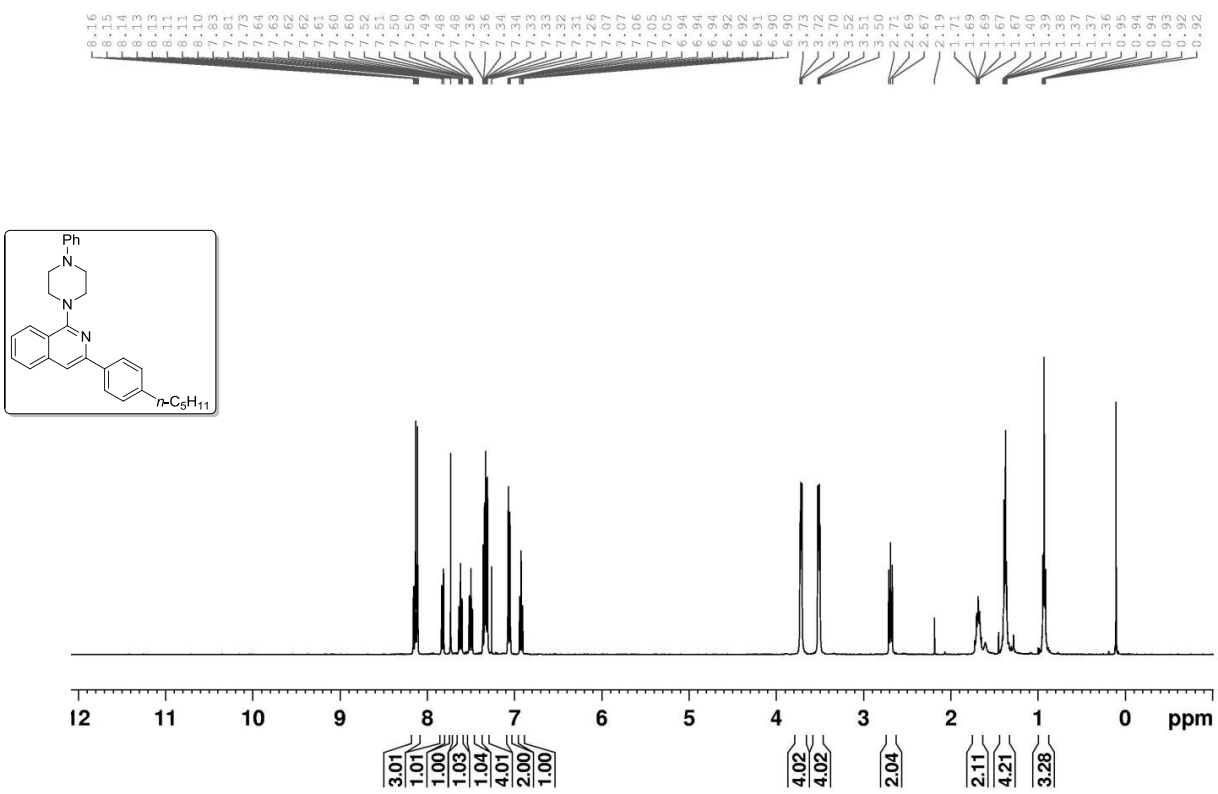
^{1}H NMR spectrum of compound **20d**



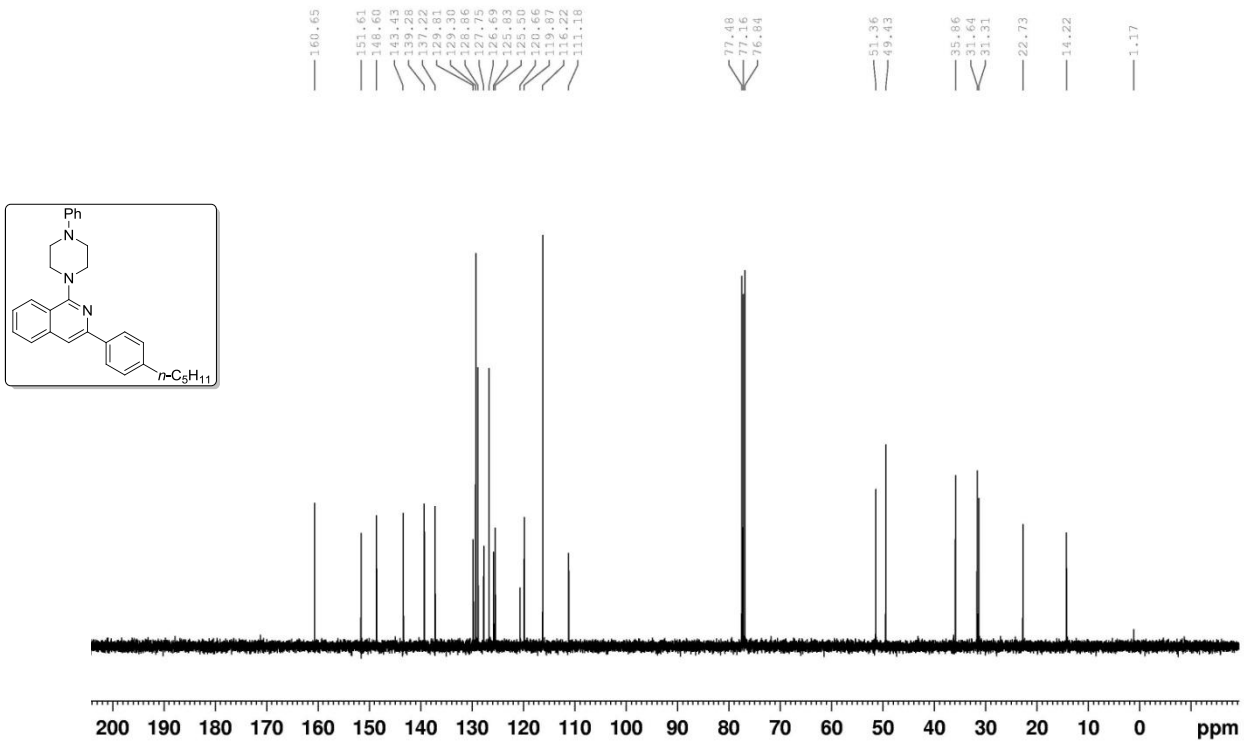
^{13}C NMR spectrum of compound **20d**



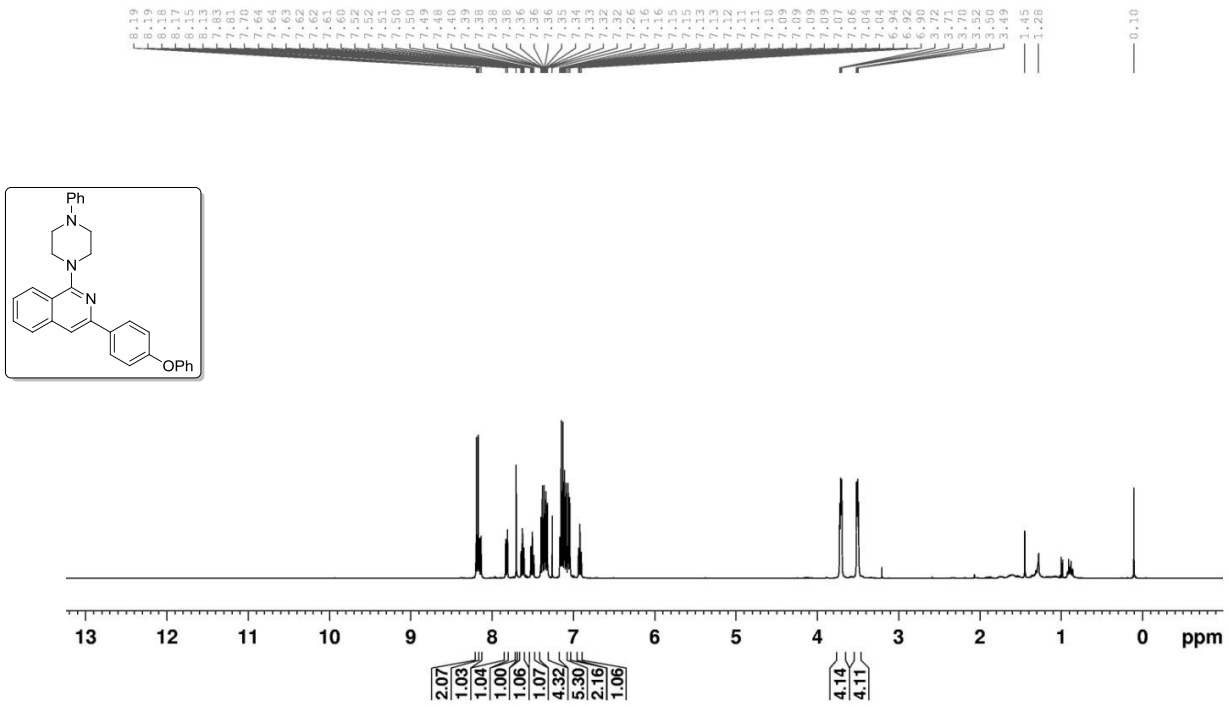
^{1}H NMR spectrum of compound **20e**



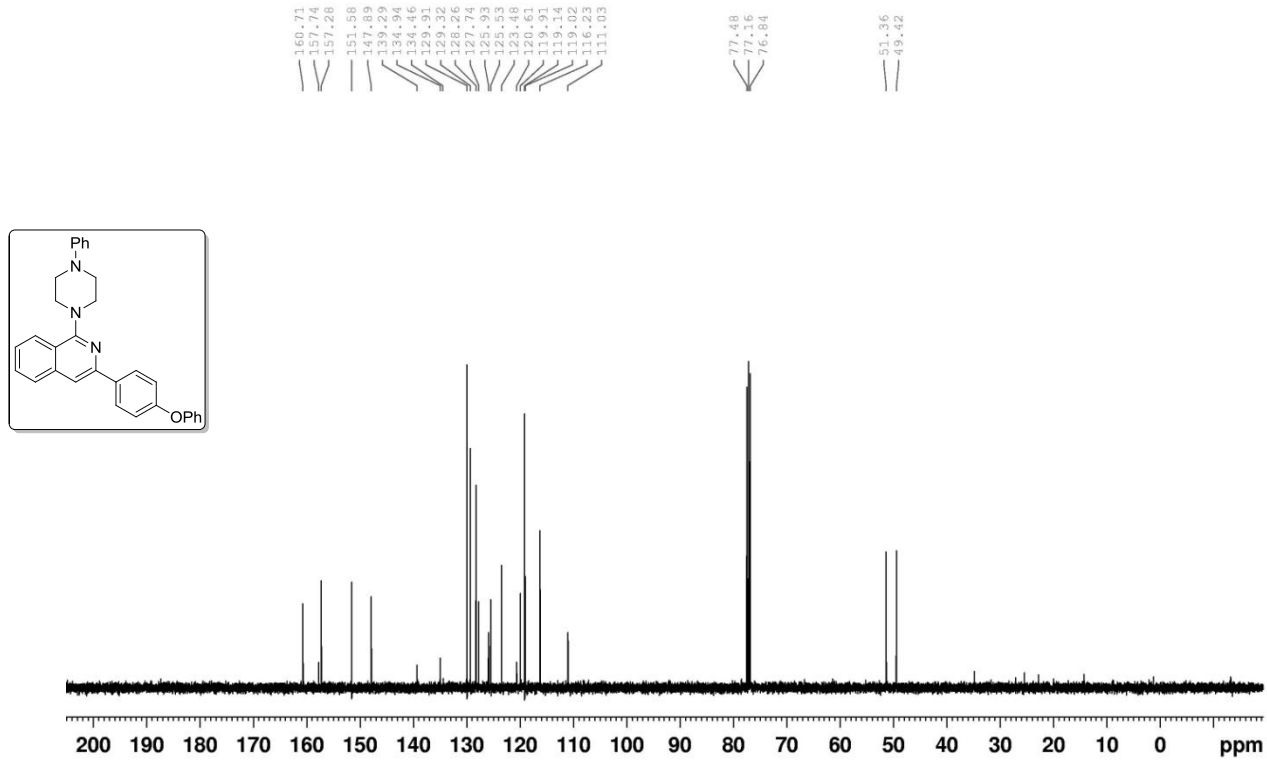
^{13}C NMR spectrum of compound **20e**



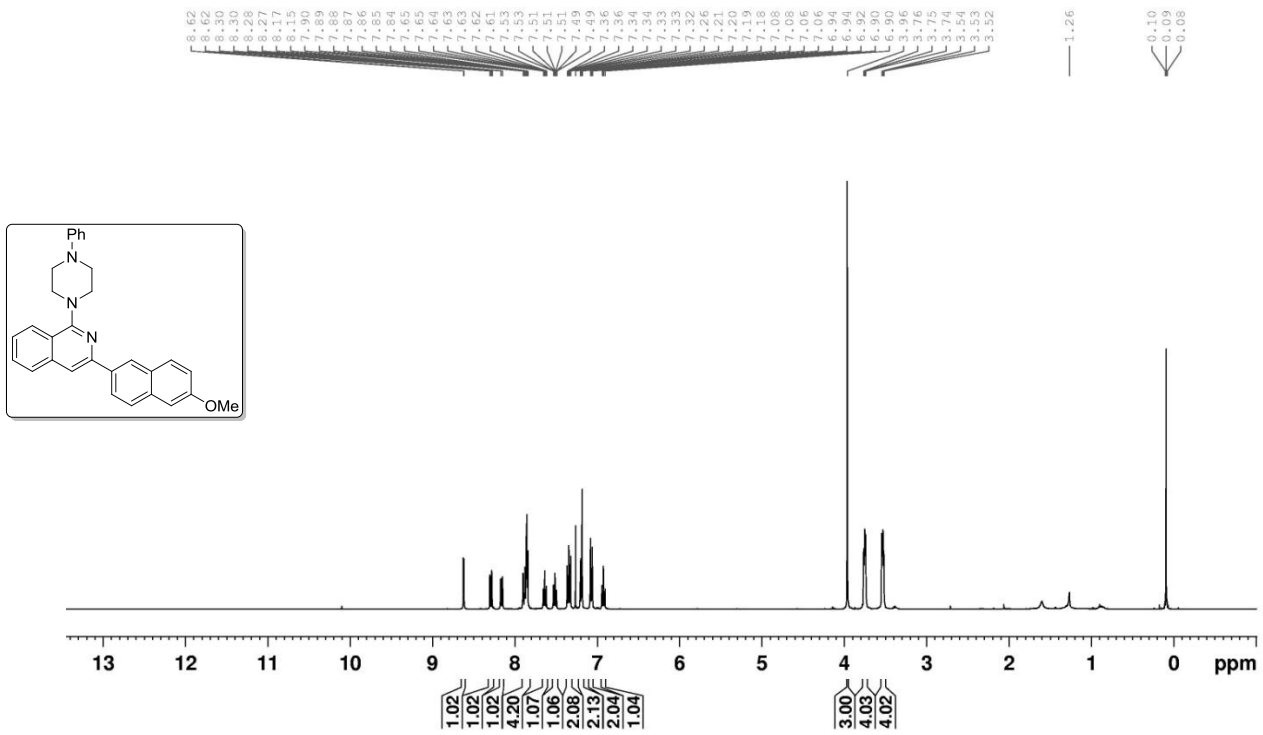
^{1}H NMR spectrum of compound **20f**



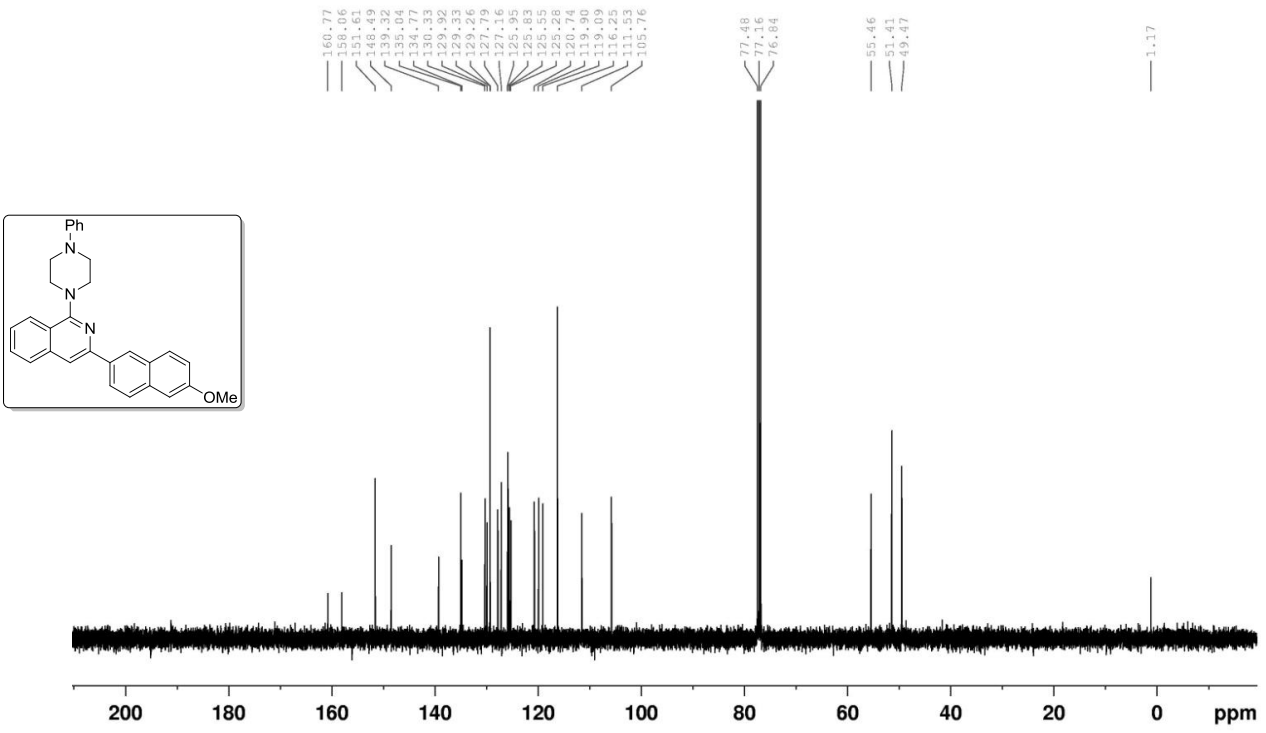
^{13}C NMR spectrum of compound **20f**



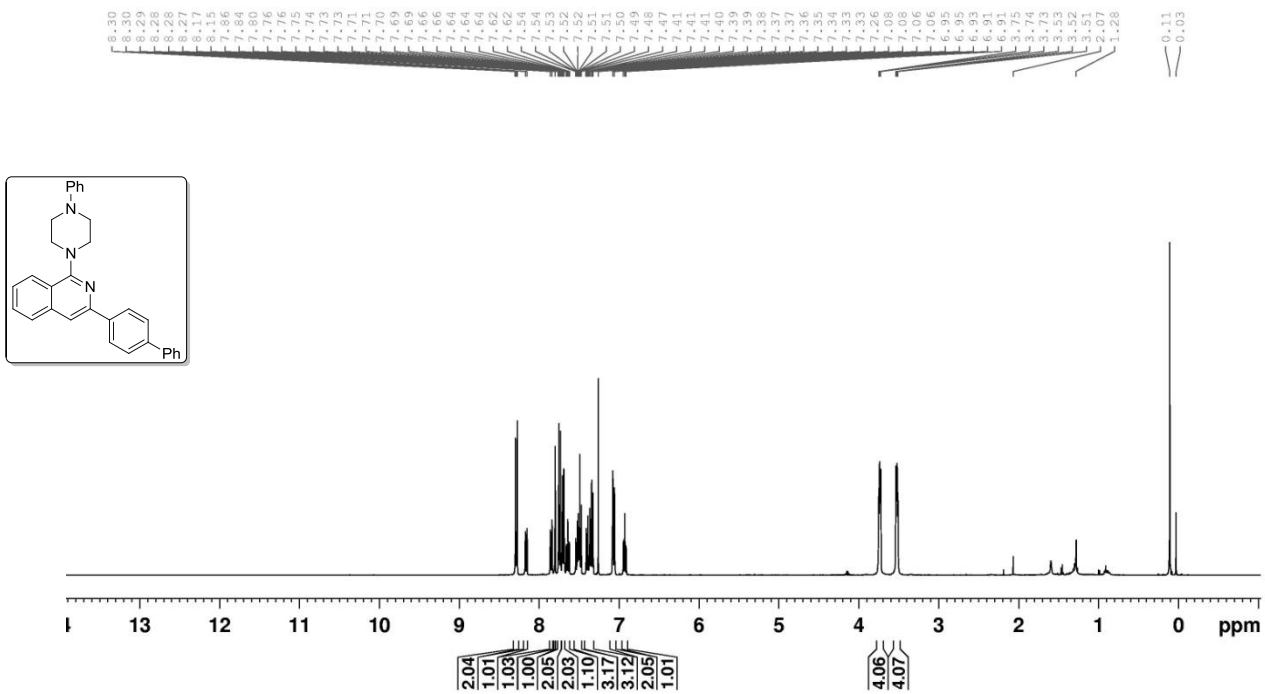
^{1}H NMR spectrum of compound **20g**



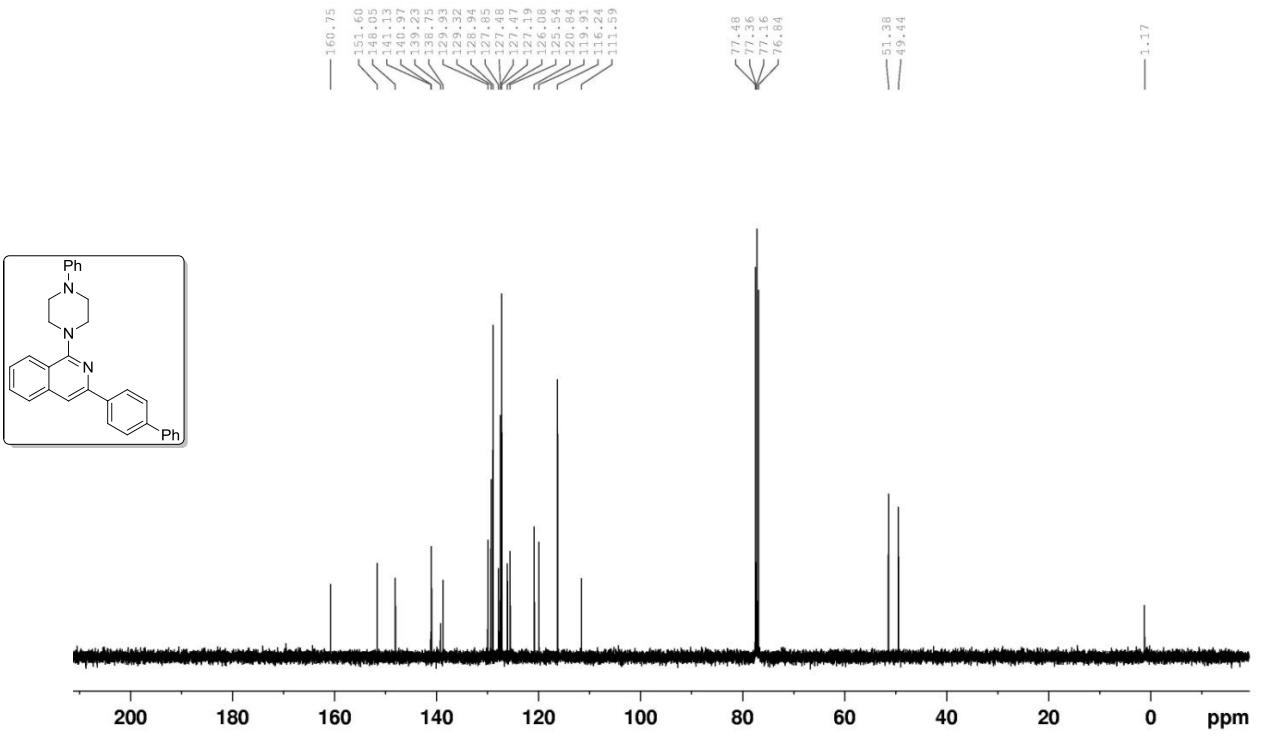
^{13}C NMR spectrum of compound **20g**



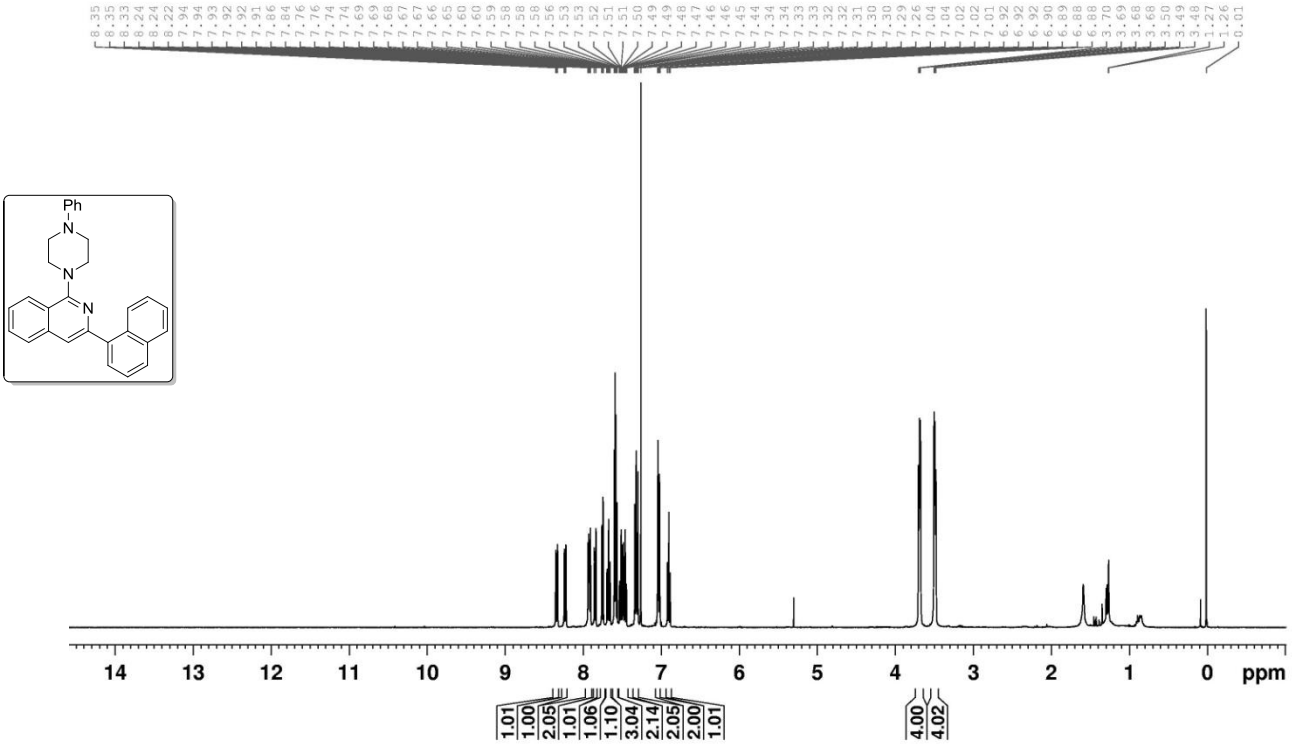
^{1}H NMR spectrum of compound **20h**



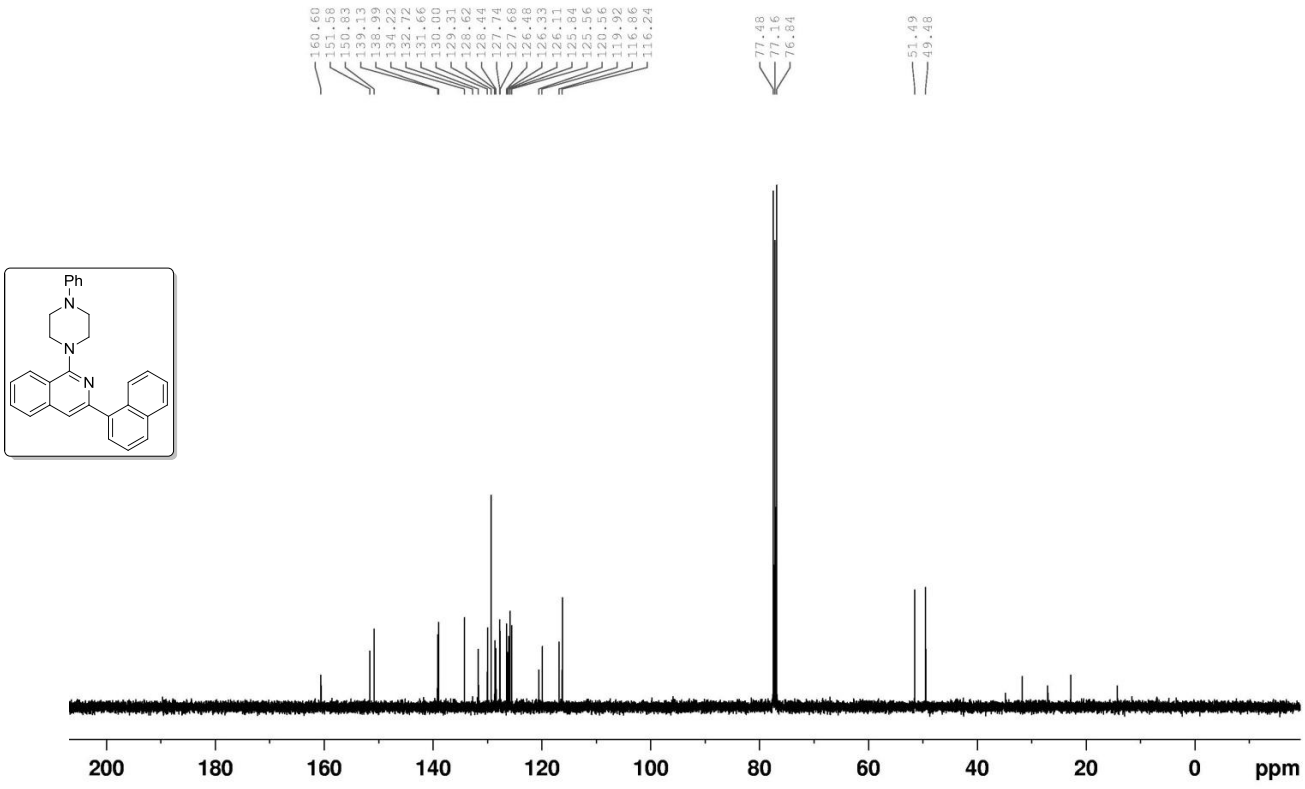
^{13}C NMR spectrum of compound **20h**



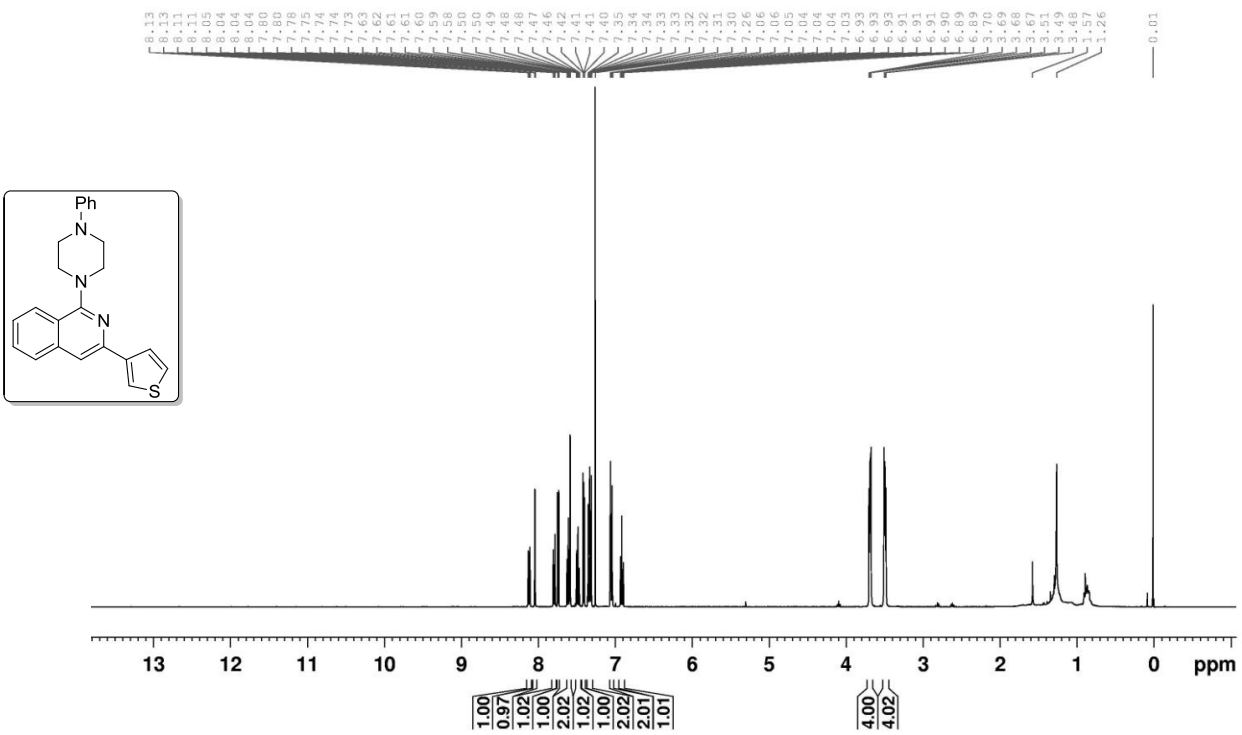
^{1}H NMR spectrum of compound **20i**



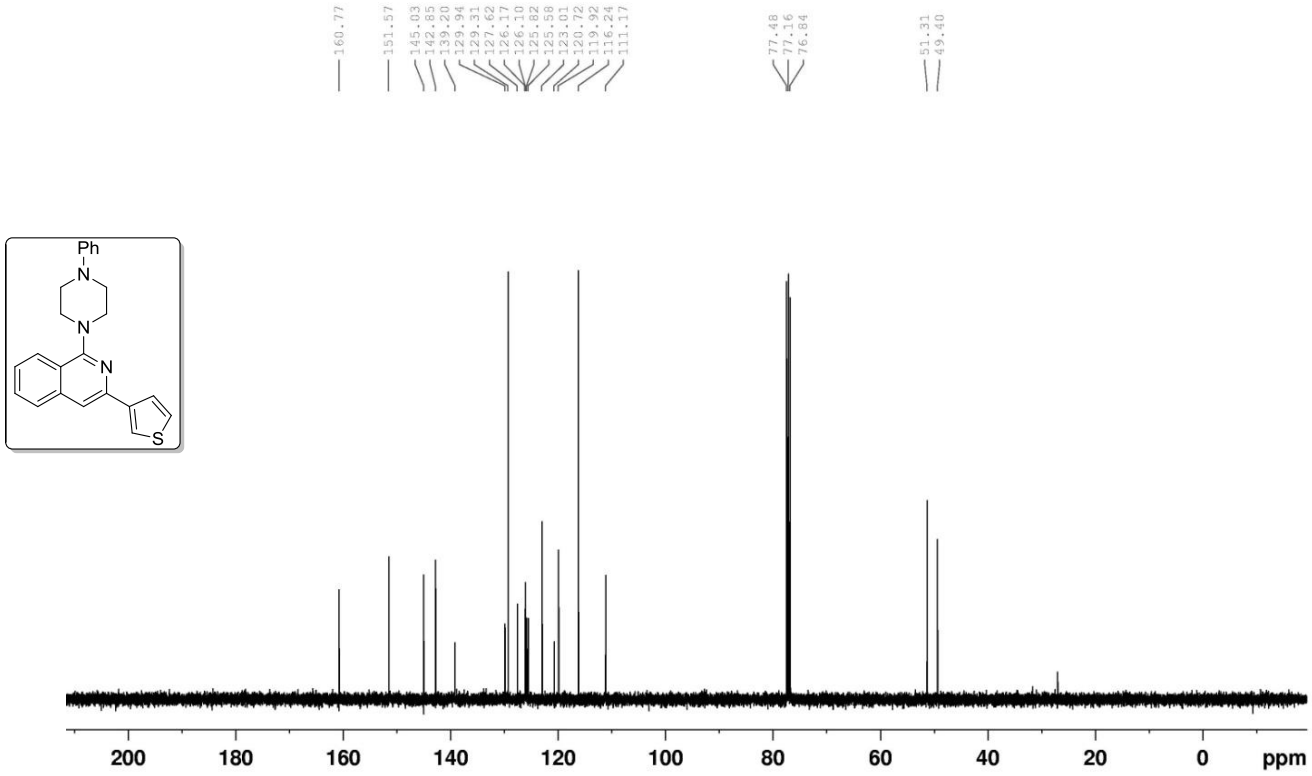
^{13}C NMR spectrum of compound **20i**



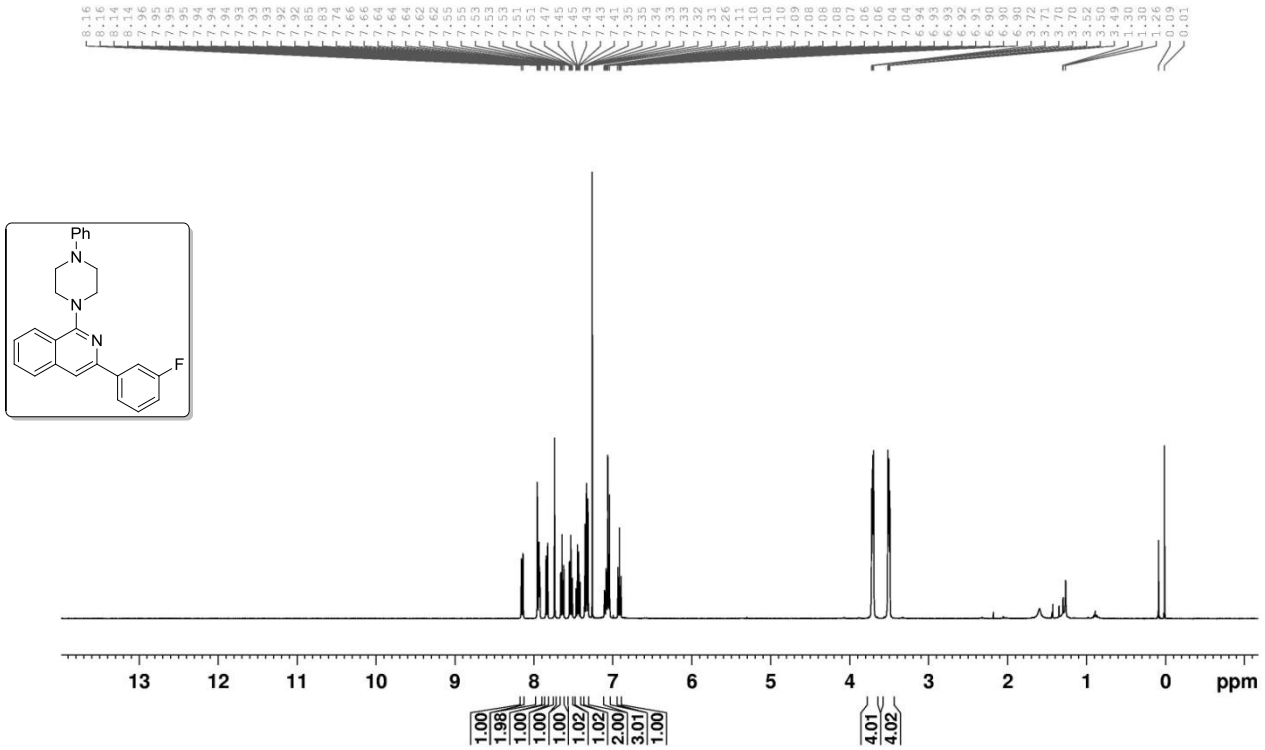
^{1}H NMR spectrum of compound **20j**



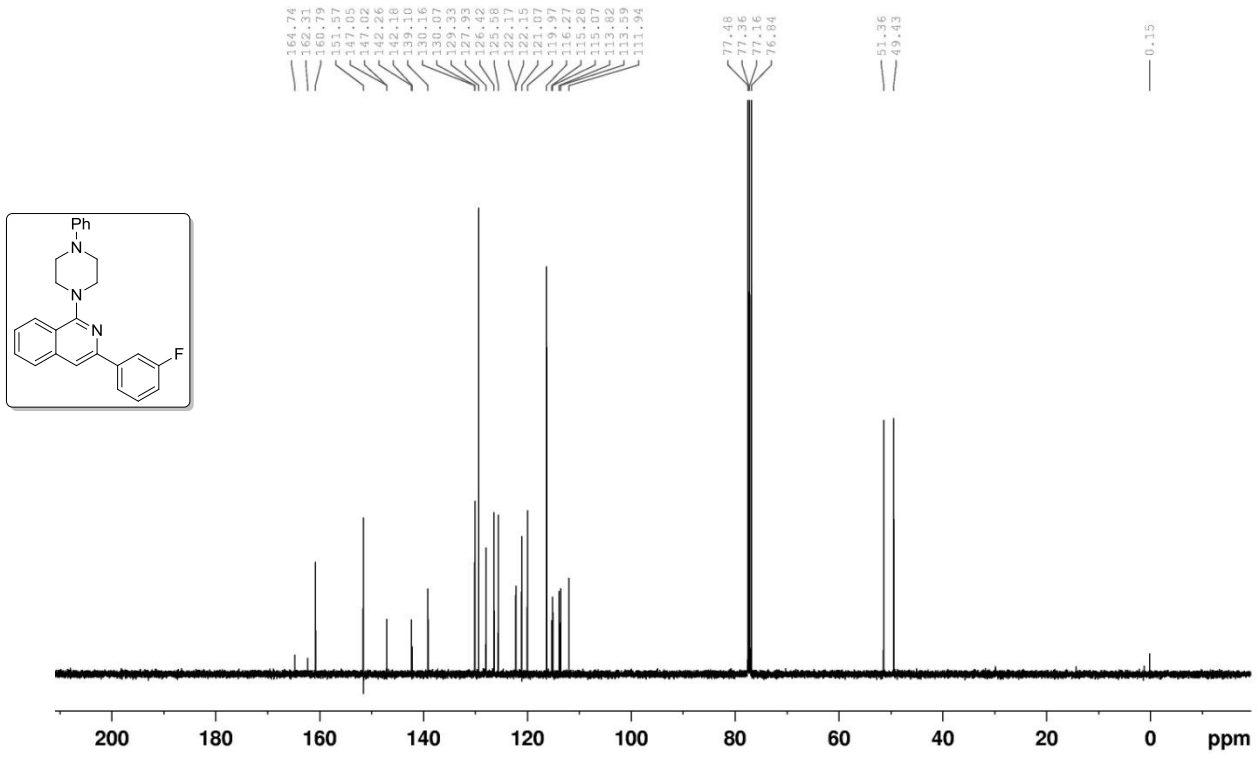
^{13}C NMR spectrum of compound **20j**



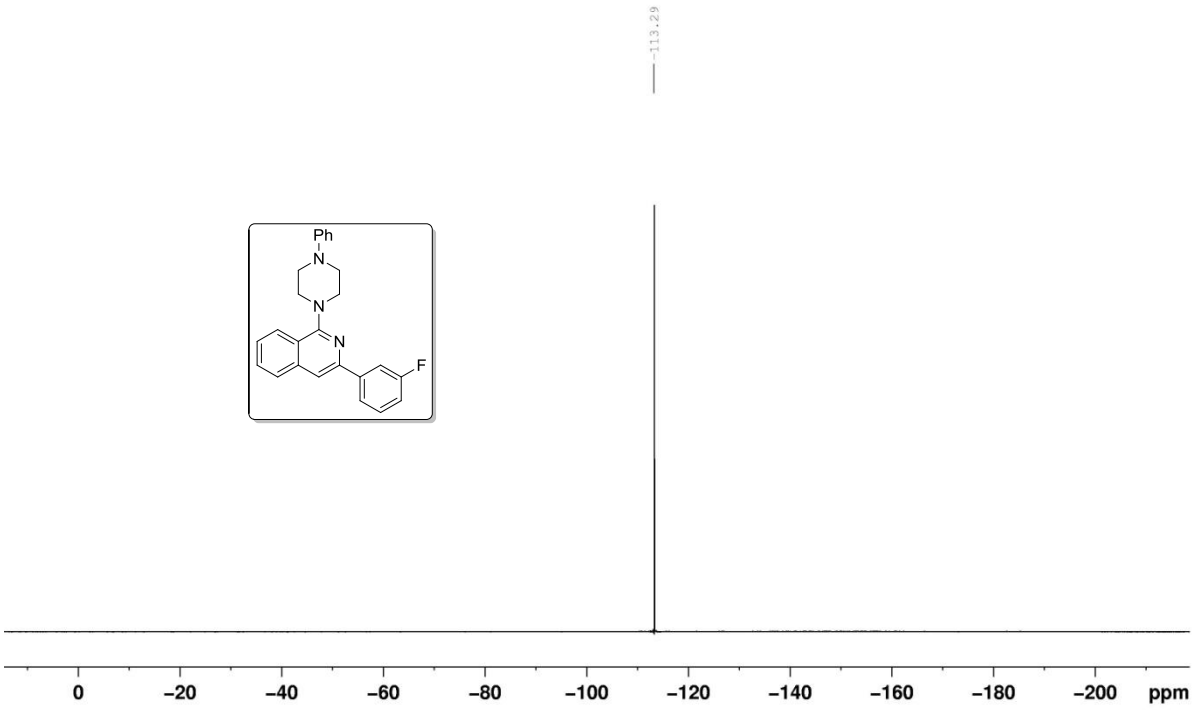
^{1}H NMR spectrum of compound **20k**



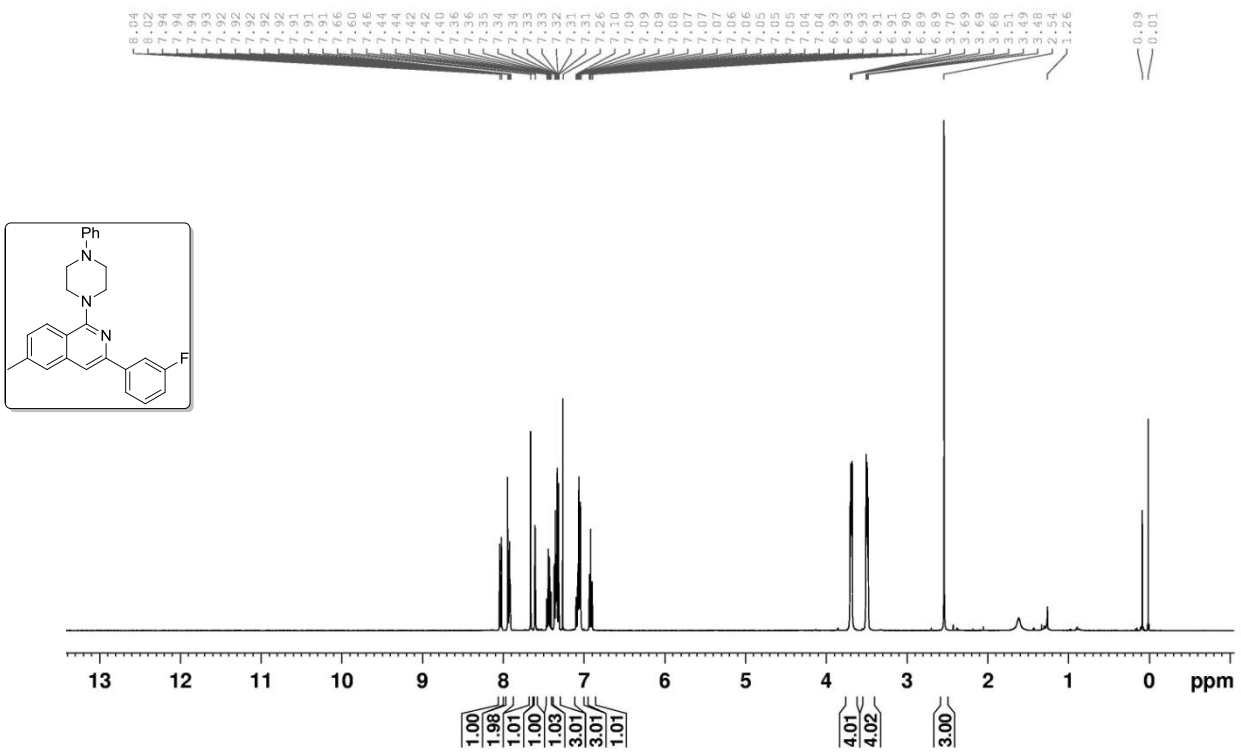
^{13}C NMR spectrum of compound **20k**



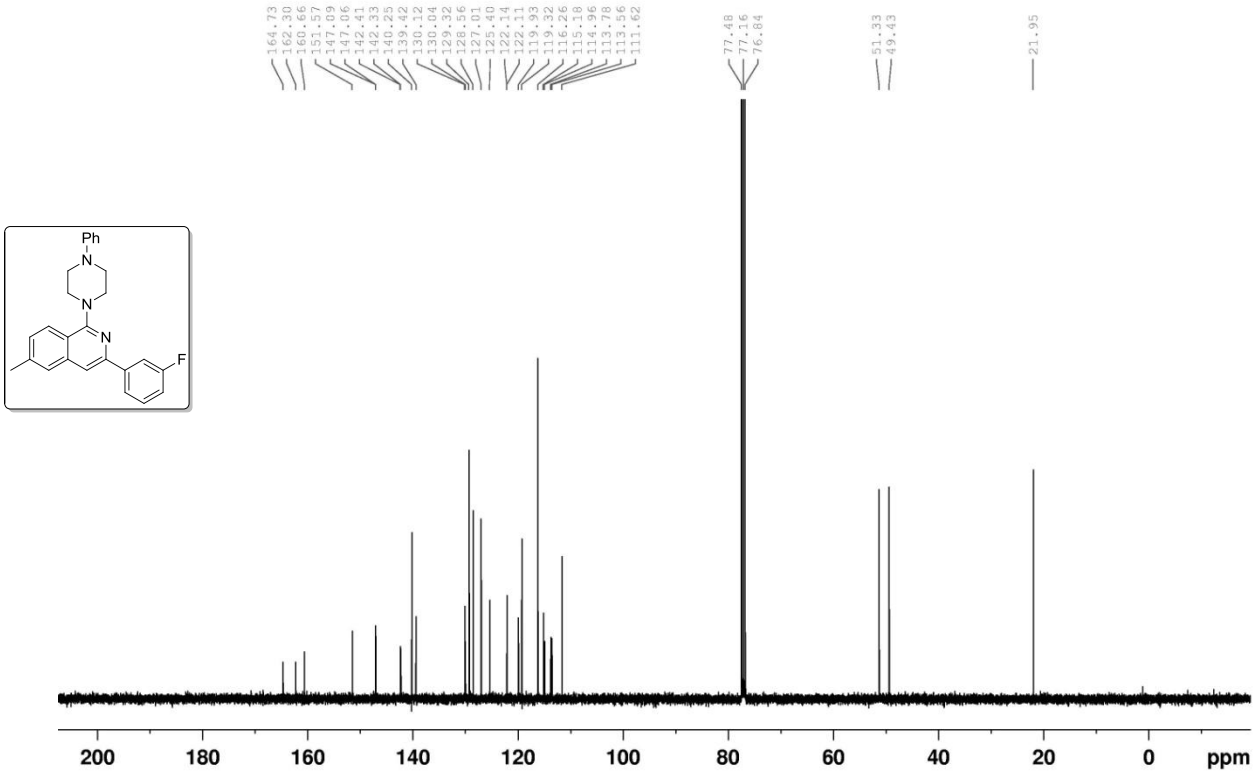
^{19}F NMR spectrum of compound **20k**



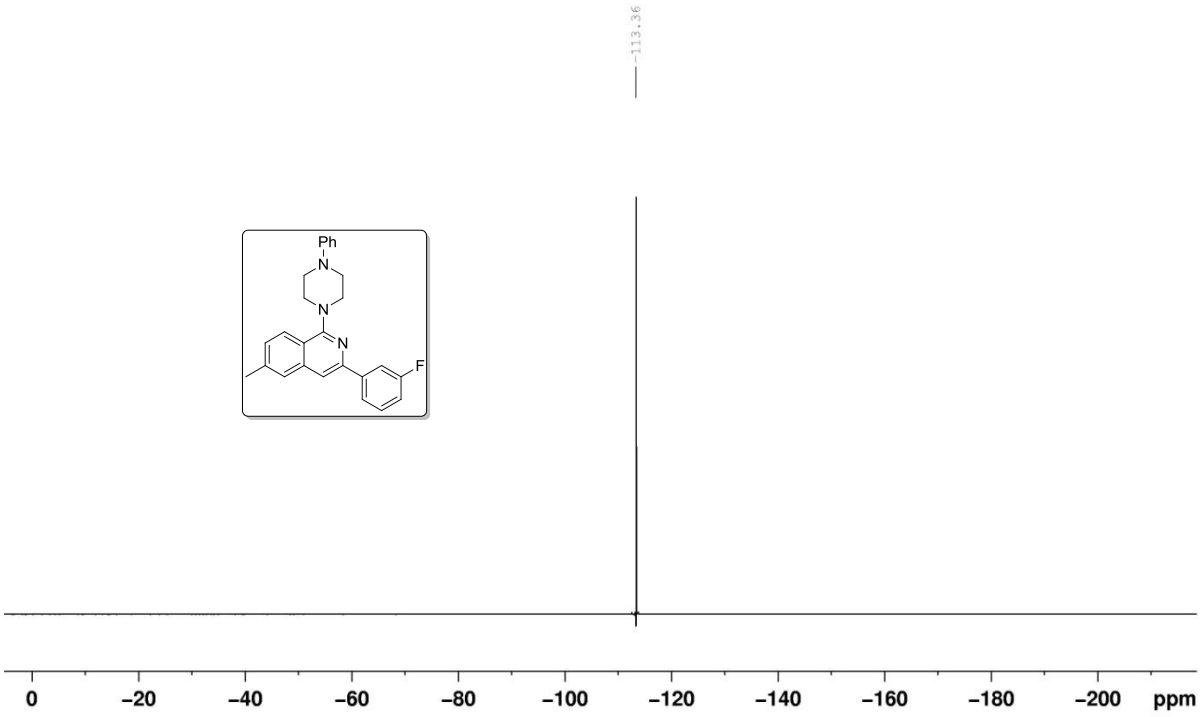
^{1}H NMR spectrum of compound **20l**



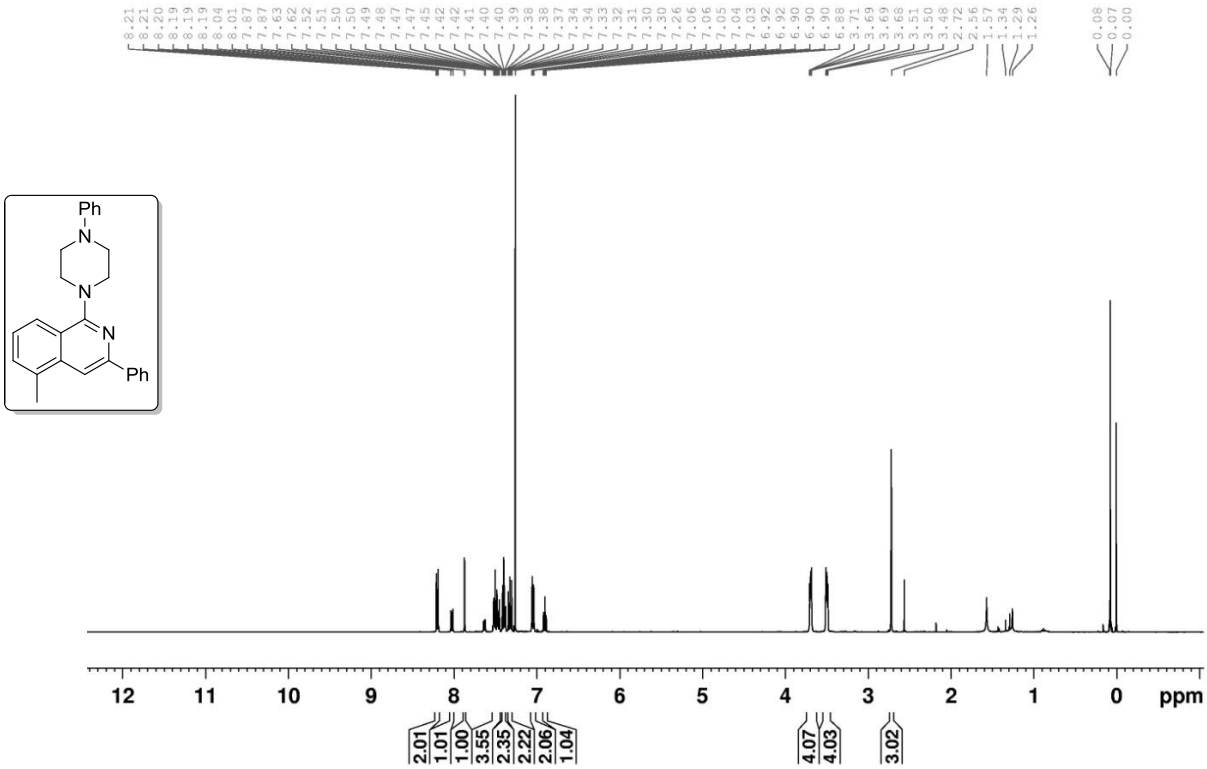
^{13}C NMR spectrum of compound **20l**



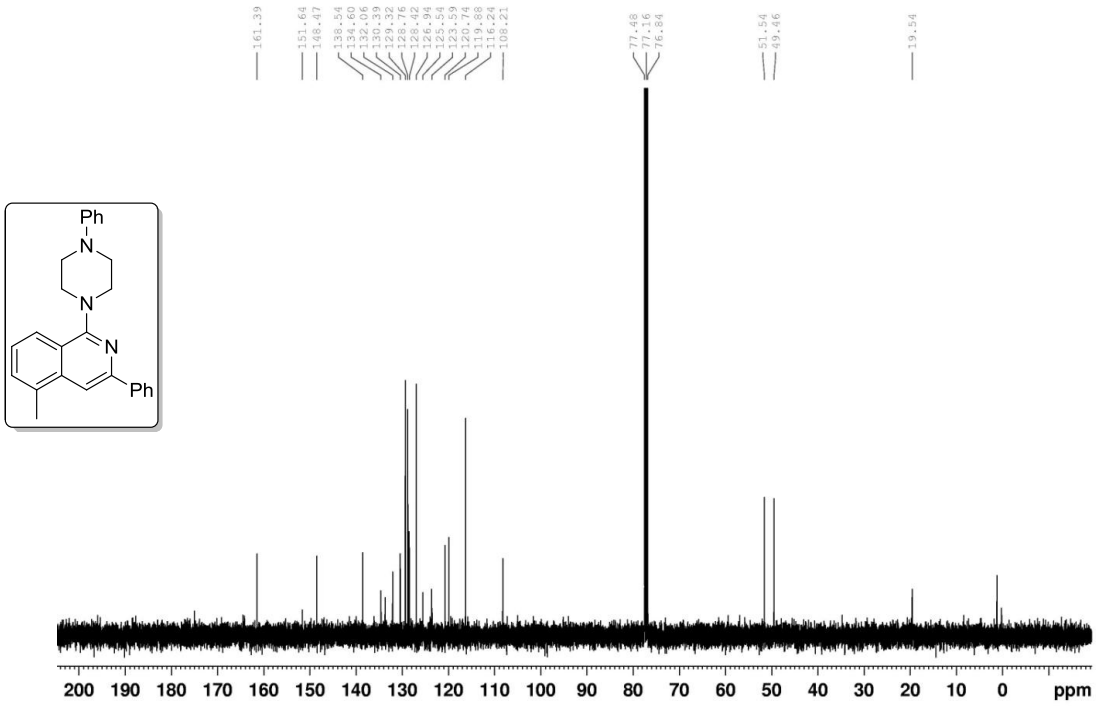
^{19}F NMR spectrum of compound **20l**



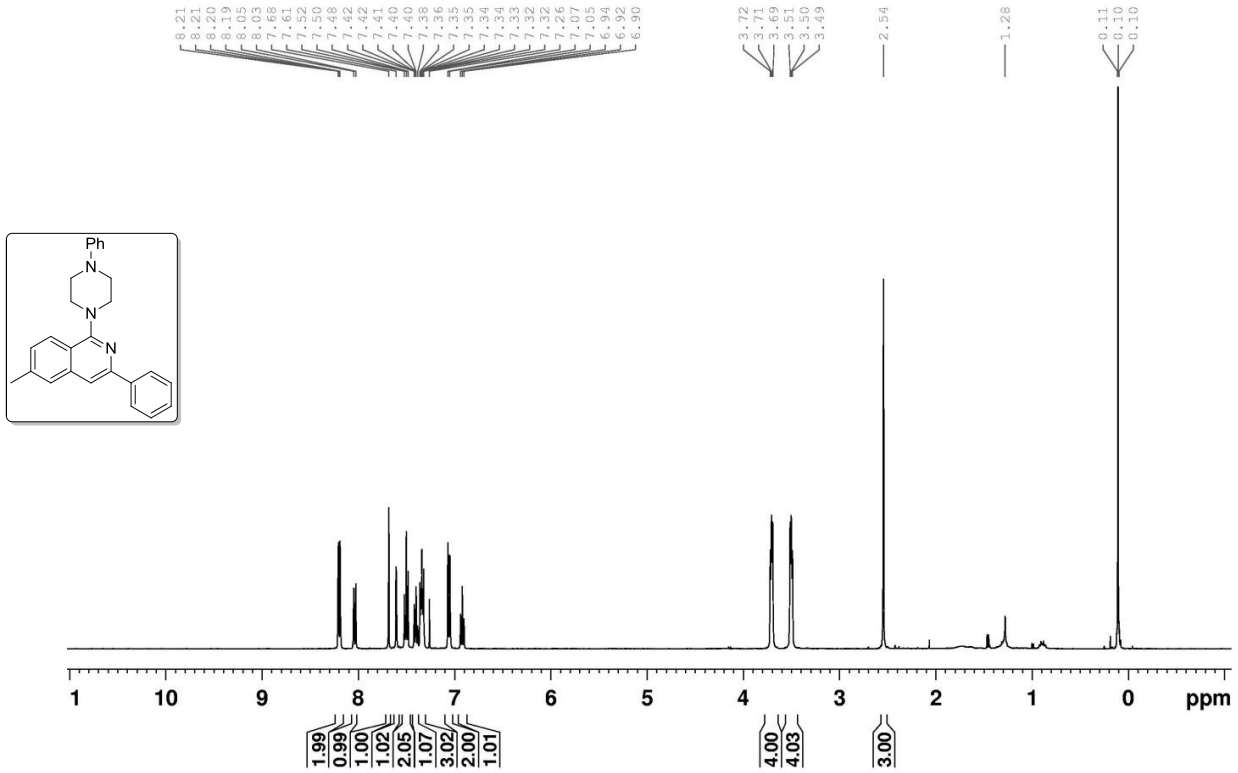
^{1}H NMR spectrum of compound **20m**



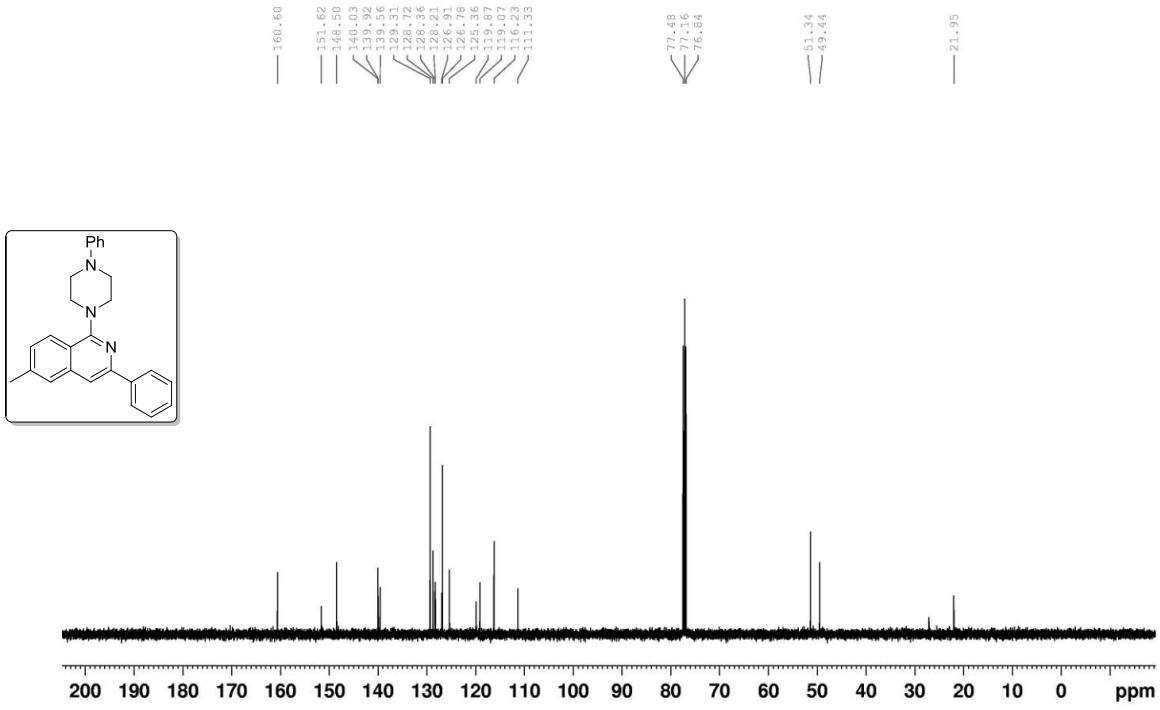
^{13}C NMR spectrum of compound **20m**



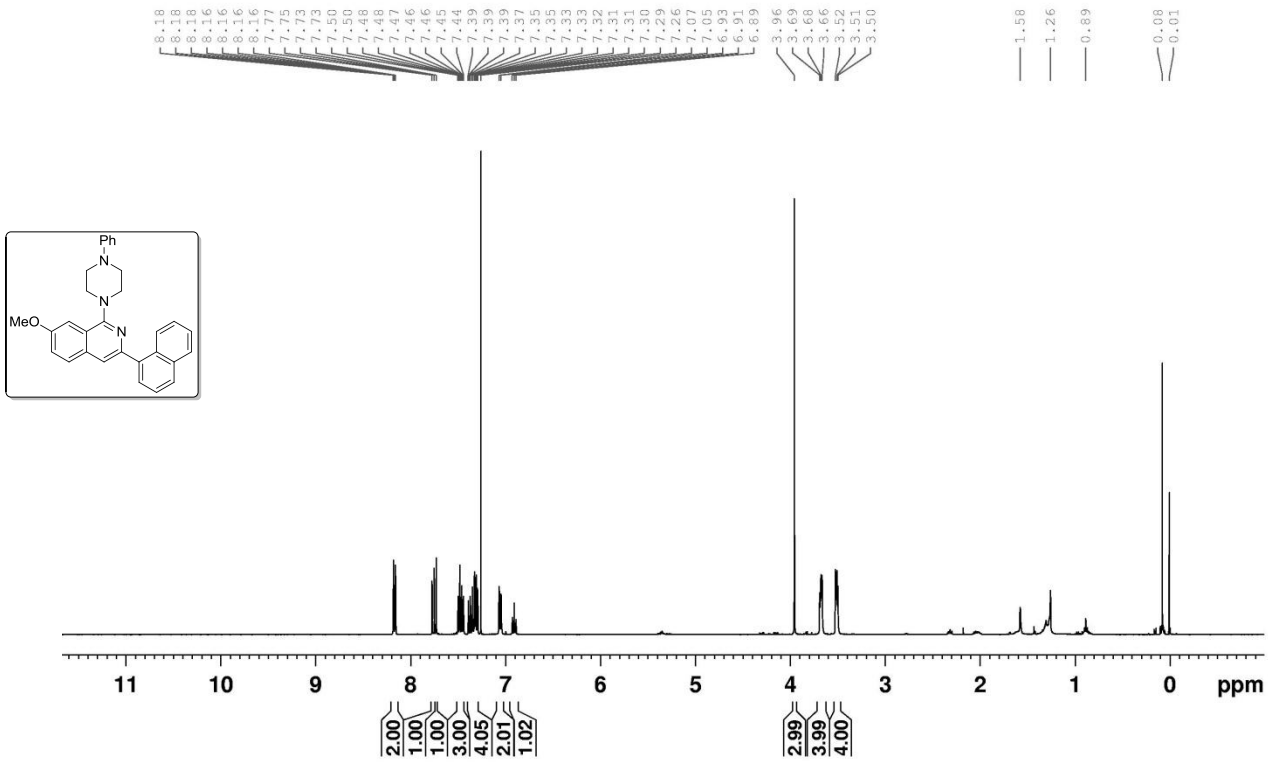
^{1}H NMR spectrum of compound **20n**



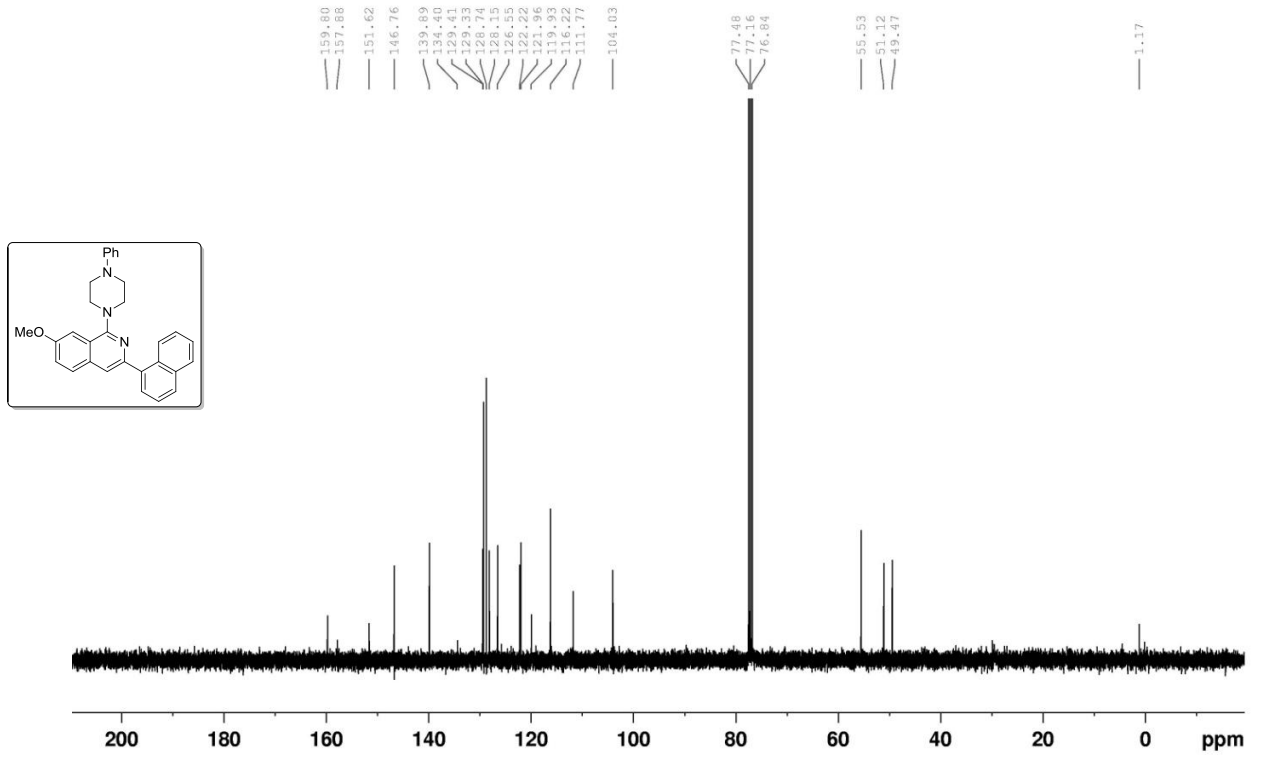
^{13}C NMR spectrum of compound **20n**



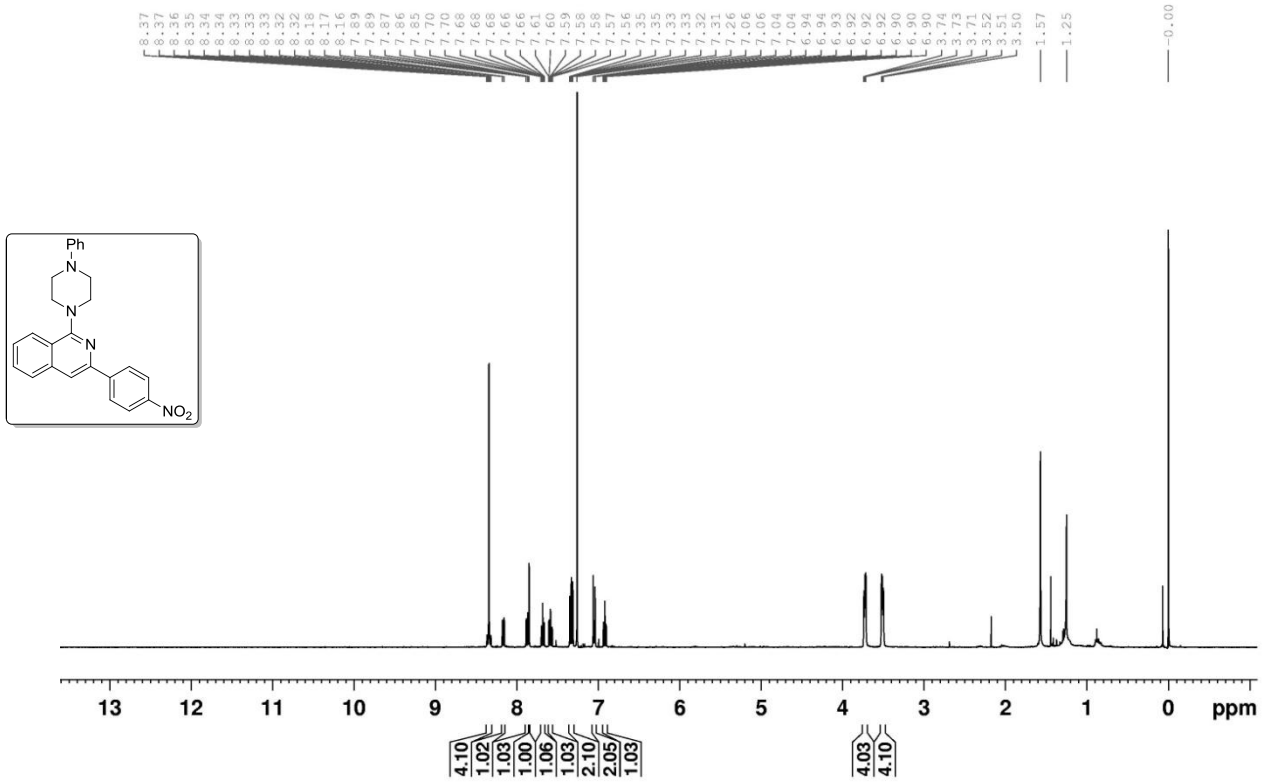
^{1}H NMR spectrum of compound **20o**



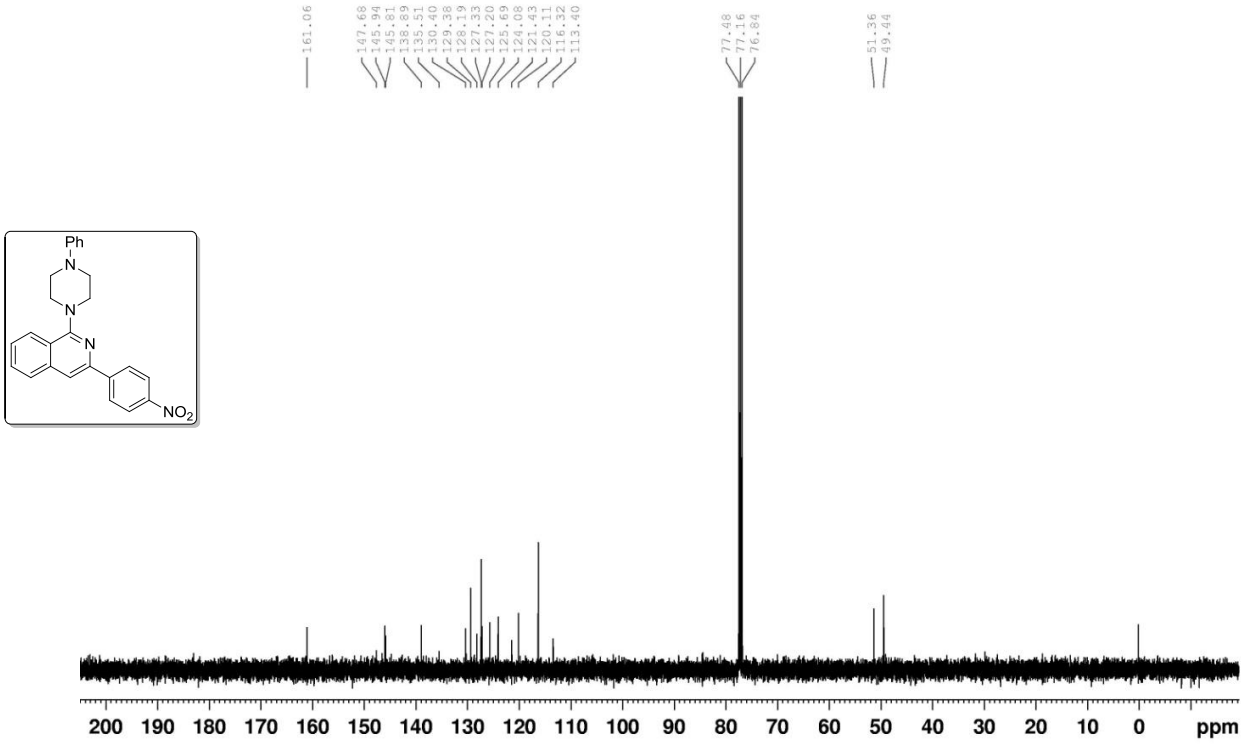
^{13}C NMR spectrum of compound **20o**



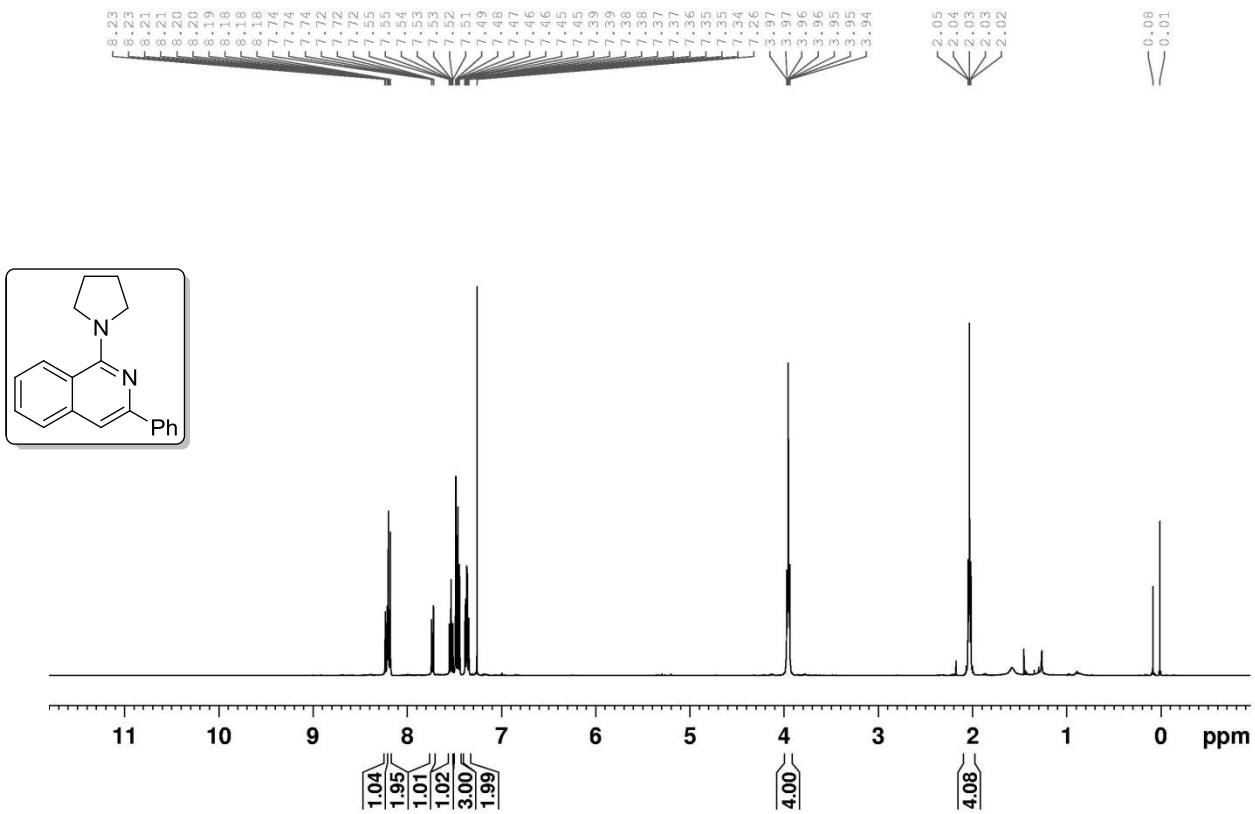
^{1}H NMR spectrum of compound **20p**



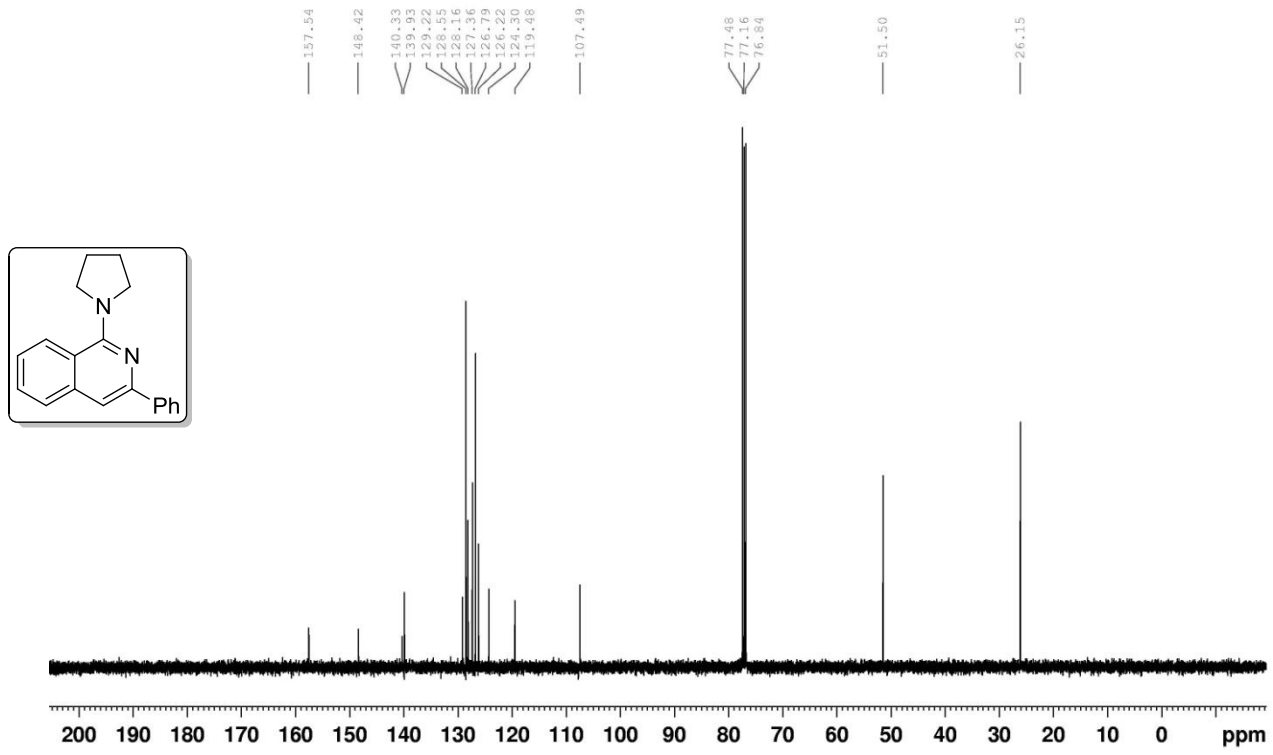
^{13}C NMR spectrum of compound **20p**



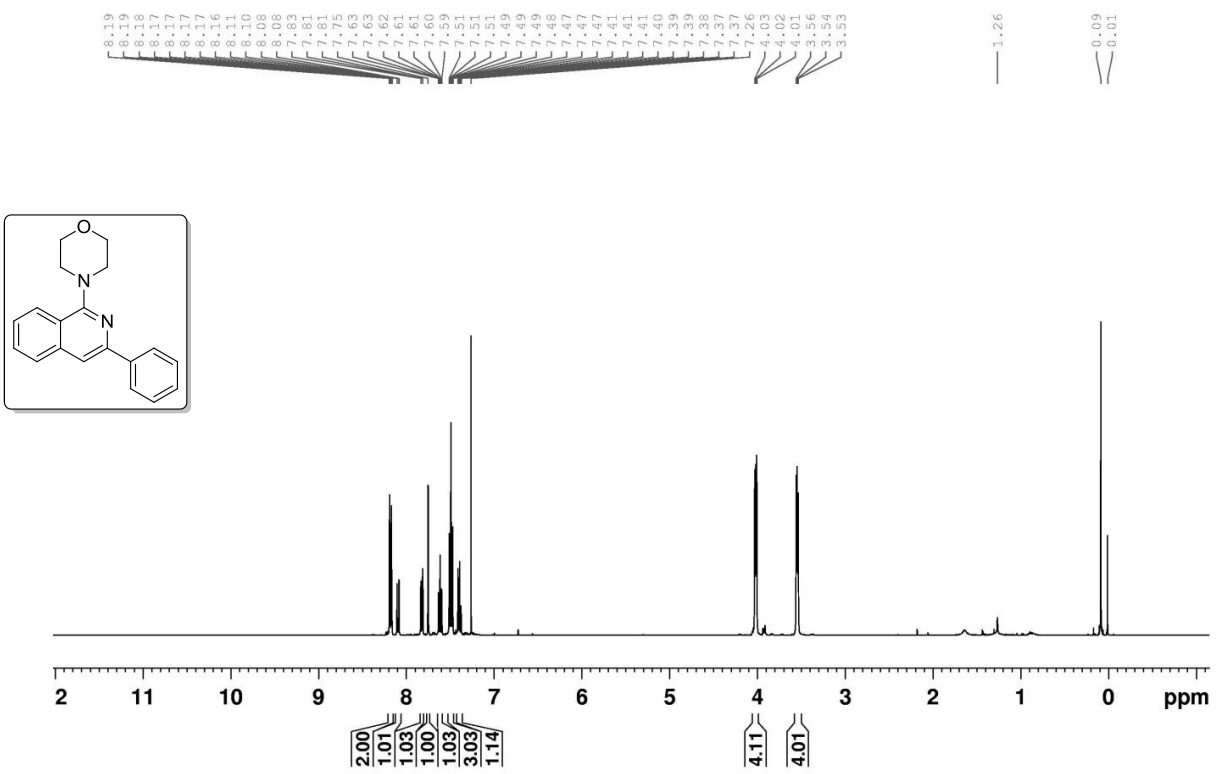
^{1}H NMR spectrum of compound **20q**



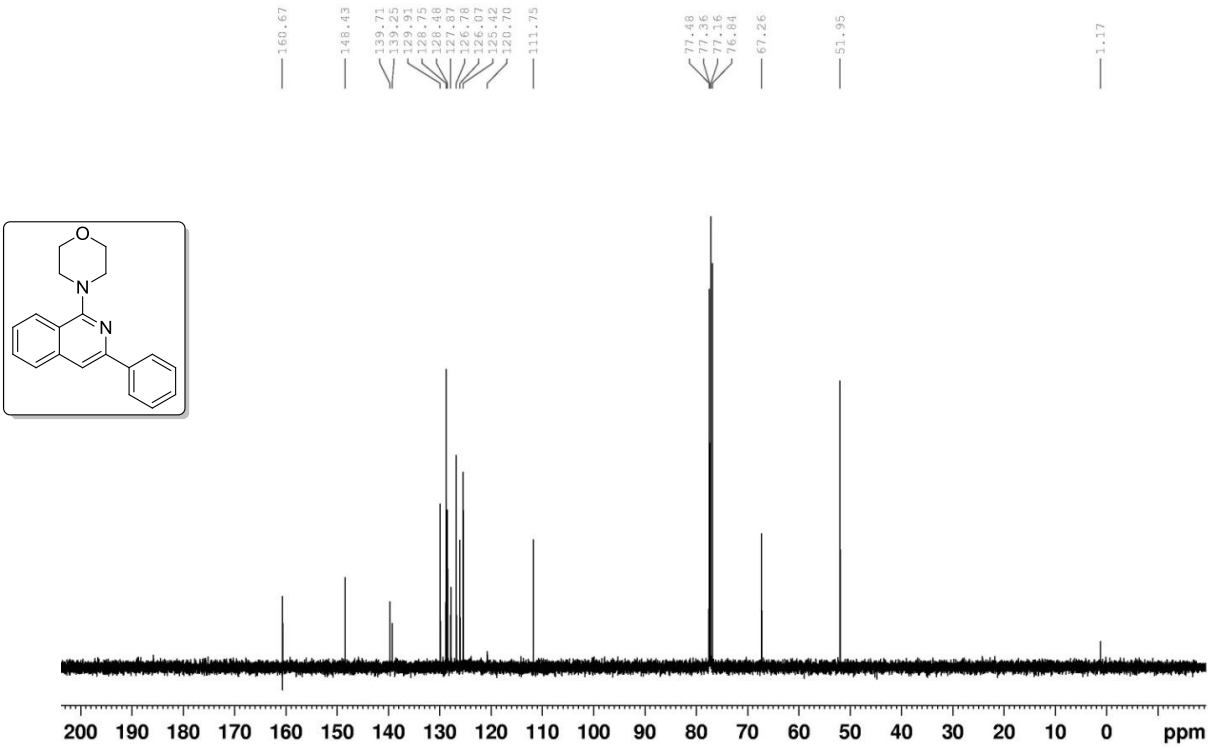
^{13}C NMR spectrum of compound **20q**



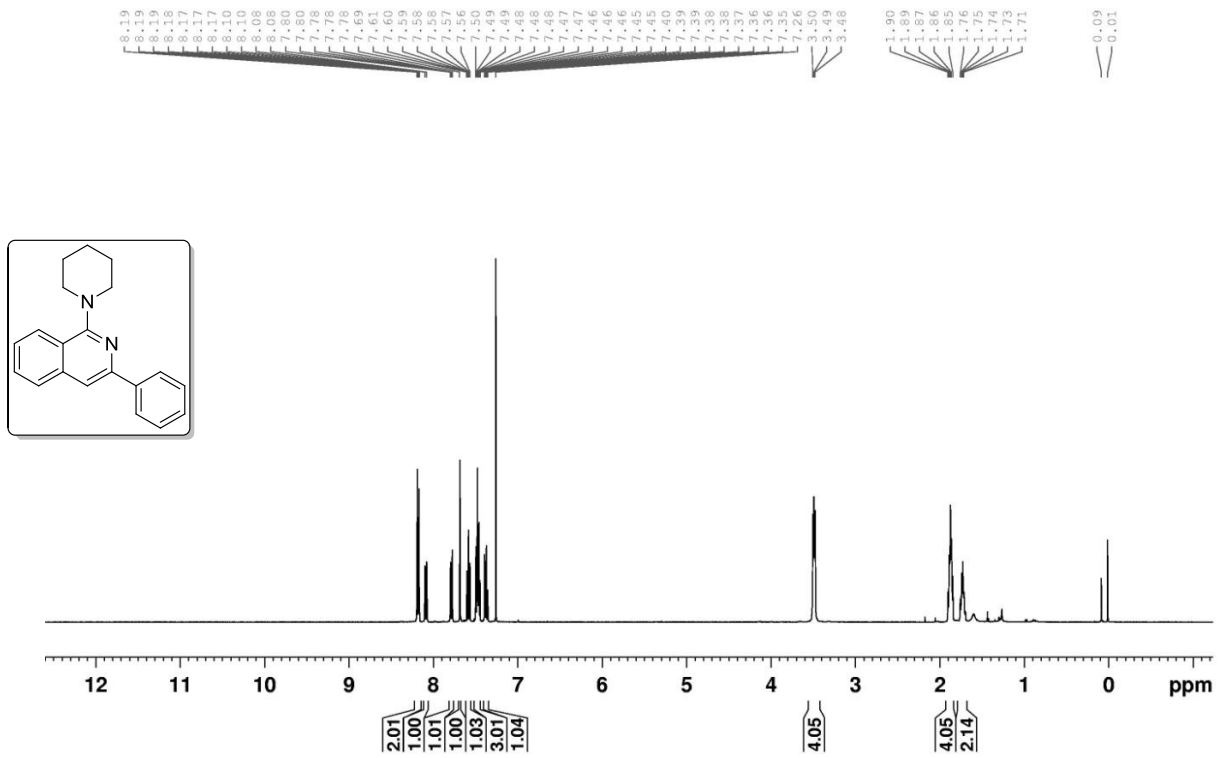
^{1}H NMR spectrum of compound **20r**



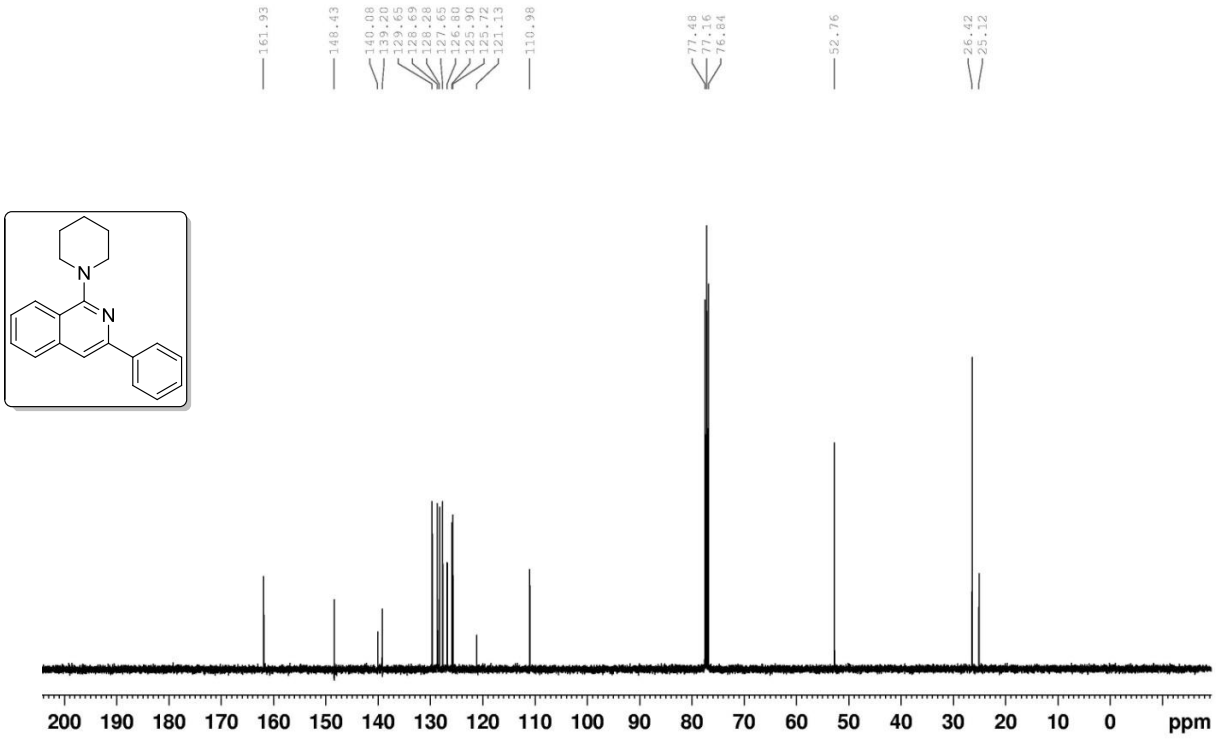
^{13}C NMR spectrum of compound **20r**



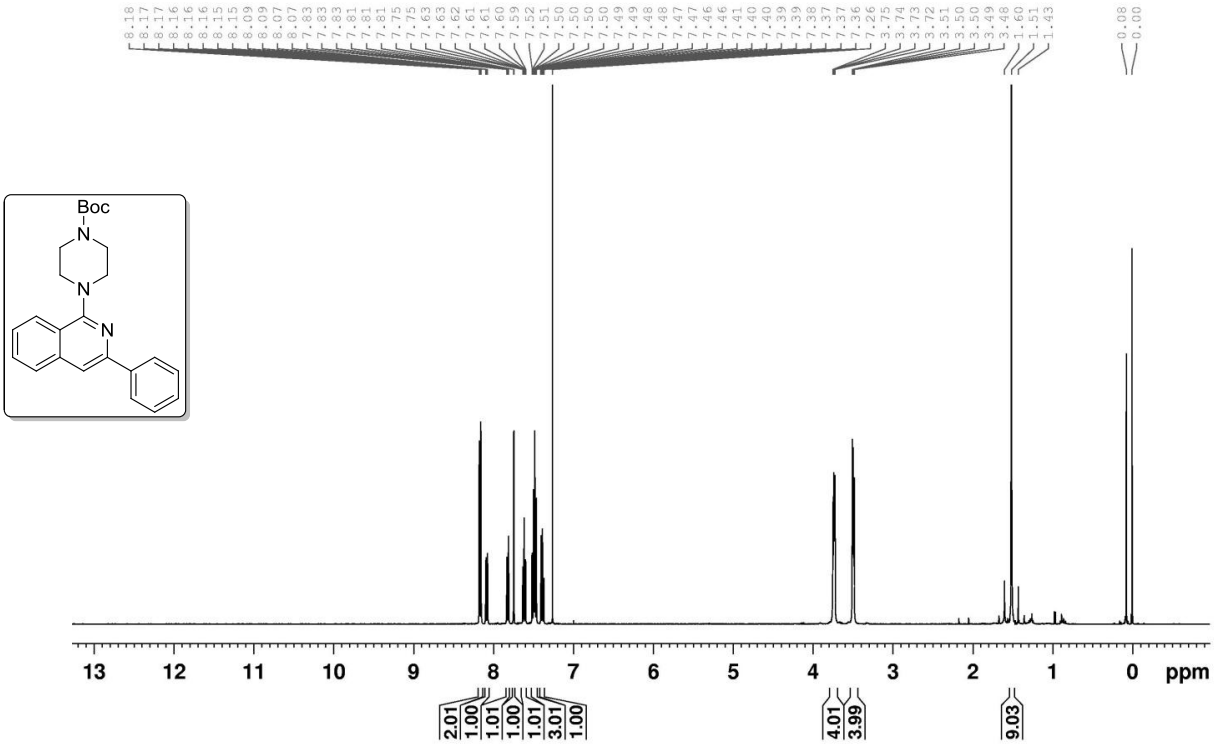
^{1}H NMR spectrum of compound **20s**



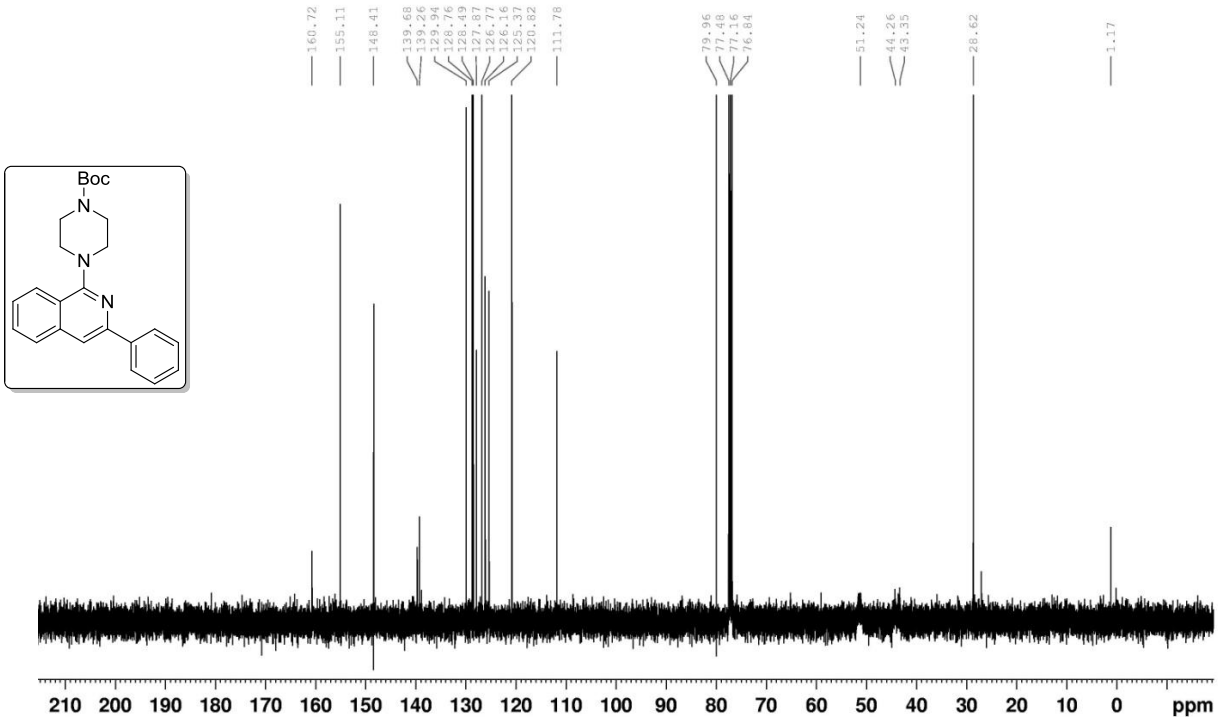
^{13}C NMR spectrum of compound **20s**



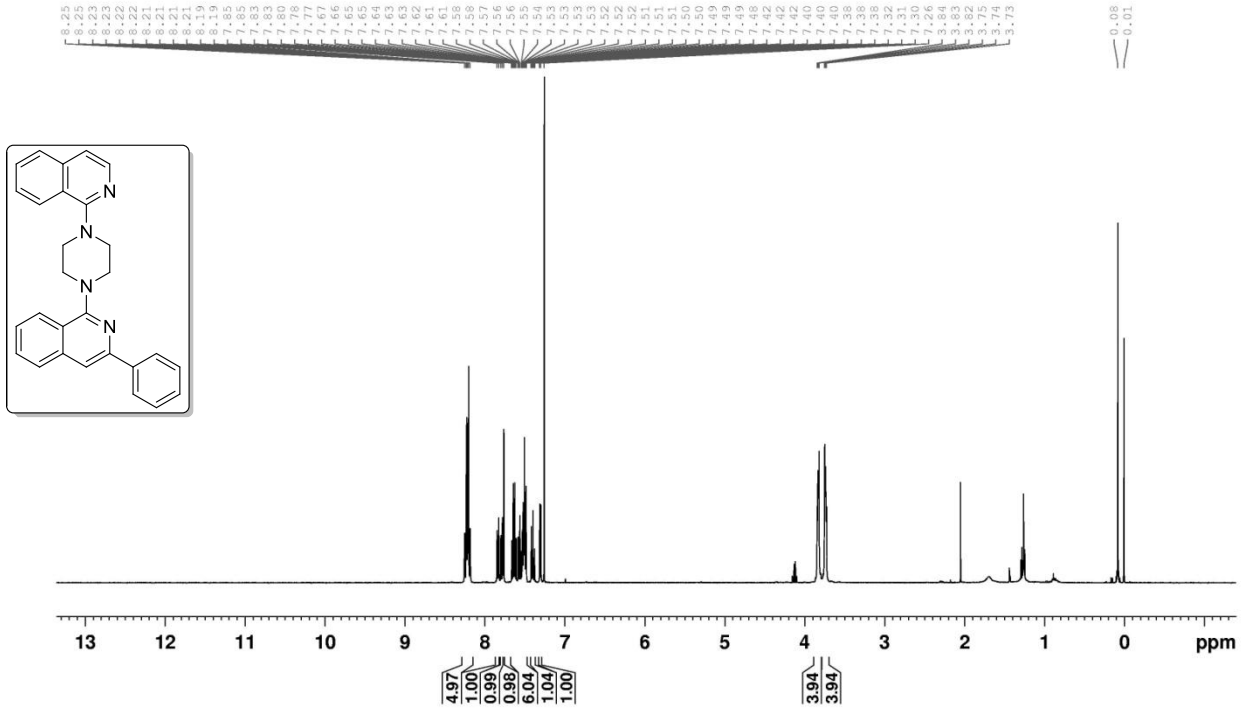
^{1}H NMR spectrum of compound **20t**



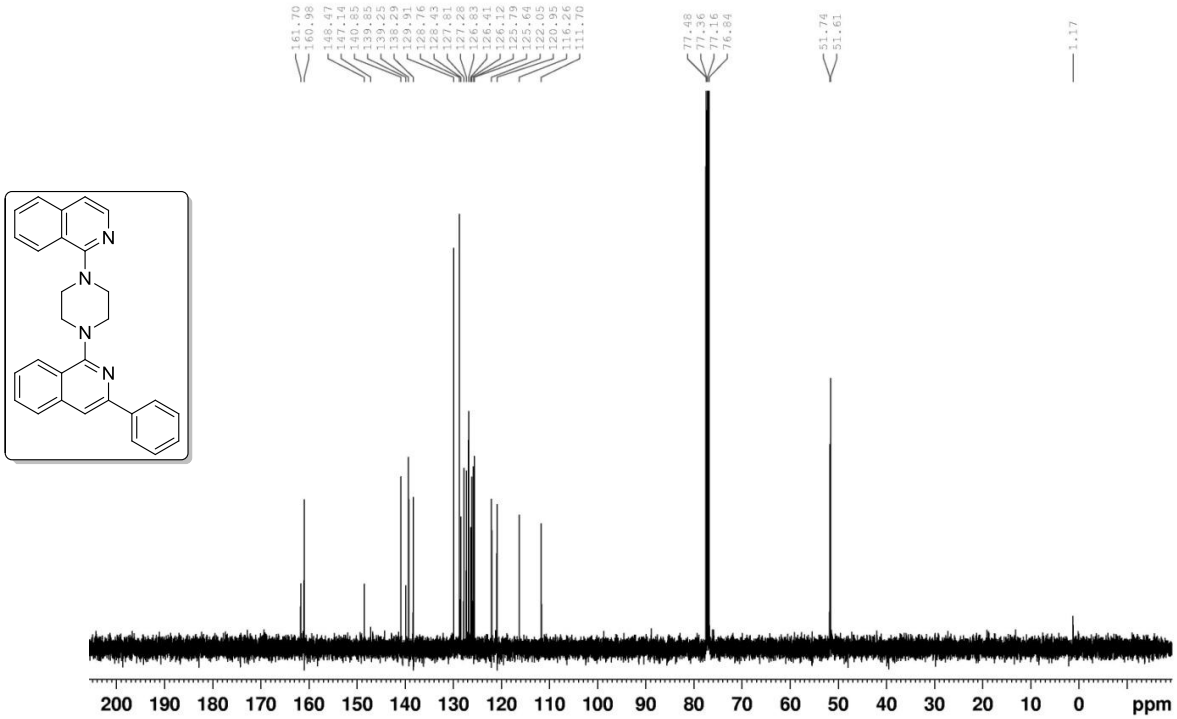
^{13}C NMR spectrum of compound **20t**



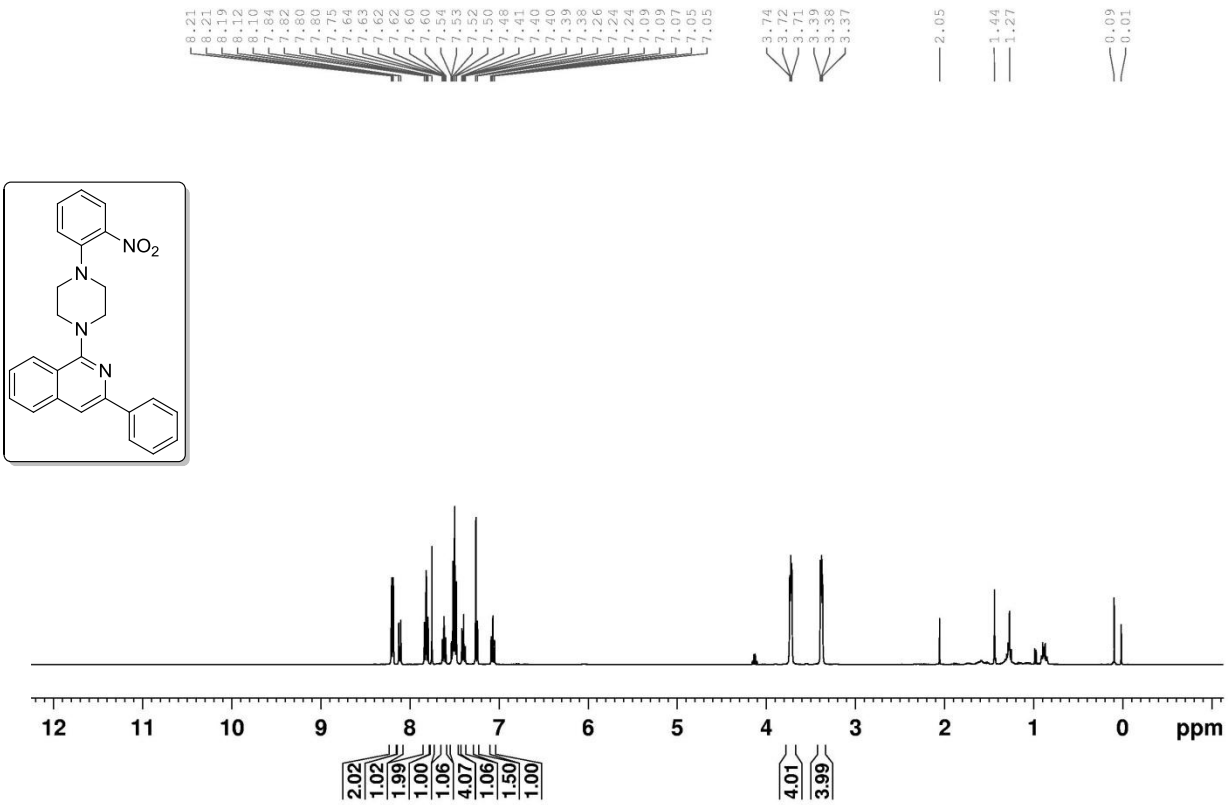
^{1}H NMR spectrum of compound **20u**



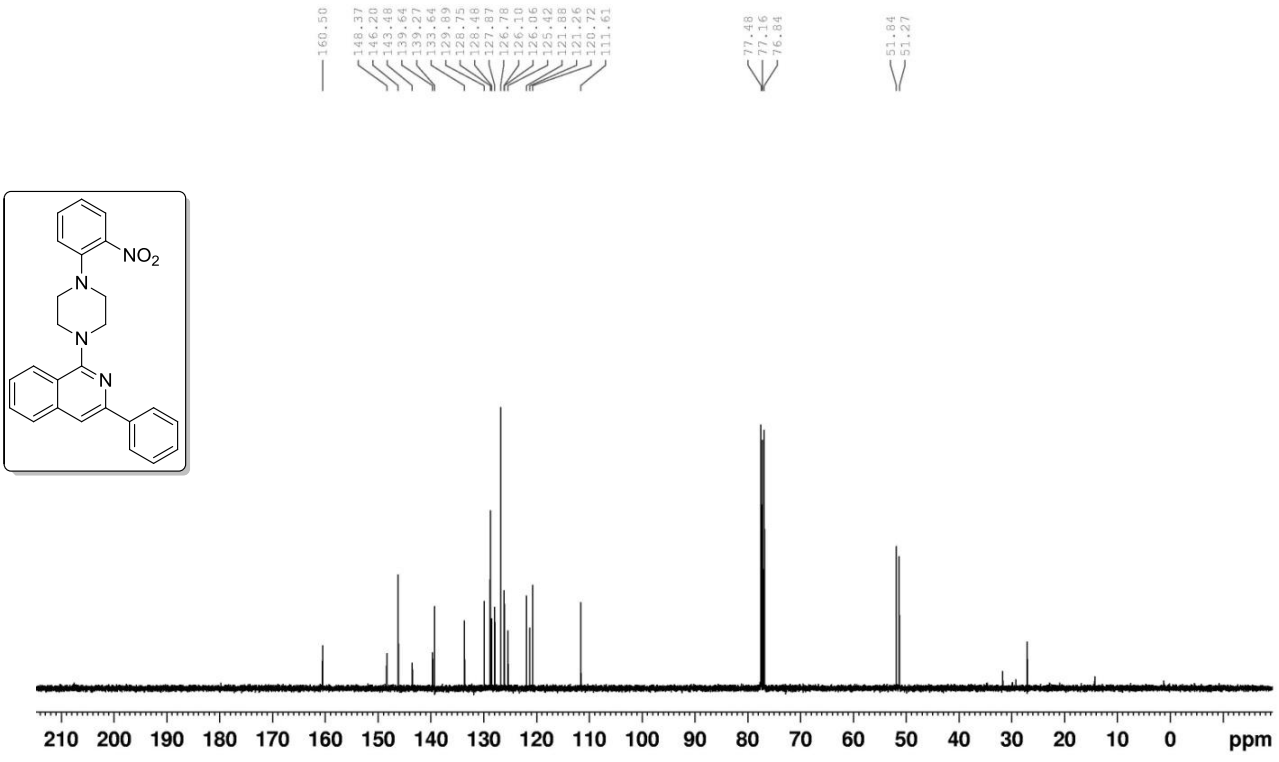
^{13}C NMR spectrum of compound **20u**



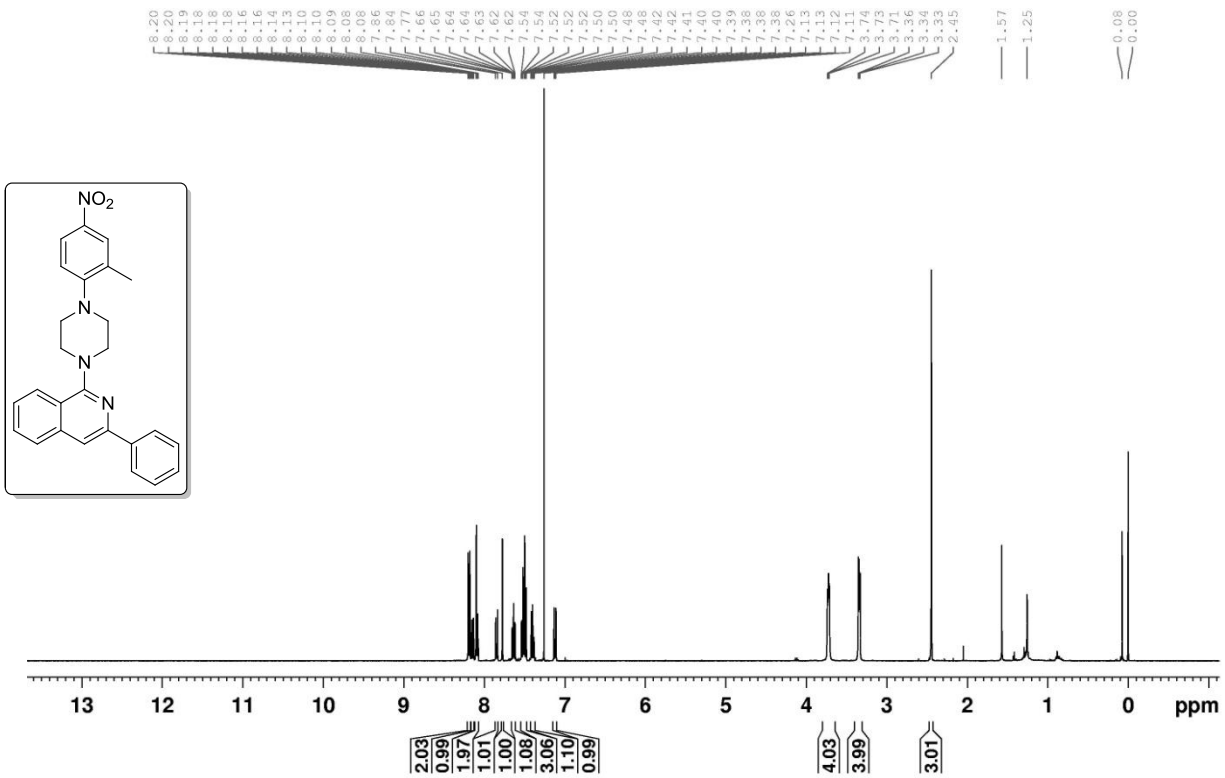
^{1}H NMR spectrum of compound **20v**



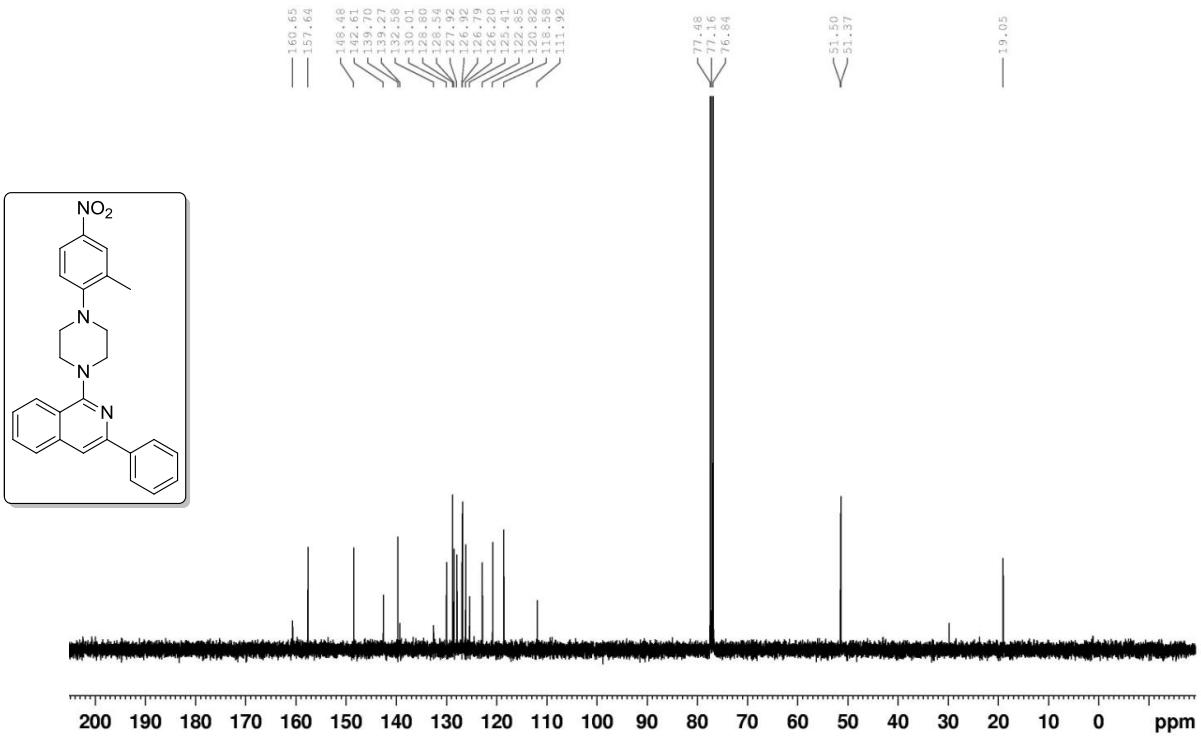
^{13}C NMR spectrum of compound **20v**



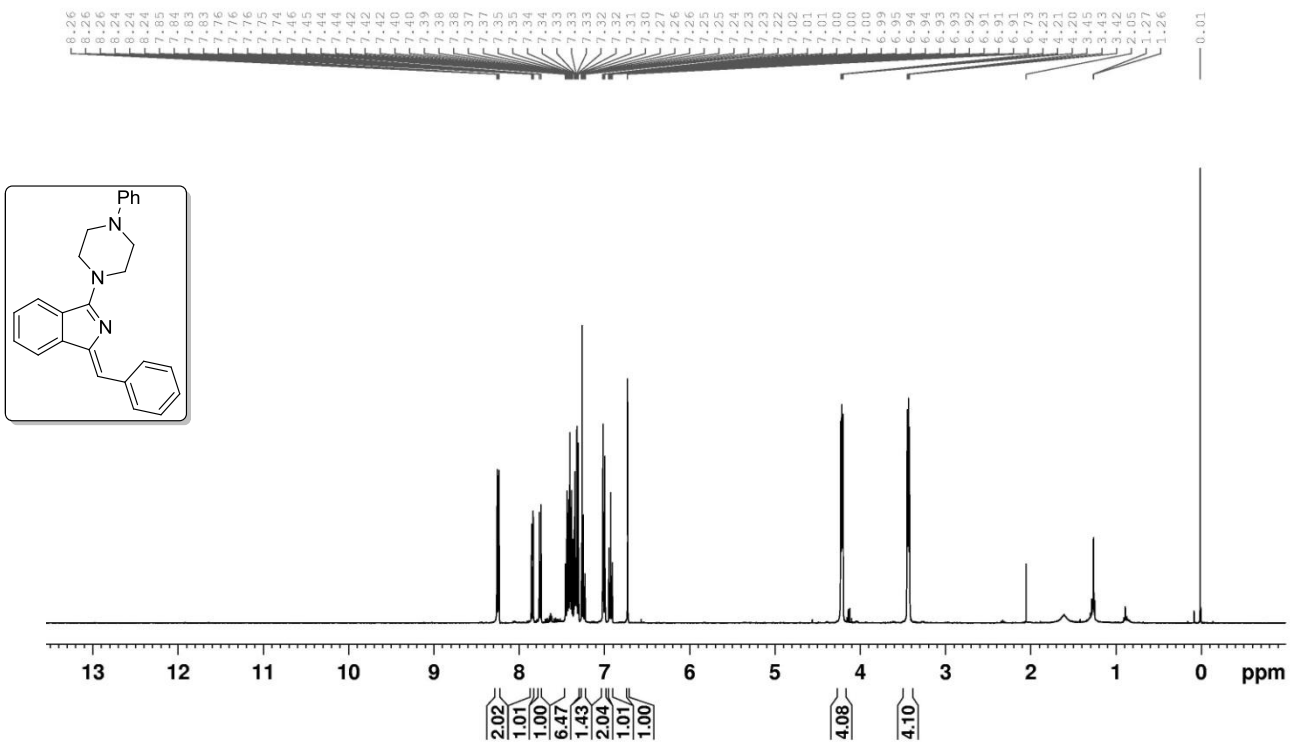
^{1}H NMR spectrum of compound **20w**



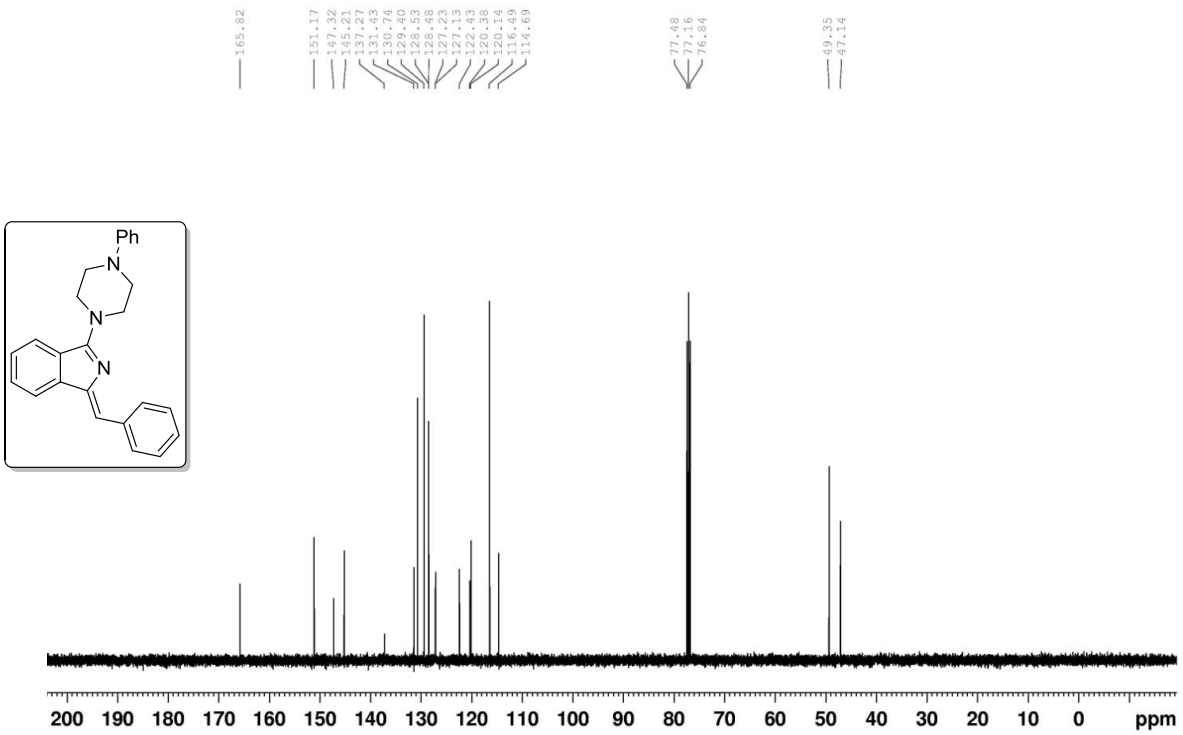
^{13}C NMR spectrum of compound **20w**



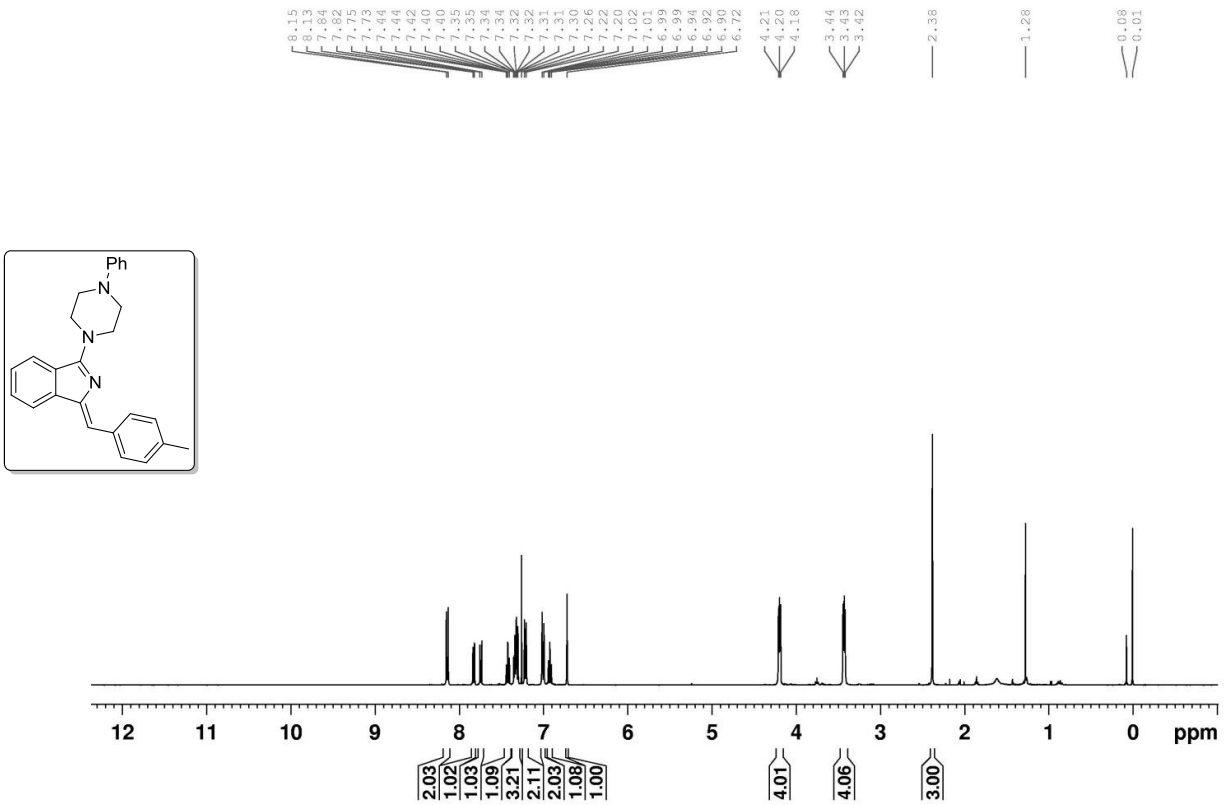
^{1}H NMR spectrum of compound **21**



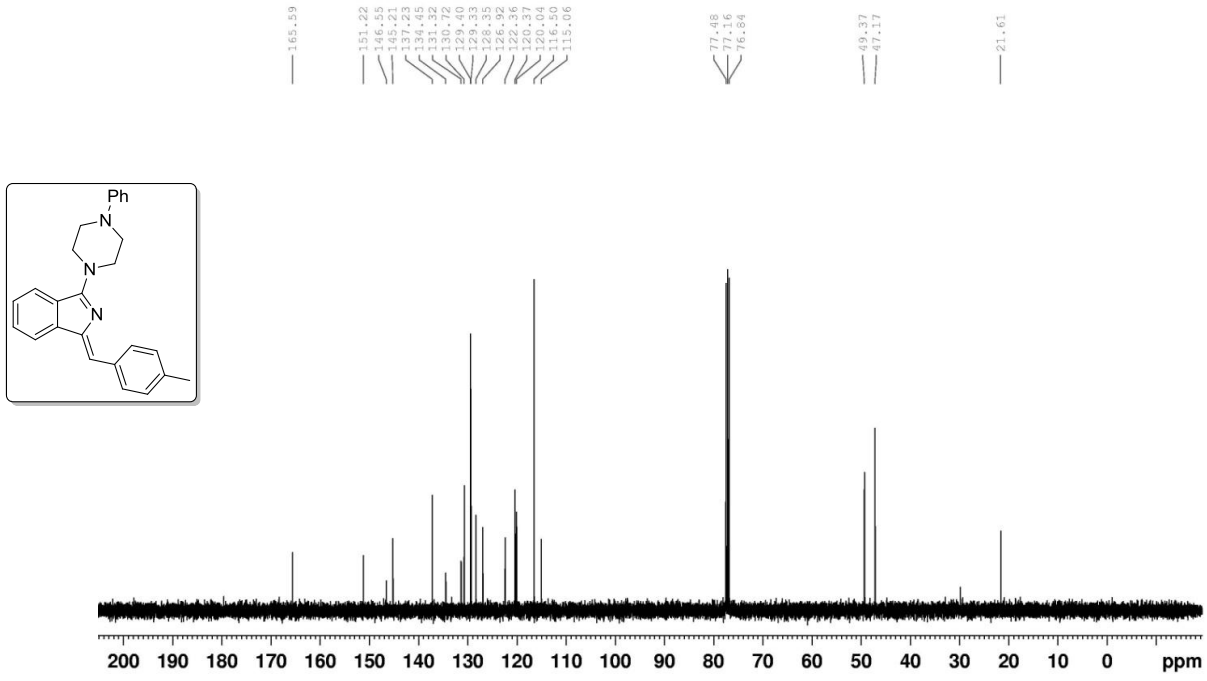
^{13}C NMR spectrum of compound **21**



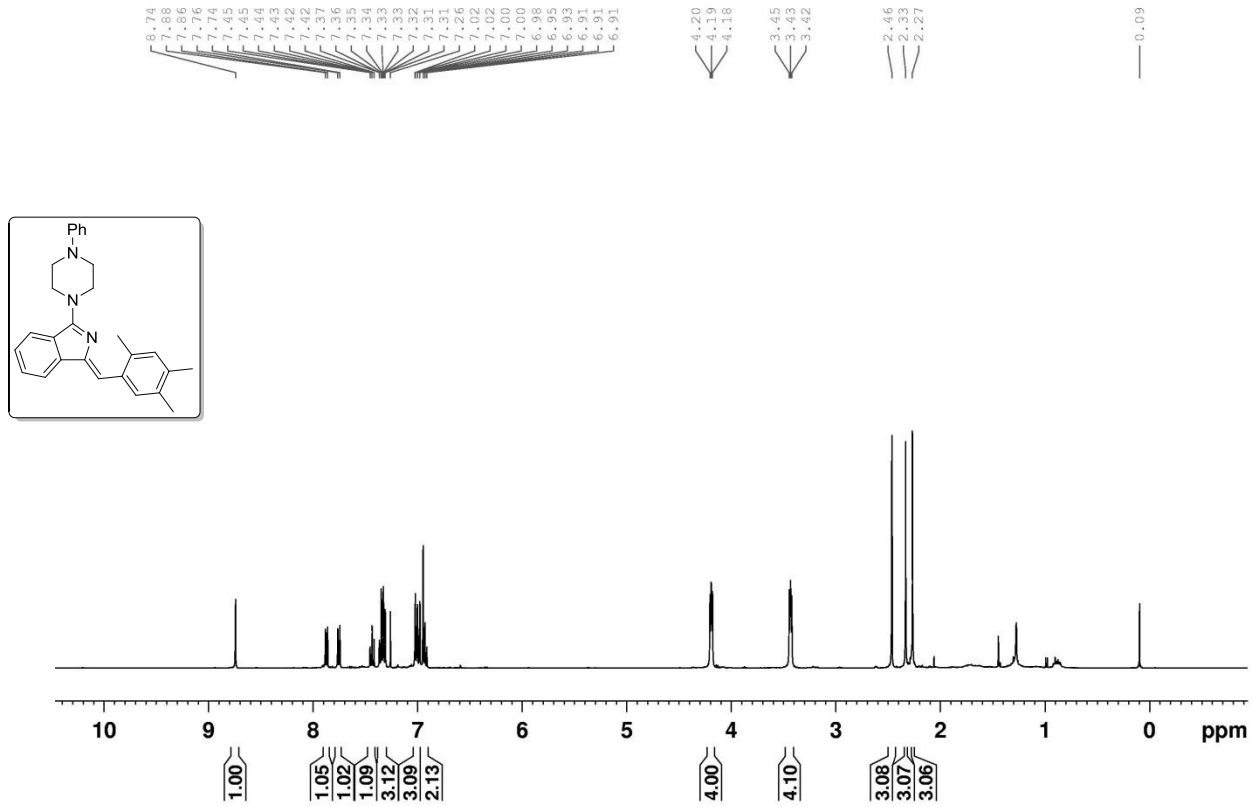
^{1}H NMR spectrum of compound **21a**



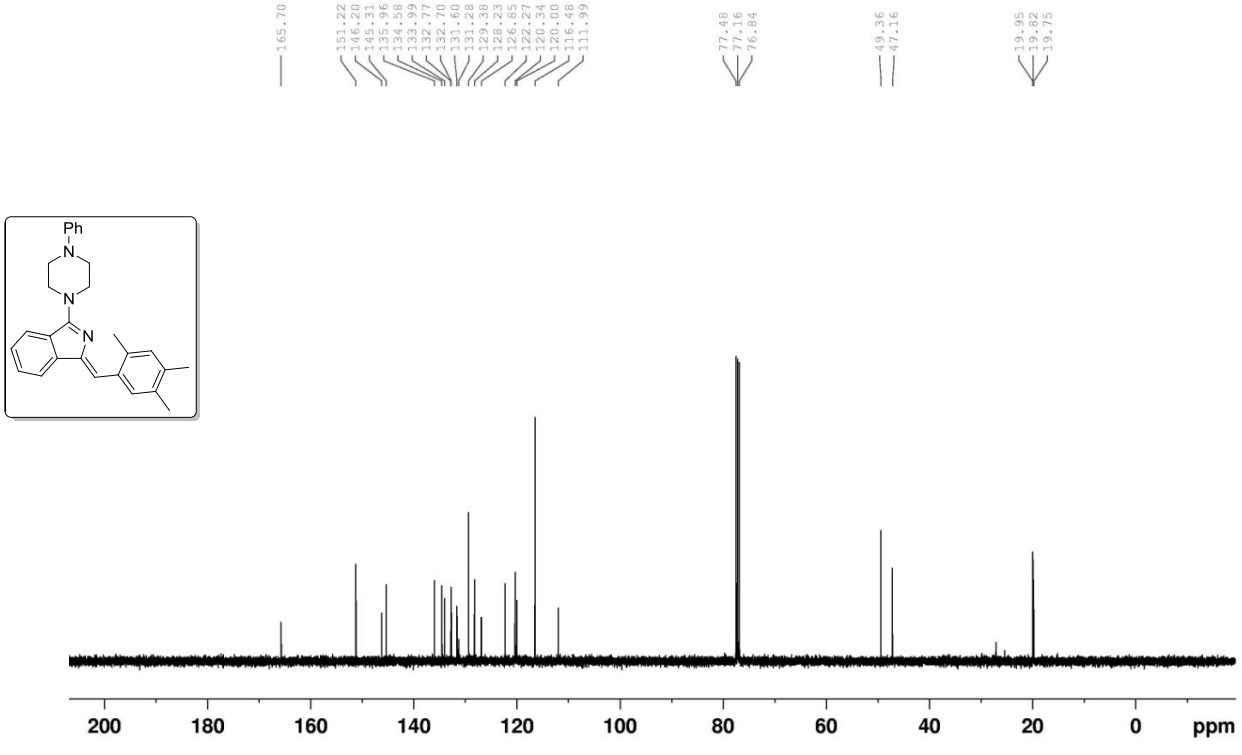
^{13}C NMR spectrum of compound **21a**



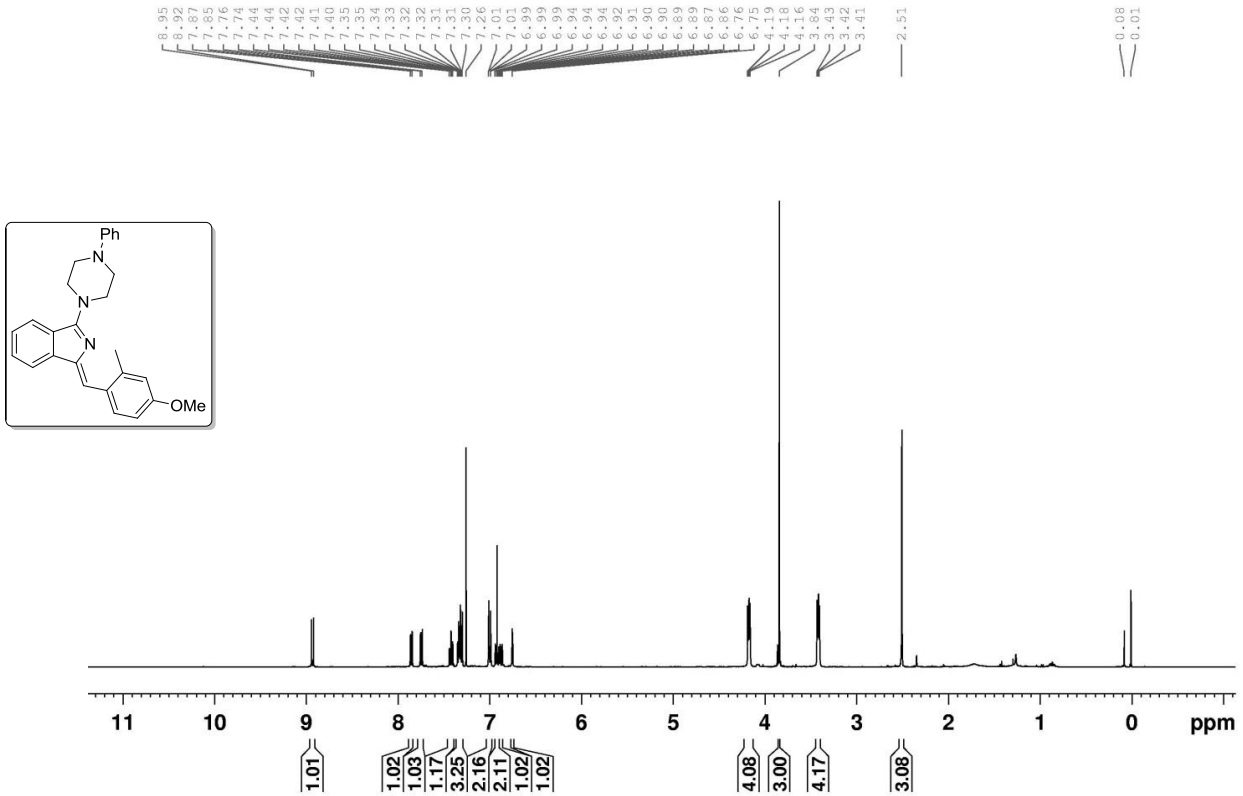
^{1}H NMR spectrum of compound **21b**



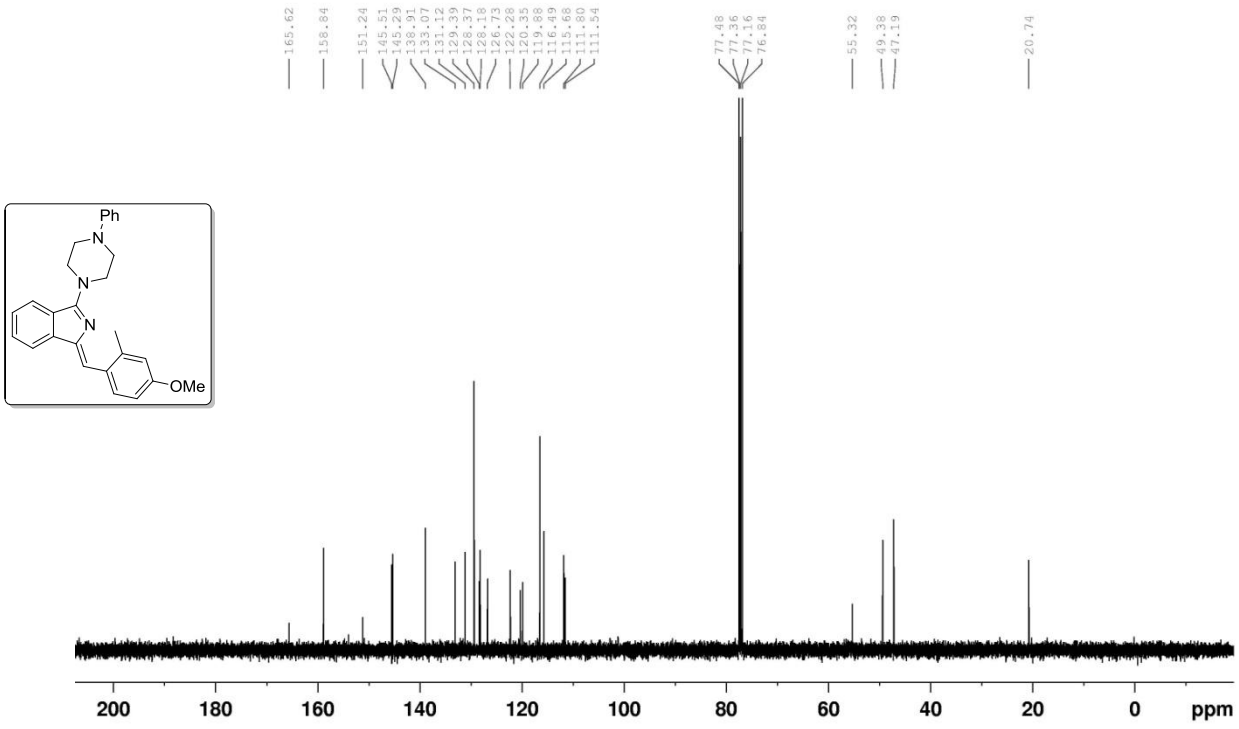
^{13}C NMR spectrum of compound **21b**



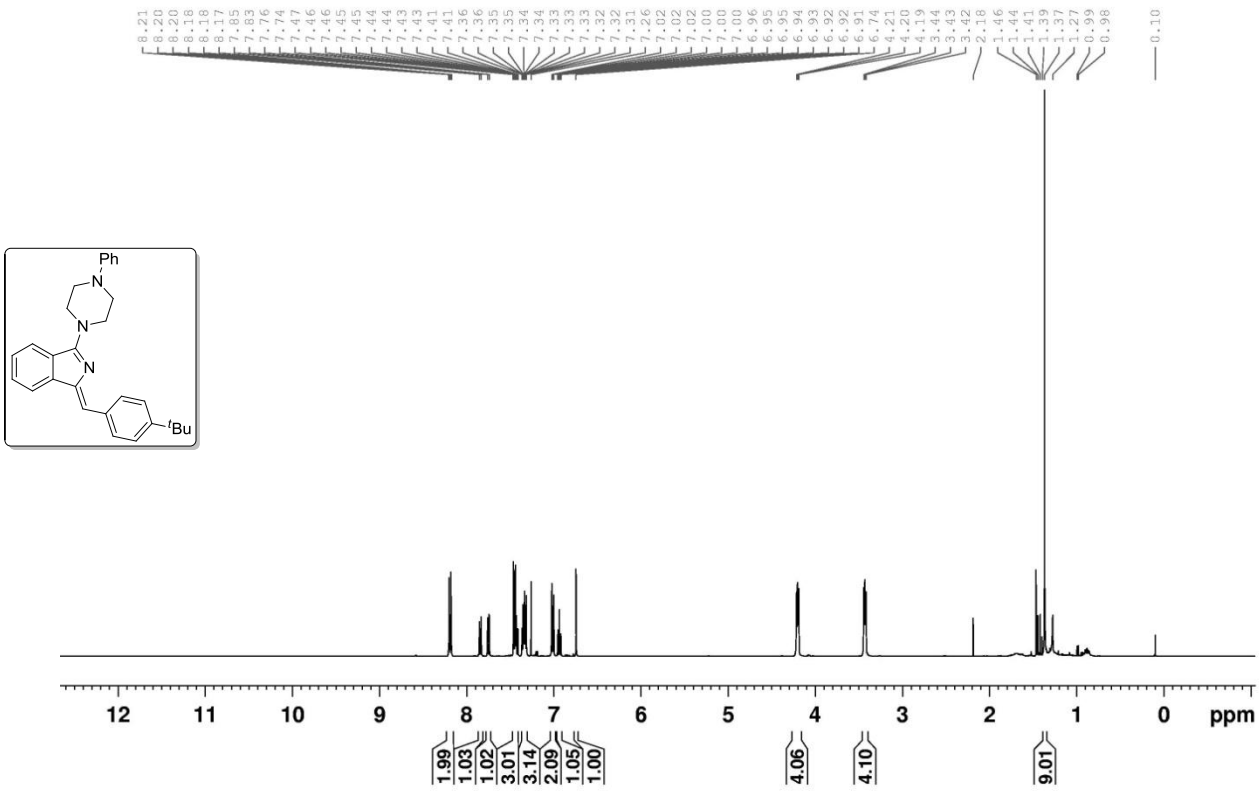
^{1}H NMR spectrum of compound **21c**



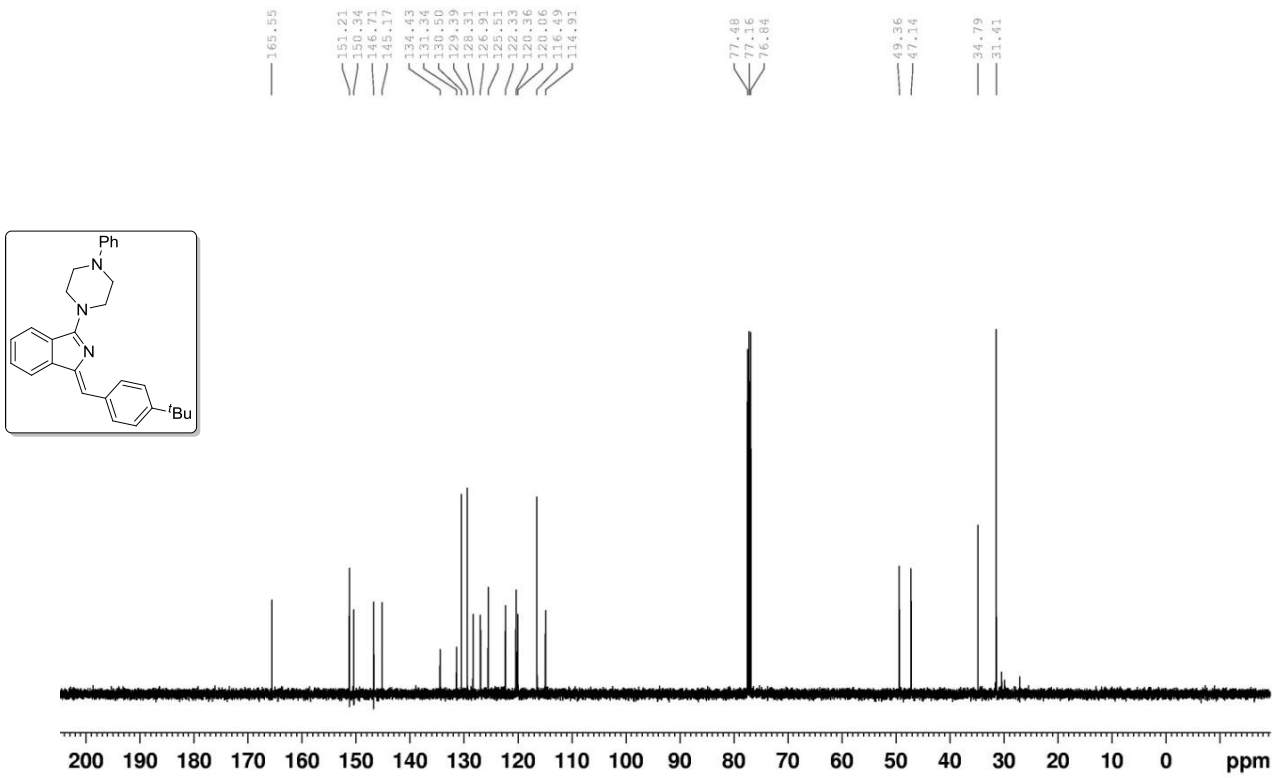
^{13}C NMR spectrum of compound **21c**



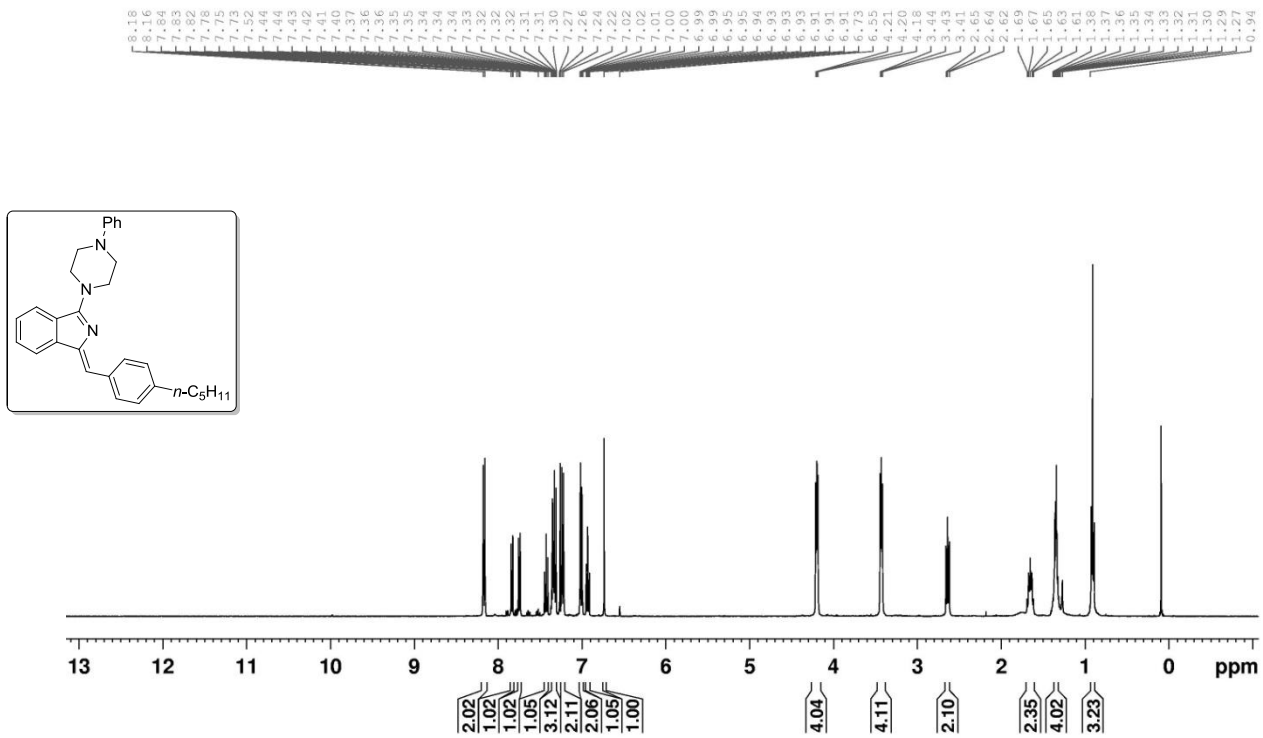
^{1}H NMR spectrum of compound **21d**



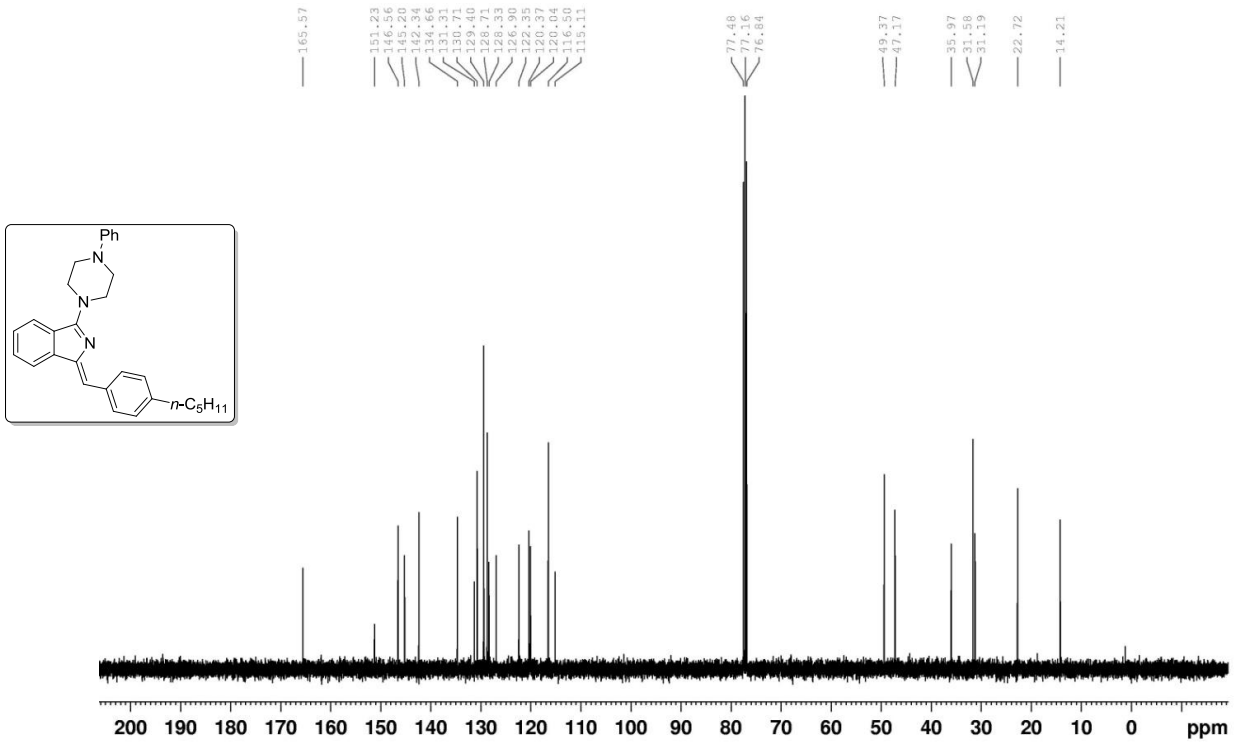
^{13}C NMR spectrum of compound **21d**



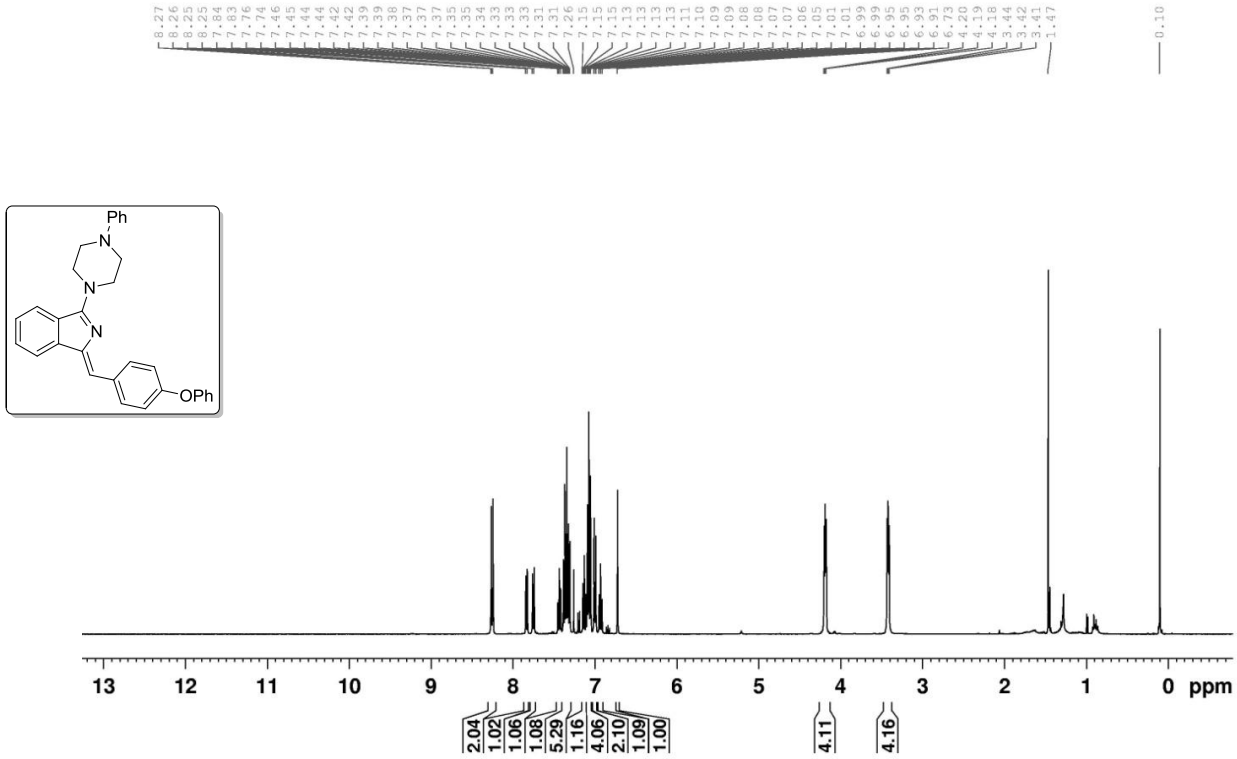
^{1}H NMR spectrum of compound **21e**



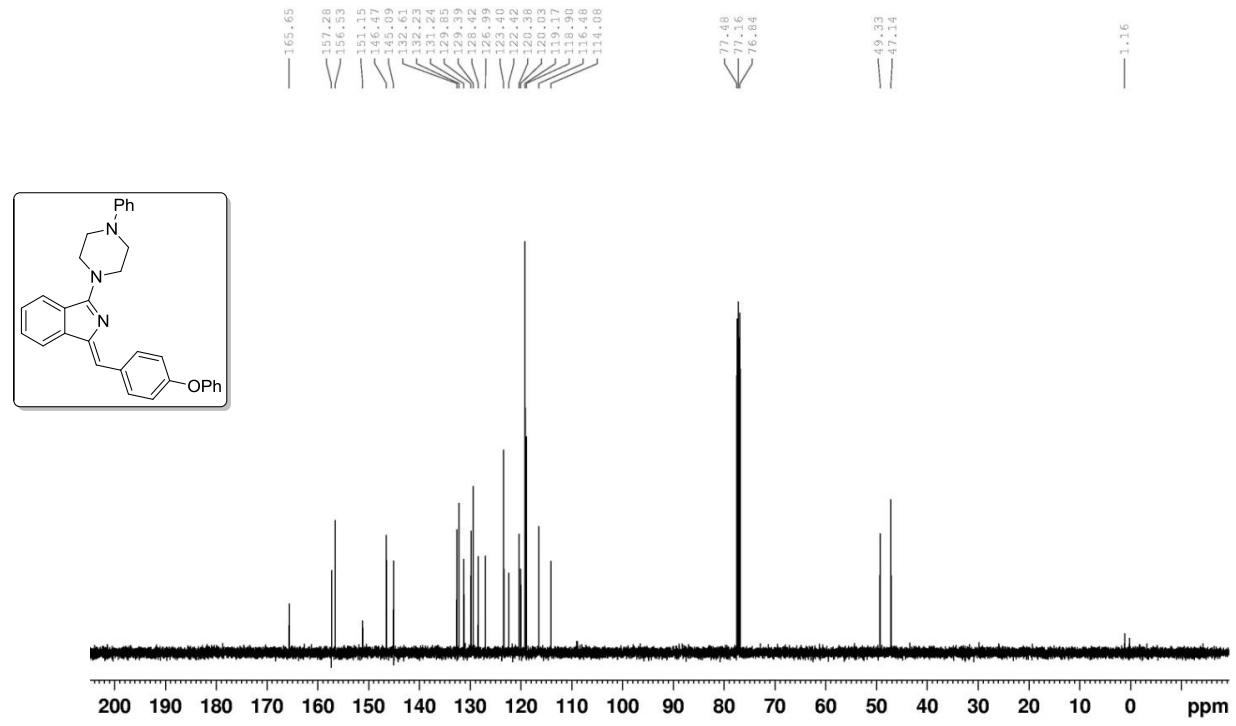
^{13}C NMR spectrum of compound **21e**



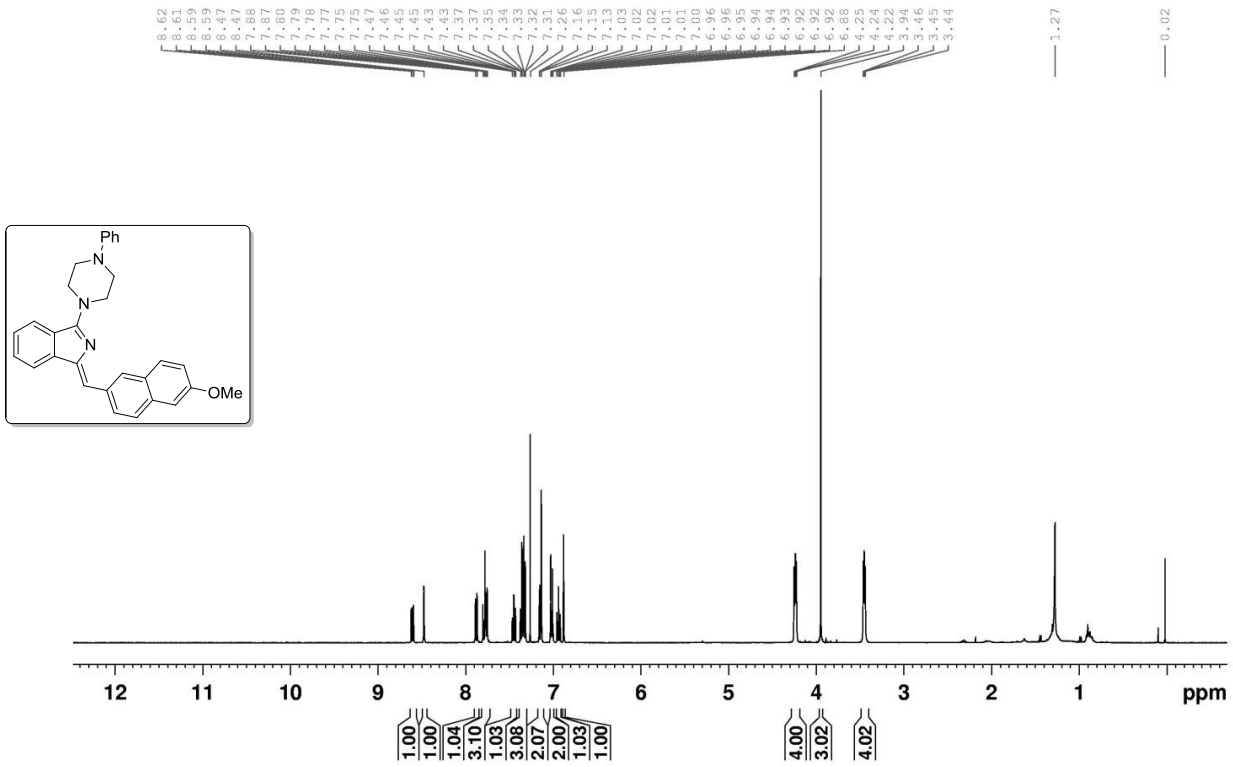
^{1}H NMR spectrum of compound **21f**



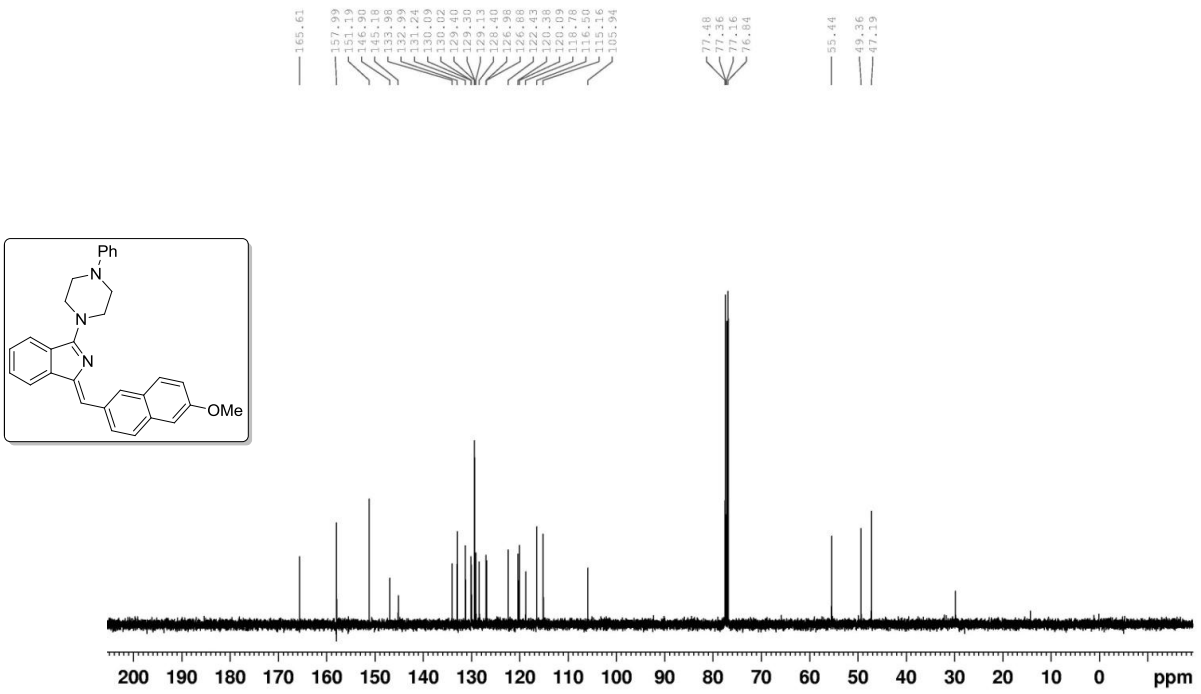
^{13}C NMR spectrum of compound **21f**



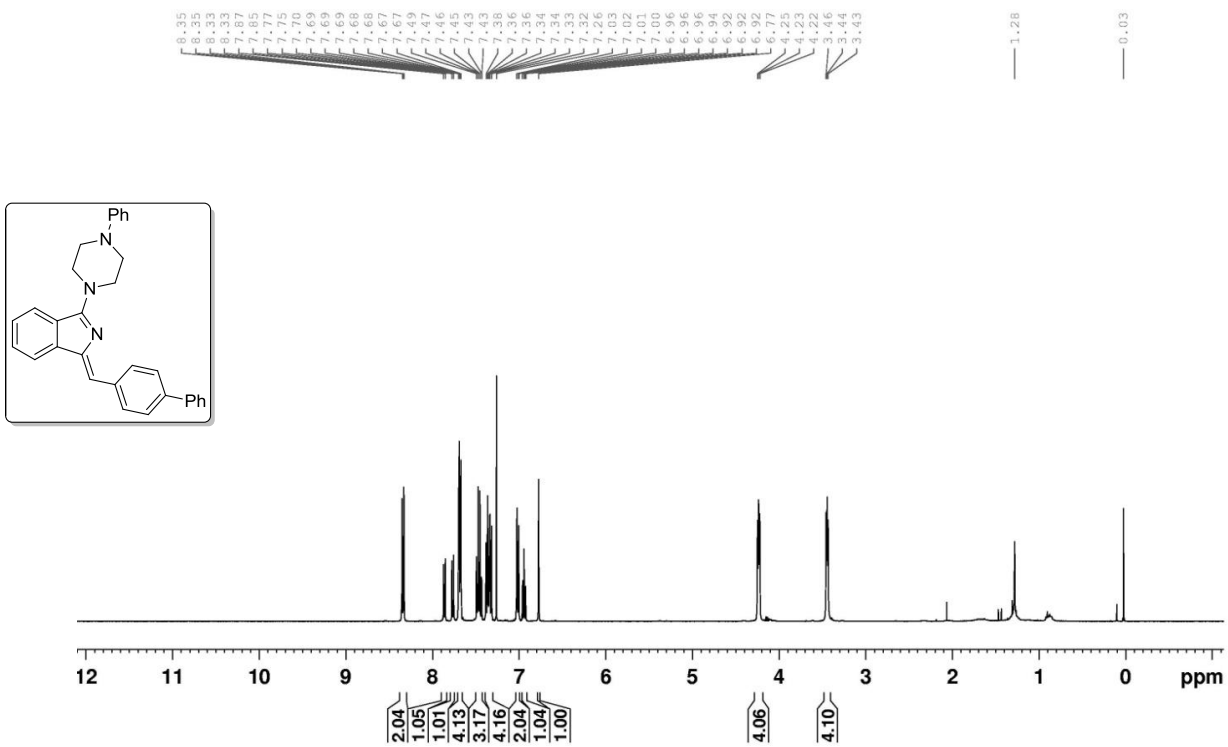
^{1}H NMR spectrum of compound **21g**



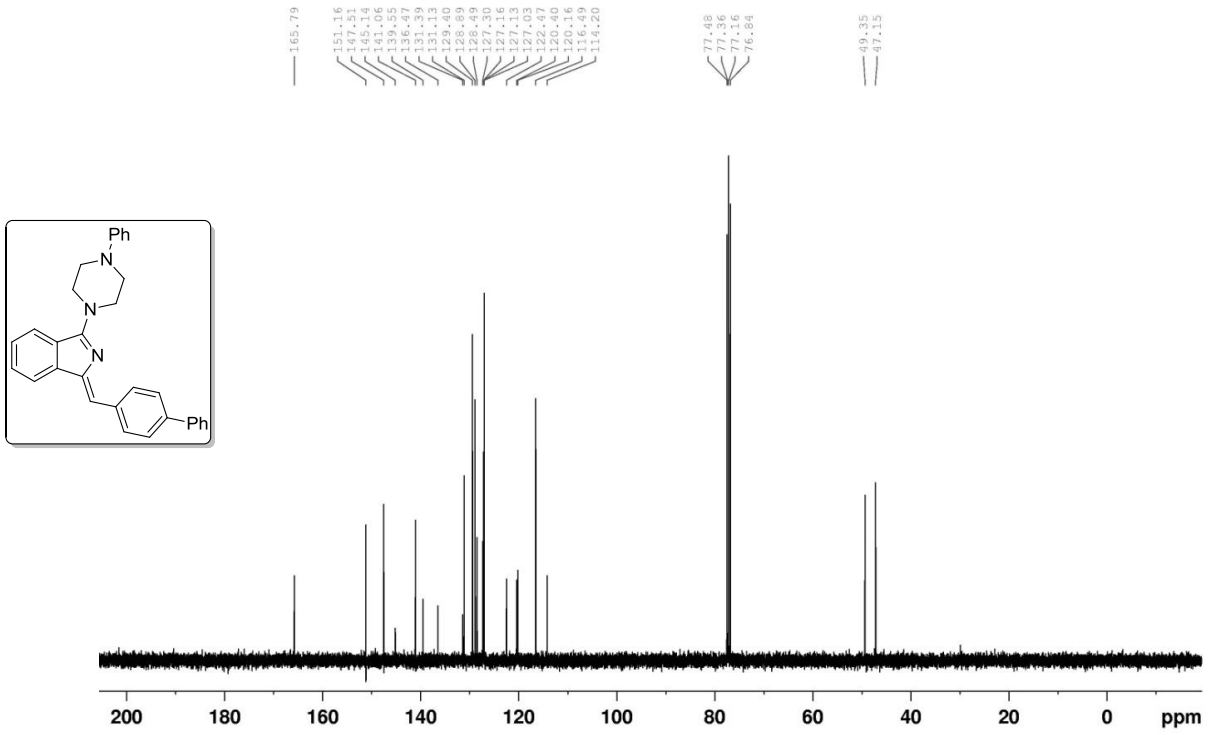
^{13}C NMR spectrum of compound **21g**



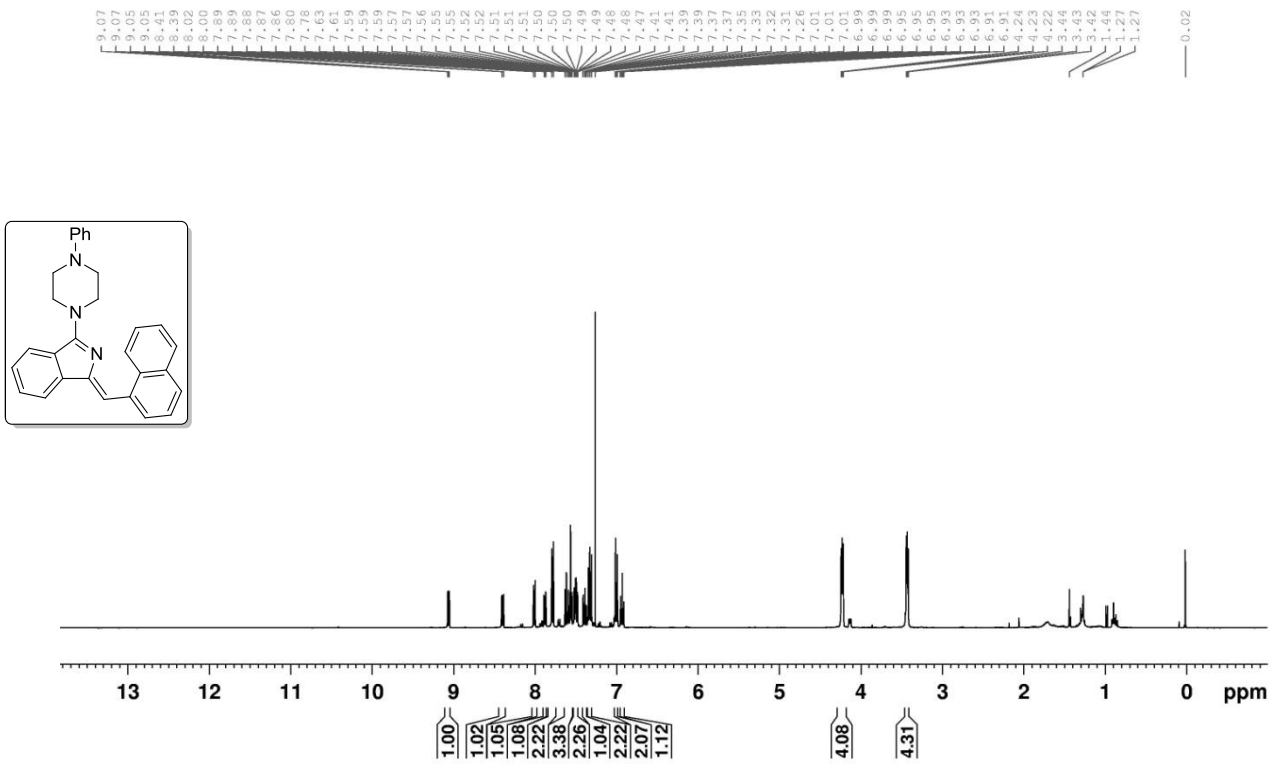
^{1}H NMR spectrum of compound **21h**



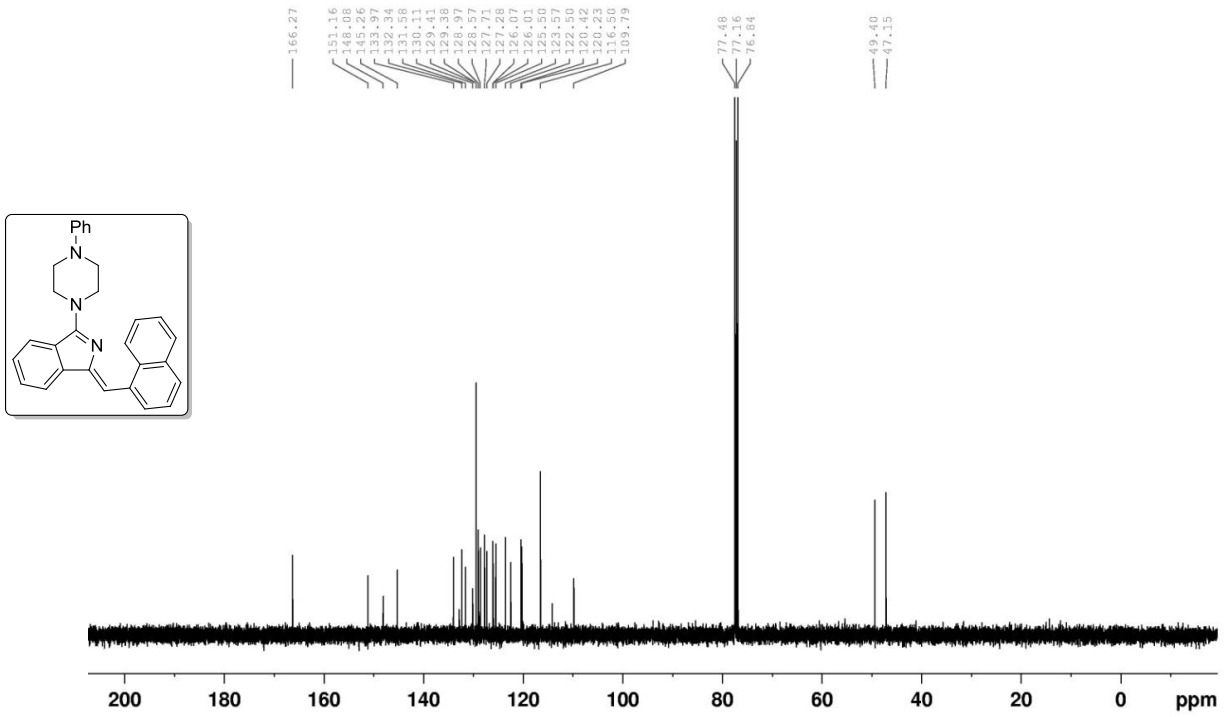
^{13}C NMR spectrum of compound **21h**



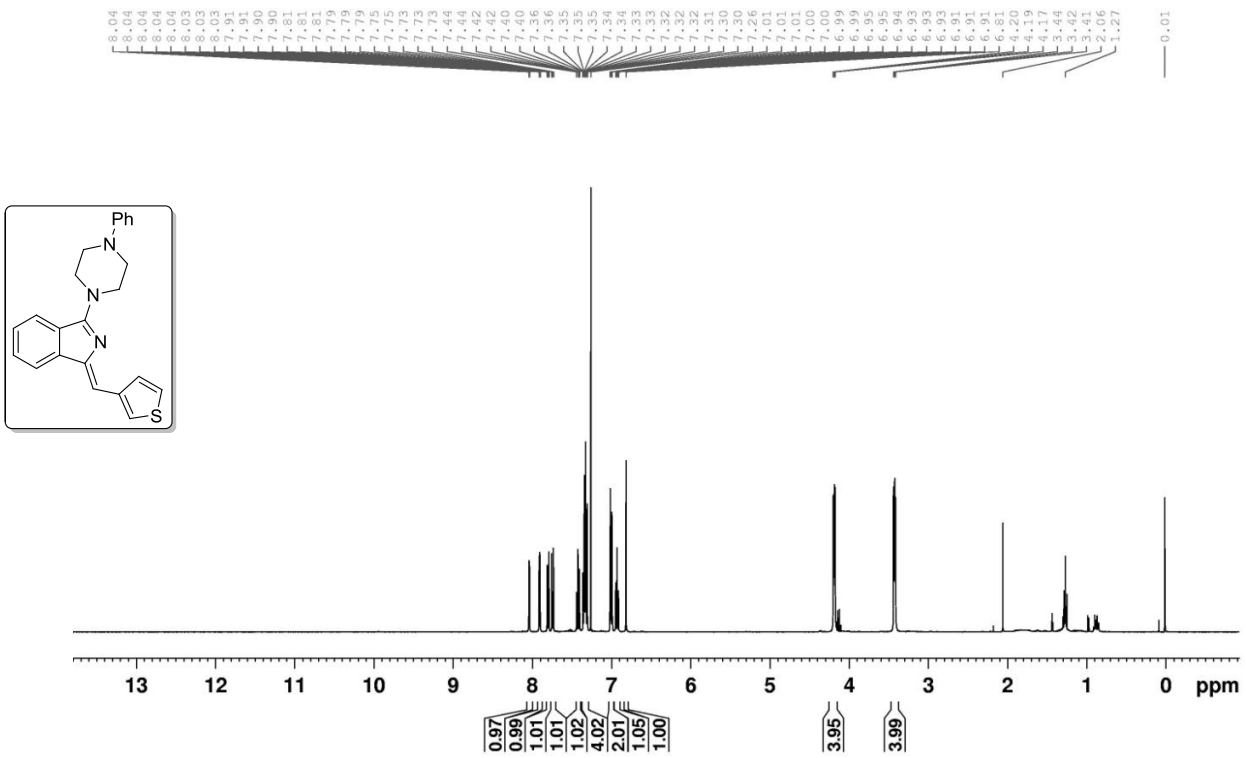
^{1}H NMR spectrum of compound **21i**



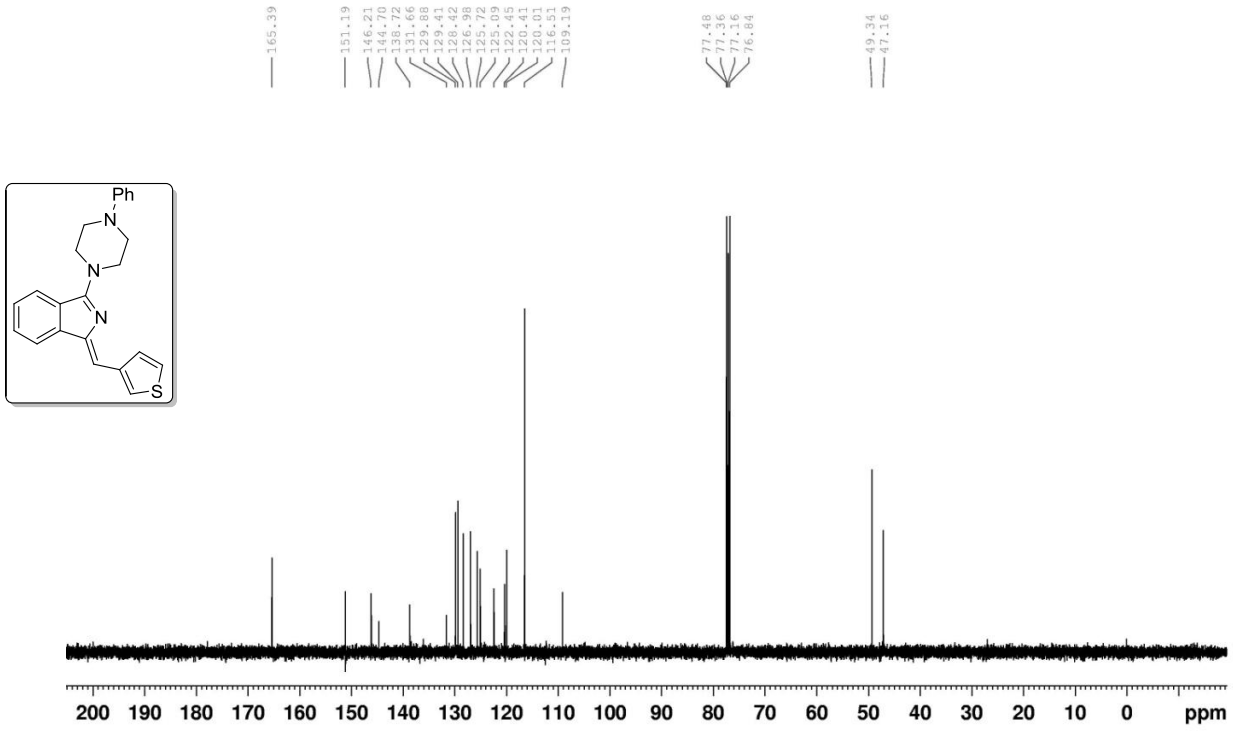
^{13}C NMR spectrum of compound **21i**



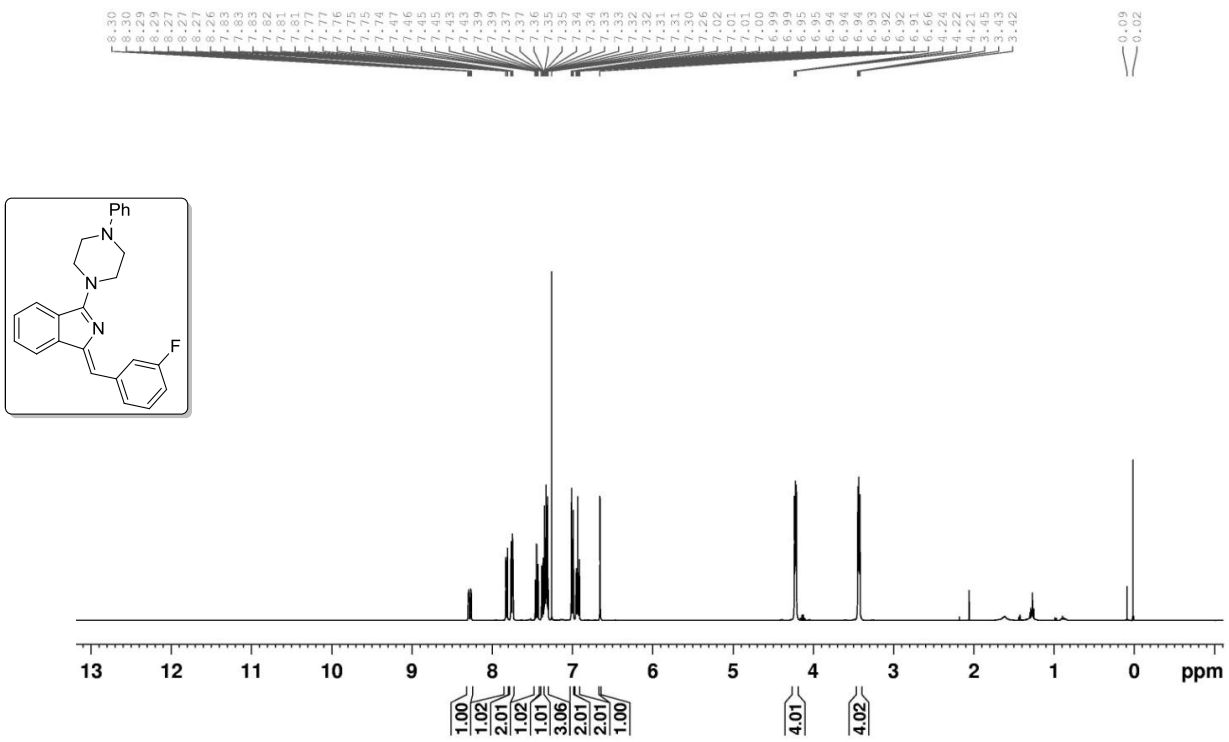
^{1}H NMR spectrum of compound **21j**



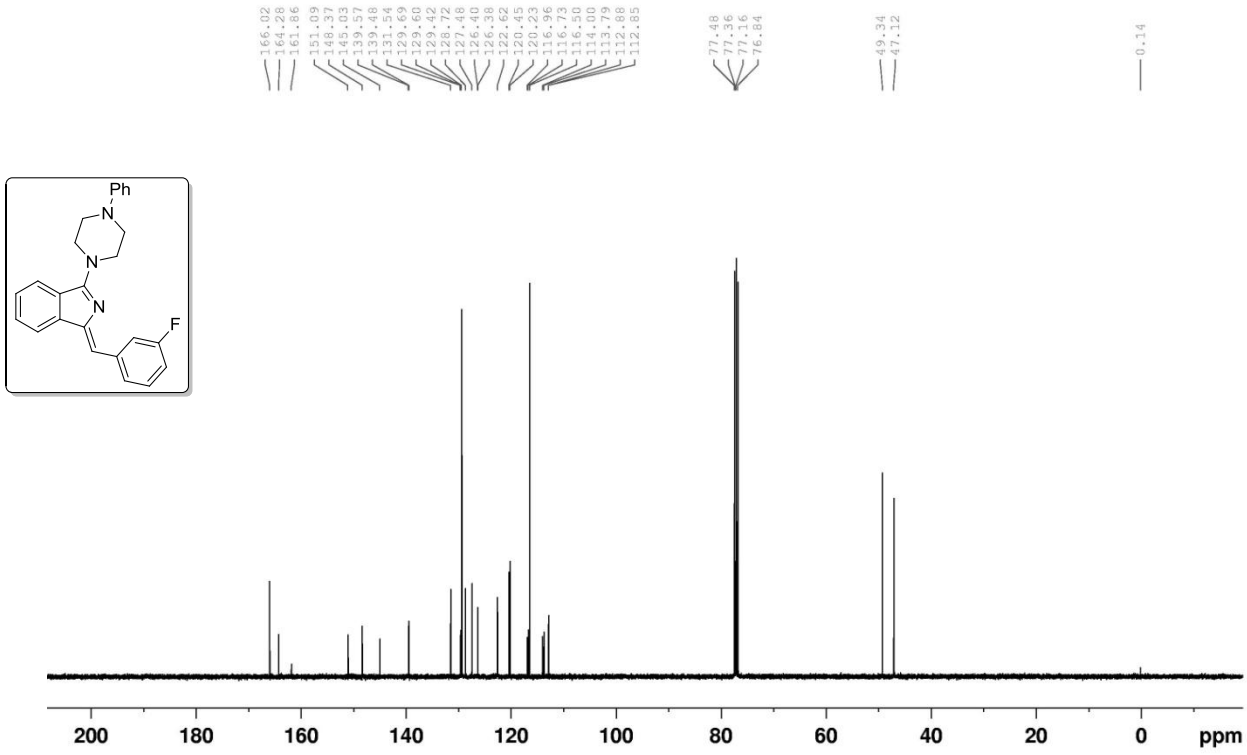
^{13}C NMR spectrum of compound **21j**



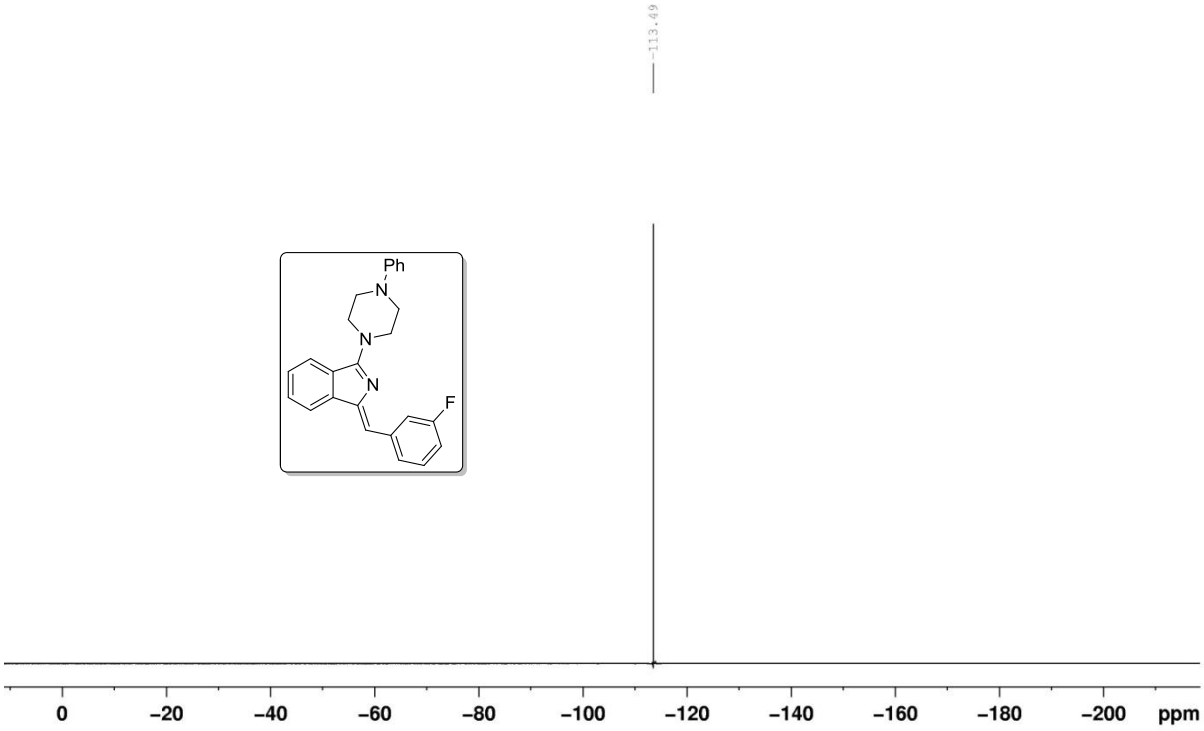
^{1}H NMR spectrum of compound **21k**



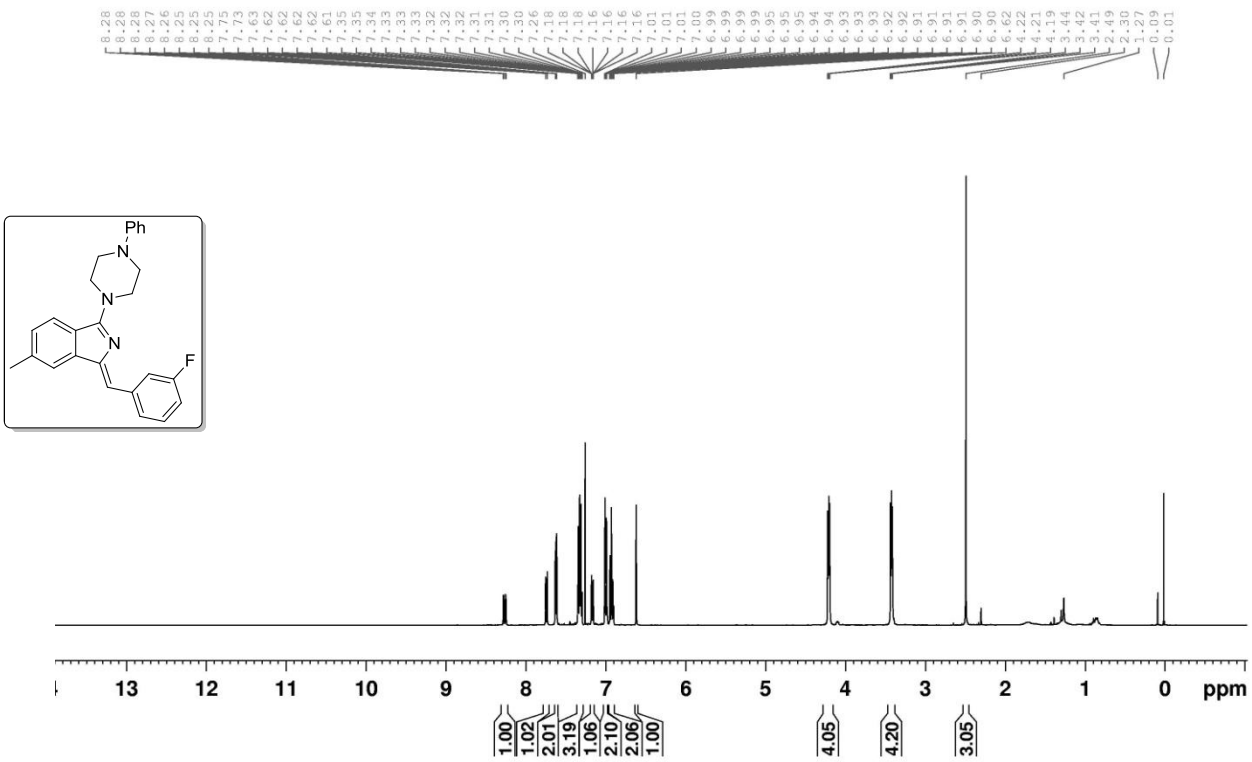
^{13}C NMR spectrum of compound **21k**



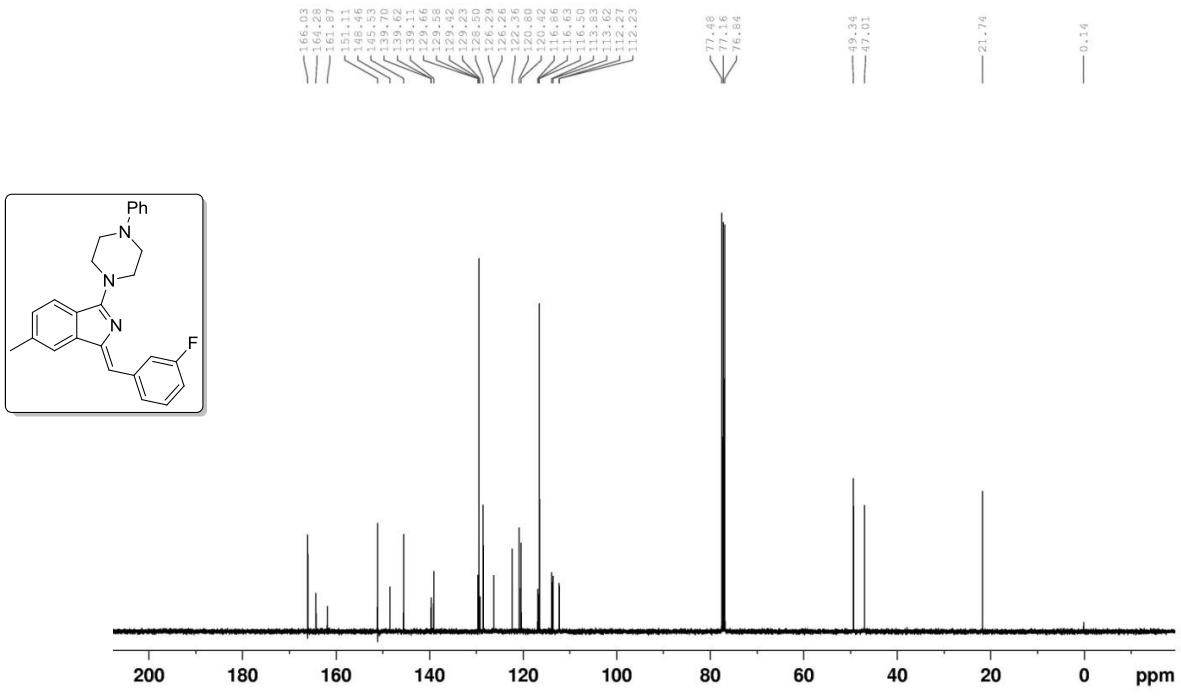
^{19}F NMR spectrum of compound **21k**



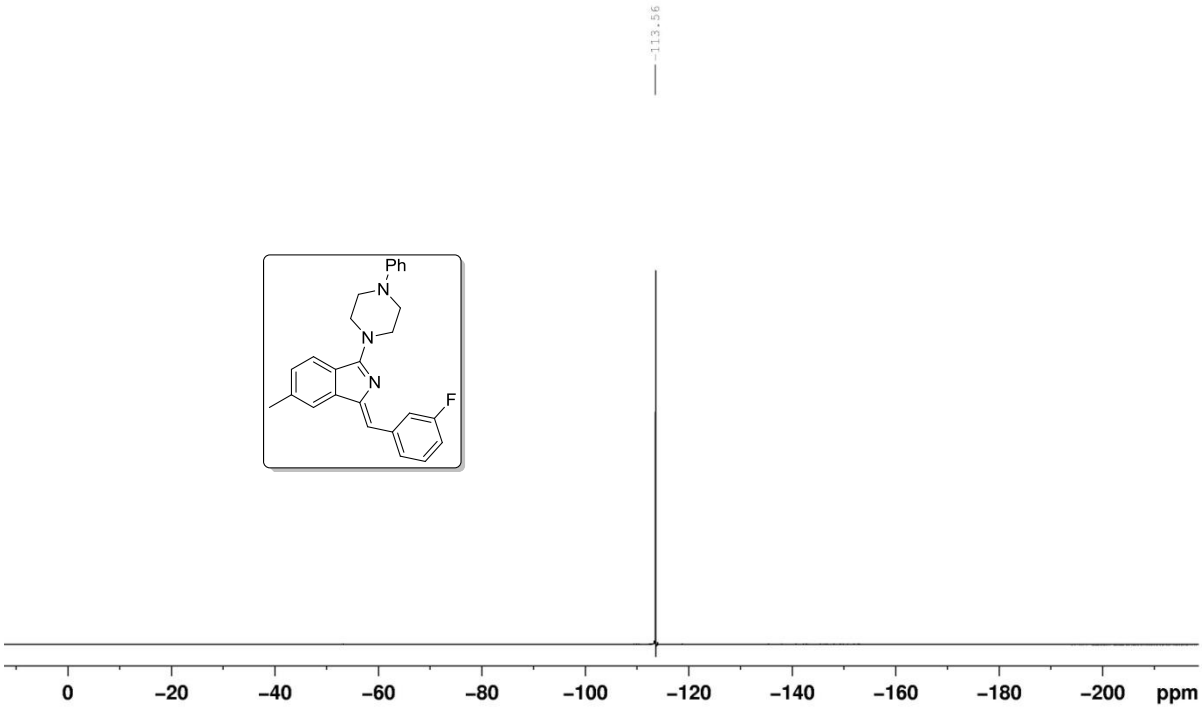
^{1}H NMR spectrum of compound **21l**



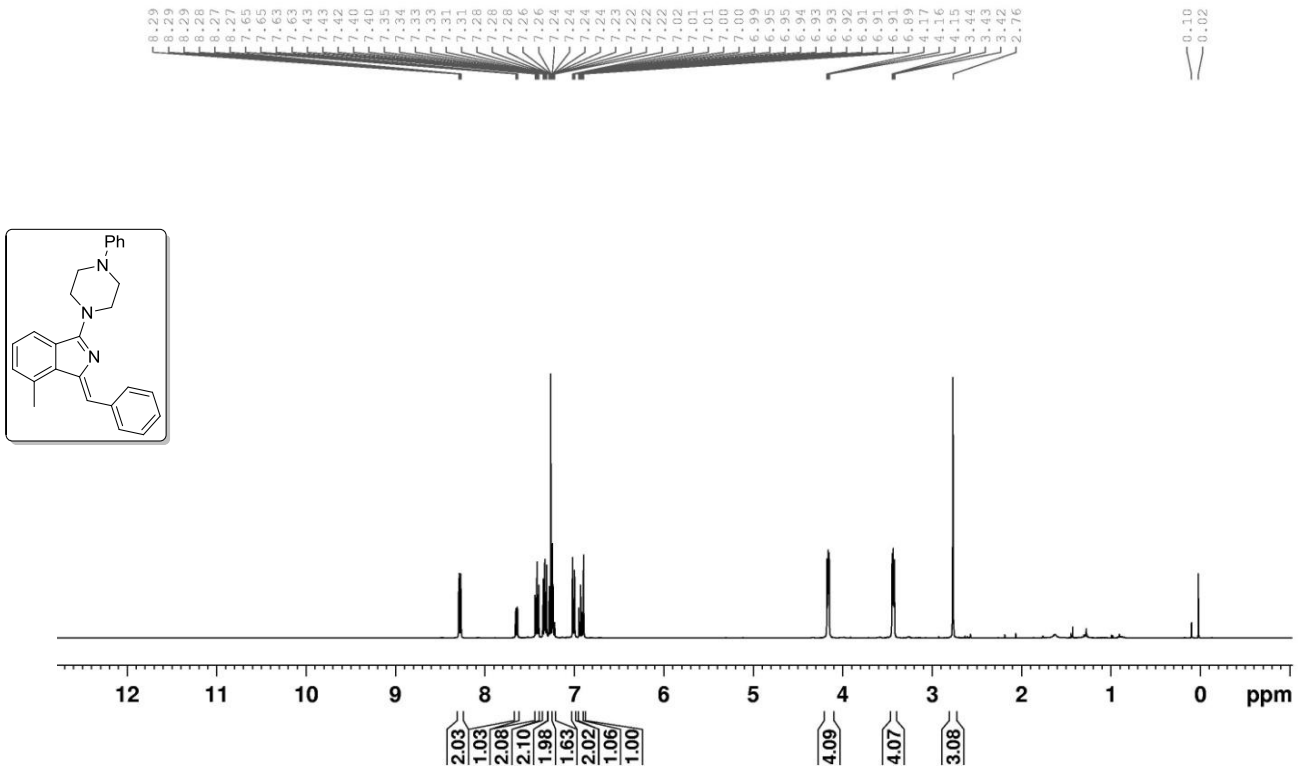
^{13}C NMR spectrum of compound **21l**



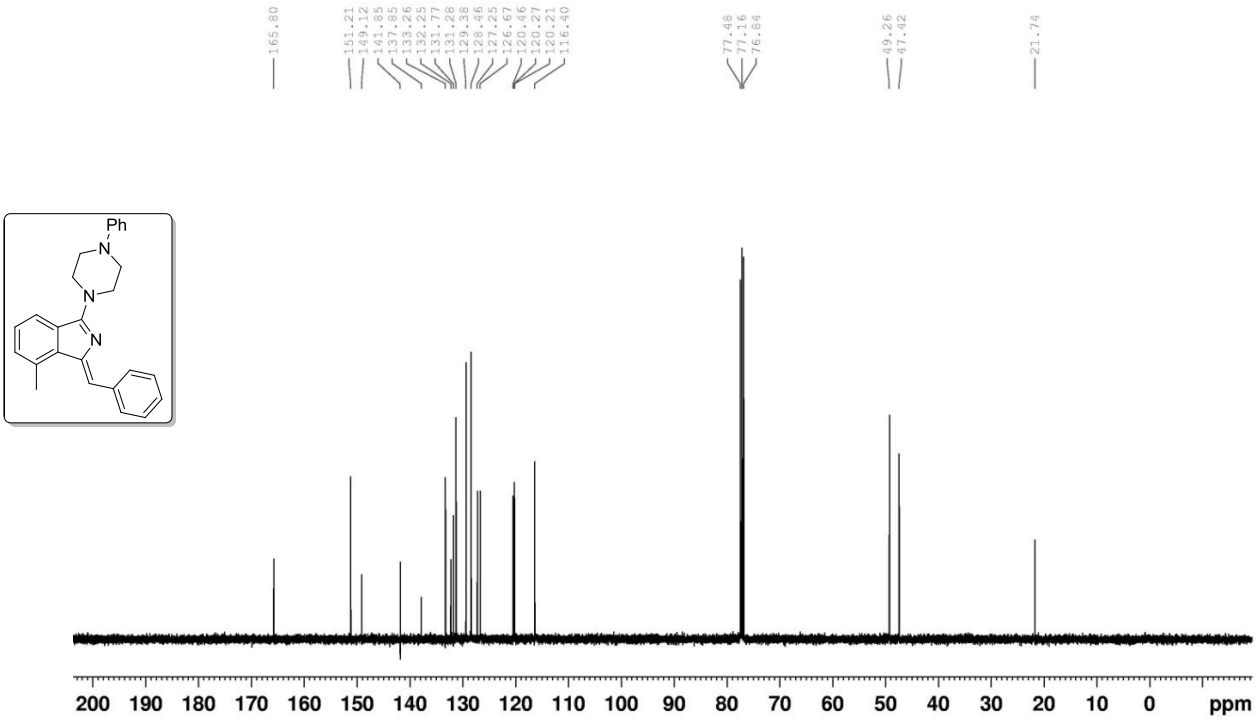
^{19}F NMR spectrum of compound **21l**



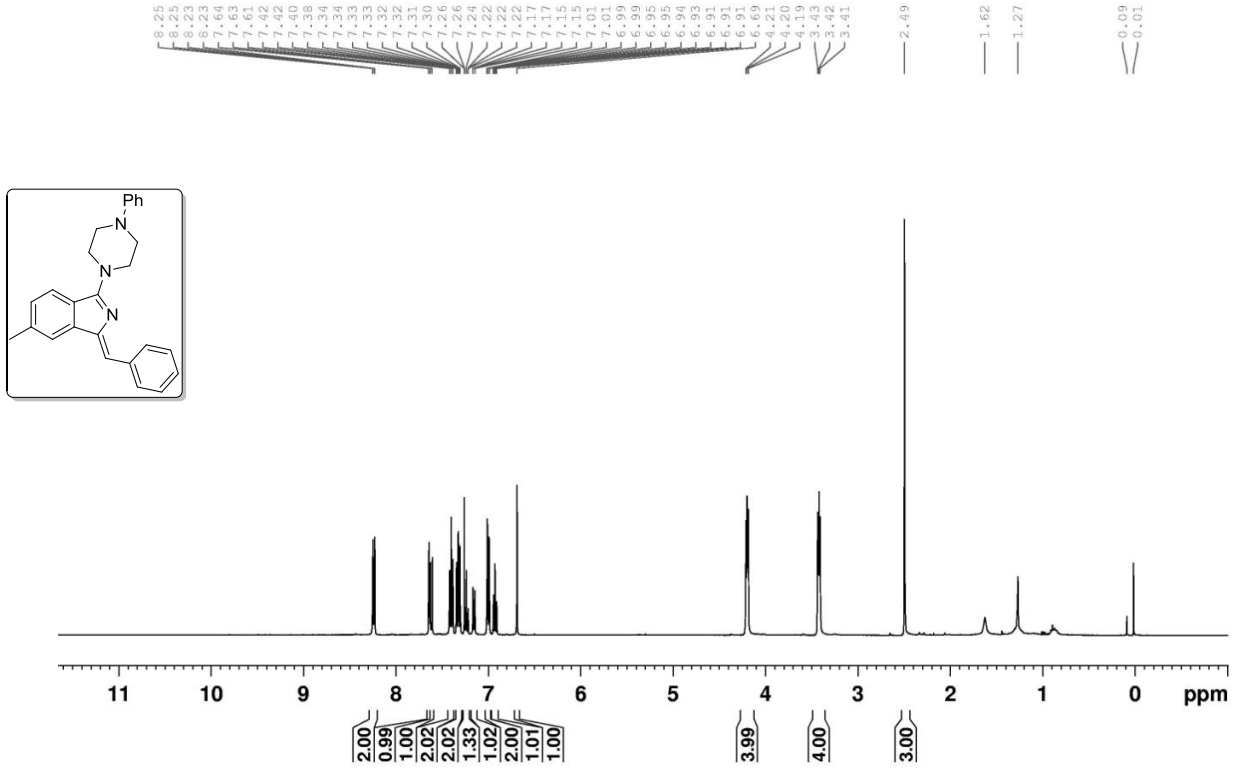
^{1}H NMR spectrum of compound **21m**



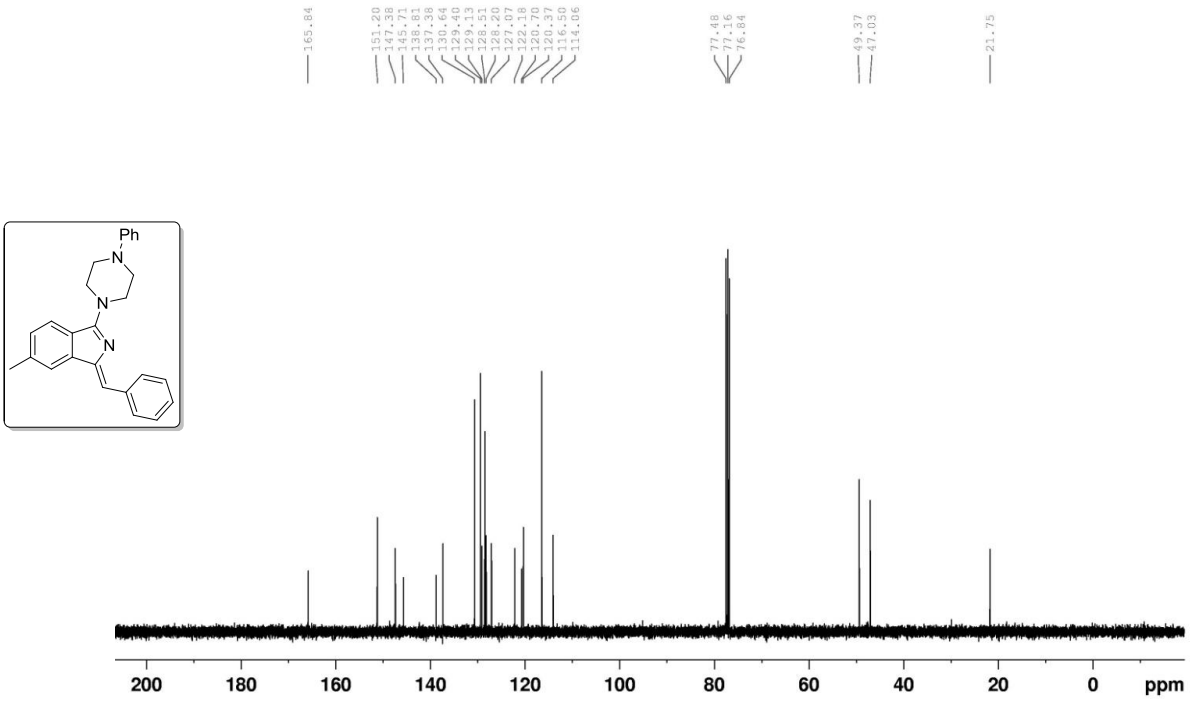
^{13}C NMR spectrum of compound **21m**



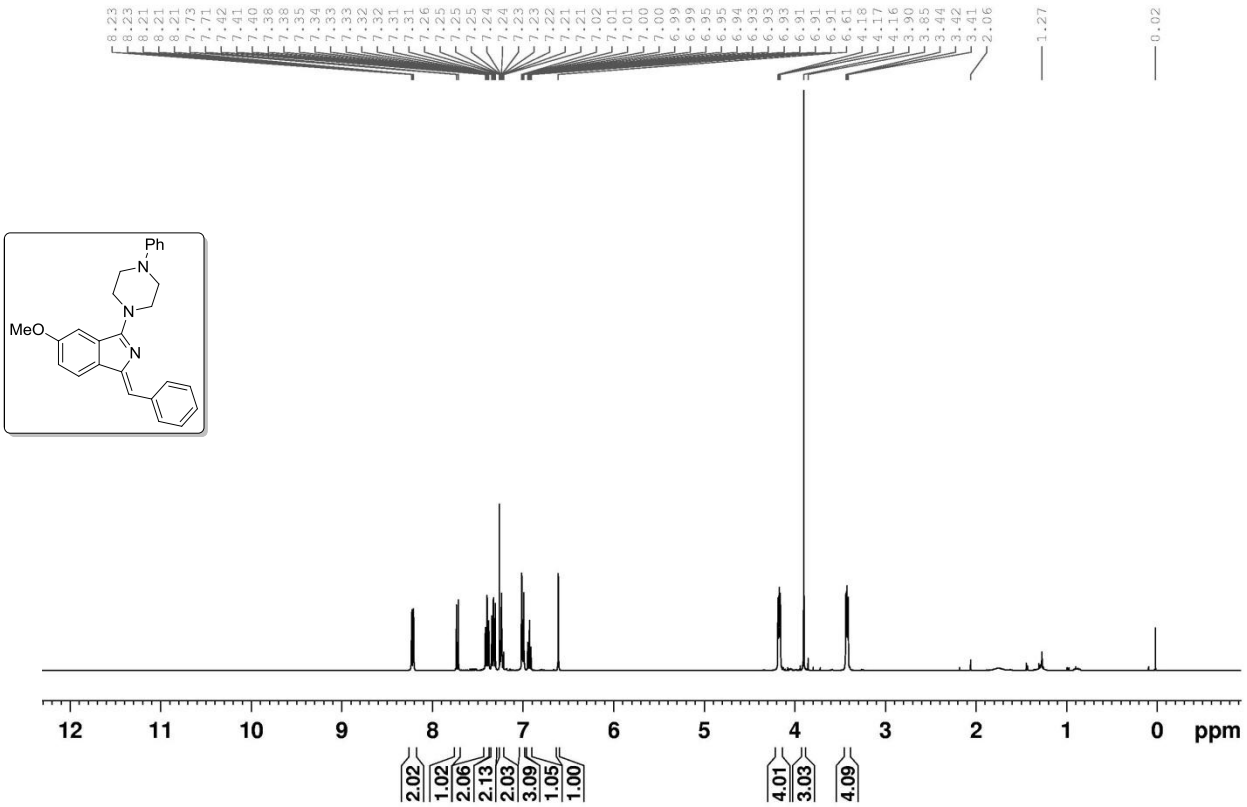
^{1}H NMR spectrum of compound **21n**



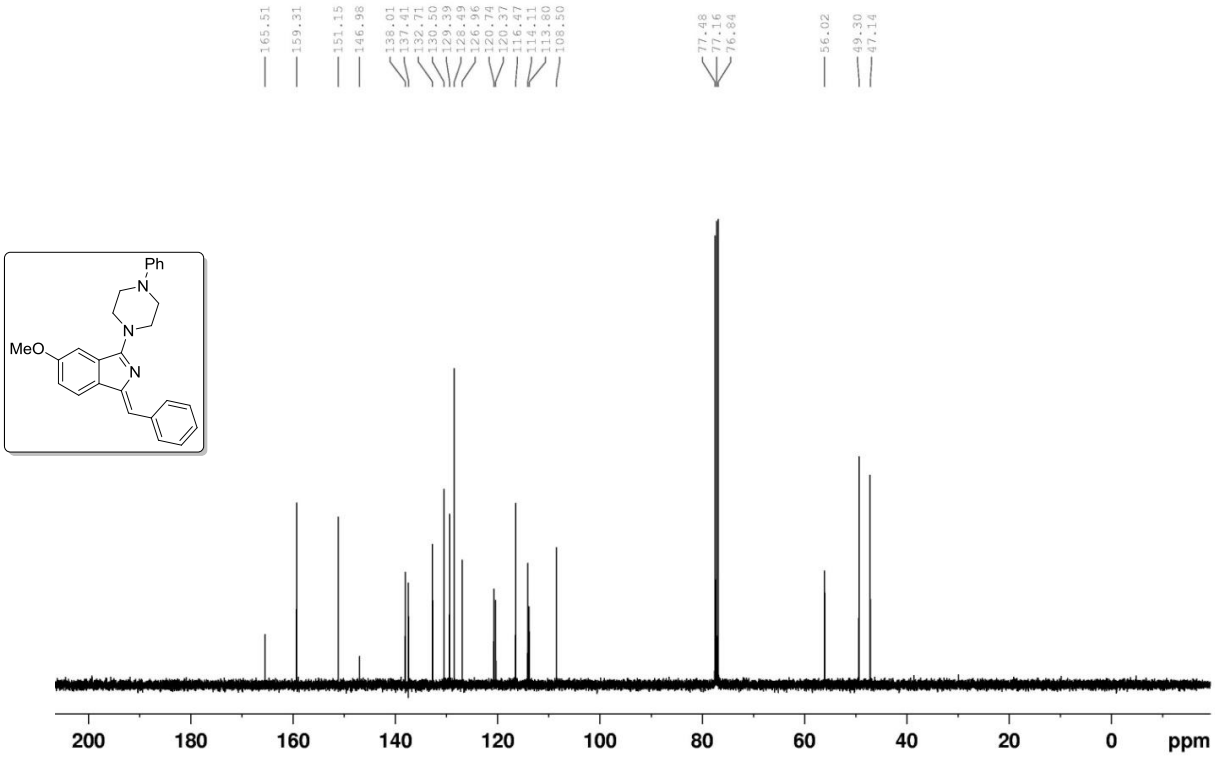
^{13}C NMR spectrum of compound **21n**



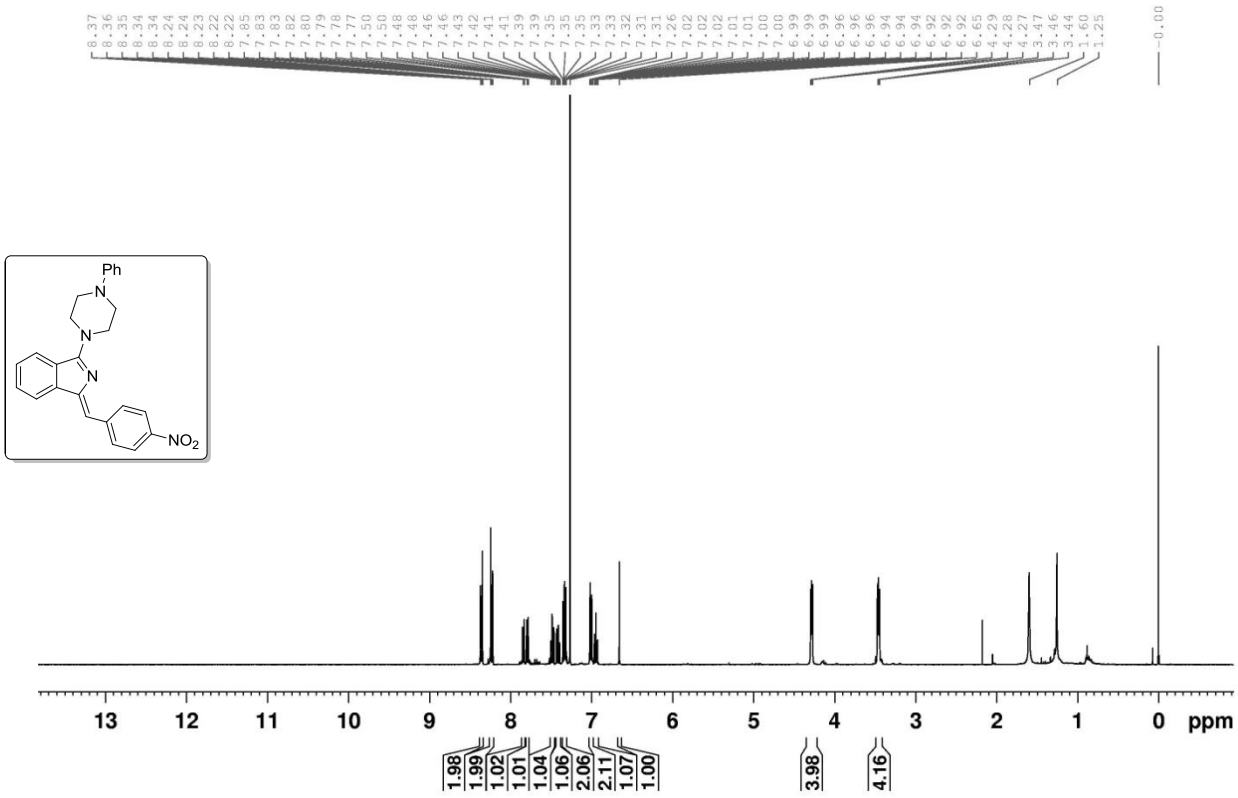
^{1}H NMR spectrum of compound **21o**



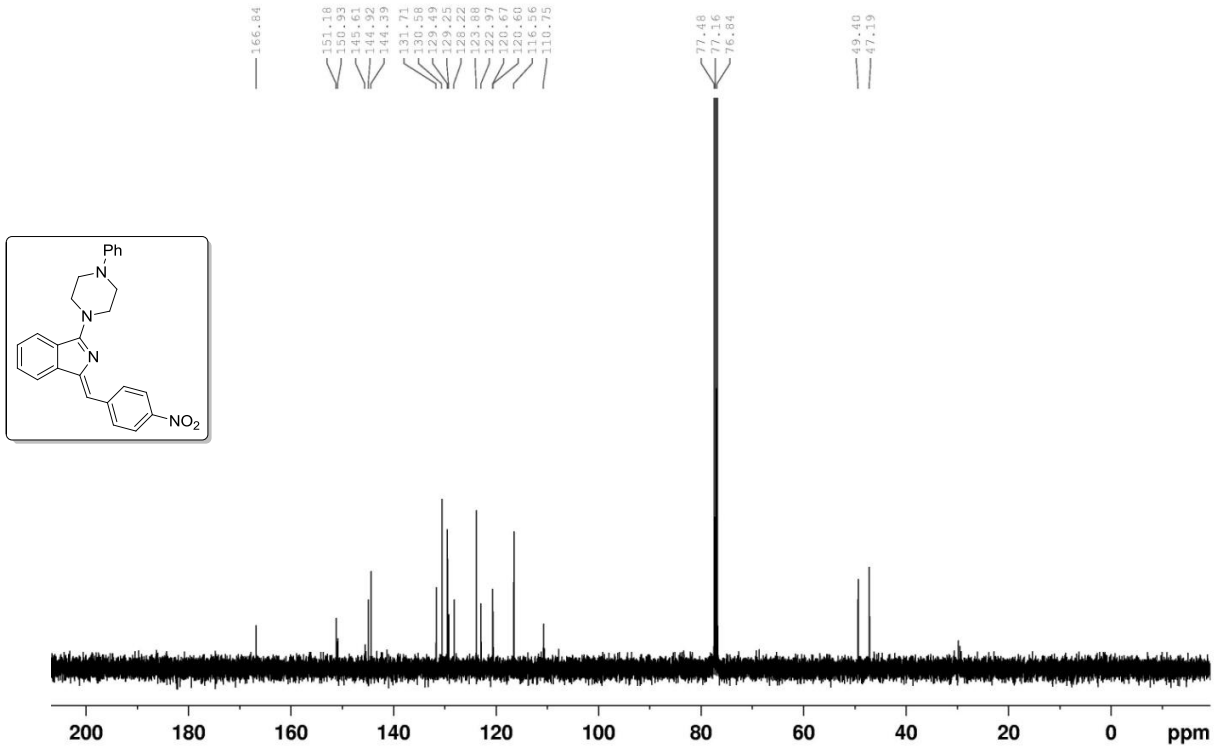
^{13}C NMR spectrum of compound **21o**



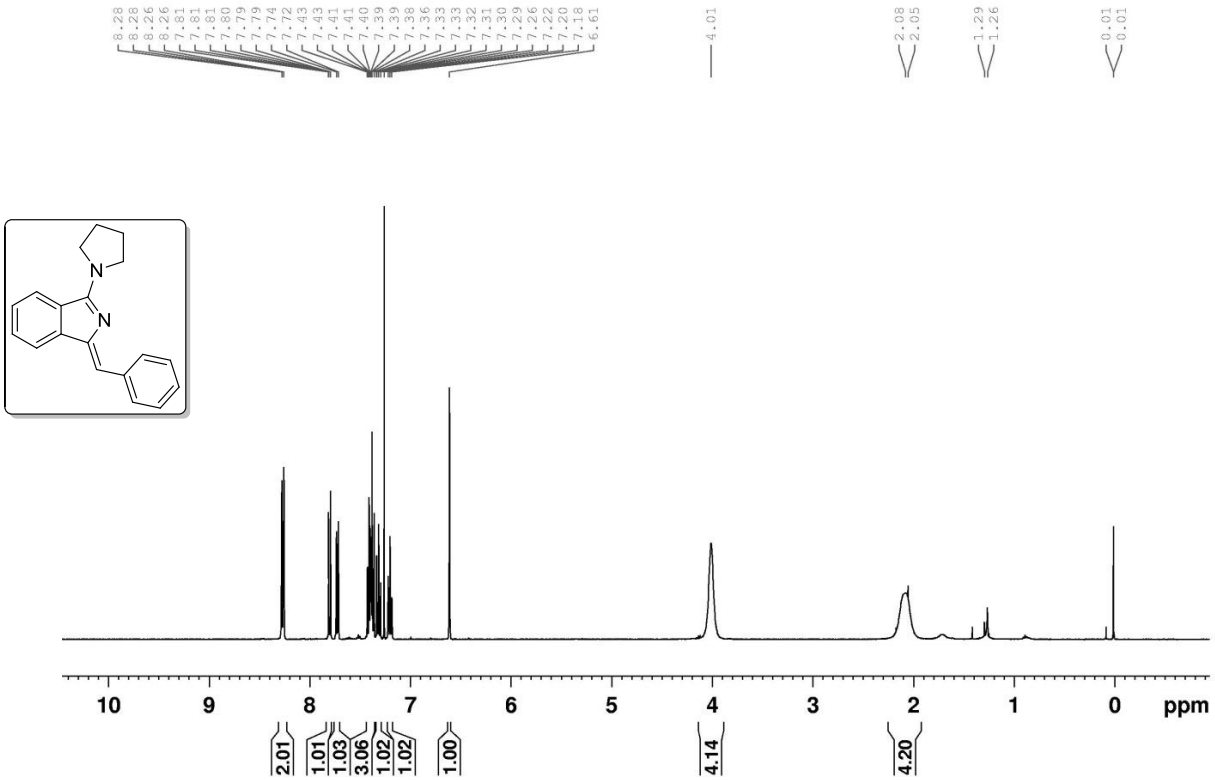
^{1}H NMR spectrum of compound **21p**



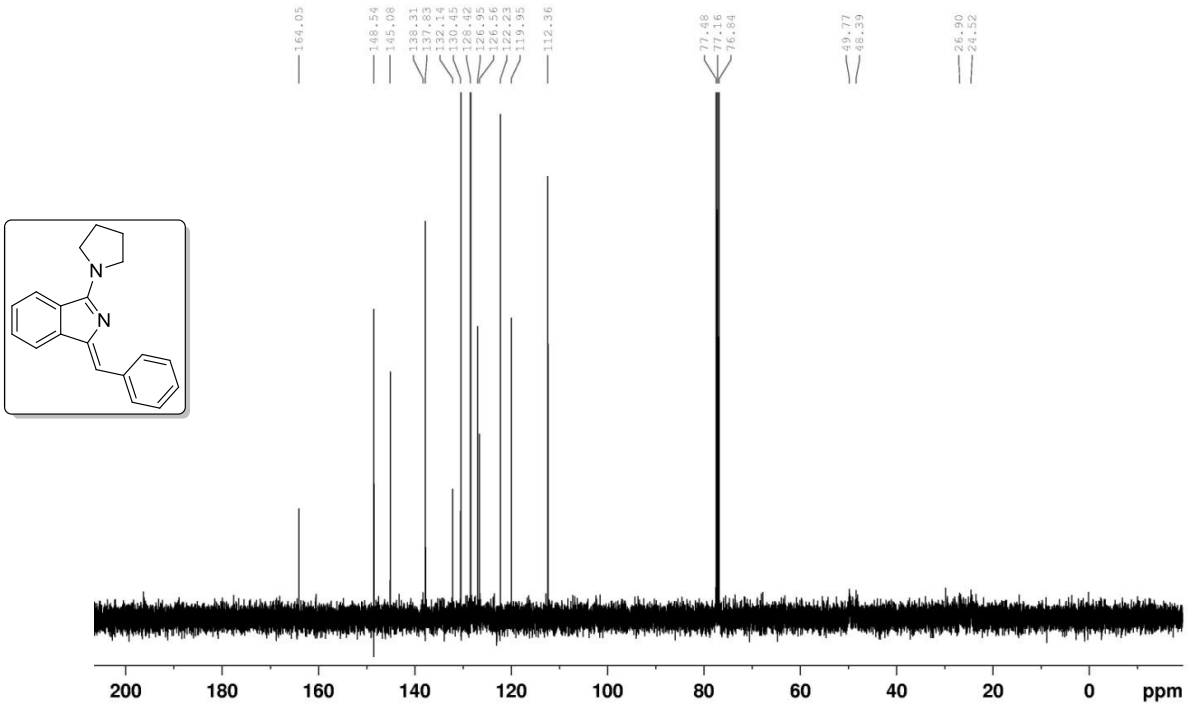
^{13}C NMR spectrum of compound **21p**



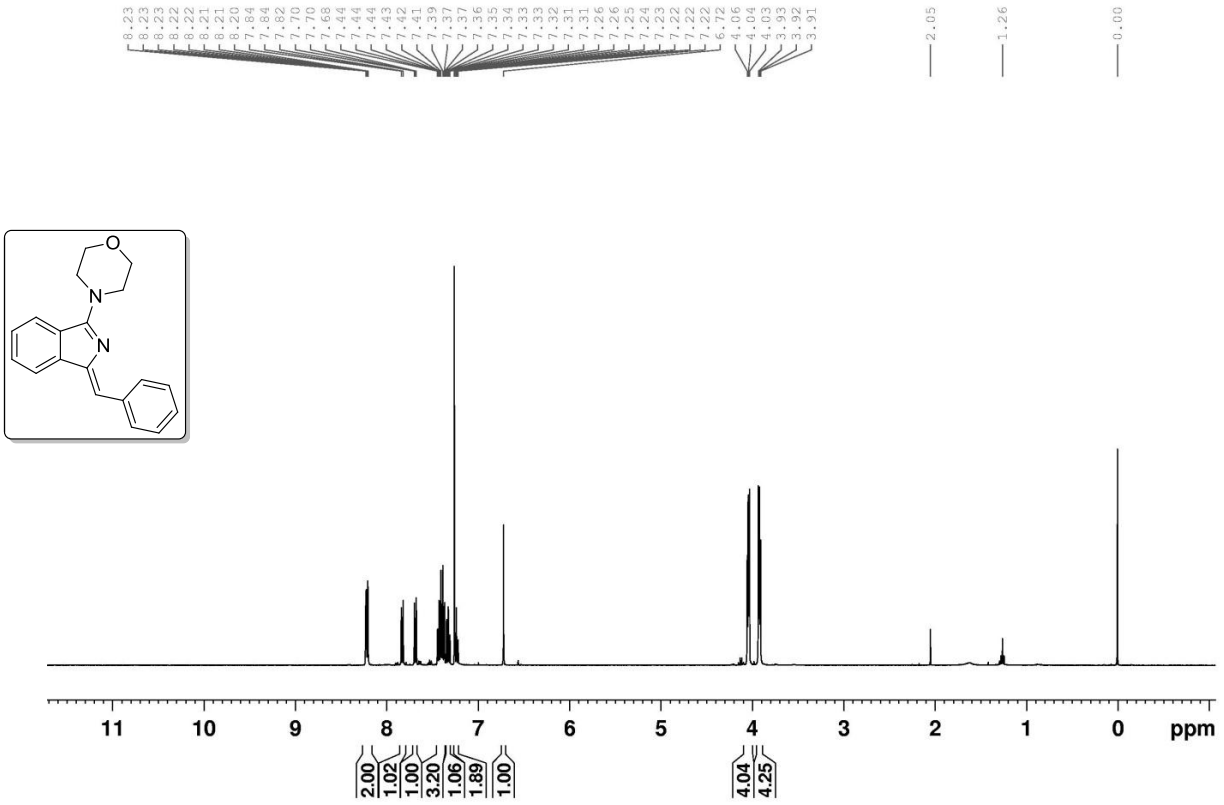
^{1}H NMR spectrum of compound **21q**



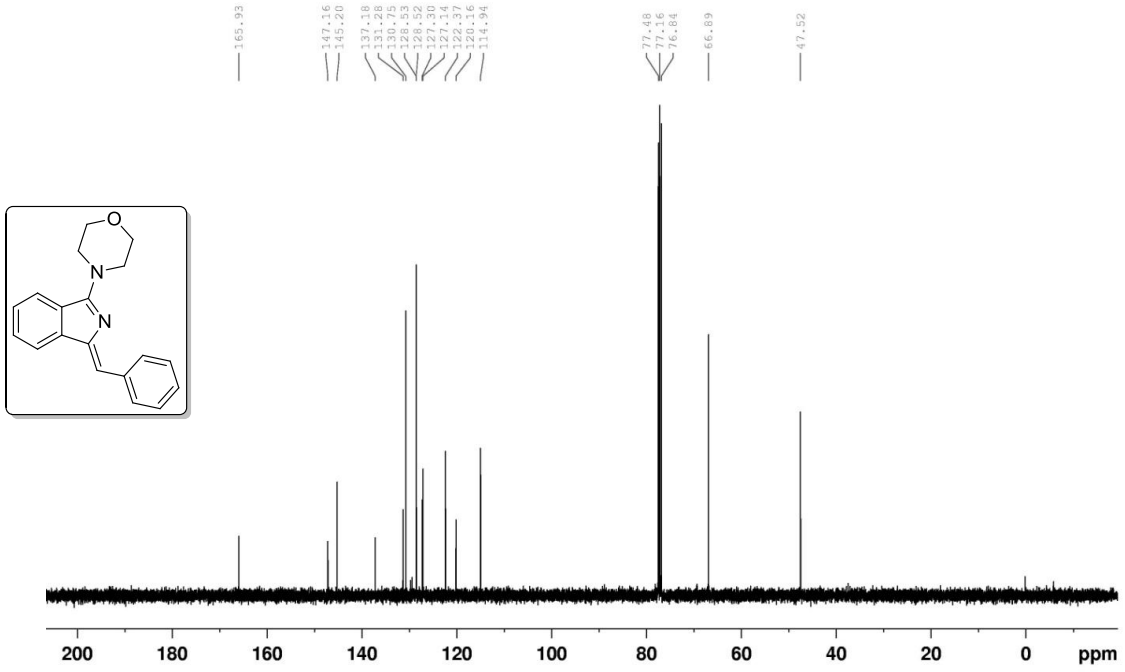
^{13}C NMR spectrum of compound **21q**



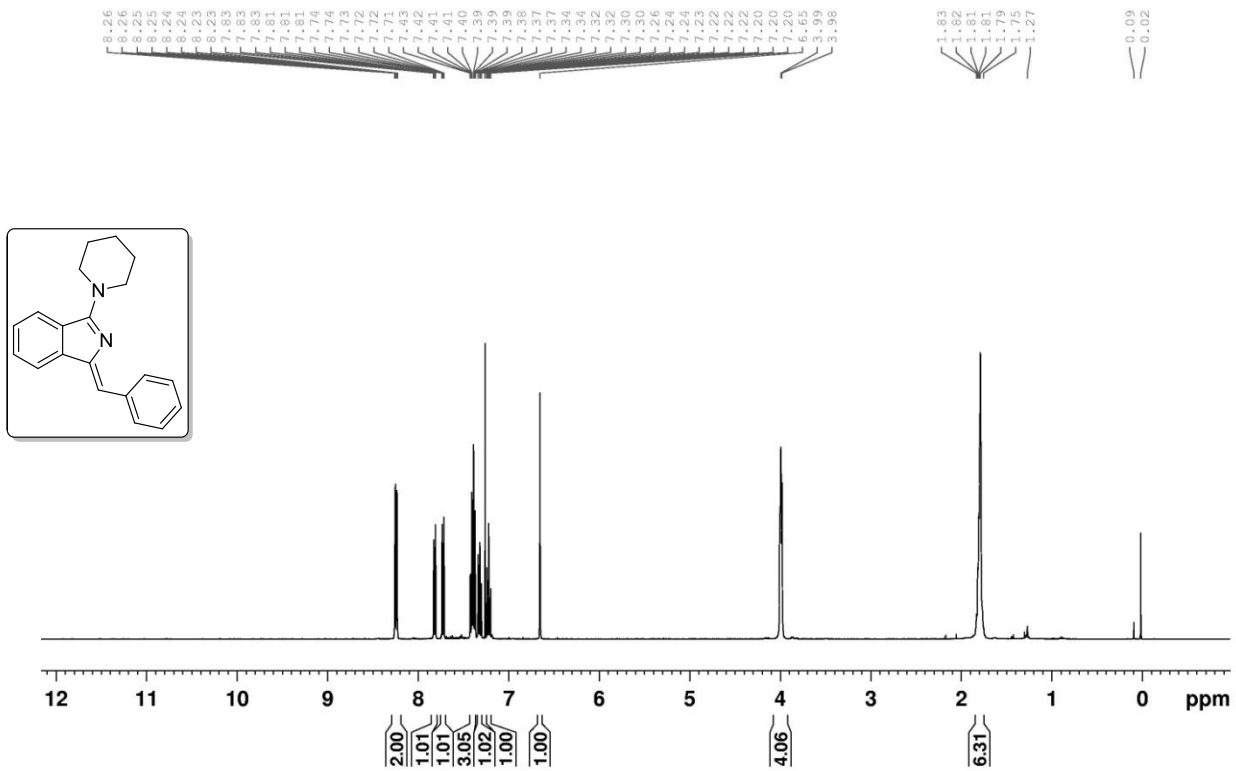
^{1}H NMR spectrum of compound **21r**



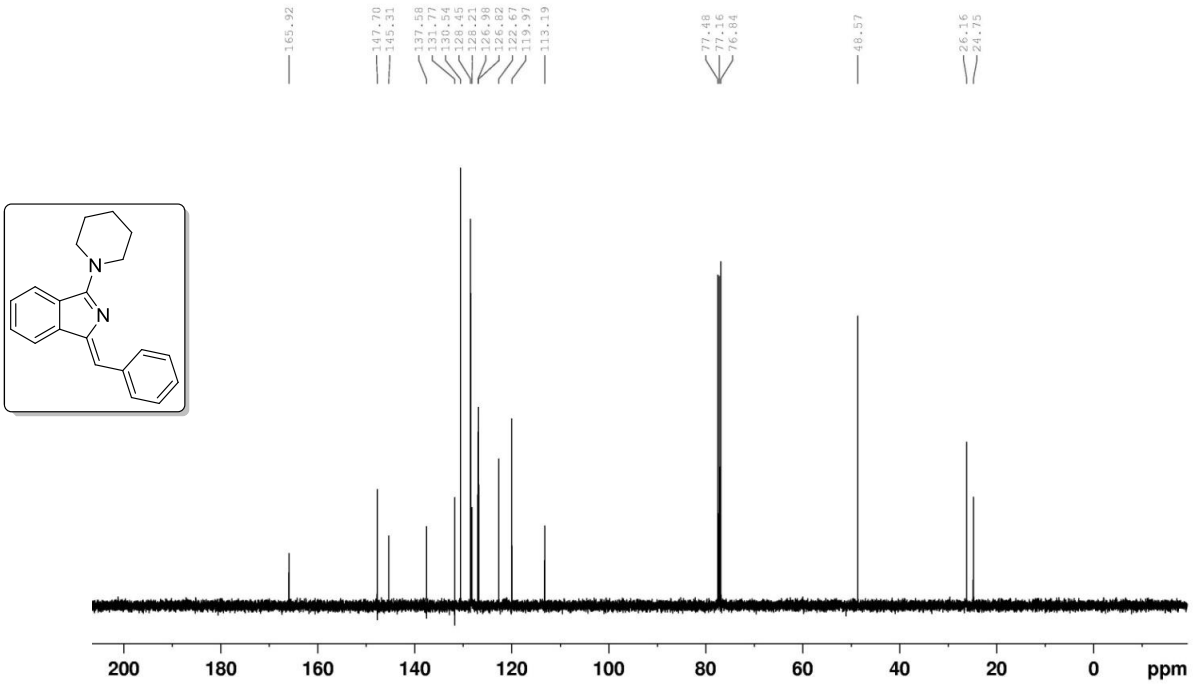
^{13}C NMR spectrum of compound **21r**



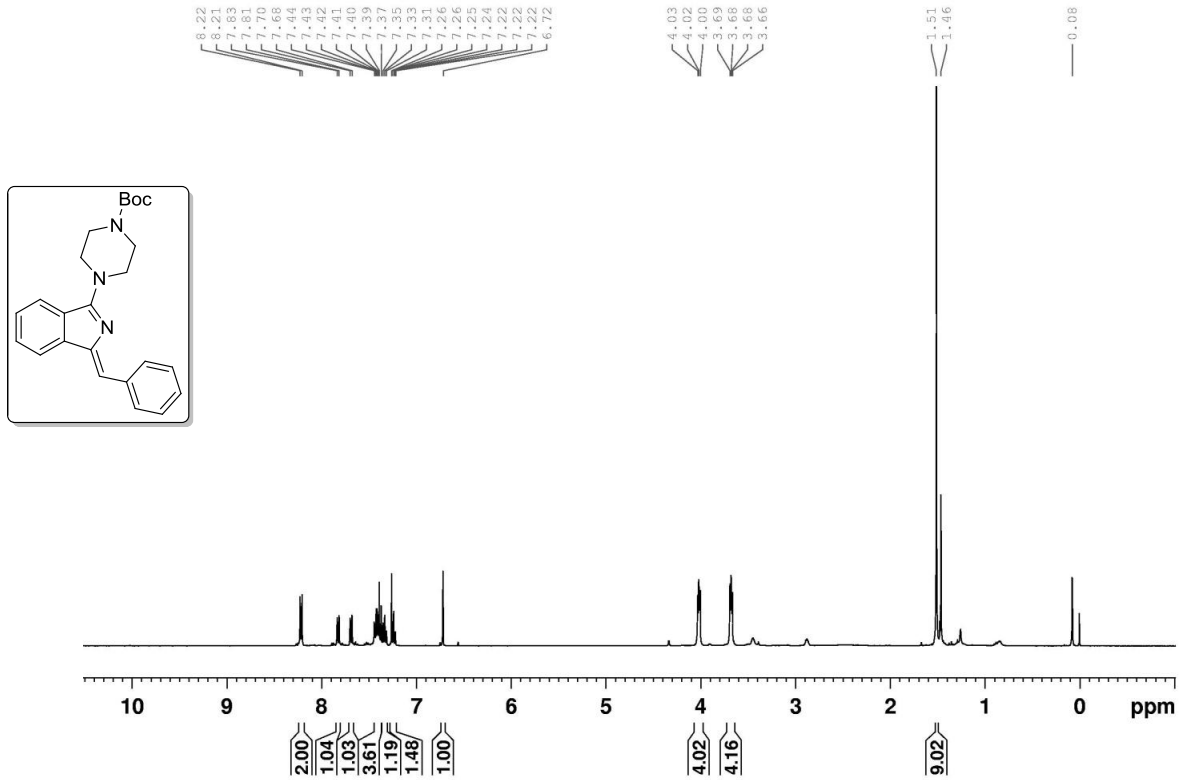
^{1}H NMR spectrum of compound **21s**



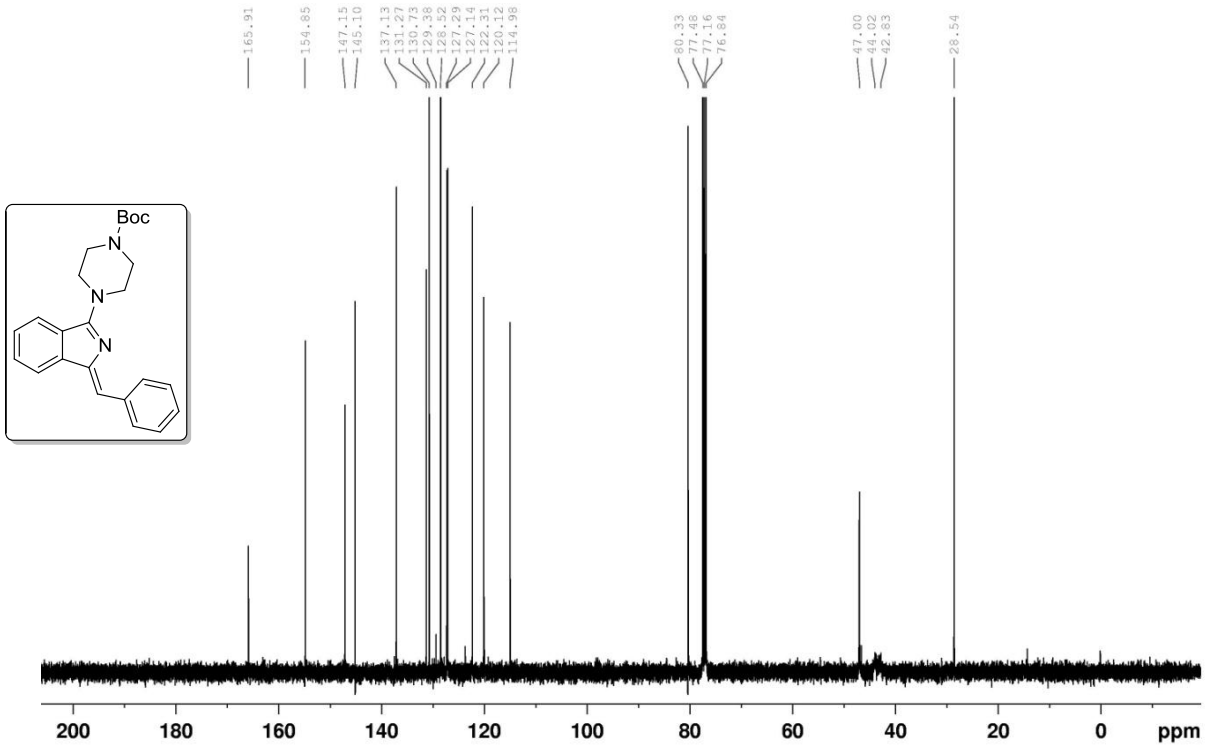
^{13}C NMR spectrum of compound **21s**



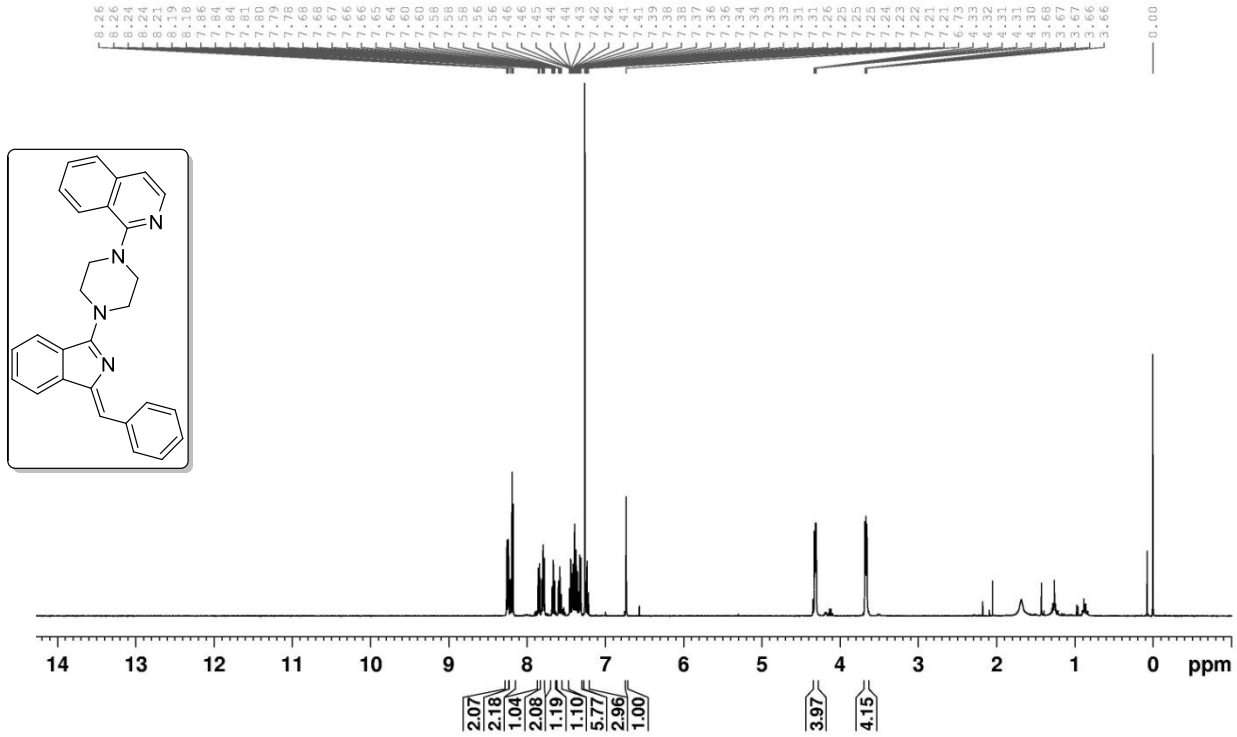
^{1}H NMR spectrum of compound **21t**



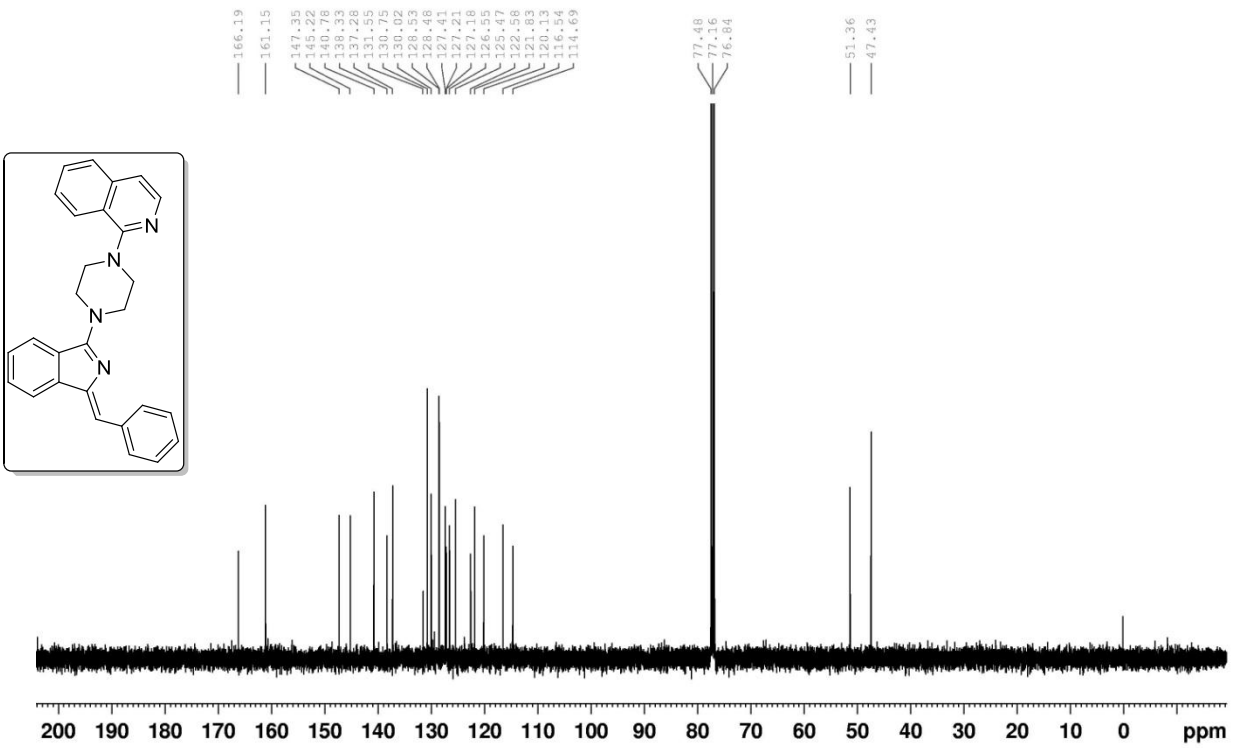
^{13}C NMR spectrum of compound **21t**



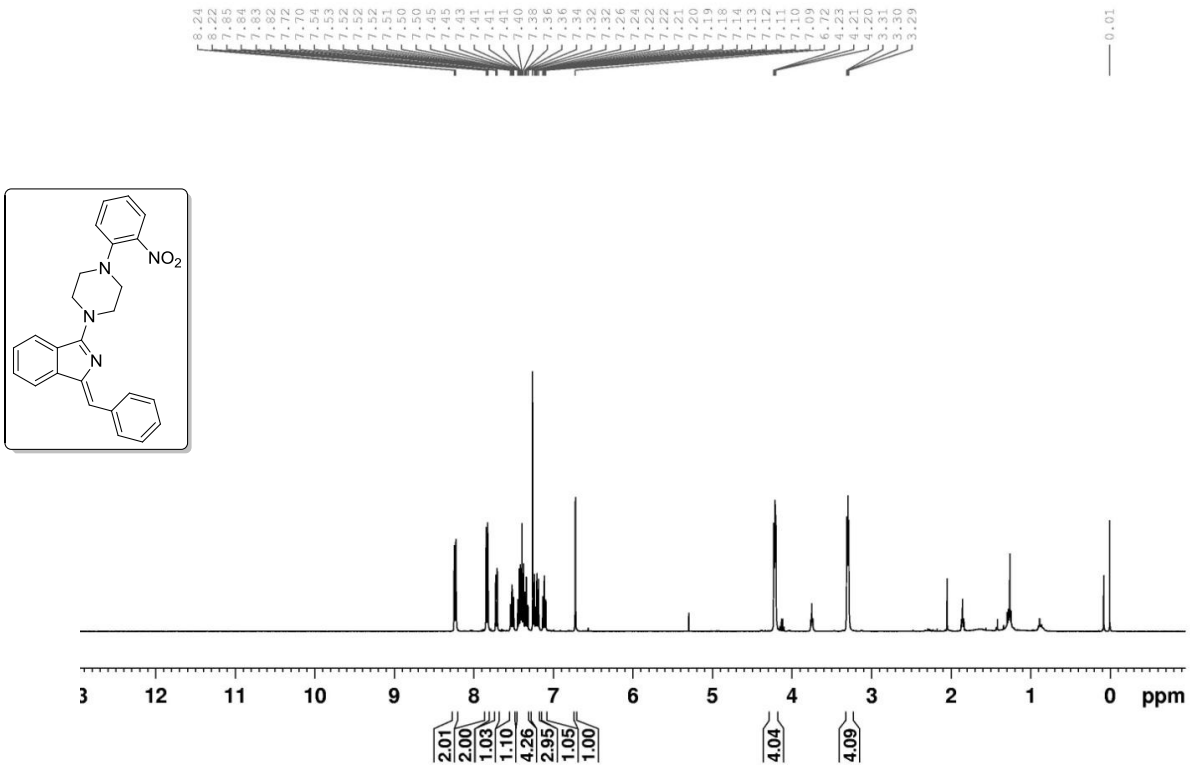
^{1}H NMR spectrum of compound **21u**



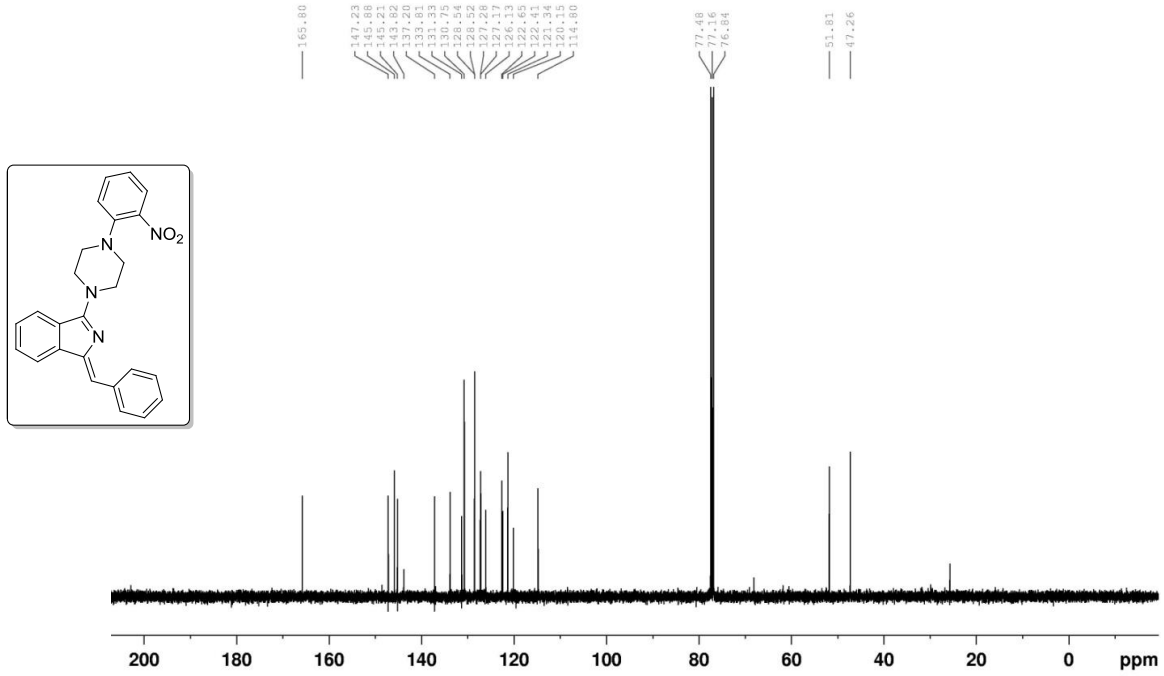
^{13}C NMR spectrum of compound **21u**



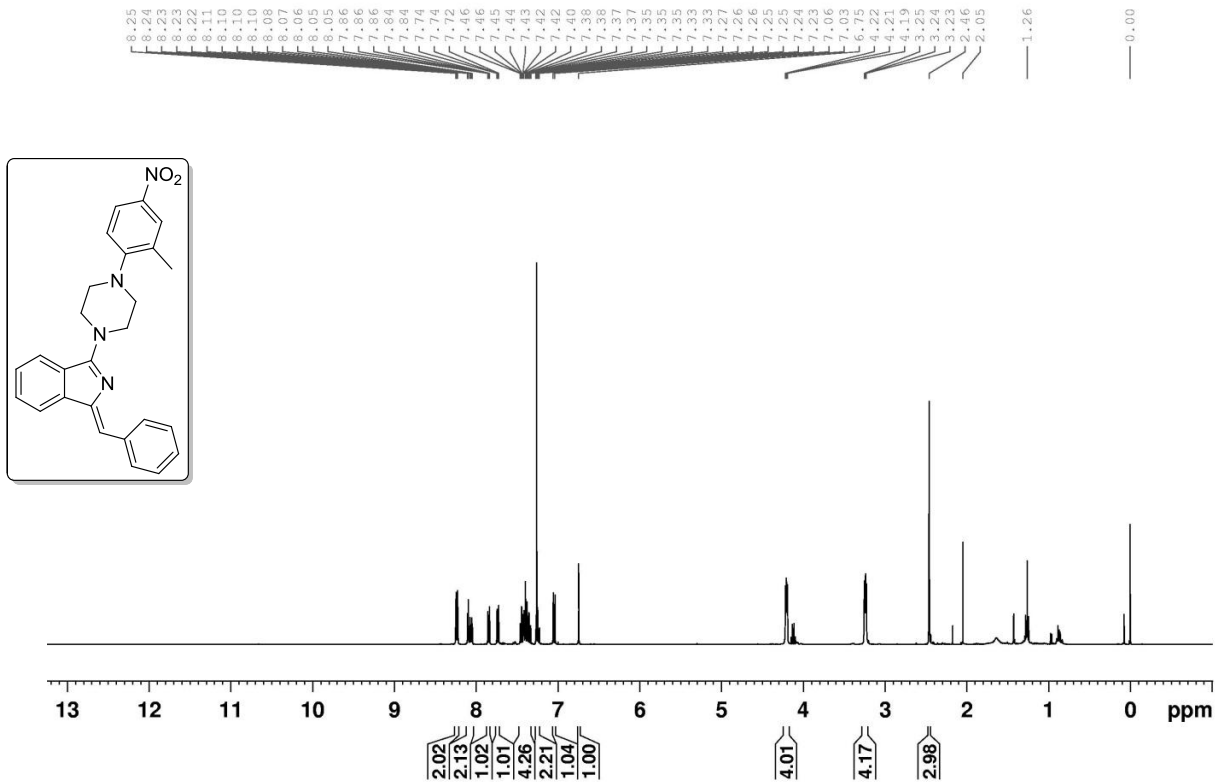
^{1}H NMR spectrum of compound **21v**



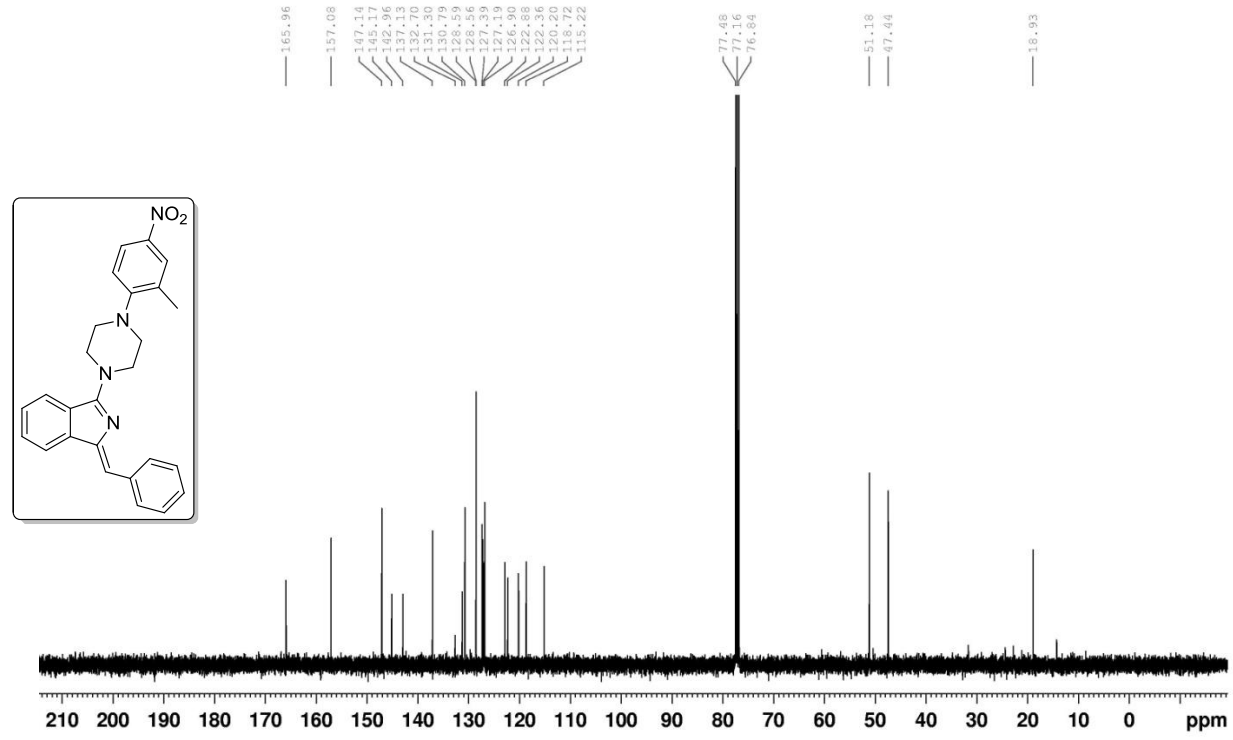
^{13}C NMR spectrum of compound **21v**



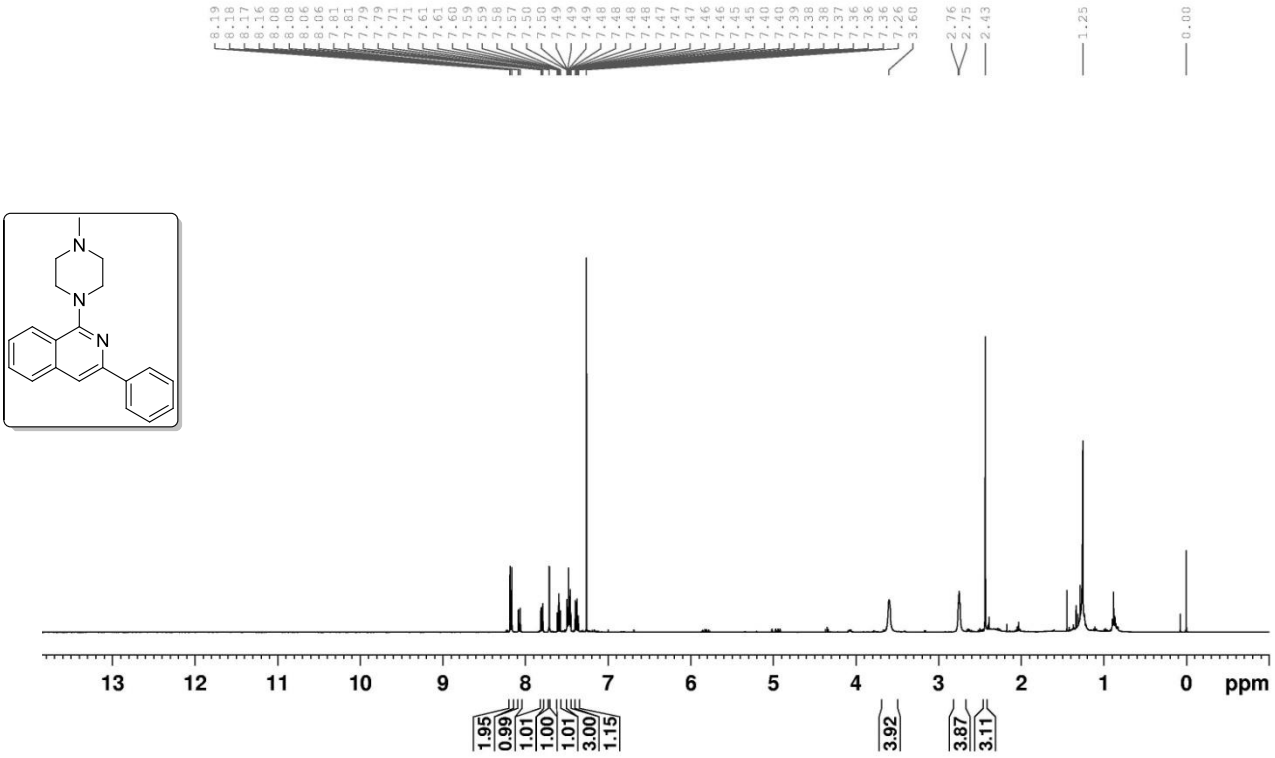
^{1}H NMR spectrum of compound **21w**



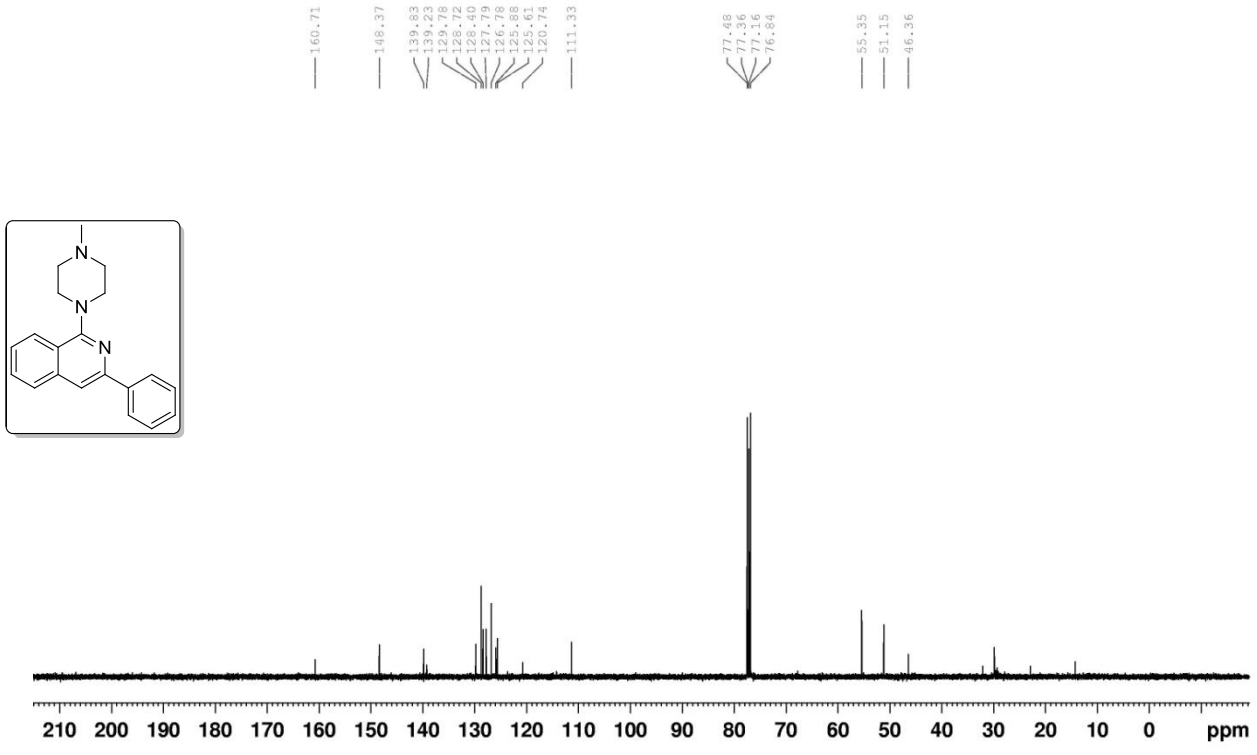
^{13}C NMR spectrum of compound **21w**



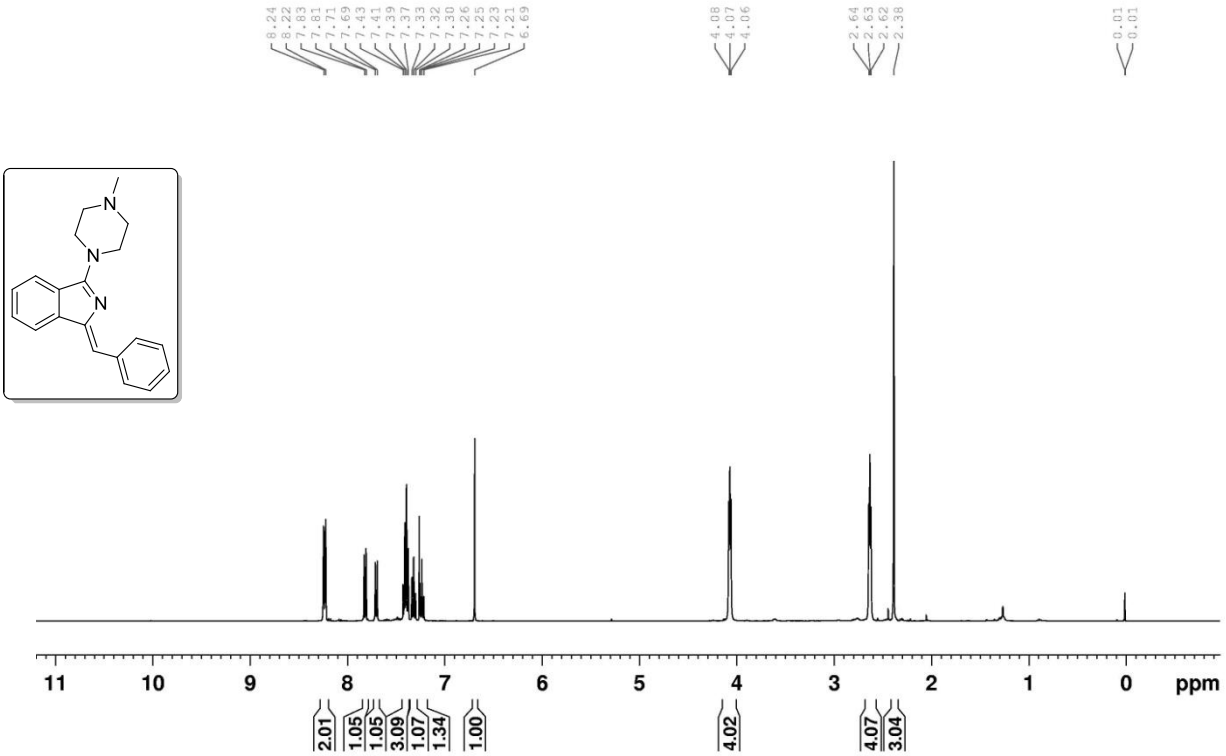
^{1}H NMR spectrum of compound **1c**



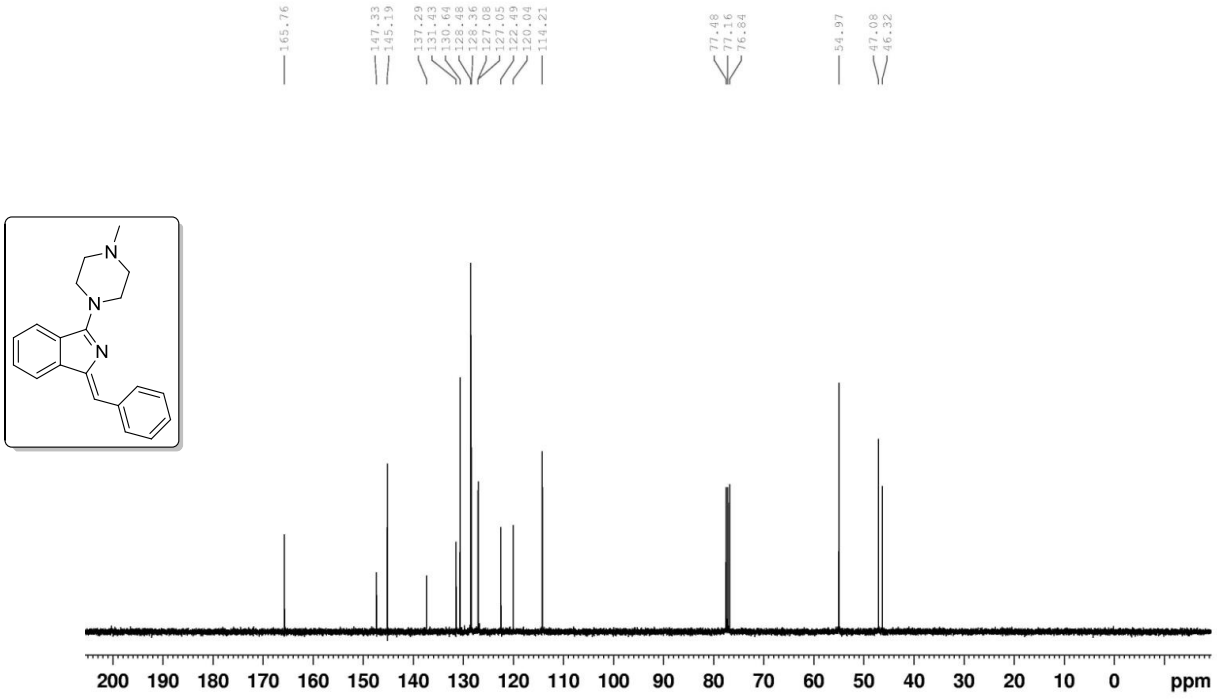
^{13}C NMR spectrum of compound **1c**



^{1}H NMR spectrum of compound **1c'**



^{13}C NMR spectrum of compound **1c'**



3.8) References

1) (a) Allen, M. P.; Chappie, T. A.; Humphery, J. M.; Liras, S. U. S. Pat. Appl. 2005/0182079, **2005**; (b) Subasinghe, N. L.; Lanter, J.; Markotan, T.; Opas, E.; McKenney, S.; Crysler, C.; Hou, C.; O'Neill, J.; Johnson, D.; Sui, Z. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 1063; (c) Bolton, S. A.; Sutton, J. C.; Anumula, R.; Bisacchi, G. S.; Jacobson, B.; Slusarchyk, W. A.; Treuner, U. D.; Wu, S. C.; Zhao, G.; Pi, Z.; Sheriff, S.; Smirk, R. A.; Bisaha, S.; Cheney, D. L.; Wei, A.; Schumacher, W. A.; Hartl, K. S.; Liu, E.; Zahler, R.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5239.

2) (a) Cho, W.-J.; Kim, E.-K.; Il Park, Y.; Jeong, E. Y.; Kim, T. S.; Le, T. N.; Kim, D.-D.; Lee, E.-S. *Bioorg. Med. Chem*. **2002**, *10*, 2953; (b) Cho, W.-J.; Min, S. Y.; Le, T. N.; Kim, T. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4451; (c) Yang, S. H.; My Van, H. T.; Le, T. N.; Khadka, D. B.; Cho, S. H.; Lee, K.-T.; Chung, H.-J.; Lee, S. K.; Ahn, C.-H.; Lee, Y. B.; Cho, W. J. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5277; (d) Yang, S. H.; My Van, H. T.; Le, T. N.; Khadka, D. B.; Cho, S. H.; Lee, K.-T.; Chung, H.-J.; Lee, S. K.; Ahn, C.-H.; Lee, Y. B.; Cho, W.-J. *Eur. J. Med. Chem*. **2010**, *45*, 5493; (e) Pierre, F.; Chua, P. C.; O'Brien, S. E.; Siddiqui-Jain, A.; Bourbon, P.; Haddach, M.; Michaux, J.; Nagasawa, J.; Schwaebe, M. K.; Stefan, E.; Vialettes, A.; Whitten, J. P.; Chen, T. K.; Darjania, L.; Stansfield, R.; Anderes, K.; Bliesath, J.; Drygin, D.; Ho, C.; Omori, M.; Proffitt, C.; Streiner, N.; Trent, K.; Rice, W. G.; Ryckman, D. M. *J. Med. Chem.* **2011**, *54*, 635. (f) My Van, H. T.; Woo, H.; Jeong, H. M.; Khadka, D. B.; Yang, S. H.; Zhao, C.; Jin, Y.; Lee, E.-S.; Lee, K. Y.; Kwon, Y.; Cho, W.-J. *Eur. J. Med. Chem*. **2014**, *82*, 181.

3) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Van der Goot, H.; Menge, W. M. P. B.; von Drabbe Künzel, J. F.; de Groote, M.; IJzerman, A. P. *J. Med. Chem.* **2000**, *43*, 2227.

4) Govek, S. P.; Oshiro, G.; Anzola, J. V.; Beauregard, C.; Chen, J.; Coyle, A. R.; Gamache, D. A.; Hellberg, M. R.; Hsien, J. N.; Lerch, J. M.; Liao, J. C.; Malecha, J. W.; Staszewski, L. M.; Thomas, D. J.; Yanni, J. M.; Noble, S. A.; Shiau, A. K. *Bioorg. Med. Chem. Lett*. **2010,** *20*, 2928.

5) Smith, A. L.; DeMorin, F. F.; Paras, N. A.; Huang, Q.; Petkus, J. K.; Doherty, E. M.; Nixey, T.; Kim, J. L.; Whittington, D. A.; Epstein, L. F.; Lee, M. R.; Rose II, M. J.; Babij, C.; Fernando, M.; Hess, K.; Le, Q.; Beltran, P.; Carnahan, J. *J. Med. Chem.* **2009**, *52*, 6189.

6) Nagesh, H. N.; Naidu, K. M.; Rao, D. H.; Sridevi, J. P.; Sriram, D.; Yogeeswari, P.; Chandra Sekhar, K. V. G. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6805.

7) Ghosh, B.; Antonio, T.; Zhen, J.; Kharkar, P.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2010**, *53*, 1023.

8) (a) Marcel, A. H.; Zwart, D.; Van der Goot, H.; Timmerman, H. *J. Med. Chem*. **1989**, *32*, 487; (b) Katritzky, A. R.; Qiu, G.; Long, Q.-H.; He, H.-Y.; Steel, P. J. *J. Org. Chem.* **2000**, *65*, 9201; (c) Bibas, H.; Moloney, D. W. J.; Neumann, R.; Shtaiwi, M.; Bernhardt, P. V.; Wentrup, C. *J. Org. Chem*. **2002**, *67*, 2619; (d) Manivel, P.; Prabakaran, K.; Banerjee, U.; Nawaz Khan, F.-R.; Jeong, E. D.; Chung, E. H. *RSC Adv*. **2015**, *5*, 3781.

9) Zeldis, J. B.; Rohane, P. E. W.; Schafer, P. H. U. S. Pat. Appl. 2007/0155791, **2007**.

10) (a) Chay, R. S.; Luzyanin, K. V.; Kukushkin, V. Y.; Fatima C. M.; da Silva, G.; Pombeiro, A. J. L. *Organometallic*s **2012**, *31*, 2379; (b) Diaz-Moscoso, A.; Tizzard, G. J.; Coles, S. J.; Cammidge, A. N. *Angew. Chem. Int. Ed*. **2013**, *52*, 10784; (c) Remiro-Buenamanana, S.; Diaz-Moscoso, A.; Hughes, D. L.; Bochmann, M.; Tizzard, G. J.; Coles, S. J.; Cammidge, A. N. *Angew. Chem. Int. Ed*. **2015**, *54*, 7510.

11) (a) Diaz-Moscoso, A.; Emond, E.; Hughes, D. L.; Tizzard, G. J.; Coles, S. J.; Cammidge, A. N. *J. Org. Chem*. **2014**, *79*, 8932; (b) Liu, H.; Lu, H.; Xu, J.; Liu, Z.; Li, Z.; Mack, J.; Shen, Z. *Chem. Commun*. **2014**, *50*, 1074.

12) Csonka, R.; Speier, G.; Kaizer, J. *RSC Adv*. **2015**, *5*, 18401.

13) (a) Lagu, B.; Tian, D.; Nagarathnam, D.; Marzabadi, M. R.; Wong, W. C.; Miao, S. W.; Zhang, F.; Sun, W.; Chiu, G.; Fang, J.; Forray, C.; Chang, R. S. L.; Ransom, R. W.; Chen, T. B.; O'Malley, S.; Zhang, K.; Vyas, K. P.; Gluchowski, C. *J. Med. Chem.* **1999**, *42*, 4794; (b) Fish, P. V.; Barber, C. G.; Brown, D. G.; Butt, R.; Collis, M. G.; Dickinson, R. P.; Henry, B. T.; Horne, V. A.; Huggins, J. P.; King, E.; O'Gara, M.; McCleverty, D.; McIntosh, F.; Phillips, C.; Webster, R. *J. Med. Chem.* **2007**, *50*, 2341; (c) Frohn, M.; Burli, R. W.; Riahi, B.; Hungate, R. W. *Tetrahedron Lett*. **2007**, *48*, 487; (d) Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457; (e) Miller-Moslin, K.; Peukert, S.; Jain, R. K.; McEwan, M. A.; Karki, R.; Llamas, L.; Yusuff, N.; He, F.; Li, Y.; Sun, Y.; Dai, M.; Perez, L.; Michael, W.; Sheng, T.; Lei, H.; Zhang, R.; Williams, J.; Bourret, A.; Ramamurthy, A.; Yuan, J.; Guo, R.; Matsumoto, M.; Vattay, A.; Maniara, W.; Amaral, A.; Dorsch, M.; Kelleher III, J. F. *J. Med. Chem.* **2009**, *52*, 3954; (f) Asagarasu, A.; Matsui, T.; Hayashi, H.; Tamaoki, S.; Yamauchi, Y.; Sato, M. *Chem. Pharm. Bull.* **2009**, *57*, 34; (g) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett*. **2010**, *12*, 5254; (h) Rouchet, J.-B. E. Y.; Schneider, C.; Fruit, C.; Hoarau, C. *J. Org. Chem*. **2015**, *80*, 5919.

14) (a) Rewinkel, J. B. M.; Lucas, H.; van Galen, P. J. M.; Noach, A. B. J.; van Dinther, T. G.; Rood, A. M. M.; Jenneboer, A. J. S. M.; van Boeckel, C. A. A. *Bioorg. Med. Chem*. **1999**, *9*, 685; (b) Song, Y.; Clizbe, L.; Bhakta, C.; Teng, W.; Li, W.; Wong, P.; Huang, B.; Sinha, U.; Park, G.; Reed, A.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2043; (c) Saari, R.; Torma, J.-C.; Nevalainen, T. *Bioog. Med. Chem*. **2011**, *19*, 939; (d) Gutteridge, C. E.; Hoffman, M. M.; Bhattacharjee, A. K.; Milhous, W. K.; Gerena, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 786; (e) Ray, P.; Wright, J.; Adam, J.; Bennett, J.; Boucharens, S.; Black, D.; Cook, A.; Brown, A. R.; Epemolu, O.; Fletcher, D.; Haunso, A.; Huggett, M.; Jones, P.; Laats, S.; Lyons, A.; Mestres, J.; de Man, J.; Morphy, R.; Rankovic, Z.; Sherborne, B.; Sherry, L.; van Straten, N.; Westwood, P.; Zaman, G. Z. R. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 97.

15) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805; (b) Hartwig, J. F. *Angew. Chem. Int. Ed*. **1998**, *37*, 2046; c) Hartwig, J. F. *Pure Appl. Chem*. **1999**, *71*, 1416; (d) Muci, A. R.; Buchwald, S. L. *Topics in Curr. Chem.* **2002**, *219*, 131.

16) (a) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2005**, *44*, 1371; (b) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett*. **2003**, *5*, 4373; (c) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem*. **2006**, *71*, 6522; (d) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Bottcher, H.; Beller, M. *Chem. Eur. J*. **2004**, *10*, 746.; (e) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 6586; (f) Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. *Chem. Asian. J*. **2007**, *2*, 306; (g) Doherty, S.; Knight, J. G.; McGrady, J. P.; Ferguson, A. M.; Ward, N. A. B.; Harrington, R. W.; Clegg, W. *Adv. Synth. Catal.* **2010**, *352*, 201; (h) Lee, B. K.; Biscoe, M. R.; Buchwald, S. L. *Tetrahedron Lett*. **2009**, *50*, 3672.

17) (a) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem*. **2007**, *72*, 4554; (b) Li, J.; Chen, L.; Chin, E.; Lui, A. S.; Zecic, H. *Tetrahedron Lett.* **2010**, *51*, 6422.

18) Si, C.; Myers, A. G. *Angew. Chem. Int. Ed*. **2011**, *50*, 10409.

19) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. *Org. Lett*. **2014**, *16*, 1840.

20) He, L.; Nie, H.; Qiu, G.; Gao, Y.; Wu, J. *Org. Biomol. Chem*. **2014**, *12*, 9045.

21) (a) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal*. **2009**, *351*, 2702; (b) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem*. **2010**, 6436.

22) (a) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120; (b) Li, W.; Wang, Y.; Lu, T. *Tetrahedron* **2012**, *68*, 6843; (c) Ye, C.; Chen, Z.; Wang, H.; Wu, J. *Tetrahedron* **2012**, *68*, 5197.

23) (a) Zheng, D.; Chen, Z.; Liu, J.; Wu, J. *Org. Biomol. Chem*. **2011**, *9*, 4763; (b) Wang, T.; Li, R.; Yu, D.; Gu, C.; Xiong, F.; Chen, Z. *Synthesis* **2014**, *46*, 3213.

24) (a) Li, Y.; Gao, L.; Zhu, H.; Li, G.; Chen, Z. *Org. Biomol. Chem*. **2014**, *12*, 6982; (b) Song, J.; Fan, C.; Liu, G.; Qiu, G. *Org. Chem. Front.* **2014**, *1*, 1045.

25) (a) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett*. **2011**, *13*, 4636; (b) Li, J.; John, M.; Ackermann, L. *Chem. Eur. J.* **2014**, *20*, 5403.

26) Jayakumar, J.; Parthasarathy, K.; Chen, Y.-H.; Lee, T.-H.; Chuang, S.-C.; Cheng, C.-H. *Angew. Chem. Int. Ed*. **2014**, *53*, 9889.

27) Long, Y.; She, Z.; Liu, X.; Chen. Y. *J. Org. Chem*. **2013**, *78*, 2579.

28) (a) Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett*. **2000**, *41*, 1215.; (b) Fustero, S.; Diaz, M. D.; Carrio, J. S.; Aguilar, E. *Eur. J. Org. Chem*. **2001**, 1195; (c) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508; (d) Alharbi, N.; Diaz-Moscoso, A.; Tizzard, G. J.; Coles, S. J.; Cook, M. J.; Cammidge, A. N. *Tetrahedron* **2014**, *70*, 7370.

29) Shen, H.; Xie, Z. *J. Am. Chem. Soc*. **2010**, *132*, 11473.

30) For reviews on solvent free reactions: (a) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480; (b)Tanaka, K.; Toda, F. *Chem. Rev*. **2000**, *100*, 1025; (c) Sheldon, R. A. *Green Chem*. **2005**, *7*, 267; (d) Singh, M. S.; Chowdhury, S. *RSC Adv*. **2012**, *2*, 4547; (e) Poudel, T. N.; Lee, Y. R.; Kim, S. H. *Green Chem*. **2015**, *17*, 4579.

31) Anastas, P. T.; Warner, J. C. 1998; *Green Chemistry: theory and practice*. Oxford [England]; New York: Oxford University Press. ISBN9780198502340.

32) (a) Sakthivel, K.; Srinivasan, K. *J. Org. Chem*. **2014**, *79*, 3244; (b) He, Y.; Zhang, X.; Fan, X. *Chem. Commun*. **2014**, *50*, 5641.

33) (a) Reddy, V.; Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem*. **2015**, *13*, 3732; (b) Reddy, V.; Anand, R. V. *Org. Lett.* **2015**, *17*, 3390.

34) CCDC No:1415396.

35) CCDC No: 1420374.

Conferences/Symposia:

- Participated in the *National Seminar on Biocatalysis and Biomimetic Catalysis in Organic Synthesis* organized by Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University (Dr. B.A.M.U), Aurangabad, Maharashtra, India (20-21st March 2009).
- Participated in the *6th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, Hyderabad Central University (HCU), Hyderabad, India, (28-31st January, 2011).
- Participated in the *7th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (15-18th December, 2011).
- Participated in the *National Seminar on Crystallography 43A* held at Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30th March 2014).
- Poster presented entitled "A room-temperature protocol to access isoquinolines through Ag(I) catalyzed annulation of o-(1-alkynyl) arylaldehydes and ketones with NH_4OAc: Elaboration to Berberine and Palmatine." Reddy, V.; Jadhav, A. S.; Anand, R. V. in the *10th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, Indian Institute of Technology (IIT) Madras, India (4-6th December 2014).

List of publications:

1) **Reddy, V**.; Anand, R. V. *Org. Lett*. **2015**, *17*, 3390.

2) **Reddy, V**.; Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem*. **2015**, *13*, 3732.

3) **Reddy, V**.; Jadhav, A. S.; Anand, R. V. *Eur. J. Org. Chem.* **2016**, 453.

4) Shirke, R. P.; Reddy, V.; Anand, R. V.; Ramasastry, S. S. V. *Synthesis* **2016**, *48*, 1865.

5) Arde, P.; **Reddy, V**.; Anand, R. V. *RSC Adv*. **2014**, *4*, 49775.

6) Ramanjaneyulu, B. T.; Pareek, M.; **Reddy, V**.; Anand, R. V. *Helv. Chimica. Acta*. **2014**, *97*, 431.

7) Anjaneyulu, B. T.; **Reddy, V**.; Arde, P.; Mahesh, S.; Anand, R. V. *Chem. Asian J*. **2013**, *8*, 1489.

8) Arde, P.; Ramanjaneyulu, B. T.; **Reddy, V**.; Saxena, A.; Anand R. V. *Org. Biomol. Chem*. **2012**, *10*, 848.