Synthesis of Heterocycles of Biological Interests via Metal Catalyzed Cyclizations of Acetylenic Compounds

Thesis Submitted to Jadavpur University

For the Degree of

Doctor of Philosophy (Science)

By

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2022

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled "**Synthesis of Heterocycles of Biological Interests via Metal Catalyzed Cyclizations of Acetylenic Compounds**" Submitted by Smt. **Sukanya De** who got her name registered on **07.08.2019 (Index No: 5/19/Chem./26)** for the award of Ph. D. (Science) Degree of Jadavpur University, is absolutely based upon her own work under the supervision of **Dr. Chinmay Chowdhury** and that neither this thesis nor any part of it has been submitted for either any degree / diploma or any other academic award anywhere before.

Chinmay Chowdhury
8/12/2022

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(Signature of the Supervisor date with official seal)

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Declaration

I, **Sukanya De**, declare that the research work embodied in this thesis is my own work, which has been carried out at CSIR-Indian Institute of Chemical Biology, Kolkata under the supervision of **Dr. Chinmay Chowdhury**, Chief Scientist, Organic & Medicinal Chemistry Division, Indian Institute of Chemical Biology, Kolkata. The whole work is completely original and has not been submitted in part or full, for any degree or diploma to this or any other university.

……..

Date: (Sukanya De)

***D**edicated to*

My Parents,

My Sister & Sister-in-law,

My Niece Sharanya

and

My beloved

Acknowledgments

"No one who achieves success does so without acknowledging the help of others. The wise and confident acknowledge this help with gratitude."

……. Alfred North Whitehead

This thesis is the outcome of a long journey of my Ph.D. life filled with lots of ups and downs, where I have been encouraged and supported by many people. It is a pleasant moment to express my gratitude to all those people who made this journey an unforgettable experience for me.

I would like to express my profound gratitude to my guide and mentor **Dr. Chinmay Chowdhury**, Chief Scientist, Organic & Medicinal Chemistry Division, Indian Institute of Chemical Biology (I.I.C.B.), whose innovative thinking, high perception of knowledge, practical insight and experience in the subject has resulted in the success of the entire endeavor. I hold him in high esteem for his constant guidance, encouragement and concern throughout the period of my research work.

I am extremely grateful to **Dr. Arun Bandyopadhyay**, Director, Indian Institute of Chemical Biology for providing me with laboratory facilities and to the CSIR, Government of India, for providing a fellowship to me during the course of the study. I am also grateful to **Dr. P. Jaishankar**, Head of the Department, Organic & Medicinal Chemistry Division.

I would like to express my deepest appreciation to **Dr. Basudeb Achari,** former scientist, for his precious suggestions, advices and kind help. His profound knowledge and interest in chemistry has enriched me over the years and helped me get out of many difficulties.

I'm extremely grateful to **Dr. Ramalingam Natarajan** for his precious suggestions and guidance to make me learn the concepts of crystallography.

I would like to thank the members of the Instrumental Division of I.I.C.B., Tapas Da, Khan Da, E. Padmanaban, Sandip Da (Kundu), Goutam Da, Sandip Da (Chowdhury), Diptendu Da, Soumik Da for recording spectral and analytical data in addition to Sandip Da's (Kundu) invaluable suggestions for solving crystal data.

I thank all my Lab mates Gargi Di, Moumita Di, Amrita Di, Subhendu Da, Debasmita, Rumjhum, Sarat, Arghyadip for providing me kind suggestions and spontaneous cooperation in all the time of crisis. I wish all of them every success in their days ahead.

The sweet tempered relationship with Subhadeep Da, Ritesh Da, Dipendu Da, Bhim, Mayank, Laxmi, Saswati, Bhaswati, Sandipan and my room-mates cum sisters Ghanti (Mousumi), Soyera and many more from IICB and outside have made the period of my research memorable. It was the sheer joy of learning and sharing of knowledge among us, which held us together, and the fun and frolic we enjoyed together made my stay in this institute a joyous voyage.

Whatever I am today or whatever I will be tomorrow, these are all because of my living gods, my parents **Golak Behari De** and **Sabita De**. I am nothing without them. Thank you for your silent blessings and encouragement enabling me to reach my goal. Without you I would have been lost in the dark with no perspective of life. The greatest possible gift god has given me is my parents. Thank you for believing in me and to taught me to never compromise for anything. Thank you to make me strong. Words can't express my love and gratitude towards you. My whole life is dedicated to you **Maa** and **Babai**.

I am fortunate to have my elder sister **Shramana De** and sister-in-law **Surajit Ghosh** to be in my life. I express my heartfelt gratitude to them for their constant guidance and encouragement. Thank you Didivai to be there for me in every step of my life. Thank you to be so lovable to me.

I would like to express my deepest appreciation to all of my Family members for their constant encouragement and blessing.

I am extremely fortunate to have my little angel, my niece, **Sharanya Ghosh** in my life, who never let me feel the age gap between us and being so close to me. I wish her all the luck and success for her future.

This endeavor would not have been possible without the constant support and encouragement of my best friend, my beloved **Sudipta Ghosh**. Thank you to be with me, to giving me endless support and indeed to tolerate me and supporting me in every circumstances

of life and to accept me for what I am. I am really blessed to have you in my life. Your matured opinion to survive in my Ph.D. life made all the woks possible.

Above all, I would like to thank from the deepest core of my heart to **Almighty**, who have created me. Thank you for bestowing your constant blessings on me, for giving me strength to fight against every adversity and for all your unconditional and endless love, mercy and grace.

.....

Date: Sukanya De

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Abbreviations

^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	13 Nuclear magnetic resonance spectroscopy
Ar	Aryl
AcOH	Acetic acid
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
CuI	Copper iodide (I)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
EIMS	Electron impact mass spectroscopy
ESI-MS	Electron spray ionization mass spectroscopy
Et_3N	Triethylamine
$FeCl_3$	Iron(III) chloride
$Fe(OTf)_3$	Iron(III) trifluoromethanesulfonate
HRMS	High resolution mass spectroscopy
MeCN	Acetonitrile
MsCl	Mesyl chloride
$NaBH_4$	Sodium borohydride
NaN_3	Sodium azide
Ns	4-Nitro-benzenesulfonyl (nosyl) group
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II)dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	Palladium acetate
$PdCl_2$	Palladium chloride
PPh_3	Triphenylphosphine
rt	Room temparature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofurane
TLC	Thin layer chromatography
Ts	*p*-Toluenesulfonyl (tosyl) group
D-CSA	*D*-Camphor sulphonic acid

General remarks

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60-80 °C. DCM was dried over CaH_2, distilled, and stored over 3Å molecular sieves in sealed container. THF was distilled over sodium and benzophenone. All the reactions were carried out under argon or nitrogen atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Silica gel 60 F_{254} aluminium TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance or iodine exposure. For purification, column chromatography was performed using 100-200 or 230- 400 mesh silica gel. All the reagents including $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ were purchased from Aldrich, Merck, SRL, TCI etc. $Fe(OTf)_3$ and dry DCE (1,2-Dichloroethane) were purchased from Sigma-Aldrich. ^1H and ^{13}C NMR spectra were recorded using a Bruker 300, 400 or 600 MHz NMR using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) were given from TMS (δ=0.00) in parts per million (ppm) with the residual protons of deuterated solvent used [$CDCl_3$: ^1H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm (t)]. Coupling constants (*J*) were expressed in hertz (Hz) and spin multiplicities were given as s (singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), tt (triple triplet), q (quartet), qui (quintet), six (sextet), m (multiplet) and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were recorded in ESITOF or JEOL JMS600 or GCMS-SHIMADZU-QP5050A DI-EI mass spectrometer. Crystallographic data were obtained using Brüker Kuppa Apex 2 instrument or Bruker D8 Venture system.

Preface

The research work embodied in this thesis describes efficient and elegant protocols for the synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols, 9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15H)-one and benzo[*g*]indoles via Pd-catalyzed heteroannulation reactions and also describes Fe-catalyzed synthesis of Spiro-indenyl 1,4-Benzoxazines, 2-(2,2-Diarylvinyl)quinoxalines, 4-(2,2-Diarylvinyl)quinolines and 4-(2,2-Diarylvinyl)-2*H*-chromenes under one-pot. The work has been presented in four chapters.

Chapter-1 describes an one-pot efficient approach for the synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols and 9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15H)-ones through palladium-catalyzed intramolecular cascade reaction and provides easy access to 1,3,5,7-Cyclooctatetraenes (COTs).

Chapter-2 describes a direct and straightforward method for the general synthesis of Spiro-indenyl 1,4-Benzoxazines and 2-(2,2-Diarylvinyl)quinoxalines via iron(III)-catalyzed heteroannulations of propargylic alcohols.

Chapter-3 describes facile method for the general synthesis of 4-(2,2-Diarylvinyl)quinolines and 4-(2,2-Diarylvinyl)-2*H*-chromenes via iron(III)-catalyzed carboannulations of acetylenic compounds under one-pot.

Chapter-4 represents an efficient pathway for the construction of Benzo[*g*]indoles through palladium(II)-catalyzed cascade reactions of ene-ynes substrates.

The brief review of the literatures is given in **Part-I** of each chapter, which deals with the importance and synthetic methods of compounds of our interest; whereas **Part-II** of each chapter describes our developed methods for the synthesis of aforesaid compounds. Experimental procedures with characterization data, references and copies of spectra of important compounds are included in **Part-II** of each chapter also.

The research work has been carried out in the Department of Organic & Medicianl Chemistry, CSIR-Indian Institute of Chemical Biology, Kolkata (India), under the guidance of Dr. Chinmay Chowdhury, Chief Scientist of the same Institute.

List of Author's Publications and Presentations

List of Publications

1. Palladium(II)-Catalyzed Cascade Reactions of Ene-Ynes Tethered to Cyano/Aldehyde: Access to Naphtho[1,2-*b*]furans and Benzo[*g*]indoles; Moumita Jash, **Sukanya De**, Subhendu Pramanik, and Chinmay Chowdhury*; ***J. Org. Chem.,* 2019**, *84*, 8959−8975.
2. Palladium(II) catalysed cascade strategy for the synthesis of dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols/-10(15*H*)-ones: easy access to 1,3,5,7-cyclooctatetraenes (COTs); **Sukanya De**, Moumita Jash and Chinmay Chowdhury*; ***Chem. Commun.***, **2020**, *56*, 15659-15662.
3. Substrate Controlled Product Divergence in Iron(III)-Catalyzed Reactions of Propargylic Alcohols: Easy Access to Spiro-indenyl 1,4-Benzoxazines and 2-(2,2 Diarylvinyl)quinoxalines; **Sukanya De** and Chinmay Chowdhury*; ***Manuscript is under communication***.
4. Iron(III)-Catalyzed Carboannulations of Acetylenic Compounds: A Straightforward and General Synthesis of 4-(2,2-Diarylvinyl)quinolines and 4-(2,2-Diarylvinyl)-2*H*-chromenes Under One-pot; **Sukanya De** and Chinmay Chowdhury*; ***Manuscript is under communication.***

List of Presentations

1. Poster presentation at One day Symposium in Chemical Sciences at Indian Association for the Cultivation of Science, Kolkata, India on June 4, 2022 organized by Chemical research Society of India (CRSI), Kolkata Chapter School of Applied and Interdisciplinary Sciences, IACS, Kolkata, entitled: "*Synthesis of Important Heterocycles via Palladium Catalyzed One Pot Tandem Reactions and their Further Implications*" by **Sukanya De**, Chinmay Chowdhury*.
2. Oral presentation at International Conference on Emerging Trends in Synthetic Organic Chemistry–2021 (ICETSOC-2021) held in December 06-07, 2021 organized by the Department of Chemistry, National Institute of Technology Puducherry, Karaikal, entitled "*Palladium(II) Catalysed Convenient Synthesis of 10,15-dihydro-9H-*

dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ols and 9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-ones in One Pot: Easy Access to Tri-fused 1,3,5,7-Cyclooctatetraenes (COTs)" by **Sukanya De**, Chinmay Chowdhury*.

3. Poster presentation at Emerging Trends in Chemical Sciences (January 07, 2020) organized by Department of Chemistry, Jadavpur University, Kolkata 700032, entitled "*Synthesis of Benzo[g]indoles via Palldium(II)-Catalyzed Cascade Reactions"* by **Sukanya De**, Chinmay Chowdhury*.

Reprints of Author's Publications

JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. 2019, 84, 8959–8975 Article pubs.acs.org/joc

Palladium(II)-Catalyzed Cascade Reactions of Ene−Ynes Tethered to Cyano/Aldehyde: Access to Naphtho[1,2-*b*]furans and Benzo[*g*]indoles

Moumita Jash, Sukanya De, Subhendu Pramanik, and Chinmay Chowdhury*

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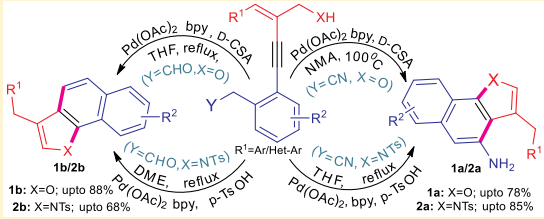
Supporting Information

ABSTRACT: An efficient palladium(II)-catalyzed cascade reaction of ene−yne substrates carrying cyano/aldehyde group is described. It involves successive hetero- and benz-annulations in one pot via *trans*-oxo/aminopalladation onto alkyne, followed by 1,2-addition to cyano/aldehyde, providing a convenient synthesis of both naphtho[1,2-*b*]furans and benzo[*g*]indoles. The reaction constitutes a fast intramolecular assembly through several carbon−carbon and carbon−heteroatom bond formations taking place in one pot. The reactions are operationally simple, compatible with a range of functional groups and atom-economical in nature.



INTRODUCTION

Benzo-fused benzofurans and indoles belong to the group of privileged structures in the area of drug discovery. In particular, naphtho[1,2-*b*]furans[1a−c] (**1**, Figure 1) and benzo[*g*]indoles[1d−f] (**2**, Figure 1) are structural components of a large number of biologically active natural and synthetic compounds.

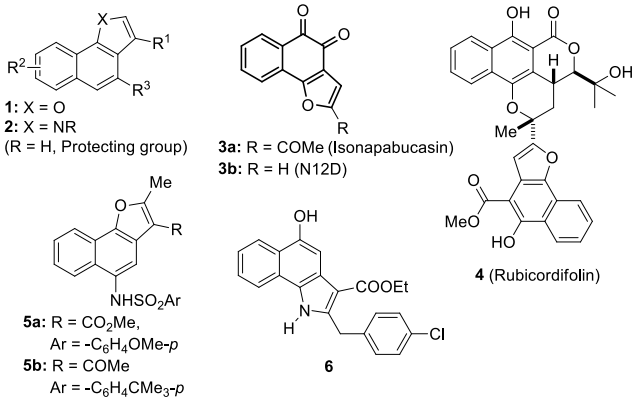


Figure 1. Few biologically active naphtho[1,2-*b*]furans and benzo[*g*]-indoles.

Notable among the former class are isonapabucasin **3a**[2] (Figure 1), which strongly inhibited the growth of human breast cancer cells and naphtho[1,2-*b*]furan-4,5-dione or N12D (**3b**, Figure 1) isolated from mangrove plants, which exhibited significant biological activity against hepatoma, squamous cell carcinoma, breast cancer,[3] and methicillin-resistant *Staphylococcus aureus*.[4] Rubicordifolin (**4**, Figure 1), a constituent of *Rubia cordifolia*, displayed significant efficacy by inhibiting the growth of sarcoma ascites in mice at low concentrations.[5] On the other hand, the arylsulfonamide naphtho[1,2-*b*]furan derivative **5a** is a selective inhibitor of triple-negative breast cancer,[6a] while **5b** displayed significant activity in lung and colon cancer cells.[6b] Finally, naphtho[1,2-*b*]furans have potential applications in functional materials, such as electrically conducting light-emitting diodes,[7a] and photochromic[7b] and organic materials.[7c]

On the other hand, benzo[*g*]indoles (**2**, Figure 1) were reported to be potent anticancer agents[8a] and inhibitors of microsomal prostaglandin E_2 synthase-1,[8b] and expressed significant affinity for dopamine D2-like receptors.[8c] In particular, benzo[*g*]indole **6** (Figure 1) displayed a 10-fold higher 5-lipoxygenase activity than 5-hydroxy indoles.[9] Besides, benzo[*g*]indoles (**2**) have found various applications in material sciences such as yellow-light-emitting activity,[10a] high performance in electrochromic devices,[10b] fluorescence "turn-off" sensing properties of metal ion,[10c] etc.

In view of the immense importance of naphtho[1,2-*b*]furans, various synthetic efforts have been devoted to their constructions. Although there are several examples[11] on their preparation as part of the synthesis of different oxygen heterocycles, there are only few reports on their general synthesis.[12] Representative examples are copper-mediated [3 + 2] cycloaddition of cyclic ketones and olefins or alkynes,[12a] platinum(II)-catalyzed cycloisomerization of allenyl ketones,[12b] base-promoted substitution/elimination reaction between naphthols and nitroallylic acetates,[12c] and use of metal catalysts such as Fe−Pd bimetallic nanoparticles,[12d] indium(III) triflate,[12e] and rhenium oxide[12f] (Re_2O_7) on quinone substrates. However, development of a convenient, scalable, and practical

Received: March 27, 2019
Published: June 26, 2019

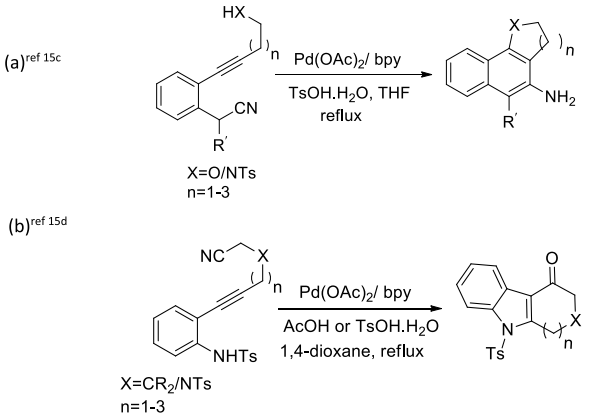
DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

method using readily available and cheap substrates remains a challenge.

Regarding benzo[*g*]indoles, scrutiny of the literature reveals only few methods for the general synthesis[13] involving mostly multicomponent reactions, although several reports exist on the preparation of **2**[14] during the synthesis of other nitrogen heterocycles. Consequently, a straightforward and reliable method for their general synthesis continues to be fascinating.

In recent years, cascade reactions have gained immense interest because of several advantages and many pioneering works in this regard have been well-documented in the literature.[15] Among them, palladium(II)-catalyzed synthesis of 2,3-dihydro derivatives of naphtho[1,2-*b*]furans and benzo[*g*]-indoles (Scheme 1a) and of tosylated derivatives of indoles fused

Scheme 1. Lu's Works: Synthesis of Fused Heterocycles via Pd(II)-Catalyzed Reactions



with carbo- or heterocycles (Scheme 1b) utilizing *ortho*-alkynyl benzenes as substrates, reported by Lu et al. (Scheme 1), deserves particular mention.

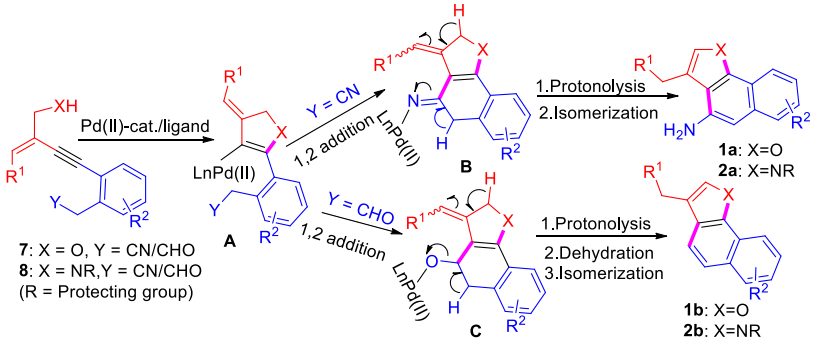
In view of the reported works and in continuation of our work[16] on palladium-catalyzed reactions, we envisioned that compounds **1** and **2** could be built up by exploring the palladium-catalyzed cascade reactions of ene−ynes **7** and **8** containing cyano/aldehyde group, as depicted in Scheme 2. Activation of the triple bond of the substrates by Pd(II) catalyst was expected to trigger a 5-*endo-dig* heteroannulation resulting in an intermediate **A** that might undergo subsequent intramolecular 1,2-addition onto suitably placed carbon−heteroatom multiple bond (e.g., −C═O/−C≡N) resulting in the transient species **B**/**C**. Protonolysis and isomerization of **B** could lead to the formation of **1a**/**2a**, while protonolysis and isomerization followed by dehydration of **C** could easily deliver **1b**/**2b**. Herein, we describe the results obtained so far in this effort.

RESULTS AND DISCUSSION

Synthesis of Naphtho[1,2-*b*]furans 1a and 1b. Initially, we set out with a model study for the synthesis of **1aa** using substrate **7aa** (R^1 = Ph, R^2 = H, X = O, Y = CN) through variation of reaction parameters; selected results are presented in Table 1. Carrying out this reaction in 1,4-dioxane employing $Pd(OAc)_2$/bipyridine (bpy) and using *p*-toluenesulfonic acid (*p*-TsOH) as an additive led to the desired naphtho[1,2-*b*]furan **1aa** with only 30% yield (Table 1, entry 1). Replacing the additive by D-(+)-camphorsulfonic acid (D-CSA) and employing a polar solvent like dimethylacetamide (DMA) or *N*-methylacetamide (NMA) afforded (Table 1, entries 2 and 3) the product **1aa** with 44 and 62% yields, respectively, proving NMA as the better solvent. Gratifyingly, changing the catalyst to $Pd(OAc)_2$bpy enhanced the yield to 72% (Table 1, entry 4). On the contrary, use of the less polar solvent tetrahydrofuran (THF) lowered the yield (Table 1, entry 5). Therefore, we executed few more reactions in NMA using $Pd(OAc)_2$ and different ligands (i.e., 1,10-phenanthroline and 4,4′-dimethoxy-2,2′-bipyridine), but the product **1aa** was obtained in lower yields (Table 1, entries 6 and 7 vs entry 4). Furthermore, replacement of the additive (i.e., D-CSA) by AcOH under the described conditions (i.e., entry 4 of Table 1) proved still less satisfactory (Table 1, entry 8). Thus, reaction conditions of entry 4 emerged to be optimal.

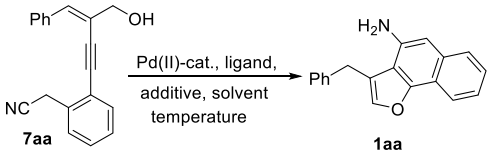
To assess the scope and limitations of this reaction, diversely substituted ene−yne substrates **7a** were then exposed to the optimized reaction conditions; the results are summarized in Scheme 3. When electron-donating methoxy groups are placed at both meta and para positions of the substrate (**7ab**), the desired product **1ab** was formed within 1.5 h with 75% yield. The presence of an electron-withdrawing group (R^2 = CF_3) at the para position of substrate (**7ac**) also led to the formation of product **1ac** within 2 h, albeit with somewhat lower yield (66%). Next, the influence of substituents on the other ring (R^1) of the substrates was studied. Both electron-withdrawing (viz., Cl, CF_3) and electron-donating (viz., OMe) substituents placed at the para position (**7ad**−**af**) delivered products (**1ad**−**af**) smoothly within 1−1.5 h in very good yields (65−76%), showing insignificant effect of such substituents. However, incorporation of electron-donating groups at ortho and meta positions (**7ag**) enhanced the yield of product **1ag** to 78%. Replacement of the aryl group by a heteroaryl one (R^1 = Het-aryl) reduced the yield of products (**1ah**/**ai**) to 25−35% even

Scheme 2. Present Work: Envisaged Pathways for the Formation of Products 1a, 1b, 2a, and 2b



DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

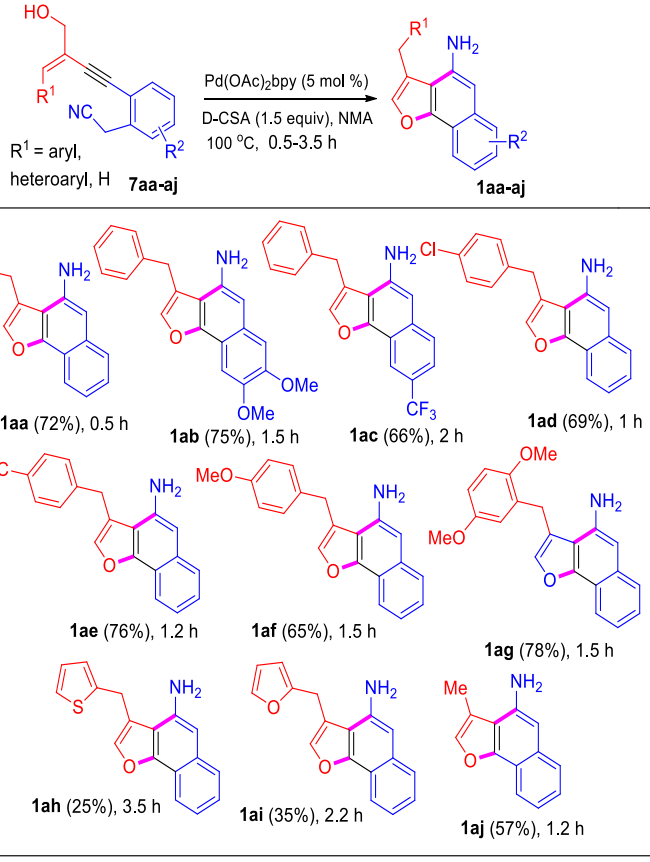
Table 1. Optimization of Reaction Conditions for the Synthesis of Naphtho[1,2-*b*]furan 1aa[a,b]



entry	catalyst	ligand	additives	solvents	time (h)	temp (°C)	yield[b] (%)
1	$Pd(OAc)_2$	bpy[c]	*p*-TsOH	1,4-dioxane	2	100	30
2.	$Pd(OAc)_2$	bpy	D-CSA[d]	DMA	2	100	44
3.	$Pd(OAc)_2$	bpy	D-CSA	NMA	1	100	62
4.	$Pd(OAc)_2$bpy	bpy	D-CSA	NMA	0.5	100	72
5.	$Pd(OAc)_2$bpy		D-CSA	THF	1.5	reflux	65
6.	$Pd(OAc)_2$	Phen[e]	D-CSA	NMA	1.5	100	60
7.	$Pd(OAc)_2$	dmbpy[f]	D-CSA	NMA	2	100	66
8.	$Pd(OAc)_2$bpy		ACOH	NMA	4	100	21

[a]Reaction conditions: **7aa** (0.25 mmol), catalyst (5 mol %), ligand (6 mol %), and additive (1.5 equiv) in solvent (3 mL) at stated temperature under argon atmosphere. [b]Yields of the isolated pure products. [c]bpy: 2,2′-bipyridine. [d]D-CSA: D-(+)-camphorsulfonic acid. [e]Phen: 1,10-phenanthroline. [f]dmbpy: 4,4′-dimethoxy-2,2′-bipyridine.

Scheme 3. Synthesis of 4-Amino Naphtho[1,2-*b*]furan Derivatives 1aa–aj[a]



[a]Reaction conditions: A mixture of **7aa** (0.25 mmol), $Pd(OAc)_2$bpy (5 mol %), and D-CSA (1.5 equiv) in 3 mL of NMA was heated at 100 °C under argon atmosphere.

after slightly longer reaction times (2.2–3.5 h). The moderate yield could be accounted for by the polymerization of the substrates, as a tarry material was observed during the progress of the reaction. But the absence of any substituent (R^1 = H) produced the product **1aj** (57%) within 1.2 h only.

With a view to expanding the scope of this reaction further, we replaced the cyano group of **7aa** by an aldehyde one as in the substrates **7ba–bg** (for preparation, see the Supporting Information). To our dismay, exposure of **7ba** (R^1 = Ph, R^2 = H) to the optimized reaction conditions (entry 4 of Table 1) resulted in the formation of the desired product **1ba** with only moderate yield (42%). Thus, further screening of solvent system and other reaction parameter was needed (Table 2). Changing the solvent from NMA to the less polar 1,4-dioxane increased the yield (80%) and reduced the reaction time (1 h) remarkably (Table 2, entry 2). But the yield of **1ba** dropped to 31% (Table 2,

DOI: 10.1021/acs.joc.9b00861
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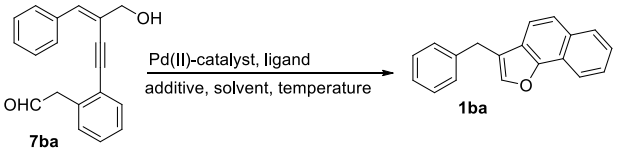
Table 2. Optimization of Reaction Conditions for the Synthesis of Naphtho[1,2-*b*]furan 1ba[a]



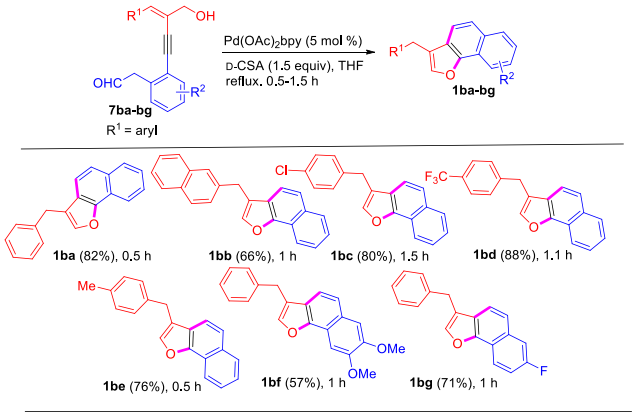
entry	catalyst	ligand	additive	solvent	temp (°C)	time (h)	yield (%)
1	$Pd(OAc)_2bpy$		D-CSA	NMA	100	3	42
2.	$Pd(OAc)_2bpy$		D-CSA	1,4-dioxane	100	1	80
3.	$Pd(OAc)_2$	bpy	D-CSA	1,4-dioxane	100	2	31
4.	$Pd(OAc)_2bpy$		D-CSA	THF	reflux	1	82
5.	$Pd(OAc)_2$	bpy	D-CSA	THF	reflux	4	42
6.	$Pd(OAc)_2bpy$		AcOH	THF	reflux	4	nr

[a]Reaction conditions: **7ba** (0.18 mmol), catalyst (5 mol %), ligand (6 mol %), and additive (1.5 equiv) in 3 mL of solvent heated at specified temperature under argon atmosphere.

entry 3) when $Pd(OAc)_2$ and bpy were separately used instead of $Pd(OAc)_2bpy$ in 1,4-dioxane, underlining the necessity of using $Pd(OAc)_2bpy$ in the reaction. Interestingly, executing the reaction in a less polar solvent like THF successfully increased the yield to 82% (Table 2, entry 4). However, using the catalyst and the ligand separately in THF decreased the yield to 42% (Table 2, entry 5). When the additive was changed to acetic acid instead of D-CSA, product formation did not take place at all proving D-CSA to be a better additive (Table 2, entry 6). Thus, the reaction conditions of entry 4 were found to be optimal. So, we pursued this reaction in THF for further exploration as discussed below.

Accordingly, a number of diversely substituted ene−yne substrates **7b** were investigated (Scheme 4). Different functional

Scheme 4. Synthesis of the Naphtho[1,2-*b*]furan Derivatives 1ba−bg[a]



[a]Reaction conditions: **7ba** (0.18 mmol), $Pd(OAc)_2bpy$ (5 mol %), and D-CSA (1.5 equiv) in refluxing THF (3 mL) under argon atmosphere.

groups (viz., F, Cl, CF_3, Me, OMe, etc.) were found to be compatible for this reaction. Nevertheless, replacing phenyl group attached to the double bond in substrate by a bulky naphthyl group (R^1 = 2-naphthyl) required slightly longer reaction time (1 h) and reduced the yield (of **1bb**) to 66%. In contrast, employment of electron-withdrawing group at the para position of the phenyl ring in substrates (R^1 = *p*-ClC_6H_4−/*p*-$CF_3C_6H_4$−) afforded the products (**1bc**/**bd**) within 1.1−1.5 h with excellent yields (80−88%), while introduction of an electron-donating methyl group at the same position (R^1 = *p*-MeC_6H_4−) furnished the product **1be** within 0.5 h, but with a slightly reduced yield (76%). On the other hand, the electron-donating methoxy group (R^2 = OMe) placed at meta and para positions (substrate **7bf**) produced the expected product **1bf** within 1 h with a moderate yield of 57%, whereas an electron-withdrawing group (i.e., F) at para position enhanced the yield (of **1bg**) to 71%. Furthermore, in contrast to the previous observations (Scheme 3), replacement of the aryl moiety in substrates by a heteroaryl one (R^1 = het-aryl) did not work well since only a trace amount of the desired product was observed in few cases. But employment of the heterocyclic moiety (viz., 2,4-dimethoxy pyrimidine) at the other end of the substrate (i.e., **9**) proved to be effective although NMA had to be used in place of THF and the masked aldehyde was necessary as the free aldehyde could not be generated despite repeated efforts (Scheme 5). The desired product **1bh** was thus produced within 2 h with 85% yield.

In view of the immense importance of the uracil derivatives in cancer chemotherapy[17a,b] and our own interest,[17c] we planned to convert our product **1bh** to the uracil derivative **10**. Pleasingly, treatment of **1bh** with sodium iodide and trimethylsilyl chloride in dry acetonitrile at room temperature (rt) was found to be successful for the formation of **10** albeit in moderate yield (52%). The synthesis of more uracil derivatives and testing the anticancer activity (in vitro) of product **10** in different cancer cell lines are under study.

Synthesis of Benzo[*g*]indoles 2a and 2b. The scope of this reaction was next expanded to nitrogen heterocycles, i.e., benzo[*g*]indoles **2**, utilizing substrate **8** as envisaged in Scheme 2. At the outset, we prepared (see the Supporting Information) the requisite substrate **8aa** (R^1 = Ph, R^2 = H, X = NTs, Y = CN) and treated it under the optimized reaction conditions of Table 1. To our disappointment, the expected product **2aa** was obtained in moderate yield (42%) along with a pyrrole derivative **11a** as side product (Table 3, entry 1), suggesting the necessity of tweaking the reaction parameters. Switching over to other palladium catalysts [viz., $Pd(OAc)_2bpy$, $Pd(OAc)_2Phen$] instead of $Pd(OAc)_2$ was first attempted, but without success (Table 3, entries 2 and 3). After replacing the polar solvent NMA with the relatively less polar 1,4-dioxane, the reaction was complete within 2 h but delivered only modest yield of **2aa** (34%) along with 39% of **11a** (Table 3, entry 4). Experiments with other solvents revealed THF to be the most promising one, although it required somewhat longer reaction times (2.1−10 h). Carrying out this reaction initially in refluxing THF required 6 h to afford the product **2aa** (45%) in addition to **11a** (Table 3,

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

Scheme 5. Synthesis of Naphtho[1,2-*b*]furan 1bh and Its Conversion to Uracil Derivative 10

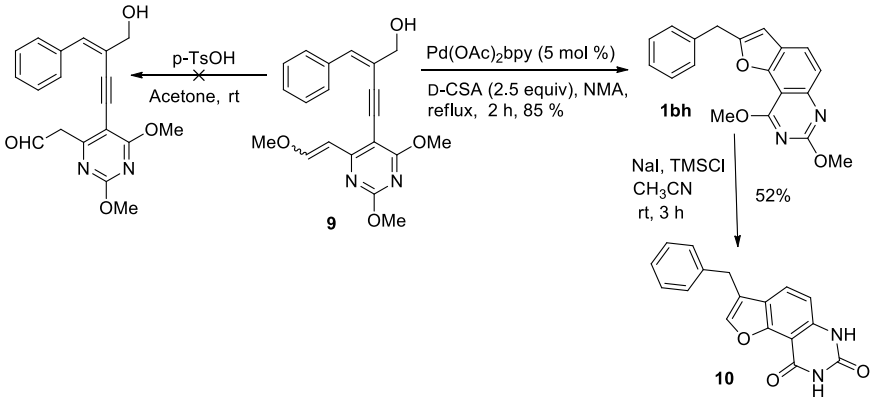
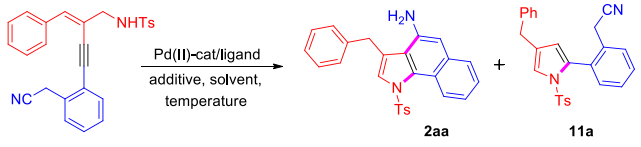


Table 3. Optimization of Reaction Conditions for the Synthesis of 4-Amino Benzo[*g*]indole 2aa[a]



entry	catalyst	ligand	additive	solvent	temp (°C)	time (h)	yield **2aa**	**11a** (%)
1.	$Pd(OAc)_2$	bpy	D-CSA	NMA	100	6	42	32
2.	$Pd(OAc)_2$bpy		D-CSA	NMA	100	6	41	38
3.	$Pd(OAc)_2$phen		D-CSA	NMA	100	5	40	32
4.	$Pd(OAc)_2$	bpy	D-CSA	1,4-dioxane	75	2	34	39
5.	$Pd(OAc)_2$	bpy	D-CSA	THF	reflux	6	45	26
6.	$Pd(OAc)_2$bpy		D-CSA	THF	reflux	2.1	60	25
7.	$PdCl_2(MeCN)_2$	bpy	D-CSA	THF	reflux	9	trace	trace
8.	$Pd(OAc)_2$bpy		$MeSO_3H$	THF	reflux	9	nr	nr
9.	$Pd(OAc)_2$bpy		AcOH−H_2O (1:1)	THF	reflux	10	nr	nr
10.	$Pd(OAc)_2$bpy		*p*-TsOH·H_2O	THF	reflux	3.5	66	25
11.	$Pd(OAc)_2$	bpy	*p*-TsOH·H_2O	THF	reflux	4	74	12
12.	$Pd(OAc)_2$	bpy	TfOH	THF	reflux	7	trace	trace

[a]Reaction conditions: A mixture of **8aa** (0.23 mmol), catalyst (5 mol %), ligand (10 mol %), except entries 2, 3, 6, and 8−10, and additive (2.0 equiv) in solvent (3 mL) was heated at specified temperatures (see table) under argon atmosphere.

entry 5). Interestingly, use of $Pd(OAc)_2$bpy as catalyst instead of $Pd(OAc)_2$/bpy reduced the reaction time (1.2 h) and enhanced the yield of **2aa** to 60% (Table 3, entry 6); the other catalyst tried [i.e., $PdCl_2(MeCN)_2$] proved unsuccessful (Table 3, entry 7). We also checked the role of different additives in this reaction. Although methanesulfonic acid ($MeSO_3H$) and aqueous acetic acid (AcOH/H_2O = 1:1) failed (Table 3, entries 8 and 9), *p*-toluenesulfonic acid (*p*-TsOH·H_2O) could complete the reaction within 3.5 h and furnished **2aa** with 66% yield (Table 3, entry 10) along with **11a** (25%). To our gratification, use of $Pd(OAc)_2$ catalyst and bipyridine individually instead of preformed $Pd(OAc)_2$bpy further improved the yield of **2aa** (74%) and suppressed the yield of the side product **11a** considerably (Table 3, entry 11). But change of the additive to triflic acid proved unsuccessful (Table 3, entry 12). Thus, the reaction conditions of entry 11 appeared to be optimal.

We next sought to explore the scope of the reaction (Scheme 6). Replacing the phenyl ring in **8aa** by naphthyl had little effect as **8ab** (R^1 = 2-naphthyl, R^2 = H) delivered the product **2ab** (78%) with equal ease. Introduction of a heteroaryl moiety also proved to be equally effective affording the respective products **2ac**/**ad** with very good yields (68−76%). Installation of either an electron-withdrawing (viz., Cl) or electron-donating group (viz., Me) at the para position as in **8ae** (R^1 = *p*-ClC_6H_4−) or **8af** (R^1 = *p*-MeC_6H_4−) provided the desired product **2ae** (82%) or **2af** (78%) easily within 4−5 h. In contrast, placement of a strong electron-donating group (OMe) at the same position had detrimental effect, making the reaction sluggish (t = 12 h) and affording the product **2ag** with low yield (24%), though the same substituent located at meta position ensured very good yield (80%) of the corresponding product (**2ah**) in a short reaction time (5 h). Presumably, the low yield of **2ag** may be attributed to the electron-donating effect of the methoxy group to the acetylenic carbon (of **8ag**), thereby reducing the electrophilicity sufficiently and making the *trans*-aminopalladation process [see species **A** (X = NTs) of Scheme 2] somewhat difficult. In contrast, methoxy groups placed at both meta and para positions delivered the desired product **2ai** in 4 h with 65% yield. Even a strongly electron-withdrawing group (CO_2Me) incorporated at the same position also produced the desired product **2aj**, though in moderate yield (55%).

We then turned our attention to synthesize **2b** (R = NTs), as depicted in Scheme 2. Accordingly, the requisite starting material **8ba** (R^1 = Ph, R^2 = H, X = NTs, Y = CHO) was prepared (see the Supporting Information) and allowed to react under the optimum reaction conditions (entry 11 of Table 3).

DOI: 10.1021/acs.joc.9b00861
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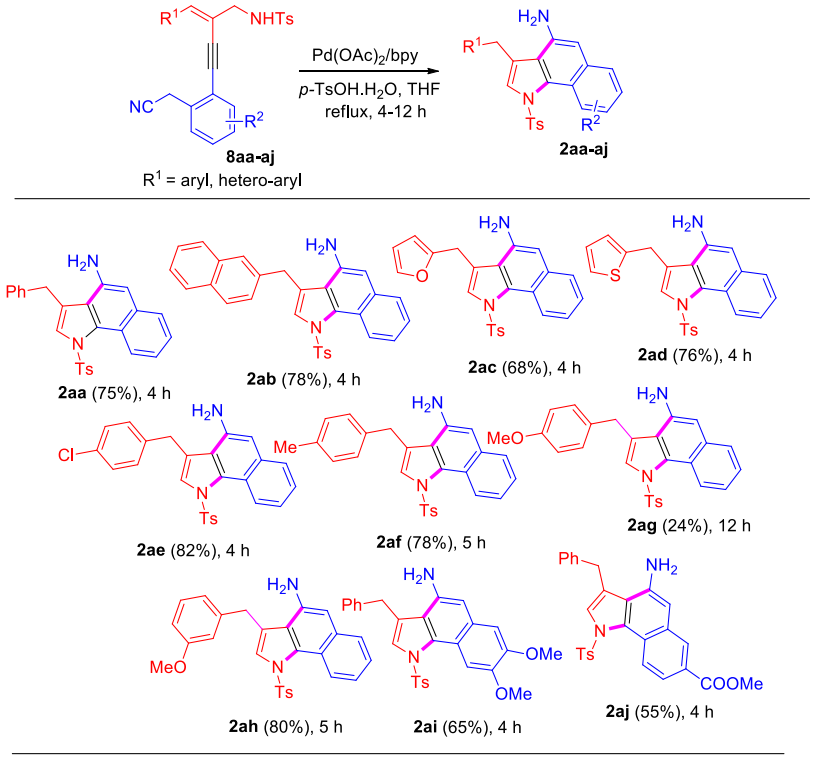
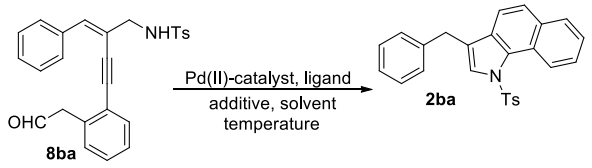
Scheme 6. Synthesis of 4-Amino Benzo[*g*]indole Derivatives 2aa−aj[a,b]



[a]Reaction conditions: **8a** (0.23 mmol), $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), and *p*-TsOH·H_2O (2.0 equiv) in refluxing THF (3 mL) under argon atmosphere. [b]Product **2a** was formed along with a minor amount (8−19%) of the corresponding pyrrole derivative (e.g., **11a** during the use of **8aa**) as side product resulting from monocyclization.

Table 4. Optimization of Reaction Conditions for Benzo[*g*]indole 2ba[a]



entry	catalyst	ligand	additive	solvent	temp (°C)	time (h)	yield **2ba**
1.	$Pd(OAc)_2$	bpy	*p*-TsOH·H_2O	THF	reflux	12	trace
2.	$Pd(OAc)_2$	bpy	*p*-TsOH·H_2O	1,4-dioxane	80	3	25
3.	$Pd(OAc)_2$bpy		*p*-TsOH·H_2O	1,4-dioxane	80	3.5	47
4.	$Pd(OAc)_2$bpy		AcOH−H_2O (1:1)	1,4-dioxane	100	4	nr
5.	$Pd(OAc)_2$bpy		*p*-TsOH·H_2O	DME	85	2	61
6.	$Pd(OAc)_2$	bpy	*p*-TsOH·H_2O	NMA	80	3	nr

[a]Reaction conditions: A mixture of **8ba** (0.14 mmol), catalyst (5 mol %), ligand (10 mol %), and additive (1.5 equiv) was heated at mentioned temperatures under argon atmosphere.

Unlike the case of **2aa**, this reaction showed (entry 1 of Table 4) the formation of the desired product **2ba** only in traces even after heating for 12 h. However, conducting this reaction in 1,4-dioxane using $Pd(OAc)_2$/bpy or $Pd(OAc)_2$bpy did afford **2ba** to the extent of 25−47% (Table 4, entries 2 and 3). When the additive was changed to AcOH−H_2O instead of *p*-TsOH·H_2O, no desired product was formed (Table 4, entry 4), suggesting the necessity of *p*-TsOH in this reaction. Gratifyingly, executing this reaction in 1,2-dimethoxyethane (DME) led to the formation of **2ba** within 2 h with 61% yield (Table 4, entry 5). As changing the solvent to a more polar one such as NMA failed to deliver the desired product **2ba** (Table 4, entry 6), the reaction conditions of entry 5 emerged to be optimal.

We thereafter decided to explore the scope and limitation of this reaction, as shown in Scheme 7. This revealed that the presence of the bulky naphthyl ring in substrate **8bb** produced the desired product **2bb** in moderate yield (44%), presumably due to the steric effect of this ring. Also, contrary to our previous observations, a reactant carrying a heteroaryl ring (R^1 = thienyl/furanyl, etc.) in place of naphthyl turned out to be inert even after prolonged heating (>12 h), although the reason is not very clear at this moment. Furthermore, incorporation of the electron-withdrawing group (viz., Cl/CF_3) at the para position of the benzene ring in substrate **8bc**/**bd** facilitated the reaction, producing the product **2bc**/**bd** in good yield (68/65%). In contrast, the presence of an electron-donating group (viz., CH_3,

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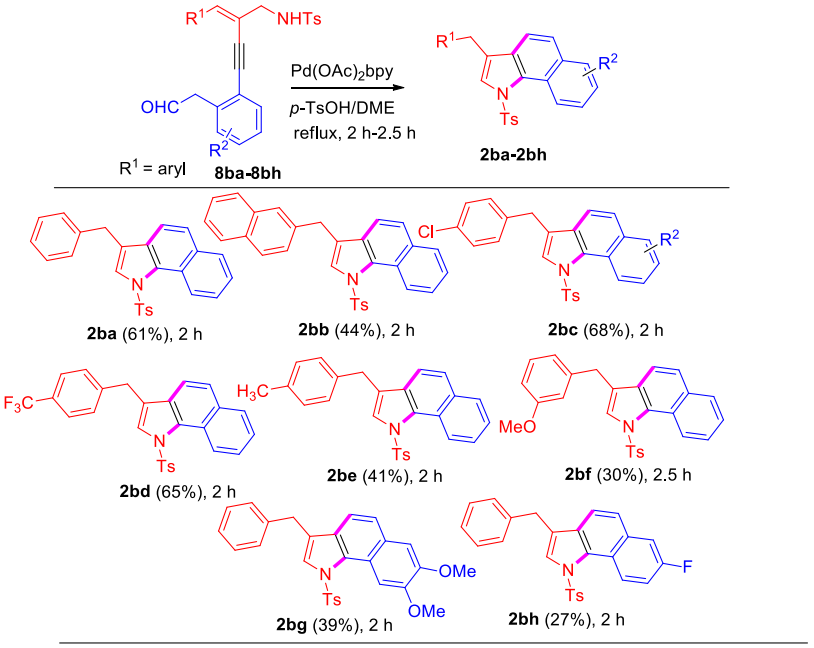
J. Org. Chem. 2019, 84, 8959−8975

Scheme 7. Synthesis of Benzo[*g*]indole Derivatives 2ba–bh[a]

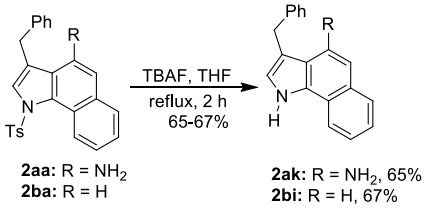


[a]Reaction conditions: **8a** (0.23 mmol), $Pd(OAc)_2bpy$ (5 mol %), and *p*-TsOH·H_2O (1.5 equiv) were refluxed in DME (3 mL) under argon atmosphere.

OMe) in the same phenyl ring of substrate (**8be**/**bf**) somewhat hindered the reaction, leading to the formation of the respective products **2be** and **2bf** in moderate yields (30–41%), while an electron-withdrawing (viz., F) or electron-donating group (viz., OMe) in the other benzene ring furnished product **2bg** or **2bh** within 2 h though in modest yields (27–39%).

Owing to the presence of benzo[*g*]indoles with free NH group in a large number of bioactive compounds,[8b,c,9] we attempted to deprotect the tosyl group of the products **2aa** and **2ba**, as shown in Scheme 8. The detosylation was carried out successfully within 2 h using tetrabutylammonium fluoride (TBAF) in refluxing THF to furnish the products **2ak–bi** with 65–67% yield.

Scheme 8. Detosylation of Benzo[*g*]indoles 2aa/ba



In conclusion, we have developed a Pd(II)-catalyzed cascade reaction for a facile and general synthesis of naphtho[1,2-*b*]furans **1** and benzo[*g*]indoles **2** using simple and readily available substrates. The newly developed method constitutes a fast intramolecular assembly involving *trans*-oxo/aminopalladation of alkyne, followed by nucleophilic 1,2-addition to cyano/aldehyde group. The reactions are operationally simple, compatible with a range of functional groups, and atom-economical. The method is applicable to both oxygen and nitrogen heterocycles. Because of the structural similarity of 4-amino naphtho[1,2-*b*]furans **1a** to potent anticancer agents **5**,[6a] the anticancer activities of the products **1a** (Scheme 3) and their various sulfonamide derivatives (along with compound **10**) are currently under investigation. We believe that this novel method will find significant applications in organic, medicinal, and material chemistry as well.

EXPERIMENTAL SECTION

General. All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60–80 °C. Dichloromethane (DCM) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane was distilled over sodium and benzophenone. Commercial grade dry dimethylformamide (DMF), dimethylacetamide (DMA), *N*-methylacetamide (NMA), and 1,2-dimethoxyethane (DME) were used as solvents. All reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance or iodine exposure. For purification, column chromatography was performed using 100–200 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a 300, 400, or 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given from TMS ($\delta = 0.00$) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [$CDCl_3$: ^1H NMR $\delta = 7.26$ ppm (s); ^{13}C NMR $\delta = 77.0$ ppm]. Coupling constants (J) are expressed in hertz (Hz), and spin multiplicities are given as singlet (s), doublet (d), double doublet (dd), triplet (t), triple doublet (td), quartet (q), multiplet (m), and broad (br), apparent (app). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using electrospray ionization (ESI) time-of-flight or electron ionization (EI) mode.

Procedure for the Preparation of Starting Materials 7a. 2-(2-Ethynylphenyl)acetonitrile derivatives **S1** (see Scheme S1 in the Supporting Information) were prepared in two steps comprising "Sonogashira reaction" of 2-iodophenylacetonitrile derivatives with trimethylsilylacetylene followed by deprotection of the silyl group of the resulting product using potassium carbonate[18] (Scheme S1a in the Supporting Information). Thereafter, the desired starting material **7a** was prepared in three steps starting from benzaldehyde derivatives, as

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959–8975

shown in Scheme S1b (in the Supporting Information). In the first step, the benzaldehyde derivatives were converted into their corresponding α,β-unsaturated ester **S2** employing a halo-Wittig reaction, and the product reduced to the corresponding α,β-unsaturated alcohol **S3** using diisobutylaliminium hydride (DIBAL-H).[19] Finally, compound **S3** underwent "Sonogashira coupling" with acetylenic compound **S1** synthesized previously leading to the formation of the desired starting material **7a**.

General Synthesis of α,β-Unsaturated Esters S2 via Halo-Wittig Reaction (See Scheme S1b in the Supporting Information). To a well-stirred and cooled (−5 °C) solution of (ethoxycarbonylmethyl)triphenylphosphonium bromide (500 mg, 1.17 mmol) dissolved in dry MeOH (10 mL) were added molecular iodine (572 mg, 2.26 mmol) and freshly activated K_2CO_3 (160 mg, 1.17 mmol) successively. The temperature of the reaction mixture was strictly maintained between −5 and 5 °C over a period of 1.5 h, resulting in the formation of a brown-colored suspension. To this, the aldehyde derivatives (0.98 mmol), tetrabutylammonium bromide (16.1 mg, 0.05 mmol), and K_2CO_3 (22.3 mg, 0.16 mmol) were added successively and stirred for few minutes. The reaction pot was then removed from the low-temperature bath (using ice−salt mixture) and heated at 40 °C for another 2−8 h. During this time period, additional amount of K_2CO_3 (2 × 0.05 mmol) was added in two portions at 2 h intervals. Upon completion of reaction (TLC), MeOH was evaporated under vacuum and the crude residue was treated with 2 M sodium thiosulfate solution to remove the excess iodine. It was then extracted with ethyl acetate (2 × 20 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography eluting with 10−40% ethyl acetate−petroleum ether to obtain α,β-unsaturated esters **S2** in 60−75% yield.

General Synthesis of α,β-Unsaturated Alcohols S3 (See Scheme S1b in the Supporting Information). To a well-stirred and cooled (using ice−salt mixture) solution of unsaturated ester **S2** (0.69 mmol, 1.0 equiv) dissolved in dry DCM (5 mL) was added DIBAL hydride (1.2 M in toluene, 1.74 mL, 2.08 mmol, 3 equiv) solution dropwise under argon atmosphere and stirring was continued for another 2−3 h at the same temperature. Upon completion of the reaction (TLC), the reaction mixture was quenched with 15% sodium hydroxide solution (15 mL) and diluted with DCM (20 mL). The resulting thick reaction mixture was filtered through a bed of celite to obtain a clear layer separation. The organic layer was taken out and washed successively with water (8 mL) and brine solution (8 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by silica gel (100−200 mesh) column chromatography using 15−25% ethyl acetate in pet−ether (v/v) as eluent. The pure α,β-unsaturated alcohols **S3** were obtained in 42−76% yields.

General Procedure for the Preparation of Alkynyl Allyl Alcohols 7a (See Scheme S1b in the Supporting Information). Alcohols **7a** were prepared via Sonogashira reaction, as depicted in Scheme S1. Accordingly, acetylene **S1** (0.42 mmol, 1.1 equiv) and the vinyl iodide derivative **S3** (0.38 mmol, 1 equiv) were dissolved in dry Et_3N (2 mL) under argon atmosphere. To this solution was added $Pd(PPh_3)_2Cl_2$ (8.0 mg, 0.011 mmol, 3 mol %). After stirring the whole reaction mixture for another 10 min, copper(I) iodide (2.2 mg, 0.011 mmol, 3 mol %) was added and it was then heated at 65 °C for 16 h. Upon completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified through silica gel (100−200 mesh) column chromatography to obtain the desired compounds **7a** in 40−80% yield.

*Spectral Data of Starting Materials **7aa**−**aj**. (E)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetonitrile (**7aa**).* Brown solid (75.8 mg, 75%), R_f = 0.43 (30% ethyl acetate in petroleum ether, v/v), mp 68−70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.84 (d, J = 7.2 Hz, 2H), 7.56−7.45 (m, 2H), 7.42−7.32 (m, 5H), 6.91 (s, 1H), 4.43 (s, 2H), 3.88 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 135.8, 135.1, 132.5, 131.6, 129.3, 128.7, 128.6, 128.4, 128.2, 122.6, 121.1, 117.6, 93.5, 92.9, 67.1, 22.7; high-resolution mass spectrometry (HRMS) (ESI) m/z calcd for $C_{19}H_{15}NNaO$ $[M + Na]^+$ 296.1051, found 296.1056.

*(E)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)-4,5-dimethoxyphenyl)acetonitrile (**7ab**).* White solid (94.9 mg, 77%), R_f = 0.19 (30% ethyl acetate in petroleum ether, v/v), mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.82 (d, J = 7.2 Hz, 2H), 7.40−7.37 (m, 2H), 7.33−7.30 (m, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 4.41 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.83 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 150.0, 148.5, 135.9, 134.5, 128.6, 128.5, 128.3, 124.8, 121.3, 117.8, 115.2, 114.6, 111.1, 93.3, 91.9, 67.2, 56.1, 22.3; HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 334.1443, found 334.1445.

*(E)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)-4-(trifluoromethyl)phenyl)acetonitrile (**7ac**).* Brown solid (50.5 mg, 40%), R_f = 0.74 (30% ethyl acetate in petroleum ether, v/v), mp 120−122 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.80−7.77 (m, 3H), 7.62 (s, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 4.44 (s, 2H), 3.91 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 136.5, 135.6, 135.4, 131.0 (q, J = 33.0 Hz), 129.3 (q, J_{C-F} = 3.5 Hz), 129.0, 128.9, 128.7, 128.5, 125.8 (q, J_{C-F} = 3.6 Hz), 123.6, 123.3 (q, J = 270.9 Hz), 120.7, 116.7, 95.2, 91.2, 67.0, 22.8; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3NO$ $[M + H]^+$ 342.1106, found 342.1111.

*(E)-2-(2-(4-(4-Chlorophenyl)-3-(hydroxymethyl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7ad**).* Pale yellow solid (90.8 mg, 80%), R_f = 0.36 (30% ethyl acetate in petroleum ether, v/v), mp 80−82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.78 (d, J = 8.4 Hz, 2H), 7.54−7.52 (m, 1H), 7.48−7.42 (m, 1H), 7.40−7.35 (m, 4H), 6.86 (s, 1H), 4.43 (d, J = 5.4 Hz, 2H), 3.88 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 134.3, 134.2, 133.6, 132.6, 131.6, 129.9, 129.5, 128.6, 128.4, 122.5, 121.6, 117.5, 93.6, 93.2, 67.0, 22.9; HRMS (ESI) m/z calcd for $C_{19}H_{14}ClNNaO$ $[M + Na]^+$ 330.0662, found 330.0657.

*(E)-2-(2-(3-(Hydroxymethyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7ae**).* Pale brown solid (78.2 mg, 62%), R_f = 0.69 (30% ethyl acetate in petroleum ether, v/v), mp 126−128 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.94 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 6.94 (s, 1H), 4.46 (s, 2H), 3.87 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 139.2, 133.1, 132.7, 131.7, 130.1 (q, J_{C-F} = 32.6 Hz), 129.7, 128.8, 128.7, 128.5, 125.4 (q, J_{C-F} = 3.6 Hz), 124.0 (q, J_{C-F} = 270 Hz), 123.7, 122.3, 117.5, 94.0, 92.8, 66.9, 22.9; HRMS (ESI) m/z calcd for $C_{20}H_{14}F_3NNaO$ $[M + Na]^+$ 364.0925, found 364.0933.

*(E)-2-(2-(3-(Hydroxymethyl)-4-(4-methoxyphenyl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7af**).* Pale yellow solid (86.3 mg, 77%), R_f = 0.66 (30% ethyl acetate in petroleum ether, v/v), mp 60−62 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.82 (d, J = 8.4 Hz, 2H), 7.56−7.54 (m, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.39 (td, J = 7.4, 1.2 Hz, 1H), 7.37−7.34 (m, 1H), 6.93−6.92 (m, 2H), 6.83 (s, 1H), 4.40 (s, 2H), 3.91 (s, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 159.9, 135.2, 132.5, 131.6, 130.2, 129.2, 128.6, 128.4, 128.3, 122.9, 118.5, 117.7, 113.8, 113.8, 94.0, 92.8, 67.6, 55.4, 22.9; HRMS (ESI) m/z calcd for $C_{20}H_{18}NO_2$ $[M + H]^+$ 304.1338, found 304.1328.

*(Z)-2-(2-(4-(2,5-Dimethoxyphenyl)-3-(hydroxymethyl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7ag**).* Brown solid (83.8 mg, 68%), R_f = 0.71 (30% ethyl acetate in petroleum ether, v/v), mp 78−180 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.86 (d, J = 3.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.38−7.35 (m, 1H), 7.32−7.29 (m, 1H), 7.23 (s, 1H), 6.86−8.82 (m, 2H), 4.43 (s, 2H), 3.91 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 151.5, 132.4, 131.8, 129.9, 129.2, 127.9, 125.5, 122.5, 121.4, 117.6, 115.0, 113.9, 111.4, 93.6, 92.9, 67.3, 56.0, 55.7, 22.8; HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 334.1443, found 334.1434.

*(Z)-2-(2-(3-(Hydroxymethyl)-4-(thiophen-2-yl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7ah**).* Dark brown gummy liquid (57.8 mg, 56%), R_f = 0.43 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.68−7.56 (m, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.42−7.37 (m, 2H), 7.36−7.34 (m, 1H), 7.27−7.26 (m, 1H), 7.12 (s, 1H), 7.06−7.04 (m, 1H), 4.42 (s, 2H), 3.99 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 139.8, 132.4, 131.6, 130.1, 129.4, 128.9, 128.4, 128.3, 127.2, 126.7, 122.7, 118.2, 117.6, 96.3, 93.6, 66.5, 22.9; HRMS

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

(ESI) m/z calcd for $C_{17}H_{13}NNaOS$ $[M + Na]^+$ 302.0616, found 302.0616.

*(E)-2-(2-(4-(Furan-2-yl)-3-(hydroxymethyl)but-3-en-1-yn-1-yl)-phenyl)acetonitrile (**7ai**).* Dark brown gum (51.6 mg, 53%), R_f = 0.41 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.58−7.56 (m, 1H), 7.51−7.47 (m, 2H), 7.42−7.33 (m, 2H), 6.90 (d, J = 3.6 Hz, 1H), 6.79 (s, 1H), 6.49−6.48 (m, 1H), 4.40 (s, 2H), 4.00 (s, 2H), 2.07 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 151.9, 142.6, 132.4, 131.6, 129.2, 128.3, 128.2, 122.9, 122.7, 118.1, 117.7, 111.9, 111.4, 94.0, 93.5, 66.2, 22.6; HRMS (ESI) m/z calcd for $C_{17}H_{13}NNaO_2$ $[M + Na]^+$ 286.0844, found 286.0971.

*2-(2-(3-(Hydroxymethyl)but-3-en-1-yn-1-yl)phenyl)acetonitrile (**7aj**).* Brown gum (32.9 mg, 44%), R_f = 0.38 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.55−7.50 (m, 2H), 7.46−7.41 (m, 1H), 7.39−7.36 (m, 1H), 7.34−7.31 (m, 1H), 5.65 (d, J = 18.6 Hz, 1H), 4.45 (s, 1 H), 4.28 (s, 1H), 3.90 (d, J = 10.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 133.5, 132.4, 130.1, 129.2, 128.3, 128.2, 121.7, 82.5, 78.9, 51.6, 22.8; HRMS (ESI+) m/z calcd for $C_{13}H_{12}NO$ $[M + H]^+$ 198.0919, found 198.0923.

General Procedure for the Synthesis of 1a. A mixture of $Pd(OAc)_2$bpy (4.8 mg, 0.01 mmol, 5 mol %) and D-CSA (87 mg, 0.38 mmol) in dry NMA (1.5 mL) was stirred at 95 °C for 5 min under argon atmosphere. Then, the starting material **7a** (0.25 mmol) dissolved in NMA (1.5 mL) was added to the reaction mixture dropwise at the same temperature and the whole mixture was stirred at 100 °C for few hours (see Scheme 2 in the text) until completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized by adjusting the pH (∼7) with dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 5−15% ethyl acetate−petroleum ether (v/v) as eluent to afford the desired product **1aa**−**aj** in 25−78% yield.

Procedure for the Gram-Scale Synthesis of 1aa. A mixture of $Pd(OAc)_2$bpy (69.6 mg, 0.18 mmol, 5 mol %) and D-CSA (1273.7 mg, 5.49 mmol) in dry NMA (7 mL) was stirred at 95 °C for 5 min under argon atmosphere. Then, **7a** (1.0 g, 3.66 mmol, 1 equiv) dissolved in NMA (6 mL) was added dropwise at the same temperature and the mixture was stirred at 100 °C for 1.5 h. Then, the reaction mixture was neutralized by adjusting the pH (∼7) with dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 5% ethyl acetate−petroleum ether (v/v) as eluent to afford the desired product **1aa** in 73% yield (729.4 mg).

*Spectral Data of Products **1aa**−**aj**. 3-Benzylnaphtho[1,2-b]furan-4-amine (**1aa**).* Brown solid (49.1 mg, 72%), R_f = 0.47 (10% ethyl acetate in petroleum ether), mp 118−120 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.39−7.36 (m, 1H), 7.35−7.32 (m, 3H), 7.30−7.25 (m, 3H), 6.71 (s, 1H), 4.27 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 141.7, 139.4, 139.2, 132.9, 129.0, 128.4, 126.9, 125.8, 125.7, 122.8, 120.0, 119.2, 117.1, 115.6, 104.0, 30.7; HRMS (ESI) m/z calcd for $C_{19}H_{16}NO$ $[M + H]^+$ 274.1232, found 274.1238.

*3-Benzyl-7,8-dimethoxynaphtho[1,2-b]furan-4-amine (**1ab**).* Pale yellow solid (62.4 mg, 75%), R_f = 0.10 (10% ethyl acetate in petroleum ether), mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.47 (d, J = 8.4 Hz, 2H), 7.34−7.32 (m, 2H), 7.29−7.25 (m, 3H), 6.98 (s, 1H), 6.58 (s, 1H), 4.24 (s, 2H), 4.03 (s, 3H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.5, 149.3, 147.3, 140.9, 139.6, 138.2, 128.9, 128.4, 128.3, 126.8, 119.3, 114.2, 111.4, 105.5, 103.4, 99.8, 55.9, 55.8, 30.7; HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 334.1443, found 334.1446.

*3-Benzyl-8-(trifluoromethyl)naphtho[1,2-b]furan-4-amine (**1ac**).* Brown solid (56.2 mg, 66%), R_f = 0.36 (10% ethyl acetate in petroleum ether), mp 120−122 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.45 (s, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.35−7.33 (m, 2H), 7.28−7.26 (m, 3H), 6.69 (s, 1H), 4.26 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 153.0, 142.2, 141.8, 139.0, 134.5, 129.1, 128.3, 127.0, 126.3, 124.8 (q, J_{C-F} = 269.9 Hz), 124.2 (q, J_{C-F} = 32.0 Hz), 121.3 (q, J_{C-F} = 3.1 Hz), 119.3, 118.1 (q, J_{C-F} = 4.7 Hz), 116.2, 115.4, 102.9, 30.6; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −161.6 (s, 3F); HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3NO$ $[M + H]^+$ 342.1106, found 342.1108.

*3-(4-Chlorobenzyl)naphtho[1,2-b]furan-4-amine (**1ad**).* White solid (52.9 mg, 69%), R_f = 0.38 (10% ethyl acetate in petroleum ether), mp 80−82 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.38 (t, J = 6.9 Hz, 1H), 7.34 (t, J = 6.9 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 4.22 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 141.7, 139.1, 137.9, 133.0, 132.7, 129.7, 129.1, 125.9, 125.8, 122.9, 120.0, 118.8, 117.0, 115.4, 104.1, 30.2; HRMS (EI) m/z calcd for $C_{19}H_{14}ClNO$ $[M]^+$ 307.0764, found 307.0756.

*3-(4-(Trifluoromethyl)benzyl)naphtho[1,2-b]furan-4-amine (**1ae**).* Brown solid (64.8 mg, 76%), R_f = 0.38 (10% ethyl acetate in petroleum ether), mp 94−96 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.17 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.8 Hz, 2H), 7.51 (s, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 6.70 (s, 1H), 4.31 (s, 2H), 3.77 (bs, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 143.6, 141.7, 139.2, 133.0, 129.2 (app q, J_{C-F} = 32.7 Hz), 128.7, 125.8 (q, J_{C-F} = 3.6 Hz), 124.1 (app q, J_{C-F} = 270.5 Hz), 122.9, 119.9, 118.3, 116.9, 115.3, 104.1 30.7; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −162.4 (s, 3F); HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3NO$ $[M + H]^+$ 342.1106, found 342.1146.

*3-(4-Methoxybenzyl)naphtho[1,2-b]furan-4-amine (**1af**).* Pale yellow solid (49.2 mg, 65%), R_f = 0.36 (10% ethyl acetate in petroleum ether), mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.52 (s, 1H), 7.39−7.36 (m, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 4.20 (s, 2H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 158.5, 152.9, 141.6, 141.5, 133.0, 131.4, 129.3, 125.9, 125.8, 125.7, 122.7, 120.0, 119.6, 114.3, 55.3, 29.8; HRMS (ESI) m/z calcd for $C_{20}H_{18}NO_2$ $[M + H]^+$ 304.1338, found 304.1348.

*2-(2,5-Dimethoxybenzyl)naphtho[1,2-b]furan-4-amine (**1ag**).* Brown solid (56.6 mg, 78%), R_f = 0.27 (10% ethyl acetate in petroleum ether), mp 96−98 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.51 (s, 1H), 7.37−7.35 (m, 1H), 7.33−7.30 (m, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.75 (dd, J = 9.0, 3.0 Hz, 1H), 6.69−6.68 (d, 2H), 4.19 (s, 2H), 4.02 (s, 2H), 3.86 (s, 3H), 3.64 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 153.8, 152.6, 151.0, 141.5, 139.8, 132.9, 129.1, 125.7, 125.5, 122.5, 119.9, 118.8, 116.8, 115.9, 115.5, 117.7, 113.3, 103.3, 55.9, 55.6, 24.3; HRMS (ESI) m/z calcd for $C_{21}H_{19}NNaO_3$ $[M + Na]^+$ 356.1263, found 356.1264.

*3-(Thiophen-2-ylmethyl)naphtho[1,2-b]furan-4-amine (**1ah**).* Brown gum (23.0 mg, 25%), R_f = 0.41 (10% ethyl acetate in petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (d, J = 7.8 Hz, 1H), 7.65−7.63 (m, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 4.8 Hz, 1H), 6.97−6.95 (m, 1H), 6.90−6.89 (m, 1H), 6.70 (s, 1H), 4.41 (s, 2H), 3.89 (brs, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.8, 143.3, 141.2, 139.5, 133.0, 127.2, 125.8, 125.7, 125.2, 124.8, 122.7 119.9, 119.1, 116.9, 115.3, 103.8, 25.5; HRMS (ESI) m/z calcd for $C_{17}H_{14}NOS$ $[M + H]^+$ 280.0796, found 280.0789.

*3-(Furan-2-ylmethyl)naphtho[1,2-b]furan-4-amine (**1ai**).* Brown solid (23.0 mg, 35% yield), R_f = 0.38 (10% ethyl acetate in petroleum ether), mp 60−62 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.15 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.39−7.37 (m, 2H), 7.36−7.33 (m, 1H), 6.85 (s, 1H), 6.32−6.31 (m, 1H), 6.08−6.07 (m, 1H), 4.25 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 153.6, 152.6, 142.0, 141.5, 132.8, 125.9, 125.7, 123.0, 119.9, 116.9, 115.6, 110.6, 106.6, 24.1; HRMS (ESI) m/z calcd for $C_{17}H_{14}NO_2$ $[M + H]^+$ 264.1025, found 264.1034.

*3-Methylnaphtho[1,2-b]furan-4-amine (**1aj**).* Brown solid (22.5 mg, 57%), R_f = 0.29 (10% ethyl acetate in petroleum ether), mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.13 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.39−7.36 (m, 1H), 7.34−7.32 (m, 1H), 6.83 (s, 1H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.4, 140.4, 132.8, 126.0, 125.6, 122.9, 120.0, 117.3, 116.1, 115.7,

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

104.1, 10.4; HRMS (EI) m/z calcd for $C_{13}H_{11}NO$ $[M]^+$ 197.0841, found 197.0829.

Preparation of the Starting Materials 7b (See Scheme S2 of the Supporting Information). The acetylenic compound **S5** was prepared from iodo compound **S4** via Sonogashira reaction, as shown in Scheme S2a in the Supporting Information. Next, **S5** underwent the coupling reaction with **S3** via the aforesaid reaction process to furnish the product **S6**. Finally, the exposure of **S6** to acidic conditions led to the formation of the desired substrate **7b** (Scheme S2b in the Supporting Information).

Preparation of Acetylenic Compounds S5 (See Scheme S2a in the Supporting Information). To a well-stirred and ice-cooled solution of **S4**[20] (1.92 mmol, 1 equiv) in Et_3N (5 mL) were added $PdCl_2(PPh_3)_2$ (40.4 mg, 0.057 mmol, 3 mol %), CuI (21.9 mg, 0.115 mmol, 6 mol %), and trimethylsilylacetylene (1.1 equiv) sequentially. The reaction mixture was allowed to reach rt and stirring was continued for 1−1.5 h until completion of the reaction (TLC). Thereafter, the solvent was removed under reduced pressure, diluted with water (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude mass was purified through column chromatography using silica gel (100−200 mesh) to afford pure silylated acetylenic compound (90−95% yield), which was then desilylated. Thus, silylated compound (1.82 mmol, 1 equiv) dissolved in methanol was stirred at rt for 0.5−1 h in the presence of K_2CO_3 (0.1 equiv). Upon completion of reaction, the reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (2 × 15 mL), and concentrated under reduced pressure. The crude product obtained was purified by silica gel (100−200 mesh) column chromatography to obtain the acetylenic compounds **S5** in 56−60% yield.

Preparation of the Intermediates S6 (See Scheme S2b in the Supporting Information). To a well-stirred and ice-cooled solution of **S3** (0.77 mmol, 1 equiv) in Et_3N (2 mL) were added $Pd(PPh_3)_2Cl_2$ (16.2 mg, 0.023 mmol, 3 mol %), acetylenic intermediate **S5** (0.846 mmol, 1.1 equiv), and CuI (8.8 mg, 0.046 mmol, 6 mol %) successively. The reaction mixture was then stirred at rt under argon atmosphere for 1−2 h until the completion of the reaction (TLC). Thereafter, the solvent was removed under reduced pressure and the resulting crude mixture was extracted with ethyl acetate (3 × 30 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified through silica gel (100−200 mesh) column chromatography eluting with 10−40% ethyl acetate−petroleum ether (v/v) to afford the desired compounds **S6** in 78−90% yield.

Preparation of the Ene−Yne Substrates 7b (See Scheme S2b in the Supporting Information). To a well-stirred and ice-cooled solution of **S6** (0.69 mmol, 1 equiv) in dry acetone, *p*-TsOH (210.9 mg, 1.11 mmol, 1.6 equiv) was added in portions over a period of 20 min and the reaction mixture was stirred at rt for another 3−4 h until completion of reaction (TLC). Next, the reaction mixture was neutralized with dilute sodium bicarbonate solution and extracted with DCM (2 × 10 mL). The combined organic extracts were evaporated under reduced pressure; the resulting crude product was purified by silica gel (100−200 mesh) column chromatography to afford the desired starting materials **7b** in 42−76% yield.

*Spectral Data for Starting Materials **7ba**−**bg**. (Z)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde (**7ba**).* Yellow gum (144.7 mg, 76%), R_f = 0.36 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, J = 2.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 7.8 Hz, 3H), 7.33−7.31 (m, 3H), 6.85 (s, 1H), 4.39 (s, 2H), 3.89 (d, J = 1.8 Hz, 2H), 3.32 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 135.8, 135.2, 132.5, 131.6, 129.3, 128.7, 128.4, 128.2, 122.6, 121.1, 117.6, 93.5, 92.9, 67.1, 22.8; HRMS (ESI) m/z calcd for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1229, found, 277.1228.

*(Z)-2-(2-(3-(Hydroxymethyl)-4-(naphthalen-2-yl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**7bb**).* Yellow gum (150.7 mg, 67%), R_f = 0.31 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, J = 2.1 Hz, 1H), 8.26 (s, 1H), 7.84−7.82 (m, 5H), 7.50−7.48 (m, 5H), 7.01 (s, 1H), 4.45 (s, 2H), 3.91 (d, J = 1.8 Hz, 2H), 2.84 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 199.4, 134.8, 133.8, 133.5, 133.2, 132.4, 130.5, 129.2, 128.5, 128.3, 127.9, 127.8, 127.6, 126.5, 126.3, 126.1, 123.8, 121.7, 67.5, 49.6; HRMS (ESI) m/z calcd for $C_{23}H_{19}O_2$ $[M + H]^+$ 327.1385, found 327.1375.

*(Z)-2-(2-(4-(4-Chlorophenyl)-3-(hydroxymethyl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**7bc**).* Yellow gum (98.4 mg, 46%), R_f = 0.31 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.68 (t, J = 2.1 Hz, 1H), 7.76 (d, J = 9 Hz, 2H), 7.34−7.32 (m, 4H), 7.29−7.28 (m, 2H), 6.78 (s, 1H), 4.37 (d, J = 4.2 Hz, 2H), 3.87 (d, J = 1.8 Hz, 2H), 3.32 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 199.3, 134.4, 134.0, 133.8, 133.2, 132.5, 130.5, 129.9, 129.3, 128.5, 127.8, 123.6, 122.0, 95.1, 91.9, 67.2, 49.7; HRMS (ESI) m/z calcd for $C_{19}H_{15}ClNaO_2$ $[M + Na]^+$ 333.0658, found 333.0662.

*(Z)-2-(2-(3-(Hydroxymethyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**7bd**).* Yellow liquid (163.8 mg, 69%), R_f = 0.28 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, J = 2.1 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.41 (td, J = 7.5, 1.2 Hz, 1H), 7.35 (td, J = 7.65, 1.4 Hz 1H), 7.31 (d, J = 7.2 Hz, 1H), 6.88 (s, 1H), 4.42 (d, J = 6.6Hz, 2H), 3.88 (d, J = 2.4 Hz, 2H), 2.57 (t, J = 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.3, 139.3, 133.9, 132.5, 130.3,129.9 (q, J_{C-F} = 32.4 Hz), 129.5, 128.7, 127.8, 125.2 (q, J_{C-F} = 3.7 Hz), 124.1, 124.0 (q, J_{C-F} = 270.3 Hz), 123.4, 95.5, 91.6, 66.9, 49.7; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3NaO_2$ $[M + Na]^+$ 367.0922, found 367.0922.

*(Z)-2-(2-(3-(Hydroxymethyl)-4-(p-tolyl)but-3-en-1-yn-1-yl)-phenyl)acetaldehyde (**7be**).* Yellow gum (84.0 mg, 42%), R_f = 0.37 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.71 (t, J = 2.25 Hz, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.58−7.55 (m, 1H), 7.37−7.29 (m, 3H), 7.19 (d, J = 7.8 Hz, 2H), 6.81 (s, 1H), 4.38 (s, 2H), 3.90 (d, J = 2.1 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 199.5, 138.6, 134.8, 133.8, 133.2, 132.5, 130.4, 129.0, 128.7, 127.7, 123.9, 120.3, 94.4, 92.7, 67.4, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{20}H_{18}NaO_2$ $[M + Na]^+$ 313.1204, found 313.1202.

*(Z)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)-4,5-dimethoxyphenyl)acetaldehyde (**7bf**).* Yellow gum (115.9 mg, 50%), R_f = 0.21 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 1.8 Hz, 1H), 7.79 (d, J = 6.8 Hz, 2H), 7.32−7.31 (m, 2H), 7.28−7.26 (m, 1H), 6.98 (s, 1H), 6.80 (s, 1H), 6.68 (s, 1H), 4.35 (s, 2H), 3.87 (s, 1H), 3.86 (s, 3H), 3.858 (s, 3H), 3.78 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.4, 149.9, 148.1, 136.1, 133.7, 128.6, 128.2, 127.2, 121.7, 115.7, 114.7, 112.9, 94.7, 90.7, 67.1, 56.0, 55.9, 49.0; HRMS (ESI) m/z calcd for $C_{21}H_{21}O_4$ $[M + H]^+$ 337.1440, found 337.1437.

*(Z)-2-(4-Fluoro-2-(3-(hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde (**7bg**).* Yellow gum (97.4 mg, 48%), R_f = 0.35 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.67 (t, J = 1.8 Hz, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.53−7.51 (m, 1H), 7.37 (t, J = 7.8 Hz, 3H), 7.02 (td, J = 8.4, 2.4 Hz, 1H), 6.99 (dd, J = 9, 2.4 Hz, 1H), 6.85 (s, 1H), 4.37 (s, 2H), 3.87 (d, J = 1.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 198.4, 162.5 (d, J = 249 Hz), 136.5 (d, J = 7.5 Hz), 135.9, 134.8, 134.2 (d, J = 9 Hz), 128.6, 128.5, 128.3, 121.2, 119.8, 117.6 (d, J = 22.5 Hz), 115.1 (d, J = 21.0 Hz), 93.4, 91.9, 67.2, 49.3; HRMS (ESI) m/z calcd for $C_{19}H_{15}FKO_2$ $[M + K]^+$ 333.0693, found 333.0689.

General Procedure for the Synthesis of Products 1b. A mixture of $Pd(OAc)_2$bpy (3.4 mg, 0.009 mmol, 5 mol %) and D-CSA (62.6 mg, 0.27 mmol, 1.5 equiv) in dry THF (2 mL) was stirred at 60 °C under argon atmosphere. Then, **7b** (0.18 mmol) dissolved in dry THF (1.0 mL) was added at the same temperature (i.e., 60 °C) and the mixture was refluxed for 1−2 h until the completion of the reaction (TLC). The mixture was neutralized by adjusting the pH (~7) through dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh)

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

column chromatography using 1−8% ethyl acetate−petroleum ether (v/v) as eluent to afford desired product **1ba**−**bg** in 57−88% yield.

*Spectral Data for Products **1ba**−**bg**. 3-Benzylnaphtho[1,2-b]furan (**1ba**).* Brown solid (38.1 mg, 82%), R_f = 0.71 (5% ethyl acetate in petroleum ether, v/v), mp 80−82 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.62−7.58 (m, 2H), 7.56 (s, 1H), 7.51−7.47 (m, 2H), 7.33 (s, 2H), 7.32 (d, J = 1.8 Hz, 2H), 7.26−7.23 (m, 1H), 4.13 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.1, 141.4, 139.4, 131.4, 128.6, 128.5, 128.3, 126.4, 126.2, 125.1, 123.4, 123.0, 121.5, 120.7, 119.9, 118.4, 30.0; HRMS (ESI) m/z calcd for $C_{19}H_{14}NaO$ $[M + Na]^+$ 281.0942, found 281.0945.

*3-(Naphthalen-2-ylmethyl)naphtho[1,2-b]furan (**1bb**).* White solid (36.6 mg, 66%), R_f = 0.62 (5% ethyl acetate in petroleum ether, v/v), mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.34 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.79−7.77 (m, 2H), 7.62−7.59 (m, 3H), 7.51−7.45 (m, 5H), 4.29 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.2, 141.6, 136.9, 133.6, 132.2, 131.4, 128.3, 128.2, 127.65, 127.57, 127.2, 126.8, 126.3, 126.0, 125.4, 125.1, 123.5, 123.1, 121.5, 120.6, 120.0, 118.5, 30.2; HRMS (ESI) m/z calcd for $C_{23}H_{16}NaO$ $[M + Na]^+$ 331.1099, found 331.1098.

*3-(4-Chlorobenzyl)naphtho[1,2-b]furan (**1bc**).* Yellow gum (42.1 mg, 80%), R_f = 0.71 (5% ethyl acetate in petroleum ether, v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.29 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.61−7.56 (m, 2H), 7.54 (t, J = 1 Hz, 1H), 7.50−7.46 (m, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.28−7.21 (m, 4H), 4.07 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 151.3, 141.5, 137.9, 132.3, 131.5, 130.0, 128.7, 128.4, 126.5, 125.3, 123.3, 121.6, 120.3, 120.1, 118.3, 29.5; HRMS (ESI) m/z calcd for $C_{19}H_{14}ClO$ $[M + H]^+$ 293.0733, found 293.0733.

*3-(4-(Trifluoromethyl)benzyl)naphtho[1,2-b]furan (**1bd**).* Yellow solid (51.6 mg, 88%), R_f = 0.60 (5% ethyl acetate in petroleum ether, v/v), mp 60−62 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.32 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.63−7.59 (m, 2H), 7.58−7.56 (m, 3H), 7.52−7.50 (m, 1H), 7.43−7.42 (m, 3H), 4.18 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.2, 143.5, 141.5, 131.5, 128.8, 128.7, 128.3, 126.4, 125.5 (q, J_{C-F} = 3.8 Hz), 125.3, 124.2 (app q, J_{C-F} = 270.1 Hz), 123.2, 123.1, 121.5, 119.9, 119.7, 118.1, 29.9; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −162.2 (s, 3F); HRMS (ESI) m/z calcd for $C_{20}H_{14}F_3O$ $[M + H]^+$ 327.0997, found 327.0993.

*3-(4-Methylbenzyl)naphtho[1,2-b]furan (**1be**).* Brown solid (37.2 mg, 76%), R_f = 0.73 (5% ethyl acetate in petroleum ether, v/v); mp 44−46 °C ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.62−7.57 (m, 2H), 7.55 (s, 1H), 7.50−7.47 (m, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 4.09 (s, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.1, 141.4, 136.3, 135.8, 131.4, 129.2, 128.5, 128.3, 126.2, 125.0, 123.5, 122.9, 121.5, 120.9, 119.9, 118.5, 29.7, 21.0; HRMS (ESI) m/z calcd for $C_{20}H_{16}NaO$ $[M + Na]^+$ 295.1099, found 295.1100.

*3-Benzyl-7,8-dimethoxynaphtho[1,2-b]furan (**1bf**).* White solid (32.6 mg, 57%), R_f = 0.17 (5% ethyl acetate in petroleum ether, v/v), mp 120−122 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.59 (s, 1H), 7.49−7.47 (m, 2H), 7.35−7.32 (m, 5H), 7.26−7.23 (m, 2H), 4.10 (s, 2H), 4.08 (s, 3H), 4.01 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 150.8, 149.7, 148.7, 140.7, 139.5, 128.6, 128.5, 126.9, 126.3, 122.4, 121.6, 120.8, 116.6, 116.5, 107.4, 99.3, 56.0, 55.8, 30.1; HRMS (ESI) m/z calcd for $C_{21}H_{18}NaO_3$ $[M + Na]^+$ 341.1154, found 341.1150.

*3-Benzyl-7-fluoronaphtho[1,2-b]furan (**1bg**).* Brown solid (35.3 mg, 71%), R_f = 0.69 (5% ethyl acetate in petroleum ether, v/v), mp 48−50 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31−8.828 (m, 1H), 7.56−7.53 (m, 3H), 7.51−7.49 (m, 1H), 7.36 (td, J = 8.7, 2.4 Hz, 1H), 7.34−7.33 (m, 4H), 7.27−7.25 (m, 1H), 4.12 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 160.2 (d, J = 243.0 Hz), 151.2, 141.3, 139.3, 132.3 (d, J = 9.0 Hz), 128.6, 128.5, 126.4, 122.9, 122.4 (d, J = 9.0 Hz), 122.3 (d, J = 4.5 Hz), 120.8, 119.8, 118.5, 116.3, 116.1, 111.8, 111.7, 30.1; ^{19}F NMR{^{1}H} (376 MHz, $CDCl_3$) δ = −115.6 (s, 1F); HRMS (ESI) m/z calcd for $C_{19}H_{13}OFK$ $[M + K]^+$ 315.0588, found 315.0585.

*Procedure for the Synthesis of 7-Benzyl-2,4-dimethoxyfuro[3,2-h]quinazoline (**1bh**).* A mixture of $Pd(OAc)_2$bpy (2.7 mg, 0.007 mmol, 5 mol %) and D-CSA (82.4 mg, 0.355 mmol, 1.5 equiv) in dry THF (2 mL) was stirred at 60 °C under argon atmosphere. The substrate **10** (50 mg, 0.14 mmol) dissolved in NMA (1.0 mL) was then added to the reaction mixture, which was heated at 70 °C until the completion of the reaction (TLC). The reaction mixture was neutralized by adjusting the pH (∼7) through dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 10% ethyl acetate−petroleum ether (v/v) as eluent to afford desired product **1bh** in 85% yield.

*7-Benzyl-2,4-dimethoxyfuro[3,2-h]quinazoline (**1bh**).* Brown solid (38.6 mg, 85%), R_f = 0.39 (20% ethyl acetate in petroleum ether, v/v), mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.72 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.32−7.27 (m, 4H), 7.25−7.22 (m, 1H), 4.29 (s, 3H), 4.11 (s, 3H), 4.10 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.8, 161.6, 151.9, 149.8, 142.5, 139.0, 128.7, 128.6, 126.6, 126.2, 123.9, 121.3, 120.5, 101.8, 54.9, 54.8, 29.8; HRMS (ESI) m/z calcd for$C_{19}H_{17}N_2O_3$ $[M + H]^+$ 321.1239, found 321.1244.

Procedure for the Synthesis of Uracil Derivative 10. To a well-stirred solution of **1bh** (30 mg, 0.085 mol, 1 equiv) in dry acetonitirile was added NaI (380 mg, 2.55 mmol, 3.0 equiv); this was followed by dropwise addition of trimethylsilyl chloride (0.3 mL, 2.55 mmol, 3.0 equiv), and the reaction was stirred at rt for 3 h until TLC showed complete conversion. The solvent was removed under vacuum and the crude mass was filtered, washed with ethyl acetate followed by water, and dried to obtain the pure product **10** in 52% yield.

*7-Benzylfuro[3,2-h]quinazoline-2,4(1H,3H)-dione (**10**).* Yellow solid (11.2 mg, 52%), mp > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 11.28 (s, 1H), 11.26 (s, 1H), 7.89 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.30−7.27 (m, 4H), 7.19−7.17 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 4.01 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 161.0, 152.5, 150.6, 143.1, 139.84, 139.83, 128.9, 127.0, 126.7, 123.3, 119.9, 111.2, 101.6, 29.0; HRMS (ESI) m/z calcd for $C_{17}H_{13}N_2O_3$ $[M + H]^+$ 293.0926, found 293.0923.

Synthesis of Ene−Yne Substrates 8a (See Scheme S3 in the Supporting Information). The starting α,β-unsaturated alcohols **S3** utilized in this reaction (Scheme S3) were prepared from commercially available benzaldehyde derivatives, as shown previously under Scheme S1. The α,β-unsaturated alcohols **S3**, however, were converted into azide derivatives **S7** using NaN_3 in DMF. The azide compounds were reduced to the amine derivatives **S8** using 1,3-propanedithiol. In the next step, the amine derivatives were tosylated and the resulting compounds were allowed to undergo Sonogashira reaction with trimethylsilylacetylene. The deprotection of the silyl group using potassium carbonate led to the production of the desired acetylene derivatives **S10**, which underwent Sonogashira coupling with commercially available 2-iodophenylacetonitrile derivatives to afford the requisite ene−yne substrates **8a**.

Procedure for the Synthesis of Azide Derivatives S7 (See Scheme S3 in the Supporting Information). To a well-stirred ice-cooled solution of the α,β-unsaturated alcohols **S3** (3.85 mmol, 1 equiv) in dry DCM (10 mL), Et_3N (643 μL, 4.62 mmol, 1.2 equiv) was added dropwise and the stirring was continued for 10 min at the same temperature. Methanesulfonyl chloride (293 μL, 3.85 mmol, equiv) was then added dropwise at 0 °C, and the temperature of the reaction was increased up to rt with continuation of the stirring. After completion of reaction (TLC), the reaction was quenched with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to obtain a crude mixture. The crude product (without purification) was dissolved in dry DMF (5 mL) and treated with NaN_3 (1.5 equiv), and the mixture was stirred at rt for 1−2.5 h. After completion of reaction (TLC), the solvent (DMF) was removed in vacuo, diluted with water, and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude mixture was subjected to silica gel (100−200 mesh) column chromatography and eluted with 5−10% ethyl acetate in

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

petroleum ether (v/v) to obtain the pure azide derivatives **S7** in 50−93% yields.

Procedure for the Synthesis of Amine Derivatives S8 (See Scheme S3 in the Supporting Information). To a well-stirred solution of azide derivative **S7** (2.81 mmol, 1 equiv) in a mixture of solvents (i.e., MeOH/MeCN = 1:1, 10 mL) was dropwise added *N*,*N*-diisopropylethylamine (1.5 mL, 8.42 mmol, 3 equiv) and the reaction mixture was stirred at rt for 5 min. Thereafter, 1,3-propanedithiol (0.6 mL, 5.61 mmol, 2 equiv) was added dropwise and the whole reaction mixture was stirred at rt for 2−4 h. After completion of reaction (TLC), the reaction was quenched with water (20 mL) and extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure; and the crude product was purified by silica gel (100−200 mesh) column chromatography eluting with 3−5% methanol in chloroform (v/v) to obtain the desired pure amine derivatives **S8** in 64−95% yields.

Procedure for the Synthesis of N-Tosylated Derivatives S9 (See Scheme S3 in the Supporting Information). To a well-stirred and cooled solution of amine derivative **S8** (2.32 mmol, 1 equiv) in dry DCM (8 mL) was added pyridine (242 μL, 3.01 mmol, 1.3 equiv) dropwise. Thereafter, *p*-toluenesulfonyl chloride (529 mg, 2.78 mmol, 1.2 equiv) was added portionwise at the same temperature and the reaction mixture was stirred at rt for 1−4 h. Upon completion of the reaction (TLC), it was quenched with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Then, the crude product was purified by silica gel (100−200 mesh) column chromatography eluting with 10−26% ethyl acetate in petroleum ether (v/v) to obtain the pure tosylated products **S10** in 72−90% yields.

Procedure for the Synthesis of Acetylene Derivatives S10 (See Scheme S3 in the Supporting Information). To a well-stirred solution of iodoamine derivative **S9** (1.21 mmol, 1 equiv) in a mixture of solvents (i.e., Et_3N/DMF = 2:1, 3 mL), $PdCl_2(PPh_3)_2$ (25.4 mg, 0.036 mmol, 3 mol %) was added. The reaction mixture was then cooled to 0 °C, and trimethylsilylacetylene (189 μL, 1.33 mmol, 1.1 equiv) and CuI (13.7 mg, 0.072 mmol, 6 mol %) were added subsequently to the reaction mixture. After stirring few minutes at 0 °C, the temperature of the reaction was allowed to rise to rt and stirring was continued for 1.5−4 h. Upon completion of reaction (TLC), solvent was removed under reduced pressure and extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was then purified by silica gel (100−200 mesh) column chromatography eluting with 10−26% ethyl acetate in petroleum ether to obtain a silylated acetylenic intermediate (70−85% yields), which (1.04 mmol, 1 equiv) was later dissolved in dry MeOH (10 mL) and treated with K_2CO_3 (14.4 mg, 0.104 mmol, 0.1 equiv); the reaction mixture was then stirred at room temperature for 0.5−1.75 h until completion (TLC). The reaction was immediately quenched with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified by silica gel (100−200 mesh) column chromatography eluting with 10−30% ethyl acetate in petroleum ether (v/v) to obtain pure acetylene derivatives **S10** in 85−96% yields.

Procedure for the Synthesis of the Ene−Yne Substrates 8a (See Scheme S3 in the Supporting Information). To a well-stirred solution of commercially available 2-iodophenylacetonitrile (0.41 mmol, 1 equiv) in a mixture of solvents (Et_3N/DMF = 2:1, 2 mL) was added $PdCl_2(PPh_3)_2$ (8.6 mg, 0.012 mmol, 3 mol %). The whole reaction mixture was then cooled to 0 °C and the acetylenic intermediate **S10** (0.45 mmol, 1.1 equiv) dissolved in a mixture of solvents (i.e., Et_3N/DMF = 2:1) was added dropwise followed by CuI (4.6 mg, 0.024 mmol, 6 mol %). The temperature of the reaction was then increased to rt, and the stirring was continued for 1−8 h until completion of the reaction. Upon completion of reaction (TLC), the solvent was removed under reduced pressure and the crude material was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified by silica gel (100−200 mesh) column chromatography eluting with 10−30% ethyl acetate in petroleum ether (v/v) to obtain the requisite ene−yne substrates **8a** in 60−96% yields.

*Spectral Data of Starting Materials **8aa**−**aj**. (E)-N-(2-Benzylidene-4-(2-(cyanomethyl)phenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (**8aa**).* Pale yellow solid (105 mg, 60%), R_f = 0.35 (25% ethyl acetate in petroleum ether, v/v), mp 106−108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.77 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 6.9 Hz, 2H), 7.46−7.43 (m, 2H), 7.40−7.31 (m, 5H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.69 (s, 1H), 5.29 (t, *J* = 6 Hz, 1H), 3.95 (d, *J* = 6 Hz, 2H), 3.79 (s, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 137.4, 137.3, 135.3, 132.6, 131.7, 129.6, 129.4, 128.9, 128.6, 128.4, 128.3, 128.2, 127.1, 122.3, 117.6, 116.6, 93.1, 49.9, 22.8, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{23}N_2O_2S$ $[M + H]^+$ 427.1480, found 427.1480.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(naphthalen-2-ylmethylene)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ab**).* Light yellow solid (147 mg, 75%), R_f = 0.26 (25% ethyl acetate in petroleum ether, v/v), mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.06 (s, 1H), 7.90−7.77 (m, 6H), 7.51−7.34 (m, 6H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.85 (s, 1H), 5.11 (t, *J* = 6.3 Hz, 1H), 4.02 (d, *J* = 6 Hz, 2H), 3.81 (s, 2H), 2.32(s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 137.5, 137.4, 133.3, 133.0, 132.8, 132.6, 131.7, 129.6, 129.5, 128.7, 128.5, 128.3, 128.2, 127.8, 127.7, 127.2, 126.7, 126.5, 125.7, 116.8, 93.4, 93.3, 50.1, 22.9, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{24}N_2NaO_2S$ $[M + Na]^+$ 499.1456, found 499.1469.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(furan-2-ylmethylene)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ac**).* Brown solid (130 mg, 76%), R_f = 0.31 (25% ethyl acetate in petroleum ether, v/v), mp 102−104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.75 (d, *J* = 8.4 Hz, 2H), 7.48−7.31 (m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 3.3 Hz, 1H), 6.57 (s, 1H), 6.46−6.44 (m, 1H), 5.29−5.25 (m, 1H), 3.91 (s, 2H), 3.88 (d, *J* = 6.3 Hz, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 151.3, 143.4, 142.8, 137.2, 132.5, 131.8, 129.5, 129.4, 128.3, 128.1, 127.1, 124.9, 122.4, 117.8, 113.5, 111.9, 111.8, 94.2, 93.1, 49.0, 22.6, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{20}N_2NaO_3S$ $[M + Na]^+$ 439.1092, found 439.1092.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(thiophen-2-ylmethylene)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ad**).* Yellow solid (160 mg, 90%), R_f = 0.33 (25% ethyl acetate in petroleum ether, v/v), mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.74 (d, *J* = 8.4 Hz, 2H), 7.58−7.55 (m, 1H), 7.47−7.36 (m, 3H), 7.32 (d, *J* = 5.1 Hz, 1H), 7.19−7.16 (m, 3H), 7.03−7.00 (m, 1H), 6.91 (s, 1H), 5.34 (t, *J* = 6 Hz, 1H), 3.92 (d, *J* = 6.3 Hz, 2H), 3.89 (s, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 139.3, 137.4, 132.5, 131.7, 131.0, 130.6, 129.6, 129.5, 128.4, 128.2, 127.5, 127.1, 126.6, 122.4, 117.8, 113.6, 96.4, 93.3, 49.2, 23.0, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{20}N_2NaO_2S_2$ $[M + Na]^+$ 455.0864, found 455.0868.

*(E)-N-(2-(4-Chlorobenzylidene)-4-(2-(cyanomethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ae**).* Pale yellow solid (165 mg, 87%), R_f = 0.33 (25% ethyl acetate in petroleum ether, v/v), mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.46−7.31 (m, 6H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.66 (s, 1H), 5.14 (t, *J* = 6.3 Hz, 1H), 3.95 (d, *J* = 6.3 Hz, 2H), 3.80 (s, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 137.5, 135.8, 134.5, 133.7, 132.7, 131.7, 129.8, 129.7, 129.6, 128.6, 128.5, 128.3, 127.1, 122.2, 117.4, 117.3, 93.8, 92.8, 49.9, 22.9, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{21}ClN_2NaO_2S$ $[M + Na]^+$ 483.0910, found 483.0910.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(4-methylbenzylidene)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8af**).* White solid (174 mg, 96%), R_f = 0.38 (25% ethyl acetate in petroleum ether, v/v), mp 116−118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.45−7.43 (m, 2H), 7.39−7.29 (m, 2H), 7.20−7.14 (m, 4H), 6.64 (s, 1H), 5.40 (brs, 1H), 3.92 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.3, 139.0, 137.4, 137.3, 132.5, 131.6, 129.5, 129.3, 128.9, 128.5, 128.2, 128.1, 127.1, 122.3, 117.7, 115.4, 93.3, 92.9, 49.9, 22.7, 21.4, 21.3; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{24}N_2NaO_2S$ $[M + Na]^+$ 463.1456, found 463.1458.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(4-methoxybenzylidene)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ag**).* Yellow solid (173 mg, 92%), R_f = 0.29 (25% ethyl acetate in petroleum ether, v/

DOI: 10.1021/acs.joc.9b00861
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v), mp 118−120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.46−7.43 (m, 2H), 7.40−7.31 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.62 (s, 1H), 5.25−5.23 (m, 1H), 3.91 (d, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 160.0, 143.4, 137.5, 137.1, 132.6, 131.6, 130.2, 129.6, 129.3, 128.4, 128.2, 128.1, 127.2, 122.5, 117.7, 113.9, 113.7, 93.6, 92.8, 55.3, 50.1, 22.9, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{24}N_2NaO_3S$ [M + Na]$^+$ 479.1405, found 479.1409.

*(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(3-methoxybenzylidene)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ah**).* Pale yellow solid (163 mg, 87%), R_f = 0.29 (25% ethyl acetate in petroleum ether, v/v), mp 124−126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.77 (d, J = 8.1 Hz, 2H), 7.48−7.28 (m, 6H), 7.26−7.15 (m, 3H), 6.87 (dd, J = 8.1, 1.8 Hz, 1H), 6.67 (s, 1H), 5.13 (t, J = 6.4 Hz, 1H), 3.95 (d, J = 6.3 Hz, 2H), 3.83 (s, 2H), 3.80 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 159.3, 143.4, 137.4, 137.1, 136.6, 132.6, 131.8, 129.6, 129.5, 129.3, 128.2, 128.1, 127.1, 122.2, 121.4, 117.7, 117.0, 114.2, 113.9, 93.5, 93.0, 55.2, 49.9, 22.9, 21.4; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ [M + H]$^+$ 457.1586, found 457.1590.

*(E)-N-(2-Benzylidene-4-(2-(cyanomethyl)-4,5-dimethoxyphenyl)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ai**).* Yellow solid (162 mg, 81%), R_f = 0.13 (25% ethyl acetate in petroleum ether, v/v), mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.78 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 6.9 Hz, 2H), 7.39−7.31 (m, 3H), 7.26−7.23 (m, 2H), 6.95 (s, 1H), 6.90 (s, 1H), 6.65 (s, 1H), 5.05 (t, J = 6.4 Hz, 1H), 3.95−3.94 (m, 5H), 3.90 (s, 3H), 3.75 (s, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 150.3, 148.6, 143.5, 137.6, 136.6, 135.6, 129.7, 128.8, 128.6, 128.3, 127.2, 125.1, 118.0, 117.1, 114.9, 114.4, 111.2, 93.7, 91.6, 56.3, 56.2, 50.0, 22.4, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{26}N_2NaO_4S$ [M + Na]$^+$ 509.1511, found 509.1514.

*(E)-Methyl 3-(Cyanomethyl)-4-(3-((4-methylphenylsulfonamido)methyl)-4-phenylbut-3-en-1-yn-1-yl)-benzoate (**8aj**).* Light yellow solid (175 mg, 88%), R_f = 0.22 (25% ethyl acetate in petroleum ether, v/v), mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.09 (s, 1H), 7.98 (dd, J = 8.1, 1.2 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.66−7.63 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.37−7.32 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 5.33 (t, J = 6.4 Hz, 1H), 3.96−3.94 (m, 5H), 3.83 (s, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 165.8, 143.5, 138.5, 137.4, 135.1, 132.7, 132.0, 130.5, 129.6, 129.5, 129.3, 129.1, 128.7, 128.4, 127.1, 126.8, 117.2, 116.4, 96.0, 92.2, 52.5, 49.8, 22.8, 21.4; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_4S$ [M + H]$^+$ 485.1535, found 485.1539.

General Procedure for the Synthesis of Products 2a. To a well-stirred solution of $Pd(OAc)_2$ (2.58 mg, 0.011 mmol, 5 mol %) and bpy (3.59 mg, 0.023 mmol, 10 mol %) in dry THF (1.5 mL), *p*-TsOH·H_2O (87.4 mg, 0.46 mmol, 2 equiv) was added and the mixture was heated to reflux under argon atmosphere. Next, **8a** (0.23 mmol, 1 equiv) dissolved in dry THF (1.5 mL) was added dropwise and heating was continued for another 4−12 h. Upon completion of reaction (TLC), the reaction mixture was neutralized by adding 10% aqueous sodium bicarbonate solution (to pH ∼ 7) dropwise. It was then extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 10−18% ethyl acetate in petroleum ether to afford the pure products (**2aa**−**aj**) in 24−82% yields.

*Spectral Data of Products **2aa**−**aj**. 3-Benzyl-1-tosyl-1H-benzo-[g]indol-4-amine (**2aa**).* Brown solid (73.5 mg, 75%), R_f = 0.24 (15% ethyl acetate in petroleum ether, v/v), mp 146−148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.93 (d, J = 8.1 Hz, 1H), 7.60−7.54 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.34−7.26 (m, 5H), 7.12−7.08 (m, 4H), 6.70 (s, 1H), 4.28 (s, 2H), 3.73 (brs, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.8, 139.3, 139.0, 135.0, 133.92, 133.90, 129.7, 129.0, 128.5, 128.3, 127.0, 126.9, 126.3, 125.3, 124.4, 122.8, 122.1, 121.2, 119.1, 107.6, 32.8, 21.6; HRMS (ESI) m/z calcd for $C_{26}H_{22}N_2NaO_2S$ [M + Na]$^+$ 449.1300, found 449.1300.

*3-(Naphthalen-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ab**).* Brown solid (85.4 mg, 78%), R_f = 0.25 (15% ethyl acetate in petroleum ether, v/v), mp 196−198 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.97 (d, J = 9 Hz, 1H), 7.84−7.82 (m, 1H), 7.80 (d, J = 9 Hz, 1H), 7.69 (s, 1H), 7.66−7.64 (m, 1H), 7.56−7.54 (m, 3H), 7.49−7.46 (m, 3H), 7.34−7.28 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 6.68 (s, 1H), 4.45 (s, 2H), 3.76 (brs, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.8, 139.0, 137.0, 135.0, 133.8, 133.7, 133.6, 132.4, 129.7, 128.8, 128.5, 127.7, 127.6, 126.9, 126.6, 126.5, 126.4, 126.3, 125.9, 125.3, 124.3, 122.8, 122.1, 120.7, 118.9, 107.6, 32.9, 21.6; HRMS (ESI) m/z calcd for $C_{30}H_{25}N_2O_2S$ [M + H]$^+$ 477.1637, found 477.1639.

*3-(Furan-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ac**).* Brown solid (65.1 mg, 68%), R_f = 0.20 (15% ethyl acetate in petroleum ether, v/v), mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.90 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.39−7.38 (m, 1H), 7.33−7.30 (m, 1H), 7.27−7.25 (m, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.76 (s, 1H), 6.30−6.29 (m, 1H), 5.86−5.85 (m, 1H), 4.27 (s, 2H), 3.96 (brs, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 153.7, 144.8, 142.1, 138.9, 134.9, 133.7, 133.3, 129.7, 128.2, 126.9, 126.3, 125.2, 124.1, 122.8, 121.8, 118.9, 118.5, 110.6, 107.9, 106.7, 26.3, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_3S$ [M + H]$^+$ 417.1273, found 417.1304.

*3-(Thiophen-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ad**).* Brown solid (75.5 mg, 76%), R_f = 0.21 (15% ethyl acetate in petroleum ether, v/v), mp 174−176 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.94 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.28−7.26 (m, 1H), 7.21 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.93−6.92 (m, 1H), 6.73 (s, 1H), 6.70−6.69 (m, 1H), 4.43 (s, 2H), 3.86 (brs, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.9, 143.4, 138.9, 134.9, 133.8, 133.6, 129.8, 128.1, 127.2, 126.9, 126.3, 125.3, 125.2, 125.1, 124.2, 122.8, 121.7, 120.7, 118.9, 107.7, 27.7, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_2S_2$ [M + H]$^+$ 433.1044, found 433.1046.

*3-(4-Chlorobenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ae**).* Brown solid (86.7 mg, 82%), R_f = 0.22 (15% ethyl acetate in petroleum ether, v/v), mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 8.4 Hz, 1H), 7.58−7.56 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.29−7.25 (m, 3H), 7.11 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 4.24 (s, 2H), 3.71 (brs, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.9, 138.7, 137.7, 134.9, 133.8, 133.7, 132.7, 129.7, 129.6, 129.1, 128.4, 126.9, 126.3, 125.4, 124.3, 122.9, 121.8, 120.5, 118.9, 107.7, 32.2, 21.6; HRMS (ESI) m/z calcd for $C_{26}H_{22}ClN_2O_2S$ [M + H]$^+$ 461.1091, found 461.1097.

*3-(4-Methylbenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2af**).* Brown solid (78.9 mg, 78%), R_f = 0.27 (15% ethyl acetate in petroleum ether, v/v), mp 178−180 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 9 Hz, 1H), 7.59 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.33−7.30 (m, 1H), 7.28−7.25 (m, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 7.8 Hz, 2H), 6.70 (s, 1H), 4.23 (s, 2H), 3.77 (brs, 2H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.7, 139.0, 136.5, 136.1, 134.9, 133.8, 129.7, 129.6, 128.4, 128.1, 126.9, 126.2, 125.3, 124.3, 122.7, 122.1, 121.4, 119.0, 107.5, 32.3, 21.6, 21.1; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_2S$ [M + H]$^+$ 441.1637, found 441.1640.

*3-(4-Methoxybenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ag**).* Pale brown solid (25.2 mg, 24%), R_f = 0.18 (15% ethyl acetate in petroleum ether, v/v), mp 190−192 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.31 (td, J = 7.5, 0.8 Hz, 1H), 7.28−7.26 (m, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 6.70 (s, 1H), 4.21 (s, 2H), 3.79−3.77 (m, 5H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 158.5, 144.6, 138.9, 134.9, 133.81, 133.80, 131.0, 129.6, 129.2, 128.3, 126.9, 126.2, 125.2, 124.3, 122.7, 122.0, 121.6, 118.9, 114.3, 107.4, 55.2, 31.8, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ [M + H]$^+$ 457.1586, found 457.1592.

*3-(3-Methoxybenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (**2ah**).* Pale yellow solid (83.9 mg, 80%), R_f = 0.16 (15% ethyl acetate in petroleum ether, v/v), mp 142−144 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.95 (d, J = 9 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.29−7.27 (m, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 8.1, 2.1 Hz, 1H), 6.72 (s, 1H), 6.69−6.67 (m, 2H), 4.25 (s, 2H), 3.76 (s, 5H), 2.29 (s, 3H);

DOI: 10.1021/acs.joc.9b00861
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$^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 160.1, 144.7, 140.9, 138.9, 134.9, 133.8, 133.7, 129.9, 129.6, 128.4, 126.8, 126.2, 125.2, 124.2, 122.7, 121.9, 120.8, 120.4, 118.9, 114.2, 111.9, 107.5, 55.1, 32.7, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ $[M + H]^+$ 457.1586, found 457.1576.

*3-Benzyl-7,8-dimethoxy-1-tosyl-1H-benzo[g]indol-4-amine (**2ai**).* Brown solid (72.7 mg, 65%), R_f = 0.08 (15% ethyl acetate in petroleum ether, v/v), mp 148−150 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.46 (s, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.28−7.22 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 6.6 Hz, 2H), 6.89 (s, 1H), 6.62 (s, 1H), 4.24 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.62 (brs, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 148.6, 146.7, 144.6, 139.2, 137.4, 134.8, 133.8, 129.6, 129.5, 128.9, 128.2, 127.9, 126.8, 126.6, 121.9, 120.9, 114.1, 107.4, 105.4, 104.9, 56.0, 55.6, 32.7, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{27}N_2O_4S$ $[M + H]^+$ 487.1692, found 487.1684.

*Methyl 4-Amino-3-benzyl-1-tosyl-1H-benzo[g]indole-7-carboxylate (**2aj**).* Yellow solid (61.2 mg, 55%), R_f = 0.14 (15% ethyl acetate in petroleum ether, v/v), mp 178−180 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.97 (d, J = 9 Hz, 1H), 8.29 (s, 1H), 7.84 (dd, J = 8.7, 1.8 Hz, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.31−7.29 (m, 2H), 7.27−7.25 (m, 1H), 7.13−7.10 (m, 4H), 6.77 (s, 1H), 4.29 (s, 2H), 3.94 (s, 3H), 3.84 (brs, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 167.5, 145.1, 139.8, 139.0, 134.7, 133.2, 133.0, 129.8, 129.5, 129.1, 129.0, 128.2, 127.1, 126.9, 126.4, 124.4, 123.6, 122.2, 120.9, 120.8, 108.1, 52.2, 32.7, 21.6; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_4S$ $[M + H]^+$ 485.1535, found 485.1538.

Preparation of the Ene−Yne Substrates 8b (See Scheme S4 in the Supporting Information). The requisite starting material **8b** was synthesized as depicted in Scheme S4. The starting compound **S4**[19] was synthesized by executing the Wittig reaction on 2-iodobenzaldehyde derivative, which underwent coupling with **S10** (see Scheme S3 in the Supporting Information) under Sonogashira reaction conditions resulting in the formation of **S11**. Finally, exposure of **S11** under acidic conditions led to **8b**.

Procedure for the Synthesis of Intermediates S11 (See Scheme S4 in the Supporting Information). To a well-stirred solution of **S4** (0.77 mmol, 1 equiv) in dry Et_3N/DMF (3:1, 0.7 mL) was added $Pd(PPh_3)_2Cl_2$ (16.2 mg, 0.023 mmol, 3 mol %). The whole reaction mixture was cooled to 0 °C; thereafter, **S10** (0.85 mmol, 1.1 equiv) dissolved in a mixture of solvents [i.e., Et_3N/DMF (2:1), 0.6 mL] and CuI (8.74 mg, 0.046 mmol, 6 mol %) was added sequentially. The reaction mixture was then stirred at rt for 2−7 h. After completion of the reaction (TLC), solvent was removed in vacuo, diluted with water (15 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. Then, the crude product was subjected to silica gel (100−200 mesh) column chromatography and eluted with 10−15% ethyl acetate in petroleum ether (v/v) to obtain pure **S11** derivatives in 60−85% yields.

Synthesis of the Ene−Yne Substrates 8b (See Scheme S4 in the Supporting Information). To a well-stirred and cooled (0 °C) solution of the masked aldehydes **S11** (0.45 mmol, 1 equiv) in a minimum amount of dry acetone (3 mL) was added p-TsOH·H_2O (0.72 mmol, 1.6 equiv, 136.8 mg) portionwise. The temperature of the reaction mixture was allowed to reach rt and stirring was continued for another 3.5−5 h. After completion of reaction (TLC), the reaction mixture was neutralized with dilute sodium bicarbonate solution and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, and the crude residue was subjected to silica gel (100−200 mesh) column chromatography eluting with 17−30% ethyl acetate in petroleum ether (v/v) to obtain the desired starting materials **8b** in 47−70% yields.

*Spectral Data of Starting Materials **8ba−bh**. (E)-N-(2-Benzylidene-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8ba**).* White solid (118 mg, 61%), R_f = 0.22 (20% ethyl acetate in petroleum ether, v/v), mp 94−96 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.2 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.39−7.28 (m, 6H), 7.19 (d, J = 7.8 Hz, 2H), 6.62 (s, 1H), 5.46 (t, J = 6 Hz, 1H), 3.93 (d, J = 6.6 Hz, 2H), 3.85−3.84 (m, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 143.2, 137.6, 136.9, 135.4, 133.7, 132.6, 130.5, 129.5, 129.3, 128.7, 128.6, 128.2, 127.7, 127.2, 123.5, 116.6, 94.4, 91.7, 50.1, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{23}NNaO_3S$ $[M + Na]^+$ 452.1296, found 452.1298.

*(E)-4-Methyl-N-(2-(naphthalen-2-ylmethylene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)benzene-sulfonamide (**8bb**).* Pale yellow solid (112 mg, 52%), R_f = 0.19 (20% ethyl acetate in petroleum ether, v/v), mp 108−110 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.4 Hz, 1H), 8.06 (s, 1H), 7.86−7.84 (m, 1H), 7.82−7.78 (m, 5H), 7.51−7.47 (m, 3H), 7.40−7.37 (m, 1H), 7.35−7.33 (m, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 6.77(s, 1H), 5.56 (t, J = 6.3 Hz, 1H), 3.99 (d, J = 6.6 Hz, 2H), 3.87 (d, J = 2.4 Hz, 2H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 143.2, 137.7, 136.9, 133.7, 133.3, 133.1, 133.0, 132.5, 130.5, 129.5, 129.4, 128.6, 128.2, 127.8, 127.7, 127.6, 127.2, 126.6, 126.4, 125.8, 123.5, 117.0, 94.6, 92.1, 50.2, 49.7, 21.4; HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1456.

*(E)-N-(2-(4-Chlorobenzylidene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8bc**).* White solid (137 mg, 66%), R_f = 0.20 (20% ethyl acetate in petroleum ether, v/v), mp 136−138 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.1 Hz, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.45−7.43 (m, 1H), 7.41−7.38 (m, 1H), 7.35−7.33 (m, 1H), 7.32−7.30 (m, 3H), 7.19 (d, J = 7.8 Hz, 2H), 6.58 (s, 1H), 5.50 (t, J = 6.6 Hz, 1H), 3.92 (d, J = 6.6 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 143.3, 137.7, 135.4, 134.3, 133.8, 133.6, 132.6, 130.6, 129.8, 129.6, 129.5, 128.4, 127.8, 127.2, 123.3, 117.4, 95.1, 91.4, 50.0, 49.7, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{22}ClNNaO_3S$ $[M + Na]^+$ 486.0907, found 486.0908.

*(E)-4-Methyl-N-(4-(2-(2-oxoethyl)phenyl)-2-(4-(trifluoromethyl)-benzylidene)but-3-yn-1-yl)benzene-sulfonamide (**8bd**).* White solid (155 mg, 70%), R_f = 0.30 (25% ethyl acetate in petroleum ether, v/v), mp 154−156 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.1 Hz, 1H), 7.78−7.74 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 7.8, 0.9 Hz, 1H), 7.41−7.39 (m, 1H), 7.35−7.30 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 5.67 (t, J = 6.6 Hz, 1H), 3.94 (d, J = 6.6 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 143.3, 138.8, 137.7, 134.8, 133.7, 132.6, 130.6, 130.1 (q, J_{C-F} = 32.3 Hz), 129.7, 129.5, 128.7, 127.8, 127.2, 125.1 (q, J_{C-F} = 3.6 Hz), 123.9 (app q, J = 270.5 Hz), 123.1, 119.5, 95.5, 91.1, 49.9, 49.7, 21.3; HRMS (ESI) m/z calcd for $C_{27}H_{22}F_3NNaO_3S$ $[M + Na]^+$ 520.1170 found, 520.1169.

*(E)-4-Methyl-N-(2-(4-methylbenzylidene)-4-(2-(2-oxoethyl)-phenyl)but-3-yn-1-yl)benzene-sulfonamide (**8be**).* White solid (119 mg, 60%), R_f = 0.22 (20% ethyl acetate in petroleum ether, v/v), mp 96−98 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.67−9.66 (m, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.37−7.26 (m, 3H), 7.18 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.59 (s, 1H), 5.53 (t, J = 6.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 2H), 3.85 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.2, 143.2, 138.8, 137.6, 137.0, 133.7, 132.6, 132.5, 130.4, 129.5, 129.2, 128.9, 128.6, 127.6, 127.2, 123.6, 115.5, 94.4, 92.0, 50.1, 49.6, 21.4, 21.3; HRMS (ESI) m/z calcd for $C_{27}H_{25}NNaO_3S$ $[M + Na]^+$ 466.1453 found 466.1455.

*(E)-N-(2-(3-Methoxybenzylidene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8bf**).* Yellow liquid (97 mg, 47%), R_f = 0.15 (20% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66−9.65 (m, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.37−7.34 (m, 1H), 7.31−7.29 (m, 2H), 7.27−7.23 (m, 2H), 7.19−7.17 (m, 3H), 6.84 (dd, J = 7.8, 2.1 Hz, 1H), 6.60 (s, 1H), 5.62 (t, J = 6.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 2H), 3.86−3.85 (m, 2H), 3.77 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 159.3, 143.2, 137.6, 136.7, 133.8, 132.5, 130.5, 129.5, 129.3, 129.2, 127.6, 127.2, 123.4, 121.4, 117.0, 114.2, 113.9, 94.8, 91.7, 55.2, 50.0, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{27}H_{25}NNaO_4S$ $[M + Na]^+$ is 482.1402, found 482.1407.

*(E)-N-(2-Benzylidene-4-(4,5-dimethoxy-2-(2-oxoethyl)phenyl)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8bg**).* Yellow gum (125 mg, 57%), R_f = 0.06 (20% ethyl acetate in petroleum ether, v/

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.64 (t, J = 2.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.33−7.31 (m, 2H), 7.29−7.28 (m, 1H), 7.20 (d, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 5.43 (t, J = 6.6 Hz, 1H), 3.92−3.91 (m, 5H), 3.89 (s, 3H), 3.78 (d, J = 2.4 Hz, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 150.1, 148.2, 143.3, 137.6, 136.0, 135.5, 129.5, 128.6, 128.5, 128.2, 127.2, 127.1, 117.0, 115.4, 114.8, 113.0, 94.9, 90.3, 56.1, 56.0, 50.1, 49.2, 21.4; HRMS (ESI) m/z calcd for $C_{28}H_{27}NNaO_5S$ [M + Na]$^+$ 512.1508, found 512.1503.

*(E)-N-(2-Benzylidene-4-(4-fluoro-2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (**8bh**).* White solid (110 mg, 55%), R_f = 0.23 (20% ethyl acetate in petroleum ether, v/v), mp 80−82 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.67 (t, J = 1.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.45−7.43 (m, 1H), 7.34−7.28 (m, 3H), 7.20 (d, J = 7.8 Hz, 2H), 7.03−6.98 (m, 2H), 6.62 (s, 1H), 5.44 (t, J = 6.3 Hz, 1H), 3.90 (d, J = 6.6 Hz, 2H), 3.86−3.85 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 198.2, 162.6 (d, J = 250.6 Hz), 143.3, 137.5, 136.9, 136.5 (d, J = 7.8 Hz), 135.4, 134.4 (d, J = 8.5 Hz), 129.6, 128.7, 128.6, 128.2, 127.1, 119.6 (d, J = 3.3 Hz), 117.6 (d, J = 22.2 Hz), 116.7, 115.0 (d, J = 21.6 Hz), 93.5, 91.4, 50.0, 49.3, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{22}FNNaO_3S$ [M + Na]$^+$ 470.1202, found 470.1200.

General Procedure for the Synthesis of Products 2b. To a well-stirred and heated (85 °C) reaction mixture of $Pd(OAc)_2$bpy (4.37 mg, 0.011 mmol, 5 mol %) and p-TsOH·H_2O (65.5 mg, 0.34 mmol, 1.5 equiv) in dry DME (1.5 mL) was dropwise added a solution of **8b** (0.23 mmol, 1 equiv) dissolved in dry DME (1.5 mL). The heating was continued until completion of the reaction (TLC). The solvent was then removed under reduced pressure. The crude material obtained was directly loaded onto silica gel (100−200 mesh) column for purification. The desired products **2ba**−**bh** were eluted with 1−6% ethyl acetate−petroleum (v/v) and isolated in 27−68% yields.

*Spectral Data of Products **2ba**−**bh**. 3-Benzyl-1-tosyl-1H-benzo[g]indole (**2ba**).* White solid (57.7 mg, 61%), R_f = 0.56 (10% ethyl acetate in petroleum ether, v/v), mp 106−108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.09 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.62−7.39 (m, 7H), 7.31−7.16 (m, 5H), 7.08 (d, J = 8.1 Hz, 2H), 4.09 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.6, 139.1, 135.0, 132.3, 131.6, 129.9, 129.6, 128.8, 128.52, 128.50, 127.6, 126.7, 126.4, 126.2, 125.8, 124.7, 124.1, 123.6, 122.9, 118.1, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{26}H_{22}NO_2S$ [M + H]$^+$ 412.1371, found 412.1368.

*3-(Naphthalen-2-ylmethyl)-1-tosyl-1H-benzo[g]indole (**2bb**).* Light brown solid (46.4 mg, 44%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 160−162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.13 (d, J = 9 Hz, 1H), 7.85−7.82 (m, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.48−7.43 (m, 4H), 7.33 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 4.26 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.6, 136.7, 135.0, 133.5, 132.3, 132.2, 131.7, 130.0, 129.6, 128.8, 128.1, 127.7, 127.6, 127.5, 127.1, 126.8, 126.7, 126.3, 126.0, 125.9, 125.5, 124.7, 124.1, 123.6, 122.7, 118.2, 31.4, 21.5; HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_2S$ [M + H]$^+$ 462.1528, found 462.1526.

*3-(4-Chlorobenzyl)-1-tosyl-1H-benzo[g]indole (**2bc**).* White solid (69.6 mg, 68%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.08 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.62−7.41 (m, 6H), 7.36 (d, J = 8.4 Hz, 1H), 7.25−7.22 (m, 2H), 7.11−7.07 (m, 4H), 4.06 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 144.8, 137.7, 135.0, 132.3, 132.2, 131.8, 131.7, 129.9, 129.6, 128.9, 128.6, 127.6, 126.7, 126.4, 125.9, 124.9, 124.1, 123.6, 122.3, 118.0, 30.6, 21.5; HRMS (ESI) m/z calcd for $C_{26}H_{21}ClNO_2S$ [M + H]$^+$ 446.0982, found 446.0984.

*1-Tosyl-3-(4-(trifluoromethyl)benzyl)-1H-benzo[g]indole (**2bd**).* Pale yellow solid (71.6 mg, 65%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 126−128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.09 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.64−7.61 (m, 2H), 7.57−7.42 (m, 6H), 7.36 (d, J = 8.4 Hz, 1H), 7.30−7.26 (m, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.15 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.8, 143.3, 135.0, 132.3, 131.6, 129.6, 129.5, 128.9, 128.8, 128.7 (q, J_{C-F} = 32.3 Hz), 127.6, 126.7, 126.4, 126.0, 125.4 (q, J_{C-F} = 3.8 Hz), 124.9, 124.2 (q, J_{C-F}= 270.2 Hz), 124.1, 123.5, 121.7, 117.8, 31.0, 21.5; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −162.3 (s, 3F); HRMS (ESI) m/z calcd for $C_{27}H_{21}F_3NO_2S$ [M + H]$^+$ is 480.1245, found 480.1240.

*3-(4-Methylbenzyl)-1-tosyl-1H-benzo[g]indole (**2be**).* Yellow gum (40.1 mg, 41%), R_f = 0.56 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.09 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.60−7.58 (m, 2H), 7.54−7.50 (m, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.44−7.39 (m, 2H), 7.09−7.05 (m, 6H), 4.04 (s, 2H), 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_c 144.7, 136.1, 136.0, 135.2, 132.4, 131.8, 130.1, 129.7, 129.3, 128.9, 128.5, 127.6, 126.8, 126.3, 125.9, 124.8, 124.3, 123.7, 123.5, 118.3, 30.9, 21.6, 21.1; HRMS (ESI) m/z calcd for $C_{27}H_{24}NO_2S$ [M + H]$^+$ 426.1528, found 426.1526.

*3-(3-Methoxybenzyl)-1-tosyl-1H-benzo[g]indole (**2bf**).* Yellow solid (30.4 mg, 30%), R_f = 0.39 (10% ethyl acetate in petroleum ether, v/v), mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.10 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.63−7.60 (m, 2H), 7.55−7.52 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.45−7.42 (m, 2H), 7.20 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.78−6.77 (m, 3H), 4.07 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_c 159.7, 144.6, 140.7, 135.0, 132.3, 131.6, 129.9, 129.6, 129.5, 128.8, 127.6, 126.7, 126.2, 125.8, 124.7, 124.1, 123.6, 122.6, 120.9, 118.1, 114.5, 111.4, 55.1, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{24}NO_3S$ [M + H]$^+$ 442.1477, found 442.1477.

*3-Benzyl-7,8-dimethoxy-1-tosyl-1H-benzo[g]indole (**2bg**).* Light brown solid (42.2 mg, 39%), R_f = 0.15 (10% ethyl acetate in petroleum ether, v/v), mp 158−160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.60 (s, 1H), 7.49−7.47 (m, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.28−7.21 (m, 4H), 7.16−7.15 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 4.06−4.05 (m, 5H), 3.99 (s, 3H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_c 149.2, 148.1, 144.5, 139.1, 135.0, 131.8, 129.5, 129.2, 128.5, 128.4, 128.1, 127.2, 126.4, 126.3, 124.5, 123.7, 119.2, 116.2, 107.6, 104.5, 56.1, 55.7, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{26}NO_4S$ [M + H]$^+$ 472.1583, found 472.1584.

*3-Benzyl-7-fluoro-1-tosyl-1H-benzo[g]indole (**2bh**).* Yellow solid (26.6 mg, 27%), R_f = 0.54 (10% ethyl acetate in petroleum ether, v/v), mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.14−9.12 (m, 1H), 7.58 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.47−7.42 (m, 4H), 7.32−7.26 (m, 3H), 7.24−7.22 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 4.08 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_c 159.6 (d, J = 244.5 Hz), 144.8, 139.0, 134.8, 133.5 (d, J = 8.5 Hz), 131.8, 129.6, 129.4, 128.5, 128.4, 127.4, 126.8 (d, J = 8.7 Hz), 126.7, 126.4, 125.0 (d, J = 4.5 Hz), 123.1, 120.6, 119.4, 115.9 (d, J = 24.0 Hz), 112.1 (d, J = 20.5 Hz), 31.2, 21.5; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −116.5 (s, 1F); HRMS (ESI) m/z calcd for $C_{26}H_{21}FNO_2S$ [M + H]$^+$ 430.1277, found 430.1275.

Procedure for the Preparation of Detosylated Products 2ak and 2bi. To a well-stirred solution of **2aa** or **2ba** (0.12 mmol, 1 equiv) in dry THF was added tetrabutylammonium fluoride (1 M solution in THF, 5 equiv), and the mixture was stirred for 2 h under refluxing conditions. It was then poured into water (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 5−10% ethyl acetate in petroleum ether as eluent to afford pure detosylated products **2ak** and **2bi** in 65−67% yield.

*4-Amino-3-benzyl-1H-benzo[g]indole (**2ak**).* Light brown solid (21.2 mg, 65%), R_f = 0.32 (20% ethyl acetate in petroleum ether, v/v), mp 160−162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.72 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.33−7.26 (m, 6H), 7.24−7.21 (m, 1H), 6.98 (s, 1H), 6.56 (s, 1H), 4.37 (s, 2H), 3.89 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_c 141.2, 140.4, 132.9, 132.3, 128.7, 128.4, 126.4, 126.1, 124.5, 121.8, 121.1, 119.0, 117.3, 115.8, 115.6, 101.0, 32.9; HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2$ [M + H]$^+$ 273.1392, found 273.1380.

*3-Benzyl-1H-benzo[g]indole (**2bi**).* Light brown solid (20.7 mg, 67%), R_f = 0.48 (20% ethyl acetate in petroleum ether, v/v), mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.68 (s, 1H), 7.95 (d, J = 8.0

DOI: 10.1021/acs.joc.9b00861
J. Org. Chem. 2019, 84, 8959−8975

Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.52−7.46 (m, 2H), 7.43−7.39 (m, 1H), 7.32−7.24 (m, 4H), 7.21−7.17 (m, 1H), 6.97 (s, 1H), 4.19 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_c 141.4, 131.1, 130.5, 129.0, 128.7, 128.4, 126.0, 125.5, 123.9, 123.3, 121.8, 120.6, 120.3, 119.4, 119.3, 117.6, 31.7; HRMS (ESI) m/z calcd for $C_{19}H_{16}N$ $[M + H]^+$ 258.1283, found 258.1277.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00861.

Oak ridge thermal ellipsoid plots of products **1ba**, **2aa**, **2ah**, and **2bd** along with their some important crystal data; schemes for the preparation of starting materials **7** and **8**; ^1H and ^{13}C NMR spectra for all compounds synthesized; and ^{19}F spectra of all fluorine-containing products (PDF)

Single-crystal data of products **1ba** (CIF)

Single-crystal data of products **2aa** (CIF)

Single-crystal data of products **2ah** (CIF)

Single-crystal data of products **2bd** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.J. acknowledges UGC, New Delhi, and S.D. and S.P. acknowledge CSIR, New Delhi, for fellowship. C.C. acknowledges CSIR-IICB for financial support.

■ DEDICATION

This paper is dedicated to Dr. Nitya G. Kundu, former Professor and Head, Dept. of Organic Chemistry, IACS, Kolkata, on the occasion of his 83rd birth anniversary.

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J. Org. Chem. 2019, 84, 8959−8975

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View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2020, **56**, 15659

Received 1st October 2020,
Accepted 18th November 2020

DOI: 10.1039/d0cc06538b

rsc.li/chemcomm

Palladium(II) catalysed cascade strategy for the synthesis of dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols/-10(15*H*)-ones: easy access to 1,3,5,7-cyclooctatetraenes (COTs)†

Sukanya De, Moumita Jash and Chinmay Chowdhury *

An atom-economic Pd(II)-catalysed cascade cyclisation of 2-(biphenylethynyl)anilines tethered to an aldehyde or cyano group leads to the formation of dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols 6 or dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-ones 8 with high yields (up to 95%). The reaction proceeds *via* amino-palladation of the alkyne followed by nucleophilic addition onto the aldehyde/cyano group. Treatment of 6 with *p*-TsOH·H_2O smoothly provided cyclooctatetraene (COT) derivatives 7.

Eight-membered carbocyclic rings serve as core structures in several important classes of bioactive natural products[1a] but are relatively difficult to access[1b,c] using conventional synthetic methods. Among them, 1,3,5,7-cyclooctatetraenes (COTs) find immense applications in diverse fields.[2] Besides, they have been identified to serve as a complement motif of cubane, a bioisostere of a phenyl ring, through validation in a number of pharmaceuticals and agrochemicals.[3] COTs fused with other rings give rise to diverse scaffolds which find potential applications in drug developments,[4] and in ligands for d- and f-block metals,[5] catalysts,[5a,6] and molecular devices[7] along with many uses in materials science.[8] In this regard, the degree and type of fusion[9] in COTs play a critical role in determining their usefulness.

Despite the availability of various synthetic variants,[10] COTs are rare in nature. To date, few indole alkaloids having a COT moiety as the core structure [*e.g.*, *caulerpin* (**1a**), its analogues **1b** and **1c**,[11a] and *jolynamine*[11b] (**2**)] have been reported (Fig. S1, ESI†). *Caulerpin* exhibits potent inhibitory activity[12a] (IC_{50} = 3.77 μM) against hPTP1B (human protein tyrosine phosphate 1B), a key target for the treatment of type II diabetes and obesity,[12b] in addition to its role as an antitumor agent.[12c] Nevertheless, there have been limited achievements to date for the efficient construction of indole-fused COTs.[13]

Though COTs fused with arenes/hetero-arenes at four[8a,14] or two[4,5a,15] double bonds are well-studied, the synthesis of COTs fused at three double bonds[16] are less in number. Among them, the synthesis of hybrid COTs, *i.e.*, those fused with an indole ring and two arene rings, has not yet been reported, underlining the urgency for their facile and general synthesis.

In contrast to COTs, 2,4,6-cyclooctatrien-1-ones are less explored though their synthesis has become an active area of research in the last century leading to the development of a number of reactions.[17] The synthesis of the same scaffold fused with arenes and heteroarenes stimulated more research interest because of their prevalence in bioactive natural products[18] and synthetic intermediates[6b,19] among others. For example, *racemosin C* (**3**, Fig. S1, ESI†), isolated from *Caulerpa racemosa*, displayed significant hPTP1B inhibitory activity,[18] marginally lower than that of *caulerpin* (**1a**).[12a] Despite the importance of this field, only a few reports[6b,19] on the synthesis of some specific examples of 2,4,6-cyclooctatrien-1-ones fused with arenes or other rings are known; this clearly indicates the requirement of a reliable method for their general synthesis.

In continuation of our work[20] on palladium catalysed reactions, we anticipated that a general synthesis of fused 2,4,6-cyclooctatrien-1-ols **6** and 2,4,6-cyclooctatrien-1-ones **8** could be achieved in one-pot from acetylenic substrates **4** and **5**, respectively, employing an appropriate catalyst (Scheme 1). Furthermore, the synthesis of fused COTs **7** could also be accomplished conveniently by the acid-mediated dehydration of products **6**. The synthetic pathways proved to be viable upon the deployment of an appropriate catalyst and reaction conditions as described herein.

Initially, we took up the model synthesis of compound **6a** (R^1 = R^2 = R^3 = H, PG = Ts) from acetylenic substrate **4a**. Thus, carrying out this reaction in 1,4-dioxane employing $Pd(OAc)_2$/bipyridine (bpy) and D-(+)-camphorsulfonic acid (D-CSA) as an additive led to product **6a** with 27% yield (Table S1 in ESI†, entry 1). Replacing the catalyst by $Pd(OAc)_2$bpy made it still less attractive (Table S1, ESI†, entry 2). We, therefore, persisted with the previous catalytic system but changed the additive to *p*-TsOH·H_2O (Table S1, ESI†, entry 3). Switching to other solvent

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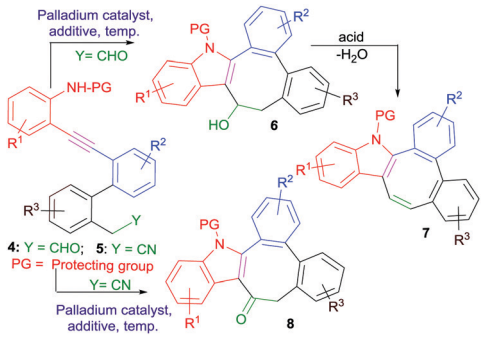
† Electronic supplementary information (ESI) available. CCDC 2034270–2034274. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc06538b



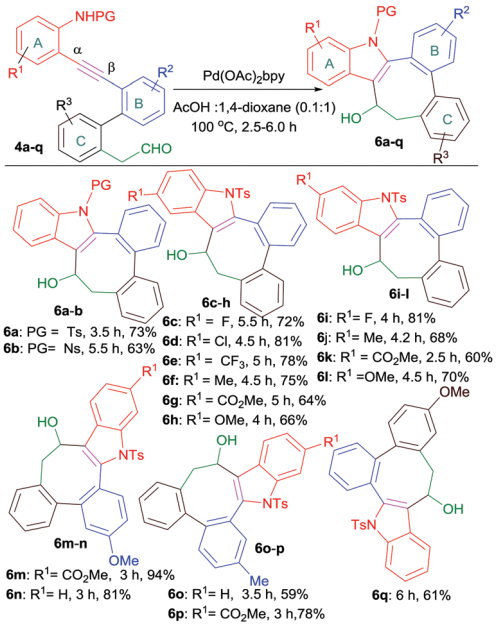
Scheme 1 Envisaged route for the synthesis of **6–8**.

systems failed to provide the product (Table S1, ESI†, entries 4 and 5) suggesting the importance of 1,4-dioxane in this reaction. We, therefore, reverted to $Pd(OAc)_2$bpy and pursued this reaction further in 1,4-dioxane; to our surprise, **6a** (21%) was formed together with 20% of COT derivative **7a** (Table S1, ESI†, entry 6). Employment of aliphatic sulphonic acids did not improve the outcome (Table S1, ESI†, entries 7 and 8). Nevertheless, replacing the additive with benzoic acid was found to be encouraging, though 2,3-naphthalenedicarboxylic acid failed to provide **6a** (Table S1, ESI†, entries 9 and 10). Next, switching to low cost acetic acid (2 equiv.) led to 36% yield of **6a**; to our delight, increasing the amount of AcOH (*i.e.*, 10% in 1,4-dioxane, v/v) afforded **6a** within 3.5 h in 73% yield (Table S1, ESI†, entry 12). But decreasing the catalyst loading had a detrimental effect (Table S1, ESI†, entry 13). Employment of other Pd(II) catalysts [*viz.* $PdCl_2$, $Pd(MeCN)_4(BF_4)_2$ and $Pd(MeCN)_2Cl_2$] failed to give the desired product **6a** (Table S1, ESI†, entries 14–16). Thus the reaction conditions of entry 12 of Table S1 (ESI†) were considered as optimal.

With the optimised reaction conditions in hand, the generality of the reaction protocol was explored by carrying out the reactions of acetylenic substrates **4a–q** (Scheme 2).

Interestingly, when the nosyl group (–Ns) was used as an *N*-protecting group instead of tosyl (–Ts) as in **4b**, the reaction required a longer reaction time (*i.e.*, 5.5 h) and the yield of the product **6b** decreased (Scheme 2, product **6a** *vs.* **6b**) underlining the importance of the *N*-tosyl group.

Thereafter, we studied the effects of different functional groups at the *meta* and *para* positions (with respect to the acetylenic group) in ring A of substrate **4**. For the *meta* position, both moderate electron-withdrawing (*i.e.*, R^1 = F/Cl/CF_3) and -donating (R^1 = Me) groups performed well, resulting in the formation of products **6c–e** and **6f**, respectively, within 4.5–5.5 h in 72–81% yields. But a strong EWG (R^1 = CO_2Me) or EDG (R^1 = OMe) did not favour this reaction resulting in lower yields [*i.e.*, **6g** (64%), **6h** (66%)]. For the *para* position, incorporation of a moderate EWG (*viz.*, R^1 = F; substrate **4i**) facilitated the reaction affording **6i** in 81% yield, compared to an EDG (*viz.*, R^1 = Me) as in **4j** which furnished **6j** in a lower yield (68%). These substituent effects are perhaps predictable keeping in view the importance of electrophilicity of the β-carbon (of the triple bond of **4**) for the cyclisation to proceed smoothly. To our surprise, a strong EWG (*viz.*, R^1 = CO_2Me) or EDG (*viz.*, R^1 = OMe) placed at the same position in the substrates (**4k** or **4l**) delivered the product

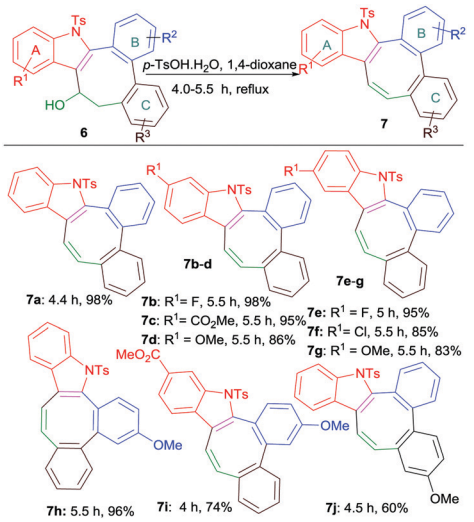


Scheme 2 Palladium-catalysed synthesis of dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols **6a–q**. Reaction conditions: a mixture of **4** (0.086 mmol) and $Pd(OAc)_2$bpy (6 mol%) in a solution (1.1 mL) containing AcOH : 1,4-dioxane (0.1 : 1, v/v) was heated at 100 °C under argon.

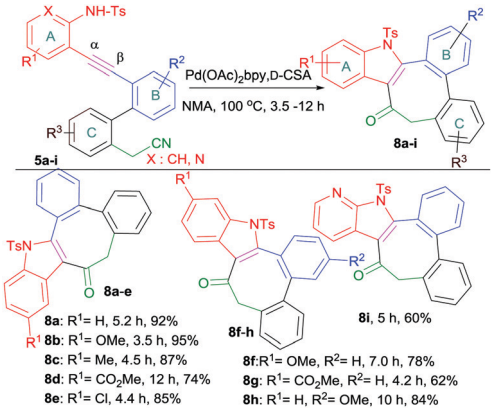
6k or **6l** to an extent of 60–70%. The reason behind these results is not very clear at this moment.

Interestingly, when a strong EWG (*viz.*, R^1 = CO_2Me) in ring A and EDG (*viz.*, R^2 = OMe) in ring B are simultaneously placed *para* to the acetylenic group, product **6m** (94%) was formed within 3 h. When the ester group was absent (as in **4n**), **6n** was furnished in a somewhat lower yield (81%), while removing the methoxy group from **4n** and incorporating a moderate EDG (R^2 = Me) as in substrate **4o** led to the formation of **6o** in 59% yield. Furthermore, the incorporation of an additional EWG (R^1 = CO_2Me) in ring A (**4p**) benefited the reaction by producing product **6p** (78%) within 3 h. Surprisingly, the reaction of substrate **4q** having an EDG (R^3 = OMe) at the *para* position of the C ring was somewhat sluggish to furnish the product **6q** in 61% yield.

To further probe the synthetic utility of this methodology, we then attempted to transform the products **6** into COT derivatives **7** as envisioned previously (Scheme 1). Toward this goal, we treated 2,4,6-cyclooctatriene-1-ol **6a** with a number of Lewis and Brønsted acids; this led to the identification of *p*-TsOH·H_2O as the best acid , allowing the formation of COT **7a** in 1,4-dioxane within 4.4 h with an almost quantitative (98%) yield. We then established the generality of this protocol by applying it to a number of compounds **6** as depicted in Scheme 3. Substrates **6i**/**6k** bearing an EWG (*viz.*, R^1 = F/CO_2Me) in ring A *meta* to the N–Ts group were found to be highly reactive, producing the desired COTs **7b**/**7c** within 5.5 h in excellent yields (95–98%), though an EDG (*viz.*, R^1 = OMe) at the same position furnished the desired product (**7d**) in a somewhat lower yield (86%). A similar trend of reactivity was followed when an EWG (R^1 = F/Cl) or EDG (R^1 = OMe) was



Scheme 3 Synthesis of 1,3,5,7-cyclooctatetraene (COT) derivatives **7a–7j**. Reaction conditions: a mixture of **6** (0.062 mmol) and *p*-TsOH·H_2O (0.186 mmol) in 1,4-dioxane (1.0 mL) was refluxed under argon.



Scheme 4 Synthesis of dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-ones **8a–i**. Reaction conditions: a mixture of **5** (0.14 mmol), $Pd(OAc)_2$bpy (6 mol%) and D-CSA (2.0 equiv.) was heated at 100 °C in NMA (1.5 mL) under argon.

present at the *para* position, leading to the formation of product **7e** (95%), **7f** (85%) or **7g** (83%). For ring B, the placement of an EDG (*viz.* R^2 = OMe) promoted the reaction furnishing **7h** within 5.5 h in 96% yield. But the incorporation of an additional EWG (*viz.* CO_2Me) in ring A reduced the yield of the product (**7i**) to 74%. On the contrary, an EDG (*viz.* R^3 = OMe) placed in ring C hindered the reaction to some extent affording the COT derivative **7j** within 4.5 h in a moderate yield (60%).

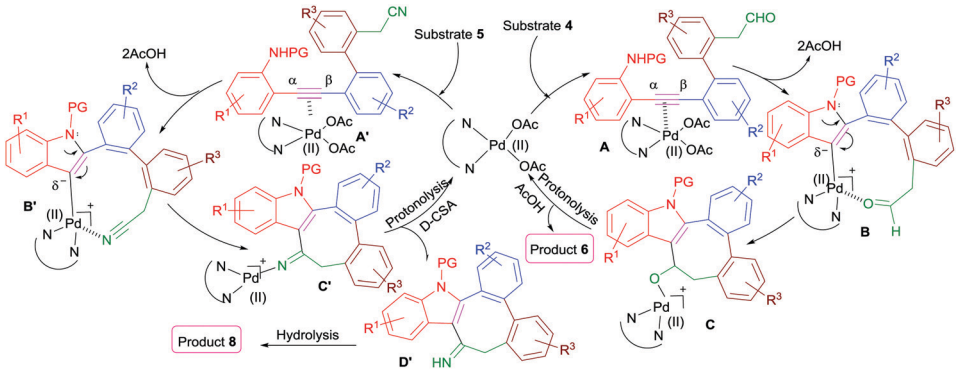
With a view to expanding the scope of this reaction further, we replaced the aldehyde group of **4a** by a cyano group as in **5a** which can be synthesised easily in a few steps (see Scheme S2 in the ESI†). Initially, we carried out the reaction of **5a** under the optimised reaction conditions for **4a**; to our disappointment, the desired product 2,4,6-cyclooctatrien-1-one **8a** was formed only in 50% yield. To find the optimised conditions, we therefore carried out a few more reactions on **5a** by changing the catalyst, ligand, additive, solvent, temperature, *etc.* (see Table S2 in the ESI†). From this study, the best result was obtained when the reaction of **5a** was carried out at 100 °C for 5.2 h in NMA using $Pd(OAc)_2$bpy (6 mol%) and D-CSA (2.0 equiv.) leading to the generation of **8a** in 92% yield (entry 7 of Table S2 in the ESI†).

With the optimised reaction conditions in hand, we then established the generality of the reaction for the formation of 2,4,6-cyclooctatrien-1-ones **8** (Scheme 4). Substrates **5b**/**5c** bearing an EDG (R^1 = OMe/Me) in ring A *meta* to the alkyne moiety facilitated the reaction, furnishing the products **8b** (95%)/**8c** (87%) within 3.5–4.5 h. But **5d**/**5e** having an EWG (R^1 = CO_2Me/Cl) at the same position formed products **8d**/**8e** within 4.4–12 h in lower yields (74–85%). Nevertheless, the placement of an EDG (*viz.*, R^1 = OMe) rather than an EWG (R^1 = CO_2Me) even at the *para* position also proved beneficial (substrate **5f** *vs.* **5g**) though the former took a longer reaction time (Scheme 4, see **8f** *vs.* **8g**). For ring B, when a strong EDG (R^2 = OMe) was placed *para* to the alkyne moiety (in **5h**), the desired product **8h** (84%) was formed albeit with a longer reaction time (10 h). Interestingly substrate **5i** containing a pyridyl ring (X = N) was still conducive to the reaction, the product **8i** (60%) being formed within 5 h.

Owing to the presence of a free NH group in bioactive compounds,[18] we attempted to check the feasibility of N-deprotection of product **8a**; to our delight product **9** was formed easily within 3 h in 82% yield (Scheme S3 in the ESI†).

On the basis of the experimental results and the known palladium chemistry, a plausible reaction mechanism is outlined in Scheme 5. Initially, palladated species **A** and **A′** are generated from the substrates **4** and **5**, respectively, through the action of the Pd(II) catalyst acting like a Lewis acid. Under acidic conditions, **A** and **A′** would then trigger the heteroannulation *via* a *trans*-aminopalladation pathway[20a] resulting in the formation of transient cationic palladated species[21] **B** and **B′** which are stabilised through coordination of the tethered nucleophile (–CHO/–CN) as shown in Scheme 5. Next, species **B** and **B′** having the polar C–Pd bond caused by the electron-donating effect of the nitrogen atom of the indole ring[22a] (shown using an arrow) could promote nucleophilic 1,2-addition onto the tethered aldehyde and nitrile groups, respectively, resulting in the generation of palladated species **C**[22b] and **C′**.[22c] Subsequent protonolysis of **C** using AcOH would afford the product **6** along with a Pd(II) species which keeps the catalytic cycle active. On the other hand, protonolysis of **C′** with D-CSA would lead to the regeneration of the Pd(II) catalyst in addition to the formation of imine intermediate **D′** which upon subsequent hydrolysis under acidic conditions would furnish the product **8**.

In conclusion, we have disclosed an atom economic method for the expedient synthesis of products **6** and **8** *via* palladium catalysed intramolecular cascade reactions of amino-alkynes **4** and **5**, respectively. The hallmarks of the synthesis are high yield (up to 95%), atom-economy, tolerance of functional groups and formation of two new rings (*i.e.*, cyclooctatriene and indole) fused to each other. Furthermore, treatment of products **6** with *p*-TsOH·H_2O could provide easy access to COT derivatives. Syntheses of higher homologues (*i.e.*, nine and ten membered rings) of products **6** and **8** are currently underway.



Scheme 5 Plausible mechanism for the formation of products **6–8**.

This work was financially supported by CSIR-IICB from project MLP-116.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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Contents

Summary

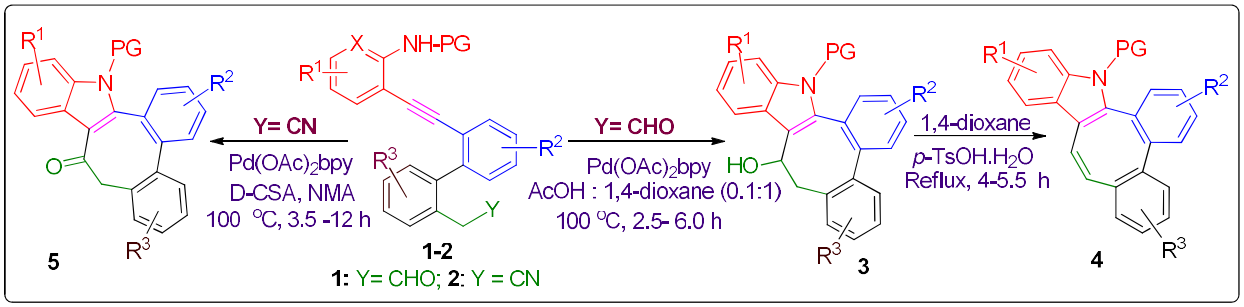
Synthesis of Heterocycles of Biological Interests via Metal Catalyzed Cyclizations of Acetylenic Compounds

The Thesis entitled "*Synthesis of Heterocycles of Biological Interests via Metal Catalyzed Cyclizations of Acetylenic Compounds*" is divided into four chapters, each chapter consists of two parts. Where **Part I** deals with a general survey about the importance of the field and literature review for the synthesis of compounds of our interests. On the other hand, **Part II** deals with the results and discussions of various experiments pertinent to the methodology developed. However, the following section summarizes the work as described in the whole thesis.

Chapter 1

Palladium(II) Catalysed Cascade Strategy for the Synthesis of Dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols/-10(15*H*)-ones: Easy Access to 1,3,5,7-Cyclooctatetraenes (COTs)

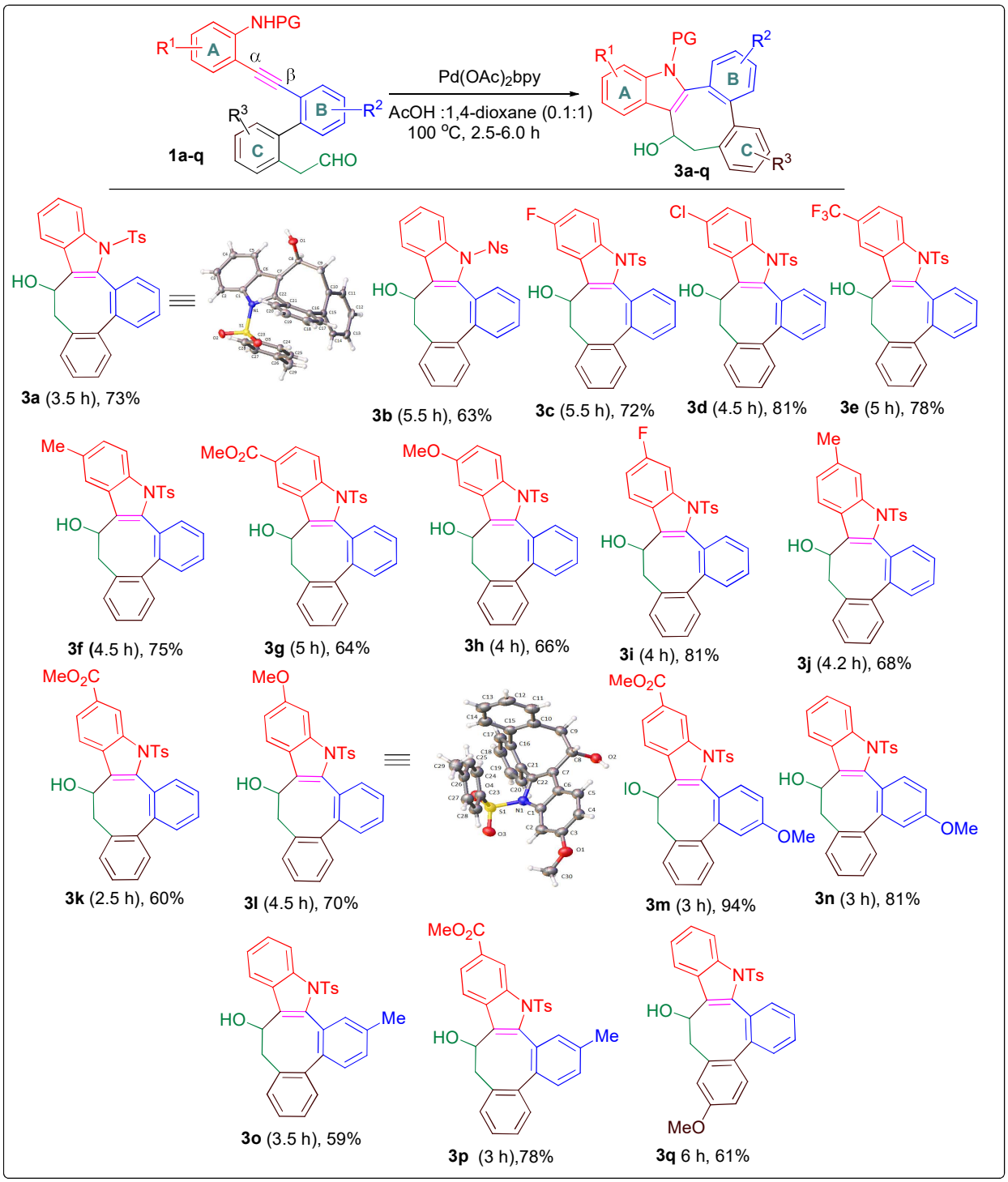
The first chapter of this thesis deals with an atom-economic one-pot synthesis of eight-membered heterocycles 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ol **3** and 9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one **5** via Pd(II)-catalyzed intra-molecular cascade cyclizations of 2-(biphenylethynyl)anilines (**1** or **2**) tethered to an aldehyde or cyano group respectively. The reaction follows *trans*-aminopalladation of the alkyne followed by nucleophilic addition onto the tethered aldehyde/cyano group. Furthermore, treatment of compound **3** with *p*-TsOH.H_2O smoothly produced the cyclooctatetraene (COT) derivatives **4** fused at three double bonds (**Scheme 1**).



Scheme 1: Pd(II) catalyzed synthesis of Dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols/-10(15*H*)-ones **3**, **5** and access to 1,3,5,7-Cyclooctatetraenes (COTs) **4**

Towards this objective, the model substrate **1a** (Y = CHO, R^1=R^2=R^3=H) was exposed under various reaction conditions by variation of the catalyst, ligand, additive, solvent, temperature etc. After several control experiments, the optimized reaction conditions were achieved where heating a mixture of **1a** (0.086 mmol) in 1,4-dioxane (1 mL) at 100 °C in presence of 6 mol% Pd(OAc)bpy catalyst and AcOH (0.1 mL) as an additive under argon atmosphere leads to the formation of the desired product **3a** within 3.5 h with 73% yield.

Scheme 2: Synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols **3a-q**[a]

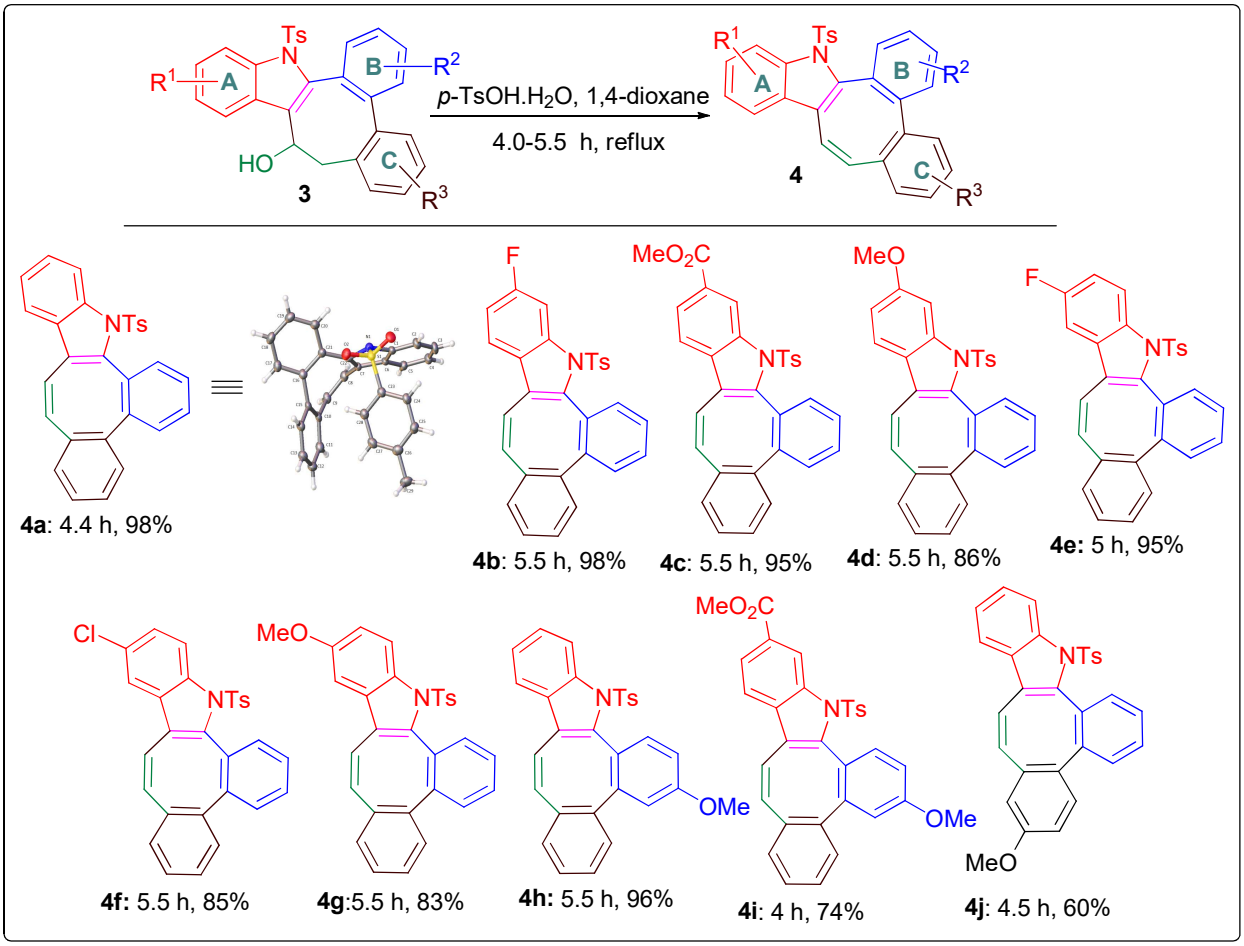


[a]Reaction conditions: a mixture of **1** (0.086 mmol) and $Pd(OAc)_2bpy$ (6 mol%) in a solution (1.1 mL) containing AcOH: 1,4-dioxane (0.1: 1, v/v) was heated at 100 °C under argon.

Thereafter, the scope and limitations of the procedure were checked by exposing the substrates **1a-q** containing wide ranges of functional groups under optimized reaction conditions and all of them responded very well affording the products **3a-q** with 59-94% yield (**Scheme 2**).

Next, we targeted to explore the synthetic utility of this methodology by transforming the derivatives of **3** into 1,3,5,7-cyclooctatetraene (COT) derivatives **4** via dehydration reaction. Towards this goal, we treated compound **3a** ($R^1 = R^2 = R^3 = H$) with various types of Lewis and Brønsted acids; among them, *p*-TsOH.H_2O proved to be the best for this transformation. Next, we set out to explore the generality of this strategy (**Scheme 3**), where diversely substituted substrates were compatible to this reaction producing the products **4a-j** with very good to excellent yields (60-98%).

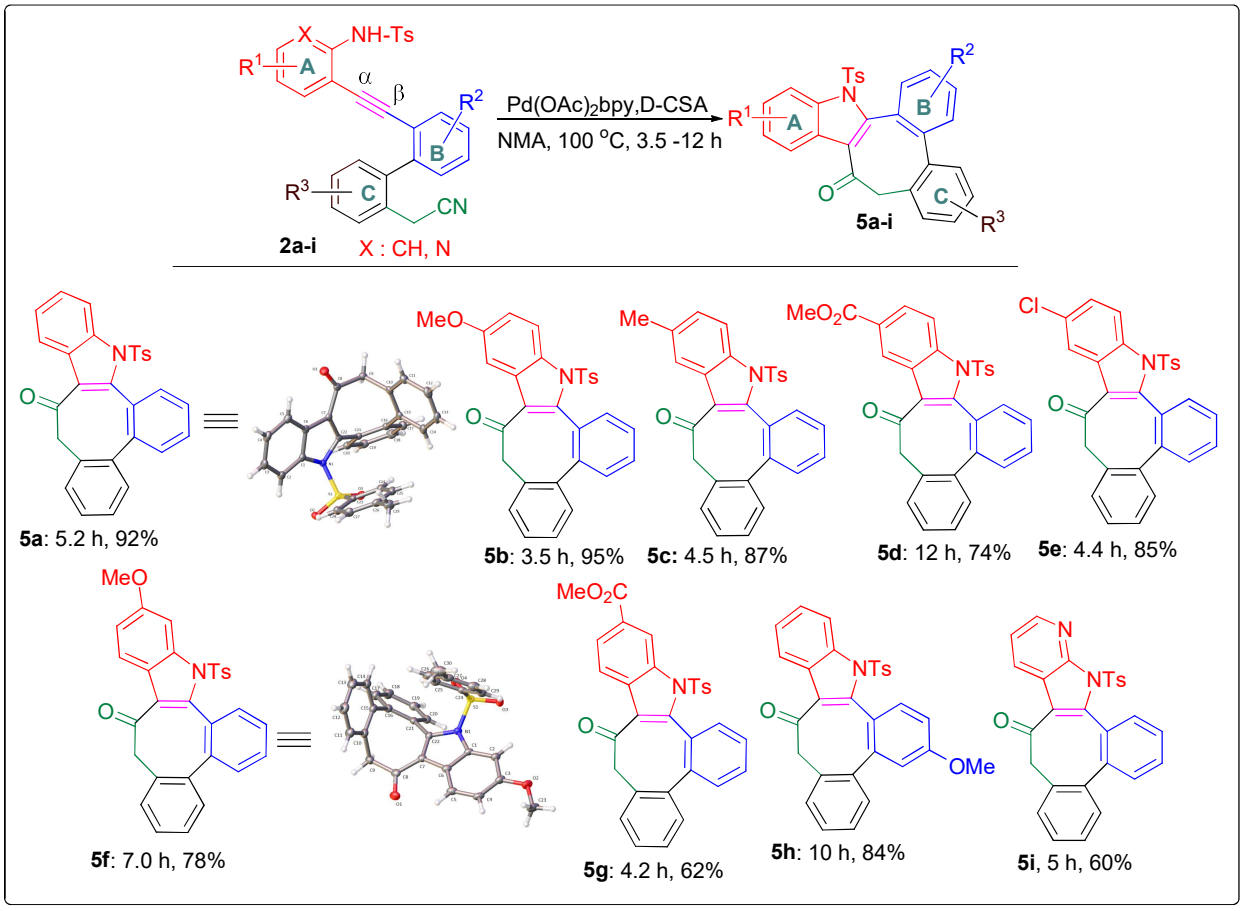
Scheme 3. Synthesis of (*Z*)-15-tosyl-15*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indoles **4a-j**[a]



[a]Reaction conditions: a mixture of **3** (0.062 mmol) and *p*-TsOH.H_2O (0.186 mmol) in 1,4-dioxane (1.0 mL) was refluxed under argon.

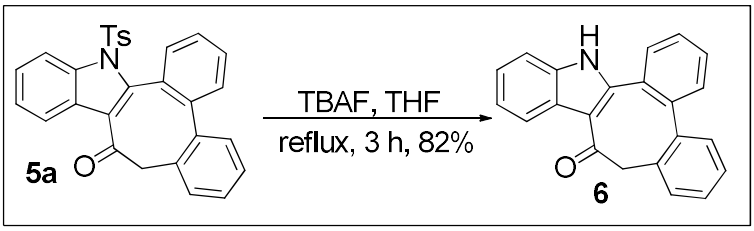
Encouraged by the above results, we decided to expand the scope of this reaction further. At this outset, we replaced the aldehyde group of substrates **1** by cyano group leading to the formation of substrates **2**. Treatment of **2a** ($R^1 = R^2 = R^3 = H$) under the optimized conditions for the synthesis of **3a** was disappointing, delivering the product **5a** with only 50% yield. Next, further optimization of the reaction conditions revealed that heating a mixture of **2a** (0.14 mmol) in NMA (1.5 mL) at 100 °C in presence of $Pd(OAc)_2$bpy (6 mol%) and *D*-CSA (2.0 equiv) delivered the desired product **5a** within 5.2 h with 92% yield. Next, various derivatives of substrates **2a-i** were exposed to the optimized conditions and these substrates smoothly produced the desired products **5a-i** with 60-95% yields (**Scheme 4**).

Scheme 4: Synthesis of 15-tosyl-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one **5a-i**[a]



[a]Reaction conditions: a mixture of **2** 0.14 mmol), $Pd(OAc)_2$bpy (6 mol%) and D-CSA (2.0 equiv.) was heated at 100 °C in NMA (1.5 mL) under argon

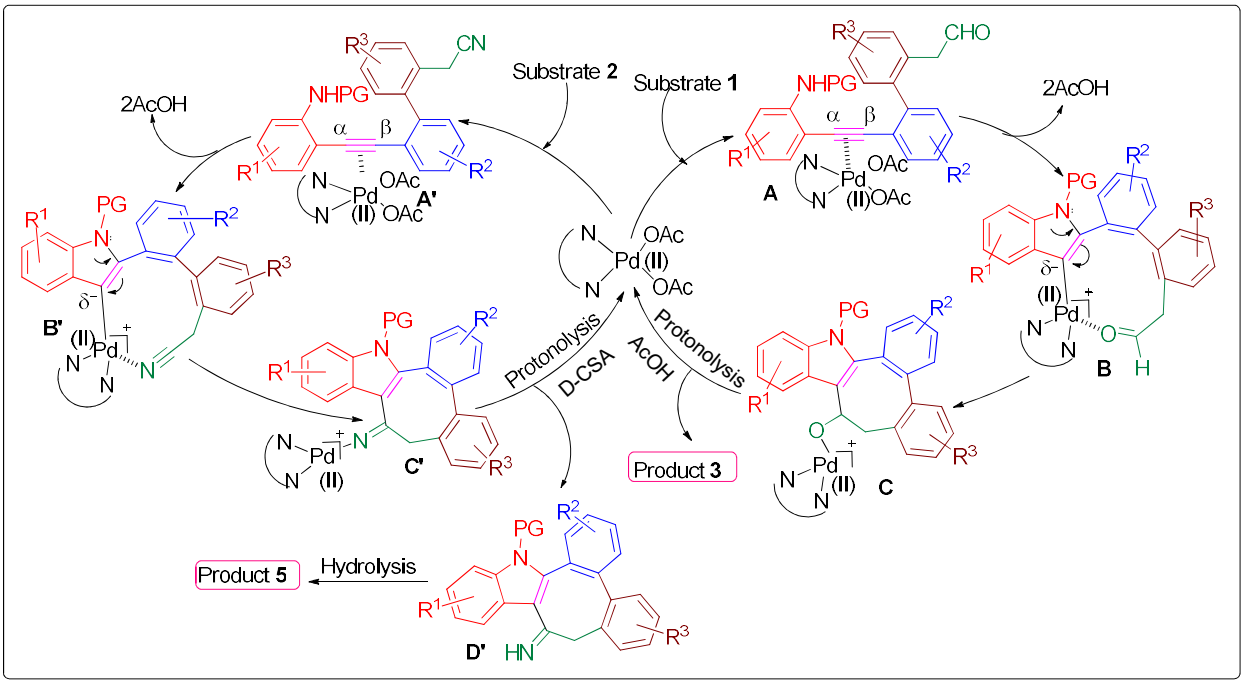
Due to the presence of free NH groups in various bio-active compounds, we then attempted to de-protect compound **5a**. Treatment of **5a** with TBAF in refluxing THF afforded compound **6** within 3 h with 82% yield (**Scheme 5**).



Scheme 5: De-protection of compound **5a**

The structure of all products were unambiguously deduced by spectral (^{1}H, ^{13}C, Mass Spectrometry) and analytical data. Detailed discussion of structural elucidation has been provided in **Part II** of Chapter 1. Finally, the structural conclusion was confirmed by the single crystal X-ray diffraction compounds **3a**, **3l**, **4a**, **5a** and **5f** (see, **Schemes 2-4**)

A plausible reaction mechanism is depicted in **Scheme 6**. Initially, palladated species **A** and **A′** are generated from the substrates **1** and **2**, respectively, through the action of the Pd(II) catalyst acting like a Lewis acid. Under acidic conditions, **A** and **A′** would then trigger the heteroannulation via a *trans*-aminopalladation pathway resulting in the formation of transient cationic palladated species **B** and **B′** which are stabilized through coordination of the tethered nucleophile (–CHO/–CN). Next, species **B** and **B′** having the polar C–Pd bond caused by the electron-donating effect of the nitrogen atom of the indole ring (shown using an arrow) could promote nucleophilic 1,2-addition onto the tethered aldehyde and nitrile groups, respectively, resulting in the generation of palladated species **C** and **C′**. Subsequent protonolysis of **C** using AcOH would afford the product **3** along with a Pd(II) species which keeps the catalytic cycle active. On the other hand, protonolysis of **C′** with *D*-CSA would lead to the regeneration of the Pd(II) catalyst in addition to the formation of imine intermediate **D′** which upon subsequent hydrolysis under acidic conditions would furnish the product **5**.

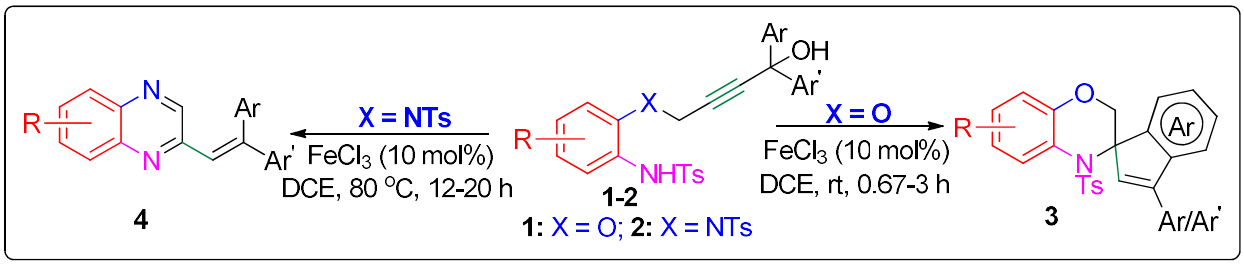


Scheme 6. Plausible reaction mechanism for formation products **3-5**

Chapter 2

Substrate Controlled Product Divergence in Iron(III)-Catalyzed Reactions of Propargylic Alcohols: Easy Access to Spiro-indenyl 1,4-Benzoxazines and 2-(2,2 Diarylvinyl)quinoxalines

In the second chapter, unprecedented Fe(III)-catalyzed cascade reactions are disclosed for the general synthesis of spiro-indenyl 1,4-benzoxazines **3** and 2-(2,2-diarylvinyl)quinoxalines **4** from the propargylic substrates such as *O*-propargyl-*N*-tosyl-amino phenols **1** and *N*-propargyl-*N*-tosyl-amines **2**, respectively (**Scheme 1**).



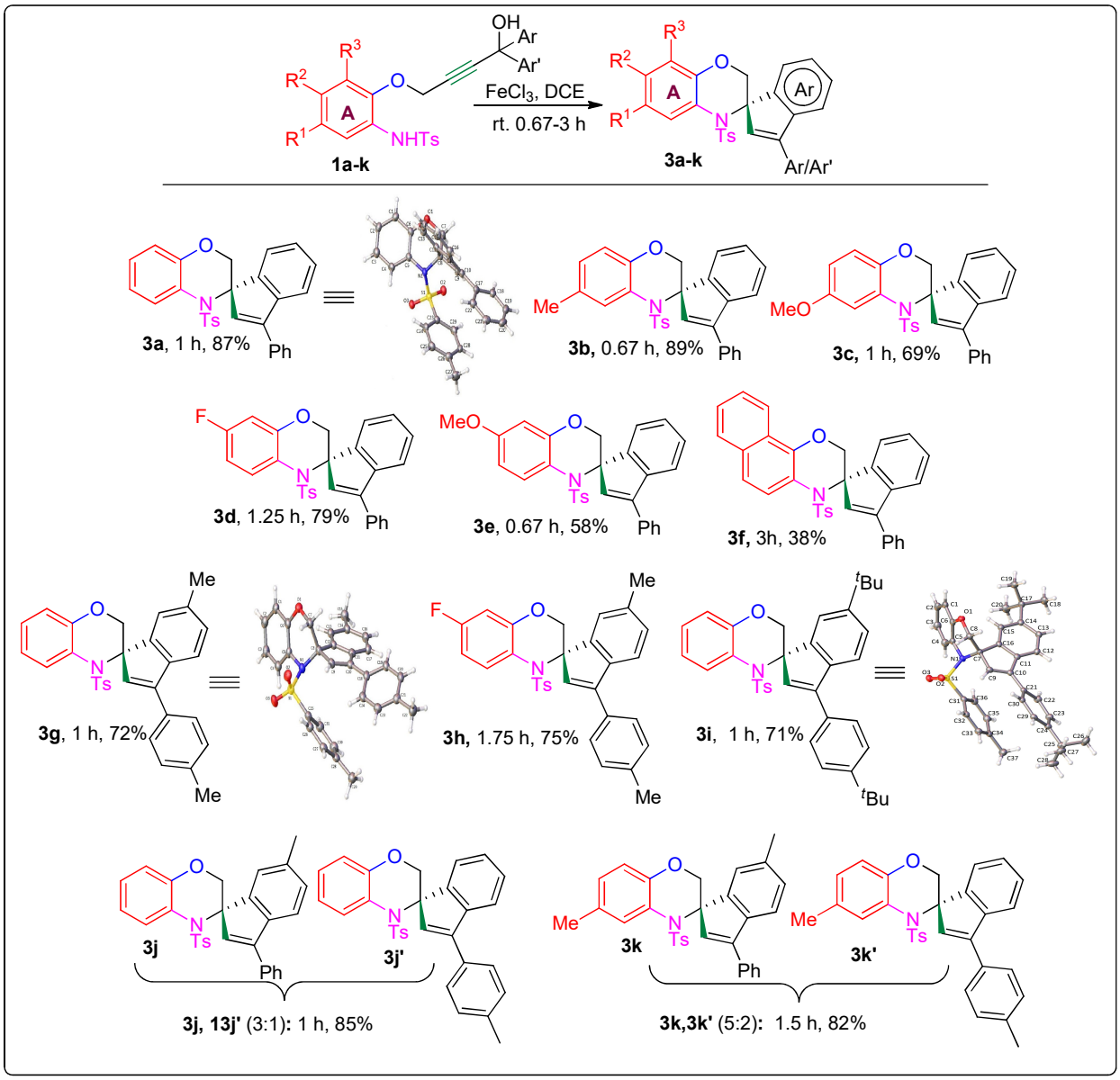
Scheme 1: Fe(III) catalyzed synthesis of Spiro-indenyl 1,4-Benzoxazines **3** and 2-(2,2-Diarylvinyl)quinoxalines **4**

Initially, in order to find out the optimized reaction conditions for the synthesis of spiro-indenyl 1,4-Benzoxazines **3**, treatment of substrate **1a** (X = O, R = H, Ar = Ar′ = Ph) under various reaction conditions led to the identification of optimized reaction conditions where the exposure of substrate **1a** (0.07 mmol) with $FeCl_3$ (0.007 mmol, 0.1 equiv) in 1,2-dichloroethane (DCE) (1.5 mL) at room temperature under argon atmosphere provided the spiro-indenyl 1,4-benzoxazine product **3a** with 87% yield within just 1 h.

With the optimized reaction conditions in hand, we then set out to explore the scope and limitations of the synthesis (**Scheme 2**). Towards this goal, we first tested the effects of substitutions in the aryl ring (A) of substrates **1**. Though placement of an electron-donating group (EDG) like methyl (R^1=Me) *para* to the oxygen (substrate **1b**) facilitated the reaction forming the product **3b** within 0.67 h with 89% yield, a stronger EDG (R^1=OMe) at the same

position (in **1c**) slightly hindered the reaction leading to the formation of product **3c** within 1 h but with somewhat lower yield (69%). Next, when a EWG like fluoro (R^2=F) was placed *para* to NHTs (substrate **1d**), product **3d** was produced within 1.25 h with 79% yield. But a stronger

Scheme 2. Synthesis of Spiro-indenyl 1,4-Benzoxazines **3a-k**[a,b]



[a]Reaction conditions: A mixture of **1** (0.07 mmol, 1 equiv) and $FeCl_3$ (0.007 mmol, 0.1 equiv) in DCE (1.5 mL) was stirred at room temperature under argon atmosphere for the specified time. [b]All products were obtained in racemic mixture.

EDG (R^2 = OMe) as in substrate **1e** lowered the yield of product **3e** (58%) though with a shortened reaction time (0.67 h). The lower yields observed with OMe substituted products could possibly be attributed to the poisoning of the catalyst through chelation of the group to the Fe(III) having vacant *d*-orbitals. To our disappointment, replacing the phenyl ring (A) of substrate **1a** by naphthyl one as in substrate **1f** inhibited the reaction considerably requiring longer reaction time (3 h) for the production of **3f** with lower yield (38%).

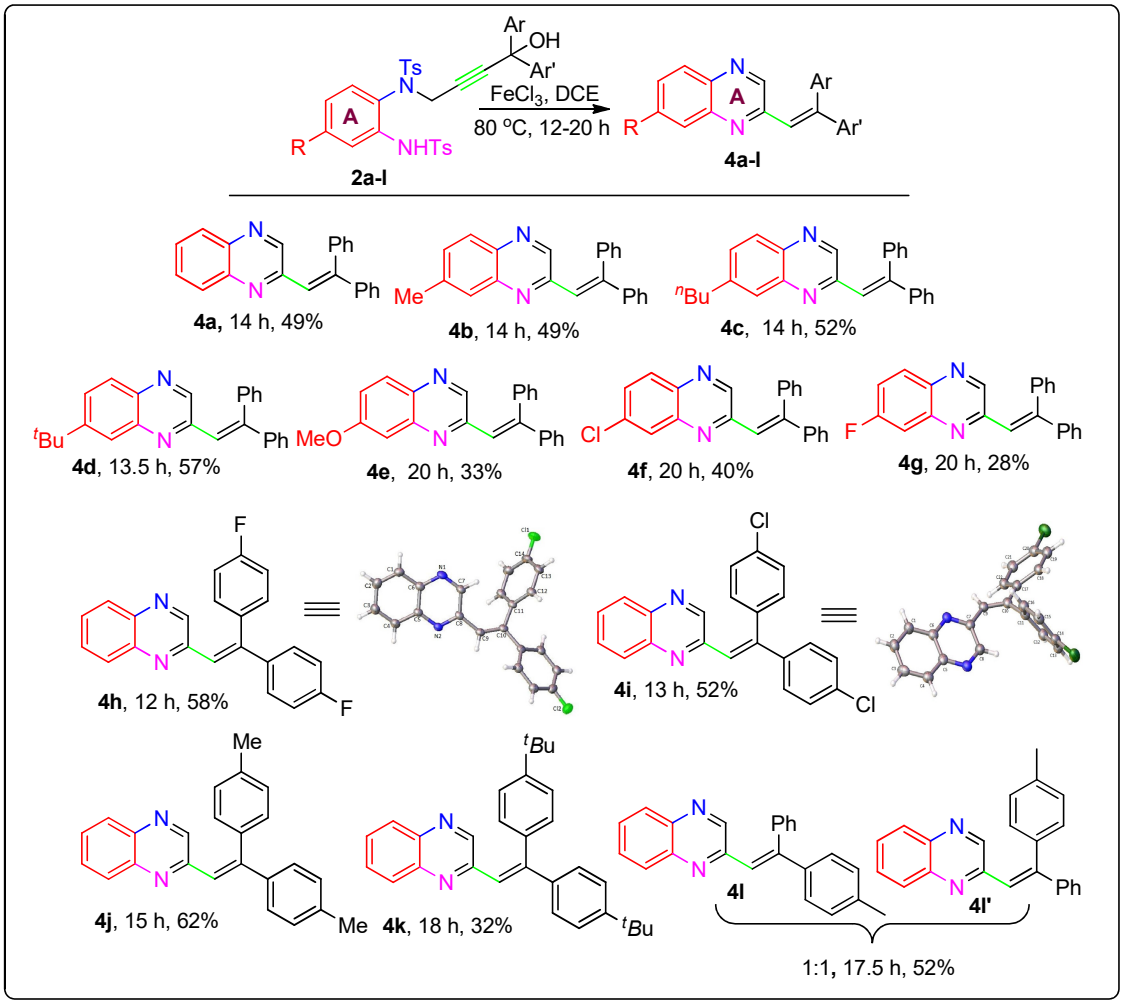
Next, the substitution effects of the aryl rings (Ar, Ar') attached to the propargylic carbon of substrates **1** were examined. Substrate **1g** (Ar = Ar' = *p*-Me-C_6H_4) bearing an EDG like methyl at the *para*-position of the phenyl ring smoothly delivered the product **3g** within 1 h with 72% yield. The trend continued even in presence of an extra EWG (R^1=F) in the other aryl ring A (product **3h** formed with 75% yield) though with slightly longer reaction time. Even after incorporation of a bulky *tert*-butyl group in place of the methyl group as in substrate **1i** (Ar = Ar' = *p*-^{t}Bu-C_6H_4), the reaction furnished the product **3i** in 1 h with 71% yield. Interestingly, use of two different aryl groups (Ar = Ph, Ar′ = *p*-Me-C_6H_4) in substrate **1j** or **1k** led to the formation of inseparable regio-isomeric mixture of products **3j/3j'** (3:1) or **3k**/**3k'** (5:2) within 1-1.5 h with very good yield (82-85%). The higher nucleophilicity of the tolyl ring (Ar') compared to phenyl one (Ar) appears to dictate the formation of major isomers **3j** and **3k** (see, species **E** of **Scheme 4** vide infra).

The structures of the products were corroborated by NMR and mass spectral data, and X-ray diffraction analysis of compounds **3a**, **3g** and **3i** (see, **Scheme 2**). Though configuration of one of the isomer of products **3** is shown (**Scheme 2**), the products were obtained in racemic mixture.

With a view to expand the scope of this reaction further, we targeted to achieve the nitrogen heterocycles. Towards this objective, we replaced the oxygen atom of substrates **1** by –NTs group generating substrate **2**. Though exposure of **2a** (R = H, Ar = Ar′ = Ph) under the optimized condition for the formation of **3** proved to be inert, heating the mixture at 80 ^oC produced a new compound **4a**, which was identified as quinoxaline. In view of this unprecedented result, we became keen to establish the scope and generality of this new reaction by employing a number of substrates as depicted in **Scheme 3**.

Thus, introduction of a moderate EDG (R = Me, *n*-Bu, *tert*-Bu) in aryl ring A of substrates **2b-d** easily delivered the products **4b-d** after 13.5-14 h with 49-57% yields. But placement of either strong EDG (R=OMe) or EWG (R = Cl/F) at the same position (substrate **2e** or **2f**/**2g**) lowered the yield (28-40%) of the product (**4e** or **4f**/**4g**) and necessitated longer reaction time (20 h).

Scheme 3. Synthesis of 2-(2,2-diarylvinyl)quinoxalines **4a-l**[a]



[a]Reaction conditions: A mixture of **2** (0.12 mmol, 1 equiv) and $FeCl_3$ (0.012 mmol, 0.1 equiv) in DCE (4.4 mL) was heated at 80 °C under argon atmosphere for the mentioned time.

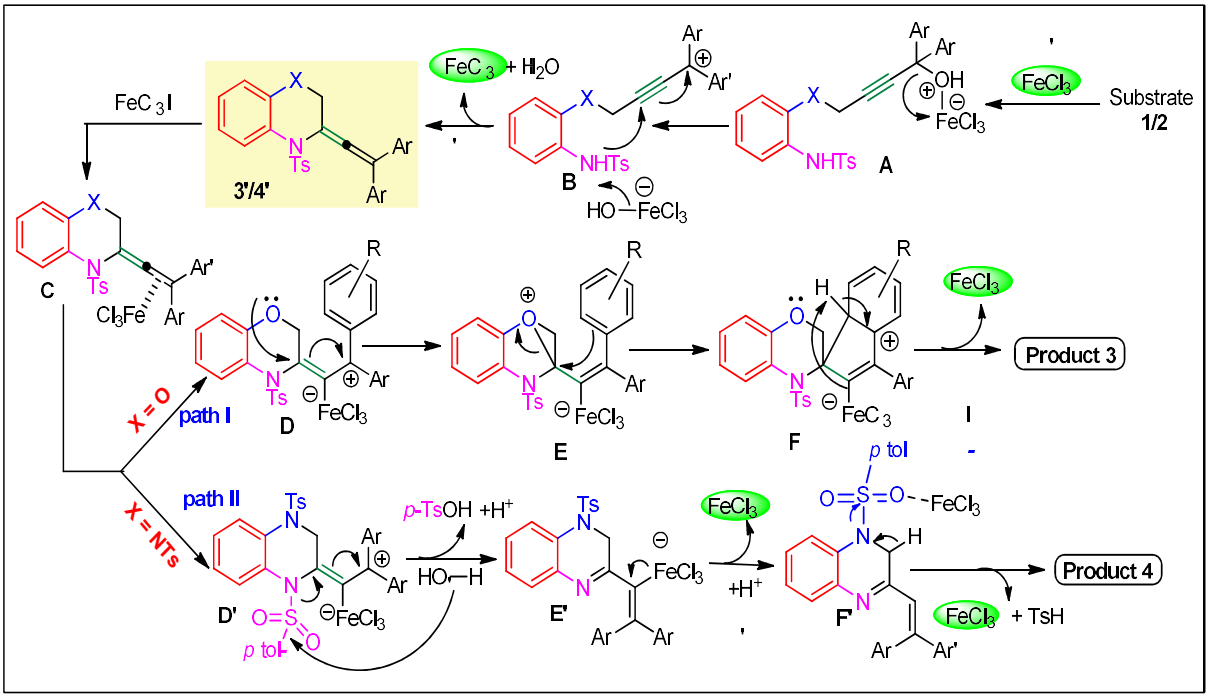
Next, we checked the substituent effects on the other aryl rings (Ar, Ar') of substrate **2**. Contrary to our previous observations (on **4f**, **4g**), installation of a EWG (viz., F/Cl) at the para position as in substrate **2h** (Ar = Ar′ = *p*-F-C_6H_4) or **2i** (Ar = Ar′ = *p*-Cl-C_6H_4) delivered the product **4h**/**4i** in 12-13 h with good yields (52-58%). On the other hand, introduction of a EDG

like methyl at the same position generated the product **4j** after 15 h with 62% yield; even a bulky EDG as in substrate **2k** (Ar = Ar′ = *p*-^{t}Bu-C_6H_4) afforded the product **4k** after 18 h albeit in moderate yield (32%). Similar to our previous observations, deployment of substrate **2l** having two unsymmetrical aryl rings (Ar = Ph, Ar' = *p*-Me-C_6H_4) delivered an inseparable mixture of products **4l**/**4l'** (1:1) with 52% yield within 17.5 h.

Structures of all products were undoubtedly confirmed by spectral (^{1}H, ^{13}C, Mass Spectrometry) and analytical data. Detailed discussion of structural elucidation is provided in **Part II** of Chapter 2. Finally, the structural conclusion was confirmed by the single crystal structures of compounds **3a**, **3g**, **3i**, **4h** and **4i** (see, **Schemes 2-3**).

A plausible reaction mechanism is proposed in **Scheme 4**. At first, the alcohol group of the substrate **1/2** is activated (species **A**) through co-ordination with Fe(III)-catalyst that leads to the generation of a transient propargylic carbocation **B**. Next, species **B** may undergo intramolecular nucleophilic attack by the tethered NHTs group to generate an allenic intermediate **3′** (X=O)/**4′** (X=NTs) which forms a complex with $FeCl_3$ (species **C**) to give rise to the product **3**/**4** following pathway I or II respectively. In path I (X=O), $FeCl_3$ acting like a Lewis-acid affords a benzylic carbocation intermediate **D** which may isomerizes into bicyclo[3.1.0] epoxonium ion **E** through intramolecular nucleophilic addition of oxygen onto the transient carbenium ion adjacent to the NTs group. Species **E** is now poised to undergo *intramolecular Fridel-Crafts* (IMFC) type cyclization preferably via 5-*exo* epoxide-ring opening. Next, aromatization by deprotonation followed by demetalation affords the product **3** along with regeneration of $FeCl_3$ which enters into catalytic cycle.

In path II (X=NTs), on the contrary, the NTs group in place of oxygen is unable to stabilize the incipient carbenium ion as in **E**. Instead, at higher temperature the tosyl group is lost from intermediate **D′** produced from **C** (X=NTs) with the aid of water generated previously (from step 3), assisted by $FeCl_3$. This triggers the formation of intermediate **E′** with concurrent release of *p*-TsOH and a proton that helps the demetalation of **E′** to furnish the intermediate **F′**. Finally, subsequent 1,2-elimination (-TsH) from **F′** with the assistance of $FeCl_3$ would give rise to the product **4** and regenerate the Fe (III) catalyst.

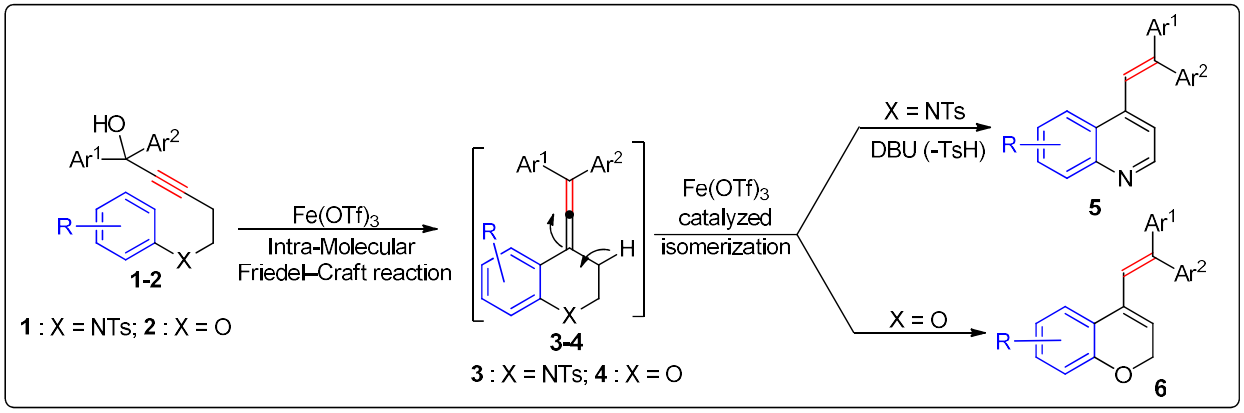


Scheme 4. Plausible reaction mechanism for the formation of products **3** and **4**

Chapter 3

Iron(III)-Catalyzed Carboannulations of Acetylenic Compounds: A Straightforward and General Synthesis of 4-(2,2-Diarylvinyl)quinolines and 4-(2,2-Diarylvinyl)-2*H*-chromenes Under One-pot

The third chapter deals with a convenient and efficient approach for the synthesis of 4-(2,2-Diarylvinyl)quinolines **5** and 4-(2,2-Diarylvinyl)-2*H*-chromenes **6** via a Fe(III) catalyzed *intramolecular Friedel-Crafts* reaction (IMFC) of homopropargyl amines **1** and ethers **2**, respectively. It was envisioned that the allenic compound (i.e., **3** and **4**) would serve as potential intermediate for this transformation (**Scheme 1**).

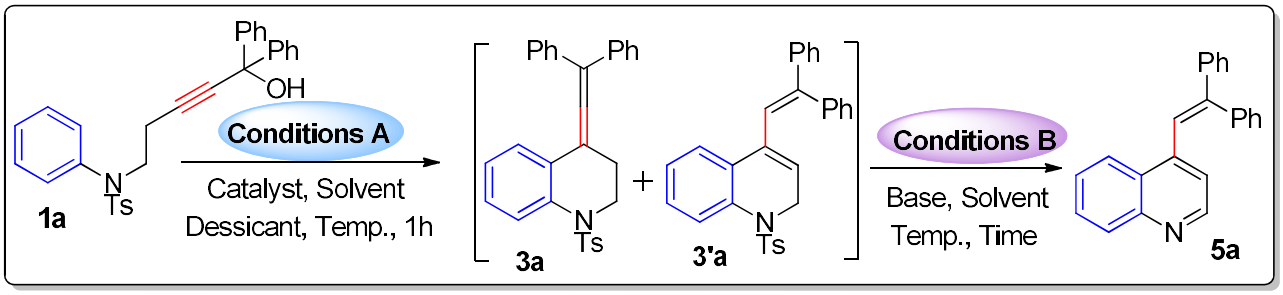


Scheme 1: Fe(III)-catalyzed synthesis of synthesis of 4-(2,2-Diarylvinyl)quinolines **5** and 4-(2,2-Diarylvinyl)-2*H*-chromenes **6**

Towards this goal, initially, a series of reactions were carried out (see Table 1) through the variation of different reaction parameters to achieve the optimized reaction conditions for the model synthesis of **5a** (Ar^1=Ar^2=Ph, R=H) from **1a** (Ar^1=Ar^2=Ph, R=H). Indeed, the optimization study was carried out in two steps; our first target was to find out the suitable reaction conditions (conditions **A**, see entry 4 Table 1) for achieving the synthesis of the 1,3-diene intermediate **3´a** (Ar^1=Ar^2=Ph, R=H) from **1a**. Efforts were then made to find out an appropriate base and solvent (Conditions **B**) to transform **3´a** into quinoline **5a** in one-pot. After several experimentations, we found an optimized reaction conditions where a mixture of **1a**

(0.062 mmol), $Fe(OTf)_3$ (10 mol%), and 4A° M.S. (12 mg) in DCE (1.7 mL) was heated at 80 °C under argon atmosphere for 1 h; the resulting crude intermediate **3´a** obtained (upon removal of

Table 1. Optimization of reaction conditions for the one-pot synthesis of 4-(2,2-diarylvinyl)quinolines 5a[a]



Reaction Conditions A					Reaction Conditions B				Products (%Yield)		
Entry	**Catalyst**	**Solvent**	**Temp. (°C)**	**Desiccant[b]**	**Base**	**Solvent**	**Temp.(°C)**	**Time (h)**	**3a**	**3'a**	**5a[c]**
1	$FeCl_3$	$MeNO_2$	60	CaH_2	---	---	---	---	95	---	---
2	$Fe(OTf)_3$	$MeNO_2$	60	CaH_2	---	---	---	---	95	---	---
3[d]	$Fe(OTf)_3$	MeOH	100	CaH_2	---	---	---	---	---	---	---
4	**$Fe(OTf)_3$**	**DCE**	**80**	**4Å M.S.**	**---**	**---**	**---**	**---**	**trace**	**80**	**---**
5[d]	$Fe(acac)_3$	DCE	80	4Å M.S.	---	---	---	---	---	---	---
6	AgOTf	DCE	80	4Å M.S.	---	---	---	---	11	66	---
7	$In(OTf)_3$	DCE	80	4Å M.S.	---	----	---	---	88	---	---
8	$Cu(OTf)_2$	DCE	80	4Å M.S.	---	----	---	----	trace	---	----
9	$Fe(OTf)_3$	DCE	80	4Å M.S.	K^{t}BuO	DMF	120	22	trace	80	trace
10	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMF	120	20	trace	---	45
11	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMSO	120	4.0	trace	---	53
12	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	MeOH	Reflux	3.5	trace	---	62
13	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	NMA	120	2.5	trace	---	65
14	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMA	120	4.5	trace	---	50
15	**$Fe(OTf)_3$**	**DCE**	**80**	**4Å M.S.**	**DBU**	**DBU**	**80**	**2**	**trace**	**---**	**70**

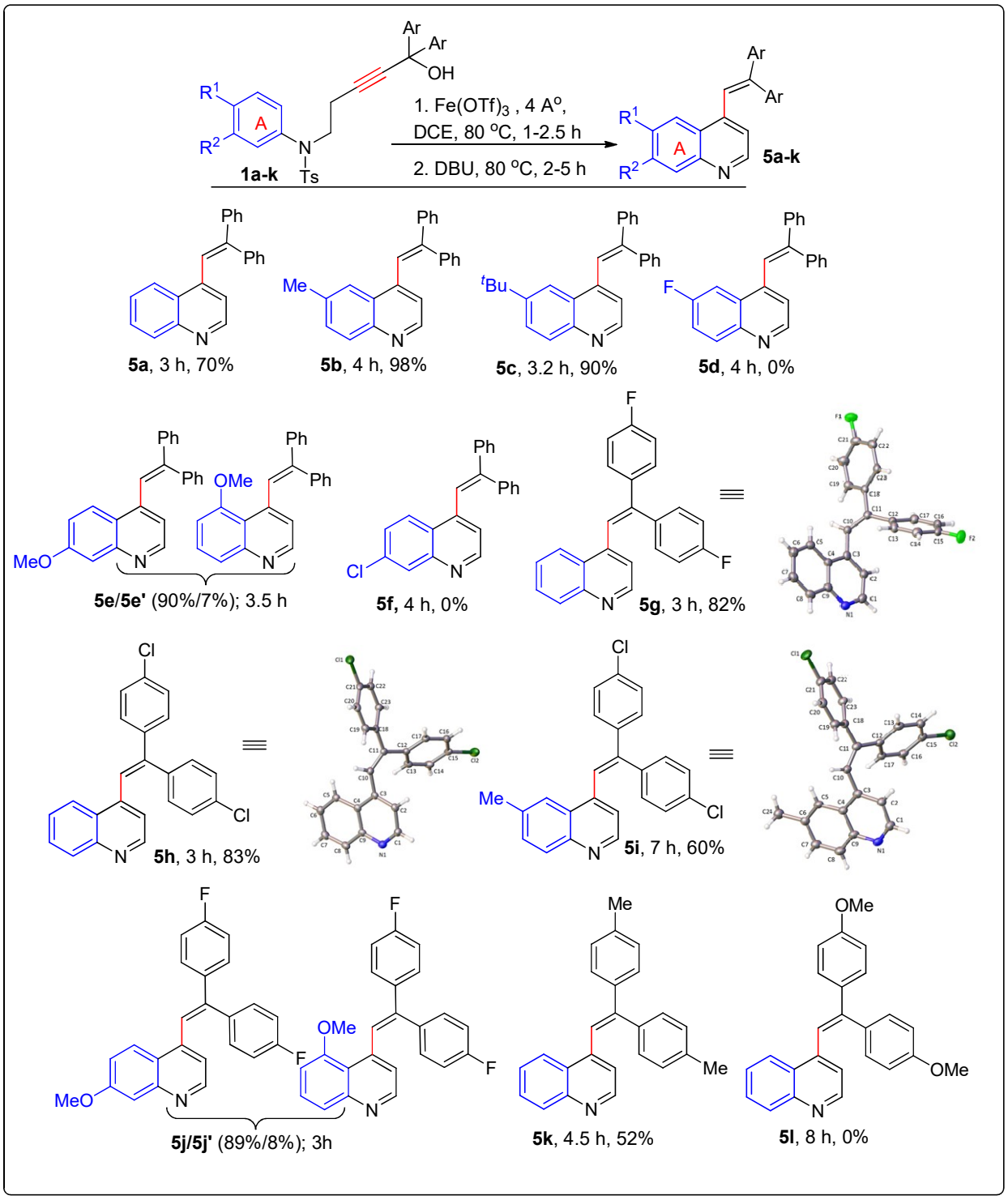
[a]ReactionConditions: **1a** (0.062 mmol), catalyst (10 mol %), and 12 mg of desiccant in solvent (1.7 mL) was heated at mentioned temperature under argon atmosphere for 1 h; the resulting crude intermediate obtained (upon removal of DCE) was then heated in a solvent (2 mL) in the presence of a base (6 equiv) under an atmosphere of argon at indicated temperature [except entry 15 where DBU (0.62 mL) was used as solvent cum base]. [b]M.S. represents molecular sieves. [c]Yields of pure products. [d]Reaction time is 4 h.

DCE) was then heated at 80 ^{o}C in DBU (0.62 mL) which led to the formation of **5a** in 70% yield (see entry 15 of Table 1).

After achieving the optimized conditions, a multiple number of substrates (**1a-l**) containing diverse functional groups were then exposed to the optimized reaction conditions. The results are summarized in **Scheme 2**. First, we sought the effects of substitutions on aryl ring (A) attached to nitrogen atom of substrate **1**. This showed that incorporation of electron-donating groups (EDG) such as methyl or *t*-butyl (R^1 = Me or ^{t}Bu, R^2 = H) as in **1b** or **1c** led to the formation of quinolines **5b** (98%) or **5c** (90%) smoothly within 3.2-4 h. Surprisingly, when an electron-withdrawing group (EWG) like F is placed at the same position of **1d**, there was no product (**5d**) formation. Placement of a strongly EDG (R^1 = H, R^2 = OMe) at meta position of **1e** delivered the anticipated products **5e**(90%)/**5e´**(7%) in regio-isomeric mixture which were separated through column chromatography. As expected, an EWG like Cl at the same position failed to provide any desired product **5f**.

To check the substituent effects on the other aryl rings of **1**, incorporation of EWG (viz., F/Cl) at the para position of **1g**/**1h** easily afforded the product **5g**/**5h** in very good yields. But installation of an additional EDG in the *para*-position (viz., R^1= Me, R^2 = H) in ring A of **1h** (resulting in substrate **1i**) had a detrimental effect on **5i** (produced after 7h with 60% yield), though placement of a strong EDG (OMe) at the meta-position of the same ring (viz., R^1= H, R^2 = OMe) in **1g** facilitated the reaction (of **1j**) significantly generating a separable mixture of products [**5j** (89%) and **5j´**(8%)] after 3h. A moderate EDG (viz. Me) as in substrate **1k** appeared to hinder the reaction to some extent, delivering 52% of **5k** in 4.5 h, whereas a strong EDG (viz. OMe) in **1l** prevented the reaction completely.

Scheme 2. Synthesis of 4-(2,2-Diarylvinyl)quinolines **5a-k**[a] in one-pot

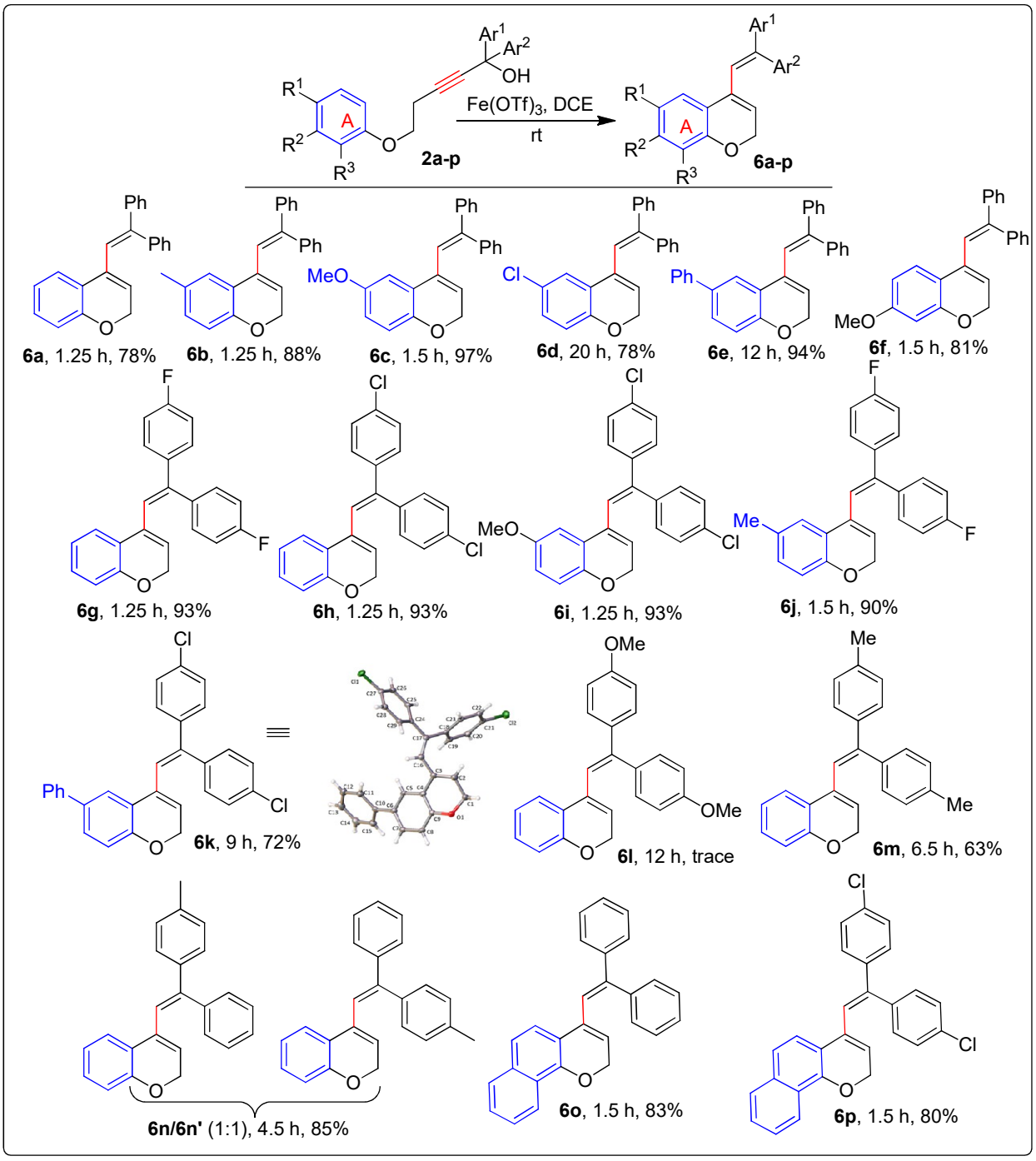


[a]Reaction conditions: A mixture of **1a** (0.062 mmol), $Fe(OTf)_3$ (0.006, 0.1 equiv), and desiccant (12 mg) in DCE (1.7 mL) was heated at 80 ºC under argon atmosphere for 1-2.5 h; the resulting crude intermediate obtained (upon removal of DCE) was then heated at 80 ºC in DBU (0.62 mL).

Encouraged by the above results, we decided to check the viability of the method on an oxygen carrying substrate **2** prepared in two steps. To our pleasure, exposure of substrate **2a** [$R^1 = R^2 = R^3 = H$, $Ar^1 = Ar^2 = Ph$] to 10 mol% of $Fe(OTf)_3$ alone in DCE at room temperature led to the formation of the desired (2,2-phenylvinyl)-2*H*-chromene **6a** within 1.25 h in 78% yield. We therefore decided to establish the scope and generality of this reaction by using a number of substrates **2** (**Scheme 3**).

Thus incorporation of an EDG (R^1= Me/OMe, R^2=R^3=H) at the *para*-position of the phenyl ring (A) of **2b**/**2c** led to the formations of 2*H*-chromenes **6b**/**6c** in 88-97% yield. Contrary to our previous observation (with **5d** in **Scheme 2**), an EWG (R^1 = Cl, $R^2 = R^3 = H$) in the same place delivered **6d** in 20 h with 78% yield. A phenyl substitution (R^1 = Ph, R^2 =R^3 =H) at the same position (as in **2e**) also proved effective, furnishing **6e** in 94% yield within 12 h. Even incorporation of an EDG at the meta-position ($R^1 = R^3 = H$, R^2 = OMe) of **2f** afforded **6f** in 1.5 h with 81% yield. Installation of a EWG (F/Cl) at the para-position of the other phenyl ring (of **2g/2h**) continued to deliver the products (**6g/6h**) smoothly with excellent yields. This high reactivity was maintained even after incorporation of an extra EDG (i.e., R^1 = OMe/Me, $R^2 = R^3$ = H) in the other phenyl ring (A) of substrate (**2i**/**2j**) affording product **6i/6j** with 90-93% yields. But possession of a phenyl ring (R^1 = Ph) at the same position (of **2k**) slightly hindered the reaction, producing **6k** in 9 h with 72% yield. Similar to our previous observations with products **5k** and **5l** of **Scheme 2**, substrate **2l** possessing a strong EDG (OMe) proved to be almost inert; but presence of a mild EDG (Me) in **2m** did afford **6m** in 63% yield after 6.5 h. Furthermore, substrate **2n** having unsymmetrical aryl moieties (viz., Ar^1 = *p*-Me-C_6H_4, Ar^2 = Ph) furnished an inseparable mixture of **6n** and **6n´** (85% yield, 1:1) after 4.5 h. Even naphthyl analogs (**2o** and **2p**) of the substrate were also found to be compatible, delivering the products (**6o** and **6p**) in 1.5 h with very good yields (80-83%).

Scheme 3. Synthesis of 4-(2,2-diarylvinyl)-2*H*-Chromenes **6a-p**[a]

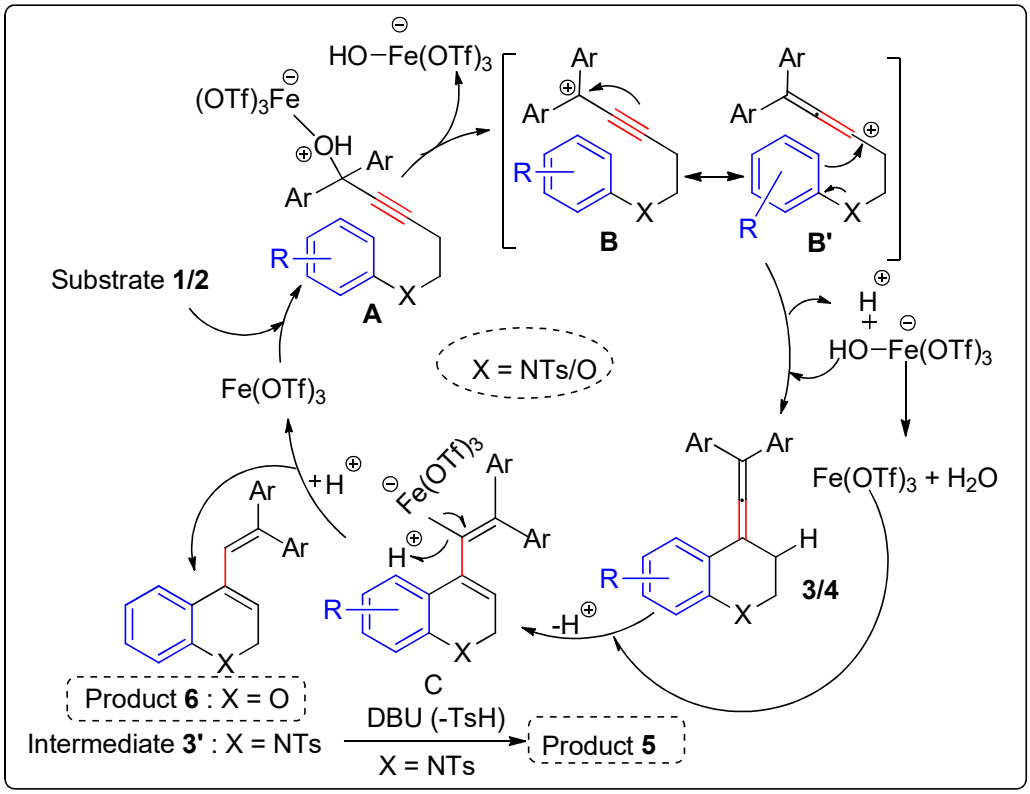


[a]Reaction conditions: A mixture of **2** (0.076 mmol) and $Fe(OTf)_3$ (0.008 mmol, 0.1 equiv) in DCE was stirred at room temperature under argon atmosphere.

Structures of all products were undoubtedly confirmed by spectral (^1H, ^{13}C, Mass Spectrometry) and analytical data. Detailed discussion of structural elucidation is provided in

Part II of Chapter 3. Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compound **5g, 5h, 5i** and **6k** (see, **Schemes 2-3**).

A plausible reaction mechanism is proposed as depicted under **Scheme 4**. It is expected that $Fe(OTf)_3$ would first activate the propargylic alcohol of substrates **1/2** forming intermediate **A** (**Scheme 4**) and thus facilitate the formation of carbocation **B** (or **B´**) by acting like a Lewis acid. The allenyl cation **B´** would then undergo an intramolecular nucleophilic attack by the adjacent aryl ring resulting in the formation of the carboannulated allene intermediates **3/4**; deprotonation from this step would regenerate $Fe(OTf)_3$ which triggers the formation of 1,3-diene intermediate **C** by acting like a Lewis acid again. Protonolysis of intermediate **C** would lead to the formation of either *2H*-chromene **6** (X=O) or the dihydroquinoline intermediate **3´**(X=NTs) with concurrent release of $Fe(OTf)_3$ which keeps the catalytic cycle active. Finally, intermediate **3´** undergoes a base (DBU) promoted 1,2-elimination (-TsH) to furnish the desired 4-(2,2-diarylvinyl)quinoline **5**.

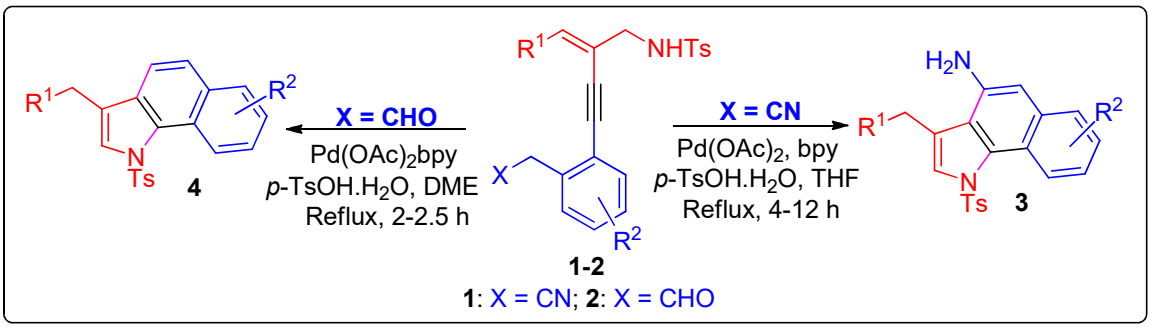


Scheme 4. A plausible mechanism for the formation of products **5/6**

Chapter 4

Palladium(II)-Catalyzed Cascade Reactions of Ene-Ynes Tethered to Cyano/Aldehyde: Access to Benzo[*g*]indoles

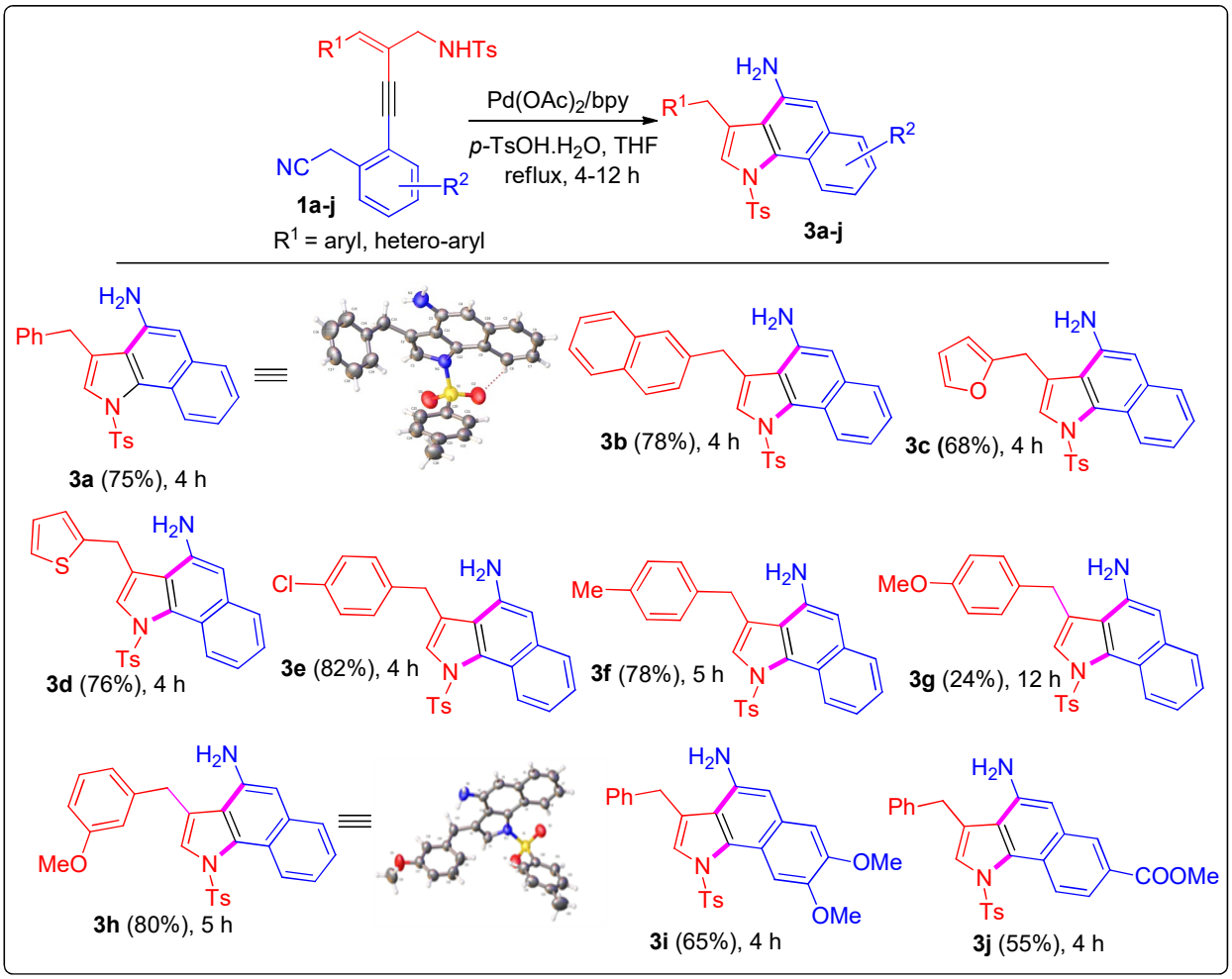
The fourth chapter deals with a simple and concise approach for an efficient construction of benzo[*g*]indoles **3-4** via Pd(II) catalyzed cascade cylizations of en-yne substrates **1** and **2** containing cyano and aldehyde groups, respectively (**Scheme 1**).



Scheme 1: Pd(II)-catalyzed synthesis of Benzo[*g*]indoles **3-4**

At the outset, an optimization study was conducted in which **1a** (R^1 = Ph, R^2 = H, X = CN) was used as model substrate which was treated under different reaction conditions with variation of different reaction parameters, i.e., catalyst, ligand, additive, solvent, temperature etc. The optimal reaction conditions was established where a mixture of **1a** (0.23 mmol) in THF (3 mL) was heated under reflux in presence of $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), and *p*-$TsOH{\cdot}H_2O$ (2.0 equiv) leading to the formation of the product **3a** with 75% yield within 4 h. Next, a series of substrates **1a-j** containing different functional groups were exposed to the optimized conditions to establish the generality of the method. The results are summarized in **Scheme 2**.

Scheme 2. Synthesis of 4-Amino Benzo[*g*]indole Derivatives **3a-j**[a]

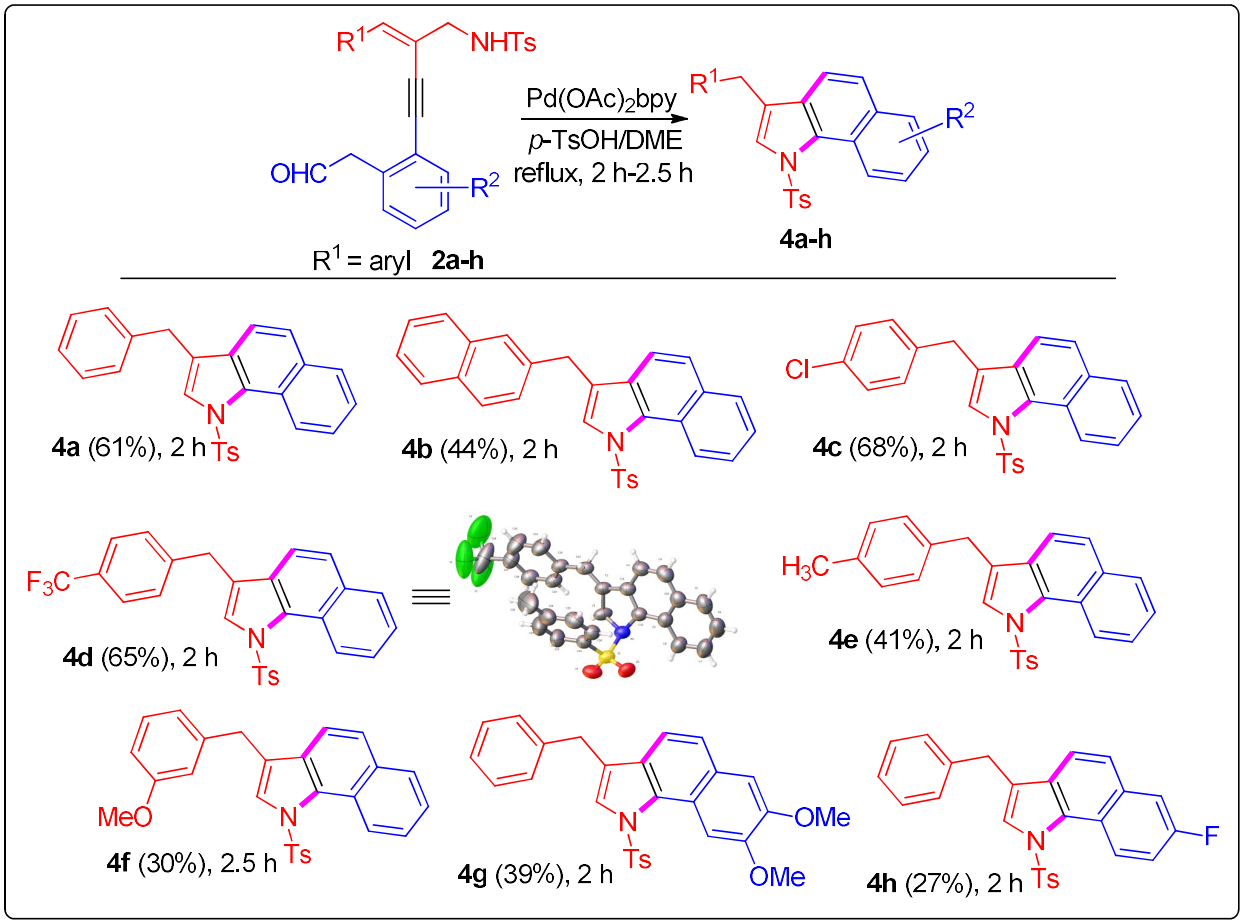


[a]Reaction conditions: **1** (0.23 mmol), $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), and *p*-TsOH·H_2O (2.0 equiv) in refluxing THF (3 mL) under argon atmosphere.

After successfully establishing the general protocol for the synthesis of 4-amino benzo[*g*]indole derivatives **3**, efforts were made on the synthesis of products **4** from substrate **2** containing a tethered aldehyde group (in place of cyano group of substrate **1**). In this context, substrate **2a** (R^1 = Ph, R^2 = H) was treated under the optimized conditions for the formation of product **3a**, but to our disappointment, the desired product **4a** was formed with only trace amount even after heating for the mixture for 12 h. We then set out to find the optimized conditions for the said synthesis; after several experimentations, refluxing a mixture of **2a** (0.23 mmol) in DME (3 mL) in presence of $Pd(OAc)_2$bpy (5 mol %) and *p*-TsOH·H_2O (1.5 equiv) under argon atmosphere produced the desired product **4a** within 2 h with highest yield (61%). Next, we

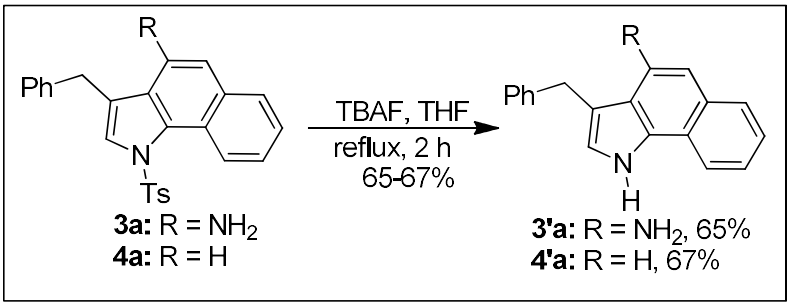
checked out the viability of this strategy over a number of substrates **2a-h** possessing different functional groups. The results are summarized in **Scheme 3**.

Scheme 3: Synthesis of Benzo[g]indole Derivatives **4a−h**[a]



[a]Reaction Conditions: **2a** (0.23 mmol), $Pd(OAc)_2bpy$ (5 mol %), *p*-TsOH.H_2O (1.5 equiv) were refluxed in DME (3 mL) under argon atmosphere.

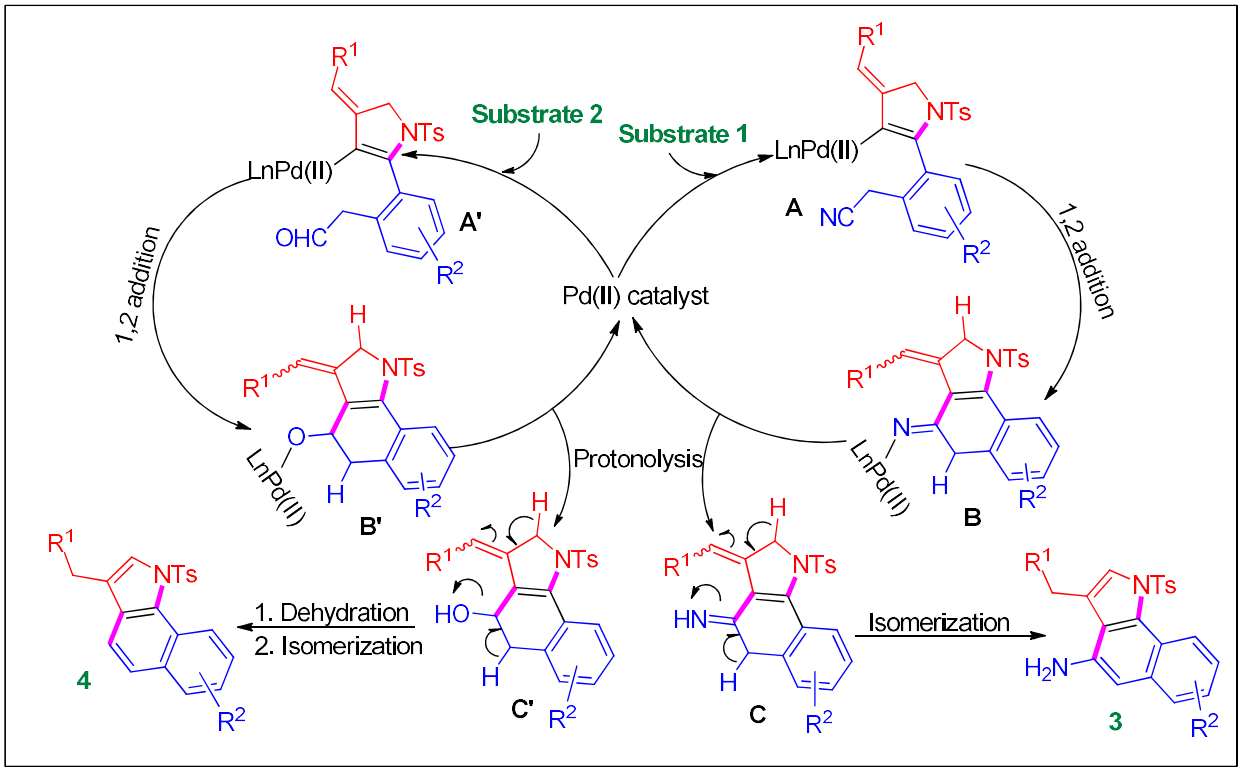
Owing to the presence of benzo[*g*]indoles with free NH group in a large number of bioactive compounds, we then attempted the detosylation of products **3a** and **4a** by treating them in a refluxing mixture of THF in presence of TBAF which delivered the compounds **3′a** and **4′a** respectively within 2 h with 65-67% yield (**Scheme 4**).



Scheme 4: Deprotection of compounds **3a** and **4a**

The structural conclusion of all products were drawn from the spectral (^{1}H, ^{13}C, Mass Spectrometry) and analytical data. Detailed discussion of structural elucidation is provided in **Part II** of Chapter 4. Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compound **3a, 3h** and **4d** (see, **Schemes 2-3**).

A plausible reaction mechanism for the formation of the products are depicted in **Scheme 5**. At first Pd(II) activates the triple bond of substrates **3** and **4** which triggers the formation of intermediate and **A** and **A′**, respectively via 5-*endo-dig* heteroannulation. Subsequent intramolecular 1,2-addition of the carbon-palladium bond of intermediate **A/A′** onto suitably placed carbon-heteroatom multiple bond (-C≡N/-C=O) leads to the formation of intermediate **B** and **B′** respectively. Next, protonolysis of **B** and **B′** delivered intermediate **C** and **C′**. Finally, isomerization of intermediate **C** afforded product **3** whereas dehydration and isomerization of **C′** leads to the formation of product **4**.



Scheme 5: A plausible reaction mechanism for the formation products **3** and **4**

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CHAPTER 1

Palladium(II) Catalysed Cascade Strategy for the Synthesis of Dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols/-10(15*H*)-ones: Easy Access to 1,3,5,7-Cyclooctatetraenes (COTs)

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Part I – A Short Review

1.1.1. Introduction: Cyclooctanes an unusual scaffold with huge activity

1.1.1.1. Importance of Cyclooctanoids:

Medium sized carbo/heterocycles are usually very difficult to access in laboratory through conventional method due to their entropic factors, transannular interactions and high degree of ring strain.[1] But they are widely found in natural products particularly in higher plants and marine organisms.[2] The fused core is present in numerous number of natural sesquiterpenoids,[3] diterpenoids,[3a,4] sesteterpenoids,[3a,5] and lignans.[3a,6] In particular, diterpenoids are the most diverse group of cyclooctanoid natural products[3a] to exhibit interesting phytohormone activities[7] and displays impressive pharmacological profiles;[4] e.g. *Taxol* (**1**, Figure 1), an important compound from Taxenes subclass,[8] is considered to be the most important diterpenoid due to its unique antimitotic properties[4a] in addition to its uses for the treatment of various types of cancer.[4b] Whereas *Pleuromutilin* (**2**, Fig. 1) and its derivatives are used as an antibiotic drug,[4c] *Kalmanol* (**3**, Fig. 1) is used as cardiotoxic agents.[4d] Among the sesteterpenoids, *Variecolin*[5a] (**4**, Fig. 1) has secured an important place in medicinal chemistry due to its antihypertensive

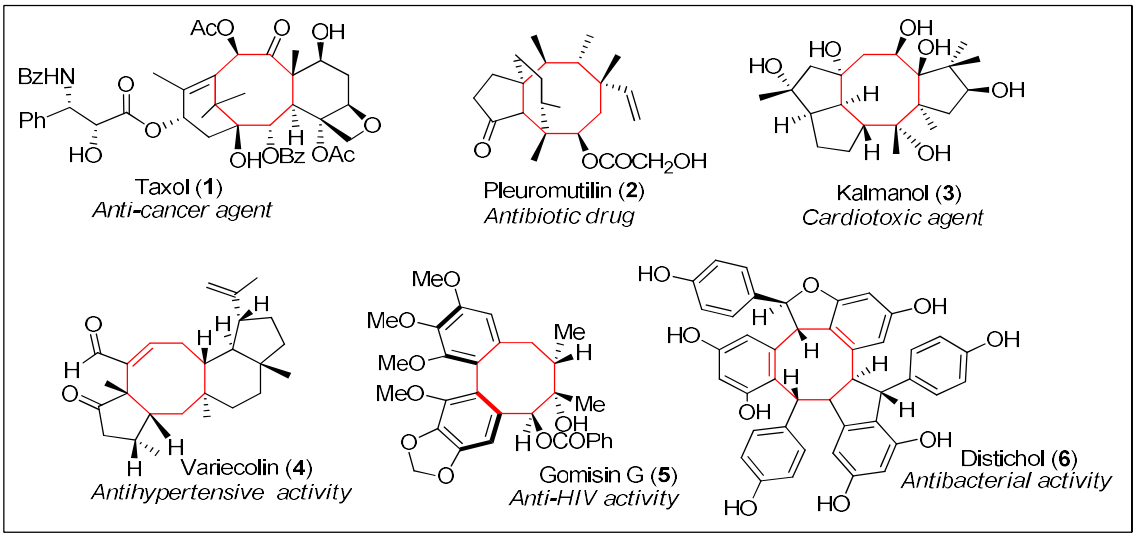


Figure 1: Some natural products with medicinal importance containing cyclooctanoid scaffold

property. In addition, several dibenzocyclooctadiene lignans possess significant antileukemic activity,[6a-b] antiviral activity,[6c] anti-HIV activity.[6d-e] In particular, among the lignans isolated from the stems of *Kadsura interior, Gomisin-G* (**5**, Fig. 1) exhibited the most potent anti-HIV activity with EC_{50} and therapeutic index (TI) values of 0.006 μg/mL and 300, respectively.[6e] Besides, *Distichol* (**6**, Fig. 1) a polyphenol lignan, shows antibacterial activity.[6f]

1.1.1.2. Importance of Cyclooctatetraenes (COT):

Among the eight-membered carbocycles, 1,3,5,7 cyclooctatetraenes (COTs) have attracted a great deal of interest and are known to be a fascinating class of molecules due to its electronic properties in addition to its nonplanar tub-shaped like structure with D_{2d} conformation[9] with widespread application in medicinal chemistry[10-15] as well as in material science.[16-20]

1.1.1.2.1. Importance of Cyclooctatetraenes (COT) in medicinal chemistry:

COTs find potential applications in diverse fields,[21] and are identified to be served as a complement motif of cubane, a bioisostere of a phenyl ring through validation in a number of pharmaceuticals and agrochemicals; where it shows either higher or similar activity in comparison to cubane in numerous cases.[10] Fused COTs give rise to diverse scaffolds with potential applications in drug developments;[11] e.g., compound **7** (Figure 2) containing dibenzocyclooctatetraene as the core structural unit proved to be a potent inhibitor of NF-κB signalling pathway with significant antitumor activity against several human tumor cell lines (GI_{50} 1.38–1.45 μM).[11] In addition to this, it inhibits LPS-induced NF-κB activation in RAW264.7 cells with an IC_{50} value of 0.52 μM, prevented IκB-α degradation and p65 nuclear translocation, and suppressed LPS-induced NO production in a dose dependent manner and one of the most important fact is that it proved to be more potent than paclitaxel against the drug-resistant KBvin cell line.[11]

Besides, COT was also even found to be prevalent in bioactive natural products. To date, few indole alkaloids having COT moiety as the core structure [e.g., *Caulerpin* **8a** (Fig. 2), its analogues **8b** and **8c** (Fig. 2),[12a] *Jolynamine*[12b] **9** (Fig. 2)] have been reported. Among them, *Caulerpin* is the most important compound in this class possessing numerous pharmacological activities including anti-nociceptive, anti-inflammatory, anti-tuberculosis activity etc.[13] It is used

as drug against herpes simplex virus type 1[14a] and shows antiviral effect against Chikungunya.[14b] Most importantly, it is reported to be an antitumor agent.[14c] In addition, it displays a potent inhibitory activity[15a] (IC_{50} = 3.77 μM) against hPTP1B (human protein tyrosine phosphate 1B), a key target for the treatment of type II diabetes and obesity.[15b]

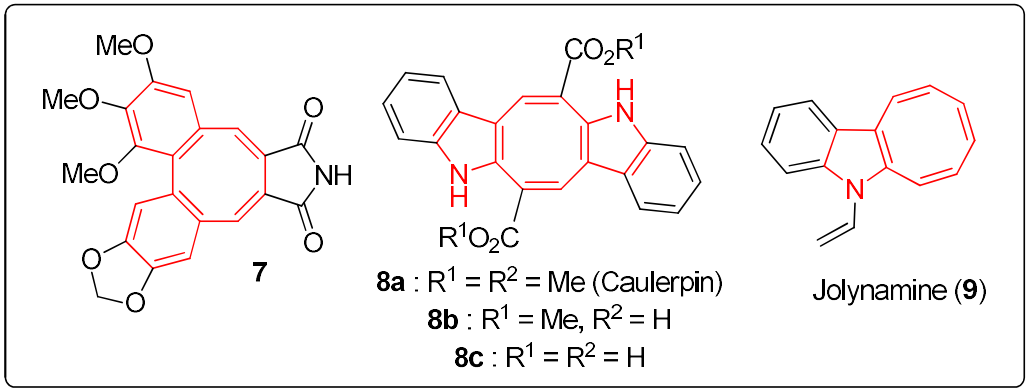


Figure 2. Natural products containing indole-fused COTs

1.1.1.2.2. Importance of Cyclooctatetraenes (COT) in material Science:

Besides the medicinal importance, COTs fused with other rings resulted in the generation of diverse scaffolds which find numerous applications in the fields of material science; e.g., they are used as catalysts,[16] ligands for *d*- and *f*-block metals.[16a,17] In addition to this, they find potential applications in molecular devices[18](e.g. dynamic molecular tweezers), fluxional materials,[19a] conducting polymers,[19b] light emitting devices[19c] etc. Notably, hetero aromatic fused COT systems has drawn considerable attention in recent times to explore the property of *excited-state aromaticity reversal* which would result in the generation of new type of AIE (aggregation-induced emission) systems[20] and found significant applications in biomedical and optoelectronics.

1.1.2. Synthesis of Cyclooctatetraenes (COTs):

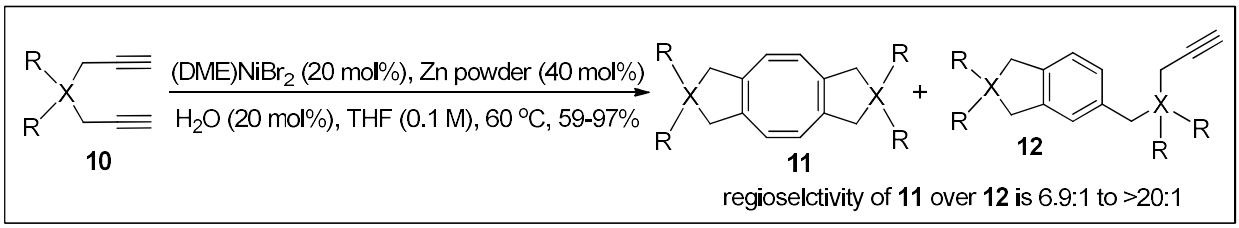
The fascinating structures of COT derivatives having potential applications surely have created a landmark in science. Therefore, immense study has been done for their general synthesis. But scrutiny of literature reveals that maximum reports are based on the synthesis of unsubstituted/substituted COTs[22a] comprising classical and multistep reactions (or ring

expansion reaction) carried out under harsh reaction conditions resulting in low overall yield. Though COTs fused with arenes/hetero-arenes at two or four double bonds are well-studied,[22] the synthesis of COTs fused at three double bonds are less in number. Some of the reports for the synthesis of di-, tri- and tetra fused COTs are briefly discussed.

1.1.2.1. Synthesis of cyclooctatetraenes (COTs) with fusion at two double bonds:

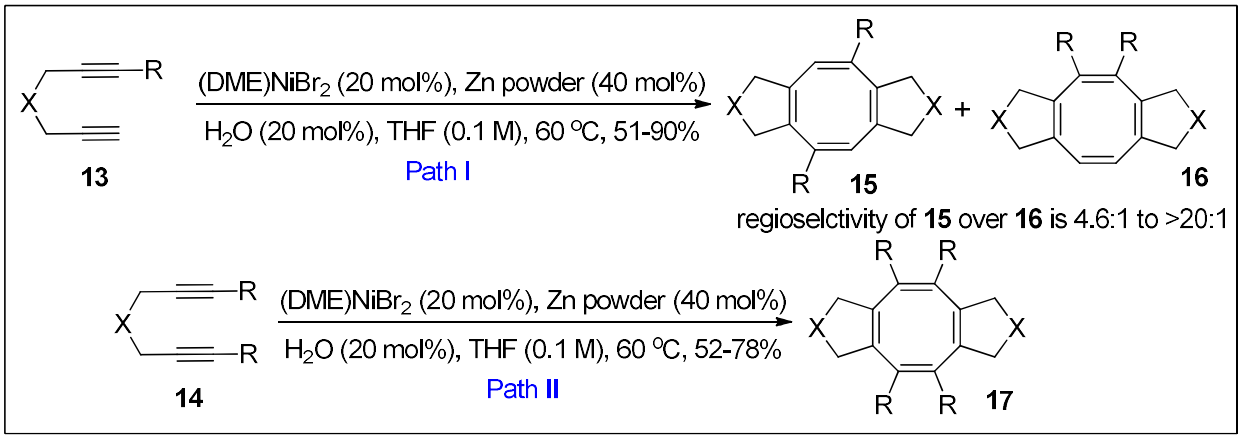
1.1.2.1.1. One-pot approach:

Wender and coworkers[23a] disclosed an efficient synthetic route for the formation of cyclooctatetraenes **11** (**Scheme 1**) with fusion at two double bonds via Ni(0)-catalyzed [2 + 2 + 2 + 2] intermolecular cyclotetramerization of 1,6-terminal diynes **10** under heating conditions in presence of Zn powder. The tetramerized product **11** was formed selectively (from 6.9:1 to >20:1) over the side product **12**. The overall yield of the reaction was excellent.



Scheme 1: Synthesis of cyclooctatetraenes **11** with fusion at two double bonds

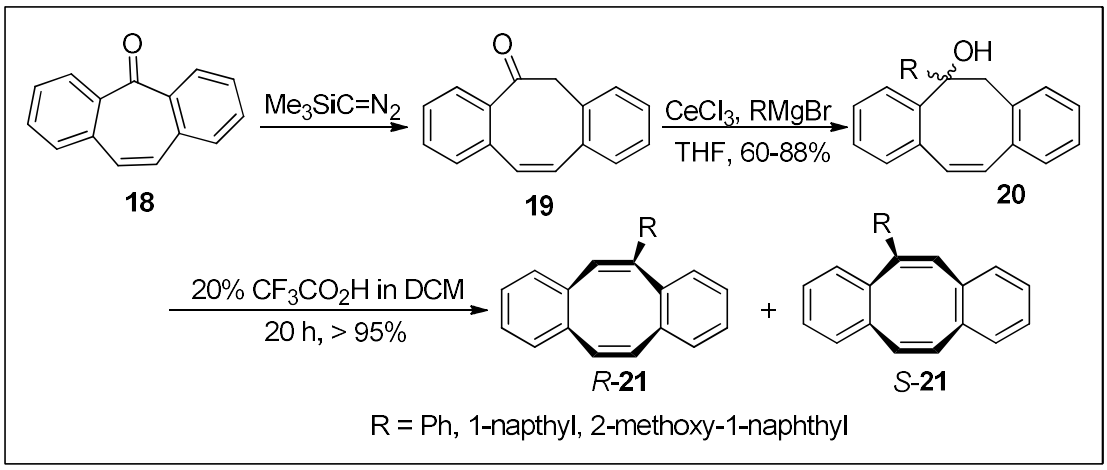
In continuation to this work, **Wender** and coworkers[23b] developed another synthetic pathway to access di-fused cyclooctatetraenes **15**, **16** (**Scheme 2,** path I) and **17** (**Scheme 2,** path II) from mixed internal/terminal 1,6-diynes **13** and internal 1,6-diynes **14**, respectively via nickel(0)-catalyzed [2+2+2+2] cycloadditions. When mixed internal/terminal diynes **13** were used as substrates, the regioselctive products **15** having less steric interactions were formed in majority than the other products **16** having steric congestion. Whereas di-yne **14** under the same reaction conditions using same nickel-catalyst produced exclusively product **17** as shown under Scheme 2 (path II).



Scheme 2: Synthesis of cyclooctatetraenes (i.e., **15**, **16** and **17**) fused at two-double bonds

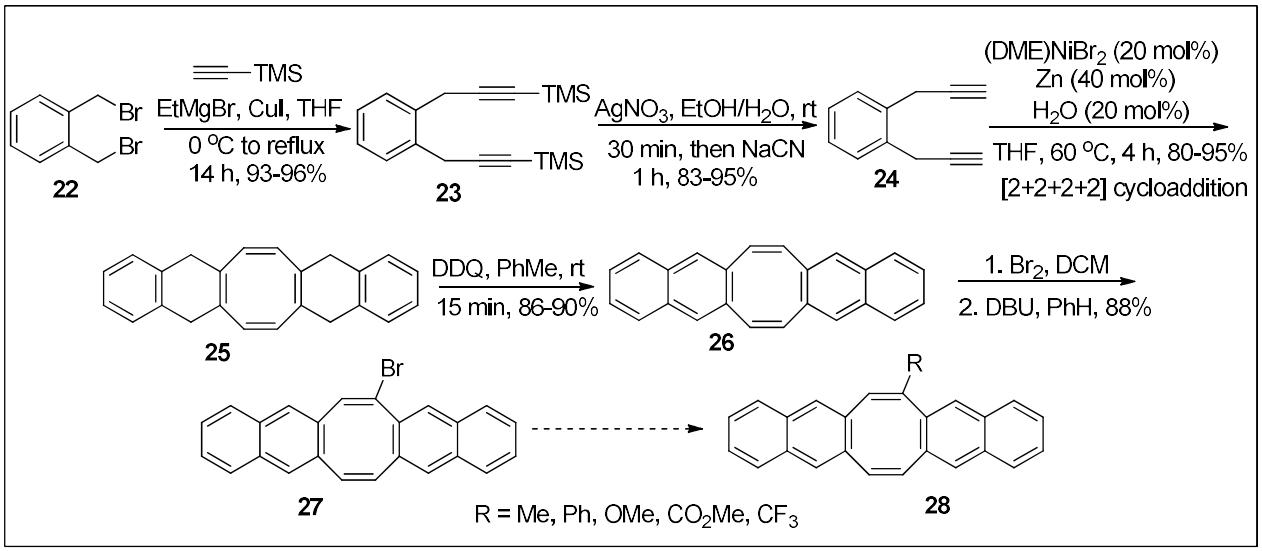
1.1.2.1.2. Multistep approach:

Grützmacher and coworker[16c] developed a simple pathway using three-steps reaction protocol for the generation of chiral dibenzo[*a,e*]cyclooctenes (**21**, **Scheme 3**) starting from commercially available dibenzosuberenone **18**. At first, the ring expansion of dibenzosuberenone **18** could easily be taken place to generate a eight membered core (**19**) through the reaction of (trimethylsilyl)diazomethane. Next, treatment of **19** with arylmagnesium bromide (RMgBr) in presence of $CeCl_3$ delivered **20** in 60-88% yields. Finally, dehydration of **20** leads to the formation of a mixture of enantiomeric products *R*-**21** and *S*-**21** with overall >95% yield. In particular note, the products are used as ligands of transition metal catalysts.



Scheme 3: Synthesis of chiral dibenzo[*a,e*]cyclooctenes **21**

Wender and coworkers[16a] developed a multistep pathway for the general synthesis of dinaptho[*a,e*]cyclooctatetraenes (dncot) **28** (**Scheme 4**). Towards this goal, at first, they treated commercially available 1,2-bis(bromomethyl)benzene **22** with trimethylsilylacetylene in presence of ethylmegnesium bromide and copper iodide leading to the formation of the silylated compound **23**, which upon deprotection in presence of $AgNO_3$ deliveres the diyne compound **24**. Next, compound **24** was transformed into **25** in excellent yields via Ni-catalyzed [2+2+2+2] cycloaddition. Further, oxidation of **25** in presence of DDQ at room temperature affords **26**. It is important to mention that the compound **26** acts as ligand and can complexes with Rh metal. Next, bromination of **26** affords bromo derivative **27** which upon further substitution or cross-coupling reactions deliveres varieties of dncot derivatives **28**.



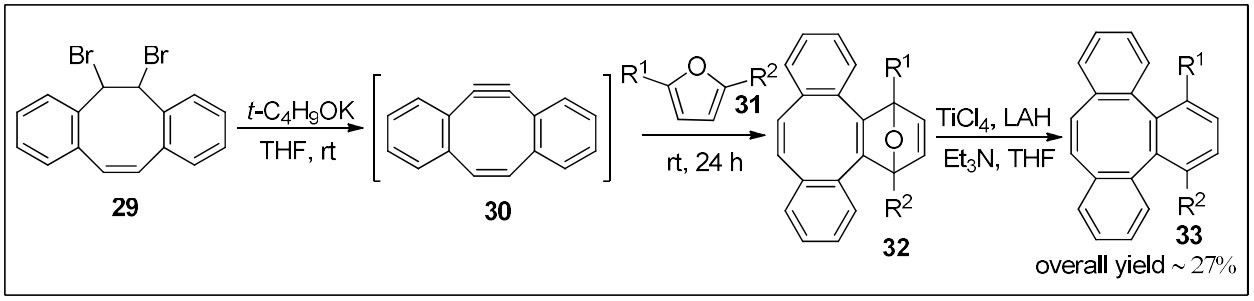
Scheme 4: Synthesis of dncot derivatives **26, 27** and **28**

1.1.2.2. Synthesis of cyclooctatetraenes (COTs) fused at three double bonds:

1.1.2.2.1. Multi-step pathway:

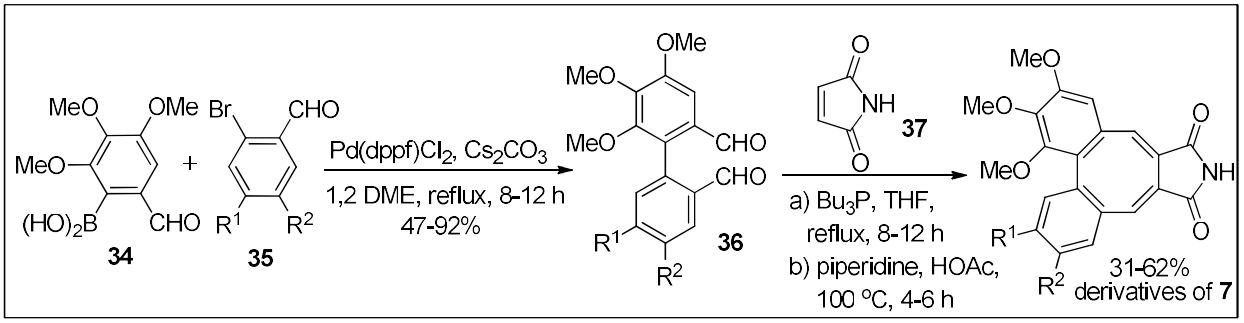
Wong et al[24] reported the formation of 1,4-disubstituted tribenzo[*a,c,e*]cyclooctenes **33** from 5,6-dibromo-5,6-dihydrodibenzo[*a,e*]cyclooctene **29** in three steps following classical pathway (**Scheme 5**). At first the benzyne intermediate **30** was generated from **29** in presence of *t*-C_4H_9OK in THF, which upon *Diels-Alder reaction* with substituted furans **31** leads to the

formation of intermediate **32**. Finally, aromatization of **32** using $LiAlH_4/TiCL_4$ in presence of Et_3N in THF gives rise to the desired products **33**. The overall yields of the reactions found to be around 27%.



Scheme 5: Synthesis of COT derivatives **33** with fusion at three double bonds

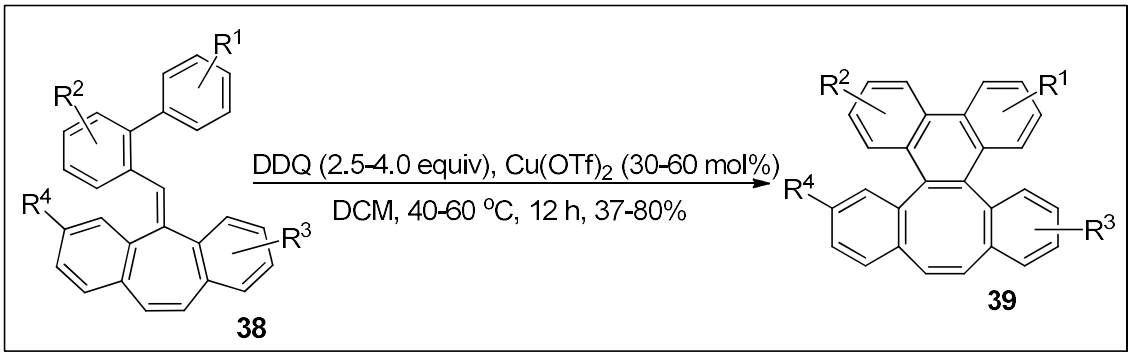
Xie and coworkers[11] synthesized few derivatives of fused cyclooctatetraenes **7** (**Scheme 6**) in two steps starting from phenylboronic acid **34** and bromobenzene **35**. The key di-formylbiphenyl intermediate **36** was synthesized via *Suzuki cross-coupling* in between **34** and **35**. The biphenyl intermediate was then reacted with a stable phosphorane Wittig reagent formed through the reaction between Bu_3P and maleimide **37**, which upon intramolecular *Knoevenagel condensation* affords the dibenzocyclooctatetraene succinimides **7**. In particular note, derivatives of **7** (see, Figure 2) show antitumor activity in addition to other biological activities as discussed earlier in this part.



Scheme 6: Synthesis of dibenzocyclooctatetraene succinimides **7**

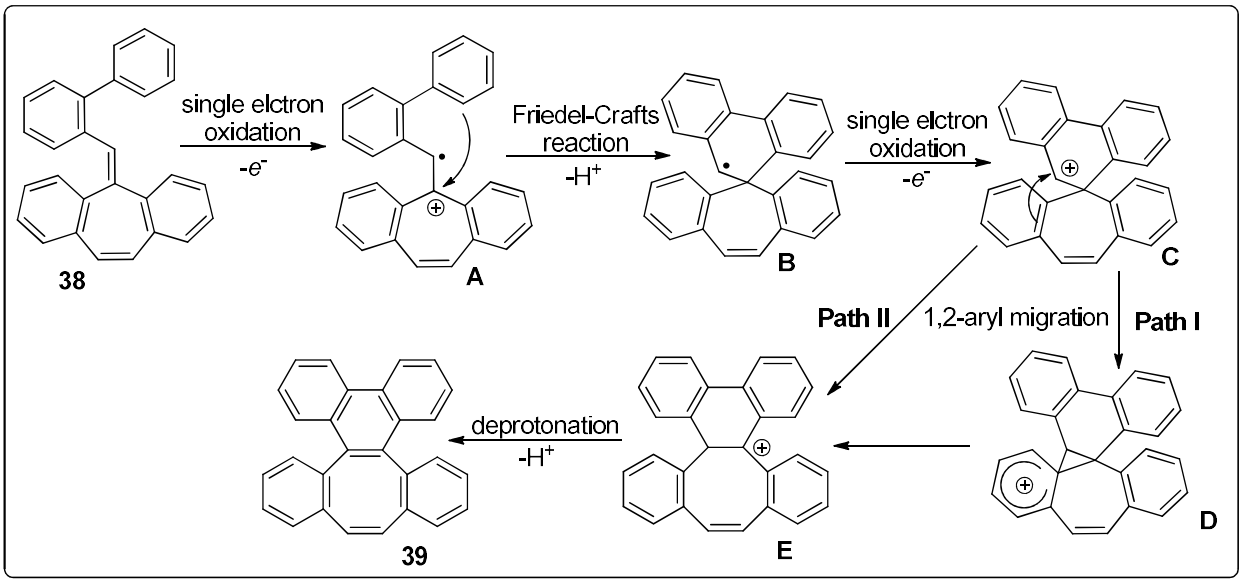
1.1.2.2.2. Modern synthesis of COTs with fusion at three double bonds:

Jin and coworkers[25] disclosed a convenient tandem pathway for the construction of dibenzocyclooctaphenanthrenes (dbCOTPs) **39** (**Scheme 7**) via novel oxidative ring expansion of dibenzo[7]annulenes **38** in presence of $Cu(OTf)_2$ and DDQ. The ring expansion reaction proceeds through a selective single-electron oxidation of the benzylidene moiety, intramolecular spirocyclization, and 1,2-aryl migration sequence respectively.



Scheme 7: Pathway for the formation of dibenzocyclooctaphenanthrenes (dbCOTPs) **39**

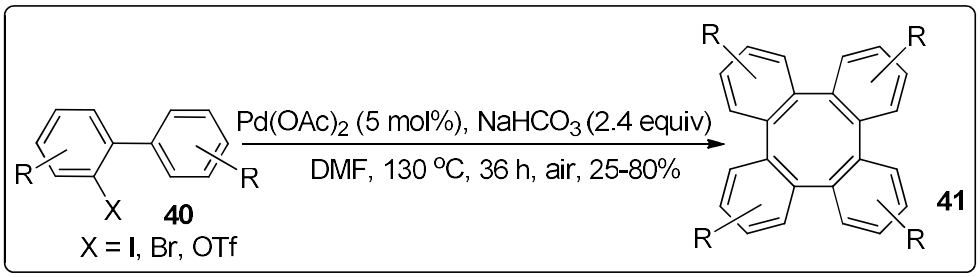
A probable reaction mechanism is depicted in **Scheme 8**. From the mechanistic point of view, at first, the substrate **38** is transformed into a radical cation species **A** via single-electron oxidation at the electron-rich alkene moiety of the substrate by the DDQ/$Cu(OTf)_2$ system. Next, *intramolecular Friedel-Crafts reaction* of species **A** leads to the formation of a spirocyclic radical species **B**, which upon further oxidation transforms into the spirocyclic cation **C**. Now, intermediate **C** undergoes a 1,2-aryl migration through the formation of an arenium cation **D** (path I) or through the direct migration (path II), affording the cation **E**. Finally, deprotonation of intermediate **E** leads to the formation of the desired product **39**.



Scheme 8: Plausible reaction mechanism for the formation of dbCOTPs

1.1.2.3. Synthesis of cyclooctatetraenes (COTs) fused at four double bonds:

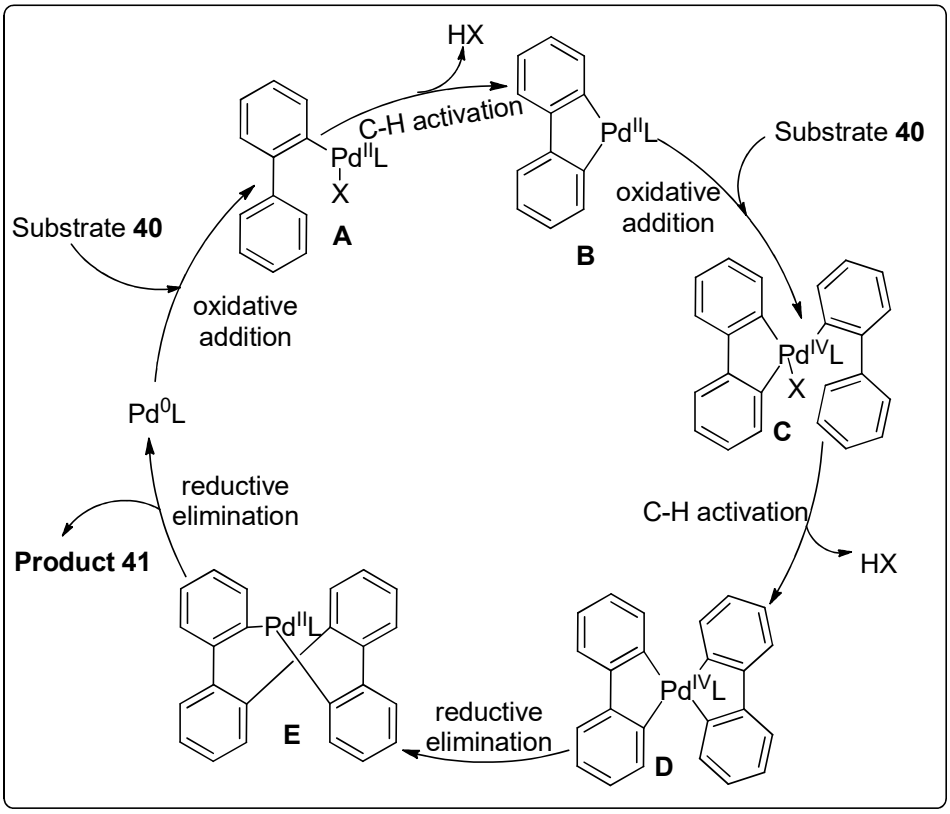
Zhu et al[26a] developed an attractive alternative pathway of traditional cross-coupling reactions for the formation of tetra-fused COT derivatives **41** (**Scheme 9**) via Pd(II)-catalyzed coupling reaction of *o*-halobiaryls **40** through direct arylation and cyclization in presence of air under ligand free conditions; where oxygen acts as promoter to give excellent transformations for the formation of the products **41**.



Scheme 9: Synthetic pathway for the formation of product **41**

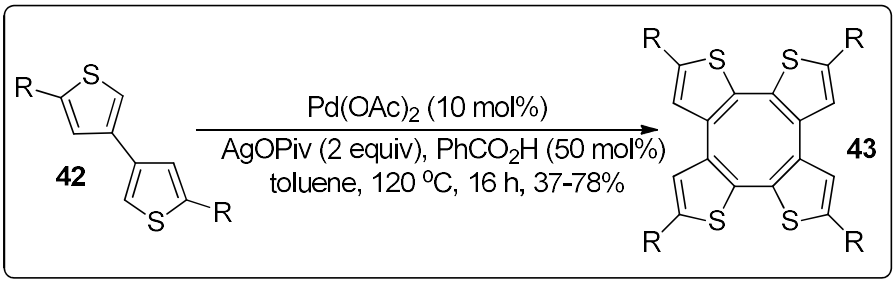
According to the reaction mechanism (**Scheme 10**), initially, oxidative addition of the starting material **40** onto the Pd species leads to the formation of the transient intermediate **A**, which upon activation of the neighbouring C-H bond triggers the formation of intermediate **B**.

Next, intermediate **B** undergoes an intramolecular oxidative addition to deliver intermediate **C** which undergoes another intramolecular C-H activation (of the neighbourig C-H bond) to afford intermediate **D**. Finally, the desired product **41** is afforded from intermediate **D** via two successive reductive elimination through formation of intermediate **E** with elimination of the Pd(0) species which keep the catalytic cycle active.



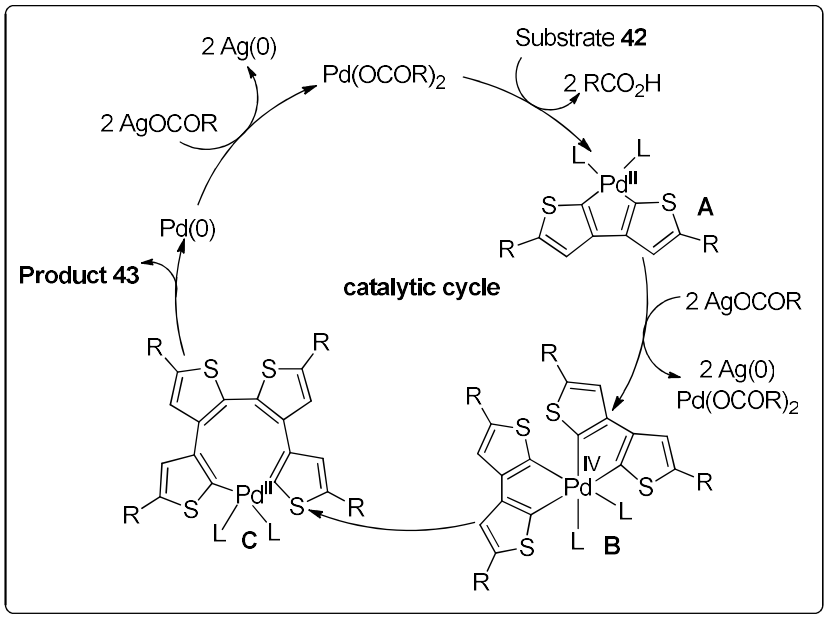
Scheme 10: Plausible reaction mechanism for the formation of product **41**

Miura and coworkers[26b] disclosed a convenient Pd(II)-catalyzed dehydrogenative cyclodimerization approach for the general synthesis of heteroarene-fused cyclooctatetraenes **43** (**Scheme 11**) from biheteroarenes **42** through four-fold C–H activation.



Scheme 11: Synthesis of product **43**

Mechanistic overview is depicted in **Scheme 12**. At first the starting material **42** reacts with the activated Pd(II) species to afford intermediate **A** via two fold C-H activation and eliminates RCO_2H, which upon dimerization and fragmentation in presence of the added silver additive leads to the formation of the high-valent Pd(IV)-complex **B**. Next reductive elimination of **B** affords a nine-membered complex **C**. Finally, intermediate **C** liberates the cyclodimeic product **43** with regeneration of the Pd(0) catalyst which keeps the catalytic cycle active.

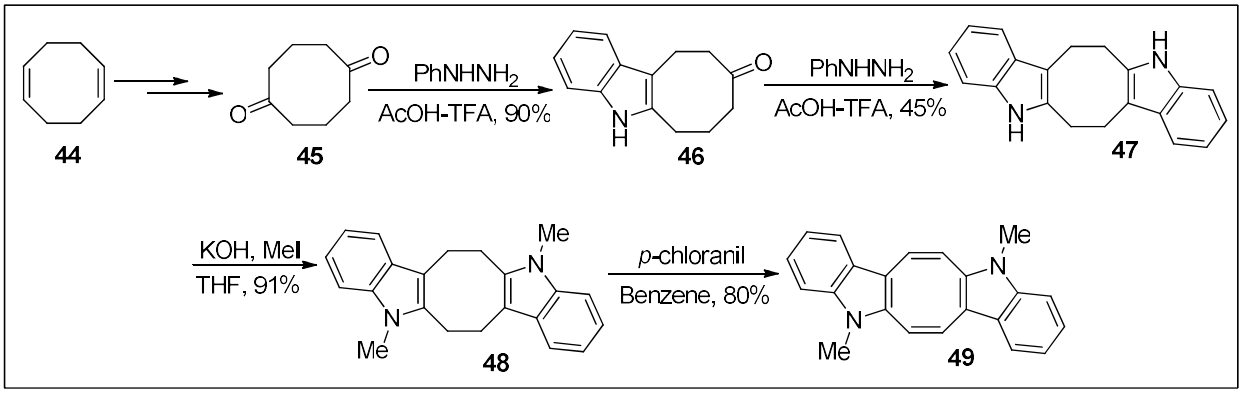


Scheme 12: A plausible reaction mechanism for the formation of product **43**

1.1.2.4. Synthesis of indole-fused cyclooctatetraenes (COTs):

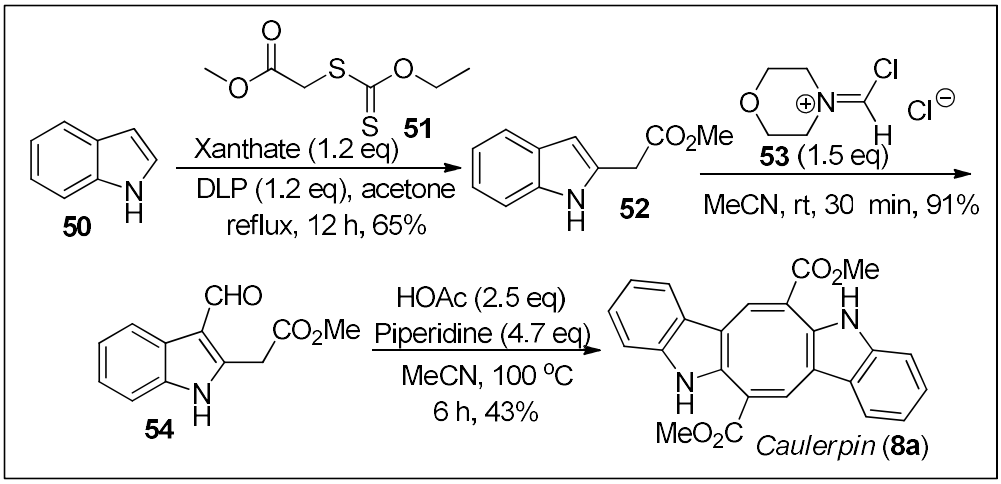
1.1.2.4.1. Fusion of indole at two double bonds of cyclooctatetraenes (COTs):

Saracoglu and coworkers[27a] synthesized an indole fused COT derivative **49** in multi-step pathway starting from 1,5-cyclooctadiene **44** (**Scheme 13**). At first, respective hydroboration and oxidation of **44** produced the diketone intermediate **45**, which upon two successive treatments with phenylhydrazine in acetic acid under refluxing conditions in the presence of trifluoroacetic acid (TFA) affords the bis-indole **47**. Next methylation of **47** leads to the formation of the **48**; which upon treatment with *p*-chloranil in benzene produced the product **49** in 80% yield.



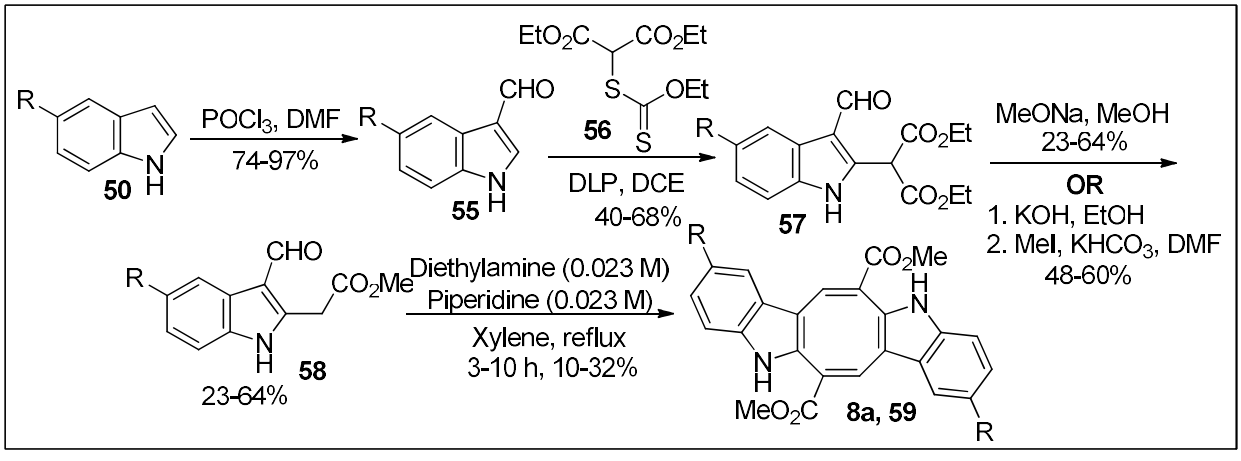
Scheme 13: Synthesis of product **49**

Li and coworkers[27b] reported a synthetic pathway for the generation of the natural product *Caulerpin* **8a** in few steps starting from indole **50** (**Scheme 14**). Initially methyl indole-2-acetate **52** was synthesized from indole **50** using xanthate **51** in presence of dilauroyl peroxide (DLP). Next, **52** was transformed into the corresponding formylated derivative **54** in presence of the imine salt **53** which acts as the formylating agent for the transformation. Finally, dimerization of **54** deliveres the product **8a**.



Scheme 14: Synthetic approach for the synthesis of *Caulerpin* **8a**.

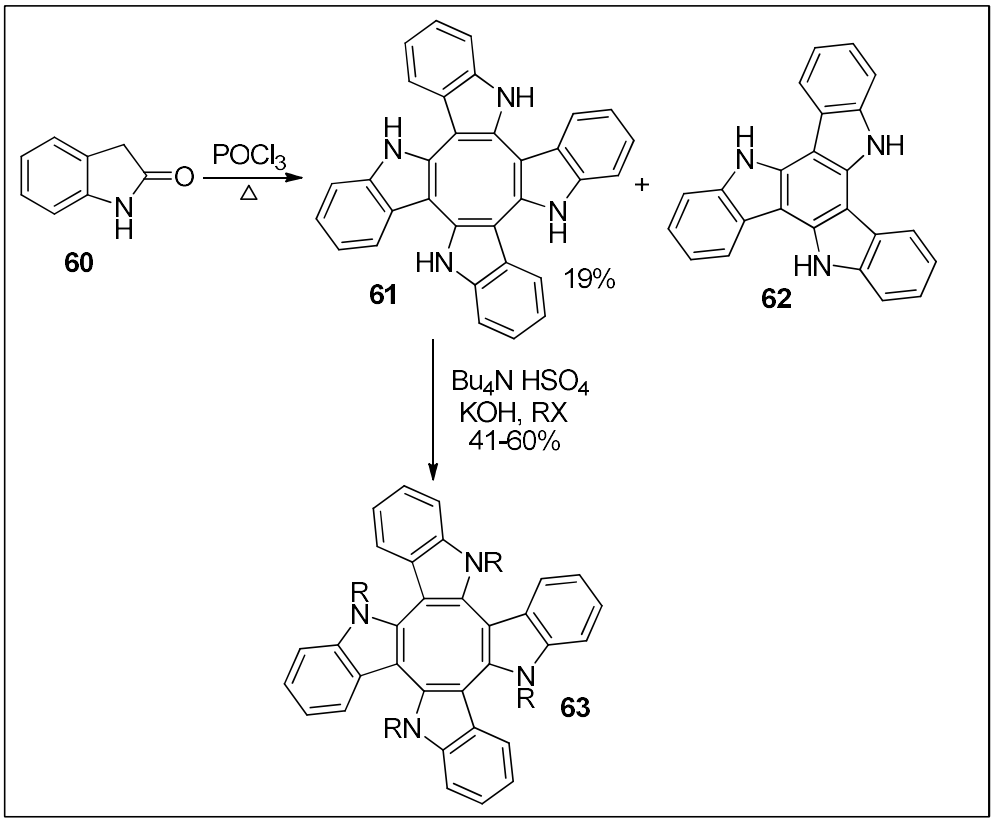
Martínez and coworkers[13b] reported a synthetic route to access *Caulerpin* **8a** and its several derivatives **59** (**Scheme 15**). The synthesis started with the formylation of commercially available 5-substituted-indole derivatives **50** in presence of $POCl_3$ in DMF leading to the formation of indole 3-carboxaldehyde **55**. Next, the malonic derivatives **57** was obtained via reaction of **55** with xanthate **56** and dilauroyl peroxide (DLP); where DLP act as the initiator and oxidizing agent. The subsequent decarboxylation and *trans*-esterification reactions of **57** was carried out in two steps employing MeONa or KOH, followed by the treatment of MeI delivering intermediate compound **58**. Finally, *Caulerpin* **8a** and its derivatives **59** were obtained from **58** in presence of diethylamine and piperidine in refluxing xylene as shown in **Scheme 15**.



Scheme 15: Synthesis of *Caulerpin* **8a** and its derivatives **59**

1.1.2.4.2. Fusion of indole at four double bonds of cyclooctatetraenes (COTs):

Gòmez-Lor and coworkers[27c] documented the synthetic approach for the synthesis of few derivatives of indole fused COT derivatives, where indole moiety is fused at all the double bonds (four) and studied their fundamental electronic properties in an attempt to make the construction of semiconductors (**Scheme 16**). Thus, reaction of 2-oxindole **60** with $POCl_3$ generates the tetra-fused compound **61** with 19% yield along with the formation side product **62**. Further treatment of **61** with alkyl halide (RX) produces the respective *N*-alkylated products **63**.



Scheme 16: Synthesis of indole fused COTs **61** and **63**

1.1.3. Importance of 2,4,6-cyclooctatrien-1-one:

In comparison to COT systems, 2,4,6-cyclooctatrien-1-ones **64** (Figure 3) are quietly less explored. To the best of our knowledge, scrutiny of the literature reveals that till date only one natural product is reported containing the core structure of **64** i.e. *racemosin C* **65** (Fig. 3), isolated from *Caulerpa racemosa*, displayed significant hPTP1B inhibitory activity.[28] Other than

that, some reports reveal their use as important synthetic intermediates leading to the formation different important compounds.[16c,29] Importantly, only few reports are based on the synthesis of some specific examples of substituted and fused derivatives of **64**.[29f,30]

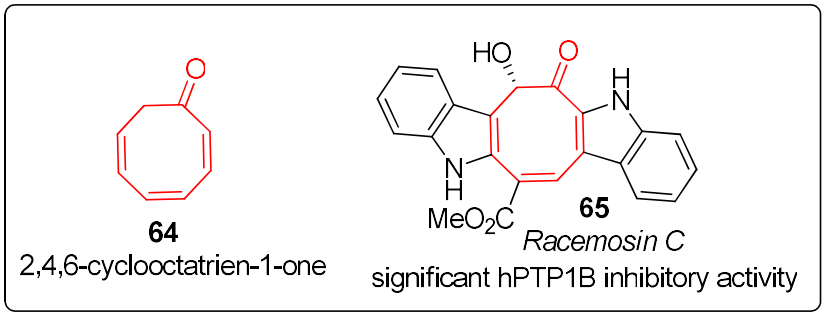
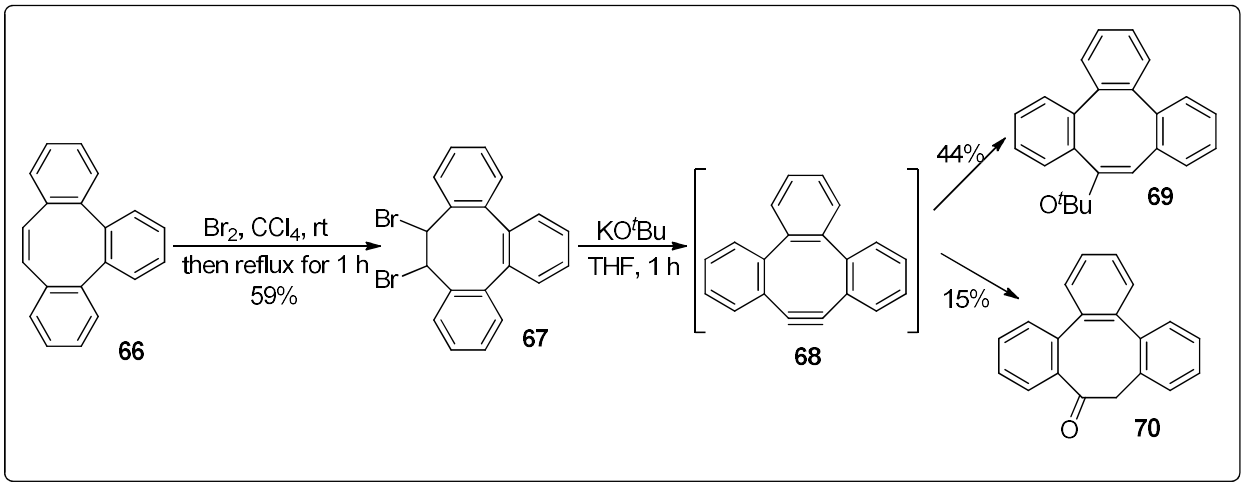


Figure 3. 2,4,6-Cyclooctatrien-1-one (**64**) and its bio-active derivative

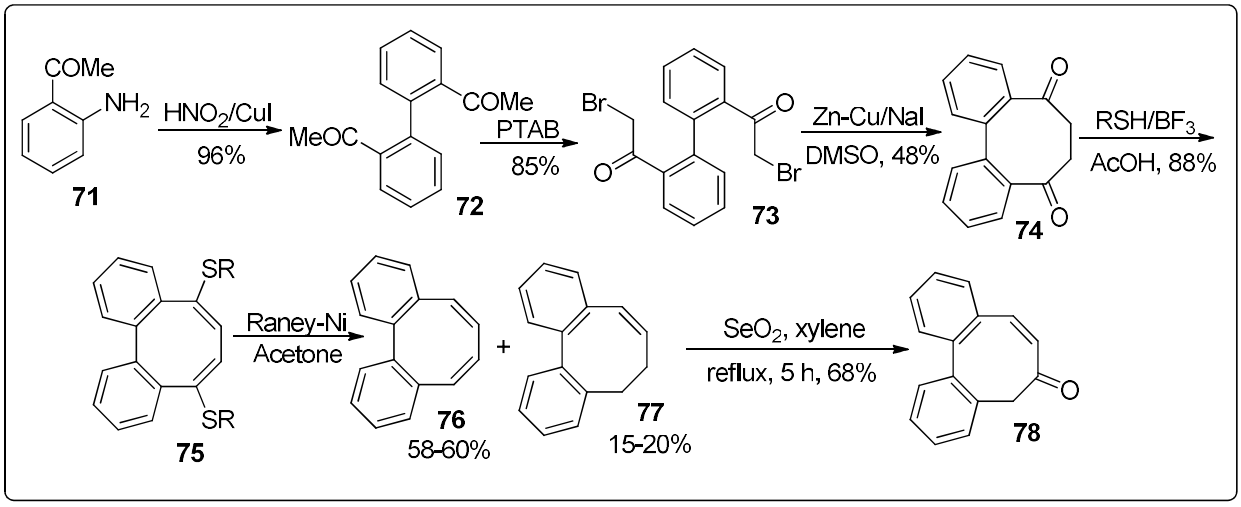
1.1.4. Synthesis of 2,4,6-cyclooctatrien-1-one derivatives:

Huang and coworkers[29f] reported one example for the synthesis of tri-fused derivative of 2,4,6-cyclooctatrienone **70** (**Scheme 17**) in multiple steps from COT derivative **66** fused at three double bonds. At first, bromination of the starting substrate **66** delivered compound **67**, which upon base promoted elimination leads to an unstable benzyne intermediate **68** which undergoes further transformation to form the product **70** (in 15% yield) in addition to a side product **69** (in 44% yield).



Scheme 17: Synthesis of 2,4,6-cyclooctatrienone **70** fused at three double bonds

Burger and coworkers[30] reported the synthesis of 2,4,6-cyclooctatrienone **78** fused at two double bonds (**Scheme 18**) in multiple steps starting from the substrate **71**. At first, the starting material **71** was transformed into a bi-aryl intermediate **72** which upon reaction with PTAB produces compound **73**. Next reaction of **73** with Zn-Cu/NaI leads to the formation of an eight-membered diketone **74**, which upon treatment with thiophenol affords compound **75**. Next desulfurization of **75** affords the di-fused COT derivative **76** in 58-60% yield along with formations of **77** in 15-20% yields. Finally, reaction of **77** with SeO_2 in refluxing xylene resulted in the formation of product **78** in 68% yields.



Scheme 18: Synthesis of 2,4,6-cyclooctatrienone **78** fused at two-double bonds

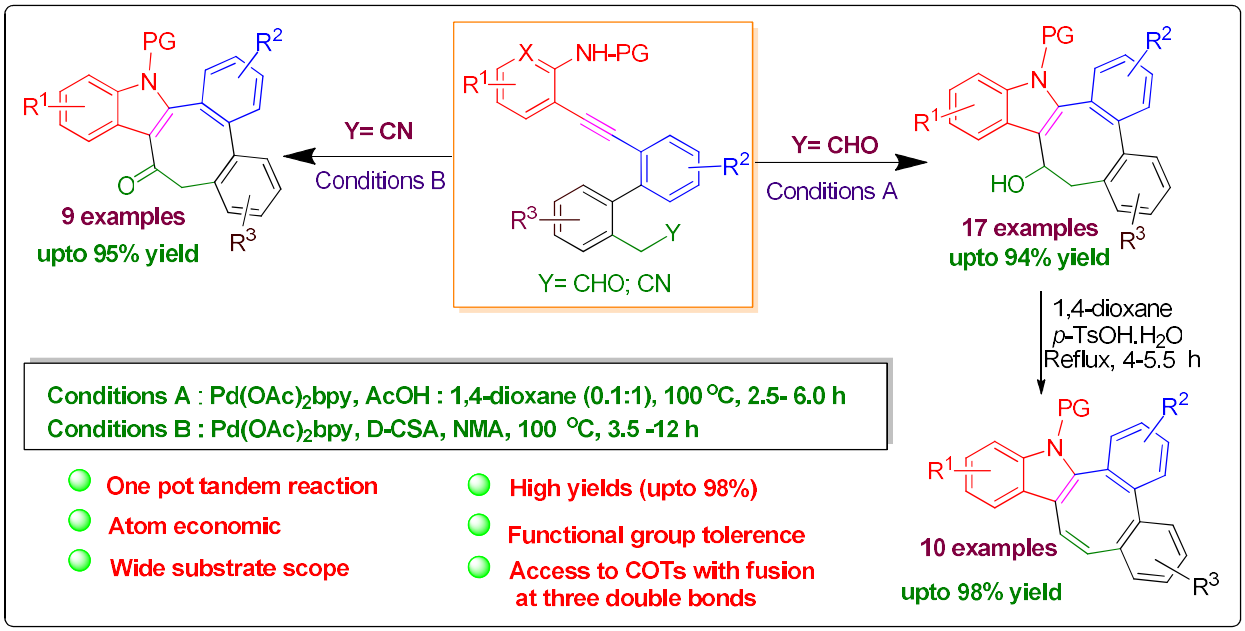
1.1.5. Concluding remarks:

Scrutiny of literature reveals that, fused COT proved to be an important carbocyclic moiety and secures an important place in medicinal chemistry as well as in material science due to its unique structural diversification. In particular note, fusion plays an unambiguous role in their activity as discussed earlier. But unfortunately though there are many reports on the synthesis of substituted COTs, reports on the synthesis of fused COTs are considerably less. More specifically, tri-fused COTs are the most unexplored field as only few specific reports are documented for their general synthesis. Therefore, disclosure of simple one-pot strategy using low cost catalyst and starting materials would be of high interest. In this content, a one-pot cascade strategy for the general synthesis of tri-fused COTs, where the COT is fused with both

carbocycle and heterocycle is reported; providing an interesting structural diversification; detailed results are discussed in **Part II** of this chapter.

On the other hand, 2,4,6-cyclooctatrienones are quietly less explored field, where only specific examples are reported for their synthesis. So development of an atom-economic efficient strategy for their general synthesis is highly desirable so that more studies could be done on this scaffold. Towards this goal, a new Pd(II) catalyzed simple one-pot tandem strategy for their general synthesis have been developed; detailed outcomes of the study are discussed in **Part II** of this chapter.

Part II – Results and Discussion



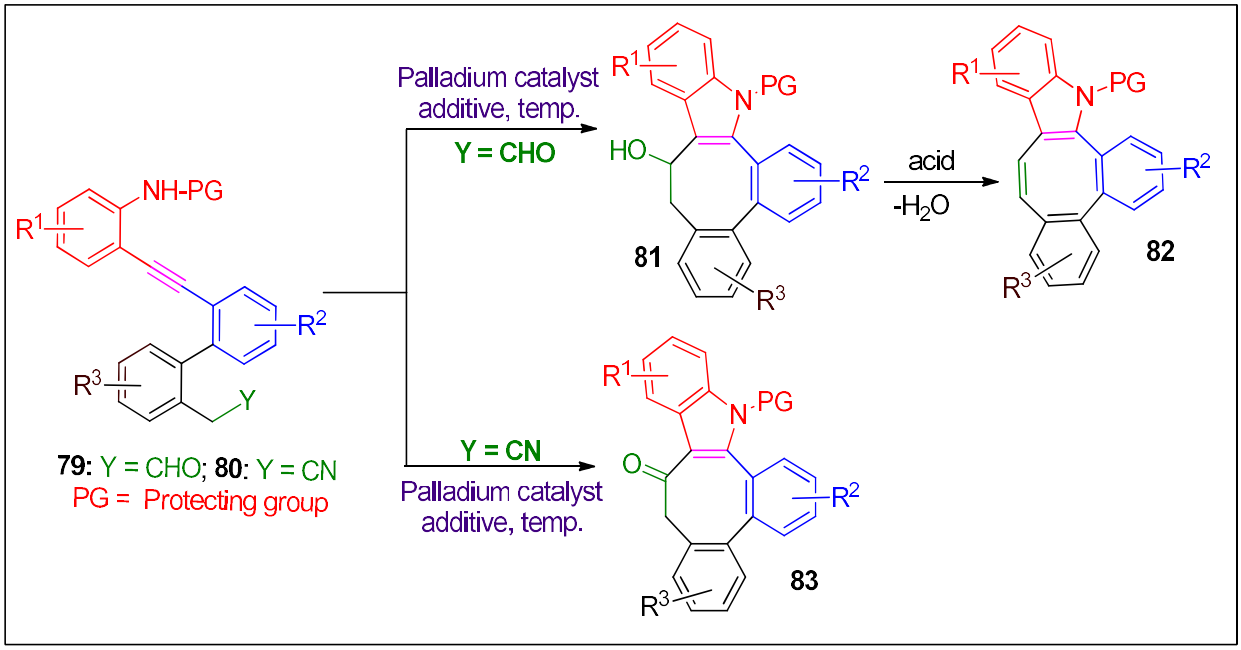
Reference: **Sukanya De**, Moumita Jash and Chinmay Chowdhury*; *Chem. Commun.*, **2020**, *56*, 15659-15662.

1.2.1. Introduction

From the literature survey (as discussed in **Part I** of this chapter), it is quite evident that COT systems are considered as an important carbocylic scaffold possessing unique structural diversity. Particularly, fused COT systems are of special interest due to their wide spread applications in medicinal chemistry and material sciences as well; where the degree of fusion of COT plays an important role in their structural activity. Though there are many reports for the synthesis of COTs fused at two or four double bonds (as discussed in **Part I** of this chapter), reports for the synthesis of the synthesis of COTs fused at three double bonds are less in number (**Scheme 5**, **6** and **7** in **Part I**) using mainly classical reactions where only limited achievements for the efficient construction of indole-fused COTs[13b,27] (**Scheme 13**, **14**, **15** and **16** in **Part I**) are accomplished. Among them, to the best of our knowledge, the synthesis of hybrid COTs, i.e., those fused with an indole ring and two arene rings, has not yet been reported, underlining the urgency for their facile and general synthesis.

In contrast to COTs, 2,4,6-cyclooctatrien-1-ones are quite less though their synthesis has become an active area of research in the last century leading to the development of a number of reaction. Despite the importance of this field, only a few reports on the synthesis of some specific examples of 2,4,6-cyclooctatrien-1-ones fused with arenes or other rings are known; this clearly indicates the requirement of a reliable method for their general synthesis.

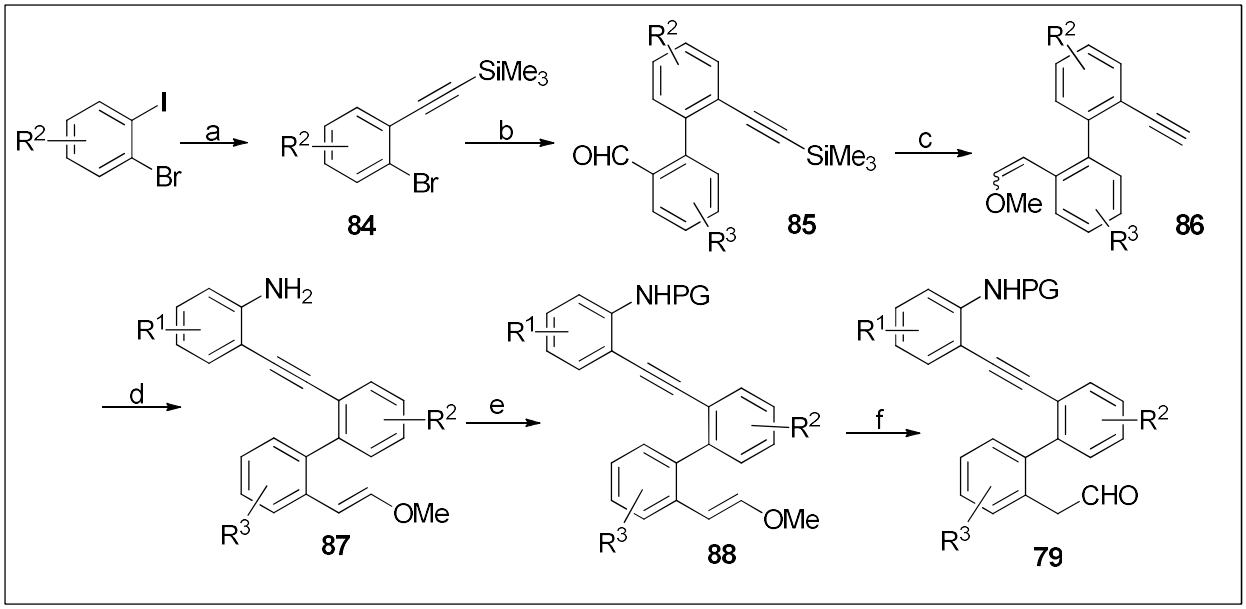
Towards this goal, in continuation of our work[31a-c] on palladium catalyzed reaction, it was anticipated that a general synthesis of fused 2,4,6-cyclooctatrien-1-ols **81** and 2,4,6-cyclooctatrien-1-ones **83** could be achieved in one-pot from acetylenic substrates **79** and **80**, respectively, employing an appropriate catalyst (**Scheme 19**). Furthermore, the synthesis of fused COTs **82** could also be accomplished conveniently by the acid-mediated dehydration of products **81**. The synthetic pathways proved to be viable upon the deployment of an appropriate catalyst and reaction conditions. Herein, the results obtained so far for the cost-economic synthesis of fused 2,4,6-cyclooctatrien-1-ols, COTs and 2,4,6-cyclooctatrien-1-ones from simple substrates (Scheme 19)[31d] is reported.



Scheme 19: Strategy for the synthesis of eight-membered heterocycles **81**, **82** and **83**

1.2.2. Synthesis of Starting Material 79

The desired starting materials **79** were prepared in few steps starting from 2-bromoiodobenzene derivatives. In the first step, silylated derivative of 2-bromoiodobenze **84** was obtained via "*Sonogashira reaction"*. The silylated compound formed was then allowed to undergo "*Suzuki coupling*" with commercially available 2-formylbenzeneboronic acid derivatives to form **85**[32] which on desilylation[32] followed by Wittig reaction delivered the masked aldehyde derivatives **86**. The **86** derivatives were then underwent "*Sonogashira coupling"* with 2-iodoanilines to produce **87** derivatives. Later, the amine group of **87** was protected (tosylated/ nosylated) to form **88** and finally the desired starting material **79** was formed by demasking aldehyde group of **88** using *p*-TsOH.H_2O.



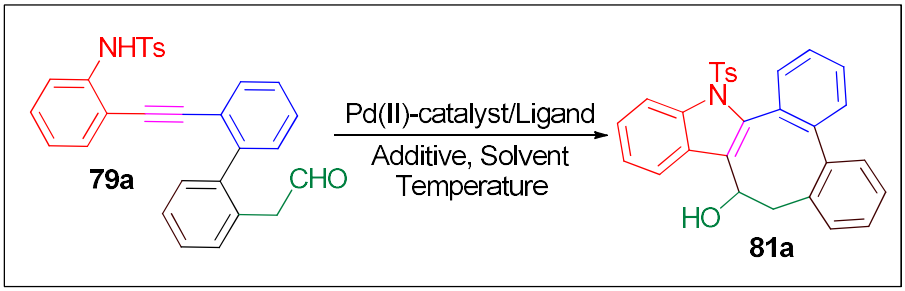
Scheme 20. Reagents and Conditions: (a) Trimethylsilyl acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF ,0 ^oC-rt, 1.5-2.5 h, 92-94%; (b) 2-Formylbenzeneboronic acid derivatives, $Pd(OAc)_2$, dppf, K_2CO_3, DME, 80^oC, overnight, 50-80%; (c) (i) K_2CO_3, MeOH, rt, overnight, 92-95%, (ii) (Methoxymethyl)triphenylphosphonium chloride, NaHDMS (2M), THF, 0 ^oC-rt, 1-1.5 h, 78-82%; (d) 2-iodoaniline derivative, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF ,0 ^oC-rt, 5-15 h, 72-88%; (e) TsCl/ NsCl, pyridine, DCM, 0 ^oC- rt, 12-24 h, 66-85%; (f) *p*-TsOH.H_2O, acetone, 0 ^oC-rt, 3.5-5.5 h, 49-91%.

1.2.3. Synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols 81

1.2.3.1. Optimization of the reaction conditions for the synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols 81a

Towards this goal, we set out to explore the optimized conditions for the transformation. Initially, we took up the model synthesis of compound **81a** ($R^1 = R^2 = R^3 = H$, PG = Ts) from acetylenic substrate **79a**. Thus, performing the reaction in 1,4-dioxane using $Pd(OAc)_2$/bipyridine (bpy) as catalyst and ligand respectively in presence *D*-(+)-camphorsulfonic acid (*D*-CSA) as an additive produced the product **81a** with 27% yield (Table 1, entry 1). Replacing the catalyst by $Pd(OAc)_2$bpy made it still less attractive (Table 1, entry 2). We, therefore, persisted with the previous catalytic system but changed the additive to

Table 1. Optimization of the reaction conditions for the formation of product 81a[a]



Entry	Catalyst	Ligand	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%) 81a
1[b]	$Pd(OAc)_2$	bpy	D-CSA	1,4-dioxane	100	8	27
2	$Pd(OAc)_2$bpy	---	D-CSA	1,4-dioxane	100	5	trace
3[b]	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	1,4-dioxane	100	8	40
4	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	NMA	100	5.5	nr
5	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	THF	reflux	6	nr
6[c]	$Pd(OAc)_2$bpy	---	*p*-TsOH.H_2O	1,4-dioxane	100	7	21
7	$Pd(OAc)_2$bpy	---	$MeSO_3H$	1,4-dioxane	100	6	trace
8	$Pd(OAc)_2$bpy	---	Triflic Acid	1,4-dioxane	100	5	16
9	$Pd(OAc)_2$bpy	---	$PhCO_2H$	1,4-dioxane	100	4.5	47
10	$Pd(OAc)_2$bpy	---	2,3-Naphthalene-dicarboxylic acid	1,4-dioxane	100	6	nr
11	$Pd(OAc)_2$bpy	---	AcOH	1,4-dioxane	100	6	36
12[d]	**$Pd(OAc)_2$bpy**	**---**	**AcOH**	**1,4-dioxane**	**100**	**3.5**	**73**
13[d,e]	$Pd(OAc)_2$bpy	---	AcOH	1,4-dioxane	100	4.2	70
14[d,f]	$PdCl_2$	bpy	AcOH	1,4-dioxane	100	12	nr
15[d,f]	$Pd(MeCN)_4(BF_4)_2$	bpy	AcOH	1,4-dioxane	100	6	nr
16[d,f]	$Pd(MeCN)_2Cl_2$	bpy	AcOH	1,4-dioxane	100	6	nr

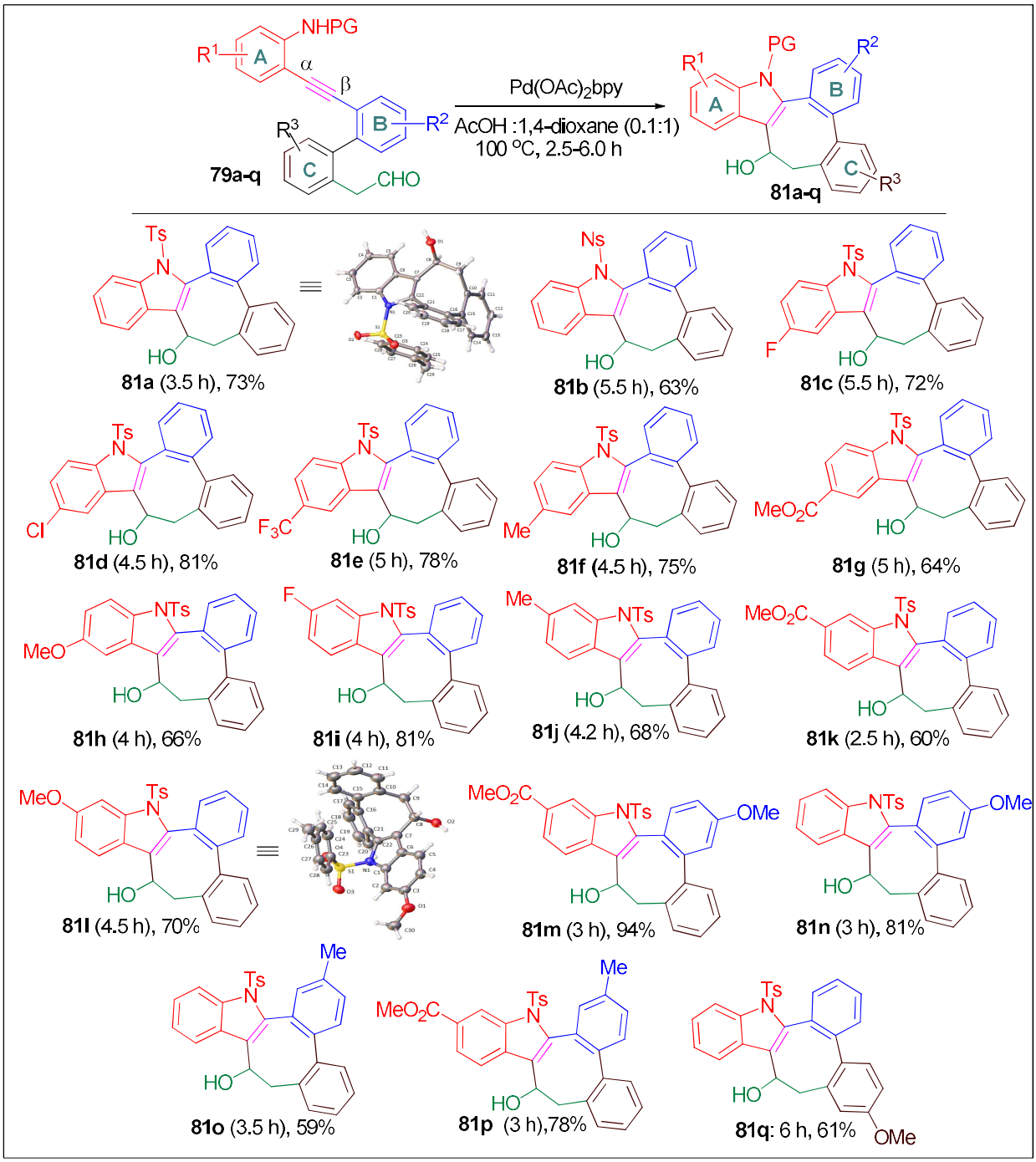
[a]Reaction conditions: **79a** (0.086 mmol), catalyst (6 mol%), ligand (6 mol%), and additive (2 equiv.) in solvent (1 mL) heated at 100 °C (except entry 5). [b]Starting material recovered (40% in the case of entry 1 and 28% in the case of entry 3). [c]Cyclooctatetraene derivative **82a** (20%) formed along with **81a**. [d]AcOH (10%, v/v) in 1,4-dioxane. [e]5 mol% palladium catalyst. [f]Multiple other spots (TLC) were formed which were not characterized, nr:no reaction.

p-TsOH.H_2O (Table 1, entry 3). Switching to other solvent systems failed to provide the product (Table 1, entries 4 and 5) suggesting the importance of 1,4-dioxane in this reaction. Therefore, we reverted to $Pd(OAc)_2$bpy and pursued this reaction further in 1,4-dioxane; to our surprise, **81a** (21%) was formed together with 20% of COT derivative **82a** (Table 1, entry 6). Employment of aliphatic sulphonic acids did not improve the outcome (Table 1, entries 7 and 8). Nevertheless, replacing the additive with benzoic acid was found to be encouraging, though 2,3 naphthalenedicarboxylic acid failed to provide **81a** (Table 1, entries 9 and 10). Next, switching to low cost acetic acid (2 equiv.) led to 36% yield of **81a** (Table 1, entries 9 and 11); to our delight, increasing the amount of AcOH (i.e., 10% in 1,4-dioxane, v/v) afforded **81a** within 3.5 h in 73% yield (Table 1, entry 12). But decreasing the catalyst loading had a detrimental effect (Table 1, entry 13). Employment of other Pd(II) catalysts [viz. $PdCl_2$, $Pd(MeCN)_4(BF_4)_2$ and $Pd(MeCN)_2Cl_2$] failed to give the desired product **81a** (Table 1, entries 14–16). Thus the reaction condition of entry 12 of Table 1 was considered as optimal.

1.2.3.2. Scope of the reaction

With the optimized conditions in hand, the generality of the reaction protocol was explored by carrying out the reactions of acetylenic substrates **79a-q** (**Scheme 21**). Interestingly, when the nosyl group (–Ns) was used as an N-protecting group instead of tosyl (–Ts) as in **79b**, the reaction required a longer reaction time (i.e., 5.5 h) and the yield of the product **81b** decreased (**Scheme 21**, product **81a** vs. **81b**) underlining the importance of the N-tosyl group. Thereafter, the effects of different functional groups at the *meta* and *para* positions (with respect to the acetylenic group) in ring A of substrate **79** were studied. For the *meta* position, both moderate electron withdrawing (i.e., R^1 = F/Cl/CF_3) and -donating (R^1 = Me) groups performed well, resulting in the formation of products **81c–e** and **81f**, respectively, within 4.5–5.5 h in 72–81% yields. But a strong EWG (R^1 = CO_2Me) or EDG (R^1 = OMe) did not favour this reaction resulting in lower yields [i.e., **81g** (64%), **81h** (66%)]. For the *para* position, incorporation of a moderate EWG (viz., R^1 = F; substrate **79i**) facilitated the reaction affording **81i** in 81% yield, compared to an EDG (viz., R^1 = Me) as in **79j** which furnished **81j** in a lower yield (68%). These substituent effects are perhaps predictable keeping in view the importance of electrophilicity of

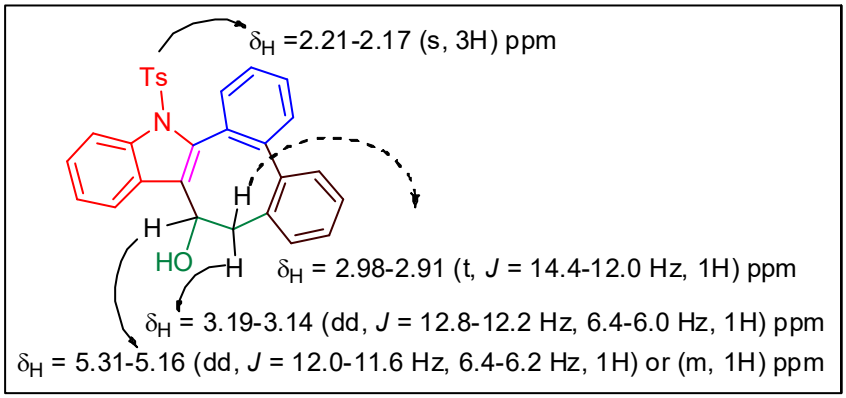
Scheme 21: Synthesis of 10,15-dihydro-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10-ols 81a-q[a]



[a]Reaction conditions: a mixture of **79** (0.086 mmol) and $Pd(OAc)_2bpy$ (6 mol%) in a solution (1.1 mL) containing AcOH: 1,4-dioxane (0.1: 1, v/v) was heated at 100 °C under argon.

the *β*-carbon (of the triple bond of **79**) for the cyclization to proceed smoothly. To our surprise, a strong EWG (viz., R^1 = CO_2Me) or EDG (viz., R^1 = OMe) placed at the same position in the substrates (**79k** or **79l**) delivered the product **81k** or **81l** to an extent of 60–70%. The reason behind these results is not very clear at this moment. Interestingly, when a strong EWG (viz., R^1 = CO_2Me) in ring A and EDG (viz., R^2 = OMe) in ring B are simultaneously placed *para* to the acetylenic group, product **81m** (94%) was formed within 3 h. When the ester group was absent (as in **79n**), **81n** was furnished in a somewhat lower yield (81%), while removing the methoxy group from **79n** and incorporating a moderate EDG (R^2 = Me) as in substrate **79o** led to the formation of **81o** in 59% yield. Furthermore, the incorporation of an additional EWG (R^1 = CO_2Me) in ring A (**79p**) benefited the reaction by producing product **81p** (78%) within 3 h. Surrprisingly, the reaction of substrate **79q** having an EDG (R^3 = OMe) at the *para* position of the C ring was somewhat sluggish to furnish the product **81q** in 61% yield.

1.2.3.3. Nature and characterization of products 81



The structures of the products were undoubtedly deduced by NMR spectroscopy (^1H, ^{13}C) and HRMS data. In mass spectra (EI and ESI), the molecular ion peak in positive mode of all the compounds appeared as M^+ or protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^1H NMR, the proton attached to the carbon connected with a hydroxyl group (–OH) displayed as either double doublet (dd) or multiplet (m) at the range 5.31-5.16 ppm. Whereas –CH_2– protons adjacent to the same carbon (attached with hydroxyl group) appears as doublet doublet (dd) and triplet (t) , respectively at 3.19-3.14 ppm and 2.98-2.91 ppm. The methyl protons of the tosyl group attached to the nitrogen atom appears as singlet at 2.21-2.17 ppm. Further, the ^{13}C NMR gave additional support in the favour to the structure.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compounds **81a** and **81l**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolving dissolved in minimum volume of Petroleum ether/ dichoromethane or Petroleum ether/ ethyl acetate mixture. The ORTEP diagrams of thecrystal structures are shown in Figure 4 and 5.

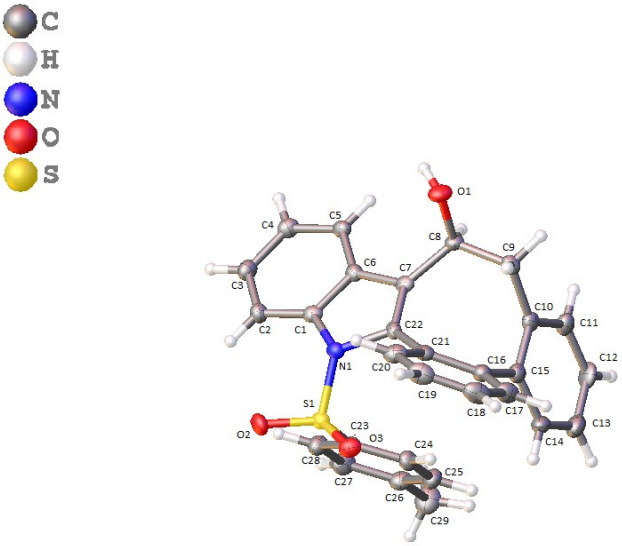


Figure 4. ORTEP Diagram (thermal ellipsoid plot) of Product **81a** (drawn at 50% probability level)

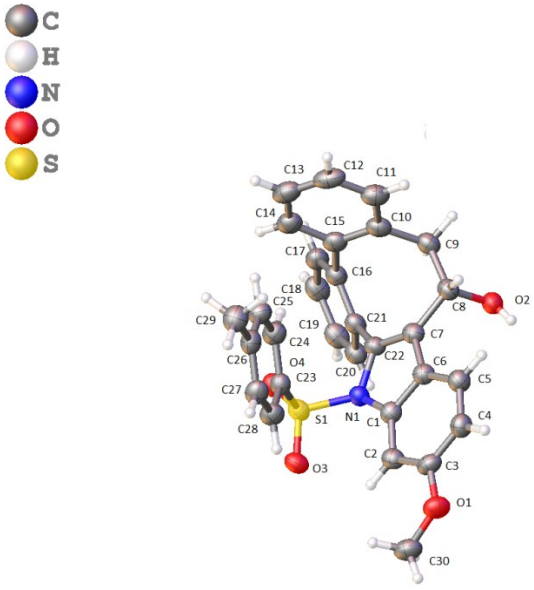


Figure 5. ORTEP Diagram (thermal ellipsoid plot) of Product **81l** (drawn at 50% probability level)

Table 2: Important crystal data of product **(81a)**

Empirical formula	$C_{29}\ H_{23}\ N\ O_3\ S$
Formula weight	1016.01
Temperature	100 K
Wavelength	1.54178
Crystal system	Monoclinic
Space group	P 1 21/n 1
Unit cell dimensions	a = 8.3459(3) Å α = 90.00°
	b = 31.8448(10) Å β = 92.018(2)
	c = 18.0413(6) Å γ = 90.00°
Volume	4791.9(3) $Å^3$
Z	4
Density (calculated)	1.408 g/cm^3
Absorption coefficient (Mu)	2.498 mm^{-1}
F(000)	2120.0
Theta range for data collection	2.775° to 66.672°
Index ranges	-9<=h<=6, -37<=k<=37, -21<=l<=21
Reflection collected	88704
Independent reflections	8465 [R(int) = 0.1452]
Completeness to theta= 25.44°	99.9 %
Absorption correction	multi-scan
Max. and min. transmission	0.972 and 0.850
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8465 /0/645
Goodness-of-fit on F^2	1.222
Final R indices [I>2sigma(I)]	R1 = 0.0876, wR2 = 0.1861
R indices (all data)	R1 = 0.0949, wR2 = 0.1904
Largest diff. peak and hole	0.469 & -0.452e.A^{-3}

The single crystal of the product **81a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **81a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2034270**.

Table 3: Important crystal data of product **(81l)**

Empirical formula	$C_{30}\ H_{25}\ N\ O_4\ S$
Formula weight	1079.24
Temperature	100 K
Wavelength	1.54178
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 8.748(3) Å α = 97.243(9)°
	b = 14.050(5) Å β = 100.218(5)°
	c = 22.585(8) Å γ = 97.968(9)°
Volume	2673.0(16) $Å^3$
Z	2
Density (calculated)	1.341 g/cm^3
Absorption coefficient (Mu)	1.430 mm^{-1}
F(000)	1136.0
Theta range for data collection	2.012° to 62.501°
Index ranges	-10<=h<=10, -16<=k<=16, -25<=l<=25
Reflection collected	63419
Independent reflections	8479 [R(int) = 0.1163]
Completeness to theta= 25.44°	99.6 %
Absorption correction	multi-scan
Max. and min. transmission	0.972 and 0.850
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8479 /0/712
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0680, wR2 = 0.1607
R indices (all data)	R1 = 0.0768, wR2 = 0.1666
Largest diff. peak and hole	0.586 & -0.377 $e.A^{-3}$

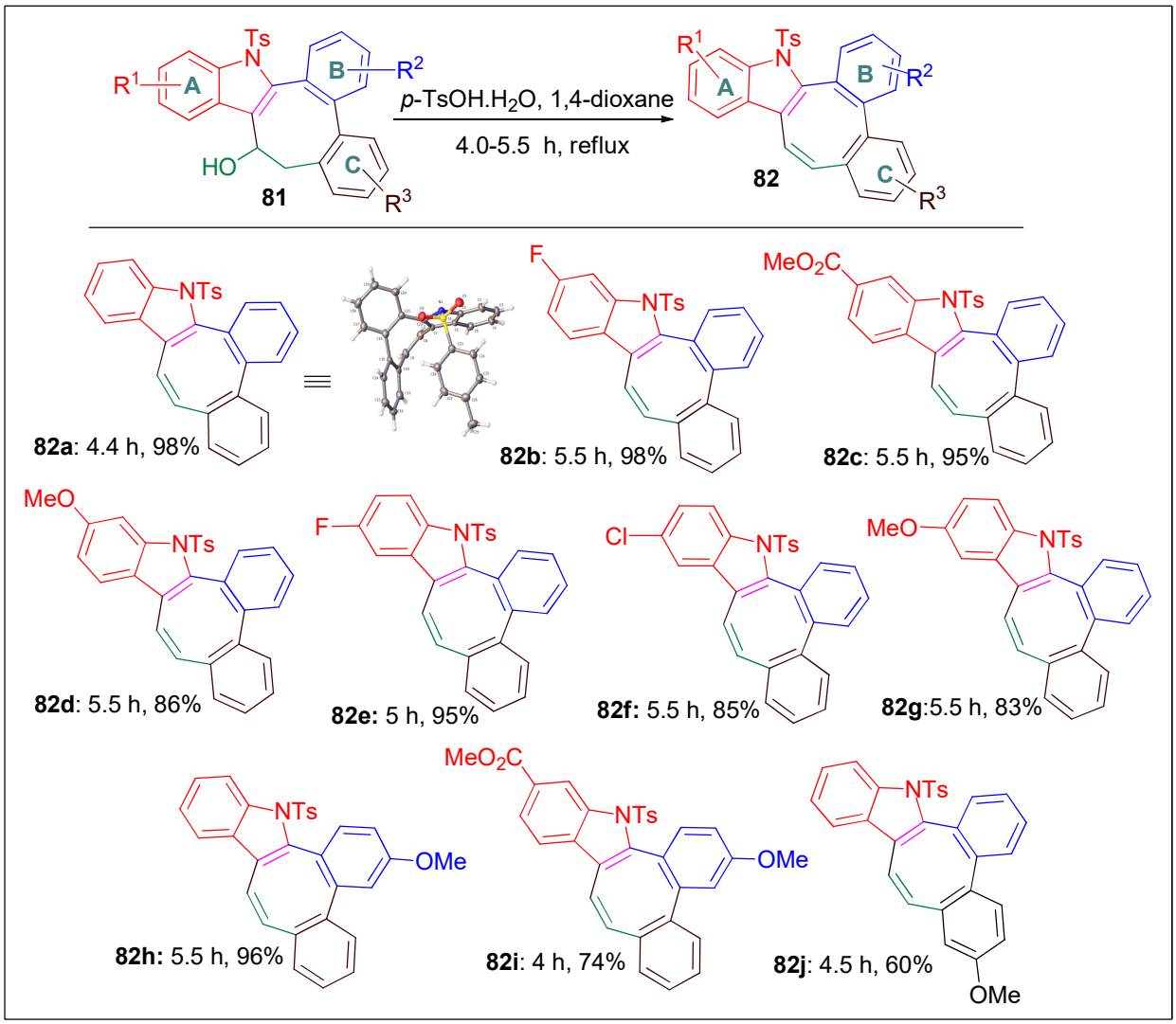
The single crystal of the product **81l** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ ethyl acetate mixture. The crystal data of product **81l** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2034271**.

1.2.4. Synthesis of (*Z*)-15-tosyl-15*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indoles 82

1.2.4.1. Scope of the reaction

To further probe the synthetic utility of this methodology, attempt was carried out to transform the products **81** into their respective COT derivatives **82** as depicted previously in **Scheme 19**. Toward this goal, 2,4,6-cyclooctatriene-1-ol **81a** was treated with a number of Lewis and Brønsted acids; which led to the identification of *p*-TsOH.H_2O as most efficient

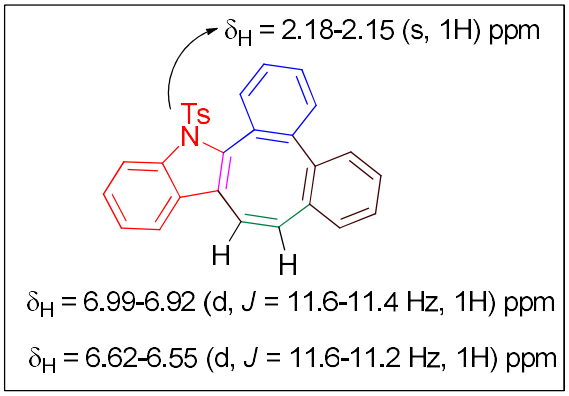
Scheme 22: Synthesis of (*Z*)-15-tosyl-15*H*-dibenzo[5,6:7,8]cycloocta[1,2-b]indole 82a-j[a]



[a]Reaction conditions: a mixture of **81** (0.062 mmol) and *p*-TsOH.H_2O (0.186 mmol) in 1,4-dioxane (1.0 mL) was refluxed under argon.

candidate, allowing the formation of COT **82a** from **81a** in 1,4-dioxane within 4.4 h with an almost quantitative (98%) yield. Then the generality of this protocol was established by applying it to a number of compounds **81** as depicted in **Scheme 22**. Substrates **81i/81k** bearing an EWG (viz., R^1 = F/CO_2Me) in ring A *meta* to the -NTs group were found to be highly reactive, producing the desired COTs **82b/82c** within 5.5 h in excellent yields (95–98%), though an EDG (viz., R^1 = OMe) at the same position furnished the desired product (**82d**) in a somewhat lower yield (86%). A similar trend of reactivity was followed when an EWG (R^1 = F/Cl) or EDG (R^1 = OMe) was present at the *para* position, leading to the formation of product **82e** (95%), **82f** (85%) or **82g** (83%). For ring B, the placement of an EDG (viz. R^2 = OMe) promoted the reaction furnishing **82h** within 5.5 h in 96% yield. But the incorporation of an additional EWG (viz. CO_2Me) in ring A reduced the yield of the product (**82i**) to74%. On the contrary, an EDG (viz. R^3 = OMe) placed in ring C hindered the reaction to some extent affording the COT derivative **82j** within 4.5 h in a moderate yield (60%).

1.2.4.2. Nature and characterization of products 82



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (ESI), the molecular ion peak in positive mode of all the compounds appeared as protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR, the two bare protons attached directly to the COT system appears as doublet at around 6.99-6.92 ppm and 6.62-6.55 ppm, respectively; whereas the methyl protons of the tosyl group appears as singlet at the range of 2.18-2.15 ppm. Further, the ^{13}C NMR gave additional support in the favour of the structures.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **82a**.The single crystal of the product was obtained by slow evaporation of the solution of the product dissolved in minimum volume of petroleum ether/ dichoromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 6.

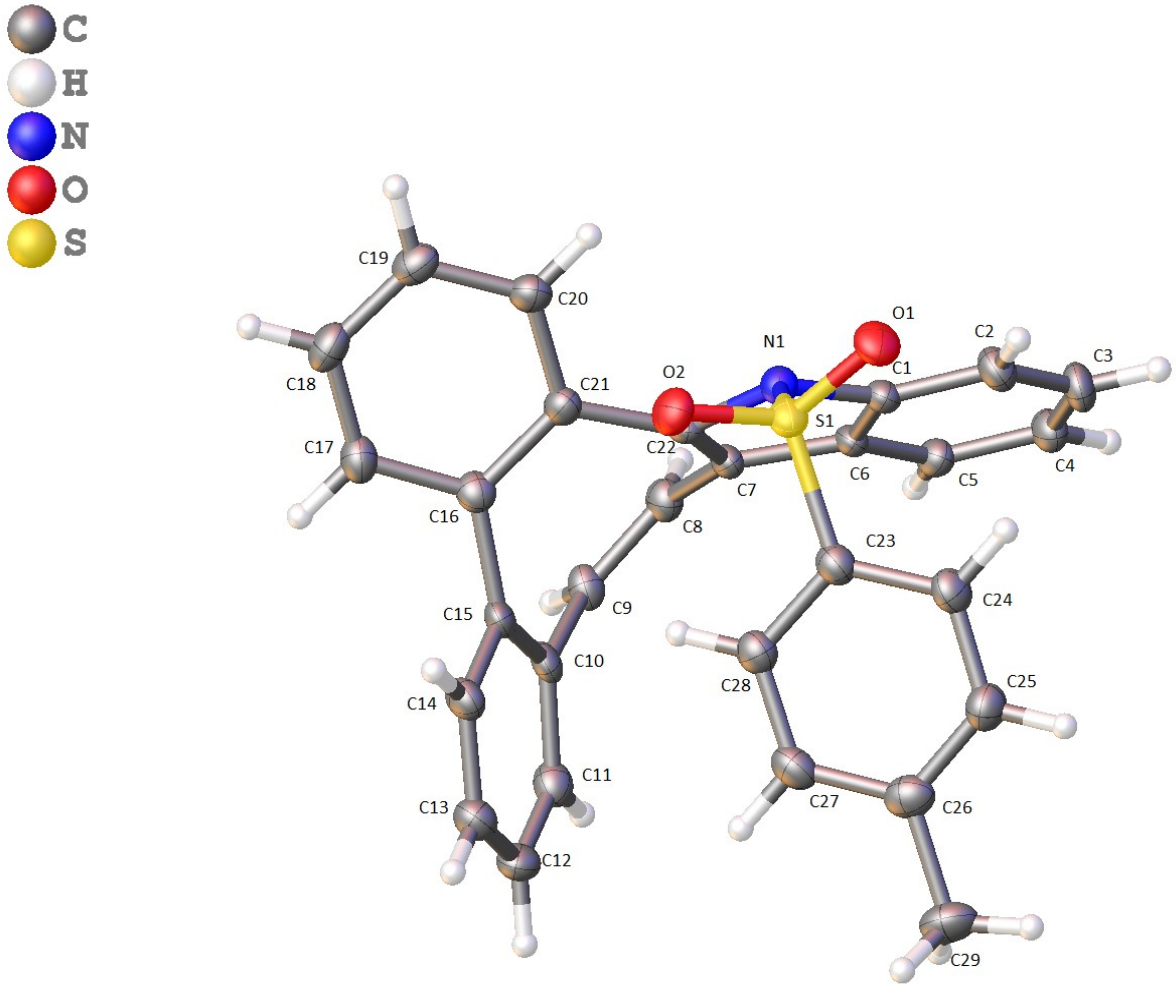


Figure 6. ORTEP Diagram (thermal ellipsoid plot) of Product **82a** (drawn at 50% probability level)

Table 4: Important crystal data of product **(82a)**

Empirical formula	$C_{29}\ H_{21}\ N\ O_2\ S$
Formula weight	447.53
Temperature	116 K
Wavelength	1.54178
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 8.5406(7) Å α = 89.172(4)°
	b = 10.0271(8) Å β = 79.068(4)°
	c = 13.9349(11) Å γ = 66.547(3)°
Volume	1072.43(15) $Å^3$
Z	2
Density (calculated)	1.386 g/cm^3
Absorption coefficient (Mu)	1.561mm^{-1}
F(000)	468.0
Theta range for data collection	5.839° to 66.825°
Index ranges	-10<=h<=9, -11<=k<=11, -16<=l<=16
Reflection collected	11582
Independent reflections	3659 [R(int) = 0.0746]
Completeness to theta= 25.44°	96.2 %
Absorption correction	multi-scan
Max. and min. transmission	0.753 and 0.473
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3659 /0/299
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0713, wR2 = 0.1868
R indices (all data)	R1 = 0.0745, wR2 = 0.1905
Largest diff. peak and hole	0.425 &-0.770 $e.A^{-3}$

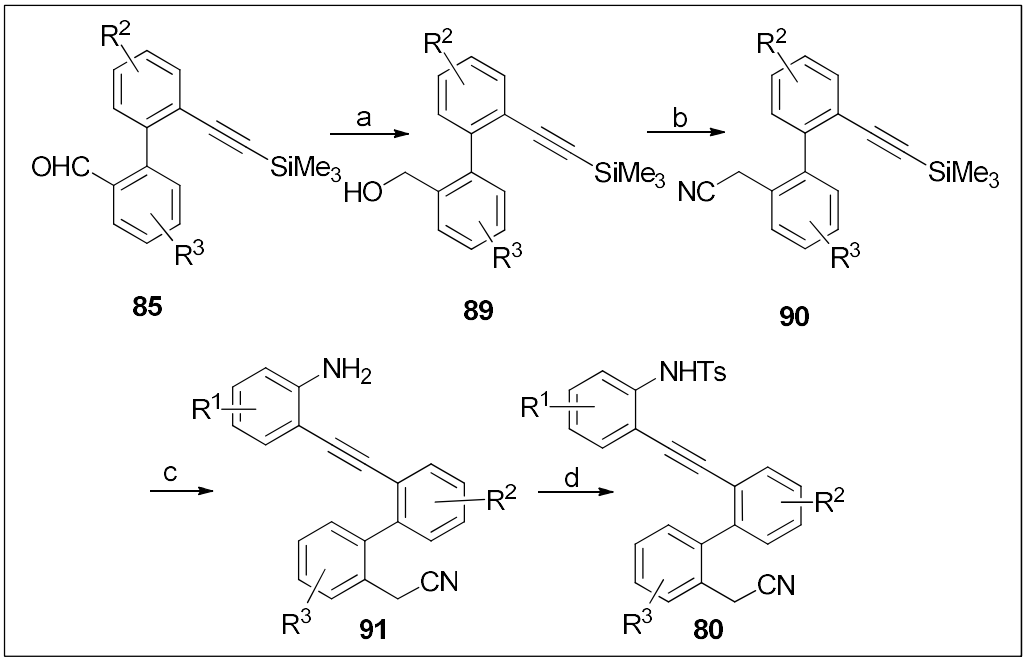
The single crystal of the product **82a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **82a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2034272**.

1.2.5. Extension of the methodology for the synthesis 9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one 83

Encouraged by the above results, we decided to explore the methodology for the general synthesis of 15-tosyl-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one from the substrate **80** obtained by replacing the –CHO group of **79** by –CN group.

1.2.5.1. Synthesis of starting material 80

The desired starting material **80** was synthesized in few steps from the previously derived **85** derivatives. Reduction of the **85** derivatives leads to the formation of **89** derivatives. Successive treatment of **89** with mesyl chloride and sodium cyanide affords the cyanated **90** derivatives in two steps. Next, desilylation of **90** derivatives followed by *"Sonogashira coupling*" with commercially available 2-iodo aniline derivatives affords **91**. Finally, tosylation of **91** produced the expected starting substrate **80**.



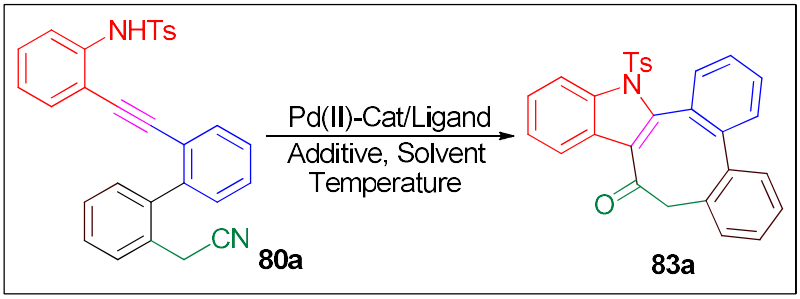
Scheme 23. Reagents and Conditions: (a) $NaBH_4$, MeOH, 0 ^oC, 0.5-0.6 h, 88-92%; (b) (i) MsCl, Et_3N, DCM, 0 ^oC-rt, 1.5-2.5 h; (ii) NaCN, DMF, rt, 2.5-3.0 h, 45-55%, (c) (i) K_2CO_3, MeOH, rt, 1.5-3.0 h, 70-80%; (ii) 2-iodoaniline derivatives, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF ,0 ^oC-rt, 10-18 h, 70-85%; (d) TsCl, pyridine, DCM, 0 ^oC- rt, 15-28 h, 35-98%.

1.2.5.2. Synthesis of 15-tosyl-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-ones 83

1.2.5.2.1. Optimization of reaction conditions for the synthesis 15-tosyl-9*H*-dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one 83a

Towards this goal substrate **80a** was treated under the optimized reaction conditions for the synthesis of **83a** (Table 1, entry 12); but unfortunately, the desire product 2,4,6-cyclooctatrien-1-one **83a** was formed in 50% yield only (Table 5, entry 1). Next, to find the optimized conditions, few more reactions were carried out on **80a** by changing the

Table 5. Optimization of Reaction Conditions for the Synthesis of 15-tosyl-9*H*-Dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one 83a[a]



Entry	Catalyst	Ligand	Additive	Solvent	Temp.(°C)	Time (h)	Yield(%) 83a
1[b]	$Pd(OAc)_2bpy$	----	AcOH	1,4-dioxane	100	10	50
2	$Pd(OAc)_2bpy$	----	*p*-TsOH.H_2O	1,4-dioxane	100	4.5	75
3	$Pd(OAc)_2bpy$	----	D-CSA	1,4-dioxane	100	6	87
4[c]	$Pd(OAc)_2bpy$	----	D-CSA	THF	Reflux	22	48
5	$Pd(OAc)_2bpy$	----	*p*-TsOH.H_2O	THF	Reflux	17	86
6	$Pd(OAc)_2bpy$	----	*p*-TsOH.H_2O	NMA	100	4.5	88
7	**$Pd(OAc)_2bpy$**	**----**	**D-CSA**	**NMA**	**100**	**5.2**	**92**
8[d]	$Pd(OAc)_2bpy$	----	D-CSA	NMA	100	7	73
9[e]	$Pd(OAc)_2$	bpy	D-CSA	NMA	100	6.5	84

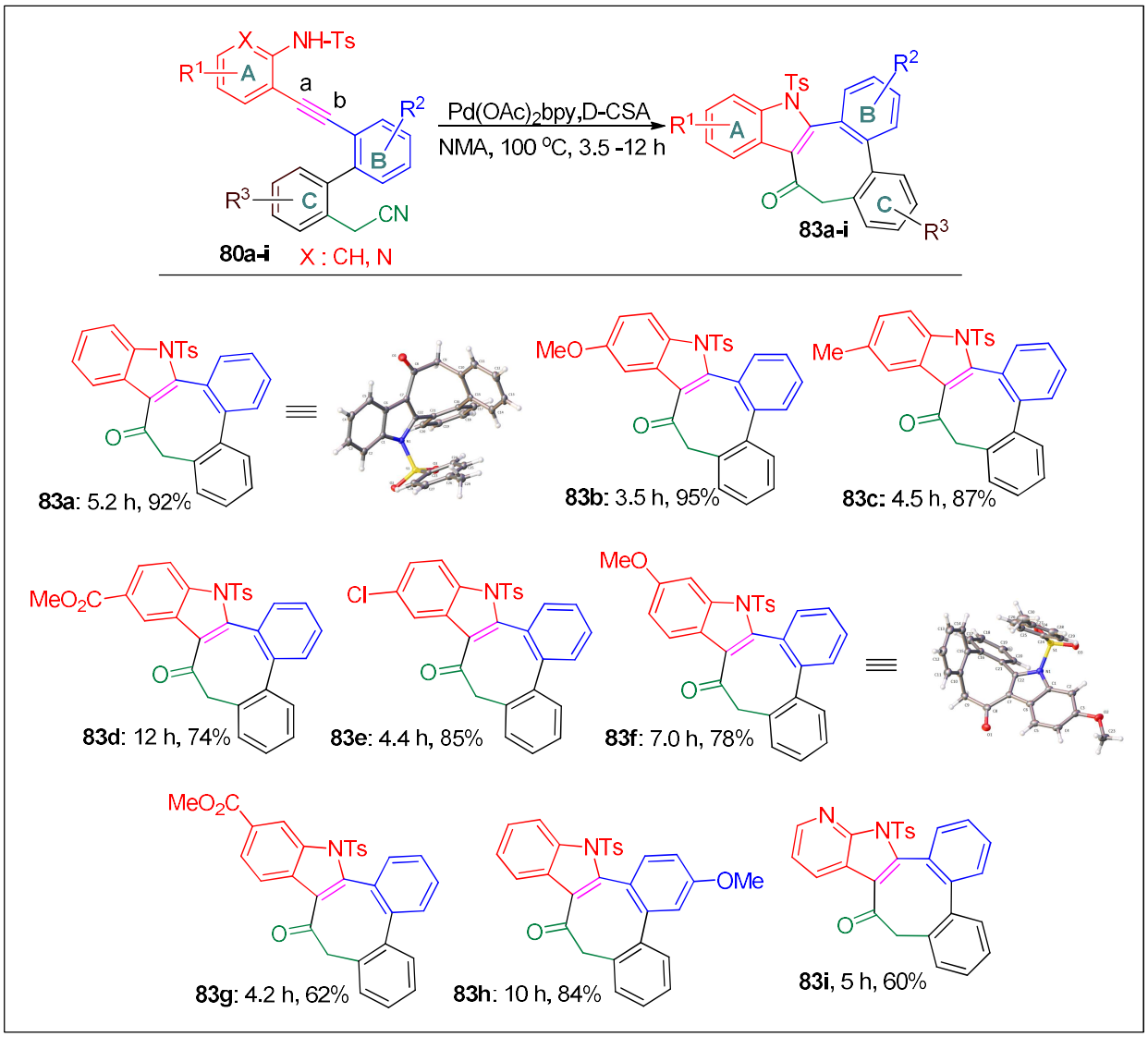
[a]Reaction conditions: **80a** (0.14 mmol), Catalyst (6 mol %) and D-CSA (2 equiv) was heated at 100 °C in NMA (1.5 mL) under argon. [b]AcOH (10%, v/v) in 1,4-dioxane.[c]55% Starting material Recovered. [d]D-CSA used 1.5 equiv. [e]Catalyst and Ligand used are 5 and 6 mol % respectively.

catalyst, ligand, additive, solvent, temperature, etc. But replacing the additive AcOH either by *p*-TsOH.H_2O or D-CSA improved the reaction considerably by delivering the product **83a** with higher yields (75-87%) and reducing the reaction time (i.e, 4.5-6 h) (Table 5, entries 2 & 3). A change in the solvent from 1,4-dioxane to THF necessitated the use of longer reaction time (17-22 h); though the yield of the product **83a** was found to be very good (86%) upon employment of *p*-TsOH.H_2O as an additive (Table 5, entries 4 and 5). While carrying out the reaction in polar solvent (NMA) and using *p*-TsOH.H_2O as an additive improved the efficiency of the reaction by reducing the reaction time considerably (Table 5, entry 6). Furthermore, to our pleasure, switching to D-CSA acid as an additive proved to be still better by improving the yield of **83a** to 92% (Table 5, entry 7). But reducing the amount of additive (1.5 equiv instead of 2.0 equiv) or changing the catalytic system (i.e., $Pd(OAc)_2$/bpy) made the reaction sluggish and diminished the yield of product (Table 5, entry 8 and 9). From this study, reaction conditions of entry 7 of Table 5 were considered as the optimal.

1.2.5.2.2. Scope of the reaction

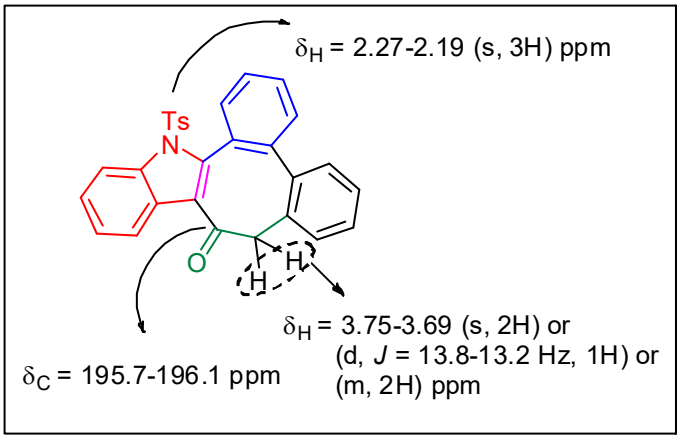
With the optimized reaction conditions, the generality of the reaction was established for the formation of 2,4,6-cyclooctatrien-1-ones **83** (**Scheme 24**). Substrates **80b/80c** bearing an EDG (R^1 = OMe/Me) in ring A *meta* to the alkyne moiety facilitated the reaction, furnishing the products **83b** (95%)/**83c** (87%) within 3.5–4.5 h. But **80d/80e** having an EWG (R^1 = CO_2Me/Cl) at the same position formed products **83d/83e** within 4.4–12 h in lower yields (74–85%). Nevertheless, the placement of an EDG (viz., R^1 = OMe) rather than a EWG (R^1 = CO_2Me) even at the *para* position also proved beneficial (substrate **80f** vs. **80g**) though the former took a longer reaction time (**Scheme 24**, see **83f** vs. **83g**). For ring B, when a strong EDG (R^2 = OMe) was placed *para* to the alkyne moiety (in **80h**), the desired product **83h** (84%) was formed albeit with a longer reaction time (10 h). Interestingly substrate **80i** containing a pyridyl ring (X = N) was still conducive to the reaction, the product **83i** (60%) being formed within 5 h.

Scheme 24: Synthesis of 15-tosyl-9*H*-Dibenzo[5,6:7,8]cycloocta[1,2-*b*]indol-10(15*H*)-one 83a-i[a]



Reaction conditions: a mixture of **80** (0.14 mmol), $Pd(OAc)_2$bpy (6 mol%) and D-CSA (2.0 equiv.) was heated at 100 °C in NMA (1.5 mL) under argon.

1.2.5.2.3. Nature and characterization of products 83



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (ESI), the molecular ion peak in positive mode of all the compounds appeared as protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR, the two protons ($-CH_2-$) attached to the carbon adjacent to the carbonyl group appears as either singlet (s) or doublets (d) or multiplet (m) (depending on the substituent) at around 3.75-3.69 ppm. The methyl protons of the tosyl group appears as singlet at around 2.27-2.19 ppm. Furthermore, in ^{13}C NMR, the carbonyl carbon appears at 195.7-196.1 ppm which confirms the generation of the carbonyl group and thus corroborates the structure of the products.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compounds **83a** and **83f**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolving dissolved in minimum volume of Petroleum ether/dichoromethane mixture. The ORTEP diagrams of the crystal structures are shown in Figure 7 and 8.

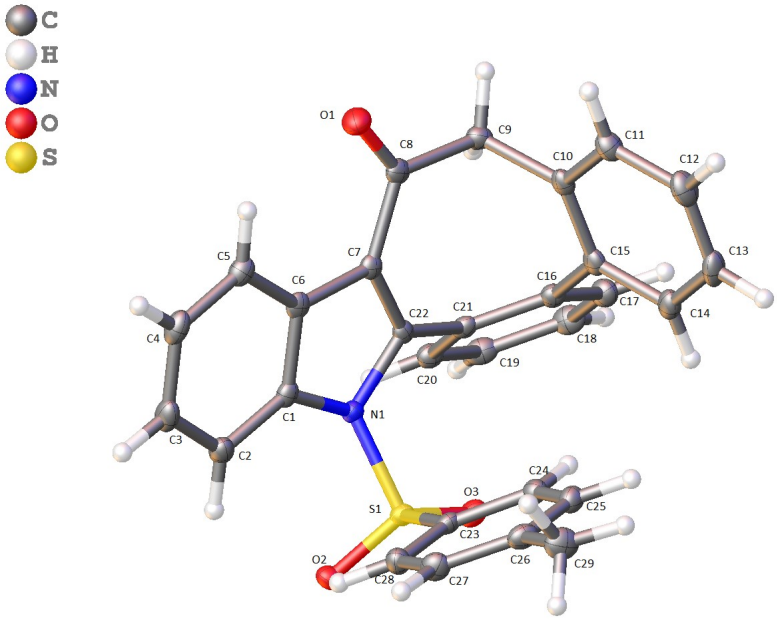


Figure 7. ORTEP Diagram (thermal ellipsoid plot) of Product **83a** (drawn at 50% probability level)

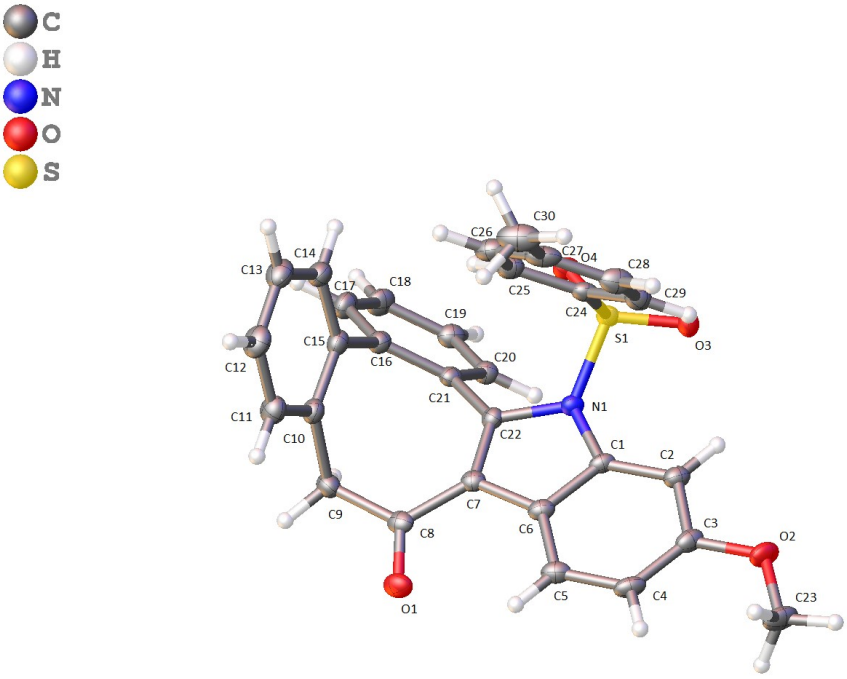


Figure 8. ORTEP Diagram (thermal ellipsoid plot) of Product **83f** (drawn at 50% probability level)

Table 6: Important crystal data of product **(83a)**

Empirical formula	$C_{29}H_{21}NO_3S$
Formula weight	463.53
Temperature	100 K
Wavelength	1.54178
Crystal system	monoclinic
Space group	C 1 2/c 1
Unit cell dimensions	a = 17.1953(3) Å α = 90°
	b = 11.2998(3) Å β = 99.631(1)°
	c = 23.4679(5) Å γ = 90°
Volume	4495.62(17) $Å^3$
Z	8
Density (calculated)	1.370 g/cm^3
Absorption coefficient (Mu)	1.544 mm^{-1}
F(000)	1936.0
Theta range for data collection	3.821° to 66.632°
Index ranges	-20<=h<=20, -13<=k<=13, -27<=l<=27
Reflection collected	86526
Independent reflections	3971 [R(int) = 0.0792]
Completeness to theta= 25.44°	99.7 %
Absorption correction	multi-scan
Max. and min. transmission	0.972 and 0.850
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3971 /0/308
Goodness-of-fit on F^2	1.120
Final R indices [I>2sigma(I)]	R1 = 0.0394, wR2 = 0.0958
R indices (all data)	R1 = 0.0399, wR2 = 0.0962
Largest diff. peak and hole	0.314 & -0.528 $e.A^{-3}$

The single crystal of the product **83a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **83a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2034273**.

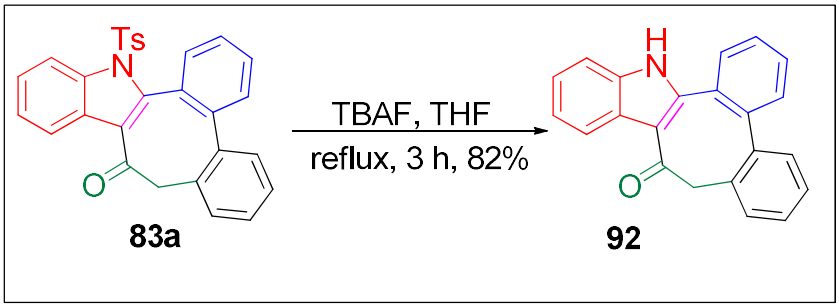
Table 7: Important crystal data of product **(83f)**

Empirical formula	$C_{30}\ H_{23}\ N\ O_4\ S$
Formula weight	493.55
Temperature	102 K
Wavelength	1.54178
Crystal system	monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 12.6739(9)Å α = 90°
	b = 16.317(3)Å β = 109.725(12)°
	c = 12.1213(13)Å γ = 90°
Volume	2359.6 (5)$Å^3$
Z	4
Density (calculated)	1.389 g/cm^3
Absorption coefficient (Mu)	1.538 mm^{-1}
F(000)	1032.0
Theta range for data collection	4.73° to 72.464°
Index ranges	-15<=h<=15, -19<=k<=20, -14<=l<=14
Reflection collected	35390
Independent reflections	4631 [R(int) 0.0629]
Completeness to theta= 25.44°	99.2 %
Absorption correction	multi-scan
Max. and min. transmission	0.754 and 0.656
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4631 /0/327
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1155
R indices (all data)	R1 = 0.0506, wR2 = 0.1174
Largest diff. peak and hole	0.352 &-0.557 $e.A^{-3}$

The single crystal of the product **83f** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ ethyl acetate mixture. The crystal data of product **83f** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2034274**.

1.2.6. Synthesis of deprotected derivative of 83a

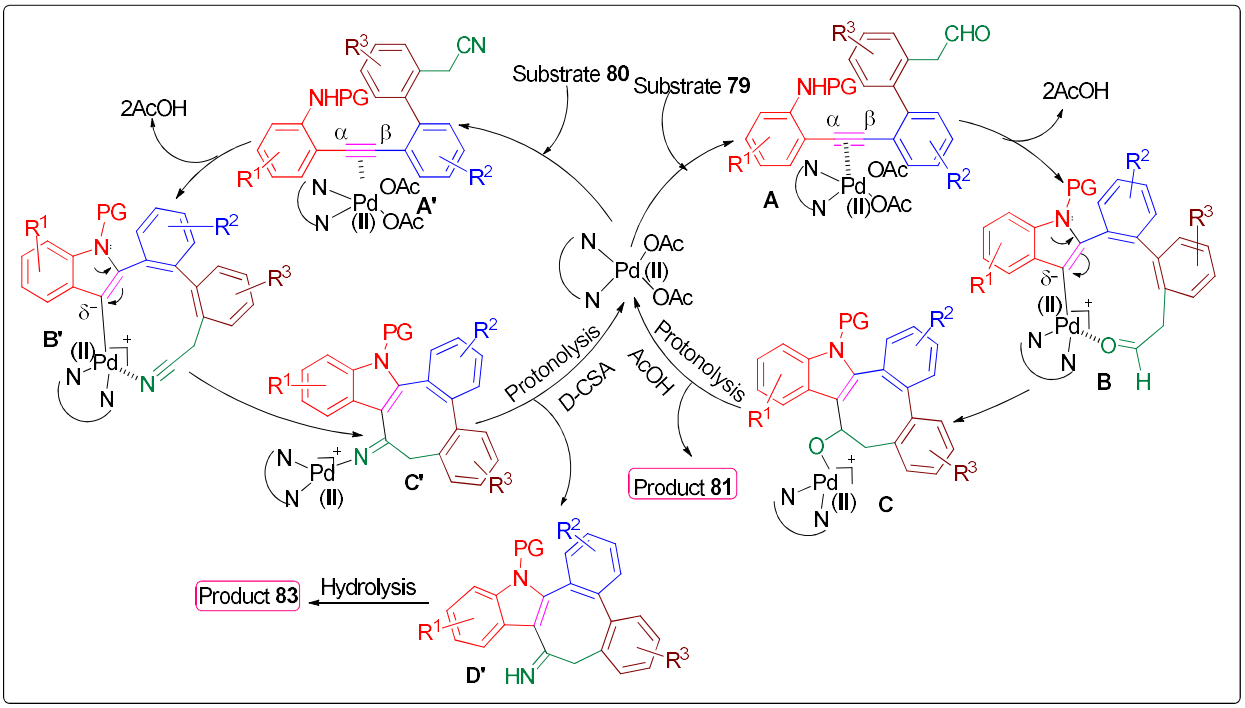
Owing to the presence of a free NH group in bioactive compounds,[28] efforts were done to check the feasibility of N-deprotection of product **83a**; to our delight, product **92** was formed easily within 3 h in 82% yield (**Scheme 25**).



Scheme 25. *N*-Detosylation of product **83a**.

1.2.7. Plausible mechanism for the formation of products 81-83

On the basis of the experimental results and the known palladium chemistry, a plausible reaction mechanism is outlined in **Scheme 26**. Initially, palladated species **A** and **A′** are generated from the substrates **79** and **80**, respectively, through the action of the Pd(II) catalyst acting like a Lewis acid. Under acidic conditions, **A** and **A′** would then trigger the heteroannulation via a trans-aminopalladation pathway[31a] resulting in the formation of transient cationic palladated species[33] **B** and **B′** which are stabilized through coordination of the tethered nucleophile (–CHO/–CN) as shown in **Scheme 26**. Next, species **B** and **B′** having the polar C–Pd bond caused by the electron-donating effect of the nitrogen atom of the indole ring[34a] (shown using an arrow) could promote nucleophilic 1,2-addition onto the tethered aldehyde and nitrile groups, respectively, resulting in the generation of palladated species C[34b] and C′.[34c] Subsequent protonolysis of **C** using AcOH would afford the product **81** with regeneration of the Pd(II) species which keeps the catalytic cycle active. On the other hand, protonolysis of **C′** with D-CSA would lead to the regeneration of the Pd(II) catalyst in addition to the formation of imine intermediate **D′** which upon subsequent hydrolysis under acidic conditions would furnish the product **83**.



Scheme 26. Plausible reaction mechanism for the formation of products

1.2.8. Conclusions

In conclusion, an atom economic method for the expedient synthesis of products **81** and **83** via palladium catalyzed intramolecular cascade reactions of amino-alkynes **79** and **80**, respectively have been disclosed. The hallmarks of the synthesis are high yield (up to 95%), atom-economy, tolerance of functional groups and formation of two new rings (i.e., cyclooctatriene and indole) fused to each other. Furthermore, treatment of products **81** with *p*-TsOH.H_2O could provide easy access to COT derivatives **82**.

1.2.9. Experimental section

1.2.9.1. General Information:

Only distilled solvents were used in all purposes. Petroleum ether refers to fraction boiling in the range 60−80 °C. Dichloromethane was dried over phosphorous pentaoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane was distilled over sodium and benzophenone. Commercial grade dry DMF (Dimethylformamide), DMA

(Dimethylacetamide), NMA (N-Methylacetamide) were used as a solvent. All the reactions were performed out under an argon atmosphere and anhydrous conditions unless otherwise mentioned. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance . For purification, column chromatography was performed using 100−200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on 300, 400 or 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given from TMS (δ = 0.00) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [$CDCl_3$: ^{1}H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm]. Coupling constants (*J*) are expressed in Hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), q (quartet), m (multiplet), and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF or EI mode.

1.2.9.2. X-Ray crystallographic information of products **81a, 81l, 82a, 83a** and **83f**

Single crystal of products **81a, 81l, 82a, 83a** and **83f** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether or ethyl acetate-petroleum ether. A single crystal of **81a, 81l, 82a, 83a** and **83f** were attached to a glass fiber with epoxy glue and transferred to a X-ray diffractometer, equipped with a graphite-monochromator. Diffraction data of products **81a, 81l, 82a, 83a** and **83f** were measured with CuKα radiation (λ = 1.54178 Å) at 100 K. The structure was solved by direct methods using the SHELXS-97 program.[35] Refinements were carried out with a full matrix least squares method against F 2 using SHELXL-97.[36] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The important crystal data and ORTEP diagram (drawn at 50% probability level) of products **81a, 81l, 82a, 83a** and **83f** are provided earlier.

1.2.9.3. General procedure for the preparation of the starting materials 79

Synthesis of silylated derivatives **84 :**

To a well stirred solution of commercially available 2-bromoiodobenzene derivatives (7.12 mmol, 1 equiv) in Et_3N and DMF (Et_3N: DMF= 1.5 : 1, 4.5 mL), $PdCl_2(PPh_3)_2$ (49.9 mg, 0.071 mmol, 1 mol %) was added. Then the mixture was cooled to 0 ^oC and trimethylsilylacetylene (1.11 ml, 7.83 mmol, 1.1 equiv) was added dropwise followed by addition of CuI (27.0 mg, 0.142 mmol, 2 mol %,). Next the mixture was allowed to rotate at that temperature for few minutes. After that the temperature of the mixture was raised to rt and the stirring was continued for another 1.5-2.5 h. Upon completion of reaction (TLC), solvent was removed under reduced pressure and extracted with ethyl acetate (3x 50 mL); the combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with petroleum ether to obtain a silylated acetylenic intermediate **84** (92-94% yield).

Synthesis of the acetylenic derivatives **85:**[32]

A mixture of $Pd(OAc)_2$ (118.7 mg, 0.531 mmol, 8 mol %), DPPF [1,1′-Ferrocenediyl-bis(diphenylphosphine)] (440.6 mg, 0.795 mmol, 12 mol %) and K_2CO_3 (2743.6 mg, 19.88 mmol, 3 equiv) were stirred in DME (30 mL) for 30 min. Then **84** (6.63 mmol, 1 equiv) and 2-formylbenzeneboronic acid (1491.1 mg, 9.94 mmol, 1.5 equiv) were sequentially added to the solution and the resulting mixture was heated at 80 ^oC for overnight. Upon completion of reaction (TLC), the mixture was extracted with ethyl acetate (3x 60 mL); the combined organic extracts were washed with brine (22 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 2-4% ethyl acetate-petroleum ether (v/v) to obtain the acetylenic derivatives **85** (50-80% yield).

Synthesis of **86** *derivatives :*

To a well stirred solution of the acetylenic derivatives **85** (2.52 mmol, 1 equiv), K_2CO_3 (1042.4 mg, 7.55 mmol, 3 equiv) was added in MeOH (5 mL) and stirring was continued for

overnight. After completion of reaction (TLC), the mixture was extracted with ethyl acetate (3 x 40 mL); the combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 4-5% ethyl acetate-petroleum ether (v/v) to obtain the desilyated acetylinic aldehyde derivatives[32] (92-95% yield).

Then a suspension of (Methoxymethyl)triphenylphosphonium chloride (1603.7 mg, 4.69 mmol, 2.1 equiv) in THF (1.0 mL) was cooled using ice-salt mixture (temperature around -5 to -10 ^oC) and to it, 2M NaHDMS in THF (2.34 mL, 2.1 equiv) was added dropwise and the colour of the solution changed from white to red to dark brown. The solution was allowed to stirred for 30 min at the same temperature, after which the desilylated acetylinic aldehyde derivatives of **85** (2.23 mmol, 1 equiv) dissolved in dry THF (0.4 mL) was added dropwise to the solution at the same temp.; after stirring for 15 min, the solution was then stirred at rt for 1-1.5 h. After completion of reaction (TLC), the mixture was extracted with ethyl acetate (3x 25 mL); the combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 2-3% ethyl acetate-petroleum ether (v/v) to obtain the **86** derivatives (78-82% yield).

Synthesis of Amine derivatives **87** *:*

To a well stirred solution of 2-iodoaniline derivatives (1.32 mmol, 1 equiv) in mixture of Et_3N and DMF (Et_3N : DMF = 2 : 1, 1.5 mL), $PdCl_2(PPh_3)_2$ (37.1 mg, 0.053 mmol, 4 mol %) was added. The mixture was then cooled to 0 ^oC and **86** derivative (1.72 mmol, 1.3 equiv) was added dropwise followed by the addition of CuI (20.1 mg, 0.106 mmol, 8 mol %). After stirring few minutes at 0 ^oC, the temperature of the reaction was raised to room temperature and stirring was continued for 5-15 h. Upon completion of reaction (TLC), solvent was removed under reduced pressure and extracted with ethyl acetate (3 x 20 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 10-24% ethyl acetate-petroleum ether (v/v) to obtain **87** derivatives (72-88% yield).

*Synthesis of N-protected amine derivatives **88** :*

To a well stirred solution of amine derivative **87** (0.92 mmol, 1 equiv) in dry DCM (3 mL) at 0 ^{o}C was added pyridine (186.03 µL, 2.31 mmol, 2.5 equiv) dropwise. Thereafter, TsCl or NsCl (2.49 mmol, 2.7 equiv) was added portion-wise at the same temperature and whole reaction mixture was allowed to stir at rt for 12-24 h. Upon completion of the reaction (TLC), solvent was removed in *vaccuo* and then extracted with ethyl acetate (3x 25 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 12-30% ethyl acetate-petroleum ether (v/v) to obtain the pure tosylated/nosylated product **88** in 66-85% yield.

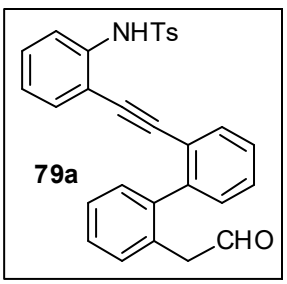
*Synthesis of Final Substrates **79**:*

To a well-stirred and ice-cooled solution of **88** (0.625 mmol, 1 equiv) in dry acetone *p*-TsOH.H_2O (190.0 mg, 1.00 mmol, 1.6 equiv) was added portion-wise and the whole reaction mixture was then allowed to stir at rt for another 3.5-5.5 h until completion of reaction (TLC). Next, the reaction mixture was neutralized with dilute sodium bicarbonate solution and extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vaccuo.* The resulting crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-27% ethyl acetate in petroleum ether (v/v) to afford the desired starting material **79** in (49-91%) yield.

1.2.9.4. Spectral Data of starting substrates 79a-q:

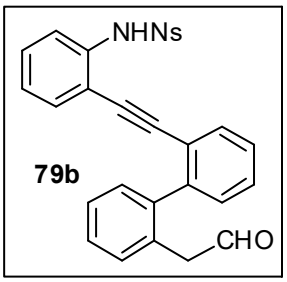
***4-Methyl-N-(2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)benzenesulfonamide (79a)*:**

Yellow gummy liquid (223.8 mg, 77%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.55 (t, *J* = 2.0 Hz, 1H, -CHO), 7.58-7.55 (m, 1H, Ar-H), 7.53 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.49-7.46 (m, 3H, Ar-H), 7.43 (td, *J* = 6.9, 1.8 Hz, 2H, Ar-H), 7.38-7.34 (m, 2H, Ar-H), 7.29-7.26 (m, 1H, Ar-H), 7.21-7.17 (m, 1H, Ar-H), 7.13 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (dd, *J* = 7.8,



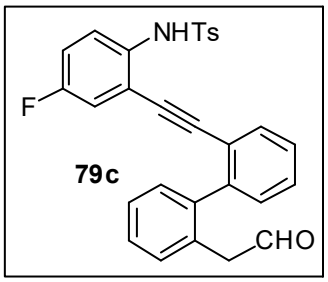
1.4 Hz, 1H, Ar-H), 6.94 (td, J = 7.5, 1.1 Hz, 1H, Ar-H), 6.63 (s, 1H, -NHTs), 3.64 (dd, J = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.56 (dd, J = 16.8, 2.0 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.3 (-CHO), 143.8 (Ar-C), 143.0 (Ar-C), 141.1 (Ar-C), 137.3 (Ar-C), 136.0 (Ar-C) , 132.1 (Ar-C), 130.7 (Ar-C), 130.4 (Ar-C), 130.2 (Ar-C), 129.8 (Ar-C), 129.5 (Ar-C), 129.4 (3C, Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 127.2 (2C, Ar-C), 124.2 (Ar-C), 121.9 (Ar-C), 119.9 (Ar-C), 114.0 (Ar-C), 94.9 (-C≡C-), 87.4 (-C≡C-), 48.2 (-CH_2-), 21.5 (-SO_2PhCH_3); High-resolution mass spectrometry (HRMS) (ESI) m/z calcd for $C_{29}H_{23}NNaO_3S$ $[M + Na]^+$ 488.1296, found 488.1297.

4-Nitro-N-(2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)benzenesulfonamide (79b) :



Yellow gummy liquid (235.6 mg, 76%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.6 Hz, 1H, -CHO), 8.12 (d, J = 8.8 Hz, 2H, Ar-H), 7.73 (d, J = 8.8 Hz, 2H, Ar-H), 7.51-7.39 (m, 6H, Ar-H), 7.37-7.34 (m, 2H, Ar-H), 7.30-7.23 (m, 2H, Ar-H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H, Ar-H), 7.04 (td, J = 7.5, 0.9 Hz, 1H, Ar-H), 6.67 (s, 1H, -NHTs), 3.65 (dd, J = 17.4, 1.8 Hz, 1H, H_a of -CH_2-), 3.57 (dd, J = 17.2, 1.6 Hz, 1H, H_b of -CH_2-); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C199.1 (-CHO), 150.2 (Ar-C), 144.6 (Ar-C), 143.1 (Ar-C), 141.1 (Ar-C), 136.2 (Ar-C), 132.4 (Ar-C), 132.1 (Ar-C), 131.0 (Ar-C), 130.6 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.4 (Ar-C), 128.9 (Ar-C), 128.6 (2C, Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 125.6 (Ar-C), 124.0 (2C, Ar-C), 121.7 (Ar-C), 121.6 (Ar-C), 115.4 (Ar-C), 95.2 (-C≡C-), 87.1 (-C≡C-), 48.3 (-CH_2-); HRMS (ESI) m/z calcd for $C_{28}H_{20}N_2NaO_5S$ $[M + Na]^+$ 519.0991, found 519.0973.

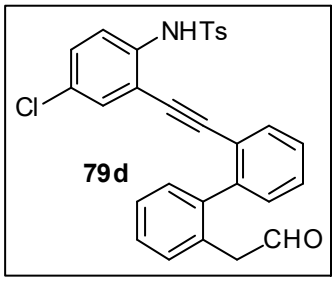
***N-(4-Fluoro-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4 methylbenzenesulfonamide (79c)* :**



Yellow gummy liquid (256.6 mg, 85%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 7.54-7.52 (m, 1H, Ar-H), 7.49-7.45 (m, 5H, Ar-H), 7.44-7.39 (m, 2H, Ar-H), 7.36-7.33 (m, 2H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.11 (d, J = 8.0 Hz, 2H, Ar-H), 6.94-6.89 (m, 1H, Ar-H), 6.71 (dd, J = 8.6, 3.0 Hz, 1H, Ar-H), 6.45

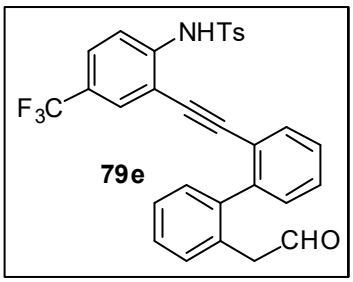
(s, 1H, -NHTs), 3.62 (dd, J = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.54 (dd, J = 17, 1.8 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.2 (-CHO), 159.2 (d, J_{C-F} = 244.1 Hz, Ar-C), 144.0 (Ar-C), 143.4 (Ar-C), 141.0 (Ar-C), 135.8 (Ar-C), 133.6 (d, J_{C-F} = 2.4 Hz, Ar-C), 132.2 (Ar-C), 130.9 (Ar-C), 130.5 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.6 (2C, Ar-C), 129.4 (Ar-C), 128.9 (Ar-C), 127.92 (Ar-C), 127.91 (Ar-C), 127.3 (2C, Ar-C), 123.2 (d, J_{C-F}= 8.7 Hz, Ar-C), 121.6 (Ar-C), 118.4 (d, J_{C-F} = 24.1 Hz, Ar-C), 116.9 (d, J_{C-F} = 22.6 Hz, Ar-C), 116.6 (d, J_{C-F} = 9.9 Hz, Ar-C), 95.5 (-C≡C-), 86.6 (-C≡C-), 48.3 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{29}H_{22}FNNaO_3S$ $[M + Na]^+$ 506.1202, found 506.1201.

N-(4-Chloro-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (79d) **:**



Yellow solid (265.1 mg, 85%), mp 56-58 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.55 (s, 1H, -CHO), 7.56-7.54 (m, 1H, Ar-H), 7.51-7.47 (m, 4H, Ar-H), 7.46-7.40 (m, 3H, Ar-H), 7.37-7.34 (m, 2H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.15-7.13 (m, 3H, Ar-H), 7.01 (d, J = 2.4 Hz, 1H, Ar-H), 6.59 (s, 1H, -NHTs), 3.64 (d, J = 17.2 Hz, 1H, H_a of -CH_2-), 3.55 (d, J = 17.2 Hz, 1H, H_b of -CH_2-), 2.34 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.2 (-CHO), 144.2 (Ar-C), 143.4 (Ar-C), 141.0 (Ar-C), 136.1 (Ar-C), 135.8 (Ar-C), 132.2 (Ar-C), 131.6 (Ar-C), 131.0 (Ar-C), 130.5 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C) , 129.7 (2C, Ar-C), 129.68 (Ar-C), 129.66 (Ar-C), 129.4 (Ar-C), 128.9 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.3 (2C, Ar-C), 121.6 (Ar-C), 121.4 (Ar-C), 115.7 (Ar-C), 96.0 (-C≡C-), 86.3 (-C≡C-), 48.3 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{29}H_{22}ClNNaO_3S$ $[M + Na]^+$ 522.0907, found 522.0903.

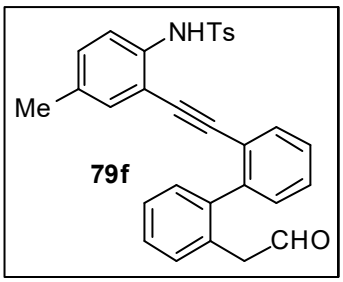
4-Methyl-N-(2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-4-(trifluoromethyl)phenyl)-benzenesulfonamide (79e):



Yellow gummy liquid (209.9 mg, 63%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.56 (t, J = 1.6 Hz, 1H, -CHO), 7.62-7.58 (m, 3H, Ar-H), 7.52 (d, J = 8.8 Hz, 1H, Ar-H), 7.49-7.47 (m, 2H, Ar-H), 7.46-7.44 (m, 1H, Ar-H), 7.43-7.35 (m, 4H, Ar-H), 7.33-7.32 (m, 1H, Ar-H),

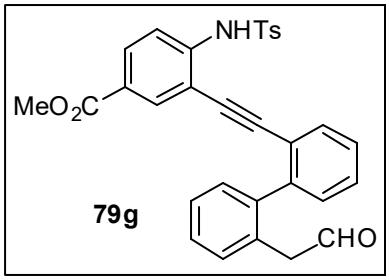
7.30-7.28 (m, 1H, Ar-H), 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 6.98 (s, 1H, -NHTs), 3.69 (dd, J = 17.0, 1.4 Hz, 1H, H_a of -CH_2-), 3.59 (dd, J = 17.2, 1.4 Hz, 1H, H_b of -CH_2-), 2.36 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.1 (-CHO), 144.5 (Ar-C), 143.5 (Ar-C), 141.1 (Ar-C), 140.4-140.3 (m, Ar-C), 135.8 (Ar-C), 132.3 (Ar-C), 131.1 (Ar-C), 130.5 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (2C, Ar-C), 129.53 (Ar-C), 129.5 (q, J_{C-F} = 3.8 Hz, Ar-C), 128.9 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.3 (2C, Ar-C), 126.3 (q, J_{C-F} = 3.7 Hz, Ar-C), 125.9 (q, J_{C-F} = 33.2 Hz, Ar-C), 123.5 (q, J_{C-F} = 262.6 Hz, Ar-C), 121.5 (Ar-C), 118.3 (Ar-C), 113.4 (Ar-C), 96.5 (-C≡C-), 86.1 (-C≡C-), 48.4 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{22}F_3NNaO_3S$ $[M + Na]^+$ 556.1170, found 556.1166.

4-Methyl-N-(4-methyl-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)benzenesulfonamide (79f) **:**



Yellow gummy liquid (227.5 mg, 76%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 7.54-7.45 (m, 5H, Ar-H), 7.42 (td, J = 7.0, 1.7 Hz, 2H, Ar-H), 7.38-7.34 (m, 3H, Ar-H), 7.28-7.26 (m, 1H, Ar-H), 7.10 (d, J = 8.0 Hz, 2H, Ar-H), 7.00 (d, J = 9.6 Hz, 1H, Ar-H), 6.84 (s, 1H, Ar-H/ -NHTs), 6.45 (s, 1H, -NHTs/ Ar-H), 3.65-3.53 (m, 2H, -CH_2-), 2.32 (s, 3H, -SO_2PhCH_3), 2.18 (s, 3H, -CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.5 (-CHO), 143.8 (Ar-C), 143.1 (Ar-C), 141.3 (Ar-C), 136.1 (Ar-C), 134.9 (Ar-C), 134.3 (Ar-C), 132.4 (Ar-C), 132.1 (Ar-C), 130.8 (Ar-C), 130.6 (Ar-C), 130.5 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.5 (2C, Ar-C), 129.0 (Ar-C), 128.8 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.3 (2C, Ar-C), 122.1 (Ar-C), 120.8 (Ar-C), 114.4 (Ar-C), 94.5 (-C≡C-), 87.8 (-C≡C-), 48.3 (-CH_2-), 21.6 (-SO_2PhCH_3), 20.6 (-CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1451.

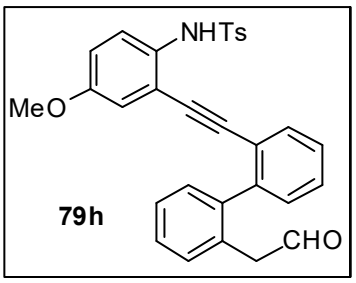
Methyl 4-(4-methylphenylsulfonamido)-3-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)benzoate (79g) **:**



Yellow solid (170.0 mg, 52%), mp 64-66 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.56 (t, J = 1.8 Hz, 1H, -CHO), 7.82-7.79 (m, 2H, Ar-H), 7.63-7.60 (m, 1H, Ar-H), 7.57 (d, J = 8.4 Hz, 2H, Ar-H),

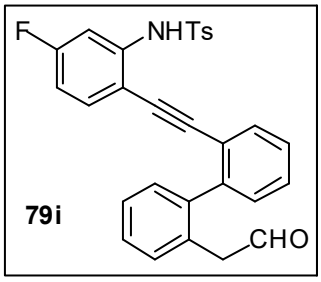
7.49-7.42 (m, 5H, Ar-H), 7.40-7.36 (m, 2H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.17 (d, J = 8.0 Hz, 2H, Ar-H), 6.98 (s, 1H, -N<u>H</u>Ts), 3.85 (s, 3H, -CO_2CH_3), 3.69 (dd, J = 17.2, 1.6 Hz, 1H, H_a of -CH_2-), 3.60 (dd, J = 17.0, 2.0 Hz, 1H, H_b of -CH_2-), 2.35 (s, 3H,-$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.2 (-CHO), 165.8 (-$\underline{C}O_2CH_3$), 144.4 (Ar-C), 143.3 (Ar-C), 141.3 (Ar-C), 141.1 (Ar-C), 135.8 (Ar-C), 133.9 (Ar-C), 132.4 (Ar-C), 131.1 (Ar-C), 130.8 (Ar-C), 130.4 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.8 (2C, Ar-C), 129.4 (Ar-C), 128.9 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.4 (2C, Ar-C), 125.5 (Ar-C), 121.7 (Ar-C), 117.6 (Ar-C), 112.9 (Ar-C), 96.0 (-$\underline{C}$≡C-), 86.4 (-C≡$\underline{C}$-), 52.3 (-$CO_2\underline{C}H_3$), 48.4 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{31}H_{25}NNaO_5S$ $[M + Na]^+$ 546.1351, found 546.1332.

N-(4-Methoxy-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (79h) **:**



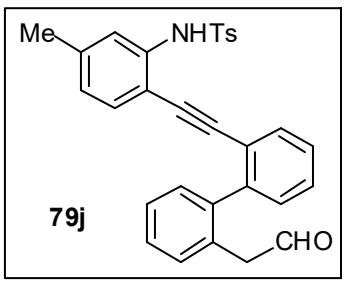
Yellow gummy liquid (241.3 mg, 78%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.52 (t, J = 2.0 Hz, 1H, -CHO), 7.50-7.40 (m, 8H, Ar-H), 7.36-7.32 (m, 2H, Ar-H), 7.28-7.26 (m, 1H, Ar-H), 7.07 (d, J = 8.0 Hz, 2H, Ar-H), 6.78 (dd, J = 9.0, 3.0 Hz, 1H, Ar-H), 6.48 (d, J = 3.2 Hz, 1H, Ar-H), 6.23 (s, 1H, -N<u>H</u>Ts), 3.69 (s, 3H, -OCH_3), 3.59 (dd, J = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.52 (dd, J = 17.2, 2.0 Hz, 1H, H_b of -CH_2-), 2.31 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.4 (-CHO), 156.7 (Ar-C), 143.7 (Ar-C), 143.3 (Ar-C), 141.2 (Ar-C), 136.0 (Ar-C), 131.9 (Ar-C), 130.7 (Ar-C), 130.6 (Ar-C), 130.4 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.4 (2C, Ar-C), 129.1 (Ar-C), 128.8 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.3 (2C, Ar-C), 124.0 (Ar-C), 122.0 (Ar-C), 116.7 (Ar-C), 116.2 (Ar-C), 116.1 (Ar-C), 94.3 (-$\underline{C}$≡C-), 87.9 (-C≡$\underline{C}$-), 55.5 (-OCH_3), 48.2 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1404.

N-(5-Fluoro-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (79i) :



Yellow gummy liquid (226.4 mg, 75%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.55 (t, J = 2.0 Hz, 1H, -CHO), 7.58-7.56 (m, 3H, Ar-H), 7.48-7.46 (m, 2H, Ar-H), 7.43 (td, J = 7.2, 1.9 Hz, 2H, Ar-H), 7.37-7.34 (m, 2H, Ar-H), 7.28-7.26 (m, 1H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.18 (d, J = 8.0 Hz, 2H, Ar-H), 7.05-7.02 (m, 1H, Ar-H), 6.78 (s, 1H, -N<u>H</u>Ts), 6.64 (td, J = 8.4, 2.4 Hz, 1H, Ar-H), 3.66 (dd, J = 17.2, 1.6 Hz, 1H, H_a of -CH_2-), 3.57 (dd, J = 17.2, 2.0 Hz, 1H, H_b of -CH_2-), 2.36 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.3 (-CHO), 162.9 (d, J_{C-F} = 248.9 Hz, Ar-C), 144.3 (Ar-C), 143.1 (Ar-C), 141.2 (Ar-C), 139.2 (d, J_{C-F}= 11.4 Hz, Ar-C), 135.8 (Ar-C), 133.6 (d, J_{C-F} = 9.7 Hz, Ar-C), 132.2 (Ar-C), 130.9 (Ar-C), 130.5 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.7 (2C, Ar-C), 129.1 (Ar-C), 128.8 (Ar-C), 127.92 (Ar-C), 127.90 (Ar-C), 127.3 (2C, Ar-C), 121.9 (Ar-C), 111.4 (d, J_{C-F} = 22.4 Hz, Ar-C), 109.3 (d, J_{C-F} = 3.4 Hz, Ar-C), 106.8 (d, J_{C-F} = 27.6 Hz, Ar-C), 86.52 (-<u>C</u>≡C-), 86.51 (-C≡<u>C</u>-), 48.3 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{23}FNO_3S$ $[M + H]^+$ 484.1383, found 484.1387.

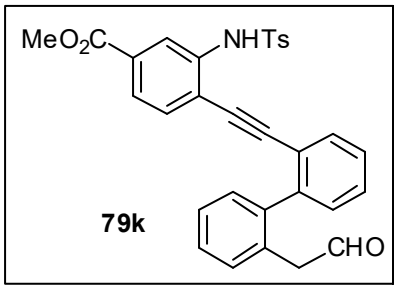
4-Methyl-N-(5-methyl-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)benzenesulfonamide (79j) :



Yellow gummy liquid (269.4 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 7.56-7.51 (m, 3H, Ar-H), 7.48-7.45 (m, 2H, Ar-H), 7.44-7.40 (m, 2H, Ar-H), 7.37-7.33 (m, 2H, Ar-H), 7.30 (s, 1H, Ar-H), 7.28-7.26 (m, 1H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 6.93 (d, J = 7.6 Hz, 1H, Ar-H), 6.77 (d, J = 8.0 Hz, 1H, Ar-H), 6.56 (s, 1H, -N<u>H</u>Ts), 3.62 (dd, J = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.56 (dd, J = 17.0,1.8 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -$SO_2PhC\underline{H}_3$), 2.27 (s, 3H, -CH_3); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.5 (-CHO), 143.9 (Ar-C), 143.1 (Ar-C), 141.3 (Ar-C), 140.3 (Ar-C), 137.3 (Ar-C), 136.2 (Ar-C), 132.0 (Ar-C), 131.9 (Ar-C), 130.8 (Ar-C), 130.6 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.5 (2C, Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.3 (2C, Ar-C), 125.4 (Ar-C), 122.2 (Ar-C), 120.9 (Ar-C), 111.3

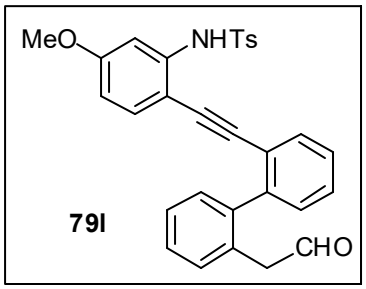
(Ar-C), 94.4 (-C≡C-), 87.8 (-C≡C-), 48.3 ($-CH_2-$), 21.8 ($-CH_3$/ SO_2PhCH_3), 21.6 (SO_2PhCH_3/-CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1452.

Methyl 3-(4-methylphenylsulfonamido)-4-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)benzoate (79k) **:**



Yellow gummy liquid (258.2 mg, 79%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 2.0 Hz, 1H, -CHO), 8.11 (s, 1H, Ar-H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H, Ar-H), 7.59-7.55 (m, 3H, Ar-H), 7.48-7.40 (m, 4H, Ar-H), 7.37-7.34 (m, 2H, Ar-H), 7.29-7.27 (m, 1H, Ar-H), 7.14 (d, J = 8.4 Hz, 2H, Ar-H), 7.10 (d, J = 8.0 Hz, 1H, Ar-H), 6.72 (s, 1H, -NHTs), 3.88 (s, 3H, $-CO_2CH_3$), 3.65 (dd, J = 17.0, 1.8 Hz, 1H, H_a of $-CH_2-$), 3.56 (dd, J = 17.2, 1.6 Hz, 1H, H_b of $-CH_2-$), 2.33 (s, 3H, $-SO_2PhCH_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.2 (-CHO), 166.0 ($-CO_2CH_3$), 144.2 (Ar-C), 143.4 (Ar-C), 141.0 (Ar-C), 137.6 (Ar-C), 135.9 (Ar-C), 132.3 (Ar-C), 132.1 (Ar-C), 131.0 (Ar-C), 130.9 (Ar-C), 130.5 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.7 (2C, Ar-C), 129.6 (Ar-C), 128.9 (Ar-C), 127.95 (Ar-C), 127.92 (Ar-C), 127.4 (2C, Ar-C), 125.1 (Ar-C), 121.6 (Ar-C), 120.6 (Ar-C), 118.2 (Ar-C), 97.6 (-C≡C-), 86.9 (-C≡C-), 52.5 ($-CO_2CH_3$), 48.3 ($-CH_2-$), 21.6 ($-SO_2PhCH_3$); HRMS (ESI) m/z calcd for $C_{31}H_{25}NNaO_5S$ $[M + Na]^+$ 546.1351, found 546.1356.

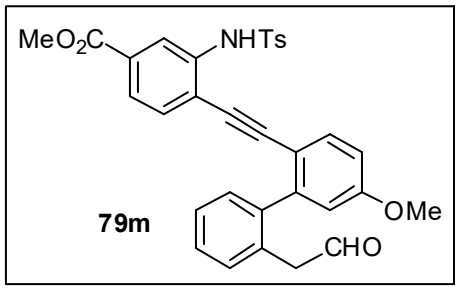
N-(5-Methoxy-2-((2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (79l) **:**



Yellow gummy liquid (151.6 mg, 49%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 7.56-7.54 (m, 3H, Ar-H), 7.48-7.43 (m, 2H, Ar-H), 7.42-7.39 (m, 2H, Ar-H), 7.38-7.34 (m, 2H, Ar-H), 7.27-7.25 (m, 1H, Ar-H), 7.15 (d, J = 8.4 Hz, 2H, Ar-H), 7.03 (d, J = 2.8 Hz, 1H, Ar-H), 6.95 (d, J = 8.8 Hz, 1H, Ar-H), 6.65 (s, 1H, -NHTs), 6.49 (dd, J = 8.6, 2.6 Hz, 1H, Ar-H), 3.75 (s, 3H, $-OCH_3$), 3.63 (dd, J = 17.0, 1.8 Hz, 1H, H_a of $-CH_2-$), 3.57 (dd, J = 17.0 , 1.8 Hz, 1H, H_b of $-CH_2-$), 2.34 (s, 3H, $-SO_2PhCH_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.5 (-CHO),

160.6 (Ar-C), 144.0 (Ar-C), 142.9 (Ar-C), 141.4 (Ar-C), 138.9 (Ar-C), 136.0 (Ar-C), 133.2 (Ar-C), 132.0 (Ar-C), 130.8 (Ar-C), 130.6 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.6 (3C, Ar-C), 128.7 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 127.4 (2C, Ar-C), 122.4 (Ar-C), 110.9 (Ar-C), 106.0 (Ar-C), 105.1 (Ar-C), 93.9 (-C≡C-), 87.6 (-C≡C-), 55.5 (-OCH_3), 48.3 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_4S$ $[M + H]^+$ 496.1583, found 496.1584.

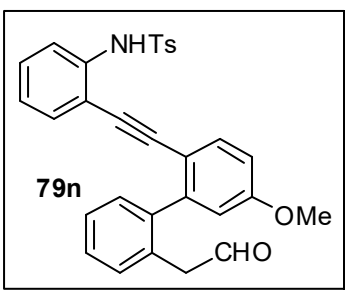
Methyl 4-((5-methoxy-2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-3-(4-methylphenylsulfonamido)benzoate (79m):



79m

Yellow gummy liquid (314.5 mg, 91%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.58 (t, *J* = 1.8 Hz, 1H, -CHO), 8.09 (s, 1H, Ar-H), 7.59 (dd, *J* = 8.0, 1.6 Hz, 1H, Ar-H), 7.55 (d, *J* = 8.0, 2H, Ar-H), 7.51-7.45 (m, 3H, Ar-H), 7.38-7.34 (m, 2H, Ar-H), 7.14 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.06 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.95 (dd, *J* = 8.6, 2.6 Hz, 1H, Ar-H), 6.81 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.67 (s, 1H, -NHTs), 3.88 (s, 3H, -CO_2CH_3/-OCH_3), 3.86 (s, 3H, -OCH_3/-CO_2CH_3), 3.67 (dd, *J* = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.58 (dd, *J* = 17.0, 1.8 Hz, 1H, $H_b$of -CH_2-), 2.33 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.3 (-CHO), 166.0 (-CO_2CH_3), 160.4 (Ar-C), 145.2 (Ar-C), 144.1 (Ar-C), 140.9 (Ar-C), 137.3 (Ar-C), 135.9 (Ar-C), 133.8 (Ar-C), 131.8 (Ar-C), 130.9 (Ar-C), 130.5 (Ar-C), 130.4 (Ar-C), 130.1 (Ar-C), 129.6 (2C, Ar-C), 128.9 (Ar-C), 127.9 (Ar-C), 127.4 (2C, Ar-C), 125.2 (Ar-C), 120.5 (Ar-C), 118.7 (Ar-C), 115.4 (Ar-C), 114.0 (Ar-C), 113.6 (Ar-C), 97.9 (-C≡C-), 85.6 (-C≡C-), 55.6 (-CO_2CH_3/-OCH_3), 52.5 (-OCH_3/-CO_2CH_3), 48.3 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{32}H_{27}NNaO_6S$ $[M + Na]^+$ 576.1457, found 576.1453.

N-(2-((5-Methoxy-2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (79n) **:**

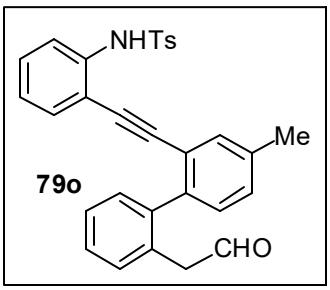


79n

Yellow gummy liquid (259.9 mg, 84%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.58 (t, *J* = 2.0 Hz, 1H, -CHO), 7.52 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.50-7.44 (m, 4H, Ar-H), 7.38-7.33 (m, 2H, Ar-H), 7.18-7.17 (m, 1H, Ar-H), 7.13 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.02 (dd, *J* =

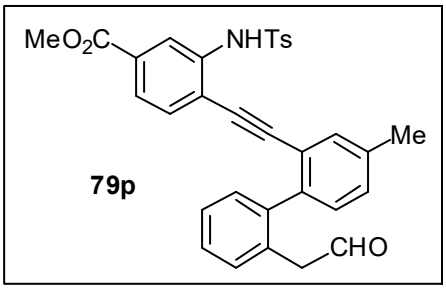
7.8, 1.4 Hz, 1H, Ar-H), 6.96-6.91 (m, 2H, Ar-H), 6.80 (d, J = 2.8 Hz, 1H, Ar-H), 6.62 (s, 1H, -N<u>H</u>Ts), 3.85 (s, 3H, -OCH_3), 3.66 (dd, J = 17.0, 1.8 Hz, 1H, H_a of -CH_2-), 3.58 (dd, J = 16.8, 2.0 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 199.5 (-CHO), 160.0 (Ar-C), 144.9 (Ar-C), 143.9 (Ar-C), 141.2 (Ar-C), 137.2 (Ar-C), 136.1 (Ar-C), 133.6 (Ar-C), 131.9 (Ar-C), 130.8 (Ar-C), 130.5 (Ar-C), 130.1 (Ar-C), 129.5 (2C, Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 127.9 (Ar-C), 127.3 (2C, Ar-C), 124.3 (Ar-C), 119.9 (Ar-C), 115.3 (Ar-C), 114.5 (Ar-C), 114.1 (Ar-C), 114.0 (Ar-C), 95.2 (-<u>C</u>≡C-), 86.0 (-C≡<u>C</u>-), 55.6 (-OCH_3), 48.3 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1405.

4-Methyl-N-(2-((4-methyl-2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)benzenesulfonamide (79o) **:**



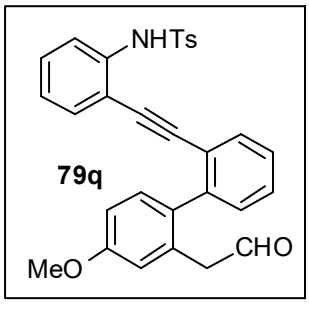
Yellow gummy liquid (152.7 mg, 51%); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.54 (s, 1H, -CHO), 7.53 (d, J = 8.4 Hz, 2H, Ar-H), 7.48-7.44 (m, 3H, Ar-H), 7.38 (s, 1H, Ar-H), 7.36-7.34 (m, 2H, Ar-H), 7.26-7.24 (m, 1H, Ar-H), 7.20-7.15 (m, 2H, Ar-H), 7.13 (d, J = 7.8 Hz, 2H, Ar-H), 7.03 (d, J = 7.2 Hz, 1H, Ar-H), 6.94 (t, J = 7.5 Hz, 1H, Ar-H), 6.65 (s, 1H, -N<u>H</u>Ts), 3.63 (d, J = 16.8 Hz, 1H, H_a of -CH_2-), 3.57 (d, J = 16.8 Hz, 1H, H_b of -CH_2-), 2.44 (s, 3H, -CH_3), 2.34 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.5 (-CHO), 143.8 (Ar-C), 141.1 (Ar-C), 140.2 (Ar-C), 137.6 (Ar-C), 137.3 (Ar-C), 136.0 (Ar-C), 132.5 (Ar-C), 132.1 (Ar-C), 130.7 (Ar-C), 130.6 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 129.5 (2C, Ar-C), 128.5 (Ar-C), 127.8 (Ar-C), 127.2 (2C, Ar-C), 124.2 (Ar-C), 121.6 (Ar-C), 119.8 (Ar-C), 114.0 (Ar-C), 95.2 (-<u>C</u>≡C-), 86.9 (-C≡<u>C</u>-), 48.2 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$/-CH_3), 21.0 (-CH_3/-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_3S$ $[M + H]^+$ 480.1633, found 480.1638.

Methyl 4-((4-methyl-2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-3-(4-methylphenylsulfonamido)benzoate (79p) :



Yellow solid (292.0 mg, 87%), mp 66-68 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 8.10 (d, J = 1.2 Hz, 1H, Ar-H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H, Ar-H), 7.56 (d, J = 8.4 Hz, 2H, Ar-H), 7.47-7.44 (m, 2H, Ar-H), 7.40-7.39 (m, 1H, Ar-H), 7.36-7.32 (m, 2H, Ar-H), 7.29-7.26 (m, 1H, Ar-H), 7.17-7.14 (m, 3H, Ar-H), 7.09 (d, J = 8.0 Hz, 1H, Ar-H), 6.71 (s, 1H, -N<u>H</u>Ts), 3.89 (s, 3H, -$CO_2C\underline{H_3}$), 3.65 (dd, J = 16.8, 1.6 Hz, 1H, H_a of -CH_2-), 3.56 (dd, J = 17.0, 1.8 Hz, 1H, H_b of -CH_2-), 2.44 (s, 3H, -CH_3), 2.34 (s, 3H, -$SO_2PhC\underline{H_3}$); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 199.4 (-CHO), 166.0 (-<u>C</u>O_2CH_3), 144.1 (Ar-C), 141.0 (Ar-C), 140.6 (Ar-C), 137.8 (Ar-C), 137.5 (Ar-C), 135.9 (Ar-C), 132.8 (Ar-C), 132.1 (Ar-C), 130.9 (Ar-C), 130.6 (Ar-C), 130.5 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.7 (2C, Ar-C), 128.8 (Ar-C), 127.9 (Ar-C), 127.4 (2C, Ar-C), 125.1 (Ar-C), 121.3 (Ar-C), 120.5 (Ar-C), 118.2 (Ar-C), 100.0 (Ar-C), 97.9 (-<u>C</u>≡C-), 86.5 (-C≡<u>C</u>-), 52.5 (-$CO_2\underline{C}H_3$), 48.3 (-CH_2-), 21.6 (-CH_3/-$SO_2Ph\underline{C}H_3$), 21.1 (-$SO_2Ph\underline{C}H_3$ /-CH_3); HRMS (ESI) m/z calcd for $C_{32}H_{27}NNaO_5S$ $[M + Na]^+$ 560.1508, found 560.1511.

***N-(2-((4'-Methoxy-2'-(2-oxoethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide(79q)* :**



Yellow gummy liquid (204.2 mg, 66%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (t, J = 1.8 Hz, 1H, -CHO), 7.57-7.55 (m, 1H, Ar-H), 7.52 (d, J = 8.4 Hz, 2H, Ar-H), 7.46 (d, J = 8.4 Hz, 1H, Ar-H), 7.40 (td, J = 7.6, 1.9 Hz, 2H, Ar-H), 7.30 (d, J = 8.4 Hz, 1H, Ar-H), 7.26-7.24 (m, 1H, Ar-H), 7.21-7.17 (m, 1H, Ar-H), 7.15-7.12 (m, 3H, Ar-H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H, Ar-H), 6.96 (td, J = 7.6, 0.8 Hz, 1H, Ar-H), 6.89 (d, J = 2.8 Hz, 1H, Ar-H), 6.65 (s, 1H, -N<u>H</u>Ts), 3.87 (s, 3H, -OCH_3), 3.61 (dd, J = 16.8, 1.6 Hz, 1H, H_a of -CH_2-), 3.55 (dd, J = 16.8, 1.6 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -$SO_2PhC\underline{H_3}$); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 199.3 (-CHO), 159.7 (Ar-C), 143.9 (Ar-C), 142.9 (Ar-C), 137.5 (Ar-C), 136.2 (Ar-C), 133.5 (Ar-C), 132.3 (Ar-C), 132.2 (Ar-C), 131.8 (Ar-C), 131.3 (Ar-C), 130.4

(Ar-C), 129.6 (2C, Ar-C), 129.5 (Ar-C), 129.1 (Ar-C), 127.7 (Ar-C), 127.3 (2C, Ar-C), 124.2 (Ar-C), 122.4 (Ar-C), 119.7 (Ar-C), 116.4 (Ar-C), 113.9 (Ar-C), 113.3 (Ar-C), 95.3 (-C≡C-), 87.3 (-C≡C-), 55.5 ($-OCH_3$), 48.5 ($-CH_2-$), 21.6 ($-SO_2PhCH_3$); HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_4S$ $[M + H]^+$ 496.1583, found 496.1584.

1.2.9.5. General Procedure for the Synthesis of Starting Material 80:

Synthesis of Silylated alcohol derivatives **89** *:*

To a well-stirred ice-cooled solution of previously synthesized **85** derivatives (2.52 mmol, 1 equiv) in dry methanol (4 mL) $NaBH_4$ (191.4 mg, 5.03 mmol, 2 equiv) was added portion-wise and the whole mixture was then allowed to stir at 0 ^oC for 0.5-0.6 h until completion of reaction (TLC). Next, the reaction mixture was diluted with water and extracted with DCM (3 x 40 mL), dried over anhydrous Na_2SO_4 and concentrated *in vaccuo.* The resulting crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 3-6% ethyl acetate in petroleum ether (v/v) to afford the silylated alcohol derivatives **89** in (88-92%) yield.

Synthesis of cyano derivatives **90** *:*

To a well-stirred ice cooled solution of the silylated alcohol derivatives **89** (2.21 mmol, 1 equiv) in dry DCM (7 mL) Et_3N (528.04 µL, 3.76 mmol, 1.7 equiv) was added dropwise and the stirring was continued for 5 min at the same temperature. Methanesulfonyl chloride (252.43 µL, 3.32 mmol, 1.5 equiv) was then added dropwise at 0 °C, and the temperature of the reaction was increased upto rt with continuation of the stirring. After completion of reaction 1.5-2.5 h (TLC), the reaction was quenched with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vaccuo* to obtain a crude product of silylated mesyl-alcohol derivatives. The crude product (without purification) (0.29 mmol, 1 equiv) was dissolved in dry DMF (1.2 mL) (7 batches of reaction was set up with 0.29 mmol of crude) and treated with NaCN (62.0 mg, 1.24 mmol, 4.2 equiv), and the mixture was stirred at rt for 2.5-3.0 h. After completion of reaction (TLC) of each batch, reaction mixture was diluted with water and the combined reaction mixtures was extracted with DCM (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and

concentrated in *vaccuo*. The resulting crude mixture was subjected to silica gel (100−200 mesh) column chromatography and eluted with 1-2% ethyl acetate in petroleum ether (v/v) to afford the silylated acetylenic intermediates **90** in 45-55% yield.

Synthesis of amine derivatives **91** *:*

K_2CO_3 (385.4 mg, 2.79 mmol, 3 equiv) was added to a well stirred solution of the aforesaid intermediate **90** (0.93 mmol, 1 equiv) in MeOH (5 mL) and stirred for 1.5-3.0 h. After completion of reaction (TLC), the mixture was extracted with ethyl acetate (3 x 25 mL); the combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 4-5% ethyl acetate-petroleum ether (v/v) to obtain the desilylated acetylenic derivativesin 70-80% yield.

Next, To a well stirred solution of 2-iodoaniline derivatives (0.64 mmol, 1 equiv) in a mixture of solvents (i.e., Et_3N : DMF = 2:1, 0.9 mL), $PdCl_2(PPh_3)_2$ (13.4 mg, 0.019 mmol, 3 mol %) was added. The reaction mixture was then cooled to 0 ^oC and the desilylated acetylenic derivative (0.70 mmol, 1.1 equiv) was added dropwise followed by the addition of CuI (7.3 mg, 0.038 mmol, 6 mol %,). After stirring few minutes at 0 ^oC, the temperature of the reaction was allowed to rise to rt and stirring was continued for 10-18 h. Upon completion of reaction (TLC), solvent was removed under reduced pressure and extracted with ethyl acetate (3x 25 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 10-27% ethyl acetate-petroleum ether (v/v) to obtain the amine derivatives **91** in 70-85% yield.

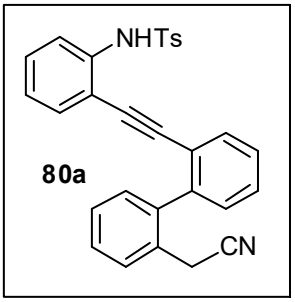
Synthesis of the Final Substrates ***80****:*

To a well stirred solution of amine derivative **91** (0.454 mmol, 1 equiv) in dry DCM (2.5 mL) at 0 ^oC was added pyridine (146.6 µL, 1.82 mmol, 4 equiv) dropwise. Thereafter, TsCl (431.8 mg, 2.27 mmol, 5 equiv) was added portion-wise at the same temperature and whole reaction mixture was allowed to stir at rt for 15-28 h. Upon completion of the reaction (TLC), solvent was removed in *vaccuo* and then extracted with ethyl acetate (3x 30 mL); the combined

organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-32% ethyl acetate-petroleum ether (v/v) to obtain the pure Final Substrates **80** in 35-98% yield.

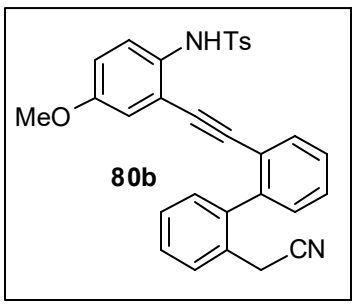
1.2.9.6. Spectral Data of Starting Substrates 80a-i :

N-(2-((2'-(Cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (80a) :



White solid (146.8 mg, 70%), mp 132-134 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.61-7.59 (m, 2H, Ar-H), 7.53 (d, J = 8.4 Hz, 2H, Ar-H), 7.52-7.44 (m, 5H, Ar-H), 7.36-7.33 (m, 2H, Ar-H), 7.22-7.18 (m, 1H, Ar-H), 7.14 (d, J = 8.0 Hz, 2H, Ar-H), 7.02 (dd, J = 7.6, 1.6 Hz, 1H, Ar-H), 6.95 (td, J = 7.5, 0.9 Hz, 1H, Ar-H), 6.55 (s, 1H, -N<u>H</u>Ts), 3.63 (d, J = 18.4 Hz, 1H, H_a of -CH_2-), 3.49 (d, J = 18.4 Hz, 1H, H_b of -CH_2-), 2.34 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.0 (Ar-C), 142.1 (Ar-C), 140.1 (Ar-C), 137.4 (Ar-C), 136.1 (Ar-C), 132.3 (Ar-C), 132.2 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 129.6 (2C, Ar-C), 129.5 (Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 127.3 (2C, Ar-C), 124.5 (Ar-C), 121.9 (Ar-C), 120.1 (Ar-C), 118.0 (Ar-C), 113.9 (Ar-C), 94.5 (-<u>C</u>≡C-), 87.6 (-C≡<u>C</u>-), 21.8 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{22}N_2NaO_2S$ $[M + Na]^+$ 485.1300, found 485.1303.

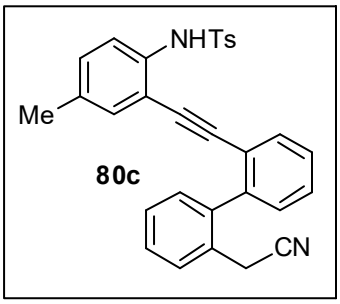
***N-(2-((2'-(Cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (80b)* :**



Pale white gummy liquid (102.7 mg, 46%); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.59 (d, J = 7.2 Hz, 1H, Ar-H), 7.53-7.49 (m, 4H, Ar-H), 7.47-7.44 (m, 3H, Ar-H), 7.40 (d, J = 9.0 Hz, 1H, Ar-H), 7.34 (t, J = 7.2 Hz, 2H, Ar-H), 7.09 (d, J = 8.4 Hz, 2H, Ar-H), 6.80 (dd, J = 9.0, 3.0 Hz, 1H, Ar-H), 6.46 (d, J = 3.0 Hz, 1H, Ar-H), 6.19 (s, 1H, -N<u>H</u>Ts), 3.70 (s, 3H, -OCH_3), 3.58 (d, J = 18.6 Hz, 1H, H_a of -CH_2-), 3.46 (d, J = 18.6 Hz, 1H, H_b of -CH_2-), 2.32 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$,

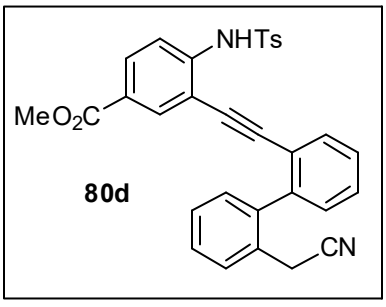
150 MHz) δ_C 156.7 (Ar-C), 143.6 (Ar-C), 142.1(Ar-C), 140.0 (Ar-C), 135.9 (Ar-C), 132.0 (Ar-C), 130.3 (Ar-C), 130.2 (Ar-C), 129.6 (Ar-C), 129.4 (Ar-C), 129.3 (2C, Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 127.2 (2C, Ar-C), 124.0 (Ar-C), 121.7 (Ar-C), 117.9 (Ar-C), 116.5 (Ar-C), 116.2 (Ar-C), 116.1 (Ar-C), 93.6 (-C≡C-), 87.8 (-C≡C-), 55.4 (-OCH_3), 21.7 (-CH_2-), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{24}N_2NaO_3S$ [M + Na]$^+$ 515.1405, found 515.1421.

N-(2-((2'-(Cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-4-methylphenyl)-4-methylbenzenesulfonamide (80c) **:**



Pale yellow gummy liquid (207.4 mg, 96%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.61-7.55 (m, 2H, Ar-H), 7.53-7.43 (m, 6H, Ar-H), 7.38-7.33 (m, 3H, Ar-H), 7.12 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-H), 6.82 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.36 (s, 1H, -NHTs), 3.62 (d, *J* = 18.4 Hz, 1H, H_a of -CH_2-), 3.48 (d, *J* = 18.4 Hz, 1H, H_b of -CH_2-), 2.33 (s, 3H, -SO_2PhCH_3), 2.19 (s, 3H, -CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 143.8 (Ar-C), 142.1 (Ar-C), 140.2 (Ar-C), 136.1 (Ar-C), 134.9 (Ar-C), 134.5 (Ar-C), 132.4 (Ar-C), 132.2 (Ar-C), 130.7 (Ar-C), 130.4 (Ar-C), 129.7 (Ar-C), 129.5 (2C, Ar-C), 129.4 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 127.3 (2C, Ar-C), 122.0 (Ar-C), 120.8 (Ar-C), 118.0 (Ar-C), 114.2 (Ar-C), 94.0 (-C≡C-), 87.9 (-C≡C-), 21.8 (-CH_2-), 21.6 (-SO_2PhCH_3), 20.6 (-CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{24}N_2NaO_2S$ [M + Na]$^+$ 499.1456, found 499.1454.

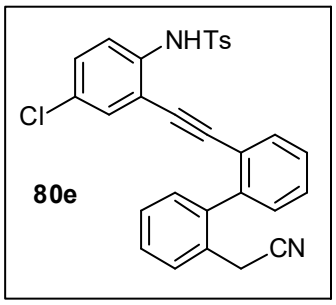
Methyl 3-((2'-(cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-4-(4-methylphenylsulfonamido)benzoate (80d) **:**



Pale white solid (186.5 mg, 79%), mp 62-64 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.82 (dd, *J* = 9.0, 1.8 Hz, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.65 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.62 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.58 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.55-7.50 (m, 3H, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 7.38-7.35 (m, 2H, Ar-H), 7.19 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.80 (s, 1H, -NHTs), 3.86 (s, 3H,

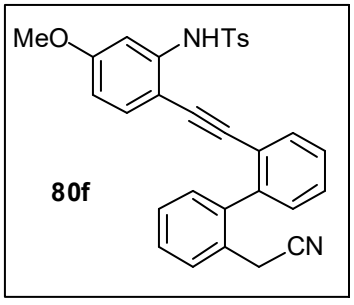
-CO_2CH_3), 3.64 (d, J = 18.6 Hz, 1H, H_a of -CH_2-), 3.52 (d, J = 18.6 Hz, 1H, H_b of -CH_2-), 2.36 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 165.6 (-CO_2CH_3), 144.4 (Ar-C), 142.1 (Ar-C), 141.1 (Ar-C), 139.9 (Ar-C), 135.6 (Ar-C), 133.8 (Ar-C), 132.4 (Ar-C), 130.9 (Ar-C), 130.2 (Ar-C), 129.7 (2C, Ar-C), 129.66 (Ar-C), 129.64 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 127.2 (2C, Ar-C), 125.5 (Ar-C), 121.4 (Ar-C), 117.8 (Ar-C), 117.5 (Ar-C), 112.6 (Ar-C), 95.4 (-C≡C-), 86.4 (-C≡C-), 52.2 (-CO_2CH_3), 21.8 (-CH_2-), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{31}H_{25}N_2O_4S$ $[M + H]^+$ 521.1535, found 521.1533.

N-(4-Chloro-2-((2'-(cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (80e) **:**



Yellow gummy liquid (184.6 mg, 82%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.61-7.46 (m, 8H, Ar-H), 7.40 (d, J = 8.8 Hz, 1H, Ar- H), 7.37-7.33 (m, 2H, Ar- H), 7.17-7.14 (m, 3H, Ar- H), 6.99 (d, J = 2.4 Hz, 1H, Ar- H), 6.45 (s, 1H, -NHTs), 3.59 (d, J = 18.0 Hz, 1H, H_a of -CH_2-), 3.48 (d, J = 18.0 Hz, 1H, H_b of -CH_2-), 2.35 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.3 (Ar-C), 142.3 (Ar-C), 140.0 (Ar-C), 136.0 (Ar-C), 135.8 (Ar-C), 132.4 (Ar-C), 131.7 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.81 (Ar-C), 129.80 (Ar-C), 129.77 (Ar-C), 129.73 (2C, Ar-C), 129.3 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 127.3 (2C, Ar-C), 121.5 (Ar-C), 121.4 (Ar-C), 117.9 (Ar-C), 115.6 (Ar-C), 95.5 (-C≡C-), 86.4 (-C≡C-), 21.9 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{29}H_{21}ClN_2NaO_2S$ $[M + Na]^+$ 519.0910, found 519.0918.

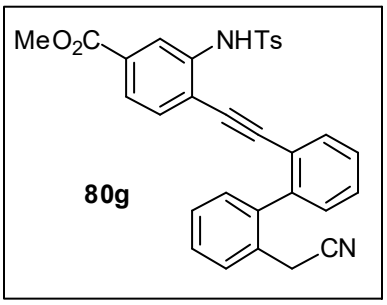
N-(2-((2'-(Cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-5-methoxyphenyl)-4-methylbenzenesulfonamide (80f):



Pale white gummy liquid (218.9 mg, 98%); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.60-7.57 (m, 2H, Ar-H), 7.55 (d, J = 8.8 Hz, 2H, Ar-H), 7.51-7.42 (m, 4H, Ar-H), 7.35-7.31 (m, 2H, Ar-H), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 7.02 (d, J = 2.4 Hz, 1H, Ar-H), 6.93 (d, J = 8.8 Hz,

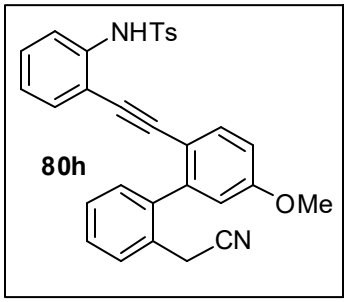
1H, Ar-H), 6.56 (s, 1H, -NHTs), 6.49 (dd, J = 8.6, 2.6 Hz, 1H, Ar-H), 3.74 (s, 3H, -OCH_3), 3.63 (d, J = 18.4 Hz, 1H, H_a of -CH_2-), 3.49 (d, J = 18.4 Hz, 1H, H_b of -CH_2-), 2.35 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C*160.7* (Ar-C), 144.1 (Ar-C), 141.8 (Ar-C), 140.3 (Ar-C), 138.8 (Ar-C), 136.0 (Ar-C), 133.2 (Ar-C), 132.1 (Ar-C), 130.3 (Ar-C), 129.7 (Ar-C), 129.6 (2C, Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 127.3 (2C, Ar-C), 122.2 (Ar-C), 118.1 (Ar-C), 111.0 (Ar-C), 105.8 (Ar-C), 105.2 (Ar-C), 100.0 (Ar-C), 93.4 (-C≡C-), 87.7 (-C≡C-), 55.5 (-OCH_3), 21.8 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{24}N_2NaO_3S$ $[M + Na]^+$ 515.1405, found 515.1422.

Methyl 4-((2'-(cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)-3-(4-methylphenylsulfonamido)benzoate (80g) **:**



Pale white solid (224.3 mg, 95%), mp 122-124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.09 (s, 1H, Ar-H), 7.63-7.59 (m, 3H, Ar-H), 7.56 (d, J = 8.4 Hz, 2H, Ar-H), 7.54-7.45 (m, 4H, Ar-H), 7.36-7.33 (m, 2H, Ar-H), 7.16 (d, J = 8.4 Hz, 2H, Ar-H), 7.08 (d, J = 8.4 Hz, 1H, Ar-H), 6.59 (s, 1H, -NHTs), 3.89 (s, 3H, -CO_2CH_3), 3.60 (d, J = 18.4 Hz, 1H, H_a of -CH_2-), 3.49 (d, J = 18.4 Hz, 1H, H_b of -CH_2-), 2.34 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 165.9 (-CO_2CH_3), 144.3 (Ar-C), 142.3 (Ar-C), 140.0 (Ar-C), 137.5 (Ar-C), 135.9 (Ar-C), 132.5 (Ar-C), 132.1 (Ar-C), 131.1 (Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.7 (2C, Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 127.4 (2C, Ar-C), 125.3 (Ar-C), 121.4 (Ar-C), 120.6 (Ar-C), 118.1 (Ar-C), 117.9 (Ar-C), 97.0 (-C≡C-), 87.0 (-C≡C-), 52.5 (-CO_2CH_3), 21.9 (-CH_2-), 21.6 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{31}H_{24}N_2NaO_4S$ $[M + Na]^+$ 543.1354, found 543.1379.

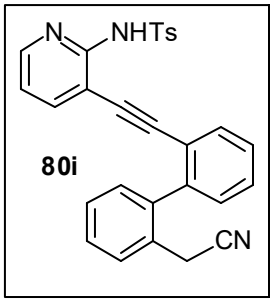
N-(2-((2'-(Cyanomethyl)-5-methoxy-[1,1'-biphenyl]-2-yl)ethynyl)phenyl)-4-methylbenzenesulfonamide (80h) :



Pale yellow solid (127.3 mg, 57%), mp 118-120 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.60-7.58 (m, 1H, Ar-H), 7.53-7.47 (m, 5H, Ar-H), 7.44 (d, J = 8.4 Hz, 1H, Ar-H), 7.36-7.34 (m, 1H, Ar-H),

7.19-7.17 (m, 1H, Ar-H), 7.14 (d, J = 8.4 Hz, 2H, Ar-H), 7.01-6.92 (m, 3H, Ar-H), 6.87 (d, J = 2.8 Hz, 1H, Ar-H), 6.55 (s, 1H, -N<u>H</u>Ts), 3.89 (s, 3H, -OCH_3), 3.65 (d, J = 18.4 Hz, 1H, H_a of -CH_2-), 3.51 (d, J = 18.4 Hz, 1H, H_b of -CH_2-), 2.34 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.3 (Ar-C), 144.0 (Ar-C), 143.8 (Ar-C), 140.1 (Ar-C), 137.2 (Ar-C), 136.1 (Ar-C), 133.8 (Ar-C), 131.9 (Ar-C), 130.2 (Ar-C), 129.6 (2C, Ar-C), 129.4 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 127.3 (2C, Ar-C), 124.4 (Ar-C), 120.0 (Ar-C), 118.1 (Ar-C), 115.1 (Ar-C), 114.4 (Ar-C), 114.3 (Ar-C), 113.9 (Ar-C), 94.7 (-<u>C</u>≡C-), 86.1 (-C≡<u>C</u>-), 55.7 (-OCH_3), 21.8 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{25}N_2O_3S$ $[M + H]^+$ 493.1586, found 493.1583.

N-(3-((2'-(Cyanomethyl)-[1,1'-biphenyl]-2-yl)ethynyl)pyridin-2-yl)-4-methylbenzenesulfonamide (80i) **:**



White solid (73.6 mg, 35%), 70-72 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.06 (d, J = 4.0 Hz, 1H, Ar-H), 7.95 (d, J = 8.4 Hz, 2H, Ar-H), 7.70-7.68 (m, 1H, Ar-H), 7.62-7.60 (m, 1H, Ar-H), 7.53-7.44 (m, 4H, Ar-H), 7.39-7.33 (m, 3H, Ar-H), 7.28-7.26 (m, 2H, Ar-H), 6.80-6.77 (m, 1H, Ar-H), 3.67 (d, J = 18.4 Hz, 1H, -H_a of CH_2-), 3.53 (d, J = 18.0 Hz, 1H, H_b of -CH_2-), 2.40 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 150.9 (Ar-C), 144.0 (Ar-C), 142.3 (Ar-C), 140.6 (Ar-C), 140.1 (Ar-C), 132.6 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.7(Ar-C), 129.3 (Ar-C), 129.2 (2C, Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 128.42 (Ar-C), 128.41 (Ar-C), 128.40 (Ar-C) 128.3 (Ar-C), 121.6 (Ar-C), 118.1 (Ar-C), 96.2 (-<u>C</u>≡C-), 85.9 (-C≡<u>C</u>-), 21.9 (-CH_2-) 21.7 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{28}H_{22}N_3O_2S$ $[M + H]^+$ 464.1433, found 464.1435.

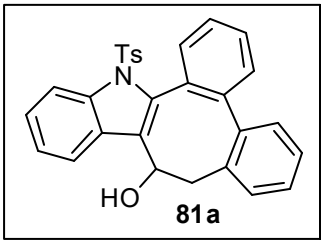
1.2.9.7. General Procedure for the Synthesis of Products 81:

To a well-stirred solution of $Pd(OAc)_2$bpy (1.96 mg, 0.005 mmol, 6 mol %) in 1,4-dioxane (0.5 mL), AcOH (0.1 mL) was added and the resulting mixture was heated at 100 ^oC. Next, the starting material **79** (0.086 mmol, 1 equiv) dissolved in dry 1,4-dioxane (0.5 mL) was added drop-wise to the reaction mixture and it was then stirred at the same temperature for another 2.5-6.0 h. Upon completion of reaction (TLC), the reaction mixture was neutralized by

drop-wise addition of dilute aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vaccuo.* The resulting crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 15-28% ethyl acetate in petroleum ether (v/v) to afford the desired product **81** in (59-94%) yield.

1.2.9.8. Spectral Data of Products 81a-q :

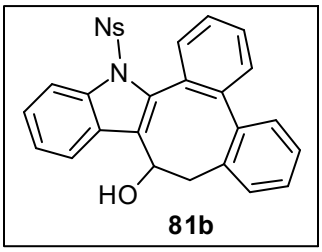
***15-Tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81a)*:**



81a

White solid (29.2 mg, 73%), mp 128-130 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.08-8.05 (m, 1H, Ar-H), 7.72 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 7.57-7.45 (m, 3H, Ar-H), 7.43-7.38 (m, 2H, Ar-H), 7.32-7.20 (m, 5H, Ar-H), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.76 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.26 (dd, *J* = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.16 (dd, J = 12.8, 6.4 Hz, 1H, H_a of -CH_2-), 2.94 (t, *J* = 12.4 Hz, 1H, H_b of-CH_2-), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.1 (Ar-C), 141.4 (Ar-C), 139.4 (Ar-C), 137.6 (Ar-C), 137.1 (Ar-C), 135.7 (Ar-C), 134.3 (Ar-C), 134.0 (Ar-C), 130.7 (Ar-C), 130.5 (Ar-C), 129.5 (Ar-C), 129.1 (3C, Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 127.9 (Ar-C), 126.6 (2C, Ar-C), 126.5 (Ar-C), 126.2 (Ar-C), 125.3 (Ar-C), 124.3 (Ar-C), 123.6 (Ar-C), 119.2 (Ar-C), 116.2 (Ar-C), 68.7 (-CHOH), 39.3 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{23}NNaO_3S$ $[M+Na]^+$ 488.1296 , found 488.1298.

***15-((4-Nitrophenyl)sulfonyl)-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81b)*:**

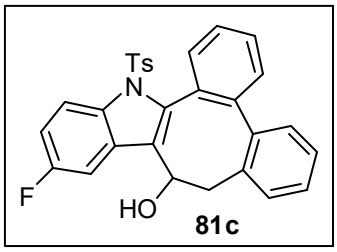


81b

Yellow solid (26.9 mg, 63%), mp >250 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.04-8.02 (m, 1H, Ar-H), 7.75-7.73 (m, 3H, Ar-H), 7.59-7.51 (m, 3H, Ar-H), 7.48-7.44 (m, 2H, Ar-H), 7.39-7.35 (m, 2H, Ar-H), 7.34-7.28 (m, 2H, Ar-H), 7.27-7.26 (m, 1H, Ar-H), 7.21-7.18 (m, 2H, Ar-H), 5.25 (dd, *J* = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.19 (dd, *J* = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.96 (t, *J* = 12.2 Hz, 1H, H_b of -CH_2-); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 141.7 (Ar-C), 141.2 (Ar-C), 139.1 (Ar-C), 137.3 (Ar-C), 137.1 (Ar-C), 135.6 (Ar-

C), 134.0 (Ar-C), 130.9 (Ar-C), 130.4 (Ar-C), 129.7 (Ar-C), 129.4 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.4 (Ar-C), 127.8 (2C, Ar-C), 126.9 (Ar-C), 126.4 (Ar-C), 126.0 (Ar-C), 125.24 (Ar-C), 125.23 (Ar-C), 123.6 (3C, Ar-C), 119.8 (Ar-C), 116.3 (Ar-C), 68.6 (-CHOH), 39.2 (-CH_2-); HRMS (EI)$^+$ m/z calcd for $C_{28}H_{20}N_2O_5S$ $[M]^+$ 496.1093 , found 496.1085.

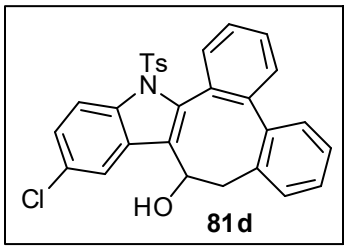
***12-Fluoro-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol* (*81c*) :**



81c

Pale yellow solid (29.9 mg, 72%), mp > 250°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.02-7.99 (m, 1H, Ar-H), 7.71 (dd, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.54 (td, J = 7.5, 1.5 Hz, 1H, Ar-H), 7.49 (td, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.43-7.39 (m, 2H, Ar-H), 7.33-7.29 (m, 3H, Ar-H), 7.21 (dd, J = 8.4, 2.4 Hz, 1H, Ar-H), 6.99-6.94 (m, 3H, Ar-H), 6.77 (d, J = 8.0 Hz, 2H, Ar-H), 5.16 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.15 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.93 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.19 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.5 (d, $J_{C\text{-}F}$ = 238.3 Hz, Ar-C), 144.3 (Ar-C), 141.2 (Ar-C), 139.3 (Ar-C), 137.5 (Ar-C), 136.9 (Ar-C), 134.0 (2C, Ar-C), 130.4 (Ar-C), 129.5 (Ar-C), 129.2 (Ar-C), 129.1 (3C, Ar-C), 128.5 (Ar-C), 128.1 (Ar-C), 126.6 (Ar-C), 126.5 (2C, Ar-C), 126.3 (Ar-C), 123.5 (d, $J_{C\text{-}F}$ = 4.1 Hz, Ar-C), 117.4 (d, $J_{C\text{-}F}$= 9.0 Hz, Ar-C), 113.1 (d, $J_{C\text{-}F}$ = 25.0 Hz, Ar-C), 105.1 (d, $J_{C\text{-}F}$ = 24.1 Hz, Ar-C), 68.8 (-CHOH), 39.3 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −118.0 (s, 1F); HRMS (ESI) m/z calcd for $C_{29}H_{23}FNO_3S$ $[M + H]^+$ 484.1383, found 484.1387.

***12-Chloro-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81d)* :**

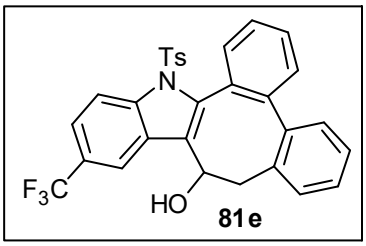


81d

Yellow solid (34.8 mg, 81%), mp 170-172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.97 (d, J = 8.8 Hz, 1H, Ar-H), 7.70 (d, J = 7.6 Hz, 1H, Ar-H), 7.55-7.45 (m, 3H, Ar-H), 7.40-7.38 (m, 2H, Ar-H), 7.32-7.26 (m, 3H, Ar-H), 7.18 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.95 (d, J = 8.4 Hz, 2H, Ar-H), 6.78 (d, J = 8.4 Hz, 2H, Ar-H), 5.18 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.14 (dd, J = 12.8, 6.4 Hz, 1H, H_a of -CH_2-), 2.91 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.4 (Ar-C), 141.2 (Ar-C), 139.4 (Ar-C), 137.1 (Ar-C), 136.9 (Ar-C), 135.9 (Ar-C), 134.1 (Ar-C),

134.0 (Ar-C), 131.9 (Ar-C), 130.2 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 129.25 (Ar-C), 129.21 (2C, Ar-C), 129.1 (Ar-C), 128.5 (Ar-C), 128.1 (Ar-C), 126.6 (Ar-C), 126.5 (2C, Ar-C), 126.3 (Ar-C), 125.4 (Ar-C), 122.9 (Ar-C), 119.1 (Ar-C), 117.3 (Ar-C), 68.6 (-CHOH), 39.3 (-CH_2-), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{29}H_{22}ClNNaO_3S$ $[M + Na]^+$ 522.0907, found 522.0898.

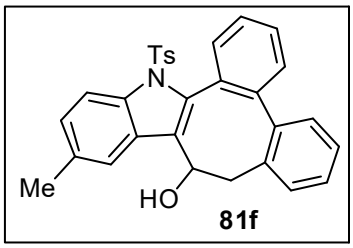
15-Tosyl-12-(trifluoromethyl)-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81e) **:**



81e

White solid (35.7 mg, 78%), mp 138-140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.17 (d, J = 8.8 Hz, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.68 (dd, J = 7.6, 1.2 Hz, 1H, Ar-H), 7.55 (td, J = 7.5, 1.5 Hz, 1H, Ar-H), 7.50-7.46 (m, 2H, Ar-H), 7.40-7.35 (m, 2H, Ar-H), 7.32-7.28 (m, 3H, Ar-H), 7.00 (d, J = 8.4 Hz, 2H, Ar-H), 6.82 (d, J = 8.8 Hz, 2H, Ar-H), 5.27 (dd, J = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.17 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.93 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.21 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.7 (Ar-C), 141.1 (Ar-C), 139.5 (Ar-C), 139.1 (q, J_{C-F}= 1.6 Hz, Ar-C), 137.3 (Ar-C), 136.9 (Ar-C), 134.3 (Ar-C), 133.9 (Ar-C), 131.1 (q, J_{C-F} = 286.6 Hz, Ar-C), 130.3 (Ar-C), 129.9 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 129.3 (2C, Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 126.61 (Ar-C), 126.60 (3C, Ar-C), 126.5 (d, J_{C-F} = 32.3 Hz, Ar-C), 123.1 (Ar-C), 121.9 (q, J_{C-F} = 3.4 Hz, Ar-C), 116.9 (q, J_{C-F} = 4.3 Hz, Ar-C), 116.4 (Ar-C), 68.5 (-CHOH), 39.4 (-CH_2-), 21.5 (-SO_2PhCH_3); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −61.2 (s, 3F); HRMS (ESI) m/z calcd for $C_{30}H_{22}F_3NNaO_3S$ $[M + Na]^+$ 556.1170, found 556.1174.

12-Methyl-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81f) **:**

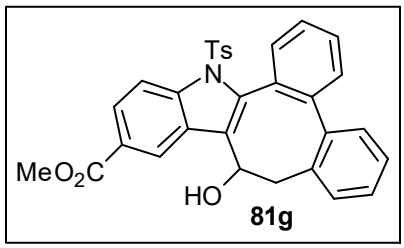


81f

Pale yellow solid (30.9 mg, 75%), mp 160-162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.93 (d, J = 8.4 Hz, 1H, Ar-H), 7.73-7.71 (m, 1H, Ar-H), 7.54-7.45 (m, 2H, Ar-H), 7.42-7.35 (m, 3H, Ar-H), 7.31-7.29 (m, 3H, Ar-H), 7.08-7.06 (m, 1H, Ar-H), 6.97 (d, J = 8.0 Hz, 2H, Ar-H), 6.76 (d, J = 8.0 Hz, 2H, Ar-H), 5.23 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.15 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.93 (t, J = 12.2 Hz, 1H, H_b

of -CH_2-), 2.37 (s, 3H, -CH_3), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.0 (Ar-C), 141.4 (Ar-C), 139.3 (Ar-C), 137.1 (Ar-C), 135.7 (Ar-C), 134.3 (Ar-C), 134.1 (Ar-C), 134.0 (Ar-C), 130.8 (Ar-C), 130.6 (Ar-C), 129.4 (Ar-C), 129.1 (Ar-C), 129.0 (2C, Ar-C), 128.9 (Ar-C), 128.5 (Ar-C), 127.9 (Ar-C), 126.7 (Ar-C), 126.6 (3C, Ar-C), 126.5 (Ar-C), 126.2 (Ar-C), 123.4 (Ar-C), 119.1 (Ar-C), 115.9 (Ar-C), 68.7 (-CHOH), 39.3 (-CH_2-), 21.5 (-CH_3/-$SO_2Ph\underline{C}H_3$), 21.4 (-$SO_2Ph\underline{C}H_3$/-CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1443.

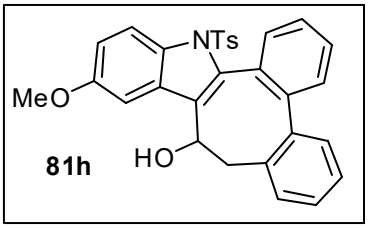
Methyl 10-hydroxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-12-carboxylate (81g):



81g

White solid (28.8 mg, 64%), mp 246-248 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.27-8.26 (m, 1H, Ar-H), 8.08 (d, J = 8.8 Hz, 1H, Ar-H), 7.92 (dd, J = 8.8, 1.6 Hz, 1H, Ar-H), 7.70 (dd, J = 7.6, 1.2 Hz, 1H, Ar-H), 7.53 (td, J = 7.4, 1.5 Hz, 1H, Ar-H), 7.47 (td, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.40-7.36 (m, 2H, Ar-H), 7.31-7.28 (m, 3H, Ar-H), 6.97 (d, J = 8.4 Hz, 2H, Ar-H), 6.78 (d, J = 8.0 Hz, 2H, Ar-H), 5.31 (dd, J = 12.0, 6.4 Hz, 1H, -C$\underline{H}$OH), 3.89 (s, 3H, -CO_2CH_3), 3.17 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.94 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.19 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.1 (-$\underline{C}O_2CH_3$), 144.5 (Ar-C), 141.2 (Ar-C), 140.2 (Ar-C), 139.5 (Ar-C), 137.1 (Ar-C), 137.0 (Ar-C), 134.2 (Ar-C), 133.9 (Ar-C), 130.4 (Ar-C), 130.2 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 129.2 (2C, Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 126.6 (2C, Ar-C), 126.5 (Ar-C), 126.4 (Ar-C), 126.3 (Ar-C), 126.2 (Ar-C), 123.5 (Ar-C), 121.3 (Ar-C), 115.9 (Ar-C), 68.4 (-CHOH), 52.2 (-$CO_2\underline{C}H_3$), 39.3 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{31}H_{25}NNaO_5S$ $[M + Na]^+$ 546.1351, found 546.1353.

12-Methoxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81h) **:**

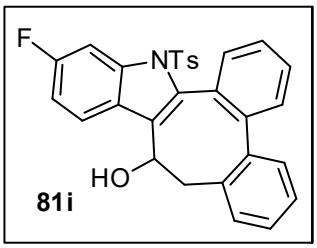


81h

Pale yellow solid (28.1 mg, 66%), mp 168-170 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.94 (d, J = 8.8 Hz, 1H, Ar-H), 7.73-7.71 (m, 1H, Ar-H), 7.54-7.47 (m, 2H, Ar-H), 7.45-7.38 (m, 2H, Ar-H), 7.32-7.29 (m, 3H, Ar-H), 6.98 (d, J = 2.4 Hz, 1H, Ar-H),

6.96 (d, J = 8.4 Hz, 2H, Ar-H), 6.85 (dd, J = 9.2, 2.8 Hz, 1H, Ar-H), 6.75 (d, J = 8.0 Hz, 2H, Ar-H), 5.20 (dd, J = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.80 (s, 3H, -OCH_3), 3.15 (dd, J = 12.4, 6.4 Hz, 1H, H_a of -CH_2-), 2.94 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.17 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 157.1 (Ar-C), 144.0 (Ar-C), 141.4 (Ar-C), 139.2 (Ar-C), 137.1 (Ar-C), 136.5 (Ar-C), 134.2 (Ar-C), 134.1 (Ar-C), 132.0 (Ar-C), 131.6 (Ar-C), 130.7 (Ar-C), 129.5 (Ar-C), 129.1 (Ar-C), 129.0 (2C, Ar-C), 128.9 (Ar-C), 128.5 (Ar-C), 128.0 (Ar-C), 126.6 (2C, Ar-C), 126.5 (Ar-C), 126.2 (Ar-C), 123.7 (Ar-C) , 117.2 (Ar-C), 114.1 (Ar-C), 101.6 (Ar-C), 68.8 (-CHOH), 55.7 (-OCH_3), 39.3 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402 , found 518.1416.

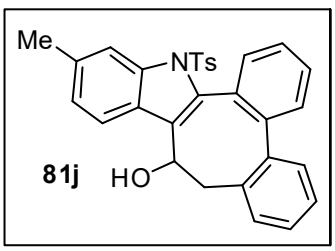
13-Fluoro-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81i) **:**



81i

White solid (33.6 mg, 81%), mp 244-246 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.81 (dd, J = 10.2, 2.2 Hz, 1H, Ar-H), 7.71-7.68 (m, 1H, Ar-H), 7.54-7.45 (m, 3H, Ar-H), 7.40-7.37 (m, 2H, Ar-H), 7.33-7.27 (m, 3H, Ar-H), 7.00-6.95 (m, 3H, Ar-H), 6.80 (d, J = 8.0 Hz, 2H, Ar-H), 5.20 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.14 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.91 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 161.2 (d, $J_{C\text{-}F}$ = 241.1 Hz, Ar-C), 144.4 (Ar-C), 141.3 (Ar-C), 139.3 (Ar-C), 137.9 (d, $J_{C\text{-}F}$ = 12.4 Hz, Ar-C), 137.0 (Ar-C), 135.9 (d, $J_{C\text{-}F}$= 4.1 Hz, Ar-C), 134.1 (Ar-C), 134.0 (Ar-C), 130.3 (Ar-C), 129.5 (Ar-C), 129.2 (2C, Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.0 (Ar-C), 126.7 (d, $J_{C\text{-}F}$= 6.0 Hz, Ar-C) 126.6 (2C, Ar-C), 126.5 (Ar-C), 126.3 (Ar-C), 123.1 (Ar-C), 120.1 (d, $J_{C\text{-}F}$ = 9.7 Hz, Ar-C), 112.5 (d, $J_{C\text{-}F}$ = 24.0 Hz, Ar-C), 103.7 (d, $J_{C\text{-}F}$ = 28.5 Hz, Ar-C), 68.6 (-CHOH), 39.3 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −115.2 (s, 1F); HRMS (ESI) m/z calcd for $C_{29}H_{22}FNNaO_3S$ $[M + Na]^+$ 506.1202, found 506.1216.

13-Methyl-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81j):

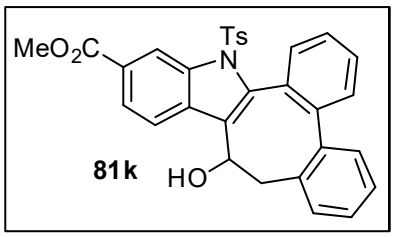


81j

Pale yellow solid (28.0 mg, 68%), mp 148-150 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.88 (s, 1H, Ar-H), 7.71-7.69 (m, 1H, Ar-H), 7.53-7.36 (m, 5H, Ar-H), 7.30-7.27 (m, 3H, Ar-H), 7.05 (d, J = 8.0

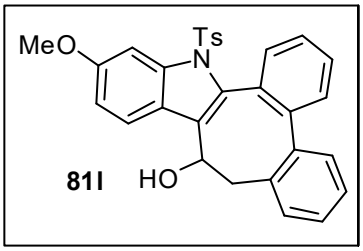
Hz, 1H, Ar-H), 6.96 (d, J = 8.4 Hz, 2H, Ar-H), 6.77 (d, J = 8.4 Hz, 2H, Ar-H), 5.23 (dd, J = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.15 (dd, J = 12.6, 6.4 Hz, 1H, H_a of -CH_2-), 2.92 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.43 (s, 3H, -C<u>H</u>$_3$), 2.18 (s, 3H, -SO_2PhC<u>H</u>$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 143.9 (Ar-C), 141.3 (Ar-C), 139.2 (Ar-C), 137.9 (Ar-C), 137.0 (Ar-C), 135.4 (Ar-C), 134.8 (Ar-C), 134.3 (Ar-C), 133.9 (Ar-C), 130.7 (Ar-C), 129.3 (Ar-C), 128.9 (3C, Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 127.8 (Ar-C), 126.4 (2C, Ar-C), 126.3 (Ar-C), 126.1 (Ar-C), 125.5 (Ar-C), 123.5 (Ar-C), 118.6 (Ar-C), 116.3 (Ar-C), 68.6 (-CHOH), 39.1 (-CH_2-), 21.9 (-SO_2Ph<u>C</u>H_3/-CH_3), 21.4 (-CH_3/-SO_2Ph<u>C</u>H_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ [M + Na]$^+$ 502.1453, found 502.1456.

Methyl 10-hydroxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (81k) :



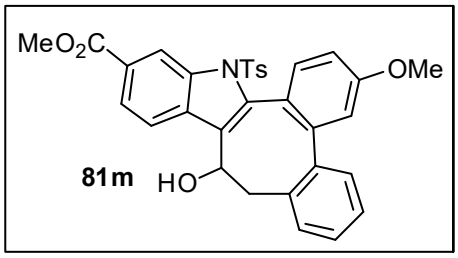
White solid (27.0 mg, 60%), mp 188-190 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.75 (s, 1H, Ar-H), 7.91 (dd, J = 8.4, 1.2 Hz, 1H, Ar-H), 7.70 (dd, J = 7.8, 1.4 Hz, 1H, Ar-H), 7.59 (d, J = 8.4 Hz, 1H, Ar-H), 7.55 (td, J = 7.5, 1.4 Hz, 1H, Ar-H), 7.48 (td, J = 7.5, 1.3 Hz, 1H, Ar-H), 7.41-7.38 (m, 2H, Ar-H), 7.32-7.29 (m, 3H, Ar-H), 7.00 (d, J = 8.4 Hz, 2H, Ar-H), 6.78 (d, J = 8.0 Hz, 2H, Ar-H), 5.26 (m, 1H, -C<u>H</u>OH), 3.94 (s, 3H, -CO_2CH_3), 3.16 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.94 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.19 (s, 3H, -SO_2PhC<u>H</u>$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.2 (-<u>C</u>O_2CH_3), 144.4 (Ar-C), 141.1 (Ar-C), 139.4 (Ar-C), 138.7 (Ar-C), 137.0 (Ar-C), 136.9 (Ar-C), 134.24 (Ar-C), 134.21 (Ar-C), 134.0 (Ar-C), 130.2 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 129.2 (2C, Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 127.0 (Ar-C), 126.7 (2C, (Ar-C), 126.6 (Ar-C), 126.3 (Ar-C), 125.4 (Ar-C), 123.3 (Ar-C), 119.0 (Ar-C), 117.8 (Ar-C), 68.6 (-CHOH), 52.3 (-CO_2<u>C</u>H_3), 39.3 (-CH_2-), 21.5 (-SO_2Ph<u>C</u>H_3); HRMS (ESI) m/z calcd for $C_{31}H_{26}NO_5S$ [M + H]$^+$ 524.1532, found 524.1529.

13-Methoxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81l):



Pale yellow solid (29.8 mg, 70%), mp 172-174 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.72-7.70 (m, 1H, Ar-H), 7.61-7.60 (m, 1H, Ar-H), 7.52-7.46 (m, 2H, Ar-H), 7.45-7.37 (m, 3H, Ar-H), 7.32-7.29 (m, 3H, Ar-H), 6.96 (d, J = 8.4 Hz, 2H, Ar-H), 6.84 (dd, J = 8.6, 2.2 Hz, 1H, Ar-H), 6.76 (d, J = 8.0 Hz, 2H, Ar-H), 5.20 (dd, J = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.83 (s, 3H, -OCH_3), 3.14 (dd, J = 12.4, 6.4 Hz, 1H, H_a of -CH_2-), 2.92 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.4 (Ar-C), 144.1 (Ar-C), 141.5 (Ar-C), 139.2 (Ar-C), 138.7 (Ar-C), 137.2 (Ar-C), 134.3 (Ar-C), 134.2 (Ar-C), 134.0 (Ar-C), 130.9 (Ar-C), 129.4 (Ar-C), 129.1 (Ar-C), 129.0 (2C, Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 127.9 (Ar-C), 126.52 (2C, Ar-C), 126.51 (Ar-C), 126.2 (Ar-C), 124.3 (Ar-C), 123.6 (Ar-C), 119.8 (Ar-C), 113.4 (Ar-C), 100.6 (Ar-C), 68.8 (-CHOH), 55.9 (-OCH_3), 39.3 (-CH_2-), 21.5 (-$SO_2PhC\underline{H}_3$); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ [M + Na]$^{+}$ 518.1402, found 518.1400.

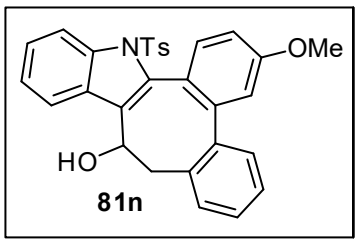
Methyl 10-hydroxy-3-methoxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (81m):



White solid (44.7 mg, 94%), mp 142-144 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.74 (s, 1H, Ar-H), 7.89 (dd, J = 8.4, 1.2 Hz, 1H, Ar-H), 7.61 (d, J = 8.4 Hz, 1H, Ar-H), 7.56 (d, J = 8.4 Hz, 1H, Ar-H), 7.37-7.34 (m, 1H, Ar-H), 7.30-7.27 (m, 3H, Ar-H), 7.03-6.98 (m, 3H, Ar-H), 6.88 (d, J = 2.8 Hz, 1H, Ar-H), 6.78 (d, J = 8.0 Hz, 2H, Ar-H), 5.23 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.93 (s, 3H,-CO_2CH_3/ -OCH_3), 3.90 (s, 3H, -OCH_3/ -CO_2CH_3), 3.15 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.97 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.3 ($\underline{C}O_2CH_3$), 160.2 (Ar-C), 144.4 (Ar-C), 141.1 (Ar-C), 140.9 (Ar-C), 138.9 (Ar-C), 136.9 (Ar-C), 136.8 (Ar-C), 135.5 (Ar-C), 134.4 (Ar-C), 134.3 (Ar-C), 129.2 (2C, Ar-C), 128.9 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 126.7 (Ar-C), 126.6 (2C, Ar-C), 126.3 (Ar-C), 125.4 (Ar-C), 122.8 (Ar-C), 122.5 (Ar-C), 118.9 (Ar-C), 117.8 (Ar-C), 114.7 (Ar-C), 112.5 (Ar-C), 68.6 (-CHOH), 55.5 (-$CO_2\underline{C}H_3$/-OCH_3), 52.3 (-OCH_3/ -$CO_2\underline{C}H_3$), 39.3 (-CH_2-

), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{32}H_{27}NNaO_6S$ $[M + Na]^+$ 576.1457, found 576.1459.

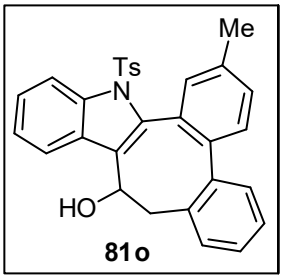
3-Methoxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81n):



81n

White solid (34.5 mg, 81%), mp 178-180 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.07 (d, J = 8.4 Hz, 1H, Ar-H), 7.64 (d, J = 8.4 Hz, 1H, Ar-H), 7.55 (d, J = 7.2 Hz, 1H, Ar-H), 7.39-7.38 (m, 1H, Ar-H), 7.29-7.21 (m, 5H, Ar-H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H, Ar-H), 6.98 (d, J = 7.8 Hz, 2H, Ar-H), 6.89 (d, J = 2.4 Hz, 1H, Ar-H), 6.77 (d, J = 7.8 Hz, 2H, Ar-H), 5.24 (dd, J = 11.7, 6.3 Hz, 1H, -C<u>H</u>OH), 3.91 (s, 3H, -OCH_3), 3.16 (dd, J = 12.6, 6.0 Hz, 1H, H_a of -CH_2-), 2.98 (t, J = 12.0 Hz, 1H, H_b of -CH_2-), 2.18 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 159.7 (Ar-C) , 143.9 (Ar-C), 141.2 (Ar-C), 140.7 (Ar-C), 137.3 (Ar-C), 136.9 (Ar-C), 135.7 (Ar-C), 135.4 (Ar-C), 134.3 (Ar-C), 130.5 (Ar-C), 128.9 (2C, Ar-C), 128.8 (Ar-C), 128.4 (Ar-C), 127.9 (Ar-C), 126.5 (2C, Ar-C), 126.1 (Ar-C), 125.0 (Ar-C), 124.1 (Ar-C), 122.9 (Ar-C), 122.8 (Ar-C), 118.9 (Ar-C), 116.2 (Ar-C), 114.5 (Ar-C), 112.3 (Ar-C), 68.6 (-CHOH), 55.3 (-OCH_3), 39.2 (-CH_2-), 21.4 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1401.

***2-Methyl-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81o)* :**

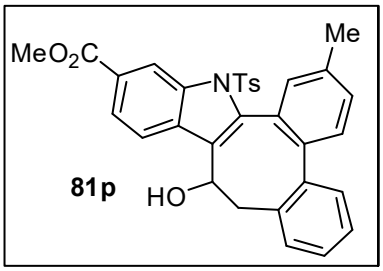


81o

White solid (24.3 mg, 59%), mp 172-174 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.08-8.06 (m, 1H, Ar-H), 7.56-7.54 (m, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.42-7.39 (m, 1H, Ar-H), 7.34-7.20 (m, 7H, Ar-H), 7.00 (d, J = 8.4 Hz, 2H, Ar-H), 6.77 (d, J = 8.4 Hz, 2H, Ar-H), 5.25 (dd, J = 11.6, 6.4 Hz, 1H, -C<u>H</u>OH), 3.15 (dd, J = 12.4, 6.4 Hz, 1H, H_a of -CH_2-), 2.95 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.45 (s, 3H, -CH_3), 2.18 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.0 (Ar-C), 141.4 (Ar-C), 137.6 (Ar-C), 137.1 (Ar-C), 136.6 (Ar-C), 136.1 (Ar-C), 135.9 (Ar-C), 134.5 (2C, Ar-C), 130.5 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-C), 129.0 (2C, Ar-C), 128.5 (Ar-C), 127.7 (Ar-C), 126.6 (2C, Ar-C), 126.2 (Ar-C), 125.2 (Ar-C), 124.2 (Ar-C), 123.4 (Ar-C), 119.1 (Ar-C), 116.2

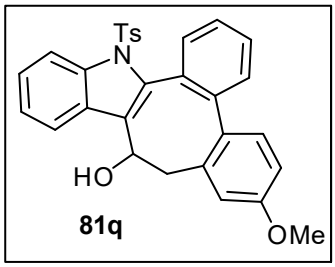
(Ar-C), 68.7 (-CHOH), 39.4 (-CH_2-) , 21.5 (-SO_2PhCH_3/-CH_3), 21.2 (-CH_3/-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1470.

Methyl 10-hydroxy-2-methyl-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (81p) :



White solid (36.0 mg, 78%), mp 142-144 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.75 (s, 1H, Ar-H), 7.91 (dd, J = 8.2, 1.4 Hz, 1H, Ar-H), 7.58 (d, J = 8.4 Hz, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.40-7.27 (m, 6H, Ar-H), 7.03 (d, J = 8.4 Hz, 2H, Ar-H), 6.80 (d, J = 8.4 Hz, 2H, Ar-H), 5.25 (dd, J = 12.0, 6.4 Hz, 1H, -C<u>H</u>OH), 3.94 (s, 3H, -CO_2CH_3), 3.15 (dd, J = 12.6, 6.2 Hz, 1H, H_a of -CH_2-), 2.94 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.45 (s, 3H, -CH_3), 2.19 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.3 (<u>C</u>O_2CH_3), 144.4 (Ar-C), 141.2 (Ar-C), 138.9 (Ar-C), 137.0 (Ar-C), 136.9 (Ar-C), 136.7 (Ar-C), 136.2 (Ar-C), 134.4 (Ar-C), 134.3 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.4 (Ar-C), 129.2 (3C, Ar-C), 129.1 (Ar-C), 128.5 (Ar-C), 127.9 (Ar-C), 126.9 (Ar-C), 126.7 (2C, Ar-C), 126.3 (Ar-C), 125.4 (Ar-C), 123.1 (Ar-C), 118.9 (Ar-C), 117.8 (Ar-C), 68.6 (-CHOH), 52.3 (-CO_2<u>C</u>H_3), 39.4 (-CH_2-), 21.5 (-SO_2PhCH_3 /-CH_3), 21.2 (-CH_3/-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{32}H_{27}NNaO_5S$ $[M+Na]^+$ 560.1508, found 560.1505.

***7-Methoxy-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10-ol (81q)* :**



White solid (26.0 mg, 61%), mp 166-168 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.09-8.07 (m, 1H, Ar-H), 7.69 (dd, J = 7.6, 1.2 Hz, 1H, Ar-H), 7.58-7.56 (m, 1H, Ar-H), 7.50 (td, J = 7.4, 1.3 Hz, 1H, Ar-H), 7.44 (td, J = 7.6, 1.6 Hz, 1H, Ar-H), 7.37-7.22 (m, 4H, Ar-H), 7.01 (d, J = 8.4 Hz, 2H, Ar-H), 6.85-6.79 (m, 4H, Ar-H), 5.26 (dd, J = 11.8, 6.2 Hz, 1H, -C<u>H</u>OH), 3.83 (s, 3H, -OCH_3), 3.11 (dd, J = 12.4, 6.4 Hz, 1H, H_a of -CH_2-), 2.91 (t, J = 12.2 Hz, 1H, H_b of -CH_2-), 2.19 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3 (Ar-C), 144.1 (Ar-C), 139.1 (Ar-C), 138.4 (Ar-C), 137.5 (Ar-C), 135.8 (Ar-C), 134.4 (Ar-C), 134.1 (Ar-C), 133.9 (Ar-C), 130.7 (Ar-C), 130.5 (Ar-C), 130.0 (Ar-C), 129.6 (Ar-C), 129.1 (2C, Ar-C), 128.9 (Ar-C), 126.6 (2C, Ar-C), 126.2 (Ar-C), 125.3 (Ar-C), 124.2 (Ar-C),

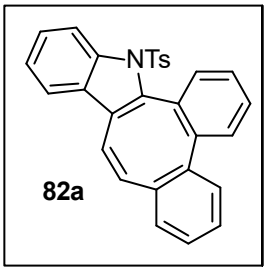
123.5 (Ar-C), 119.1 (Ar-C), 116.2 (Ar-C), 113.6 (Ar-C), 111.9 (Ar-C), 68.6 (-CHOH), 55.4 (-OCH_3), 39.6 (-CH_2-), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1401.

1.2.9.9. General Procedure for the Synthesis of Products 82:

To a well-stirred solution of **81** (0.062 mmol, 1 equiv) in dry 1,4-dioxane (1.0 mL) *p*-TsOH.H_2O (35.6 mg, 0.186 mmol, 3 equiv) was added. The resulting mixture was then refluxed for 4.0-5.5 h under argon atmosphere. Upon completion of reaction (TLC), the mixture was neutralized by drop-wise addition of dilute aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vaccuo.* The resulting crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 5-15 % ethyl acetate in petroleum ether (v/v) to afford the desired product **82** in (60-98%) yield.

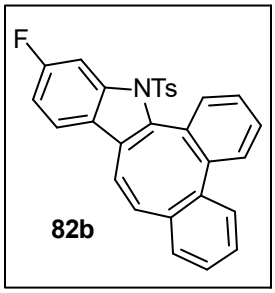
1.2.9.10. Spectral Data of Products 82a-j:

(Z)-15-Tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82a) **:**



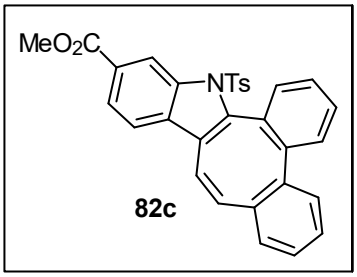
Pale yellow solid (27.2 mg, 98%), mp >250 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.10 (d, J = 8.8 Hz, 1H, Ar-H), 7.54-7.52 (m, 1H, Ar-H), 7.48-7.27 (m, 7H, Ar-H), 7.24-7.20 (m, 2H, Ar-H), 7.18-7.15 (m, 2H, Ar-H), 7.06 (d, J = 8.0 Hz, 1H, Ar-H), 6.97 (d, J = 11.6 Hz, 1H, =CH), 6.73 (d, J = 8.4 Hz, 2H, Ar-H), 6.62 (d, J = 11.6 Hz, 1H, =CH), 2.15 (s, 3H, -SO_2PhCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.2 (Ar-C), 142.3 (Ar-C), 141.9 (Ar-C), 137.9 (Ar-C), 137.86 (Ar-C), 137.81 (Ar-C), 136.2 (Ar-C), 133.7 (Ar-C), 133.0 (Ar-C), 132.8 (Ar-C), 131.4 (Ar-C), 130.6 (Ar-C), 130.1 (Ar-C), 129.0 (2C, Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 127.2 (Ar-C), 126.9 (2C, Ar-C), 126.7 (Ar-C), 126.3 (Ar-C), 125.2 (Ar-C), 124.3 (Ar-C), 124.2 (Ar-C), 123.7 (Ar-C), 119.3 (Ar-C), 116.0 (Ar-C), 21.5 (-SO_2PhCH_3); HRMS (ESI) m/z calcd for $C_{29}H_{21}NNaO_2S$ $[M+Na]^+$ 470.1191, found 470.1196.

(Z)-13-Fluoro-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82b) **:**



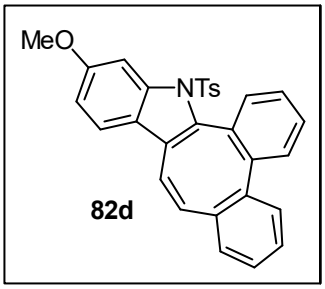
White solid (28.2 mg, 98%), mp 244-246 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.85 (dd, J = 10.0, 2.0 Hz, 1H, Ar-H), 7.53-7.38 (m, 4H, Ar-H), 7.34-7.21 (m, 4H, Ar-H), 7.17 (d, J = 8.4 Hz, 2H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 6.98-6.93 (m, 2H, Ar-H and =CH), 6.77 (d, J = 8.4 Hz, 2H, Ar-H), 6.57 (d, J = 11.6 Hz, 1H, =CH), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 161.3 (d, J_{C-F} = 241.2 Hz, Ar-C), 144.5 (Ar-C), 142.2 (Ar-C), 141.9 (Ar-C), 138.2 (d, J_{C-F} = 12.5 Hz, Ar-C), 138.0 (Ar-C), 137.8 (Ar-C), 136.5 (Ar-C), 133.6 (Ar-C), 132.8 (Ar-C), 132.7 (Ar-C), 131.4 (Ar-C), 130.6 (Ar-C), 129.2 (2C, Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 127.3 (Ar-C), 126.9 (Ar-C), 126.8 (2C, Ar-C), 126.35 (Ar-C), 126.34 (Ar-C), 123.7 (d, J_{C-F} = 1.3 Hz, Ar-C), 123.3 (Ar-C), 120.1 (d, J_{C-F}= 9.8 Hz, Ar-C), 112.4 (d, J_{C-F} = 24.1 Hz, Ar-C), 103.6 (d, J_{C-F} = 28.5 Hz, Ar-C), 21.5 (-$SO_2Ph\underline{C}H_3$); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = −115.3 (s, 1F); HRMS (ESI) m/z calcd for $C_{29}H_{21}FNO_2S$ $[M + H]^+$ 466.1277, found 466.1278.

(Z)-Methyl 15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (82c):



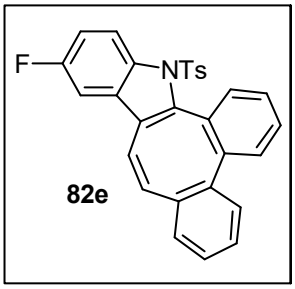
White solid (29.7 mg, 95%), mp 218-220 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.79 (s, 1H, Ar-H), 7.91 (dd, J = 8.2, 1.4 Hz, 1H, Ar-H), 7.54-7.28 (m, 7H, Ar-H), 7.25-7.23 (m, 1H, Ar-H), 7.17 (d, J = 8.4 Hz, 2H, Ar-H), 7.08 (d, J = 7.2 Hz, 1H, Ar-H), 6.99 (d, J = 11.6 Hz, 1H, =CH), 6.76 (d, J = 8.0 Hz, 2H, Ar-H), 6.61 (d, J = 11.2 Hz, 1H, =CH), 3.96 (s, 3H, -CO_2CH_3), 2.16 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.3 (-$\underline{C}O_2CH_3$), 144.6 (Ar-C), 142.0 (Ar-C), 141.9 (Ar-C), 140.9 (Ar-C), 137.5 (Ar-C), 137.3 (Ar-C), 136.7 (Ar-C), 133.7 (Ar-C), 133.6 (Ar-C), 132.8 (Ar-C), 132.4 (Ar-C), 131.4 (Ar-C), 130.7 (Ar-C), 129.2 (2C, Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.9 (2C, Ar-C), 126.8 (Ar-C), 126.4 (Ar-C), 125.5 (Ar-C), 123.8 (Ar-C), 123.1 (Ar-C), 119.1 (Ar-C), 117.6 (Ar-C), 52.3 (-$CO_2\underline{C}H_3$), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{31}H_{24}NO_4S$ $[M + H]^+$ 506.1426, found 506.1427.

***(Z)-13-Methoxy-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82d)* :**



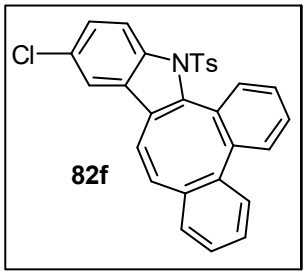
White solid (25.4 mg, 86%), mp 226-228 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.67-7.66 (m, 1H, Ar-H), 7.54-7.52 (m, 1H, Ar-H), 7.47-7.38 (m, 3H, Ar-H), 7.34-7.28 (m, 2H, Ar-H), 7.23-7.19 (m, 2H, Ar-H), 7.15 (d, J = 8.0 Hz, 2H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 6.95 (d, J = 11.6 Hz, 1H, =CH), 6.82 (dd, J = 8.6, 2.2 Hz, 1H, Ar-H), 6.74 (d, J = 8.0 Hz, 2H, Ar-H), 6.58 (d, J = 11.2 Hz, 1H, =CH), 3.87 (s, 3H, -OCH_3), 2.17 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.4 (Ar-C), 144.2 (Ar-C), 142.4 (Ar-C), 141.7 (Ar-C), 139.0 (Ar-C), 138.0 (Ar-C), 136.0 (Ar-C), 133.6 (Ar-C), 133.4 (Ar-C), 132.7 (Ar-C), 131.4 (Ar-C), 130.5 (Ar-C), 129.1 (2C, Ar-C), 128.9 (Ar-C), 128.5 (Ar-C), 127.2 (Ar-C), 126.8 (Ar-C), 126.7 (2C, Ar-C), 126.3 (Ar-C), 124.4 (Ar-C), 124.0 (Ar-C), 123.7 (Ar-C), 119.9 (Ar-C), 113.1 (Ar-C), 100.5 (Ar-C), 100.0 (Ar-C), 55.9 (-OCH_3), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_3S$ $[M+H]^+$ 478.1477, found 478.1479.

(Z)-12-Fluoro-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82e) :



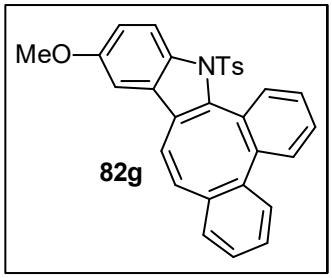
Pale yellow solid (27.4 mg, 95%), mp >250 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.06-8.02 (m, 1H, Ar-H), 7.54-7.38 (m, 4H, Ar-H), 7.35-7.28 (m, 2H, Ar-H), 7.24-7.22 (m, 1H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 7.01-6.96 (m, 3H, Ar-H and =CH), 6.74 (d, J = 8.0 Hz, 2H, Ar-H), 6.54 (d, J = 11.2 Hz, 1H, =CH), 2.17 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 161.1 (d, J_{C-F} = 242.4 Hz, Ar-C), 144.5 (Ar-C), 142.1 (Ar-C), 141.9 (Ar-C), 139.7 (Ar-C), 137.6 (Ar-C), 136.6 (Ar-C), 133.5 (Ar-C), 132.8 (Ar-C), 132.6 (Ar-C), 131.5 (Ar-C), 130.7 (Ar-C), 129.1 (2C, Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.7 (2C, Ar-C), 126.4 (Ar-C), 123.9 (d, J_{C-F} = 4.0 Hz, Ar-C), 123.8 (d, J_{C-F} = 10.8 Hz, Ar-C), 123.1 (Ar-C), 117.2 (d, J_{C-F}= 9.2 Hz, Ar-C), 112.9 (d, J_{C-F} = 24.8 Hz, Ar-C), 105.2 (d, J_{C-F} = 24.1 Hz, Ar-C), 100.0 (Ar-C), 21.5 (-$SO_2Ph\underline{C}H_3$); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = −118.2 (s, 1F); HRMS (ESI) m/z calcd for $C_{29}H_{20}FNaNO_2S$ $[M+Na]^+$ 488.1096, found 488.1097.

(Z)-12-Chloro-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82f):



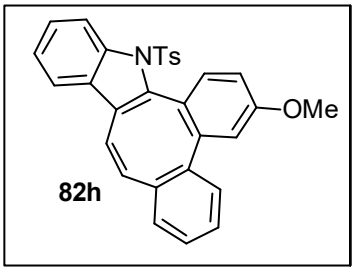
White solid (25.3 mg, 85%), mp >250 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.02 (d, J = 8.8 Hz, 1H, Ar-H), 7.54-7.38 (m, 4H, Ar-H), 7.35-7.26 (m, 3H, Ar-H), 7.24-7.21 (m, 2H, Ar-H), 7.13 (d, J = 8.4 Hz, 2H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 6.98 (d, J = 11.6 Hz, 1H, =CH), 6.76 (d, J = 8.0 Hz, 2H, Ar-H), 6.55 (d, J = 11.6 Hz, 1H, =CH), 2.18 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.6 (Ar-C), 142.0 (Ar-C), 141.9 (Ar-C), 139.3 (Ar-C), 137.6 (Ar-C), 136.7 (Ar-C), 136.1 (Ar-C), 133.5 (Ar-C), 132.8 (Ar-C), 132.5 (Ar-C), 131.4 (Ar-C), 131.3 (Ar-C), 130.7 (Ar-C), 130.1 (Ar-C), 129.2 (2C, Ar-C), 129.1 (Ar-C), 128.9 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.7 (2C, Ar-C), 126.4 (Ar-C), 125.3 (Ar-C), 123.4 (Ar-C), 123.0 (Ar-C), 119.2 (Ar-C), 117.1 (Ar-C), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{21}ClNO_2S$ $[M + H]^+$ 482.0982, found 482.0980.

***(Z)-12-Methoxy-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82g)*:**



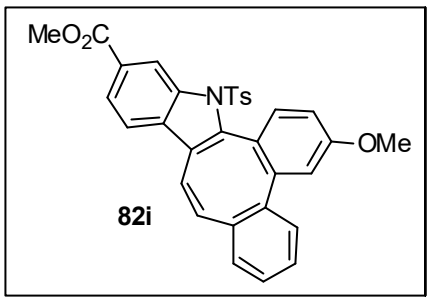
Pale yellow solid (24.5 mg, 83%), mp 224-226 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.99 (d, J = 8.8 Hz, 1H, Ar-H), 7.55-7.53 (m, 1H, Ar-H), 7.49-7.39 (m, 3H, Ar-H), 7.34-7.29 (m, 2H, Ar-H), 7.24-7.21 (m, 1H, Ar-H), 7.14 (d, J = 8.4 Hz, 2H, Ar-H), 7.07 (d, J = 7.2 Hz, 1H, Ar-H), 6.97 (d, J = 11.6 Hz, 1H, =CH), 6.87 (dd, J = 9.0, 2.6 Hz, 1H, Ar-H), 6.77-6.72 (m, 3H, Ar-H), 6.57 (d, J = 11.6 Hz, 1H, =CH), 3.79 (s, 3H, -OCH_3), 2.16 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 157.1 (Ar-C), 144.1 (Ar-C), 142.3 (Ar-C), 141.8 (Ar-C), 137.8 (Ar-C), 136.2 (Ar-C), 133.6 (Ar-C), 133.0 (Ar-C), 132.8 (Ar-C), 132.2 (Ar-C), 131.5 (Ar-C), 131.1 (Ar-C), 130.6 (Ar-C), 129.0 (2C, Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 127.2 (Ar-C), 126.9 (Ar-C), 126.7 (2C, Ar-C), 126.3 (Ar-C), 124.3 (Ar-C), 123.7 (Ar-C), 117.0 (Ar-C), 113.8 (Ar-C), 101.9 (Ar-C), 100.0 (Ar-C), 55.6 (-OCH_3), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_3S$ $[M + H]^+$ 478.1477, found 478.1479.

***(Z)-3-Methoxy-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82h)*:**



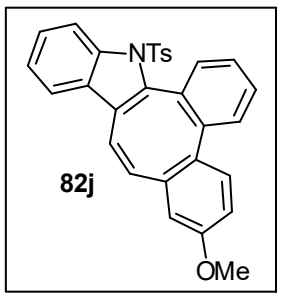
Yellow solid (28.4 mg, 96%), mp 200-202 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.10 (d, J = 8.0 Hz, 1H, Ar-H), 7.46 (d, J = 8.4 Hz, 1H, Ar-H), 7.40-7.36 (m, 1H, Ar-H), 7.33-7.24 (m, 4H, Ar-H), 7.21-7.14 (m, 3H, Ar-H), 7.07-7.05 (m, 1H, Ar-H), 7.00 (dd, J = 8.8, 2.8 Hz, 1H, Ar-H), 6.96 (d, J = 11.6 Hz, 1H, =CH), 6.75-6.73 (m, 3H, Ar-H), 6.61 (d, J = 11.6 Hz, 1H, =CH), 3.87 (s, 3H, -OCH_3), 2.15 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.8 (Ar-C), 144.2 (Ar-C), 143.3 (Ar-C), 142.1 (Ar-C), 137.9 (Ar-C), 137.8 (Ar-C), 137.7 (Ar-C), 135.9 (Ar-C), 134.2 (Ar-C), 133.8 (Ar-C), 131.2 (Ar-C), 130.2 (Ar-C), 129.0 (2C, Ar-C), 128.9 (Ar-C), 127.1 (Ar-C), 127.0 (Ar-C), 126.7 (2C, Ar-C), 125.1 (Ar-C), 125.0 (Ar-C), 124.1 (Ar-C), 123.9 (Ar-C), 123.6 (Ar-C), 119.2 (Ar-C), 116.1 (Ar-C), 115.4 (Ar-C), 112.7 (Ar-C), 55.4 (-OCH_3), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_3S$ $[M + H]^+$ 478.1477, found 478.1479.

(Z)-Methyl 3-methoxy-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (82i) :



Yellow solid (24.5 mg, 74%), mp 238-240 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.79 (s, 1H, Ar-H), 7.91 (dd, J = 8.2, 1.4 Hz, 1H, Ar-H), 7.46 (d, J = 8.4 Hz, 1H, Ar-H), 7.41-7.28 (m, 4H, Ar-H), 7.17 (d, J = 8.4 Hz, 2H, Ar-H), 7.07 (d, J = 7.2 Hz, 1H, Ar-H), 7.03-6.96 (m, 2H, Ar-H), 6.77-6.75 (m, 3H, Ar-H), 6.60 (d, J = 11.6 Hz, 1H, =CH), 3.95 (s, 3H, -CO_2CH_3/-OCH_3), 3.87 (s, 3H, -OCH_3/-CO_2CH_3), 2.16 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.3 (-$\underline{C}O_2CH_3$), 160.2 (Ar-C), 144.5 (Ar-C), 143.4 (Ar-C), 141.8 (Ar-C), 141.0 (Ar-C), 137.5 (Ar-C), 137.2 (Ar-C), 136.5 (Ar-C), 134.3 (Ar-C), 133.7 (Ar-C), 133.6 (Ar-C), 131.3 (Ar-C), 129.2 (2C, Ar-C), 129.0 (Ar-C), 127.2 (Ar-C), 127.1 (Ar-C), 126.8 (Ar-C), 126.7 (2C, Ar-C), 125.5 (Ar-C), 124.5 (Ar-C), 123.4 (Ar-C), 123.2 (Ar-C), 118.9 (Ar-C), 117.7 (Ar-C), 115.6 (Ar-C), 112.7 (Ar-C), 55.4 (-$CO_2\underline{C}H_3$/-OCH_3), 52.3 (-OCH_3/-$CO_2\underline{C}H_3$), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{32}H_{26}NO_5S$ $[M + H]^+$ 536.1532, found 536.1535.

(Z)-7-Methoxy-15-tosyl-15H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole (82j) **:**



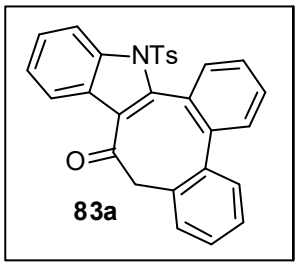
Pale yellow solid (17.7 mg, 60%), mp 238-240 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.12 (d, J = 8.4 Hz, 1H, Ar-H), 7.52 (d, J = 7.2 Hz, 1H, Ar-H), 7.47-7.44 (m, 1H, Ar-H), 7.42-7.40 (m, 1H, Ar-H), 7.35 (d, J = 7.2 Hz, 1H, Ar-H), 7.29 (t, J = 7.5 Hz, 1H, Ar-H), 7.22-7.19 (m, 5H, Ar-H), 6.96 (dd, J = 8.4, 2.4 Hz, 1H, Ar-H), 6.92 (d, J = 11.4 Hz, 1H, =CH), 6.78 (d, J = 8.4 Hz, 2H, Ar-H), 6.62 (d, J = 11.4 Hz, 1H, =CH), 6.59-6.58 (m, 1H, Ar-H), 3.82 (s, 3H, -OCH_3), 2.17 (s, 3H, -$SO_2PhC\underline{H}_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 158.4 (Ar-C), 144.1 (Ar-C), 141.5 (Ar-C), 138.9 (Ar-C), 137.8 (Ar-C), 137.7 (Ar-C), 135.9 (Ar-C), 134.6 (Ar-C), 133.7 (Ar-C), 133.0 (Ar-C), 132.7 (Ar-C), 132.4 (Ar-C), 130.6 (Ar-C), 130.0 (Ar-C), 129.0 (2C, Ar-C), 128.6 (Ar-C), 126.7 (2C, Ar-C), 125.9 (Ar-C), 125.1 (Ar-C), 124.1 (Ar-C), 124.0 (Ar-C), 123.6 (Ar-C), 119.2 (Ar-C), 115.9 (Ar-C), 113.7 (Ar-C), 113.0 (Ar-C) , 55.3 (-OCH_3), 21.4 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_3S$ $[M + H]^+$ 478.1477, found 478.1468.

1.2.9.11. General Procedure for the Synthesis of Products 83:

To a well stirred solution of $Pd(OAc)_2$bpy (3.21 mg, 0.008 mmol, 6 mol %) in dry NMA (0.5 mL) was added D-CSA (65.3 mg, 0.28 mmol, 2 equiv) and the resulting mixture was heated at 100 ^{o}C under argon atmosphere. Next, the acetylenic substrate **80** (0.14 mmol, 1 equiv) was added drop-wise dissolving in NMA (1.0 mL) at the same temperature and the resulting mixture was allowed to stir for another 3.5-12 h. Upon completion of reaction (TLC), the mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were then washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the resulting residue was purified by silica gel (100-200 mesh) column chromatography eluting with 8-20% ethyl acetate-petroleum ether (v/v) to obtain the pure product **83** in 60-95% yield.

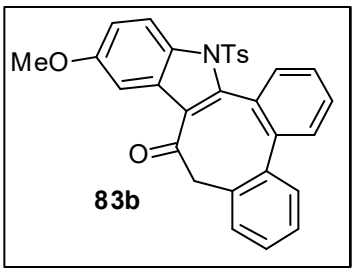
1.2.9.12. Spectral Data of Products 83a-i:

15-Tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83a) **:**



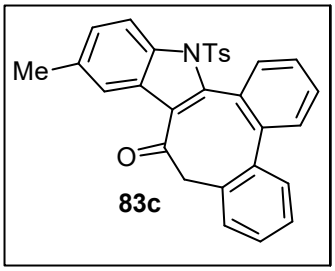
Yellow solid (59.6 mg, 92%), mp 220-222 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.33 (d, J = 7.2 Hz, 1H, Ar-H), 8.07 (d, J = 7.8 Hz, 1H, Ar-H), 7.71 (d, J = 7.8 Hz, 1H, Ar-H), 7.62 (t, J = 7.5 Hz, 1H, Ar-H), 7.52 (d, J = 7.6 Hz, 1H, Ar-H), 7.50 (t, J = 6.3 Hz, 2H, Ar-H), 7.37-7.26 (m, 5H, Ar-H), 7.06 (d, J = 7.8 Hz, 2H, Ar-H), 6.82 (d, J = 8.4 Hz, 2H, Ar-H), 3.71 (s, 2H, -CH_2-), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 196.1 (C=O), 144.7 (Ar-C), 144.6 (Ar-C), 144.2 (Ar-C), 140.2 (Ar-C), 139.8 (Ar-C), 138.7 (Ar-C), 137.0 (Ar-C), 136.2 (Ar-C), 134.2 (Ar-C), 134.1 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.2 (Ar-C), 129.03 (Ar-C), 129.00 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 126.8 (Ar-C), 126.5 (2C, Ar-C)), 126.4 (Ar-C), 125.8 (Ar-C), 125.2 (Ar-C), 122.8 (Ar-C), 121.5 (Ar-C), 115.2 (Ar-C), 49.8 (-CH_2-), 21.4 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{22}NO_3S$ $[M + H]^+$ 464.1320, found 464.1318.

12-Methoxy-15-tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83b) **:**



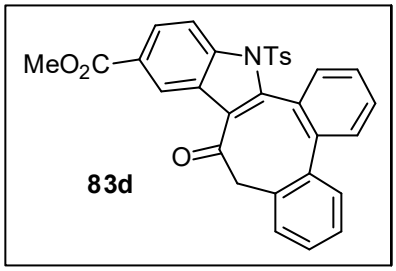
Pale yellow solid (65.6 mg, 95%), mp 206-208 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.96 (d, J = 9.0 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.72 (d, J = 7.8 Hz, 1H, Ar-H), 7.61 (t, J = 7.5 Hz, 1H, Ar-H), 7.54-7.48 (m, 3H, Ar-H), 7.38-7.32 (m, 3H, Ar-H), 7.04 (d, J = 8.4 Hz, 2H, Ar-H), 6.90 (dd, J = 9.0, 2.4 Hz, 1H, Ar-H), 6.81 (d, J = 8.4 Hz, 2H, Ar-H), 3.83 (s, 3H, -OCH_3), 3.73 (d, J = 13.2 Hz, 1H, H_a of -CH_2-), 3.69 (d, J = 13.8 Hz, 1H, H_b of -CH_2-), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 196.2 (C=O), 157.6 (Ar-C), 144.8 (Ar-C), 144.7 (Ar-C), 140.2 (Ar-C), 139.7 (Ar-C), 136.2 (Ar-C), 134.3 (Ar-C), 134.1 (Ar-C), 131.4 (Ar-C), 130.4 (Ar-C), 129.8 (Ar-C), 129.2 (3C, Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 126.8 (Ar-C), 126.5 (2C, Ar-C), 126.4 (Ar-C), 121.5 (Ar-C), 116.2 (Ar-C), 115.3 (Ar-C), 104.4 (Ar-C), 55.5 (-OCH_3), 49.7 (-CH_2-), 21.4 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_4S$ $[M + H]^+$ 494.1426, found 494.1428.

12-Methyl-15-tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83c):



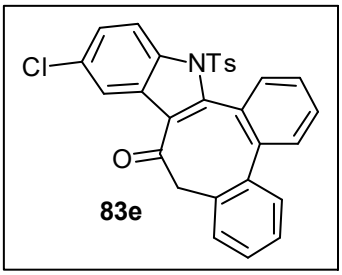
White solid (58.1 mg, 87%), 220-222 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.14 (s, 1H, Ar-H), 7.94 (d, J = 8.4 Hz, 1H, Ar-H), 7.72 (d, J = 7.8 Hz, 1H, Ar-H), 7.61 (t, J = 7.5 Hz, 1H, Ar-H), 7.53-7.48 (m, 3H, Ar-H), 7.37-7.32 (m, 3H, Ar-H), 7.11 (d, J = 8.4 Hz, 1H, Ar-H), 7.06 (d, J = 8.4 Hz, 2H, Ar-H), 6.82 (d, J = 7.8 Hz, 2H, Ar-H), 3.71 (s, 2H, -CH_2-), 2.39 (s, 3H, -CH_3), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 196.2 (C=O), 144.6 (Ar-C), 144.3 (Ar-C), 140.2 (Ar-C), 139.7 (Ar-C), 136.3 (Ar-C), 135.1 (Ar-C), 135.0 (Ar-C), 134.2 (Ar-C), 134.1 (Ar-C), 130.5 (Ar-C), 129.7 (Ar-C), 129.2 (2C, Ar-C), 129.0 (2C, Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 127.2 (Ar-C), 126.8 (Ar-C), 126.5 (2C, Ar-C), 126.4 (Ar-C), 122.6 (Ar-C), 121.4 (Ar-C), 114.9 (Ar-C), 49.8 (-CH_2-), 21.4 (-CH_3/-$SO_2Ph\underline{C}H_3$), 21.3 (-$SO_2Ph\underline{C}H_3$ /-CH_3); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_3S$ $[M + H]^+$ 478.1477, found 478.1481.

Methyl 10-oxo-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-12-carboxylate (83d) :



White solid (54.0 mg, 74%), mp 196-198 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.98 (s, 1H, Ar-H), 8.10 (d, J = 9.2 Hz, 1H, Ar-H), 7.98 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 7.70 (dd, J = 7.8, 1.4 Hz, 1H, Ar-H), 7.63 (td, J = 7.5, 1.3 Hz, 1H, Ar-H), 7.55-7.46 (m, 3H, Ar-H), 7.38-7.32 (m, 3H, Ar-H), 7.05 (d, J = 8.4 Hz, 2H, Ar-H), 6.83 (d, J = 8.4 Hz, 2H, Ar-H), 3.90 (s, 3H, -CO_2CH_3), 3.75-3.68 (m, 2H, -CH_2-), 2.21 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 195.7 (C=O), 167.1 (-$\underline{C}O_2CH_3$), 145.4 (Ar-C), 145.2 (Ar-C), 140.2 (Ar-C), 140.0 (Ar-C), 139.7 (Ar-C), 136.1 (Ar-C), 134.2 (Ar-C), 134.1 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.5 (2C, Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.8 (Ar-C), 128.6 (2C, Ar-C), 127.9 (Ar-C), 127.3 (Ar-C), 127.1 (Ar-C), 127.0 (Ar-C), 126.7 (Ar-C), 126.6 (Ar-C), 125.0 (Ar-C), 121.5 (Ar-C), 115.2 (Ar-C), 52.2 (-$CO_2\underline{C}H_3$), 49.9 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{31}H_{24}NO_5S$ $[M + H]^+$ 522.1375, found 522.1373.

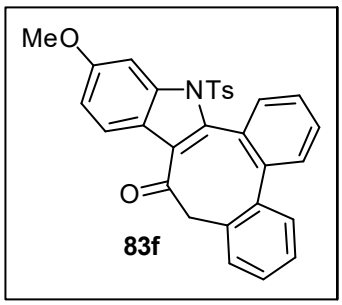
12-Chloro-15-tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83e) :



83e

White solid (59.1 mg, 85%), mp 166-168 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.34-8.33 (m, 1H, Ar-H), 7.98 (d, J = 8.8 Hz, 1H, Ar-H), 7.71-7.69 (m, 1H, Ar-H), 7.63 (td, J = 7.5, 1.3 Hz, 1H, Ar-H), 7.55-7.47 (m, 3H, Ar-H), 7.38-7.32 (m, 3H, Ar-H), 7.26-7.23 (m, 1H, Ar-H), 7.03 (d, J = 8.4 Hz, 2H, Ar-H), 6.84 (d, J = 8.4 Hz, 2H, Ar-H), 3.69 (s, 2H, -CH_2-), 2.22 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 195.7 (C=O), 145.4 (Ar-C), 145.2 (Ar-C), 140.2 (Ar-C), 139.9 (Ar-C), 136.1 (Ar-C), 135.4 (Ar-C), 134.3 (Ar-C), 134.1 (Ar-C), 131.3 (Ar-C), 130.2 (Ar-C), 130.0 (Ar-C), 129.5 (2C, Ar-C), 129.3 (Ar-C), 129.2 (Ar-C), 129.1 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 127.0 (Ar-C), 126.7 (2C, Ar-C), 126.6 (Ar-C), 126.1 (Ar-C), 122.6 (Ar-C), 120.9 (Ar-C), 116.4 (Ar-C), 49.7 (-CH_2-), 21.6 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{29}H_{21}ClNO_3S$ $[M + H]^+$ 498.0931, found 498.0906.

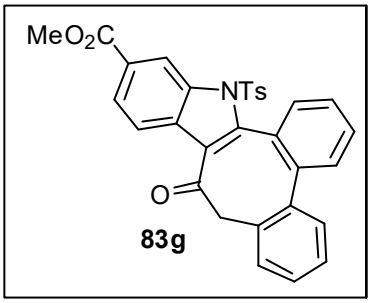
13-Methoxy-15-tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83f):



83f

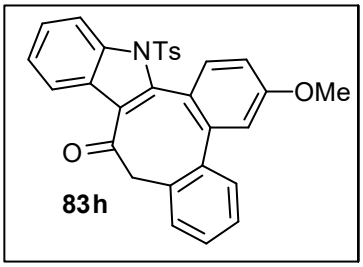
Yellow solid (53.8 mg, 78%), mp 212-214 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.19 (d, J = 8.8 Hz, 1H, Ar-H), 7.73-7.70 (m, 1H, Ar-H), 7.61-7.57 (m, 2H, Ar-H), 7.53-7.47 (m, 3H, Ar-H), 7.37-7.33 (m, 3H, Ar-H), 7.03 (d, J = 8.4 Hz, 2H, Ar-H), 6.89 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 6.81 (d, J = 8.0 Hz, 2H, Ar-H), 3.84 (s, 3H, -OCH_3), 3.69 (s, 2H, -CH_2-), 2.20 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 196.2 (C=O), 158.6 (Ar-C), 144.8 (Ar-C), 143.2 (Ar-C), 140.4 (Ar-C), 139.8 (Ar-C), 138.3 (Ar-C), 136.5 (Ar-C), 134.25 (Ar-C), 134.20 (Ar-C), 130.7 (Ar-C), 129.7 (Ar-C), 129.3 (2C, Ar-C), 129.1 (2C, Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 126.9 (Ar-C), 126.6 (Ar-C), 126.5 (2C, Ar-C), 123.6 (Ar-C), 121.8 (Ar-C), 121.7 (Ar-C), 114.2 (Ar-C), 99.7 (Ar-C), 55.8 (-OCH_3), 49.8 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_4S$ $[M + H]^+$ 494.1426, found 494.1427.

Methyl 10-oxo-15-tosyl-10,15-dihydro-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indole-13-carboxylate (83g) :



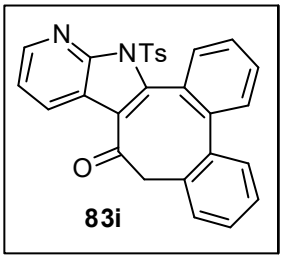
Yellow solid (45.2 mg, 62%), mp 212-214 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.77 (s, 1H, Ar-H), 8.37 (d, J = 8.4 Hz, 1H, Ar-H), 7.96 (d, J = 8.4 Hz, 1H, Ar-H), 7.70 (d, J = 7.8 Hz, 1H, Ar-H), 7.64 (t, J = 7.5 Hz, 1H, Ar-H), 7.53 (t, J = 7.5 Hz, 1H, Ar-H), 7.50-7.49 (m, 2H, Ar-H), 7.38-7.34 (m, 3H, Ar-H), 7.09 (d, J = 8.4 Hz, 2H, Ar-H), 6.84 (d, J = 7.8 Hz, 2H, Ar-H), 3.95 (s, 3H, -CO_2CH_3), 3.71 (s, 2H, -CH_2-), 2.21 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 195.7 (C=O), 166.9 (-$\underline{C}O_2CH_3$), 146.7 (Ar-C), 145.1 (Ar-C), 140.1 (Ar-C), 139.8 (Ar-C), 136.5 (Ar-C), 135.9 (Ar-C), 134.1 (Ar-C), 134.0 (Ar-C), 131.6 (Ar-C), 130.2 (Ar-C), 129.9 (Ar-C), 129.4 (2C, Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 127.4 (Ar-C), 127.0 (Ar-C), 126.6 (2C, Ar-C), 126.5 (Ar-C), 126.2 (Ar-C), 122.6 (Ar-C), 121.1 (Ar-C), 116.9 (Ar-C), 52.3 (-$CO_2\underline{C}H_3$), 49.7 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{31}H_{24}NO_5S$ $[M + H]^+$ 522.1375, found 522.1381.

3-Methoxy-15-tosyl-9H-dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (83h):



Yellow solid (58.0 mg, 84%), mp 176-178 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.33-8.31 (m, 1H, Ar-H), 8.09-8.06 (m, 1H, Ar-H), 7.65 (d, J = 8.8 Hz, 1H, Ar-H), 7.49-7.46 (m, 1H, Ar-H), 7.37-7.32 (m, 3H, Ar-H), 7.29-7.26 (m, 2H, Ar-H), 7.08-7.04 (m, 3H, Ar-H), 6.96 (d, J = 2.8 Hz, 1H, Ar-H), 6.81 (d, J = 8.0 Hz, 2H, Ar-H), 3.94 (s, 3H, -OCH_3), 3.75 (d, J = 13.6 Hz, 1H, H_a of -CH_2-), 3.69 (d, J = 13.6 Hz, 1H, H_b of -CH_2-), 2.19 (s, 3H, -$SO_2PhC\underline{H}_3$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 196.1 (C=O), 160.5 (Ar-C), 144.8 (2C, Ar-C), 141.4 (Ar-C), 140.3 (Ar-C), 137.0 (Ar-C), 136.2 (Ar-C), 136.0 (Ar-C), 134.4 (Ar-C), 129.3 (2C, Ar-C), 129.0 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 126.9 (Ar-C), 126.6 (2C, Ar-C), 125.7 (Ar-C), 125.3 (Ar-C), 122.9 (Ar-C), 122.8 (Ar-C), 121.4 (Ar-C), 115.5 (Ar-C), 114.1 (Ar-C), 112.6 (Ar-C), 55.5 (-OCH_3), 49.9 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_4S$ $[M + H]^+$ 494.1426, found 494.1423.

15-Tosyl-9H-dibenzo[3',4':5',6']cycloocta[1',2':4,5]pyrrolo[2,3-b]pyridin-10(15H)-one (83i) :



83i

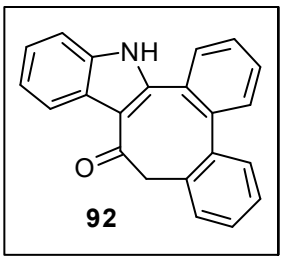
White solid (39.0 mg, 60%), mp 186-188 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.56 (d, J = 7.8 Hz, 1H, Ar-H), 8.42-8.41 (m, 1H, Ar-H), 7.65-7.57 (m, 5H, Ar-H), 7.53-7.51 (m, 2H, Ar-H), 7.41-7.37 (m, 1H, Ar-H), 7.34-7.33 (m, 2H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.00 (d, J = 7.8 Hz, 2H, Ar-H), 3.75-3.70 (m, 2H, -CH_2-), 2.27 (s, 3H, -$SO_2PhC\underline{H}_3$); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 195.8 (C=O), 149.1 (Ar-C), 145.8 (Ar-C), 145.1 (Ar-C), 144.0 (Ar-C), 140.3 (Ar-C), 139.9 (Ar-C), 135.9 (Ar-C), 135.1 (Ar-C), 132.8 (Ar-C), 131.4 (Ar-C), 130.4 (Ar-C), 130.0 (Ar-C), 129.1 (3C, Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.0 (2C, Ar-C), 127.2 (Ar-C), 126.7 (Ar-C), 120.6 (Ar-C), 120.4 (Ar-C), 118.4 (Ar-C), 49.7 (-CH_2-), 21.5 (-$SO_2Ph\underline{C}H_3$); HRMS (ESI) m/z calcd for $C_{28}H_{21}N_2O_3S$ $[M + H]^+$ 465.1273, found 465.1278.

1.2.9.13. General Procedure for the Synthesis of Product 92:

To a well stirred solution of **83a** (0.065 mmol, 1 equiv) in dry THF (2 mL), TBAF (93.64 µL, 0.324 mmol, 5 equiv) was added and the resulting mixture was refluxed under argon atmosphere. After 3 h, upon completion of reaction (TLC), the mixture was diluted with water (8 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were then washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the resulting residue was purified by silica gel (100-200 mesh) column chromatography eluting with 15% ethyl acetate-petroleum ether (v/v) to obtain the pure product **92** in 82% yield.

1.2.9.14. Spectral Data of Products 92:

***9H-Dibenzo[5,6:7,8]cycloocta[1,2-b]indol-10(15H)-one (92)* :**



92

White solid (16.5 mg, 82%), mp >250 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.52-8.48 (m, 1H, Ar-H), 8.40 (brs, 1H, -NH-), 7.69-7.67 (m, 1H, Ar-H), 7.62-7.53 (m, 3H, Ar-H), 7.43 (d, J = 8.0 Hz, 1H, Ar-H), 7.34-7.30 (m, 3H, Ar-H), 7.29-7.22 (m, 3H, Ar-H), 3.88 (d, J = 12.4 Hz, 1H, H_a of -CH_2-), 3.67 (d, J = 12.4 Hz, 1H, H_b of -CH_2-); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 194.7 (C=O), 142.3 (Ar-C), 141.0 (Ar-C), 139.4 (Ar-C), 136.7 (Ar-C),

135.2 (Ar-C), 132.2 (Ar-C), 131.0 (Ar-C), 129.6 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 127.4 (Ar-C), 126.9 (Ar-C), 124.1 (Ar-C), 123.0 (Ar-C), 122.7 (Ar-C), 115.2 (Ar-C), 110.5 (Ar-C), 48.6 (-CH_2-); HRMS (ESI) m/z calcd for $C_{22}H_{16}NO$ $[M + H]^+$ 310.1232, found 310.1236.

1.2.10. References:

1. (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.,* **1981**, *14,* 95. (b) Yet, L. *Chem. Rev.,* **2000**, *100*, 2963.
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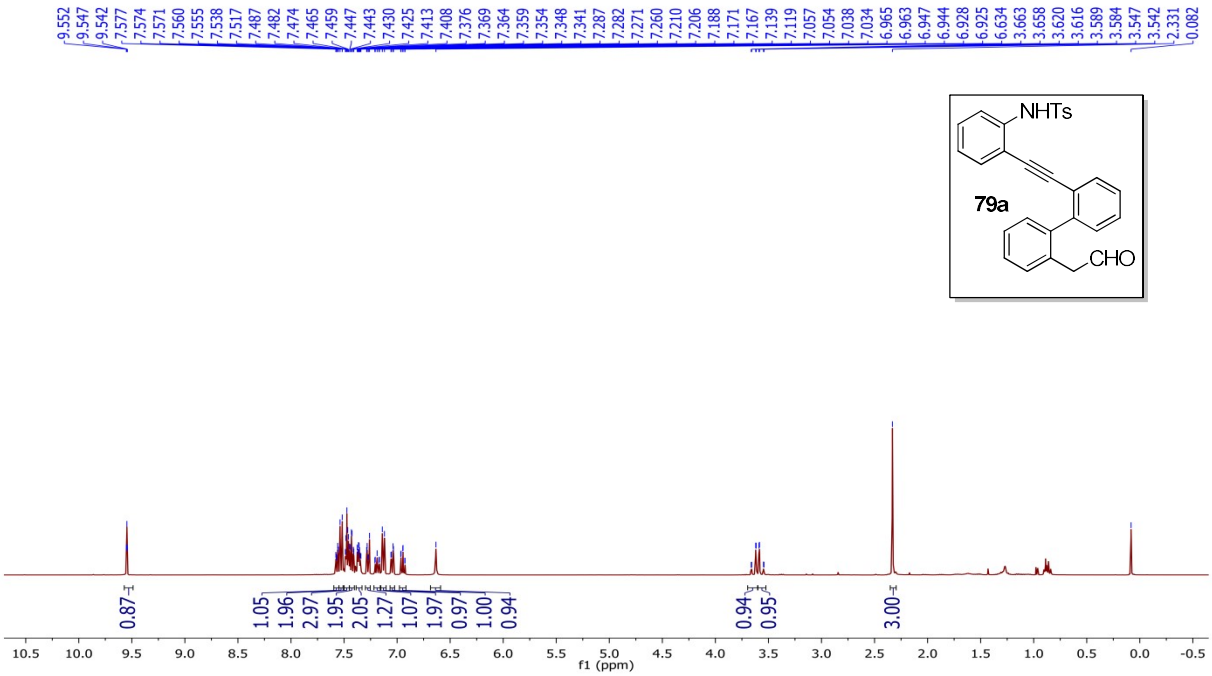
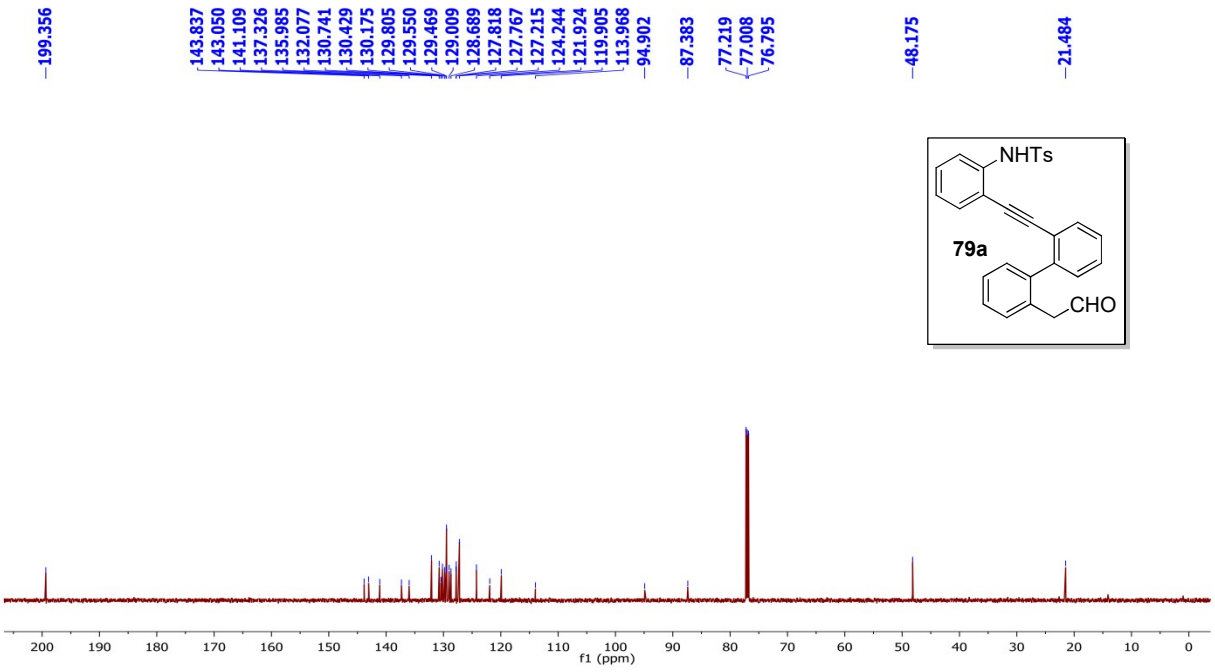
1.2.11. Copies of NMR Spectra

1.2.11.1. NMR Spectra of Compounds 79a-q:

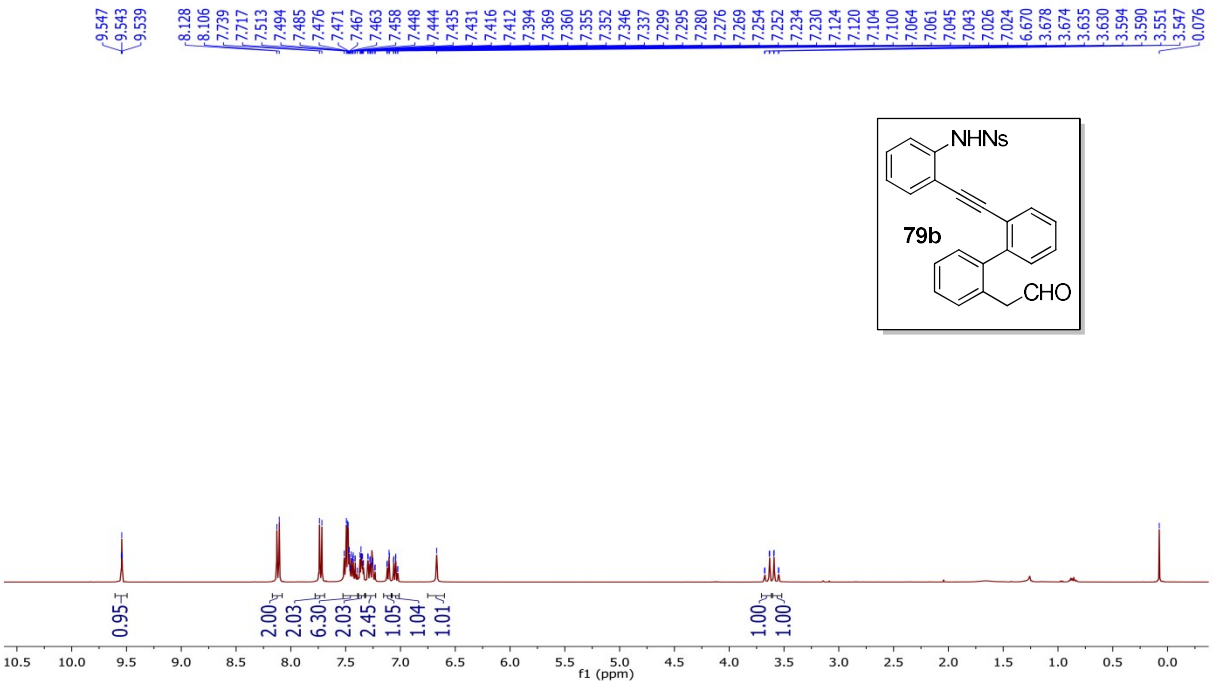
^{1}H NMR (400 MHz) of **79a :**



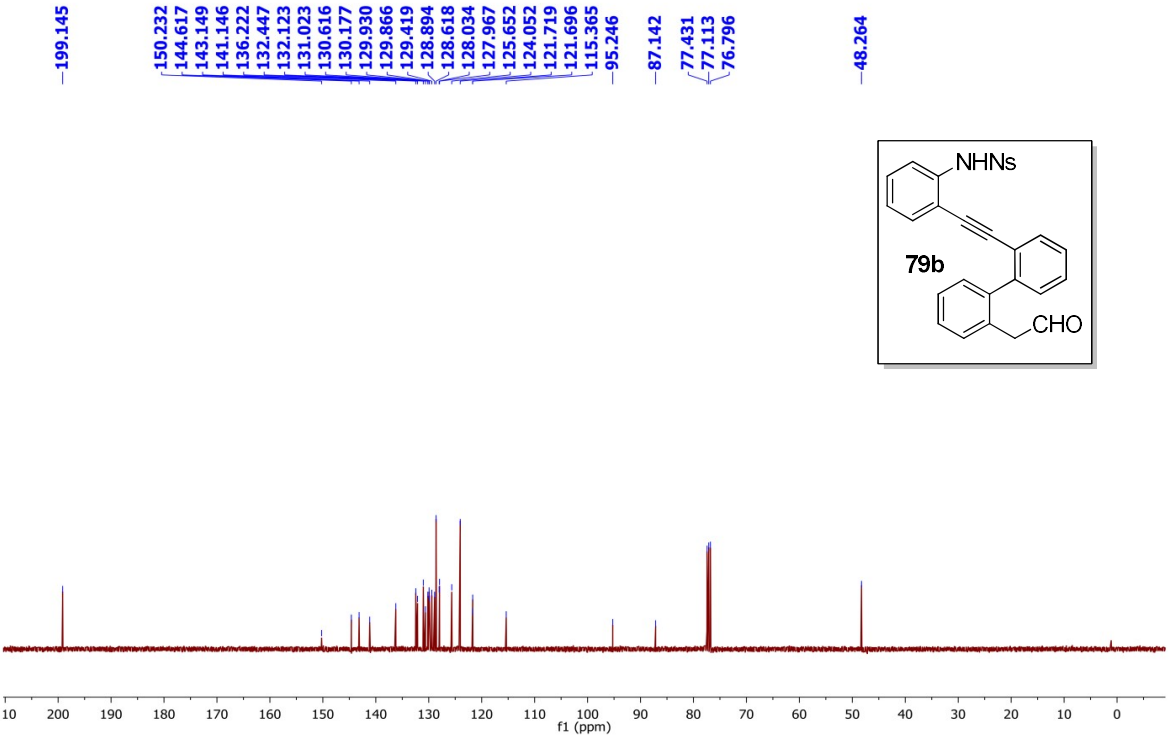
^{13}C{^{1}H} NMR (150 MHz) of **79a :**



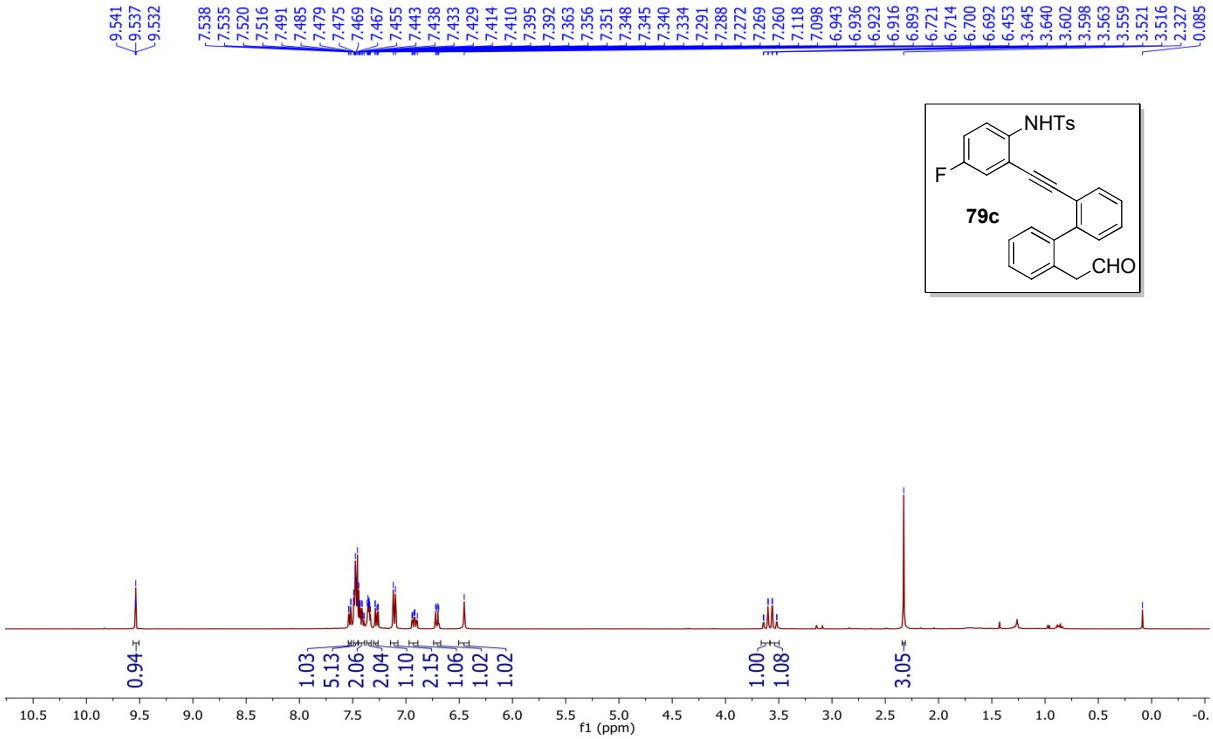
^{1}H NMR (400 MHz) of **79b :**



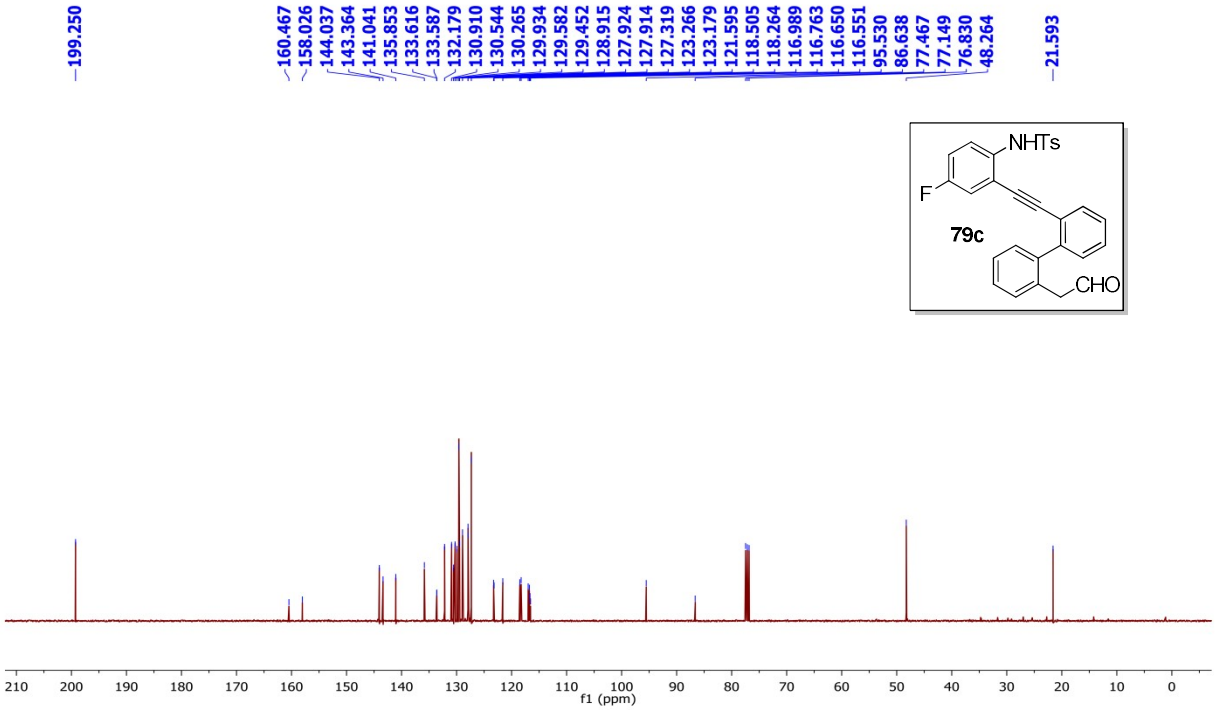
^{13}C{^{1}H} NMR (100 MHz) of **79b :**



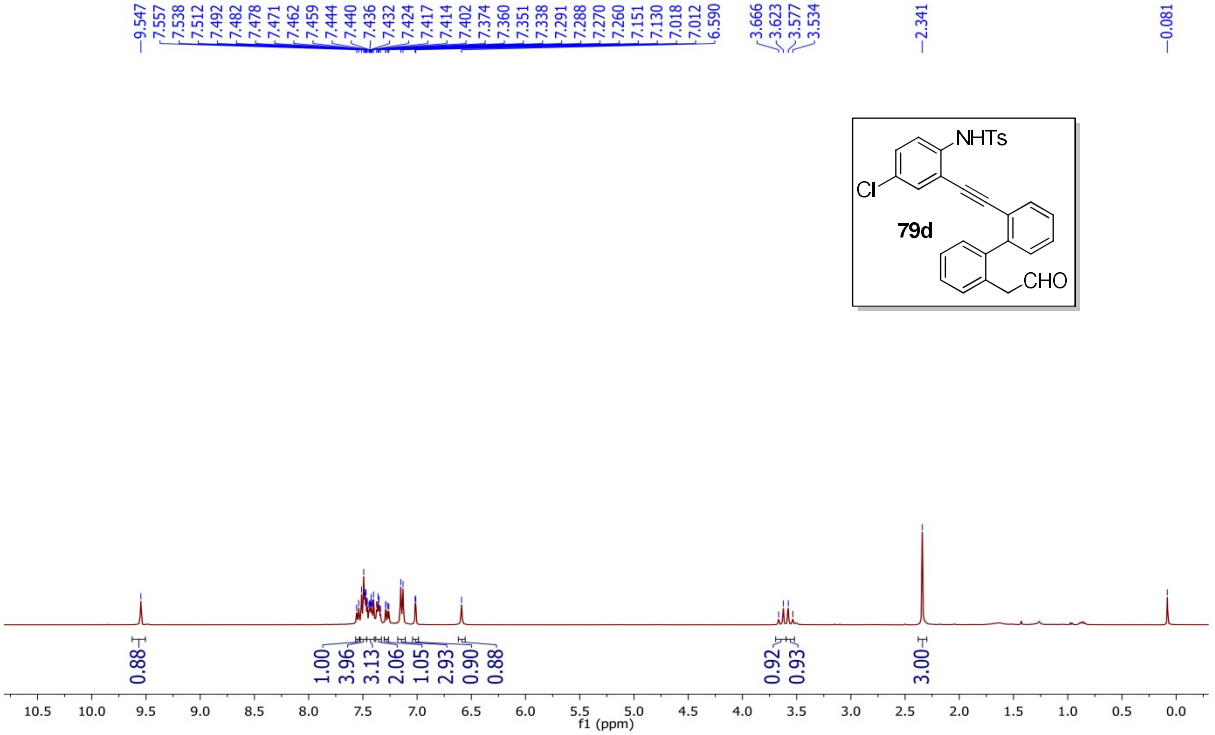
^{1}H NMR (400 MHz) of **79c :**



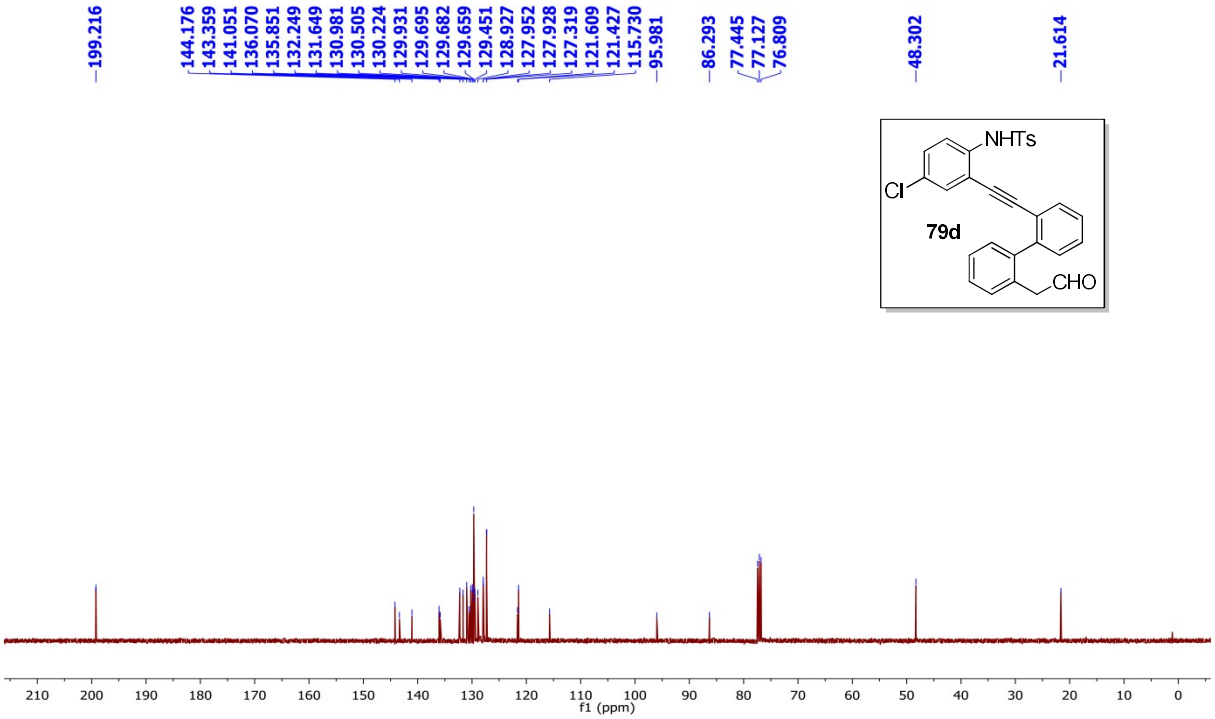
^{13}C{^{1}H} NMR (100 MHz) of **79c :**



^{1}H NMR (400 MHz) of **79d :**



^{13}C{^{1}H} NMR (100 MHz) of **79d:**



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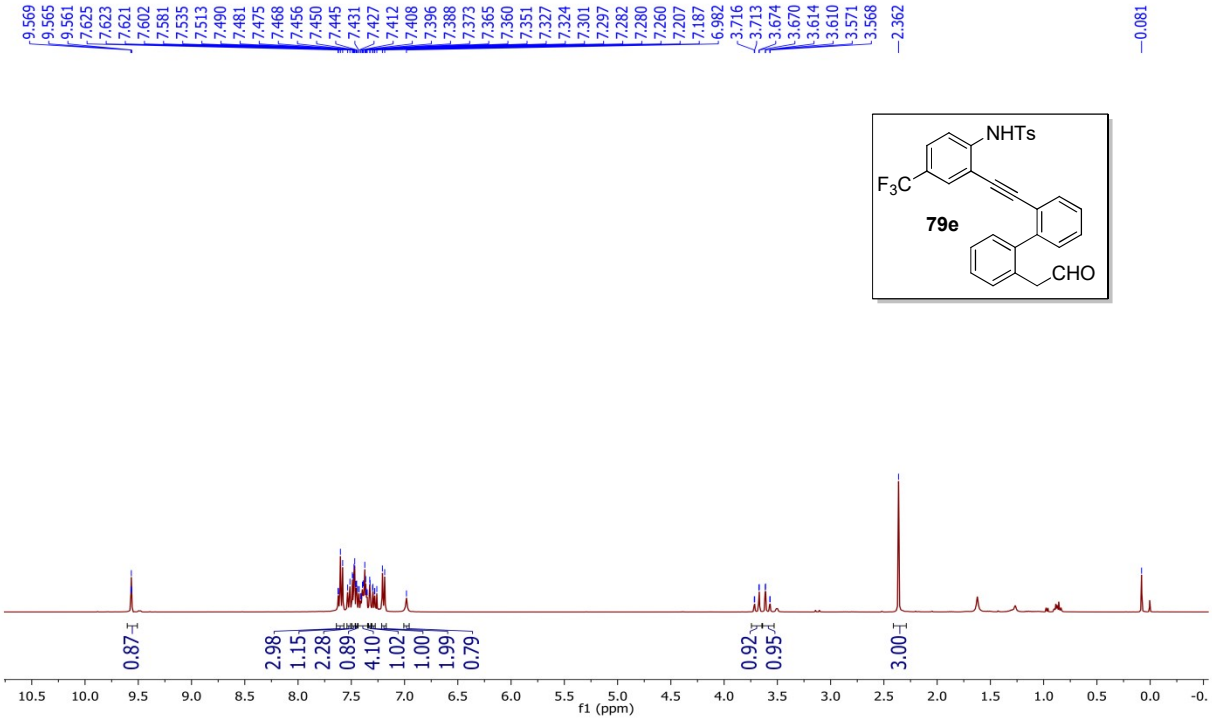
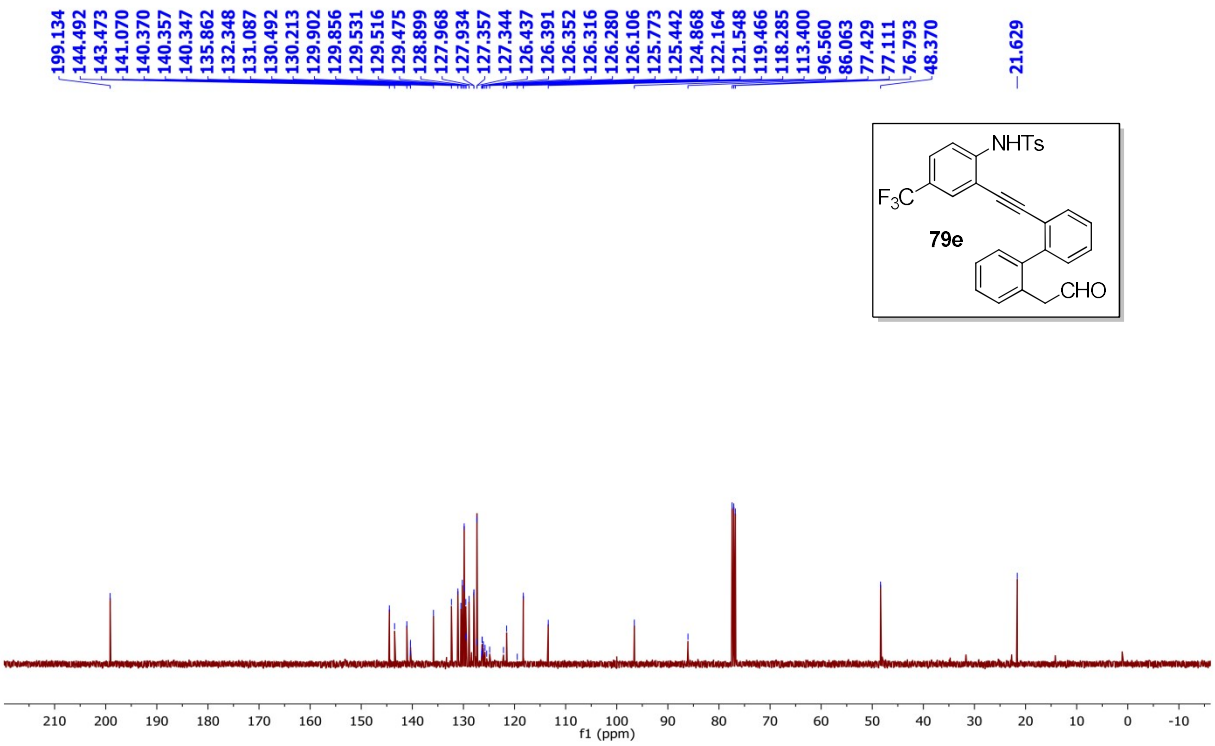
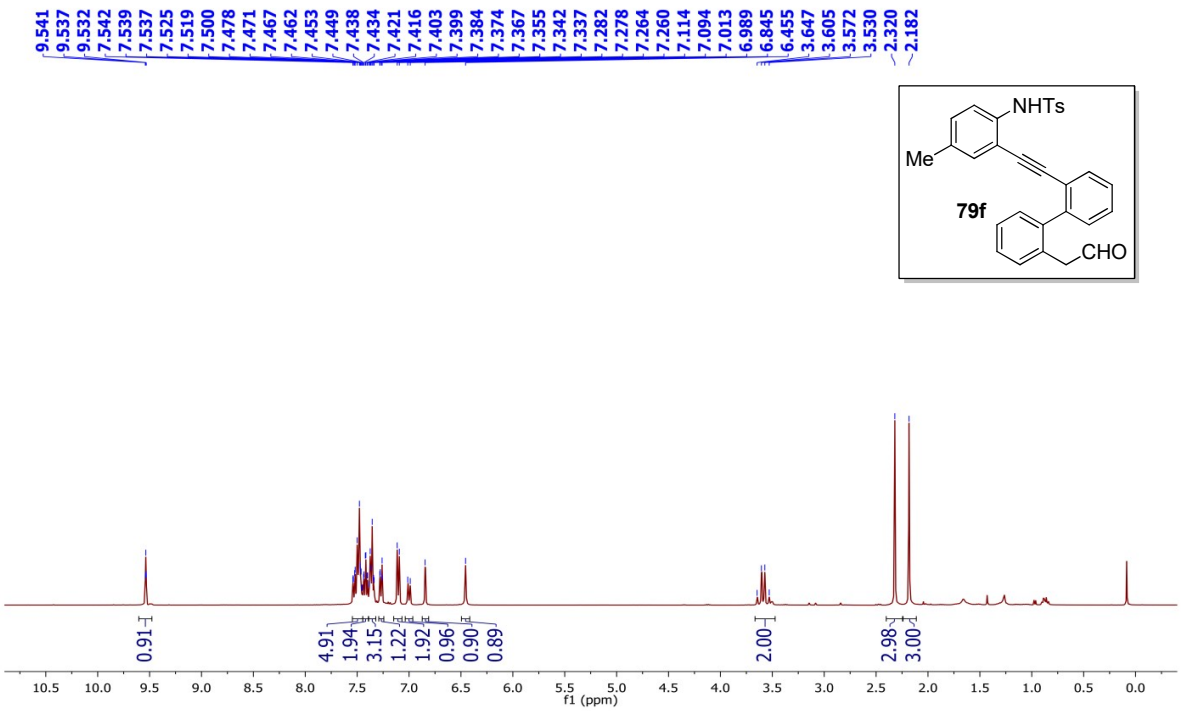


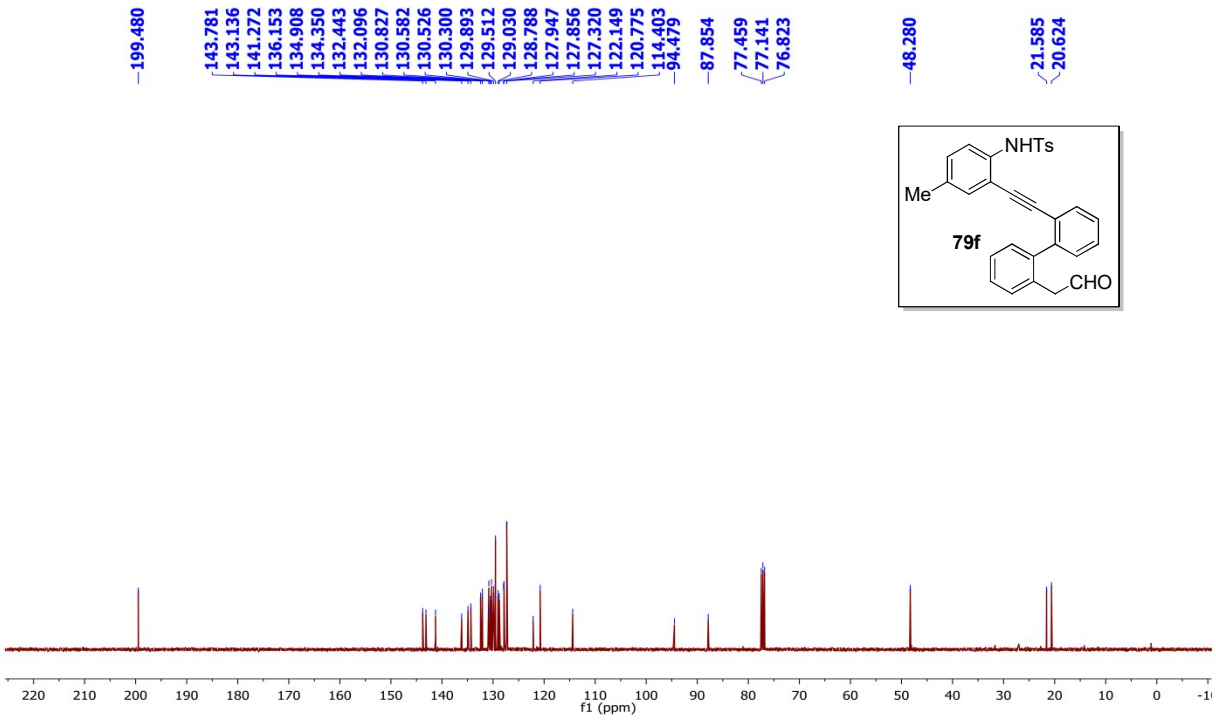
^{13}C{^{1}H} NMR (100 MHz) of **79e :**



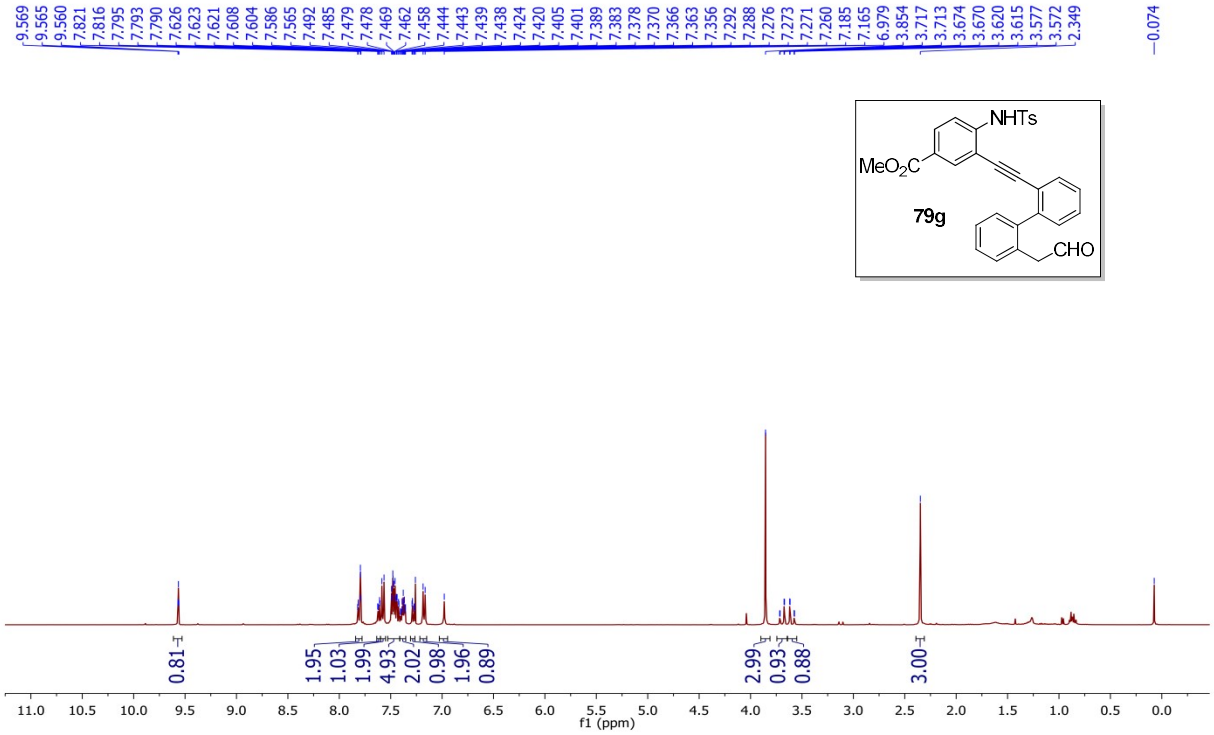
^{1}H NMR (400 MHz) of **79f :**



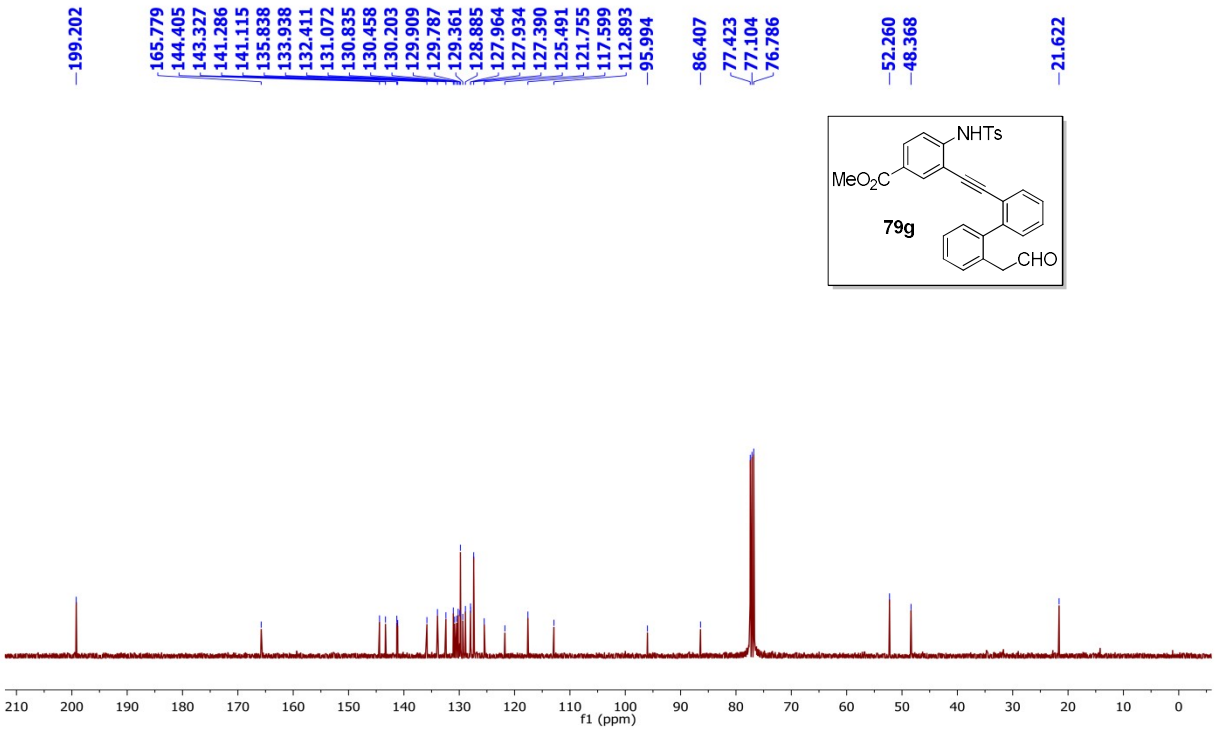
^{13}C{^{1}H} NMR (100 MHz) of **79f :**



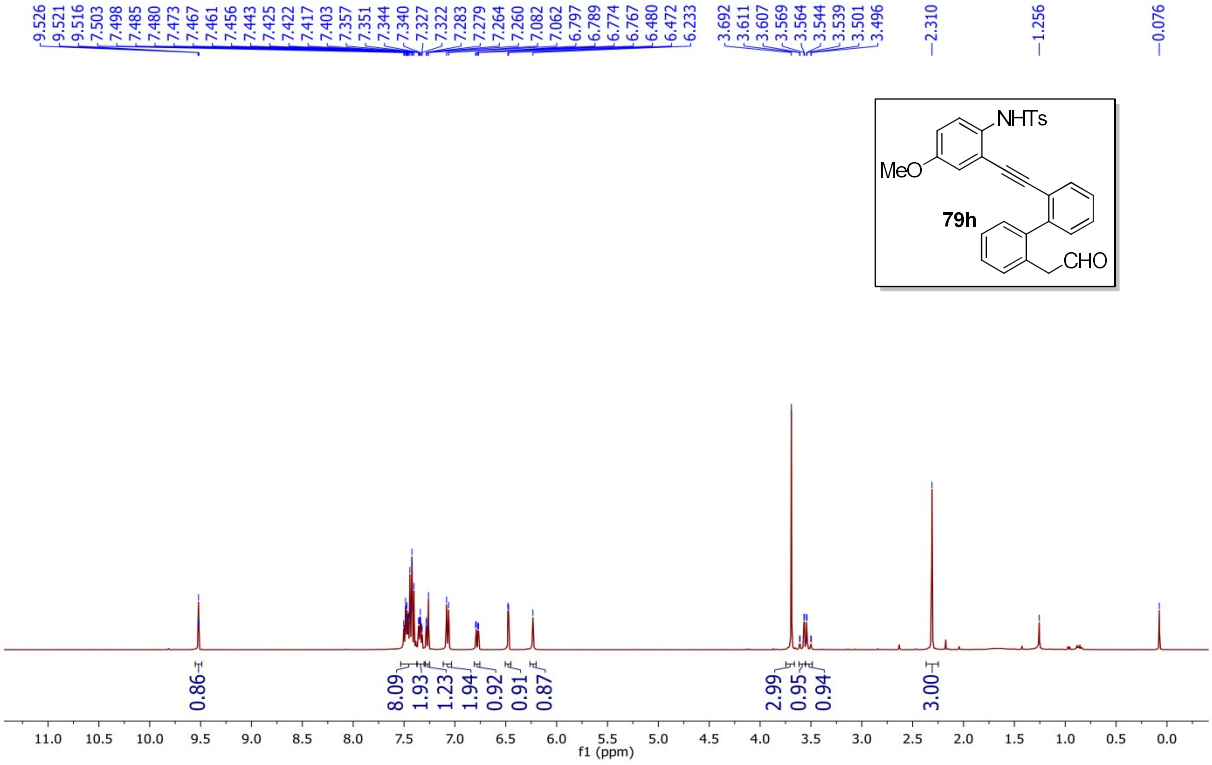
^{1}H NMR (400 MHz) of **79g :**



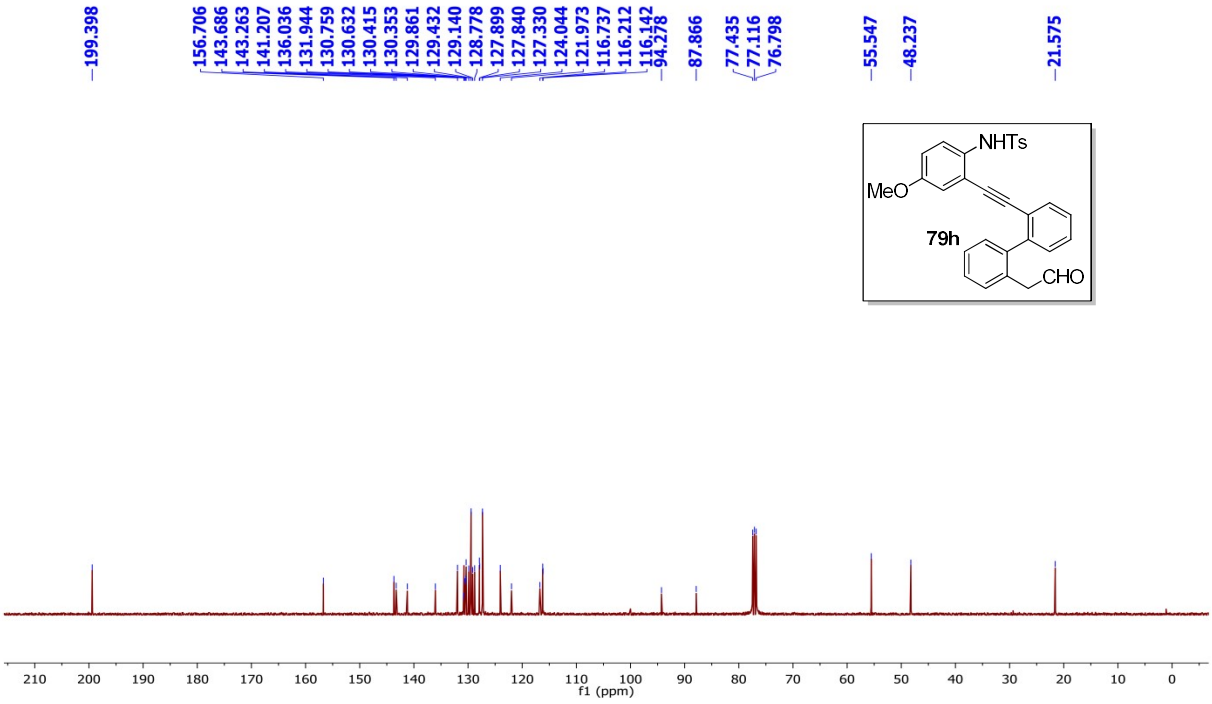
^{13}C{^{1}H} NMR (100 MHz) of **79g :**



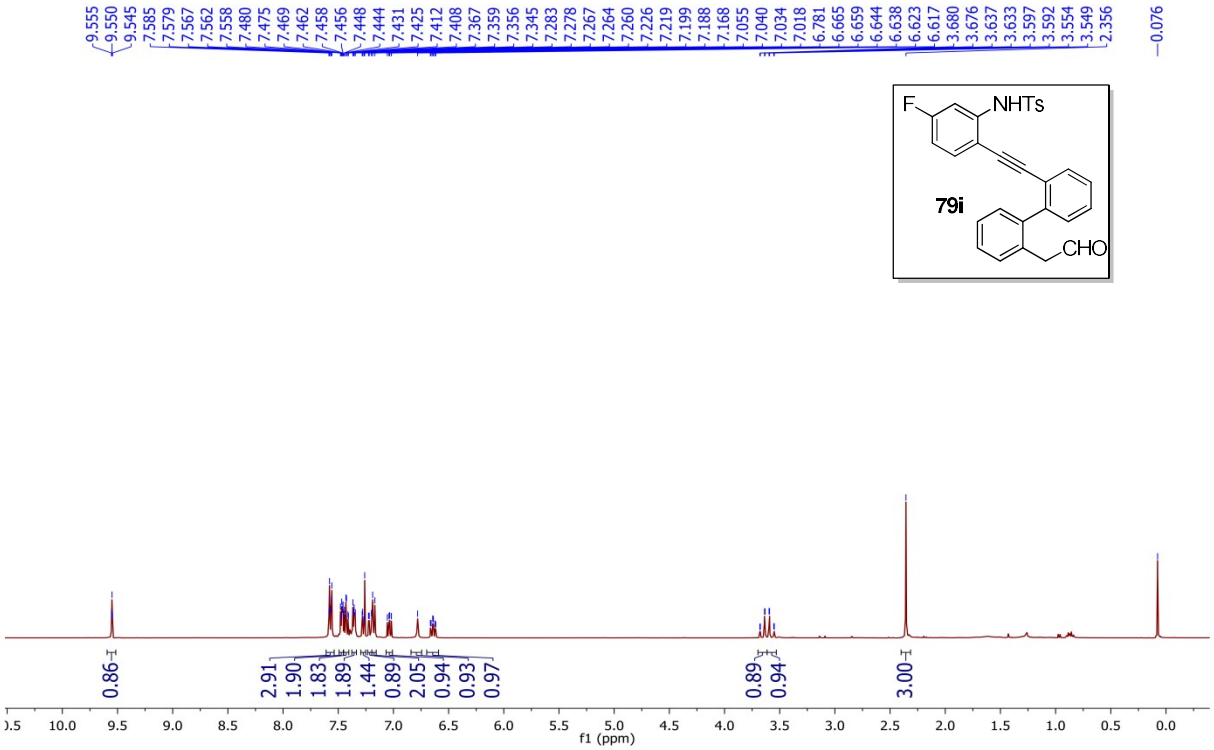
^{1}H NMR (400 MHz) of **79h :**



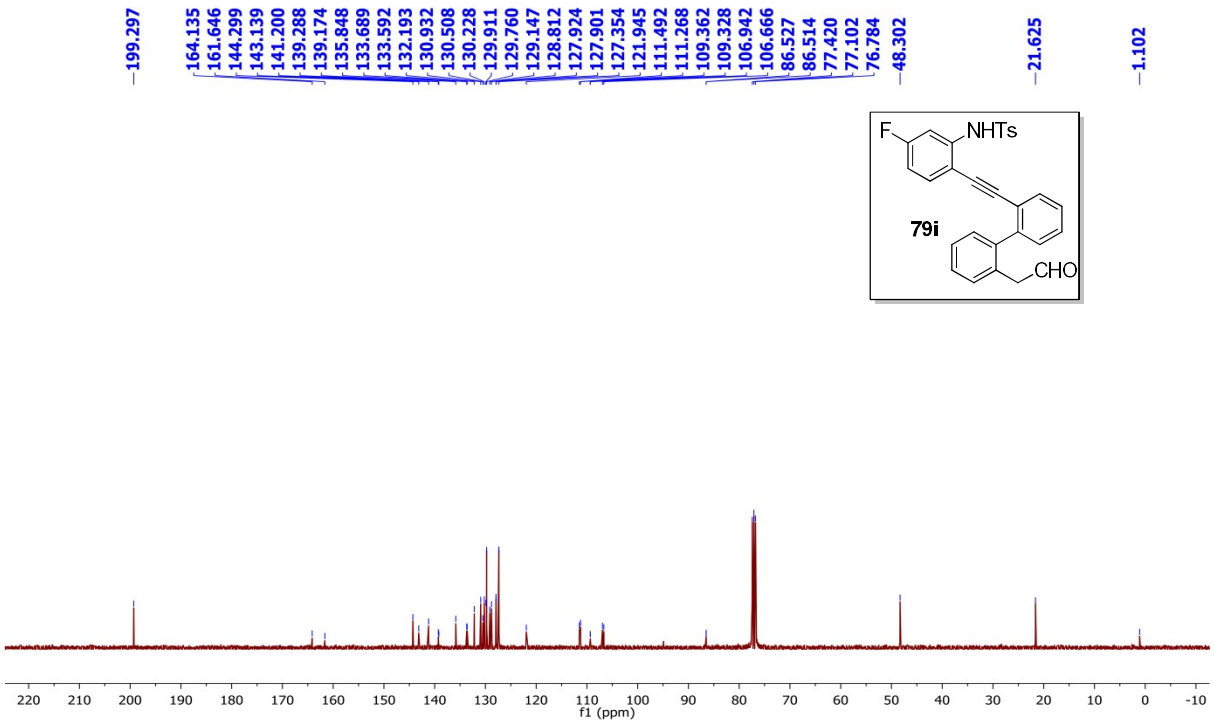
^{13}C{^{1}H} NMR (100 MHz) of **79h :**



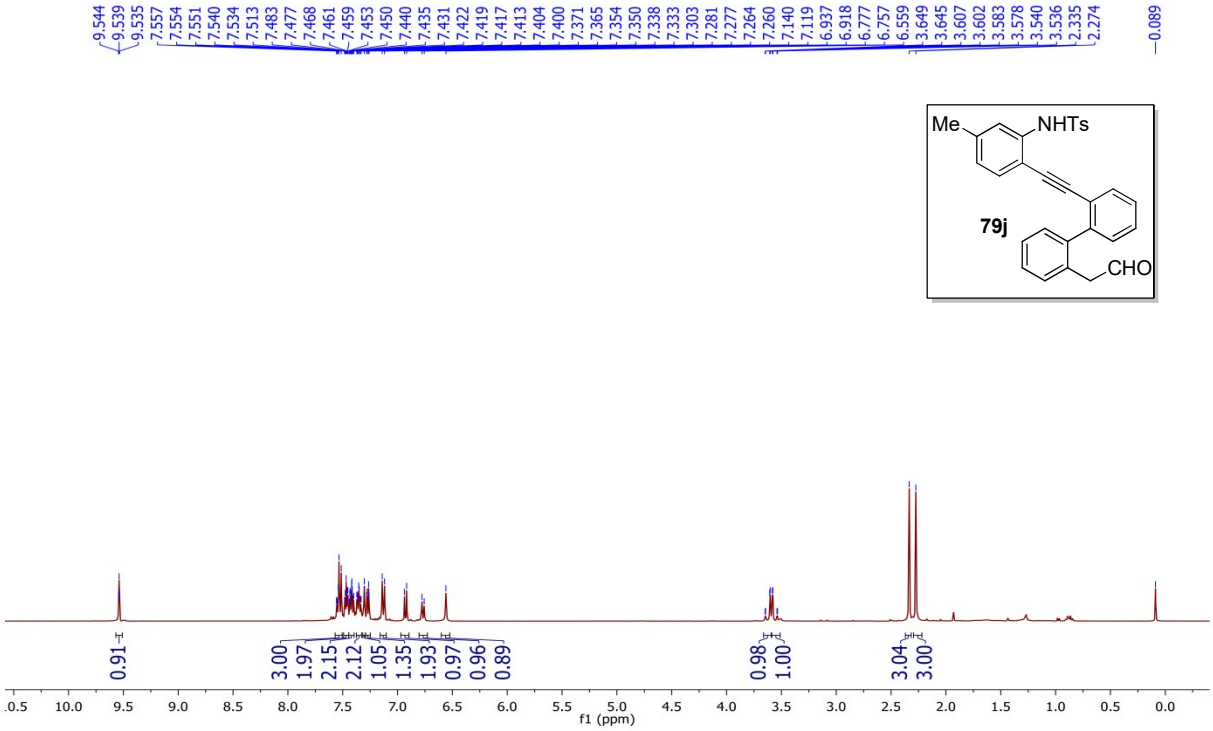
^{1}H NMR (400 MHz) of **79i :**



^{13}C{^{1}H} NMR (100 MHz) of **79i :**



^{1}H NMR (400 MHz) of **79j :**



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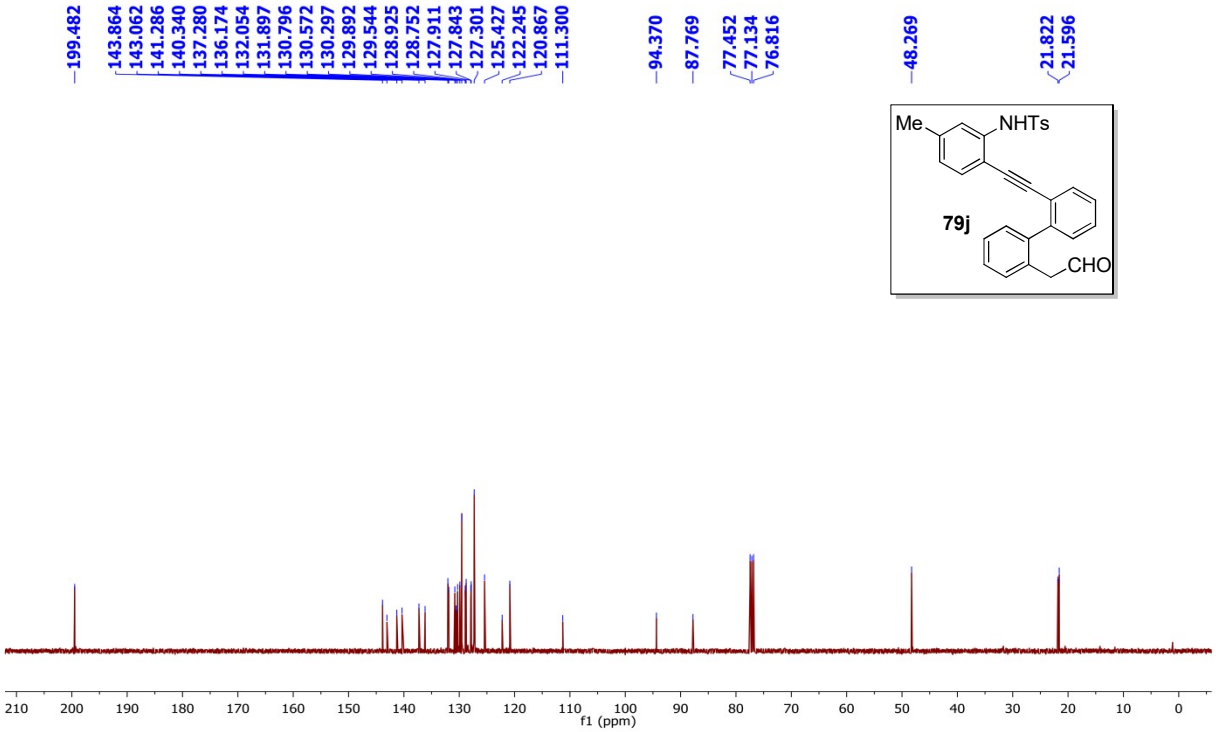
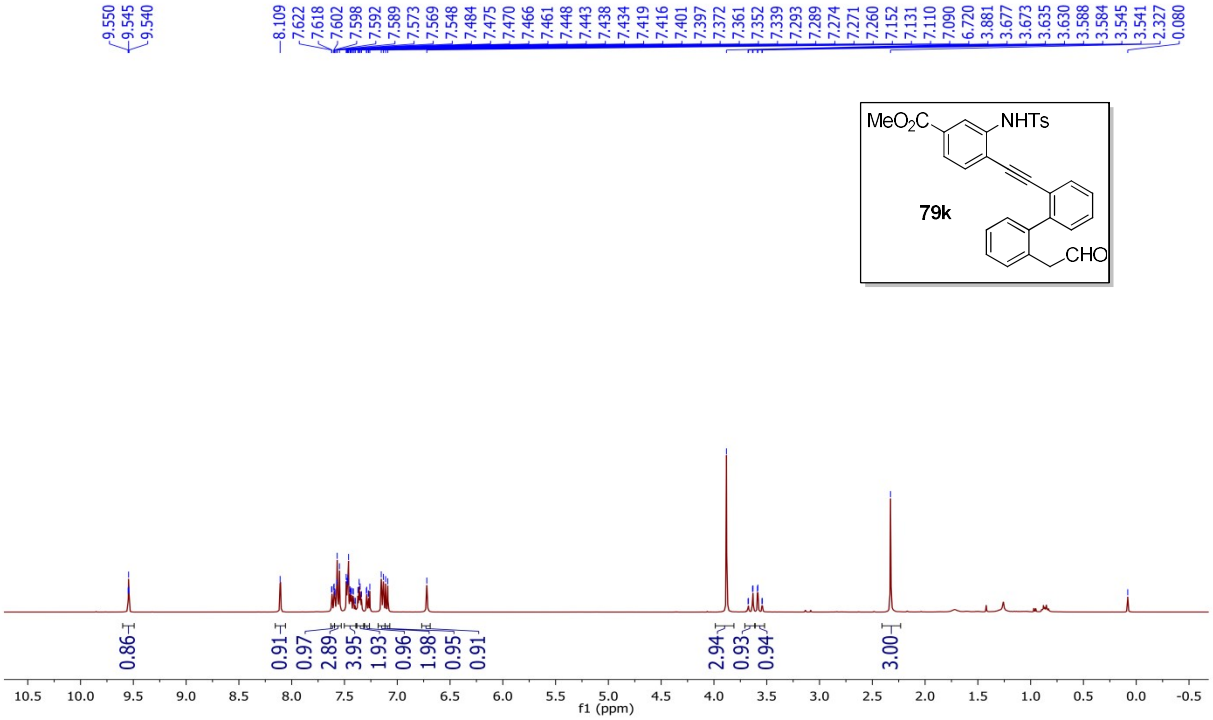


^{1}H NMR (400 MHz) of **79k :**



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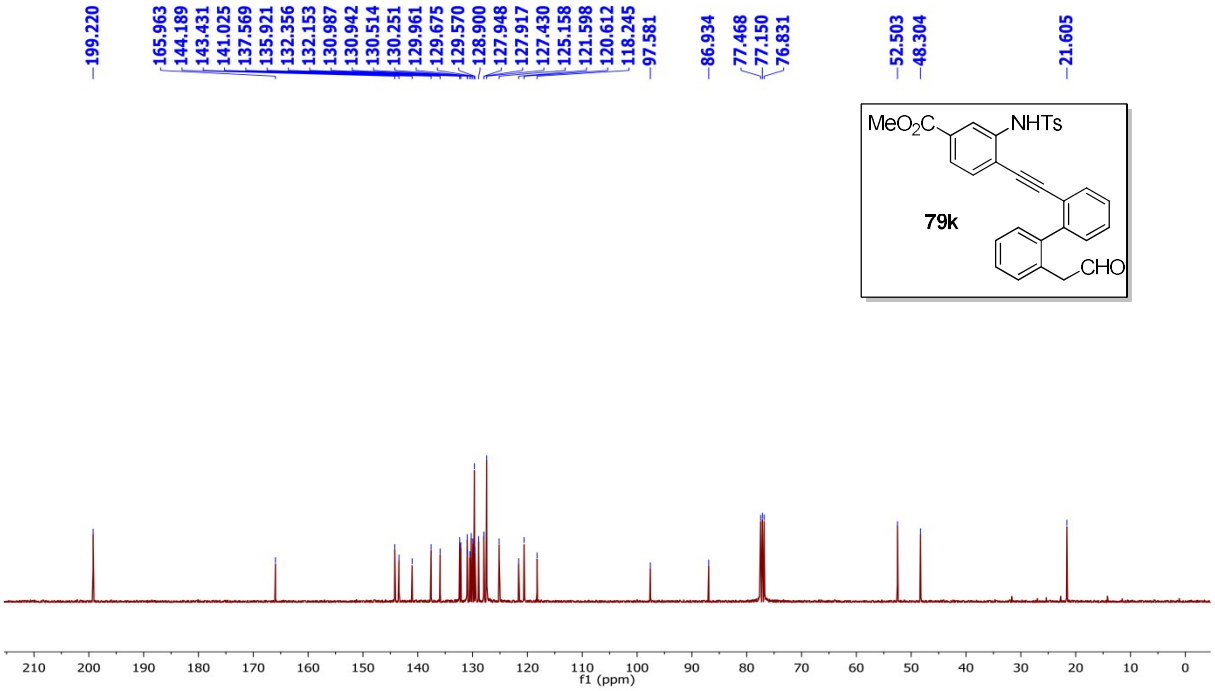
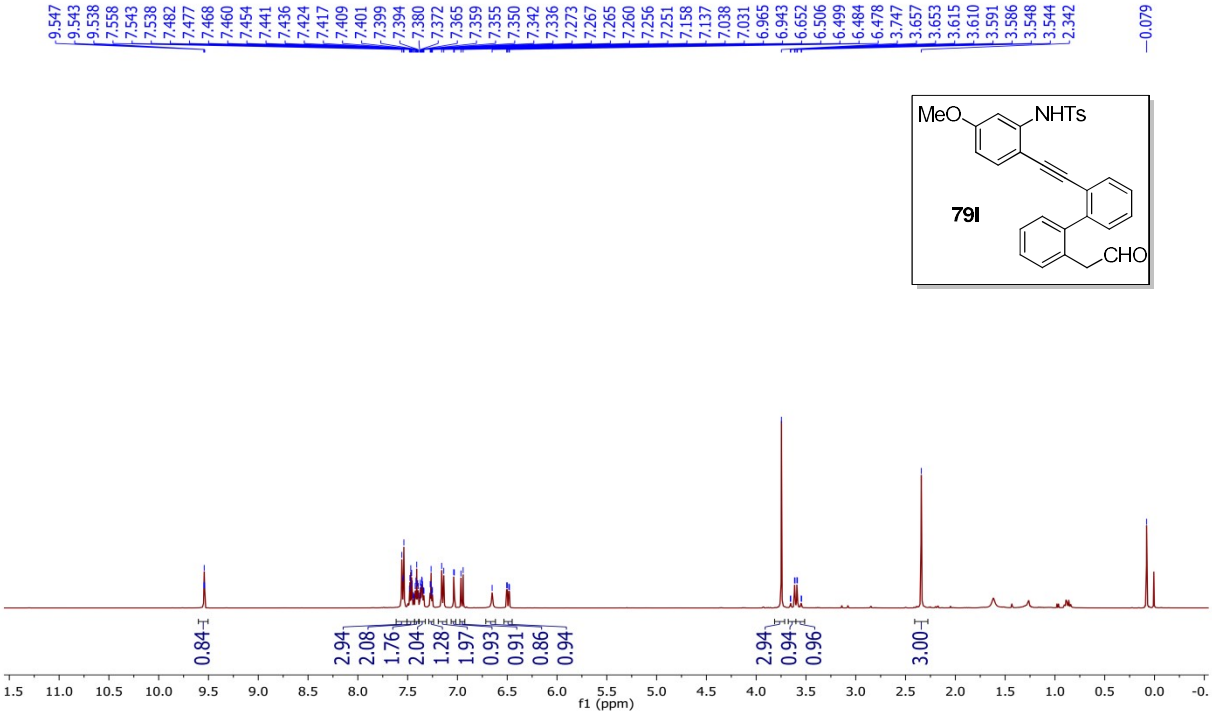
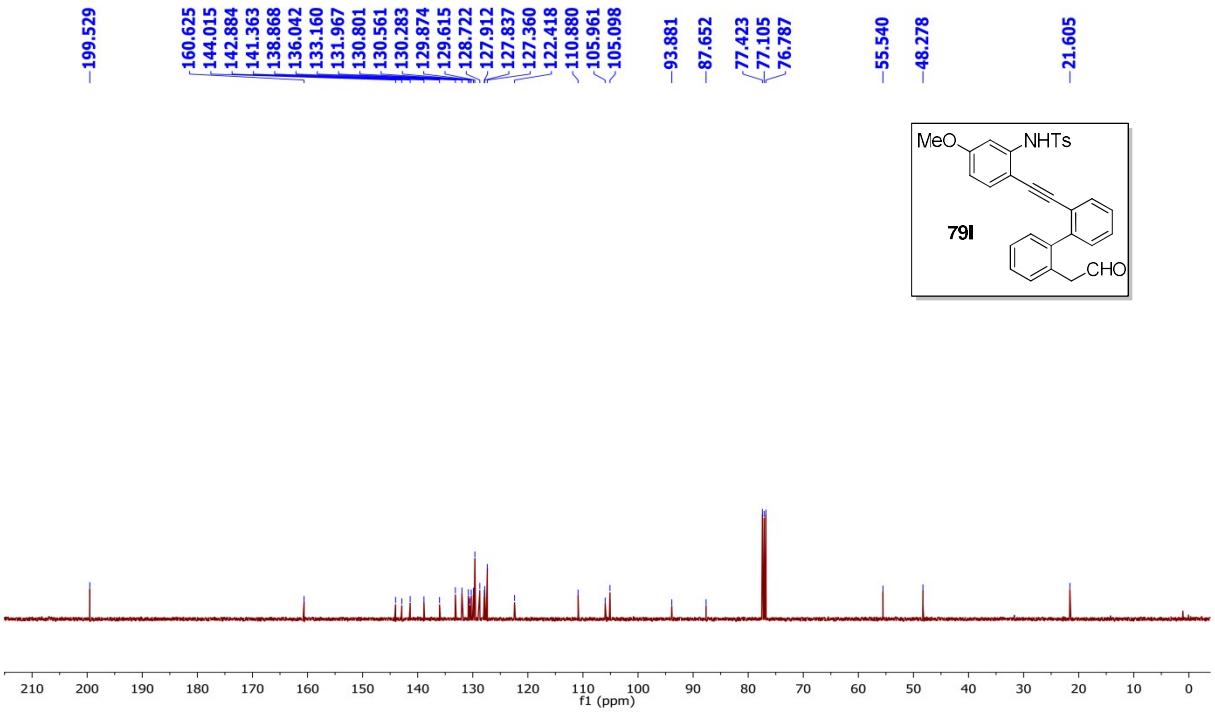


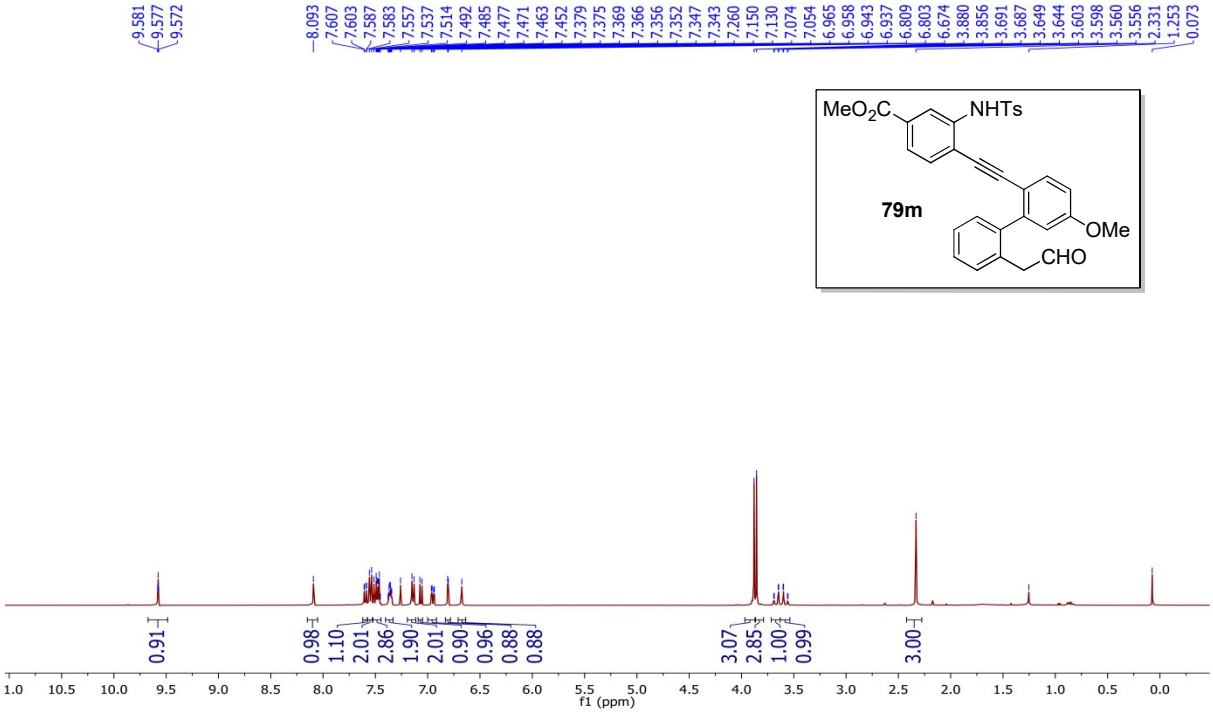
^{1}H NMR (400 MHz) of **79l :**



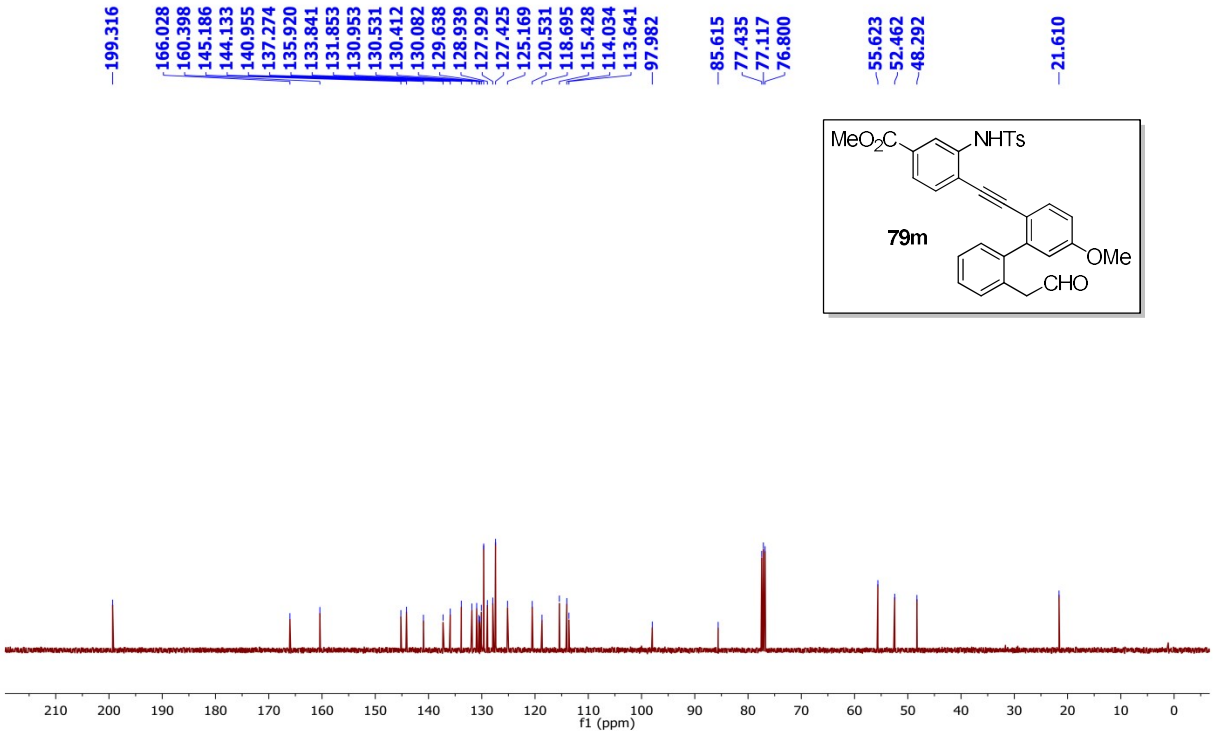
^{13}C{^{1}H} NMR (100 MHz) of **79l :**



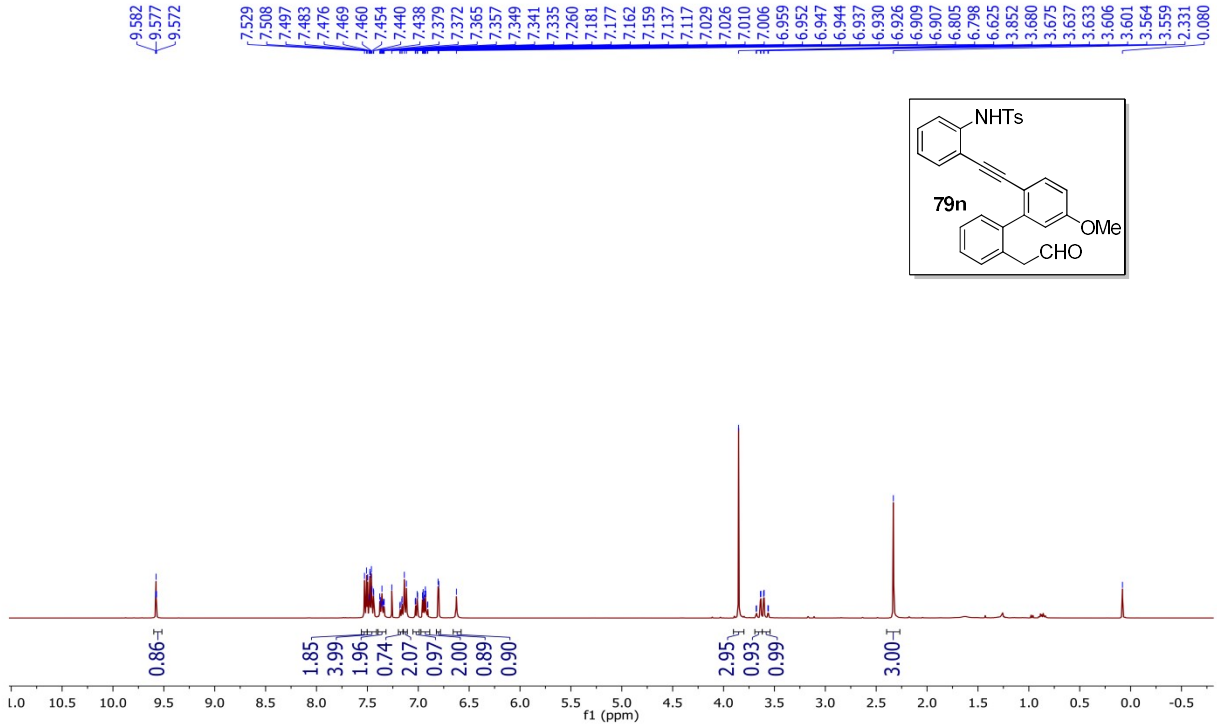
^{1}H NMR (400 MHz) of **79m :**



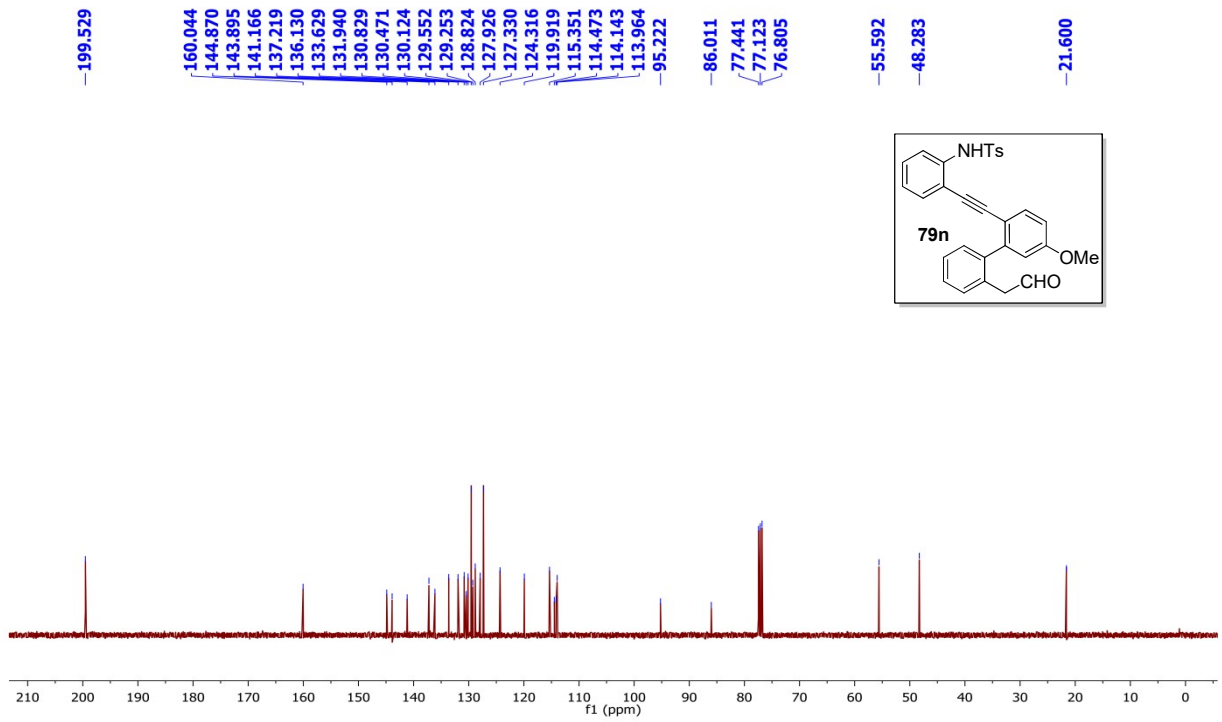
^{13}C{^{1}H} NMR (100 MHz) of **79m :**



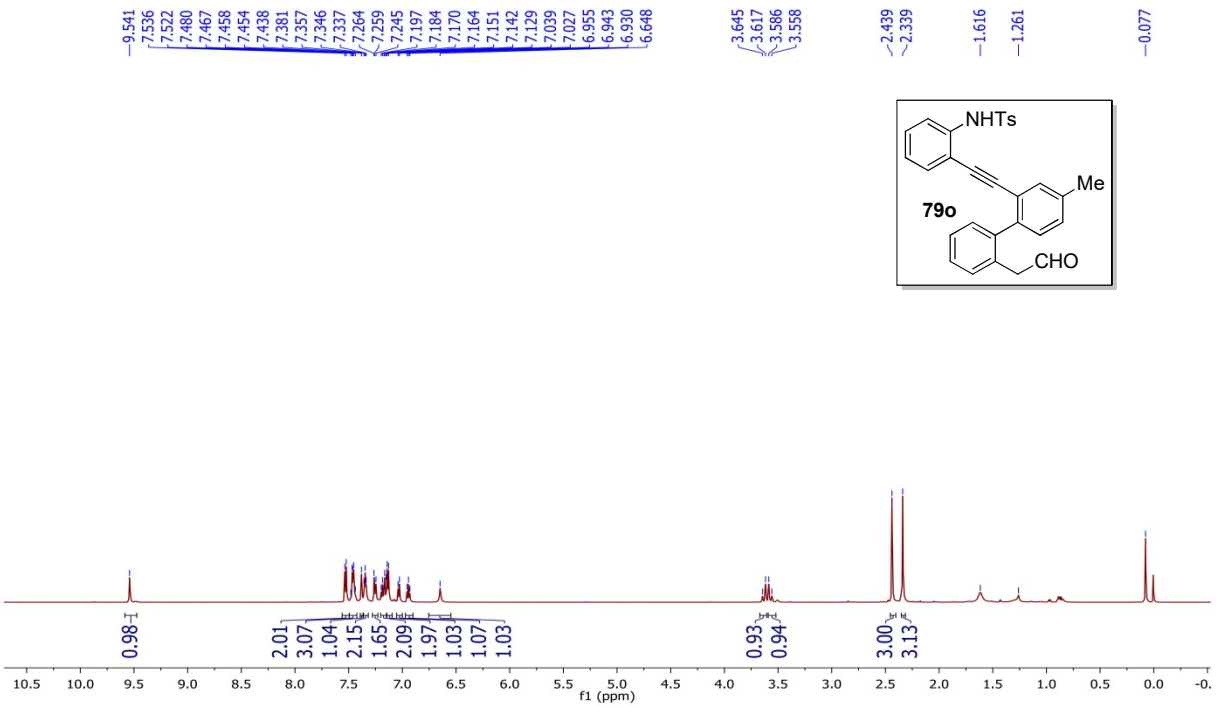
^{1}H NMR (400 MHz) of **79n :**



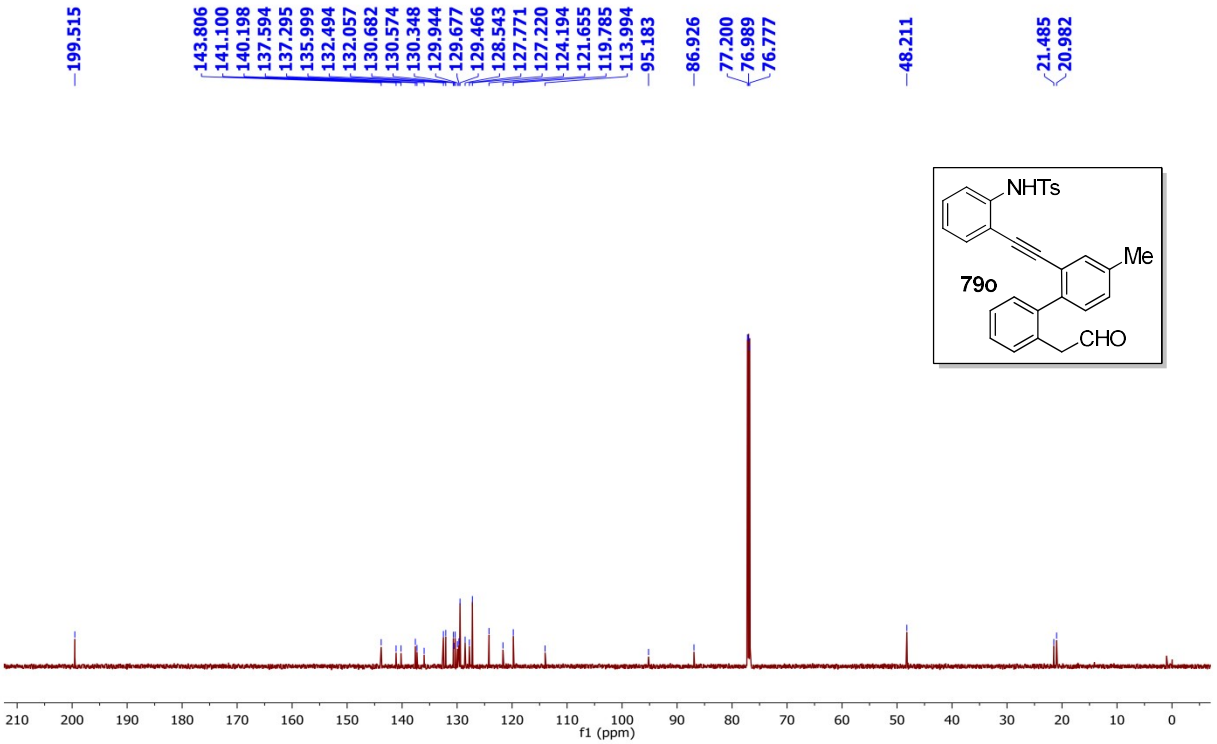
^{13}C{^{1}H} NMR (100 MHz) of **79n :**



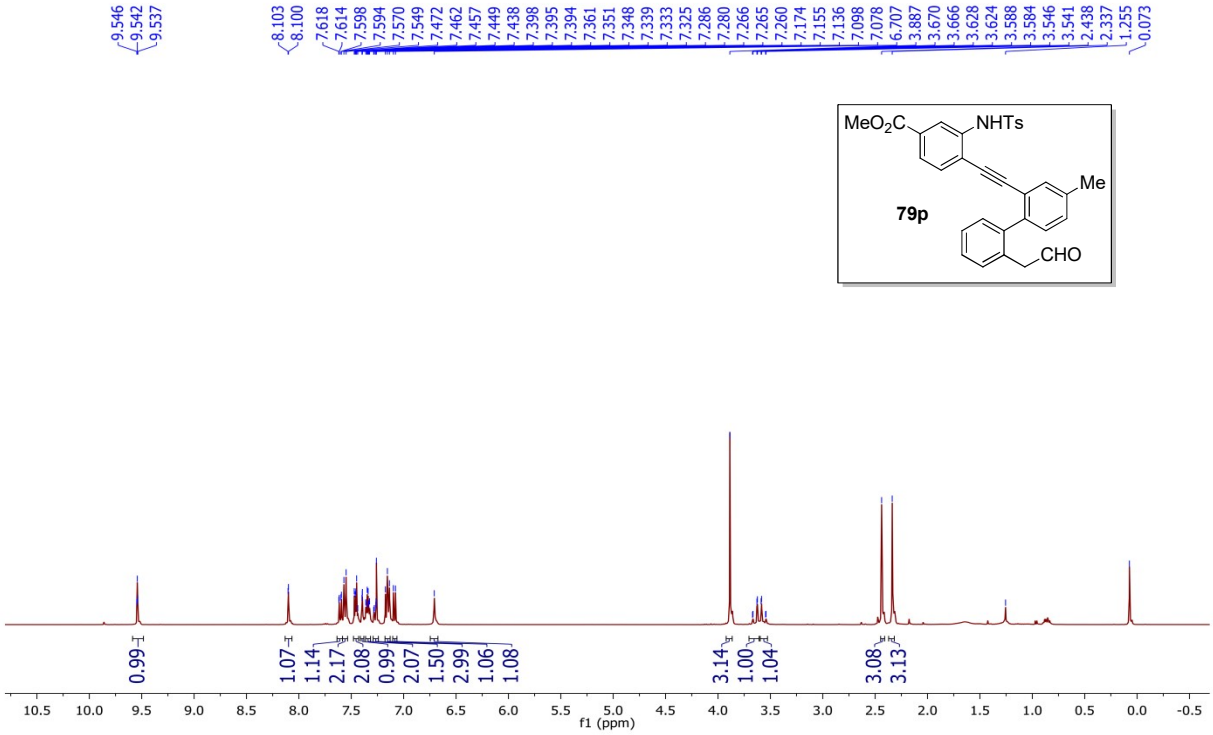
^{1}H NMR (600 MHz) of **79o :**



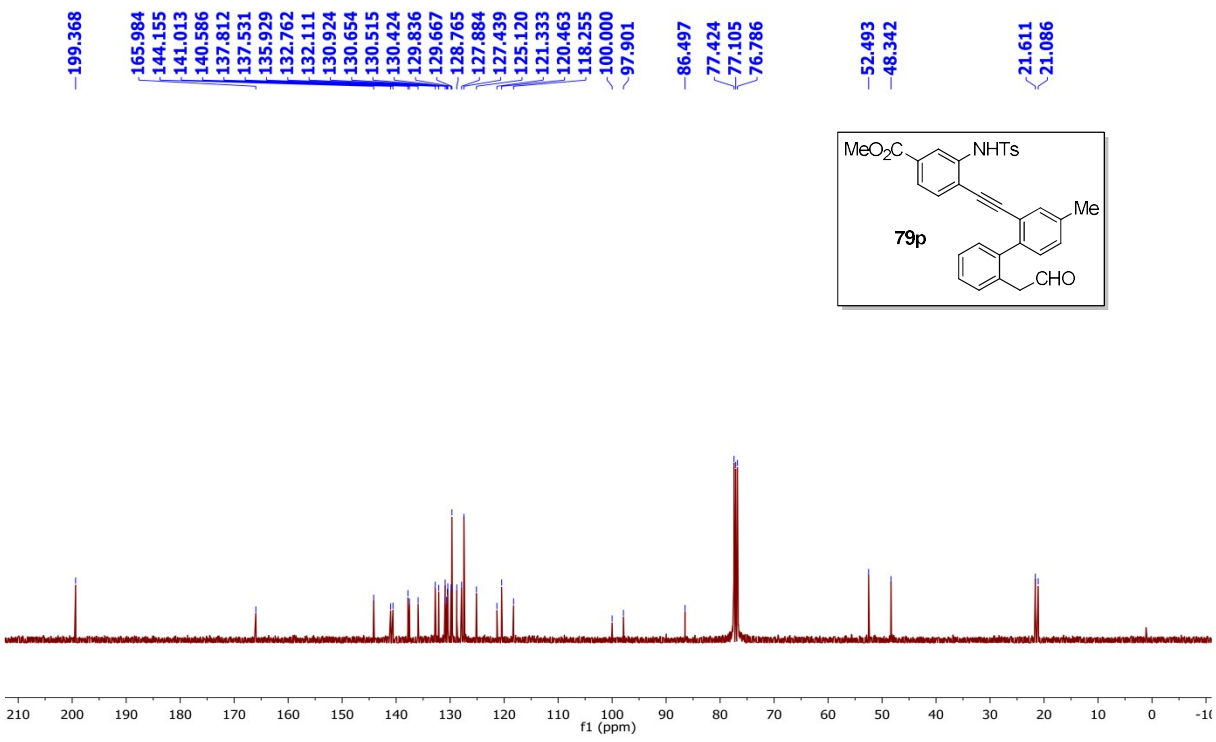
^{13}C{^{1}H} NMR (150 MHz) of **79o :**



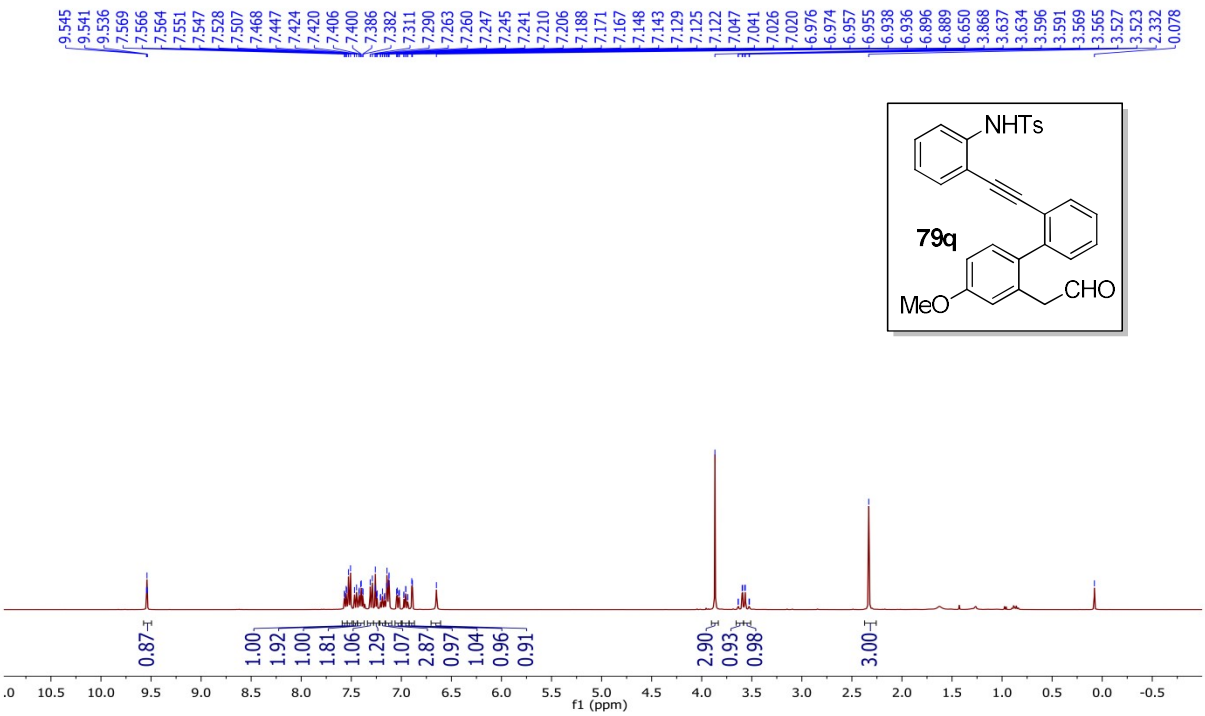
^{1}H NMR (400 MHz) of **79p :**



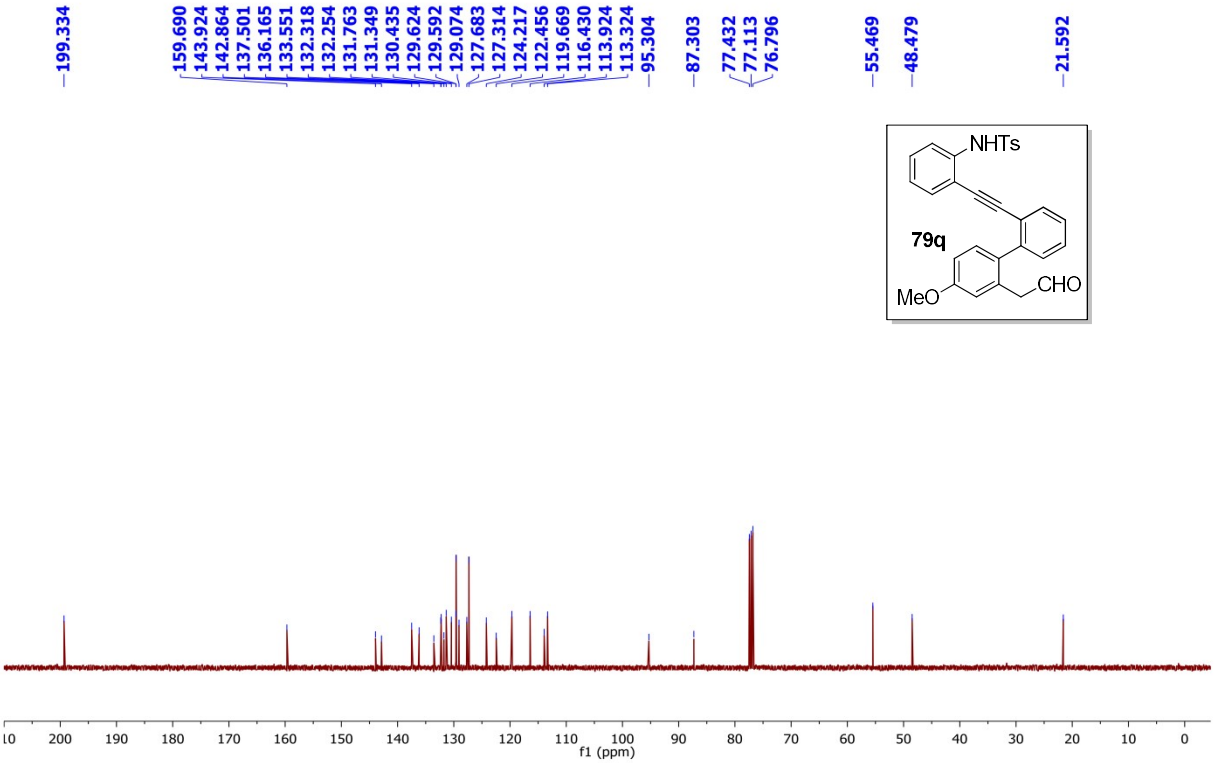
^{13}C{^{1}H} NMR (100 MHz) of **79p :**



^{1}H NMR (400 MHz) of **79q :**

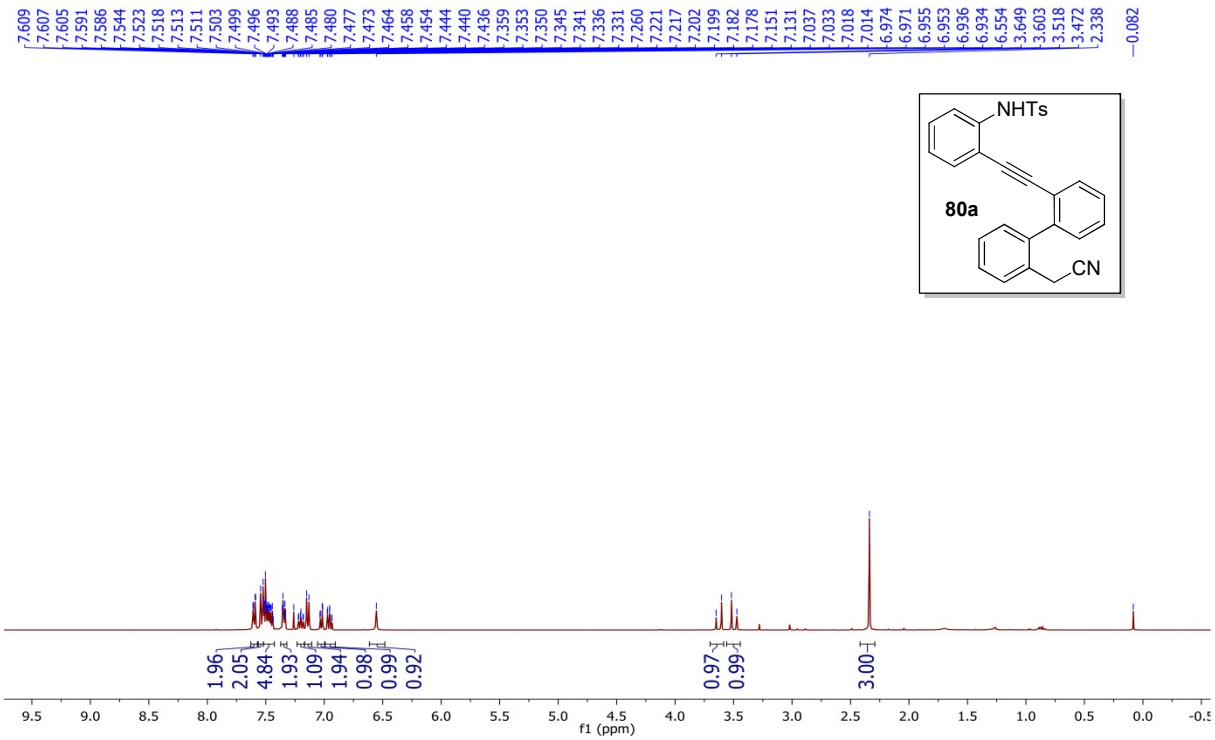


^{13}C{^{1}H} NMR (100 MHz) of **79q :**

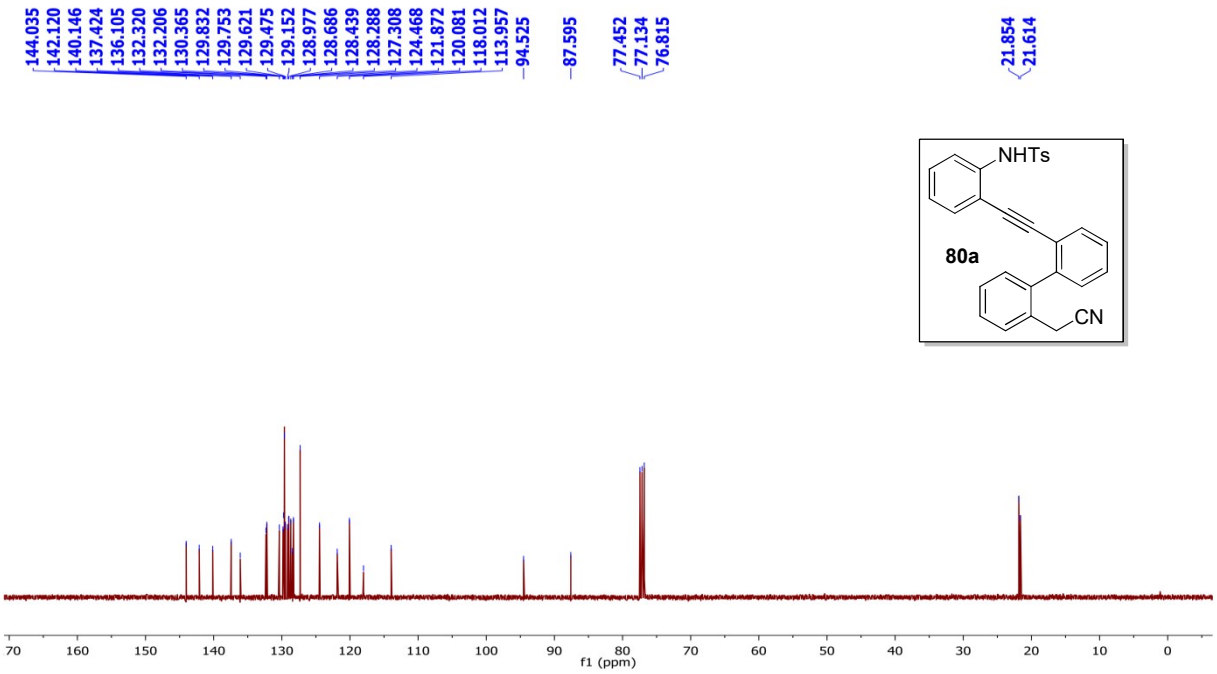


1.2.11.2. NMR Spectra of Compounds 80a-i :

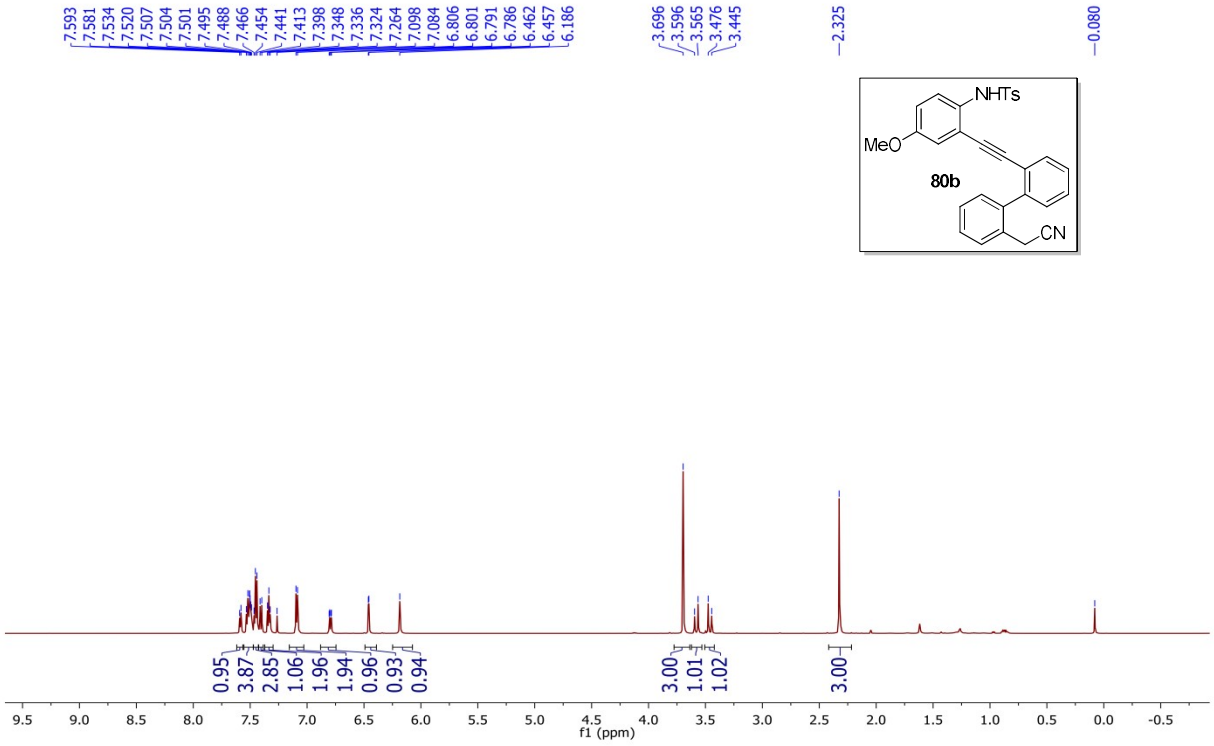
^{1}H NMR (400 MHz) of **80a :**



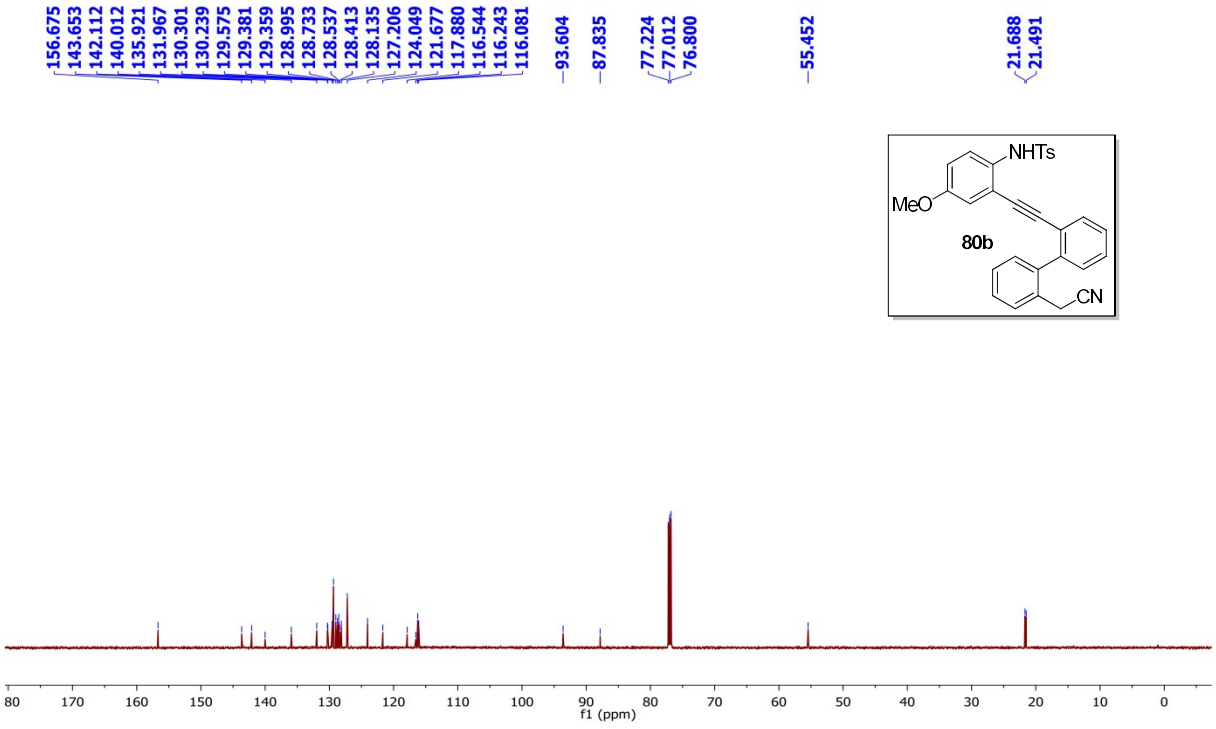
^{13}C{^{1}H} NMR (100 MHz) of **80a:**



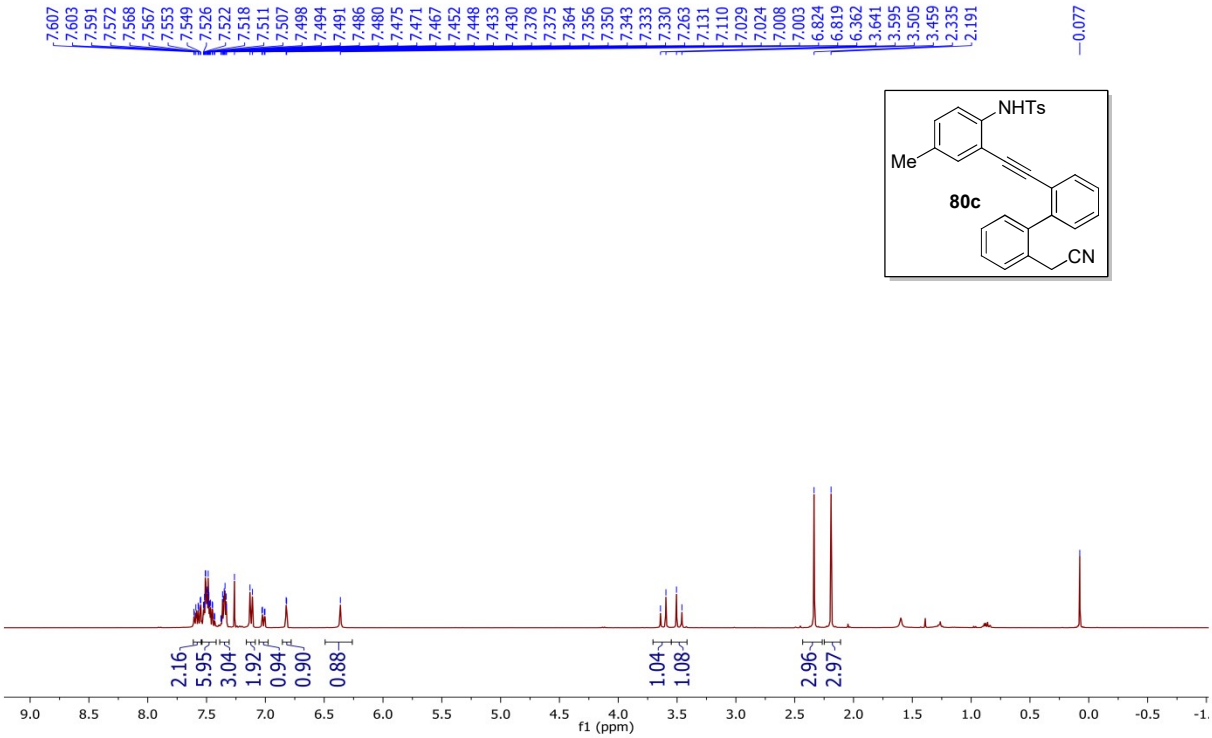
^{1}H NMR (600 MHz) of **80b :**



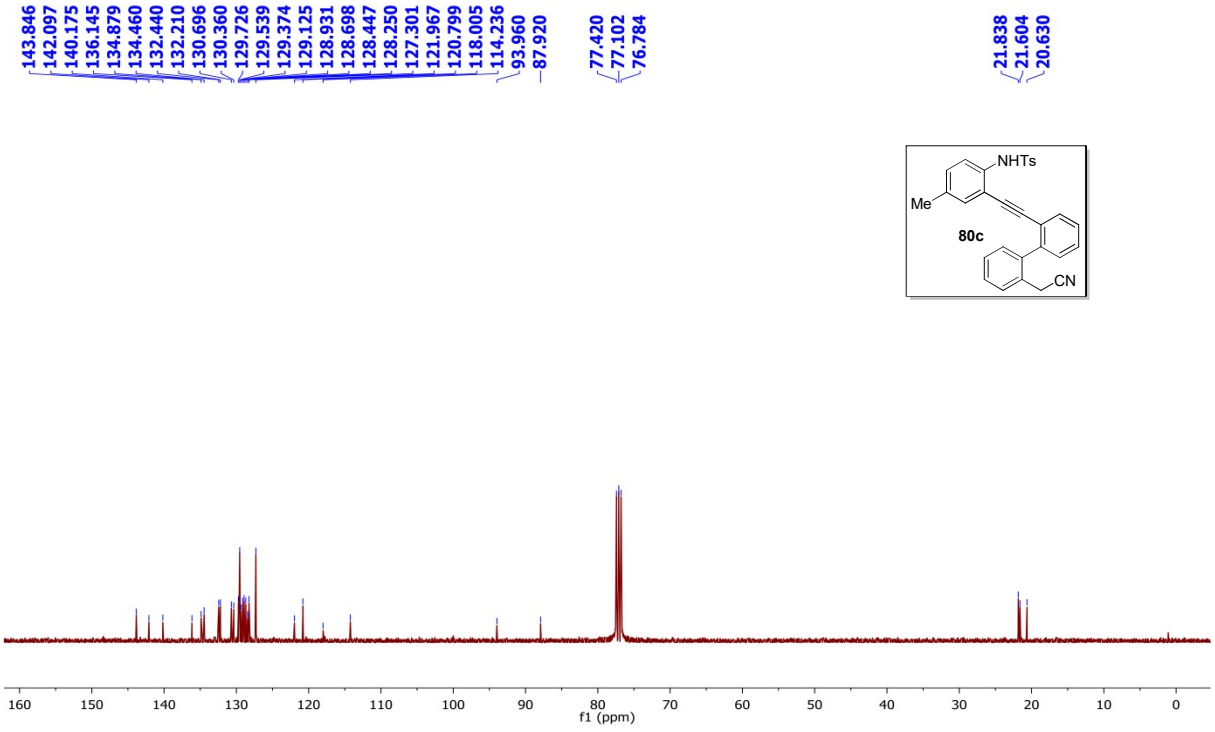
^{13}C{^{1}H} NMR (150 MHz) of **80b :**



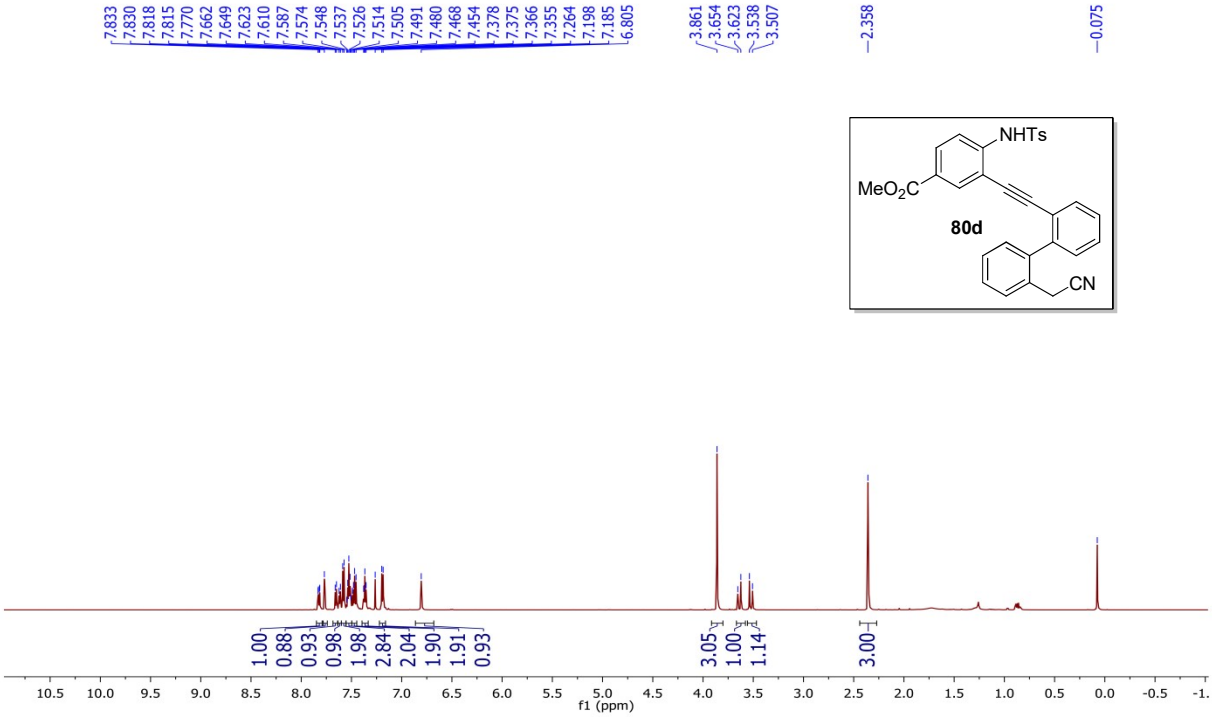
^{1}H NMR (400 MHz) of **80c :**



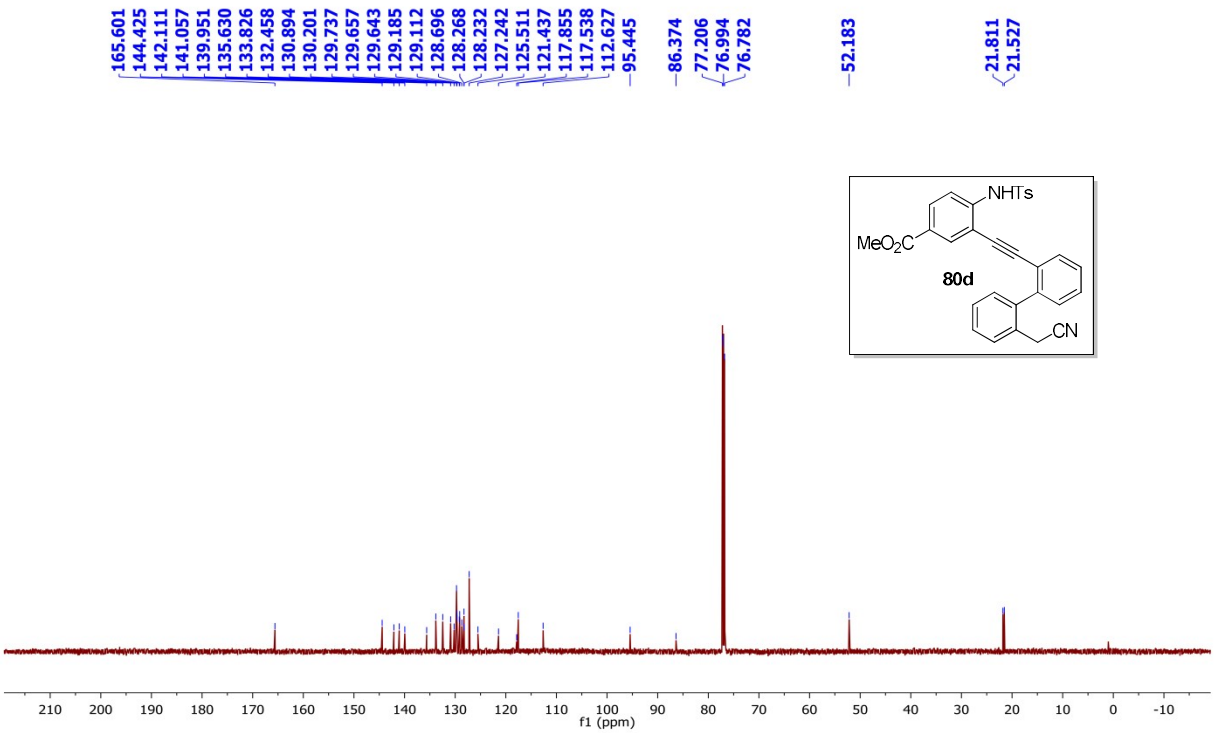
^{13}C{^{1}H} NMR (100 MHz) of **80c :**



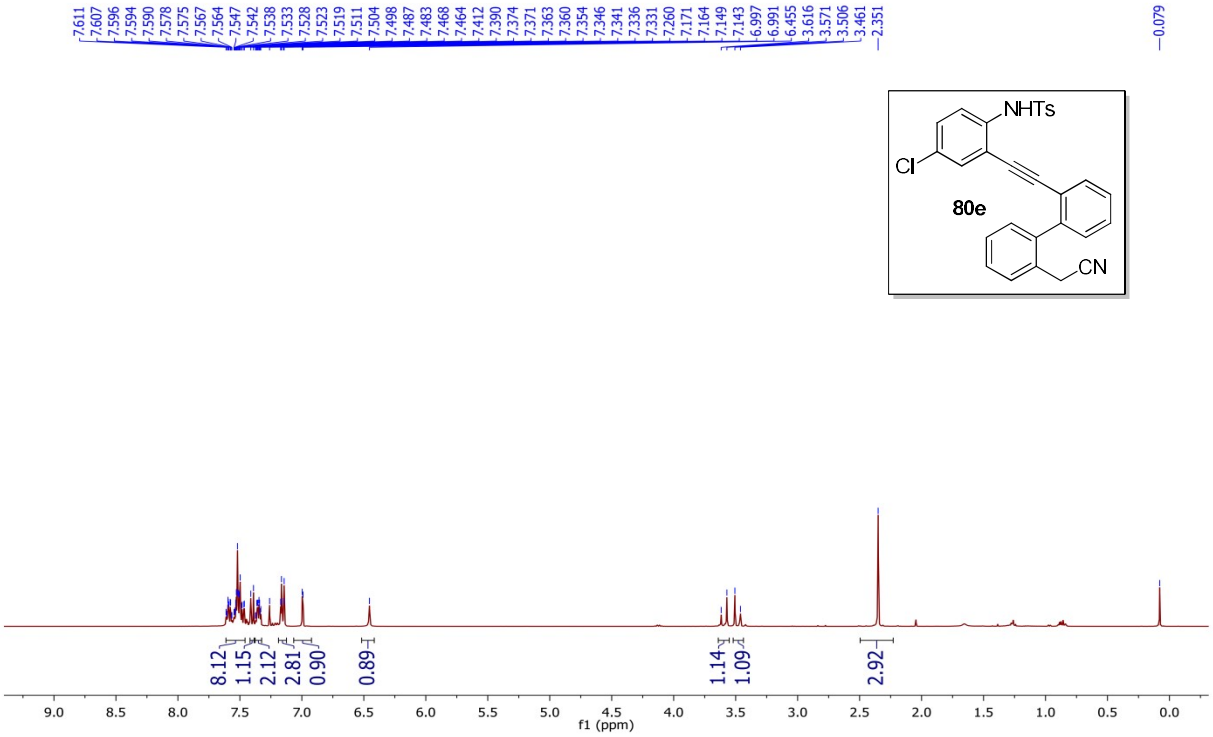
^{1}H NMR (600 MHz) of **80d :**



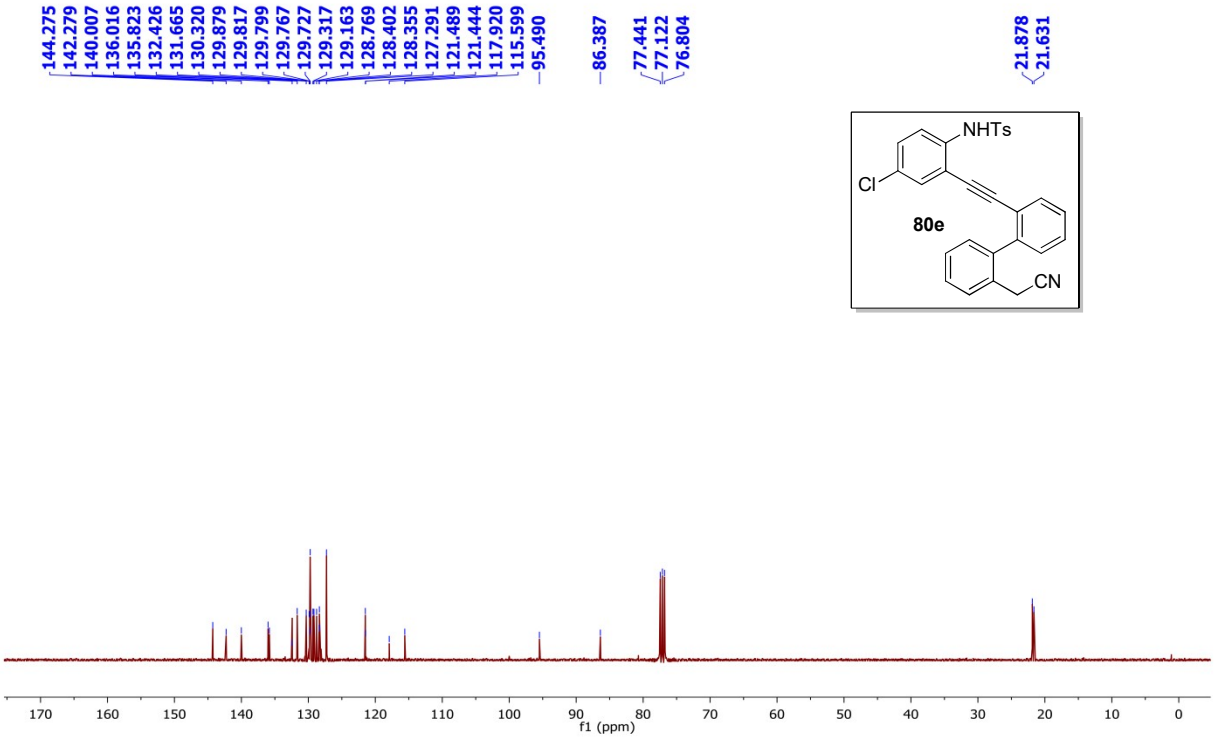
^{13}C{^{1}H} NMR (150 MHz) of **80d :**



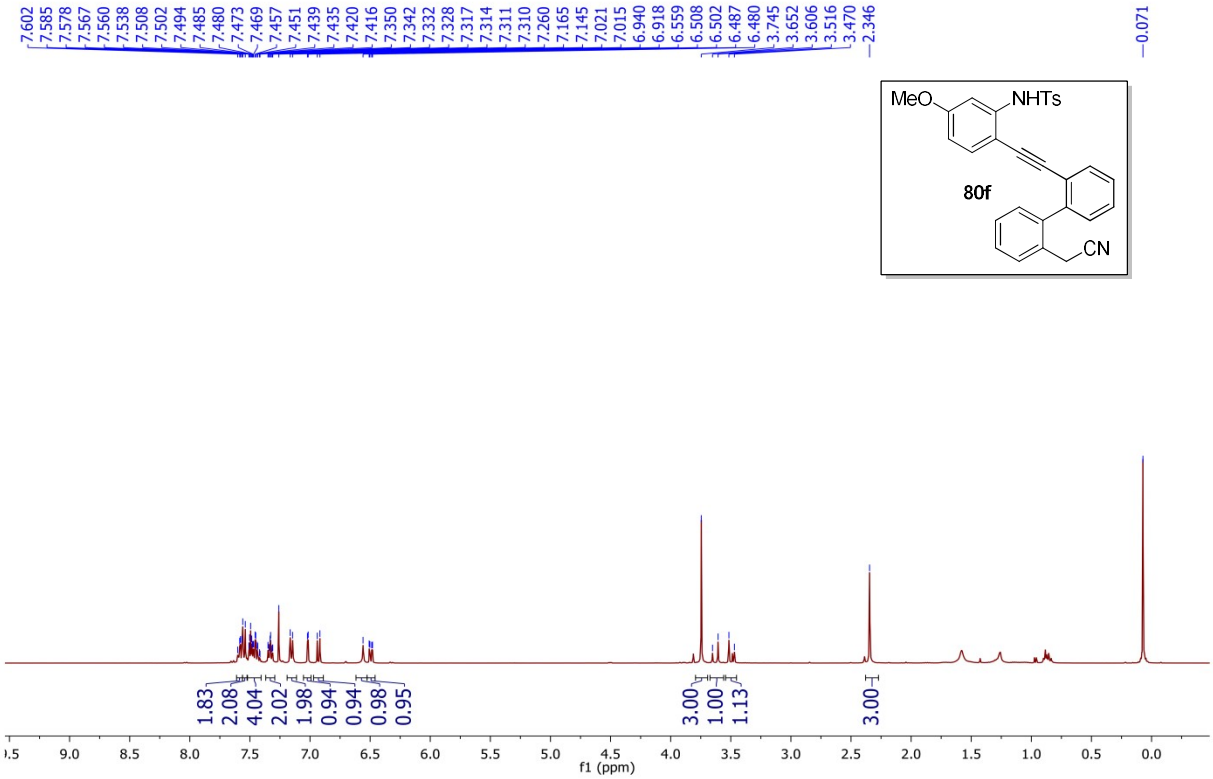
^{1}H NMR (400 MHz) of **80e :**



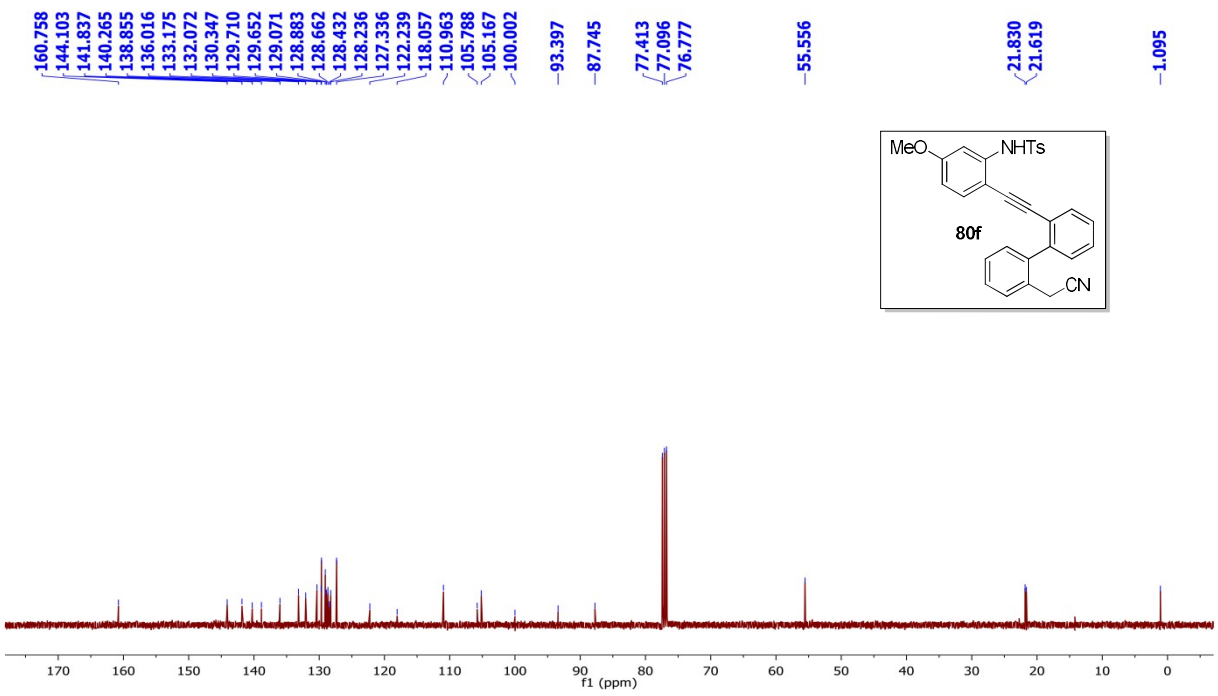
^{13}C{^{1}H} NMR (100 MHz) of **80e :**



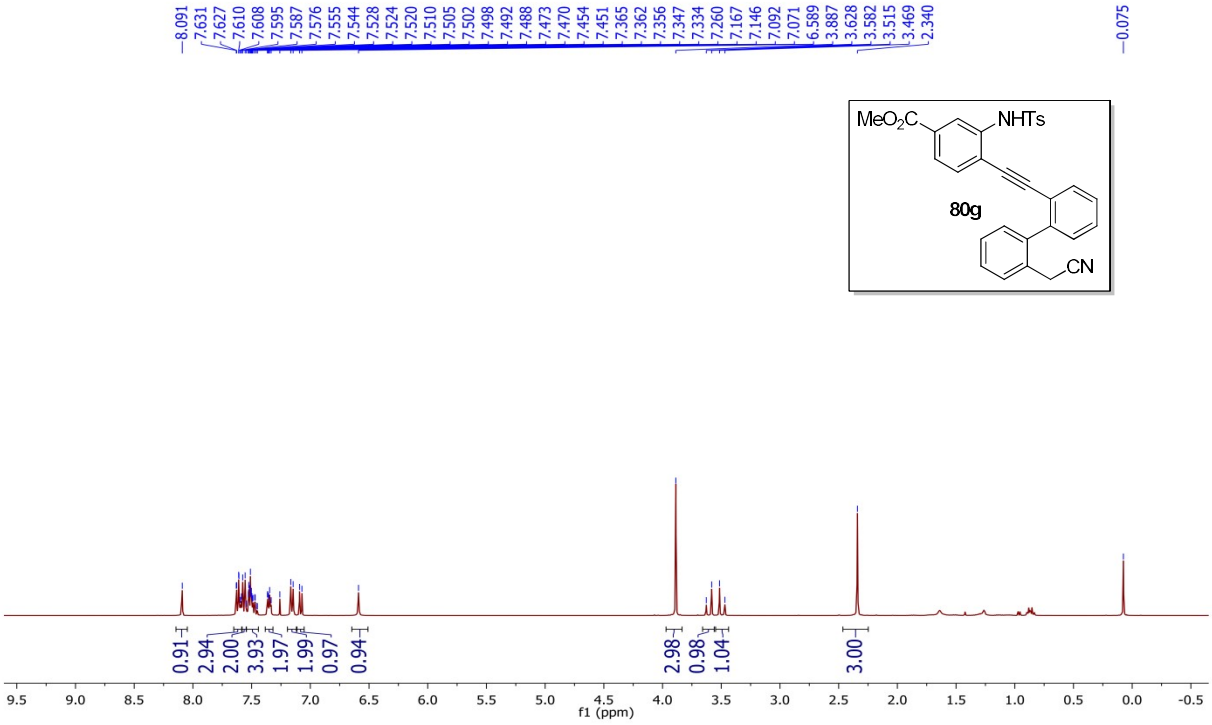
^{1}H NMR (400 MHz) of **80f :**



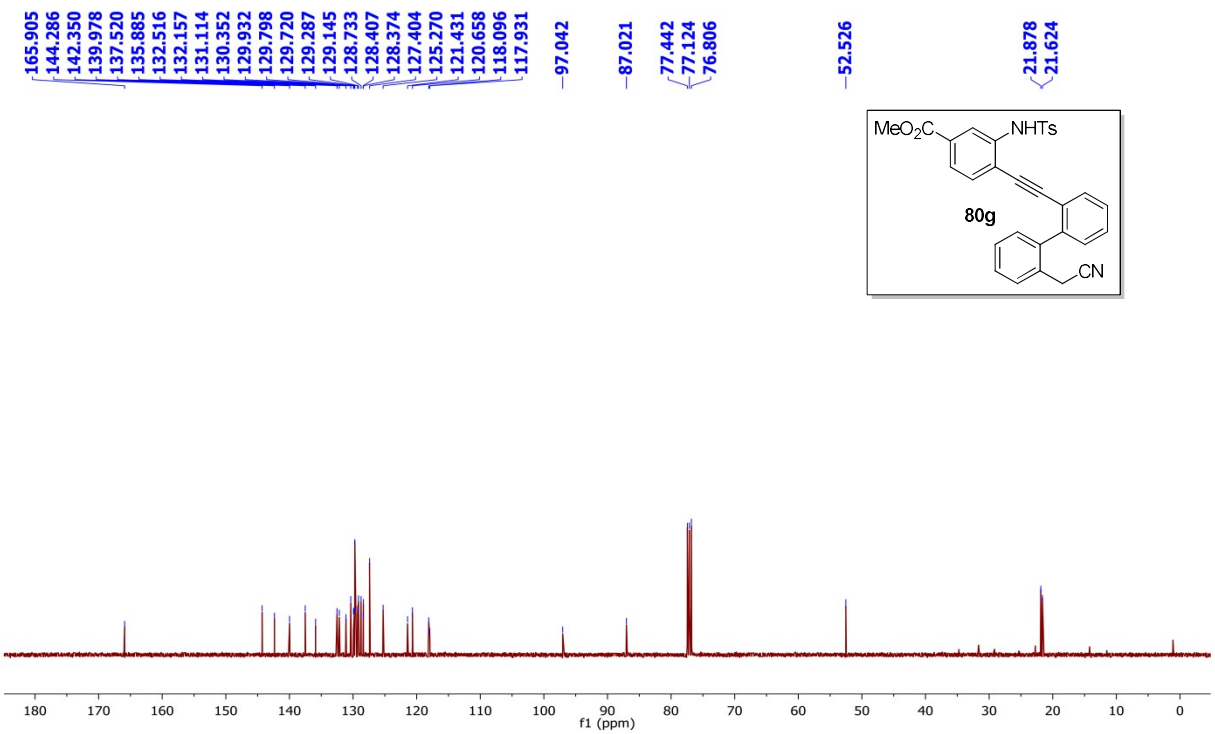
^{13}C{^{1}H} NMR (100 MHz) of **80f :**



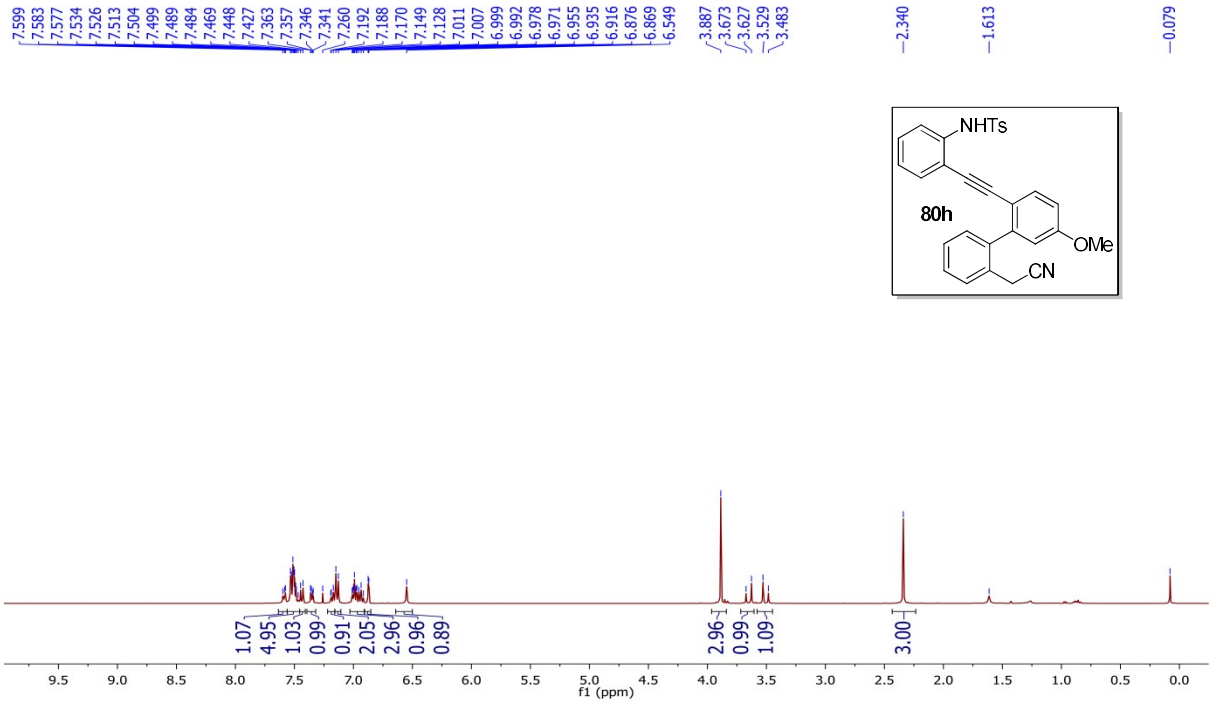
^{1}H NMR (400 MHz) of **80g :**



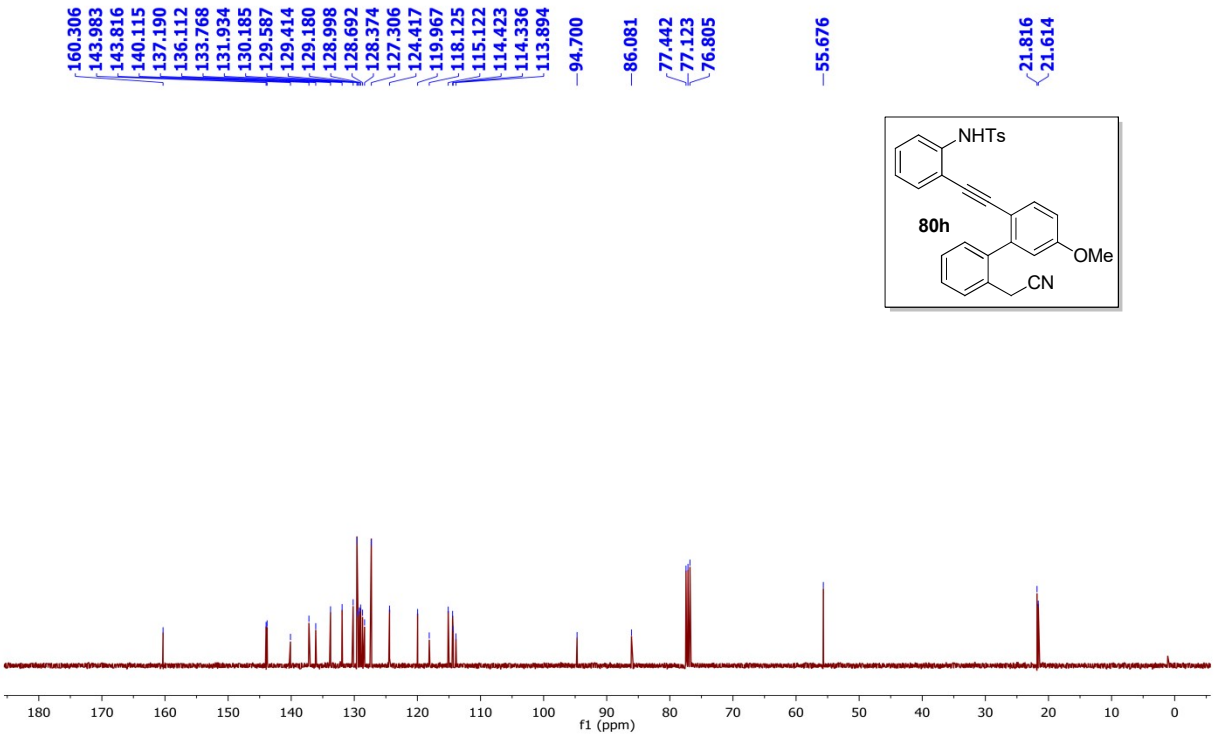
^{13}C{^{1}H} NMR (100 MHz) of **80g :**



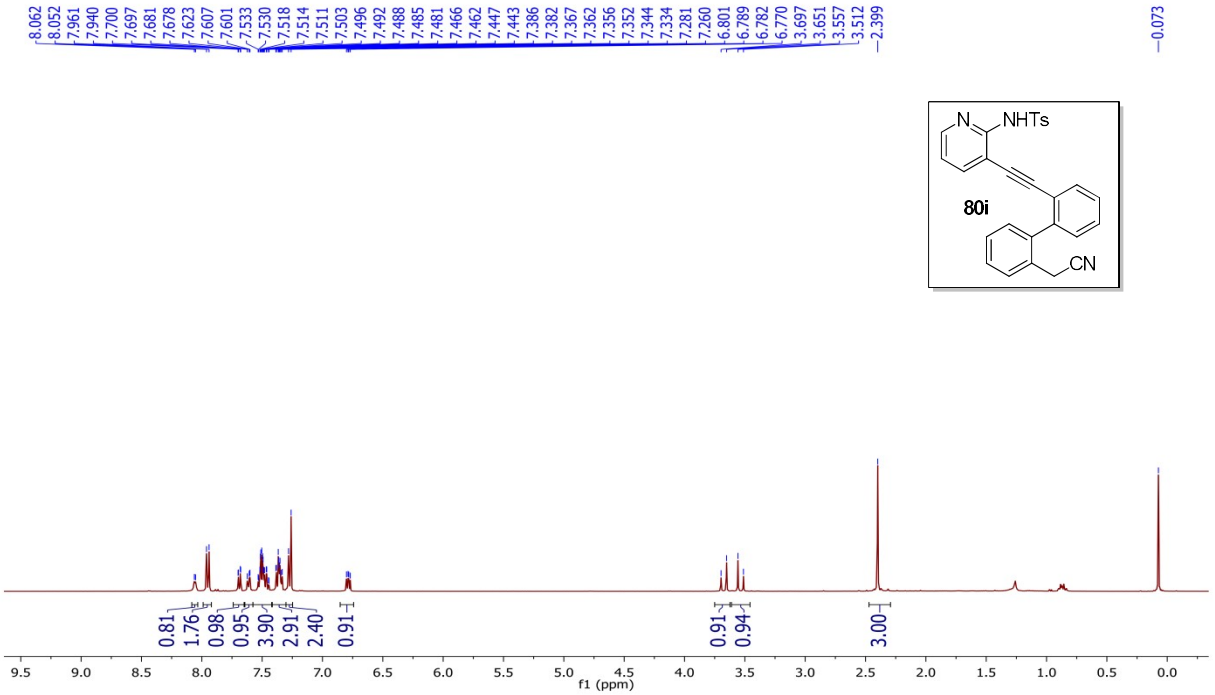
^{1}H NMR (400 MHz) of **80h :**



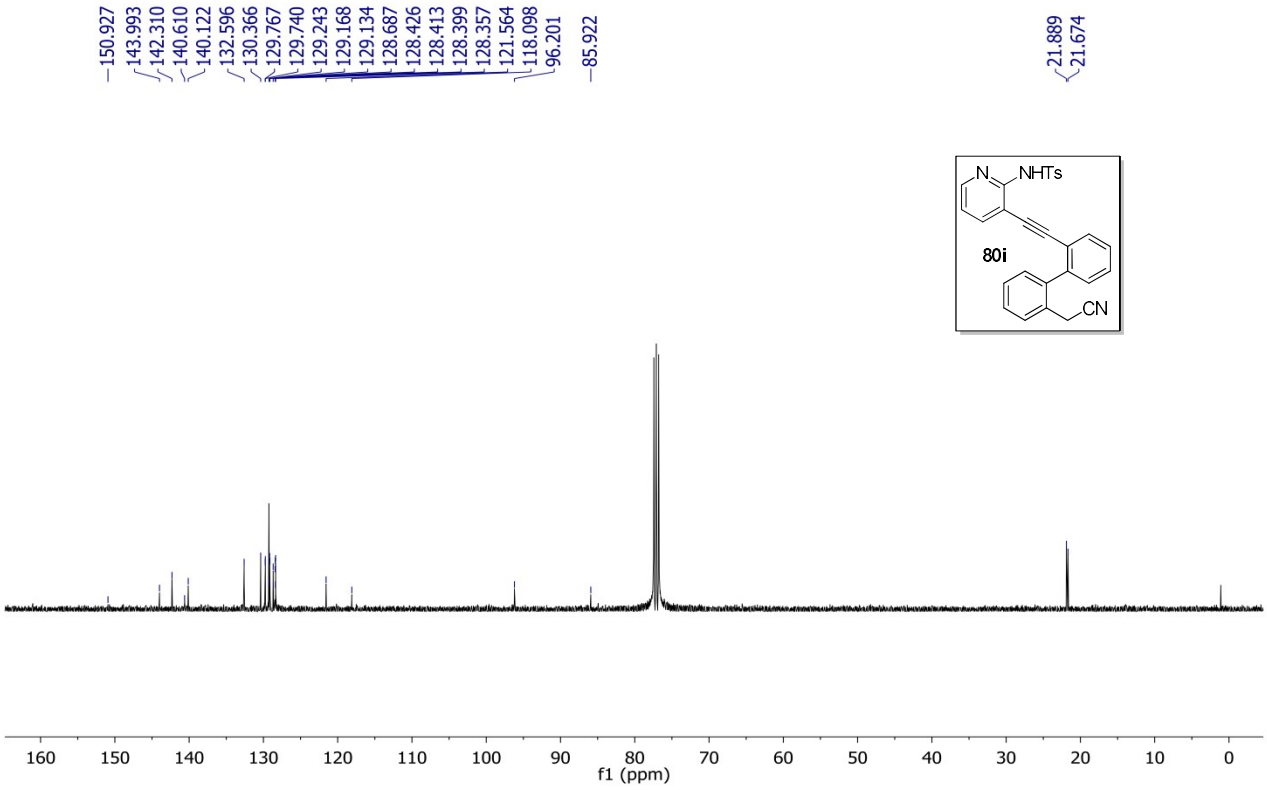
^{13}C{^{1}H} NMR (100 MHz) of **80h :**



^{1}H NMR (400 MHz) of **80i :**

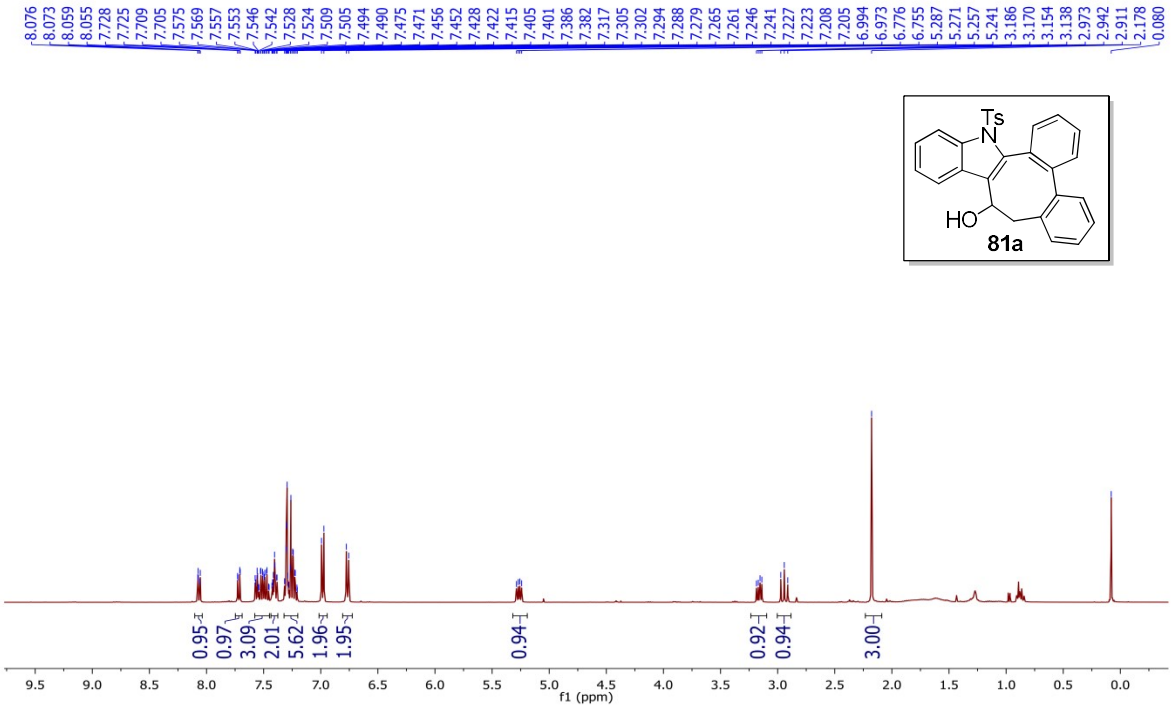


^{13}C{^{1}H} NMR (100 MHz) of **80i :**

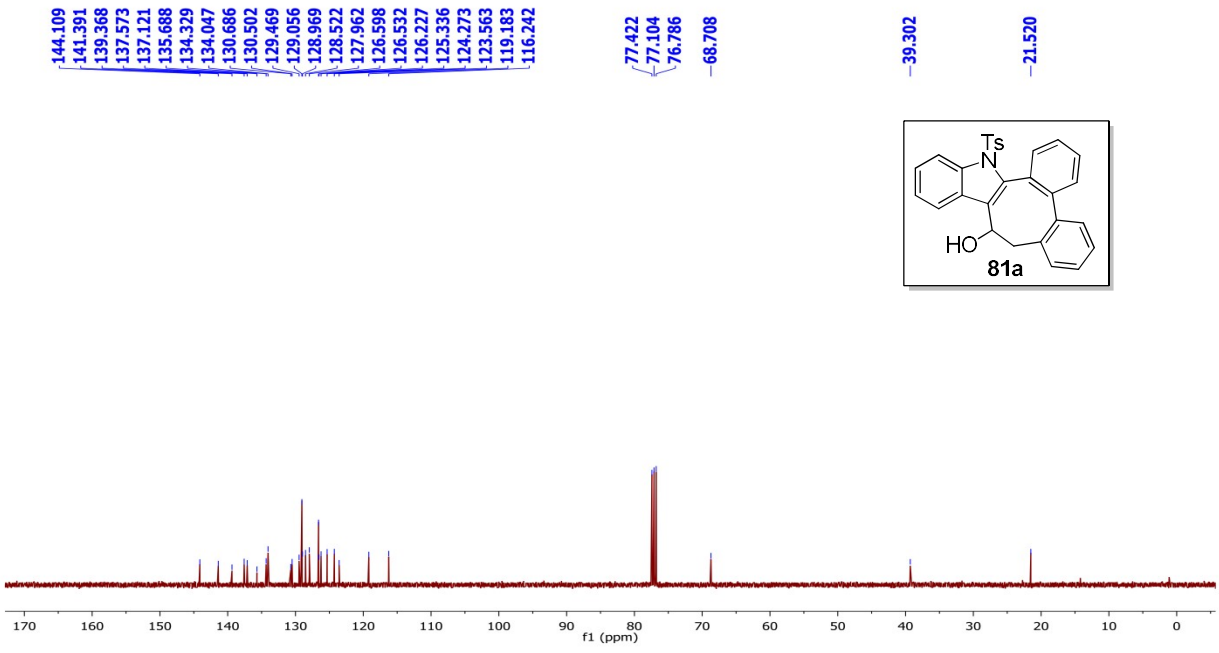


1.2.11.3. NMR Spectra of Compounds 81a-q:

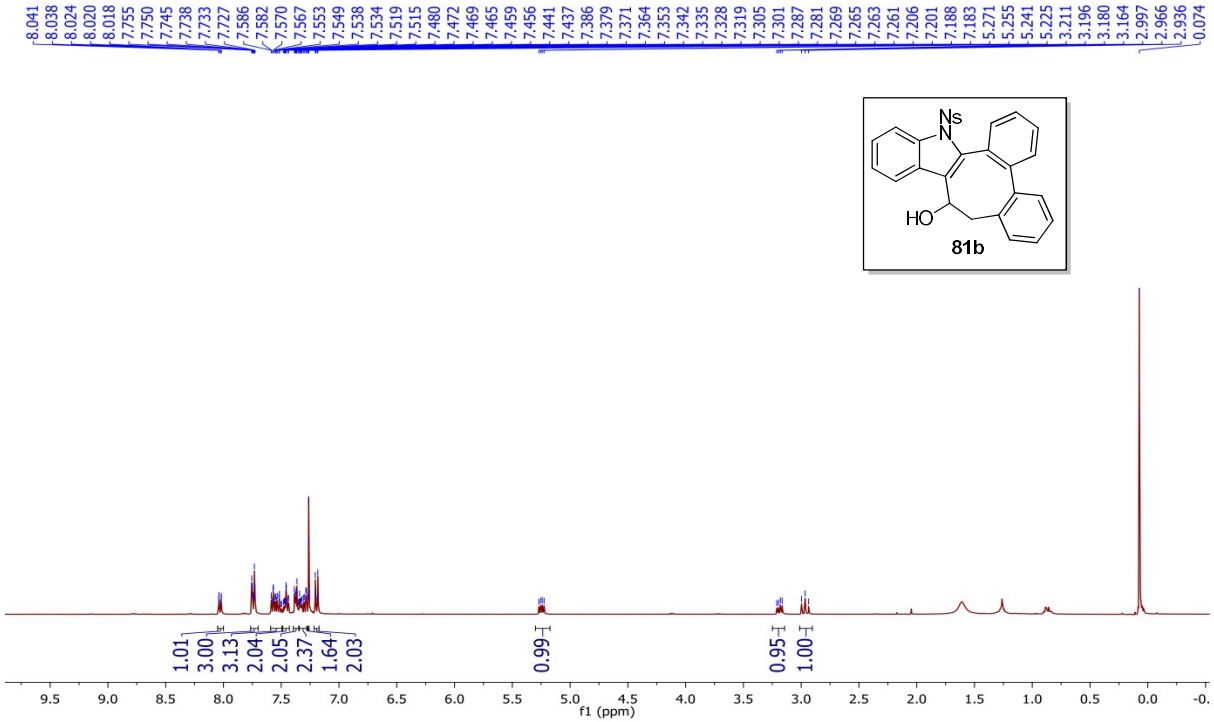
^{1}H NMR (400 MHz) of **81a :**



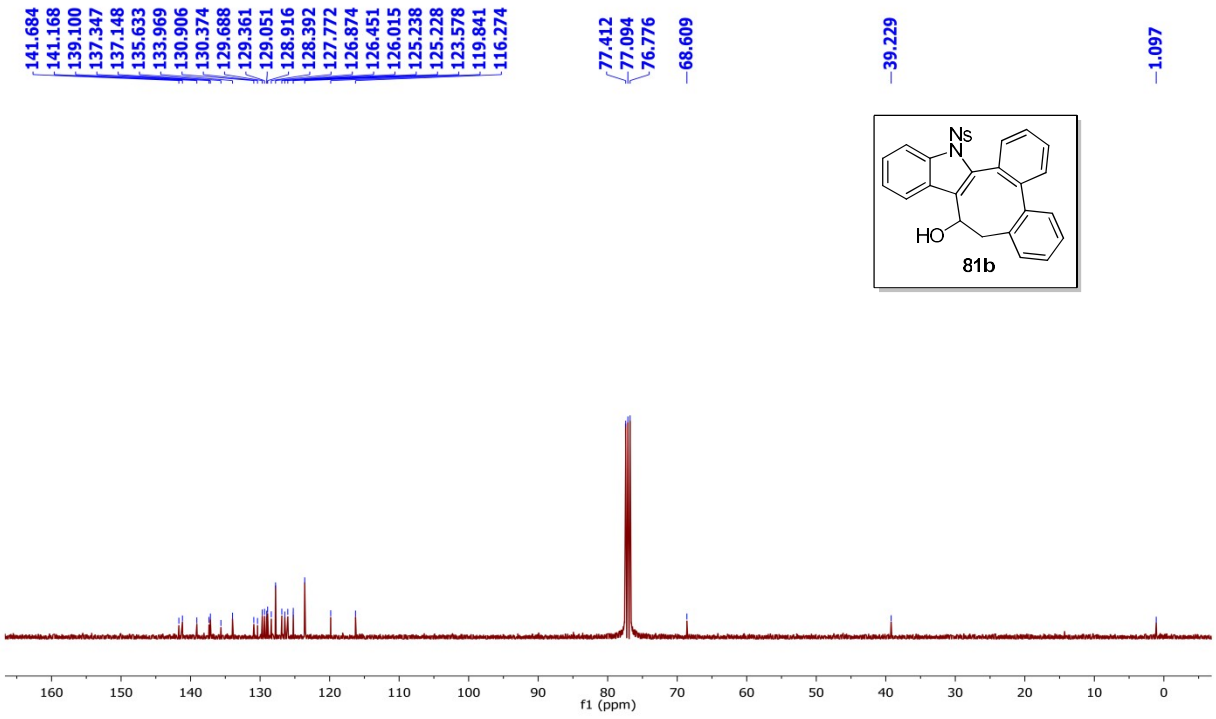
^{13}C{^{1}H} NMR (100 MHz) of **81a :**



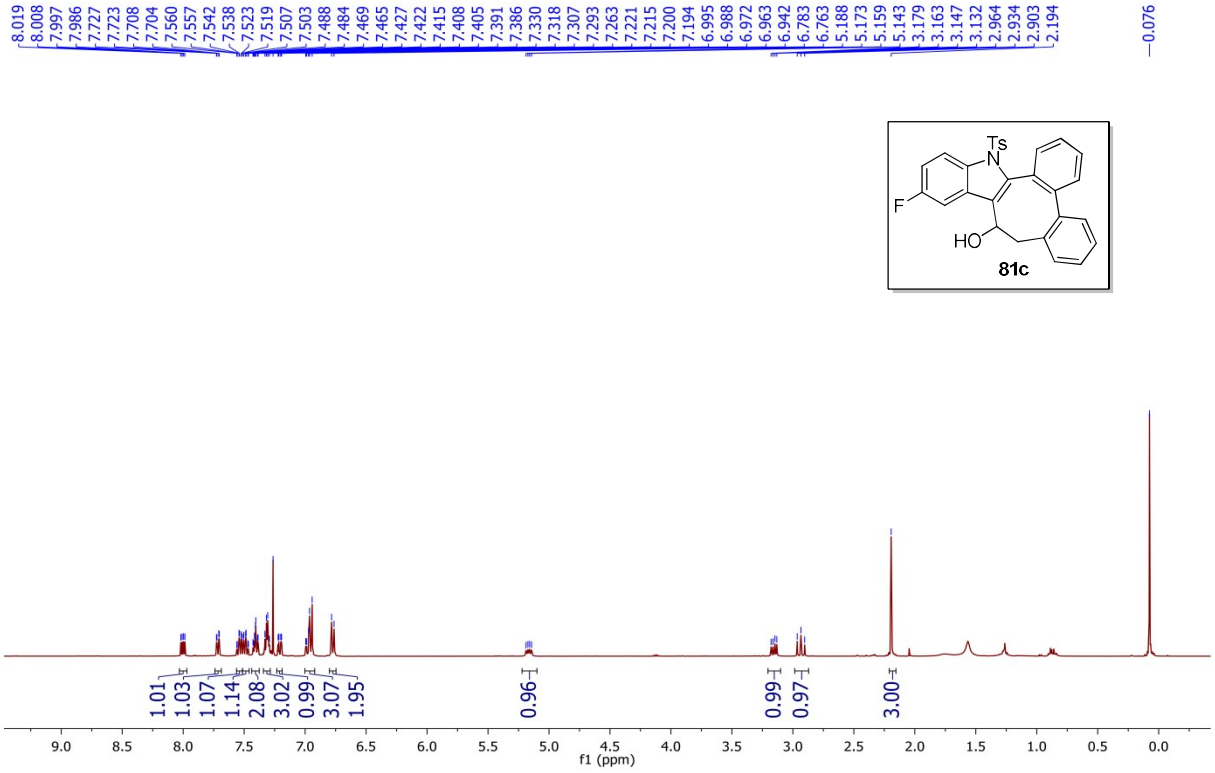
^{1}H NMR (400 MHz) of **81b :**



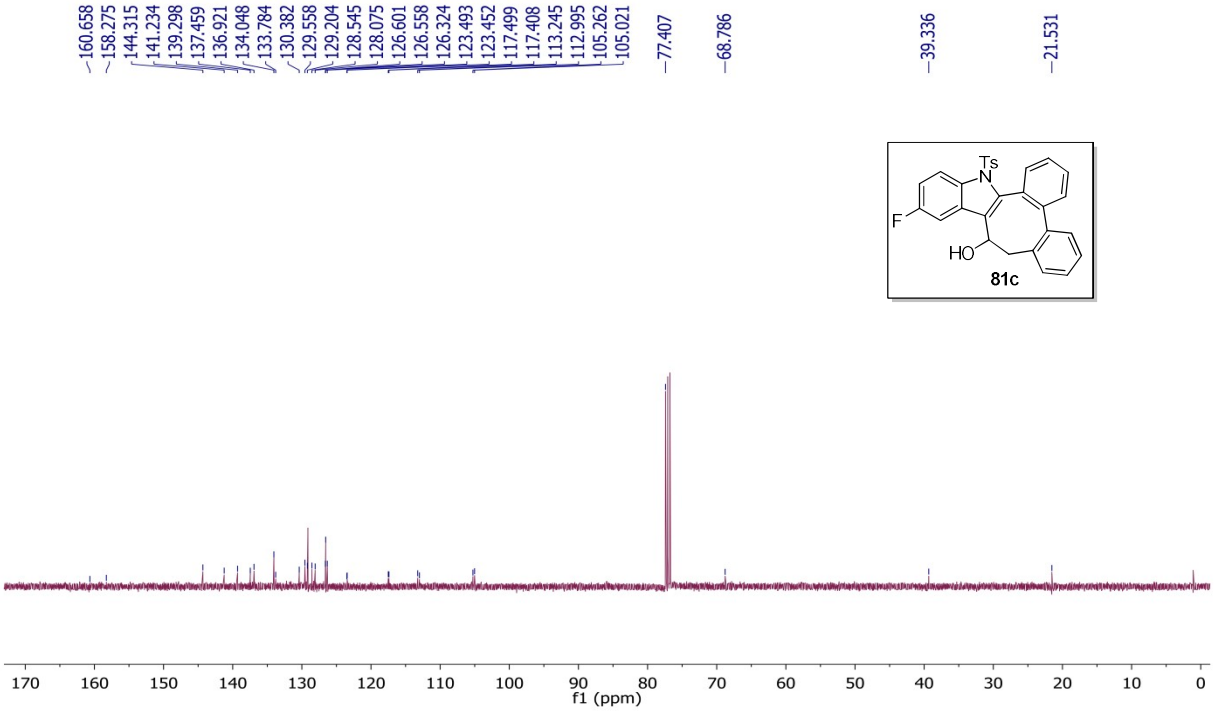
^{13}C{^{1}H} NMR (100 MHz) of **81b :**



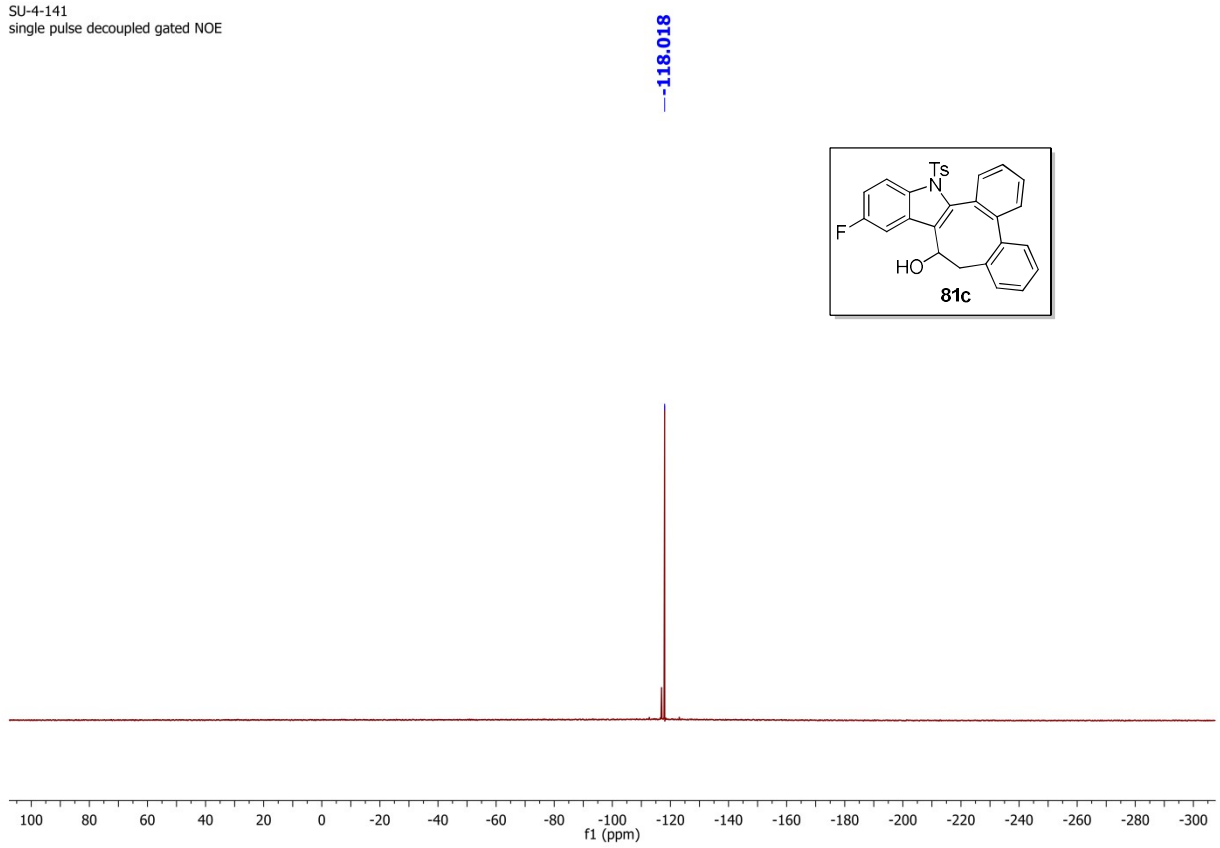
^{1}H NMR (400 MHz) of **81c :**



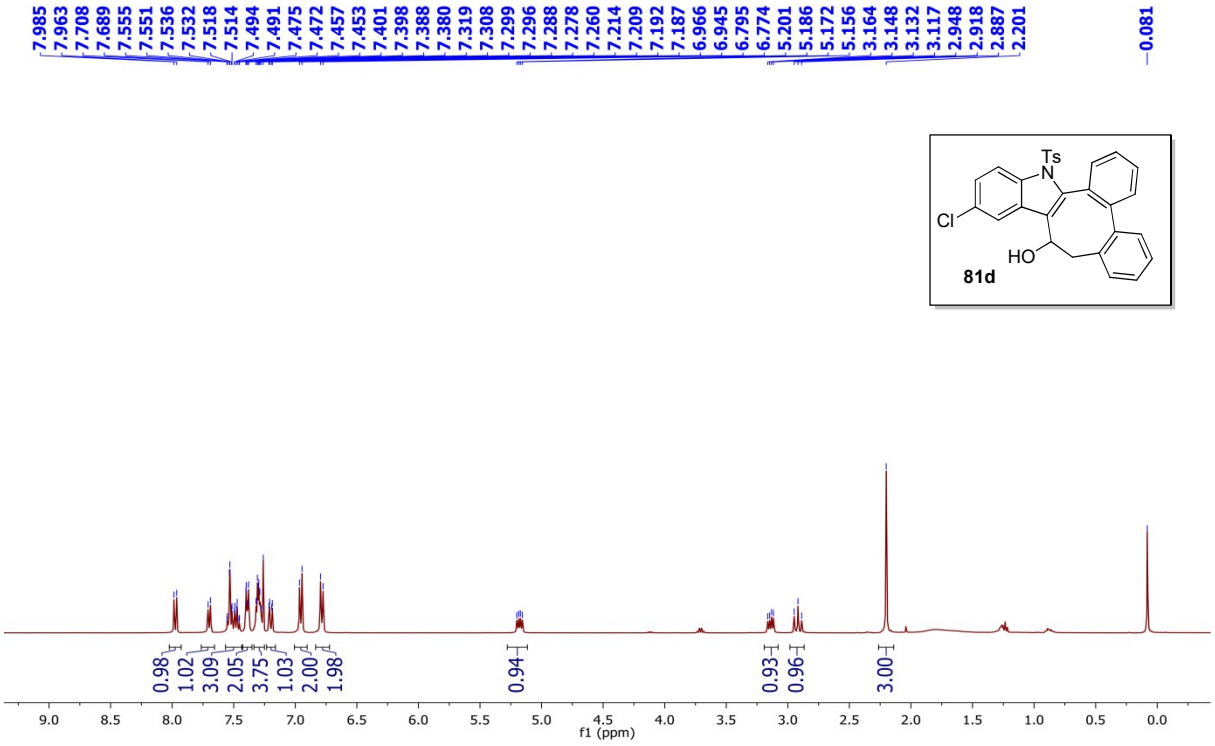
^{13}C{^{1}H} NMR (100 MHz) of **81c :**



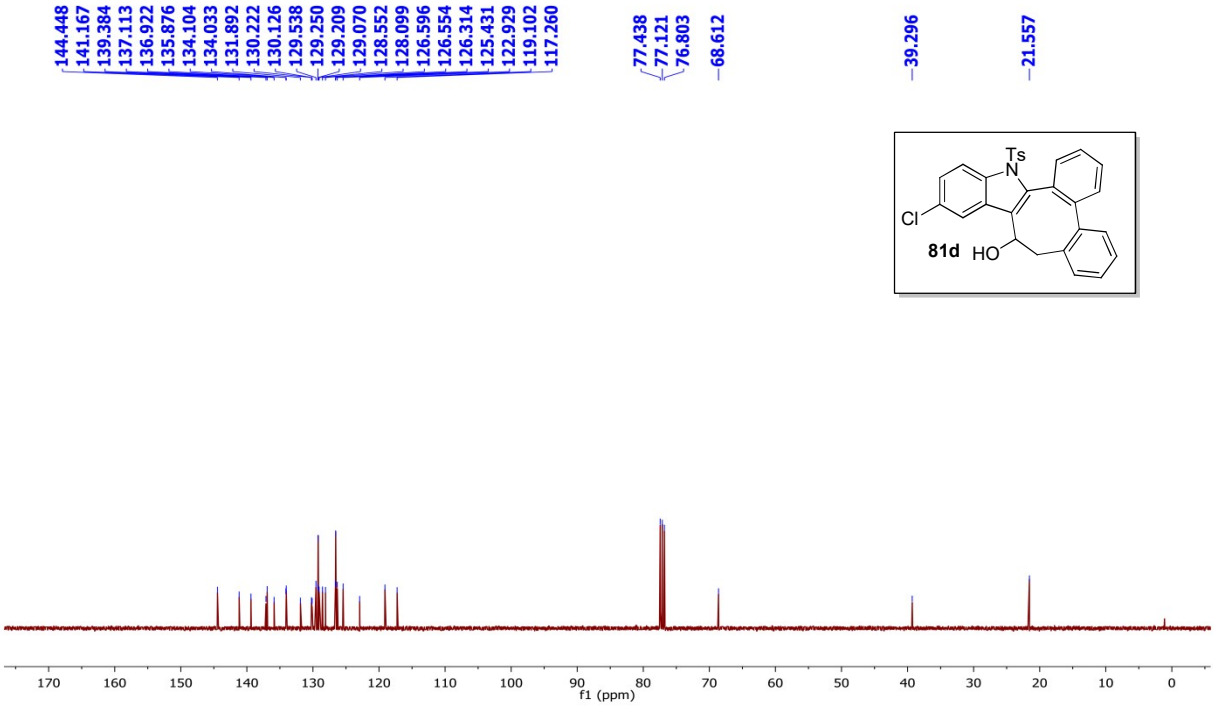
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **81c**:



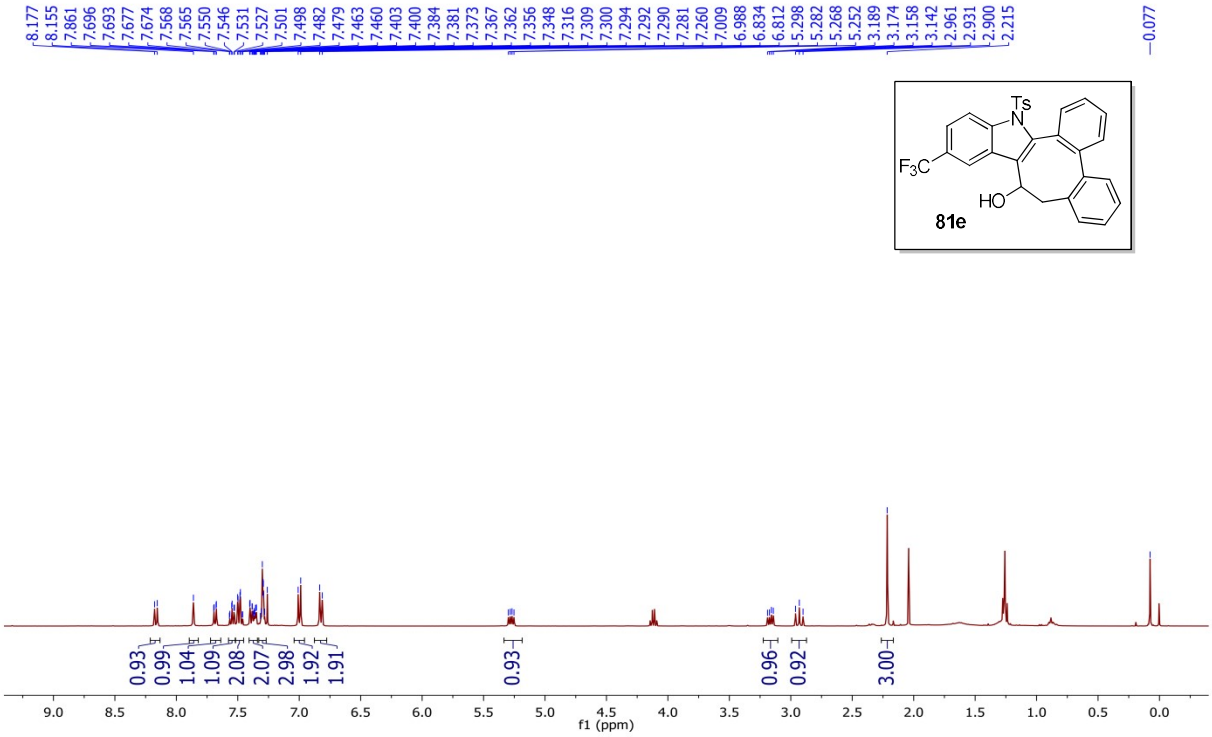
^{1}H NMR (400 MHz) of **81d :**



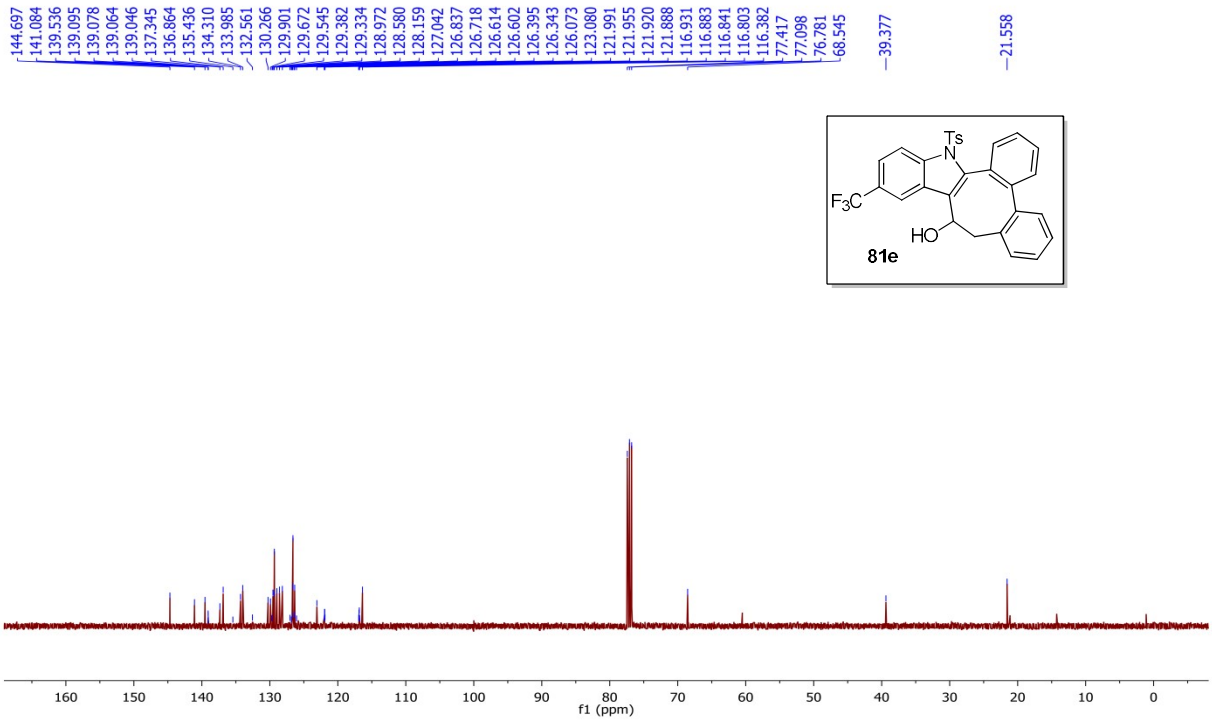
^{13}C{^{1}H} NMR (100 MHz) of **81d :**



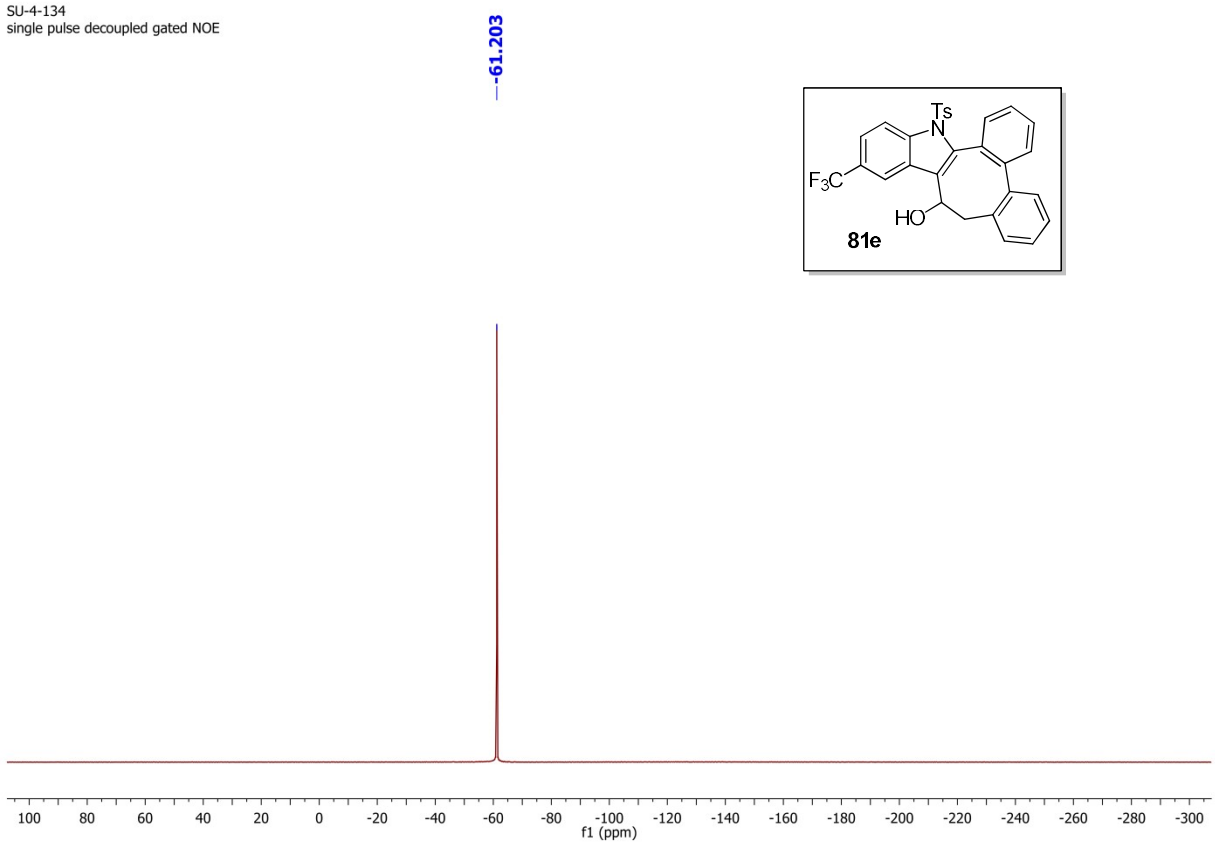
^{1}H NMR (400 MHz) of **81e :**



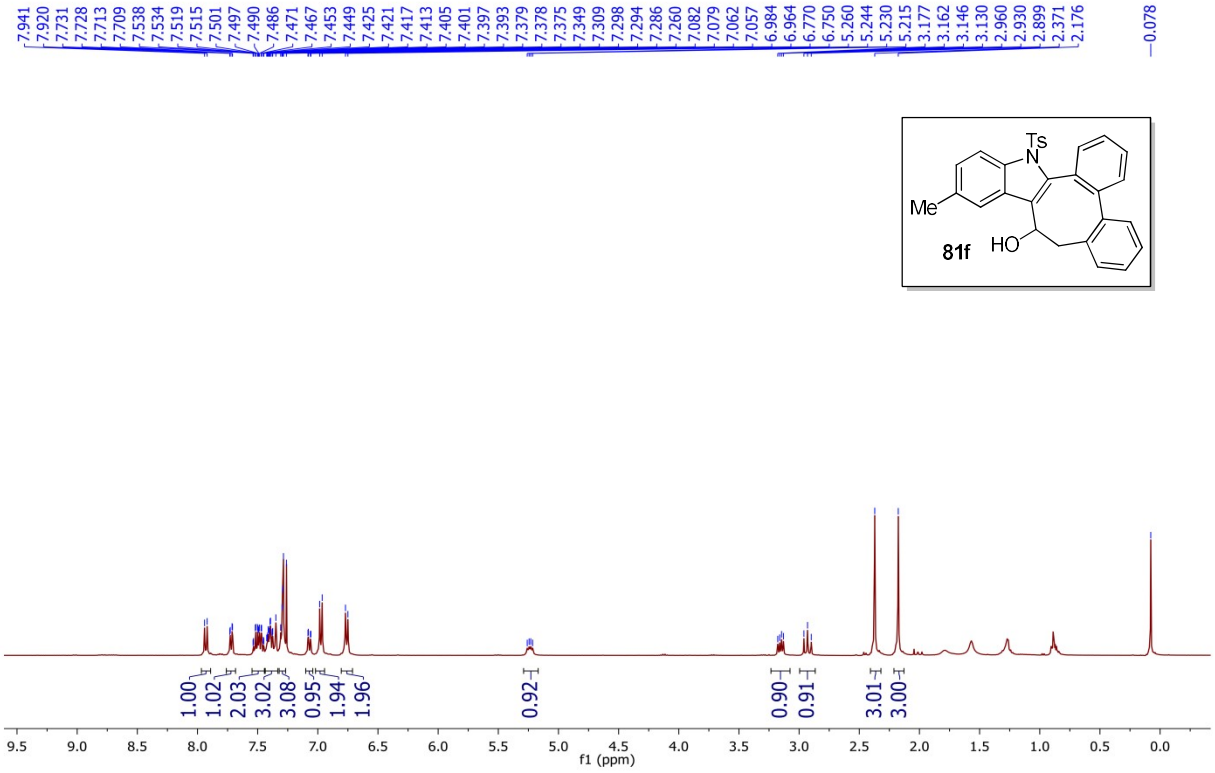
^{13}C{^{1}H} NMR (100 MHz) of **81e :**



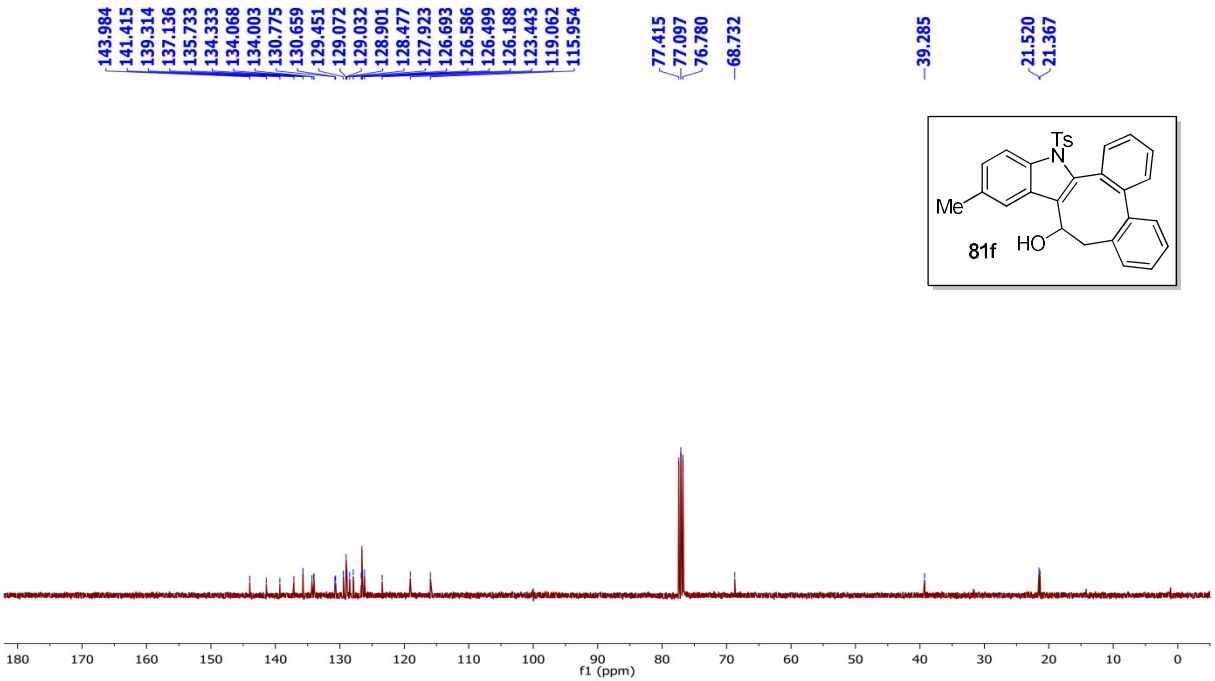
$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) **81e :**



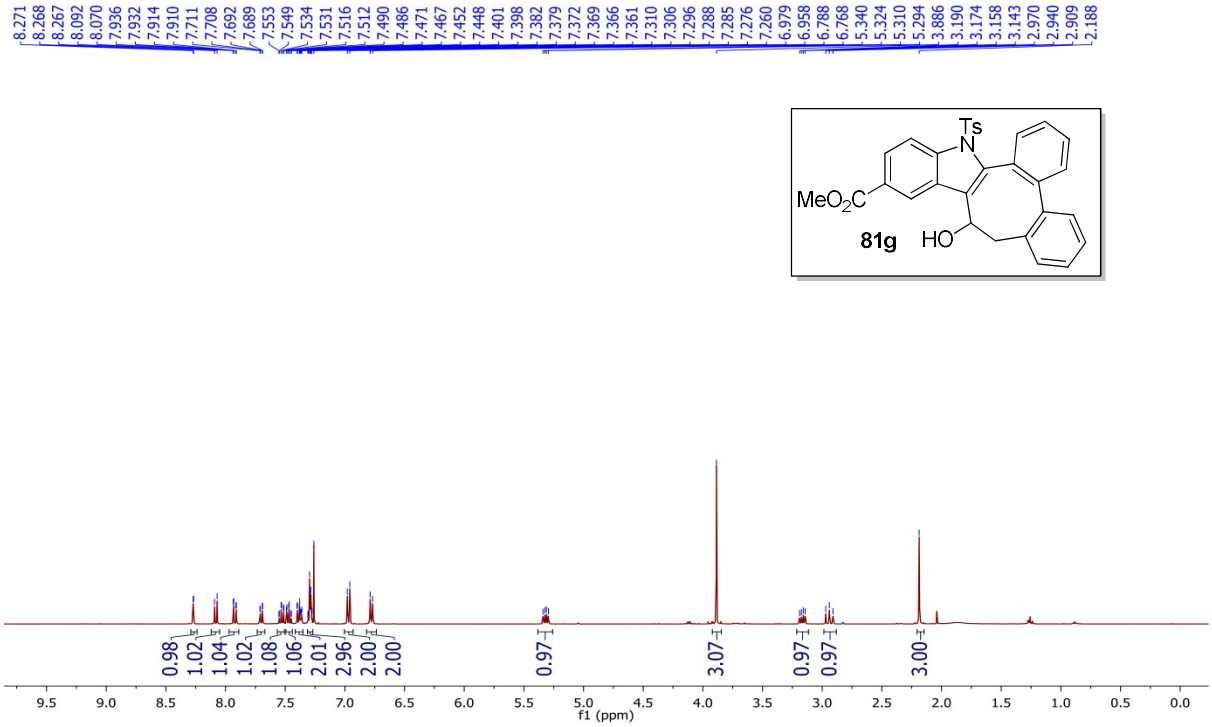
^{1}H NMR (400 MHz) of **81f :**



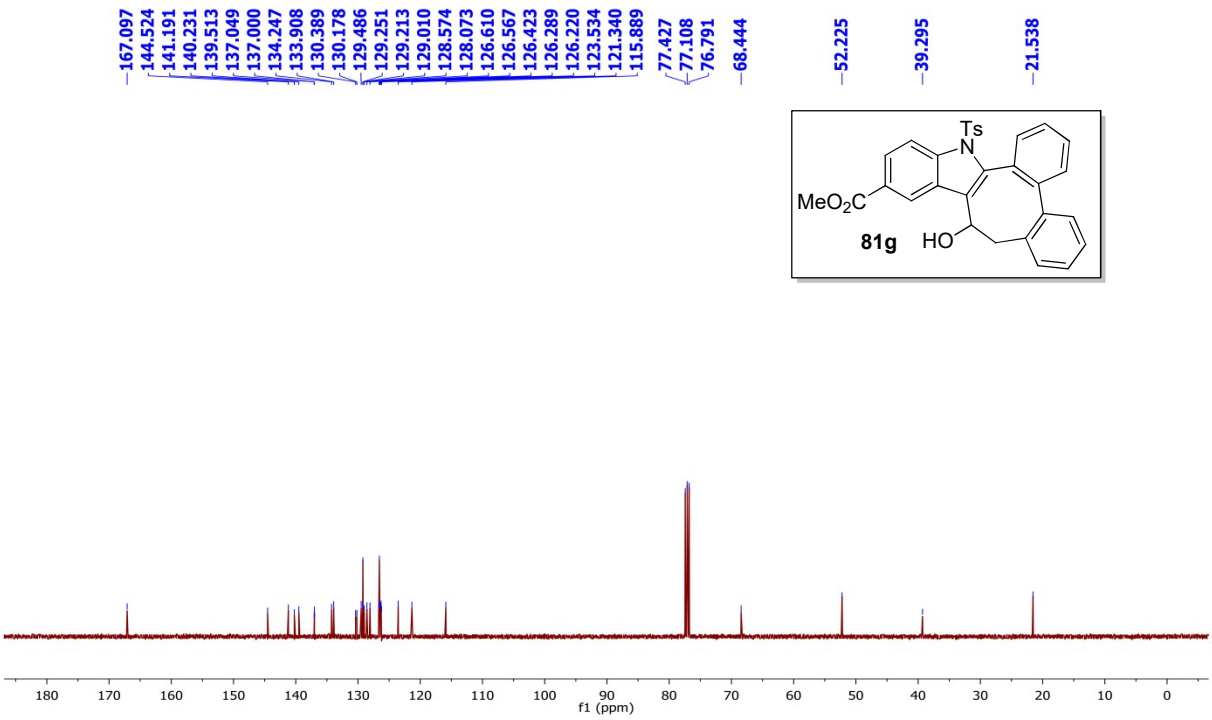
^{13}C{^{1}H} NMR (100 MHz) of **81f :**



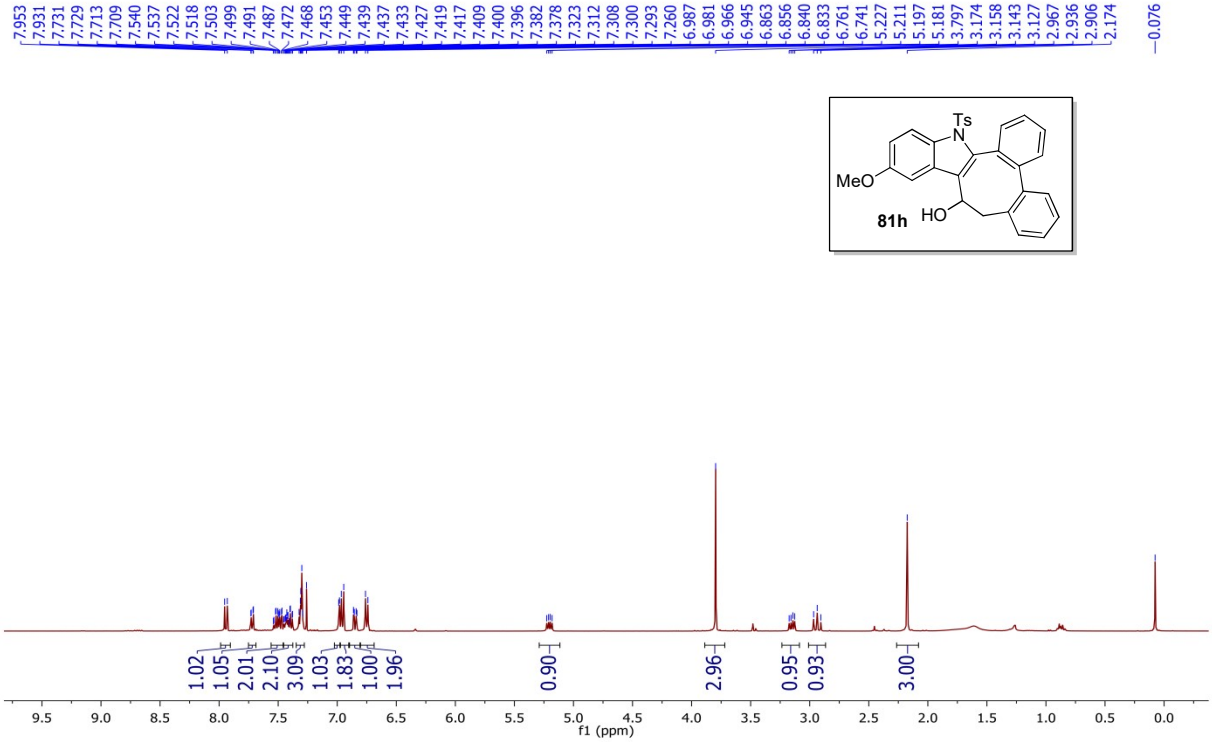
^{1}H NMR (400 MHz) of **81g :**



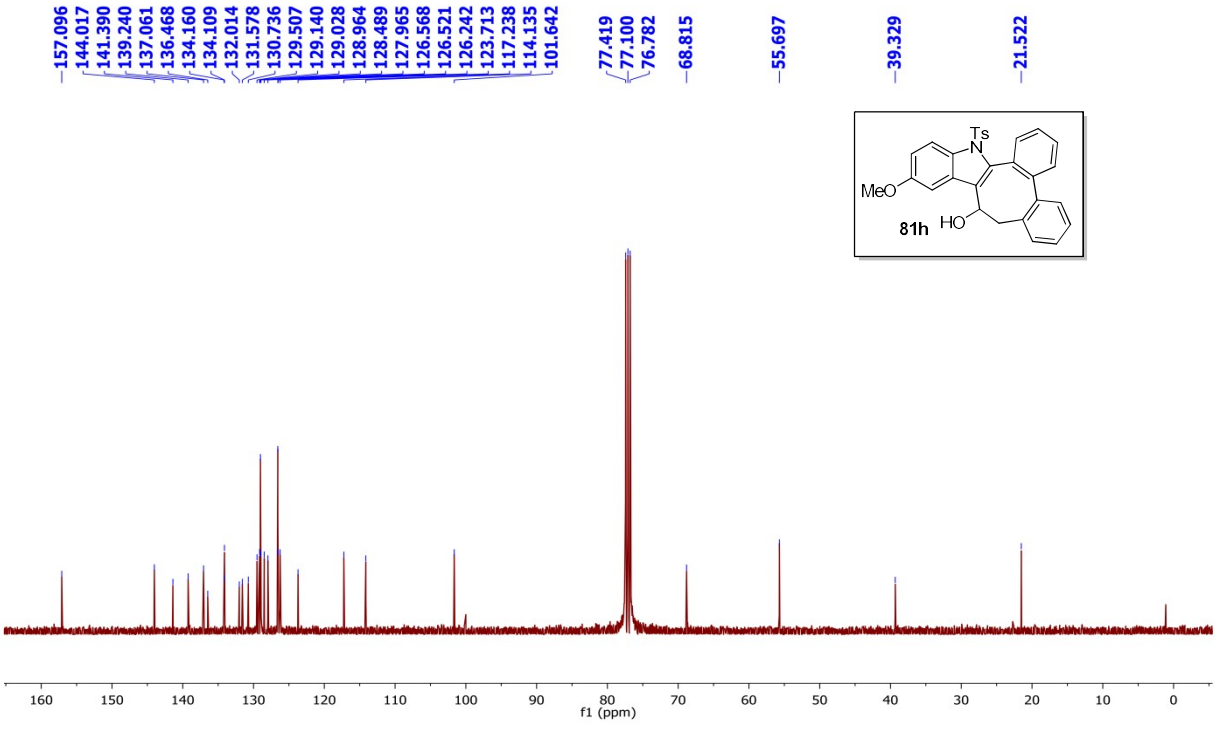
^{13}C{^{1}H} NMR (100 MHz) of **81g :**



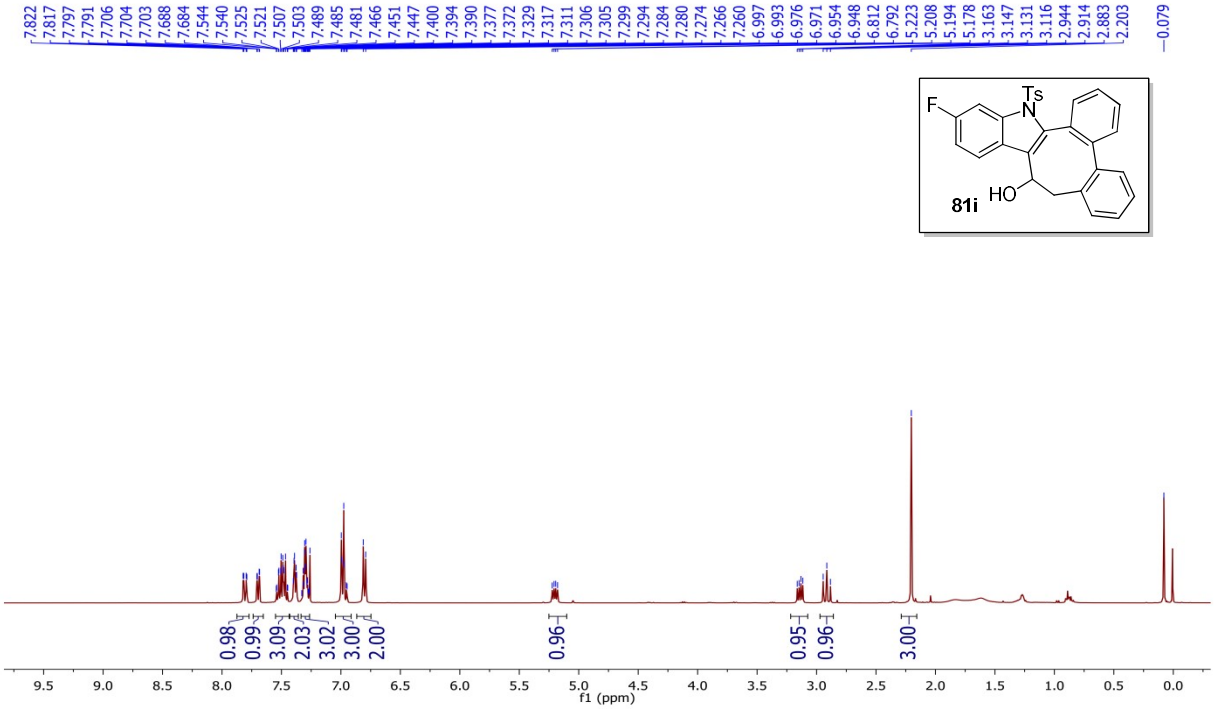
^{1}H NMR (400 MHz) of **81h :**



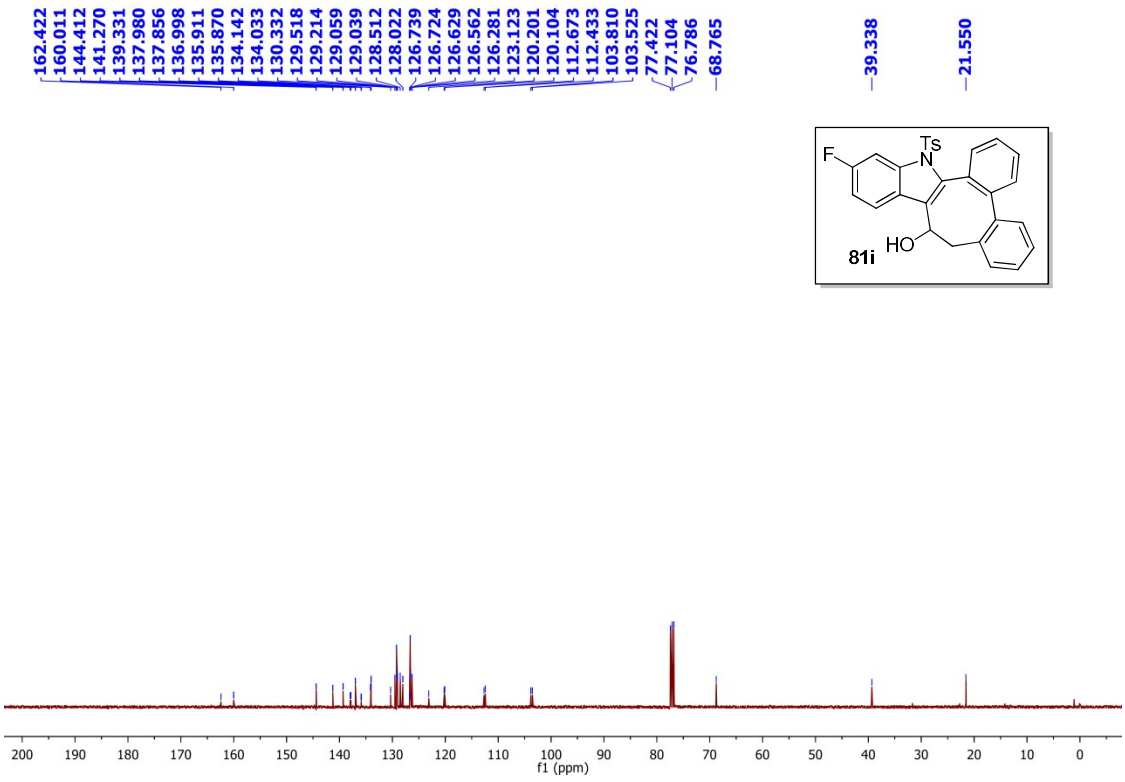
^{13}C{^{1}H} NMR (100 MHz) of **81h :**



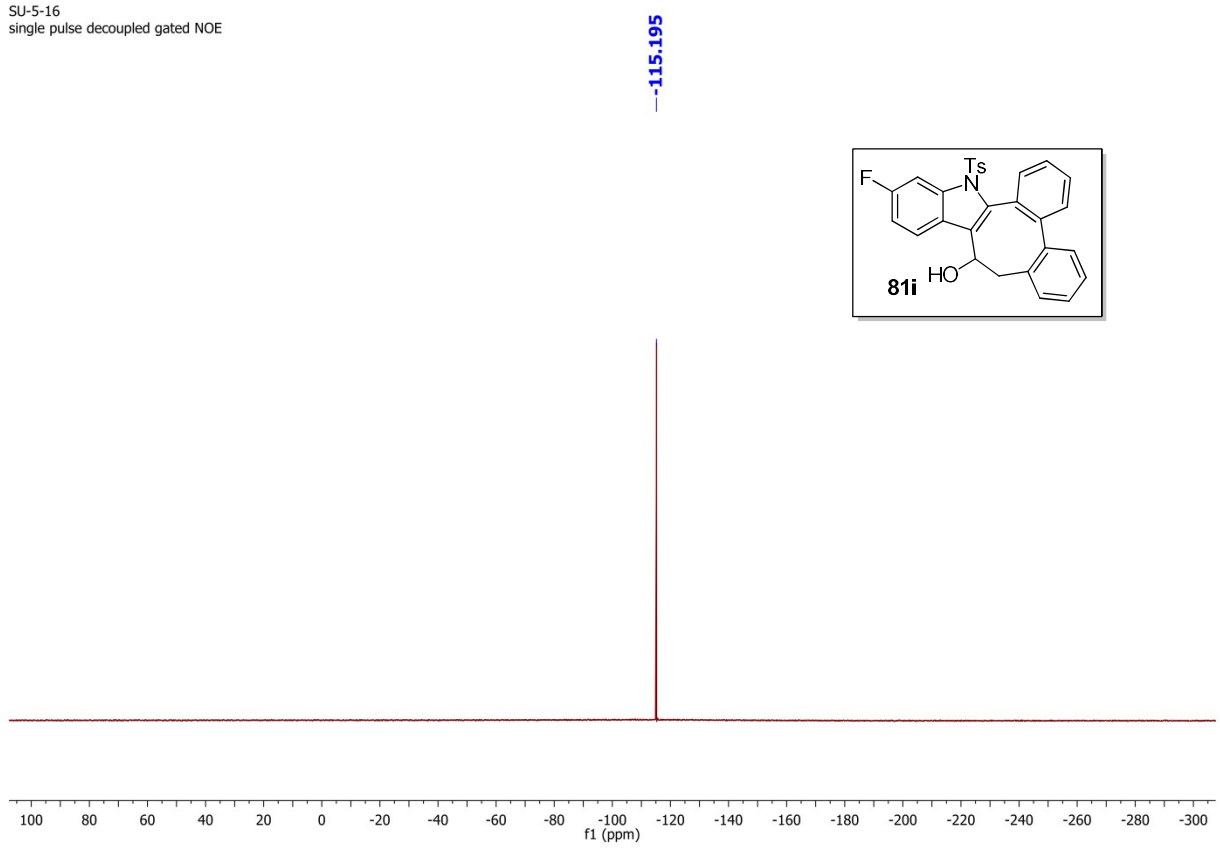
^{1}H NMR (400 MHz) of **81i :**



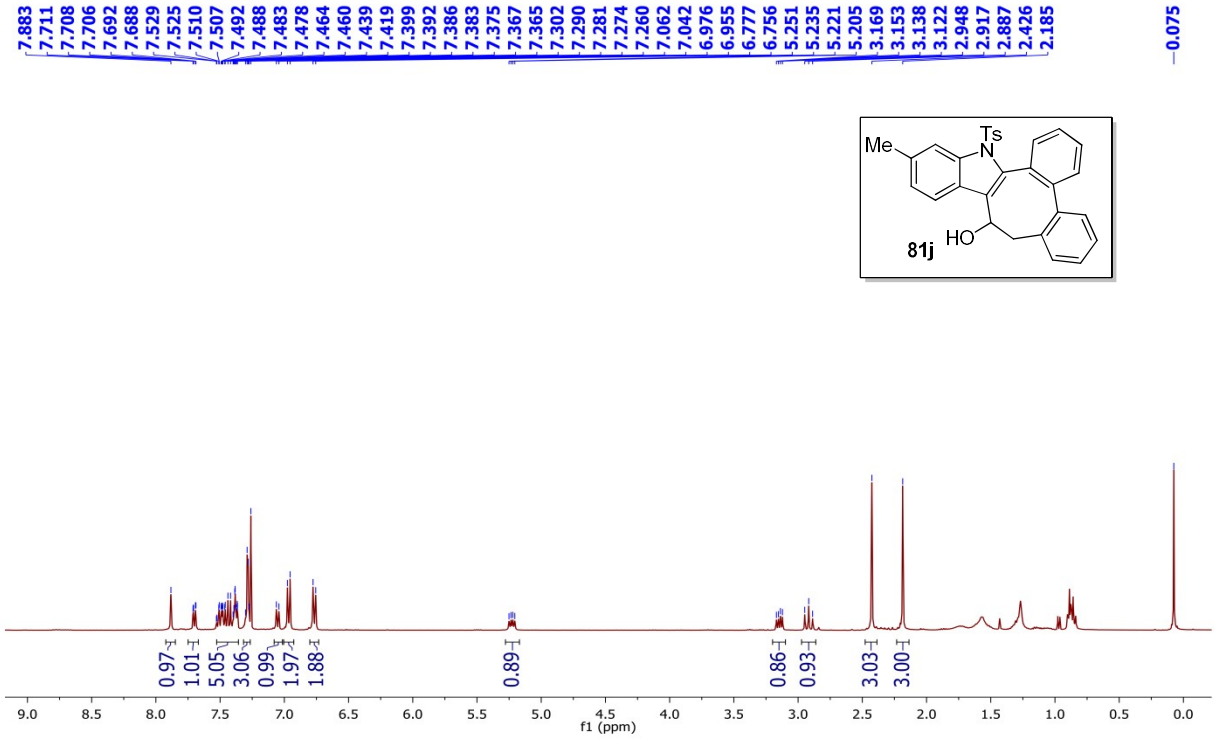
^{13}C{^{1}H} NMR (100 MHz) of **81i :**



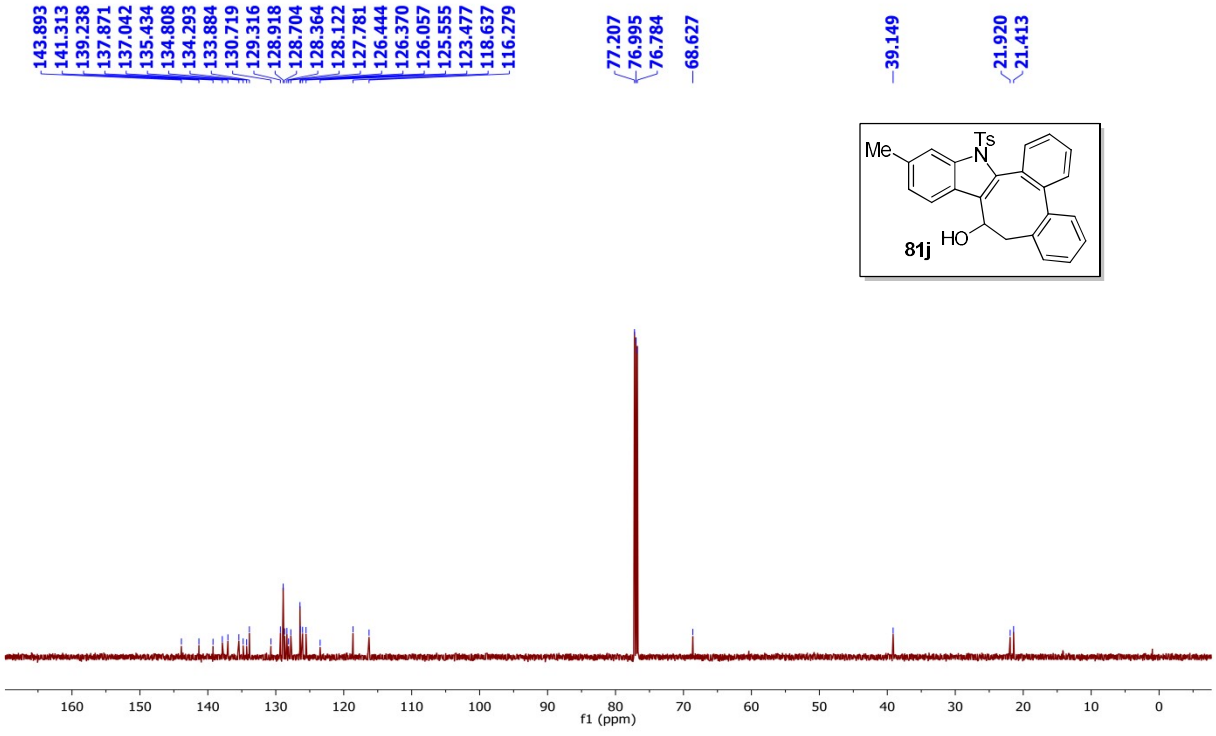
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **81i** :



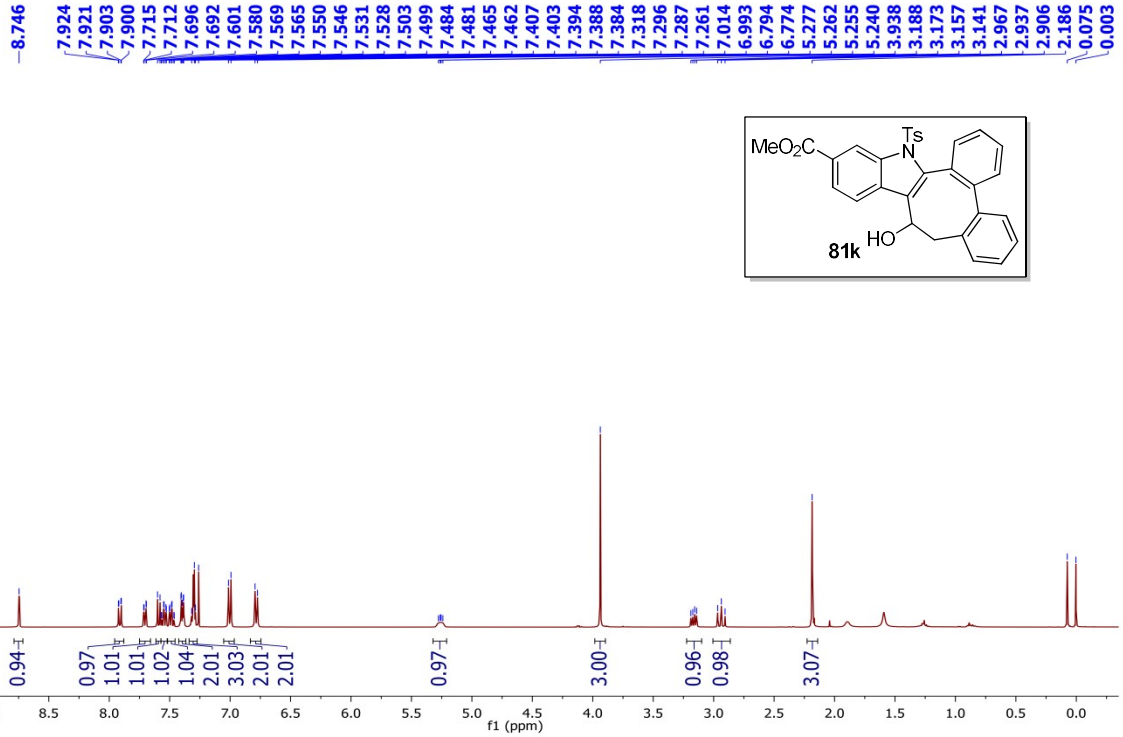
^{1}H NMR (400 MHz) of **81j :**



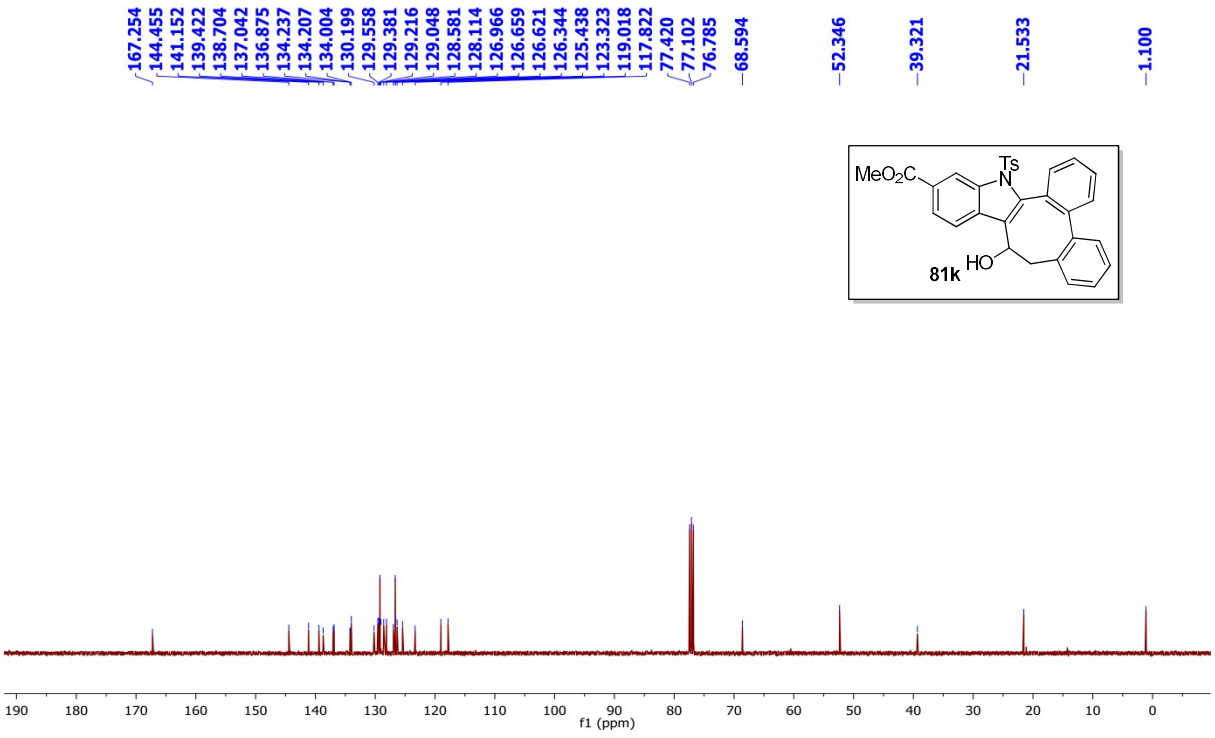
^{13}C{^{1}H} NMR (150 MHz) of **81j :**



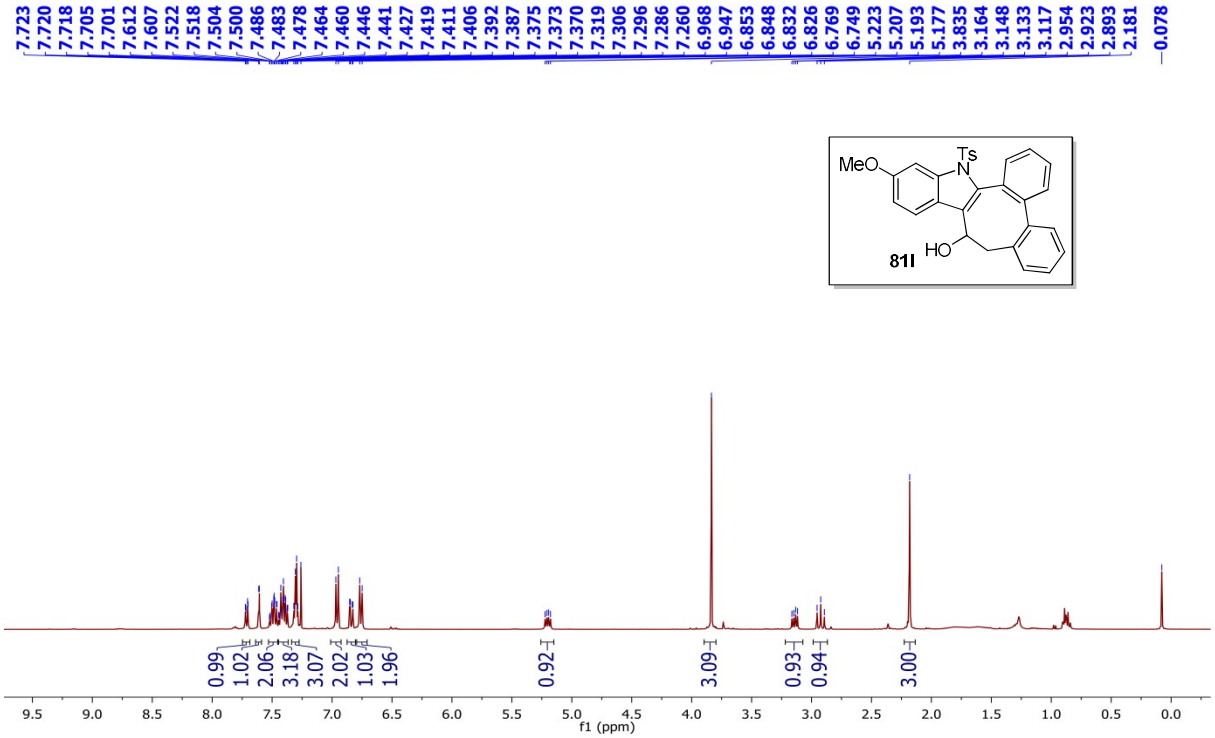
^{1}H NMR (400 MHz) of **81k :**



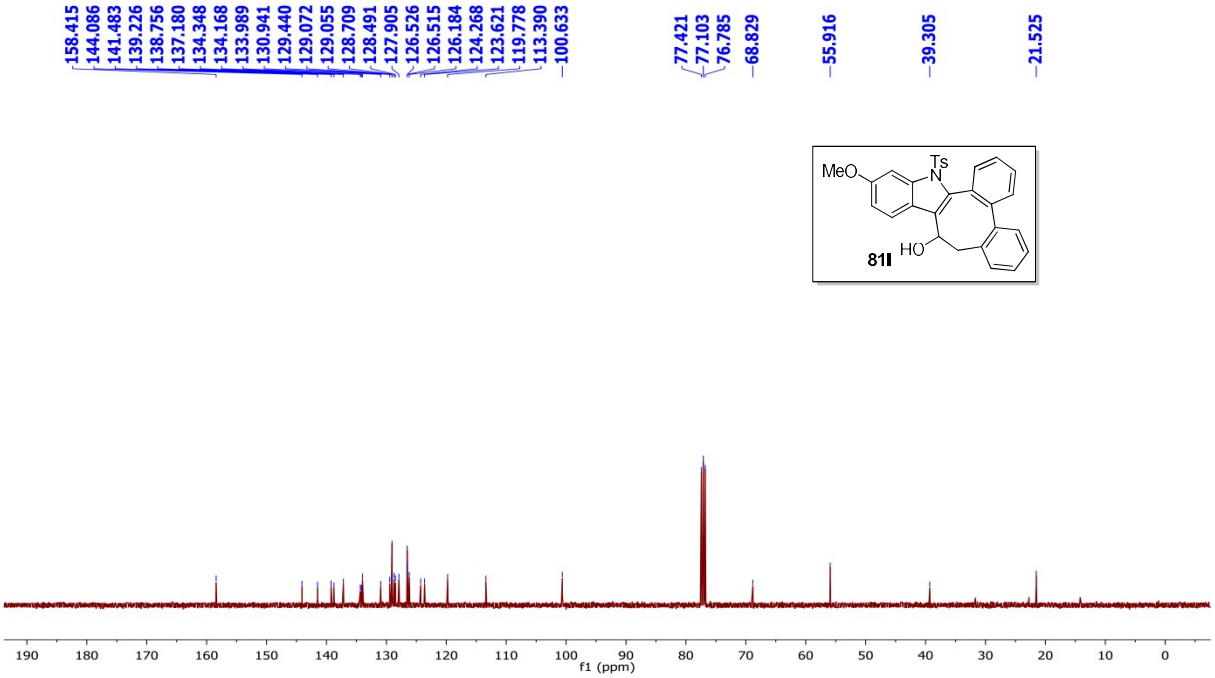
^{13}C{^{1}H} NMR (100 MHz) of **81k :**



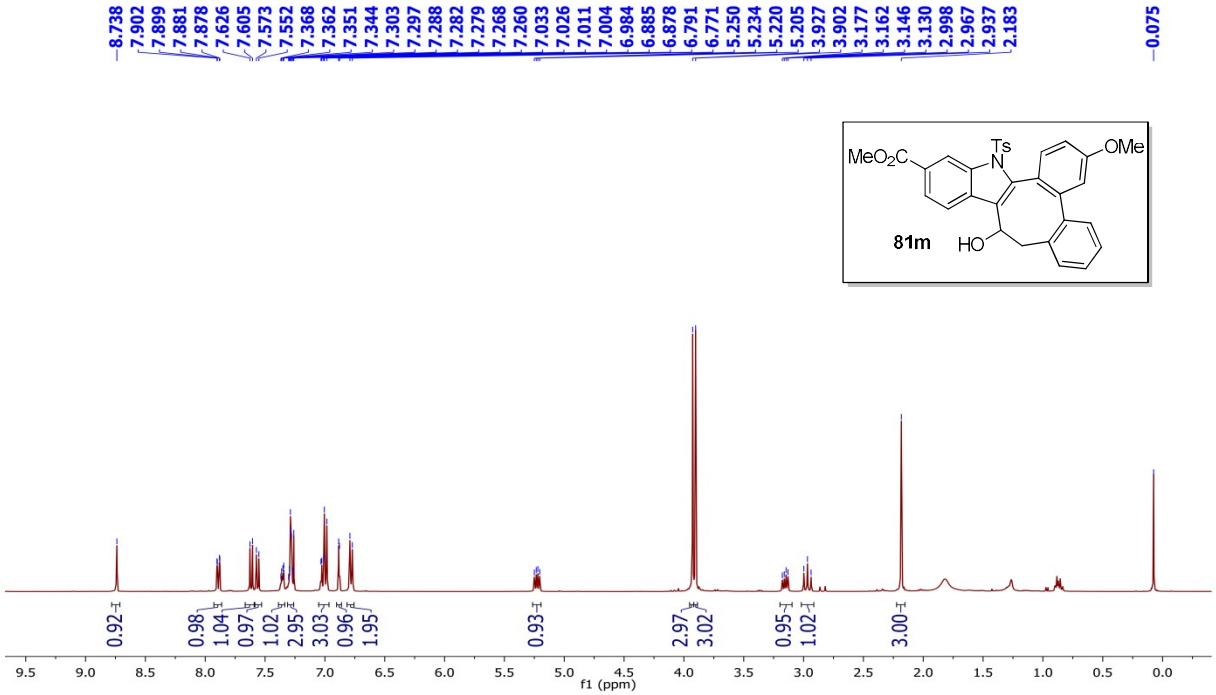
^{1}H NMR (400 MHz) of **81l :**



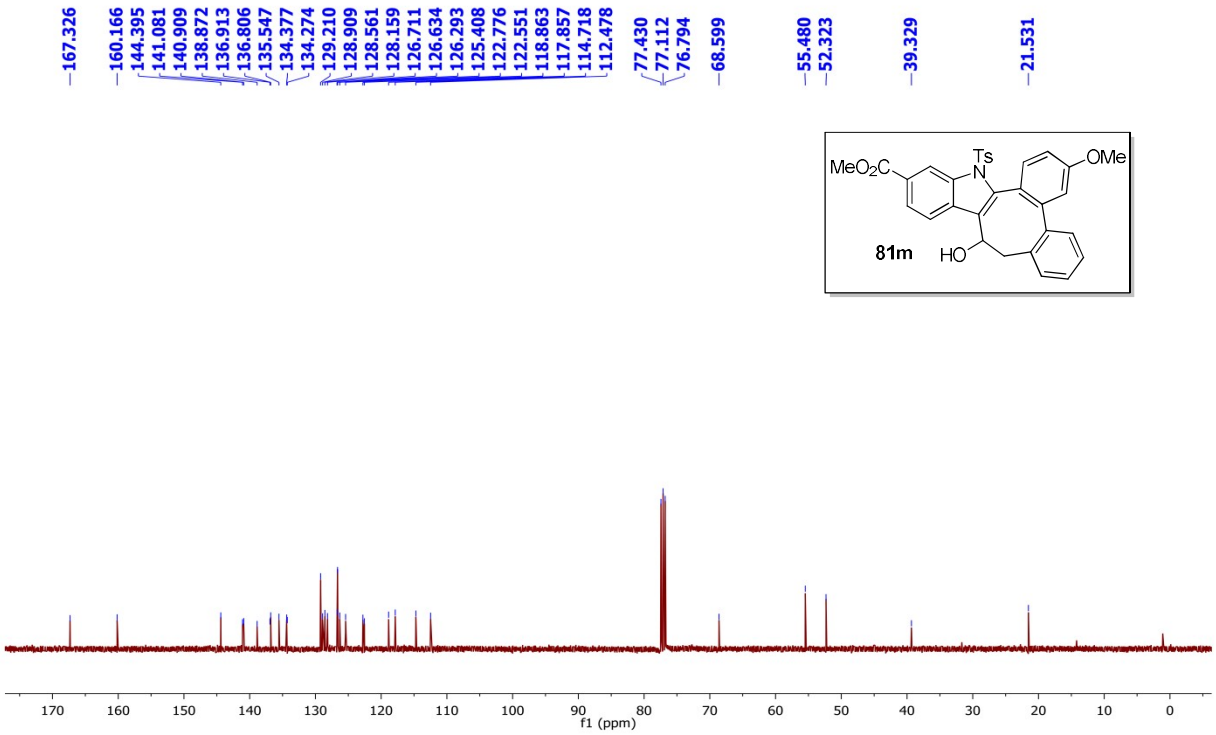
^{13}C{^{1}H} NMR (100 MHz) of **81l :**



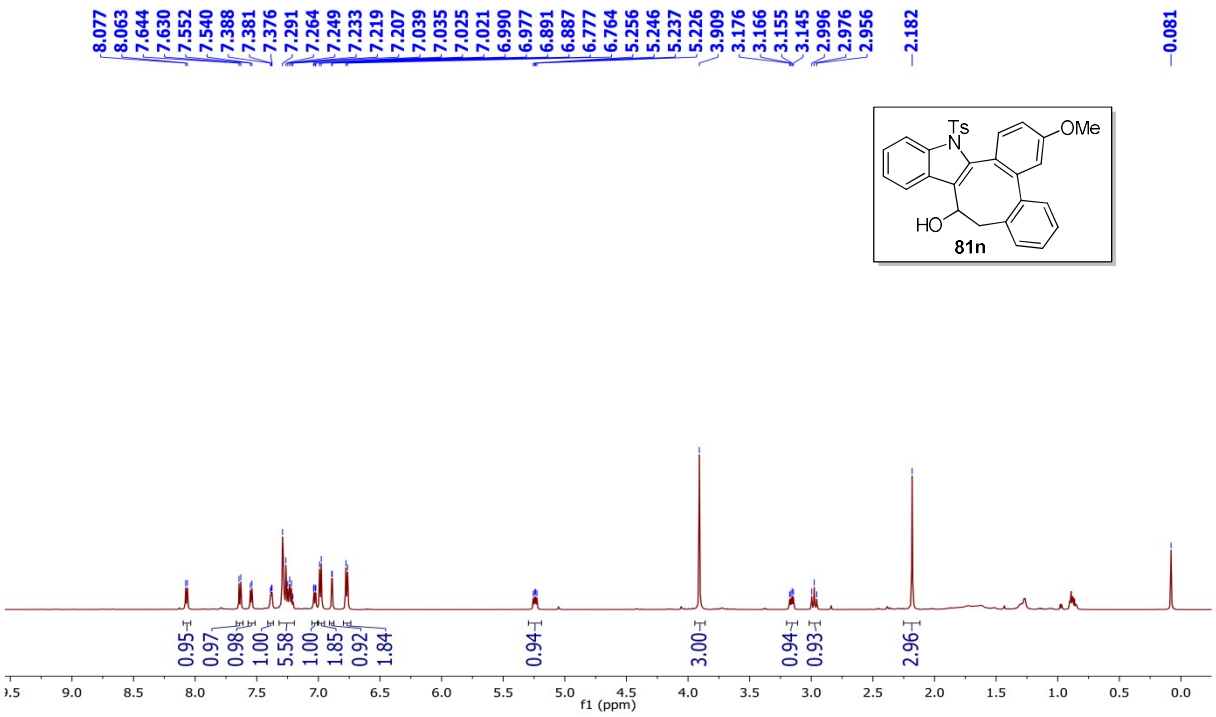
^{1}H NMR (400 MHz) of **81m :**



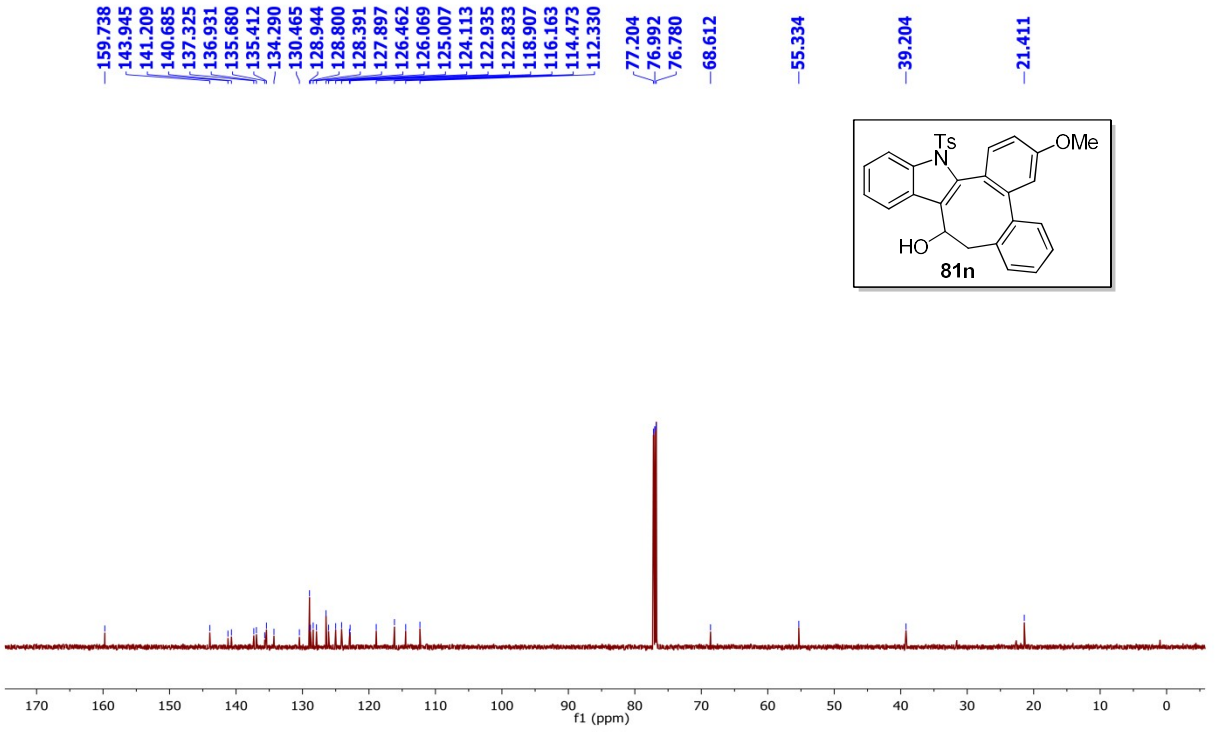
^{13}C{^{1}H} NMR (100 MHz) of **81m :**



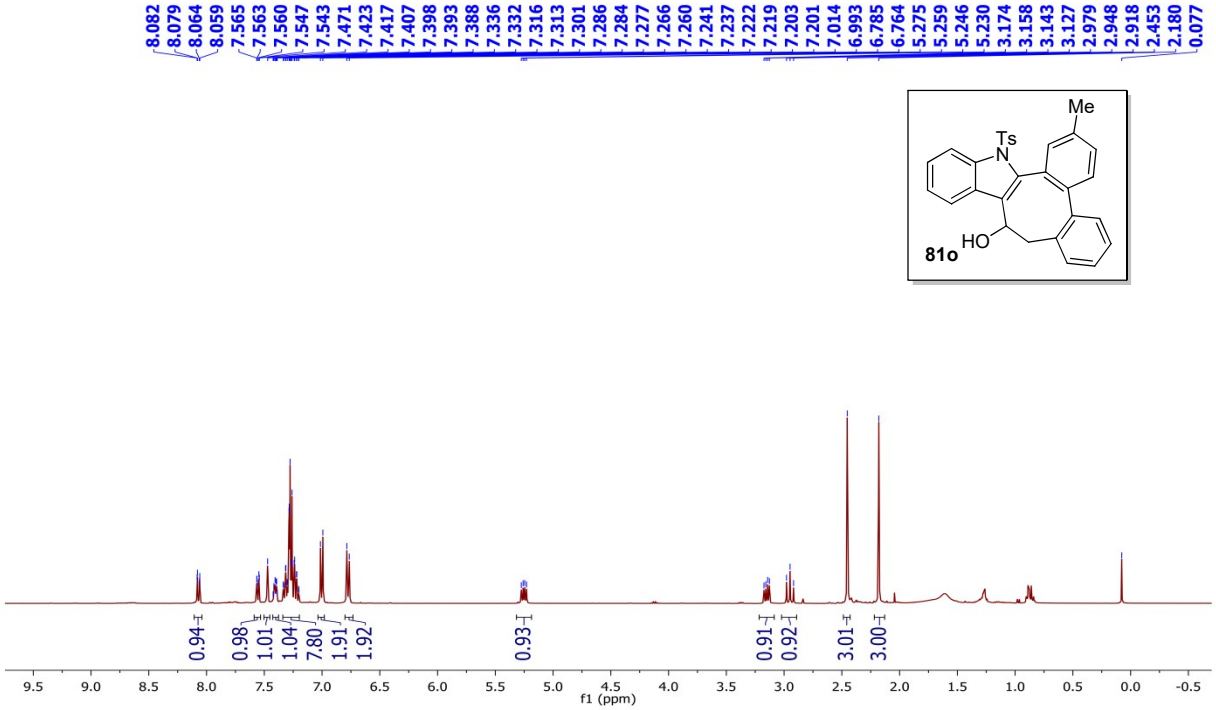
^{1}H NMR (600 MHz) of **81n :**



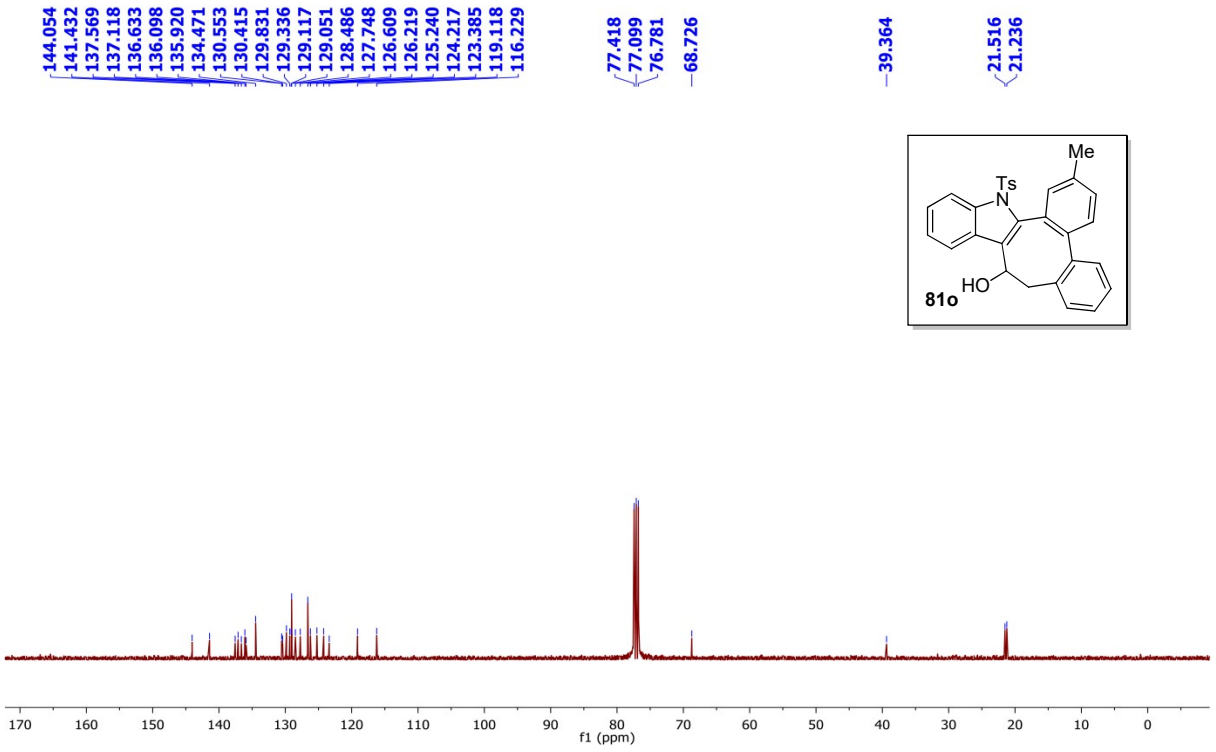
^{13}C{^{1}H} NMR (150 MHz) of **81n :**



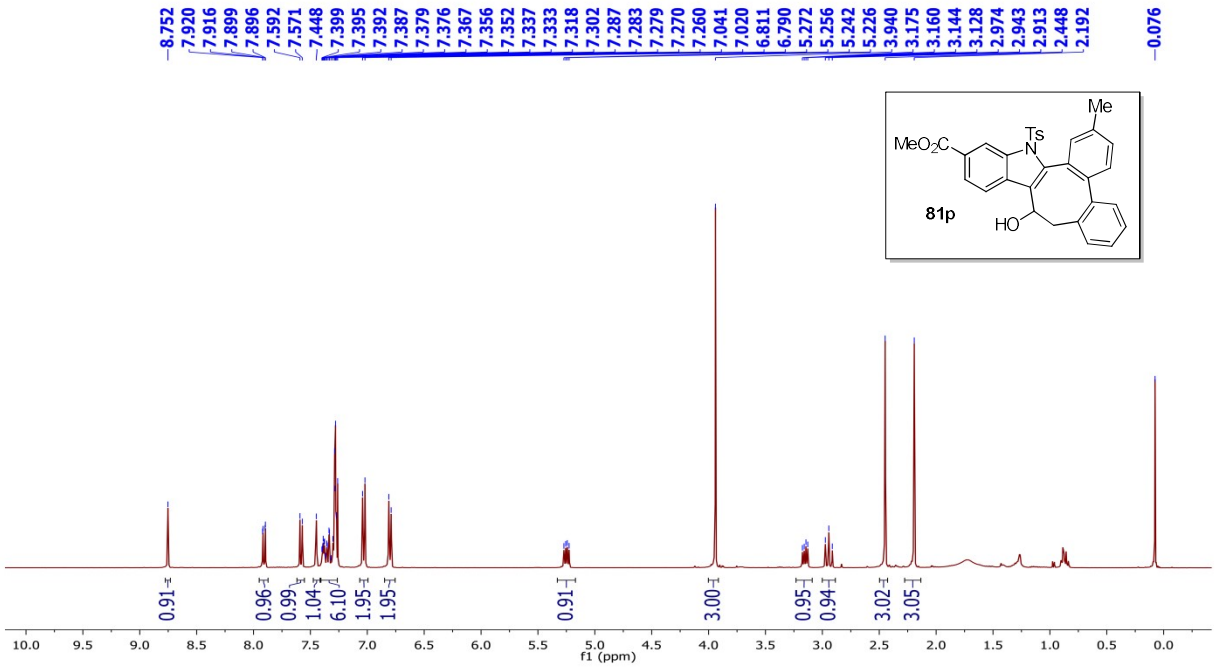
^{1}H NMR (400 MHz) of **81o :**



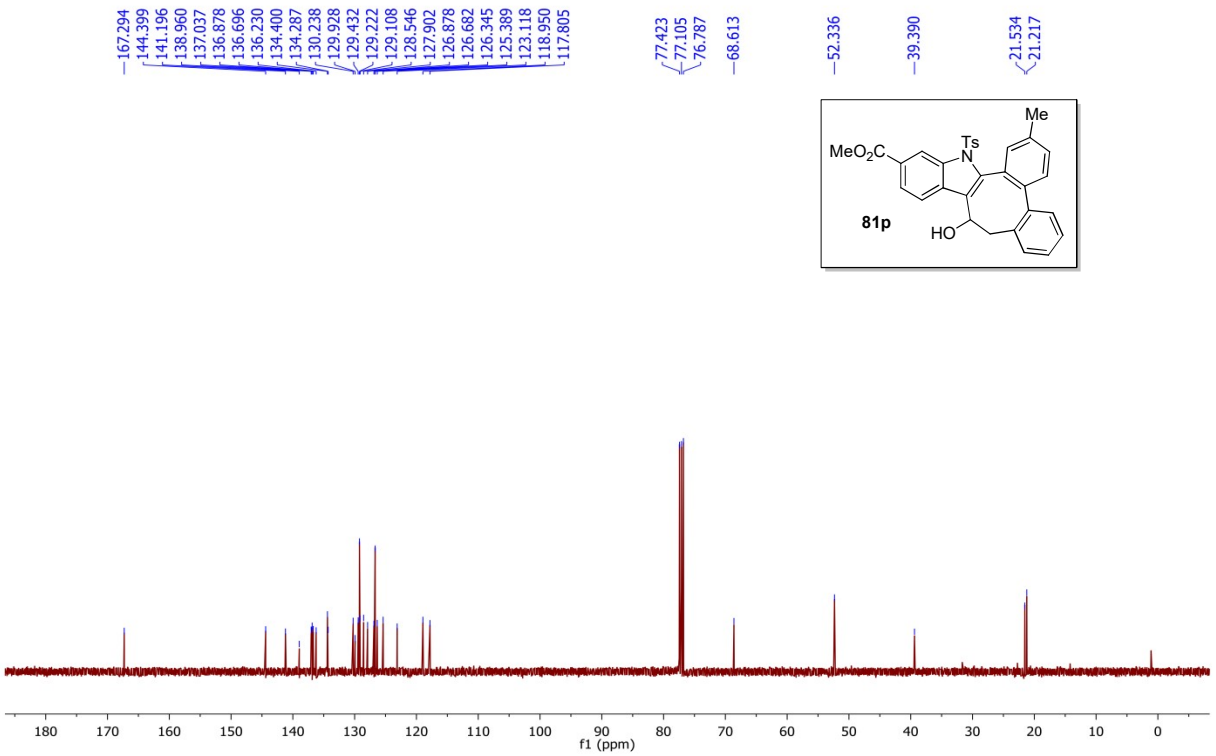
^{13}C{^{1}H} NMR (100 MHz) of **81o :**



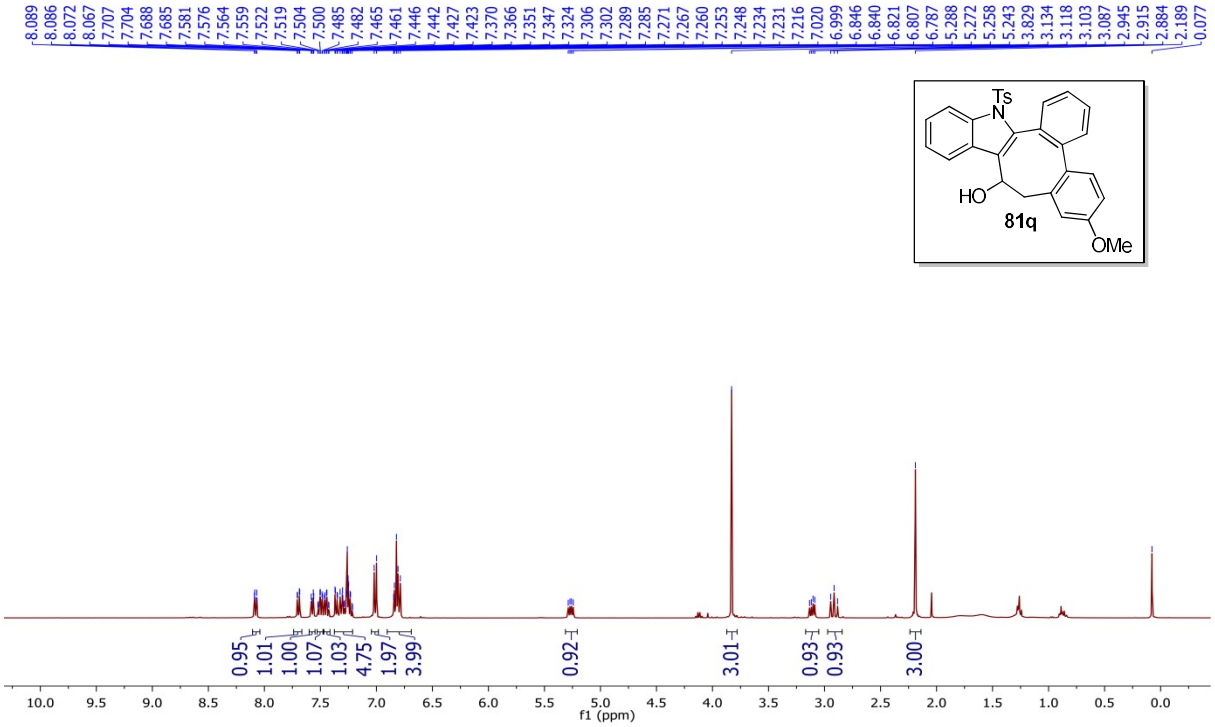
^{1}H NMR (400 MHz) of **81p :**



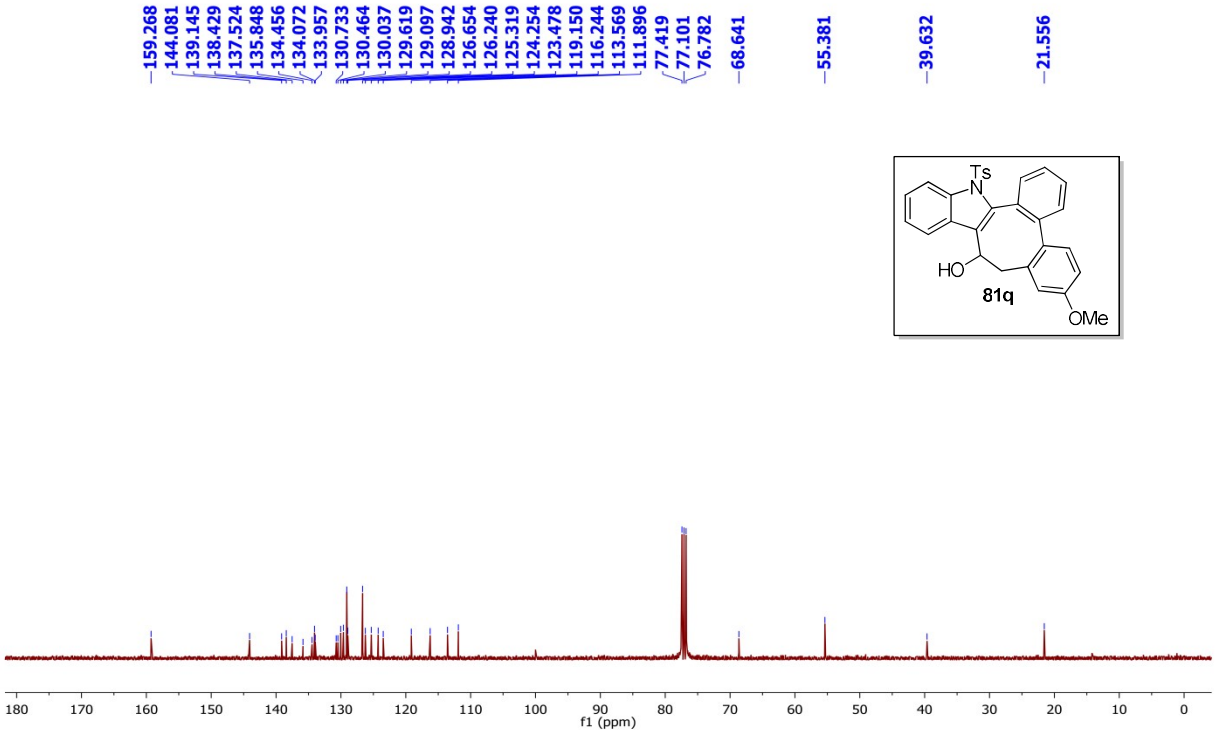
^{13}C{^{1}H} NMR (100 MHz) of **81p :**



^{1}H NMR (400 MHz) of **81q :**

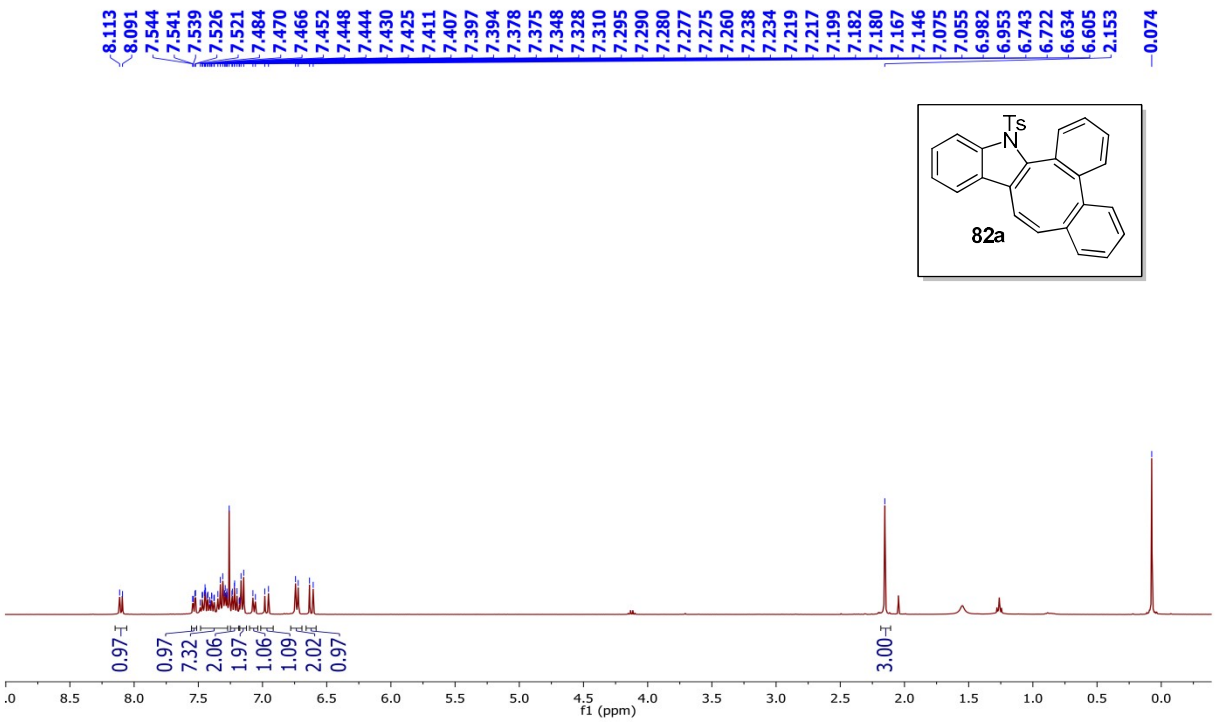


^{13}C{^{1}H} NMR (100 MHz) of **81q :**

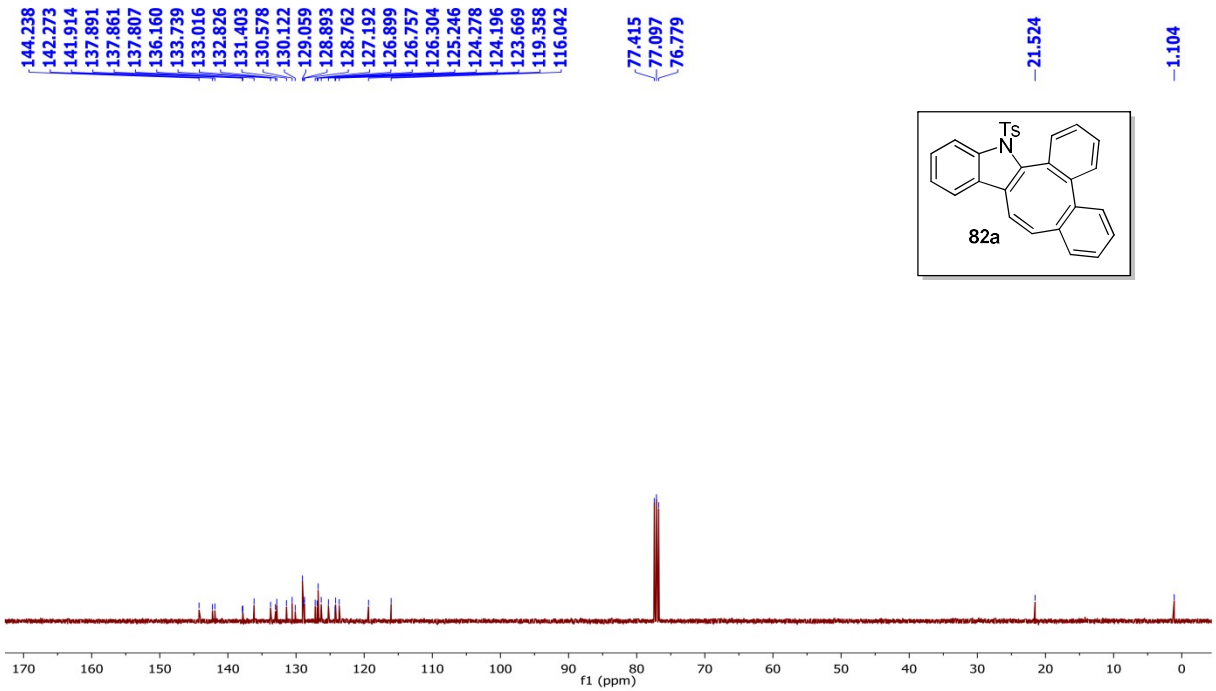


1.2.11.4. NMR Spectra of Compounds 82a-j:

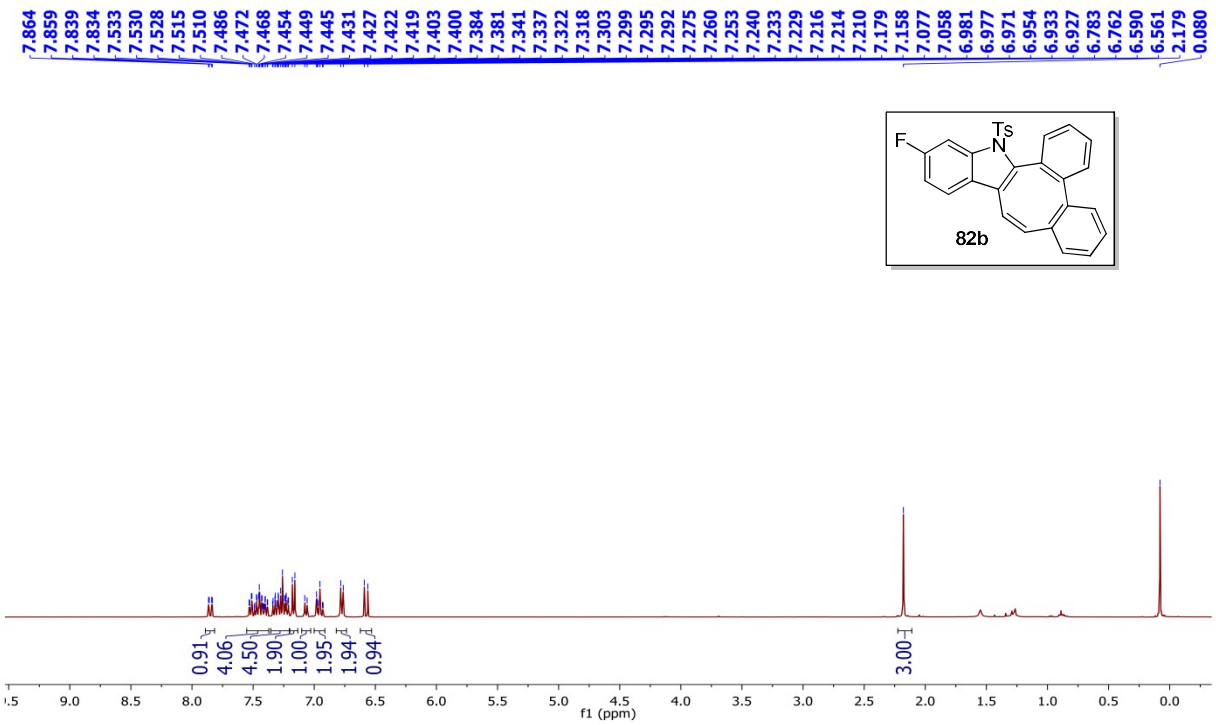
^{1}H NMR (400 MHz) of **82a :**



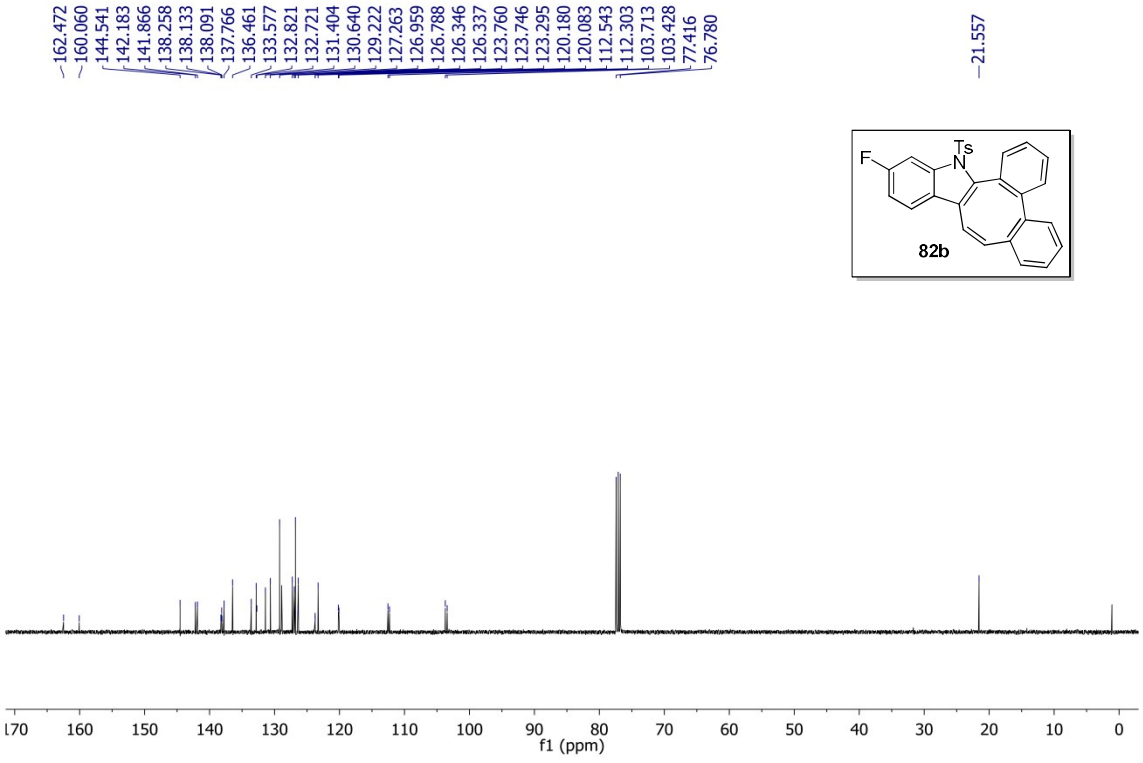
^{13}C{^{1}H} NMR (100 MHz) of **82a :**



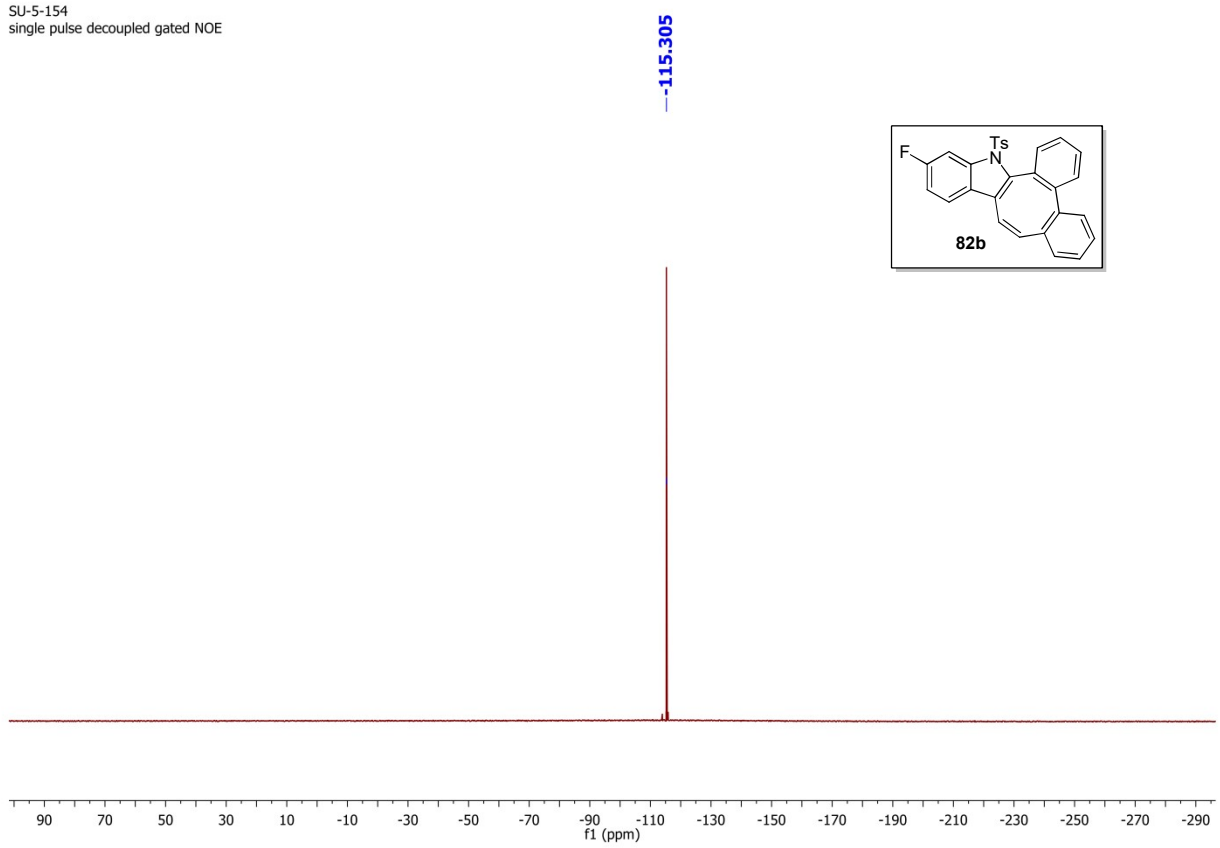
^{1}H NMR (400 MHz) of **82b :**



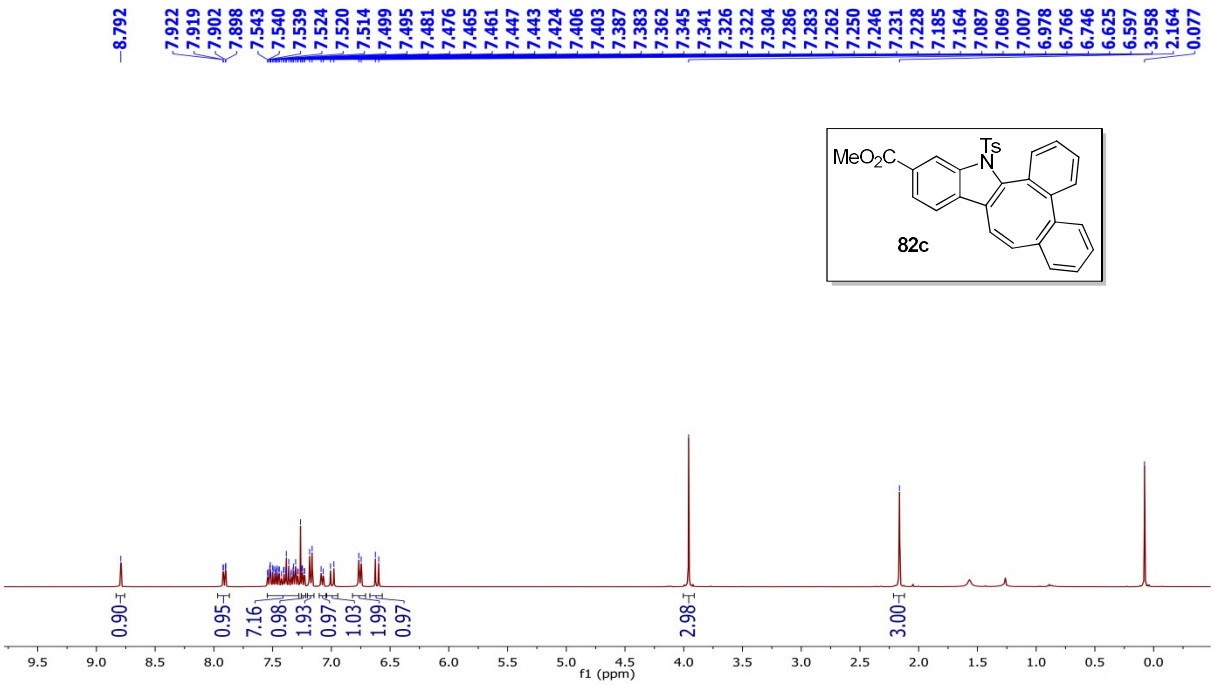
^{13}C{^{1}H} NMR (100 MHz) of **82b :**



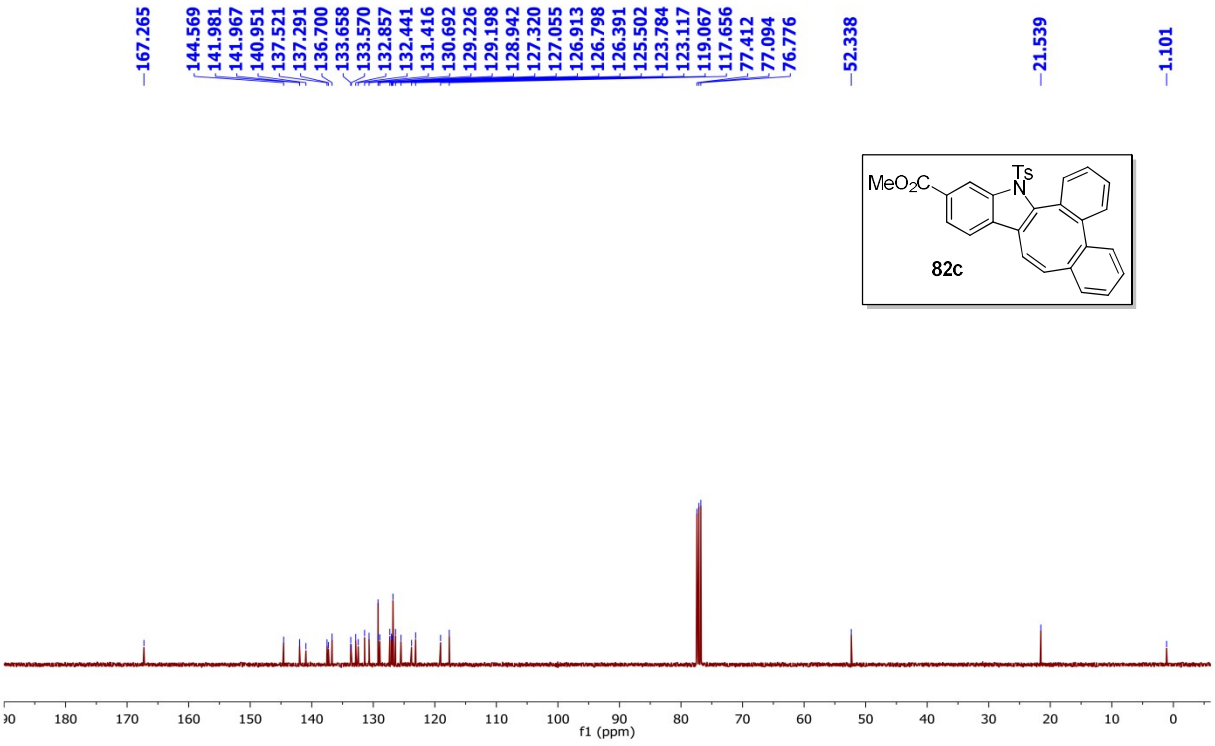
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **82b :**



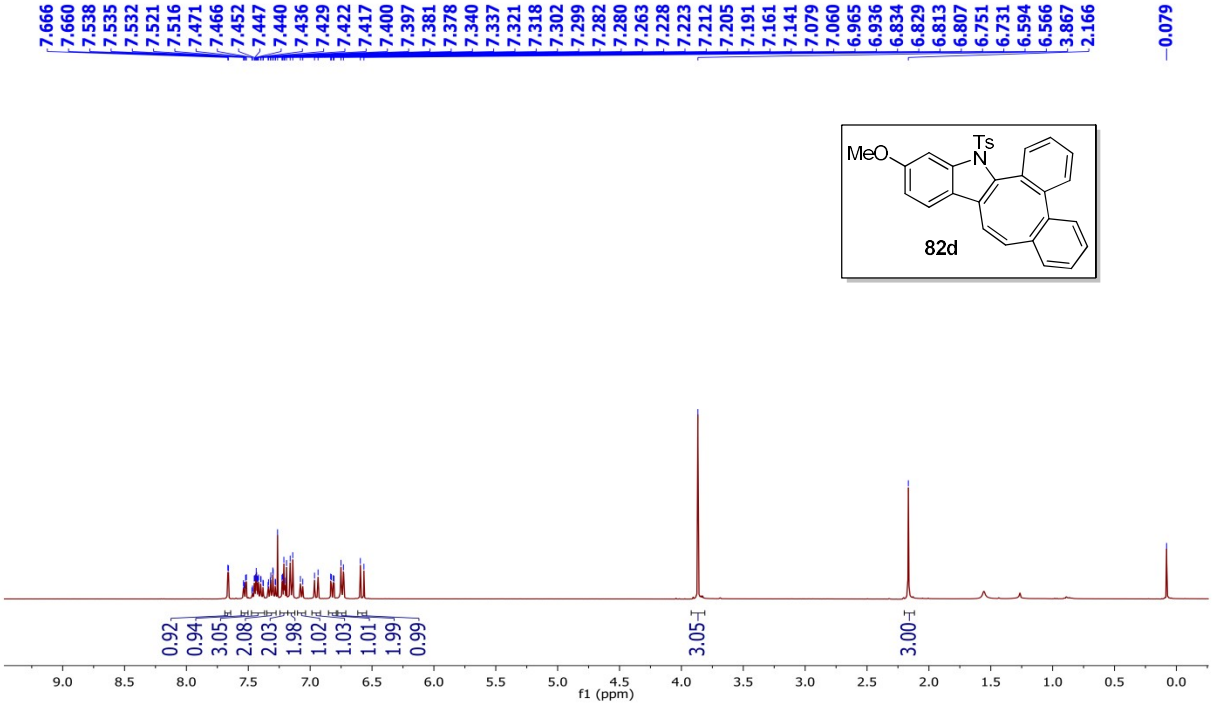
^{1}H NMR (400 MHz) of **82c :**



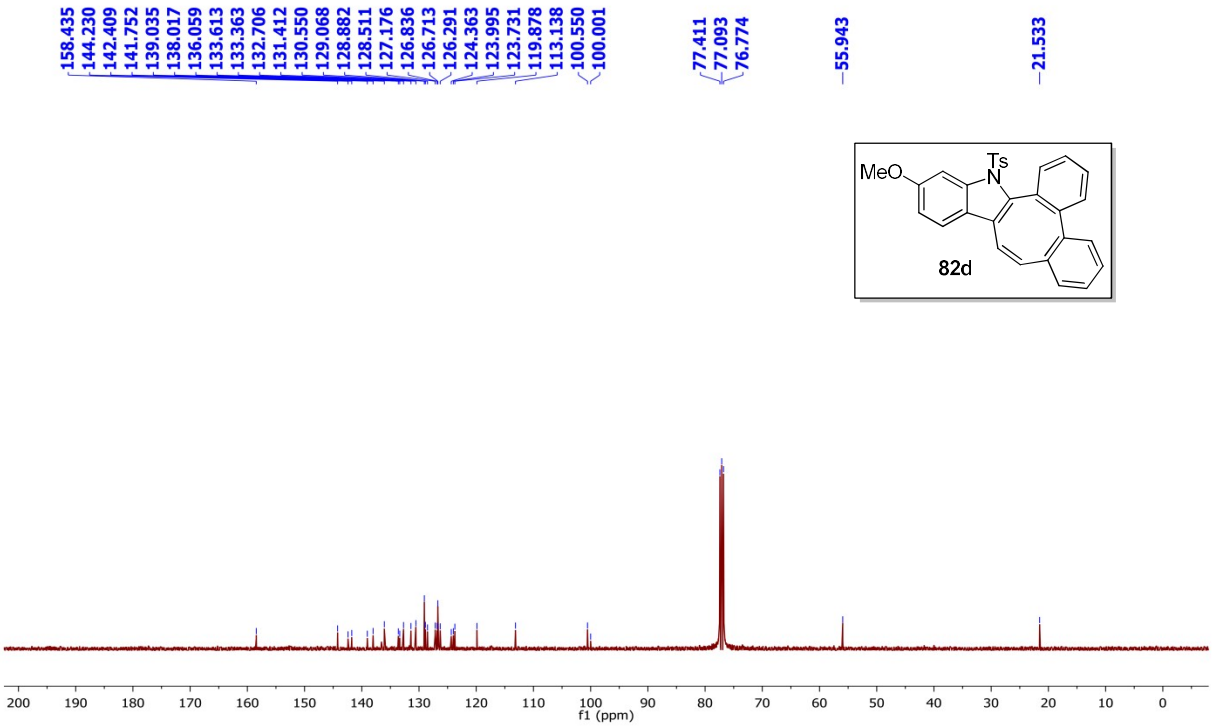
^{13}C{^{1}H} NMR (100 MHz) of **82c :**



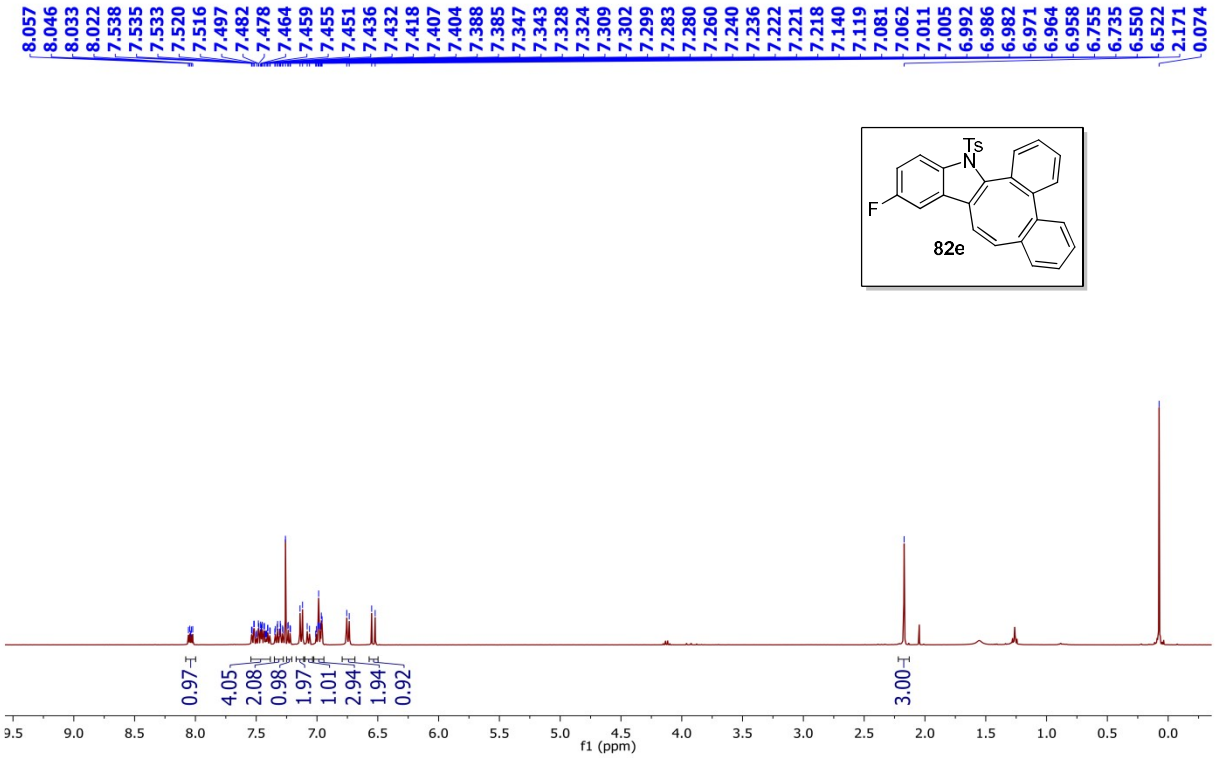
^{1}H NMR (400 MHz) of **82d :**



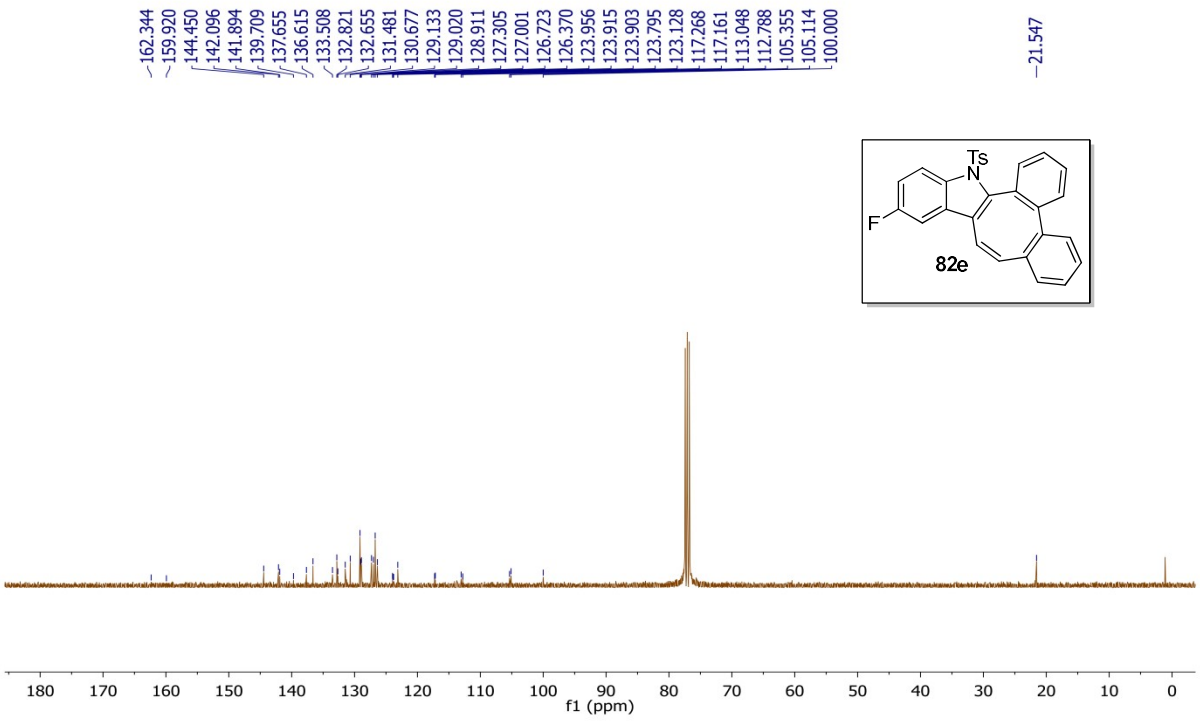
^{13}C{^{1}H} NMR (100 MHz) of **82d :**



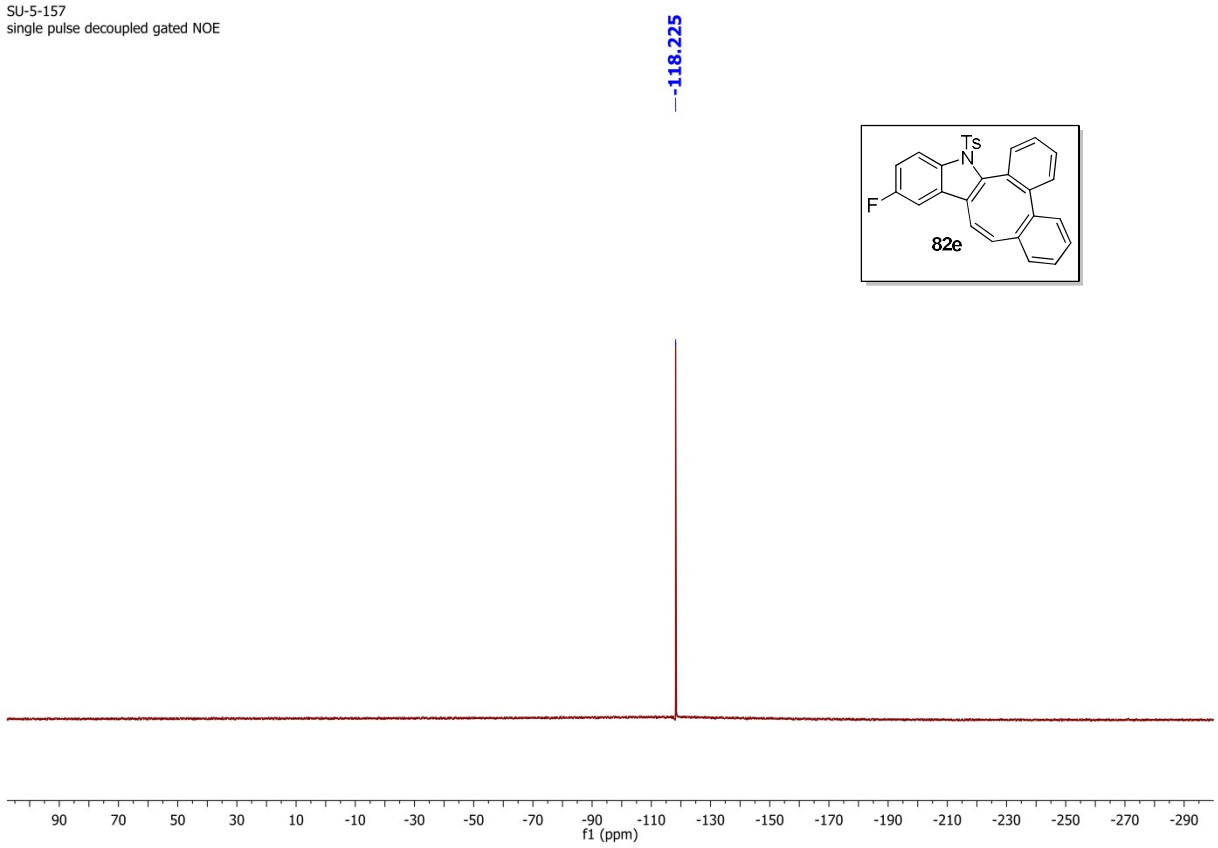
^{1}H NMR (400 MHz) of **82e :**



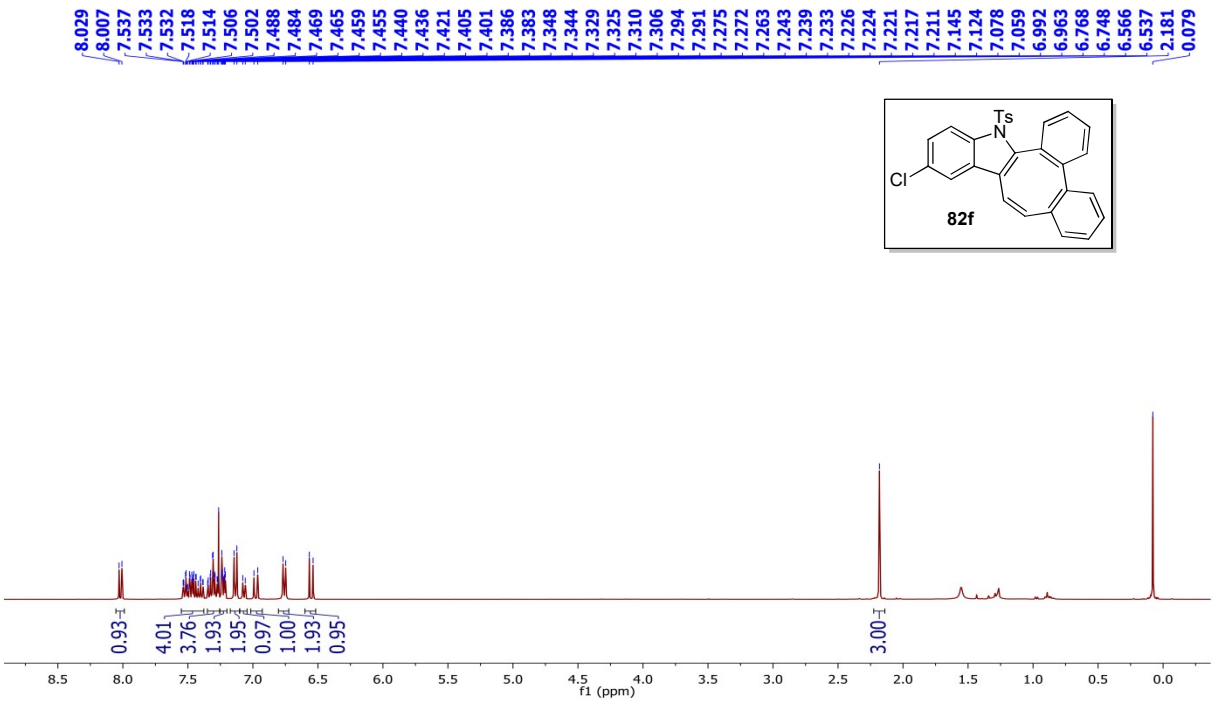
^{13}C{^{1}H} NMR (100 MHz) of **82e :**



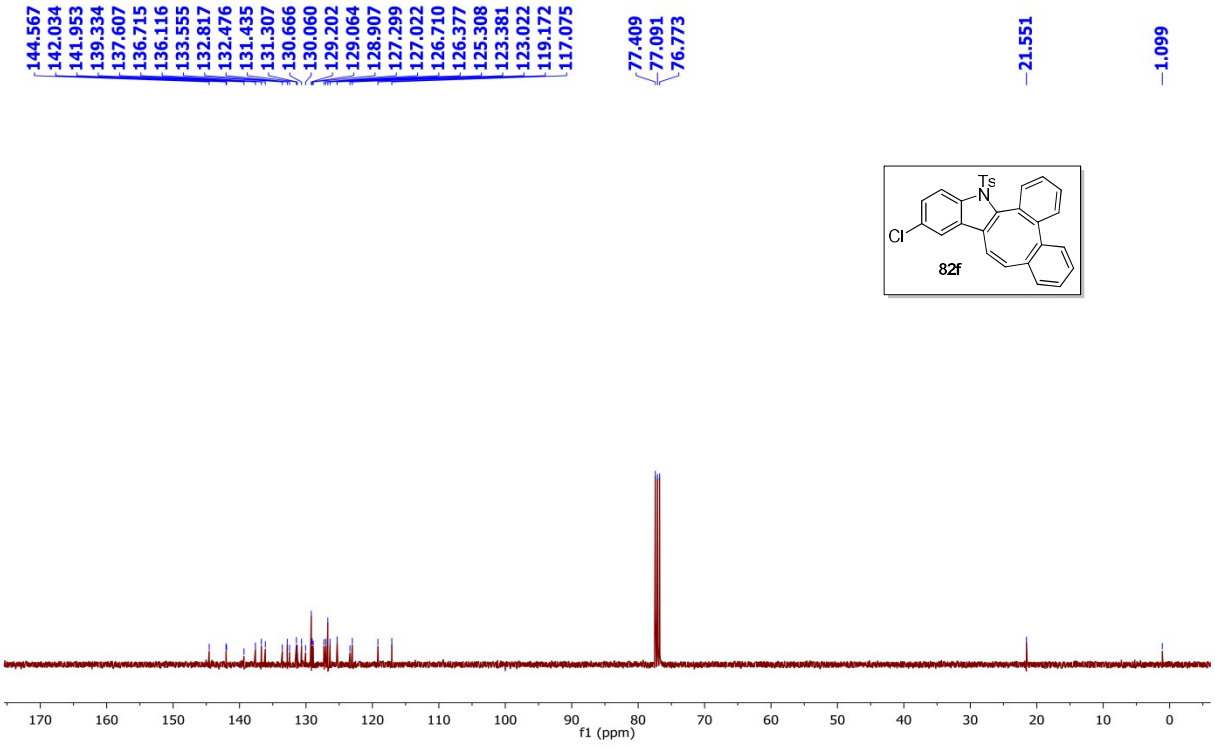
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **82e :**



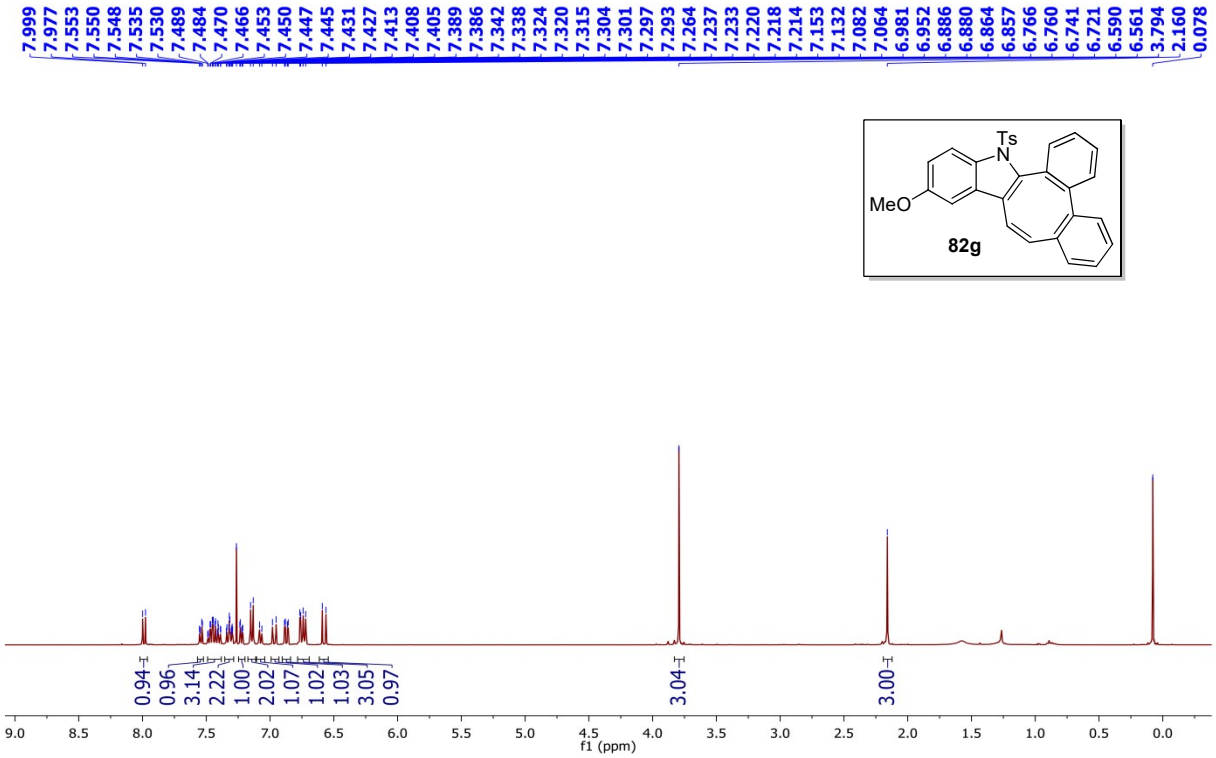
^{1}H NMR (400 MHz) of **82f :**



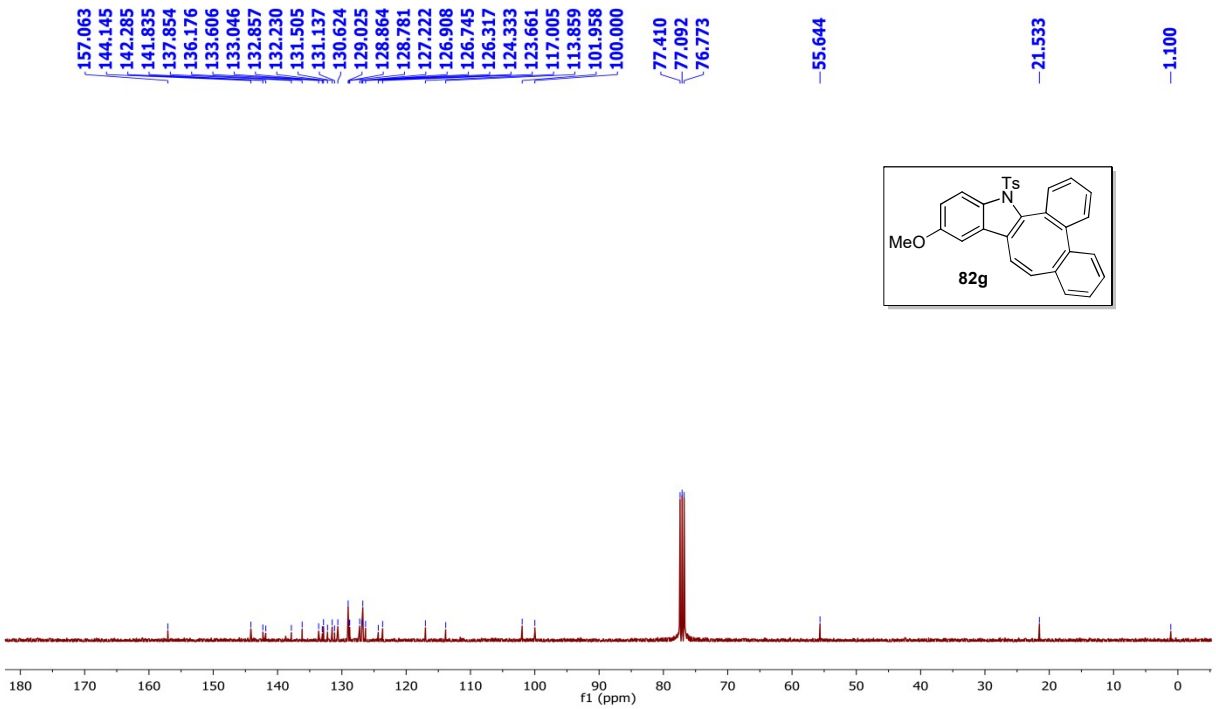
^{13}C{^{1}H} NMR (100 MHz) of **82f :**



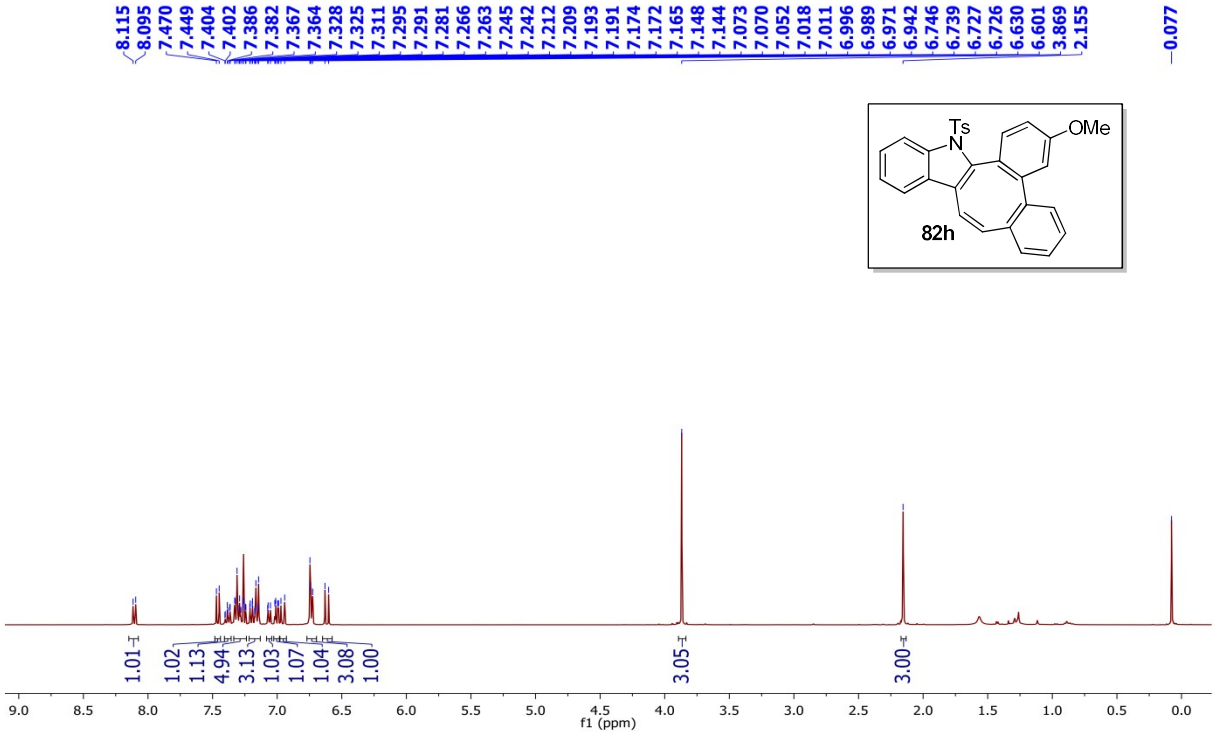
^{1}H NMR (400 MHz) of **82g :**



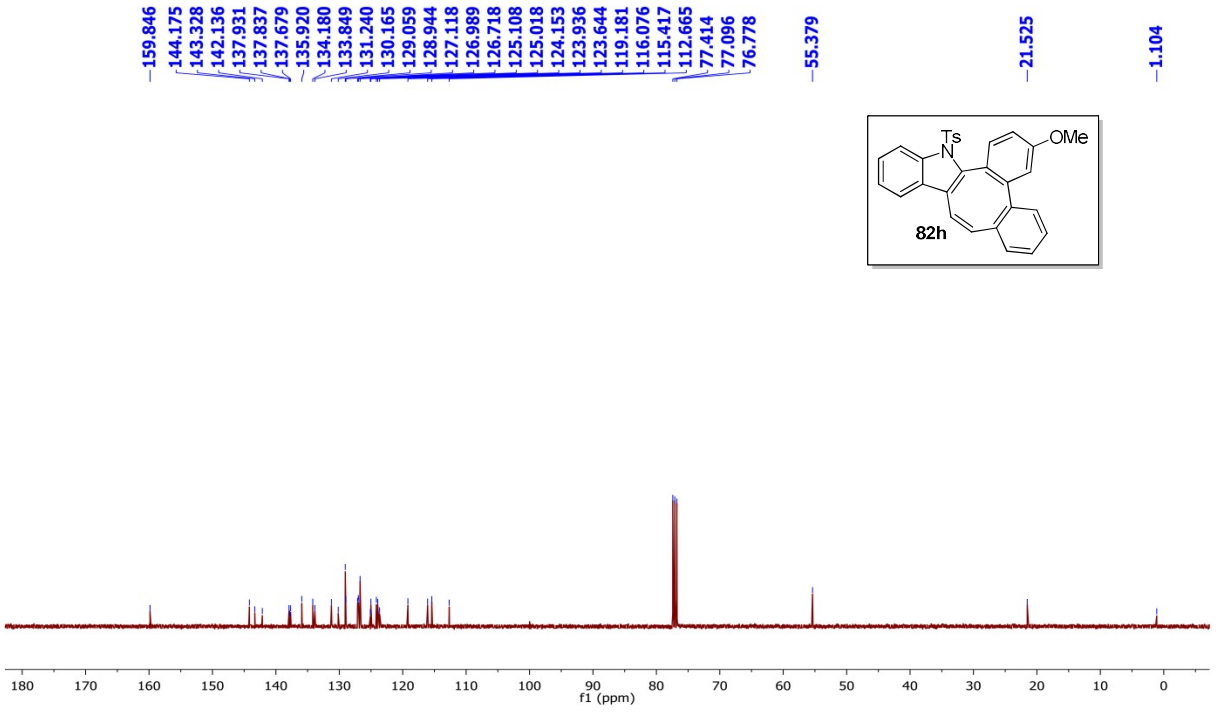
^{13}C{^{1}H} NMR (100 MHz) of **82g :**



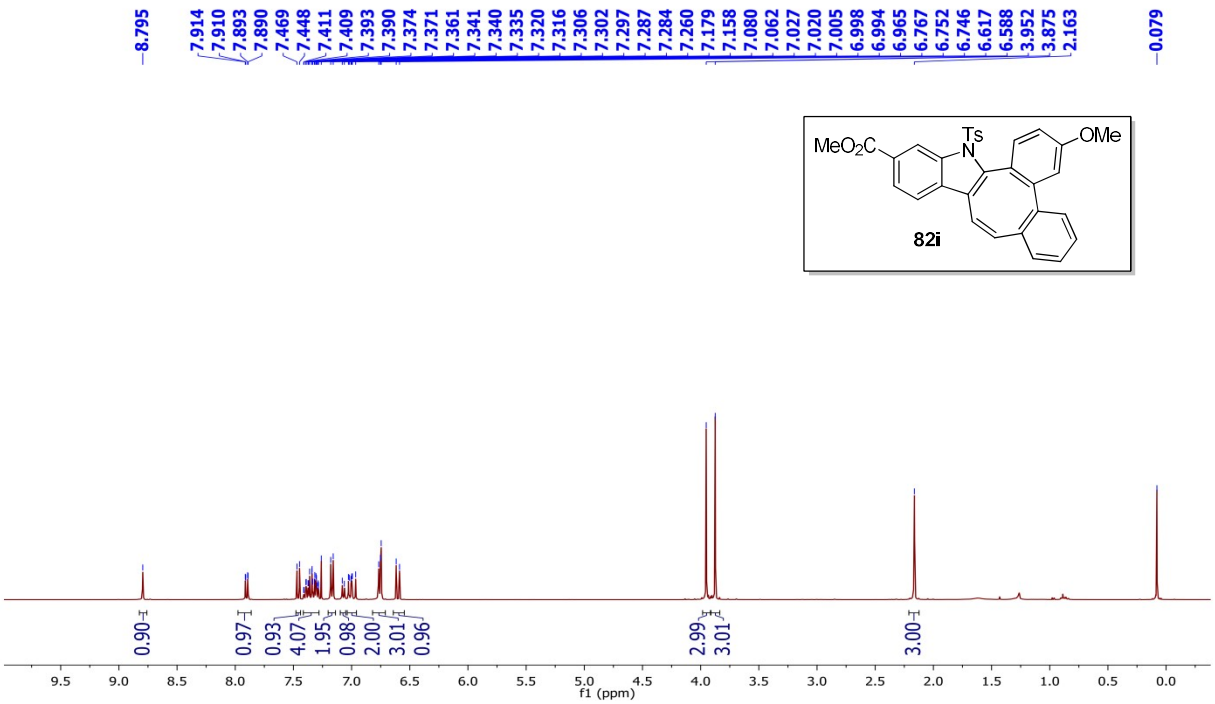
^{1}H NMR (400 MHz) of **82h :**



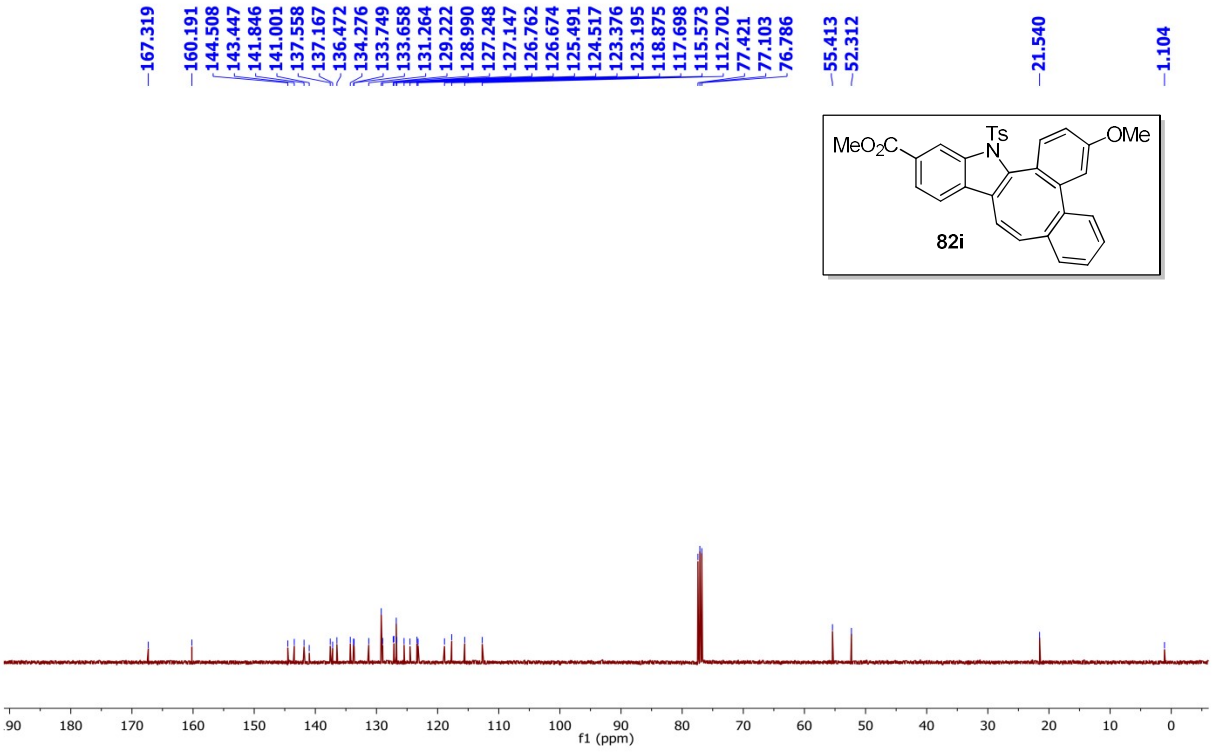
^{13}C{^{1}H} NMR (100 MHz) of **82h :**



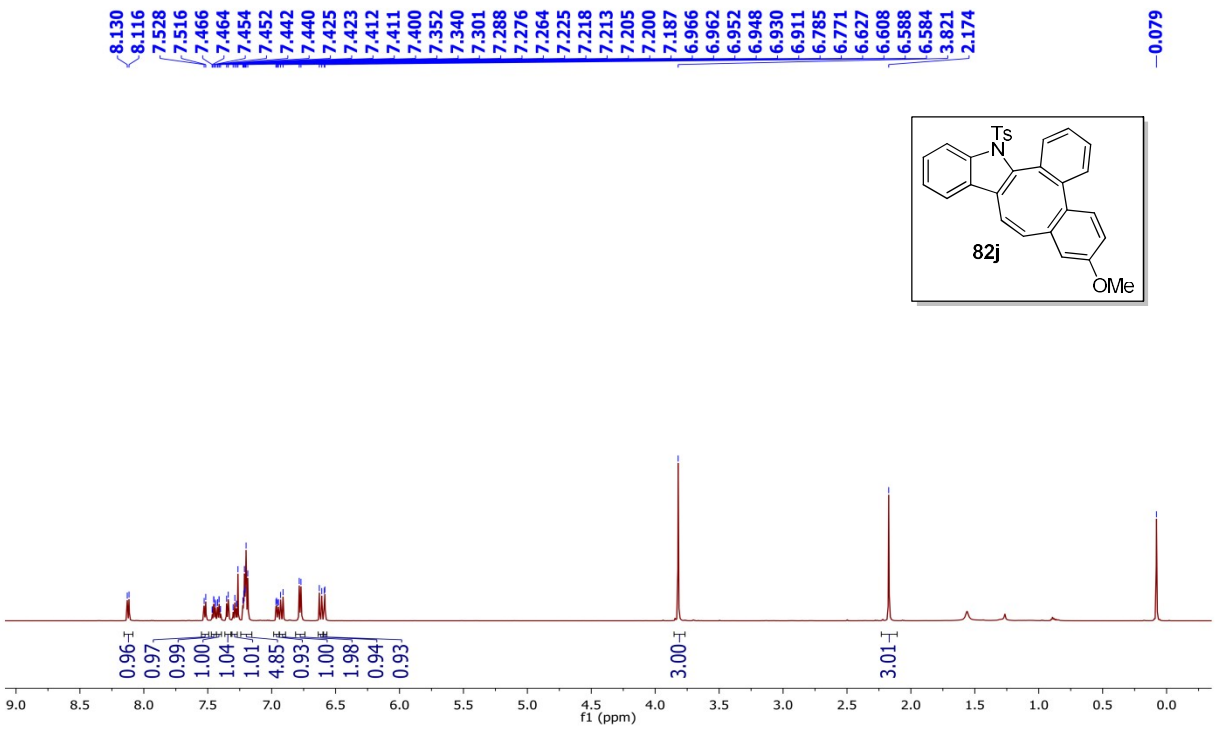
^{1}H NMR (400 MHz) of **82i :**



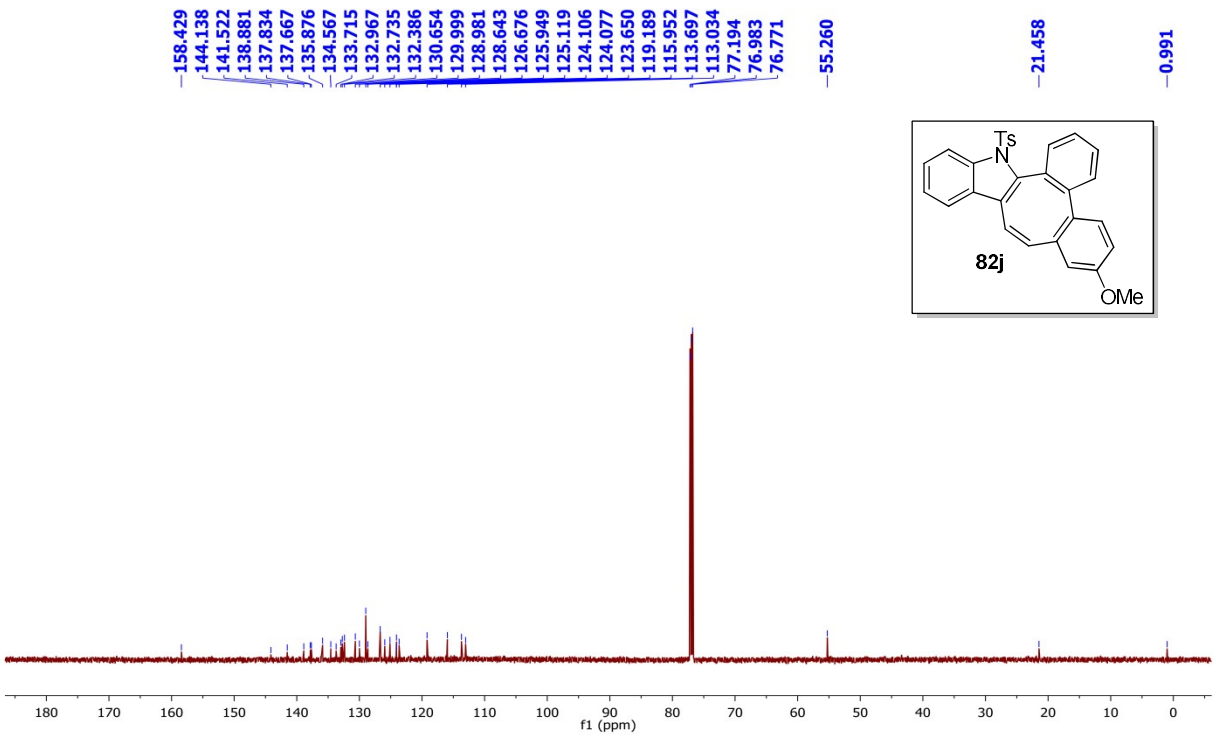
^{13}C{^{1}H} NMR (100 MHz) of **82i :**



^{1}H NMR (600 MHz) of **82j :**

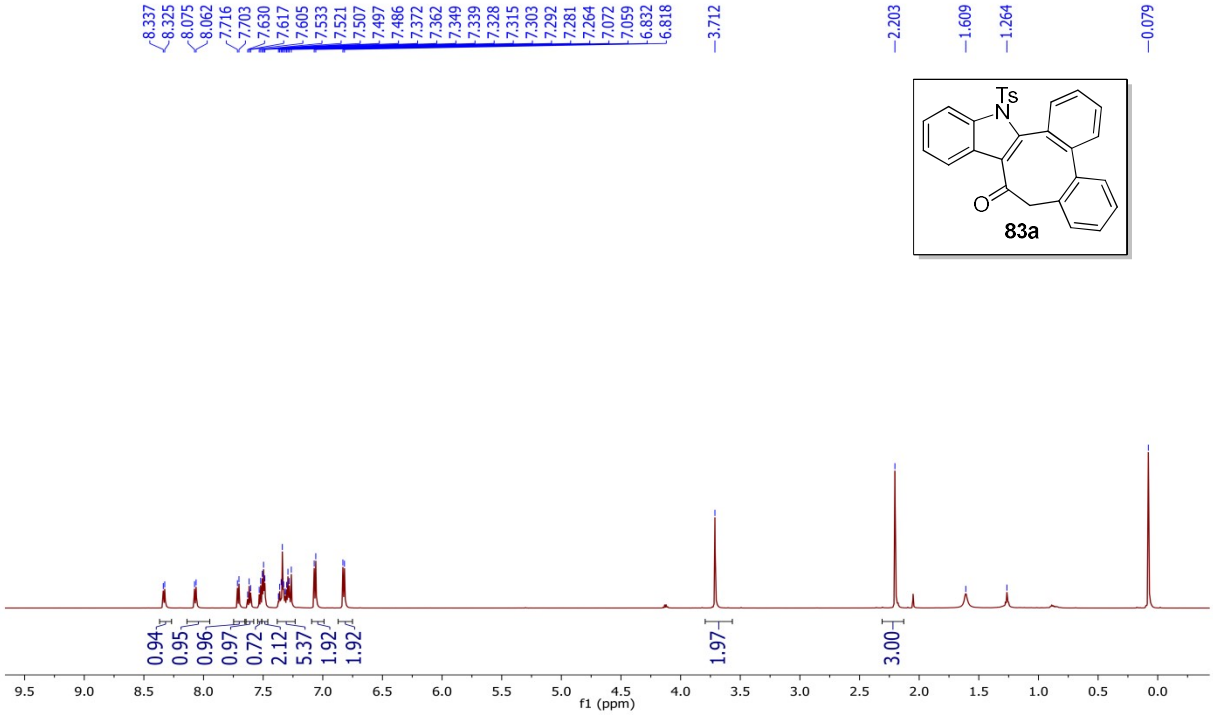


^{13}C{^{1}H} NMR (150 MHz) of **82j :**

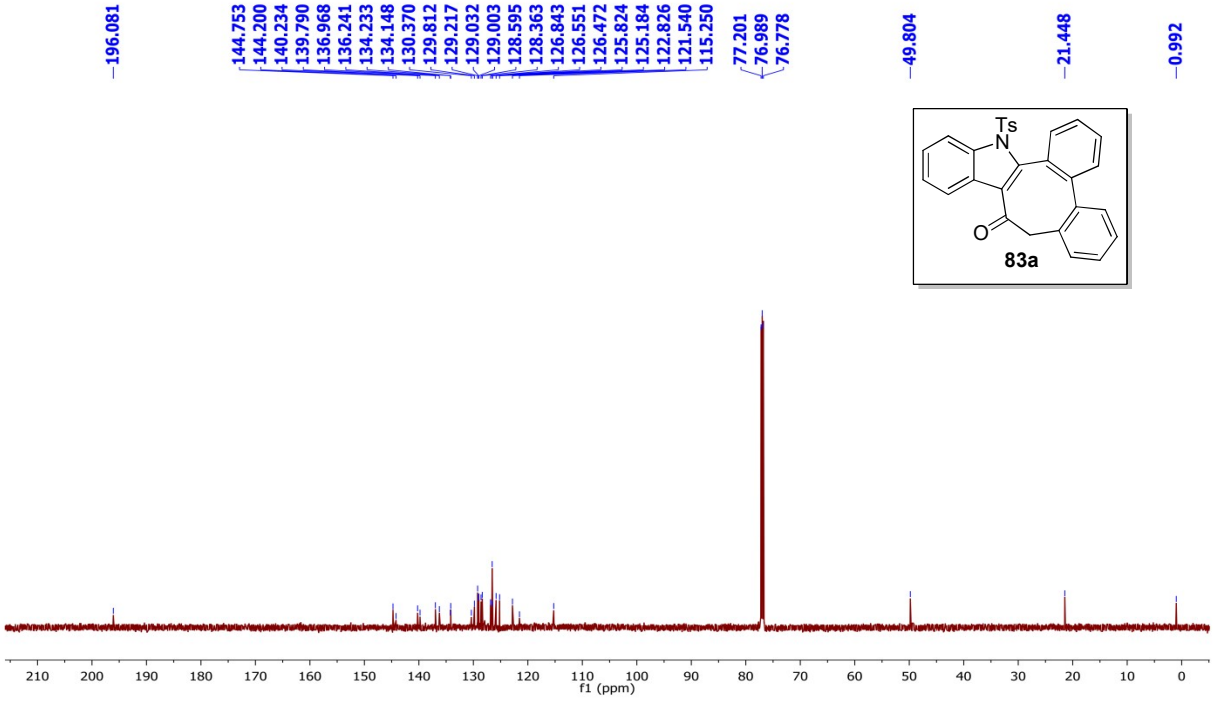


1.2.11.5. NMR Spectra of Compounds 83a-i:

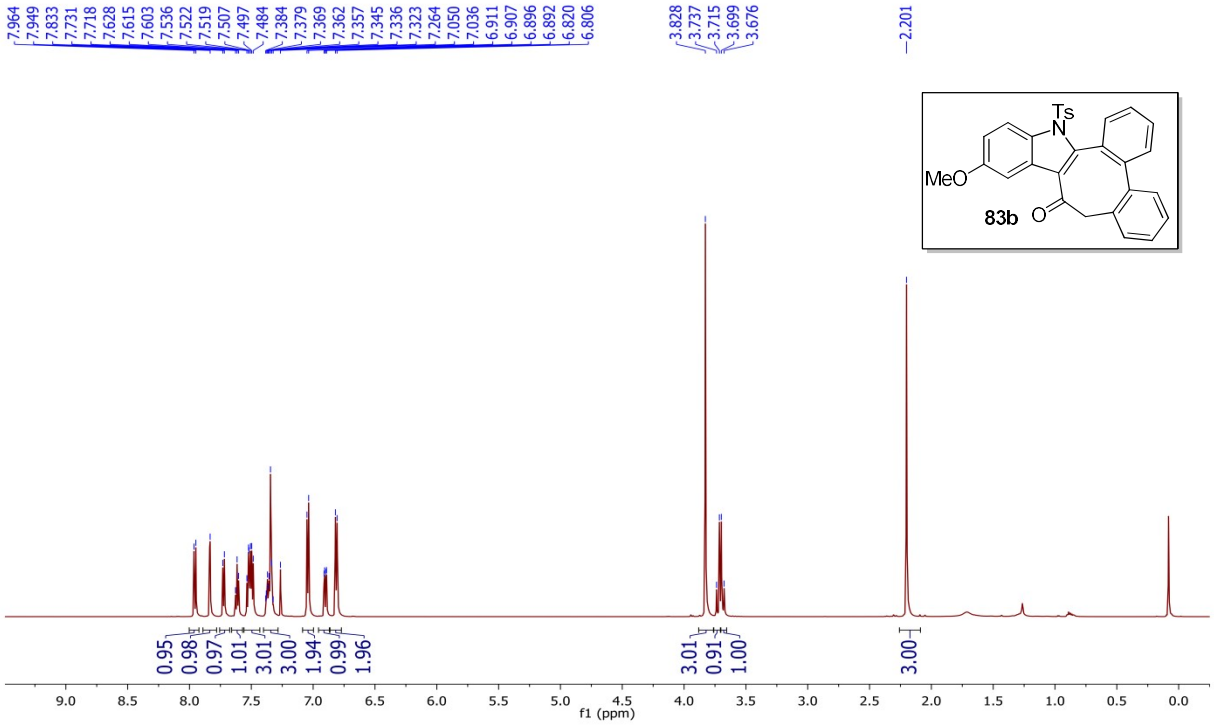
^{1}H NMR (600 MHz) of **83a :**



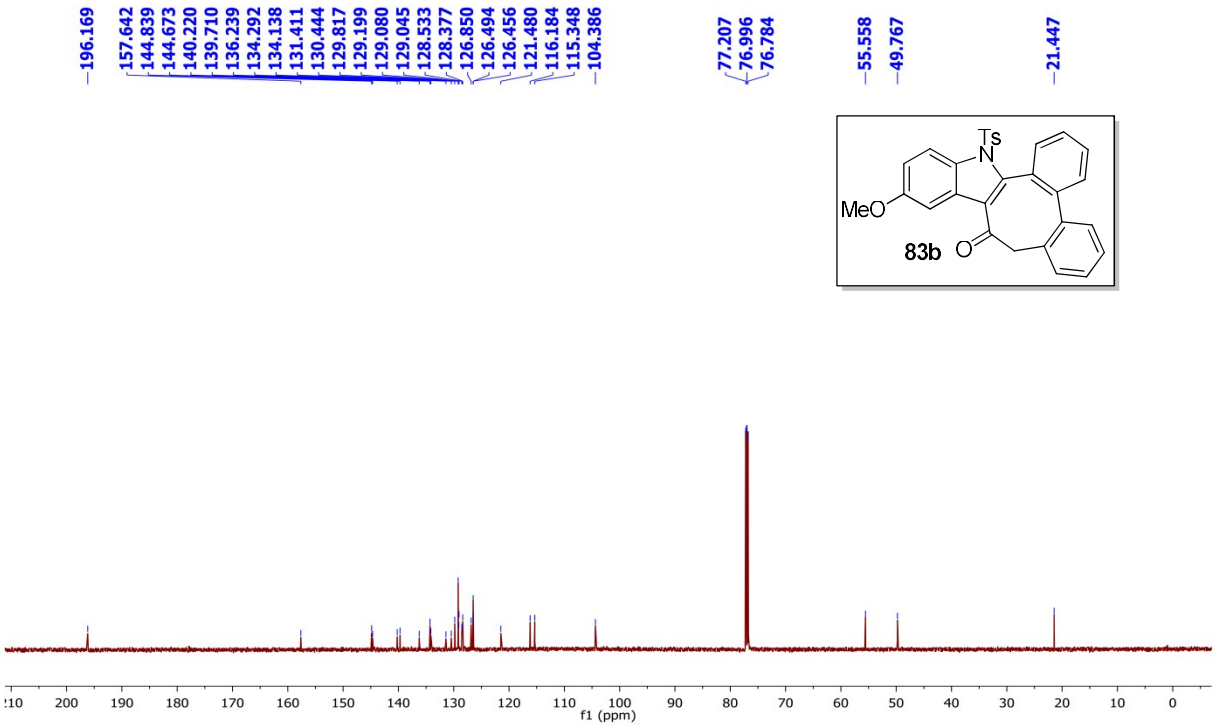
^{13}C{^{1}H} NMR (150 MHz) of **83a :**



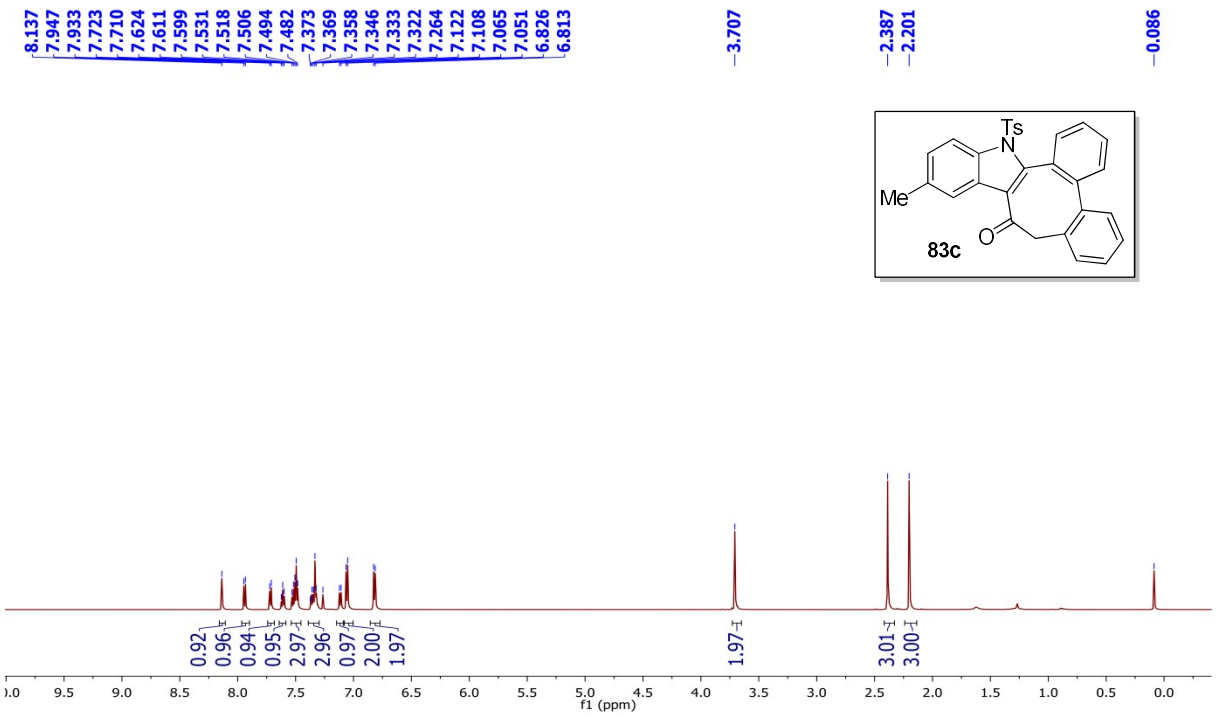
^{1}H NMR (600 MHz) of **83b :**



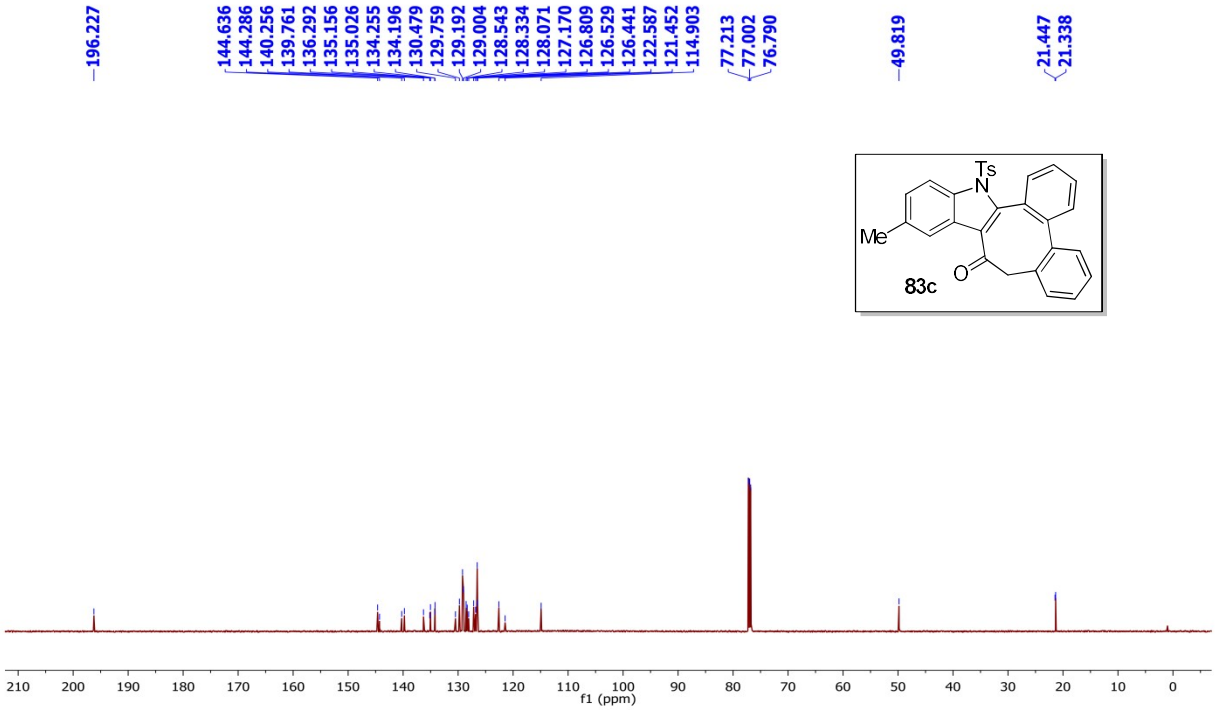
^{13}C{^{1}H} NMR (150 MHz) of **83b :**



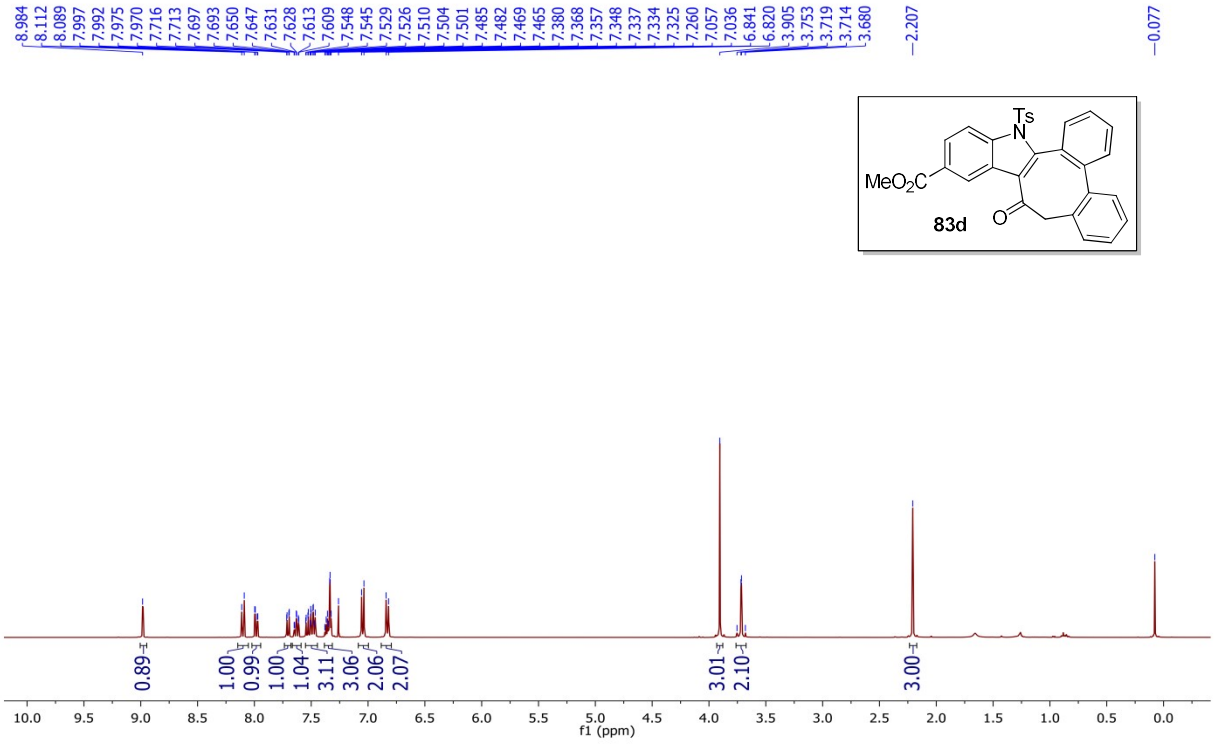
^{1}H NMR (600 MHz) of **83c :**



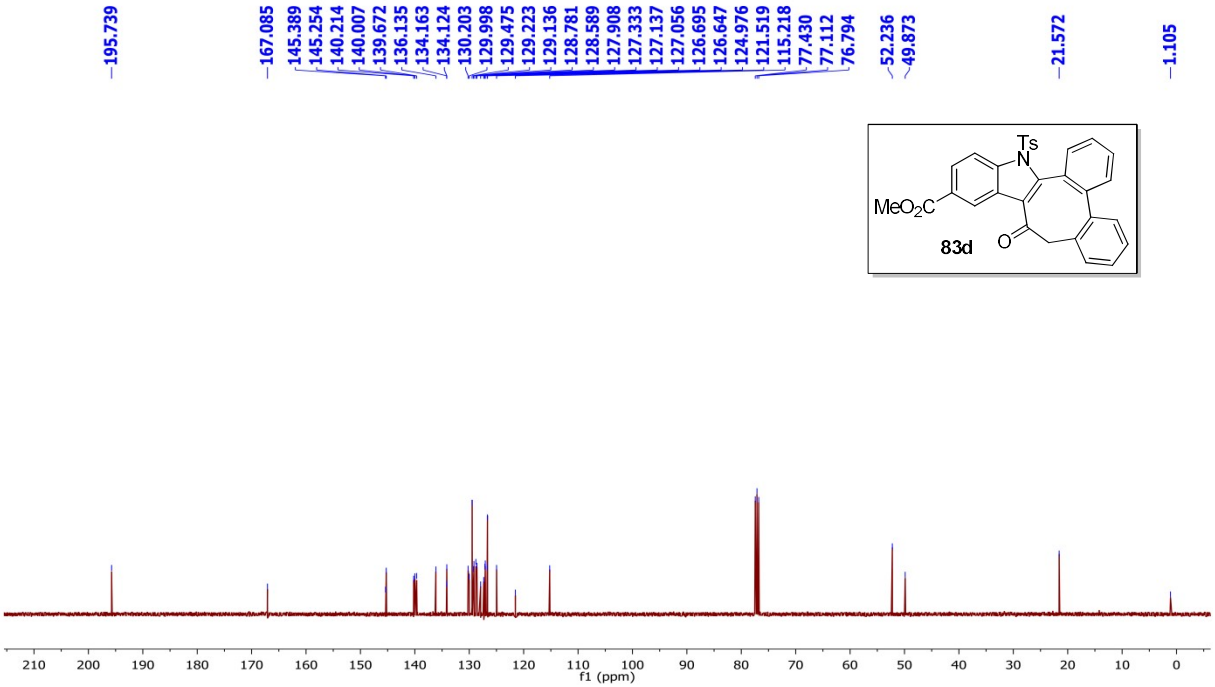
^{13}C{^{1}H} NMR (150 MHz) of **83c:**



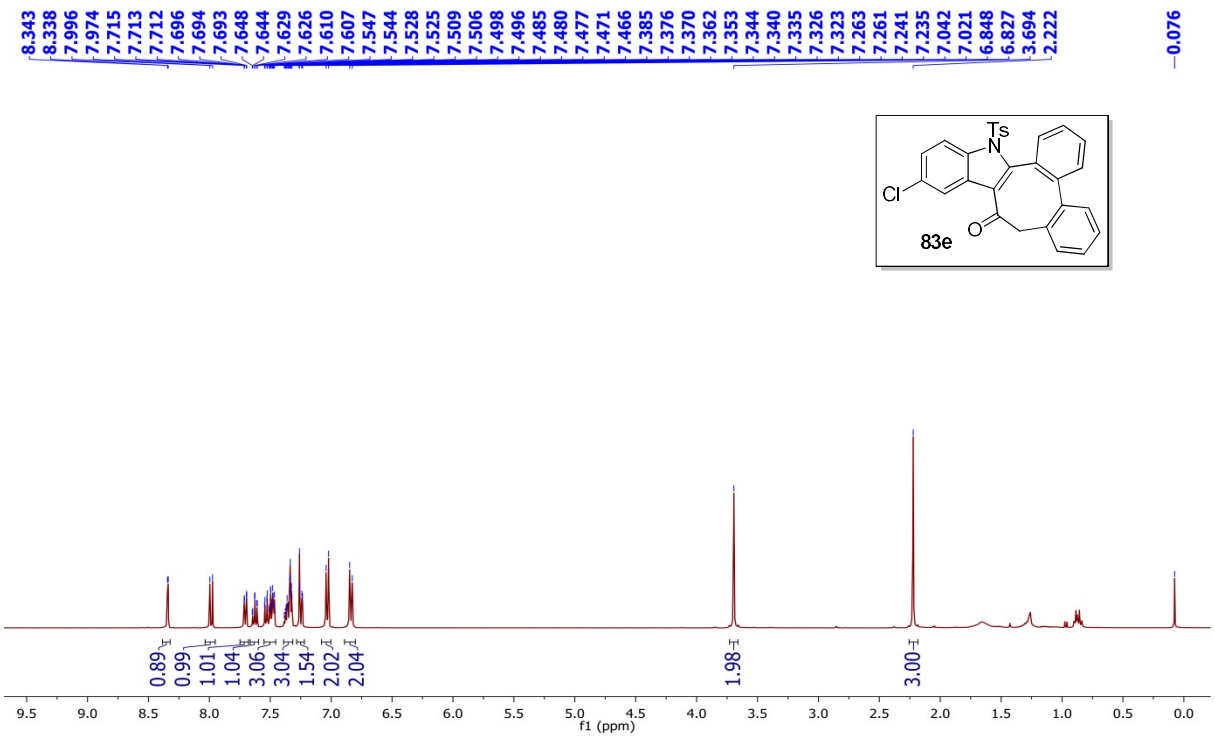
^{1}H NMR (400 MHz) of **83d :**



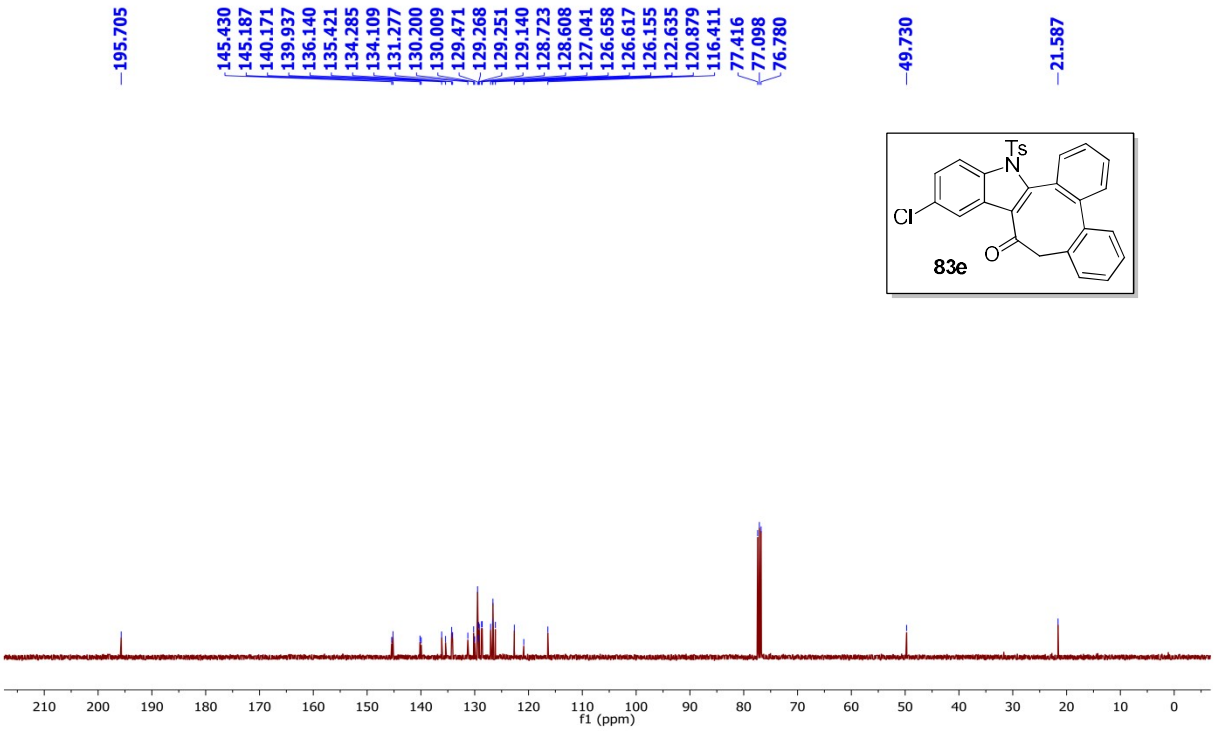
^{13}C{^{1}H} NMR (100 MHz) of **83d :**



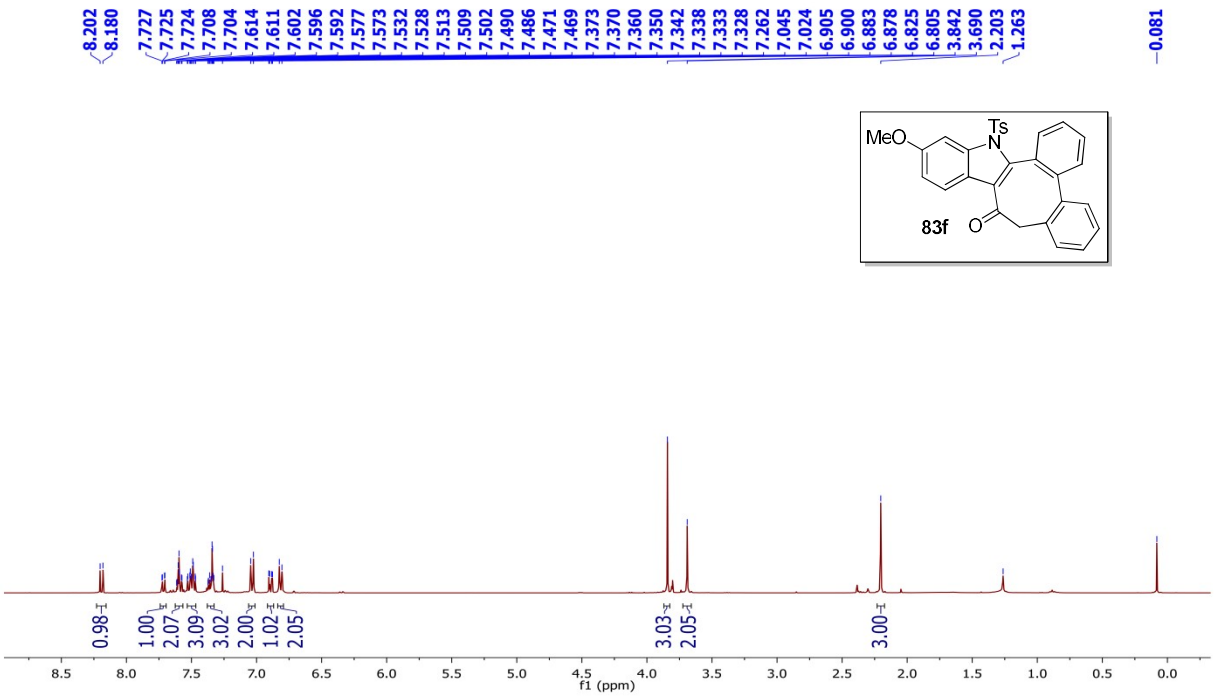
^{1}H NMR (400 MHz) of **83e :**



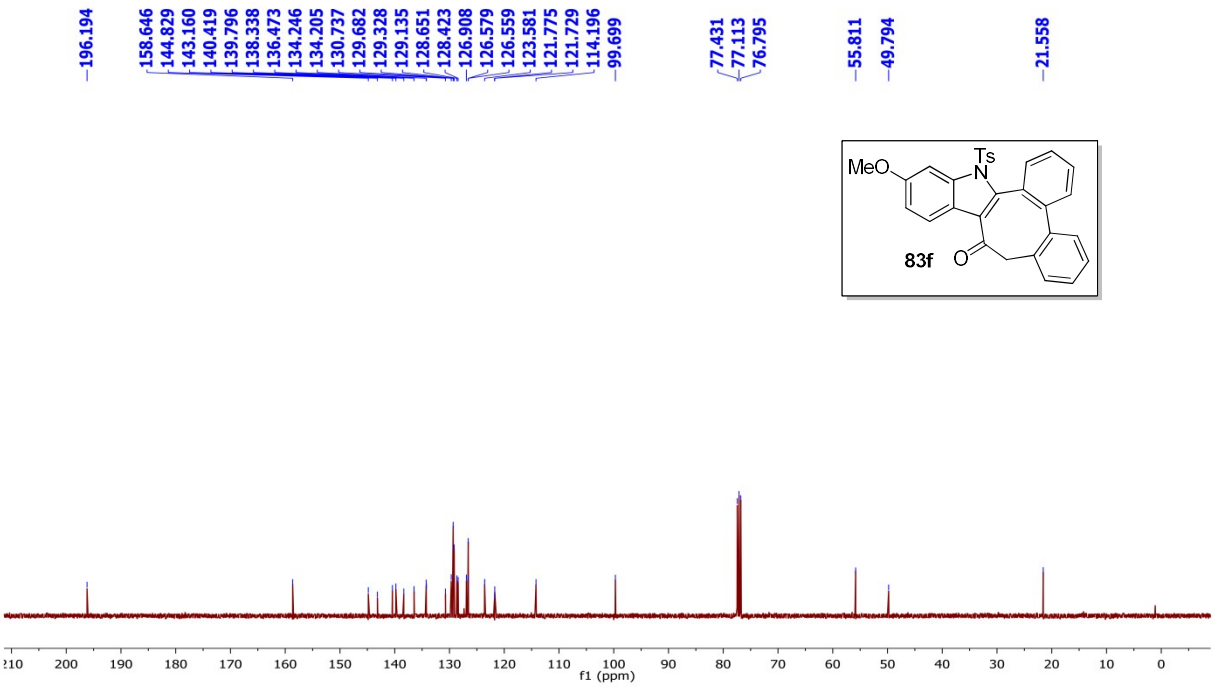
^{13}C{^{1}H} NMR (100 MHz) of **83e :**



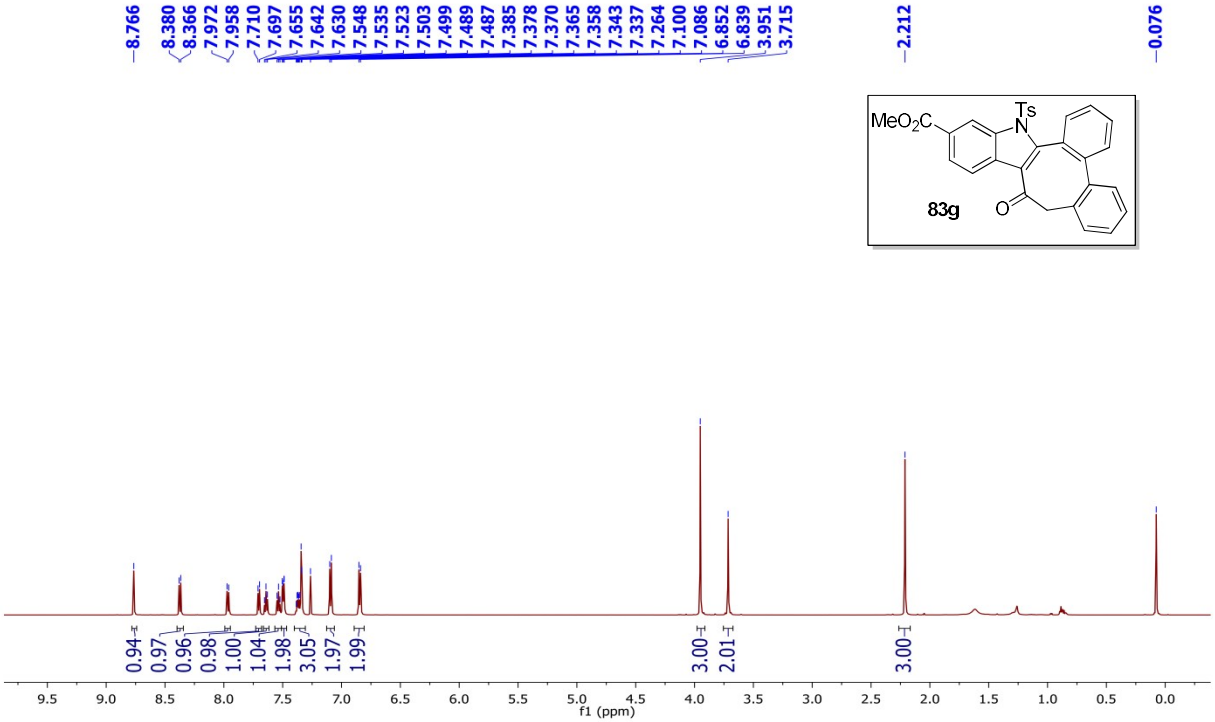
^{1}H NMR (400 MHz) of **83f :**



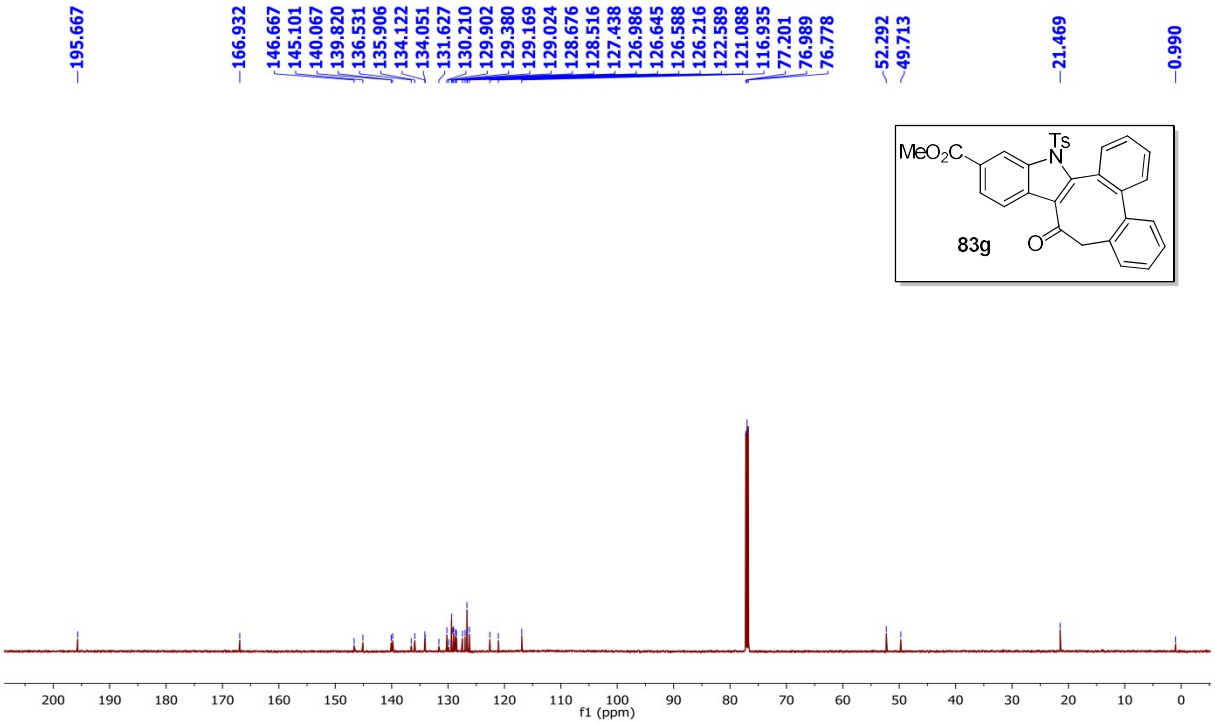
^{13}C{^{1}H} NMR (100 MHz) of **83f :**



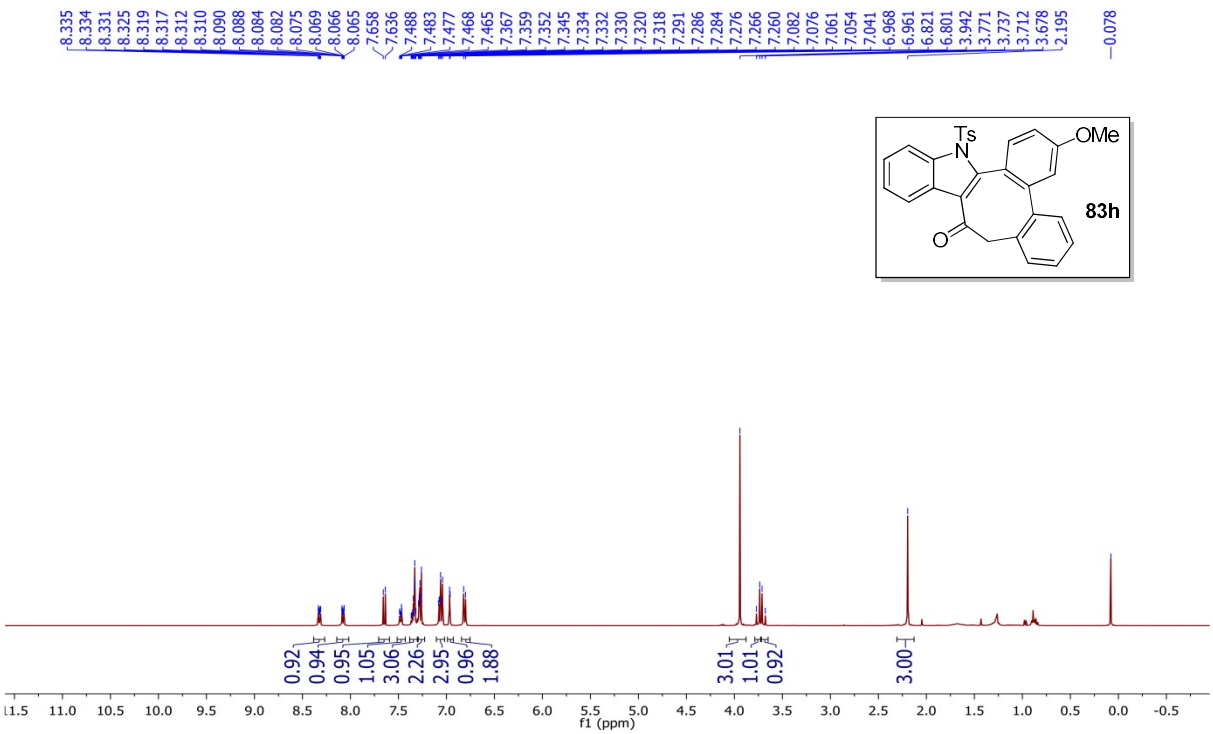
^{1}H NMR (600 MHz) of **83g :**



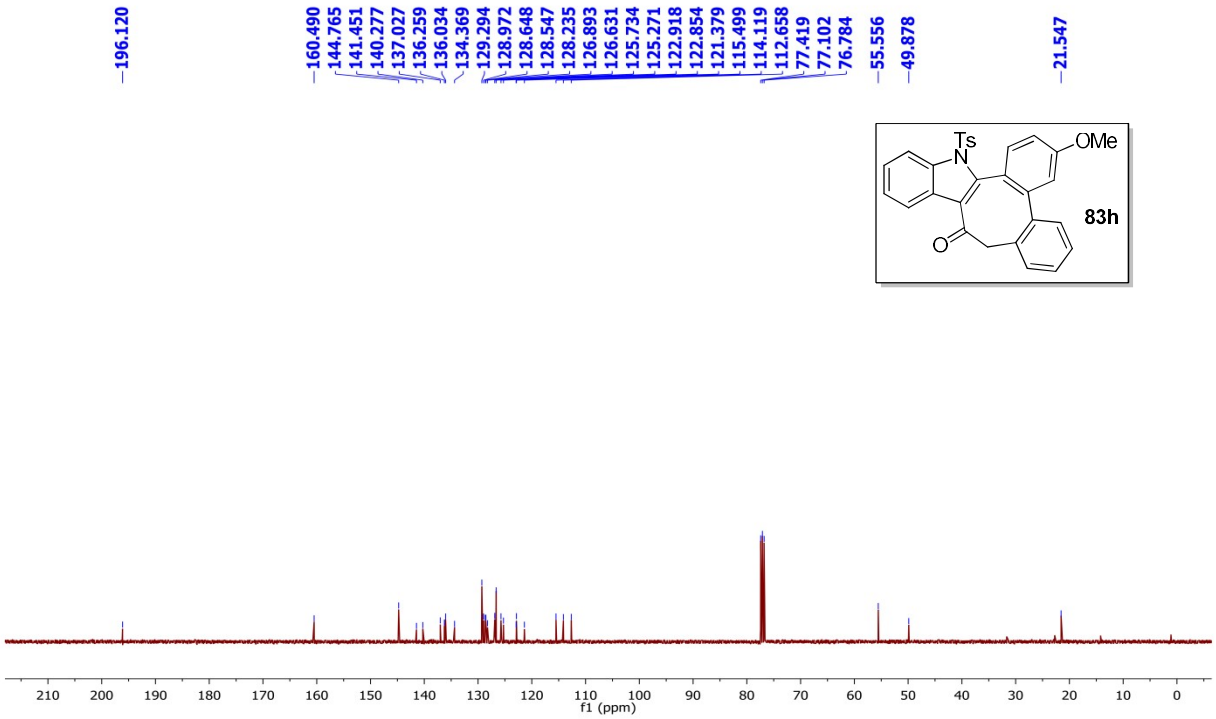
^{13}C{^{1}H} NMR (150 MHz) of **83g :**



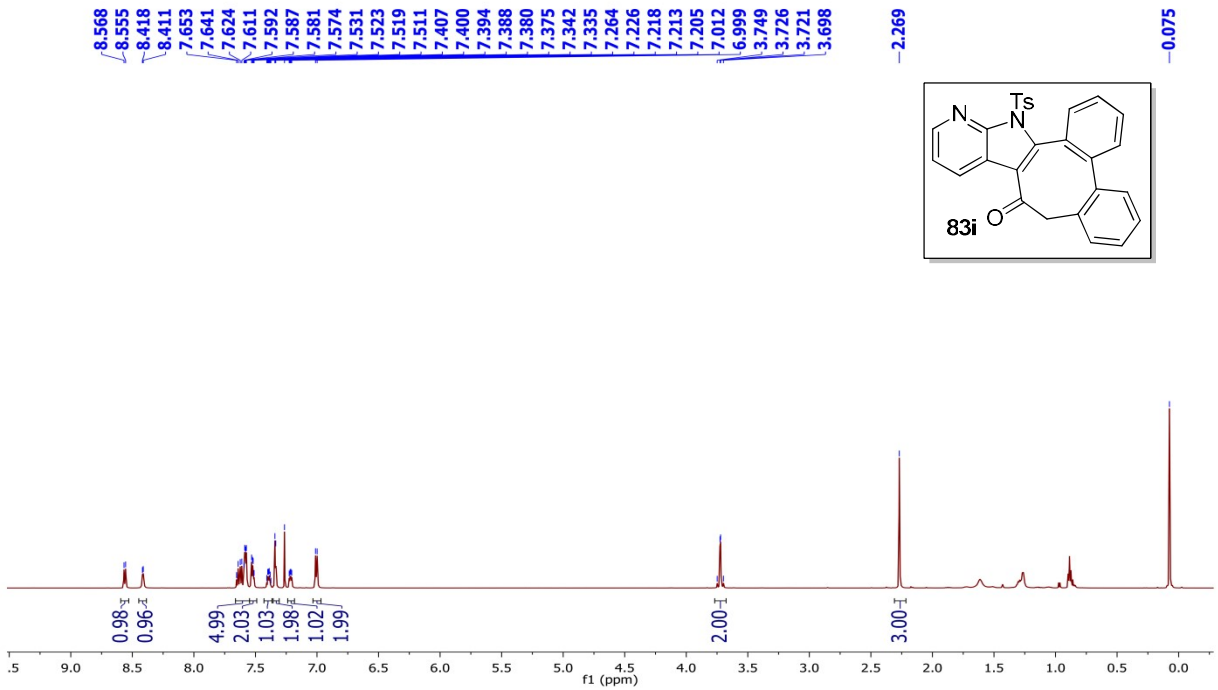
^{1}H NMR (400 MHz) of **83h :**



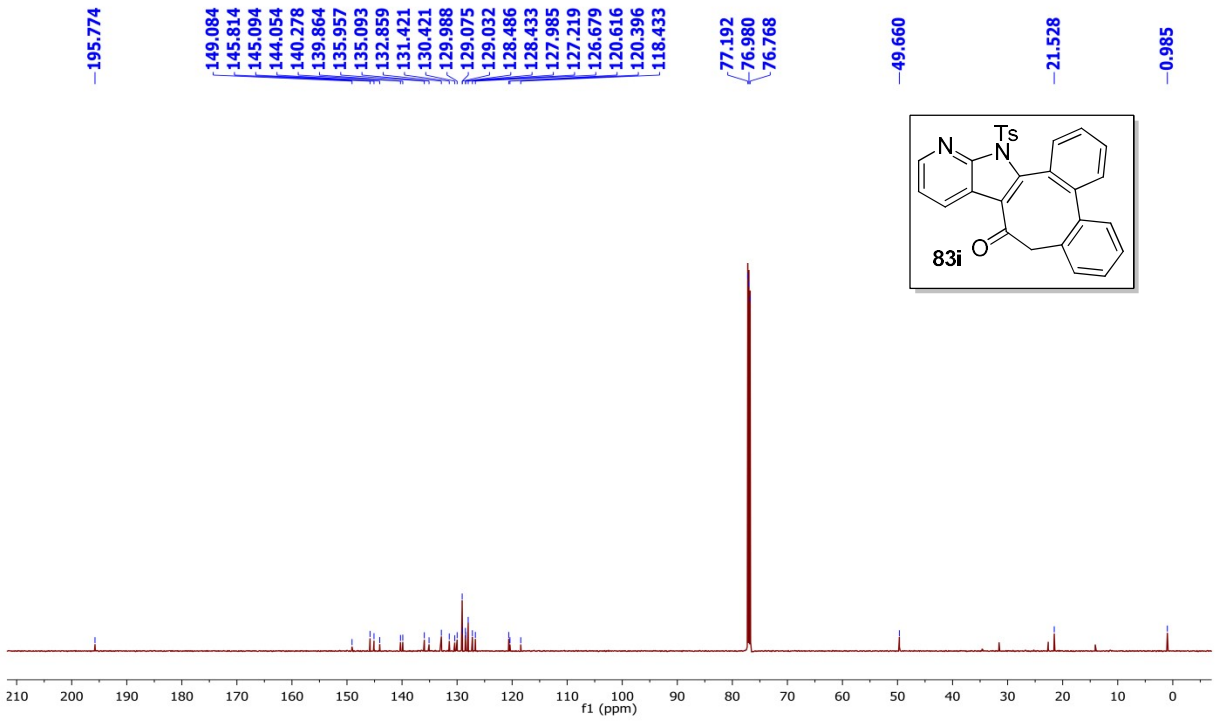
^{13}C{^{1}H} NMR (100 MHz) of **83h :**



^{1}H NMR (600 MHz) of **83i :**

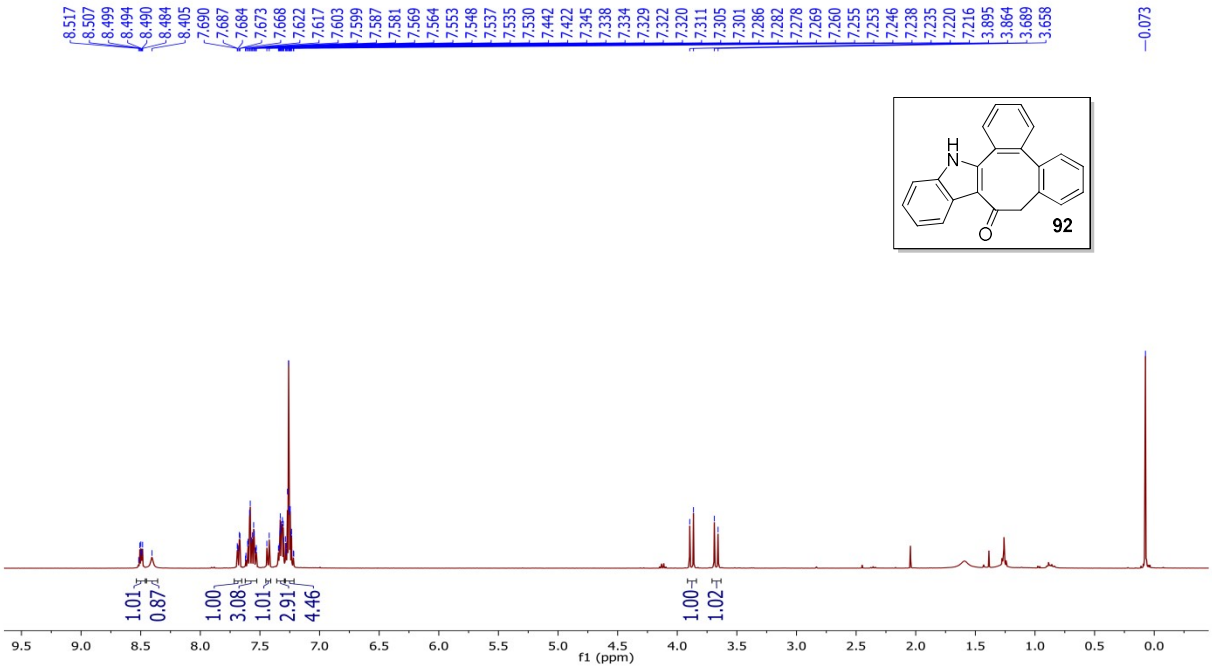


^{13}C{^{1}H} NMR (150 MHz) of **83i :**

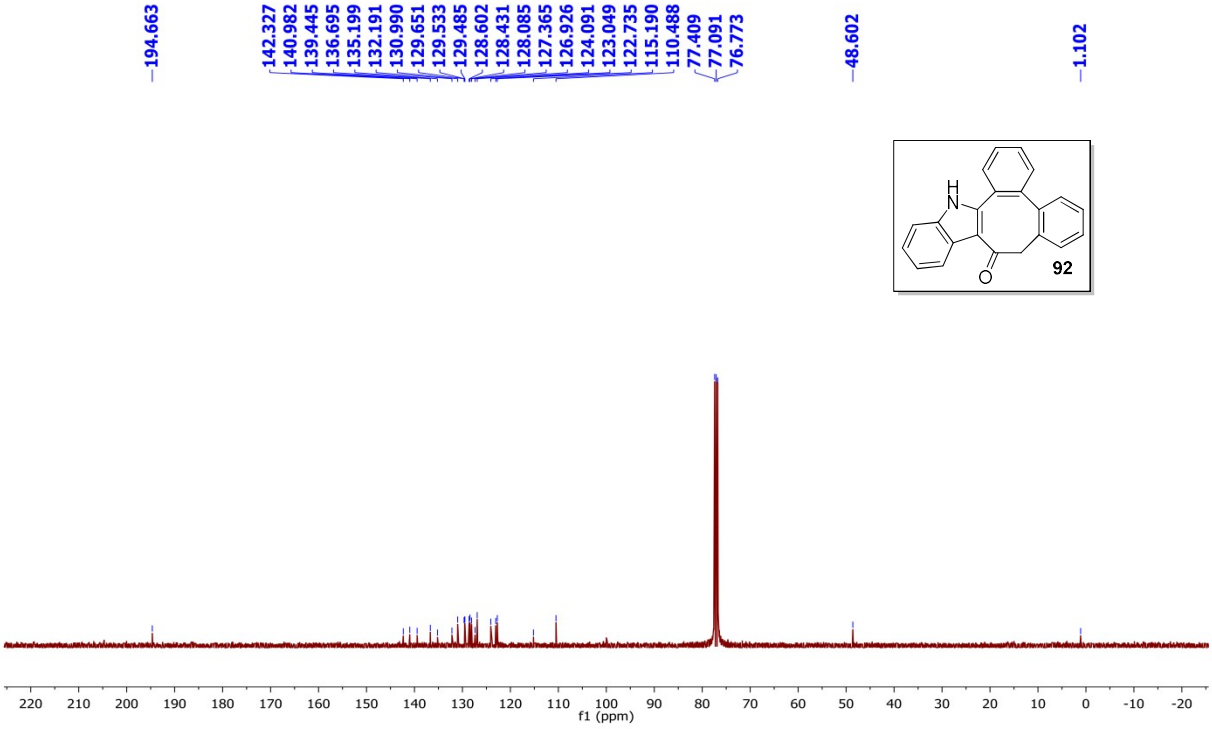


1.2.11.6. NMR Spectra of Compound 92:

^{1}H NMR (400 MHz) of **92:**



^{13}C{^{1}H} NMR (100 MHz) of **92:**



CHAPTER 2

Substrate Controlled Product Divergence in Iron(III)-Catalyzed Reactions of Propargylic Alcohols: Easy Access to Spiro-indenyl 1,4-Benzoxazines and 2-(2,2 Diarylvinyl)quinoxalines

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Part I – A Short Review

2.1.1. Introduction: 1,4-Benzoxazine - an important heterocycle

1, 4-Benzoxazine is considered as an important and privileged heterocyclic scaffold containing two hetero-atoms (i.e., N and O) and recognized as the structural core in large number of natural products,[1-2] and also finds widespread application in various fields.[3-11] For instance, *Blepharin* **1** (Figure 1) and some other glycosides isolated from gramineous plants have been suggested to act as plant resistance factors against microbial diseases and insects.[2a-b] *Actinomycin-D* **2** (Fig. 1) isolated from streptomyces is a marketed anticancer drug.[2c] *Pipofezine (*also known as *Azafen*) **3** (Fig. 1), a tricyclic compound fused with pyridazine is a marketed antidepressant drug and also act as serotonin reuptake inhibitor.[3a] *Bemoradan* **4** (Fig. 1), an antihypertensive agent, expresses cardiotonic effect by acting as an inhibitor of cardiac muscle cyclic AMP phosphodiesterase (PDE).[3b] *Levofloxacin* **5** (Fig. 1) is a therapeutically interesting drug candidate for the treatment of cancer[3c] an also used as antibiotics.[3d] In addition, various derivatives of 1,4-benzoxazine are used for the treatment of infections,[4a] diabetes,[4b] neurodegenerative,[4c-d] inflammatory,[4c-d] autoimmune,[4c-d] cardiovascular disorders[4c-d] and also acts as various types of inhibitor[5] (viz. **6**[5a] is a rennin inhibitor, Fig. 1), antiarrhythmic agents[6] (viz. **7**, Fig. 1) against ischemia-reperfusion injury, antagonists,[7] potassium channel modulators[8] etc. In addition to this, they exert huge applications as CRAC (Calcium release-activated calcium channel) modulators,[9a] antibacterial agent,[9b] activators of the tumor cell specific M2 isoform of pyruvate kinase[9c] and also serve as synthetic building blocks for the construction of more complex molecular structures useful for medical and industrial applications.[10] Besides, there are few reports of their use as antioxidants.[11]

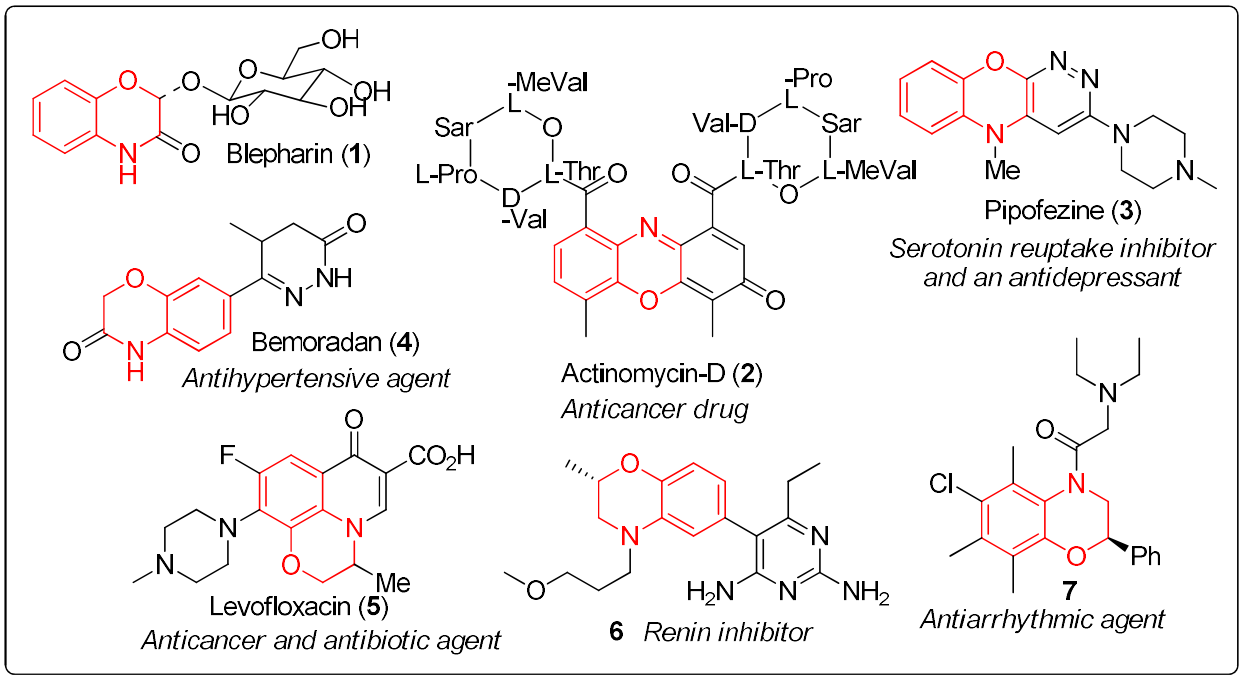


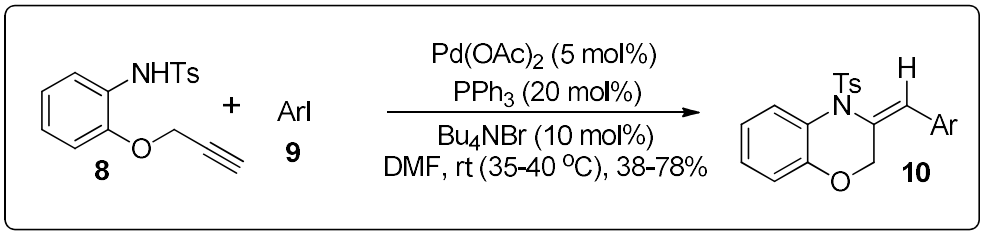
Figure 1: Few natural products containing 1,4-benzoxazine as core structure and some of their biologically active derivatives

2.1.2. Synthesis of 1,4-Benzoxazine:

Due to the widespread applications of diversely substituted 1,4-benzoxaxines in various fields substantial efforts were devoted for their synthesis including mostly inter- and intramolecular cyclizations of acetylenic substrates employing either conventional or metal catalyzed reactions. Few of them are briefly discussed below.

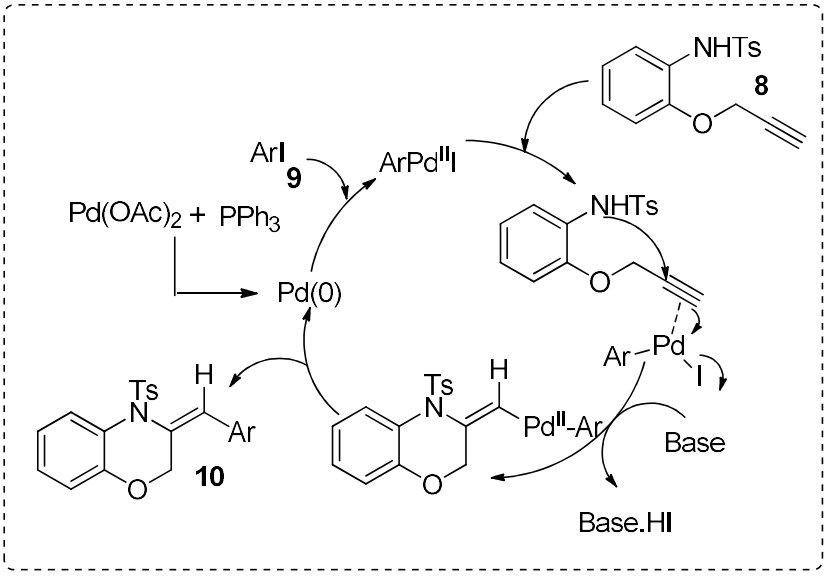
2.1.2.1. Synthesis of 1,4-Benzoxazines via intermolecular reactions of acetylenic substrates:

Chowdhury and coworkers[12] disclosed a new palladium catalyzed intermolecular cyclization strategy for the general synthesis of (*E*)-3-arylidene-3,4-dihydro-2*H*-1,4 benzoxazines **10** from the acetylenic substrate **8** and aryl iodide **9** at room temperature in moderate to good yields (**Scheme 1**). The reaction is operationally simple and totally regio- and stereoselective.



Scheme 1: Schematic representation for the synthesis of product **10**

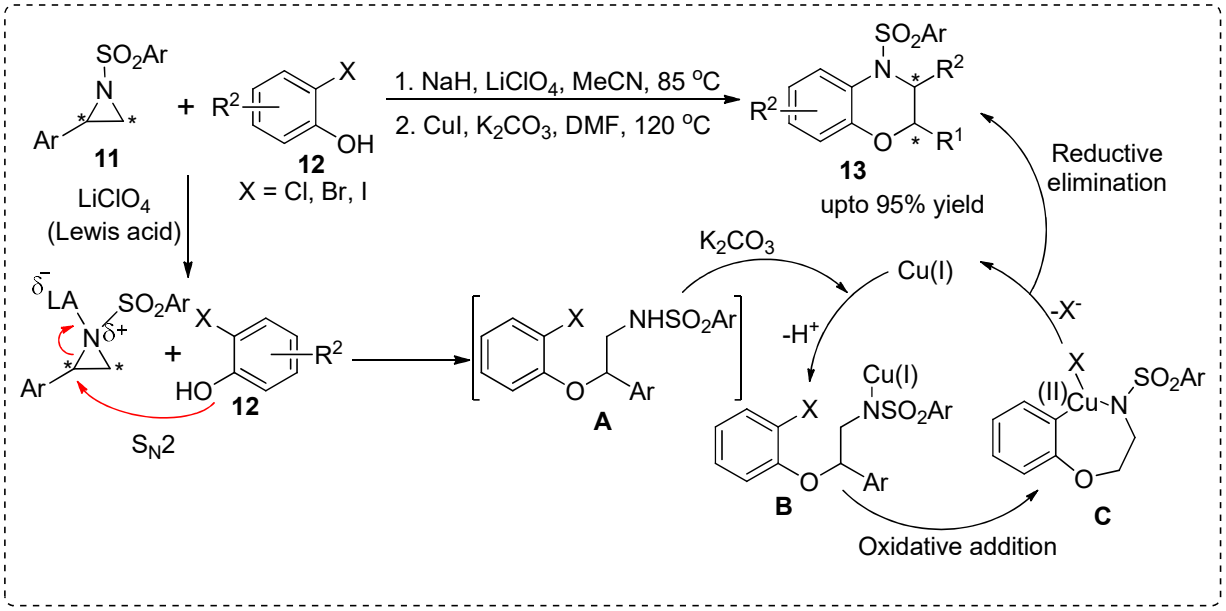
Mechanistically, at first reaction of $Pd(OAc)_2$ and PPh_3 generates Pd(0) *in situ* (**Scheme 2**), which on oxidative addition to the aryl iodide **9** generates the σ-arylpalladium(II) iodide ($ArPd^{II}I$). Next, the σ-arylpalladium(II) iodide ($ArPd^{II}I$) complex activates the triple bond of the acetyleic substrate **8**, which undergoes an intramolecular nucleophilic attack on the activated alkyne via *6-exo-dig* mode resulting in the generation of 1,4-benzoxazine ring with exo-methylene attached with Pd^{II}-Ar moiety. Finally reductive elimination of palladium regenerates Pd(0) and affords the desired product **10** with E-stereochemistry.



Scheme 2: Plausible mechanism for the formation of product **10**

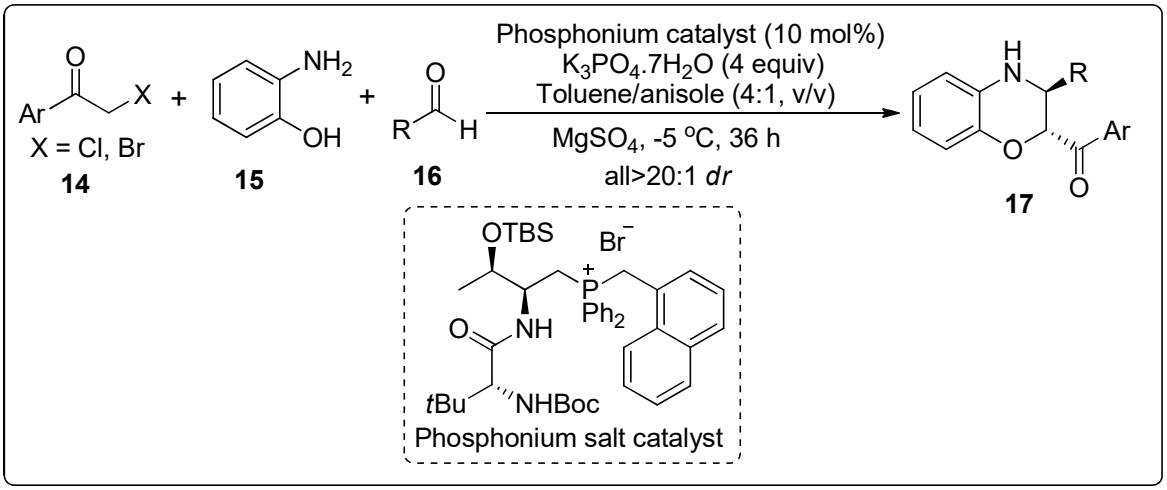
Ghorai and coworkers[13] disclosed a simple and efficient approach for the synthesis of novel 3,4-dihydro-1,4-benzoxazine derivatives **13** (**Scheme 3**) with high enantio- and diastereospecificity (ee > 99%, de > 99%) via Lewis acid-catalyzed S_N2-type ring opening of activated aziridines **11** with halophenols **12** followed by Cu(I)-catalyzed intramolecular C-N

cyclization in a stepwise fashion under one-pot in excellent yields. The strategy offers a short and efficient synthesis of the products. According to the proposed mechanism, the reaction proceeds through the ring opening of aziridines **11** by 2-halophenols **12** in a S_N2 manner generating intermediate **A**, which on CuI-mediated C-N cyclization leads to the subsequent formations of intermediates **B** and **C.** Finally, a reductive elimination of **C** leads to the desired product **13**.



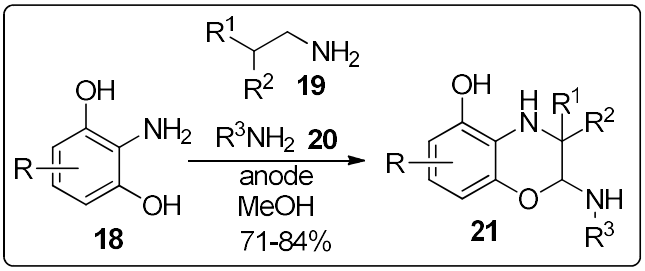
Scheme 3: Schematic presentation for the formation of **13**

Wang and coworkers[14] demonstrated an efficient construction of various 2*H*-1,4-benzoxazine derivatives **17** (**Scheme 4**) with excellent diastereo- and enantioselectivities under mild reaction conditions via a transition metal free multi-component cascade reaction of readily available α-halogenated ketones **14**, ortho-aminophenols **15** and aldehydes **16** using a novel dipeptide-based phosphonium salt catalyst. The products were found to be formed with good to excellent yields and diverse functional groups were well tolerated.



Scheme 4: Schematic presentation for the formation of product **17**

Largeron and coworkers[15] reported a unique pathway for the general synthesis of poly-functionalized 1,4-benzoxaxine derivatives **21** (**Scheme 5**) starting from 2-amino resorcinols **18** and an amine $R^1R^2CHCH_2NH_2$ **19** in presence of a second primary aliphatic amine R^3NH_2 **20** via an electrochemically induced cascade reaction through the variation of the structure of the o-azaquinone mediator, where both cycloaddition partners were generated in situ, at room temperature, under metal-free conditions.

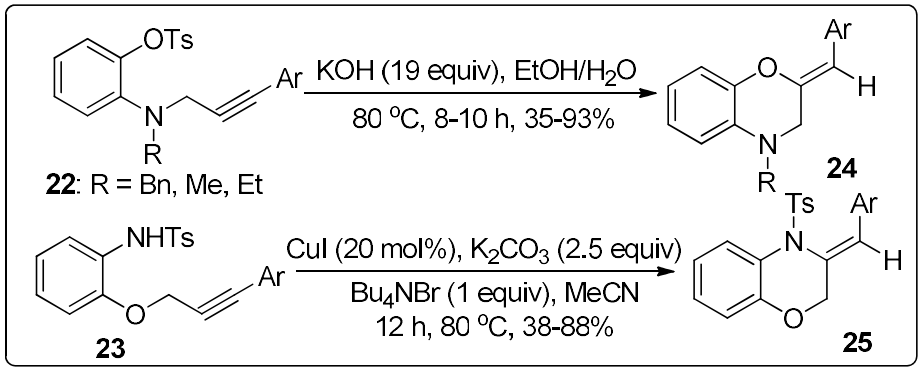


Scheme 5: Synthesis of product **21**

2.1.2.2. Synthesis of 1,4-Benzoxazines via intramolecular cyclizations of alkynes/alkenes

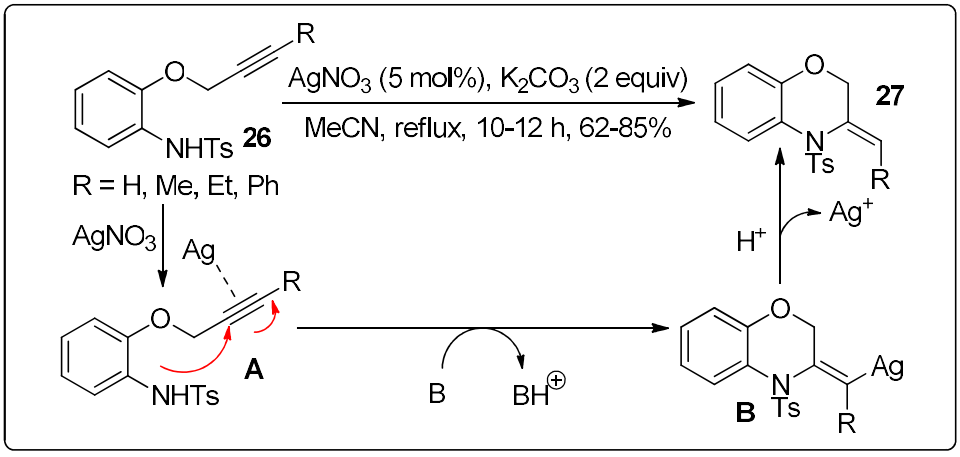
Kundu and coworkers[16] disclosed a convenient approach for synthesis of two different 1,4-benzoxazine derivatives, (*Z*)-4-alkyl-2-(aryl)idene-3,4-dihydro-2*H*-1,4-benzoxazines (**24**, **Scheme 6)** and (*Z*)-4-tosyl-3-(aryl)idene-3,4-dihydro-2*H*-1,4-benzoxazines (**25**, **Scheme 6)** from the respective tosylated starting materials **22** and **23,** respectively. Products **24** are formed under base-mediated reaction. Whereas products **25** are formed under CuI catalyzed reactions of **23**.

Moreover, the reactions are highly regio- and stereoselective, delivering only the (*Z*)-isomer in moderate to excellent yields.



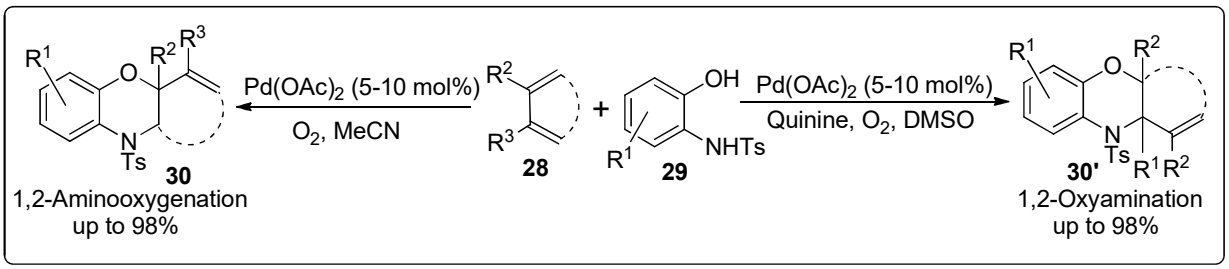
Scheme 6: Synthesis of products **24** and **25** from acetylenic substrates

Karunanidhi *et al.*[17] reported an efficient synthetic strategy for the straightforward synthesis of alkyl/aryl substituted 1,4-benzoxazine **27** (**Scheme 7**) based on Ag(I) catalyzed cyclizations of propargylated amines **26**. According to the mechanism, at first, the triple bond of the substrate **26** coordinates with the metal salt delivering intermediate **A** (**Scheme 7**). Next, a base promoted cyclization following a *6-exo-dig* pathway affords intermediate **B** which on subsequent protodemetalation affords the desired *exo*-cyclic product **27** with regeneration of the catalyst which keeps the catalytic system alive.



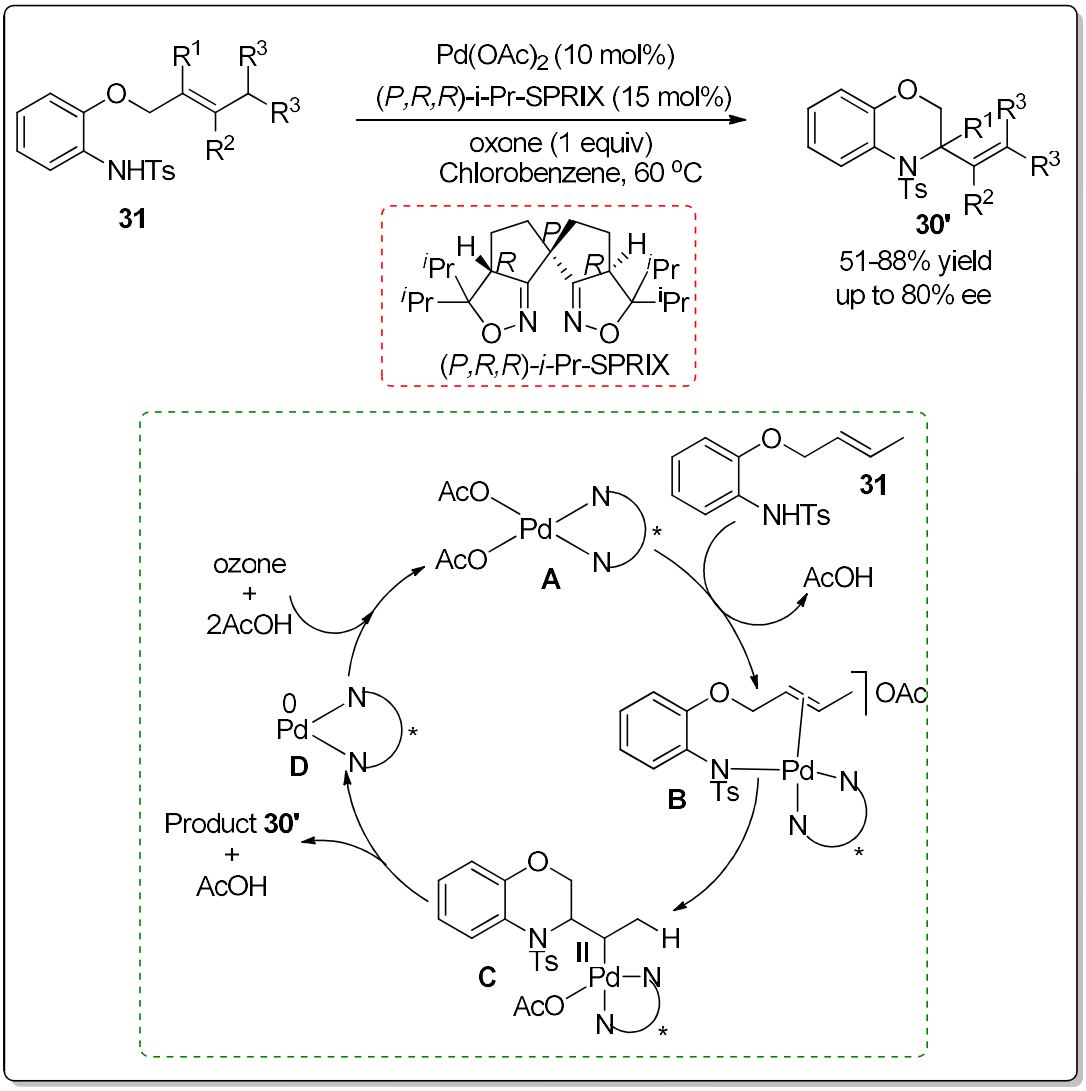
Scheme 7: Synthesis of product **27** with plausible reaction mechanism

Zhang and coworkers[18] developed Pd(II)-catalyzed aerobic intermolecular 1,2-aminooxygenation and 1,2-oxyamination of conjugated dienes **28** in presence of N-tosyl protected 2-aminophenol **29** for the preparation of a variety of functionalized 1,4-benzoxazines **30** and **30′,** respectively (**Scheme 8**). Oxygen was used as terminal oxidant in the oxidative difunctionalization of alkenes. In most cases, the products were delivered in good yields with good selectivities.



Scheme 8: Synthetic pathway for the formation of products **30** and **30′**

Sen *et al.*[19] disclosed a new enantioselective Aza-Wacker-type cyclizations of alkenyl sulfonamide substrates **31**, for the construction of 1,4-bemzoxazine derivatives **30′** (**Scheme 9**) in the presence of *in situ* generated Pd-SPRIX catalyst. Mechanistically, the alkenyl sulfonamide substrates **31** reacts with the Pd-SPRIX catalyst in the presence of oxone as an oxidant, then the olefin moiety undergoes an intramolecular nucleophilic attack by the nitrogen atom to generate the heterocyclic ring. Interestingly, the use of the unique (*P, R, R*)-i-Pr-SPRIX ligand play a key role in the efficient formation of the enantioenriched product **30'**. According to the mechanism, at first the coordination of the substrate **31** with Pd-SPRIX complex **A** leads to the formation of the chelated complex **B** via ligand exchange of the acetate with the sulfonamide and the olefin. Next, intermediate **B** is transformed (via *syn-aminopalladation)* into intermediate **C**, which on subsequent *β*-hydride elimination from alkyl-Pd intermediate delivers the product **30′** and a Pd-H intermediate, the latter of which is re-enters the catalytic cycle after reductive elimination followed by oxidation of the resulting Pd(0) complex **D**.



Scheme 9: Synthetic approach for the formation of product **30′** with plausible reaction mechanism

2.1.3. Spiro-Benzoxazines: An importance organic scaffold

Spirocycles have proved to be a promising organic molecule with a unique three dimentional structure and are considered as privileged scaffolds in medicinal chemistry resulting in the generation of several marketed drugs.[20] For example, *Fenspiride* **32** (Fig. 2) is an anti-inflammatory drug used for the treatment of endotoxemia.[20b] *Enadoline* **33** (Fig. 2), an arylacetamide is a highly selective κ-opioid agonist.[20c] *Cevimeline* **34** (Fig. 2) is a cholinergic agonist and is used for the treatment of dry mouth in patients with Sjögren's Syndrome.[20d] *Fluspirilene* **35** (Fig. 2) is a antipsychotic drug and also act as a potential anti-glioma stem cell

drug.[20e] Besides, spiro-benzoxazines are widely distributed in natural products[21] and functional material.[22] Due to the unique three dimensional structure, incorporation of these compound in other molecules increases the rigidity of the whole scaffold.[23] In addition, the higher sp^3 character of spirocycles enhances various types of physical properties[23] e.g. water solubility, metabolic stability and oral bioavailability etc. A number of spiro compounds shows potential biological activities, e.g. anticancer,[21b] antibacterial,[24a] antituberculosis,[24b] pain killer[24c] etc. beside their use as antioxidants.[24d] Additionally, they play important role in agrochemicals[24e] and in material sciences[25] (e.g., laser dyes,[25a] electroluminiscient devices[25b] and organic photochromic materials[25c]) as well.

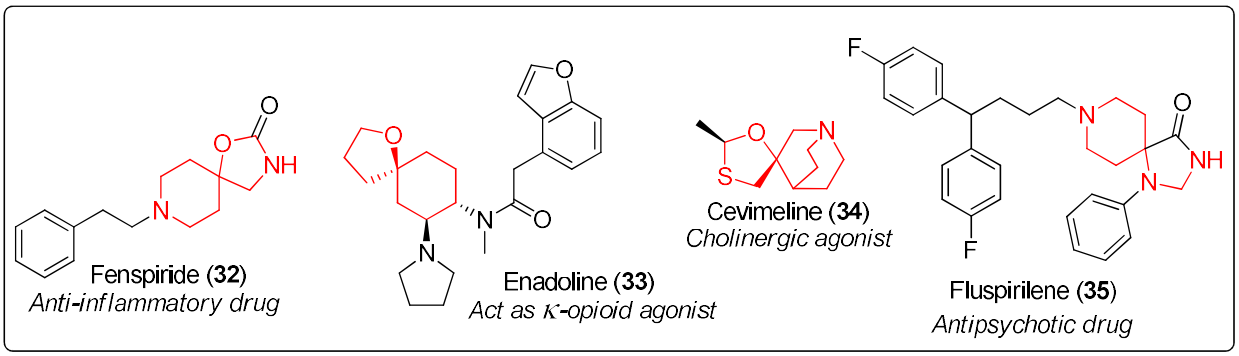


Figure 2. Some marketed drugs containing spirocyclic scaffolds

Among the various spirocycles, spirobenzoxazines are of special interests as these possess broad spectrum of biological activities[26] which make them attractive synthetic targets compare to 1,4-benzoxazines; e.g., Compound **36**[26b] **(**Fig. 3) is an anti-inflammatory agent and also useful as glucocorticoid receptor regulator, while compound **37**[26c](Fig. 1) is a usefull anti-diabetic agent. Compound **38** and its several derivatives are reported to act as inhibitor for MDM2 and p53 interaction, in particular modulators of the MDM2-proteasome interaction;[26d] whereas derivatives of compound **39** acts as highly potent soluble epoxide hydrolase inhibitors and are also orally active drug candidates for the treatment of chronic kidney diseases.[26e] In addition, some spiromorpholine derivatives containing the scaffold of spirobenzoxazines are known to exhibit a broad spectrum of biological activities such as antiproliferative, NK_1 receptor antagonist activity etc.[27]

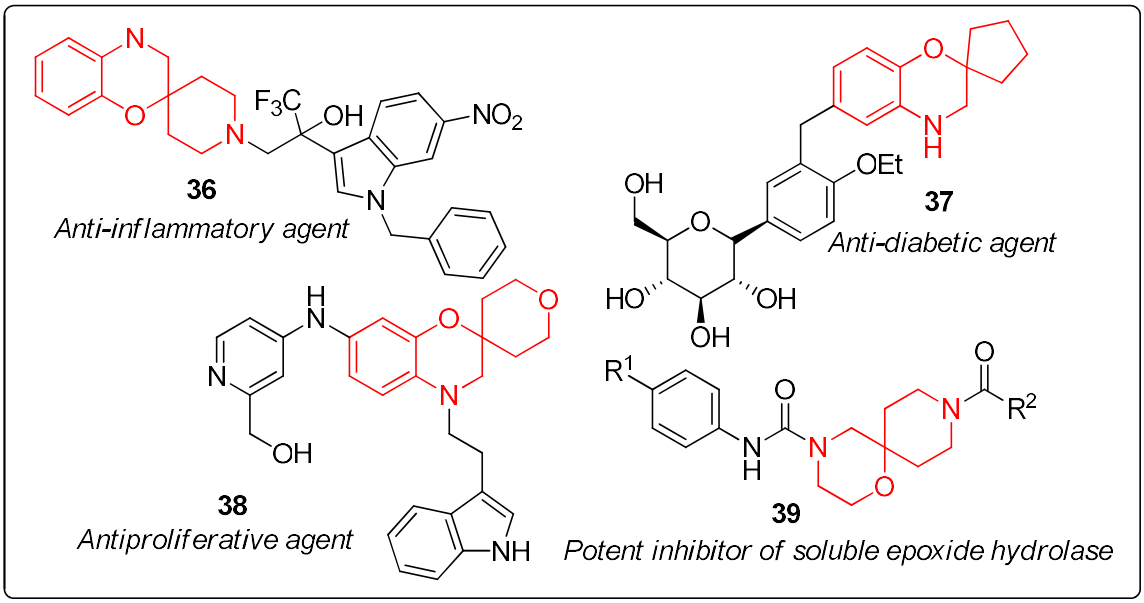


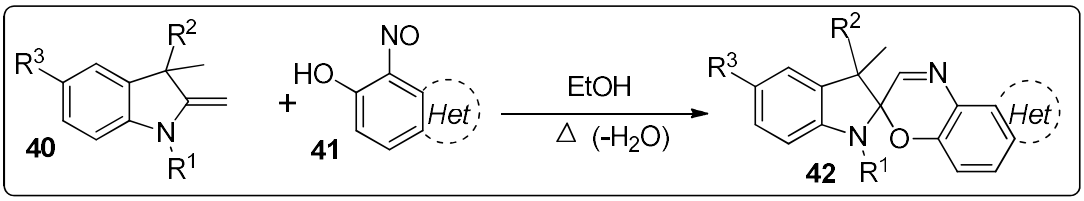
Figure 3. Medicinally active derivatives of Spiro-benzoxazines

2.1.4. Synthesis of Spiro-1,4-Benzoxazines :

There are plenty of synthetic pathway for the construction of 1,4-benzoxazines via conventional or metal catalyzed reactions. However, synthesis of spiro-1,4-benzoxazine under one-pot where simultaneous formations of 1,4-benzoxazine and spiro-annulation taking place in a single step are limited. Some of them are discussed below.

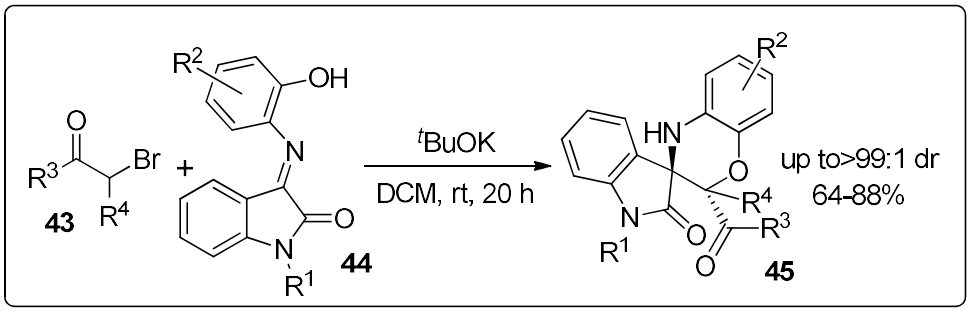
2.1.4.1. Metal free approach for the synthesis of Spiro-1,4-Benzoxazines in one-step:

Tardieu *et al.*[28] reported a general synthesis of spiroannulated indole-1,4-benzoxazine derivatives fused with various heterocycles **42** (**Scheme 10**) via intermolecular dehydration reaction of commercially available *N*-substituted 3,3-dialkyl/aryl-2-methyleneindoline **40** and an intermediate *β*-hydroxy-*α*-nitrosoheterocycles **41** in ethanol in presence of heat.



Scheme 10: Schematic representation for the synthesis of product **42**

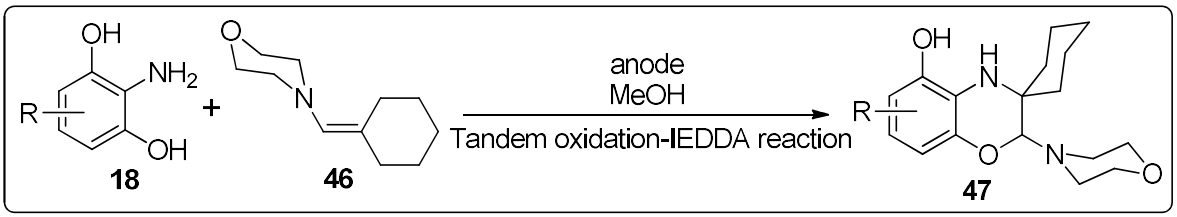
Xie and coworkers[29] developed a mild and convenient pathway for the synthesis of a series of functionalized spiro 1,4-benzoxazine oxindole derivatives **45** (**Scheme 11**) via a base promoted domino *Mannich-alkylation* of α-halocarbonyl compounds **43** with imines **44**. The methodology provides facile access to various new analogues of bioactive spiro-1,4-benzoxazine oxindole derivatives. The products were produced with good to excellent yields.



Scheme 11: Synthetic strategy for the formation of product **45**

2.1.4.2. Electrochemically induced pathway for the synthesis of Spiro-1,4-Benzoxazines in one-step:

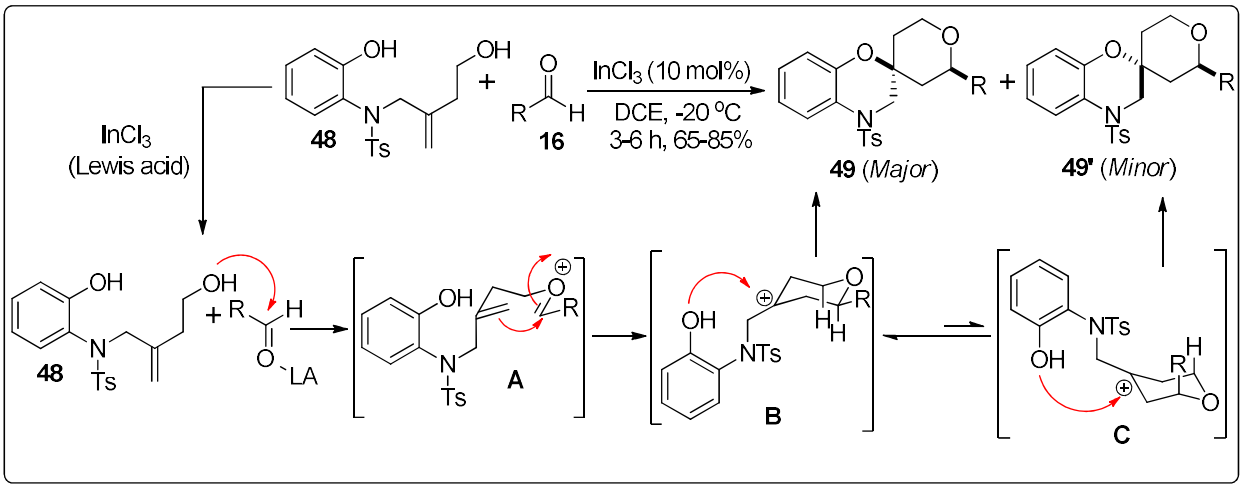
Largeron and coworkers[15] reported an alternative pathway for the general synthesis of spiro-1,4-benzoxazines **47** (**Scheme 12**), where formation of the 1,4-benzoxaine ring and spiroannulation occurs in a single step via an electrochemically induced cascade reaction of 2-aminoresorcinols **18** and an pre-formd enamine **46**. In this reaction, an *Inverse-electron-demand-Diels-Alder* (IED.DA) reaction of the *o*-azaquinone with the enamine delivered the spiro-annulated product **47**.



Scheme 12: Synthesis of Products **47**

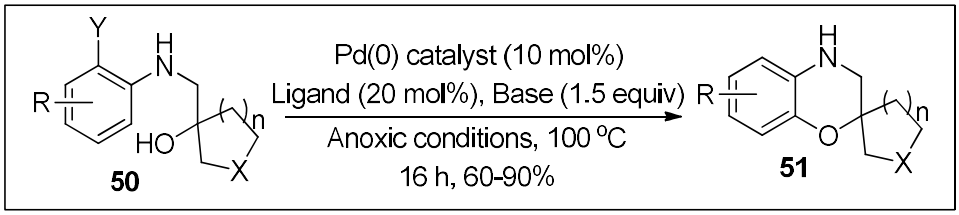
2.1.4.3. Metal catalyzed synthetic pathway for the formation of Spiro-1,4-Benzoxazines in one-step:

Reddy *et al.*[30] disclosed a novel synthetic pathway for the general synthesis of spiro[benzo[*b*][1,4]oxazine-2,40-pyran] derivatives **49** and **49′** (**Scheme 13**) through the reaction of *N*-(4-hydroxy-2-methylenebutyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide **48** and an aldehyde **16** employing $InCl_3$ catalyzed *Prins bicyclization strategy*. The spirocyclization of **48** with **16** proceeds at -20 °C to afford the desired products with good diastereoselectivity. The products were afforded with good yields within few hours. Mechanistically, at first $InCl_3$ activates the aldehyde **16** by acting as a Lewis acid which was then attacked by the homoallylic alcohol of **48** leading to the formation of oxocarbenium ion **A** (**Scheme 13**). Next, the oxocarbenium ion **A** was further attacked by an internal olefin resulting in the formation of a tertiary carbocation **B** which is in equilibrium with intermediate **C**. Next the intermediate **B** (or **C**) undergoes nucleophilic attack by a tethered phenolic group resulting in the formation of the desired spirocycles. Notably, the product **49** was formed as major one from intermediate **B**; the high diastereoselectivity may be attributed by favourable trapping of the carbocation from a less hindered equatorial side and thus, it avoids the unfavorable 1,3-diaxial interactions. Whereas intermediate **C** suffers 1,3-diaxial interactions resulting in the formation of the minor product **49′**.



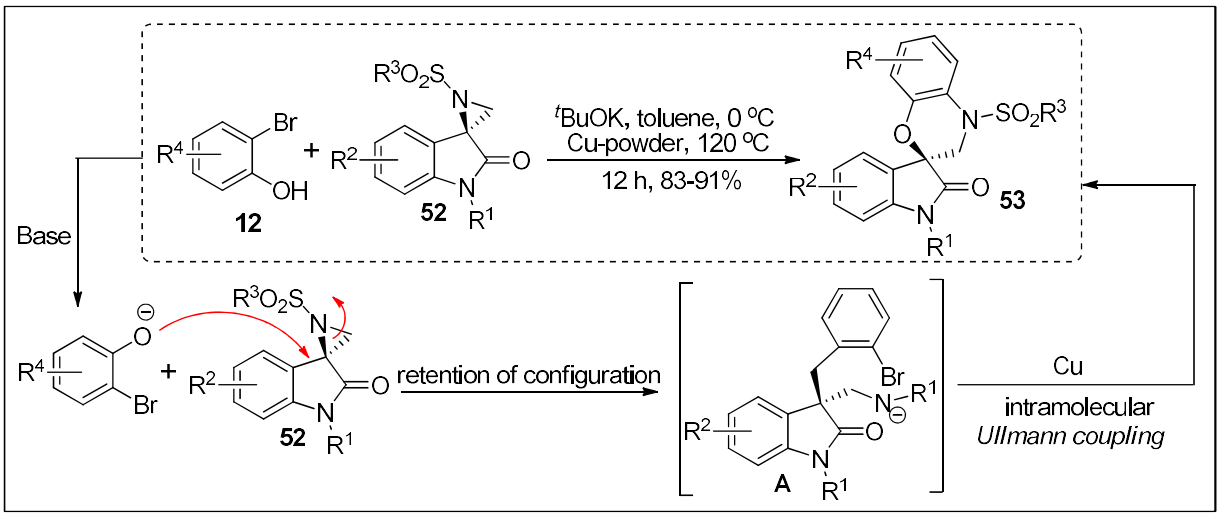
Scheme 13: In(III) catalyzed synthesis of products **49** and **49′**

Kurissery *et al.*[31] reported a versatile and mild approach for the general synthesis of spirocyclic-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine derivatives **51** (**Scheme 14**) via a palladium-catalyzed intramolecular cyclization of starting material **50** leading to the formation of spiroannulated 1,4-benzoxaxines in one pot. The products were delivered with moderate to excellent yields.



Scheme 14: Synthesis of product **51**

Hajra *et al.*[32] demonstrated an efficient one-pot synthesis of enantiopure spiro[3,4-dihydrobenzo[*b*][1,4]oxazine-2,3′-oxindole] **53** (**Scheme 15**) starting from 2-bromophenols **12** and spiroaziridine **52** with high regio- and stereoselectivity via a tandem ring opening/cyclization reation. Mechanistically, at first, 2-bromophenols **12** were transformed into the corresponding 2-bromophenoxide ions with the means of base, which then attacks the spiroaziridines **52** and undergoes a nucleophilic ring opening reaction leading to the formation of intermediate **A** which on further tandem cyclization under an *Ullmann/Goldberg coupling* condition to produce enantiopure desired products **53** with retention of configuration with good to excellent yields.



Scheme 15: Synthetic approach for the formation of product **53**

2.1.5. Importance of indene ring:

Indene and its derivatives are considered as one of the most important and simple carbocyclic core, due to the presence of the scaffold in enormous natural products[33] and also serve as the building block for the construction of many biologically active compounds[34] leading to the development of several drug candidates.[35] *Sulindac* **54** (Figure 4), a non-steroidal anti-inflammatory drug, is known to act against breast cancer serving its role as immune modulator.[35a] *Aprindine* **55** (Fig. 4) is an effective anti-arrhythmic agent and used as drug.[35b] *Rasagiline* **56** (Fig. 4) is a MAO-B inhibitor drug used for the treatment of Parkinson's Disease with neuroprotective potential.[35c] *Dimethindene* **57** (Fig. 4) is a widely used histamine H_1 receptor antagonist.[34b] *R-Indenestrol* **58** (Fig. 4) acts as a potency-selective agonist for Estrogen Receptors (ER) in a cell type-specific manner.[34c] Besides, they are also be used as ligands in organometallic chemistry,[36a] as structural units in molecular machines[36b] and as organic photovoltaics.[36c] It is therefore anticipated that 1,4-benzoxazine pharmacophore spiroannulated with indene could result into novel lead(s) with improved pharmacological profiles.[37]

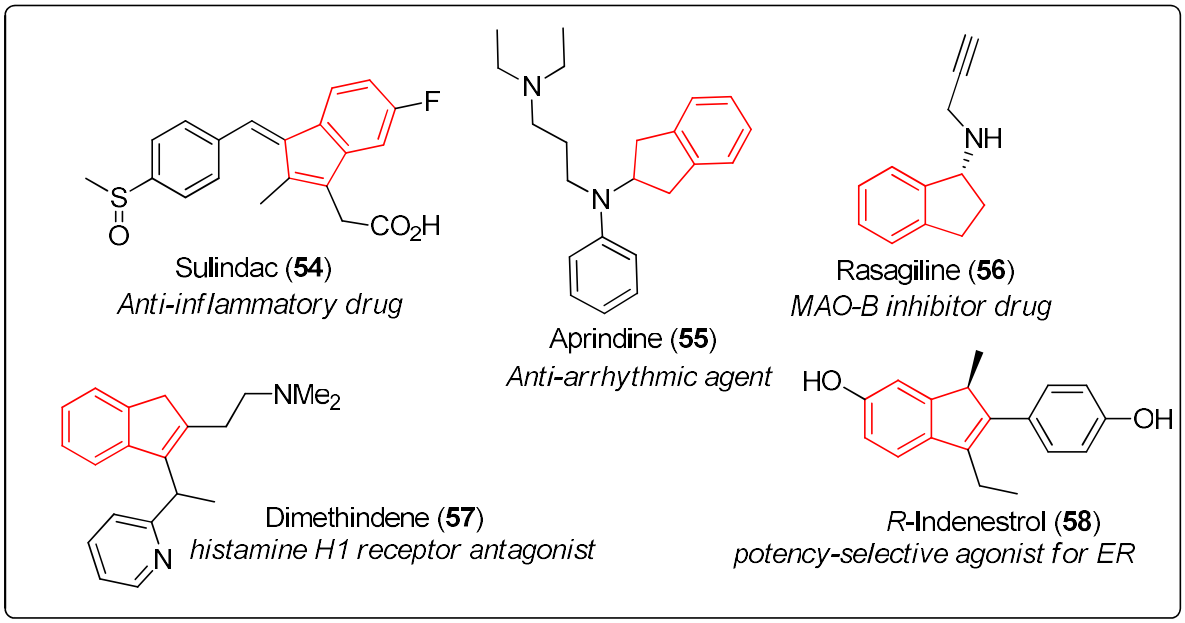


Figure 4: Representative examples of some bioactive indene derivatives

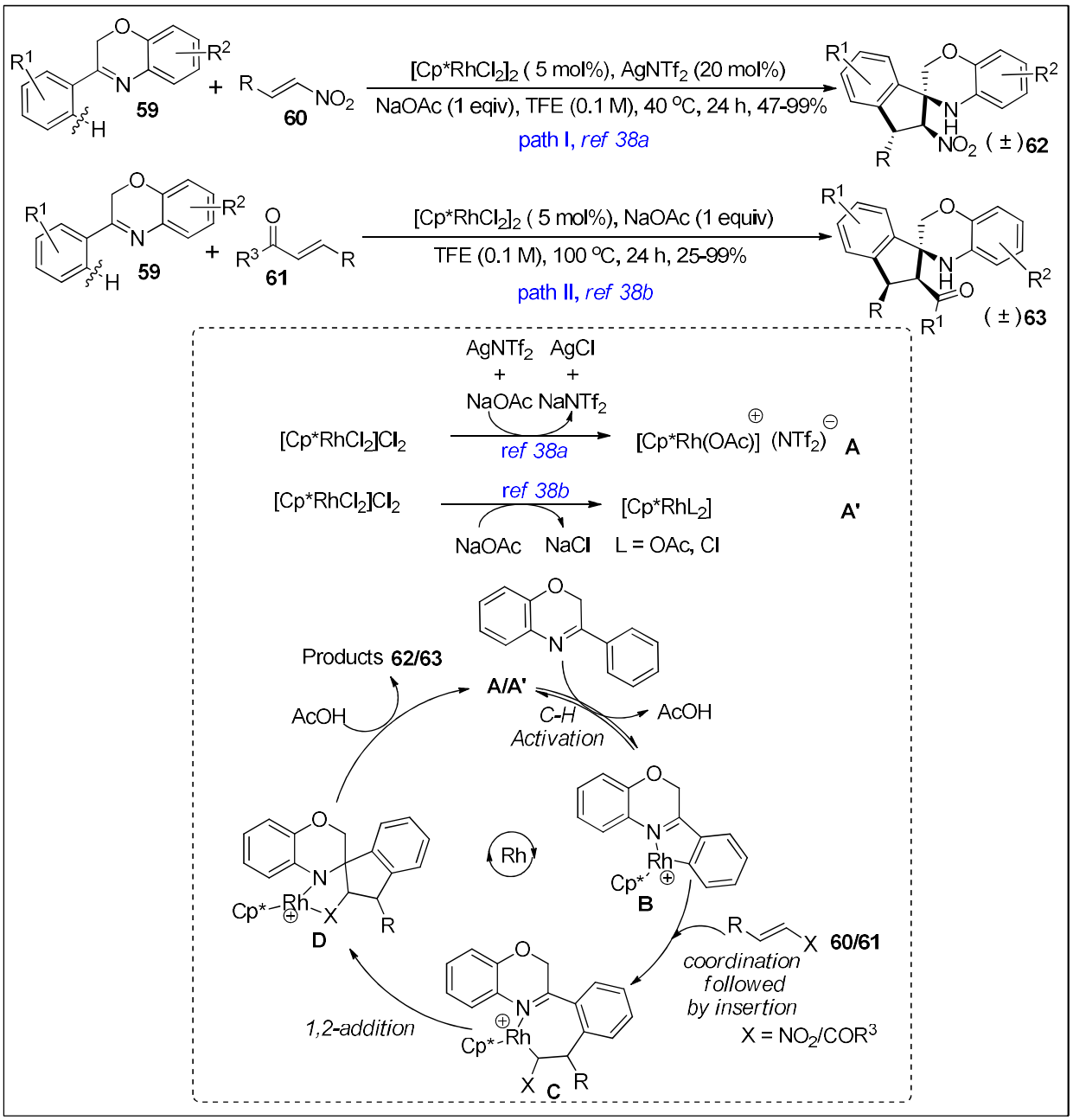
2.1.6. Synthesis of Spiro-indenyl 1,4-Benzoxazines:

To our surprise, scrutiny of literature revels that in spite of the widespread applications of spiro-indenyl 1,4-benzoxazines, there are only couple of methods for their general synthesis using high cost metal catalysts, e.g., Rh, Ag and/or using by-catalytic system involving C-H activation/[3 + 2] annulation, where spirocyclization on pre-formed 1,4-benzoxazine is made. They are demonstrated below.

2.1.6.1.

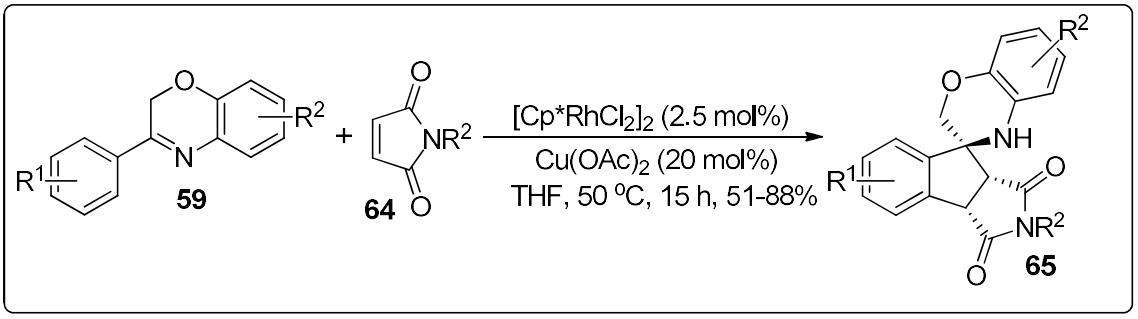
Deb and coworkers[38a] disclosed an efficient atom economic synthetic route for the general synthesis of spirocyclic 2,3-dihydro-1,4-benzoxazine derivatives **62** (**Scheme 16**, path I) via a Rh(III)-catalyzed [3 + 2] spirocyclization of benzoxazines **59** with nitroalkenes **60** via redox-neutral C-H functionalization/annulation with good to excellent yields under mild reaction conditions. Mechanistically, at first a monomeric cationic Rh(III) species **A** is formed via *in situ* reaction of the reagents comprising $[Cp^*RhCl_2]_2$, $AgNTf_2$ and NaOAc. Then, reversible C-H activation of substrate **59** by the intermediate **A** leads to the formation of intermediate **B**. Subsequent coordination followed by insertion of nitroalkene generates complex **C**. Finally, 1,2-addition of C-Rh bond on electrophilic imine center lead to **D** which upon proto-demetalation deliveres the desired product **62** and regenerates the activated species **A**, which keeps alive the catalytic system.

In continuation to the aforesaid work, in 2022, the same group reported[38b] (**Scheme 16**, path II) another regio- and diastereoselective atom economic synthetic pathway for the formation *α*-aroyl spiro-indanamines **63** via a Rh(III)-catalyzed [3 + 2]-spiroannulation reaction between benzoxazine **59** and *α*,*β*-unsaturated carbonyl compounds **61** containing three stereogenic centers in one pot. In this case, the reaction does not require any silver additives or external oxidants like earlier report.[38a] Mechanistically, the reaction proceeds through the similar pathway as discussed in report but in contrary to the previous report,[38a] only the Rh-catalyst intermediate **A′** is formed via *in situ* reaction of the employed Rh catalyst $[Cp^*RhCl_2]_2$ and NaOAC in place of species **A**.



Scheme 16: Synthesis of the products **62** and **63** with mechanistic rational

Luo and coworkers[38c] reported a general synthesis of the spiro-indenyl 1,4-benzoxazines **65** (**Scheme 17**) via a rhodium-catalyzed C-H activation triggered by [3 + 2] annulation of general aromatic ketimines **59** and *N*-substituted maleimides **64**. The products were formed with good yields with excellent diastereoselectivity.

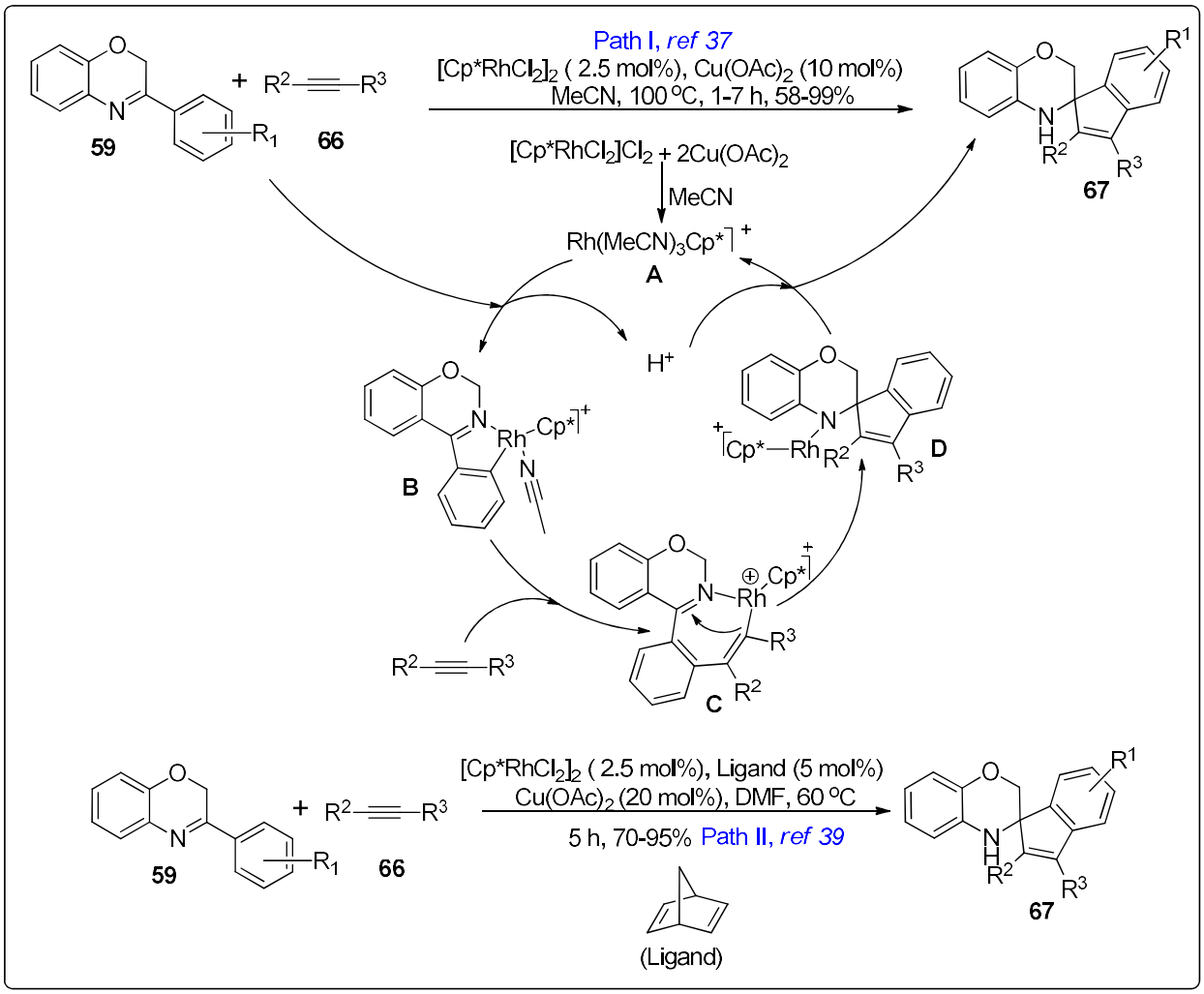


Scheme 17: Synthesis of products **65**

2.1.6.2.

Chen and coworkes[37] demonstrated a general synthetic strategy for the formation of spiro-indenyl 1,4-benzoxazines **67 (**Path I, **Scheme 18)** via a rhodium (III) catalyzed C-H activation/annulation of 3-aryl-2*H*-benzo[*b*][1,4]oxazines **59** and alkynes **66**. This reaction affords a series of spiro indenyl benzoxazines in high yields under mild reaction condition with good functional group tolerance. According to the mechanism, at first, an active Rh-catalytic species **A** is generated by an *in situ* reaction of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$. The imine nitrogen atom of the benzoxazine directs an ortho C-H activation to form a five membered rhodacycle intermediate **B** similar to the previous mechanism (**Scheme 16**). Subsequent insertion of the alkyne onto the intermediate **B** leads to the formation of a seven-membered intermediate **C** which undergoes a Grignard-like migration to the imine group to generate intermediate **D**. Protonolysis of **D** deliveres the final desired product **67** with regeneration of the catalyst which keeps the catalytic cycle alive.

Another synthetic pathway for the formations of **67** (Path II, **Scheme 18**) was reported by **Luo** and coworkers[39] via a Rh-catalyzed C-H-activation/ [3 + 2] annulation of ketimines **59** and alkynes **66** in presence of a ligand, where ligand effects were also studied for the conversion. The olefin promoted the reaction by increasing both the turnover rate and conversion of $[Cp^*RhCl_2]_2$ in the formation of rhodacycle in the C-H activation step. The products were delivered with good to excellent yields within 5 h.



Scheme 18: Synthesis of product **67** and plausible reaction mechanism

2.1.7. Quinoxaline: An important heterocyclic moiety

2.1.7.1. Importance of quinoxalines and their 2-substituted derivatives

N-Heterocycles are present in many bio-active and naturally occurring molecules with wide range of applications in numerous fields.[40] Among the various nitrogen heterocycles, quinoxalines and their related derivatives represent an important class of compounds serving as core structure of various natural products[41a] and pharmacologically active compounds[41b-e] including drugs.[41f-h] For example, *Brimonidine* **68** (Figure 5) is a drug used in the management of glaucoma throughout the world and is the most modern α_2-adrenoceptor agonist available.[41g] While *Varenicline* **69** (Fig. 5) is a medication used for smoking cessation.[41h] In addition, they are

used as building-blocks in the synthesis of potent DNA binding agents,[42a] anionic receptors,[42b] cavitands,[42c] dehydroannulenes[42d] among others and are also identified as antihypertensive agents and animal growth promoters.[43] Moreover, some quinoxaline-diones are used for the treatment of epilepsy, pain and other neurodegenerative disorders.[44] The scaffold is present as the core structure of a number of antibiotics, which are known to inhibit the growth of gram-positive bacteria and are also active against various transplantable tumors.[45] Besides their biological importance, they find huge applications in material sciences such as electroluminescent materials,[46a] organic semiconductors,[46b] OLEDs[46c] etc.

Furthermore, quinioxalines having substitutions at C2 or C3 have drawn attention due to their potent applications. Many quinoxalines were patented as antitumor agents;[47] among them, both *XK-469* **70** (Fig. 5) and the chloroquinoxaline sulfonamide (CQS) **71** (Fig. 5) posses anti-cancer activity against solid tumors.[48] Nevertheless, compound **72** (Fig. 5) and its few derivatives are reported to exhibit potent anti-inflammatory and analgesic activities.[49] Whereas some quinoxaline derivatives act as potent inhibitors of epidermal growth factor receptor (EGFR); e.g. *AG 1295* **73** (Fig. 5).[50a] 4'-acetoxybenzyl 2-quinoxalinecarboxylate (**74**, Fig. 5) containing the core structure of 2-vinyl quinoxaline is reported to show potent activity against *M. tuberculosis* (Mtb).[50b] Besides the medicinal importance, they are also used as pesticide (e.g. compound **75**, Fig. 5)[50c] and find applications in material science; such as derivatives of **76** (Fig. 5) act as efficient electroluminescent materials.[46a]

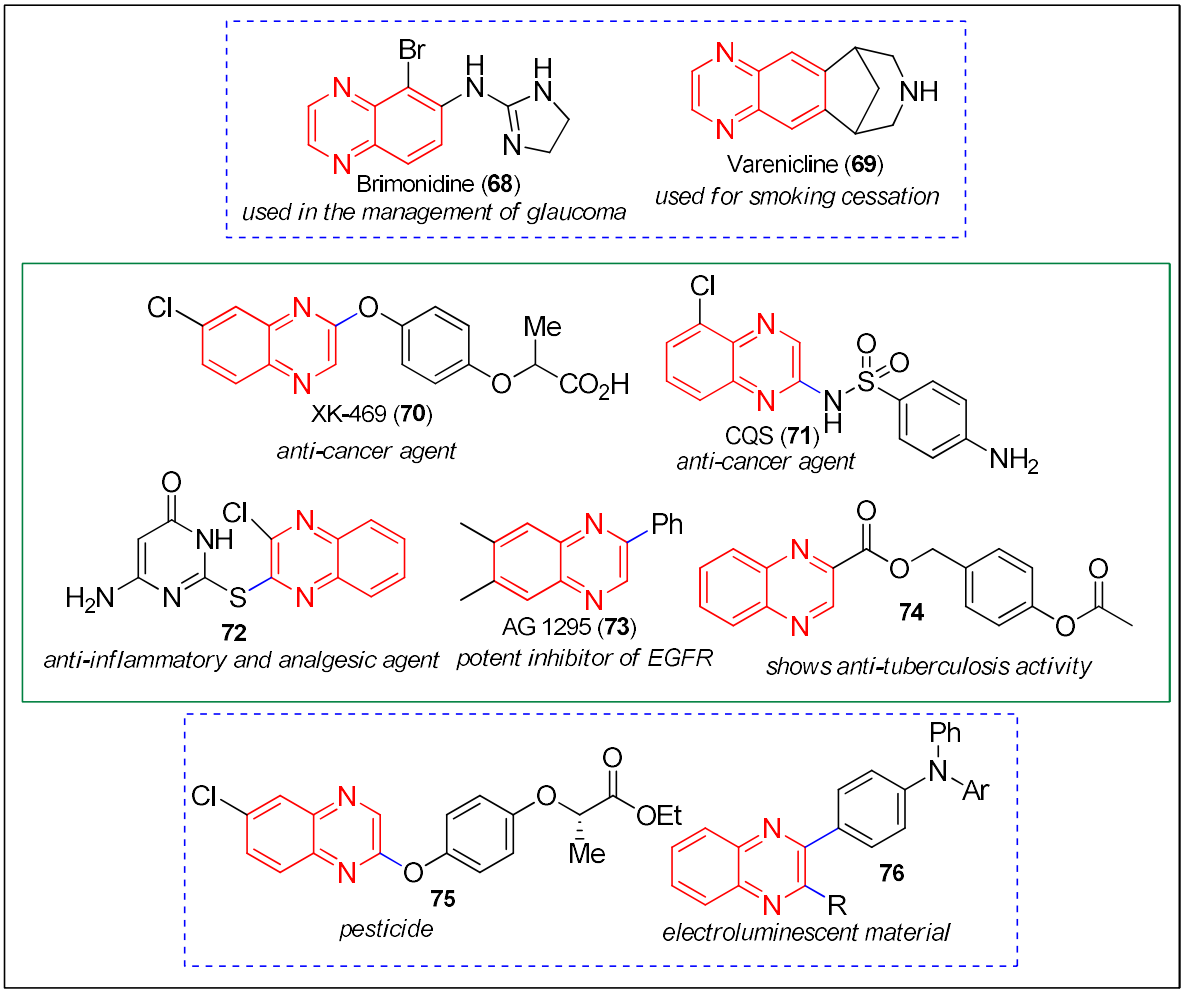


Figure 5. Some important C2/C3 substituted quinoxalines derivatives

2.1.7.2. Importance of vinyl substituted quinoxalines derivatives (at C2 or C3 position)

Notably, among the C2 or C3 substituted quinoxalines, their vinyl substituted derivatives (at C2 or C4 position) are also considered as one of the important subclass of substituted quinoxalines because of their therapeutic importance and are emerged as novel pharmacophore in contemporary research of medicinal chemistry. Some 2-vinyl quinoxaline derivatives show potent activity against various cancer cell lines. For example, compounds **77** (Figure. 6) show activity against various cancer cell lines such as ovarian cancer (OVCAR-4) and leukemia (HL-60).[50a] Besides, derivatives of **78** (Fig. 6) exhibited remarkable activity[51a] against few tumor cell lines (viz., H460, Hct116, Hela229, and B16-F10) which are known to express high levels of FGFR1.[51b-c] Compound **79** (Fig. 6) serve as useful rigid subunits in the glucagon receptor

antagonist.[51d] Compound **80** (Fig. 6) is reported to be a VEGFR-2 inhibitor,[51e] whereas compound **81** (Fig. 6) is reported to show potent anti-tuberculosis activity[51f] and **82** (Fig. 6) shows antioxidant properties.[51g]

More specifically, in recent past, (2,2-diarylvinyl)-3-arylquinoxaline[52a] **83** (Fig. 6) proved to be a potential inhibitor of *sirtuins* (promising targets[52b-c] for cancer therapeutics) which was supported by *in-silico* binding studies followed by *in-vitro* and toxicity studies. Besides, compound **84** (Fig. 6) shows significant photophysical properties.[53]

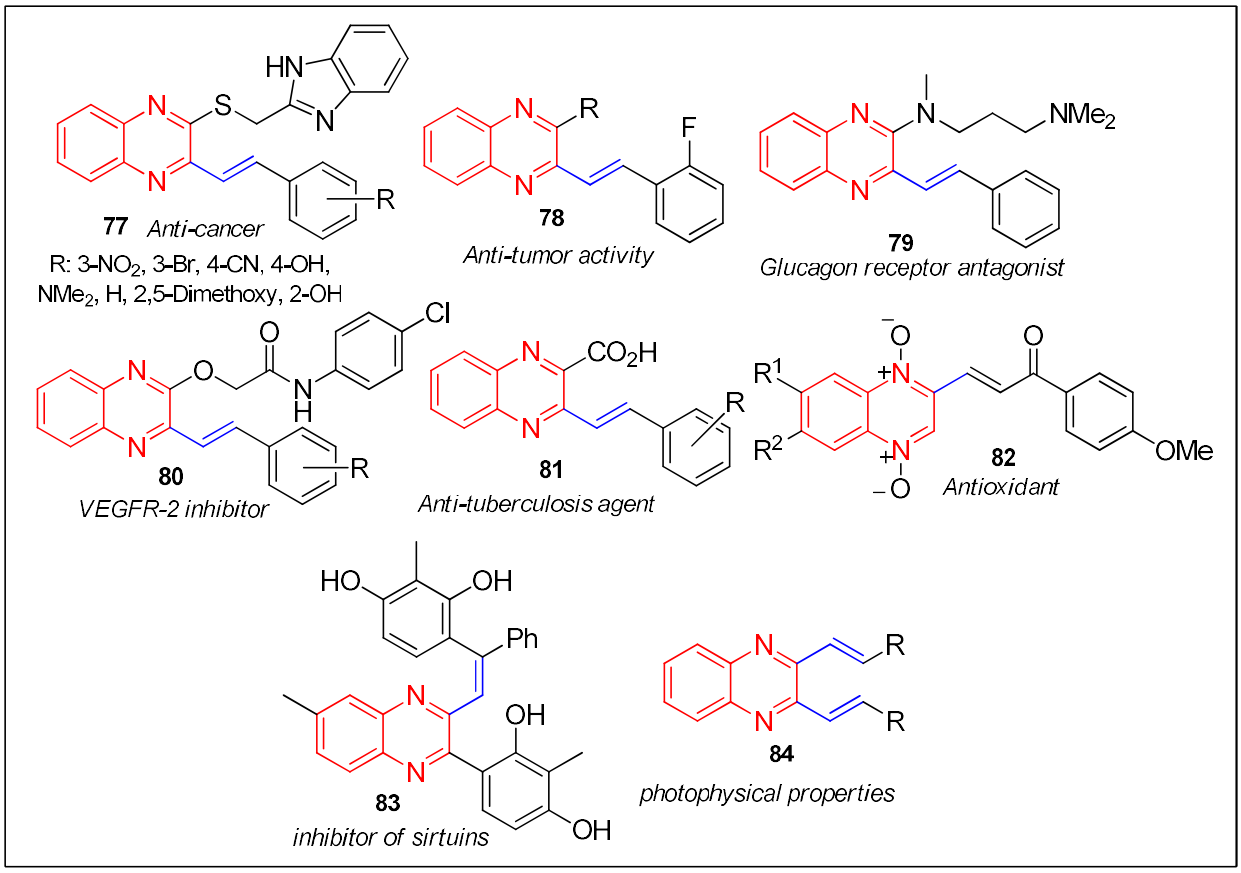


Figure 6. Some important vinyl-substituted (at C2 or C4) quinoxalines

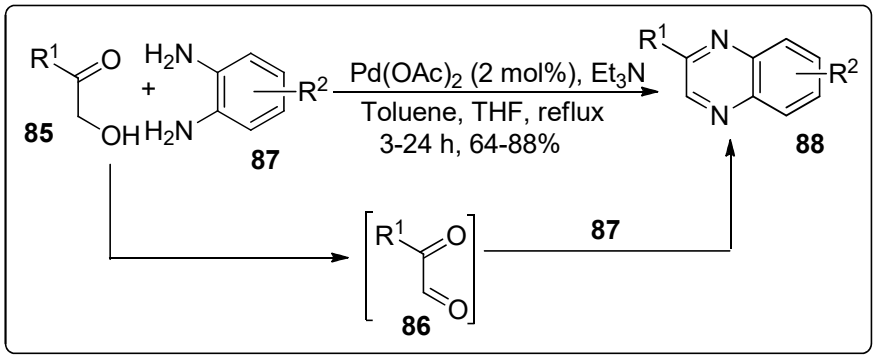
2.1.8. Synthesis of C2/C3-substituted quinoxalines

In view of the strong biological activity and wide utilities of substituted quinoxalines, diverse well-established methods have been developed to construct these structural motifs.[54] Most of the methods deals with various multicomponent reactions[54b] or oxidative cyclization[55a-c]

of various substrates involving classical, conventional or metal catalyzed pathways or condensation reactions.[55d-e] Few of the reports are illustrated briefly.

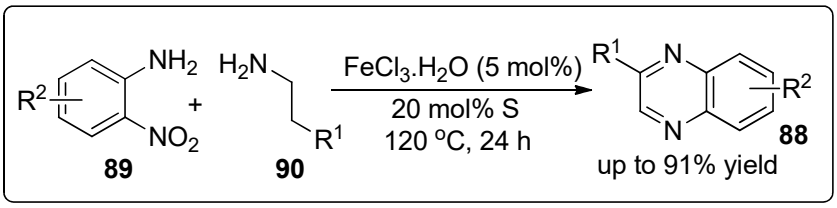
2.1.8.1. Synthesis of C2/C3-substituted quinoxalines

Taylor and coworker[55a] reported a direct synthesis of 2-substituted quinoxalines **88** (**Scheme 19**) from α-hydroxy ketones **85** and 1,2-diaminoarenes **87** via a Pd(II) catalyzed aerobic oxidation in presence of triethylamine. The product **88** is formed via the condensation of *in situ* formed 1,2-dicarbonyl **86** and 1,2-diaminoarene **87**. The products were formed within few hours with good to excellent yields.



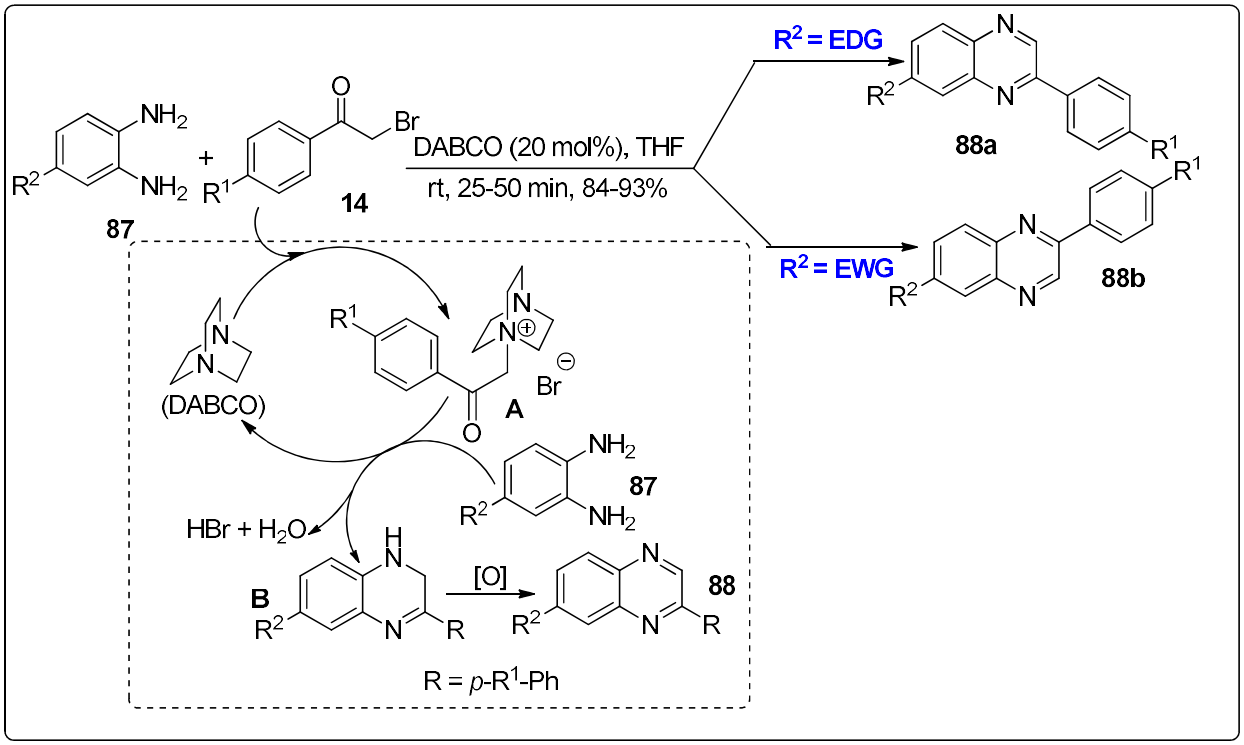
Scheme 19: Synthesis of quinoxalines **88**

Nguyen and coworkers[55b] disclosed a unique pathway for the synthesis of **88** (**Scheme 20**) from *ortho*-nitroanilines **89** and phenethylamines **90** via a redox condensation reaction catalyzed by an iron/sulfur cluster. The cluster is generated *in situ* from elemental sulfur and ferric chloride. The pathway provided is highly economical and delivers the product with high yield.



Scheme 20: Synthesis of quinoxalines **88**

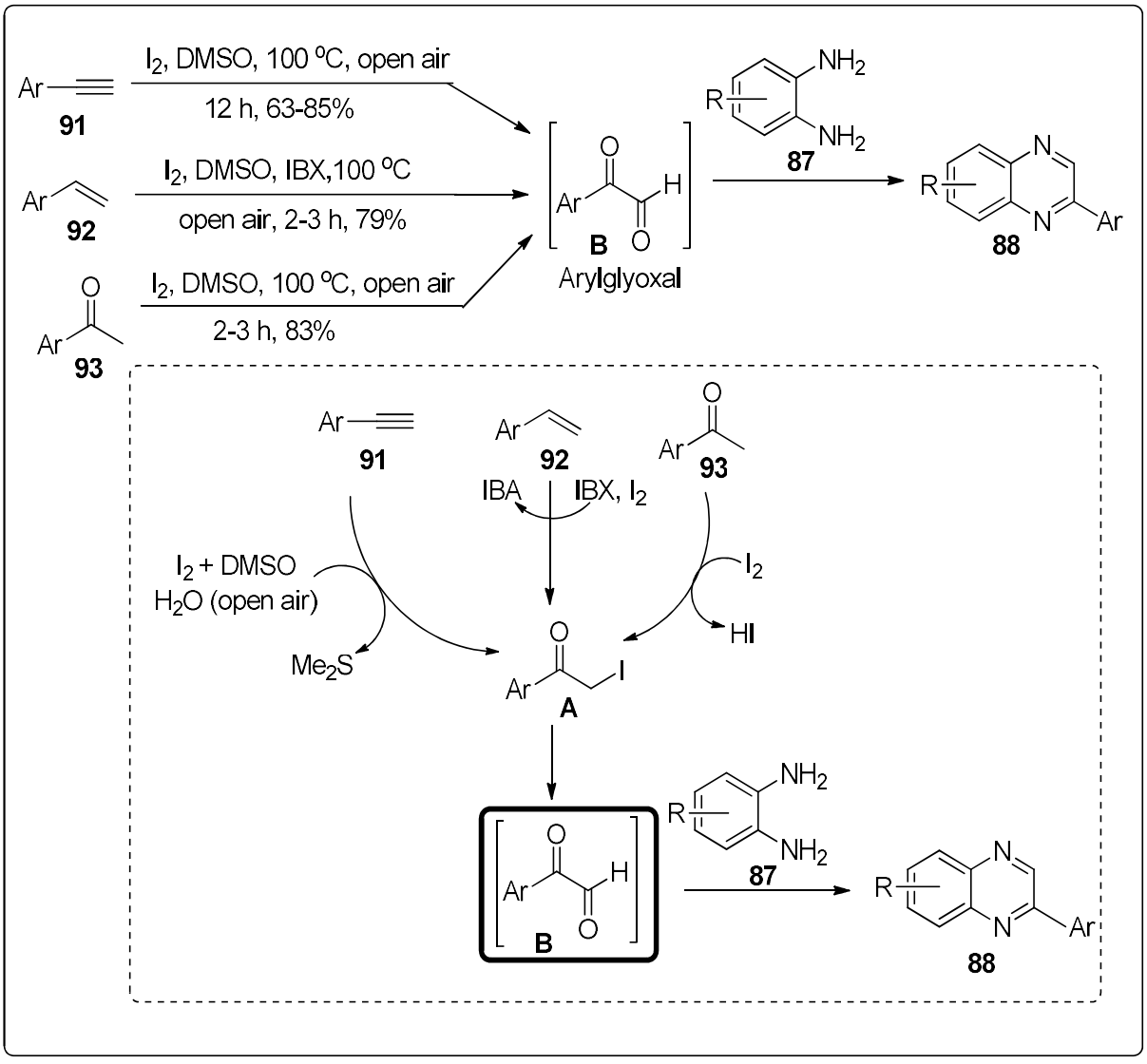
Meshram and coworkers[55c] disclosed an efficient metal free approach for the general synthesis of quinoxalines **88a** and **88b** (**Scheme 21**) from 1,2-diamines **87** and phenacyl bromides **14** in presence of catalytic amount of DABCO via a cyclization-oxidation process leading to the formation of the products in very good to excellent yields. Mechanistically, at first, a quaternary amine salt (**A**) is formed via the nucleophilic attack of DABCO on the phenacyl bromide **14** (**Scheme 21**). Next, the addition of *o*-diaminoarenes **87** onto the intermediate **A** leads to the formation of intermediate **B** with regeneration of DABCO which keeps the catalytic system active and eliminates water and HBr as by-products. Finally, intermediate **A** on further oxidation provides the product **88**. Interestingly, the substrate 1,2-diamine **87** containing strong electron-donating group (EDG) and electron-withdrawing group (EWG) delivers different regio-isomers (i.e., **88a** and **88b**) as depicted in the Scheme.



Scheme 21: Synthesis of quinoxaline **88** with mechanistic rational

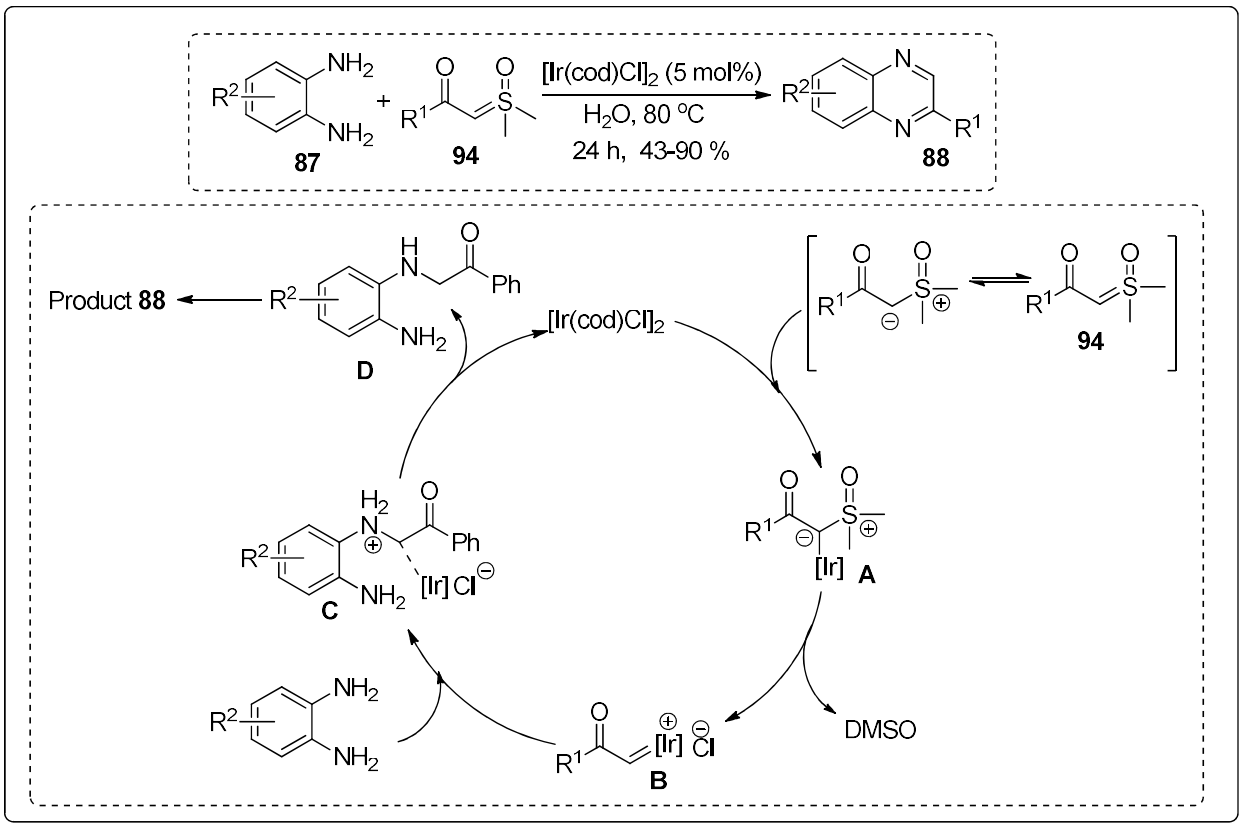
Bathula and coworkers[55d] disclosed a metal free approach for the regioselective synthesis of **88** (**Scheme 22**). The work deals with iodine-mediated oxidative annulation of 1,2-diamines **87** with aryl acetylenes **91**, olefins **92** and aromatic ketones **93**, respectively. The reactions are well tolerated with wide range of functional groups and the products were delivered with very

good yields. Mechanistically, the reaction proceeds through the formation of a common intermediate arylglyoxal (**Scheme 22)**. At first the starting materials **91**, **92** and **93** are converted into an iodide intermediate (**A**) through consecutive iodination and oxidation with I_2 or I_2/IBX. Intermediate **A** was further converted into arylglyoxal (**B**) in presence of DMSO. Finally, condensation reaction of 1,2-diamines **87** with arylglyoxal (**B)** leads to the formation of the desired product **88**.



Scheme 22: A diversified approach for the synthesis of **88**

Xu *et al.*[55e] reported an efficient green approach for the facile synthesis of 2-substituted quinoxalines **88** (**Scheme 23**) via iridium-catalyzed carbenoid insertion of sulfoxonium ylides (**94**) onto 1,2 diamine **87** in water. Here, the sulfoxonium ylides (**94**) are used as the safe carbene precursors for the conversion. A library of products was synthesized with high functional group tolerance. According to the reported mechanism (**Scheme 23**), at first the sulfoxonium ylide (**94**) was activated by the Iridium catalyst leading to the formation of the Ir-complex **A**, which on elimination of DMSO transforms into the iridium carbene complex **B**, which inserts into the N-H bond of anilines to afford the complex **C**. Finally, intermediate **C** regenerates the iridium catalyst via elimination of intermediate **D**, which on further cyclocondensation rapidly transforms into the product **88**.



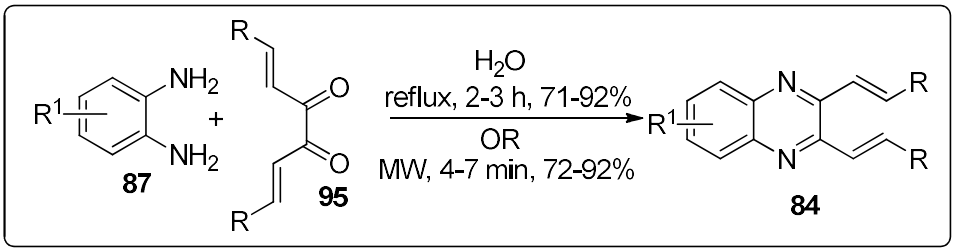
Scheme 23: Synthesis of **88** and possible reaction pathway

2.1.8.2. Synthesis of C2/C3- styryl/vinyl-substituted quinoxalines

Among the C2/C3-substituted quinoxalines, their vinyl substituted derivatives are quite less explored despite of their widespread applications, where most of the reports deal with functionalization of pre-built quinoxaline moiety, adopting either classical or metal catalyzed pathway. Few of them are discussed below.

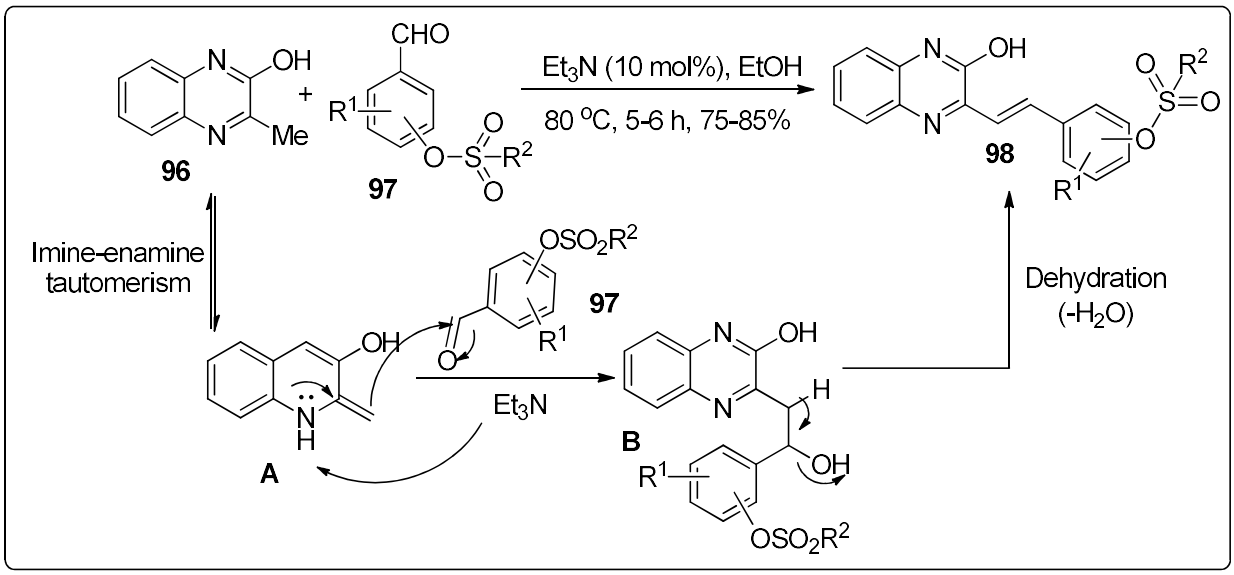
2.1.8.2.1. Metal free pathway for the formation of C2/C3- styryl/vinyl-substituted quinoxalines

Perumal and coworkers[53] demonstrated a simple and facile method for the synthesis of 2,3-bis[(*E*)-2-aryl vinyl]-quinoxaline (**84**, **Scheme 24**) via either heating or microwave irradiated condensation of 1,2 diaminobenzenes **87** and cinnamils **95** in water. The products were formed within just few minutes with good to excellent yields and are reported to show photophysical properties.



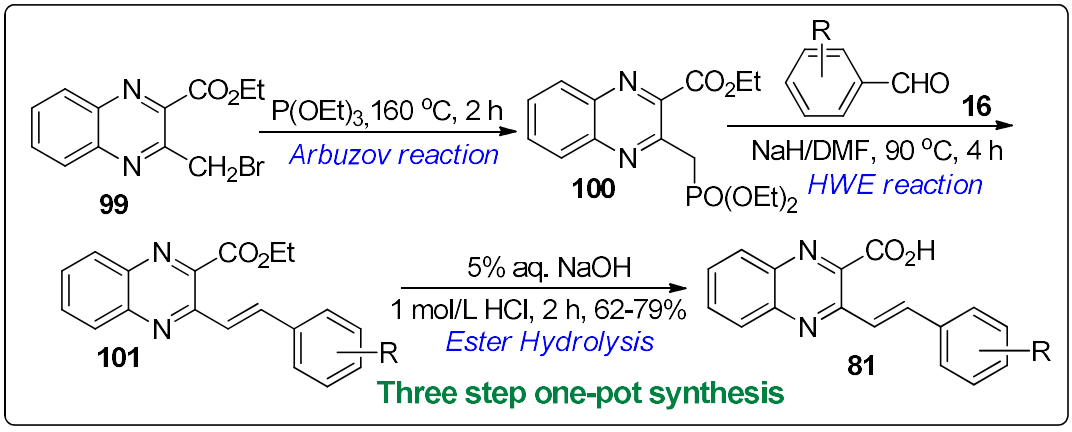
Scheme 24: Synthesis of **84**

Satyanarayana *et al.*[56] reported a general synthetic pathway for the formation of 3-styryl-quinoxaline (**98**, **Scheme 25**) via sp^3 C–H functionalization of the methyl group of a pre-built quinoxaline derivative **96** in presence of a catalytic amount of base (i.e., triethylamine) and sunfonates containing aldehydes **97**. The products were formed with very good yields within few hours. According to the mechanism (**Scheme 25**), at first the methyl group of quinoxaline undergoes imine–enamine type tautomerism leading to the formation of the enamine **A**. Next, Et_3N abstracts the proton from the enamine **A** which on nucleophilic attack on the aldehyde (**97**) lead to the formation of intermediate **B**. Finally, dehydration of **B** affords the product **98**.



Scheme 25: Synthesis of **98** from 2-methylquinoxaline derivatives

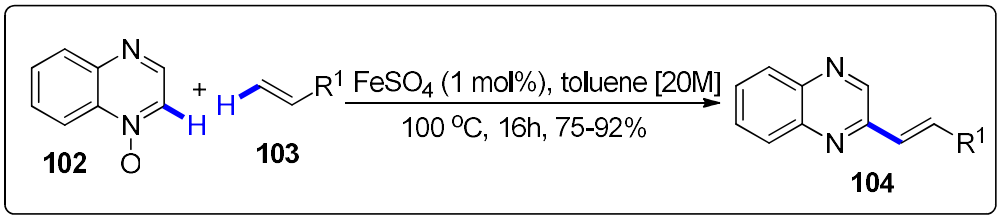
Yang *et al.*[51f] reported a simple and facile synthesis of a new series of 3-arylvinylquinoxaline-2-carboxylic acids (**81**, **Scheme 26**) from newly-synthesized ethyl 3-bromomethylquinoxaline-2-carboxylate **99** via three step one-pot synthetic pathway. At first the substrate **99** undergoes Michaelis-*Arbuzov reaction* in presence of $P(OEt)_3$ leading to the formation of compound **100** in almost quantitative yields. In the next step, *in situ* HWE (*Horner-Wadsworth-Emmons*) olefination reaction of **100** delivers the vinylated quinoxaline derivative **101**. Finally, ester hydrolysis of **101** affords the product **81** in very good yield and the products are reported to be anti-tuberculosis agent.



Scheme 26: Three step one-pot synthesis of **81**

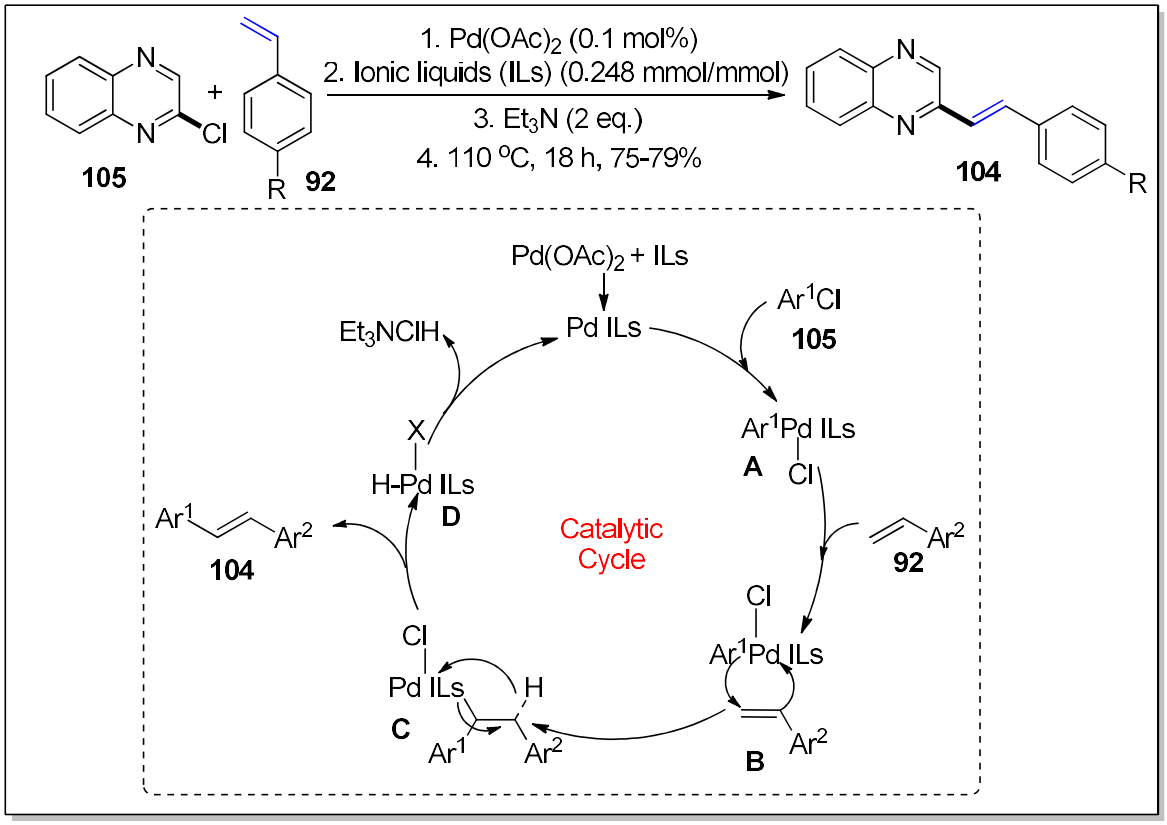
2.1.8.2.2. Synthesis of C2/C3-styryl/vinyl-substituted quinoxalines in presence of metal

Vaccaro and coworkers[57a] disclosed an efficient regioselective and waste-minimized synthesis of C2 functionalized quinoxalines **104** in absence of any external oxidant via iron-catalyzed C-H activation of quinoxaline-*N*-oxides **102** (**Scheme 27**). The reaction deals with iron-catalyzed C-H alkenylation of quinoxaline *N*-oxide **102** in presence of an olefin **103**. The protocol is based on the use of inexpensive and easily accessible $FeSO_4$, showed broad applicability to a wide range of substrates. The only by-product of the reaction is water, thus tracing a green pathway.



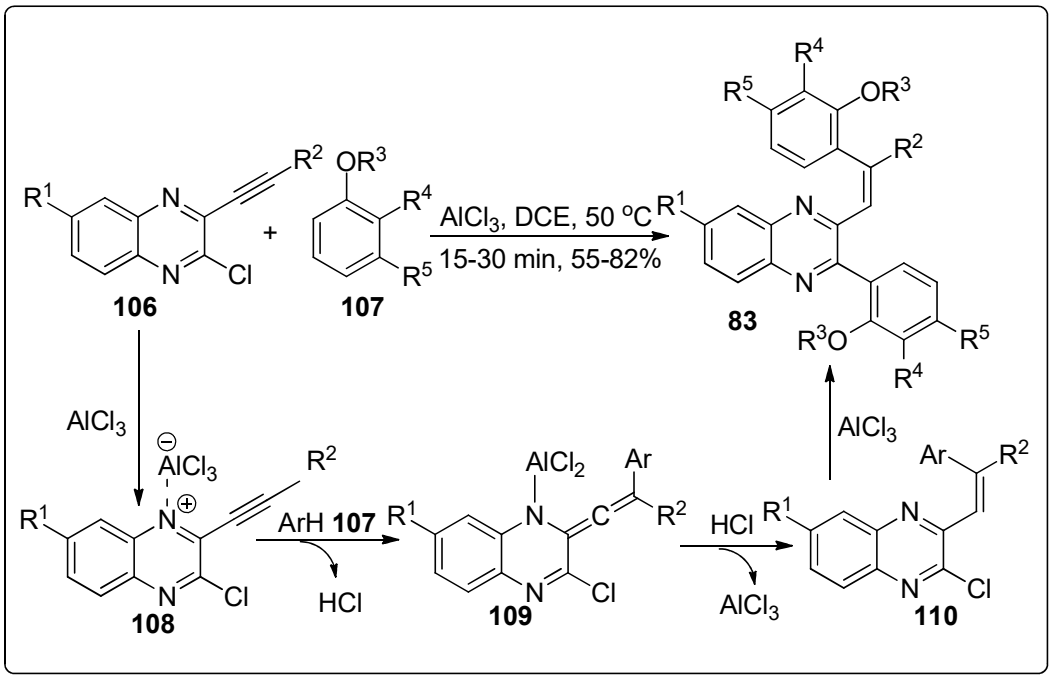
Scheme 27: Fe catalyzed synthesis of **104**

Girase *et al.*[57b] reported an efficient approach for the synthesis of 2-styryl substituted quinoxalines **104** (**Scheme 28**) through a $Pd(OAc)_2$/[Cpy][Br] catalyzed *Heck-cross coupling* between pre-built halogenated derivative of quinoxaline **105** and an olefin **92**, where [CPy][Br] act as a surfactant ionic liquid (ILs) which is biologically important and easily degradable surfactant material-providing an environmental benign alternative. Mechanistically, at first $Pd(OAc)_2$ react with the ionic liquid (ILs) to produce an active palladium species Pd ILs, which on oxidative addition with Ar^1X **105** delivered intermediate **A** (**Scheme 28**). Subsequently insertion of the olefin **92** onto intermediate **A** affords intermediate **C** via formation of intermediate **B**. Finally reductive elimination of **C** affords the desired product **104** with formation of intermediate **D** which then again transforms into the active palladium species to keep the catalytic system alive via elimination of Et_3NClH.



Scheme 28: Formation of **104** and mechanistic overview

Pal and coworkers[52a] disclosed an unprecedented $AlCl_3$-mediated method for the synthesis of densely functionalized novel olefins, i.e., 2-(2,2-diarylvinyl)-3-arylquinoxalines (**83**, **Scheme 29**) via the reaction between a pre-built quinoxaline scaffold **106** and an arene **107** involving aromatic C–H bond addition to the alkyne and heteroarylation of the arene in one pot. More importantly the synthesized compounds are reported to be potent inhibitors of sirtuins. According to the mechanism (**Scheme 29**), the N4 nitrogen of **106** first complexes with $AlCl_3$, delivering intermediate **108**, which facilitates the nuceophilic attack by the arene **107** at the adjacent alkynyl moiety of **108** (the hydroarylation step), affording an allene intermediate **109**, which upon release of $AlCl_3$ delivers **110**. Next, the second nitrogen of **110** again complexes with $AlCl_3$ followed by the attack of **107** at the adjacent carbon afforded the product **83** (the heteroarylation step). The products are delivered within few minutes with very good yield.

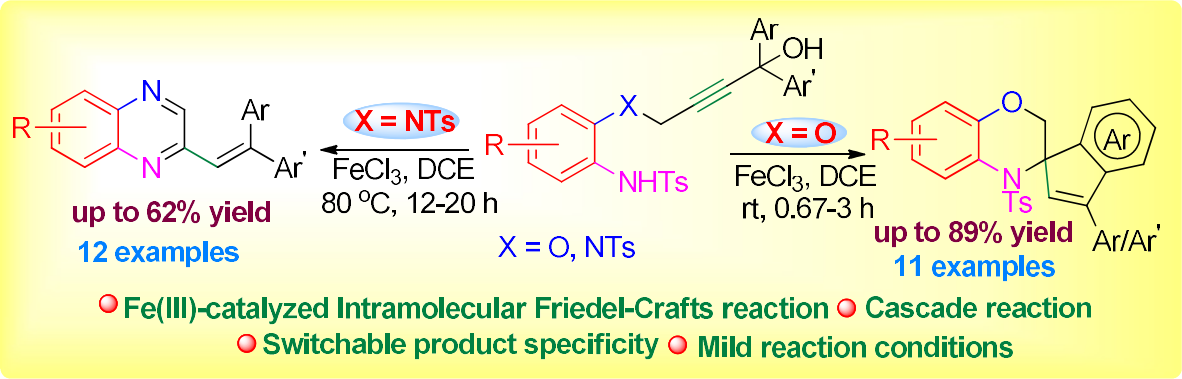


Scheme 29: Synthesis of product **83**

2.1.9. Concluding remarks:

From the literature review it is clear that both Spiro-indenyl 1,4-benzoxazines and 2-styryl/vinyl substituted quinoxalines secure a important place in the heterocyclic family due to their diverse applications. But unfortunately their general synthetic approach is not been well explored yet. Though plethora of methods are well documented for the individual general synthesis of 1,4 benzoxazine, indene and spirocycles, but only few reports are on the general synthesis of spiro-indenyl 1,4-benzoxazines and that too employing costly Rh-catalyst from pre-built 1,4-benzoxazine; whereas there are only few reports on the general synthesis of 2-styryl/vinyl substituted quinoxalines involving condensation reaction, *Heck reaction* etc. of pre-built quinoxaline scaffold. Thus development of one-pot strategy for their general synthesis via cyclization is highly desirable. In this context, we have developed a Fe(III) catalyzed mild synthetic route for their general synthesis; detailed results are discussed in **Part II** of this chapter.

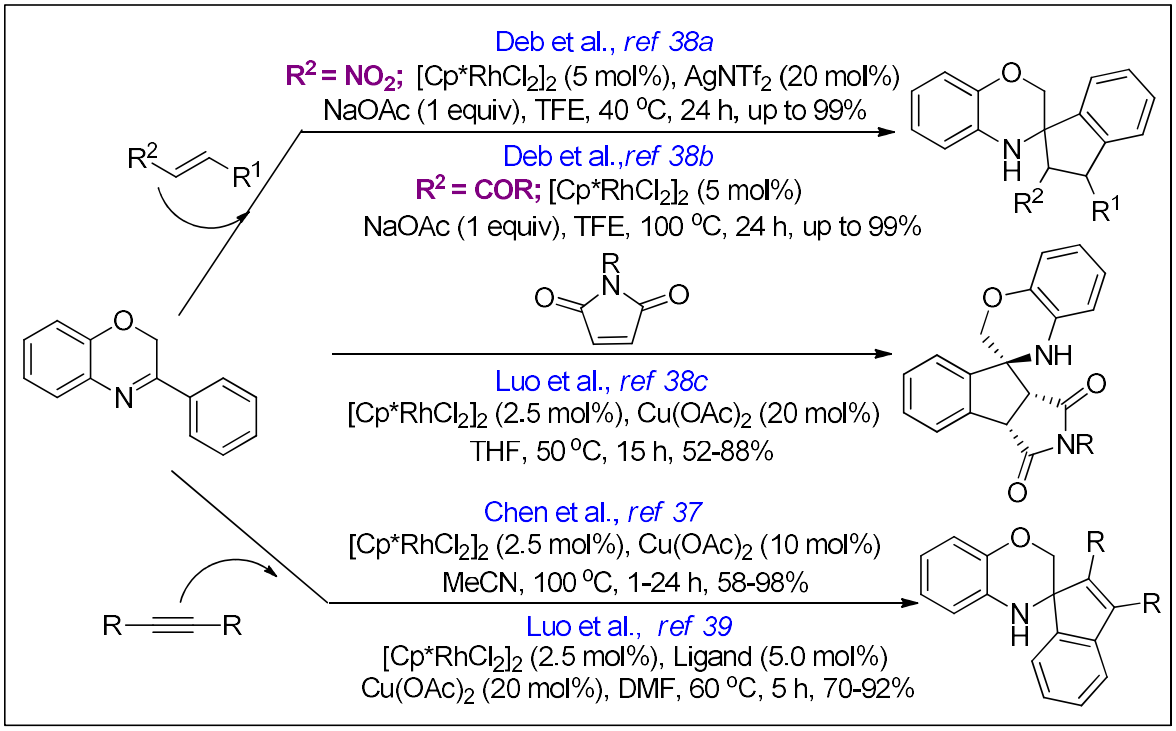
Part II – Results and Discussion



Sukanya De and Chinmay Chowdhury*; ***Manuscript under communication***

2.2.1. Introduction

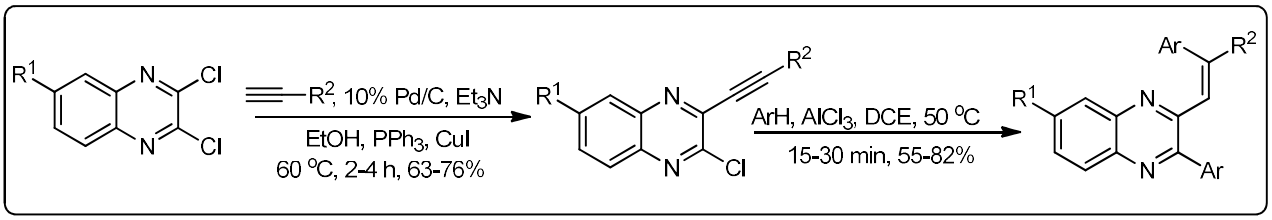
From the literature review (as discussed in **Part I** of this chapter), it is evident that spiro-benzoxazines are very important scaffold having potential applications in various fields. Despite of their widespread applications, only few reports are available for their general synthesis (**Schemes 10-15** in **Part I**). More specifically, only couple of methods are documented for the general synthesis of spiro-indenyl 1,4-benzoxazines via C-H functionalization/ annulation cascade reactions at high temperature with long reaction time from pre-built 1,4-benzoxazines moiety in the presence of high cost Rhodium catalyst as shown in **Scheme 30** (detailed discussion in **Part I** of this chapter). Therefore, the development of alternative cost-economic methods to synthesize them from simple substrates preferably under one-pot in which concurrent formations of 1,4-benzoxazine and fused indene ring take place easily, would be worthwhile.



Scheme 30: Previous works for the synthesis of of spiro-indenyl 1,4-benzoxazines

On the other hand, among the library of nitrogen heterocycles, quinoxalines represent an important class of molecules serving as core structure of various natural products, pharmacologically active compounds, resulting in the formation of drugs in addition to their

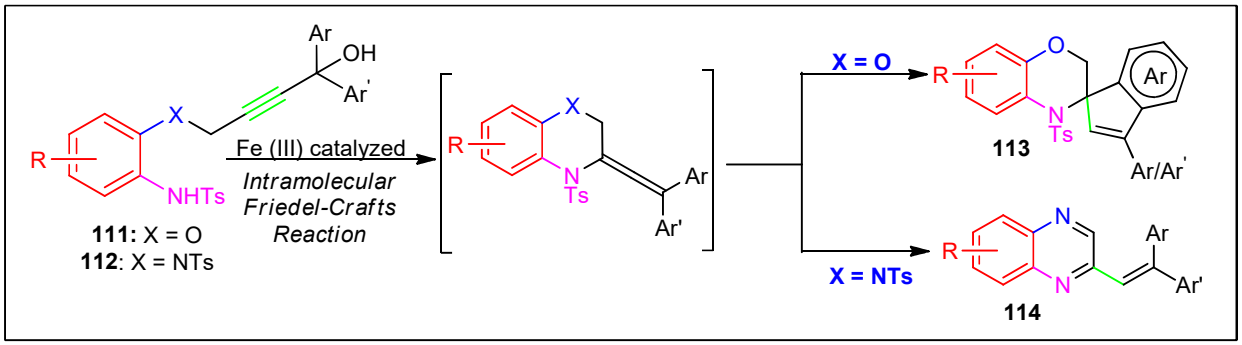
widespread applications in material sciences (as discussed in **Part I** of this chapter). In particular note, C2/C3-vinyl substituted quinoxalines emerged as a novel pharmacophore featuring many potential bio-active compounds; due to their unambiguous importance, substantial efforts have been devoted for their general synthesis (**Scheme 19-23**, **Part I**). In particular, few reports are on the synthesis of C2/C3-stryl substituted quinoxalines where functionalizations of pre-built quinoxlines are made utilizing classical (**Scheme 24-26**, **Part I**) and metal catalyzed reactions (**Scheme 27-28**, **Part I**). Surprisingly, scrutiny of literature reveals that, only one synthetic pathway is reported till date for the general synthesis of C2-vinyl substituted quinoxalines from prebuilt quinoxaline using two-steps reactions (**Scheme 31**). Consequently, development of newer method comprising one-pot reaction using simple substrates for the general synthesis of 2-vinyl-quinoxalines involving simultaneous formations of quinoxaline ring and the vinyl moiety would be important.



Scheme 31: Previous work for the synthesis of 2-vinyl quinoxalines

Recently, iron catalysts are gaining increasing research interests[58] because of their low price, non-toxicity and environment benign character. On the other hand, intramolecular Friedel-Crafts (IMFC) reactions[59] have shown high efficiency for C-C bond formations in the construction of polycyclic frameworks. In this context and in continuation of previous works on palladium catalyzed reactions, on the synthesis of heterocycles of biological significance,[60] it was envisioned that the alcohol group of propargyl ethers **111** could be activated through co-ordination with a Fe(III)-catalyst resulting in the formation of a transient allenyl cation which may undergo subsequent intramolecular nucleophilic attack by the tosylated amine group (-NHTs) of the tethered arene ring of **111** to form 1,4-benzoxazine possessing an allene moiety at C3 (*vide infra* **113'a**, see Table 1); surprisingly, a spiro-indenyl 1,4-benzoxazine **113** was isolated instead (**Scheme 32**). More interestingly, deployment of substrate **112** (X = NTs) for the same Fe(III)-catalyzed reaction at 80 ^{o}C in DCE led to the formation of a completely

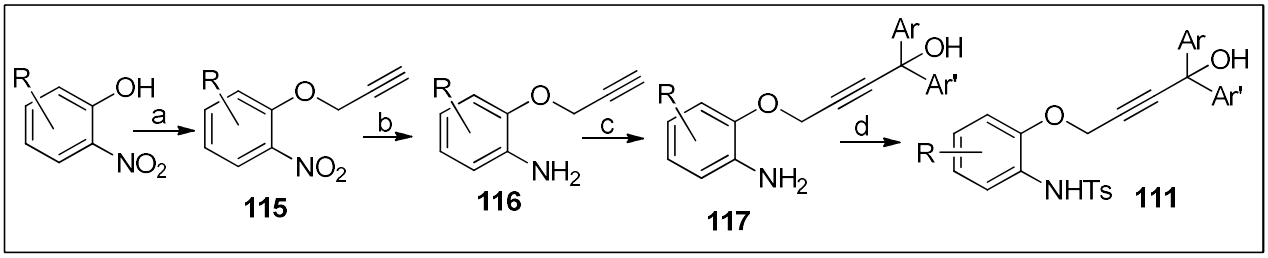
unexpected (2,2-diarylvinyl)-quinoxaline **114** (**Scheme 32**). Herein, preliminary results obtained so far are reported.



Scheme 32: Strategy for the synthesis of Spiro-indenyl 1,4-benzoxazines **113** and 2-(2,2-Diarylvinyl)quinoxalines **114**

2.2.2. Synthesis of starting material 111

The desired starting material **111** was prepared in four steps starting from commercially available 2-nitro phenol derivatives (**Scheme 33)**. The first step is the propargylation of nitro phenols leading to the formation of **115**. Next, the nitro group of the propargylated derivative **115** was reduced to amine derivative **116** which was then reacted with substituted benzophenones in the presence of BuLi to produce **117**. Finally, tosylation of the amine group of **117** delivered the desired starting material **111**.



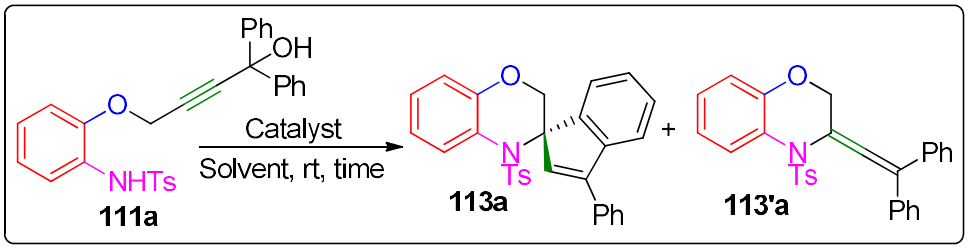
Scheme 33: Reagents and Conditions: (a) Propargyl bromide, K_2CO_3, Acetonitrile, 80 ^oC, overnight, 72-96%; (b) Fe powder, NH_4Cl, EtOH:H_2O (1:1), 80 ^oC, 2-3.5 h, 30-88%; (c) Benzophenone derivatives, BuLi (1.6 M in hexane), THF, 0 ^oC-rt, 45 min-2 h, 36-87%; (d) TsCl, Pyridine, DCM, reflux, 2-4 h, 60-97%.

2.2.3. Synthesis of Spiro-indenyl 1,4-Benzoxazines 113 in One-pot

2.2.3.1. Optimization of reaction conditions for the synthesis of Spiro-indenyl 1,4-benzoxazine 113a

Towards this objective, the study was initiated by exploring the model reaction on substrate **111a** under acidic conditions (Table 1). Initially, exposure of **111a** to 10 mol% of triflic acid in DCE afforded the spiro-annulated product **113a** (13%) instead of **113'a**. Use of *p*-TsOH.H_2O (10 mol%) instead merely caused decomposition (TLC) of the starting material

Table 1. Optimization of Reaction Conditions for the Synthesis of Spiro-indenyl 1,4-benzoxazine 113a[a]



Entry	Catalyst	Solvent	Temp.	Time (h)	Yield[b] (%)	
					113a[c]	113′a
1.	Triflic acid	DCE	rt	1	13	---
2.	*p*-TsOH.H_2O	DCE	rt	6	---	---
3.	$BF_3.Et_2O$	DCE	rt	1	56	---
4.	$Cu(OTf)_2$	DCE	rt	4	---	---
5.	$InCl_3$	DCM	rt	4	---	---
6.	$FeCl_3$	$MeNO_2$	rt	1	62	---
7.	$FeCl_3$	DCM	rt	1	75	---
8.	**$FeCl_3$**	**DCE**	**rt**	**1**	**87**	---
9.	$Fe(OTf)_3$	DCE	rt	1	---	78
10.	$Fe(acac)_3$	DCE	rt	4	---	---
11 .	$In(OTf)_3$	DCE	rt	1	---	70
12.	AgOTf	DCE	rt	1	---	93

[a]Reaction conditions: A mixture of **111a** (0.07 mmol, 1 equiv) and catalyst (10 mol%, 0.1 equiv) in DCE (1.5 mL) was stirred at room temperature under argon atmosphere for the specified period. [b]Isolated yields of pure products. [c]Product **113a** was obtained as racemic mixture .

(Table 1, entries 1-2). To our pleasure, employment of 10 mol % of $BF_3.Et_2O$ led to the formation of **113a** within 1 h with 56% yield (Table 1, entry 3). To improve the yield further, various metal catalysts acting like a Lewis acid were deployed. Though $Cu(OTf)_2$ or $InCl_3$ proved to be inert for this transformation (Table 1, entries 4-5), use of $FeCl_3$ (10 mol %) in nitromethane delivered the product **113a** in 62% yield (Table 1, entry 6); pleasingly, the yield of **113a** was found to be improved (75-87%) further by carrying out the reaction in solvents like DCM or DCE (Table 1, entries 7-8). To our surprise, use of $Fe(OTf)_3$ in DCE triggered the exclusive formation of 1,4-benzoxazine **113'a** (78%) having an allene moiety at C3 position within 1 h though $Fe(acac)_3$ failed to deliver any product (Table 1, entries 9-10). Whereas both $In(OTf)_3$ and AgOTf used as catalyst afforded only **113'a** with very good yields (Table 1, entries 11-12). Thus, the reaction conditions of entry 8 of Table 1 were considered to be optimal to prepare **113a**.

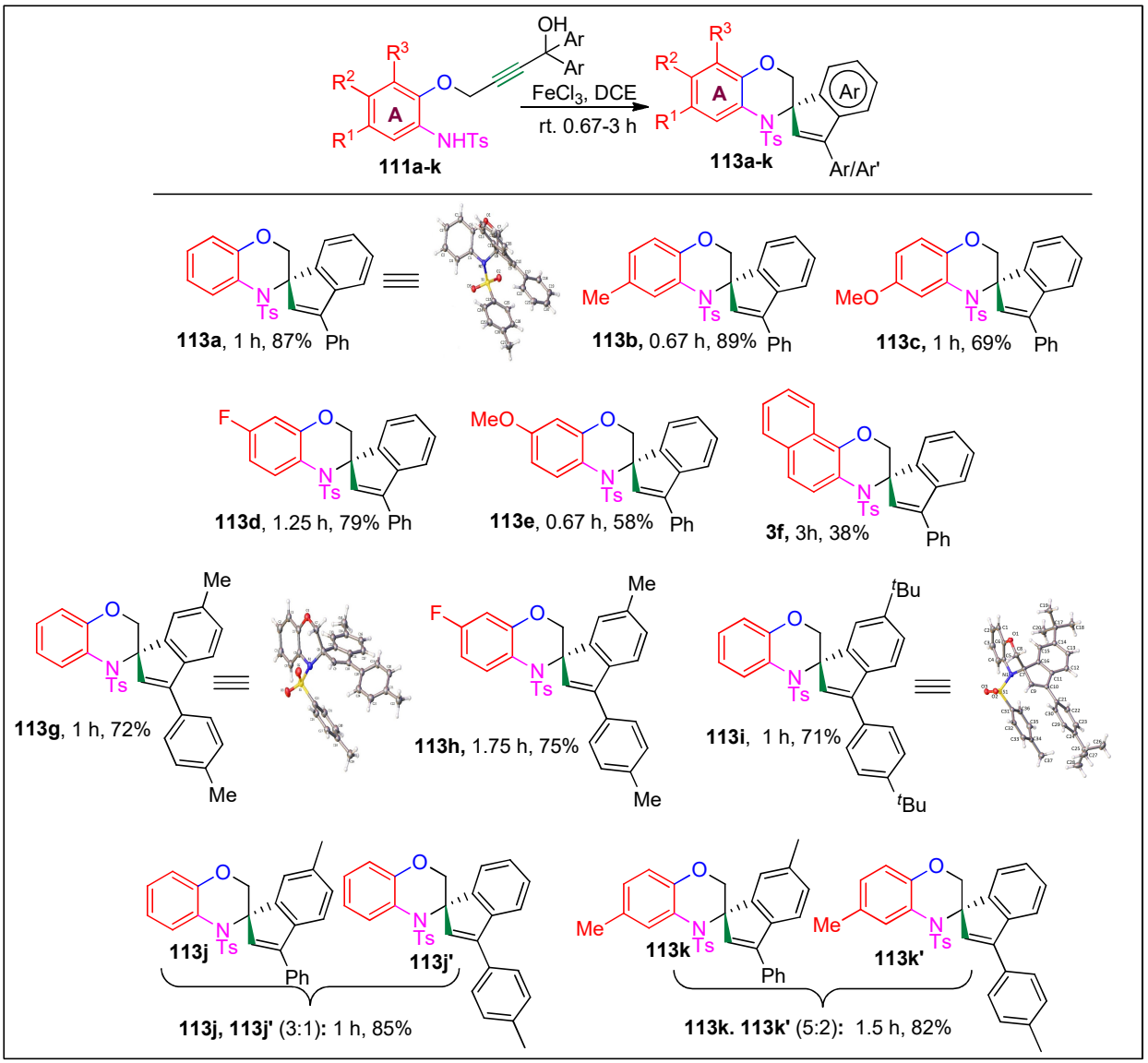
2.2.3.2. Scope of the reaction

With the optimized reaction conditions in hand, we then set out to explore the scope and limitations of the synthesis (**Scheme 34**). Towards this goal, first the effects of substitutions in the aryl ring (A) of substrates **111** were tested. Though placement of an electron-donating group (EDG) like methyl (R^1=Me) *para* to the oxygen (substrate **111b**) facilitated the reaction forming the product **113b** within 0.67 h with 89% yield, a stronger EDG (R^1=OMe) at the same position (in **111c**) slightly hindered the reaction leading to the formation of product **113c** within 1 h but with somewhat lower yield (69%). Next, when a EWG like fluoro (R^2=F) was placed *para* to NHTs (substrate **111d**), product **113d** was produced within 1.25 h with 79% yield. But a stronger EDG (R^2 = OMe) as in substrate **111e** lowered the yield of product **113e** (58%) though with a shortened reaction time (0.67 h). The lower yields observed with OMe substituted products could possibly be attributed to the poisoning of the catalyst through chelation of the group to the Fe(III) having vacant *d*-orbitals. To our disappointment, replacing the phenyl ring (A) of substrate **111a** by naphthyl one as in substrate **111f** inhibited the reaction considerably requiring longer reaction time (3 h) for the production of **113f** with lower yield (38%).

Next, the substitution effects of the aryl rings (Ar, Ar') attached to the propargylic carbon of substrates **111** were examined. Substrate **111g** (Ar = Ar' = *p*-Me-C_6H_4) bearing an EDG like methyl at the *para* position of the phenyl ring smoothly delivered the product **113g** within 1 h

with 72% yield. The trend continued even in presence of an extra EWG (R^1=F) in the other aryl ring A (product **113h**) though with slightly longer reaction time. Even after incorporation of a bulky *tert*-butyl group in place of the methyl group as in substrate **111i** (Ar = Ar' = *p*-^{t}Bu-C_6H_4),

Scheme 34: Synthesis of Spiro-indenyl 1,4-benzoxazines 113a-k[a,b]



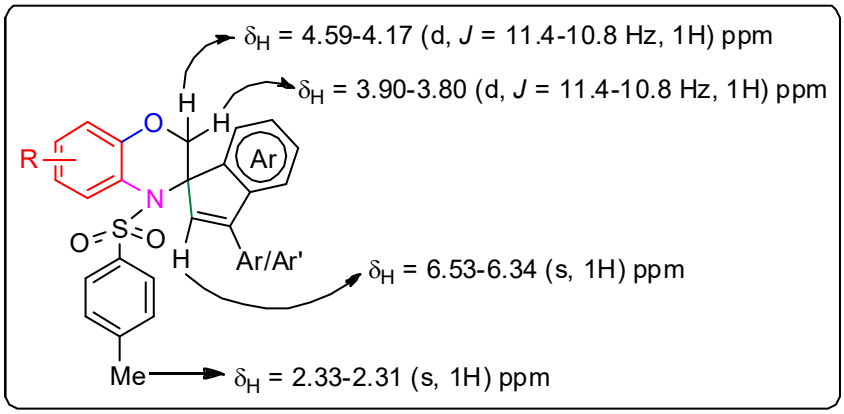
[a]Reaction conditions: A mixture of **111** (0.07 mmol, 1 equiv) and $FeCl_3$ (0.007 mmol, 0.1 equiv) in DCE (1.5 mL) was stirred at room temperature under argon atmosphere for the specified time. [b]All products were obtained in racemic mixture.

the reaction furnished the product **113i** in 1 h with 71% yield. Interestingly, use of two different aryl groups (Ar = Ph, Ar' = *p*-Me-C_6H_4) in substrate **111j** or **111k** led to the formation of inseparable regio-isomeric mixture of products **113j/113j'** (3:1) or **113k/113k'** (5:2) within 1-1.5

h with very good yield. The higher nucleophilicity of the tolyl ring (Ar') compared to phenyl one (Ar) appears to dictate the formation of major isomers **113j** and **113k** (see, species **E** of Scheme **37** *vide infra*).

The structures of the products were corroborated by NMR and mass spectral data, and X-ray diffraction analysis. Though configuration of one of the isomer of products **113** is shown (**Scheme 34**), the products were obtained in racemic mixtures.

2.2.3.3. Nature and characterization of products 113



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (ESI), the molecular ion peak (in positive mode) of all compounds appeared as protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR, the proton attached with the indene ring appears as singlet at around 6.53-6.34 ppm. The two protons adjacent to the oxygen atom of the 1,4-benzoxazine ring appeared as two doublets at 4.59-4.17 ppm and 3.90-3.80 ppm respectively with coupling constant (*J*) 11.4-10.8 Hz. While methyl protons of the tosyl group were displayed around 2.33-2.31 ppm as singlet. Furthermore, the ^{13}C provided additional support in the favour of the structures.

Finally, the structural conclusion was also supported by single crystal X-ray diffraction analysis of compounds **113a**, **113g** and **113i**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolved in minimum volume of petroleum ether/ dichoromethane or petroleum ether/ethyl acetate mixture. The ORTEP diagrams of the crystal structures are shown in Figures 7, 8 and 9.

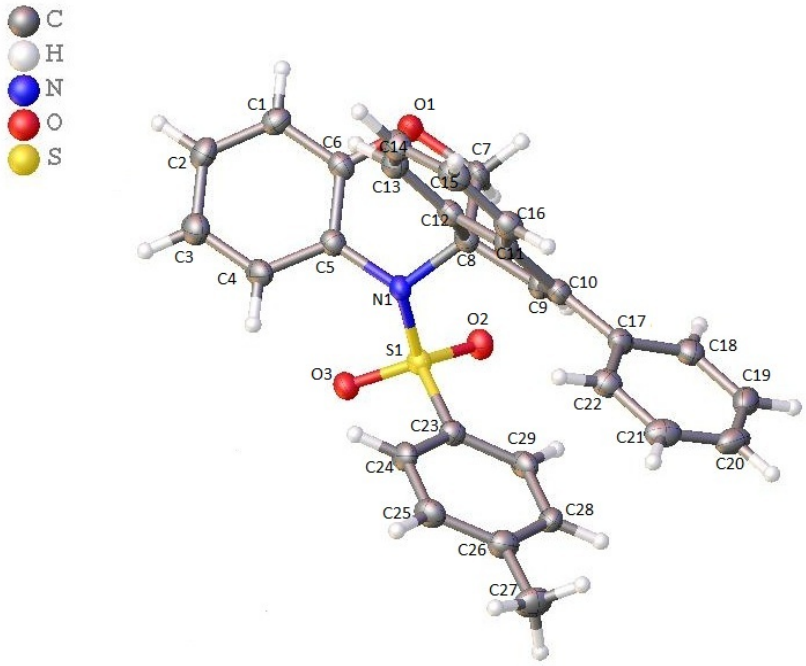


Figure 7. ORTEP Diagram (thermal ellipsoid plot) of Product **113a** (drawn at 50% probability level)

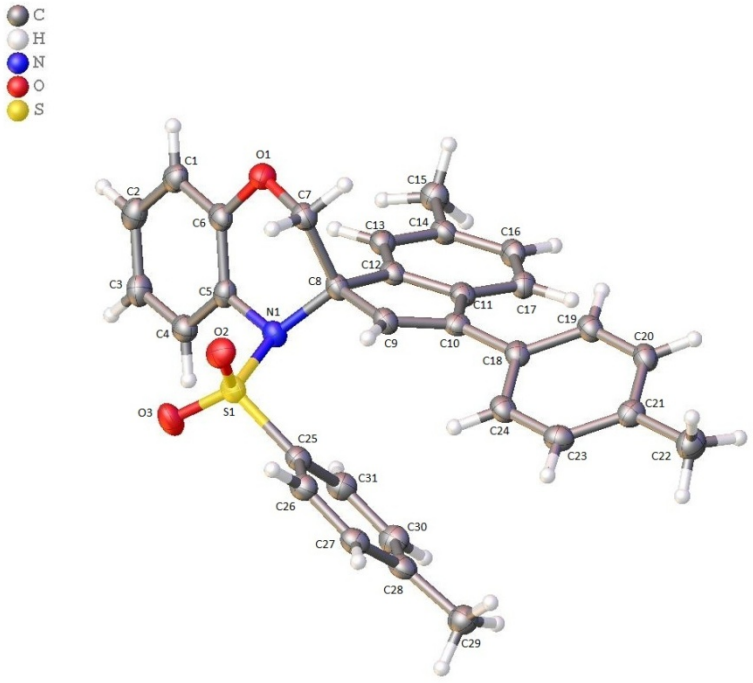


Figure 8. ORTEP Diagram (thermal ellipsoid plot) of Product **113g** (drawn at 50% probability level)

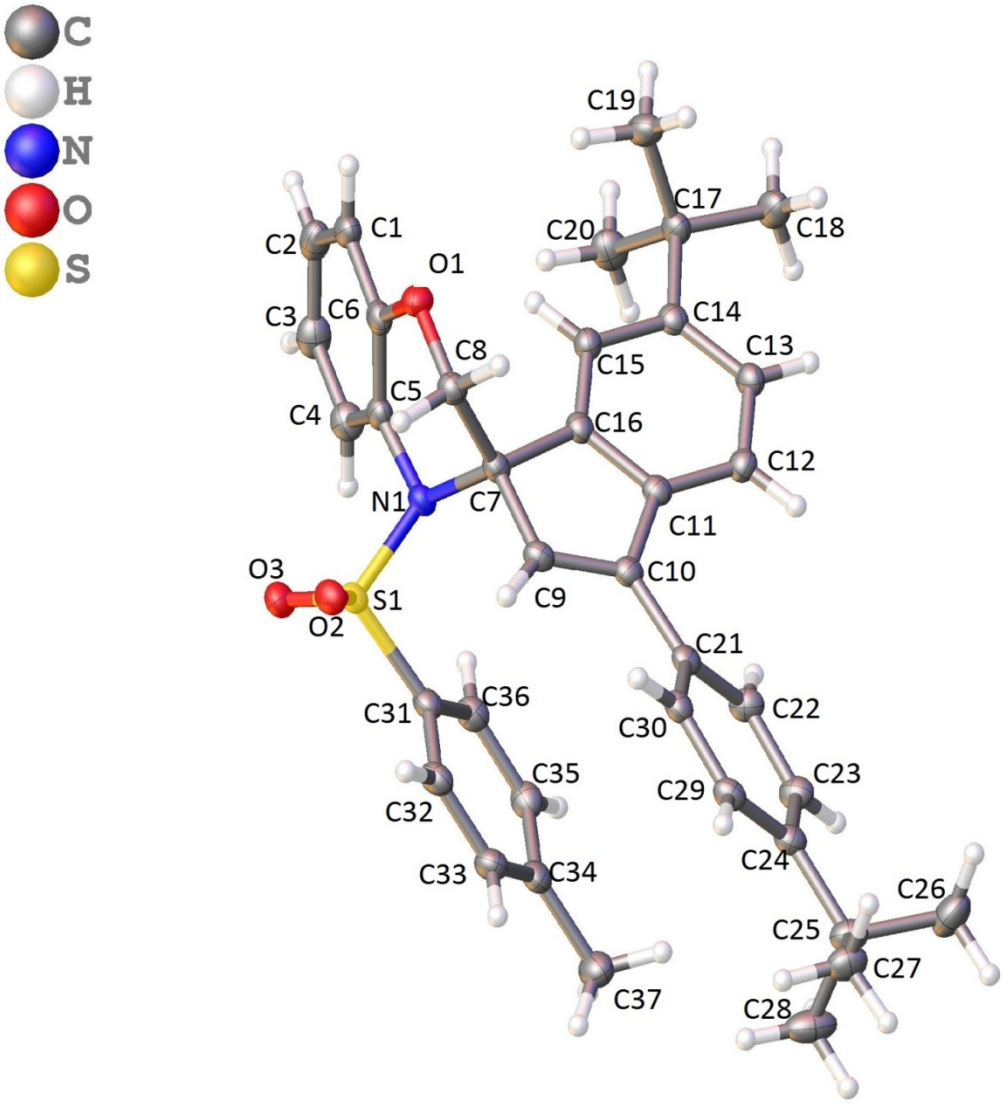


Figure 9. ORTEP Diagram (thermal ellipsoid plot) of Product **113i** (drawn at 50% probability level)

Table 2: Important crystal data of product **113a**

Empirical formula	$C_{29}H_{23}NO_3S$
Formula weight	465.54
Temperature/K	100.00
Crystal system	triclinic
Space group	P-1
a/Å	10.1361(6)
b/Å	10.6354(6)
c/Å	22.2771(13)
α/°	92.378(2)
β/°	90.255(2)
γ/°	110.739(2)
Volume/Å^3	2243.5(2)
Z	4
ρ_{calc}g/cm^3	1.378
μ/mm^{-1}	1.547
F(000)	976.0
Crystal size/mm^3	0.23 × 0.21 × 0.15
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	3.97 to 132.098
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $0 \leq l \leq 26$
Reflections collected	7553
Independent reflections	7553 [R_{int} = ?, R_{sigma} = 0.0480]
Data/restraints/parameters	7553/0/616
Goodness-of-fit on F^2	1.083
Final R indexes [I>=2σ (I)]	R_1 = 0.0738, wR_2 = 0.2070
Final R indexes [all data]	R_1 = 0.0778, wR_2 = 0.2130
Largest diff. peak/hole / e Å^{-3}	0.56/-0.54

The single crystal of the product **113a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **113a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2214680.**

Table 3: Important crystal data of product **113g**

Empirical formula	$C_{31}H_{27}NO_3S$
Formula weight	493.59
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	13.5207(5)
b/Å	24.0952(9)
c/Å	7.3547(3)
α/°	90
β/°	93.461(2)
γ/°	90
Volume/Å^3	2391.67(16)
Z	4
ρ_{calc}g/cm^3	1.371
μ/mm^{-1}	1.482
F(000)	1040.0
Crystal size/mm^3	0.25 × 0.02 × 0.01
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	6.55 to 133.414
Index ranges	$-14 \leq h \leq 16$, $-28 \leq k \leq 28$, $-8 \leq l \leq 8$
Reflections collected	41193
Independent reflections	4213 [R_{int} = 0.1702, R_{sigma} = 0.0973]
Data/restraints/parameters	4213/0/329
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0592, wR_2 = 0.1465
Final R indexes [all data]	R_1 = 0.0889, wR_2 = 0.1551
Largest diff. peak/hole / e Å^{-3}	0.36/-0.38

The single crystal of the product **113g** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **113g** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2214681.**

Table 4: Important crystal data of product **113i**

Empirical formula	$C_{37}H_{39}NO_3S$
Formula weight	577.75
Temperature/K	101.00
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.6815(17)
b/Å	11.0162(13)
c/Å	19.481(2)
α/°	90
β/°	105.009(4)
γ/°	90
Volume/Å^3	3043.3(6)
Z	4
ρ_{calc}g/cm^3	1.261
μ/mm^{-1}	1.236
F(000)	1232.0
Crystal size/mm^3	0.67 × 0.47 × 0.14
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	11.866 to 133.604
Index ranges	$-17 \leq h \leq 17$, $-13 \leq k \leq 13$, $-23 \leq l \leq 23$
Reflections collected	38696
Independent reflections	5284 [R_{int} = 0.0674, R_{sigma} = 0.0426]
Data/restraints/parameters	5284/0/387
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0467, wR_2 = 0.1252
Final R indexes [all data]	R_1 = 0.0472, wR_2 = 0.1258
Largest diff. peak/hole / e Å^{-3}	0.26/-0.42

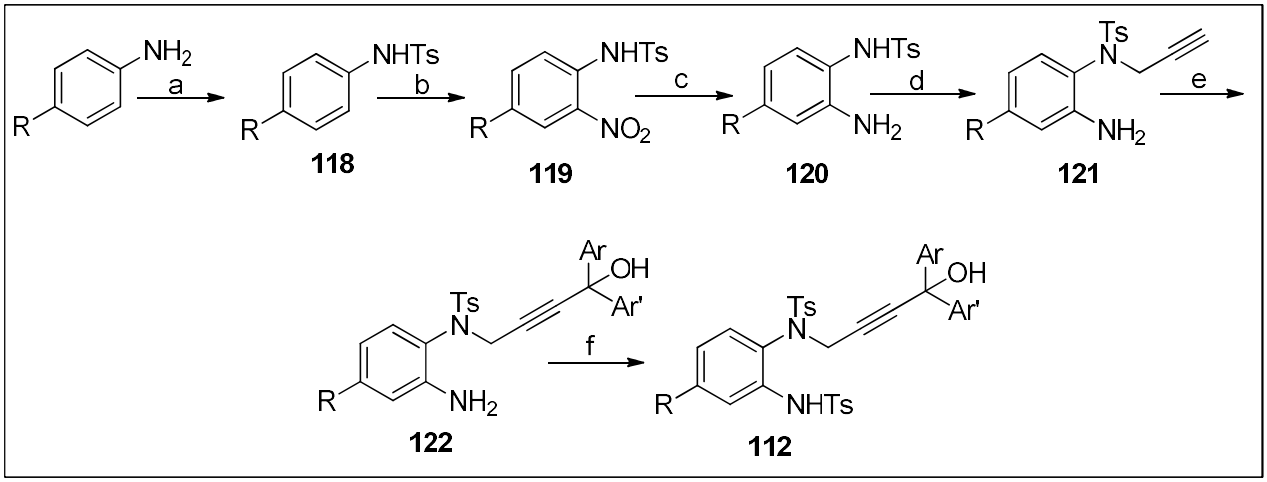
The single crystal of the product **113i** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of petroleum ether/ethyl acetate mixture. The crystal data of product **113i** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2214682.**

2.2.4. Extension of the methodology for the synthesis of 2-(2,2-Diarylvinyl)quinoxalines 114

Encouraged by the above results, we decided to explore the methodology on nitrogen heterocycles by implying the optimized condition on substrate **112** obtained by replacing the oxygen atom (O) of **111** by –NTs group attached to the benzene ring directly.

2.2.4.1. Synthesis of starting material 112

The desired starting material **112** was prepared in six steps starting from commercially available aniline derivatives (**Scheme 35**). The first step involves the tosylation of the amines delivering **118** which then undergoes nitration reaction to deliver the intermediate **119**. Next, the nitro group of **119** was reduced to amine derivative **120** which upon propargylation reaction produced **121**. Next, **121** derivative reacted with substituted benzophenones in presence of BuLi to produce **122**. Finally, tosylation of the amine group of **122** leads to the formation of the desired starting materials **112**.

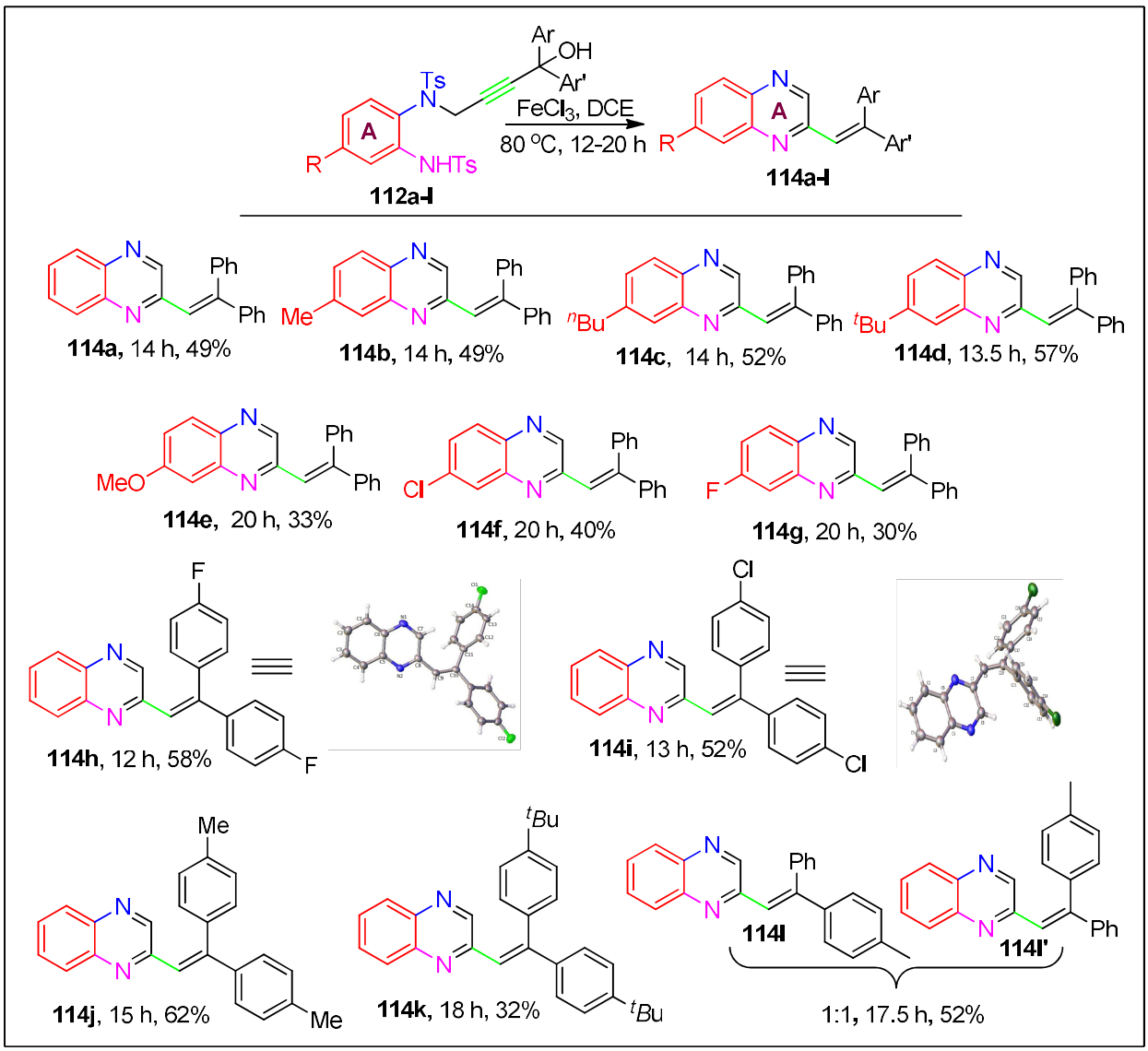


Scheme 35. Reagents and Conditions: (a) TsCl, Et_3N, DCM, 0 ^oC-rt, 2.5-8 h, 70-94%; (b) HNO_3, H_2SO_4, 0 ^oC-rt or 50 ^oC, 15-40 mins, 35-60%; (c) Fe powder, NH_4Cl, EtOH:H_2O (1:1), 80 ^oC, 2.5-4 h, 42-73%; (d) Propargyl bromide, K_2CO_3, Acetonitrile, 80 ^oC, 5-8 h, 42-64%; (e) Benzophenone derivatives, BuLi, THF, 0 ^oC-rt, 1.5-3 h, 30-71%; (f) TsCl, Pyridine, DCM, reflux, 8-24 h, 35-81%.

2.2.4.2. Synthesis of 2-(2,2-diarylvinyl)quinoxalines 114

Exposure of substrate **112a** under the optimized condition (Table 1, entry 8) for the formation of spiro-indenyl 1,4-benzoxazines proved to be inert; but, heating the same mixture at 80 °C for 14 h provided a product which was identified as quinoxaline **114a** (49%) instead of any spiro-indenyl 1,4-quinoxaline derivative as expected. In view of this unprecedented result, we became keen to establish the scope and generality of this new reaction by employing a number of

Scheme 36: Synthesis of 2-(2,2-diarylvinyl)quinoxalines 114a-l[a]

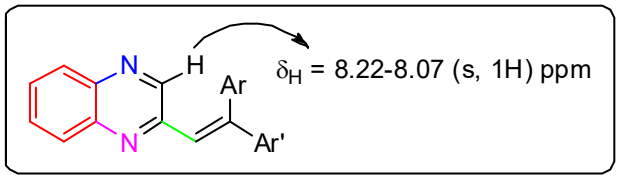


[a]Reaction conditions: A mixture of **112** (0.12 mmol, 1 equiv) and $FeCl_3$ (0.012 mmol, 0.1 equiv) was heated at 80 °C in DCE (4.4 mL) under argon atmosphere for the mentioned time.

substrates **112** (**Scheme 36**). Thus, introduction of a moderate EDG (R = Me, *n*-Bu, *tert*-Bu) in aryl ring A of substrates **112b-d** easily delivered the products **114b-d** after 13.5-14 h with 49-57% yields. But placement of either strong EDG (R = OMe) or EWG (R = Cl/F) at the same position (**112e** or **112f/112g**) lowered the yield (30-40%) of the product (**114e** or **114f/114g**) and necessitated longer reaction time (20 h).

Next, the substituent effects on the other aryl rings (Ar, Ar′) of substrate **112** were checked. Contrary to the previous observations (on **114f**, **114g**), installation of a EWG (viz., F/Cl) at the *para* position as in substrate **112h** (Ar = Ar′ = *p*-F-C_6H_4) or **112i** (Ar = Ar′ = *p*-Cl-C_6H_4) delivered the product **114h/114i** in 12-13 h with good yields (52-58%). On the other hand, introduction of a EDG like methyl at the same position generated the product **114j** after 15 h with 62% yield; even a bulky EDG as in substrate **112k** (Ar = Ar′ = *p*-^{t}Bu-C_6H_4) afforded the product **114k** after 18 h albeit in moderate yield (32%). Similar to the previous observations, deployment of substrate **112l** having two unsymmetrical aryl rings (Ar = Ph, Ar' = *p*-Me-C_6H_4) delivered an inseparable regio-isomeric mixture of products **114l/114l'** (1:1) with 52% yield.

2.2.4.3. Nature and characterization of products 114



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (EI and ESI), the molecular ion peak (in positive mode) of all the compounds appeared as M^+ or protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR, the adjacent proton of the nitrogen atom of the quinoxaline ring appears as singlet at 8.22-8.07 ppm. Further, the ^{13}C NMR gave additional support in the favour of the structures.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compounds **114h** and **114i**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The ORTEP diagrams of the crystal structures are shown in Figure 10 and 11.

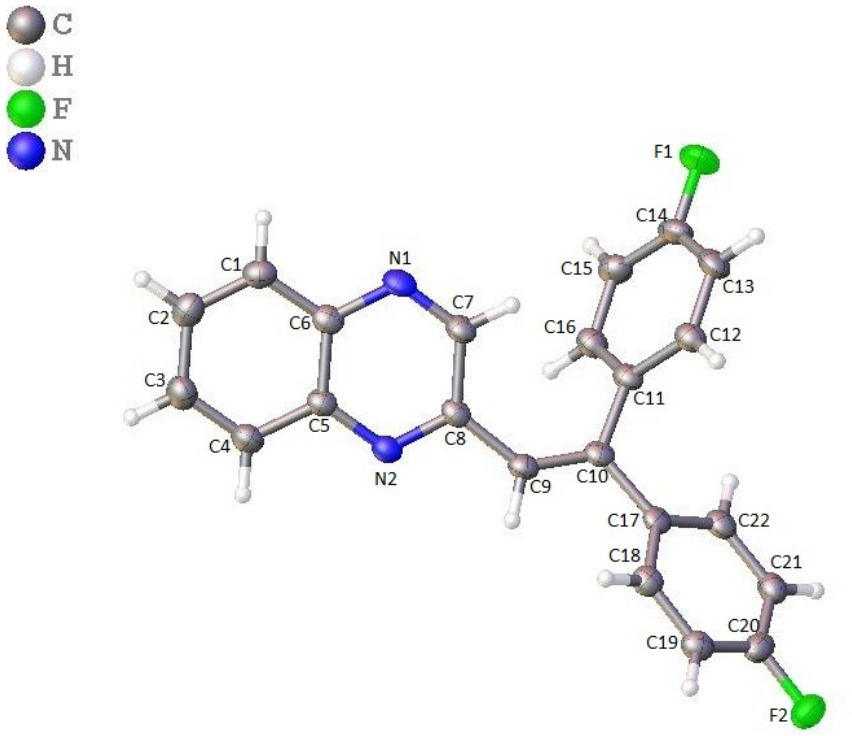


Figure 10. ORTEP Diagram (thermal ellipsoid plot) of Product **114h** (drawn at 50% probability level)

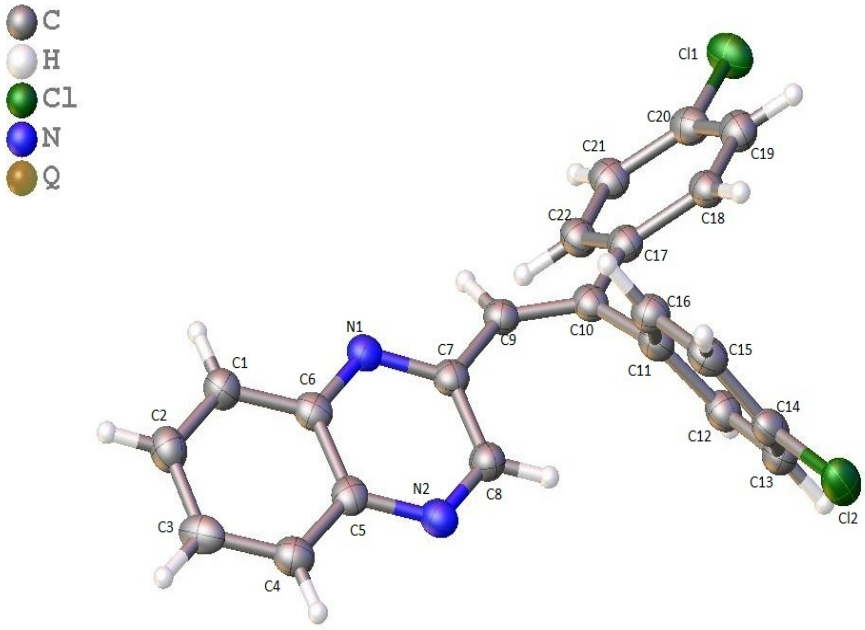


Figure 11. ORTEP Diagram (thermal ellipsoid plot) of Product **114i** (drawn at 50% probability level)

Table 5: Important crystal data of product **114h**

Empirical formula	$C_{44}H_{28}F_4N_4$
Formula weight	688.70
Temperature/K	104.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.4773(8)
b/Å	18.3269(16)
c/Å	19.1141(18)
α/°	90
β/°	97.499(4)
γ/°	90
Volume/Å^3	3291.5(5)
Z	4
ρ_{calc}g/cm^3	1.390
μ/mm^{-1}	0.809
F(000)	1424.0
Crystal size/mm^3	0.35 × 0.25 × 0.05
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.71 to 133.498
Index ranges	$-8 \leq h \leq 11$, $-21 \leq k \leq 21$, $-22 \leq l \leq 22$
Reflections collected	63061
Independent reflections	5813 [R_{int} = 0.1799, R_{sigma} = 0.0634]
Data/restraints/parameters	5813/0/470
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0590, wR_2 = 0.1533
Final R indexes [all data]	R_1 = 0.0655, wR_2 = 0.1599
Largest diff. peak/hole / e Å^{-3}	0.32/-0.31

The single crystal of the product **114h** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of petroleum ether/dichoromethane mixture. The crystal data of product **114h** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2214685.**

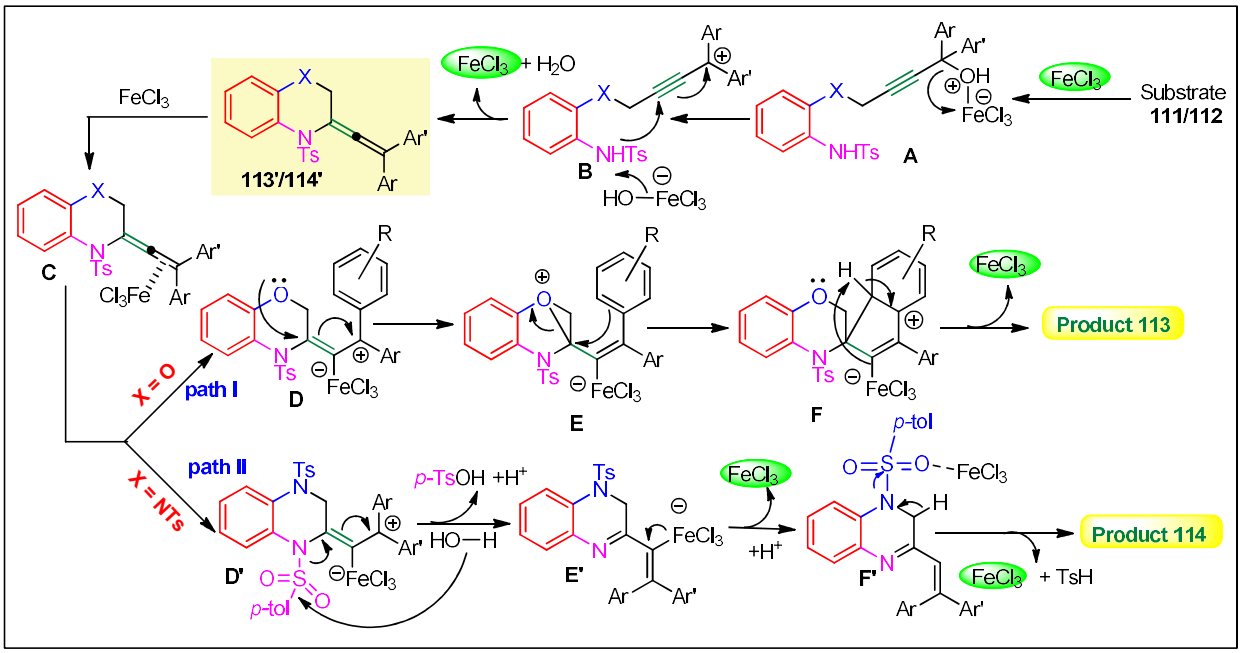
Table 6: Important crystal data of product **114i**

Empirical formula	$C_{44}H_{28}Cl_4N_4$
Formula weight	754.50
Temperature/K	102.00
Crystal system	triclinic
Space group	P-1
a/Å	9.4351(5)
b/Å	11.6009(6)
c/Å	17.5045(9)
α/°	80.703(2)
β/°	78.233(2)
γ/°	71.876(2)
Volume/Å^3	1772.70(16)
Z	2
ρ_{calc}g/cm^3	1.414
μ/mm^{-1}	3.342
F(000)	776.0
Crystal size/mm^3	0.25 × 0.06 × 0.05
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	5.186 to 133.358
Index ranges	$-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-20 \leq l \leq 20$
Reflections collected	78539
Independent reflections	6248 [R_{int} = 0.0871, R_{sigma} = 0.0418]
Data/restraints/parameters	6248/0/470
Goodness-of-fit on F^2	1.061
Final R indexes [I>=2σ (I)]	R_1 = 0.0510, wR_2 = 0.1323
Final R indexes [all data]	R_1 = 0.0530, wR_2 = 0.1342
Largest diff. peak/hole / e Å^{-3}	0.43/-0.43

The single crystal of the product **114i** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of petroleum ether/ dichoromethane mixture. The crystal data of product **114i** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2214684.**

2.2.5. Plausible mechanism for the formation of products 113 and 114

Based on the experimental results and known iron (III) chemistry,[61] a plausible reaction mechanism is proposed (**Scheme 37**). At first, the alcohol group of the substrate **111/112** is activated (species **A**) through co-ordination with Fe(III)-catalyst that leads to the generation of a transient propargylic carbocation **B**.[61a,b] Next, species **B** may undergo intramolecular nucleophilic attack by the tethered NHTs group to generate an allenic intermediate **113′** (X=O)/**114′** (X=NTs)[62a] which forms a complex[61a,62b] with $FeCl_3$ (species **C**) to give rise to the product[63] **113**/**114** following pathway I or II respectively. In path I (X=O), $FeCl_3$ acting like a Lewis-acid[61a,62b] affords a benzylic carbocation intermediate **D** which may isomerizes into bicyclo[3.1.0] epoxonium ion **E** through intramolecular nucleophilic addition of oxygen onto the transient carbenium ion adjacent to the NTs group.[64] Species **E** is now poised to undergo intramolecular Fridel-Crafts (IMFC) type cyclization[65] preferably via 5-*exo* epoxide-ring opening (as depicted in **Scheme 37**) which is consistent with the Baldwin rule[64a] and the prediction made in a study[64b] of recent past following experimental and computational evidences. Next, aromatization by deprotonation followed by demetalation[61a] affords the product **113** along with regeneration of $FeCl_3$ which enters into catalytic cycle.



Scheme 37. Plausible reaction mechanism for the formation of products **113** and **114**

In path II (X=NTs), on the contrary, the NTs group in place of oxygen is unable to stabilize the incipient carbenium ion as in **E**. Instead, at higher temperature the tosyl group is lost from intermediate **D′** produced from **C** (X=NTs) with the aid of water generated previously (from step 3), assisted by $FeCl_3$. This triggers the formation of intermediate **E′** with concurrent release of *p*-TsOH and a proton[61a] that helps the demetalation of **E′** to furnish the intermediate **F′**.[61a] Finally, subsequent 1,2-elimination[61b] (-TsH) from **F** with the assistance of $FeCl_3$ (as depicted in **Scheme 37)** would give access to the product **114** and regenerate the Fe (III) catalyst.

2.2.6. Conclusion

In conclusion, an expeditious approach for the synthesis of spiro-indenyl 1,4-benzoxazines **113** via $FeCl_3$ catalyzed cascade reaction of substrates **111** in DCE at room temperature have been developed. The reaction constitutes a fast intramolecular assembly wherein concurrent formation of 1,4-benzoxazine and indene ring takes place easily under one-pot. Replacing the oxygen atom of **111** by -NTs group resulted in substrates **112** which upon Fe(III)-catalyzed reactions on heating at 80 ^{o}C in DCE produced 2-(2,2-diarylvinyl)quinoxalines **114** instead. A plausible reaction mechanism is proposed to explain the formation of the aforesaid products. The method utilizes low cost substrates and environmentally benign iron catalyst, and shows high tolerance towards various functional groups.

2.2.7. Experimental section

2.2.7.1. General Information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 °C. Dichloromethane (DCM) was dried over phosphorous pentaoxide distilled, and stored over 3 Å molecular sieves in a sealed container. THF was distilled over sodium and benzophenone. Commercial grade dry 1,2 Dichloroethane (DCE), nitromethane were used as solvent. Ethanol was purchased Merck. All the reactions were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance. For purification, column chromatography was performed using 100−200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard.

Chemical shifts (δ) are given from TMS (δ = 0.00) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [$CDCl_3$: ^{1}H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm]. Coupling constants (*J*) are expressed in Hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), q (quartet), qui (quintet), six (sextet), m (multiplet), and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF or EI mode.

2.2.7.2. X-Ray crystallographic information of products 113a, **113g**, **113i**, **114h** and **114i**

Single crystal of products **113a**, **113g**, **113i**, **114h** and **114i** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether or ethyl acetate-petroleum ether. The single crystal X-ray diffraction (XRD) data were collected on a Bruker D8 Venture system with a microfocus optics using CuK_α radiation. The data were analyzed and processed with Bruker Apex III software suite[66] incorporated with multiple tools such as cell_now and RLATT for the determination of the unit cell, SAINT-plus for data reduction and SADABS for absorption correction. The structure solutions were performed with SHELXT[67] and the full-matrix least-squares refinements were performed with SHELXL[68] suite of programs incorporated in either Apex III suite[66] or Olex 2.[69] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The important crystal data and ORTEP diagram (drawn at 50% probability level) of product **113a**, **113g**, **113i**, **114h** and **114i** are provided earlier.

2.2.7.3. General procedure for the preparation of the starting materials 111

Synthesis of propargylated nitro derivatives **115:**

To a well stirred solution of commercially available 2-nitrophenol derivatives (7.19 mmol, 1 equiv) in dry MeCN (10 mL), K_2CO_3 (1191.4 mg, 8.63 mmol, 1.2 equiv) was added at 0 ^oC and the mixture was stirred for 2-3 minutes, followed by dropwise addition of propargyl bromide (80% in toluene) (923.86 μL, 8.63 mmol, 1.2 equiv) in the reaction mixture maintaining the said temperature. After 5-10 minutes, ice was removed and the mixture was allowed to stir for additionl 5 minutes. Aftet that the mixture was heated at 80 ^oC for overnight. Upon completion of reaction (TLC), the mixture was passed through celite 545 and the filtrate was

removed under reduced pressure and extracted with ethyl acetate (3x 40 mL); the combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 17-28% ethyl acetate-petroleum ether (*v/v*) to obtain the pure **115** derivatives (72-96% yield).

Synthesis of propargylated amino derivatives **116:**

To a well stirred solution of **115** derivatives (5.60 mmol, 1 equiv) in a mixture of EtOH (25 mL)/H_2O (25 mL) (1:1), Fe powder (1254.1 mg, 22.39 mmol, 4 equiv) and NH_4Cl (3023.4 mg, 55.99 mmol, 10 equiv) were added. Next the whole mixture was heated at 80 ^oC for 2-3.5 h. Upon completion of reaction (TLC), the mixture was cooled to room temperature and passed through celite 545. The organic layer of the filtrate was then removed *in vacuo*. The mixture was then neutralized by adjusting the pH (~7) through dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 35 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 20-28% ethyl acetate-petroleum ether (*v/v*) to obtain the propargylated amine **116** derivatives (30-88% yield).

Synthesis of **117** *derivatives***:**

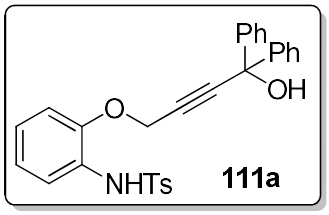
To a well stirred ice-cold solution of **116** derivatives (3.40 mmol, 1 equiv) dissolved in dry THF (3.5 mL), BuLi (1.6 M in cyclohexane) (2.12 mL, 3.40 mmol, 1 equiv) was added dropwise followed by the addition of benzophenone derivatives (3.40 mmol, 1 equiv). After stirring the mixture at 0 ^oC for 10-15 min, ice was removed and the mixture was allowed to stir at rt for additional 45 min to 2h. After that, the reaction mixture was then quenched with water and the reaction mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 15-30% ethyl acetate-petroleum ether (*v/v*) to obtain pure **117** derivatives (36-87% yield).

*Synthesis of Final Substrates **111**:*

To a well stirred solution of **117** derivatives (0.76 mmol, 1 equiv) in dry DCM (3 mL) pyridine (61.25 µL, 0.76 mmol, 1 equiv) was added dropwise at 0 °C followed by portion wise addition of tosyl chloride (TsCl) (144.4 mg, 0.76 mmol, 1 equiv). After stirring the mixture for 5-10 minute at 0 °C, ice was removed and it was stirred for additional 5 minutes. After that the mixture was refluxed for another two to four hours. Upon completion of reaction (TLC), solvents were removed under reduced pressure and the mixture was then extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (17 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 15-30% ethyl acetate-petroleum ether (*v/v*) to obtain the desired starting materials **111** in 60-97% yields.

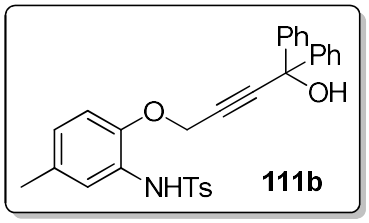
2.2.7.4. Spectral Data of Compounds 111a-k:

N-(2-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)phenyl)-4-methylbenzenesulfonamide (111a):



Pale yellow solid (220.2 mg, 60%) isolated using 28% ethyl acetate-petroleum ether (v/v), mp 148-150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.62 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.48-7.45 (m, 4H), 7.31-7.25 (m, 6H), 7.10-7.06 (m, 3H), 7.04-6.99 (m, 1H), 6.96-6.92 (m, 1H), 6.88 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.63 (s, 2H), 2.94 (brs, 1H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 147.7, 144.3, 143.8, 136.2, 129.5, 128.4, 128.0, 127.3, 126.8, 126.7, 126.0, 125.3, 122.3, 121.5, 112.8, 90.8, 81.3, 74.4, 57.1, 21.6; HRMS (ESI) m/z calcd for $C_{29}H_{25}NNaO_4S$ $[M + Na]^+$ 506.1402, found 506.1405.

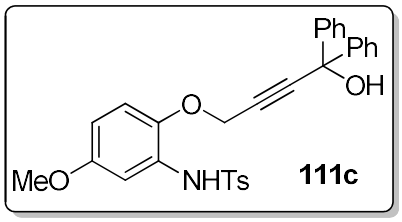
N-(2-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)-5-methylphenyl)-4-methylbenzene-sulfonamide (111b):



Yellow solid (271.9 mg, 72%) isolated using 25% ethyl acetate-petroleum ether (v/v); mp 118-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63 (d, *J* = 8.4 Hz, 2H), 7.49-7.46 (m, 4H), 7.37 (d, *J* = 1.6 Hz, 1H), 7.32-7.26 (m, 6H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.03 (s, 1H), 6.83-6.76 (m, 2H), 4.59 (s, 2H), 2.28-2.27 (m, 6H); ^{13}C{^{1}H}

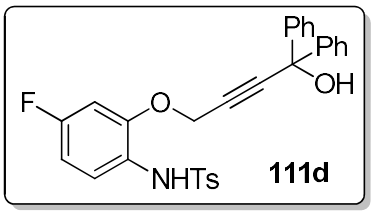
NMR ($CDCl_3$, 100 MHz) δ_C 145.7, 144.3, 143.7, 136.4, 132.0, 129.5, 128.4, 128.0, 127.3, 126.6, 126.0, 125.7, 122.2, 113.0, 90.7, 81.5, 74.4, 57.4, 21.5, 20.9; HRMS (ESI) m/z calcd for $C_{30}H_{27}NNaO_4S$ $[M + Na]^+$ 520.1558, found 520.1564.

N-(2-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)-5-methoxyphenyl)-4-methylbenzene-sulfonamide (111c):



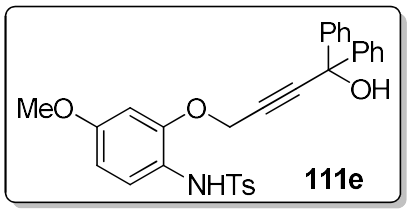
Brown solid (261.2 mg, 67%) isolated using 25% ethyl acetate-petroleum ether (v/v), mp 134-136 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.66 (d, J = 8.4 Hz, 2H), 7.48-7.46 (m, 4H), 7.32-7.26 (m, 6H), 7.15-7.10 (m, 4H), 6.83 (d, J = 8.8 Hz, 1H), 6.52 (dd, J = 8.8, 2.8 Hz, 1H), 4.59 (s, 2H), 3.74 (s, 3H), 2.88 (brs, 1H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.9, 144.3, 143.9, 141.5, 136.2, 129.6, 128.4, 128.0, 127.3, 126.0, 114.8, 109.9, 106.9, 90.8, 81.6, 74.4, 58.2, 55.8, 21.6; HRMS (ESI) m/z calcd for $C_{30}H_{27}NNaO_5S$ $[M + Na]^+$ 536.1508, found 536.1494.

N-(4-fluoro-2-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)phenyl)-4-methylbenzensulfonamide (111d):



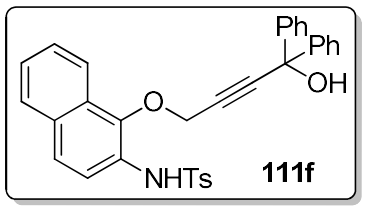
Brownish white solid (289.4 mg, 76%) isolated using 22% ethyl acetate-petroleum ether (v/v), mp 110-112 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.58 (d, J = 8.4 Hz, 2H), 7.51-7.48 (m, 5H), 7.33-7.24 (m, 6H), 7.08 (d, J = 8.0 Hz, 2H), 6.99 (s, 1H), 6.69-6.62 (m, 2H), 4.53 (s, 2H), 3.20 (brs, 1H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.5 (d, J_{C-F} = 244.1Hz), 149.5 (d, J_{C-F} = 10.3 Hz), 144.3, 143.9, 136.0, 129.5, 128.4, 128.0, 127.4, 126.0, 124.3 (d, J_{C-F} = 9.9 Hz), 122.4 (d, J_{C-F} = 3.5 Hz), 108.4 (d, J_{C-F} = 22.3 Hz), 101.2 (d, J_{C-F} = 27.0 Hz), 91.4, 80.5, 74.4, 57.3, 21.5; HRMS (ESI) m/z calcd for $C_{29}H_{24}FNNaO_4S$ $[M + Na]^+$ 524.1308, found 524.1321.

N-(2-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)-4-methoxyphenyl)-4-methylbenzenesulfonamide (111e):



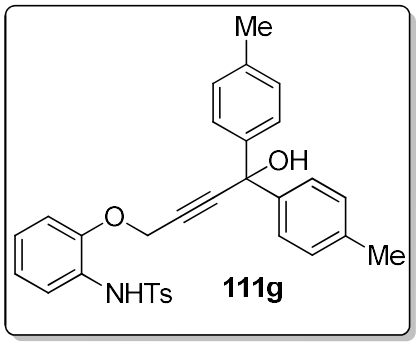
Yellow gummy liquid (280.7 mg, 72%) isolated using 28% ethyl acetate-petroleum ether (v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.55-7.50 (m, 6H), 7.44 (d, J = 8.8 Hz, 1H), 7.31-7.23 (m, 6H), 7.04 (d, J = 8.0 Hz, 2H), 6.88 (s, 1H), 6.49-6.44 (m, 2H), 4.42 (s, 2H), 3.65 (s, 3H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.3, 150.3, 144.6, 143.5, 136.2, 129.3, 128.4, 127.9, 127.4, 126.1, 125.3, 119.1, 106.0, 100.4, 91.0, 81.1, 74.3, 57.0, 55.5, 21.5; HRMS (ESI) m/z calcd for $C_{30}H_{27}NNaO_5S$ $[M + Na]^+$ 536.1508, found 536.1512.

N-(1-((4-hydroxy-4,4-diphenylbut-2-yn-1-yl)oxy)naphthalen-2-yl)-4-methylbenzene-sulfonamide (111f):



Brown gummy liquid (275.4 mg, 68%) isolated using 25% ethyl acetate-petroleum ether (v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.89 (d, J = 8.0 Hz, 1H), 7.79-7.75 (m, 2H), 7.67-7.59 (m, 4H), 7.55-7.53 (m, 4H), 7.47-7.38 (m, 2H), 7.35-7.28 (m, 6H), 7.11 (d, J = 8.0 Hz, 2H), 4.64 (s, 2H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 156.1, 144.4, 144.1, 141.3, 136.3, 131.8, 129.8, 128.4, 128.3, 127.9, 127.4, 127.2, 126.9, 126.1, 125.7, 125.5, 121.4, 119.3, 111.9, 100.0, 92.5, 81.8, 74.4, 62.7, 21.6; HRMS (ESI) m/z calcd for $C_{33}H_{27}NNaO_4S$ $[M + Na]^+$ 556.1558, found 556.1561.

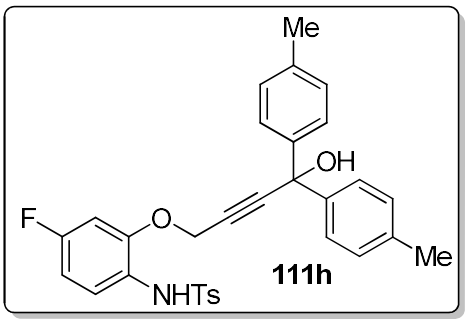
N-(2-((4-hydroxy-4,4-di-p-tolylbut-2-yn-1-yl)oxy)phenyl)-4-methylbenzenesulfonamide (111g):



Yellow solid (376.7 mg, 97%) isolated using 28% ethyl acetate-petroleum ether (v/v), mp 96-98 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63 (d, J = 8.0 Hz, 2H), 7.56 (dd, J = 7.8, 1.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 4H), 7.10-7.07 (m, 7H), 7.05-7.00 (m, 1H), 6.98-6.94 (m, 1H), 6.89 (dd, J = 8.2, 1.4 Hz, 1H), 4.63 (s, 2H), 2.78 (brs, 1H), 2.32 (s, 6H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 147.7, 143.7, 141.6,

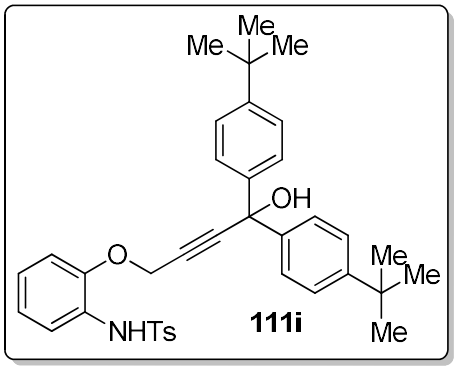
137.7, 136.3, 129.5, 129.0, 127.3, 126.8, 125.9, 125.3, 122.2, 121.6, 112.8, 91.2, 80.9, 74.2, 57.2, 21.5, 21.1; HRMS (ESI) m/z calcd for $C_{31}H_{29}NNaO_4S$ $[M + Na]^+$ 534.1715, found 534.1698.

N-(4-fluoro-2-((4-hydroxy-4,4-di-p-tolylbut-2-yn-1-yl)oxy)phenyl)-4-methylbenzene-sulfonamide (111h):



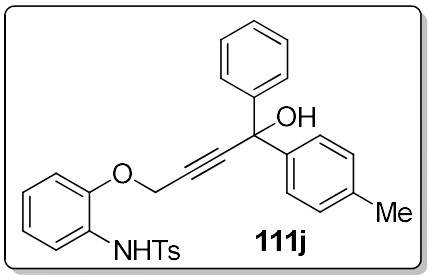
White solid (357.8 mg, 89%) isolated using 25% ethyl acetate-petroleum ether (v/v), mp 114-116 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.57 (d, J = 8.4 Hz, 2H), 7.53-7.49 (m, 1H), 7.35 (d, J = 8.4 Hz, 4H), 7.12-7.08 (m, 6H), 6.85 (s, 1H), 6.70-6.62 (m, 2H), 4.53 (s, 2H), 2.83 (brs, 1H), 2.32 (s, 6H), 2.28 (s, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ_C 160.5 (d, J_{C-F} = 244.1 Hz), 149.4 (d, J_{C-F} = 10.3 Hz), 143.8, 141.5, 137.8, 136.1, 129.5, 129.1, 127.3, 125.9, 124.2 (d, J_{C-F} = 9.8 Hz), 122.4 (d, J_{C-F} = 3.5 Hz), 108.4 (d, J_{C-F} = 22.2 Hz), 101.2 (d, J_{C-F} = 27.1 Hz), 91.7, 80.1, 74.2, 57.3, 21.5, 21.1; HRMS (ESI) m/z calcd for $C_{31}H_{28}FNNaO_4S$ $[M + Na]^+$ 552.1621, found 552.1610.

N-(2-((4,4-bis(4-(tert-butyl)phenyl)-4-hydroxybut-2-yn-1-yl)oxy)phenyl)-4-methylbenzene-sulfonamide (111i):



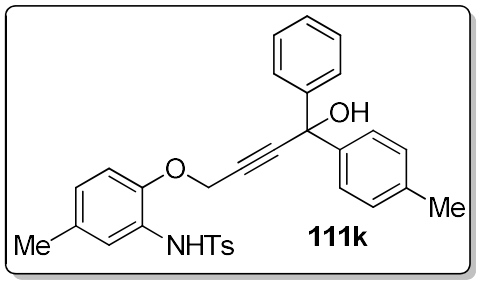
Brown gummy liquid (316.5 mg, 70%) isolated using 23% ethyl acetate-petroleum ether (v/v), ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.64 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 4H), 7.33 (d, J = 8.4 Hz, 4H), 7.16 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.05-7.00 (m, 1H), 6.98-6.94 (m, 1H), 6.90 (dd, J = 8.0, 1.2 Hz, 1H), 4.61 (s, 2H), 2.96 (brs, 1H), 2.25 (s, 3H), 1.32 (s, 18H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 150.8, 147.9, 143.7, 141.5, 136.3, 129.5, 127.3, 126.7, 125.8, 125.4, 125.3, 122.2, 121.8, 112.8, 91.3, 80.8, 74.2, 57.2, 34.6, 31.4, 21.5; HRMS (ESI) m/z calcd for $C_{37}H_{41}NNaO_4S$ $[M + Na]^+$ 618.2654, found 618.2643.

N-(2-((4-hydroxy-4-phenyl-4-(p-tolyl)but-2-yn-1-yl)oxy)phenyl)-4-methylbenzenesulfonamide (111j):



White solid (351.3 mg, 93%) isolated using 25% ethyl acetate-petroleum ether (v/v), mp 120-122 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 7.8, 1.8 Hz, 1H), 7.48-7.45 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.31-7.25 (m, 3H), 7.11-7.00 (m, 6H), 6.96 (td, J = 7.7, 1.5 Hz, 1H), 6.89 (dd, J = 8.0, 1.6 Hz, 1H), 4.64 (s, 2H), 2.78 (s, 1H), 2.32 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 147.7, 144.4, 143.7, 141.5, 137.8, 136.3, 129.5, 129.1, 128.4, 127.9, 127.3, 126.8, 125.99, 125.96, 125.3, 122.3, 121.5, 112.8, 91.0, 81.1, 74.3, 57.1, 21.5, 21.1; HRMS (ESI) m/z calcd for $C_{30}H_{27}NNaO_4S$ $[M + Na]^+$ 520.1558, found 520.1553.

N-(2-((4-hydroxy-4-phenyl-4-(p-tolyl)but-2-yn-1-yl)oxy)-5-methylphenyl)-4-methylbenzene-sulfonamide (111k):



Pale brown solid (345.6 mg, 89%) isolated using 25% ethyl acetate-petroleum ether (v/v), mp 100-102 ^{o}C;^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.64 (d, J = 8.4 Hz, 2H), 7.51-7.49 (m, 2H), 7.39-7.37 (m, 3H), 7.32-7.26 (m, 3H), 7.17 (s, 1H), 7.12-7.08 (m, 4H), 6.84-6.77 (m, 2H), 4.56 (s, 2H), 3.23 (brs, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.9, 144.6, 143.7, 141.7, 137.7, 136.3, 131.9, 129.5, 129.1, 128.3, 127.8, 127.3, 126.5, 126.1, 126.0, 125.8, 122.5, 113.0, 90.9, 81.4, 74.3, 57.4, 21.5, 21.2, 21.0; HRMS (ESI) m/z calcd for $C_{31}H_{29}NNaO_4S$ $[M + Na]^+$ 534.1715, found 534.1715.

2.2.7.5. General Procedure for the Synthesis of Starting Material 112:

Synthesis of tosylated derivatives **118:**

To a well stirred solution of commercially available aniline derivatives (9.34 mmol, 1 equiv) in dry DCM (6 mL), Et_3N (1490.41 µL, 11.21 mmol, 1.2 equiv) was added dropwise at 0 ^oC followed by portion-wise addition of TsCl (2130.8 mg, 11.21 mmol, 1.2 equiv). After stirring the reaction mixture at 0 ^oC for another two to four minutes, it was allowed to reach at rt and the stirring was continued at this temperature for another 2.5 to 8 h. Upon completion of reaction (TLC), the solvent was removed under reduced pressure and extracted with DCM (3 × 35 mL). The combined organic extracts were washed with brine (25 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 12-28% ethyl acetate-petroleum ether (*v/v*) to obtain the tosylated **118** derivatives in 70-94% yield.

Synthesis of the nitro derivatives **119:**

To a round bottom flask containing **118** derivative (3.83 mmol, 1 equiv), H_2NO_3 (286.75 µL, 7.66 mmol, 2 equiv) and H_2SO_4 (41.03 µL, 0.77 mmol, 0.2 equiv) were added successively at 0 ^oC at ice-cold conditions. The reaction mixture was then stirred at the same temperature for 10-15 min, then it was allowed to reach to rt and stirred for additional 20-40 min (except the few cases where the reaction did not take place at rt, the mixture was heated at 50 ^oC for 15-30 min). Upon completion of the reaction (TLC), the mixture was quenched with a saturated solution of aqueous sodium bicarbonate to neutralize the mixture adjusting the pH (~7). Next, the solution was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 5-12% ethyl acetate-petroleum ether (*v/v*) to obtain the nitro **119** derivative (35-60% yields).

Synthesis of tosylated amino derivatives **120:**

To a well stirred solution of **119** derivative (2.0 mmol, 1 equiv) in mixture of EtOH (9 mL) and H_2O (9 mL) (1:1), Fe powder (448.0 mg, 8.0 mmol, 4 equiv) and NH_4Cl (1080.0 mg, 20 mmol, 10 equiv) were added and the reaction mixture was heated at 80 ^oC for 2.5 to 4 h. Upon

completion of the reaction (TLC), the mixture was cooled to room temperature and passed through celite 545. The organic layer of the filtrate was then removed in *vacuo* and the mixture was neutralized by adjusting the pH (~7) through dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3× 30 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 8-17% ethyl acetate-petroleum ether (*v/v*) to obtain the propargylated amine derivatives **120** (42-73% yield).

Synthesis of propargylated **121** *derivatives*:

To a well stirred solution of **120** derivatives (1.27 mmol, 1 equiv) dissolved in dry MeCN (5 mL), K_2CO_3 (210.0 mg, 1.52 mmol, 1.2 equiv) was added at 0 ^oC and the mixture was stirred for 2-3 minutes followed by dropwise addition of propargyl bromide (80% in toluene) (162.85 µL, 1.52 mmol, 1.2 equiv) maintaining the temperature. Next the temperature of the reaction was allowed to attain at rt and the whole reaction mixture was heated at 80 ^oC for five to eight hours. Upon completion of reaction (TLC), the mixture was passed through celite 545. The filtrate was removed under reduced pressure and extracted with ethyl acetate (3x 40 mL); the combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 5-15% ethyl acetate-petroleum ether (*v/v*) to obtain the pure **121** derivative (42-64% yield).

Synthesis of **122** *derivatives*:

To a well stirred ice-cold solution of **121** derivatives (0.64 mmol, 1 equiv) dissolved in dry THF (1.2 mL), BuLi (1.6 M in cyclohexane) (437.90 µL, 0.70 mmol, 1.1 equiv) was added dropwise followed by addition of the benzophenone derivatives (0.64 mmol, 1 equiv). After stirring the mixture at 0 ^oC for 10-15 min, the temperature of the reaction was allowed to rise to rt and stirring was continued (1.5-3 h) at rt until the completion of the reaction (TLC). The reaction was then quenched with water (5 mL) and the reaction mixture was then extracted with ethyl acetate (3 × 18 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by

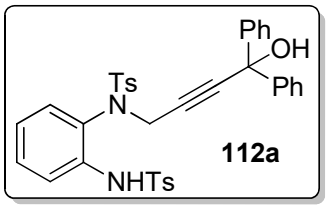
silica gel (100-200 mesh) column chromatography eluting with 15-26% ethyl acetate-petroleum ether (*v/v*) to obtain pure **122** derivative (30-71% yield).

Synthesis of Final Substrates **112:**

To a well stirred solution of **122** derivative (0.35 mmol, 1 equiv) in dry DCM (2 mL) pyridine (28.21 µL, 0.35 mmol, 1 equiv) was added dropwise at 0 ^{o}C followed by portion wise addition of tosyl chloride (TsCl) (86.4 mg, 0.45 mmol, 1.3 equiv). After stirring the mixture for 5-10 minute at 0 ^{o}C, the temperature of the reaction was allowed to rise to rt. The whole reaction mixture was then refluxed for another eight to twenty four hours. Upon completion of reaction (TLC), solvent was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (17 mL) dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 15-26% ethyl acetate-petroleum ether (*v/v*) to obtain the desired starting material **112** (35-81% yields).

2.2.7.6. Spectral Data of Compounds 112a-l:

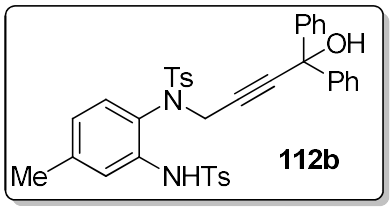
N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide(112a):



112a

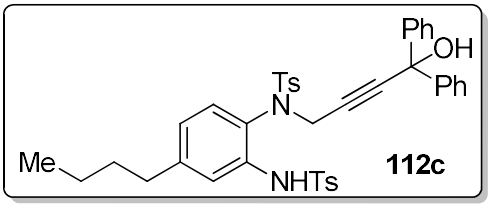
White Solid (131.3 mg, 59%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 78-80 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.83 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37-7.23 (m, 13H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.74 (td, *J* = 7.8, 1.6 Hz, 1H), 6.61 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.51 (d, *J* = 17.6 Hz, 1H), 3.70 (d, *J* = 17.6 Hz, 1H), 2.96 (brs, 1H), 2.37-2.35 (m, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.6, 144.3, 144.1, 136.9, 136.5, 134.2, 130.0, 129.8, 129.7, 129.6, 129.3, 128.6, 128.3, 127.9, 127.5, 126.1, 126.0, 124.5, 121.7, 88.9, 80.6, 74.2, 41.8, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{36}H_{32}N_2NaO_5S_2$ $[M + Na]^+$ 659.1650, found 659.1626.

N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methyl-N-(4-methyl-2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112b):



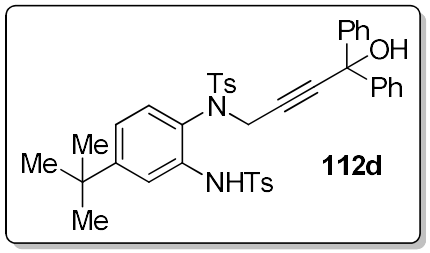
White Solid (152.4 mg, 67%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 74-76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.77-7.75 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.36-7.23 (m, 13H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.56-6.54 (m, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.47 (d, *J* = 18.0 Hz, 1H), 3.62 (d, *J* = 17.6 Hz, 1H), 2.90 (brs, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.5, 144.3, 144.0, 140.4, 137.0, 136.0, 134.3, 129.8, 129.5, 128.8, 128.6, 128.3, 127.8, 127.5, 127.2, 126.1, 126.0, 125.4, 122.5, 88.7, 80.7, 74.2, 41.8, 21.7, 21.64, 21.60; HRMS (ESI) m/z calcd for $C_{37}H_{34}N_2NaO_5S_2$ $[M + Na]^+$ 673.1807, found 673.1789.

N-(4-butyl-2-(4-methylphenylsulfonamido)phenyl)-N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methylbenzenesulfonamide (112c):



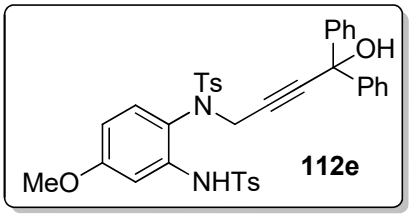
White Solid (164.7 mg, 68%) isolated using 18% ethyl acetate-petroleum ether (v/v), mp 104-106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.75 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.38-7.22 (m, 13H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.57-6.51 (m, 2H), 4.50 (d, *J* = 18.0 Hz, 1H), 3.62 (d, *J* = 17.6 Hz, 1H), 2.84 (s, 1H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 2.34 (s, 3H), 1.50 (qui, *J* = 7.6 Hz, 2H), 1.28 (six, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.3, 144.5, 144.3, 144.0, 136.9, 135.9, 134.5, 129.7, 129.5, 128.9, 128.6, 128.3, 127.9, 127.6, 127.3, 126.1, 126.0, 124.7, 121.8, 88.7, 80.8, 74.2, 41.8, 35.4, 33.0, 22.3, 21.7, 21.6, 14.0; HRMS (ESI) m/z calcd for $C_{40}H_{40}N_2NaO_5S_2$ $[M + Na]^+$ 715.2276, found 715.2247.

N-(4-(tert-butyl)-2-(4-methylphenylsulfonamido)phenyl)-N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methylbenzenesulfonamide (112d):



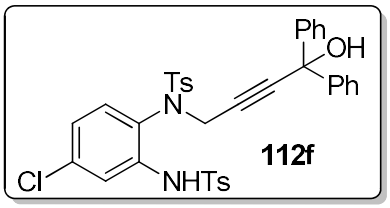
White Solid (157.4 mg, 65%) isolated using 18% ethyl acetate-petroleum ether (v/v), mp 98-100 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.76 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.39-7.26 (m, 10H), 7.25-7.23 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.72 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 18 Hz, 1H), 3.66 (d, *J* = 18.0 Hz, 1H), 2.72 (brs, 1H), 2.38-2.35 (m, 6H), 1.21 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 153.4, 144.4, 144.3, 144.0, 137.0, 135.6, 134.8, 129.7, 129.5, 128.6, 128.3, 127.9, 127.7, 127.2, 121.5, 119.4, 88.6, 81.0, 74.2, 41.7, 35.0, 31.1, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{40}H_{40}N_2NaO_5S_2$ $[M + Na]^+$ 715.2276, found 715.2248.

N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-N-(4-methoxy-2-(4-methylphenylsulfonamido)phenyl)-4-methylbenzenesulfonamide (112e):



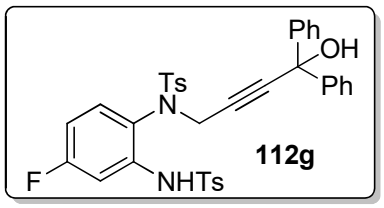
White Solid (156.2 mg, 67%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 92-94 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.78 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.31-7.24 (m, 10H), 7.07-7.04 (m, 3H), 6.46 (d, *J* = 9.2 Hz, 1H), 6.22 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.50 (d, *J* = 17.6 Hz, 1H), 3.75-3.70 (m, 4H), 2.77 (brs, 1H), 2.38-2.35 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.2, 144.5, 144.2, 144.1, 137.6, 136.8, 134.4, 130.0, 129.8, 129.5, 128.6, 128.3, 127.9, 127.6, 126.1, 126.0, 121.8, 110.2, 106.1, 88.8, 80.8, 74.2, 55.5, 41.9, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{37}H_{34}N_2NaO_6S_2$ $[M + Na]^+$ 689.1756, found 689.1732.

N-(4-chloro-2-(4-methylphenylsulfonamido)phenyl)-N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methylbenzenesulfonamide (112f):



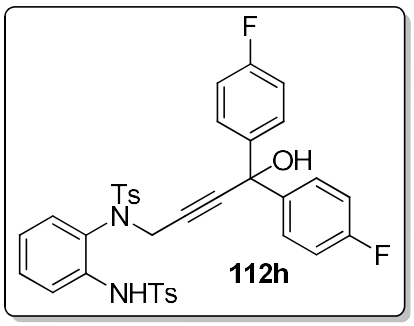
White Solid (133.7 mg, 57%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 102-104 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.80-7.77 (m, 3H), 7.54 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.34-7.26 (m, 12H), 7.08 (d, J = 8.0 Hz, 2H), 6.66 (dd, J = 8.4, 2.4 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 4.50 (d, J = 17.6 Hz, 1H), 3.81 (d, J = 17.6 Hz, 1H), 2.80 (brs, 1H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.9, 144.4, 144.1, 137.8, 136.4, 135.8, 133.9, 130.1, 129.9, 129.7, 128.6, 128.3, 128.0, 127.6, 127.5, 126.0, 125.9, 124.2, 121.0, 89.2, 80.3, 74.2, 41.8, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{36}H_{31}ClN_2NaO_5S_2$ $[M + Na]^+$ 693.1261, found 693.1251.

N-(4-fluoro-2-(4-methylphenylsulfonamido)phenyl)-N-(4-hydroxy-4,4-diphenylbut-2-yn-1-yl)-4-methylbenzenesulfonamide (112g):



Yellowish white Solid (119.0 mg, 52%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 102-104 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.80-7.78 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.36-7.34 (m, 2H), 7.30-7.24 (m, 11H), 7.09 (d, J = 8.4 Hz, 2H), 6.52-6.48 (m, 1H), 6.38-6.34 (m, 1H), 4.54 (d, J = 17.6 Hz, 1H), 3.86 (d, J = 18.0 Hz, 1H), 2.81 (brs, 1H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.7 (d, $J_{C\text{-}F}$ = 248.4 Hz), 144.8, 144.4, 138.4 (d, $J_{C\text{-}F}$ = 11.9 Hz), 136.3, 134.0, 130.7 (d, $J_{C\text{-}F}$ = 10.1 Hz), 129.9, 129.7, 128.6, 128.32, 128.30, 128.2, 127.9, 127.6, 126.0, 125.9, 124.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 110.8 (d, $J_{C\text{-}F}$ = 22.9 Hz), 107.8 (d, $J_{C\text{-}F}$ = 27.6 Hz), 89.1, 80.4, 74.2, 41.9, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{36}H_{31}FN_2NaO_5S_2$ $[M + Na]^+$ 677.1556, found 677.1548.

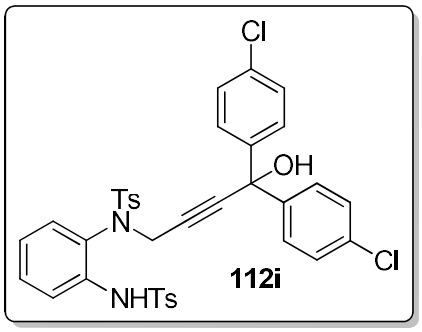
N-(4,4-bis(4-fluorophenyl)-4-hydroxybut-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112h):



112h

Yellowish white Solid (190.5 mg, 81%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 88-90 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.79-7.77 (m, 3H), 7.46 (d, J = 8.4 H, 2H), 7.42 (dd, J = 8.2, 1.4 Hz, 1H), 7.33-7.19 (m, 7H), 7.13 (d, J = 8.4 Hz, 2H), 6.96-6.90 (m, 4H), 6.80-6.76 (m, 1H), 6.52 (dd, J = 8.0, 1.2 Hz, 1H), 4.35 (d, J = 17.2 Hz, 1H), 4.10 (d, J = 17.2 Hz, 1H), 3.13 (brs, 1H), 2.38 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.3 (d, J_{C-F} = 245.8 Hz), 144.8, 144.2, 136.9 (d, J_{C-F} = 7.5 Hz), 134.0, 130.0, 129.8, 129.7, 129.2, 128.8, 128.5, 127.8 (d, J_{C-F} = 8.3 Hz), 127.6, 124.1, 120.7, 115.1 (d, J_{C-F} = 21.5 Hz), 88.5, 80.8, 73.2, 42.0, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{36}H_{30}F_2N_2NaO_5S_2$ $[M + Na]^+$ 695.1462, found 695.1459.

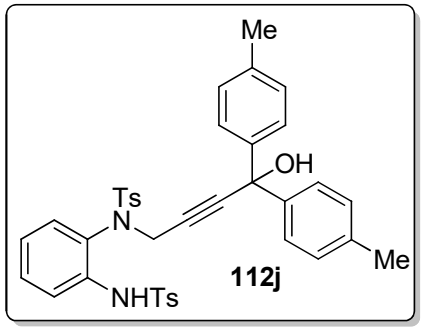
N-(4,4-bis(4-chlorophenyl)-4-hydroxybut-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112i):



112i

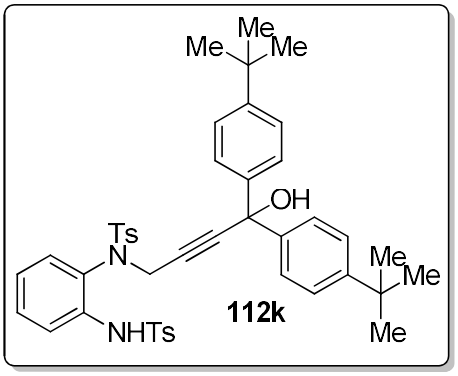
White Solid (194.6 mg, 79%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 132-134 ^{o}C;^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.81-7.77 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 8.4, 1.2 Hz, 1H), 7.29-7.20 (m, 11H), 7.15 (d, J = 8.0 Hz, 2H), 6.80 (td, J = 7.8, 1.6 Hz, 1H), 6.52 (dd, J = 8.0, 1.6 Hz, 1H), 4.34 (d, J = 17.2 Hz, 1H), 4.15 (d, J = 17.2 Hz, 1H), 3.32 (s, 1H), 2.40-2.39 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.8, 144.2, 137.0, 136.8, 133.9, 133.8, 130.1, 129.8, 129.7, 129.1, 128.8, 128.5, 127.6, 127.4, 124.2, 120.7, 88.0, 81.1, 73.2, 42.0, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{36}H_{30}Cl_2N_2NaO_5S_2$ $[M + Na]^+$ 727.0871, found 727.0845.

N-(4-hydroxy-4,4-di-p-tolylbut-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112j):



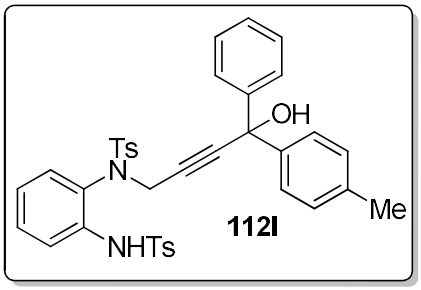
White Solid (81.3 mg, 35%) isolated using 20% ethyl acetate-petroleum ether (v/v), mp 76-78 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.79 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.55 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.26-7.16 (m, 7H), 7.08-7.03 (m, 6H), 6.75 (td, *J* = 7.8, 1.6 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.50 (d, *J* = 17.6 Hz, 1H), 3.63 (d, *J* = 17.6 Hz, 1H), 2.67 (brs, 1H), 2.38 (s, 3H), 2.35-2.32 (m, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.5, 144.0, 137.5, 136.9, 136.4, 134.3, 130.0, 129.8, 129.7, 129.5, 129.3, 128.9, 128.6, 127.5, 126.0, 125.9, 124.5, 121.9, 100.0, 89.1, 80.3, 74.0, 41.8, 21.7, 21.6, 21.1; HRMS (ESI) m/z calcd for $C_{38}H_{36}N_2NaO_5S_2$ $[M + Na]^+$ 687.1963, found 687.1931.

N-(4,4-bis(4-(tert-butyl)phenyl)-4-hydroxybut-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112k):



Yellowish white Solid (104.7 mg, 40%) isolated using 15% ethyl acetate-petroleum ether (v/v), mp 144-146 ^{o}C;^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.80 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.57 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.31-7.22 (m, 11H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.75-6.71 (m, 1H), 6.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.53 (d, *J* = 18.0 Hz, 1H), 3.58 (d, *J* = 18.0 Hz, 1H), 2.69 (brs, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 1.31 (s, 18H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.5, 144.0, 136.9, 136.4, 134.4, 129.9, 129.8, 129.7, 129.5, 129.4, 128.7, 127.5, 125.8, 125.7, 125.1, 124.5, 122.0, 89.3, 80.2, 74.0, 41.7, 34.6, 31.4, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{44}H_{48}N_2NaO_5S_2$ $[M + Na]^+$ 771.2902, found 771.2905.

N-(4-hydroxy-4-phenyl-4-(p-tolyl)but-2-yn-1-yl)-4-methyl-N-(2-(4-methylphenylsulfonamido)phenyl)benzenesulfonamide (112l):



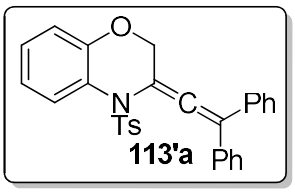
Yellowish white Solid (113.7 mg, 50%) isolated using 17% ethyl acetate-petroleum ether (v/v), mp 80-82 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.84 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 8.4, 1.2 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.36-7.17 (m, 10H), 7.09-7.04 (m, 4H), 6.75 (td, J = 7.7, 1.3 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 4.51 (d, J = 17.6 Hz, 1H), 3.66 (d, J = 18.0 Hz, 1H), 2.88 (brs, 1H), 2.37-2.33 (m, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.6, 144.4, 144.1, 137.6, 136.9, 136.5, 134.2, 130.0, 129.8, 129.7, 129.6, 129.3, 128.9, 128.6, 128.2, 127.8, 127.5, 126.0, 124.5, 121.8, 89.0, 80.5, 74.1, 41.8, 21.7, 21.6, 21.2; HRMS (ESI) m/z calcd for $C_{37}H_{34}N_2NaO_5S_2$ $[M + Na]^+$ 673.1807, found 673.1788.

2.2.7.7. General Procedure for the Synthesis of Spirocyclic 1,4-Benzoxazines 113

To a well stirred solution of propargylic alcohol **111** (0.07 mmol, 1 equiv) in dry DCE (1.5 mL), $FeCl_3$ (0.007 mmol, 0.1 equiv, 10 mol%) was added. Next, the whole reaction mixture was carefully deoxygenated and it was then allowed to stir at rt under argon atmosphere for 0.67-3 h. Upon completion of reaction (TLC), the solvent was evaporated *in vacuo* and the crude product was purified by direct silica gel (100-200) column chromatography avoiding the standard work-up; the spirocyclic product **113** was obtained (in 38-89% yields) by eluting with 3-4% ethyl acetate-petroleum ether (*v/v*).

2.2.7.8. Spectral Data of Intermediate 113′a

3-(2,2-diphenylvinylidene)-4-tosyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (113'a):

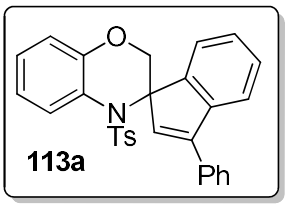


Pale yellow liquid (30.3 mg, 93%) isolated using 5% ethyl acetate-petroleum ether (v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.91 (dd, J = 8.4, 1.6 Hz, 1H), 7.40-7.33 (m, 12H), 7.14-7.10 (m, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.03-6.99 (m, 1H), 6.87 (dd, J = 8.0, 1.6 Hz, 1H), 4.26 (s, 2H),

2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 201.9, 147.5, 144.3, 135.5, 134.6, 129.6, 129.2, 128.5, 128.4, 127.8, 126.5, 125.6, 125.2, 121.4, 117.7, 117.4, 102.9, 66.0, 21.7; HRMS (ESI) m/z calcd for $C_{29}H_{24}NO_3S$ $[M + H]^+$ 466.1477, found 466.1474.

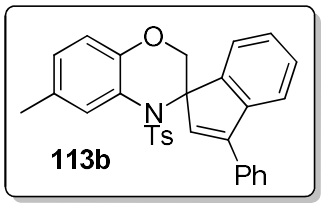
2.2.7.9. Spectral Data of Products 113a-k

3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113a):



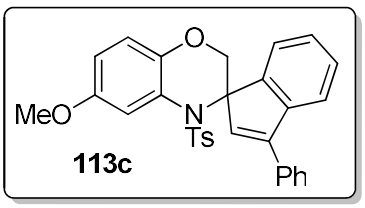
Yellowish white solid (28.3 mg, 87%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 144-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.98-7.96 (m, 1H), 7.50-7.40 (m, 8H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.19-7.14 (m, 1H), 7.10-7.08 (m, 3H), 7.06-7.00 (m, 2H), 6.93-6.91 (m, 1H), 6.50 (s, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 148.4, 145.7, 145.1, 143.9, 141.3, 137.5, 134.4, 131.5, 129.4, 128.7, 128.6, 128.5, 127.7, 127.6, 126.6, 125.8, 125.4, 125.1, 123.8, 121.6, 121.4, 117.4, 71.7, 69.3, 21.6; HRMS (ESI) m/z calcd for $C_{29}H_{24}NO_3S$ $[M + H]^+$ 466.1477, found 466.1468.

6-methyl-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113b):



Yellowish white solid (29.8 mg, 89%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 174-176 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.77 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45-7.40 (m, 6H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.11-7.08 (m, 3H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.49 (s, 1H), 4.27 (d, *J* = 11.4 Hz, 1H), 3.87 (d, *J* = 10.8 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 145.7, 145.1, 144.7, 143.4, 140.8, 137.0, 133.9, 131.1, 130.5, 128.9, 128.1, 128.0, 127.9, 127.2, 127.1, 126.13, 126.08, 124.9, 124.4, 123.3, 120.8, 116.5, 71.1, 68.8, 21.0, 20.6; HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_3S$ $[M + H]^+$ 480.1633, found 480.1635.

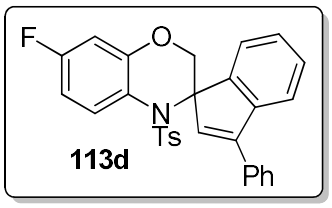
6-methoxy-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113c):



White solid (23.9 mg, 69%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 180-182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63-7.62 (m, 1H), 7.52-7.40 (m, 8H), 7.32 (td, *J* = 7.6,

1.2 Hz, 1H), 7.13-7.08 (m, 3H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.49 (s, 1H), 4.17 (d, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.1, 145.29, 145.27, 143.9, 142.4, 141.3, 137.2, 134.5, 132.0, 129.4, 128.7, 128.6, 128.5, 127.7, 127.6, 126.6, 126.2, 123.7, 121.4, 117.8, 111.8, 109.2, 100.0, 72.3, 70.0, 55.9, 21.6, HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1390.

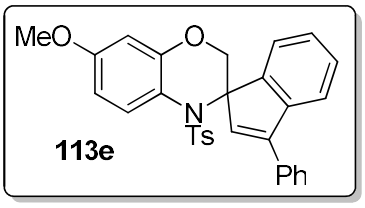
7-fluoro-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113d):



113d

Yellow solid (26.7 mg, 79%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 190-192 ^{o}C;^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.86-7.81 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45-7.36 (m, 6H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.13 (d, *J* = 8.0. Hz, 2H), 7.07 (td, *J* = 7.5 Hz, 1H), 6.81-6.75 (m, 3H), 6.45 (s, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 3.86 (d, *J* = 11.2 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.8 (d, J_{C-F} = 244.2 Hz), 149.6 (d, J_{C-F} = 12.1 Hz), 146.4, 144.8, 144.1, 141.3, 137.6, 134.2, 130.5, 129.6, 128.8, 128.65, 128.63, 127.9 (d, J_{C-F} = 9.6 Hz), 127.7, 127.5, 126.8, 123.8, 121.4, 120.8 (d, J_{C-F} = 3.3 Hz), 108.6 (d, J_{C-F} = 22.4 Hz), 104.3 (d, J_{C-F} = 25.5 Hz), 70.8, 68.2, 21.6; HRMS (ESI) m/z calcd for $C_{29}H_{23}FNO_3S$ $[M + H]^+$ 484.1383, found 484.1378.

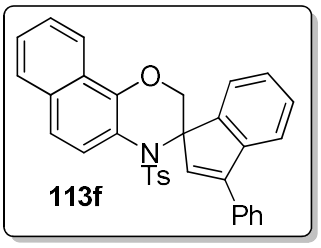
7-methoxy-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113e):



113e

Yellow solid (20.1 mg, 58%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 142-144 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.76 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.43-7.40 (m, 3H), 7.39-7.37 (m, 2H), 7.28 (td, *J* = 7.5, 1.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.63 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.45 (s, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 3.86 (s, 3H), 3.80 (d, *J* = 10.8 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 157.9, 149.1, 145.6, 144.5, 143.3, 140.8, 137.2, 133.8, 130.2, 129.0, 128.1, 128.0, 127.5, 127.2, 127.0, 126.2, 123.4, 120.7, 117.0, 107.5, 101.2, 70.0, 67.6, 55.1, 21.1; HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_4S$ $[M + Na]^+$ 518.1402, found 518.1388.

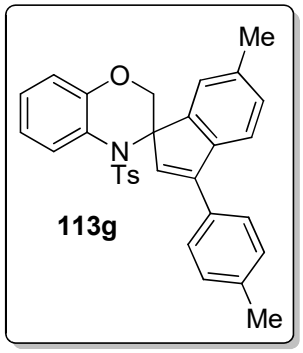
3-phenyl-4'-tosyl-2',4'-dihydrospiro[indene-1,3'-naphtho[1,2-b][1,4]oxazine] (113f):



113f

Brownish gummy liquid (13.7 mg, 38%) isolated using 5% ethyl acetate-petroleum ether (v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.23-8.20 (m, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.87-7.80 (m, 2H), 7.59-7.57 (m, 2H), 7.54-7.52 (m, 2H), 7.51-7.49 (m, 1H), 7.43-7.39 (m, 4H), 7.38-7.35 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.95 (td, *J* = 7.6, 0.8 Hz, 1H), 6.69-6.67 (m, 1H), 6.53 (s, 1H), 4.59 (d, *J* = 10.8 Hz,1H), 4.09 (d, *J* = 10.8 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 146.4, 145.1, 143.9, 141.4, 137.9, 134.3, 132.5, 132.2, 130.7, 130.1, 129.6, 128.7, 128.6, 128.5, 128.3, 127.7, 127.54, 127.50, 126.8, 126.4, 125.9, 125.3, 124.9, 124.0, 121.9, 121.3, 120.5, 119.1, 71.0, 68.0, 21.5; HRMS (ESI) m/z calcd for $C_{33}H_{26}NO_3S$ $[M + H]^+$ 516.1633, found 516.1629.

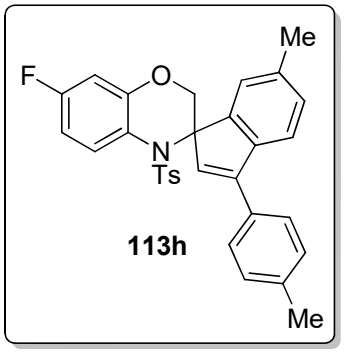
6'-methyl-3'-(p-tolyl)-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113g):



113g

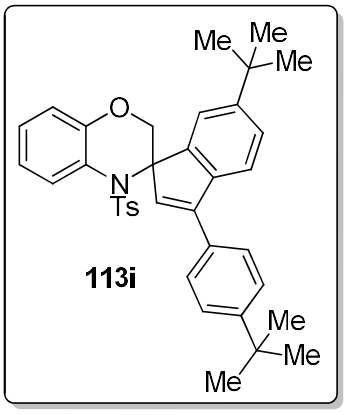
Brownish solid (24.8 mg, 71%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 190-192 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.05 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.16-7.13 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.05-7.00 (m, 2H), 6.73 (s, 1H), 6.38 (s, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 3.90 (d, *J* = 11.4 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 148.0, 144.8, 144.7, 143.2, 138.3, 137.8, 136.8, 135.8, 131.2, 129.9, 128.8, 128.7, 128.6, 127.1, 127.0, 125.4, 125.0, 124.2, 124.0, 121.2, 120.6, 117.0, 71.7, 69.3, 21.1, 21.0, 20.9; HRMS (ESI) m/z calcd for $C_{31}H_{28}NO_3S$ $[M + H]^+$ 494.1790, found 494.1768.

7-fluoro-6'-methyl-3'-(p-tolyl)-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113h):



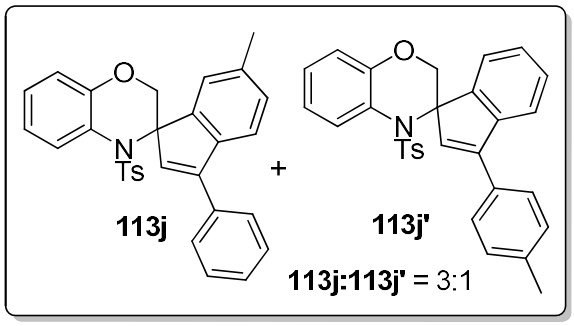
Pale yellow solid (26.8 mg, 75%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 182-184 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.94-7.89 (m, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.32-7.28 (m, 3H), 7.24-7.21 (m, 2H), 7.12-7.10 (m, 3H), 6.80-6.75 (m, 2H), 6.62 (s, 1H), 6.34 (s, 1H), 4.31 (d, J = 11.2 Hz, 1H), 3.86 (d, J = 11.2 Hz, 1H), 2.41(s, 3H), 2.34 (s, 3H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.5 (d, J_{C-F} = 244.0 Hz), 149.6 (d, J_{C-F} = 12.0 Hz), 145.9, 145.0, 143.9, 138.8, 138.4, 137.5, 136.5, 131.5, 129.5, 129.4, 129.3, 129.2, 127.5, 127.2 (d, J_{C-F} = 9.6 Hz), 124.8, 121.3 (d, J_{C-F} = 3.4 Hz), 121.2, 108.6 (d, J_{C-F} = 22.4 Hz), 104.4 (d, J_{C-F} = 25.3 Hz), 71.4, 68.6, 21.6, 21.5, 21.4; HRMS (ESI) m/z calcd for $C_{31}H_{27}FNO_3S$ $[M + H]^+$ 512.1696, found 512.1683.

6'-(tert-butyl)-3'-(4-(tert-butyl)phenyl)-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113i):



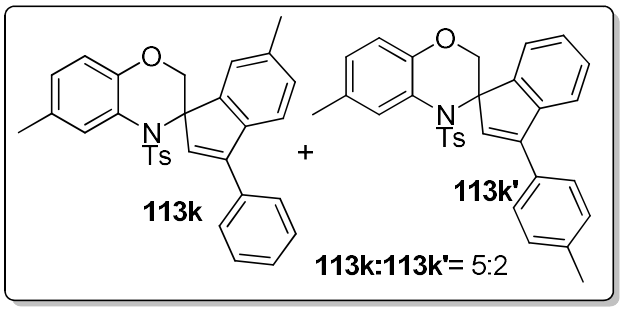
Pale brownish white solid (28.7 mg, 71%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 174-176 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.87 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.40-7.37 (m, 3H), 7.29 (dd, J = 8.1, 1.5 Hz, 1H), 7.19 (t, J = 8.4 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 6.87 (s, 1H), 6.42 (s, 1H), 4.30 (d, J = 10.8 Hz, 1H), 3.88 (d, J = 10.8 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 9H), 1.13 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.0, 149.2, 148.4, 144.9, 144.4, 143.2, 138.2, 137.3, 131.2, 129.5, 129.0, 127.0, 126.8, 125.75, 125.71, 125.0, 124.7, 120.8, 120.7, 120.3, 116.6, 70.8, 68.0, 34.3, 34.2, 30.9, 30.8, 21.0; HRMS (ESI) m/z calcd for $C_{37}H_{40}NO_3S$ $[M + H]^+$ 578.2729, found 578.2716.

6'-methyl-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] and 3'-(p-tolyl)-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113j:113j'):



Yellow solid (28.5 mg, 85%) isolated using 5% ethyl acetate-petroleum ether (*v/v*), mp 138-140 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.07 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.98-7.95 (m, 1H), 7.51-7.24 (m, 16H), 7.19-7.00 (m, 12H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.75 (s, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 3.92-3.88 (m, 2H), 2.42 (s, 3H), 2.32 (s, 6H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 148.5, 145.6, 145.4, 145.3, 145.2, 143.9, 143.8, 141.5, 138.7, 138.4, 137.5, 137.4, 136.4, 134.7, 131.5, 131.1, 130.9, 129.4, 129.35, 139.30, 129.1, 128.7, 128.6, 128.4, 127.68, 127.67, 127.61, 127.60, 126.6, 126.0, 125.9, 125.5, 125.4, 125.3, 124.8, 124.4, 123.7, 121.8, 121.6, 121.4, 121.1, 117.5, 117.4, 72.3, 71.7, 69.9, 69.2, 21.6, 21.56, 21.54, 21.4; HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_3S$ $[M + H]^+$ 480.1633, found 480.1634.

6,6'-dimethyl-3'-phenyl-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] and 6-methyl-3'-(p-tolyl)-4-tosyl-2,4-dihydrospiro[benzo[b][1,4]oxazine-3,1'-indene] (113k:113k'):



White solid (28.3 mg, 82%) isolated using 5% ethyl acetate-petroleum ether (v/v), mp 160-162 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.88 (s, 1H), 7.77 (s, 1H), 7.52-7.39 (m, 12H), 7.36-7.28 (m, 2H), 7.26-7.23 (m, 2H), 7.13-7.06 (m, 6H), 6.98-6.88 (m, 5H), 6.78 (s, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 3.90-3.85 (m, 2H), 2.72 (s, 3H), 2.37-2.36 (m, 6H), 2.33 (s, 6H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 146.33, 146.31, 145.6, 145.5, 145.2, 143.8, 143.7, 141.5, 138.7, 138.4, 137.6, 137.4, 136.3, 134.7, 131.6, 131.3, 131.2, 131.0, 130.9, 129.4, 129.3, 129.2, 129.1, 128.6, 128.5, 128.4, 127.7, 127.68, 127.63, 127.61, 126.59, 126.57, 126.1, 125.6, 125.5, 124.9, 124.8, 124.5, 123.8, 121.4, 121.1, 117.1, 117.0, 72.3, 71.6, 70.0, 69.2, 21.6, 21.57,

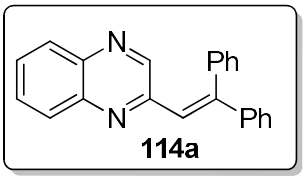
21.55, 21.4, 21.3, 21.2; HRMS (ESI) m/z calcd for $C_{31}H_{28}NO_3S$ $[M + H]^+$ 494.1790, found 494.1786.

2.2.7.10. General Procedure for the Synthesis of Quinoxalines 114

To a well stirred solution of propargyl alcohol **112** (0.12 mmol, 1 equiv) in dry DCE (4.4 mL), $FeCl_3$ (0.012 mmol, 0.1 equiv, 10 mol%) was added. Next, the whole reaction mixture was deoxygenated carefully and it was then heated at 80 ^oC for 12-20 h. Upon completion of reaction (TLC), the solvent was evaporated in *vacuo* and the crude product was purified by direct silica gel (100-200) column chromatography avoiding any standard work-up procedure; the quinoxaline product **114** was obtained (in 30-62% yields) by eluting with 3-4% ethyl acetate-petroleum ether (v/v).

2.2.7.11. Spectral Data of Compounds 114a-l:

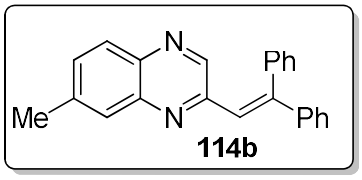
2-(2,2-diphenylvinyl)quinoxaline (114a):



114a

Yellow solid (18.1 mg, 49%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 76-78 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.14 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 7.6, 1.4 Hz, 1H), 7.68 (td, J = 7.5, 1.2 Hz, 1H), 7.44-7.37 (m, 8H), 7.31 (s, 1H), 7.26-7.25 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 145.5, 141.2, 139.6, 138.7, 129.8, 129.6, 129.0, 128.7, 128.5, 128.45, 128.42, 128.0, 127.7; HRMS (ESI) m/z calcd for $C_{22}H_{17}N_2$ $[M + H]^+$ 309.1392, found 309.1377.

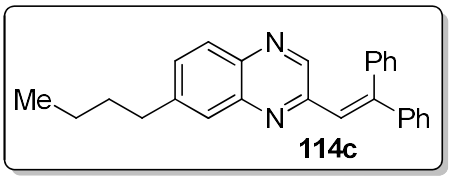
2-(2,2-diphenylvinyl)-7-methylquinoxaline (114b):



114b

Yellow solid (18.9 mg, 49%) isolated using 3% ethyl acetate-petroleum ether (v/v), mp 112-114 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.07 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.43-7.35 (m, 8H), 7.27-7.24 (m, 3H), 2.57 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 151.9, 148.8, 144.6, 141.9, 141.3, 140.0, 138.8, 138.1, 131.2, 129.8, 128.6, 128.3, 128.0, 127.9, 127.6, 127.4, 125.8, 21.4; HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2$ $[M + H]^+$ 323.1548, found 323.1533.

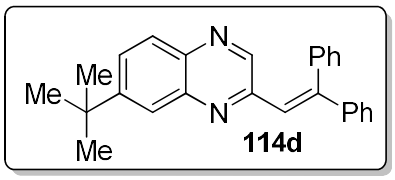
7-butyl-2-(2,2-diphenylvinyl)quinoxaline (114c):



114c

Yellow solid (22.7 mg, 52%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 44-46 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.07 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.51 (dd, J = 8.8, 2.0 Hz, 1H), 7.44-7.41 (m, 2H), 7.39-7.35 (m, 6H), 7.28 (s, 1H), 7.26-7.24 (m, 2H), 2.83 (t, J = 7.6 Hz, 2H), 1.76-1.68 (m, 2H), 1.41 (six, J = 7.4 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 152.4, 149.3, 145.4, 145.1, 142.4, 141.9, 139.4, 138.8, 136.6, 131.1, 130.3, 130.2, 129.4, 129.1, 128.8, 128.6, 128.5, 128.2, 127.7, 127.3, 126.3, 35.8, 33.2, 22.3, 14.0; HRMS (EI) m/z calcd for $C_{26}H_{24}N_2$ $[M]^+$ 364.1939, found 364.1936.

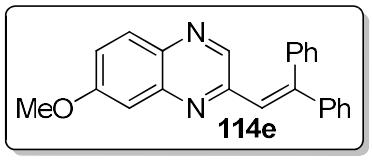
7-(tert-butyl)-2-(2,2-diphenylvinyl)quinoxaline (114d):



114d

Yellow solid (24.9 mg, 57%) isolated using 3% ethyl acetate-petroleum ether (v/v), mp 52-54 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.07 (s, 1H), 7.94 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.76 (dd, J = 8.7, 2.1 Hz, 1H), 7.44-7.42 (m, 2H), 7.39-7.35 (m, 6H), 7.29 (s, 1H), 7.26-7.24 (m, 2H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 153.0, 148.7, 144.8, 141.7, 141.3, 138.8, 138.0, 129.8, 128.6, 128.3, 127.94, 127.91, 127.8, 127.6, 125.7, 123.7, 34.8, 30.6; HRMS (EI) m/z calcd for $C_{26}H_{24}N_2$ $[M]^+$ 364.1939, found 364.1943.

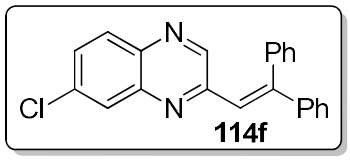
2-(2,2-diphenylvinyl)-7-methoxyquinoxaline (114e):



114e

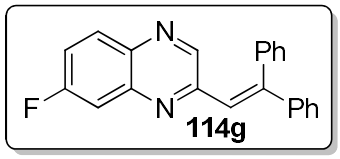
Brownish yellow solid (13.4 mg, 33%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 130-132 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.99 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.44-7.42 (m, 2H), 7.39- 7.35 (m, 6H), 7.31 (dd, J = 8.8, 2.8 Hz, 1H), 7.28-7.24 (m, 4H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.9, 152.4, 149.3, 143.9, 143.5, 141.9, 139.4, 136.2, 130.3, 129.9, 129.1, 128.8, 128.7, 128.5, 128.1, 126.3, 122.5, 106.5, 55.8; HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O$ $[M + H]^+$ 339.1497, found 339.1492.

7-chloro-2-(2,2-diphenylvinyl)quinoxaline (114f):



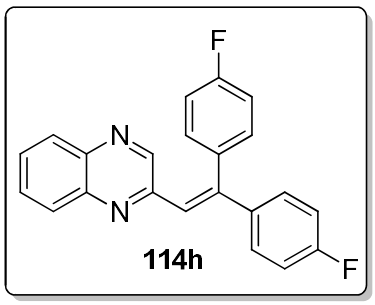
Yellow solid (16.4mg, 40%) isolated using 3.5% ethyl acetate-petroleum ether (v/v), mp 100-102 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.10 (s, 1H), 7.96-7.95 (m, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.60 (dd, J = 8.7, 2.1 Hz, 1H), 7.43-7.37 (m, 8H), 7.26-7.23 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 149.9, 145.6, 142.2, 141.1, 138.6, 138.1, 135.2, 129.79, 129.78, 129.71, 128.69, 128.5, 128.5, 128.0, 127.7, 127.4, 125.2; HRMS (ESI) m/z calcd for $C_{22}H_{16}ClN_2$ $[M + H]^+$ 343.1002, found 343.0996.

2-(2,2-diphenylvinyl)-7-fluoroquinoxaline (114g):



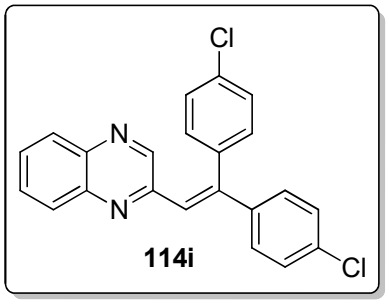
Yellow solid (11.7 mg, 30%) isolated using 3.5% ethyl acetate-petroleum ether (v/v), mp 108-110 ^{o}C;^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.09 (s, 1H), 7.93-7.91 (m, 1H), 7.59 (dd, J = 9.3, 2.7 Hz, 1H), 7.43-7.37 (m, 9H), 7.26-7.24 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 162.4 (d, J_{C-F} = 249.9 Hz), 152.8, 149.8, 144.7 (d, J_{C-F} = 2.8 Hz), 141.1, 138.7, 136.8, 130.5 (d, J_{C-F} = 10.0 Hz), 129.8, 128.7, 128.5 (d, J_{C-F} = 11.2 Hz), 128.0, 127.7, 125.3, 119.0 (d, J_{C-F} = 25.6 Hz), 112.0 (d, J_{C-F} = 21.4 Hz), HRMS (ESI) m/z calcd for $C_{22}H_{16}FN_2$ $[M + H]^+$ 327.1298, found 327.1298.

2-(2,2-bis(4-fluorophenyl)vinyl)quinoxaline (114h):



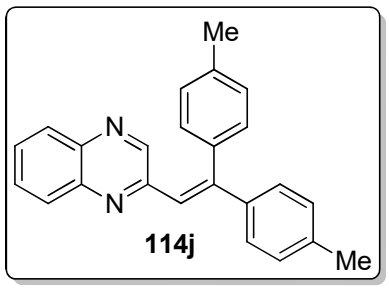
White solid (23.9 mg, 58%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 120-122 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.18 (s, 1H), 7.97-7.94 (m, 2H), 7.75-7.66 (m, 2H), 7.40-7.36 (m, 2H), 7.23-7.19 (m, 3H), 7.09-7.03 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 163.3 (d, J_{C-F} = 248.2 Hz), 163.1 (d, J_{C-F} = 248.1 Hz), 152.1, 147.4, 145.8, 142.3, 140.2, 137.9 (d, J_{C-F} = 4.1 Hz), 135.0 (d, J_{C-F} = 3.7), 132.2 (d, J_{C-F} = 8.1 Hz), 130.2, 129.9 (d, J_{C-F} = 8.2 Hz), 129.6, 129.1, 129.0, 126.12, 126.10, 116.4 (d, J_{C-F} = 21.4 Hz), 115.6 (d, J_{C-F} = 21.6 Hz); HRMS (ESI) m/z calcd for $C_{22}H_{15}F_2N_2$ $[M + H]^+$ 345.1203, found 345.1193.

2-(2,2-bis(4-chlorophenyl)vinyl)quinoxaline (114i):



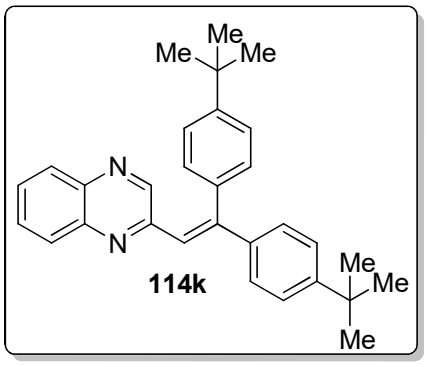
Pale yellow solid (23.5 mg, 52%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 134-136 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.22 (s, 1H), 7.96 (dd, *J* = 7.8, 2.2 Hz, 2H), 7.76-7.67 (m, 2H), 7.36-7.31 (m, 6H), 7.25 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 151.8, 147.0, 145.7, 142.3, 140.3, 140.0, 137.3, 135.16, 135.14, 131.7, 130.3, 129.8, 129.6, 129.4, 129.1, 129.0, 128.8, 126.7; HRMS (ESI) m/z calcd for $C_{22}H_{15}Cl_2N_2$ [M + H]$^{+}$ 377.0612, found 377.0614.

2-(2,2-di-p-tolylvinyl)quinoxaline (114j):



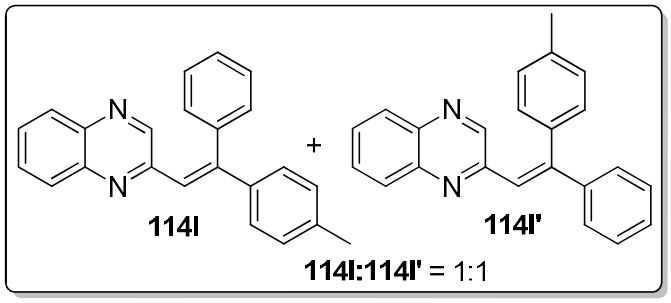
Yellow solid (25.0 mg, 62%) isolated using 4% ethyl acetate-petroleum ether (v/v), mp 76-78 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.16 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.18 (d, *J* = 7.8 Hz, 4H), 7.15-7.14 (m, 2H), 2.40 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 152.4, 149.2, 145.6, 141.9, 139.5, 138.6, 138.4, 138.3, 136.1, 135.9, 129.7, 129.4, 129.3, 128.9, 128.7, 128.6, 128.46, 128.39, 127.6, 127.2, 124.6, 20.9, 20.8; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2$ [M + H]$^{+}$ 337.1705, found 337.1693.

2-(2,2-bis(4-(tert-butyl)phenyl)vinyl)quinoxaline (114k):



Yellow solid (16.1 mg, 32%) isolated using 3% ethyl acetate-petroleum ether (v/v), mp 138-140 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.21 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.40-7.37 (m, 6H), 7.28-7.27 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 1.37-1.36 (m, 18H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 152.4, 151.5, 151.4, 149.0, 145.6, 141.9, 139.5, 138.6, 136.0, 135.8, 129.7, 129.5, 129.4, 128.9, 128.7, 128.4, 127.4, 127.1, 125.4, 124.8, 124.7, 34.3, 34.2, 30.9, 30.8; HRMS (EI) m/z calcd for $C_{30}H_{32}N_2$ [M]$^{+}$ 420.2565, found 420.2571.

(E)-2-(2-phenyl-2-(p-tolyl)vinyl)quinoxaline and (Z)-2-(2-phenyl-2-(p-tolyl)vinyl)quinoxaline (114l:114l')



Yellow gummy liquid (20.1 mg, 52%) isolated using 3% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.17 (s, 1H), 8.11 (s, 1H), 8.00-7.96 (m, 2H), 7.95-7.91 (m, 2H), 7.74-7.63 (m, 4H), 7.44-7.31 (m, 10H), 7.27-7.24 (m, 4H), 7.18-7.12 (m, 6H), 2.39 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 152.8, 152.7, 149.8, 149.6, 146.1, 146.0, 142.4, 142.3, 142.0, 140.1, 139.5, 139.0, 138.9, 138.8, 136.3, 130.3, 130.2, 130.0, 129.9, 129.35, 129.32, 129.2, 129.1, 129.02, 129.01, 128.97, 128.95, 128.83, 128.81, 128.4, 128.2, 128.1, 125.9, 125.3, 21.5, 21.3; HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2$ $[M + H]^+$ 323.1548, found 323.1536.

2.2.8. References

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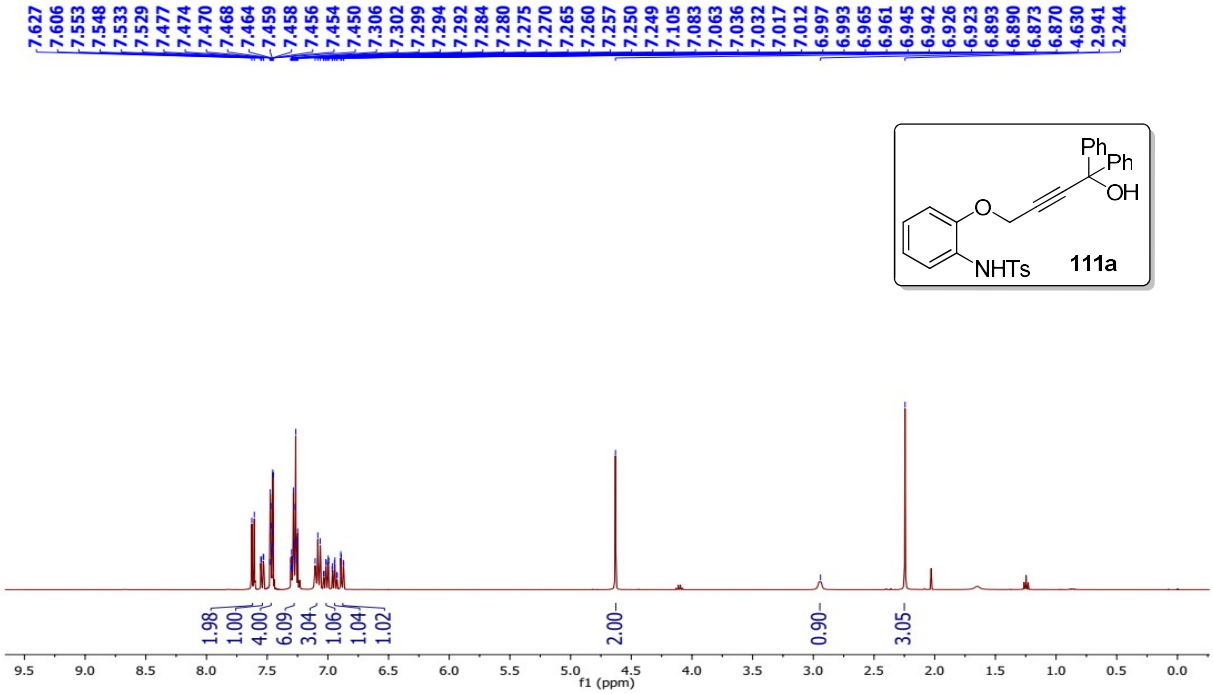
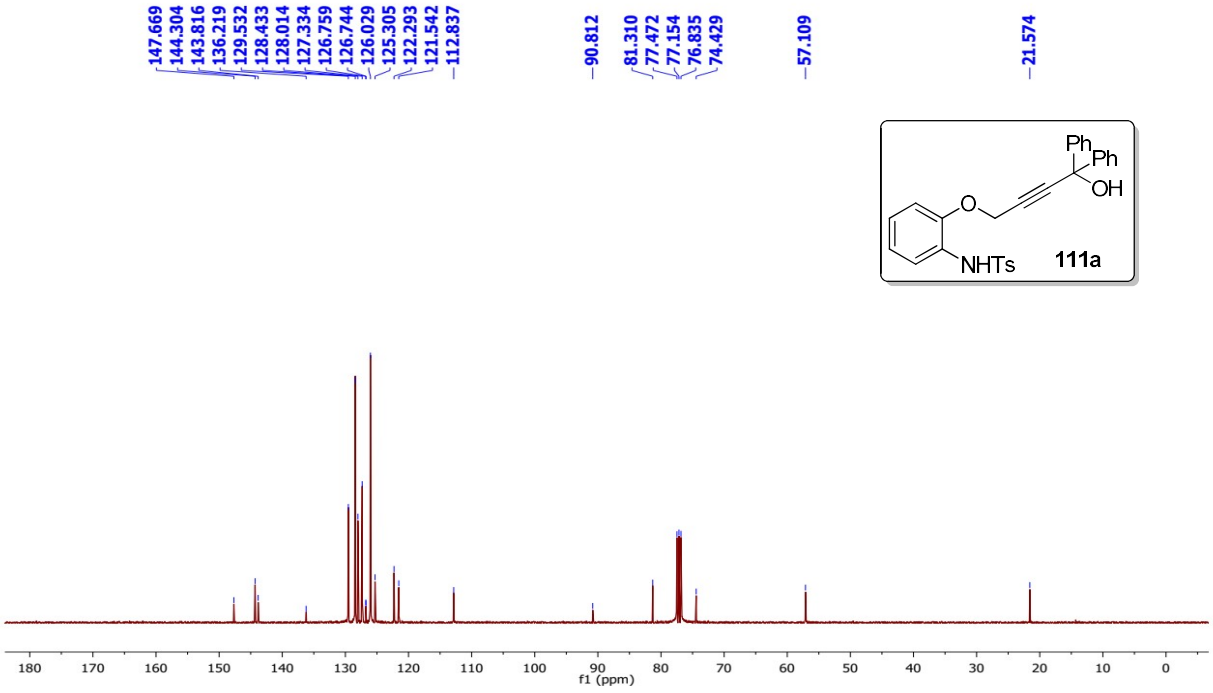
2.2.9. Copies of NMR Spectra

2.2.9.1. NMR Spectra of Compounds 111a-k:

^{1}H NMR (400 MHz) of **111a**:



^{13}C{^{1}H} NMR (100 MHz) of **111a** :



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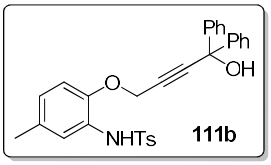

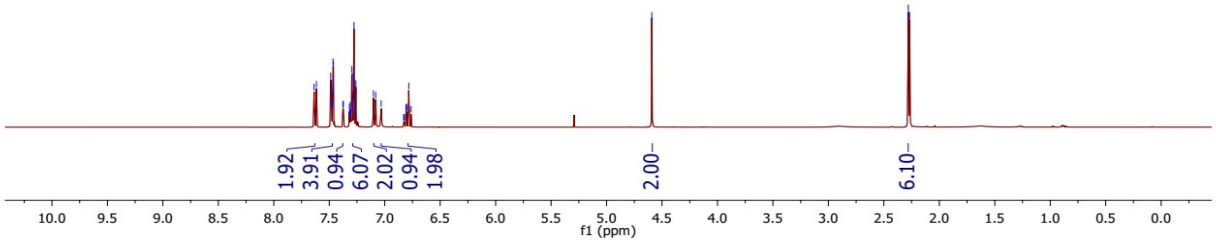

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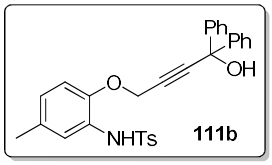
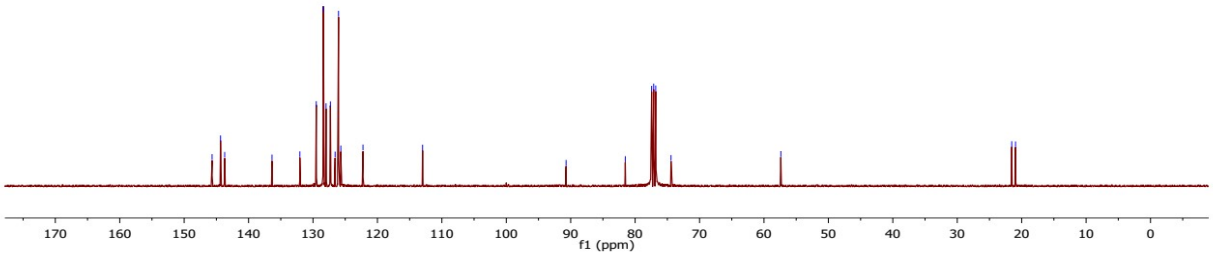
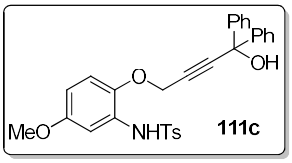
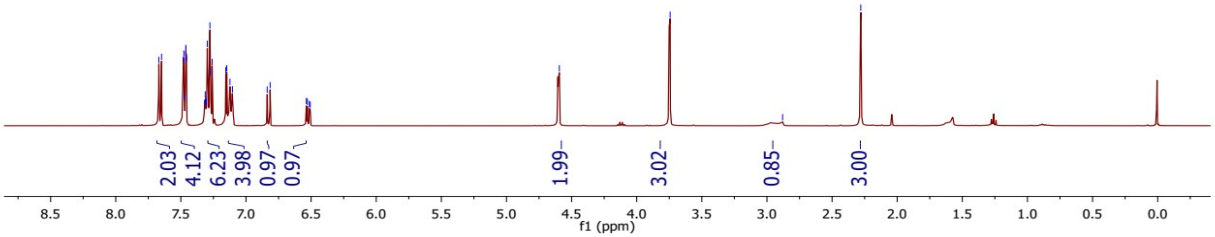




^{1}H NMR (400 MHz) of **111c**:





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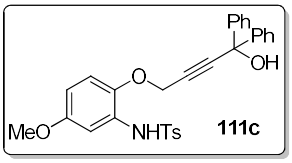
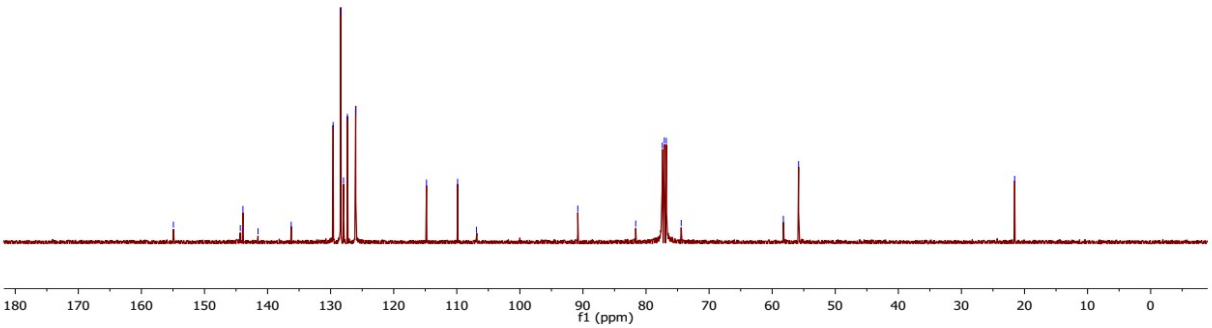
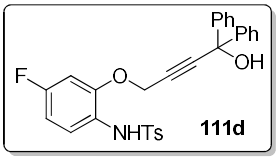
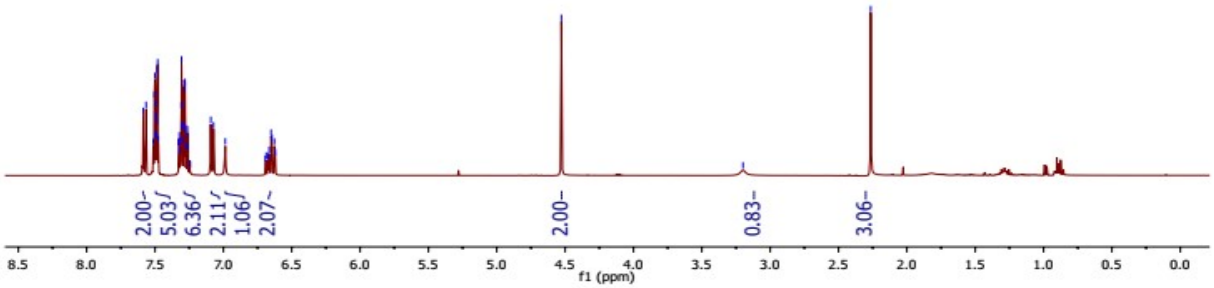


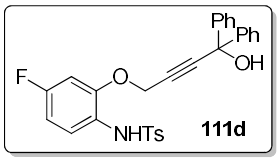


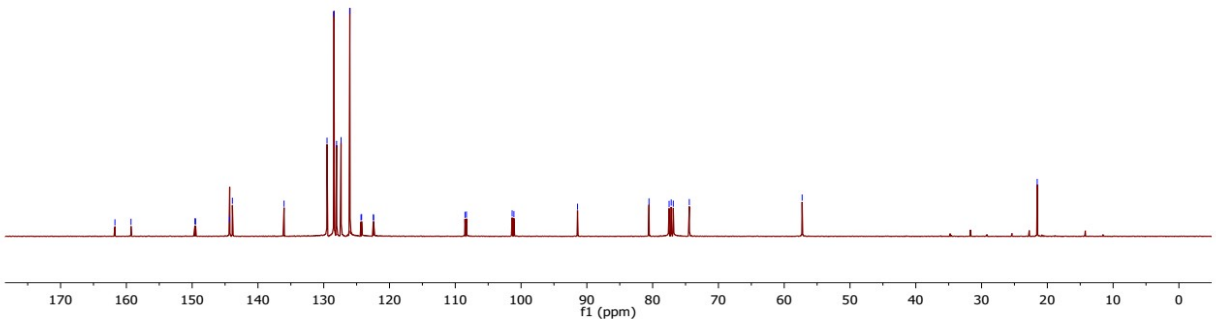
^{1}H NMR (400 MHz) of **111d**:



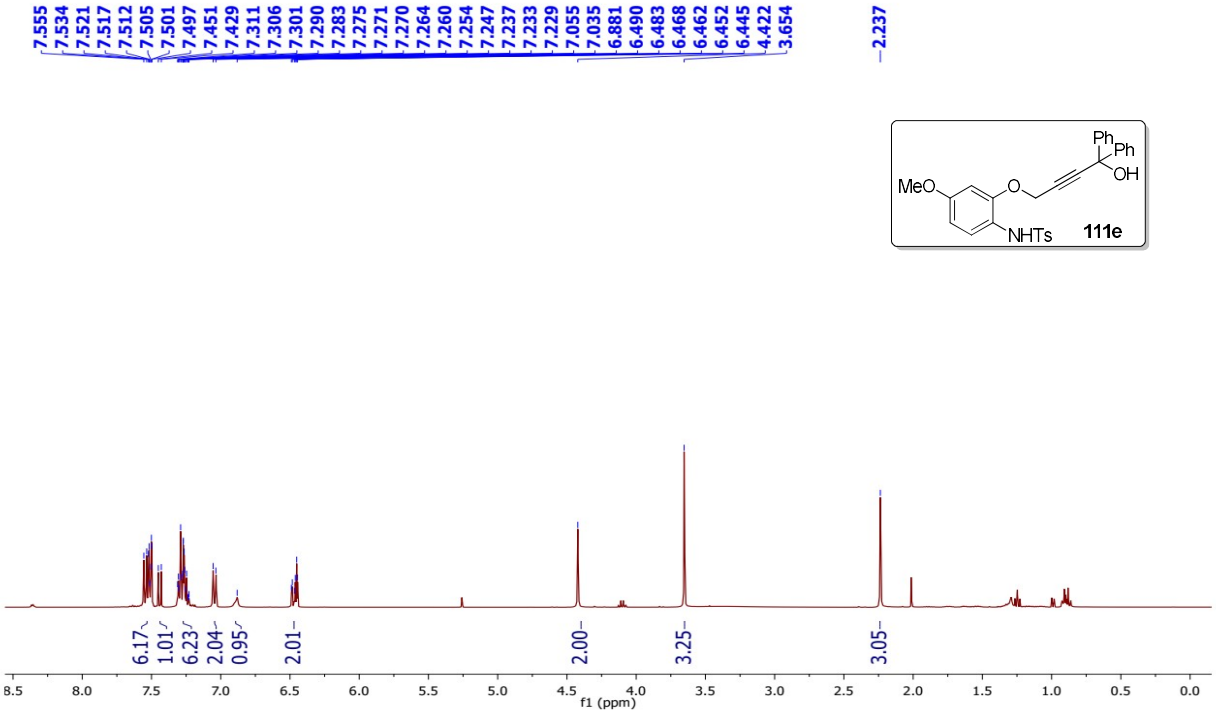


^{13}C{^{1}H} NMR (100 MHz) of **111d** :

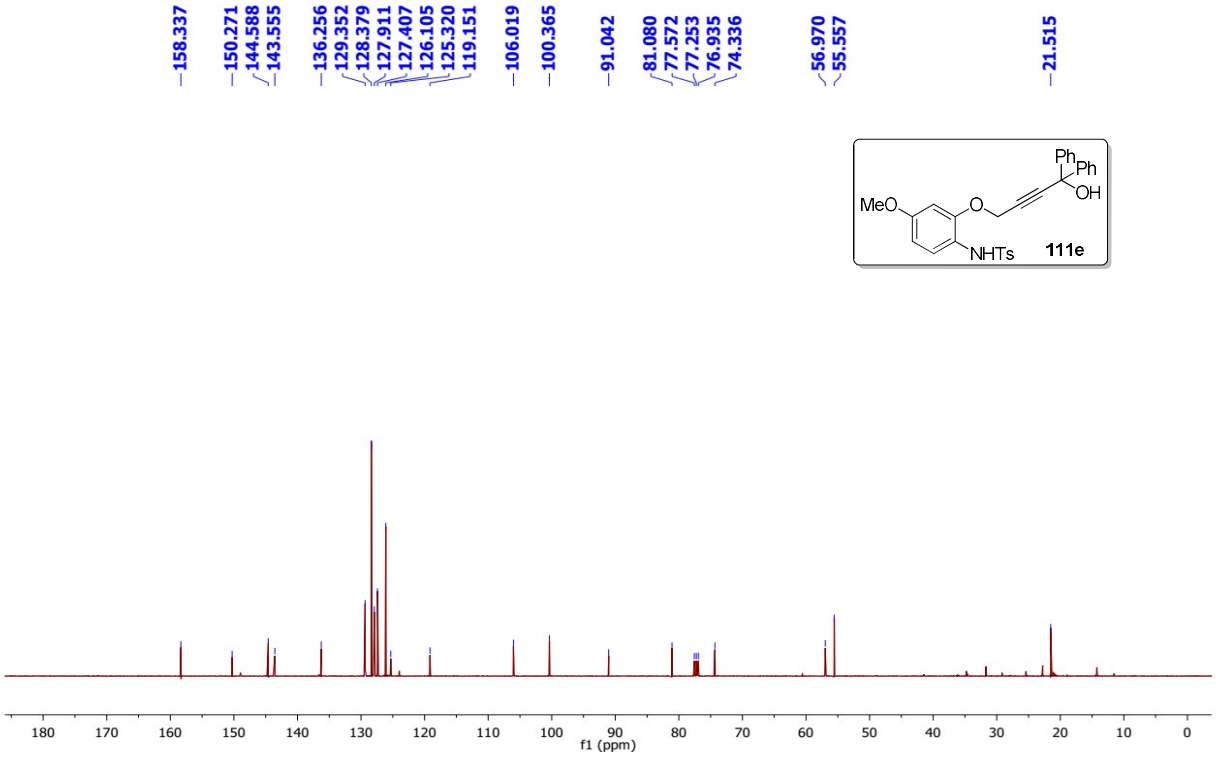




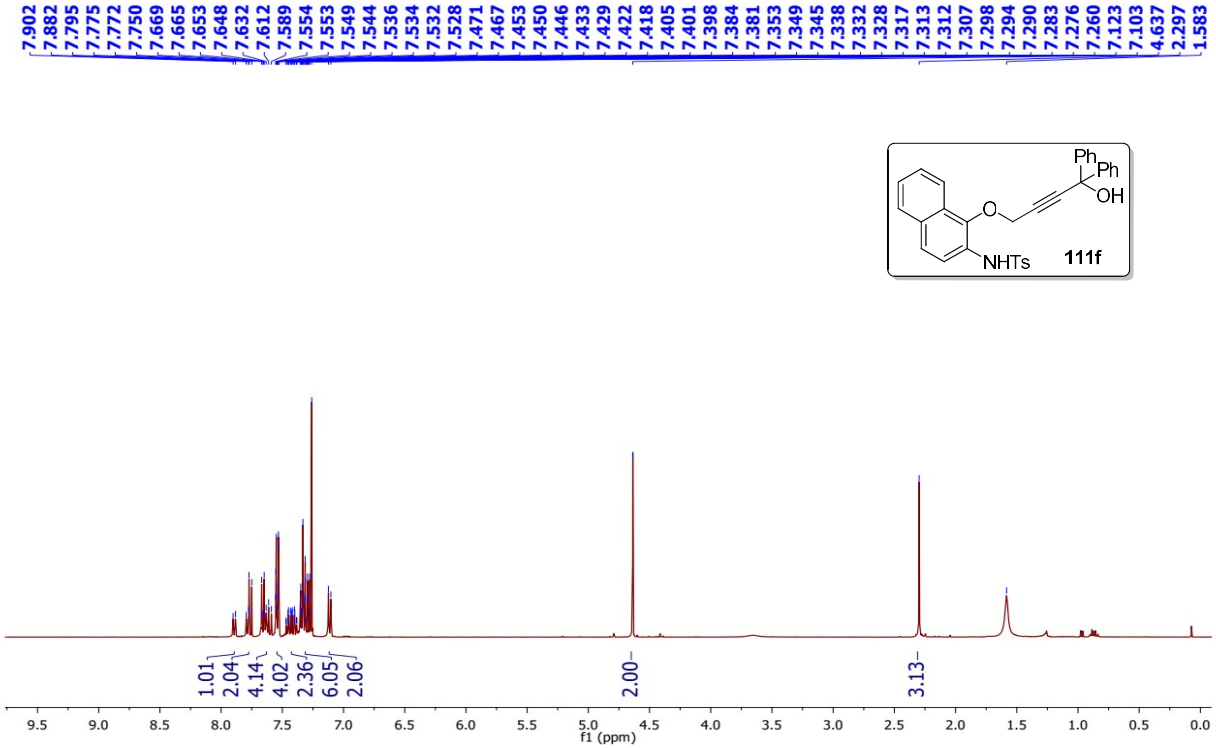
^{1}H NMR (400 MHz) of **111e**:



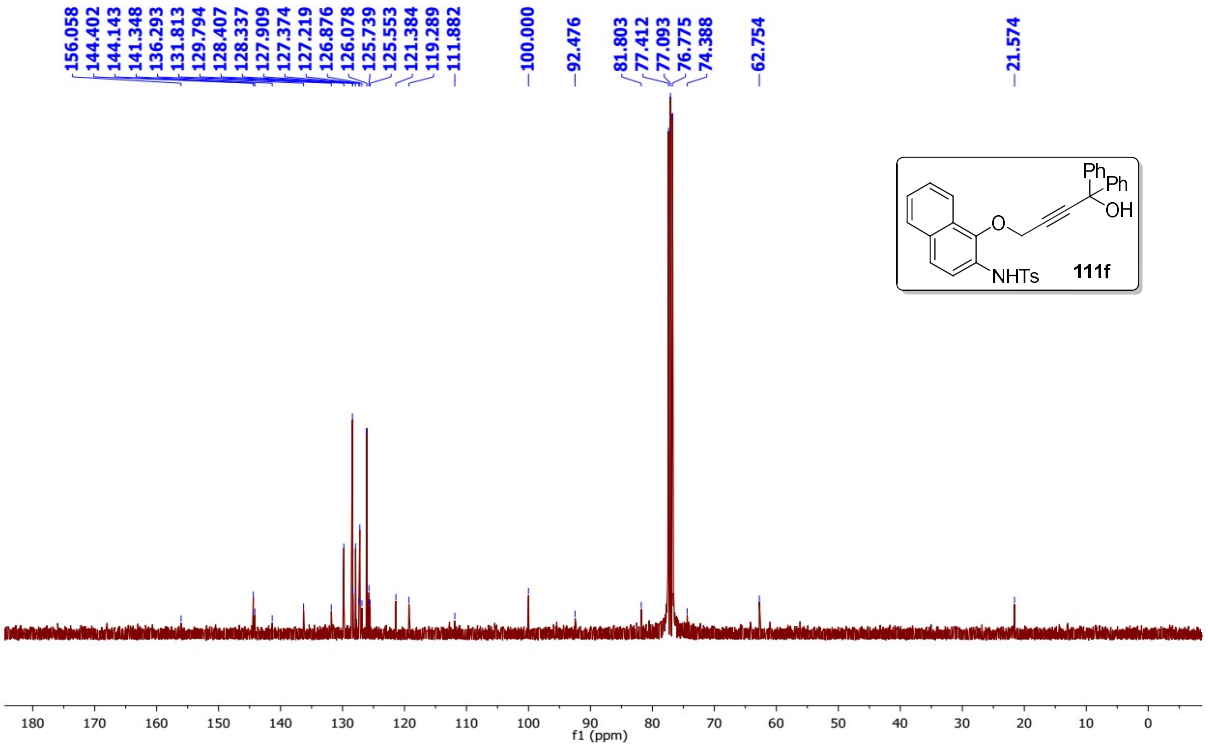
^{13}C{^{1}H} NMR (100 MHz) of **111e** :



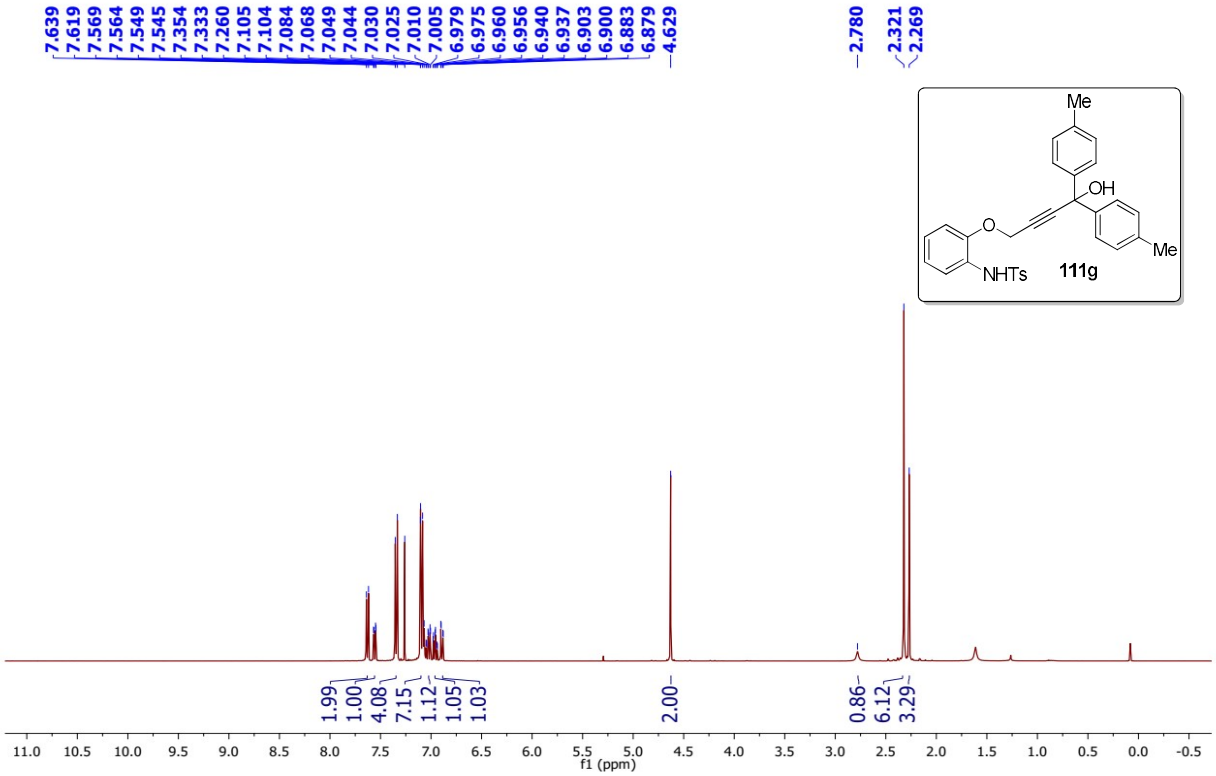
^{1}H NMR (400 MHz) of **111f**:



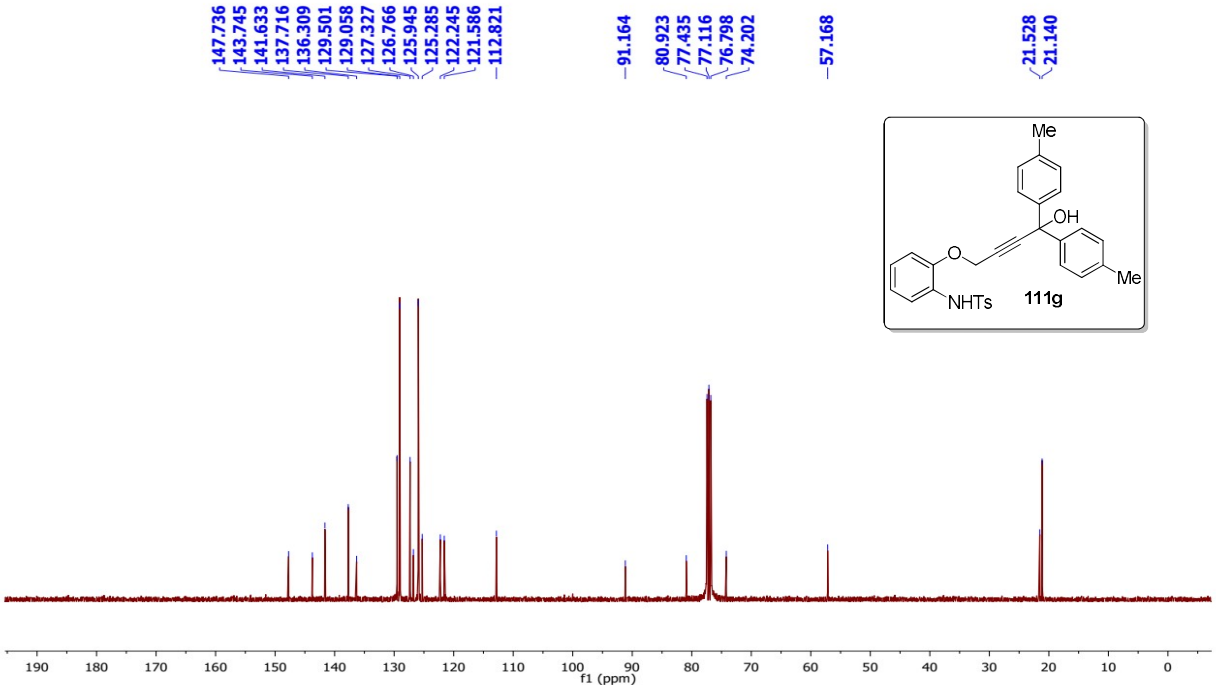
^{13}C{^{1}H} NMR (100 MHz) of **111f** :



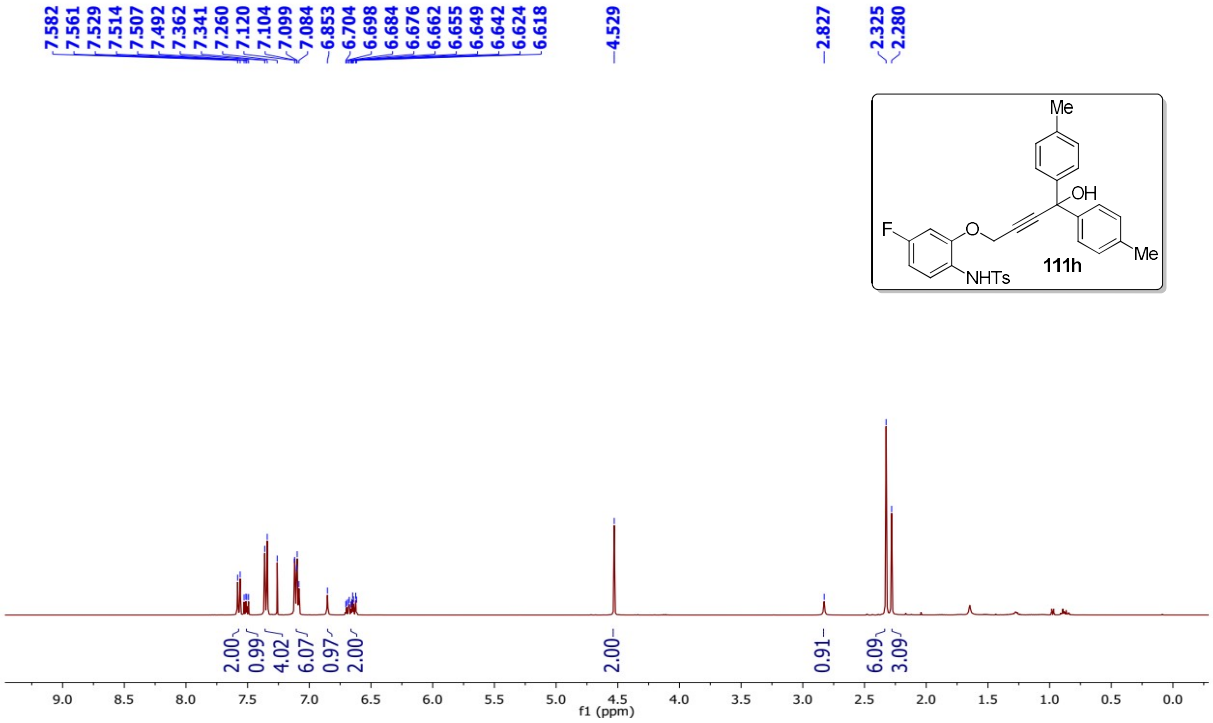
^{1}H NMR (400 MHz) of **111g**:



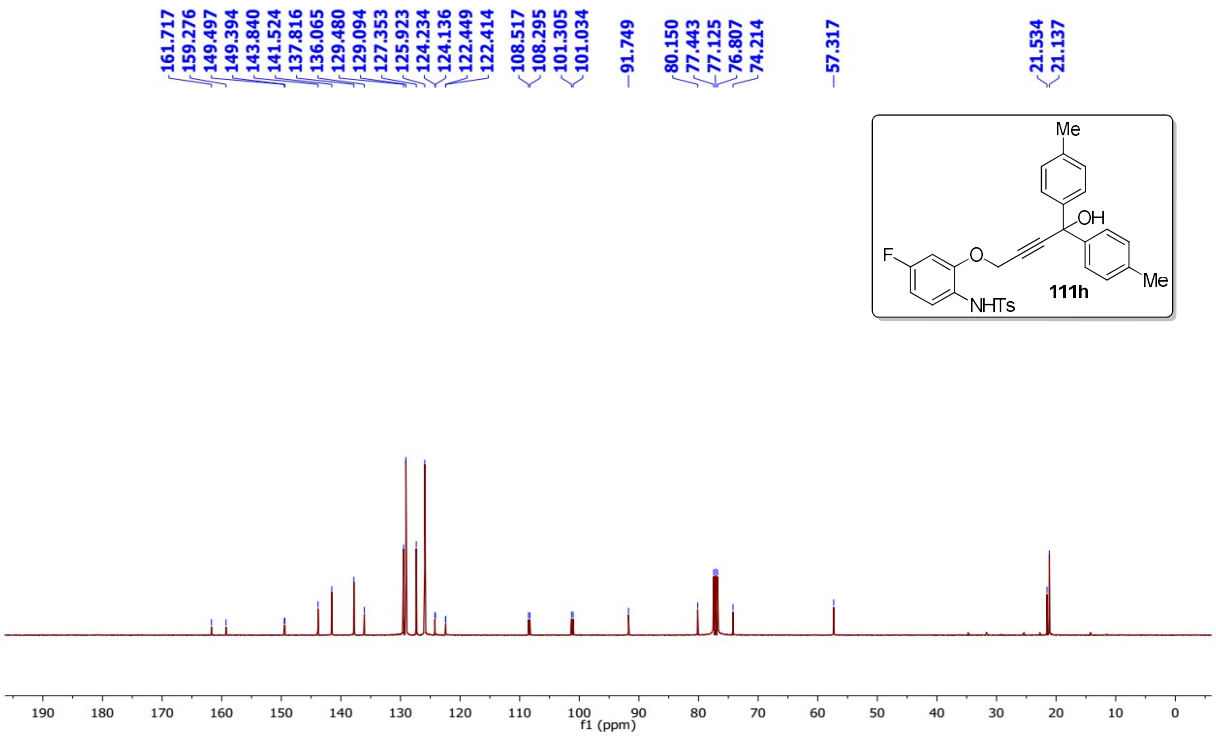
^{13}C{^{1}H} NMR (100 MHz) of **111g** :



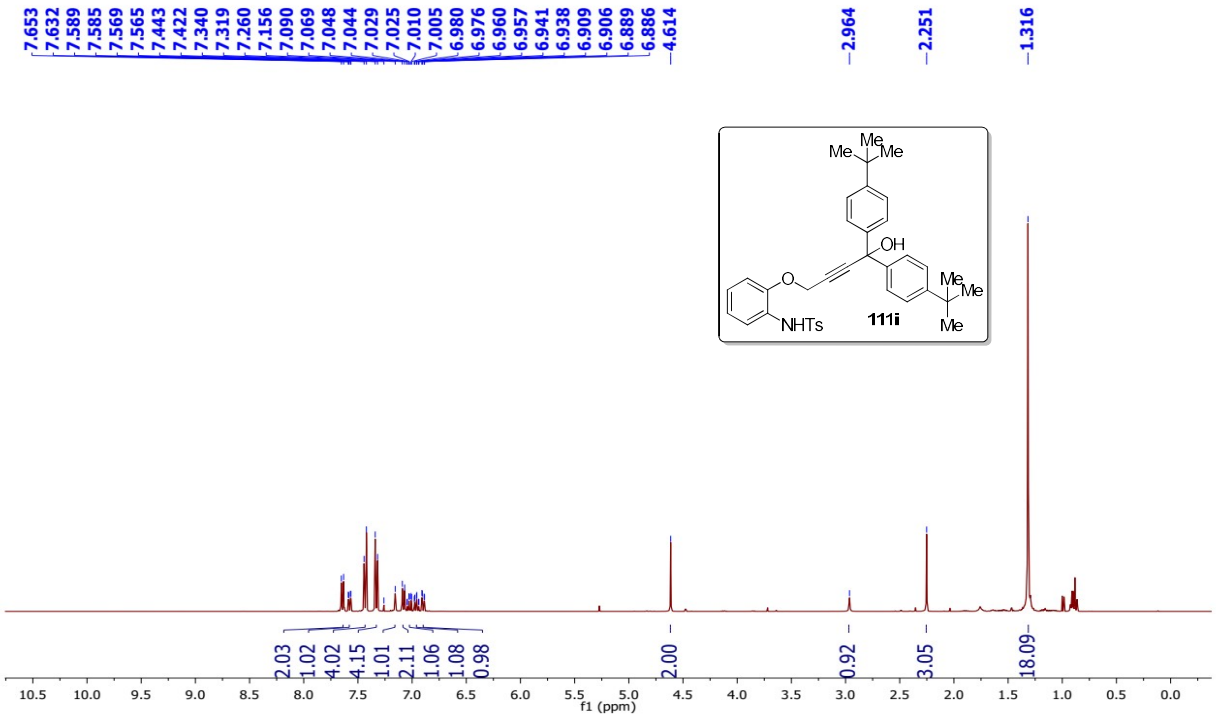
^{1}H NMR (400 MHz) of **111h**:



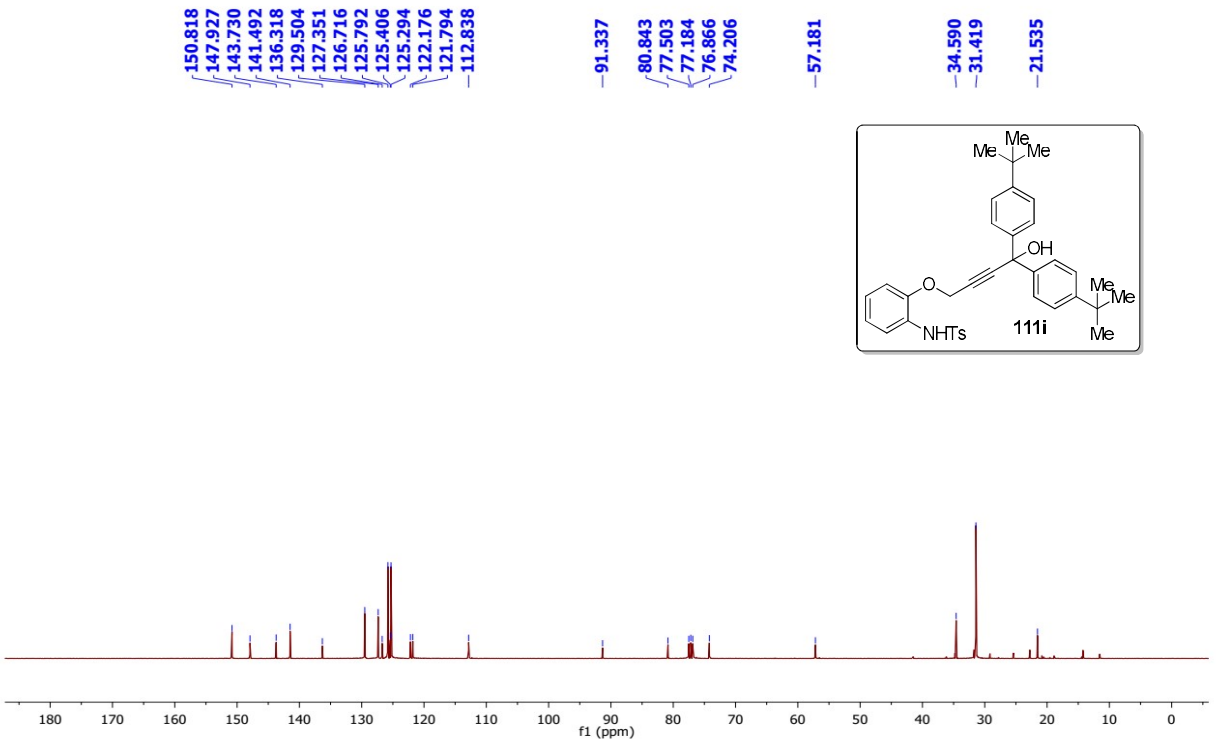
^{13}C{^{1}H} NMR (100 MHz) of **111h** :



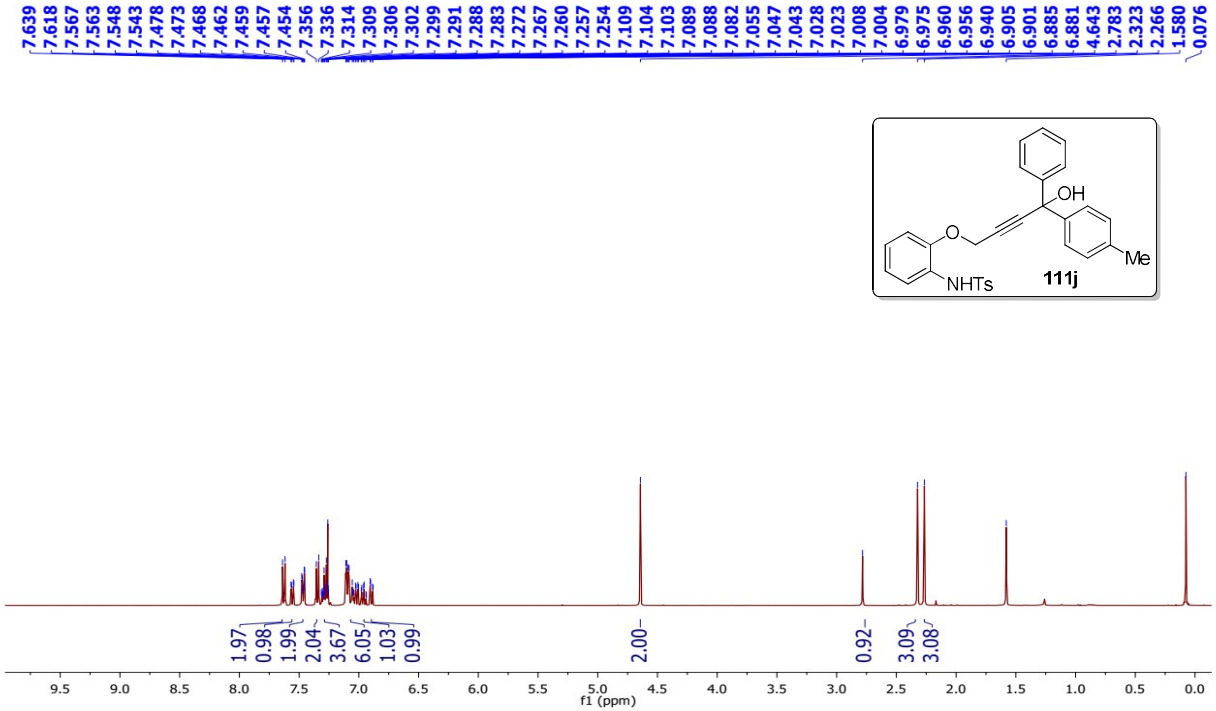
^{1}H NMR (400 MHz) of **111i**:



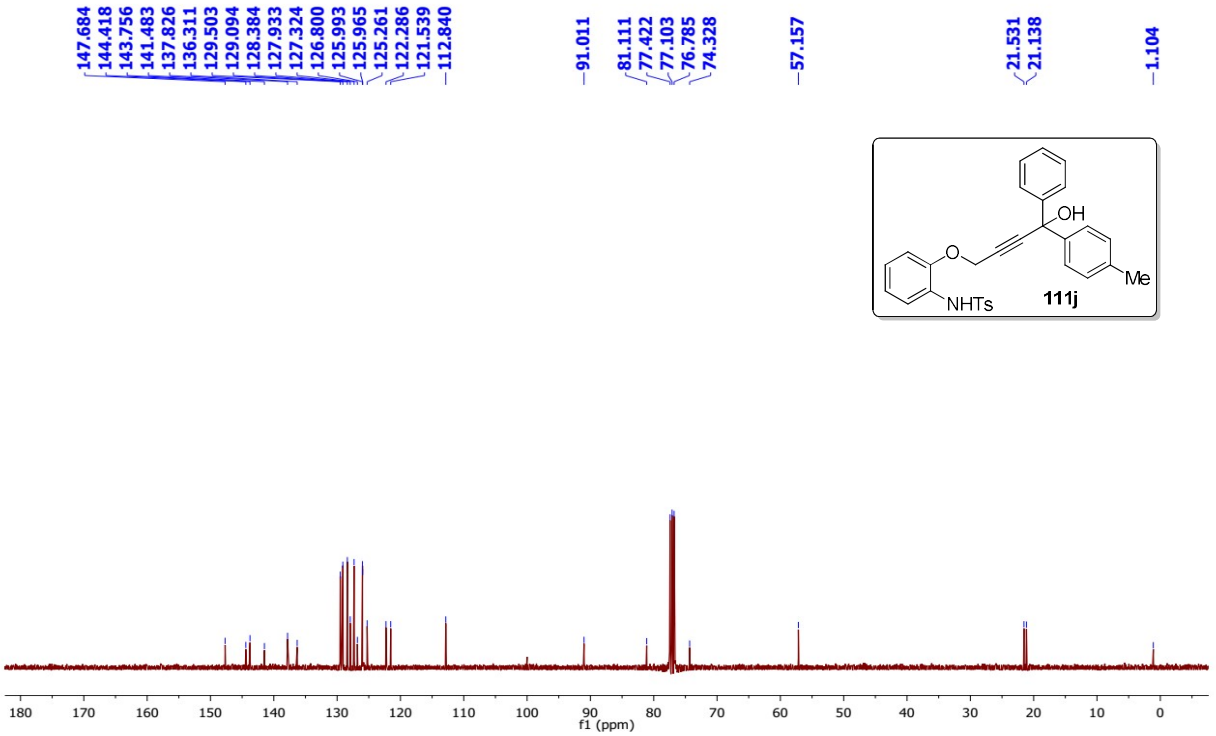
^{13}C{^{1}H} NMR (100 MHz) of **111i** :



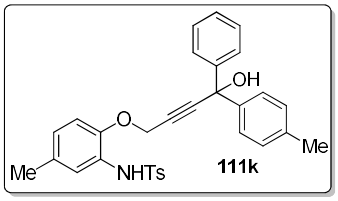
^{1}H NMR (400 MHz) of **111j**:

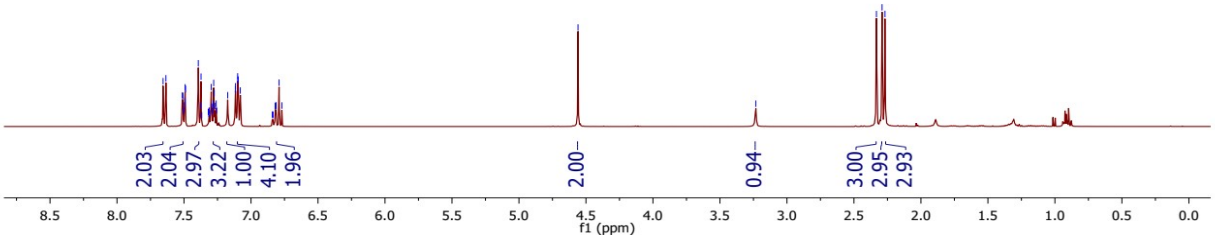


^{13}C{^{1}H} NMR (100 MHz) of **111j** :

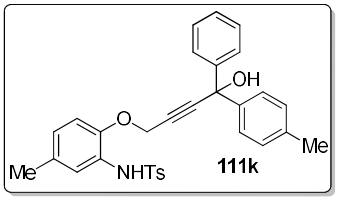


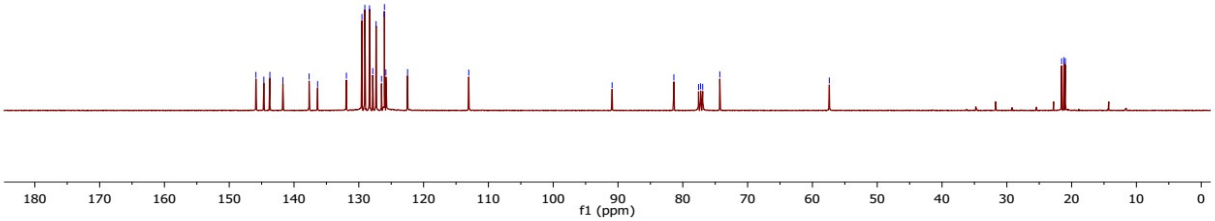
^{1}H NMR (400 MHz) of **111k**:





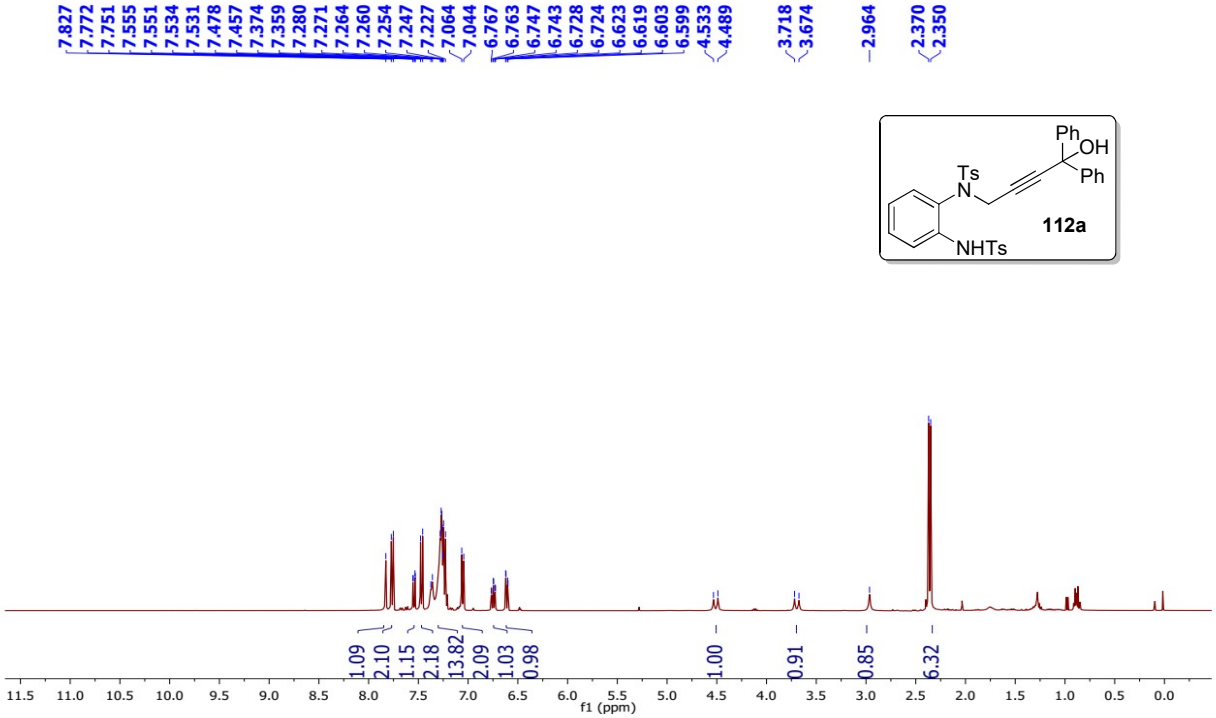
^{13}C{^{1}H} NMR (100 MHz) of **111k** :



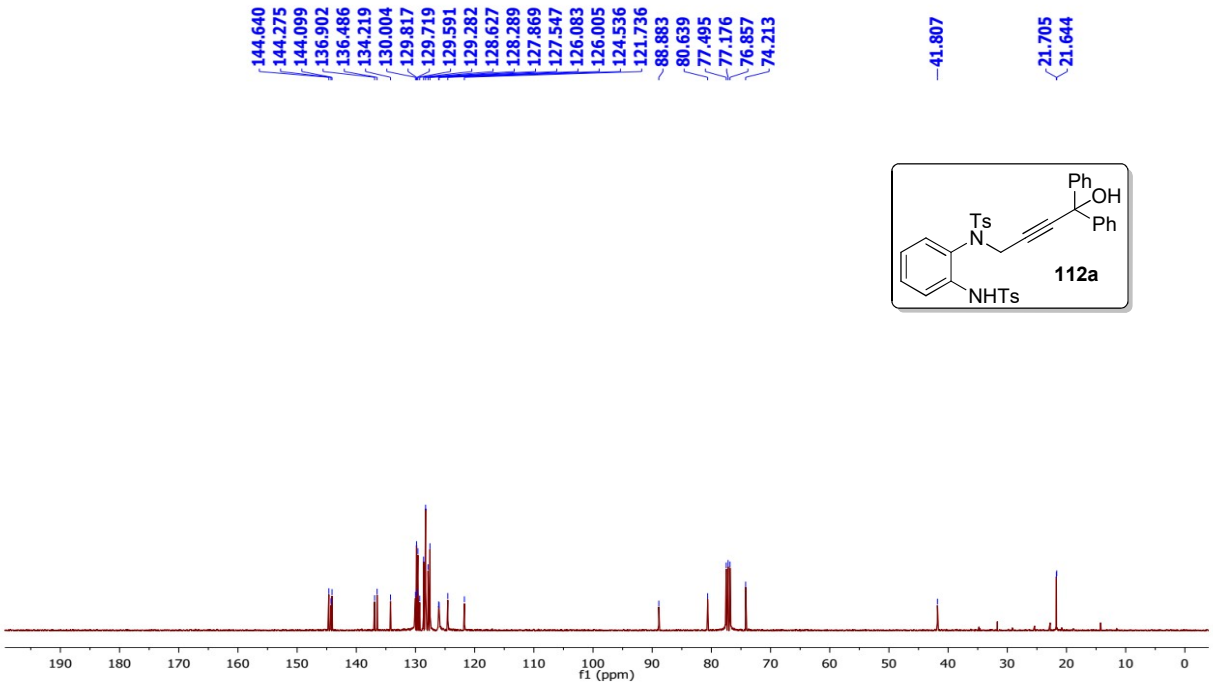


2.2.9.2. NMR Spectra of Compounds 112a-l:

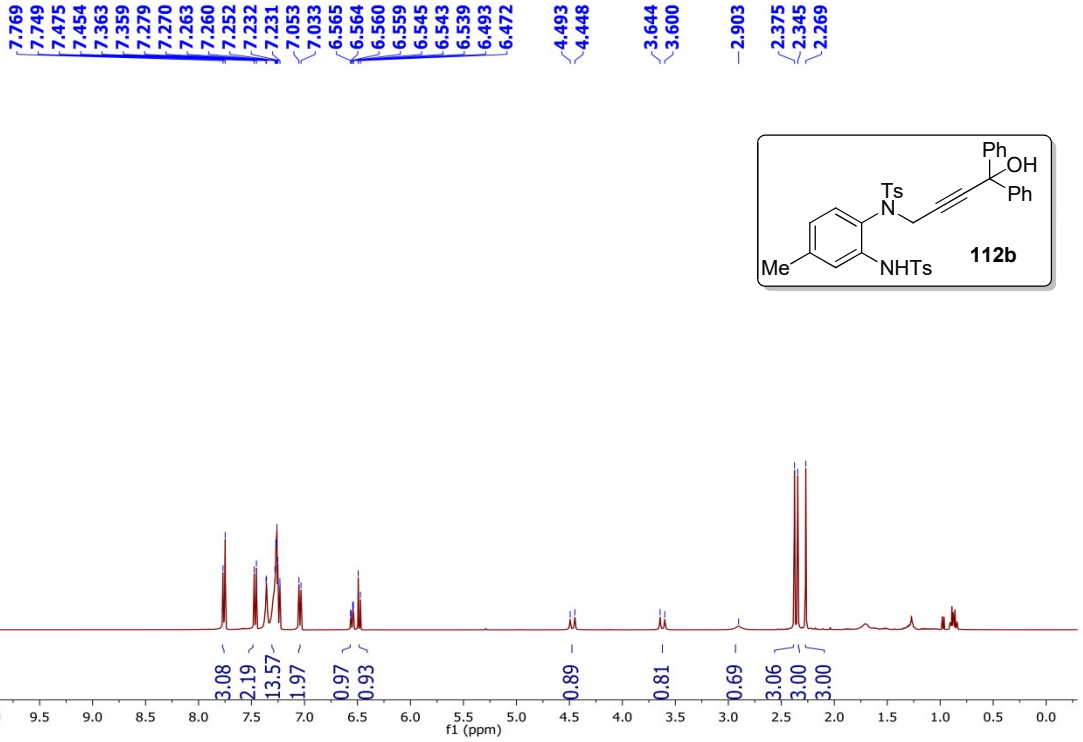
^{1}H NMR (400 MHz) of **112a**:



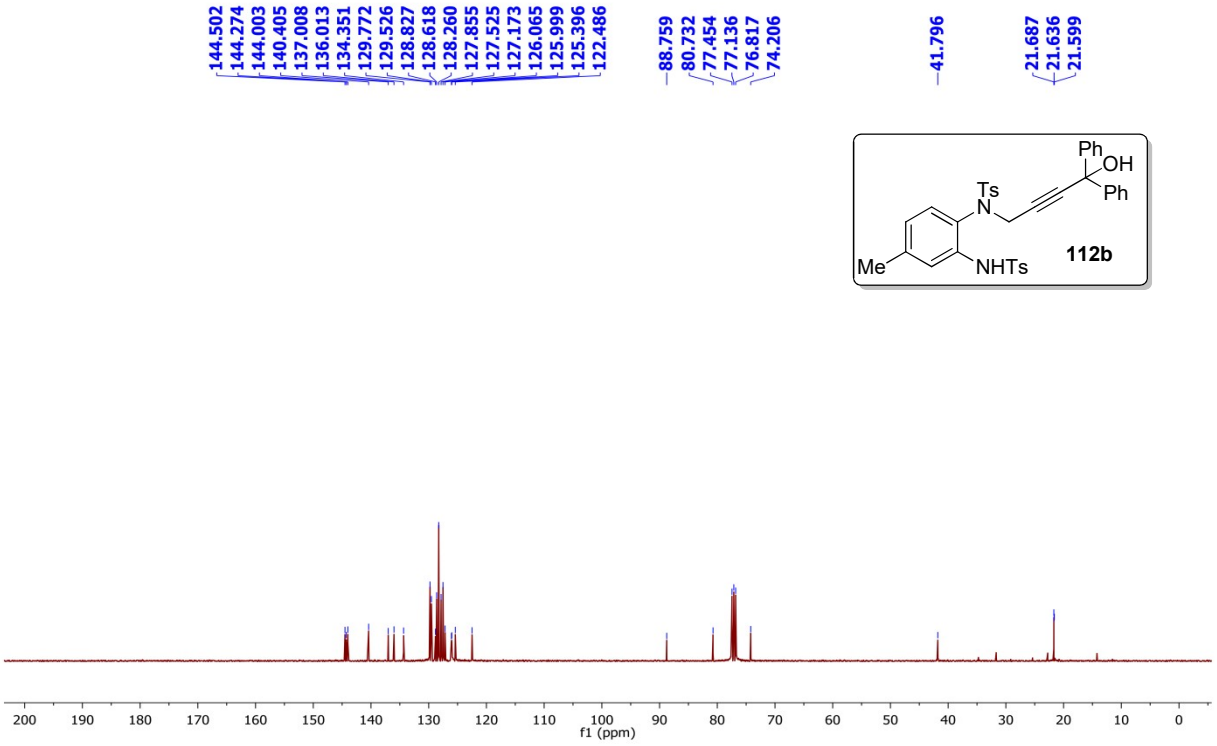
^{13}C{^{1}H} NMR (100 MHz) of **112a** :



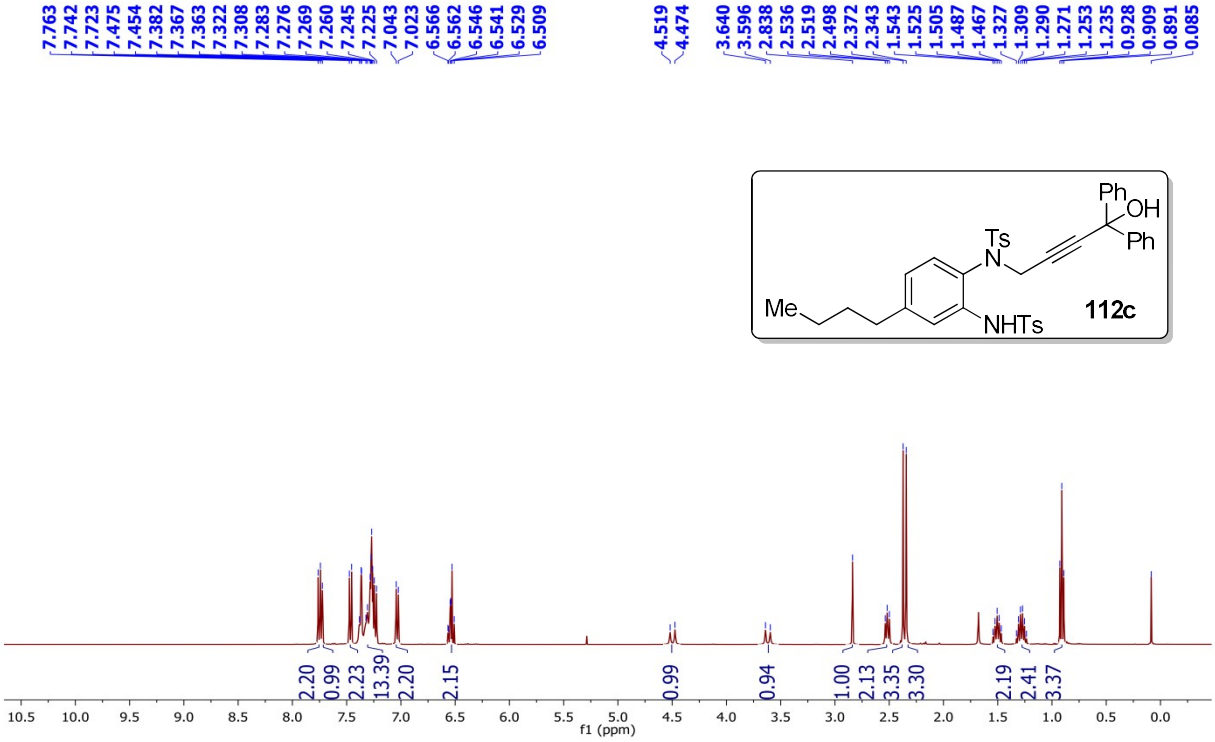
^{1}H NMR (400 MHz) of **112b**:



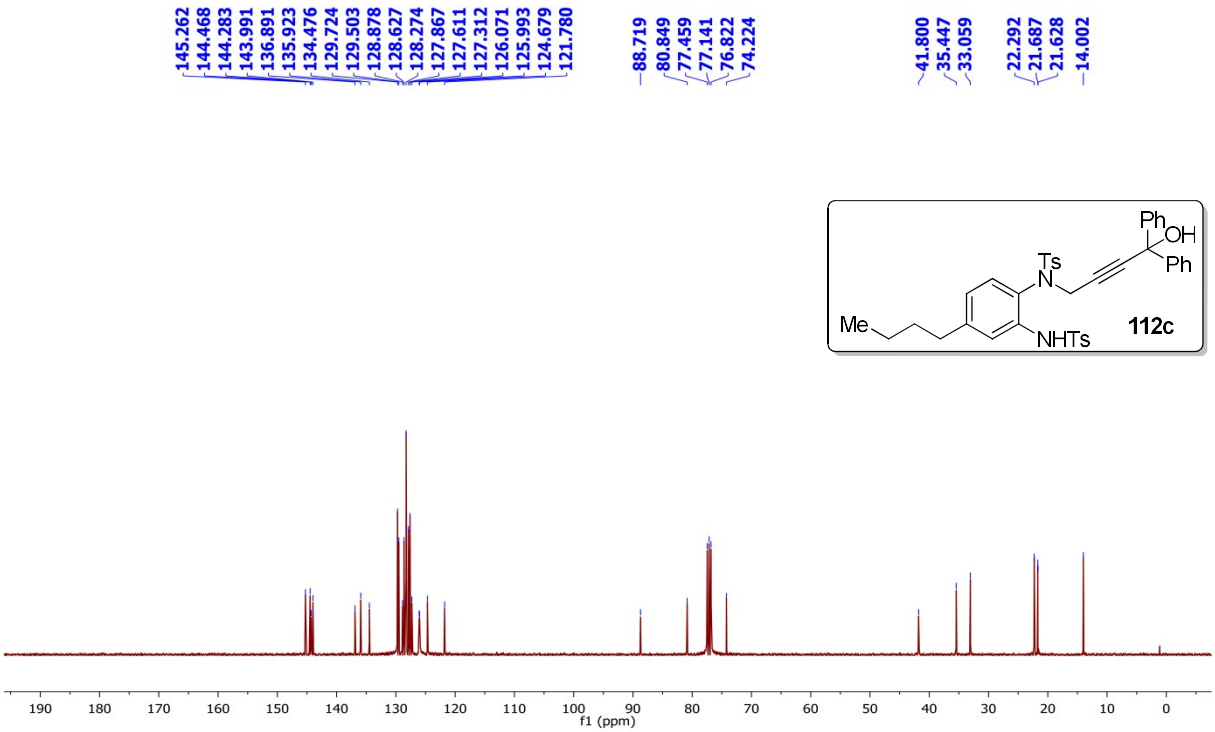
^{13}C{^{1}H} NMR (100 MHz) of **112b** :



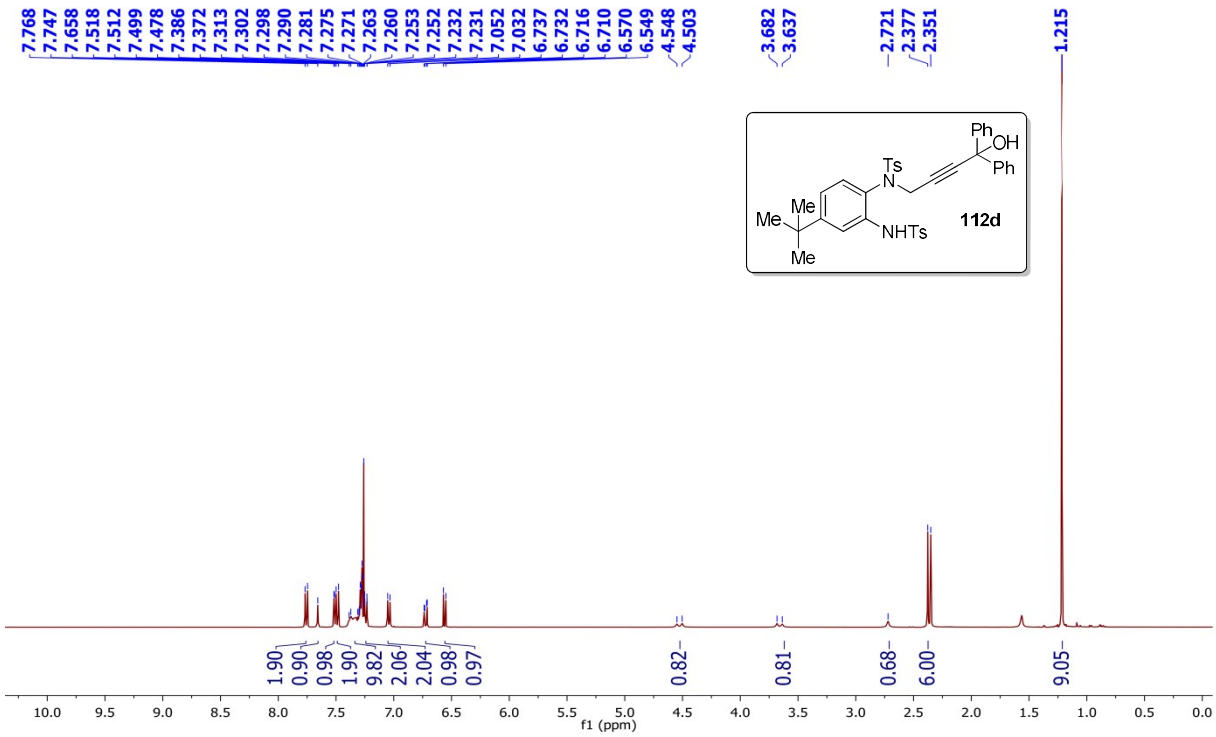
^{1}H NMR (400 MHz) of **112c**:



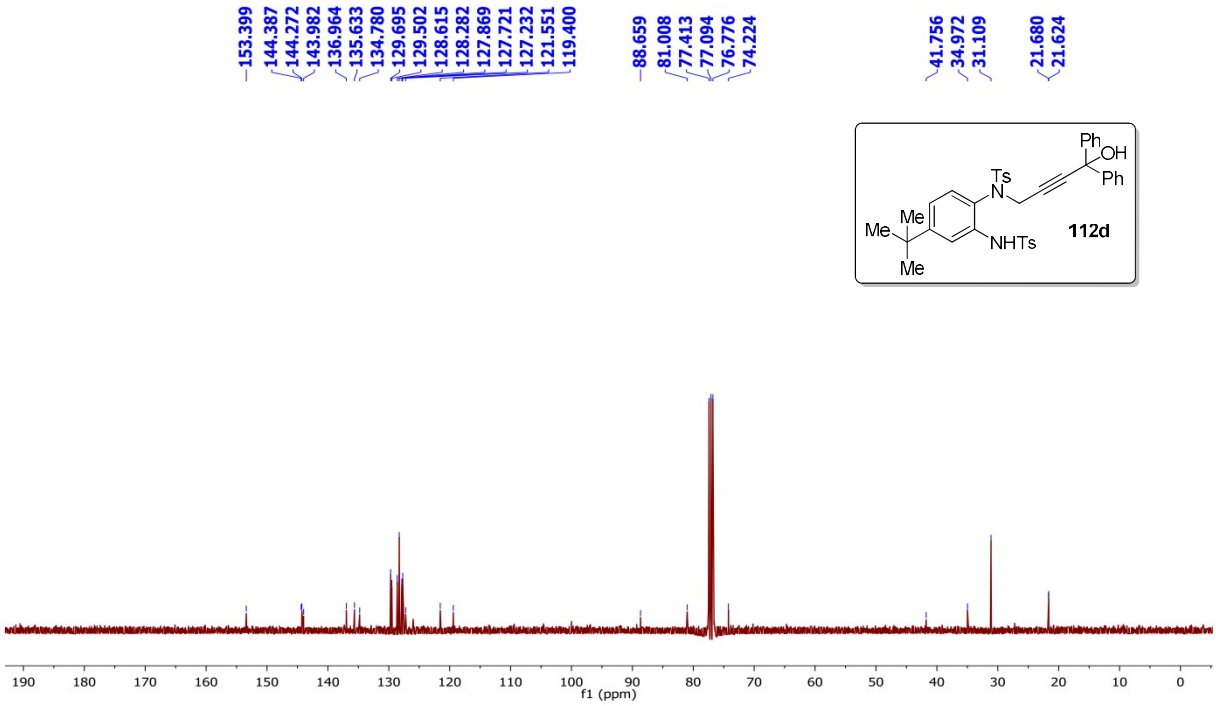
^{13}C{^{1}H} NMR (100 MHz) of **112c**:



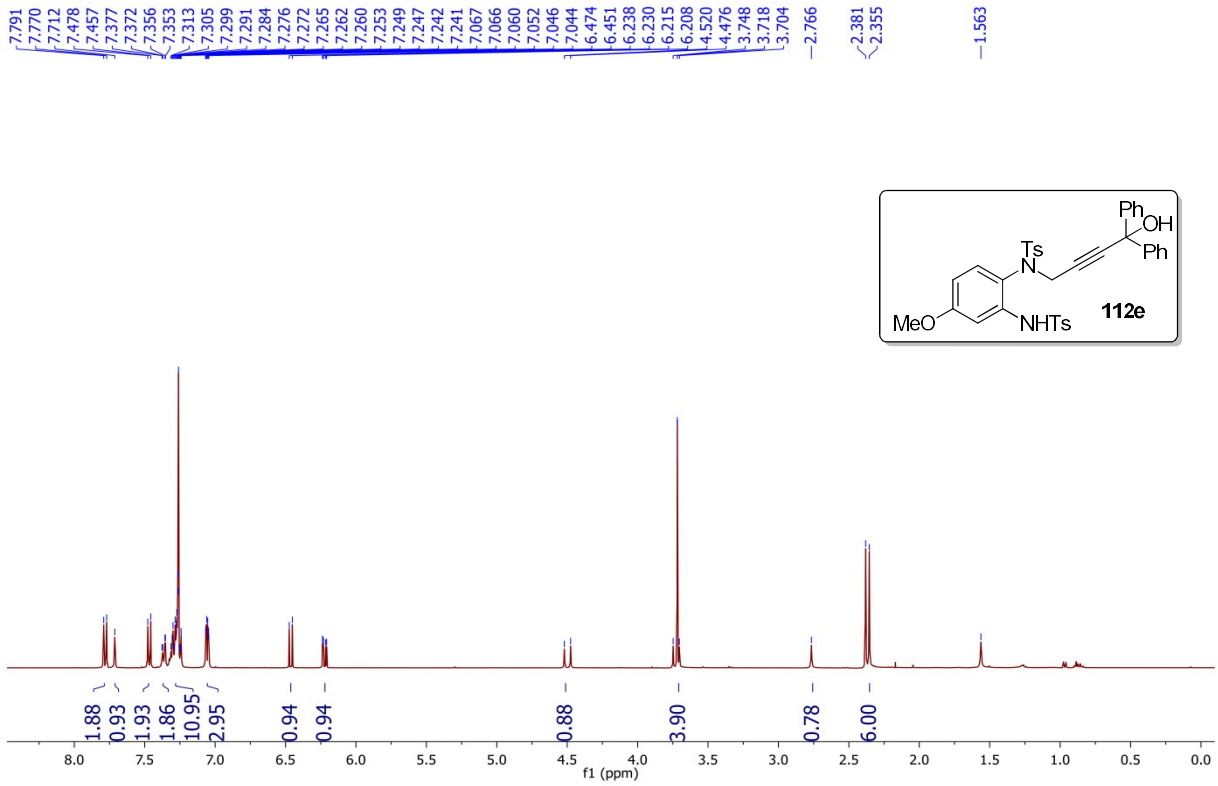
^{1}H NMR (400 MHz) of **112d**:



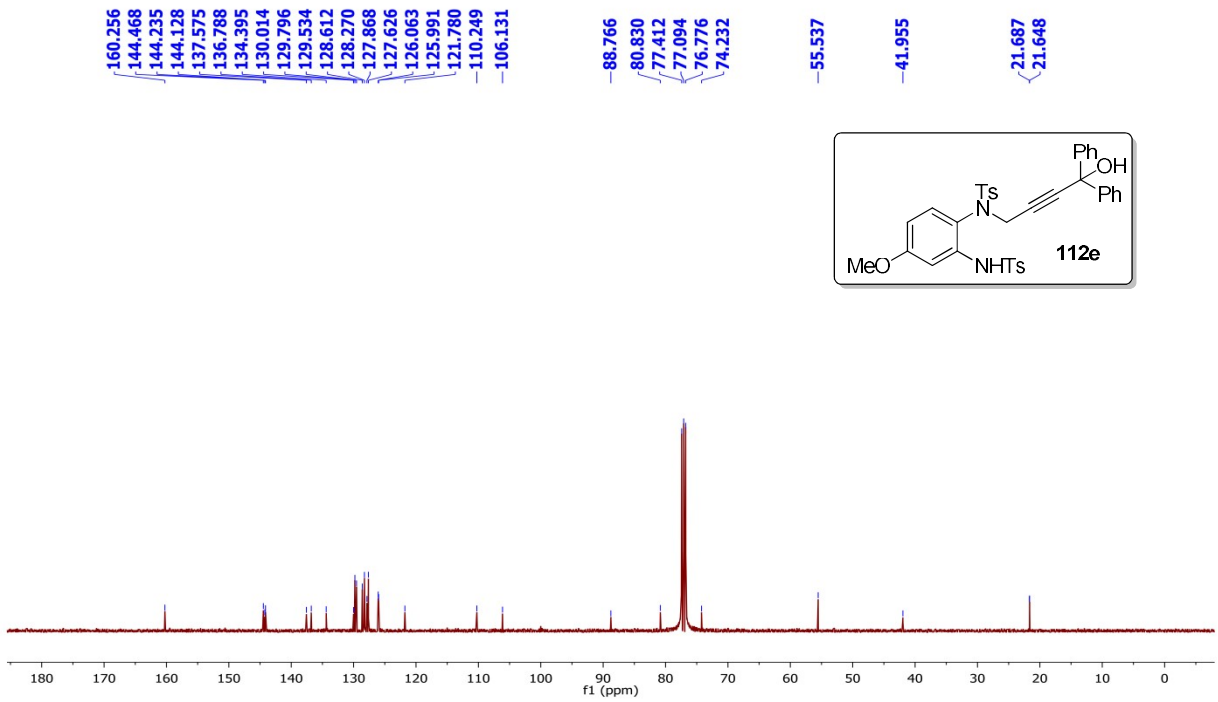
^{13}C{^{1}H} NMR (100 MHz) of **112d**:



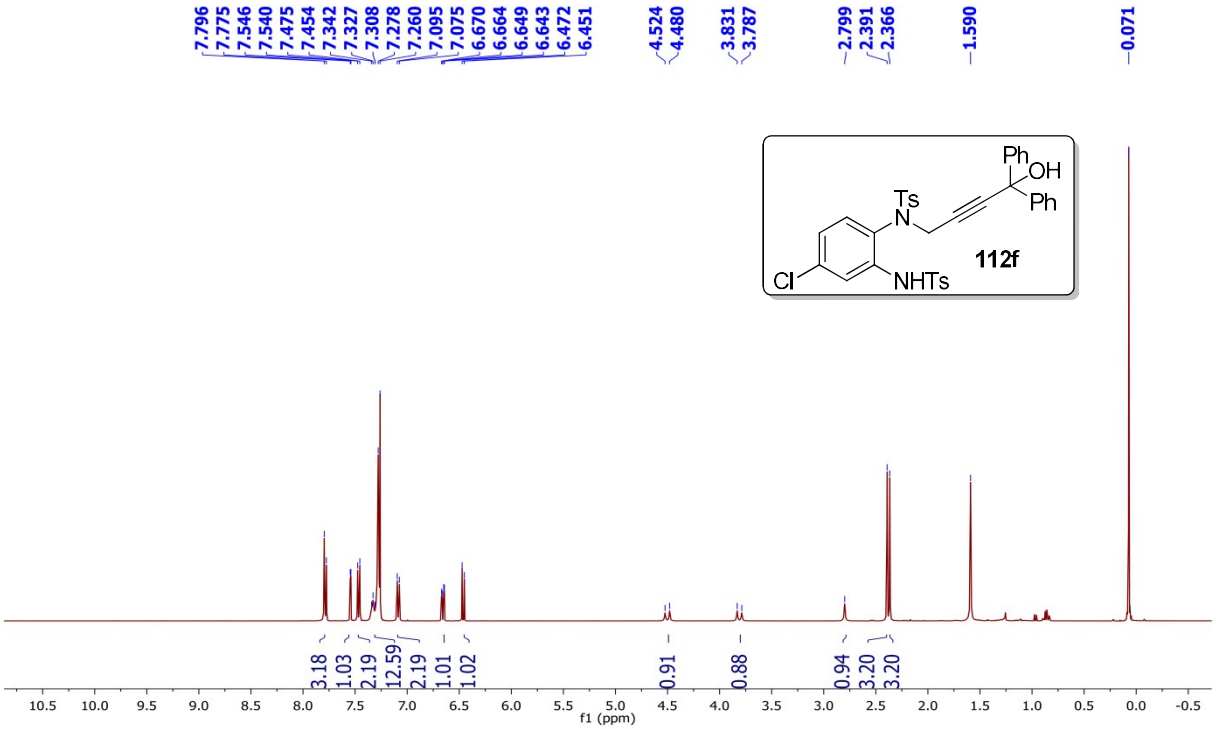
^{1}H NMR (400 MHz) of **112e**:



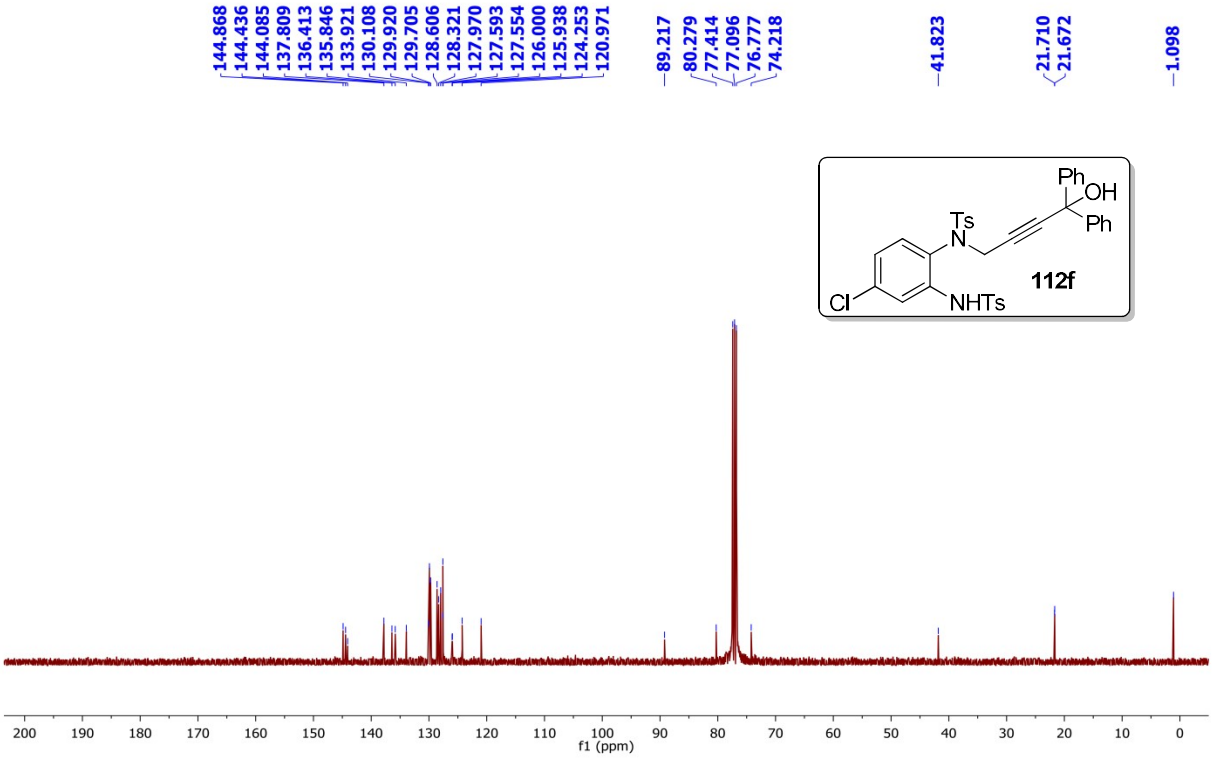
^{13}C{^{1}H} NMR (100 MHz) of **112e**:



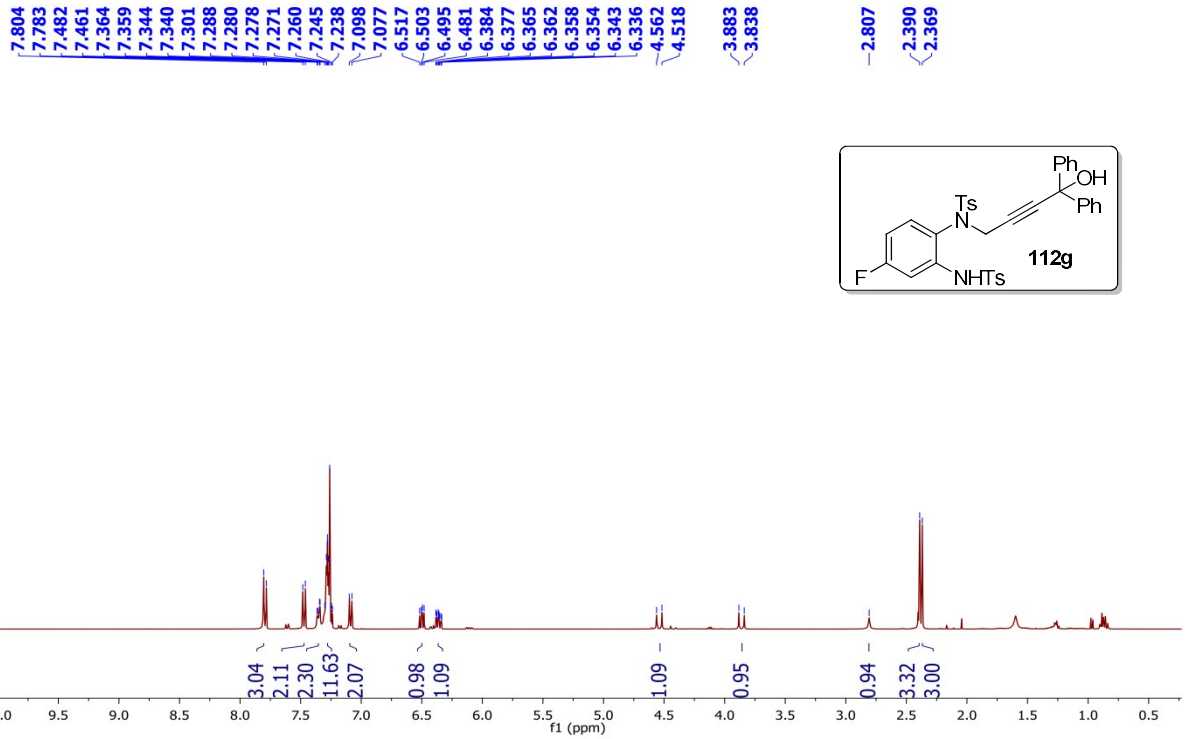
^{1}H NMR (400 MHz) of **112f**:



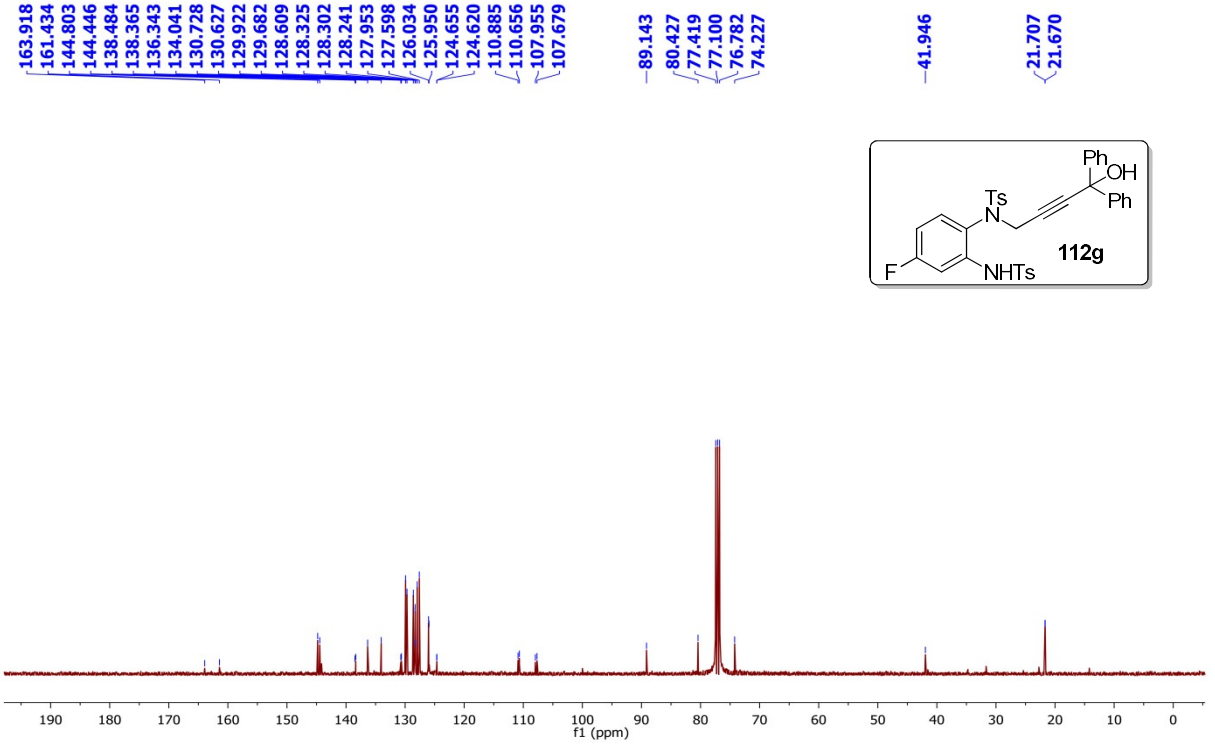
^{13}C{^{1}H} NMR (100 MHz) of **112f** :



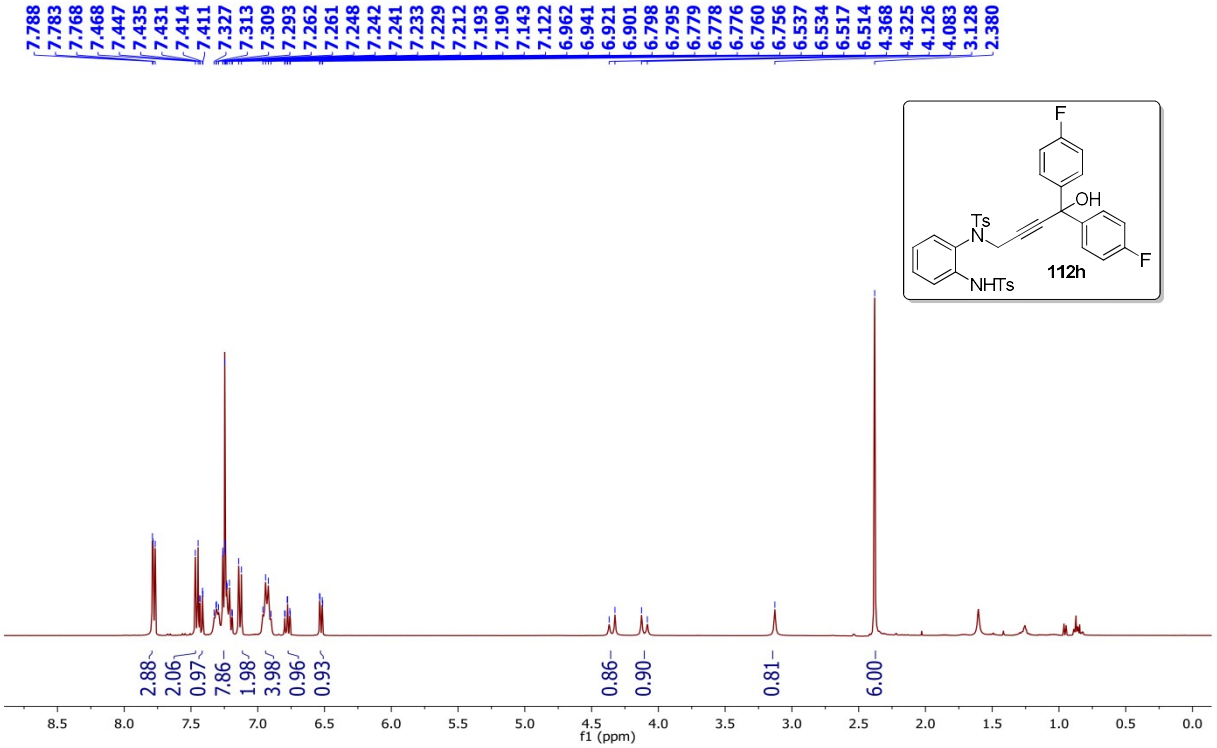
^{1}H NMR (400 MHz) of **112g**:



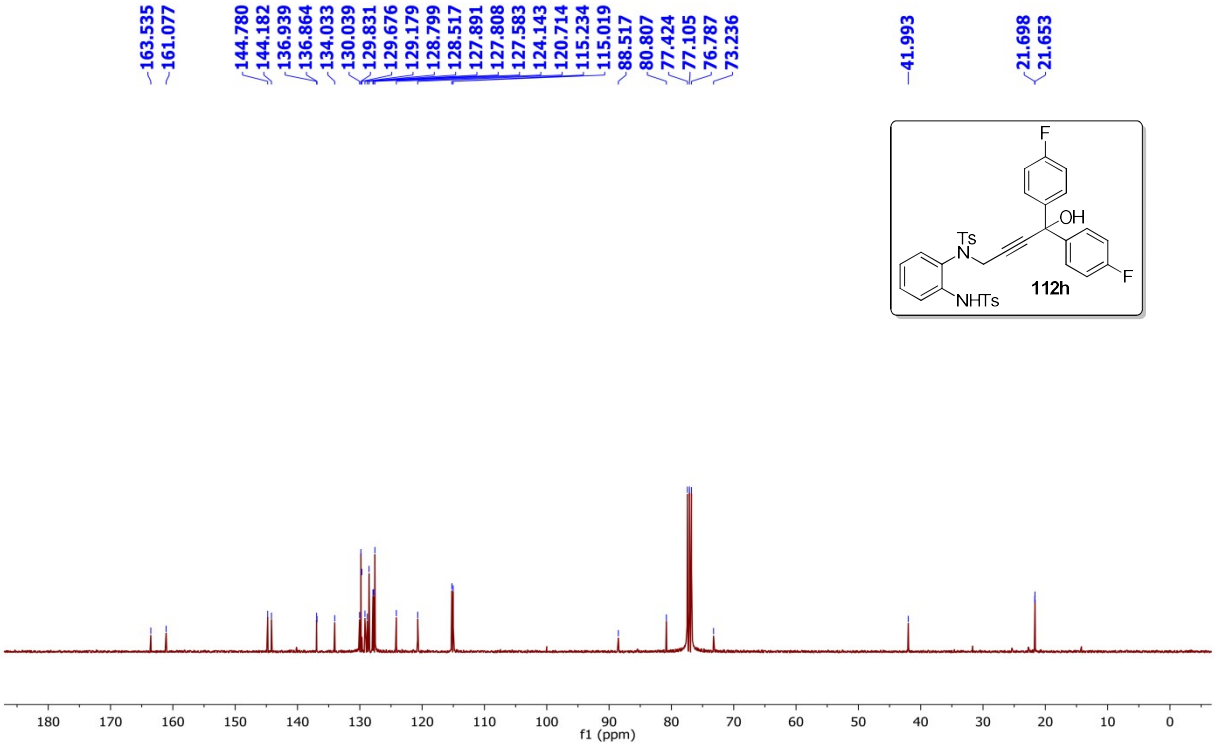
^{13}C{^{1}H} NMR (100 MHz) of **112g**:



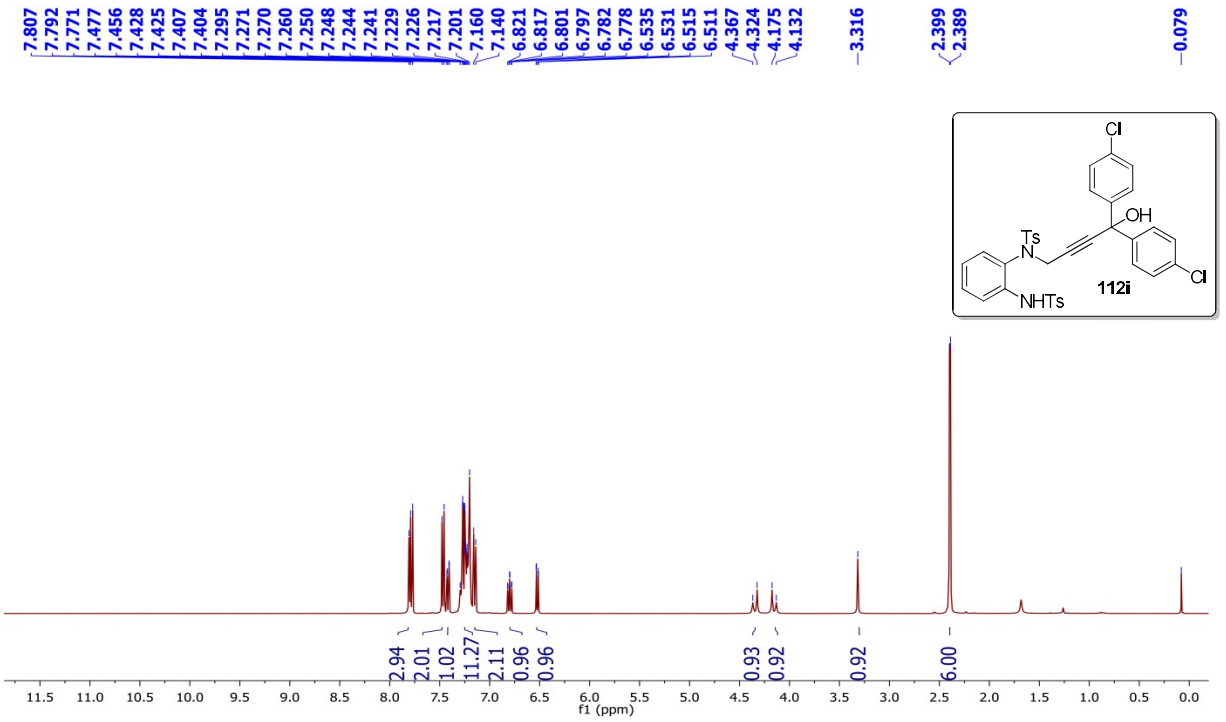
^{1}H NMR (400 MHz) of **112h**:



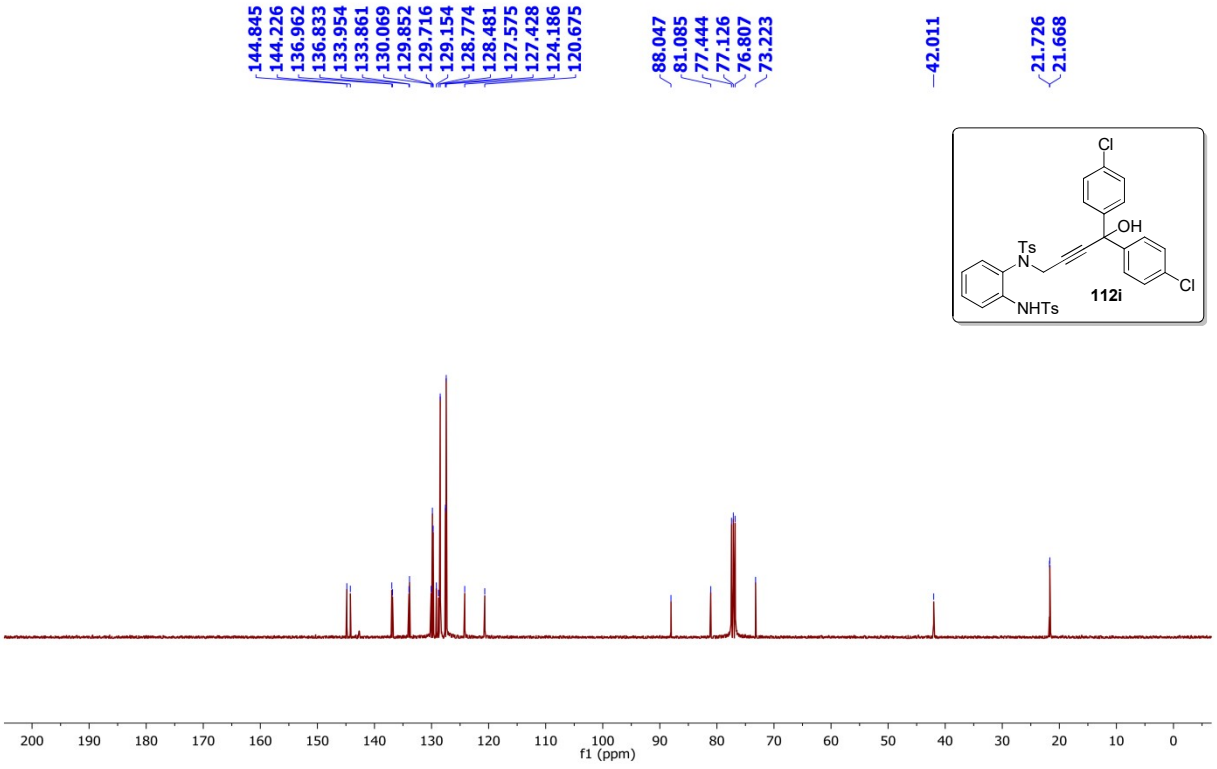
^{13}C{^{1}H} NMR (100 MHz) of **112h**:



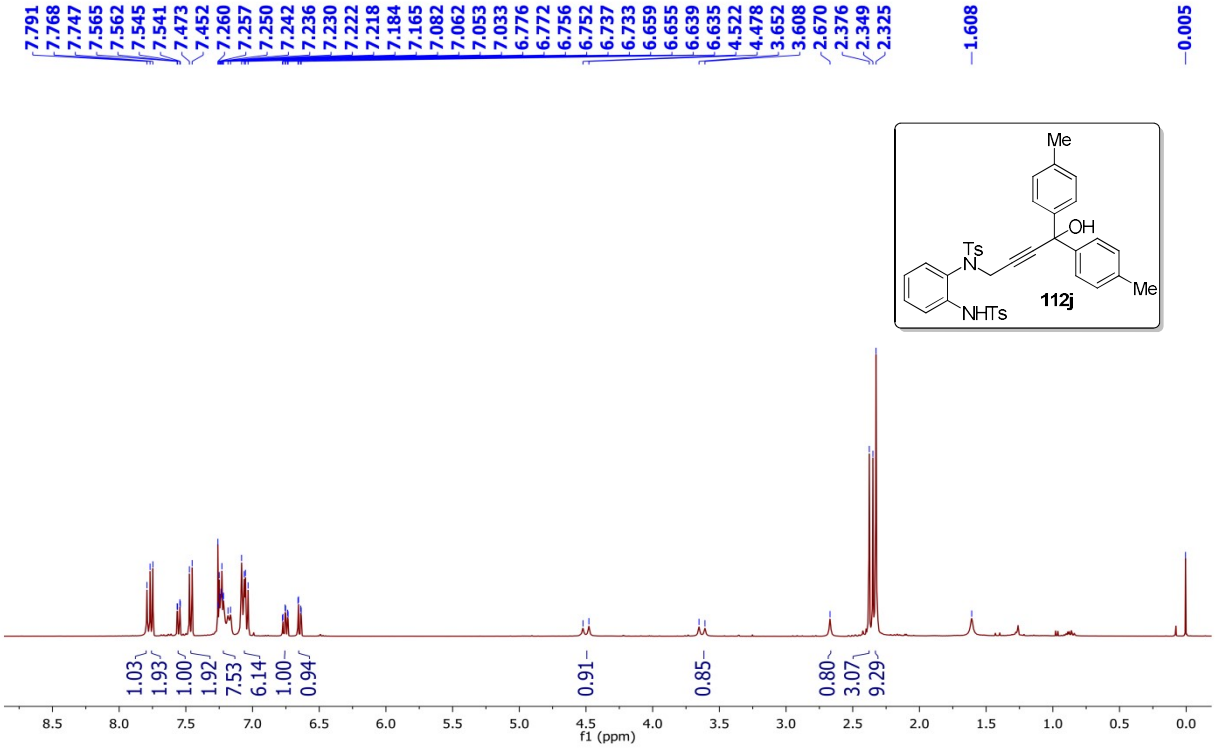
^{1}H NMR (400 MHz) of **112i**:



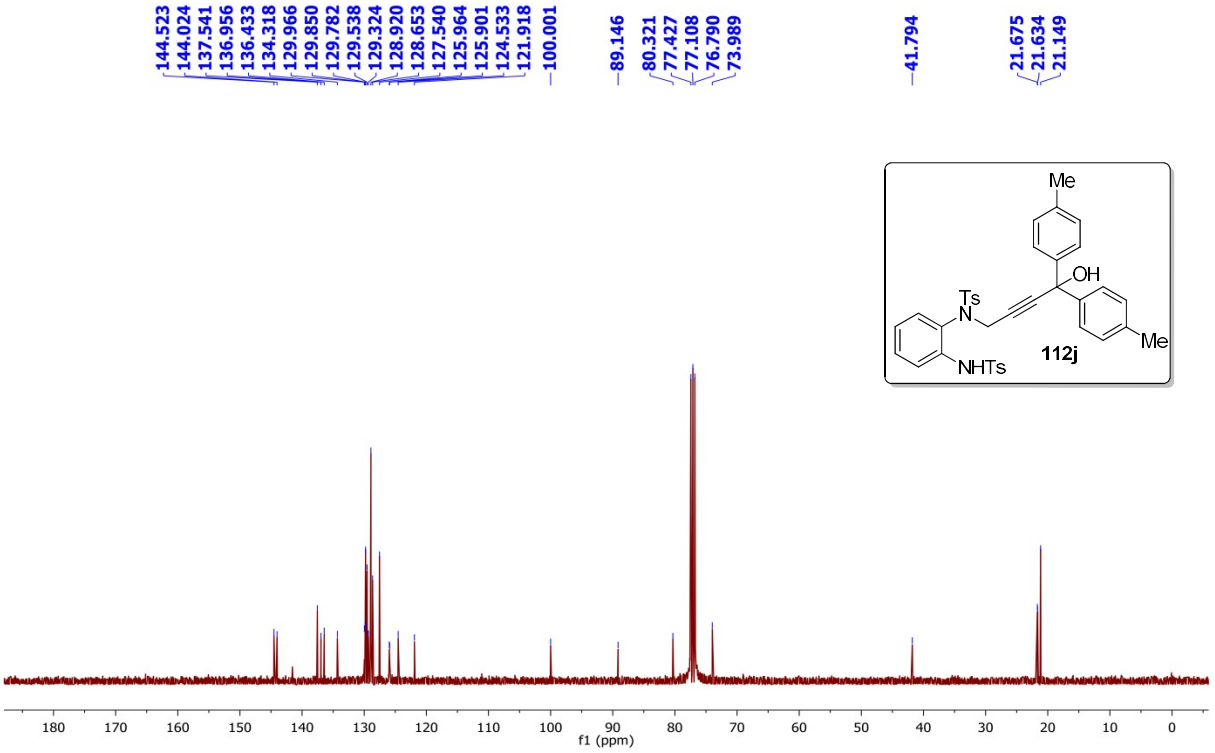
^{13}C{^{1}H} NMR (100 MHz) of **112i:**



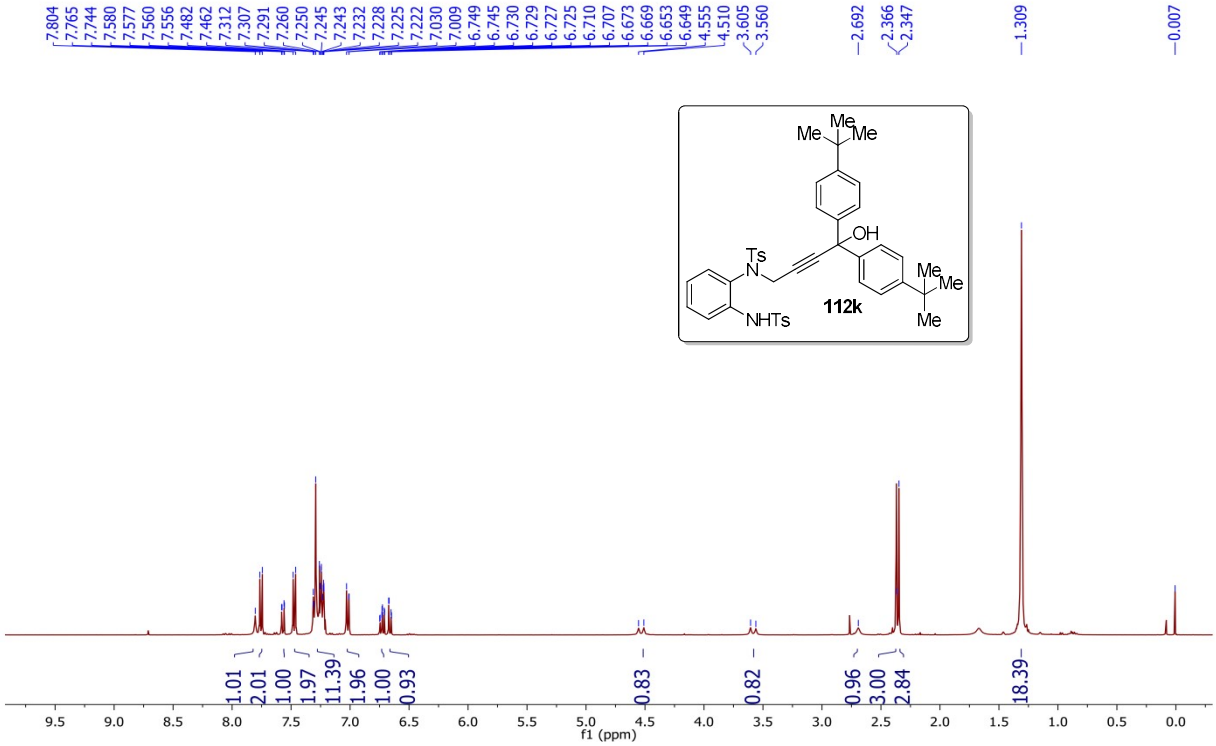
^{1}H NMR (400 MHz) of **112j**:



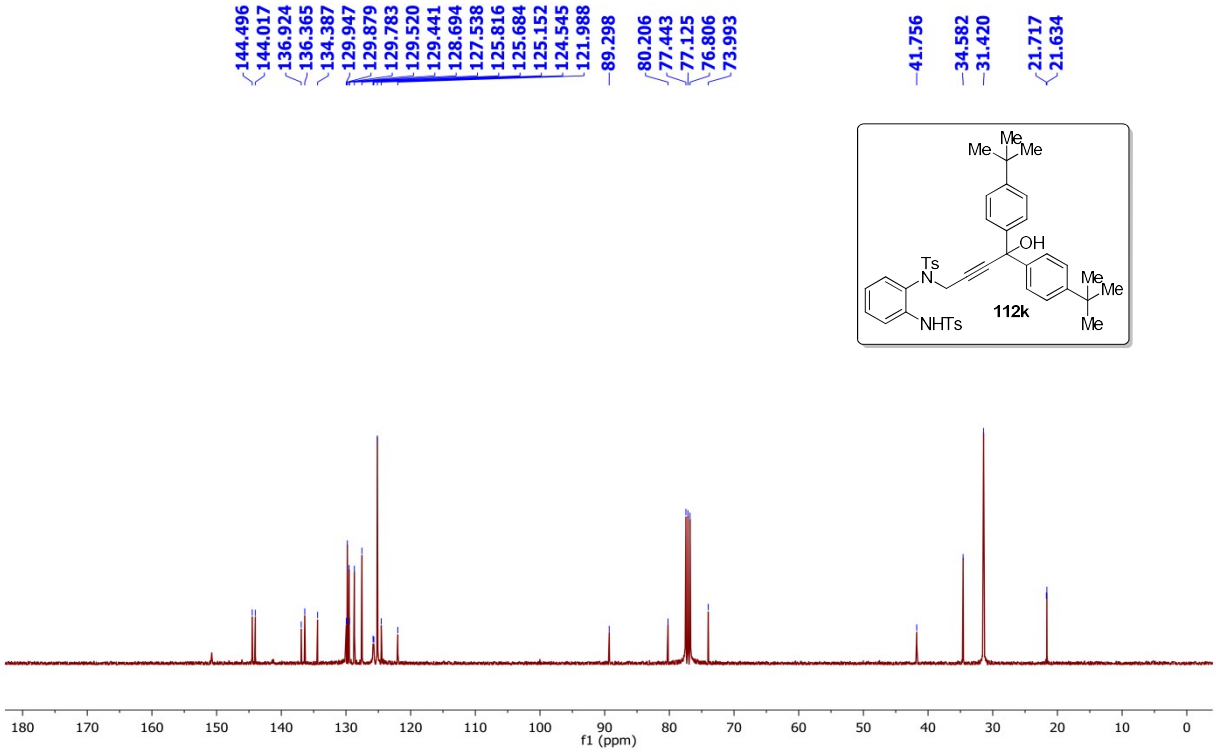
^{13}C{^{1}H} NMR (100 MHz) of **112j:**



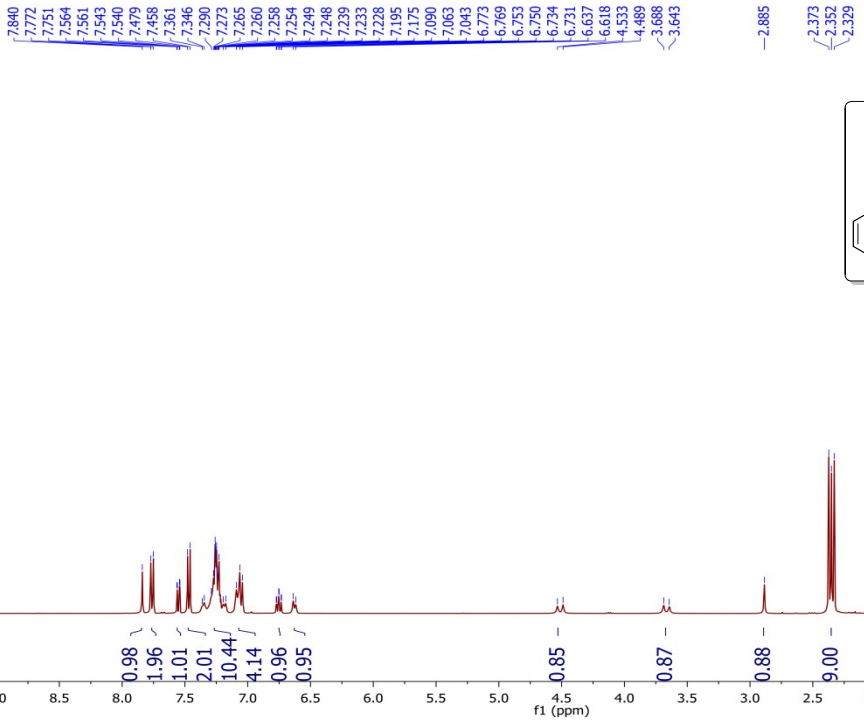
^{1}H NMR (400 MHz) of **112k:**



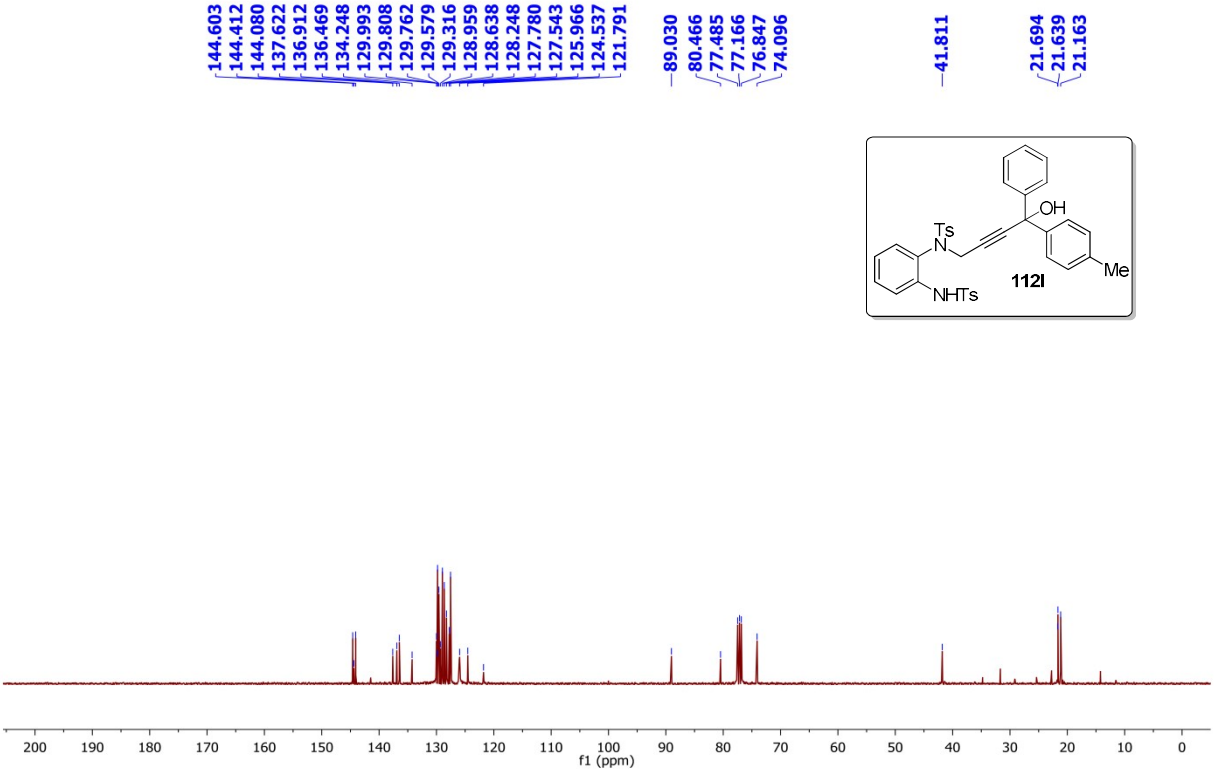
^{13}C{^{1}H} NMR (100 MHz) of **112k**:



^{1}H NMR (400 MHz) of **112l**:

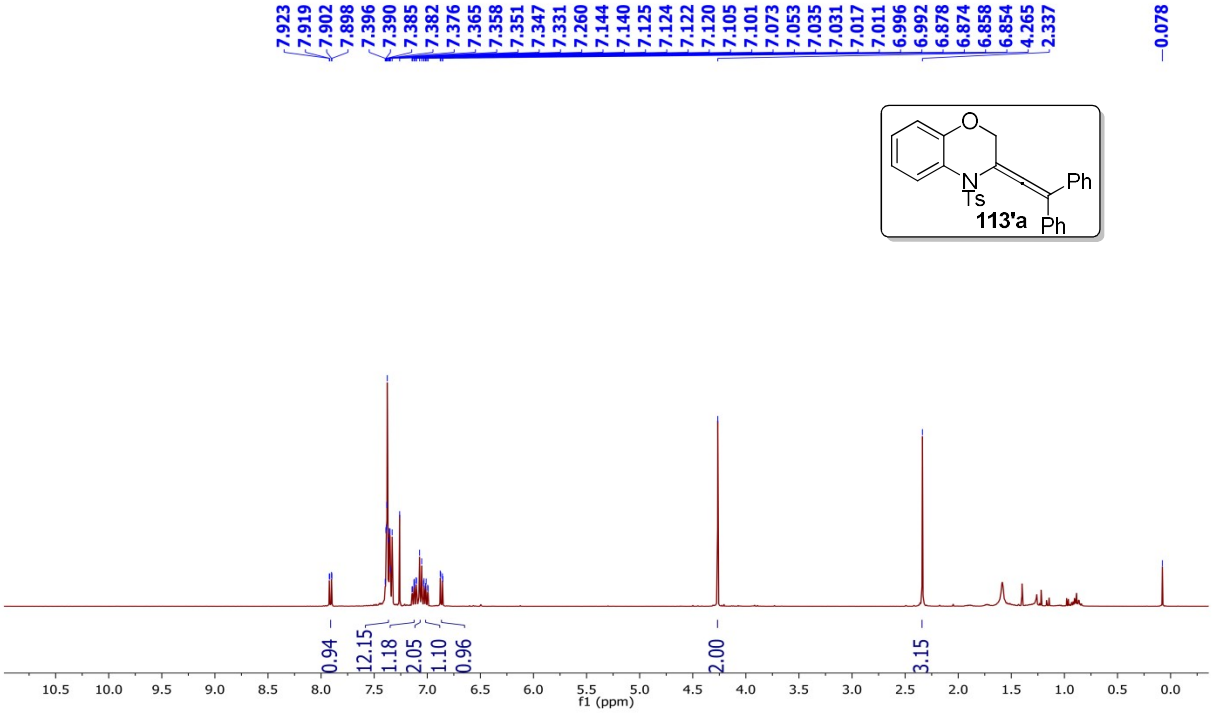


^{13}C{^{1}H} NMR (100 MHz) of **112l**:

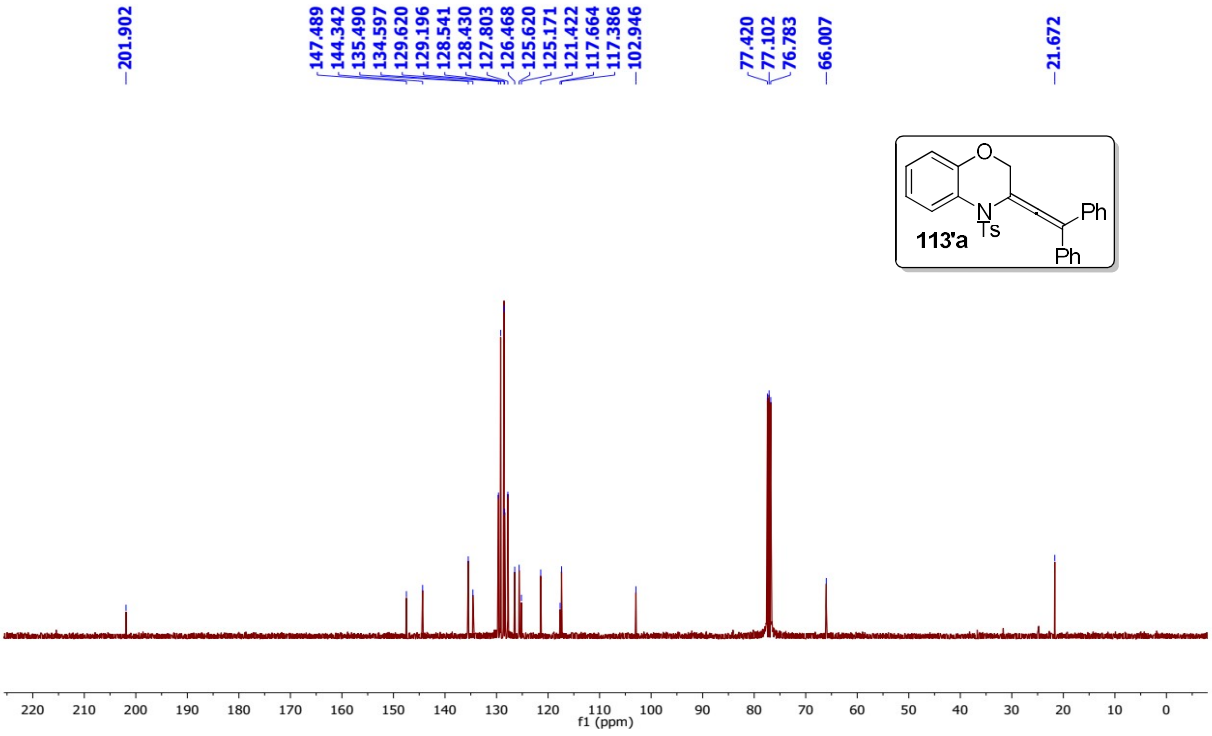


2.2.9.3. NMR spectra of compound 113′a:

^{1}H NMR (400 MHz) of **113'a**:

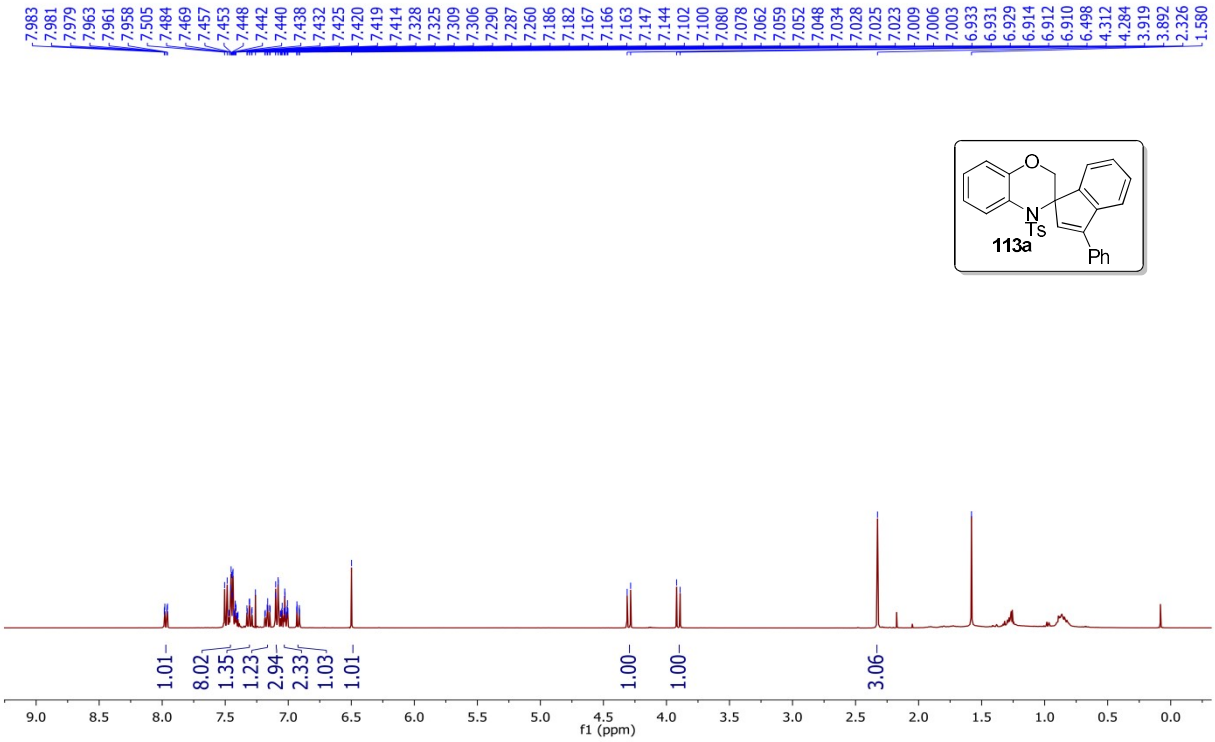


^{13}C{^{1}H} NMR (100 MHz) of **113'a**:

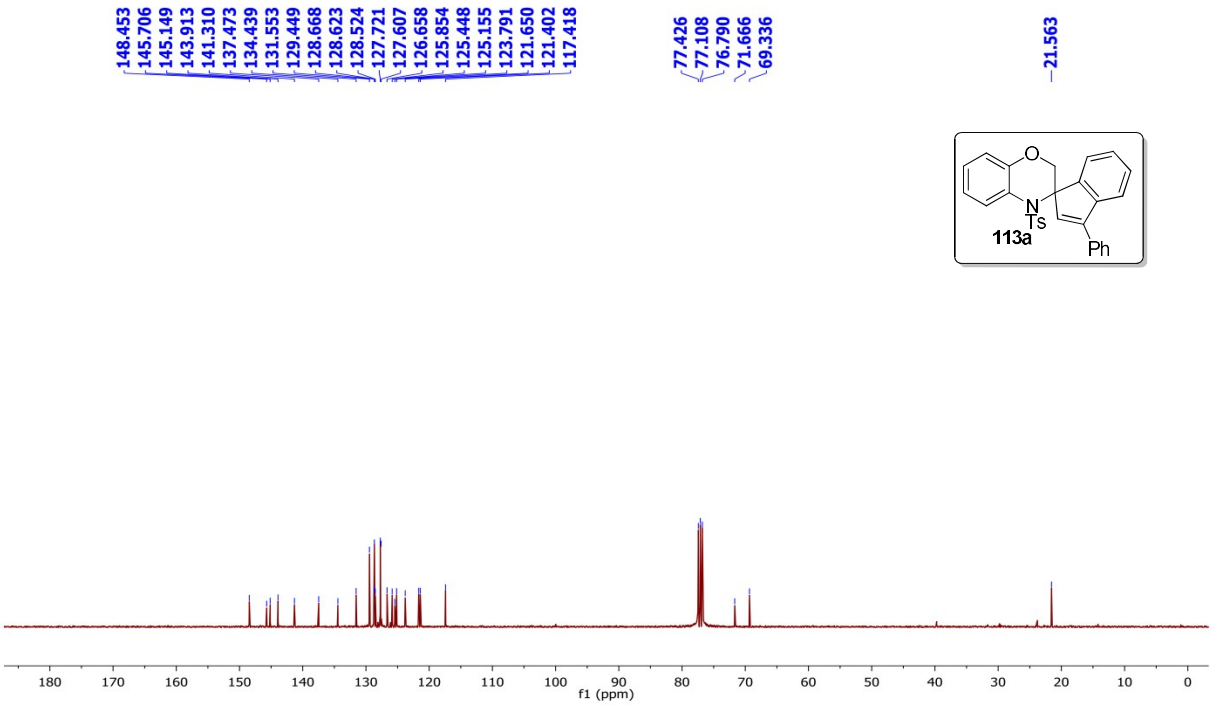


2.2.9.4. NMR spectra of compound 113a-k:

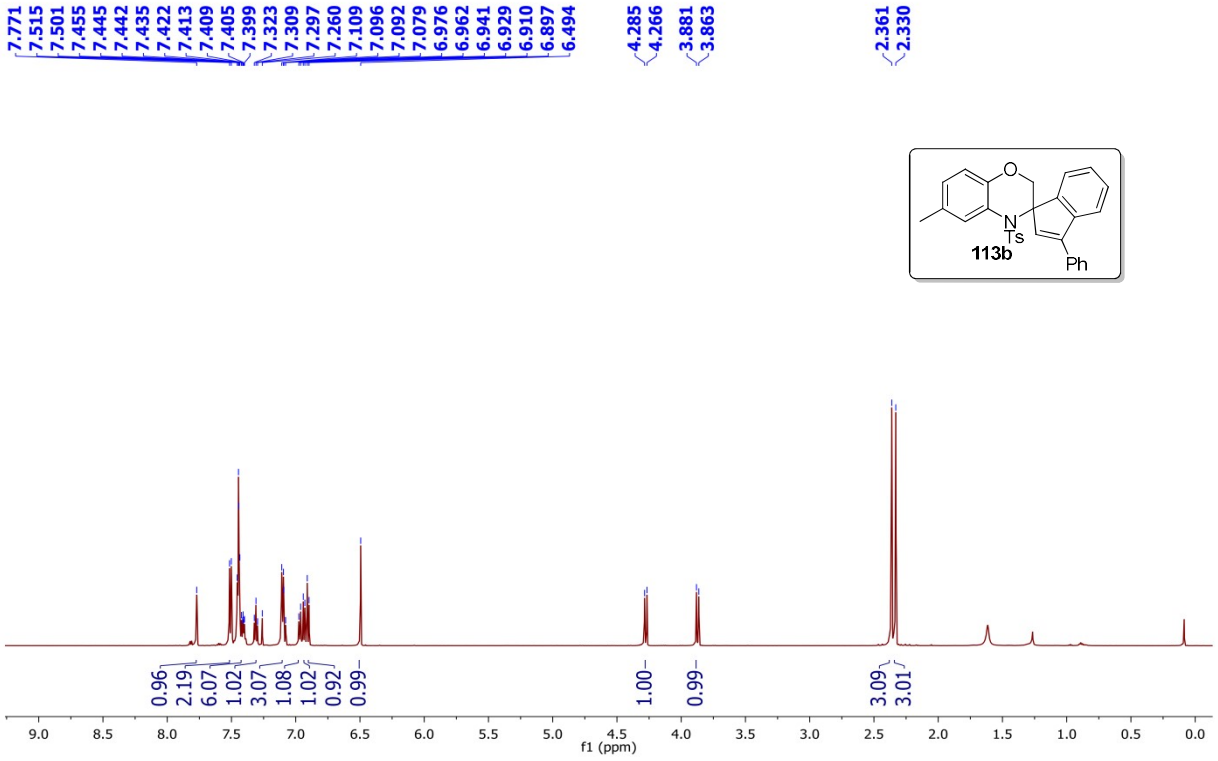
^{1}H NMR (400 MHz) of **113a**:



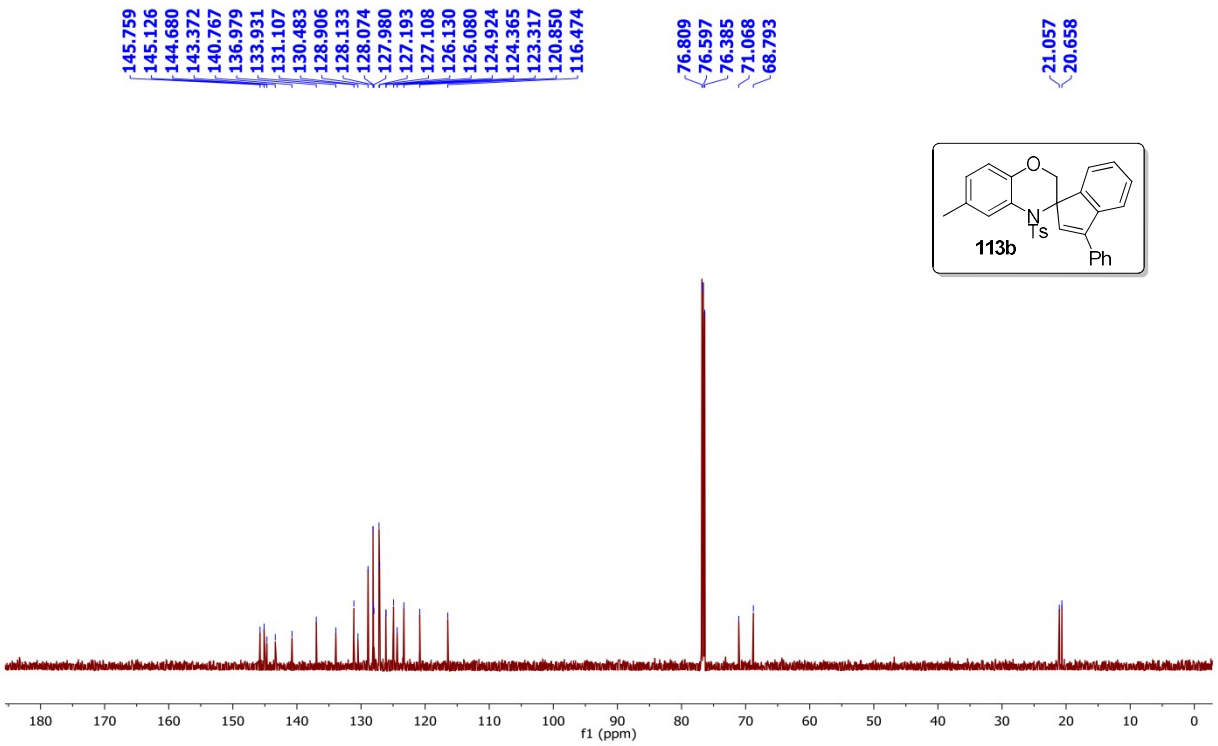
^{13}C{^{1}H} NMR (100 MHz) of **113a**:



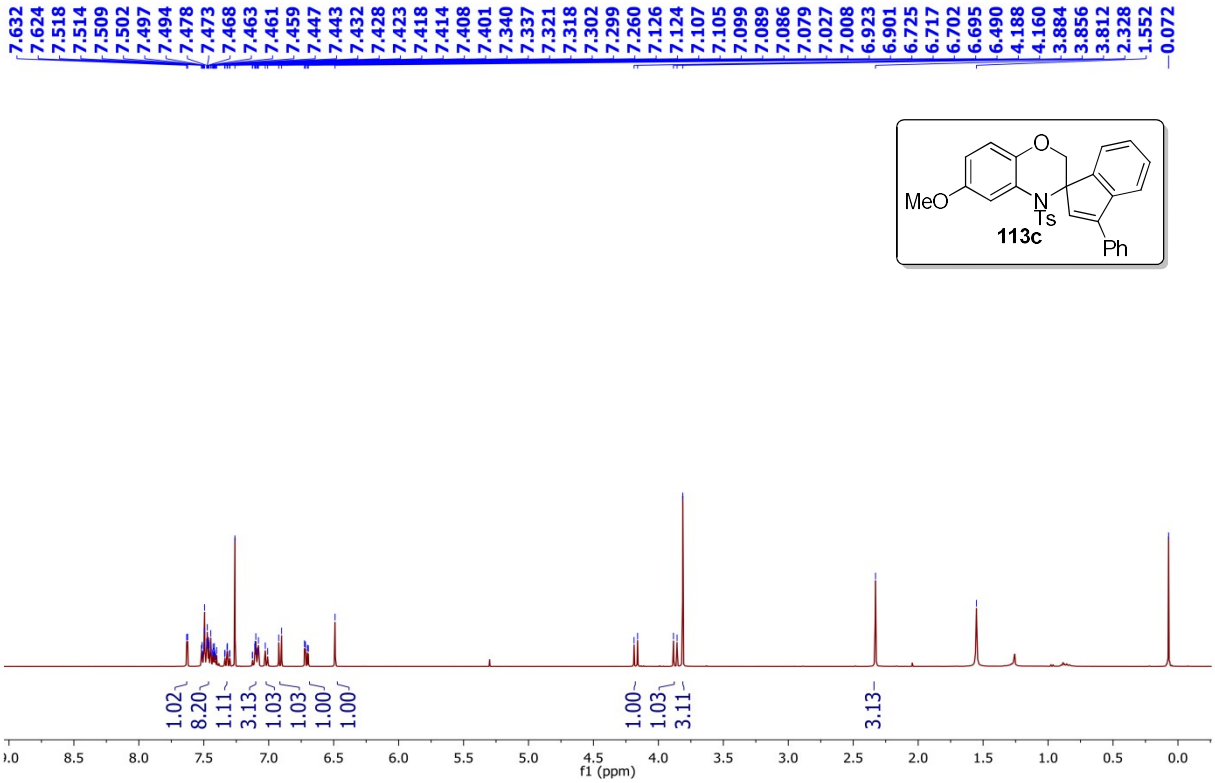
^{1}H NMR (600 MHz) of **113b**:



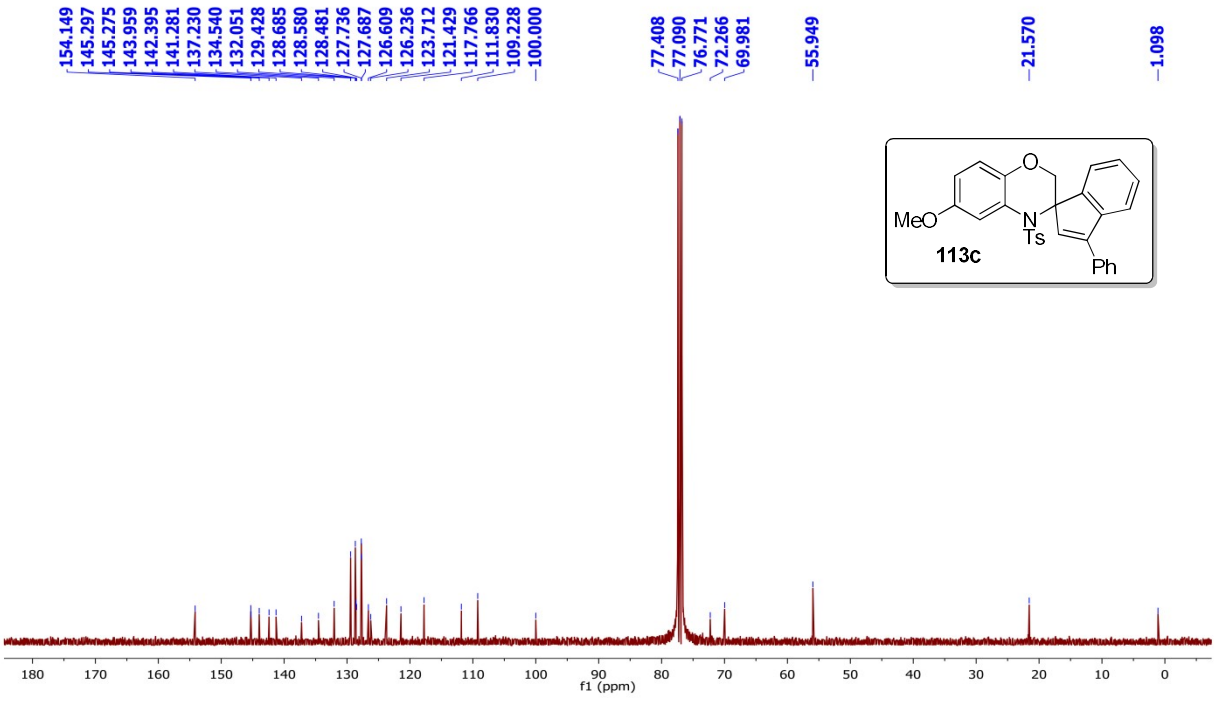
^{13}C{^{1}H} NMR (150 MHz) of **113b**:



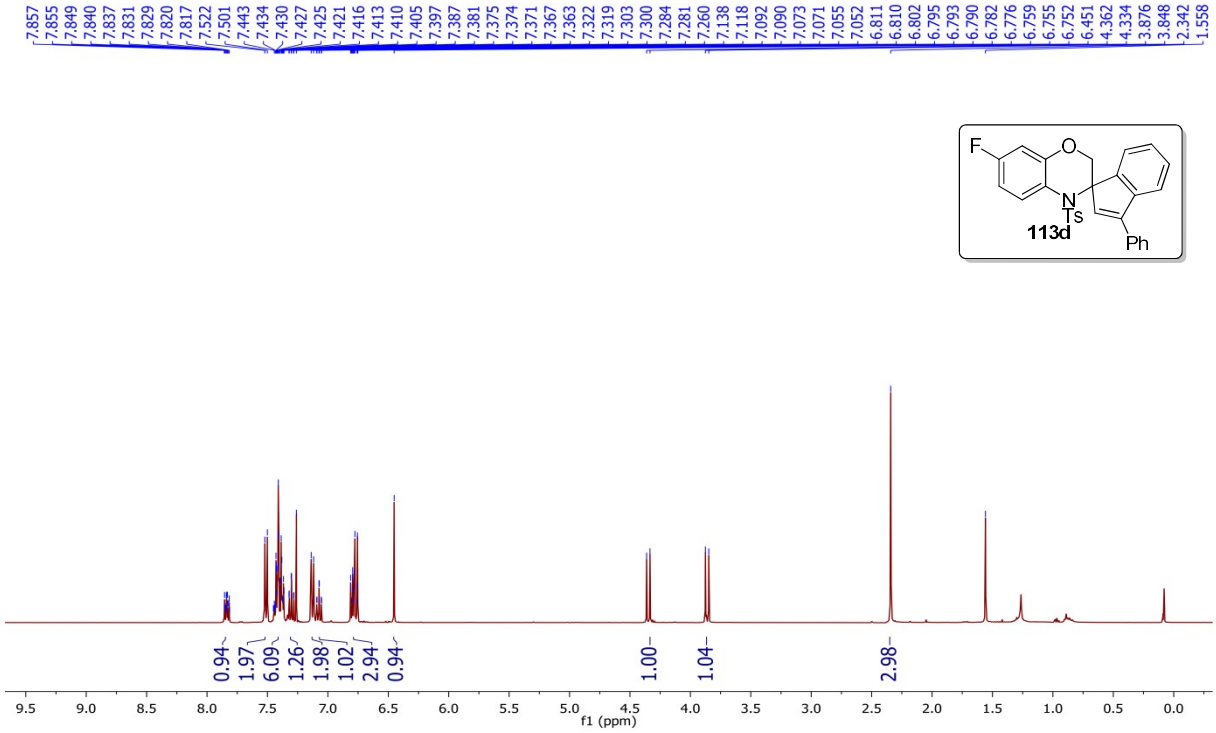
^{1}H NMR (400 MHz) of **113c**:



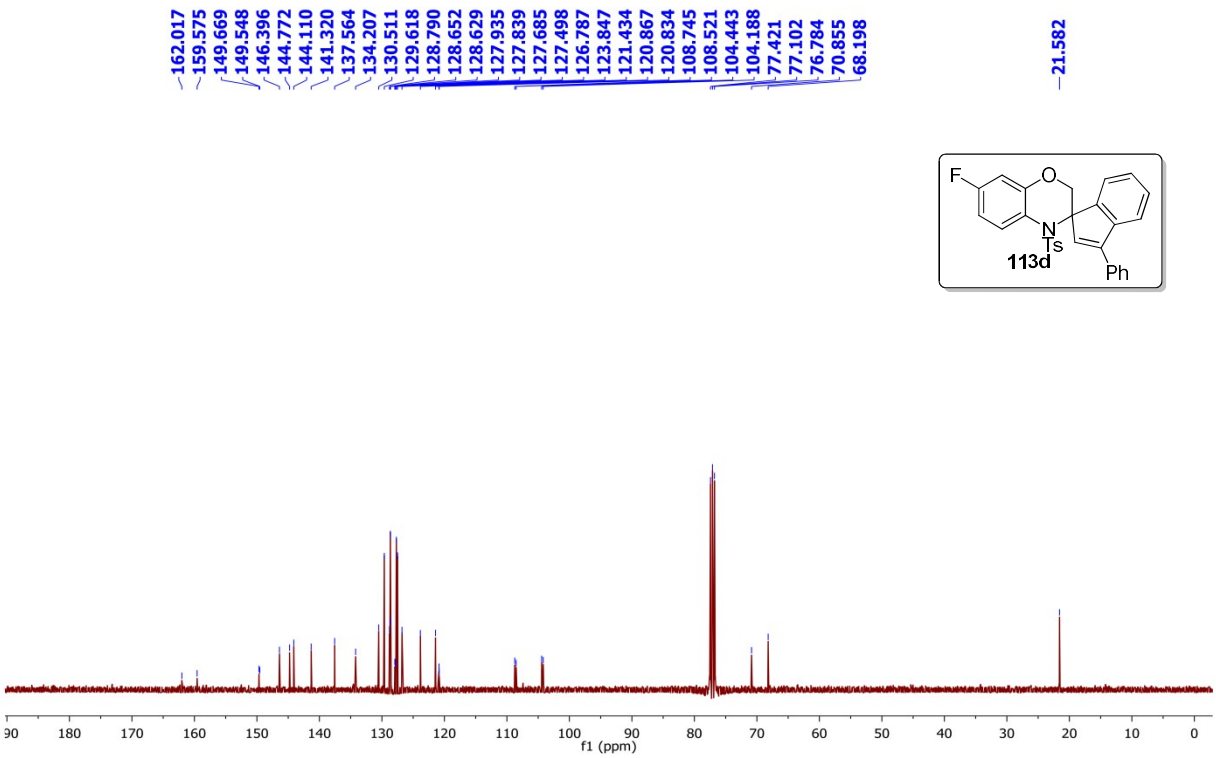
^{13}C{^{1}H} NMR (100 MHz) of **113c**:



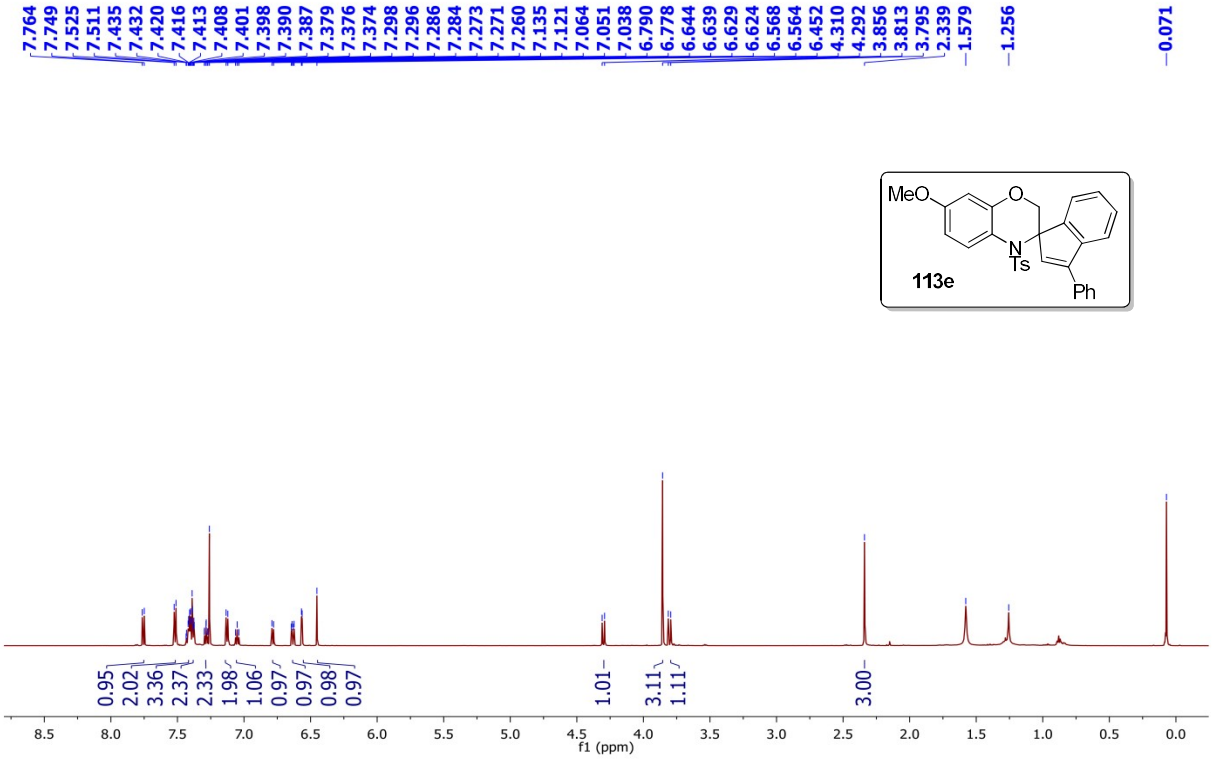
^{1}H NMR (400 MHz) of **113d**:



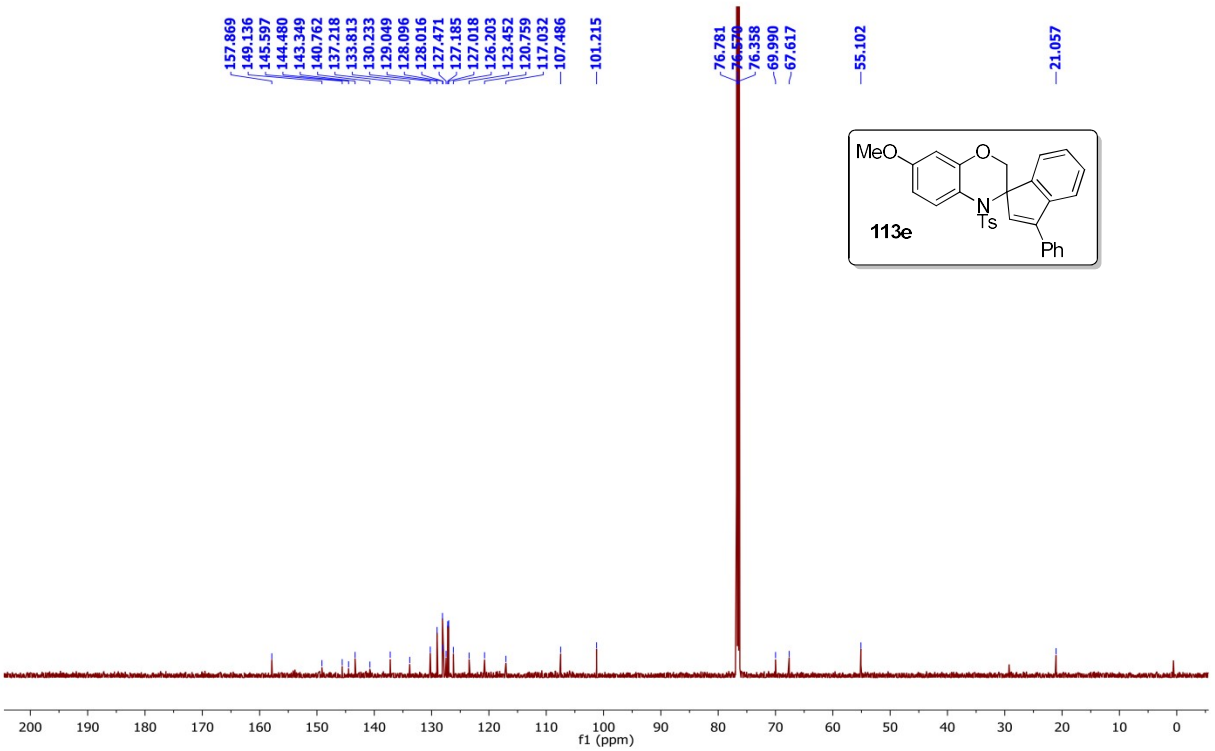
^{13}C{^{1}H} NMR (100 MHz) of **113d**:



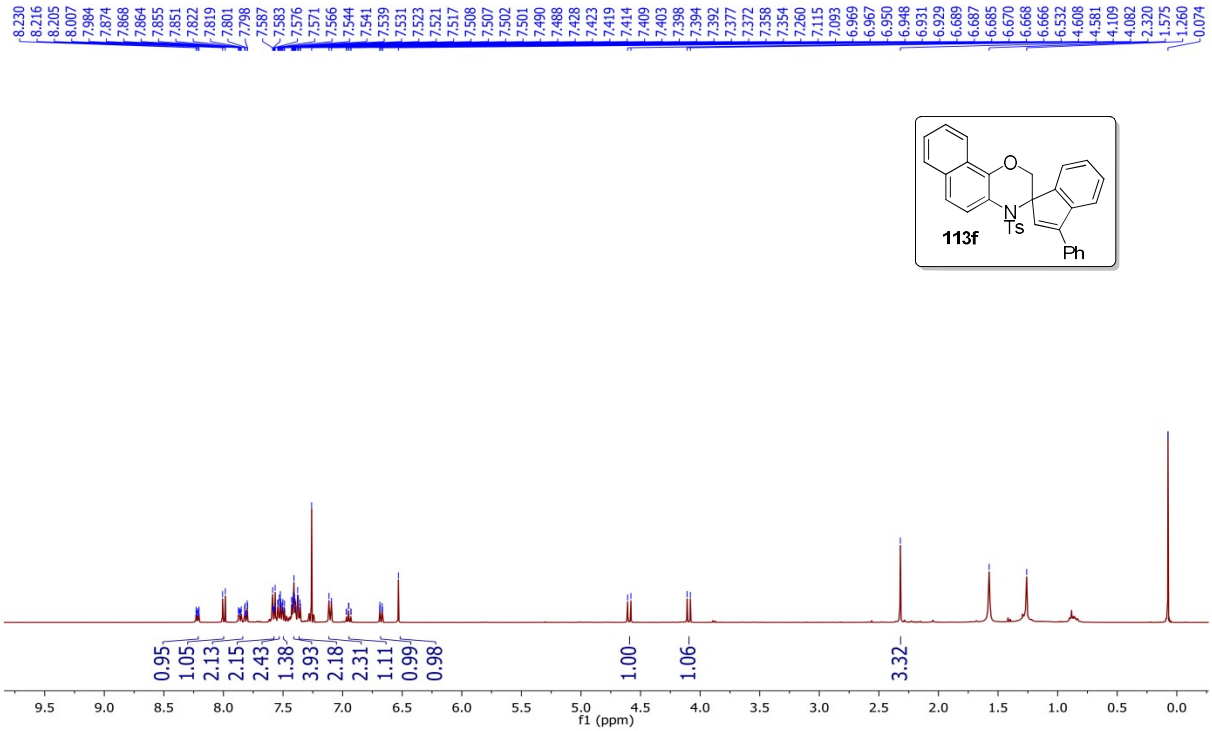
^{1}H NMR (600 MHz) of **113e**:



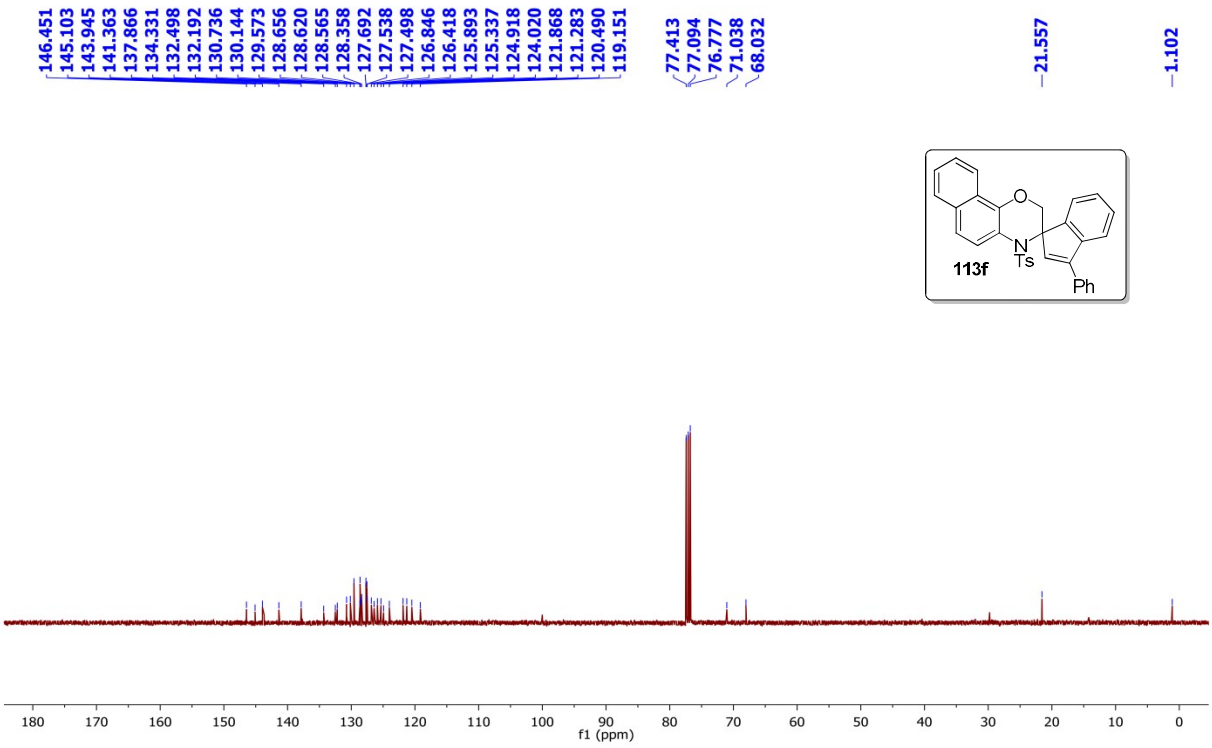
^{13}C{^{1}H} NMR (150 MHz) of **113e**:



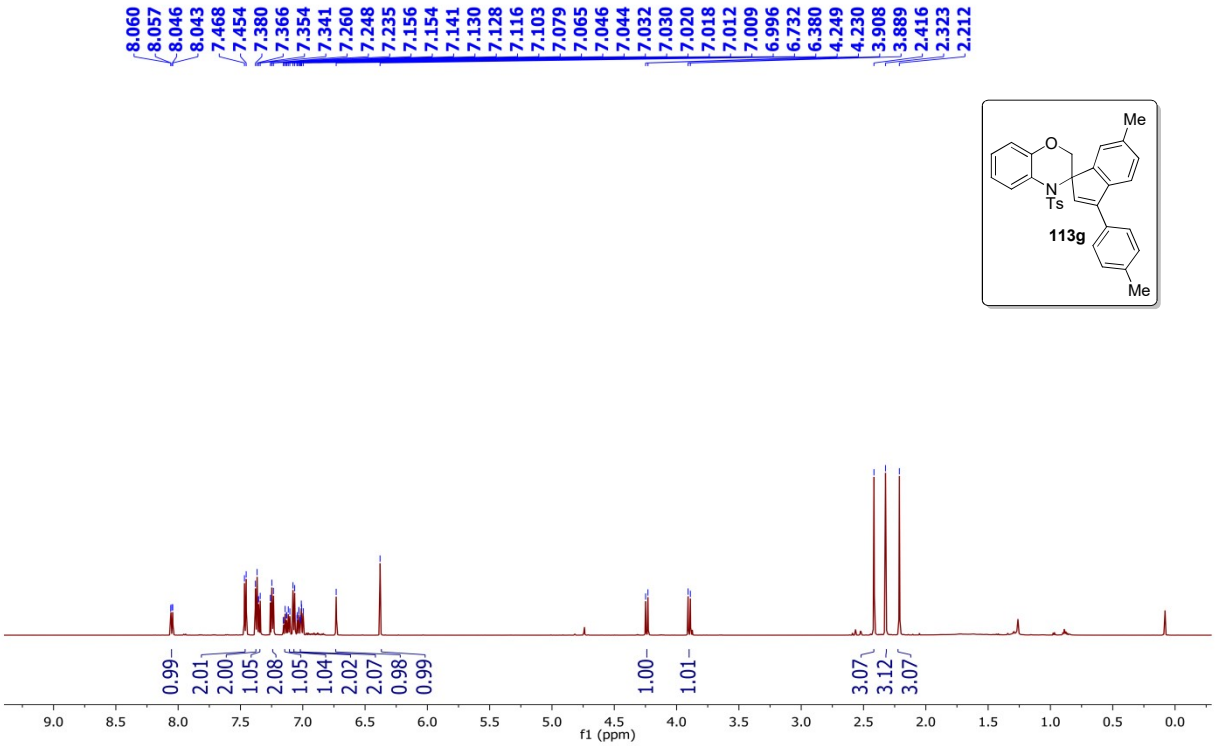
^{1}H NMR (400 MHz) of **113f**:



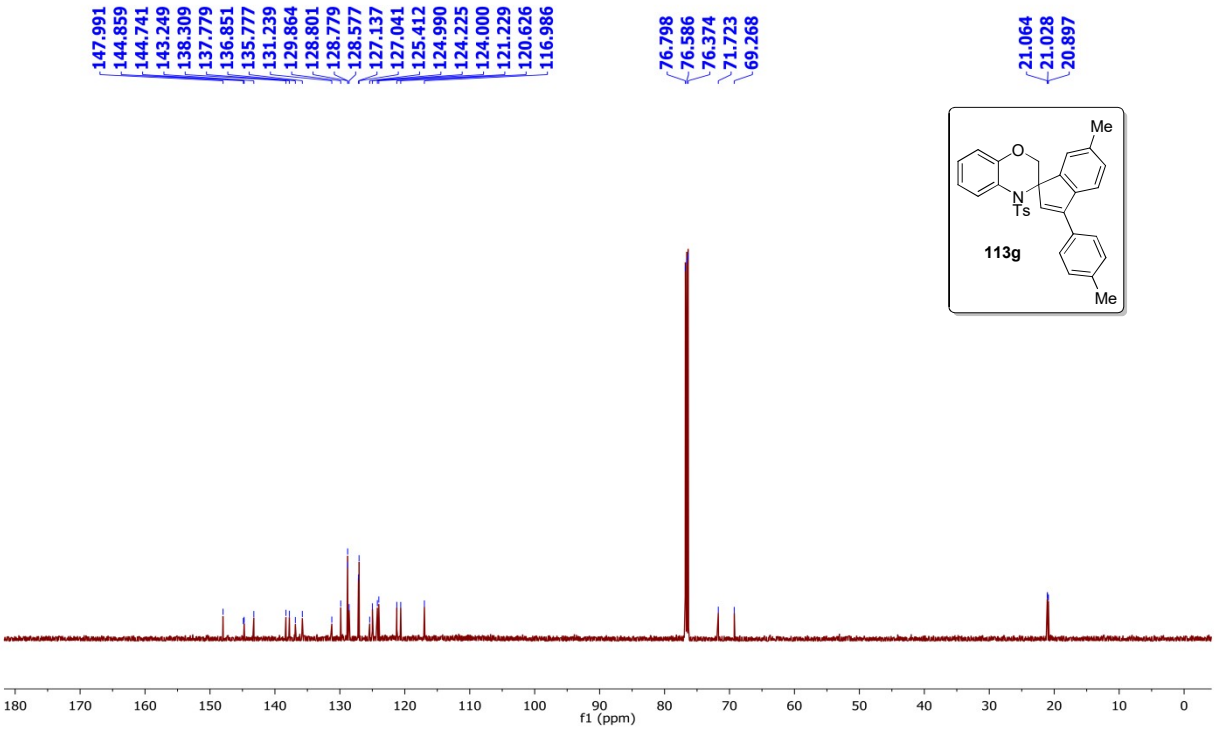
^{13}C{^{1}H} NMR (100 MHz) of **113f**:



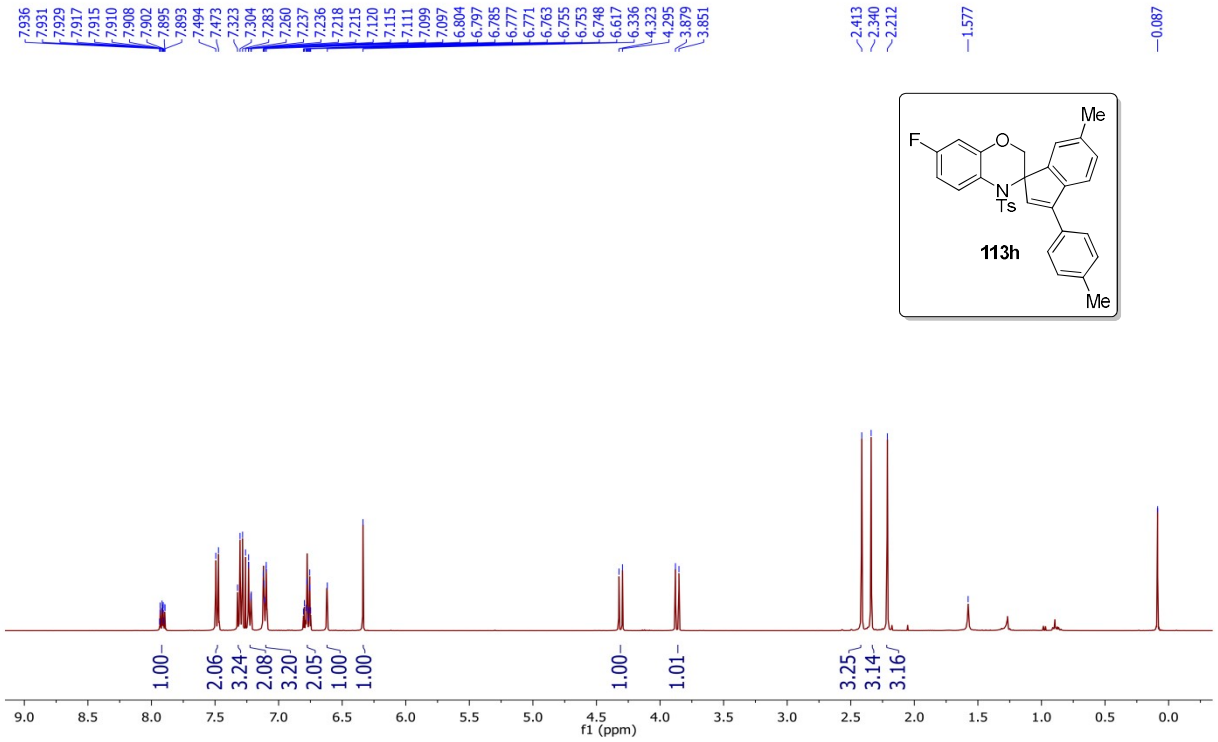
^{1}H NMR (600 MHz) of **113g:**



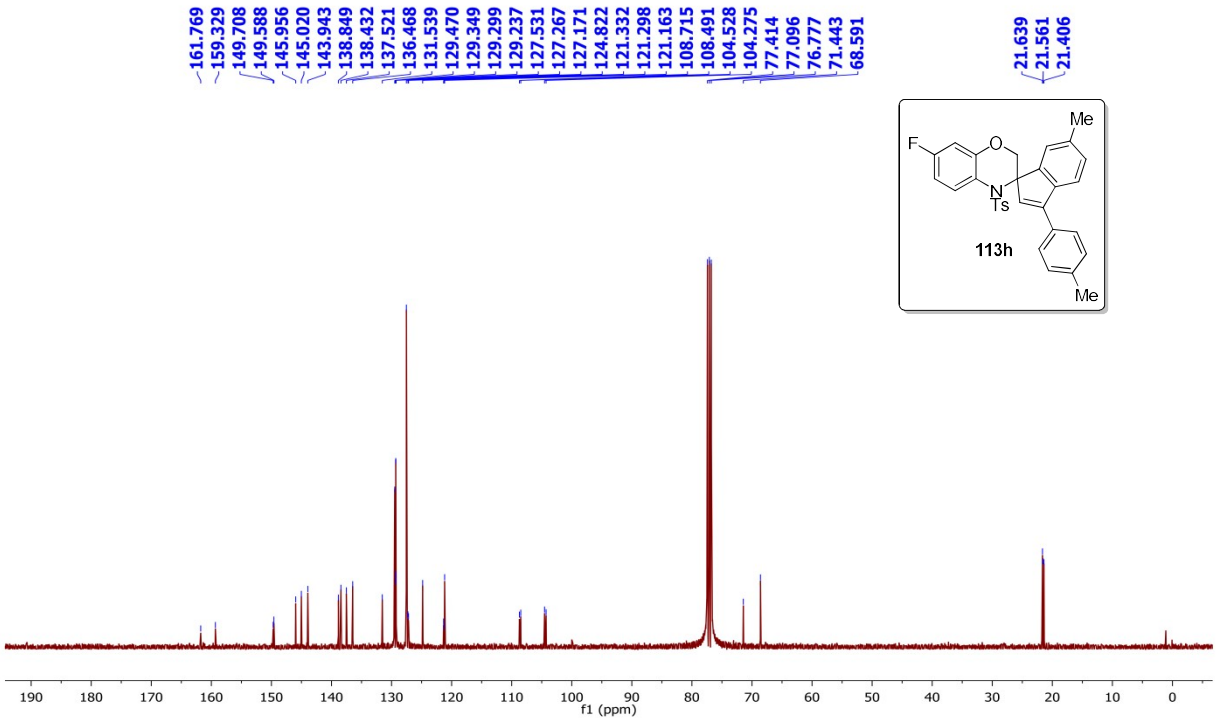
^{13}C{^{1}H} NMR (150 MHz) of **113g:**



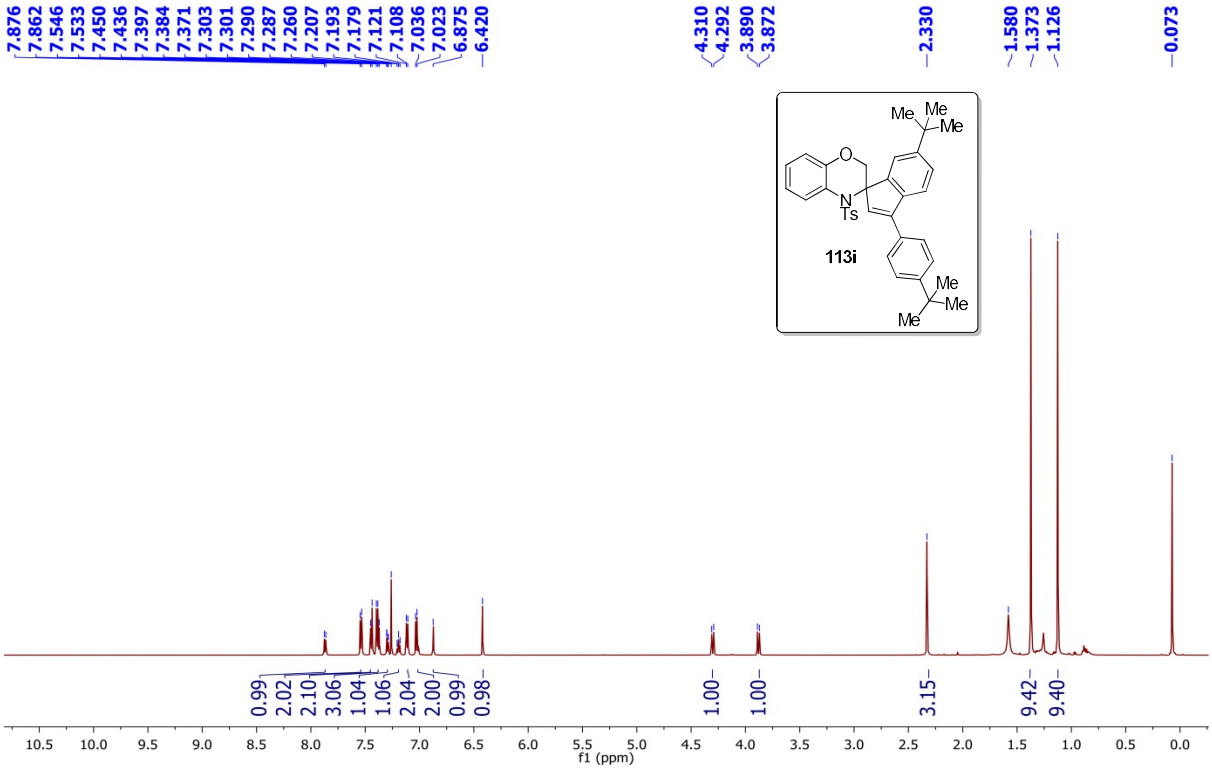
^{1}H NMR (400 MHz) of **113h**:



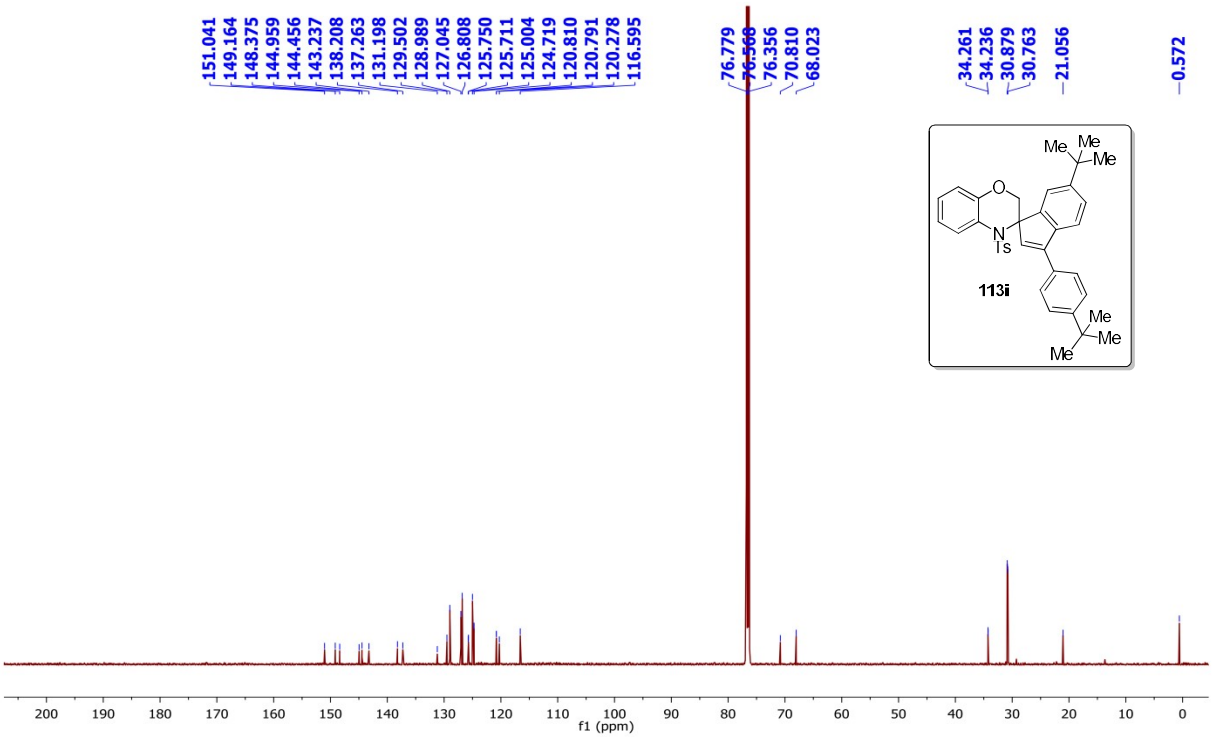
^{13}C{^{1}H} NMR (100 MHz) of **113h:**



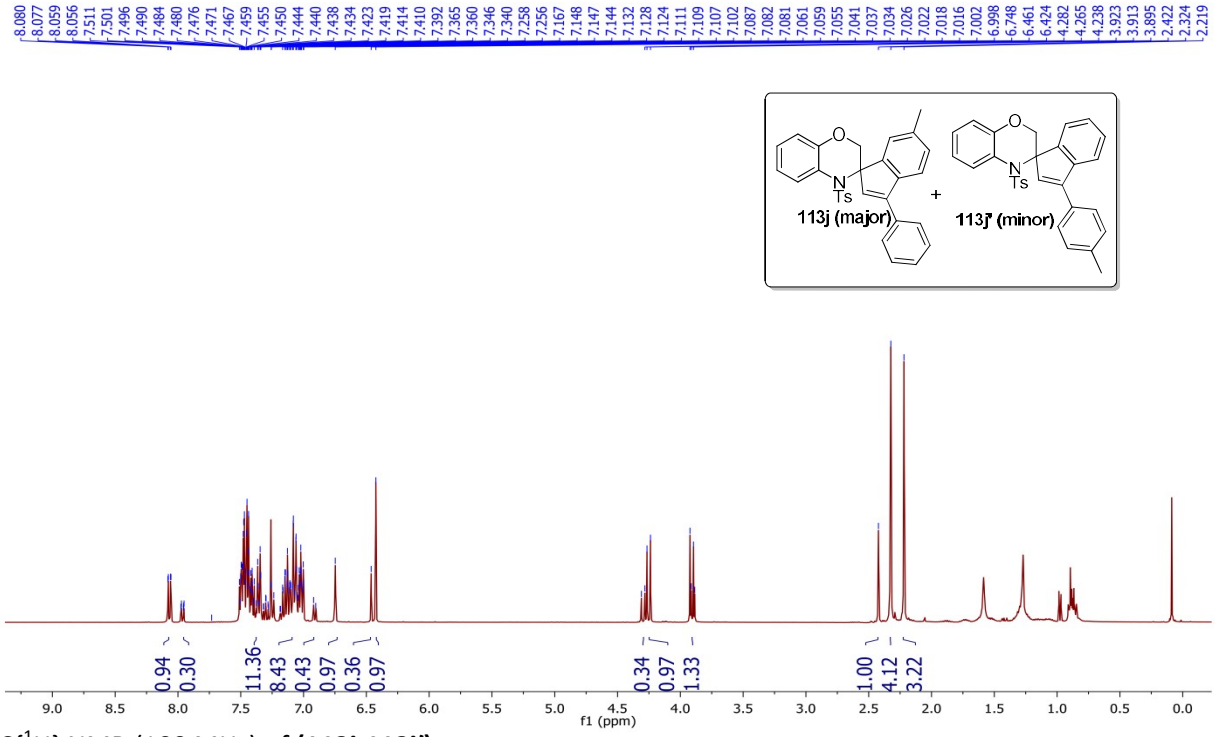
^{1}H NMR (600 MHz) of **113i**:



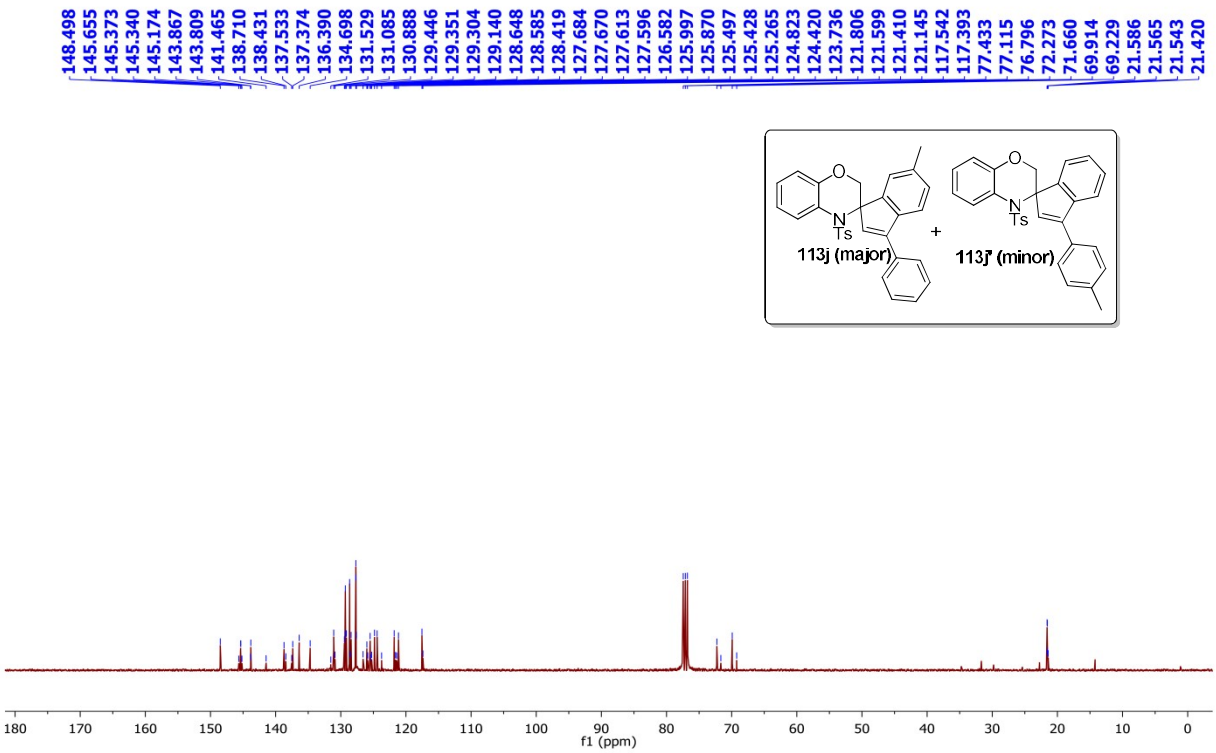
^{13}C{^{1}H} NMR (600 MHz) of **113i**:



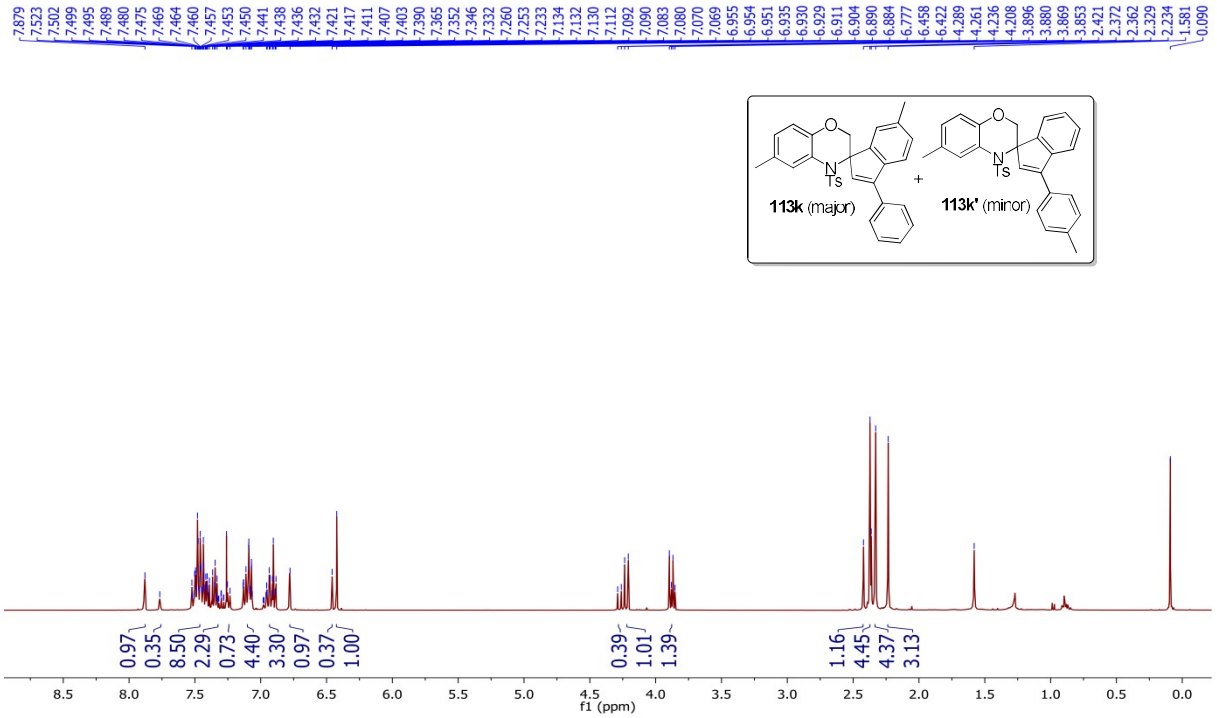
^{1}H NMR (400 MHz) of **(113j:113j')**:



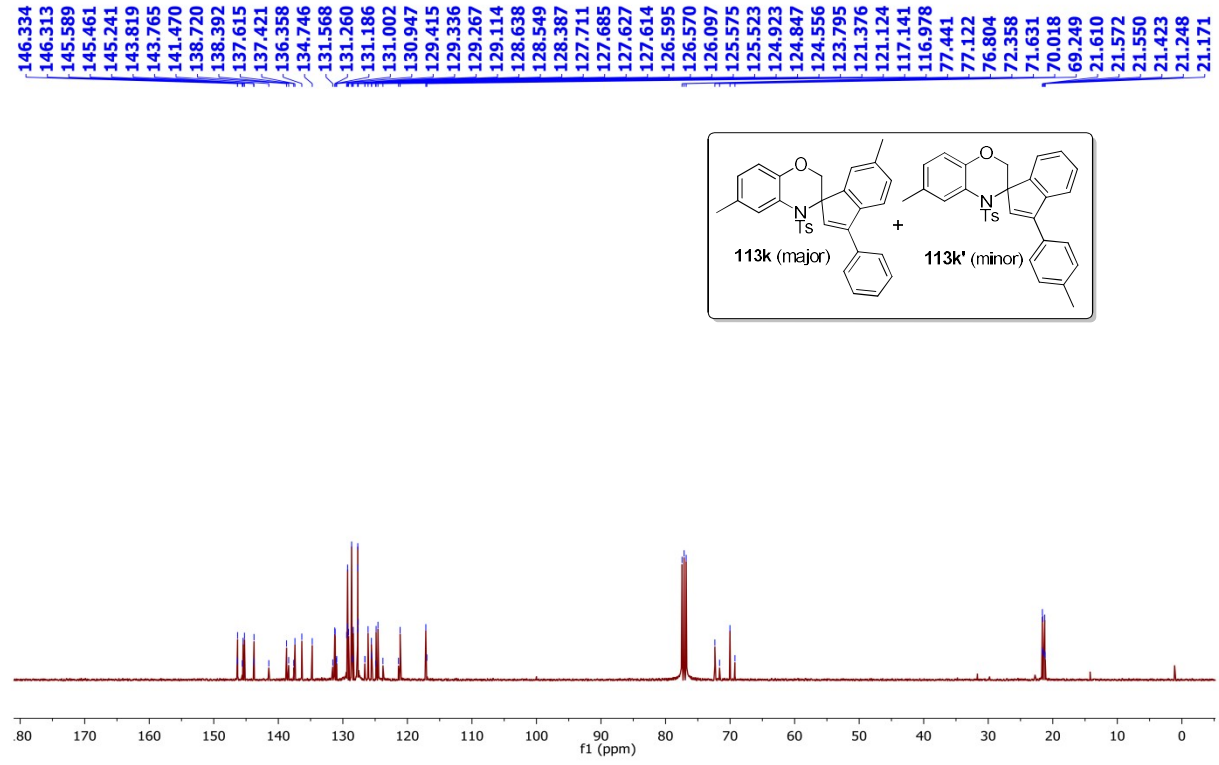
^{13}C{^{1}H} NMR (100 MHz) of **(113j:113j')**:



^{1}H NMR (400 MHz) of **(113k:113k')**:

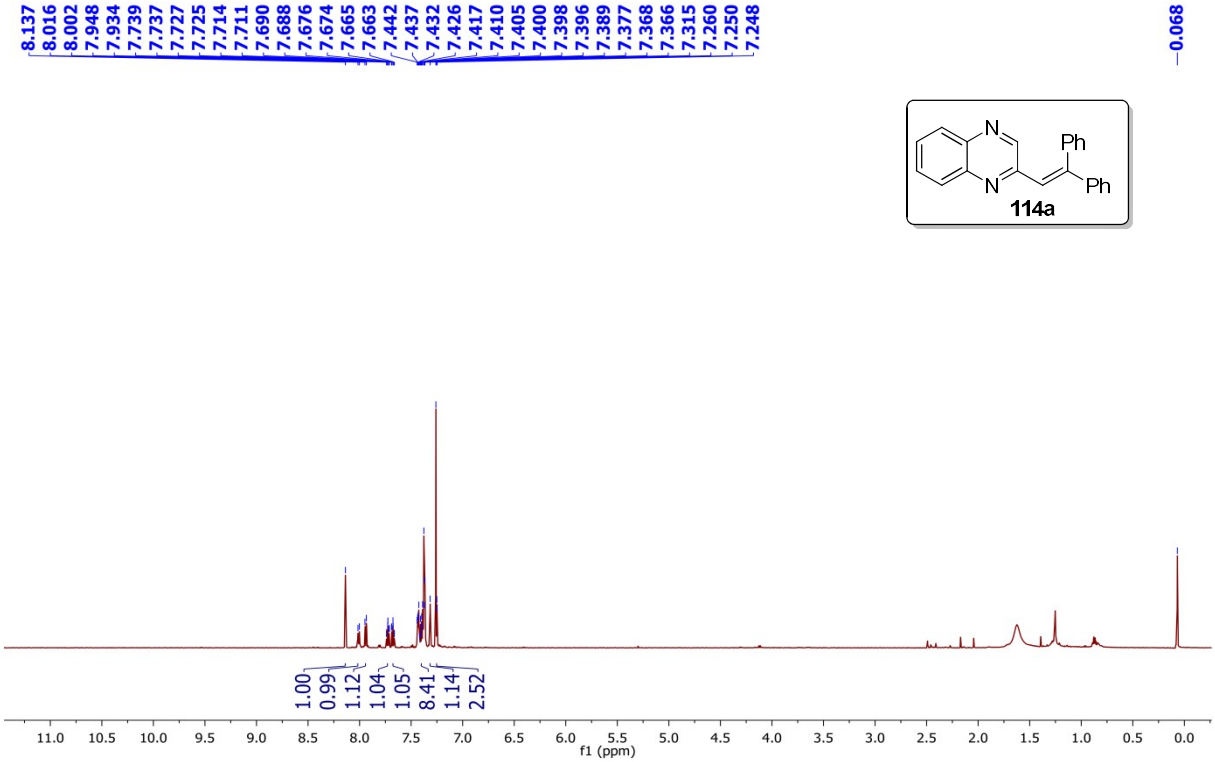


^{13}C{^{1}H} NMR (100 MHz) of **(113k:113k')**:

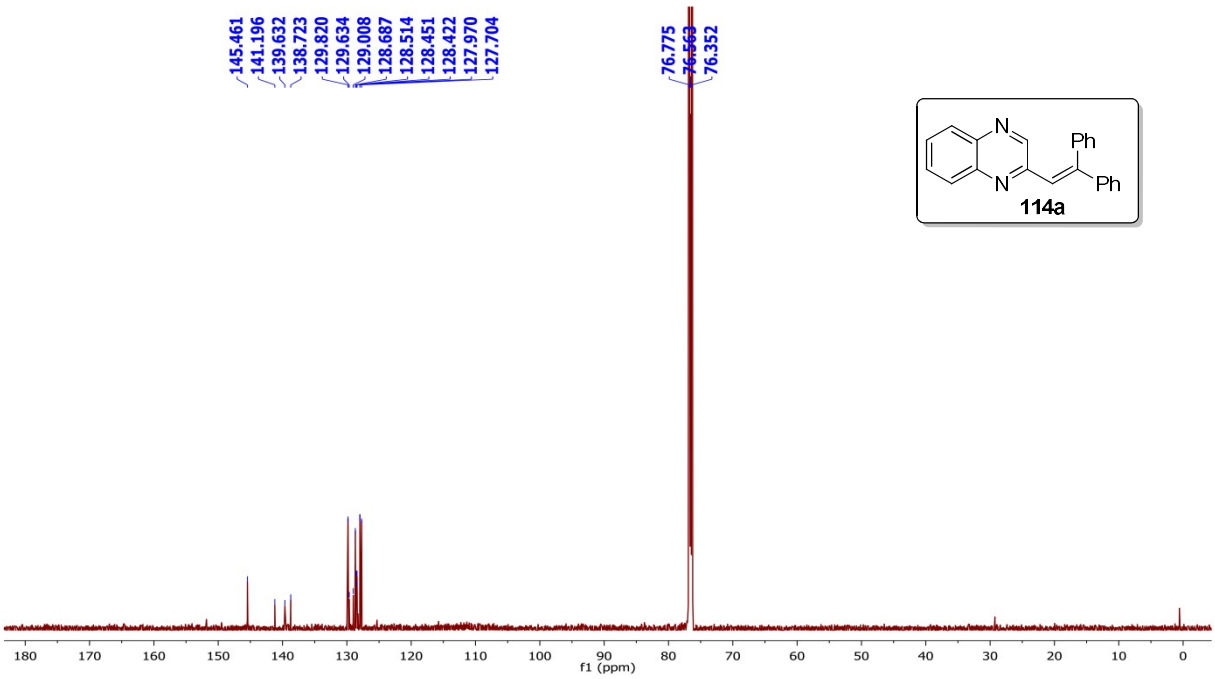


2.2.9.5. NMR Spectra of Compounds 114a-l:

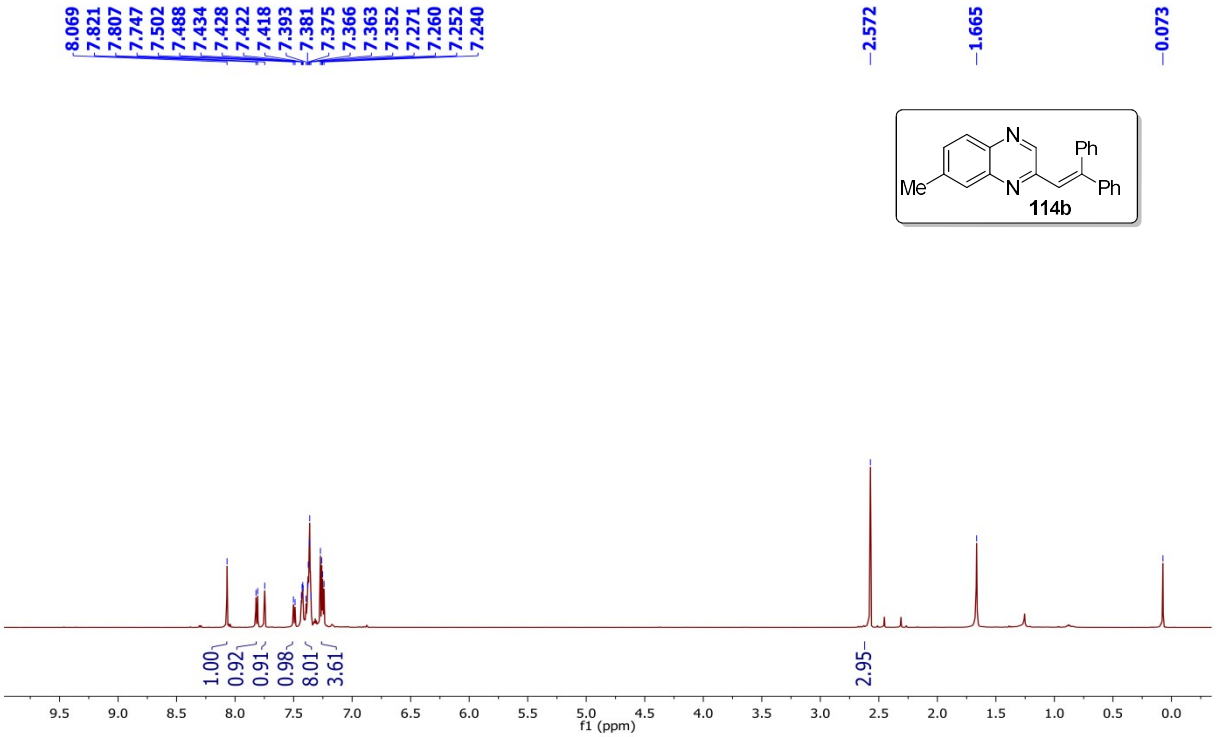
^{1}H NMR (600 MHz) of **114a**:



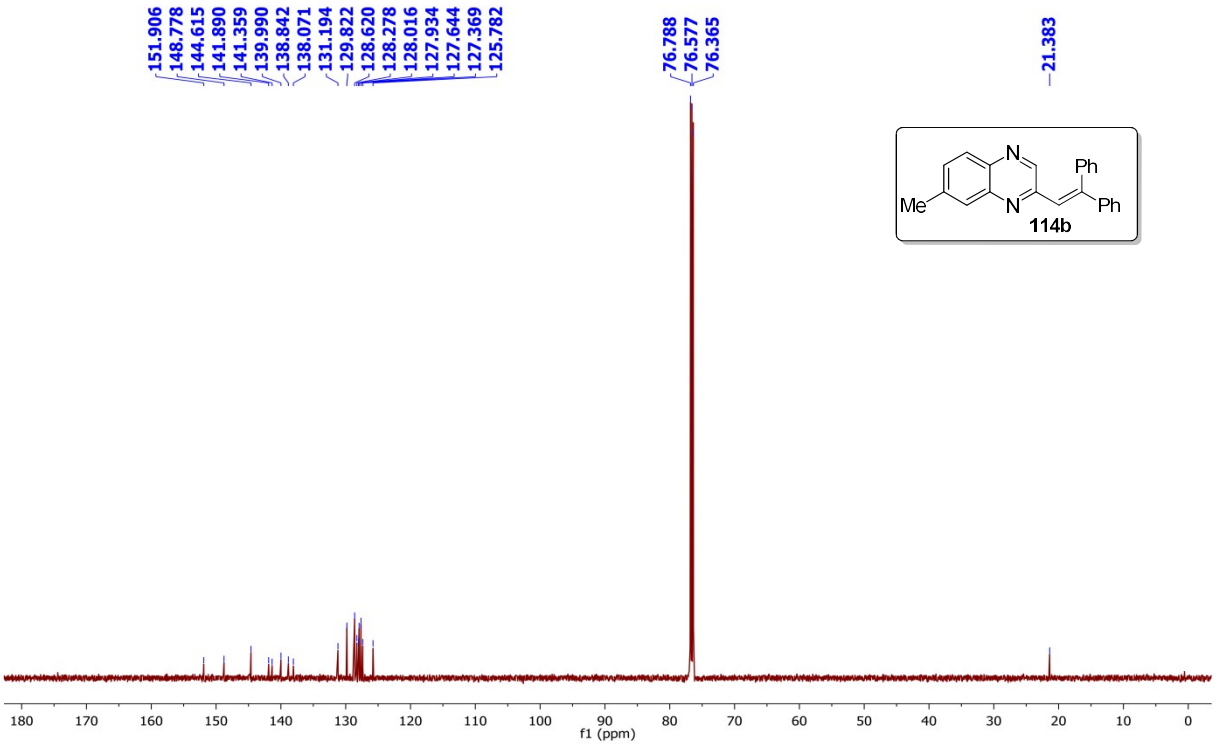
^{13}C{^{1}H} NMR (150 MHz) of **114a**:



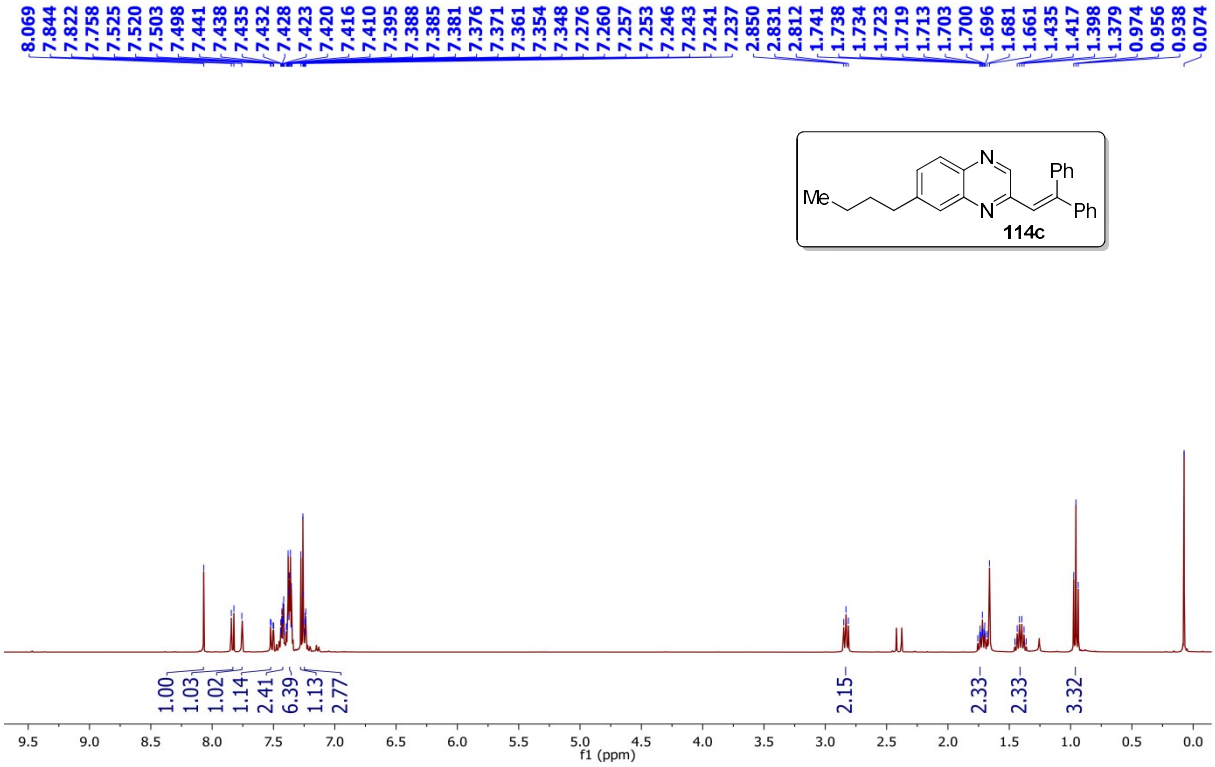
^{1}H NMR (600 MHz) of **114b**:



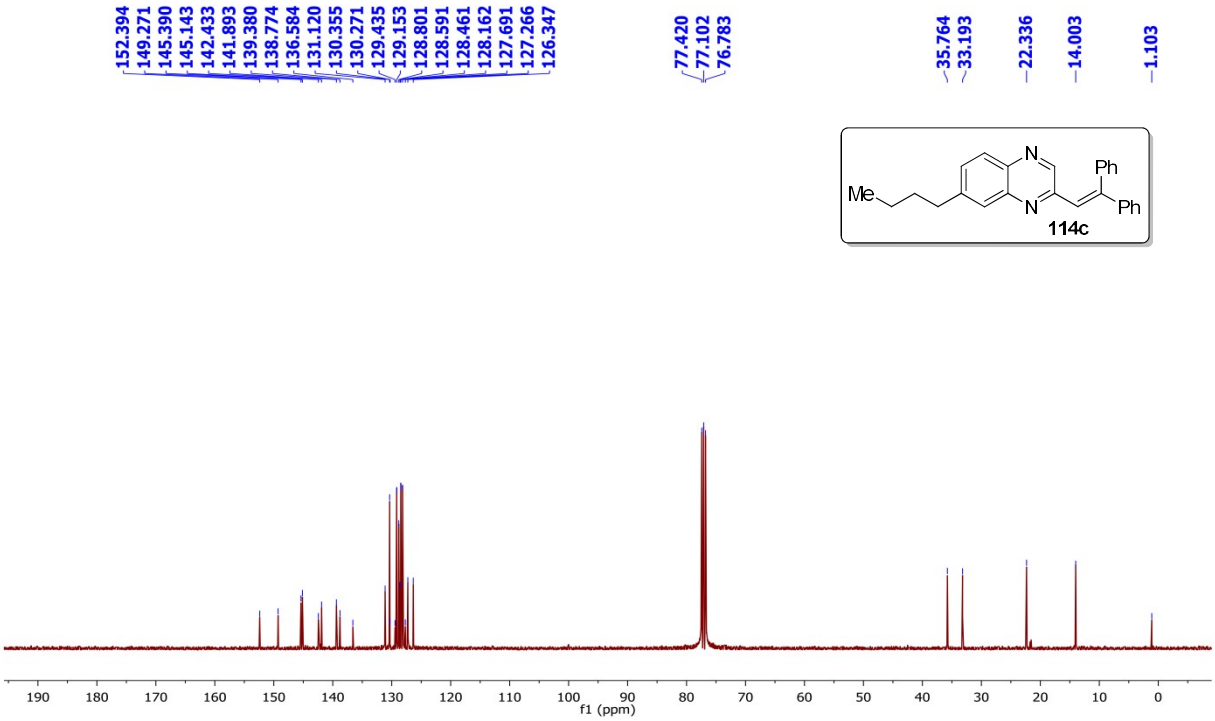
^{13}C{^{1}H} NMR (150 MHz) of **114b**:



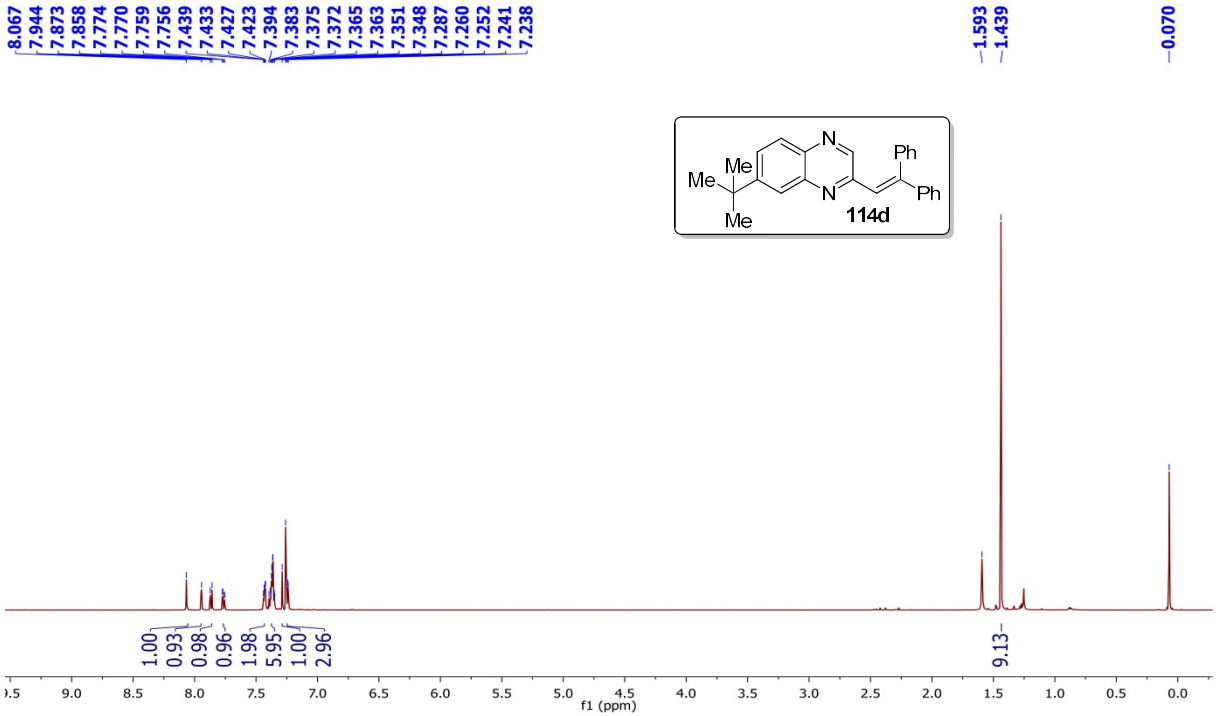
^{1}H NMR (400 MHz) of **114c**:



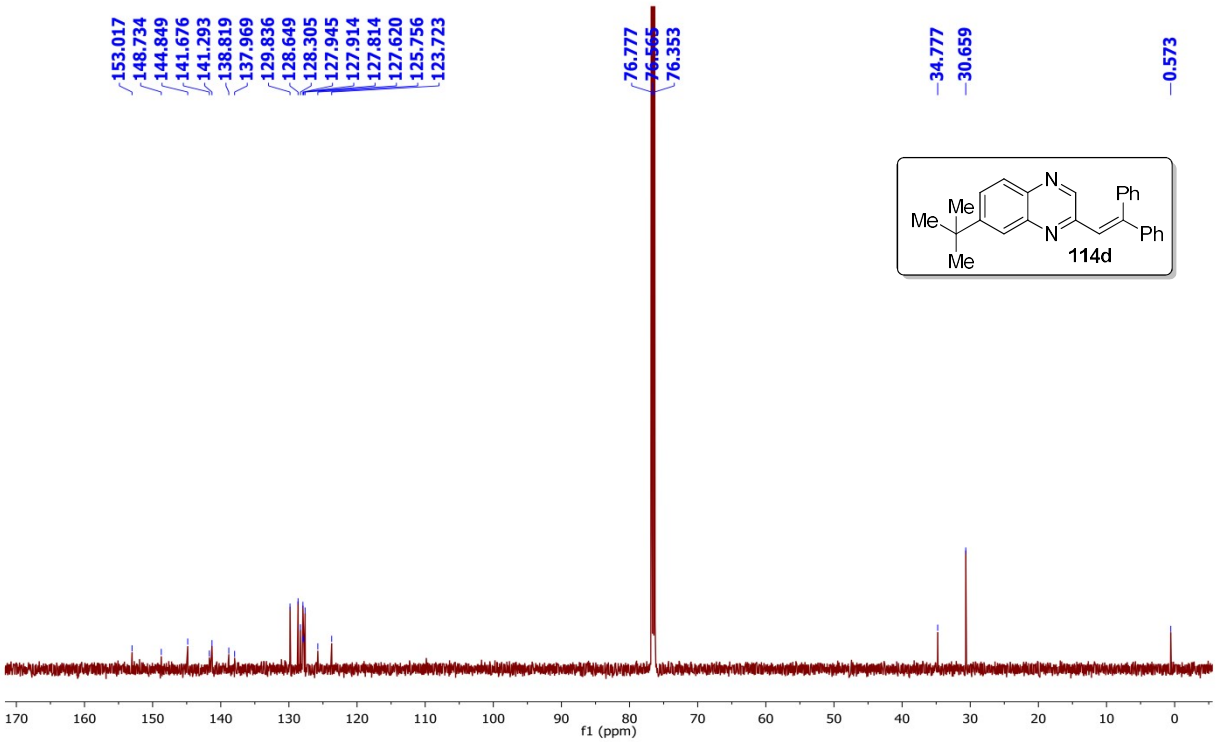
^{13}C{^{1}H} NMR (100 MHz) of **114c**:



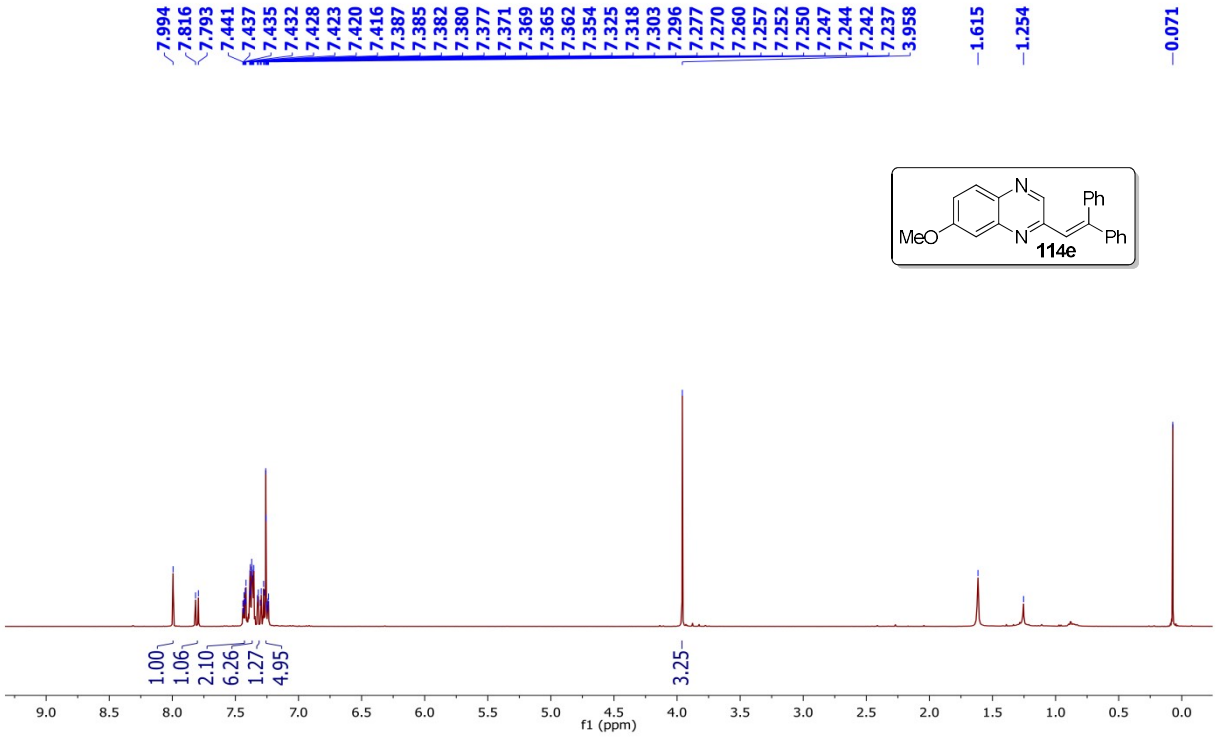
^{1}H NMR (600 MHz) of **114d**:



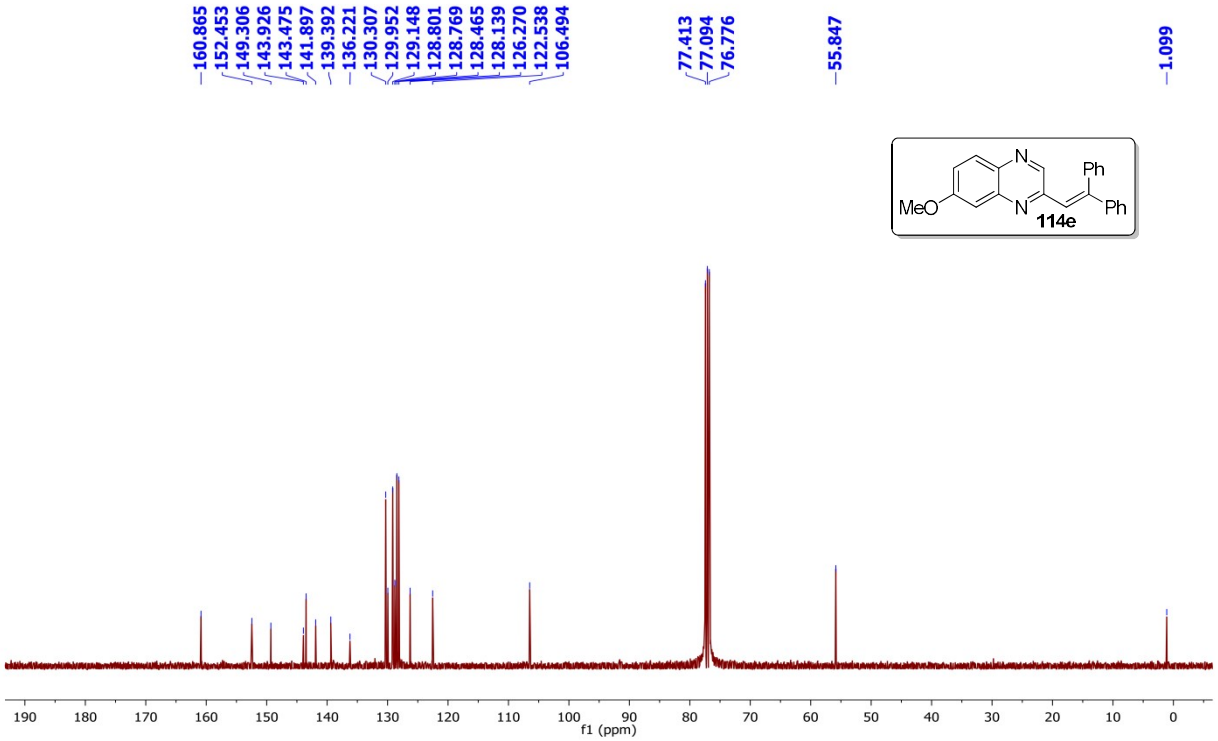
^{13}C{^{1}H} NMR (600 MHz) of **114d**:



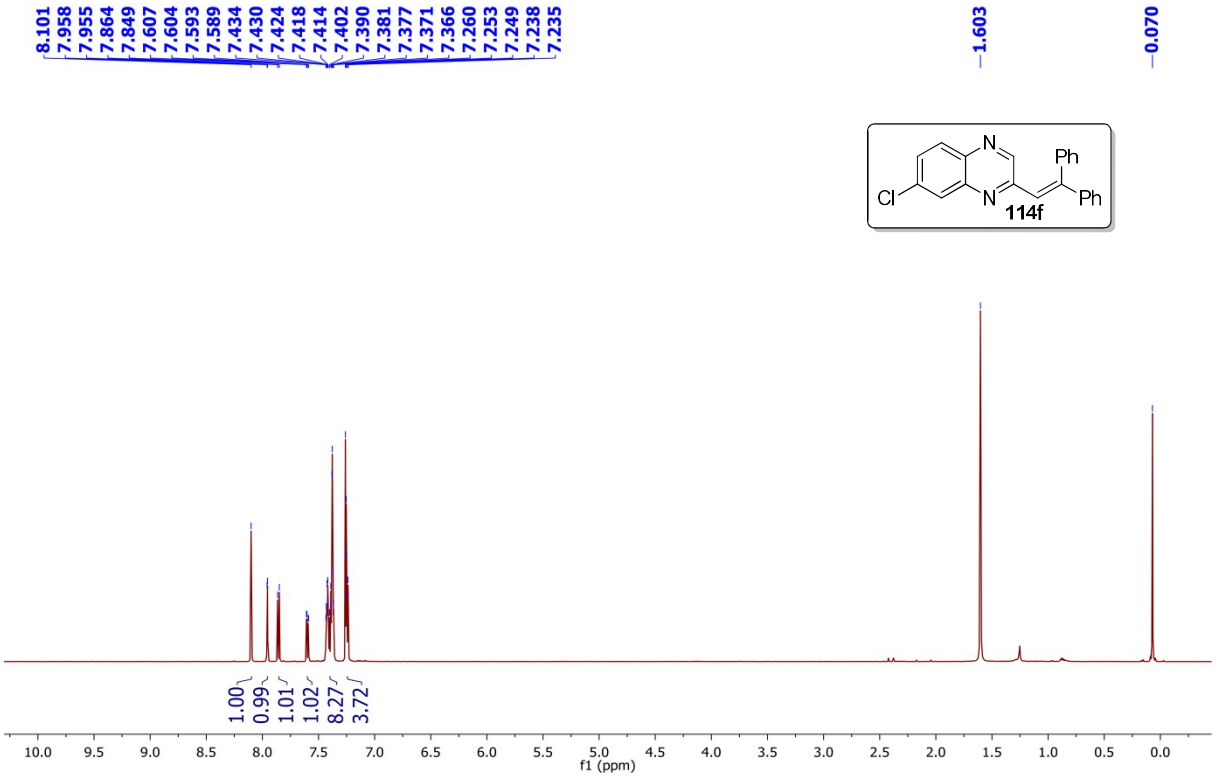
^{1}H NMR (400 MHz) of **114e**:



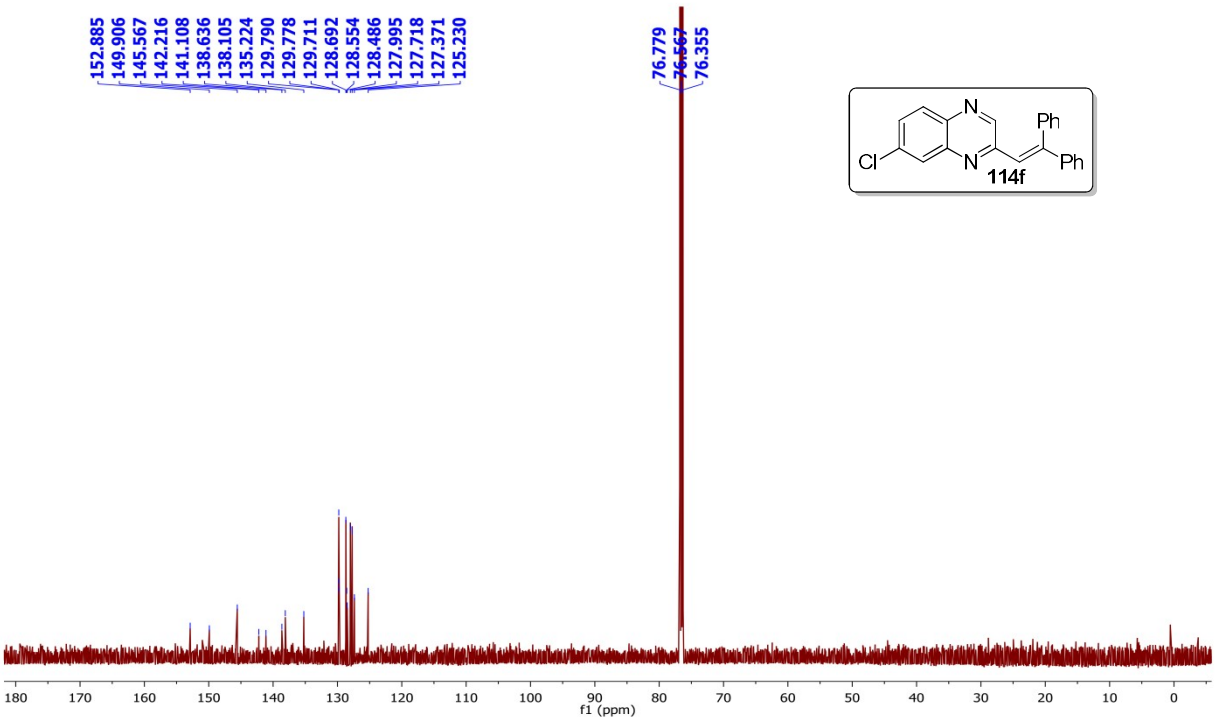
^{13}C{^{1}H} NMR (100 MHz) of **114e**:



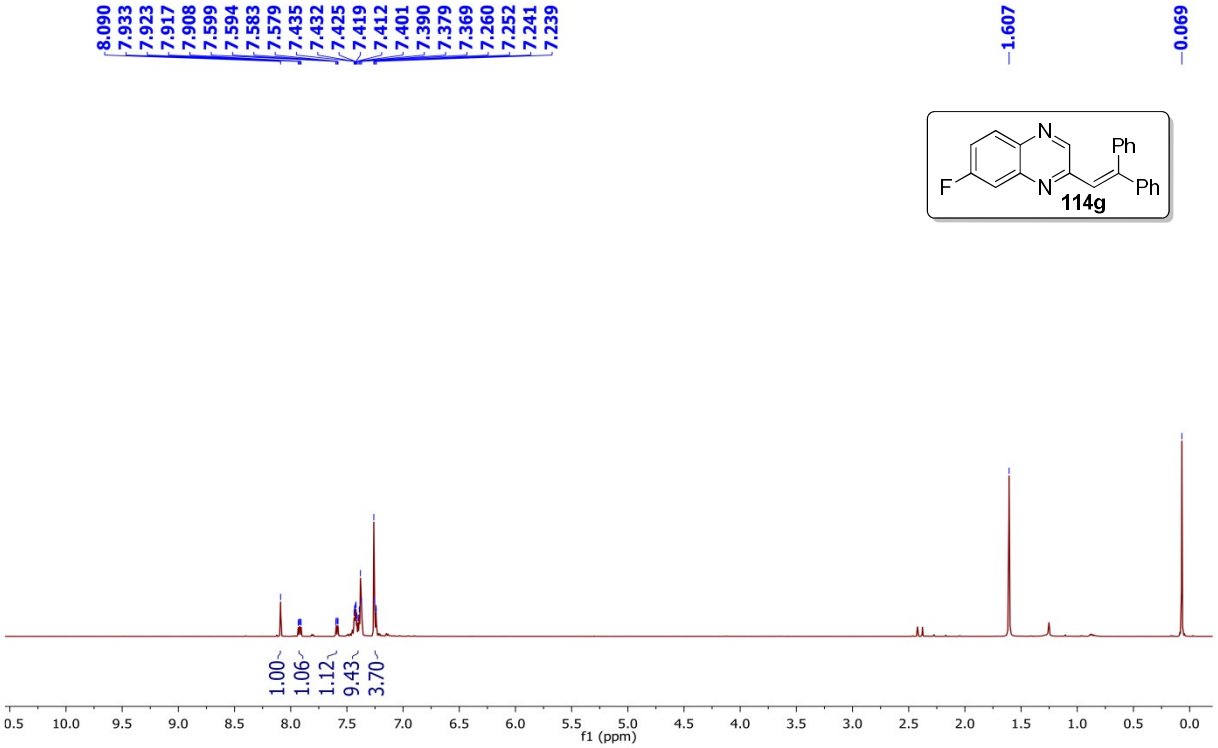
^{1}H NMR (600 MHz) of **114f**:



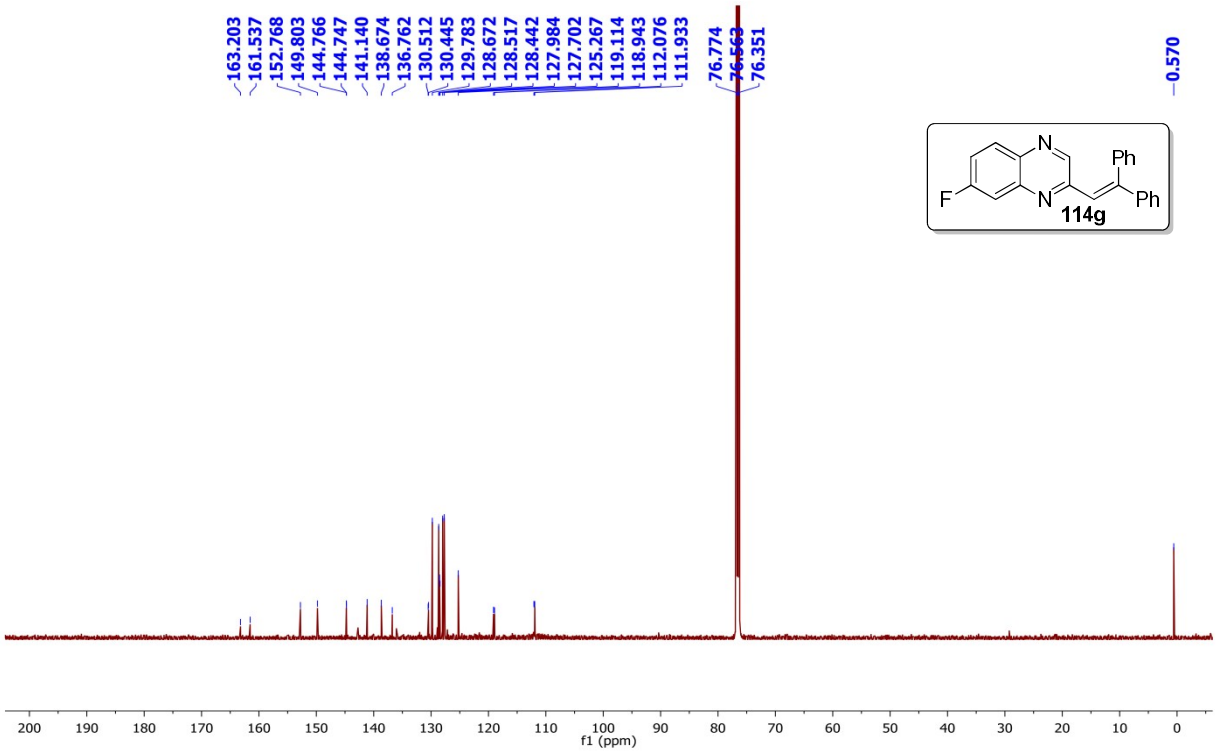
^{13}C{^{1}H} NMR (150 MHz) of **114f**:



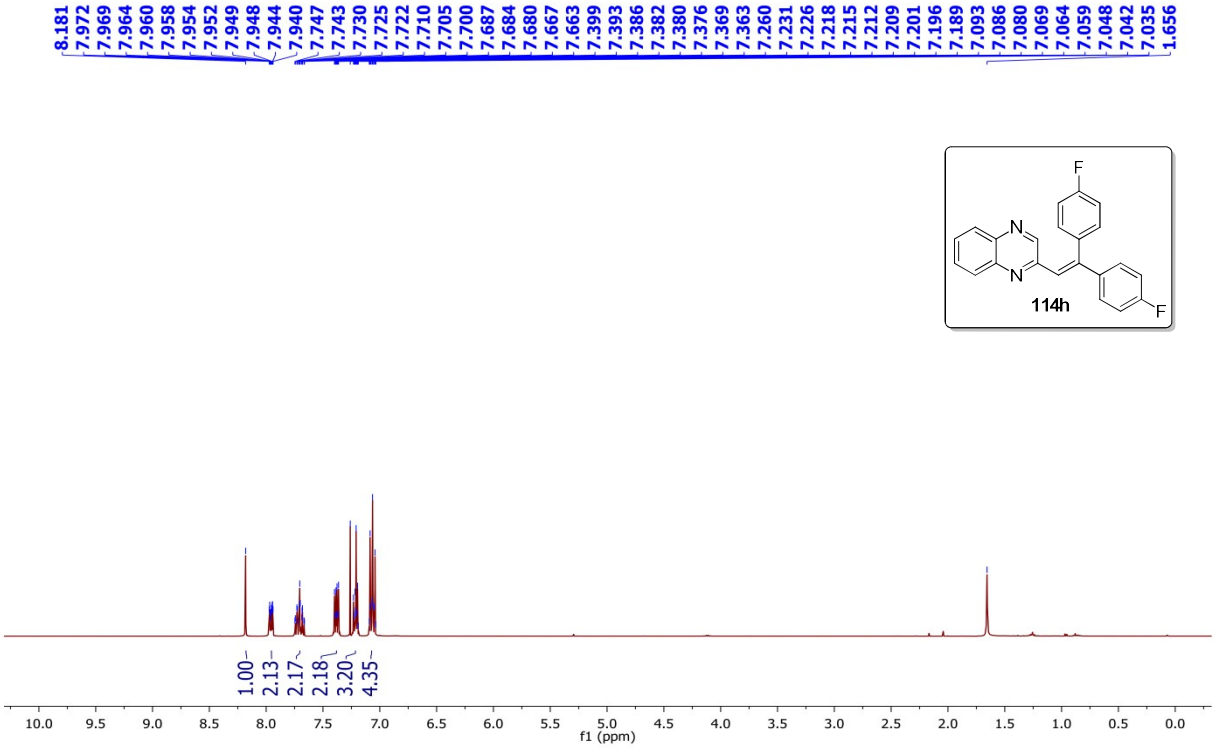
^{1}H NMR (600 MHz) of **114g**:



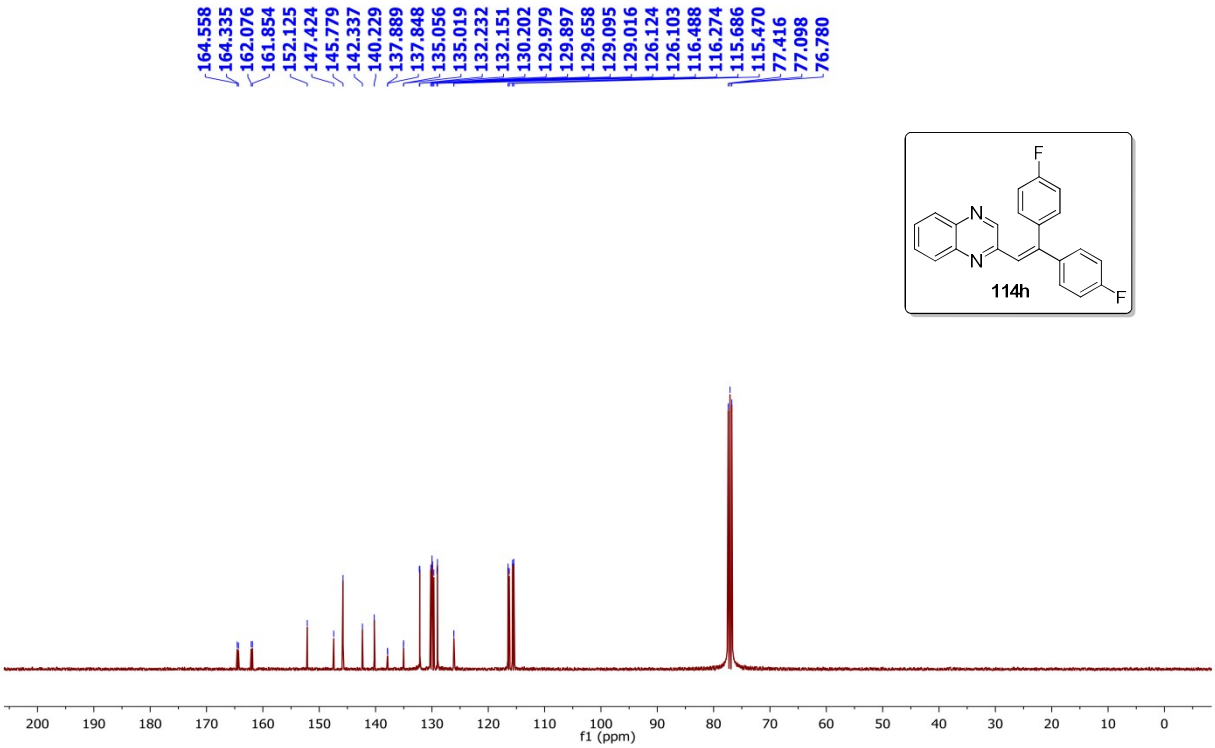
^{13}C{^{1}H} NMR (150 MHz) of **114g:**



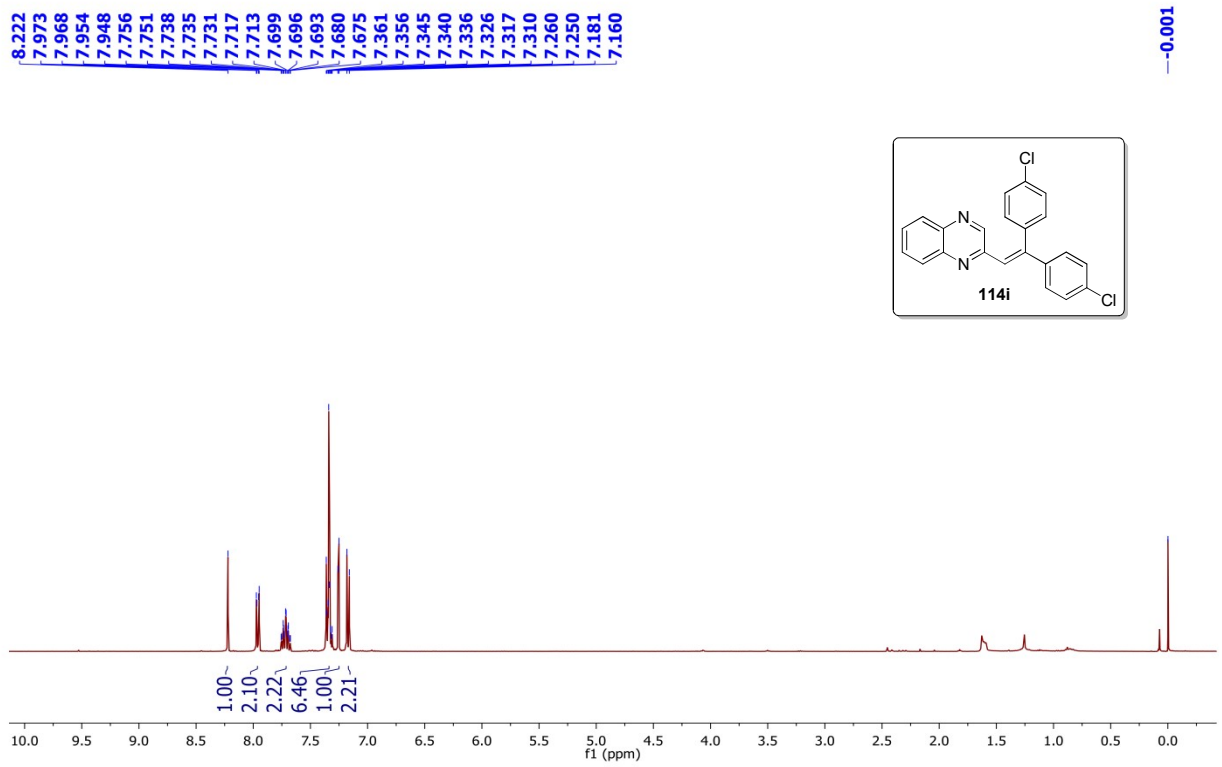
^{1}H NMR (400 MHz) of **114h**:



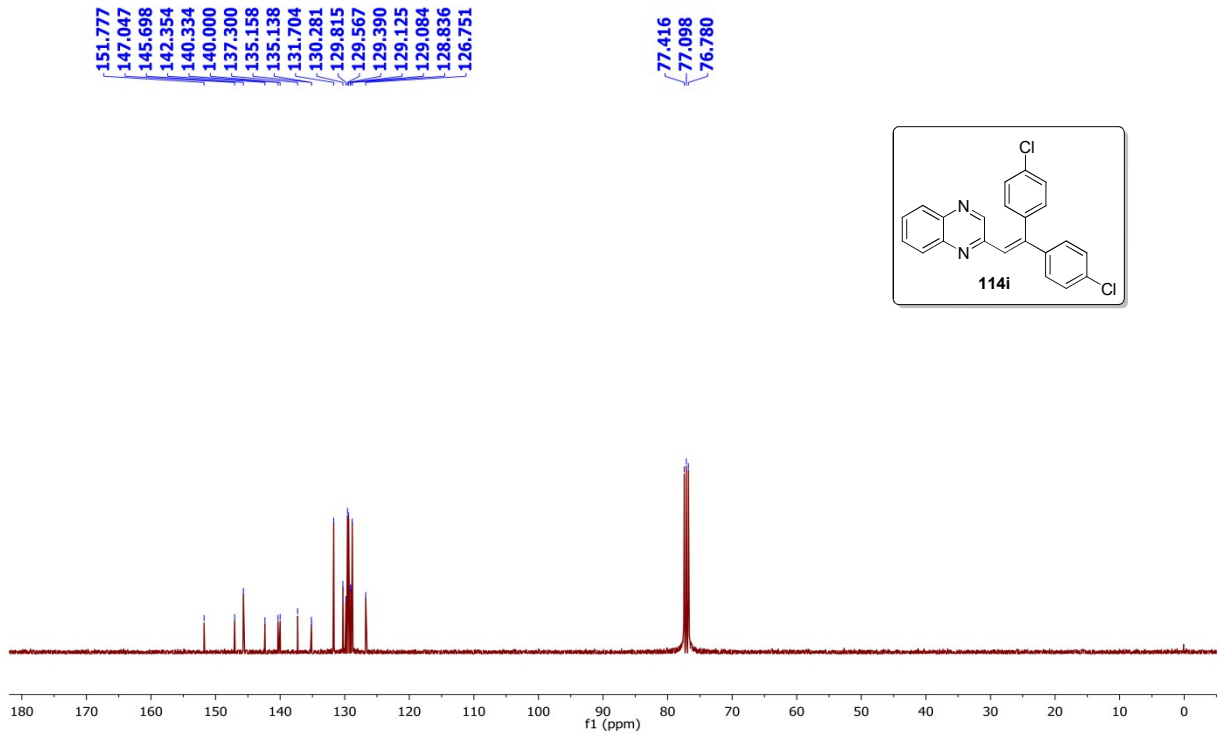
^{13}C{^{1}H} NMR (100 MHz) of **114h**:



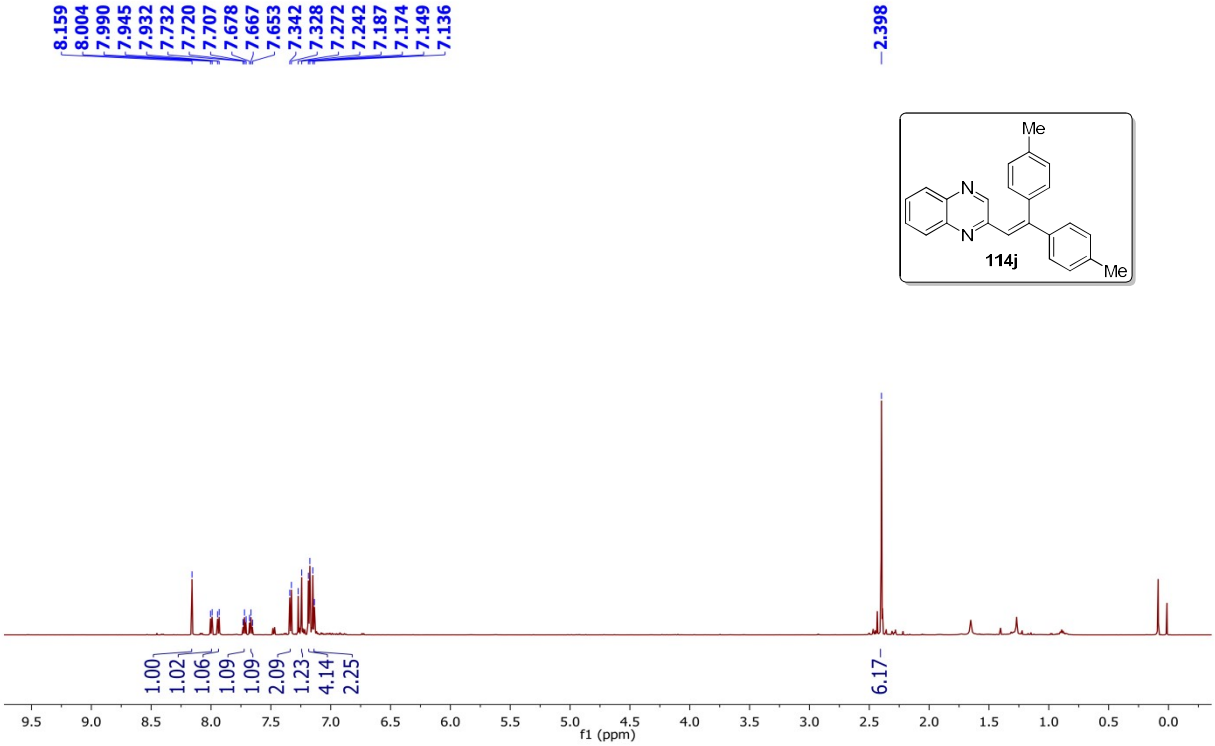
^{1}H NMR (400 MHz) of **114i**:



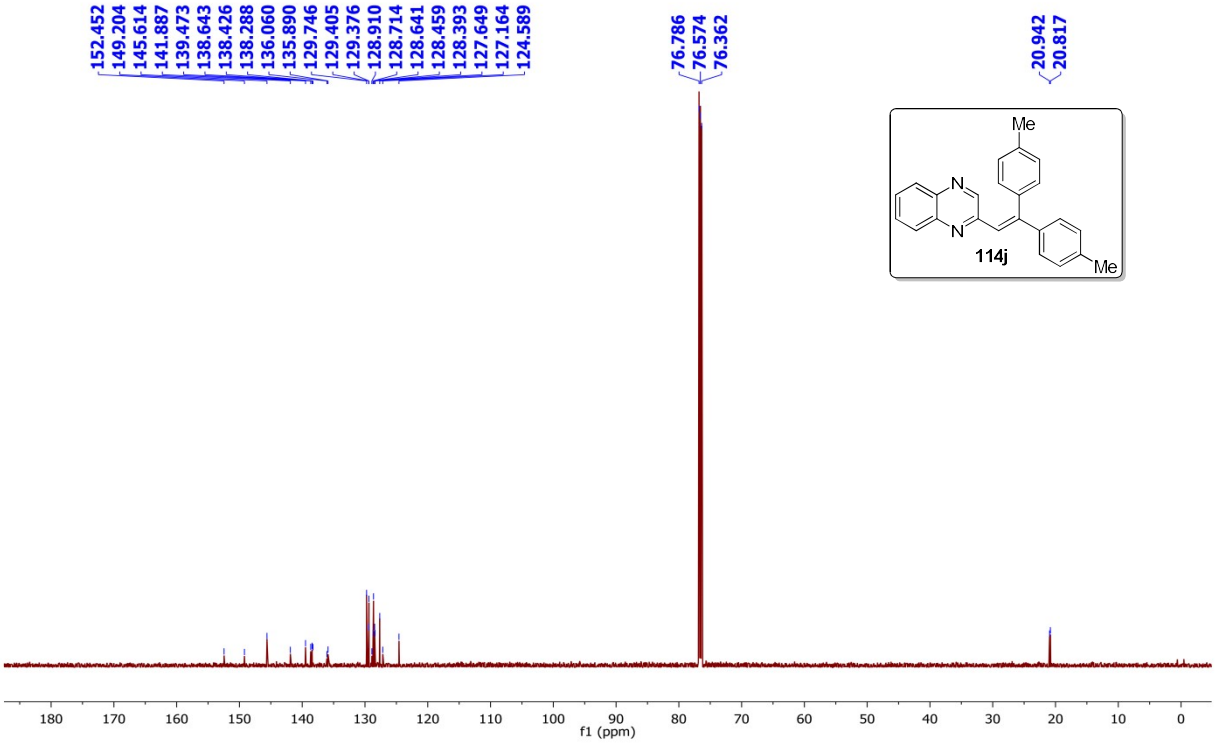
^{13}C{^{1}H} NMR (100 MHz) of **114i**:



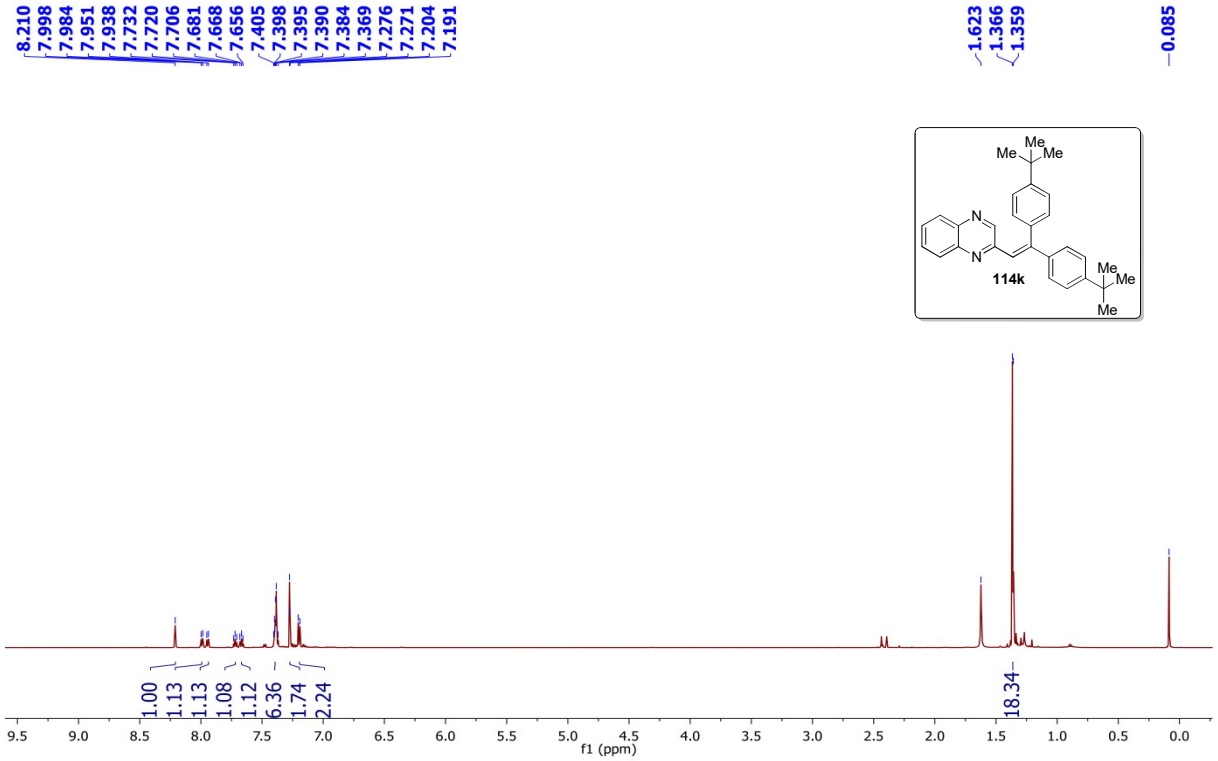
^{1}H NMR (600 MHz) of **114j**:



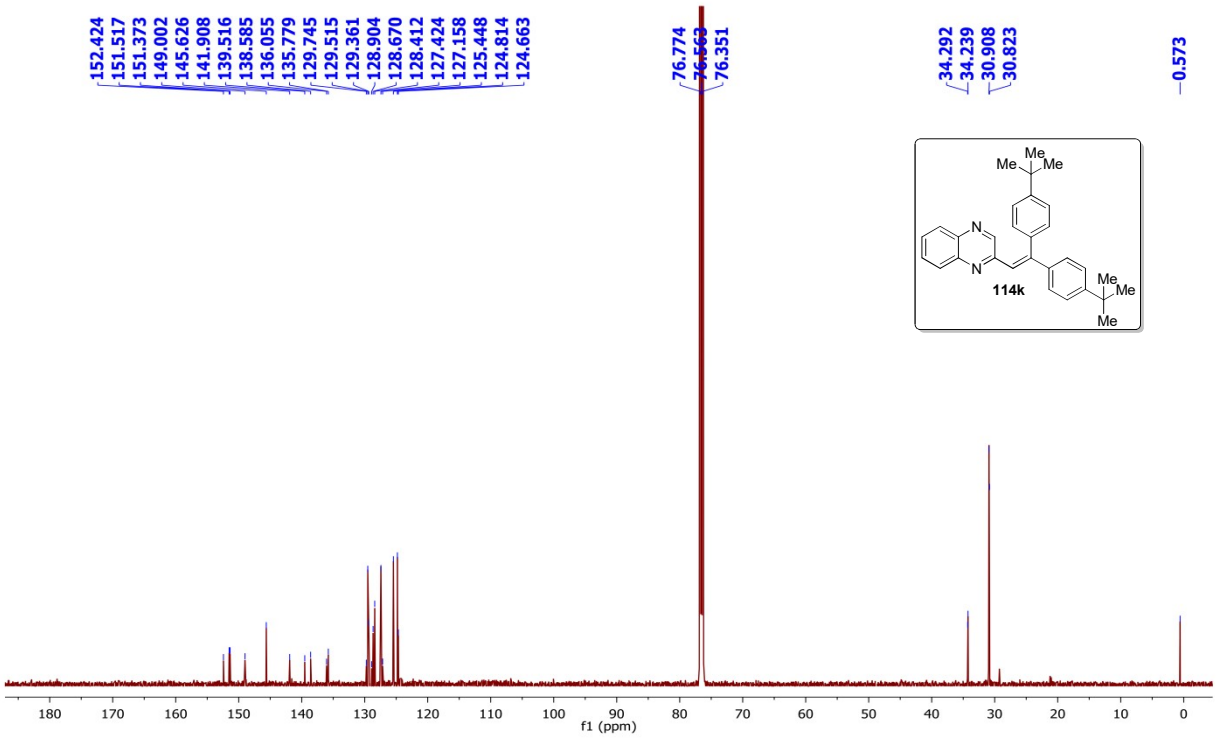
^{13}C{^{1}H} NMR (150 MHz) of **114j**:



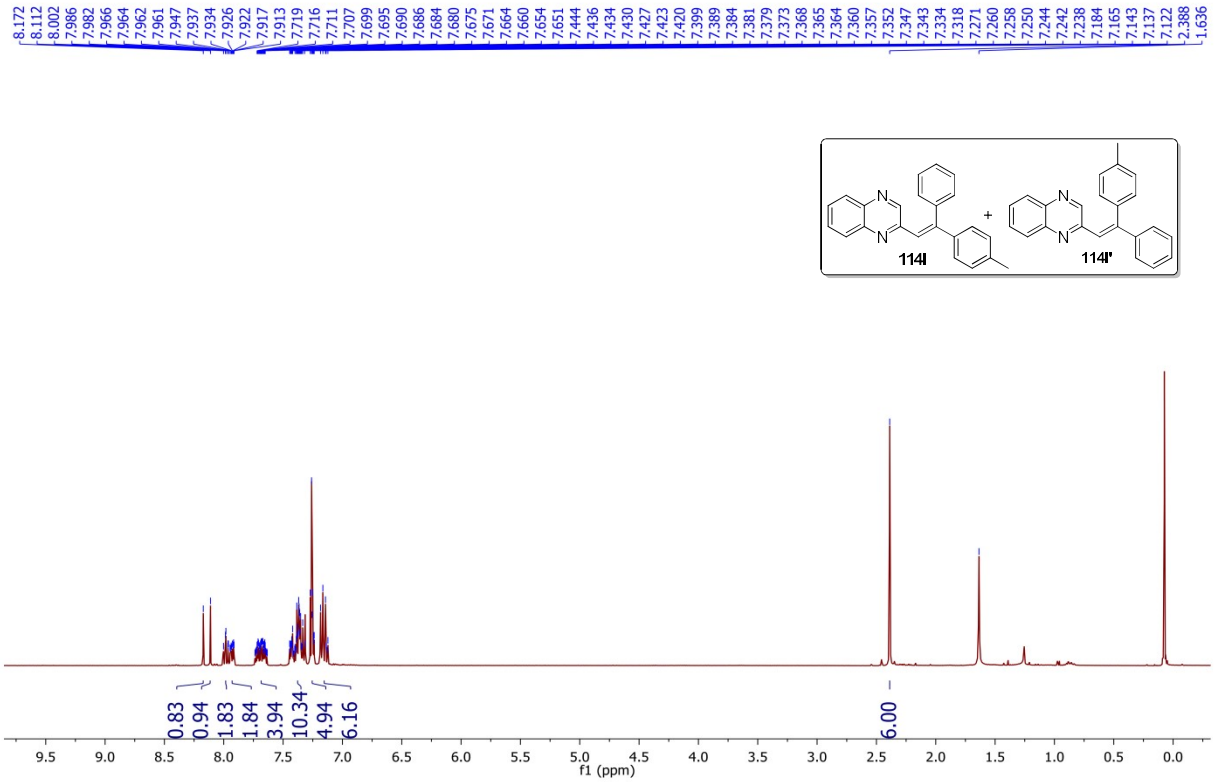
^{1}H NMR (600 MHz) of **114k**:



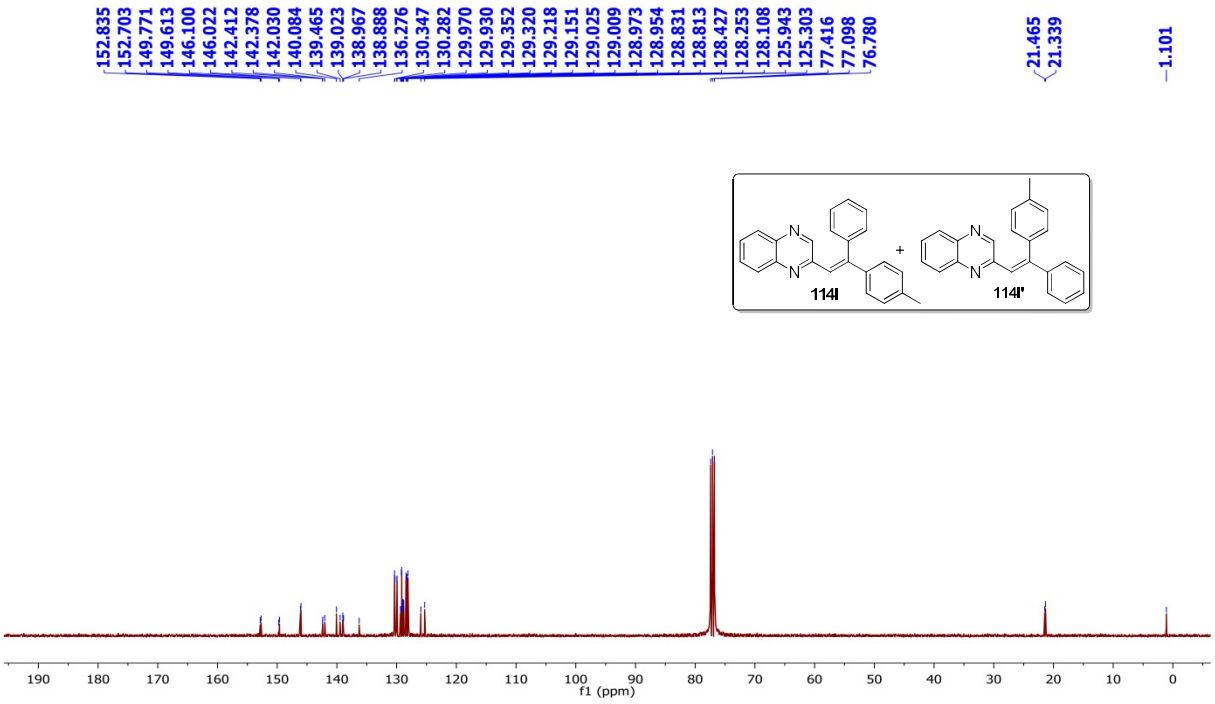
^{13}C{^{1}H} NMR (150 MHz) of **114k**:



^{1}H NMR (400 MHz) of **(114l:114l')**:



^{13}C{^{1}H} NMR (100 MHz) of **(114l:114l')**:



CHAPTER 3

Iron(III)-Catalyzed Carboannulations of Acetylenic Compounds: A Straightforward and General Synthesis of 4-(2,2-Diarylvinyl)quinolines and 4-(2,2-Diarylvinyl)-2*H*-chromenes Under One-pot

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Part I – A Short Review

3.1.1. Introduction: Quinoline a privileged heterocycle

3.1.1.1. Importance of Quinoline

Quinoline (**1**, Figure 1) is considered as an important and privileged class of heterocycles. Notably, the said structural moiety is prevalent as the key structural unit in large number of natural products, bioactive compounds, pharmaceuticals, and agrochemicals. [1] Many derivatives of quinoline found various applications in medicinal chemistry; e.g., *Tacrine* (**2,** Fig. 1) was the first drug approved for alzheimer's disease.[2] *Graveolinine* (**3,** Fig. 1) a natural alkaloid isolated from *Ruta graveolens L*. (Common Rue Herb) in the south of China[3a] shows potent antiplatelet aggregation activity[3b] and some of its derivatives also act as potential anti-alzheimer agents.[3c] *Tafenoquine* (**4,** Fig. 1) proved to be a promising antimalarial drug.[4] *TAS-103* (**5,** Fig. 1) is an anticancer[5a] agent with inhibitory effects on topoisomerases I and II and classified as a topoisomerase II-targeted drug.[5b] Besides, some 8-hydroxyquinolines are used as antifungals; [6] while their metal complexes are used in agriculture and healthcare.[7] Few 4-hydroxyquinolines act as histone acetyltransferase (HAT) inhibitors.[8] Moreover Some quinolines are also used as drug for the treatment of schizophrenia (PF-2545920)[9a] and as pain killer[9b](JTC-801).

Besides the medicinal importance they are also considered as an important molecule in material science due to their applications as electroluminescent materials,[10a] ligands,[10b-c] third generation photovoltaics,[10d] hole-transporter[10e] etc.

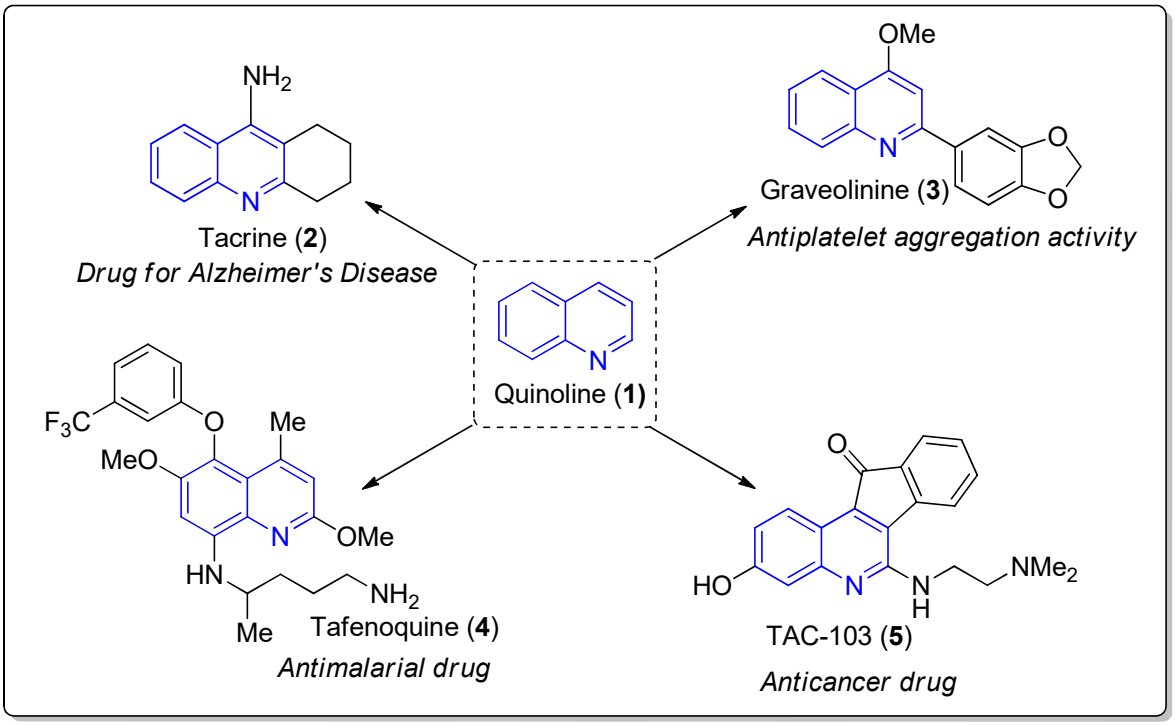


Figure 1: Some important quinoline derivatives

3.1.1.2. Importance of 4-Substituted Quinolines

Among the various quinoline derivatives, 4-substituted quinolines have received immense interests soon after the discovery of *quinine,* a potent anti-malarial agent[11a] (**6**, Figure 2) and these are used as template in medicinal chemistry[1g,11] for the development of many drugs; e.g. *chloroquinine* (**7,** Fig. 2) is a well-known antimalarial drugs.[11b-c] While *mefloquine* (**8,** Fig. 2) is another antimalarial and antibacterial drug.[12] Besides, some novel anilidoquinoline derivatives (**9,** Fig. 2) are reported to have significant antiviral activity (*in vitro*) and anti-apoptotic against Japanese encephalitis virus.[13] In addition, quinoline derivatives **10** (Fig. 2) and **11** (Fig. 2) are known as anti-tuberculosis[11d] and anti-cancer[1g] agent, respectively. Besides they also show inhibitory applications[1e,14] and act as antagonists,[15a] receptor ligands,[15b] e.g., EKB1 (**12,** Fig. 2) is a quinoline based EGFR-TK inhibitor.[1e] Some quinoline derivatives have also been used as antimicrobial agents.[16]

In addition to its bioactivity, they are also used as chemosensor,[17a] catalysts[17b] etc.

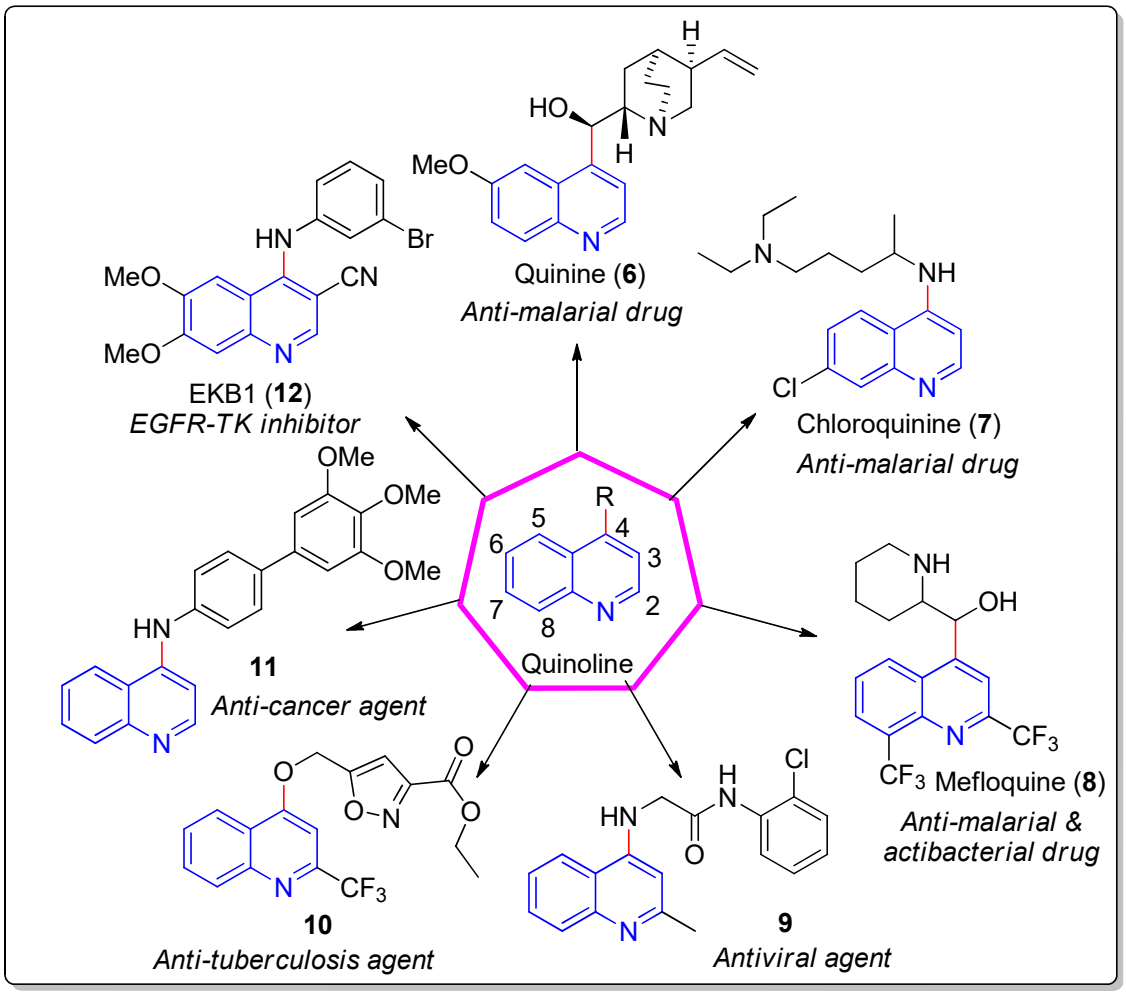


Figure 2. Some important 4-substituted quinoline derivatives

3.1.1.3. Importance of Quinolines Substituted (at C2 or C4) with Vinyl Group

Notably, quinolines having vinyl substitution (at C2 or C4 position) are also considered as important subclass of quinolines because of their therapeutic importance.

Among the various 2-vinyl substituted quinolines, few specific examples are: VUF 5017 (**13**, Figure 3) which acts as a potent *CysLT*$_1$ antagonist[18a] and quinoline derivative **14** (Fig. 3) act as potent anti-leishmanial agent.[18b] Besides, *Montelukast* (**15,** Fig. 3) is used as drug candidate against asthma being a leukotriene receptor antagonist.[18c] In addition, few styrylquinolines are also used as drugs for the treatment of HIV.[18d]

On the other hand, 4-vinyl quinolines also proved to be of interests due to their pharmacological profile. For example, 4-vinyl quinolines **16** (Fig. 3) is reported as PI3K$_\alpha$ inhibitors. [19] Furthermore, 4-vinyl substituted quinolines are also used as dyes,[20a] such as ethyl red (**17**, Fig. 2), quinoline blue (**18,** Fig. 2) beside their use as photosensitizers.[20b]

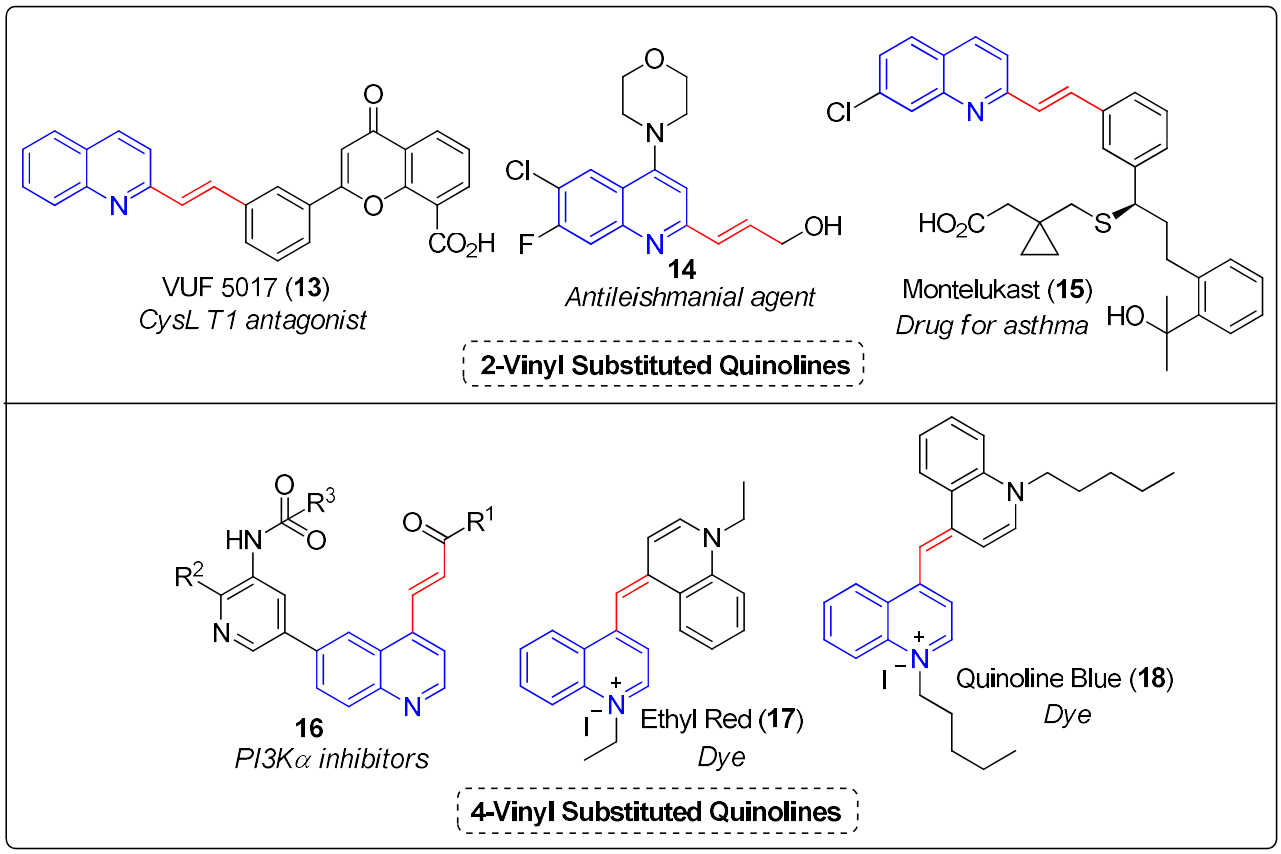


Figure 3. Some important vinyl-substituted (at C2 or C4) quinolines

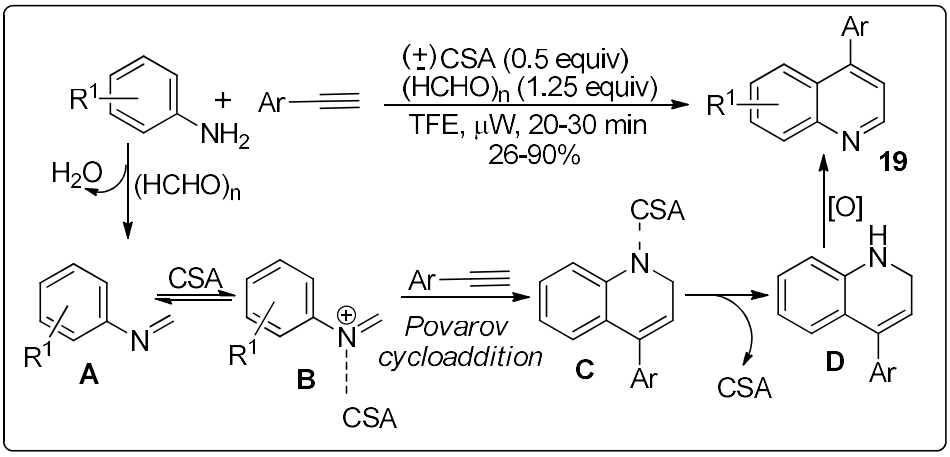
3.1.2. Synthesis of 4-substituted quinolines

In view of the immense importance of 4-substituted quinolines, many efforts have been made to achieve their synthesis. Scrutiny of the literature reveals that most of the reports on the synthesis of 4-substituted quinolines are based on cyclizations of acetylenic substrates under metal catalyzed and metal free conditions. Few of them are illustrated briefly.

3.1.2.1. Synthesis of 4-substituted quinolines through intermolecular cyclization of acetylinic substrates

3.1.2.1.1. Metal free methods for the synthesis of 4-substituted quinolines

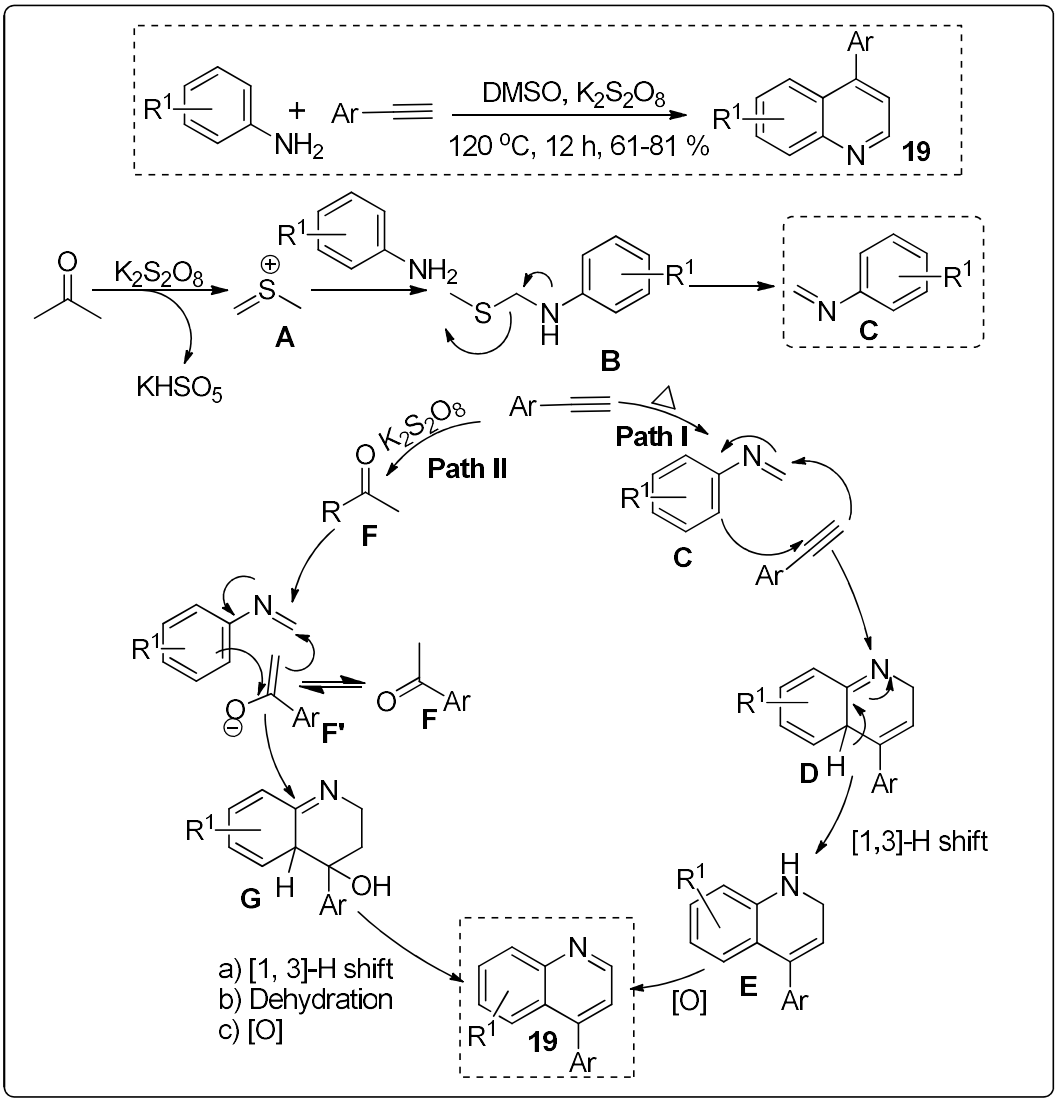
Sharma and coworkers[21] disclosed a convenient metal free approach for the synthesis of 4-aryl substituted quinolines **19** through *Povarov* type cycloaddition reaction where readily available and simple substrates (anilines, alkynes, paraformaldehyde and (±) camphor-10-sulfonic acid) were heated under microwave for 20-30 min (**Scheme 1**). The reaction is believed to proceed through the formation of an imine intermediate (**A**) by condensation of the aniline and paraformldehyde, which on coordination with CSA transforms into the activated imine form (**B**). Next *Povarov* type cycloaddition between the intermediate **B** and aryl acetylene affords intermediate **C**. Next, rapid release of CSA from intermediate **C** followed by oxidation delivers the desired 4-substituted quinoline **19**.



Scheme 1: Synthetic pathway for the formation of 4-substitued quinolines **19**

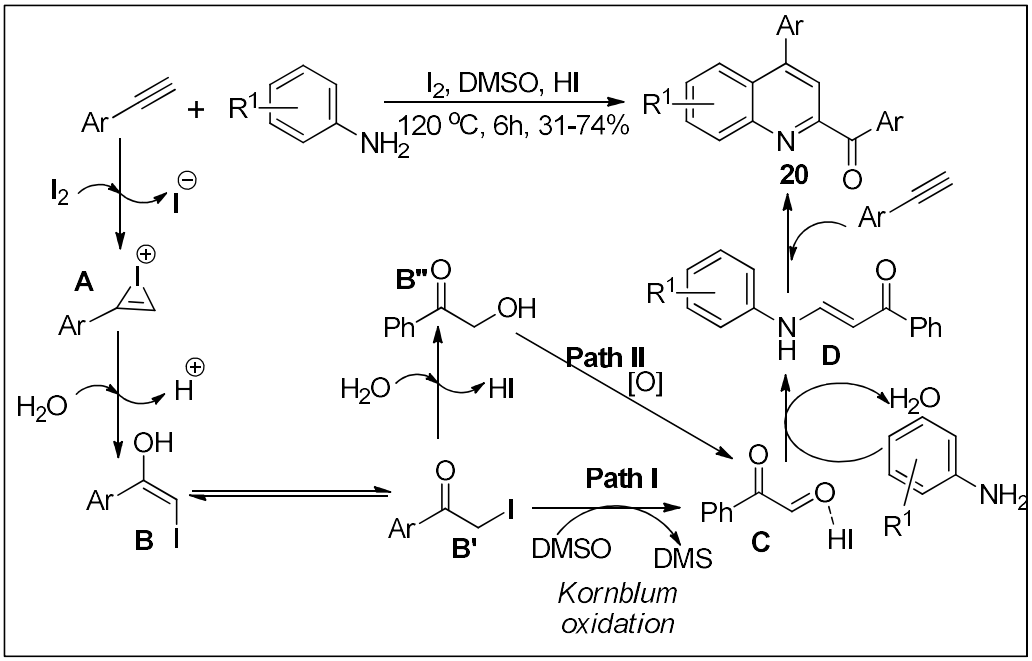
Tiwari and coworkers[22] disclosed another efficient metal free approach for the formation of 4-aryl substituted quinolines **19** (**Scheme 2**) from readily available substrates (anilines and acetylenes) in presence of DMSO and $K_2S_2O_8$ through one pot cascade reaction. Here DMSO is used as solvent as well as one carbon source thus providing a highly atom economic and environfriendly pathway. Mechanistically, firstly DMSO transform into the sulfenium ion (**A**) in presense of $K_2S_2O_8$ which further reacts with aniline to form the intermediate **B**. It then

undergoes demethylthiolation (-CH_3SH) to deliver the iminium intermediate **C**. Next the formation of the product **19** can occur in two pathways. In path **I,** intermediate **C** reacts with the alkyne in a *Diels-Alder* fashion through a [4 + 2] cycloaddition reaction to generate **D**, which undergoes [1,3]-*H* shift to convert into species **E**. Next, oxidation of **E** leads to the formation of the product **19**. Whereas, in path **II**, the alkyne is first oxidized into acetophenone **F** which subsequently enolizes to **F′**. Next nucleophilic attack of **F′** on the iminium intermediate **C** delivers intermediate **G**, which on subsequent [1,3]-*H* shift followed by dehydration and oxidation leads to the formation of product **19**.



Scheme 2: Schematic representation and mechanistic overview for the synthesis of product **19**

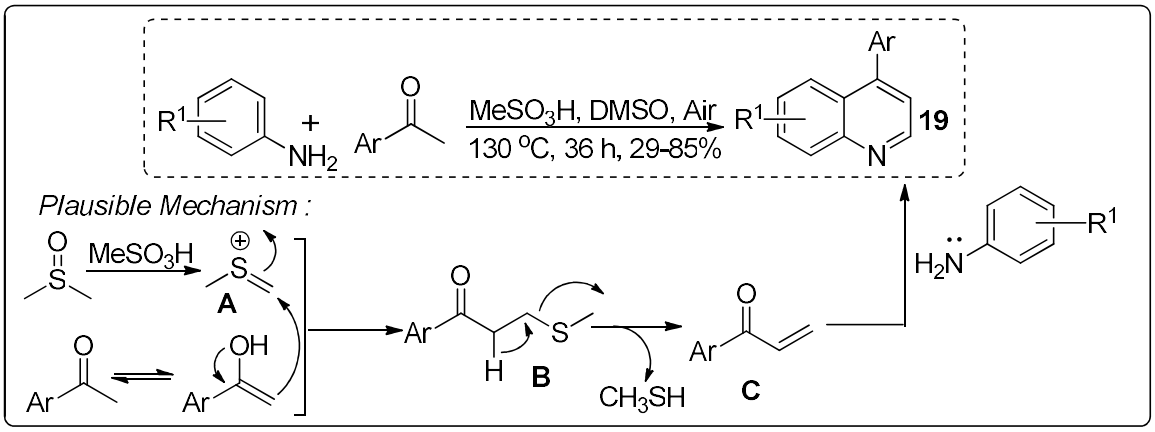
Yu *et al.*[23] disclosed a novel metal free synthetic route for the formation of wide ranges of 2,4-substituted quinolines **20** via novel I_2-mediated *Povarov reaction* of aryl acetylenes and anilines (**Scheme 3**). Here aryl acetylene plays dual role like diene precursor and dienophile as well. From the mechanistic point of view, at first I_2 reacts with aryl acetylene to generate a three membered cationic iodonium intermediate (**A**), which on reaction with water followed by isomerization is transformed into iodo-intermediate **B′**. Next, the transformation of **B′** to **C** can occur in two different pathways. In path I, **B′** can convert into **C** by *Kornblum oxidation*, whereas in path II, it can react with water to form intermediate **B′′** which on further oxidation delivers **C**. Next nucleophilic attack of aniline onto the intermediate **C** forms intermediate **D** which on further reaction with another molecule of aryl acetylene via *Poravov* cycloaddition generates **20**.



Scheme 3: Synthesis of product **20** with mechanistic rational

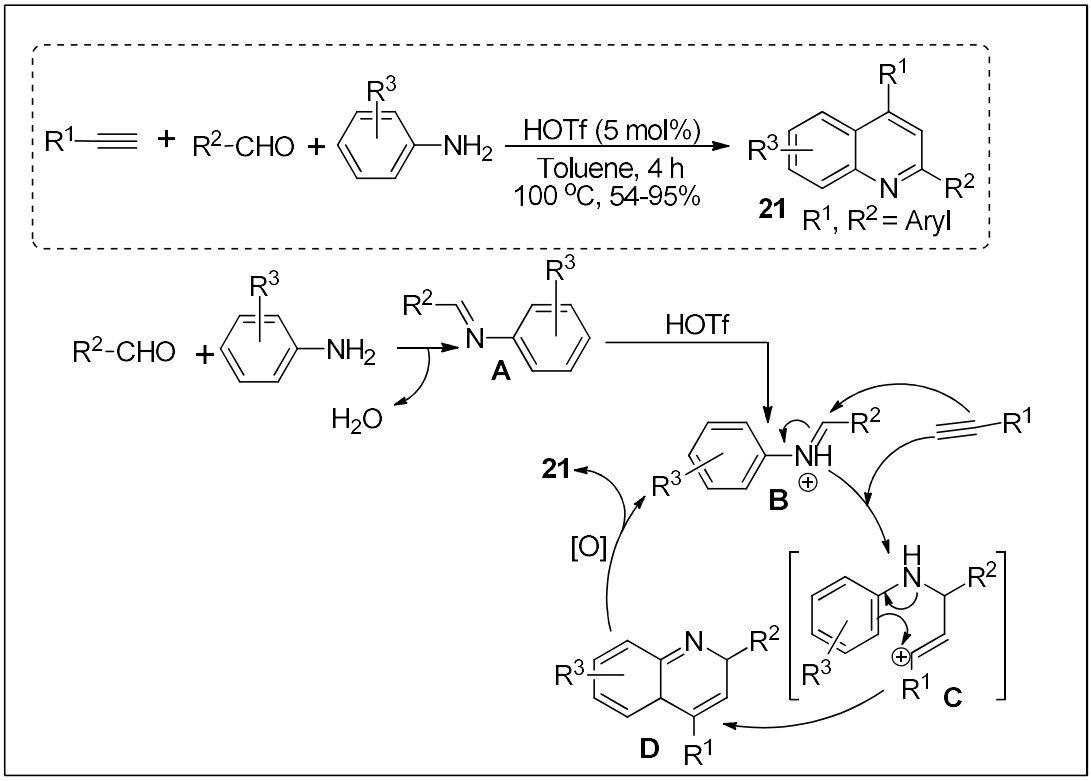
Jiang *et al.*[24] demonstrated a convenient metal free approach for the synthesis of 4-aryl substituted quinolines **19** (**Scheme 4**) via acid mediated reaction of aniline and acetophenone in DMSO under air. Similar to the previous report, here also DMSO acts as solvent as well as one carbon donor. According to the mechanism, at first, DMSO transforms into sulfenium ion (**A**) by the action of the brϕnsted acid ($MeSO_3H$). Species **A** then undergoes a nucleophilic attack by

the enolized form of acetophenone leading to the formation of intermediate **B**. Elimination of MeSH from the intermediate **B** delivers an enone intermediate **C** which on further nucleophilic attack by aniline followed by cyclization and oxidation delivers the product **19**.



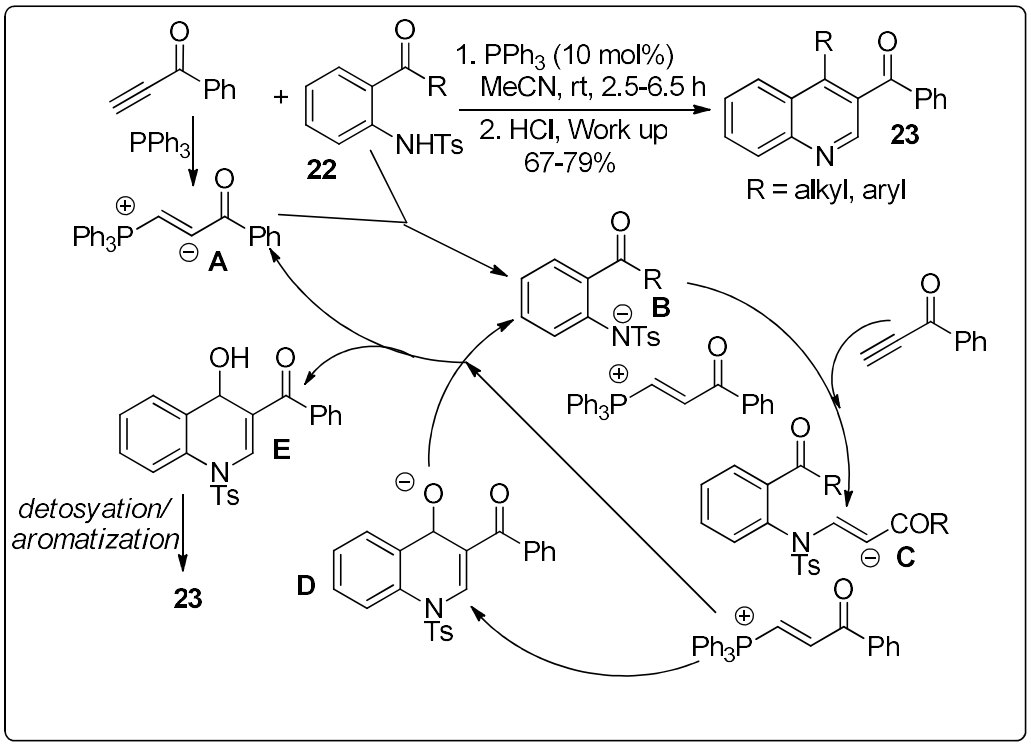
Scheme 4: Synthesis of 4-aryl quinoline **19**

Zhang and coworkers[25] disclosed a metal free approach for the synthesis of synthesis of 2,4 disubstituted quinolines **21**, in which HOTf-catalysed multi-component reaction was carried out in toluene at 100 °C as depicted under **Scheme 5**. Mechanistically, the reaction proceeds through the condensation of the respective amine and aldehyde leading to the formation of the imine intermediate (**A**) which on protonation forms intermediate **B**. Next, nucleophilic attack by the alkyne moiety onto **B** followed by carboannulation of the resulting transient intermediate (**C**) generates the species **D** which on rapid oxidation furnishes the desired product **21**.



Scheme 5: Formation of product **21** and plausible reaction mechanism

Kwon and coworkers[26] demonstrated another metal free reaction where synthesis of 3,4-disubstituted quinolines **23** (**Scheme 6**) is achieved from simple substrates like acetylenes and *o*-tosylamidophenones (**22**). Mechanistically, nucleophilic addition of the free phosphine to the activated alkyne results in the formation of phosphonium allenolate **A**, which acts as a base to activate the pro-nucleophile **22** through deprotonation and generate intermediate **B**, which upon subsequent base-catalyzed *Michael/aldol* reaction affords **D**. Next, protonolysis of **D** provides intermediate **E** which on further detosyation/aromatization affords the product **23**.



Scheme 6: Synthesis and plausible reaction mechanism for the synthesis of **23**

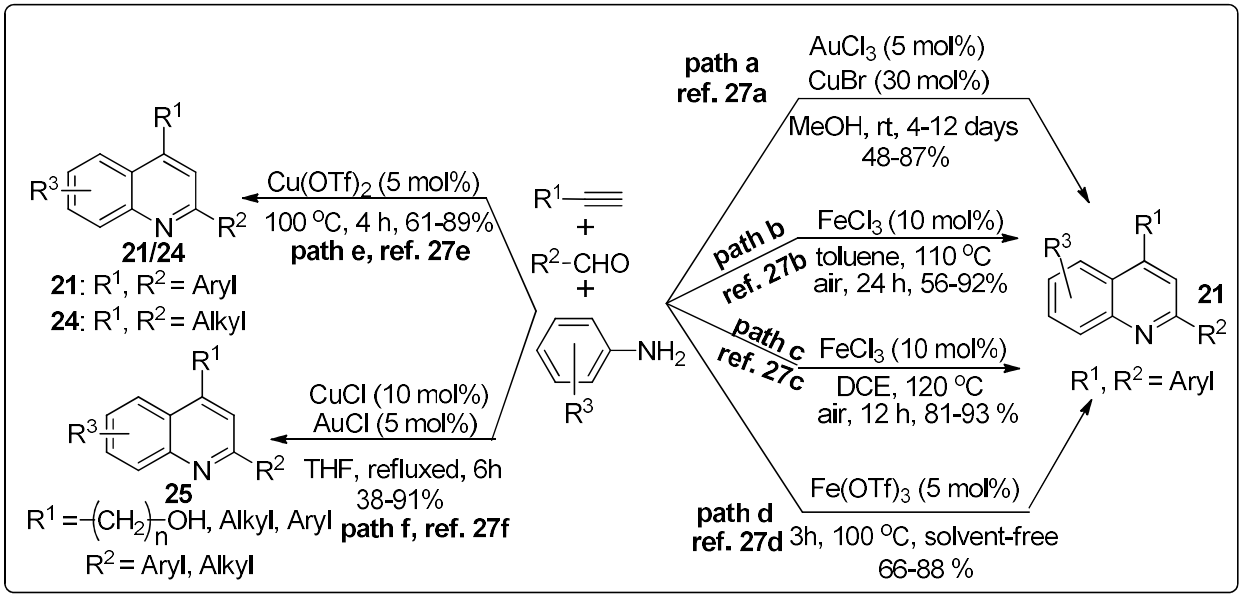
3.1.2.1.2 Metal catalyzed methods for the synthesis of 4-substituted quinolines

Wang and coworkers[27a] reported a one pot facile atom economic sequential catalytic process for the synthesis of 2,4-diarylquinolines **21** (**Scheme 7,** path a) in presence of $AuCl_3$/CuBr-catalyzed (*Alkyne-Aldehyde-Amine*) A^3 coupling reaction.

In 2009, **Tu** and coworkers[27b] first disclosed an efficient iron (III)-catalyzed synthesis of **21** (**Scheme 7,** path b) by formation of carbon–carbon bond via the activation of a terminal alkyne C–H. In continuaion to this work, **Wang** and coworkers[27c] and **Yao** and coworkers[27d] demonstrated a modified version of this report (**Scheme 7**, path c and path d respectively). Specifically, the later one reported an eco-friendly and convenient solvent-free method for the green synthesis of 2,4-diarylquinolines **21** (**Scheme 7,** path d).

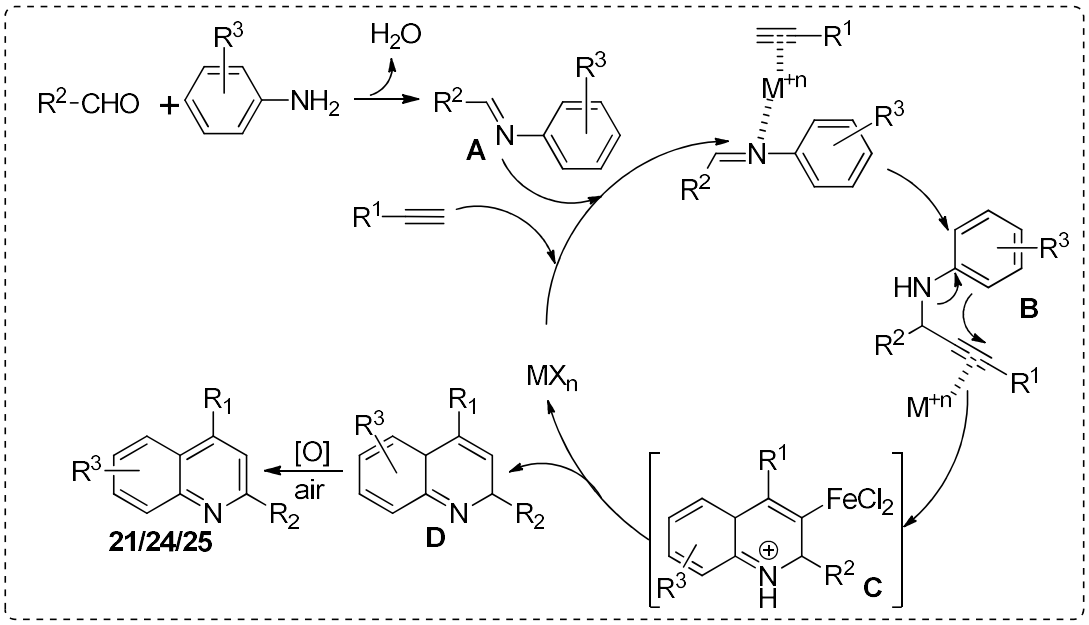
Larsen and coworkers *et al.*[27e] illustrated another solvent free green pathway for the formation 2,4-diarylquinolines **21** and 2,4-dialkyllquinolines **24** via Cu(II)-catalyzed cyclization (**Scheme 7,** path e).

Jiang *et al.*[27f] disclosed a new method based on (*Alkyne-Aldehyde-Amine*) A^3 coupling reaction to construct 4-hydroxalkyl-quinoline derivatives via Cu(I) and Au(I) sequential catalyzed cyclizations of anilines with aldehyde derivatives and aliphatic alkynes, respectively. The three-component cascade reaction provides an efficient approach for easy access to various new 4-alkyl substituted quinoline derivatives **25** (**Scheme 7,** path d).



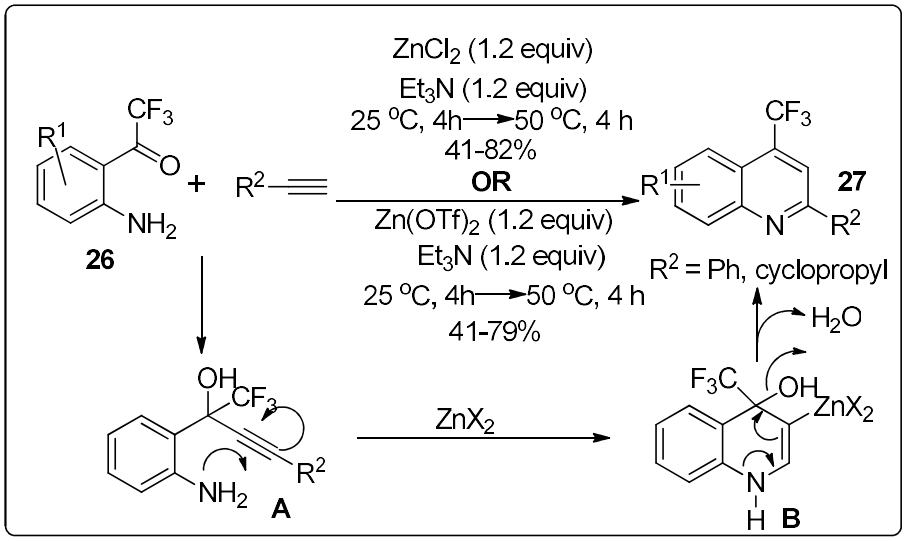
Scheme 7: Various approaches for the synthesis of 4-substituted quinolines **21**, **24** and **25**

A plausible mechanism overview for the formations of products **21**/**24**/**25** is depicted in **Scheme 8**. The reaction proceeds through a tandem condensation of the respective aldehyde and amine delivering an imine intermediate **A**. Next, coordination of the metal catalyst with the aforesaid imine moiety of intermediate **A** and alkyne moiety followed by the attack of the imine by activated phenylacetylene leads to the formation of propargylamine **B**, which upon intramolecular hydroarylation produces dihydroquinoline intermediate **D,** the rapid aerial oxidation of which finally generates the products **21/24/25** with moderate to excellent yields.



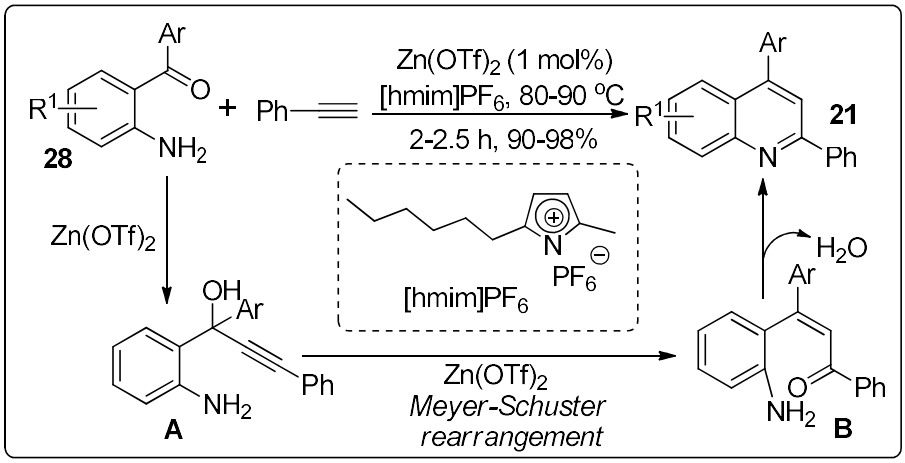
Scheme 8: A plausible reaction mechanism for the synthesis of quinolines **21/24/25**

Jiang and cowokers[28] disclosed an efficient one-pot tandem route towards the synthesis of 4-trifluoromethyl substituted quinoline derivatives **27** (**Scheme 9**) through Zn(II)-mediated alkynylation-cyclization of *o*-trifluoroacetyl anilines **26** and alkyne. The reaction proceeds through nucleopholic attack of the activated triple bond (by the metal catalyst acting as a Lewis acid) to *o*-trifluoroacetyl aniline **26** resulting in the formation of intermediate **A,** which upon intramolecular cyclization forms another intermediate **B**. Furthermore, the protonolysis and dehydration of **B** leads to the formation of the desired product **27** with moderate to excellent yield. The reaction shows high compatibility with diverse range of functional groups.



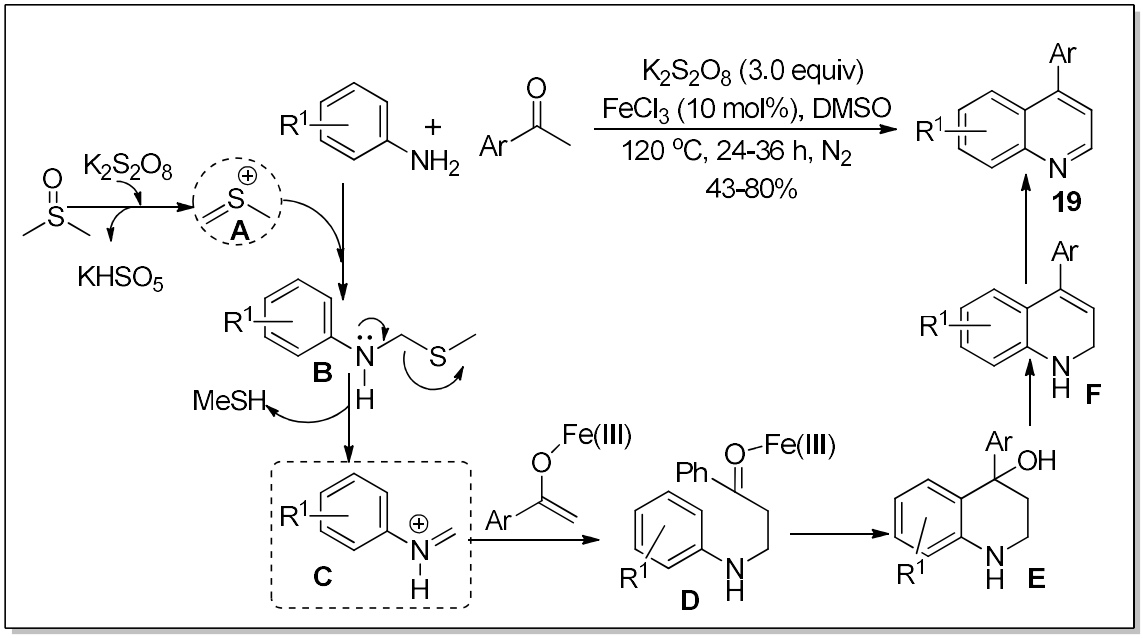
Scheme 9: Synthesis of product **27** and plausible mechanism

Sarma *et al.*[29] reported an another improved and eco-friendly method for the synthesis of 2,4-diarylsubstituted quinolines **21** (**Scheme 10**) via *Meyer–Schuster rearrangement* of 2-aminoaryl ketones **28** and phenylacetylenes in the presence of zinc trifluoromethanesulfonate in [hmim]PF_6 in excellent yields. According to the mechanism, it seems likely that the reaction proceeds through the formation of intermediate **A** by the alkynylation of the 2-aminoaryl ketone with phenyl acetylene which undergoes a *Meyer–Schuster rearrangement* followed by cyclization resulting in the formation of the product **21**.



Scheme 10: Synthesis of product **21**

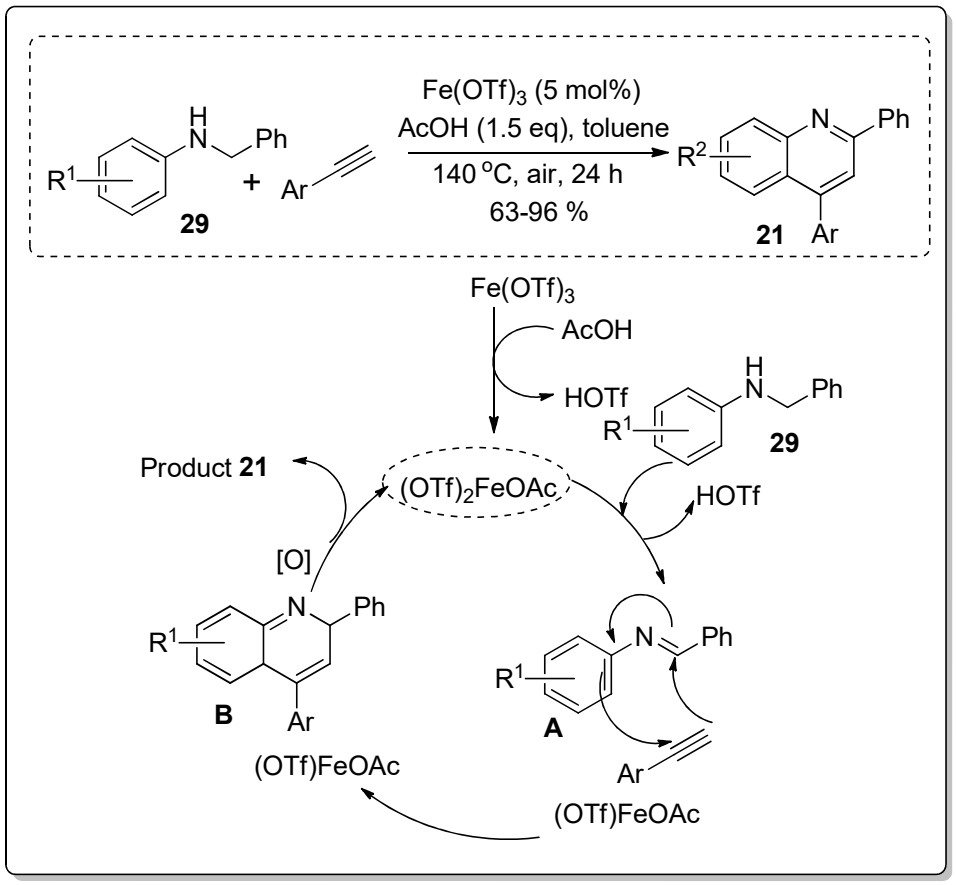
Singh and coworkers[30] demonstrated an efficient strategy toward the formation of 4-arylquinolines **19,** (**Scheme 11**) from readily available precursors (anilines and ketones) through $K_2S_2O_8$ mediated oxidative annulations involving DMSO. Mechanistically, the reaction proceeds with the formation of an sulfenium intermediate **A** from DMSO and $K_2S_2O_8$, which on subsequent nucleophilic attack by the aniline moiety followed by elimination of MeSH leads to the formation of the iminium intermediate **C**. On the other hand, aryl ketone transforms into enol form with the aid of Fe(III) catalyst; this enol undergoes a nucleophilic attack onto the intermediate **C** thereby forming the species **D**. Finally, intramolecular carboannulation of **D** followed by subsequent dehydration and oxidation affords the product **19**.



Scheme 11: Schematic representation for the synthetic approach towards product **19**

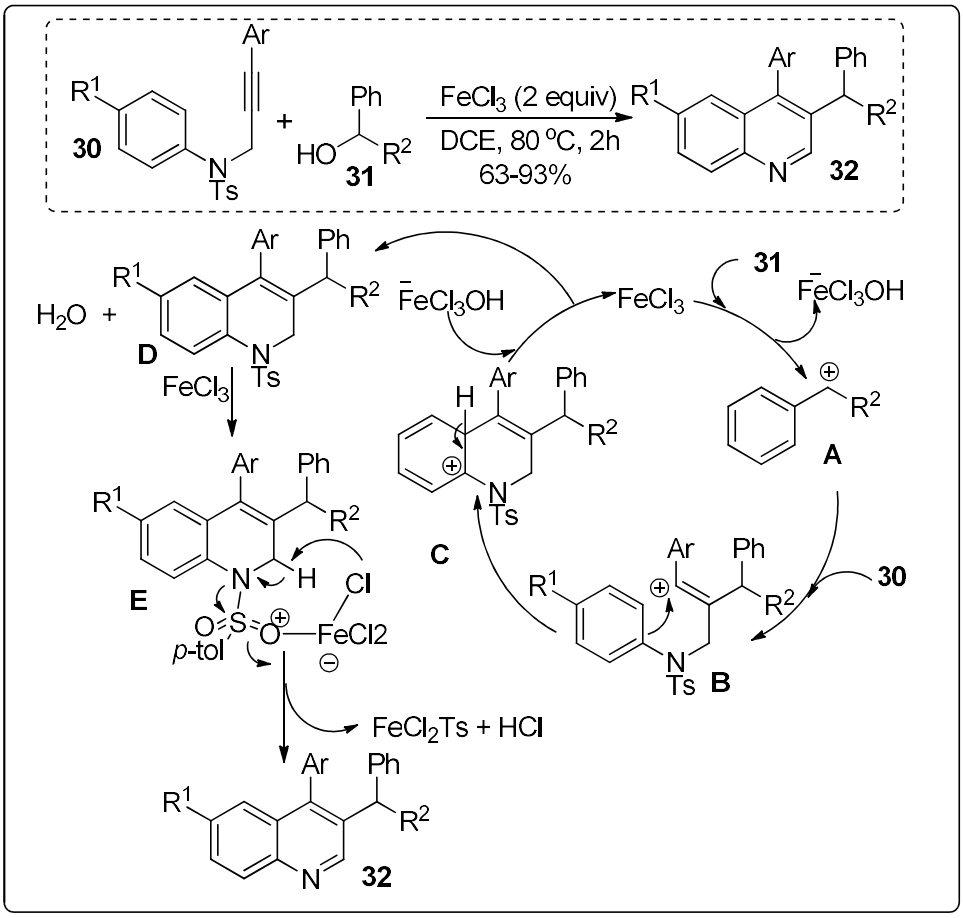
Yang *et al.*[31] reported the first acid-promoted and iron-catalysed dehydrogenative [4 + 2] cycloaddition reaction between *N*-benzylanilines **29** and aryl acetylenes in presence of air and acetic acid resulting in formation of 2,4 disubstituted quinolines **21** (**Scheme 12**). Here air act as terminal oxidant and acid as co-catalyst. Mechanistically, at first, an active catalytic species $(OTf)_2FeOAc$ is generated from the ligand exchange reaction in between $Fe(OTf)_3$ and AcOH; $(OTf)_2FeOAc$ then triggers an oxidative dehydrogenation of aniline derivative resulting in the formation of an imine intermediate (**A**) and intermediate (OTf)FeOAc with release of HI. Next,

a [4 + 2] cycloaddition of the imine with the alkyne leads to the formation of intermediate **B** which upon arial oxidation delivers product **21** and $(OTf)_2FeOAc$ which keeps the catalytic system alive.



Scheme 12: Synthesis of product **21**

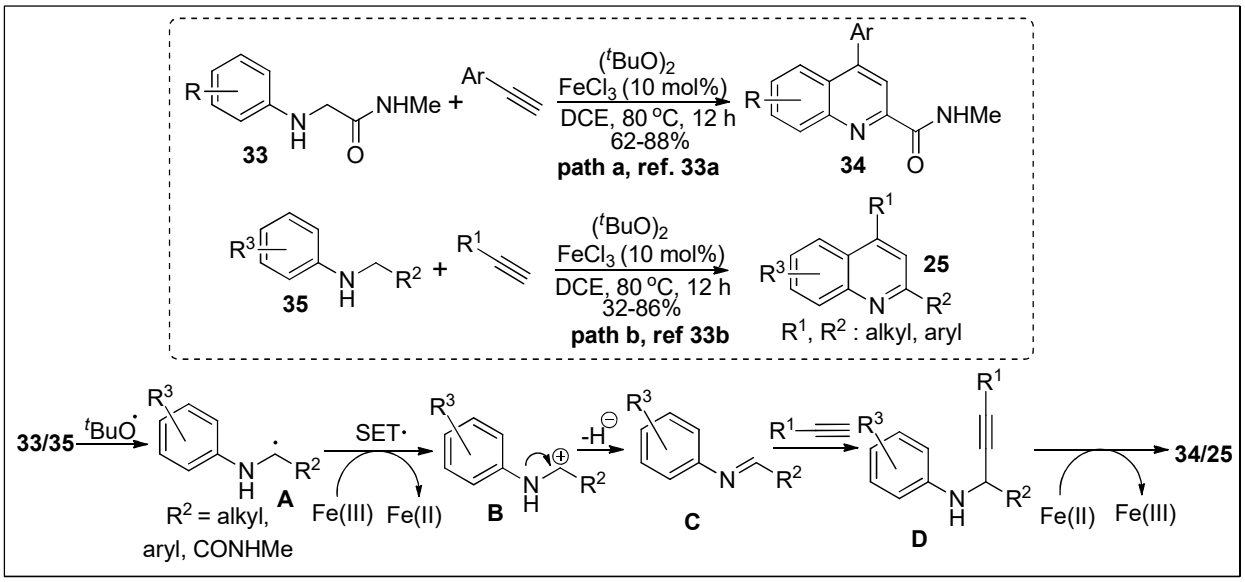
Jana and coworkers[32] demonstrated a straightforward and efficient approach for the synthesis of 3,4 disubstituted quinolines **32** (**Scheme 13**) from *N*-propargyl anilides **30** and π-activated alcohols **31** via Fe(III) catalyzed carboannulation followed by Fe(III) mediated detosylation and aromatization. The products were delivered within 2 h with high yields. According to the mechanism, Fe(III) first reacts with the π-activated alcohol **31** to generate a benzylic carbocation **A**, which on reaction with the alkyne moiety of **30** generates a more stable aryl substituted vinyl carbocation **B**. Next, intramolecular carboannulation of **B** produces **C** which upon deprotonation leads to the formation of dihydroquinolines **D**. Finally $FeCl_3$ promoted detosylaytion of **D** affords the product **32**.



Scheme 13: Synthesis of product **32** and plausible reaction mechanism

Liu *et al.*[33a] disclosed a simple, efficient one pot synthesis of 2, 4-disubstituted quonolines **34** (**Scheme 14**, path a) via iron-catalyzed oxidative C–H/C–H coupling reactions of simple *N*-aryl glycines **33** and aryl acetylene. In continuation to the aforesaid method, **Liu** *et al.*[33b] reported another work for the synthesis of **25** via iron-catalyzed oxidative coupling reactions from simple N-alkyl anilines **35** (**Scheme 15**, path b) and mono substituted alkynes. In both cases, the reaction proceeds through a single electron transfer (SET) mechanism. Mechanistically, the reaction initiates through the generation *tert*-butoxyl radical by iron-catalysed decomposition of $(^{t}BuO)_2$ followed by abstraction of a hydrogen atom from the *N*-aryl/alkyl derivatives (**33**/**35**) to form radical **A**. Single electron transfer from **A** leads to the formation of the iminium ion **B,** which upon deprotonation transforms into imine **C**. Subsequent nucleophilic attack of the alkyne on **C** generates **D**, which undergoes an intramolecular *Friedel–*

Crafts reaction followed by oxidation of iron catalyst [Fe(II) to Fe(III)] by excess (^{t}BuO)$_2$ furnishing the products **34/25**.



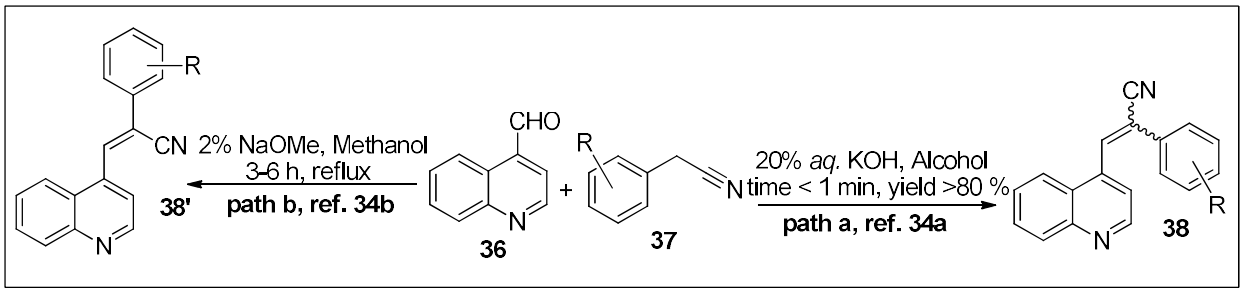
Scheme 14: Synthetic route for the formation of products **25** and **34**

3.1.2.2 Synthesis of 4-vinyl substituted quinolines

Among the 4-substituted quinolines, 4-vinyl quinolines are less explored. Surprisingly there are only few methods for their general synthesis and most are reported adopting classical reactions carried out under harsh reaction conditions requiring long reaction times. Few of these are illustrated briefly below.

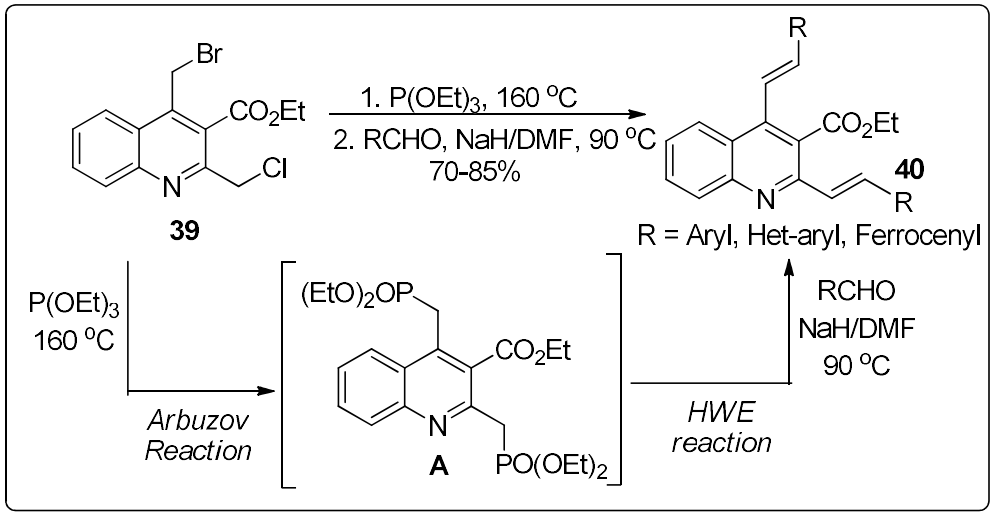
In 1952, **Phillips** *et al*.[34a] reported the synthesis of *α*-(substituted-phenyl)-*β*-(4-quinolyl)-acrylonitriles **38** (**Scheme 15**, path a) via rapid condensations of cinchoninaldehyde **36** and phenylacetonitriles **37** in presence of 20% *aq.* KOH in alcohol. The products formed within less than a minute with high yields (>80 %).

Crooks and coworkers[34b] disclosed another synthetic pathway for the synthesis of few 4-quinolyl-cyanostilbenes **38′** (**Scheme 15**, path b) via the condensation of **36** and **37** in presence of 2% NaOMe in methanol under refluxing conditions.



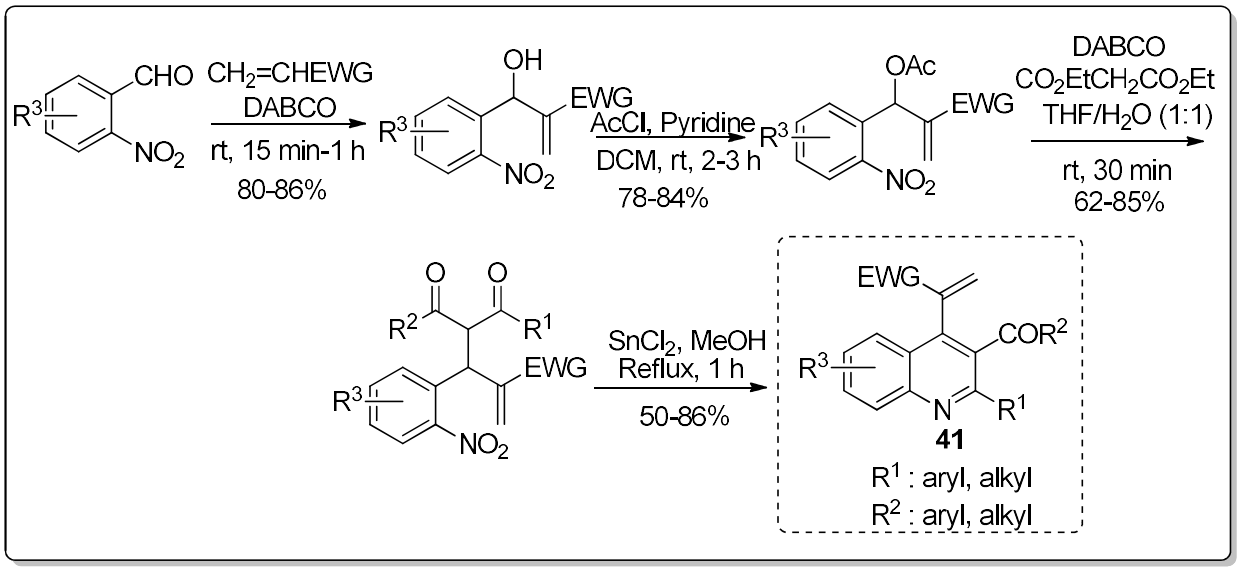
Scheme 15: Synthesis of products **38** and **38′**

Li and coworkers [35] disclosed the first synthetic pathways for the one-pot synthesis of 2,4-bis((*E*)-styryl)quinoline-3-carboxylate derivatives **38** (**Scheme 16**) in good yields via successive *Arbuzov*/*Horner–Wadsworth–Emmons* (HWE) reaction using ethyl 4-(bromomethyl)-2-(chloromethyl)quinoline-3-carboxylate (**39**) as the substrate. The route affords wide range of products with high yield. Mechanistically the reaction is completed in two steps. First, *Arbuzov reaction* of the starting compound **39** and $P(OEt)_3$ produces the intermediate **A** which on subsequent *Horner–Wadsworth–Emmons* (HWE) reaction with an aldehyde affords the desired product **40**.



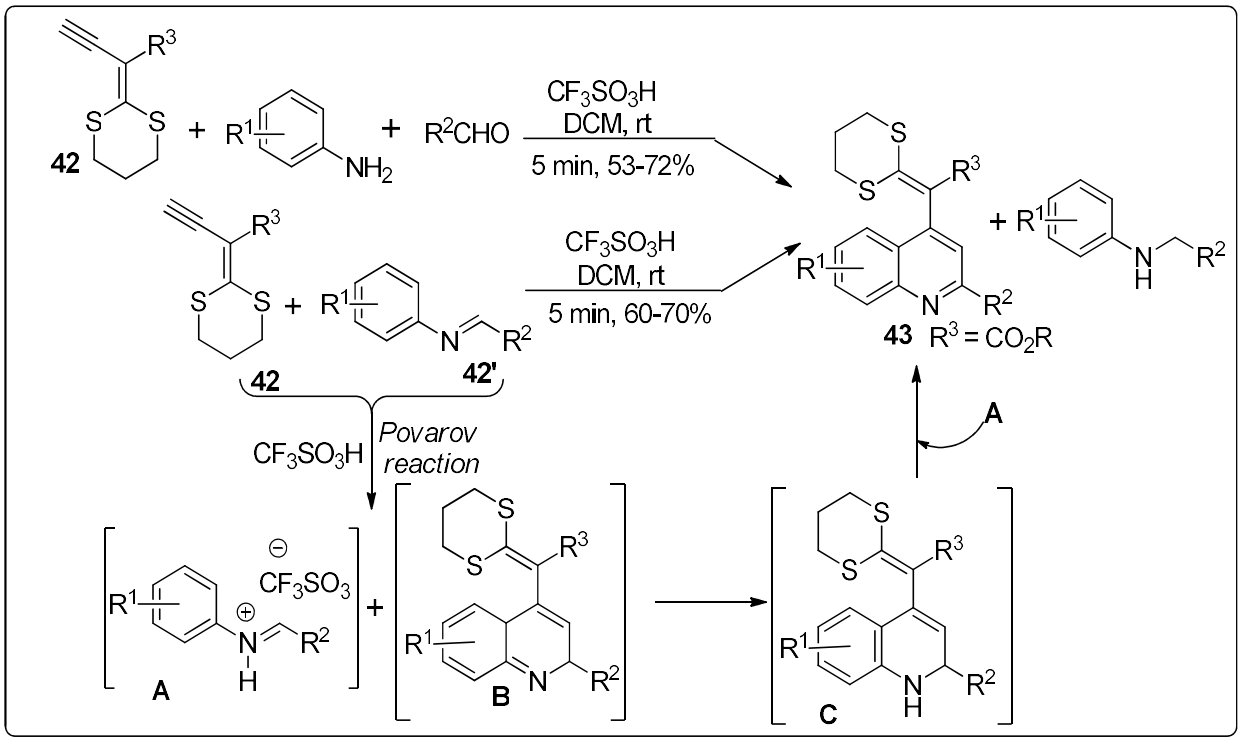
Scheme 16: Synthesis of product **40**

Batra and coworkers[36] disclosed a $SnCl_2$-mediated tandem reaction toward synthesis of 4-(substituted vinyl)-quinolines **41** (**Scheme 17**) via *Baylis–Hillman* reaction in multistep starting from commercially available 2-nitro benzaldehyde derivatives.



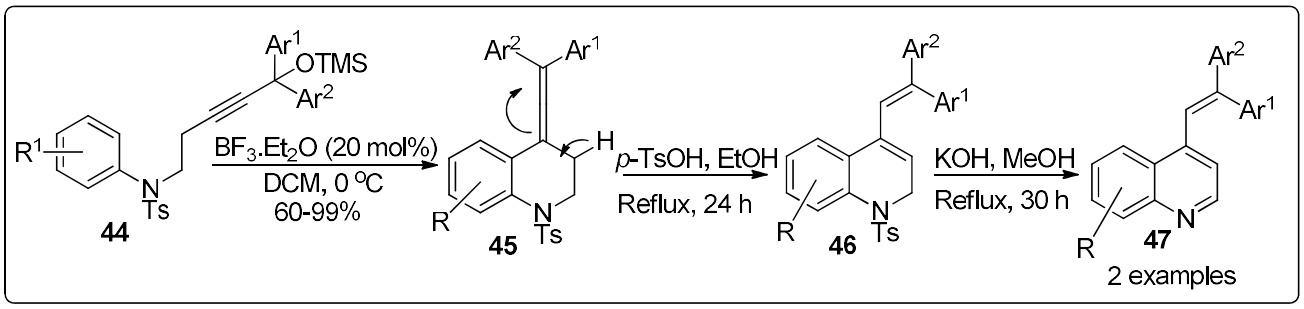
Scheme 17: Synthetic route for the formation of product **41**

Zhao *et al.*[37] developed an efficient metal free synthetic method for the synthesis of 4-(1,3-dithian-2-ylidene)methyl)quinolines **43** (**Scheme 18**) in one pot within just few minutes from ethynyl ketene-*S,S*-acetal **42**, arylamines and aldehydes in presence of trifluoromethanesulfonic acid (CF_3SO_3H). The reaction proceeds through the formation of an arylimine (**42′**) from arylamines and aldehydes, which on regiospecific aza-Diels-Alder (*Povarov*) reaction with **42** followed by reductive amination delivers the desired product **43**. The product can also be achieved from the reaction between **42** *in situ* generated aylimine (**42′**) under the same condition.



Scheme 18: Synthesis of product **43**

Ishikawa *et al.*[38] disclosed an multistep synthetic pathway for the syhthesis of 4-(2,2-diarylvinyl)quinoline **47** (**Scheme 19**) from the acetylinic substrate **44**. The reaction proceeds through the formation of an allene (**45**) via Lewis $BF_3.Et_2O$ catalyzed intramolecur *Friedel-Crafts* reaction (IMFC) which on acid mediated isomerization form the 1,3-diene **46**. A subsequent base promoted 1,2-elimination from **46** delivered 4-vinyl substituted quinolines **47**.



Scheme 19: Synthesis of product **47**

3.1.3. 2*H*-Chromene: An important heterocycle

3.1.3.1. Importance of 2*H*-Chromenes

2*H*-Chromene (2H-1-benzopyran derivatives) is an important structural moiety among the bi-cyclic oxygen heterocycles and found wide applications in various fields. More specifically, they are present as the core structure in a large number of natural products[39] and bioactive compounds; including drugs.[40] For example, *Candenatenin E* (**49**, Figure 4) isolated from *D. candenatensis* heartwood exhibits potent cancer cell cytotoxicity,[40b] *Gaudichaudianic acid* (**50**, Fig. 4) acts as an antifungal agent,[40c] *Iclaprim* (**51**, Fig. 4) is a antibiotic used for the treatment of acute bacterial skin and skin structure infections (ABSSSI),[40d] *Cordiachromene* (**52**, Fig. 4) possesses antibacterial properties and act as inhibitor against cyclooxygenase,[40e] *Anthyllisone* (**53**, Fig. 4) acts as a nonsteroidal anti-inflammatory agent.[40f] Besides, some of them also serve as tyrosine-kinase inhibitor,[40g] anti-bacterial,[40h] anti-diabetic[40i] agents and some 2*H*-chromenes, and their derivatives have gained great therapeutic importance for the discovery of novel antimycobacterial and anti-cancer compounds.[41]

In addition to their medicinal importance, 2*H*-chromene derivatives provides various applications of material sciences[42] such as triplet sensitizers,[42a] photochromic materials, laser dyes;[42b-d] [e.g. **54** (Fig. 4) is used in plastic photochromic lenses.[42d]] and are employed as precursors to flavylium dyes for solar cells and optical memories.[42e]

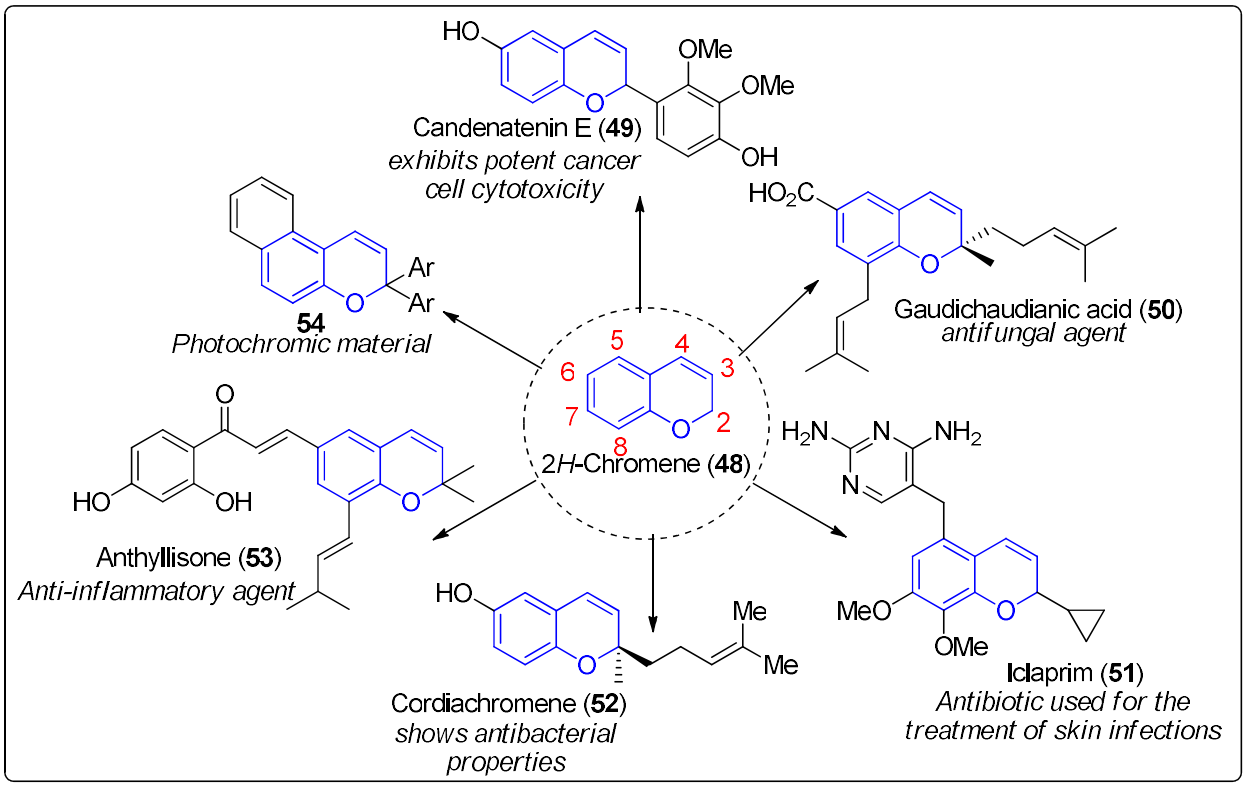


Figure 4. Some important 2*H*-Chromene derivatives

3.1.3.2. Importance of 4-substituted 2*H*-Chromenes

Among the 2*H*-chromenes, 4 substituted 2*H*-chromenes are of special interests due to their usefulness in potent bioactive agents.[43] For example, *Acolbifene* (**55**, Figure 5) is nonsteroidal selective estrogen receptor modulator (SERM) for the treatment of breast cancer.[43a-b] EM-800 (**56**, Fig. 5) a precursor of acolbifene **55**, is also found to be highly effective nonsteroidal antiestrogen for the treatment of breast cancer.[43a] Compound **57** (Fig. 5) acts as an adrenergic receptor agonists.[43c] Whereas compound **58**, a neoflavonoid isolated from *Dalbergia sissoo* heartwood was found to possess significant anti-osteoporotic activity,[43d] and compound **59** (a 4-aryl chromene derivative) acts as potent anticancer agent[43e] etc.

Besides the medicinal importance, they found applications in material science also; e.g., some derivatives of 4 vinyl 2-oxo-2*H*-chromene (**60**, Fig. 5) are discovered to be a new class of dyes are useful for NLO (Non-linear optical) devices and other applications.[44]

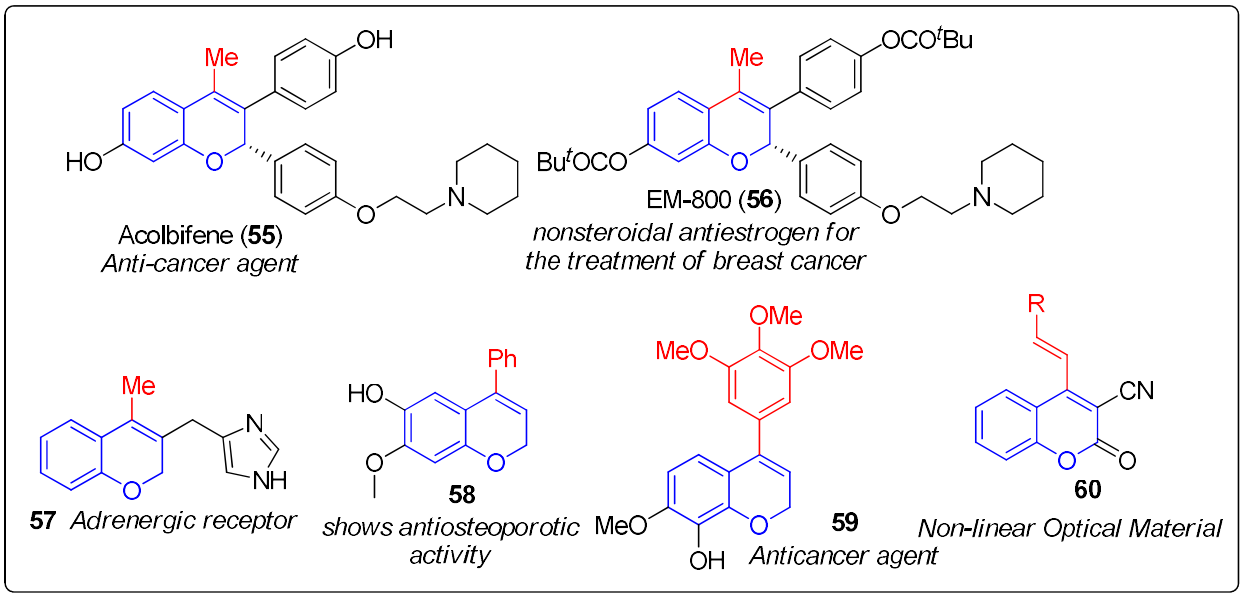


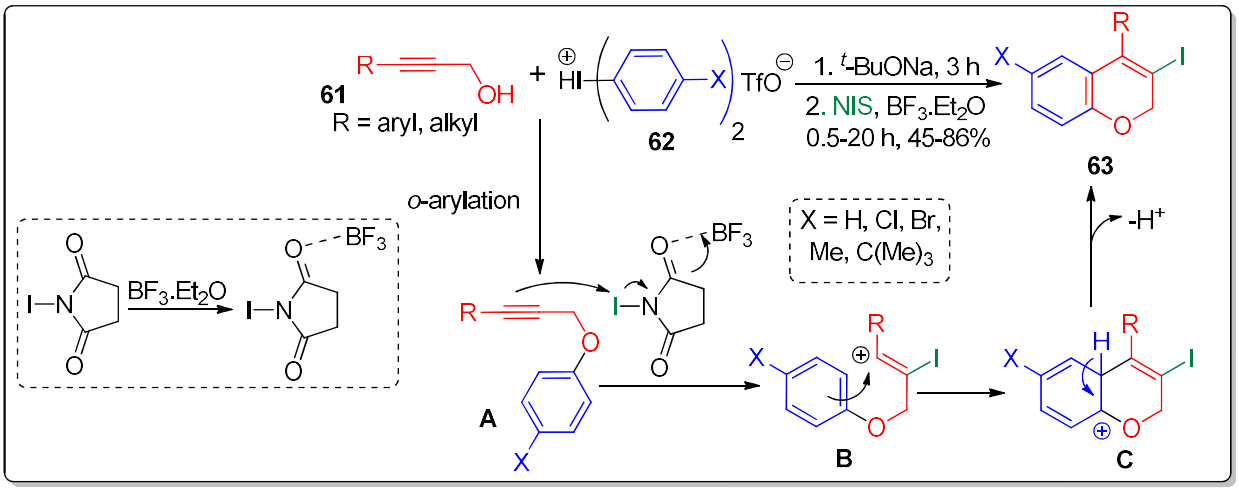
Figure 5. Some 4-substituted 2*H*-Chromene derivatives

3.1.4. Synthesis of 4-substituted 2*H*-Chromenes via cyclizations of acetylenic substrates

Due to the wide spread applications of 2*H*-chromenes in various fields, substantial efforts were devoted for their synthesis. Scrutiny of literature reveals that most of the synthetic routes are based on the synthesis of 2-substituted 2H-chromenes,[45] in contrast, only few methods are reported for 4-substituted 2*H*-chromenes, usually involving metal catalyzed or metal free cyclizations of acetylenic substrates. Some of them are illustrated briefly below.

3.1.4.1. Synthesis of 4-substituted 2*H*-Chromenes through intermolecular cyclizations of acetylinic substrates in presence of electrophile

In 2016, **Sasaki** *et al.*[46] disclosed an efficient transition metal free mild route for the synthesis of 4-substituted 2*H*-Chromenes **63** (**Scheme 20**) in two steps comprising an intermolecular reaction of 3-aryl/alkyl-2-propyn-1-ols **61** with diaryliodonium triflates **62** in the presence of ^{t}BuONa followed by intramolecular cyclization of the resulting product (i.e., **A**) with the aid of NIS and $BF_3.OEt_2$. Mechanistically, *o*-arylation of **61** with **62** delivers the ether intermediate **A** which then reacts with NIS in the presence of $BF_3.OEt_2$ delivering intermediate **B** which upon intramolecular carboannulation followed by a deprotonation leads to the desired product **63** with good to moderate yields.

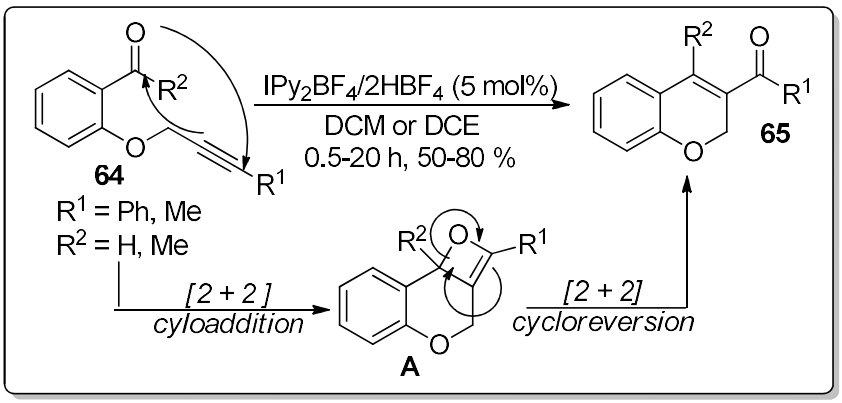


Scheme 20: Synthesis of 2*H*-Chromene **63**

3.1.4.2. Synthesis of 4-substituted 2*H*-chromenes through intramolecular cyclizations of acetylenic substrates in absence of any electrophile

3.1.4.2.1. Metal free approach for the synthesis of 4-substituted 2*H*-Chromenes

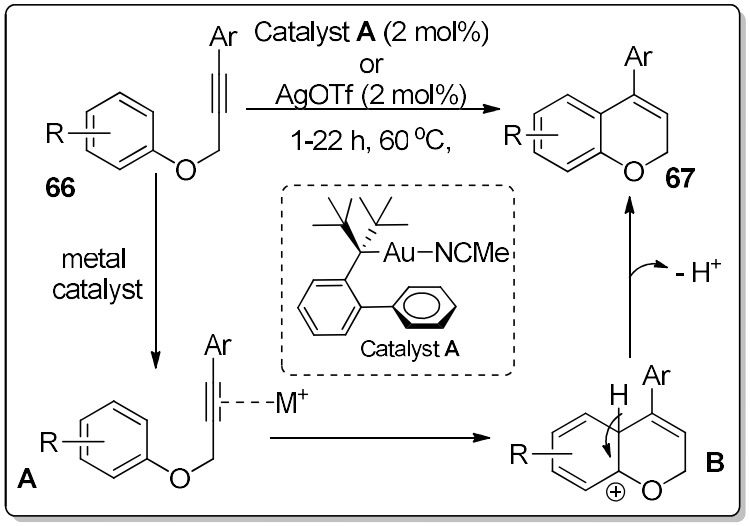
Saito and coworkers[47] demonstrated the first synthetic pathway for the formations of 4-substiuted 2*H*-chromenes **65** (**Scheme 21**) using catalytic amount of *Barluenga's reagent* (IPy_2BF_4, Py = pyridine) in presence of HBF_4 at room temperature. Mechanistically the reaction proceeds through an alkyne-carbonyl metathesis in which intramolecular [2 + 2]-cycloaddition of **64** deliveres intermediate **A** which upon [2 + 2]-cycloreversion affords the product **65** in 50-80% yields.



Scheme 21: Synthesis of product **65**

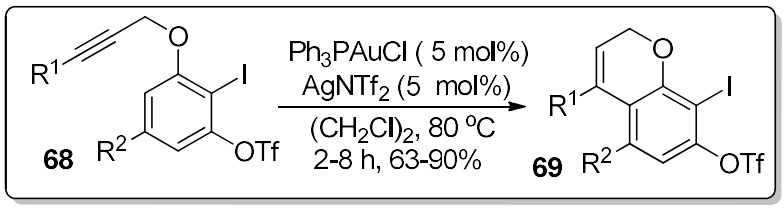
3.1.4.2.2. Metal catalyzed approach for the synthesis of 4-substituted 2*H*-Chromenes

Arcadi and coworkers[48] reported a convenient one-pot synthesis for the formation of 4-aryl substited 2*H* chromenes **67** (**Scheme 22**) from [(3-arylprop-2-ynyl)oxy]-benzenes (**66**) in presence of gold or silver catalyzed intramolecular hydroarylation reactions. The products were exclusively formed via *6-endo-dig* cyclization reactions. According to the mechanism, the catalyst at first activates the substrate **66** by coordinating with the alkylenic bond forming intermediate **A**, which on subsequent intramolecular cyclization followed by deprotonation delivered the desired product **67**.



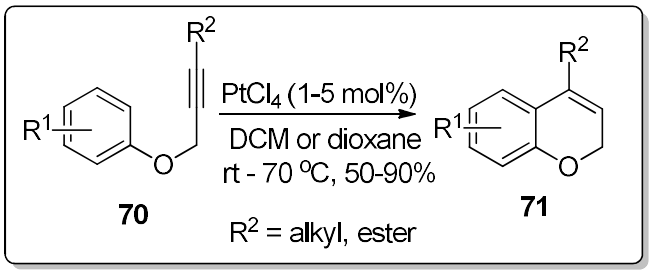
Scheme 22: Synthesis of 4-aryl substitute 2*H*-Chromene **67**

Yoshida and coworkers[49] disclosed an efficient gold catalyzed synthetic pathway for the synthesis of 4-substituted benzopyran derivatives **69** (**Scheme 23**) from the propargylated substrate **68**. The reaction proceeds through metal catalyzed *6-endo-dig* cyclizations and aryne reactions.



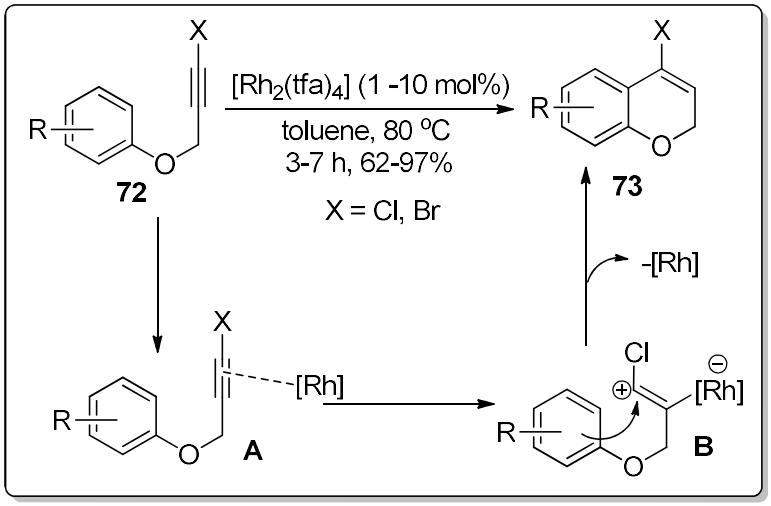
Scheme 23: Schematic representation for the synthesis product **69**

Sames and coworkers[50] demonstrated a concise pathway towards the synthesis of 4-disubstituted 2*H*-chromenes **71** (**Scheme 24**) via Pt(IV)-catalyzed cyclization of *o*-propargylated substrates **70** through intramolecular electrophilic hydroarylation. The reaction is expected to proceed via a *6-endo-dig* cyclization pathway.



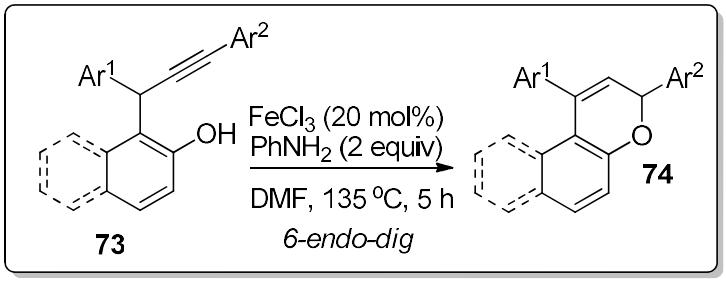
Scheme 24: Synthesis of 4-substituted 2*H*-Chromene **71**

Urabe and coworkers[51] reported a general synthetic pathway for the formation of 4-halo-substituted 2*H*-Chromenes **73** (**Scheme 25**) *via* regio-selective intramolecular hydroarylation of (3-halo-2-propynyl) aryl ethers **72** in the presence of a rhodium catalyst. Mechanistically, the metal catalyst at first activates the acetylenic bond of the substrate **72** leading to the formation of intermediate **A**, which is transformed regioselectively into cataionic species **B**. Next, Species **B** undergoes an intramolecular carboannulation followed by demetallation resulting in the formation of the desired halo-chromenes **73**.



Scheme 25: Synthesis of product **73**

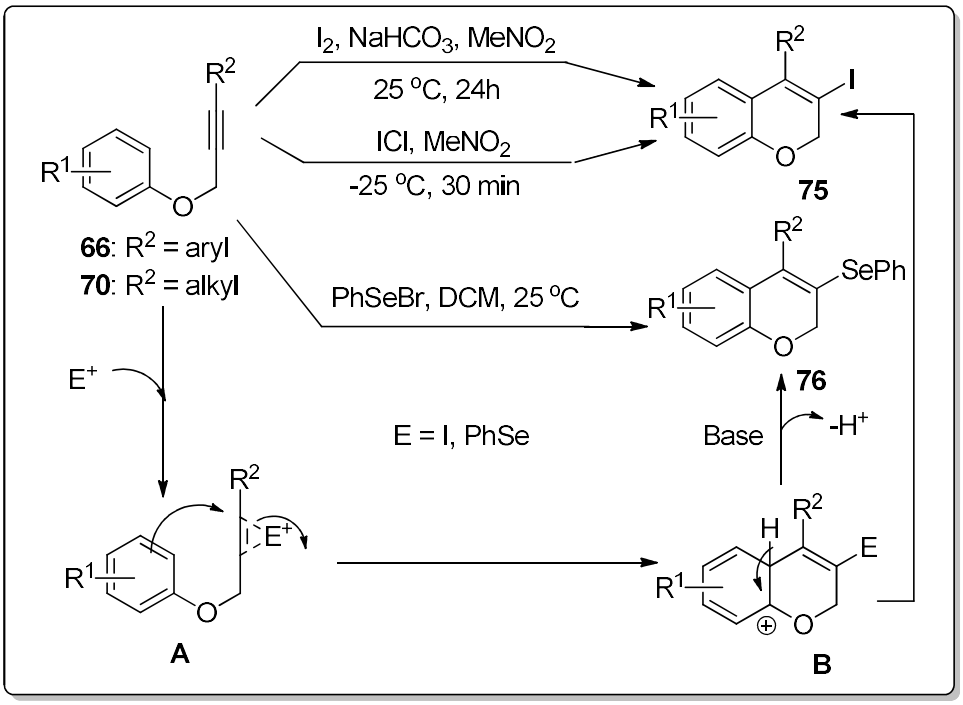
Li and coworkers[52] developed a convenient strategy to access 2*H*-1-benzopyran derivatives **74** (**Scheme 26**) from 2-propargylphenols (or naphthols) **73** via iron(III)-catalyzed regio-selective intramolecular heteroannulation (6-*endo-dig*) with the assistance of aniline as additive. Similar to the previous reports here also the reactions proceed through an *endo-dig* cyclization.



Scheme 26

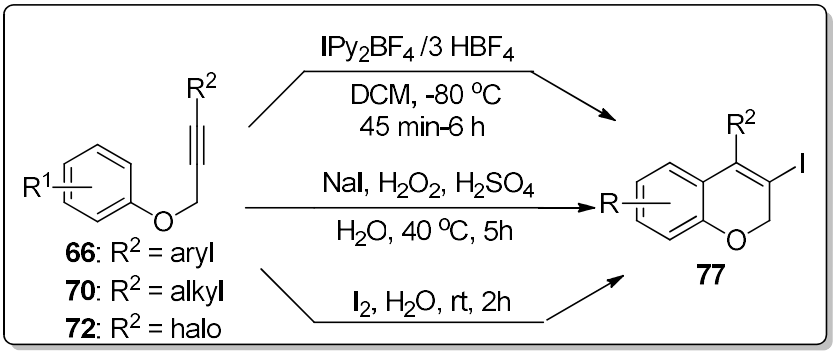
3.1.4.3. Synthesis of 4-Substituted 2*H*-Chromenes via intramolecular cyclizations of acetylenic substrates in presence of electrophile

Larock and coworkers[53] demonstrated an efficient synthetic strategy towards 3,4-disubstituted 2*H*-chromenes **75** and **76** (**Scheme 27**) in excellent yields and this reaction was found to be applicable to a wide range of substrates. Thus, propargylic ether substrates **66/70** undergo intramolecular electrophilic cyclizations (*6-endo-dig*) where I_2, ICl and PhSeBr were used as electrophile. The methodology thus affords the product (**75**/**76**) under mild reaction conditions and tolerates a variety of functional groups. According to their mechanism, acetylenic bond of the substrates **66/70** first reacts with the electrophile (E^+) leading to the formation of intermediate **A** which on subsequent intramolecular carboannulation followed by deprotonation leads to the formations of the products **75/76**.



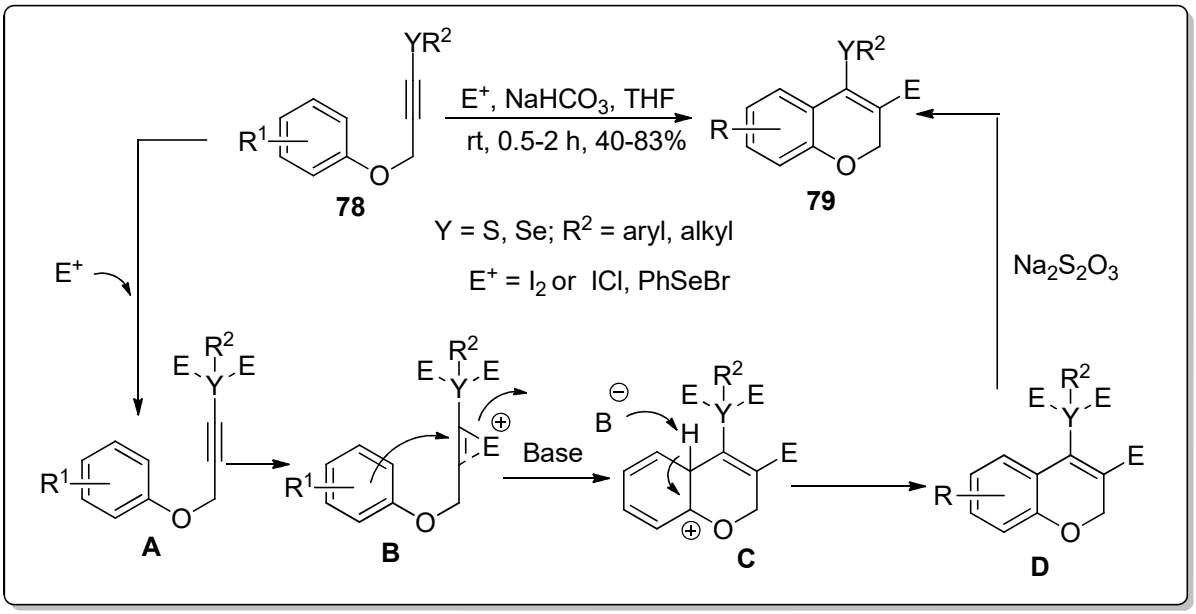
Scheme 27: Synthesis of product **75** and **76**

Barluenga and coworkers[54] reported versatile synthetic strategies for the formation of 4-substituted-3-iodo-2*H*-chromenes **77** (**Scheme 28**) *via* iodo-arylation reaction of heteroatom-tethered ω-arylalkynes **66/70/72**. This reaction could also be carried out in aqueous medium (instead of using dry solvent) where NaI or I_2 is used as iodinating reagent as depicted in Scheme 28. Reportedly this was the first report of electrophilic cyclization in water.



Scheme 28: Routes for the synthesis of product **77**

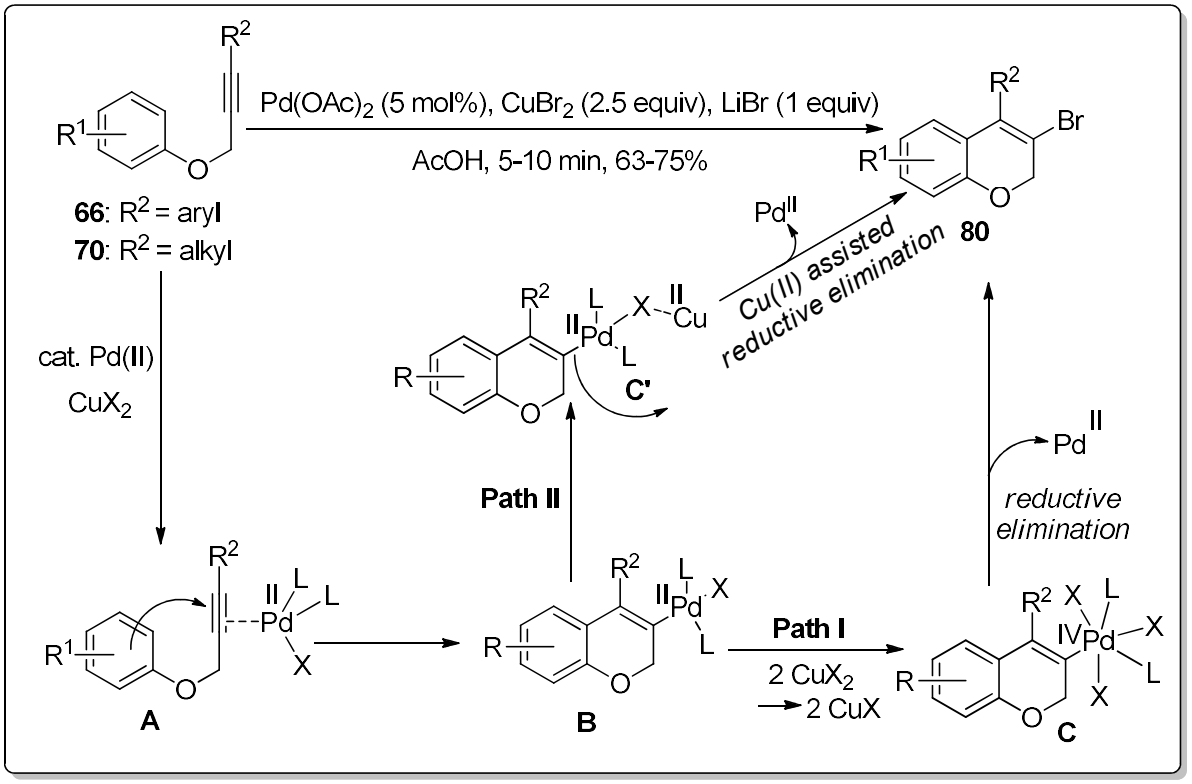
Zeni and coworkers[55] disclosed a concise synthetic route for the formation of 3-halo-4-chalcogen-2*H*-benzopyrans **79** (**Scheme 29**) from the propargylic ethers **78** bearing a chalcogen group. The substrates underwent highly selective intramolecular cyclizations upon treatment with with I_2 or ICl or PhSeBr affording the desired product **79**. According to the mechanism, at first the chalcogen group of the propargyl ether **78** react with the electrophile (I_2 or ICl or PhSeBr) and form intermediate **A**. Next the triple bond of intermediate **A** coordinate with the elctrophile generating intermediate **B**. This selenium/sulphur atom exerts a high stabilization of the positive charge in the carbon one next to it (of iodonium intermediate **B**), thereby promoting the subsequent intramolecular nucleophilic attack by the tethered arene ring to generate the intermediate species **C**. Next, deprotonation of species **C** with the assistance of a base affords intermediate **D** which on further reduction with $Na_2S_2O_3$ affords the desired product **79**.



Scheme 29: Synthetic route for the formation of product **79**

Savitha *et al.*[56] disclosed a novel synthetic pathway for the formations of 4-substitued-2*H*-chromenes **80** (**Scheme 30**) via an intramolecular cyclization of aryl/alkyl propargyl ethers **66/70** in the presence of catalytic amount of $Pd(OAc)_2$, stoichiometric amount of $CuBr_2$ (2.5 equiv.) and LiBr (1.0 equiv.) to afford the product **80** within 5-10 minutes in good yields.

The mechanism involves a carbopalladation of substrate through the activation of triple bond by coordination with the Pd(II) species leading to an intermediate **A** which on subsequent intramolecular carboannuation through the adjacent arene ring furnished a palladated intermediate **B**. Next, intermediate **B** could easily be transformed into the product in two pathways. In path **I**, intermediate **B** transforms into palladated (Pd^{IV}) intermediate **C** with the aid of Cu(II), which upon reductive elimination (-Pd^{II}) affords the desired product **80**. Whereas in path II, copper assisted ligand transfer reaction of intermediate forms intermediate **C′** retaining the oxidation state of palladium in +2 which delivers the product **80**.

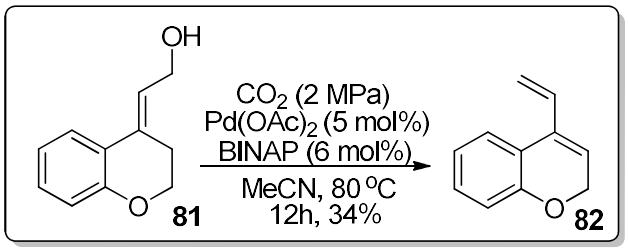


Scheme 30: Mechanistic overview for the synthesis of product **80**

3.1.5. Synthesis of 4-vinyl- 2*H*-Chromenes

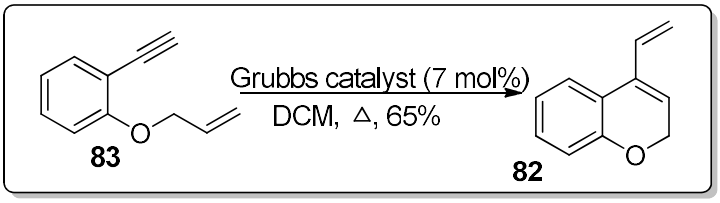
Zhang and coworkers[57a] showed one specific example for the synthesis of 4-vinyl-2H-chromene (**82**, **Scheme 31**) in poor yield (34%) in high reaction time during disclosure of a general synthetic pathway of substituted 1,3-dienes from primary allylic alcohols (**81**) via carbon dioxide-promoted palladium-catalyzed dehydration reaction, where carbon dioxide acts as a

promoter to facilitate the alcoholic C–O bond cleavage via the formation of an allylic bicarbonate ester.



Scheme 31: Synthesis of product **82**

In 2001, **Rosillo** *et al.*[57b] reported one specific example of synthesis of 4-vinyl-2H-chromene (**82**, **Scheme 32**) from **83** via enyne metathesis in presence of Grubbs catalyst.



Scheme 32: Synthesis of product **82**

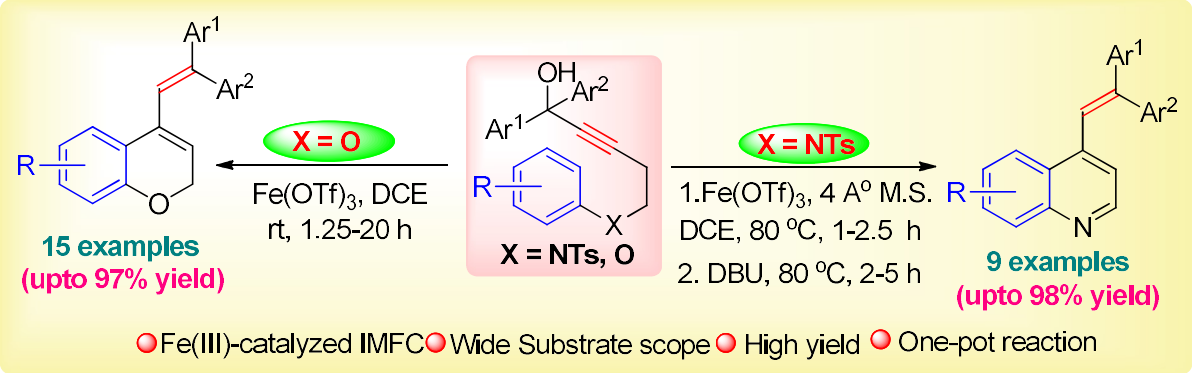
3.1.6. Conclusion

From the literature review it is evident that both 4-vinyl-quinolines and 4-vinyl-2*H*-chromenes are important classes of heterocycles having huge applications in medicinal chemistry and material sciences as well. Most of the reports towards the synthesis of 4-substituted quinolines are based on multi-component intermolecular coupling reaction using conventional method. There is only one general synthetic pathway for the formation of 4-(2,2-diarylvinyl)quinolines that too employing multistep reactions and requires harsh reaction condition in addition to longer reaction time. Thus, the development of a convenient and expeditious method for the general synthesis of 4-vinyl-quinolines is urgently needed.

Whereas for 2*H*-chromenes though there are several methods towards the synthesis of 4-substituted 2*H*-chromenes from phenyl propargylated ethers involving intramolecular cyclization, only few specific examples are available for the synthesis of 4-vinyl substituted 2*H*-

chromenes. So a practical and concise synthetic pathway for the synthesis of 4-(2,2-diarylvinyl)-2*H*-chromenes are in need. In this context, we have developed a convenient and desirable synthetic pathway for their general synthesis. The detailed results are discussed in **Part-II** of this chapter.

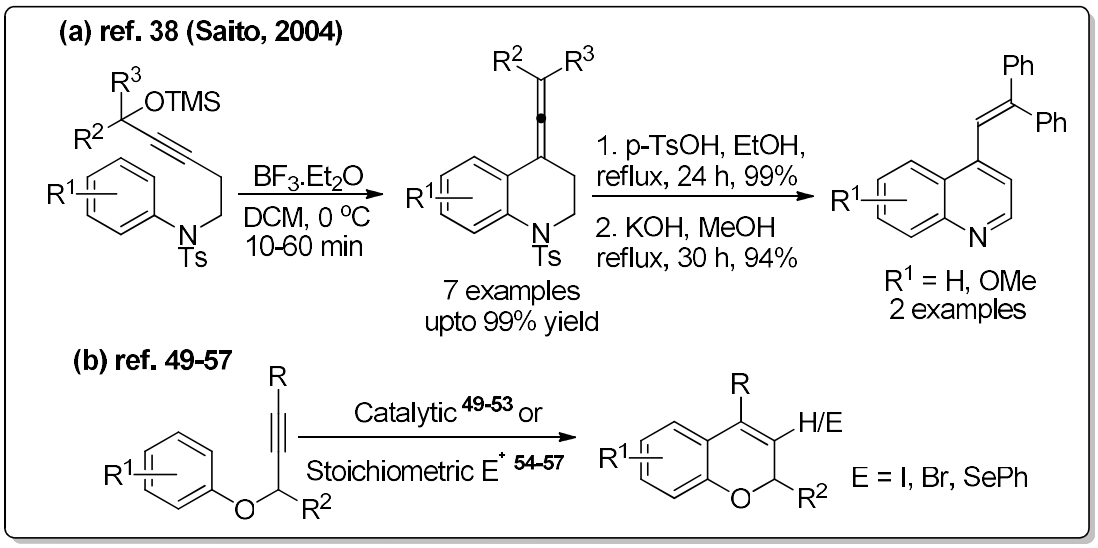
Part II – Results and Discussion



Sukanya De and Chinmay Chowdhury*; ***Manuscript under communication***

3.2.1. Introduction

In view of the immense importance of quinolines in medicinal chemistry and material sciences (as discussed in **Part I** of this chapter), substantial efforts were devoted for their synthesis. But surprisingly, to date, there are only few reports for the synthesis of 4-vinyl substituted quinolines involving conventional methods (**Schemes 15-19** in **Part I**); among them there is only one report for the general synthesis of 4-(2,2-diarylvinyl)quinolines in multiple steps with long reaction time under harsh reaction conditions as shown under **Scheme 33a** (**Scheme 19** in **Part I**).

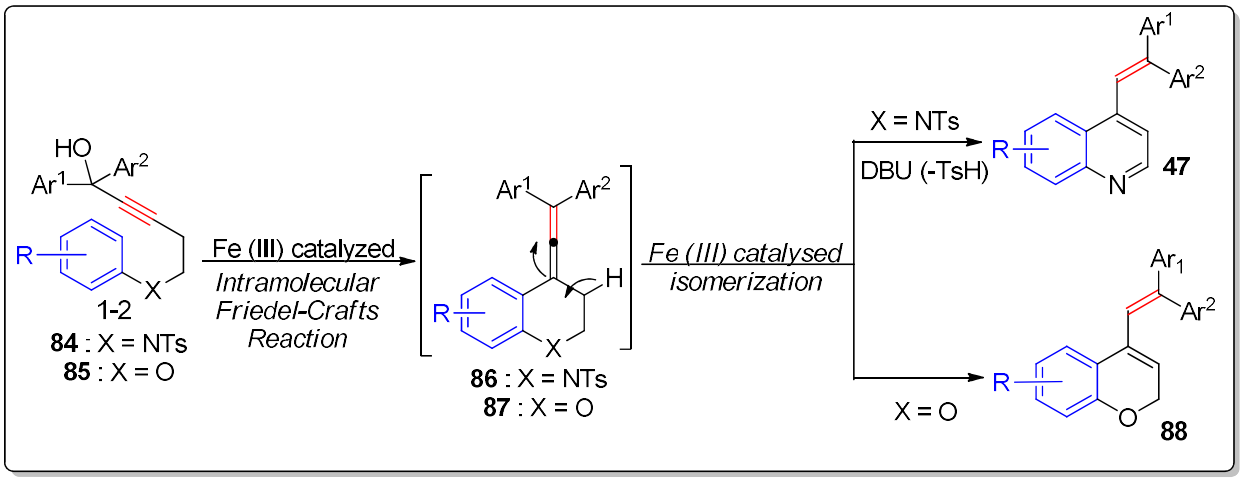


Scheme 33: Previous works for the synthesis of 4-vinyl substituted quinolines and 4-substituted 2*H*-chromenes

On the other hand, 2*H*-chromenes have drawn attention due to their immense applications in various fields (as discussed in **Part I**). Consequently, substantial amount of works has been done towards the synthesis of 4-substituted chromenes, involving mostly intramolecular carboannulations of acetylenic substrates as shown in **Scheme 33b** (**Schemes 20-30** in **Part I**). Towards this objective, either various types of metal catalysts (**Schemes 22-26** in **Part I**) or stoichiometric amounts of various reagents acting as electrophiles are employed (**Schemes 27-30**). But to our surprise, there is no report for the general synthesis of 4-vinyl substituted 2*H*-chromenes except few specific examples of the same reported during the synthesis of other heterocycles wherein costly metal catalysts like palladium or ruthenium are usually used

(**Scheme 31-32**, **Part I**). Therefore, the development of practical and general methods to synthesize them from readily available substrates would be worthwhile.

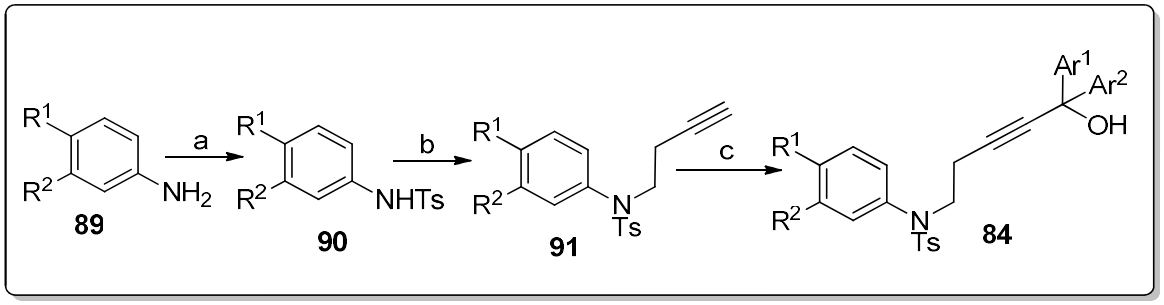
Recently, iron catalysts are gaining increasing research interests[58] because of their low price, non-toxicity, and environment benign character. On the other hand, intramolecular Friedel-Crafts (IMFC) reactions[59] have shown high efficiency for C-C bond formations in the construction of polycyclic frameworks. In this context and in continuation of previous works on palladium catalyzed reactions,[60] it was envisioned that the alcohol group of homopropargyl amines/ethers, **84/85** could be activated by means of coordination with Fe catalyst, which on intramolecular *Friedel–Crafts* (IMFC) of the adjacent arene moiety lead to deliver the allene intermediates **86/87**, which on isomerization followed by detosylation lead to the formation of product **47** from **86**, whereas simple isomarization of **87** affords **88**. Our concept proved to be viable by choosing the appropriate catalyst and reaction conditions. We report herein our preliminary results in this direction. To the best of our knowledge, though there are many reports on isomerizations of allenes (1,2 dienes) into 1,3-dienes using acids or high cost metal catalysts,[61] there is no report on the use of any iron catalysts for the same.



Scheme 34. Strategy for the synthesis of **47** and **88**

3.2.2. Synthesis of starting material 84

The desired starting material **84** was prepared in three steps starting from the commercially available aniline derivatives **89** (**Scheme 35**). In the first step, **90** was synthesized by the tosylation of the respective anilines derivatives **89** which was then allowed to undergo "*Mitsunobu Reaction*" with 3-Butyn-1-ol to produce **91** derivatives. Finally, the **91** derivative was allowed to react with substituted ketone to prepare the desired starting material **84.**



Scheme 35. Reagents and Conditions: (a) TsCl, Et_3N, DCM, 0 ^oC- rt, 2-5 h, 72-90%; (b)[38] 3-Butyn-1-ol, DIAD, PPh_3, THF, 0 ^oC- rt, 4-12 h, 50-76%; (c)[38] Ketone, BuLi (1.6 M in hexane), 0 ^oC- rt, 0.5-1 h, 54-83%.

3.2.3. Synthesis of 4-(2,2-Diarylvinyl)quinolines 47 under one-pot

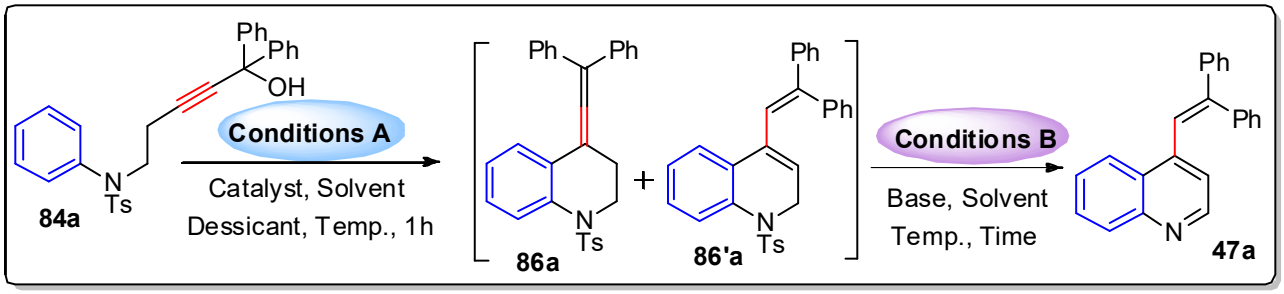
3.2.3.1. Optimization of reaction conditions for the synthesis of Quinoline 47a

The first objective was to optimize the reaction conditions to achieve the synthesis of the quinoline **47a** under one-pot. Towards this goal, a model study for the synthesis of **47a** from substrate **84a** (R^1 = R^2 = H, Ar^1 = Ar^2 = Ph) was carried out through variation of reaction parameters; few selected results are presented in Table 1. In this context, our first target was to achieve the isomerized product **86′a** from the substrate **84a** through a intramolecular *Friedel-Craft* reaction (IMFC) with the aid of a metal catalyst, acting as Lewis acid via formation of a allene intermediate **86a** (Conditions A). Next, efforts were made to find out an appropriate base and solvent (Conditions **B**) to transform **86´a** into quinoline **47a** in one-pot.

Towards this objective at first substrate **84a** was treated with $FeCl_3$ (10 mol%) in nitromethane in the presence of CaH_2 as desiccant; to our disappointment, **86a** was formed

exclusively (Table 1, entry 1). Employing $Fe(OTf)_3$ in nitromethane or MeOH did not improve the situation (Table 1, entries 2-3). Pleasingly, $Fe(OTf)_3$ in DCE (1, 2 Dichloroethane) in the

Table 1. Optimization of reaction conditions for the one-pot synthesis of 4-(2,2-diarylvinyl)quinolines 47a[a]



Reaction Conditions A					Reaction Conditions B				Products (%Yield)		
Entry	**Catalyst**	**Solvent**	**Temp. (°C)**	**Desiccant[b]**	**Base**	**Solvent**	**Temp.(°C)**	**Time (h)**	**86a**	**86'a**	**47a[c]**
1	$FeCl_3$	$MeNO_2$	60	CaH_2	---	---	---	---	95	---	---
2	$Fe(OTf)_3$	$MeNO_2$	60	CaH_2	---	---	---	---	95	---	---
3[d]	$Fe(OTf)_3$	MeOH	100	CaH_2	---	---	---	---	---	---	---
4	**$Fe(OTf)_3$**	**DCE**	**80**	**4Å M.S.**	**---**	**---**	**---**	**---**	**trace**	**80**	**---**
5[d]	$Fe(acac)_3$	DCE	80	4Å M.S.	---	---	---	---	---	---	---
6	AgOTf	DCE	80	4Å M.S.	---	---	---	---	11	66	---
7	$In(OTf)_3$	DCE	80	4Å M.S.	---	----	---	---	88	---	---
8	$Cu(OTf)_2$	DCE	80	4Å M.S.	---	----	---	----	trace	---	----
9	$Fe(OTf)_3$	DCE	80	4Å M.S.	K^{t}BuO	DMF	120	22	trace	80	trace
10	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMF	120	20	trace	---	45
11	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMSO	120	4.0	trace	---	53
12	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	MeOH	Reflux	3.5	trace	---	62
13	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	NMA	120	2.5	trace	---	65
14	$Fe(OTf)_3$	DCE	80	4Å M.S.	K_2CO_3	DMA	120	4.5	trace	---	50
15	**$Fe(OTf)_3$**	**DCE**	**80**	**4Å M.S.**	**DBU**	**DBU**	**80**	**2**	**trace**	**---**	**70**

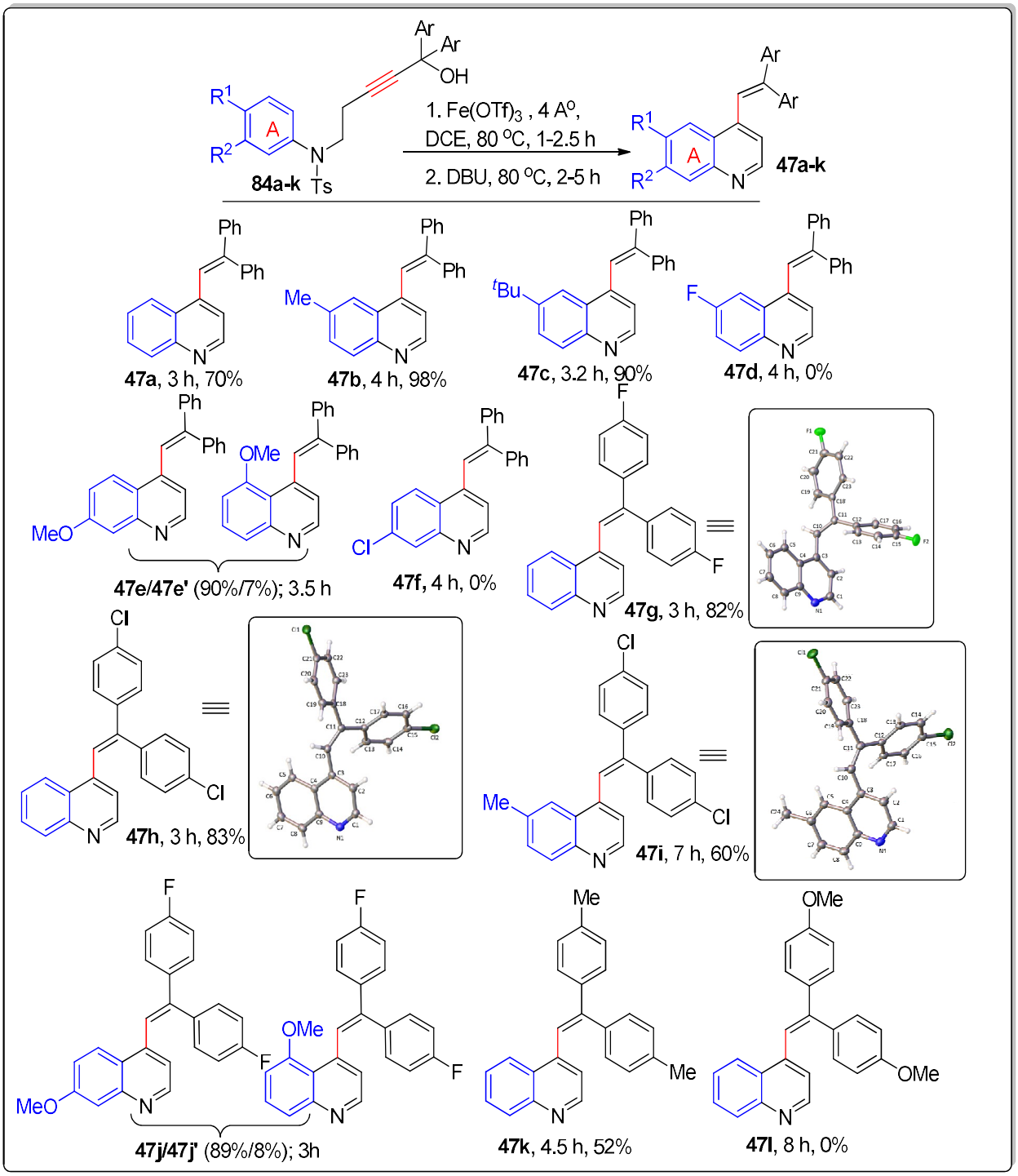
[a]ReactionConditions: **84a** (0.062 mmol), catalyst (10 mol %), and 12 mg of desiccant in solvent (1.7 mL) was heated at mentioned temperature under argon atmosphere for 1 h; the resulting crude intermediate obtained (upon removal of DCE) was then heated in a solvent (2 mL) in the presence of a base (6 equiv) under an atmosphere of argon at indicated temperature [except entry 15 where DBU (0.62 mL) was used as solvent cum base]. [b]M.S. represents molecular sieves. [c]Yields of pure products. [d]Reaction time is 4 h.

presence of molecular sieves (4Å) resulted in the formation of **86´a** within 1 h in 80% yield (Table 1, entry 4). Surprisingly, $Fe(acac)_3$ in DCE failed to provide any **86´a** though AgOTf produced the same in 66% yield (Table 1, entries 5-6). Besides, deployment of $In(OTf)_3$ or $Cu(OTf)_2$ did not produce any **86´a**; only **86a** was isolated (Table 1, entries 7-8). Thus the reaction conditions (**A**) of entry 4 of Table 1 could be considered as optimal for the formation **86´a**. The next objective was to optimize the conditions (**B**) to convert **86´a** into **47a** under one-pot. Accordingly, after treating **84a** under the aforesaid optimized conditions, the solvent (DCE) was evaporated; the crude residue (of **86´a**) obtained was dissolved in a suitable solvent and the resulting solution was heated in presence of an appropriate base (Table 1, entries 9-15). Thus use of K^{t}BuO or K_2CO_3 in DMF led to the formation of **47a** after 20-22 h albeit intrace or moderate yields (Table 1, Entries 9-10). Then the reaction was pursued with K_2CO_3 in polar solvent systems (viz. DMSO, MeOH, NMA, DMA; Table 1, entries 11-14); among them, NMA improved the yield of **47a** to 65%. Gratifyingly, using DBU as base as well as solvent and heating the reaction at 80 ^oC for 2 h furnished the desired product **47a** with 70% yield (Table 1, entry 15). Therefore entry 15 of Table 1 was considered as the optimal reaction condition to explore the scope and generality of this reaction (**Scheme 36**) as discussed below.

3.2.3.2. Scope of the reaction

With the optimized reaction conditions in hand, we set out to explore the scope and generality of the reaction for the formations of 4-(2,2-diarylvinyl)quinolines **47** (**Scheme 36**). First, the effects of substitutions on aryl ring (A) attached to nitrogen atom of substrate **84** were studied. This showed that incorporation of electron-donating groups (EDG) such as methyl or *t*-butyl (R^1 = Me or ^{t}Bu, R^2 = H) as in **84b** or **84c** led to the formation of quinolines **47b** (98%) or **47c** (90%) smoothly within 3.2-4 h. Surprisingly, when an electron-withdrawing group (EWG) like F was placed at the same position of **84d**, there was no product (**47d**) formation; instead the precursor allene intermediate **86d** was recovered in 32% yield. Placement of a strongly EDG (R^1 = H, R^2 = OMe) at *meta* position of **84e** delivered the anticipated products **47e**(90%)/**47e´**(7%) in regio-isomeric mixture which were separated through column chromatography. As expected, an EWG like Cl at the same position failed to provide any desired product **47f**; only the precursor allenic intermediates **86f** and **86f′** were isolated in an inseparable region-isomeric mixture

Scheme 36. Synthesis of 4-(2,2-diarylvinyl)Quinolines 47a-k[a] under One-pot

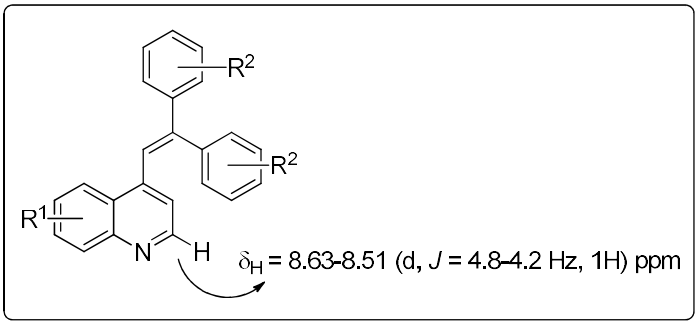


[a]Reaction conditions: A mixture of **84a** (0.062 mmol), $Fe(OTf)_3$ (0.006, 0.1 equiv), and desiccant (12 mg) in DCE (1.7 mL) was refluxed at 80 °C under argon atmosphere for 1-2.5 h; the resulting crude intermediate obtained (upon removal of DCE) was then heated at 80 °C in DBU (0.62 mL).

(**86f**/**86f′**: 2.2/1) in overall 47% yield.

To check the substituent effects on the other aryl rings of **84**, incorporation of EWG (viz., F/Cl) at the *para* position of **84g**/**84h** easily afforded the product **47g**/**47h** in very good yields. But installation of an additional EDG in the *para*-position (viz., R^1= Me, R^2 = H) in ring A of **84h** (resulting in substrate **84i**) had a detrimental effect on **47i** (produced after 7h with 60% yield), though placement of a strong EDG (OMe) at the *meta*-position of the same ring (viz., R^1= H, R^2 = OMe) in **84g** (leading to the generation of substrate **84j**) facilitated the reaction significantly generating a separable mixture of products [**47j** (89%) and **47j′**(8%)] after 3h. A moderate EDG (viz. Me) as in substrate **84k** appeared to hinder the reaction to some extent, delivering 52% of **47k** in 4.5 h, whereas a strong EDG (viz. OMe) in **84l** prevented the reaction completely. The inertness of **84l** or low reactivity of **84k** could possibly be attributed to the diminished positive charge on the allenic cation (see, species **B** of **Scheme 39** vide infra) due to the electron-donating effect of OMe/Me, thereby decreasing the electrophilicity of the allylic cation making the cyclization via intramolecular nucleophilic attack by the phenyl ring (A) somewhat sluggish.

3.2.3.3. Nature and characterization of products 47



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (ESI), the molecular ion peak in positive mode of all the compounds appeared as protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR the proton adjacent to the nitrogen atom appears in the range of 8.63-8.51 as a doublet with coupling constant (*J*) 4.8-4.2 Hz. Further, the ^{13}C NMR gave support in favour of the structures.

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of compounds **47g**, **47h** and **47i**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolved in minimum volume of petroleum

ether/dichoromethane mixture. The ORTEP diagrams of the crystal structures are shown in Figures 6, 7 and 8.

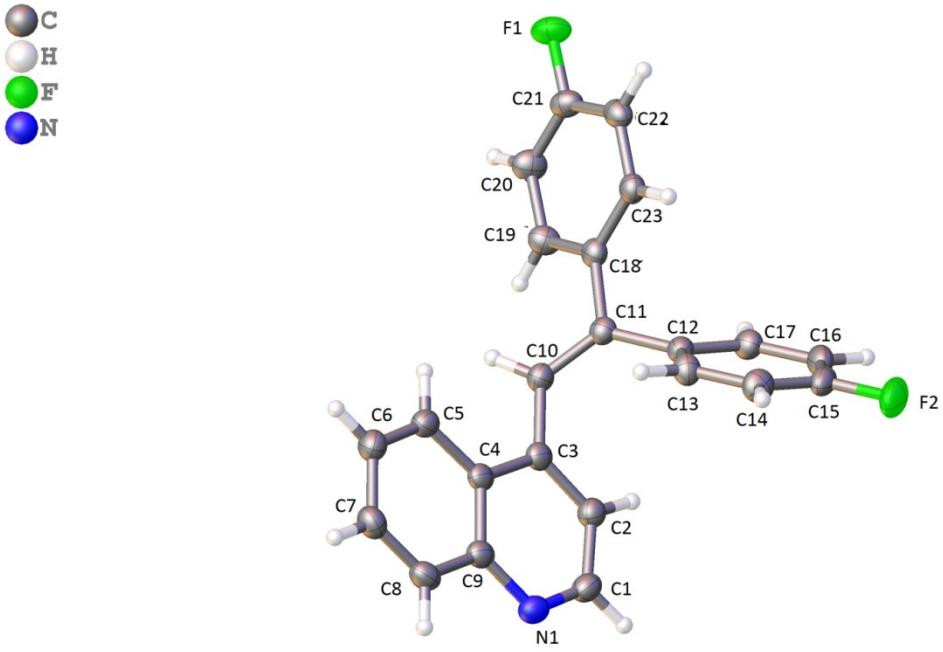


Figure 6. ORTEP Diagram (thermal ellipsoid plot) of Product **47g** (drawn at 50% probability level)

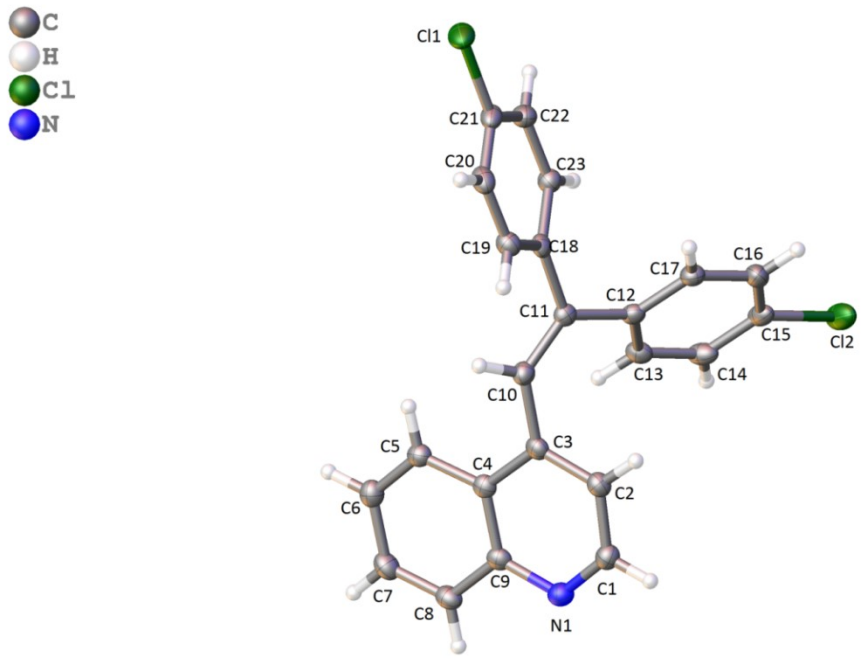


Figure 7. ORTEP Diagram (thermal ellipsoid plot) of Product **47h** (drawn at 50% probability level)

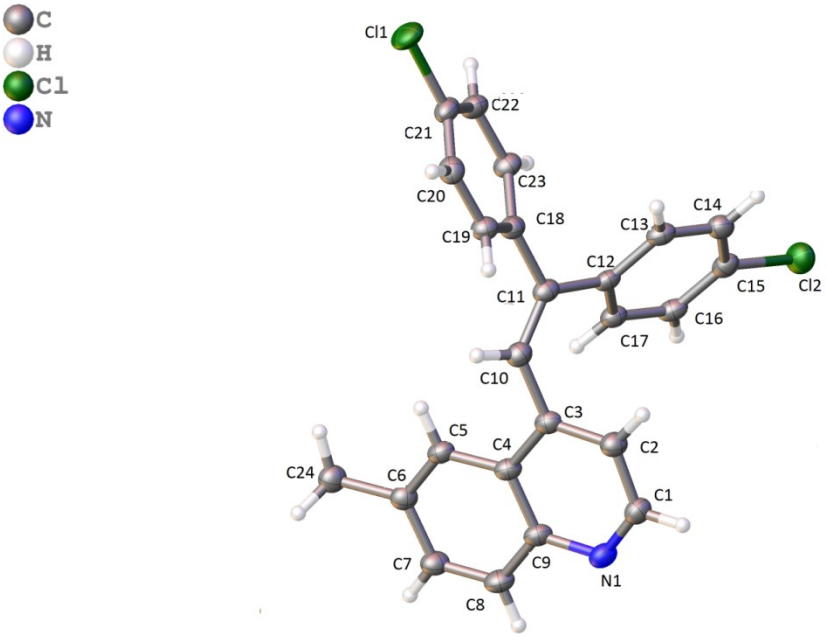


Figure 8. ORTEP Diagram (thermal ellipsoid plot) of Product **47i** (drawn at 50% probability level)

Table 2: Important crystal data of product **(47g)**

Empirical formula	$C_{23}H_{15}F_2N$
Formula weight	343.36
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.8355(7)
b/Å	27.245(2)
c/Å	7.4107(6)
α/°	90
β/°	105.815(3)
γ/°	90
Volume/Å^3	1716.4(2)
Z	4
ρ_{calc}g/cm^3	1.329
μ/mm^{-1}	0.757
F(000)	712.0
Crystal size/mm^3	0.4 × 0.1 × 0.08
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.447 to 130.03
Index ranges	$-10 \leq h \leq 10$, $-32 \leq k \leq 31$, $-8 \leq l \leq 8$
Reflections collected	26041
Independent reflections	2903 [R_{int} = 0.0452, R_{sigma} = 0.0249]
Data/restraints/parameters	2903/0/236
Goodness-of-fit on F^2	1.261
Final R indexes [I>=2σ (I)]	R_1 = 0.0470, wR_2 = 0.1266
Final R indexes [all data]	R_1 = 0.0517, wR_2 = 0.1399
Largest diff. peak/hole / e Å^{-3}	0.38/-0.36

The single crystal of the product **47g** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **47g** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2192350.**

Table 3: Important crystal data of product **(47h)**

Empirical formula	$C_{23}H_{15}Cl_2N$
Formula weight	376.26
Temperature/K	100.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	4.92790(10)
b/Å	18.3686(5)
c/Å	19.8564(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1797.37(8)
Z	4
ρ_{calc}g/cm^3	1.390
μ/mm^{-1}	3.278
F(000)	776.0
Crystal size/mm^3	0.5 × 0.03 × 0.02
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.554 to 132.972
Index ranges	$-5 \leq h \leq 5$, $-20 \leq k \leq 21$, $-23 \leq l \leq 23$
Reflections collected	24245
Independent reflections	3140 [R_{int} = 0.0586, R_{sigma} = 0.0375]
Data/restraints/parameters	3140/0/236
Goodness-of-fit on F^2	1.078
Final R indexes [I>=2σ (I)]	R_1 = 0.0282, wR_2 = 0.0691
Final R indexes [all data]	R_1 = 0.0299, wR_2 = 0.0696
Largest diff. peak/hole / e Å^{-3}	0.20/-0.28

The single crystal of the product **47h** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **47h** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2192349.**

Table 4: Important crystal data of product **(47i)**

Empirical formula	$C_{24}H_{17}Cl_2N$
Formula weight	390.28
Temperature/K	101.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	17.7941(4)
b/Å	5.23950(10)
c/Å	20.5021(4)
α/°	90
β/°	91.0930(10)
γ/°	90
Volume/Å^3	1911.11(7)
Z	4
ρ_{calc}g/cm^3	1.356
μ/mm^{-1}	3.102
F(000)	808.0
Crystal size/mm^3	0.2 × 0.02 × 0.01
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	6.516 to 130.148
Index ranges	$-20 \leq h \leq 20$, $-6 \leq k \leq 6$, $-24 \leq l \leq 24$
Reflections collected	36646
Independent reflections	3246 [R_{int} = 0.0796, R_{sigma} = 0.0388]
Data/restraints/parameters	3246/0/246
Goodness-of-fit on F^2	1.092
Final R indexes [I>=2σ (I)]	R_1 = 0.0463, wR_2 = 0.1193
Final R indexes [all data]	R_1 = 0.0498, wR_2 = 0.1221
Largest diff. peak/hole / e Å^{-3}	0.29/-0.45

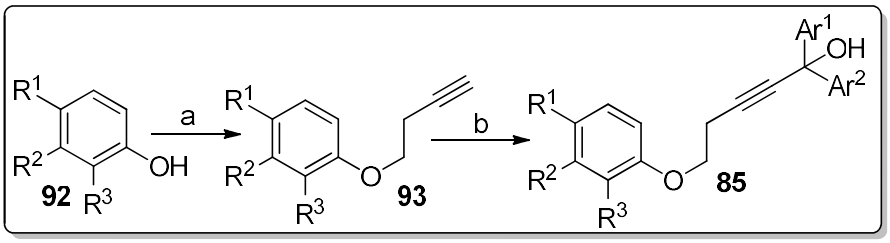
The single crystal of the product **47i** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **47i** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2192351.**

3.2.4. Extension of the methodology for the synthesis of 4-(2,2-diarylvinyl)-2*H*-chromenes 88

Encouraged by the above results, we decided to check the viability of the methodology for achieving the synthesis oxygen-heterocycles, i.e., (2,2-diarylvinyl)-2*H*-chromenes **88** where the -NTs group of **84** was replaced by an oxygen atom affording substrate **85.**

3.2.4.1. Synthesis of starting material 85

The desired starting material **85** was prepared in two steps starting from the commercially available phenol derivatives. In the first step the phenol derivatives **92** were allowed to undergo "*Mitsunobu Reaction*" with 3-Butyn-1-ol to form **93** derivatives. Then the **93** derivatives were simply reacted with the substituted ketones to deliver the desired starting material **85.**



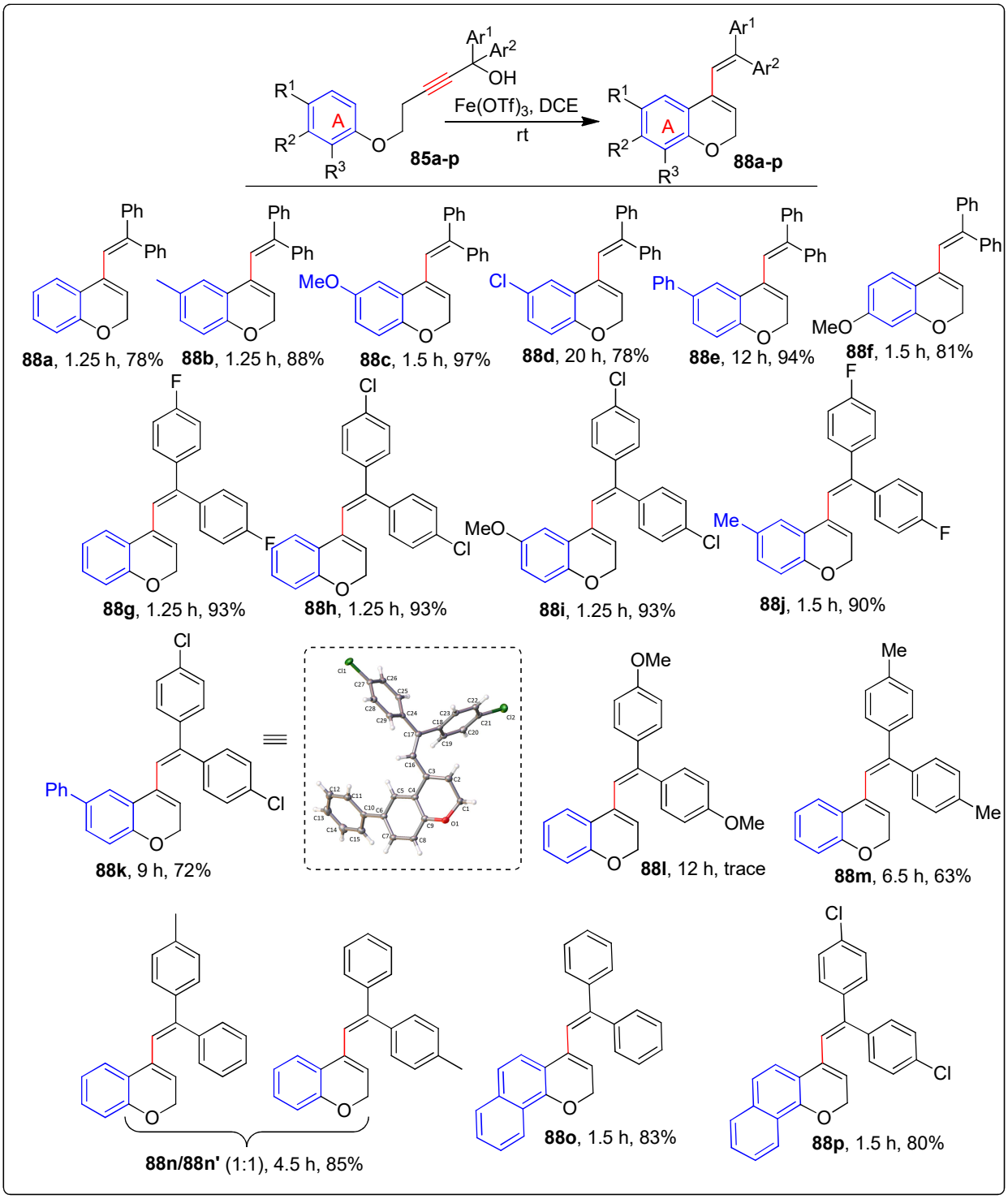
Scheme 37. Reagents and Conditions: (a) 3-Butyn-1-ol, DIAD, PPh_3, THF, 0 ^oC- rt, 4-12 h, 50-72%; (c) Ketone, BuLi (1.6 M in hexane), 0 ^oC- rt, 0.5-1 h, 32-64%

3.2.4.2. Synthesis of 4-(2,2-diarylvinyl)-2*H*-Chromenes 88

To our pleasure, exposure of the oxygenated substrate **85a** [$R^1 = R^2 = R^3 = H$, $Ar^1 = Ar^2 =$ Ph] to 10 mol% of $Fe(OTf)_3$ alone in DCE at rt led to the formation of the desired (2,2-phenylvinyl)-2*H*-chromene **88a** within 1.25 h in 78% yield. We therefore decided to establish the scope and generality of this reaction by employing the optimized condition on various substrates containing diverse functional groups (**Scheme 38**).

Towards this goal at first substitution effects of ring A directly attached to the oxygen atom were checked. Thus incorporation of an EDG (R^1= Me/OMe, R^2=R^3=H) at the *para*-position of the phenyl ring (A) of **85b**/**85c** led to the formations of 2*H*-chromenes **88b**/**88c** in 88-97% yield. Contrary to the previous observation (with **47d** in **Scheme 36**), an EWG (R^1 = Cl,

Scheme 38. Synthesis of 4-(2,2-diarylvinyl)-2*H*-Chromenes 88a-p[a]



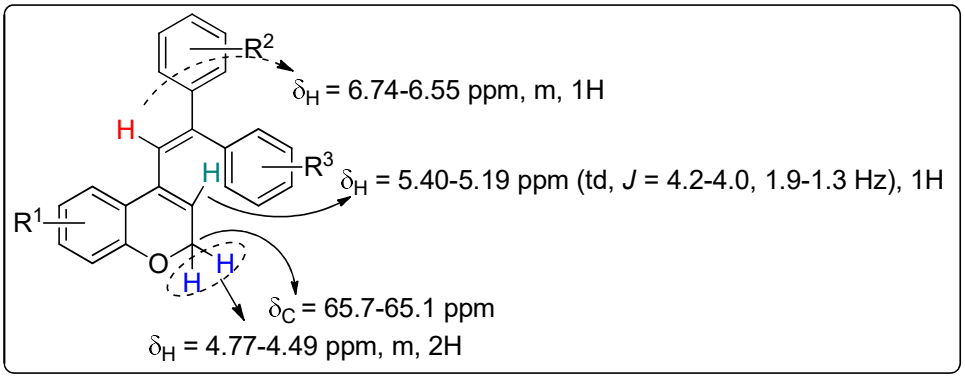
[a]Reaction conditions: A mixture of **85** (0.076 mmol) and $Fe(OTf)_3$ (0.008 mmol, 0.1 equiv) in DCE was stirred at room temperature under argon atmosphere.

$R^2 = R^3 = H$) in the same place delivered **88d** in 20 h with 78% yield. A phenyl substitution (R^1 = Ph, $R^2 = R^3 = H$) at the same position (as in **85e**) also proved effective, furnishing **88e** in 94% yield within 12 h. Even incorporation of an EDG at the *meta*-position ($R^1 = R^3 = H$, R^2 = OMe) of **85f** afforded **88f** in 1.5 h with 81% yield.

Next, effect of substitution on the other phenyl ring was checked. Installation of a EWG (F/Cl) at the *para*-position of the phenyl rings (substrate **85g/85h**) continued to deliver the products (**88g/88h**) smoothly with excellent yields. This high reactivity was maintained even after incorporation of an extra EDG (i.e., R^1 = OMe/Me, $R^2 = R^3 = H$) in the other phenyl ring (A) of substrate (**85i**/**85j**) affording product **88i/88j** with 90-93% yields within 1.25-1.5 h. But possession of a phenyl ring (R^1 = Ph) at the same position (of **85k**) slightly hindered the reaction, producing **88k** in 9 h with 72% yield.

Similar to our previous observations (with the substrates **84k** and **84l** of **Scheme 36**), substrate **85l** possessing a strong EDG (OMe) proved counterproductive; but presence of a mild EDG (Me) in **85m** afforded **88m** in 63% yield after 6.5 h. Furthermore, substrate **85n** having unsymmetrical aryl moieties (viz., Ar^1 = *p*-Me-C_6H_4, Ar^2 = Ph) furnished an inseparable mixture of products **88n** and **88n´** (85% yield, 1:1) after 4.5 h. Even naphthyl analogs (**85o** and **85p**) of the substrate were also found to be compatible, delivering the products (**88o** and **88p**) in 1.5 h with very good yields (80-83%).

3.2.4.3. Nature and characterization of products 88



The structures of the products were unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (EI and ESI), the molecular ion peak in positive mode of

all the compounds appeared as M^+ or protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^1H NMR the two protons adjacent to the oxygen atom (blue coloured) appears in the range of 4.77-4.49 ppm as a multiplet (m). The next proton (sea green coloured) appears in the range of 5.40-5.19 ppm as a triple doublet (td) with coupling constant 4.2-4.0 Hz and the red coloured proton appeared at the range of 6.74-6.55 as a multiplet. The ^{13}C NMR gave further support to the in favour of the structures. The carbon atom adjacent to the oxygen appeared at 65.7-65.1 ppm at ^{13}C NMR.

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of compound **88k**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 9.

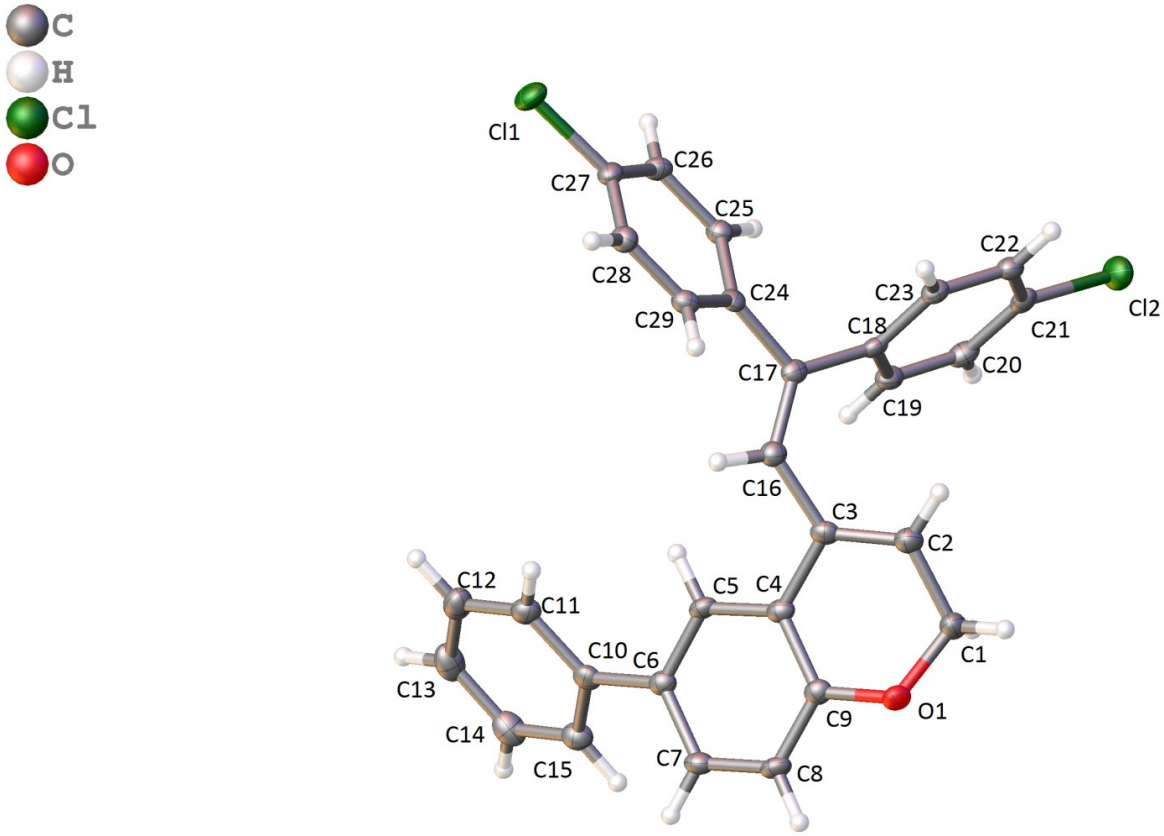


Figure 9. ORTEP Diagram (thermal ellipsoid plot) of Product **88k** (drawn at 50% probability level)

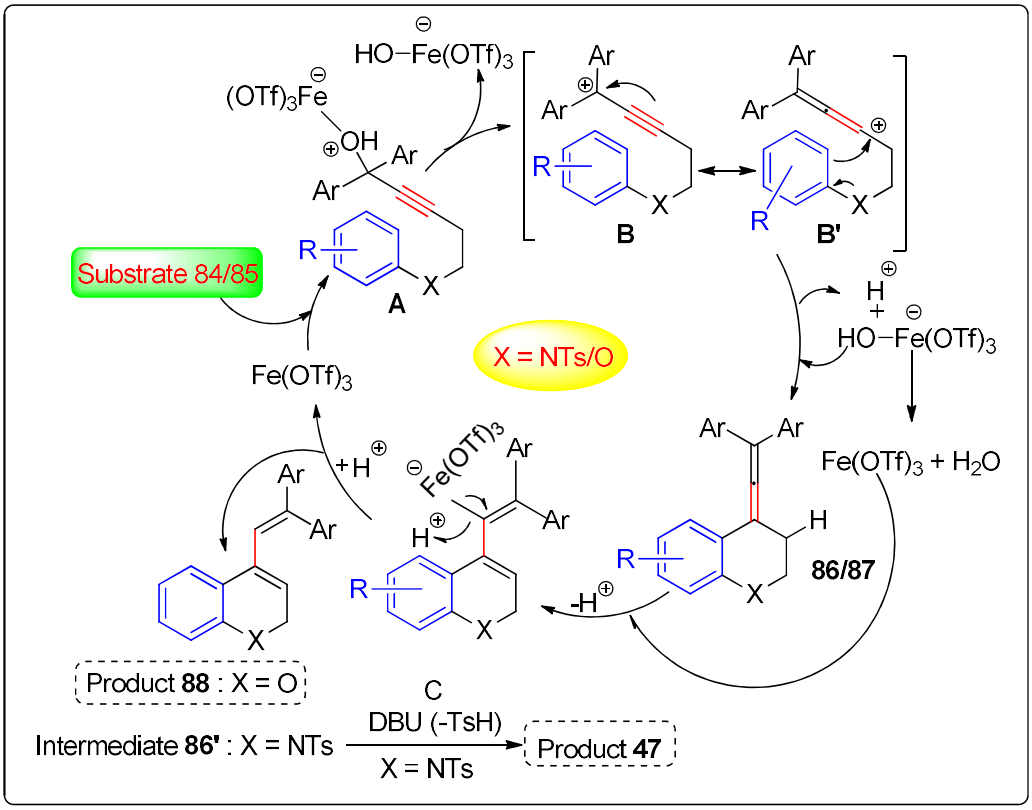
Table 5: Important crystal data of product **(88k)**

Empirical formula	$C_{29}H_{20}Cl_2O$
Formula weight	455.35
Temperature/K	102.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	11.0828(3)
b/Å	11.1395(4)
c/Å	18.1177(6)
α/°	90
β/°	95.432(2)
γ/°	90
Volume/Å^3	2226.71(12)
Z	4
ρ_{calc}g/cm^3	1.358
μ/mm^{-1}	2.767
F(000)	944.0
Crystal size/mm^3	0.5 × 0.45 × 0.35
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.99 to 136.258
Index ranges	$-13 \leq h \leq 13$, $-13 \leq k \leq 13$, $-19 \leq l \leq 21$
Reflections collected	40874
Independent reflections	4047 [R_{int} = 0.0696, R_{sigma} = 0.0338]
Data/restraints/parameters	4047/0/290
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0385, wR_2 = 0.0893
Final R indexes [all data]	R_1 = 0.0395, wR_2 = 0.0901
Largest diff. peak/hole / e Å^{-3}	0.30/-0.30

The single crystal of the product **88k** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Petroleum ether/ dichoromethane mixture. The crystal data of product **88k** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2192352.**

3.2.5. A Plausible mechanism for the formation of products 47 and 88

Based on our experimental observations and previous reports, a plausible reaction mechanism is proposed as depicted under **Scheme 39**. It is expected that $Fe(OTf)_3$ would first activate the propargylic alcohol of substrates **84/85** through coordination forming intermediate **A** and thus facilitate the formation of carbocation[62] **B** (or **B´**) by acting like a Lewis acid. The allenyl cation **B´** would then undergo an intramolecular nucleophilic attack by the adjacent aryl ring (by means of intramolecular *Friedel-Crafts* reaction) resulting in the formation of the carboannulated allene intermediates **86/87**; deprotonation from this step would regenerate $Fe(OTf)_3$ which triggers the formation of 1,3-diene intermediate **C**[60b,63] by acting like a Lewis acid again. Protonolysis of intermediate **C** would lead to the formation of either 2*H*-chromene **88** (X=O) or the dihydroquinoline intermediate **86´**(X=NTs) with concurrent release of $Fe(OTf)_3$ which keeps the catalytic cycle active. Finally, intermediate **86´** undergoes a base (DBU) promoted 1,2- elimination (-TsH) to furnish the desired 4-(2,2-diarylvinyl)quinoline **47**.



Scheme 39. A plausible mechanism for the formation of products **47/88**

3.2.6. Conclusion

In conclusion, an efficient straight method for the general synthesis of 4-(2,2-diarylvinyl)quinolones **47** via low cost iron(III)-catalyzed heteroannulation of homopropargyl amines **84** through IMFC have been disclosed. Replacing the substrates with homopropargyl ethers **85** easily led to the formation of 4-vinyl substituted 2*H*-chromenes **88** at room temparature in the presence of the same catalyst. A plausible reaction mechanism is proposed to explain the product formations. Importantly, the method utilizes low cost and environmental benign iron catalyst and simple substrates as well, shows high tolerance towards various functional groups, and produces water as the only by-product, thus tracing a green path.

3.2.7. Experimental section

3.2.7.1. General Information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 °C. Dichloromethane (DCM) was dried over phosphorous pentaoxide distilled, and stored over 3 Å molecular sieves in a sealed container. THF was distilled over sodium and benzophenone. Commercial grade dry 1,2 Dichloroethane (DCE), toluene, nitromethane were used as a solvent. Iron(III) trifluoromethanesulfonate was purchased from Sigma-Aldrich. All the reactions were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance. For purification, column chromatography was performed using 100−200 and 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given from TMS (δ = 0.00) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [$CDCl_3$: ^{1}H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm]. Coupling constants (*J*) are expressed in Hertz (Hz), and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), tt (triple triplet), q (quartet), m (multiplet), and br (broad). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF or EI mode.

3.2.7.2. X-Ray crystallographic information of products 47g, 47h, 47i and 88k

Single crystal of products **47g, 47h, 47i** and **88k** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum. The single crystal X-ray diffraction (XRD) data were collected on a Bruker D8 Venture system with a microfocus optics using CuK_α radiation. The data were analyzed and processed with Bruker Apex III software suite[64] incorporated with multiple tools such as cell_now and RLATT for the determination of the unit cell, SAINT-plus for data reduction and SADABS for absorption correction. The structure solutions were performed with SHELXT[65] and the full-matrix least-squares refinements were performed with SHELXL[66] suite of programs incorporated in either Apex III suite[64] or Olex 2.[67] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The important crystal data and ORTEP diagram (drawn at 50% probability level) of product **47g, 47h, 47i** and **88k** are provided earlier.

3.2.7.3. General procedure for the preparation of the starting materials 84

*Synthesis of tosylated derivatives **90**:*

To a well stirred solution of amine derivative **89** (2.7 mmol, 1 equiv) in dry DCM (3 mL) at 0 ^oC Et_3N was added (452.51 µL, 3.2 mmol, 1.2 equiv) dropwise. Thereafter, TsCl (612.9 mg, 3.2 mmol, 1.2 equiv) was added portion-wise at the same temperature and whole reaction mixture was allowed to stir at rt for 2-5 h. Upon completion of the reaction (TLC), solvent was removed in *vacuo* and then extracted with DCM (3x 25 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-25% ethyl acetate-petroleum ether (v/v) to obtain the pure tosylated **90** in 72-90% yield.

*Synthesis of **91** derivatives:*

To a well stirred solution of **90** (1.0 mmol, 1 equiv) in dry THF (3 mL), PPh_3 (340.6 mg, 1.3 mmol, 1.3 equiv) and 3-Butyn-1-ol (120.43 µL, 1.6 mmol, 1.6 equiv) were added. The reaction mixture was then cooled to 0 ^oC and DIAD [Diisopropyl azodicarboxylate] (291.17 µL, 1.6 mmol, 1.6 equiv) was added dropwise at that temperature. After stirring the mixture at 0 ^oC

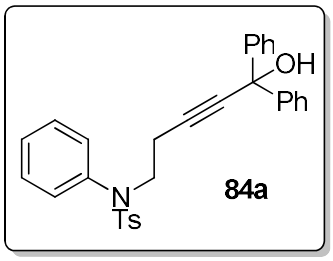
for 2-3 minutes, the temperature of the reaction was allowed to rise to rt and the mixture was stirred for additional 4-12 h. Then the mixture was quenched with water and extracted with ethyl acetate (3 x 25 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 8-17% ethyl acetate-petroleum ether (v/v) to obtain the pure **91** derivatives in 50-76% yield.

Synthesis of Final Stating Material **84:**

To well stirred ice cold solution of **91** (0.3 mmol, 1 equiv) in dry THF (0.5 mL), BuLi (1.6 M in hexane) (225.00 µL, 0.4 mmol, 1.2 equiv) was added dropwise followed by addition of ketone (54.60 mg, 0.3 mmol, 1 equiv). The reaction was then allowed to stir at the same temperature for 0.5-1 h. Then quenched by the addition of water and extracted with ethyl acetate (3 x 20 mL); the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-23% ethyl acetate-petroleum ether (v/v) to obtain the pure **84** derivative in 54-83% yield.

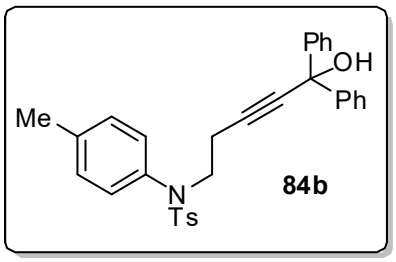
3.2.7.4. Spectral Data of Compounds 84a-l:

***N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-4-methyl-N-phenylbenzenesulfonamide (84a)*:**



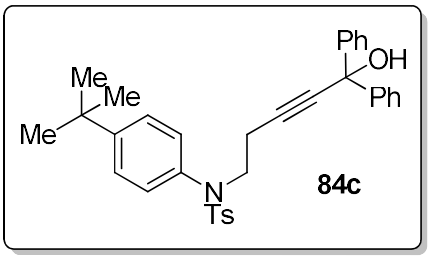
White solid (118.3 mg, 82%) isolated using 17% ethyl acetate-petroleum ether (v/v); mp 120-122 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.57-7.54 (m, 4H), 7.47 (d, J = 8.0 Hz, 2H), 7.32-7.20 (m, 11H), 7.05-7.02 (m, 2H), 3.76 (t, J = 7.0 Hz, 2H), 2.77 (s, 1H), 2.53 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.2, 143.6, 139.0, 135.5, 129.5, 129.2, 129.1, 128.3, 127.7, 127.6, 126.1, 85.2, 84.2, 74.4, 49.8, 21.6, 19.9; High-resolution mass spectrometry (HRMS) (ESI) m/z calcd for $C_{30}H_{27}NNaO_3S$ $[M + Na]^+$ 504.1609, found 504.1610.

***N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-4-methyl-N-(p-tolyl)benzenesulfonamide (84b)*:**



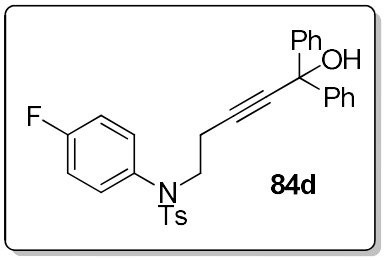
White solid (111.4 mg, 75%) isolated using 17% ethyl acetate-petroleum ether (v/v); mp 88-90 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.59-7.56 (m, 4H), 7.49 (d, J = 8.0 Hz, 2H), 7.33-7.29 (m, 4H), 7.26-7.21 (m, 4H), 7.06 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 3.74 (t, J = 7.0 Hz, 2H), 2.94 (s, 1H), 2.52 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.3, 143.5, 138.3, 136.2, 135.7, 129.9, 129.5, 129.0, 128.2, 127.8, 127.6, 126.1, 85.2, 84.3, 74.4, 49.8, 21.6, 21.2, 19.8; HRMS (ESI) m/z calcd for $C_{31}H_{29}NNaO_3S$ $[M + Na]^+$ 518.1766, found 518.1790.

N-(4-(tert-butyl)phenyl)-N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-4-methylbenzenesulfonamide (84c):



Clear solid (87.9 mg, 54%) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 62-64 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.57-7.55 (m, 4H), 7.50 (d, J = 8.0 Hz, 2H), 7.33-7.21 (m, 10 H), 6.95 (d, J = 8.8 Hz, 2H), 3.72 (t, J = 7.0 Hz, 2H), 2.81 (brs, 1H), 2.52 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.28 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 151.4, 145.2, 143.5, 136.2, 135.8, 129.5, 128.6, 128.2, 127.7, 127.6, 126.2, 126.1, 85.1, 84.3, 74.4, 49.9, 34.7, 31.4, 21.6, 19.9; HRMS (ESI) m/z calcd for $C_{34}H_{35}NNaO_3S$ $[M + Na]^+$ 560.2235, found 560.2255.

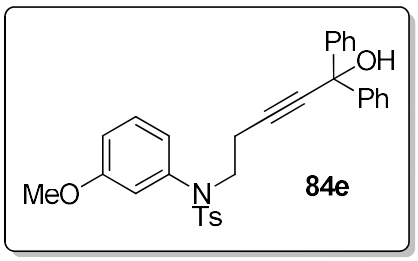
N-(4-fluorophenyl)-N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-4-methylbenzenesulfonamide (84d):



White solid (106.3 mg, 71%) isolated using 17% ethyl acetate-petroleum ether (v/v); mp 114-116 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.61-7.60 (m, 4H), 7.50 (d, J = 7.8 Hz, 2H), 7.34 (t, J = 7.5 Hz, 4H), 7.29-7.25 (m, 4H), 7.03-7.00 (m, 2H), 6.97-6.94 (m, 2H), 3.75 (t, J = 6.9, 2H), 3.10 (brs, 1H), 2.54 (t, J = 6.9 Hz, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 161.6 (d,

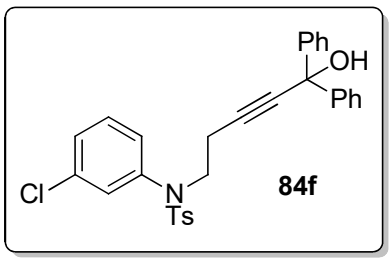
$J_{C\text{-}F}$ = 247.3 Hz), 144.7, 143.3, 134.7, 134.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.5 (d, $J_{C\text{-}F}$ = 8.7 Hz), 129.1, 127.8, 127.2 (d, $J_{C\text{-}F}$ = 7.5 Hz), 125.6, 115.6 (d, $J_{C\text{-}F}$ = 22.2 Hz), 84.9, 83.4, 73.9, 49.4, 21.1, 19.2; HRMS (ESI) m/z calcd for $C_{30}H_{26}FNNaO_3S$ $[M + Na]^+$ 522.1515, found 522.1506.

N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-N-(3-methoxyphenyl)-4-methylbenzenesulfonamide (84e) :



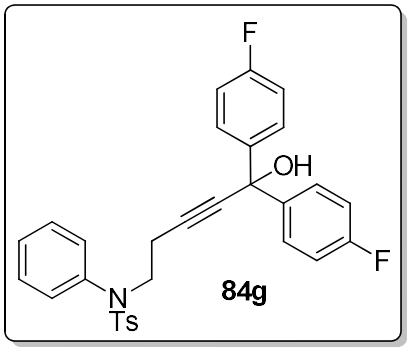
White solid (111.98 mg, 73%) isolated using 18% ethyl acetate-petroleum ether (v/v); mp 78-80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.59-7.56 (m, 4H), 7.51 (d, J = 8.4 Hz, 2H), 7.34-7.29 (m, 4H), 7.26-7.22 (m, 4H), 7.15 (t, J = 8.2 Hz, 1H), 6.84-6.81 (m, 1H), 6.67 (t, J = 2.2 Hz, 1H), 6.59-6.57 (m, 1H), 3.75 (t, J = 7.0 Hz, 2H), 3.66 (s, 3H), 2.91 (brs, 1H), 2.54 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.1, 145.2, 143.6, 140.1, 135.5, 129.7, 129.5, 128.3, 127.8, 127.6, 126.1, 120.8, 115.1, 114.2, 85.2, 84.2, 74.4, 55.4, 49.8, 21.6, 19.8; HRMS (ESI) m/z calcd for $C_{31}H_{29}NNaO_4S$ $[M + Na]^+$ 534.1715, found 534.1721.

N-(3-chlorophenyl)-N-(5-hydroxy-5,5-diphenylpent-3-yn-1-yl)-4-methylbenzenesulfonamide (84f):



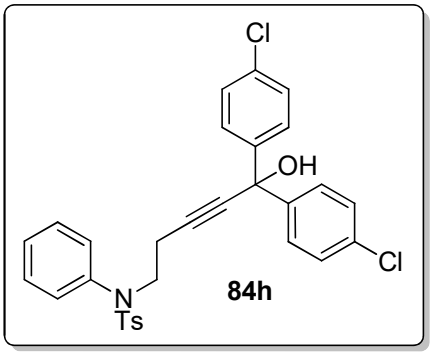
White solid (128.2 mg, 83%) isolated using 12% ethyl acetate-petroleum ether (v/v); mp 108-110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.57-7.55 (m, 4H), 7.48 (d, J = 8.4 Hz, 2H), 7.33-7.29 (m, 4H), 7.27-7.22 (m, 5H), 7.18 (t, J = 8.0 Hz, 1H), 7.06 (t, J = 1.8 Hz, 1H), 6.97-6.94 (m, 1H), 3.72 (t, J = 7.0 Hz, 2H), 2.97 (brs, 1H), 2.52 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.2, 144.0, 140.2, 135.1, 134.6, 130.1, 129.7, 129.2, 128.5, 128.3, 127.7, 127.6, 127.4, 126.1, 85.5, 83.8, 74.4, 49.6, 21.7, 19.8; HRMS (ESI) m/z calcd for $C_{30}H_{26}ClNNaO_3S$ $[M + Na]^+$ 538.1220, found 538.1209.

N-(5,5-bis(4-fluorophenyl)-5-hydroxypent-3-yn-1-yl)-4-methyl-N-phenylbenzenesulfonamide (84g):



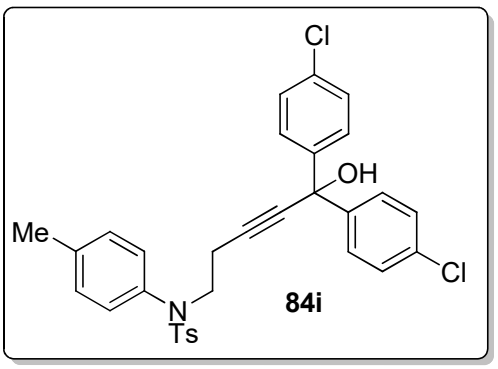
White solid (116.3 mg, 75%) isolated using 22% ethyl acetate-petroleum ether (v/v); mp 96-98 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.55-7.51 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.29-7.22 (m, 5H), 7.05-6.98 (m, 6H), 3.77 (t, J = 6.8 Hz, 2H), 3.01 (s, 1H), 2.51 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.3 (d, J_{C-F} = 245.2 Hz), 143.7, 141.0 (d, J_{C-F} = 3.7 Hz), 138.8, 135.5, 129.6, 129.2 (d, J_{C-F} = 10.7 Hz), 128.3, 127.9 (d, J_{C-F} = 8.2 Hz), 127.7, 115.1 (d, J_{C-F} = 21.5 Hz), 85.0, 84.7, 73.5, 49.7, 21.6, 19.7; HRMS (ESI) m/z calcd for $C_{30}H_{25}F_2NNaO_3S$ $[M + Na]^+$ 540.1421, found 540.1427.

N-(5,5-bis(4-chlorophenyl)-5-hydroxypent-3-yn-1-yl)-4-methyl-N-phenylbenzenesulfonamide (84h):



White solid (116.9 mg, 71%) isolated using 18% ethyl acetate-petroleum ether (v/v); mp 132-134 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.50-7.44 (m, 6H), 7.30-7.24 (m, 7H), 7.22 (d, J = 8.0 Hz, 2H), 7.02 (dd, J = 7.8, 1.8 Hz, 2H), 3.75 (t, J = 6.8 Hz, 2H), 3.04 (s, 1H), 2.49 (t, J = 6.8 Hz, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 143.7, 143.5, 138.8, 135.5, 133.7, 129.6, 129.3, 129.1, 128.5, 128.3, 127.7, 127.6, 85.0, 84.5, 73.5, 49.7, 21.6, 19.7; HRMS (ESI) m/z calcd for $C_{30}H_{25}Cl_2NNaO_3S$ $[M + Na]^+$ 572.0830, found 572.0833.

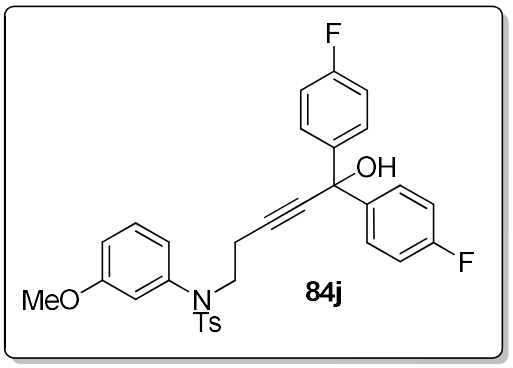
N-(5,5-bis(4-chlorophenyl)-5-hydroxypent-3-yn-1-yl)-4-methyl-N-(p-tolyl)benzenesulfonamide (84i):



White solid (109.8 mg, 65%) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 136-138 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.50-7.47 (m, 6H), 7.29-7.27 (m, 4H), 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H),

6.90 (d, J = 8.4 Hz, 2H), 3.74 (t, J = 6.8 Hz, 2H), 3.07 (brs, 1H), 2.49 (t, J = 6.6 Hz, 2H), 2.42 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 143.6, 143.5, 138.4, 136.1, 135.6, 133.7, 129.9, 129.5, 128.9, 128.5, 127.7, 127.5, 100.0, 85.1, 84.5, 73.5, 49.7, 21.6, 21.2, 19.7; HRMS (ESI) m/z calcd for $C_{31}H_{27}Cl_2NNaO_3S$ $[M + Na]^+$ 586.0986, found 586.0983.

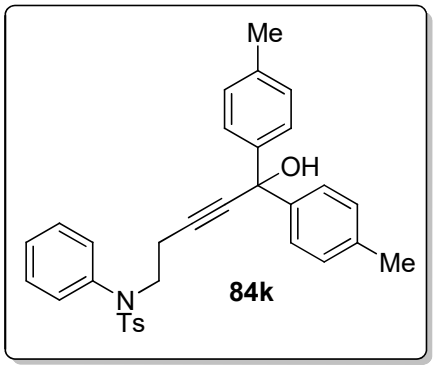
N-(5,5-bis(4-fluorophenyl)-5-hydroxypent-3-yn-1-yl)-N-(3-methoxyphenyl)-4-methylbenzenesulfonamide (84j):



84j

Colourless liquid (124.7 mg, 76%) isolated using 23% ethyl acetate-petroleum ether (v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.55-7.49 (m, 6H), 7.24 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.2 Hz, 1H), 7.02-6.96 (m, 4H), 6.84-6.81 (m, 1H), 6.65 (t, J = 2.2 Hz, 1H), 6.58-6.55 (m, 1H), 3.75 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 3.08 (brs, 1H), 2.51 (t, J = 6.8 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 162.3 (d, J_{C-F} = 245.2 Hz), 160.1, 143.7, 141.0 (d, J_{C-F} = 3.3 Hz), 139.9, 135.5, 129.7, 129.6, 127.9 (d, J_{C-F} = 8.2 Hz), 127.7, 120.8, 115.3, 115.1 (d, J_{C-F} = 21.5 Hz), 114.1, 85.0, 84.7, 73.5, 55.4, 49.7, 21.6, 19.7; HRMS (ESI) m/z calcd for $C_{31}H_{27}F_2NNaO_4S$ $[M + Na]^+$ 570.1527, found 570.1522.

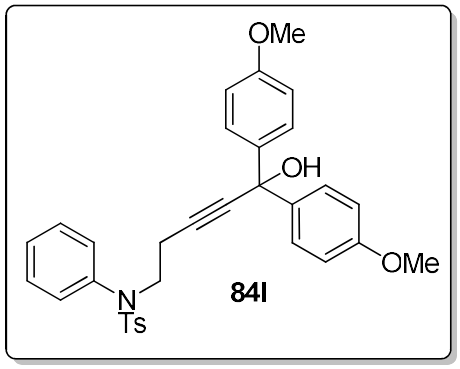
N-(5-hydroxy-5,5-di-p-tolylpent-3-yn-1-yl)-4-methyl-N-phenylbenzenesulfonamide (84k):



84k

White solid (108.4 mg, 71%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 114-116 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.49 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 4H), 7.30-7.26 (m, 3H), 7.23 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 4H), 7.07-7.05 (m, 2H), 3.76 (t, J = 7.2 Hz, 2H), 2.79 (s, 1H), 2.53 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 2.32 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 143.6, 142.6, 139.0, 137.2, 135.5, 129.6, 129.2, 129.1, 128.9, 128.2, 127.8, 126.0, 85.5, 83.7, 74.2, 49.8, 21.6, 21.2, 19.8; HRMS (ESI) m/z calcd for $C_{32}H_{31}NNaO_3S$ $[M + Na]^+$ 532.1922, found 532.1925.

N-(5-hydroxy-5,5-bis(4-methoxyphenyl)pent-3-yn-1-yl)-4-methyl-N-phenylbenzenesulfonamide (84l):



84l

Brown gummy liquid (87.6 mg, 54%) isolated using 20% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.49-7.44 (m, 6H), 7.28-7.22 (m, 5H), 7.06-7.04 (m, 2H), 6.83 (d, J = 9.2 Hz, 4H), 3.79-3.74 (m, 8H), 2.70 (brs, 1H), 2.52 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.0, 143.6, 139.0, 137.7, 135.5, 129.5, 129.2, 129.1, 128.2, 127.7, 127.4, 113.5, 85.5, 83.7, 73.8, 55.4, 49.8, 21.6, 19.8; HRMS (ESI) m/z calcd for $C_{32}H_{31}NNaO_5S$ $[M + Na]^+$ 564.1821, found 564.1805.

3.2.7.5. General procedure for the preparation of the starting materials 85

Synthesis of tosylated **93** *derivatives:*

To a well stirred solution of phenol derivative **92** (2.0 mmol, 1 equiv) in dry THF (3 mL), PPh_3 (681.2 mg, 2.6 mmol, 1.3 equiv) and 3-Butyn-1-ol (240.86 µL, 3.2 mmol, 1.6 equiv) were added. The reaction mixture was then cooled to 0 ^{o}C and DIAD [Diisopropyl azodicarboxylate] (582.34 µL, 3.2 mmol, 1.6 equiv) was added dropwise at that temperature. After stirring the mixture at 0 ^{o}C for 2-3 minutes, the temperature of the reaction was allowed to rise to rt and the mixture was stirred for additional 4-12 h. Then the mixture was quenched with water and extracted with ethyl acetate (3 x 25 mL); the combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 2-5% ethyl acetate-petroleum ether (v/v) to obtain the pure **93** derivatives in 50-72% yield.

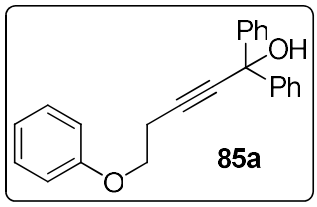
Synthesis of Final Stating Materials ***85:***

To a ice cold solution of **93** (0.6 mmol, 1 equiv) in dry THF (0.8 mL), BuLi (1.6 M in hexane) (375.0 µL, 0.6 mmol, 1 equiv) was added dropwise followed by addition of ketone (109.2 mg, 0.6 mmol, 1 equiv). The reaction mixture was then allowed to stir at the same temperature for 0.5-1h. The reaction was quenched with ethyl acetate (3 x 20 mL); the combined

organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 4-8% ethyl acetate-petroleum ether (v/v) to obtain the pure **2** derivatives in 32-64% yield.

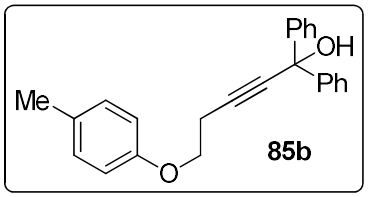
3.2.7.6. Spectral Data of Compounds 85a-p:

5-phenoxy-1,1-diphenylpent-2-yn-1-ol (85a):



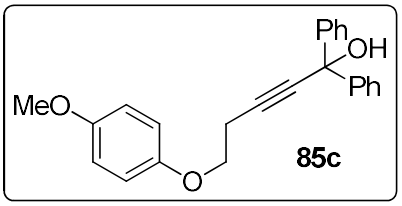
White solid (118.1 mg, 60%) isolated using 6% ethyl acetate-petroleum ether (v/v); mp 70-72 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.67-7.64 (m, 4H), 7.37-7.27 (m, 8H), 7.02 (tt, J = 7.4, 1.0 Hz, 1H), 6.98-6.96 (m, 2H), 4.18 (t, J = 6.8 H, 2H), 3.01 (s, 1H), 2.85 (t, J = 6.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.6, 145.3, 129.7, 128.3, 127.7, 126.2, 121.3, 114.9, 84.8, 84.2, 74.5, 66.1, 20.2; HRMS $(EI)^+$ m/z calcd for $C_{23}H_{20}O_2$ $[M]^+$ 328.1463, found 328.1465.

1,1-diphenyl-5-(p-tolyloxy)pent-2-yn-1-ol (85b) :



Colourless liquid (131.3 mg, 64%) isolated using 6% ethyl acetate-petroleum ether (v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.71-7.68 (m, 4H), 7.40-7.35 (m, 4H), 7.34-7.29 (m, 2H), 7.17-7.15 (m, 2H), 6.92-6.88 (m, 2H), 4.16 (t, J = 7.0 Hz, 2H), 3.10 (brs, 1H), 2.85 (t, J = 7.0 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 156.5, 145.4, 130.5, 130.1, 128.4, 127.7, 126.2, 114.9, 84.8, 84.4, 74.6, 66.4, 20.7, 20.2; HRMS $(EI)^+$ m/z calcd for $C_{24}H_{22}O_2$ $[M]^+$ 342.1620, found 342.1618.

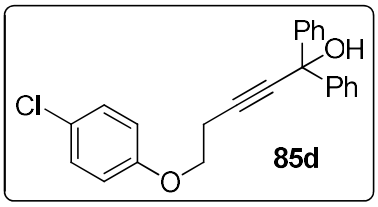
5-(4-methoxyphenoxy)-1,1-diphenylpent-2-yn-1-ol (85c):



White solid (105.2 mg, 49%) isolated using 5% ethyl acetate-petroleum ether (v/v); mp 78-80 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.63 (d, J = 8.4 Hz, 4H), 7.33 (t, J = 7.5 Hz, 4H), 7.27 (t, J = 7.5 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.12 (t, J = 6.9 Hz, 2H), 3.79 (s, 3H), 2.84 (s, 1H), 2.82 (t, J = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR

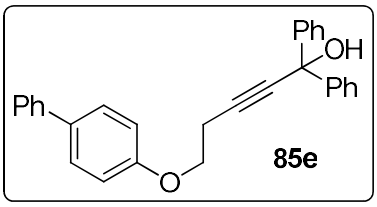
($CDCl_3$, 150 MHz) δ_C 154.1, 152.5, 145.2, 128.2, 127.6, 126.0, 115.9, 114.7, 84.5, 84.2, 74.4, 66.8, 55.7, 20.1; HRMS $(EI)^+$ m/z calcd for $C_{24}H_{22}O_3$ $[M]^+$ 358.1569, found 358.1567.

5-(4-chlorophenoxy)-1,1-diphenylpent-2-yn-1-ol (85d):



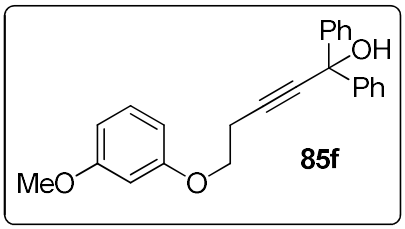
Colourless liquid (97.7 mg, 45%) isolated using 5% ethyl acetate-petroleum ether (v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.62-7.59 (m, 4H), 7.34-7.22 (m, 8H), 6.84 (d, J = 9.2 Hz, 2H), 4.10 (t, J = 6.8 Hz, 2H), 2.93 (brs, 1H), 2.81 (t, J = 6.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 157.2, 145.2, 129.5, 128.3, 127.8, 126.1, 116.1, 84.9, 83.9, 74.5, 66.5, 20.1; HRMS $(EI)^+$ m/z calcd for $C_{23}H_{19}ClO_2$ $[M]^+$ 362.1074, found 362.1071.

5-([1,1'-biphenyl]-4-yloxy)-1,1-diphenylpent-2-yn-1-ol (85e):



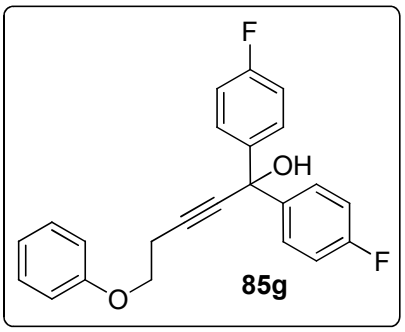
White solid (109.1 mg, 45%) isolated using 5% ethyl acetate-petroleum ether (v/v); mp 108-110 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.64-7.62 (m, 4H), 7.58-7.53 (m, 4H), 7.45-7.41 (m, 2H), 7.35-7.30 (m, 5H), 7.28-7.24 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 4.21 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2H), 2.81 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.1, 145.2, 140.8, 134.3, 128.8, 128.3, 127.7, 126.8, 126.1, 115.1, 84.8, 84.1, 74.5, 66.2, 20.2; HRMS $(EI)^+$ m/z calcd for $C_{29}H_{24}O_2$ $[M]^+$ 404.1776, found 404.1783.

5-(3-methoxyphenoxy)-1,1-diphenylpent-2-yn-1-ol (85f):



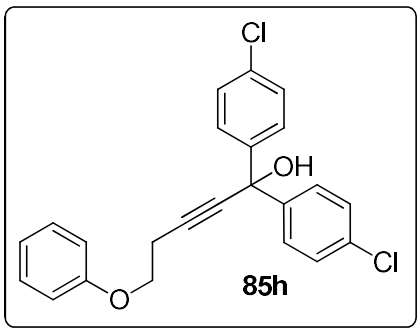
White solid (77.3 mg, 36%) isolated using 6% ethyl acetate-petroleum ether (v/v); mp 72-74 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.63 (d, J = 7.2 Hz, 4H), 7.33 (t, J = 7.5 Hz, 4H), 7.27 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 8.1 Hz, 1H), 6.56-6.55 (m, 2H), 6.52 (t, J = 2.1 Hz, 1H), 4.16 (t, J = 6.9 Hz, 2H), 3.80 (s, 3H), 2.87 (s, 1H), 2.84 (t, J = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 160.8, 159.7, 145.1, 129.9, 128.2, 127.6, 126.0, 106.8, 106.7, 101.2, 84.6, 84.0, 74.4, 66.0, 55.3, 20.0; HRMS $(EI)^+$ m/z calcd for $C_{24}H_{22}O_3$ $[M]^+$ 358.1569, found 358.1573.

1,1-bis(4-fluorophenyl)-5-phenoxypent-2-yn-1-ol (85g):



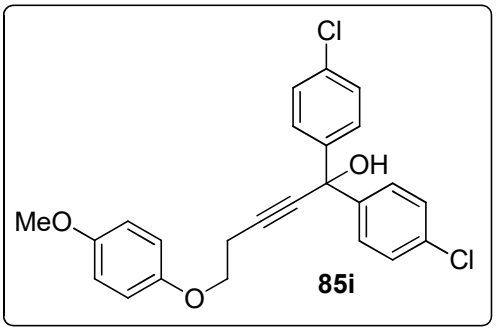
Yellow liquid (135.4 mg, 62%) isolated using 7% ethyl acetate-petroleum ether (v/v) **;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.58-7.54 (m, 4H), 7.34-7.30 (m, 2H), 7.03-6.98 (m, 5H), 6.95-6.93 (m, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.06 (brs, 1H), 2.82 (t, J = 6.6 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.3 (d, $J_{C\text{-}F}$ = 245.4 Hz), 158.5, 141.1 (d, $J_{C\text{-}F}$ = 3.8 Hz), 129.7, 127.9 (d, $J_{C\text{-}F}$ = 8.3 Hz), 121.4, 115.1 (d, $J_{C\text{-}F}$ = 21.5 Hz), 114.8, 84.8, 84.4, 73.6, 66.0, 20.2; HRMS (EI)$^+$ m/z calcd for $C_{23}H_{18}F_2O_2$ $[M]^+$ 364.1275, found 364.1280.

1,1-bis(4-chlorophenyl)-5-phenoxypent-2-yn-1-ol (85h):



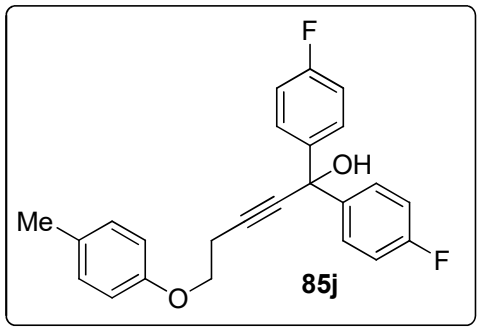
Yellow liquid (137.8 mg, 58%) isolated using 5% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.53-7.50 (m, 4H), 7.34-7.27 (m, 6H), 7.00 (tt, J = 7.3, 1.1 Hz, 1H), 6.94-6.92 (m, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.01 (brs, 1H), 2.82 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.4, 143.5, 133.8, 129.7, 128.5, 127.5, 121.4, 114.8, 85.2, 83.9, 73.6, 65.9, 20.2; HRMS (EI)$^+$ m/z calcd for $C_{23}H_{18}Cl_2O_2$ $[M]^+$ 396.0684, found 396.0686.

1,1-bis(4-chlorophenyl)-5-(4-methoxyphenoxy)pent-2-yn-1-ol (85i):



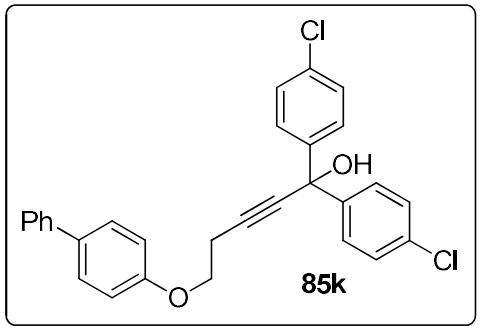
Colourless liquid (115.0 mg, 45%) isolated using 5% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.51-7.47 (m, 4H), 7.27-7.24 (m, 4H), 6.84-6.82 (m, 4H), 4.08 (t, J = 6.8 Hz, 2H), 3.76 (s, 3H), 3.00 (s, 1H), 2.77 (t, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 154.3, 152.5, 143.5, 133.8, 128.5, 127.5, 116.0, 114.8, 85.2, 83.8, 73.6, 66.9, 55.8, 20.2; HRMS (EI)$^+$ m/z calcd for $C_{24}H_{20}Cl_2O_3$ $[M]^+$ 426.0789, found 426.0794.

1,1-bis(4-fluorophenyl)-5-(p-tolyloxy)pent-2-yn-1-ol (85j):



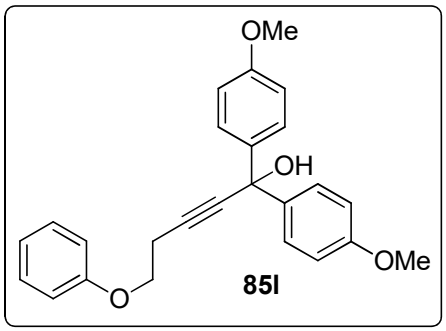
Colourless liquid (145.1 mg, 64%) isolated using 7% ethyl acetate-petroleum ether (v/v**);** ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.60-7.57 (m, 4H), 7.14 (d, J = 8.4 Hz, 2H), 7.02 (t, J = 8.7 Hz, 4H), 6.86 (d, J = 8.4 Hz, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.12 (s, 1H), 2.82 (t, J = 6.9 Hz, 2H), 2.35 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 162.2 (d, $J_{C\text{-}F}$ = 245.4 Hz), 156.2, 141.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.6, 130.0, 127.9 (d, $J_{C\text{-}F}$ = 8.4 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.4 Hz), 114.7, 84.8, 84.2, 73.5, 66.1, 20.5, 20.1; HRMS (EI)$^+$ m/z calcd for $C_{24}H_{20}F_2O_2$ $[M]^+$ 378.1431, found 378.1434.

5-([1,1'-biphenyl]-4-yloxy)-1,1-bis(4-chlorophenyl)pent-2-yn-1-ol (85k):



Colourless liquid (90.6 mg, 32%) isolated using 4% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.61-7.57 (m, 3H), 7.56-7.53 (m, 5H), 7.48-7.44 (m, 2H), 7.37-7.29 (m, 5H), 7.01 (d, J = 8.8 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.14 (brs, 1H), 2.85 (t, J = 6.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 143.5, 140.7, 134.5, 133.8, 128.9, 128.6, 128.4, 127.6, 127.0, 126.9, 115.2, 85.1, 84.0, 73.6, 66.1, 20.2; HRMS (EI)$^+$ m/z calcd for $C_{29}H_{22}Cl_2O_2$ $[M]^+$ 472.0997, found 472.0998.

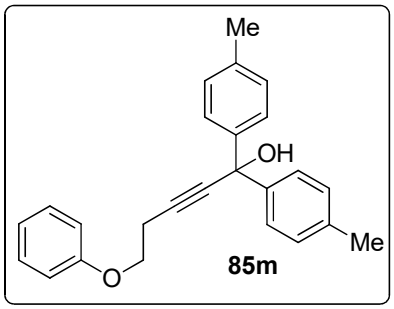
1,1-bis(4-methoxyphenyl)-5-phenoxypent-2-yn-1-ol (85l):



Deep yellow liquid (79.1 mg, 34%) isolated using 8% ethyl acetate-petroleum ether (v/v) ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.52 (d, J = 8.8 Hz, 4H), 7.34-7.31 (m, 2H), 7.02-6.94 (m, 3H), 6.85 (d, J = 9.2 Hz, 4H), 4.15 (t, J = 6.8 Hz, 2H), 3.79 (s, 6H), 2.96 (brs, 1H), 2.82 (t, J = 6.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.0, 158.6, 137.9, 129.6,

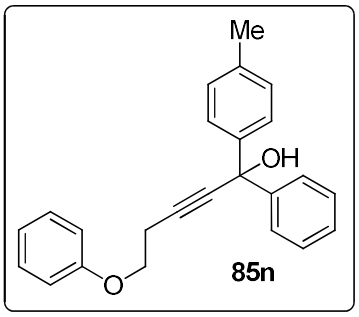
127.5, 121.2, 114.8, 113.6, 85.2, 83.7, 73.8, 66.1, 55.4, 20.2; HRMS (ESI) m/z calcd for $C_{25}H_{24}NaO_4$ $[M + Na]^+$ 411.1572, found 411.1571.

5-phenoxy-1,1-di-p-tolylpent-2-yn-1-ol (85m):



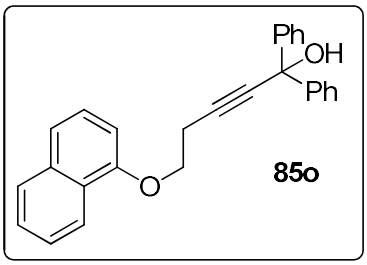
Pale yellow liquid (136.7 mg, 64%) isolated using 4% ethyl acetate-petroleum ether (v/v) **;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.58-7.55 (m, 4H), 7.38-7.34 (m, 2H), 7.18 (d, J = 8.0 Hz, 4H), 7.04 (tt, J = 7.4 , 0.9 Hz, 1H), 7.01-6.98 (m, 2H), 4.19 (t, J = 6.8 Hz, 2H), 2.97 (s, 1H), 2.87 (t, J = 6.8 Hz, 2H), 2.39 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.6, 142.7, 137.3, 129.7, 129.0, 126.1, 121.3, 114.9, 85.1, 83.8, 74.3, 66.2, 21.2, 20.2; HRMS (ESI) m/z calcd for $C_{25}H_{25}O_2$ $[M + H]^+$ 357.1855, found 357.1865.

5-phenoxy-1-phenyl-1-(p-tolyl)pent-2-yn-1-ol (85n):



Yellow liquid (88.2 mg, 43%) isolated using 5% ethyl acetate-petroleum ether (v/v) **;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.69-7.66 (m, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.38-7.28 (m, 5H), 7.17 (d, J = 8.4 Hz, 2H), 7.06-7.01 (m, 1H), 7.00-6.97 (m, 2H), 4.18 (t, J = 6.8 Hz, 2H), 2.99 (s, 1H), 2.86 (t, J = 6.8 Hz, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.6, 145.5, 142.6, 137.4, 129.7, 129.0, 128.3, 127.7, 126.2, 126.1, 121.3, 114.9, 85.0, 84.0, 74.4, 66.1, 21.2, 20.2; HRMS $(EI)^+$ m/z calcd for $C_{24}H_{22}O_2$ $[M]^+$ 342.1620, found 342.1610.

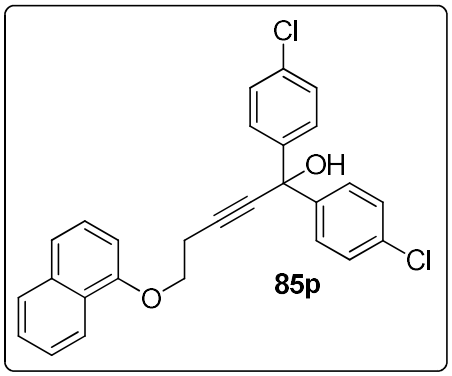
5-(naphthalen-1-yloxy)-1,1-diphenylpent-2-yn-1-ol (85o):



Pale brown liquid (111.4 mg, 49%) isolated using 5% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.42-8.39 (m, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.68-7.65 (m, 4H), 7.57-7.48 (m, 3H), 7.41 (t, J = 7.8 Hz, 1H), 7.33-7.25 (m, 6H), 6.84 (d, J = 6.8 Hz, 1H), 4.33 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.6

Hz, 2H), 2.94 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.4, 145.3, 134.7, 128.4, 127.7, 127.6, 126.6, 126.2, 125.9, 125.8, 125.5, 122.2, 120.8, 105.2, 84.8, 84.5, 74.6, 66.4, 20.3; HRMS $(EI)^+$ m/z calcd for $C_{27}H_{22}O_2$ $[M]^+$ 378.1620, found 378.1619.

1,1-bis(4-chlorophenyl)-5-(naphthalen-1-yloxy)pent-2-yn-1-ol (85p):



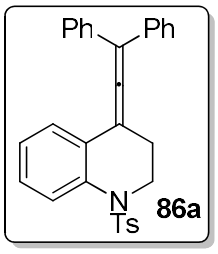
Pale yellow solid (139.1 mg, 52%) isolated using 5% ethyl acetate-petroleum ether (v/v); mp 96-98 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.32 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.56-7.45 (m, 7H), 7.39 (t, J = 8.0 Hz, 1H), 7.24-7.21 (m, 4H), 6.83 (d, J = 7.6 Hz, 1H), 4.33 (t, J = 6.4 Hz, 2H), 2.96 (t, J = 6.4 Hz, 2H), 2.91 (brs, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.3, 143.5, 134.7, 133.8, 128.5, 127.7, 127.5, 126.7, 125.9, 125.7, 125.5, 122.0, 120.9, 105.2, 85.3, 83.9, 73.6, 66.3, 20.3; HRMS $(EI)^+$ m/z calcd for $C_{27}H_{20}Cl_2O_2$ $[M]^+$ 446.0840, found 446.0841.

3.2.7.7. General procedure for the synthesis of products 47:

To a well stirred solution of starting material **84** (0.062 mmol, 1 equiv.) in dry 1, 2 dichloroethane (DCE) (1.7 mL), 4 A^o molecular sieves (12 mg) and $Fe(OTf)_3$ (0.006 mmol, 0.1 equiv.) were added. The reaction mixture was then heated at 80 ^oC for 1-2.5 h. Upon completion of reaction (TLC), the solvent was evaporated in *vacuo* and 1,8-Diazabicyclo(5.4.0)undec-7-ene (0.62 mL) [DBU] was added. The whole reaction mixture was then heated at 80 ^oC for another 2-5 h. Upon completion of reaction (TLC), the reaction mixture was purified by silica gel (100-200 mesh) column chromatography eluting in 7-15% ethyl acetate-petroleum ether (v/v) to afford the desired product **47** in (52-98%) yield.

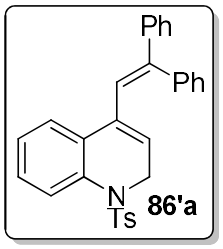
3.2.7.8. Spectral data of isolated intermediates 86a, 86′a, 86d and (86f, 86f′):

4-(2,2-diphenylvinylidene)-1-tosyl-1,2,3,4-tetrahydroquinoline (86a):



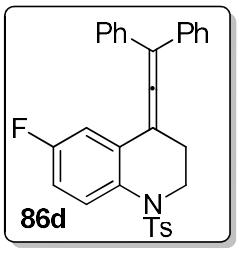
Colourless liquid (27.3 mg, 95%) isolated using 5% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.79 (dd, J = 8.2, 1.0 Hz, 1H), 7.54-7.52 (m, 3H), 7.35-7.29 (m, 6H), 7.26-7.23 (m, 5H), 7.21-7.19 (m, 2H), 7.14-7.10 (m, 1H), 3.98-3.95 (m, 2H), 2.50-2.47 (m, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 205.2, 143.8, 137.6, 136.3, 135.9, 129.8, 128.6, 128.5, 127.9, 127.7, 127.2, 127.1, 126.2, 125.9, 125.0, 114.3, 100.5, 45.6, 25.8, 21.7; HRMS (ESI) m/z calcd for $C_{30}H_{26}NO_2S$ $[M + H]^+$ 464.1684, found 464.1679.

4-(2,2-diphenylvinyl)-1-tosyl-1,2-dihydroquinoline (86'a):



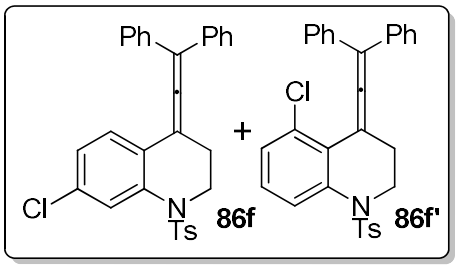
Colourless liquid (23.0 mg, 80%) isolated using 5% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.69-7.66 (m, 1H), 7.33-7.25 (m, 5H), 7.24-7.22 (m, 3H), 7.20-7.17 (m, 3H), 7.13-7.09 (m, 4H), 7.01-6.99 (m, 2H), 5.84-5.82 (m, 1H), 5.03 (td, J = 4.6, 1.5 Hz, 1H), 4.13-4.12 (m, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.8, 143.3, 142.7, 139.7, 136.3, 135.6, 134.0, 131.4, 129.8, 129.1, 128.3, 128.28, 128.24, 127.9, 127.8, 127.7, 127.5, 127.3, 127.0, 124.7, 124.1, 123.4, 45.3, 21.6; HRMS $(EI)^+$ m/z calcd for $C_{30}H_{25}NO_2S$ $[M]^+$ 463.1606, found 463.16595.

4-(2,2-diphenylvinylidene)-6-fluoro-1-tosyl-1,2,3,4-tetrahydroquinoline (86d):



Pale yellow solid (9.5 mg, 32%) isolated using 5% ethyl acetate-petroleum ether (v/v); mp 122-124 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.78-7.75 (m, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.34-7.30 (m, 6H), 7.22-7.16 (m, 7H), 6.96-6.93 (m, 1H), 3.94-3.92 (m, 2H), 2.42-2.40 (m, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 204.6, 160.1 (d, J_{C-F} = 243.3 Hz), 143.4, 136.8, 135.3, 131.4, 129.4, 128.1, 128.0 (d, J_{C-F} = 7.9 Hz), 127.9, 127.4, 126.8 (d, J_{C-F} = 8.1 Hz), 126.7, 114.7 (d, J_{C-F} = 22.9 Hz), 114.2, 112.1 (d, J_{C-F} = 23.5 Hz), 99.5, 45.0, 24.6, 21.2; HRMS (ESI) m/z calcd for $C_{30}H_{25}FNO_2S$ $[M + H]^+$ 482.1590, found 464.1581.

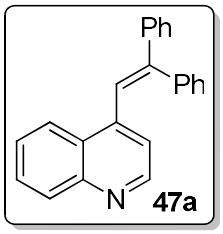
7-chloro-4-(2,2-diphenylvinylidene)-1-tosyl-1,2,3,4-tetrahydroquinoline (86f) and and 5-chloro-4-(2,2-diphenylvinylidene)-1-tosyl-1,2,3,4-tetrahydroquinoline (86f') (2.2:1) :



Colourless liquid (14.5 mg, 47%) isolated using 5% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.83 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 8.2, 1.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 1H), 7.35-7.28 (m, 12H), 7.24-7.22 (m, 9H), 7.15 (t, J = 8.0 Hz, 2H), 7.11-7.07 (m, 4H), 3.95-3.90 (m, 4H), 2.57-2.54 (m, 2H), 2.48-2.45 (m, 2H), 2.38 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 206.9, 205.0, 144.1, 144.0, 138.2, 137.24, 137.21, 136.75, 136.72, 136.0, 133.2, 130.0, 129.9, 128.65, 128.62, 128.4, 128.1, 127.9, 127.4, 127.2, 127.2, 126.1, 125.8, 124.7, 124.4, 123.4, 114.6, 111.7, 100.0, 97.0, 45.6, 45.5, 28.7, 25.7, 21.7, 21.6; HRMS (EI)$^{+}$ m/z calcd for $C_{30}H_{24}ClNO_2S$ $[M]^{+}$ 497.1216, found 497.1222.

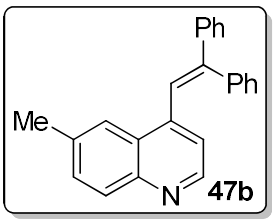
3.2.7.9. Spectral data of compounds 47a-k:

4-(2,2-diphenylvinyl)quinoline (47a) :



Pale yellow solid (13.3 mg, 70%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 78-80 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.58 (d, J = 4.4 Hz, 1H), 8.15 (dd, J = 8.4, 0.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.73-7.69 (m, 1H), 7.56-7.52 (m, 1H), 7.44-7.38 (m, 6H), 7.24-7.17 (m, 3H), 7.10-7.07 (m, 2H), 6.87 (d, J = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 149.9, 148.5, 148.0, 143.7, 142.6, 139.3, 130.5, 130.1, 129.3, 128.49, 128.48, 128.43, 128.3, 127.9, 127.7, 126.5, 124.5, 123.3, 121.6; HRMS (ESI) m/z calcd for $C_{23}H_{18}N$ $[M + H]^{+}$ 308.1439, found 308.1444.

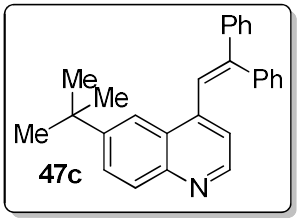
4-(2,2-diphenylvinyl)-6-methylquinoline (47b):



Pale yellow solid (19.5 mg, 98%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 178-180 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.51 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.54 (dd,

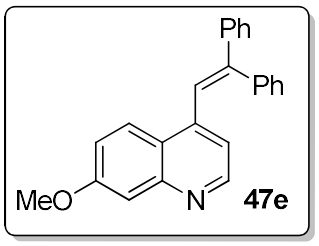
J = 8.8, 2.0 Hz, 1H), 7.46-7.39 (m, 6H), 7.24-7.17 (m, 3H), 7.10-7.07 (m, 2H), 6.82 (d, J = 4.4 Hz, 1H), 2.54 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 149.0, 147.6, 147.0, 143.0, 142.7, 139.4, 136.5, 131.6, 130.5, 129.8, 128.5, 128.43, 128.39, 128.33, 127.9, 127.7, 123.6, 123.4, 121.6, 21.9; HRMS (ESI) m/z calcd for $C_{24}H_{20}N$ $[M + H]^+$ 322.1596, found 322.1582.

6-(tert-butyl)-4-(2,2-diphenylvinyl)quinoline (47c):



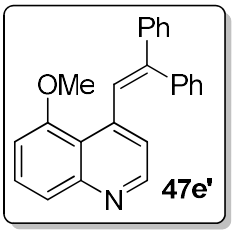
Pale yellow solid (20.2 mg, 90%) isolated using 8% ethyl acetate-petroleum ether (v/v); mp 108-110 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.54 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.99-7.98 (m, 1H), 7.79 (dd, J = 8.8, 2.0 Hz, 1H), 7.47-7.43 (m, 2H), 7.42-7.39 (m, 4H), 7.24-7.15 (m, 3H), 7.11-7.08 (m, 2H), 6.88 (d, J = 4.8 Hz, 1H), 1.40 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 149.4, 149.1, 147.8, 147.0, 143.7, 142.8, 139.5, 130.6, 129.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.0, 123.4, 121.9, 119.3, 35.2, 31.4; HRMS (ESI) m/z calcd for $C_{27}H_{26}N$ $[M + H]^+$ 364.2065, found 364.2064.

4-(2,2-diphenylvinyl)-7-methoxyquinoline (47e):



Pale yellow solid (18.8 mg, 90%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 122-124 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.49 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.43-7.36 (m, 7H), 7.25-7.16 (m, 4H), 7.08-7.06 (m, 2H), 6.74 (dd, J = 4.8, 0.8 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.6, 150.1, 149.9, 147.9, 143.8, 142.6, 139.3, 130.4, 128.5, 128.45, 128.38, 128.3, 127.9, 125.7, 123.4, 122.8, 119.7, 119.6, 107.7, 55.6; HRMS (ESI) m/z calcd for $C_{24}H_{20}NO$ $[M + H]^+$ 338.1545, found 338.1547.

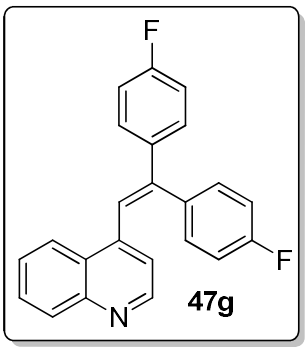
4-(2,2-diphenylvinyl)-5-methoxyquinoline (47e'):



Pale yellow solid (1.5 mg, 7%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 168-170 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.47 (d, J = 4.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.61-7.53 (m, 2H), 7.43-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.17-7.14 (m, 3H), 7.08-7.06 (m, 2H), 6.89 (dd, J = 7.8, 1.0

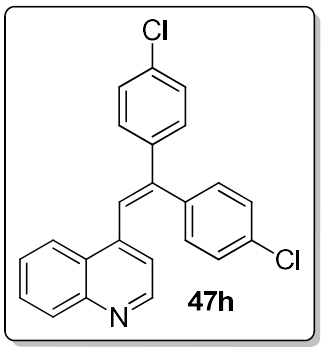
Hz, 1H), 6.79 (dd, J = 4.4, 0.8 Hz, 1H), 3.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 157.3, 150.2, 149.8, 144.3, 143.0, 141.8, 139.7, 137.7, 131.0, 129.7, 129.0, 128.5, 128.35, 128.32, 128.2, 128.1, 127.7, 127.3, 127.2, 126.9, 123.0, 122.5, 105.7, 56.2; HRMS (ESI) m/z calcd for $C_{24}H_{20}NO$ $[M + H]^+$ 338.1545, found 338.1529.

4-(2,2-bis(4-fluorophenyl)vinyl)quinoline (47g):



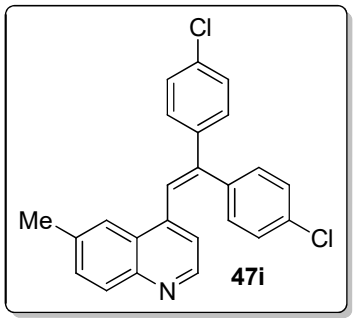
Pale brown solid (17.4 mg, 82%) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 100-102 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.62 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.39-7.37 (m, 2H), 7.33 (s, 1H), 7.08 (t, J = 8.4 Hz, 2H), 7.04-7.02 (m, 2H), 6.88 (t, J = 8.7 Hz, 2H), 6.85 (d, J = 4.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 162.5 (d, J_{C-F} = 247.5 Hz), 162.0 (d, J_{C-F} = 246.7 Hz), 149.4, 147.9, 145.3, 143.0, 138.0 (d, J_{C-F} = 3.1 Hz), 134.5 (d, J_{C-F} = 3.6 Hz), 131.6 (d, J_{C-F} = 7.9 Hz), 129.6, 129.5 (d, J_{C-F} = 7.8 Hz), 129.0, 127.0, 126.2, 123.9, 122.9, 121.0, 115.1 (d, J_{C-F} = 21.1 Hz), 115.0 (d, J_{C-F} = 21.1 Hz); HRMS (ESI) m/z calcd for $C_{23}H_{16}F_2N$ $[M + H]^+$ 344.1251, found 344.1258.

4-(2,2-bis(4-chlorophenyl)vinyl)quinoline (47h):



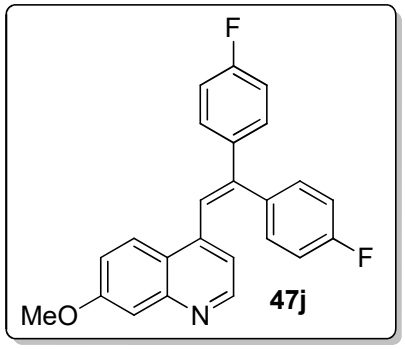
Pale yellow solid (19.3 mg, 83%) isolated using 7% ethyl acetate-petroleum ether (v/v); mp 142-144 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.63 (d, J = 4.2 Hz, 1H), 8.12-8.08 (m, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.38-7.35 (m, 3H), 7.32 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 4.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 149.9, 148.4, 145.4, 143.0, 140.5, 137.2, 134.6, 134.1, 131.6, 130.1, 129.5, 129.4, 128.8, 128.7, 127.4, 126.7, 124.2, 121.4; HRMS (ESI) m/z calcd for $C_{23}H_{16}Cl_2N$ $[M + H]^+$ 376.0660, found 376.0670.

4-(2,2-bis(4-chlorophenyl)vinyl)-6-methylquinoline (47i):



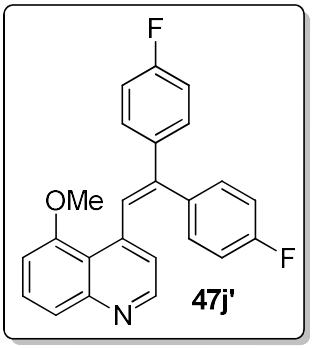
Yellowish white solid (14.5 mg, 60%) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 152-154 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.54 (d, J = 4.4 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.54 (dd, J = 8.6, 1.8 Hz, 1H), 7.38-7.31 (m, 5H), 7.16 (d, J =8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 4.8 Hz, 1H), 2.53 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 149.0, 147.1, 145.2, 142.3, 140.7, 137.4, 136.8, 134.6, 134.1, 131.8, 131.7, 129.9, 129.5, 128.84, 128.81, 127.4, 124.6, 123.2, 121.5, 21.9; HRMS (ESI) m/z calcd for $C_{24}H_{18}Cl_2N$ $[M + H]^+$ 390.0816, found 390.0816.

4-(2,2-bis(4-fluorophenyl)vinyl)-7-methoxyquinoline (47j):



Pale yellow solid (20.6 mg, 89%) isolated using 11% ethyl acetate-petroleum ether (v/v); mp 140-142 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.53 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.38-7.35 (m, 2H), 7.28 (brs, 1H), 7.18 (dd, J = 9.2, 2.8 Hz, 1H), 7.09-6.99 (m, 4H), 6.88 (t, J = 8.8 Hz, 2H), 6.73 (dd, J = 4.6, 1.0 Hz, 1H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 163.0 (d, $J_{C\text{-}F}$ = 247.3 Hz), 162.5 (d, $J_{C\text{-}F}$ = 246.9 Hz), 160.7, 150.2, 150.0, 145.7, 143.4, 138.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 135.1 (d, $J_{C\text{-}F}$ = 3.5 Hz), 132.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 125.5, 123.6, 122.6, 119.8, 119.6, 115.6 (d, $J_{C\text{-}F}$ = 21.5 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.4 Hz), 107.8, 55.6; HRMS (ESI) m/z calcd for $C_{24}H_{18}F_2NO$ $[M + H]^+$ 374.1356, found 374.1349.

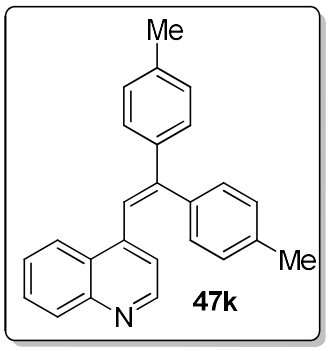
4-(2,2-bis(4-fluorophenyl)vinyl)-5-methoxyquinoline (47j'):



Pale yellow gummy liquid (1.9 mg, 8%) isolated using 11% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.50 (d, J = 4.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.1 Hz, 2H), 7.37-7.34 (m, 2H), 7.07-6.97 (m, 4H), 6.89 (d, J = 7.8 Hz, 1H), 6.84 (t, J = 8.7 Hz, 2H), 6.75 (d, J = 4.2 Hz, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR

($CDCl_3$, 150 MHz) δ_C 162.1 (d, J_{C-F} = 241.3 Hz), 161.5 (d, J_{C-F} = 245.4 Hz), 156.6, 149.8, 149.3, 143.4, 139.1, 134.9 (d, J_{C-F} = 3.9 Hz), 132.1 (d, J_{C-F} = 7.9 Hz), 129.4, 129.3, 129.2 (d, J_{C-F} = 8.1 Hz), 128.6, 126.7, 122.3, 122.1, 114.8 (d, J_{C-F} = 21.0 Hz), 105.2, 55.6; HRMS (ESI) m/z calcd for $C_{24}H_{18}F_2NO$ $[M + H]^+$ 374.1356, found 374.1343.

4-(2,2-di-p-tolylvinyl)quinoline (47k):



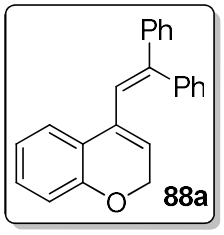
Yellow solid (10.8 mg, 52%) isolated using 12% ethyl acetate-petroleum ether (v/v); mp 154-156 ^oC; ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.58 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.73-7.68 (m, 1H), 7.55-7.51 (m, 1H), 7.33-7.31 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.00-6.95 (m, 4H), 6.87 (dd, J = 4.4, 0.8 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 149.9, 148.4, 147.9, 144.1, 140.1, 138.4, 137.7, 136.4, 130.4, 130.0, 129.3, 129.15, 129.11, 128.2, 126.4, 124.6, 122.1, 121.6, 21.33, 21.31; HRMS (ESI) m/z calcd for $C_{25}H_{22}N$ $[M + H]^+$ 336.1752, found 336.1743.

3.2.7.10. General procedure for the synthesis of products 88:

To a well stirred solution of starting material **85** (0.076 mmol, 1 equiv) in dry 1, 2 dichloroethane (1.5 mL), $Fe(OTf)_3$ (0.008 mmol, 0.1 equiv.) was added, thereafter the mixture was deoxygenated carefully and allowed to rotate at room temparature for 1.25-20 h. Upon completion of reaction (TLC), the solvent was evaporated in *vacuo* and the crude product was purified by silica gel (100-200 or 230-400 mesh) column chromatography eluting with 0.1-1% ethyl acetate-petroleum ether (v/v) to obtain afford the desired product **88** in (63-97%) yield.

3.2.7.11. Spectral Data of Compounds 88a-p

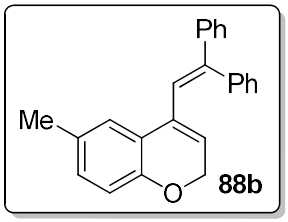
4-(2,2-diphenylvinyl)-2H-chromene (88a):



Yellow liquid (18.4 mg, 78%) isolated using 0.2% ethyl acetate-petroleum ether (v/v)**;** ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.35-7.32 (m, 5H), 7.30-7.21 (m, 6H), 7.15 (td, J = 7.6, 1.6 Hz, 1H), 6.89 (td, J = 7.4, 1.2 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 6.64-6.63 (m, 1H), 5.35 (td, J = 4.0, 1.6 Hz, 1H), 4.56-

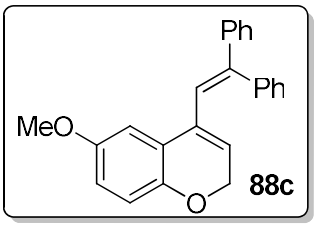
4.55 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.4, 146.0, 142.8, 140.2, 132.3, 130.1, 129.3, 128.3, 128.2, 128.0, 127.9, 127.4, 124.6, 124.0, 123.9, 121.8, 121.4, 116.0, 65.3; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{23}H_{18}O$ [M]+ 310.1358, found 310.1363.

4-(2,2-diphenylvinyl)-6-methyl-2H-chromene (88b):



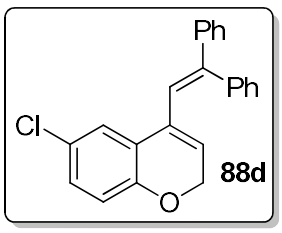
Colourless liquid (21.7 mg, 88%) isolated using 0.2% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.36-7.32 (m, 5H), 7.27-7.19 (m, 5H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.63-6.61 (m, 1H), 5.33 (td, *J* = 4.0, 1.6 Hz, 1H), 4.50-4.49 (m, 2H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 152.2, 145.9, 142.9, 140.2, 132.4, 130.6, 130.1, 129.6, 128.3, 128.2, 128.1, 127.9, 127.4, 125.1, 124.2, 123.8, 122.0, 115.7, 65.2, 20.7; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{24}H_{20}O$ $[M]^+$ 324.1514, found 324.1509.

4-(2,2-diphenylvinyl)-6-methoxy-2H-chromene (88c):



Colourless liquid (25.1 mg, 97%) isolated using 1% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.34-7.31 (m, 5H), 7.27-7.22 (m, 3H), 7.21-7.18 (m, 2H), 6.82 (d, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.68 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.60-6.59 (m, 1H), 5.39 (td, *J* = 4.1, 1.3 Hz, 1H), 4.48-4.46 (m, 2H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.3, 148.3, 146.1, 142.8, 140.1, 132.4, 130.1, 128.3, 128.2, 128.1, 127.9, 127.4, 124.8, 123.8, 122.8, 116.4, 114.2, 110.2, 65.2, 56.0; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{24}H_{20}O_2$ $[M]^+$ 340.1463, found 340.1456.

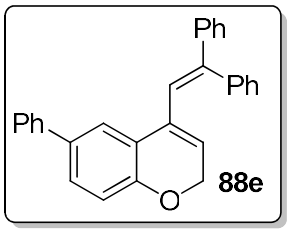
6-chloro-4-(2,2-diphenylvinyl)-2H-chromene (88d):



Yellow liquid (20.4 mg, 78%) isolated using 0.1% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.35-7.33 (m, 5H), 7.28-7.24 (m, 3H), 7.20-7.18 (m, 3H), 7.06 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.57-6.56 (m, 1H), 5.39 (td, *J* = 4.1, 1.3 Hz, 1H), 4.55-5.54 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 152.9, 146.7, 142.5, 139.9, 131.6, 130.0, 128.7, 128.4, 128.2, 128.1, 128.0, 127.5, 126.2, 125.2,

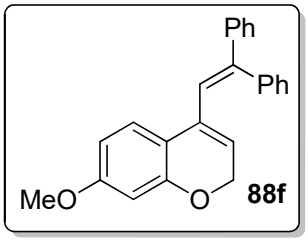
124.4, 123.0, 122.9, 117.2, 65.4; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{23}H_{17}ClO$ $[M]^+$ 344.0968, found 344.0978.

4-(2,2-diphenylvinyl)-6-phenyl-2H-chromene (88e):



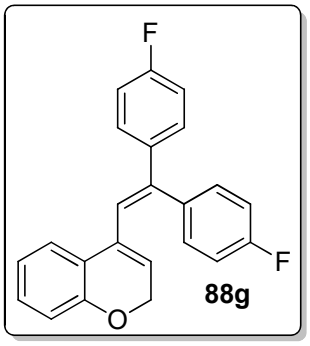
Colourless liquid (27.6 mg, 94%) isolated using 0.2% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.53-7.50 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.41-7.31 (m, 8H), 7.30-7.21 (m, 6H), 6.89 (d, J = 8.0 Hz, 1H), 6.69-6.67 (m, 1H), 5.40 (td, J = 4.0, 1.6 Hz, 1H), 4.60-4.58 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.0, 146.3, 142.8, 141.0, 140.2, 134.7, 132.3, 130.1, 128.7, 128.3, 128.2, 128.1, 127.97, 127.95, 127.5, 126.9, 126.8, 124.1, 123.8, 123.3, 122.3, 116.3, 65.4; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{29}H_{22}O$ $[M]^+$ 386.1671, found 386.1675.

4-(2,2-diphenylvinyl)-7-methoxy-2H-chromene (88f):



Colourless liquid (20.9 mg, 81%) isolated using 0.15% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.33-7.30 (m, 5H), 7.26-7.22 (m, 3H), 7.20-7.17 (m, 3H), 6.60-6.58 (m, 1H), 6.43 (dd, J = 8.4, 2.8 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 5.19 (td, J = 4.1, 1.3 Hz, 1H), 4.52-4.51 (m, 2H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.7, 155.7, 145.8, 142.9, 140.2, 132.1, 130.1, 128.3, 128.1, 128.0, 127.8, 127.3, 125.3, 124.2, 118.9, 117.2, 107.0, 101.9, 65.5, 55.4; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{24}H_{20}O_2$ $[M]^+$ 340.1463, found 340.1465.

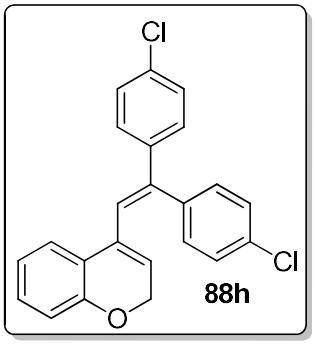
4-(2,2-bis(4-fluorophenyl)vinyl)-2H-chromene (88g):



Yellow liquid (24.4 mg, 93%) isolated using 1% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.30-7.26 (m, 2H), 7.22 (dd, J = 7.4, 1.8 Hz, 1H), 7.17-7.14 (m, 3H), 7.02 (t, J = 8.8 Hz, 2H), 6.96 (t, J = 8.8 Hz, 2H), 6.87 (td, J = 7.4, 1.2 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 6.56-6.55 (m, 1H), 5.34 (td, J = 4.1, 1.9 Hz, 1H), 4.58-4.56 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 162.7

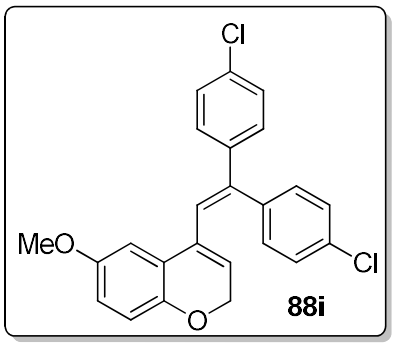
(d, $J_{C\text{-}F}$ = 246.4 Hz), 162.2 (d, $J_{C\text{-}F}$ = 245.7 Hz), 154.4, 143.9, 138.7 (d, $J_{C\text{-}F}$ = 4.3 Hz), 135.8 (d, $J_{C\text{-}F}$ = 3.8 Hz), 132.2, 131.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.6 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.4, 124.5, 124.1, 123.7, 121.9, 121.4, 116.1, 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 65.2; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{23}H_{16}F_2O$ $[M]^+$ 346.1169, found 346.1164.

4-(2,2-bis(4-chlorophenyl)vinyl)-2H-chromene (88h):



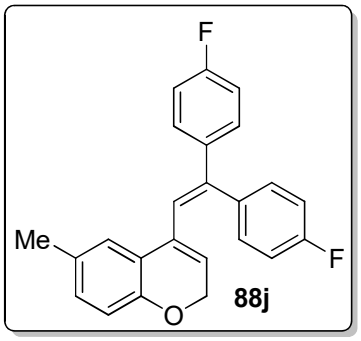
Yellow liquid (26.6 mg, 93%) isolated using 1% ethyl acetate-petroleum ether (v/v**);** ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.32-7.29 (m, 2H), 7.27-7.20 (m, 5H), 7.17-7.11 (m, 3H), 6.88 (td, J = 7.5, 1.3 Hz, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 6.61-6.60 (m, 1H), 5.35 (td, J = 4.1, 1.5 Hz, 1H), 4.58-4.57 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.4, 143.7, 140.8, 138.1, 134.0, 133.5, 132.0, 131.4, 129.6, 129.2, 128.6, 125.0, 124.4, 123.5, 122.2, 121.4, 116.1, 65.2; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{23}H_{16}Cl_2O$ $[M]^+$ 378.0578, found 378.0577.

4-(2,2-bis(4-chlorophenyl)vinyl)-6-methoxy-2H-chromene (88i):



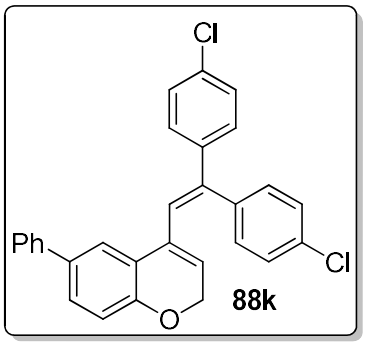
Yellow gummy liquid (28.8 mg, 93%) isolated using 0.2% ethyl acetate-petroleum ether (v/v**);** ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.31-7.29 (m, 2H), 7.26-7.21 (m, 4H), 7.13-7.10 (m, 2H), 6.78-6.75 (m, 2H), 6.70 (dd, J = 8.6, 3.0 Hz, 1H), 6.58-6.57 (m, 1H), 5.40 (td, J = 4.0, 1.6 Hz, 1H), 4.51-4.50 (m, 2H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.3, 148.3, 143.8, 140.8, 138.1, 134.1, 133.6, 132.2, 131.4, 129.3, 128.6, 124.8, 124.4, 123.2, 116.6, 114.1, 110.3, 65.1, 55.9; HRMS $(EI)^+$ m/z calcd for Chemical Formula: $C_{24}H_{18}Cl_2O_2$ $[M]^+$ 408.0684, found 408.0680.

4-(2,2-bis(4-fluorophenyl)vinyl)-6-methyl-2H-chromene (88j):



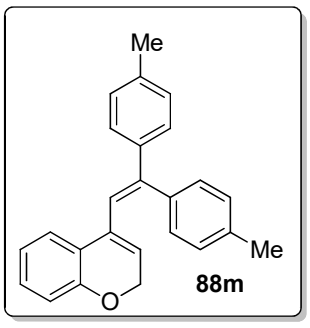
Yellow liquid (24.6 mg, 90%) isolated using 0.1% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.31-7.28 (m, 3H), 7.17-7.14 (m, 2H), 7.05-7.01 (m, 3H), 6.98-6.93 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.55-6.54 (m, 1H), 5.34 (td, J = 4.1, 1.3 Hz, 1H), 4.53-4.51 (m, 2H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.7 (d, J_{C-F} = 246.4 Hz), 162.2 (d, J_{C-F} = 245.7 Hz), 152.2, 143.8, 138.8 (d, J_{C-F} = 3.7 Hz), 135.9 (d, J_{C-F} = 3.6 Hz), 132.4, 131.7 (d, J_{C-F} = 8.0 Hz), 130.6, 129.8, 129.7 (d, J_{C-F} = 8.0 Hz), 125.0, 124.3, 123.4, 122.1, 115.8, 115.3 (d, J_{C-F} = 21.4 Hz), 115.2 (d, J_{C-F} = 21.4 Hz), 65.1, 20.7; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{24}H_{18}F_2O$ $[M]^+$ 360.1326, found 360.1328.

4-(2,2-bis(4-chlorophenyl)vinyl)-6-phenyl-2H-chromene (88k):



White solid (24.8 mg, 72%) isolated using 0.2% ethyl acetate-petroleum ether (v/v); mp 180-182 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.51-7.49 (m, 2H), 7.42-7.37 (m, 4H), 7.33-7.30 (m, 3H), 7.26-7.23 (m, 4H), 7.16-7.13 (m, 2H), 6.91 (d, J = 8.8 Hz, 1H), 6.67-6.65 (m, 1H), 5.42 (td, J = 4.1, 1.5 Hz, 1H), 4.63-4.61 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 154.0, 143.9, 140.9, 140.8, 138.1, 134.8, 134.1, 133.6, 132.1, 131.4, 129.7, 129.4, 128.9, 128.8, 128.65, 128.64, 128.2, 126.9, 126.8, 124.8, 123.6, 123.2, 122.7, 116.5, 65.3; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{29}H_{20}Cl_2O$ $[M]^+$ 454.0891, found 454.0894.

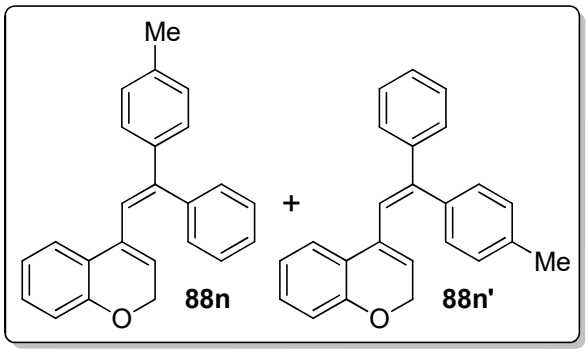
4-(2,2-di-p-tolylvinyl)-2H-chromene (88m):



Colourless liquid (16.2 mg, 63%) isolated using 0.1% ethyl acetate-petroleum ether (v/v)**;** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.28 (dd, J = 7.6, 1.6 Hz, 1H), 7.24-7.21 (m, 2H), 7.16-7.06 (m, 7H), 6.88 (td, J = 7.4, 1.2 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 6.55-6.54 (m, 1H), 5.34 (td, J = 4.1, 1.3 Hz, 1H), 4.56-4.55 (m, 2H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 154.4, 145.9, 140.3,

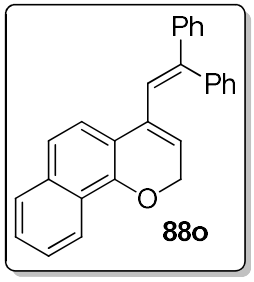
137.7, 137.3, 137.0, 132.4, 130.0, 129.2, 129.0, 128.9, 127.9, 124.6, 124.2, 122.9, 121.4, 121.3, 115.9, 65.3, 21.3, 21.2; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{25}H_{22}O$ $[M]^+$ 338.1671, found 338.1675.

(E)-4-(2-phenyl-2-(p-tolyl)vinyl)-2H-chromene (88n) and (Z)-4-(2-phenyl-2-(p-tolyl)vinyl)-2H-chromene (88n'):



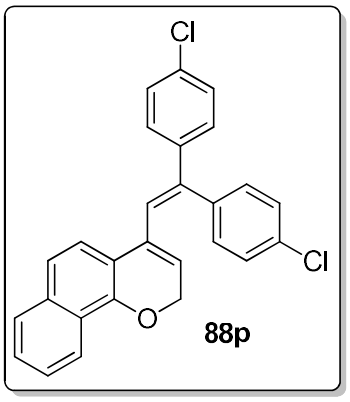
Colourless liquid (20.9 mg, 85%) isolated using 0.1% ethyl acetate-petroleum ether (v/v**);** ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.34-7.22 (m, 14H), 7.16-7.09 (m, 8H), 6.89 (tt, *J* = 7.6, 1.5 Hz, 2H), 6.83 (dd, *J* = 3.2, 1.2 Hz, 1H), 6.81 (dd, *J* = 3.2, 1.2 Hz, 1H), 6.61-6.58 (m, 2H), 5.36 (td, *J* = 4.0, 1.6 Hz, 1H), 5.32 (td, *J* = 4.1, 1.5 Hz, 1H), 4.58-4.56 (m, 2H), 4.55-4.53 (m, 2H), 2.38 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.4, 146.0, 145.9, 143.1, 140.3, 140.0, 137.8, 137.1, 137.0, 132.3, 132.2, 130.1, 130.0, 129.2, 129.0, 128.9, 128.3, 128.1, 128.0, 127.9, 127.8, 127.3, 124.56, 124.55, 124.12, 124.11, 123.6, 123.2, 121.7, 121.5, 121.4, 121.3, 116.0, 65.3, 65.2, 21.3, 21.2; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{24}H_{20}O$ $[M]^+$ 324.1514, found 324.1513.

4-(2,2-diphenylvinyl)-2H-benzo[h]chromene (88o):



Yellow solid (22.7 mg, 83%) isolated using 0.15% ethyl acetate-petroleum ether (v/v); mp 114-116 ^oC ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.17-8.14 (m, 1H), 7.76-7.74 (m, 1H), 7.47-7.42 (m, 3H), 7.39-7.32 (m, 6H), 7.28-7.24 (m, 5H), 6.74-6.72 (m, 1H), 5.38 (td, *J* = 4.2, 1.6 Hz, 1H), 4.74-4.73 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 150.0, 142.9, 140.2, 136.1, 134.4, 133.1, 130.2, 128.3, 128.2, 128.1, 127.9, 127.6, 127.4, 126.4, 125.5, 124.4, 122.5, 122.1, 120.4, 120.0, 118.5, 65.7; HRMS (EI)$^+$ m/z calcd for Chemical Formula: $C_{27}H_{20}O$ $[M]^+$ 360.1514, found 360.1508.

4-(2,2-bis(4-chlorophenyl)vinyl)-2H-benzo[h]chromene (88p):



White solid (26.0 mg, 80%) isolated using 0.15% ethyl acetate-petroleum ether (v/v); mp 172-174 ^{o}C ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.16-8.14 (m, 1H), 7.76-7.73 (m, 1H), 7.46-7.44 (m, 2H), 7.37 (s, 2H), 7.33-7.30 (m, 2H), 7.28-7.22 (m, 4H), 7.17-7.14 (m, 2H), 6.70-6.69 (m, 1H), 5.38 (td, J = 4.2, 1.6 Hz, 1H), 4.77-4.75 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 150.1, 143.7 140.9, 138.2, 134.5, 134.0, 133.5, 132.9, 131.5, 129.3, 128.64, 128.60, 127.6, 126.6, 125.7, 125.4, 124.6, 122.2, 122.1, 120.6, 120.3, 118.0, 65.6; HRMS (ESI)$^{+}$ m/z calcd for Chemical Formula: $C_{27}H_{19}Cl_2O$ $[M+H]^{+}$ 429.0813, found 429.0817.

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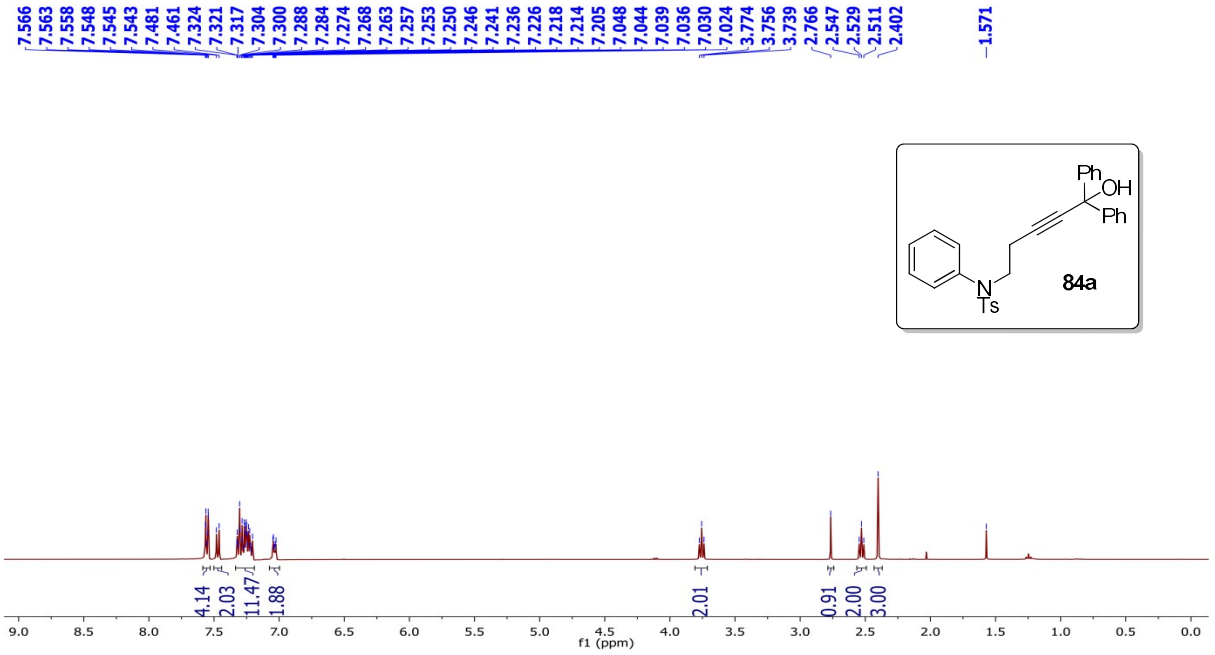
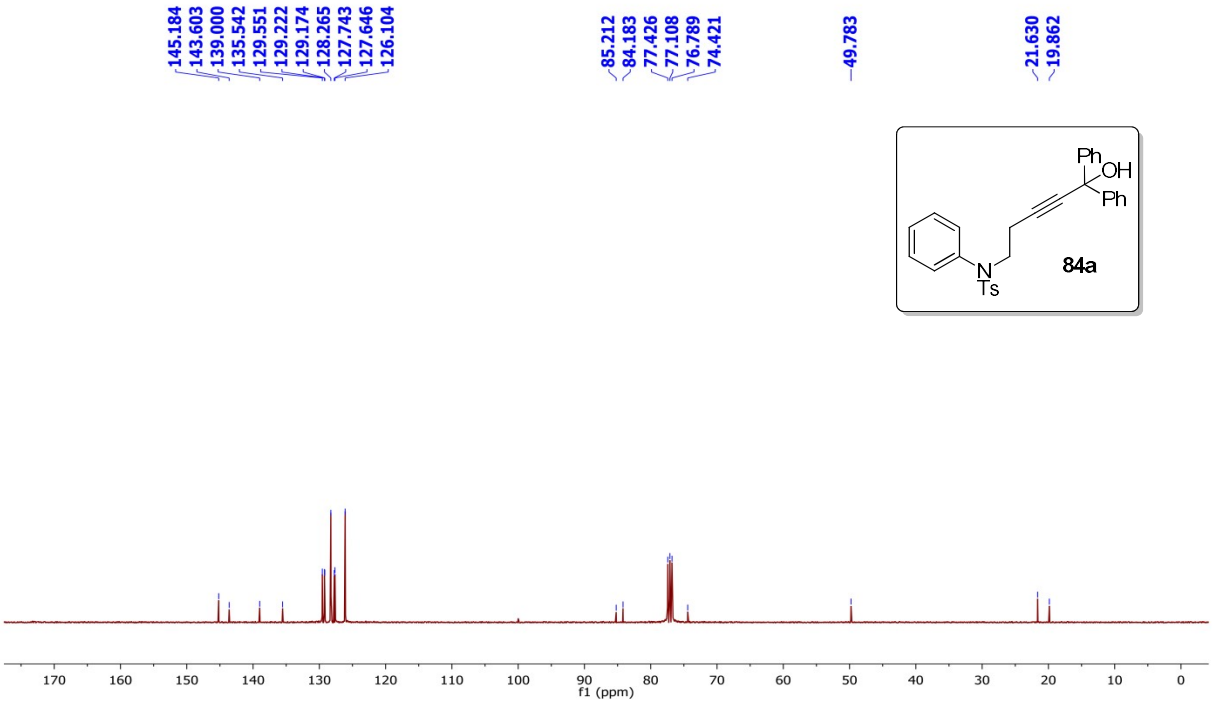
3.2.9. Copies of NMR Spectra

3.2.9.1. NMR Spectra of Compounds 84a-l:

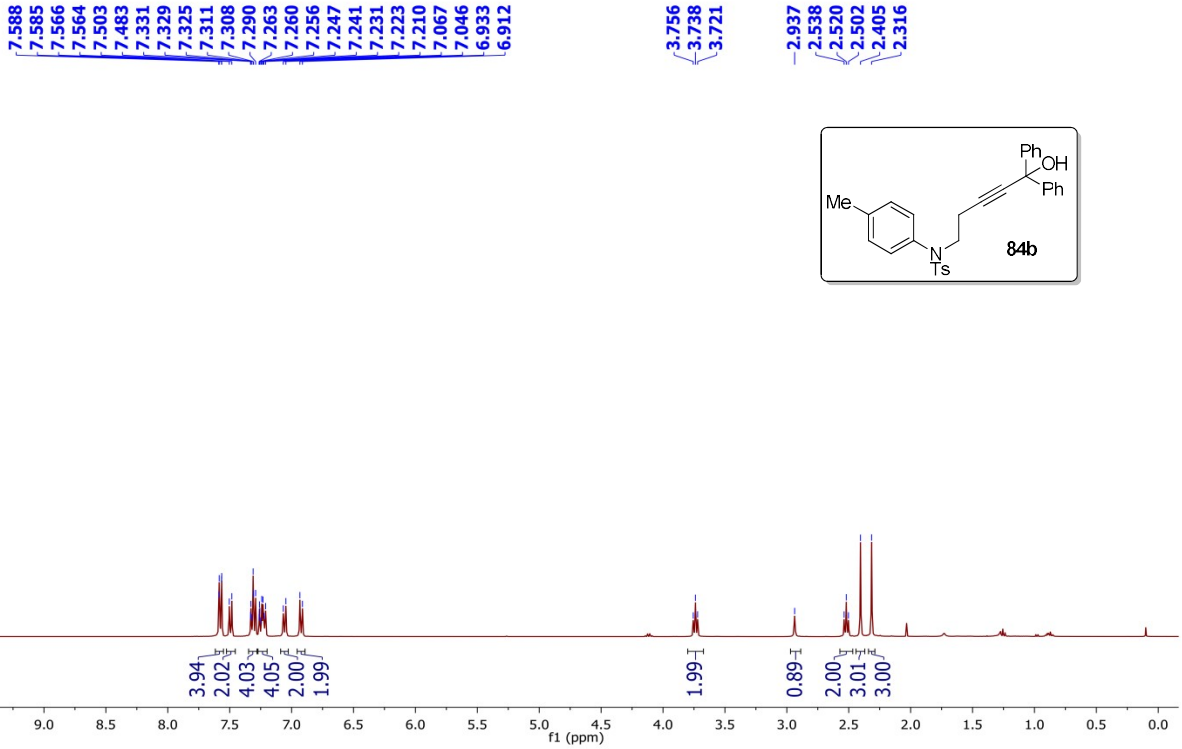
^{1}H NMR (400 MHz) of **84a**:



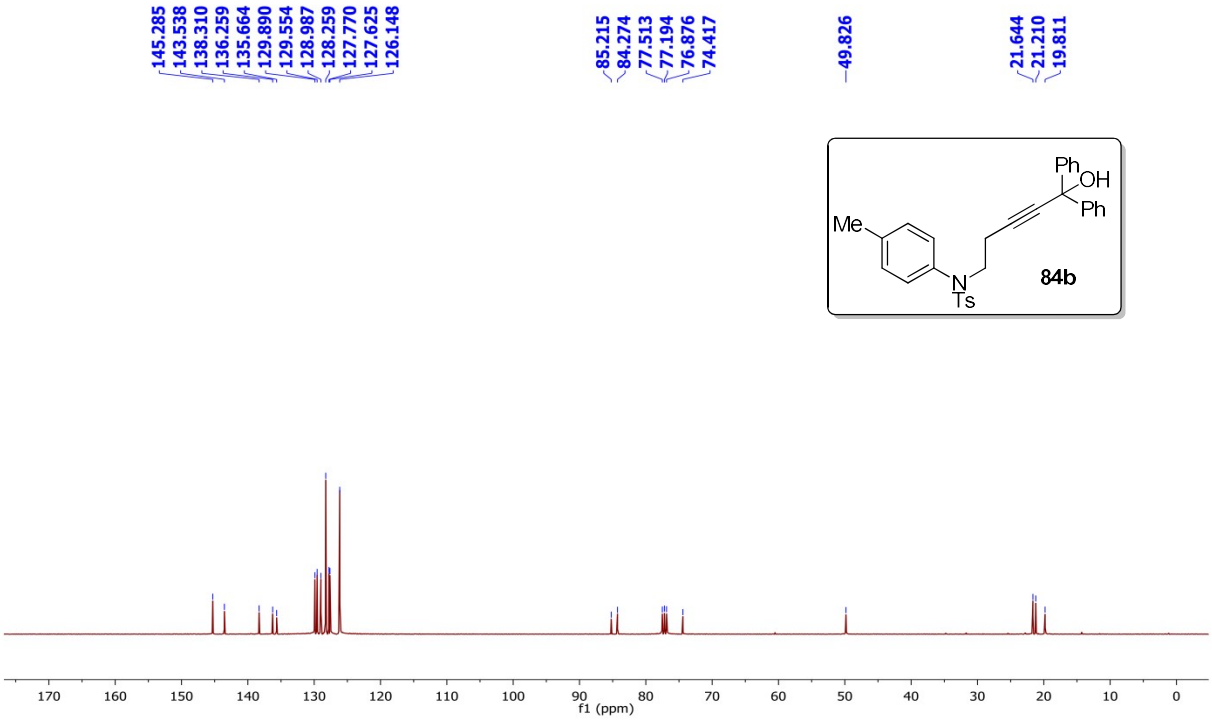
^{13}C{^{1}H} NMR (100 MHz) of **84a** :



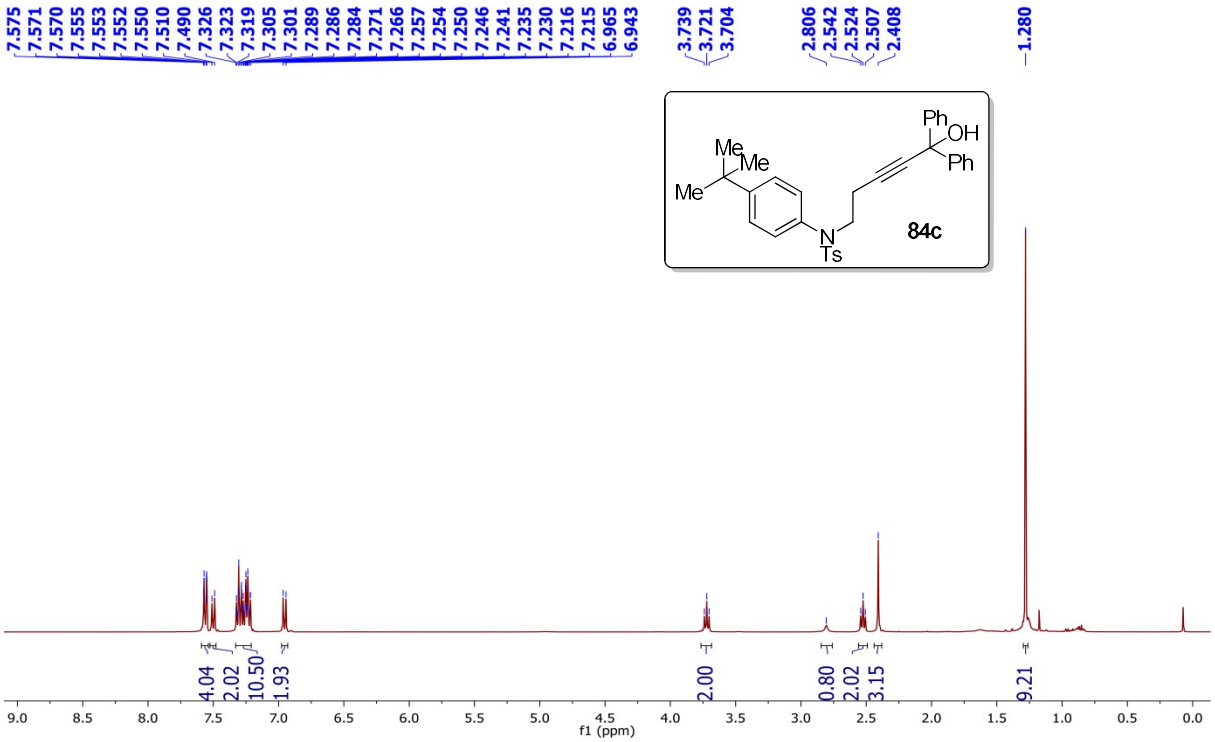
^{1}H NMR (400 MHz) of **84b**:



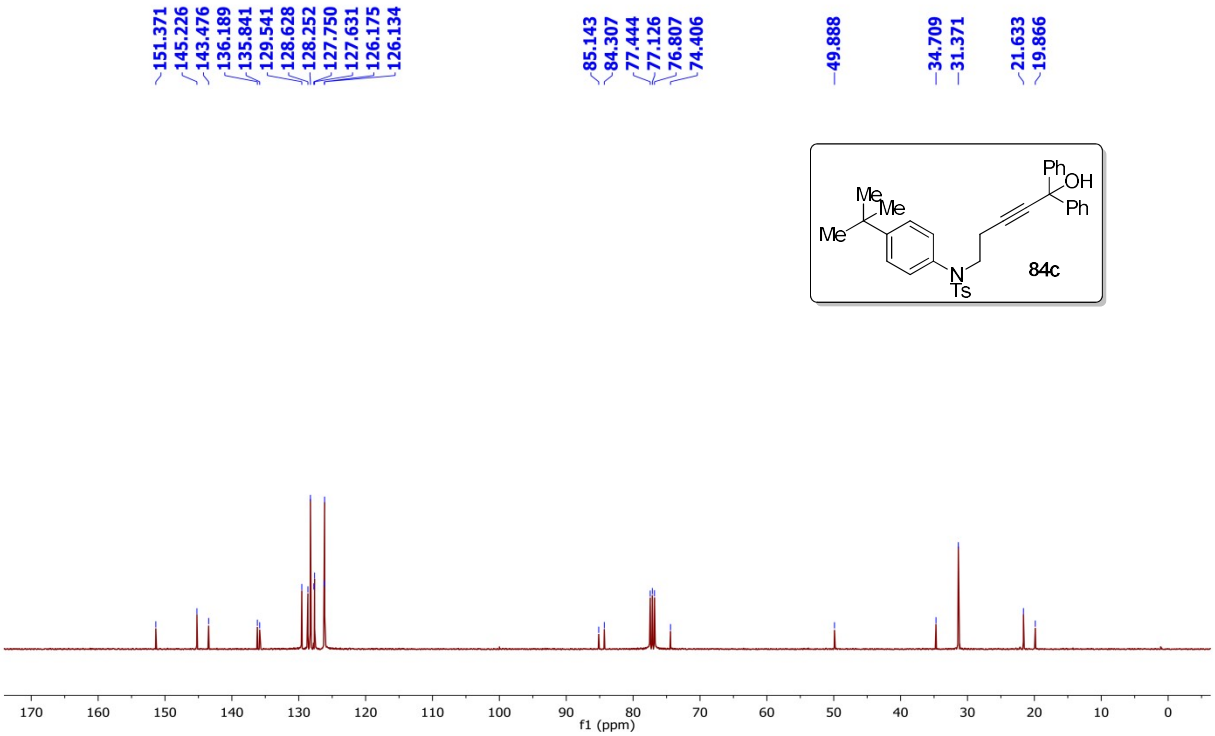
^{13}C{^{1}H} NMR (100 MHz) of **84b** :



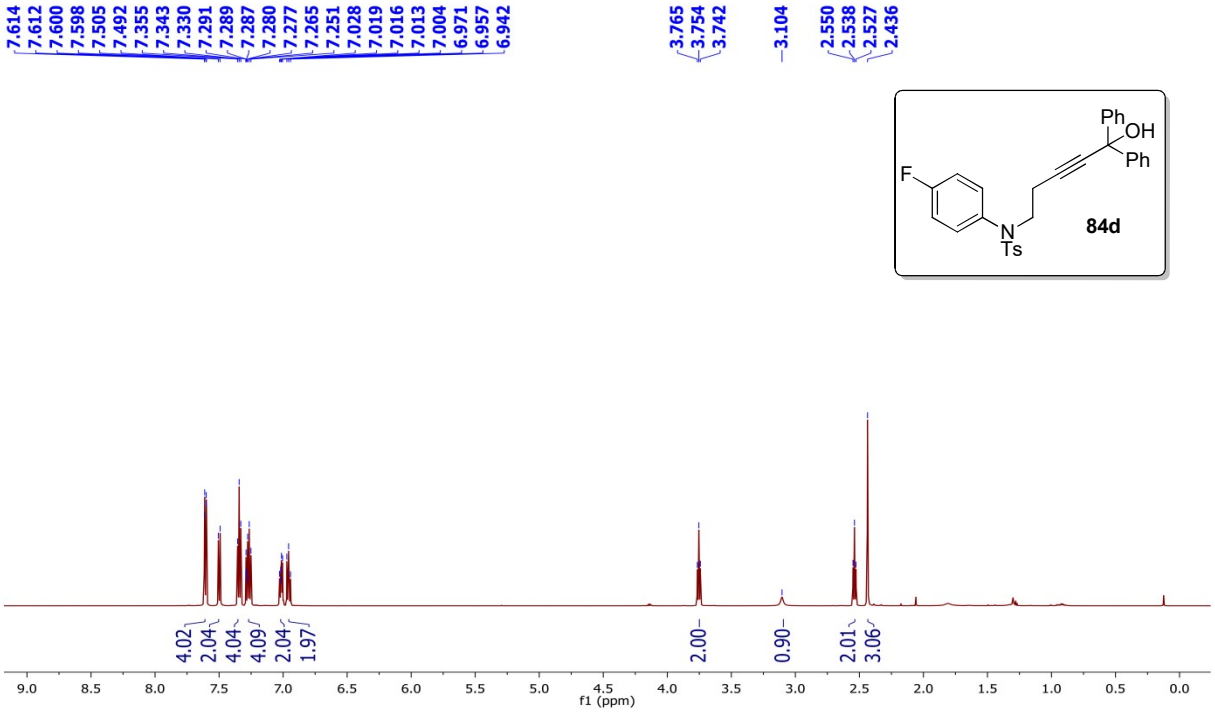
^{1}H NMR (400 MHz) of **84c**:



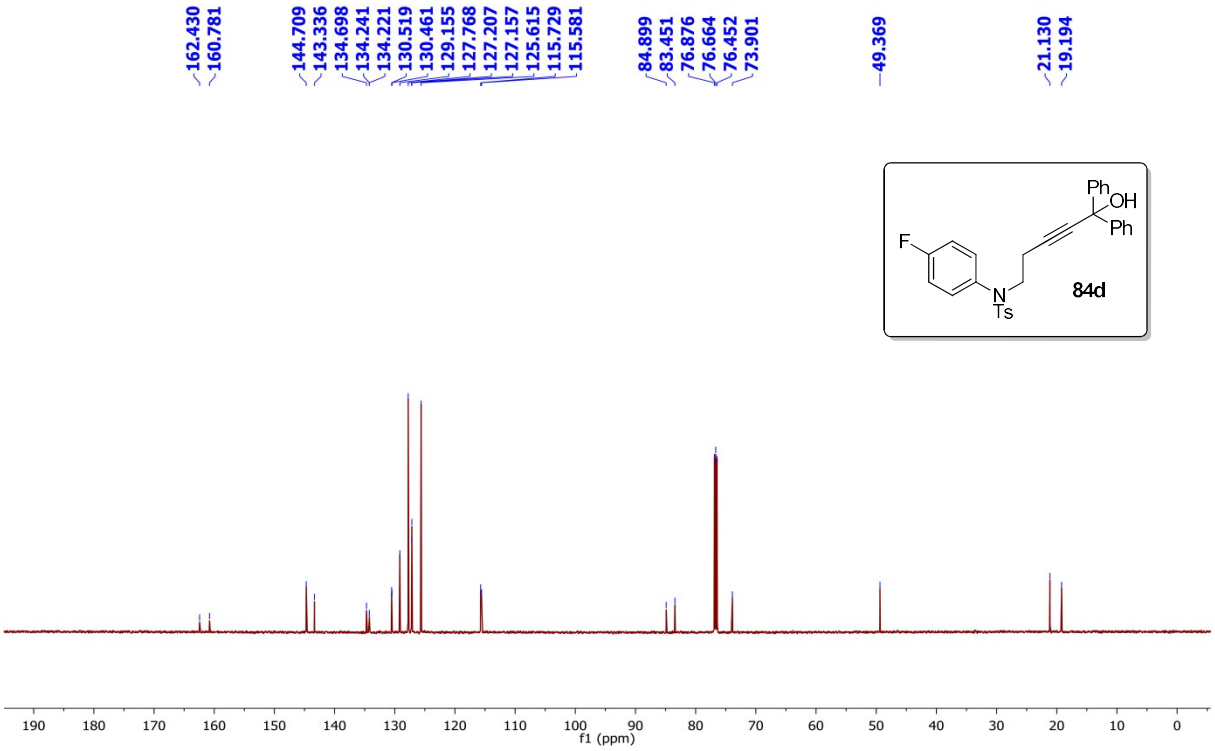
^{13}C{^{1}H} NMR (100 MHz) of **84c**:



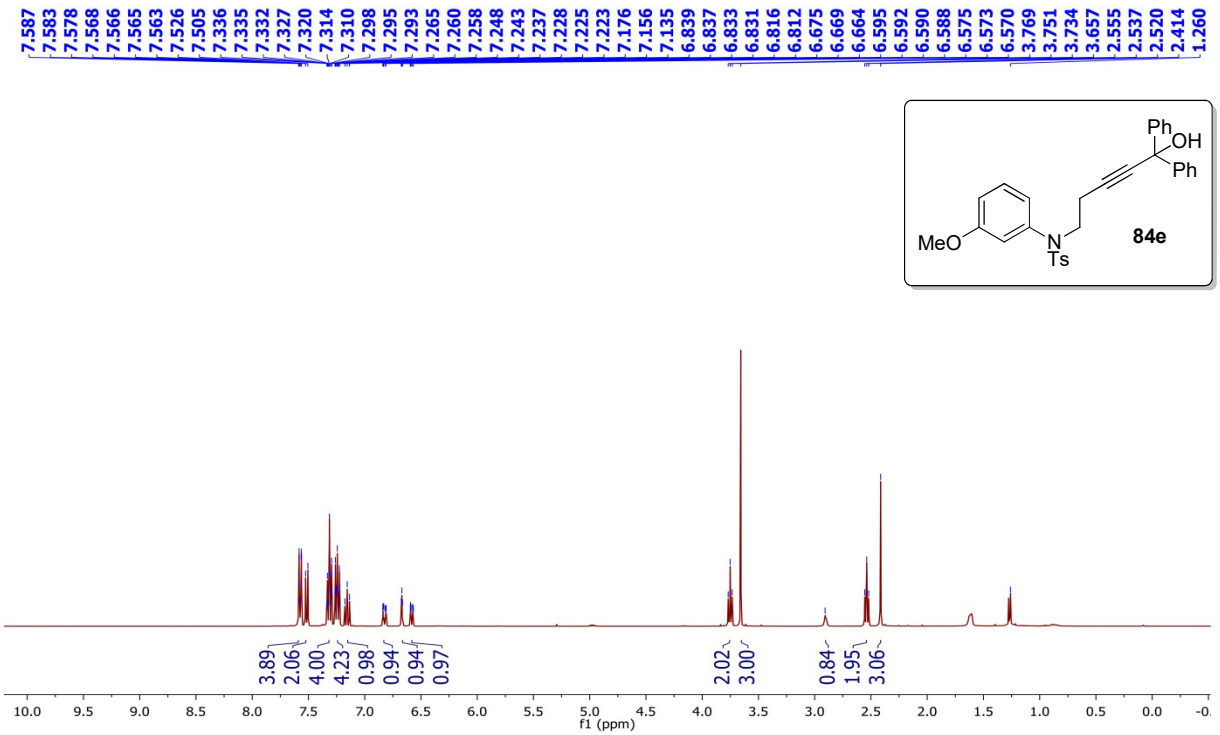
^{1}H NMR (600 MHz) of **84d**:



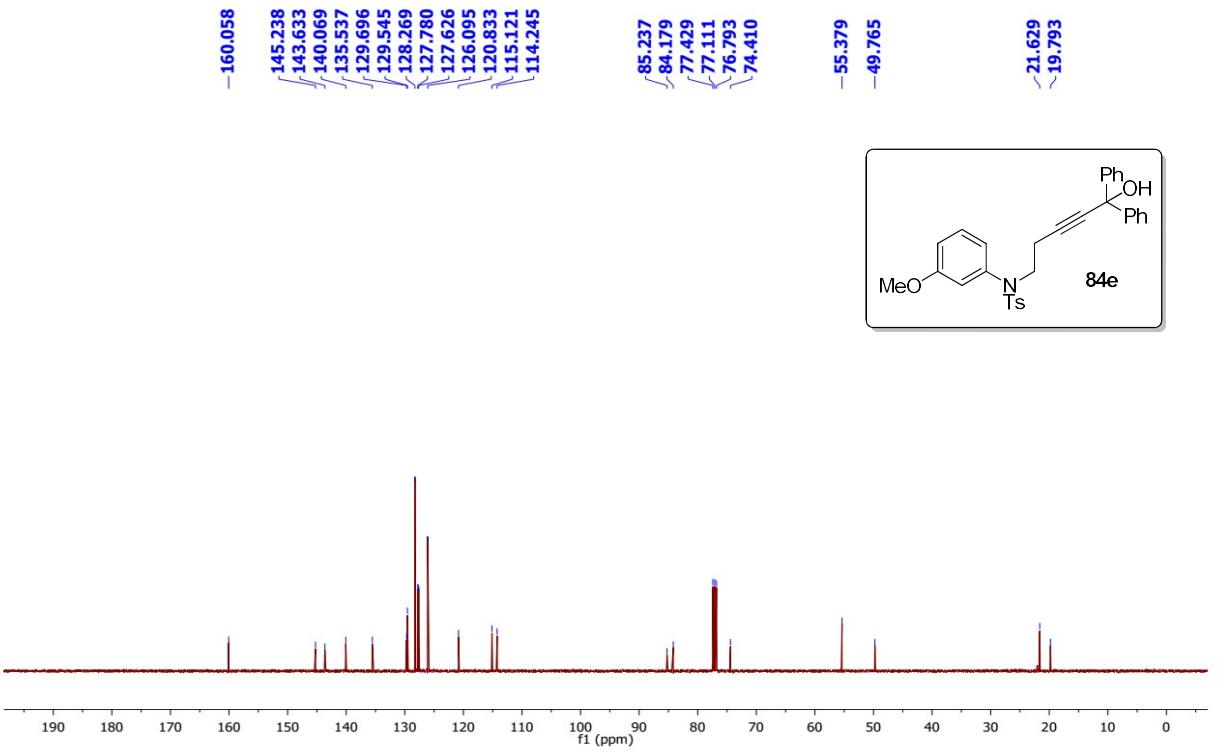
^{13}C{^{1}H} NMR (150 MHz) of **84d** :



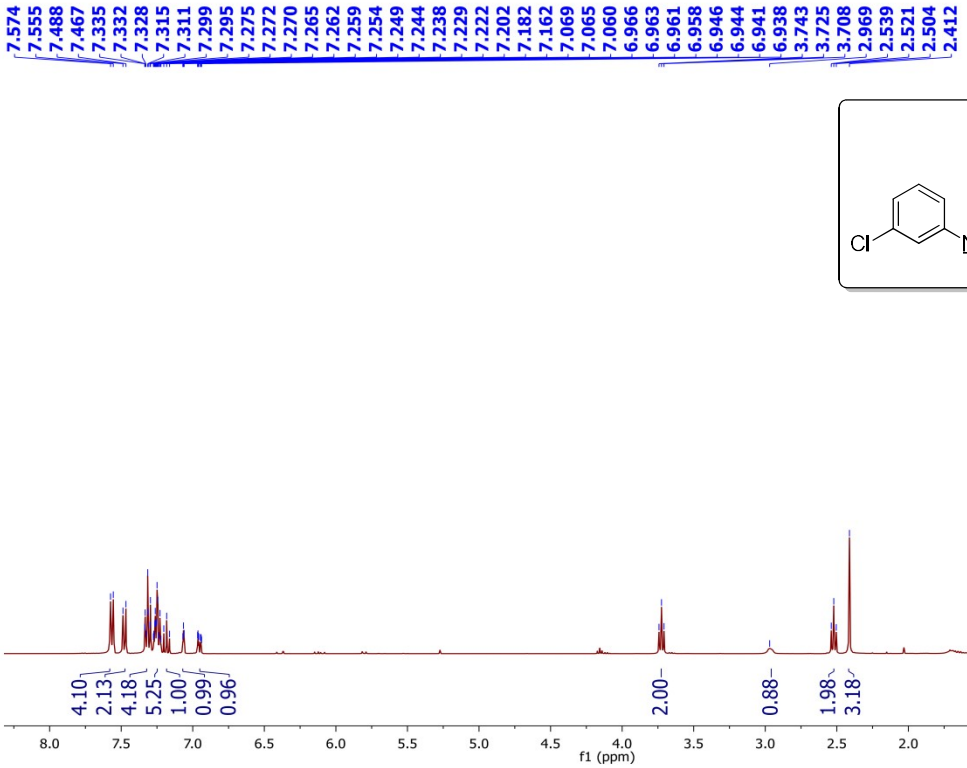
^{1}H NMR (400 MHz) of **84e**:



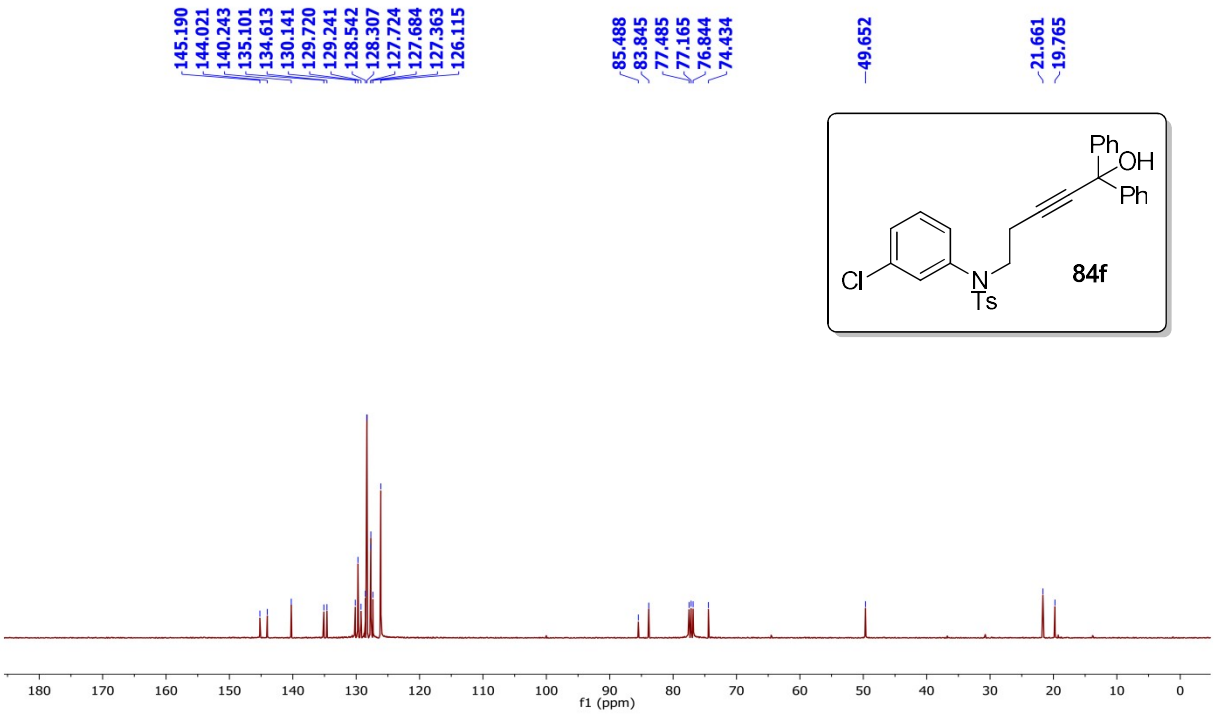
^{13}C{^{1}H} NMR (100 MHz) of **84e** :



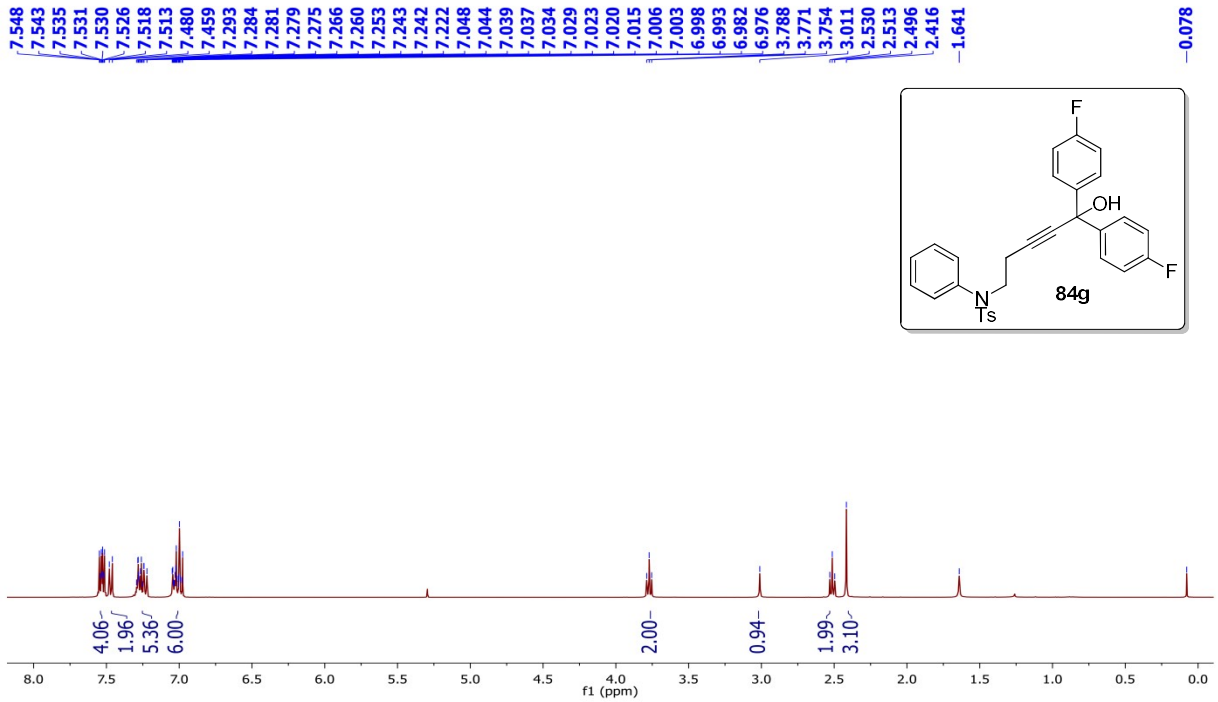
^{1}H NMR (400 MHz) of **84f**:



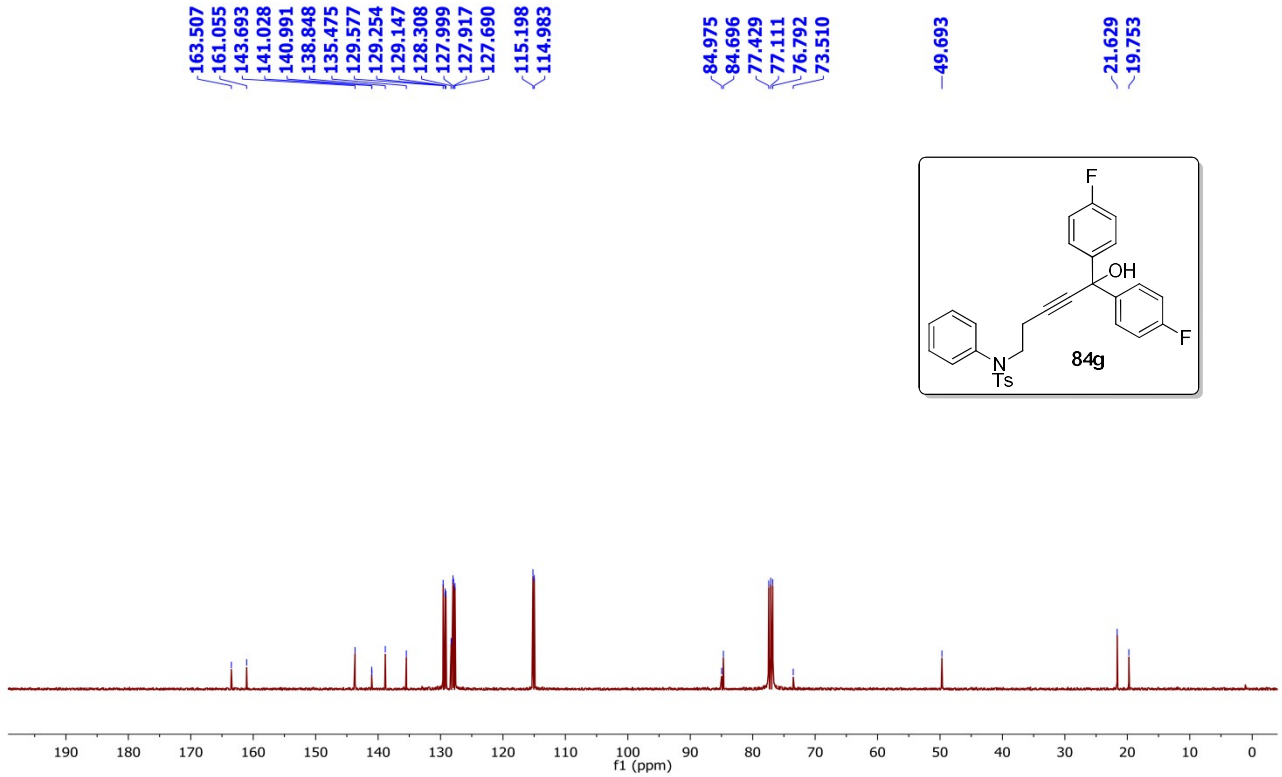
^{13}C{^{1}H} NMR (100 MHz) of **84f** :



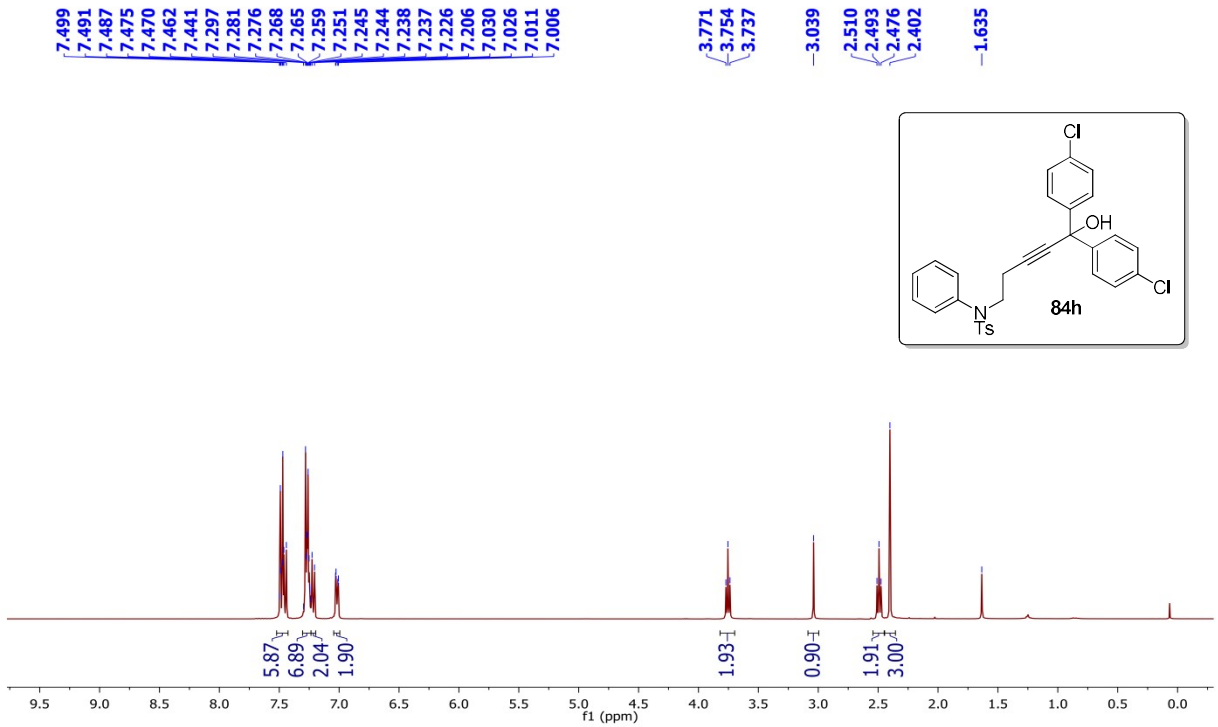
^{1}H NMR (400 MHz) of **84g**:



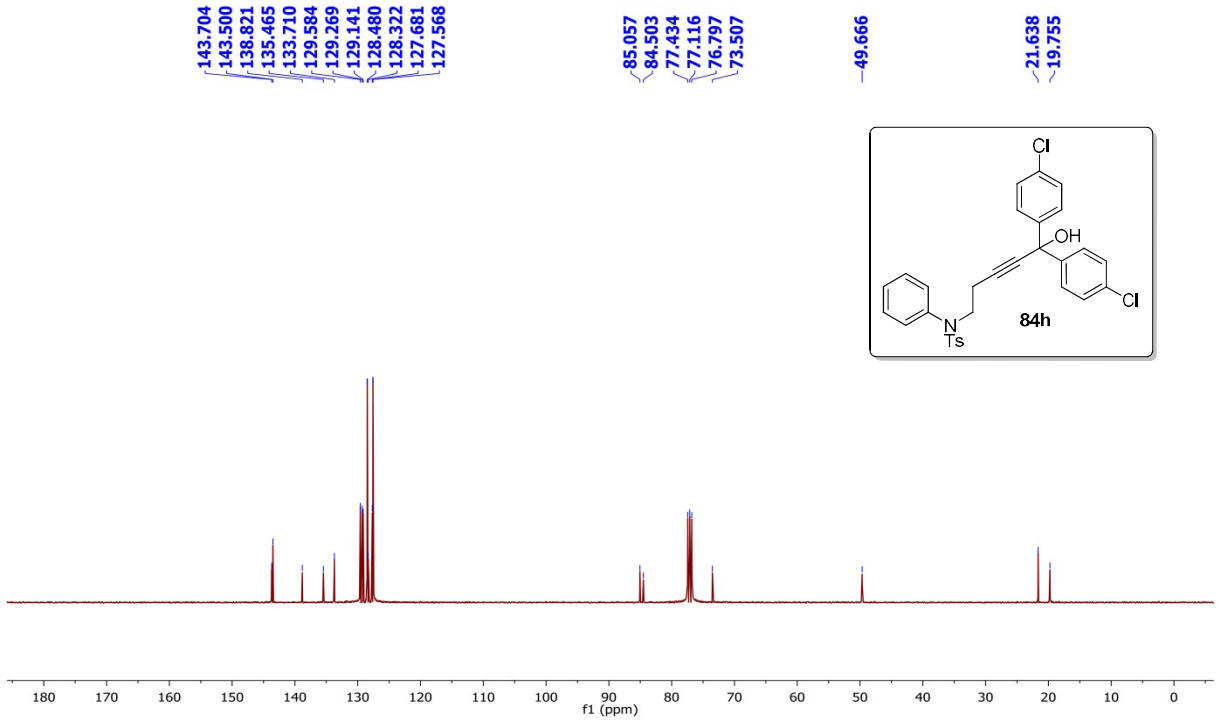
^{13}C{^{1}H} NMR (100 MHz) of **84g** :



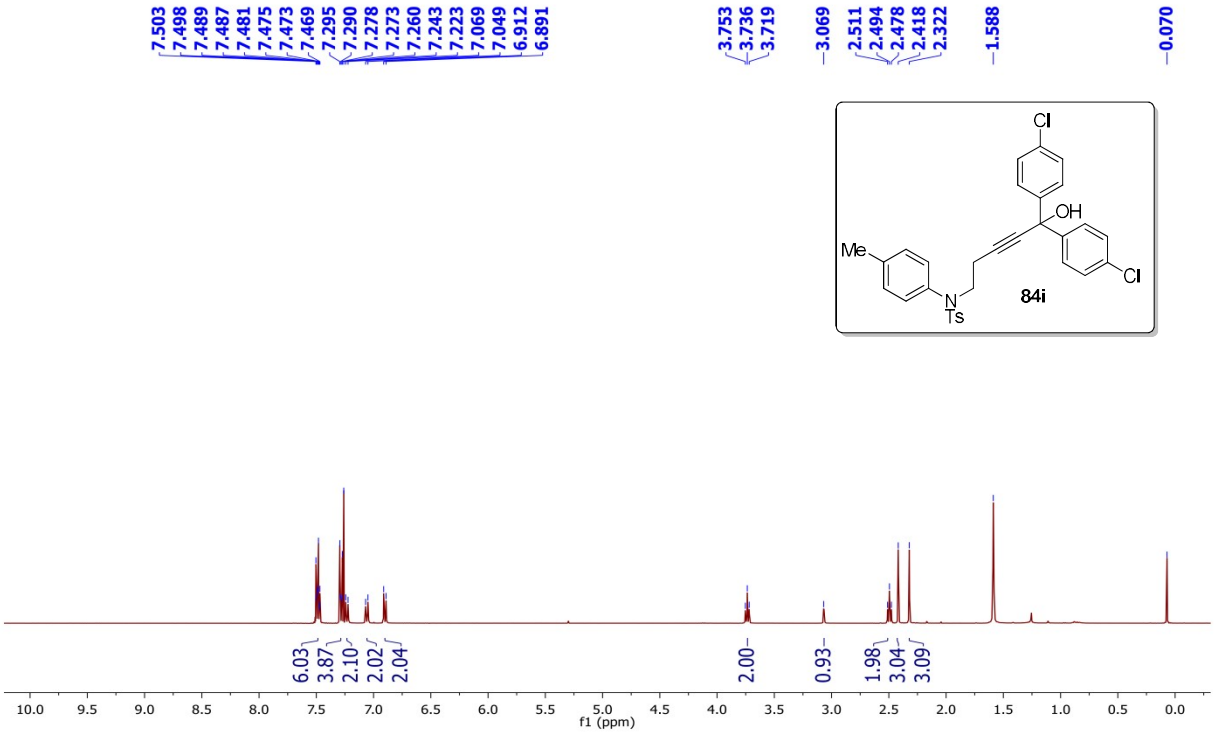
^{1}H NMR (400 MHz) of **84h**:



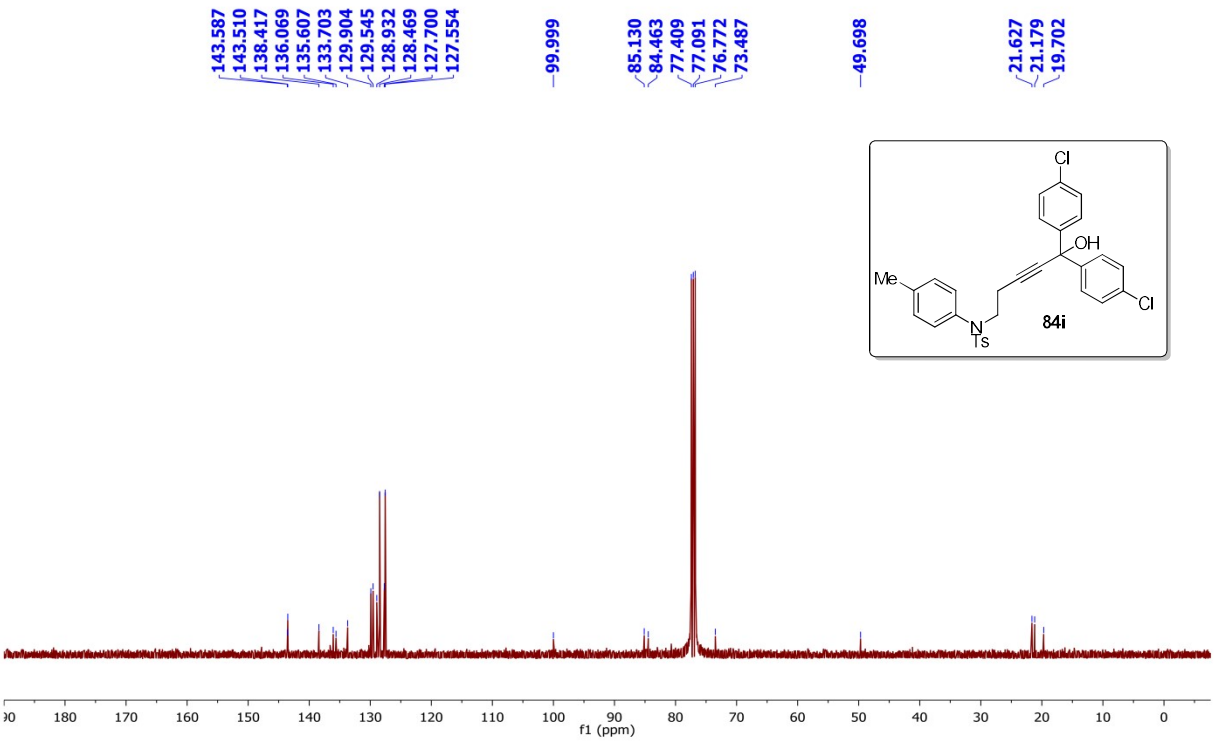
^{13}C{^{1}H} NMR (100 MHz) of **84h** :



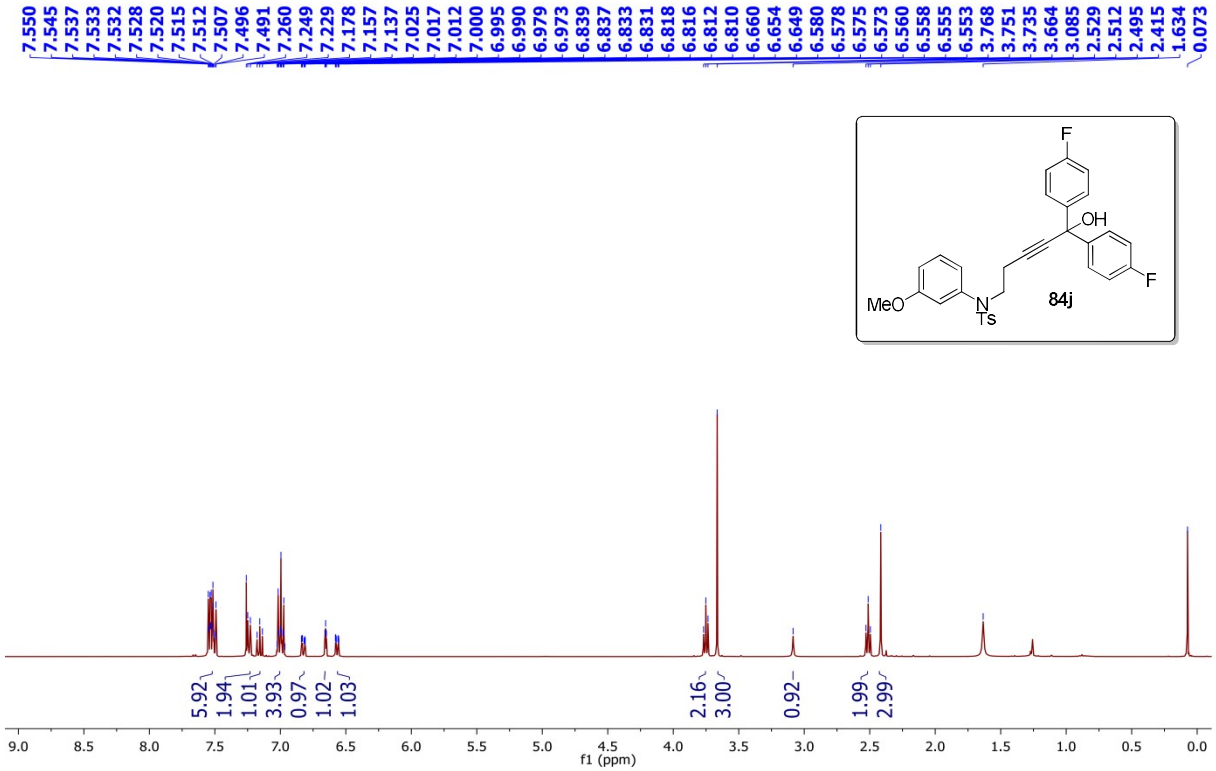
^{1}H NMR (400 MHz) of **84i**:



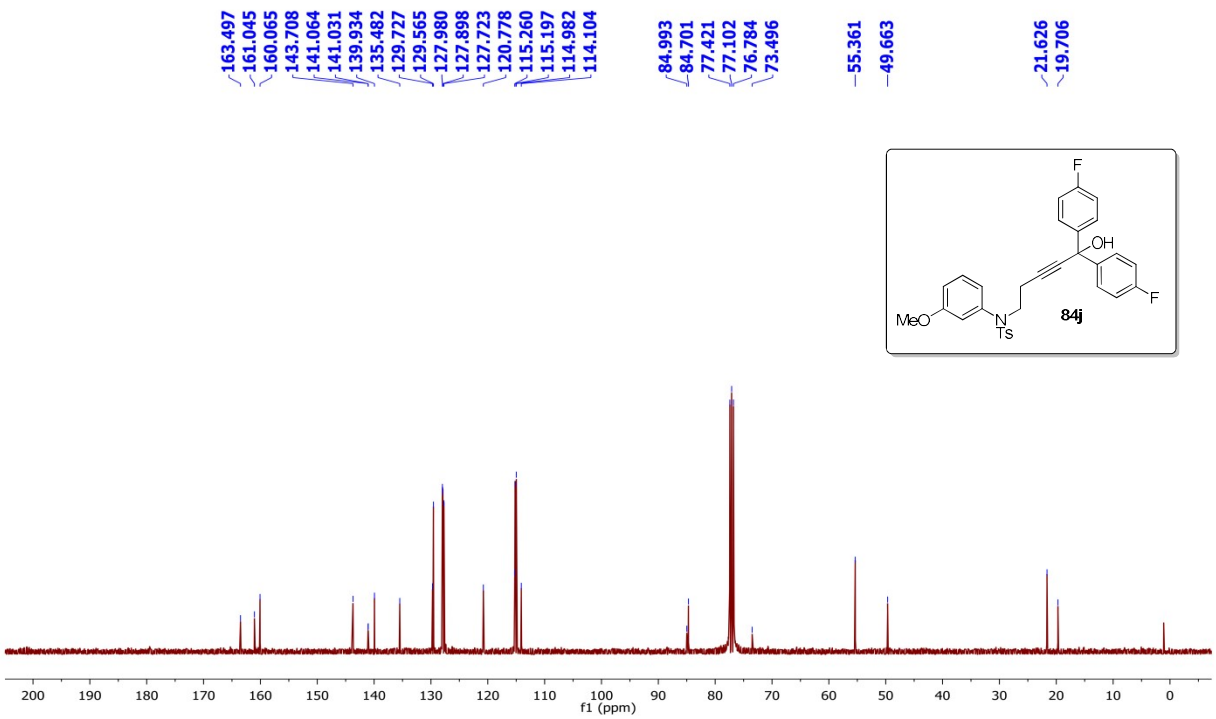
^{13}C{^{1}H} NMR (100 MHz) of **84i** :



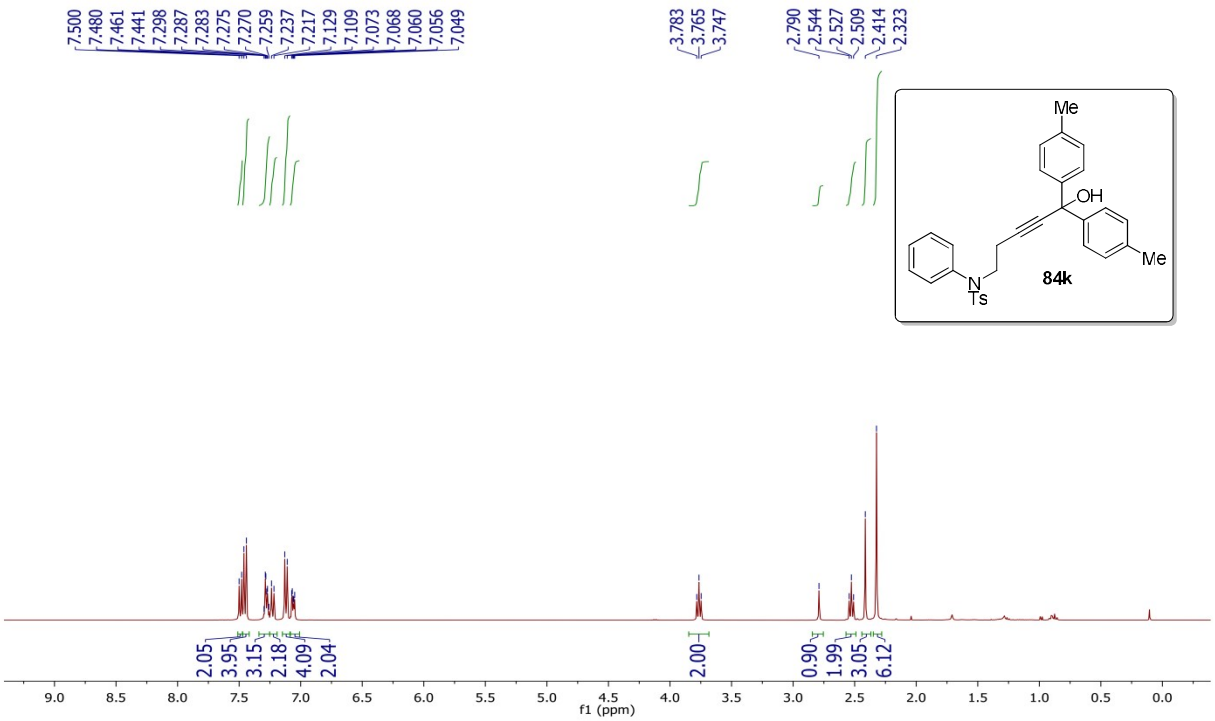
^{1}H NMR (400 MHz) of **84j**:



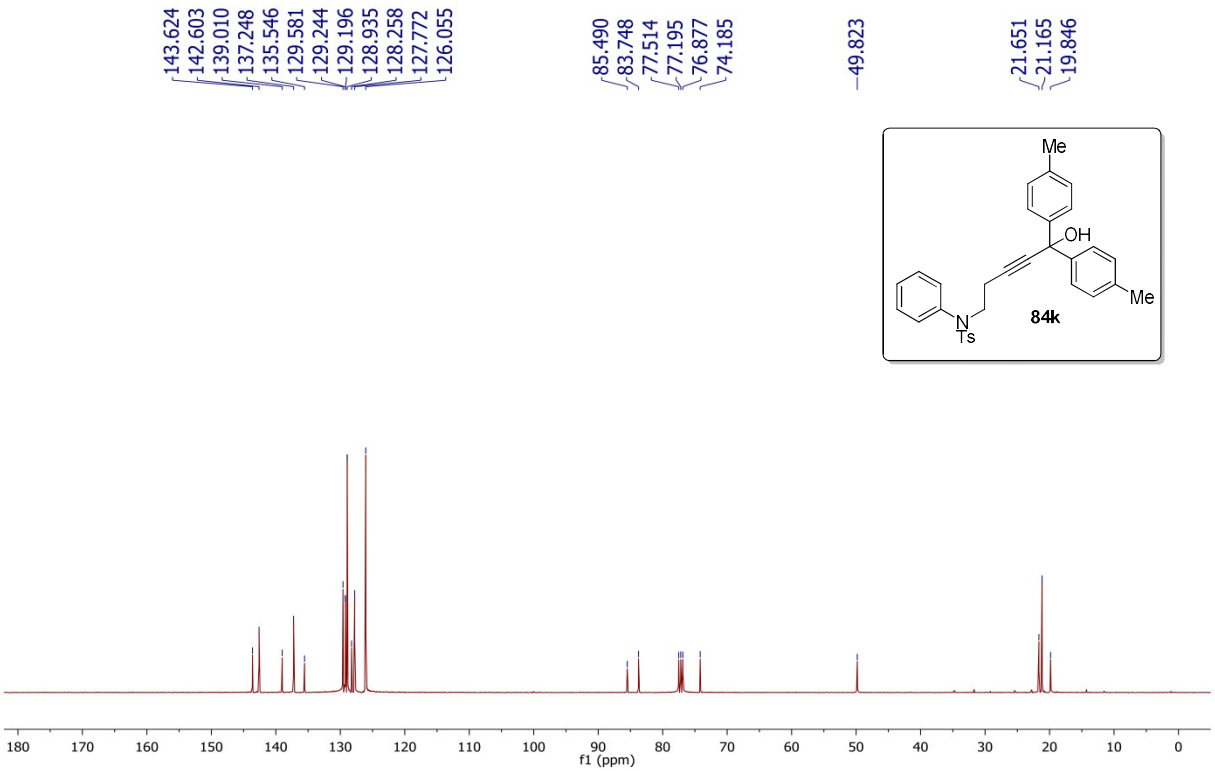
^{13}C{^{1}H} NMR (100 MHz) of **84j** :



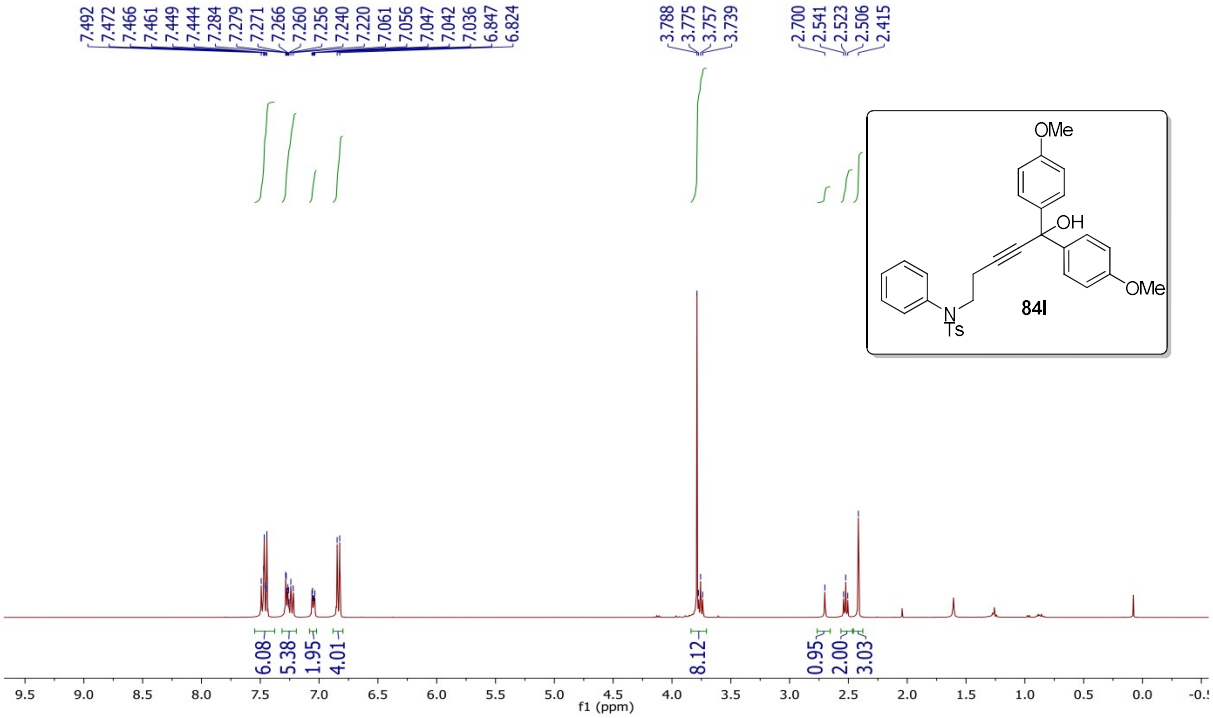
^{1}H NMR (400 MHz) of **84k**:



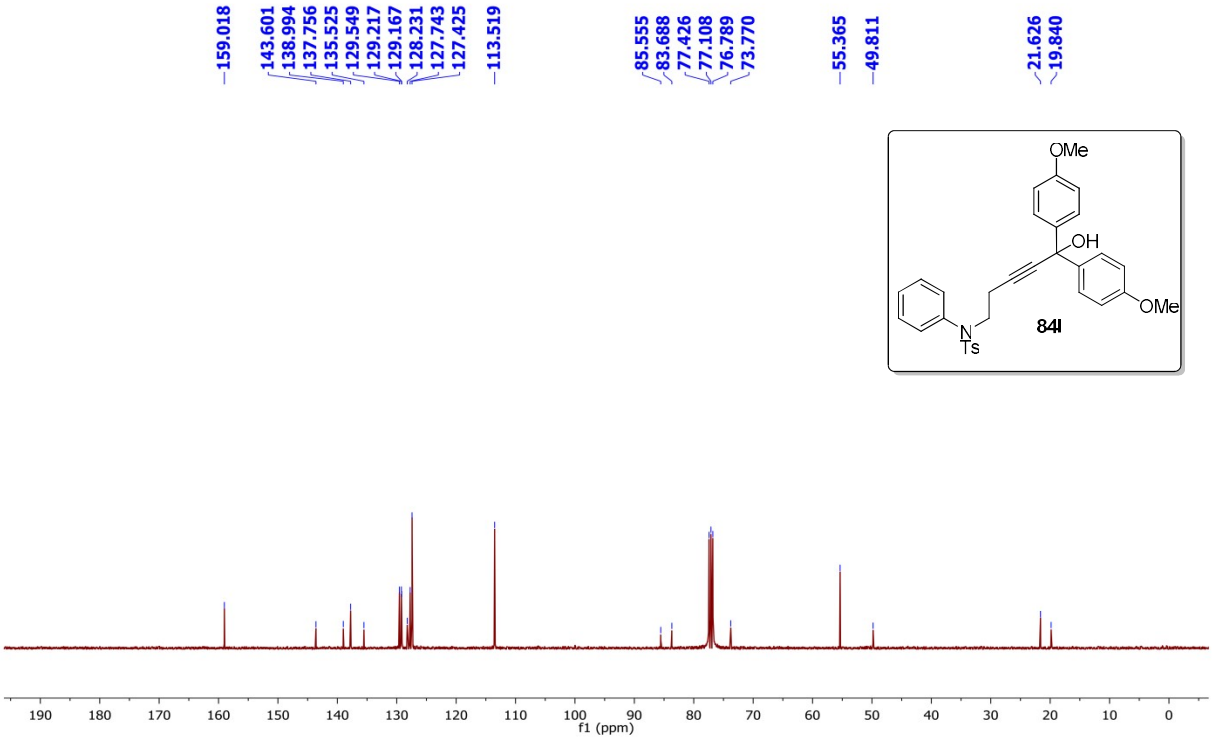
^{13}C{^{1}H} NMR (100 MHz) of **84k** :



^{1}H NMR (400 MHz) of **84l**:

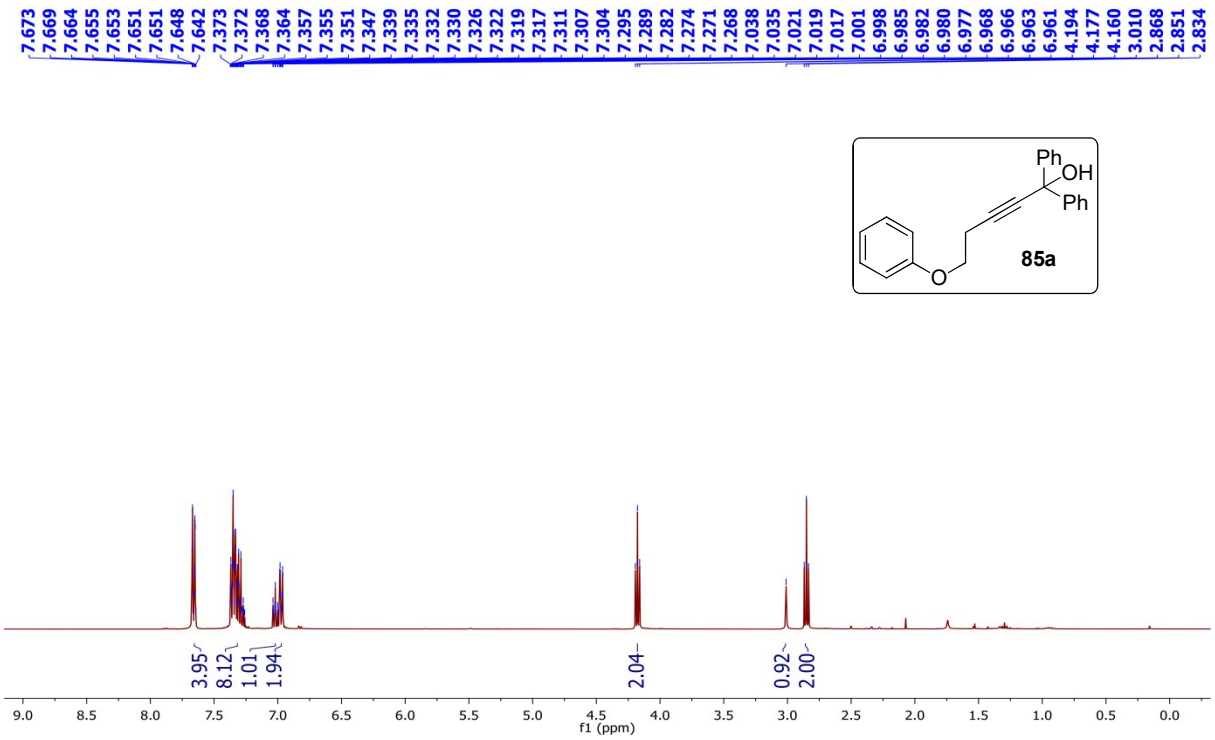


^{13}C{^{1}H} NMR (100 MHz) of **84l**:

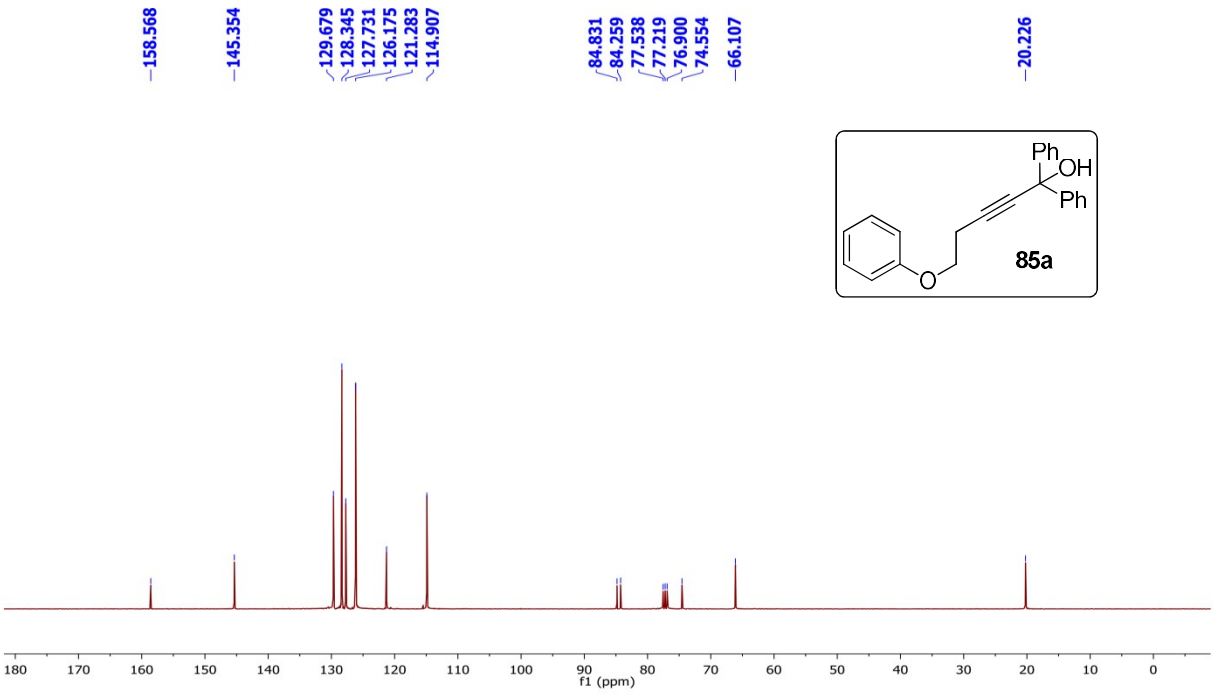


3.2.9.2. NMR Spectra of Compounds 85a-p

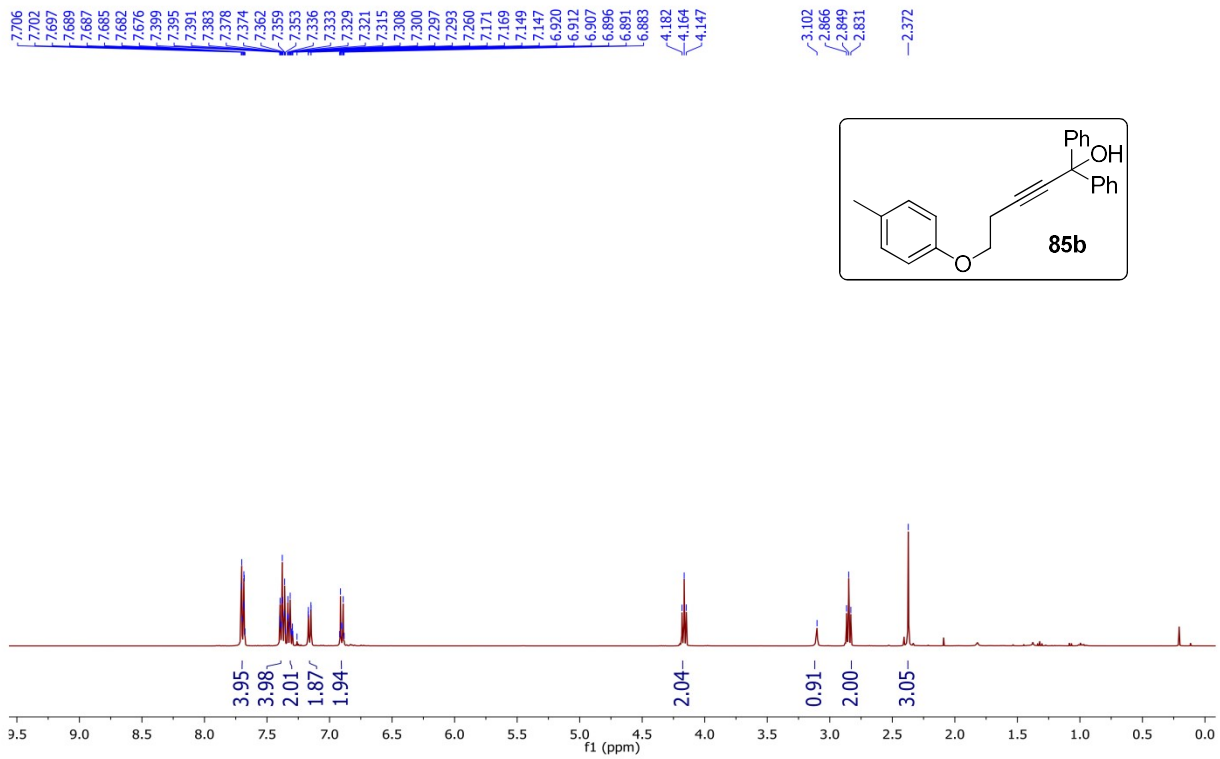
^{1}H NMR (400 MHz) of **85a**:



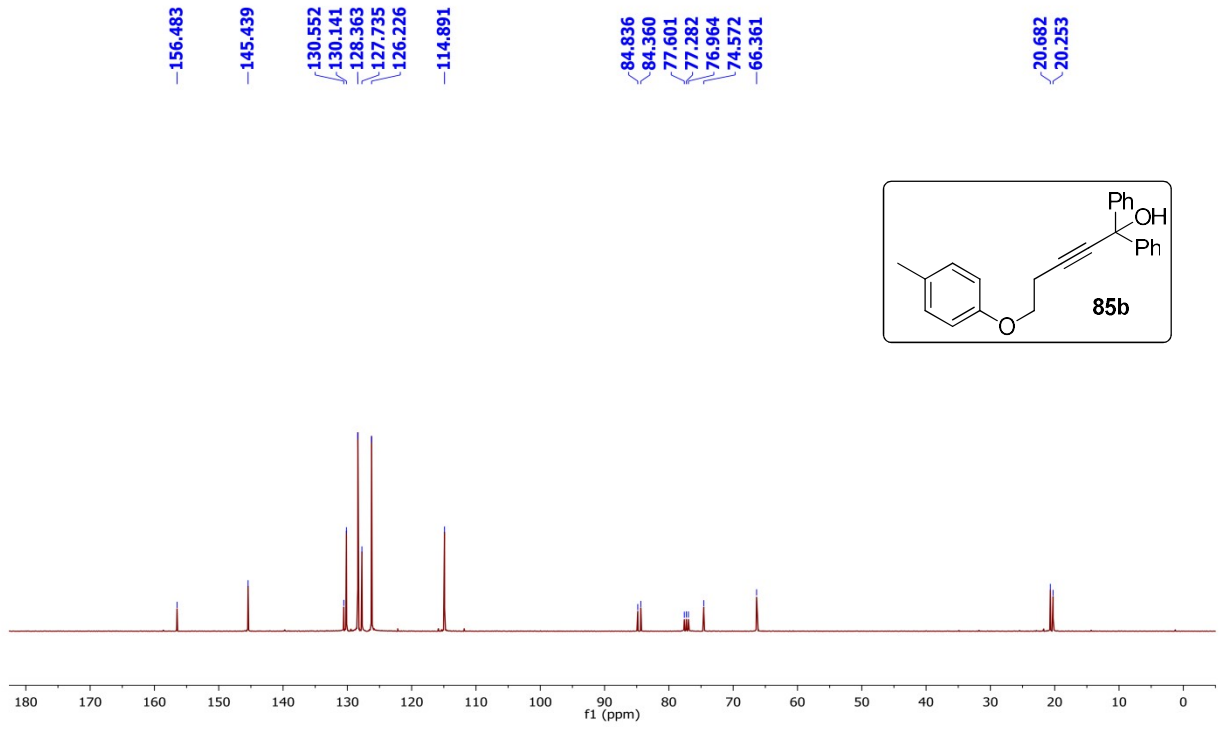
^{13}C{^{1}H} NMR (100 MHz) of **85a**:



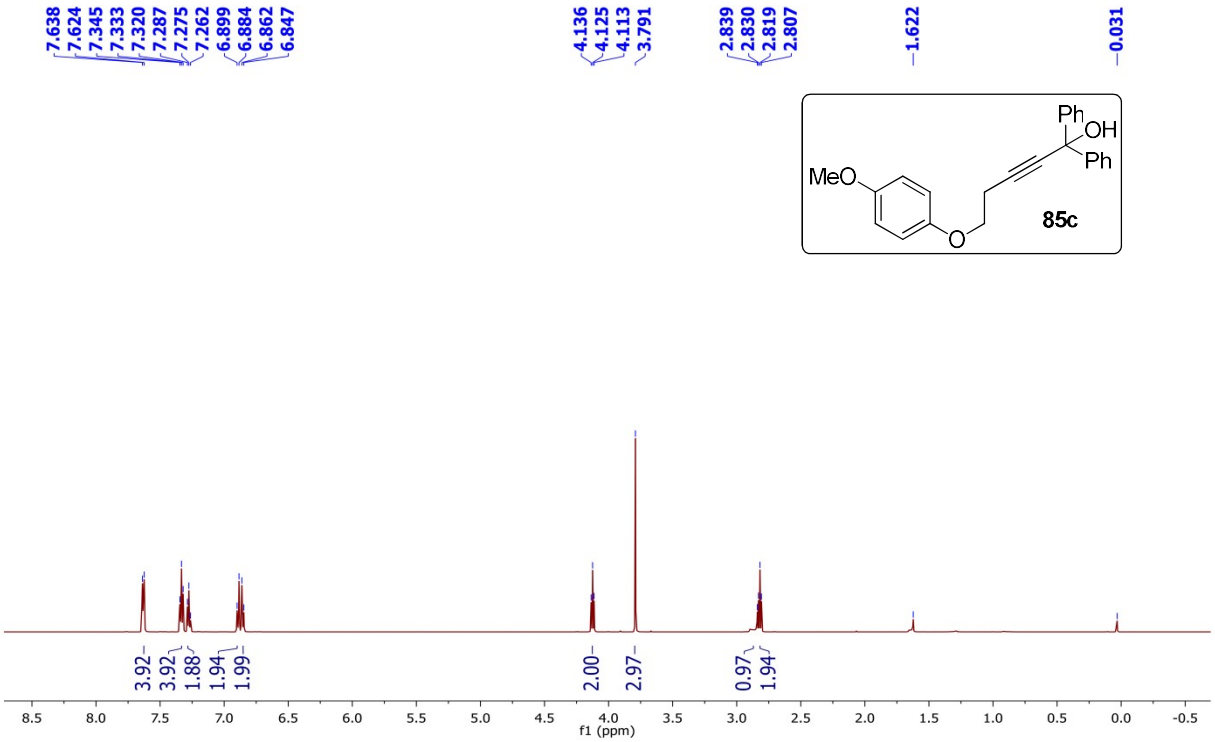
^{1}H NMR (400 MHz) of **85b**:



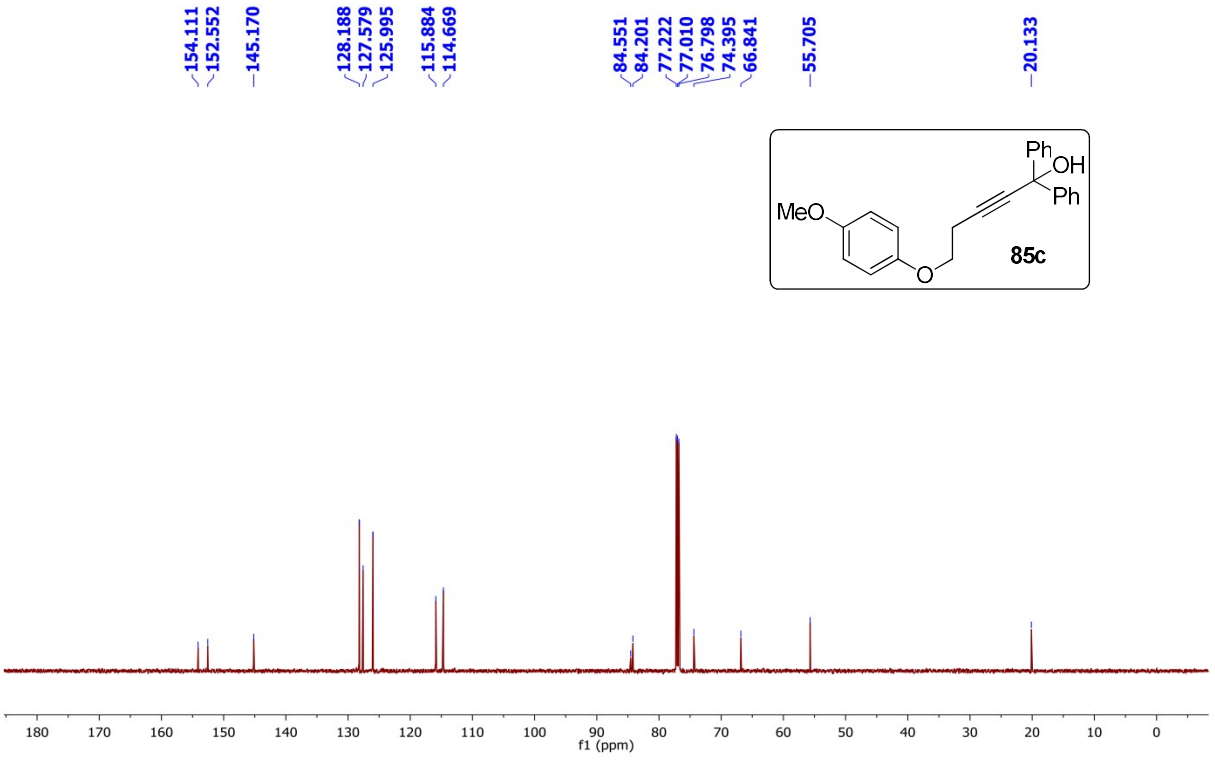
^{13}C{^{1}H} NMR (100 MHz) of **85b**:



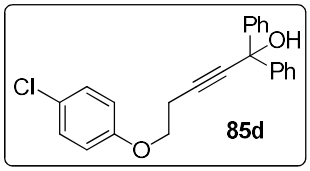
^{1}H NMR (600 MHz) of **85c**:

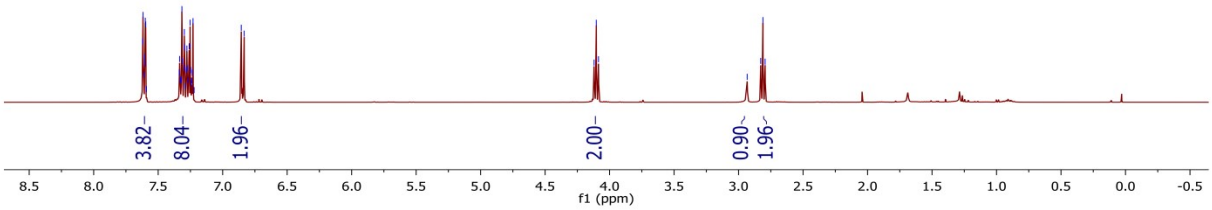


^{13}C{^{1}H} NMR (150 MHz) of **85c**:

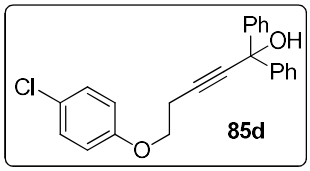


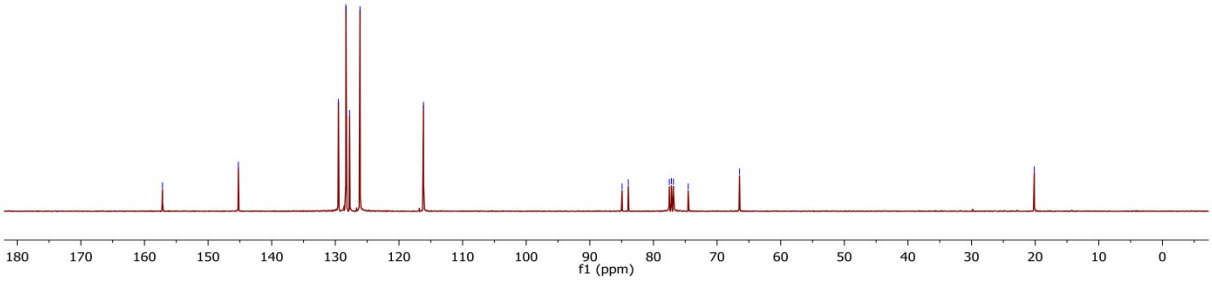
^{1}H NMR (400 MHz) of **85d**:



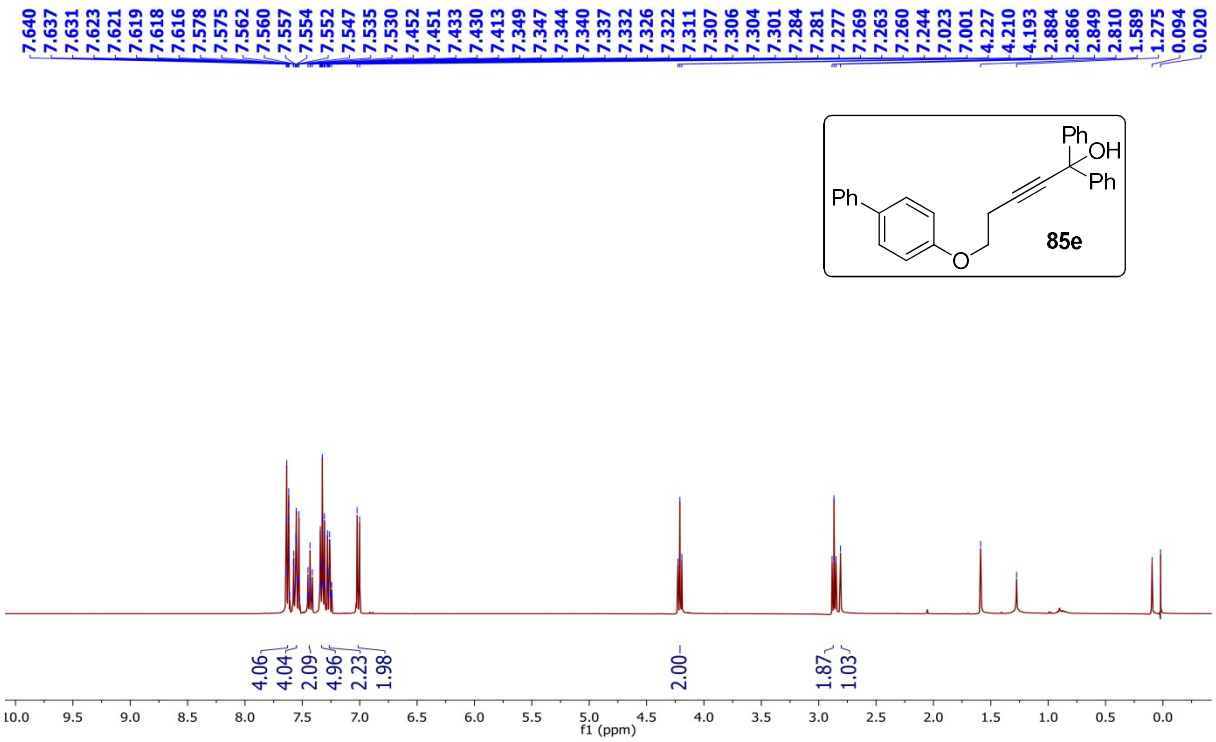


^{13}C{^{1}H} NMR (100 MHz) of **85d**:

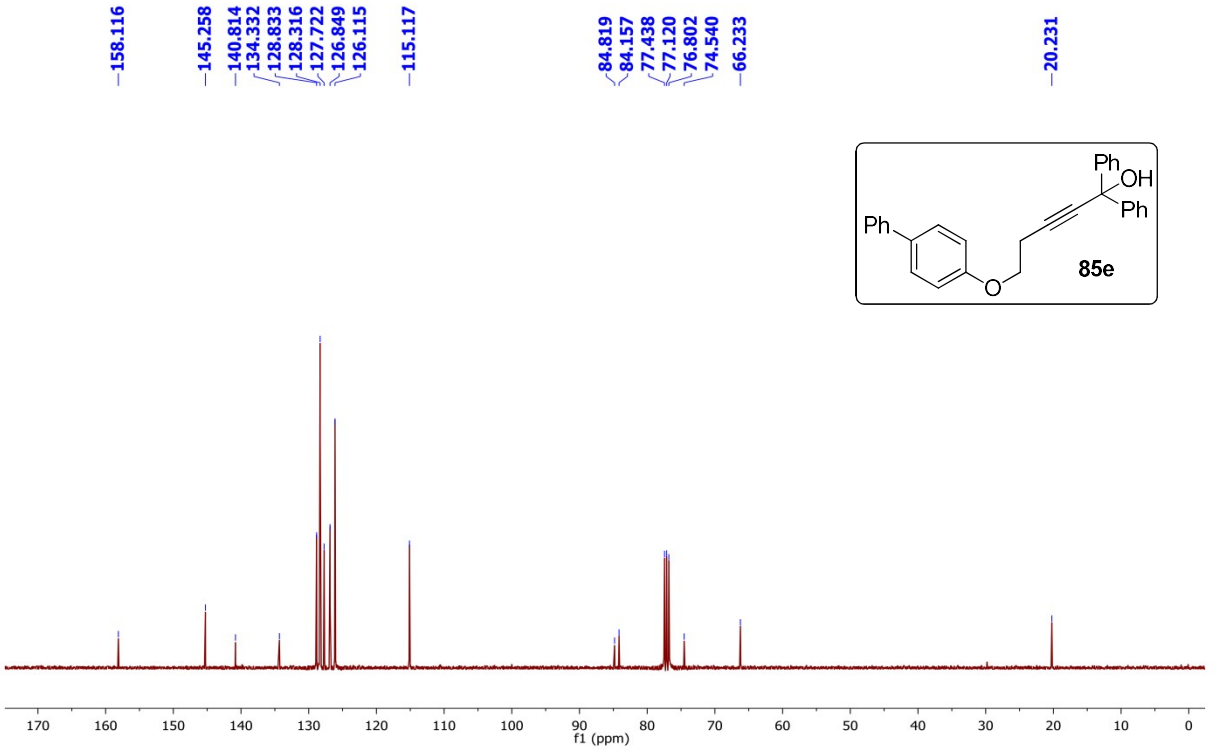




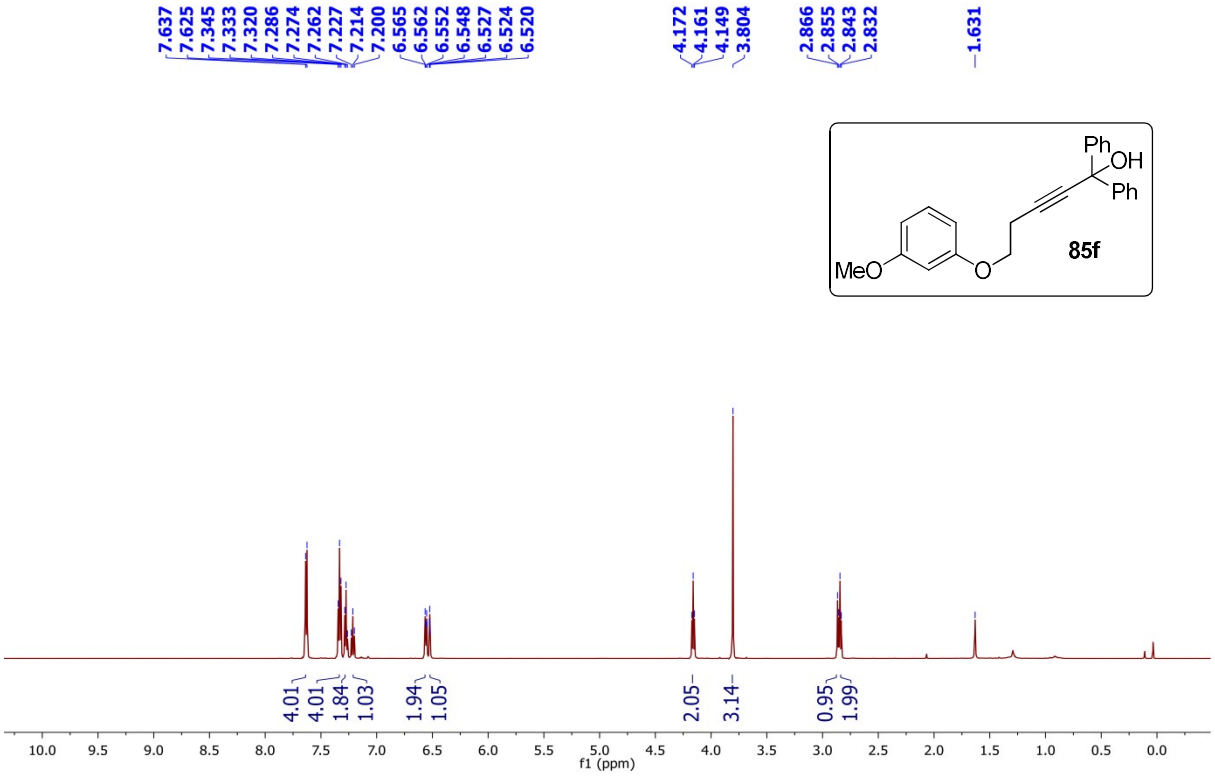
^{1}H NMR (400 MHz) of **85e**:



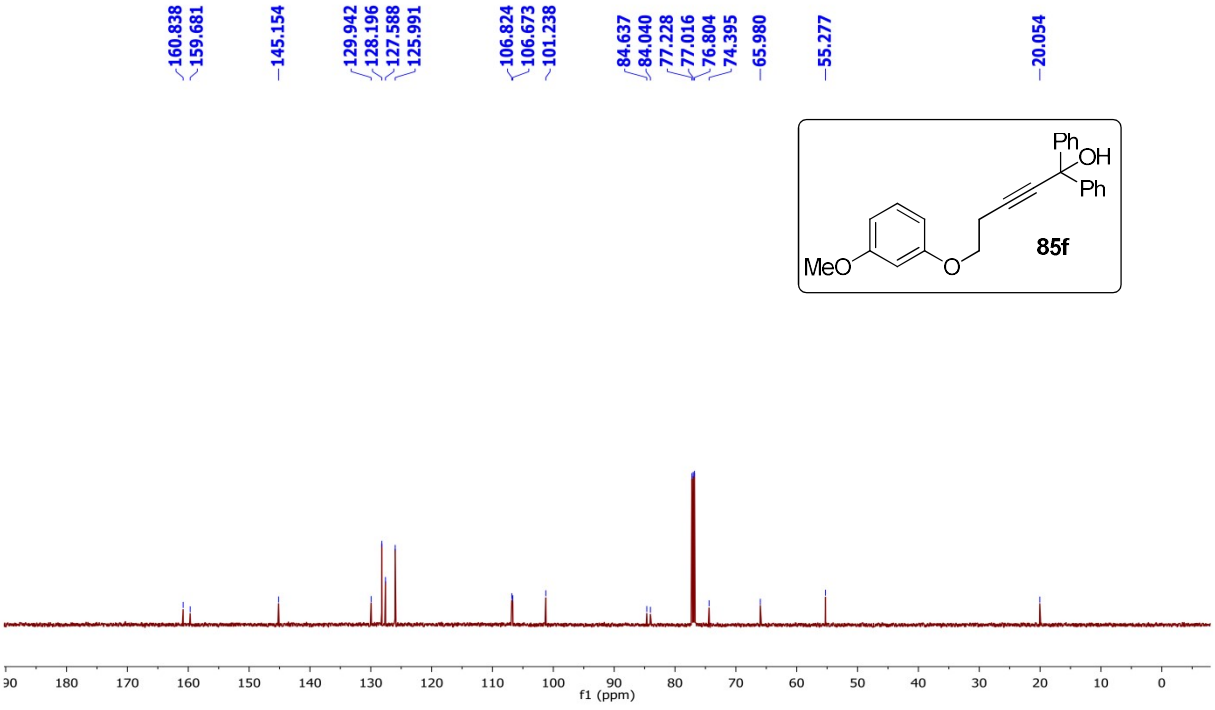
^{13}C{^{1}H} NMR (100 MHz) of **85e**:



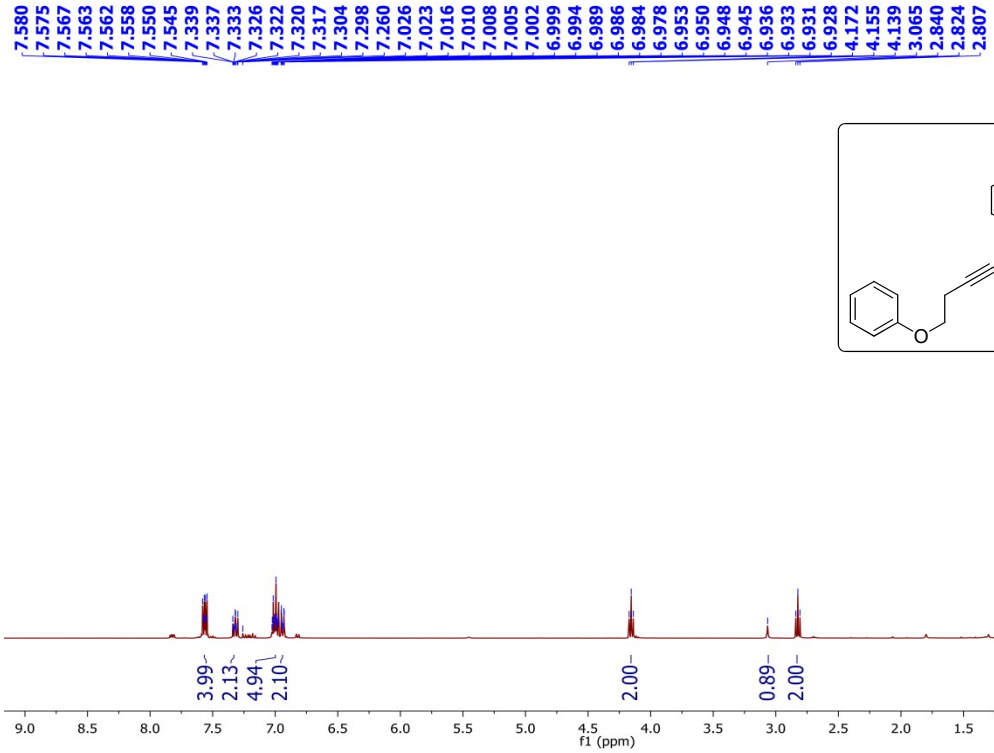
^{1}H NMR (600 MHz) of **85f**:



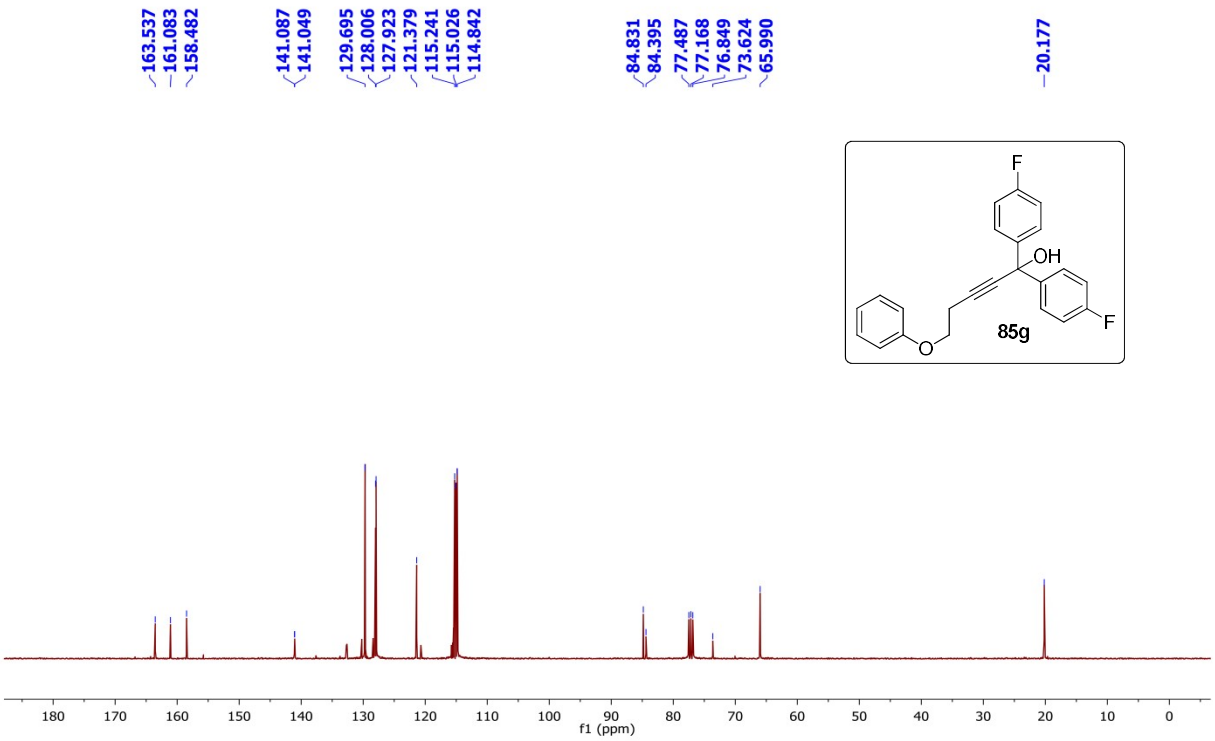
^{13}C{^{1}H} NMR (150 MHz) of **85f**:



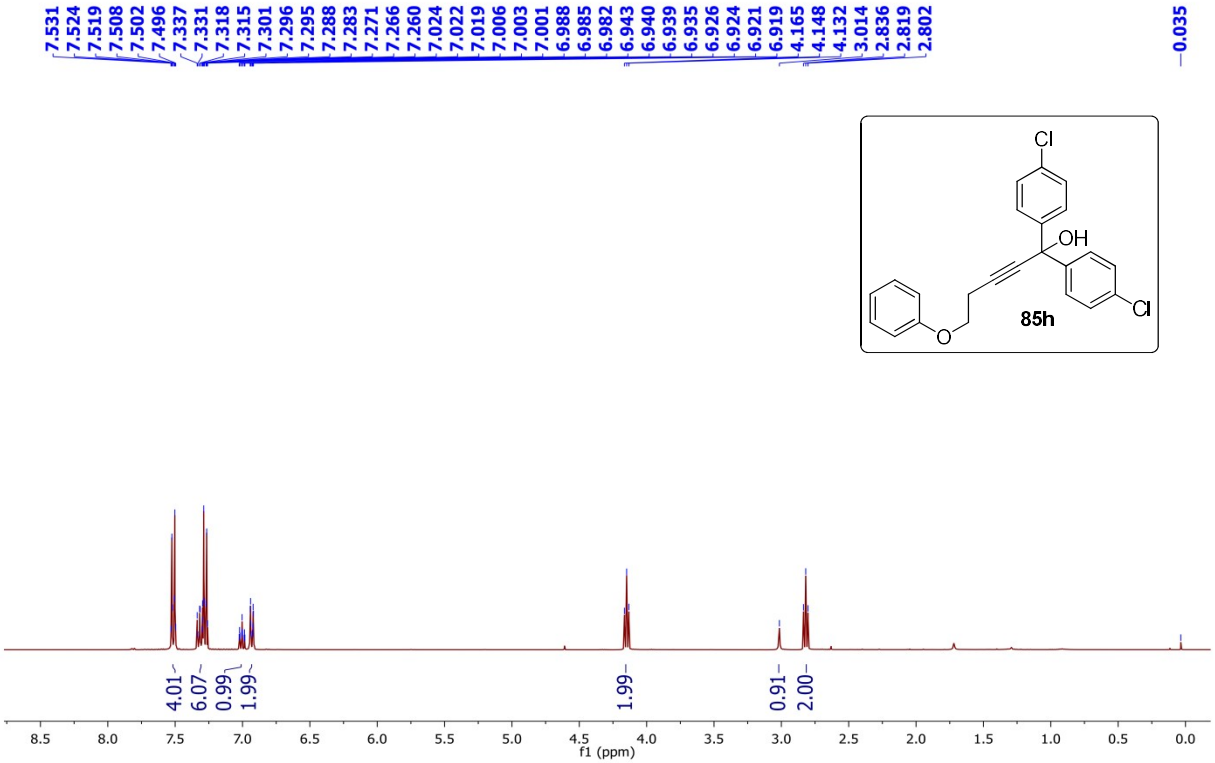
^{1}H NMR (400 MHz) of **85g:**



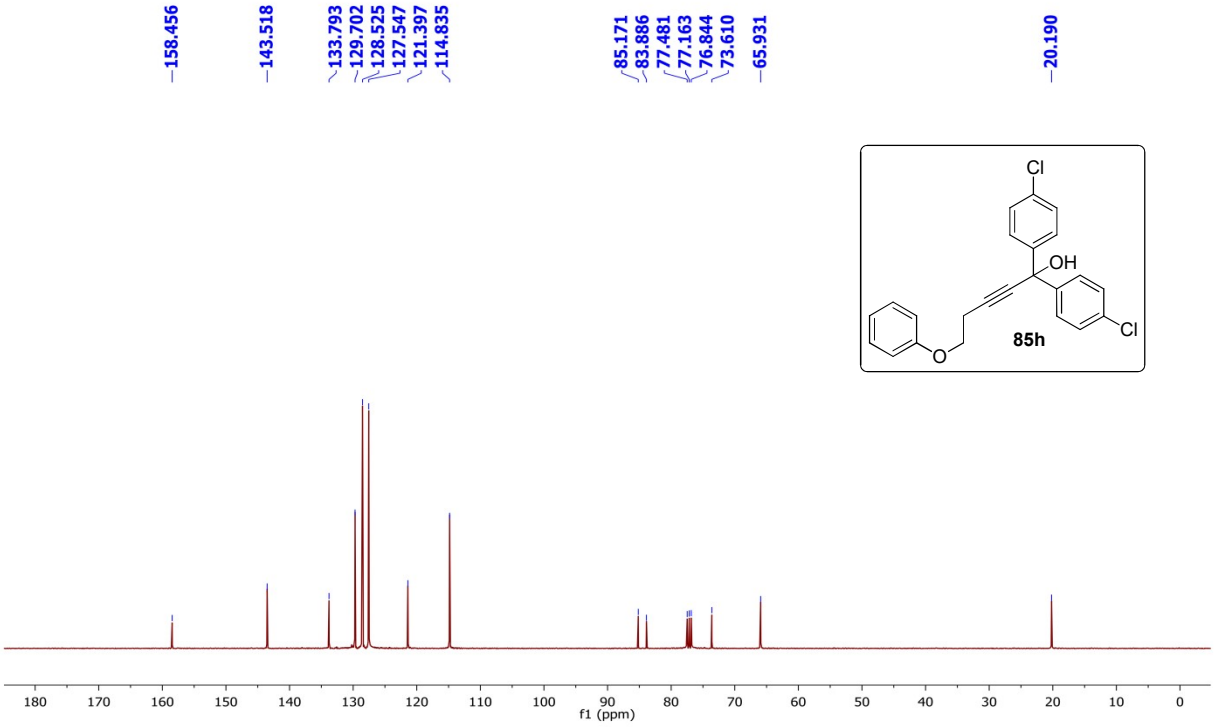
^{13}C{^{1}H} NMR (100 MHz) of **85g:**



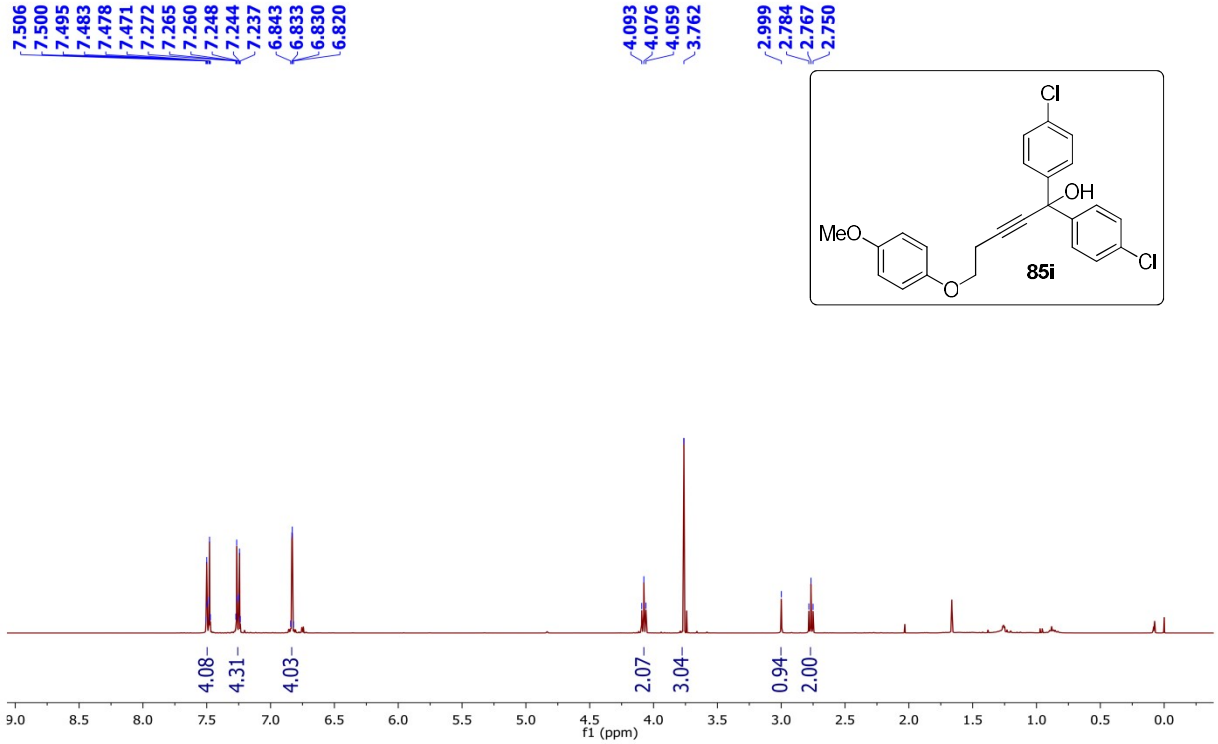
^{1}H NMR (400 MHz) of **85h**:



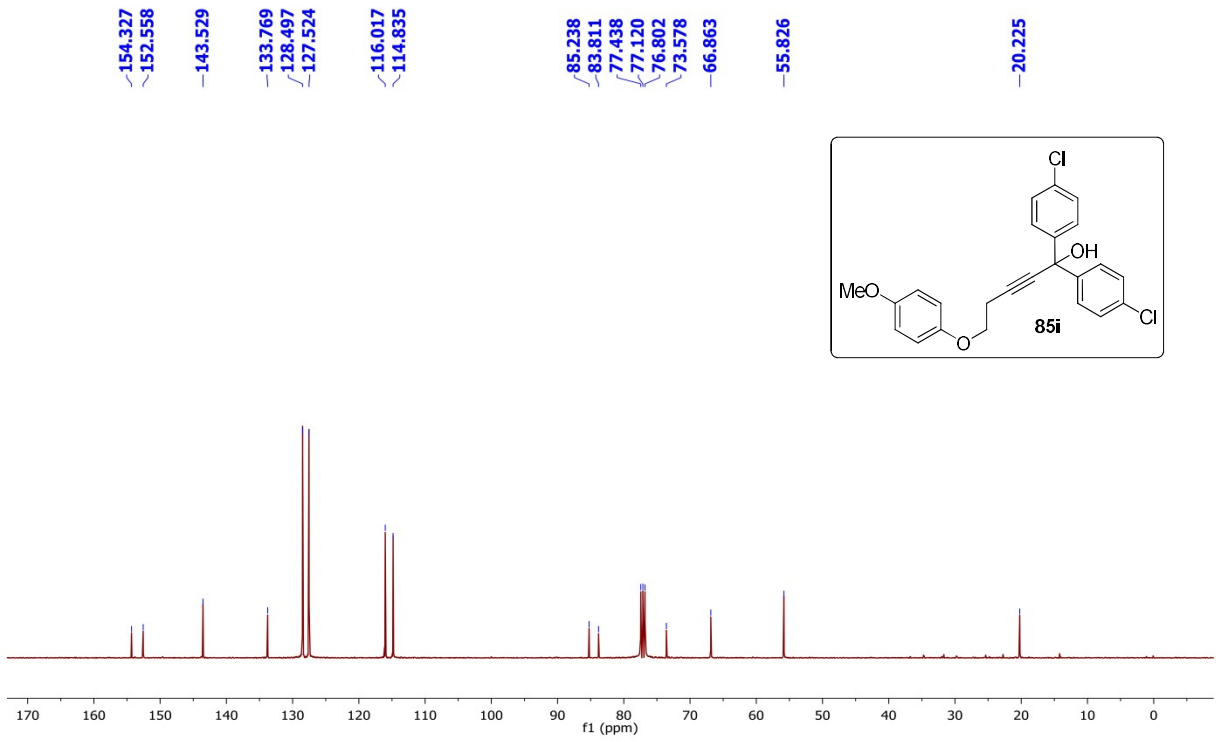
^{13}C{^{1}H} NMR (100 MHz) of **85h**:



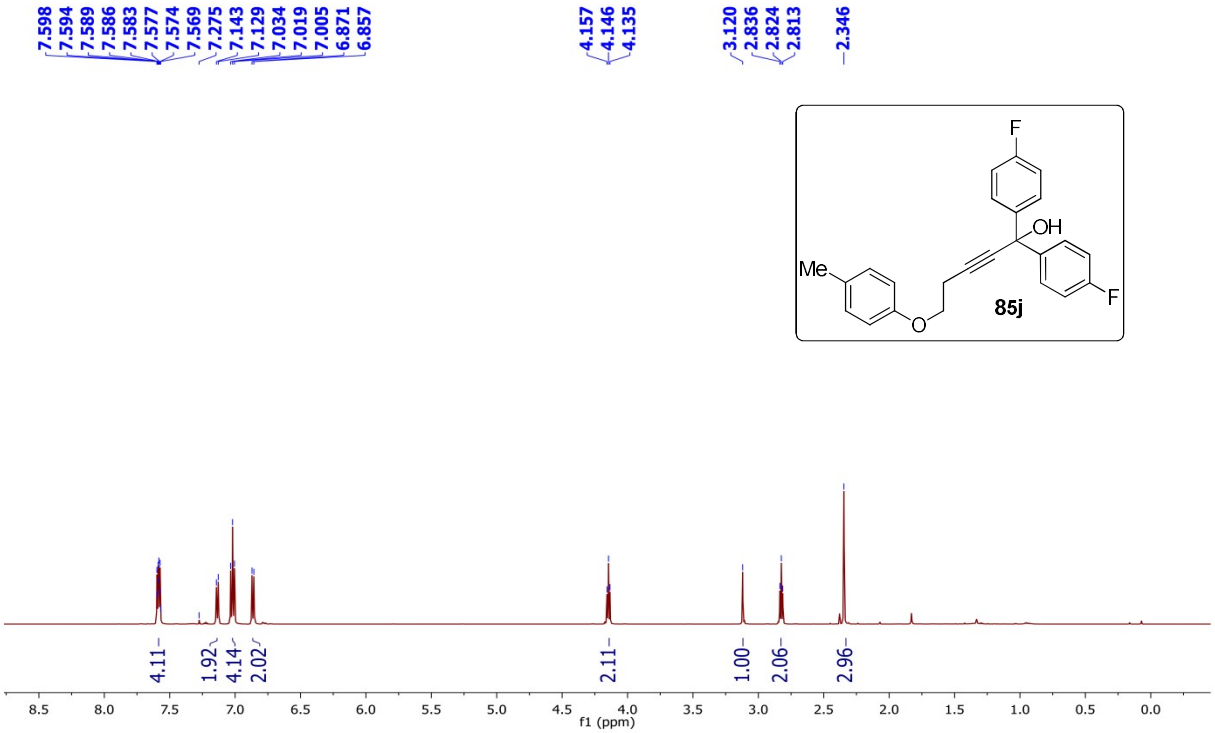
^{1}H NMR (400 MHz) of **85i**:



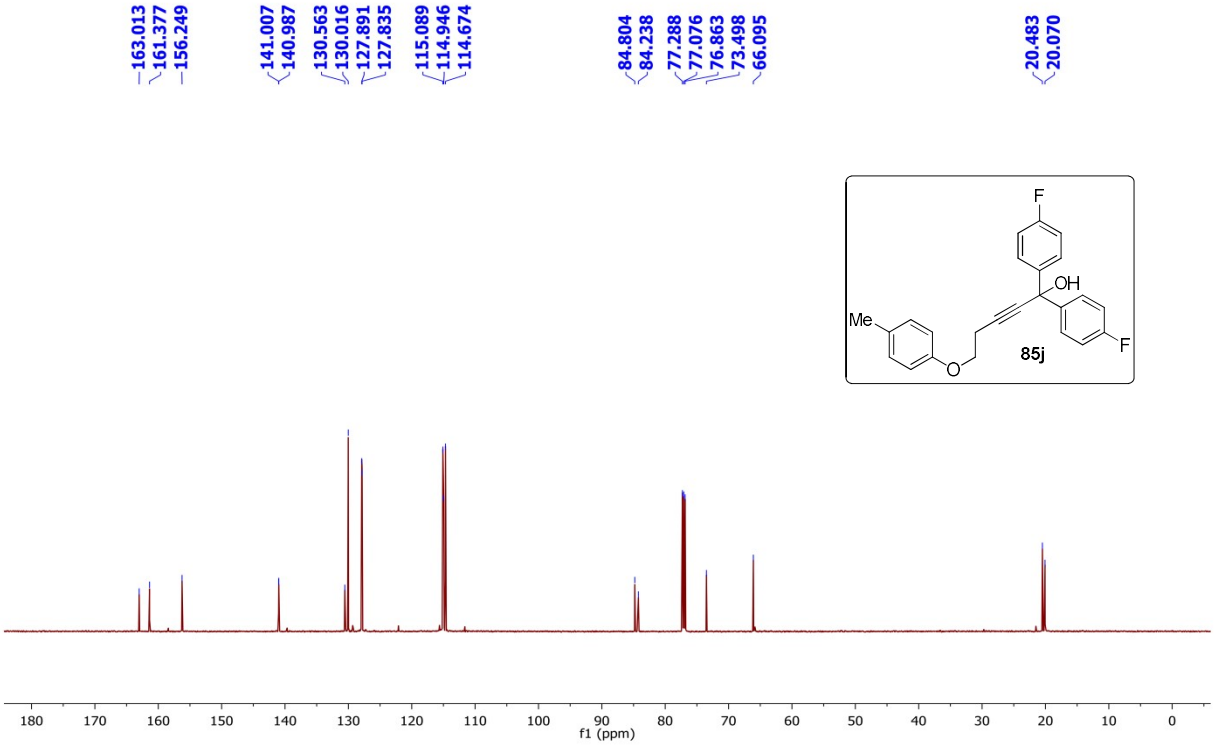
^{13}C{^{1}H} NMR (100 MHz) of **85i**:



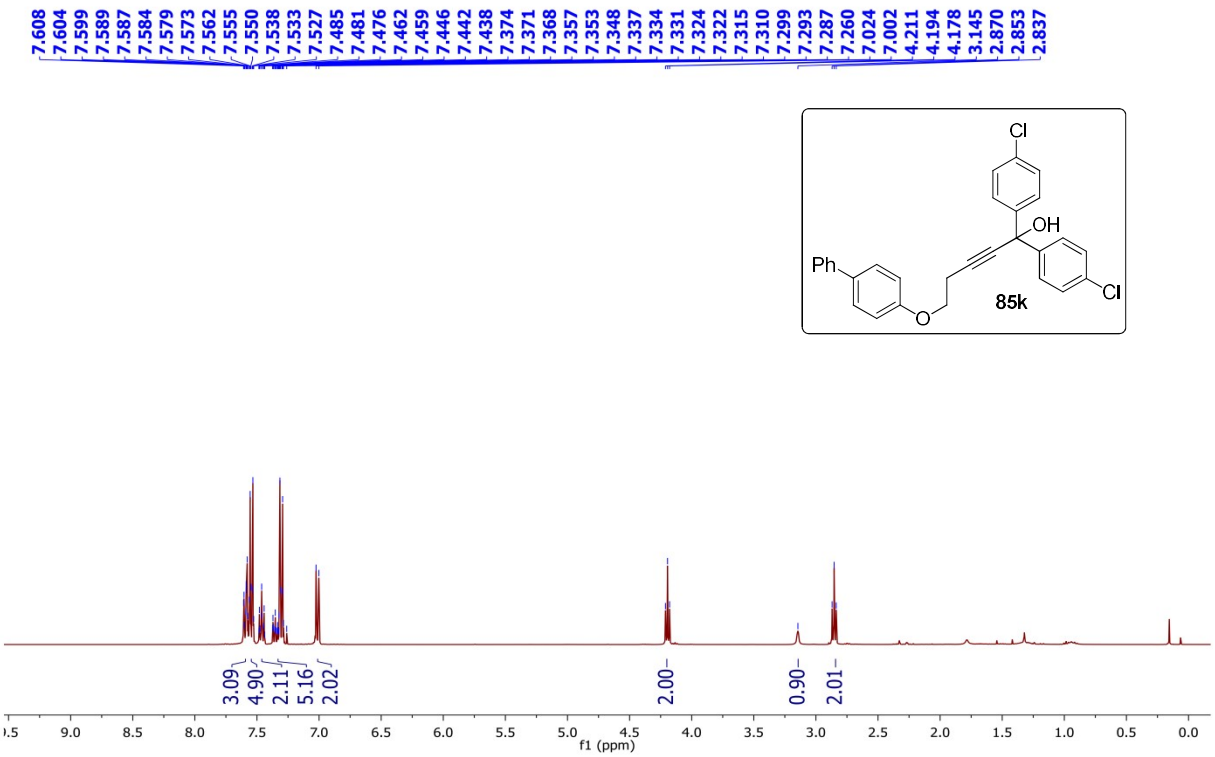
^{1}H NMR (600 MHz) of **85j**:



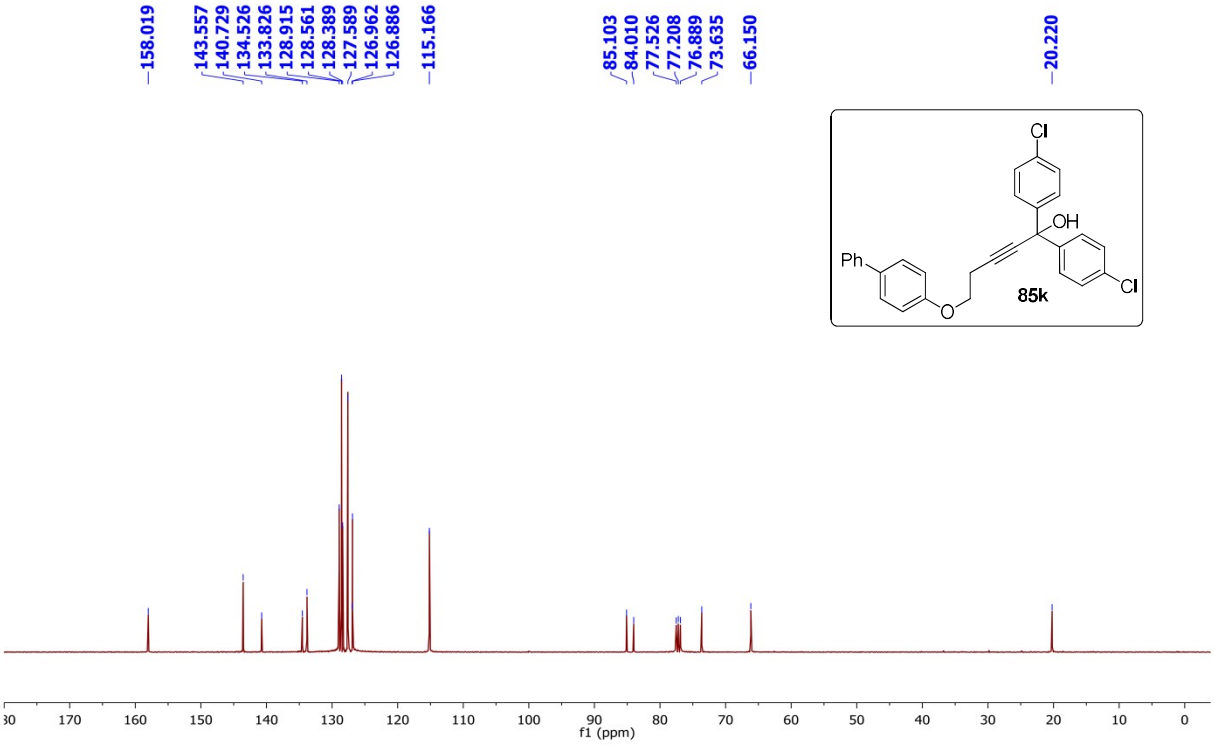
^{13}C{^{1}H} NMR (150 MHz) of **85j**:



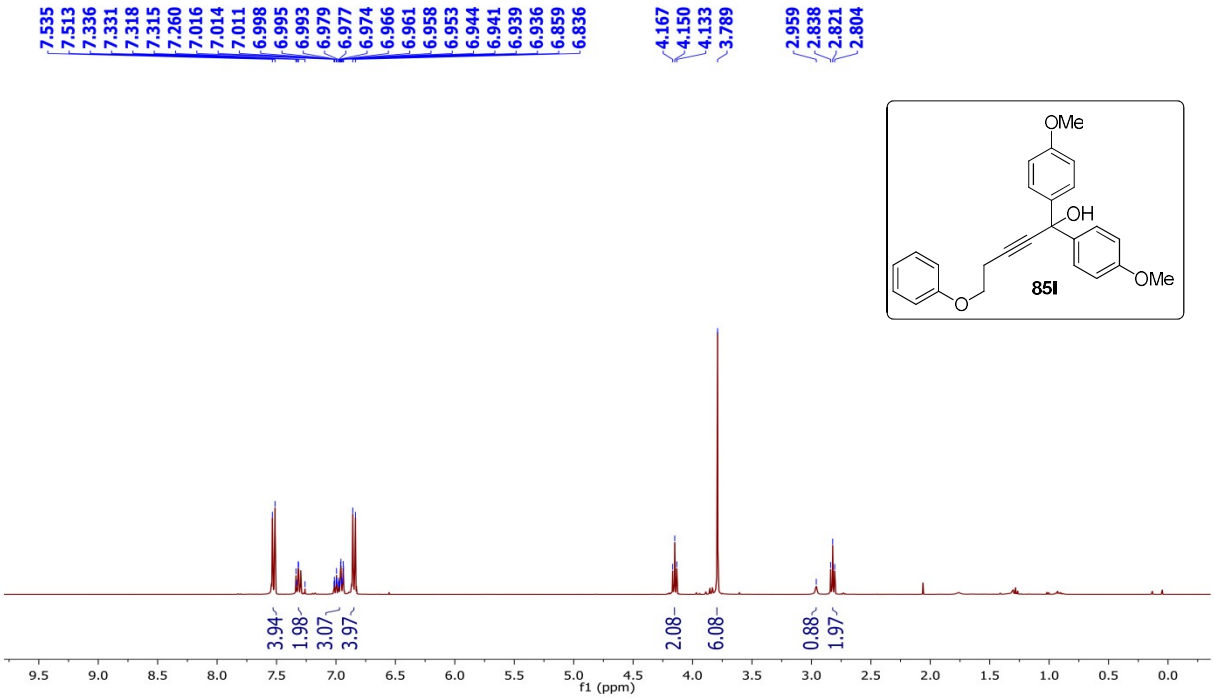
^{1}H NMR (400 MHz) of **85k**:



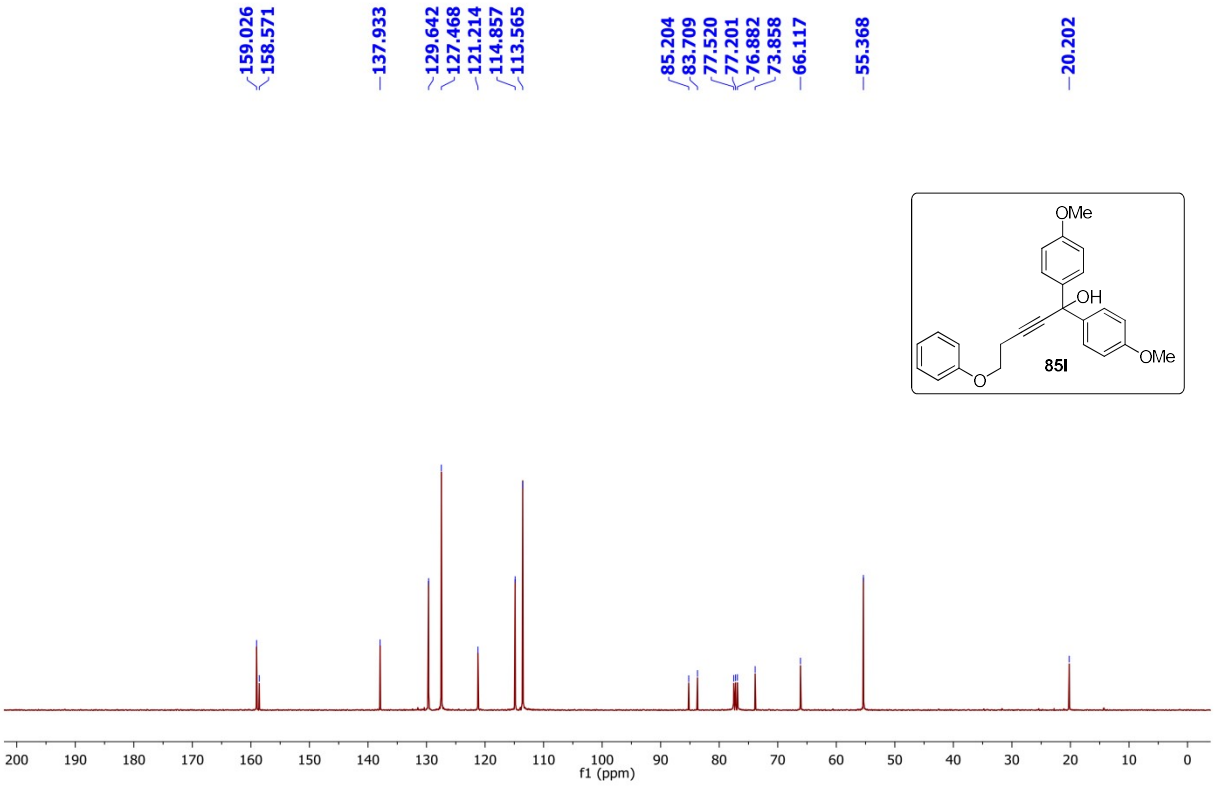
^{13}C{^{1}H} NMR (100 MHz) of **85k**:



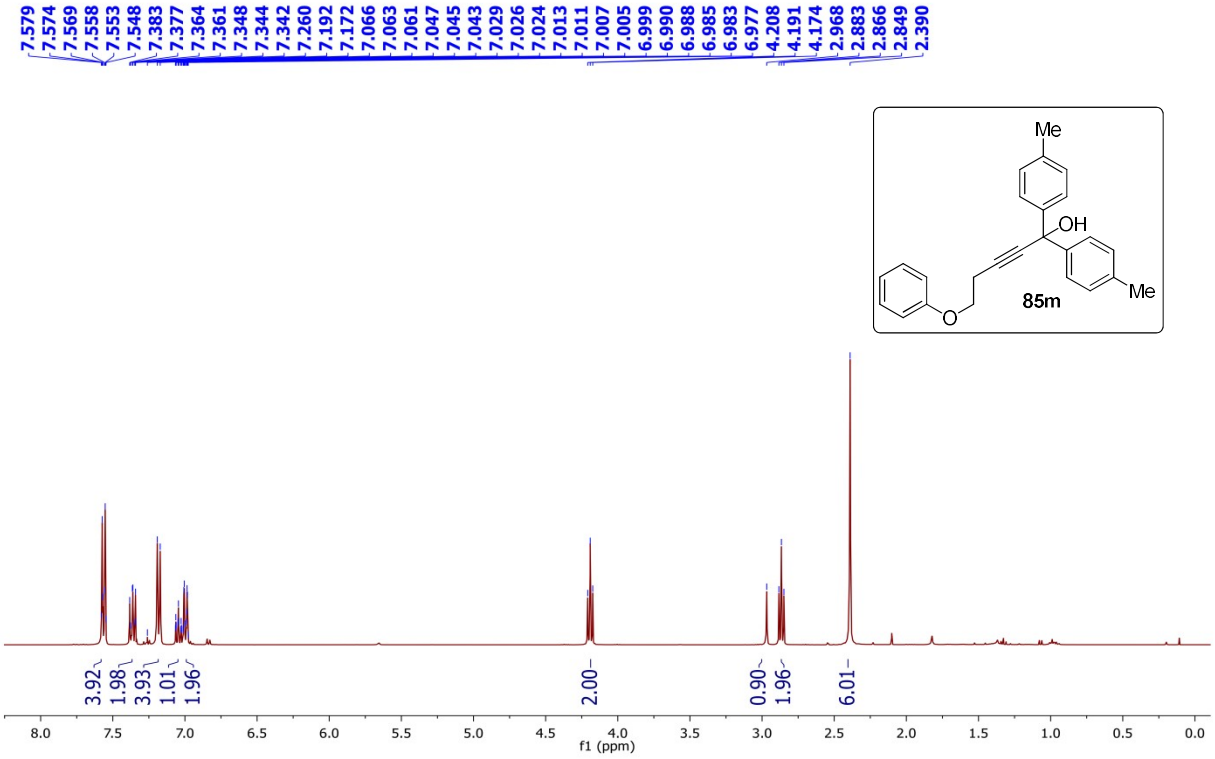
^{1}H NMR (400 MHz) of **85l**:



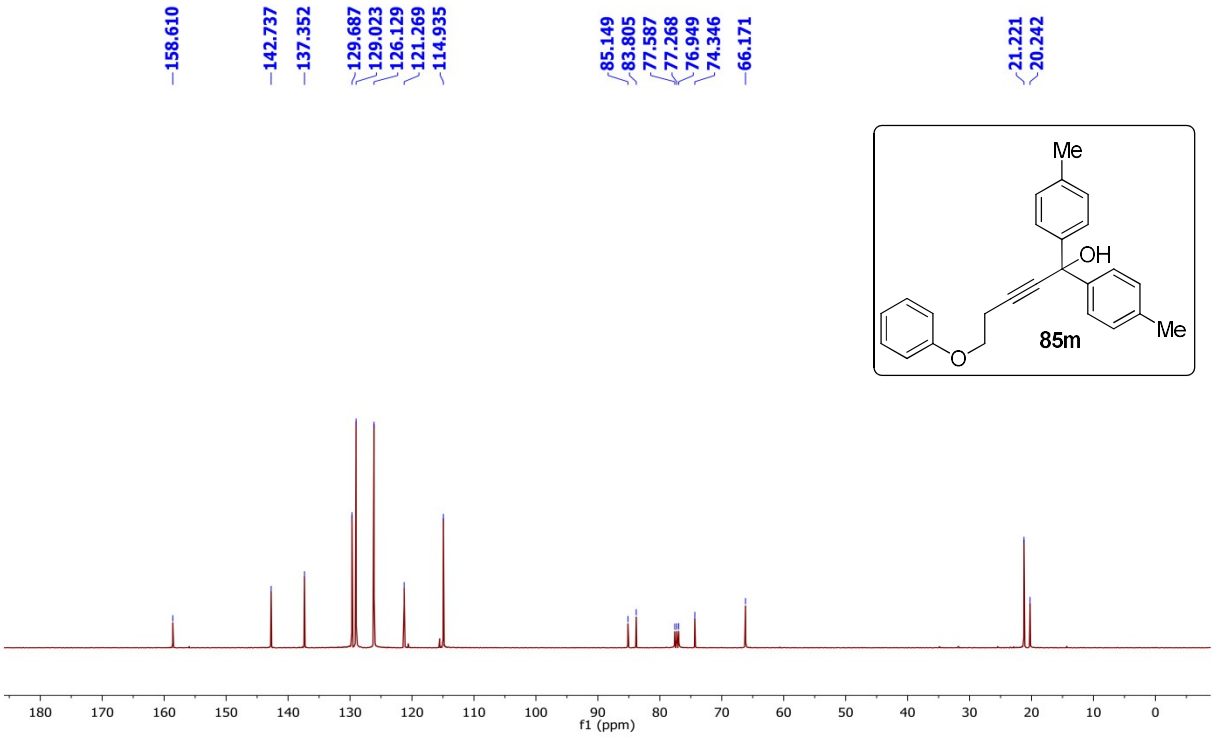
^{13}C{^{1}H} NMR (100 MHz) of **85l**:



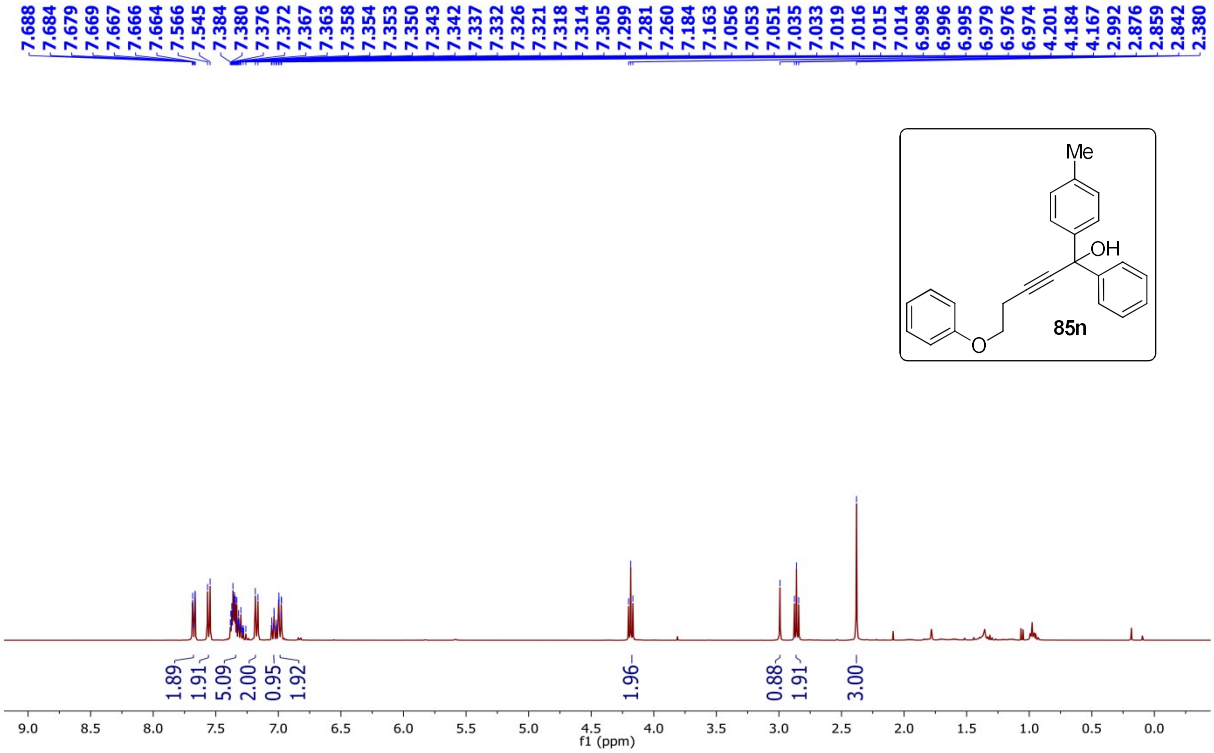
^{1}H NMR (400 MHz) of **85m**:



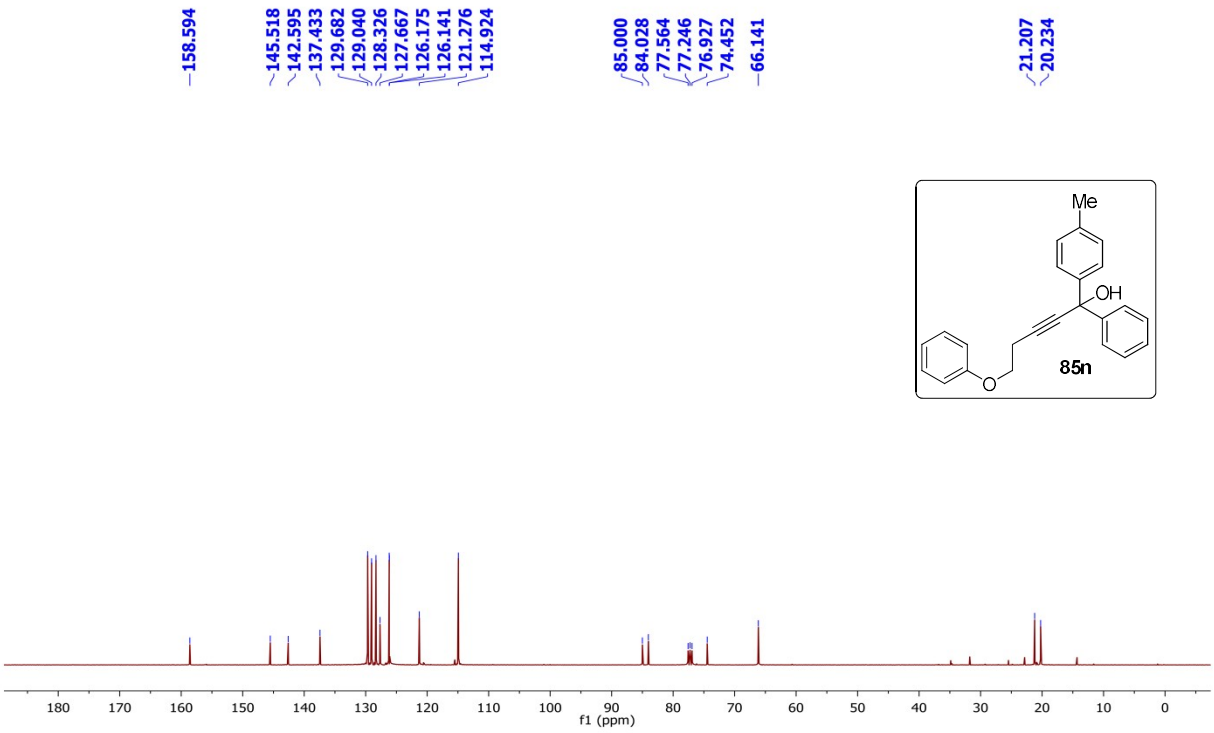
^{13}C{^{1}H} NMR (100 MHz) of **85m:**



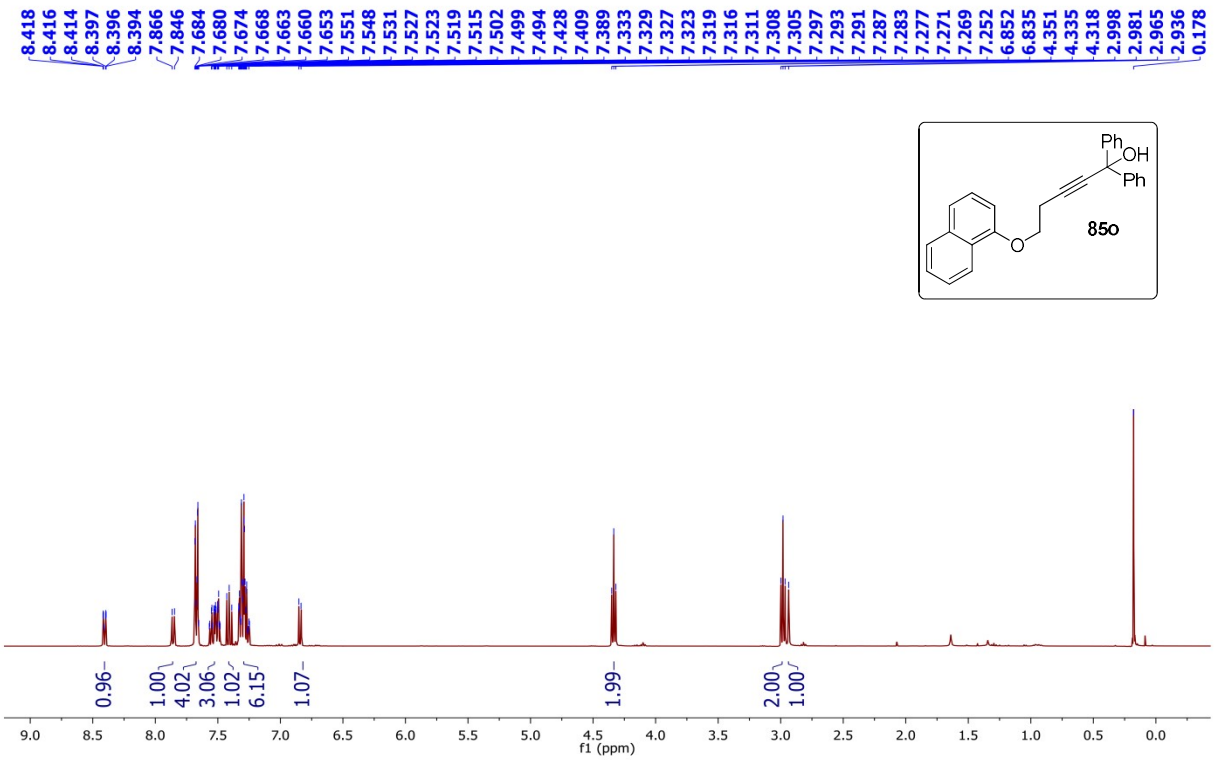
^{1}H NMR (400 MHz) of **85n**:



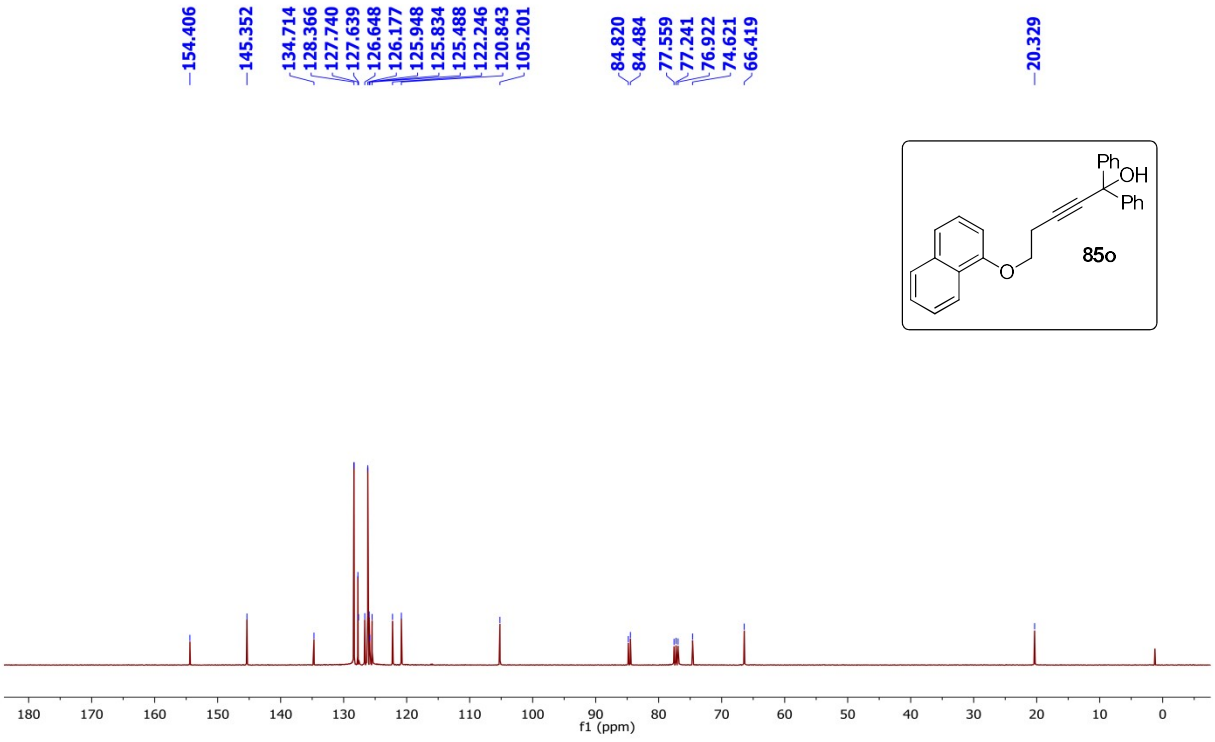
^{13}C{^{1}H} NMR (100 MHz) of **85n**:



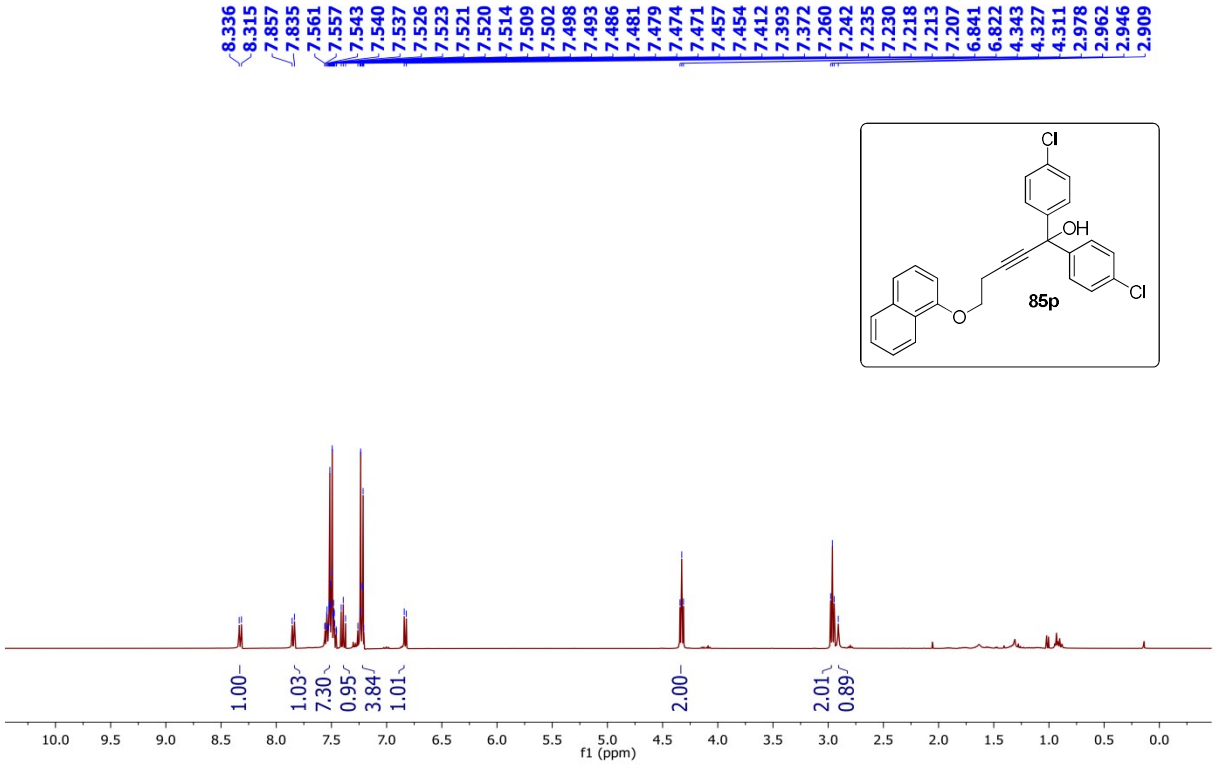
^{1}H NMR (400 MHz) of **85o**:



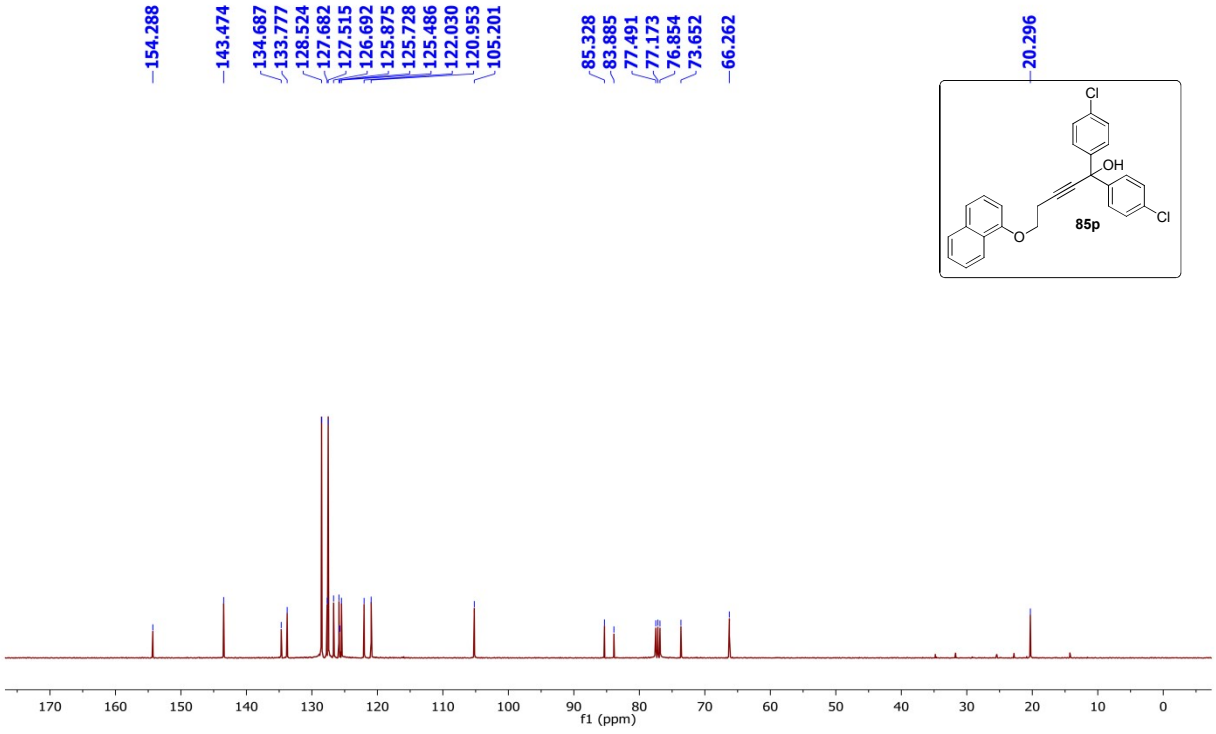
^{13}C{^{1}H} NMR (100 MHz) of **85o**:



^{1}H NMR (400 MHz) of **85p**:

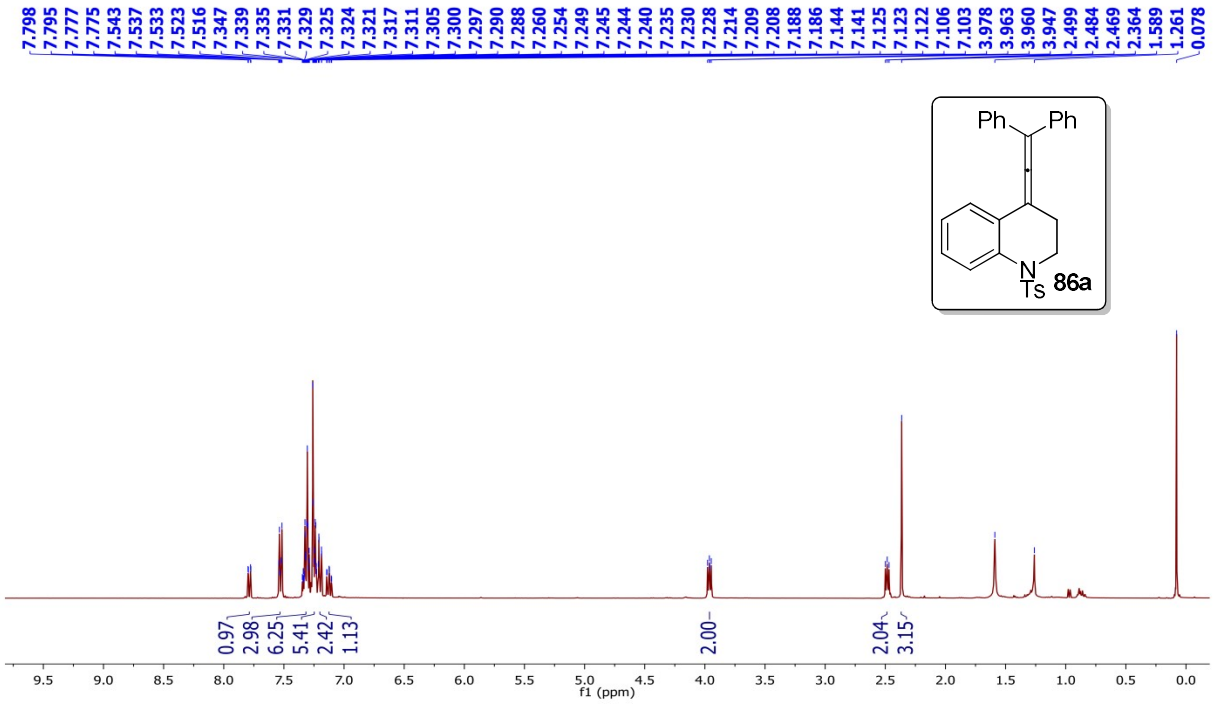


^{13}C{^{1}H} NMR (100 MHz) of **85p:**

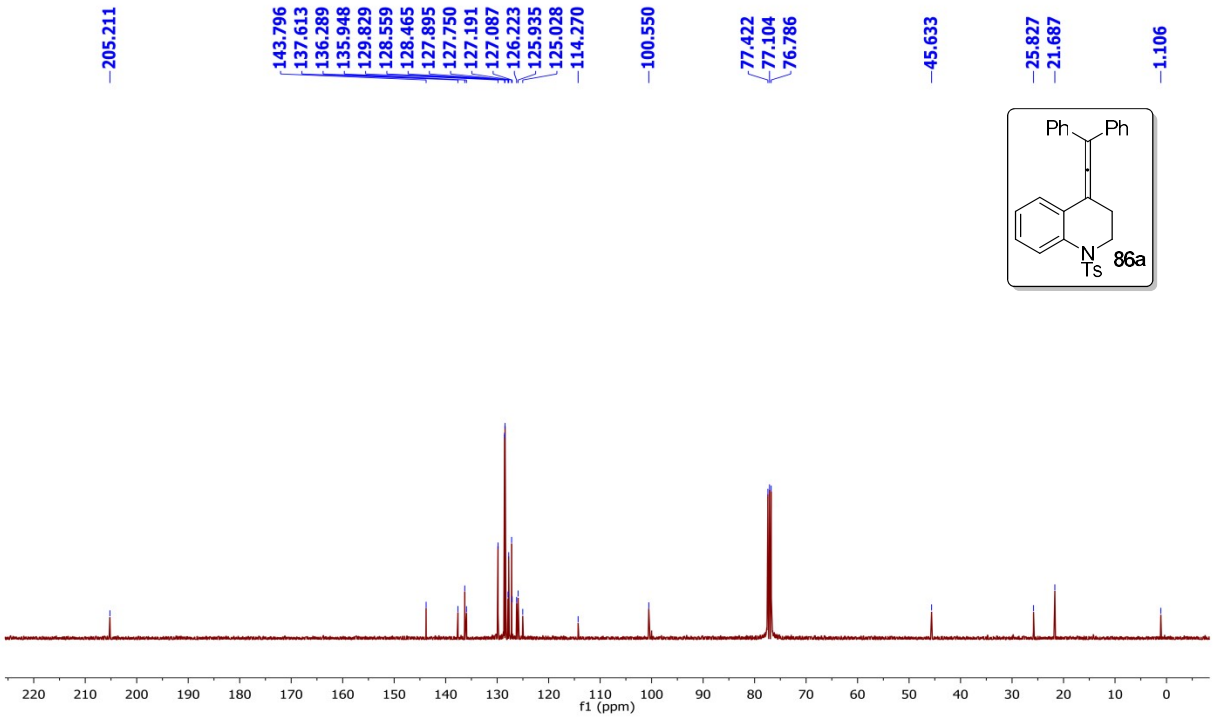


3.2.9.3. NMR Spectra of Intermediates 86a, 86′a, 86d and (86f, 86f′)

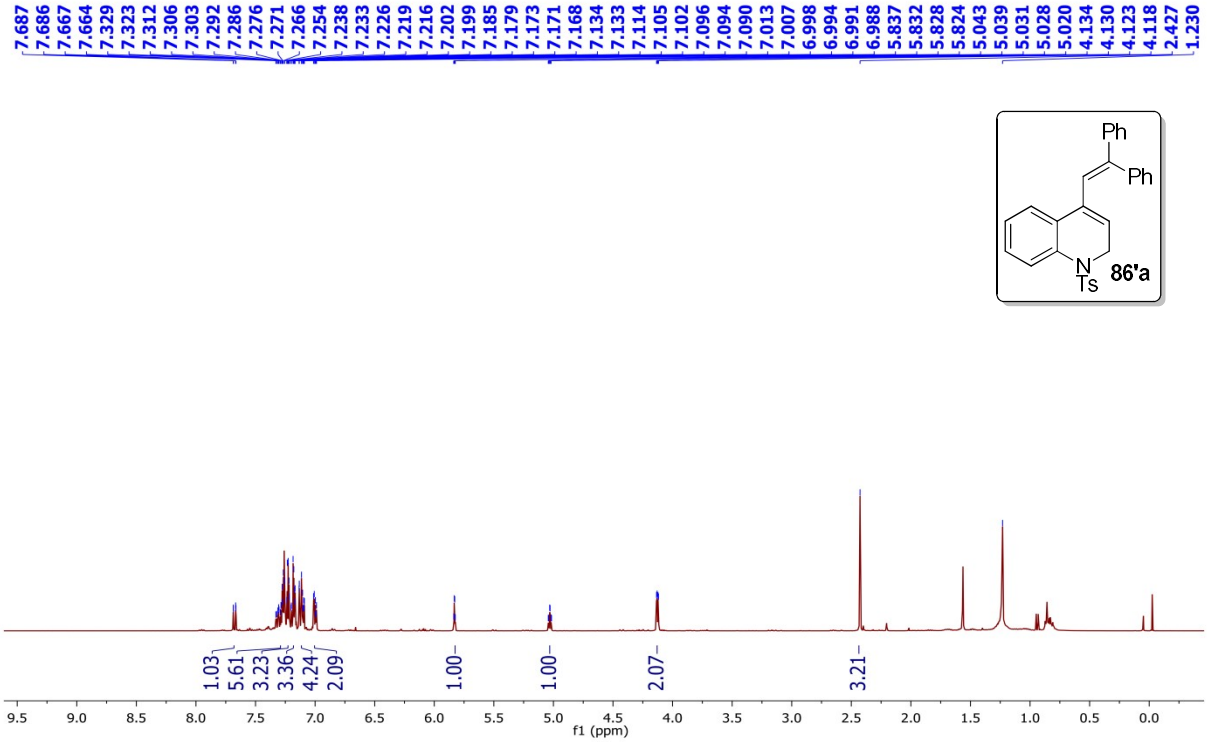
^{1}H NMR (400 MHz) of **86a**:



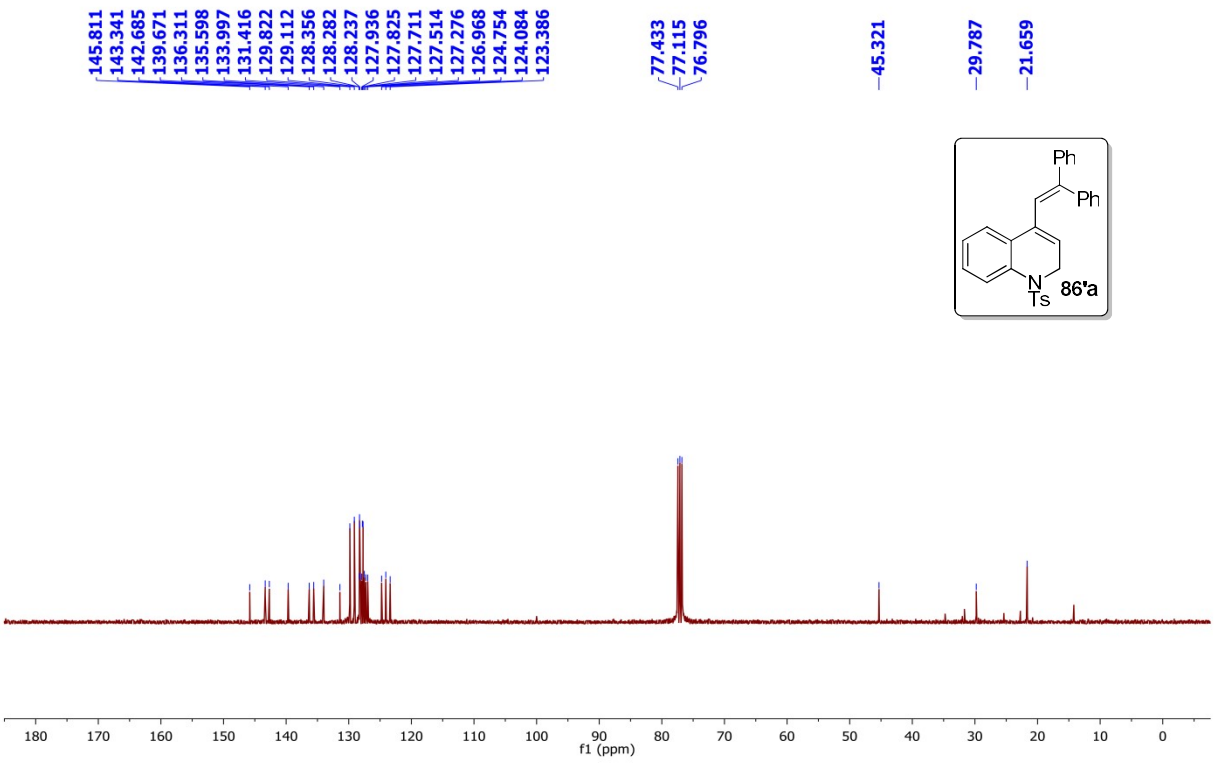
^{13}C{^{1}H} NMR (100 MHz) of **86a:**



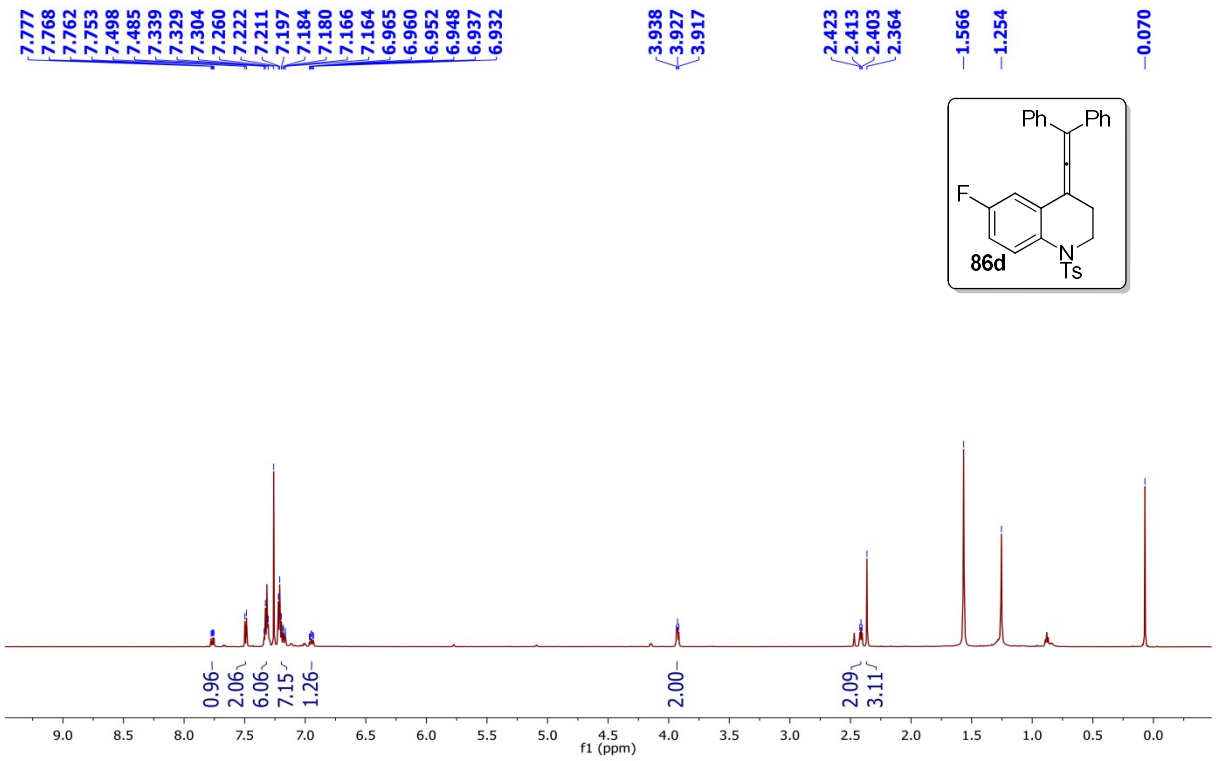
^{1}H NMR (400 MHz) of **86'a**:



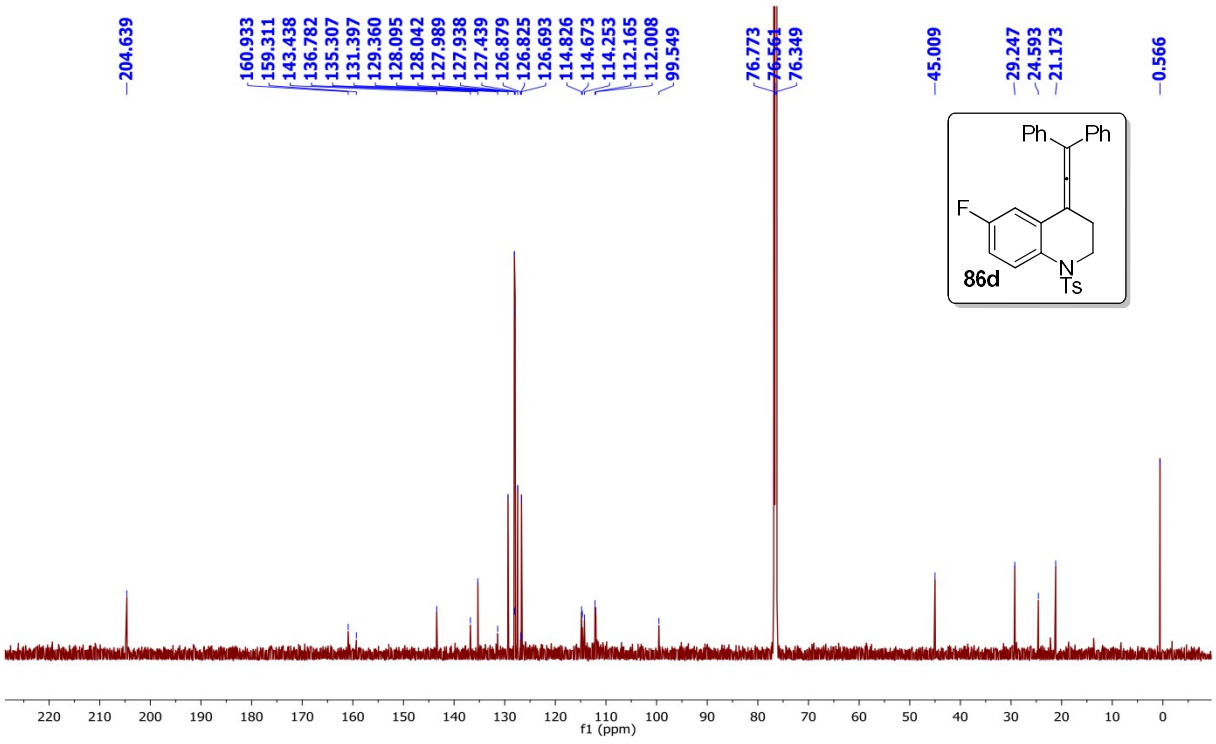
^{13}C{^{1}H} NMR (100 MHz) of **86'a:**



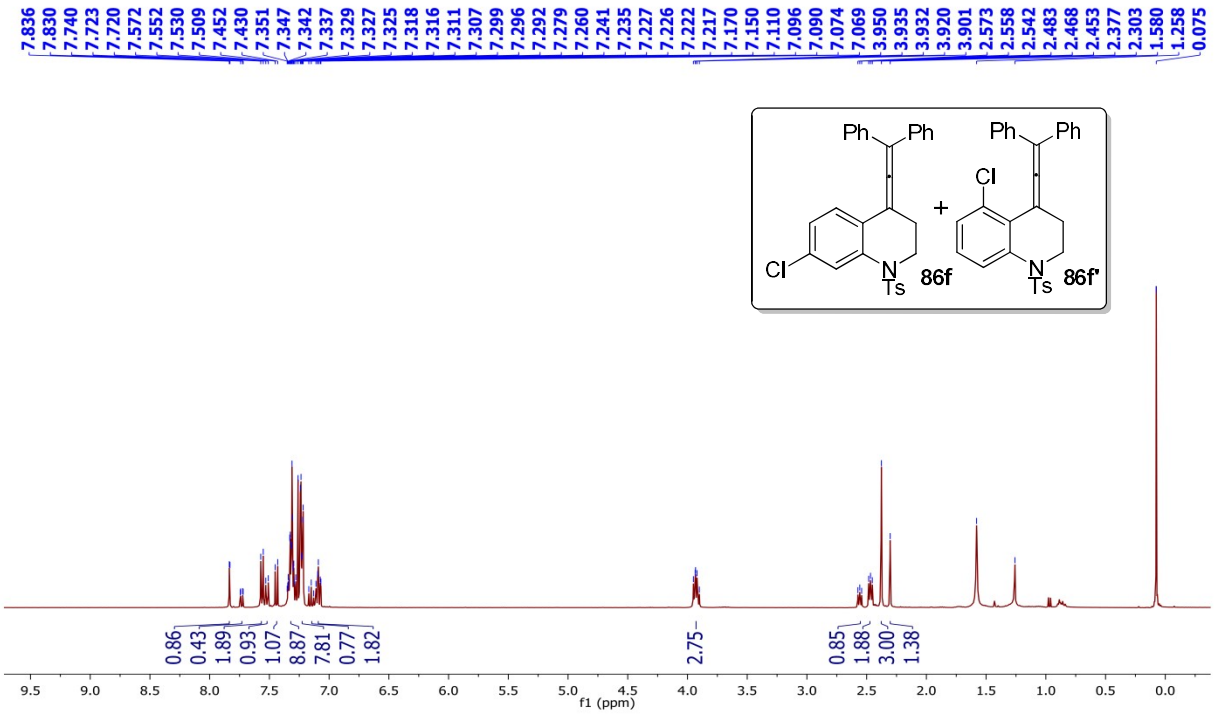
^{1}H NMR (600 MHz) of **86d**:



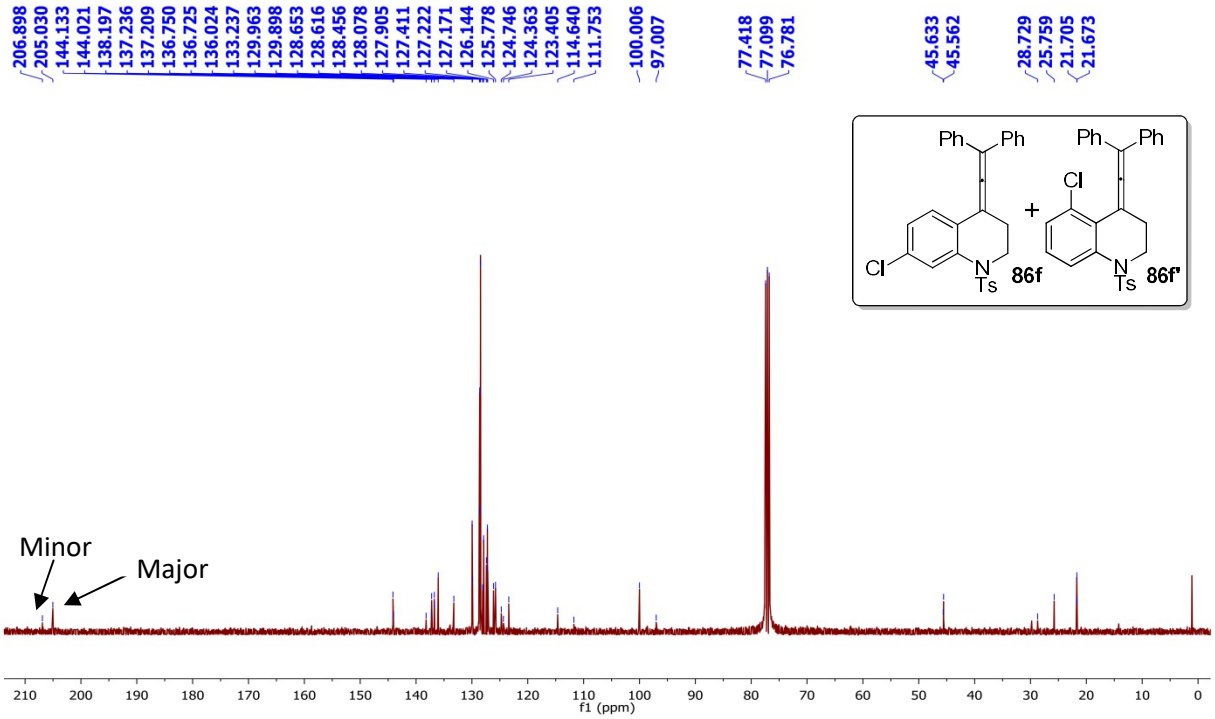
^{13}C{^{1}H} NMR (150 MHz) of **86d:**



^{1}H NMR (400 MHz) of **86f** and **86f'**:

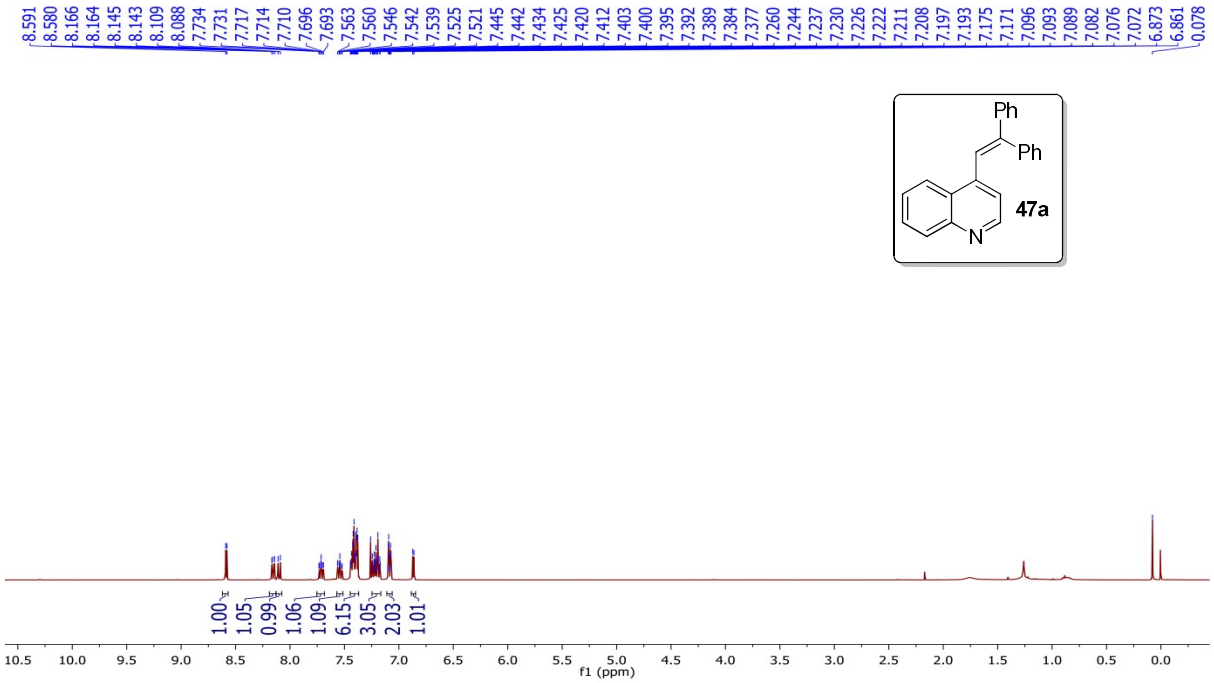


^{13}C{^{1}H} NMR (100 MHz) of **86f** and **86f':**

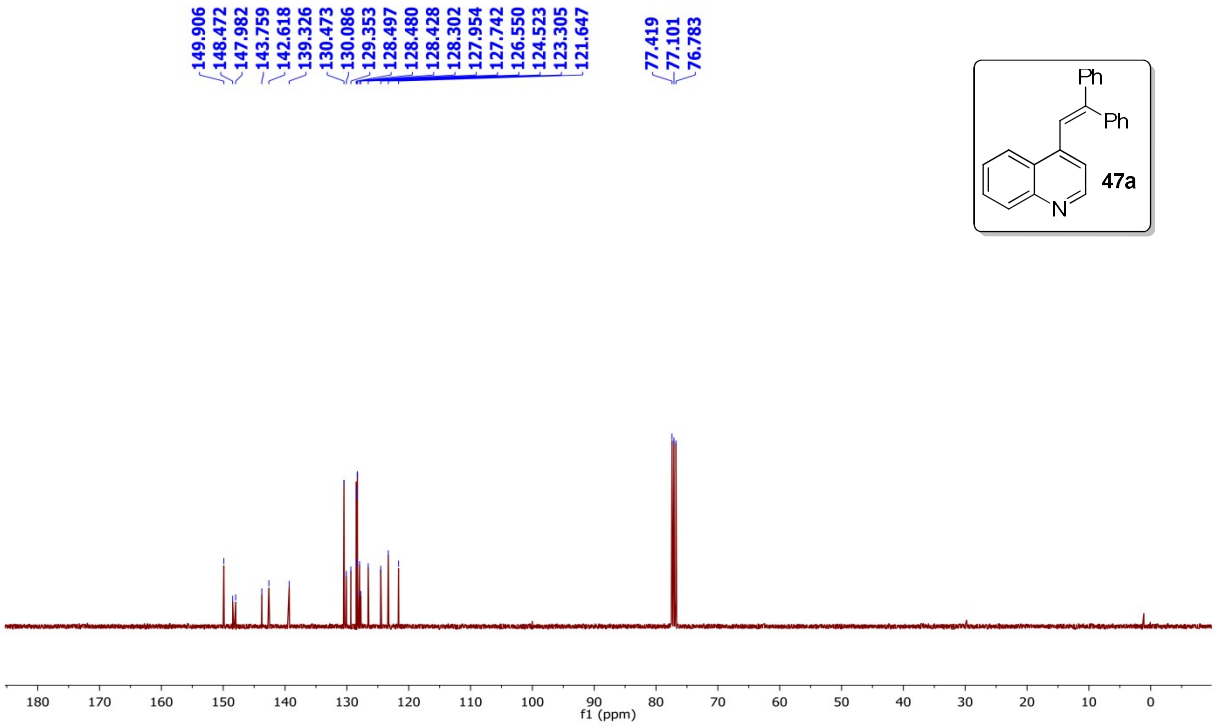


3.2.9.4. NMR Spectra of Compounds 47a-k:

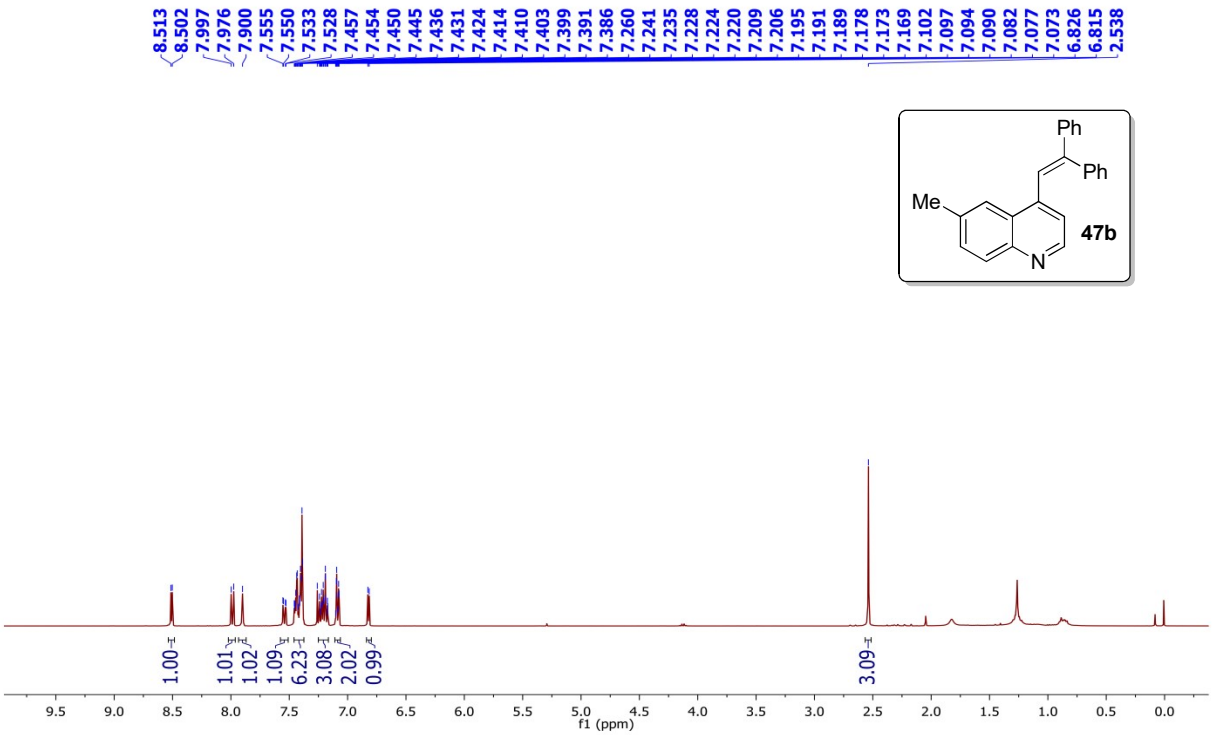
^{1}H NMR (400 MHz) of **47a**:



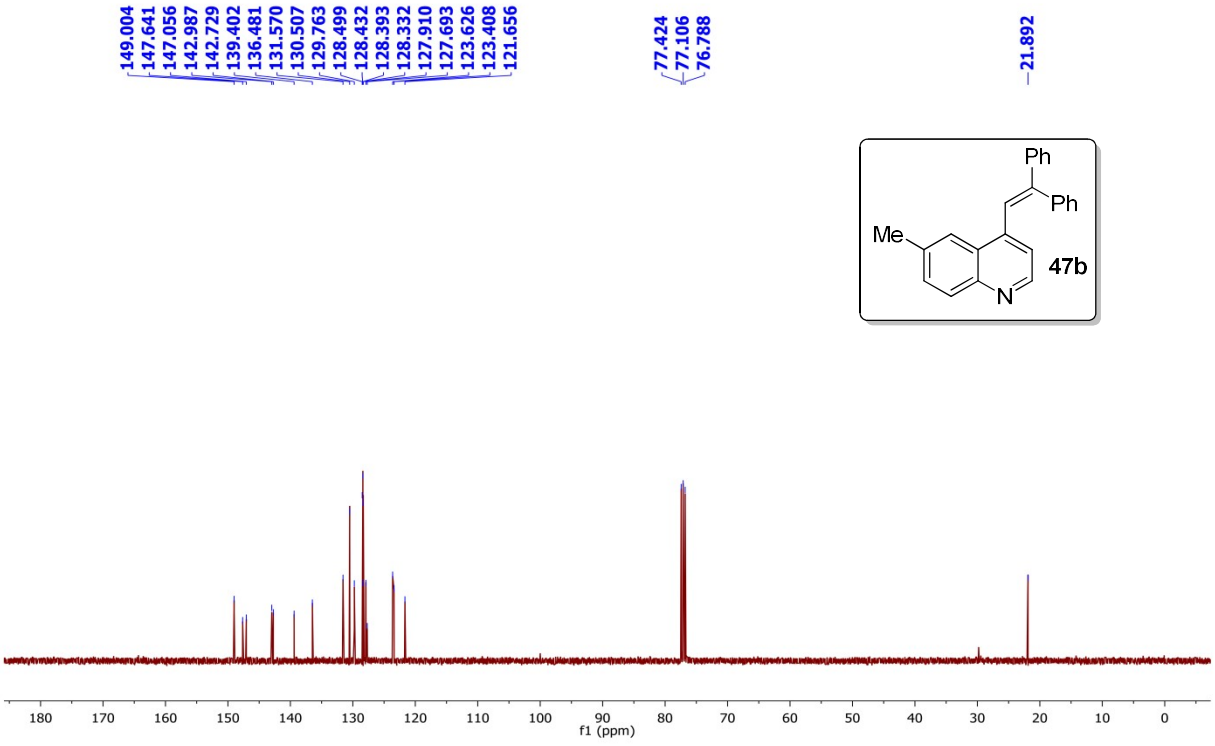
^{13}C{^{1}H} NMR (100 MHz) of **47a**:



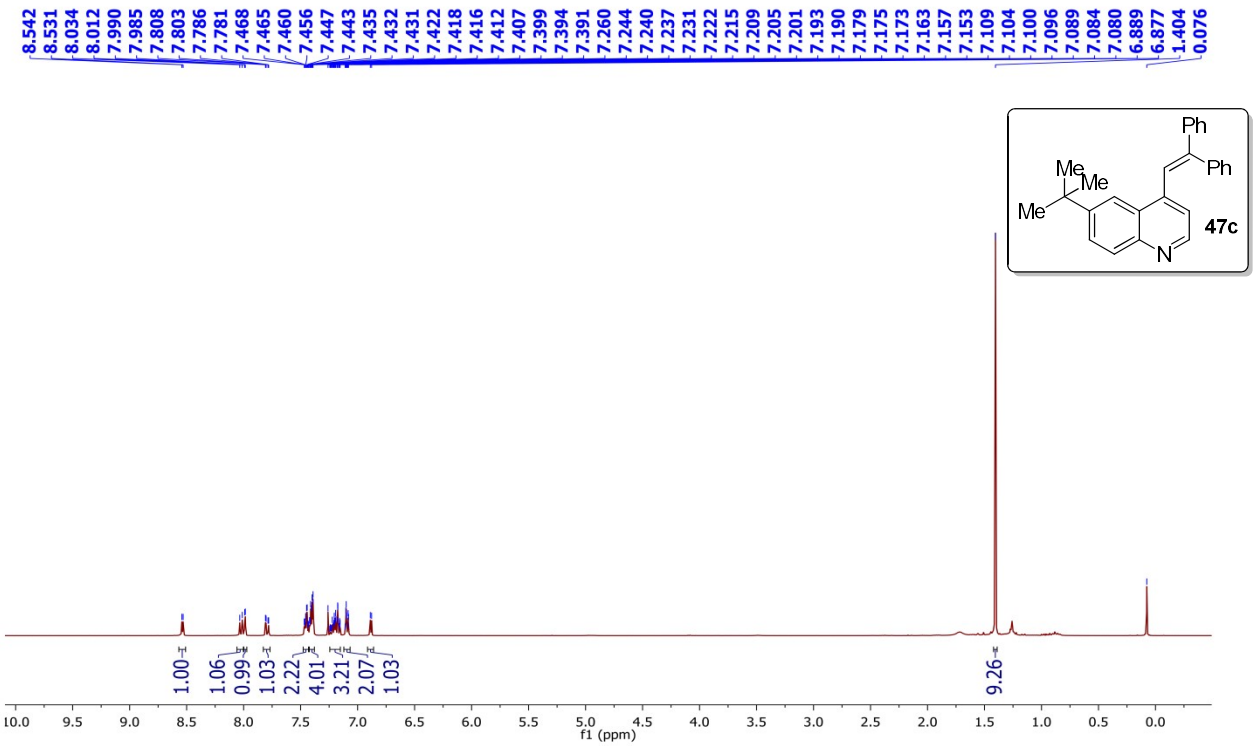
^{1}H NMR (400 MHz) of **47b**:



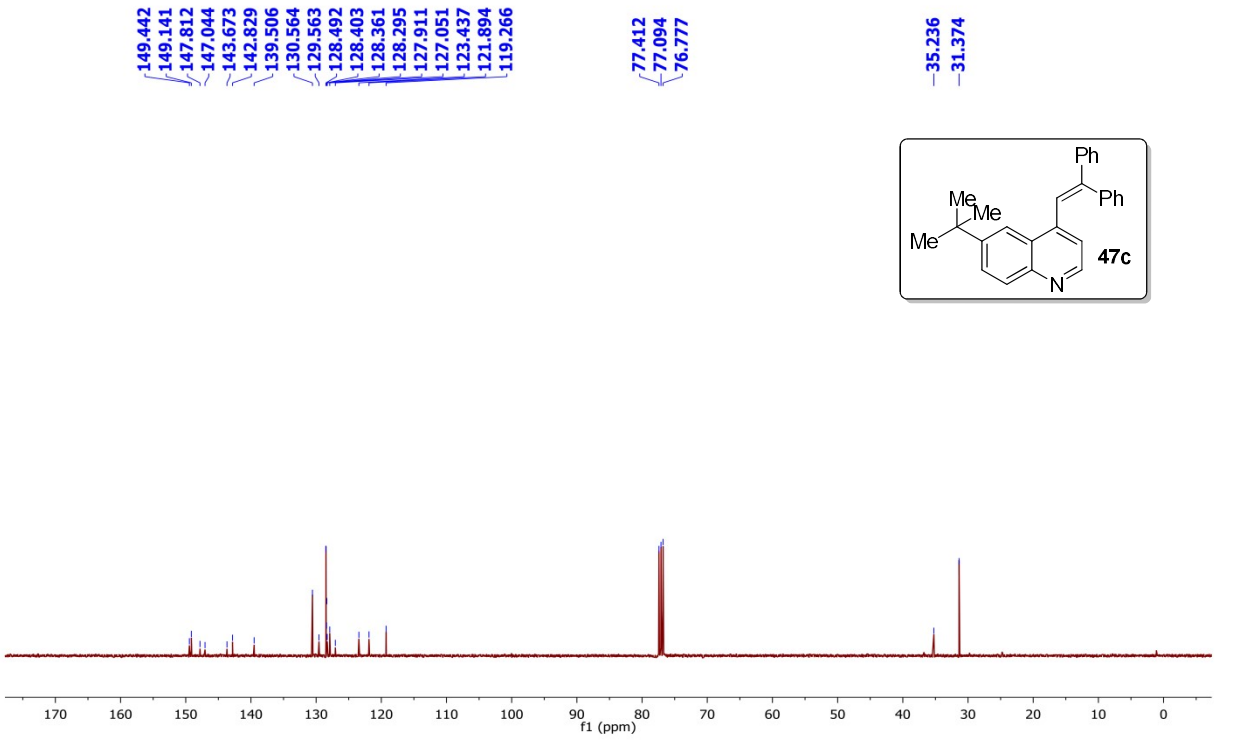
^{13}C{^{1}H} NMR (100 MHz) of **47b**:



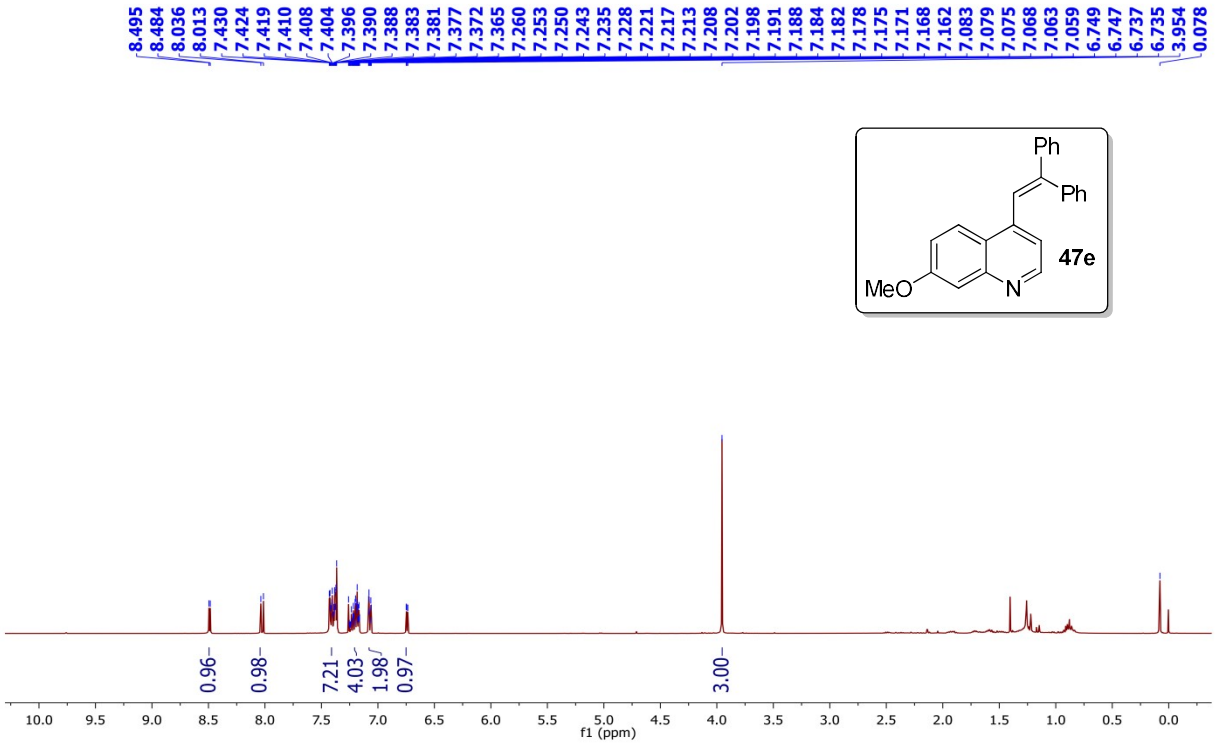
^{1}H NMR (400 MHz) of **47c**:



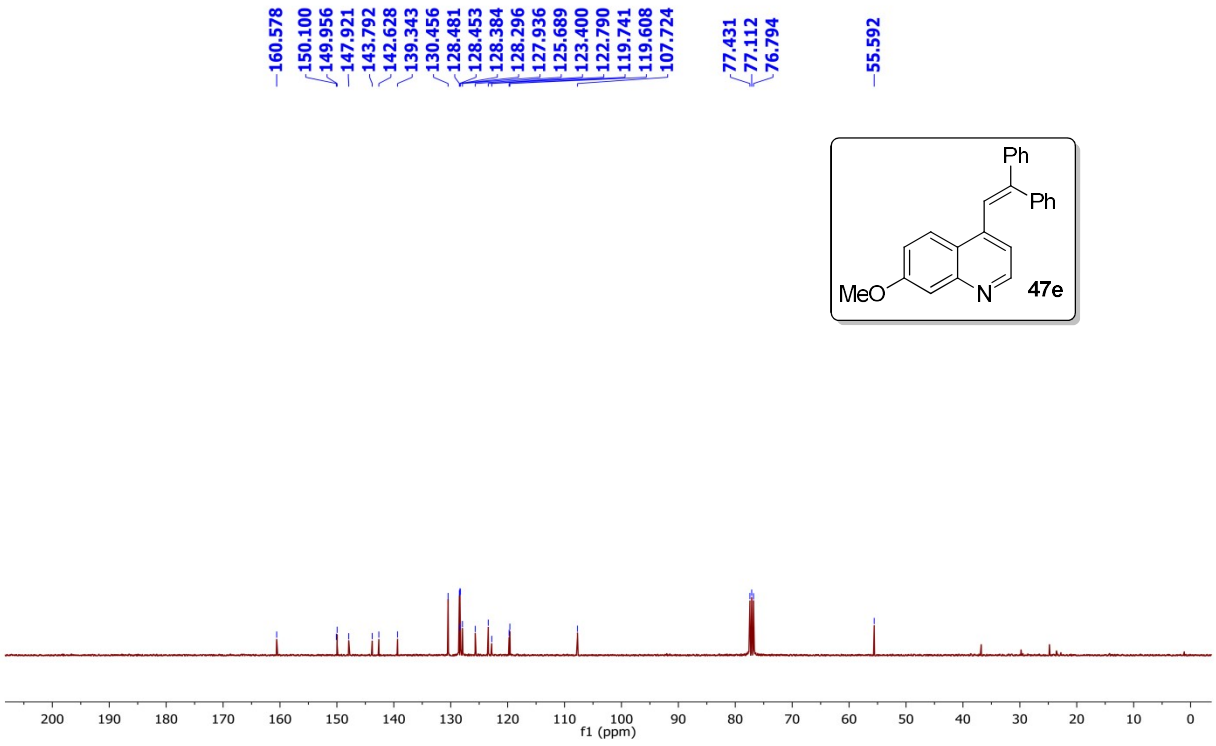
^{13}C{^{1}H} NMR (100 MHz) of **47c**:



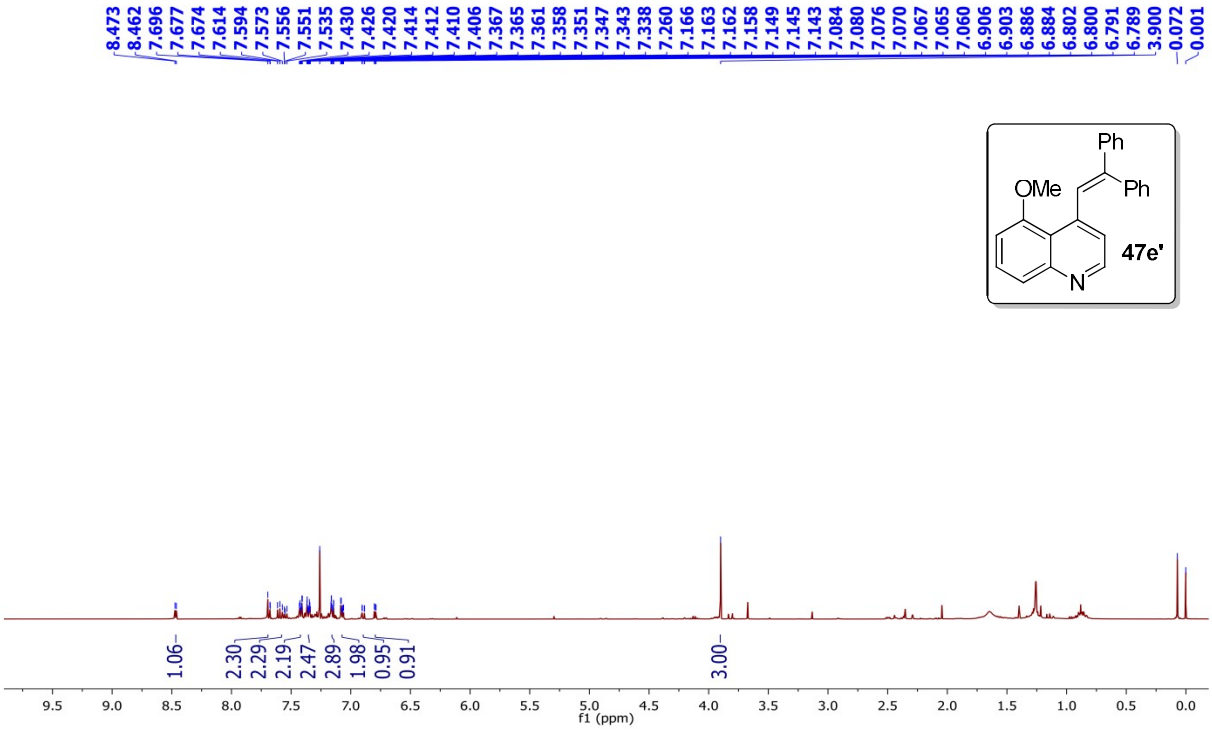
^{1}H NMR (400 MHz) of **47e**:



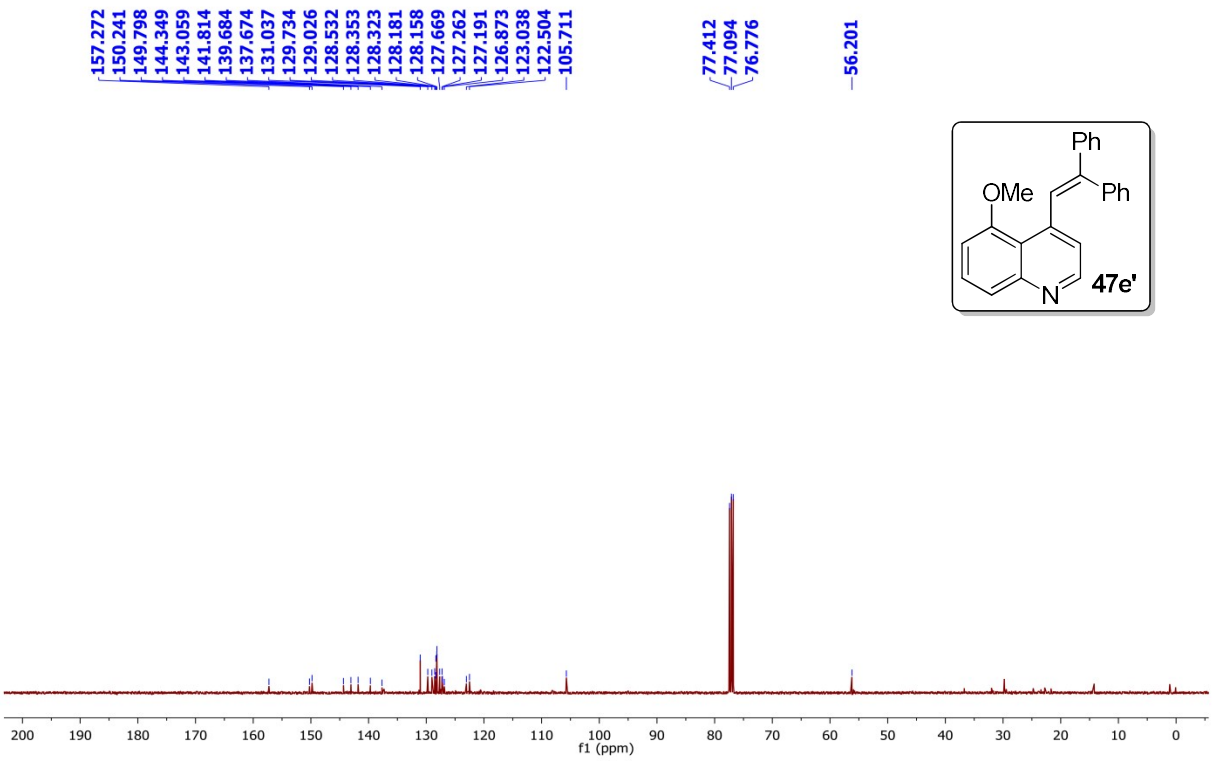
^{13}C{^{1}H} NMR (100 MHz) of **47e**:



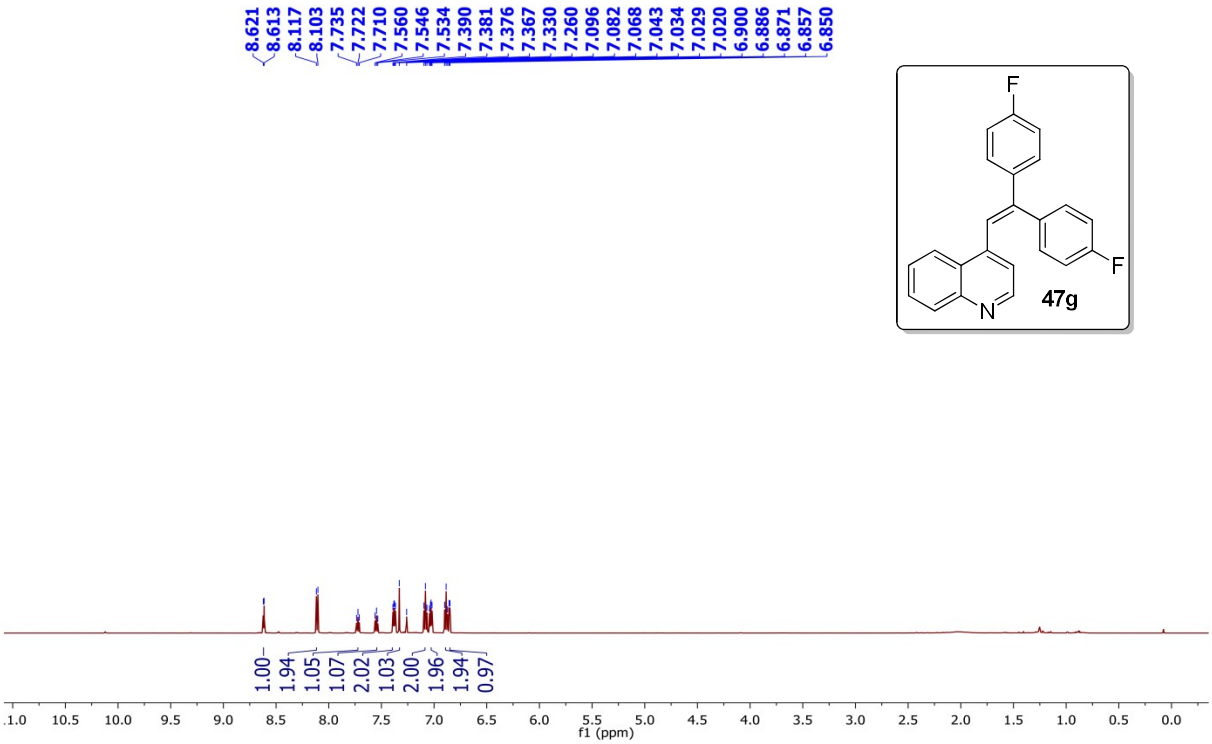
^{1}H NMR (400 MHz) of **47e'**:



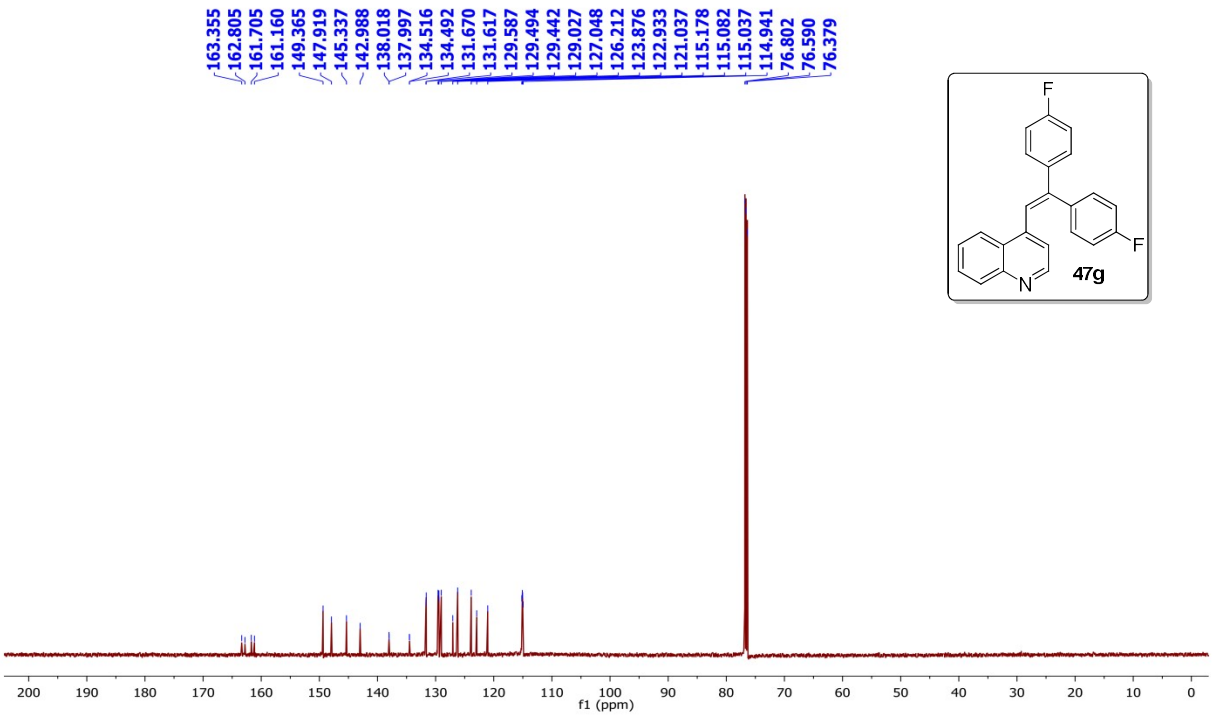
^{13}C{^{1}H} NMR (100 MHz) of **47e'**:



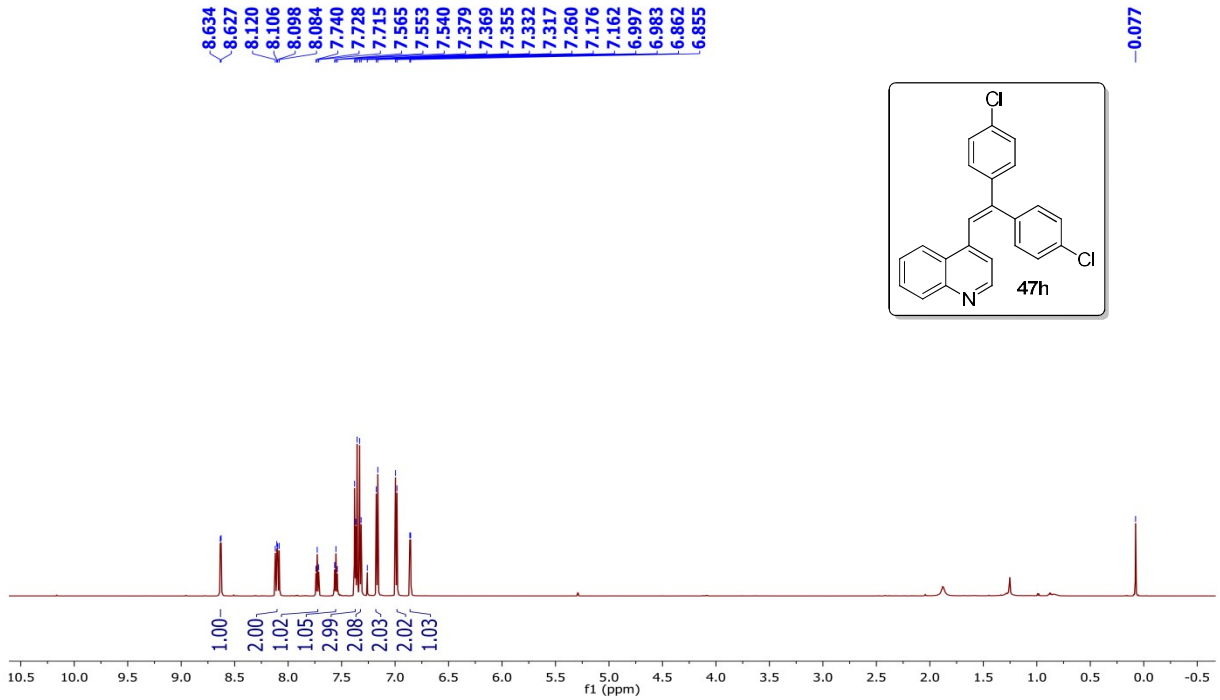
^{1}H NMR (600 MHz) of **47g**:



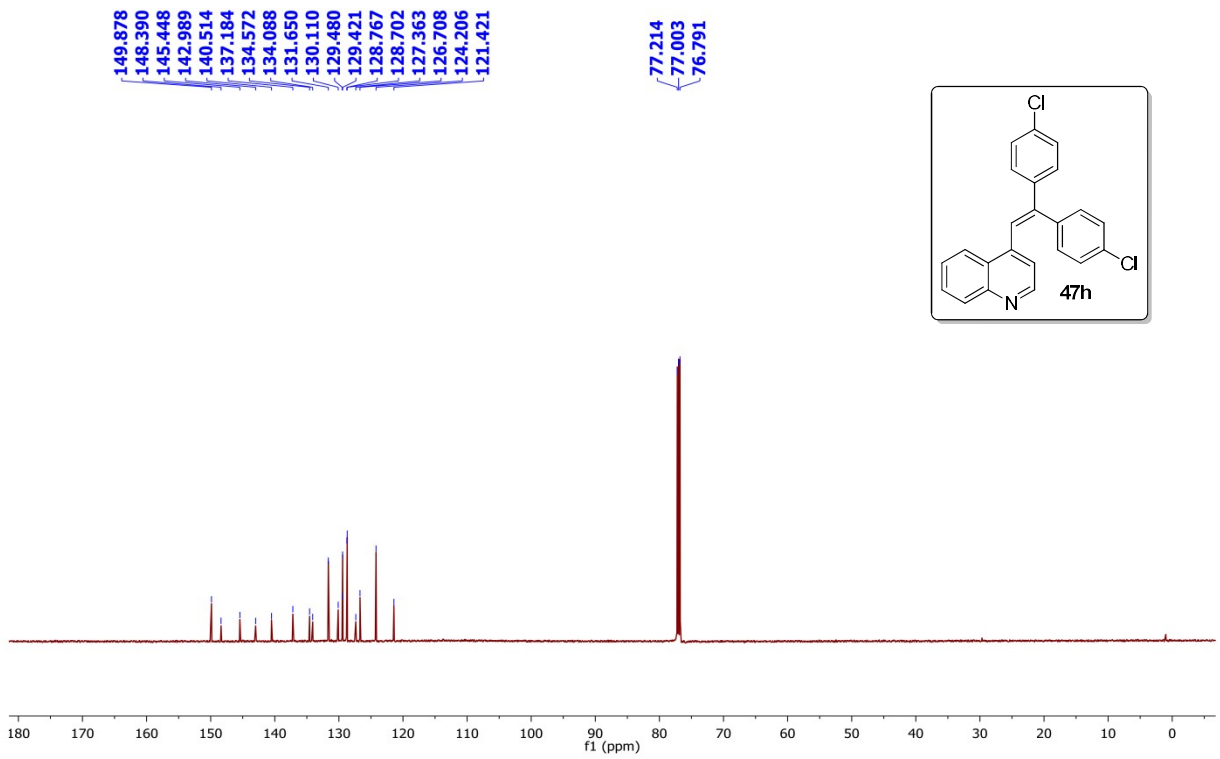
^{13}C{^{1}H} NMR (150 MHz) of **47g**:



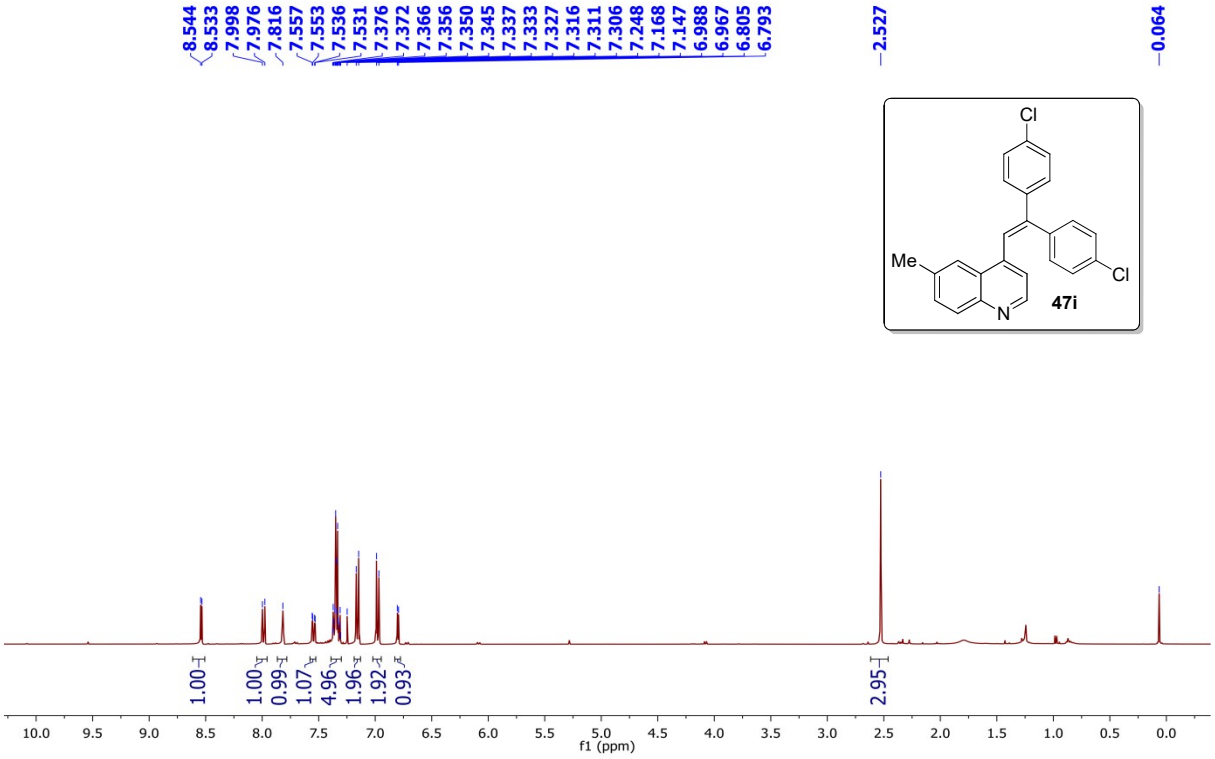
^{1}H NMR (600 MHz) of **47h**:



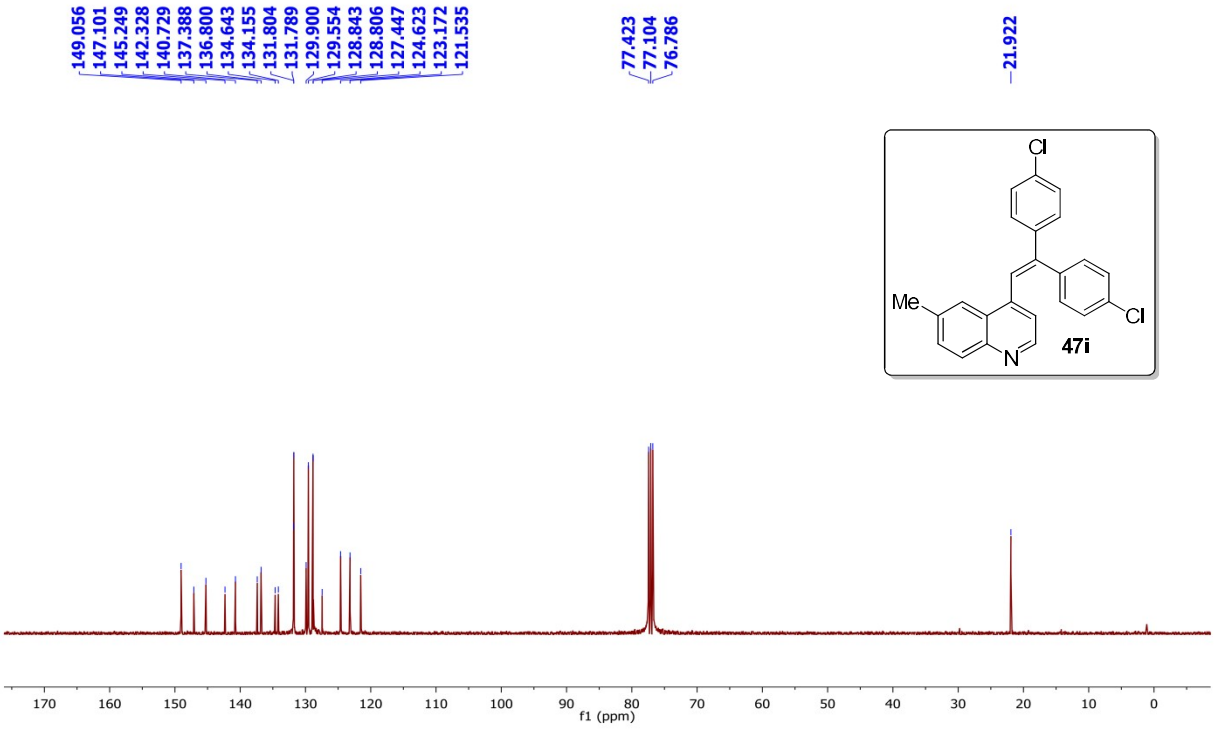
^{13}C{^{1}H} NMR (150 MHz) of **47h**:



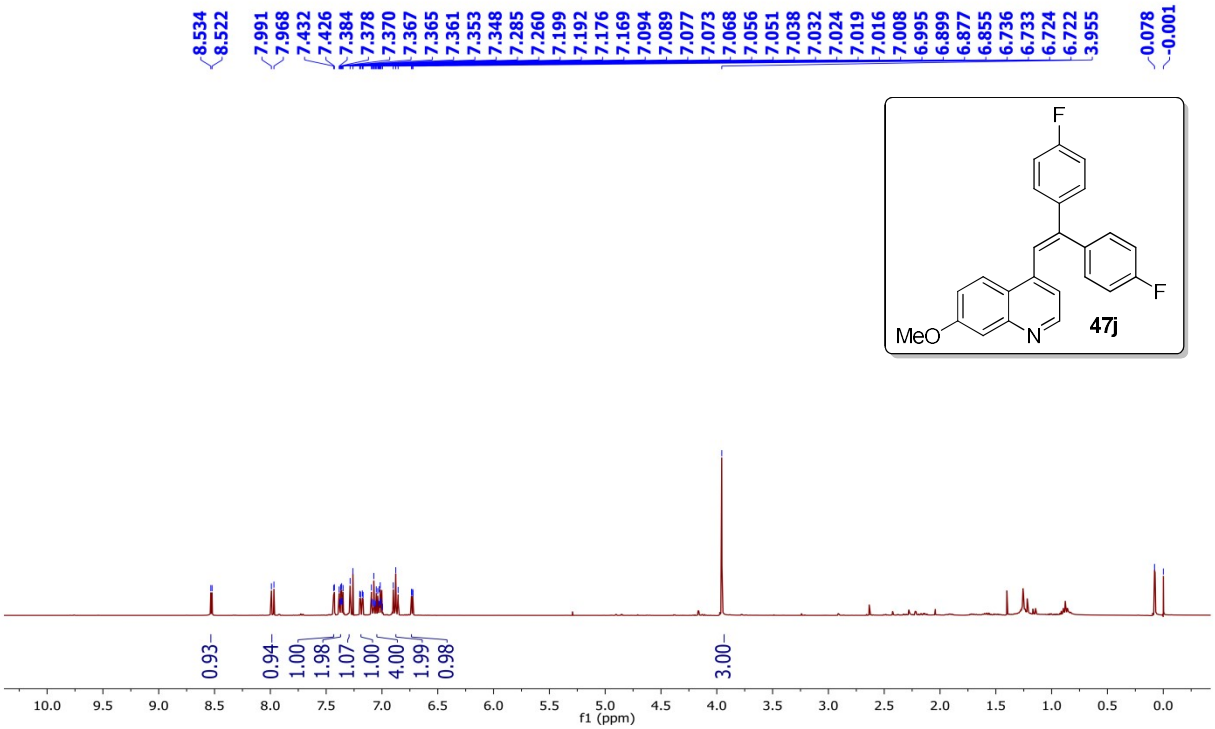
^{1}H NMR (400 MHz) of **47i**:



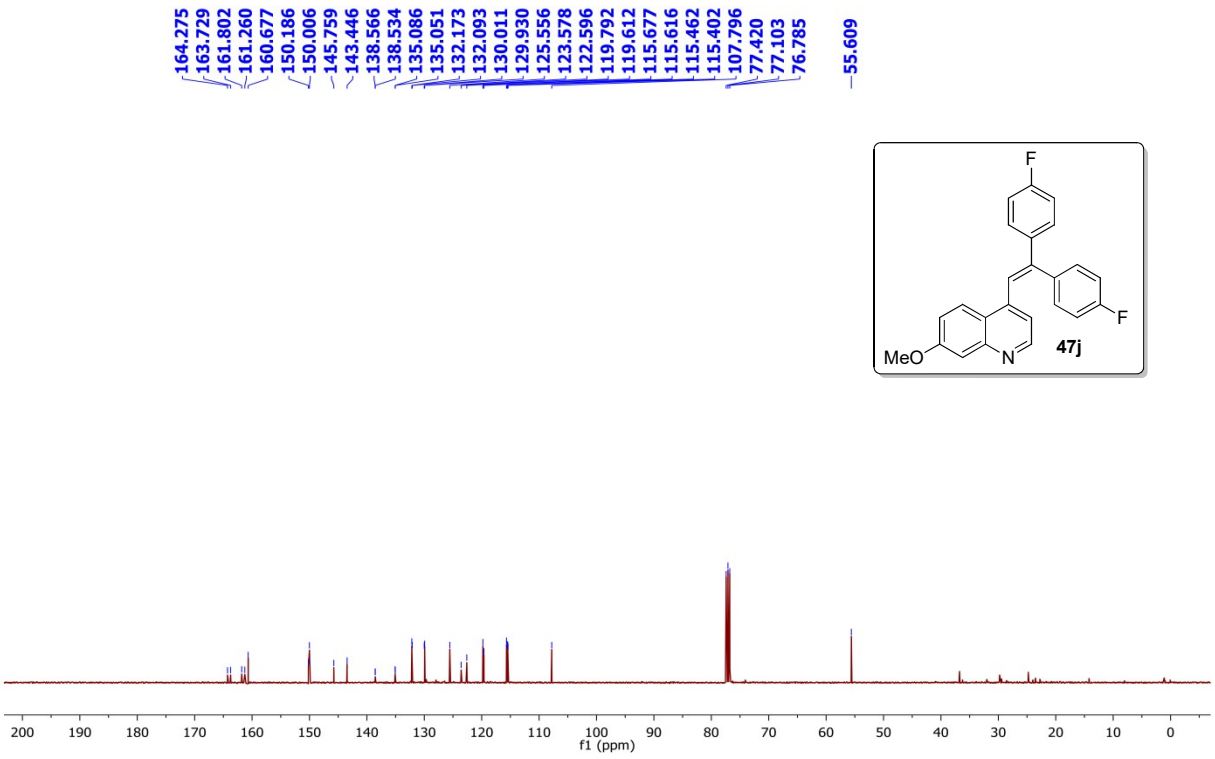
^{13}C{^{1}H} NMR (100 MHz) of **47i**:



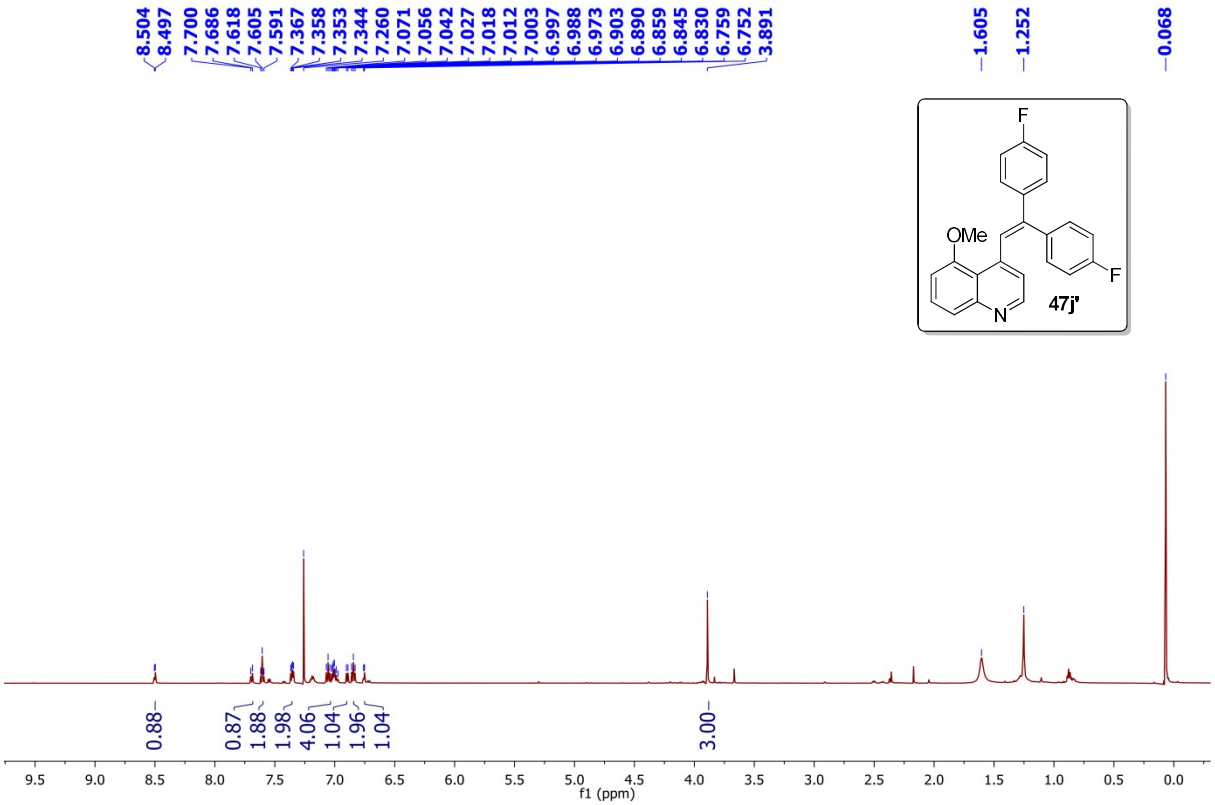
^{1}H NMR (400 MHz) of **47j**:



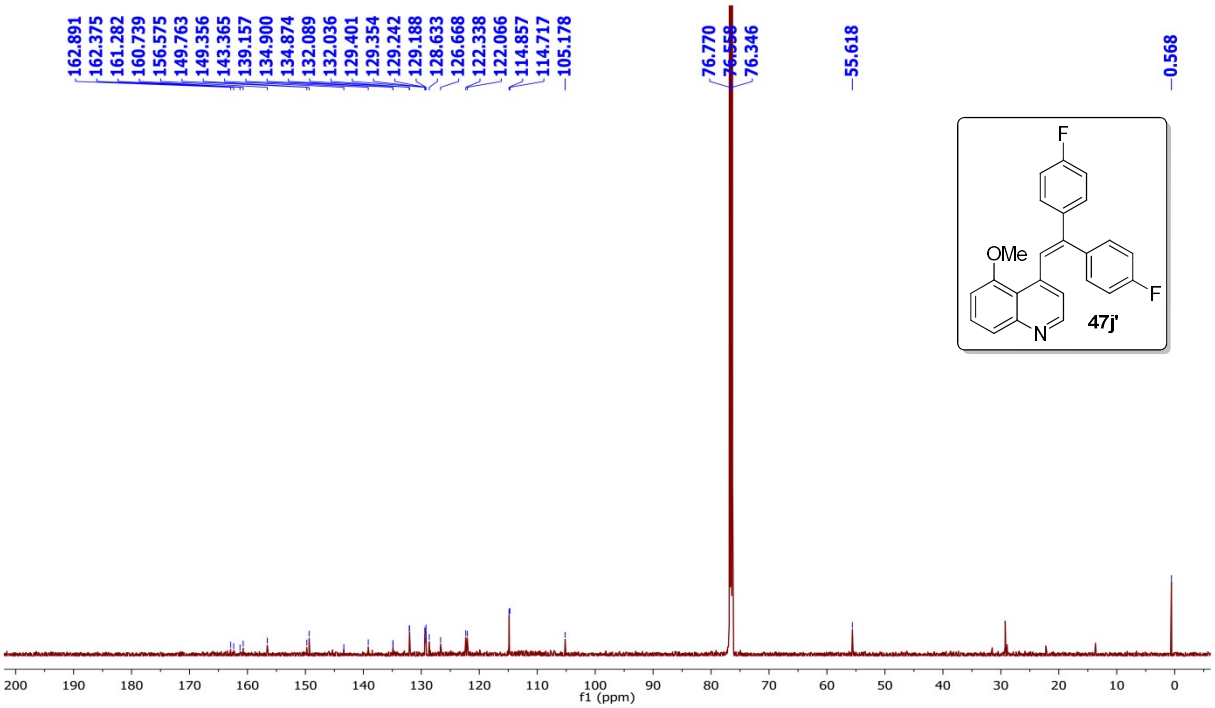
^{13}C{^{1}H} NMR (100 MHz) of **47j**:



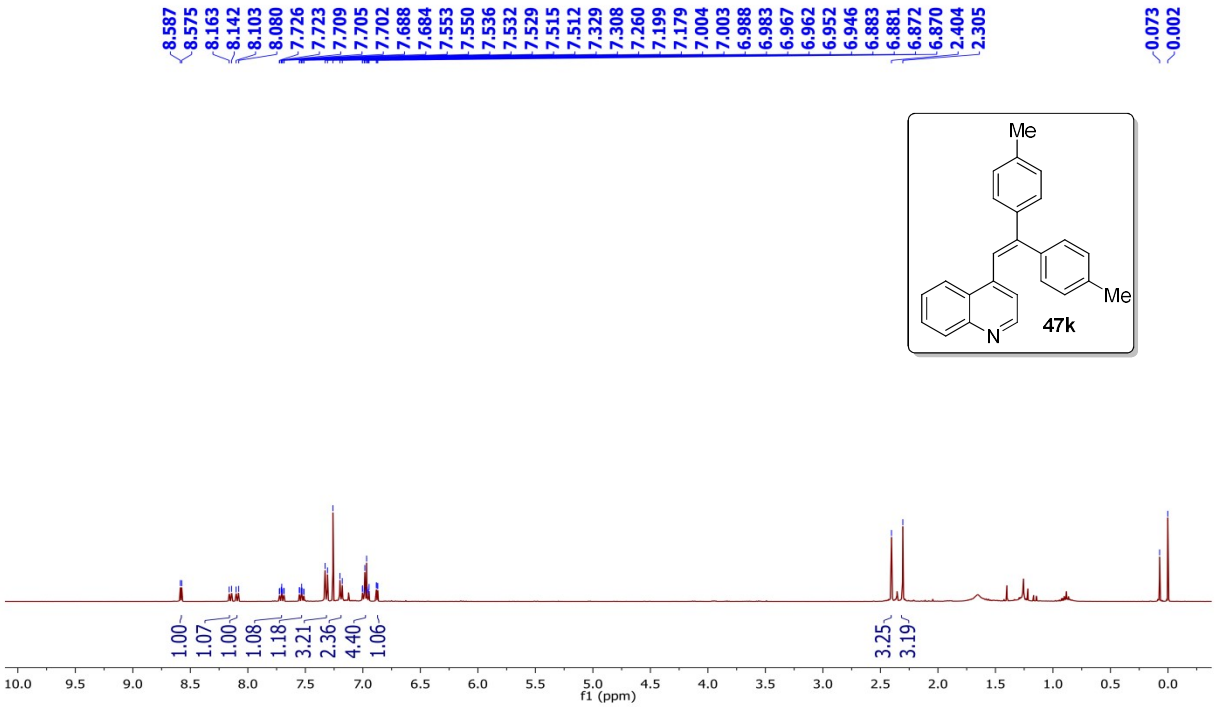
^{1}H NMR (600 MHz) of **47j'**:



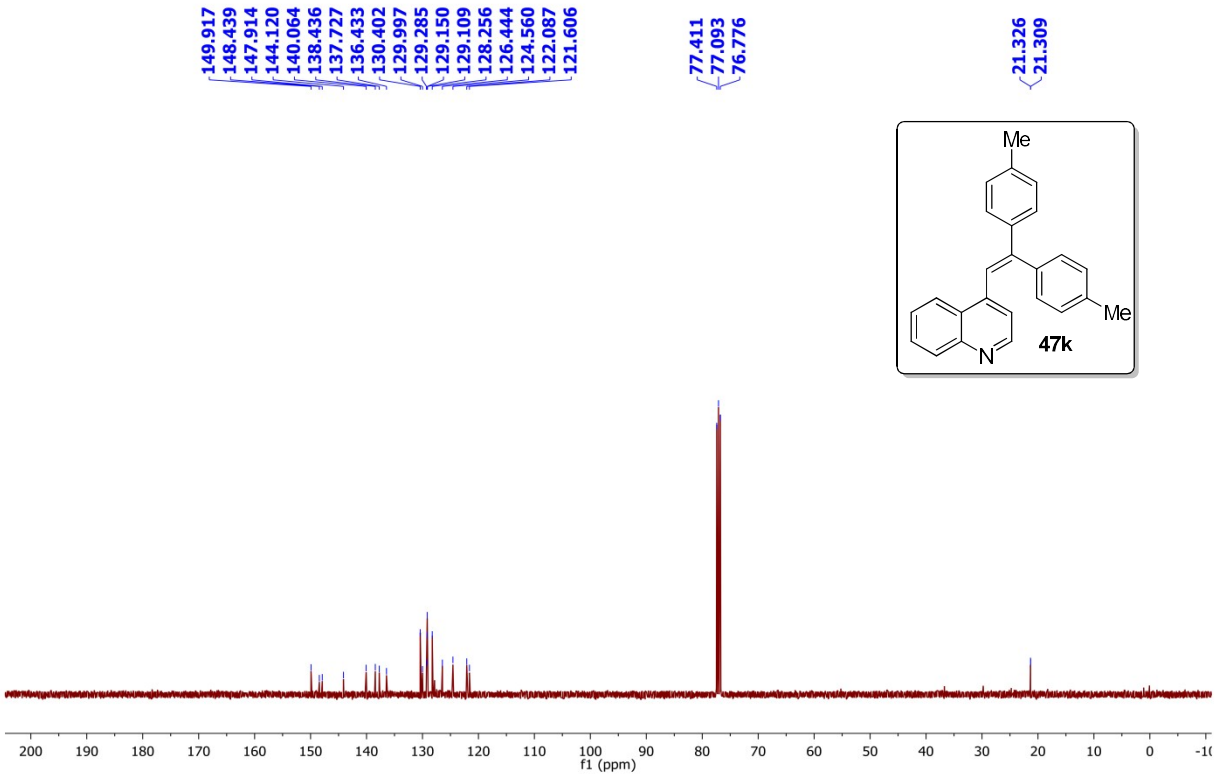
^{13}C{^{1}H} NMR (150 MHz) of **47j'**:



^{1}H NMR (400 MHz) of **47k**:

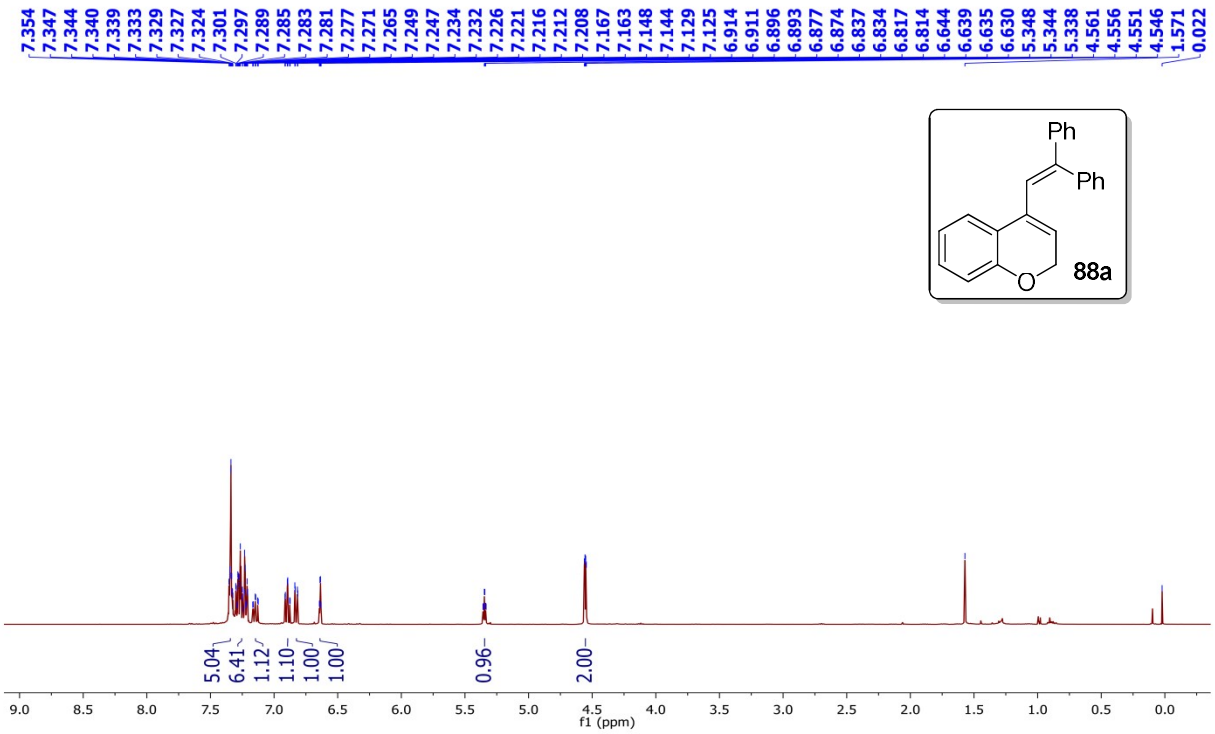


^{13}C{^{1}H} NMR (100 MHz) of **47k**:

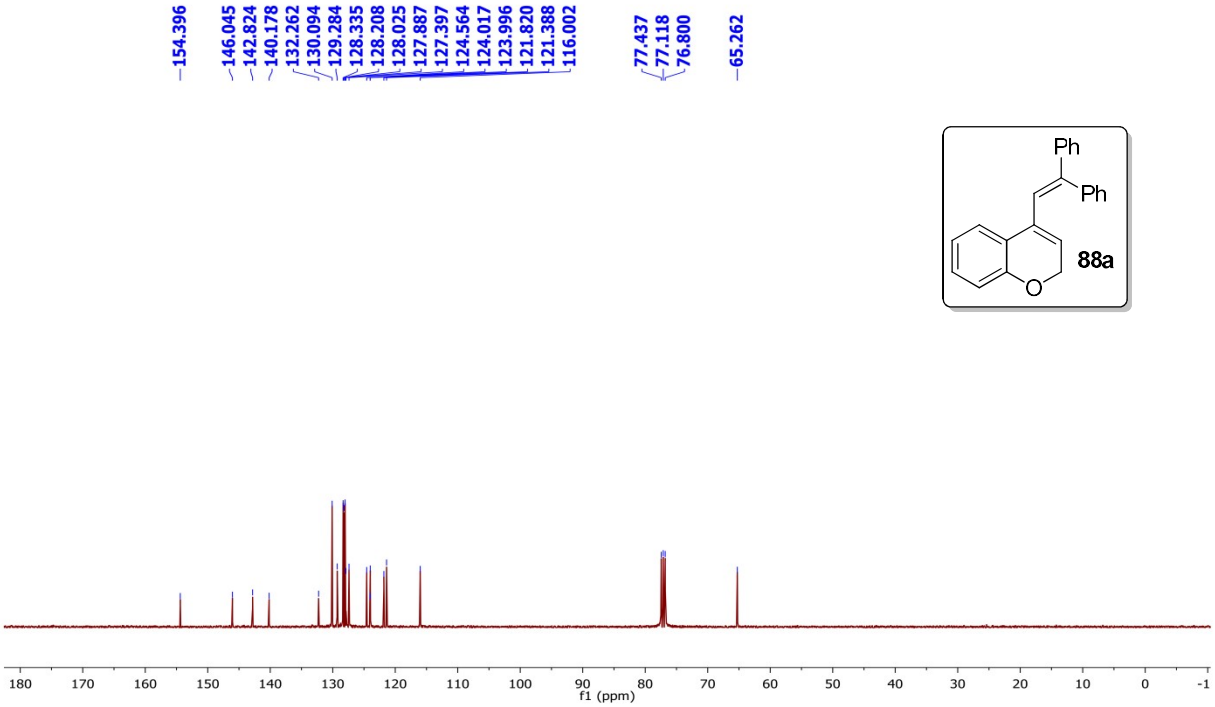


3.2.9.5. NMR Spectra of Compounds 88a-p:

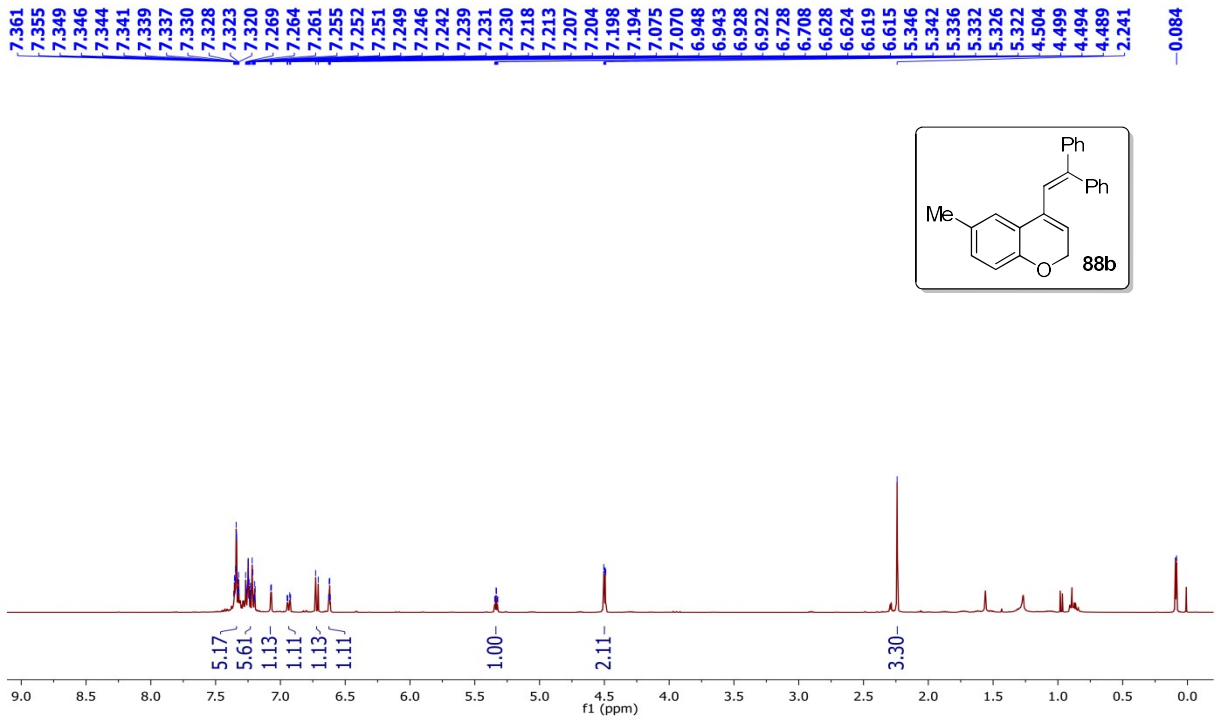
^{1}H NMR (400 MHz) of **88a**:



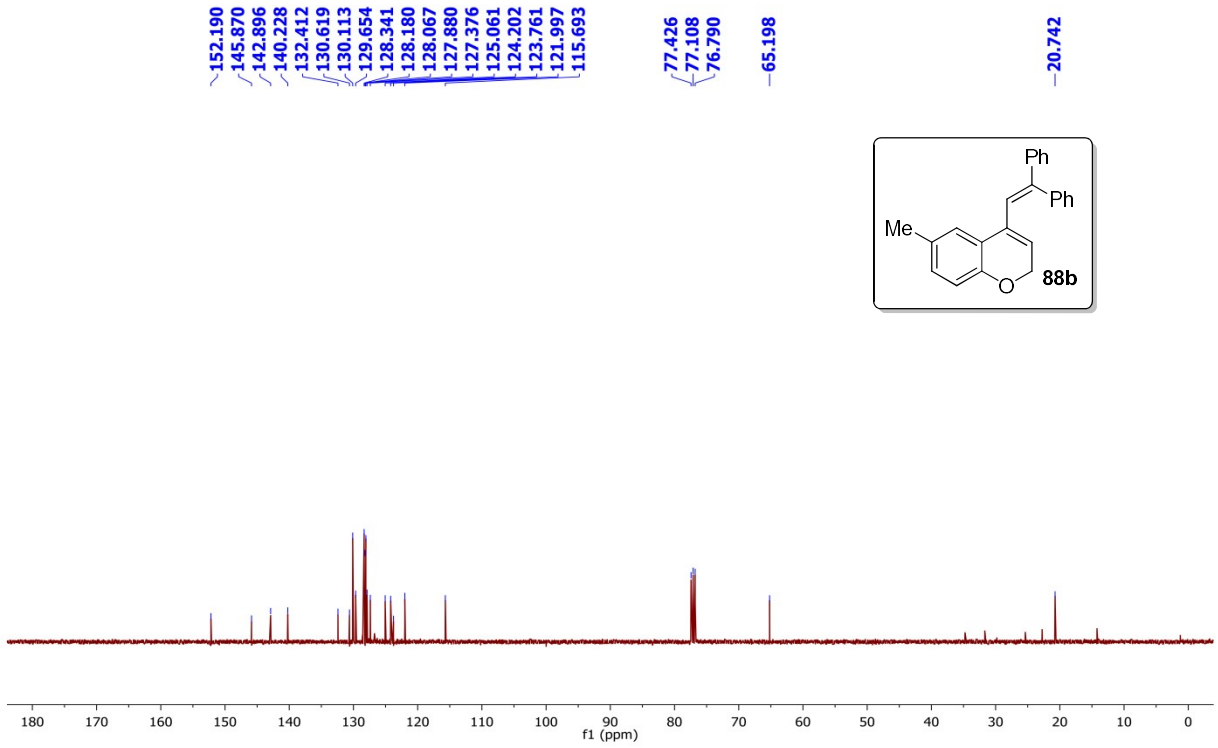
^{13}C{^{1}H} NMR (100 MHz) of **88a**:



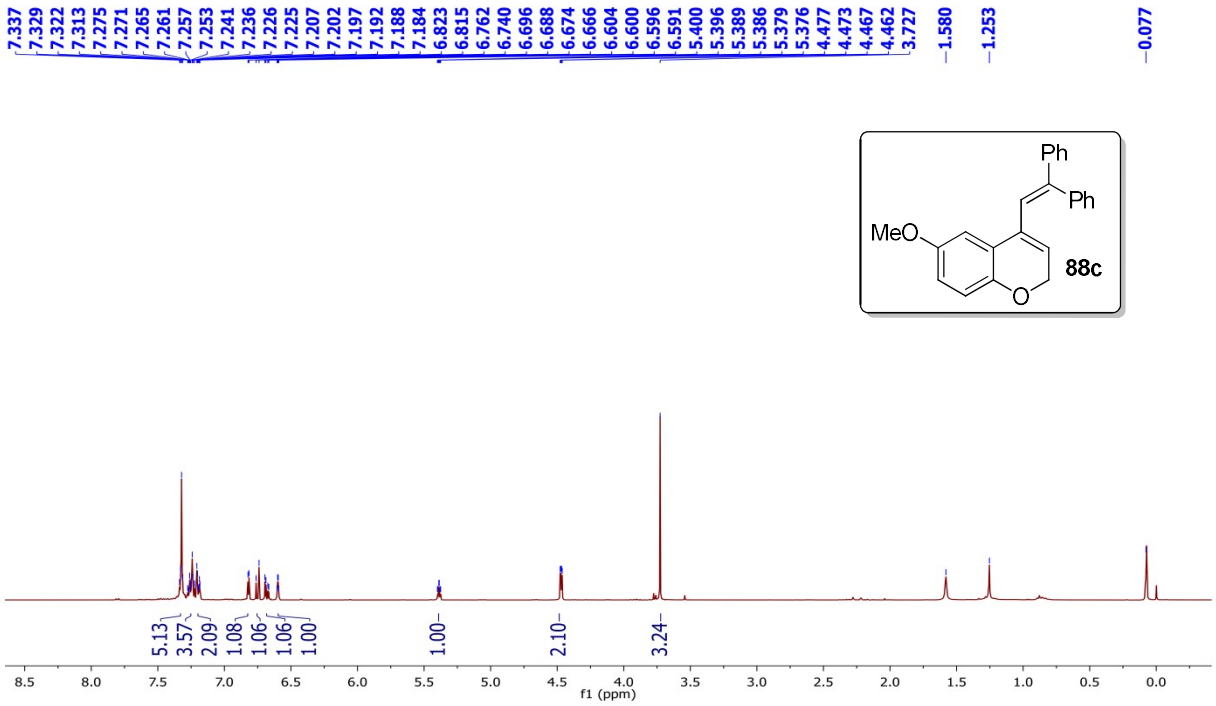
^{1}H NMR (400 MHz) of **88b**:



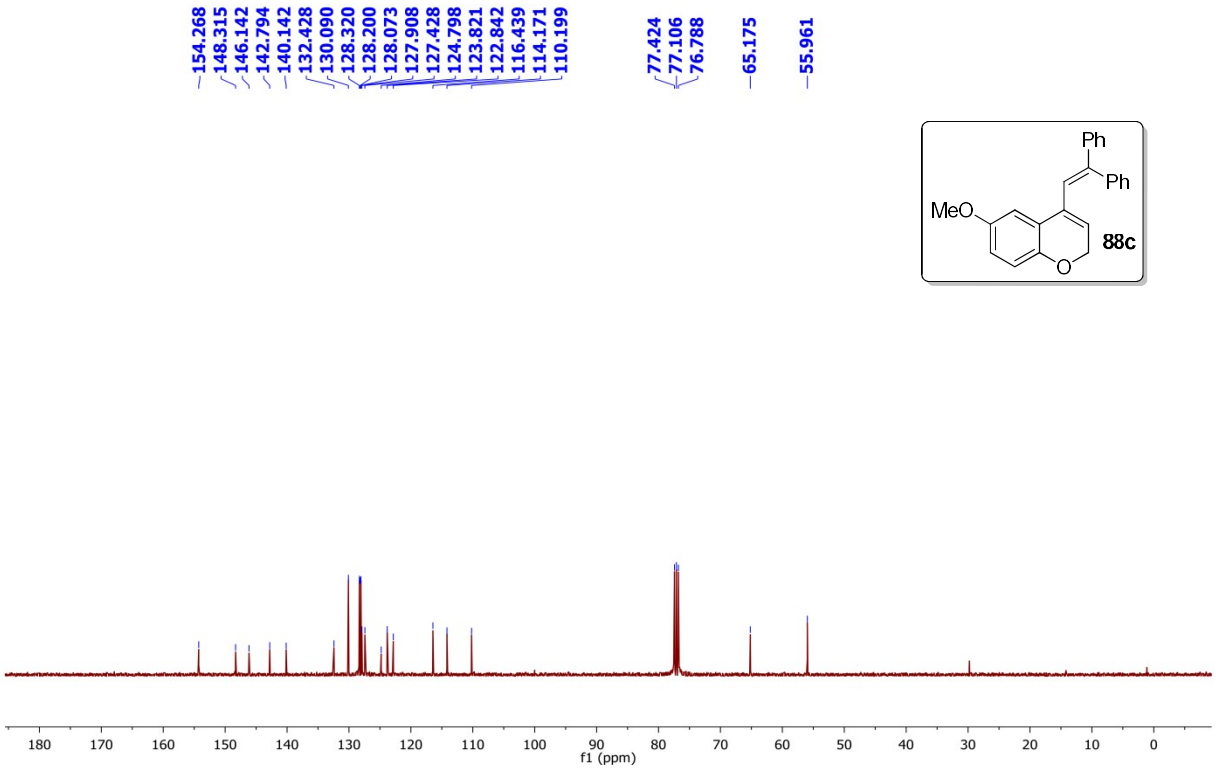
^{13}C{^{1}H} NMR (100 MHz) of **88b**:



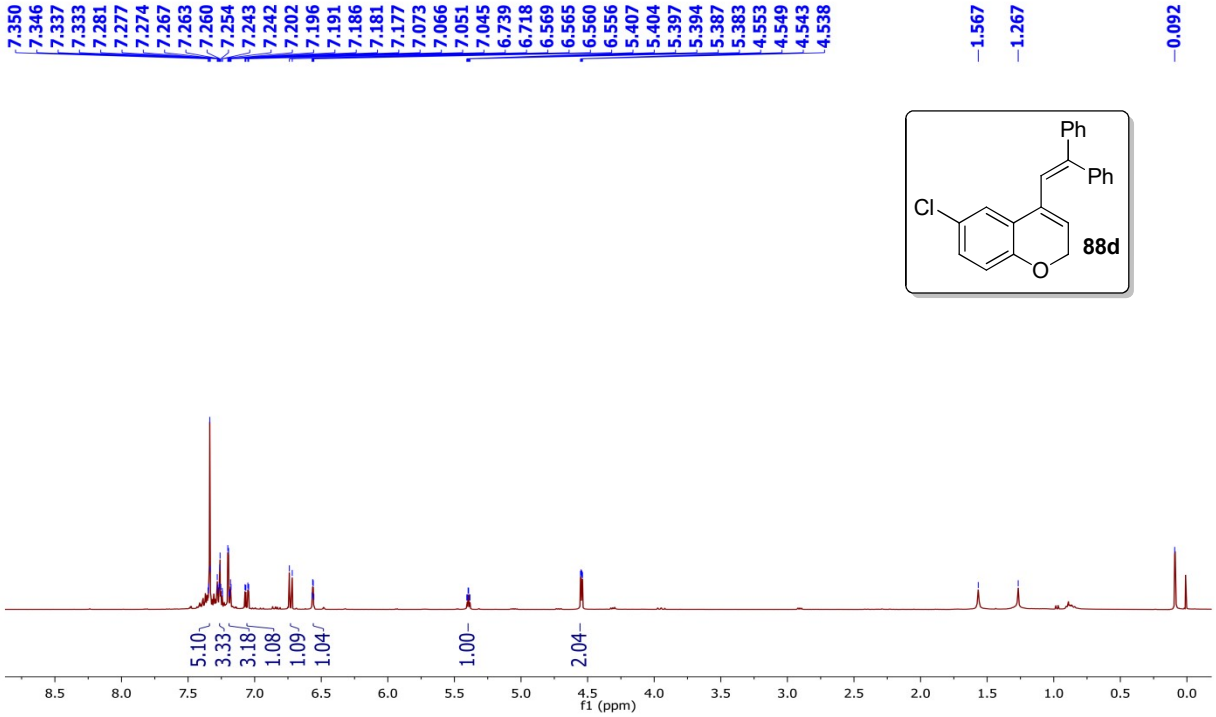
^{1}H NMR (400 MHz) of **88c**:



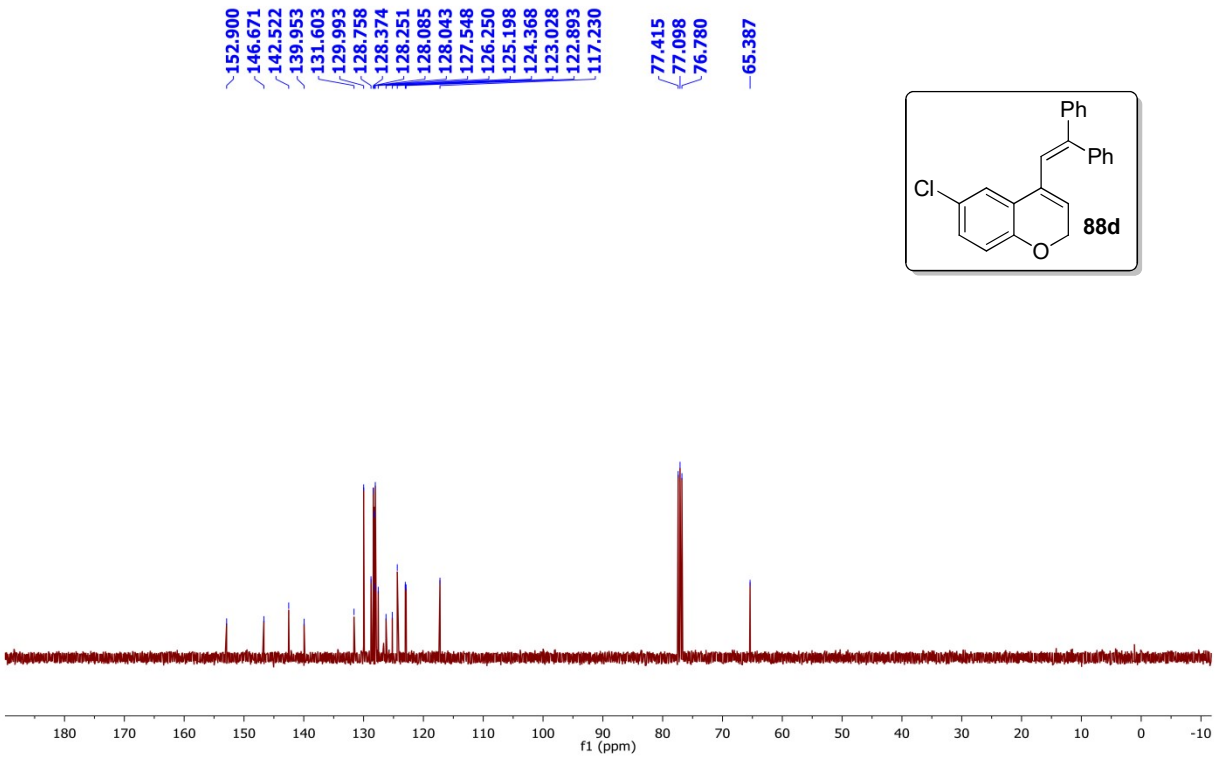
^{13}C{^{1}H} NMR (100 MHz) of **88c**:



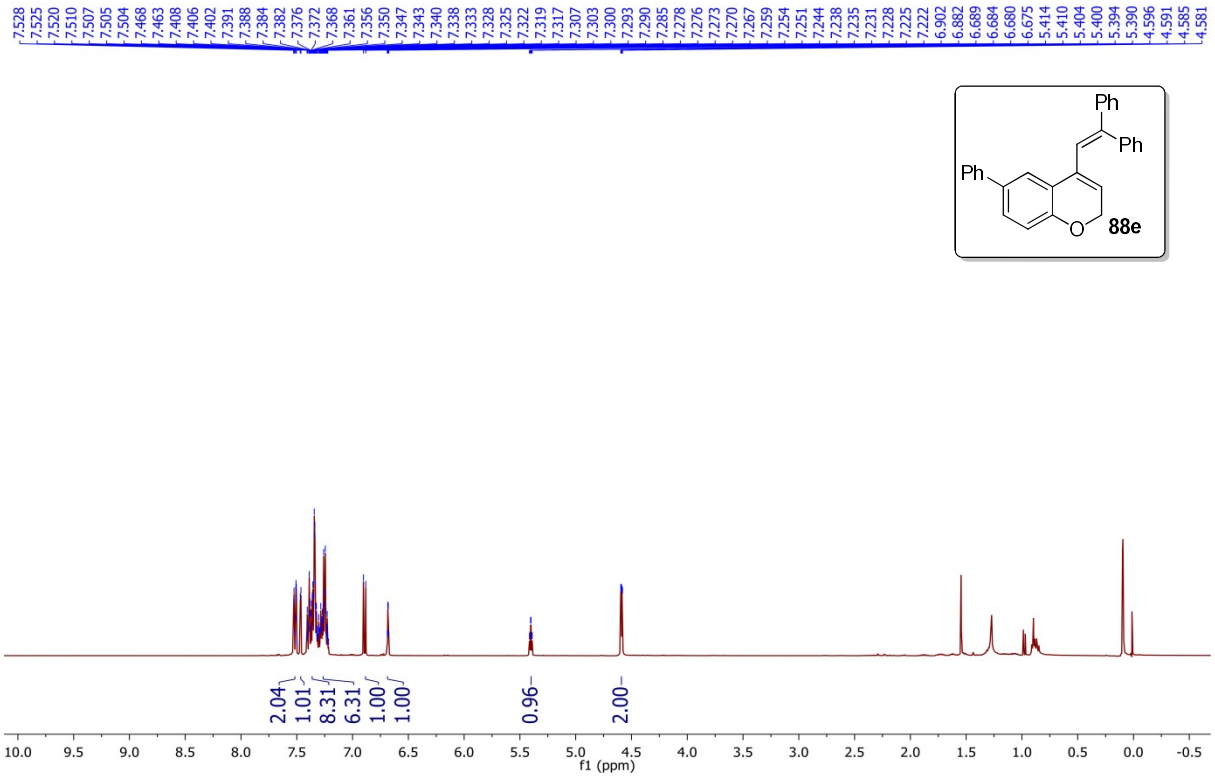
^{1}H NMR (400 MHz) of **88d**:



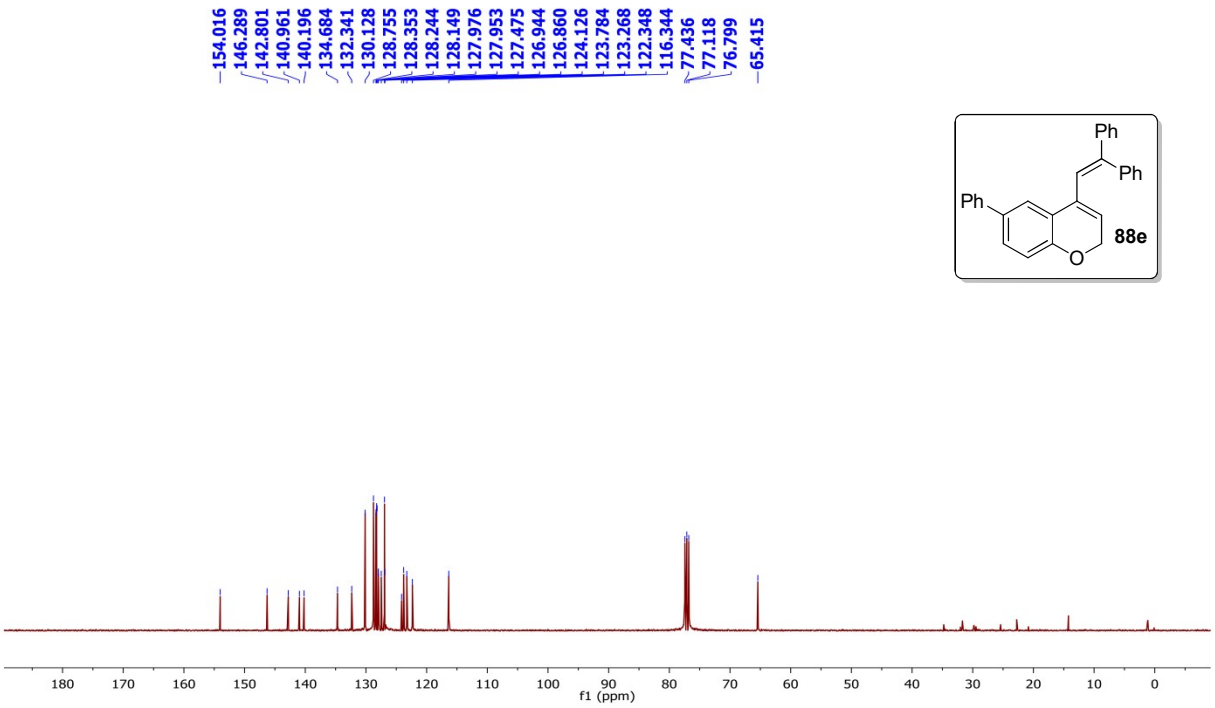
^{13}C{^{1}H} NMR (100 MHz) of **88d**:



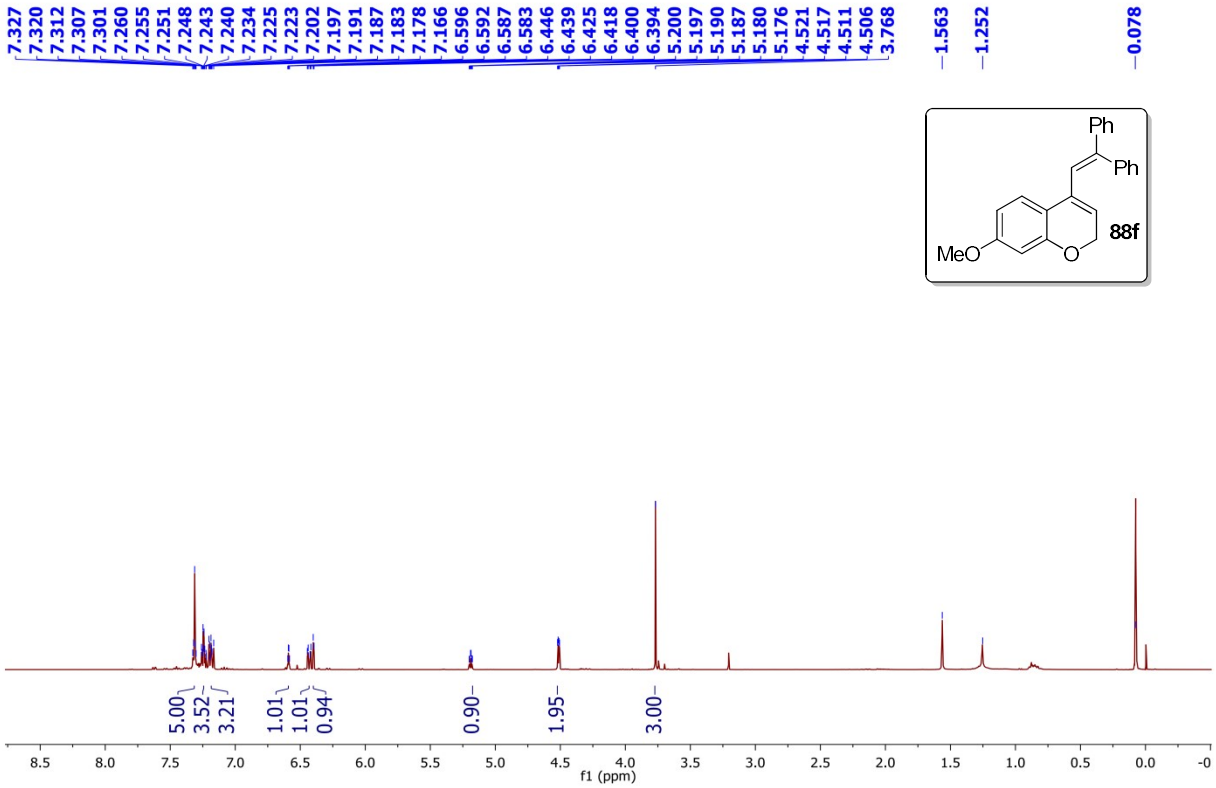
^{1}H NMR (400 MHz) of **88e**:



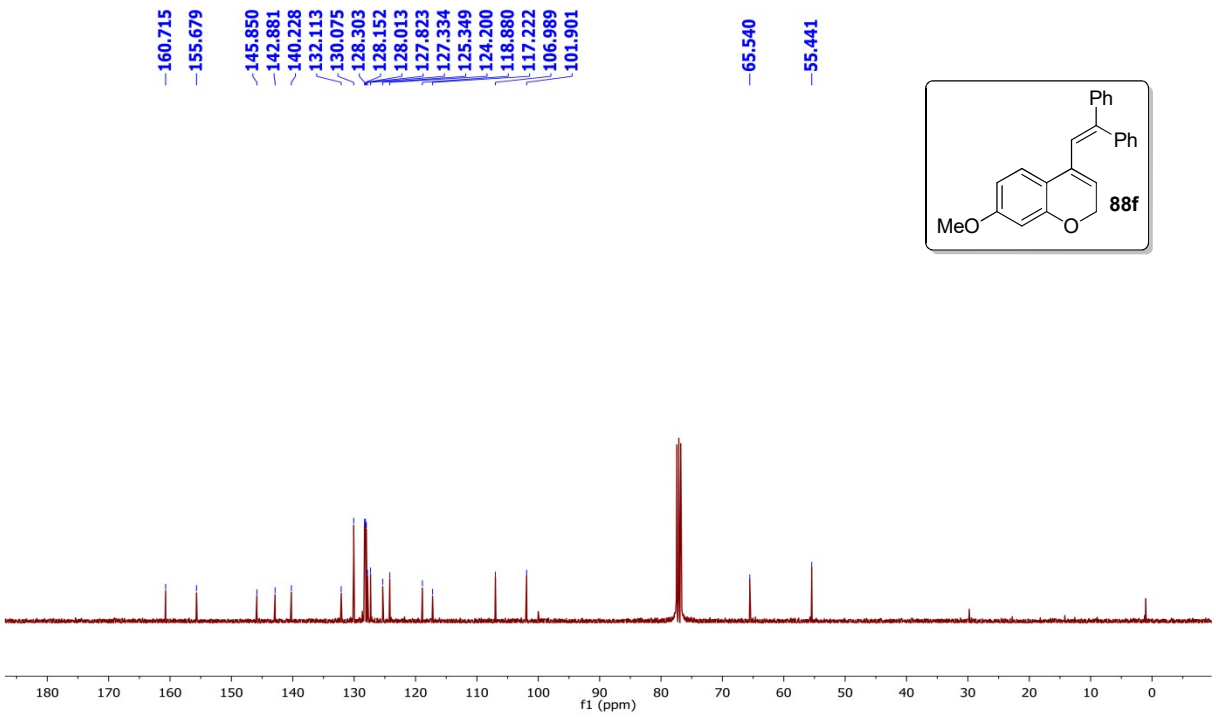
^{13}C{^{1}H} NMR (100 MHz) of **88e**:



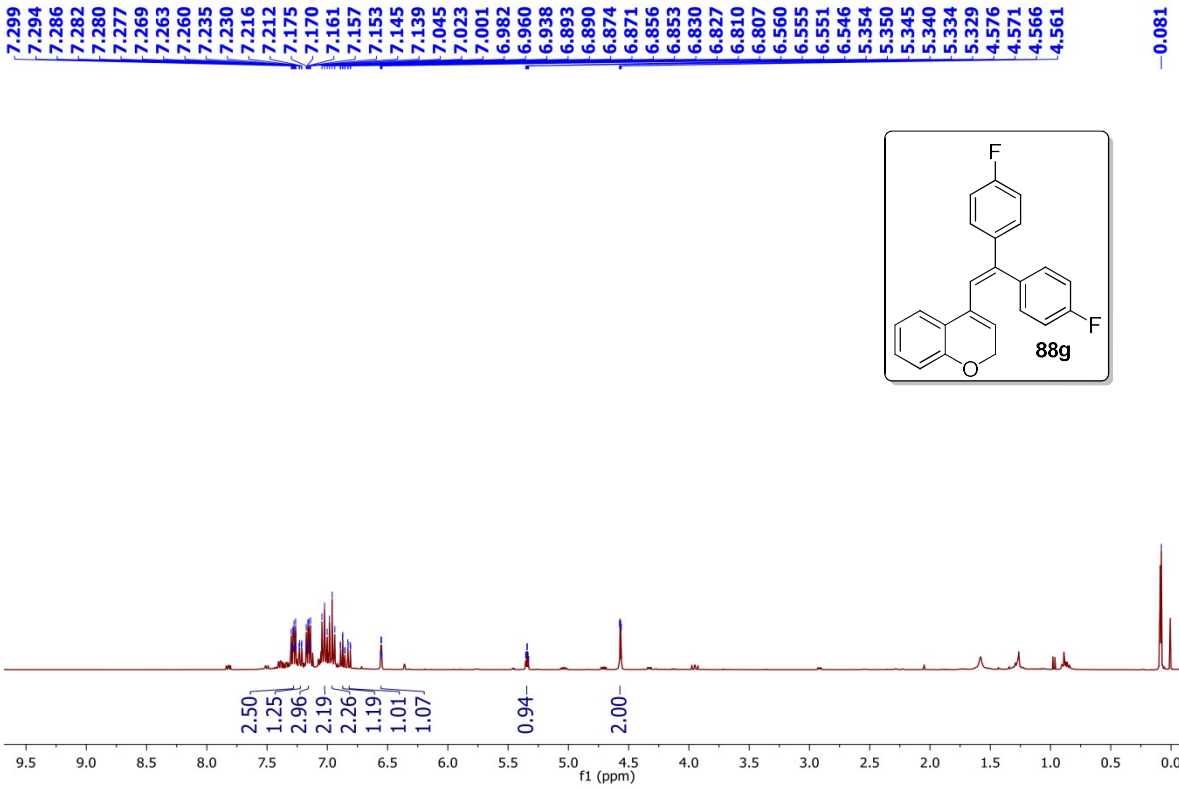
^{1}H NMR (400 MHz) of **88f**:



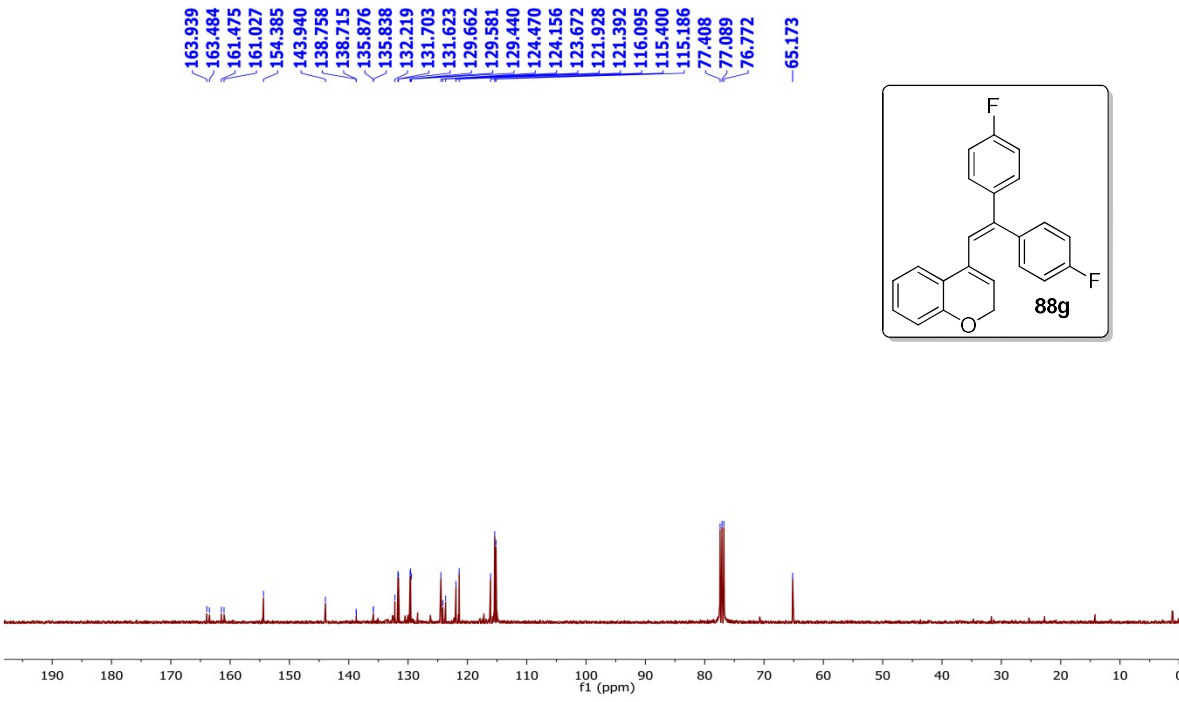
^{13}C{^{1}H} NMR (100 MHz) of **88f**:



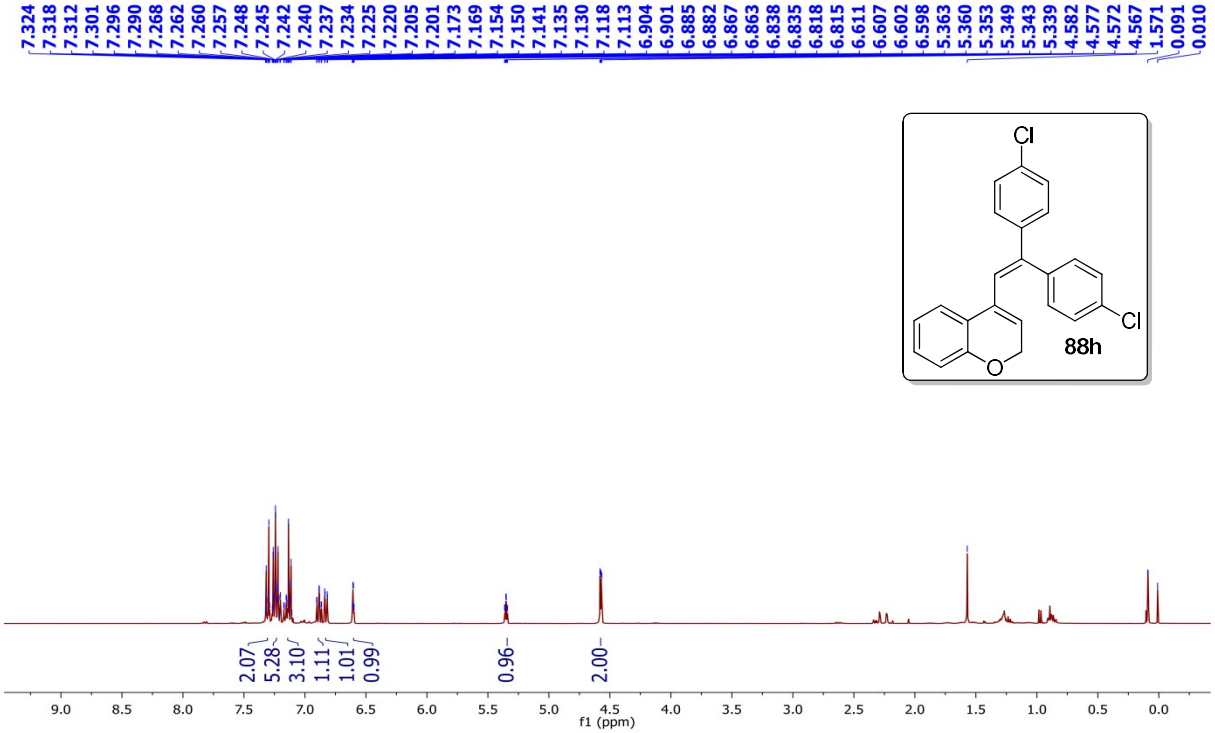
^{1}H NMR (400 MHz) of **88g**:



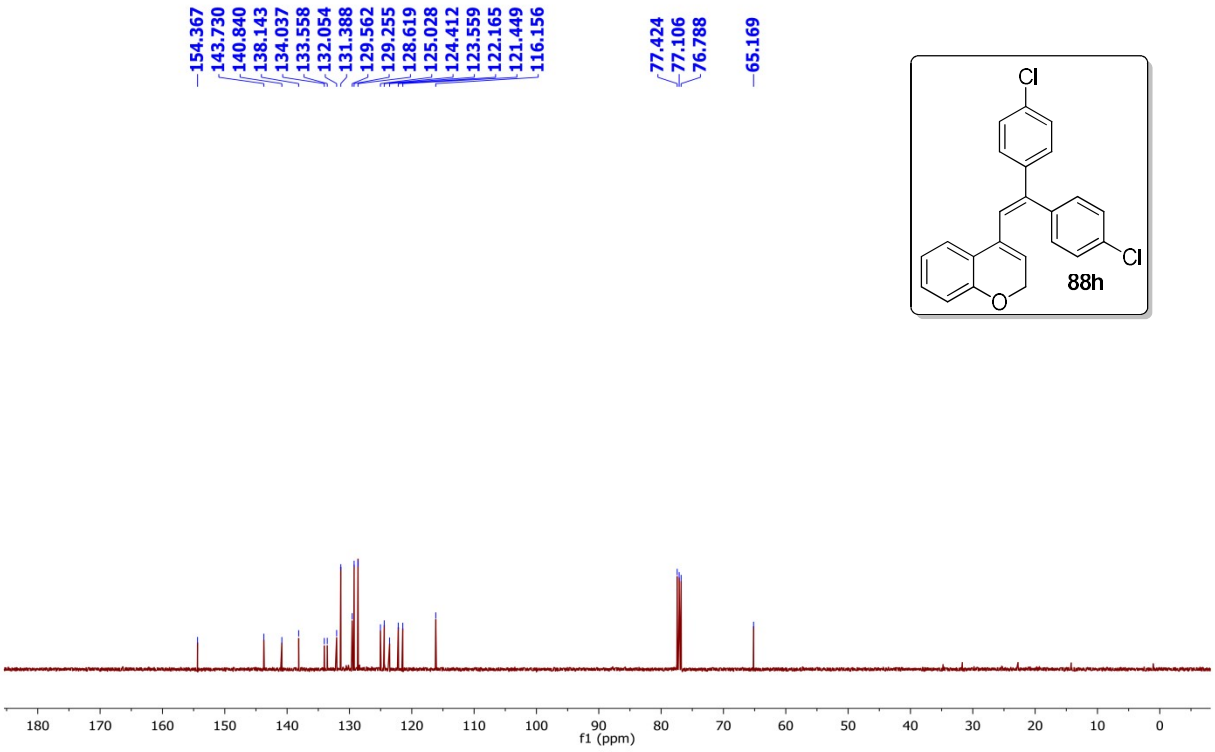
^{13}C{^{1}H} NMR (100 MHz) of **88g**:



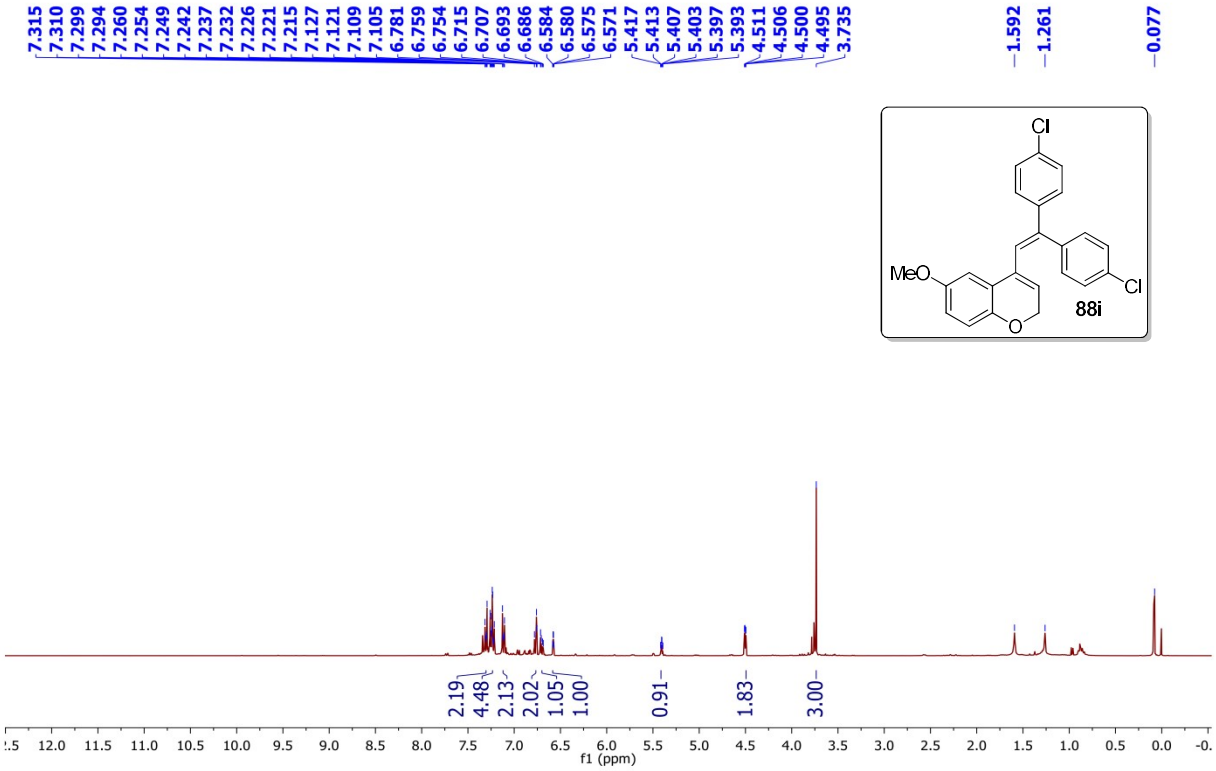
^{1}H NMR (400 MHz) of **88h**:



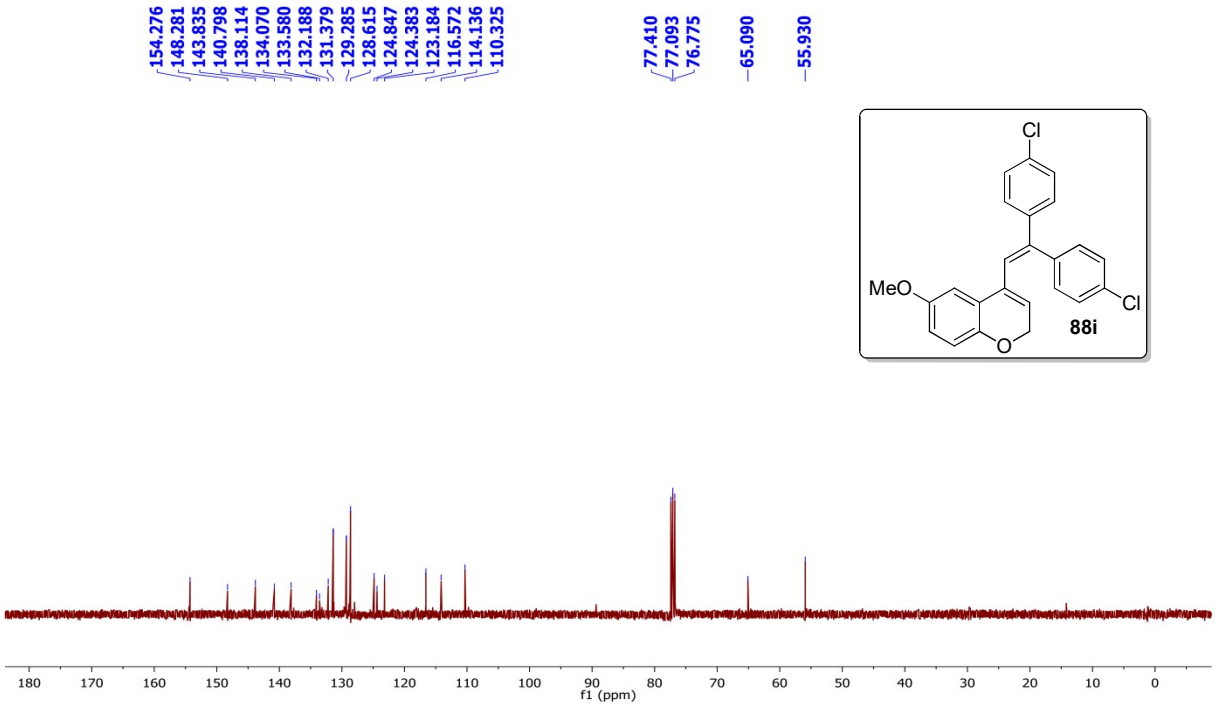
^{13}C{^{1}H} NMR (100 MHz) of **88h**:



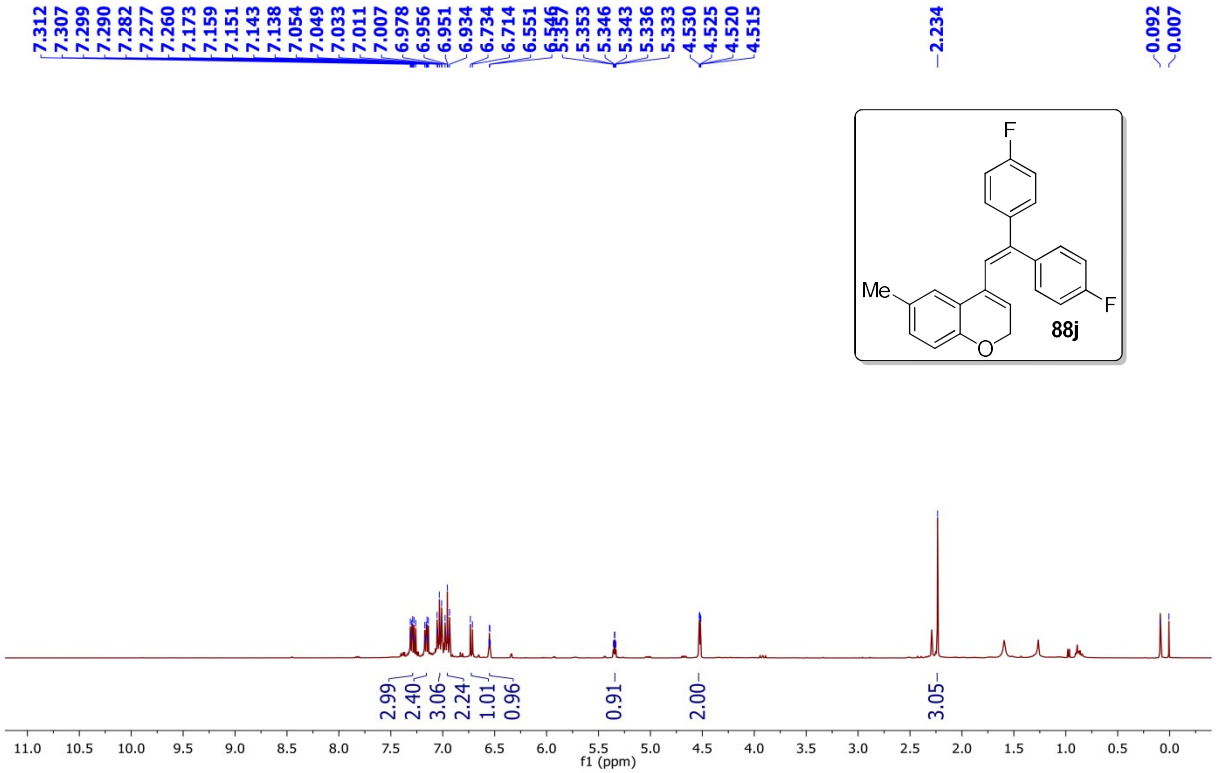
^{1}H NMR (400 MHz) of **88i**:



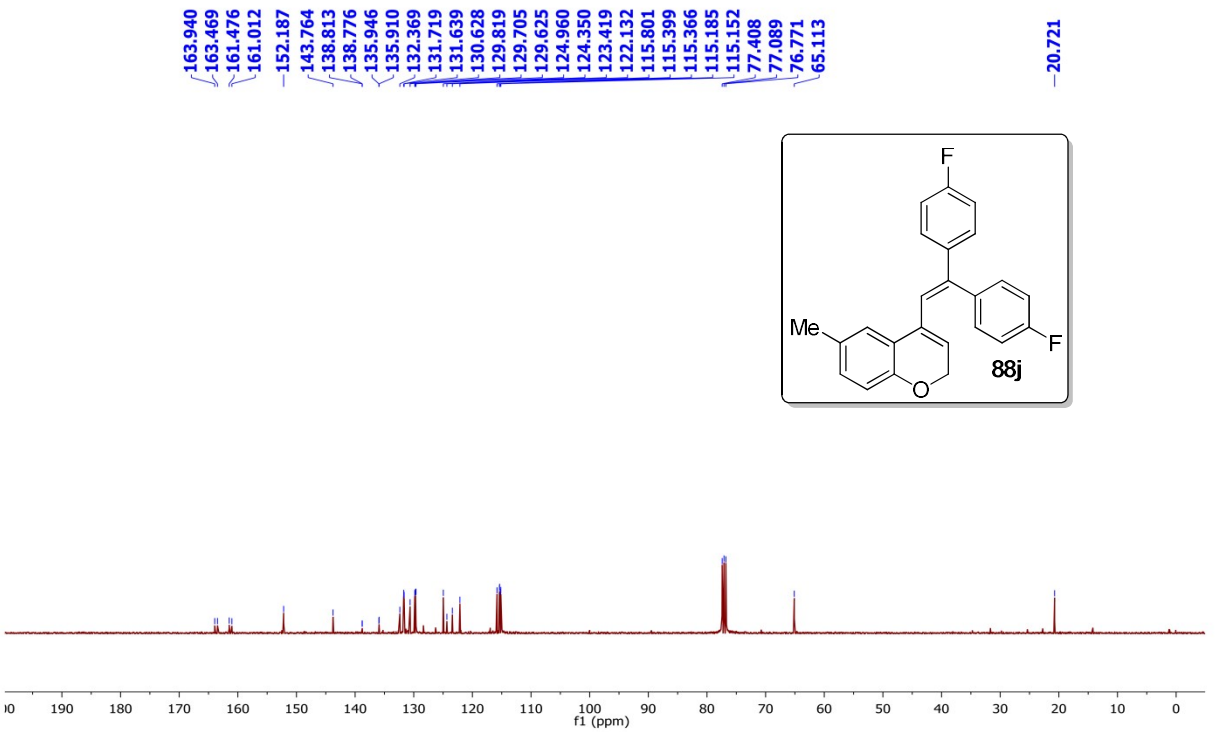
^{13}C{^{1}H} NMR (100 MHz) of **88i**:



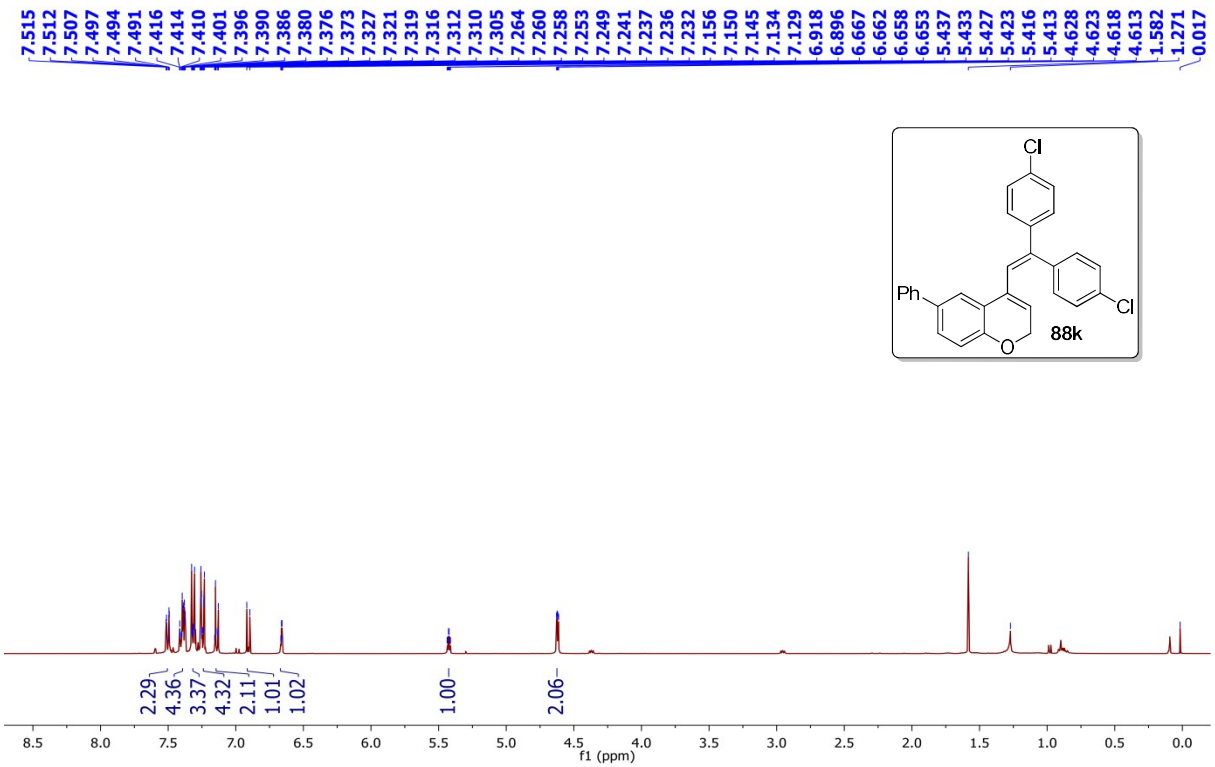
^{1}H NMR (400 MHz) of **88j**:



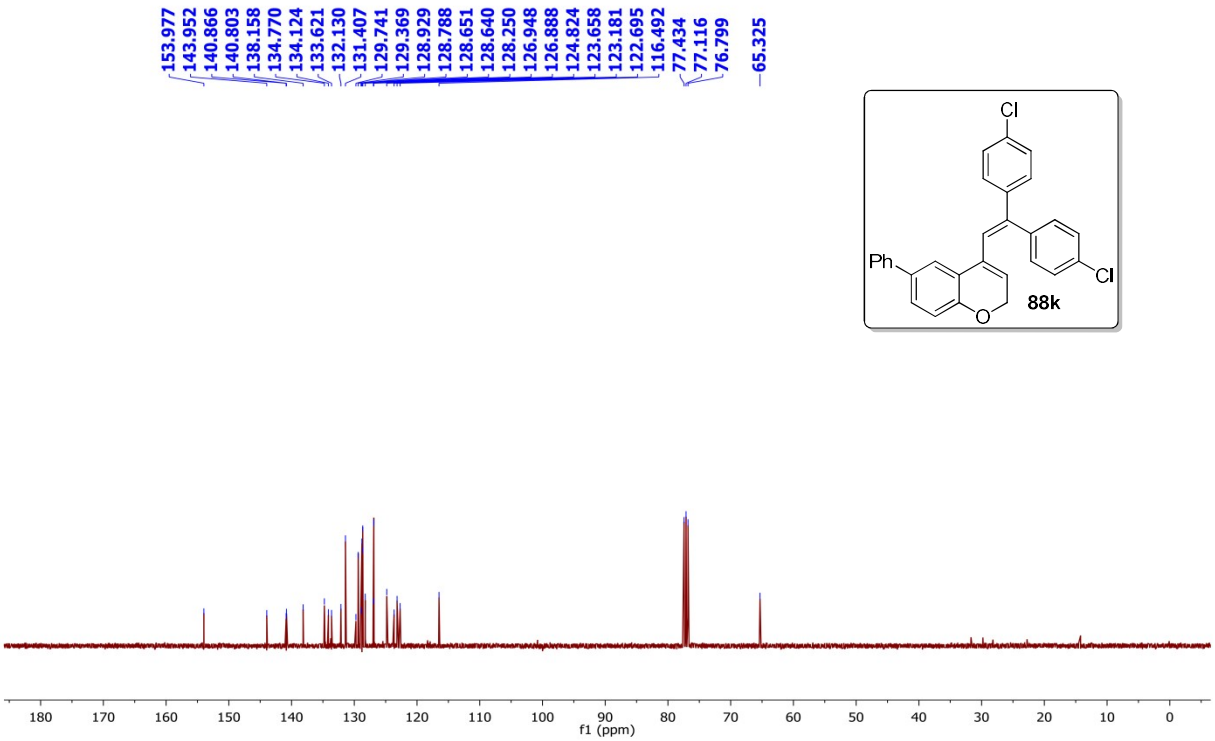
^{13}C{^{1}H} NMR (100 MHz) of **88j**:



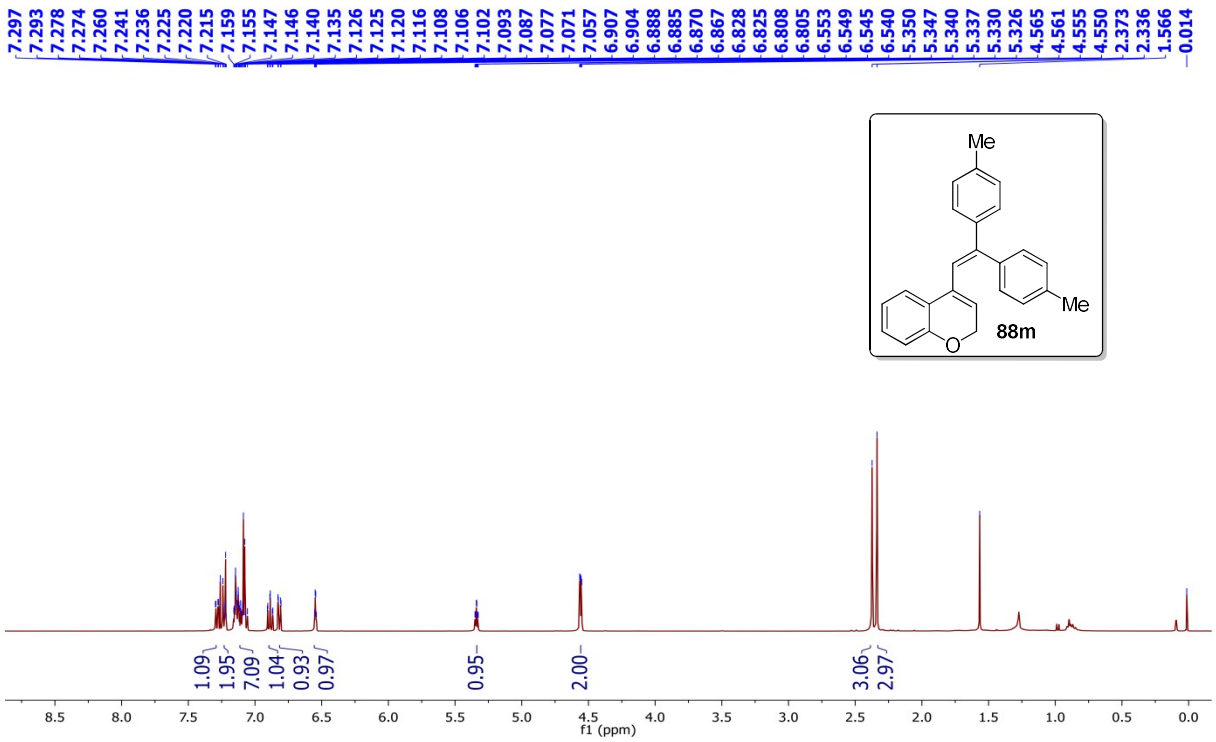
^{1}H NMR (400 MHz) of **88k**:



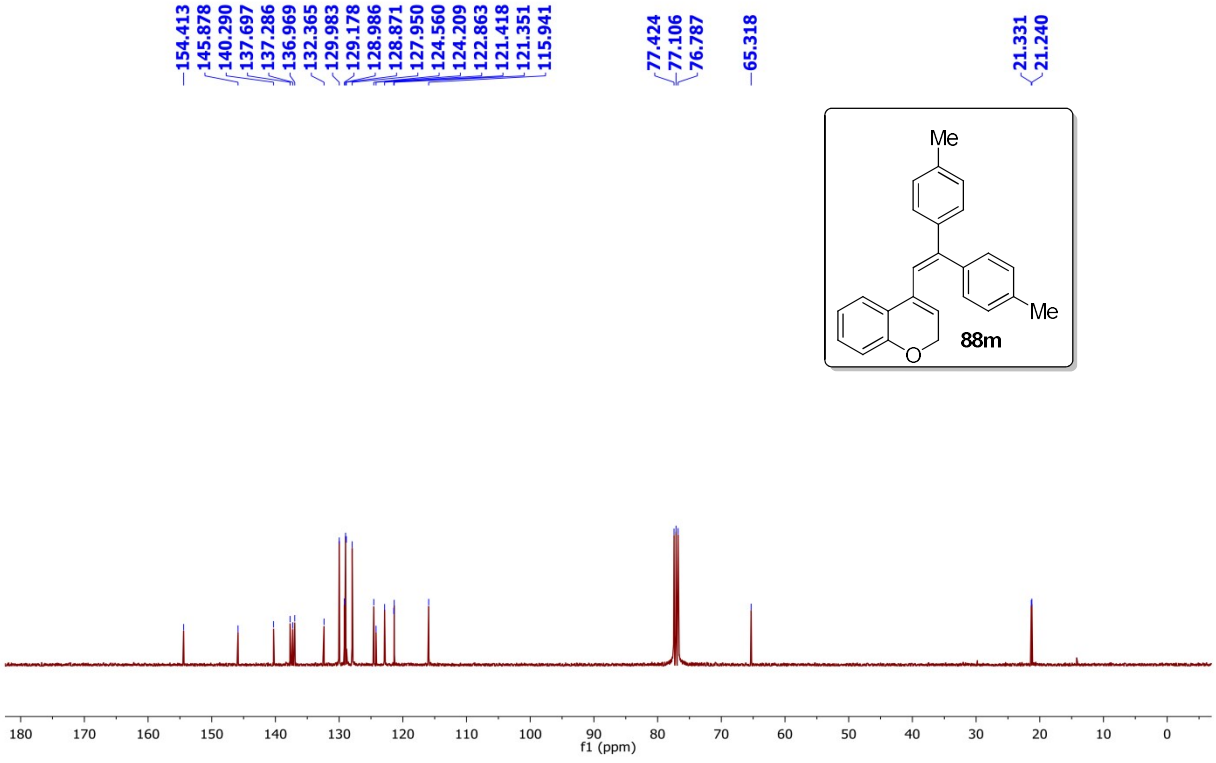
^{13}C{^{1}H} NMR (100 MHz) of **88k**:



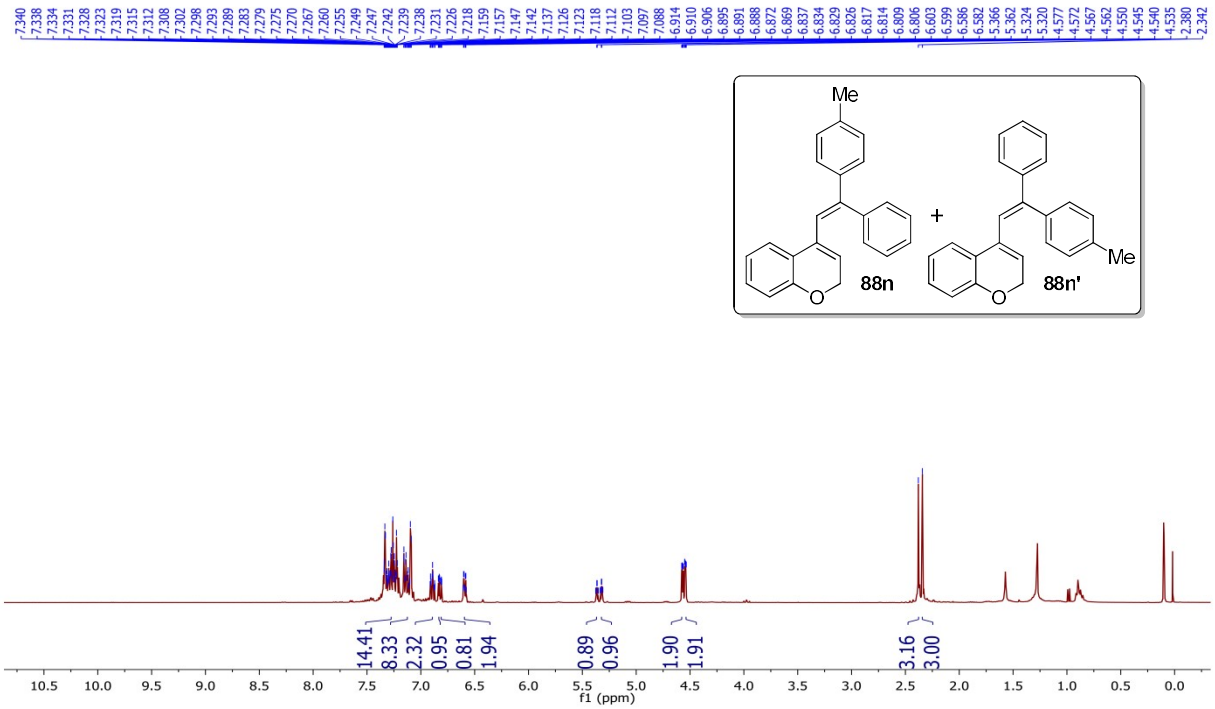
^{1}H NMR (400 MHz) of **88m**:



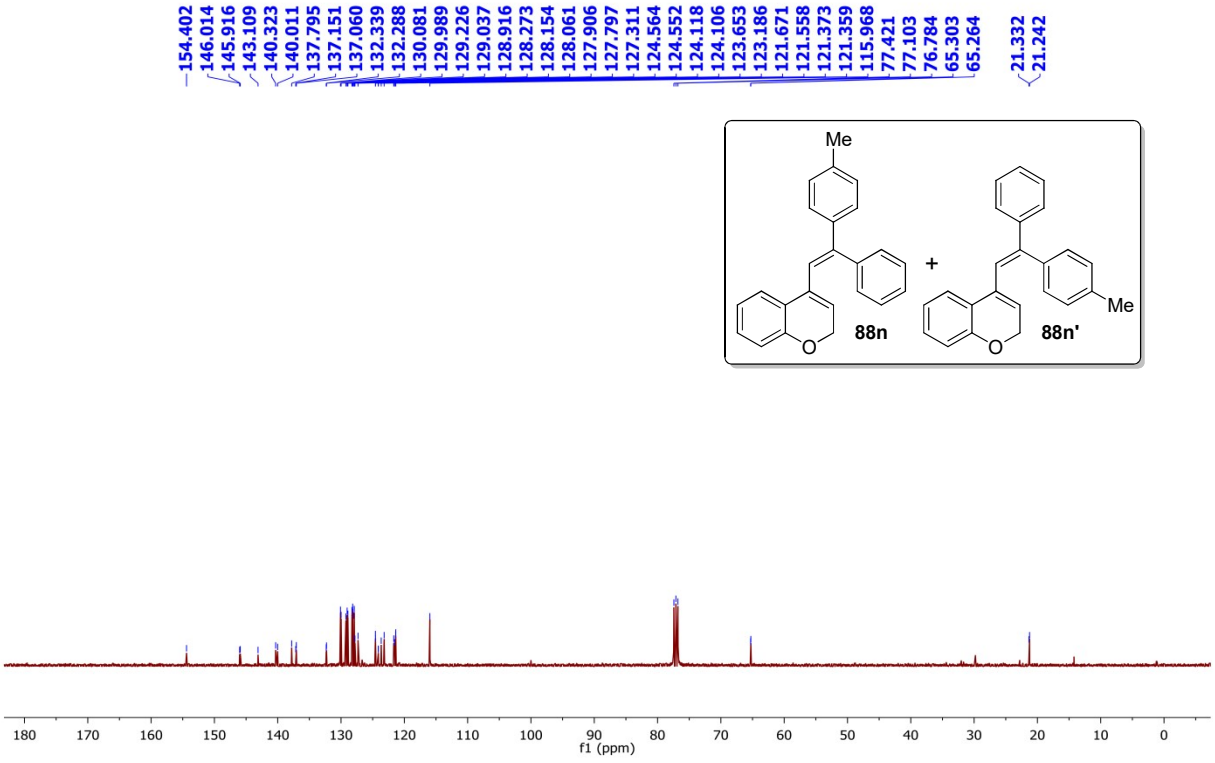
^{13}C{^{1}H} NMR (100 MHz) of **88m**:



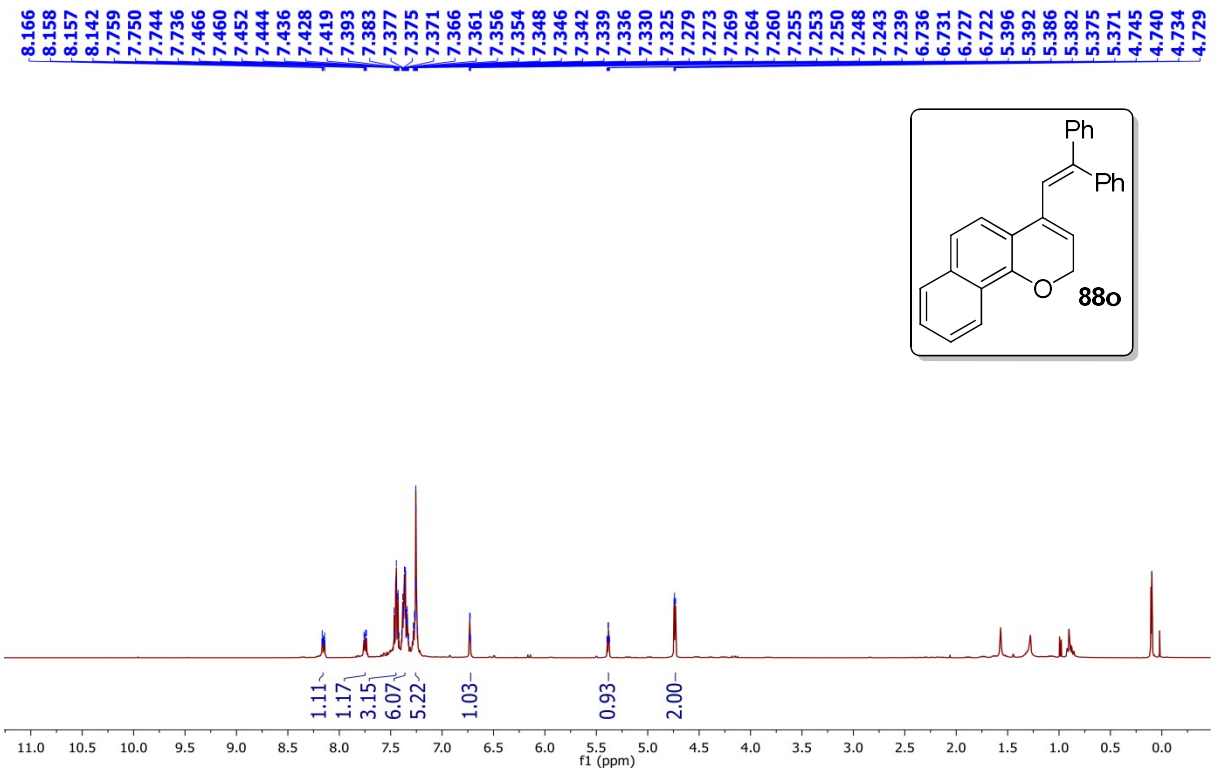
^{1}H NMR (400 MHz) of **88n**:



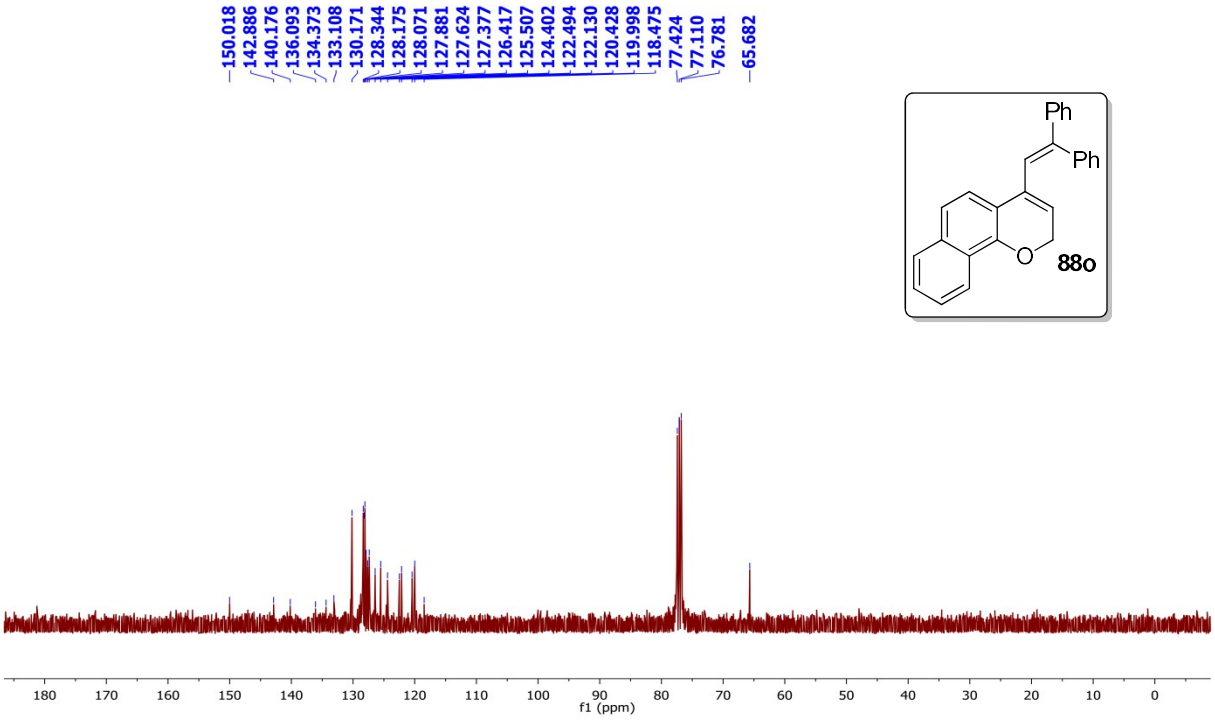
^{13}C{^{1}H} NMR (100 MHz) of **88n**:



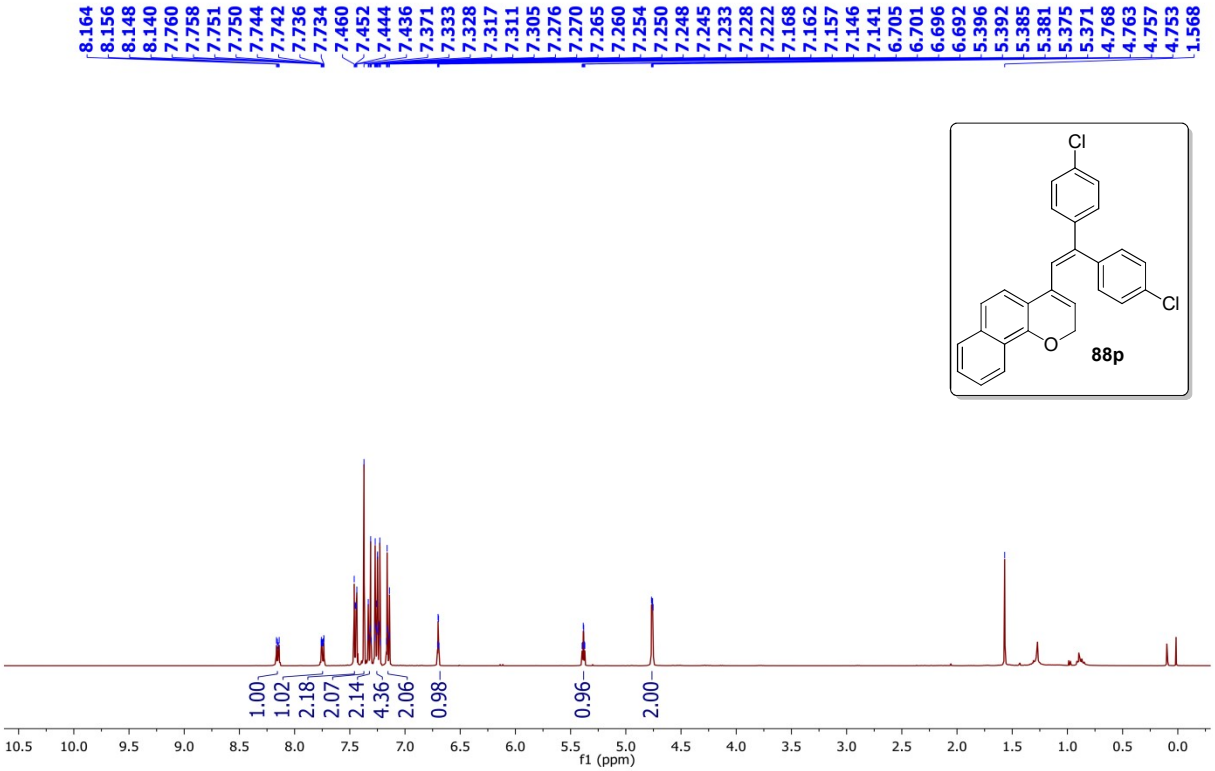
^{1}H NMR (400 MHz) of **88o**:



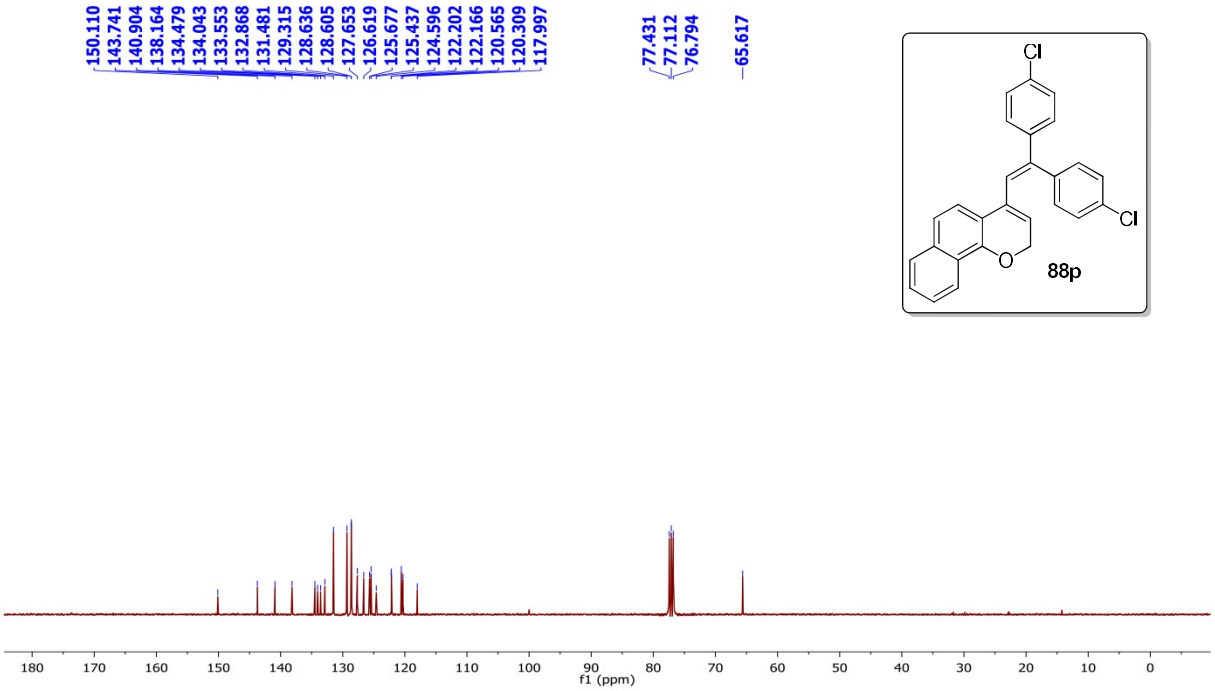
^{13}C{^{1}H} NMR (100 MHz) of **88o**:



^{1}H NMR (400 MHz) of **88p**:



^{13}C{^{1}H} NMR (100 MHz) of **88p**:



CHAPTER 4

Palladium(II)-Catalyzed Cascade Reactions of Ene−Ynes Tethered to Cyano/Aldehyde: Access to Benzo[*g*]indoles

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Part I – A Short Review

4.1.1. Introduction: Benzo[*g*]indole an important heterocycle

Indole (**1**, Figure 1) is considered to be one of the most important and privileged class of heterocycles having numerous applications in wide ranges of medicinal chemistry.[1] The said structural motif is found in a large number of naturally occurring molecules and considered as the most important single class of heterocyclic systems.[2] The scaffold has drawn the attention due to its powerful therapeutically interesting biological activities.[3] Among various fused-indoles, benzo-fused indoles comprising benzo[*g*]indole (**2**, Fig. 1), benzo[*e*]indole (**3**,Fig. 1) and benzo[*f*]indole (**4**, Fig. 1)[4] are considered as an important subclass. Among them, benzo[*g*]indoles **2** are the structural components of a large number of biologically active natural and synthetic compounds and considered as one of the important heterocyclic moiety due their extended applications in medicinal science[5-8] as well as in material science.[9]

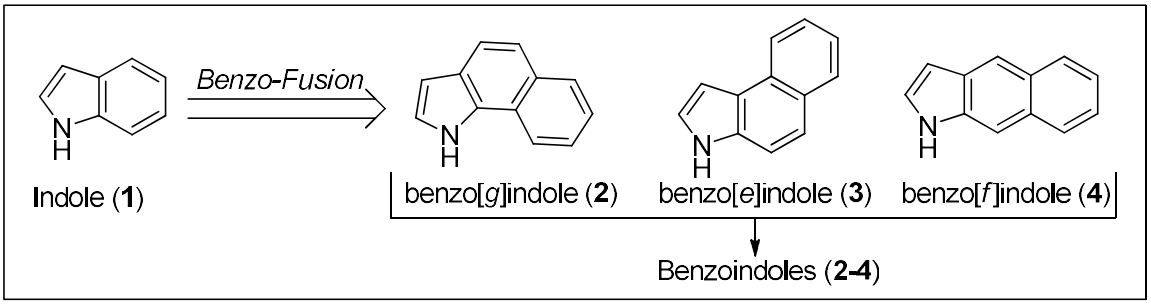


Figure 1: Structures of different benzo-fused indoles **2**-**4**

For example, benzo-fused isotryptamine **5** (Figure 2) shows a high binding affinity with 5-HT_{2A} receptors;[5a] compound **6** (Fig. 2) and derivatives **7** (Fig. 2) containing the core structure of benzo[*g*]indole are reported to show significant *in vivo* anti-inflammatory activity[5b]and affinity for dopamine D_2-like receptors[5c]respectively. Some 2-(Aryldiazenyl)-3-methyl-1*H*-benzo[*g*]indole derivatives **8** (Fig. 2) are reported to exhibit interesting cytotoxicity against various cancer cell lines, e.g. leukemia, melanoma, breast cancer cell lines etc.[5d] Besides, compound **9** (Fig. 2) possess good growth inhibitory activity,[5e]whereas compound **10** (Fig. 2) exhibit strong Keap1-Nrf2 PPI inhibitory activity with high metabolic stability and low cytotoxicity.[5f]In addition to this, some benzo[*g*]indol-3-carboxylates are reported to be potent

inhibitors of microsomal prostaglandin E_2 synthase-1,[6]in particular compound **11′** (Fig. 2) possessing a 5-hydroxybenzo[*g*]indole moiety displayed 10-fold higher 5-lipoxygenase activity than the normal 5-hydroxy indole (**11**, Fig. 2).[6b] Some benzo[*g*]pyrido[4,3-*b*]indole derivatives (**12** , Fig. 2) are also reported to be DNA intercalater.[7a] Moreover derivatives of **13** (Fig. 2) are reported to be promising anti-cancer agents.[7b]In particular note, few derivatives of bis-benzo[*g*]indole carboxamides **14** (Fig. 2) are documented to show good cytotoxicity against cancer cells *in vitro*.[8]

In addition to their medicinal importance,[5-8]they have huge applications in various fields of material sciences e.g. some novel poly(1H-benzo[*g*]indole) derivatives shows high performances in electrochromic devices[9a] and also acts as Yellow-Light-Emitter;[9b] whereas some 5-hydroxy benzo[*g*]indoles show fluorescence "Turn-off" sensing properties of Fe(III) ions[9c] in conjunction to their reports on 5-lipoxygenase activity.[6b]

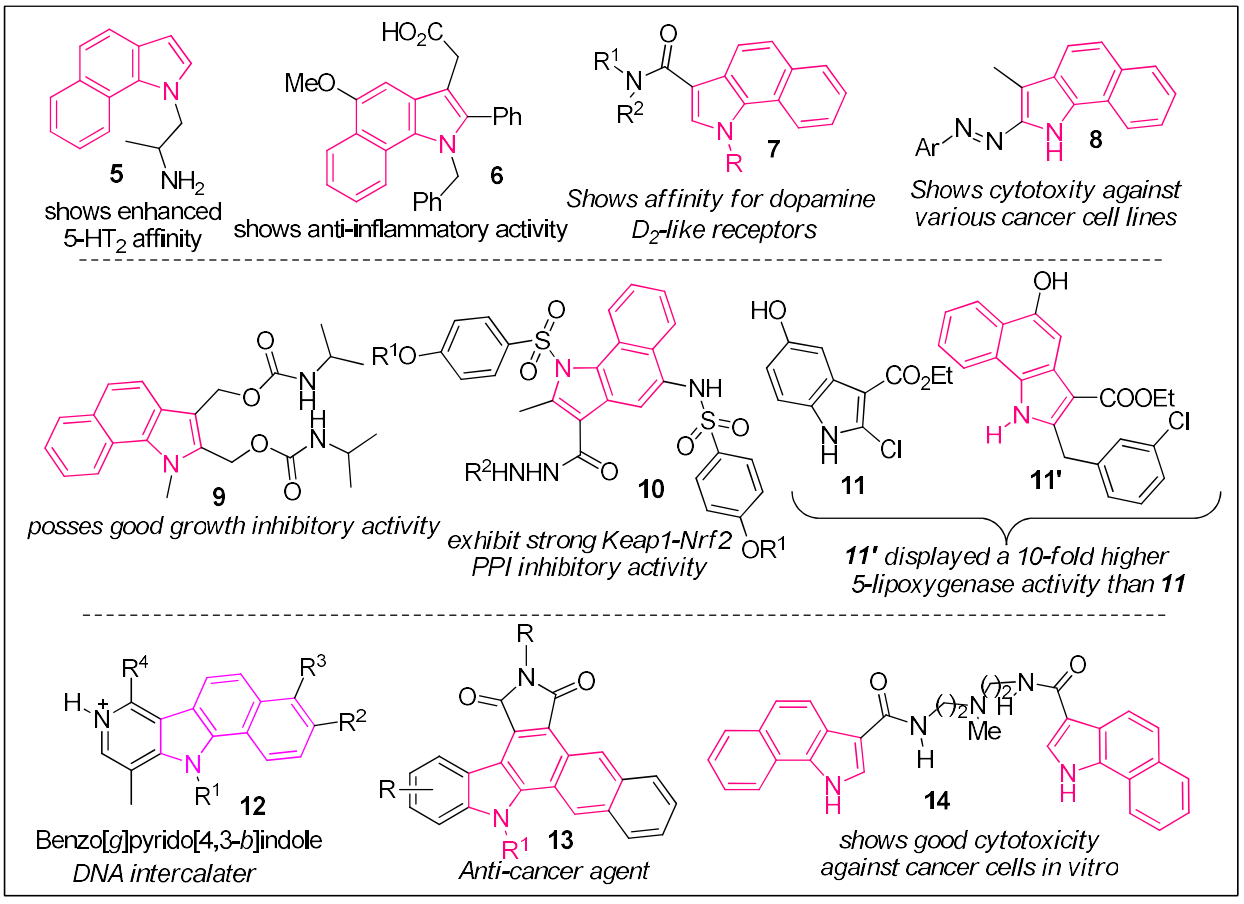


Figure 2: Some important Benzo[*g*]indole derivatives

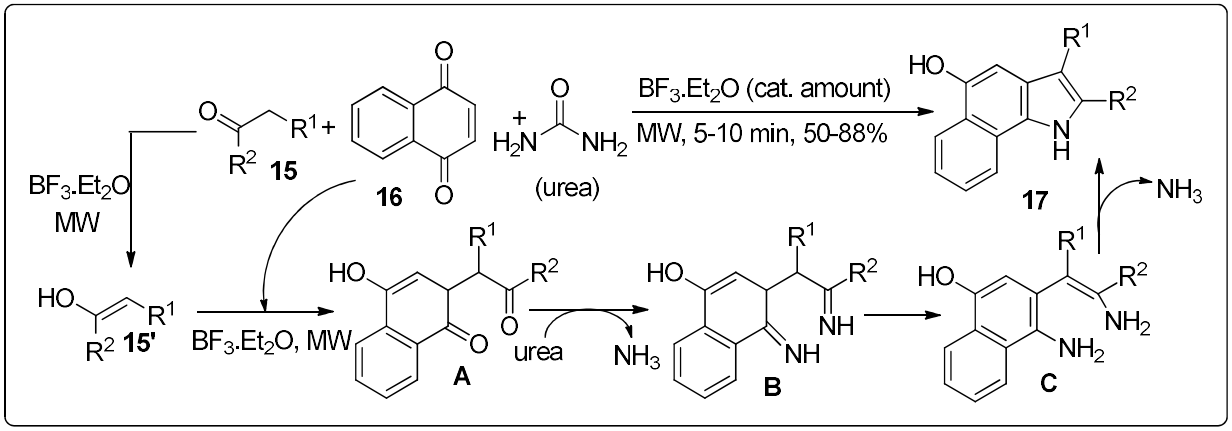
4.1.2. Synthesis of Benzo[*g*]indoles and their variously substituted derivatives

Due to the immense importance and widespread applications of benzo[*g*]indoles in various field of science, plenty of efforts have been made for their general synthesis; where most of the reports are on either multi-component or multistep reactions involving classical or conventional pathway requiring high reaction time; Besides, some metal catalyzed synthesis of benzo[*g*]indoles are also accomplished. Few of them are illustrated briefly below.

4.1.2.1. Metal free pathway for the synthesis of Benzo[*g*]indoles

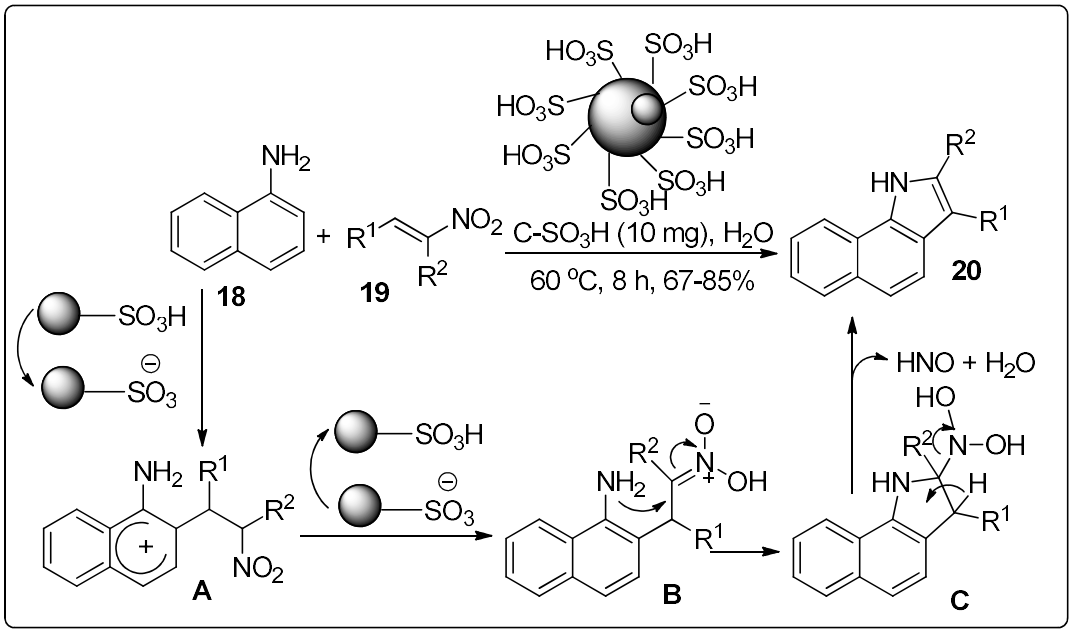
4.1.2.1.1. One-pot approach for the synthesis of Benzo[*g*]indoles:

Boruah and coworkers[10a]reported a fast, multi-component solvent-free Lewis acid catalyzed one-pot synthesis of 5-hydroxy-benzo[*g*]indoles (**17**, **Scheme 1**) *via* reaction of ω-morpholinoacetophenone **15**, naphthoquinone **16** and urea through modified *Nenitzescu reaction* under microwave irradiation. Mechanistically (**Scheme 1**), the reaction begins with the $BF_3.OEt_2$-catalyzed tautomerisation of **15** to **15′** under microwave heating conditions, which upon *Michael addition* with **16** delivers intermediate **A**. Meanwhile NH_3 is generated from urea under microwave heating, which on reaction with intermediate **A** delivers a diimine intermediate **B** which is further isomerized into the 1,4-diamino intermediate **C**. Finally, intramolecular cyclocondensation of **B** affords the desired product **17** with concomitant loss of ammonia.



Scheme 1: Schematic representation and mechanistic rational for the formation of product **17**

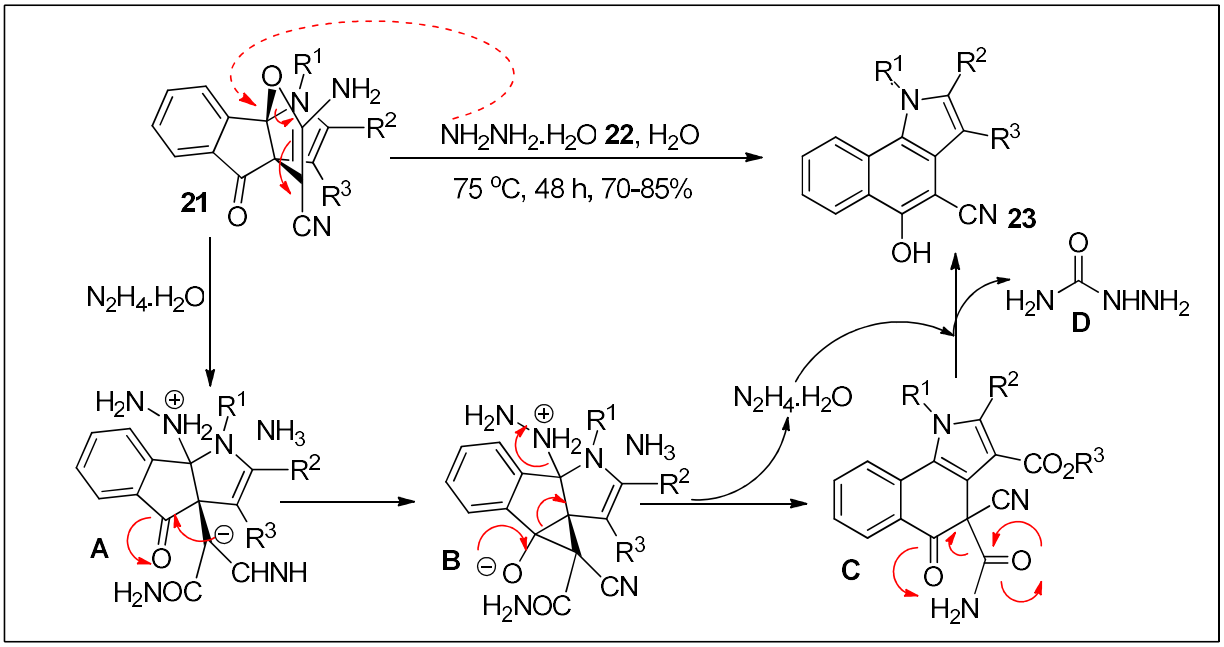
Qi and coworkers[10b] demonstrated a facile and efficient protocol for the synthesis of benzo[*g*]indole derivatives **20** (**Scheme 2**) through carbonaceous material (C–SO_3H)-catalyzed inter-molecular reaction of 1-naphthylamines **18** and nitro-olefins **19** in water. The interesting feature of the report is that the carbonaceous material can be recycled which makes the method cost-effective and environmentally benign compared to traditional acid-catalyzed methods whereas use of water as solvent makes the approach greener and convenient. From the mechanistic point of view, initially, intermediate **A** is generated *via* a *Michael addition reaction* of 1-naphthylamine **18** and nitro-olefin **19** (**Scheme 2**), which on imine-enamine tautomerization affords intermediate **B** in presence of the carbonaceous material (C–SO_3H). Subsequent intramolecular cyclization of intermediate **B** leads to the formation of intermediate **C** which on elimination of H_2O and HNO finally affords the desired benzo[*g*]indole **20**.



Scheme 2: Synthetic pathway for formation of benzo[*g*]indoles **20**

Alizadeh and coworkers[10c] reported a metal free approach for the general synthesis of 5-hydroxybenzo[*g*]indoles **23** (**Scheme 3**) in very good yields via nucleophilic addition of hydrazine hydrate ($N_2H_4.H_2O$) **22** on substrate **21** in water. A plausible reaction mechanism for the formation of the product is depicted under **Scheme 3**. Initially, nucleophilic attack of hydrazine hydrate **22** on the bridgehead carbon of the substrate **21** (which is between the electronegative oxygen and nitrogen atoms) leads to the formation of intermediate **A** via ring

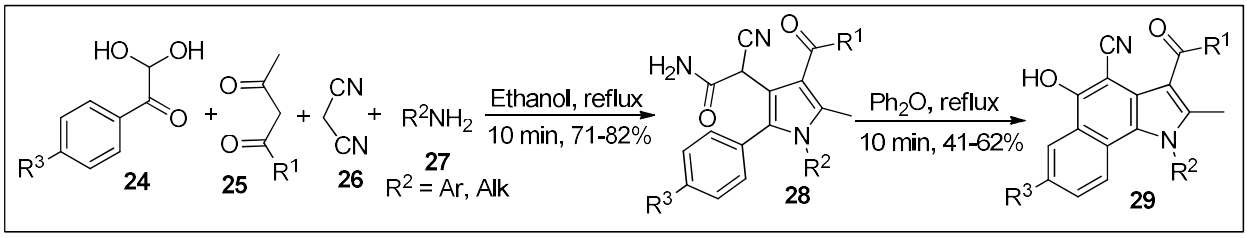
opening. Then nucleophilic attack of the generated carbanion on the adjacent carbonyl group leads to the formation of intermediate **B**, which on subsequent ring expansion and elimination delivers intermediate **C**. Finally, intermediate **C** in converted to product **23** in presence of **22** via elimination of **D**.



Scheme 3: Reaction pathway for the synthesis of **23**

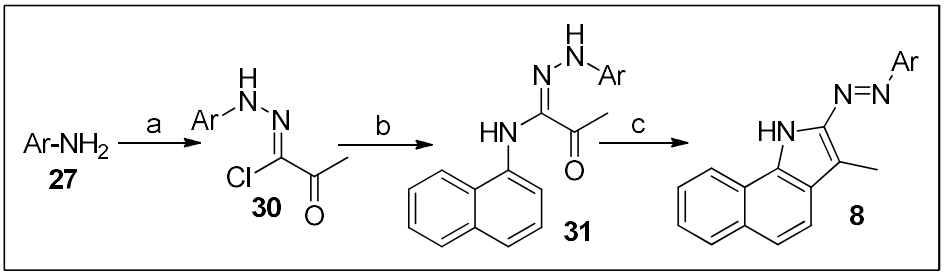
4.1.2.1.2. Multi-step approach for the synthesis of Benzo[*g*]indoles:

Pramanik and coworkers[9c] disclosed a two-step metal-free approach for the synthesis of substituted benzo[*g*]indoles **29** (**Scheme 4**) via the formation of highly substituted 2-pyrrolyl-2 cyanoacetamides **28**, which were easily prepared from multi-component domino condensation of aryl glyoxals **24**, 1,3-dicarbonyl compounds **25**,malononitrile **26** and amines **27**. Subsequent thermal cyclization of the formed cyanoacetamide derivatives **28** leads to the formation of the product **29** in diphenyl ether under refluxing condition. The synthesized compounds **29** were reported to be fluorescence active with good quantum yields and also shows fluorescence "Turn-off" sensing property for sensing of Fe^{3+}ions.



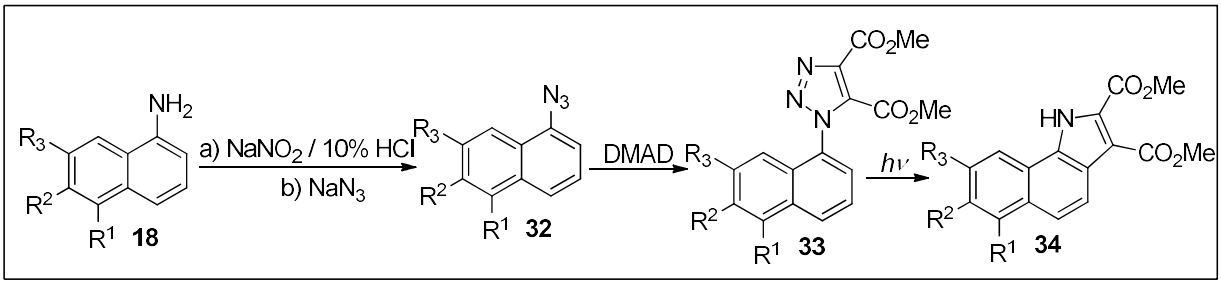
Scheme 4: Synthetic route to access benzo[*g*]indoles **29**

Abdel-Jalil and coworkers[5d]reported the synthesis of a series of novel 2-(aryldiazenyl)-3-methyl-1*H* benzo[*g*]indoles (**8**, **Scheme 5**) *via* cyclization of corresponding aryl amidrazones **31** employing polyphosphoric acid (PPA) as a cyclizing agent. Notably, the starting material **31** was prepared in two steps only starting from arylamines **27** and the products are reported to exhibit interesting cytotoxicity against a various cancer cell lines.



Scheme 5. Reagent and conditions:(a) dil. HCl, $NaNO_2$, 5 ^oC, 30 min then 3-chloro-2,4 pentanedione in AcOH, 5 ^oC, 2 h, 70-80%; (b) 1-Napthylamine, TEA, EtOH, reflux, 2 h, 52-80%; (c) PPA, 80-115 ^oC, 15-20 min, 50-60%.

Sasaki and coworkers[11] reported a multi-step approach for the synthesis of 1*H*-benz[*g*]indole-2,3-dicarboxylates (**34**, **Scheme 6**) starting from 1-napthylamines **18**. At first, the amine derivatives **18** were transformed into the respective triazoles **33** via the formation of **32**. Finally, product **34** was achieved through photocyclization of **33**.

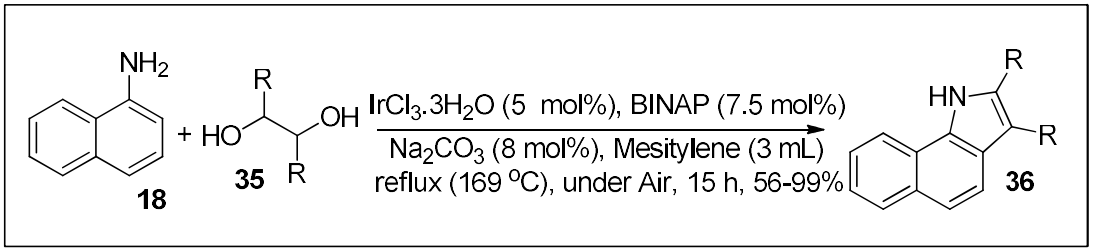


Scheme 6: Reaction pathway for the formation of product **34**

4.1.2.2. Synthetic pathways for the formations of Benzo[*g*]indoles in presence of metal

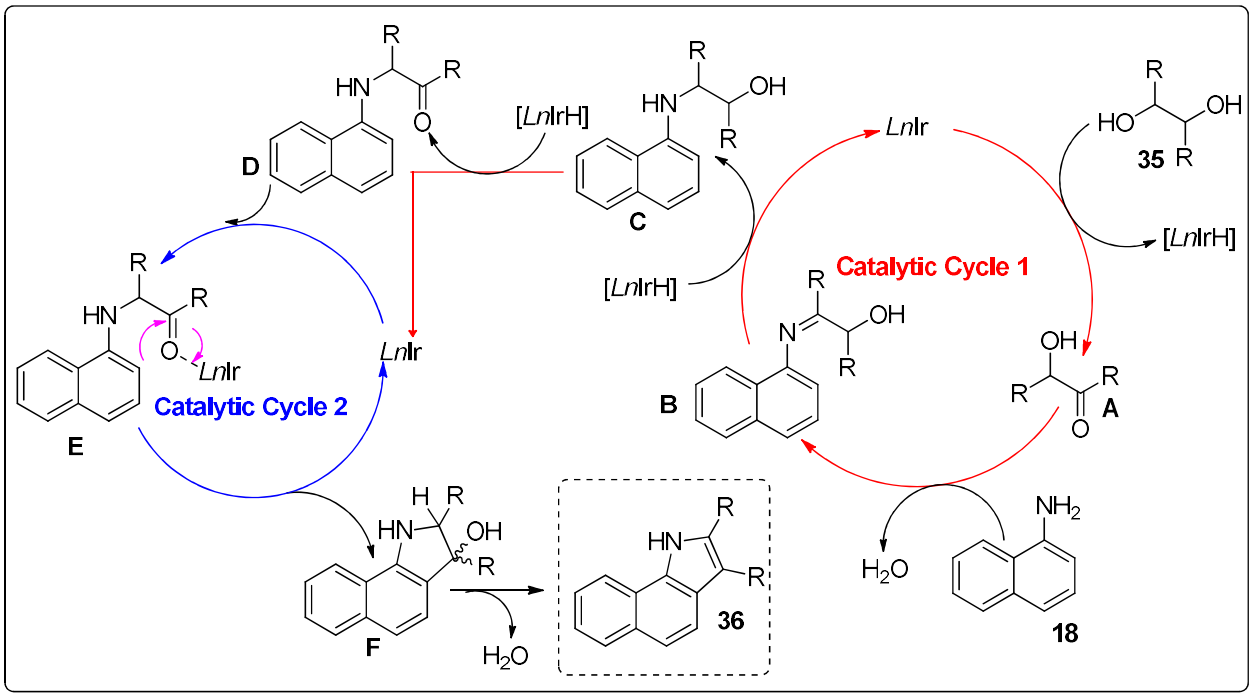
4.1.2.2.1. Intermolecular approach for the synthesis of Benzo[*g*]indoles:

Ishii and coworkers[12a]disclosed a one-pot approach for the synthesis of substituted benzo[*g*]indoles **36** (**Scheme 7**) via Ir(III)-catalyzed cyclization of 1-napthylamine **18** and 1,2 diols **35** with very good to excellent yields in the presence of BINAP as a ligand. Reportedly, the *N*-heterocyclizations are markedly affected by the presence of ligand.



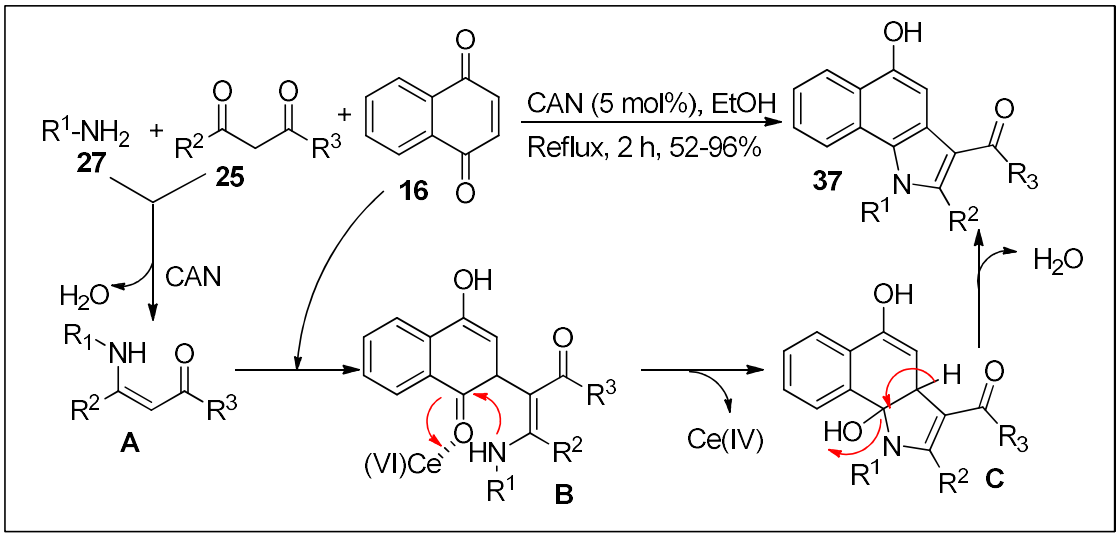
Scheme 7: Synthesis ofbenzo[*g*]indoles **36**

A plausible reaction mechanism is depicted in **Scheme 8**. According to the mechanism, the reaction initiates via Ir-catalyzed dehydrogenation of the diol **35** leading to the formation of intermediate **A** which further reacts with 1-napthyl amine **18** to deliver an imine intermediate **B** with concurrent release of water. Next, hydrogenation of intermediate **B** by *in situ* generated Ir-hydride [*Ln*IrH] affords **C** (Catalytic cycle 1)**,** which then transforms into intermediate **D** and regenerates the catalyst. Next intermediate **D** again co-ordinates with the metal catalyst and forms intermediate **E**, which eliminates the intermediate **F** with the regeneration of the catalyst to keep the catalytic cycle active (Catalytic cycle 2). At last intermediate **F** affords product **36** through dehydration.



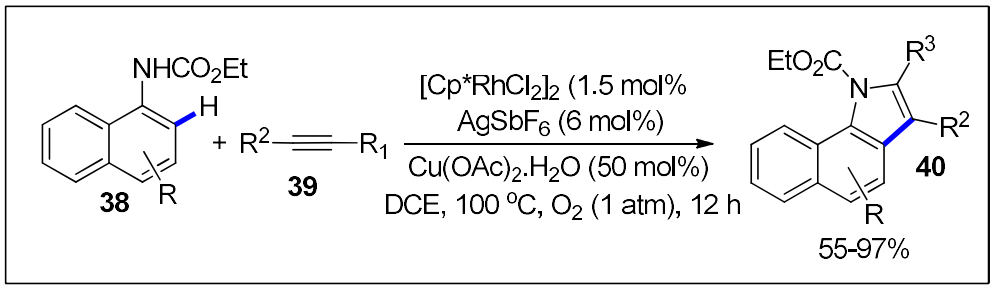
Scheme 8: A plausible reaction mechanism for the formation product **36**

Menéndez and coworkers[12b]reported an expedient, one-pot synthesis of 5- hydroxyl benzo[g]indoles **37** (**Scheme 9**) via CAN [Cerium(IV) ammonium nitrate] catalyzed multi-component domino reaction of primary amines **27**, *β*-dicarbonyls **25** and naphthoquinones **16**. The products were delivered within 2 h with very good to excellent yields. Mechanistic insight reveals that the reaction proceeds through a redox pathway (**Scheme 9**). At first, an enamine intermediate **A** is formed via the reaction between primary amines **27**, *β*-dicarbonyls **25** in presence of CAN. Next, reaction of intermediate **A** with the naphthoquinone **16** affords intermediate **B**. Finally, fast intramolecular nucleophilic cyclization prompted by co-ordination of Ce(IV) to its carbonyl group leads to the formation of intermediate **C**, which finally on dehydration delivers the desired product **37**.



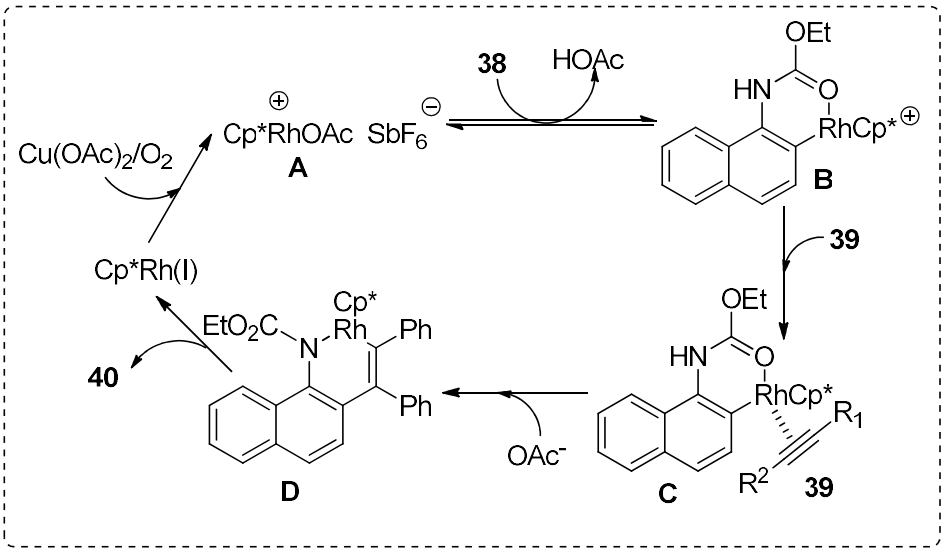
Scheme 9: Reaction pathway and plausible mechanism for the synthesis of product **37**

Jin and cowokers[12c] demonstrated a highly efficient and regioselective Rh-catalyzed synthetic pathway for the general synthesis of benzo[*g*]indoles **40** (**Scheme 10**) via C-H functionalization of carbamates **38** via oxidative annulation with alkynes **39**.



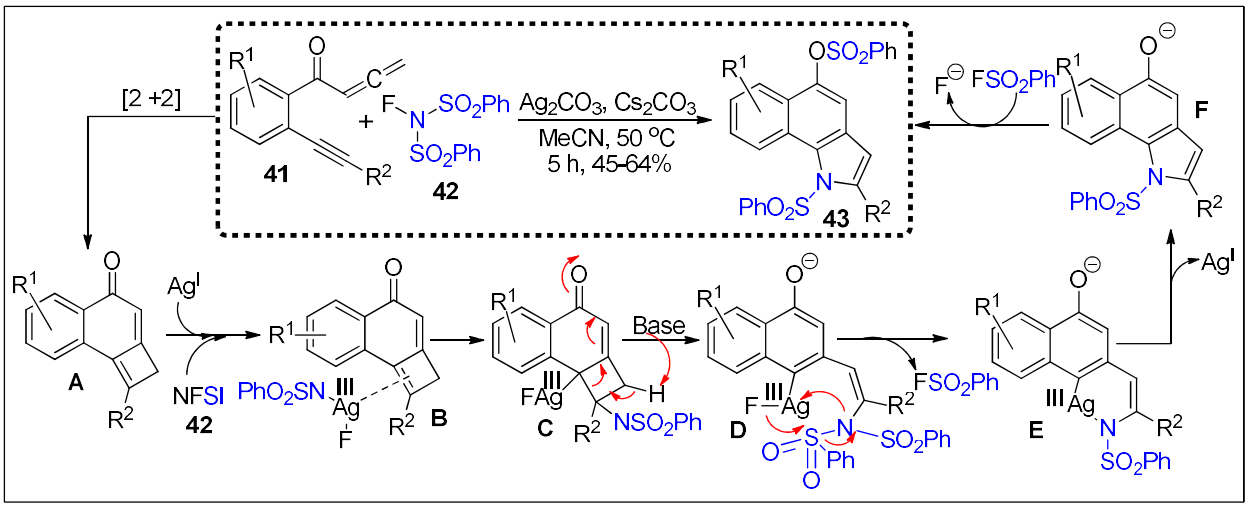
Scheme 10: Synthetic route for the synthesis of product **40**

According to the mechanism (**Scheme 11**), at first, the activated Rh(III) complex **A** preferentially coordinates with the oxygen atom of the carbamate **38** affording intermediate **B**. Subsequent, coordination of the alkyne **39** with intermediate **B** produces intermediate **C**, which upon reaction with acetate ion present *in situ* delivers the desired product **40** with regeneration of the catalyst via formation of intermediate **D**.



Scheme 11: Reaction mechanism for the formation of product **40**

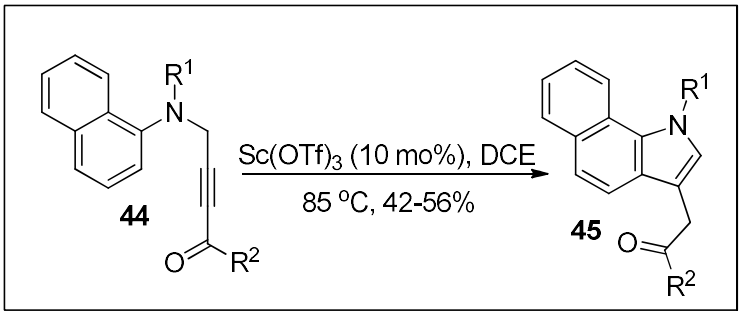
Wang *et al.*[12d] reported a convenient and novel synthetic approach for the formation of functionalized benzo[*g*]indoles **43** (**Scheme 12**) from benzene-linked allene-ynes **41** and *N*-fluorobenzenesulfonimide (NFSI) **42** in presence of $AgNO_3$ and Cs_2CO_3. According to the mechanism (**Scheme 12**), at first, intramolecular [2 + 2] cycloaddition of allene-ynes **41** leads to the formation of cyclobutene intermediate **A**, which on oxidation-coordination with silver salt and NFSI delivers Ag^{III} coordinated butane complex intermediate **B**. Next, the vinyl-Ag^{III} fluoride intermediate **D** is formed *via* migratory insertion and base-promoted ring-opening of cyclobutane intermediate **B** through formation of intermediate **C**. Next, one of the sulfonyl group of intermediate **D** is substituted by the fluoride ion and intermediate **E** is delivered by N-S bond cleavage with elimination of benzenesulfonyl fluoride. Subsequent reductive elimination of intermediate **E** affords intermediate **F**, which upon base-promoted nucleophilic substitution with benzenesulfonyl fluoride yields poly-substituted benzo[*g*]indole **43**.



Scheme 12: Schematic representation for the formation of benzo[*g*]indoles **43**

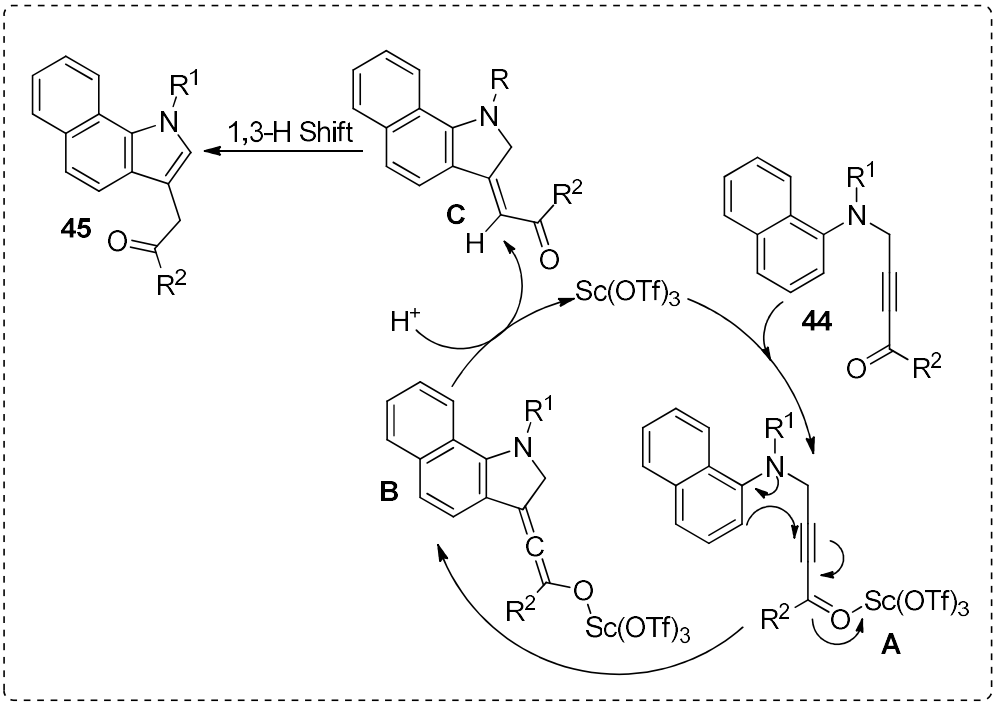
4.1.2.2.2. Intramolecular approach for the synthesis of Benzo[*g*]indoles:

Liang and coworkers[13] reported synthesis of benzo[*g*]indoles **45** bearing both alkyl and aryl moieties via $Sc(OTf)_3$-catalyzed *Friedel-Crafts* alkenylation of substrate **44** (**Scheme 13**).



Scheme 13: Synthesis of product **45**

A plausible mechanism is depicted in **Scheme 14**. At first co-ordination of the starting material **44** with $Sc(OTf)_3$ catalyst gives rise to complex **A**, which on subsequent intramolecular *Friedel-Crafts alkenylation* leads to the formation of intermediate **B**. Isomerization of intermediate **B** regenerates the catalyst to keep the catalytic cycle active with elimination of intermediate **C**. Subsequent 1,3-H shift of intermediate **C** affords the desire product **45**.

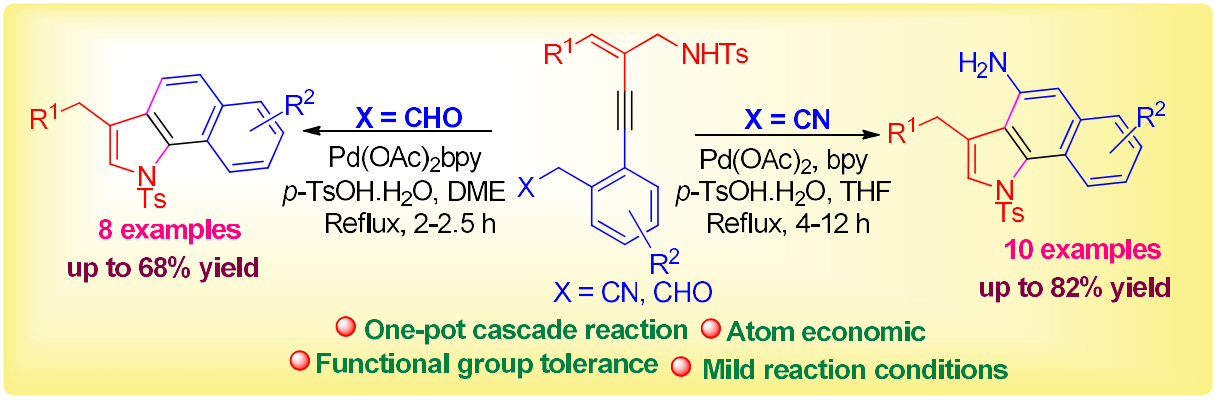


Scheme 14: Reaction mechanism for the synthesis of product **45**

4.1.3. Concluding Remarks

Literature review revels that, benzo[*g*]indoles have received considerable attention over the years due to its widespread applications in various fields. But surprisingly, despite of the great utility of the scaffold, the synthetic route for their formations are quite less explored and most of the procedures are either multi-step or multi-component reaction utilizing conventional methods demanding higher reaction time except few examples. Thus development of straightforward and efficient approach for their general synthesis is highly desirable. In this context, we have developed an efficient atom-economic Pd catalyzed one-pot approach for their general synthesis. Results are discussed in details in **Part II** of this chapter.

Part II – Results and Discussion

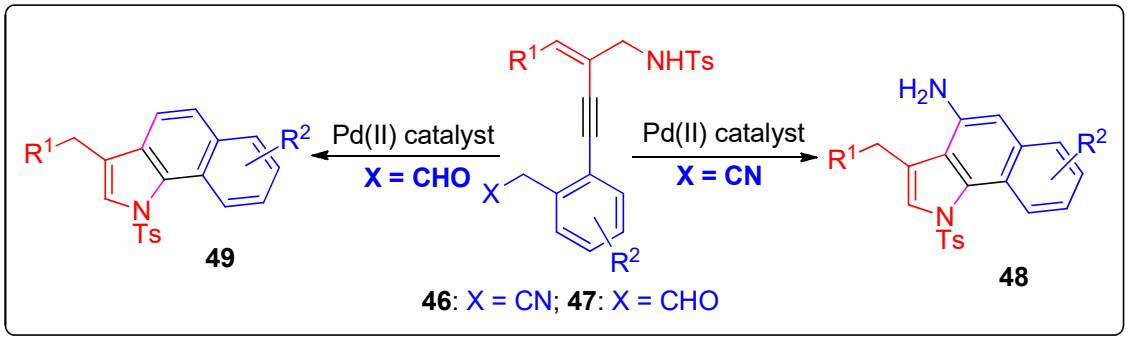


Reference: Moumita Jash, **Sukanya De**, Subhendu Pramanik and Chinmay Chowdhury*;*J. Org. Chem.,***2019**, *84*, 8959-8975

4.2.1. Introduction

Literature survey of benzo[*g*]indoles describes the widespread applications of this scaffold in medicinal chemistry as well in material sciences (see **Part I** of this chapter). But to our surprise, scrutiny of literature reveals that only few synthetic methods are available for their general synthesis (as discussed in **Part I** of this chapter), comprising mostly multistep reaction or multiple component and few specific examples exist on the preparation of this scaffold during the synthesis of other nitrogenheterocycles.[12a,14] Therefore development of a straightforward and convenient one-pot approach for their general synthesis would be worthwhile.

In recent past, cascade reaction has drawn the attention and secured an important field of synthetic chemistry because of several advantages including formation of structurally complex and diversified molecules.[15] In this context, many pioneering works have been well-documented in the literature. In view of this and in continuation of our palladium catalyzed works,[16a-d] it was envisioned that the ene-yne substrates **46** or **47** containing cyano or aldehyde group, could be transformed into their corresponding benzo[*g*]indole derivatives **48** or **49** via Pd(II) catalyst*5-endo-dig*heteroannulation reactions as depicted in **Scheme 15**. Choosing the appropriate catalyst and reaction conditions, our concept proved to be viable.[16e] Herein the detailed outcomes of the results are discussed.

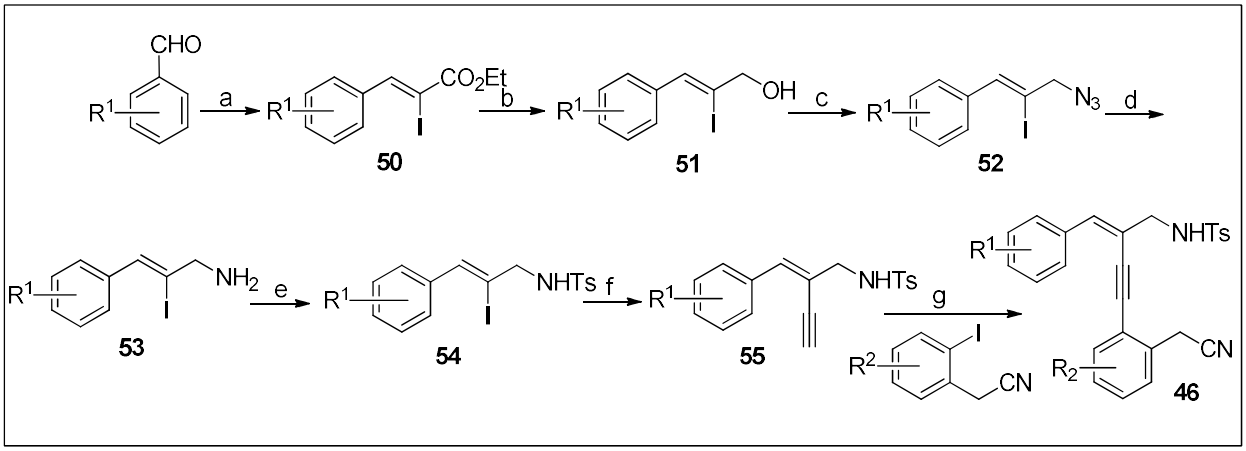


Scheme 15: Our strategy for the synthesis of Benzo[*g*]indole derivatives **48-49**

4.2.2. Synthesis of starting material 46:

The desired starting material **46** was prepared in few steps from commercially available benzaldehyde derivatives. At first, the banzaldehyde derivatives were transformed into their corresponding *α,β*-unsaturated esters **50** via Halo-Wittig reaction, which was then reduced into

α,β-unsaturated alcohols **51** in presence of DIBAL-H. Next, mesylation of **51** followed by reaction with NaN_3 in DMF leads to the formation of the azide derivatives **52**, which upon reduction afforded the respective the amine derivatives **53** using 1,3-propanedithiol. In next step, the amines were tosylated to form the tosylated derivatives **54** which was then allowed to undergo '*Sonogashira Coupling*' with trimethylsilylacetylene resulting in an intermediate product which upon deprotection of the silyl group led to the formation of the acetylene derivatives **55**. Finally,'*Sonogashira Coupling'* of **55** with commercially available 2-iodophenylacetonitrile derivatives delivered the requisite ene-yne substrates **46**.



Scheme 16: Reagents and Conditions: (a)[17a] (i) $Ph_3P^+CH_2CO_2Et.Br^-$, I_2, K_2CO_3, MeOH, 0- 5 °C, 1.5 h; (ii) Tetrabutylammonium bromide, K_2CO_3, 40 °C, 2-8 h, 60-75%; (b)[17a] DIBAL-H, DCM, -5 °C-rt, 2-6 h, 42-76%; (c) [17a] (i) MsCl, Et_3N, DCM, 0 °C-rt, 0.25-1.5 h ; (ii) NaN_3, DMF, rt, 1-2.5 h, 50-93%; (d) 1,3-propanedithiol, N,N-diisopropylethylamine, MeOH:MeCN (1:1), rt, 2-4 h, 64-95%;(e) TsCl, pyridine, DCM, 0 °C- rt, 1-4 h; 72-90%; (f) (i) Trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF , 0 °C-rt, 1.5-4 h, 70-85%; (ii) K_2CO_3, MeOH, rt,0.5-1.75 h, 85-96%; (g) $PdCl_2(PPh_3)_2$, CuI , Et_3N, DMF, 0 °C-rt, 1-8 h, 60-96%.

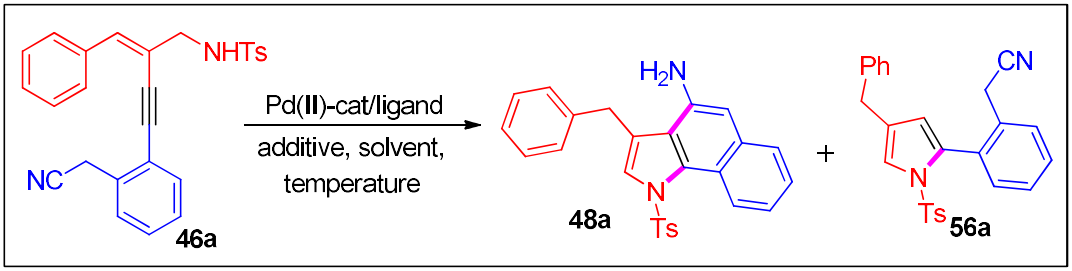
4.2.3. Synthesis of 4-Amino Benzo[*g*]indole 48 in one-pot

4.2.3.1. Optimization of reaction conditions for the synthesis of 4-Amino Benzo[*g*]indole 48a[a]

Towards this goal, the en-yne substrate **46a** was treated under various reaction conditions by changing the reactions parameters. At first, treatment of the model substrate **46a** with

$Pd(OAc)_2$in presence of bipyridine (bpy) and *D*-(+)-camphorsulfonic acid (D-CSA) in heating NMA (100 ^oC) for 6 h afforded the desired product **48a** with 42% yield along with a pyrrole derivative **56a** as side product (Table 1, entry 1), suggesting the necessity of tweaking the reaction parameters. Switching over to other palladium catalysts [viz., $Pd(OAc)_2$bpy, $Pd(OAc)_2$Phen] instead of $Pd(OAc)_2$ was also attempted but without success (Table 1, entries 2 and 3). After replacing the polar solvent NMA with relatively less polar 1,4-dioxane, the reaction was completed within 2 h but delivered only modest yield of **48a** (34%) along with 39% of **56a** (Table 1, entry 4).

Table 1.Optimization of reaction conditions for the synthesis of 4-Amino Benzo[*g*]indole 48a[a]



Entry	Catalyst	Ligand	Additive	Solvent	Temp (^{o} C)	Time (h)	Yield (%) 48a	56a
1.	$Pd(OAc)_2$	bpy	D-CSA	NMA	100	6	42	32
2.	$Pd(OAc)_2$bpy	---	D-CSA	NMA	100	6	41	38
3.	$Pd(OAc)_2$phen	---	D-CSA	NMA	100	5	40	32
4.	$Pd(OAc)_2$	bpy	D-CSA	1,4-dioxane	75	2	34	39
5.	$Pd(OAc)_2$	bpy	D-CSA	THF	reflux	6	45	26
6.	$Pd(OAc)_2$bpy	---	D-CSA	THF	reflux	2.1	60	25
7.	$PdCl_2(MeCN)_2$	bpy	D-CSA	THF	reflux	9	trace	trace
8.	$Pd(OAc)_2$bpy	---	$MeSO_3H$	THF	reflux	9	nr	nr
9.	$Pd(OAc)_2$bpy	---	AcOH-H_2O (1:1)	THF	reflux	10	nr	nr
10.	$Pd(OAc)_2$bpy	---	*p*-TsOH.H_2O	THF	reflux	3.5	66	25
11.	**$Pd(OAc)_2$**	**bpy**	***p*-TsOH.H_2O**	**THF**	**reflux**	**4**	**75**	**12**
12.	$Pd(OAc)_2$	bpy	TfOH	THF	reflux	7	trace	trace

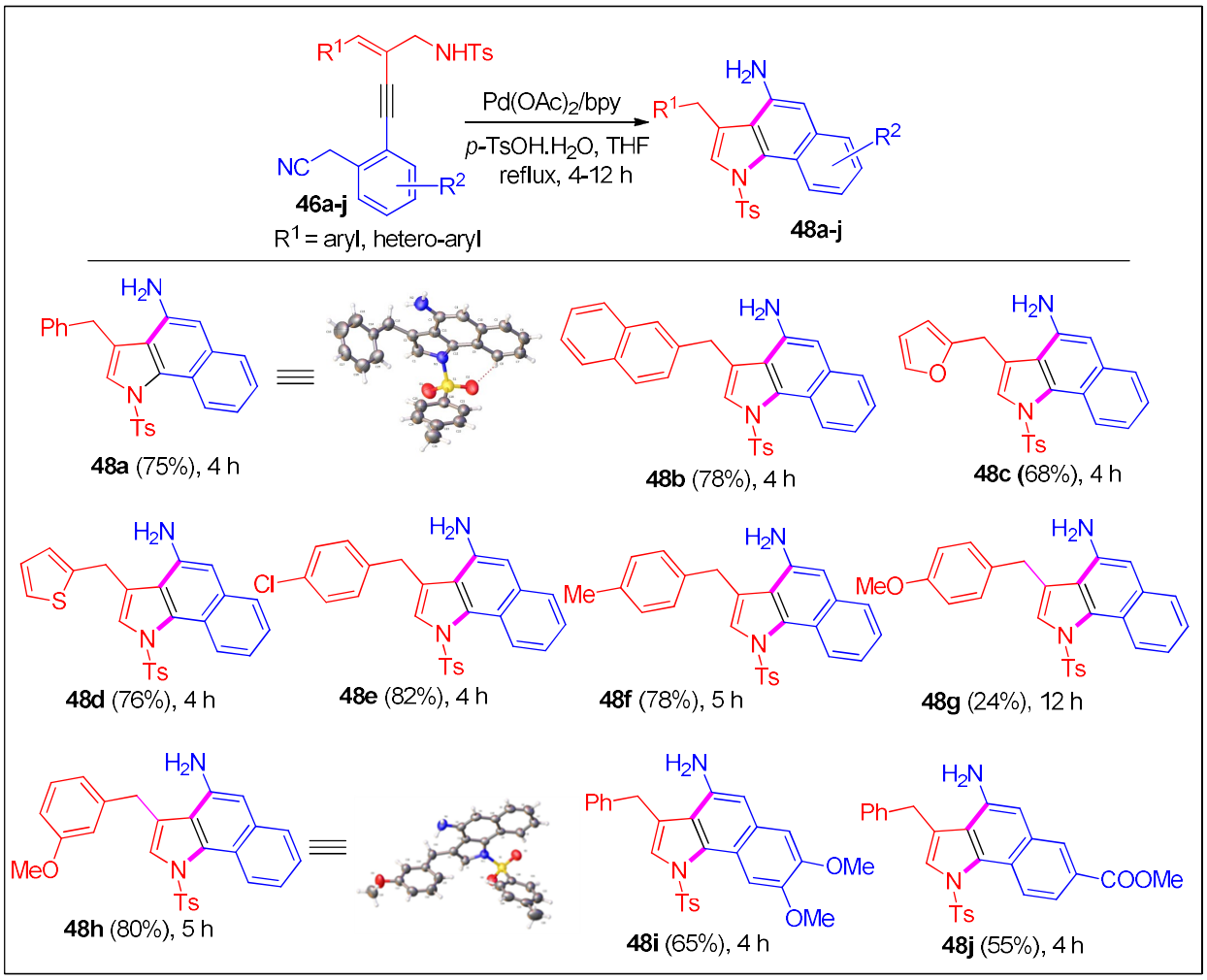
[a]Reaction conditions: A mixture of **46a** (0.23 mmol), catalyst (5 mol %), ligand (10 mol %), except entries 2, 3, 6 and 8-10, and additive (2.0 equiv) in solvent (3 mL) was heated at temperature (see table) under argon atmosphere.

Experiments with other solvents revealed THF to be the best candidate for the transformation, although it required somewhat longer reaction times (2.1-10 h). Carrying out this reaction initially in refluxing THF required 6 h to afford the product **48a** (45%) in addition to 26% of **56a** (Table 1, entry 5). Interestingly, use of $Pd(OAc)_2$bpy as catalyst instead of $Pd(OAc)_2$/bpy reduced the reaction time (2.1 h) and enhanced the yield of **48a** to 60% (Table 1, entry 6); the other catalyst tried [i.e., $PdCl_2(MeCN)_2$] proved unsuccessful (Table 1, entry 7). Next the role of different additives in this reaction were checked. Although methanesulfonic acid ($MeSO_3H$) and aqueous acetic acid ($AcOH/H_2O$ = 1:1) failed (Table 1, entries 8 and 9) to afford any desired product, *p*-toluenesulfonic acid (*p*-$TsOH\cdot H_2O$) could complete the reaction within 3.5 h and furnished **48a** with 66% yield (Table 1, entry 10) along with **56a** (25%). To our gratification, use of $Pd(OAc)_2$ as catalyst and bipyridine individually instead of preformed $Pd(OAc)_2$bpy further improved the yield of **48a** (75%) and suppressed the yield of the side product **56a** considerably (Table 1, entry 11). But change of the additive to triflic acid proved unsuccessful (Table 1, entry 12). Thus, the reaction conditions of entry 11 of Table 1 appeared to be optimal.

4.2.3.2. Scope of the reaction

With the optimized condition, we set out to explore the fate and compatibility of variously substituted **46** derivatives under the optimized reaction condition (**Scheme 17**). Towards this goal, at first the phenyl ring in **46a** was replaced by naphthyl one, affording substrate **46b** (R^1 = 2-naphthyl, R^2 = H), which upon exposure under the optimized condition delivered the product **48b** (78%) with equal ease. Introduction of a heteroaryl moiety also proved to be equally effective affording the respective products **48c/48d** with very good yields (68-76%). Installation of either an electron-withdrawing (viz., Cl) or electron-donating group (viz., Me) at the *para* position as in **46e** (R^1 = *p*-Cl-C_6H_4) or **46f** (R^1 = *p*-Me-C_6H_4) afforded the desired product **48e** (82%) or **48f** (78%) easily within 4-5 h. In contrast, placement of a strong electron-donating group (OMe) at the same position had detrimental effect, making the reaction sluggish (t = 12 h) and affording the product **48g** with low yield (24%), though the same substituent located at *meta* position ensured very good yield (80%) of the corresponding product (**48h**) in a short reaction time (5 h). Presumably, the low yield of **48g** may be attributed to the electron-donating effect of the methoxy group to the acetylenic carbon (of **46g**), thereby reducing the electrophilicity sufficiently and making the *trans*-aminopalladation process [see, species **A**

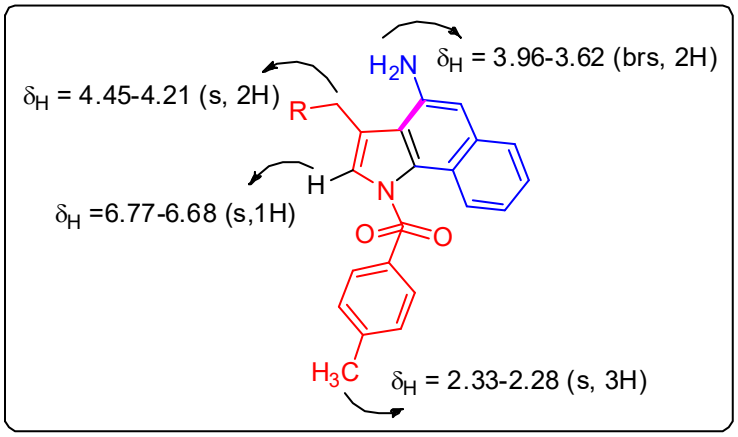
Scheme 17. Synthesis of 4-Amino Benzo[*g*]indole Derivatives 48a-j[a,b]



[a]Reaction conditions: **46** (0.23 mmol), $Pd(OAc)_2$ (5 mol %), bpy (10 mol %), and *p*-TsOH·H_2O (2.0 equiv) in refluxing THF (3 mL) under argon atmosphere. [b]Product **48** was formed along with a minor amount (8-19%) of the corresponding pyrrole derivative (e.g., **56a** during the use of **46a**) as side product resulting from monocyclization.

(X = NTs) of **Scheme 21**, *vide infra*] somewhat difficult. In contrast, placement of methoxy at both *meta* and *para* positions delivered the desired product **48i** in 4 h with 65% yield. Even a strongly electron-withdrawing group (CO_2Me) incorporated at the same position also produced the desired product **48j**, though in moderate yield (55%).

4.2.3.3. Nature and characterization of products 48



The structure of the products were unambiguously deduced by NMR spectroscopy (^{1}H and ^{13}C-NMR) and HRMS data. In mass spectra (ESI, positive), the molecular ion peak of all compounds appeared as protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^{1}H NMR, the proton adjacent to the *N*-atom appears as singlet at around 6.77-6.68 ppm. The two methylene protons appear as singlet at around 4.45-4.21 ppm. The protons of the amine group show a broad singlet around 3.96-3.62 ppm. The methyl protons of the tosyl group appear at 2.33-2.28 ppm as singlet. Furthermore, the ^{13}C NMR gave additional support in favor of the structures.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compounds **48a** and **48h**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolved in minimum volume of petroleum ether/ dichoromethane mixture. The ORTEP diagrams of the crystal structures are shown in Figures 3 and 4.

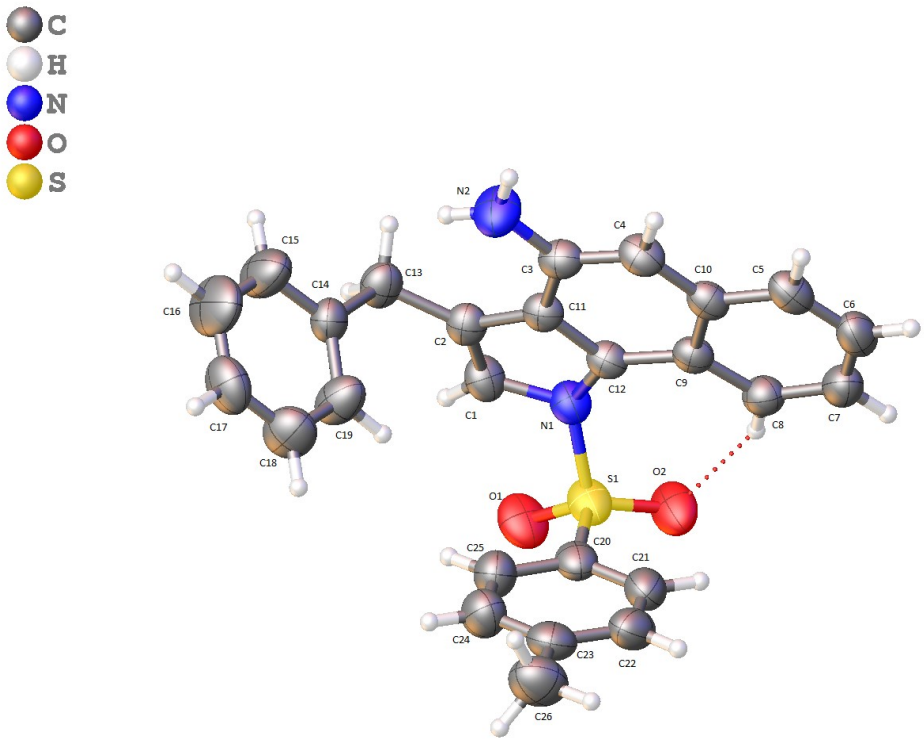


Figure 3. ORTEP Diagram (thermal ellipsoid plot) of Product **48a** (drawn at 50% probability level)

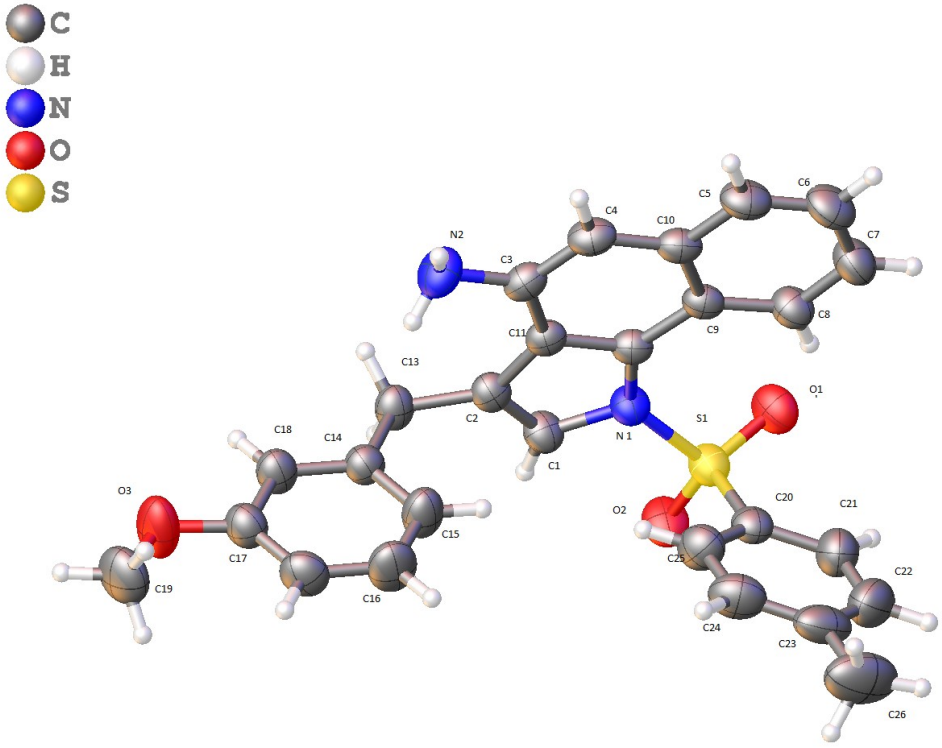


Figure 4. ORTEP Diagram (thermal ellipsoid plot) of Product **48h** (drawn at 50% probability level)

Table 2: Important crystal data of product **48a**

Empirical formula	$C_{26}H_{22}N_2O_2S$
Formula weight	426.51
Temperature	296 K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.2355(18) Å α = 101.008(4) °
	b = 10.5110(19) Å β = 110.170(4) °
	c = 11.803(2) Å γ = 93.425(4) °
Volume	1045.8(3) $Å^3$
Z	2
Density (calculated)	1.354 g/cm^3
Absorption coefficient (Mu)	0.181mm^{-1}
F(000)	448.0
Theta range for data collection	2.37 ° to 26.97 °
Index ranges	-10<=h<=10, -12<=k<=12, -14<=l<=14
Reflection collected	20661
Independent reflections	3667 [R(int) = 0.0269]
Completeness to theta= 25.44°	99.9 %
Absorption correction	none
Max. and min. transmission	1.0 and 0.8
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3667 /0/281
Goodness-of-fit on F^2	0.844
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.1184
R indices (all data)	R1 = 0.0456, wR2 = 0.1304
Largest diff. peak and hole	0.245 & - 0.224e.A^{-3}

The single crystal of the product **48a** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of petroleum ether and dichoromethane mixture.The crystal data has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1897157**.

Table 3: Important crystal data of product **48h**

Empirical formula	$C_{27}H_{24}N_2O_3S$
Formula weight	456.54
Temperature	296 K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.1850(5)Å α = 66.694(2)°
	b = 10.8127(6)Å β = 82.606(2)°
	c = 13.1573(7)Å γ = 70.197(2)°
Volume	1129.10(11) $Å^3$
Z	2
Density (calculated)	1.343g/cm^3
Absorption coefficient (Mu)	0.176 mm^{-1}
F(000)	480.0
Theta range for data collection	2.18 ° to 27.449 °
Index ranges	-11<=h<=11, -13<=k<=13, -17<=l<=17
Reflection collected	25612
Independent reflections	5136 [R(int) = 0.0276]
Completeness to theta= 25.44°	99.6 %
Absorption correction	multi-scan
Max. and min. transmission	1.0 and 0.7
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5136 /0/301
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0442, wR2 = 0.1218
R indices (all data)	R1 = 0.0491, wR2 = 0.1290
Largest diff. peak and hole	0.403 &-0.237 e.A^{-3}

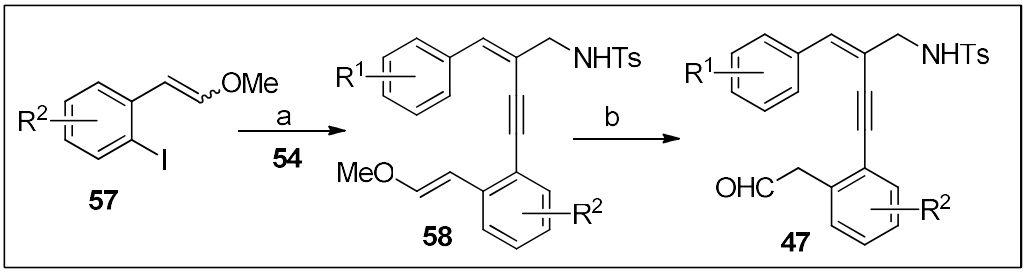
The single crystal of the product **48h** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Pet-ether/ dichoromethane mixture. The crystal data has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1897158**.

4.2.4. Extension of the methodology for the synthesis of Benzo[g]indole Derivatives 49

Encouraged by the above results, we decided to turn our attention for the synthesis of benzo[*g*]indole derivatives **49** from the en-yne substrate **47**, obtained by replacing the cyano group (X = CN) of **46** by aldehyde group (X = CHO).

4.2.4.1. Synthesis of starting material 47

The requisite starting material **47** was synthesized in few steps starting from commercially available 2-iodo benzaldehyde derivatives. Compound **57**[17b] was synthesized by executing *Wittig reaction* on 2-iodobenzaldehyde derivative which undergo "*Sonogashira reaction*" with previously synthesized **54** derivatives (see **Scheme 16**) to afford derivatives of **58**. Finally exposure of **58** under acidic conditions led to the formation of the desired starting material **47**.



Scheme 18: Reagents and Conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 0 ^oC–rt, 2-7 h, 60-85%; (b) *p*-TsOH.H_2O, Acetone, 0 ^oC-rt, 3.5-5 h, 47-70%.

4.2.4.2. Synthesis of Benzo[*g*]indoles 49 in one-pot

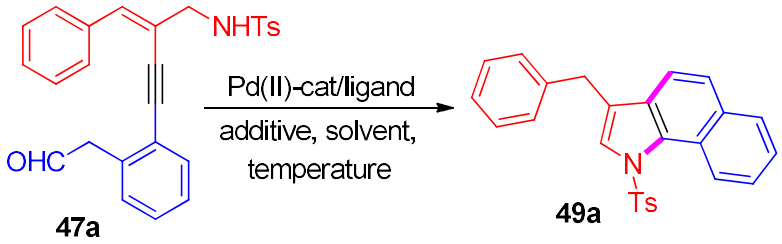
4.2.4.2.1. Optimization of reaction conditions for the synthesis of Benzo[*g*]indole 49a[a]

In order to get the convenient reaction conditions for the transformation of the substrate **47a** (R^1 = Ph, R^2 = H, X = NTs, Y = CHO) to **49a**, **47a** was treated under various reaction conditions by changing the reaction parameters, e.g., catalyst, ligand, additive, solvent temperature etc. The outcomes are depicted under Table 4.

Unlike the case of **46a**, this reaction proved to be inert under the optimized conditions of Table 1, affording only trace amount of product **49a** even after heating for 12 h (entry 1 of Table

4). However, conducting the reaction in 1,4-dioxane using $Pd(OAc)_2$/bpy or $Pd(OAc)_2$bpy afforded the product **49a** to the extent of 25-47% (Table 4, entries 2 and 3). When the additive was changed to AcOH-H_2O instead of *p*-TsOH·H_2O, no desired product was formed (Table 4, entry 4), suggesting the necessity of *p*-TsOH in this reaction. Gratifyingly, executing this reaction in 1,2-dimethoxyethane (DME) led to the formation of **49a** within 2 h with 61% yield (Table 4, entry 5). As changing the solvent to a more polar one such as NMA failed to deliver the desired product **49a** (Table 4, entry 6). Thus, the reaction conditions of entry 5 of Table 4 emerged to be optimal.

Table 4: Optimization of reaction conditions for Benzo[*g*]indole 49a[a]



Entry	Catalyst	Ligand	Additive	Solvent	Temp (°C)	Time (h)	Yield (%) 49a
1.	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	THF	Reflux	12	trace
2.	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	1,4-dioxane	80	3	25
3.	$Pd(OAc)_2$ bpy	---	*p*-TsOH.H_2O	1,4-dioxane	80	3.5	47
4.	$Pd(OAc)_2$ bpy	---	AcOH-H_2O (1:1)	1,4-dioxane	100	4	nr
5.	**$Pd(OAc)_2$bpy**	**---**	**p-TsOH.H_2O**	**DME**	**Reflux**	**2**	**61**
6.	$Pd(OAc)_2$	bpy	*p*-TsOH.H_2O	NMA	80	3	nr

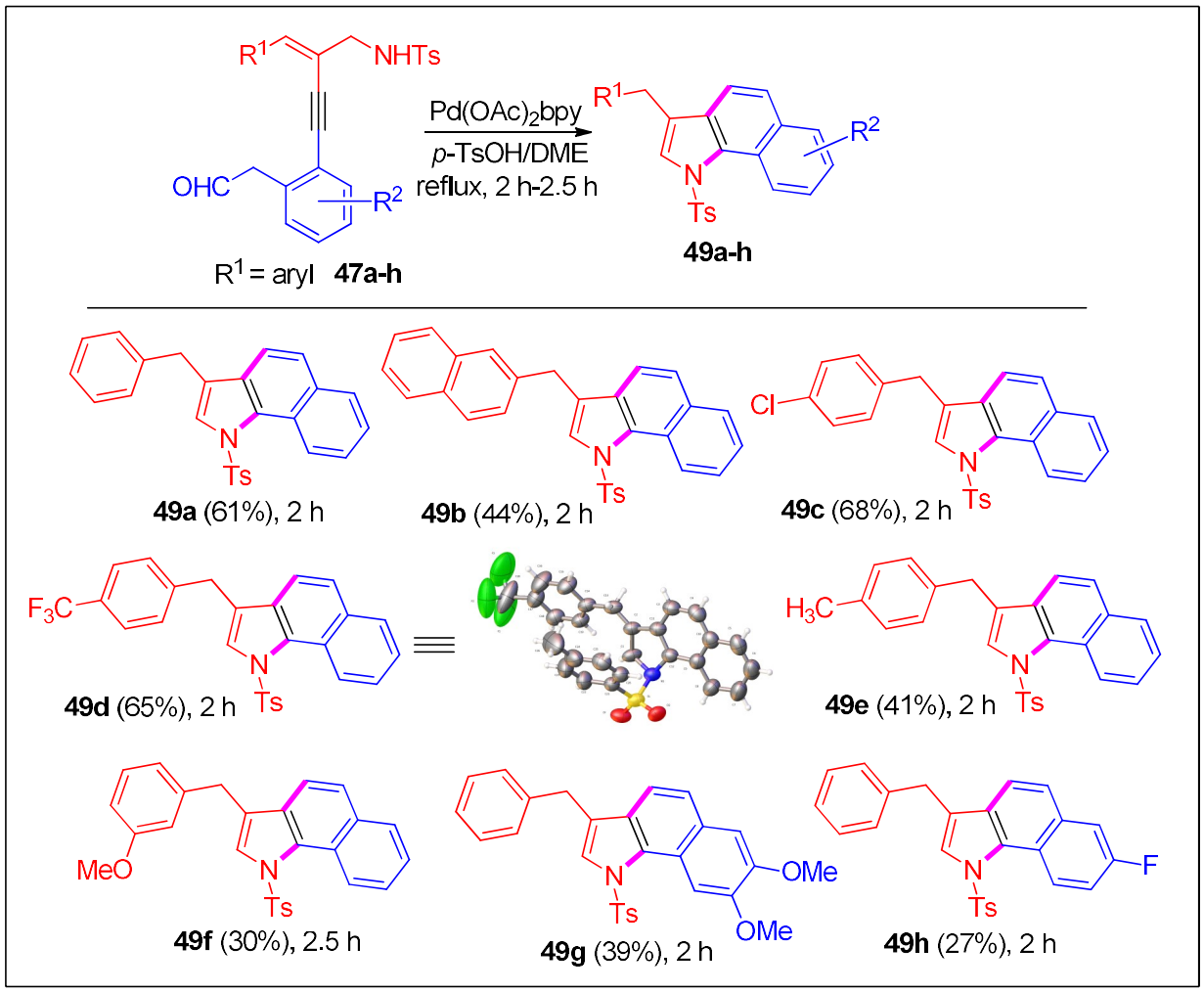
[a]Reaction Conditions: A mixture of **47a** (0.14 mmol), catalyst (5 mol %), ligand (10 mol %), and additive (1.5 equiv) was heated at mentioned temperature under argon atmosphere.

4.2.4.2.2. Scope of the reaction

We thereafter set out to explore the scope and limitation of this reaction, as shown in **Scheme 19**. This revealed that the presence of the bulky naphthyl ring in substrate **47b** produced the desired product **49b** in moderate yield (44%), presumably due to the steric effect of this ring.

Also, contrary to our previous observations, a reactant carrying a heteroaryl ring (R^1 = thienyl/ furanyl, etc.) in place of naphthyl turned out to be inert even after prolonged heating (>12 h), although the reason is not very clear at this moment. Furthermore, incorporation of the electron-withdrawing group (viz., Cl/CF_3) at the *para* position of the benzene ring in substrate **47c/47d** facilitated the reaction, producing the product **49c/49d** in good yield (68%/65%). In contrast, the presence of an electron-donating group (viz., CH_3, OMe) in the same phenyl ring of the substrate (**47e/47f**) somewhat hindered the reaction, leading to the formation of the respective

Scheme 19: Synthesis of Benzo[g]indole Derivatives 49a–h[a]

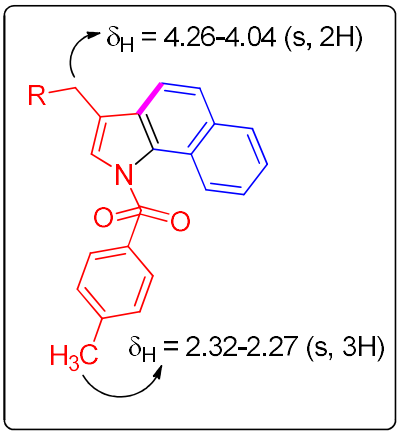


[a]Reaction Conditions: **47a** (0.23 mmol), $Pd(OAc)_2bpy$ (5 mol %), *p*-TsOH.H_2O (1.5 equiv) were refluxed in DME (3 mL) under argon atmosphere.

products **49e** and **49f** in moderate yields (30-41%), while an electron-withdrawing (viz., F) or electron-donating group (viz., OMe) in the other benzene ring furnished product **49g** or **49h** within 2 h though in modest yields (27-39%).

4.2.4.2.3.Nature and characterization of products 49

The structure of the products was unambiguously deduced by NMR spectroscopy (^{1}H, ^{13}C) and HRMS data. In mass spectra (ESI, positive mode), the molecular ion peak of all the compounds appeared as protonated $[M+H]^{+}$ and/or sodiated $[M+Na]^{+}$ ion. In ^{1}H NMR, the methylene protons (-CH_2R) and the methyl (CH_3) protons of the tosyl group appear as singlet at around 4.26-4.04 and 2.32-2.27 ppm, respectively. Furthermore, the ^{13}C NMR spectra gave additional support in the favor of the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **49d**. The single crystal of the products was obtained by slow evaporation of the solution of the product dissolving in minimum volume of petroleum ether/ ethyl acetate mixture. The ORTEP diagram of the crystal structure is shown in Figure 5.

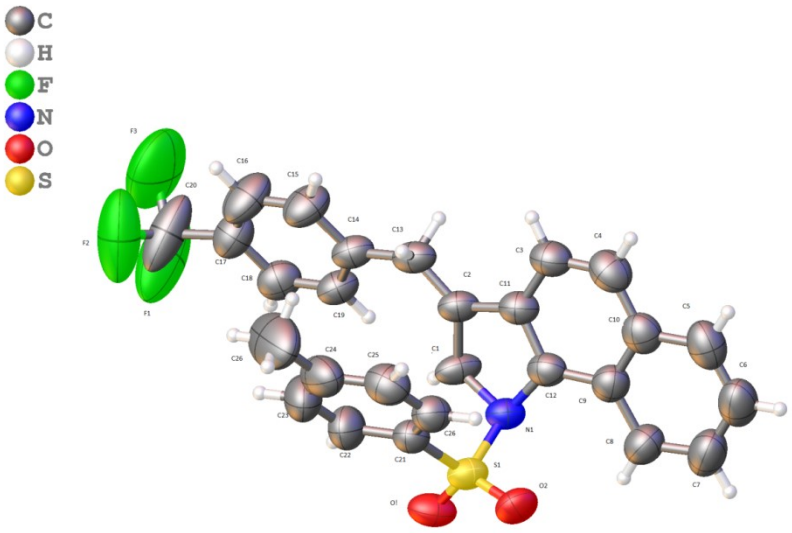


Figure 5. ORTEP Diagram (thermal ellipsoid plot) of Product **49d** (drawn at 50% probability level)

Table 5: Important crystal data of product **49d**

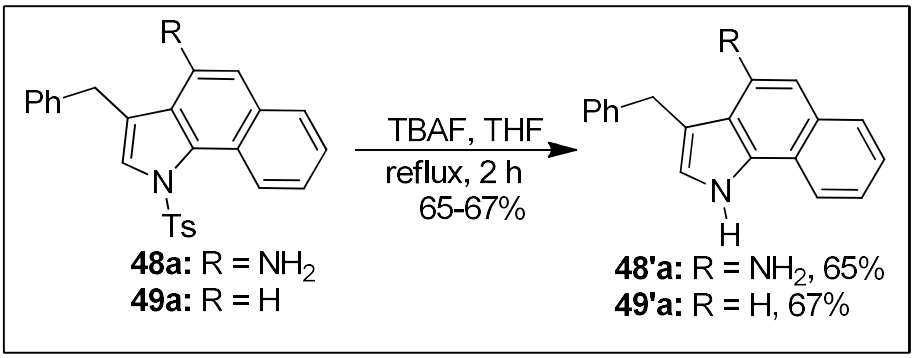
Empirical formula	$C_{27}H_{20}F_3NO_2S$
Formula weight	456.54
Temperature	296 K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P 1 21/c 1
Unit cell dimensions	a = 12.690(9) Å, $\alpha = 90^o$
	b = 11.602(8) Å, $\beta = 95.24(1)^o$
	c = 16.618(11) Å, $\gamma = 90^o$
Volume	2436 (3)$Å^3$
Z	4
Density (calculated)	1.307 g/cm^3
Absorption coefficient (Mu)	0.180 mm^{-1}
F(000)	992.0
Theta range for data collection	2.38 ^{o} to 23.34^o
Index ranges	-16<=h<=15, -14<=k<=14, -21<=l<=21
Reflection collected	30428
Independent reflections	5464 [R(int) = 0.0766]
Completeness to theta= 25.44^o	97.9 %
Absorption correction	multi-scan
Max. and min. transmission	1.0 and 0.7
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5137 /105/309
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0811, wR2 = 0.2393
R indices (all data)	R1 = 0.1562, wR2 = 0.2925
Largest diff. peak and hole	0.706 & -0.452e.A^{-3}

The single crystal of the procuct **49d** was obtained by slow evaporation of the solvent when the compound was dissolved in minimum volume of Pet-ether/ ethyl acetate mixture The crystal data already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1897159.**

4.2.5. Synthesis of N-deprotected derivatives of 48 and 49

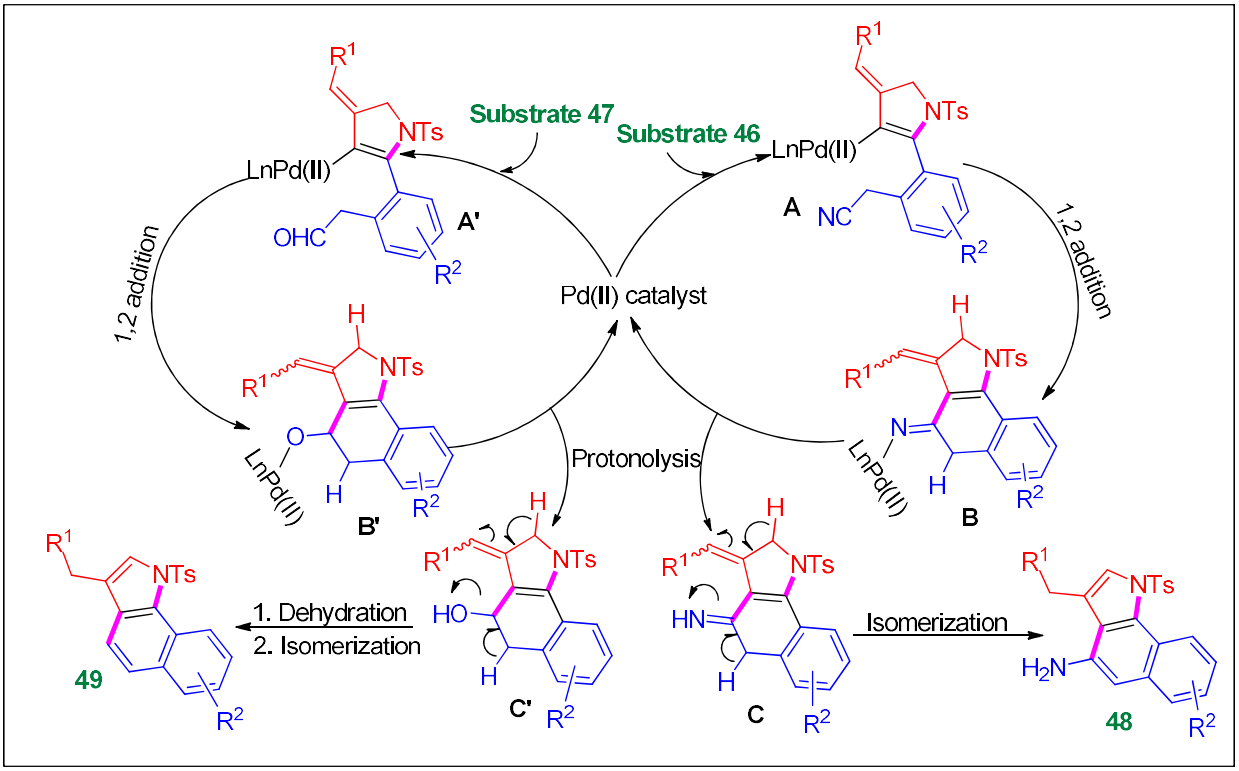
Benzo[*g*]indoles with free NH group are present in a large number of bioactive compounds.[5c,6a-b] Therefore we attempted to deprotect the tosyl group of products **48a** and **49a**, as depicted in **Scheme 20**. The detosylation was carried out successfully within 2 h using tetrabutylammonium fluoride (TBAF) in refluxing THF to furnish the products **48′a** and **49′a** with 65% and 67% yield respectively.

Scheme 20: Detosylation of Benzo[g]indoles 48a/49a



4.2.6. Plausible mechanism for the formation of products 48 and 49

A plausible reaction mechanism for the formationof the products are depicted in **Scheme 21**. At first Pd(II) activates the triple bond of substrates **46** and **47** which triggers the formation of intermediate and **A** and **A′** respectively via 5-*endo-dig* heteroannulation. Subsequent intramolecular 1,2-addition of the carbon-palladium bond of intermediate **A/A′** onto suitably placed carbon-heteroatom multiple bond (-C≡N/-C=O) leads to the formation of intermediate **B** and **B′** respectively. Next, protonolysis of **B** and **B′** delivered intermediate **C** and **C′**. Finally isomerization of intermediate **C** afforded product **48**; whereas dehydration and isomerization of **C′** leads to the formation of product **49**.



Scheme 21: A plausible reaction mechanism for the formation products **48** and **49**

4.2.7. Conclusion

In conclusion, a convenient Pd(II)-catalyzed cascade reaction for a facile and general synthesis benzo[g]indole derivatives **48** and **49** from simple and readily available substrates have been disclosed utilizing low cost metal catalyst. The method constitutes a fast intramolecular assembly involving *trans*-aminopalladation of alkynes, followed by nucleophilic 1,2-addition to cyano/ aldehyde group. The reactions are operationally simple, compatible with a range of functional groups, and atom economical in nature. We believe that this novel method will find significant applications in organic, medicinal, and material chemistry as well.

4.2.8. Experimental section

4.2.8.1. General Information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60-80 °C. Dichloromethane (DCM) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane was distilled over sodium

and benzophenone. Commercial grade dry dimethylformamide (DMF), dimethylacetamide (DMA), N-methylacetamide (NMA), and 1,2-dimethoxyethane (DME) were used as solvents. All reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance or iodine exposure. For purification, column chromatography was performed using 100-200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 300, 400 and 600 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are given from TMS (δ = 0.00) in parts per million (ppm) with reference to the residual nuclei of the deuterated solvent used [$CDCl_3$: ^{1}H NMR δ = 7.26 ppm (s); ^{13}C NMR δ = 77.0 ppm]. Coupling constants (*J*) are expressed in hertz (Hz), and spin multiplicities are given as singlet (s), doublet (d), double doublet (dd), triplet (t), triple doublet (td), quartet (q), multiplet (m), and broad (br), apparent (app). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using electrospray ionization (ESI) time-of-flight or electron ionization (EI) mode.

4.2.8.2. X-Ray crystallographic information of products 48a, 48h and 49d

Single crystal of products **48a**, **48h** and **49d** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether or (for product **48a**, **48h**) or ethyl acetate-petroleum ether (for product **49d**). A single crystal of **48a**, **48h** and **49d** were attached to a glass fiber with epoxy glue and transferred to a X-ray diffractometer, equipped with a graphite monochromator. Diffraction data of products **48a**, **48h** and **49d** were measured with MoKα radiation (λ = 0.71073 Å) at 296 K. The structure was solved by direct methods using the SHELXS-97 program.[18] Refinements were carried out with a full matrix least squares method against F2 using SHELXL-97.[19] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The ORTEP diagrams and important crystal data of products**48a**, **48h** and **49d** are provided earlier.

4.2.8.3. General procedure for the preparation of the starting materials 46

Synthesis of α,β- unsaturated esters **50:**

To a well-stirred and cooled (-5 °C) solution of (ethoxycarbonylmethyl) triphenylphosphonium bromide (500 mg, 1.17 mmol) in dry MeOH (10 mL), molecular iodine (572 mg, 2.26 mmol) and freshly activated K_2CO_3 (160 mg, 1.17 mmol) were added successively. The temperature of the reaction mixture was strictly maintained between -5 and 5 °C (using ice-salt mixture) over a period of 1.5 h, resulting in the formation of a brown-colored suspension. Next, the aldehyde derivatives (0.98 mmol), tetrabutylammonium bromide (16.1 mg, 0.05 mmol) and K_2CO_3 (22.3 mg, 0.16 mmol) were added successively to the preformed brown suspension and stirred for few minutes after that the mixture was heated at 40 °C for another 2-8 h. During this time period, additional amount of K_2CO_3 (2 × 0.05 mmol) was added in two portions at 2 h intervals. Upon completion of reaction (TLC), MeOH was evaporated under vacuum and the crude residue was treated with 2 M sodium thiosulfate solution to remove the excess iodine. It was then extracted with ethyl acetate (2 × 20 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography eluting with 10-40% ethyl acetate-petroleum ether to obtain *α,β*-unsaturated esters **50**in 60-75% yield.

Synthesis of α,β- unsaturated alcohols **51:**

To a well-stirred,cooled (using ice-salt mixture) solution of the ester derivatives **50** (0.69 mmol, 1.0 equiv) in dry DCM (5 mL), DIBAL hydride (1.2 M in toluene, 1.74 mL, 2.08 mmol, 3 equiv) was added drop-wise and the mixture was allowed to stir for 2-3 h at the same temperature. Upon completion of the reaction (TLC), the mixture was quenched with 15% sodium hydroxide solution (15 mL) and diluted with DCM (20 mL). Next, the resulting thick reaction mixture was filtered through a bed of celite to obtain a clear layer separation. The organic layer was taken out and washed successively with water (8 mL) and brine solution (8 mL). The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by silica gel (100-200 mesh) column chromatography using 15-25% ethyl acetate in pet-ether (v/v) as eluent. The pure *α,β*- unsaturated alcohols **51** were obtained in 42-76% yields.

Synthesis of azide derivatives **52:**

To a well-stirred ice cooled solution of **51** (3.85 mmol, 1 equiv) in dry DCM (10 mL), Et_3N (643 µL, 4.62 mmol, 1.2 equiv) was added drop-wise and the stirred for 10 min. Next, methanesulfonyl chloride (293 µL, 3.85 mmol, equiv) was added drop-wise to the solution at 0 °C, and the temperature of the reaction was increased up to rt with continuation of the stirring. After completion of reaction (TLC), the mixture was quenched with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo* to obtain a crude mixture. The crude product (without purification) was dissolved in dry DMF (5 mL) and treated with NaN_3 (1.5 equiv), and the mixture was stirred at rt for 1-2.5 h. After completion of reaction (TLC), the solvent (DMF) was removed in *vacuo*, diluted with water, and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The resulting crude mixture was subjected to silica gel (100-200 mesh) column chromatography and eluted with 5-10% ethyl acetate in petroleum ether (v/v) to obtain the pure azide derivatives **52** in 50-93% yields.

Synthesis of amine derivatives **53:**

To a well-stirred solution of azide derivative **52** (2.81 mmol, 1 equiv) in MeOH/MeCN (MeOH/MeCN = 1:1, 10 mL), N,N diisopropylethylamine (1.5 mL, 8.42 mmol, 3 equiv) was added dropwise and the mixture was stirred at rt for 5 min. Next 1,3-propanedithiol (0.6 mL, 5.61 mmol, 2 equiv) was added dropwise to the mixture and the whole system was allowed to stir at rt for another 2-4 h. After completion of reaction (TLC), the reaction was quenched with water (20 mL) and extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure; and the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 3-5% methanol in chloroform (v/v) to obtain the desired pure amine derivatives **53** in 64-95% yields.

Synthesis of tosylated derivatives **54:**

To a well-stirred and cooled solution of amine derivative **53** (2.32 mmol, 1 equiv) in dry DCM (8 mL), pyridine was added (242 µL, 3.01 mmol, 1.3 equiv) drop-wise. Thereafter, *p*-toluenesulfonyl chloride (529 mg, 2.78 mmol, 1.2 equiv) was added portion-wise at the same

temperature and the reaction mixture was stirred at rt for 1-4 h. Upon completion of the reaction (TLC), the mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Then, the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-26% ethyl acetate in petroleum ether (v/v) to obtain the pure tosylated products **54** in 72-90% yields.

Synthesis of acetylene derivatives **55:**

To a well-stirred solution of **54** derivatives (1.21 mmol, 1 equiv) in Et_3N/DMF (Et_3N/DMF = 2:1, 3 mL), $PdCl_2(PPh_3)_2$ (25.4 mg, 0.036 mmol, 3 mol %) was added. The reaction mixture was then cooled to 0 °C and trimethylsilylacetylene (189 µL, 1.33 mmol, 1.1 equiv) and CuI (13.7 mg, 0.072 mmol, 6 mol %) were added subsequently to the mixture. After stirring it for few minutes at 0 °C, the temperature of the reaction was raised to rt and stirring was continued for 1.5-4 h. Upon completion of reaction (TLC), solvent was removed under reduced pressure and extracted with ethyl acetate (3 x 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 10-26% ethyl acetate in petroleum ether to obtain a silylated acetylenic intermediate (70-85% yields), which (1.04 mmol, 1 equiv) was later dissolved in dry MeOH (10 mL) and treated with K_2CO_3 (14.4 mg, 0.104 mmol, 0.1 equiv); the reaction mixture was then stirred at room temperature for 0.5-1.75 h until completion (TLC). The reaction was immediately quenched with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 10-30% ethyl acetate in petroleum ether (v/v) to obtain pure acetylene derivatives **55** in 85-96% yields.

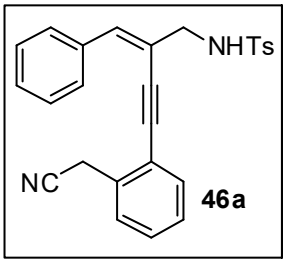
Synthesis of en-yne substrates **46:**

To a well-stirred solution of commercially available 2-iodophenylacetonitriles (0.41 mmol, 1 equiv) in Et_3N/DMF (Et_3N/DMF = 2:1, 2 mL), $PdCl_2(PPh_3)_2$ (8.6 mg, 0.012 mmol, 3 mol %) was added and the mixture was cooled to 0 °C and the acetylenic intermediate **55** (0.45 mmol, 1.1 equiv) was added drop-wise dissolving in Et_3N/DMF (Et_3N/DMF = 2:1) followed by

addition of CuI (4.6 mg, 0.024 mmol, 6 mol %). The temperature of the reaction was then increased to rt, and stirred for 1-8 h until completion of the reaction. Upon completion of reaction (TLC), the solvent was removed under reduced pressure and the crude material was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL); the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified by silica gel (100-200 mesh) column chromatography eluting with 10-30% ethyl acetate in petroleum ether (v/v) to obtain the requisite ene-yne substrates **46** in 60-96% yields.

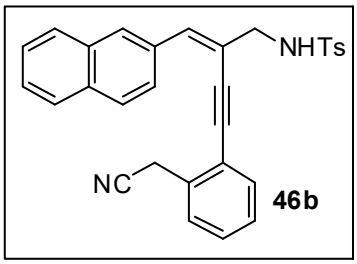
4.2.8.4. Spectral Data of Compounds 46a-j:

(E)-N-(2-Benzylidene-4-(2-(cyanomethyl)phenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (46a):



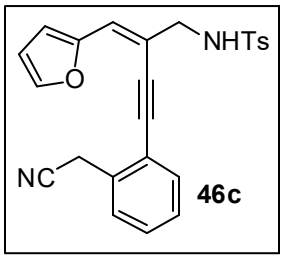
Pale yellow solid (105 mg, 60%), R_f = 0.35 (25% ethyl acetate in petroleum ether, v/v), mp 106-108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.77 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 6.9 Hz, 2H), 7.46-7.43 (m, 2H), 7.40-7.31 (m, 5H), 7.20 (d, J = 8.1 Hz, 2H), 6.69 (s, 1H), 5.29 (t, J = 6.0 Hz, 1H), 3.95 (d, J = 6.0 Hz, 2H), 3.79 (s, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 137.4, 137.3, 135.3, 132.6, 131.7, 129.6, 129.4, 128.9, 128.6, 128.4, 128.3, 128.2, 127.1, 122.3, 117.6, 116.6, 93.1, 49.9, 22.8, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{23}N_2O_2S$ $[M + H]^+$ 427.1480, found 427.1480.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(naphthalen-2-ylmethylene)but-3-yn-1-yl)-4 methylbenzene-sulfonamide (46b):



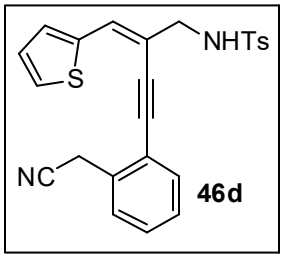
Light yellow solid (147 mg, 75%), R_f = 0.26 (25% ethyl acetate in petroleum ether, v/v), mp 150-152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.06 (s, 1H), 7.90-7.77 (m, 6H), 7.51-7.34 (m, 6H), 7.22 (d, J = 8.1 Hz, 2H), 6.85 (s, 1H), 5.11 (t, J = 6.3 Hz, 1H), 4.02 (d, J = 6.0 Hz, 2H), 3.81 (s, 2H), 2.32(s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 137.5, 137.4, 133.3, 133.0, 132.8, 132.6, 131.7, 129.6, 129.5, 128.7, 128.5, 128.3, 128.2, 127.8, 127.7, 127.2, 126.7, 126.5, 125.7, 116.8, 93.4, 93.3, 50.1, 22.9, 21.4; HRMS (ESI) m/z calcd for $C_{30}H_{24}N_2NaO_2S$ $[M + Na]^+$ 499.1456, found 499.1469.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(furan-2-ylmethylene)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46c):



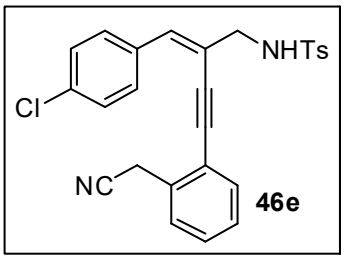
Brown solid (130 mg, 76%), R_f = 0.31 (25% ethyl acetate in petroleum ether, v/v), mp 102-104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.75 (d, J = 8.4 Hz, 2H), 7.48-7.31 (m, 5H), 7.21 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 3.3 Hz, 1H), 6.57 (s, 1H), 6.46-6.44 (m, 1H), 5.29-5.25 (m, 1H), 3.91 (s, 2H), 3.88 (d, J = 6.3 Hz, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 151.3, 143.4, 142.8, 137.2, 132.5, 131.8, 129.5, 129.4, 128.3, 128.1, 127.1, 124.9, 122.4, 117.8, 113.5, 111.9, 111.8, 94.2, 93.1, 49.0, 22.6, 21.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2NaO_3S$ $[M + Na]^+$ 439.1092, found 439.1092.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(thiophen-2-ylmethylene)-but-3-yn-1-yl)-4 methylbenzene-sulfonamide (46d):



Yellow solid (160 mg, 90%), R_f = 0.33 (25% ethyl acetate in petroleum ether, v/ v), mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.74 (d, J = 8.4 Hz, 2H), 7.58-7.55 (m, 1H), 7.47-7.36 (m, 3H), 7.32 (d, J = 5.1 Hz, 1H), 7.19-7.16 (m, 3H), 7.03-7.00 (m, 1H), 6.91 (s, 1H), 5.34 (t, J = 6.0 Hz, 1H), 3.92 (d, J = 6.3 Hz, 2H), 3.89 (s, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 143.4, 139.3, 137.4, 132.5, 131.7, 131.0, 130.6, 129.6, 129.5, 128.4, 128.2, 127.5, 127.1, 126.6, 122.4, 117.8, 113.6, 96.4, 93.3, 49.2, 23.0, 21.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2NaO_2S_2$ $[M + Na]^+$ 455.0864, found 455.0868.

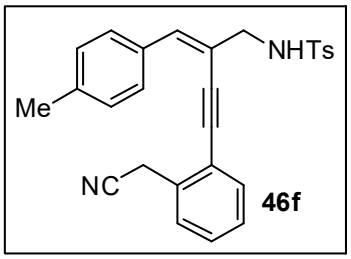
(E)-N-(2-(4-Chlorobenzylidene)-4-(2-(cyanomethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46e):



Pale yellow solid (165 mg, 87%), R_f = 0.33 (25% ethyl acetate in petroleum ether, v/v), mp 148-150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.46-7.31 (m, 6H), 7.22 (d, J = 7.8 Hz, 2H), 6.66 (s, 1H), 5.14 (t, J = 6.3 Hz, 1H), 3.95 (d, J = 6.3 Hz, 2H), 3.80 (s, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR

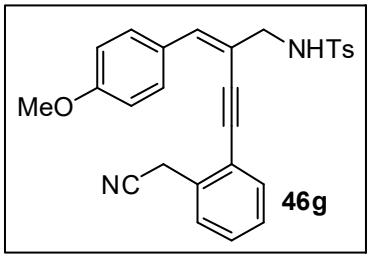
($CDCl_3$, 75 MHz) δ_C 143.4, 137.5, 135.8, 134.5, 133.7, 132.7, 131.7, 129.8, 129.7, 129.6, 128.6, 128.5, 128.3, 127.1, 122.2, 117.4, 117.3, 93.8, 92.8, 49.9, 22.9, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{21}ClN_2NaO_2S$ $[M + Na]^+$ 483.0910, found 483.0910.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(4-methylbenzylidene)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46f):



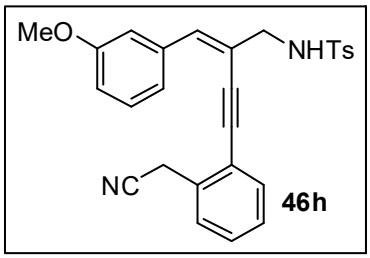
White solid (174 mg, 96%), R_f = 0.38 (25% ethyl acetate in petroleum ether, v/v), mp 116-118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.45-7.43 (m, 2H), 7.39-7.29 (m, 2H), 7.20-7.14 (m, 4H), 6.64 (s, 1H), 5.40 (brs, 1H), 3.92 (d, J = 6.3 Hz, 2H), 3.79 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 143.3, 139.0, 137.4, 137.3, 132.5, 131.6, 129.5, 129.3, 128.9, 128.5, 128.2, 128.1, 127.1, 122.3, 117.7, 115.4, 93.3, 92.9, 49.9, 22.7, 21.4, 21.3; HRMS (ESI) m/z calcd for $C_{27}H_{24}N_2NaO_2S$ $[M + Na]^+$ 463.1456, found 463.1458.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(4-methoxybenzylidene)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46g):



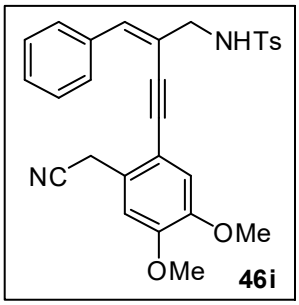
Yellow solid (173 mg, 92%), R_f = 0.29 (25% ethyl acetate in petroleum ether, v/v), mp 118-120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.76 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.46-7.43 (m, 2H), 7.40-7.31 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.62 (s, 1H), 5.25-5.23 (m, 1H), 3.91 (d, J = 6.3 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 2H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (CDCl3, 75 MHz) δ_C 160.0, 143.4, 137.5, 137.1, 132.6, 131.6, 130.2, 129.6, 129.3, 128.4, 128.2, 128.1, 127.2, 122.5, 117.7, 113.9, 113.7, 93.6, 92.8, 55.3, 50.1, 22.9, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{24}N_2NaO_3S$ $[M + Na]^+$ 479.1405, found 479.1409.

(E)-N-(4-(2-(Cyanomethyl)phenyl)-2-(3-methoxybenzylidene)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46h):



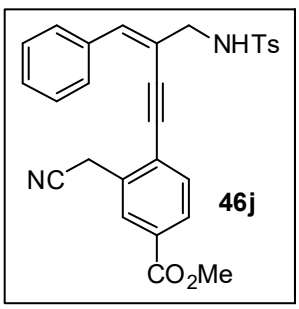
Pale yellow solid (163 mg, 87%), R_f = 0.29 (25% ethyl acetate in petroleum ether, v/v), mp 124-126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.77 (d, J = 8.1 Hz, 2H), 7.48-7.28 (m, 6H), 7.26-7.15 (m, 3H), 6.87 (dd, J = 8.1, 1.8 Hz, 1H), 6.67 (s, 1H), 5.13 (t, J = 6.4 Hz, 1H), 3.95 (d, J = 6.3 Hz, 2H), 3.83 (s, 2H), 3.80 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 159.3, 143.4, 137.4, 137.1, 136.6, 132.6, 131.8, 129.6, 129.5, 129.3, 128.2, 128.1, 127.1, 122.2, 121.4, 117.7, 117.0, 114.2, 113.9, 93.5, 93.0, 55.2, 49.9, 22.9, 21.4; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ $[M + H]^+$ 457.1586, found 457.1590.

(E)-N-(2-Benzylidene-4-(2-(cyanomethyl)-4,5-dimethoxyphenyl)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (46i):



Yellow solid (162 mg, 81%), R_f = 0.13 (25% ethyl acetate in petroleum ether, v/ v), mp 140-142 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.78 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 6.9 Hz, 2H), 7.39-7.31 (m, 3H), 7.26-7.23 (m, 2H), 6.95 (s, 1H), 6.90 (s, 1H), 6.65 (s, 1H), 5.05 (t, J = 6.4 Hz, 1H), 3.95-3.94 (m, 5H), 3.90 (s, 3H), 3.75 (s, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 150.3, 148.6, 143.5, 137.6, 136.6, 135.6, 129.7, 128.8, 128.6, 128.3, 127.2, 125.1, 118.0, 117.1, 114.9, 114.4, 111.2, 93.7, 91.6, 56.3, 56.2, 50.0, 22.4, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{26}N_2NaO_4S$ $[M + Na]^+$ 509.1511, found 509.1514.

(E)-Methyl 3-(cyanomethyl)-4-(3-((4-methylphenylsulfonamido)methyl)-4-phenylbut-3-en-1-yn-1-yl)benzoate (46j):



Light yellow solid (175 mg, 88%), R_f = 0.22 (25% ethyl acetate in petroleum ether, v/v), mp 128-130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.09 (s, 1H), 7.98 (dd, J = 8.1, 1.2 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.66-7.63 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.37-7.32 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 5.33 (t, J = 6.4 Hz, 1H), 3.96-3.94 (m,

5H), 3.83 (s, 2H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 165.8, 143.5, 138.5, 137.4, 135.1, 132.7, 132.0, 130.5, 129.6, 129.5, 129.3, 129.1, 128.7, 128.4, 127.1, 126.8, 117.2, 116.4, 96.0, 92.2, 52.5, 49.8, 22.8, 21.4; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_4S$ $[M + H]^+$ 485.1535, found 485.1539.

4.2.8.5. General Procedure for the Synthesis of Starting Material 47:

Synthesis of masked aldehyde derivatives **58:**

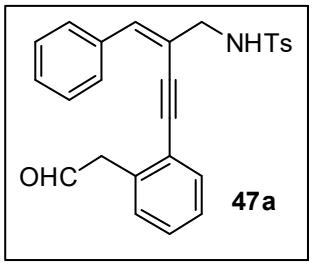
To a well-stirred solution of **57**[17b](0.77 mmol, 1 equiv) in dry Et_3N/DMF (3:1, 0.7 mL), $Pd(PPh_3)_2Cl_2$ (16.2 mg, 0.023 mmol, 3 mol %) was added and the mixture was cooled to 0 °C; thereafter, a solution of **54** (0.85 mmol, 1.1 equiv) dissolved in Et_3N/DMF (2:1, 0.6 mL] was added drop-wise followed by the addition of and CuI (8.74 mg, 0.046 mmol, 6 mol %) and then whole mixture was allowed to rotate at rt for 2-7 h. After completion of the reaction (TLC), solvent was removed in *vacuo*, diluted with water (15 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. Finally, the crude product was subjected to silica gel (100-200 mesh) column chromatography and eluted with 10-15% ethyl acetate in petroleum ether (v/v) to obtain the masked aldehyde derivatives **58** in 60-85% yields.

Synthesis of ene-yne substrates **47:**

To a well-stirred and cooled (0 °C) solution of the masked aldehydes **58** (0.45 mmol, 1 equiv) in a minimum amount of dry acetone (3 mL), *p*-TsOH·H_2O (0.72 mmol, 1.6 equiv, 136.8 mg) was added portion-wise and the temperature of the mixture was allowed to reach rt with continuation of the stirring for another 3.5-5 h. After completion of reaction (TLC), the reaction mixture was neutralized with dilute sodium bicarbonate solution and extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*, and the crude residue was subjected to silica gel (100-200 mesh) column chromatography eluting with 17-30% ethyl acetate in petroleum ether (v/v) to obtain the desired starting materials **47** in 47-70% yields.

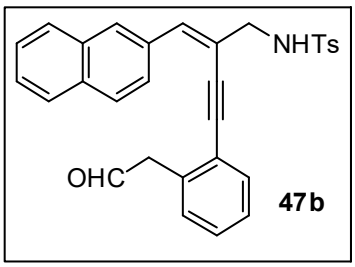
4.2.8.6. Spectral Data of Compounds 47a-h:

(E)-N-(2-Benzylidene-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (47a):



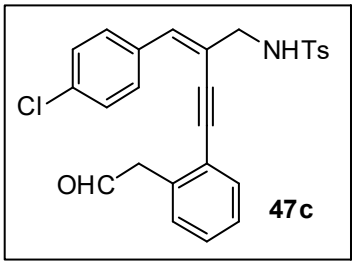
White solid (118 mg, 61%), R_f = 0.22 (20% ethyl acetate in petroleum ether, v/v), mp 94-96 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.2 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.39-7.28 (m, 6H), 7.19 (d, J = 7.8 Hz, 2H), 6.62 (s, 1H), 5.46 (t, J = 6.0 Hz, 1H), 3.93 (d, J = 6.6 Hz, 2H), 3.85-3.84 (m, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 143.2, 137.6, 136.9, 135.4, 133.7, 132.6, 130.5, 129.5, 129.3, 128.7, 128.6, 128.2, 127.7, 127.2, 123.5, 116.6, 94.4, 91.7, 50.1, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{23}NNaO_3S$ $[M + Na]^+$ 452.1296, found 452.1298.

(E)-4-Methyl-N-(2-(naphthalen-2-ylmethylene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)benzene-sulfonamide (47b):



Pale yellow solid (112 mg, 52%), R_f = 0.19 (20% ethyl acetate in petroleum ether, v/v), mp 108-110 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.4 Hz, 1H), 8.06 (s, 1H), 7.86-7.84 (m, 1H), 7.82-7.78 (m, 5H), 7.51-7.47 (m, 3H), 7.40-7.37 (m, 1H), 7.35-7.33 (m, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 6.77(s, 1H), 5.56 (t, J = 6.3 Hz, 1H), 3.99 (d, J = 6.6 Hz, 2H), 3.87 (d, J = 2.4 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 143.2, 137.7, 136.9, 133.7, 133.3, 133.1, 133.0, 132.5, 130.5, 129.5, 129.4, 128.6, 128.2, 127.8, 127.7, 127.6, 127.2, 126.6, 126.4, 125.8, 123.5, 117.0, 94.6, 92.1, 50.2, 49.7, 21.4; HRMS (ESI) m/z calcd for $C_{30}H_{25}NNaO_3S$ $[M + Na]^+$ 502.1453, found 502.1456.

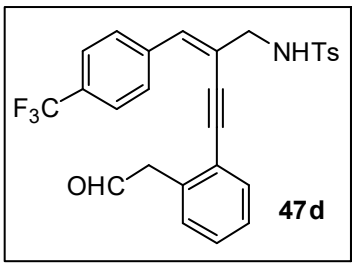
(E)-N-(2-(4-Chlorobenzylidene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (47c):



White solid (137 mg, 66%), R_f = 0.20 (20% ethyl acetate in petroleum ether, v/v), mp 136-138 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.1 Hz, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.59 (d,

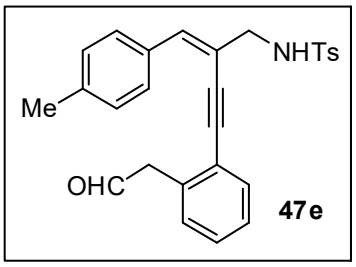
J = 8.4 Hz, 2H), 7.45-7.43 (m, 1H), 7.41- 7.38 (m, 1H), 7.35-7.33 (m, 1H), 7.32-7.30 (m, 3H), 7.19 (d, J = 7.8 Hz, 2H), 6.58 (s, 1H), 5.50 (t, J = 6.6 Hz, 1H), 3.92 (d, J = 6.6 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 143.3, 137.7, 135.4, 134.3, 133.8, 133.6, 132.6, 130.6, 129.8, 129.6, 129.5, 128.4, 127.8, 127.2, 123.3, 117.4, 95.1, 91.4, 50.0, 49.7, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{22}ClNNaO_3S$ $[M + Na]^+$ 486.0907, found 486.0908.

(E)-4-Methyl-N-(4-(2-(2-oxoethyl)phenyl)-2-(4-(trifluoromethyl)-benzylidene)but-3-yn-1-yl)benzene-sulfonamide (47d):



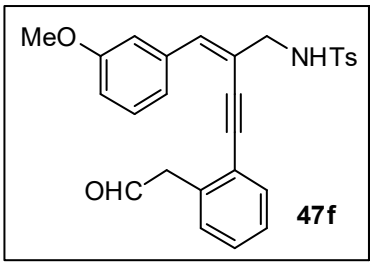
White solid (155 mg, 70%), R_f = 0.30 (25% ethyl acetate in petroleum ether, v/v), mp 154-156 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, J = 2.1 Hz, 1H), 7.78-7.74 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 7.8, 0.9 Hz, 1H), 7.41-7.39 (m, 1H), 7.35-7.30 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 5.67 (t, J = 6.6 Hz, 1H), 3.94 (d, J = 6.6 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 2.31 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 143.3, 138.8, 137.7, 134.8, 133.7, 132.6, 130.6, 130.1 (q, J_{C-F} = 32.3 Hz), 129.7, 129.5, 128.7, 127.8, 127.2, 125.1 (q, J_{C-F} = 3.6 Hz), 123.9 (app q, J_{C-F} = 270.5 Hz), 123.1, 119.5, 95.5, 91.1, 49.9, 49.7, 21.3; HRMS (ESI) m/z calcd for $C_{27}H_{22}F_3NNaO_3S$ $[M + Na]^+$ 520.1170 found, 520.1169.

(E)-4-Methyl-N-(2-(4-methylbenzylidene)-4-(2-(2-oxoethyl)-phenyl)but-3-yn-1-yl)benzene-sulfonamide (47e):



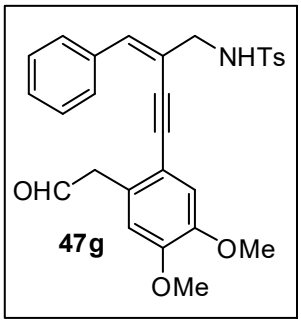
White solid (119 mg, 60%), R_f = 0.22 (20% ethyl acetate in petroleum ether, v/v), mp 96-98 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.67-9.66 (m, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.37-7.26 (m, 3H), 7.18 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.59 (s, 1H), 5.53 (t, J = 6.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 2H), 3.85 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.2, 143.2, 138.8, 137.6, 137.0, 133.7, 132.6, 132.5, 130.4, 129.5, 129.2, 128.9, 128.6, 127.6, 127.2, 123.6, 115.5, 94.4, 92.0, 50.1, 49.6, 21.4, 21.3; HRMS (ESI) m/z calcd for $C_{27}H_{25}NNaO_3S$ $[M + Na]^+$ 466.1453 found 466.1455.

(E)-N-(2-(3-Methoxybenzylidene)-4-(2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (47f):



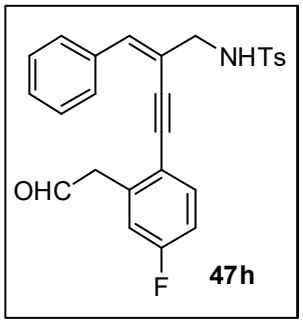
Yellow liquid (97 mg, 47%), R_f = 0.15 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66-9.65 (m, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.37-7.34 (m, 1H), 7.31-7.29 (m, 2H), 7.27-7.23 (m, 2H), 7.19-7.17 (m, 3H), 6.84 (dd, J = 7.8, 2.1 Hz, 1H), 6.60 (s, 1H), 5.62 (t, J = 6.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 2H), 3.86- 3.85 (m, 2H), 3.77 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 159.3, 143.2, 137.6, 136.7, 133.8, 132.5, 130.5, 129.5, 129.3, 129.2, 127.6, 127.2, 123.4, 121.4, 117.0, 114.2, 113.9, 94.8, 91.7, 55.2, 50.0, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{27}H_{25}NNaO_4S$ $[M + Na]^+$ is 482.1402, found 482.1407.

(E)-N-(2-Benzylidene-4-(4,5-dimethoxy-2-(2-oxoethyl)phenyl)-but-3-yn-1-yl)-4-methylbenzene-sulfonamide (47g):



Yellow gum (125 mg, 57%), R_f = 0.06 (20% ethyl acetate in petroleum ether, v/ v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.64 (t, J = 2.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.33-7.31 (m, 2H), 7.29-7.28 (m, 1H), 7.20 (d, J = 7.8 Hz, 2H), 6.95 (s, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 5.43 (t, J = 6.6 Hz, 1H), 3.92-3.91 (m, 5H), 3.89 (s, 3H), 3.78 (d, J = 2.4 Hz, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.0, 150.1, 148.2, 143.3, 137.6, 136.0, 135.5, 129.5, 128.6, 128.5, 128.2, 127.2, 127.1, 117.0, 115.4, 114.8, 113.0, 94.9, 90.3, 56.1, 56.0, 50.1, 49.2, 21.4; HRMS (ESI) m/z calcd for $C_{28}H_{27}NNaO_5S$ $[M + Na]^+$ 512.1508, found 512.1503.

(E)-N-(2-Benzylidene-4-(4-fluoro-2-(2-oxoethyl)phenyl)but-3-yn-1-yl)-4-methylbenzene-sulfonamide (47h):



White solid (110 mg, 55%), R_f = 0.23 (20% ethyl acetate in petroleum ether, v/v), mp 80-82 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.67 (t, J = 1.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.45-7.43 (m, 1H), 7.34-7.28 (m, 3H), 7.20 (d, J = 7.8 Hz, 2H),

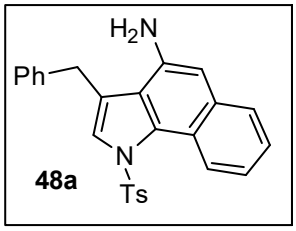
7.03-6.98 (m, 2H), 6.62 (s, 1H), 5.44 (t, J = 6.3 Hz, 1H), 3.90 (d, J = 6.6 Hz, 2H), 3.86-3.85 (m, 2H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 198.2, 162.6 (d, $J_{C\text{-}F}$ = 250.6 Hz), 143.3, 137.5, 136.9, 136.5 (d, $J_{C\text{-}F}$ = 7.8 Hz), 135.4, 134.4 (d, $J_{C\text{-}F}$ = 8.5 Hz), 129.6, 128.7, 128.6, 128.2, 127.1, 119.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 117.6 (d, $J_{C\text{-}F}$ = 22.2 Hz), 116.7, 115.0 (d, $J_{C\text{-}F}$ = 21.6 Hz), 93.5, 91.4, 50.0, 49.3, 21.4; HRMS (ESI) m/z calcd for $C_{26}H_{22}FNNaO_3S$ $[M + Na]^+$ 470.1202, found 470.1200.

4.2.8.7. General Procedure for the Synthesis of 4-Amino Benzo[*g*]indole 48

To a well-stirred solution of $Pd(OAc)_2$ (2.58 mg, 0.011 mmol, 5 mol %) and bpy (3.59 mg, 0.023 mmol, 10 mol %) in dry THF (1.5 mL), *p*-TsOH·H_2O (87.4 mg, 0.46 mmol, 2 equiv) was added and the mixture was heated to reflux under argon atmosphere. Next, the en-yne substrate **46** (0.23 mmol, 1 equiv) dissolved in dry THF (1.5 mL) was added dropwise and heating was continued for another 4−12 h. Upon completion of reaction (TLC), the mixture was neutralized by drop-wise addition of 10% aqueous sodium bicarbonate solution (to pH ∼7). Thereafter, the mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography using 10-18% ethyl acetate in petroleum ether to afford the pure products (**48a-j**) in 24-82% yields.

4.2.8.8. Spectral Data of Compounds 48a-j

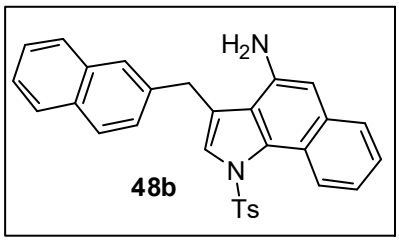
3-Benzyl-1-tosyl-1H-benzo-[g]indol-4-amine (48a):



48a

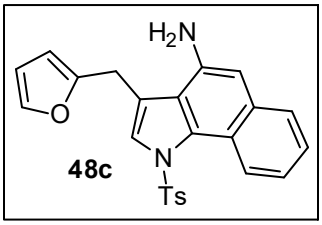
Brown solid (73.5 mg, 75%), R_f = 0.24 (15% ethyl acetate in petroleum ether, v/v), mp 146-148 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 8.93 (d, J = 8.1 Hz, 1H), 7.60-7.54 (m, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.34-7.26 (m, 5H), 7.12-7.08 (m, 4H), 6.70 (s, 1H), 4.28 (s, 2H), 3.73 (brs, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.8, 139.3, 139.0, 135.0, 133.92, 133.90, 129.7, 129.0, 128.5, 128.3, 127.0, 126.9, 126.3, 125.3, 124.4, 122.8, 122.1, 121.2, 119.1, 107.6, 32.8, 21.6; HRMS (ESI) m/z calcd for $C_{26}H_{22}N_2NaO_2S$ $[M + Na]^+$ 449.1300, found 449.1300.

3-(Naphthalen-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (48b):



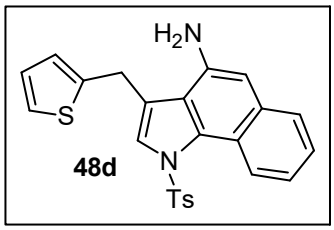
Brown solid (85.4 mg, 78%), R_f = 0.25 (15% ethyl acetate in petroleum ether, v/v), mp 196-198 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.97 (d, J = 9.0 Hz, 1H), 7.84-7.82 (m, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.69 (s, 1H), 7.66-7.64 (m, 1H), 7.56-7.54 (m, 3H), 7.49-7.46 (m, 3H), 7.34-7.28 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 6.68 (s, 1H), 4.45 (s, 2H), 3.76 (brs, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.8, 139.0, 137.0, 135.0, 133.8, 133.7, 133.6, 132.4, 129.7, 128.8, 128.5, 127.7, 127.6, 126.9, 126.6, 126.5, 126.4, 126.3, 125.9, 125.3, 124.3, 122.8, 122.1, 120.7, 118.9, 107.6, 32.9, 21.6; HRMS (ESI) m/z calcd for $C_{30}H_{25}N_2O_2S$ $[M + H]^+$ 477.1637, found 477.1639.

3-(Furan-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (48c):



Brown solid (65.1 mg, 68%), R_f = 0.20 (15% ethyl acetate in petroleum ether, v/v), mp 134-136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.90 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.39-7.38 (m, 1H), 7.33-7.30 (m, 1H), 7.27-7.25 (m, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.76 (s, 1H), 6.30-6.29 (m, 1H), 5.86-5.85 (m, 1H), 4.27 (s, 2H), 3.96 (brs, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 153.7, 144.8, 142.1, 138.9, 134.9, 133.7, 133.3, 129.7, 128.2, 126.9, 126.3, 125.2, 124.1, 122.8, 121.8, 118.9, 118.5, 110.6, 107.9, 106.7, 26.3, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_3S$ $[M + H]^+$ 417.1273, found 417.1304.

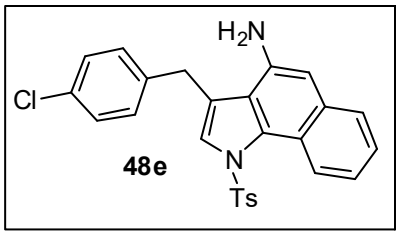
3-(Thiophen-2-ylmethyl)-1-tosyl-1H-benzo[g]indol-4-amine (48d):



Brown solid (75.5 mg, 76%), R_f = 0.21 (15% ethyl acetate in petroleum ether, v/v), mp 174-176 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.94 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.28-7.26 (m, 1H), 7.21 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.93-6.92 (m, 1H), 6.73 (s, 1H), 6.70-6.69 (m, 1H), 4.43 (s, 2H), 3.86 (brs, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.9, 143.4, 138.9, 134.9, 133.8, 133.6, 129.8, 128.1, 127.2, 126.9,

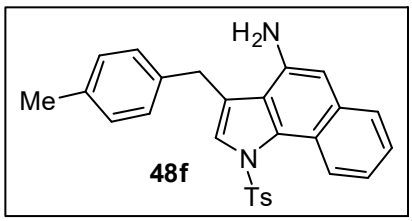
126.3, 125.3, 125.2, 125.1, 124.2, 122.8, 121.7, 120.7, 118.9, 107.7, 27.7, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_2S_2$ $[M + H]^+$ 433.1044, found 433.1046.

3-(4-Chlorobenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (48e):



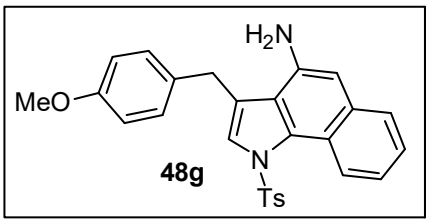
Brown solid (86.7 mg, 82%), R_f = 0.22 (15% ethyl acetate in petroleum ether, v/v), mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 8.4 Hz, 1H), 7.58-7.56 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.29-7.25 (m, 3H), 7.11 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 4.24 (s, 2H), 3.71 (brs, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.9, 138.7, 137.7, 134.9, 133.8, 133.7, 132.7, 129.7, 129.6, 129.1, 128.4, 126.9, 126.3, 125.4, 124.3, 122.9, 121.8, 120.5, 118.9, 107.7, 32.2, 21.6; HRMS (ESI) m/z calcd for $C_{26}H_{22}ClN_2O_2S$ $[M + H]^+$ 461.1091, found 461.1097.

3-(4-Methylbenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (48f):



Brown solid (78.9 mg, 78%), R_f = 0.27 (15% ethyl acetate in petroleum ether, v/v), mp 178-180 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 9.0 Hz, 1H), 7.59 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.33-7.30 (m, 1H), 7.28-7.25 (m, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 7.8 Hz, 2H), 6.70 (s, 1H), 4.23 (s, 2H), 3.77 (brs, 2H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δC 144.7, 139.0, 136.5, 136.1, 134.9, 133.8, 129.7, 129.6, 128.4, 128.1, 126.9, 126.2, 125.3, 124.3, 122.7, 122.1, 121.4, 119.0, 107.5, 32.3, 21.6, 21.1; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_2S$ $[M + H]^+$ 441.1637, found 441.1640.

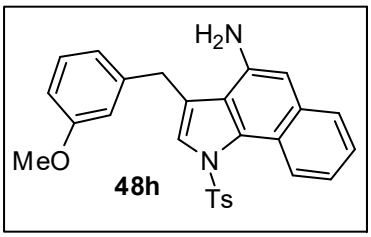
3-(4-Methoxybenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (48g):



Pale brown solid (25.2 mg, 24%), R_f= 0.18 (15% ethyl acetate in petroleum ether, v/v), mp 190-192 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.92 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.31 (td, J = 7.5, 0.8 Hz, 1H), 7.28-7.26 (m, 1H), 7.11 (d, J = 8.4 Hz,

2H), 6.99 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 6.70 (s, 1H), 4.21 (s, 2H), 3.79-3.77 (m, 5H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 158.5, 144.6, 138.9, 134.9, 133.81, 133.80, 131.0, 129.6, 129.2, 128.3, 126.9, 126.2, 125.2, 124.3, 122.7, 122.0, 121.6, 118.9, 114.3, 107.4, 55.2, 31.8, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ $[M + H]^+$ 457.1586, found 457.1592.

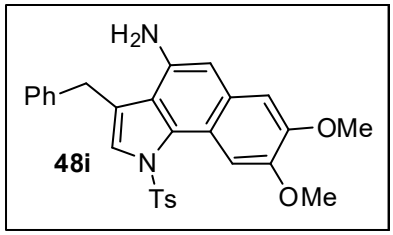
3-(3-Methoxybenzyl)-1-tosyl-1H-benzo[g]indol-4-amine (48h):



48h

Pale yellow solid (83.9 mg, 80%), R_f = 0.16 (15% ethyl acetate in petroleum ether, v/v), mp 142-144 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.95 (d, J = 9.0 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.29-7.27 (m, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.79 (dd, J = 8.1, 2.1 Hz, 1H), 6.72 (s, 1H), 6.69-6.67 (m, 2H), 4.25 (s, 2H), 3.76 (s, 5H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 160.1, 144.7, 140.9, 138.9, 134.9, 133.8, 133.7, 129.9, 129.6, 128.4, 126.8, 126.2, 125.2, 124.2, 122.7, 121.9, 120.8, 120.4, 118.9, 114.2, 111.9, 107.5, 55.1, 32.7, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{25}N_2O_3S$ $[M + H]^+$ 457.1586, found 457.1576.

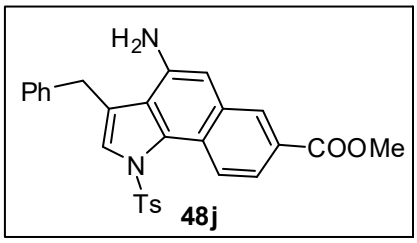
3-Benzyl-7,8-dimethoxy-1-tosyl-1H-benzo[g]indol-4-amine (48i):



48i

Brown solid (72.7 mg, 65%), R_f = 0.08 (15% ethyl acetate in petroleum ether, v/v), mp 148-150 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 8.46 (s, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.28-7.22 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 6.6 Hz, 2H), 6.89 (s, 1H), 6.62 (s, 1H), 4.24 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.62 (brs, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 148.6, 146.7, 144.6, 139.2, 137.4, 134.8, 133.8, 129.6, 129.5, 128.9, 128.2, 127.9, 126.8, 126.6, 121.9, 120.9, 114.1, 107.4, 105.4, 104.9, 56.0, 55.6, 32.7, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{27}N_2O_4S$ $[M + H]^+$ 487.1692, found 487.1684.

Methyl 4-Amino-3-benzyl-1-tosyl-1H-benzo[g]indole-7-carboxylate (48j):



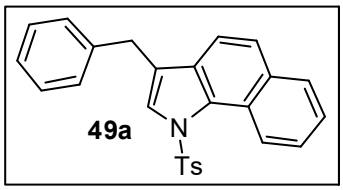
Yellow solid (61.2 mg, 55%), R_f = 0.14 (15% ethyl acetate in petroleum ether, v/v), mp 178-180 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.97 (d, J = 9.0 Hz, 1H), 8.29 (s, 1H), 7.84 (dd, J = 8.7, 1.8 Hz, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.31-7.29 (m, 2H), 7.27-7.25 (m, 1H), 7.13-7.10 (m, 4H), 6.77 (s, 1H), 4.29 (s, 2H), 3.94 (s, 3H), 3.84 (brs, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 167.5, 145.1, 139.8, 139.0, 134.7, 133.2, 133.0, 129.8, 129.5, 129.1, 129.0, 128.2, 127.1, 126.9, 126.4, 124.4, 123.6, 122.2, 120.9, 120.8, 108.1, 52.2, 32.7, 21.6; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_4S$ $[M + H]^+$ 485.1535, found 485.1538.

4.2.8.9. General Procedure for the Synthesis of Benzo[g]indoles 49

To a well-stirred and heated (85 °C) mixture of $Pd(OAc)_2$bpy (4.37 mg, 0.011 mmol, 5 mol %) and *p*-TsOH·H_2O (65.5 mg, 0.34 mmol, 1.5 equiv) in dry DME (1.5 mL) a solution of **47** (0.23 mmol, 1 equiv) dissolved in dry DME (1.5 mL) was added dropwise. The heating was continued until completion of the reaction (TLC). The solvent was then removed under reduced pressure. The crude material obtained was directly loaded onto silica gel (100-200 mesh) column for purification. The desired products **49a-h** were eluted with 1-6% ethyl acetate- petroleum (v/v) and isolated in 27-68% yields.

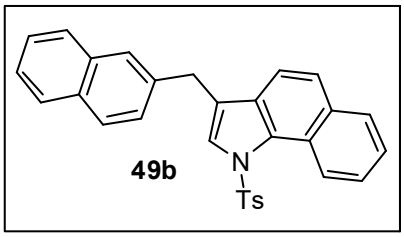
4.2.8.10. Spectral Data of Compounds 49a-h:

3-Benzyl-1-tosyl-1H-benzo-[g]indole (49a):



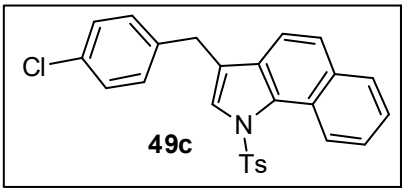
White solid (57.7 mg, 61%), R_f = 0.56 (10% ethyl acetate in petroleum ether, v/v), mp 106-108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.09 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.62-7.39 (m, 7H), 7.31-7.16 (m, 5H), 7.08 (d, J = 8.1 Hz, 2H), 4.09 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.6, 139.1, 135.0, 132.3, 131.6, 129.9, 129.6, 128.8, 128.52, 128.50, 127.6, 126.7, 126.4, 126.2, 125.8, 124.7, 124.1, 123.6, 122.9, 118.1, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{26}H_{22}NO_2S$ $[M + H]^+$ 412.1371, found 412.1368.

3-(Naphthalen-2-ylmethyl)-1-tosyl-1H-benzo[g]indole (49b):



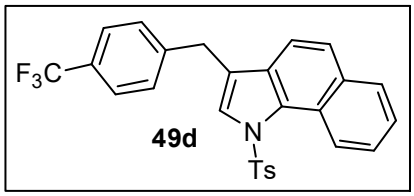
Light brown solid (46.4 mg, 44%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 160-162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.13 (d, J = 9.0 Hz, 1H), 7.85-7.82 (m, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.59 (d, J = 8.4 Hz,1H), 7.55 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.48-7.43 (m, 4H), 7.33 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 4.26 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.6, 136.7, 135.0, 133.5, 132.3, 132.2, 131.7, 130.0, 129.6, 128.8, 128.1, 127.7, 127.6, 127.5, 127.1, 126.8, 126.7, 126.3, 126.0, 125.9, 125.5, 124.7, 124.1, 123.6, 122.7, 118.2, 31.4, 21.5; HRMS (ESI) m/z calcd for $C_{30}H_{24}NO_2S$ $[M + H]^+$ 462.1528, found 462.1526.

3-(4-Chlorobenzyl)-1-tosyl-1H-benzo[g]indole (49c):



White solid (69.6 mg, 68%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.08 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.62-7.41 (m, 6H), 7.36 (d, J = 8.4 Hz, 1H), 7.25-7.22 (m, 2H), 7.11-7.07 (m, 4H), 4.06 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 144.8, 137.7, 135.0, 132.3, 132.2, 131.8, 131.7, 129.9, 129.6, 128.9, 128.6, 127.6, 126.7, 126.4, 125.9, 124.9, 124.1, 123.6, 122.3, 118.0, 30.6, 21.5; HRMS (ESI) m/z calcd for $C_{26}H_{21}ClNO_2S$ $[M + H]^+$ 446.0982, found 446.0984.

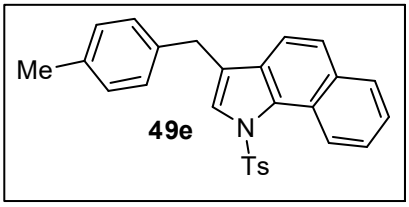
1-Tosyl-3-(4-(trifluoromethyl)benzyl)-1H-benzo[g]indole (49d):



Pale yellow solid (71.6 mg, 65%), R_f = 0.50 (10% ethyl acetate in petroleum ether, v/v), mp 126-128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.09 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.64-7.61 (m, 2H), 7.57-7.42 (m, 6H), 7.36 (d, J = 8.4 Hz, 1H), 7.30-7.26 (m, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.15 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 144.8, 143.3, 135.0, 132.3, 131.6, 129.6, 129.5, 128.9, 128.8, 128.7 (q, $J_{C\text{-}F}$ = 32.3 Hz), 127.6, 126.7, 126.4, 126.0, 125.4 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.9, 124.2 (q, $J_{C\text{-}F}$=

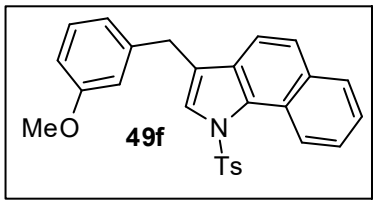
270.2 Hz), 124.1, 123.5, 121.7, 117.8, 31.0, 21.5; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = -162.3 (s, 3F); HRMS (ESI) m/z calcd for $C_{27}H_{21}F_3NO_2S$ $[M + H]^+$ is 480.1245, found 480.1240.

3-(4-Methylbenzyl)-1-tosyl-1H-benzo[g]indole (49e):



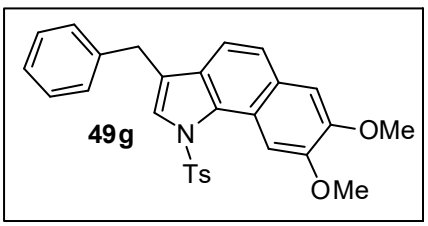
Yellow gum (40.1 mg, 41%), R_f = 0.56 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.09 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.54-7.50 (m, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.44-7.39 (m, 2H), 7.09-7.05 (m, 6H), 4.04 (s, 2H), 2.32 (s, 3H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.7, 136.1, 136.0, 135.2, 132.4, 131.8, 130.1, 129.7, 129.3, 128.9, 128.5, 127.6, 126.8, 126.3, 125.9, 124.8, 124.3, 123.7, 123.5, 118.3, 30.9, 21.6, 21.1; HRMS (ESI) m/z calcd for $C_{27}H_{24}NO_2S$ $[M + H]^+$ 426.1528, found 426.1526.

3-(3-Methoxybenzyl)-1-tosyl-1H-benzo[g]indole (49f):



Yellow solid (30.4 mg, 30%), R_f = 0.39 (10% ethyl acetate in petroleum ether, v/v), mp 150-152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.10 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.55- 7.52 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.45-7.42 (m, 2H), 7.20 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.78-6.77 (m, 3H), 4.07 (s, 2H), 3.77 (s, 3H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 159.7, 144.6, 140.7, 135.0, 132.3, 131.6, 129.9, 129.6, 129.5, 128.8, 127.6, 126.7, 126.2, 125.8, 124.7, 124.1, 123.6, 122.6, 120.9, 118.1, 114.5, 111.4, 55.1, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{27}H_{24}NO_3S$ $[M + H]^+$ 442.1477, found 442.1477.

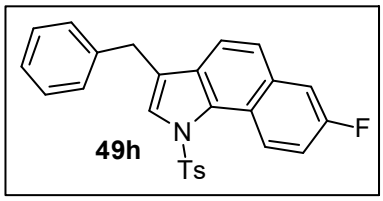
3-Benzyl-7,8-dimethoxy-1-tosyl-1H-benzo[g]indole (49g):



Light brown solid (42.2 mg, 39%), R_f = 0.15 (10% ethyl acetate in petroleum ether, v/v), mp 158-160 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.60 (s, 1H), 7.49-7.47 (m, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.28-7.21 (m, 4H), 7.16-7.15 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 4.06-4.05 (m, 5H), 3.99 (s, 3H), 2.28 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 149.2, 148.1, 144.5, 139.1, 135.0, 131.8,

129.5, 129.2, 128.5, 128.4, 128.1, 127.2, 126.4, 126.3, 124.5, 123.7, 119.2, 116.2, 107.6, 104.5, 56.1, 55.7, 31.2, 21.5; HRMS (ESI) m/z calcd for $C_{28}H_{26}NO_4S$ [M + H]+ 472.1583, found 472.1584.

3-Benzyl-7-fluoro-1-tosyl-1H-benzo[g]indole (49h):



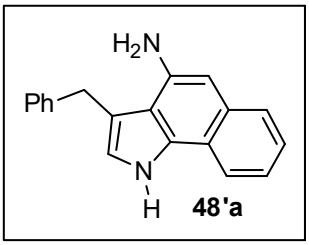
Yellow solid (26.6 mg, 27%), R_f = 0.54 (10% ethyl acetate in petroleum ether, v/v), mp 86-88 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.14-9.12 (m, 1H), 7.58 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.47-7.42 (m, 4H), 7.32-7.26 (m, 3H), 7.24-7.22 (m, 1H), 7.17 (d, J = 7.2 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 4.08 (s, 2H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 159.6 (d, $J_{C\text{-}F}$ = 244.5 Hz), 144.8, 139.0, 134.8, 133.5 (d, $J_{C\text{-}F}$ = 8.5 Hz), 131.8, 129.6, 129.4, 128.5, 128.4, 127.4, 126.8 (d, $J_{C\text{-}F}$ = 8.7 Hz), 126.7, 126.4, 125.0 (d, $J_{C\text{-}F}$ = 4.5 Hz), 123.1, 120.6, 119.4, 115.9 (d, $J_{C\text{-}F}$ = 24.0 Hz), 112.1 (d, $J_{C\text{-}F}$ = 20.5 Hz), 31.2, 21.5; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = -116.5 (s, 1F); HRMS (ESI) m/z calcd for $C_{26}H_{21}FNO_2S$ $[M + H]^+$ 430.1277, found 430.1275.

4.2.8.11. General Procedure for the Synthesis of Benzo[g]indoles 48′a and 49′a

To a well-stirred solution of **48a** or **49a** (0.12 mmol, 1 equiv) in dry THF was added tetrabutylammonium fluoride (1 M solution in THF, 5 equiv), and the mixture was stirred for 2 h under refluxing conditions. It was then poured into water (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography using 5-10% ethyl acetate in petroleum ether as eluent to afford pure detosylated products **48′a** and **49′a** in 65-67% yield.

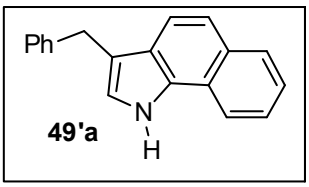
4.2.8.12. Spectral Data of Compounds 48′a and 49′a:

4-Amino-3-benzyl-1H-benzo[g]indole (48'a):



Light brown solid (21.2 mg, 65%), R_f = 0.32 (20% ethyl acetate in petroleum ether, v/v), mp 160-162 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.72 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.33-7.26 (m, 6H), 7.24- 7.21 (m, 1H), 6.98 (s, 1H), 6.56 (s, 1H), 4.37 (s, 2H), 3.89 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 141.2, 140.4, 132.9, 132.3, 128.7, 128.4, 126.4, 126.1, 124.5, 121.8, 121.1, 119.0, 117.3, 115.8, 115.6, 101.0, 32.9; HRMS (ESI) m/z calcd for $C_{19}H_{17}N_2$ $[M + H]^+$ 273.1392, found 273.1380.

3-Benzyl-1H-benzo[g]indole (49'a):



Light brown solid (20.7 mg, 67%), R_f = 0.48 (20% ethyl acetate in petroleum ether, v/v), mp 122-124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.68 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.52-7.46 (m, 2H), 7.43-7.39 (m, 1H), 7.32-7.24 (m, 4H), 7.21-7.17 (m, 1H), 6.97 (s, 1H), 4.19 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 141.4, 131.1, 130.5, 129.0, 128.7, 128.4, 126.0, 125.5, 123.9, 123.3, 121.8, 120.6, 120.3, 119.4, 119.3, 117.6, 31.7; HRMS (ESI) m/z calcd for $C_{19}H_{16}N$ [M + H]+ 258.1283, found 258.1277.

4.2.9. References

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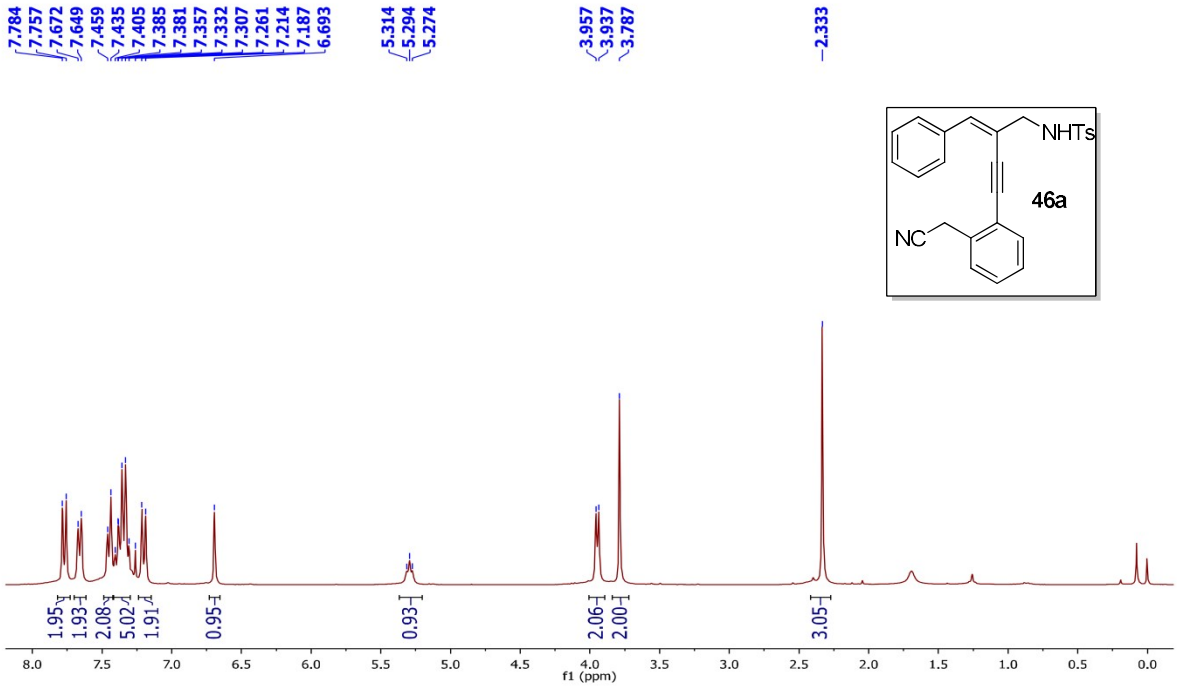
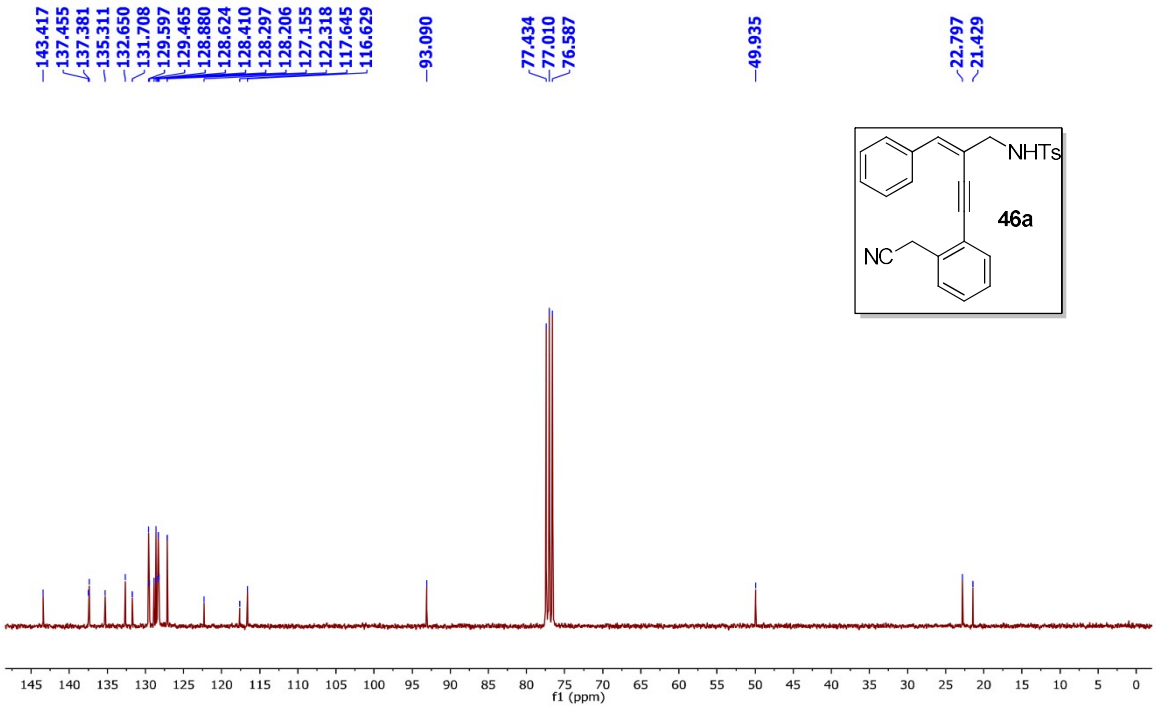
4.2.10. Copies of NMR Spectra

4.2.10.1. NMR Spectra of Compounds 46a-j

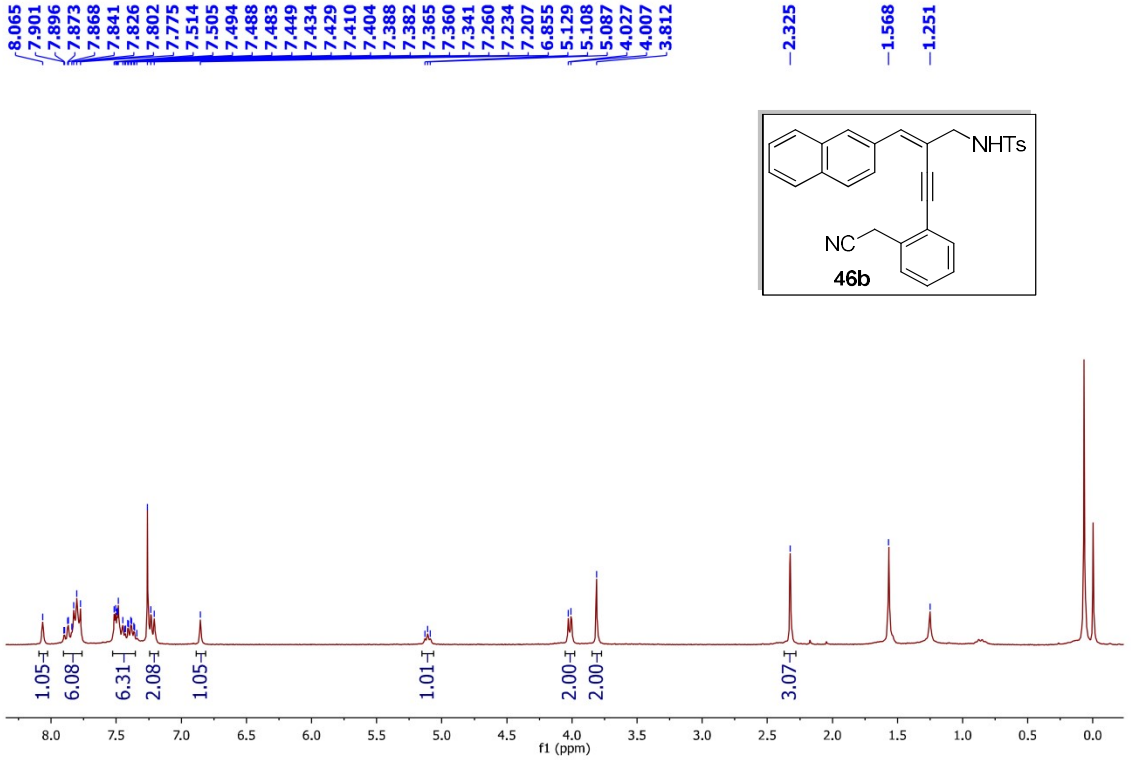
^{1}H NMR (300 MHz) of **46a :**



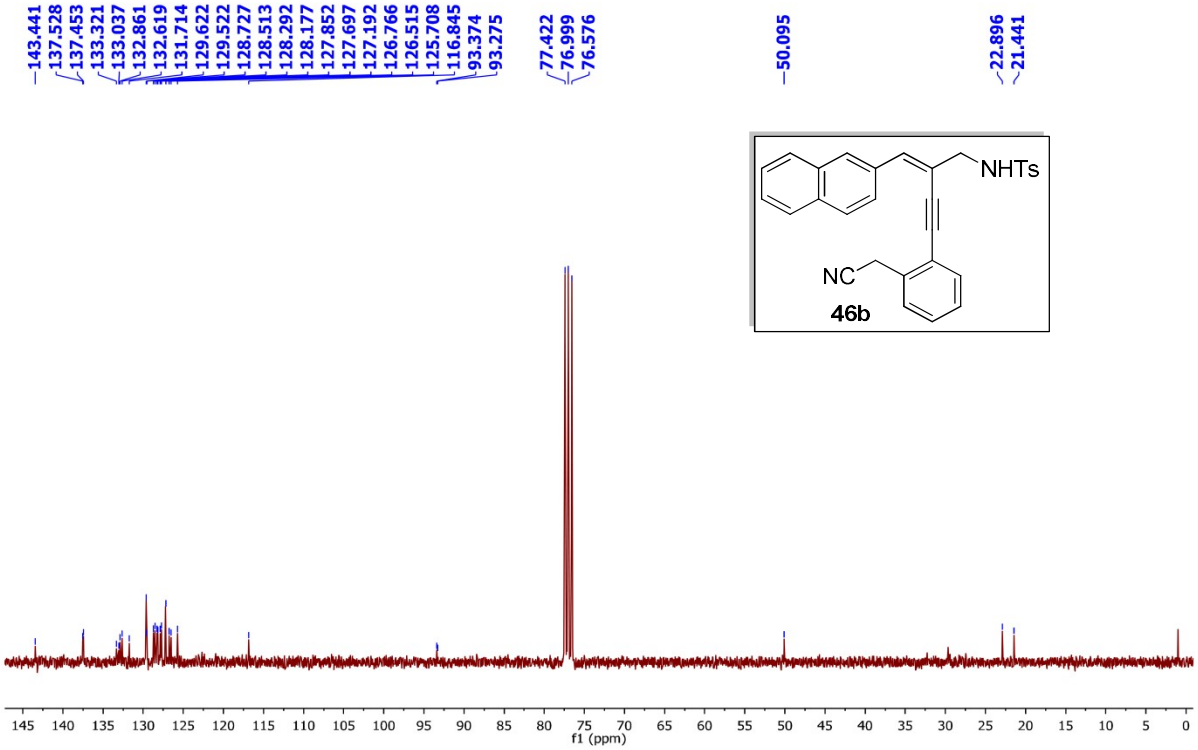
^{13}C{^{1}H} NMR (75 MHz) of **46a :**



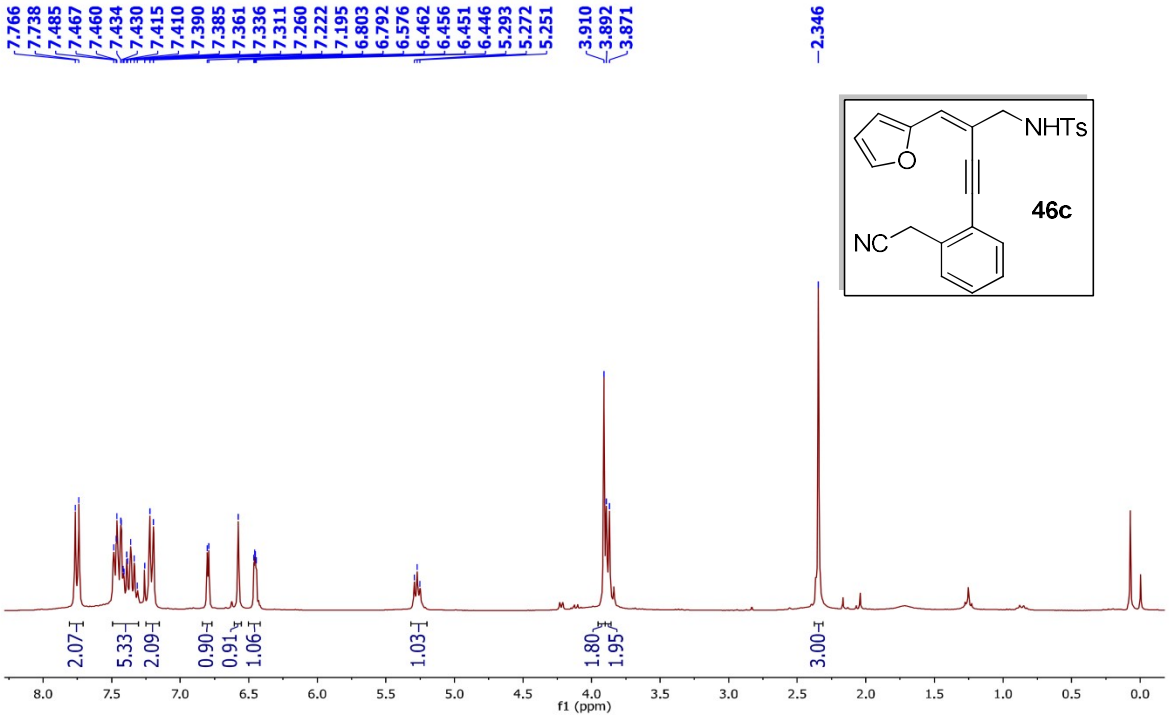
^{1}H NMR (300 MHz) of **46b :**



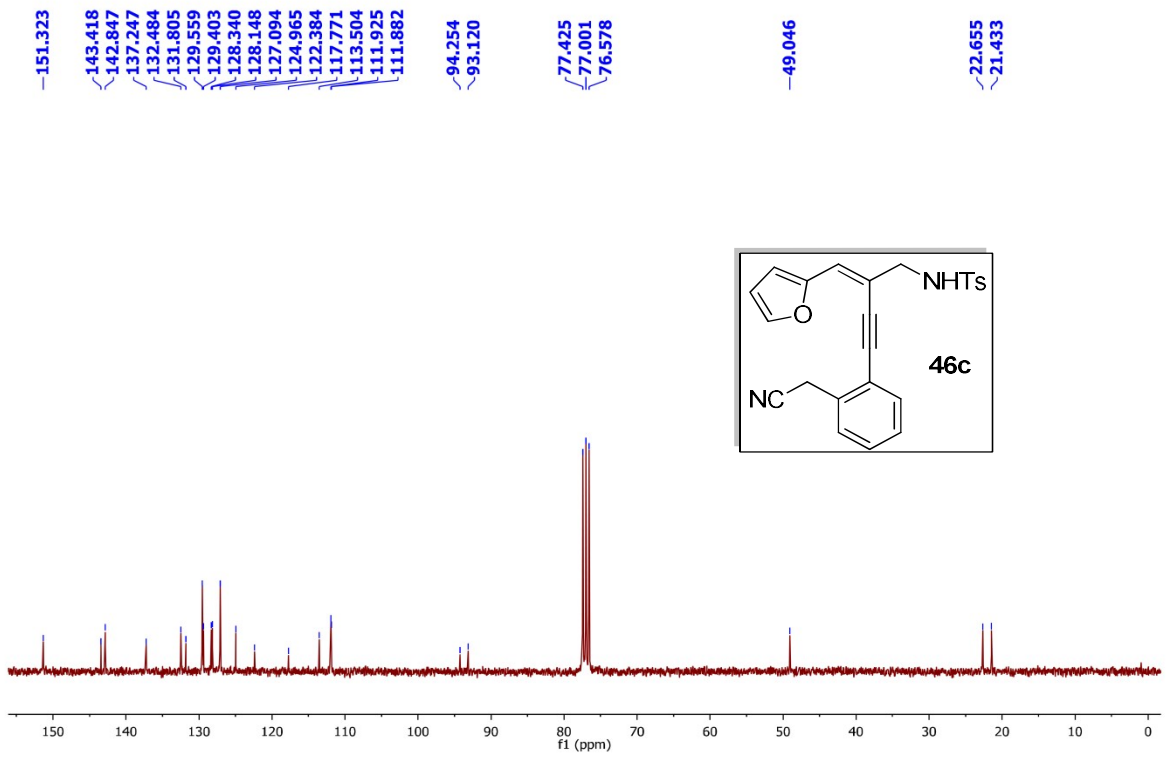
^{13}C{^{1}H} NMR (75 MHz) of **46b :**



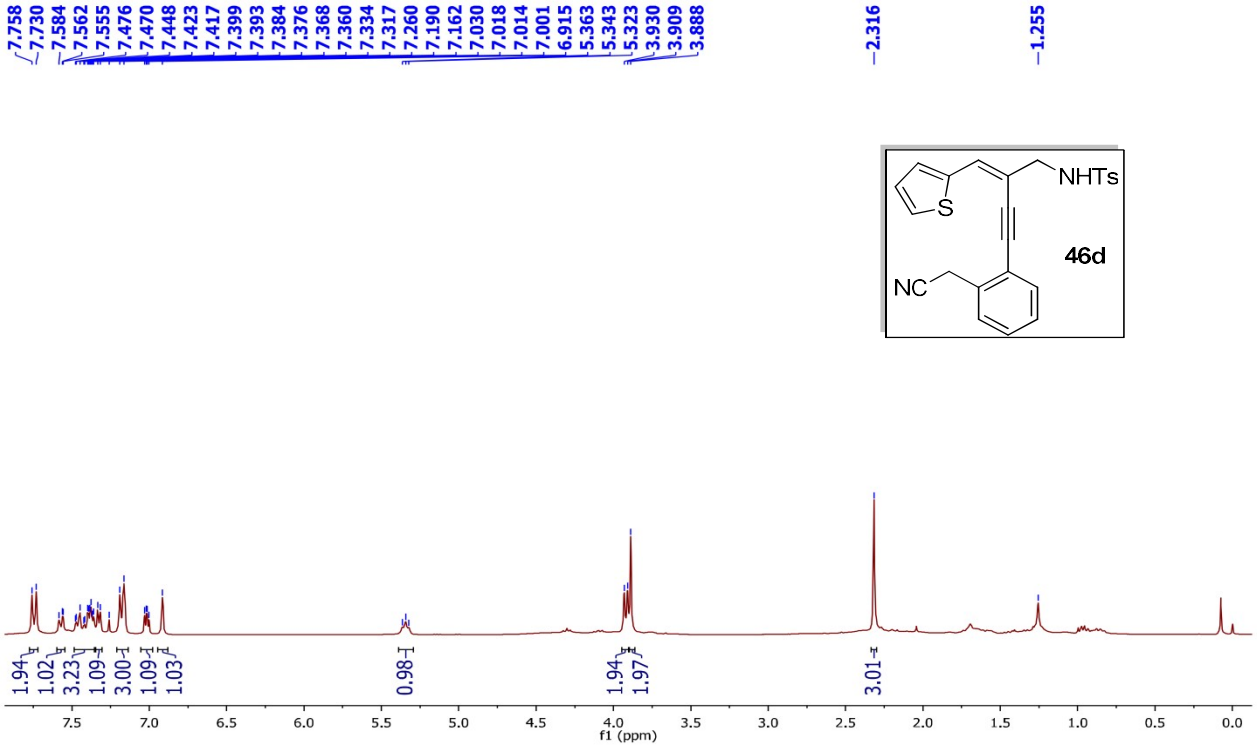
^{1}H NMR (300 MHz) of **46c :**



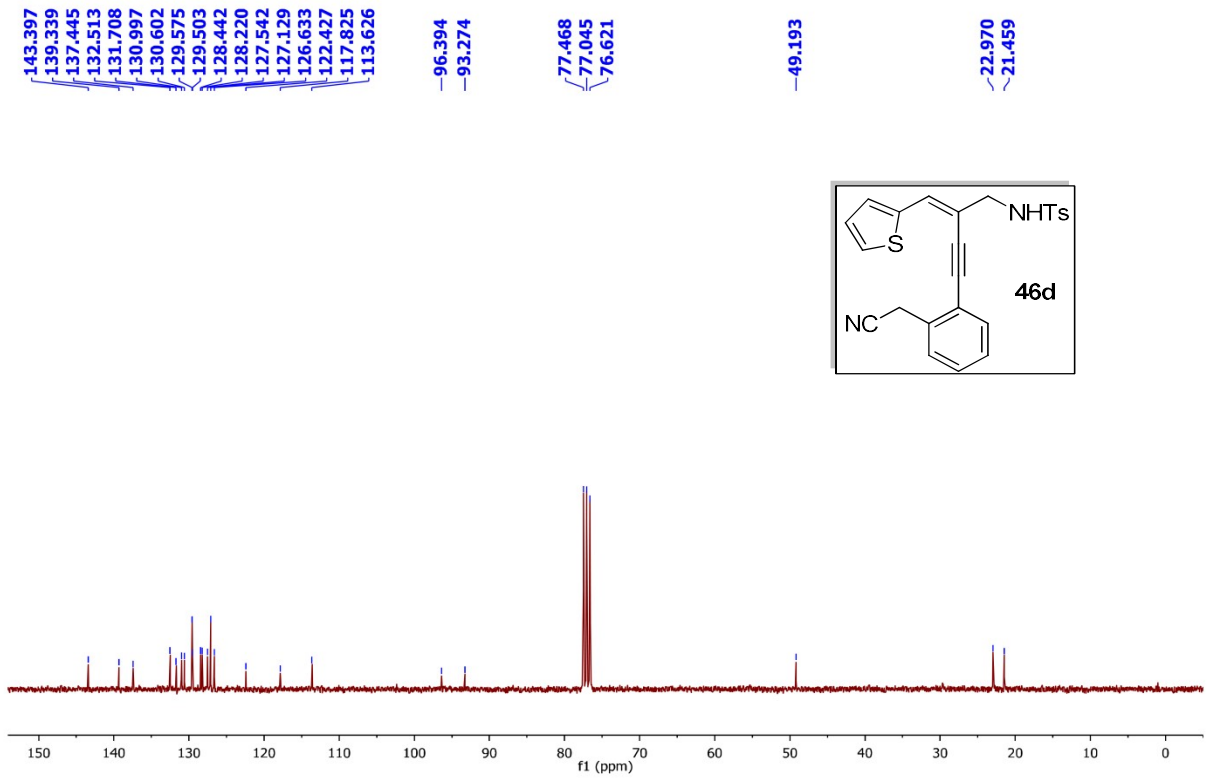
^{13}C{^{1}H} NMR (75 MHz) of **46c :**



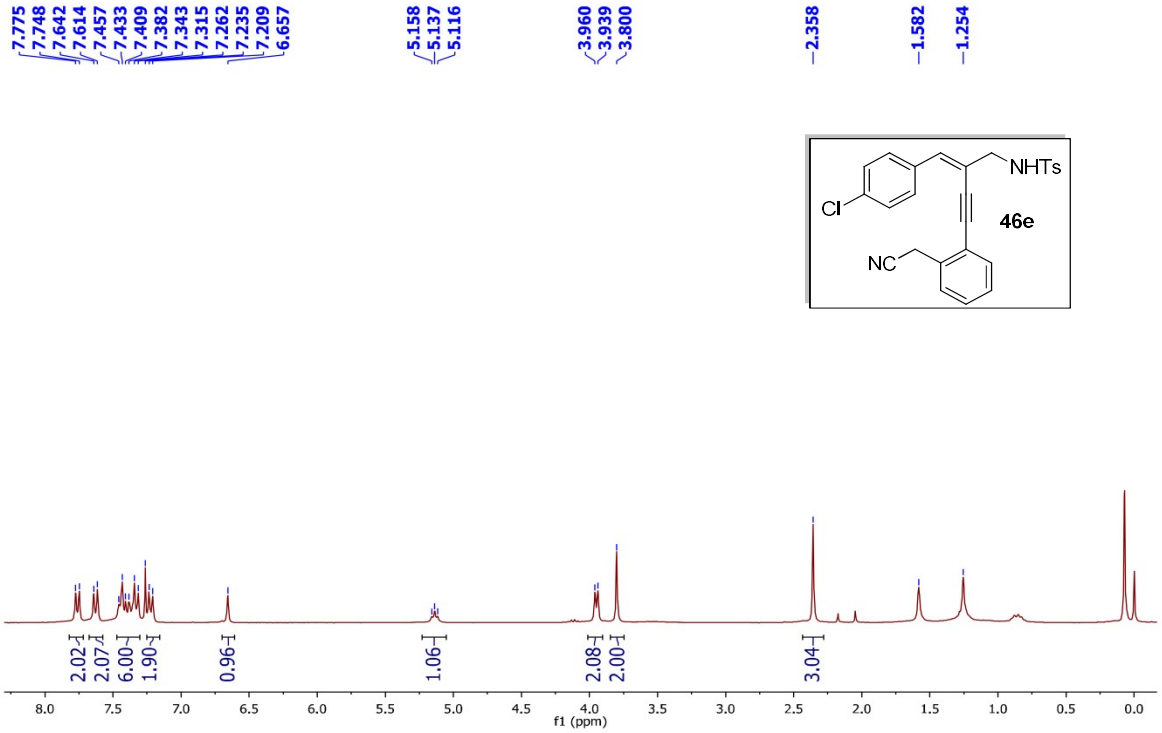
^{1}H NMR (300 MHz) of **46d :**



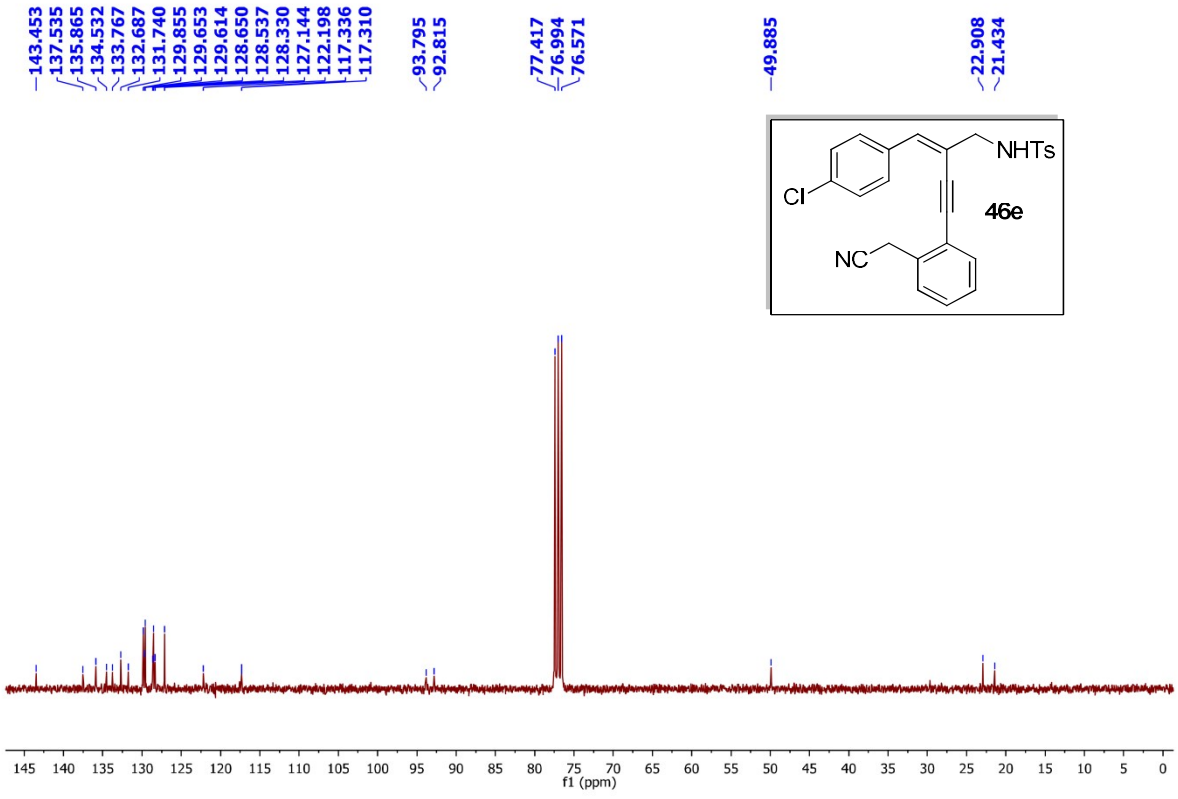
^{13}C{^{1}H} NMR (75 MHz) of **46d :**



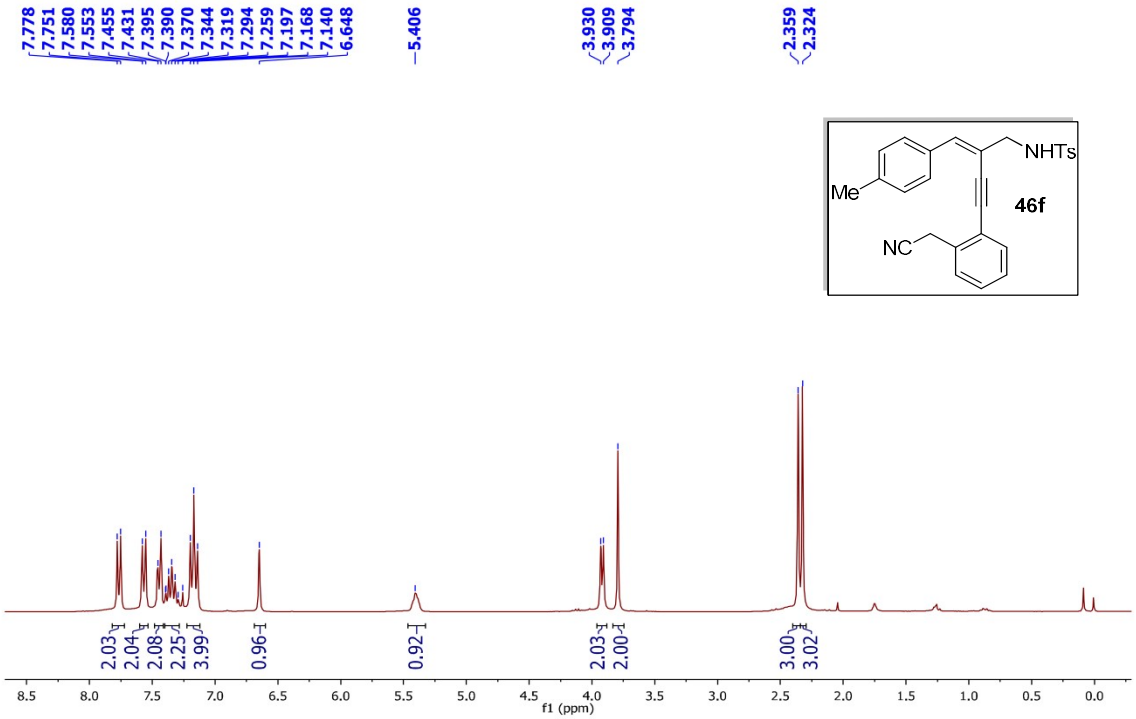
^{1}H NMR (300 MHz) of **46e :**



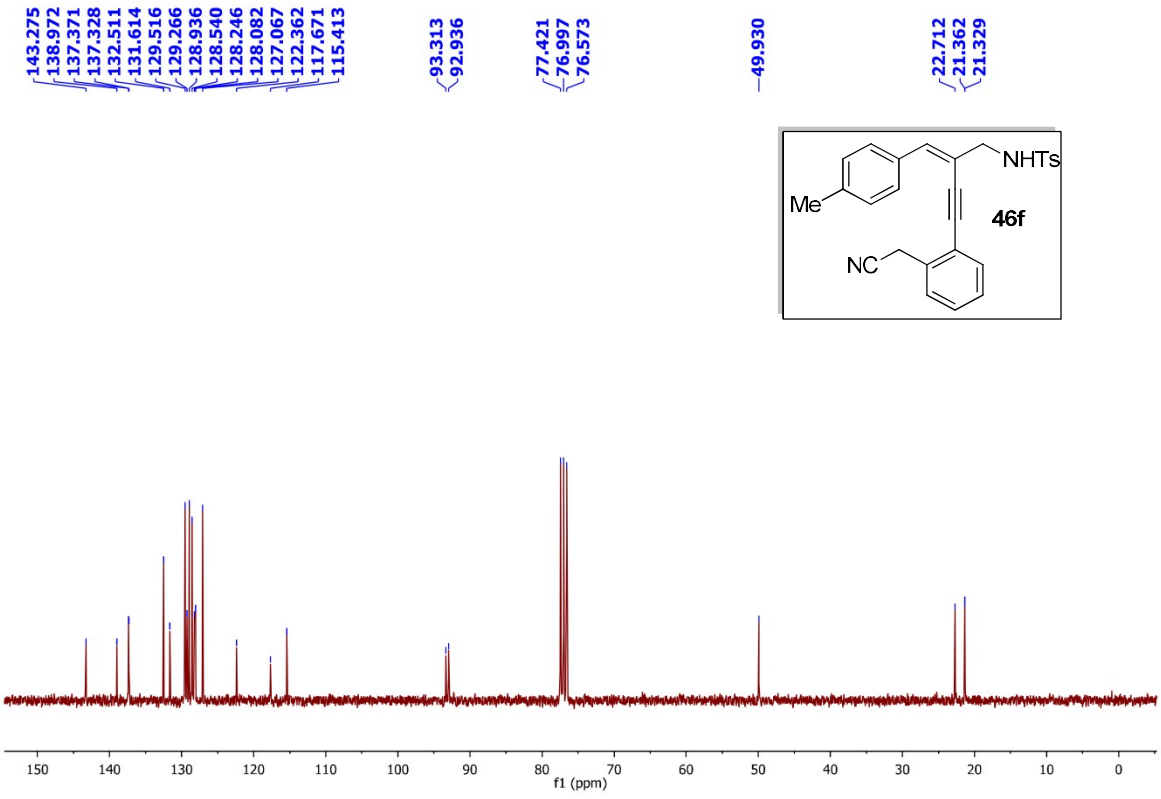
^{13}C{^{1}H} NMR (75 MHz) of **46e :**



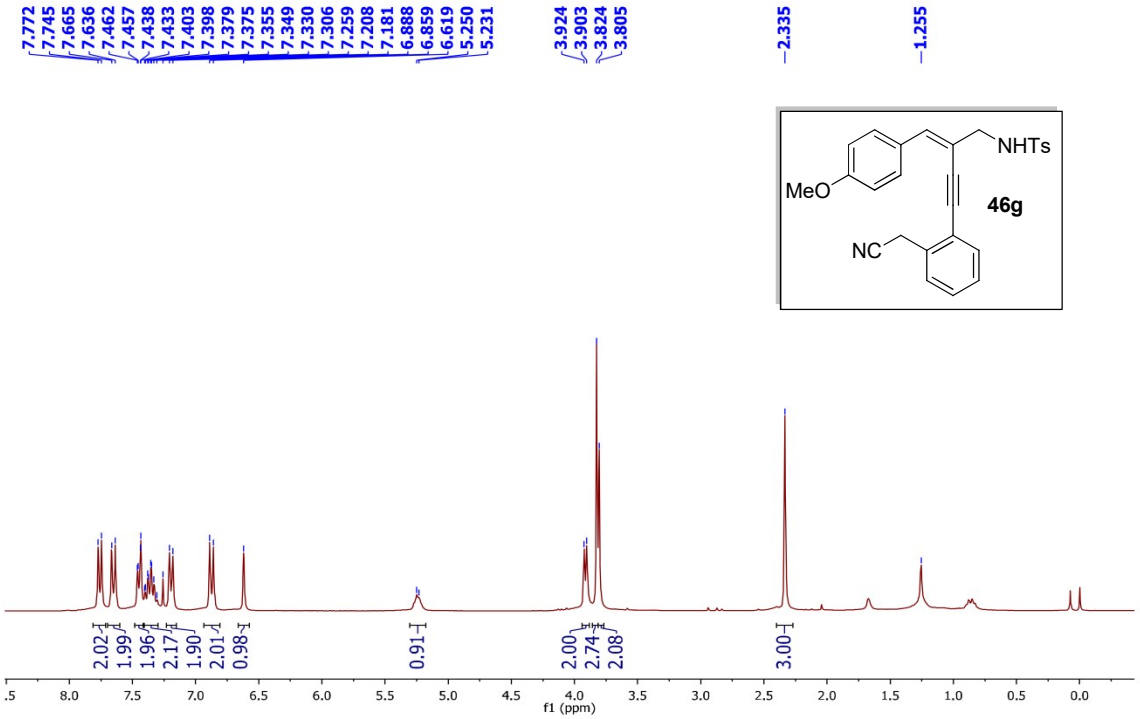
^{1}H NMR (300 MHz) of **46f :**



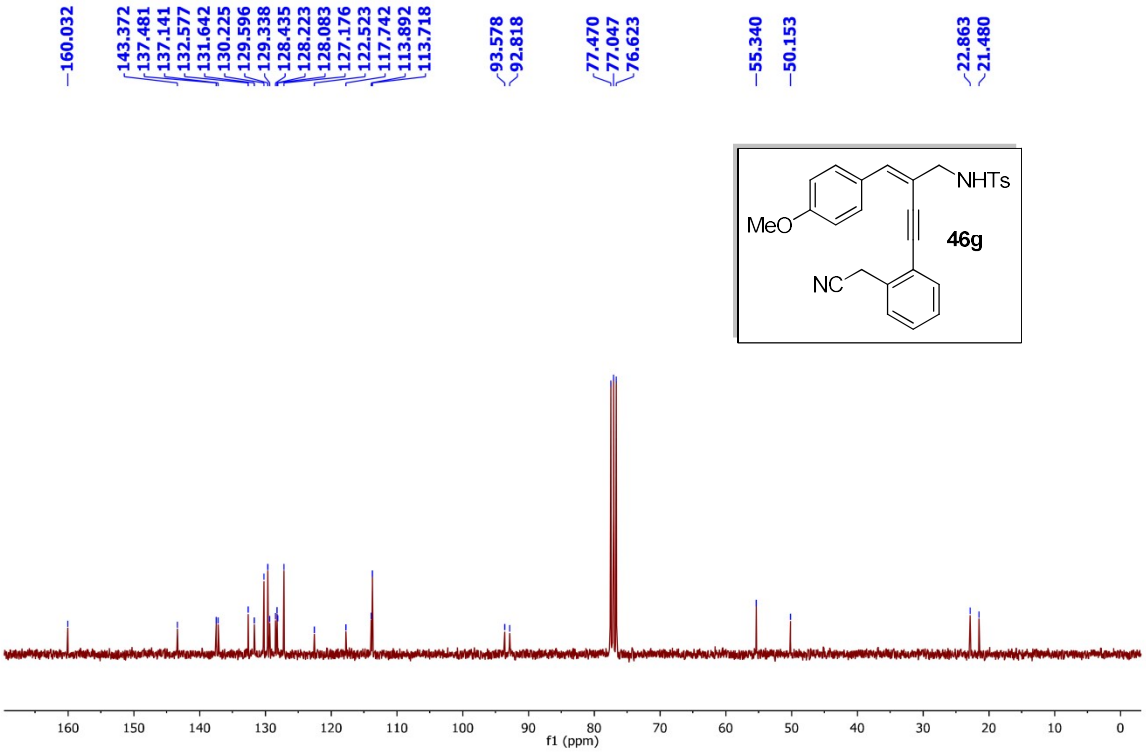
^{13}C{^{1}H} NMR (75 MHz) of **46f :**



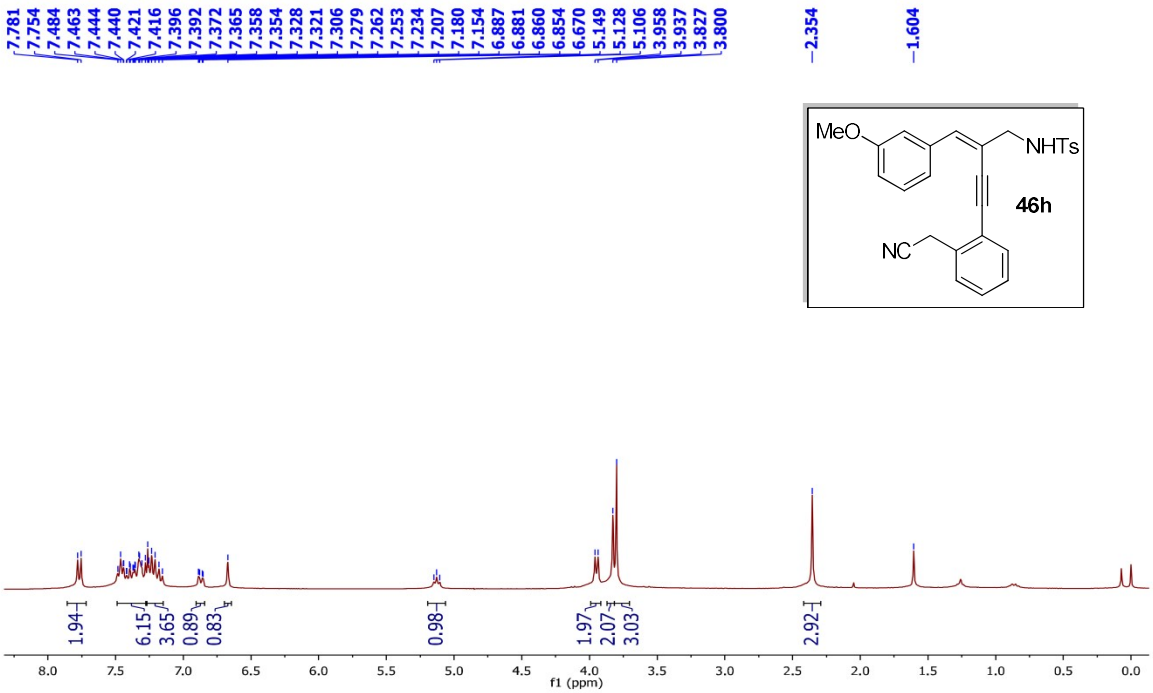
^{1}H NMR (300 MHz) of **46g :**



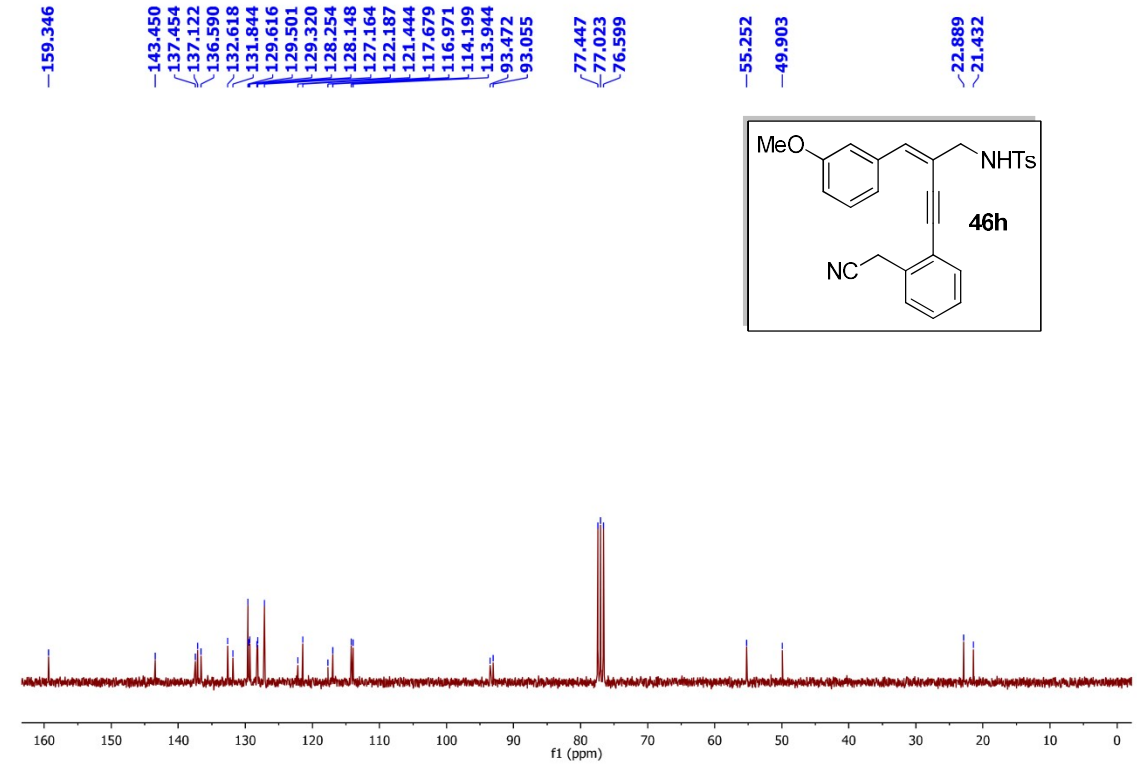
^{13}C{^{1}H} NMR (75 MHz) of **46g :**



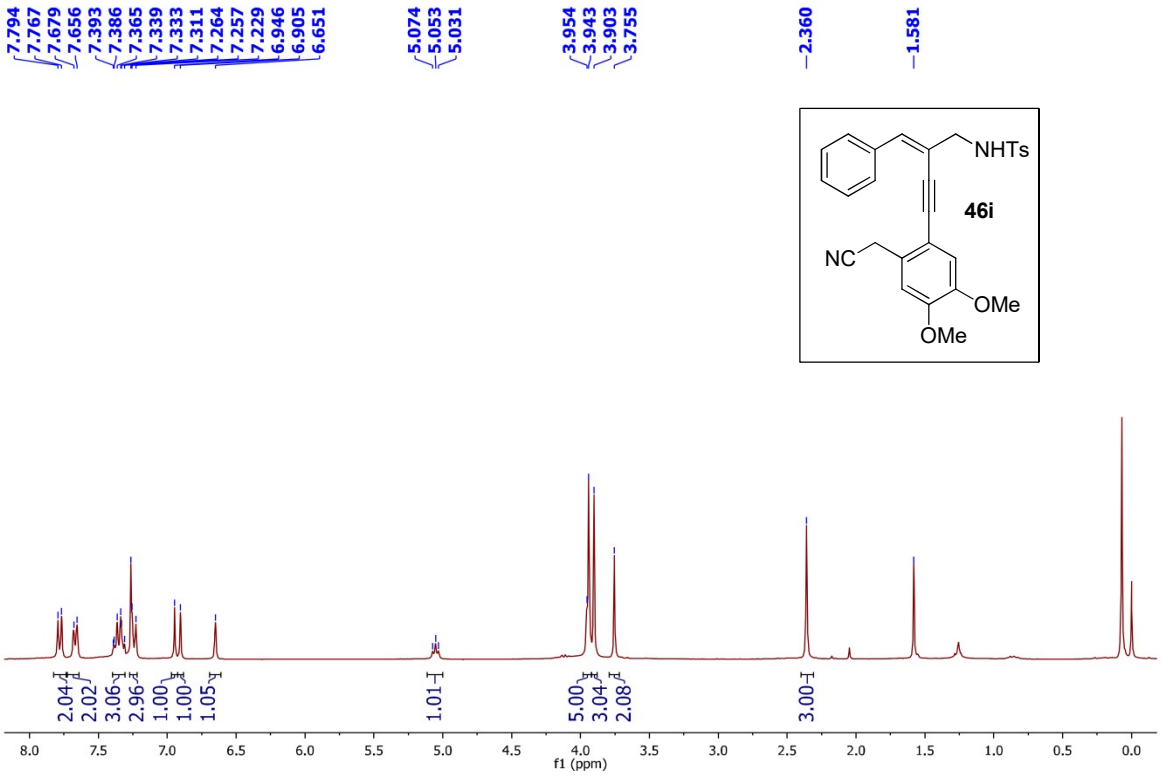
^{1}H NMR (300 MHz) of **46h :**



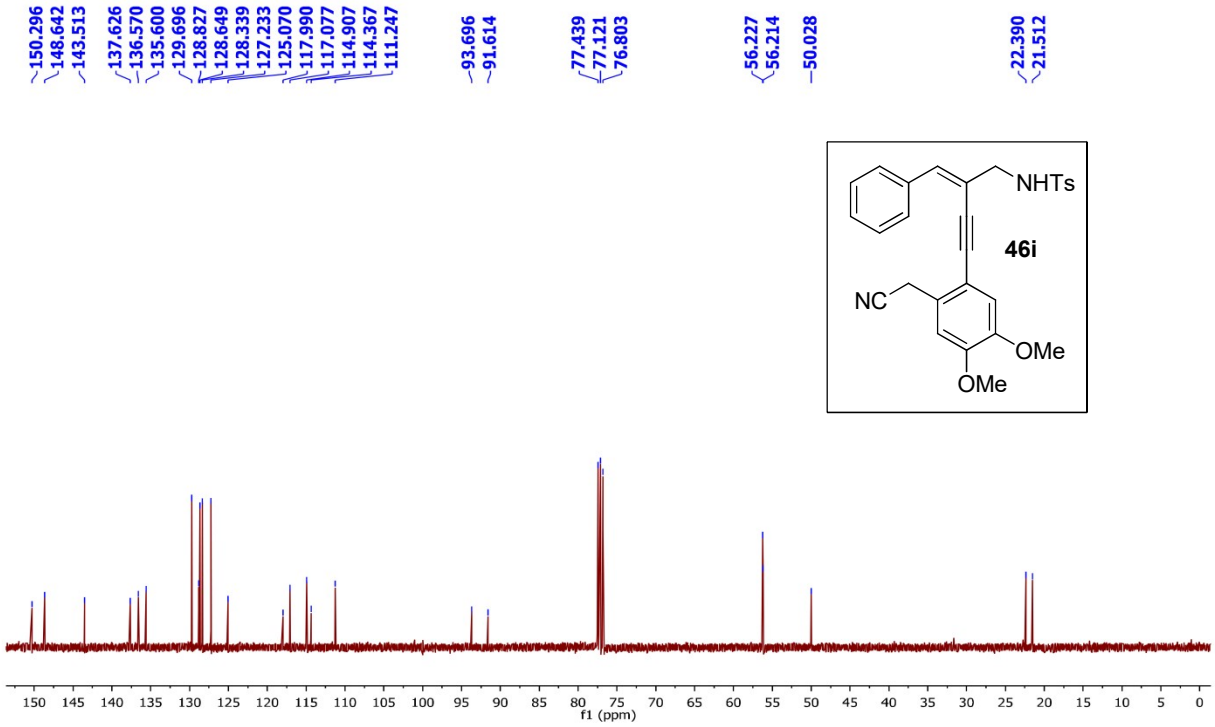
^{13}C{^{1}H} NMR (75 MHz) of **46h :**



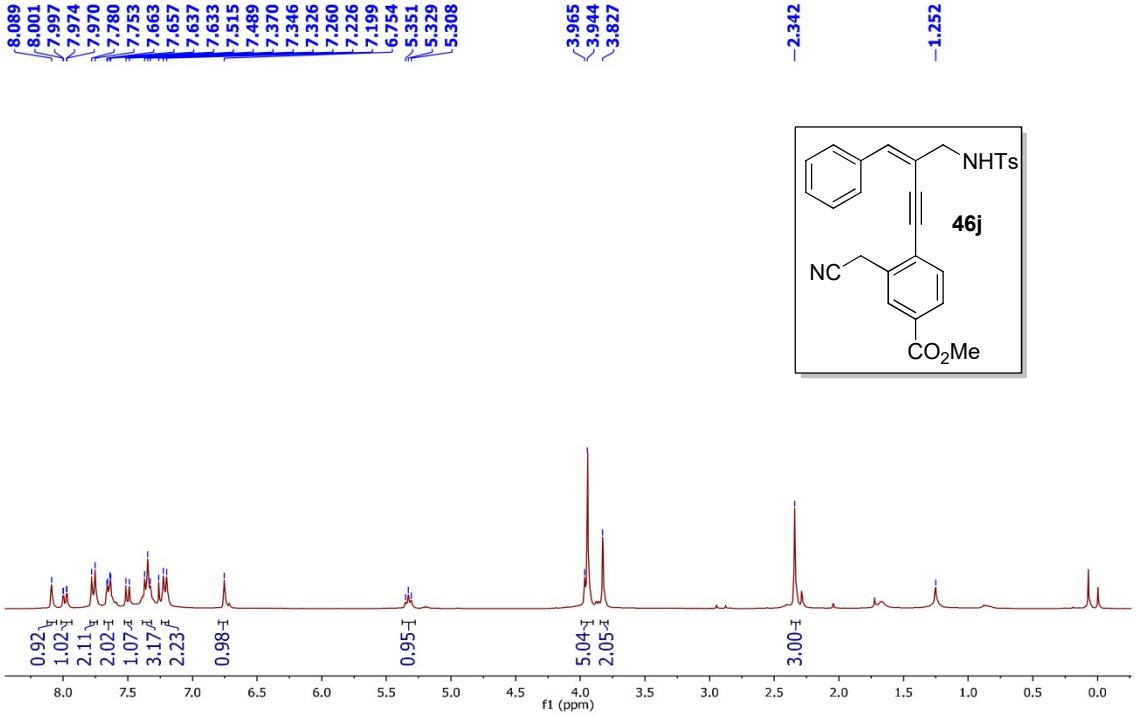
^{1}H NMR (300 MHz) of **46i :**



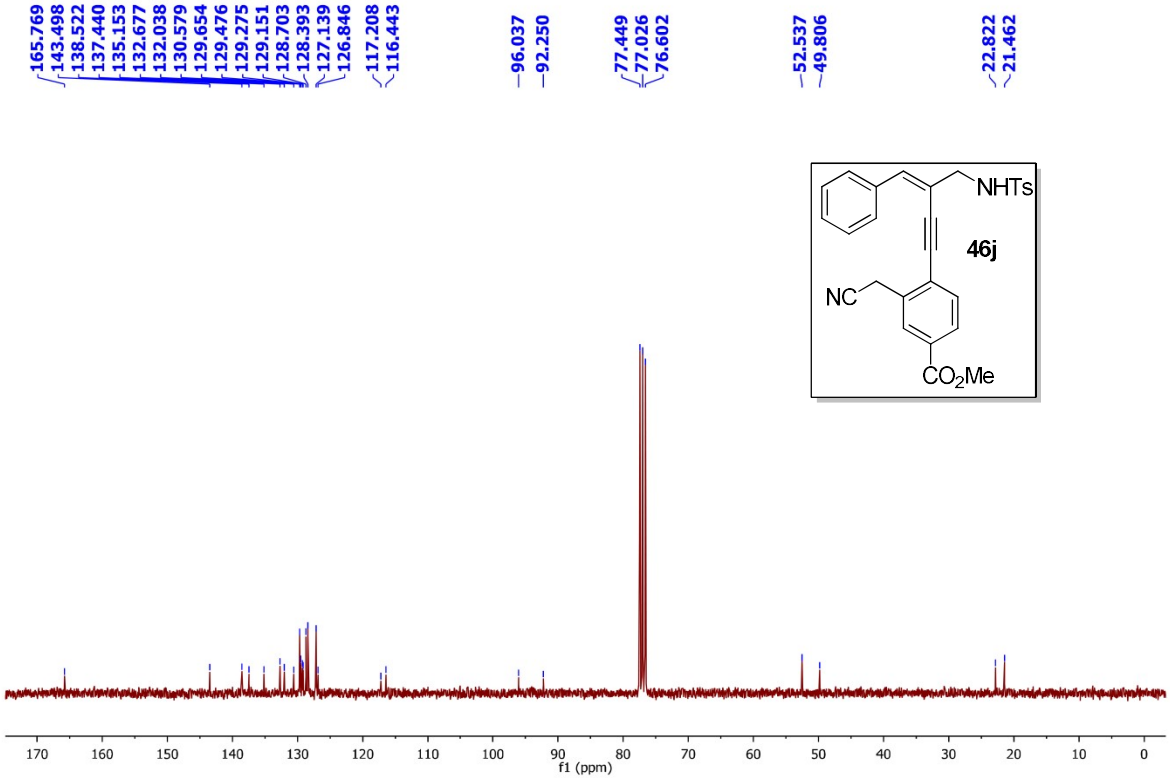
^{13}C{^{1}H} NMR (100 MHz) of **46i :**



^{1}H NMR (300 MHz) of **46j :**

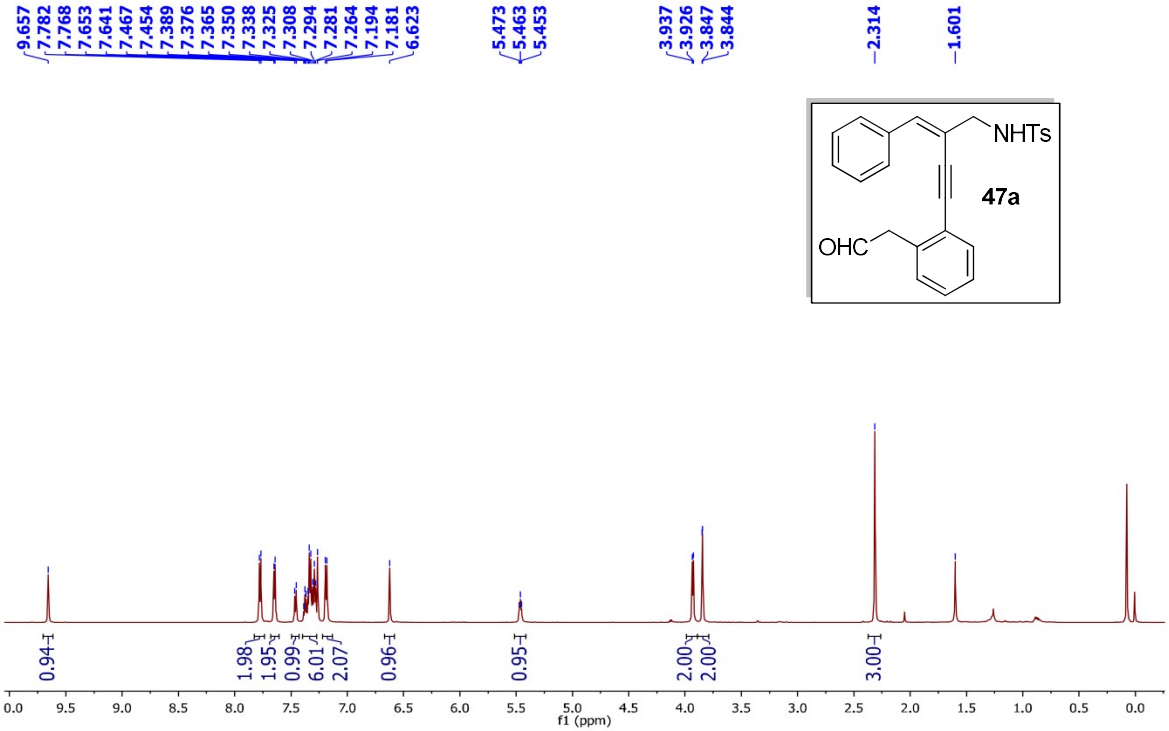


^{13}C{^{1}H} NMR (75 MHz) of **46j :**

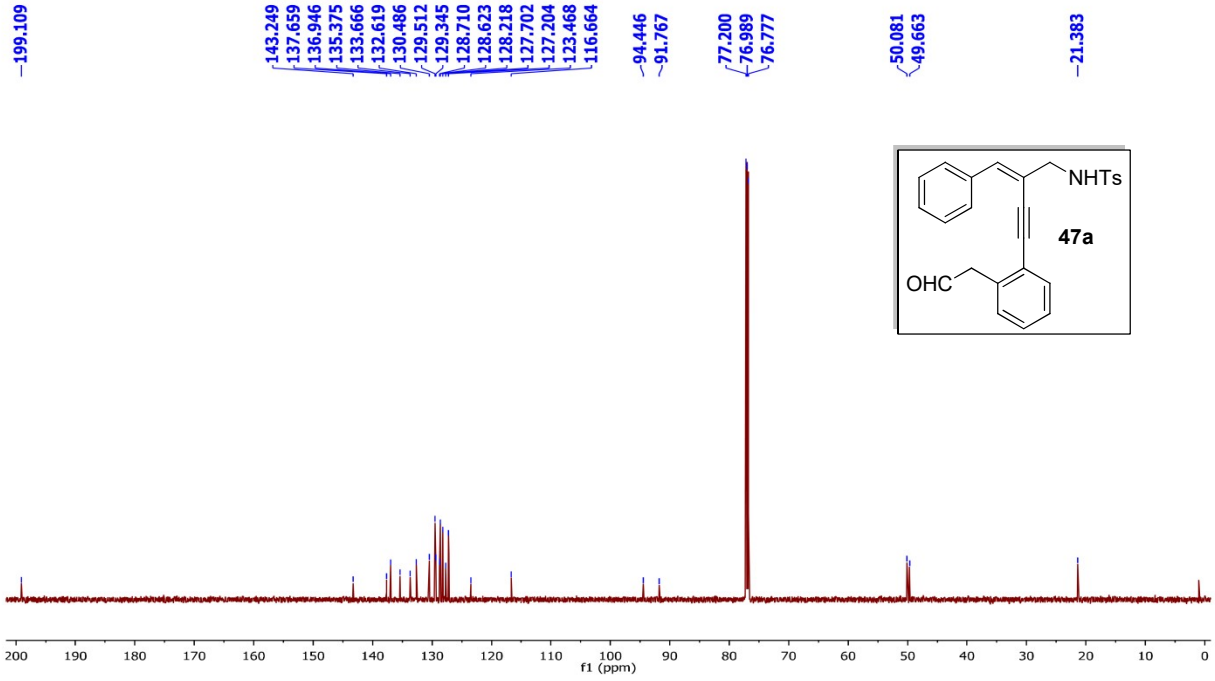


4.2.10.2. NMR Spectra of Compounds 47a-h

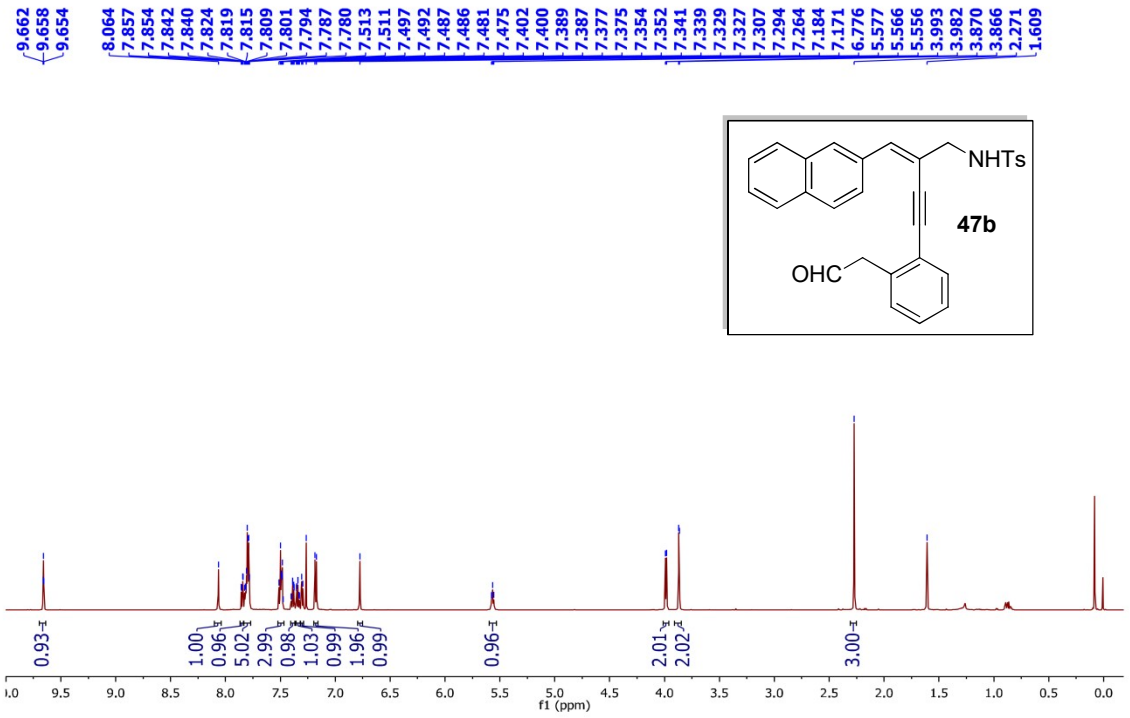
^{1}H NMR (600 MHz) of **47a :**



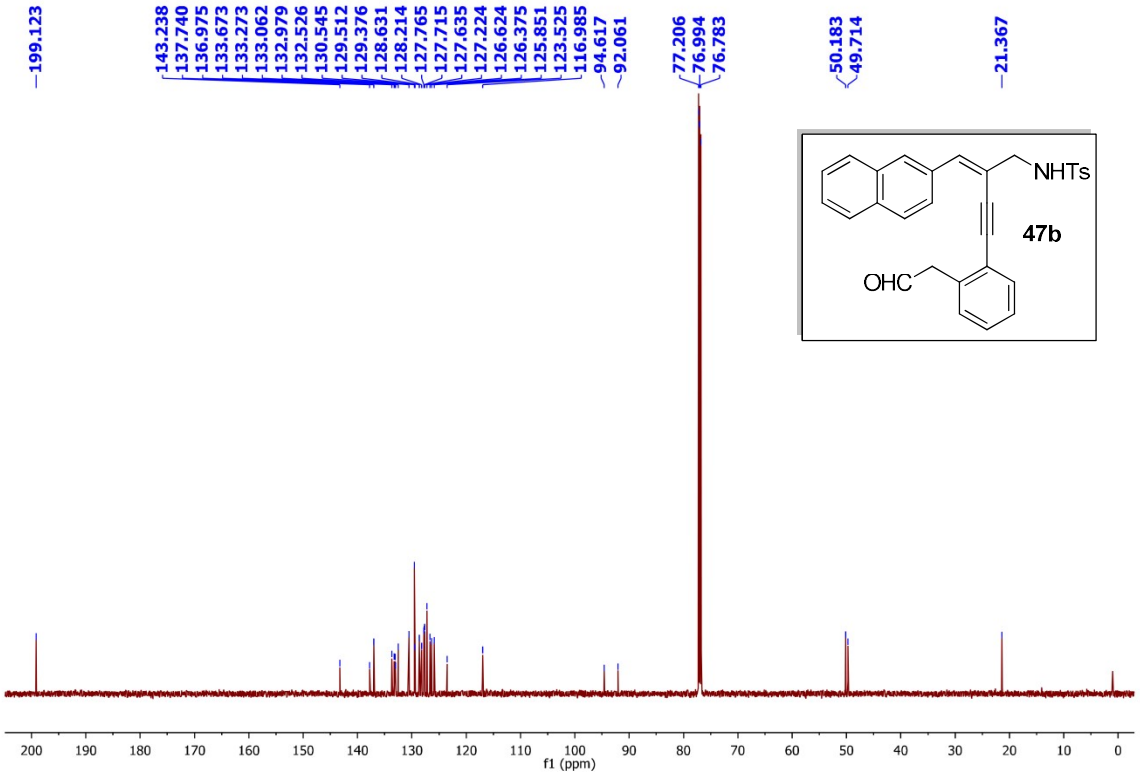
^{13}C{^{1}H} NMR (150 MHz) of **47a :**



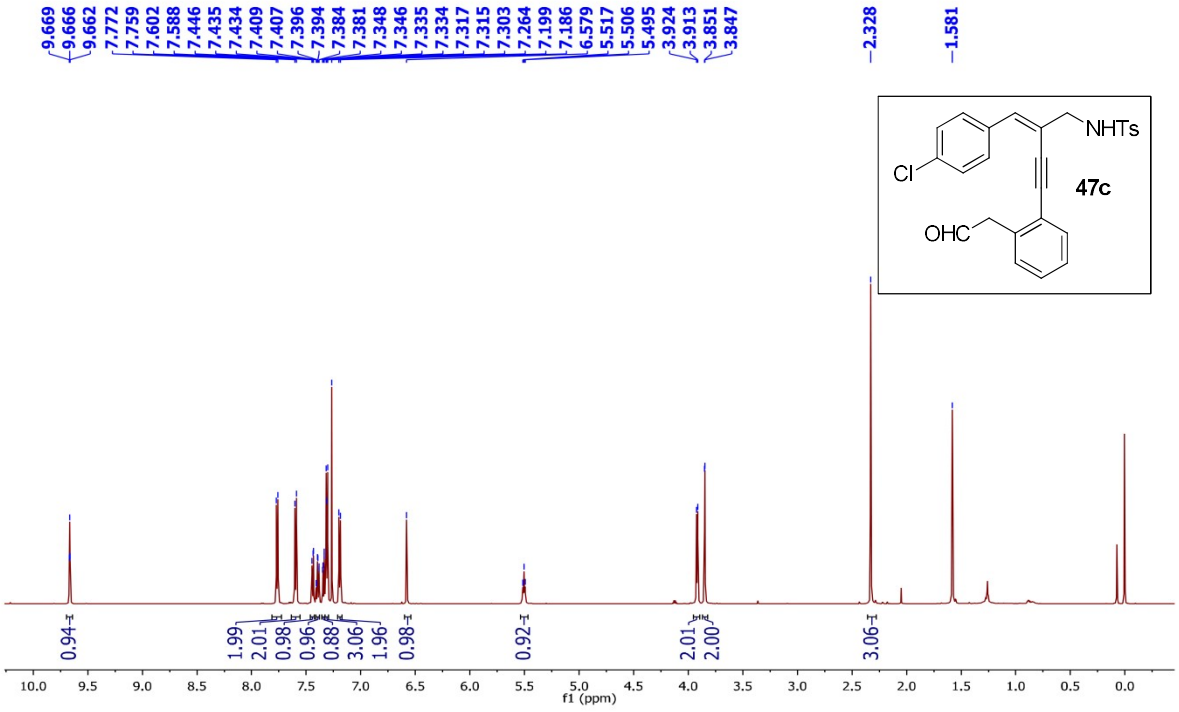
^{1}H NMR (600 MHz) of **47b :**



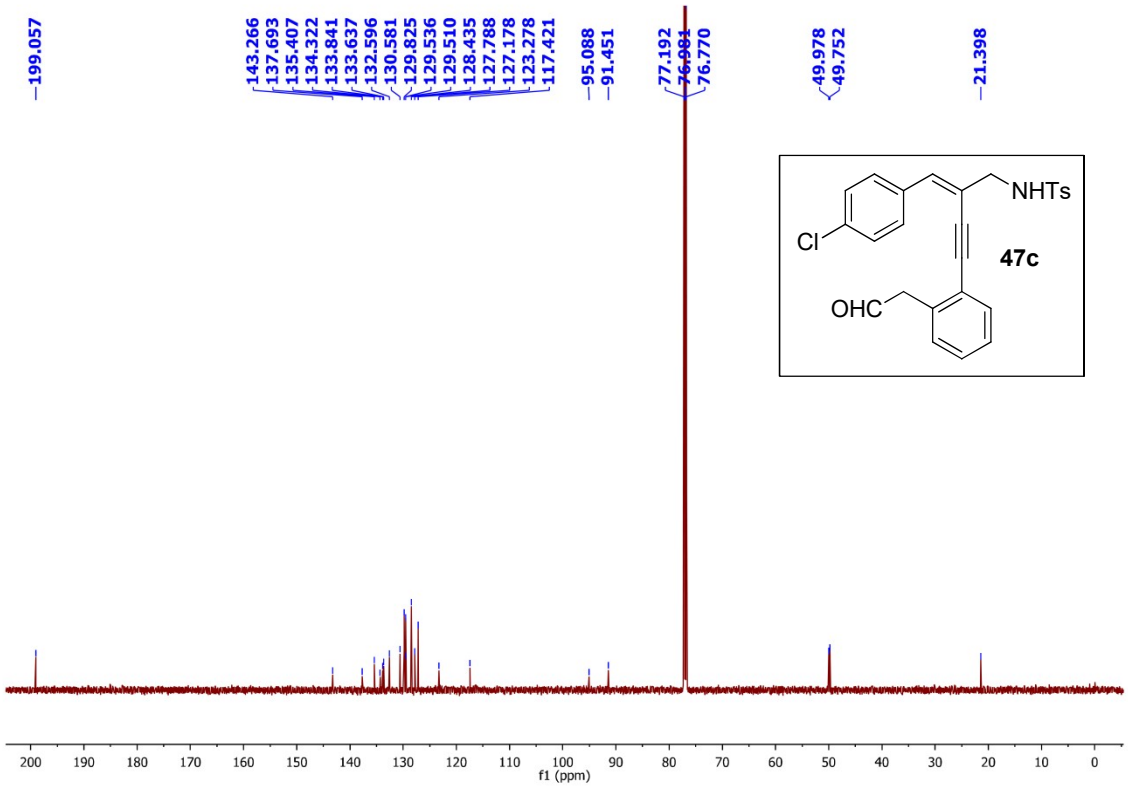
^{13}C{^{1}H} NMR (150 MHz) of **47b :**



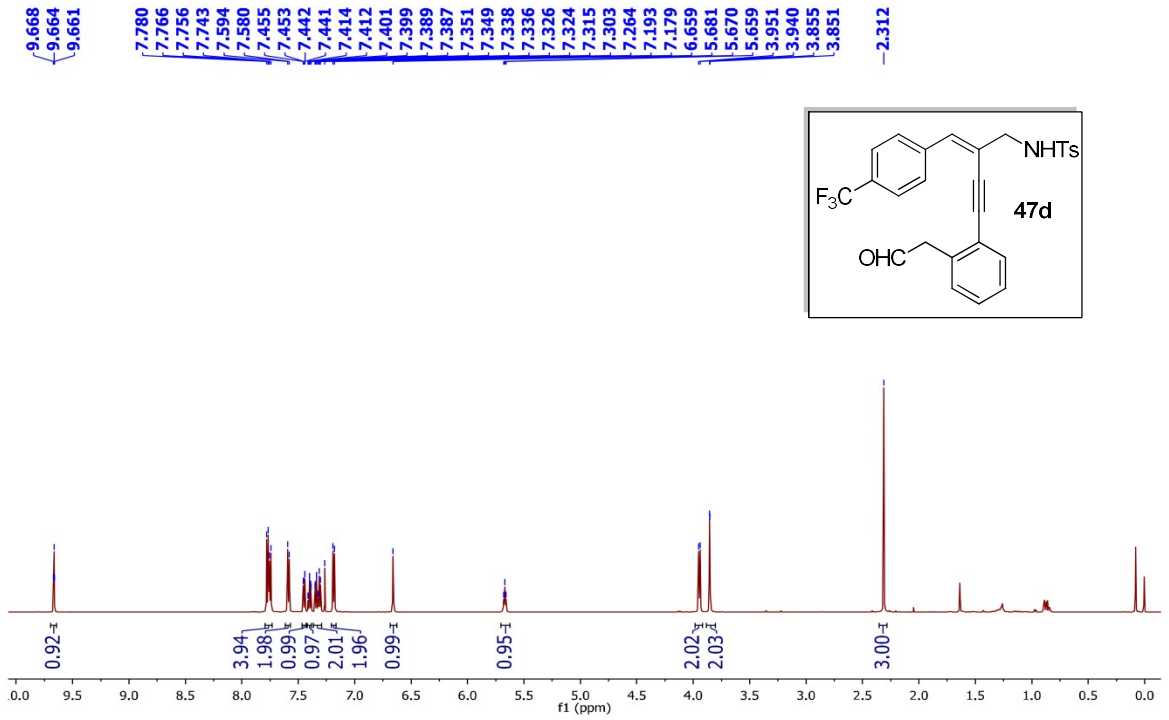
^{1}H NMR (600 MHz) of **47c :**



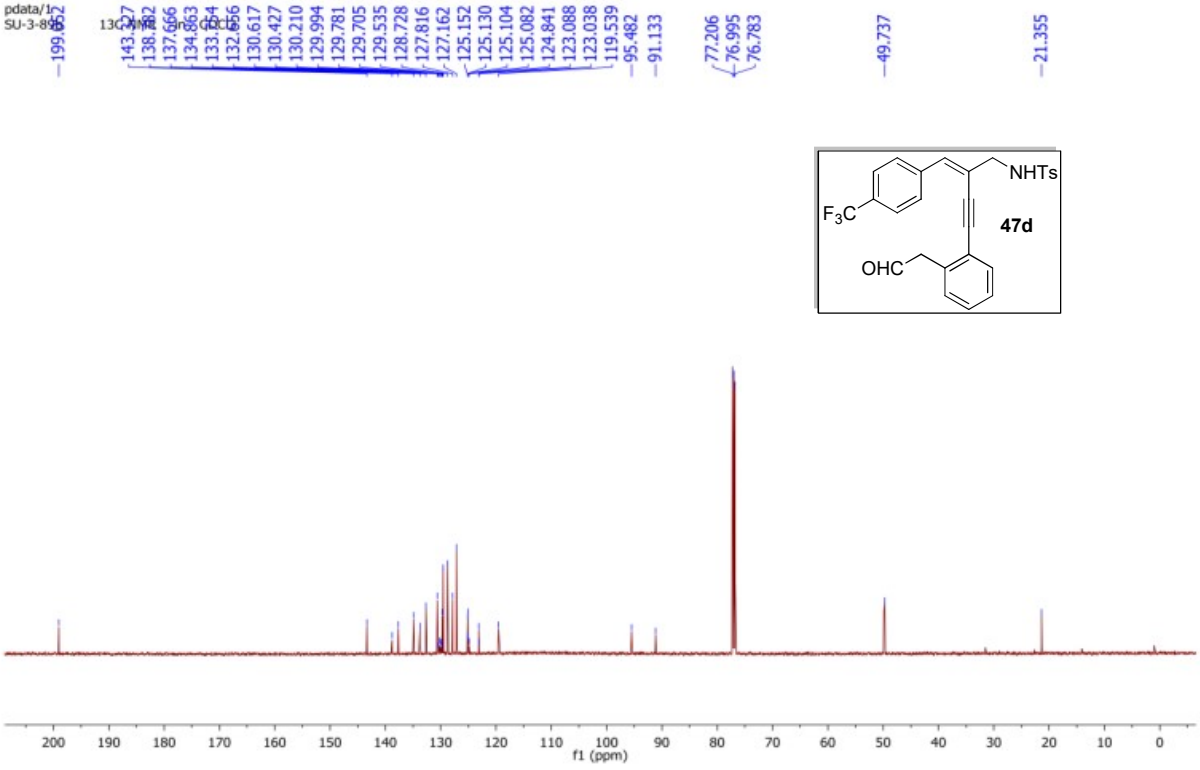
^{13}C{^{1}H} NMR (150 MHz) of **47c :**



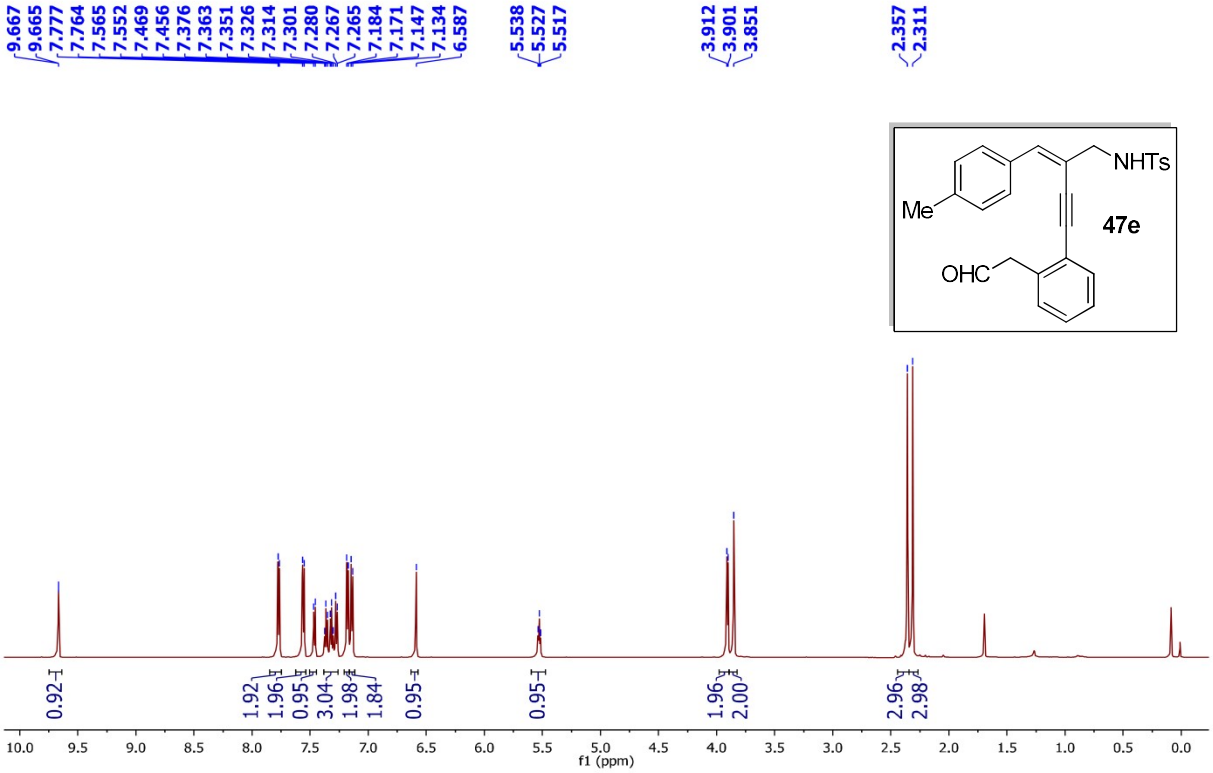
^{1}H NMR (600 MHz) of **47d :**



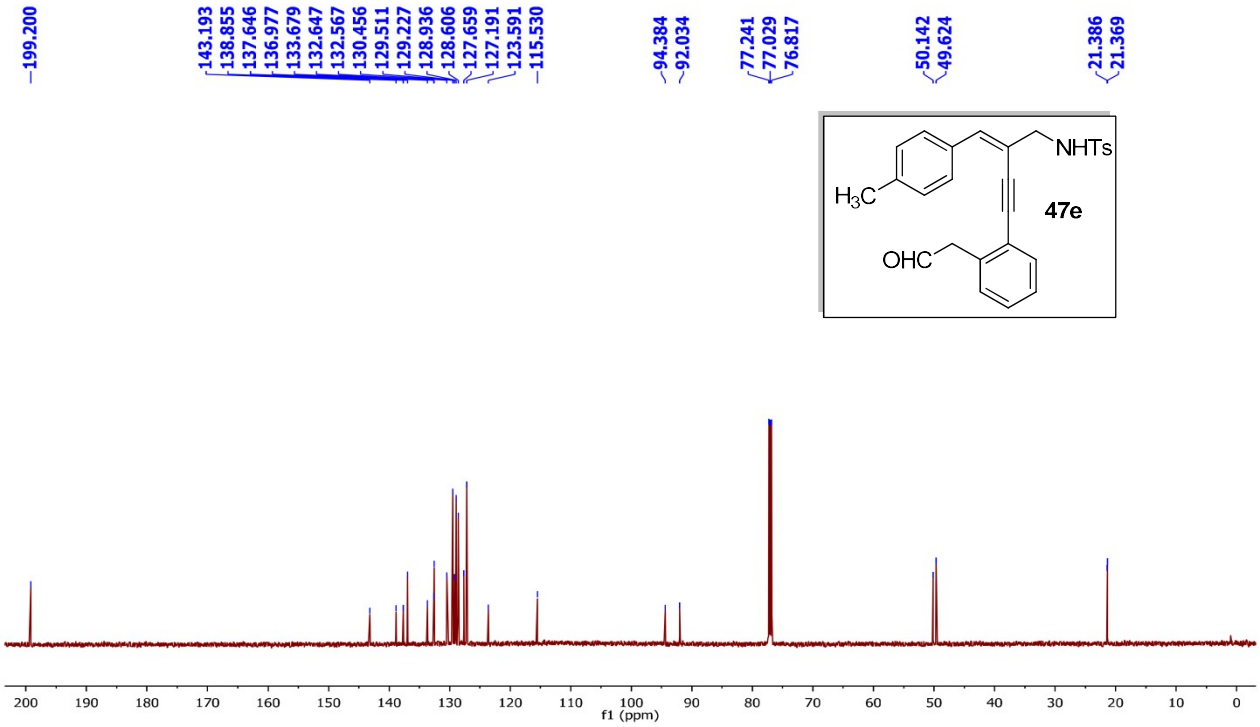
^{13}C{^{1}H} NMR (150 MHz) of **47d :**



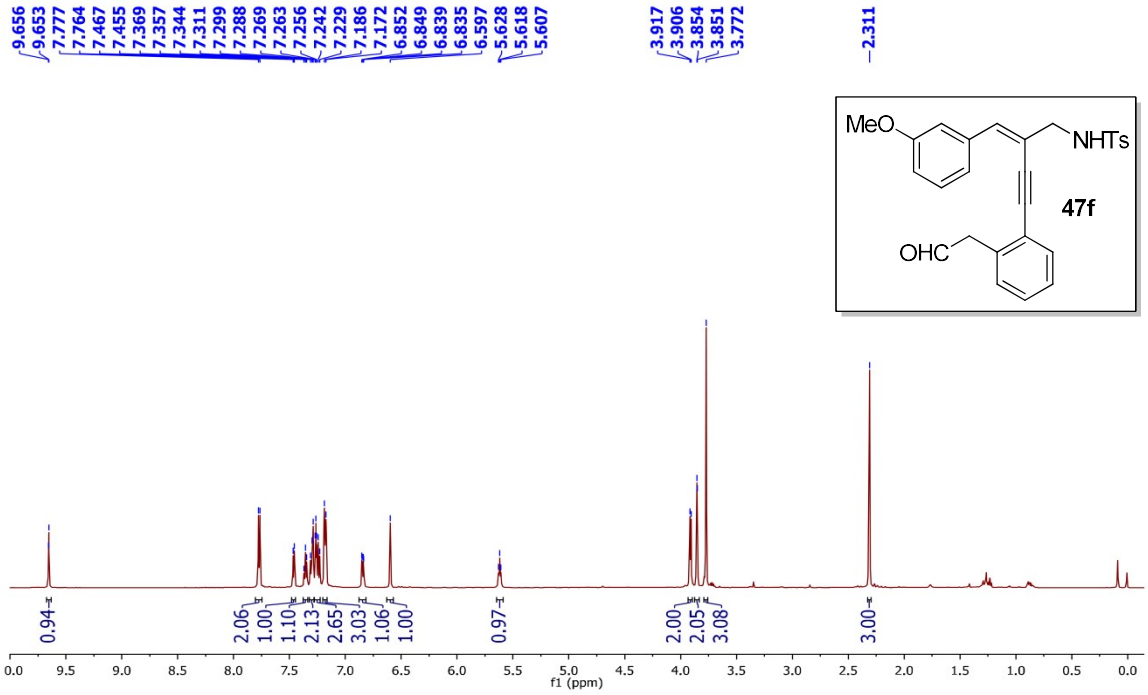
^{1}H NMR (600 MHz) of **47e :**



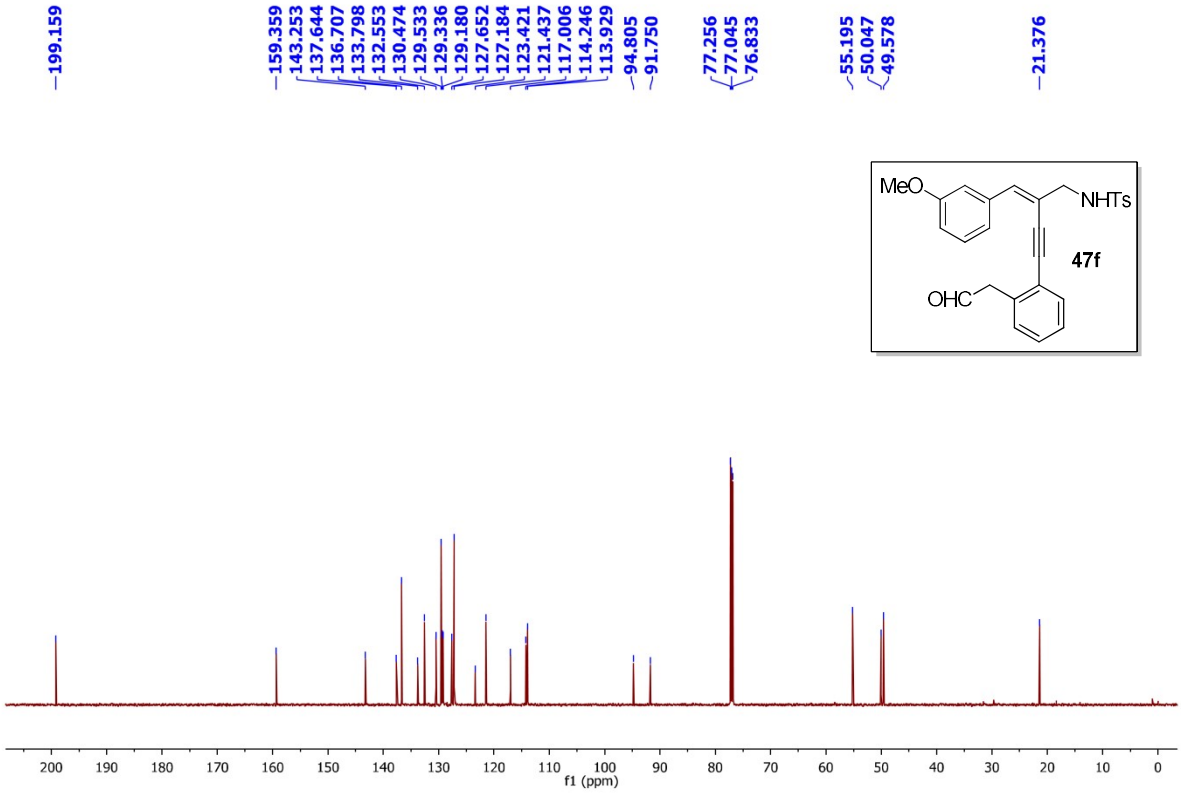
^{13}C{^{1}H} NMR (150 MHz) of **47e :**



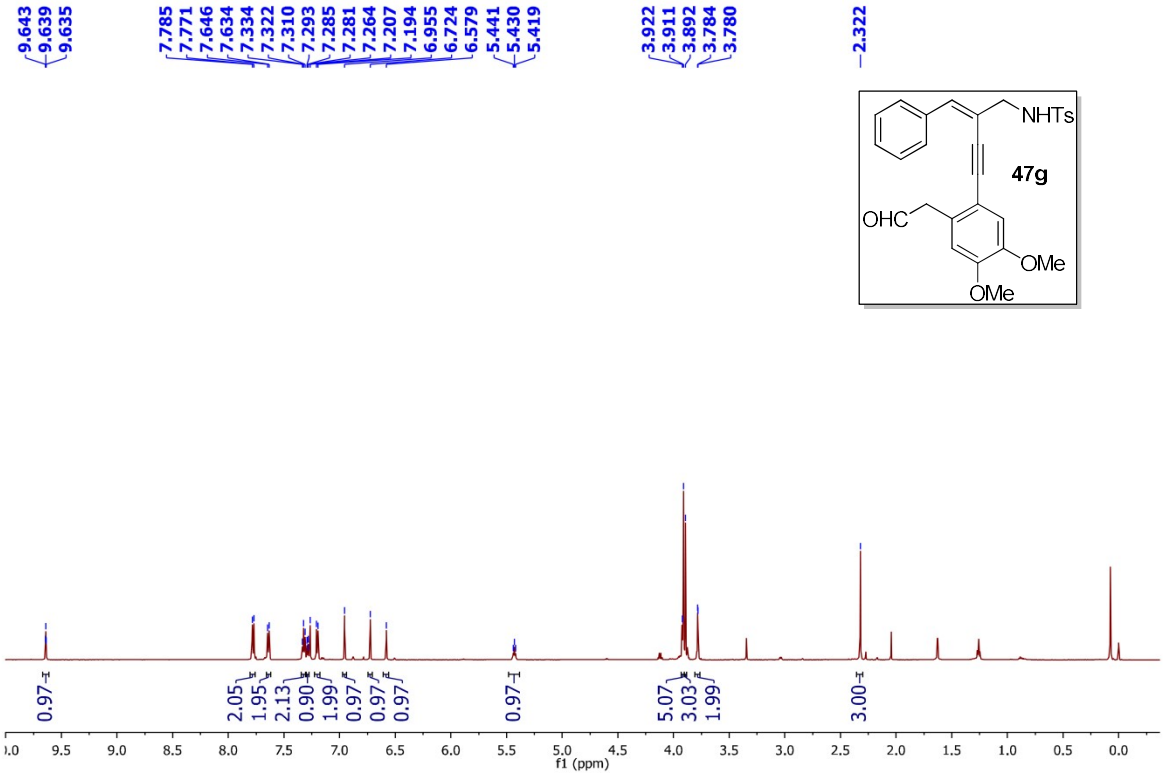
^{1}H NMR (600 MHz) of **47f :**



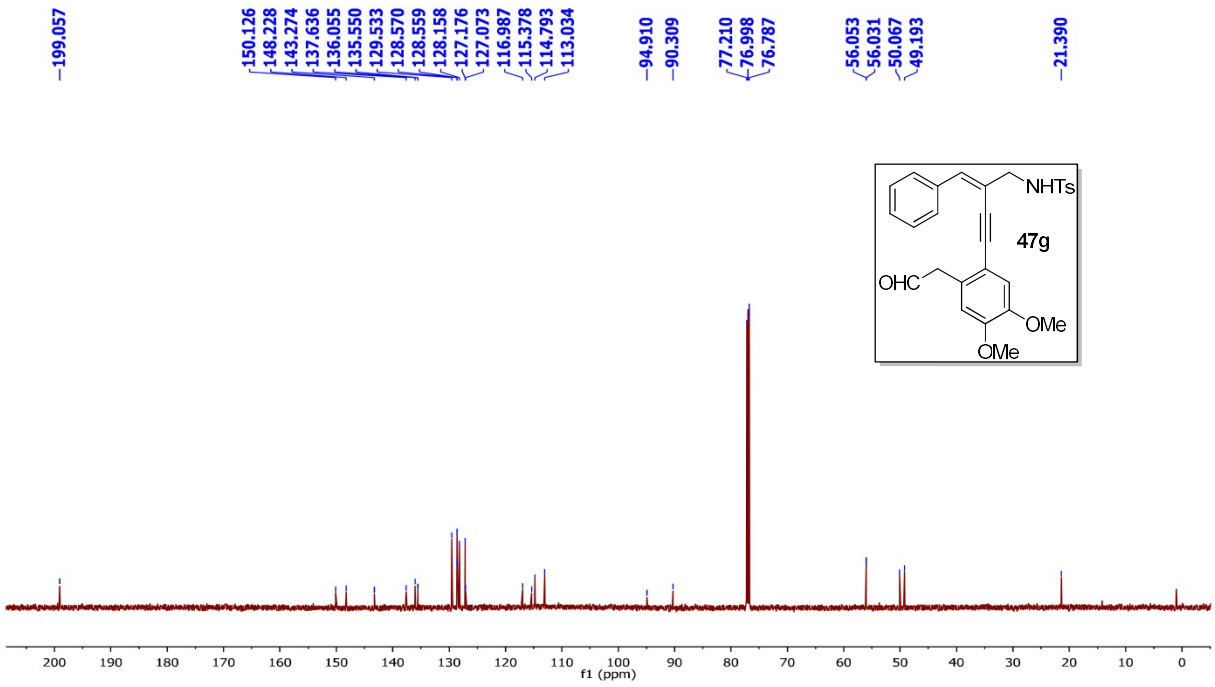
^{13}C{^{1}H} NMR (150 MHz) of **47f :**



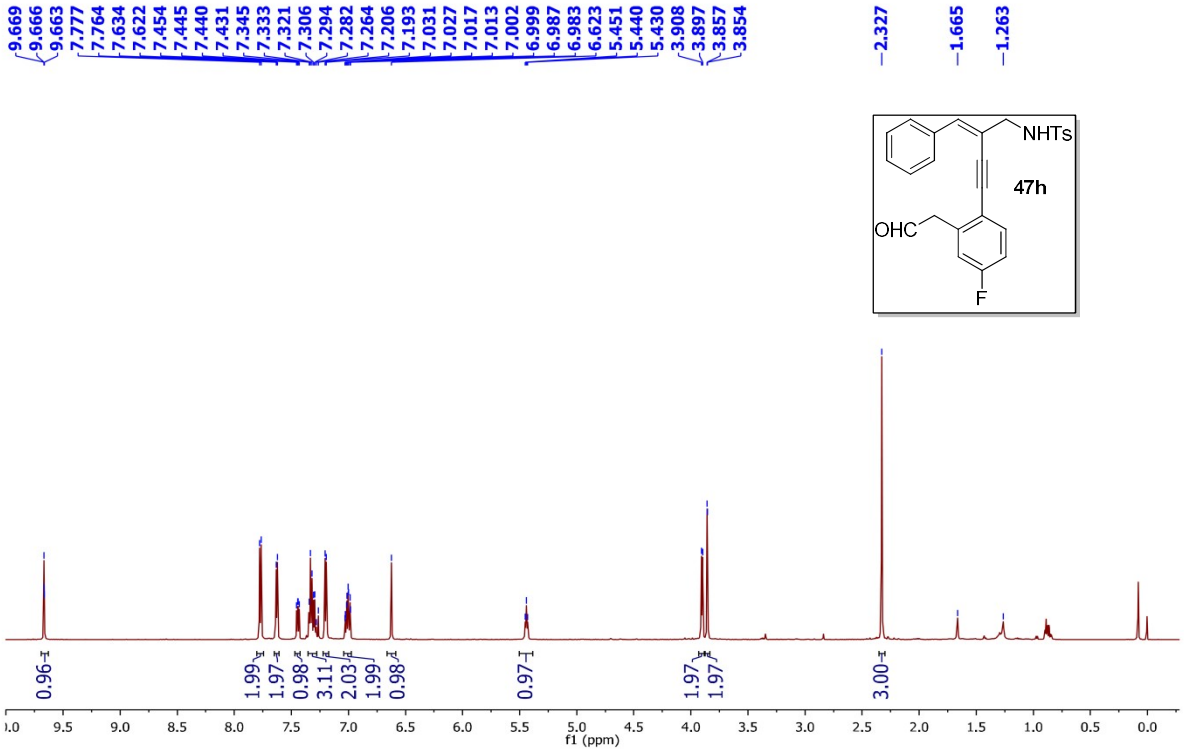
^{1}H NMR (600 MHz) of **47g :**



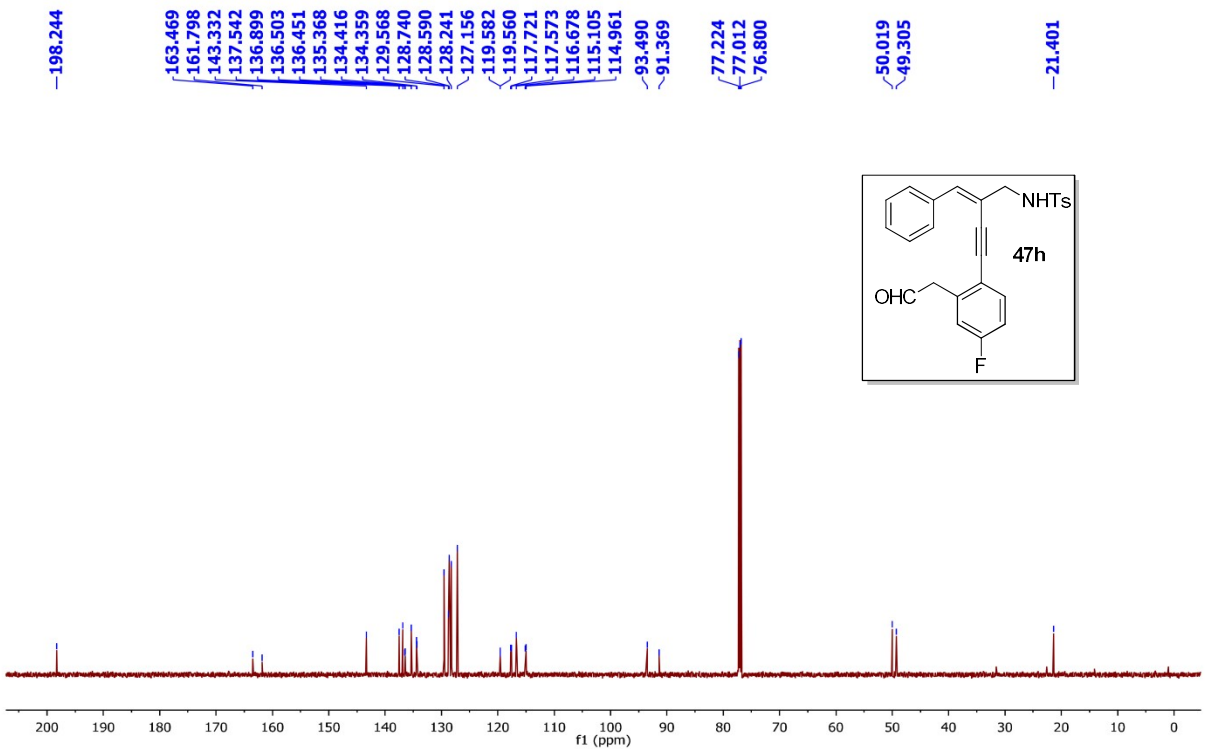
^{13}C{^{1}H} NMR (150 MHz) of **47g :**



^{1}H NMR (600 MHz) of **47h :**

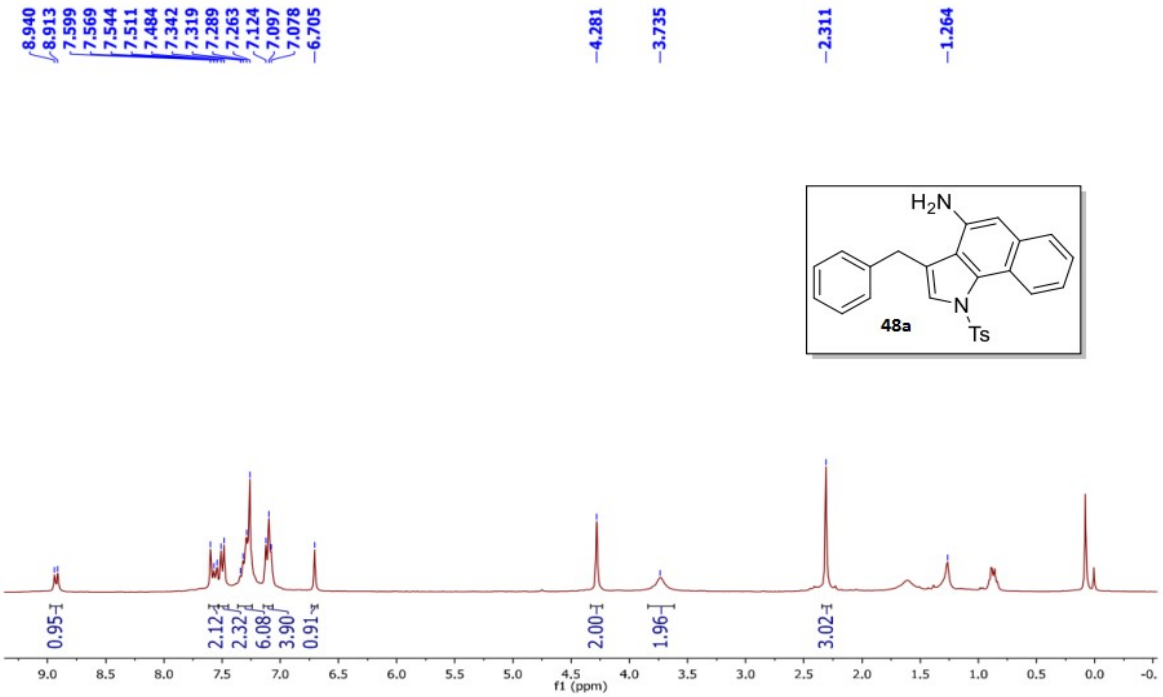


^{13}C{^{1}H} NMR (150 MHz) of **47h :**

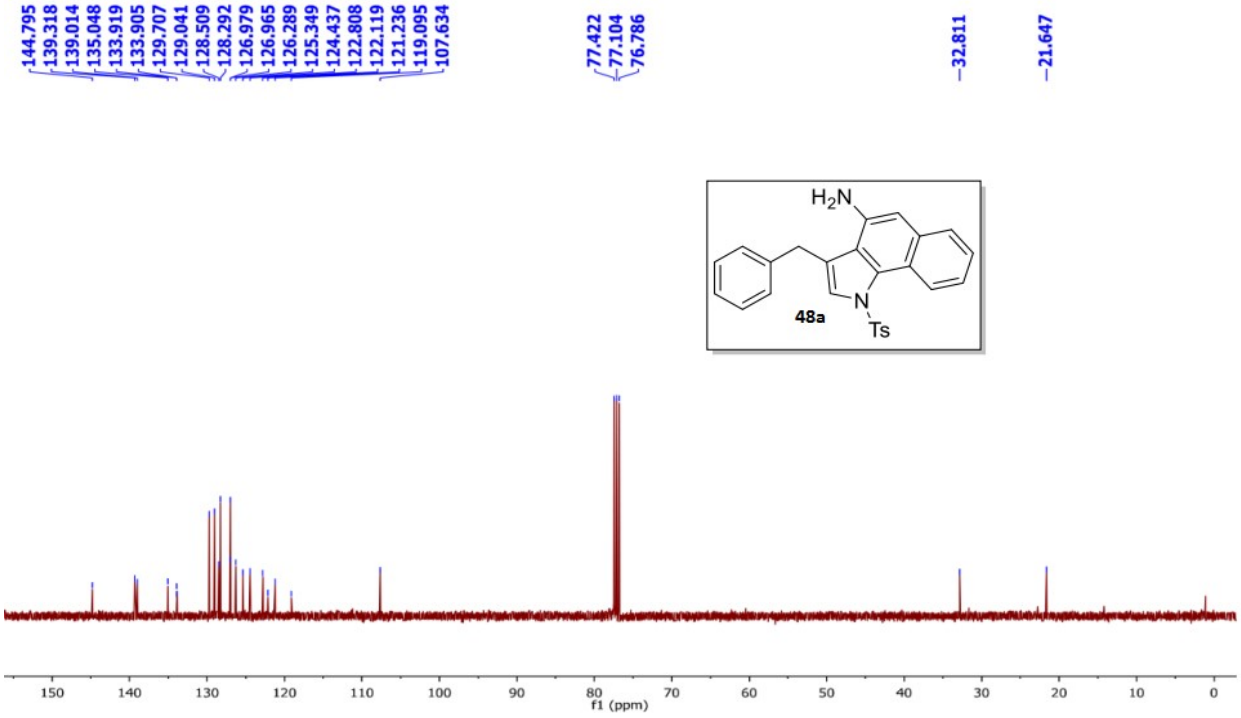


4.2.10.3. NMR Spectra of Compounds 48a-j

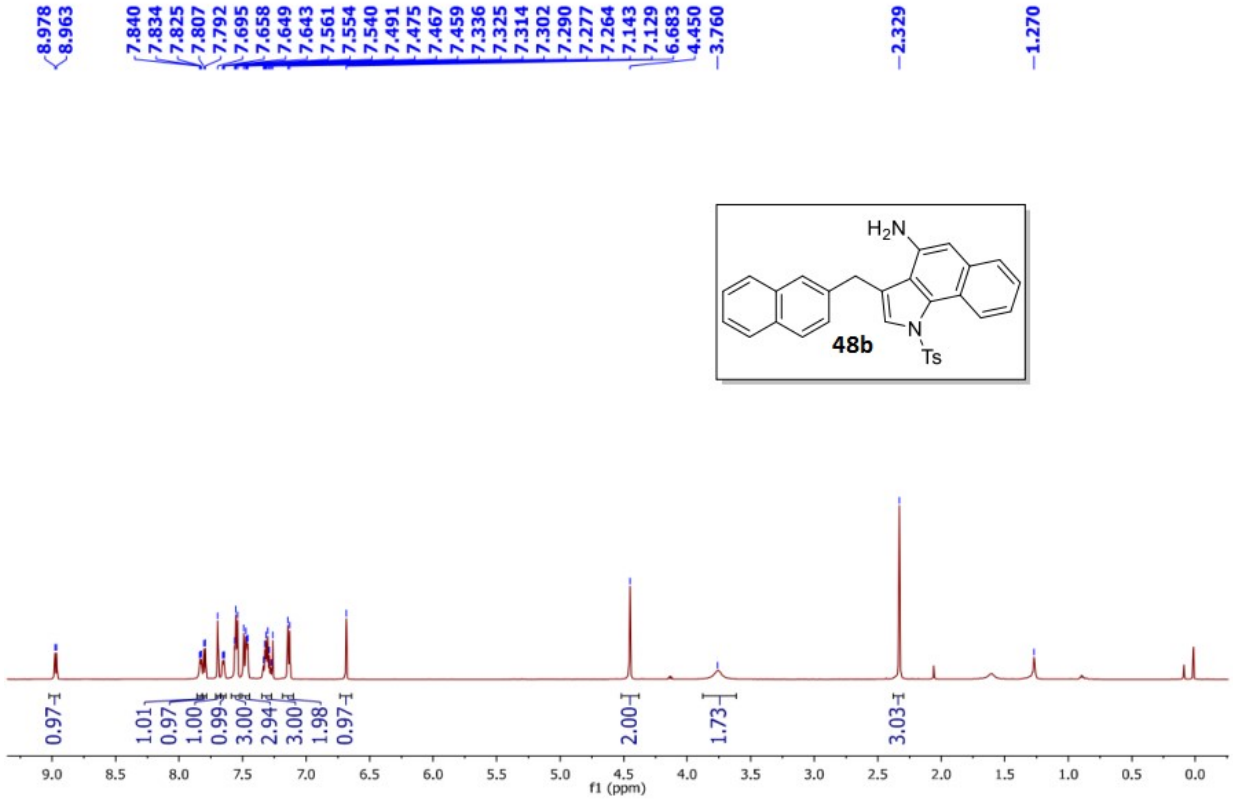
^{1}H NMR (300 MHz) of **48a:**



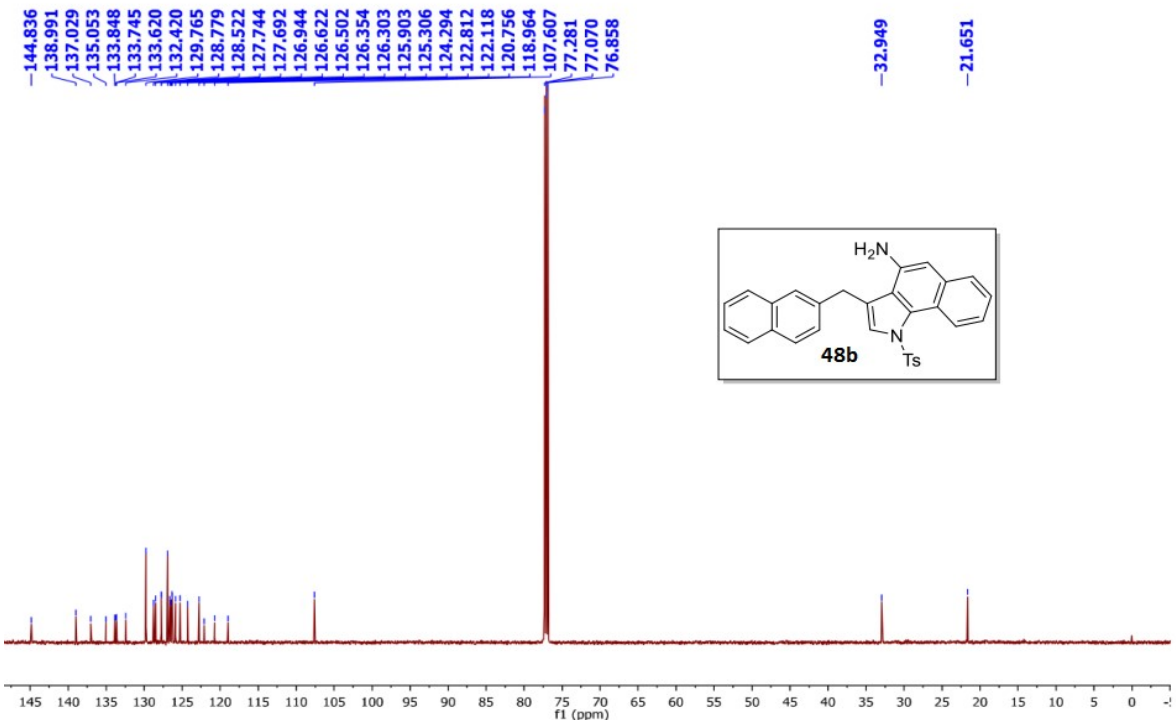
^{13}C{^{1}H} NMR (100 MHz) of **48a:**



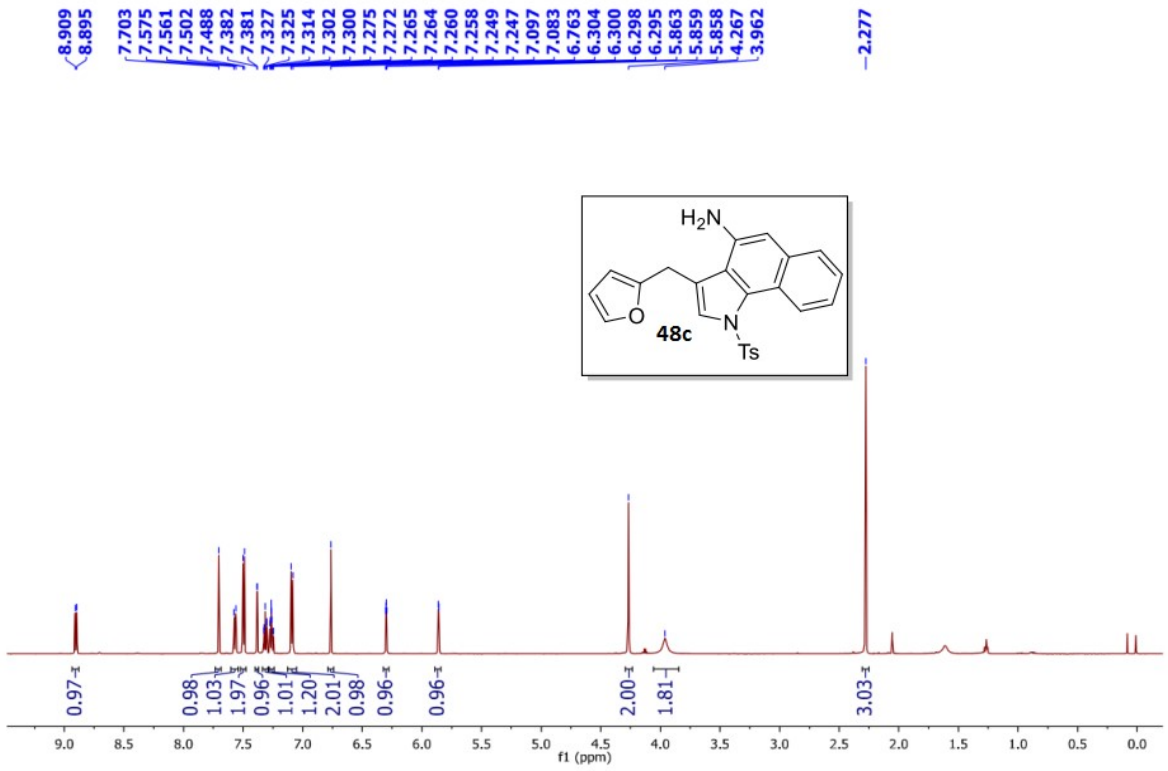
^{1}H NMR (600 MHz) of **48b:**



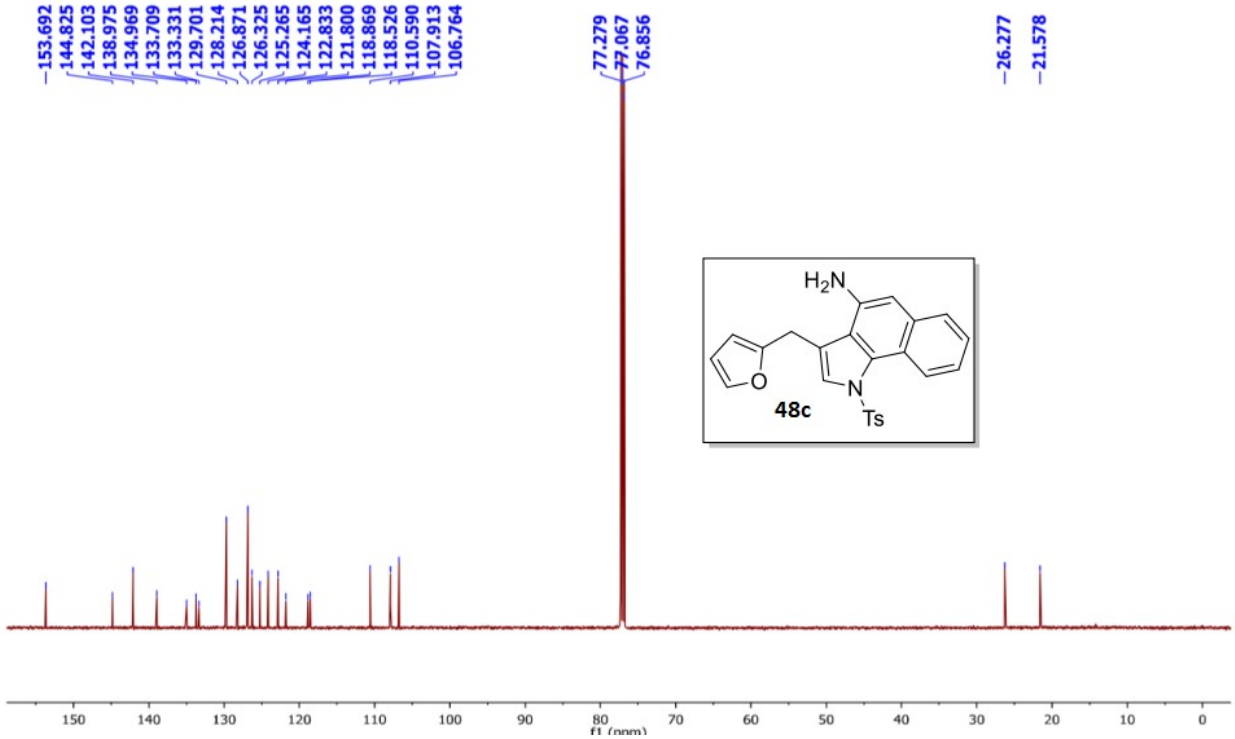
^{13}C{^{1}H} NMR (150 MHz) of **48b:**



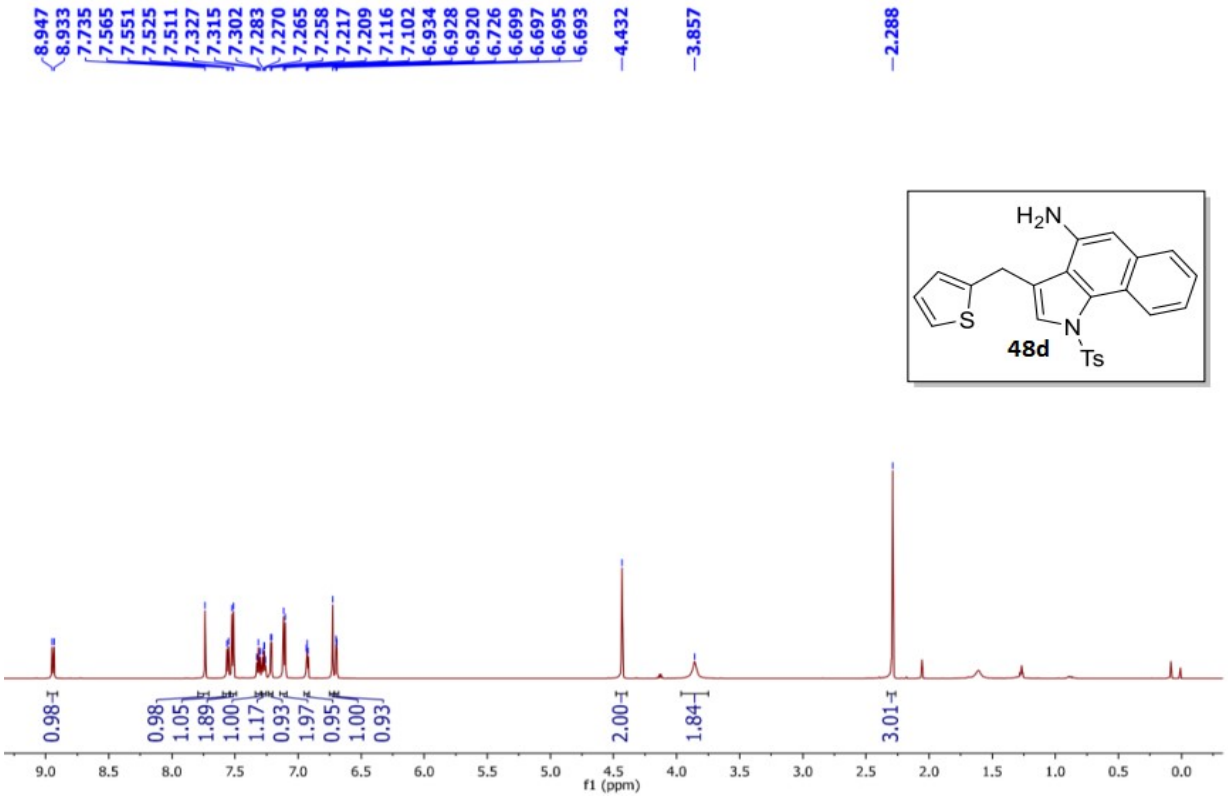
^{1}H NMR (600 MHz) of **48c:**



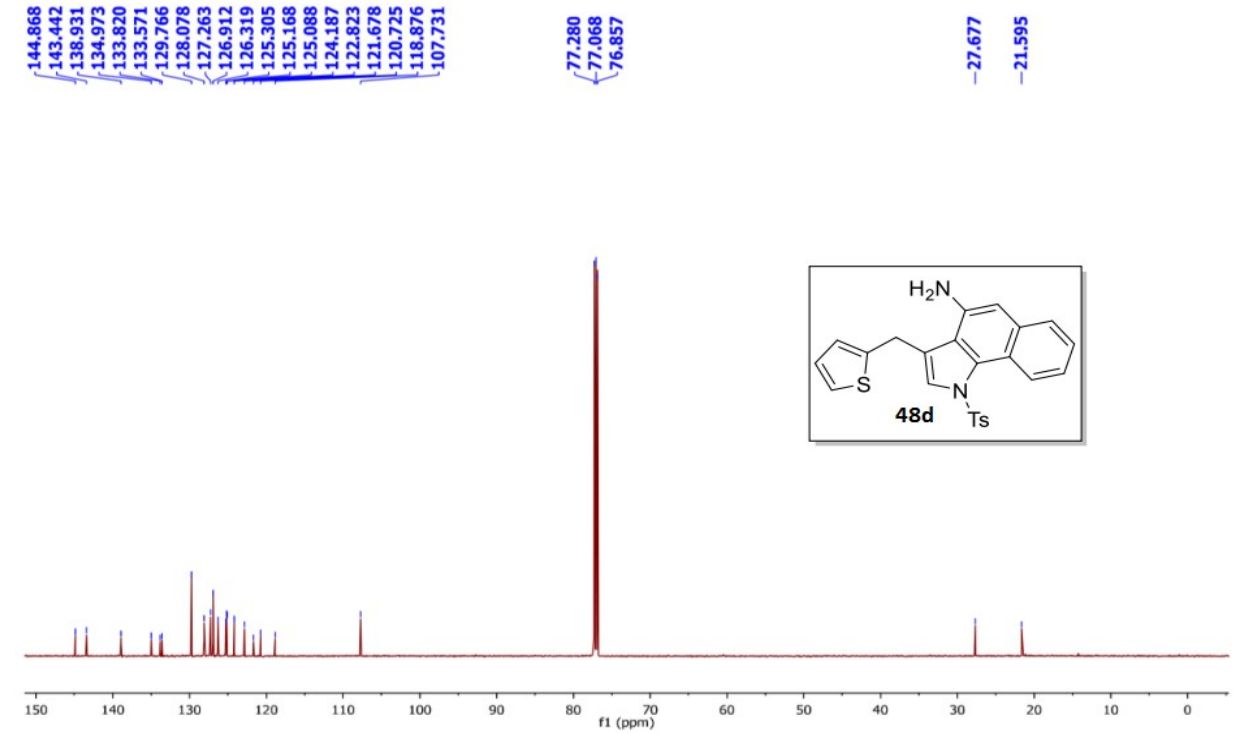
^{13}C{^{1}H} NMR (150 MHz) of **48c:**



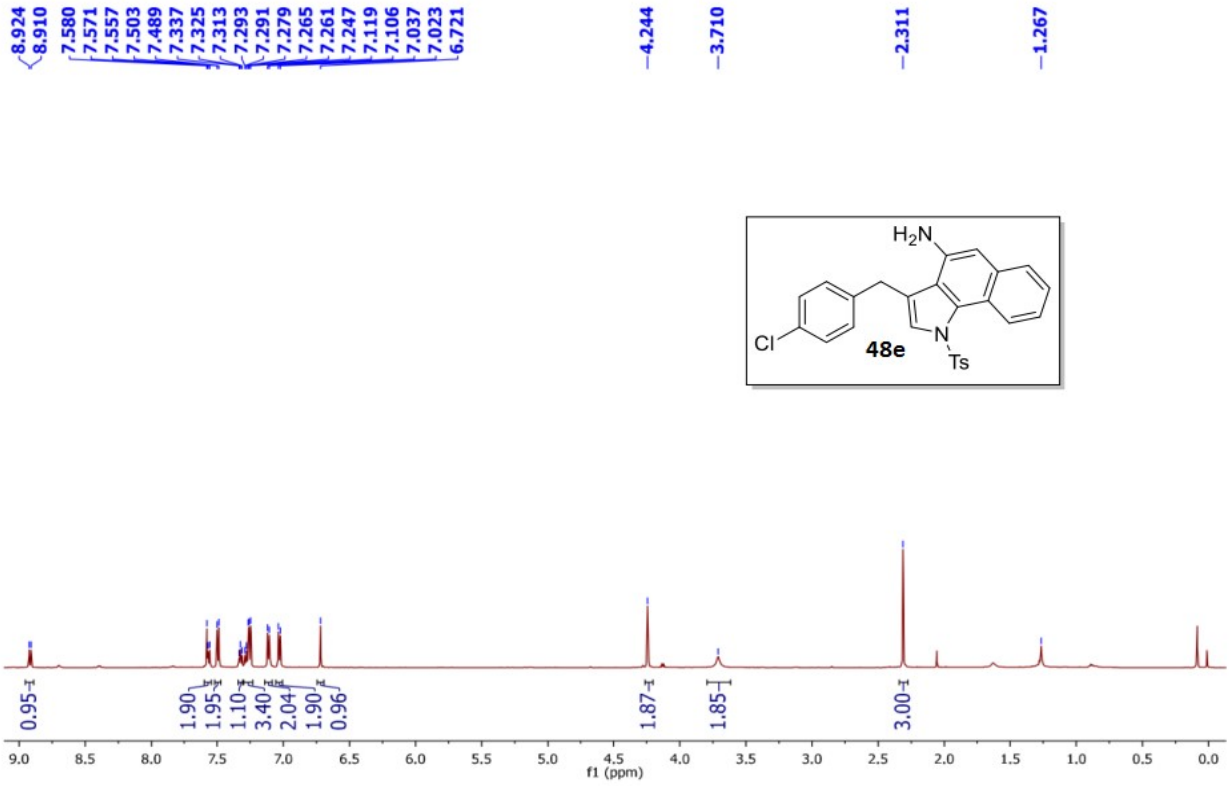
^{1}H NMR (600 MHz) of **48d:**



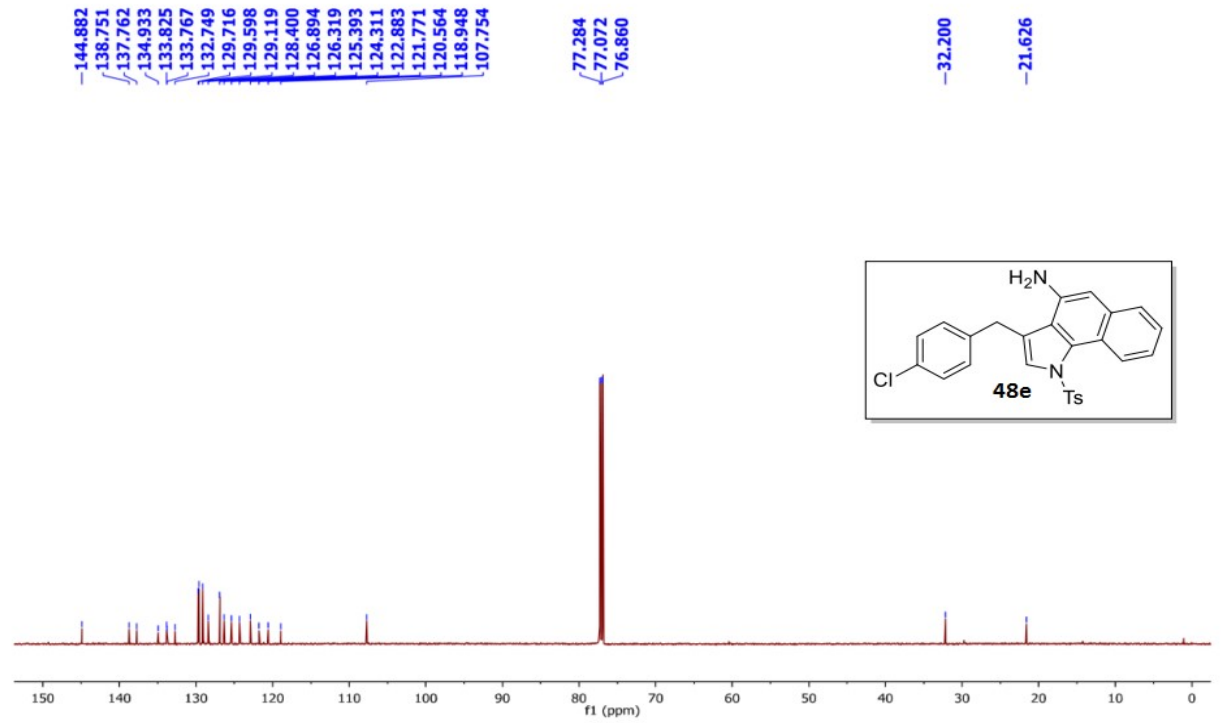
^{13}C{^{1}H} NMR (150 MHz) of **48d:**



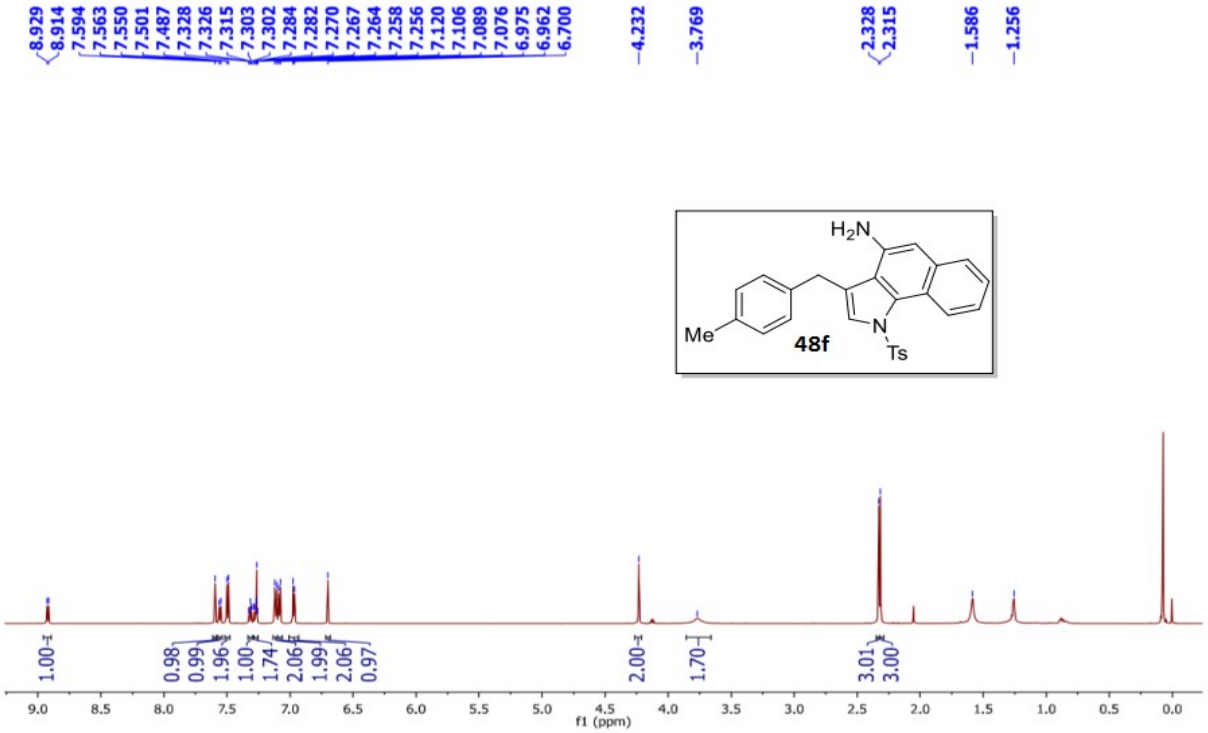
^{1}H NMR (600 MHz) of **48e:**



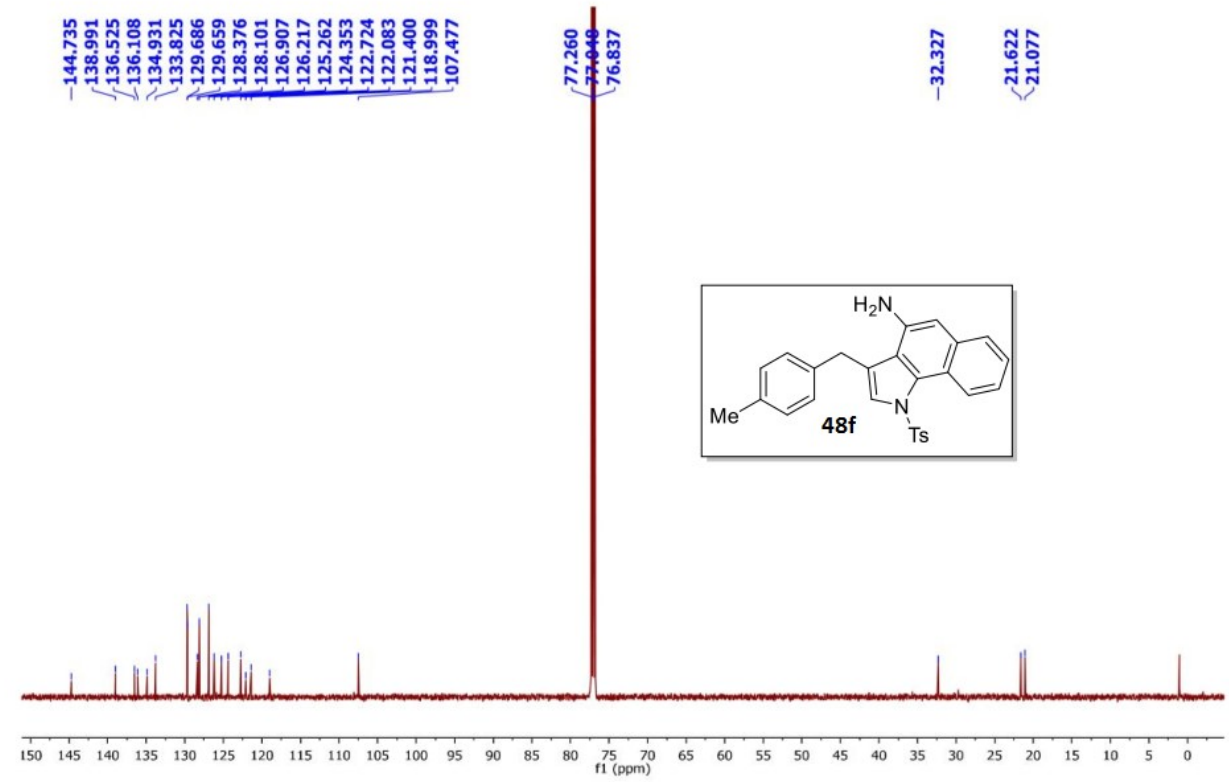
^{13}C{^{1}H} NMR (150 MHz) of **48e:**



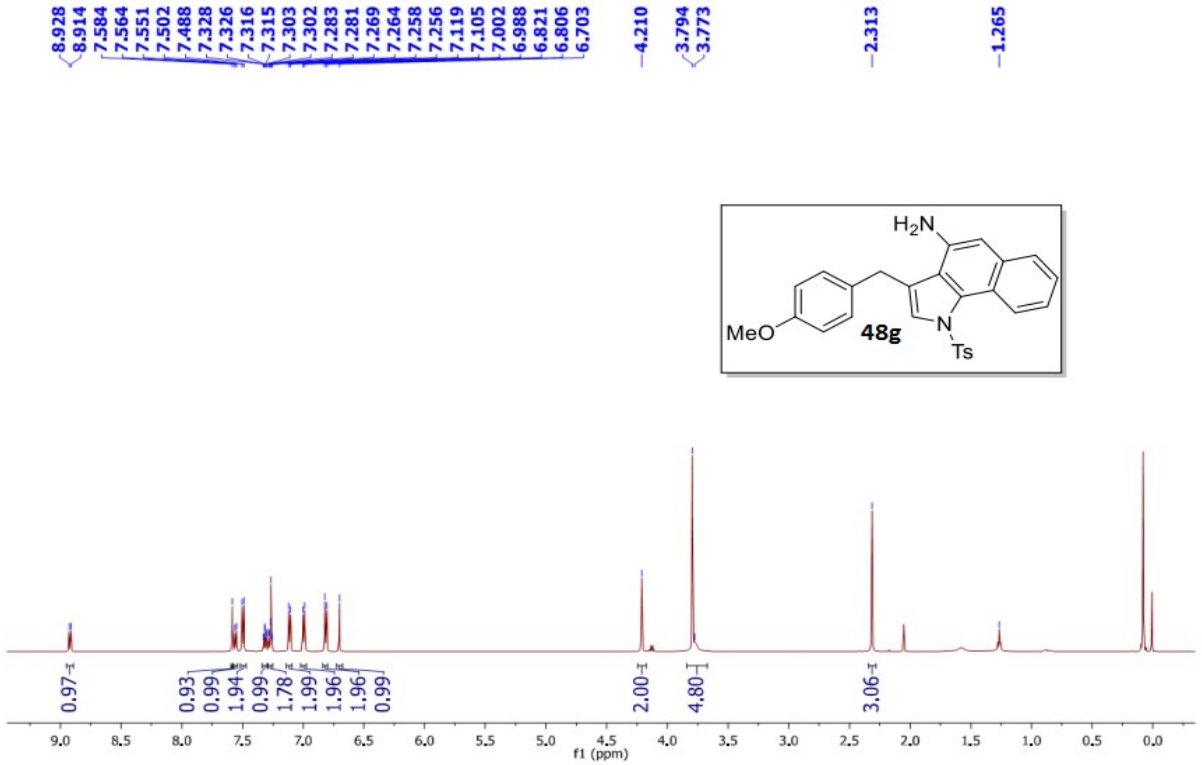
^{1}H NMR (600 MHz) of **48f:**



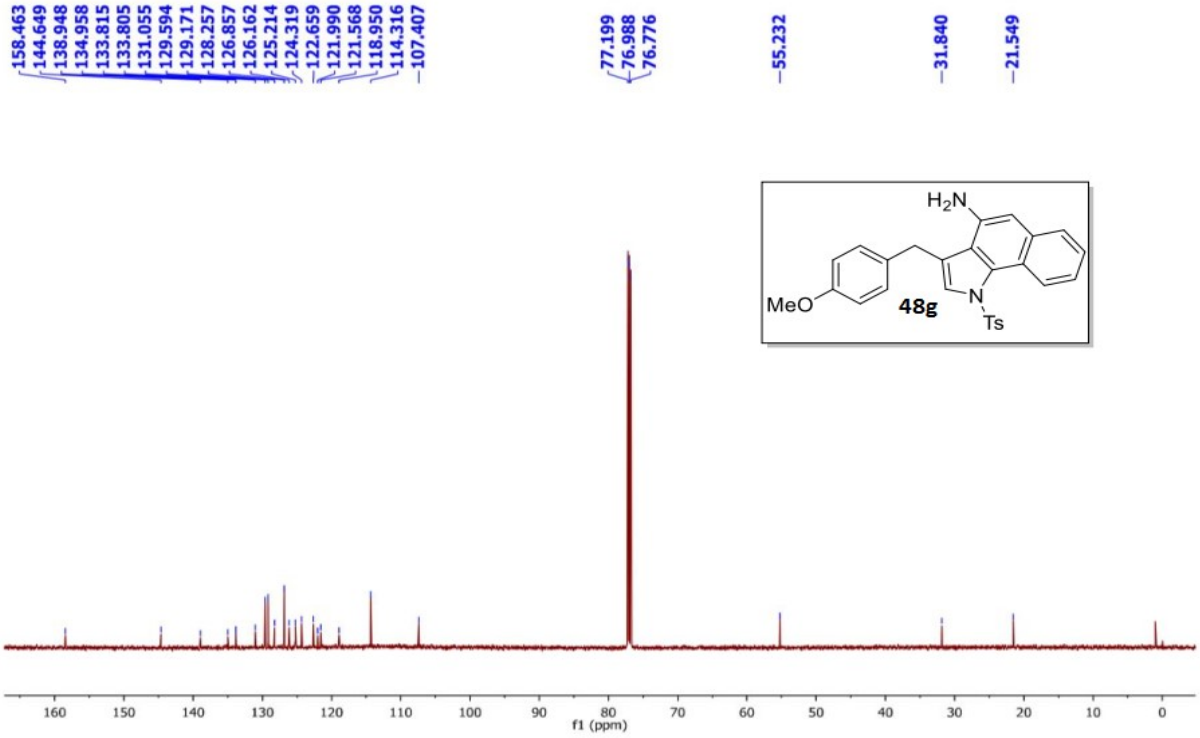
^{13}C{^{1}H} NMR (150 MHz) of **48f:**



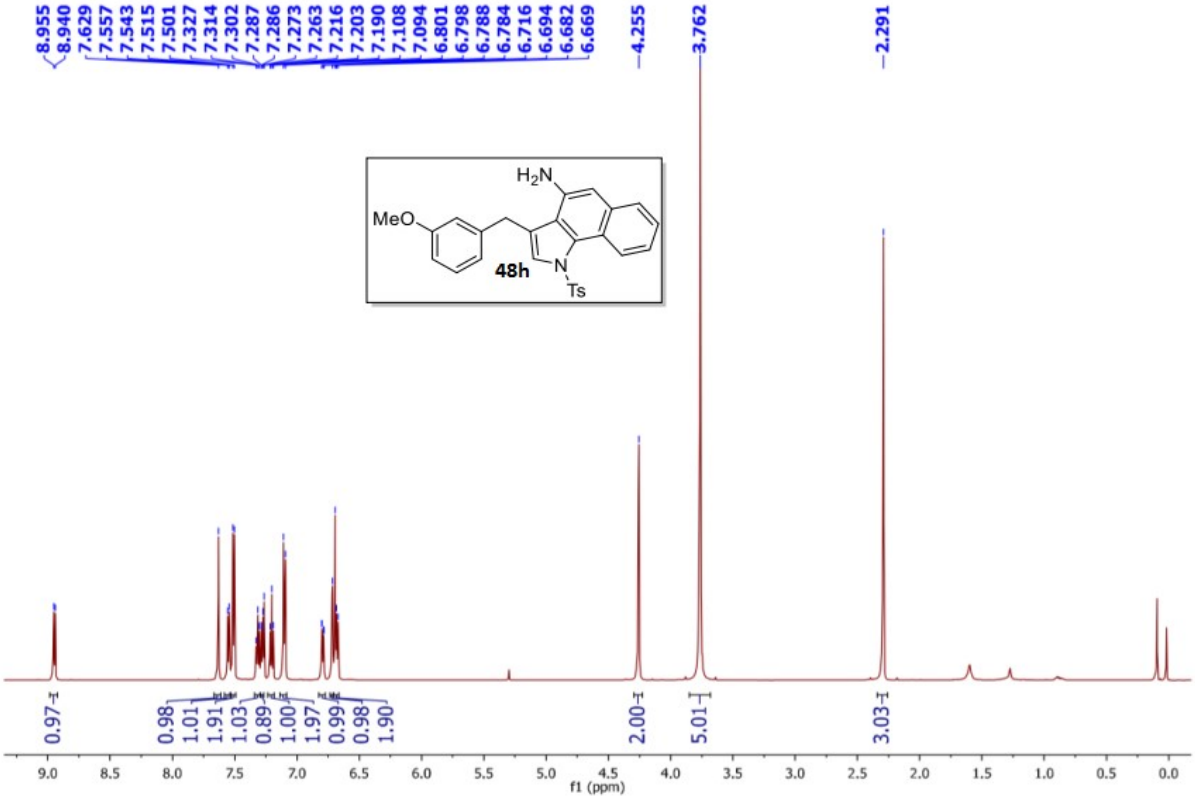
^{1}H NMR (600 MHz) of **48g:**



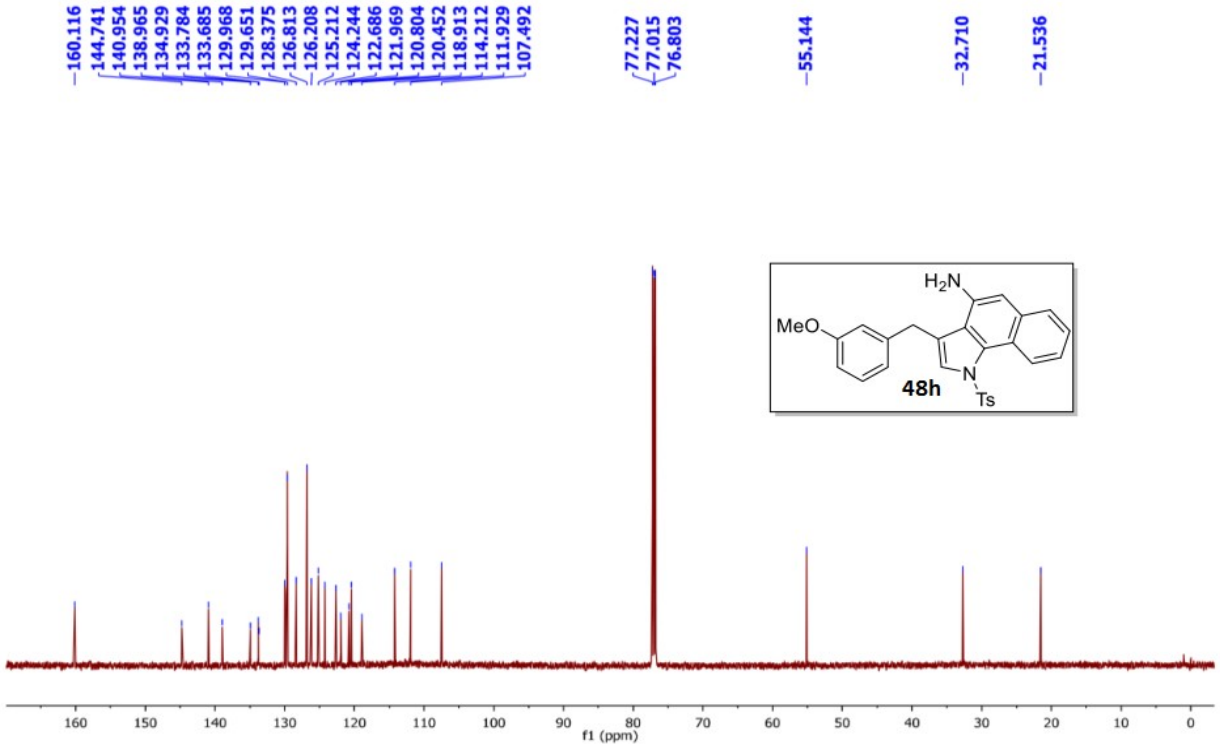
^{13}C{^{1}H} NMR (150 MHz) of **48g:**



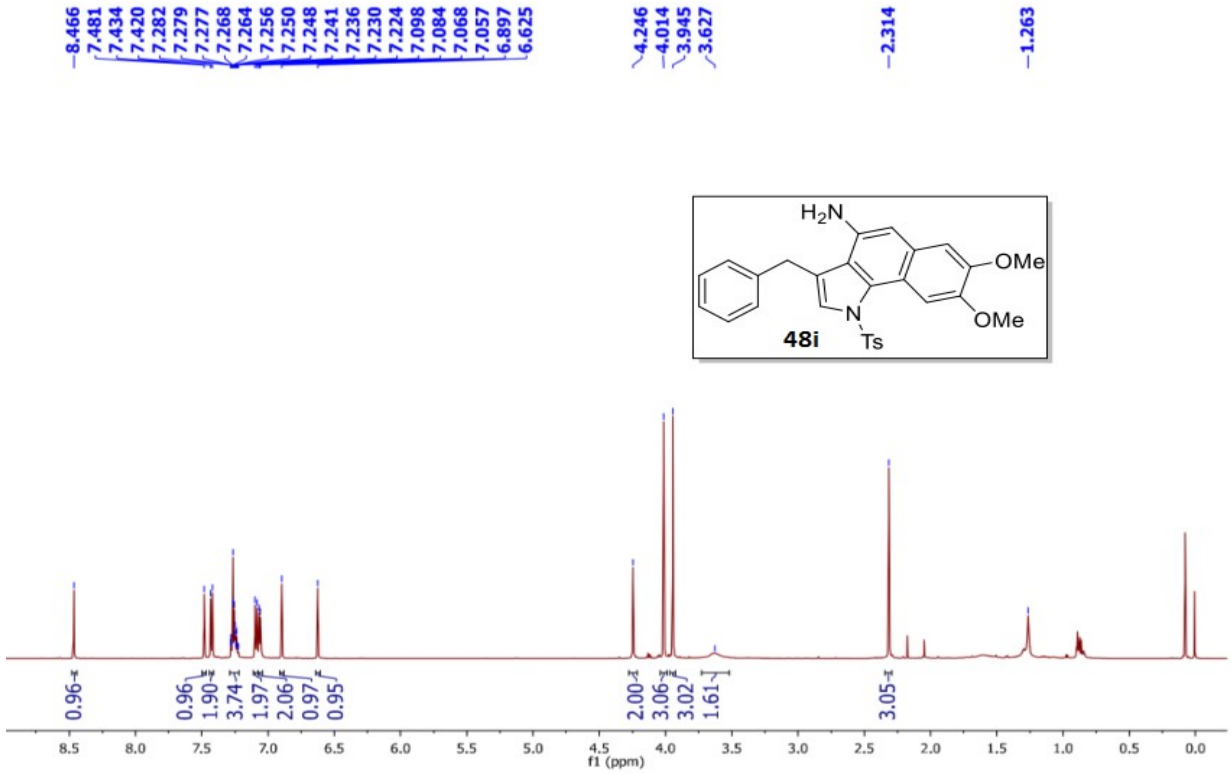
^{1}H NMR (600 MHz) of **48h:**



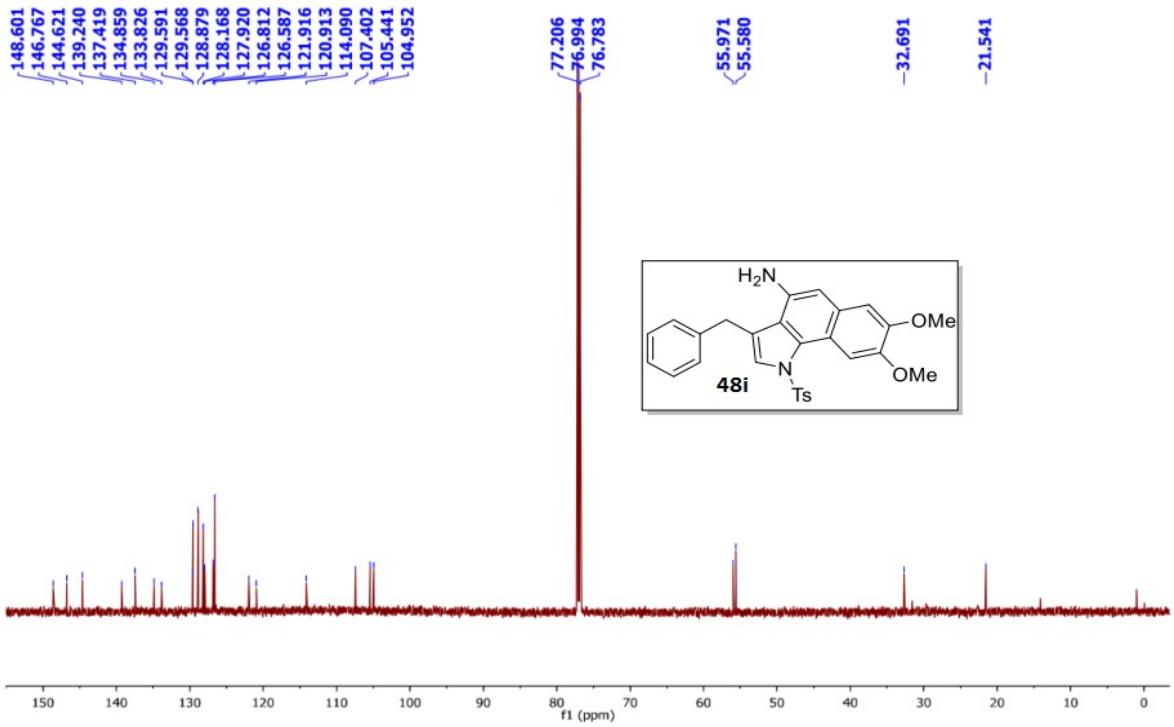
^{13}C{^{1}H} NMR (150 MHz) of **48h:**



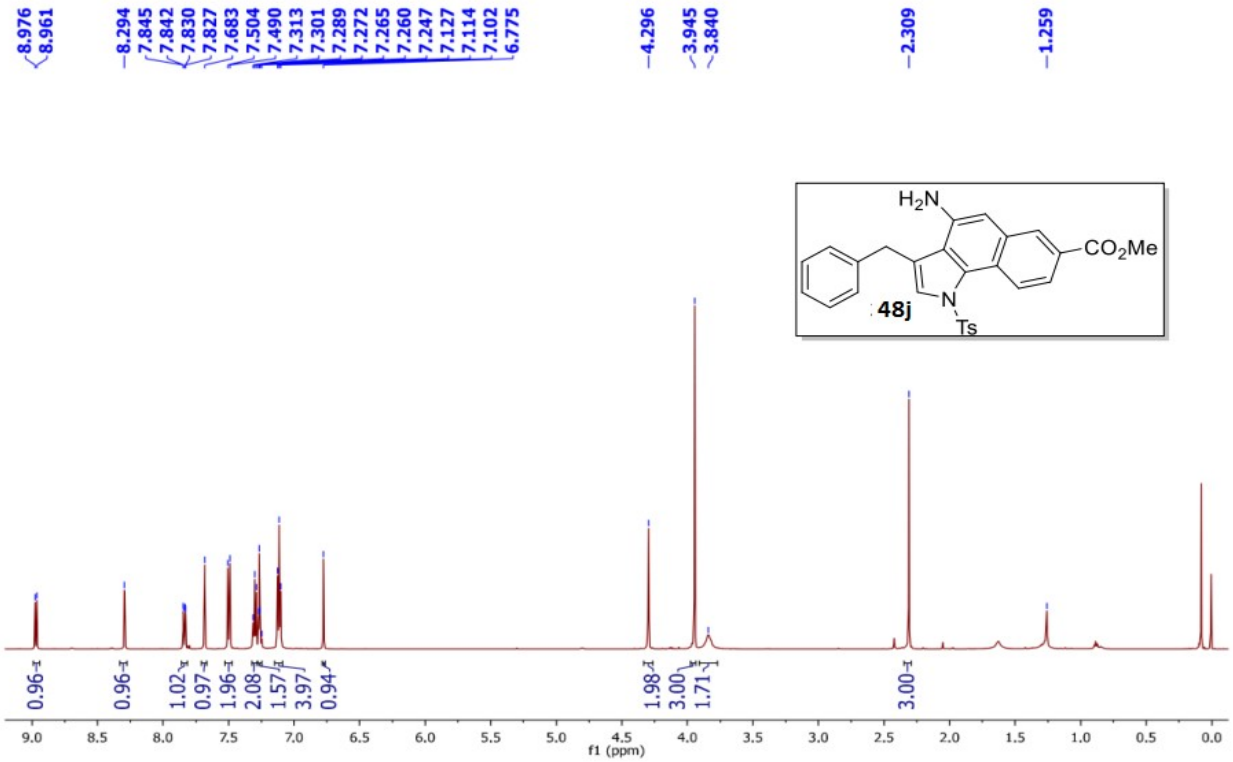
^{1}H NMR (600 MHz) of **48i:**



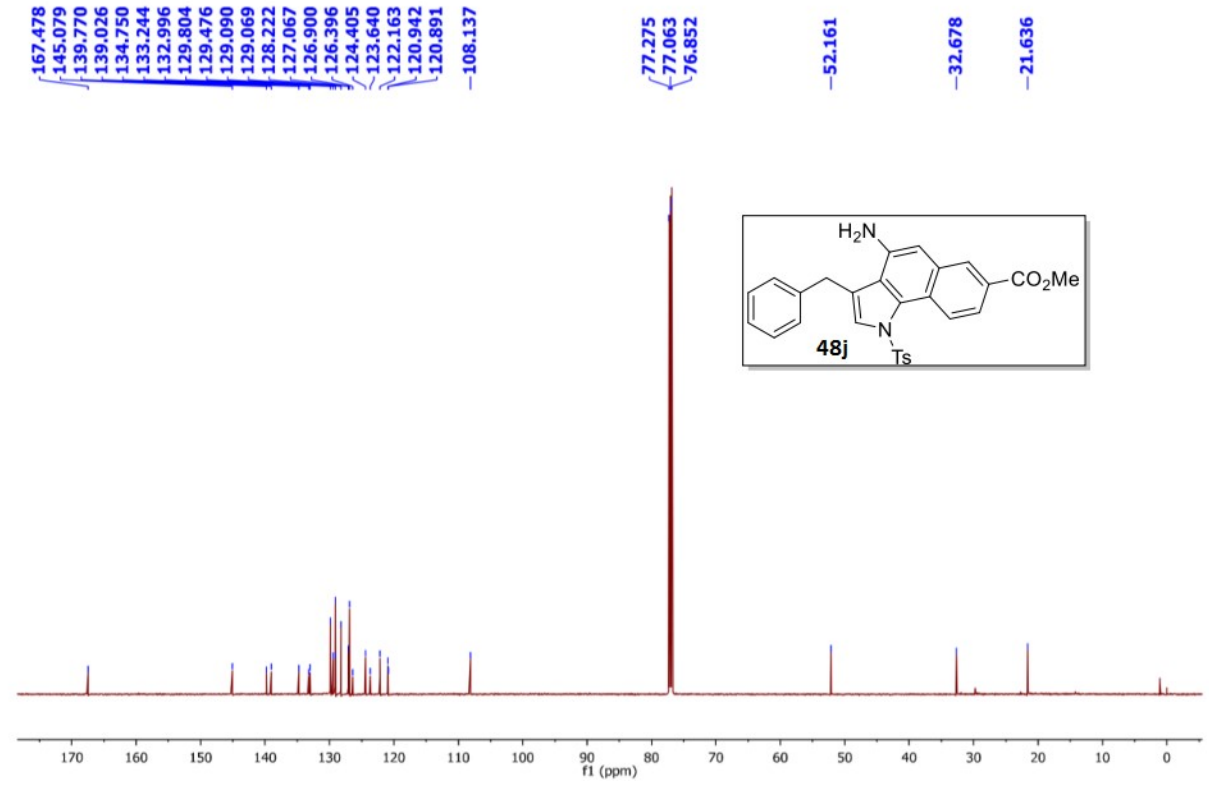
^{13}C{^{1}H} NMR (150 MHz) of **48i:**



^{1}H NMR (600 MHz) of **48j:**

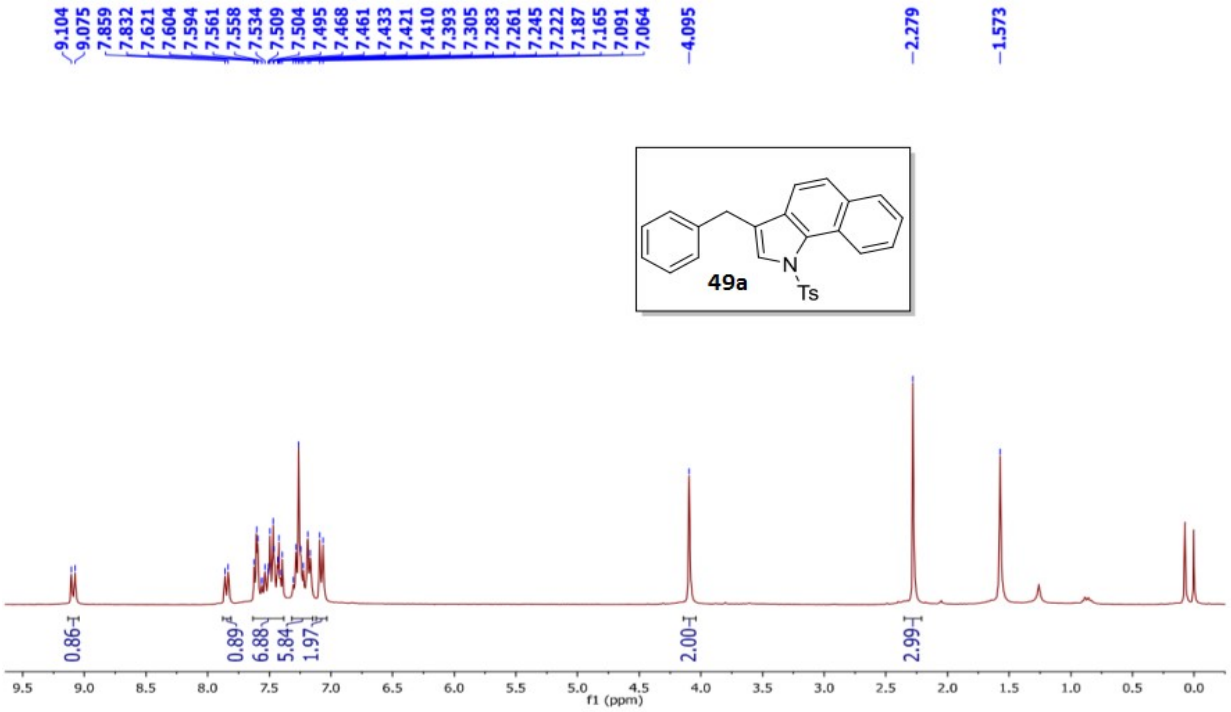


^{13}C{^{1}H} NMR (150 MHz) of **48j:**

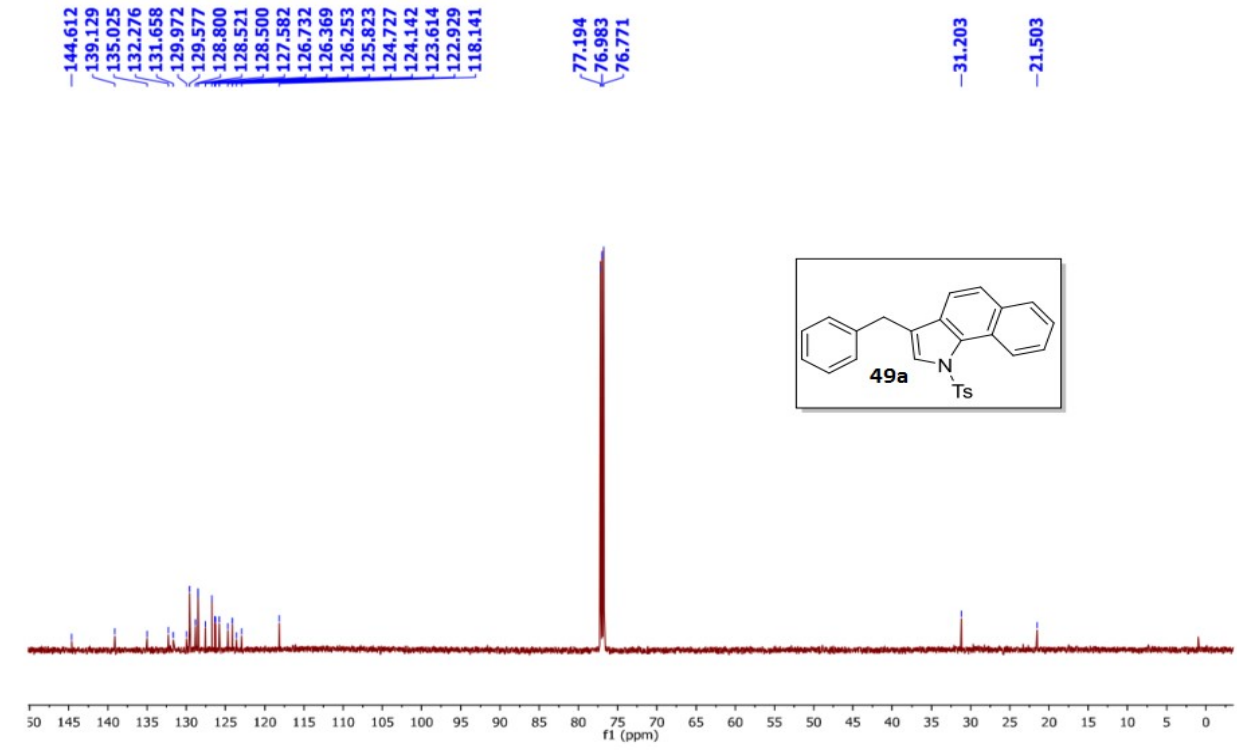


4.2.10.4. NMR Spectra of Compounds 49a-h

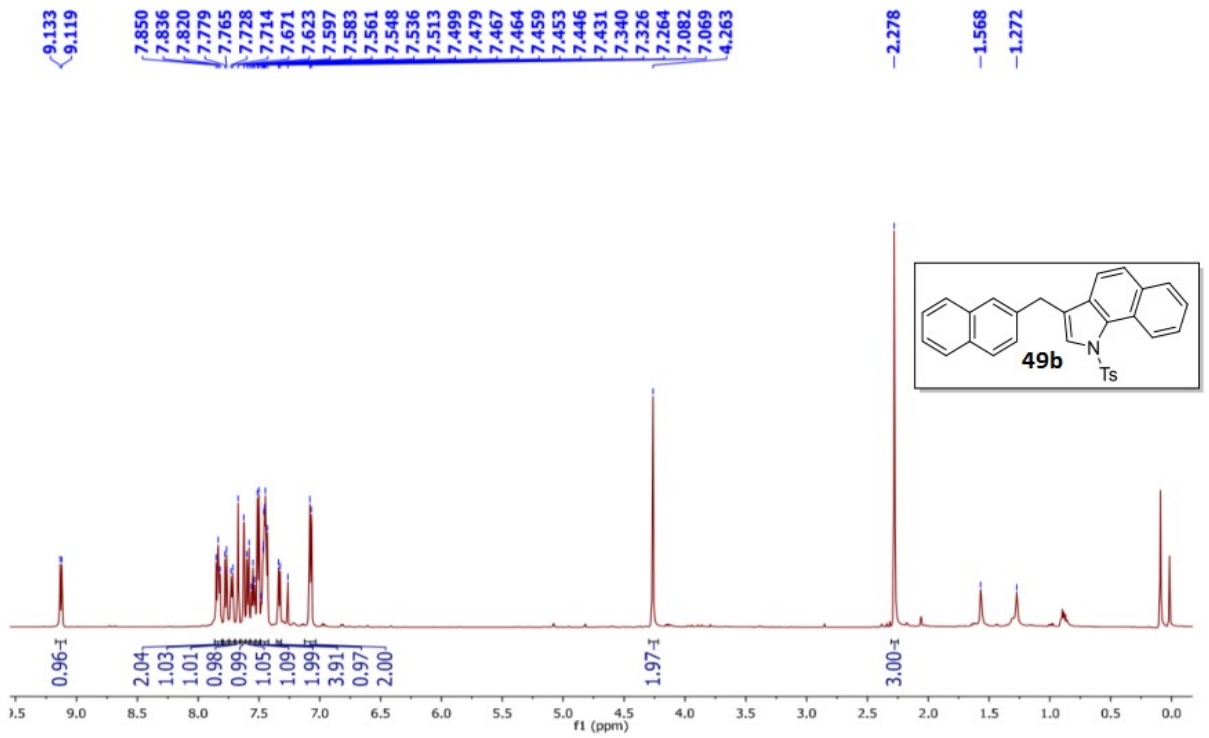
^{1}H NMR (300 MHz) of **49a:**



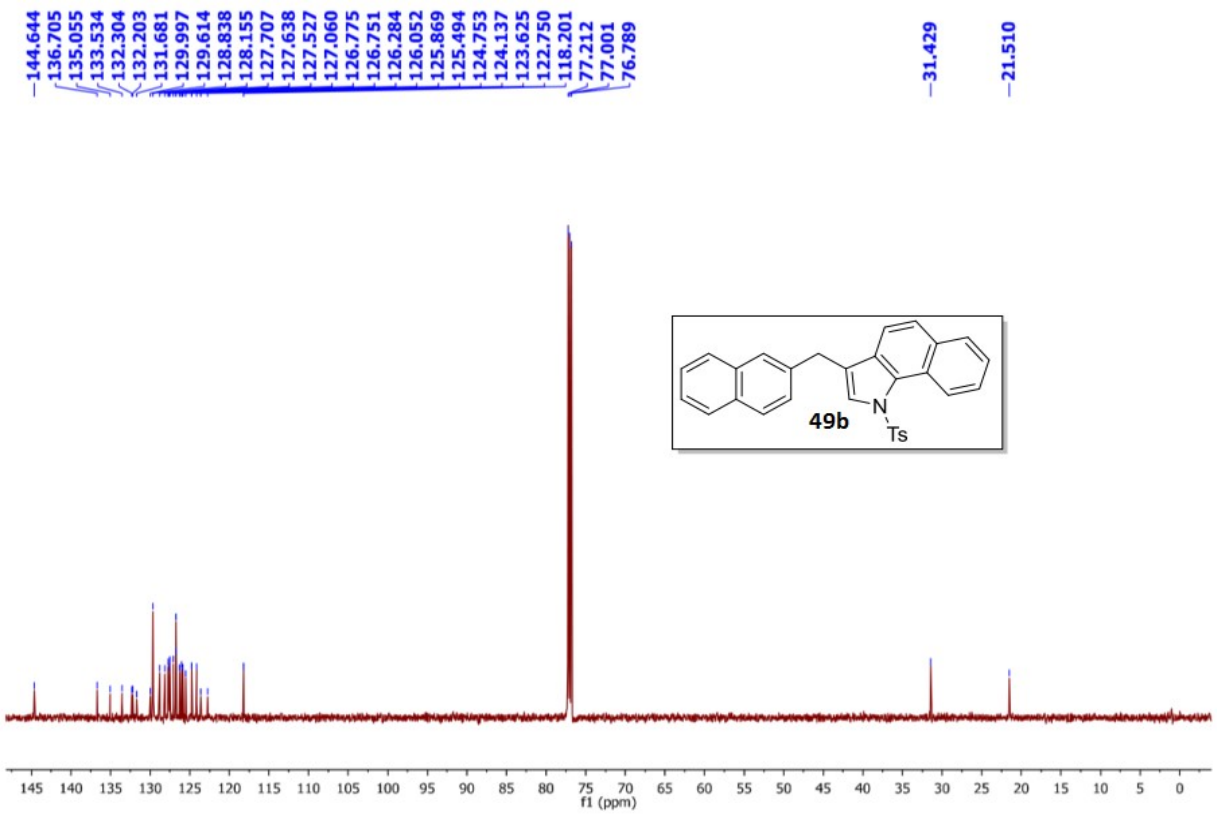
^{13}C{^{1}H} NMR (150 MHz) of **49a:**



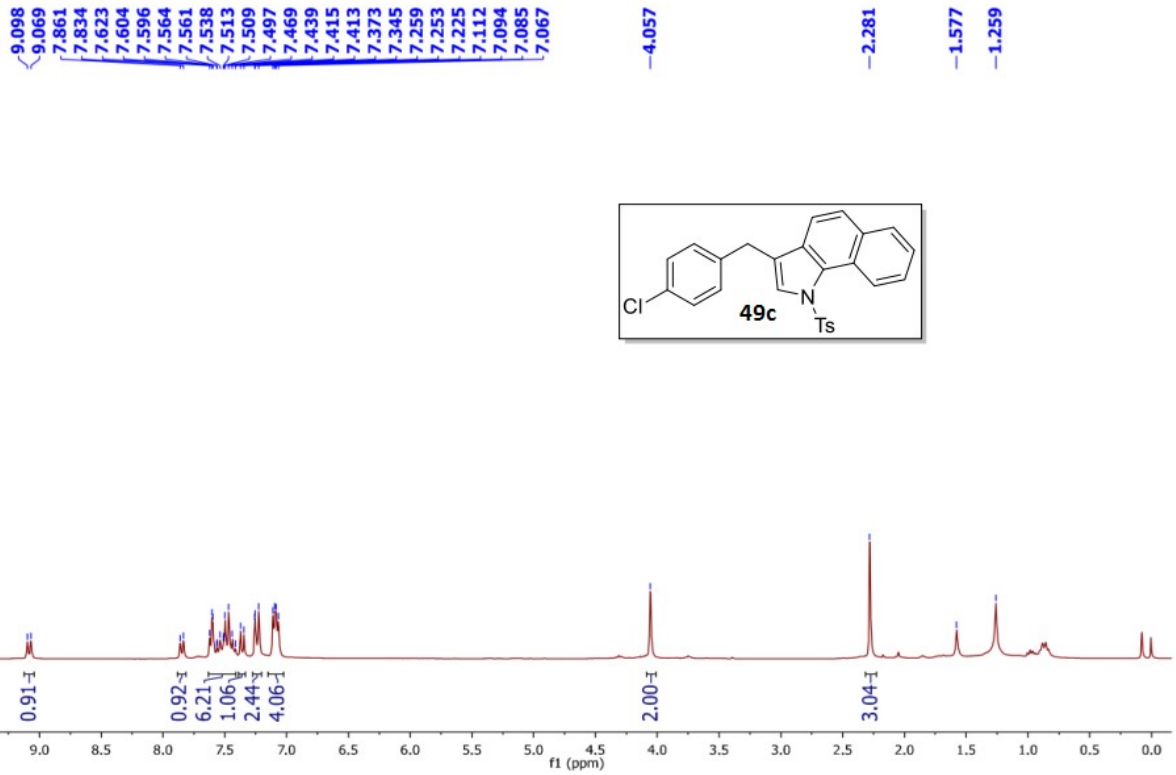
^{1}H NMR (600 MHz) of **49b:**



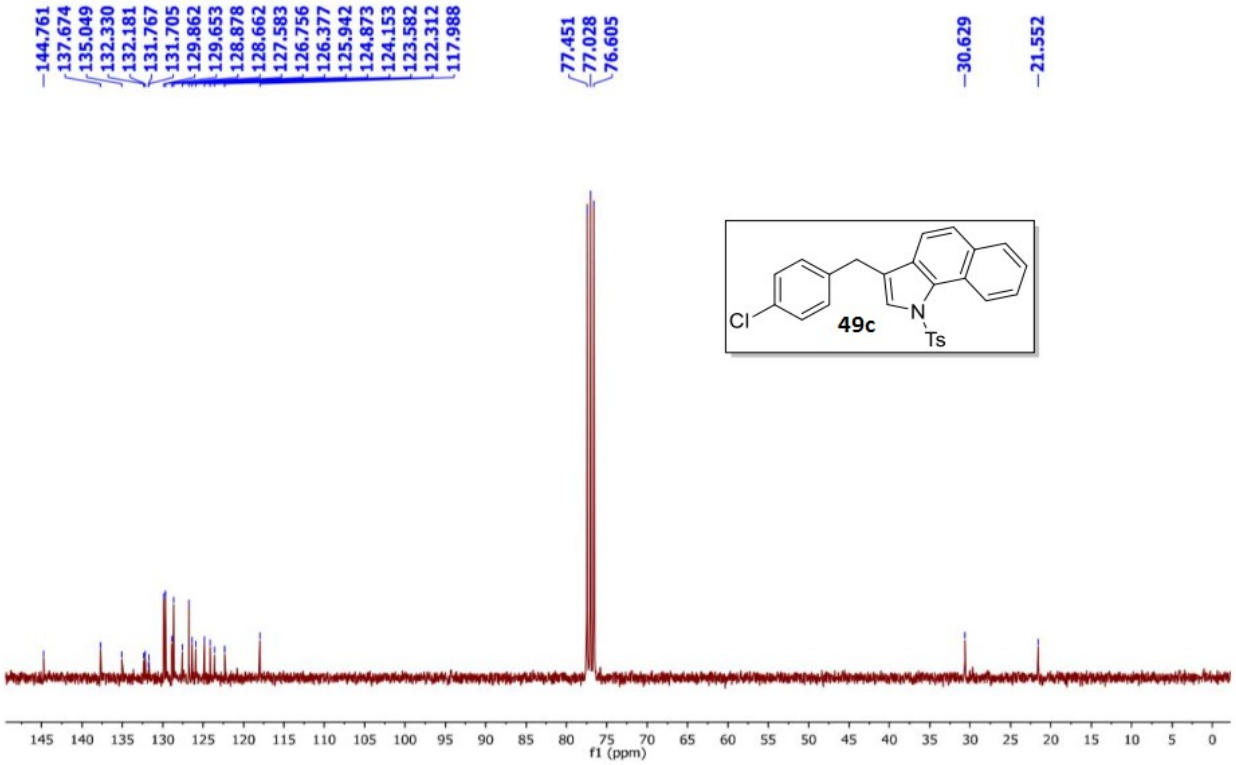
^{13}C{^{1}H} NMR (150 MHz) of **49b:**



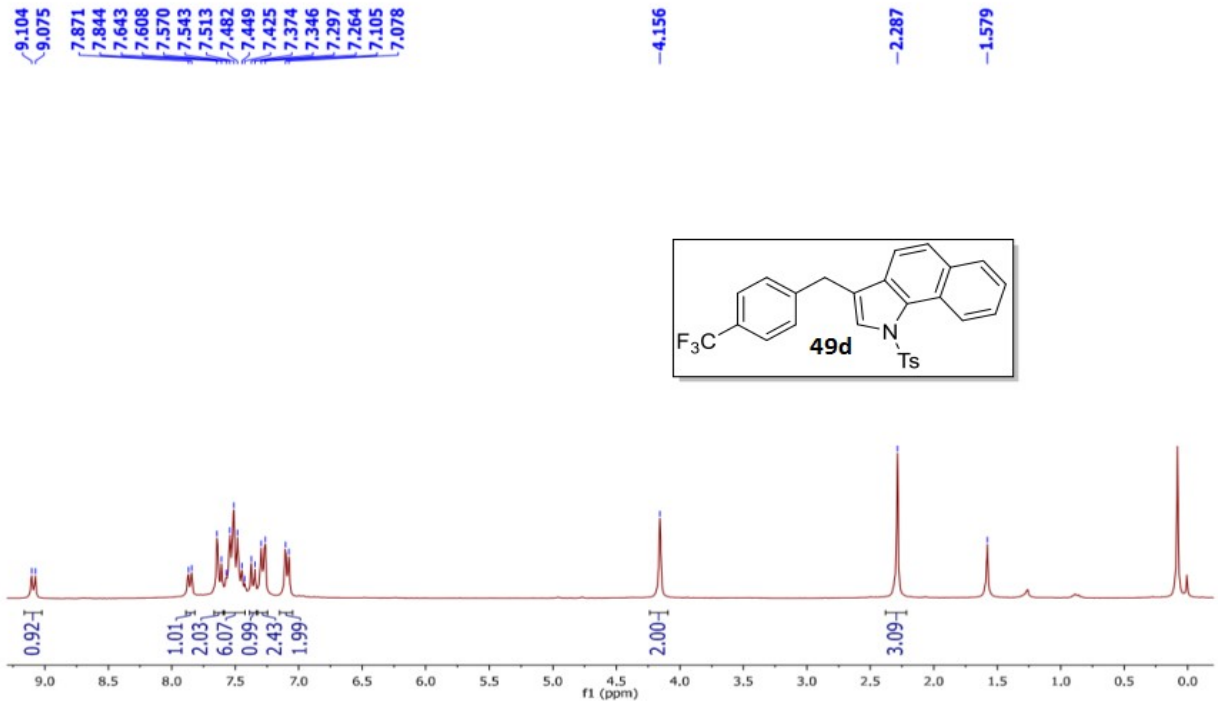
^{1}H NMR (300 MHz) of **49c:**



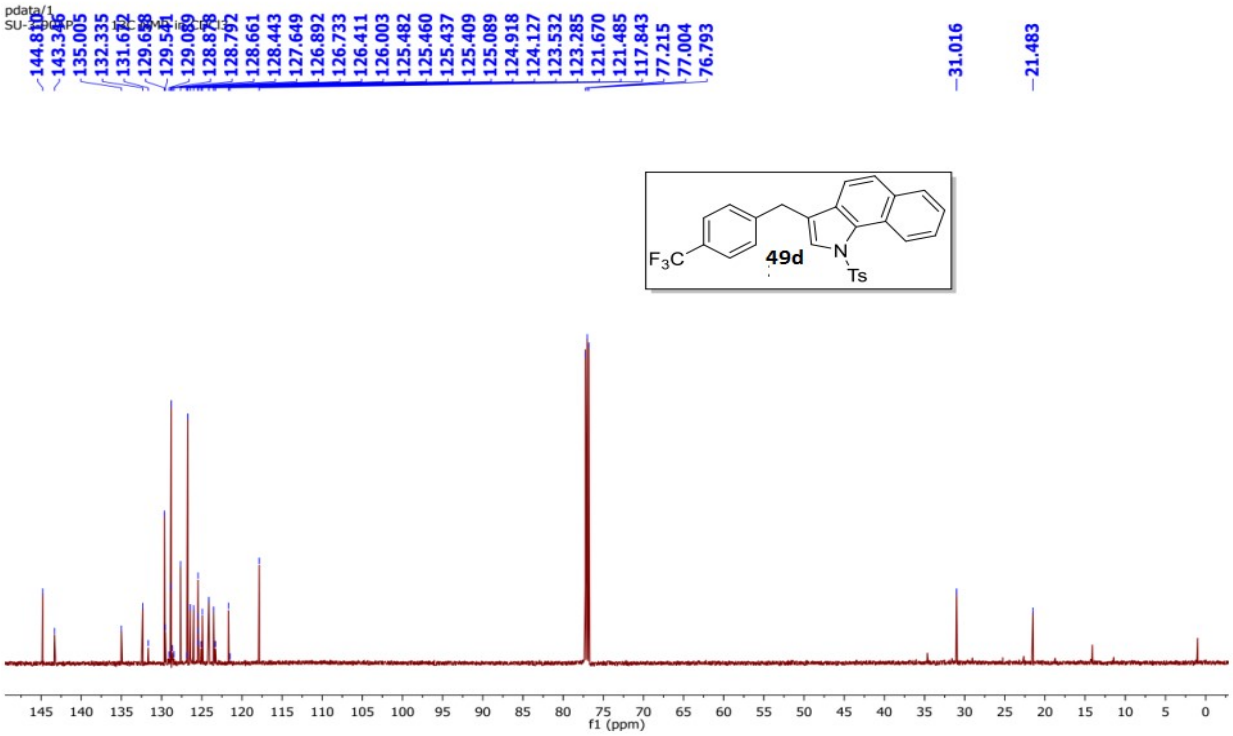
^{13}C{^{1}H} NMR (75 MHz) of **49c:**



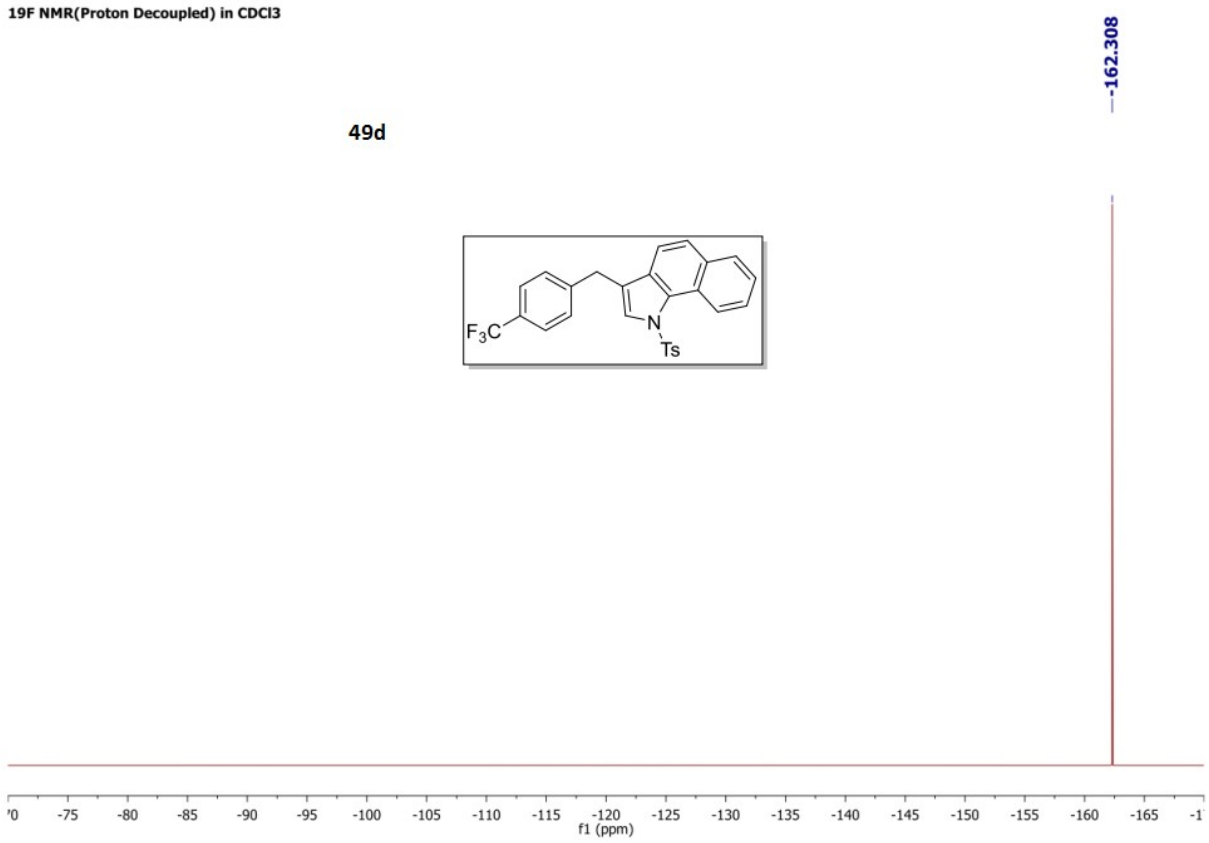
^{1}H NMR (300 MHz) of **49d:**



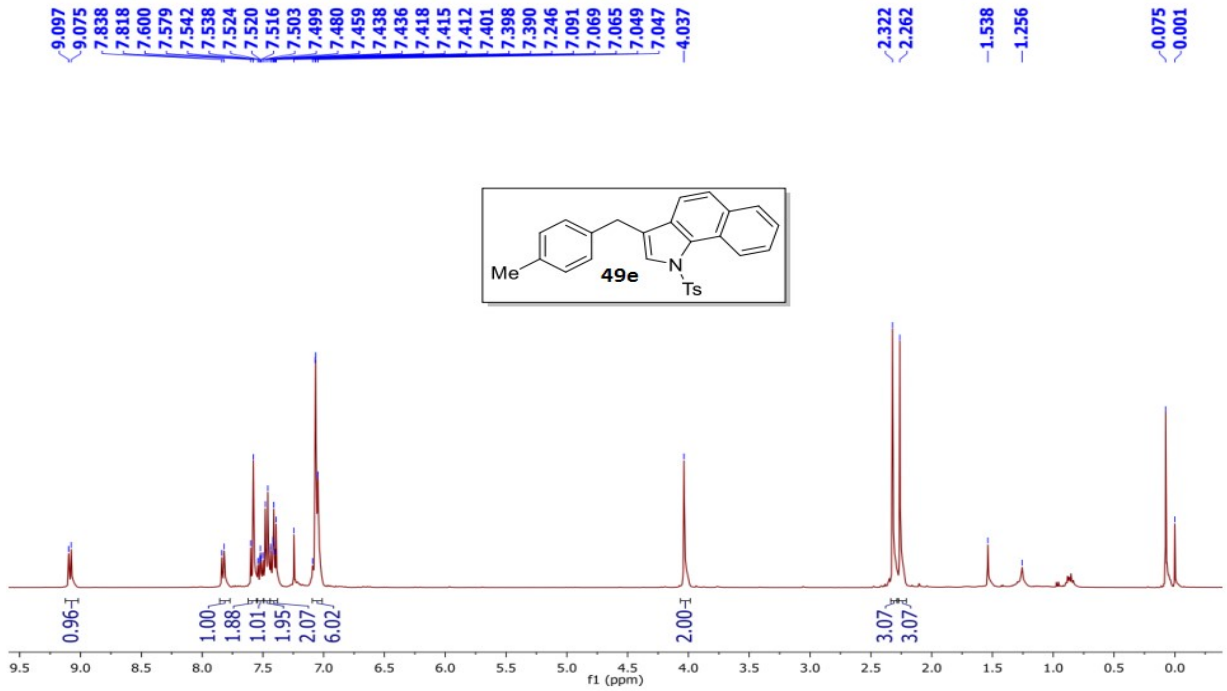
^{13}C{^{1}H} NMR (150 MHz) of **49d:**



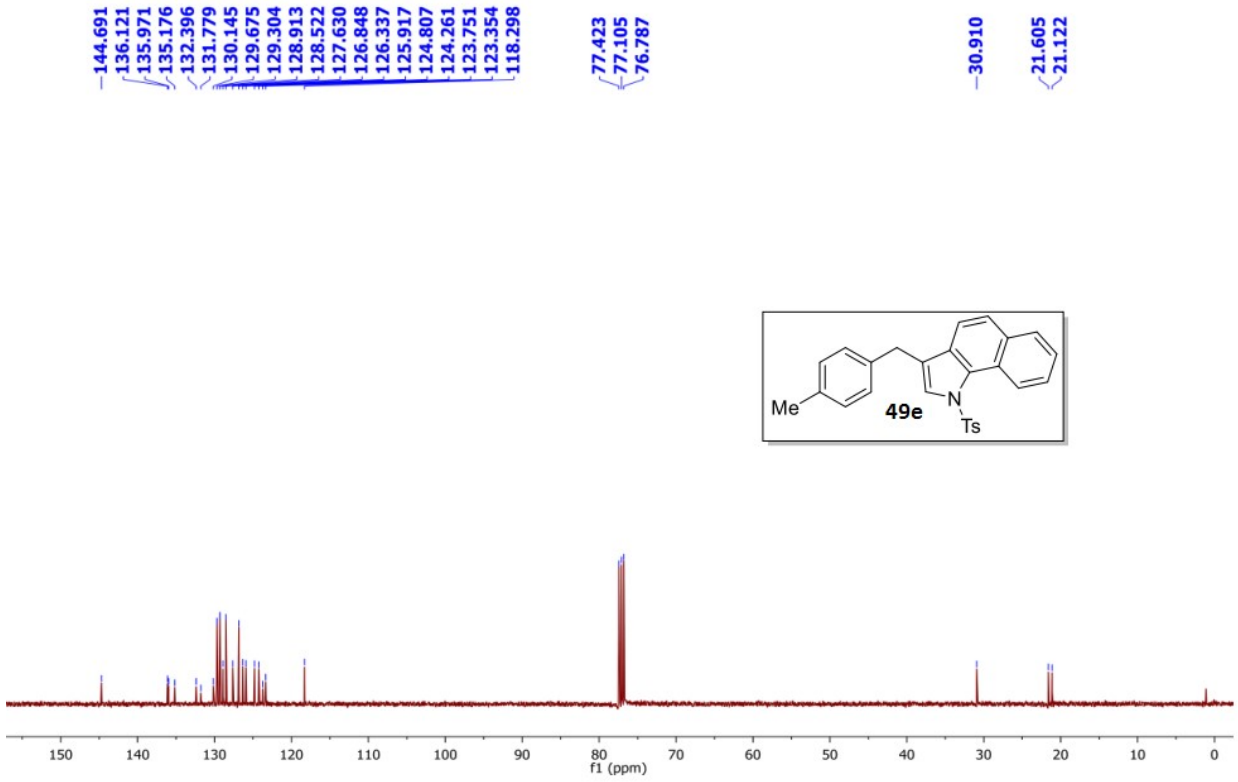
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **49d:**



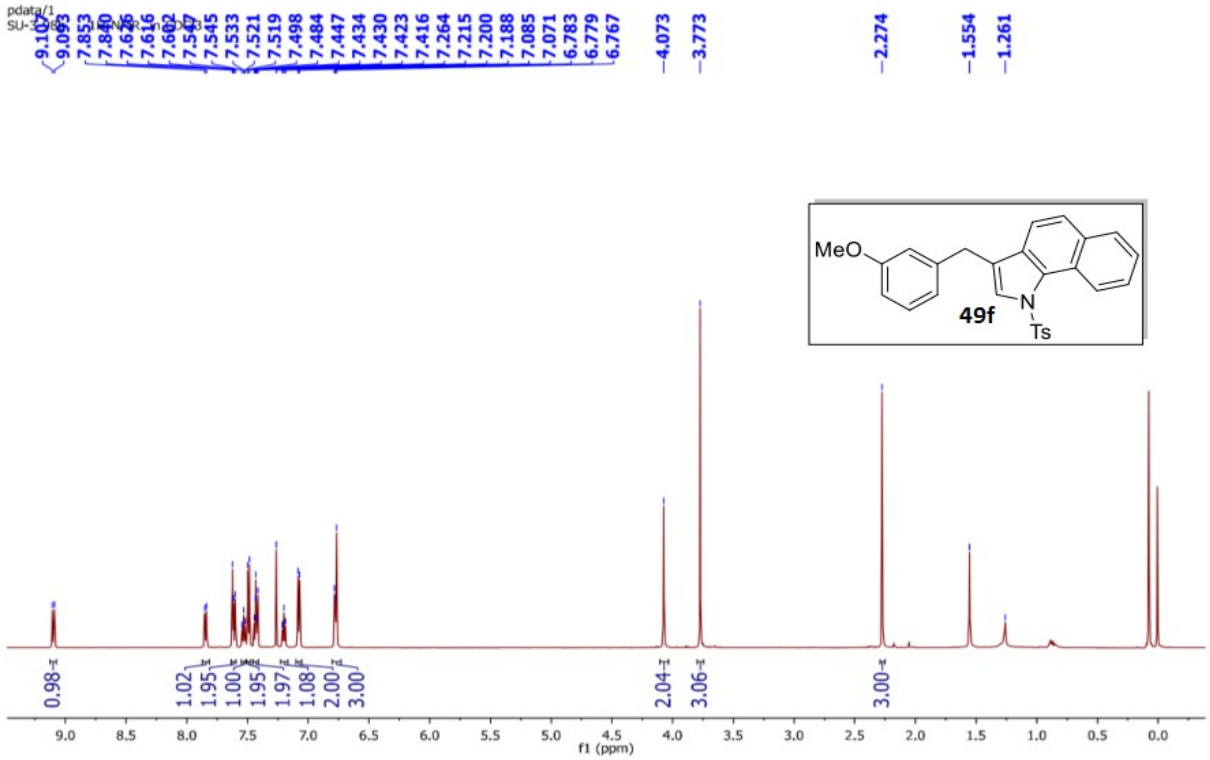
^{1}H NMR (400 MHz) of **49e:**



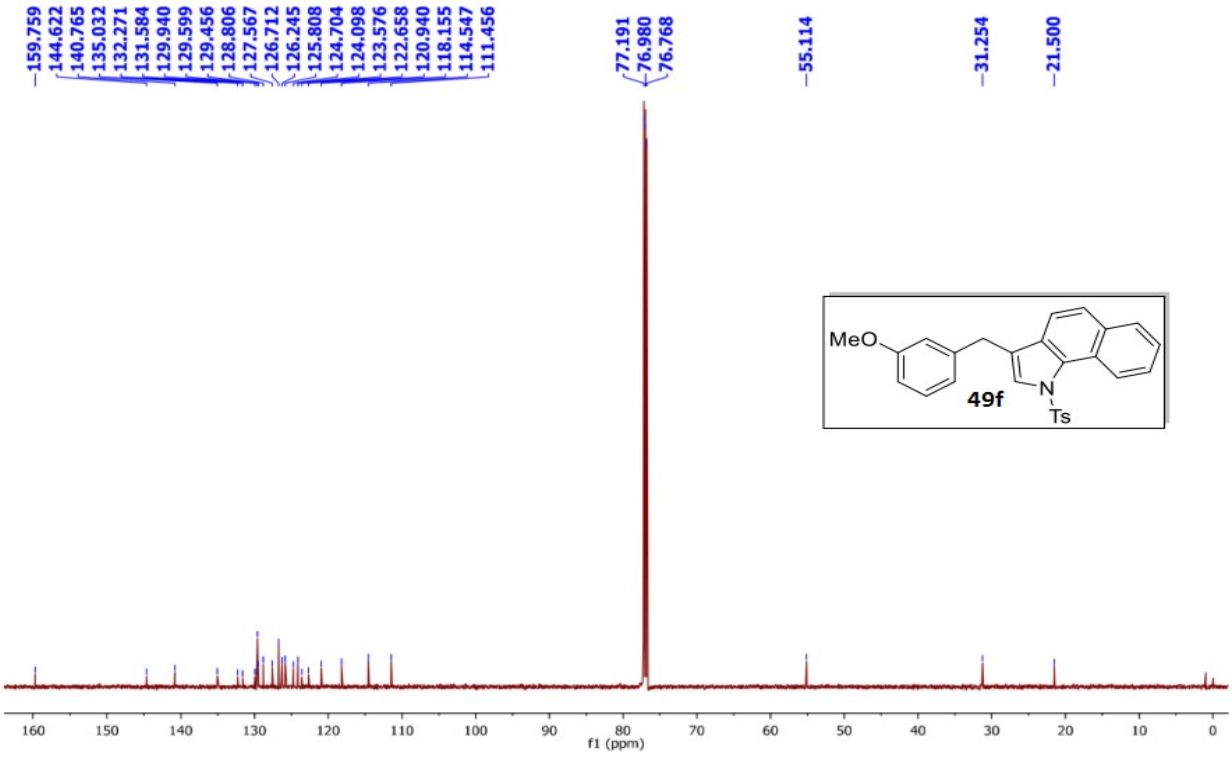
^{13}C{^{1}H} NMR (100 MHz) of **49e:**



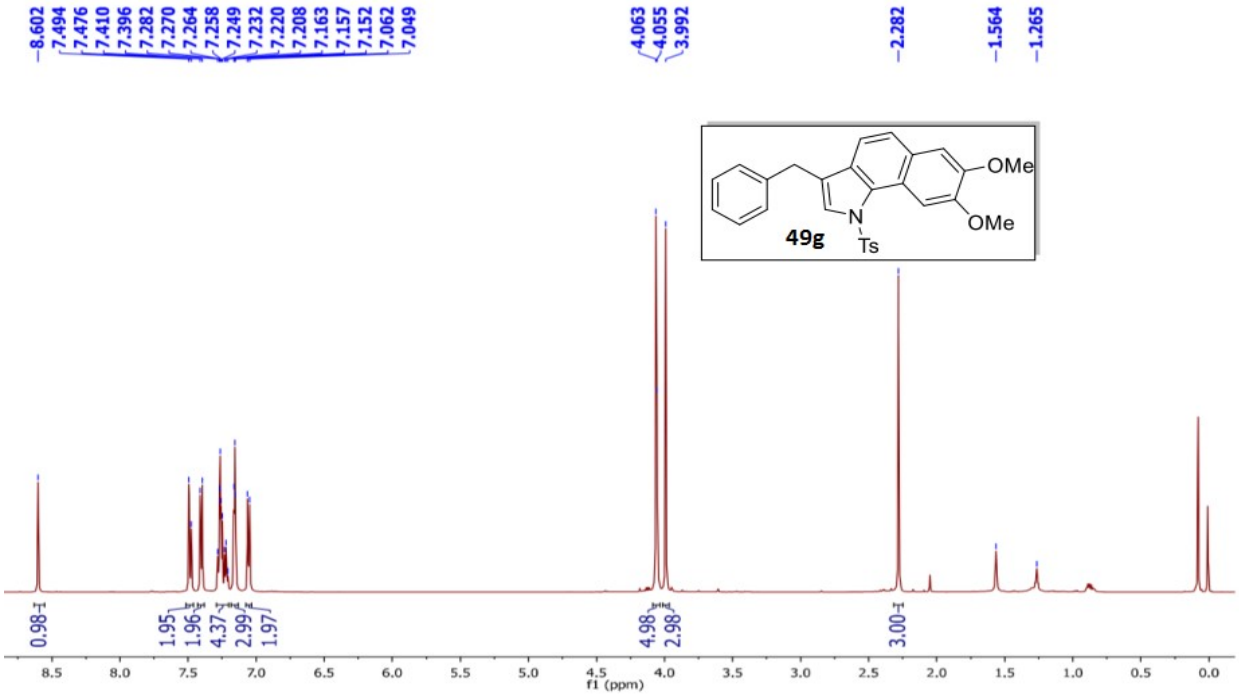
^{1}H NMR (600 MHz) of **49f:**



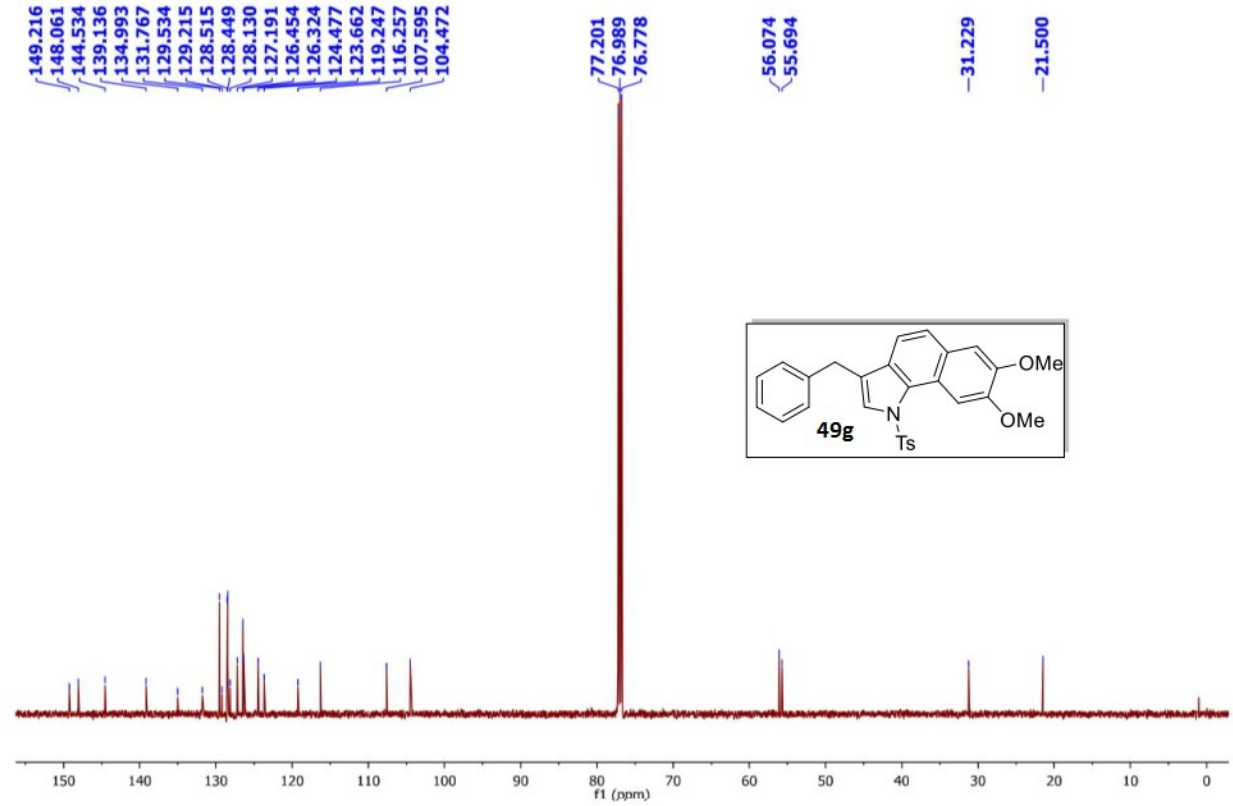
^{13}C{^{1}H} NMR (150 MHz) of **49f:**



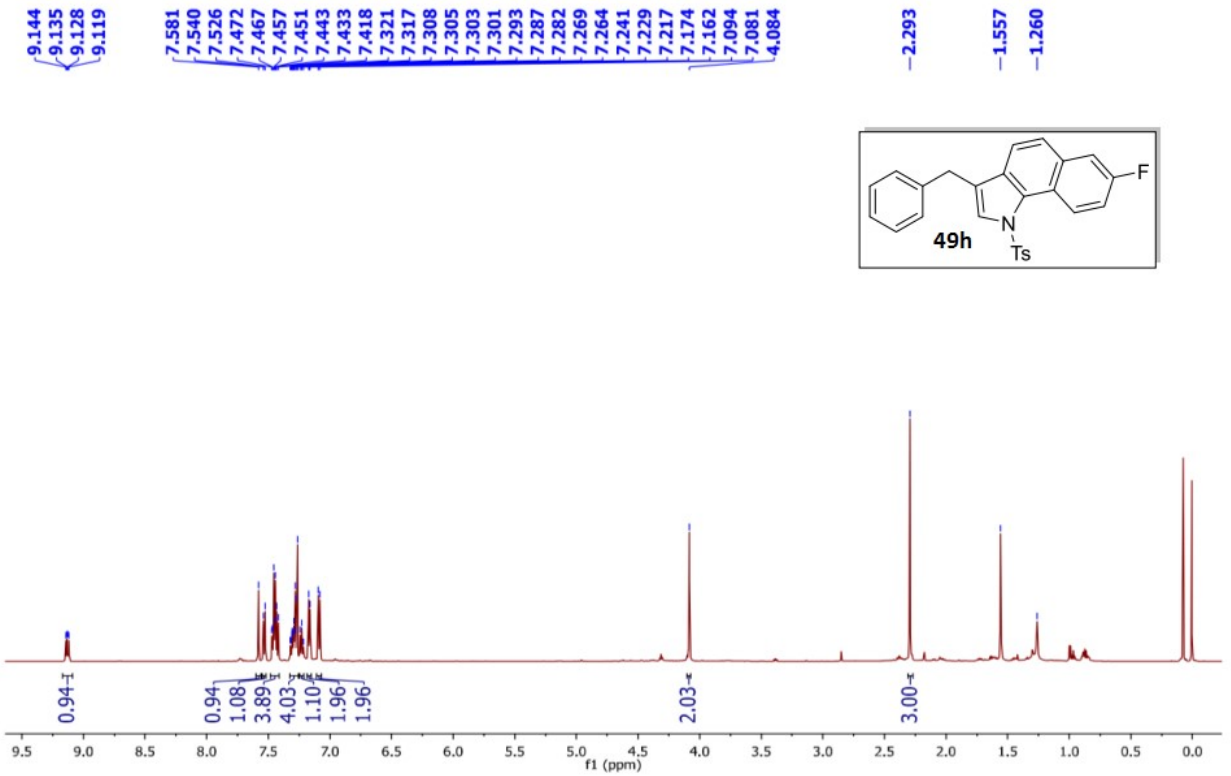
^{1}H NMR (600 MHz) of **49g:**



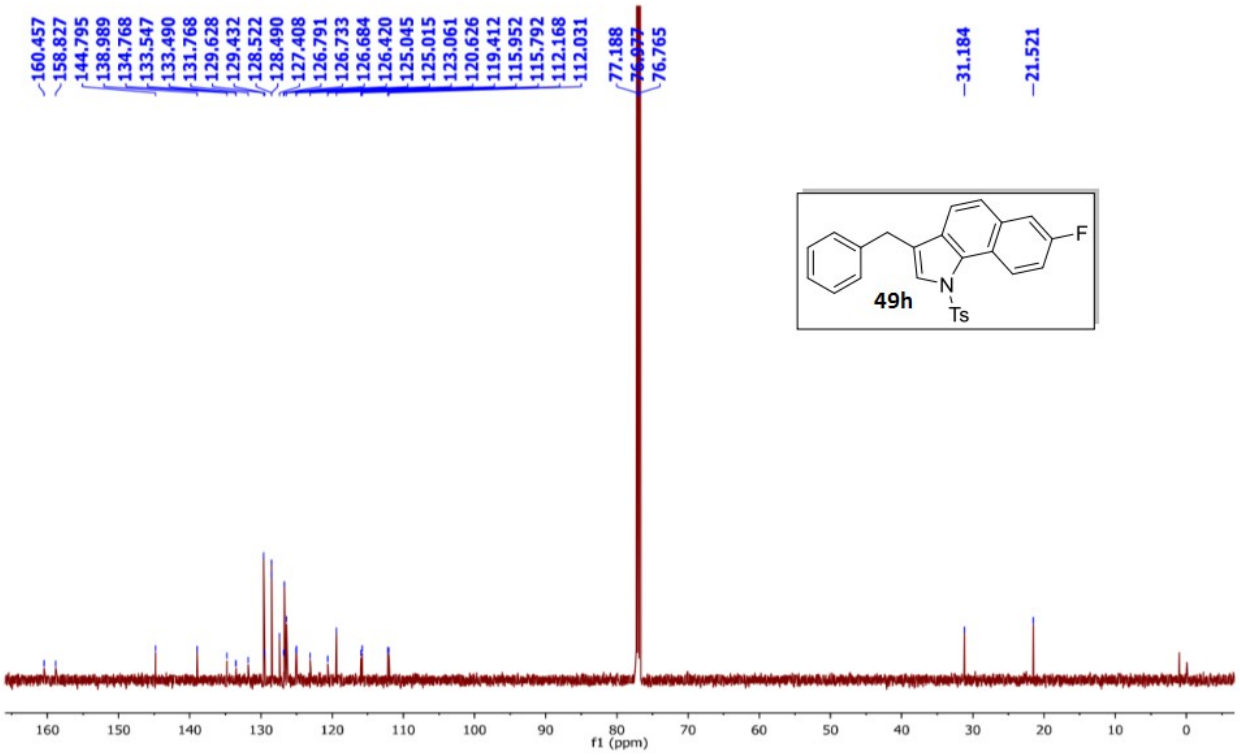
^{13}C{^{1}H} NMR (150 MHz) of **49g:**



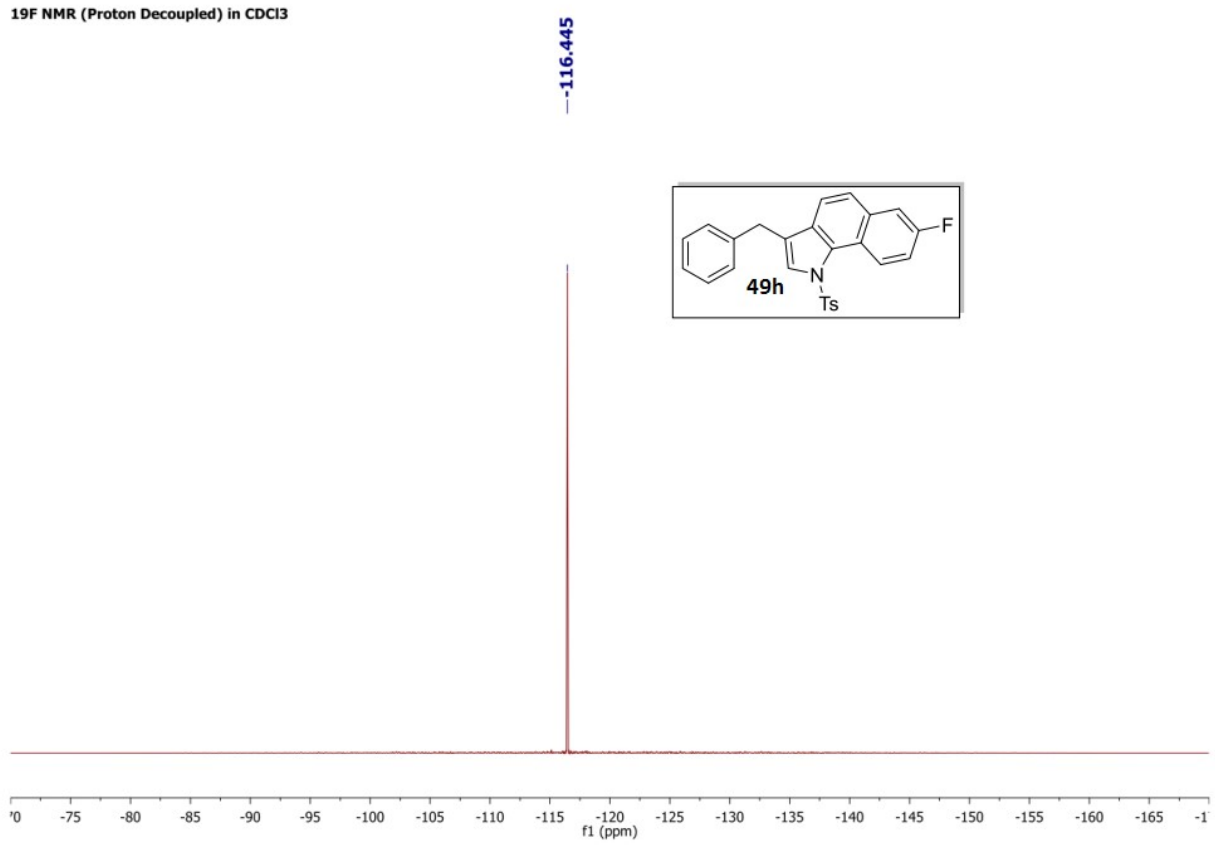
^{1}H NMR (600 MHz) of **49h:**



^{13}C{^{1}H} NMR (150 MHz) of **49h:**

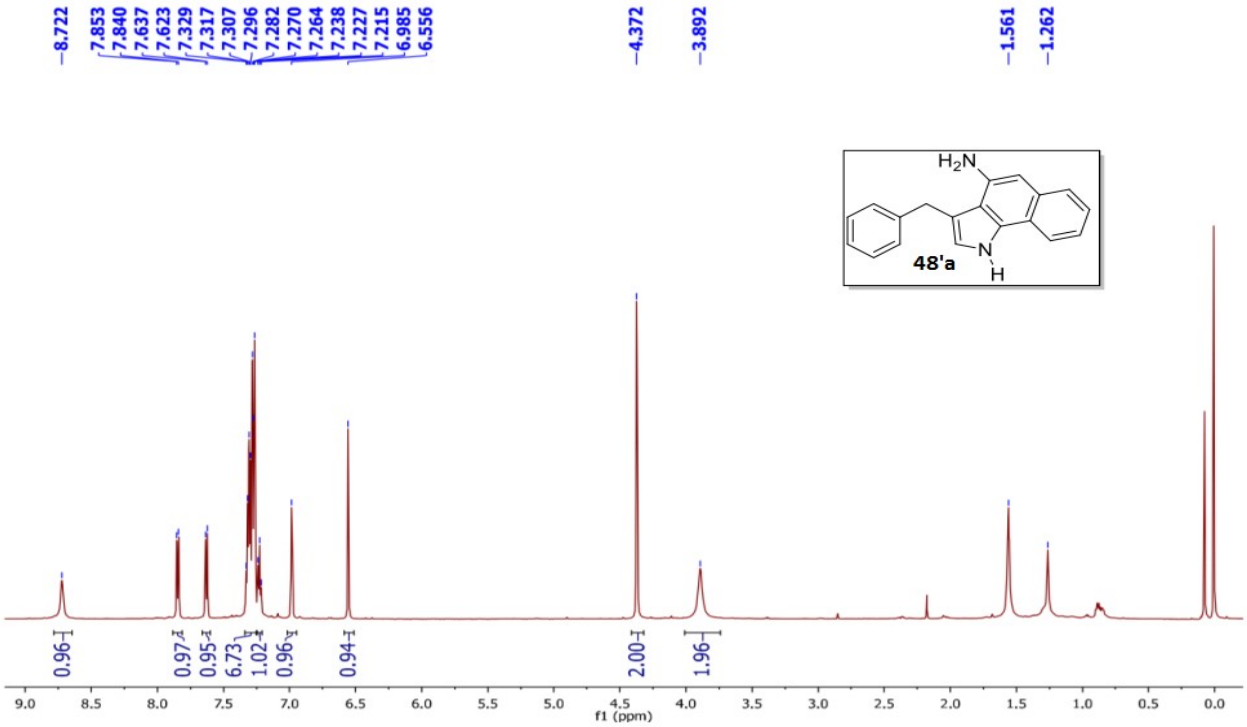


$^{19}F\{^{1}H\}$ NMR (376 MHz) of **49h:**

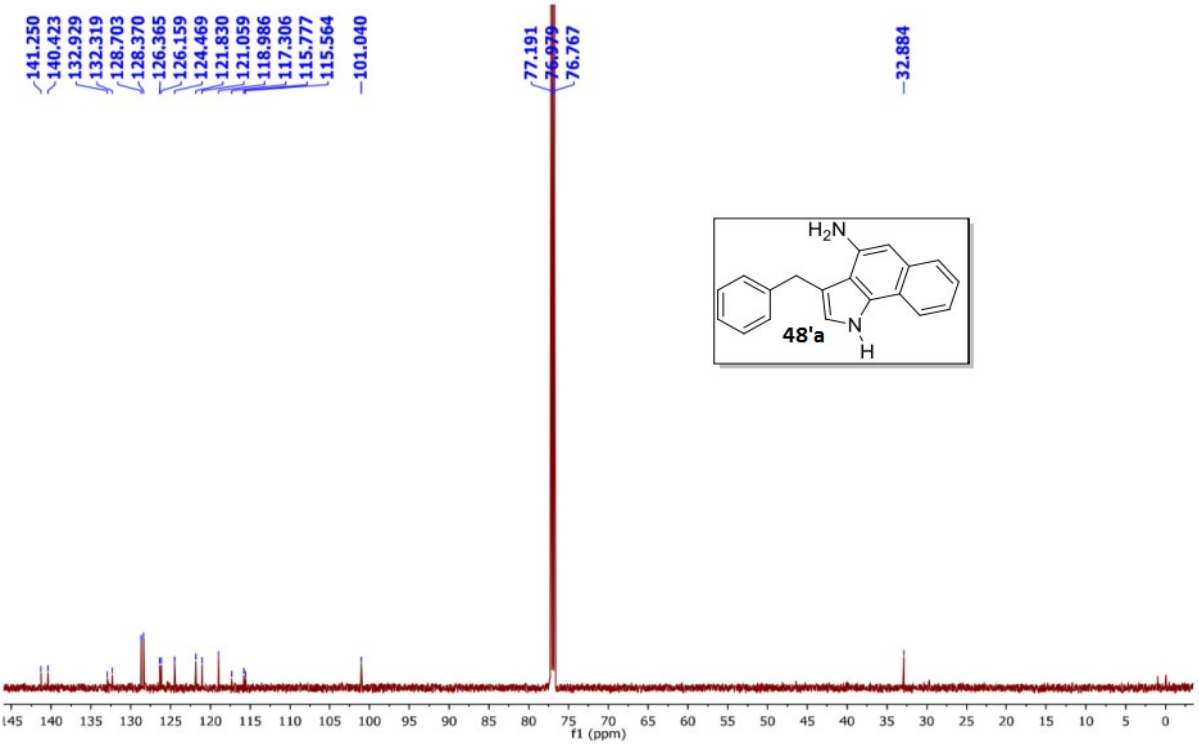


4.2.10.5. NMR Spectra of Compounds 48′a and 49′a

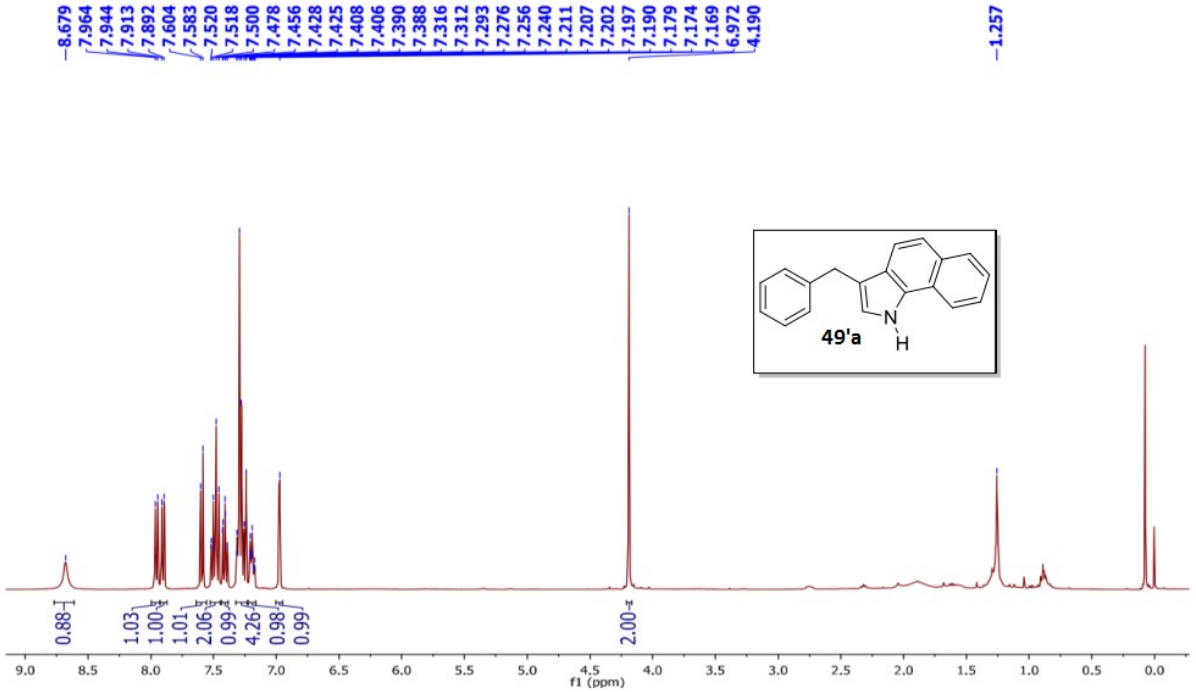
^{1}H NMR (600 MHz) of **48'a:**



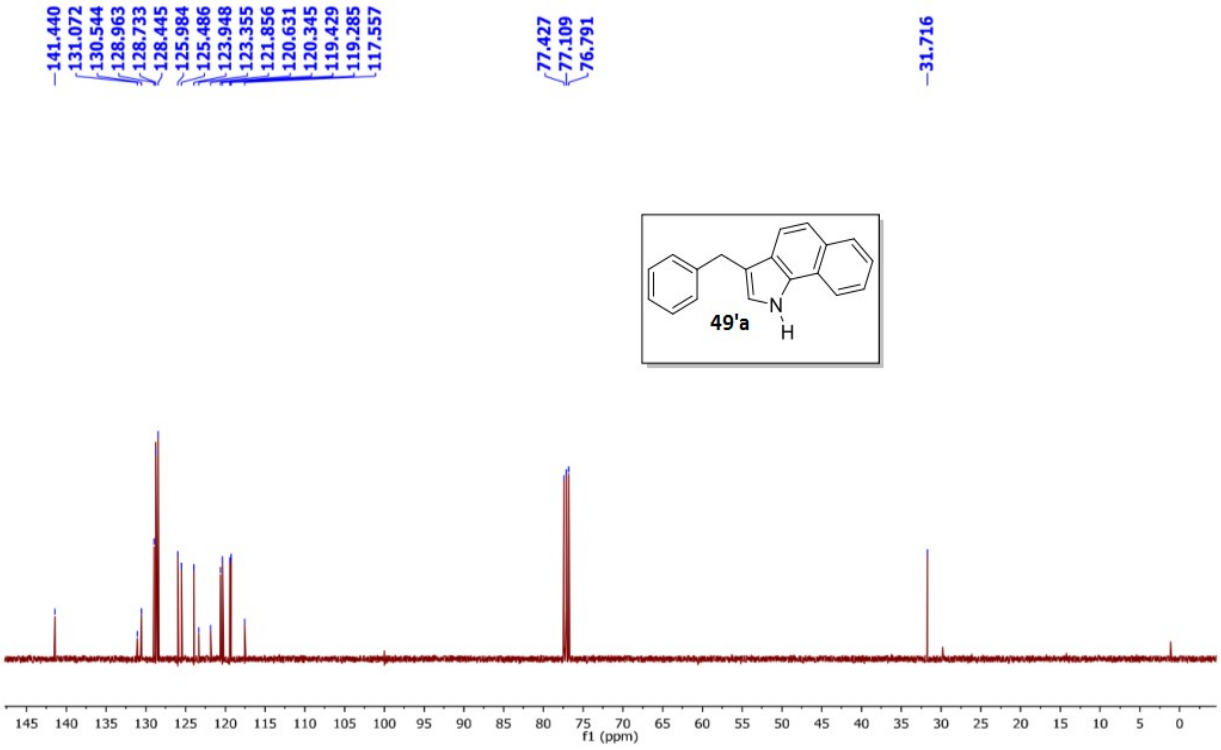
^{13}C{^{1}H} NMR (150 MHz) of **48'a:**



^{1}H NMR (400 MHz) of **49'a:**



^{13}C{^{1}H} NMR (100 MHz) of **49'a:**



ONE DAY SYMPOSIUM IN CHEMICAL SCIENCES

CERTIFICATE FOR POSTER PRESENTATION

THIS CERTIFICATE IS AWARDED TO

Sukanya De

WHO HAS PARTICIPATED IN THIS SYMPOSIUM HELD AT THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE, KOLKATA, INDIA ON JUNE 4, 2022

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(January 07, 2020)

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Certificate of Participation

This is to certify that Sukanya De

of CSIR-IICB, Kolkata *has taken part/presented a poster in the seminar organized by the Department of Chemistry, Jadavpur University, Kolkata 700 032 on January 07, 2020.*

KAJAL KRISHNA RAJAK
Convener

SAMIT GUHA
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Date: 07-01-2020
Place: Kolkata