Palladium Catalyzed Heteroannulations for Easy Accessing the Compounds of Biological Importance

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By

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled ''**Palladium Catalyzed Heteroannulations for Easy Accessing the Compounds of Biological Importance**'' Submitted by Smt. **Debasmita Mondal** who got her name registered on **27.08.2019 (Index No: 40/19/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/deploma or any other academic award anywhere before.

1/8/2023

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Declaration

I, **Debasmita Mondal**, 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: 1.8.23

Debasmita Mondal

(Debasmita Mondal)

Dedicated to

My Parents,
My Sisters and Brothers-in-law
&
My Nephew Aviraj (Pupu)

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A sister is a rock during hard times, a lighthouse against a turbulent sea, and a friend among strangers andI am lucky to have twosuch sisters in my life. I express my heartfelt gratitude to them for their constant guidance andencouragement. Thank you **Didi** (Sayantini Mondal) and **Bonu** (Ananya Mondal) for beingthere with me in every step of my life. I also want to thank my brothers-in-law (**Ayanda** and **Akash**) because it seems like they are my own brothers and they are always with me in agony and ecstasy.Thank you for encouraging me in all of my pursuits and inspiring me to fulfilmy dreams.

I am thankful to Godfor blessing me to have my cute and adorable nephew, **Aviraj Jana,** who actually keeps me smiling all day long. You are more of a son to me than a nephew. I wish you all the success and happiness in the world for your future.

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ABBREVIATIONS

^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
Ar	Aryl
Bn	Benzyl
Bu	Butyl
Boc	Di-tert-butyl dicarbonate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	N,N-dimethylformamide
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIPEA	*N*, *N*-Diisopropylethylamine
EIMS	Electron impact mass spectroscopy
ESI-MS	Electron spray ionization mass spectroscopy
HRMS	High resolution mass spectroscopy
LAH	Lithium aluminium hydride
Ts	*p*-Toluenesulfonyl (tosyl) group
Ns	4-Nitro-benzenesulfonyl (nosyl) group
Bs	2-Bromo-benzenesulfonyl group
$PdCl_2(PPh_3)_2$	Bis(triphenylphosphine)palladium(II)dichloride
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd_2(dba)_3$. $CHCl_3$	Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	Palladium acetate
$PdCl_2$	Palladium(II) chloride

PPh_3	Triphenylphosphine
CuI	Copper(I) iodide
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammoniumfluoride
NaN_3	Sodium azide
Et_3N	Triethylamine
CH_3CN	Acetonitrile
BuCN	Butyronitrile
CCl_4	Carbon Tetrachloride
THF	Tetrahydrofuran
DMF	N,N-Dimethylformamide
TLC	Thin layer chromatography
$NaIO_4$	Sodium periodate
$RuCl_3$	Ruthenium(III) chloride
$BH_3.SMe_2$	Borane dimethyl sulfide complex
$ZnBr_2$	Zinc bromide

GENERAL REMARKS

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60-80 ^{o}C. DMF and DCM were 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 or oxygen 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 60-120 or 100-200 or 230-400 mesh silica gel or neutral alumina or basic alumina. All the reagents including 10%Pd-C, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd_2(dba)_3.CHCl_3$, CuI, PPh_3, Xantphos, ^{t}BuXantPhoswere purchased from Sigma Aldrich, Alfa Aesar, TCI etc. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 300, 400 or 600 MHz 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 [$CDCl_3$: ^{1}H 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), q (quartet), p (pentet), td (triple doublet), 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 BrükerKuppa Apex 2 instrument or Brüker D8 Venture system.

Preface

The research work embodied in this thesis describes efficient and elegant protocols for the synthesis of benzofuro[3,2-*b*]pyrrole or benzofuro[3,2-*b*]indole via palladium(II)-catalyzed *5-exo-dig cyclization*/DDQ-mediated Diels-Alder reaction and also describes palladium(0)-catalyzed synthesis of δ-carbolines or benzofuro[3,2-*b*]pyridines, 3-ylidene-[1,4]benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxidesunder one-pot. The work has been presented in three chapters.

Chapter-1 described stereoselective synthesis of 3-ylidene-[1,4]benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides via palladium(0)-catalysed regioselective cyclisations of 2-amino(tosyl) benzamides/sulphonamides.

Chapter-2 describes facile method for the general synthesis of δ-carbolines or benzofuro[3,2-*b*]pyridines via palladium(0)-catalyzed reactions between allenamides and aryl iodides/bromides.

Chapter-3 describes a direct and straightforward method for the general synthesis of benzofuro[3,2-*b*]pyrrole or benzofuro[3,2-*b*]indole via palladium(II)-catalyzed *5-exo-dig cyclization*/DDQ-mediated Diels-Alder reaction.

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 & Medicinal 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. Pramanik, S., Jash, M., & **Mondal, D**., Chowdhury, C. (**2019**). Palladium-Catalyzed Synthesis of 6H-Dibenzo[*c*,*h*]chromenes and 5,6 Dihydrobenzo[*c*]phenanthridines: Application to the Synthesis of Dibenzo[*c*,*h*]chromene-6-ones, Benzo[*c*]phenanthridines, and Arnottin I. *Adv. Synth. Catal*. **2019**, *361*, 5223-5238.

2. **Mondal, D**., Pal, G., Chowdhury, C. (**2021**). Palladium(0)-catalysed regioselective cyclisations of 2-amino(tosyl) benzamides/sulphonamides: the stereoselective synthesis of 3-ylidene-[1,4]benzodiazepin- 5 ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides. *Chem. Commun.*,**2021**, 57, 5462-5465.

3. **Mondal, D**., Pramanik, S., Chowdhury, C. (**2022**). Palladium(0)-Catalyzed Heteroannulations of Allenamides: General Synthesis of δ-Carbolines and Benzofuro[3,2-*b*]pyridines. *Org. Lett*. **2022,** 47, 8698–8702.

4. **Mondal, D**., Chowdhury, C. (**2023**). Palladium-Catalyzed *5-exo-dig* Cyclization /DDQ-mediated dehydrogenative Diels–Alder reaction for the synthesis of functionalized Benzofuro[3,2-*b*]pyrrole/benzofuro[3,2-*b*]Indoles derivatives. (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: "*Palladium catalysed stereoselective synthesis of core structure of heterocycles andtheir application in medicinal chemistry*" by **Debasmita Mondal**, 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(0)-Catalyzedregio and stereoselective cyclisation Reactions betweentert-Butyl Propargyl Carbonates and 2-Amino benzamides or Sulphonamidesleading to the straightforward synthesis of [1,4]diazepin-5-ones orbenzo[f][1,2,5]thiadiazepin-1,1-dioxides'*'by **Debasmita Mondal**, Chinmay Chowdhury*.

Reprints of Author's Publications

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Advanced Synthesis & Catalysis

Palladium-Catalyzed Synthesis of 6*H*-Dibenzo[*c,h*]chromenes and 5,6-Dihydrobenzo[*c*]phenanthridines: Application to the Synthesis of Dibenzo[*c,h*]chromene-6-ones, Benzo[*c*]phenanthridines, and *Arnottin I*

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Abstract: 6*H*-Dibenzo[*c,h*]chromenes and 5,6-dihydrobenzo[*c*]phenanthridines have been synthesized via Palladium (II)-catalyzed domino reactions of acetylenic substrates involving intramolecular *trans*-oxo/amino palladation onto the triple bond followed by nucleophilic addition of the intermediate to a tethered cyano/aldehyde. The scope of this reaction was extended through one step conversion of some of the products to 6*H*-dibenzo[*c,h*]chromen-6-ones and benzo[*c*]phenanthridines. Utilization of this methodology led to a formal total synthesis of the natural product *Arnottin I.*

Keywords: Domino reaction; Palladium catalyst; 6*H*-Dibenzo[*c,h*]chromenes; 5,6-Dihydrobenzo[*c*]phenanthridines; *Arnottin I.*

1. Introduction

Fused heterocycles are of great importance because of their broad applications in different areas.[1] Among these compounds, the 6*H*-benzo[*c*]chromenes (**1 a**, Figure 1) are considered as privileged scaffolds and important substructures in modern drug discovery.[2] The related 6*H*-dibenzo[*c,h*]chromenes **2** also find extensive use as key synthetic intermediates of medicinally active compounds, besides offering easy access to dibenzo[*c,h*]chromen-6-ones **3** which constitute the core structures of a broad spectrum of natural products and others compounds possessing bactericidal properties.[3–8] These include *arnottin I*[3] (**5**, a non-alkaloidal minor component of *Xanthoxylum arnottianum*), *defucogilvocarcins* (**6 a**–**b**)[4] exhibiting antimicrobial activity, and *gilvocarcins* (**7 a**–**b**),[5] *ravidomycin* (**7 c**),[6] and *chrysomycins* (**7 d**–**e**)[7] belonging to the class of aryl C-glycoside antibiotics.[8]

Despite the promising biological effects[9] of 6*H*-dibenzo[*c,h*]chromenes **2**, this class of compounds is less explored compared to **3** in drug discovery primarily due to the lack of straightforward and convenient synthetic methods. Scrutiny of the literature revealed a single method[3h] for a general synthesis employing an intramolecular biaryl coupling reaction, while few other reports[10] deal with the preparation specific molecules during the course of the synthesis of either **1 a** or related compounds. This clearly pointed to the urgency of establishing a general and straightforward method for the synthesis of **2** starting from simple and easily accessible materials.

On the other hand, the aza-counterpart of **1 a** and its related structures such as dihydrophenanthridines (**1 b**, Figure 1), phenanthridinones (**1 c**, Figure 1) and phenanthridines are encountered in various alkaloids and synthetic compounds and display a wide range of pharmacological effects.[11] More importantly, fusion of an additional benzene ring to phenanthridines and their dihydro derivatives resulting in benzo[*c*]phenanthridines and its 5,6-dihydro derivatives (**4**) lead to products with remarkable therapeutic efficacies. For

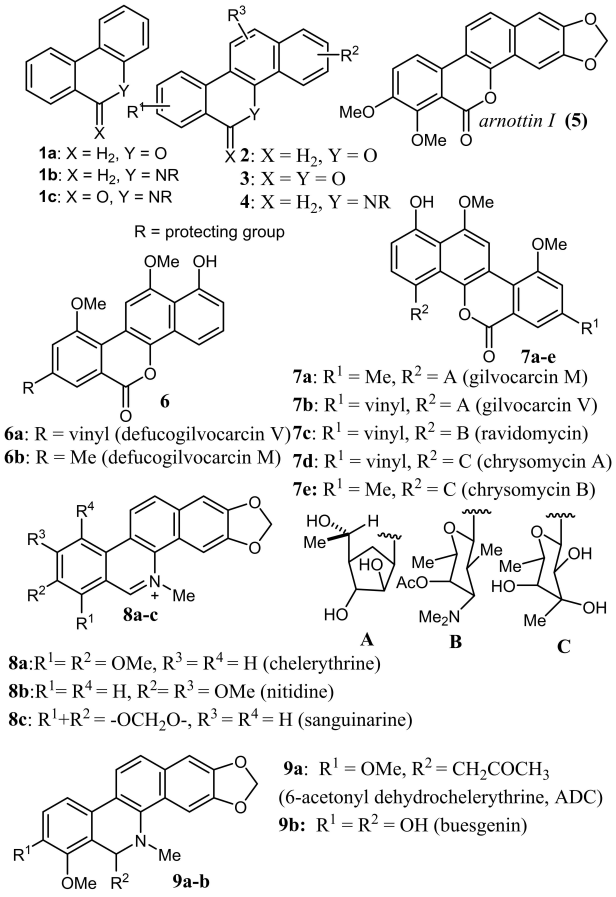


Figure 1. Biologically active dibenzo[*c,h*]chromen-6-ones 5–7, benzo[*c*]phenanthridines 8 and 5,6-dihydro- benzo[*c*]phenanthridines 9.

example, benzo[*c*]phenanthridine alkaloids **8a-c** (Figure 1) are reported to be G-quadruplex DNA stabilizer,[12a] topoisomerase I/II inhibitor,[12b] and lipoxygenase inhibitor,[12c] respectively. The 5,6-dihydro derivatives **4** are less naturally abundant but often exhibit distinct biological profiles. Thus *6-acetonyl dihydrochelerythrine* (ADC) **9a** (Figure 1) displays significant anti-HIV[13a] and anti-apoptotic[13b] effects, while *buesgenin* **9b**[13c] isolated from *Fagara tessmannii* exhibited high anti-bacterial activity while being non-toxic towards the normal cells. In spite of these encouraging results, there is no general method for the synthesis of **4** to date though few specific examples were reported[14] during the synthesis of other heterocycles. This underlined the urgency for the development of a facile and general method for the synthesis of **4**.

In recent times, domino reactions have emerged as efficient tools for the construction of complex molecules from the viewpoints of operational simplicity, atom economy and assemble efficiency.[15] In particular, reactions[16] involving 1,2-addition of a vinyl palladium species onto a carbon-heteroatom multiple bond (e.g., –CO–, –CHO, –CN) followed by protonation of the resulting intermediate have proved to be useful in the field of heterocycle synthesis after the seminal works of Larock,[16a] Lu[16b] and Wang.[16c] In continuation of our work on palladium-catalyzed reactions,[17] we therefore anticipated that a general synthesis of 6*H*-dibenzo[*c,h*]chromenes **2** and 5,6-dihydrobenzo[*c*]phenanthridines **4** could be achieved in atom economical way through one-pot domino reactions using readily available substrates. Our concept proved to be viable upon choosing appropriate reaction conditions and catalyst. The results obtained so far are described herein.

2. Results and Discussion

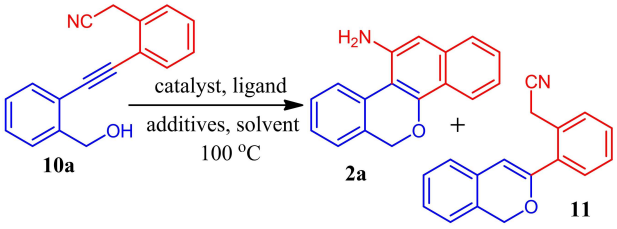
2.1. Synthesis of 6*H*-dibenzo[*c,h*]chromene derivatives 2/2′

We commenced the investigation with a model study on substrate **10a** which can be easily accessed through *Sonogashira coupling* between *o*-ethynylbenzyl alcohol and *o*-iodobenzyl cyanide (see Scheme S1 under supporting information); selected results are presented in Table 1. Notably, $Pd(OAc)_2$ or its ligated complex [i.e., $Pd(OAc)_2$bpy] turned out to be superior to other palladium catalysts (results not shown). Still, employment of 5 mol% of $Pd(OAc)_2$bpy in 1,4-dioxane furnished the desired product **2a** to the extent of 38% only along with the side product **11** resulting from mono-cyclization (Table 1, entry 1). Even deployment of catalyst and ligand separately in dry THF did not quite improve the situation (Table 1, entry 2), so we decided to test polar solvents. Indeed, carrying out this reaction in DMA enhanced the yield of **2a** to 52% with complete suppression of the side product **11**, though the relatively less polar DMF did not prove to be so efficient (Table 1, entries 3 & 4). Pleasingly, replacement of DMA by a still more polar solvent (NMA) significantly improved the yield (75%) of **2a** and reduced the reaction time from 6 h to 2 h (Table 1, entry 5). But the use of $Pd(OAc)_2$bpy or $Pd(OAc)_2$phen reduced the yield of **2a** marginally (Table 1, entry 6,7) and required longer reaction periods (Table 1, entry 7).

In order to optimize the reaction conditions further, we then replaced D-CSA with *p*-toluenesulphonic acid (*p*-TsOH); to our dismay, a mixture of the desired product **2a** and side product **11** (~1:1) resulted[18] (Table 1, entry 8), establishing the superiority of D-CSA.

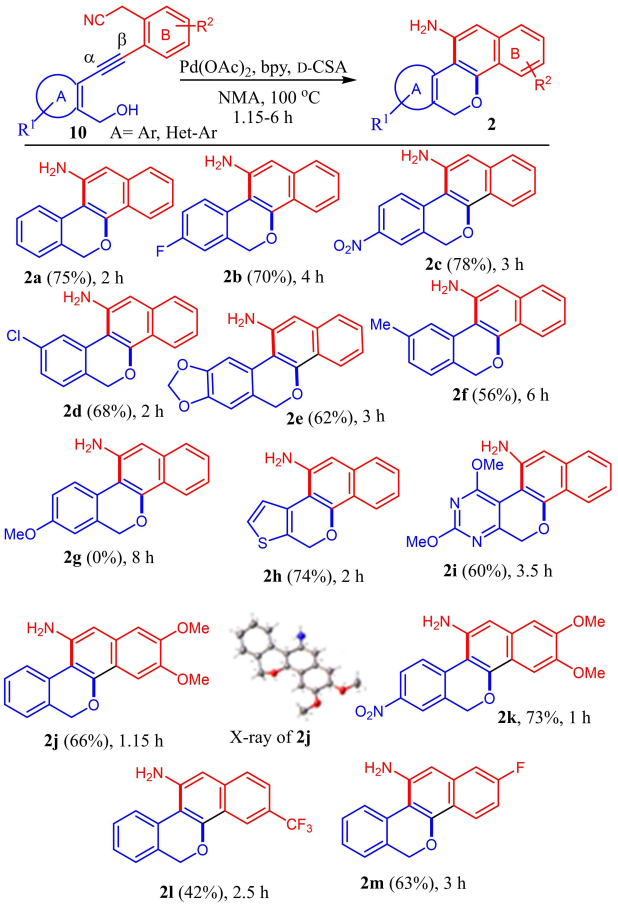
On the other hand, removal of D-CSA from the reaction did not produce **2a** at all, proving its necessity in this reaction (Table 1, entry 9), while carrying out this reaction using D-CSA alone was also unsuccessful (Table 1, entry 10). Thus reaction conditions of entry 5 of Table 1 appeared to be optimal.

Table 1. Optimization of the reaction conditions for 6*H*-dibenzo[*c*,*h*]chromen-11-amine **2a**.[a]



Entry	Catalyst	Additives	Solvents	Time	Yield[b] 2a	11
1	$Pd(OAc)_2$bpy	D-CSA	1,4-dioxane	4	38	20
2[c]	$Pd(OAc)_2$	D-CSA	THF	6	40	25
3[c]	$Pd(OAc)_2$	D-CSA	DMF	8	20	
4[c]	$Pd(OAc)_2$	D-CSA	DMA	6	52	
5[c]	**$Pd(OAc)_2$**	**D-CSA**	**NMA**	**2**	**75**	
6	$Pd(OAc)_2$bpy	D-CSA	NMA	2	72	
7	$Pd(OAc)_2$phen	D-CSA	NMA	3	68	
8[c]	$Pd(OAc)_2$	*p*-TsOH	NMA	2	45	50
9[c,d]	$Pd(OAc)_2$	-	NMA	20	nr	
10[d]	-	D-CSA	NMA	8	nr	

[a] Reaction conditions: **10a** (0.2 mmol), catalyst (5 mol%, except entry 10), bpy (6 mol%, except entries 1, 6–7 and 10), and additive (1.5 equiv.) in solvent (2 mL) at 100 °C under argon atmosphere.
[b] Isolated pure products.
[c] Ligand bpy (6 mol%) was used.
[d] The starting compound **10a** was found to remain intact (TLC).
Abbreviations: bpy: bipyridine; phen: phenanthroline; D-CSA: D-(+)-camphor sulfonic acid; NMA: N-methylacetamide; n.r.: no reaction.



[a] Reaction conditions: **10** (0.20 mmol), Pd(OAc)2 (5 mol %, bpy (6 mol %) and D-CSA (1.5 equiv.) in NMA (2 mL) under argon atmosphere.
[b] Yield of the isolated pure product.

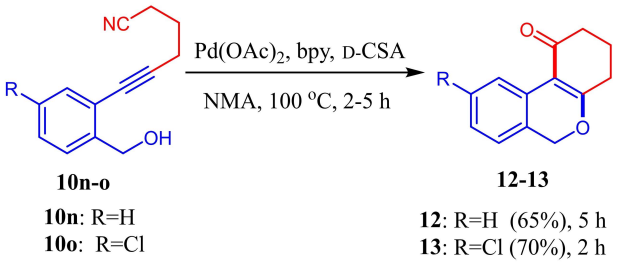
Scheme 1. Palladium-catalyzed synthesis of 11-amino-6*H*-dibenzo[*c*,*h*]chromenes **2**.[a,b]

We next set out to explore the scope and generality of the reaction on a variety of substrates **10** as shown in Scheme 1. A series of products **2a–l** could easily be prepared within 1.2–6 h with moderate to very good yields (42–78%) and a range of functional groups (viz., Me, CF_3, OMe, F, Cl, NO_2, CO_2Me, NH_2) were tolerated. An electron withdrawing group (EWG) in phenyl ring A facilitated the reaction, affording the desired products **2b–d** within 3–4 h with very good yields (68–78%). In contrast, an electron donating group at *meta* position (viz., R^1 = Me) made the reaction somewhat sluggish with lower yield (56%) of the product (**2f**), though the presence of two EDGs at *meta* and *para* positions (viz., R^1 = –OCH_2O–) delivered the product **2e** within 3 h. Notably, placement of a strong electron donating group (viz., OMe) at *para* position did not furnish any desired product **2g** even after heating for 8 h; the starting material remained intact (TLC) instead. However, replacement of the aryl ring A of **10** by a heteroaryl one (thiophene/2,4-dimethoxypyrimidine) worked well, affording the product (viz., **2h**/**2i**) within 2–3.5 h with 60–74% yields.

Regarding the effect of substituents in the other phenyl ring (i.e., B) of **10**, introduction of electron donating methoxy groups both at *meta* and *para* positions reduced the reaction time (1.15 h) significantly and produced the expected product **2j** in good yield (66%). The reaction was facilitated further by the incorporation of an additional nitro group (EWG) in ring A *para* to the alkyne group, resulting in the formation of product **2k** (73%). On the other hand, an EWG (viz., R^2 = CF_3 or F) at either *meta* or *para* position of ring B lowered the yields of the desired products (**2l** or **2m**) even after prolonging the reaction time (2.5–3 h). These substituent effects are perhaps predictable keeping in view the importance of electro-

philicity of *β*-carbon (of the triple bond of **10**) for the cyclization to proceed smoothly.

We also noted that performing this reaction with substrates having the acetylenic carbon tethered to a cyano group through a C3 chain (**10n–o**) instead of a benzylic moiety resulted in carbonylated products **12–13** within 2–5 h with 65–70% yield (Scheme 2) which is in line with previous observations. [19]



10n-o **12-13**

10n: R=H
10o: R=Cl

12: R=H (65%), 5 h
13: R=Cl (70%), 2 h

Scheme 2. Synthesis of 2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromen-1-ones **12–13**.

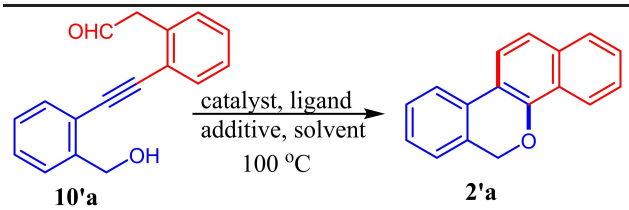
2.2. Synthesis of 6*H*-dibenzo[*c,h*]chromenes 2′

Encouraged by these results, we became interested to apply the reaction on other substrates **10′** in which an aldehyde functionality is used in place of a cyano group. To our dismay, this reaction produced **2′a** with only 42% yield (Table 2, entry 1). But use of the less polar 1,4-dioxane instead of NMA proved beneficial, delivering the expected product within 2 h with 75% yield (Table 2, entry 2). Though removal of the additive or changing the ligand to phenanthroline did not help (Table 2, entries 3 and 4), use of a ligated catalyst [i.e., $Pd(OAc)_2$bpy instead of $Pd(OAc)_2$ and bpy separately] greatly improved the yield (Table 2, entry 5). Replacing D-CSA by *p*-TsOH or decreasing the polarity of the solvent further had detrimental effect on the yield (Table 2, entries 6–8). Thus the reaction conditions of entry 5 of Table 2 appeared best.

To establish the generality of this methodology, the optimized reaction condition was then applied to a range of substrates (Scheme 3). Various substituents (e.g. NO_2, OMe, Me, F, Cl, Br etc.) in the aryl moiety of substrate **10′** were well tolerated. But a strongly electron-withdrawing group ($R^1 = NO_2$) in ring A *para* to the alkyne moiety lowered the yield of the product (**2′b**, 56%) considerably, while moderately active ones (R^1 = F/Cl/Br) either at *para* or *meta* position had little impact (**2′c**/**2′d**/**2′e**). Of particular note, employment of an electro-donating group (viz., R^1 = OMe) at *para* position in the same ring (**10′f**) yielded no product, leaving the starting material intact (TLC); this result is in line with our previous observation (see, product **2g** in Scheme 1). The inertness of these substrates (**10g**/**10′f**) is perhaps attributable to the enhanced electron density on the β-carbon of the triple bond, involved in the intramolecular nucleophilic attack, by the hydroxy methylgroup [see, species **A** (Y=O) under Scheme 10, *vide infra*]. In contrast, when the methoxy groups are placed at meta and para positions in ring B of the substrate (**10′g**), the expected product **2′g** was indeed formed smoothly with very good yield (75%); the high reactivity of this substrate is likely due to the electron-donating effect of the methoxy group making the same carbon atom (*β*) of the triple bond electron deficient, thereby facilitating the cyclization through the nucleophilic hydroxyl group.

As anticipated, employing an electron-withdrawing substituent (viz., R^2 = F) at *para* position (substrate **10′h**) indeed produced the product **2′h**, though in reduced yield (62%) as compared to **2′c**. On the other hand, the use of an electron donating methyl group at *meta* position (**10′i**) led to the product **2′i** with a moderate yield (47%). Even the substrate **10′j** with an alpha substituted aldehyde group reacted equally well, showing no influence of the steric effect at this site.

Table 2. Optimization of the reaction conditions for 6*H*-dibenzo[*c,h*]chromene **2′a**.[a]



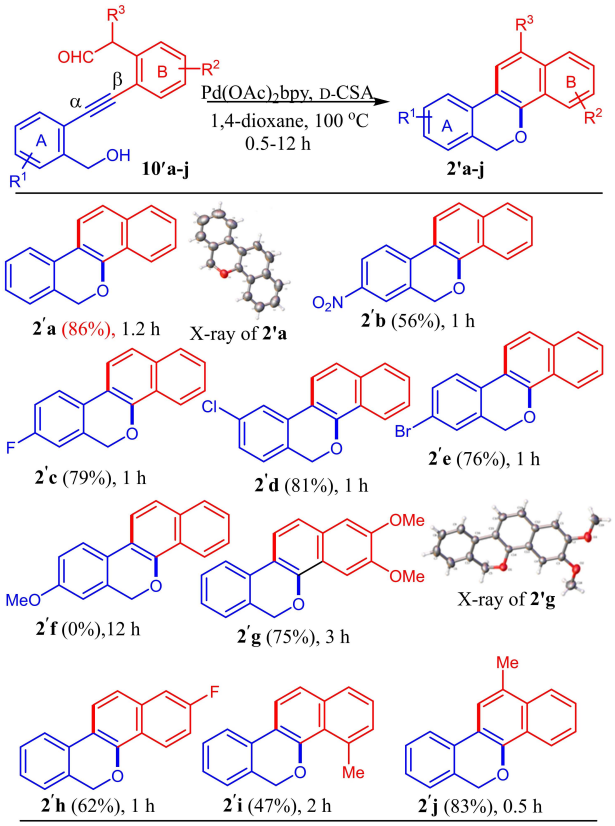
10'a **2'a**

Entry	Catalyst	Ligand	Additives	Solvent	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	bpy	D-CSA	NMA	2.5	42
2	$Pd(OAc)_2$	bpy	D-CSA	1,4 dioxane	2	75
3[c]	$Pd(OAc)_2$	bpy	-	1,4 dioxane	48	n.r.
4	$Pd(OAc)_2$	phen	D-CSA	1,4 dioxane	2	58
5	**$Pd(OAc)_2$(bpy)**	-	**D-CSA**	**1,4 dioxane**	**1.6**	**86**
6	$Pd(OAc)_2$(bpy)	-	p-TsOH	1,4 dioxane	1	80
7	$Pd(OAc)_2$(bpy)	-	D-CSA	THF	1.5	61
8	$Pd(OAc)_2$	bpy	D-CSA	THF	2.5	62

[a] Reaction conditions: **10′a** (0.2 mmol), catalyst (5 mol%,), ligand (6 mol%), and additive (1.5 equiv.) in solvent (2 mL) at 100 °C under argon atmosphere.
[b] Isolated pure products.
[c] Starting material was recovered. Abbreviations: n.r.: no reaction, bpy: bipyridine, phen: phenanthroline.

2.3. Synthesis of dibenzo[*c,h*]chromen-6-ones 3

After achieving a general synthesis of 6*H*-dibenzo[*c,h*] chromenes **2**/**2′**, we became interested to test the

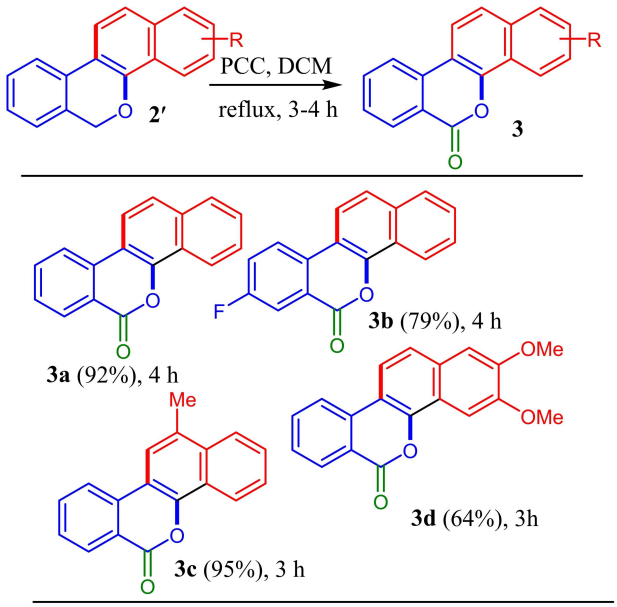


[a] Reaction conditions; **10′** (0.2 mmol), Pd(OAc)2bpy (5 mol %) and D-CSA (1.5 equiv. in 1,4-dioxane (2 mL) at 100 °C under argon atmosphere.
[b] Yield of the isolated pure products.

Scheme 3. Palladium-catalyzed synthesis of 6*H*-dibenzo[*c,h*]chromenes **2′**.[a,b]

applicability of this reaction through synthetic transformation of the products prepared. Initially we attempted benzylic oxidation of products **2′** which could provide easy access to **3**. Of the various oxidizing agents tested, PCC appeared to be the best, furnishing the desired products **3a–d** within few hours with very good to excellent yields (79–95%, Scheme 4). Thus synthesis of dibenzo[*c,h*]chromen-6-ones **3** could easily be achieved in two steps starting from acetylenic substrate **10** and overall yields were found to be between 48–81%.

In view of the prospect of synthesizing the products **3** directly, we carried out a reaction on substrate having *ortho*-carboxylic acid group in place of benzylic alcohol (of **10′a**) under our optimized reaction conditions (entry 5 of Table 2); to our surprise, the desired product **3a** was still found to be formed within 2 h but only in moderate yield (42%) (See, Scheme S4 under Supporting Information).



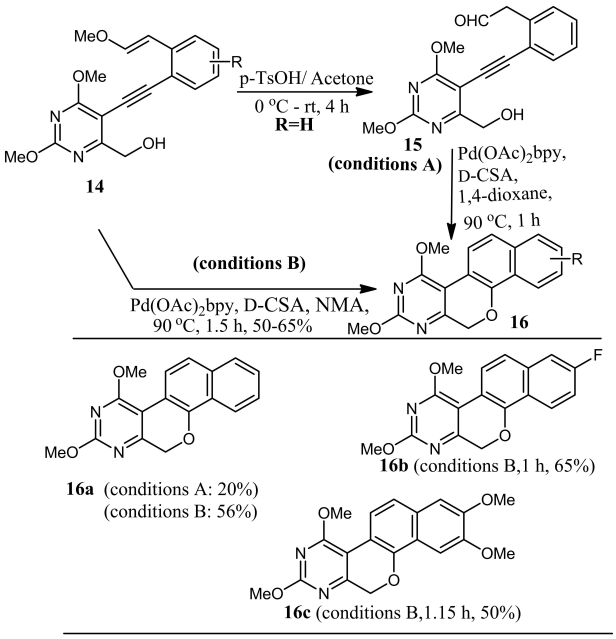
[a] Reaction conditons: A mixture of **2′** (0.086 mmol) and PCC (1.5 equiv.) in DCM (2 mL) was refluxed under argon atmosphere.
[b] Yield of the isolated pure product.

Scheme 4. Conversion of products **2′** to 6*H*-dibenzo[*c,h*]chromen-6-ones **3**.[a,b]

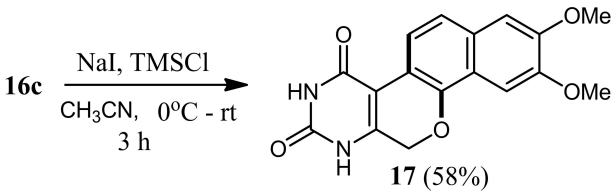
2.4. Synthesis of Pyrimidine (16) and Uracil (17) Derivatives

In view of the immense biological activity of uracil derivatives in cancer chemotherapy[20a–d] and our own interest in this field,[20e] we decided to apply the methodology for the synthesis of such molecules. The requisite starting material **15**, synthesized from precursor masked aldehyde **14a** (R=H) by treating with *p*-TsOH, was exposed to conditions A as shown in Scheme 5; to our disappointment, the desired product **16a** (R=H) was obtained only in 20% yield. Gratifyingly, the masked aldehyde **14a**, used under conditions B (where NMA is used instead of 1,4-dioxane), responded better and furnished the desired product **16a** with 56% yield. Substrates **14b** and **14c** containing electron withdrawing (R=F) and donating (R=OMe) group, respectively, also proved to be effective, affording the expected products (**16b** and **16c**) with 50–65% yield (Scheme 5).

For transformation to uracil derivatives, one of the products was tested for chemoselective demethylation. When **16c** was treated with TMSCl/NaI at room temperature (Scheme 6), the desired product **17** was formed easily albeit in moderate yield (58%). Anticancer screening of **17** in various cell lines and preparation of other related uracil derivatives are currently underway.



Scheme 5. Synthesis of 2,4-dimethoxy-12*H*-benzo[7,8]chromeno[3,4-*d*]pyrimidines **16**.



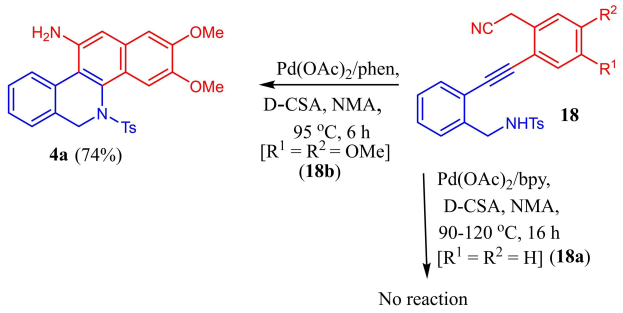
Scheme 6. Conversion of **16c** to uracil derivative **17**.

3. Synthesis of the Aza Analogues

3.1. Synthesis of N-tosyl-5,6-dihydrobenzo[c]phenanthridines 4/4′

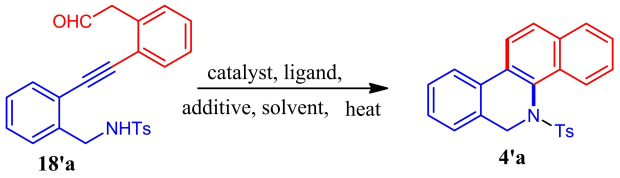
After successful exploration of the general synthesis of 6*H*-dibenzo[*c,h*]chromenes **2/2′**, we became interested to check the feasibility of this reaction for nitrogen heterocycles **4**. Initially, the starting material **18a** (R^1=R^2=H) was synthesized (see Scheme S5 under supporting information) and allowed to react under the optimized reaction conditions (entry 5 of Table 1). To our surprise, it merely yielded a tarry product (Scheme 7). The situation did not improve even after altering the catalyst, ligands, solvent systems, and temperature, or through incorporation of common substituents (R^1=Cl/F, R^2=H). Only when electron donating methoxy groups were incorporated in the substrate (R^1=R^2=OMe; **18b**), the desired product **4a** was formed.

We then planned to modify the structure of substrate **18** by replacing its cyano group with a formyl one. Towards this, the substrate **18′a** prepared in few steps (see Scheme S6 under supporting information) was subjected to the optimized reaction conditions (see entry 5 of Table 2), but the desired product **4′a** was formed with only 53% yield (Table 3, entry 1). Even the use of catalyst and ligand separately instead of preformed $Pd(OAc)_2$bpy was not helpful (Table 3, entry 2). But switching to a less polar solvent (i.e., THF) reduced the reaction time to 2 h and improved the yield to 62% (Table 3, entry 3). Use of the preformed catalyst $Pd(OAc)_2$bpy improved it further (Table 3, entry 4). But the reaction carried out in NMA required (Table 3, entries 5–6) longer time (2.5–3 h) and resulted in lower yields (38–41%), arguing against



Scheme 7. Palladium-catalyzed synthesis of 5,6-dihydrobenzo[*c*]phenanthridin-11-amines **4**.

Table 3. Optimization of the reaction conditions for *N*-tosyl-5,6-dihydrobenzo[*c*]phenanthridine **4′a**.[a,b]



Entry	Catalyst	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	$Pd(OAc)_2$bpy	-	1,4-dioxane	100	2	53
2	$Pd(OAc)_2$	bpy	1,4-dioxane	100	3	50
3	$Pd(OAc)_2$	bpy	THF	Reflux	2	62
4	**$Pd(OAc)_2$bpy**	-	**THF**	Reflux	**1.3**	**78**
5	$Pd(OAc)_2$bpy	-	NMA	100	2.5	41
6	$Pd(OAc)_2$phen	-	NMA	100	3	38

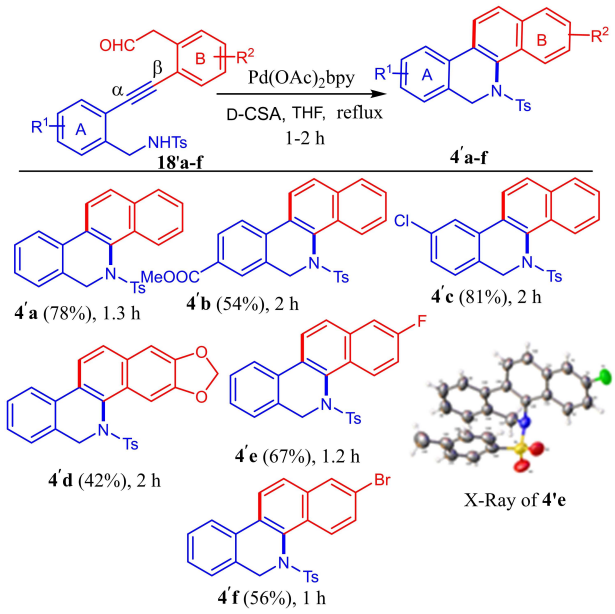
[a] In all entries, D-CSA was used as an additive.
[b] Reaction conditions: A mixture of **18′a** (0.2 mmol), catalyst (5 mol%), ligand (6 mol%), and D-CSA (1.5 equiv.) in solvent (2 mL) was heated at the mentioned temperature under argon atmosphere.
[c] Yield of the isolated pure products.

the use of polar solvent systems. Thus, the reaction conditions of entry 4 proved optimum.

To establish the generality of the synthesis of **4′**, we applied the optimized reaction conditions on substrates **18′** having various substitutions (Scheme 8). Initially, we used a strong electron-withdrawing group (viz., R^1=CO_2Me) in ring A *para* to the alkyne moiety of substrate **18′b**; indeed, it furnished the desired product **4′b** in 2 h with 54% yield, while a moderately electron-withdrawing group (i.e., R^1=Cl) at *meta* position afforded the desired product **4′c** with very good yield (81%). However, attempts to prepare a substrate containing an electron-donating methoxy group (R^1=OMe) in place of the carbomethoxy (of **18′b**) failed despite our sincere efforts.

Regarding the effect of ring B substituents, an electron-donating methylenedioxy group as in substrate **18′d** resulted in product **4′d** within 2 h albeit in moderate yield (42%). While the electron-withdrawing fluoro group at *para* position (**18′e**) afforded the product **4′e** in 1.2 h with a good yield (67%), the less electron-withdrawing bromo group (in **18′f**) lowered the reaction time (1 h) but also the yield (56%) simultaneously.

Addtionally, in order to check the role of N-protecting group in substrate **18′**, we deliberately replaced the tosyl group of the same by acetyl or Boc and the resulting substrates were allowed to react separately under optimized reaction conditions (entry 4 of Table 3); to our surprise, no trace of product formation (TLC) was observed in each case even after heating the reaction for several hours; the starting material was recovered instead.

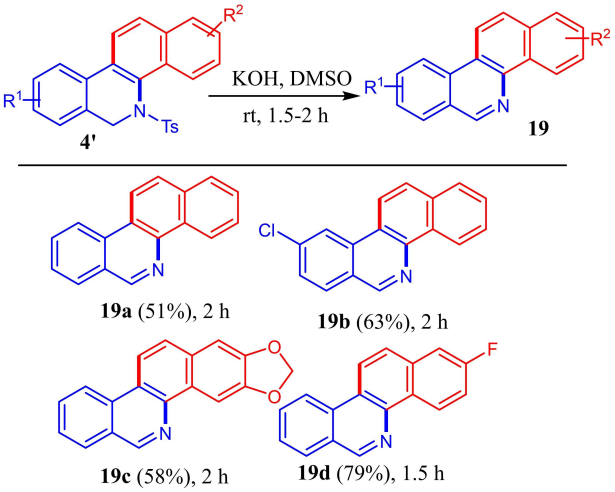


[a] Reactions conditons: **18′**(0.2 mmol), Pd(OAc)2bpy (5 mol %) and D-CSa (1.5 equiv.) in refluxing THF (2 mL) under argon atmosphere.
[b] Yield of the isolated pure products.

Scheme 8. Palladium-catalyzed synthesis of *N*-tosyl-5,6-dihydrobenzo[*c*]phenanthridines **4′**.[a,b]

3.2. Synthesis of Benzo[*c*]phenanthridines 19

Though some traditional[21a–d] and palladium-catalyzed methods[21e–g] for the synthesis of **19** exist in the literature, we felt that synthesis could easily be attained from **4′** through a base induced elimination reaction. Screening of a range of organic and inorganic bases proved potassium hydroxide to be the best for this transformation (Scheme 9). Thus the desired products were synthesized conveniently within 1.5–2 h with moderate to very good yields (51–79%) and the process was compatible with different functional groups (e.g., F, Cl and –OCH_2O–).

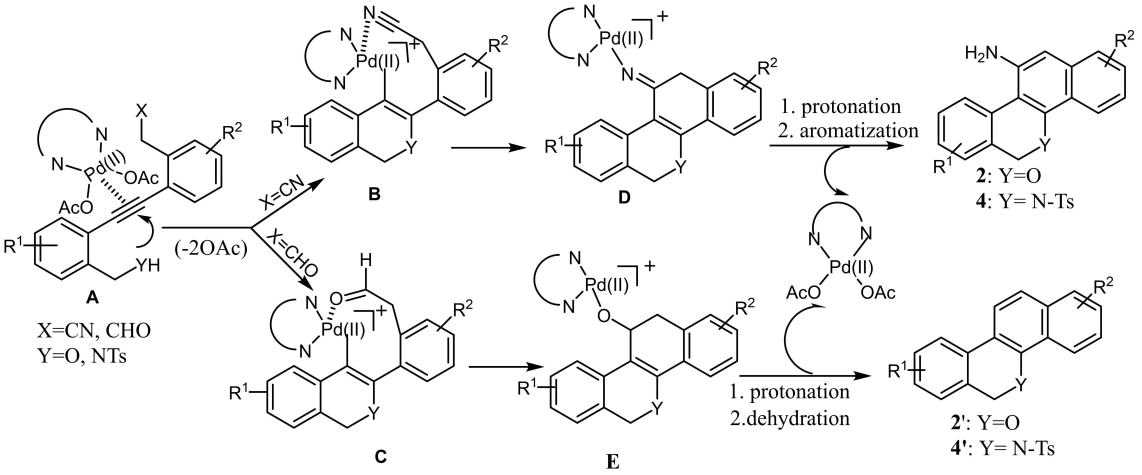


[a] Reaction condition: A mixture of **4′**(0.13 mmol) and KOH (5 equiv.) in DMSO was stirred at room temperature under argon atmosphere.
[b] Yield of the isolated product.

Scheme 9. Base promoted synthesis benzo[*c*]phenanthridines **19**.[a,b]

The structures of all products (i.e., **2/2′**, **3**, **4/4′**, **16–17, 19**) were established firmly by spectroscopic (^{1}H[22] and ^{13}C NMR, HRMS) and analytical data. In addition, single crystal X-ray analysis[23] of **2j** (Scheme 1), **2′a** and **2′g**, Scheme 3) and **4′e** (Scheme 8) provided additional support to the structural conclusion.

On the basis of our experimental results and known palladium chemistry, a plausible reaction mechanism is depicted (Scheme 10) to explain the product formation. Thus initial activation of the triple bond of the acetylenic substrate by the Pd(II) catalyst leads to the formation of species **A** which may trigger heteroannulation through *trans*-oxo/amino palladation

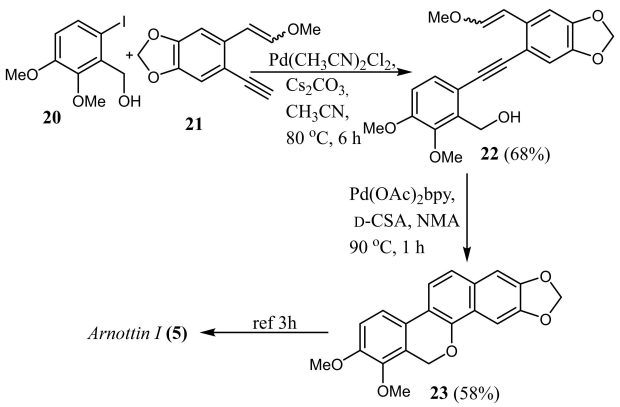


Scheme 10. Plausible mechanism for the formation of products **2/4** and **2′/4′**.

pathway[17e,24] resulting in the formation of the transient intermediate species **B** or **C**.[25] Next, species **B** and **C** may undergo intramolecular Grignard type nucleophilic addition over a tethered cyanide/aldehyde group to produce the corresponding palladated species **D**[16c] and **E**[26a–b], respectively. While species **D** upon protonolysis using D-CSA followed by aromatization would lead to the targeted product **2/4**, similar protonolysis on species **E**[27] followed by dehydration would afford the product **2′/4′**.

4. Application to the Formal Total Synthesis of *Arnottin I* (5)

In order to enlarge the scope of this heteroannulation reaction further, we undertook a total synthesis of *Arnottin I* (**5**, Figure 1) in a concise manner. This natural product was isolated as a minor constituent from the bark of *Xanthoxylum arnottianum,*[3a–b] but the biological activities have not been explored fully because of its low natural abundance. Nevertheless, related natural products have aroused significant interest in medicinal chemistry. For example, *neotanshinlactone* displayed potent activity against human breast cancer cell lines,[28] while *chelerythrine* (**8a** in Figure 1) proved to be of interest in cancer chemotherapy due to its ability to stabilize the c-MYC and c-KIT quadruplex DNAs[29a–b] (overexpression of which has been associated[29c] with numerous cancers) in addition to its role as G-quadruplex DNA stabilizer.[12a] These findings provided impetus to develop various strategies[3b–h] in order to get easy access to **5**. However, some of them use long synthetic routes using conventional reagents,[3b,f–g] while others, employing either palladium[3c–d,h] or nickel catalyst,[3e] required starting materials that were difficult to access. We felt that an intramolecular heteroannulation of intermediate **22**, which in turn could be synthesized through a palladium-catalyzed coupling between **20**[30] and **21**[14b] (see supporting information), may lead to **23** by adopting our newly developed method, the oxidation (PCC) of the benzylic hydrogens of which would provide easy access to *Arnottin I.* It is important to mention that the masked aldehyde precursor **22** should be preferred as substrate. Indeed, the desired product **23** was thus isolated in 58% yield within 1 h as shown in Scheme 11.



Scheme 11. Formal total synthesis of *Arnottin I* (**5**).

5. Conclusion

In conclusion, we have described a palladium-catalyzed expeditious approach for the general synthesis of dibenzo[*c,h*]chromen-6-ones **2/2′** and 5,6-dihydrobenzo[*c*]phenanthridines **4′** through intramolecular domino reactions of acetylenic substrates involving *trans*-oxo/aminopalladation followed by nucleophilic addition to

cyanide or aldehyde group. The method is fast, atom economical, operationally simple, and uses readily available substrates. A range of functional groups could easily be accommodated at different sites leaving enough opportunity for diversification. Simple one-step conversion of our products paved the way for easily accessing 6*H*-dibenzo[*c,h*]chromen-6-ones **3** and 5,6-dihydrobenzo[*c*]phenanthridines **19** prevalent as core structures of many medicinally active compounds. Finally, a concise formal total synthesis of *Arnottin I* was accomplished by applying the developed method. Thus we have successfully generated rapid molecular complexity under one pot using simple acetylenic substrates avoiding any by-product. We believe that this method will find applications in the total synthesis of complex natural products and medicinally relevant molecules as well.

Experimental Section

General Information

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60–80 °C. Dichloromethane 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 DMF (Dimethylformamide), DMA (Dimethylacetamide), and NMA (*N*-Methylacetamide) 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 F254 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 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.

General Procedure for the Synthesis of 6*H*-dibenzo [*c,h*]chromen-11-amine 2

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%), 2,2′-bipyridine (1.9 mg, 0.012 mmol, 6 mol%) and D-CSA(69.6 mg, 0.3 mmol, 1.5 equiv.) in dry NMA (3 mL) was stirred at 90 °C for 5 min under argon atmosphere. Next, the starting material **10** (0.20 mmol) dissolved in NMA (1.5 mL) was added to the reaction mixture at the same temperature and the whole mixture was allowed to stir at heating conditions (100 °C) for few hours until the completion of the reaction (TLC). The reaction mixture was then neutralized by adjusting the pH (~7) through drop wise 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) column chromatography using 10–40% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product **2**.

6H-Dibenzo[c,h]chromen-11-amine (2a): Brown gum (37.2 mg, 75% yield), R_f = 0.41 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.32 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz,1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.44-7.34 (m, 2H), 7.32 (d, *J* = 3.9 Hz, 2H), 7.24–7.19 (m, 1H), 6.78 (s, 1H), 5.12 (s, 2H), 4.20 (bs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 152.8, 141.9, 134.8, 132.3, 129.9, 128.5, 127.4, 127.0, 125.3, 125.2,123.6, 122.3, 122.2, 120.0, 110.7, 104.2, 69.4; HRMS (ESI+) m/z calculated for $C_{17}H_{14}NO$ $[M+H]^+$ 248.1075, found 248.1083.

8-Fluoro-6H-dibenzo[c,h]chromen-11-amine (2b)*:* Brown solid (37.1 mg, 70% yield), mp 120–122 °C, R_f = 0.41 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.34–8.29 (m, 1H), 8.08 (d, *J* = 8.4 Hz, 1H),7.54 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.23–7.20 (m, 1H), 7.13–7.01 (m, 1H), 6.78 (s, 1H), 5.08 (s, 2H), 4.12 (bs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.6 (d, *J* = 246.6 Hz), 152.3, 141.7, 134.7, 134.6, 127.5, 126.2 (d, *J* = 3.2 Hz), 125.5 (d, *J* = 7.7 Hz), 125.3,122.5, 122.2, 120.1, 115.1 (d, *J* = 21.8 Hz), 112.5 (d, *J* = 22.0 Hz), 110.2, 104.7, 69.0; HRMS (ESI+) m/z calculated for $C_{17}H_{13}FNO$ $[M+H]^+$ 266.0981, found 266.0991.

8-Nitro-6H-dibenzo[c,h]chromen-11-amine (2c)*:* Orange solid (45 mg, 78% yield), mp > 230 °C, R_f = 0.18 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.57 (d, *J* = 8.7 Hz, 1H), 8.27-8.24 (m, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.45–7.41 (m, 1H), 7.28–7.23 (m, 1H), 6.80 (s, 1H), 5.20 (s, 2H), 4.14 (bs, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 154.2, 145.9, 141.6, 136.7, 135.9, 132.6, 128.6, 125.4, 123.9, 122.9, 122.6, 120.4, 119.8, 109.4, 105.1, 68.7; HRMS (EI+) m/z calculated for $C_{17}H_{12}N_2O_3$ $[M]^+$ 292.0848, found 292.0845.

9-Chloro-6H-dibenzo[c,h]chromen-11-amine (2d)*:* Yellow solid (38.3 mg, 75% yield), mp 128–130 °C, R_f = 0.45 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.28 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.40-7.36 (m, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25-7.22 (m, 1H), 6.78 (s, 1H), 5.08 (s, 2H), 4.11 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 152.7, 141.7, 134.9, 133.9, 132.5, 128.5, 128.4, 127.6, 125.4, 125.3, 124.9, 122.5, 122.3, 119.9, 110.0, 104.6, 68.8; HRMS (ESI+) m/z calculated for $C_{17}H_{13}ClNO$ $[M+H]^+$ 282.0686, found 282.0691.

6H-[1,3]Dioxolo[4′,5′:4,5]benzo[1,2-c]benzo[h]- chromen-12-amine (2e): Pale yellow solid (36.2 mg, 62% yield), mp 184–186 °C, R_f = 0.35 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.05 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.36–7.32 (m, 1H), 7.21–7.17 (m, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 5.99 (s, 2H), 4.98 (s, 2H), 4.08 (s, 2H); ^{13}C NMR($CDCl_3$, 100 MHz) δ_C 152.1, 147.8, 146.5, 141.6, 134.4, 127.2, 126.2, 125.3, 123.9, 122.4, 122.2,

120.1, 110.0, 106.2, 104.8, 104.5, 101.3, 69.4; HRMS (ESI+) m/z calculated for $C_{18}H_{14}NO_3$ $[M+H]^+$ 292.0974, found 292.1023.

9-Methyl-6H-dibenzo[c,h]chromen-11-amine (2f): Brown solid (29.3 mg, 56%), mp 168–170 °C; R_f = 0.46 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.10 (d, J=8.1 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 7.32-7.23 (m, 3H), 7.21-7.19 (m, 1H), 6.79 (s, 1H), 5.18 (d, J=12.3 Hz, 1H), 4.81 (d, J=12.3 Hz, 1H), 3.95 (s, 2H), 2.47 (s, 3H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 154.4, 141.7, 136.3, 134.9, 134.2, 131.9, 128.7, 127.1, 126.7, 125.2, 122.3, 122.1, 121.9, 119.4, 111.8, 102.8, 71.1, 21.7; HRMS (ESI+) m/z calculated for $C_{18}H_{16}NO$ $[M+H]^+$ 262.1232, found 262.1236.

11H-Benzo[h]thieno[2,3-c]chromen-4-amine (2h):Black gum (37.4 mg, 74% yield), R_f=0.30 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.09 (d, J=8.4 Hz, 1H), 7.76 (d, J=5.1 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.37–7.33 (m, 2H), 7.25–7.20 (m, 1H), 6.78 (s, 1H), 5.38 (s, 2H), 4.07 (brs, 2H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 149.5, 140.9, 134.4, 131.3, 128.9, 126.9, 125.4, 124.2, 123.9, 122.5, 122.3, 120.0, 109.7, 104.4, 64.8; HRMS (ESI+) m/z calculated for $C_{15}H_{12}NOS$ $[M+H]^+$ 254.0640, found 254.0643.

2,4-Dimethoxy-12H-benzo[7,8]chromeno[3,4-d]pyrimidin-5-amine (2i): Brown solid (37.1 mg, 60% yield), mp 112–114 °C, R_f=0.20 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.10 (d, J=8.4 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 7.38 (t, J=7.5 Hz, 1H), 7.26–7.21 (m, 1H), 6.85 (s, 1H), 5.02 (s, 2H), 4.17 (s, 3H), 4.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 165.1, 164.9, 163.6, 152.2, 142.0, 134.7, 127.2, 125.1, 122.4, 122.1, 119.4, 106.9, 105.7, 104.6, 69.7, 55.1, 54.4; HRMS (ESI+) m/z calculated for $C_{17}H_{16}N_3O_3$ $[M+H]^+$ 310.1192, found 310.1205.

2,3-Dimethoxy-6H-dibenzo[c,h]chromen-11-amine (2j): Brown solid (40.5 mg, 66% yield), mp > 230 °C,R_f=0.11 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, J=7.8 Hz, 1H), 7.41–7.39 (m, 2H), 7.30–7.29 (m, 2H), 6.87 (s, 1H), 6.68 (s, 1H), 5.10 (s, 2H), 4.09 (s, 2H), 3.99(s, 3H), 3.98 (s, 3H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 151.8, 150.8, 147.0, 140.8, 132.0, 130.8, 130.3, 128.4, 126.6, 125.1, 123.6, 114.5, 109.2, 104.4, 103.8, 101.4, 69.4, 55.9, 55.8; HRMS (EI+) m/z calculated for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1204.

2,3-Dimethoxy-8-nitro-6H-dibenzo[c,h]chromene (2k): Reddish brown solid (51.4 mg, 73% yield), mp > 250 °C, R_f = 0.32 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.55 (d, J=8.7 Hz, 1H), 8.24 (d, J=9.0 Hz, 1H),8.17 (s, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 6.69 (s, 1H), 5.17 (s, 2H), 4.04 (s, 2H), 3.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 152.9, 151.8, 147.4, 145.5, 140.6, 137.1, 132.2, 123.8, 123.7, 120.2, 114.2, 107.9, 104.6, 104.4, 101.5, 68.6, 55.9, 55.8; HRMS (EI+) m/z calculated for $C_{19}H_{17}N_2O_5$ $[M+H]^+$ 353.1137, found 353.1151.

3-(Trifluoromethyl)-6H-dibenzo[c,h]chromen-11-amine (2l): Brown gum (25.2 mg, 42% yield), R_f=0.27 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.40 (s, 1H), 8.27 (d, J=7.8 Hz, 1H), 7.58 (d, J=8.4 Hz, 1H), 7.50 (d, J=8.7 Hz, 1H), 7.43–7.40 (m, 1H), 7.35–7.33 (m, 1H), 6.78 (s, 1H), 5.15 (s, 2H), 4.37(s, 2H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 153.4, 144.0, 135.9, 132.1, 129.3, 129.0, 128.5, 127.4, 125.8, 125.4, 123.7, 123.3, 122.8 (m), 120.4 (m), 118.6, 111.3, 103.7, 69.4; HRMS (ESI+) m/z calculated for $C_{18}H_{12}F_3O$ $[M+H]^+$ 301.0840, found 301.0838.

2-Fluoro-6H-dibenzo[c,h]chromen-11-amine (2m) : Pale yellow solid (33.5 mg, 63% yield), mp 130–132 °C, R_f=0.36 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.27 (d, J=7.8 Hz, 1H), 8.11-8.06 (m, 1H), 7.43–7.38 (m, 1H), 7.31(d, J=4.2 Hz, 2H), 7.13 (dd, J=10.5, 2.1 Hz, 1H), 6.96 (td, J=8.7, 2.4 Hz, 1H), 6.69 (s, 1H), 5.11 (s, 2H), 4.25 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 162.2 (d, J=244.6 Hz), 153.0, 143.2, 136.0 (d, J=9.9 Hz), 132.0, 129.7, 128.5, 127.0, 125.3, 125.0 (d, J=9.6 Hz), 123.4, 116.9, 112.2 (d, J=25.0 Hz), 109.8, 108.3 (d, J=21.3 Hz), 103.4 (d, J=5.1 Hz), 69.4; HRMS (ESI+) m/z calculated for $C_{17}H_{13}FNO$ $[M+H]^+$ 266.0981, found 266.0988.

Spectral data of Products 12–13

2,3,4,6-Tetrahydro-1H-benzo[c]chromen-1-one (12): White solid (26 mg, 65% yield); mp 122–124 °C; R_f=0.29 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.29 (d, J=7.8 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.21 (t, J=7.5 Hz, 1H), 7.03 (d, J=7.2 Hz, 1H), 5.12 (s, 2H), 2.58–2.54 (m, 4H), 2.03–1.99 (m, 2H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 196.5, 174.1, 128.6, 127.8, 127.0, 126.9, 124.8, 123.7, 113.1, 69.5, 38.3, 28.9, 20.1; HRMS (EI+) m/z calculated for $C_{13}H_{12}O_2$ $[M]^+$ 200.0837, found 200.0839.

9-Chloro-2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one (13): Pale yellow solid (32.8 mg, 70% yield), mp 164–166 °C, R_f = 0.28 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.36 (t, J=1.8 Hz, 1H), 7.19–7.16 (m, 1H), 6.95 (d, J=8.1 Hz, 1H), 5.09 (s, 2H), 2.59–2.51 (m, 4H), 2.04–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 196.2, 174.9, 134.4, 129.3, 126.7, 125.0, 124.9, 124.8, 112.1, 68.9, 38.1, 28.9, 19.9; HRMS (ESI+) m/z calculated for $C_{13}H_{12}ClO_2$ $[M+H]^+$ 235.0526, found 235.0522.

General Procedure for the Synthesis of 6*H*-dibenzo [*c,h*]chromenes 2′

A mixture of $Pd(OAc)_2$bpy (3.8 mg, 0.01 mmol, 5 mol%) and D-CSA (69.6 mg, 0.3 mmol, 1.5 equiv.) in dry 1,4-dioxane (2 mL) was stirred at 90 °C for 5 min under argon atmosphere. Next the starting material **10′** (0.20 mmol) dissolved in 1,4-dioxane (1.5 mL) was added to the reaction mixture at the same temperature and the whole mixture was allowed to stir at heating conditions (100 °C) for few hours until the completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized by adjusting the pH (~7) through drop wise 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) column chromatography using 0–20% ethyl acetate-petroleum ether (v/v) as eluent to afford desired product **2′**in 47–86% yield.

6H-Dibenzo[c,h]chromene (2′a): Yellow solid (39.9 mg, 86% yield), mp 100–102 °C, R_f = 0.46 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.28-8.26 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.82–7.80 (m, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.50–7.48 (m, 2H), 7.42 (t, J = 7.8 Hz 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.3, 134.4, 130.8, 130.7, 128.6, 127.6, 127.4, 126.6, 125.8, 125.3, 124.6, 122.3, 121.9, 121.6, 120.9, 117.2, 68.9; HRMS (ESI+) m/z calculated for $C_{17}H_{13}O$ $[M+H]^+$ 233.0966, found 233.0944.

8-Nitro-6H-dibenzo[c,h]chromene (2′b): Yellow solid (30.0 mg, 56% yield); mp 158–160 °C; R_f = 0.63 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.29-8.27 (m, 2H), 8.12 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.4 Hz,1H), 7.84–7.82 (m, 2H), 7.58(d, J = 8.4 Hz, 1H), 7.57-7.53 (m, 2H), 5.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 151.9, 146.6, 137.3, 135.4 131.3, 127.9, 127.8, 126.4, 125.1, 124.1, 122.6, 122.5, 122.4, 120.8, 120.2, 115.3, 68.3; HRMS (ESI+) m/z calculated for $C_{17}H_{12}NO_3$ $[M+H]^+$ 278.0817, found 278.0814.

8-Fluoro-6H-dibenzo[c,h]chromene (2′c): White solid (39.5 mg, 79% yield), mp 158–160 °C, R_f = 0.54 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.27–8.26 (m, 1H), 7.82-7.81 (m, 1H), 7.78(d, J = 8.4 Hz, 1H), 7.70-7.68 (m, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.52-7.49(m, 2H), 7.11(td, J = 8.55, 2.8 Hz, 1H), 6.94 (dd, J = 8.4, 2.4 Hz, 1H), 5.28 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 162.3 (d, J = 246 Hz), 149.8, 134.2, 132.9 (d, J = 7.5 Hz), 127.7, 126.9, 126.7, 125.9, 125.3, 123.8 (d, J = 9 Hz), 122.2, 121.8, 120.7, 116.6, 115.4 (d, J = 22.5 Hz), 111.9 (d, J = 22.5 Hz), 68.4; HRMS (ESI+) m/z calculated for $C_{17}H_{12}FO$ $[M+H]^+$ 251.0872, found 251.0876.

9-Chloro-6H-dibenzo[c,h]chromene (2′d): Yellow solid (43.1 mg, 81% yield), mp 101–103 °C, R_f = 0.49 (petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.27-8.25 (m, 1H), 7.82-7.78 (m, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 2 Hz, 1H), 7.52–7.48 (m, 3H), 7.24 (dd, J = 2 Hz,1H), 7.10 (d, J = 8 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.7, 134.8, 134.6, 132.6, 128.9, 127.8, 127.2, 127.1, 126.1, 125.9, 125.3, 122.4, 122.2, 121.9, 120.8, 116.1, 68.4; HRMS (ESI+) m/z calculated for $C_{17}H_{12}ClO$ $[M+H]^+$ 267.0577, found 267.0573.

8-Bromo-6H-dibenzo[c,h]chromene (2′e): White solid (47.1 mg, 76% yield), mp 140–142 °C, R_f = 0.54 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.26-8.24 (m, 1H), 7.81–7.79 (m, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.55–7.52 (m, 2H), 7.51–7.49 (m, 2H), 7.37 (s, 1H), 5.27 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.3, 134.5, 132.6, 131.6, 129.8, 127.7, 126.9, 126.0, 125.3, 123.6, 122.3, 121.8, 121.0, 120.6, 116.3, 68.2; HRMS (ESI+) m/z calculated for $C_{17}H_{12}BrO$ $[M+H]^+$ 311.0072, found 311.0066.

2,3-Dimethoxy-6H-dibenzo[c,h]chromene (2′g): Yellow solid (43.8 mg, 75% yield), mp 140–144 °C, R_f = 0.55 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.73–7.71 (m, 2H), 7.54 (s, 1H), 7.42–7.39 (m, 2H), 7.28 (td, J = 1.0, 7.35 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.11 (s, 1H), 5.29 (s, 2H), 4.05 (s, 3H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.1, 149.44, 149.42, 130.9, 130.5, 130.4, 128.5, 127.0, 124.6, 121.8, 120.4, 120.1, 119.4, 116.1, 106.4, 101.1, 68.9, 55.99, 55.91; HRMS (ESI+) m/z calculated for $C_{19}H_{17}O_3$ $[M+H]^+$ 293.1178, found 293.1174.

2-Fluoro-6H-dibenzo[c,h]chromene (2′h): Yellow solid (31 mg, 62% yield), mp 118–120 °C, R_f = 0.54 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.29-8.26 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.43–7.41 (m, 2H), 7.31 (t, J = 7.5 Hz 1H), 7.28–7.24 (m, 1H), 7.22 (d, J = 7.2 Hz, 1H), 5.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.4(d, J = 246 Hz), 150.5, 135.4 (d, J = 9 Hz), 130.4 (d, J = 4.5 Hz), 128.6, 127.5, 125.1(d, J = 10.5 Hz), 124.7,122.4, 121.8, 120.8(d, J = 4.5 Hz), 116.6 (d, J = 1.5 Hz), 115.9, 115.8, 111.0, 110.9, 68.9; HRMS (ESI+) m/z calculated for $C_{17}H_{12}FO$ $[M+H]^+$ 251.0872, found 251.0871.

4-Methyl-6H-dibenzo[c,h]chromene (2′i): Yellow solid (23.1 mg, 47% yield), mp 70–72 °C, R_f = 0.56 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.82 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.33-7.30 (m, 2H), 7.24–7.22 (m, 2H), 5.23 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 152.8, 135.9, 135.6, 131.0, 130.8, 128.8, 128.6, 127.2, 126.4, 126.2, 125.1, 124.4, 122.6, 122.3, 121.1, 118.5, 68.2, 25.2; HRMS (ESI+) m/z calculated for $C_{18}H_{15}O$ $[M+H]^+$ 247.1123, found 247.1122.

12-Methyl-6H-dibenzo[c,h]chromene (2′j): Yellow gum (40.8 mg, 83% yield),R_f = 0.44 (petroleum ether);^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, J = 9 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.69 (s, 1H), 7.56–7.51 (m, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 5.30 (s, 2H), 2.71 (s, 3H); ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 148.9, 133.4, 130.9, 130.7, 128.5, 127.6, 127.3, 126.5, 125.54, 125.5, 124.6, 124.2, 122.7, 121.9, 121.3, 116.6, 68.9, 19.3; HRMS (ESI+) m/z calculated for $C_{18}H_{15}O$ $[M+H]$ + 247.1123, found 247.1125.

Synthesis of 6*H*-dibenzo[*c,h*]chromen-6-ones (3) from 6*H*-dibenzo[*c,h*]chromenes 2′ by benzylic oxidation

To a solution of 2′(0.086 mmol, 1 equiv.) in dry DCM was added PCC (27.7 mg, 0.13 mmol, 1.5 equiv.) and heated at refluxing temperature for 3–4 h until complete consumption of the starting material (TLC).The crude product was filtered through a plug of silicagel (100-200 mesh size) which was washed with DCM, and the solution was concentrated *in vacuo*. The crude product was purified through silica gel (100-200 mesh) column chromatography eluting with 18–20% ethyl acetate-petroleum ether (v/v) to furnish the pure product 3 in 64–95% yield.

6H-Dibenzo[c,h]chromen-6-one (3a): White solid (19.4 mg, 92% yield), mp 188–190 °C, R_f = 0.53 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.59 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.06(d, J = 9.0 Hz, 1H), 7.89–7.85 (m, 2H), 7.77 (d, J = 8.7 Hz, 1H), 7.66-7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.3, 147.3, 135.5, 135.0, 134.3, 130.7, 128.7, 127.9, 127.7, 127.2, 124.6, 123.9, 122.4, 122.1, 121.2, 119.2, 113.1; HRMS (ESI+) m/z calculated for $C_{17}H_{11}O_2$ $[M+H]^+$ 247.0759, found 247.0764.

8-Fluoro-6H-dibenzo[c,h]chromen-6-one (3b): White solid (17.9 mg, 79% yield), mp 219–221 °C,R_f = 0.55 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.55 (d, J = 8.4 Hz, 1H), 8.19.–8.17 (m, 1H), 8.10 (dd, J = 3, 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.65–7.56 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 162.3 (d, J = 249 Hz), 160.3 (d, J = 3 Hz), 146.7, 134.1, 131.9 (d, , J = 3 Hz), 127.8 (d, J = 39 Hz), 127.3, 124.8, 124.6 (d, J = 9 Hz), 123.8, 123.3, 123.2, 122.9 (d, J = 9 Hz), 122.2, 118.9, 116.2(d, J = 22.5 Hz), 112.4; HRMS (ESI+) m/z calculated for $C_{17}H_{10}FO_2$ $[M+H]^+$ 265.0665, found 265.0644.

12-Methyl-6H-dibenzo[c,h]chromen-6-one (3c): White solid (21.2 mg, 95% yield), mp 195–197 °C, R_f = 0.58 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.63-8.61 (m, 1H), 8.47 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.01-7.99 (m, 1H), 7.88–7.85(m, 2H), 7.66–7.65 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 2.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.4, 146.0, 135.4, 134.9, 133.4, 130.8, 130.6, 128.5, 127.7, 126.8, 124.2, 123.9, 122.8, 121.9, 121.3, 119.2, 112.5, 19.5; HRMS (ESI+) m/z calculated for $C_{18}H_{12}NaO_2$ $[M+Na]^+$ 283.0735, found 283.0740.

2,3-Dimethoxy-6H-dibenzo[c,h]chromen-6-one (3d): White solid (16.8 mg, 64% yield), mp 176–178 °C, R_f = 0.57 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.44 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.84 (t, J = 7.2 Hz, 1H), 7.79 (s, 1H), 7.61–7.54 (m, 2H), 7.14 (s, 1H), 4.10 (s, 3H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.6, 150.9, 150.3, 146.5, 135.8, 134.9, 130.6, 130.4, 128.2, 122.9, 121.8, 120.7, 119.0, 117.6, 111.9, 106.4, 101.1, 56.4, 56.0; HRMS (ESI+) m/z calculated for $C_{19}H_{15}O_4$ $[M+H]^+$ 307.0970, found 307.0974.

General procedure for the synthesis of 2,4-dimethoxy-12*H*-benzo[7,8]chromeno[3,4-*d*]pyrimi- dine 16

A mixture of $Pd(OAc)_2$bpy (5.7 mg, 0.015 mmol, 5 mol%), D-CSA (139.2 mg, 0.6 mmol, 2 equiv.) in dry NMA (2 mL) was stirred at 90 °C for 5 min under argon atmosphere. The substrate **14** (0.3 mmol, 1 equiv.) dissolved in NMA (1.0 mL) was then added dropwise and the whole mixture was allowed to stir at 100 °C for few hours until completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized by adjusting the pH (~7) through drop wise addition of 20% aqueous sodium bicarbonate solution and then 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) column chromatography using 15–20% ethyl acetate-petroleum ether (v/v) as eluent to afford desired product **16** in 50–65% yield.

2,4-Dimethoxy-12H-benzo[7,8]chromeno[3,4-d]pyrimidine (16a): Pale yellow solid (49.4 mg, 56% yield), mp 119–121 °C, R_f = 0.43 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H7.84 (d, J = 1.2 Hz, 1H), 7.57 −7.55 (m,2H), 7.45 (d, J = 7.8 Hz, 1H), 7.27–7.24 (m, 1H), 7.19 (t, J = 7.5 Hz, 1H), 5.14 (s, 2H), 4.14 (s, 3H), 4.05(s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 168.7, 162.8, 160.9, 150.6, 140.7, 136.7, 129.7, 126.6, 126.3, 124.7, 121.3, 117.5, 111.4, 87.9, 85.9, 55.0, 54.6; HRMS (ESI+) m/z calculated for $C_{17}H_{15}N_2O_3$ $[M+H]^+$ 295.1083, found 295.1086.

8-Fluoro-2,4-dimethoxy-12H-benzo[7,8]chromeno [3,4-d]pyrimidine (16b): Pale yellow solid (61.0 mg, 65% yield), mp 158–160 °C, R_f = 0.41 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.80 (d, J = 1.2 Hz, 1H), 7.52 (s, 1H), 7.37–7.35 (m, 1H), 7.23 (dd, J = 2.1,9.3 Hz, 1H), 6.98–7.95 (m, 1H), 5.15 (s, 2H), 4.15 (s, 3H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 168.7, 161.8 (d, J = 209.4 Hz), 151.3, 138.5(d, J = 9 Hz), 136.8 (d, J = 2.2 Hz), 128.9 (d, J = 1.5 Hz), 122.1, 122.0, 121.6, 113.5 (d,J = 23.3 Hz), 111.4, 105.1, 104.9, 77.3, 55.1, 54.7; HRMS (ESI+) m/z calculated for$C_{17}H_{14}FN_2O_3$ $[M+H]+$ 313.0988, found 313.0991.

2,4,8,9-Tetramethoxy-12H-benzo[7,8]chromeno[3,4-d]pyrimidine (16c): Pale yellow solid (53.1 mg, 50% yield), mp 212–214 °C, R_f = 0.19 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.08 (d, J = 9.0 Hz, 1H), 7.50 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.09 (s, 1H), 5.19 (s, 2H), 4.15 (s, 3H), 4.04 (s, 3H) 4.03 (s, 3H), 4.01(s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 166.6, 163.5, 161.4, 150.1, 149.4, 148.1, 129.8, 122.5, 119.9, 119.8, 111.9, 106.1, 105.8, 100.8, 69.2, 56.0, 55.9, 54.9, 54.3; HRMS (ESI+) m/z calculated for $C_{19}H_{19}N_2O_5$ $[M+H]^+$ 355.1294, found 355.1299.

General procedure for the synthesis of 8,9-dimethoxy-1*H*-benzo[7,8]chromeno[3,4-*d*]pyri- mi- dine-2,4(3*H*,12*H*)-dione (17)

To a well stirred and ice-cooled solution of **16c** (30 mg, 0.08, 1 equiv.) in dry acetonitrile (3 mL) were added anhydrous sodium iodide (35.7 mg, 0.24 mmol, 3 equiv.) and freshly distilled trimethylsilylchloride (30 µL, 0.24 mmol, 3 equiv.) successively. The reaction mixture was then stirred at room temperature until the complete conversion of the starting material (TLC). The solvent was removed under reduced pressure; the crude product was filtered, and washed with ethyl acetate several times. The resulting yellow solid was dried *in vacuo* to afford the product **17**.

8,9-Dimethoxy-1H-benzo[7,8]chromeno[3,4-d]pyri- midine-2,4 (3H,12H)-dione (17): Pale yellow solid (16.4 mg, 58% yield), mp >260 °C; ^{1}H NMR (DMSO-d_6, 600 MHz) δ_H 11.40 (s, 1H), 11.31 (s, 1H), 8.30 (d, J = 9 Hz, 1H), 7.37 (d, J = 9 Hz, 1H), 7.29 (s, 1H), 7.24 (s,1H),5.03 (s, 2H), 3.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 162.1, 150.7, 149.9, 149.7, 145.4, 144.9,129.2, 121.2, 119.9, 119.2, 113.2, 106.9, 101.2, 100.3, 63.9, 55.9, 55.8; HRMS (ESI+) m/z calculated for $C_{17}H_{15}N_2O_5$ $[M+H]^+$ 327.0981, found 327.0990.

Synthesis of 2,3-dimethoxy-5-tosyl-5,6-dihydrobenzo[*c*]phenanthridin-11-amine 4 a

A mixture of $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 5 mol%), phenanthroline (2.38 mg, 0.013 mmol, 6 mol%) and D-CSA (76 mg, 0.33 mmol, 1.5 equiv.) in NMA(3 mL) was stirred at reflux temperature for 5 min under argon atmosphere. Then the starting material **18** (0.22 mmol) dissolved in NMA (1.5 mL) was added to the reaction mixture at the same temperature and the whole mixture was allowed to stir at 95 °C for few hours until the completion of the reaction (TLC). The reaction mixture

was then neutralized by adjusting the pH (~7) through drop wise 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) column chromatography using eluent 30% ethyl acetate-petroleum ether (v/v) to afford the desired product **4a**.

2,3-Dimethoxy-5-tosyl-5,6-dihydrobenzo[c]phenan- thridin-11-amine (4a): Brown solid (74.9 mg, 74% yield), mp 186–188 °C, R_f = 0.46 (50% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.98 (s, 1H), 7.41 (d, J= 7.8 Hz, 1H), 7.23 (d, J=7.8 Hz, 1H), 7.12 (t, J=7.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.88 (s, 1H), 6.73 (d, J=8.4 Hz, 2H), 7.68 (d, J=7.8 Hz, 2H), 5.21 (d, J=15.2 Hz, 1 Hz), 4.37 (d,,J= 16.2 Hz, 1H), 4.09 (s, 3H), 4.00 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.9, 147.5, 142.3, 139.7, 133.8, 133.7, 133.5, 131.4, 130.8, 128.3, 127.2, 127.1, 126.8, 126.6, 125.3, 120.9, 119.0, 110.9, 106.1, 103.7, 56.1, 55.8, 52.1, 21.3; HRMS (ESI+) m/z calculated for $C_{26}H_{25}N_2O_4S$ $[M+H]^+$ 461.1535, found 461.1550.

General procedure of synthesis of 5-tosyl-5,6-dihydrobenzo[*c*]phenanthridine

A mixture of $Pd(OAc)_2$bpy (3.8 mg, 0.01 mmol, 5 mol%), and D-CSA (69.6 mg, 0.3 mmol, 1.5 equiv.) in dry THF (1 mL) was stirred at 60 °C under argon atmosphere. Then the starting material **10′** (0.2 mmol) dissolved in dry THF (1 mL) was added to the reaction mixture at the same temperature and the whole mixture was allowed to stir at reflux temperature for few hours until the completion of the reaction (TLC). Thereafter the reaction mixture was neutralized by adjusting the pH (~7) through drop wise 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) column chromatography using eluent 10–40% ethyl acetate-petroleum ether (v/v) to afford desired product **4′**.

5-Tosyl-5,6-dihydrobenzo[c]phenanthridine (4′a): Yellow solid (60.1 mg, 78% yield), mp 154–156 °C, R_f = 0.44 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.72 (d, J=8.4 Hz, 1H), 7.85-7.82 (m, 2H), 7.64-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.20 (d, J=7.6 Hz, 1H), 7.14-7.04 (m, 3H), 6.80 (d, J=8.0 Hz, 2H), 6.64 (d, J=8.4 Hz, 2H), 5.29 (d, J= 16.4 Hz, 1H), 4.53 (d, J=16.4 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 142.9, 133.9, 133.7, 132.5, 132.2, 132.0, 131.5, 129.3, 128.6, 128.2, 127.9, 127.6, 127.5, 127.4, 126.9, 126.8, 126.5, 126.2, 123.2, 121.4, 51.2, 21.4; HRMS (ESI+) m/z calculated for $C_{24}H_{20}NO_2S$ $[M+H]^+$ 386.1215, found 386.1201.

Methyl 5-tosyl-5,6-dihydrobenzo[c]phenanthridine-8-carboxy-late(4′b): Brown solid (47.8 mg, 54% yield), mp 106–108 °C, R_f = 0.22 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.74 (d, J=9.0 Hz, 1H), 7.90-7.86 (m, 2H), 7.77–7.75 (m, 2H), 7.68–7.65 (m, 2H), 7.60–7.58 (m, 1H), 7.32 (d, J=8.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 2H), 6.67 (d, J= 7.8 Hz, 2H), 5.35 (d, J=16.8 Hz, 1H), 4.58 (d, J=16.8 Hz, 1H), 3.97 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 166.5, 143.3, 136.2, 134.4, 133.6, 133.57, 132.2, 131.4, 129.2, 128.8, 128.7, 128.4, 128.1, 127.7, 127.5, 127.4, 127.3, 127.0, 126.8, 123.1, 121.3, 52.4, 50.8, 21.3; HRMS (ESI+) m/z calculated for $C_{26}H_{22}NO_4S$ $[M+H]^+$ 444.1270, found 444.1270.

9-Chloro-5-tosyl-5,6-dihydrobenzo[c]phenanthri- dine (4′c): Yellow solid (67.9 mg, 81% yield), mp 140–142 °C, R_f=0.46 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.74 (d, J=8.4 Hz, 1H), 7.89–7.86 (m, 2H), 7.67-7.64 (m, 1H), 7.59–7.55 (m, 2H), 7.15–7.13 (m, 2H), 7.07 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.4 Hz, 2H), 6.75 (d, J=7.8 Hz, 2H), 5.29 (d, J=16.2 Hz, 1H), 4.48 (d, J=16.2 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 143.6, 134.2, 133.8, 133.7, 132.9, 131.3, 130.4, 128.8, 128.3, 128.2, 127.6, 127.5, 127.4, 127.2, 126.9, 126.8, 123.4, 121.1, 50.6, 21.4; HRMS (ESI+) m/z calculated for $C_{24}H_{19}ClNO_2S$ $[M+H]+$ 420.0825, found 420.0823.

12-Tosyl-12,13-dihydro-[1,3]dioxolo[4′,5′:4,5]ben-zo[1,2-c] phenanthridine (4′d): Pale yellow solid (36.1 mg, 42% yield), mp 74–78 °C, R_f = 0.55 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.05 (s, 1H), 7.66 (d, J= 8.4 Hz, 1H), 7.46 (d, J=8.4 Hz,1H), 7.15 (d, J=7.8 Hz, 1H), 7.11-7.10 (m, 3H), 7.05-7.03 (m, 1H), 6.81(d, J=7.8 Hz, 2H), 6.66 (d, J=7.8 Hz, 2H), 6.09 (d, J=8.4 Hz, 2H), 5.27 (d, J= 16.8 Hz, 1H), 4.50 (d, J=16.2 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 148.4, 142.8, 133.4, 132.2, 131.9, 131.7, 131.4, 128.9, 128.2, 128.0, 127.6, 127.57, 127.4, 127.37, 126.1, 122.9, 119.9, 103.5, 103.3, 101.4, 51.2, 21.3; HRMS (ESI+) m/z calculated for $C_{25}H_{20}NO_4S$ $[M+H]^+$ 430.1113, found 430.1125.

2-Fluoro-5-tosyl-5,6-dihydrobenzo[c]phenanthri- dine (4′e): Yellow solid (54.0 mg, 67% yield), mp 140–142 °C, R_f= 0.37 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.75–8.73 (m, 1H), 7.79 (d, J=8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.45 (dd, J=9.0, 2.4 Hz, 1H), 7.42–7.38 (m, 1H), 7.20 (d, J=7.8 Hz, 1H), 7.16-7.07 (m, 3H), 6.81 (d, J=8.4 Hz, 2H), 6.67 (d, J=7.8 Hz, 2H), 5.30 (d, J=16.8 Hz, 1H), 4.55 (d, J=16.2 Hz, 1H), 2.18 (s, 3H);^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 161.4 (d, J=247 Hz), 143.1, 134.9 (d, J=10 Hz), 133.5, 132.7 (d, J=2 Hz), 131.9, 131.7, 129.9, 129.8, 128.6 (d, J=2 Hz), 128.5 (d, J=2 Hz), 128.3, 128.1, 127.7 (d, J=5 Hz), 127.60?, 127.57, 126.3, 123.1, 122.7, 116.8 (d, J=25 Hz), 110.5 (d, J=21 Hz), 51.1, 21.4; HRMS (ESI+) m/z calculated for $C_{24}H_{18}FNNaO_2S$ $[M+Na]+$ 426.0940, found 426.0942.

9-Bromo-5-tosyl-5,6-dihydrobenzo[c]phenanthri- dine (4′f): Yellow solid (51.9 mg, 56% yield), mp 140–142 °C, R_f=0.41 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.60 (d, J=9.0 Hz, 1H), 8.00 (d, J=1.5 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.71–7.64 (m, 2H), 7.20 (d, J=7.5 Hz, 1H), 7.16–7.06 (m, 3H), 6.80 (d, J=8.4 Hz, 2H), 6.66 (d, J= 8.1 Hz, 2H), 5.30 (d, J=16.8 Hz, 1H), 4.54 (d, J=16.8 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 143.0, 134.9, 133.3, 132.6, 132.1, 131.5, 130.0, 129.9, 129.5, 129.4, 128.8, 128.3, 128.2, 127.56, 127.55, 127.5, 126.3, 123.1, 122.6, 121.2, 51.0, 21.3; HRMS (ESI+) m/z calculated for $C_{24}H_{19}BrNO_2S$ $[M+H]^+$ 464.0320, found 464.0236.

Synthesis of Benzo[*c*]phenanthridine 19

To a solution of compound **4′** (0.13 mmol,1 equiv.)in dry DMSO (3 mL)was added finely ground KOH pellets (36.4 mg, 0.65 mmol, 5 equiv.) and the reaction was allowed to stir at room temperature for 1–2 h. After completion of the reaction (TLC), the reaction mixture was diluted with water (8 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The resulting crude product was purified by silica gel (100–200 mesh) column chromatography with 4–5%ethyl acetate-pet ether (v/v) as eluent to afford the pure products **19** in 51–79% yield.

Benzo[c]phenanthridine (19a): White solid (15.2 mg, 51% yield), mp 99–101 °C, R_f = 0.40 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.51 (s, 1H), 9.42 (d, J = 8.4 Hz, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.92 (t, J = 7.8 Hz, 1H), 7.80–7.75 (m, 2H), 7.71 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 152.1, 141.5, 133.3, 132.9, 132.1, 130.9, 128.8, 127.9, 127.7, 127.4, 127.2, 127.1, 126.9, 124.7, 122.3, 121.1, 119.9; HRMS (ESI+) m/z calculated for $C_{17}H_{12}N$ $[M+H]^+$ 230.0970, found 230.0969.

9-Chlorobenzo[c]phenanthridine (19b): White solid (21.5 mg, 63% yield), mp 102–104 °C,R_f = 0.76 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.44 (s, 1H), 9.38 (d, J = 8.4 Hz, 1H), 8.64 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 9 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.80–7.77 (m, 1H), 7.74–7.71 (m, 1H), 7.67 (dd, J = 1.8, 9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 151.3, 141.9, 137.3, 133.9, 133.5, 131.9, 130.2, 128.3, 128.0, 127.8, 127.7, 127.2, 125.1, 124.8, 121.9, 120.0, 119.6; HRMS (ESI+) m/z calculated for $C_{17}H_{10}ClNNa$ $[M+Na]^+$ 286.0399, found 286.0402.

[1,3]Dioxolo[4′,5′:4,5]benzo[1,2-c]phenanthridine (19c): White solid (20.6 mg, 58% yield), mp 176–178 °C, R_f = 0.41 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.42 (s, 1H), 8.75 (s, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.45 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.91–7.88 (m, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.30 (s, 1H), 6.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 151.7, 148.54, 148.52, 141.1, 132.9, 130.8, 130.2, 129.1, 128.7, 127.1, 126.9, 126.6, 122.1, 120.3, 118.4, 104.4, 102.3, 101.4; HRMS (ESI+) m/z calculated for $C_{18}H_{12}NO_2$ $[M+H]^+$ 274.0868, found 274.0857.

2-Fluorobenzo[c]phenanthridine (19d): White solid (25.4 mg, 79% yield), mp 142–143 °C, R_f = 0.55 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.45 (s, 1H), 9.41–9.38 (m, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.55 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.89 (td, J = 1.2, 7.5 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.59 (dd, J = 2.4, 9.6 Hz, 1H), 7.50 (td, J = 2.4, 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 161.9 (d, J = 246 Hz), 152.4, 141.4, 134.4 (d, J = 10.5 Hz), 132.8, 131.0, 128.82, 128.78, 127.6 (d, J = 9 Hz), 127.2, 127.0 (d, J = 4.5 Hz), 126.7, 122.1, 121.3, 120.5, 116.4 (d, J = 24 Hz), 111.3 (d, J = 21 Hz); HRMS (ESI+) m/z calculated for $C_{17}H_{11}FN$ $[M+H]^+$ 248.0876, found 263.0879.

Formal Synthesis of *Arnottin I*

To a well stirred solution of $PdCl_2(CH_3CN)_2$ (22.0 mg, 0.085 mmol, 0.05 equiv.) in dry acetonitrile (3 mL) were added PPh_3 (89.1 mg, 0.34 mmol, 0.2 equiv.) and Cs_2CO_3 (422 mg, 1.3 mmol, 4.5 equiv.) successively. After stirring the reaction mixture at room temperature for 5 min, (6-iodo-2,3-dimethoxyphenyl)methanol **20**[30] (500 mg, 1.70 mmol, 1 equiv.) was added and the reaction was stirred at room temperature for 20 min. Next, 5-ethynyl-6-(2-methoxyvinyl)-benzo[*d*][1,3]dioxole **21**[14b] (377.7 mg, 1.87 mmol, 1.1 equiv.) was added and stirring at 80 °C was continued for another 6 hours until the completion of the reaction (TLC). The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 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 crude was purified by silica-gel column chromatography (100-200 mesh)eluting with 35% petroleum ether-ethyl acetate (v/v) to produce the desired coupling product **22** in 68% yield.

***(2,3-Dimethoxy-6-((6-(2-methoxyvinyl)benzo [d][1,3]dioxol-5-yl)ethynyl)phenyl)methanol* (22)** (an inseparable mixture of *E*/*Z* isomers in the ratio 6:4): Brown gum (47.8 mg, 68% yield); R_f = 0.22 (50% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.62 (s), 7.26 (s), 7.24 (m), 7.00 (d, J = 12.8 Hz), 6.90–6.89 (m), 6.84–6.80 (m), 6.28 (d, J = 13.0 Hz), 6.17 (d, J = 6.8 Hz), 5.93–5.92 (m), 5.78 (d, J = 7.2 Hz), 4.92–4.90 (m), 3.88-3.87 (m), 3.76 (s), 3.71 (s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 153.1, 149.5, 148.5, 148.1, 147.9, 147.6, 145.6, 145.2, 135.9, 135.8, 133.5, 132.7, 128.6, 115.9, 114.2, 113.6, 112.1, 111.5, 111.2, 108.8, 103.8, 103.5, 103.2, 101.4, 91.3, 91.1, 90.0, 89.8, 61.5, 60.8, 59.3, 56.6, 55.9; HRMS (ESI+) m/z calculated for $C_{21}H_{21}O_6$ $[M+H]^+$ 369.1338 found 369.1340.

A mixture of $Pd(OAc)_2$bpy (3.8 mg, 0.01 mmol, 5 mol%), and D-CSA (125.3 mg, 0.54 mmol, 2 equiv.) in dry NMA (3 mL) was stirred at 90 °C for 5 min under argon atmosphere. Thereafter compound **22** (100 mg, 0.27 mmol, 1 equiv.) dissolved in NMA (1.5 mL) was added drop wise to the reaction mixture at the same temperature and the whole mixture was allowed to stir at 100 °C for few hours until the completion of the reaction (TLC). Next, the reaction mixture was neutralized by adjusting the pH (~7) through drop wise 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) column chromatography using 10–40% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product **23**.

1,2-Dimethoxy-13H-[1,3]dioxolo[4′,5′:4,5]benzo [1,2-h]benzo [c]chromene (23): Yellow solid (50.2 mg, 55% yield), mp 284–286 °C, R_f = 0.43 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.61 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.04 (s, 2H), 6.36 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 151.9, 148.8, 147.9, 147.5, 144.2, 131.1, 124.8, 124.3, 121.6, 120.5, 119.2, 117.6, 116.1, 111.7, 103.9, 101.2, 98.8, 63.6, 60.9, 55.8; HRMS

(ESI+) m/z calculated for $C_{20}H_{17}O_5$ $[M+H]^+$ 337.1076, found 337.1074.

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[22] In ^{1}H NMR, all products **2** display a singlet between 5.06-5.99 ppm for benzylic protons except compound **2 f** which displayed AB type double doublets (4.81 ppm, $J=$ 12 Hz and 5.19 ppm, $J=12$ Hz for the same protons. The appearance as singlet in majority of the cases is possibly due to accidental degeneracy.

[23] a) CCDC 1901865 (**2 j**); b) CCDC 1801964 (**2′a**); c) CCDC 1901866 (**2′g**); d) CCDC 1901867 (**4′e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Palladium(0)-catalysed regioselective cyclisations of 2-amino(tosyl) benzamides/sulphonamides: the stereoselective synthesis of 3-ylidene-[1,4]benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides†

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The Pd(0) catalysed cyclisation reactions between *tert*-butyl propargyl carbonates and 2-aminotosyl benzamides or sulphonamides deliver 1, 4-benzodiazepin-5-ones or sultam derivatives, key components of many biologically active compounds. But 2-amino benzamides/sulphonamides require propargyl carbonates substituted at acetylenic carbon to undergo the reaction resulting in the stereoselective formation of the said products.

The preparation of seven, eight, and larger membered heterocycles exhibiting wide and ever evolving biological properties is a challenging task.[1] Among the seven-membered heterocycles, 1,4-benzodiazepin-5-ones (**I**, Fig. S1 in the ESI†) are considered as privileged[2] structures in medicinal chemistry, contributing to the development of many drugs.[3] Besides, bicyclic 1, 4-benzodiazepin-5-ones are considered as potential precursors of their tricyclic fused analogs, many of which have been translated into potent drugs, *viz. anthramycin*,[4a] *flumazenil*[4b] and its ^{18}F-labelled derivative,[4c] and *fuligocandin B*[4d] (Fig. S1 in the ESI†). But there are a limited number of methods for the general synthesis of 1,4-benzodiazepin-5-ones, mostly employing either traditional reactions[5] or metal-catalysed heteroannulations[6] including palladium.[6c–e] Therefore the development of methodologies to provide easy access to this scaffold (*i.e.*, **I**) specially those involving the simultaneous formation of the C–C and C–N bonds in one pot and using simple substrates would be worthwhile.

Sultams (*i.e.*, cyclic sulphonamides) display activities against a wide variety of biological targets.[7] Benzo[*f*][1,2,5]thiadiazepine-1, 1-dioxides (**II**, Fig. S1 in the ESI†), a subclass of sultams, have emerged as important pharmacophores with potential biological activities.[8] For example, pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-5, 5-dioxides[8a] (PBTDs) are anti-cancer agents, while compound **X**[8b] (see Fig. S1 in the ESI†) has anti-HIV activity. However, reports[9] on the synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides (*i.e.*, **II**, Fig. S1 in the ESI†) are few, calling for straightforward and practical methods for their general synthesis.

In continuation of our work[10] on palladium-catalysed reactions, we envisioned that simple 2-amino benzamides or their sulphonamide analogs could be employed as bis-nucleophiles in reactions with propargylic carbonates for the formations of two C–N bonds (*i.e.*, 1,2 and 3,4) in one pot, thereby offering a facile and general synthetic route to 1,4-benzodiazepine-5-ones or their sulphur analogues. The concept appeared viable upon choosing the appropriate palladium catalyst and reaction conditions as depicted in Scheme 1.

At the outset, we performed an optimisation study for the model synthesis of 1,4-benzodiazepin-5-one **4a** as shown in Table 1. Initially, the exposure of the reactants to 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 in refluxing acetonitrile afforded **4a** after 18 h albeit in a low yield (Table 1, entry 1). When $PdCl_2(PPh_3)_2$ was used a comparable result was observed (entry 2, Table 1). We therefore switched to Pd(0) catalysts. But the use of $Pd_2(dba)_3$, $Pd_2(dba)_3CHCl_3$ or $Pd(PPh_3)_4$ afforded **4a** only in moderate (22–45%) yields (Table 1, entries 3–5). Pleasingly, the use of $Pd(dba)_2$ together with Xantphos as the ligand afforded **4a** within 4 h with a 92% yield (Table 1, entry 6). Thereafter, we continued with $Pd(dba)_2$ but used different ligands like *t*-butyl Xantphos/DPEphos/dppf/dppe (Table 1, entries 7–10); these reactions furnished **4a** in 18 h with moderate (15–40%) yields.

Even changing the solvent system (Table 1, entries 11–13) by including both high (*i.e.*, DCE, DMSO) and low polar (*i.e.*, toluene) ones did not succeed well except in the case of DCE that produced **4a** in 7 h with a 89% yield. Next, decreasing the catalyst loading from 10 mol% to 5 mol% produced **4a** in 93% yield though entailing a slightly longer reaction time (Table 1, entry 14 *vs.* entry 6). We therefore considered the conditions used in entry 14 of Table 1 as the preferred ones to explore the scope of this reaction (Table 2).

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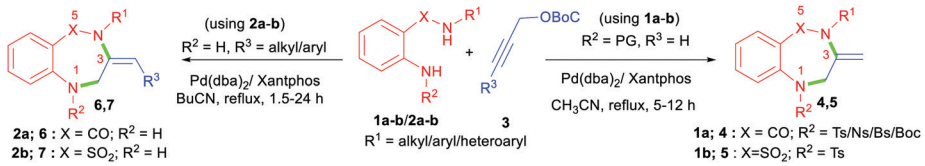
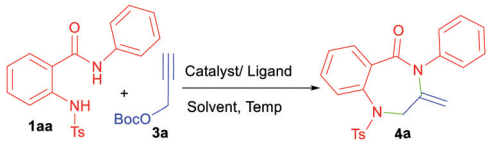
† Electronic supplementary information (ESI) available. CCDC 2062375–2062378. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc00793a



Scheme 1 Pd(0)-catalysed synthesis of 1,4-benzodiazepin-5-ones **4** and **6,** and benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **5** and **7**.

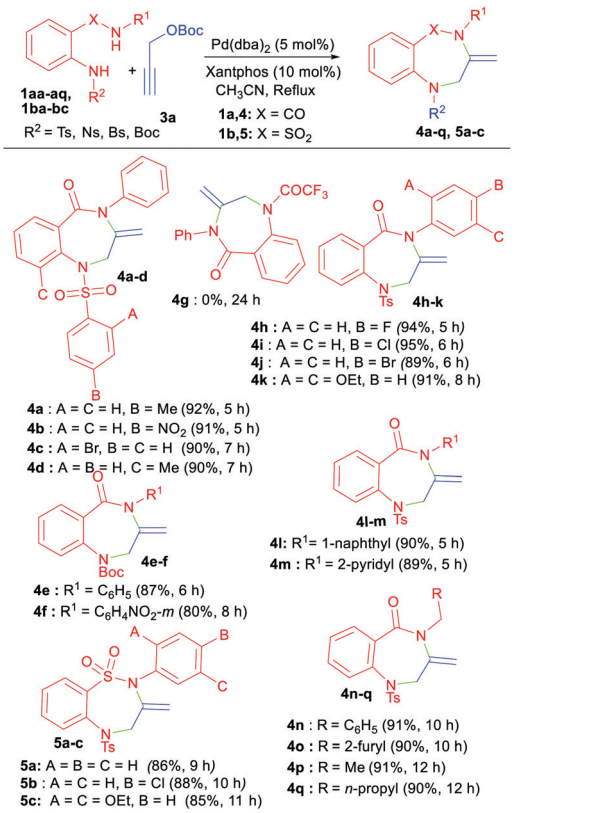
Table 1 Optimisation of the reaction conditions for the synthesis of **4a**[a]



Entry	Catalyst	Ligand	Solvent	Time (h)	Yields[b] (%)
1	$Pd(OAc)_2$	PPh_3	MeCN	18	17
2	$PdCl_2(PPh_3)_2$	Xantphos	MeCN	18	15
3	$Pd_2(dba)_3$	Xantphos	MeCN	18	40
4	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	MeCN	18	22
5	$Pd(PPh_3)_4$	Xantphos	MeCN	18	45
6	$Pd(dba)_2$	Xantphos	MeCN	4	92
7	$Pd(dba)_2$	^{t}BuXantphos	MeCN	18	30
8	$Pd(dba)_2$	DPEphos	MeCN	18	40
9	$Pd(dba)_2$	Dppf	MeCN	18	35
10	$Pd(dba)_2$	Dppe	MeCN	18	15
11	$Pd(dba)_2$	Xantphos	DCE	7	89
12	$Pd(dba)_2$	Xantphos	DMSO	18	–
13	$Pd(dba)_2$	Xantphos	Toluene	18	—
14[c]	$Pd(dba)_2$	Xantphos	MeCN	5	93

[a] Reaction conditions: **1aa** (1.0 equiv.), **3a** (1.3 equiv.), 10 mol% Pd loading, and 20 mol% ligand in 2.0 mL of solvent at 85 °C (entries 1–10 and 14) or at 100 °C (entries 11–13). [b] The yield of pure product. [c] 5 mol% $Pd(dba)_2$ and 10 mol% Xantphos were used.

Table 2 Pd(0)-catalysed synthesis of 3-methylene-[1,4]benzodiazepin-5-ones **4** and 3-methylene-[1,2,5]benzothiadiazepine-1,1-dioxide **5**[a]



[a] Reaction conditions: a mixture of **1** (1 equiv.), **3a** (1.3 equiv.), $Pd(dba)_2$ (5 mol%), and Xantphos (10 mol%) in CH_3CN (2 mL) was refluxed under argon.

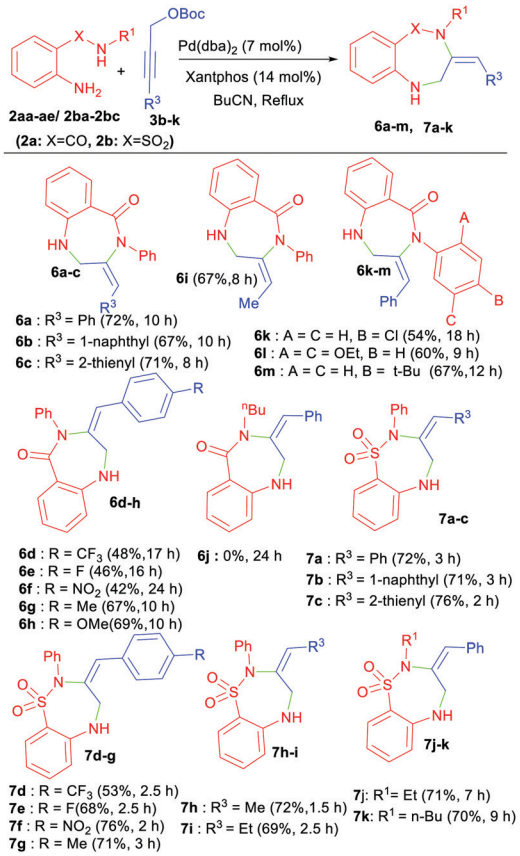
Initially, we found that the aromatic amino group of substrate **1a** could be protected with *N*-tosyl, substituted tosyl or Boc with little change in the outcome (see **4a–d** and **4e–f** in Table 2). But a trifluoroacetyl ($COCF_3$) group made the substrate inert as no formation of the product **4g** was noticed (TLC) and the starting materials were recovered (^{1}H NMR).

Regarding substituents on the aromatic rings, the incorporation of an electron-withdrawing group (EWG) like F/Cl/Br or an electron-donating group (EDG) like OEt hardly affected the outcome, delivering the products **4h–j** or **4k** within 5–8 h with 89–95% yields. Even the replacement of the phenyl ring in the amide moiety with either a bulky naphthyl or a heteroaryl one (pyridyl) worked smoothly furnishing **4l** (90%) or **4m** (89%) in 5 h. Furthermore, the replacement of amide phenyl (of **1aa**) with benzyl, furyl, methyl, or alkyl groups (Me/*n*-Pr) in substrates **1an–aq** also delivered the products **4n–q** in high yields (90–91%), although the reaction needed to be prolonged (10–12 h).

To further extend the scope for the synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **5**, the sulphonamide analogues of **4**, we prepared the requisite starting material **1ba** (X = SO_2, R^1 = Ph, R^2 = Ts) in few steps (see Scheme S6 in the ESI†) and exposed it to the optimised reaction conditions (entry 14 of Table 1). To our satisfaction, the desired product **5a** was formed in 9 h with 86% yield. The incorporation of additional substituent(s) (*p*-Cl or *o*,*m*-diethoxy) proved to be compatible, generating the product **5b** or **5c** with comparable yield, although somewhat longer reaction period (10–11 h) was necessary.

Turning our attention to the use of substituted propargyl carbonate **3** (R^3 = aryl/alkyl), we faced some difficulties as no reaction took place even after changing the reaction conditions; these observations are in agreement with the previous reports,[11] where either a low reactivity[11a,b] of such substrates or the formation of inseparable regio-isomeric mixtures of products was encountered.[11c] We therefore started investigating on the cyclisation reactions of propargyl carbonate **3b**

Table 3 Pd(0)-catalysed synthesis of (*E*)-3-aryl/alkyledene-[1,4]benzodiazepin-5-ones **6** and (*E*)-3-aryl/alkyledene-[1,2,5]benzothiadiazepine-1,1-dioxide **7**[a]



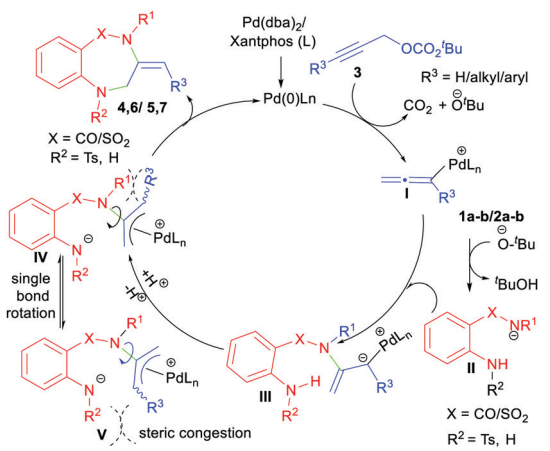
[a] Reaction conditions: a mixture of **2** (1 equiv.), **3** (1.5 equiv.), $Pd(dba)_2$ (7 mol%) and Xantphos (14 mol%) were refluxed in butyronitrile(2 mL) under argon.

(R^3 = Ph) with 2-aminotosyl benzamide **1aa** under different conditions. This revealed that the N-Ts group of **1aa** provided the main hindrance to the success of the transformation; indeed, in its absence [as in 2-amino-*N*-phenylbenzamide (**2aa**)], the reaction of **3b** under our previously optimised reaction conditions delivered the regio- and stereo-selective product **6a** in 70% yield, although a longer reaction time (12 h) was required. Further optimisation of the reaction conditions was thereafter carried out (see Table S1 in the ESI†). This showed that the highest yield (72%) of **6a** could be obtained (72%) upon carrying out the reaction (see entry 12 of Table S1, ESI†) for 10 h in refluxing butyronitrile in the presence of 7 mol% $Pd(dba)_2$ and 14 mol% Xantphos.

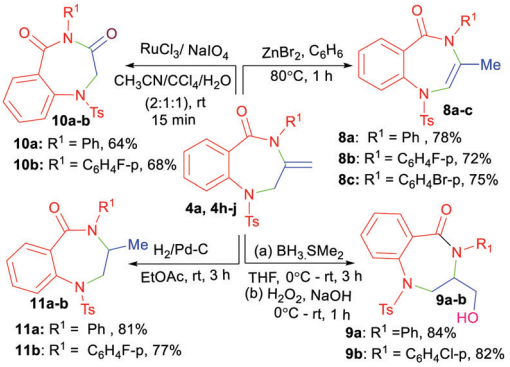
We then explored the substrate scope using the reactions of a range of substituted propargylic carbonates **3b–k** (Table 3). Thus, propargyl carbonates **3c** (R^3 = 1-naphthyl) and **3d** (R^3 = 2-thienyl) were found to be compatible by generating the products **6b** (67%) and **6c** (71%), respectively. While the use of an EWG (CF_3/F/NO_2) at the para position of the phenyl ring had a detrimental effect as the corresponding products **6d**/**6e**/**6f** were produced in moderate yields (42–48%) in 16–24 h, an EDG (Me/OMe) proved to be beneficial delivering **6g**/**6h** in 10 h with 67–69% yields. Even a substrate carrying an alkyl group (R^3 = Me) in the place of phenyl (of **3b**) was also found to be reactive towards this reaction (product **6i**, 67%), but the attachment of the alkyl group (R^1 = *n*-Bu) to the amide nitrogen made the substrate **2ab** inert preventing the formation of **6j**. Besides, the reactions of carbonate **3b** with different benzamide substrates (**2ac–ae**) having either an EWG (*viz.* Cl) or an EDG (*viz.* OEt/*t*-Bu) at the para position of the phenyl ring attached to the amide nitrogen were found to be successful, resulting in the formation of **6k** or **6l**/**6m** within 9–18 h with 54–67% yields.

The scope of this reaction was further extended by the synthesis of (*E*)-benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide **7a** that resulted from the reaction of sulphonamide **2ba** (R^1 = Ph) with **3b**. Next, the reactions of **2ba** with propargyl carbonates **3c** (R^3 = 1-naphthyl) and **3d** (R^3 = 2-thienyl) generated the products **7b** (71%) and **7c** (76%), respectively, with equal ease. Propargyl carbonate **3e**/**3f**/**3g** having an EWG (*i.e.*, CF_3/F/NO_2) or **3h** having an EDG (*i.e.*, Me) at the para position in the phenyl ring also underwent the reaction with **2ba** successfully to furnish the corresponding products **7d**/**7e**/**7f** or **7g** within 2–3 h with 53–76% yields. Propargyl carbonate **3j**/**3k** containing an alkyl group (*viz.*, Me/Et) instead of an aryl group also reacted to afford the products **7h** (72%) and **7i** (69%), respectively. Besides, the reactions of sulphonamide **2bb**/**2bc** having an alkyl group (R^1 = Et/*n*-Bu) with **3b** also proceeded well, delivering the product **7j**/**7k** in 7–9 h with 70–71% yields. But the incorporation of additional mono or di-substitution at the propargylic carbon of the substrate **3b** failed to deliver the products. The stereochemistry of the products was assigned to be trans (*E*-) based on the NOESY spectra and X-ray analysis (see the ESI†).

Mechanistically (Scheme 2), the decarboxylative oxidative addition of Pd(0) to propargyl *tert*-butyl carbonate **3** would generate the cationic palladium-allenyl species **I**[12] and a *tert*-butoxide anion which would preferentially abstract the proton from the amide (or sulphonamide) moiety[13] of the substrates (**1a–b**/**2a–b**) to form the anionic species **II**. The nucleophilic



Scheme 2 A plausible reaction mechanism for the formations of products **4**, **6**/**5**, and **7**.



Scheme 3 Transformations of 1,4-benzodiazepin-5-ones **4a** and **4h–j**.

addition of **II** onto the central carbon of Pd–allene **I** may result in the chemoselective generation of the Pd–carbenoid intermediate **III**.[14] Next, the intermolecular proton migration from the NHTs (or NH_2) group of intermediate **III** would generate the Pd–π–allyl species **IV**[15] (or **V**), which could undergo cyclisation followed by reductive elimination leading to the formation of products (**4**, **6**/**5**, and **7**) and regeneration of Pd(0). Although the precise reason behind the stereoselective formation of products (*i.e.*, **6**–**7**) is not very clear, the steric factor in intermediate **IV** (or **V**) might play an important role in determining the outcome. We also carried out a control experiment (see Scheme S1 in ESI†).

To explore the utility, the functional groups present in the products were used as synthetic handles for further transformations (Scheme 3). Thus the treatment of 3-methylene-1,4-benzodiazepin-5-ones **4a** (R^1 = Ph), **4h** (R^1 = C_6H_4F-*p*), and **4j** (R^1 = C_6H_4Br-*p*) with $ZnBr_2$ in refluxing benzene caused the isomerisation of the exocyclic double bond, providing an easy access to the products **8a**, **8b**, and **8c**, respectively, When the products **4a** and **4i** (R^1 = C_6H_4Cl-*p*) were exposed to BH_3. DMS followed by the hydrogen peroxide treatment, hydration of the exocyclic double bond took place resulting in the generation of alcohols **9a** and **9b**, respectively. Furthermore, the treatment of **4a** and **4h** with $RuCl_3$ (5 mol%) and $NaIO_4$ (6 equiv.) resulted in the oxidative cleavage of the exocyclic C=C bond affording **10a** and **10b**, respectively, within 15 min, while the Pd/C-catalysed hydrogenation of **4a** and **4h** successfully afforded **11a** and **11b**, respectively.

In conclusion, we present herein a facile method for the general synthesis of 3-methylene-1,4-benzodiazepin-5-ones/[1,2,5]benzothiadiazepine-1,1-dioxides **4**/**5** *via* palladium(0)-catalysed chemoselective cyclisation reactions of simple substrates like N-protected 2-amino benzamides/sulphonamides **1a**/**1b** and propargyl carbonate **3a**. N-Unprotected substrates **2a**/**2b** reacted only with propargyl carbonates **3b–k** carrying substitution at acetylenic carbon to yield (*E*)-3-aryl/alkyledene-1,4-benzodiazepin-5-ones/[1,2,5]benzothiadiazepine-1,1-dioxides **6**/**7**. A plausible reaction mechanism has been proposed and the synthetic transformation of some products into important heterocycles has also been demonstrated.

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Conflicts of interest

There are no conflicts to declare.

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Palladium(0)-Catalyzed Heteroannulations of Allenamides: General Synthesis of δ-Carbolines and Benzofuro[3,2-*b*]pyridines

Debasmita Mondal, Subhendu Pramanik, and Chinmay Chowdhury*

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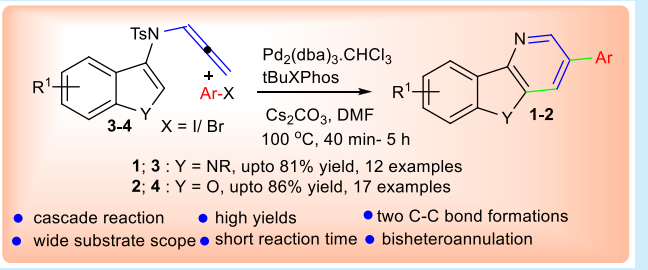
ABSTRACT: Palladium(0)-catalyzed reactions between allenamides **3** or **4** and aryl iodides/bromides **5**/**6** provide an easy access to δ-carbolines **1** or benzofuro[3,2-*b*]pyridines **2**. The reaction constitutes a fast intermolecular assembly that takes place in one pot, and the choice of the phosphine ligand is critical for success. A plausible reaction mechanism is proposed. The reaction is amenable to the synthesis of bis-heteroannulated products.



Carbolines and tetrahydrocarbolines constitute the key structural motif in compounds of biological[1a] and optoeletronical interests.[1b] Among them, δ-carbolines (**1**, Figure S1 in Supporting Information) have received increasing interest because of their prevalence in various bioactive natural products[2] and pharmacologically active compounds,[3] including drugs, and their significant applications in material sciences.[4] For example, *Jusbetonin*[5a] (**I**, Figure S1), isolated from *Justicia betonica*, exhibits antiplasmodial, anti-inflammatory, and antitumor activity, and *SYUIQ-5*[5b] (**II**, Figure S1) is a promising cancer therapeutic.

In addition to carbolines, other pyridine fused polyheterocycles are also of interest.[6] In particular, benzofuro[3,2-*b*]pyridines (BFPs **2**, Figure S1) serve as the core structure in natural products and bioactive compounds.[7] For example, *sinensine D*[8] (**III**, Figure S1) is found in fruiting bodies of *Ganoderma sinense*, a plant credited with beneficial effects in chronic hepatitis and nephritis, while compounds **IV**[9] (Figure S1) are reported as potent topoisomerase inhibitors.

Consequently, the synthesis of δ-carbolines has attracted considerable attention leading to the development of methods utilizing classical[10] and metal-catalyzed[11] reactions. More specifically, in metal-catalyzed reactions, δ-carbolines are usually prepared through fusion either of a new pyrrole ring[11a,b] generated from diaryl substrates, or of a pyridine ring[11c,d] preformed or generated in situ from indole substrates. Though applications of the latter strategy have been restricted in number, it appears to be more attractive as functionalization of the pyridine ring is easier, obviating the need for using a prefunctionalized substrate. For instance, a Ni(II)-phosphine complex catalyzed [2 + 2 + 2] cycloaddition of ynamide-nitriles with alkynes has been reported[11c] (Scheme 1a); recently, the metal-free version of the same strategy has been adopted in reactions using catalytic amount of TMSOTf.[12] Thus, rapid construction of δ-carbolines from simple substrates using a novel strategic approach is highly desirable.

On the other hand, synthesis of benzofuro[3,2-*b*]pyridines **2** (Figure S1) usually follows two approaches comprising constructions of (a) a fused furan ring[13] or (b) a fused pyridine[14] ring employing appropriate benzofuran substrates. Only the former approach is known[13a] to provide a general synthesis of **2**, though there are also few specific examples.[13b] In contrast, the latter approach provides some general methods[6,14] (Scheme 1b), relying on substrates prepared in multiple steps. Therefore, development of a straightforward method using readily available substrates would be worthwhile.

In recent times, allenamides have emerged as potential building blocks in organic synthesis.[15] In continuation of our works,[16] we envisioned that a direct construction of pyridine ring fused to indole or benzofuran could be achieved via palladium-catalyzed reactions between allenamides **3** or **4** and aryl halides **5**/**6** through intermediates **7**, which upon base induced elimination (-TsH) would form δ-carbolines **1** or benzofuro[3,2-*b*]pyridines **2** (Scheme 1c). Our concept indeed proved to be viable upon choosing the appropriate conditions.

To realize the synthesis of δ-carbolines **1a**, we carried out an optimization study using a model reaction between allenamide **3a** synthesized in few steps (see Supporting Information) and phenyl iodide **5a** (Table 1). Our initial efforts to carry out the reaction employing 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and 2.0 equiv of K_2CO_3[16b] in DMF at 100 °C for 10 h proved

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Scheme 1. Previous Reports and Our Present Work

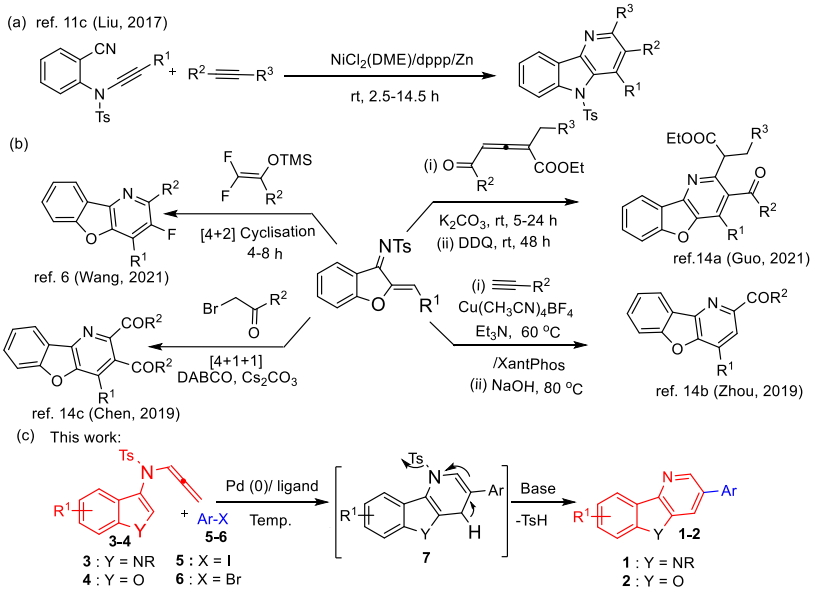
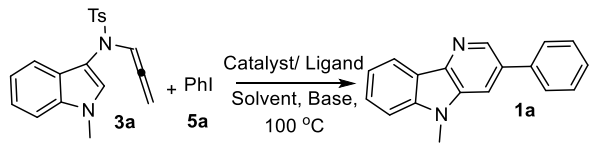


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand[b]	solvent	time (h)	yields (%)
1[c]	$Pd(OAc)_2$	PPh_3	DMF	10	–
2[d]	$Pd_2(dba)_3$	^{t}BuXantPhos	DMF	8	30
3	$Pd_2(dba)_3$	^{t}BuXPhos	DMF	6	44
4	$Pd(dba)_2$	^{t}BuXPhos	DMF	3	45
5	$Pd_2(dba)_3$	^{t}BuXPhos	DMF	2.5	72
6	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	DMF	0.5	81
7[e]	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	DMF	7	67
8[f]	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	DMF	11	55
9	$Pd_2(dba)_3{\cdot}CHCl_3$	XPhos	DMF	1	54
10	$Pd_2(dba)_3{\cdot}CHCl_3$	RuPhos	DMF	2.5	35
11	$Pd_2(dba)_3{\cdot}CHCl_3$	CyJohnPhos	DMF	1.5	45
12	$Pd_2(dba)_3{\cdot}CHCl_3$	$P(Cy)_3$	DMF	8	42
13	$Pd_2(dba)_3{\cdot}CHCl_3$	SPhos	DMF	2	trace
14	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	DMSO	2.5	32
15	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	DCE	2.5	trace
16	$Pd_2(dba)_3{\cdot}CHCl_3$	^{t}BuXPhos	THF	2.5	n.r.

[a]Reaction conditions: A mixture of **3a** (1.0 mmol), **5a** (1.2 mmol), palladium catalyst (5 mol %), ligand (10 mol %), and Cs_2CO_3 (4 mmol, except entries 1−2) was heated at 100 °C in 2.0 mL solvent. [b]For structures of ligands used, see Figure S2 (Supporting Information). [c]K_2CO_3 used as base. [d]Ag_2CO_3 used as base. [e]Heated at 80 °C. [f]3 mol % of palladium catalyst and 5 mol % of ligand used.

unsuccessful (Table 1, entry 1). Nevertheless, **1a** was found to be formed in moderate yield (30%) by using[16a] $Pd_2(dba)_3$, *t*-Bu-Xantphos, and Ag_2CO_3 as catalyst, ligand, and base, respectively (Table 1, entry 2). Interestingly, replacing the bidented ligand by a monodented one (i.e., ^{t}BuXPhos) and the base (Ag_2CO_3) by Cs_2CO_3 improved the yield and reduced the reaction time as well (Table 1, entry 3). Though use of $Pd(dba)_2$ failed to improve the outcome (Table 1, entry 4), $Pd_2(dba)_3$ furnished **1a** within 2.5 h with 72% yield (Table 1, entry 5). But $Pd_2(dba)_3{\cdot}CHCl_3$ proved to be still more efficacious, delivering **1a** within 30 min with 81% yield (Table 1, entry 6). Notably, lowering of either the reaction temperature (80 °C) or catalyst loading diminished the yields of **1a** (Table 1, entries 7, 8). Thereafter, we screened a few more ligands, but only moderate yields (35−54%) of **1a** were observed (Table 1, entries 9−12), while use of SPhos afforded only a trace amount of the product (Table 1, entry 13). We therefore persisted with ^{t}BuXPhos for further study (Table 1, entries 14−16) utilizing different solvent systems comprising both low (THF) and high (DMSO, DCE) polar ones. This showed THF and DCE to be inefficacious, while DMSO furnished **1a** in only 32% yield. Thus, the reaction conditions of entry 6 of Table 1 proved to be optimal to explore the scope of this reaction (Scheme 2) as discussed below.

Regarding N-protecting groups, use of Bu/allyl/Bn instead of Me in the indole ring of substrates **3b−d** necessitated somewhat longer reaction times (50 min to 1.2 h), and yields (42−69%) of the products **1b−d** were somewhat reduced (Scheme 2). To test the effect of an electron-withdrawing or electron-donating group (EWG or EDG) at C5 of the indole moiety, phenyl iodide (**5a**) was allowed to react with allenamides **3e** (R^1 = Cl) or **3f** (R^1 = Me); the desired carboline **1e** (25%) or **1f** (77%) was formed within 1.5 h. The electron withdrawing effect of the chloro group may account for the lower yield of **1e**. Furthermore, the bulky naphthyl iodide (**5b**) participated in the reaction with equal ease, affording the carboline **1g**.

Next, we carried out the reaction of allenamide **3a** with a range of aryl iodides/bromides **5c−i**/**6a,b** bearing EDG or EWG (Scheme 2). Iodides **5c−f** possessing moderately EWG such as F/Cl/Br/CF_3 facilitated the reaction by smoothly delivering the carbolines **1h−k**. Surprisingly, 1-iodo-4-nitrobenzene (**5g**) proved to be incompatible for the reaction, as it delivered only minor amounts (TLC) of few uncharacterized products in place of the desired product **1l**. In contrast, iodide **5h** having a strongly EDG (OMe) at the para position promoted the reaction to furnish carboline **1m** within 1.5 h with good yield. However, iodide **5i** having a moderately EDG

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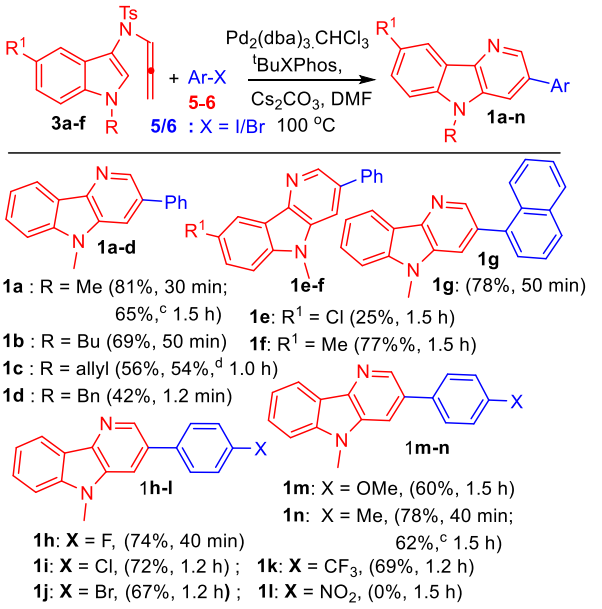
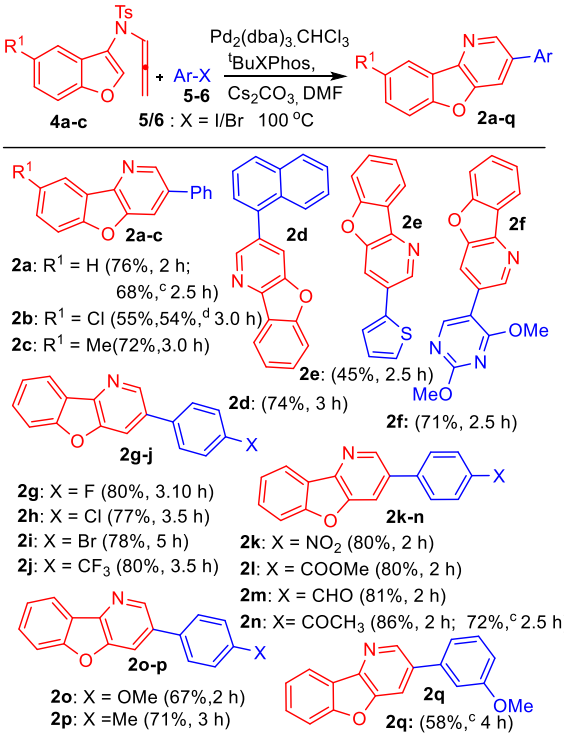
Scheme 2. Pd(0)-Catalyzed Synthesis of δ-Carbolines 1[a,b]



[a]Reaction conditions: A mixture of **3** (1 equiv), **5** or **6** (1.2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), and ^{t}BuXPhos (10 mol %) in DMF (2 mL) was refluxed. [b]Isolated yield. [c]Aryl bromide (**6**) was used. [d]1.0 mmol scale reaction (see p S15 in the SI).

Scheme 3. Pd(0)-Catalyzed Synthesis of Benzofuro[3,2-*b*]-pyridines 2[a,b]



[a]Reaction conditions: A mixture of **4** (1 equiv), **5** (1.2 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), and ^{t}BuXPhos (10 mol %) in DMF (2 mL) was refluxed under argon. [b]Isolated yield. [c]Aryl bromide (**6**) was used. [d]1.0 mmol scale reaction (see p S22 in the SI).

(Me) proved more reactive, forming carboline **1n** within 40 min with 78% yield.

Aryl bromides **6** also turned out to be reactive, though forming the products in somewhat lower yields. For instance, phenyl bromide (**6a**) delivered δ-carboline **1a** with 65% yield, while *p*-bromo toluene (**6b**) similarly afforded **1n** (62%).

Next we attempted to extend the scope of this reaction for the general synthesis of benzofuro[3,2-*b*]pyridines **2** (Scheme 3). Toward this objective, requisite benzofuran substrates **4a–c** were prepared in few steps (see Supporting Information) and utilized in subsequent reactions with various aryl iodides/bromides **5**/**6** (Scheme 3) under the optimized reaction conditions (Table 1, entry 6). Initially, allenamide **4a** (R^1 = H) was allowed to react with phenyl iodide **5a**; gratifyingly, the desired product **2a** was formed within 2 h with 76% yield. We therefore applied these conditions in subsequent reactions as shown in Scheme 3. Thus, the reactions of phenyl iodide **5a** with substrates **4b** (R^1 = Cl) and **4c** (R^1 = Me) resulted in the formation of benzofuro[3,2-*b*]pyridines **2b** and **2c** within 3 h, with 55–72% yields. Allenamide **4a** underwent reactions with naphthyl iodide **5b** and 2-iodo-thiophene **5j** too; the corresponding products **2d** (74%) and **2e** (45%) were formed within 2.5–3 h. Even 5-iodo-2,4-dimethoxy pyrimidine (**5k**) afforded the product **2f** within 2.5 h with very good yield (71%).

We then explored the reactivity of allenamide **4a** with different aryl iodides (**5c–g**, **5l–n**, **5h-i**). Substrates **5c–f** possessing a moderately EWG (viz., F, Cl, Br, CF_3) participated in the reaction with equal ease, leading to the formation of δ-carbolines **2g–j**. In contrast to **1l** (Scheme 2), iodides (**5g**, **5l–n**) having a strongly EWG (viz., NO_2, CHO, CO_2Me, COMe) formed benzofuro[3,2-*b*]pyridines **2k–n** within 2 h due to their reactive nature. When a strong or moderate EDG is present, as in iodides **5h** or **5i**, it delivered the product **2o** or **2p** in 2–3 h, though the yields were lower (67–71%).

In tune with the previous observations (of Scheme 2), aryl bromides successfully participated in this reaction though with slightly lower yields compared to aryl iodides. For instance, phenyl bromide (**6a**), 4-bromoacetophenone (**6c**), and 3-bromoanisole (**6d**) reacted with allenamide **4a** forming **2a** (68%), **2n** (72%), and **2q** (58%), respectively, within 2.5–4 h.

Mechanistically (Scheme 4), the oxidative addition of Pd(0) with aryl halides (ArX) generates $ArPd(II)X$[17] (**A**). This undergoes addition onto the allenic double bond of substrate **3** or **4** resulting in the formation of palladium(II)-Π-allyl complex **B**.[18] Intermediate **B** then undergoes (path a) intramolecular nucleophilic attack by C3 of the indole or furan moiety leading to the formation of intermediate **C**. Next, a reductive elimination of palladium(II) from species **C** would furnish a transient spiro-intermediate **D** and Pd(0). Nevertheless, a preferential allylic group migration[16a] of intermediate **D** to its C2 position would produce a carbonium intermediate **E**, which upon deprotonation would easily generate a dihydropyridine intermediate **F**. Finally, a base promoted elimination (-TsH) from **F** would deliver the products **1** (or **2**).

Alternatively (path b), an intramolecular nucleophilic attack of C2 of the indole (or furan ring) of **B** onto the palladium might result in the formation of a seven-membered palladium-(II) intermediate **C′**, the reductive elimination of which would furnish intermediate **D′** with concurrent formation of Pd(0). Next, a base assisted deprotonation of **D′** would produce

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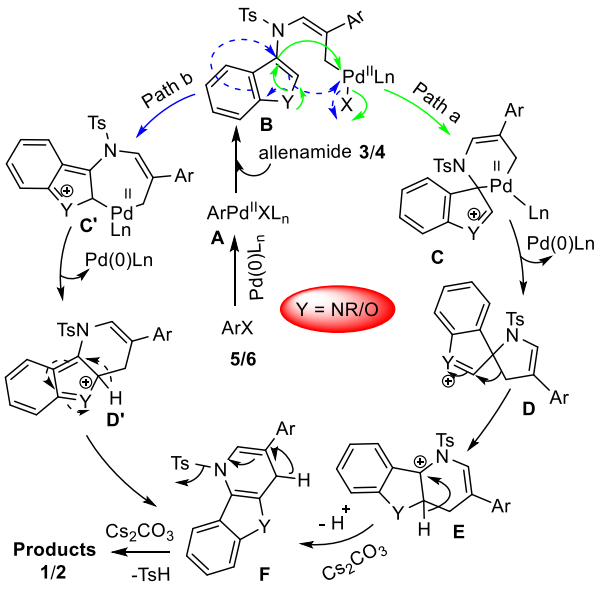
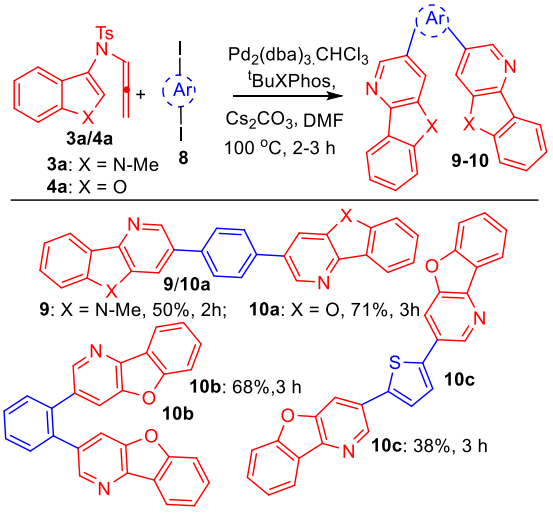
Scheme 4. Plausible Reaction Mechanism



dihydropyridine intermediate **F**, which would trigger the formation of product **1** (or **2**).

In view of the importance of bis-δ-carbolines present in bioactive alkaloids,[2] we also checked the prospect of bis-heteroannulations (Scheme 5). Thus, bis-δ-carboline **9** could

Scheme 5. Synthesis of Bis-heteroannulated Products 9–10[a,b]



[a]Reaction conditions: A mixture of **3a** or **4a** (1 equiv), **8** (0.6 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), and ^{t}BuXPhos (10 mol %) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.

easily be accessed by reacting allenamide **3a** and 1,4-diiodobenzene **8a** under the optimized reaction conditions, while bis-benzofuro[3,2-*b*]pyridines **10a–c** were isolated (38–71% yield) after reaction of **4a** with **8a**, 1,2-diiodobenzene (**8b**), and 1,2-diiodothiophene (**8c**), respectively.

In conclusion, we have successfully developed a method for the general synthesis of δ-carbolines **1** via palladium(0)-catalyzed reactions between allenamides **3** and aryl iodides or bromides **5/6** for 0.5–1.5 h. Benzofuran substrate **4** was also compatible with this reaction, triggering the formation of benzofuro[3,2-*b*]pyridines **2** within 2–5 h. A plausible reaction mechanism is proposed. The method is amenable to the synthesis of bis-heteroannulated products **9/10**, suggesting the viability of polyheteroannulation in one pot.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03625.

Experimental procedures, spectral data, and spectra of new compounds (PDF)

Accession Codes

CCDC 2195469–2195471 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Contents

Summary

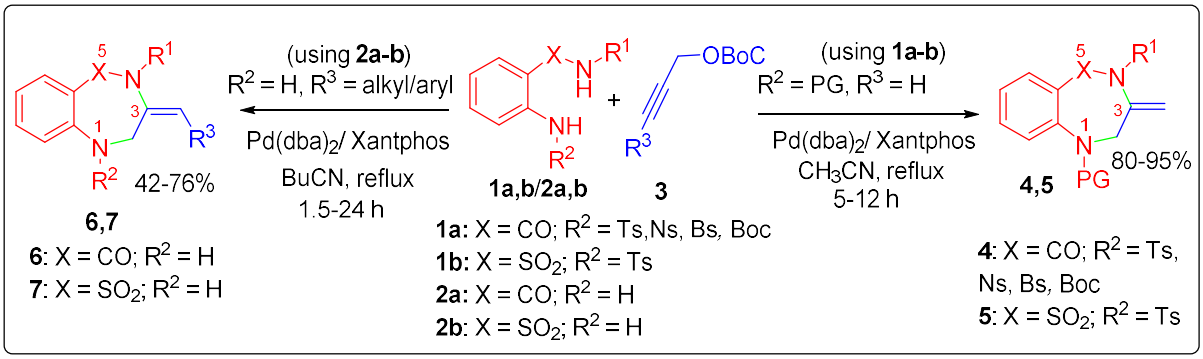
Palladium Catalyzed Heteroannulations for Easy Accessing the Compounds of Biological Importance

The thesis entitled ‘’Palladium Catalyzed Heteroannulations for Easy Accessing the Compounds of Biological Importance’’ is divided into three 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(0)-catalysed regioselective cyclisations of 2-amino(tosyl) benzamides/sulphonamides: the stereoselective synthesis of 3-ylidene-[1,4]benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides

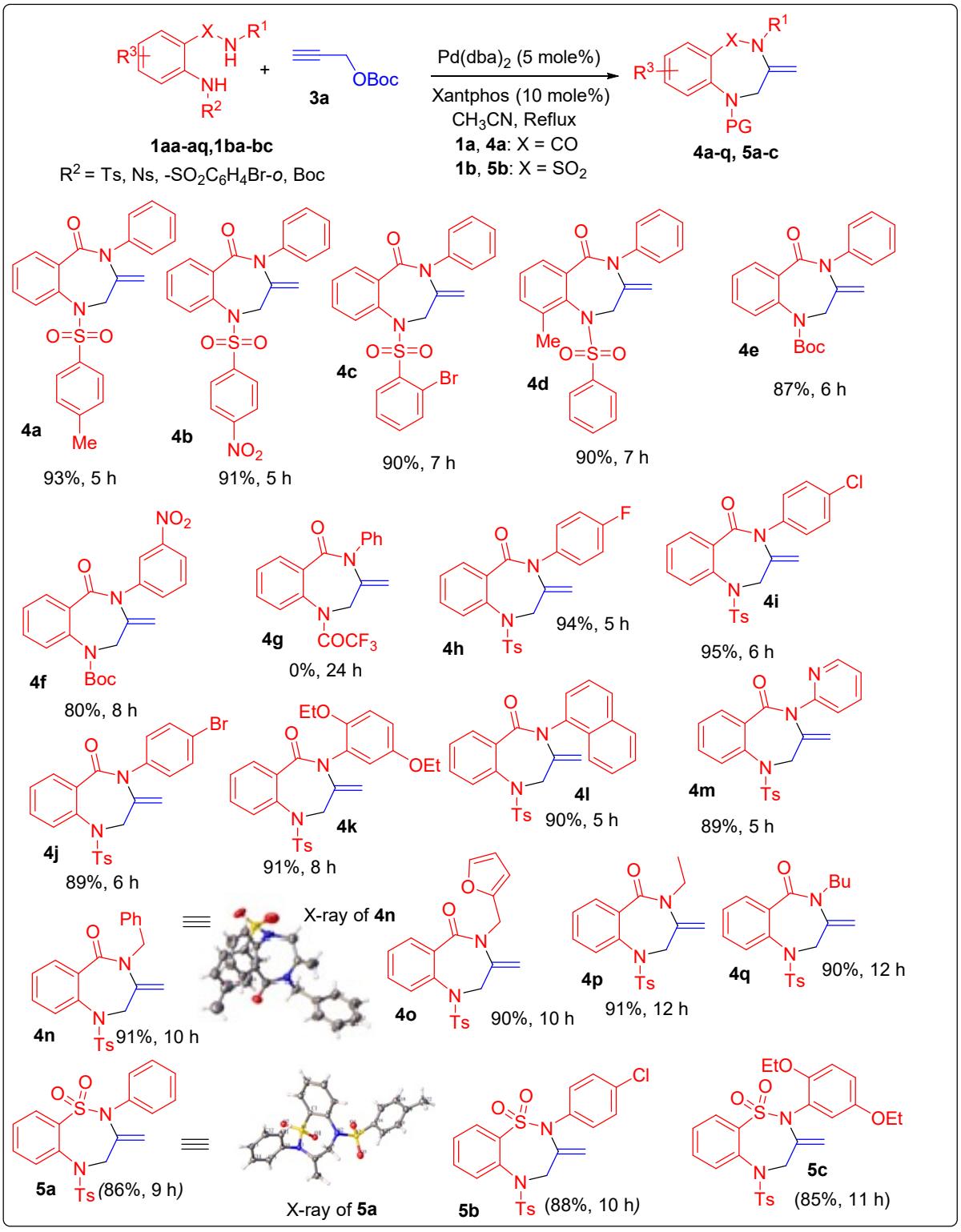
The first chapter deals with Pd(0) catalyzed cyclocondensation reactions between tert-butyl propargyl carbonates **3a** (R^3 = H) and 2-aminotosyl benzamides/sulphonamides (**1a**,**b**) resulting in the formations of 1,4-benzodiazepin-5-ones/[1,2,5]benzothiadiazepine-1,1-dioxides **4**/**5** in 80-95% yields. On the other hand, tert-butyl propargyl carbonates **3b-k** carrying substitution (R^3 = aryl/alkyl) at the acetylenic carbon reacted only with *N*-unprotected 2-amino benzamide/sulphonamides (**2a-b,** R^2 = H) that paved the way for a stereoselective synthesis of (*E*)-3-aryl/alkylidene derivatives of 1,4-benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **6**/**7** with 42-76% yields **(Scheme 1)**.



Scheme 1: Pd(0)-catalyzed synthesis of 1,4-benzodiazepin-5-ones **4**,**6** and benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **5**,**7**

Towards this objective, a series of reaction was carried out with variation of reaction parameter such as palladium catalyst, ligand, solvent, temperature for the model reaction between benzamide **1aa** and propargyl carbonate **3a.** The optimized reaction conditions werefind out where a mixture of **1aa** (1.0 equiv) and **3a** (1.3 equiv) in acetonitrile (2 ml) was heated under refluxing conditions in presence of 5 mol% $Pd(dba)_2$, 10 mol% Xantphos, generating the formation of product **4a** with 93% yield within 5 h. By using optimized reaction conditions, various bis-nucleophilic benzamides**1aa**-**1aq** containing different

Scheme 2: Pd(0)-catalyzed synthesis of 3-methylene-[1,4]benzodiazepin-5-ones **4** and 3-methylene-[1,2,5]benzothiadiazepine-1,1-dioxide **5**[a]



[a]Reaction conditions: A mixture of substrate **1a**/**1b** (1 equiv), **3a** (1.3 equiv), $Pd(dba)_2$ (5 mol%), Xantphos (10 mol%), and CH_3CN (2 ml) were refluxed under argon atmosphere.

functional groups were evaluated to determine the capability of cyclocondensation with **3a** to establish the generality of the method. The results are summarized in **Scheme 2**.

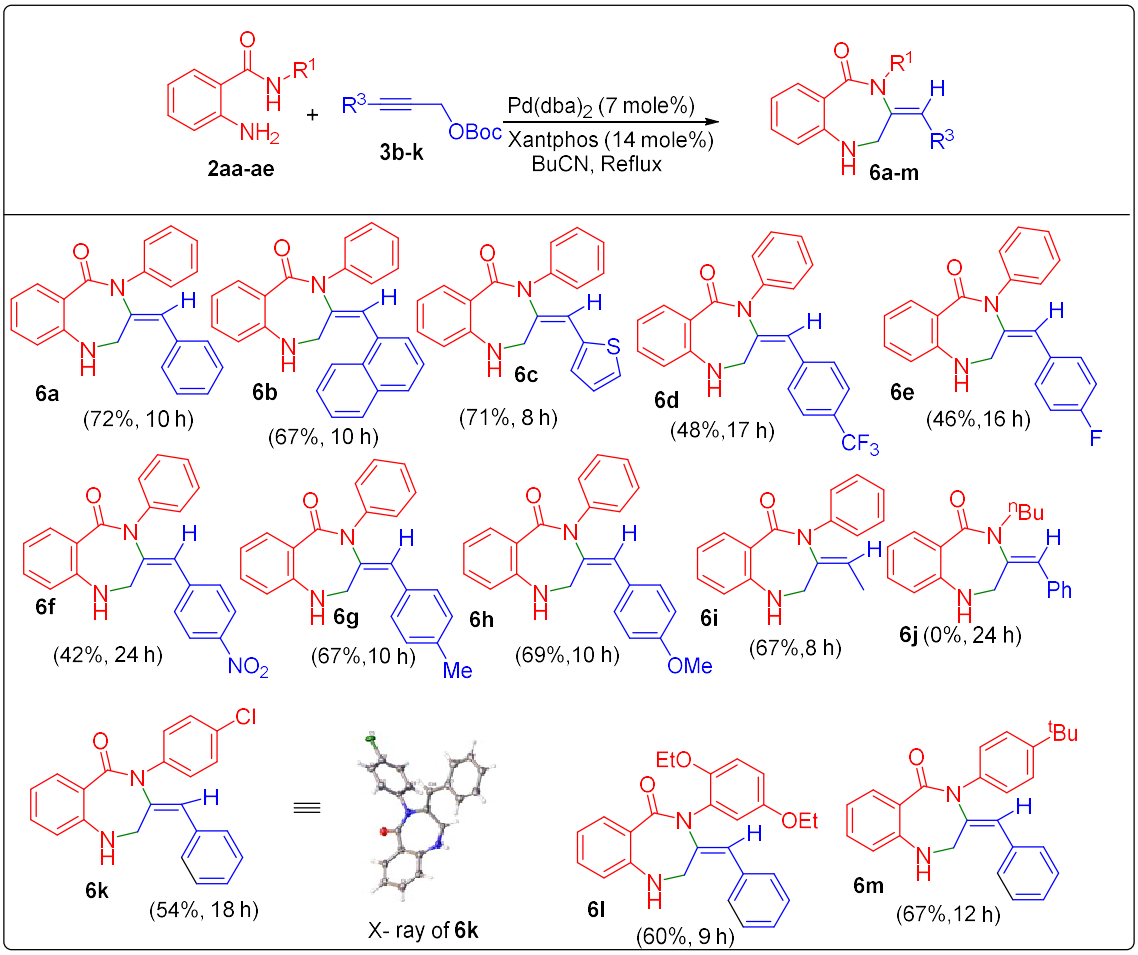
Having optimized reaction conditions, we then set out to explore the scope and limitations of the synthesis (**Scheme 2**). To achieve this goal, we first protected the aromatic amino group with Ts or Bs or Ns or Boc groups, and in all cases, the desired products **4a-f** were obtained within 5-8 h with excellent yields (80-92%). But a trifluoroacetyl ($COCF_3$) group made the substrate inert as no formation of the product **4g** was noticed (TLC) and the starting materials were recovered (^{1}H NMR). Regarding substituents on the aromatic rings, incorporation of an electron-withdrawing group (EWG) like F/Cl/Br or an electron-donating group (EDG) like OEt facilitated the reaction delivering the products **4h**–**j** or **4k** with 89–95% yields within 5-8 h. Even replacement of the phenyl ring in the amide moiety with either the bulky naphthyl or a heteroaryl one (i.e., pyridyl) worked smoothly and delivering the products **4l-m** within 5 h. Furthermore, the replacement of amide phenyl (of **1aa**) with benzyl, furyl, methyl, or an alkyl group (Me/n-Pr) in substrates **1an–aq** also delivered the products **4n–q** in high yields (90–91%), although the reaction needed to be prolonged (10–12 h).

Next, we targeted to extend the scope of this reaction by synthesizing benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **5**, the sulphonamide analogues of **4**. Accordingly, we prepared the requisite starting material **1ba** (X = SO_2, R^1 = Ph, R^2 = Ts) in few steps and exposed it to the optimized reaction conditions as depicted in **Scheme 2**. Gratifyingly, the desired product **5a** was formed in 9 h with 86% yield. Incorporation of additional substituent(s) (*p*-Cl or *o*,*m*-diethoxy) proved to be compatible, generating the product **5b** or **5c** with 85-88% yield within 10-11 h (**Scheme 2**).

Next, turning our attention to substituted propargyl carbonates **3** (R^3 = aryl/alkyl), we faced some difficulties as the substrate did not respond to this reaction even after several attempts with variation of the reaction conditions.; these observations were also corroborated by the previous reports where either limited reactivity of such substrates or formation of inseparable regio-isomeric mixtures of products were encountered. We therefore started investigation on the cyclocondensation reactions using propargyl carbonate **3b** (R^3 = Ph) as model substrate. This revealed that the N-Ts group provided the main hindrance to the success of the transformation, removal of which (as in 2-amino-*N*-phenylbenzamide, **2aa**) prior to reaction with **3b** under the optimized reaction conditions of **Scheme 2** proved to be

successful in delivering the regio- and stereo-selective formation of product **6a** in 70% yield though a longer reaction time (12 h) was required. Then, further optimization of the reaction conditions revealed that heating a mixture of **2aa** with **3b** in high boiling butyronitrile (BuCN) in presence of 7 mol% $Pd(dba)_2$ and 14 mol % Xantphos delivered the desired product **6a** within 8 h with 72% yield. Next, various bis-nucleophilic benzamide substrates **2aa-ae** and substituted propargylic substrates **3b-k** were exposed under the same optimized reaction conditions. To our pleasure, most of the substrates smoothly delivered the chemo- and stereo-selective products **6a-m** with 42-71% yields within 8-24 h as shown in **Scheme 3**. First, the substitution effects of the aryl rings (R^3 = Ar) attached to the terminal acetylenic carbon of substrates **3c-k** were examined. Thus, propargyl carbonates **3c** (R^3 = 1-naphthyl) and **3d** (R^3 = 2-thienyl) were found to be compatible by generating the products **6b** (67%)

Scheme 3:Pd(0)-catalyzed synthesis of substituted (*E*)-3-aryl/alkyledene-[1,4]benzodiazepin-5-ones **6**

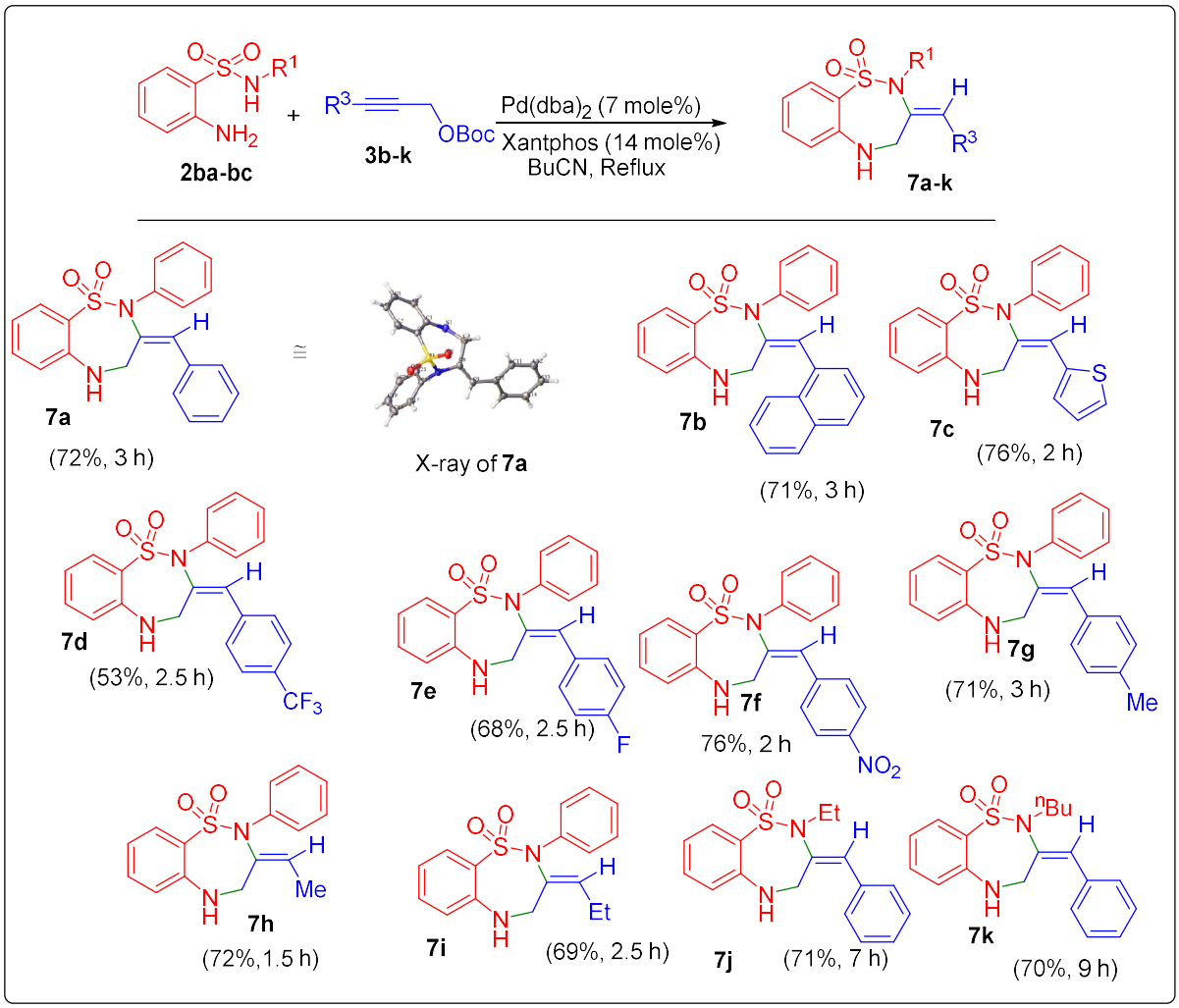


[a]Reaction conditions: A mixture of substrate **2a** (1 equiv), **3** (1.5 equiv), $Pd(dba)_2$ (7 mol%) and Xantphos (14 mol%) were refluxed in butyronitrile (2 mL) under argon.

and **6c** (71%), respectively. While the use of an EWG (CF_3/F/NO_2) at the para position of the phenyl ring had a detrimental effect as the corresponding products **6d**/**6e**/**6f** were produced inmoderate yields (42–48%) in 16–24 h. But an EDG (Me/OMe) proved to be beneficial delivering **6g**/**6h** in 10 h with 67–69% yields. Even a substrate carrying an alkyl group (R^3 = Me) in the place of phenyl (of **3b**) was also found to be reactive towards this reaction (product **6i**, 67%), but the attachment of the alkyl group (R^1 = n-Bu) to the amide nitrogen made the substrate **2ab** inert preventing the formation of **6j**. Besides, the reactions of carbonate **3b** with different benzamide substrates (**2ac–ae,** R^1 = Ar) having either an EWG (viz. Cl) or an EDG (viz. OEt/t-Bu) at the para position of the phenyl ring attached to the amide nitrogen were found to be successful, resulting in the formation of **6k** or **6l**/**6m** within 9–18 h with 54–67% yields.

With a view to expand the scope of this reaction (**Scheme 4**) further, we targeted to achieve the synthesis of (*E*)-benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide **7** by allowing the reaction of sulphonamide **2ba** (R^1 = Ph) with propargyl carbonates **3b** under the aforesaid optimized reaction conditions (of **Scheme 3**); interestingly, the desired product **7a** was obtained within 3h with 72% yield (**Scheme 4**). Next, we checked the substitution effects on the aryl/alkyl moiety attached to the acetylenic carbon of substrate **3b**. However, the reactions of **2ba** with propargyl carbonates **3c** (R^3 = 1-naphthyl) and **3d** (R^3 = 2-thienyl) generated the products **7b** (71%) and **7c** (76%), respectively, with equal ease. Thereafter the propargyl carbonate **3e/3f/3g** having an EWG (i.e., CF_3/F/NO_2) or **3h** having an EDG (i.e., Me) at the para position in the phenyl ring also underwent the reaction with **2ba** successfully to furnish the corresponding products **7d**/**7e**/**7f** or **7g** within 2–3 h with 53–76% yields. Interestingly, propargylic carbonates containing an alkyl group instead of an aryl one [viz., **3i** (R^3= Me) and **3j** (R^3= Et)] were also found to be successful towards this reaction, resulting in the formation of **7h** (72%) and **7i** (69%), respectively within 1.5-2.5 h. Besides, reactions of sulphonamides **2bb**/**2bc** having an alkyl group (R^1=Et/n-Bu) with propargylic carbonate **3b** (R^3 = Ph) proceeded well, delivering the corresponding product **7j**/**7k** in good yields (70-71%) with 7-9 h of reaction time. To our dismay, additional mono or di-substitution at the propargylic carbon of the substrate **3b** failed to deliver the products.

Scheme 4: Pd(0)-catalyzed synthesis of substituted (*E*)-3-aryl/alkyledene-[1,2,5]benzothiadiazepine-1,1-dioxide **7**[a]

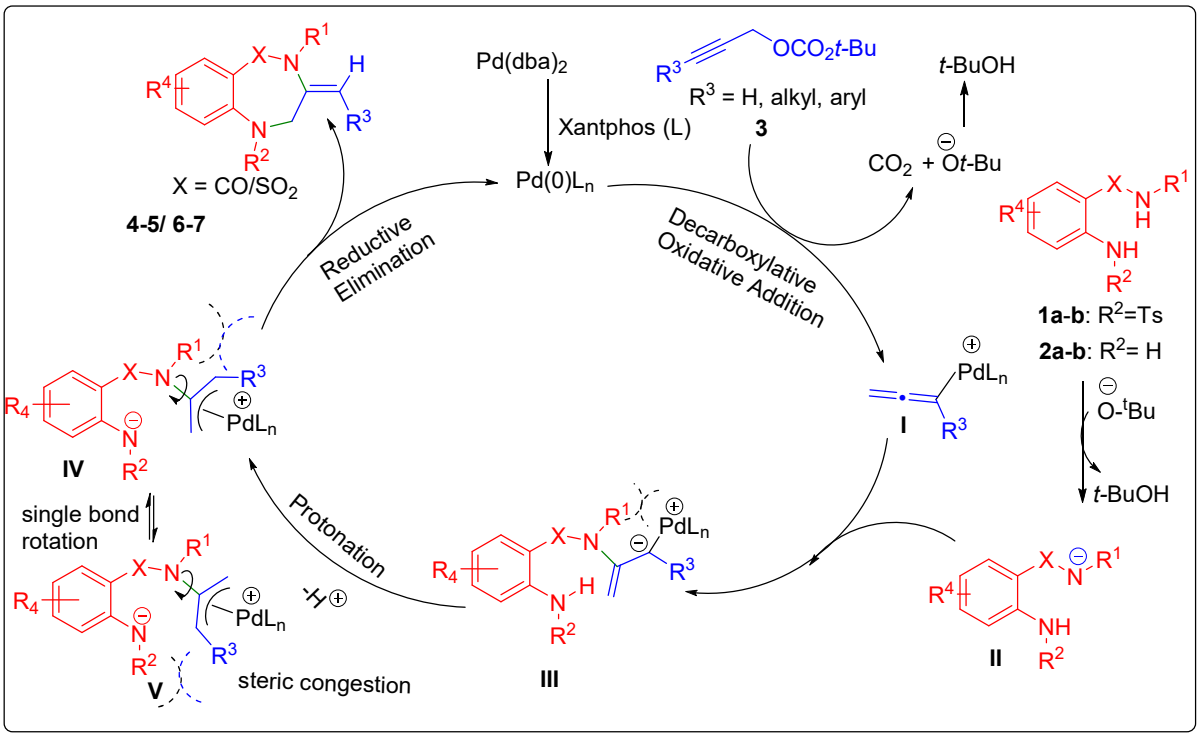


[a]Reaction conditions: A mixture of substrate **2b** (1 equiv), **3b-k** (1.5 equiv), $Pd(dba)_2$ (7 mol%) and Xantphos (14 mol%) were refluxed in butyronitrile (2 mL) under argon.

Structure of all products were confirmed by spectral (^1H, ^{13}C, mass spectroscopy) and analytical data. Detailed discussion of the structural elucidation is provided in **Part II** of Chapter 2. Finally, the structural conclusion was confirmed by the single crystal structures of compounds **4n**, **5a**, **6k** and **7a** (**Scheme 2-4**). The stereochemistry of the products was assigned to be trans (*E*-) based on the NOESY spectra and X-ray analysis.

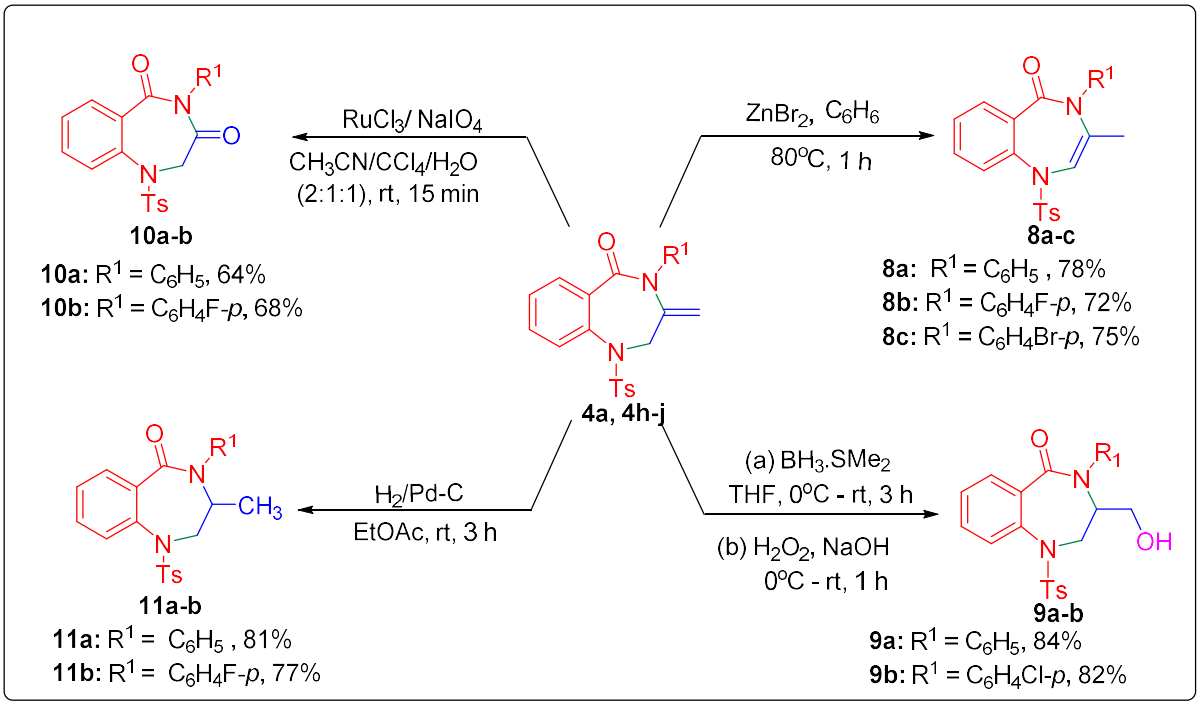
Mechanistically (**Scheme 5**), the decarboxylative oxidative addition of Pd(0) to propargyl tert-butyl carbonate **3** would generate the cationic palladium-allenyl species **I** and a tert-butoxide anion which would preferentially abstract the proton from the amide (or sulphonamide) moiety of the substrates (**1a**–**b**/**2a**–**b**) to form the anionic species **II**. The nucleophilic addition of **II** onto the central carbon of Pd–allene **I** may result in the

chemoselective generation of the Pd–carbenoid intermediate **III**. Next, the intermolecular proton migration from the NHTs (or NH_2) group of intermediate **III** would generate the Pd-π-allyl species **IV** (or **V**), which could undergo cyclisation followed by reductive elimination leading to the formation of products (**4**, **6**/**5**, and **7**) and regeneration of Pd(0). Although the precise reason behind the stereoselective formation of products (i.e., **6**–**7**) is not very clear, the steric factor in intermediate **IV** (or **V**) might play an important role in determining the outcome.



Scheme 5: Plausible reaction mechanism for the formation of products **4-5** and **6-7**

To explore the utility, the functional groups present in the products were used as synthetic handles for further transformations (**Scheme 6**). Thus the treatment of 3-methylene-1,4-benzodiazepin-5-ones **4a** (R^1 = Ph), **4h** (R^1 = -C_6H_4F-*p*), and **4j** (R^1 = -C_6H_4Br-*p*) with $ZnBr_2$ in refluxing benzene caused the isomerisation of the exocyclic double bond, providing an easy access to the products **8a**, **8b**, and **8c**, respectively, When the products **4a** and **4i** (R^1 = -C_6H_4Cl-*p*) were exposed to BH_3. DMS followed by the hydrogen peroxide treatment, hydration of the exocyclic double bond took place (following *anti-Markovnikov* rule) resulting in the generation of alcohols **9a** and **9b**, respectively. Furthermore, the treatment of **4a** and **4h** with $RuCl_3$ (5 mol%) and $NaIO_4$ (6 equiv.) resulted in the oxidative cleavage of the



Scheme 6: Transformations of 1,4-benzodiazepin-5-ones **4a** and **4h–j**

exocyclic C=C bond affording **10a** and **10b**, respectively, within 15 min, while the Pd/C-catalysed hydrogenation of **4a** and **4h** successfully afforded **11a** and **11b**, respectively.

Chapter 2

Palladium(0)-Catalyzed Heteroannulations of Allenamides: General Synthesis of δ-Carbolines and Benzofuro[3,2-*b*]pyridines

In the view of immense importance of δ-carbolines **1** and benzofuro[3,2- *b*]pyridines **2** (Fig. 1) which serve as core structure of many natural products and medicinally active compounds, the development of new methodology for these heterocyclic core structures appears to be important. In recent times, allenamides have emerged as potential building blocks in organic synthesis. During the course of palladium-catalyzed reactions, it was envisioned that a direct construction of pyridine ring fused to indole or benzofuran could be

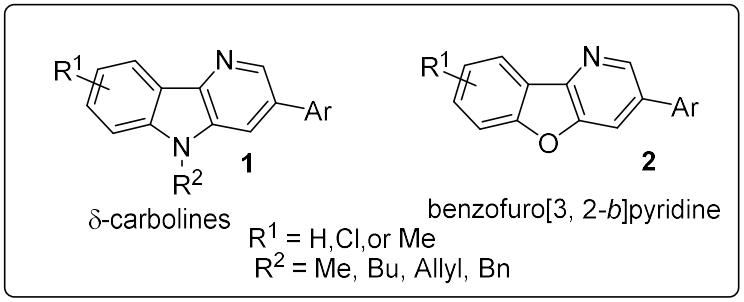
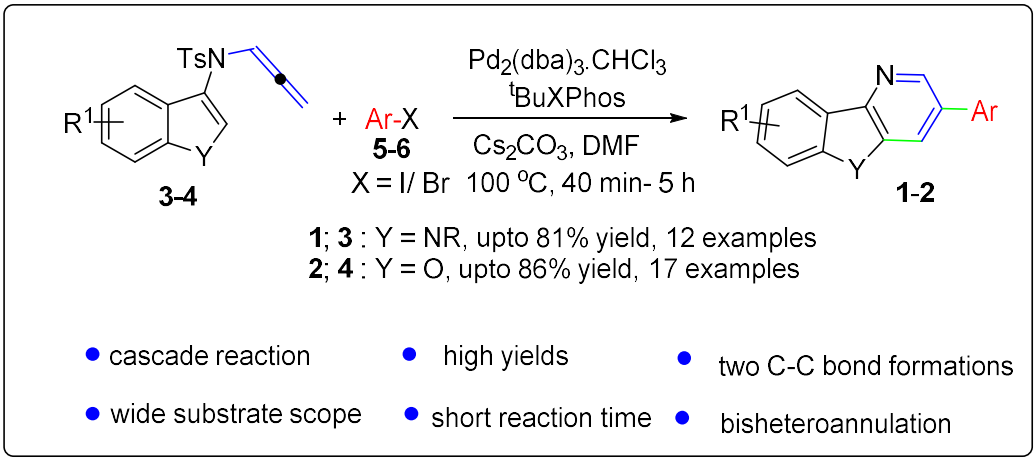


Fig. 1 Structures of δ-carbolines**1** and benzofuro[3,2- *b*]pyridines **2**

achieved via palladium-catalyzed cascade reactions between allenamides **3** or **4** and aryl halides **5**/**6** would form δ-carbolines **1** or benzofuro[3,2-*b*]pyridines **2.** The strategy appeared to be viable after choosing the appropriate reaction conditions.

In this chapter, palladium(0)-catalyzed cascade reactions of allenamides **3** or **4** with aryl iodides/bromides **5**/**6** are described for the general synthesis of δ-carbolines **1** or benzofuro[3,2-*b*]pyridines **2** as shown in **Scheme 1**.



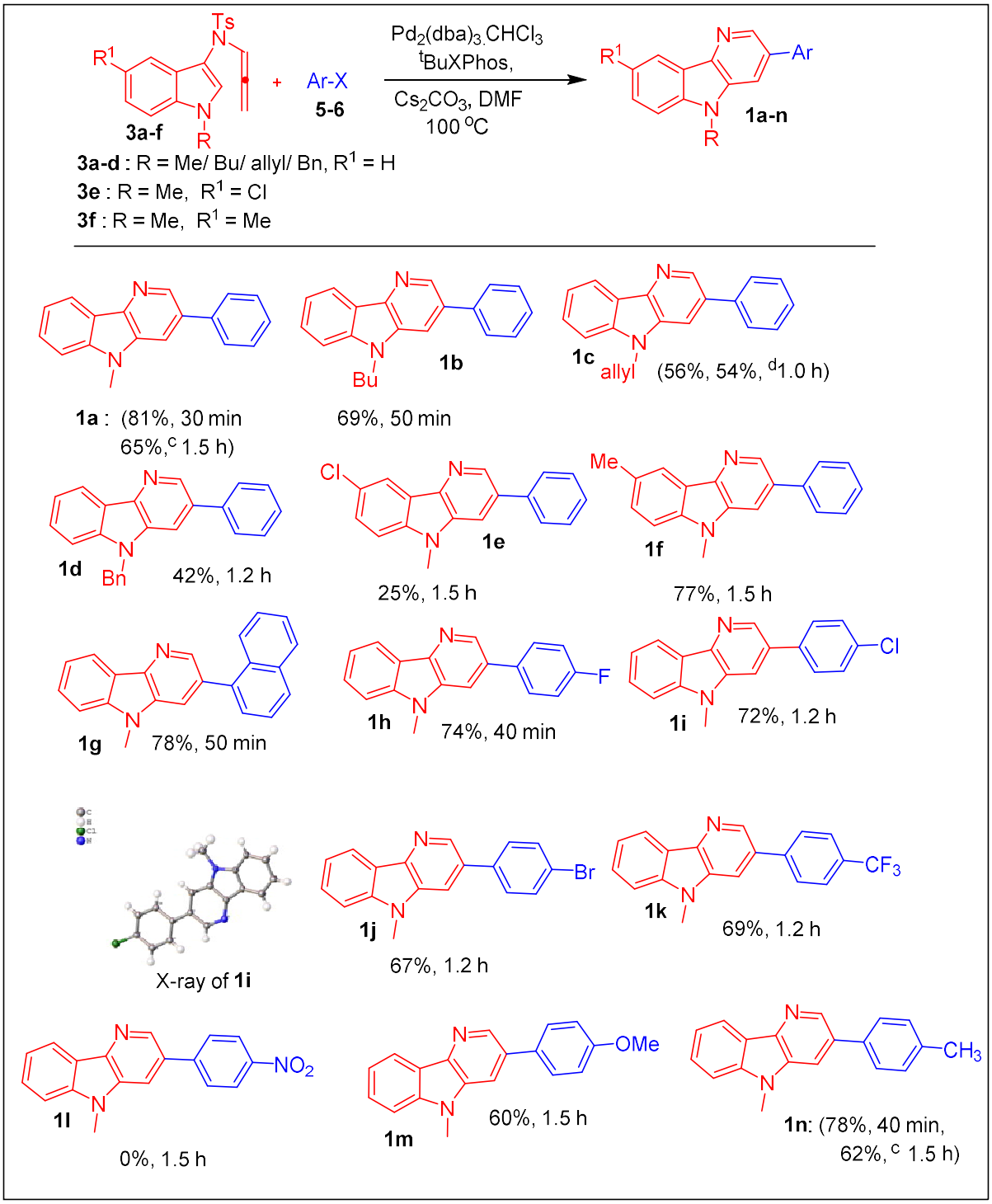
Scheme 1: Pd(0)-catalyzed synthesis of δ-carbolines**1** and benzofuro[3,2-*b*]pyridines **2**

Towards the objective, initially, a systematic optimization study has been done by performing a model reaction between allenamide **3a** and iodobenzene **5a** through the variation of catalyst, ligand, base, solvent, temperature etc. Nevertheless, this study reveals that the optimized conditions comprising 5 mol % $Pd_2(dba)_3.CHCl_3$, 10 mol % $^tBuXPhos$ and CS_2CO_3 (4 equiv.) in dry DMF with heating at 100 ^oC lead to the formation of δ-carboline **1a** within 30 min with 81% yield.

After having the optimized reaction conditions, scope of this reaction was explored where a series of allenamide substrates **3** and aryl iodides/bromides **5**/**6** have responded well to the optimized reaction condition resulting in the formation of an array of desired products **1a-k** within 0.5-1.5 h in good to moderate yields (25-81%) (**Scheme 2**). Initially, *N*-Me group of allenamide **3a** was replaced by other protecting group like Bu/allyl/Bn and the resulting allenamide substrates were allowed to react under same optimization conditions. Gratifyingly the corresponding desired products **1b-d** were obtained with 42-69% yields although somewhat longer time was necessitated (**Scheme 2**). To test the effect of electron-withdrawing or electron-donating group (EWG or EDG) at C5 of the indole moiety, phenyl iodide (**5a**) was allowed to react with allenamide **3e** (R^1 = Cl) or **3f** (R^1= Me); the desired carboline **1e** (25%) or **1f** (77%) was formed within 1.5 h. The electron withdrawing effect of the chloro group may account for the lower yield of **1e**. Furthermore, the bulky naphthyl iodide (**5b**) participated in the reaction with equal ease, affording the carboline **1g** with 78% yield.

Next, we carried out the reaction of allenamide **3a** with a range of aryl iodides/bromides **5c−i/ 6a,b** bearing EDG or EWG (**Scheme 2**). Iodides **5c−f** possessing moderately EWG such as F/Cl/Br/CF_3 facilitated the reaction by smoothly delivering the

Scheme 2: Pd(0)-catalyzed synthesis of δ-carbolines **1**[a-d]



[a]Reaction conditions: A mixture of **3** (1 equiv.), **5** or **6** (1.2 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and [t]BuXPhos (10 mol%) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.[c]Bromide (**6**) was used instead of the iodide (**5**). [d] 1.0 mmol scale reaction.

carbolines **1h**−**k**. Surprisingly, 1-iodo-4-nitrobenzene (**5g**) proved to be incompatible for the reaction, as it delivered only minor amounts (TLC) of few uncharacterized products in place

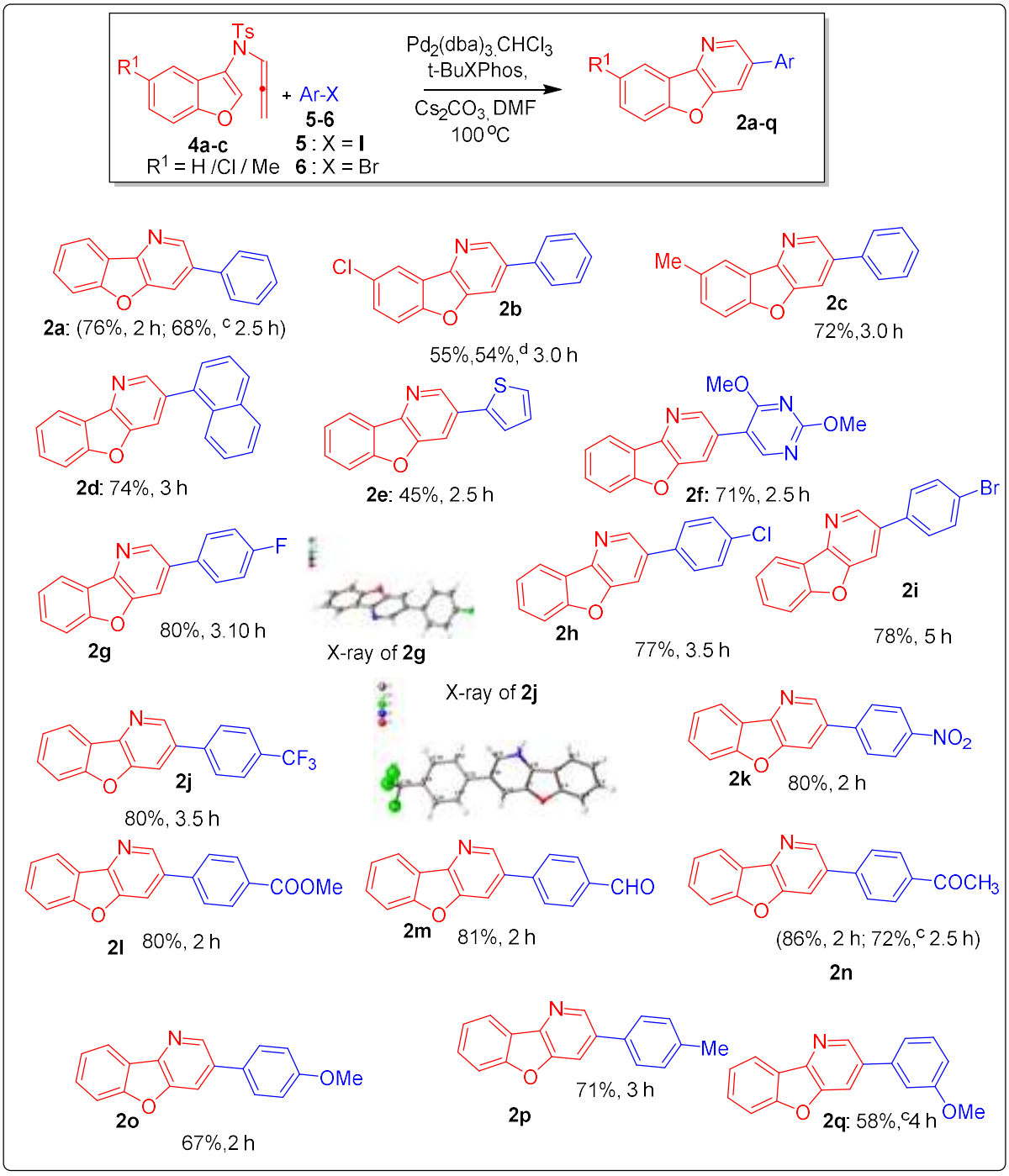
of the desired product **1l**. In contrast, iodide **5h** having a strongly EDG (OMe) at the para position promoted the reaction to furnish carboline **1m** within 1.5 h with good yield (60%). However, iodide **5i** having a moderately EDG (i.e., Me) proved more reactive, forming carboline**1n** within 40 min with 78% yield.

Aryl bromides **6** also turned out to be reactive, though forming the products in somewhat lower yields as shown in **Scheme 2**. For instance, phenyl bromide (**6a**) delivered δ-carboline **1a** with 65% yield, while *p*-bromo toluene (**6b**) similarly afforded **1n** (62%).

With a view to expand the scope of the reaction further, we targeted to achieve the synthesis of benzofuro[3,2-*b*]pyridines **2**. Towards this goal, the requisite benzofuran substrates **4a**−**c** were prepared in few steps and utilized in subsequent reactions with various aryl iodides/ bromides **5**/**6** (**Scheme 3**) under the aforesaid optimized reaction conditions. Thus the benzofuran substrate **4a** having an allenamide moiety at the C3 position was allowed to react initially with aryl iodide **5a** under the optimization conditions; this reaction afforded the corresponding product **2a** within 2 h with 76% yield . Next, phenyl iodide (**5a**) was allowed to react with allenamide **4b** (R^1 = Cl) or **4c** (R^1 = Me) having an electron-withdrawing or electron-donating group (EWG or EDG) at C5 of the benzofuran moiety; pleasingly, the desired carboline **2b** (55%) or **2c** (72%) was found to be formed within 3 h (**Scheme 3**). Next, allenamide **4a** underwent successive reactions with naphthyl iodide **5b**, 2-iodo-thiophene **5j** and 5-iodo-2,4-dimethoxy pyrimidine (**5k**); these reactions afforded the products **2d** (74%), **2e** (45%) and **2f** (71%), respectively within 2.5-3 h.

Next, the reactivity of allenamide **4a** with different aryl iodides (**5c−g**, **5l−n**, **5h-i**) containing EWG or EDG was explored (**Scheme 3**). Substrates **5c−f** possessing a moderately EWG (viz., F, Cl, Br, CF_3) participated the reaction with equal ease, leading to the formation of benzofuro[3,2-*b*]pyridines **2g−j**. In contrast to **1l** (**Scheme 2**), iodides (**5g, 5l−n**) having a strongly EWG (viz., NO_2, CHO, CO_2Me, COMe) formed benzofuro[3,2-*b*]pyridines **2k−n** within 2 h due to their reactive nature. When a strong or moderate EDG is present, as in iodides **5h** or **5i**, it delivered the product **2o** or **2p** in 2−3 h, though the yields were lower (67−71%). Similar to the line of previous observations (of **Scheme 2**), aryl bromides successfully participated in this reaction though with slightly lower yields compared to aryl iodides. For example, phenyl bromide (**6a**), 4-bromoacetophenone (**6c**), and 3- bromoanisole (**6d**) reacted with allenamide **4a** forming **2a** (68%), **2n** (72%), and **2q** (58%), respectively, within 2.5−4 h.

Scheme 3. Pd(0)-catalyzed synthesis of benzofuro[3,2-*b*]pyridines **2**[a,b]

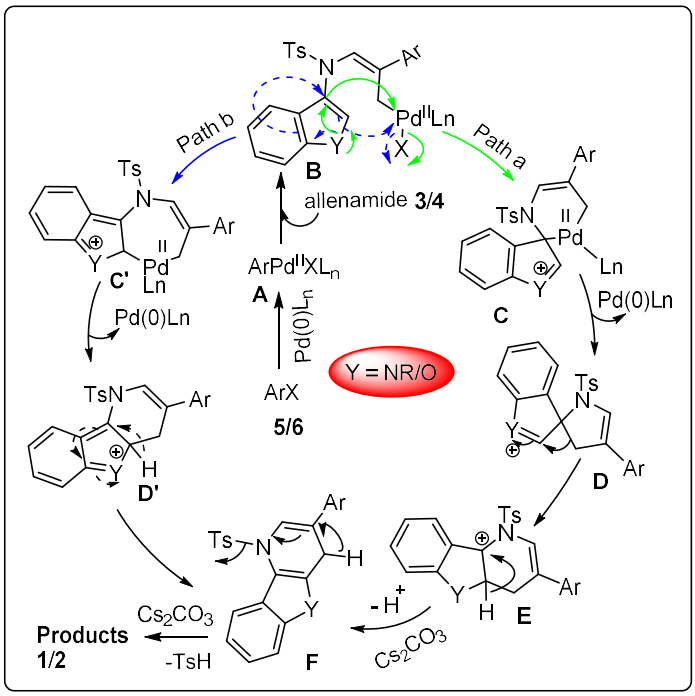


[a]Reaction conditions: A mixture of **4** (1 equiv), **5** (1.2 equiv), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and [t]BuXPhos (10 mol %) in DMF (2 mL) was refluxed under argon. [b]Isolated yield. [c]Aryl bromide (**6**) was used. [d]1.0 mmol scale reaction.

Structure of all products were undoubtedly confirmed by spectral (^1H, ^{13}C, mass spectroscopy) and analytical data. Detailed discussion of the structural elucidation is provided

in **Part II** of Chapter 2. Finally, the structural conclusion was confirmed by the single crystal structures of compounds **1i**, **2g**and **2j** as shown under aforesaid **Schemes 2-3**.

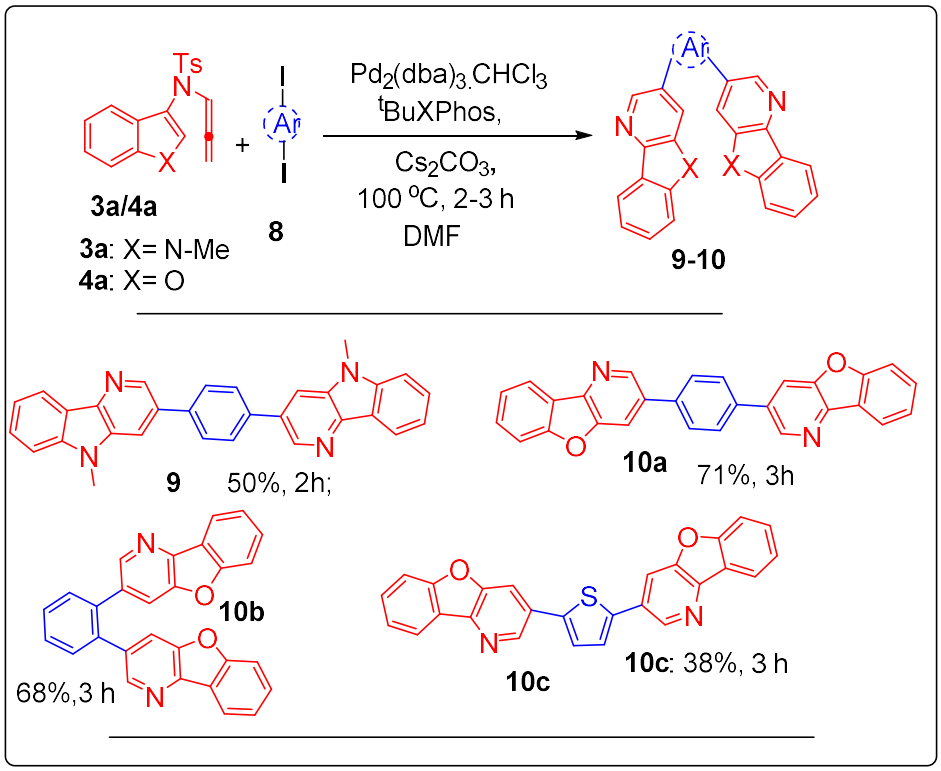
A plausible reaction mechanism is outlined in **Scheme 4** to explain the formations of products **1**/**2**. Initially, oxidative addition of aryl halides (ArX) with Pd(0) forms ArPd(II)X (**A**) which is then undergoes addition onto the allenic double bond of substrate **3/4** triggering the formation of palladium(II)-Π-allyl complex **B**.Intermediate **B** undergoes (**path a**) intramolecular nucleophilic attack by C3 of the indole or furan moiety resulting in the formation of a six-membered palladium(II) species **C**. Next, a reductive elimination of palladium(II) from species **C** would lead to the formations of a transient spiro-intermediate **D** and Pd(0). Nevertheless, a preferential allylic group migration (from C3 position of indole or furan moiety) of intermediate **D** to its C2 position would produce a carbonium intermediate **E** which upon deprotonation would easily generate a dihydropyridine intermediate **F.** Finally, a base induced elimination of TsH from **F** leads to the formations of desired products **1** (or **2**). Alternatively (**path b**), an intramolecular nucleophilic attack of C2 of the indole (or furan ring) of **B** onto the palladium might result in the formation of a seven-membered palladium-(II) intermediate **C′**, the reductive elimination of which would furnish intermediate **D′** with concurrent formation of Pd(0). Next, a base assisted deprotonation of **D′** would produce dihydropyridine intermediate **F**, which would trigger the formation of product **1** (or **2**).



Scheme 4: A Plausible reaction mechanism for the formation of products **1-2**

In view of the importance of bis-δ-carbolines present in bioactive alkaloids, we also checked the prospect of bisheteroannulations (**Scheme 5**). Thus, the reaction of allenamide **3a** with 1,4-diiodobenzene **8a** under optimized condition generates bis-δ-carboline **9a.** On the other hand, when allenamide **4a** was allowed to react successively with 1,4-diiodobenzene (**8a**), 1,2-diiodobenzene (**8b**) and 1,2-diiodothiophene (**8c**), the expected bis-benzofuro[3,2-*b*]pyridine derivatives **10a-c** were generated within 3 h with 38-71% yields.

Scheme 5. Synthesis of bis-heteroannulated products **9-10**[a,b]



[a]Reaction conditions: A mixture of **3a** or **4a** (1 equiv), **8** (0.6 equiv), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and ^{t}BuXPhos (10 mol%) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.

Chapter 3

Palladium-catalyzed *5-exo-dig* cyclization/ DDQ-mediated dehydrogenative Diels–Alder reaction for the synthesis of functionalized benzofuro[3,2-*b*]pyrrole / benzofuro[3,2-*b*]indoles derivatives

In recent times, pyrrole or indole fused heterocycles have drawn considerable interests due to their immense importance ranging from medicinal chemistry to material science. In recent past, considerable interests has been generated in the synthesis of benzofuro[3,2-*b*]pyrroles **1** (Fig. 1) and benzofuro[3,2-*b*]indoles (BFIs) **2** (Fig.1) because of their immense biological activities. For example, benzofuro[3,2-*b*]pyrroles **1** play a key role by scavenging reactive oxygen species (ROS) and reducing oxidative stress. They have shown to possess antioxidant

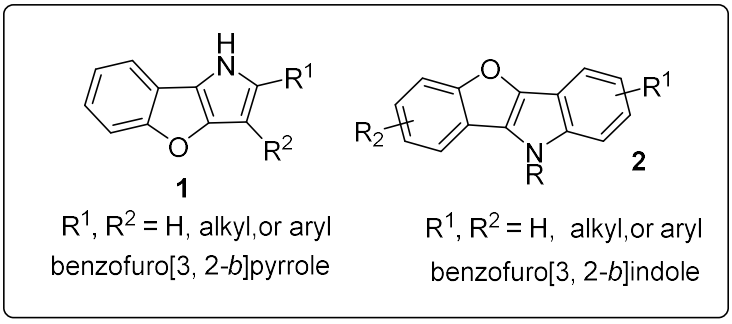
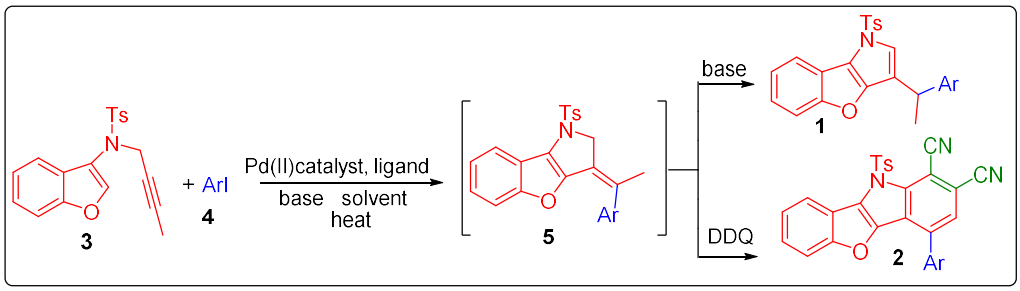


Figure 1: Structures of benzofuro[3,2-*b*]pyrrole**1** and benzofuro[3,2-*b*]indoles **2**

properties, which can protect cells from oxidative damage. Furthermore, they exhibit antimicrobial activity against bacteria and fungi by inhibiting bacterial growth and disrupting the cell wall of fungi. On the other hand, benzofuro[3,2-*b*]indoles (BFIs) **2** are considered as important scaffolds because of their uses in the treatment of sexual hormone disorders, degenerative brain diseases and different types of cancer due to their extensive anti-tumour activity.

Nevertheless, the third chapter deals with an efficient and convenient approach for the synthesis of benzofuro[3,2-*b*]pyrroles **1** via palladium(0)-catalyzed *5-exo-dig* cyclisation (**5**) followed by base induced isomerisation leading to the formation of benzofuro[3,2-*b*]pyrroles **1** or DDQ mediated cycloaddition resulting in benzofuro[3,2-*b*]indoles **2** (**Scheme 1**).



Scheme 1: Synthesis of benzofuro[3,2-*b*]pyrrole **1** and benzofuro[3,2-*b*]indole **2**

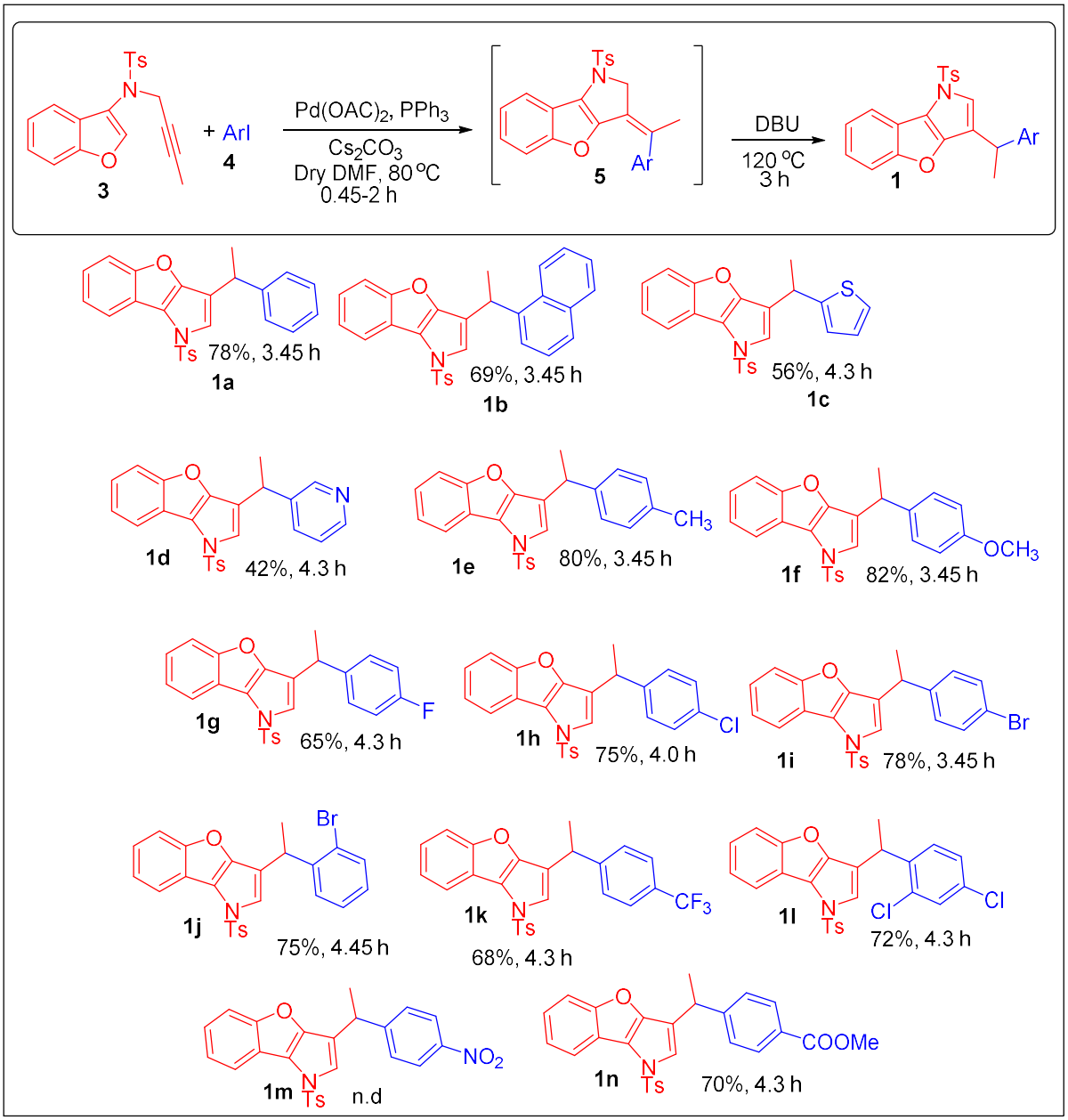
To find out the optimized reaction conditions for the synthesis of benzofuro[3,2-*b*]pyrroles **1**, initially, model reaction of substrate **3** with iodobenzene **4a** (Ar = Ph) was carried out with variation of the reaction parameter (i.e., catalyst, ligand, base, solvent, temperature etc). After several experiments, the optimized reaction condition was find out where heating a mixture of **3** and iodobenzene **4a** in dry DMF at 80 ^{o} C in the presence of 7 mol % of the $Pd(OAC)_2$ and 14 mol % PPh_3 and Cs_2CO_3 (1 equiv.) under argon armosphere led to the formation of desired intermediated product **5a** (Ar = Ph) within 45 min with 84% yield.

To explore the scope of the above reaction further, we decided to carry out a base induced isomerisation of product **5a** into **1a**. Toward this goal, we initially executed few reactions through the variation of the base, solvent and temperature to find out the optimal reaction conditions for the synthesis of benzofuro[3,2-*b*]pyrroles **1a.** Thus, after several experiments, heating (at 120 ^{o}C) of **5a** in DBU used as base as well as solvent for 3 h proved to be the best furnishing the product **1a** with 78% yield (**Scheme 2**).

Having the optimized reaction conditions in hand, we then explored the scope and generality of the reaction as shown in **Scheme 2**. A series of products **1a-n** have been synthesized within 3.45-4.3 h (i.e., total reaction time required for the conversion of substrate **3** into product **1**) with moderate to very good yields (42-78%) and a range of functional groups (viz., Me, OMe, F, Cl, Br, CF_3, COOMe) attached to the aryl ring of **4** were found to be well tolerated.

Initially, we carried out subsequent reactions of acetylenic substrate **3** with 1-iodonaphthalene (**4b**), 2-iodothiophene (**4c**) and 3-iodopyridine (**4d**); these reactions furnished the expected products **1b**, **1c** and **1d**, respectively with good to moderate yields (42−69%). Gratifyingly, iodide having an electron-donating group (EDG) (viz., Me or OMe) such as **4e** or **4f** proved to be more reactive, thereby delivering the products **1e** or **1f** within 3.45 h with excellent yields (80-82%). The trend of this reactivity was found to be continued even with substrates **4g-l** having moderately EWG (viz.; F, Cl, Br, CF_3, Cl) delivering the

Scheme 2: Pd(II)-catalyzed synthesis of benzofuro[3,2-*b*]pyrrole **1** under one-pot[a,b,c]

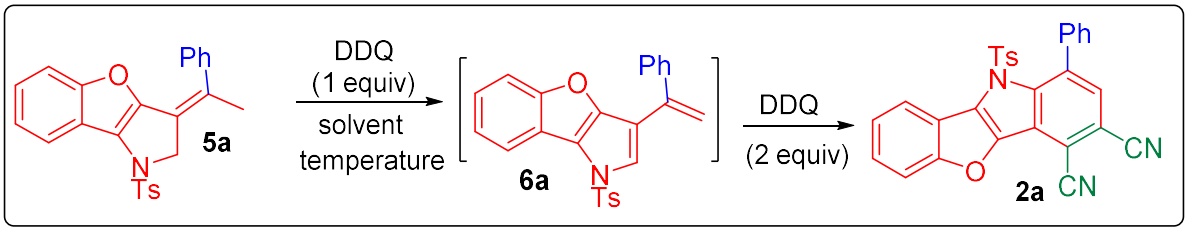


[a]Reaction conditions: A mixture of **3** (1 equiv.), **4** (1.2 equiv.), $Pd(OAc)_2$ (7 mol %), and PPh_3 (14 mol %), 1 equiv. Cs_2CO_3 in DMF (2 mL) was heated at 80 °C; after completion of the reaction (TLC), the DBU (2 equiv.) was added and the whole reaction mixture was heated to 120 °C . [b]Reaction time mentioned in **Scheme2** against each product represents the total time required for the conversion of substrates **3** into products **1**[c]Isolated yield.

products **1g-l** with 65-78% yields. In contrast, a strong EWG as in substrate 1-iodo-4-nitrobenzene (**4m**) failed to provide the desired product **1m**, instead, only few undesired spots (TLC) were found to be formed in minor amount. To our surprise, methyl 4-iodobenzoate (**4n**) participated the reaction successfully leading to the generation of benzofuro[3,2-*b*]pyrrole **1n** within 4.3 h with 70% yield.

Encouraged by the reported works by Zhou and Feng (see, reference 32 in part II of 3rd chapter) for the synthesis of 1,3-dienes (see, **Schemes 16** in part I) as requisite substrates for Diels Alder reaction, we became interested to explore the potential of products **5** into 1,3-dienes **6** which could undergo Diels Alder reaction to generate important scaffolds of biological interests. To test this hypothesis, initially, product **5a** was treated with DDQ (3 equiv.) in acetonitrile at room temperature (entry 1, Table 1); to our pleasure, 3-(1-phenylvinyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole **6a** was found to be formed at rt (12 h) with 60% yield (Table 1, of product **6a**.) In contrast, instead of isolating the intermediate **6a,**

Table 1: DDQ promoted synthesis of benzofuro[3,2-*b*]indole 2a[a]



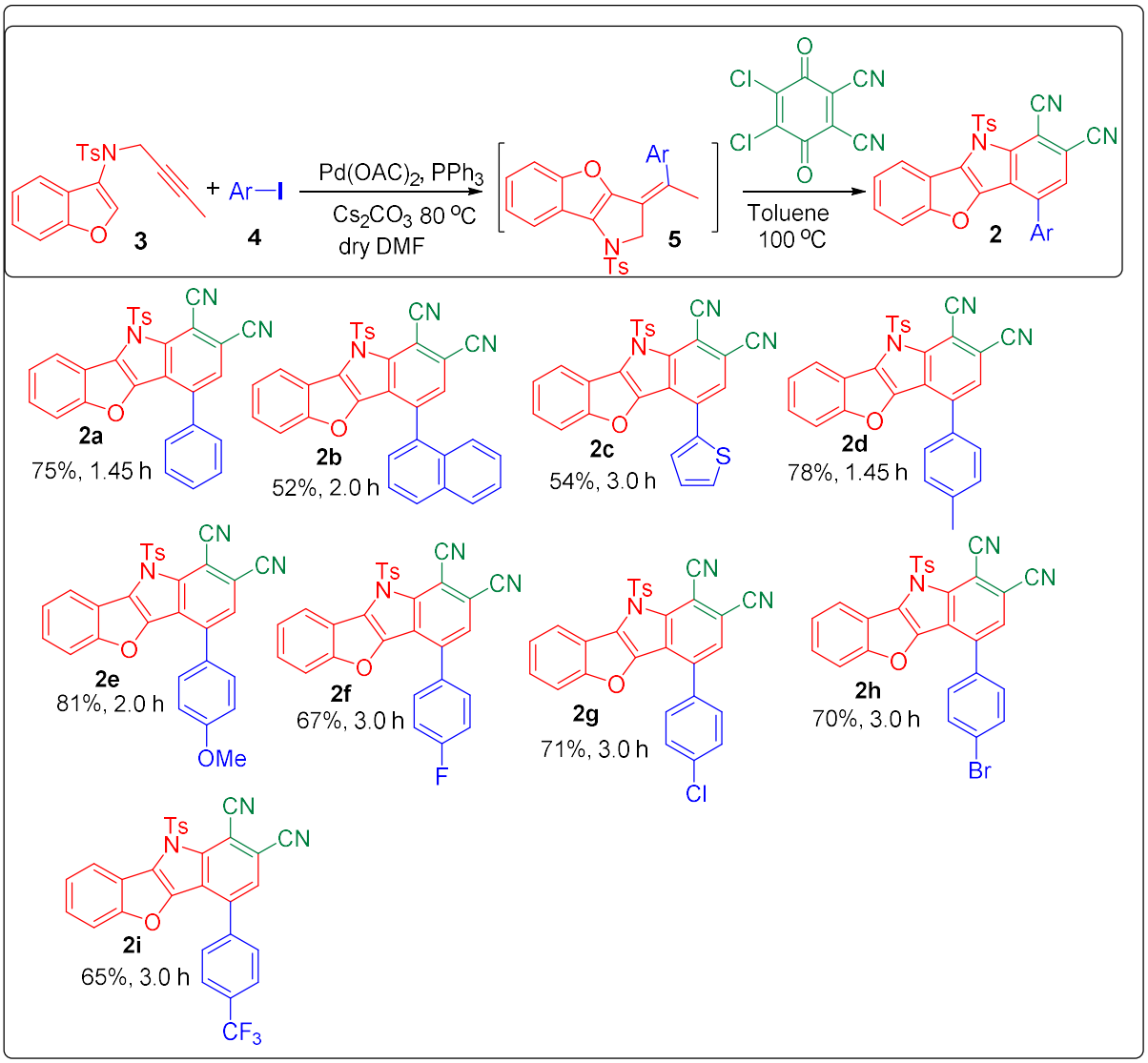
Sl no	Solvent	Temperature	Time (h)	Yield(%)[b] of 6a	Yield(%)[b] of 2a
1[a]	CH_3CN	rt	12	60	-
2	*o*-Xylene	120 °C	12	nr	nr
3	Chlorobenzene	120 °C	8	42	-
4	**Toluene**	**120 °C**	2	**-**	**89**

A mixture of 1.0 equiv of **5a** and DDQ (3 equiv.) in 2.0 mL was stirred either r.t or heated at 120 ° C under argon.[b]Isolated pure products after chromatography.

heating the same reaction (in acetonitrile) at 120 °C after the formation of intermediate **6a** failed to provide any product leading to the polymerization of the reaction (Table 1, entry 1). Next, replacing the acetonitrile with *o*-xylene and carrying out the reaction either at rt or heating at 120 °C did not provide the access of intermediate product **6a** (Table 1, entry 2). Nevertheless, changing the solvent to chlorobenzene and heating the reaction at 120 °C in same solvent provided the intermediate **6a** in moderate yield (42%) but failed to provide the targeted product **2a** (Table 1, entry 3). To our pleasure, exposer of **5a** with DDQ (3.0 equiv) and conducting this reaction in toluene at 120 °C led to the formation of cycloadduct **2a** within 2 h with 89% yield (Table 1, entry 3).

With the aforesaid encouraging result in hand, we then attempted to explore the prospect of utilizing DDQ in the synthesis of different benzofuro[3,2-*b*]indole derivatives **2** as shown in **Scheme 3**.

Scheme 3: DDQ-mediated synthesis of benzofuro[3,2-*b*]indole **2**[a,b]



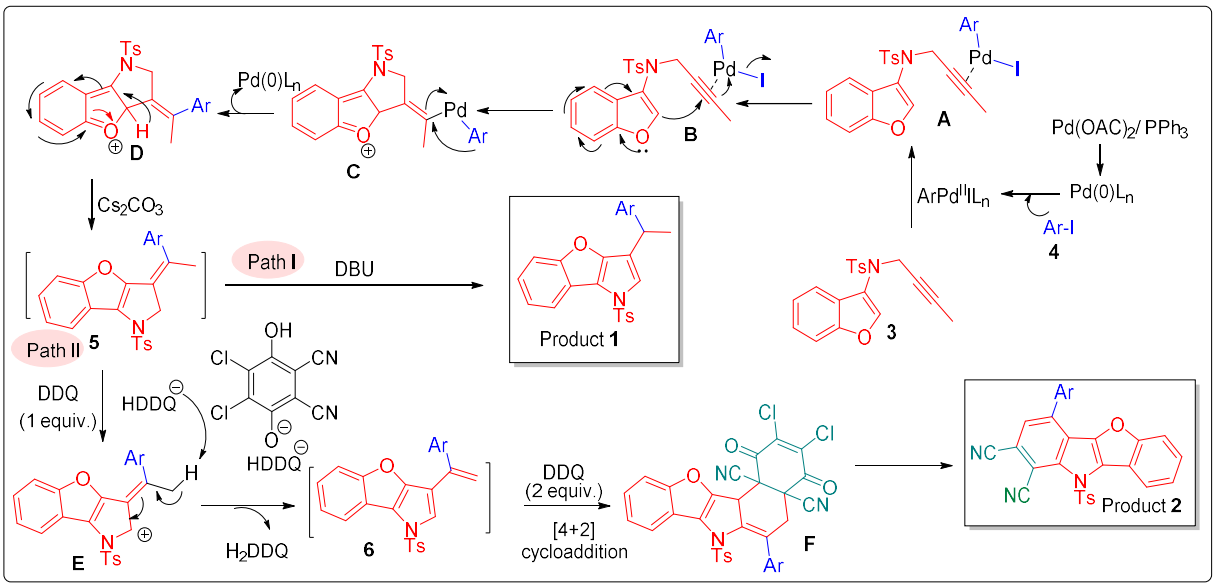
[a]Reaction conditions: A mixture of **3** (1 equiv.), **4**(1.2 equiv.), Pd $(OAc)_2$ (7 mol %), and PPh_3 (14 mol %), Cs_2CO_3 (1 equiv.)in DMF (2 mL) was heated at 80 °C. After completion of the reaction, solvent was evaporated to dryness and the resulting crude product dissolved in dry toluene (3 mL) was heated at 100 °C for few hours (1.45-3 h) in the presence of DDQ (3 equiv.). [b]Isolated yield.

The desired product **2b** was found to be formed with moderate yield (52%) possibly steric hindrance faced by the bulky naphthalene moiety during cycloaddition reaction. Nevertheless,2-iodo-thiophene (**4c**) participated this reaction successfully though the resulting product **2c** was found to be formed with moderate yield 54% after 3 h. Interestingly, attachment of moderate (Me) or strong (OMe) electron-donating group (EDG) as in intermediate **5e** or **5f** facilitated this reaction, generating the product **2d** or **2e** with excellent yield (78-81%). In contrast to the previous observations, intermediate **5g-j** possessing a moderately electron withdrawing group (EWG) (viz., F, Cl, Br, CF_3) participated in the reaction with less efficiency resulting in the products benzofuro[3,2-*b*]indole **2f-i** with lower

yields. The formation of product **2** is attributed to in situ generation of a di-ene intermediate **6** (*vide infra* under **Scheme 4**) which undergoes rapid [4+2] cycloaddition with DDQ to generate the product **2**; a detailed mechanism is depicted under **Scheme 4** below.

Based on the experimental results and known Palladium chemistry, a plausible reaction mechanism has been proposed in **Scheme 4**. First, Pd(0) generated *in situ* from $Pd(OAc)_2$ and PPh_3 undergoes oxidative addition onto aryl iodide **4** resulting the formation of ArPd(II)I (**A**) which subsequently coordinates with the triple bond of acetylenic substrate **3** to form an intermediate **B**. Then intermediate **B** undergoes intramolecular nucleophilic attack by C2 of the benzofuran moiety triggering the formation of vinyl palladium intermediate **C**. Next, reductive elimination of Pd(II) from intermediate **C** led to the generation of intermediate **D** with the concomitant regeneration of Pd (0). Next, intermediate **D** undergoes deprotonation to yield the exocyclic intermediate **5**. Isomerisation of product **1** could easily be achieved after treatment of a base like DBU (**path-a**).

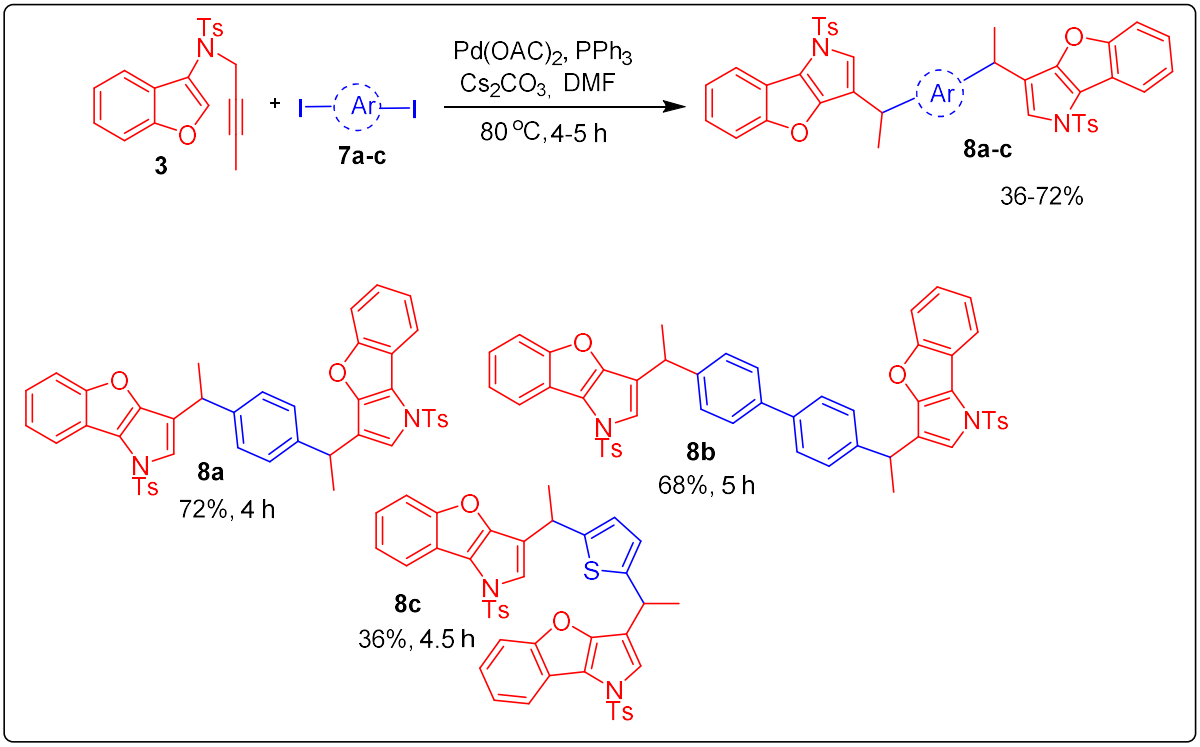
Next, in another reaction pathway (**path-b**), removal of a hydride ion from the exocyclic intermediate product **5** with the aid of DDQ generates intermediate **E** which upon deprotonation affords a di-ene intermediate **6** as shown in **Scheme 4**. Next, a [4+2]-cycloaddition of intermediate **6** with DDQ generates the cycloadduct **F** which finally furnishes the product **2**. The exact mechanism for the final step is still unknown to us and it is currently under our investigation.



Scheme 4: Plausible reaction mechanism for the formation of products 1 and 2

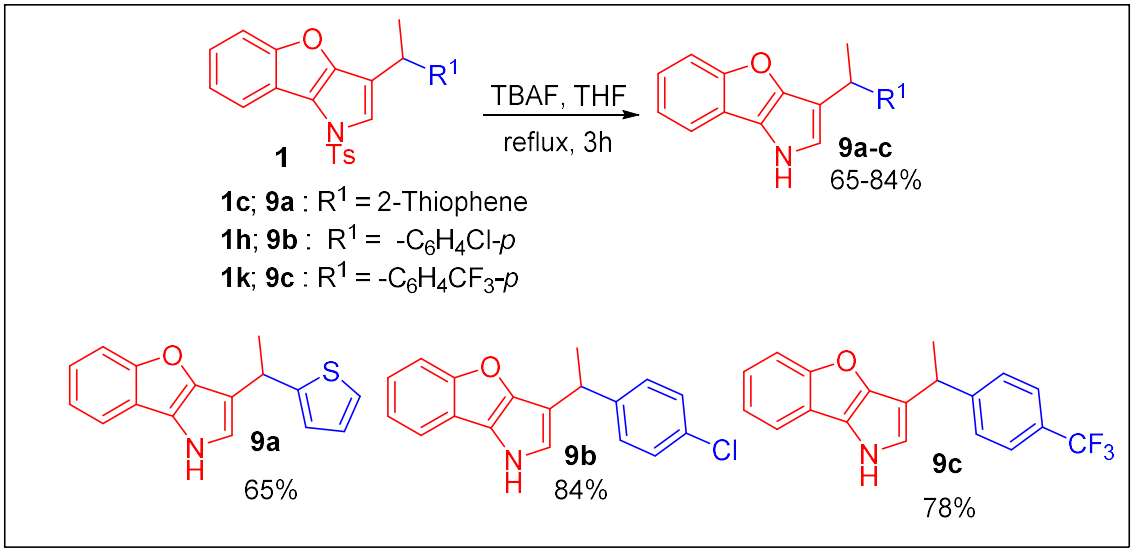
In view of the immense importance of bis-benzofuro[3,2-*b*]pyrroles which serve as core structure of bioactive alkaloids, attempts were made to check the feasibility of bis-

heteroannulations by conducting the reaction of acetylene **3** with di-iodo compounds **7**(**Scheme 5**). Accordingly, subsequent reactions of acetylenic substrate **3** with 1,4-diiodobenzene **7a,** 4,4'-diiodobiphenyl (**7b**), and 1,2-diiodothiophene (**7c**) were carried out under the optimized reaction conditions (of **Scheme 2**). Contrary to our previous observations (of **Scheme 2**), the bis-heteroannulated products **7a-c** (with isomerisation of the exocyclic double bond) were found to be formed under one-pot within 4-5 h with 36-72% yield (**Scheme 5**).



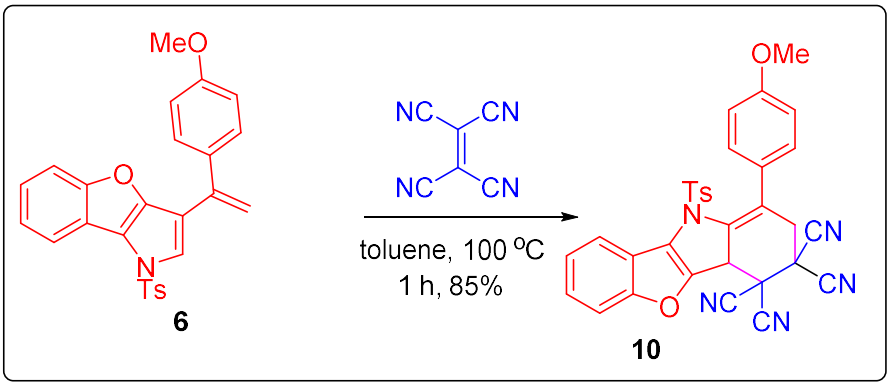
Scheme 5: Synthesis of bis-heteroannulated products **8a-c**

Thereafter we became interested to make detosylation of the synthesized products **1** which could lead to the formations of benzofuro[3,2-*b*]pyrrole **9** having a free NH group which constitute the core structure of many bioactive compounds. To check the prospect of this reaction, compounds **1c/1h/1k** were exposed to tetrabutylammonium fluride (TBAF) in refluxing THF (**Scheme 6**); gratifyingly, corresponding products **9a/9b/9c** were found to be formed easily within 3 h in 65-84% yield.



Scheme 6: N-detosylation of products **1c/1h/1k**

Besides, another diene intermediate **6** was isolated and it was allowed to react with tetracyanoethelene in toluene at 100 °C. Pleasingly, the desired cycloadduct **10** was found to be formed within 1h with 85% yield (**Scheme 7**).



Scheme 7: Synthesis of cycloadduct **10**

CHAPTER 1

Palladium(0)-catalysed regioselective cyclisations of 2-amino(tosyl) benzamides/sulphonamides: the stereoselective synthesis of 3-ylidene-[1,4]benzodiazepin-5-ones/benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides

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Part I- A Short Review

1.1.1. Introduction:

1.1.1.1 Importance of 1,4-benzodiazepin-5-ones

The preparation of seven, eight, and larger membered heterocycles displaying broad and ever evolving biological properties is a challenging task. The difficulty in accessing these medium sized rings can be attributed to enthalpically unfavourable transition states that are due to trans-annular interaction and obstruction of ring closure by several entropic factors.[1] Among them, the seven-membered heterocycles, 1,4-benzodiazepin-5-ones **1**, (Figure 1) a subclass of the large 1,4-benzodiazepine family, are considered as privileged[2] structures in medicinal chemistry, contributing to the development of many drugs,[3a-b] therapeutic leads.[3c-d] Besides, 1,4-benzodiazepin-5-ones are also found in many natural and synthetic compounds with broad range of biological activities.[3e-3i]

While sultams (i.e., cyclic sulphonamides) are not found in nature, they display activities against a wide variety of biological targets[4a,b] and thus have emerged as important pharmacophores in drug discovery with remarkable chemical and biological profiles,[4c,d] viz. benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides [5a-5c] (**2**, Fig. 1). Besides, benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **2** play an important role in medicinal chemistry, biological studies, molecular modeling. Their diverse pharmacological properties and structural characteristics make them valuable candidate for the development of new drug discovery, understanding of biological processes, and designing of new therapeutic leads.

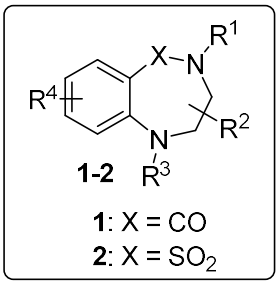


Figure 1: General structure of 1,4-benzodiazepin-5-ones **1** and [1,2,5]benzothiadiazepine-1,1-dioxides **2**

1.1.1.1.1 Importance of 1,4-benzodiazepin-5-ones in medicinal chemistry:

Bicyclic 1,4-benzodiazepin-5-ones are considered as potential precursors of their tricyclic fused analogs, many of which have been translated into potent drugs with commercial success, viz. [6a] *anthramycin* **3,** *mazethramycin* **4**, *porothramycin* **5** (**Figure 2**), *flumazenil*[6b] and its ^{18}F-labelled derivative,[6c] and *fuligocandin B*.[6d] More specifically, *anthramycin*[6a] **3** exhibits anti-bacterial activities against both gram-positive and gram-negetive bacteria and used as potential candidate for the treatment of bacterial infections. While *Flumazenil*[6b] **6** is preliminary used in the treatment of central nervous system (CNS) disorder, while its [6c]1F-labelled derivative is a useful ligand in positron emission tomography. On the other hand, *Fuligocandin B* [6d] **7** promotes the apoptosis-inducing ligand (TRAIL). The presence of either an unsaturated side chain in conjugation with a C2-C3 double bond of the core structure (e.g. *anthramycine* **3**, *mazethramycin* **4**, *porothramycin* **5**, *sibiromycin* **8**) or exocyclic unsaturation at C2 (e.g. *tomaymycin* **9**) have greatly enhance the cytotoxicity and DNA-binding ability.[3c] Besides, *sibanomycin* **10** exhibited antitumor activity in mice bearing leukemia P388 cells and weak activity against gram positive bacteria.

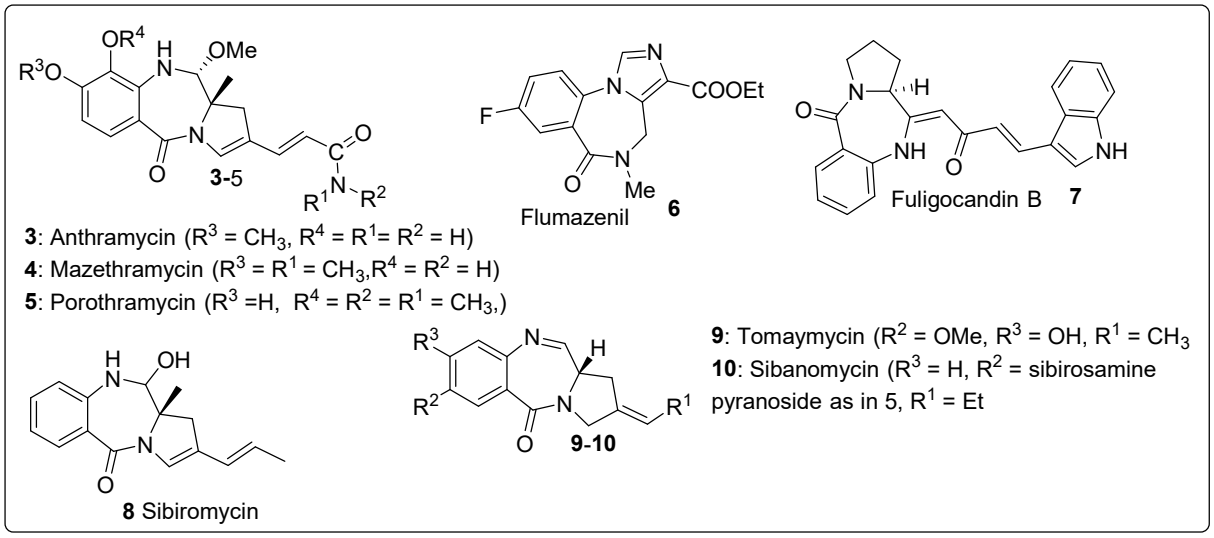


Figure 2: Few examples of bioactive compound having 1,4-benzodiazepin-5-ones moiety

1.1.1.1.2 Importance of 1,4-benzodiazepin-5-ones in natural product chemistry:

In addition to the aforesaid medicinal importance, 1,4-benzodiazepin-5-ones **1** have received attention in natural product chemistry due to their presence of various natural sources and their diverse biological activities. For example, *Sclerotigenin* **11** was isolated from sclerotia of *penicillium sclerotigenum* and exhibited a promising anti-insectan activity.[7] *Circumdatin C* **11**, isolated from terrestrial fungus *aspergillus ochraceus* and *benzomalvin A* **12** isolated from fungus *penicillium sp.* also have shown inhibitory activity against substance P (a neurokinin peptide) at the guinea pig, rat and human neurokinin NK1 receptors, respectively. Meanwhile, (-)*asperlicin* **13** is a mycotoxin, isolated from *Aspergillus alliaceus,* has been used as a lead compound for the development of a number of novel CCK-A antagonists with potential clinical applications (Figure 3).

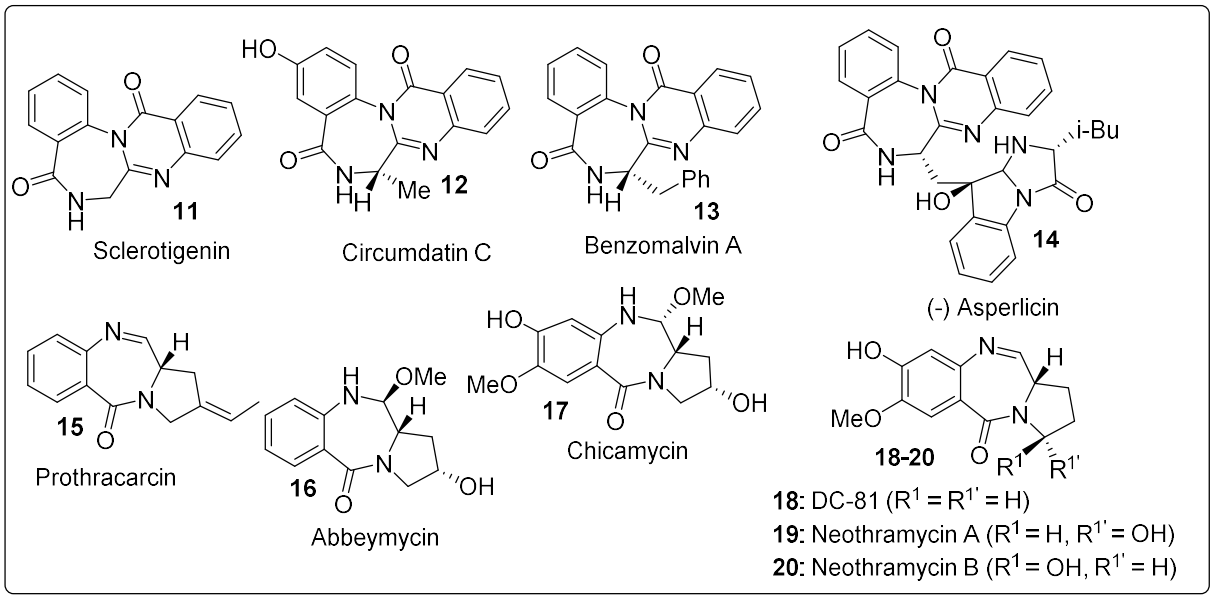


Figure 3: Some naturally occurring bioactive 1,4-benzodiazepin-5-ones

In addition, *prothracarcin* **15**[8], a novel antibiotic**,** was isolated from the culture broth of *streptomyces umbrosus subs.* Besides, the other well-known members of anthramycin class are *abbeymycin* **16**, *chicamycin* **17**, DC81 **18**, *neothramycin* A and B **19-20**, which were isolated from various *Streptomyces species,* and these compounds exhibited antitumor, antibiotic activities. Besides, these compounds are used as a potential tools such as affinity-cleavage reagents for use in molecular biology.

1.1.1.1.3 Importance of 1,4-benzodiazepin-5-ones in material sciences:

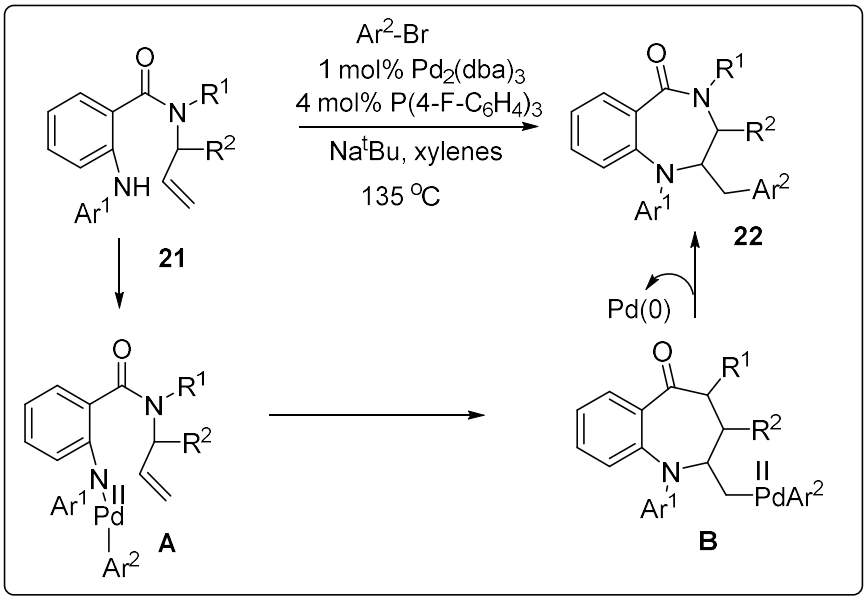
Although 1,4-benzodiazepin-5-ones **1** have received significant attention in medicinal chemistry and natural product chemistry due to presence of various natural sources and their diverse biological activity, but their application in the material sciences are limited in numbers. Nevertheless, some structural modifications of 1,4-benzodiazepin-5-ones[3a] can enhance their electrical and thermal properties and make them useful for polymer chemistry also. Besides, it has shown fluorescence properties and used in pharmaceutical application.

1.1.2. Synthesis of 1,4-benzodiazepin-5-ones:

Due to their wide applications in medicinal chemistry including drug discovery, natural product chemistry and material sciences, substantial interest were generated among the synthetic community to construct 1,4-benzodiazepin-5-ones. But methods for the general synthesis of this moiety has been limited in number, mostly employing either traditional reactions[9] or metal-catalysed heteroannulations,[10] involving specially palladium[6c,10c-e] and transition metals. Therefore, development of methodologies to get access to these scaffolds through straightforward means involving the formation of several C-C and C-N bonds taking place under one pot and using simple substrates would be worthwhile.

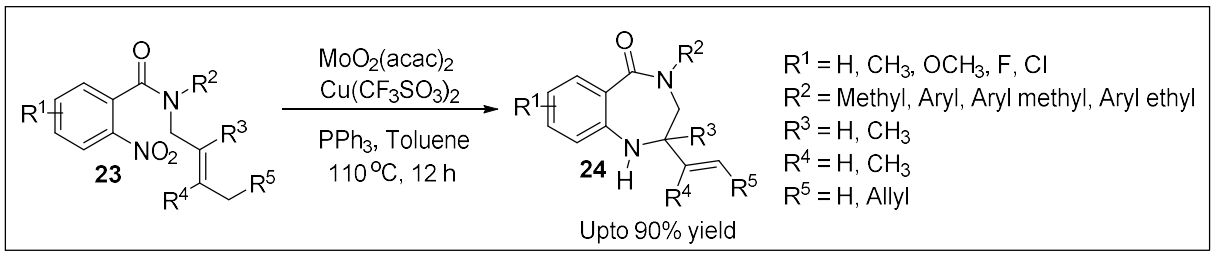
1.1.2.1 Synthetic pathways for the synthesis of 1,4-benzodiazepin-5-ones via intermolecular reactions of vinylic substrates:

Neukom *et al.* [10d] described a versatile and mild approach for the general synthesis of saturated 1,4-benzodiazepines via Pd-catalyzed amination reaction (**Scheme 1**). The proposed mechanism involves intermediate **A** generated from substrate **21** which subsequently undergoes amination to generate intermediate **B.** Finally, species **B** is transformed into product **22** via reductive elimination of Pd(0).



Scheme 1: Synthesis of 1,4-benzodiazepines **22**

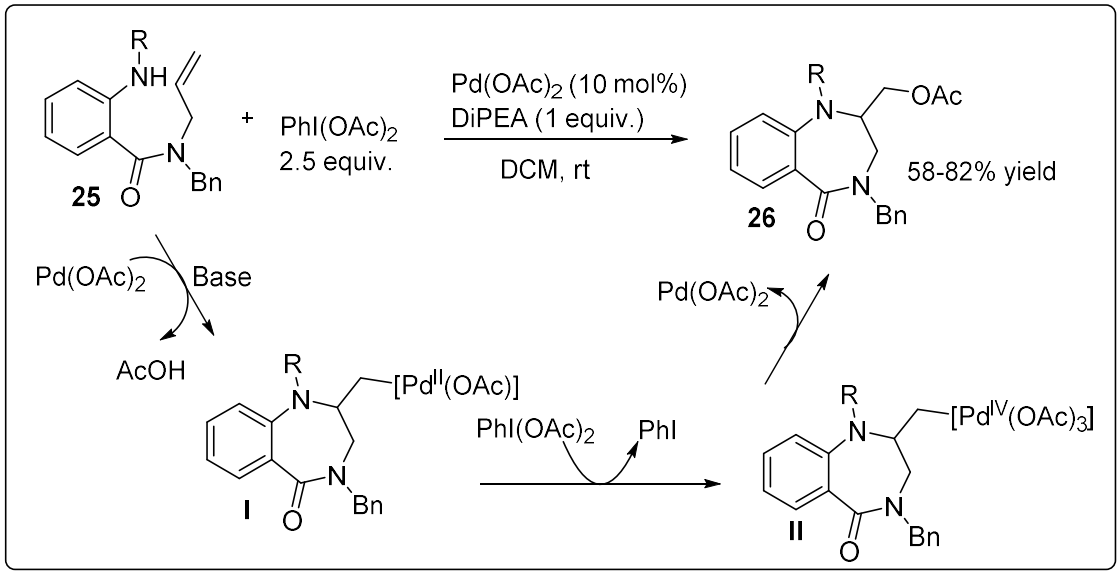
Chen and coworker[10a] described novel and efficient method for the synthesis of heterocyclic derivatives of diazepines via copper catalyzed cascade allyl amination reaction under one pot (**Scheme 2**). The synthesis process involves nitrene formation, C-H bond insertion, C=C bond rearrangement and C-N bond formation in cascade mode under one-pot reaction using duel catalyst like copper and molybdenum.



Scheme 2: Stereoselective synthesis of 1,4-benzodiazepines **24**

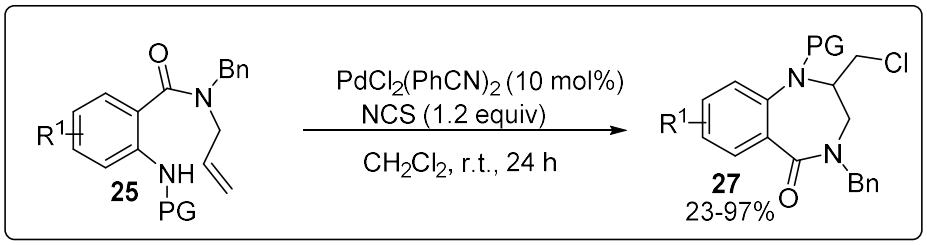
Manick *et al.* [11] demonstrated a palladium-catalyzed aminoacetoxylation to furnish 1,4-benzodiazepinones **26** through the bis-heterofunctionalization of alkenes via *7-exo-trig* ring-closure (**Scheme 3**). A plausible reaction mechanism has been proposed to explain the product formation. First, aminopalladation of the alkene moiety of substrate **25** followed by $PhI(OAc)_2$ mediated oxidation [i.e., Pd(II) to Pd(IV)] of the resulting intermediate **I** generates a transient

organopalladium(IV) complex **II** which upon reductive elimination furnishes the product **26** and regenerates the Pd(II) catalyst as depicted in **Scheme 3**.



Scheme 3: Synthesis of 1,4-benzodiazepines **26** with a plausible reaction mechanism

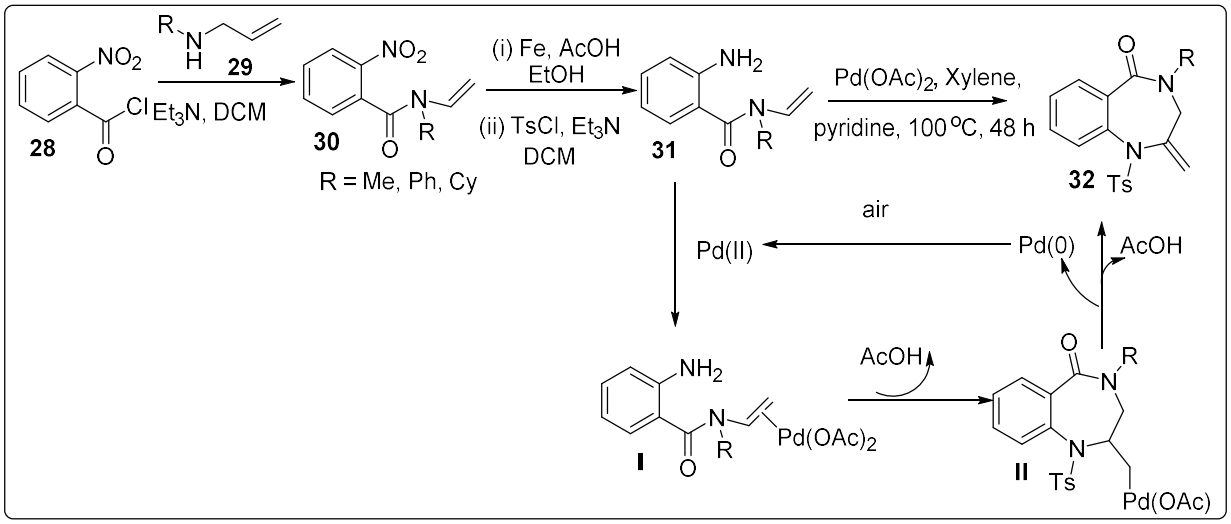
Manick *et al.* [10c] described a modified method for the general synthesis of 1,4-benzodiazepinones **27** by using almost same starting materials (i.e.; **25**) via palladium-catalyzed amino- and oxychlorination process as shown in **Scheme 4**. In that case, NCS is used as an oxidant (**Scheme 4**) and the reaction pathway is believed to be very close to previous one (**Scheme 3**).



Scheme 4: Synthesis of 1,4-benzodiazepines **27**

Beccalli *et al.*[10e] described a regio-selective synthesis of 1,4-benzodiazepin-5-ones **32** by palladium-catalyzed intramolecular amination of tosylated *N*-allyl-anthranilamide **31** (**Scheme 5**). Firstly, a base promoted coupling of **28** with allyl amines **29** afforded *o*-nitrobenzamides **30**. Then, subsequent reduction of the nitro group of intermediate **30** followed by N-tosylation of the

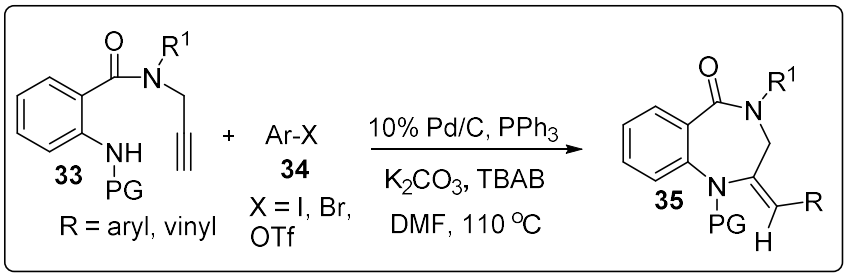
resulting compound delivered the product **31** which has been used as a substrate in subsequent palladium-catalyzed reaction (**Scheme 5**). However, Pd(II)-calatyzed reaction of **31** in the presence of air generated the desired products **32**. The necessity of the use of a base and tosylation of the the amino group (of **31**) were proven to be a pre-requisite for this cyclization. Mechanistically, an aminopalladation of intermediate **I** followed by reductive elimination of palladium from intermediate **II** delivers product **32** and Pd(0). The air played a crucial role for the oxidation of the in situ generated Pd(0) into Pd(II) which essentially enters into the catalytic cycle.



Scheme 5: Synthesis of 1,4-benzodiazepin-5-ones **32** with a plausible reaction mechanism

1.1.2.2 Synthetic pathways for the synthesis of 1,4-benzodiazepin-5-ones via intermolecular reactions of acetylenic substrates:

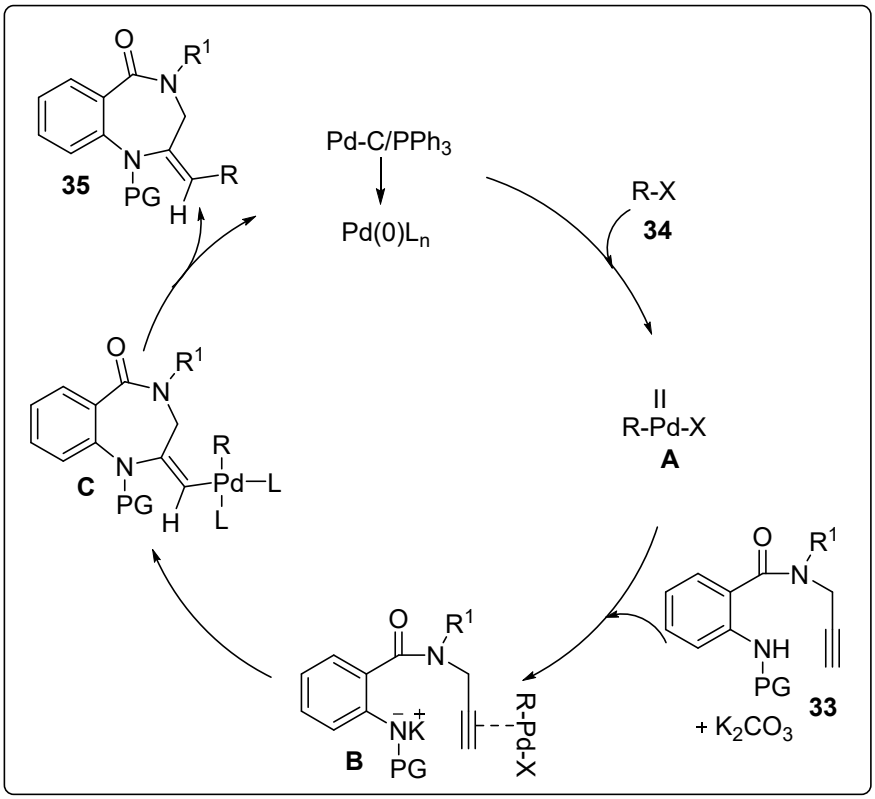
Chowdhury *et al.*[6c] developed an efficient and straightforword approach for the stereoselective synthesis of 1,4-benzodiazepin-5-ones **35** through palladium/charcoal-catalyzed



Scheme 6: Stereoselective synthesis of 1,4-benzodiazepin-5-ones **35**

reaction conditions (**Scheme 6**).

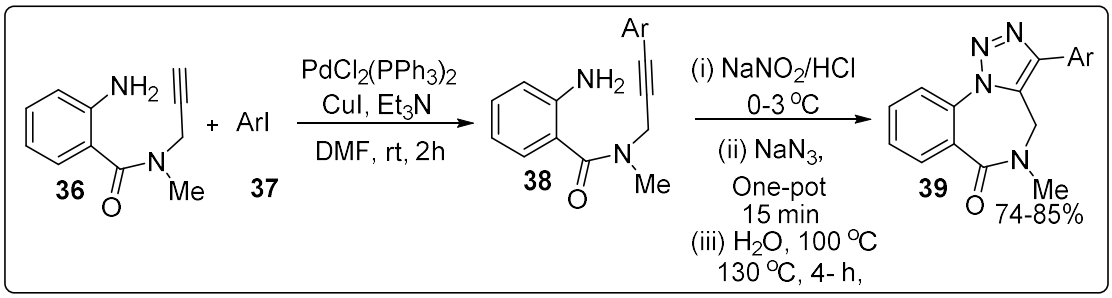
A plausable reaction mechanism is proposed to explain the formation of products **35**. Initially, $Pd(0)L_n$ complex formed *in situ* by the leaching of palladium from the Pd/C surface into the solution where it interact with phosphine ligand (**Scheme 7**). Oxidative addition of aryl(vinyl) halide/triflate **34** to Pd(0) generates RPd(II)X (**A**). Intermediate **A** activates the triple bond of substrate **33** triggering an intramolecular nucleophilic attack by the nitrogen atom of the NTs group of intermediate **B** via *trans*-aminopalladium pathway to generate the intermediate **C**. Then, intermediate **C** would undergoes reductive elimination furnishing the product **35** and Pd(0).



Scheme 7: A plausable reaction mechanism for the stereoselective synthesis of 1,4-benzodiazepines **35**

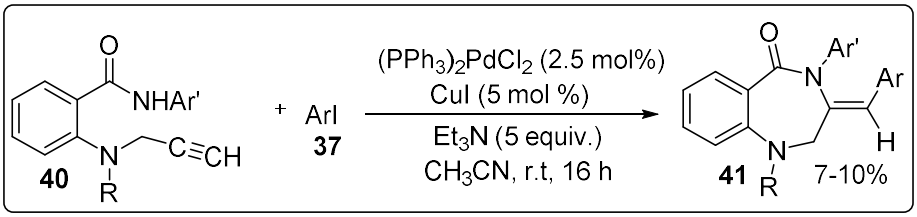
Chowdhury *et al.* [6d] described a convenient and practical approach for the general synthesis of 1,4-benzodiazepines **39** with excellent yields 74-85% (**Scheme 8**). Towards the goal, a *Sonogashira coupling* reaction between 2-amino-*N*-methyl-*N*-(prop-2-ynyl)benzamide **36** and aryl iodide **37** affords the aryl-substituted internal alkyne **38** which then undergoes successive

reactions comprising diazotization, azidation and cycloaddition under one-pot to deliver the product **39** in very good yields.



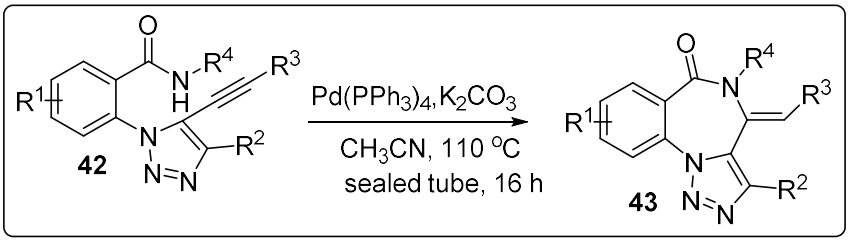
Scheme 8: Synthesis of 1,2,3-triazolo[1,5-*a*][1,4]-benzodiazepin-6-ones **39**

Kundu *et al.*[12] demonstrated a general and highly regio- and stereo-selective general synthesis of benzodiazepinones **41** via palladium (II)-catalysed reaction albeit in poor yield (7-10%). Both the palladium catalyst and cuprous iodide might play an important role for the C-arylation of the terminal alkynes (**Scheme 9**).



Scheme 9: Synthesis of 1,4- benzodiazepinones **15**

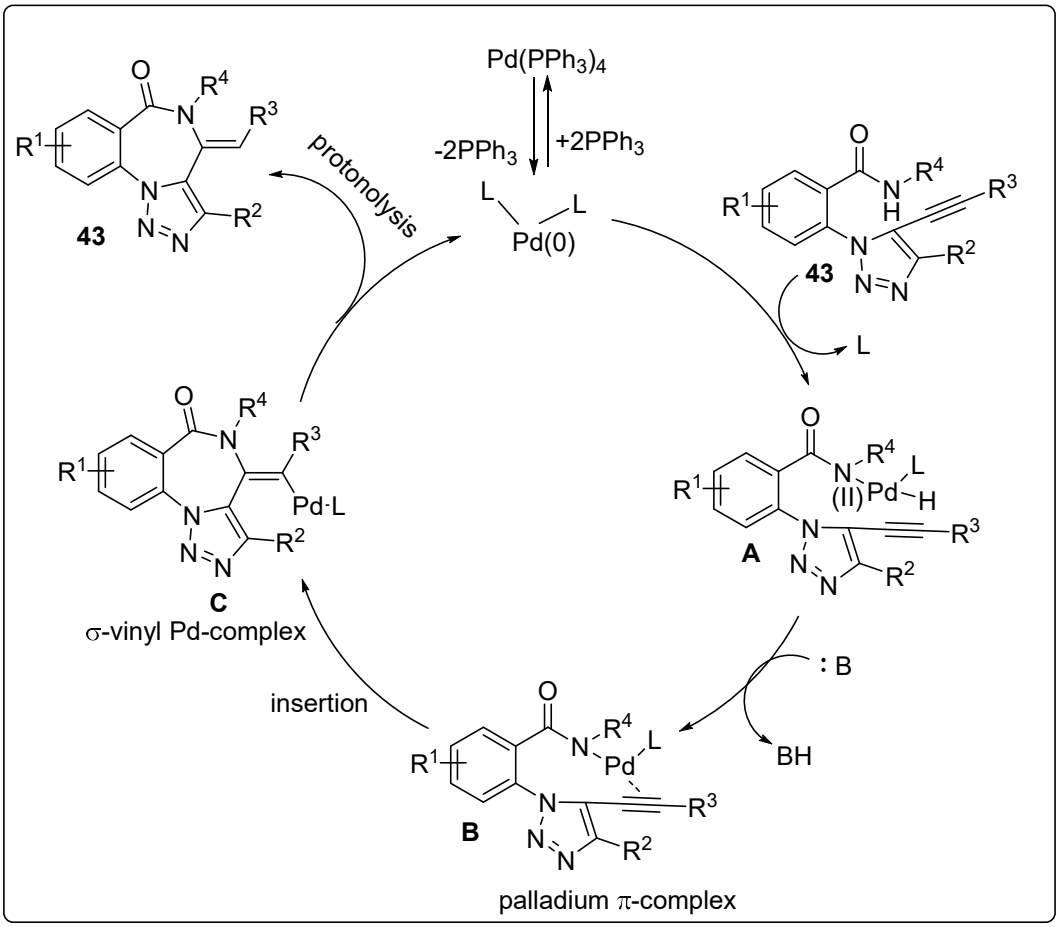
Chen *et al.*[13] demonstrated palladium catalyzed chemo- and regio-selective intramolecular cycloamidation of triazol-1-ylbenzamides **42** for the generation of substituted benzotriazlolodiazepin-7-ones **43** via 7-*exo-dig* ring closer (**Scheme 10**).



Scheme 10: Synthesis of 1,4-benzodiazepines **43**

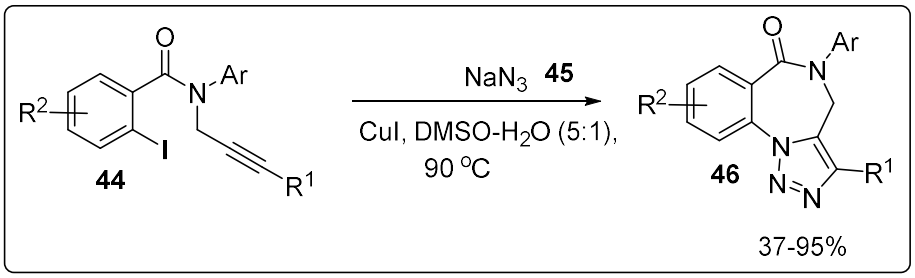
A Plausable reaction mechanism for the synthesis of benzotriazlolodiazepin-7-ones **43** is discussed below (**Scheme 11**). Initially, Pd(0)L_2 activates the -NH group of amide moiety of

substrate **43** to form the intermediate **A** (**Scheme 11**). Then, K_2CO_3 abstract the proton and subsequent coordination of palladium with alkyne moiety resulting in palladium π-complex **B**. Next, palladium complex **B** undergoes regioselective intramolecular insertion onto C-C triple bond resulting in an intermediate **C**. Finally, protonolysis of the C-Pd bond of species **C** generates product **43**.



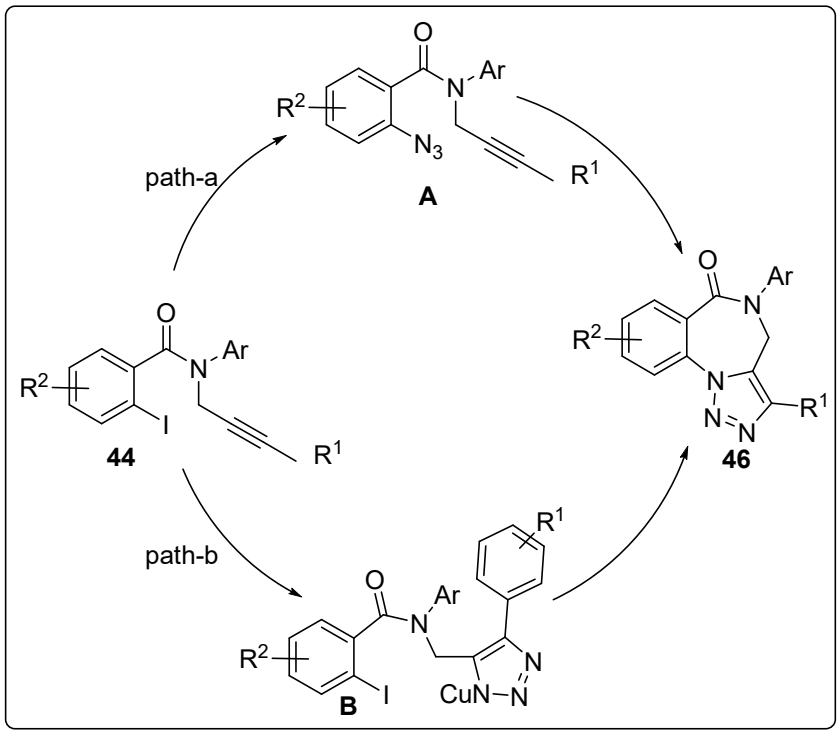
Scheme 11: A plausable reaction mechanism for synthesis of benzotriazlolodiazepin-7-ones **43**

Chen *et al.*[14] reported an efficient and versatile method for the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]-benzodiazepin-6(5*H*)-ones **46** via copper-catalyzed tandem reactions between 2-iodobenzamides **44** and sodium azide **45** (**Scheme 12**).



Scheme 12: Synthesis of triazolo-1,4-benzodiazepines **46**

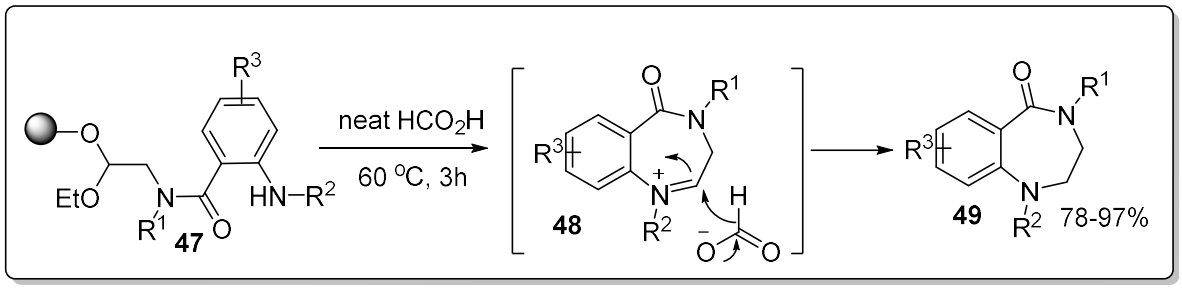
Two plausible mechanistic pathways were considered for the generation of product **46**. The **path-a** involves copper-catalyzed *Ullmann-type coupling* to form intermediate **A** that undergoes subsequent intramolecular azide-alkyne cycloaddition and generates compound **46**. Whereas the **path-b** undergoes initial formation of 1,2,3-triazole as shown in intermediate **B** which upon intramolecular *Ullmann-type coupling* affords the compound **46**.



Scheme 13: A plausible reaction mechanism for the synthesis of triazolo-1,4-benzodiazepines **46**

1.1.2.3 Solid-phase synthesis of 1,4-benzodiazepin-5-ones:

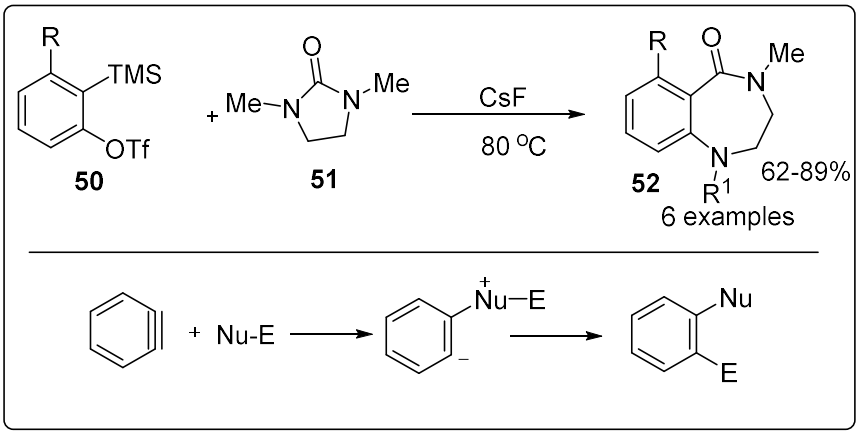
Lee *et al.*[9b] demonstrated a novel and efficient strategy for the synthesis of privileged tetrahydro-1,4-benzodiazepin-5-ones **49** in neat formic acid at 60 ^{o}C with excellent yields (78-97%). This synthetic pathway was established by adopting the *Leuckart-Wallach* (LW) reaction via solid-phase synthesis. *Leuckart-Wallach* (LW) reaction is attractive in synthetic chemistry because ketones or aldehydes can be transformed directly to corresponding primary or secondary amines without isolation of imine intermediate. The reaction involved sequiential cyclic iminium formation and hydride transfer under an acidolytic cleavage conditions that generates a saturated benzodiazepine **49** ring.



Scheme 14: Synthesis of 1,4-benzodiazepines **49**

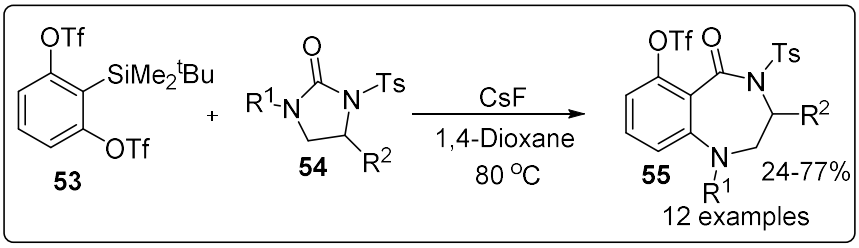
1.1.2.4 Synthetic pathway for the synthesis of 1,4-benzodiazepin-5-ones via benzyne-intermediate:

Yoshida *et al.* [9a] reported an unique and straightforward method for the general synthesis of benzodiazepin-5-ones **52** by using simple substrate 1,3-dimethyl-2-imidazolidinone (DMI) **51** and substituted 2-(trimethylsilyl)phenyl triflate **50** (**Scheme 15**). The attractive view of this reaction is that insertion of an aryne into a single bond between a nucleophile and electrophile (Nu-E).



Scheme 15: Synthesis of 1,4-benzodiazepin-5-ones **52** with a plausible mechanism

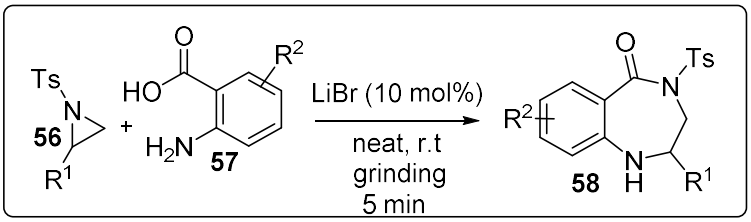
Kaneko *et al.*[9c] demonstrated an efficient and straightforward method for the general synthesis of 1,4-benzodiazepin-5-ones **55** derivatives (**Scheme 16**) through the reaction of various 2-(trimethylsilyl)phenyl triflates **53** with *N*-(*p*-toluenesulfonyl)imidazolidin-*2*-ones **54** via a benzyne intermediate. This method is almost similar to previous one (**Scheme15**).



Scheme 16: Synthesis of 1,4-benzodiazepin-5-ones **55**

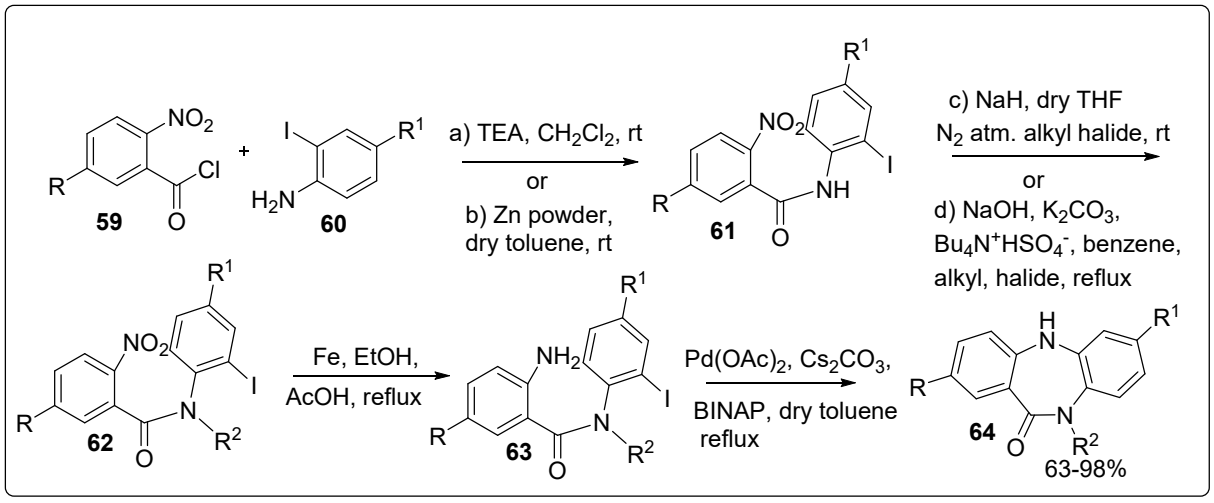
1.1.2.5 Some miscellaneous reactions for the synthesis of 1,4-benzodiazepin-5-one:

Singh *et al.* [15] reported a grinding-induced, atom-economic, rapid, efficient, one-pot protocol for the synthesis of pharmaceutically relevant benzo-1,4-diazepin-5-ones **58** with high regio-selectivity and excellent yield (72-91%) (**Scheme 17**). In presence of mild catalyst (i.e., LiBr), this reaction undergoes successive ring-opening and ring-closure cascade reactions of aziridines **56** and anthranilic acids **57** by grinding the neat reactants at room temperature. The hallmarks of this reaction are atom economic recyclable catalyst and the formation of water as the only product.



Scheme 17: Synthesis of benzo-1,4-diazepin-5-ones **58**

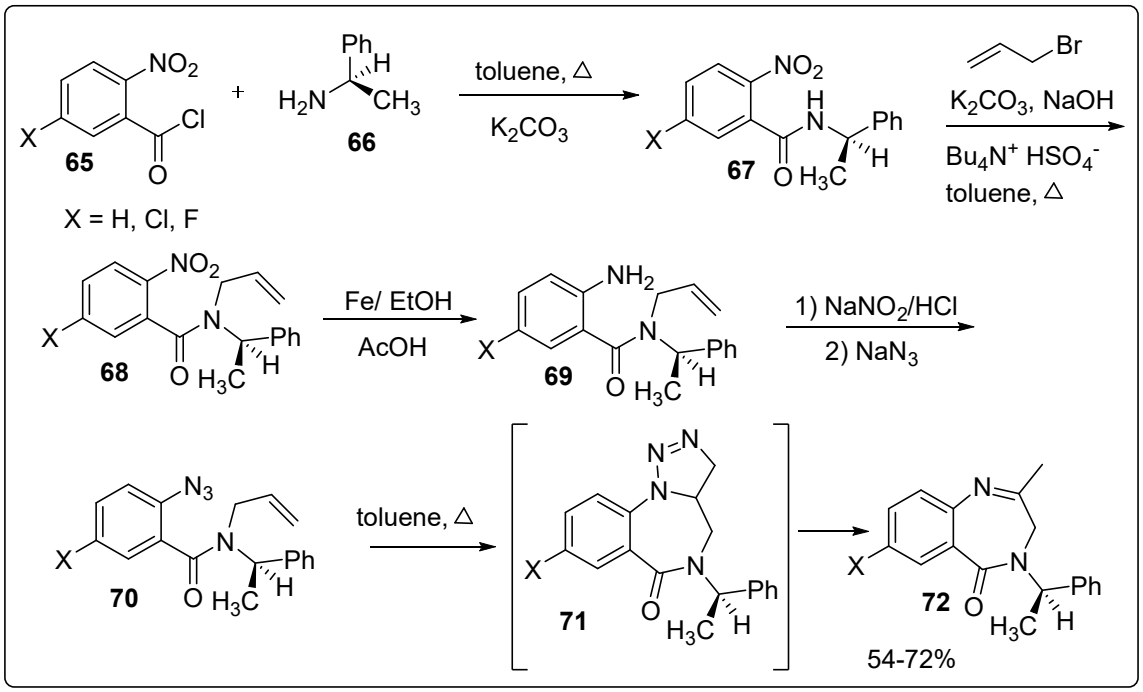
Beccalli *et al.*[16] reported an intramolecular amination approach for the synthesis of dibenzo[*b*,*e*][*1*,*4*]diazepines **64** via palladium-catalyzed reaction conditions (**Scheme 18**). Firstly, compound **61** could easily be achieved by using classical method starting from 2-nitrobenzoyl chloride **59** and 2-iodoaniline **60**. The resulting intermediate amide **61** underwent N-alkylation after a base treatment (NaH or NaOH) followed by reduction of the $-NO_2$ group of intermediate **62** to generate the amine product **63** (**Scheme 18**). The intramolecular amination reaction, i.e., *Buchwald-Hartwig reaction,* between amino and iodo group takes place via Pd-catalyzed C-N bond formation furnishing the desired products **64** with 63-98% yields.



Scheme 18: Synthesis of 1,4-benzodiazepines **64**

Beccalli and co-worker[17] demonstrated diastereoselective synthesis of enantiopure (αR)-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones **72** *via* intramolecular azide cycloaddition followed by stereoselective reduction of a bicyclic ketamine (**Scheme 19**). Compound **67** was synthesized by the base-induced reaction between amine **66** and acid chloride **65**. Next, allylation of the product **67** followed by reduction of the nitro group of intermediate **68** generated the amine product **69**. Next, diazotization of **69** carried out using sodium nitrite

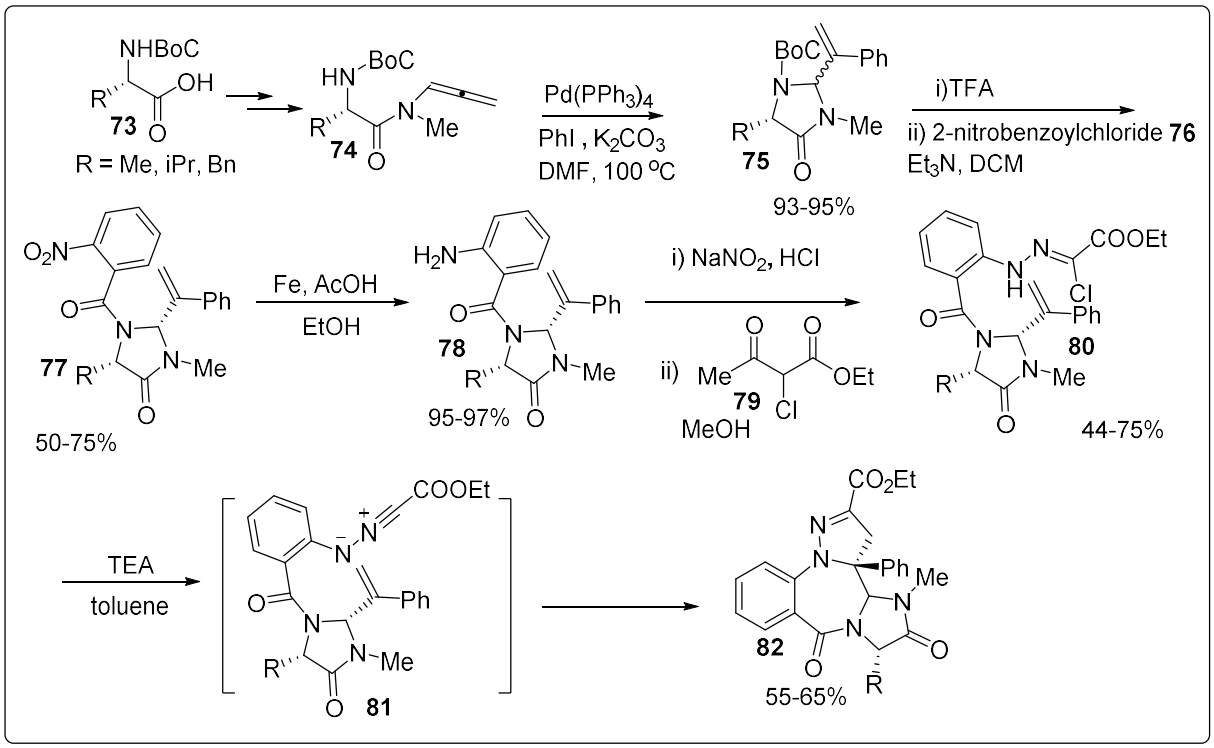
followed by treatment with sodium azide and subsequent reflux of a solution of the azide compound **70** in toluene afforded the product **72** through a transient bicyclic ketamine **71** which undergoes extrusion of nitrogen at elevated temperature.



Scheme 19: Synthesis of 1,4-benzodiazepines **72**

Basalo and coworkers [18] demonstrated a convenient method for the preparation of tetracyclic imidazo[2,1-*c*]pyrazolo[1,5-*a*][1,4]benzodiazepine-4,8-diones **82** using an intramolecular 1,3-cycloaddition between nitrilimine and vinyl groups (of intermediate **81**) as depicted in **Scheme 20**. Initially, an amino-allenylamide **74**, synthesized from N-protected amino acid **73**, was subjected to palladium-catalyzed heteroannulation to furnish 2-vinylimidazolidinone **75**. Importantly, the imidazolidinone **75** could be used as a building block for the construction of substrate **80** which is capable to undergo intramolecular 1,3-dipolar cycloaddition between nitrilimine moiety with ethylenic C-C double bond acting as dipolarophile. Toward this objective, BoC-deprotection of intermediate **75** followed by amidation using 2-nitrobenzoyl chloride resulted in the intermediate **77**. Next, the reduction of the nitro group of **77** furnished the amine compound **78**. These amine **78** then undergoes diazotization and subsequent *japp-klingemann reaction* [coupling with ethyl 2-chloroacetoacetate **79**] affording compound **80**, a

potential precursor of the transient nitrilimine species **81**. Finally, upon a base (Et_3N) of intermediate **80** led to the generation of the desired product **82** as shown in **Scheme 20**.



Scheme 20: Synthesis of 1,4-benzodiazepines **82**

1.1.3. Importance of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides

In addition to 1,4-benzodiazepines, sultams (i.e., cyclic sulphonamides) display activities against a wide variety of biological targets.[4a,b] Benzo[*f*][1,2,5]thiadiazepine-1, 1-dioxides, a subclass of sultams, have emerged as important pharmacophores with potential biological activities. The significance of benzo[*f*][1,2,5]thiadiazepine-1, 1-dioxides in medicinal chemistry and material sciences is described briefly below.

1.1.3.1 Importance of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides in medicinal chemistry:

Although compounds having core structure of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide **2** scaffold have been rarely studied, their antimicrobial, antifungal, anti-inflammatory, antiviral, antiarrhythmic, anti-HIV and anticancer activity make these molecules attractive for medicinal purposes. For example, compound **83** have shown pronounced antiarrhythmic activity[19], notably,

sudden cardiac death is caused from ventricular arrhythmia. While compound **84** have been clinically used as AIDS therapeutic[20] and endowed with anti-HIV activity even at low micromolar concentration. Besides, pyrrolo[1.2-*b*][1,2,5]benzothiadiazepine-5,5-dioxides (PBTDs) **85** and **86** induced apoptosis in human BCR-ABL-expressing leukemia cells [21] and they have been used as a valid candidate for the treatment of chronic myelogenous leukemia (CML)[23b] and have shown anti-cancer activity.

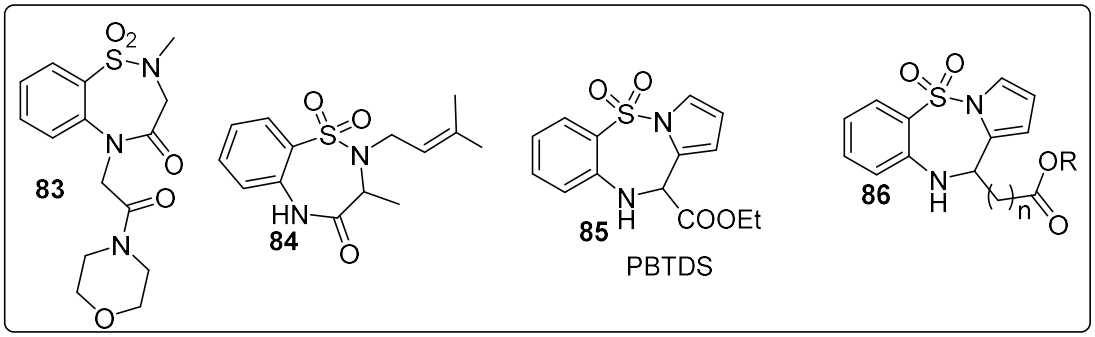


Figure 4: Few bioactive benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides

1.1.3.2 Importance of benzo[*f*][1,2,5]thiadiazepine 1,1-dioxides in material sciences :

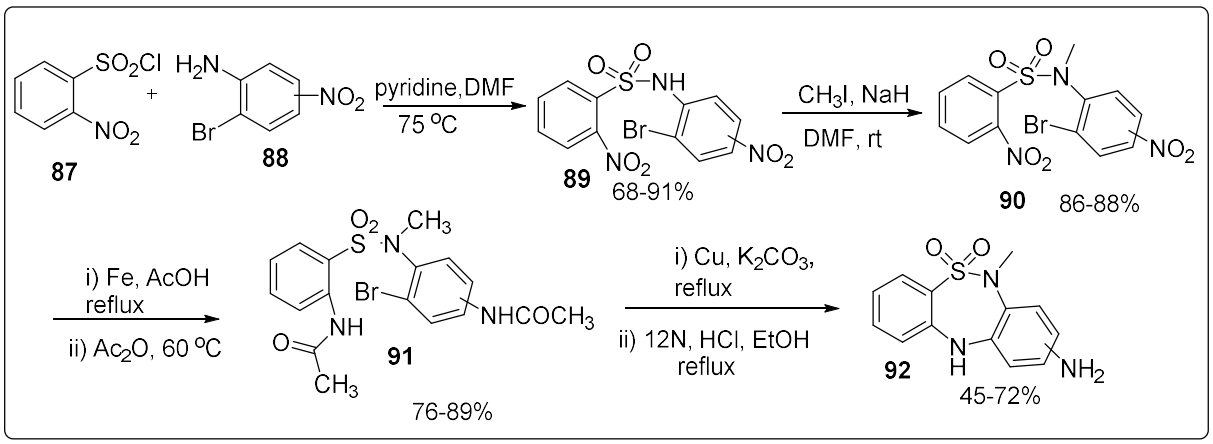
Benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **2** have been less explored in the material sciences as compared to their applications in medicinal chemistry. Nevertheless, benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **2** possess good electron-donating and -accepting abilities making them potentially useful in organic electronics and optoelectronic devices such as organic light-emitting diodes (OLEDs)[5a], organic field-effect transistors (OFETs) etc. In addition, they can also act as electron donors or acceptors[5b], enabling their use in energy storage systems, such as redox flow batteries or super capacitors although their uses are comparatively limited.

1.1.4. Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides:

Due to the important applications of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides in different fields, substantial efforts were devoted for their synthesis. However, only few reports [22] have been appeared underlining the requirement of more straightforward and practical methods for their general synthesis. Few of them are discussed below.

1.1.4.1 Synthetic pathways for the synthesis of 1,2,5-benzothiadiazepin-1,1-dioxides by using 2-nitrosulfonamide or their analog:

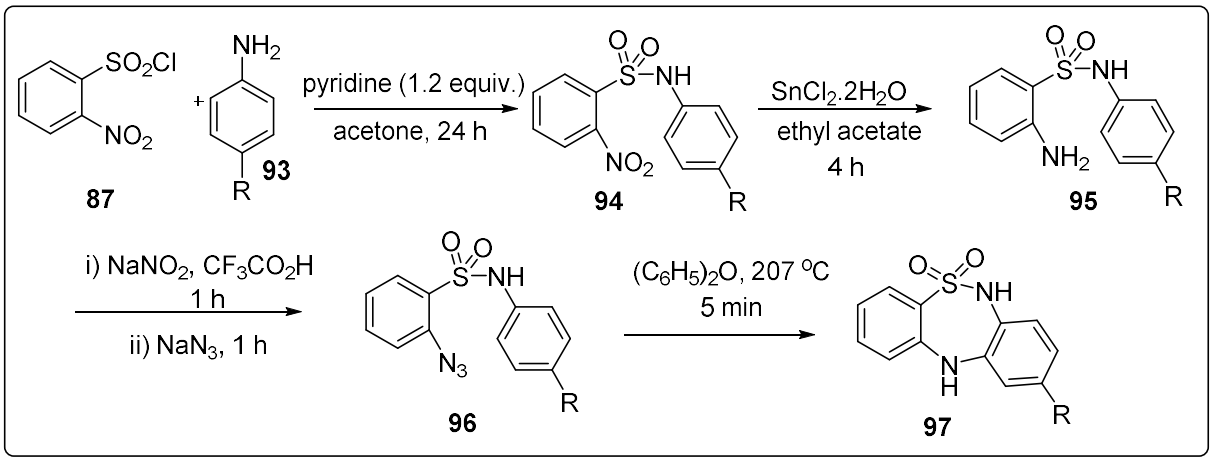
Lebegue and coworkers [22d] described multi-step pathway for the general synthesis of substituted thiadiazepinedioxides **92** (**Scheme 21**) by condensation reaction of commercially available 2-nitrobenzenesulfonyl chloride **87** and aniline derivative **88** under basic conditions to generate substrate **89** as shown in **Scheme 21**. Next, methylation of sulphonamide moiety of **89** generates the intermediate compound **90**. Reduction of nitro group of **90** with Fe/AcOH and followed by acetylation led to the generation of compound **91**. Finally, a copper mediated intramolecular cyclization of intermediate **91** adopting the *Goldberg's method*, followed by deprotection of the acetyl moiety of the resulting compound using 12N HCl led to the generation of thiadiazepinedioxides **92.**



Scheme 21: Synthesis of thiadiazepinedioxides **92**

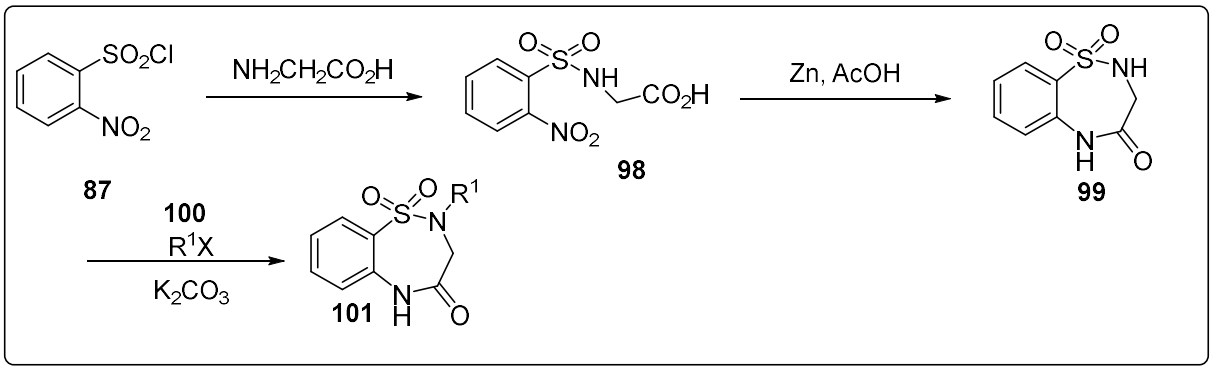
Ramirez-Martinez and coworkers [23] reported a general synthetic pathway for the formation of dibenzo[*c*,*f*][1,2,5]thiadiazepines **97** (**Scheme 22**) by using commercially available 2-nitrobenzenesulfonyl chloride **87** and 4-substituted-anilines **93**. The catalytic hydrogenation of the nitro group of 2-nitrosulfonamides **94** after the treatment of tin (I) chloride provided the access to the corresponding 2-azidobenzenesulfonamides **96** which upon diazotization with sodium nitrite in trifluoroacetic acid followed by azidation of the resulting diazo salt resulted in

the intermediate **96**. Finally, an intramolecular cyclization of **96** via the formation of nitrine intermediate led to the generation of desire product **97.**



Scheme 22: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **97**

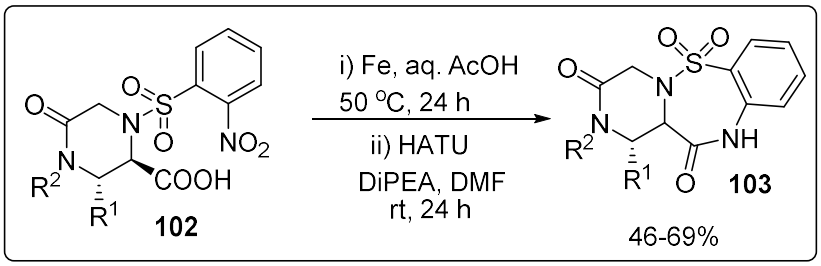
Ogawa *et al.*[22c] reported a simple pathway by using three–step method for the general synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide **100** as shown in **Scheme 23**. The condensation reaction of 2-nitrobenzenesulfonyl chloride **87** with glycine generates compound **99** which upon reductive cyclization (using zinc powder in acetic acid) led to the formation of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide **100** . Next, a chemo-selective alkylation was carried out using alkyl halide in presence of potassium carbonate to get access the targeted product **100**.



Scheme 23: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **101**

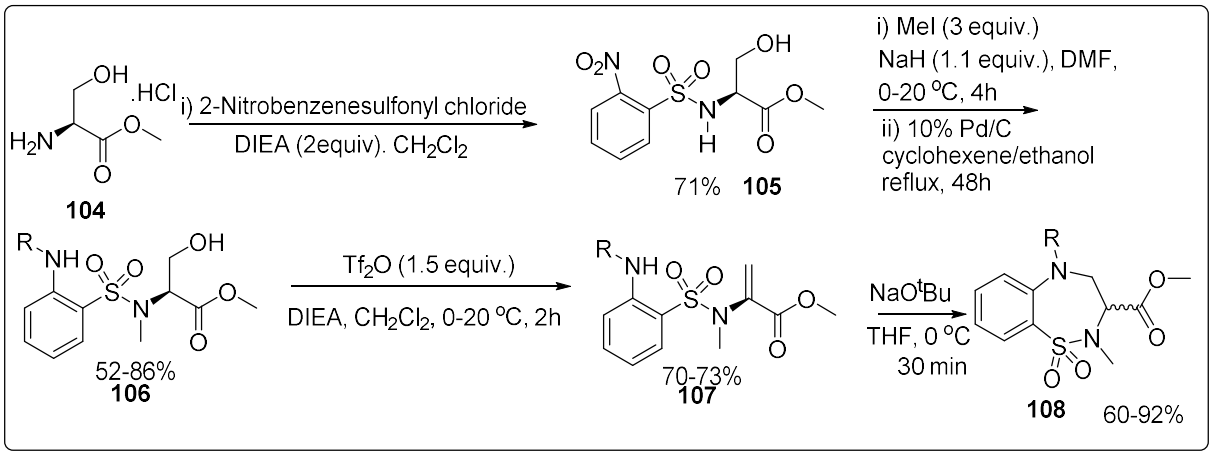
Usmanova *et al.* [22a] developed a simple method through two-step reactions pathway starting from substituted-piperazin-2-ones **102** (**Scheme 24**). After reduction of $–NO_2$ group of

compound **102**, the resulting compound underwent lactamization reaction through the treatment of HATU under basic medium to furnish the cyclized product **103** (**Scheme 24**).



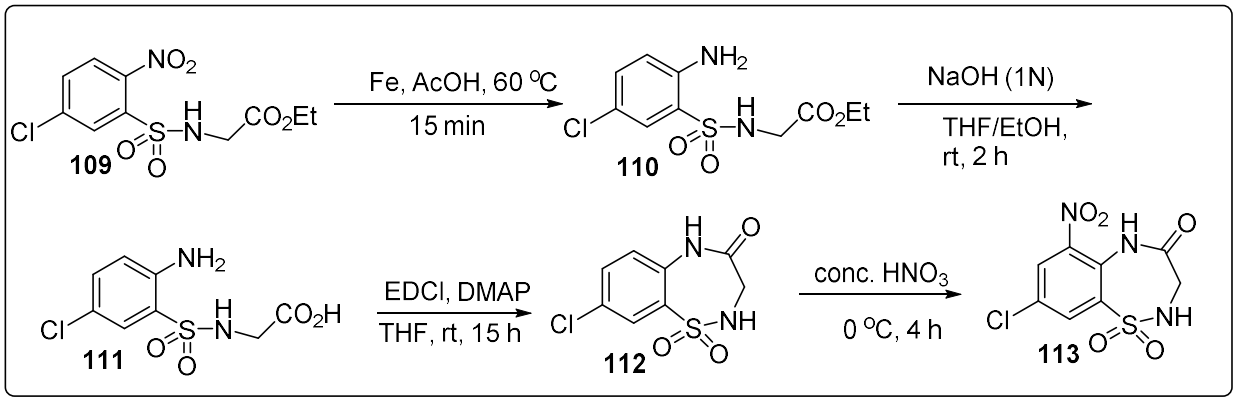
Scheme 24: Synthesis of 1,2,5-benzothiadiazepin-4-one-1,1-dioxides **103**

Kruļle *et al.*[22f] reported an efficient method for the general synthesis of 1,2,5-benzothiadiazepine-1,1-dioxides **108** by using commercially available L-serine methyl ester hydrochloride **104** (**Scheme 25**). The sulphonamide derivative **105** was obtained in a straightforward manner by treatment with L-serine methyl ester hydrochloride **104** with 2-nitrobenzenesulfonyl chloride under basic (DIEA) conditions. Next, alkylation of the intermediate **105** with methyl iodide followed by reduction of the nitro group through hydrogenolysis furnished the intermediate compound **106**. Next, intermediate **106** undergoes base-induced β-elimination in presence of triflic anhydride (Tf_2O) to generate compound **107** which upon base (NaO^tBu) treatment furnished the desired product **108** with good to excellent yields (60-92%).



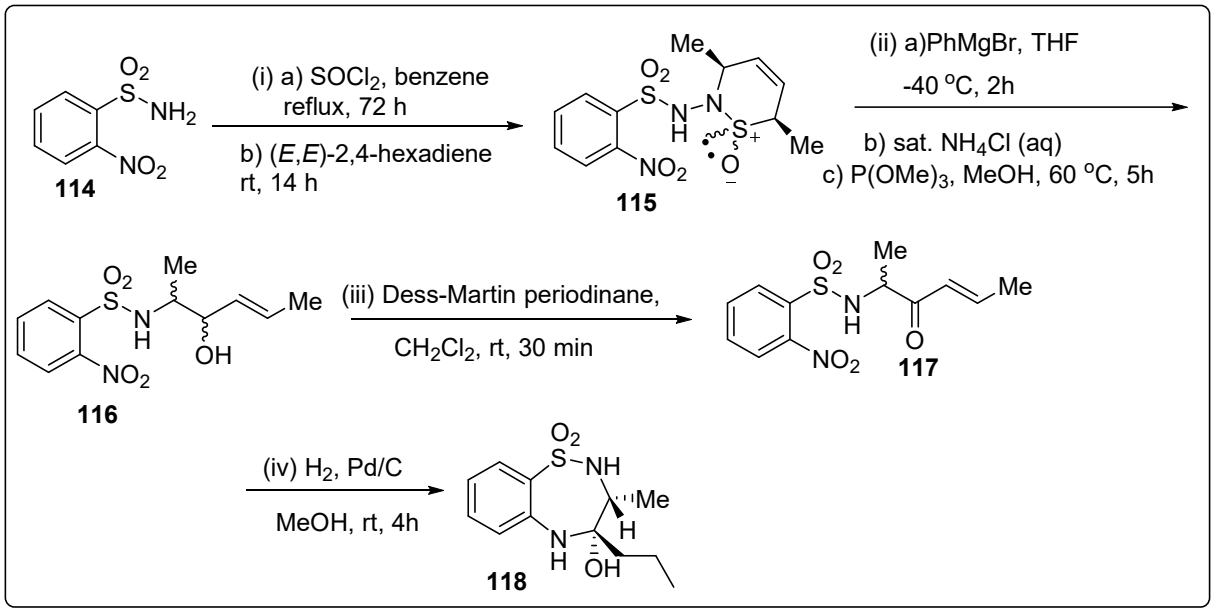
Scheme 25: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **108**

Santo and coworkers[5b] disclosed a novel and efficient method for the general synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **113** as shown in **Scheme 26**. Reduction of nitro group of substrate **109** through the treatment with iron powder with glacial acetic acid afforded the amine derivative **110** which was then hydrolysed with NaOH to generate corresponding acid **111**. However, the compound **111** was cyclized to desire product **112** using the conventional reagents (i.e., EDCl/DMAP). Finally, intermediate **112** was subjected to nitric acid to obtain the targeted product **113**.



Scheme 26: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **113**

Hemming *et al.*[9d] described a straightforward method for the synthesis of 1,2,3,4-tetrahydro-4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxides **118** with 45% yield (**Scheme 27**). Indeed, compound **117**, prepared in few steps starting from *o*-nitrosulfonamide **114,** was subjected to hydrogen pressure in the presence of palladium over activated carbon; interestingly,

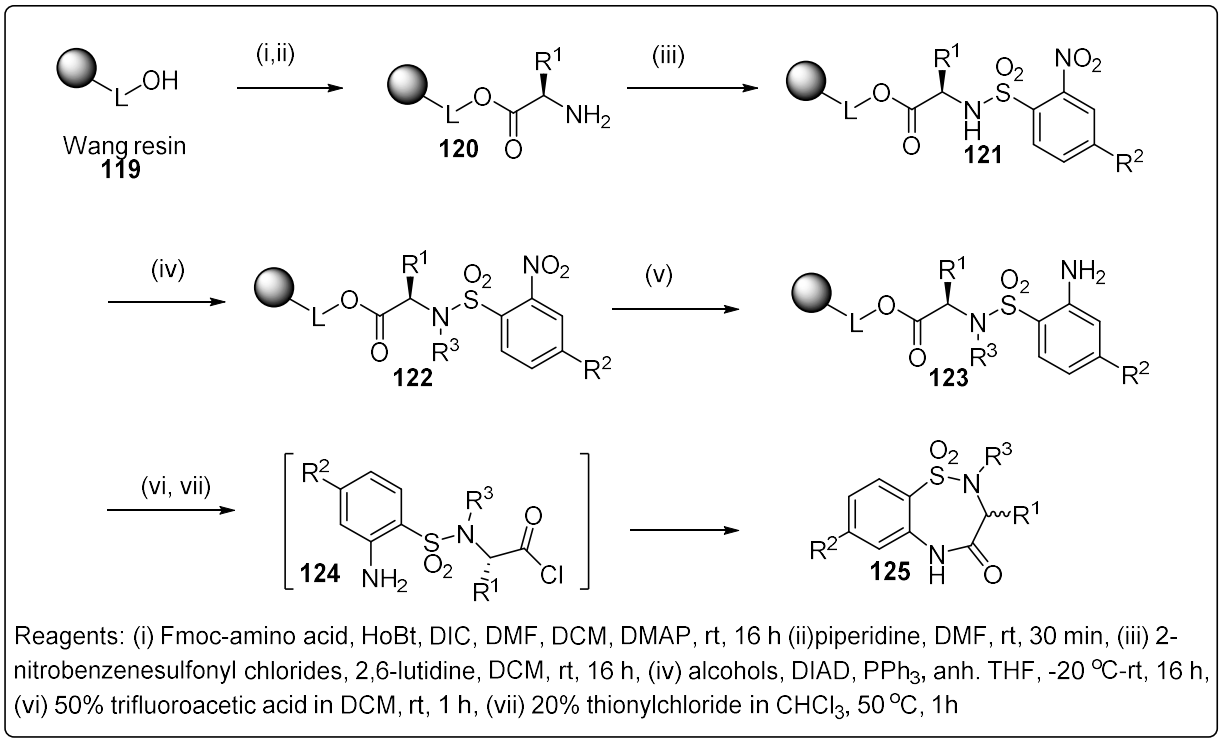


Scheme 27: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **118**

cyclization product 1,2,3,4-tetrahydro-4-hydroxy-1,2,5-benzothiadiazepin-1,1-dioxide **118** was formed within 4 h.

1.1.4.2 Solid-phase synthesis of 1,4-benzodiazepin-5-ones:

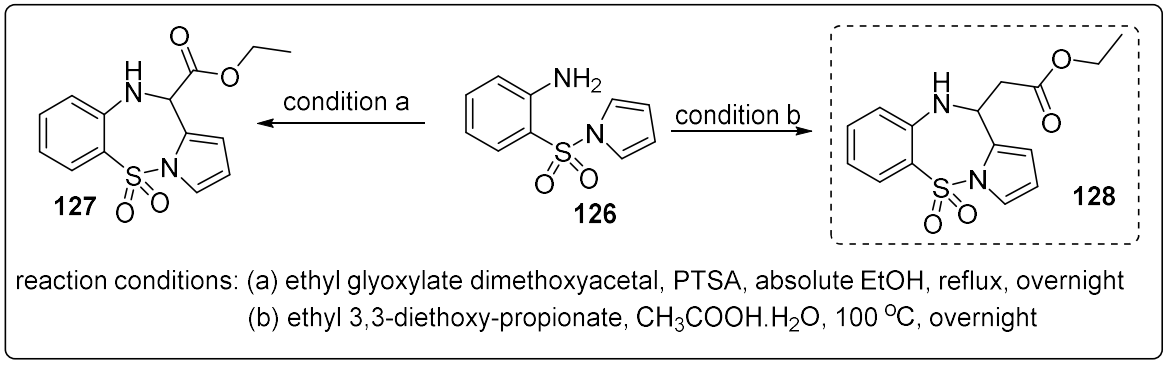
Trapani *et al.*[22e] reported novel and efficient strategy to the synthesis of 2,3-dihydrobenzo[*f*][1,2,5]thiadiazepin-4(5H)-one-1,1-dioxides **125** from polymer-supported α-amino acids as shown in **Scheme 28**. In the first step, Wang resin **119** was acylated with Fmoc-amino acid followed by deprotection with piperidine to obtain the immobilized amino acid **120**. Polymer supported 2-nitrobenzenesulfonamide **121** was obtained after protecting the amino group of **120** with 2-nitrobenzenesulfonyl chloride (NsCl). Next, N-alkylation of the sulfonamide moiety of **121** adopting the *Fukuyama-Mitsunobu* protocol generated the product **122**. Next, reduction of the nitro group of **122** with sodium dithionite resulted in the product **123** which was allowed to react with trifluoroacetic acid (TFA) for the cleavage of the polymer support. Finally, treatment with thionyl chloride triggered the intramolecular cyclization of resulting intermediate leading to the formation of the desire product **125**.



Scheme 28: Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **125**

1.1.4.3 Miscellaneous reaction for the synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides:

Silvestri and coworkers [5a] demonstrated a convenient method for the preparation of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs) by using simple substrate **126**. The compound **127** was prepared through the treatment of **126** with ethyl glyoxylate dimethoxyacetal in the presence of catalytic amount of 4-toluenesulfonic acid (PTSA) in refluxing ethanol (absolute) via *Pictet-Spengler type* reaction as shown in **Scheme 29**. Whereas the compound **128** was obtained by reaction of **126** with ethyl 3,3-diethoxy-propionate in aqueous glacial acetic acid at 100 °C.



Scheme 29: Synthesis of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepines (PBTDs) **128**

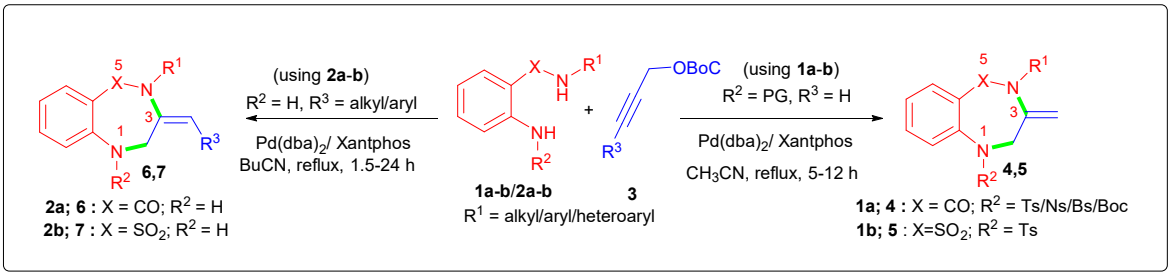
1.1.5 Concluding remarks:

Scrutinity of the aforesaid literature reveals that 1,4-benzodiazepin-5-ones have received immense importance in the field of medicinal chemistry due to their wide range of therapeutic applications, and their occurrence as core structure of many natural products. Nevertheless, though an array of methods for the synthesis of 1,4-benzodiazepin-5-ones (**1)**, fused to other rings employing either traditional or metal catalysed reactions are known; the syntheses of simple 1,4-benzodiazepin-5-ones are limited in numbers underlining the urgency of necessity of newer methods for their synthesis.

On the other hand, benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides (sultams) possess significant pharmacological properties (including anxiolytic, sedative, hypnotic, anticonvulsant, and muscle relaxant properties) and finds applications in the material sciences. However, synthesis of sultams are achieved by using traditional methods in majority of cases. Whereas the synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides employing metal-catalyst are few, calling for straightforward and practical methods for their general synthesis utilizing metal-catalyst.

Part II

Result and Discussion



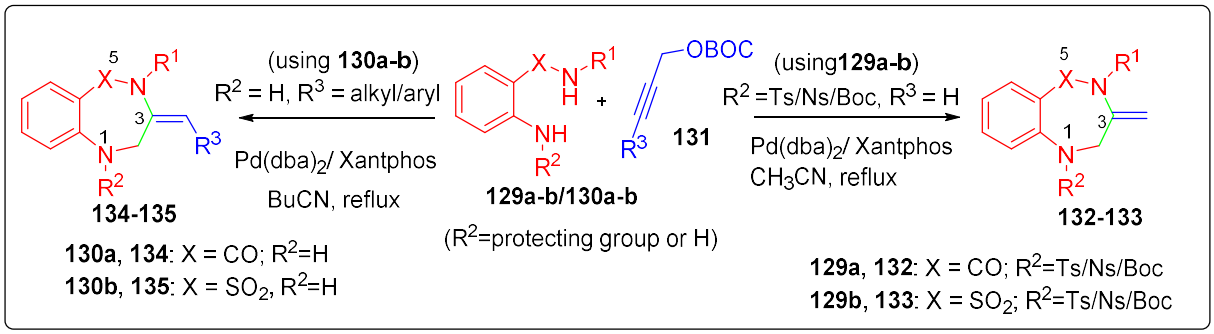
Reference: **Debasmita Mondal**, Gargi Pal and Chinmay Choudhury*; *Chem. Commun.*, **2021**, *57*, 5462–5465.

1.2.1. Introduction

From the literature survey (as discussed in **Part I** of this chapter), 1,4-benzodiazepin-5-ones (BZDs) are considered as privileged heterocycles and this structural moiety have attracted substantial attention as synthetic targets because of their presence as core structure in a large number of biologically active and structurally diverse synthetic compounds including pharmaceuticals and their utilization as a popular template in drug discovery programs. Therefore, development of new cost-economic methods to synthesize BZDs from simple substrate under one-pot would be worthwhile.

On the other hand, benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides (sultams) have emerged as important pharmacophores with potential biological activities such as antimicrobial, antibacterial and anti-cancer among others (as discussed in Part I of this chapter)and finds considerable applications in the material sciences. However, most of their syntheses are achieved through multi-step reactions using classical reagents. To our surprise, no metal-catalysed reactions have been reported so far. Therefore, more straightforward and practical methods for their general synthesis particularly the metal-catalyzed reactions carried out under one-pot would be of interest to explore their potential.

In recent years, propargyl carbonates has been widely used[24] as a masked bis-electrophile in palladium-catalyzed reactions leading to the development of elegant methodologies for the synthesis of various heterocycles. In continuation of our work[25] on palladium-catalyzed reactions for the synthesis of different heterocycles of biological and pharmacological interests, we envisioned that simple 2-aminobenzamides or their sulphonamide analogs could be employed as bis-nucleophiles in reactions with propargylic carbonates for the formations of two C-N bonds (i.e, 1,2 and 3,4) in one pot, thereby offering a facile and general synthetic route to 1,4-benzodiaazepine-5-ones or their sulphur analogues. Our concept appeared to be viable upon choosing appropriate palladium catalyst and reaction conditions as described below (**Scheme 30**).

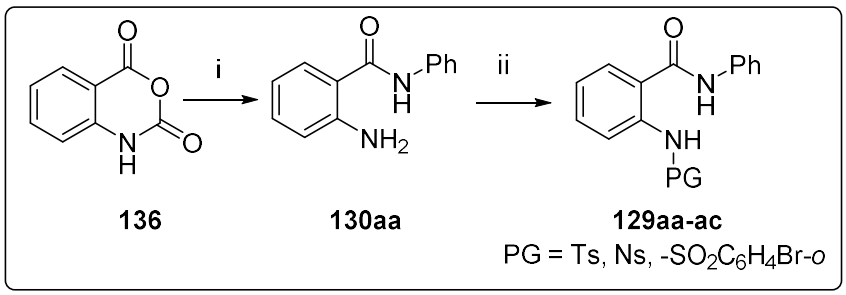


Scheme 30: Pd(0)-catalysed synthesis of 1,4-benzodiazepin-5-ones **132-133** and benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **134-135**

1.2.2. General procedure for the preparation of starting materials 129a:

1.2.2.1 Synthesis of 2-aminobenzenesulphonamide derivatives 129aa-ac[26]:

The requisite starting material **129aa-ac** were prepared through a sequence of reactions starting from commercially available isatoic anhydride **136** as shown in **Scheme 31.** In the first step, isatoic anhydride was allowed to react with aniline under refluxing condition to generate 2-amino benzamide **130aa**. Then, amine (-NH_2) group of newly generated benzamide **130aa** was protected with tosyl/nosyl or brosyl group leading to the formations of *2-aminobenzenesulphonamide derivatives* **129aa-ac**.

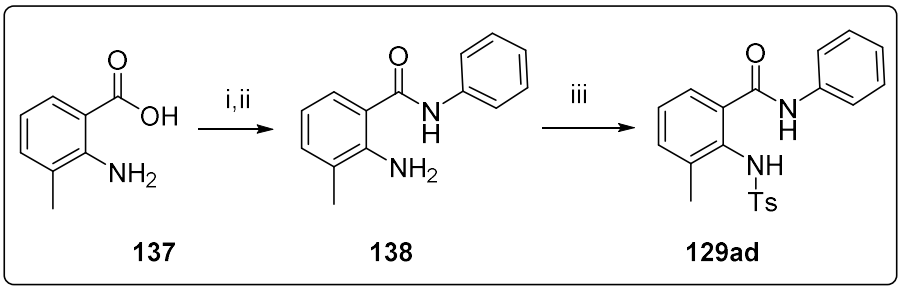


Scheme 31: Synthesis of substrates **129aa-ac**. reagent and conditions: (i) aniline, CH_3CN, reflux, 4 h, 85%; (ii) arylsulphonyl chloride, Py, 0°C-rt, 2-3 h, 88-95%.

1.2.2.2 Preparation of other 3-substituted starting material 129ad[27]

The requisite starting material **129ad** was prepared through a sequence of reactions starting from commercially available 2-amino-3-methylbenzoic acid **137.** In the first step, 2-amino-3-methylbenzoic acid was allowed to react with thionyl chloride under refluxing condition to generate crude acid chloride as yellow oil which was used immediately for the next reaction in which the intermediate 2-amino-3-methylbenzamide **138** was prepared by the treatment of

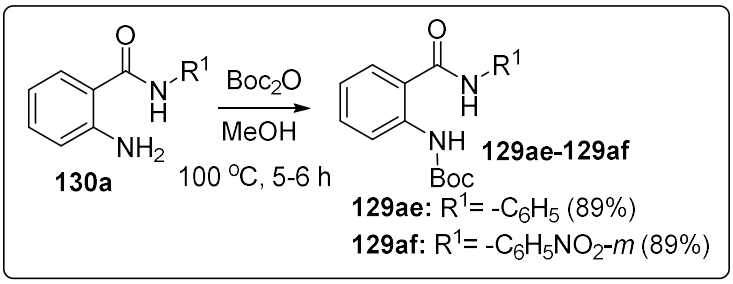
aniline under basic conditions. Finally, amine group of **138** was allowed to protect with *p*-toluenesulphonyl chloride leading to the formations of *2-aminotosyl benzamides* substrates **129ad** as shown in **Scheme 32**.



Scheme 32: Synthesis of substrate **129ad**. reagent and conditions: (i) $SOCl_2$, toluene, reflux, 9 h; (ii) aniline, Et_3N, DCM, 0°C-rt, 5 min; (iii) TsCl, 0°C-rt, 2 h, 92%

1.2.2.3 Preparation of -Boc protected starting material 129ae-af

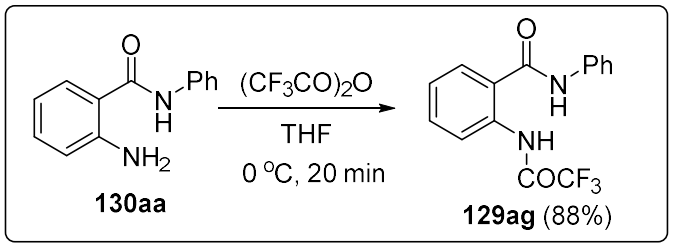
To explore the scope of the reaction, amine group of *N*-substituted-2-aminobenzamide **130a** was protected with di-*tert*-butyl dicarbonate (Boc_2O) to obtain pure *tert*-butyl(2-(arylcarbamoyl)phenyl)carbamate **129ae-af** derivatives as shown in **Scheme 33**.



Scheme 33: Preparation of the Boc-protected substrates **129ae** and **129af**

1.2.2.4 Preparation of $COCF_3$ protected starting material 129ag

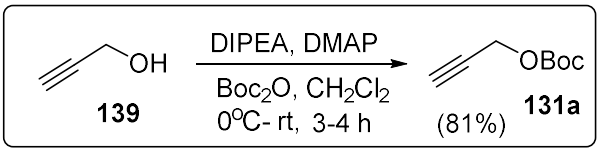
To synthesize *N*-phenyl-2-(2,2,2-trifluoroacetamido)benzamide **129ag**, 2-amino-*N*-phenylbenzamide **130aa** was allowed to treated with trifluoroacetic andydride under ice-cold condition to generate **129ag** as shown in **Scheme 34**.



Scheme 34: Preparation of the $COCF_3$-protected substrate **129ag**

1.2.3 Procedure for the preparation of starting material 131a:

Hydroxy (-OH) group of propargyl alcohol **139** was protected with -Boc after the treatment of DIPEA, DMAP and di-tert-butyl dicarbonate (Boc_2O) as shown in **Scheme 35**.



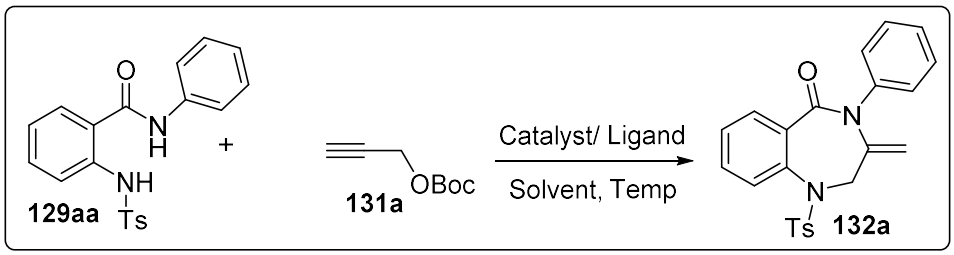
Scheme 35: Synthesis of Boc-protected propargyl alcohol **131a**

1.2.4 Synthesis of 3-methylene-[1,4]benzodiazepin-5-ones 132 through palladium-catalyzed reaction conditions:

1.2.4.1 Optimisation of the reaction condition for the synthesis of of 3-methylene-[1,4]benzodiazepin-5-ones (132)

At the outset, to assess the feasibility of the concept for the synthesis of 1,4-benzodiazepin-5-one (**132a**), we carried out an optimization study for the model reaction between 2-aminotosylbenzamide **129aa** and propargyl carbonate **131a** with variation of the reaction parameters such as palladium catalyst, ligand, solvent, temperature etc. (Table 1). Initially, exposure of the reactants to 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 in refluxing acetonitrile afforded (Table 1, entry 1) the desired 1,4-benzodiazepin-5-one **132a** after 18 h albeit in low yield (17%). To our discomfiture, changing the catalyst [viz., $(PdCl_2(PPh_3)_2]$ and ligand [viz., Xantphos] made the matters worse (entry 2, Table 2). We therefore switched to Pd(0) catalyst. Indeed use of $Pd_2(dba)_3$ provided encouraging result affording **132a** in moderate yield (40%), though use of $Pd_2(dba)_3.CHCl_3$ lowered the yield somewhat (Table 1, entries 3-4).

Table 1: Optimization of the reaction conditions for the synthesis of **132a**[a]



Sl. No.	Catalyst	Ligand	Solvent	Time (hr)	Yields (%)[d]
1	$Pd(OAc)_2$	PPh_3	CH_3CN	18	17
2	$PdCl_2(PPh_3)_2$	Xantphos	CH_3CN	18	15
3	$Pd_2(dba)_3$	Xantphos	CH_3CN	18	40
4	$Pd_2(dba)_3.CHCl_3$	Xantphos	CH_3CN	18	22
5	$Pd(PPh_3)_4$	Xantphos	CH_3CN	18	45
6	$Pd(dba)_2$	Xantphos	CH_3CN	4	92
7	$Pd(dba)_2$	^{t}BuXantphos	CH_3CN	18	30
8	$Pd(dba)_2$	DPEphos	CH_3CN	18	40
9	$Pd(dba)_2$	dppf	CH_3CN	18	35
10	$Pd(dba)_2$	dppe	CH_3CN	18	15
11[b]	$Pd(dba)_2$	Xantphos	DCE	7	89
12[b]	$Pd(dba)_2$	Xantphos	DMSO	18	-
13[b]	$Pd(dba)_2$	Xantphos	Toluene	18	-
14[c]	**$Pd(dba)_2$**	**Xantphos**	**CH_3CN**	**5**	**93**

[a]Reaction conditions: **129aa (**1.0 equiv**), 131a** (1.3 equiv)**,** 10 mol% palladium catalyst (except entry 14), 20 mol% ligand (except entry 14) in 2.0 mL solvent at 85 ^oC (entries 1-10 and 14) or at 100 ^oC (entries 11-13). [b]The reactions were performed at 100 ^oC. [c]The reaction were carried out with 5 mol% $Pd(dba)_2$ and 10 mol% Xantphos.

Employment of $Pd(PPh_3)_4$ marginally improved the yield to 45% (Table 1, entry 5). Pleasingly, the use of $Pd(dba)_2$ together with Xantphos as ligand completed the reaction within 4 h and afforded **132a** with excellent yield (Table 1, entry 6). Thereafter we pursued this reaction using $Pd(dba)_2$ but utilizing different ligands (viz., *t*-butylXantphos/DPEPhos/dppf/dppe) in order to find out better conditions (Table 1, entries 7-10). To our disappointment, these reactions necessitated longer reaction time (18 h) and furnished the product **132a** only in moderate yields (15-40%).

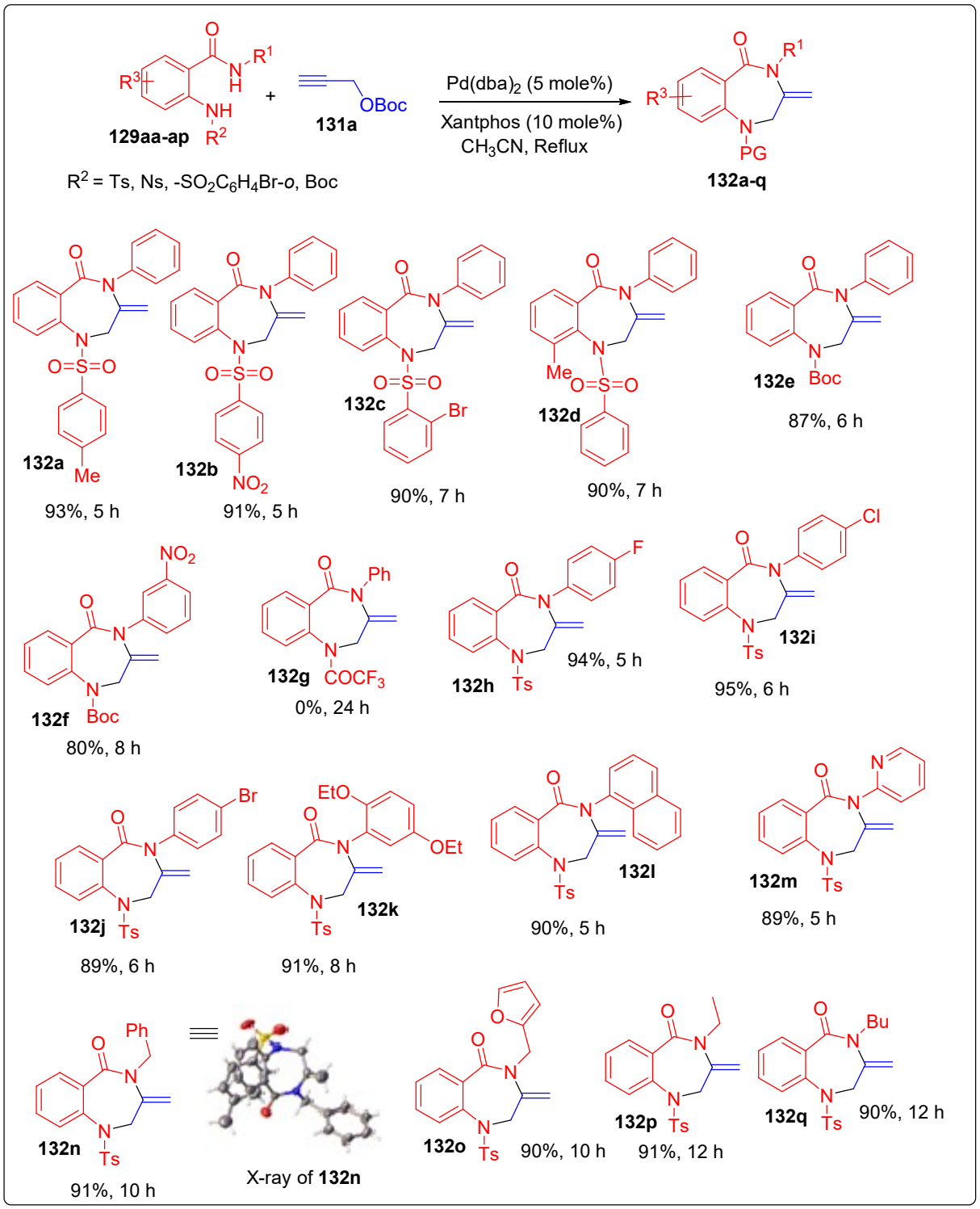
We then carried out this reaction in different solvent systems including both high (i.e., DMSO) and low polar (i.e., toluene) ones. To our surprise, the reaction did not proceed well in these solvent systems (Table 1, entries 12 and 13) though medium polar DCE was found to be better producing **132a** in 7 h with 89% yield (Table 1, entry 11). Next, we decreased the catalyst loading from 10 mol% to 5 mol% but the yield of the product remained the same even after prolonging the reaction time period (Table 1, entry 14 vs. entry 6). We therefore considered conditions used in entry 14 of Table 1 as the preferred one.

1.2.4.2 Exploration and scope of the reaction using different 2-aminotosylbenzamide and tert-butyl propargyl carbonates under optimized reaction conditions:

With the optimized reaction conditions in hand, various bis-nucleophilic benzamides **129aa-ap** were evaluated to determine the capability of cyclocondensation with **131a** (**Table 2**). The aromatic amino group could be protected with N-tosyl or substituted tosyl, with little change in the outcome. Interestingly, replacement of the tosyl group by Boc group also proved to be conducive for this reaction with comparable yield of the product (**132a** vs. **132e**), but a trifluoroacetyl ($COCF_3$) group at the same position made the substrate inert as no formation of any product **132g** was noticed (tlc) and the starting material was recovered.

Regarding substituents on the aromatic rings, the incorporation of an electron-withdrawing group (EWG) like F/Cl/Br or an electron-donating group (EDG) like OEt hardly affected the outcome, delivering the products **132h**–**j** or **132k** with 89–95% yields in almost the same time period (5-8 h). Even replacement of the phenyl ring in the amide moiety with either the bulky naphthyl or a heteroaryl one (i.e., pyridyl) worked smoothly furnishing **132l** (90%) or **132m** (89%) in 5 h. The only noticeable difference noted was if the substituent(s) was located

Table 2: Pd(0)-catalyzed synthesis of 3-methylene-[1,4]benzodiazepin-5-ones 132[a]

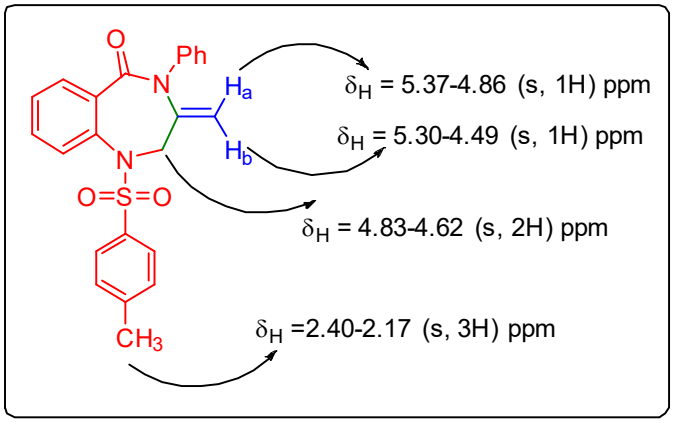


[a]Reaction conditions: A mixture of substrate **129** (1 equiv), **131a** (1.3 equiv), $Pd(dba)_2$ (5 mol%), Xantphos (10 mol%), and CH_3CN (2 ml) were refluxed under argon atmosphere.

ortho to the amide grouping (substrates **129ac**, **129ad**) when the time required was higher (7 h) perhaps to overcome the steric hindrance. Replacement of the amide phenyl with benzyl, furyl, methyl, or alkyl (n-Pr) groups (substrates **129an-129aq**) also merely prolonged the reaction time (10–12 h), the desired products continuing to form in high yields (90–91%).

1.2.4.3 Nature and characterization of products 132

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 ^{o}C) for several months. The structures of the products were unambiguously deduced by spectral (^{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, proton (H_a) attached to the vinylic position appears as singlet at the range of 5.37-4.86 ppm as expected while proton (H_b) appears as singlet at the range of 5.30-4.49 ppm. On the other hand, protons attached to the allylic position appears as singlet at the range of 4.83-4.62 ppm. However, the methyl proton of the tosyl group attached to the nitrogen atom appears as singlet at 2.40-2.17 ppm. Furthermore, ^{13}C-NMR and mass spectra gave additional support in favour of the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **132n.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 5.

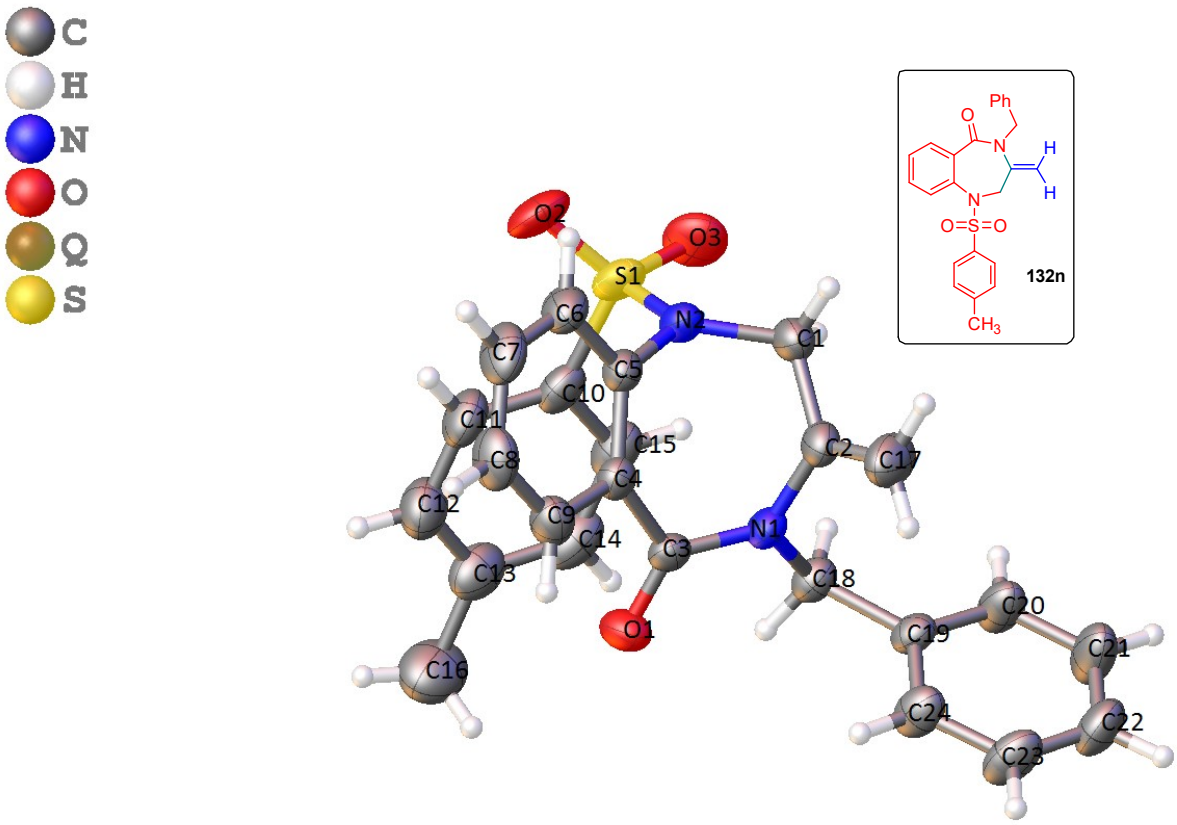


Figure 5. ORTEP diagram (thermal ellipsoid plot) of Product **132n** (drawn at 50% probability level)

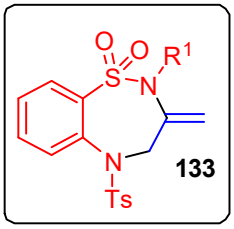
Table 3: Important crystal data of product **132n**

Empirical formula	$C_{24}H_{22}N_2O_3S$
Formula weight	418.49
Temperature	273 K
Wavelength	0.71073
Crystal system	'triclinic'
Space group	'P -1'
Unit cell dimensions	a = 8.130(3) Å α = 82.36(2)
	b = 10.804(6) Å β = 88.815(12)
	c = 12.330(5) Å γ = 80.34(2
Volume	1058.1(8) $Å^3$
Z	2
Density (calculated)	1.245 g/cm^3
Absorption coefficient (Mu)	0.181mm^{-1}
F(000)	440
Theta range for data collection	2.378^0 to 27.243^o
Index ranges	-10<=h<=10, -13<=k<=13, -15<=l<=15
Reflection collected	31258
Independent reflections	4724 [R(int) = 0.0518]
Completeness to theta	99.9 %
Absorption correction	multi-scan
Max. and min. transmission	0.7456 and 0.6875
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4724 /0/ 280
Goodness-of-fit on F^2	0.912
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1193
R indices (all data)	R1 = 0.0626, wR2 = 0.1318
Largest diff. peak and hole	0.268& -0.559e.A^{-3}

The single crystal of compound **132n** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **132n** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2062376.**

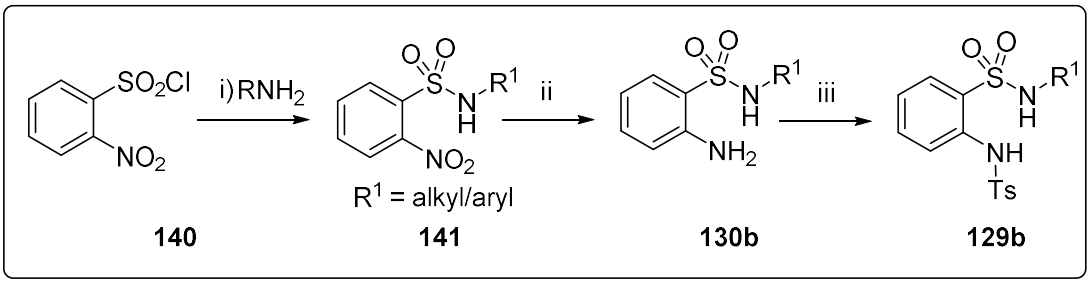
1.2.5. Extension of the methodology for the synthesis of 3-methylene-benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides 133:

Encouraged by the above results, we decided to check the viability of the methodology for a domino synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **133**. In order to explore the capability of this reaction for the formations of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides **133** (the sulphonamide analogues of **132)**, we prepared the requisite starting material **129ba** (R^1 = Ph) in few steps (as shown in **Scheme 36**) and exposed it to the optimized reaction conditions of Table 1.



1.2.6 Preparation of starting materials 129b and 130b[29]:

The requisite sulphonamide substrates **129b** were synthesized in three steps starting from commercially available 2-nitrobenzenesulfonyl chloride **140**. Thus 2-nitrosulphonamide intermediates **141** could easily be achieved upon the treatment of aryl/alkyl amine with 2-nitrobenzenesulfonyl chloride under basic condition. Next, reduction of nitro group of **141** resulted in the formation of substrate **130b** which upon treatment of *p*-toluenesulphonyl chloride under basic condition at 0 °C-r.t led to the formations of sulphonamide substrates **129b**.



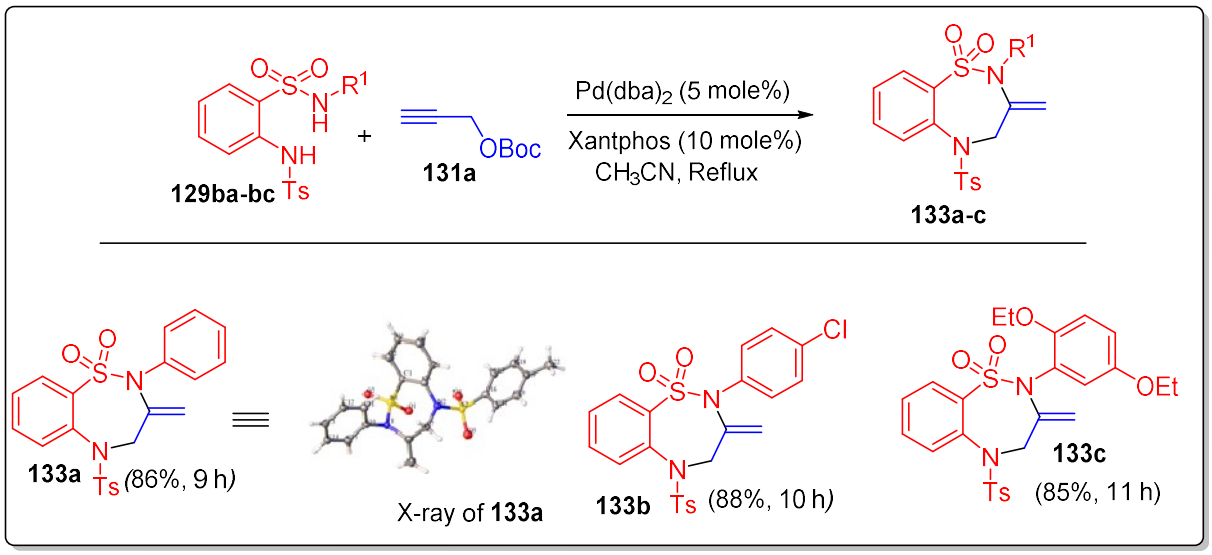
Scheme 36. Synthesis of the sulphonamide substrates **129b**. reagent and conditions: (i) amine (R^1NH_2), Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 80-90%; (ii) Zn, satd. NH_4Cl, MeOH, 0 °C-rt, 2-3 h, 71-82%; (iii) TsCl, Py, 0 °C-rt, 3-4 h, 84-87%.

1.2.7 Synthesis of benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides 133:

In order to explore the capability of this reaction, the starting material **129b** was allowed to react with tert-butyl propargyl carbonates under the optimized reaction conditions of Table 1. Surprisingly, use of the same reaction conditions, optimized previously, on **129b** delivered the desired product **133a** with excellent yield (86%) within 9 h. Therefore, we decided to explore the substrate scope by using same reaction condition (catalyst, ligand, solvent, base and temperature, Table 1, entry 6).

By using the same optimization conditions, the desired product **133a** was formed in 9 h with 86% yield. Incorporation of additional substituents either electron donating (*p*-Cl) or electron withdrawing (*o*,*m*-diethoxy) proved to be compatible, generating the product **133b** or **133c** with comparable yield though with somewhat longer reaction period.

Table 4: Pd(0)-catalyzed synthesis of 3-methylene-benzo[*f*][1,2,5]thiadiazepine-1,1-dioxides 133[a]

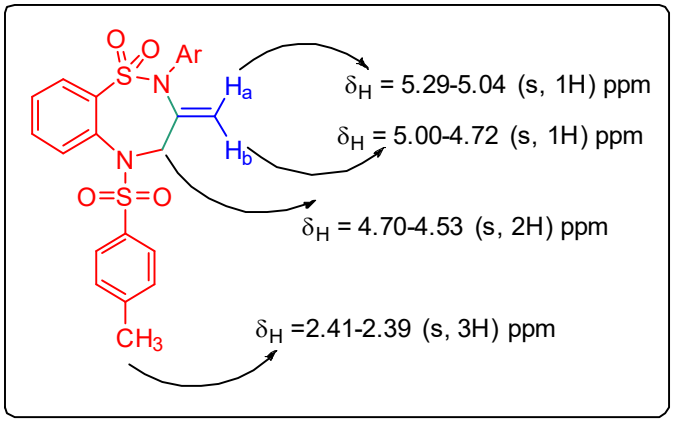


[a]Reaction conditions: A mixture of substrates **129b** (1 equiv), **131a** (1.3 equiv), $Pd(dba)_2$ (5 mol%), Xantphos (10 mol%), and CH_3CN (2 ml) were refluxed under argon atmosphere.

1.2.7.1 Nature and characterization of products 133

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 ^{o}C) for several months. The structures of the products were unambiguously deduced by spectral (^{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, proton (H_a) attached to the vinylic position appears as singlet at the range of 5.29-5.04 ppm as expected. While the other vinylic proton (H_b) appears as singlet at the range of 5.00-4.72 ppm. Whereas, protons attached to the allylic position appears as singlet at the range of 4.70-4.53 ppm. However, the methyl proton of the tosyl group attached to the nitrogen atom appears as singlet at 2.41-2.39 ppm. Furthermore, ^{13}C-NMR and mass spectra gave additional support in the favour the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **133a.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 6.

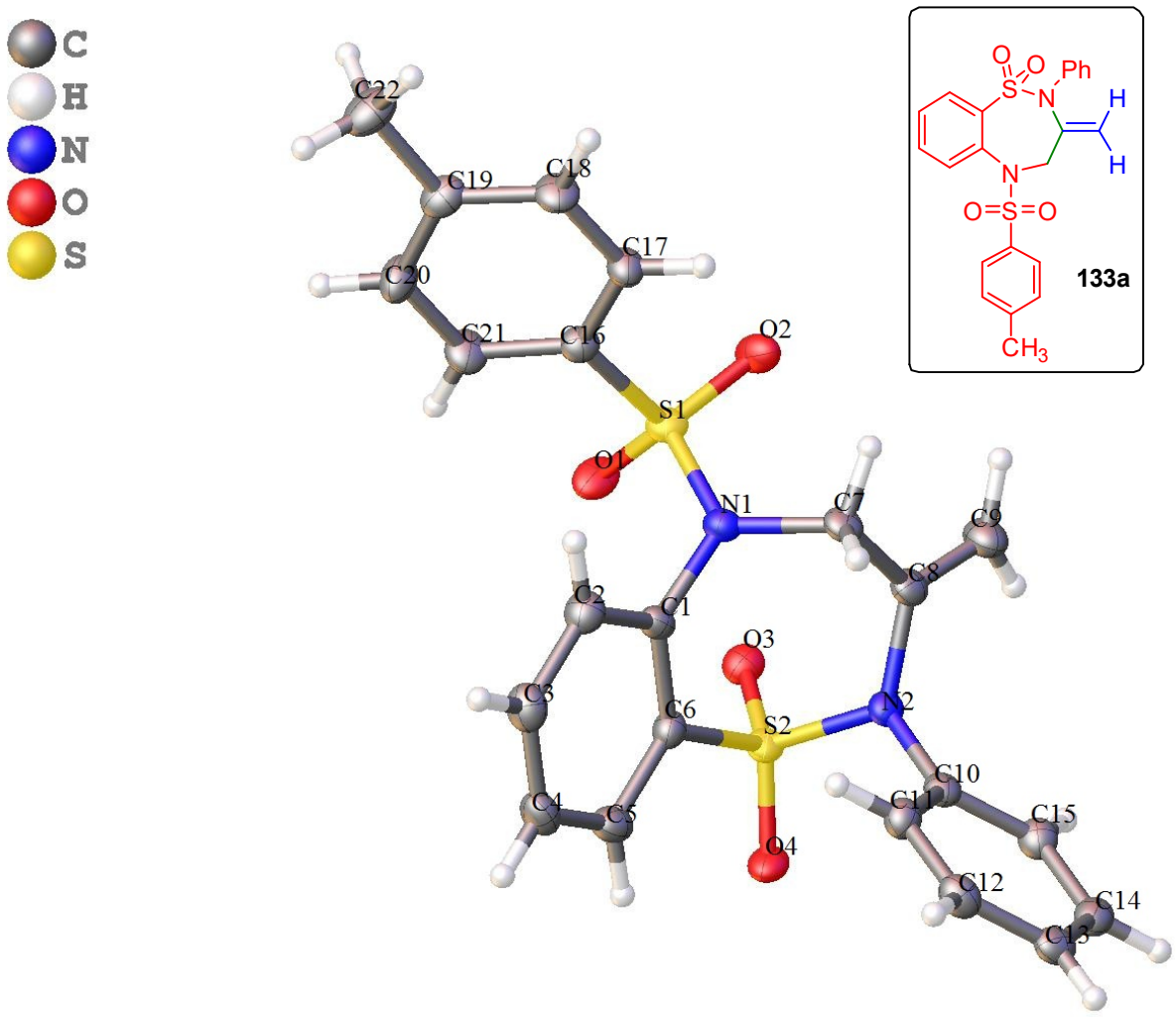


Figure 6. ORTEP diagram (thermal ellipsoid plot) of Product **133a** (drawn at 50% probability level)

Table 5: Important crystal data of product **133a**

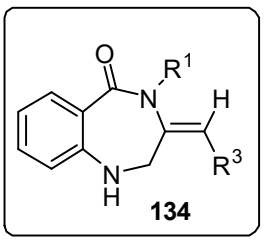
Empirical formula	$C_{22}\ H_{20}\ N_2\ O_4\ S_2$
Formula weight	440.52
Temperature	273 K
Wavelength	1.54184
Crystal system	'monoclinic'
Space group	'P 1 21/c 1'
Unit cell dimensions	a = 15.9293(11) Å α = 90 ^{0} b = 8.0486(5) Å β = 103.033(4) (12)^0 c = 16.3016(11) Å γ = 90 ^{0}
Volume	2036.2(2) $Å^3$
Z	8
Density (calculated)	1.437 g/cm^3
Absorption coefficient (Mu)	2.651 mm^{-1}
F(000)	920
Theta range for data collection	2.847 ^{o} to 69.883
Index ranges	-19<=h<=19, -9<=k<=9, -18<=l<=18
Reflection collected	58258
Independent reflections	3606 [R(int) = 0.0968]
Completeness to theta =	93.7 %
Absorption correction	multi-scan
Max. and min. transmission	0.7456 and 0.6875
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3606 / 0 / 278
Goodness-of-fit on F^2	1.274
Final R indices [I>2sigma(I)]	R1 = 0.0667, wR2 = 0.1408
R indices (all data)	R1 = 0.0670, wR2 = 0.1410
Largest diff. peak and hole	0.363 &- -0.367 $e.A^{-3}$

The single crystal of compound **133a** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **133a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2062378.**

1.2.8 Extension of the methodology for the synthesis of (*E*)-3-aryl/alkylidene-1,4-benzodiazepin-5-ones 134

1.2.8.1 Synthesis of (*E*)-3-aryl/alkylidene-1,4-benzodiazepin-5-ones 134

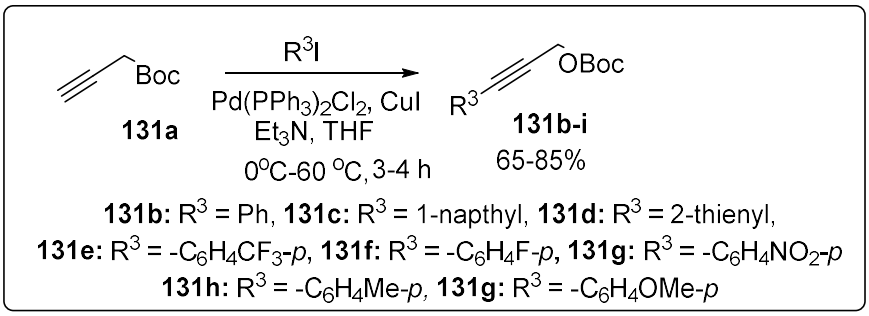
We then turned our attention to employ substituted propargyl carbonates **131** [in which the acetylenic hydrogen is replaced with aryl or alkyl group (R^3 = aryl/alkyl)] in our palladium catalyzed reaction as shown in Table 2. We therefore synthesized the substituted propargyl carbonates **131b** (R^3 = Ph) as model substrate as shown below in **Scheme 37** and used in our palladium catalysed cyclocondensation reaction (Table 2). To our surprise, initially, we faced some difficulties as the aforesaid substrate did not respond to this reaction even after several attempts with variation of the reaction conditions; these observations were also corroborated by the previous reports[28] where either limited reactivity of such substrates or formation of inseparable regio-isomeric mixtures of products were encountered.[26b-c] Having disappointing results in hand, we planned to employ 2-amino-*N*-phenylbenzamide (1**30aa**) instead of its *N*-protected version (i.e., **129aa**). Thus, substrate **130aa** was synthesized as shown previously in **Scheme 29**. Pleasingly, carrying out the reaction of **130aa** with propargyl carbonates **131b** (R^3 = Ph) under the optimized reaction conditions of Table 1 proved successful in delivering the regio- and stereo-selective product **134a** in 70% yield though a longer reaction time (12 h) was required. Thus, this revealed that the N-Ts group provided the main hindrance to the success of the transformation, removal of which (as in 2-amino-*N*-phenylbenzamide, 1**30aa**) proved to be successful. Next, further optimization of the reaction conditions was thereafter carried out with variation of parameters such as catalyst, ligand, solvent and temperature etc. as shown below in Table 6.



134

1.2.8.2 Preparation of the aryl substituted propargyl carbonates 131b-i:

Initially, substituted *tert*-butyl propargyl carbonate derivatives **131b** were prepared using "*Sonogashira reaction"* between phenyl iodide and propargyl alcohol (**131a**) protected with Boc group (**Scheme 37**). Later, the same reaction procedure was adopted in the generation of **131c-i** (65-85% yields) where various aryl iodides (ArI) were used instead of phenyl iodide (PhI).

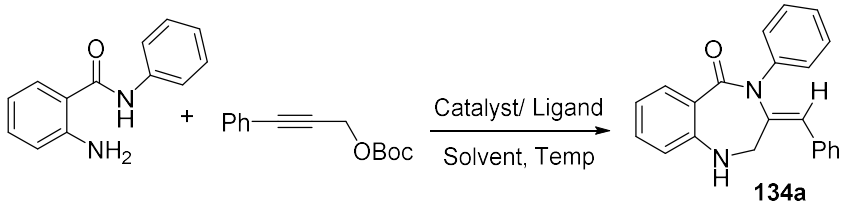


Scheme 37. Synthesis of substituted propargyl carbonates **131b-i**

1.2.8.3 Optimisation of the reaction conditions for the synthesis of product 134a:

To find the optimised reaction conditions, a model reaction was carried out between 2-amino-*N*-phenylbenzamide **130aa** and *tert*-butyl propargyl carbonate **131b** with variation of the reaction parameters such as palladium catalyst, ligand, solvent, temperature etc. (Table 6). Initially, employment of $Pd(dba)_2$, Xantphos, and acetonitrile, respectively as catalyst, ligand, and solvent with **134a** required longer reaction time (13 h) to deliver **134a** with 70% yield (entry 1, Table 6). To reduce the reaction time, we replaced $Pd(dba)_2$ with other Pd(0) catalysts (viz., $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd_2(dba)_3.CHCl_3$). But to our disappointment, the product was isolated in lower yields (45-54%) even after 18 h of reaction time (entries 2-4, Table 6). We therefore decided to persist with $Pd(dba)_2$ and planned to vary the ligand. But use of DPEphos, ^{t}BuXantphos, or Xphos instead of Xantphos delivered **134a** in lower yields after 18 h (entries 5-7, Table 6). Scrutiny of the solvent system revealed that the reaction provided **134a** with low yield in a polar solvent (i.e., DMSO) though DCE proved to be somewhat better (60% yield in 12 h, entries 8-9, Table 6). A medium polar solvent like THF failed to provide any product (entry 10, Table 6). To our pleasure, a remarkable improvement was noted when the reaction was carried out in refluxing butyronitrile (BuCN) which produced **134a** within 8 h and with 73% yield (entry 11 vs entry 1, Table 6). To decrease the reaction time, t-butanol was used as an additive to facilitate the proton transfer (see, the reaction mechanism in the text as depicted under **Scheme 40**) as unprotected aniline is not acidic enough like tosylamide. Though this significantly enhanced the reaction rate resulting in the lowering of reaction time to 3h, the yield was only 61% (entry 13 vs entry 12, Table 6).

Table 6. Optimisation of the reaction conditions for *(E)*-3-benzylidene-4-phenyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one **134a**[a]



130aa **131b** **134a**

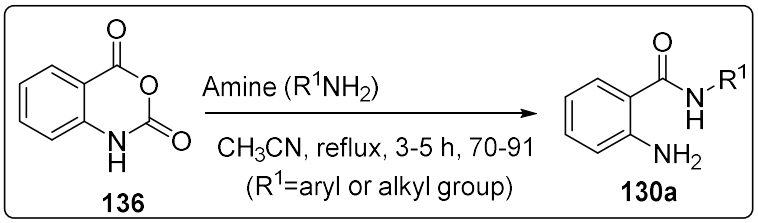
Entry	Catalyst	Ligand	Solvent	Temp(°C)	Time (h)	Yield(%)
1	$Pd(dba)_2$	Xantphos	CH_3CN	80	13	70
2	$Pd(PPh_3)_4$	Xantphos	CH_3CN	80	18	54
3	$Pd_2(dba)_3$	Xantphos	CH_3CN	80	18	51
4	$Pd_2(dba)_3.CHCl_3$	Xantphos	CH_3CN	80	18	45
5	$Pd(dba)_2$	DPEphos	CH_3CN	120	18	55
6	$Pd(dba)_2$	^{t}BuXantphos	CH_3CN	80	18	43
7	$Pd(dba)_2$	Xphos	CH_3CN	80	18	38
8	$Pd(dba)_2$	Xantphos	DCE	65	12	60
9	$Pd(dba)_2$	Xantphos	DMSO	120	18	24
10	$Pd(dba)_2$	Xantphos	THF	70	18	N.R.
11	$Pd(dba)_2$	Xantphos	BuCN	120	10	73
12[b]	**$Pd(dba)_2$**	**Xantphos**	**BuCN**	**120**	**10**	**72**
13[c]	$Pd(dba)_2$	Xantphos	BuCN	120	3	61
14[d]	$Pd(dba)_2$	Xantphos	BuCN	120	8	62
15[e]	$Pd(dba)_2$	Xantphos	BuCN	120	10	64

[a]Reaction conditions (Unless noted otherwise): A mixture of 1.0 equiv of **130aa** and 1.5 equiv of **131b** in 2.0 mL solvent in the presence of 10 mol% of the Pd(0) catalyst and 20 mol% ligand was refluxed under argon. [b]The reaction was performed with 7 mol% of $Pd(dba)_2$ along with 14 mol% Xantphos. [c]The reaction was performed with 2.0 equiv of t-butanol. [d]The reaction was performed with 5 mol% $Pd(dba)_2$ and 10 mol% Xantphos. [e]Using 2.0 equiv of **131b**.

Reduction of the catalyst loading from 10 mol% to 7 mol% slightly increased the reaction time and marginally decreased the yield of **134a** (entry 12, Table 6). Further reduction of the either catalyst loading (to 5 mol%) or amount of the *tert*-butyl propargyl carbonate **131b** resulted in a substantial reduction of the yield (entries 14-15, Table 6). We therefore considered the reaction conditions used in entry 12 of Table 6 as the optimised one for further exploration of the scope this reaction.

1.2.8.4 General procedure for the preparation of starting materials 130a[26,28]:

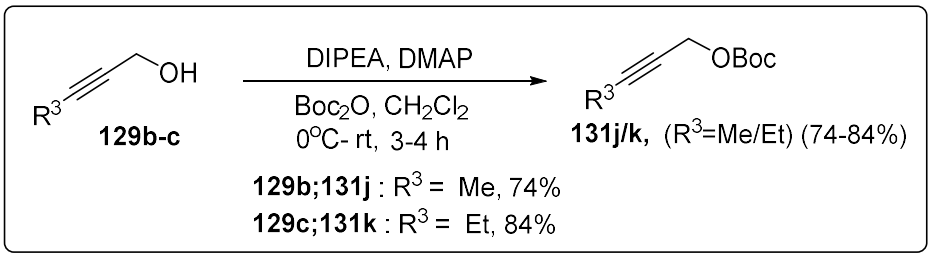
The requisite starting material **130a** were prepared according to **Scheme 31** where aryl or alkyl amines were used instead of aniline.



Scheme 38: Synthesis of substrates **130a**

1.2.8.5 Procedure for the preparation of alkyl substituted propargyl carbonates 131j-k[31]:

The requisite starting material **131j-k** were prepared according to **Scheme 35** where substituted propargyl alcohol **129b-c** were used instead of propargyl alcohol **129a**.



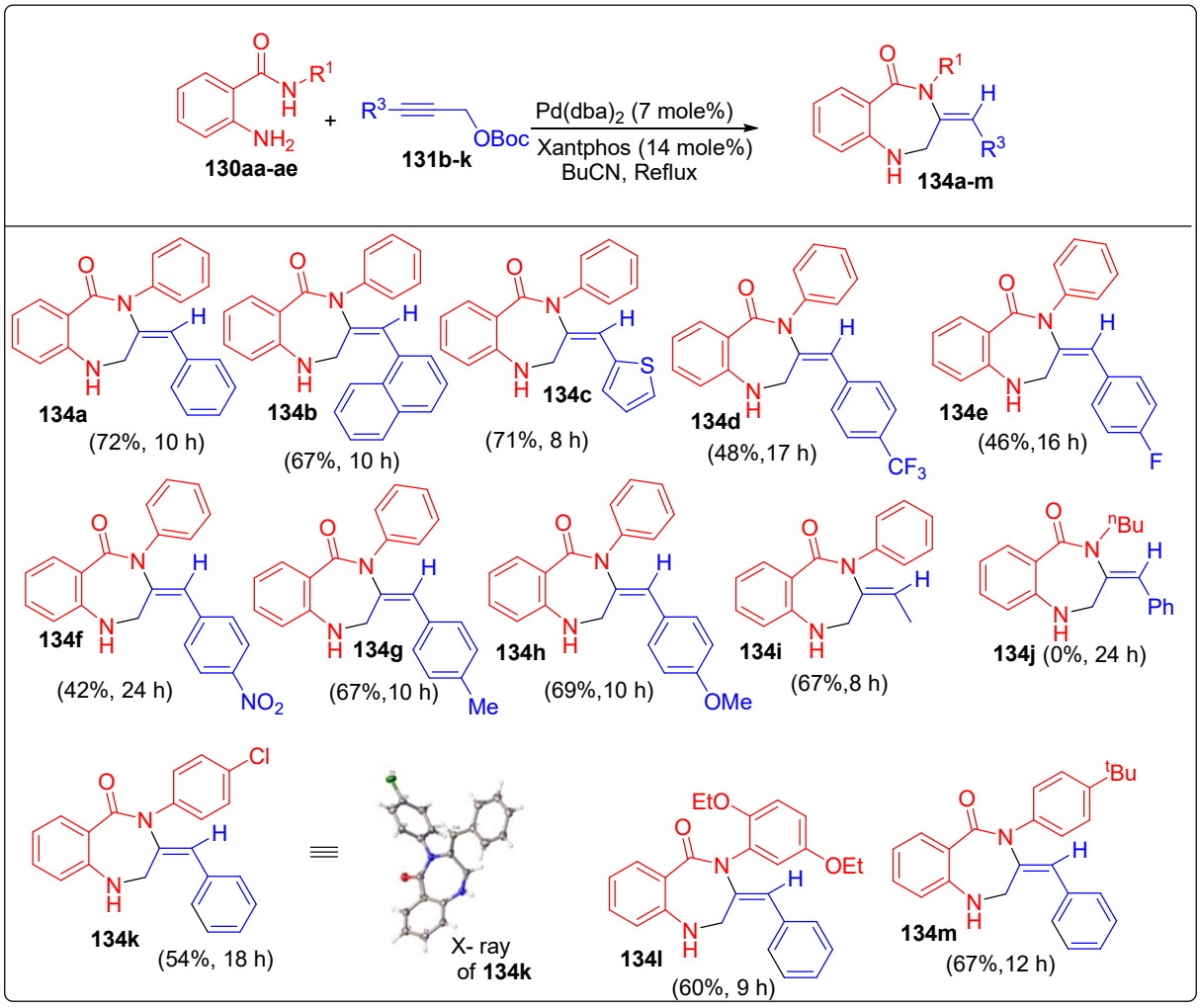
Scheme 39. Synthesis of alkyl substituted propargyl carbonates **131j-k**

1.2.8.6 Scope of the reaction:

With the optimized reaction conditions in hand, we then explored the substrate scope of this reaction protocol. Indeed, a diverse range of substituted propargylic carbonates **131b-k** successfully underwent cyclocondensation reactions with 2-amino-benzamides **130aa-ae**

culminating in chemo- and stereo-selective formation of products **134** in 42-72% yields (**Table 7**). Propargyl carbonate **131c** having a bulky naphthyl group (R^3= 1-naphthyl) or a heteroaryl moiety (R^3 = 2-thienyl) proved equally efficacious. But employment of an EWG (CF_3/F /NO_2) at the para position of the phenyl ring had detrimental effects as the corresponding products **134d**/**134e**/**134f** were produced in moderate yield (42-48%) with longer reaction time (16-24 h). On the contrary, an EDG (Me/OMe) placed at the same position removed the disadvantage (products **134g**/**134h**). Even an alkyl group (R^3 = methyl) in place of phenyl (of **131b**) was also found to be reactive toward this reaction triggering the formation of **134i** within 8 h with 67%

Table 7: Pd(0)-catalyzed synthesis of substituted (*E*)-3-aryl/alkyledene-[1,4]benzodiazepin-5-ones **134**



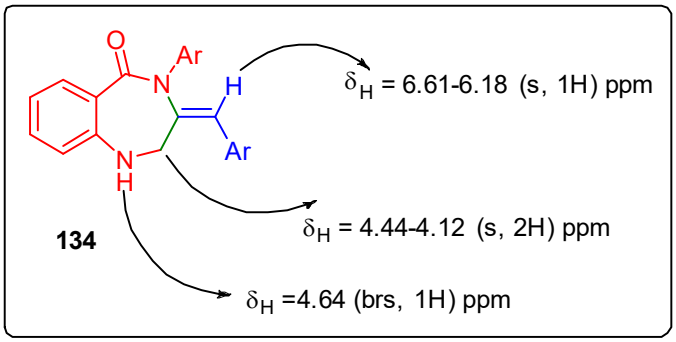
[a]Reaction conditions: A mixture of substrate **130a** (1 equiv), **131** (1.5 equiv), $Pd(dba)_2$ (7 mol%) and Xantphos (14 mol%) were refluxed in butyronitrile (2 mL) under argon.

yield. But replacement of the phenyl in the amide moiety with the bulky t-butyl group stymied the reaction fully, so that the targetted product **134j** was never formed.

We then studied the reaction of carbonate **131b** with different benzamide substrates (**130ac-ae**) having either an EWG (viz. Cl) or EDG (viz. OEt/*tert*-butyl) at the para position of the phenyl ring attached to nitrogen atom of amide moiety. Similar to the previous observations, the EWG hindered the reaction in some extent leading to the formation of **134k** (54%) with longer reaction time (18 h), while an EDG proved to be beneficial for this reaction resulting in the formation of **134l/134m** within 9-12 h with 60-67% yield.

1.2.8.7 Nature and characterization of products 134

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 °C) for several months. The structures of the products were unambiguously deduced by spectral (^{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, proton attached to the vinylic position appears as singlet at the range of 6.61-6.18 ppm as expected. Whereas, protons attached to the allylic position appears as singlet at the range of 4.44-4.12 ppm. However, proton attached to the nitrogen atom appears as broad singlet at 4.64 ppm. Furthermore, 13C-NMR and mass spectra gave additional support in the favour of the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **134k.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 7.

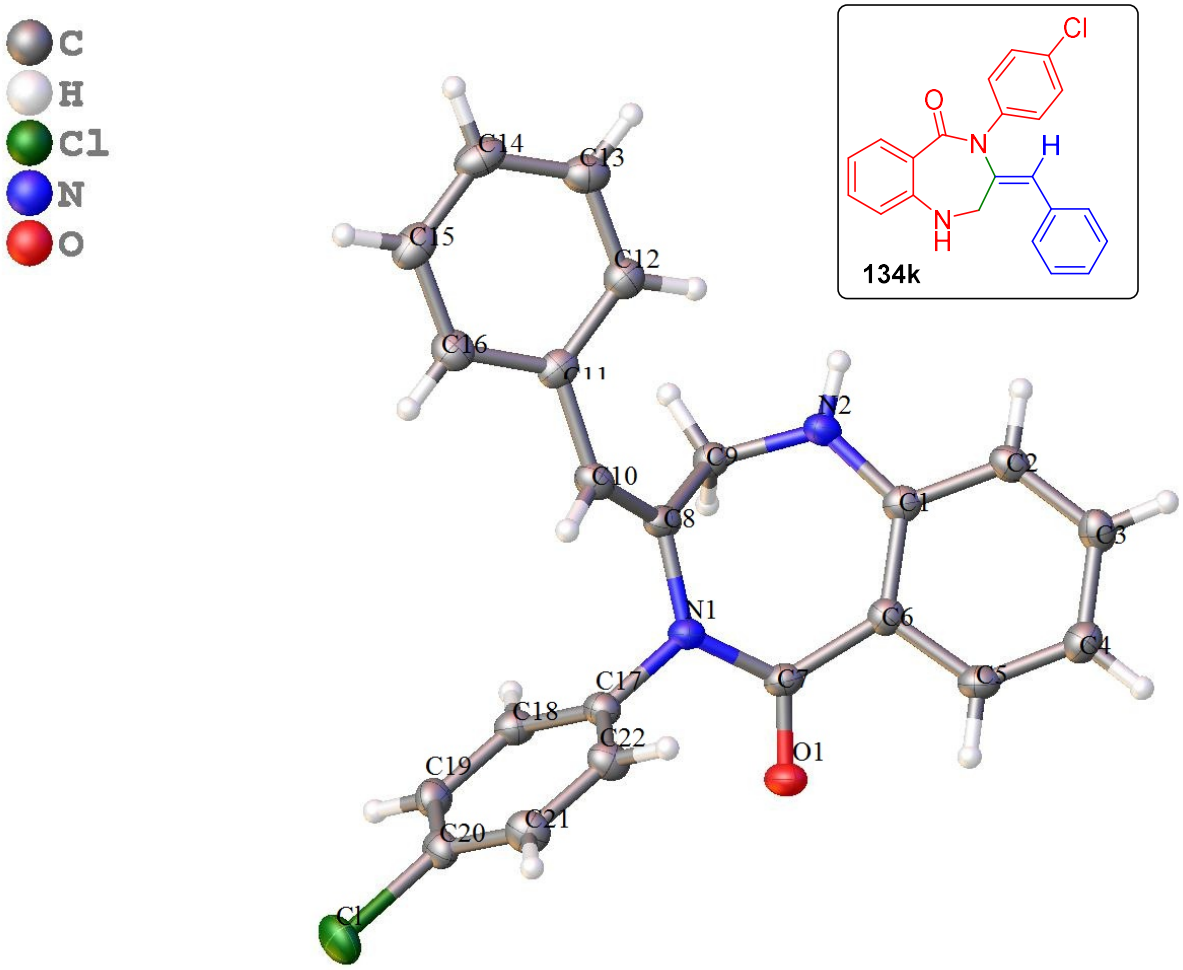


Figure 7. ORTEP Diagram (thermal ellipsoid plot) of Product **134k** (drawn at 50% probability level)

Table 8: Important crystal data of product **134k**

Empirical formula	'$C_{22}H_{17}ClN_2O$'
Formula weight	360.82
Temperature	273.15 K
Wavelength	1.54178
Crystal system	orthorhombic
Space group	'P 21 21 21'
Unit cell dimensions	a = 10.4364(17) Å α = 90.00°
	b = 12.3676(18) Å β = 90 ·00°(3)
	c = 14.215(2)Å γ = 90.00°
Volume	1834.8(5) $Å^3$
Z	4
Density (calculated)	1.306g/cm^3
Absorption coefficient (Mu)	1.936 mm^{-1}
F(000)	752.0
Theta range for data collection	4.739 to 66.876
Index ranges	-12<=h<=11, -14<=k<=14, -16<=l<=16
Reflection collected	20508
Independent reflections	3219 [R(int) = 0.0661]
Completeness to theta = 1.72/0.99	
Absorption correction	multi-scan
Max. and min. transmission	0.722 and 0.511
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3219 /0/236
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0823
R indices (all data)	R1 = 0.0351, wR2 = 0.0850
Largest diff. peak and hole	0.238 &--0.360 e.A^{-3}

Single crystal of compound **134k** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **134j** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2062375.**

1.2.9 Extension of the methodology for the synthesis of (*E*)-3-aryl/alkyledene-[1,2,5]benzothiadiazepine-1,1-dioxide 135

1.2.10 Preparation of starting material 135:

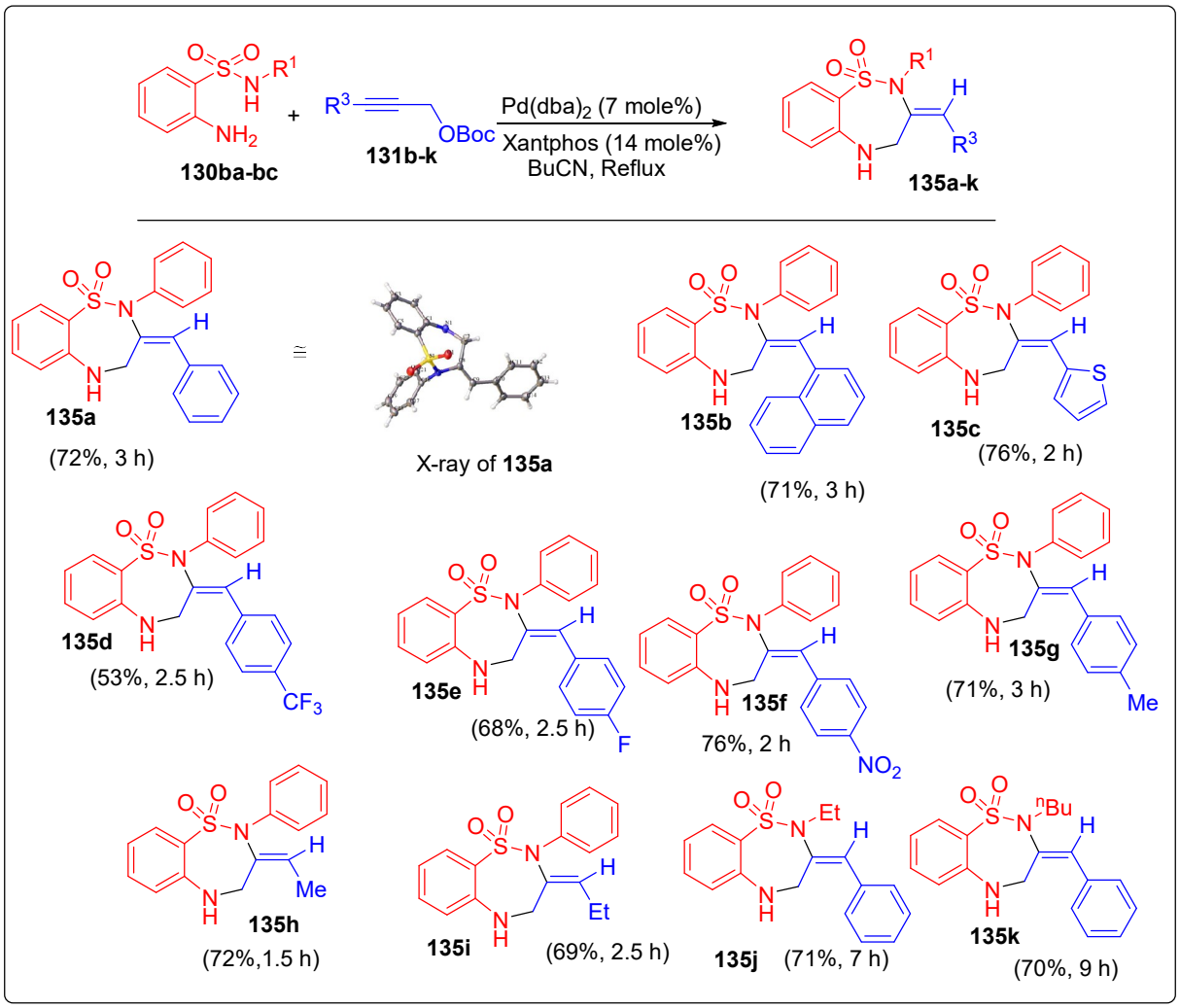
The method for the preparation of starting material **130b** has already been discussed under **Scheme 34**.

1.2.11 Synthesis of (*E*)-3-aryl/alkyledene-[1,2,5]benzothiadiazepine-1,1-dioxides 135:

To further extend the scope of this reaction and diversify the product structure, we replaced the amide substrate **130a** with sulphonamide **130b** (X=SO_2) which underwent reaction with a number of propargyl carbonates **131b-k** under the optimized reaction conditions (see entry 12 of Table 6) as shown in Table 9 below.

At the outset, the reaction of sulphonamide **130ba** (R^1= Ph) with propargyl carbonate **131b** was carried out and was found to be completed within 3 h resulting in stereoselective formation of (*E*)-benzo[*f*][1,2,5]thiadiazepine-1,1-dioxide product **135a** with 72% yield. Similar reactivity was observed with propargylic carbonate **131c** containing a bulky naphthyl group, leading to the generation of product **135b** (71%) within 3 h. Furthermore, this reaction was facilitated when carbonate **131d** containing a heteroaryl ring (i.e., R^3 = 2-thienyl) was employed, delivering the desired product (**135c**) within 2 h with 76% yield. We then checked the substituent effects by placing an EWG (i.e., CF_3/ F/ NO_2) or EDG (i.e., CH_3) at the para position in the phenyl ring; the resulting substrates (**131d**/**131e**/**131f** or **131g**) were then allowed to undergo reaction separately with **130ba**. As can be seen from Table 8, except the substrate **131d** which delivered the product **135d** in moderate yields (53%), these reactions furnished the corresponding products (**135e**/**135f or 135g**) within 2-3 h with good yields (68-76%). Of particular note, the reactions of the amine **130ba** with propargylic carbonates containing an alkyl group instead of an aryl one [viz., **131i** (R^3= Me) and **131j** (R^3= Et)] were also found to be successful, resulting in the formation of **135h** (72%) and **135i** (69%), respectively within 1.5-2.5 h. Even reactions of sulphonamides **130bb/130bc** having an alkyl group (R^1 = Et/n-Bu) with propargylic carbonate **131b** proceeded well, delivering the corresponding **135j**/**135k** in good yields (70-71%) with 7-9 h of reaction time.

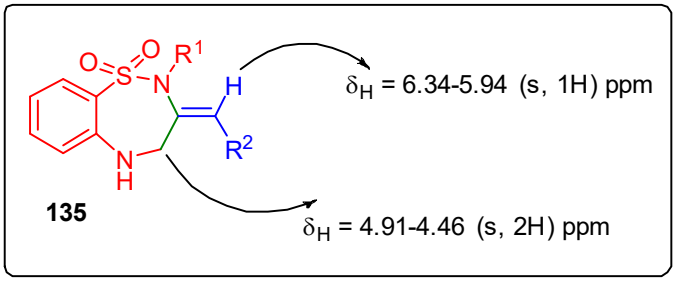
Table 9: Pd(0)-catalyzed synthesis of substituted (*E*)-3-aryl/alkyledene-[1,2,5]benzothiadiazepine-1,1-dioxide **135**[a]



[a]Reaction conditions: A mixture of substrate **130b** (1 equiv), **131** (1.5 equiv), $Pd(dba)_2$ (7 mol%) and Xantphos (14 mol%) were refluxed in butyronitrile (2 mL) under argon.

1.2.11.1 Nature and characterization of products 135

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 ^{o}C) for several months. The structures of the products were unambiguously deduced by spectral (^{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, proton attached to the vinylic position appears as singlet at the range of 6.34-5.94 ppm as expected. Whereas, protons attached to the allylic position appears as singlet at the range of 4.91-4.46 ppm. In addition, ^{13}C-NMR and mass spectra gave additional support in the favour of the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **135a.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 8.

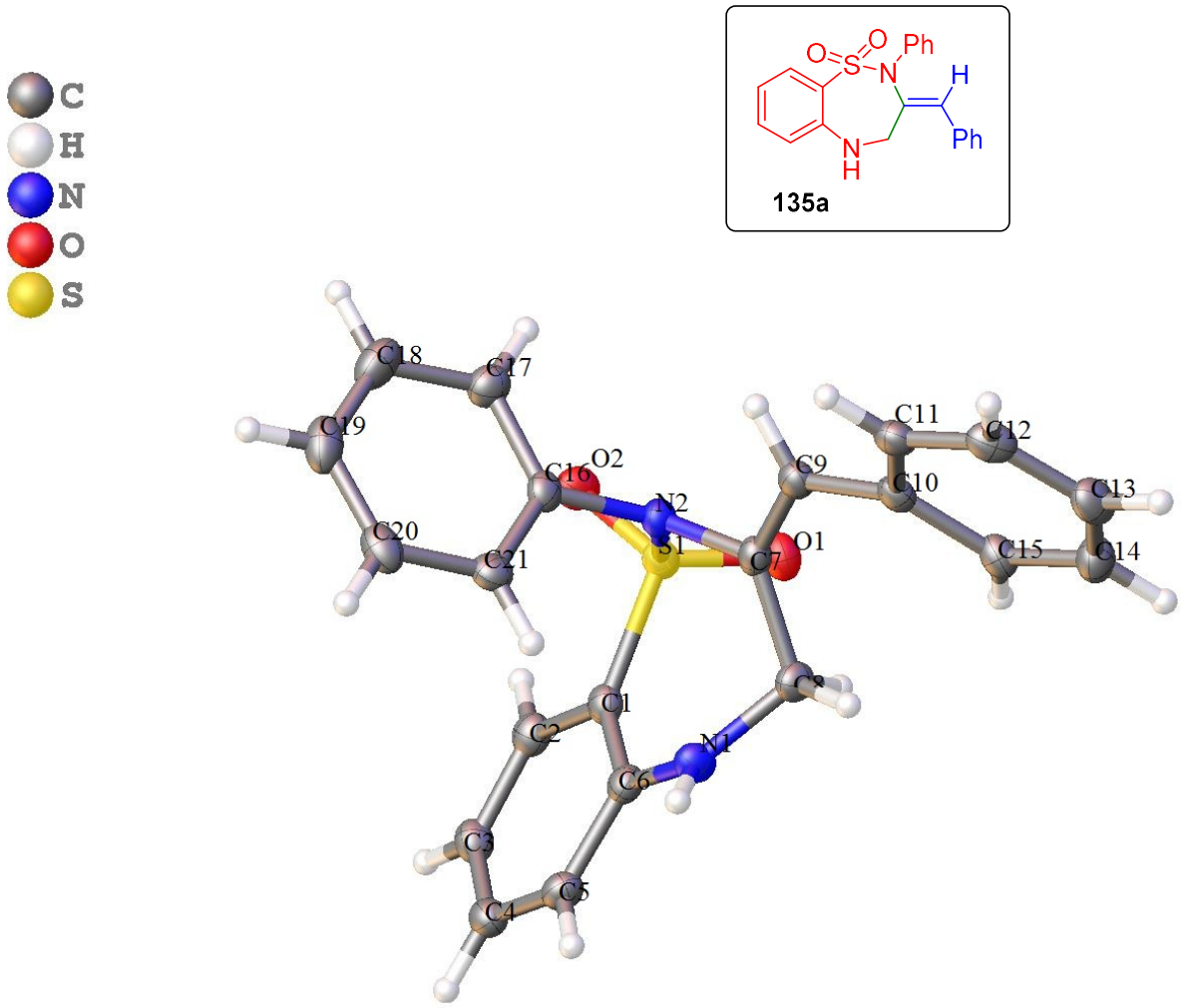


Figure 8. ORTEP Diagram (thermal ellipsoid plot) of product **135a** (drawn at 50% probability level)

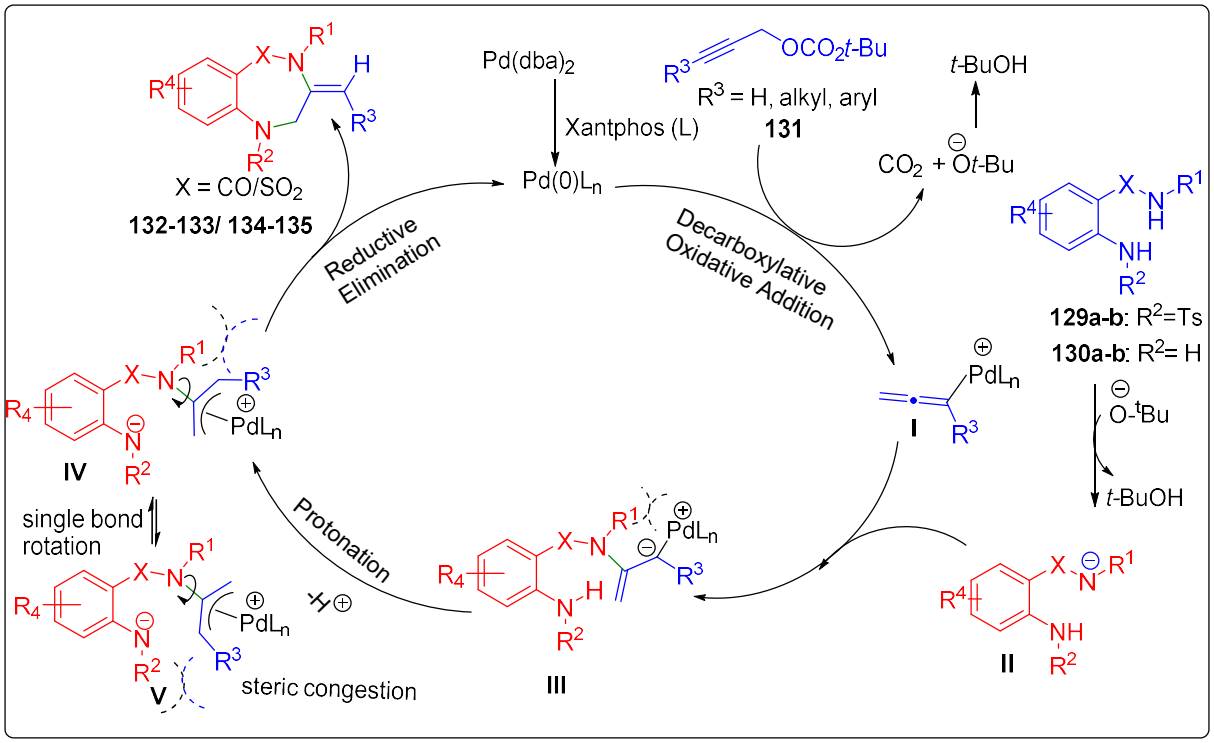
Table 10: Important crystal data of product **135a**

Empirical formula	'C_{21} H_{18} N_2 O_2 S'
Formula weight	362.43
Temperature	100
Wavelength	1.54178
Crystal system	'monoclinic'
Space group	'P 1 21/n 1'
Unit cell dimensions	a = 9.4644(6) Å α = 90
	b = 18.1620(13) Å β = 113.232(2)
	c = 10.9259(7) Å γ = 90
Volume	1725.8(2) $Å^3$
Z	4
Density (calculated)	0.459 g/cm^3
Absorption coefficient (Mu)	1.813 mm^{-1}
F(000)	760
Theta range for data collection	5.033 to 58.925
Index ranges	-10<=h<=10, -20<=k<=20, -12<=l<=12
Reflection collected	19950
Independent reflections	2392 [R(int) = 0.0476]
Completeness to theta =	96.1 %
Absorption correction	multi-scan
Max.and min. transmission	0.713 and 0.496
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2392 /0/ 236
Goodness-of-fit on F^2	1.210
Final R indices [I>2sigma(I)]	R1 = 0.0486, wR2 = 0.1342
R indices (all data)	R1 = 0.0488, wR2 = 0.1344
Largest diff. peak and hole	0.428 &- -0.401e.A^{-3}

Single crystal of compound **135a** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **135a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2062377**.

1.2.12 Plausible mechanism of the formation of products 132-133 and 134-135:

A plausible reaction mechanism is proposed to explain the product formation (**Scheme 40**). In the first step, a decarboxylative oxidative addition of Pd(0) to propargyl *tert*-butyl carbonate **131** would generate cationic palladium-allenyl species **I**[33a-b] and a *tert*-butoxide anion. Next, the *tert*-butoxide anion, an endogenous base, preferentially abstracts the proton from the amide (or sulphonamide) moiety of the substrates (**129a-b**/**130a-b**) to form the anionic species **II** which undergoes nucleophilic addition onto the central carbon of Pd-allene **I** resulting in the chemoselective generation of the Pd-carbenoid intermediate **III**,[33c,d] while protonation from the NHTs group present in the same substrate (**129a-b**/**130a-b**) would render the resulting anion less



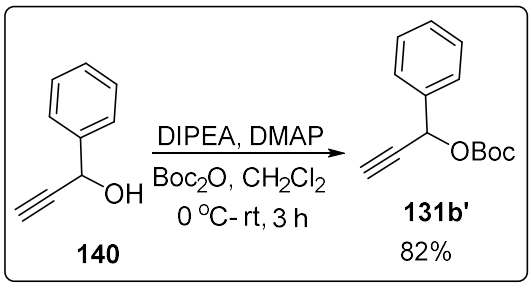
Scheme 40: Plausible reaction mechanism for the formation of products **132-133** and **134-135**

nucleophilic (because of the presence of strong electron-withdrawing tosyl group) despite the comparable pK_a values[34a,b] for both NHTs and amide groups. Upon intermolecular proton migration from the NHTs [or amine ($-NH_2$)], intermediate **III** would generate Pd-π-allyl species **IV**[34c,d] which can undergo cyclization followed by reductive elimination resulting in the formation of the products (**132-133** and **134-135**) and Pd(0) which keeps the catalytic cycle active. Though the precise reason behind the stereoselective formation of product (i.e., **134-135**)

is not very clear, the steric factor in intermediate **IV** (or **V**) might play an important role in determining the outcome.

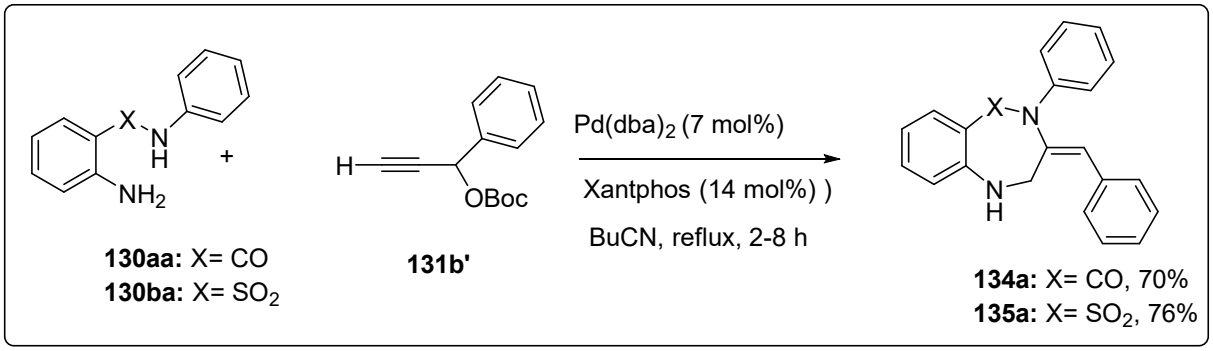
1.2.12.1 Synthesis of starting material for the control experiment:

Hydroxy (-OH) group of 1-phenylprop-2-yn-1-ol **140** was protected with -Boc after the treatment of DIPEA, DMAP and di-tert-butyl dicarbonate (Boc_2O) and the resulting substrate has been used in palladium-catalyzed reaction conditions (**Scheme 41**).



Scheme 41. Synthesis of Boc-protected substrate **131b'**

1.2.12.2 Control experiment:



Scheme 42: Control experiments using propargyl carbonate **131b'**

In order to support the proposed mechanism, we carried out control experiments (**Scheme 42**) in which propargyl carbonate **131b'** (instead of **131b**) was allowed to react with amine **130aa** and **130ba** under the optimized reaction conditions (entry 16, Table 6). These reactions, however led to the formations of the products **134a** and **135a** which were previously isolated from reactions of **131b** with **130aa** and **130ba**, respectively (see Table 6). These observations

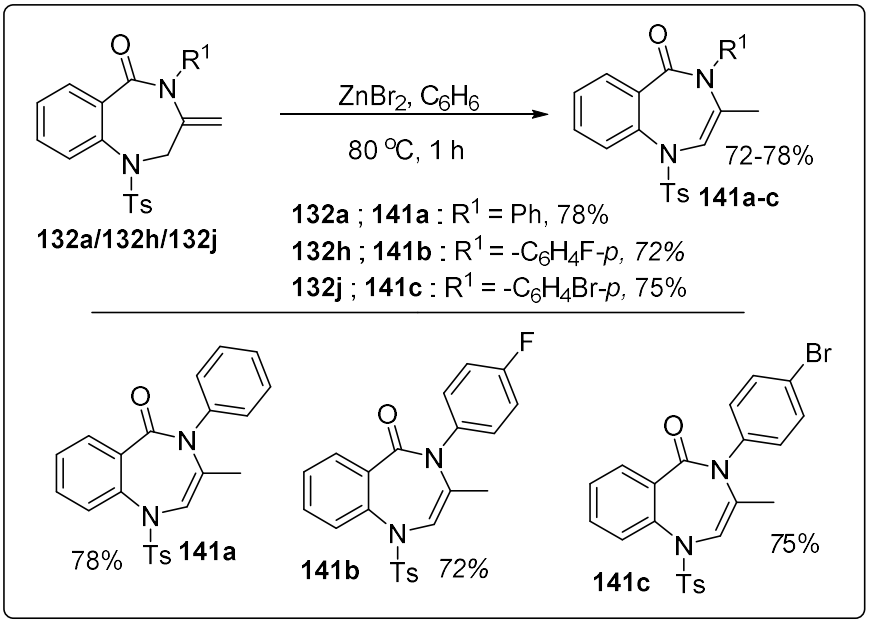
indicate that the reaction might pass through an allenic-palladium intermediate (**IV**) as proposed in the reaction mechanism under **Scheme 40**.

1.2.13 Few important transformations of 1,4-benzodiazepin-5-ones:

To explore the utility of this method further, the functional groups present in the products were used as synthetic handles for further transformations to construct privileged heterocycles as illustrated with few examples under **Scheme 43-46.**

1.2.13.1 Isomerisations of the exocyclic double bond of 132a/132h/132j into 1,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one derivatives 141a/141b/141c

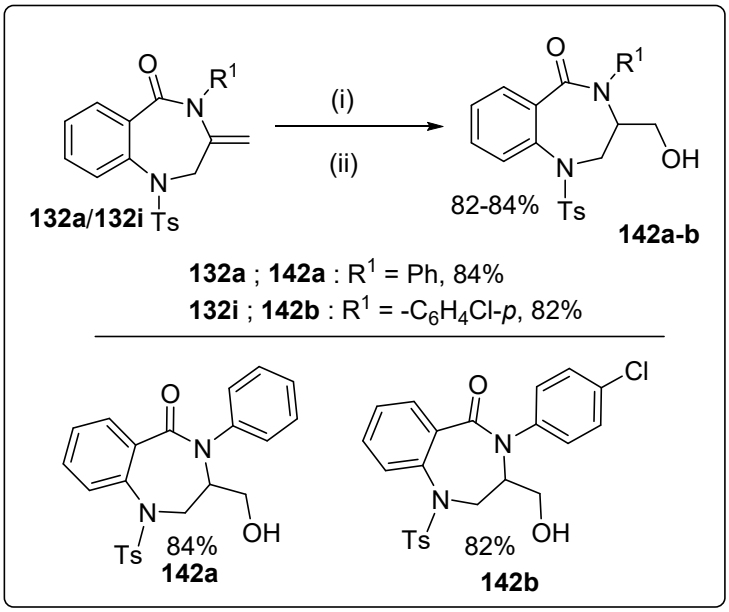
Treatment of 3-methylene-1,4-benzodiazepin-5-ones **132a, 132h** and **132j** with $ZnBr_2$ in refluxing benzene caused smooth isomerization of the exocyclic double bond, providing an easy access to the products **141a**, **141b**, and **141c,** respectively, to the extent of 72-75%.



Scheme 43. Isomerisations of the compounds **132a/132h/132j** into **141a/141b/141c**

1.2.13.2 Transformations of 132a/132i into 3-(hydroxymethyl)-1,2,3,4-tetrahydro-5H-benzo[e][1,4]di- azepin-5-ones 142a/142b

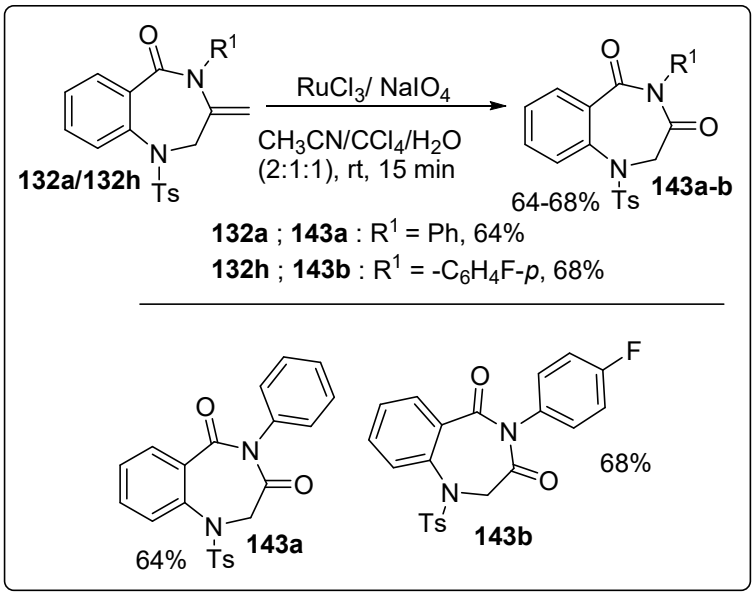
When products **132a** and **132i** (synthesized previously under Table 2) were exposed to BH_3.DMS followed by treatment with H_2O_2/NaOH, hydration of the exocyclic double bond took place easily in anti-Markovnikov mode resulting in the generation of alcohols **142a**/**142b** in high yields (82-84%).



Scheme 44. Transformations of **132a/132i** into **142a/142b**. Reagent and conditions: (i) $BH_3.SMe_2$, THF, 0 ^oC to rt, 3 h (ii) H_2O_2, NaOH, 0 ^oC to rt, 1 h, 82-84%.

1.2.13.3 Synthetic transformations of 132a/132h into 1,2-dihydro-3*H*-benzo[*e*][1,4]-diazepine-3,5(4*H*)-diones 143a/143b

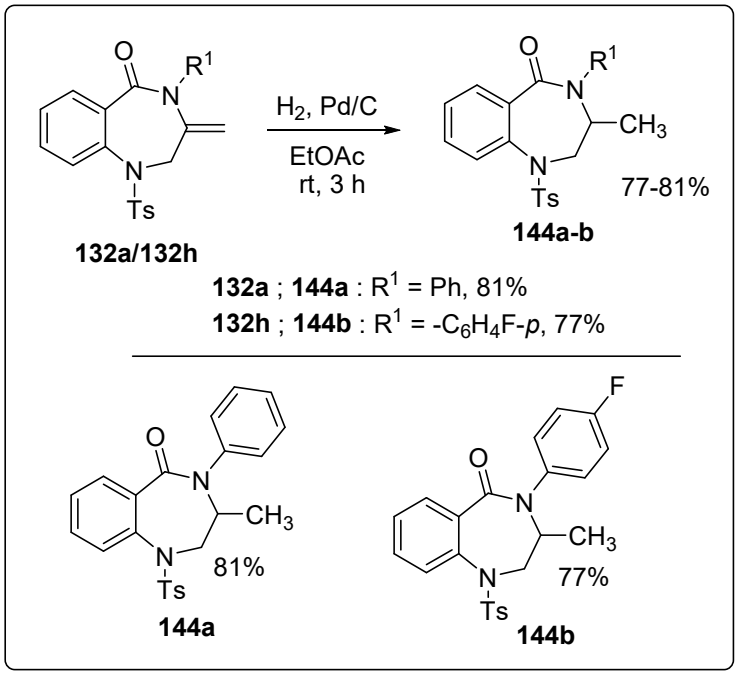
Treatment of **132a**, **132h** synthesized previously under Table 2 with $RuCl_3$ (5 mol%) and $NaIO_4$ (6 equiv.) resulted in the oxidative cleavage of the exocyclic C=C bond affording the products **143a** and **143b**, respectively within 10-15 min with 58-68% yields.



Scheme 45. Transformations of compounds **132a/132h** into products **143a**/**143b**

1.2.13.4 Procedure for the hydrogenation of 132a/132h into 3-methyl-1,2,3,4-tetrahydro-5H-benzo[*e*][1,4]diazepin-5-ones 144a/ 144b

Next, we applied Pd/C-catalyzed hydrogenation on the products **132a** and **132h** synthesized previously under Table 2**.** To our pleasure, these reactions afforded tetrahydro-5H-



Scheme 46. Hydrogenations of compounds **132a** and **132h**

benzo[*e*][1,4]diazepin-5-ones **144a** and **144b**, respectively, in 77-81% yield.

1.2.14 Conclusions

In conclusion**,** we present herein a facile and efficient method for the general synthesis of diverse and highly substituted 3-methylene derivatives of 1,4-benzodiazepin-5-ones/[1,2,5]benzothiadiazepine-1,1-dioxides **132**/**133** in 80-95% yields via palladium(0)-catalyzed chemoselective cyclocondensation reactions between *tert*-butyl propargyl carbonates and N-protected 2-amino benzamide/sulphonamides. Reaction of *tert*-butyl propargyl carbonates having substitution (R^3 = aryl/alkyl) at the acetylenic carbon needed unprotected amide or sulphonamide substrates, forming a stereoselective synthesis of (*E*)-3-aryl/alkyledene-1,4-benzodiazepin-5-ones/[1,2,5]benzothiadiazepine-1,1-dioxides **134/135** in 42-76% yields. A possible reaction mechanism is proposed to explain the product formation. To further extend the synthetic utility of this reaction, synthetic transformations of some products into other important heterocycles are also demonstrated. Our method thus uses simple and readily available substrates and constitutes a novel strategy for easy accessing to 'privileged' heterocycles, and adds to the diversity of their structures. We hope that this novel method will find applications in organic and medicinal chemistry as well.

1.2.15 Experimental section

1.2.15.1 General Information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 ^{o}C. DCE (Dichloroethane), CH_3CN (Acetonitrile) and BuCN (butyronitrile) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. Commercial grade dry DMSO (Dimethylsulfonamide), Toluene were used as a solvent. THF (Tetrahydrofuran) were predried using KOH pellets and then dried by heating under reflux over sodium with benzophenone as indicator. 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 chromate gram 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 [$CDCl_3$: ^1H 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), p (pentet), m (multiplet), and brs (broad singlet). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF.

1.2.15.2 X-Ray crystallographic information of products 132n, 133a, 134k and 135a:

Single crystal of products **132n, 133a, 134k** and **135a** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether. A single crystal of **132n, 133a**, **134k** and **135a** 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 **132n, 133a, 134k, 135a** with MoKα radiation (λ = 0.71073 Å) at 293 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. Important crystal data and ORTEP diagram (drawn at 50% probability level) of products **132n, 133a, 134k** and **135a** are provided earlier.

1.2.15.3 General procedure for the preparation of starting materials 129a and 130a:

*Synthesis of 2-aminobenzamide **130a***

To a solution of isatoic anhydride **136** (100 mg, 0.613 mmol, 1 equiv) in CH_3CN (5 mL), aryl (or alkyl) amine (62.6 mg, 0.674 mmol, 1.1 equiv) was added and the whole mixture was heated under reflux for 3-5 h. After completion of the reaction (TLC), the mixture was concentrated under reduced pressure, cooled and extracted with CH_2Cl_2 (3X10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (100-200 mesh) using eluent 25-30% ethyl acetate-petroleum ether (v/v) to give the corresponding product **130a** in 70-91% yields.

*Synthesis of 2-aminotosylbenzamide **129a***

Pyridine (38 µl, 0.47 mmol, 2 equiv) was added to a stirred solution of amino benzamide derivative **130a** (50 mg, 0.24 mmol, 1 equiv) in dry DCM (2 mL) at 0 ^{o}C under argon atmosphere. Next, arylsulphonyl chloride (59 mg, 0.31 mmol, 1.3 equiv) was added portion wise and the reaction was allowed to stir at room temperature for 2-3 h. After completion (TLC), the reaction mixture was diluted with DCM and washed with 1M HCl (3X10 mL,), satd. $NaHCO_3$ (3X10 mL), and brine (3X10 mL), respectively. The organic phase was dried over $MgSO_4$, concentrated, and purified by silica gel (100-200 mesh) column chromatography using 15-20% ethyl acetate-petroleum ether (v/v) as eluent to obtain 2-aminobenzenesulphonamide derivatives **129aa-129ac** in 88-95% yield.

*Typical procedure for preparation of starting material **129ad***

To a solution of 2-amino-3-methylbenzoic acid **137** (148 mg, 0.98 mmol, 1 equiv) in toluene (5 mL) was added thionyl chloride (0.37 ml, 4.9 mmol, 5 equiv) at room temperature and the mixture was refluxed for 9 h under nitrogen atmosphere. After completion, the solvent was evaporated under reduced pressure to obtain the crude acid chloride as yellow oil, which was instantly used for the next reaction. In the next step to prepare the intermediate **138**, Et_3N (0.16 ml, 1.2 mmol, 1.2 equiv) was added to a solution of aniline (0.1 ml, 1.2 mmol, 1.2 equiv) in dry DCM (5 mL) at 0 ^{o}C and stirred for 5 min. Then a solution of *p*-toluenesulphonyl chloride (185 mg, 0.98 mmol, 1 equiv) in dry DCM (2 mL) was added dropwise at 0 ^{o}C and stirring was continued for another 2 h. After completion (TLC), the solvent was removed under reduced pressure and the crude product was purified by silica gel (100-200 mesh) column chromatography using 20% ethyl acetate-petroleum ether (v/v) as eluent to obtain 3-methyl-2-((4-methylphenyl)sulfonamido)-*N*-phenylbenzamide (**129ad**) in 92% yield.

*Typical procedure for the preparation of starting material **129ae-af***

Di-tert-butyl dicarbonate (Boc_2O) (121 µl, 0.53 mmol, 2.2 equiv) was added to a solution of *N*-substituted-2-aminobenzamide (**130a**) (50 mg, 0.24 mmol, 1 equiv) in dry MeOH (2 mL) under argon atmosphere. Next, the mixture was allowed to stir at 100 oC for 5-6 h. After completion (TLC), the reaction mixture was poured into cold water (5 mL) and extracted with CH_2Cl^2 (3x 10 mL), dried over $MgSO_4$, and concentrated in *vacuo*. Then the residue was purified

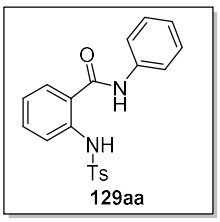
by silica gel (100-200 mesh) column chromatography eluting with 12% ethyl acetate-petroleum ether (v/v) to obtain pure tert-butyl(2-(arylcarbamoyl)phenyl)carbamate derivatives **129ae-af** in 89% yield.

*Typical procedure for the preparation of starting material **129ag***

To a solution of 2-amino-*N*-phenylbenzamide **130aa** (100 mg, 0.47 mmol, 1 equiv) in dry THF (3 mL) was added Et_3N (0.10 ml, 0.71 mmol, 1.5 equiv) at room temperature and the mixture was cooled to 0 ^{0}C under nitrogen atmosphere. Trifluoroacetic andydride (0.13 ml, 0.94 mmol, 2 equiv) was added dropwise under ice cold conditions. After 20 min, the reaction mixture was poured into cold water (5 mL) and extracted with CH_2Cl_2 (3X 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Then the residue was purified by silica gel (100-200 mesh) column chromatography eluting with 12% ethyl acetate-petroleum ether (v/v) to obtain pure *tert*-butyl(2-(arylcarbamoyl)phenyl)carbamate derivatives **129ag** in 88% yield.

1.2.15.4 Spectral Data of the substrates 129aa-129aq:

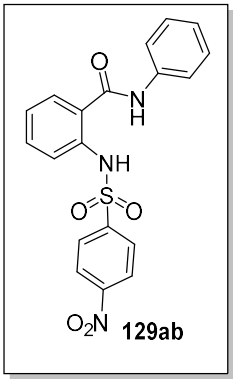
2-(4-Methylphenyl)sulfonamido)-*N*-phenylbenzamide (129aa)



129aa

White solid (78 mg, 90% yield); mp. 140-142 ^{o}C, R_f = 0.29 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.13 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.50-7.46 (m, 3H), 7.42-7.34 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.6, 143.8, 138.6, 137.1, 136.4, 132.9, 129.6, 127.3, 126.8, 125.3, 124.2, 123.2, 122.7, 120.7, 21.5; HRMS (ESI+) m/z calculated for $C_{20}H_{18}N_2NaO_3S$ $[M+Na]^+$ 389.0936, found 389.0937.

2-(4-Nitrophenyl)sulfonamido)-*N*-phenylbenzamide (129ab)

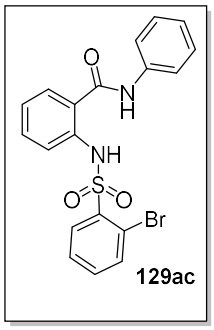


129ab

White solid (84 mg, 90% yield); mp. 166-168 ^{o}C, R_f = 0.40 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.52 (s, 1H), 8.13-8.09 (m, 2H), 7.93-7.90 (m, 2H), 7.75 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.55 (s, 1H), 7.52-7.48 (m, 2H), 7.42-7.35 (m, 4H), 7.23-7.18 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.4, 145.1, 137.9, 136.6, 133.3, 129.4, 128.7, 126.8, 125.8, 125.1, 124.2, 123.1, 120.6, 100.0;

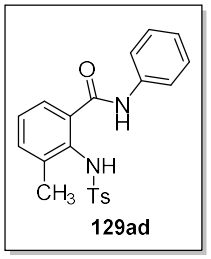
HRMS (ESI+) m/z calculated for $C_{19}H_{16}N_3O_5S$ $[M+H]^+$ 398.0811, found 398.0810.

2-(2-Bromophenyl)sulfonamido)-*N*-phenylbenzamide (129ac)



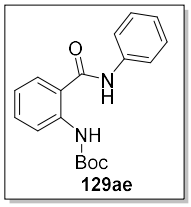
Yellow solid (93 mg, 92% yield); mp. 78-80 °C, R_f = 0.52 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 11.03 (s, 1H), 8.15 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.01 (s, 1H), 7.59-7.55 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.41-7.25 (m, 5H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.7, 138.6, 138.1, 137.2, 135.6, 134.1, 132.9, 132.0, 129.2, 127.6, 127.4, 125.4, 123.3, 121.4, 121.0, 120.5, 118.9; HRMS (ESI+) m/z calculated for $C_{19}H_{15}BrN_2NaO_3S$ $[M+Na]^+$ 452.9884, found 452.9867.

3-Methyl-2-(4-methylphenyl)sulfonamido)-*N*-phenylbenzamide (129ad)



White solid (77 mg, 92% yield); mp. >200 °C, R_f = 0.32 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.57 (s, 1H), 7.44 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.21 (d, *J* = 6.8 Hz, 2H), 7.16-7.13 (m, 1H), 6.94 (s, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 2.63 (s, 3H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.0, 143.6, 137.6, 135.01, 134.6, 133.9, 129.5, 129.0, 127.9, 127.0, 124.8 124.1, 119.3, 21.4, 19.7; HRMS (ESI+) m/z calculated for $C_{21}H_{21}N_2O_3S$ $[M+H]^+$ 381.1273, found 381.1276.

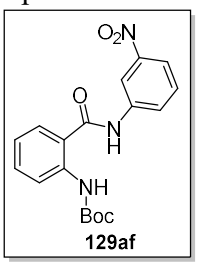
***Tert-butyl* (2-(phenylcarbamoyl)phenyl)carbamate (129ae)**



White solid (65 mg, 89% yield); mp. 148-150 °C, R_f = 0.25 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.73 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 8.04 (s, 1H), 7.59 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43-7.37 (m, 3H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 1.50 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.4, 153.3, 140.1, 137.5, 132.7, 129.2, 126.8, 125.1, 121.8, 120.8, 120.5, 80.6, 28.4; HRMS (ESI+) m/z calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1372, found 335.1367.

***Tert-butyl* (2-((3-nitrophenyl)carbamoyl)phenyl)carbamate (129af)**

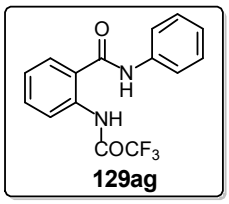
Yellow solid (62 mg, 89% yield), mp. 170-172 °C, R_f = 0.33 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.52 (s, 1H), 8.75 (s 1H), 8.63 (t, *J* = 2.2 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.03-8.01 (m, 2H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 1.55 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.4, 153.7, 148.8, 139.8, 139.2, 132.9, 130.0, 127.1, 125.9, 122.1, 120.9, 120.6, 119.3, 115.2, 100.0, 81.2, 28.5; HRMS (ESI+) m/z calculated for $C_{18}H_{19}N_3NaO_5$ $[M+Na]^+$ 380.1222, found 380.1221.



129af

N-phenyl-2-(2,2,2-trifluoroacetamido)benzamide (129ag)

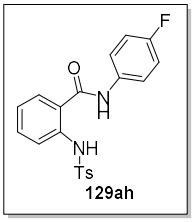
White solid (77 mg, 88% yield); mp. 145-147 °C, R_f = 0.32 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 12.25 (brs, 1H), 8.60-8.53 (m, 1H), 8.07 (brs, 1H), 7.68-7.62 (m, 1H), 7.61 (d, *J* = 1.2 Hz, 2H), 7.57-7.52 (m, 1H), 7.43-7.39 (m, 2H), 7.28-7.20 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.7, 137.6, 136.8, 133.4, 139.4, 126.8, 125.7, 125.1, 122.1, 121.0, 100.0; HRMS (ESI+) m/z calculated $C_{15}H_{12}F_3N_2O_2$ $[M+H]^+$ 309.0851, found 309.0853.



129ag

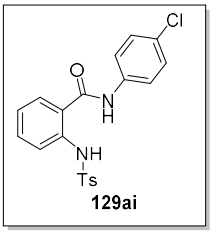
***N*-(4-fluorophenyl)-2-((4-methylphenyl)sulfonamido)benzamide (129ah)**

White solid (77 mg, 92% yield); mp. 160-162 °C, R_f = 0.21 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.25 (s, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.50-7.38 (m, 4H), 7.12-7.03 (m, 5H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.6, 160.0 (d, *J* = 244.0 Hz), 143.8, 138.7, 136.4, 133.1, 133.0, 129.7, 127.3, 126.8, 124.1, 122.7 (d, *J* = 5.0 Hz), 122.5 (d, *J* = 18.0 Hz), 115.9 (d, *J* = 22.0 Hz), 21.6; HRMS (ESI+) m/z calculated $C_{20}H_{18}FN_2O_3S$ $[M+H]^+$ 385.1022, found 385.1022.



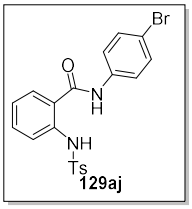
129ah

***N*-(4-chlorophenyl)-2-((4-methylphenyl)sulfonamido)benzamide (129ai)**



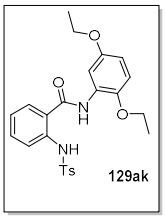
White solid (74 mg, 91% yield); mp. 158-160 °C, R_f = 0.23 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.13 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.47-7.41 (m, 4H), 7.35-7.32 (m, 2H), 7.14-7.08 (m, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.5, 143.8, 138.7, 136.4, 135.7, 133.1, 130.4, 129.6, 129.3, 127.4, 126.7, 124.2, 122.8, 122.7, 121.8, 21.6; HRMS (ESI+) m/z calculated for $C_{20}H_{17}ClN_2NaO_3S$ $[M+Na]^+$ 423.0546, found 423.0549.

***N*-(4-bromophenyl)-2-((4-methylphenyl)sulfonamido)benzamide (129aj)**



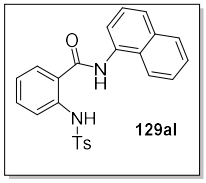
White solid (69 mg, 90% yield); mp. 152-154 °C, R_f = 0.25 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.11 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 1H), 7.50-7.38 (m, 6H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.5, 143.8, 138.7, 136.5, 136.2, 133.2, 132.2, 129.6, 127.4, 126.6, 124.2, 122.9, 122.7, 122.0, 118.1, 21.6; HRMS (ESI+) m/z calculated for $C_{20}H_{18}BrN_2O_3S$ $[M+H]^+$ 445.0222, found 445.0213.

***N*-(2,5-diethoxyphenyl)-2-((4-methylphenyl)sulfonamido)benzamide (129ak)**



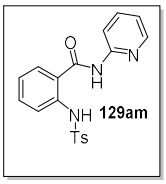
White solid (71 mg, 94% yield); mp. 180-182 °C, R_f = 0.46 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.50 (s, 1H), 8.31 (s, 1H), 8.08 (d, *J* = 3.2 Hz, 1H), 7.71 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.45-7.41 (m, 2H), 7.12 (td, *J* = 7.7, 0.8 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 1H), 6.61 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.09-4.03 (m, 4H), 2.22 (s, 3H), 1.15-1.39 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.0, 153.4, 143.7, 141.5, 139.0, 136.5, 132.8, 129.6,127.9, 127.4, 126.3, 124.01, 123.2, 122.4, 112.1, 110.2, 106.8, 100.0, 65.0, 64.3, 21.4, 15.1, 15.0; HRMS (ESI+) m/z calculated for $C_{24}H_{26}N_2NaO_5S$ $[M+Na]^+$ 477.1460, found 477.1460.

2-((4-Methylphenyl)sulfonamido)-*N*-(naphthalen-1-yl)benzamide (129al)



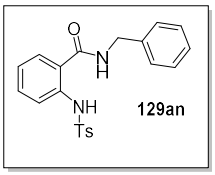
Brown solid (74 mg, 93% yield); mp. 194-196 °C, R_f = 0.45 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.43 (s, 1H), 8.00 (s, 1H), 7.92-7.89 (m, 1H), 7.79-7.76 (m, 3H), 7.70-7.67 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.54-7.46 (m, 4H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 2.19 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.3, 143.7, 139.2, 136.6, 134.3, 133.2, 131.5, 129.6, 129.1, 127.5, 127.3, 127.0, 126.8, 126.4, 125.7, 124.1, 122.4, 122.3, 121.7, 120.6, 21.5; HRMS (ESI+) m/z calculated for $C_{24}H_{21}N_2O_3S$ $[M+H]^+$ 417.1273, found 417.1270.

2-((4-Methylphenyl)sulfonamido)-*N*-(pyridin-2-yl)benzamide (129am)



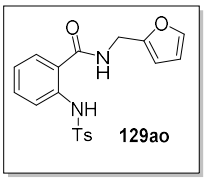
Yellow solid (76 mg, 88% yield); mp.116-118 °C, R_f = 0.33 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.12 (s, 1H), 8.53 (s, 1H), 8.25-8.19 (m, 2H), 7.81-7.77 (m, 1H), 7.72 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.49-7.44 (m, 1H), 7.15-7.09 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 144.0, 139.0, 138.8, 136.2, 133.4, 129.6, 127.3, 127.0 124.4, 123.2, 122.9, 120.5, 100.0, 21.5; HRMS (ESI+) m/z calculated for $C_{19}H_{18}N_3O_3S$ $[M+H]^+$ 368.1069, found 368.1060.

***N*-benzyl-2-((4-methylphenyl)sulfonamido)benzamide (129an)**



Yellow solid (79 mg, 95% yield); mp. 138-140 °C, R_f = 0.50 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 10.82 (s, 1H), 7.70-7.68 (m, 3H), 7.40-7.33 (m, 5H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.33 (s, 1H), 4.52 (d, *J* = 5.4 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 168.1, 143.5, 139.0, 137.3, 136.6, 132.7, 129.5, 128.9, 128.0, 127.9, 127.2, 126.6, 123.4, 121.3, 121.2, 44.1, 21.5; HRMS (ESI+) m/z calculated for $C_{21}H_{21}N_2O_3S$ $[M+H]^+$ 381.1273, found 381.1270.

***N*-(furan-2-ylmethyl)-2-((4-methylphenyl)sulfonamido)benzamide (129ao)**

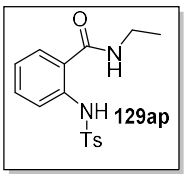


White solid (81 mg, 95% yield); mp. 110-112 °C, R_f = 0.56 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.70 (s, 1H), 7.65-7.62 (m, 3H), 7.38-7.33 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.02-6.98 (m, 1H), 6.42 (s, 1H), 6.35-

6.34 (m, 1H), 6.27-6.26 (m, 1H), 4.48 (d, J = 5.2 Hz, 2H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 168.1, 150.4, 143.7, 142.6, 139.0, 136.6, 132.8, 129.6, 127.3, 126.9, 123.6, 121.4, 121.3, 110.7, 108.2, 36.9, 21.6; HRMS (ESI+) m/z calculated for $C_{19}H_{18}N_2NaO_4S$ $[M+Na]^+$ 393.0885, found 393.0886.

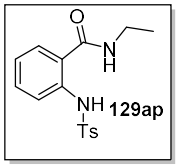
***N*-ethyl-2-((4-methylphenyl)sulfonamido)benzamide (129ap)**

White solid (90 mg, 93% yield); mp. 126-128 °C, R_f = 0.50 (15% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 10.78 (s, 1H), 7.65-7.63 (m, 3H), 7.37-7.32 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.03-6.99 (m, 1H), 6.09 (s, 1H), 3.37-3.30 (m, 2H), 2.33 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 168.3, 143.6, 138.8, 136.7, 132.5, 129.6, 127.3, 126.7, 123.6, 121.9, 121.5, 35.0, 21.6, 14.6; HRMS (ESI+) m/z calculated for $C_{16}H_{19}N_2O_3S$ $[M+H]^+$ 319.1116, found 319.1107.



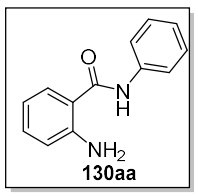
***N*-butyl-2-((4-methylphenyl)sulfonamido)benzamide (129aq)**

White solid (85 mg, 94% yield); mp. 112-114 °C, R_f = 0.53 (15% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 10.93 (s, 1H), 7.61-7.58 (m, 3H), 7.37-7.29 (m, 2H), 7.13 (d, J = 6.8 Hz, 2H), 6.97 (t, J = 7.0 Hz, 1H), 6.41 (s, 1H), 3.26 (d, J = 5.2 Hz, 2H), 2.29 (s, 3H), 1.49-1.45 (m, 2H), 1.33-1.28 (m, 2H), 0.92-0.88 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 168.4, 143.7, 138.8, 136.6, 136.5, 132.4, 129.6, 127.2, 127.0, 123.7, 121.8, 121.3, 39.8, 31.4, 21.6, 20.2, 13.8; HRMS (ESI+) m/z calculated for $C_{18}H_{23}N_2O_3S$ $[M+H]^+$ 347.1429, found 347.1428.

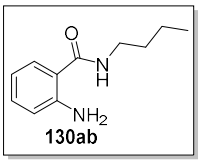


1.2.15.5 Spectral data of the substrates 130aa-130ae:

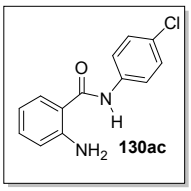
2-Amino-*N*-phenylbenzamide (130aa)[26]: White solid (118 mg, 91% yield), mp. 131-132 °C, R_f = 0.46 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.85 (brs, 1H), 7.57-7.55 (m, 2H), 7.48-7.45 (m, 1H), 7.38-7.33 (m, 2H), 7.27-7.22 (m, 1H), 7.17-7.12 (m, 1H), 6.72-6.67 (m, 2H), 5.12 (brs, 2H); HRMS (ESI+) m/z calculated for $C_{13}H_{13}N_2O$ $[M+H]^+$ 213.1028, found 213.1031.



2-Amino-N-butylbenzamide (130ab): White solid (105 mg, 89% yield), mp. 127-129 ^{o}C, R_f = 0.63 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.27 (dd, J = 7.8, 1.6 Hz, 1H), 7.19-7.15 (m, 2H), 6.66-6.60 (m, 2H), 6.10 (brs, 1H), 5.47 (brs, 2H), 3.39-3.37 (m, 2H), 1.57-1.54 (m, 2H), 1.41-1.36 (m, 2H), 0.95-0.91 (m, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ_C 169.4, 148.7, 132.2, 127.2, 117.3, 116.7, 39.5, 31.8, 20.7, 13.9; HRMS (ESI+) m/z calculated for $C_{11}H_{17}N_2O$ $[M+H]^+$ 193.1341, found 193.1339.

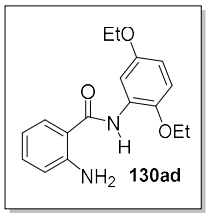


2-Amino-*N*-(4-chlorophenyl)benzamide (130ac)[26]**:** White solid (130 mg, 85% yield), mp. 139-142^{o}C , R_f = 0.46 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.82 (brs, 1H), 7.52-7.43 (m, 3H), 7.32-7.23 (m, 3H), 6.72-6.68 (m, 2H), 5.47 (brs, 2H); HRMS (ESI+) m/z calculated for $C_{13}H_{12}ClN_2O$ $[M+H]^+$ 247.0638, found 247.0639.

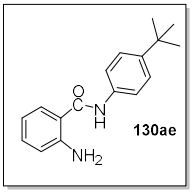


2-Amino-*N*-(2,5-diethoxyphenyl)benzamide (130ad):

White solid (129 mg, 70% yield); mp. 140-142 ^{o}C; R_f= 0.34 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.53 (s, 1H), 8.16 (d, J = 3.2 Hz, 1H), 7.45 (dd, J = 8.2, 1.4 Hz, 1H), 7.26-7.22 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.73-6.69 (m, 2H), 6.57 (dd, J = 9.0, 2.8 Hz, 1H), 4.09-4.01 (m, 4H), 1.44-1.37 (m, 6H); ^{13}C NMR ($CDCl_3$,100 MHz) δ_C 167.2, 153.3, 149.2, 141.8, 132.7, 128.9, 127.2, 117.7, 117.0, 116.7, 112.2, 109.4, 106.8, 65.0, 64.2, 15.1, 15.0; HRMS (ESI+) m/z calculated for $C_{17}H_{21}N_2O_3$ $[M+H]^+$ 301.1552, found 301.1551.



2-Amino-*N*-(4-(*tert*-butyl)phenyl)benzamide (130ae)[28]**:** White solid (145 mg, 88% yield, mp. 105-107^{o}C, R_f = 0.60 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.85 (brs, 1H), 7.50-7.45 (m, 3H), 7.40-7.37 (m, 2H), 7.27-7.19 (m, 1H), 6.72-6.70 (m, 2H), 4.95 (brs, 2H), 1.33 (9H); HRMS (ESI+) m/z calculated for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1654, found 269.1649.



1.2.15.6 General procedure for the preparation of starting materials 129b and 130b:

*Synthesis of 2-aminosulphonamide **130b***

To a solution of amine (R^1NH_2) (93 µl, 1.02 mmol, 1.5 equiv) and Et_3N (114 µl, 0.82 mmol, 1.2 equiv) in dry CH_2Cl_2 (3 mL) was added a solution of 2-nitrobenzenesulfonyl chloride **140** (150 mg, 0.68 mmol, 1 equiv) in dry CH_2Cl_2 (1 mL) dropwise at 0 ^oC (Scheme 34). Subsequently, the mixture was allowed to stir at room temperature for another 12 h. After completion (TLC) of the reaction, the reaction mixture was quenched with dilute hydrochloric acid (1N), washed with brine (3X10 mL), extracted with CH_2Cl_2 (3X10 mL), dried over $MgSO_4$, and concentrated in *vacuo*. Then the residue was purified by silica gel (100-200 mesh) column chromatography eluting with 15% ethyl acetate-petroleum ether (v/v) to obtain 2-nitro-*N*-arylbenzenesulfonamide derivatives **141** in 80-90% yield.

To a well stirred solution of 2-nitro-*N*-arylbenzenesulfonamide **141** (100 mg, 0.36 mmol, 1 equiv) in dry MeOH (2 mL) was added satd. NH_4Cl solution (125 mg, 2.34 mmol, 6.5 equiv) dropwise under argon atmosphere. Thereafter, activated Zn (118 mg, 1.8 mmol, 5 equiv,) was added portion-wise maintaining the temperature of the reaction mixture at 0 ^oC. Then the whole reaction mixture was allowed to stir at rt for 2-3 h. Upon completion of the reaction (TLC), the reaction mixture was filtered through celite, neutralized with NaOH (2N). Then the mixture was washed with brine (3X10 mL), extracted with ethyl acetate (3X10 mL), and dried over anhydrous $MgSO_4$, and concentrated in *vaccuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 17% ethyl acetate-petroleum ether (v/v) to obtain the pure 2-amino-*N*-aryl/alkylbenzenesulfonamide **130b** in 71-82% yield.

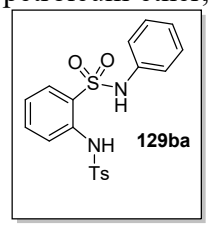
*Synthesis of 2-aminotosylsulphonamide **129b***

Pyridine (32 µl, 0.40 mmol, 2 equiv) was added to a stirred solution of 2-amino-*N*-arylbenzenesulfonamide derivative **130b** (50 mg, 0.2 mmol, 1 equiv) in dry CH_2Cl_2 (2 mL) at 0 ^oC under argon atmosphere. After 2 minute, tosyl chloride (50 mg, 0.26 mmol, 1.3 equiv) was added portion wise and the reaction was allowed to stir at room temperature for 3-4 h. After completion (TLC) of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1M HCl (3X10 mL,), satd. $NaHCO_3$ (3X10 mL), and brine (3X10 mL). The organic phase was dried over anhydrous $MgSO_4$, concentrated, and purified by silica gel (100-200 mesh)

column chromatography using 15-20% ethyl acetate-petroleum ether (v/v) as eluent to afford *N*-substituted-*N*'-protected-2-aminobenzamide **129b** in 84-87% yield.

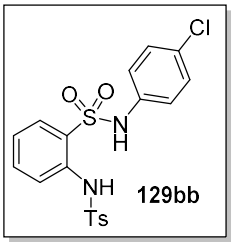
1.2.15.7 Spectral data of substrates 129ba-129bc:

2-((4-Methylphenyl)sulfonamido)-*N*-phenylbenzenesulfonamide (129ba)



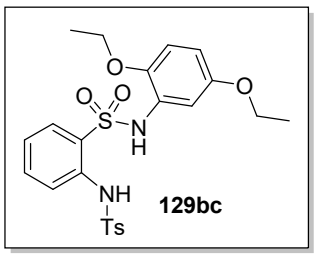
White solid (69 mg, 84% yield), mp. 194-196 °C, R_f = 0.25 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.74 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.56-7.50 (m, 2H), 7.43-7.39 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.21-7.12 (m, 3H),7.03-6.99 (m, 1H), 6.93-6.91 (m, 2H), 6.87 (s, 1H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, 144.9, 136.4, 135.3, 135.1, 134.5, 130.2, 130.1, 129.4, 127.7, 127.6, 126.6, 124.3, 123.6, 122.1, 21.7; HRMS (ESI+) m/z calculated for $C_{19}H_{19}N_2O_4S_2$ $[M+H]^+$ 403.0786, found 403.0786.

***N*-(4-chlorophenyl)-2-((4-methylphenyl)sulfonamido)benzenesulfonamide (129bb)**



Yellow gum (67 mg, 87% yield),R_f = 0.35 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.85 (d, *J* = 8.4 Hz, 2H), 7.57 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.52 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.42-7.38 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.15-7.11 (m, 2H), 7.05-7.00 (m, 1H), 6.93-6.89 (m, 2H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C, 144.9, 136.2, 135.2, 134.7, 134.2, 131.9, 130.3, 130.1, 129.5, 127.6, 127.3, 124.3, 124.2, 121.6, 21.7; HRMS (ESI+) m/z calculated for $C_{19}H_{17}ClN_2NaO_4S_2$ $[M+Na]^+$ 459.0216, found 459.0213.

***N*-(2,5-diethoxyphenyl)-2-((4-methylphenyl)sulfonamido)benzenesulfonamide (129bc)**

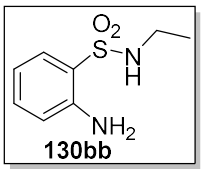


Yellow solid (63 mg, 86% yield), mp. 124-126 °C, R_f = 0.32 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.97 (s, 1H), 7.76-7.73 (m, 2H), 7.58 (dd, *J* = 8.0,1.6 Hz, 1H), 7.54 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.36-7.32 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.09 (s, 1H), 6.98-6.93 (m, 2H), 6.64-6.58 (m, 2H), 3.94 (q, *J* = 6.9 Hz, 2H), 3.76 (q, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 153.1, 144.4, 143.8, 136.2, 136.1, 134.4, 129.9, 127.5,

125.9, 125.2, 123.0, 119.1, 112.5, 109.3, 64.7, 64.3, 21.6, 14.9, 14.7; HRMS (ESI+) m/z calculated for $C_{23}H_{27}N_2O_6S_2$ $[M+H]^+$ 491.1311, found 491.1314.

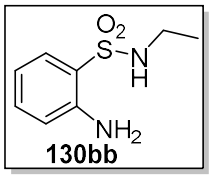
1.2.15.8 Spectral data of substrates 130ba-130bc:

2-Amino-*N*-phenylbenzenesulfonamide (130ba):[29] Brownish solid (68 mg, 76% yield), mp. 113-115 °C, R_f = 0.26 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.52 (dd, *J* = 10.8, 1.6 Hz, 1H), 7.28-7.16 (m, 4H), 7.10-7.04 (m, 2H), 6.73-6.62 (m, 2H), 4.68 (brs, 2H); HRMS (ESI+) m/z calculated for $C_{12}H_{13}N_2O_2S$ $[M+H]^+$ 249.0698, found 249.0700.



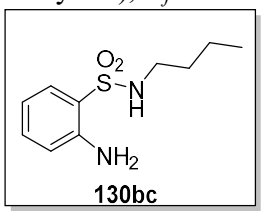
130bb

2-Amino-*N*-ethylbenzenesulfonamide (130bb): Brownish gum (72 mg, 82% yield), R_f= 0.17 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.28-7.24 (m, 1H), 6.75-6.71 (m, 2H), 5.08 (brs, 1H), 4.41 (brs, 2H), 2.87 (p, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 145.1, 134.2, 129.7, 121.5, 118.0, 117.8, 38.3, 14.9; HRMS (ESI+) m/z calculated for $C_8H_{13}N_2O_2S$ $[M+H]^+$ 201.0698, found 201.0696.



130bb

2-Amino-*N*-butylbenzenesulfonamide (130bc): Blackish liquid (81 mg, 71% yield), R_f= 0.28 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.69 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33-7.29 (m, 1H), 6.82-6.76 (m, 2H), 4.80 (brs, 1H), 4.07 (brs, 2H), 2.85 (q, *J* = 6.4 Hz, 2H), 1.42-1.35 (m, 2H), 1.29-1.20 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 144.7, 134.1, 129.8, 122.7, 118.2, 118.0, 43.0, 31.5, 19.7, 13.6; HRMS (ESI+) m/z calculated for $C_{10}H_{17}N_2O_2S$ $[M+H]^+$ 343.1480, found 343.1481.



130bc

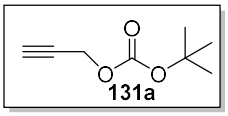
1.2.15.9 Procedure[30] for the preparation of starting material 131a, 131j-k:

To a solution of propargyl alcohol or substituted propargyl alcohol **139** (2.68 mmol, 1 equiv) in dry CH_2Cl_2 was added DIPEA (1.17 ml, 6.70 mmol, 2.5 equiv) and DMAP (33 mg, 0.27 mmol, 0.1 equiv) under argon. The reaction mixture was then cooled to 0 °C and di-*tert*-butyl dicarbonate (Boc_2O) (0.8 mL, 3.48 mmol, 1.3 equiv) was added portion wise over a period of two minutes. The reaction mixture was slowly warmed to ambient temperature over a period of 3-4 h. After completion (TLC) of the reaction, the reaction mixture was diluted with CH_2Cl_2 (10

mL) and washed with water (3X10 mL), 10% aq. HCl (3X10 mL), saturated aq. $NaHCO_3$ solution and brine (3X10 mL), respectively. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash column chromatography to give the desired product **131a** or **131j-k** in 74-84% yield.

1.2.15.10 Spectral data of substrates 131a, 131j-k:

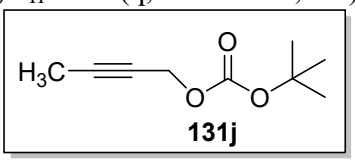
***Tert*-butyl (3-phenylprop-2-yn-1-yl) carbonate (131a)**[30]**:**



Colorless liquid (252 mg, 81% yield); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.64 (d, J = 2.4 Hz, 2H), 2.48 (t, J = 2.4 Hz, 1H), 1.47 (s, 9H).

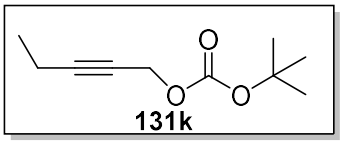
But-2-yn-1-yl *tert*-butyl carbonate (131j):

Yellowish liquid (138 mg, 84% yield), ^1H NMR ($CDCl_3$, 300 MHz) δ_H 4.59 (q, J = 2.4 Hz, 2H), 1.81 (t, J = 2.4 Hz, 3H), 1.45 (s, 9H);); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 153.0, 83.6, 82.7, 73.0, 56.7, 55.2, 27.8, 3.7; HRMS (ESI+) m/z calculated for $C_9H_{15}O_3$ $[M+H]^+$ 171.1021, found 171.1025.



***Tert*-butyl pent-2-yn-1-yl carbonate (131k):**

Colourless liquid (162 mg, 74% yield), ^1H NMR ($CDCl_3$, 400 MHz) δ_H 4.63 (t, J = 2.4 Hz, 2H), 2.23-2.19 (m, 2H), 1.47 (s, 9H), 1.18 (t, J = 10 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 153.0, 89.4, 82.7, 73.1, 55.3, 27.8, 13.6, 12.5; HRMS (ESI+) m/z calculated for $C_{10}H_{17}O_3$ $[M+H]^+$ 425.1284, found 425.1281.



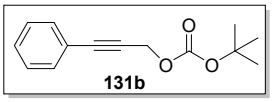
1.2.15.11 General procedure for preparation of starting material 131b-131i:

Substituted tert-butyl propargyl carbonate derivatives **131b-i** were prepared using "Sonogashira reaction" between aryl iodides (R^3I) and propargyl alcohol (**139a**) protected with Boc group (**Scheme 36**). Thus, to a solution of aryl iodide (86 µl, 0.77 mmol, 1.2 equiv) in dry THF (1 mL), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.019 mmol, 3 mol %) was added at room temperature under argon. Next, dry Et_3N (0.9 mL, 6.4 mmol, 10 equiv) was added to the resulting mixture at 0 ^oC followed by the subsequent addition of a solution of **131a** (0.64 mmol, 1 equiv) in dry THF (2

mL) and copper(I) iodide (6.1 mg, 0.032 mmol, 5 mol %). The reaction mixture was heated at 60 ^{o}C for 3-4 h. Upon completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (3X10 mL), and dried over anhydrous $MgSO_4$, and concentrated in *vaccuo*. Then the crude product was purified by silica gel (100-200 mesh) column chromatography eluting with 2-4% ethyl acetate-petroleum ether (v/v) to obtain the pure tert-butyl propargyl carbonates **131b-i** in 65-85% yield.

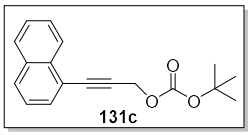
1.2.15.12 Spectral data of substrates 131b-i:

***Tert*-butyl (3-phenylprop-2-yn-1-yl) carbonate (131b)** [30]**:**



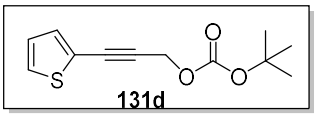
Yellowish liquid (103 mg, 69% yield), R_f = 0.77 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.46-7.43 (m, 2H), 7.33-7.30 (m, 3H), 4.90 (s, 2H), 1.51 (s, 9H).

***Tert*-butyl (3-(naphthalen-1-yl)prop-2-yn-1-yl) carbonate (131c):**



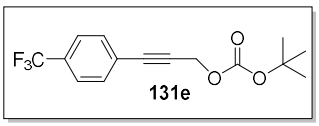
Brownish liquid (130 mg, 72% yield), R_f = 0.68 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.35-8.33 (m, 1H), 7.85-7.83 (m, 2H), 7.71-7.69 (m, 1H), 7.60-7.49 (m, 2H), 7.44-7.39 (m, 1H), 5.07 (s, 2H), 1.55 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 153.1, 133.5, 133.2, 131.0, 129.4, 128.3, 127.0, 126.6, 126.2, 125.2, 119.9, 87.7, 85.1, 83.1, 55.6, 27.9; HRMS (ESI+) m/z calculated for $C_{18}H_{19}O_3$ $[M+H]^+$ 283.1334, found 283.1329.

***Tert*-butyl (3-(thiophen-2-yl)prop-2-yn-1-yl) carbonate (131d)** [31]**:**



Yellowish liquid (126 mg, 83% yield), R_f = 0.7 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.26-7.22 (m, 2H), 6.96-6.94 (m, 1H), 4.89 (s, 2H), 1.49 (s, 9H).

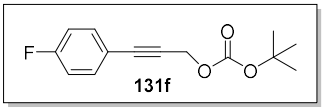
***T*ert-butyl (3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl) carbonate (131e) :**



Brownish liquid (146 mg, 76% yield), R_f = 0.47 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.56-7.50 (m, 4H), 4.88 (s, 2H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 152.9, 132.1, 125.34, 125.31, 125.27, 125.23, 85.4, 85.2, 83.2, 55.0, 27.7; HRMS (ESI+) m/z calculated for $C_{15}H_{16}F_3O_3$ $[M+H]^+$ 301.1052, found 301.1050.

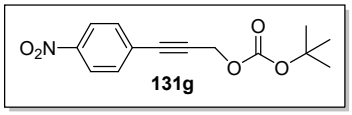
***Tert*-butyl (3-(4-fluorophenyl)prop-2-yn-1-yl) carbonate (131f)** [30]**:**

Yellowish liquid (136 mg, 85% yield), R_f = 0.7 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.43 (d, *J* = 8.8 Hz, 2H,), 7.28 (*J* = 8.4 Hz, 2H), 4.86 (s, 2H), 1.49 (s, 9H).



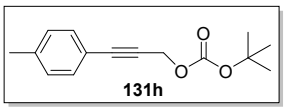
***Tert*-butyl (3-(4-nitrophenyl)prop-2-yn-1-yl) carbonate (131g)** [30]**:**

Yellowish solid (145 mg, 82% yield), mp. 70-71^{o}C, R_f= 0.56 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.18-8.12 (m, 2H), 7.58-7.56 (m, 2H), 4.87 (s, 2H), 1.47 (s, 9H).



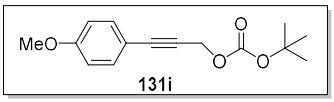
***Tert*-butyl (3-(*p*-tolyl)prop-2-yn-1-yl) carbonate (131h)** [30]**:**

Yellowish liquid (103 mg, 65% yield, R_f = 0.56 (1% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.35-7.32 (m, 2H), 7.13-7.10 (m, 2H), 4.89 (s, 2H), 2.34 (s, 3H), 1.51 (s, 9H).



***Tert*-butyl (3-(4-methoxyphenyl)prop-2-yn-1-yl) carbonate (131i)** [30]**:**

White solid; mp. 56-57 ^{o}C (110 mg, 65% yield), R_f = 0.48 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.38-7.36 (m, 2H), 6.83-6.80 (m, 2H), 4.87 (s, 2H), 3.79 (s, 3H), 1.49 (s, 9H).



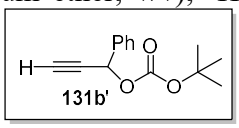
1.2.15.13 General procedure for preparation of starting material 131b'

To a solution of 1-phenylprop-2-yn-1-ol **140** (0.76 mmol, 1 equiv), in dry CH_2Cl_2 (5mL) were added DIPEA (3.2 mL, 1.9 mmol, 2.5 equiv) and DMAP (0.93 mg, 0.076 mmol, 0.1 equiv). The reaction mixture was then cooled to 0 °C, and di-tert-butyl dicarbonate (Boc_2O) (2.2 g, 0.23ml, 0.99 mmol, 1.3 equiv) was added dropwise (**Scheme 39**). The reaction mixture was slowly warmed to ambient temperature over a period of 3 h. After completion (TLC) of the reaction, the reaction mixture was diluted with CH_2Cl_2 and washed with water (3X10 mL), 10% aq. HCl (3X10 mL), sat. aq. $NaHCO_3$ (3X10 mL), and brine (3X10 mL), respectively. The crude residue was purified by silica gel (100-200 mesh) column chromatography to give the desired product **131b'** in 82% yield.

1.2.15.14 Spectral data of substrate 131b'[30]

***Tert*-butyl (1-phenylprop-2-yn-1-yl) carbonate (131b'):**

Yellowish liquid (144 mg, 82% yield), R_f = 0.77 (2% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.55-7.53 (m, 2H), 7.39-7.36 (m, 3H), 6.23 (d, *J* = 2.0 Hz, 1H), 2.67 (d, *J* = 2.0 Hz, 2H), 1.48 (s, 9H).



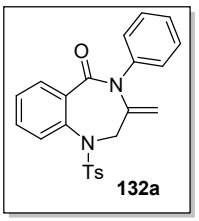
1.2.15.15 General procedure for the synthesis of products 132a-q and 133a-c:

An oven dried two-neck round bottomed flask was charged with $Pd(dba)_2$ (1.6 mg, 0.003 mmol, 5 mol%) and Xantphos (3.1 mg, 0.005 mmol, 10 mol%) followed by the addition of dry CH_3CN (1 mL) *via* syringe. The reaction flask was then purged with argon. After 5 minutes of stirring at room temperature, *tert*-butyl propargyl carbonate **131a** (11 mg, 0.07 mmol, 1.3 equiv) dissolved in CH_3CN (0.5 mL) and 2-amino benzamide **129a** (0.05 mmol, 1 equiv) [or 2-amino benzsulphonamide **129b** (0.05 mmol, 1 equiv)] dissolved in CH_3CN (1 mL) were added subsequently. The reaction mixture was heated under reflux until the completion of the reaction (5 -12 h). The reaction mixture was cooled to room temperature and diluted with 5.0 mL of water. The water layer was extracted with (3x10 mL) of ethyl acetate and the combined ethyl acetate extracts were washed with brine (1x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtained a crude product which was purified over silica gel (100-200 mesh) column chromatography using 10-15% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product **132** (or **133**) in 80-95% yield.

1.2.15.16 Spectral data of products 132a-q:

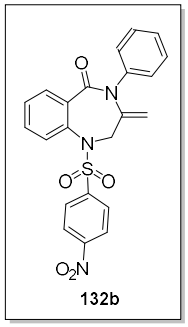
3-Methylene-4-phenyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132a)

Yellow solid (20 mg, 92% yield); mp. 148-150 ^oC; R_f = 0.31 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.74-7.72 (m, 1H), 7.54-7.52 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.45-7.41 (m, 1H), 7.27-7.24 (m, 2H), 7.21-7.17 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.98-6.95 (m, 2H), 5.18 (s, 1H), 4.99 (s, 1H), 4.65 (s, 2H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100



MHz) δ_C 166.2, 144.0, 143.4, 140.7, 136.4, 135.2, 135.1, 132.1, 130.9, 130.8, 129.9, 128.9, 128.0, 127.5, 127.4, 126.5, 124.6, 118.8, 100.0, 58.0, 21.6; HRMS (ESI+) m/z calculated for $C_{23}H_{21}N_2O_3S$ $[M+H]^+$ 405.1273, found 405.1278.

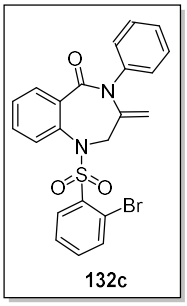
3-Methylene-1-((4-nitrophenyl)sulfonyl)-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132b)



132b

Yellow solid (20 mg, 91% yield); mp. 198-200 °C; R_f = 0.42 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.02 (d, *J* = 8.8 Hz, 2H), 7.70-7.65 (m, 3H), 7.60-7.47 (m, 4H), 7.26 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 3H), 5.29 (s, 1H), 5.09 (s, 1H), 4.76 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 165.7, 144.3, 142.8, 140.7, 135.7, 133.7, 132.4, 131.1, 130.8, 129.8, 129.0, 128.7, 128.4, 126.3, 124.5, 124.2, 122.7, 120.8, 120.6, 100.0, 58.7; HRMS (ESI+) m/z calculated for $C_{22}H_{18}N_3O_5S$ $[M+H]^+$ 436.0967, found 436.0967.

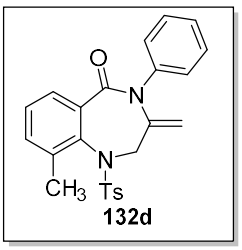
1-((2-Bromophenyl)sulfonyl)-3-methylene-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132c)



132c

White solid (19 mg, 90% yield); mp. 126-128 °C; R_f = 0.36 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.92 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.58 (td, *J* = 7.6, 1.6 Hz, 1H), 7.52-7.41 (m, 3H), 7.39 (d, *J* = 4.4 Hz, 4H), 7.29-7.26 (m, 1H), 7.76 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.37 (s, 1H), 5.30 (s, 1H), 4.82 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.8, 144.2, 137.6, 136.6, 135.2, 134.9, 131.8, 130.4, 130.2, 130.0, 129.3, 129.0, 128.8, 128.0, 127.9, 57.6, 52.8, 21.6, 16.0; HRMS (ESI+) m/z calculated for $C_{22}H_{18}BrN_2O_3S$ $[M+H]^+$ 469.0222, found 469.0229.

9-Methyl-3-methylene-4-phenyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132d)

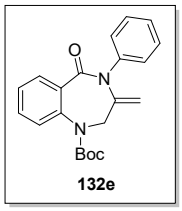


132d

White solid (20 mg, 90% yield); mp. 176-178 °C; R_f = 0.35 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.55 (d, *J* = 8.4 Hz, 2H), 7.48-7.47 (m, 1H), 7.46-7.36 (m, 2H), 7.24-7.13 (m, 5H),

6.98-6.96 (m, 2H), 5.24 (d, J = 1.2 Hz, 1H), 4.99 (d, J = 1.2 Hz, 1H), 4.89-4.85 (m, 1H), 4.35 (d, J = 15.2 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 100 MHz) δ_C 166.5, 144.2, 141.8, 139.9, 137.2, 137.0, 134.3, 134.2, 130.4, 129.5, 128.9, 127.8, 126.6, 125.5, 119.6, 57.4, 21.5, 18.8; HRMS (ESI+) m/z calculated for $C_{24}H_{23}N_2O_3S$ $[M+H]^+$ 419.1429, found 419.1423.

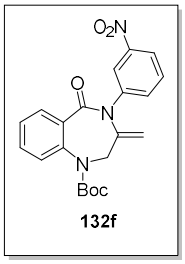
Tert-butyl 3-methylene-5-oxo-4-phenyl-2,3,4,5-tetrahydro-1_H_-benzo[_e_][1,4]diazepine-1-carboxylate (132e)



132e

White solid (19 mg, 87%yield); mp. 136-138 ^{o}C; R_f = 0.31 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.63 (dd, J = 7.6, 1.2 Hz, 1H), 7.56 (td, J = 7.6, 1.6 Hz, 1H), 7.48-7.39 (m, 3H), 7.31-7.25 (m, 4H), 5.21 (s, 1H), 5.04 (s, 1H), 4.14 (s, 2H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 100 MHz) δ_C 167.5, 153.2, 143.5, 137.6, 133.5, 132.1, 129.8, 129.6, 129.5, 128.7, 127.3, 126.7, 105.6, 81.6, 55.3, 28.2; HRMS (ESI+) m/z calculated for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1709, found 351.1707.

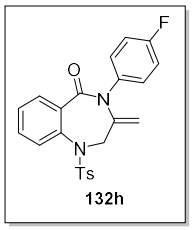
Tert-butyl 3-methylene--4-(3-nitrophenyl)-5-oxo-2,3,4,5-tetrahydro-1H- benzo[_e_][1,4] diazepine-1-carboxylate (132f)



132f

Yellow solid (18 mg, 80% yield); mp. 98-100 ^{o}C; R_f = 0.35 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.31 (t, J = 2.2 Hz, 1H), 8.16-8.13 (m, 1H), 7.81-7.77 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.54 (td, J = 7.8, 1.9 Hz, 1H), 7.45 (td, J = 7.6, 1.2 Hz, 1H), 7.28 (dd, J = 7.8, 1.0 Hz, 1H), 5.44 (s, 1H), 5.01 (s, 1H), 4.19 (s, 2H), 1.36 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 168.0, 153.2, 148.7, 143.2, 142.6, 137.7, 132.5, 132.4, 132.0, 130.1, 129.7, 129.5, 128.4, 121.9, 121.5, 105.3, 82.4, 55.8, 28.1; HRMS (ESI+) m/z calculated for $C_{21}H_{22}N_3O_5$ $[M+H]^+$ 396.1559, found 396.1558.

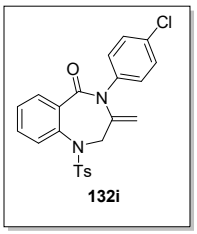
4-(4-Fluorophenyl)-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132h)



132h

White solid (21 mg, 94% yield); mp. 150-152 °C; R_f = 0.23 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.59 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.57-7.53 (m, 3H), 7.46 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.24 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.15 (d, *J* = 6.8 Hz, 4H) 5.31 (s, 1H), 5.15 (s, 1H), 4.62 (s, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 166.2, 160.7 (d, *J* = 242 Hz), 144.4, 143.6, 137.7 (d, *J* = 3.0 Hz), 137.1, 135.6 (d, *J* = 23.6 Hz), 132.6, 130.7, 130.6, 130.3, 129.5, 127.9 (d, *J* = 8.4 Hz), 127.5 , 120.1, 116.1 (d, *J* = 23.0 Hz), 57.8, 21.5; HRMS (ESI+) m/z calculated for $C_{23}H_{20}FN_2O_3S$ $[M+H]^+$ 423.1179, found 423.1178.

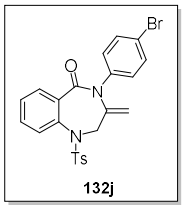
4-(4-Chlorophenyl)-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132i)



132i

White solid (21 mg, 95% yield); mp. 144-146 °C; R_f= 0.25 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.60-7.53 (m, 2H), 7.51-7.44 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.27-7.23 (m, 3H), 7.18 (d, *J* = 8.8 Hz, 2H), 5.36 (s, 1H), 5.17 (s, 1H), 4.63 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 166.1, 144.3, 143.3, 140.1, 136.9, 135.7, 135.3, 132.7, 130.9, 130.7, 130.6, 130.5, 129.5, 129.1, 127.4, 126.9, 121.0, 57.7, 21.5; HRMS (ESI+) m/z calculated for $C_{23}H_{20}ClN_2O_3S$ $[M+H]^+$ 439.0883, found 439.0881.

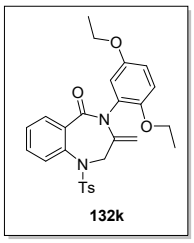
4-(4-Bromophenyl)-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132j)



132j

White solid (19 mg, 89% yield); mp. 146-148 °C; R_f= 0.27 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.60-7.54 (m, 2H), 7.50-7.47 (m, 5H), 7.27-7.22 (m, 3H), 7.15-7.13 (m, 2H), 5.37 (s, 1H), 5.17 (s, 1H), 4.63 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 166.1, 144.3, 143.2, 140.6, 136.9, 135.7, 135.3, 132.7, 132.1, 130.7, 130.5, 129.5, 127.4, 127.1, 121.1, 119.1, 57.7, 21.5; HRMS (ESI+) m/z calculated for $C_{23}H_{20}BrN_2O_3S$ $[M+H]^+$ 483.0378, found 483.0381.

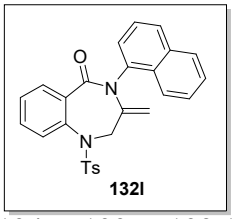
4-(2,5-Diethoxyphenyl)-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132k)



132k

White solid (20 mg, 91% yield); mp. 174-176 °C; R_f = 0.51 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.63 (d, *J* = 8.4 Hz, 2H), 7.55-7.50 (m, 2H), 7.44 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 9.2 Hz, 1H), 6.81 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.34 (d, *J* = 2.8 Hz, 1H), 5.07 (s, 1H), 4.92 (s, 1H), 4.69 (s, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 166.3, 152.7, 148.4, 144.3, 144.0, 137.2, 135.7, 135.6, 132.3, 132.0, 130.5, 129.6, 129.3, 127.6, 115.9, 115.4, 114.7, 114.2, 64.7, 64.1, 58.2, 21.6, 15.3; HRMS (ESI+) m/z calculated for $C_{27}H_{29}N_2O_5S$ $[M+H]^+$ 493.1797, found 493.1793.

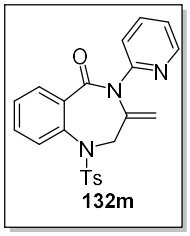
3-Methylene-4-(naphthalen-1-yl)-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132l)



132l

Yellow solid (19 mg, 90% yield); mp. 148-150 °C; R_f = 0.47 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.94 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.88-7.86 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.71-7.66 (m, 5H), 7.58 (td, *J* = 7.8, 1.4 Hz, 1H), 7.50-7.47 (m, 4H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.50 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 4.69 (s, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 166.3, 144.2, 143.0, 138.9, 136.5, 134.7, 133.7, 132.1, 131.5, 129.9, 129.8, 129.6, 128.6, 128.5, 127.7, 127.1, 126.3, 125.4, 124.6, 123.0, 112.2, 57.5, 21.6; HRMS (ESI+) m/z calculated for $C_{27}H_{23}N_2O_3S$ $[M+H]^+$ 455.1429, found 455.1432.

3-Methylene-4-(pyridin-2-yl)-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132m)



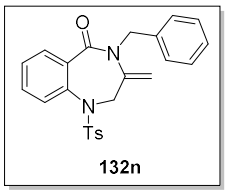
132m

Yellow solid (20 mg, 89% yield); mp.116-118 °C; R_f = 0.35 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.29 (d, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.60-7.54 (m, 3H), 7.46-7.42 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.06-7.03 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.27 (s, 1H), 5.02 (s, 1H), 4.83 (s, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 166.4, 153.5, 147.6, 143.4, 137.2, 136.0, 135.7, 134.8, 132.4, 132.1, 130.4,

129.4, 129.1, 127.0, 120.3, 120.2, 117.1, 58.6, 21.5; HRMS (ESI+) m/z calculated for $C_{22}H_{20}N_3O_3S$ $[M+H]^+$ 406.1225, found 406.1226.

4-Benzyl-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132n)

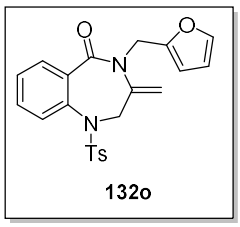
Yellow solid (20 mg, 91% yield); Mp. 192-198 °C; R_f = 0.60 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.51 (d, *J* = 7.6 Hz, 2H), 7.48-7.39 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 3H), 7.15-7.13 (m, 2H), 5.06 (s, 1H), 4.65 (s, 1H), 4.44 (s, 2H), 4.42 (s, 2H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 166.3, 144.2, 142.4, 137.9, 136.8, 135.5, 135.3, 132.2, 130.5, 130.4, 129.3, 128.9, 128.8, 127.9, 127.5, 117.3, 58.4, 50.5, 21.6; HRMS (ESI+) m/z calculated for $C_{24}H_{23}N_2O_3S$ $[M+H]^+$ 419.1429, found 419.1430.



132n

4-(Furan-2-ylmethyl)-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132o)

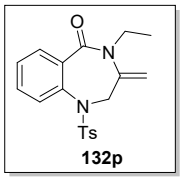
Yellow solid (20 mg, 90% yield); mp. 50-52 °C; R_f = 0.58 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 7.58 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.50-7.45 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.30-6.29 (m, 1H), 6.19 (d, *J* = 3.2 Hz, 1H) 5.03 (s, 1H), 4.76 (s, 1H), 4.51 (s, 2H), 4.35 (s, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 166.4, 150.0, 143.9, 142.6, 142.0, 136.2, 135.1, 134.9, 131.9, 131.2, 130.4, 129.8, 128.9, 127.4, 127.2, 116.8, 110.6, 109.8, 58.3, 43.6, 21.7; HRMS (ESI+) m/z calculated for $C_{22}H_{21}N_2O_4S$ $[M+H]^+$ 409.1222, found 409.1224.



132o

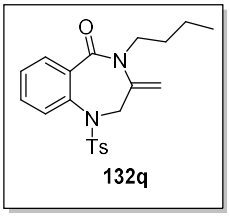
4-Ethyl-3-methylene-1-tosyl-1,2,3,4-tetrahydro-*5H*-benzo[*e*][1,4]diazepin-5-one (132p)

White solid (20 mg, 91% yield); mp. 116-118 °C; R_f = 0.56 (15% ethyl acetate-petroleum ether, v/v); ^1H NMR (DMSO-d_6, 600 MHz) δ_H 7.54-7.46 (m, 4H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* =7.8 Hz, 1H), 5.23 (s, 1H), 5.09 (s, 1H), 4.55 (s, 2H), 3.28 (q, *J* =.7.2 Hz, 2H), 2.38 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 150 MHz) δ_C 165.6, 144.0, 142.6, 136.8, 135.8, 135.2, 131.9, 130.7, 130.3, 130.2, 129.2, 127.4, 117.0, 58.7, 42.2, 21.5, 13.4 ;HRMS (ESI+) m/z calculated for $C_{19}H_{21}N_2O_3S$ $[M+H]^+$ 357.1273, found 357.1273.



132p

4-Butyl-3-methylene-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (132q)

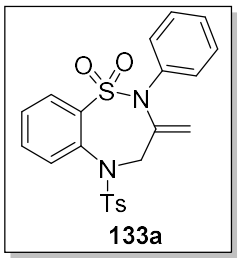


132q

White solid (20 mg, 90%yield); mp. 110-112 °C; R_f = 0.55 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 600 MHz) δ_H 7.52-7.50 (m, 3H), 7.47 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 1H), 5.24 (s, 1H), 5.08 (s, 1H), 4.52 (s, , 2H), 3.23 (t, *J* = 7.8 Hz, 2H), 2.38 (s, 3H), 1.23-1.16 (m, 4H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 150 MHz) δ_C 165.9, 144.0, 142.8, 136.9, 135.8, 135.2, 131.9, 130.4, 130.1, 129.1, 127.4, 117.1, 58.5, 47.4, 29.9, 21.5, 20.1, 14.1; HRMS (ESI+) m/z calculated for $C_{21}H_{25}N_2O_3S$ $[M+H]^+$ 385.1586, found 385.1587.

1.2.15.17 Spectral data of products 133a-c:

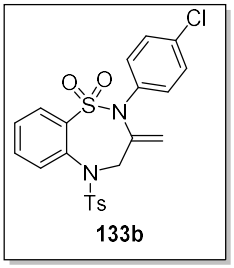
3-Methylene-2-phenyl-5-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (133a)



133a

White solid (19 mg, 86% yield), mp. 154-156 °C R_f = 0.29 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d^6, 400 MHz) δ_H 7.81 (d, *J* = 8.8 Hz, 2H), 7.75 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 (td, *J* = 7.8, 1.7 Hz 1H), 7.52-7.45 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.29-7.27 (m, 3H), 7.05-7.03 (m, 2H), 5.29 (s, 1H), 5.08 (s, 1H), 4.55 (s, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d^6, 100 MHz) δ_C 144.6, 142.8, 140.5, 138.2, 137.9, 137.5, 134.4, 130.5, 130.0, 129.2, 128.69, 128.50, 128.37, 128.01, 127.95, 117.2, 52.3, 21.6; HRMS (ESI+) m/z calculated for $C_{22}H_{21}N_2O_4S_2$ $[M+H]^+$ 441.0943, found 441.0945.

2-(4-Chlorophenyl)-3-methylene-5-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (133b)



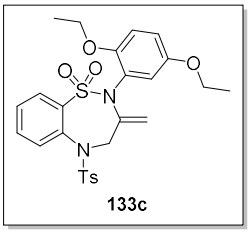
133b

Yellow solid (19 mg, 88% yield), mp. 68-70 °C R_f = 0.39 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.87 (t, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.60-7.56 (m, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.26-7.22 (m, 4H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 1H), 4.72 (s, 1H), 4.70 (s, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C,

144.5, 141.7, 137.6, 136.9, 136.5, 136.3, 134.4, 133.5, 129.8, 129.7, 129.5, 129.4, 128.1, 128.0, 127.4, 112.3, 52.9, 21.7; HRMS (ESI+) m/z calculated for $C_{22}H_{20}ClN_2O_4S_2$ $[M+H]^+$ 475.0553, found 475.0557.

2-(2,5-Diethoxyphenyl)-3-methylene-5-tosyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (133c)

White solid (18 mg, 85% yield), mp. 125-127 ^oC R_f = 0.35 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR (DMSO-d_6, 400 MHz) δ_H 7.81 (d, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.64 (td, *J* = 7.8, 1.7 Hz, 1H), 7.49-7.43 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.86-6.80 (m, 2H), 6.70 (d, *J* = 2.8 Hz, 1H), 5.14(s, 1H), 5.00 (s, 1H), 4.53 (s, 2H), 3.87 (q, *J* = 7.1 Hz, 2H), 3.64 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.71 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz) δ_C 152.5, 149.7, 144.5, 142.5, 139.7, 137.8, 137.6, 133.9, 130.4, 129.8, 128.7, 128.1, 127.6, 118.5, 116.0, 115.1, 114.3, 64.3, 64.1, 52.6, 21.6, 15.1, 14.4; HRMS (ESI+) m/z calculated for $C_{26}H_{29}N_2O_6S_2$ $[M+H]^+$ 529.1467, found 529.1466.



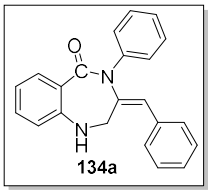
133c

1.2.15.18 Procedure for the synthesis of products 134a-m and 135a-k:

An oven dried two-neck round bottomed flask was charged with $Pd(dba)_2$ (3.8 mg, 0.006 mmol, 7 mol%) and Xantphos (7.6 mg, 0.013 mmol, 14 mol%) followed by addition of dry BuCN (1 mL) *via* syringe. The reaction flask was then purged with argon. After 5 minutes of stirring at room temperature, *tert*-butyl propargyl carbonate **131** (0.14 mmol, 1.5 equiv) having substitution at acetylenic carbon was added dropwise followed by the addition of 2-aminobenzamide derivative **130a** (0.094 mmol,1 equiv) dissolved in BuCN (1 mL). Next, the reaction mixture was heated under reflux until the completion of reaction (1.3 -24 h). The reaction mixture was cooled to room temperature and diluted with water (4.0 mL). The water layer was extracted with ethyl acetate (3x10 mL). The combined ethyl acetate extracts were washed with brine (1x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude residue which was purified over silica gel (100-200 mesh) column chromatography using 10-15% ethyl acetate-petroleum ether (v/v) as eluent to afford desired product **134** in 42-76% yield. The same reaction procedure was adopted for the synthesis of **135** where 2-amino-N-aryl/alkylbenzenesulphonaamide **130b** was used instead of **130a**.

1.2.15.19 Spectral data of products 134a-m:

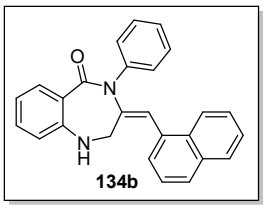
(*E*)-3-benzylidene-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134a):



134a

Brownish solid (22.7 mg, 72% yield), mp. 148-150 °C, R_f = 0.32 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.47-7.45 (m, 2H), 7.36-7.31 (m, 5H), 7.30-7.26 (m, 2H), 7.16 (d, *J* = 4.8 Hz, 2H), 6.89-6.86 (m, 1H), 6.73 (d, *J* = 5.6 Hz, 1H), 6.20 (s, 1H), 4.64 (brs, 1H), 4.28 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 168.0, 143.6, 139.9, 135.5, 134.1, 132.4, 129.4, 128.7, 128.4, 127.4, 127.1, 126.9, 125.0, 118.9, 117.9, 99.9, 48.1; HRMS (ESI+) m/z calculated for $C_{22}H_{19}N_2O$ $[M+H]^+$ 327.1497, found 327.1491.

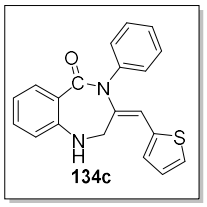
(*E*)-3-(naphthalen-1-ylmethylene)-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134b):



134b

Brown solid (24.8 mg, 70% yield), mp. 152-153 °C, R_f = 0.44 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.83-7.76 (m, 3H), 7.54-7.50 (m, 2H), 7.47-7.43 (m, 3H), 7.40-7.36 (m, 3H), 7.33-7.28 (m, 2H), 6.91-6.87 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 4.12 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.0, 144.0, 141.6, 134.4, 133.6, 132.9, 132.6, 132.2, 129.7, 129.1, 128.5, 128.2, 128.0,127.4, 127.2, 126.38, 126.35, 126.2, 125.9, 125.3, 124.8, 117.9, 100.0, 48.0; HRMS (ESI+) m/z calculated for $C_{26}H_{21}N_2O$ $[M+H]^+$ 377.1654, found 377.1651.

(*E*)-4-phenyl-3-(thiophen-2-ylmethylene)-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134c):

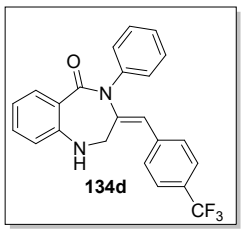


134c

Yellowish solid (22.2 mg, 71% yield), mp. 143-145 °C, R_f = 0.30, (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.14 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45-7.41 (m, 2H), 7.31-7.29 (m, 5H), 7.00-6.97 (m, 1H), 6.87-6.83 (m, 2H), 6.73 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.27 (s, 1H), 4.44 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz)δ_C 168.3, 146.5, 143.5, 138.6, 137.4, 134.4, 132.5, 129.5, 128.4, 127.5, 127.2, 127.0, 126.4, 119.9, 118.9, 118.2, 117.9, 48.5; HRMS (ESI+) m/z calculated for $C_{20}H_{17}N_2OS$ $[M+H]^+$ 333.1062, found 333.1061.

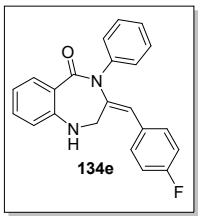
(*E*)-4-phenyl-3-(4-(trifluoromethyl)benzylidene)-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134d):

White solid (18 mg, 48% yield), mp. 166-167 °C, R_f = 0.47 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.19 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.48-7.44 (m, 3H), 7.36-7.34 (m, 1H), 7.32-7.29 (m, 3H), 7.27-7.26 (m, 1H), 6.89-6.85 (m, 1H), 6.73 (dd, *J* = 8.0, 0.4 Hz, 1H), 6.05 (s, 1H), 4.22 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.9, 147.2, 143.6, 142.0, 139.6, 134.6, 132.8, 129.7, 129.1, 127.7, 127.4, 125.41, 125.37, 121.1, 119.3, 119.0, 117.7, 100.0, 47.6; HRMS (ESI+) m/z calculated for $C_{23}H_{18}F_3N_2O$ $[M+H]^+$ 395.1371, found 395.1375.



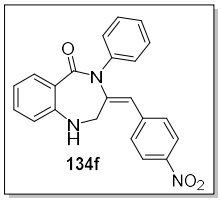
(*E*)-3-(4-fluorobenzylidene)-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134e):

Yellowish solid (14.7 mg, 46% yield), mp. 134-136 °C, R_f = 0.34 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35-7.26 (m, 6H), 7.14-7.12 (m, 4H), 6.90-6.86 (m, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.16 (s, 1H), 4.27 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.1, 146.9, 140.0, 139.6, 135.4, 134.3, 132.6, 129.0, 128.95, 128.70, 128.4, 127.5, 124.3, 119.5, 118.9, 117.7, 116.4, 116.3, 47.9; HRMS (ESI+) m/z calculated for $C_{22}H_{18}FN_2O$ $[M+H]^+$ 345.1403, found 345.1403.

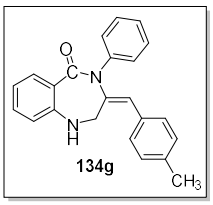


(E)-3-(4-nitrobenzylidene)-4-phenyl-1,2,3,4-tetrahydro-5H-benzo[e][1,4]diazepin-5-one (134f):

Brownish solid (12.8 mg, 42% yield), mp. 156-158 °C, R_f = 0.45, (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.94 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (d, *J* = 6.0 Hz, 2H), 7.37-7.27 (m, 6H), 7.16 (d, *J* = 6.8 Hz, 2H), 6.95-6.91 (m, 1H), 6.73 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.61 (s, 1H), 4.33 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.8, 152.7, 150.3, 146.0, 136.7, 134.3, 133.2, 133.0, 128.7, 128.5, 120.4, 119.2, 100.0, 49.5; HRMS (ESI+) m/z calculated for $C_{22}H_{18}N_3O_3$ $[M+H]^+$ 372.1348, found 372.1346.

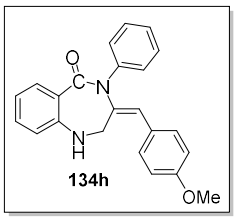


(*E*)-3-(4-methylbenzylidene)-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134g):



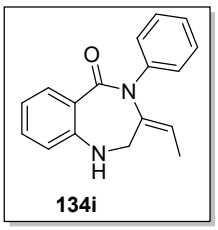
Brownish solid (21.4 mg, 67% yield), mp. 142-143°C, R_f = 0.46 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.11 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44-7.40 (m, 2H), 7.36-7.34 (m, 2H), 7.31-7.26 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.21 (s, 1H), 4.29 (s, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.1, 143.7, 137.6, 134.1, 132.5, 129.5, 129.2, 128.7, 127.1, 126.9, 118.1, 48.6, 21.3; HRMS (ESI+) m/z calculated for $C_{23}H_{21}N_2O$ $[M+H]^+$ 341.1654, found 341.1656.

(*E*)-3-(4-methoxybenzylidene)-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134h):



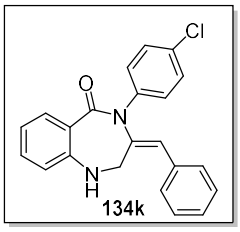
Brownish solid (23 mg, 69% yield), mp. 136-138 °C, R_f = 0.20 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.11 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.45-7.41 (m, 3H), 7.36-7.31 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.85-6.83 (m, 3H), 6.71 (dd, *J* = 7.8, 0.6 Hz, 1H), 6.20 (s, 1H), 4.27 (s, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.1, 138.5, 134.1, 132.4, 130.7, 130.1, 129.4, 128.8, 128.0, 127.0, 126.8, 125.9, 122.7, 119.0, 118.0, 113.9, 100.0, 55.4, 48.6; HRMS (ESI+) m/z calculated for $C_{23}H_{21}N_2O_2$ $[M+H]^+$ 357.1603, found 357.1609.

(*E*)-3-ethylidene-4-phenyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134i):



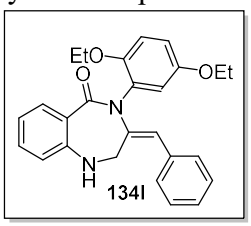
Brownish solid (16.5 mg, 67% yield), mp. 105-106 °C , R_f = 0.28 (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.81 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.55-7.53 (m, 2H), 7.37-7.33 (m, 3H), 7.18-7.13 (m, 1H), 6.93-6.89 (m, 1H), 6.72-6.65 (m, 1H), 5.63 (q, *J* = 6.9 Hz, 1H), 4.15 (s, 2H), 1.47 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.7, 145.3, 141.0, 136.9, 132.1, 131.9, 129.1, 128.9, 125.3, 124.6, 123.3, 120.6, 120.4, 119.5, 100.0, 55.9, 13.0; HRMS (ESI+) m/z calculated for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1341, found 265.1346.

(*E*)-3-benzylidene-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134k):



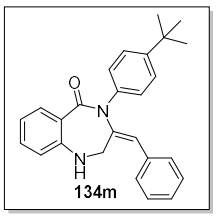
Brownish solid (15.8 mg, 54% yield), mp. 120-122 °C, R_f = 0.80 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.18 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.416-7.410 (m, 1H), 7.40-7.39 (m, 1H), 7.32-7.27 (m, 5H), 7.14 (d, *J* = 7.6 Hz, 3H), 6.88-6.84 (m, 1H), 6.72 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.18 (s, 1H), 4.25 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.1, 146.8, 142.2, 139.8, 135.4, 134.2, 132.7, 132.5, 129.7, 128.8, 128.53, 128.52, 127.7, 125.4, 119.9, 119.1, 118.0, 100.0, 48.2; HRMS (ESI+) m/z calculated for $C_{22}H_{18}ClN_2O$ $[M+H]^+$ 361.1108, found 361.1111.

(*E*)-3-benzylidene-4-(2,5-diethoxyphenyl)-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134l):



Brownish solid (16.6 mg, 60% yield), mp. 128-130 °C, R_f = 0.37 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.18 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.32-7.27 (m, 3H), 7.24-7.20 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.92-6.90 (m, 1H), 6.85-6.84 (m, 1H), 6.83-6.81 (m, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.18 (s, 1H), 4.25 (s, 2H), 4.01-3.95 (m, 4H), 1.38 (t, 7.2 Hz, 3H), 1.27-1.24 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.0, 153.2, 148.2, 146.9, 140.6, 136.2, 134.8, 133.7, 132.3, 128.8, 128.4, 127.2, 121.4, 118.6, 118.1, 117.5, 116.4, 114.6, 114.3, 100.0, 64.8, 64.1, 46.9, 15.0; HRMS (ESI+) m/z calculated for $C_{26}H_{27}N_2O_3$ $[M+H]^+$ 415.2022, found 415.2021.

(*E*)-3-benzylidene-4-(4-(tert-butyl)phenyl)-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (134m):

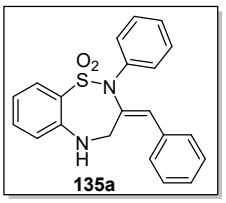


Yellowish solid (19 mg, 67% yield), mp. 194-196 °C, R_f = 0.42 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 7.79 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43-7.41 (m, 2H), 7.33-7.30 (m, 3H), 7.22-7.21 (m, 1H), 7.201-7.196 (m, 2H), 7.18-7.17 (m, 2H), 6.79 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.66-6.61 (m, 1H), 6.09 (s, 1H), 4.15 (d, *J* = 4.4 Hz, 2H), 1.28 (s, 9H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 168.0, 149.4, 148.2, 142.0, 141.0, 135.6, 133.9, 132.6, 129.2,

129.0, 127.9, 127.3, 126.4, 118.3, 116.9, 100.0, 34.8, 31.7; HRMS (ESI+) m/z calculated for $C_{26}H_{27}N_2O$ $[M+H]^+$ 383.2123, found 383.2139.

1.2.15.20 Spectral data of products 135a-k:

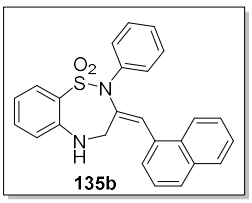
(*E*)-3-benzylidene-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135a):



135a

Brownish solid (22 mg, 76% yield), mp. 185-187 ^oC, R_f = 0.32 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.65 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.47-7.45 (m, 2H), 7.35-7.28 (m, 6H), 7.25-7.20 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.78-6.74 (m, 1H), 6.68 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.04 (s, 1H), 4.75 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 145.4, 143.3, 140.8, 135.5, 133.2, 129.5, 129.4, 129.1, 128.6, 128.5, 128.2, 127.3, 124.8, 121.3, 118.7, 118.1, 45.3; HRMS (ESI+) m/z calculated for $C_{21}H_{19}N_2O_2S$ $[M+H]^+$ 363.1167, found 363.1173.

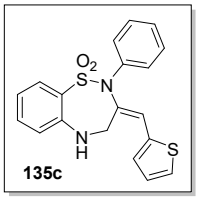
(*E*)-3-(naphthalen-1-ylmethylene)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135b):



135b

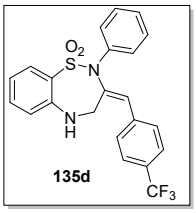
Brownish solid (23.6 mg, 70% yield), mp. 183-185 ^oC, R_f = 0.48 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.82 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.58-7.56 (m, 2H), 7.53-7.51 (m, 1H), 7.48-7.32 (m, 6H), 7.24-7.16 (m, 2H), 6.78-6.74 (m, 1H), 6.62 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.34 (s, 1H), 4.62 (d, *J* = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 145.4, 144.5, 141.0, 133.6, 133.2, 132.6, 132.2, 129.7, 129.6, 129.1, 128.6, 128.5, 128.4, 128.1, 127.2, 126.4, 126.2, 125.3, 124.9, 124.7, 118.6, 118.5, 118.0, 100.0, 45.3; HRMS (ESI+) m/z calculated for $C_{25}H_{21}N_2O_2S$ $[M+H]^+$ 413.1324, found 413.1324.

(*E*)-2-phenyl-3-(thiophen-2-ylmethylene)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135c):



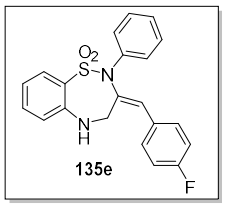
Brownish solid (22.5 mg, 76% yield), mp. 109-111 °C, R_f = 0.27 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.65 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46-7.43 (m, 2H), 7.35-7.26 (m, 5H), 6.98-6.96 (m, 1H), 6.80-6.75 (m, 2H), 6.72 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.07 (s, 1H), 4.91 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.2, 142.4, 140.4, 137.5, 133.3, 129.5, 129.3, 128.6, 128.2, 128.1, 127.4, 125.9, 124.8, 118.9, 118.3, 114.6, 100.0, 45.8; HRMS (ESI+) m/z calculated for $C_{19}H_{17}N_2O_2S_2$ $[M+H]^+$ 369.0731, found 369.0732.

(E)-2-phenyl-3-(4-(trifluoromethyl)benzylidene)-2,3,4,5 tetrahydrobenzo[f][1,2,5]thiadiazepine-1,1-dioxide (135d):



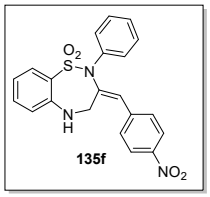
Brownish solid (18 mg, 53% yield), mp. 163-165 °C, R_f = 0.45 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.65 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.45-7.43 (m, 2H), 7.37-7.29 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.80-6.76 (m, 1H), 6.70 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.98 (s, 1H), 4.75 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.2, 140.4, 133.4, 129.9, 129.62, 129.59, 129.4, 129.2, 128.54, 128.50, 125.43, 125.39, 124.6, 122.6, 119.1, 118.8, 118.1, 112.6, 100.0, 45.1; HRMS (ESI+) m/z calculated for $C_{22}H_{18}F_3N_2O_2S$ $[M+H]^+$ 431.1041, found 431.1036.

(*E*)-3-(4-fluorobenzylidene)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135e):



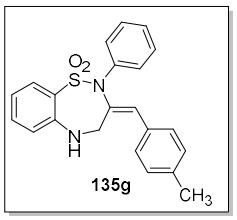
Brownish solid (20.9 mg, 68% yield), mp. 167-169 °C, R_f = 0.48 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47-7.45 (m, 2H), 7.34-7.32 (m, 2H), 7.31-7.30 (m, 1H), 7.29-7.28 (m, 1H), 7.23-7.21 (m, 2H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.79-6.75 (m, 1H), 6.68 (dd, *J* = 8.6, 0.6 Hz, 1H), 6.04 (s, 1H), 4.77 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 136.5, 134.7, 131.1, 131.0, 130.7, 129.14, 129.08, 127.41, 127.39, 125.7, 122.7, 116.1, 115.9, 100.0, 46.5; HRMS (ESI+) m/z calculated for $C_{21}H_{18}FN_2O_2S$ $[M+H]^+$ 381.1073 found 381.1075.

(*E*)-3-(4-nitrobenzylidene)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135f):



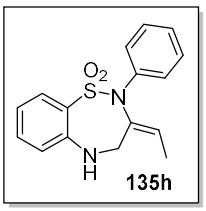
Yellow solid (25 mg, 76 % yield), mp. 208-210°C, R_f = 0.24 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 8.14 (d, *J* = 8.8 Hz, 2H), 7.41-7.37 (m, 5H), 7.33-7.29 (m, 4H), 6.85 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.69-6.65 (m, 1H), 5.94 (s, 1H), 4.63 (d, *J* = 5.2 Hz, 2H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 147.2, 146.8, 146.5, 142.7, 140.9, 134.0, 130.5, 130.2, 129.7, 128.9, 127.9, 124.1, 122.8, 118.8, 118.3, 117.6, 100.0, 43.9; HRMS (ESI+) m/z calculated for $C_{21}H_{17}N_3NaO_4S$ $[M+Na]^+$ 429.0885, found 429.0887.

(*E*)-3-(4-methylbenzylidene)-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135g):



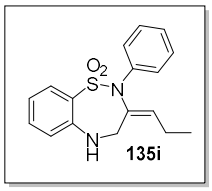
White solid (21.5 mg, 71% yield), mp. 184-186 °C, R_f = 0.40, (15% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.40-7.37 (m, 4H), 7.31-7.24 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.13 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 5.94 (s, 1H), 4.61 (d, *J* = 4.2 Hz, 2H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 146.9, 143.8, 141.4, 137.1, 133.6, 132.3, 129.8, 129.5, 129.3, 129.1, 128.3, 128.0, 123.1, 121.3, 118.7, 117.5, 44.4, 21.1; HRMS (ESI+) m/z calculated for $C_{22}H_{21}N_2O_2S$ $[M+H]^+$ 377.1324, found 377.1327.

(*E*)-3-ethylidene-2-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135h):



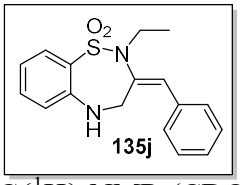
Reddish gum (17 mg, 72 % yield), R_f = 0.34 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60-7.57 (m, 1H), 7.27-7.26 (m, 1H), 7.24-7.12 (m, 4H), 6.76-6.72 (m, 1H), 6.68 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.24 (q, *J* = 6.9 Hz, 2H), 4.64 (s, 2H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 145.7, 141.0, 140.8, 133.1, 129.4, 129.2, 129.0, 128.9, 127.9, 126.9, 125.1, 119.1, 118.48, 118.46, 50.8, 12.6; HRMS (ESI+) m/z calculated for $C_{16}H_{17}N_2O_2S$ $[M+H]^+$ 301.1011, found 301.1008.

(*E*)-2-phenyl-3-propylidene-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135i):



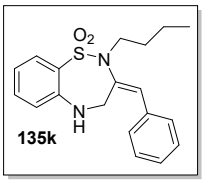
Brownish gum (17.5 mg, 69% yield), R_f = 0.64 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.63-7.58 (m, 3H), 7.21-7.14 (m, 4H), 6.75-6.66 (m, 2H), 5.09 (t, *J* = 7.2 Hz, 1H), 4.46 (s, 2H), 1.82 (p, *J* = 7.6 Hz, 2H), 0.66 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 145.7, 141.4, 139.4, 133.1, 129.4, 129.2, 129.0, 128.9, 128.1, 127.0, 125.3, 125.0, 119.1, 118.4, 50.8, 20.4, 12.6; HRMS (ESI+) m/z calculated for $C_{17}H_{19}N_2O_2S$ $[M+H]^+$ 315.1167, found 315.1166.

(*E*)-3-benzylidene-2-ethyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (7j):



Yellowish solid (22 mg, 71% yield), mp. 127-129 ^oC, R_f = 0.45 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.265-7.263 (m, 1H), 7.25-7.23 (m, 1H), 6.90-6.85 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.17 (s, 1H), 4.36 (s, 2H), 3.37 (q, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 145.9, 138.3, 134.6, 133.0, 129.1, 129.0, 128.6, 128.0, 127.5, 121.2, 119.5, 118.8, 51.6, 45.8, 12.8; HRMS (ESI+) m/z calculated for $C_{17}H_{19}N_2O_2S$ $[M+H]^+$ 315.1167, found 361.1161.

(*E*)-3-benzylidene-2-butyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine-1,1-dioxide (135k):



Brownish gum (21 mg, 70% yield), R_f = 0.59 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.52 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.39-7.35 (m, 2H), 7.29-7.21 (m, 3H), 6.84-6.82 (m, 1H), 6.75-6.70 (m, 2H), 6.44 (s, 1H), 4.33 (d, *J* = 4.4 Hz, 2H), 3.54-3.50 (m, 2H), 1.60-1.53 (m, 2H), 1.23-1.17 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 147.2, 141.7, 135.9, 133.4, 129.6, 129.0, 128.0, 127.7, 124.6, 120.0, 118.8, 117.6, 50.8, 44.7, 31.2, 19.7, 14.0; HRMS (ESI+) m/z calculated for $C_{19}H_{23}N_2O_2S$ $[M+H]^+$ 343.1480, found 343.1481.

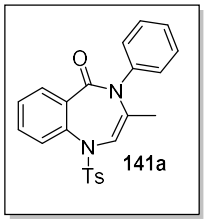
1.2.15.21 Procedure for the synthesis of isomerisations product 141a-c:

To a well stirred solution of the 1,4-benzodiazepinone **132a** (0.05 mmol, 1 equiv) in dry benzene (1 mL) was added anhydrous $ZnBr_2$ (23 mg, 0.1 mmol, 2 equiv) under argon atmosphere. The reaction mixture was then heated at 80 °C for 1 h until completion of the reaction (TLC). Upon completion of the reaction, the mixture was cooled to room temperature and quenched with water (2 mL). It was then extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was purified over silica gel (100-200 mesh) column chromatography using 10% ethyl acetate–petroleum ether (v/v) as eluent to afford pure products **141a** in 72% yield.

The same reaction procedure was adopted in the isomerisations of **132h** and **132j** into **141b** (72%) and **141c** (75%), respectively.

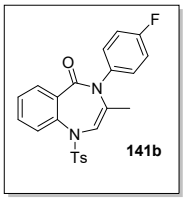
1.2.15.22 Spectral data of products 141a–141c:

3-Methyl-4-phenyl-1-tosyl-1,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (141a)



White solid (15.6 mg, 78% yield), mp. 152-154 ^{o}C, R_f = 0.58 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.85-7.83 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.55-7.54 (m, 2H), 7.42-7.38 (m, 1H), 7.27 (s, 2H), 7.24-7.23 (m, 3H),, 6.46 (d, *J* = 7.2 Hz, 2H), 6.19 (d, *J* = 1.2 Hz, 1H), 2.38 (s, 3H), 1.45 (d, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 167.1, 144.3, 143.6, 138.9, 137.8, 137.5, 132.5, 132.1, 131.7, 129.9, 128.8, 128.1, 128.0, 127.9, 127.5, 118.5, 21.6, 18.7; HRMS (ESI+) m/z calculated for $C_{23}H_{21}N_2O_3S$ $[M+H]^+$ 405.1273, found 405.1275.

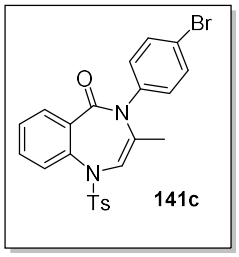
4-(4-Fluorophenyl)-3-methyl-1-tosyl-1,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (141b)



White solid (14.5 mg, 72% yield), mp 165-167 ^{o}C, R_f = 0.55 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.85 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.59-7.55 (m, 2H), 7.44-7.42 (m, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 6.44 (brs, 2H), 6.21 (s,

1H), 2.41 (s, 3H), 1.48 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 167.0, 161.7 (d, J = 247.5 Hz), 144.2, 143.5, 137.5 (d, J = 25.5 Hz), 134.6 (d, J = 3.0 Hz). 132.6, 132.0, 131.3, 129.8, 129.6 (d, J = 7.5 Hz), 128.0, 127.9, 127.4, 118.7, 115.7 (d, J = 22.4 Hz), 21.6, 18.6; HRMS (ESI+) m/z calculated for $C_{23}H_{20}FN_2O_3S$ $[M+H]^+$ 445.0998, found 445.0994.

4-(4-Bromophenyl)-3-methyl-1-tosyl-1,4-dihydro-5*H*-benzo[*e*][1,4]diazepin-5-one (141c):



141c

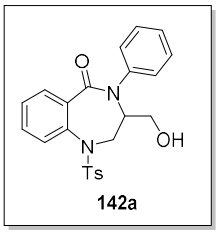
White solid (15 mg, 75% yield), mp. 164-166 ^{0}C, R_f = 0.54 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.83-7.81 (m, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.58-7.53 (m, 2H), 7.43-7.39 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.26-7.24 (m, 2H), 6.36 (d, J = 8.4 Hz, 2H), 6.21 (d, J = 1.2 Hz, 1H), 2.39 (s, 3H), 1.46 (d, J = 1.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 166.9, 144.4, 143.5, 137.9, 137.5, 137.4, 132.7, 132.1, 132.0, 131.3, 129.9, 129.7, 128.1, 128.0, 127.5, 121.8, 119.2, 21.6, 18.6; HRMS (ESI+) m/z calculated for $C_{23}H_{20}BrN_2O_3S$ $[M+H]^+$ 483.0378, found 483.0380.

1.2.15.23 Procedure for the synthesis of product 142a-b:

To a well-stirred and cooled (0 °C) solution of **132** (0.05 mmol, 1 equiv) in dry THF (2 mL), borane dimethyl sulphide complex (2 M in THF) (0.12 mL, 0.25 mmol) and butylated hydroxytoluene (BHT) (1 mg) was added slowly under argon. The whole mixture was allowed to attain to rt and stirred at rt for another 3 h. Thereafter the reaction mixture was cooled to 0 ^{o}C and H_2O_2 (100 vol., 0.1 mL) was added followed by the addition of aqueous NaOH (4 M, 0.1mL). After the completion of reaction (1 h), the reaction mixture was quenched with water (3 mL). It was then extracted with ethyl acetate (3x15 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulphate. The ethyl acetate layer was then evaporated under reduced pressure to obtain a crude residue which was purified by silica gel (100-200 mesh) column chromatography using 50% ethyl acetate–petroleum ether (v/v) as the eluent to afford a pure product **142a/142b** in 82-84% yield.

1.2.15.24 Spectral Data of Compounds 142a and 142b:

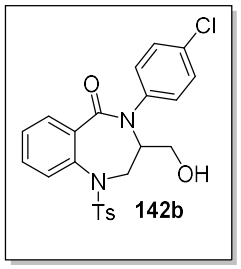
3-(Hydroxymethyl)-4-phenyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (142a)



142a

Brown solid (17.5 mg, 84% yield), mp. 169-171 °C, R_f = 0.40 (50% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.70 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.53-7.41 (m, 3H), 7.29-7.23 (m, 5H), 6.73 (d, *J* = 5.6 Hz, 2H), 4.10-4.05 (m, 1H), 3.97-3.91 (m, 1H), 3.77 (dd, *J* = 12.0, 3.8 Hz, 1H), 3.34 (s, 2H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.9, 144.2, 138.1, 136.7, 135.0, 132.0, 130.3, 130.2, 130.0, 129.3, 129.0, 128.9, 128.3, 127.9, 100.0, 60.7, 59.8, 53.6, 21.6; HRMS (ESI+) m/z calculated for $C_{23}H_{23}N_2O_4S$ $[M+H]^+$ 423.1379, found 423.1376.

4-(4-Chlorophenyl)-3-(hydroxymethyl)-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (142b)



142b

White solid (17 mg, 82% yield), mp. 150-152 °C, R_f = 0.39 (50% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.54-7.50 (m, 1H), 7.47-7.43 (m, 2H), 7.26-7.23 (m, 4H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.07-4.02 (m, 1H), 3.98-3.91 (m, 1H), 3.78 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.37 (d, *J* = 6.0 Hz, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.9, 144.3, 136.7, 135.0, 134.9, 134.1, 132.2, 130.4, 130.3, 130.1, 129.4, 129.1, 127.9, 100.0, 60.6, 59.9, 53.4, 21.6; HRMS (ESI+) m/z calculated for $C_{23}H_{22}ClN_2O_4S$ $[M+H]^+$ 457.0989, found 457.0991.

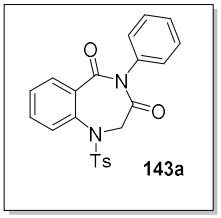
1.2.15.25 Synthetic transformations of 132a/132h into 1,2-dihydro-3*H*-benzo[*e*][1,4]diazepine-3,5(4*H*)-diones 143a/143b

To a stirred solution of the substrate **132a** or **132h** (0.05 mmol, 1 equiv) in a mixture of $CH_3CN/CCl_4/H_2O$ (1 mL, 2:1:1) was added $RuCl_3$ (0.52 mg, 0.0025 mmol, 0.05 equiv) and NaIO4 (64 mg, 0.3 mmol, 6 equiv) at 0 °C under an argon atmosphere. Stirring was continued at 0 °C for 15 min. The reaction mixture was then diluted with ethyl acetate (8 mL) and quenched with aqueous sodium thiosulfate. The ethyl acetate layer was then filtered through a plug of

celite. The filtrate was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by silica gel (100-200 mesh) column chromatography using 20% ethyl acetate–petroleum ether (v/v) as eluent to afford the pure product **143a** or **143b** in 64% or 68% yield.

1.2.15.26 Spectral data of products 143a and 143b:

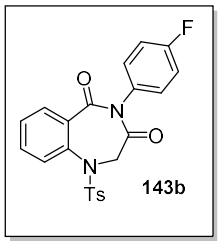
4-Phenyl-1-tosyl-1,2-dihydro-3*H*-benzo*[e]*[1,4]diazepine-3,5*(4H)*-dione (143a) :



143a

White Solid (12.8 mg, 64% yield), mp. 187-189 ^oC, R_f = 0.32 (20% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.03-8.00 (m, 1H), 7.65-7.62 (m, 4H), 7.51-7.47 (m, 1H), 7.36-7.31 (m, 5H), 6.60-6.57 (m, 2H), 4.78 (s, 2H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 202.5, 171.2, 165.9, 144.9, 136.6, 134.1, 131.2, 130.4, 129.1, 129.0, 128.9, 128.5, 128.1, 127.5, 100.0, 55.9, 21.7; HRMS (ESI+) m/z calculated for $C_{22}H_{18}N_2NaO_4S$ $[M+Na]^+$ 429.0885, found 429.0888.

4-(4-Fluorophenyl)-1-tosyl-1,2-dihydro-3*H*-benzo[*e*][1,4]diazepine-3,5(4*H*)-dione (143b):



143b

White solid (13.6 mg, 68% yield), mp. 182-184 ^oC; R_f= 0.34 (20% ethyl acetate-petroleum ether, v/v), ^1H NMR ($CDCl_3$, 400 MHz) δ_H 8.02 (dd, J = 8.0, 1.6 Hz, 1H), 7.64-7.62 (m, 3H), 7.58 (dd, J = 8.0, 1.2 Hz, 1H), 7.52-7.47 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.06-7.01 (m, 2H), 6.62-6.58 (m, 2H), 4.75 (s, 2H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 171.4, 165.8, 162.3 (d, J = 246.0 Hz), 145.0, 138.2, 136.6, 134.2 (d, J = 7.9 Hz) 133.6 (d, J = 3.5 Hz), 131.0, 130.4 129.9 (d, J = 8.3 Hz), 129.0 (d, J = 9.4 Hz), 127.6, 116.1 (d, J = 23.0 Hz), 55.9, 21.7; HRMS (ESI+) m/z calculated for $C_{22}H_{18}FN_2O_4S$ $[M+H]^+$ 425.0971, found 425.0970.

1.2.15.27 Procedure for the hydrogenation of 132a/132h into 3-methyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-ones 144a/ 144b:

To a well stirred solution of Compound **132a** (0.05 mmol, 1 equiv) in dry ethyl acetate (1 mL), 5 mg of 10% Pd/C catalyst was added and the whole reaction mixture was allowed to stir at rt under the balloon pressure of H_2. After 3 h, the catalyst was removed by filtration and washd

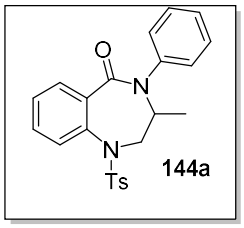
with ethyl acetate (5 mL). The combined filtrate was evaporated to dryness to give a gummy material which was purified by silica gel column chromatography using 20% ethyl acetate–petroleum ether (v/v) as the eluent to afford pure products **144a** in 81% yield.

The same procedure was adopted for the hydrogenation of **132h** to obtain the product **144b** in 77% yield.

1.2.15.28 Spectral data of products 144a and 144b:

3-Methyl-4-phenyl-1-tosyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (144a):

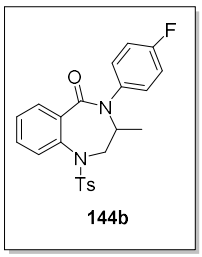
White solid (16.2 mg, 81% yield), mp. 152-154 ^{o}C; R_f= 0.36 (20% ethyl acetate-petroleum ether, v/v), mp 158-160 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.74-7.13 (m, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.55-7.49 (m, 2H), 7.46-7.42 (m, 1H), 7.26 (s, 3H), 7.25 (s, 3H), 6.57 (d, *J* = 5.2 Hz, 2H), 4.01-3.91 (m, 2H), 3.61 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.37 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 168.8, 144.2, 137.6, 136.6, 135.2, 134.9, 131.8, 130.4, 130.2, 130.0, 129.3, 129.0, 128.8, 128.0, 127.9, 57.6, 52.8, 21.6, 16.0;HRMS (ESI+) m/z calculated for $C_{23}H_{23}N_2O_3S$ $[M+Na]^+$ 429.1249, found 429.1253.



144a

4-(4-Fluorophenyl)-3-methyl-1-tosyl-1,2,3,4-tetrahydro-5H-benzo[*e*][1,4]diazepin-5-one (144b):

White Solid (15.4 mg, 77% yield), m.p. 156-157^{o}C , R_f = 0.40 (20% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.73-7.71 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.54-7.49 (m, 2H), 7.47-7.43 (m, 1H), 7.27-7.25 (m, 2H), 6.96-6.92 (m, 2H), 6.56 (s, 2H), 4.00-3.90 (m, 2H), 3.61-3.57 (m, 1H), 2.38 (s, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 169.0, 162.5 (d, *J* = 246.6 Hz) 144.2, 136.7, 135.0 (d, *J* = 9.1 Hz), 133.5, 132.0, 130.2 (d, *J* = 12.3 Hz), 130.0, 128.9, 127.9, 115.9 (d, *J* = 22.4 Hz), 57.5, 52.8, 21.6, 16.0; HRMS (ESI+) m/z calculated for $C_{23}H_{22}FN_2O_3S$ $[M+H]^+$ 425.1335, found 425.1338.



144b

1.2.16. References:

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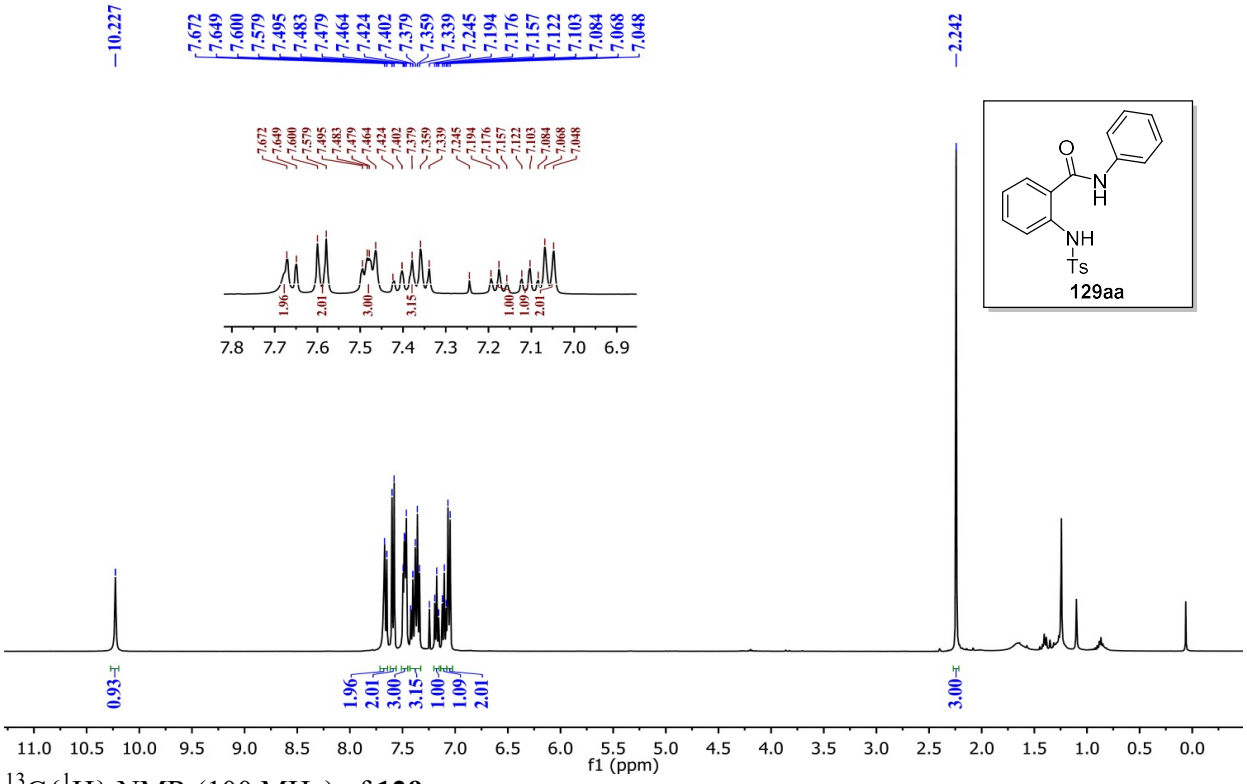
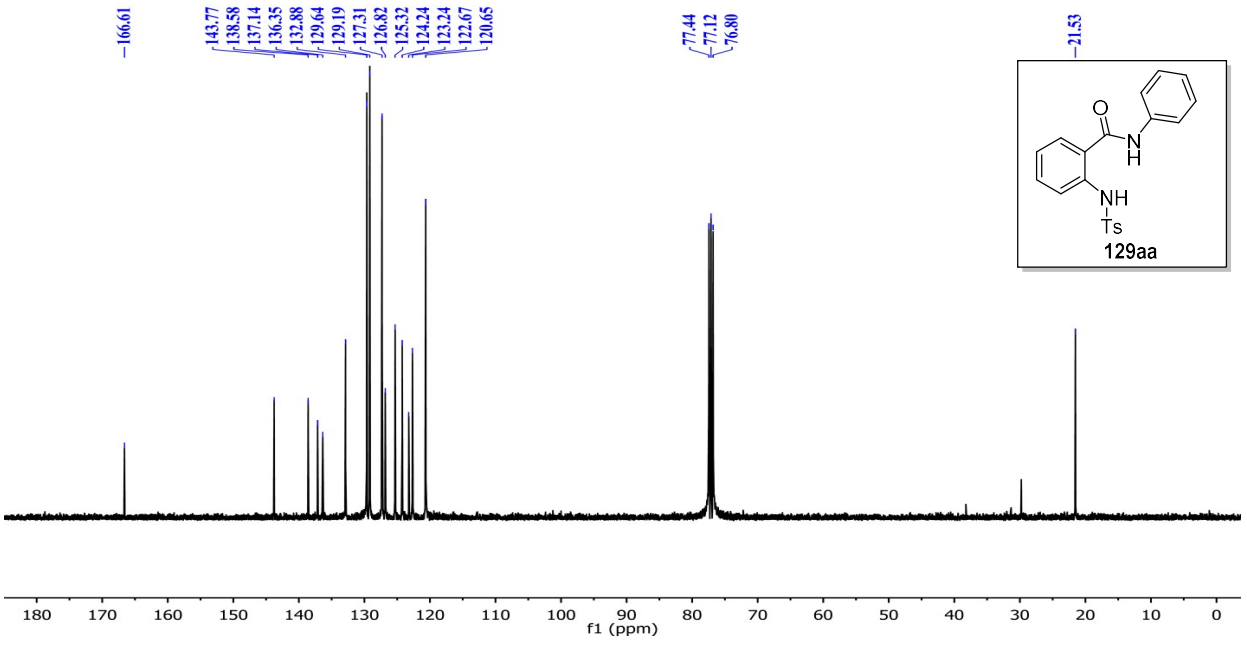
1.2.17. Copies of NMR Spectra

1.2.17.1 NMR spectra of substrates 129aa-129aq:

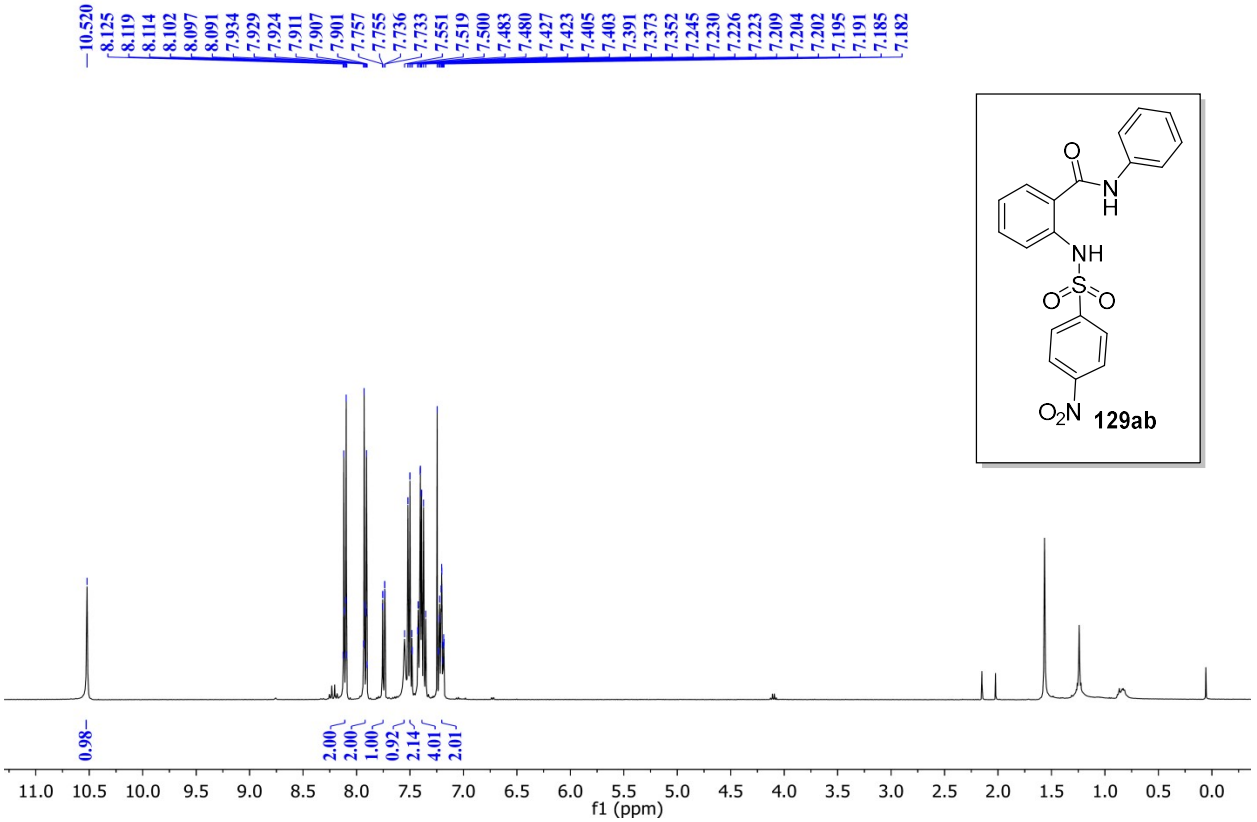
^{1}H NMR (400 MHz) of **129aa**:



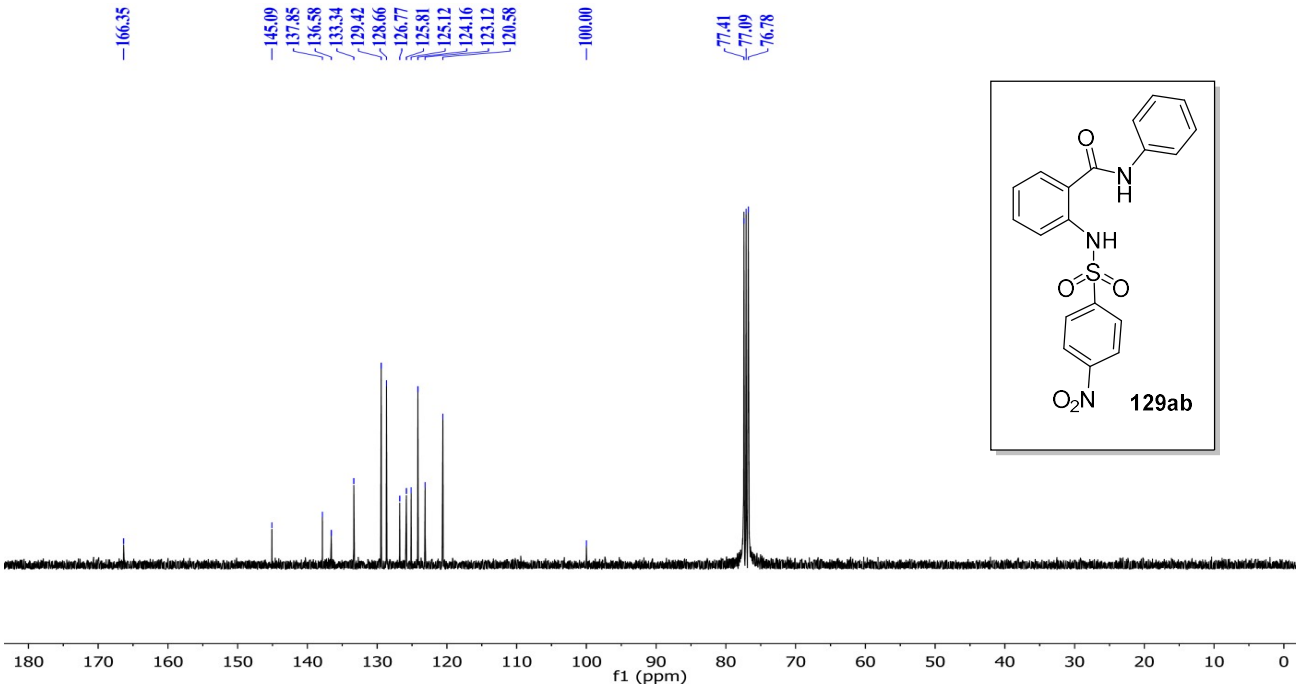
^{13}C{^{1}H} NMR (100 MHz) of **129aa**:



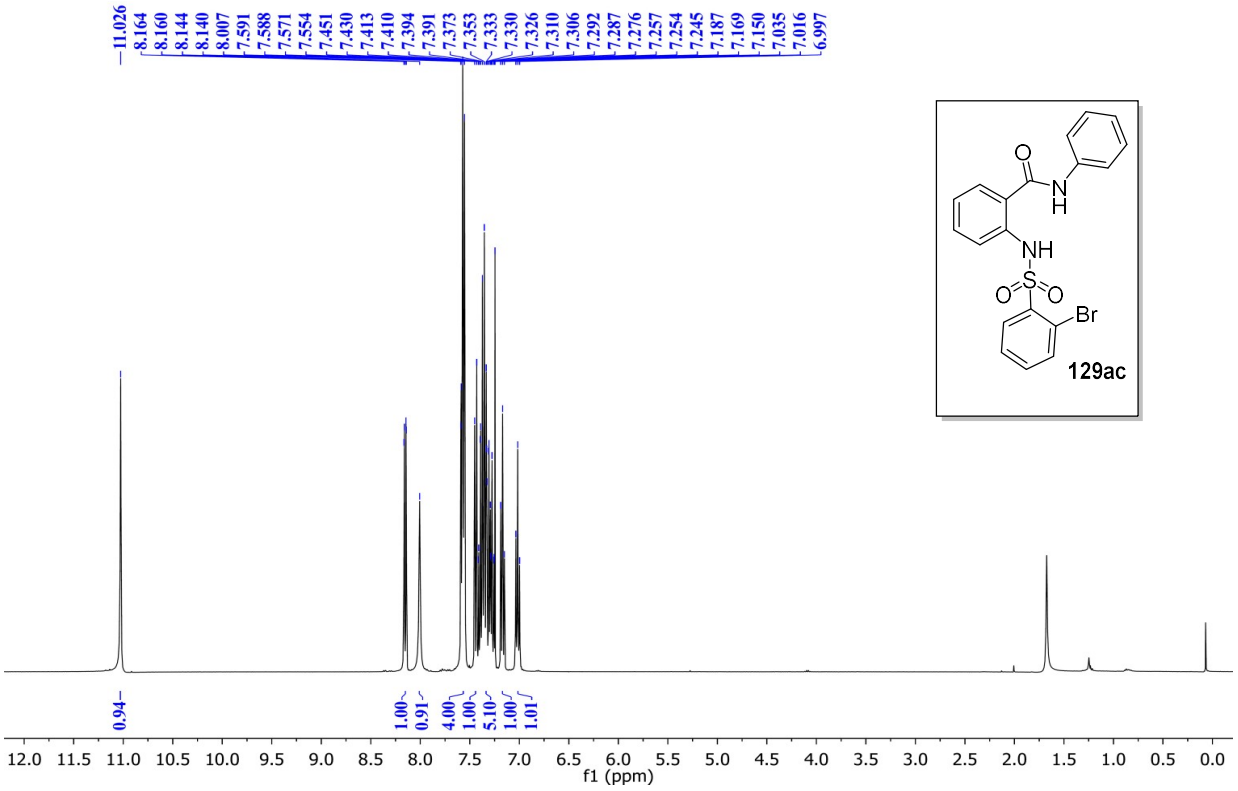
^{1}H NMR (400 MHz) of **129ab**:



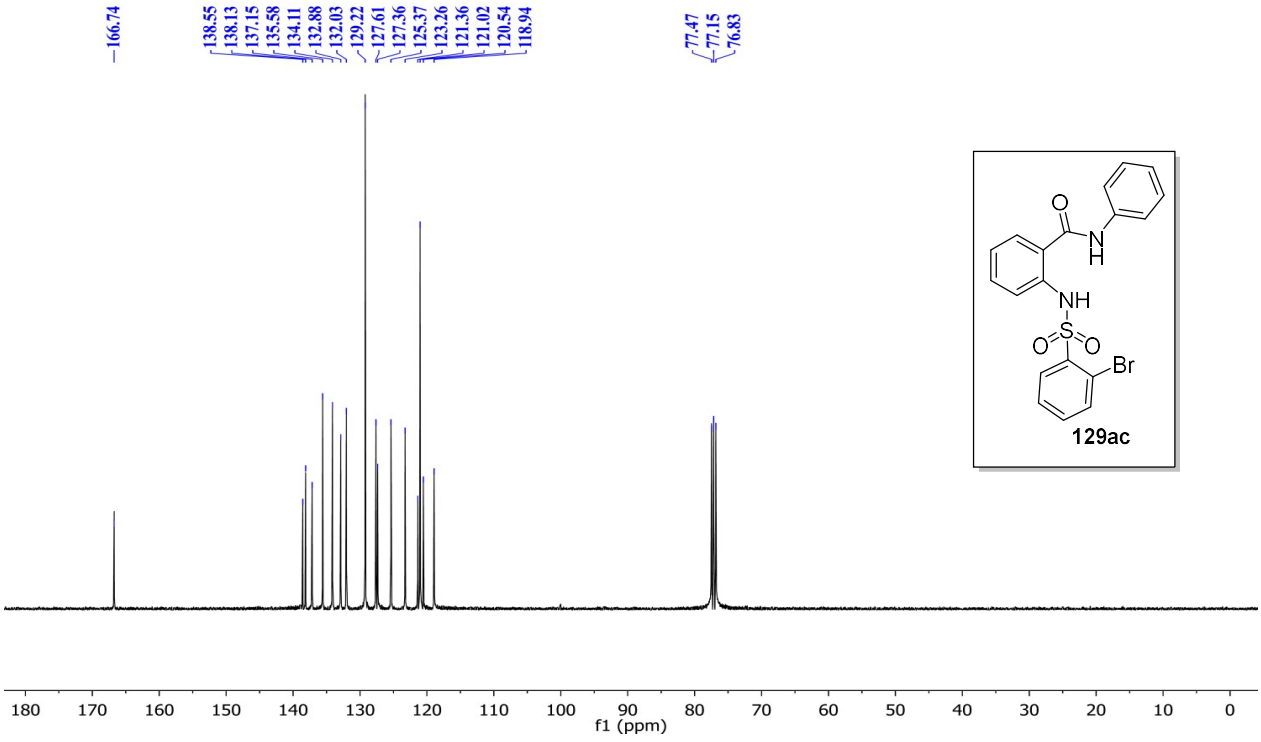
^{13}C{^{1}H} NMR (100 MHz) of **129ab**:



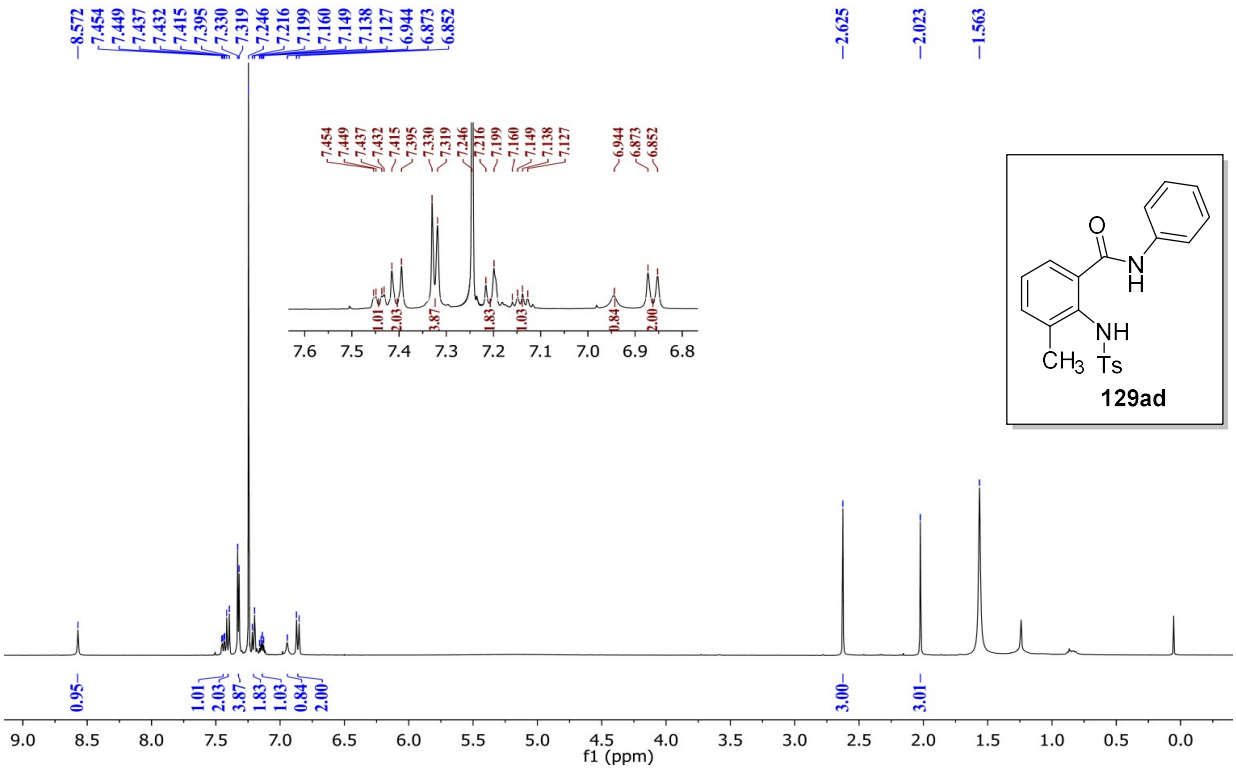
^{1}H NMR (400 MHz) of **129ac:**



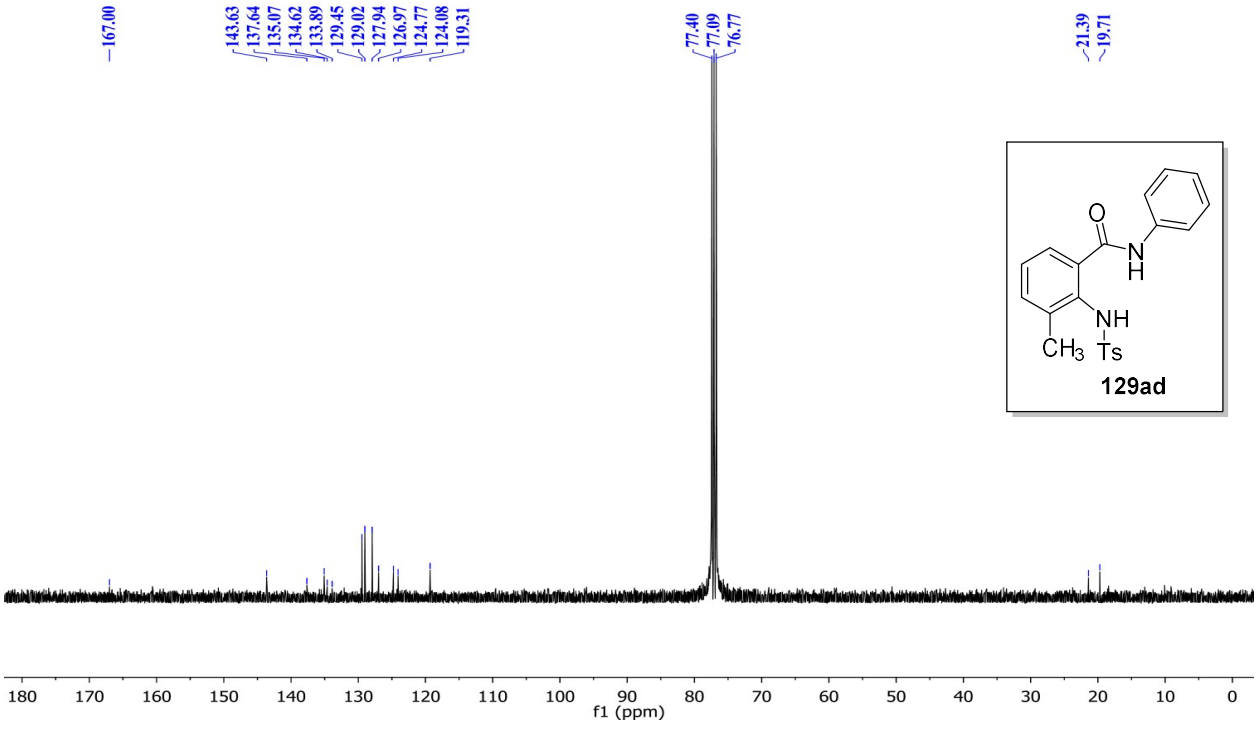
^{13}C{^{1}H} NMR (100 MHz) of **129ac**:



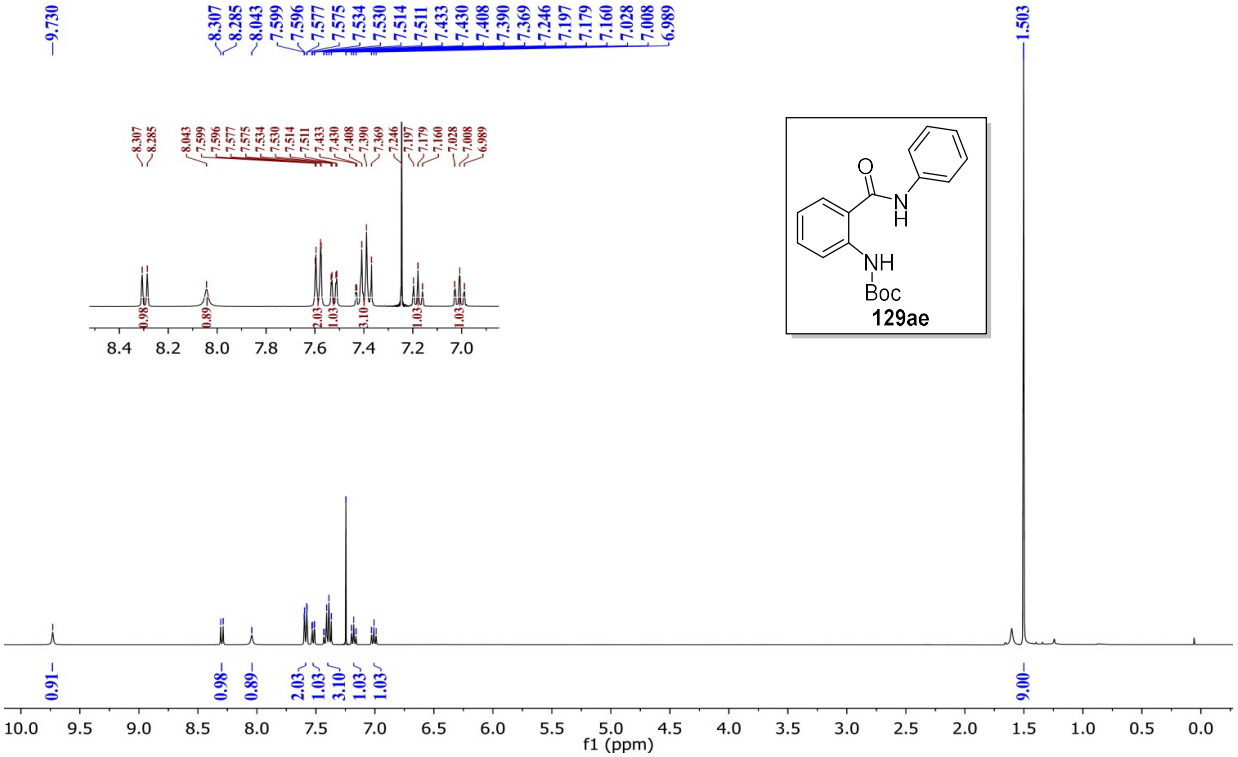
^{1}H NMR (400 MHz) of **129ad:**



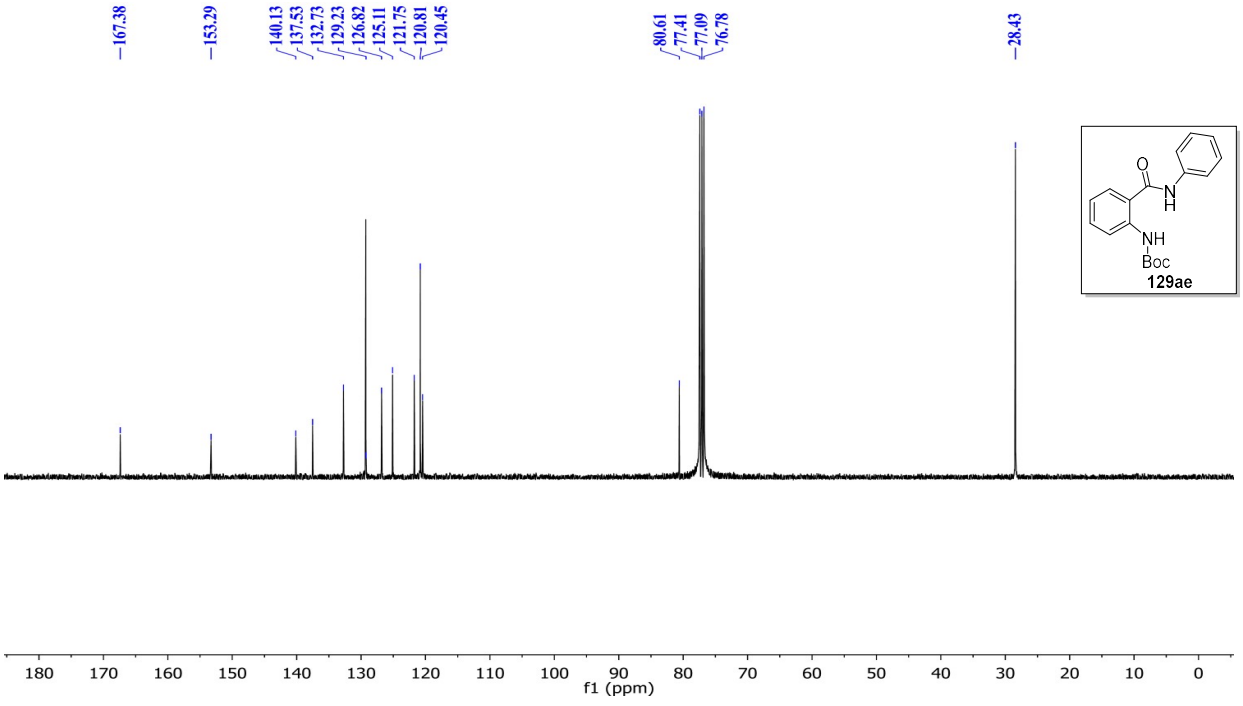
^{13}C{^{1}H} NMR (100 MHz) of **129ad**:



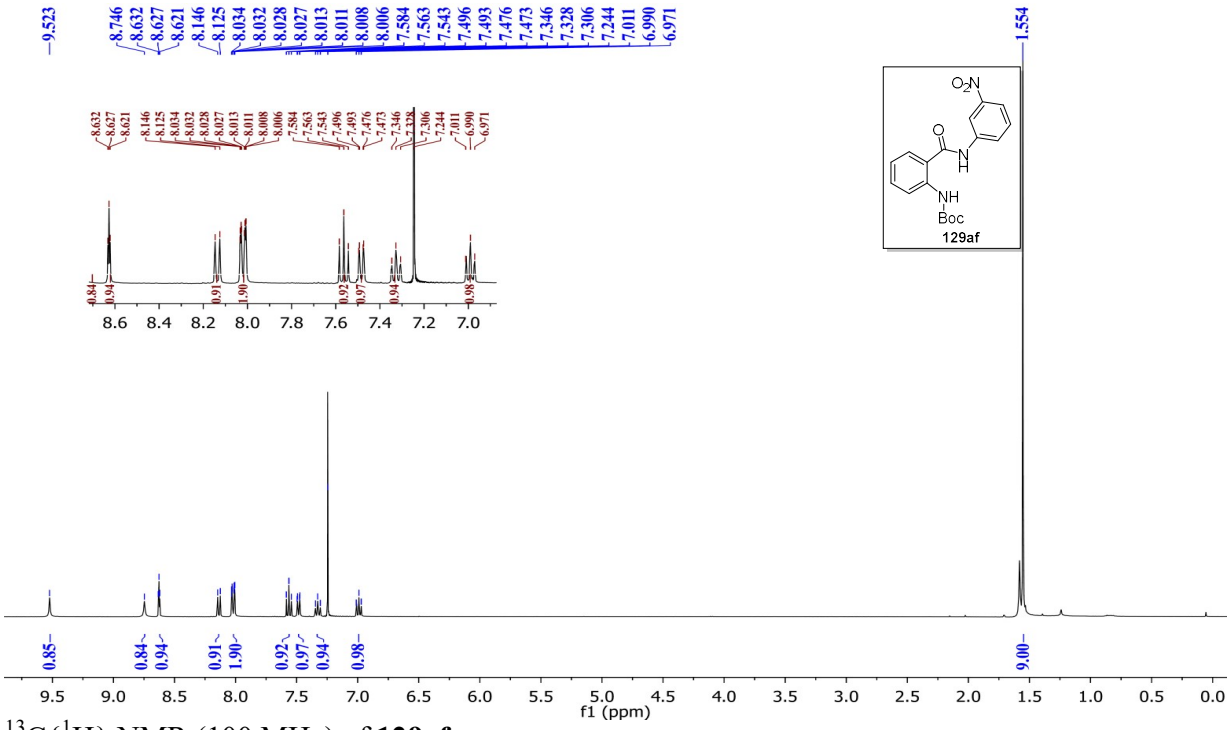
^{1}H NMR (600 MHz) of **129ae:**



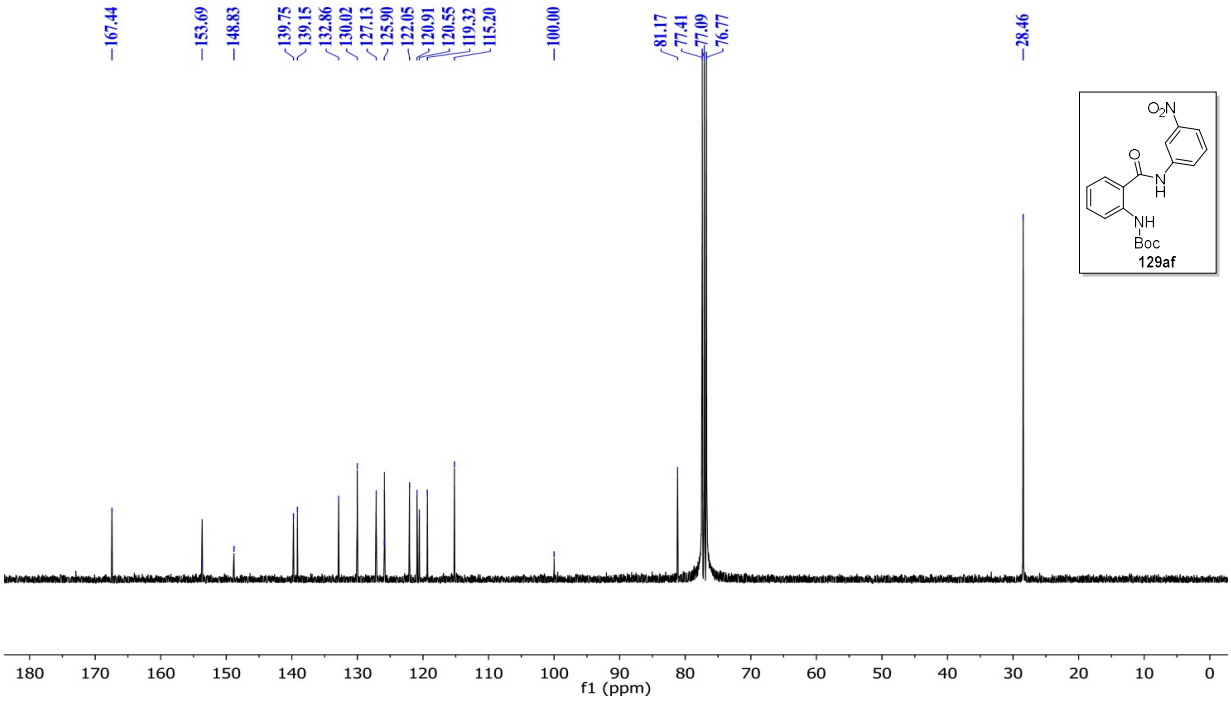
^{13}C{^{1}H} NMR (100 MHz) of **129ae**:



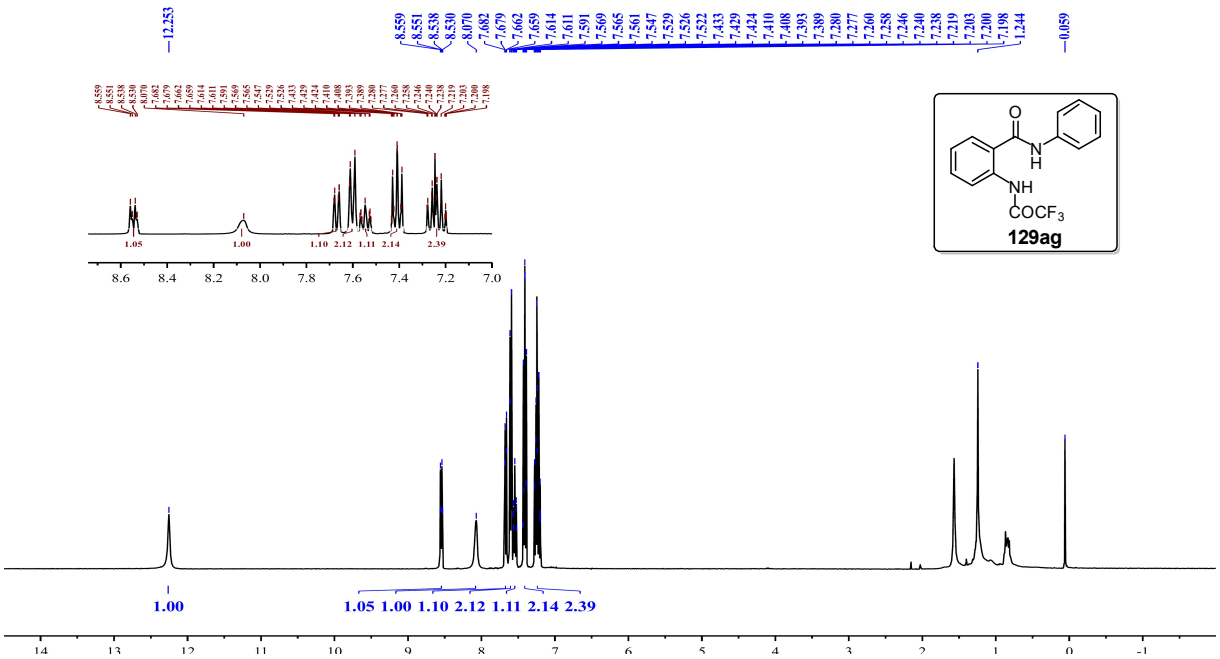
^{1}H NMR (400 MHz) of **129af**:



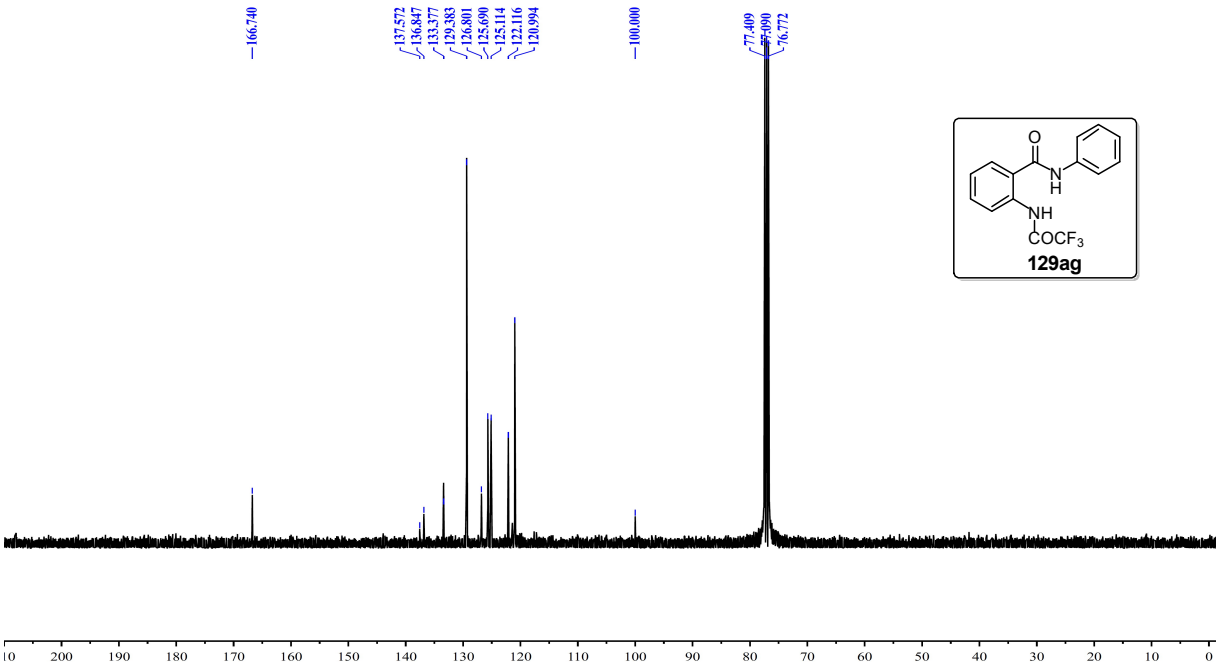
^{13}C{^{1}H} NMR (100 MHz) of **129af**:



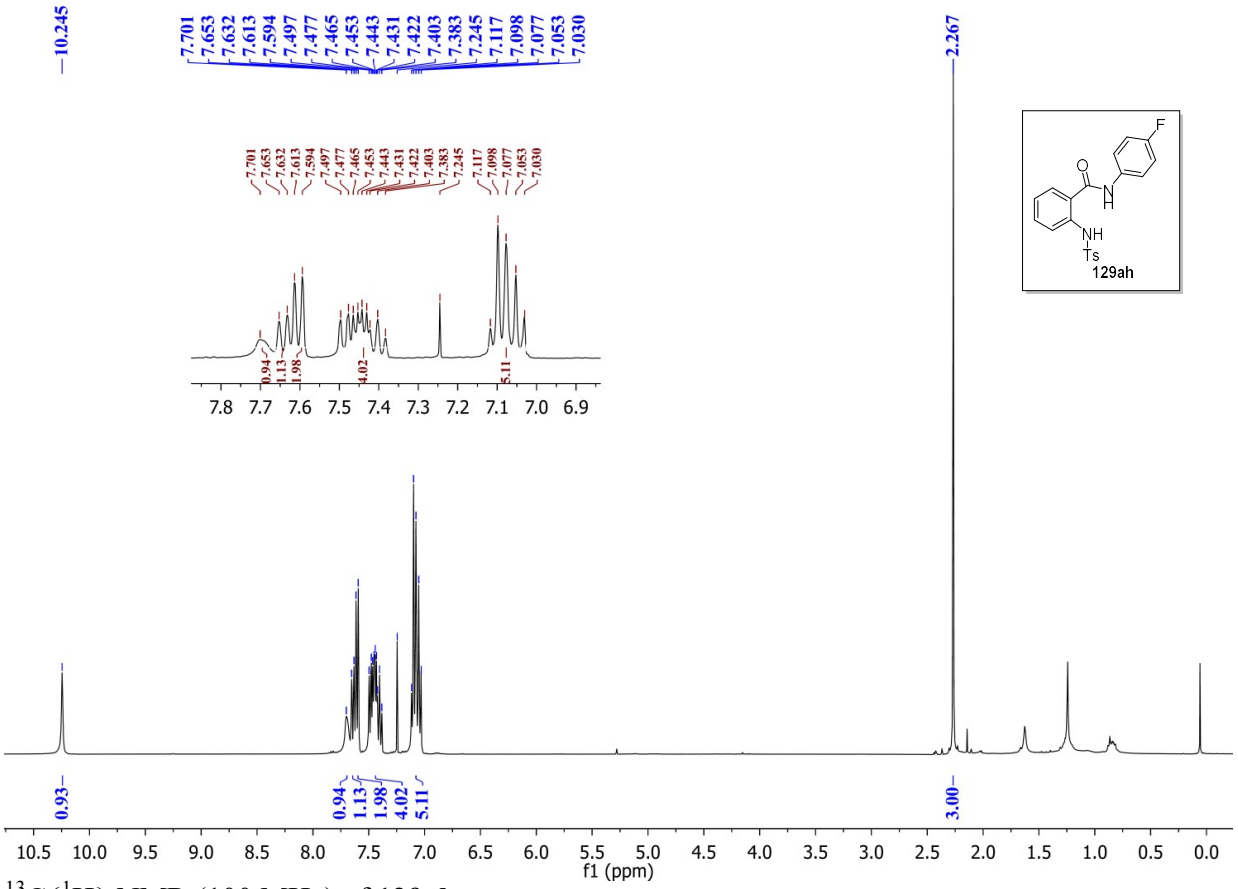
^{1}H NMR (400 MHz) of **129ag**:



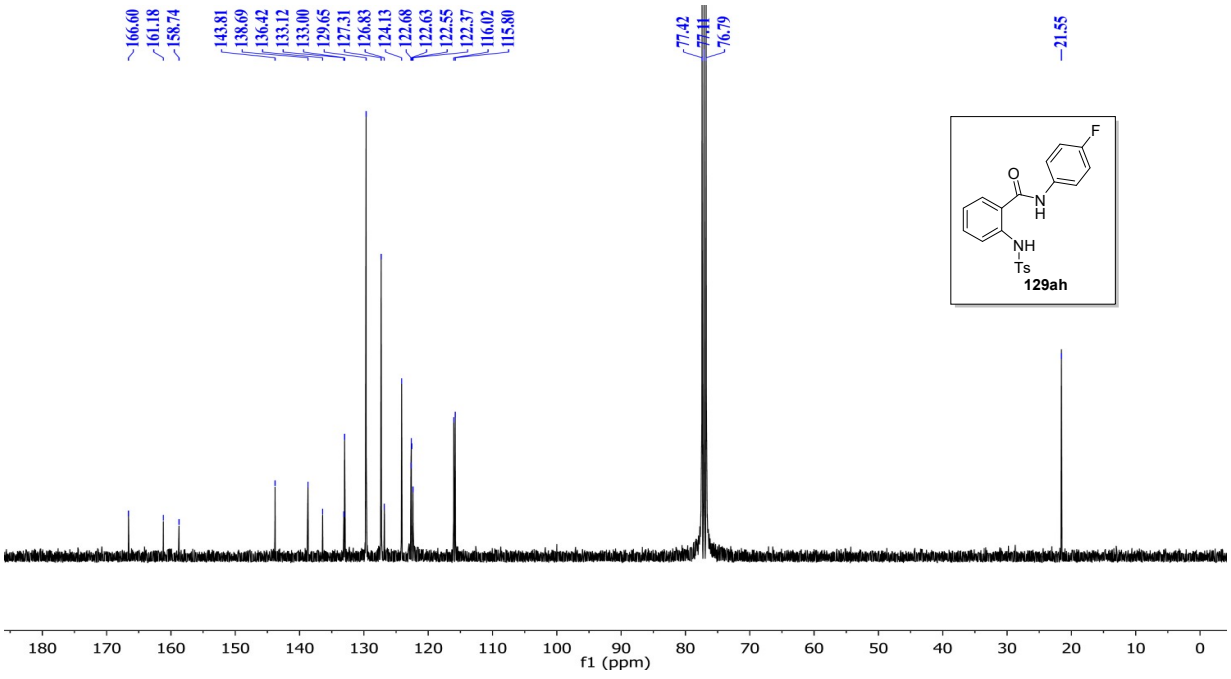
^{13}C{^{1}H} NMR (100 MHz) of **129ag**:



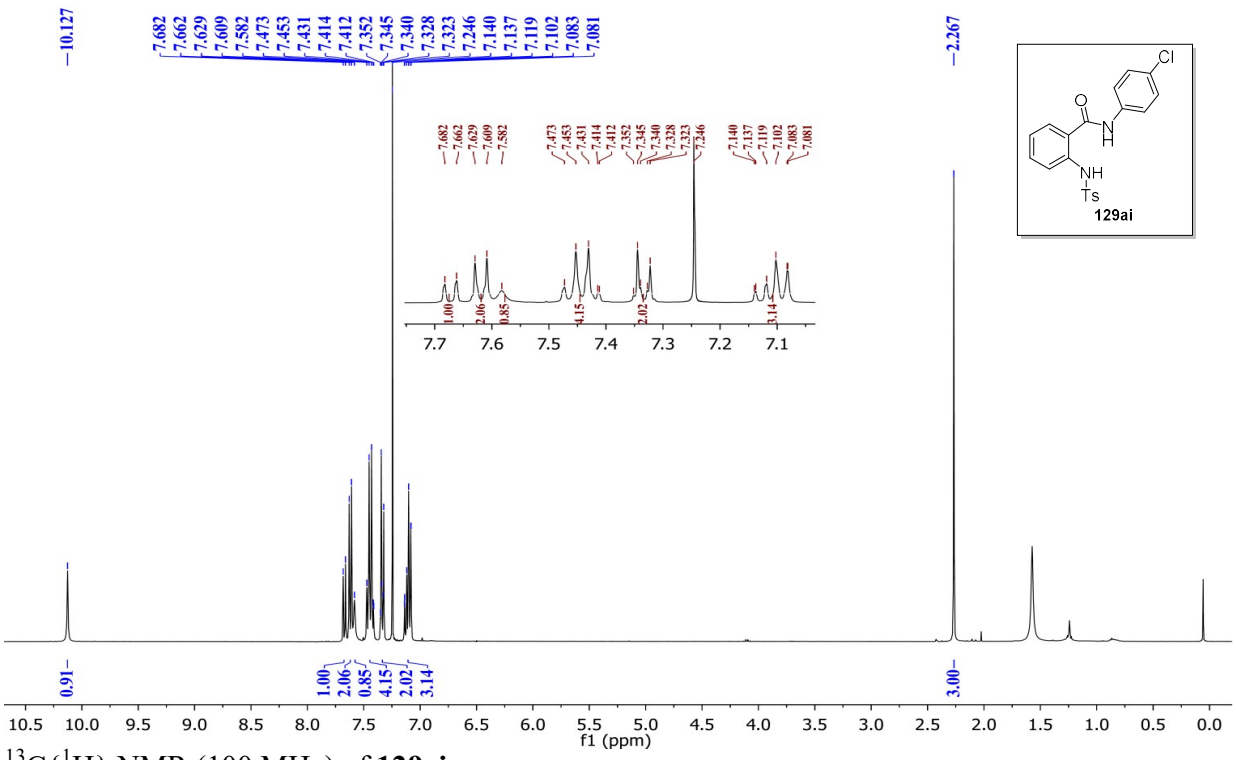
^{1}H NMR (400 MHz) of **129ah**:



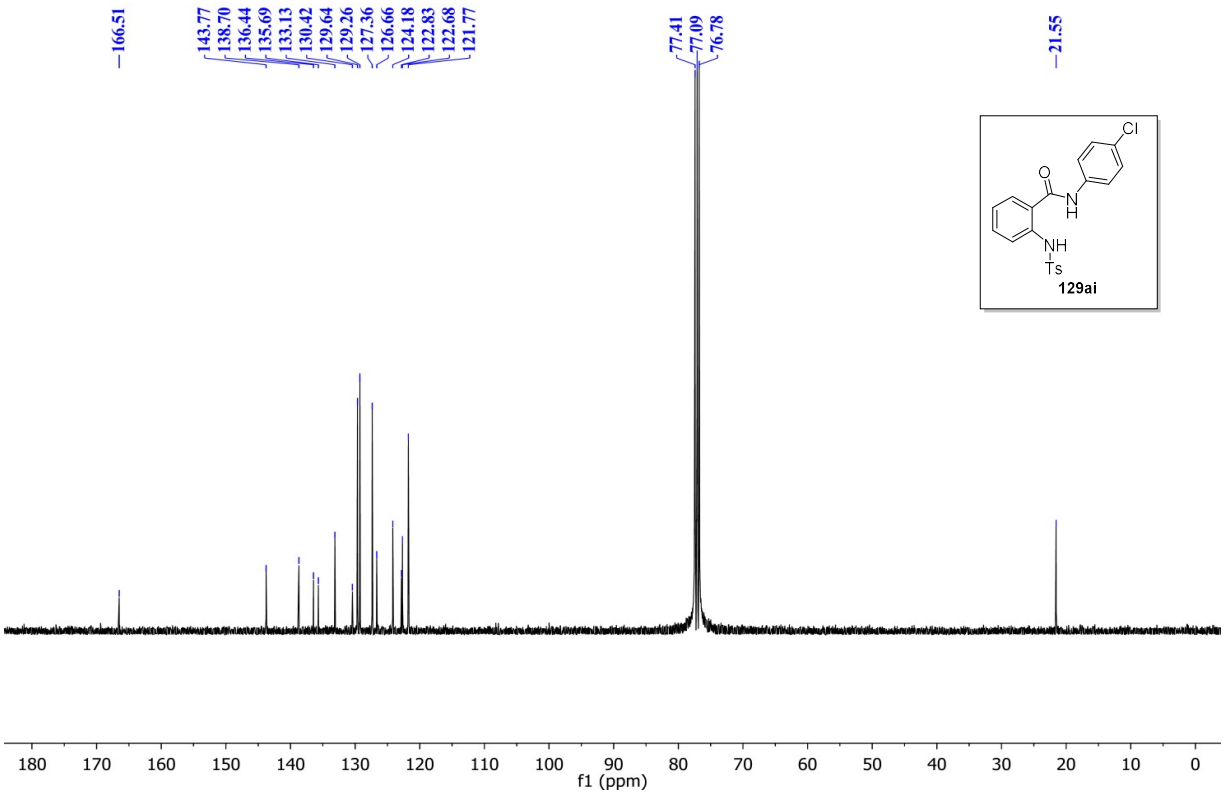
^{13}C{^{1}H} NMR (100 MHz) of **129ah**:



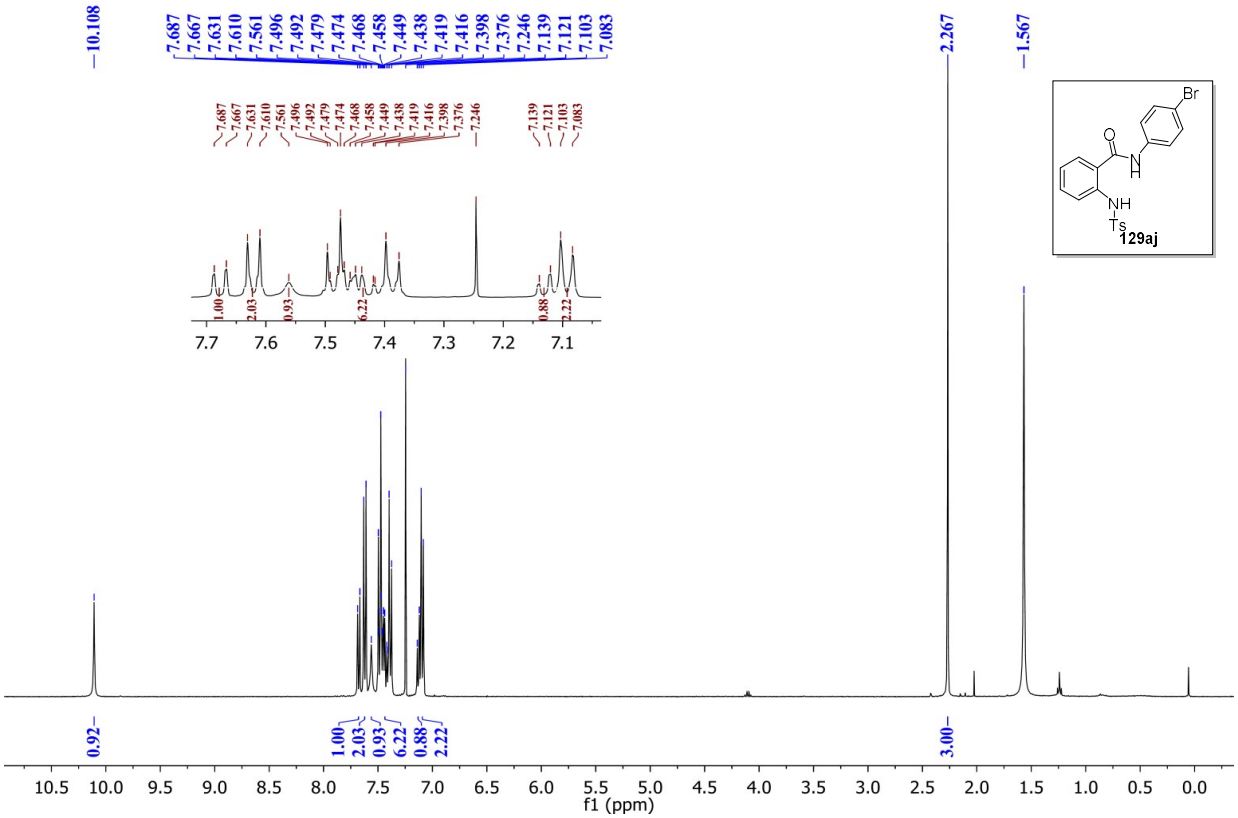
^{1}H NMR (400 MHz) of **129ai**:



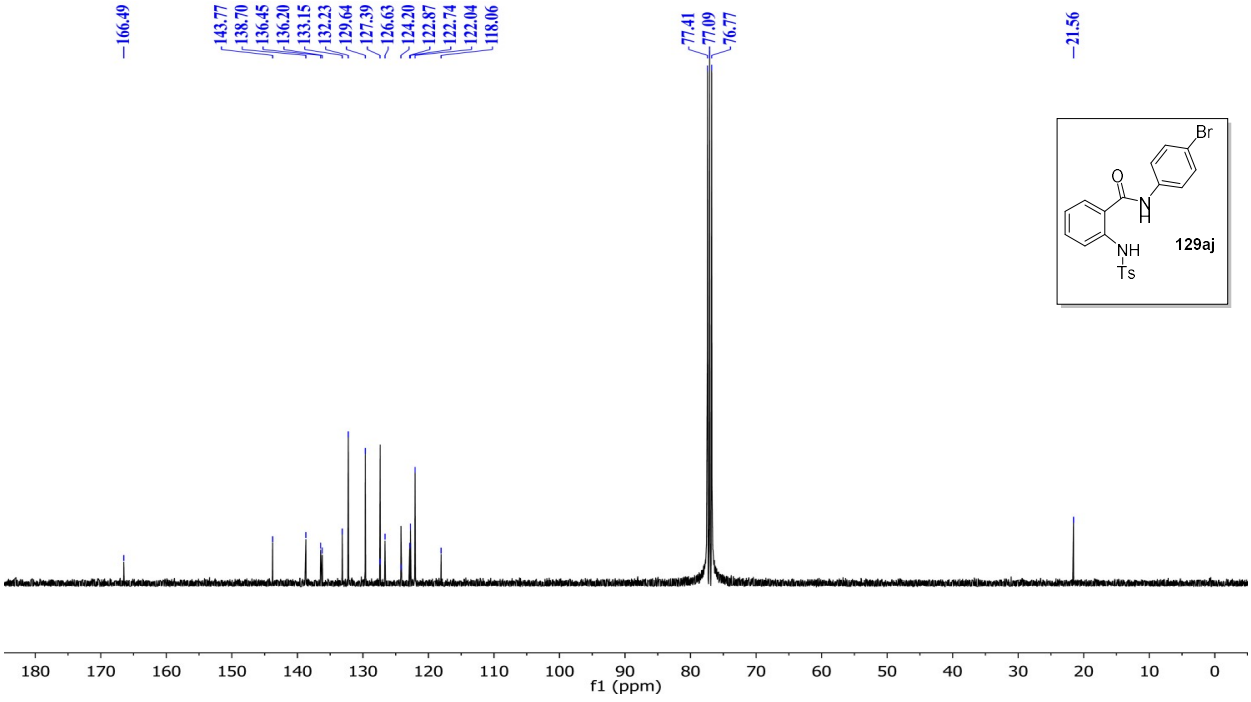
^{13}C{^{1}H} NMR (100 MHz) of **129ai**:



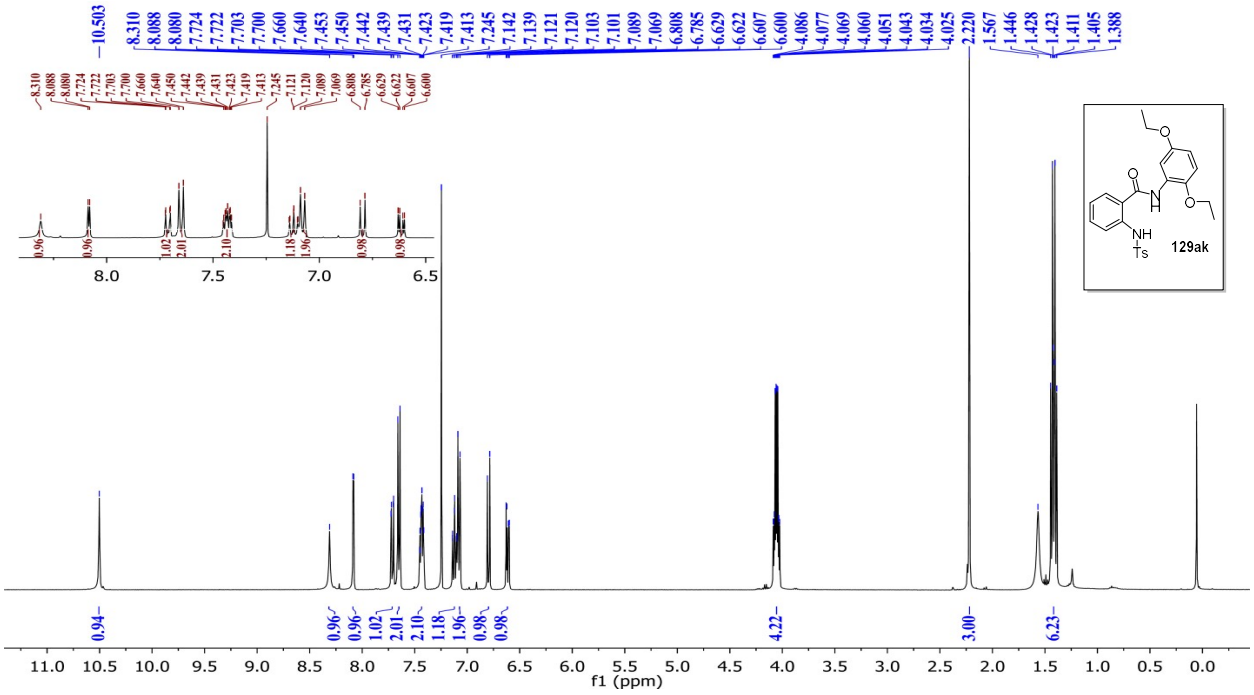
^{1}H NMR (400 MHz) of **129aj**:



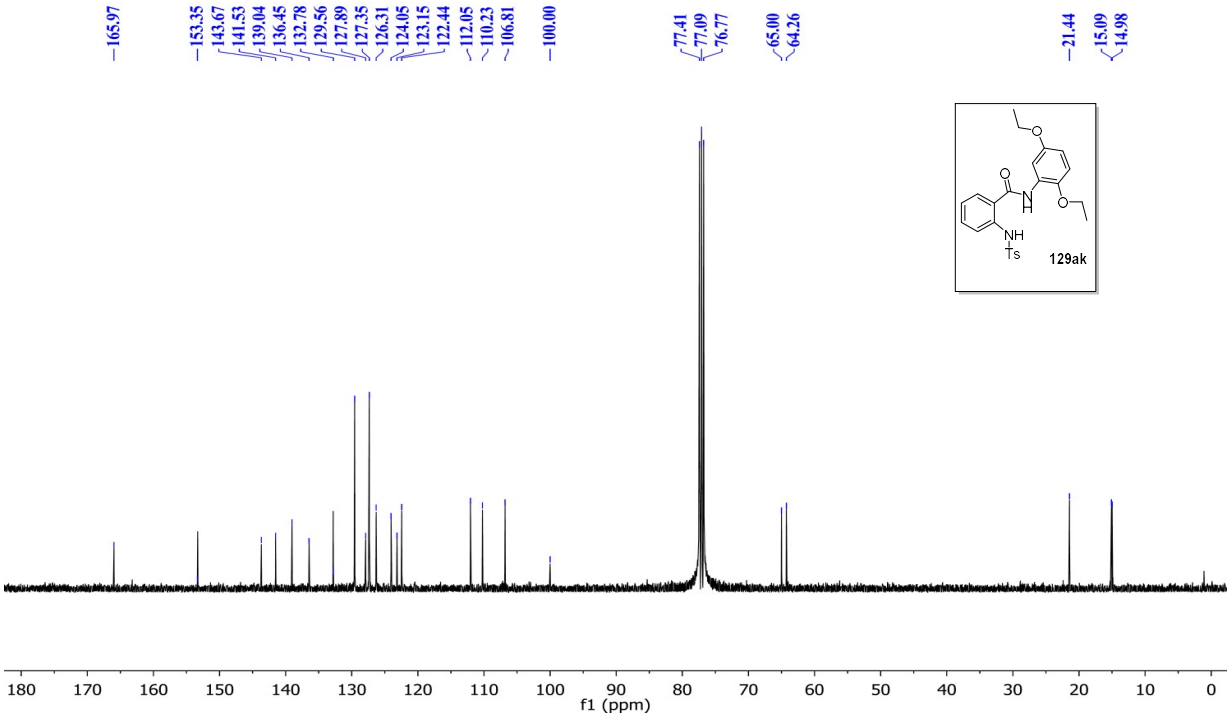
^{13}C{^{1}H} NMR (100 MHz) of **129aj**:



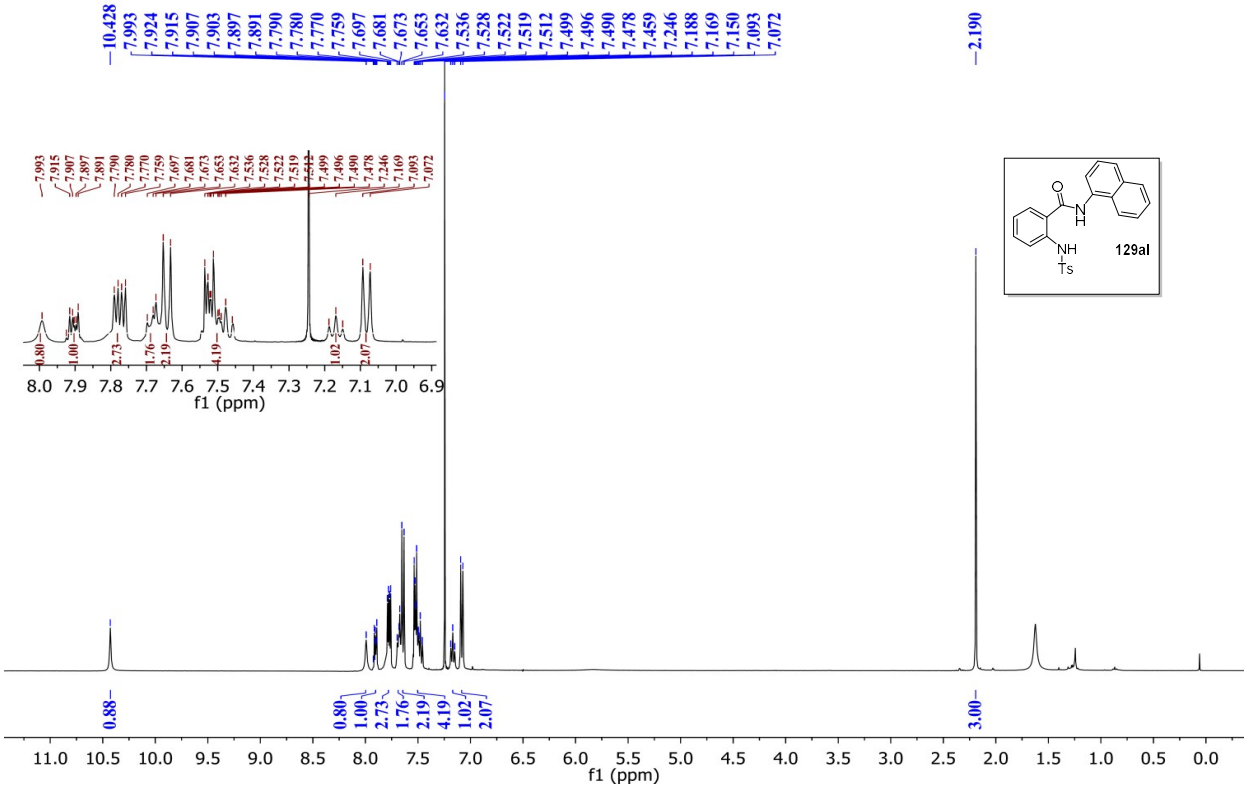
^{1}H NMR (400 MHz) of **129ak**:



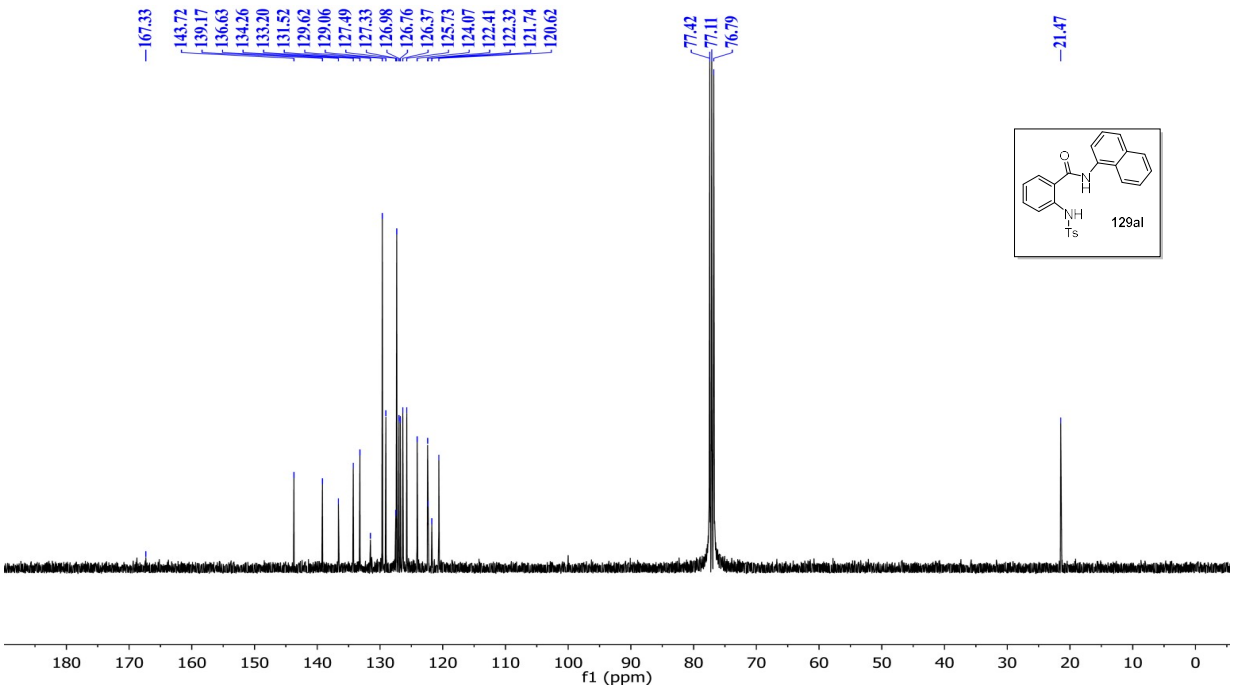
^{13}C{^{1}H} NMR (100 MHz) of **129ak**:



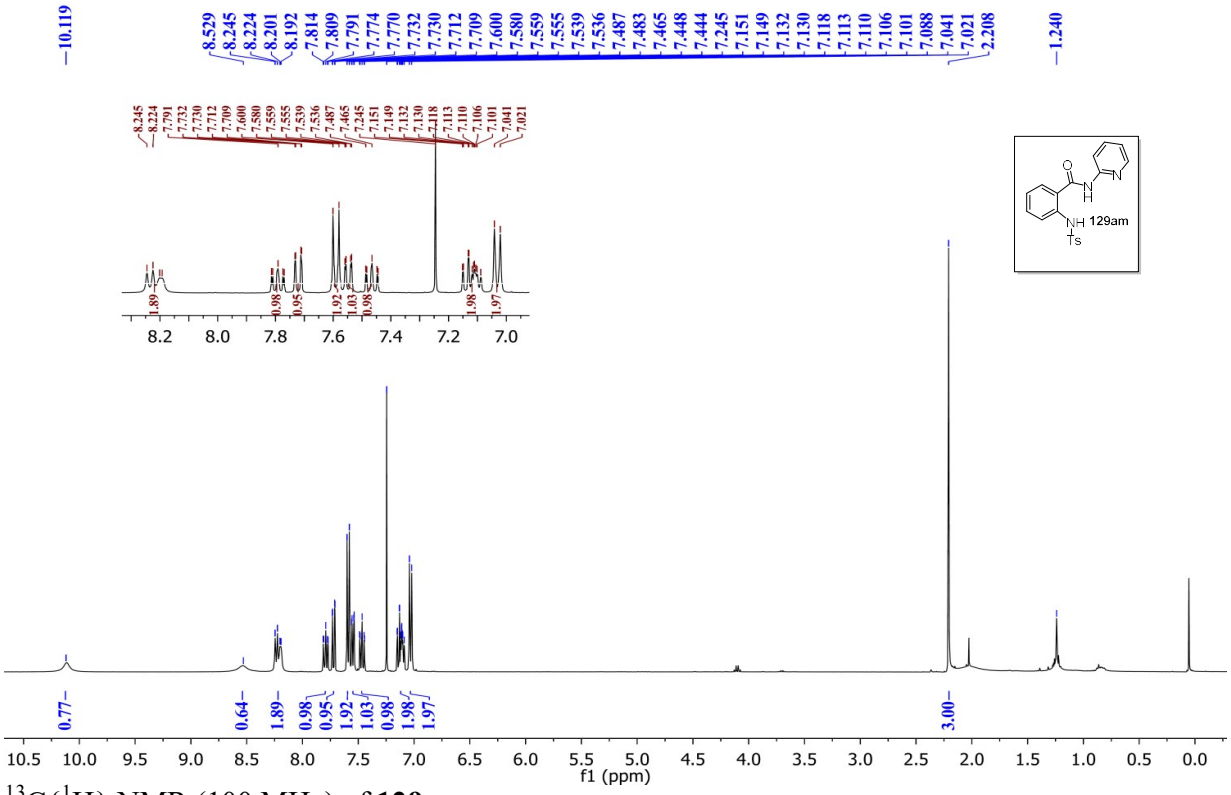
^{1}H NMR (600 MHz) of **129al:**



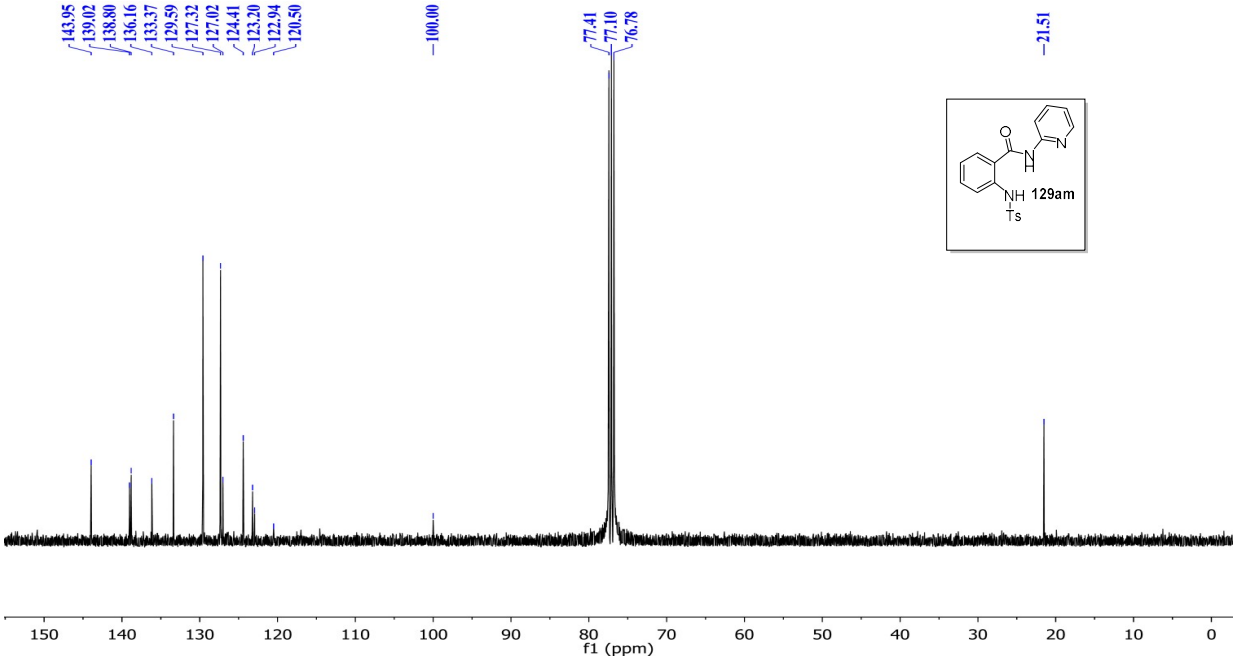
^{13}C{^{1}H} NMR (150 MHz) of **129al**:



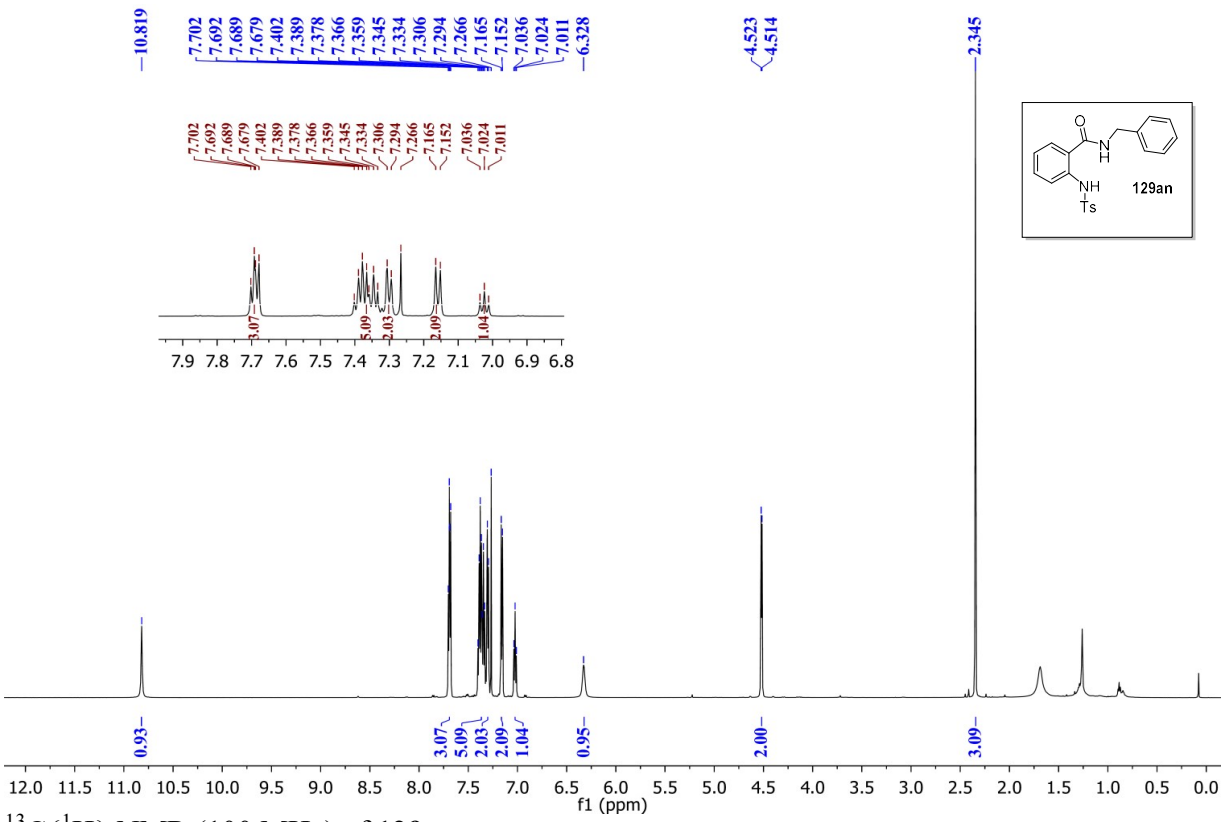
^{1}H NMR (400 MHz) of **129am**:



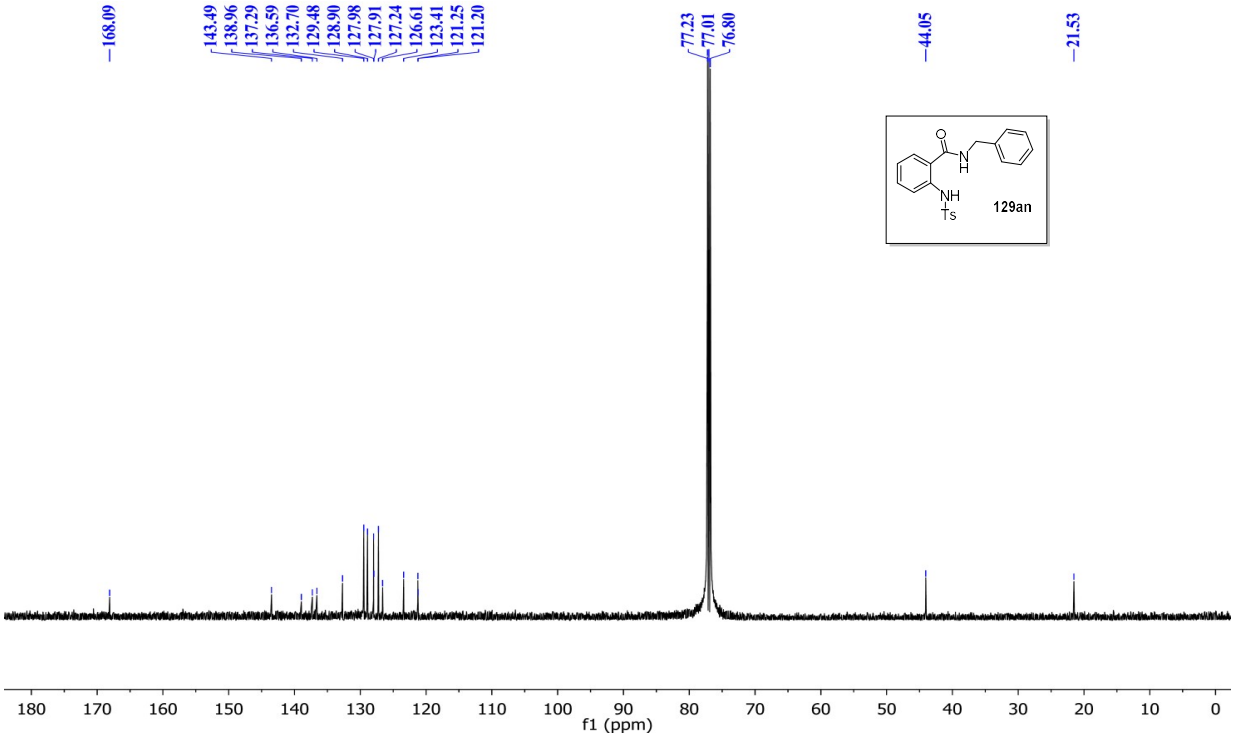
^{13}C{^{1}H} NMR (100 MHz) of **129am**:



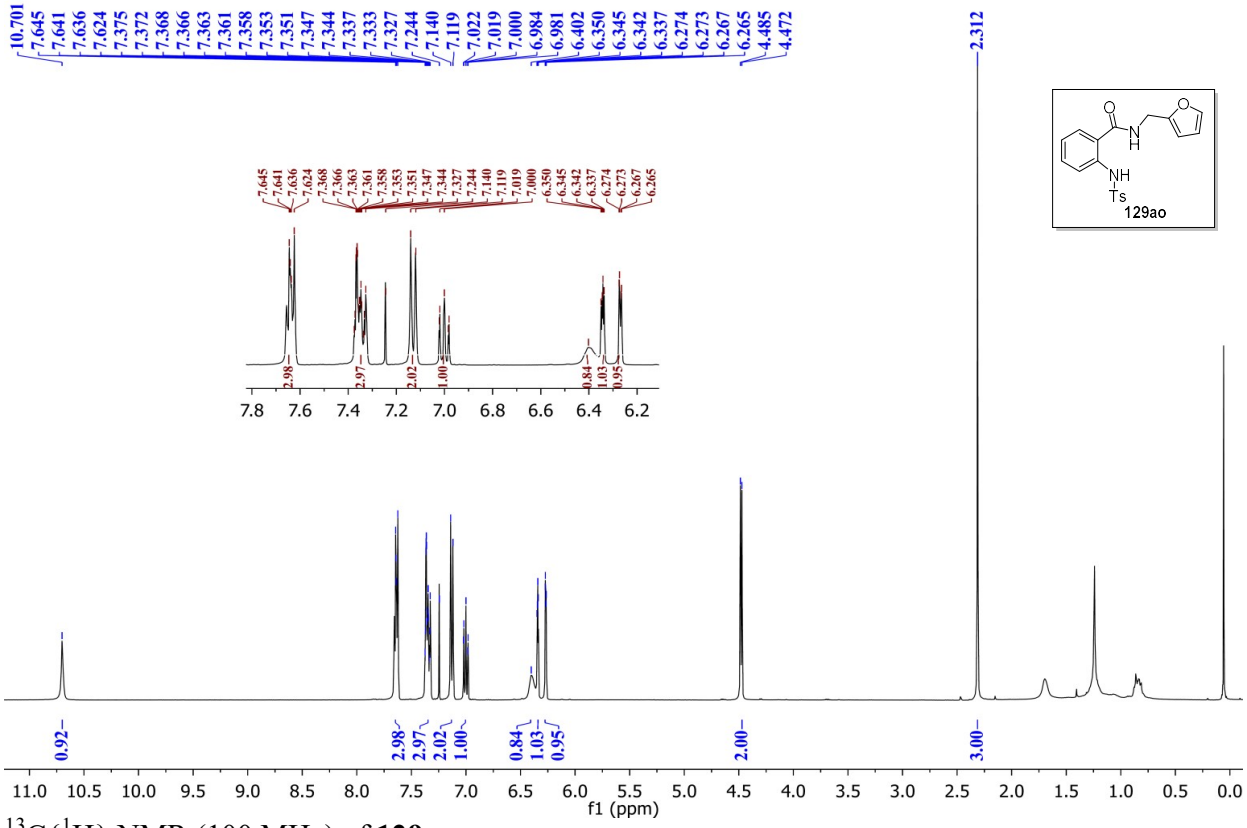
^{1}H NMR (400 MHz) of **129an**:



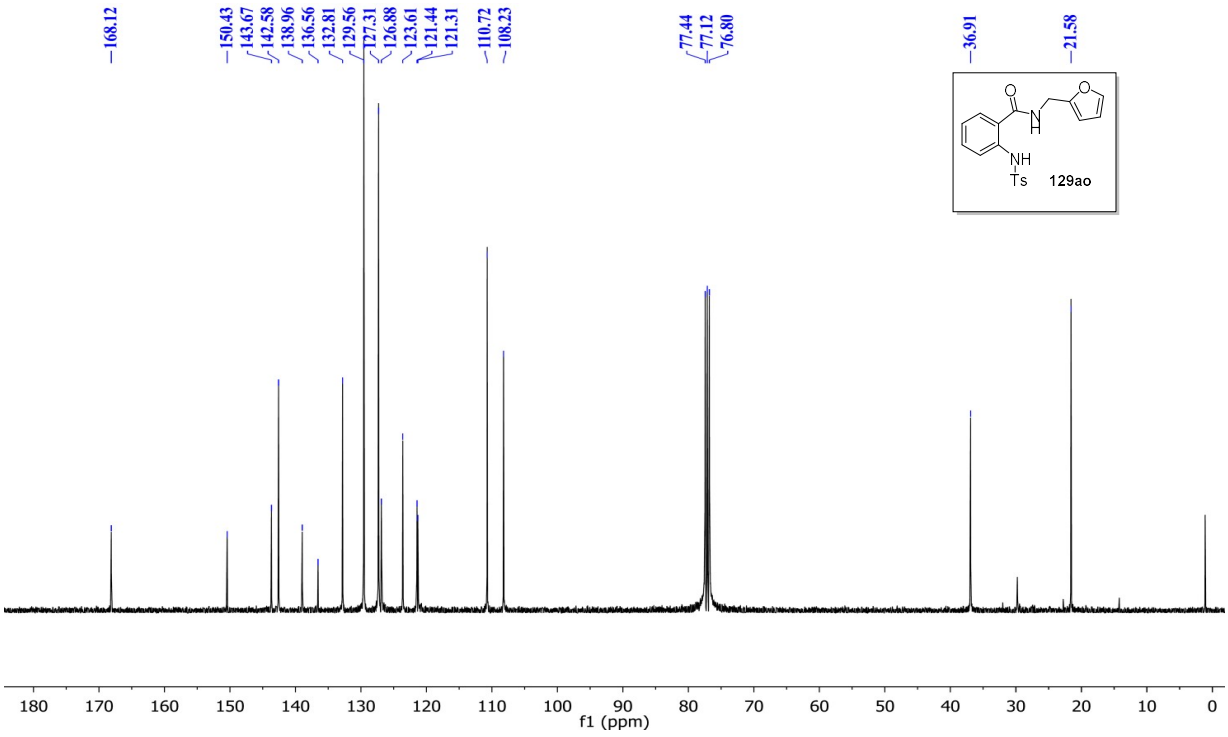
^{13}C{^{1}H} NMR (100 MHz) of **129an**:



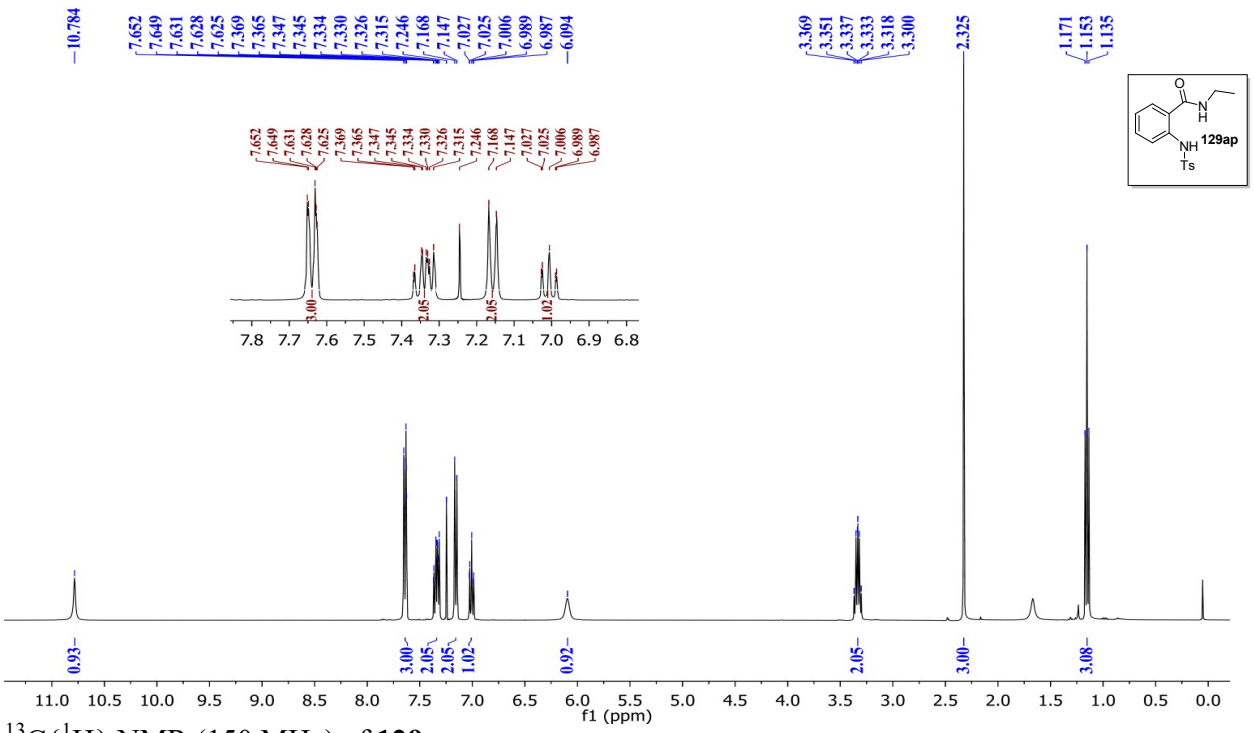
^{1}H NMR (400 MHz) of **129ao**:



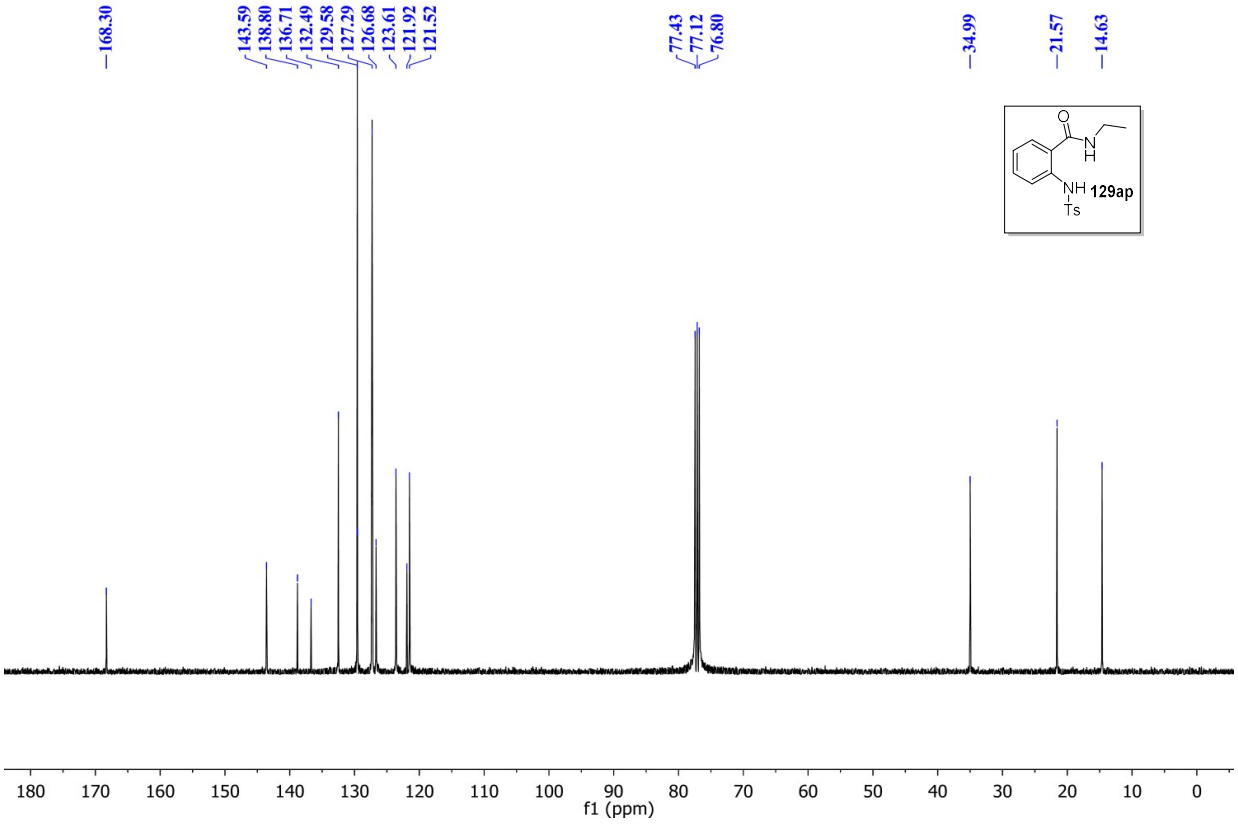
^{13}C{^{1}H} NMR (100 MHz) of **129ao**:



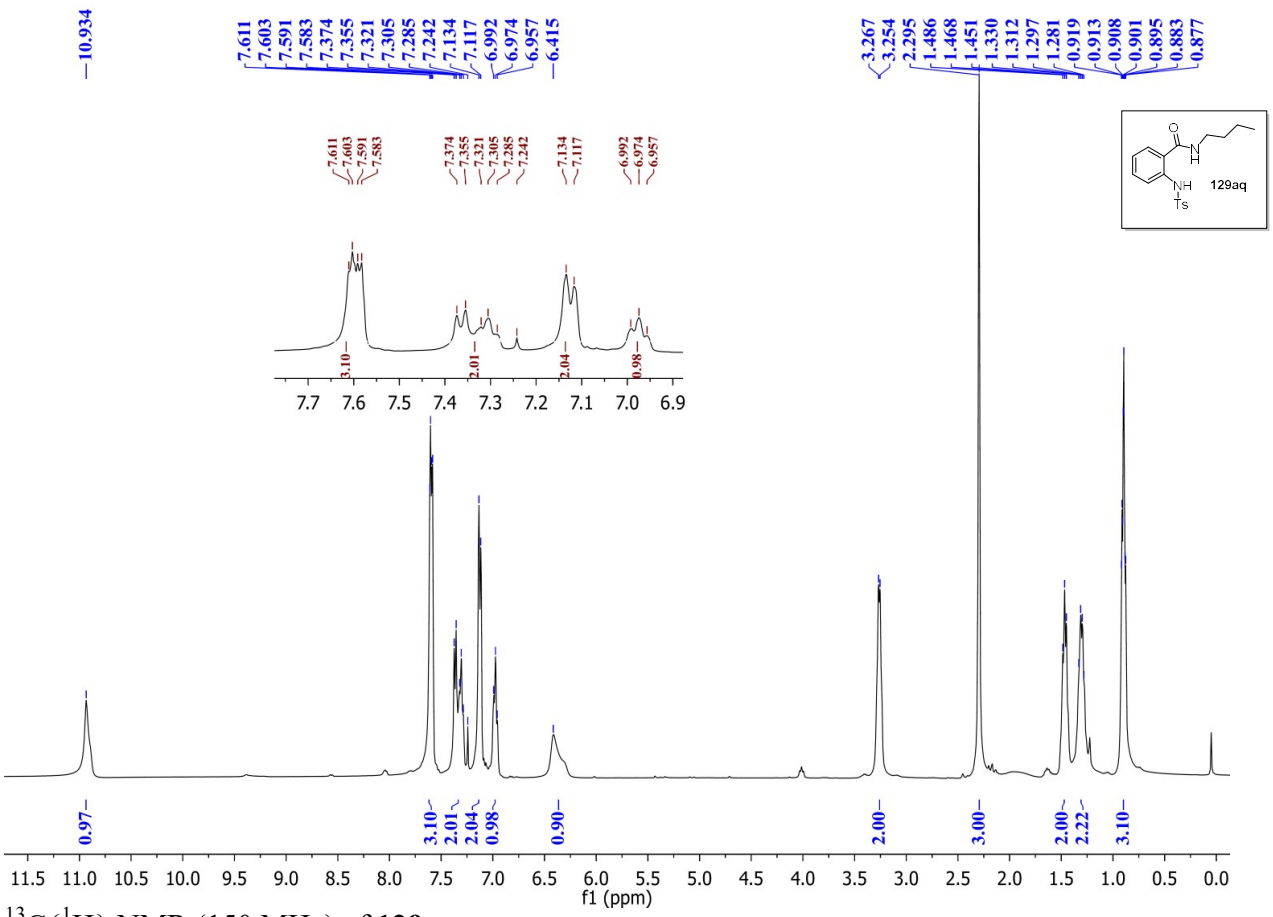
^{1}H NMR (600 MHz) of **129ap**:



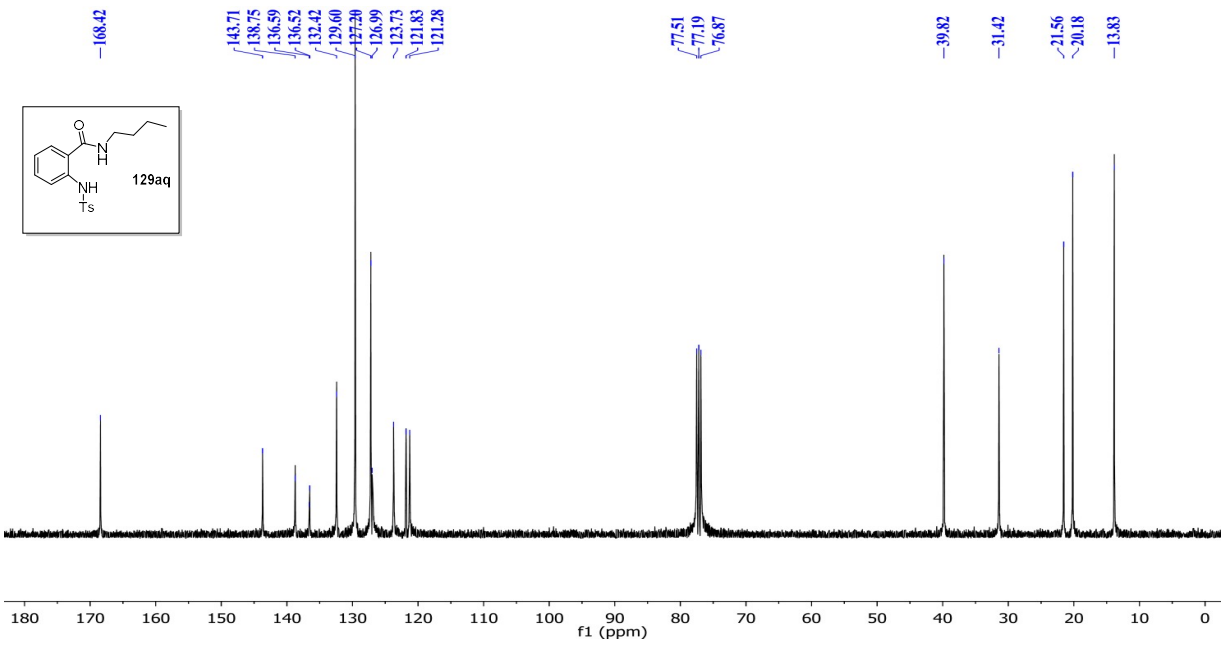
^{13}C{^{1}H} NMR (150 MHz) of **129ap**:



^{1}H NMR (600 MHz) of **129aq**:

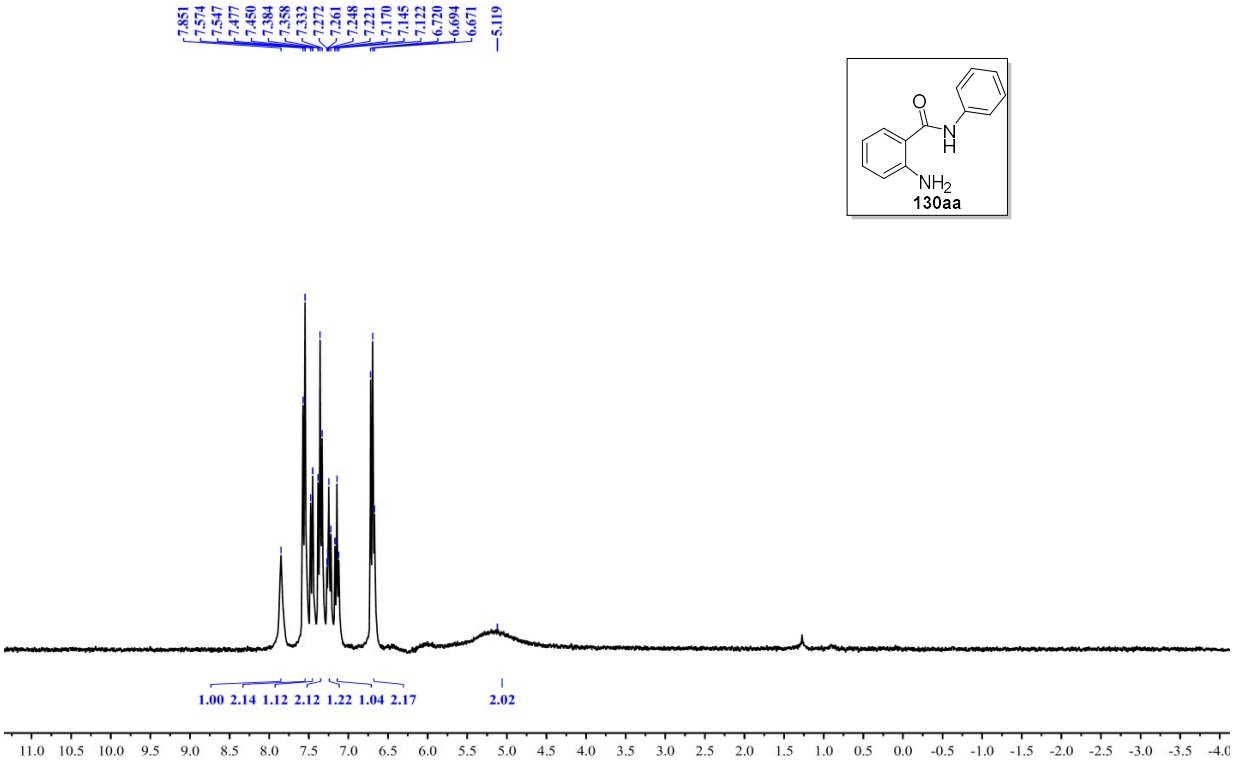


^{13}C{^{1}H} NMR (150 MHz) of **129aq**:

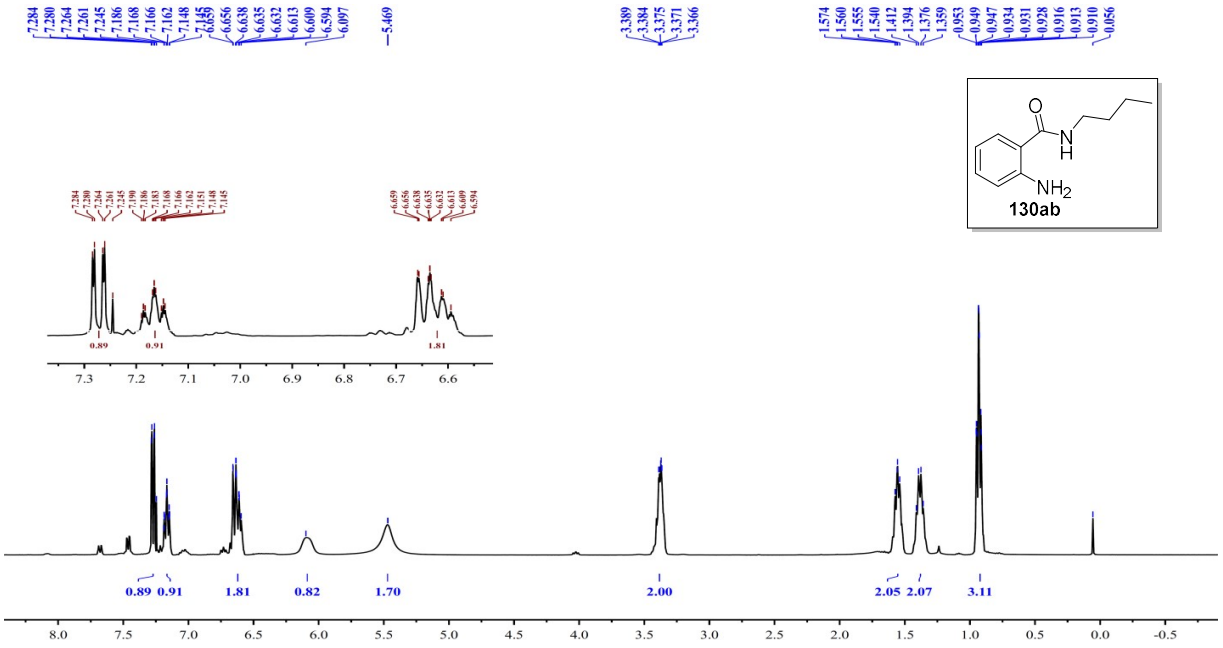


1.2.17.2 NMR Spectra of substrates 130aa-130ae:

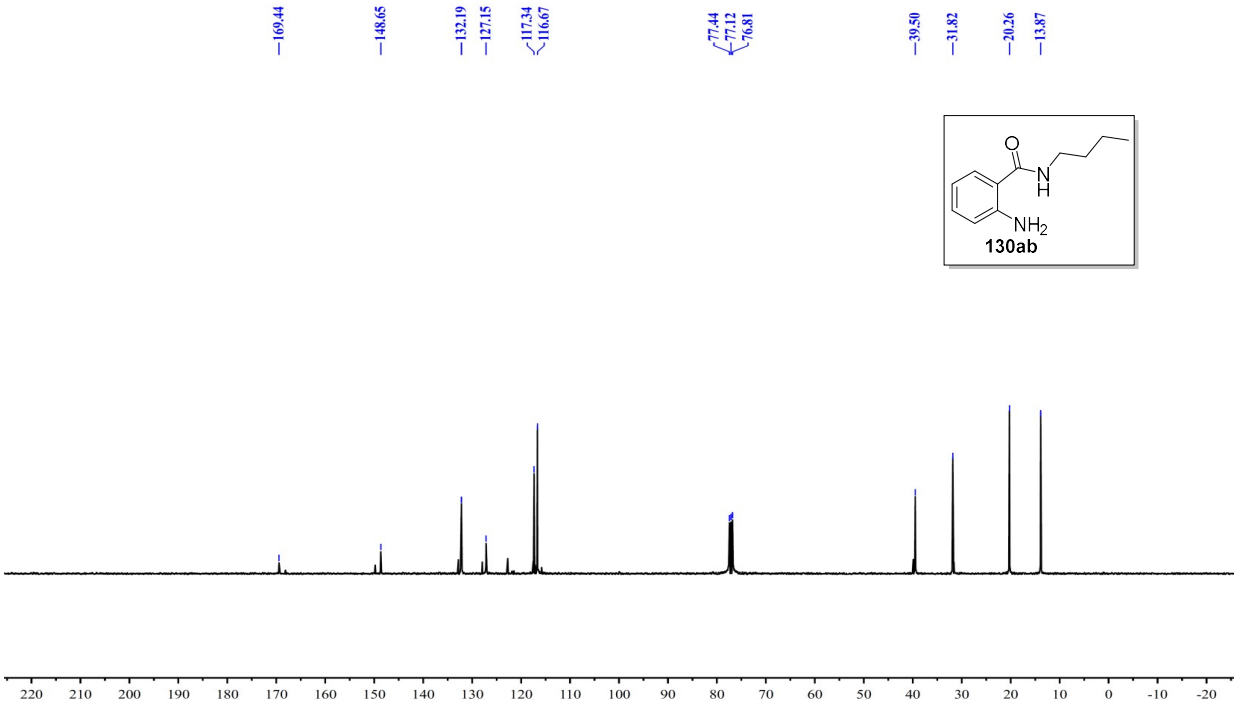
^{1}H NMR (300 MHz) of **130aa**:



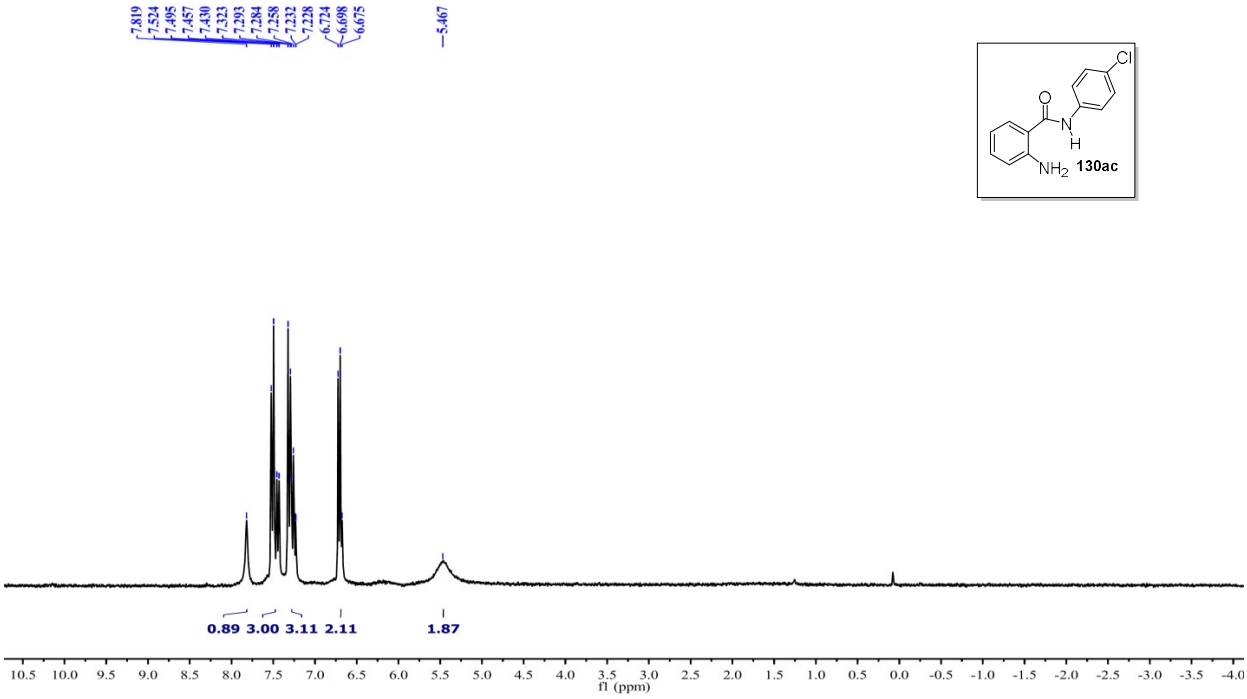
^{1}H NMR (400 MHz) of **130ab**:



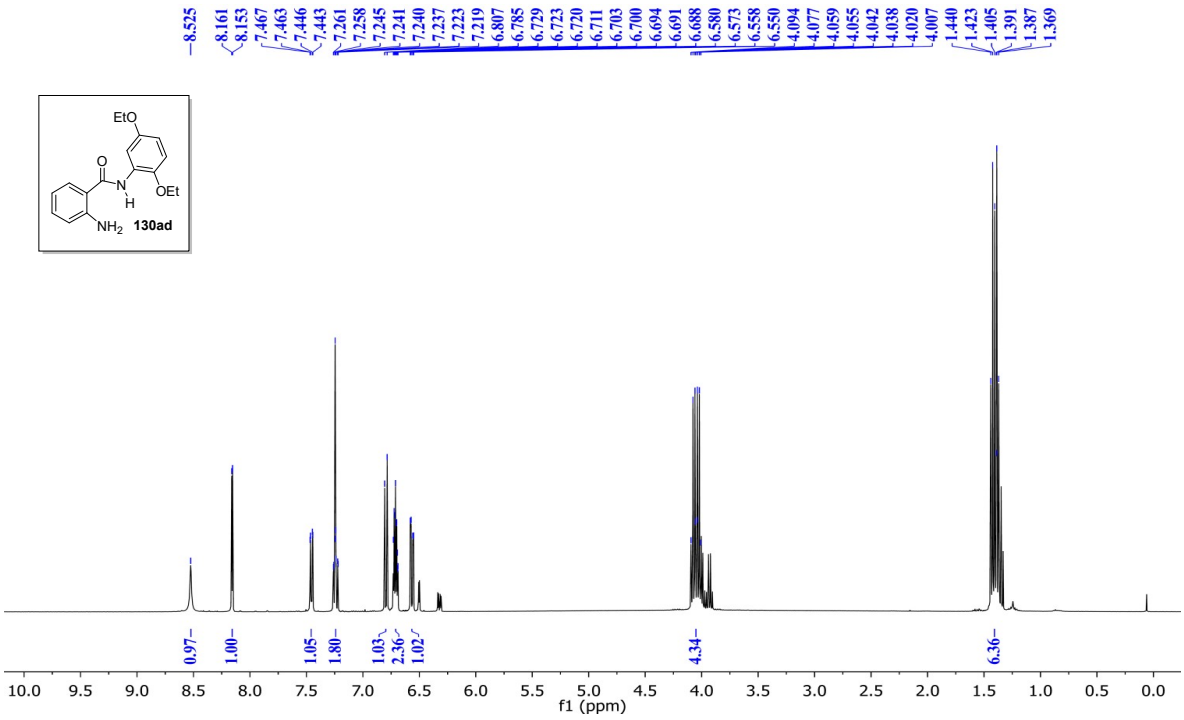
^{13}C{^{1}H} NMR (100 MHz) of **130ab**:



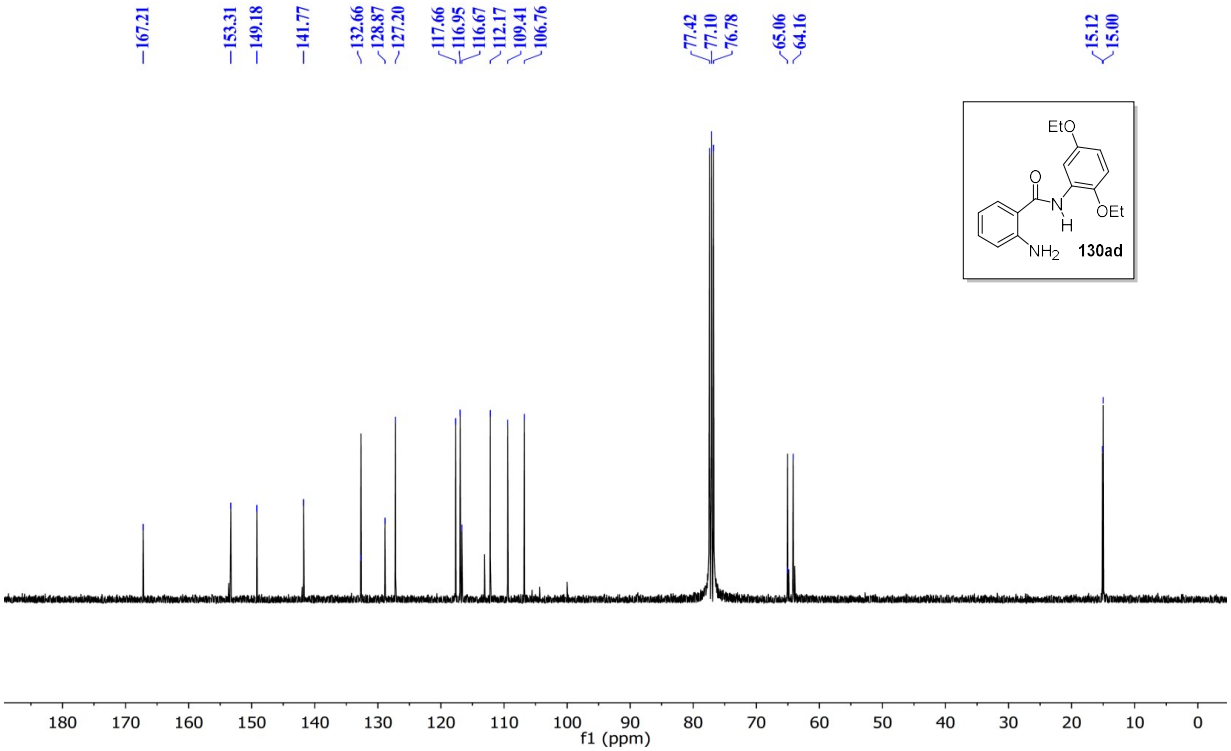
^{1}H NMR (300 MHz) of **130ac**:



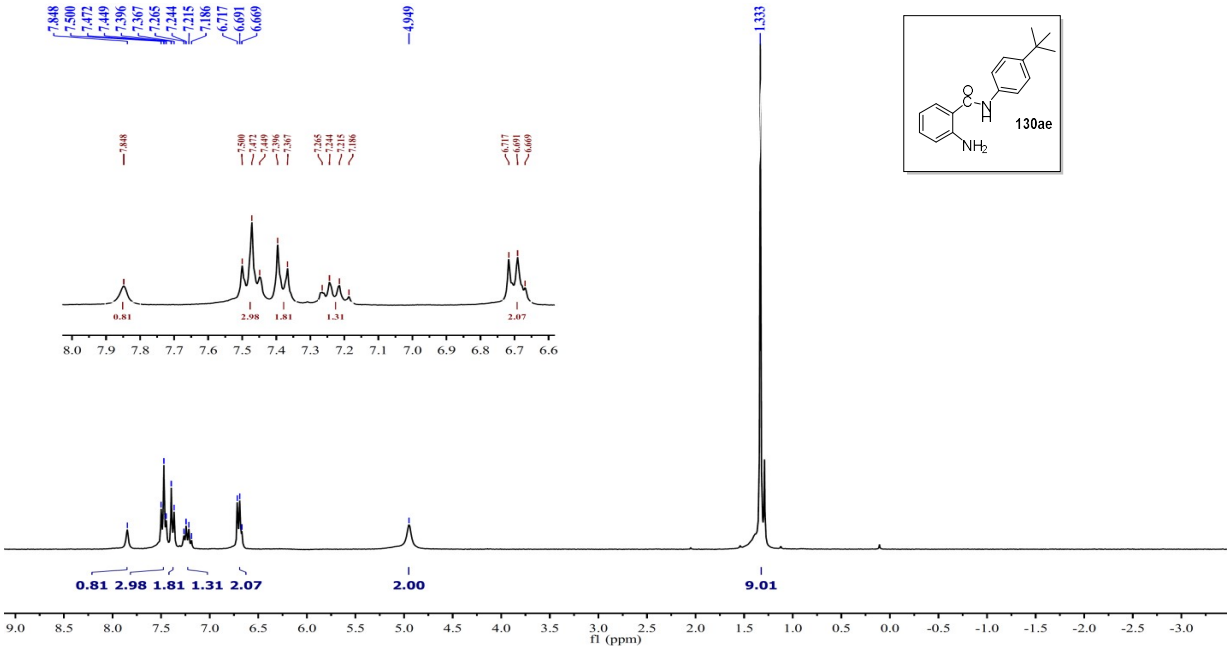
^{1}H NMR (300 MHz) of **130ad:**



^{13}C{^{1}H} NMR (100 MHz) of **130ad**:

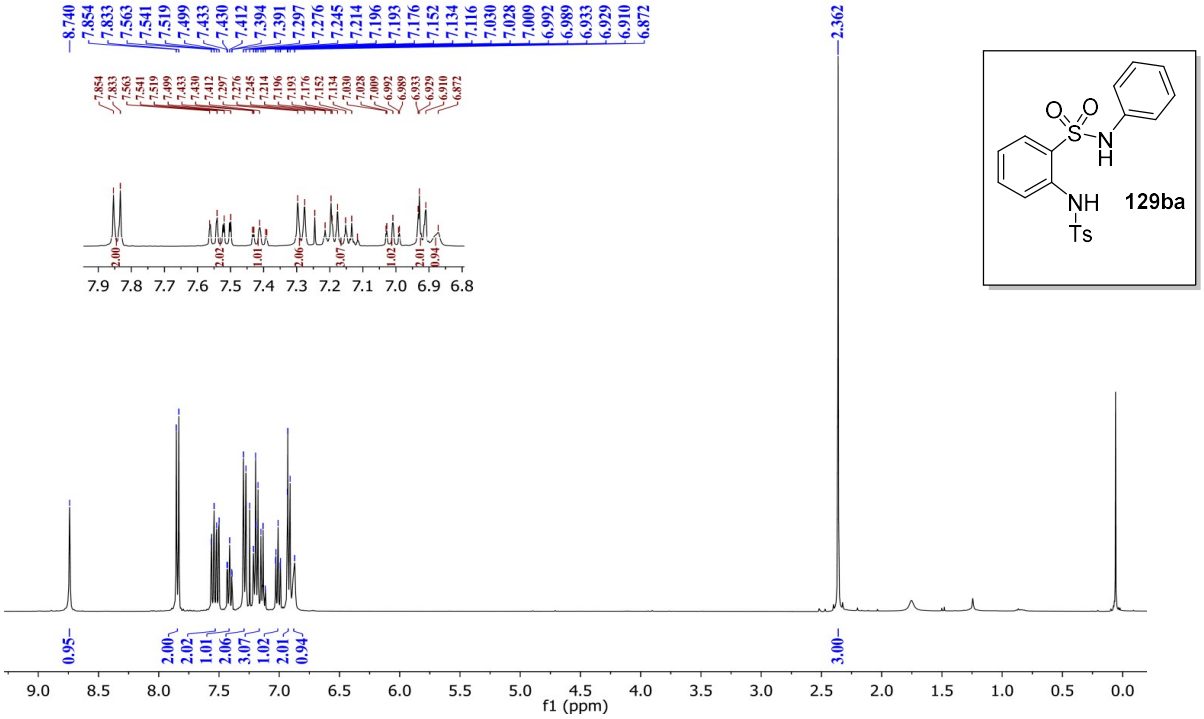


^{1}H NMR (300 MHz) of **130ae:**

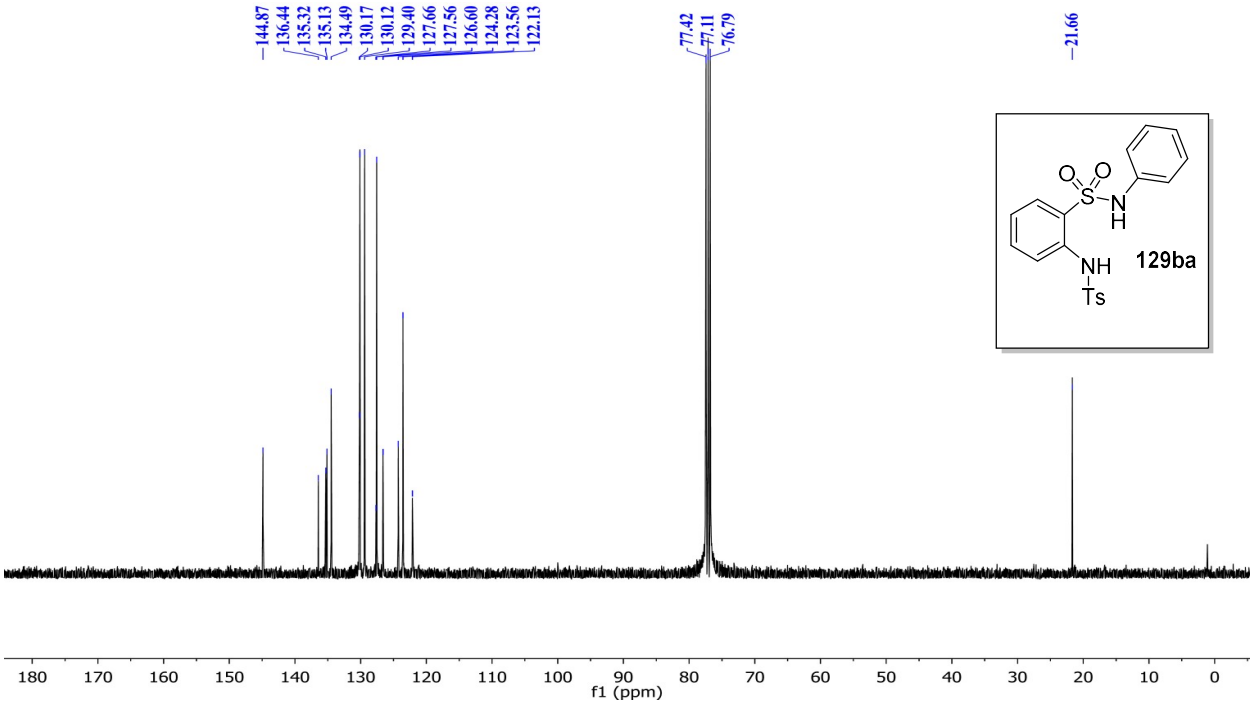


1.2.17.3 NMR spectra of substrates 129ba-129bc:

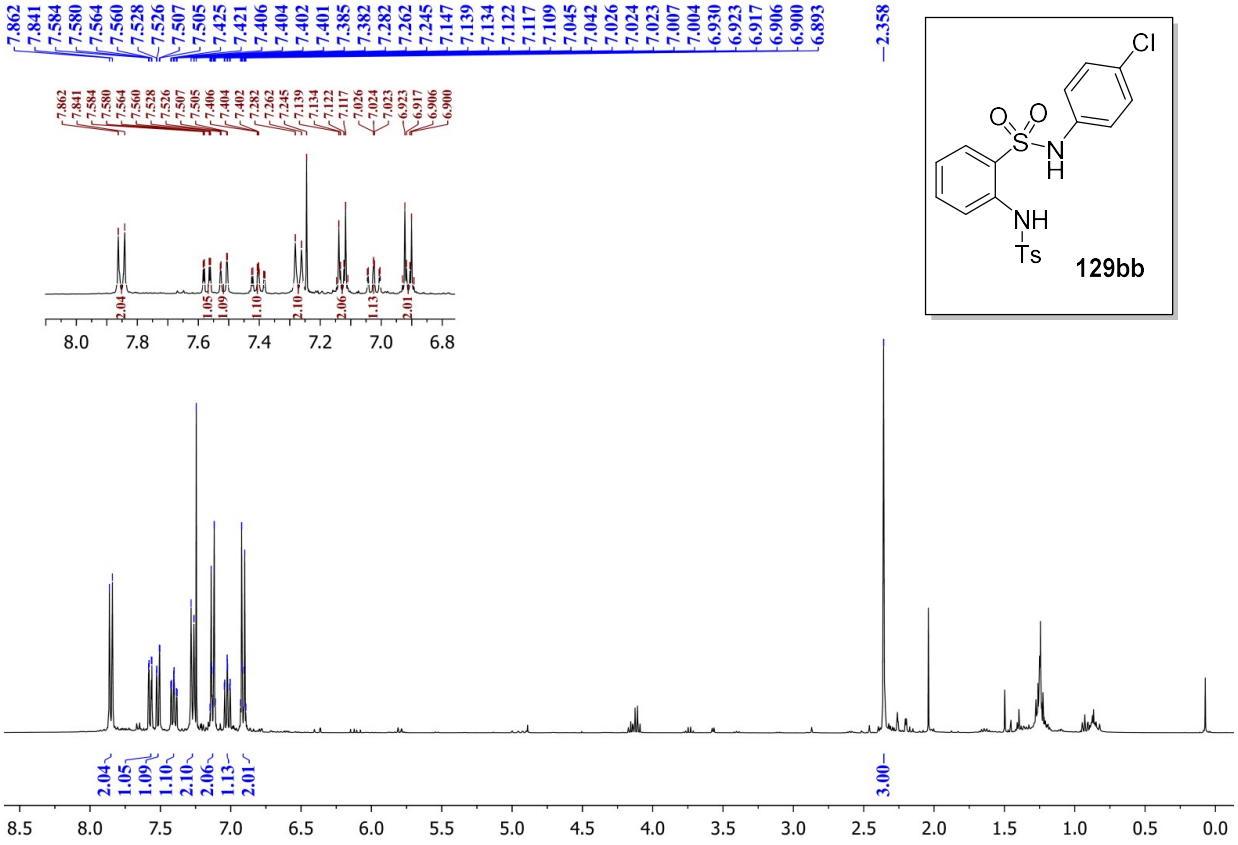
^{1}H NMR (400 MHz) of **129ba**:



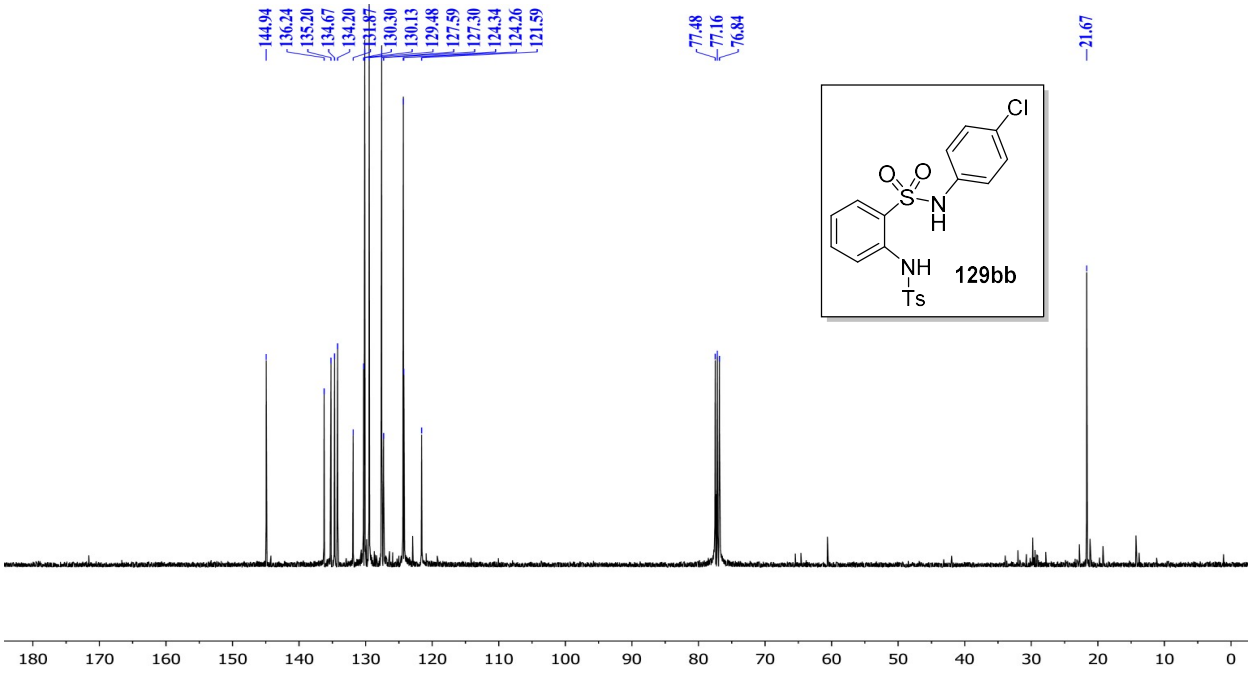
^{13}C{^{1}H} NMR (100 MHz) of **129ba**:



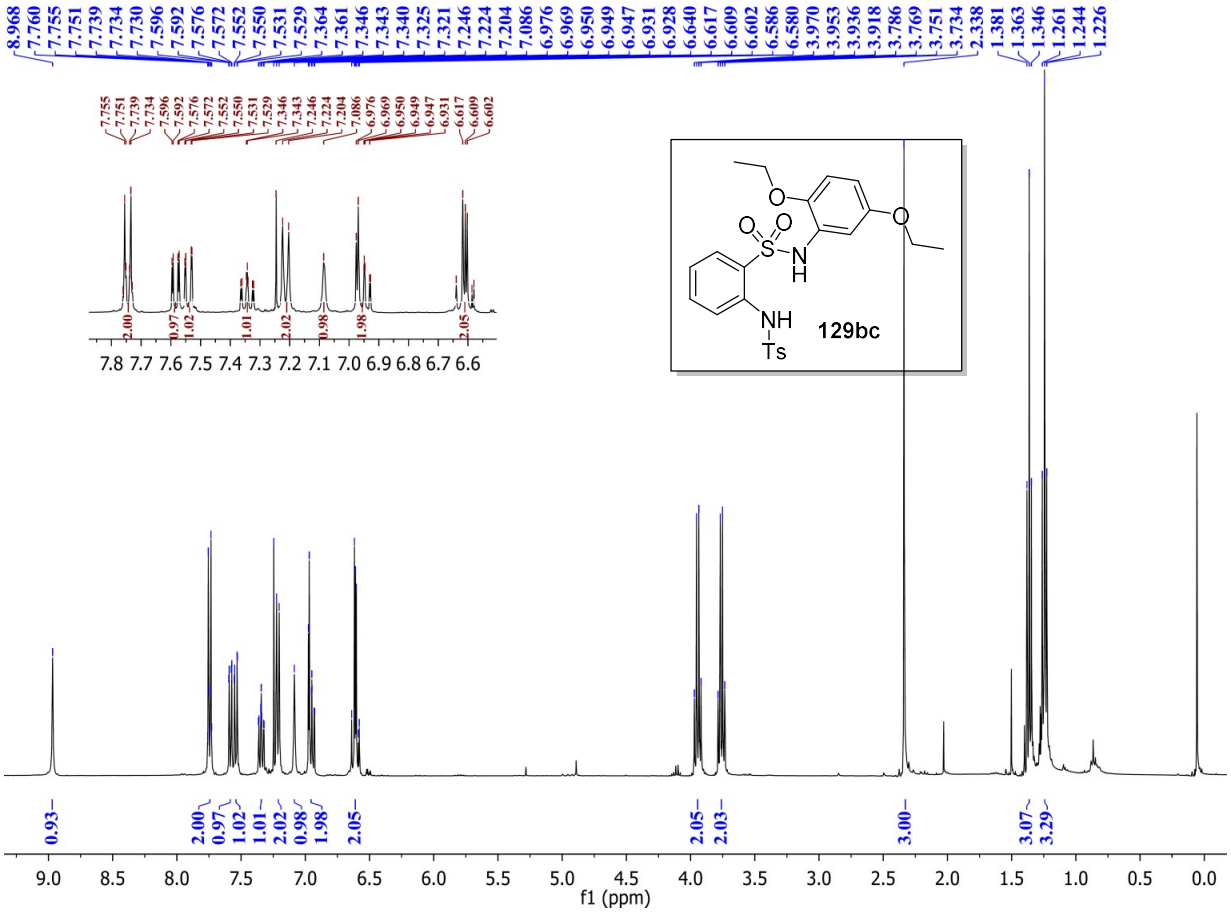
^{1}H NMR (400 MHz) of **129bb**:



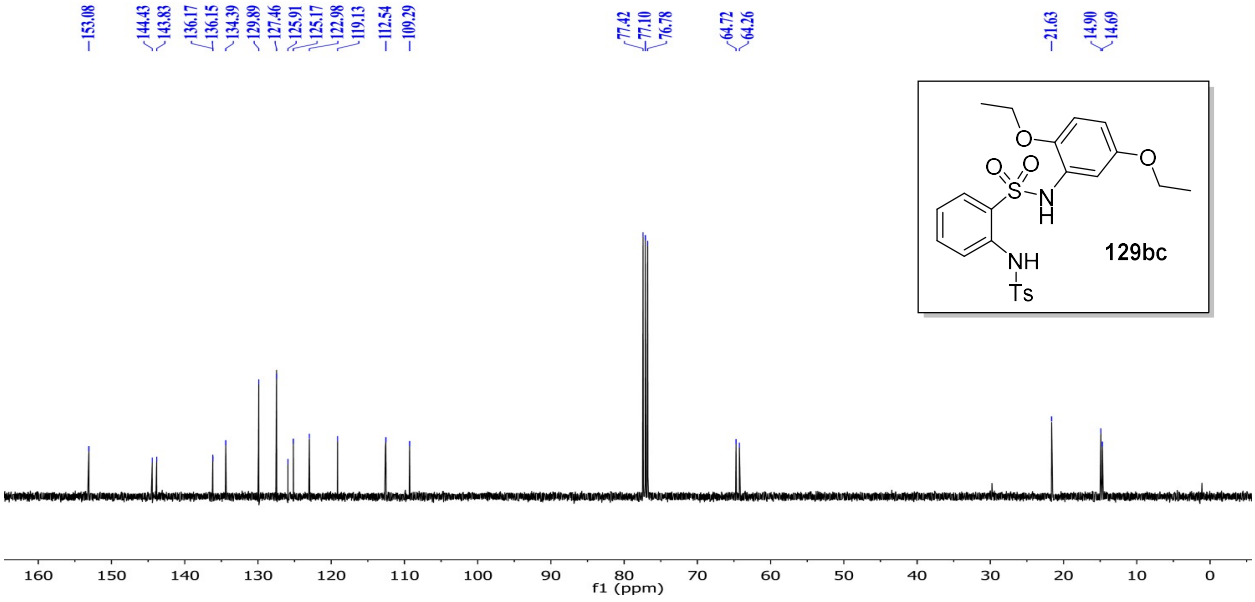
^{13}C{^{1}H} NMR (100 MHz) of **129bb**:



^{1}H NMR (400 MHz) of **129bc**:

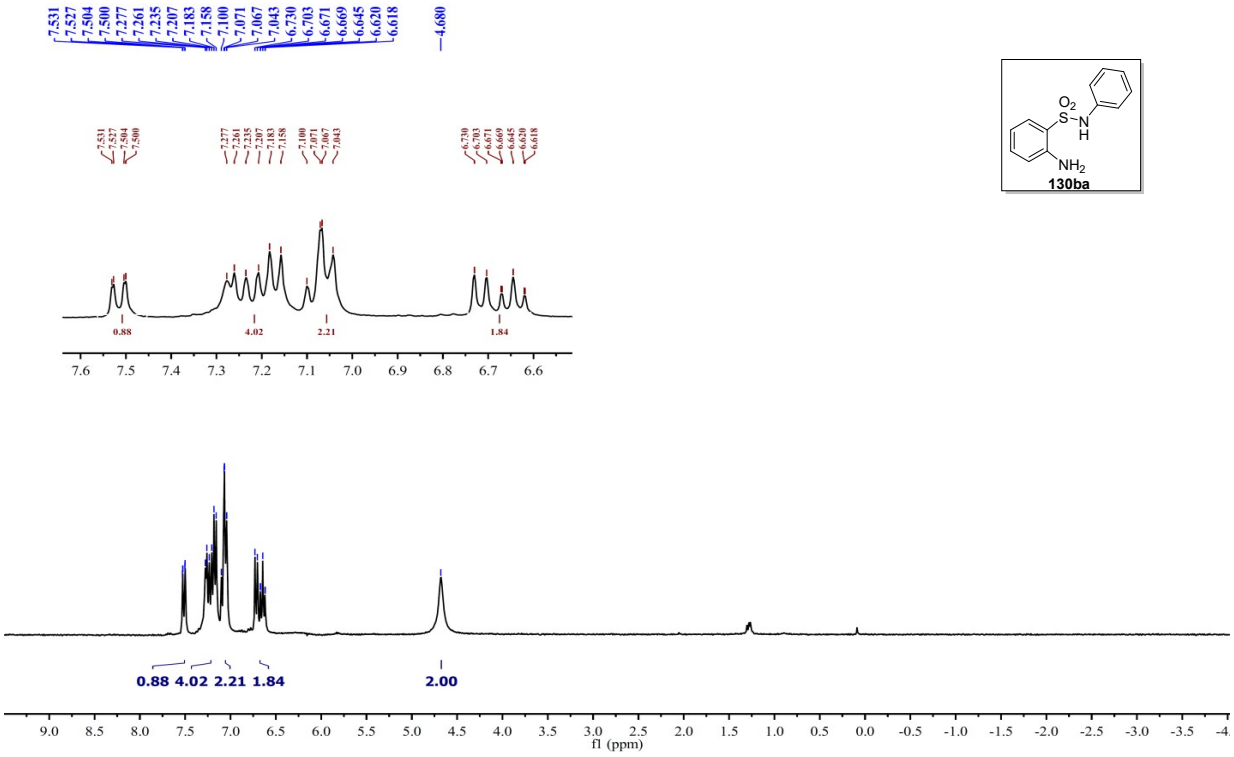


^{13}C{^{1}H} NMR (100 MHz) of **129bc**:

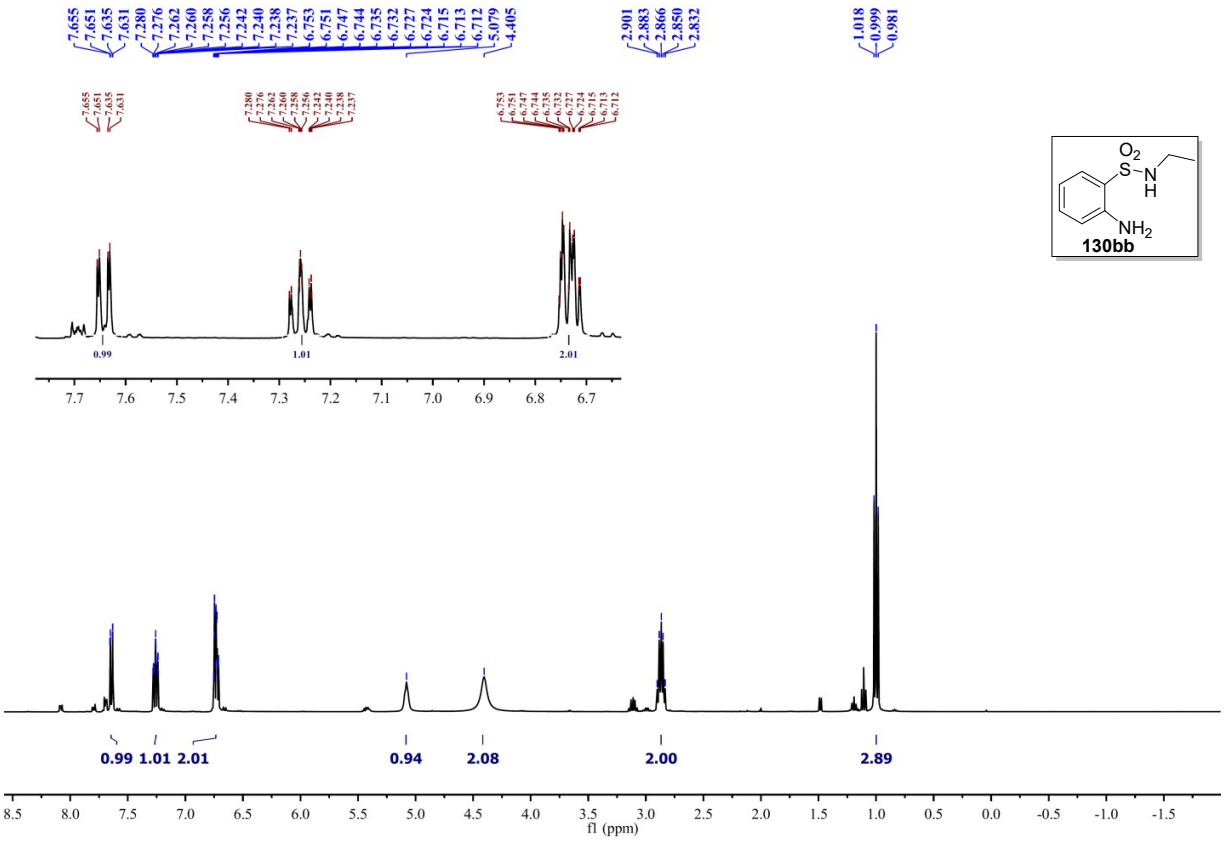


1.2.16.4 NMR spectra of substrates 130ba-130bc:

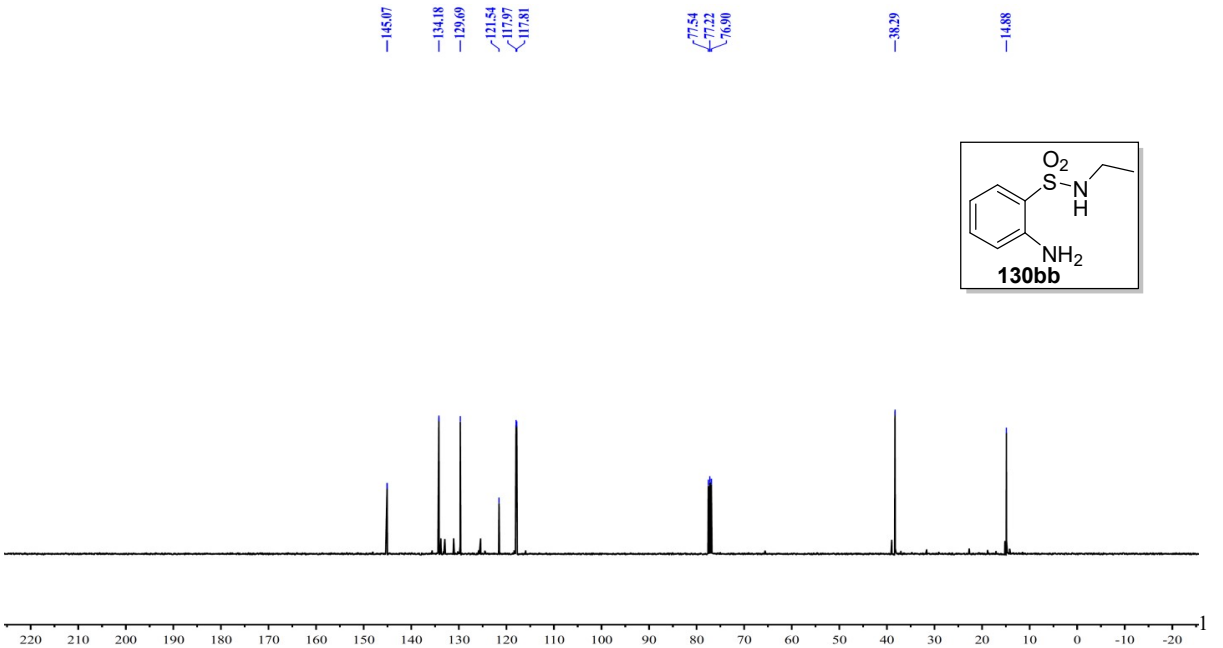
^{1}H NMR (300 MHz) of **130ba**:



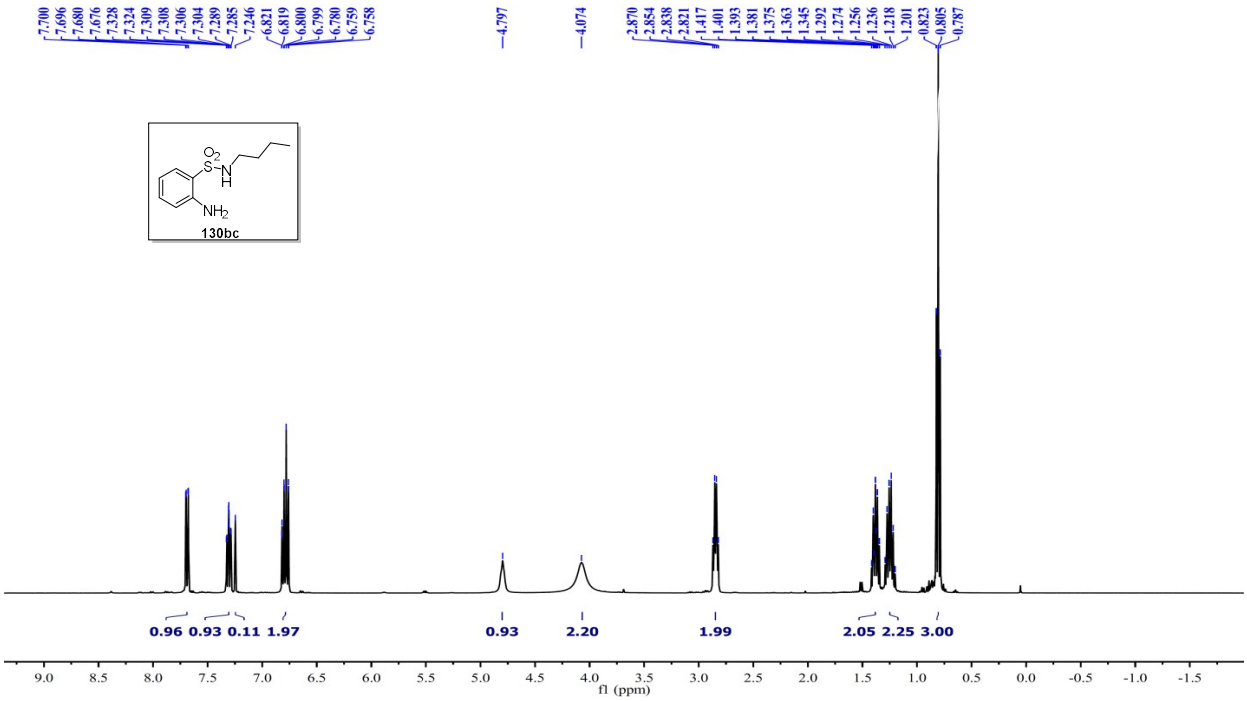
^{1}H NMR (400 MHz) of **130bb**:



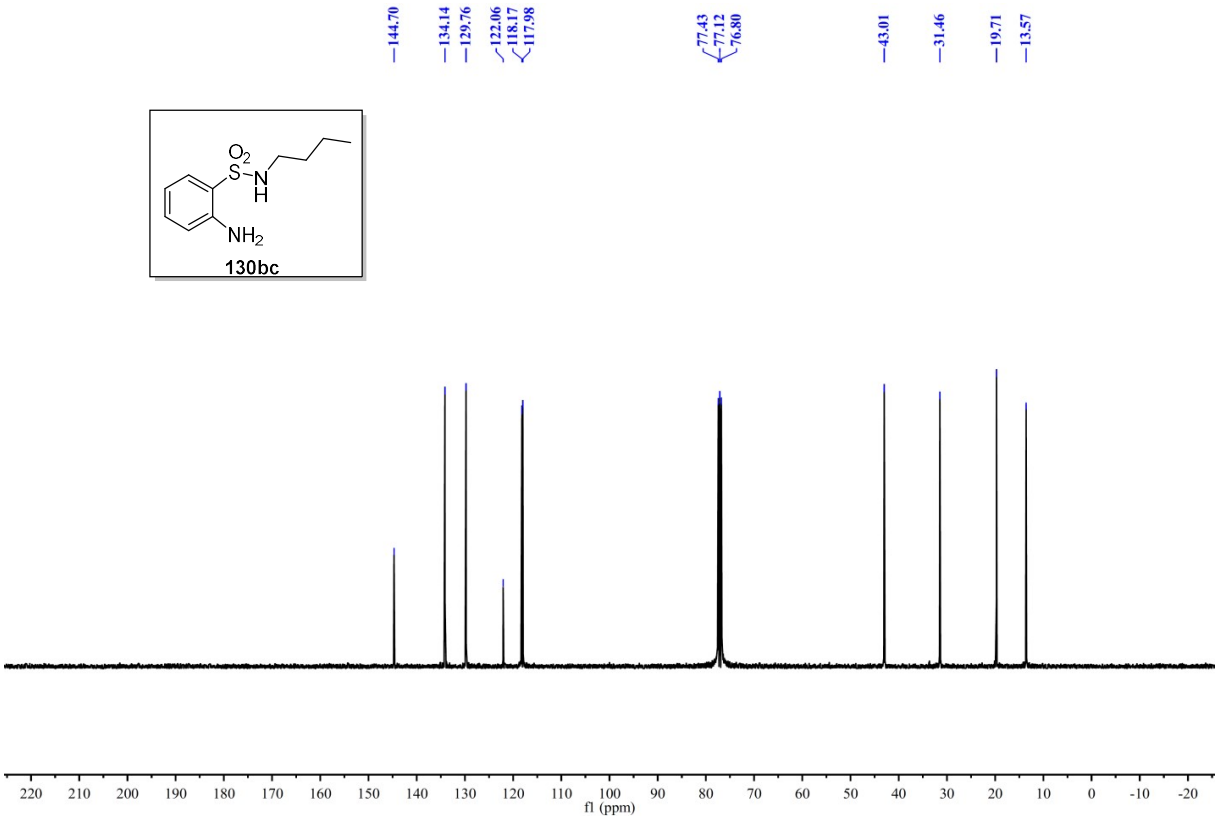
^{13}C{^{1}H} NMR (100 MHz) of **130bb**:



H NMR (400 MHz) of **130bc**:

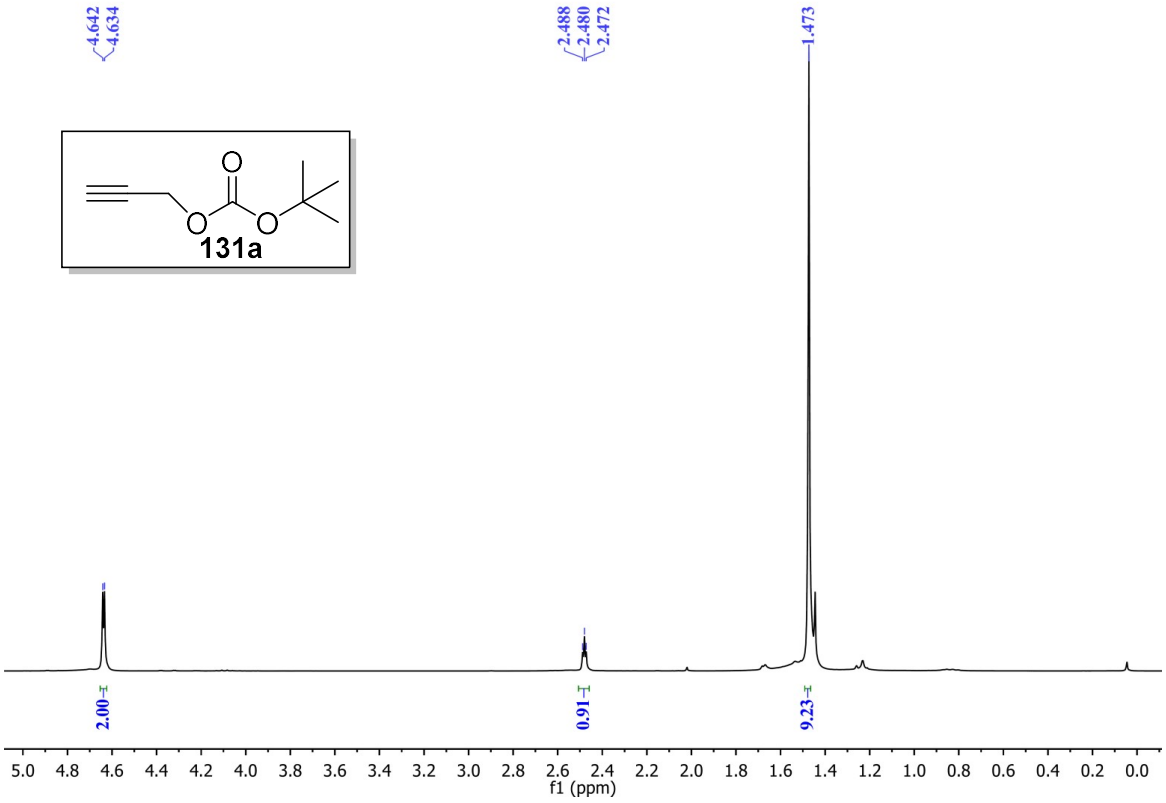


$^{13}C\{^{1}H\}$ NMR (100 MHz) of **130bc**:

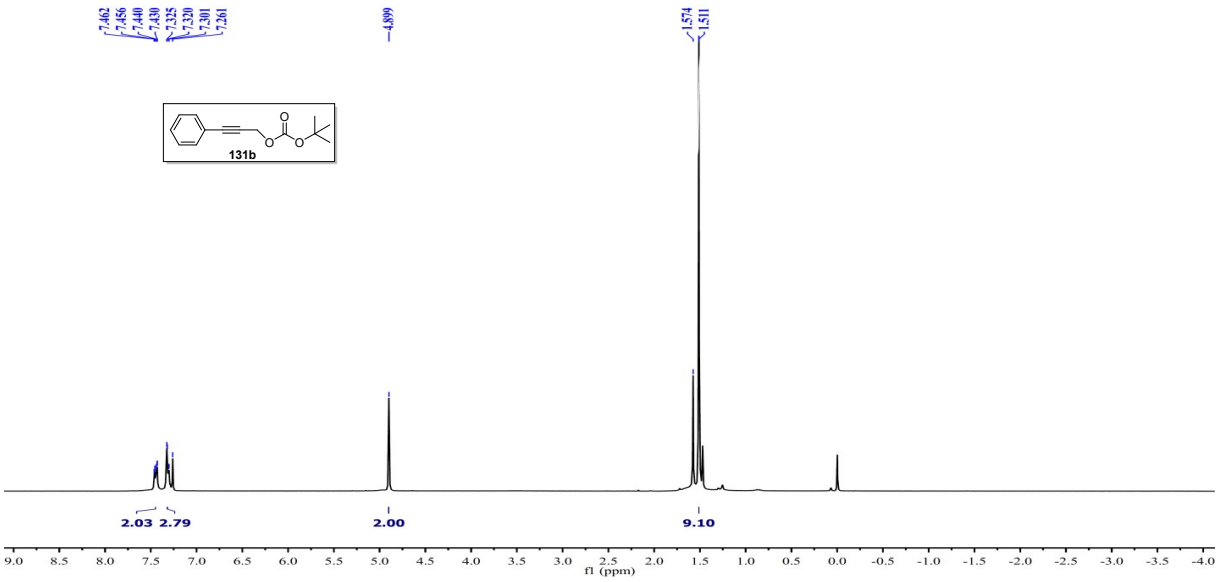


1.2.17.5 NMR spectra of substrates 131a-131k:

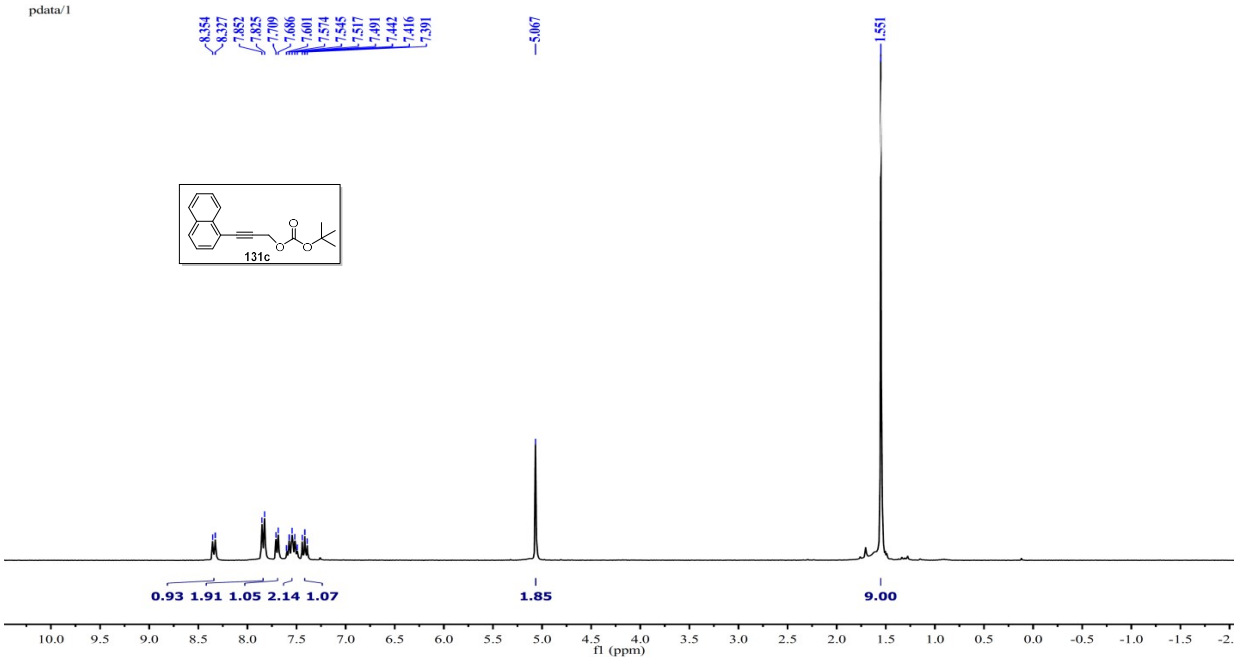
^{1}H NMR (300 MHz) of **131a**:



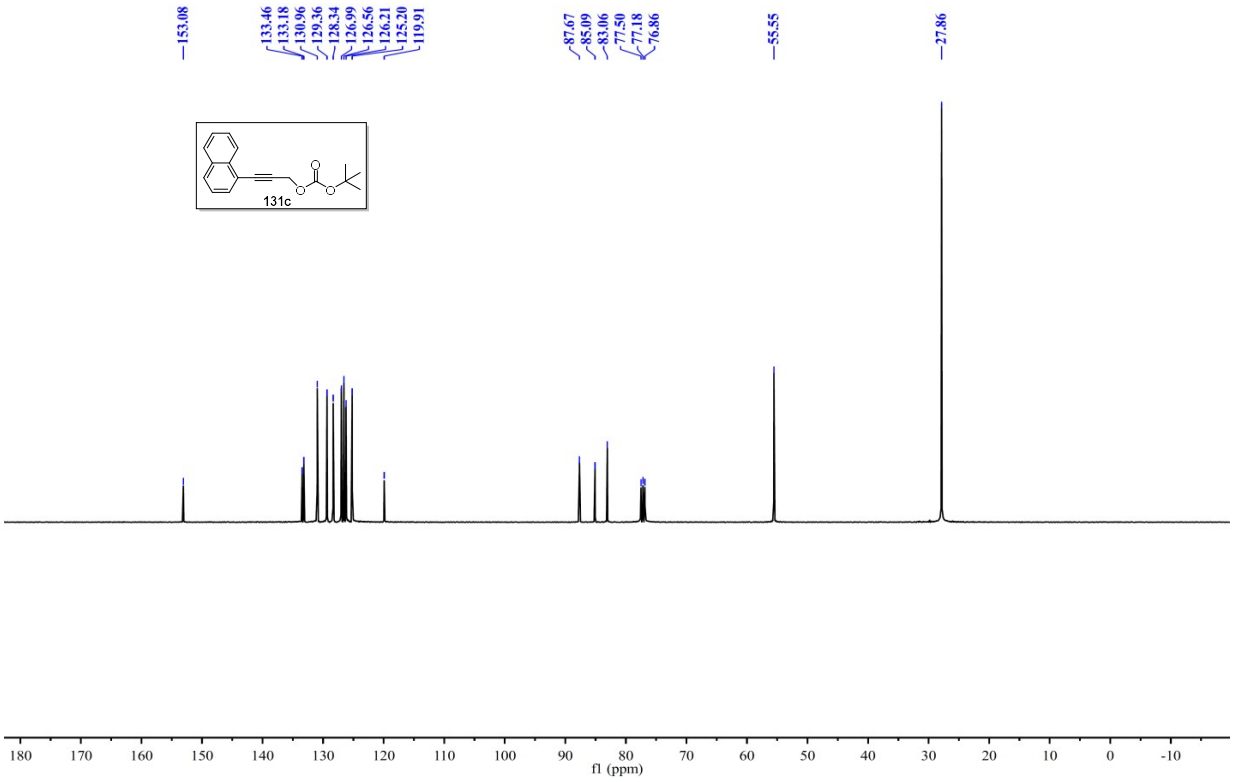
^{1}H NMR (300 MHz) of **131b**:



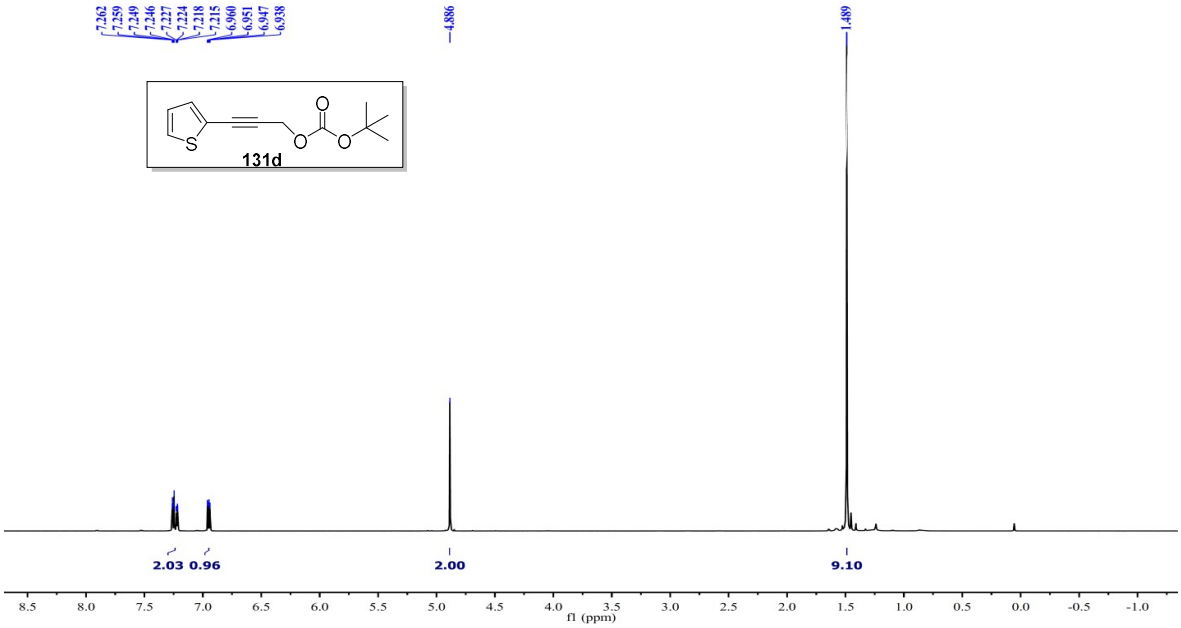
^{1}H NMR (400 MHz) of **131c:**



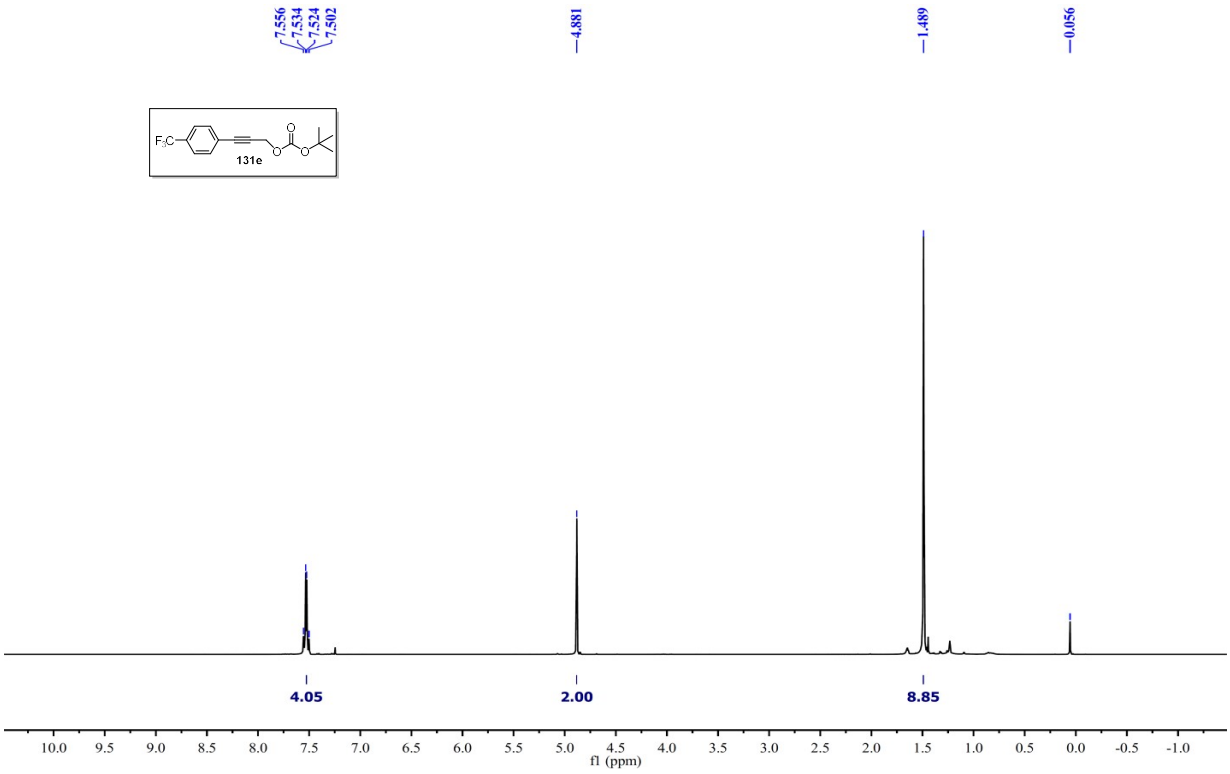
^{13}C{^{1}H} NMR (100 MHz) of **131c**:



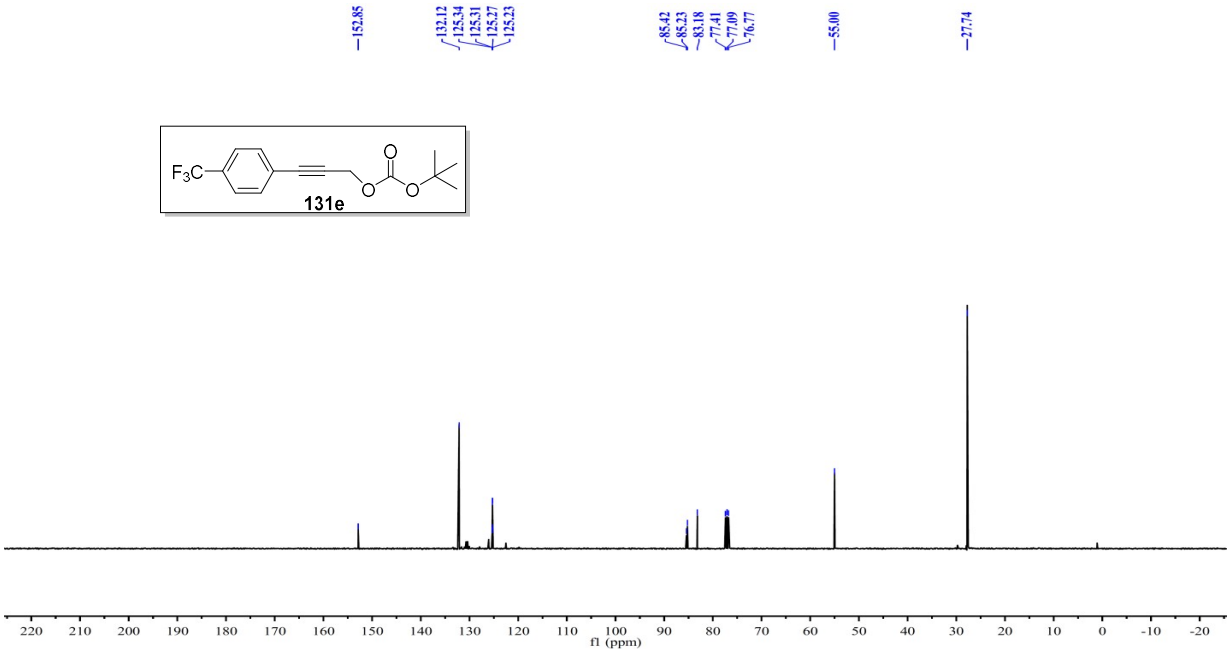
^{1}H NMR (400 MHz) of **131d:**



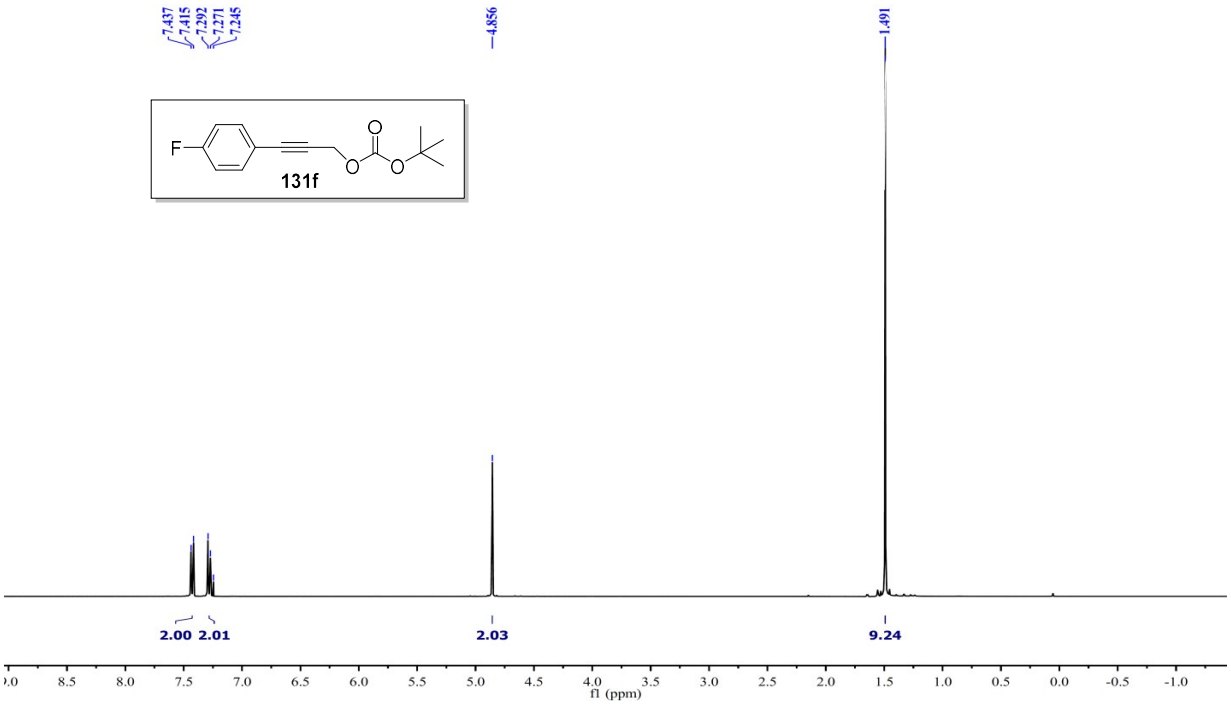
^{1}H NMR (400 MHz) of **131e:**



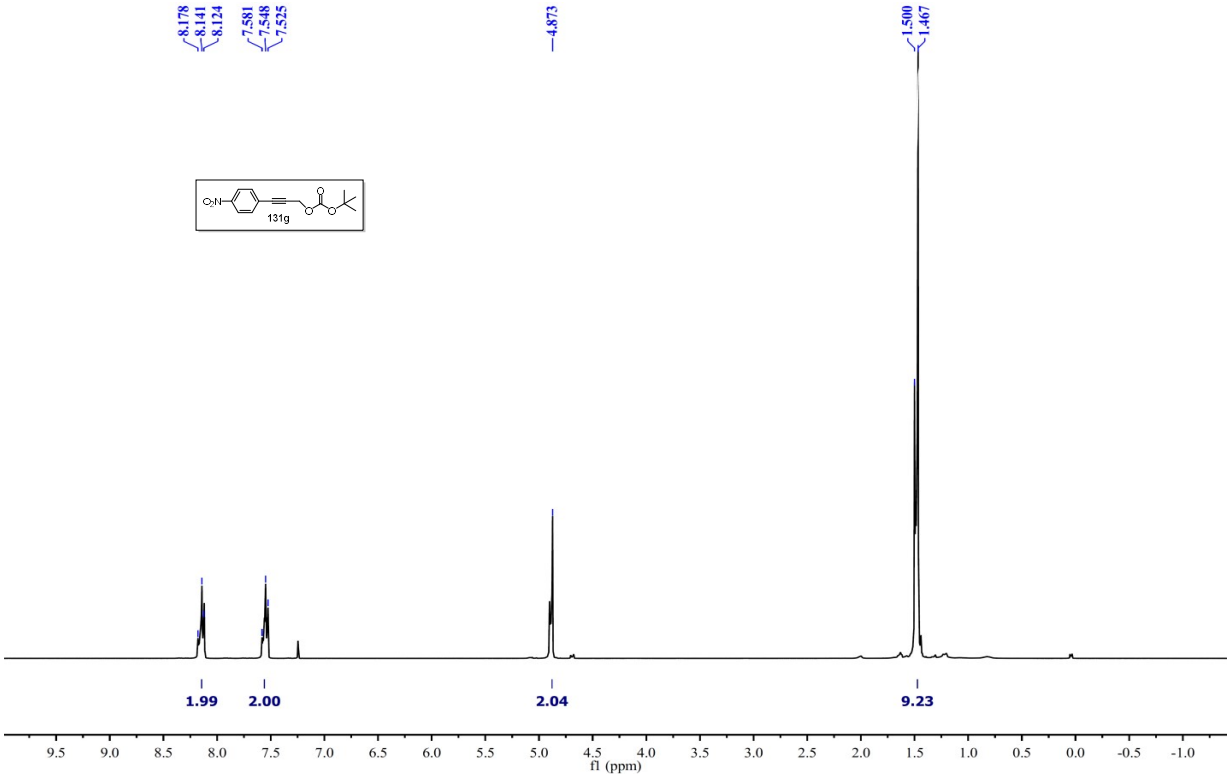
^{13}C{^{1}H} NMR (100 MHz) of **131e**:



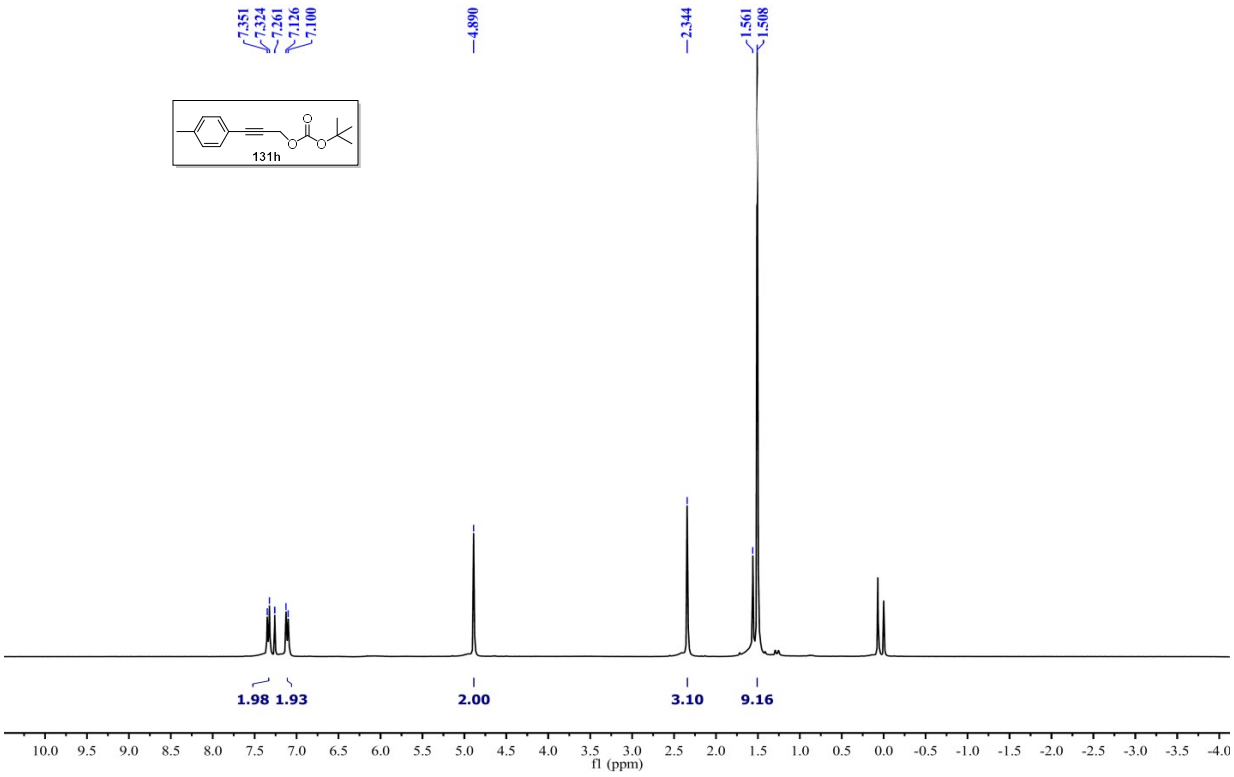
^{1}H NMR (400 MHz) of **131f:**



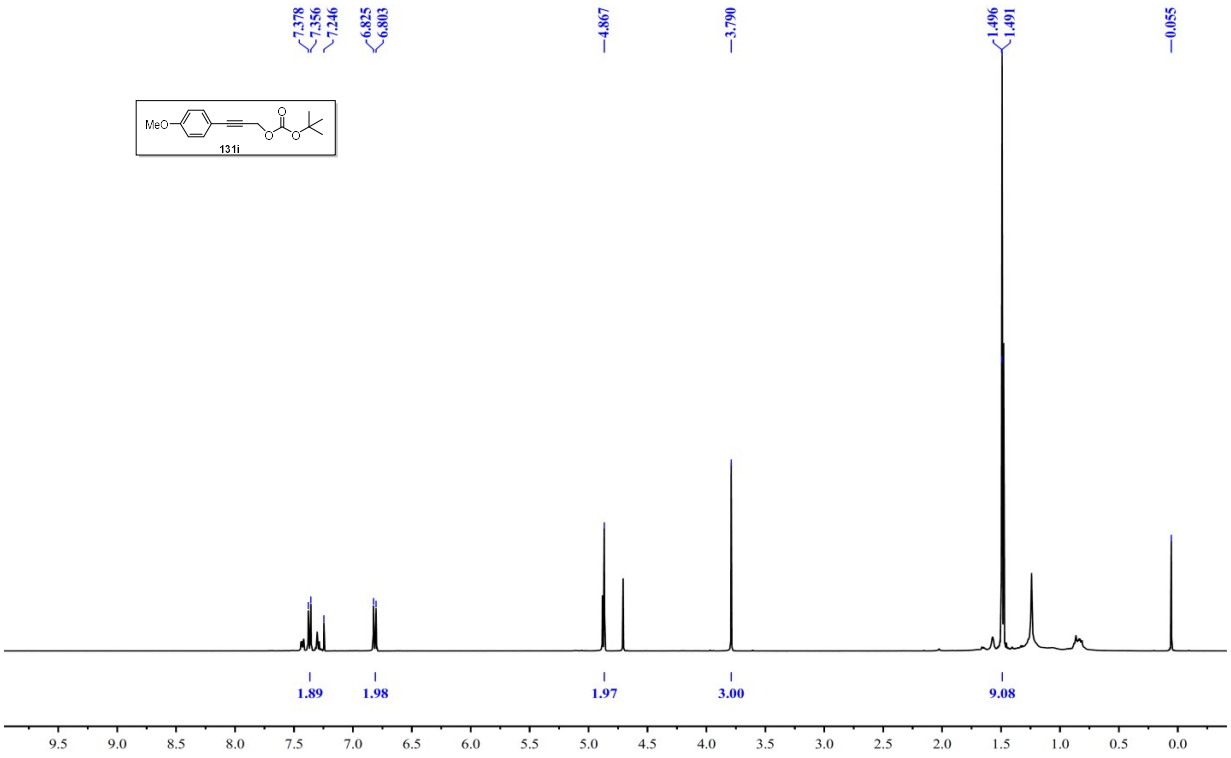
^{1}H NMR (400 MHz) of **131g:**



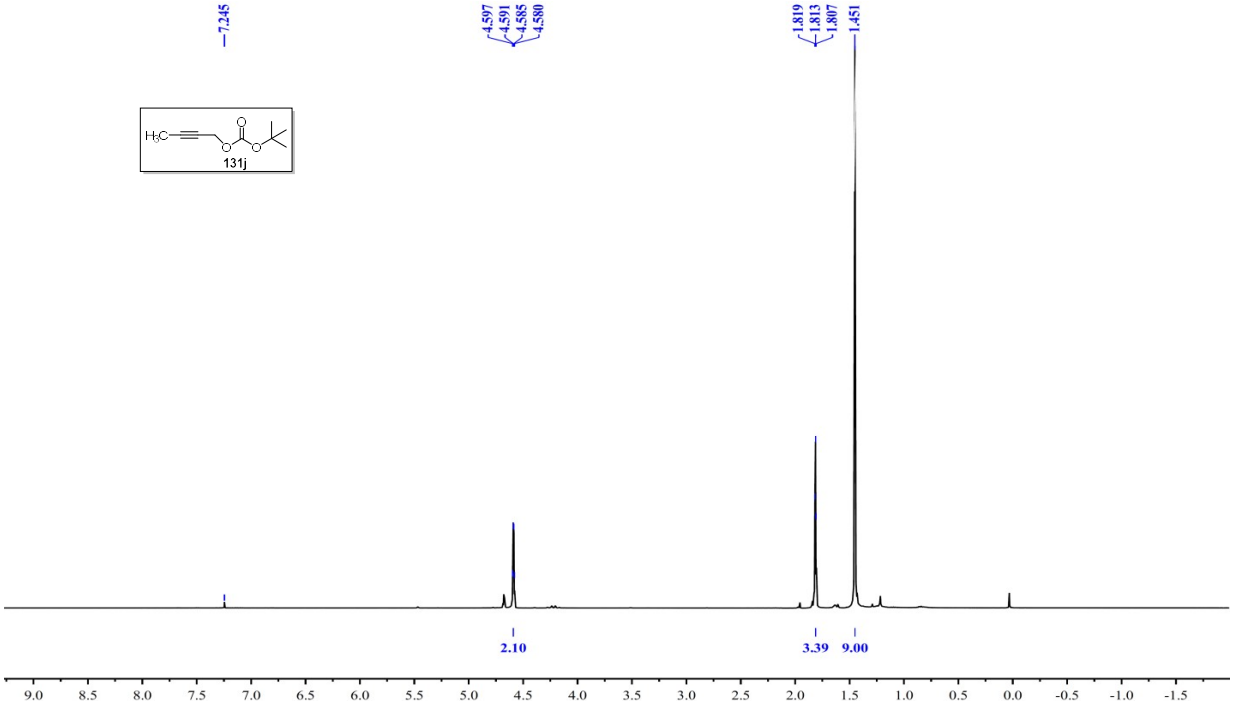
^{1}H NMR (400 MHz) of **131h:**



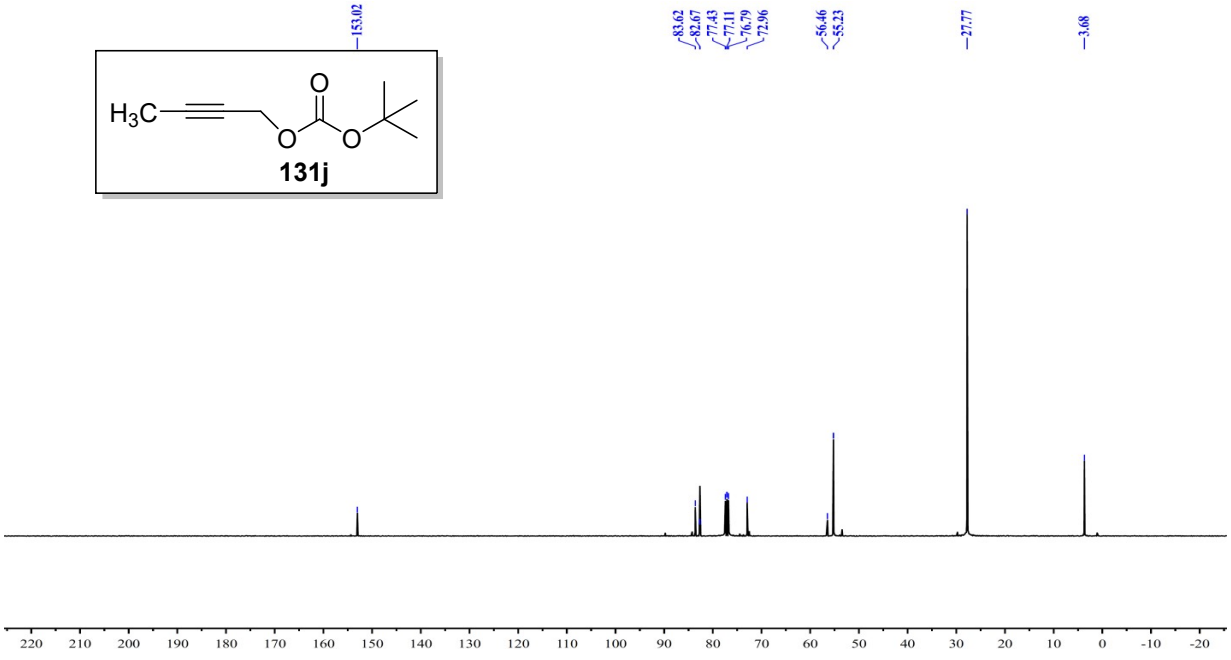
^{1}H NMR (400 MHz) of **131i:**



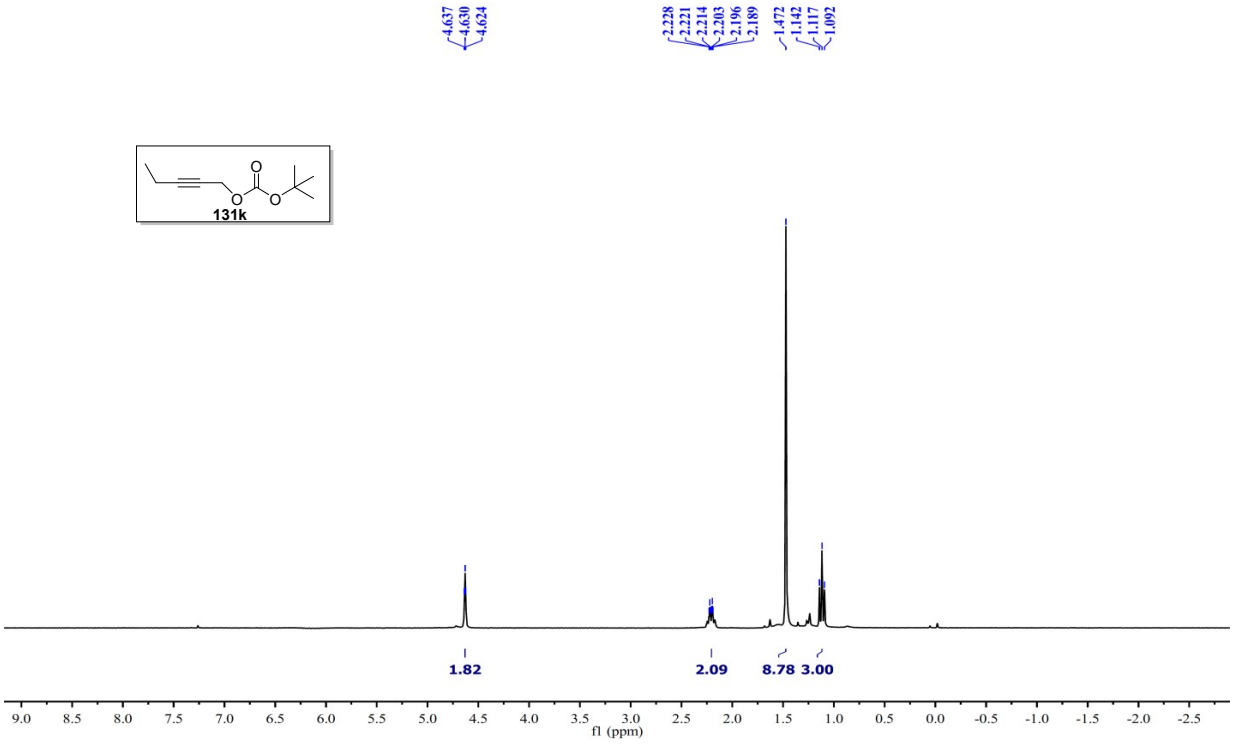
^{1}H NMR (400 MHz) of **131j:**



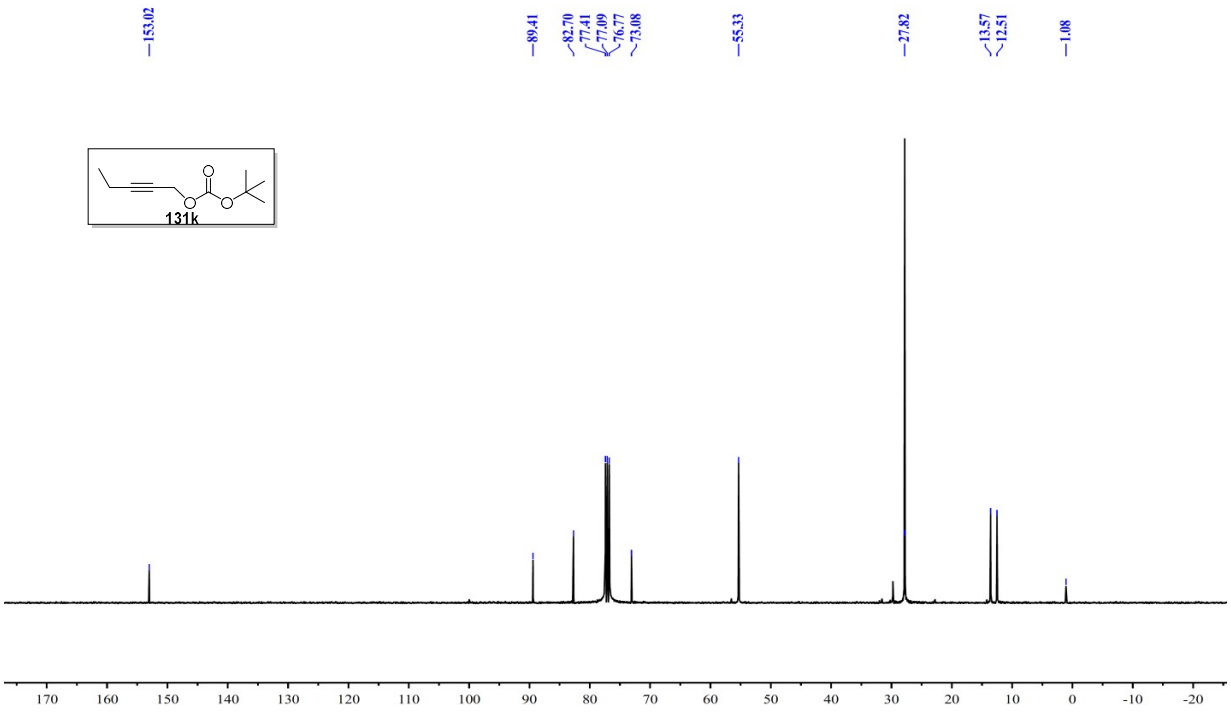
^{13}C{^{1}H} NMR (100 MHz) of **131j**:



^{1}H NMR (400 MHz) of **131k:**

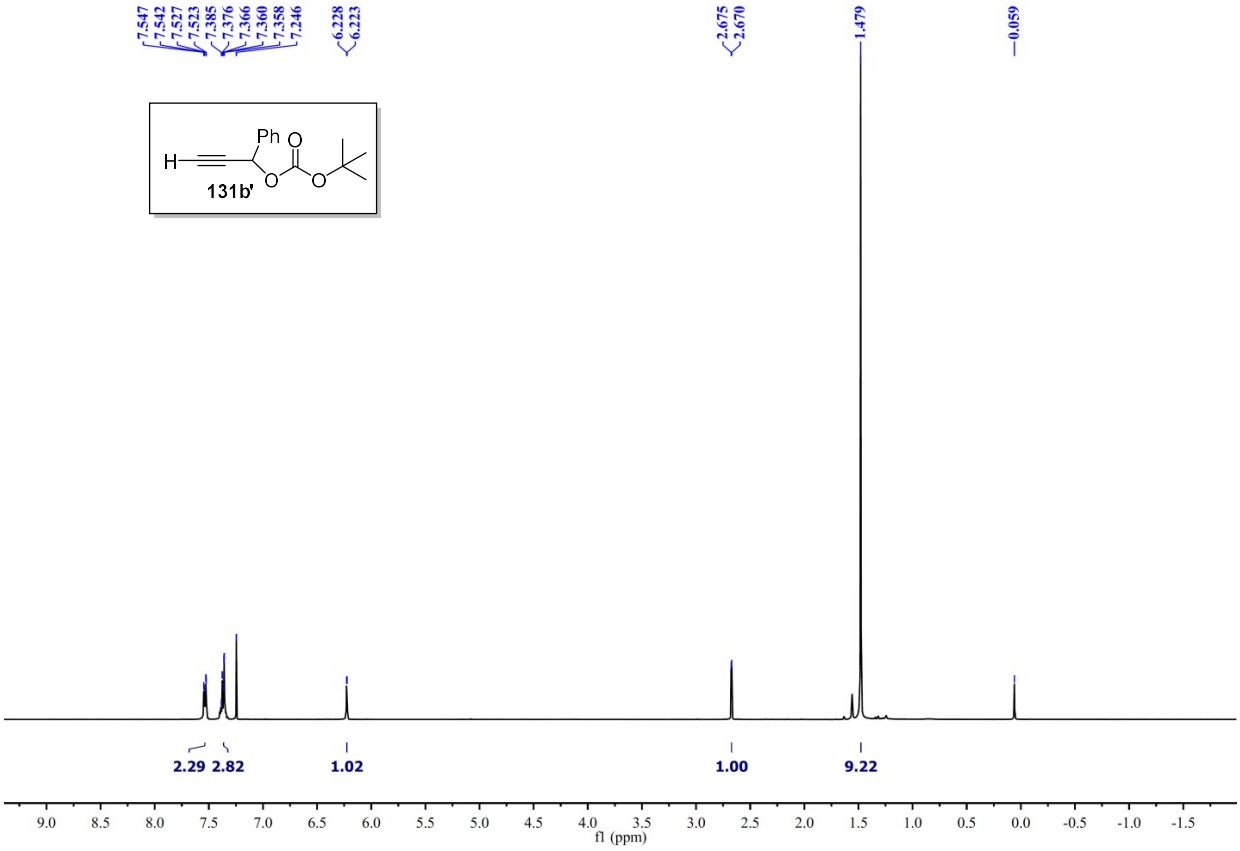


^{13}C{^{1}H} NMR (100 MHz) of **131k:**



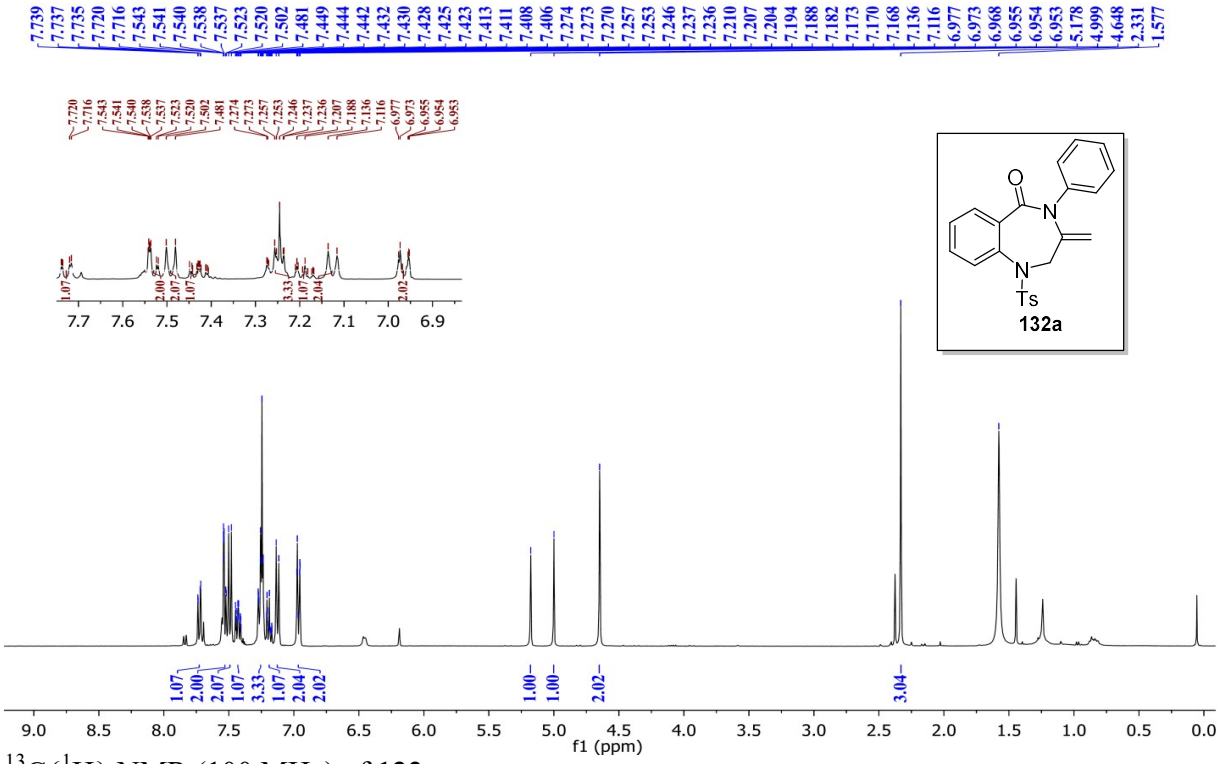
1.2.17.6 NMR spectra of substrates 131b':

^{1}H NMR (400 MHz) of **131b'**:

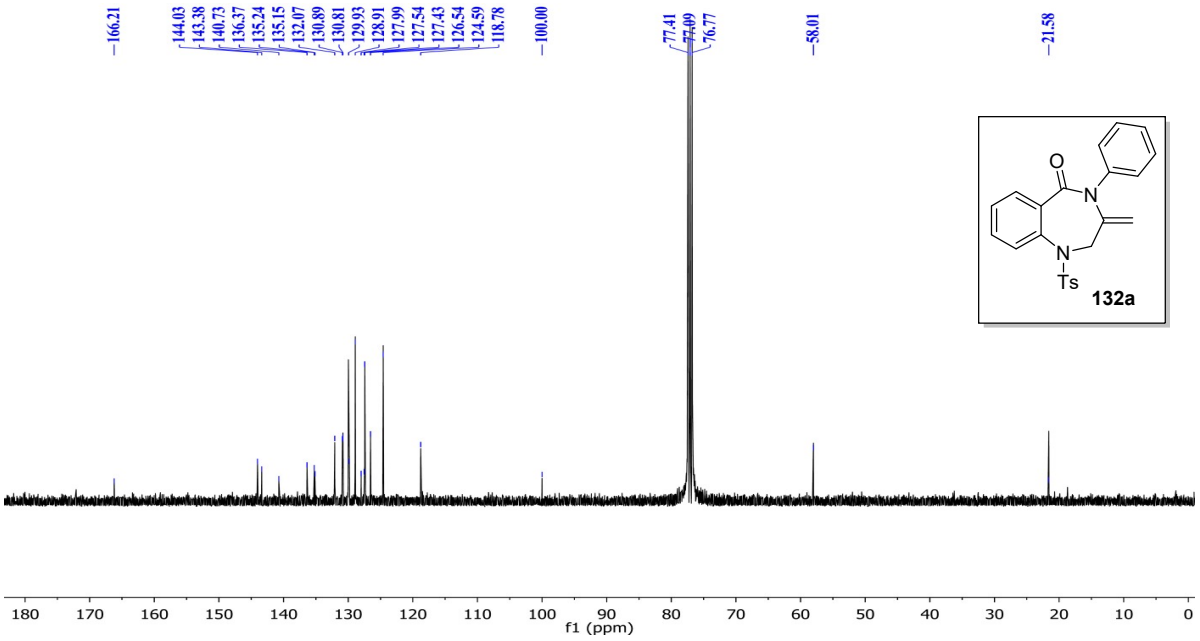


1.2.17.7 NMR spectra of products 132a-132q:

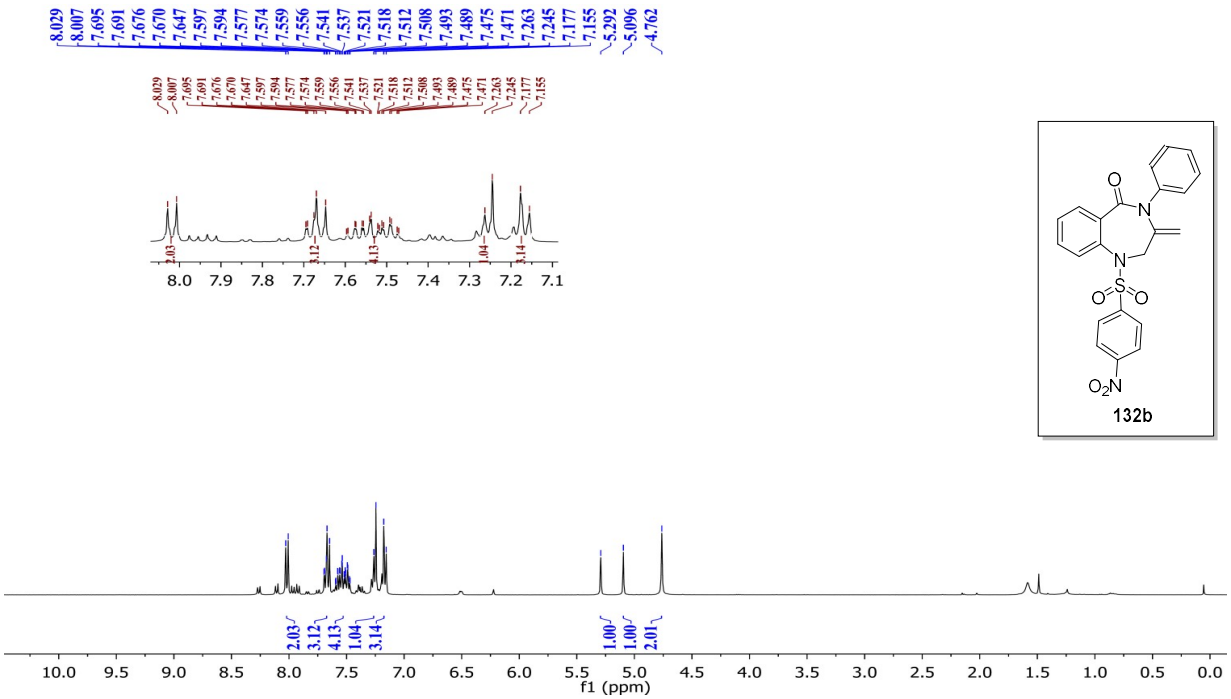
^{1}H NMR (400 MHz) of **132a**:



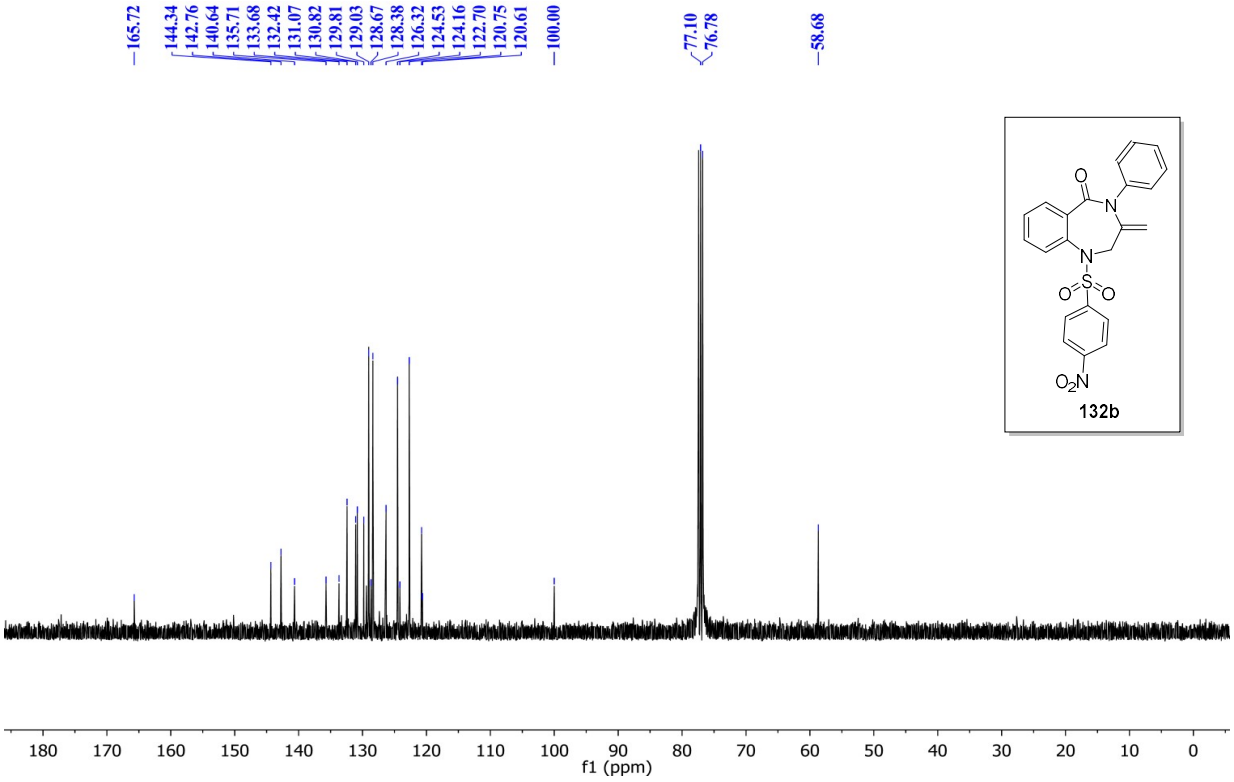
^{13}C{^{1}H} NMR (100 MHz) of **132a**:



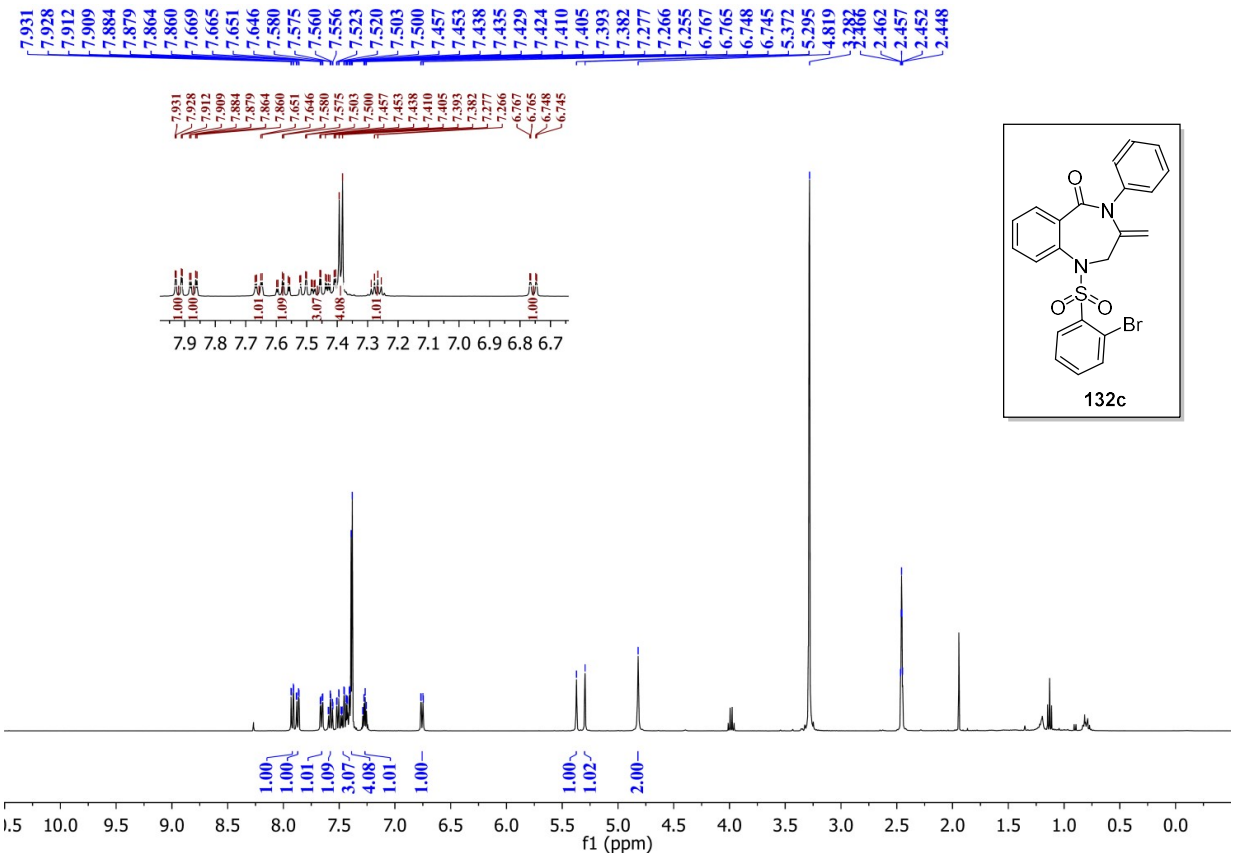
^{1}H NMR (400 MHz) of **132b**:



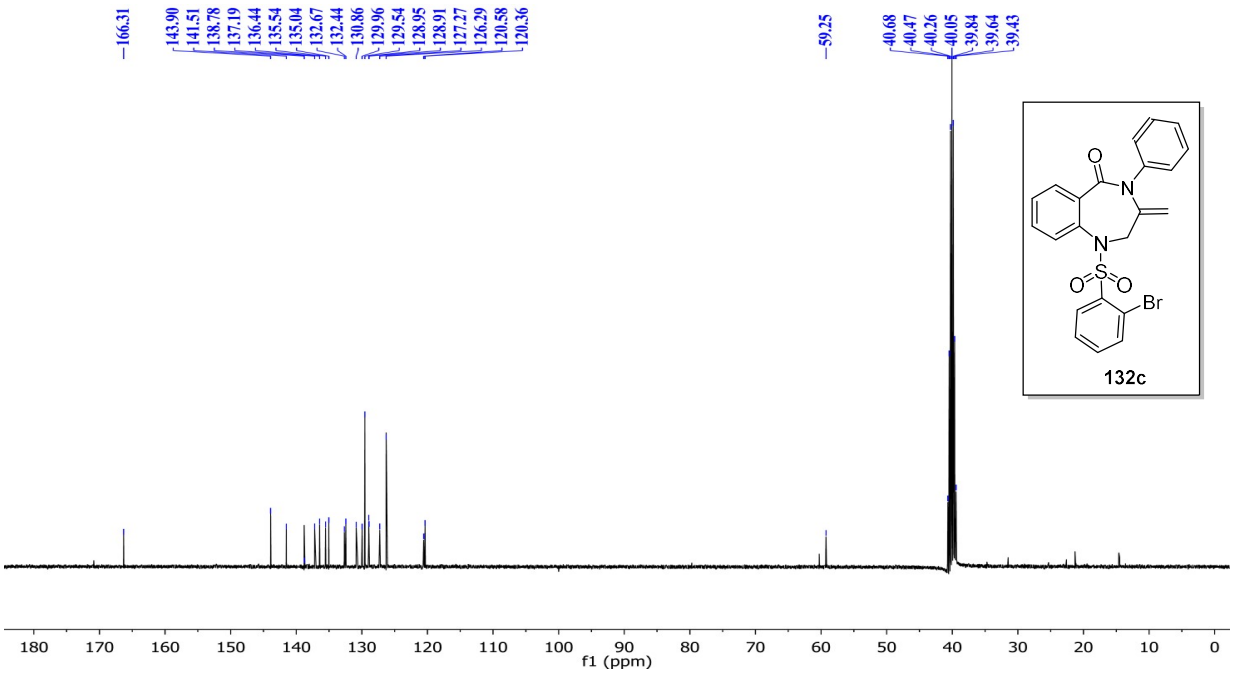
^{13}C{^{1}H} NMR (100 MHz) of **132b**:



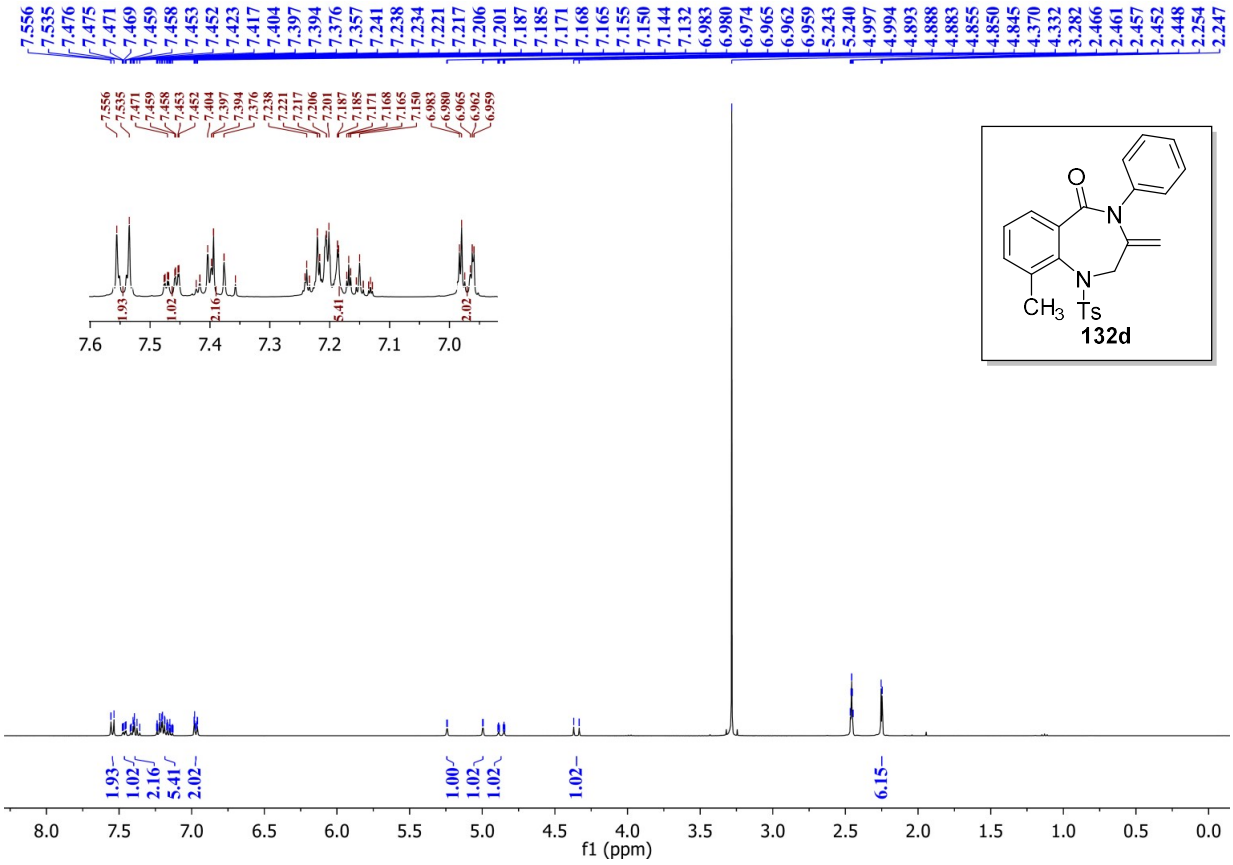
^{1}H NMR (400 MHz) of **132c:**



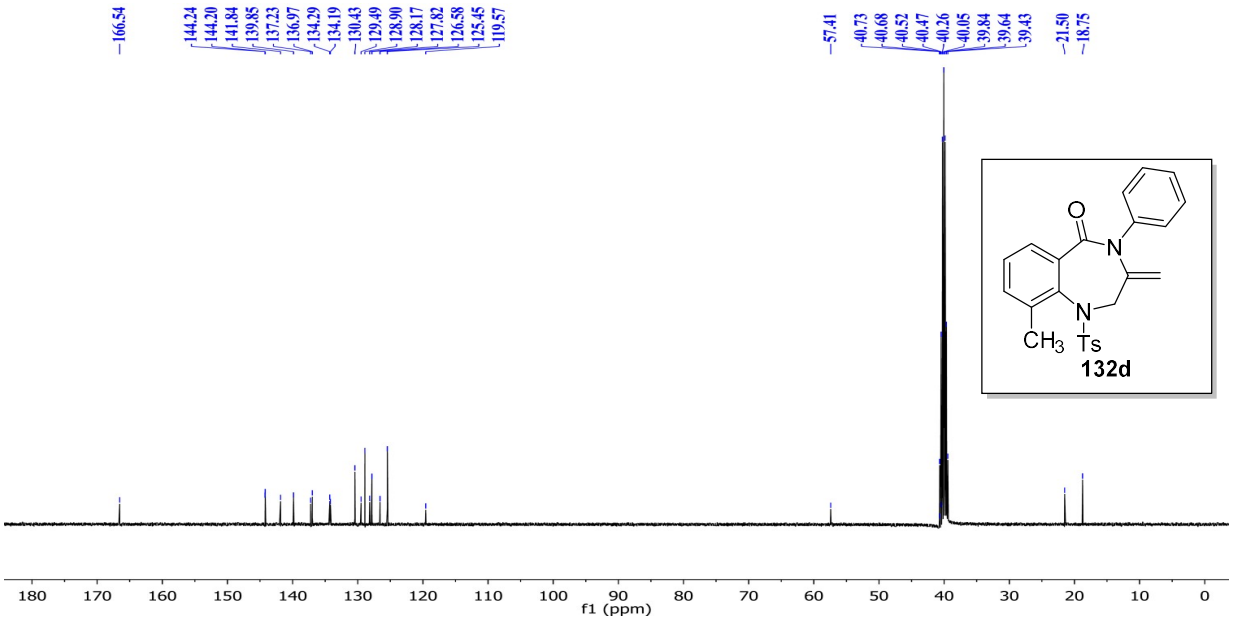
^{13}C{^{1}H} NMR (100 MHz) of **132c**:



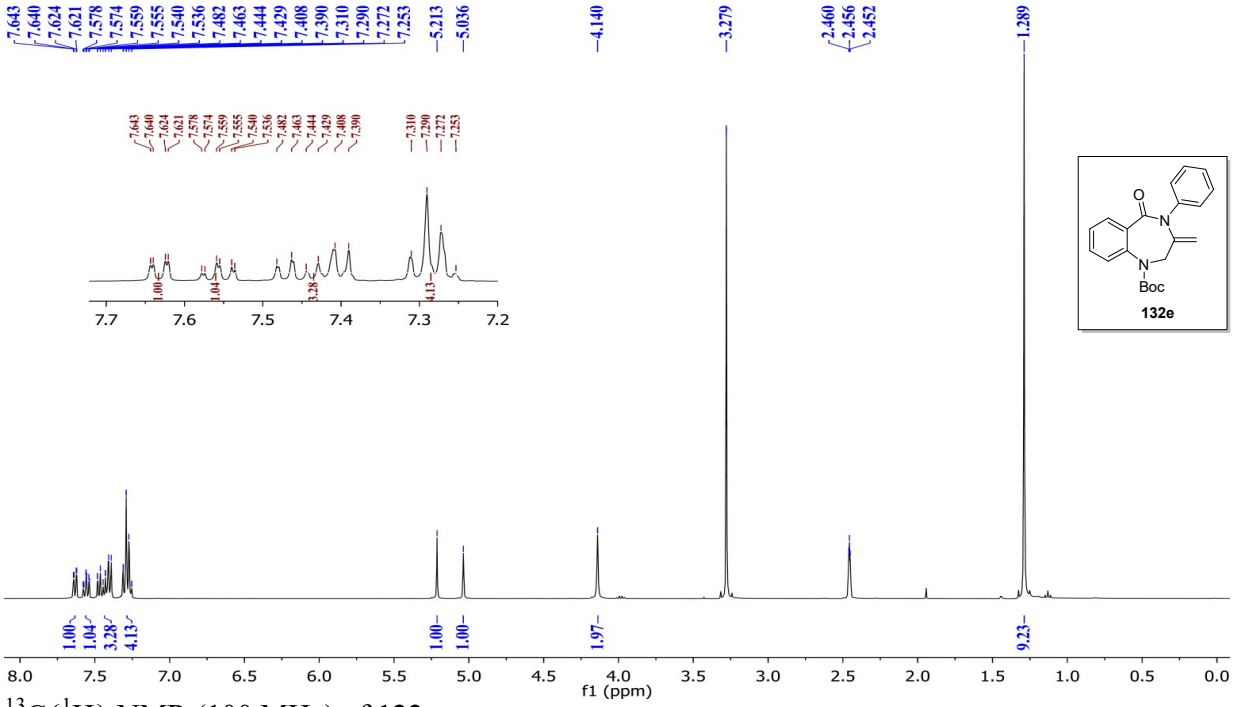
^{1}H NMR (400 MHz) of **132d:**



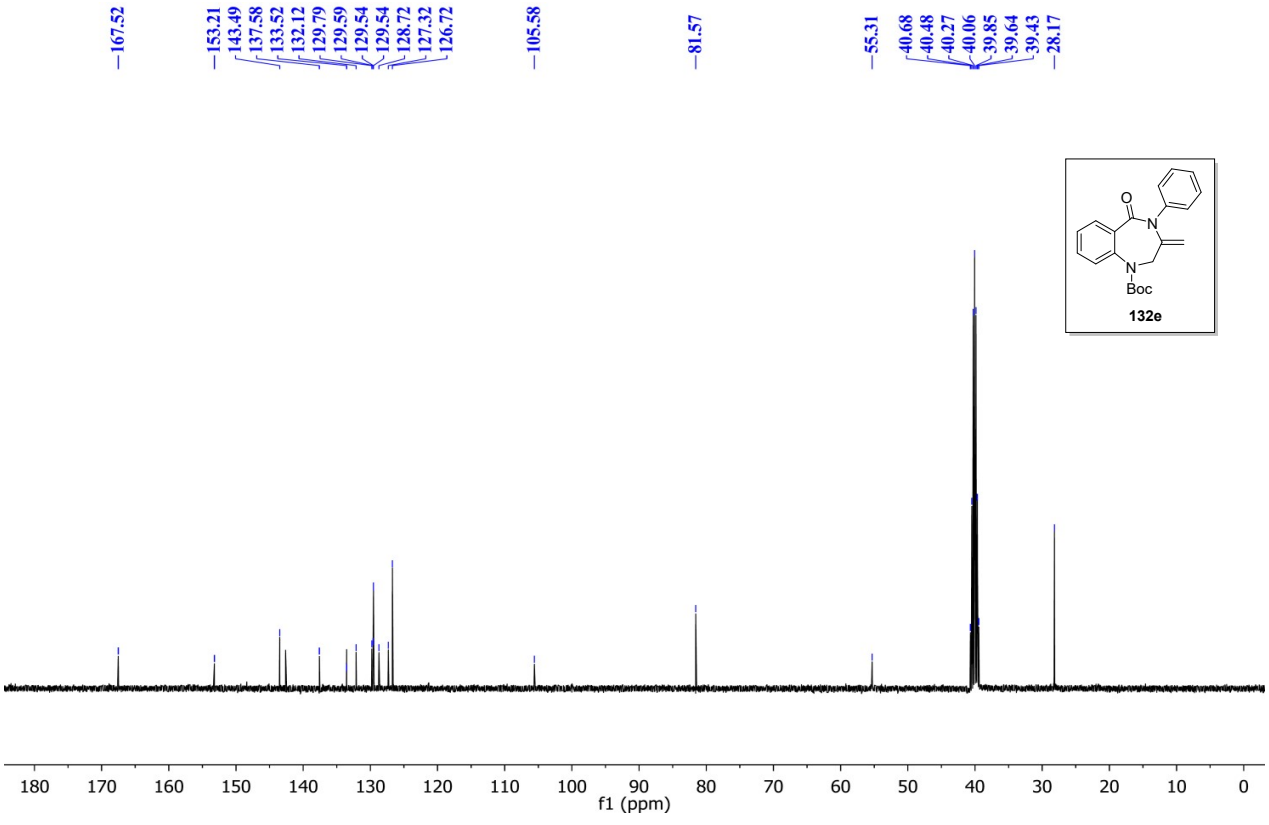
^{13}C{^{1}H} NMR (100 MHz) of **132d**:



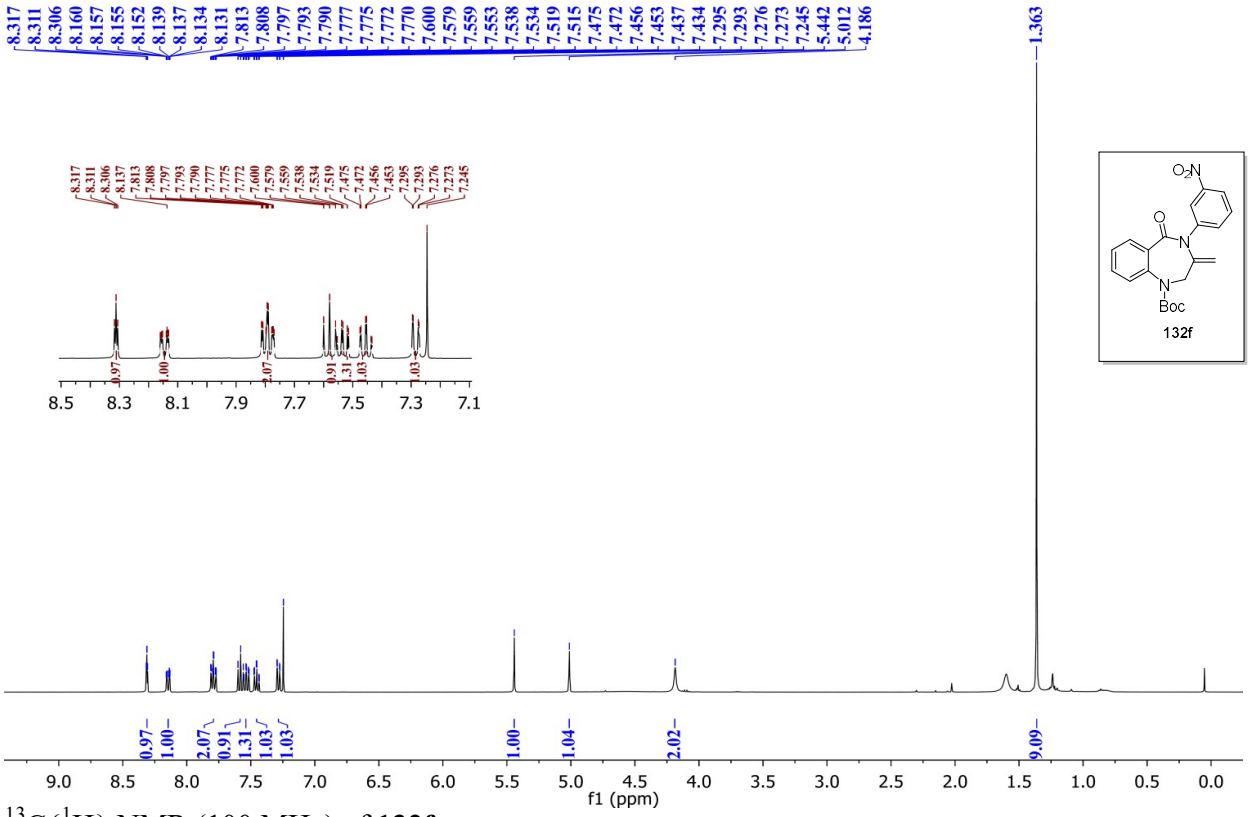
^{1}H NMR (400 MHz) of **132e**:



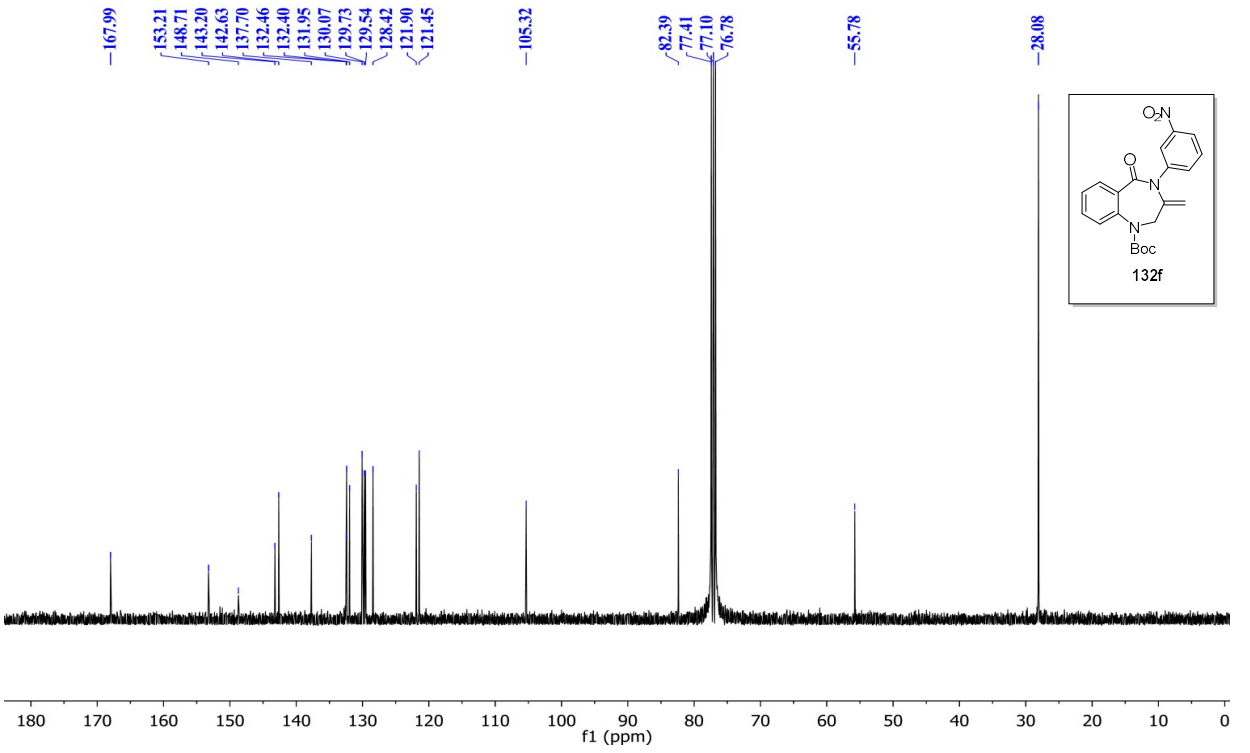
^{13}C{^{1}H} NMR (100 MHz) of **132e**:



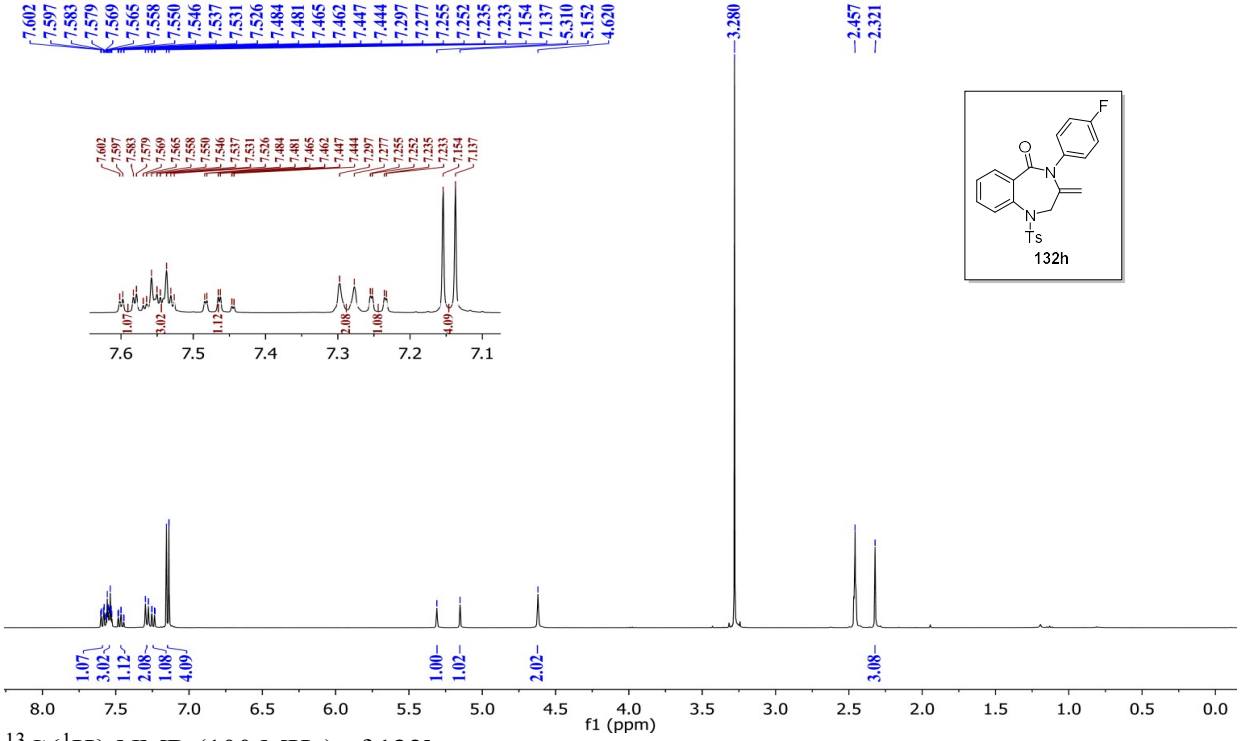
^{1}H NMR (400 MHz) of **132f**:



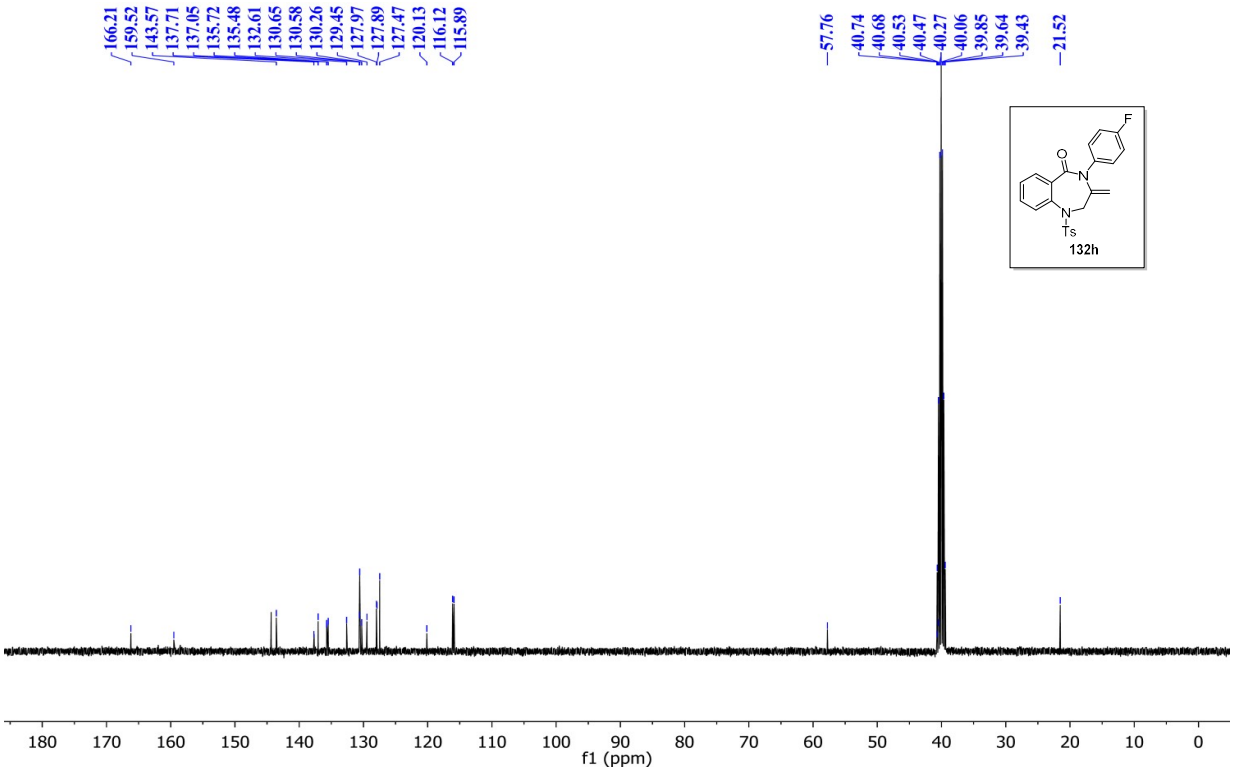
^{13}C{^{1}H} NMR (100 MHz) of **132f**:



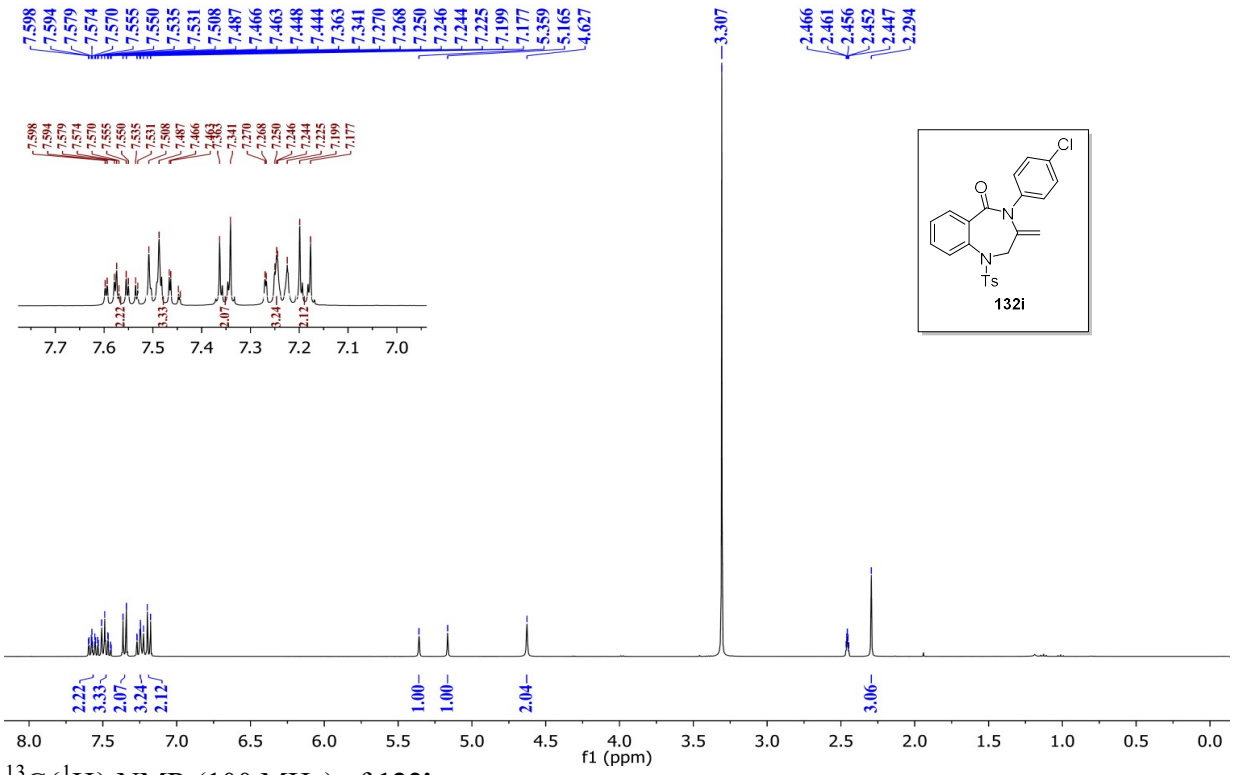
^{1}H NMR (400 MHz) of **132h**:



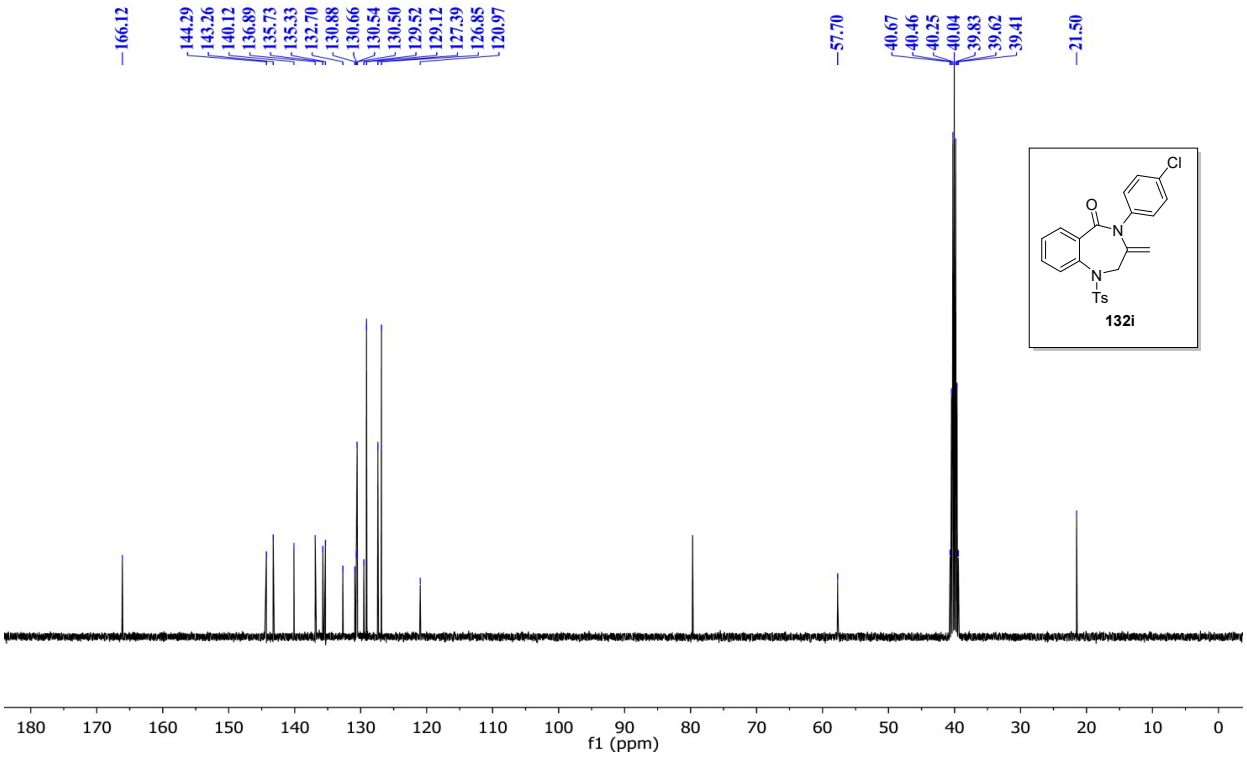
^{13}C{^{1}H} NMR (100 MHz) of **132h**:



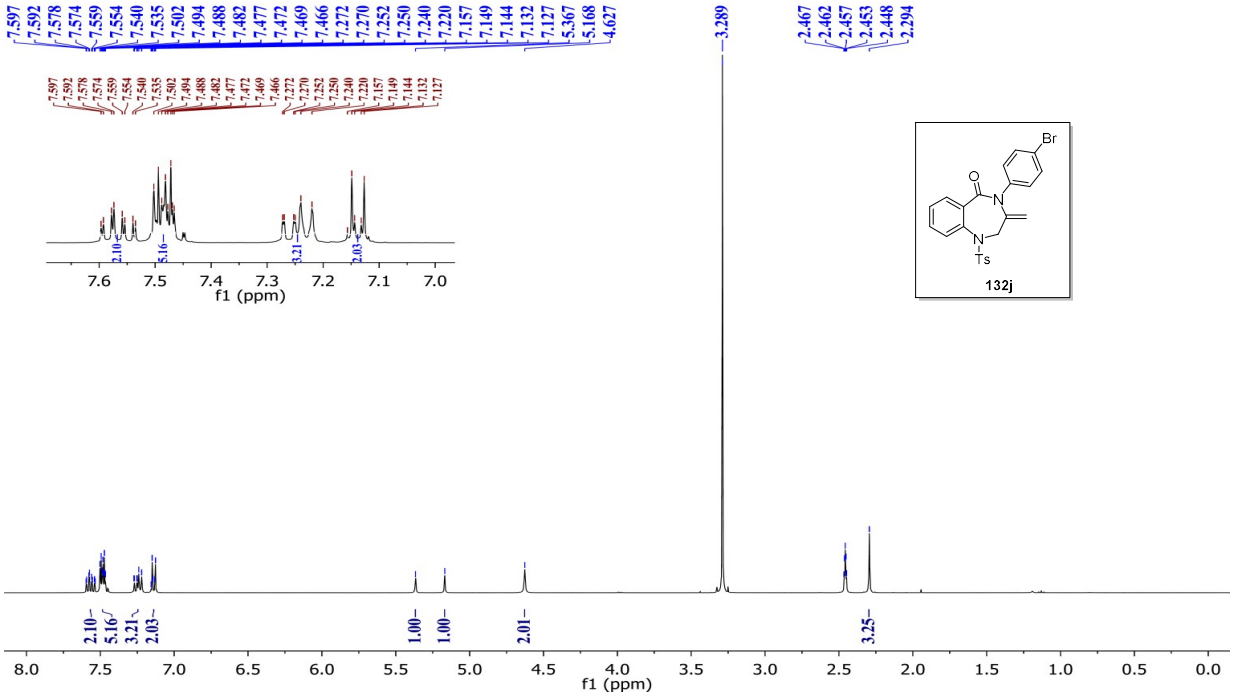
^{1}H NMR (400 MHz) of **132i**:



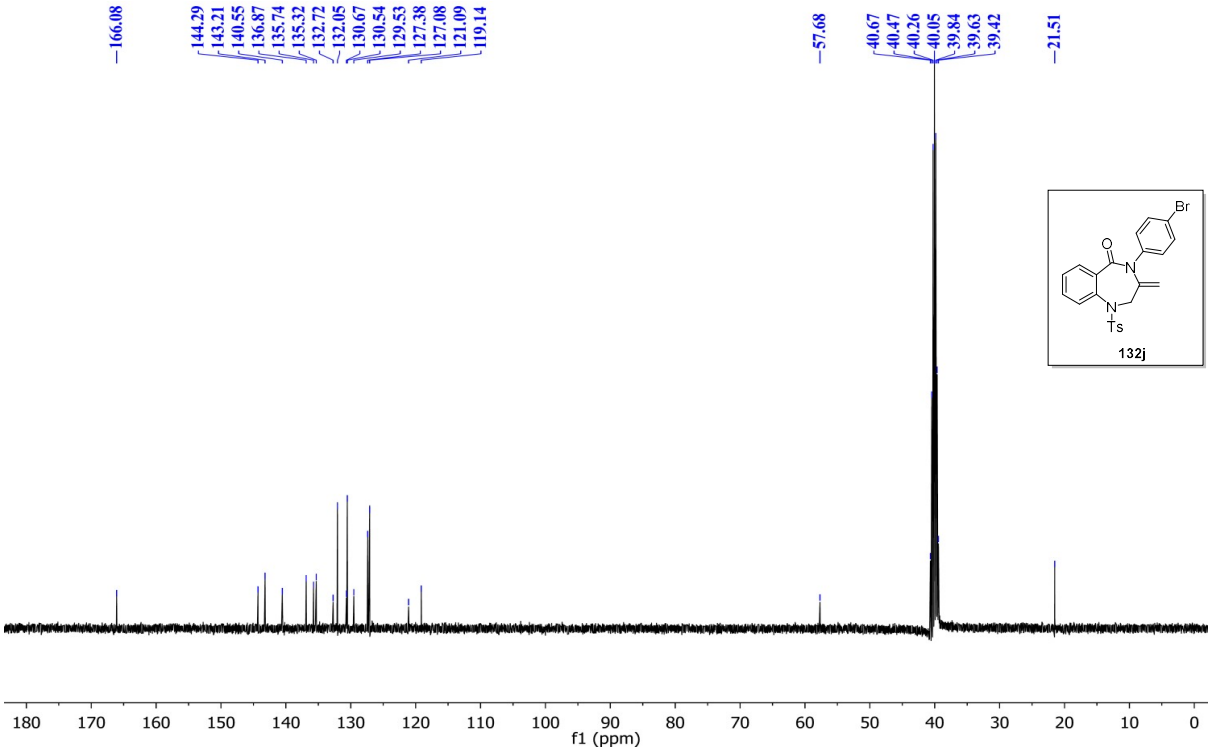
^{13}C{^{1}H} NMR (100 MHz) of **132i**:



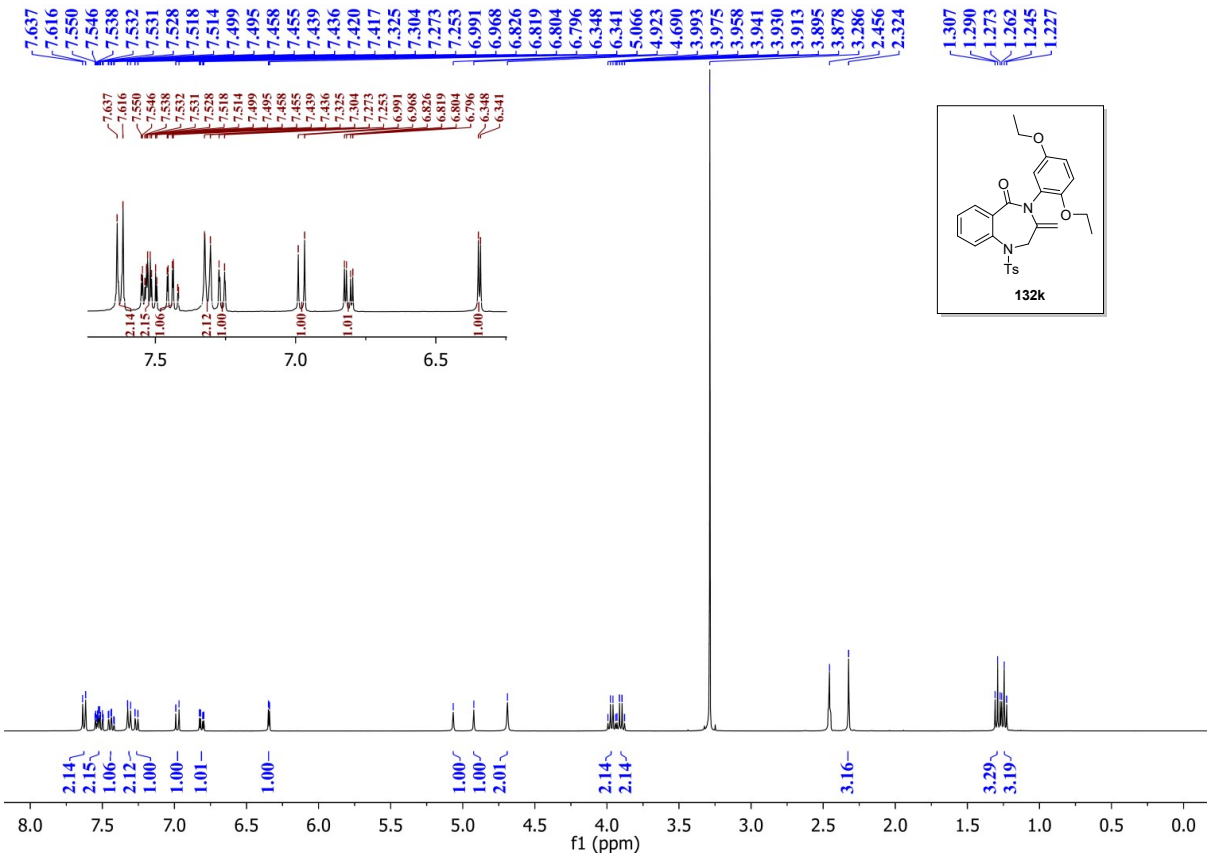
^{1}H NMR (400 MHz) of **132j**:



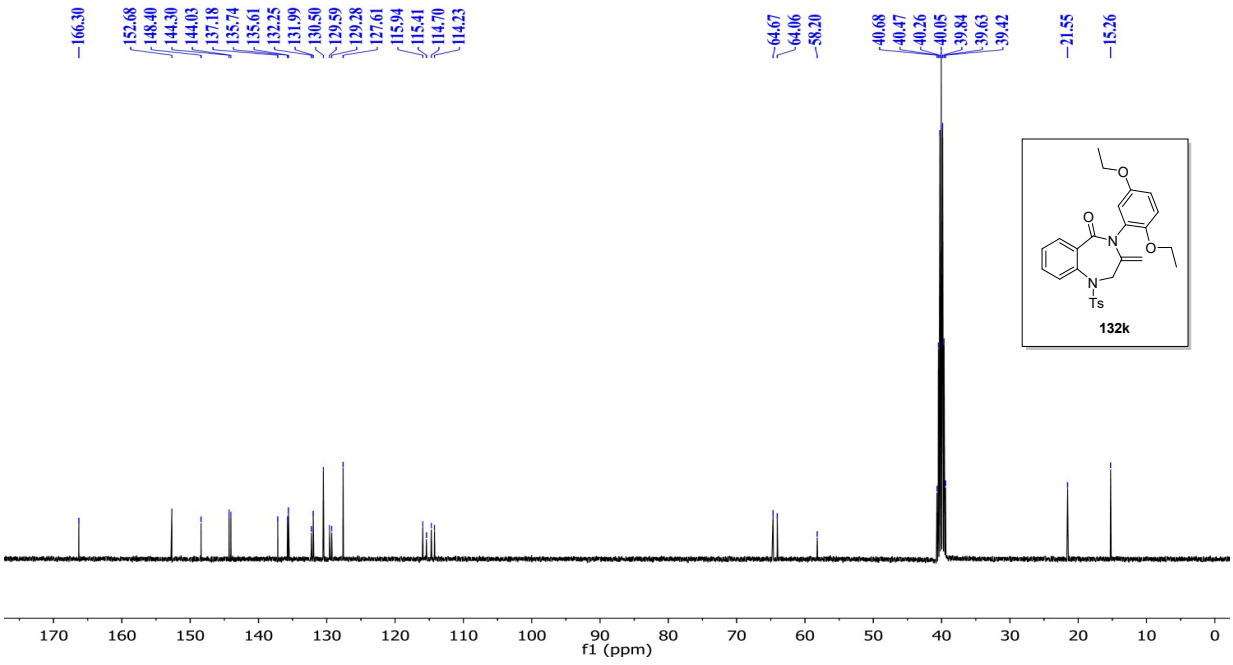
^{13}C{^{1}H} NMR (100 MHz) of **132j**:



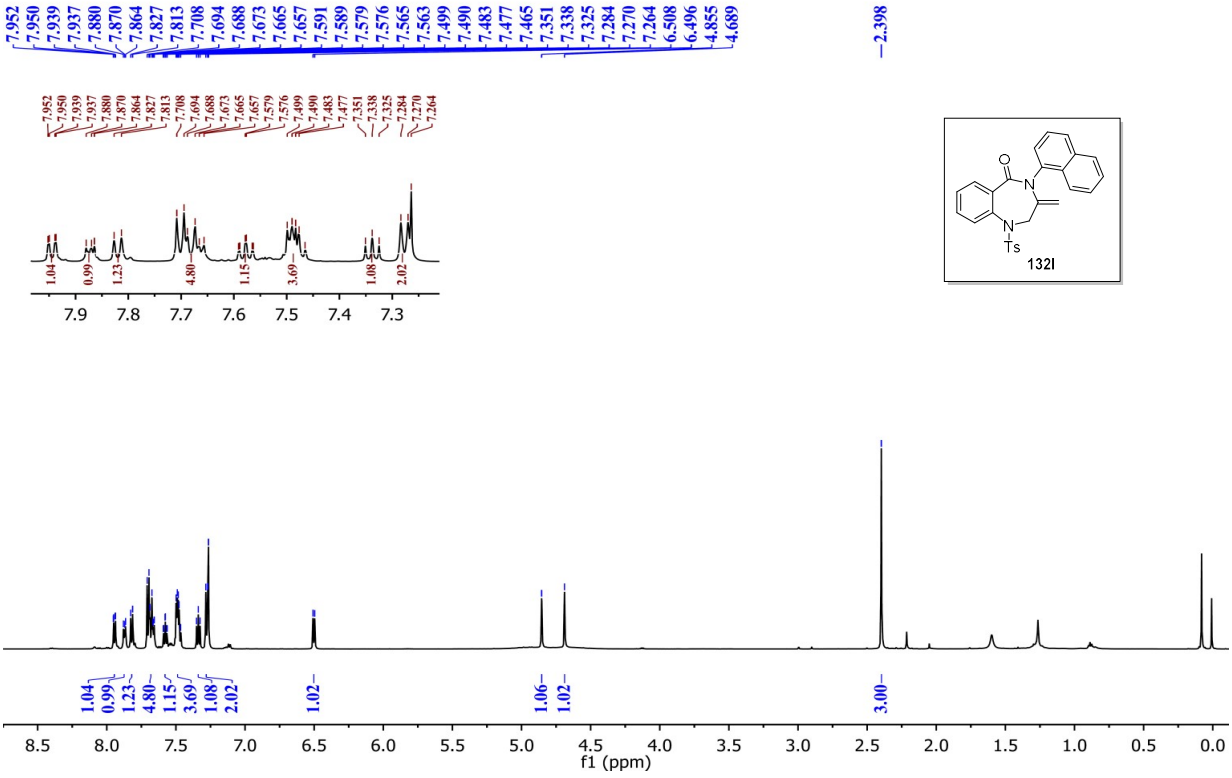
^{1}H NMR (400 MHz) of **132k**:



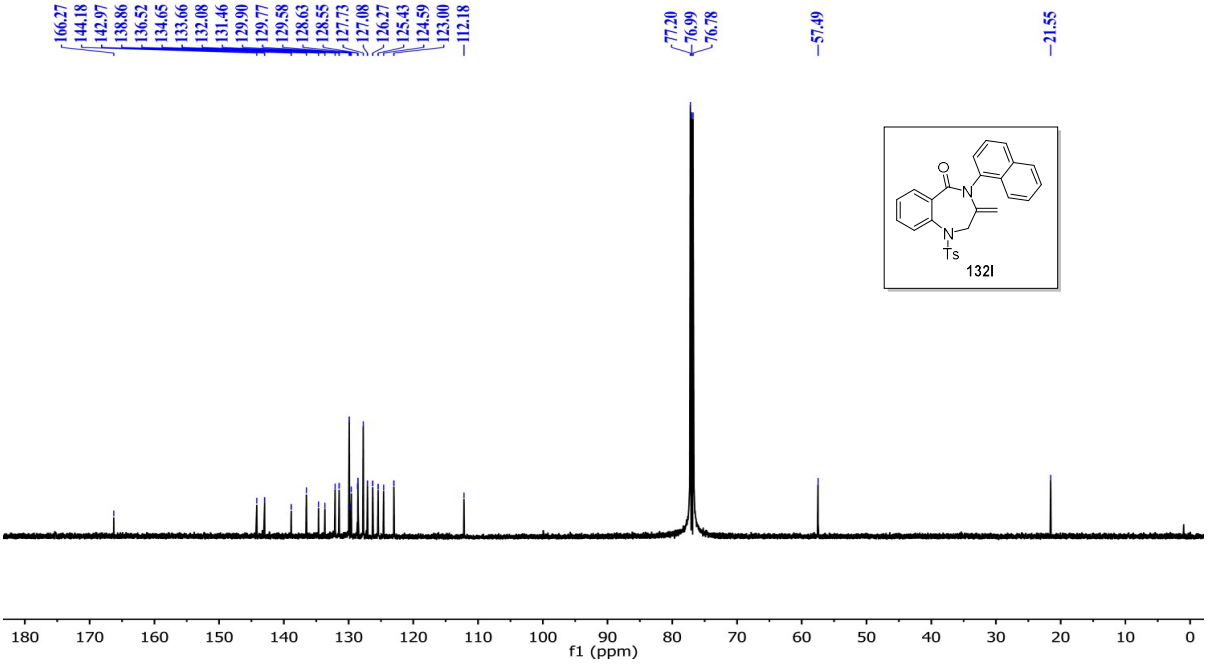
^{13}C{^{1}H} NMR (100 MHz) of **132k**:



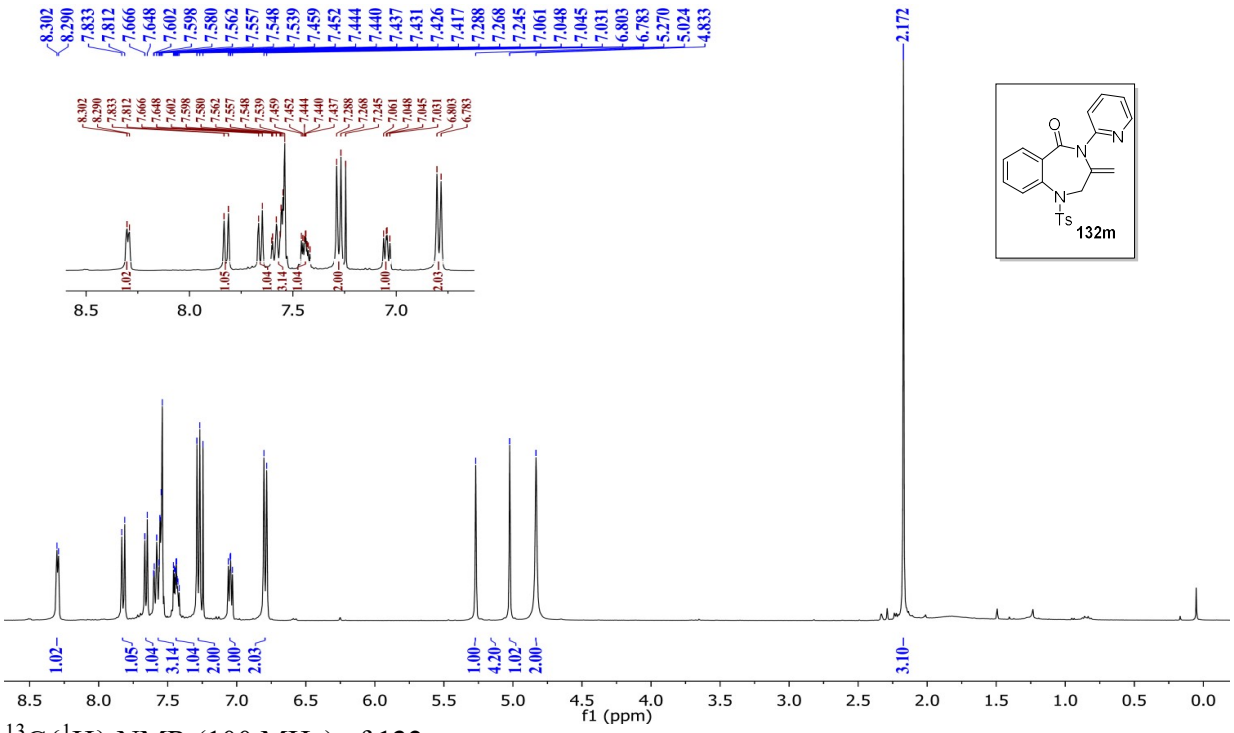
^{1}H NMR (600 MHz) of **132l:**



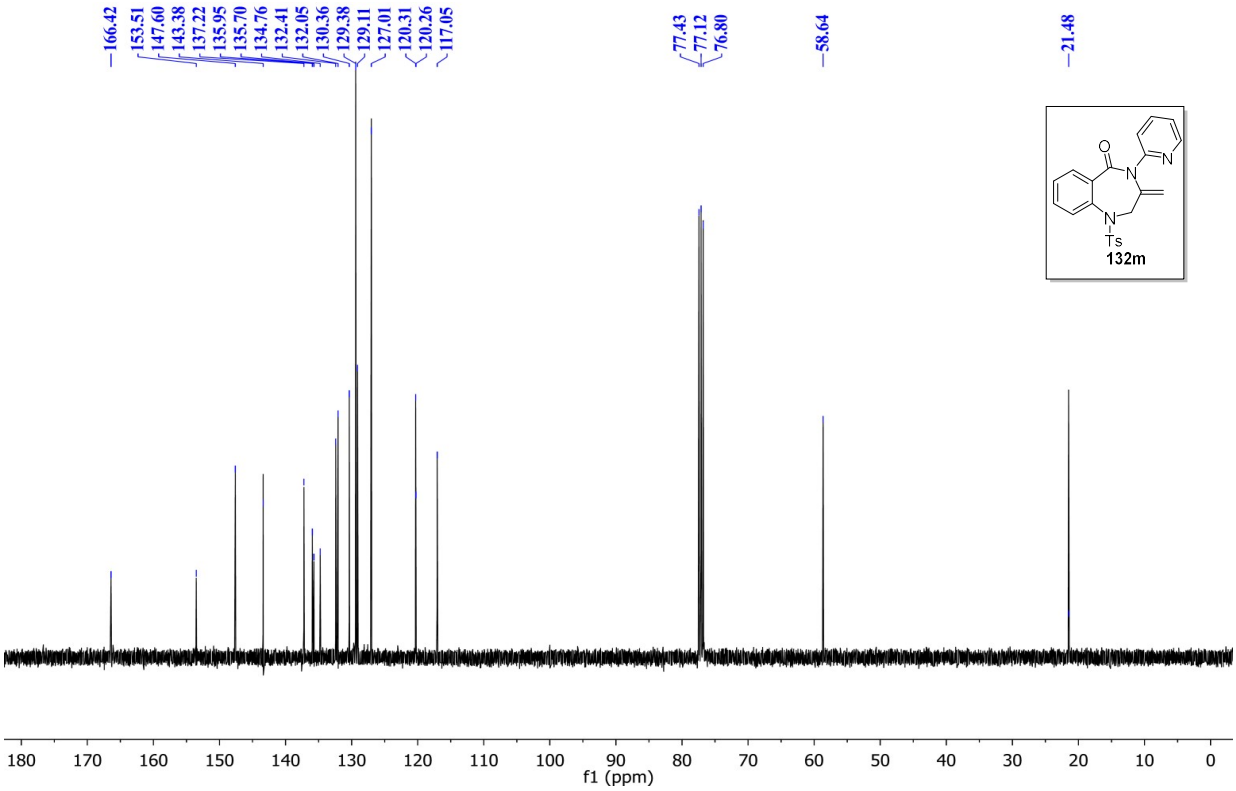
^{13}C{^{1}H} NMR (150 MHz) of **132l**:



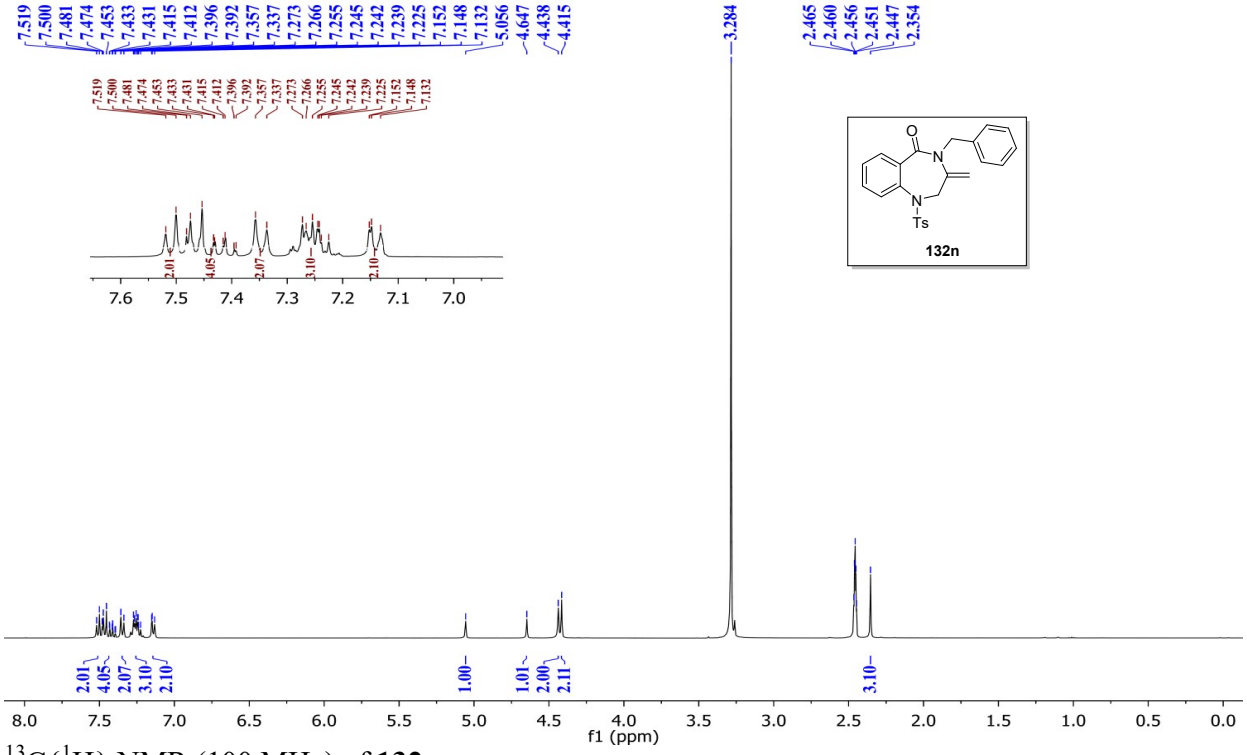
^{1}H NMR (400 MHz) of **132m**:



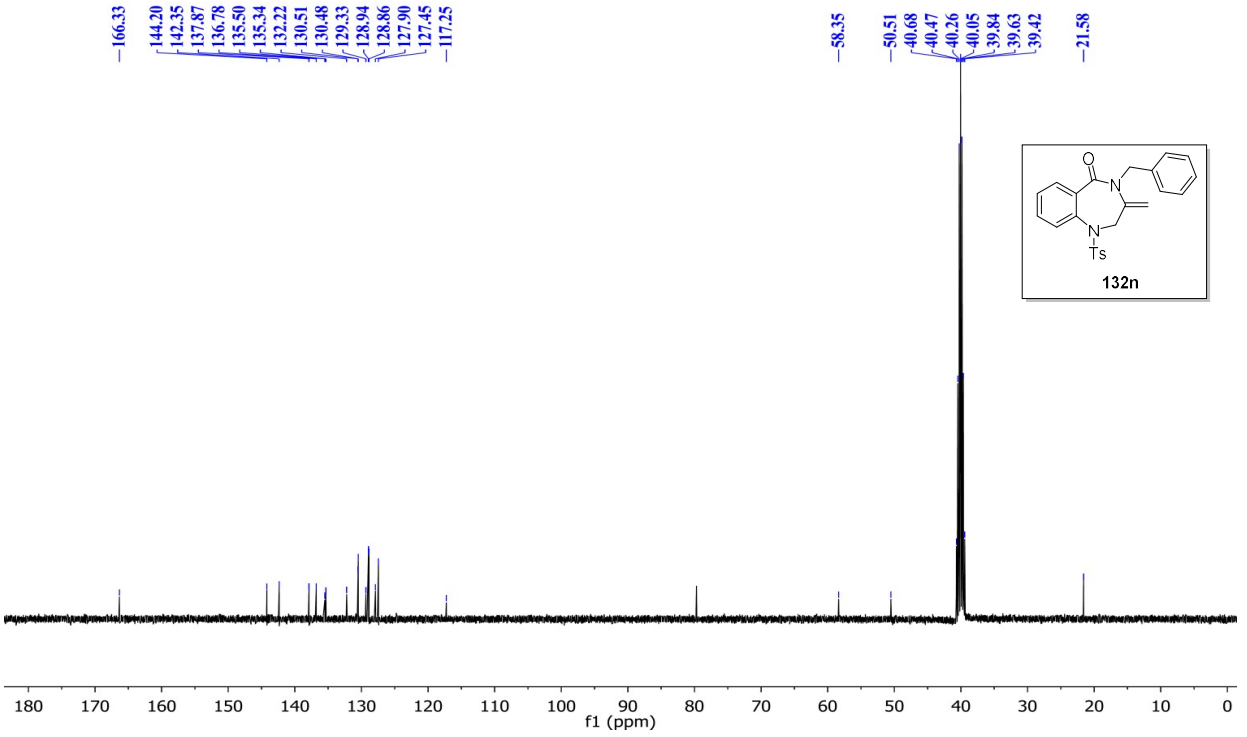
^{13}C{^{1}H} NMR (100 MHz) of **132m**:



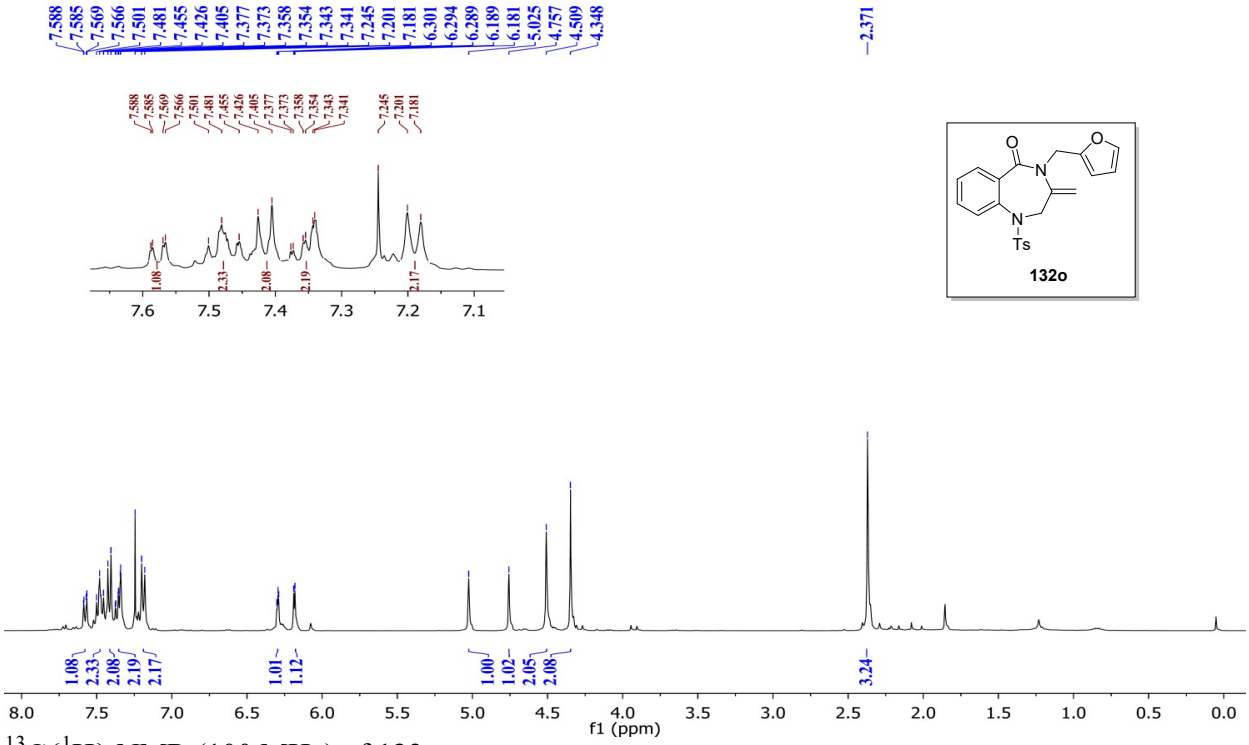
^{1}H NMR (400 MHz) of **132n**:



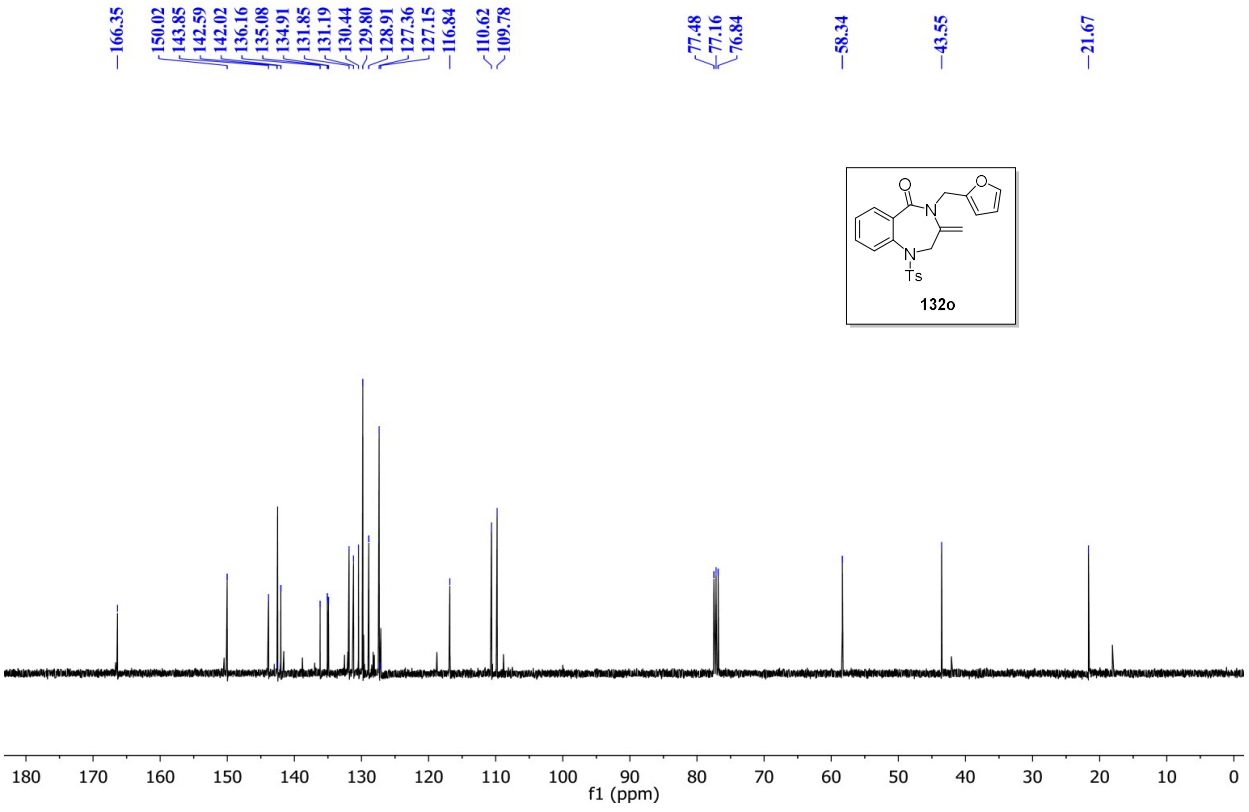
^{13}C{^{1}H} NMR (100 MHz) of **132n**:



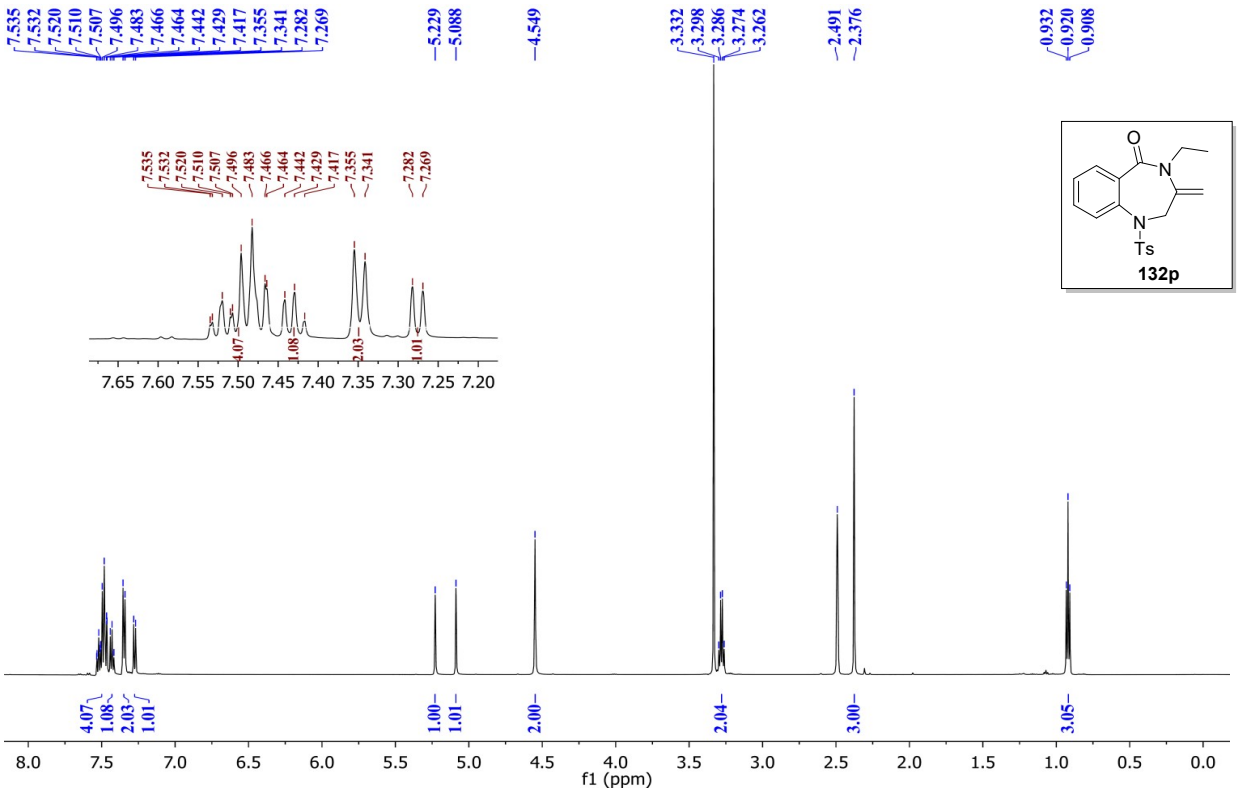
^{1}H NMR (400 MHz) of **132o**:



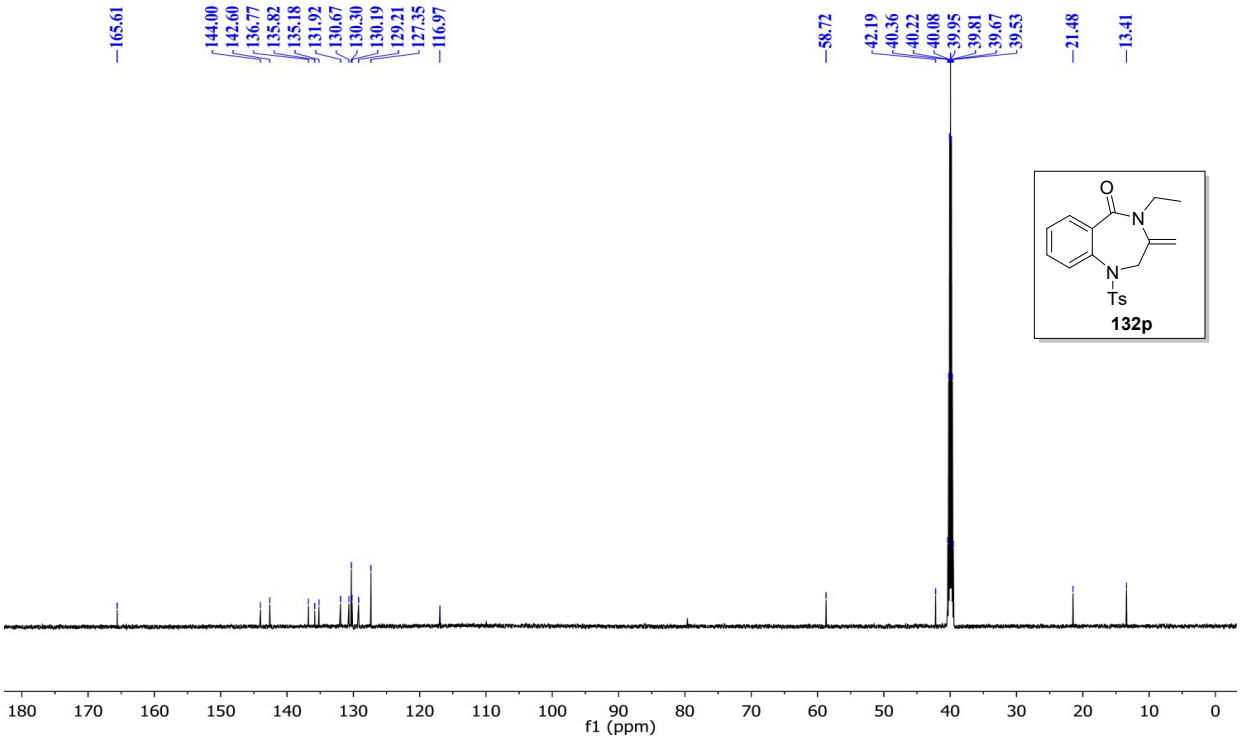
^{13}C{^{1}H} NMR (100 MHz) of **132o**:



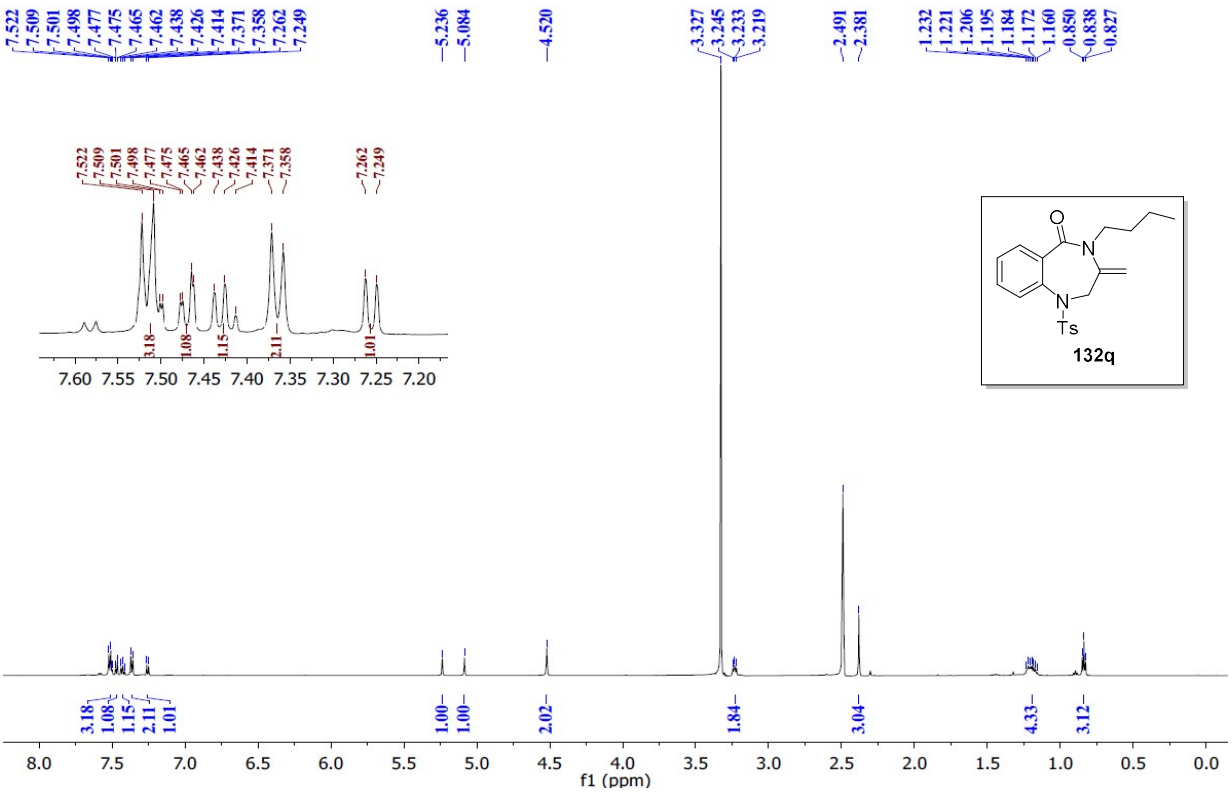
^{1}H NMR (600 MHz) of **132p**:



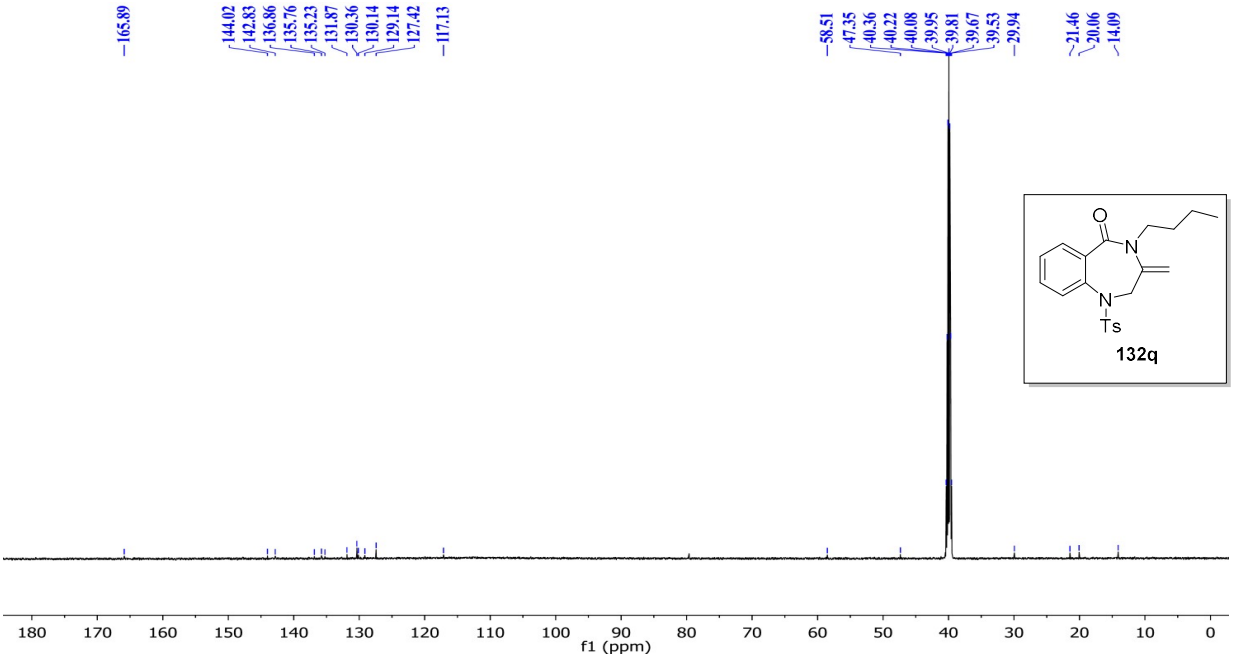
^{13}C{^{1}H} NMR (150 MHz) of **132p**:



^{1}H NMR (600 MHz) of **132q**:

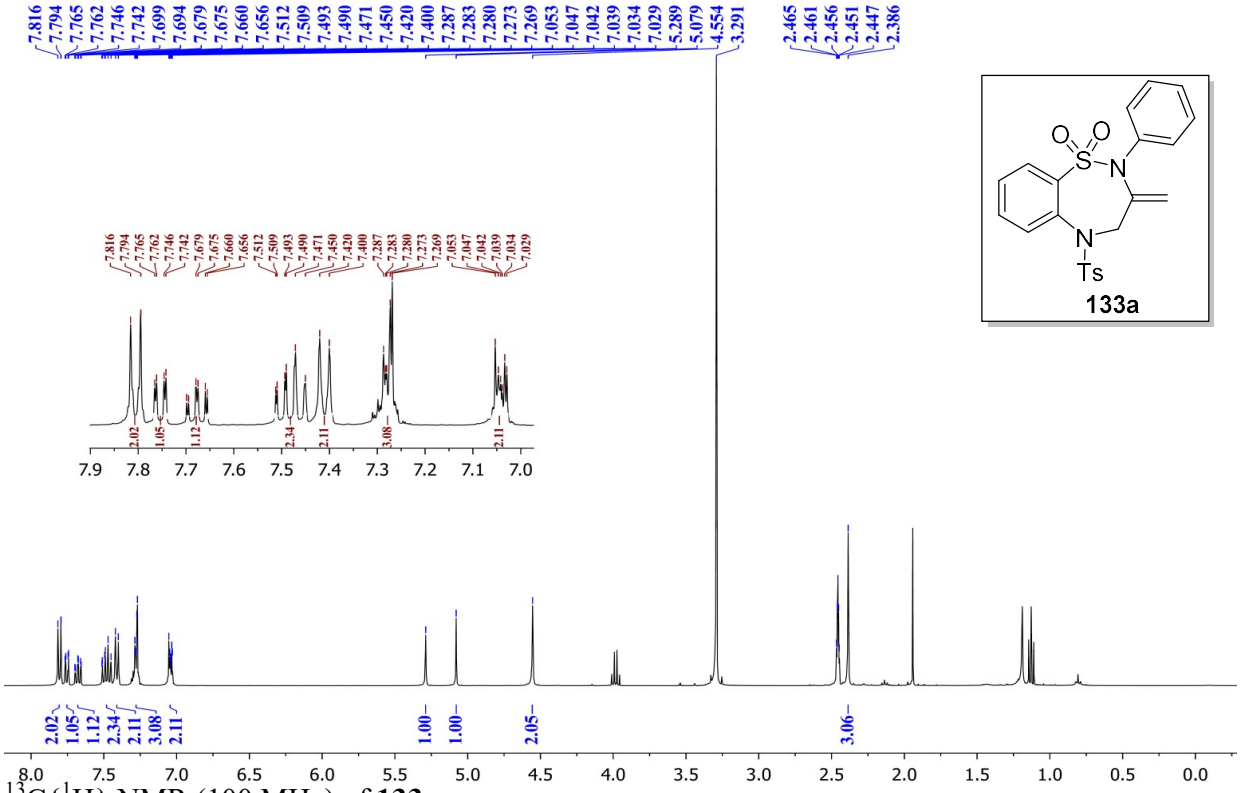


^{13}C{^{1}H} NMR (150 MHz) of **132q**:

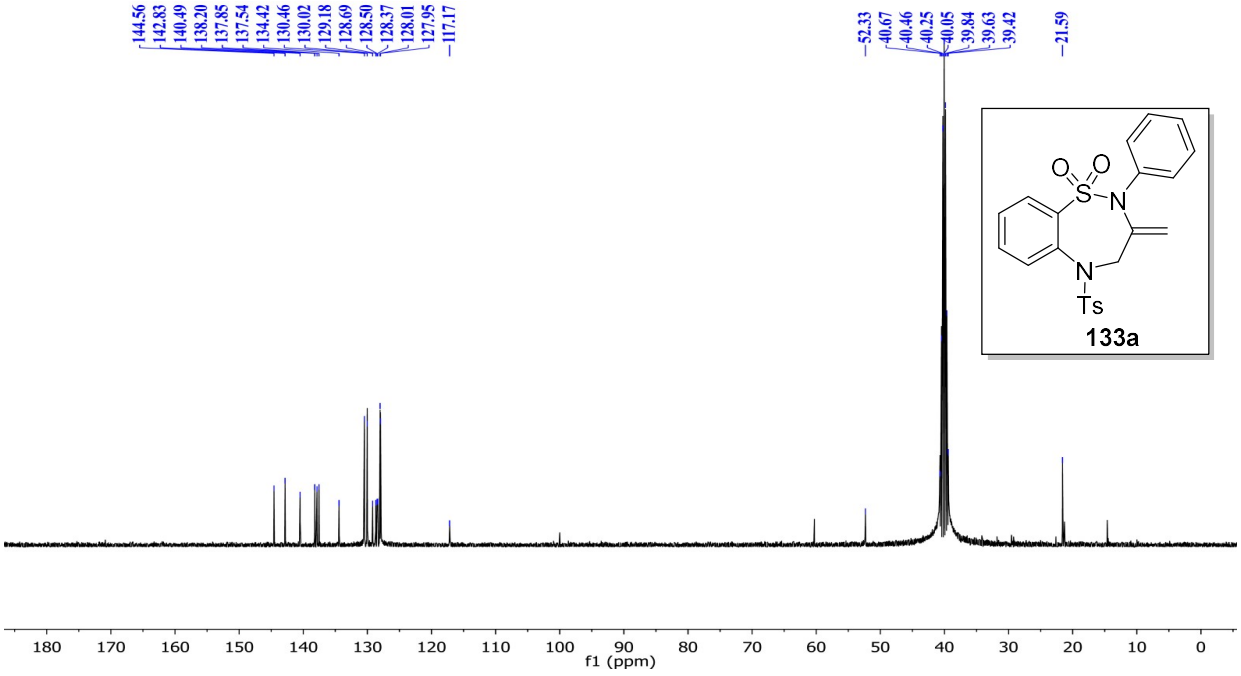


1.2.17.8 NMR spectra of products 133a-133c:

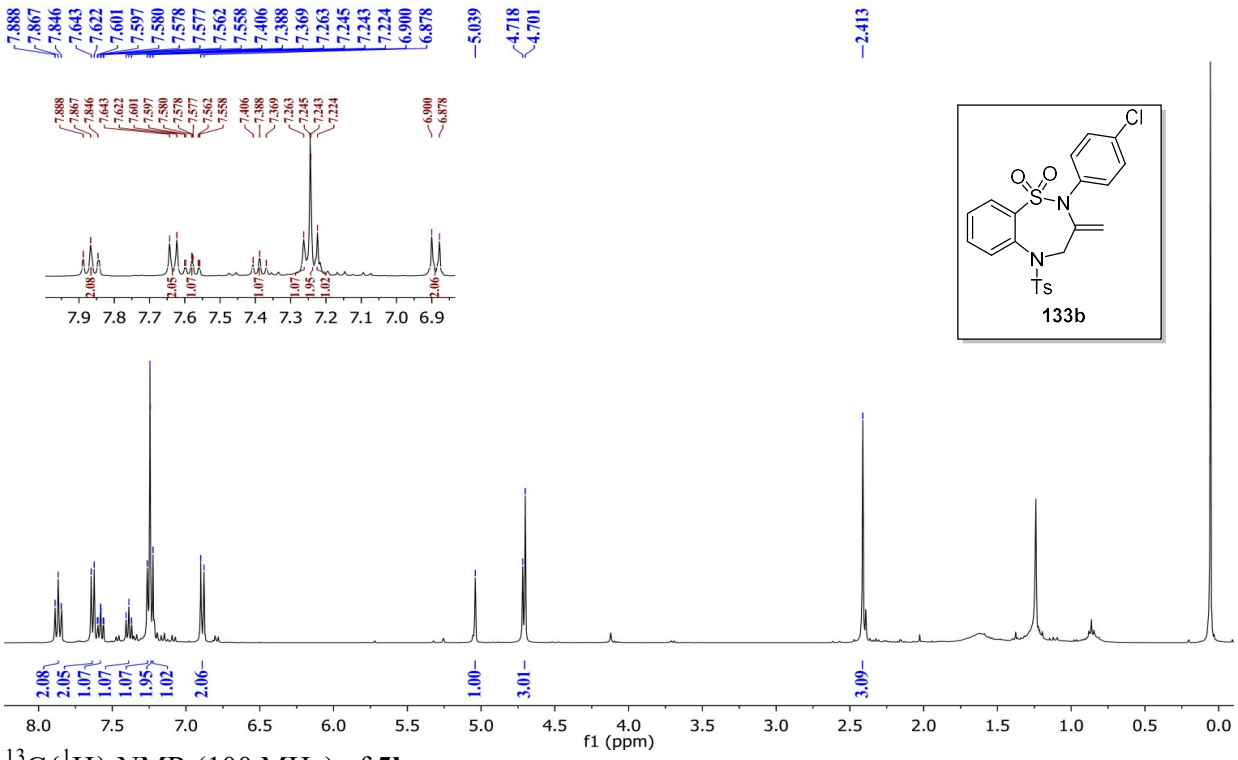
^{1}H NMR (400 MHz) of **133a**:



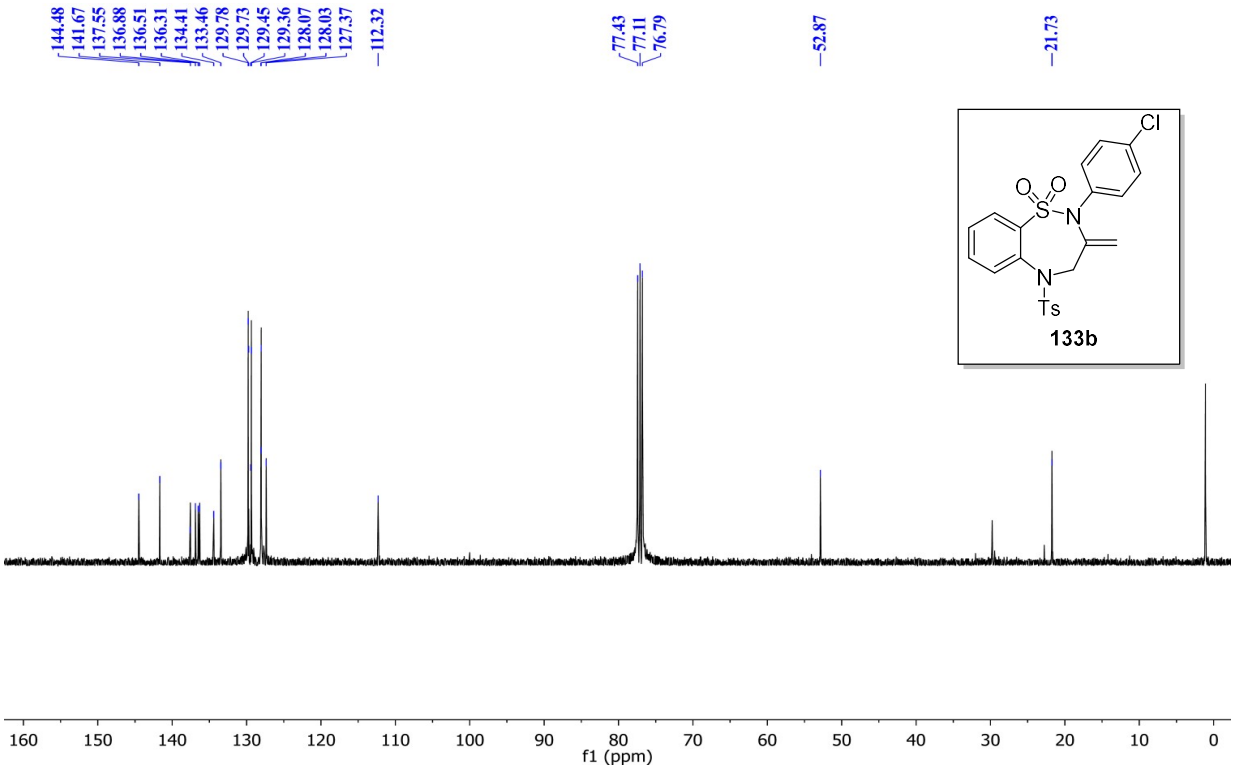
^{13}C{^{1}H} NMR (100 MHz) of **133a**:



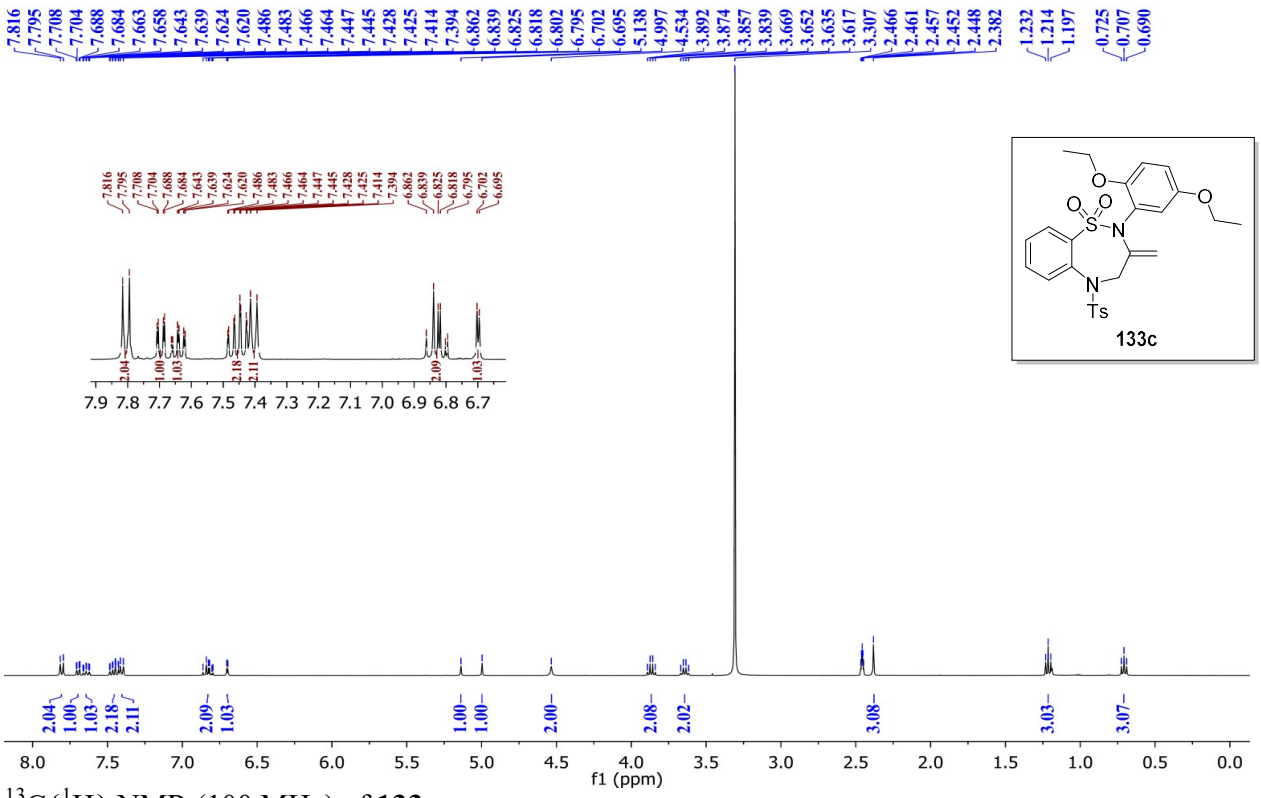
^{1}H NMR (400 MHz) of **133b**:



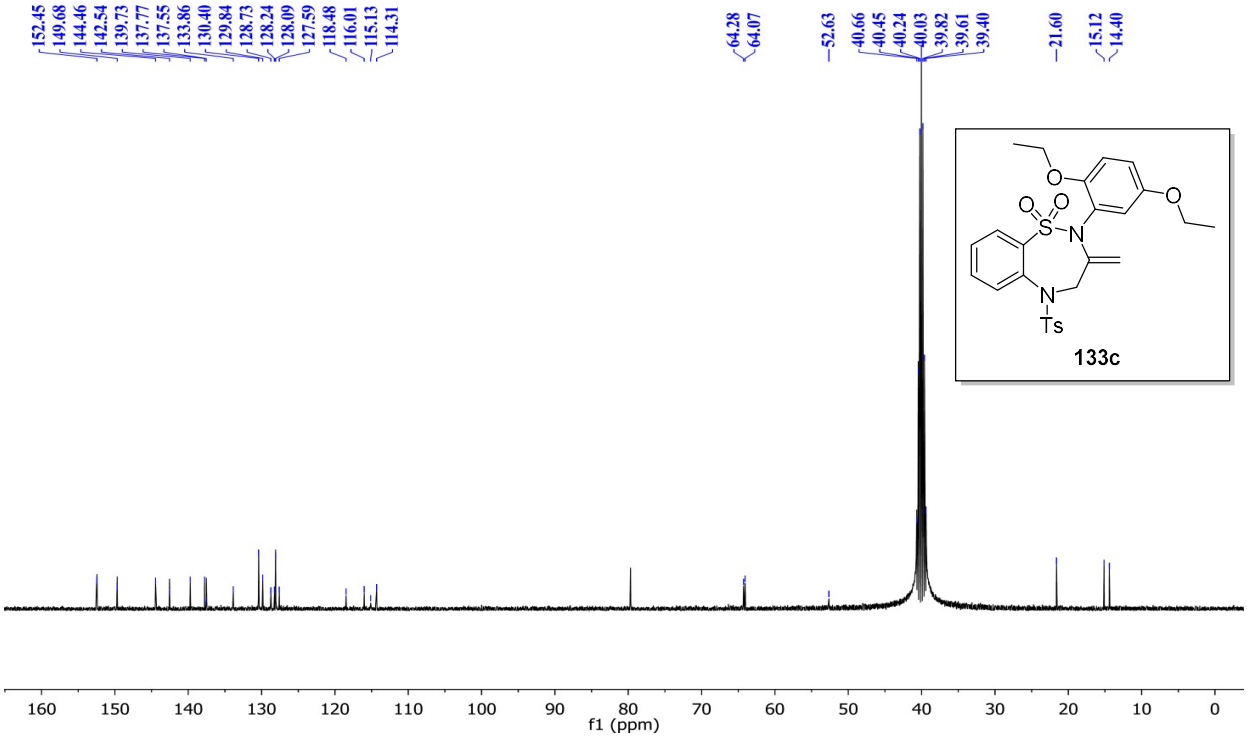
^{13}C{^{1}H} NMR (100 MHz) of **5b**:



^{1}H NMR (400 MHz) of **133c**:

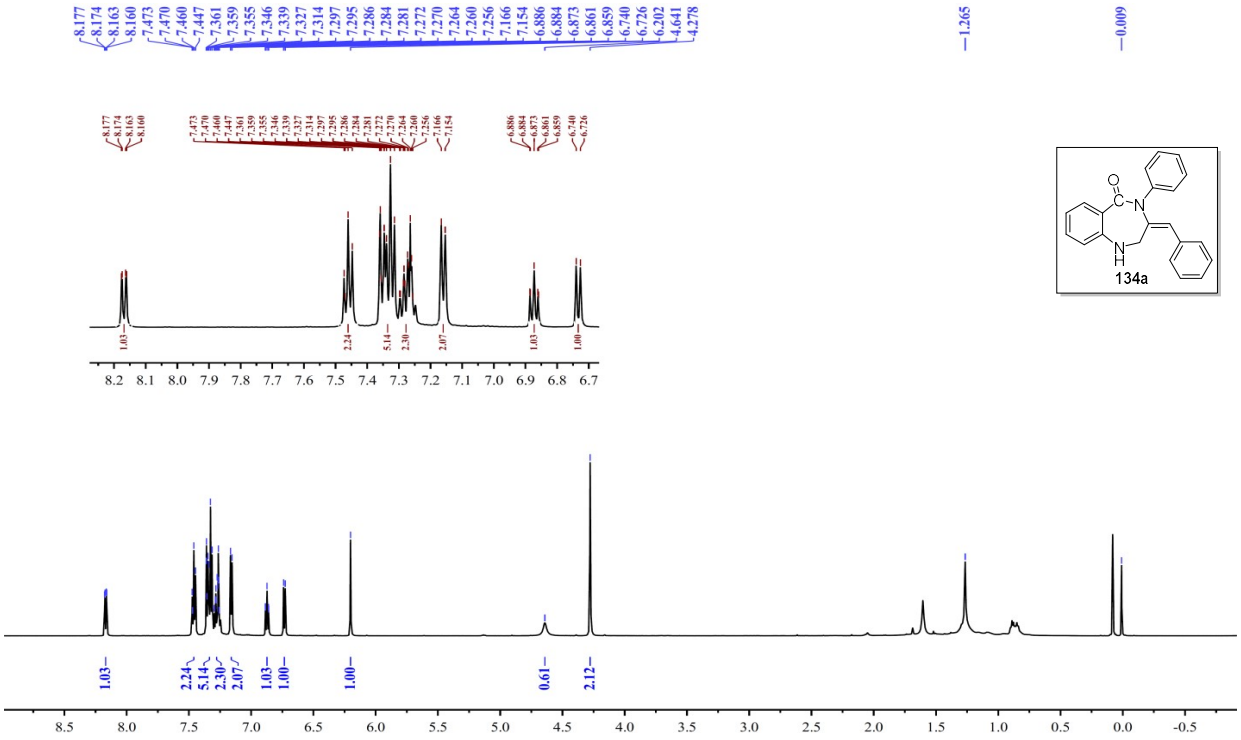


^{13}C{^{1}H} NMR (100 MHz) of **133c**:

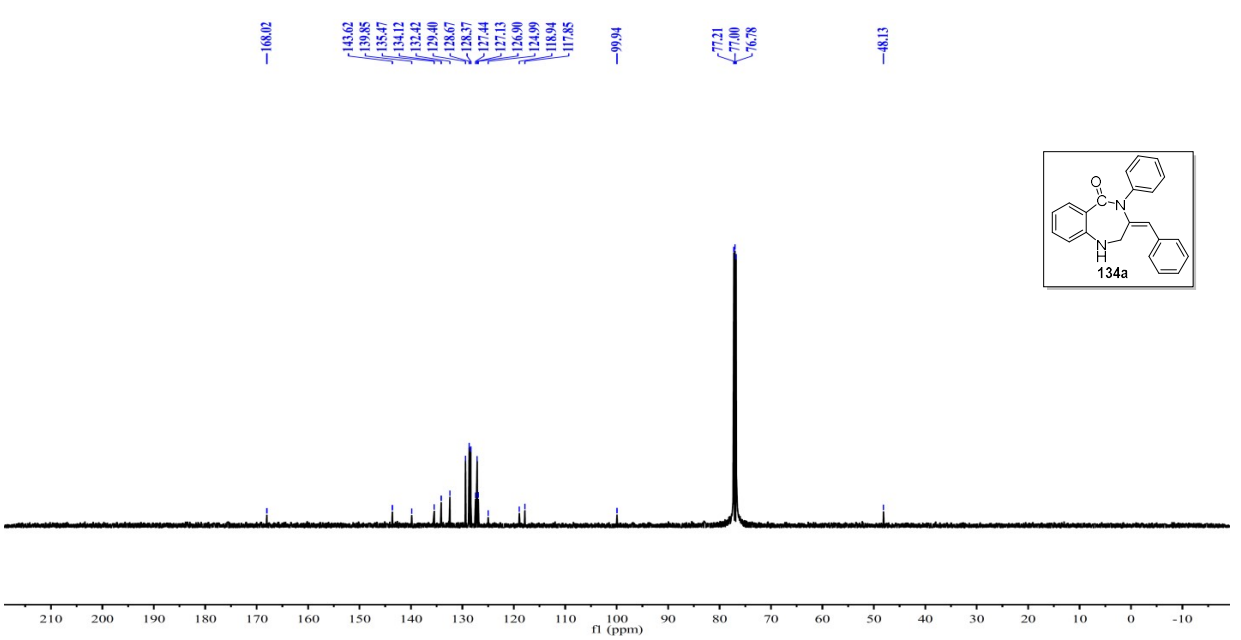


1.2.17.9 NMR spectra of products 134a-134m:

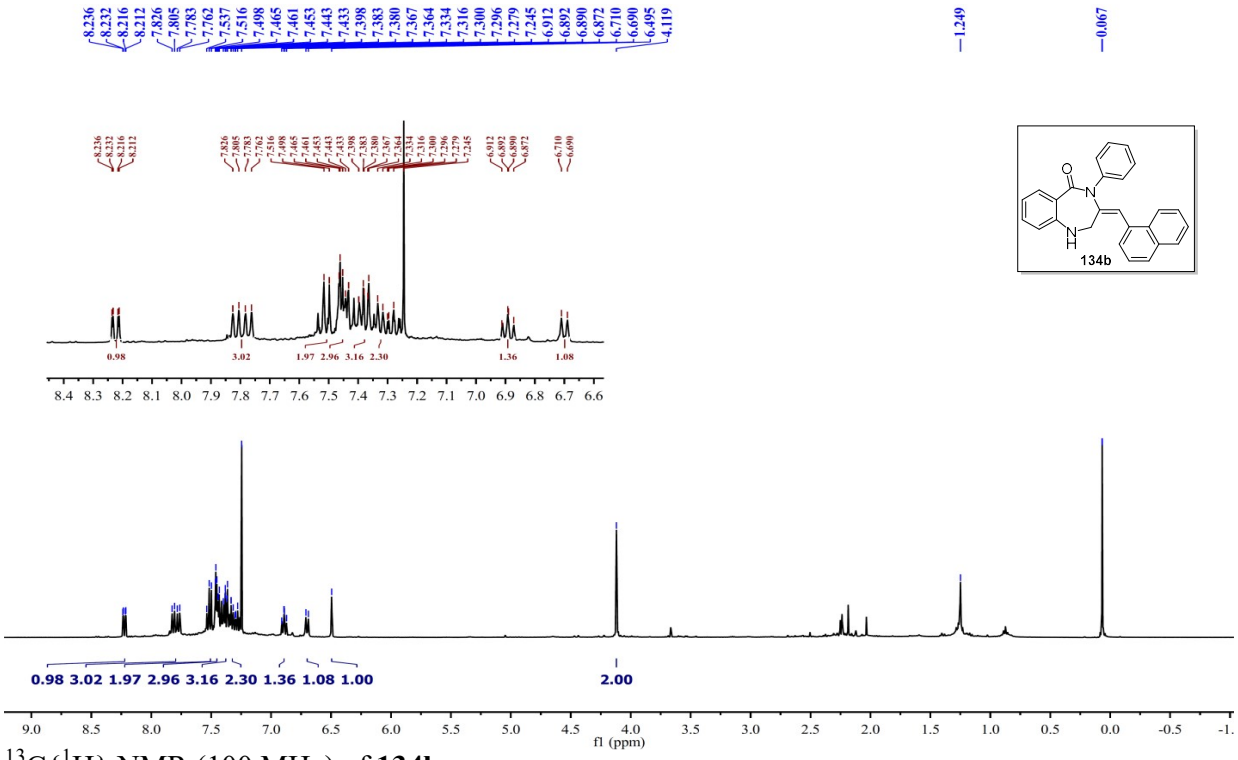
^{1}H NMR (600 MHz) of **134a**:



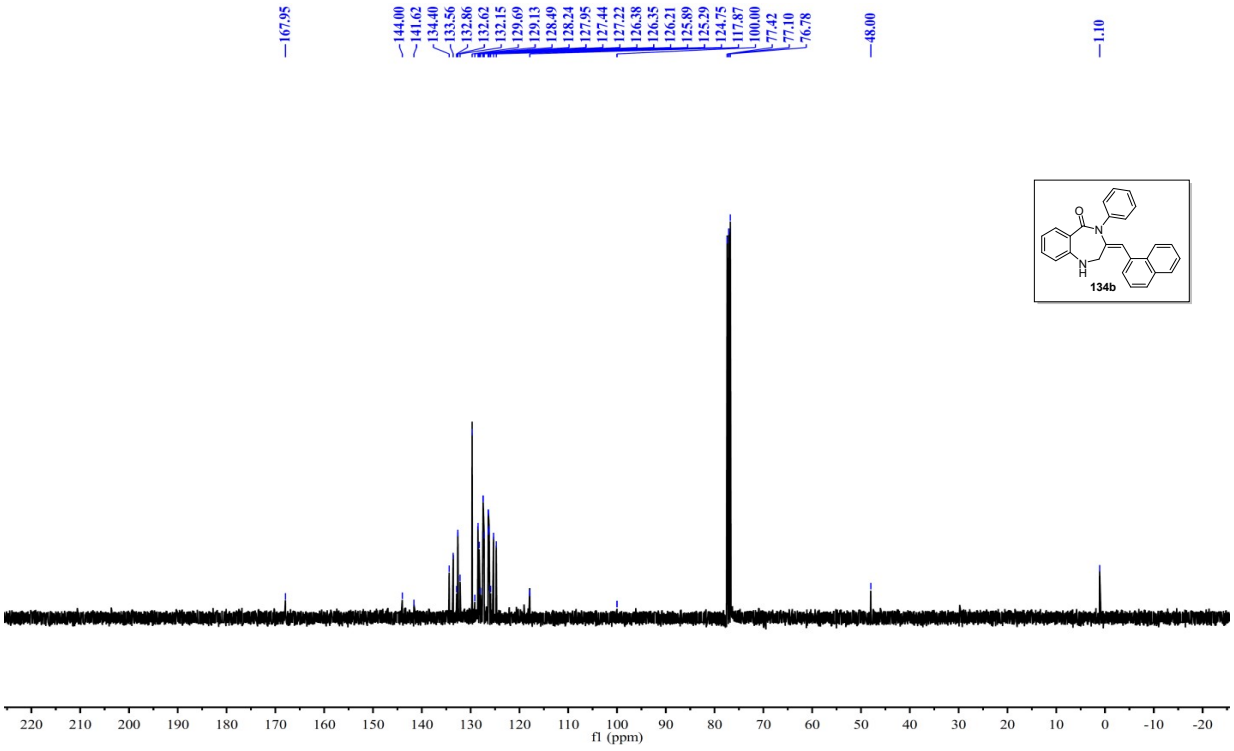
^{13}C{^{1}H} NMR (150 MHz) of **134a**:



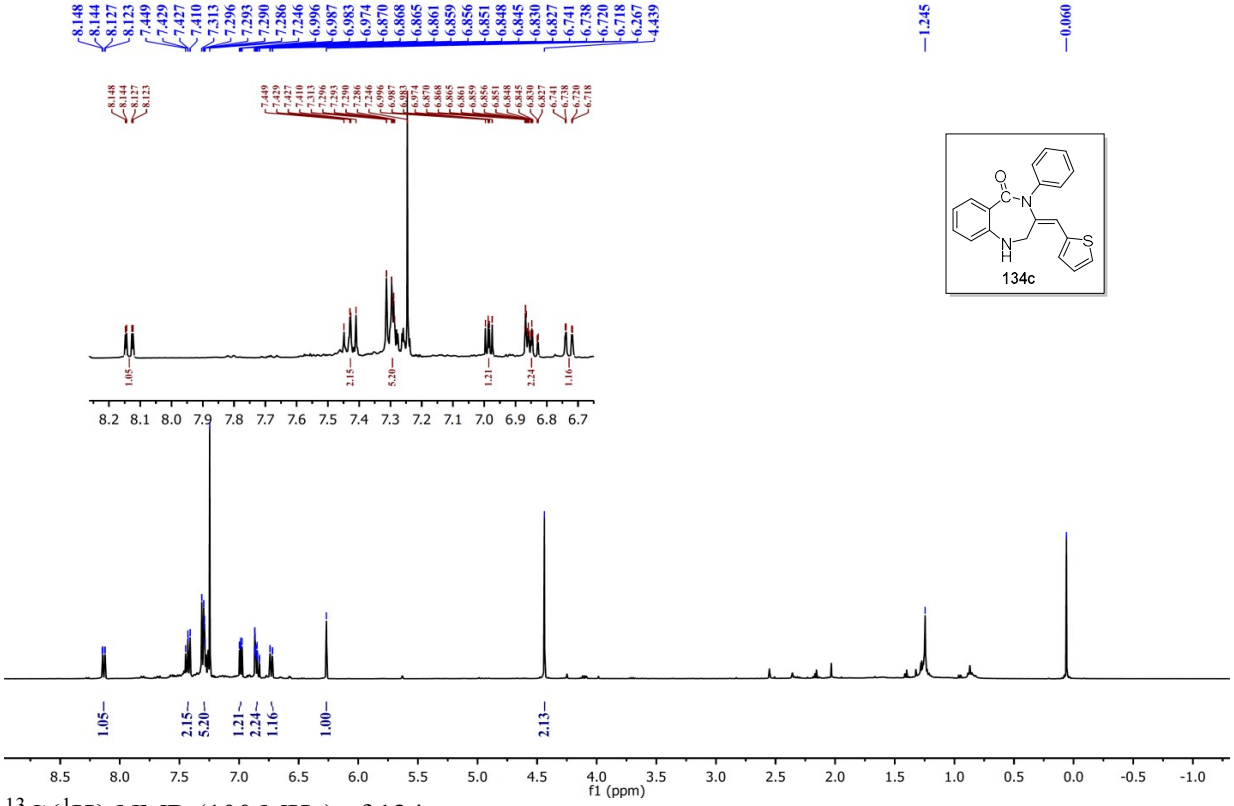
^{1}H NMR (400 MHz) of **134b**:



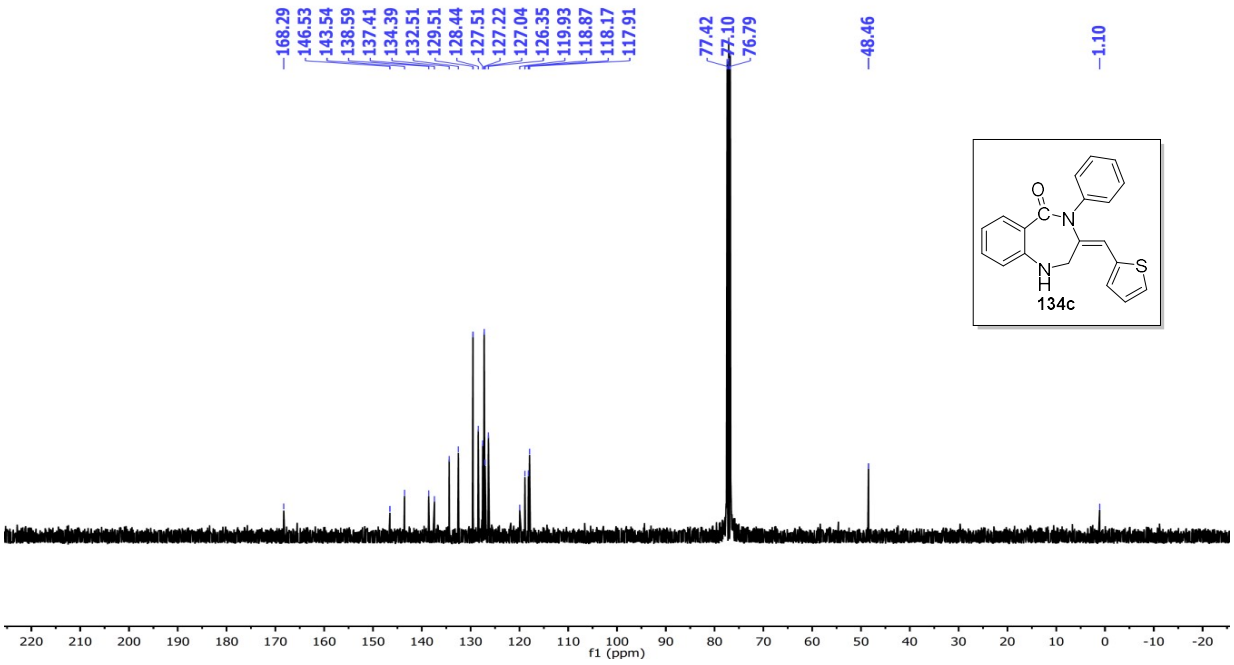
^{13}C{^{1}H} NMR (100 MHz) of **134b**:



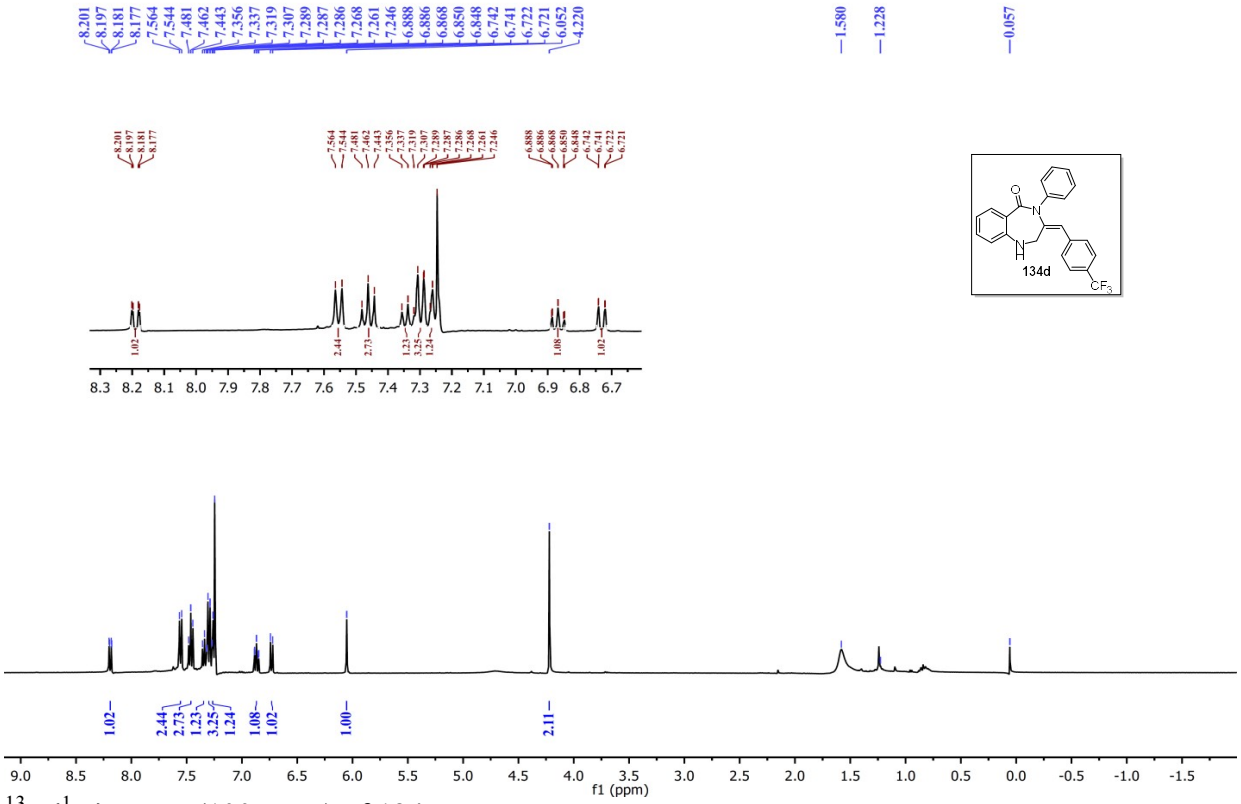
^{1}H NMR (400 MHz) of **134c**:



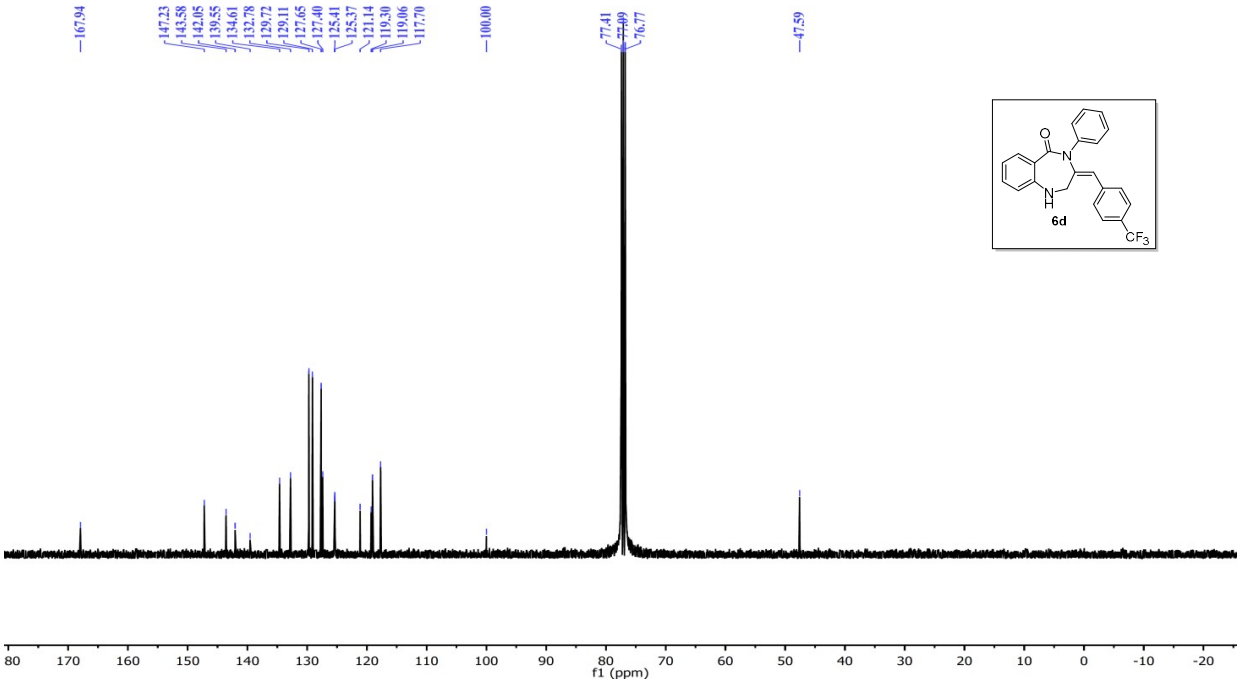
^{13}C{^{1}H} NMR (100 MHz) of **134c** :



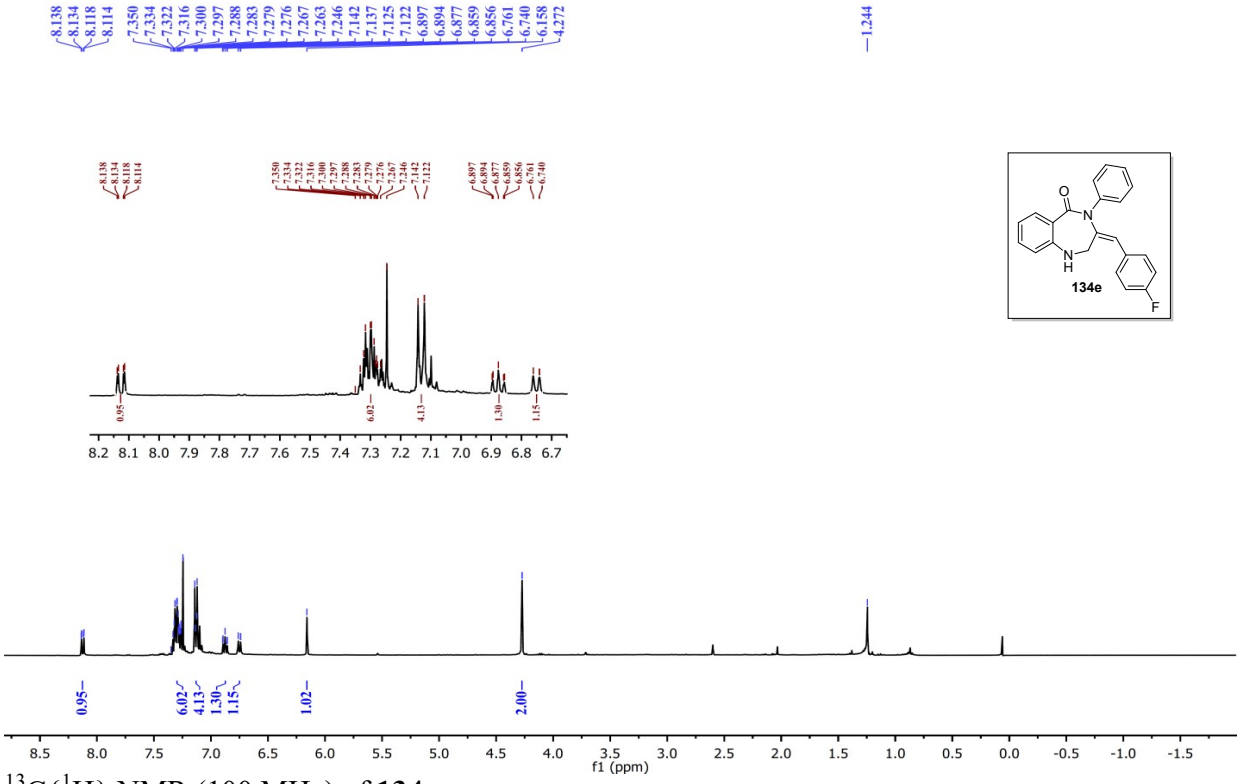
^{1}H NMR (400 MHz) of **134d**:



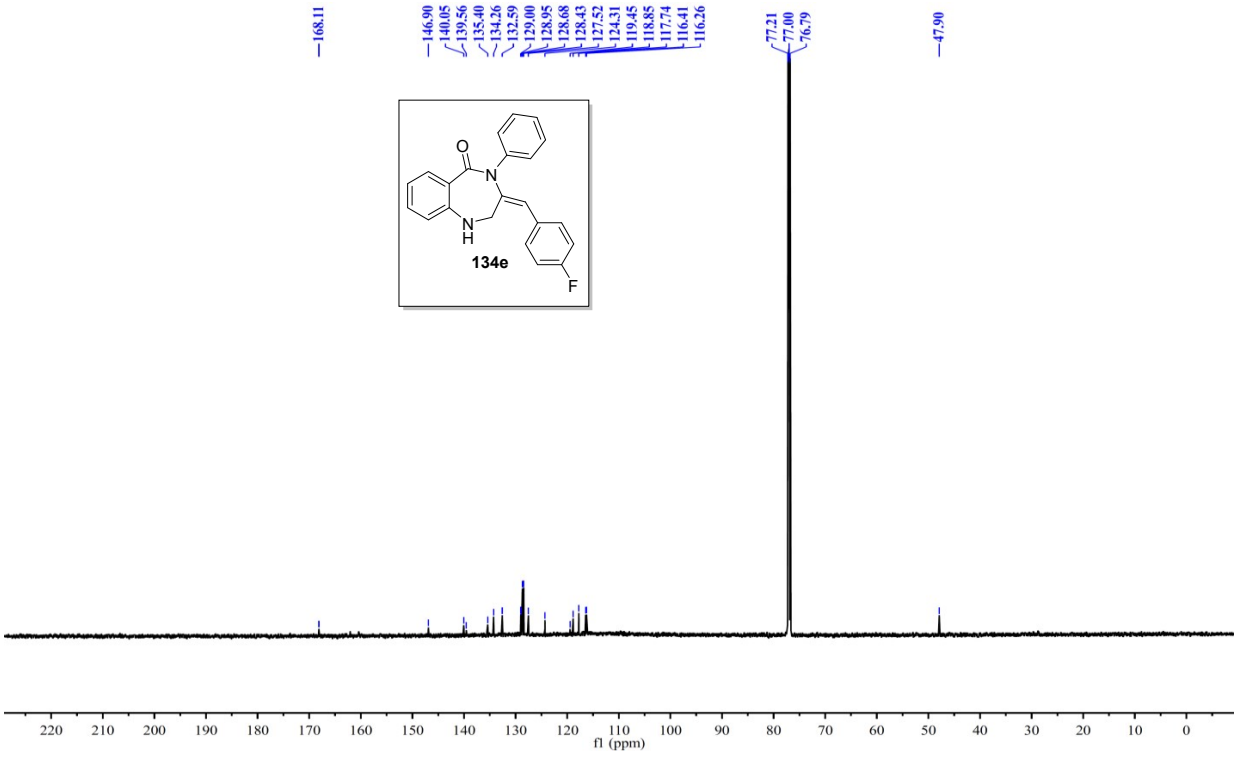
^{13}C{^{1}H} NMR (100 MHz) of **134d**:



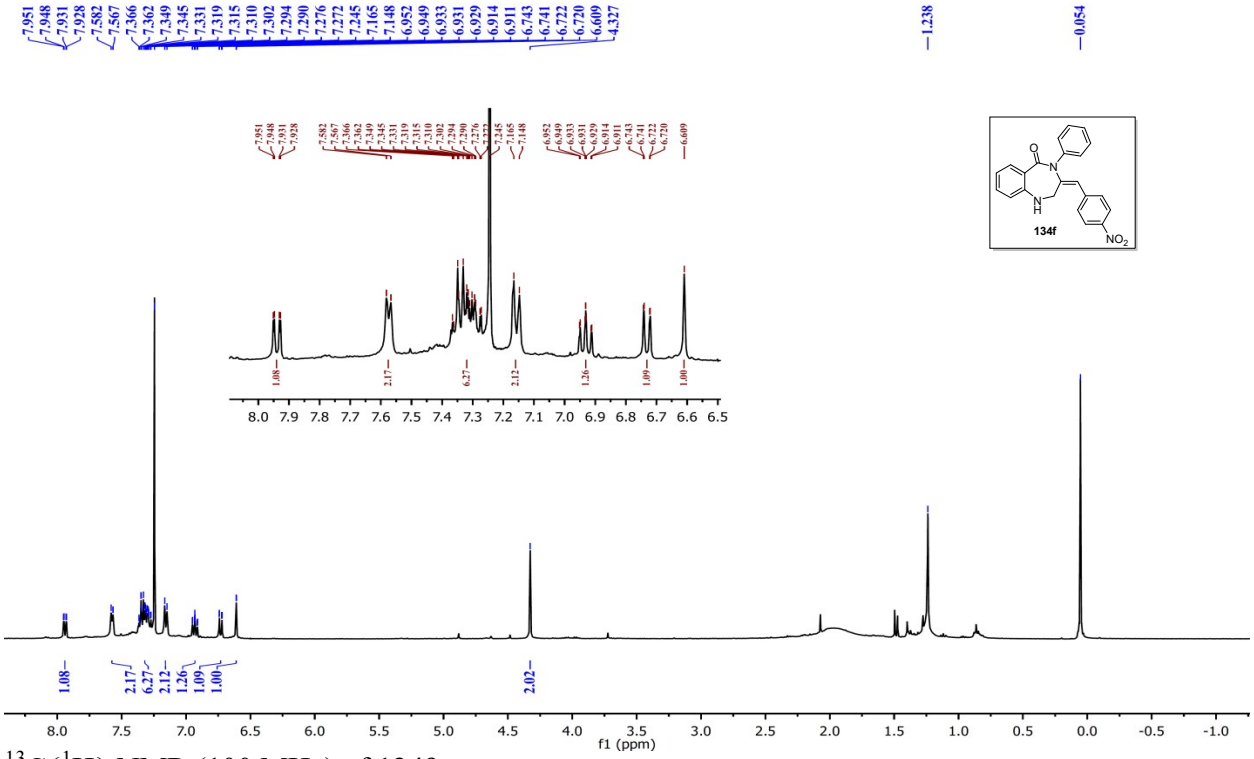
^{1}H NMR (400 MHz) of **134e**:



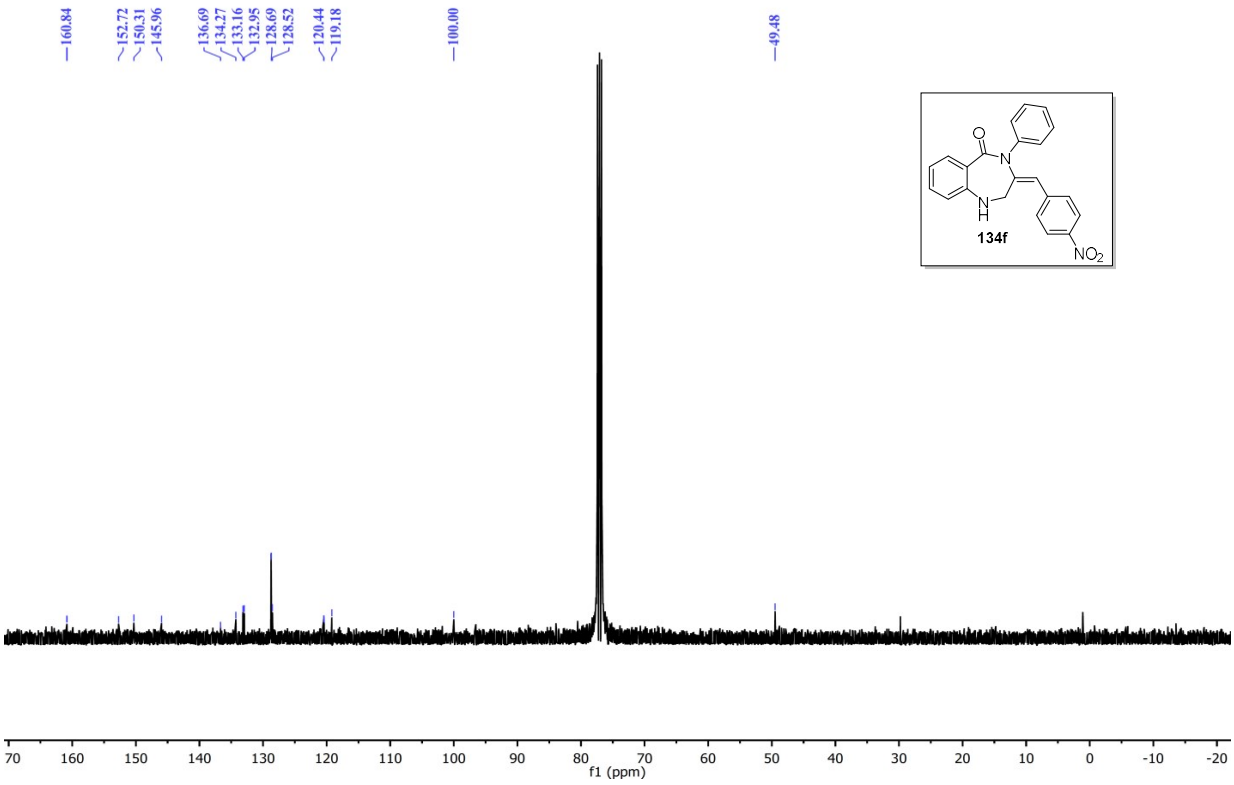
^{13}C{^{1}H} NMR (100 MHz) of **134e**:



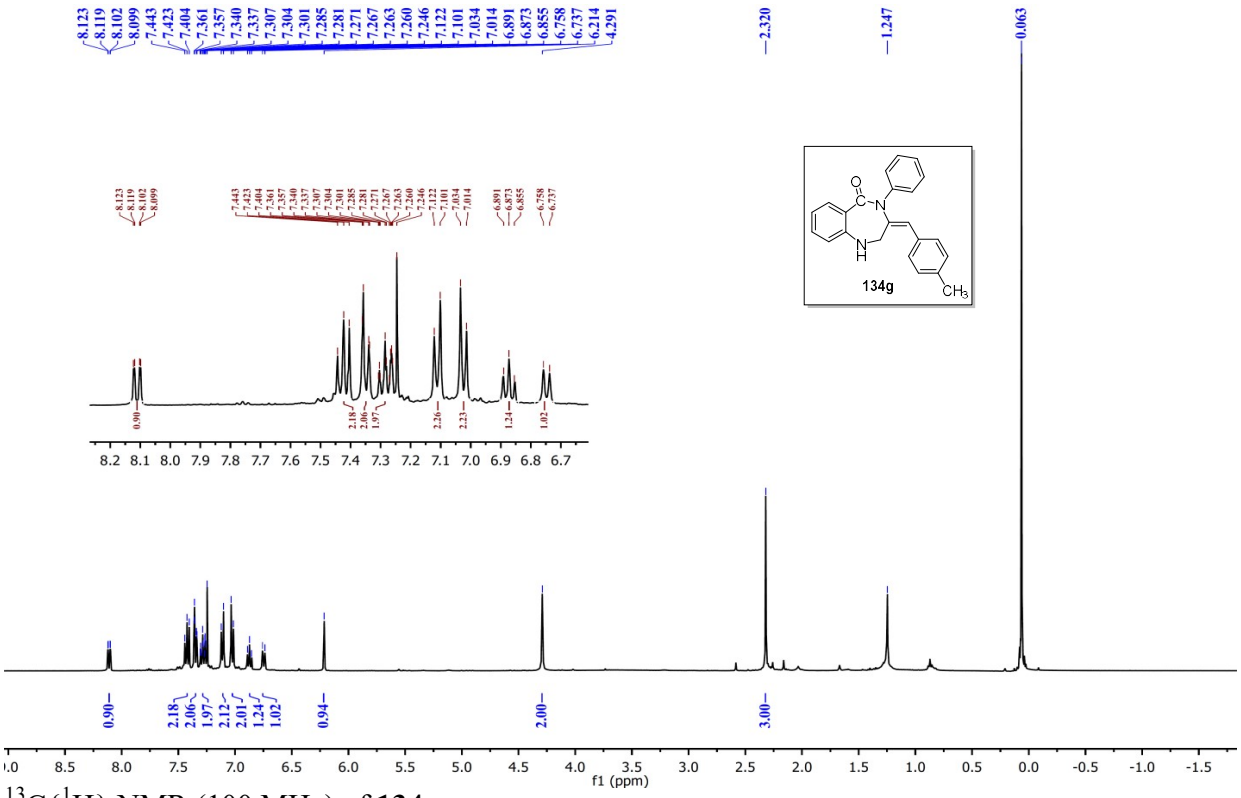
^{1}H NMR (400 MHz) of **134f**:



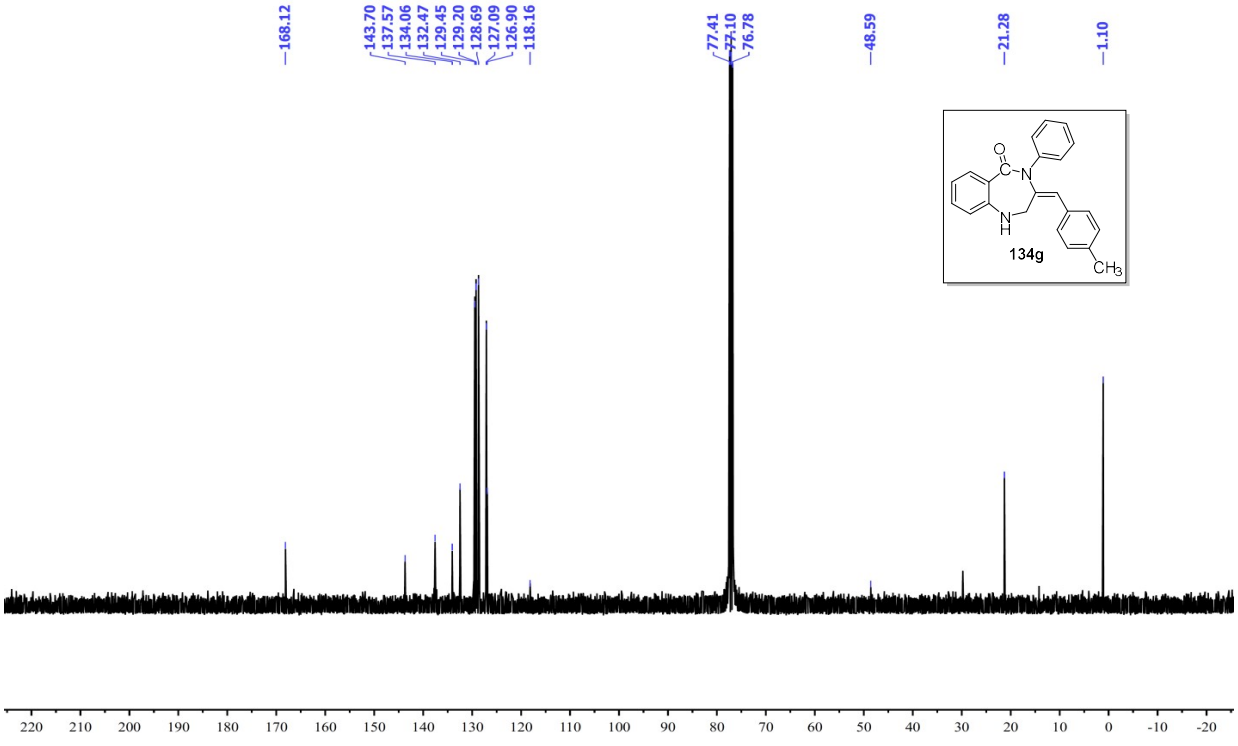
^{13}C{^{1}H} NMR (100 MHz) of **134f**:



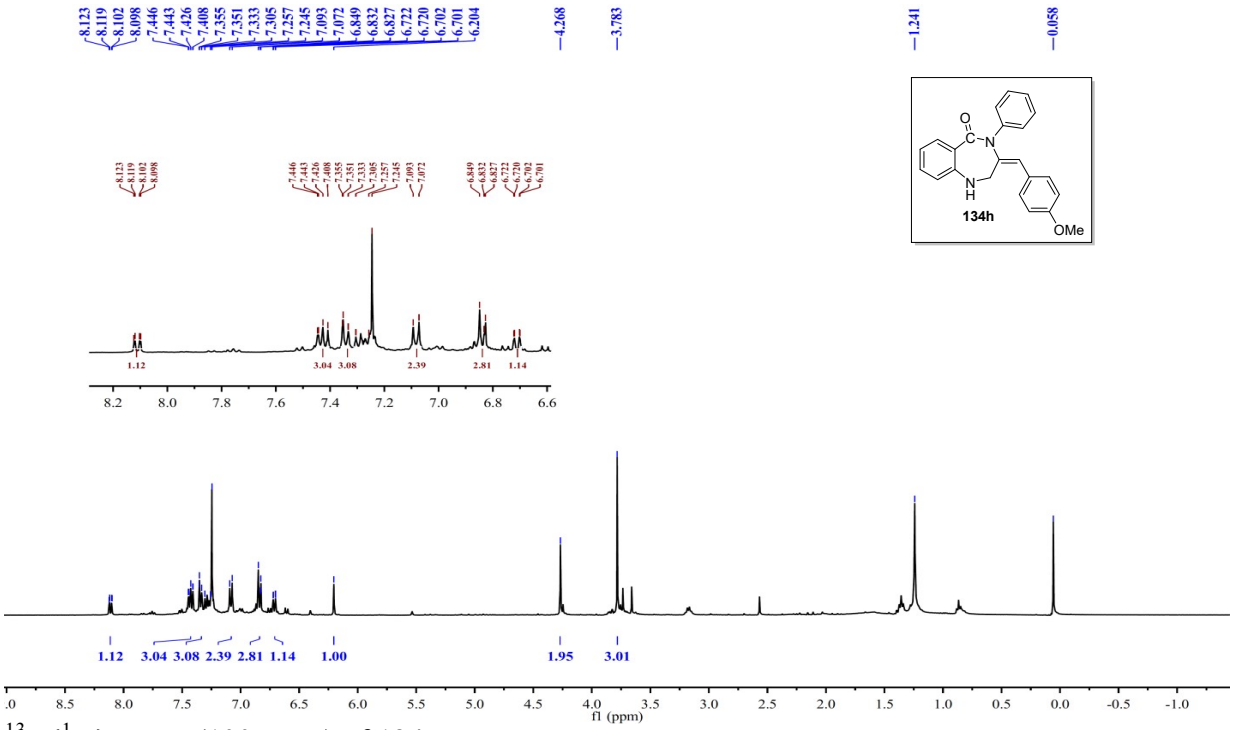
^{1}H NMR (400 MHz) of **134g**:



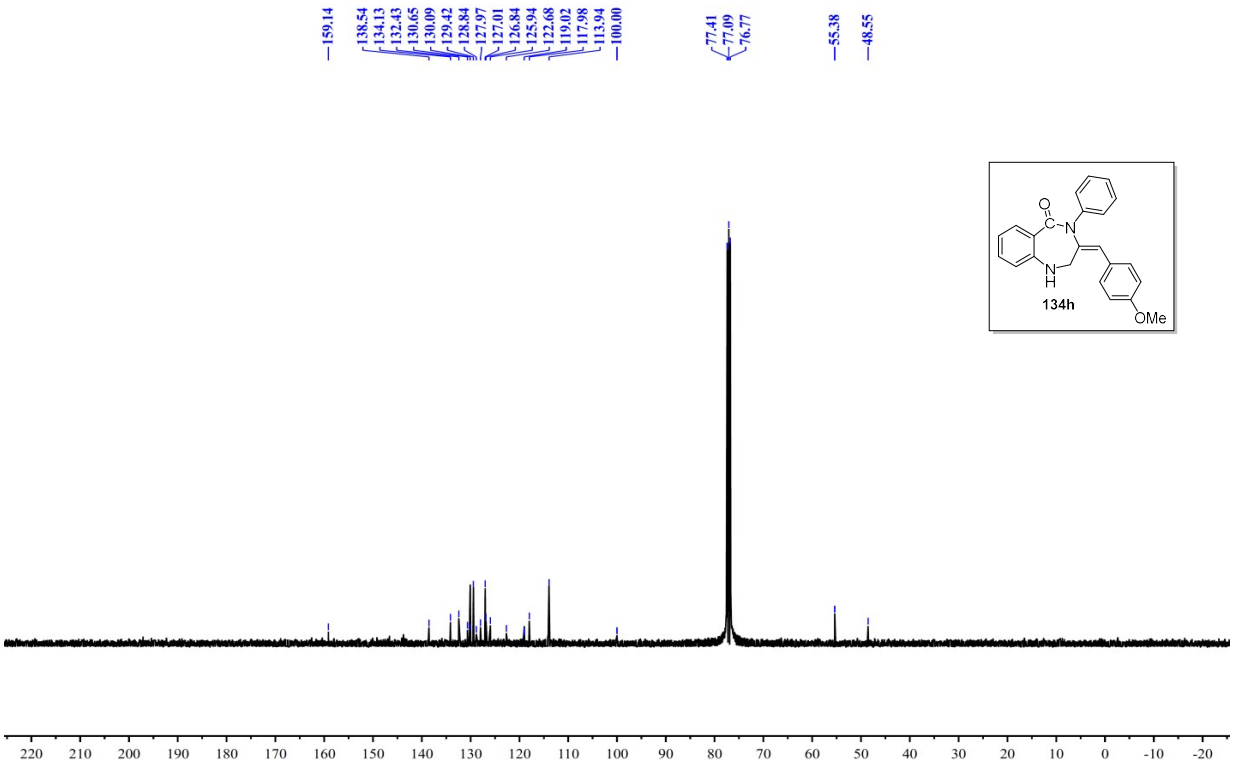
^{13}C{^{1}H} NMR (100 MHz) of **134g**:



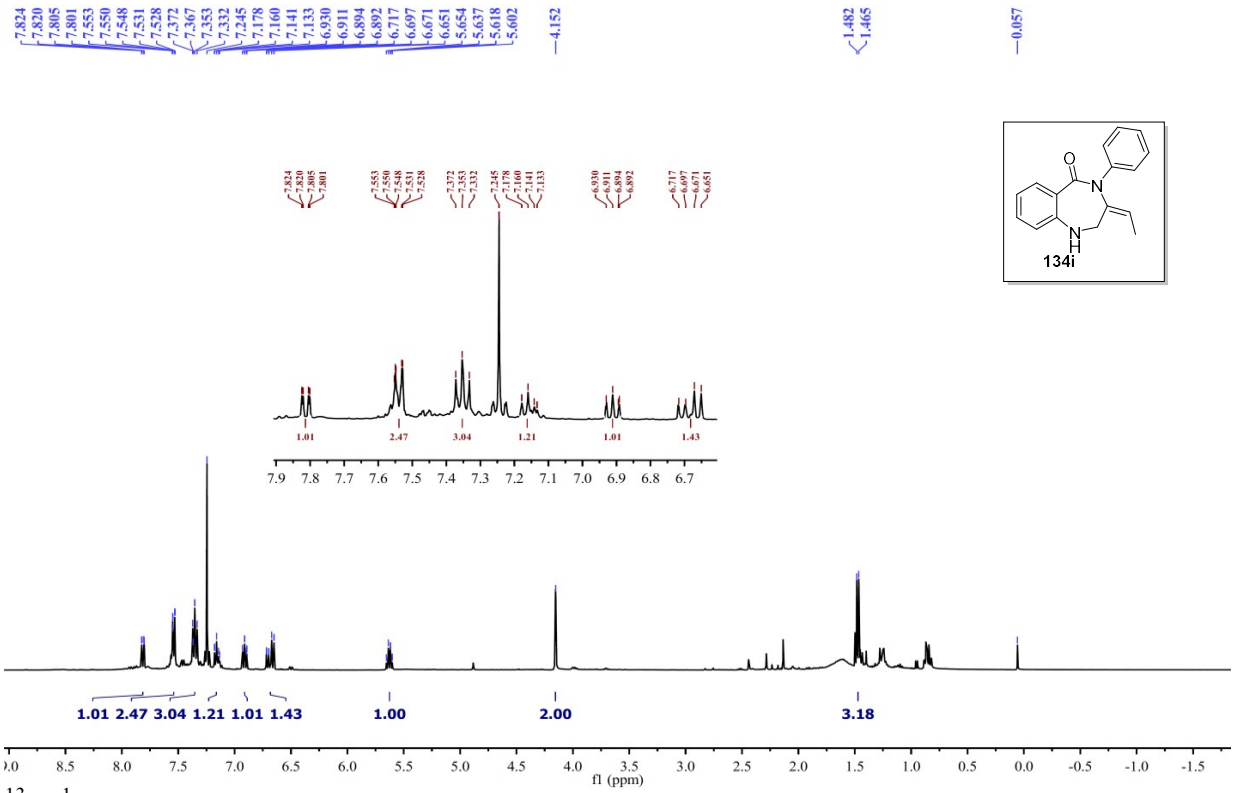
^{1}H NMR (400 MHz) of **134h**:



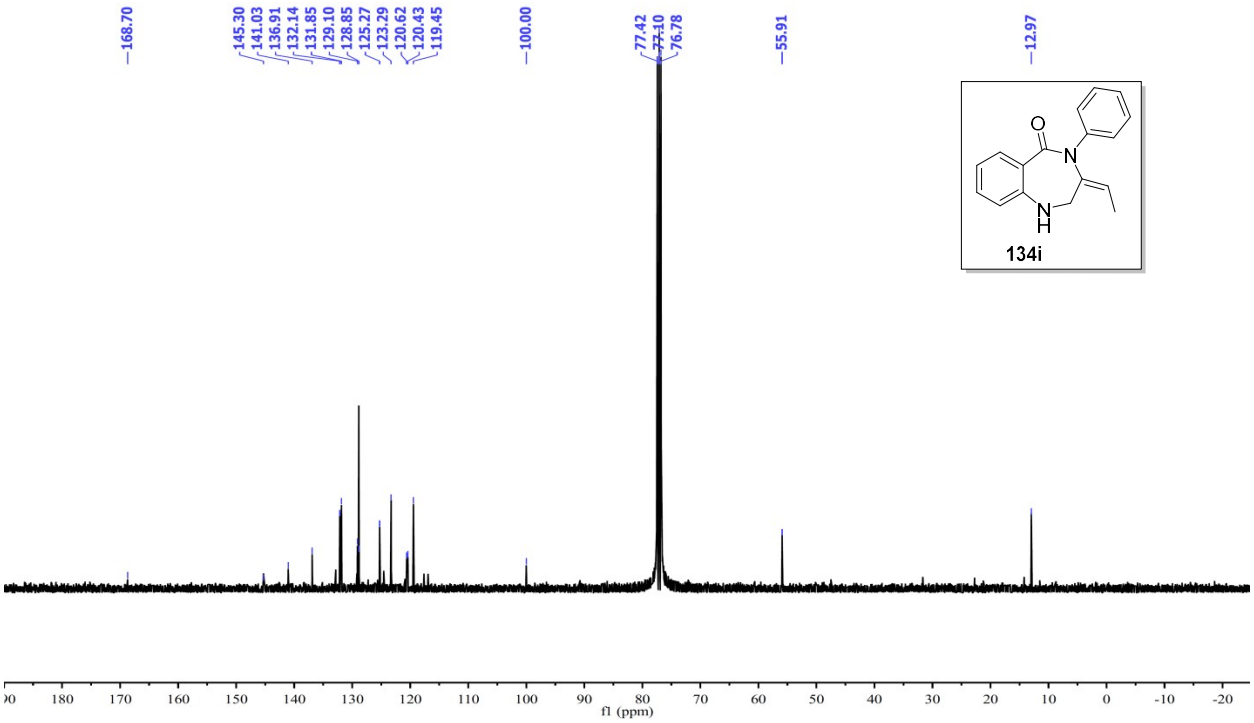
^{13}C{^{1}H} NMR (100 MHz) of **134h**:



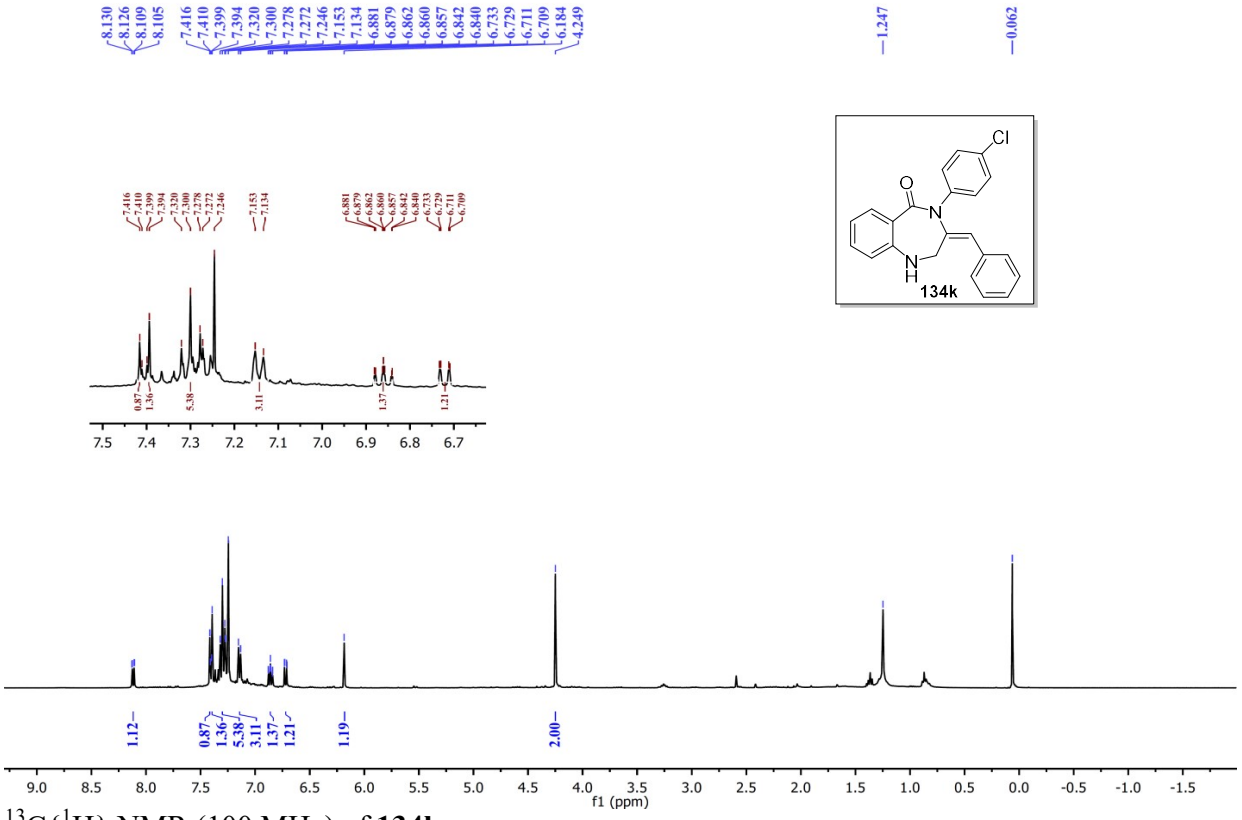
1H NMR (400 MHz) of **134i**:



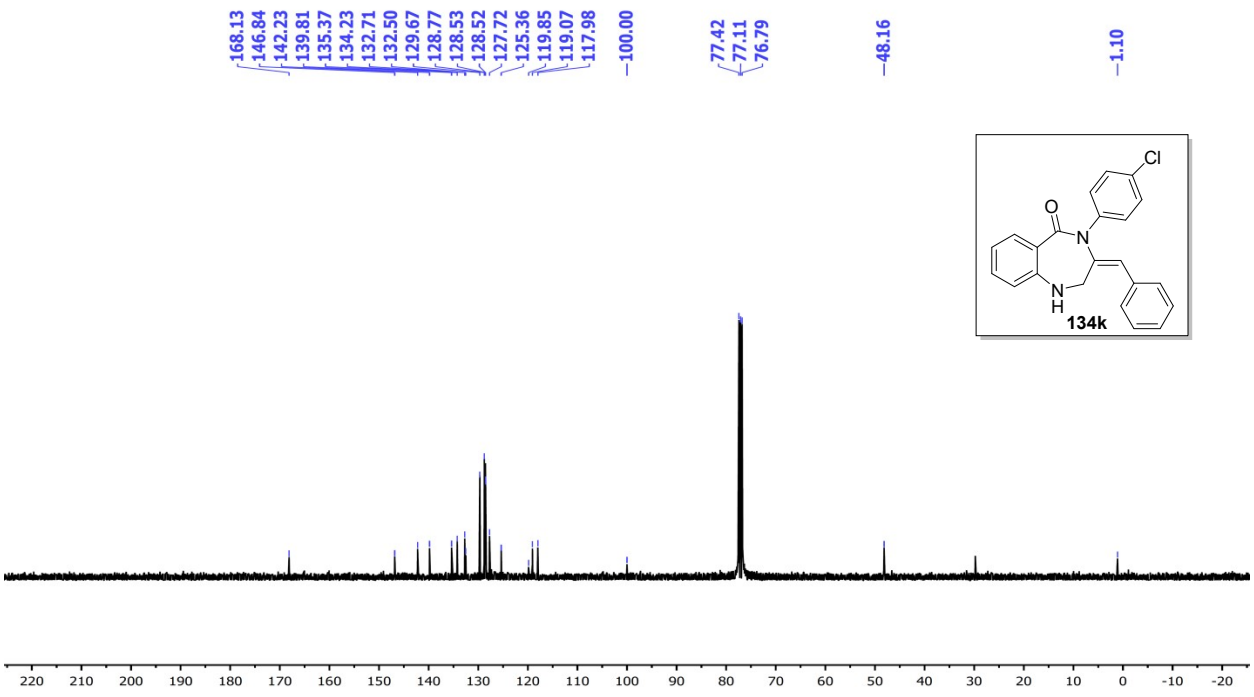
$^{13}C\{^{1}H\}$ NMR (100 MHz) of **134i:**



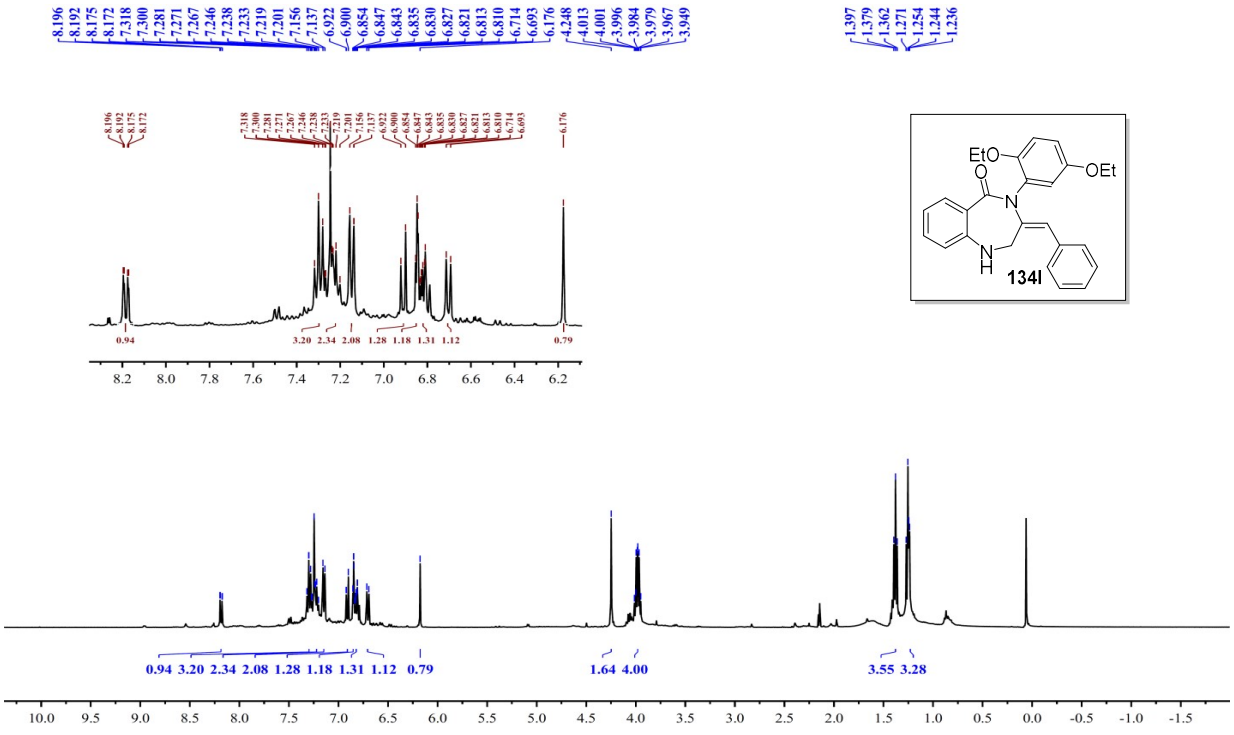
^{1}H NMR (400 MHz) of **134k**:



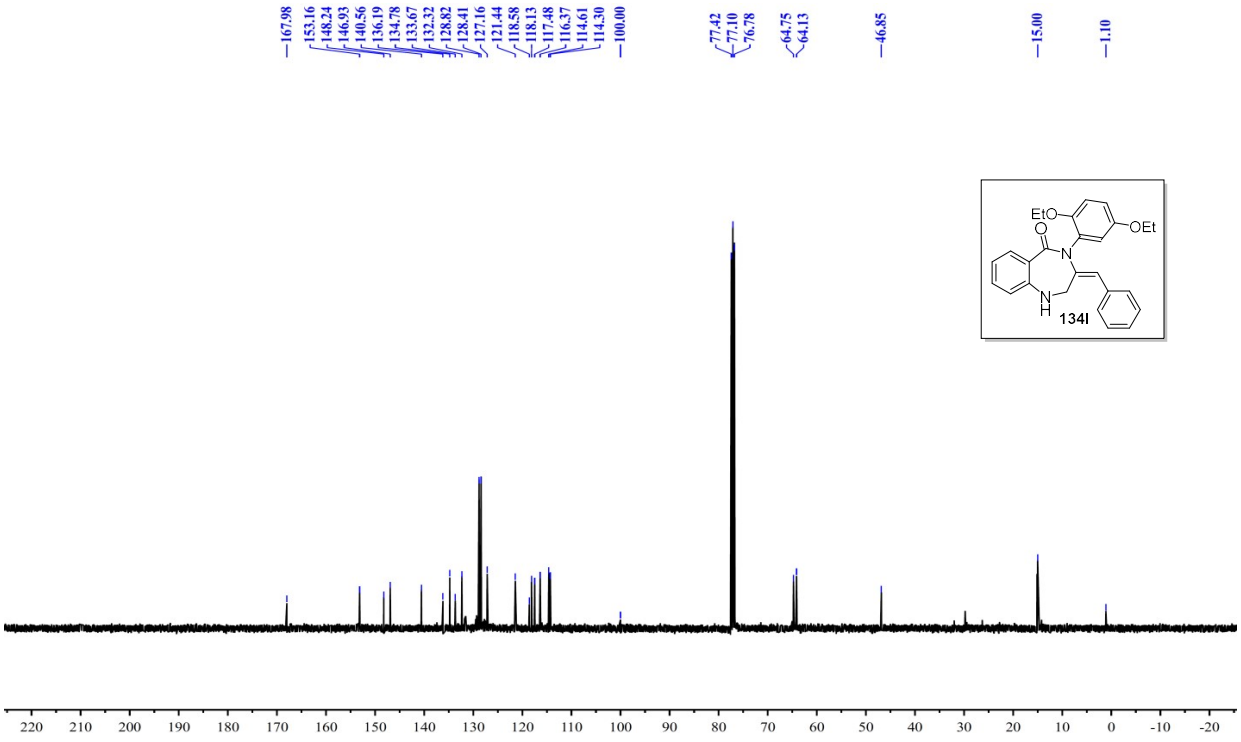
^{13}C{^{1}H} NMR (100 MHz) of **134k:**



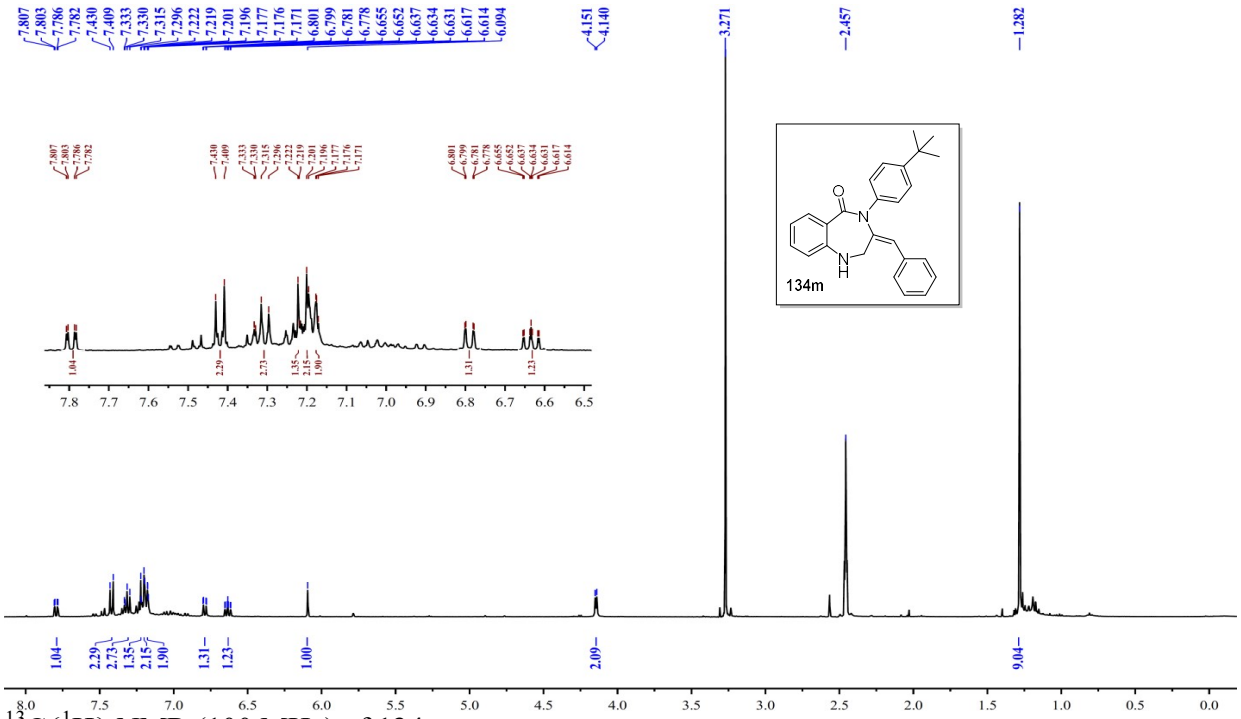
^{1}H NMR (400 MHz) of **134l**:



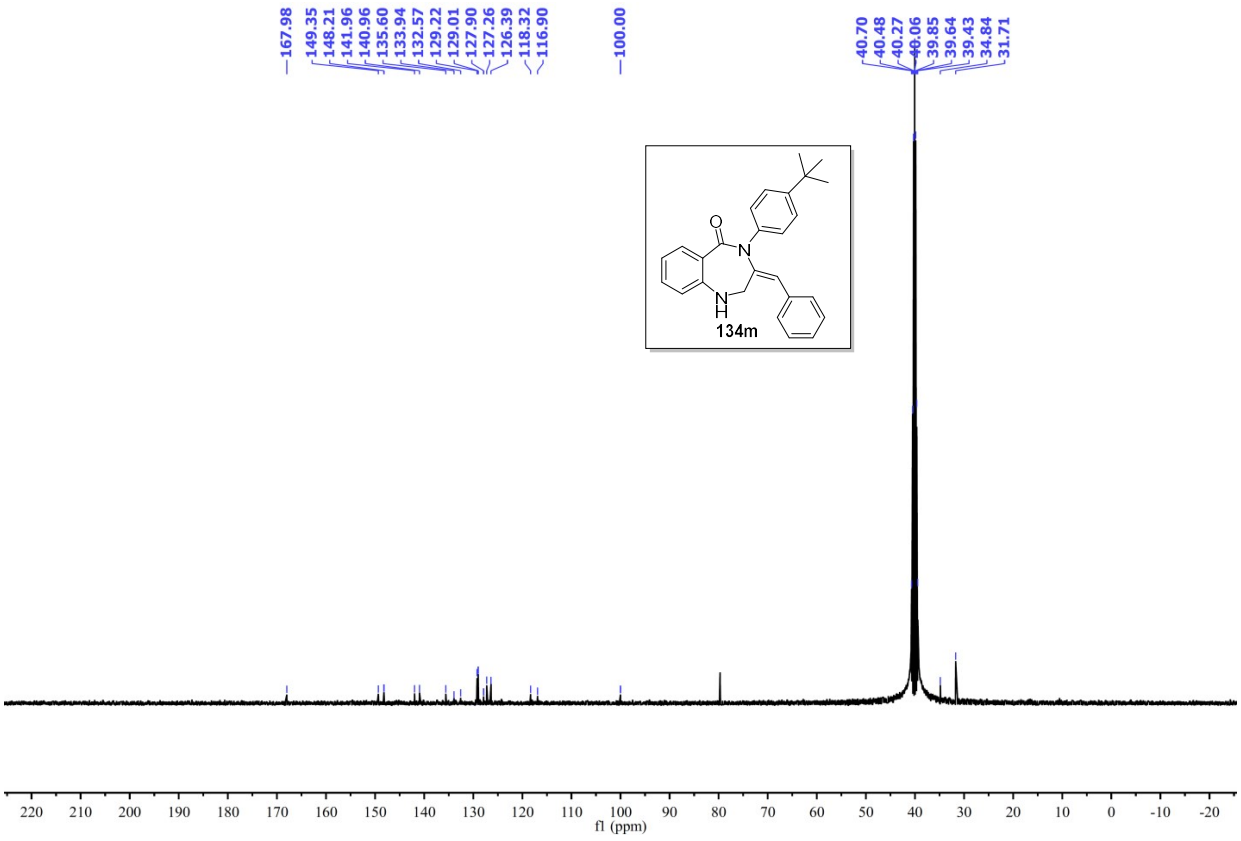
^{13}C{^{1}H} NMR (100 MHz) of **134l**:



^{1}H NMR (400 MHz) of **134m**:

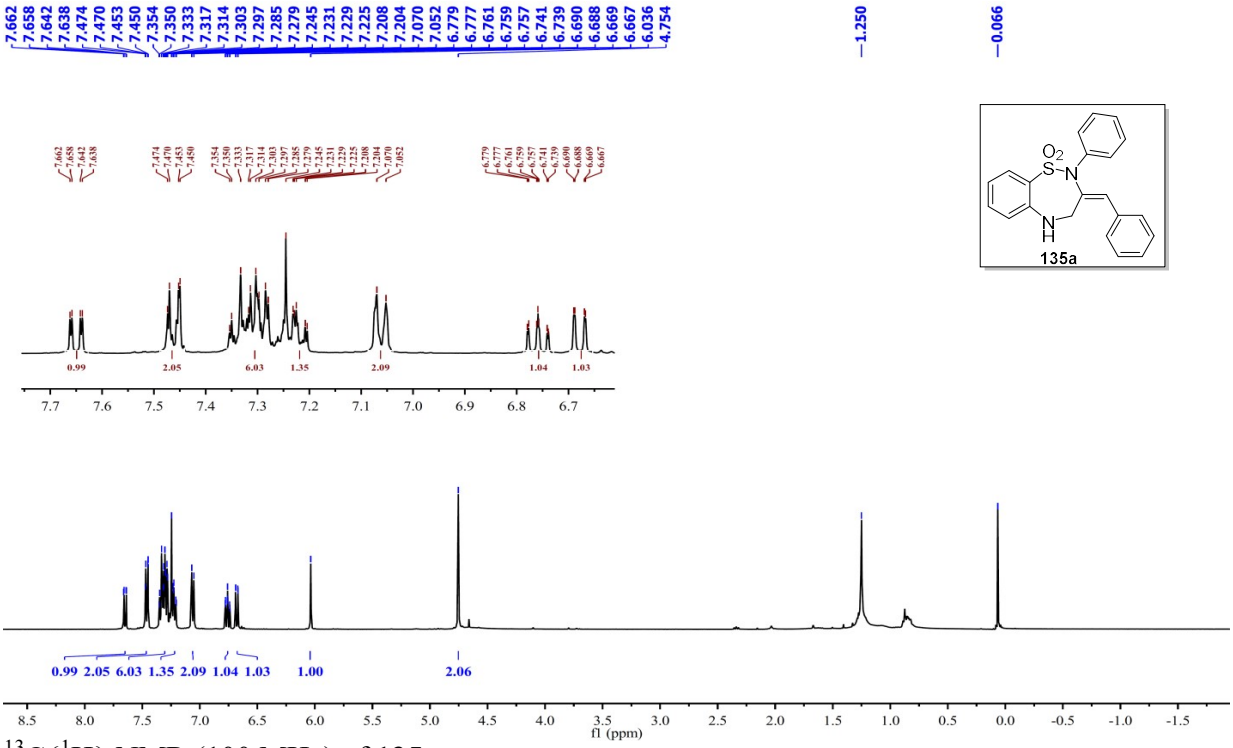


^{13}C{^{1}H} NMR (100 MHz) of **134m**:

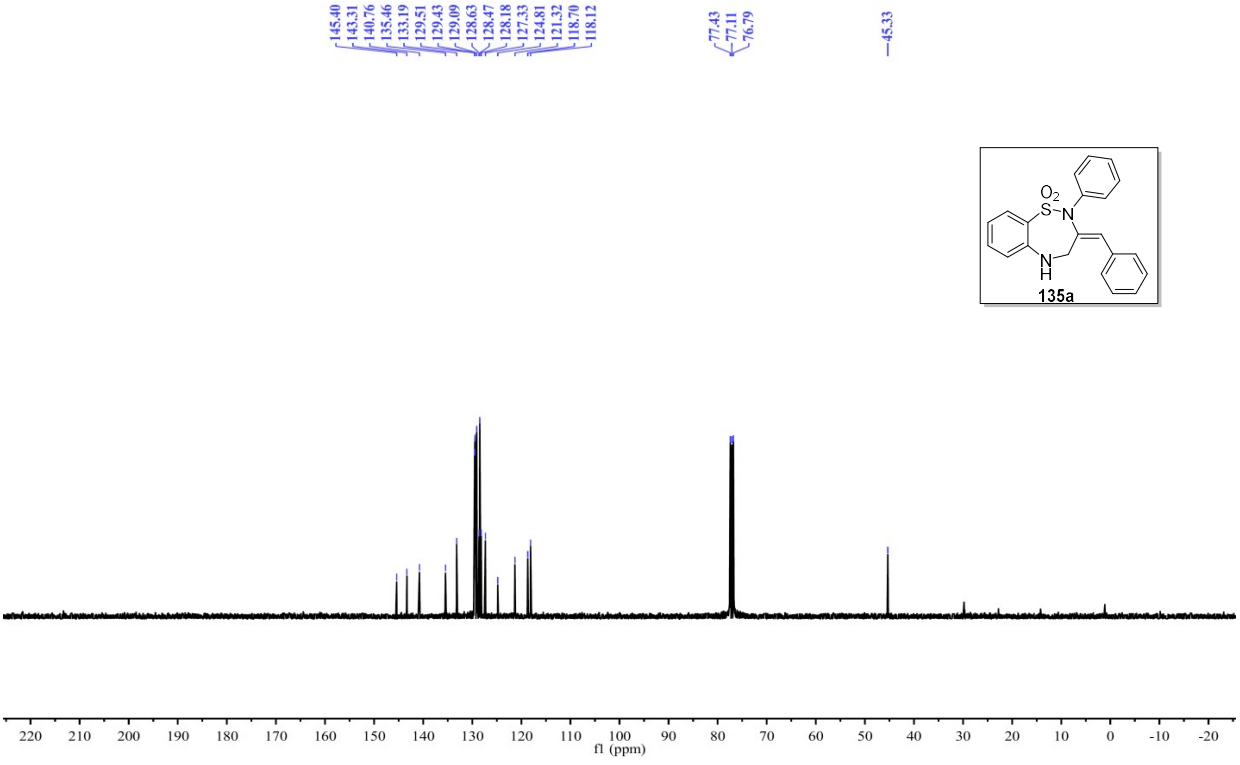


1.2.17.10 NMR spectra of products 135a-135k:

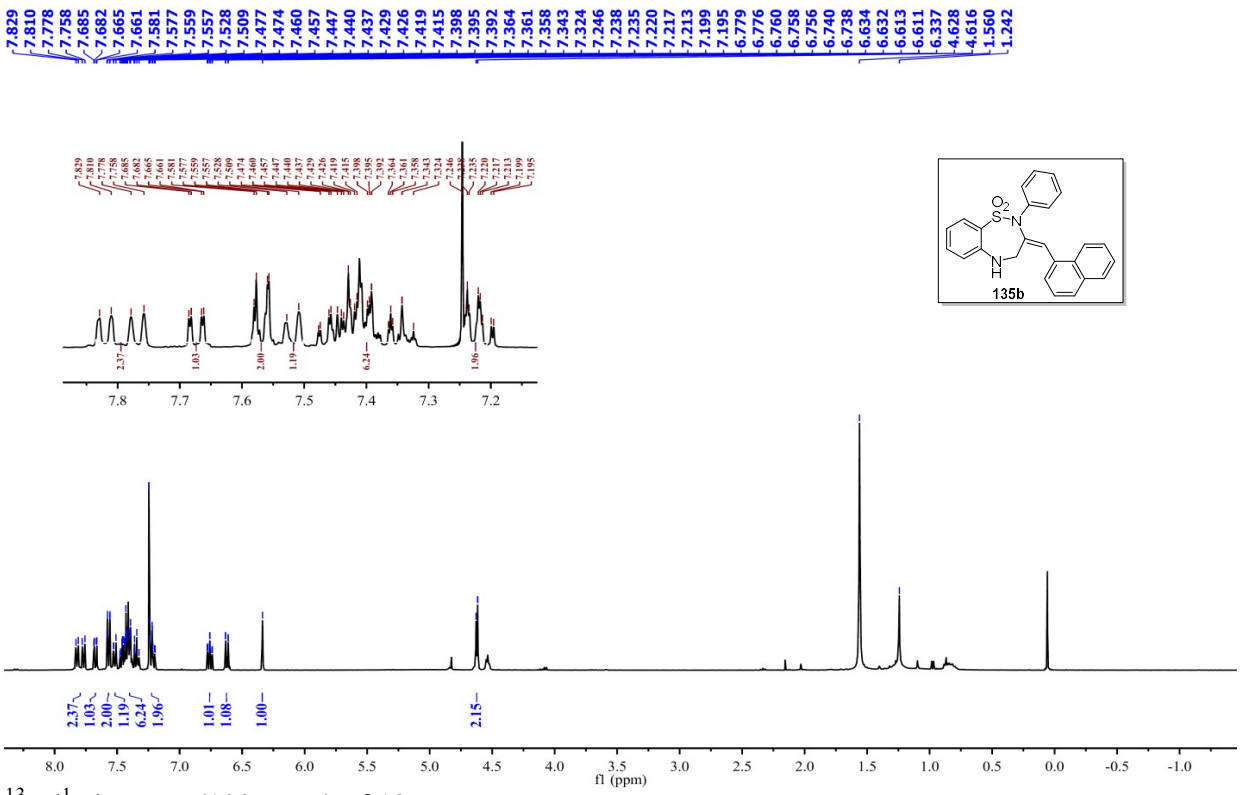
^{1}H NMR (400 MHz) of **135a**:



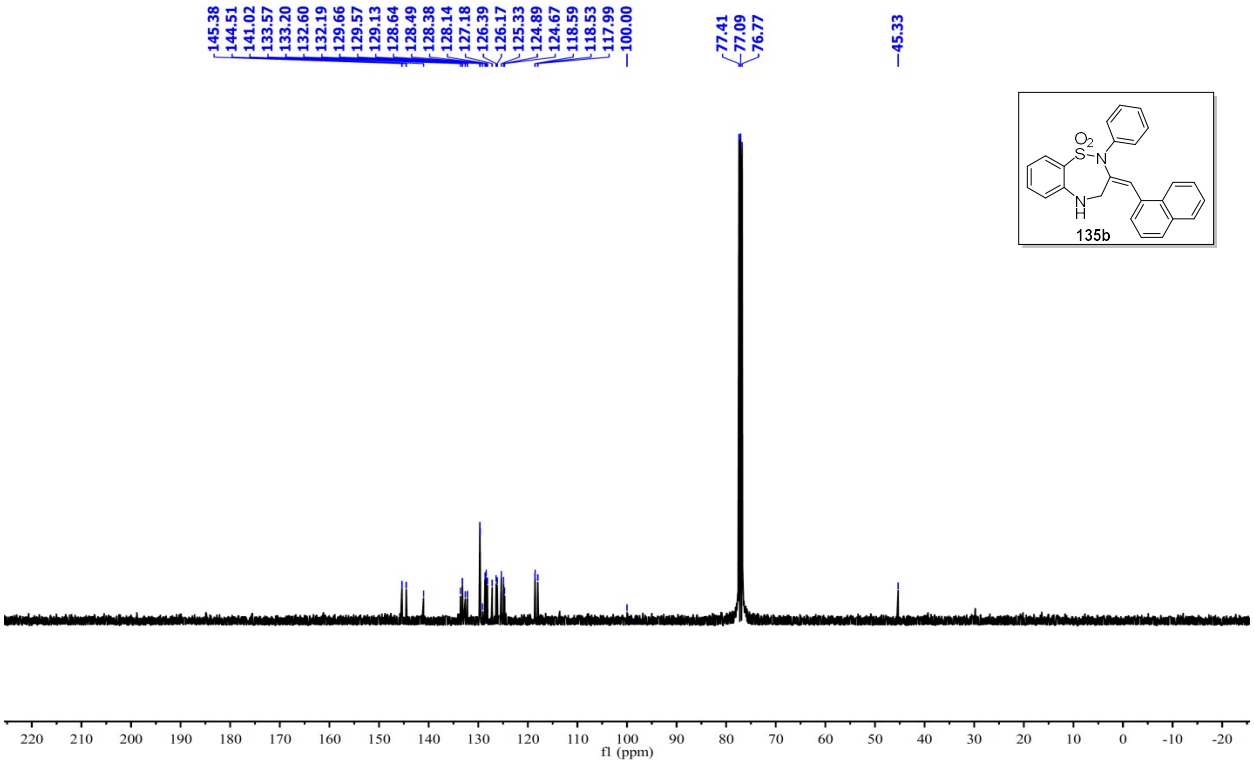
^{13}C{^{1}H} NMR (100 MHz) of **135a**:



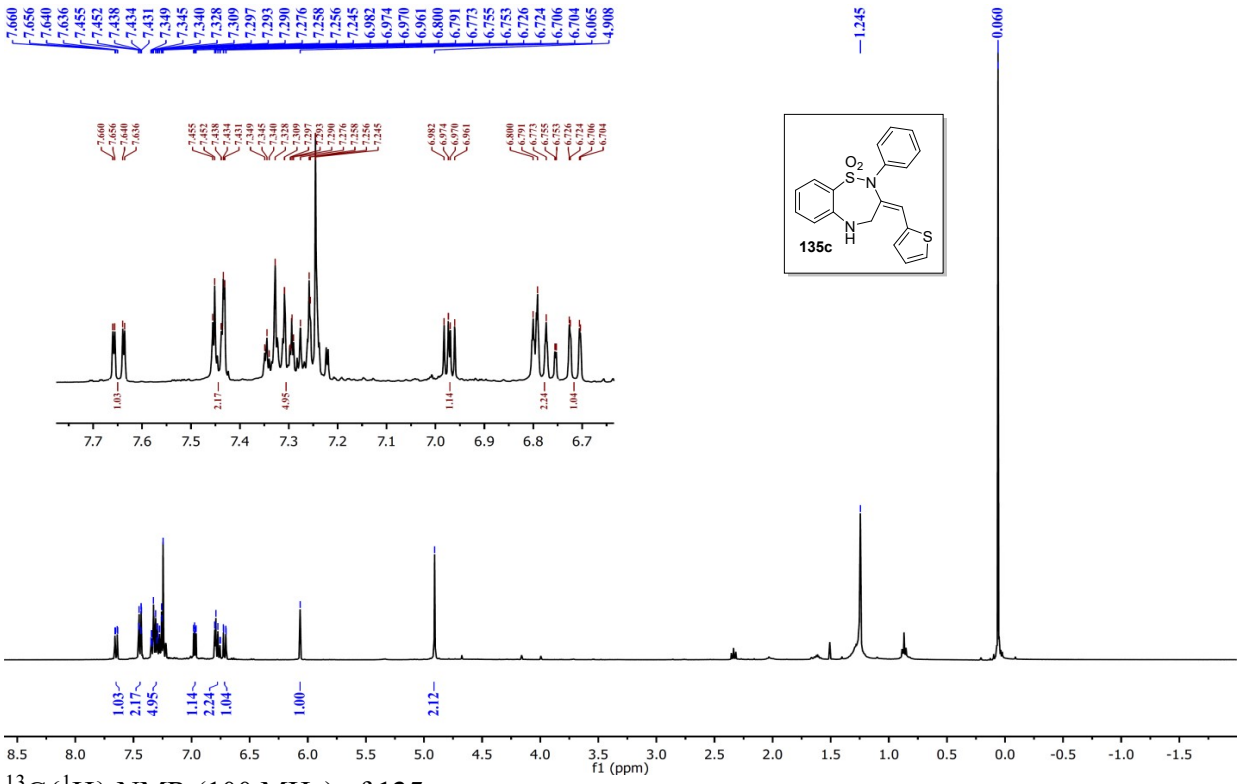
^{1}H NMR (400 MHz) of **135b**:



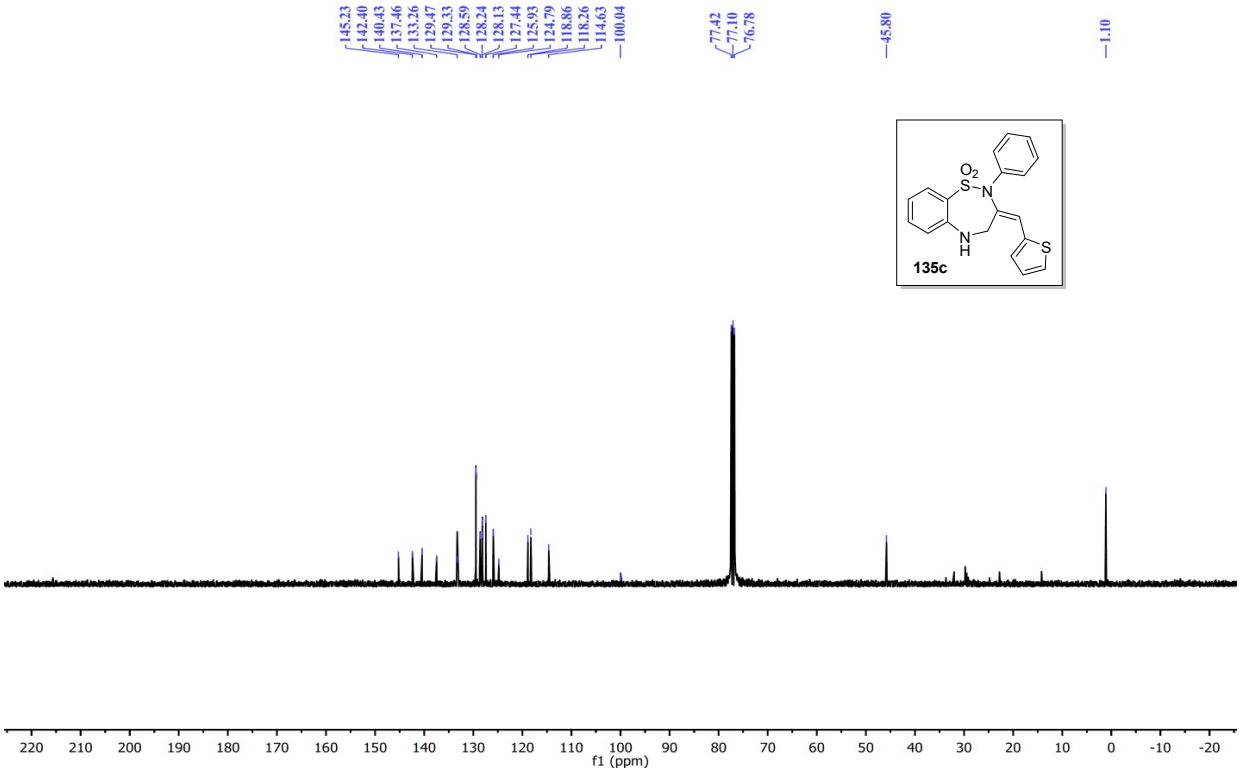
^{13}C{^{1}H} NMR (100 MHz) of **135b**:



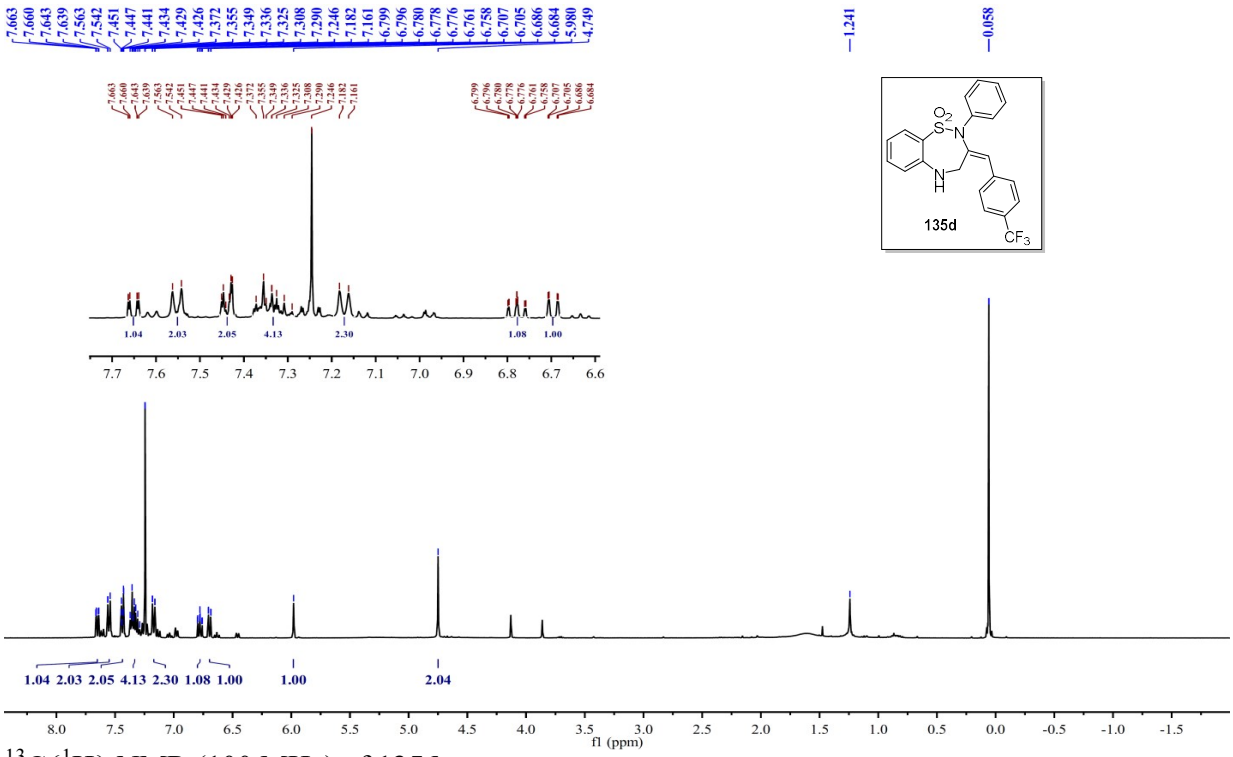
^{1}H NMR (400 MHz) of **135c**:



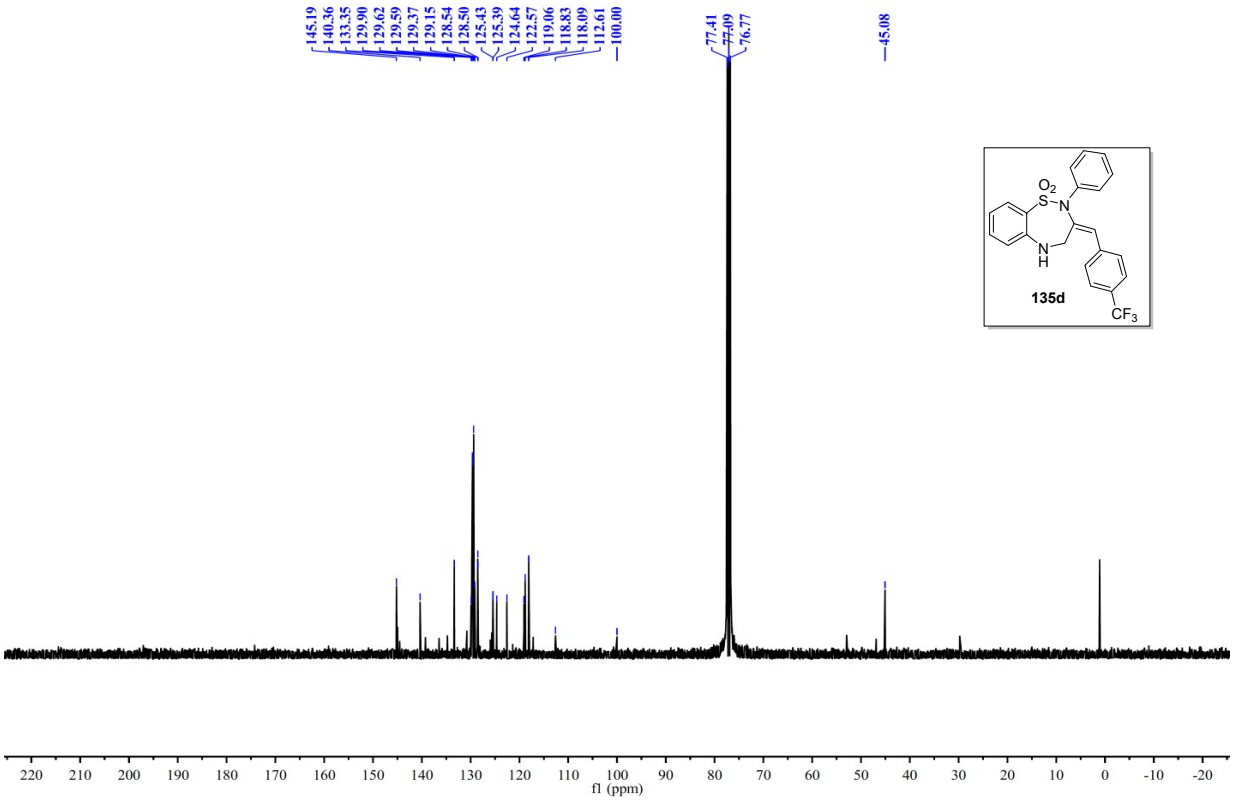
^{13}C{^{1}H} NMR (100 MHz) of **135c**:



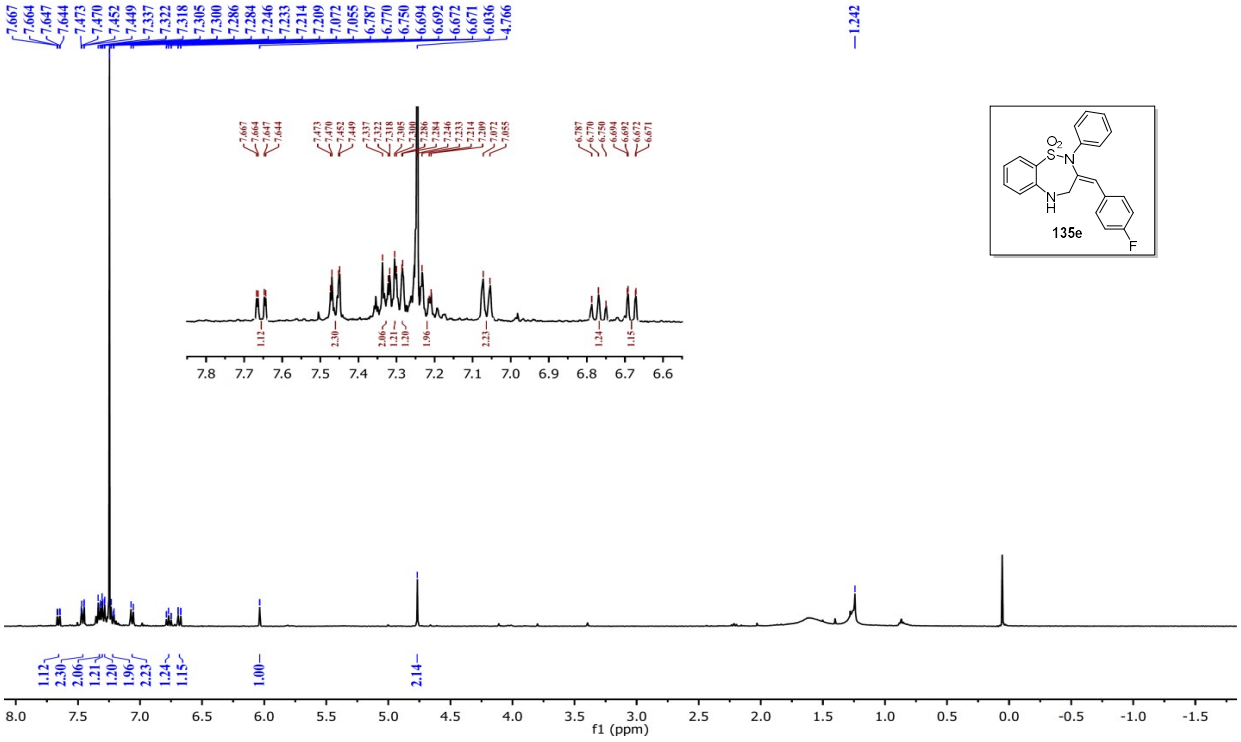
^{1}H NMR (400 MHz) of **135d**:



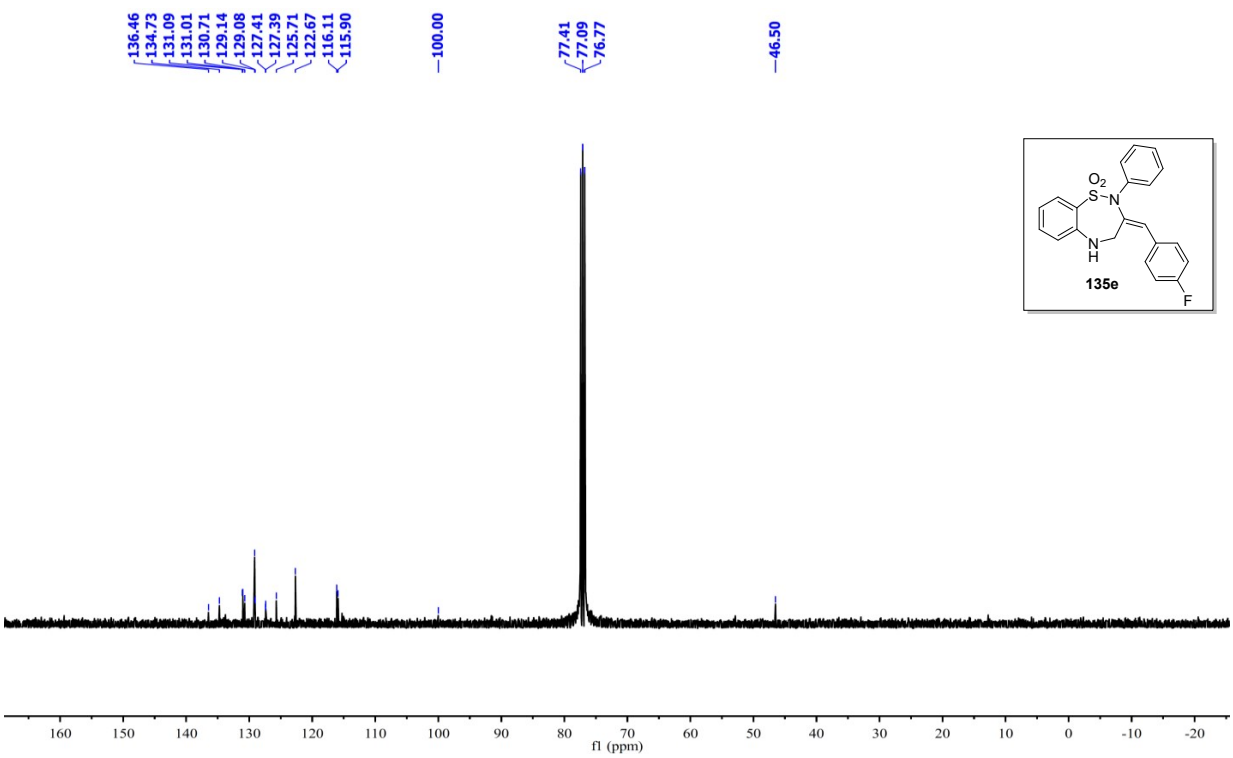
^{13}C{^{1}H} NMR (100 MHz) of **135d**:



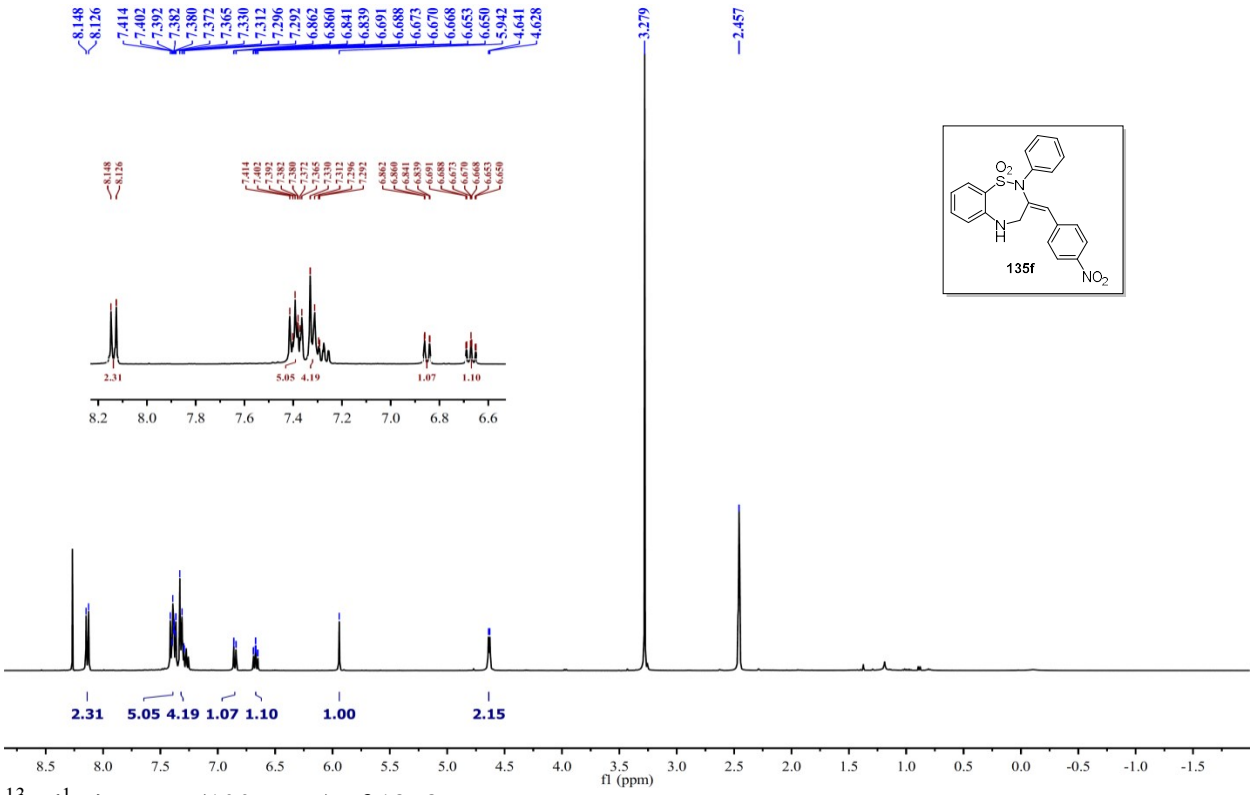
^{1}H NMR (400 MHz) of **135e**:



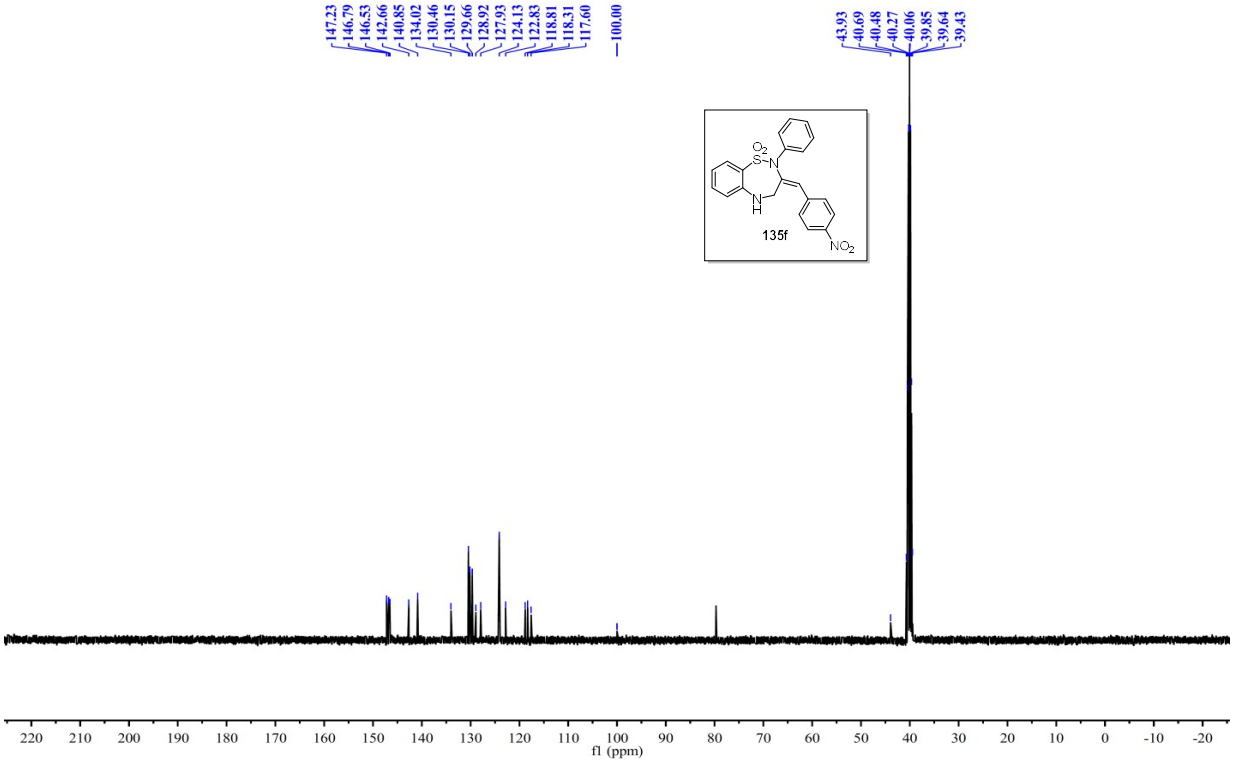
^{13}C{^{1}H} NMR (100 MHz) of **135e**:



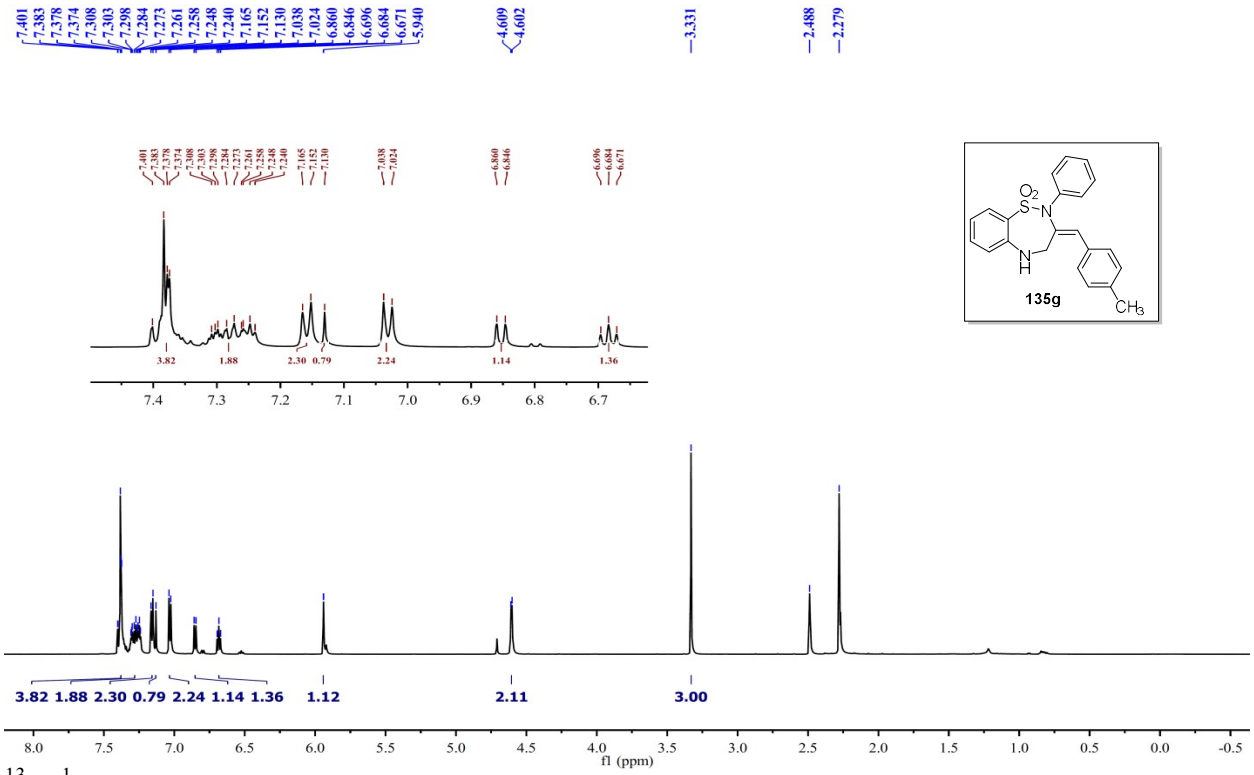
^{1}H NMR (400 MHz) of **135f**:



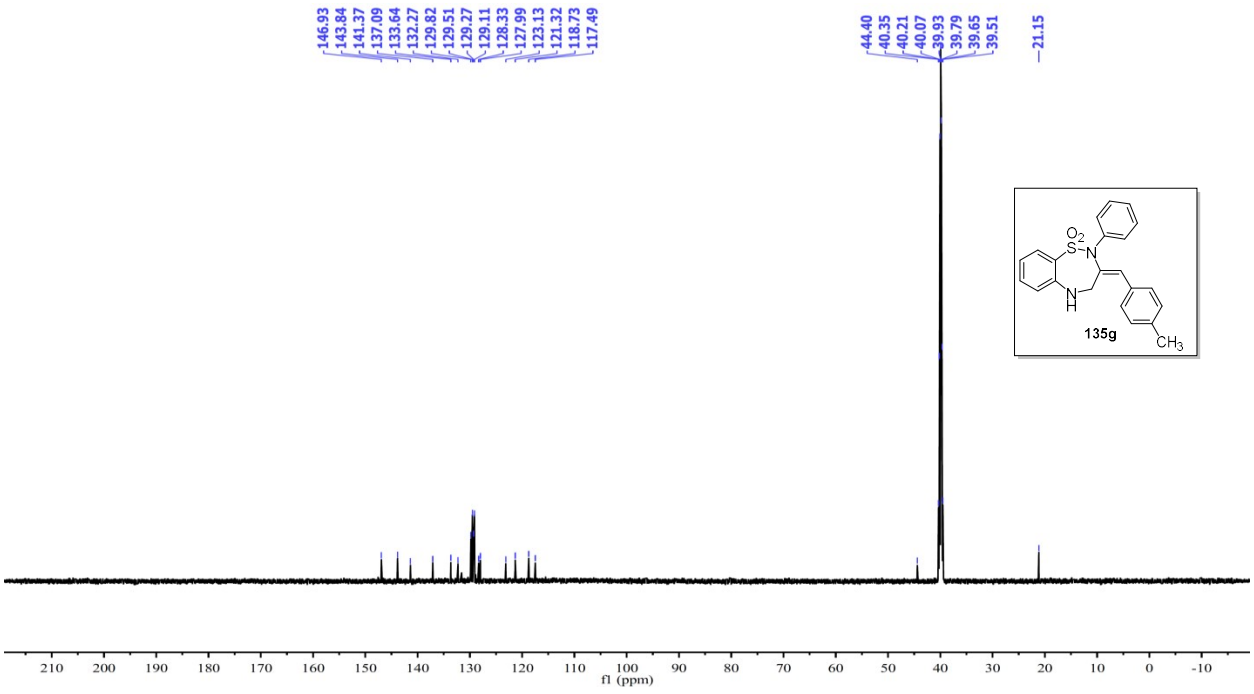
^{13}C{^{1}H} NMR (100 MHz) of **135f**:



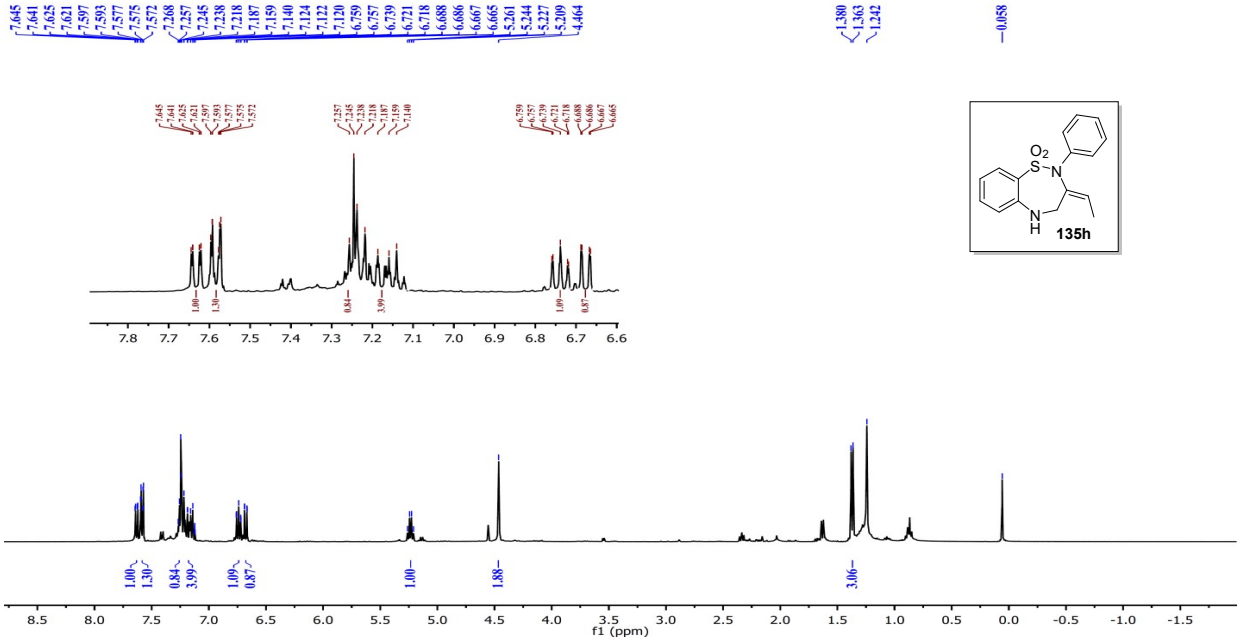
^{1}H NMR (600 MHz) of **135g**:



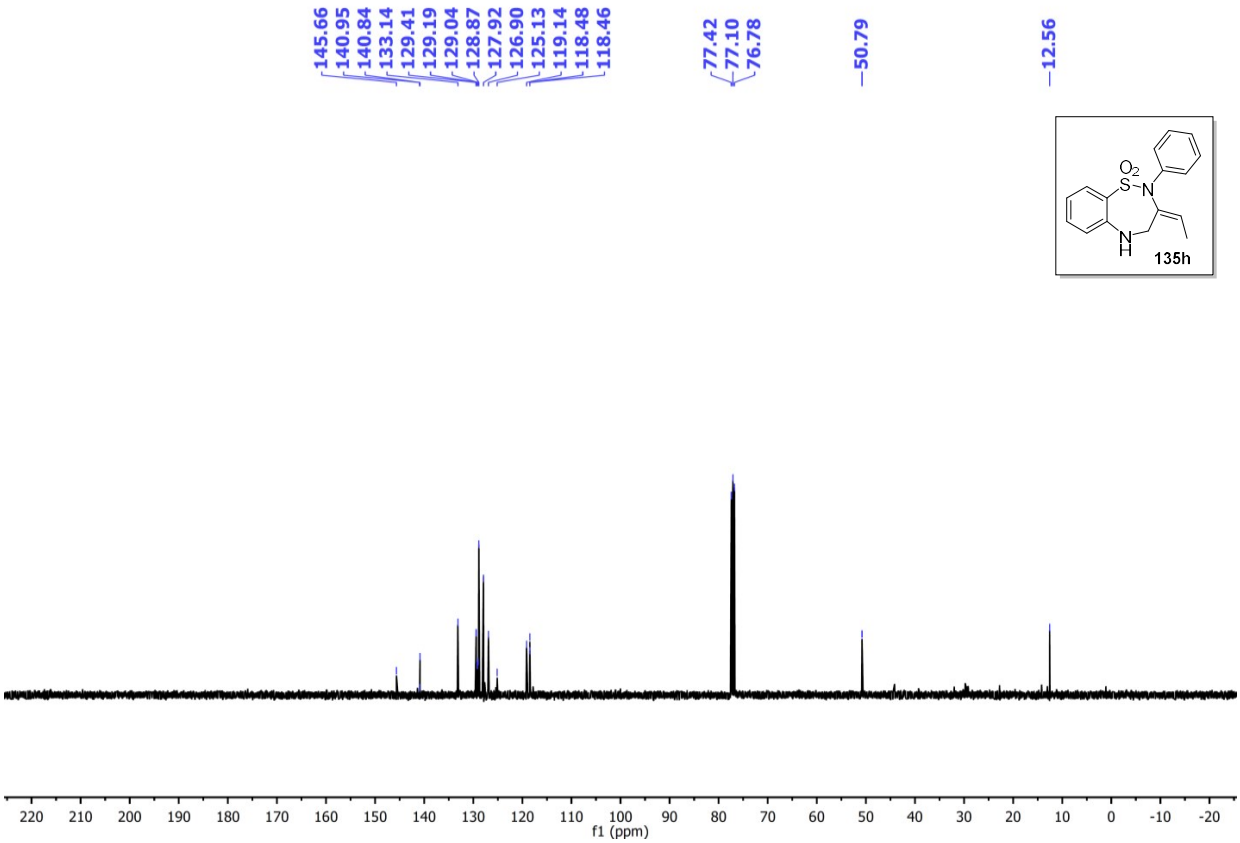
^{13}C{^{1}H} NMR (150 MHz) of **135g**:



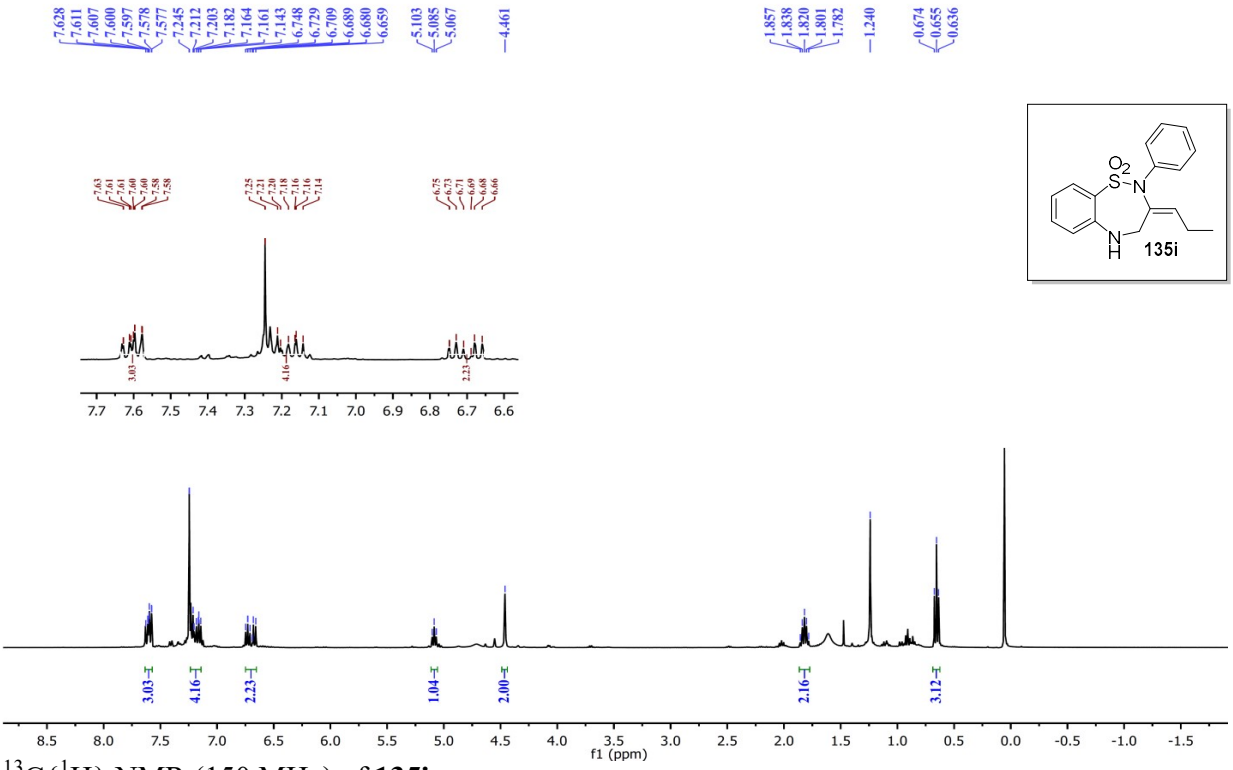
^{1}H NMR (400 MHz) of **135h**:



^{13}C{^{1}H} NMR (150 MHz) of **135h**:



^{1}H NMR (400 MHz) of **135i**:



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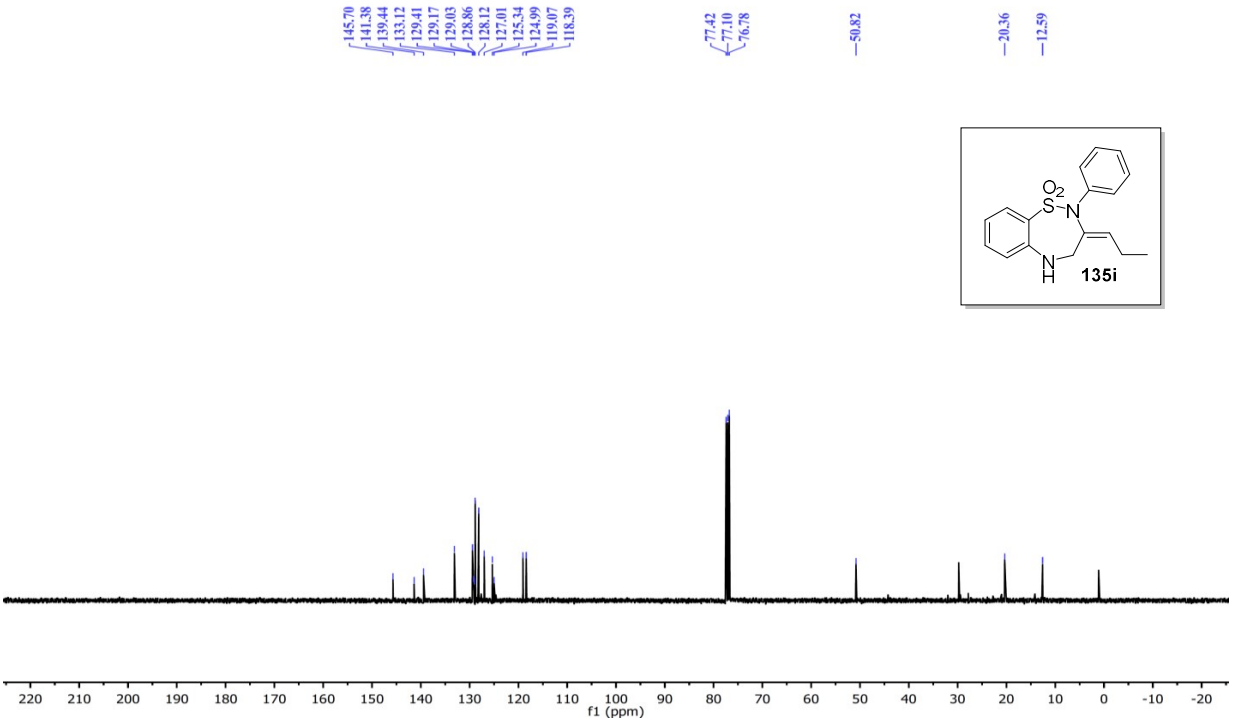

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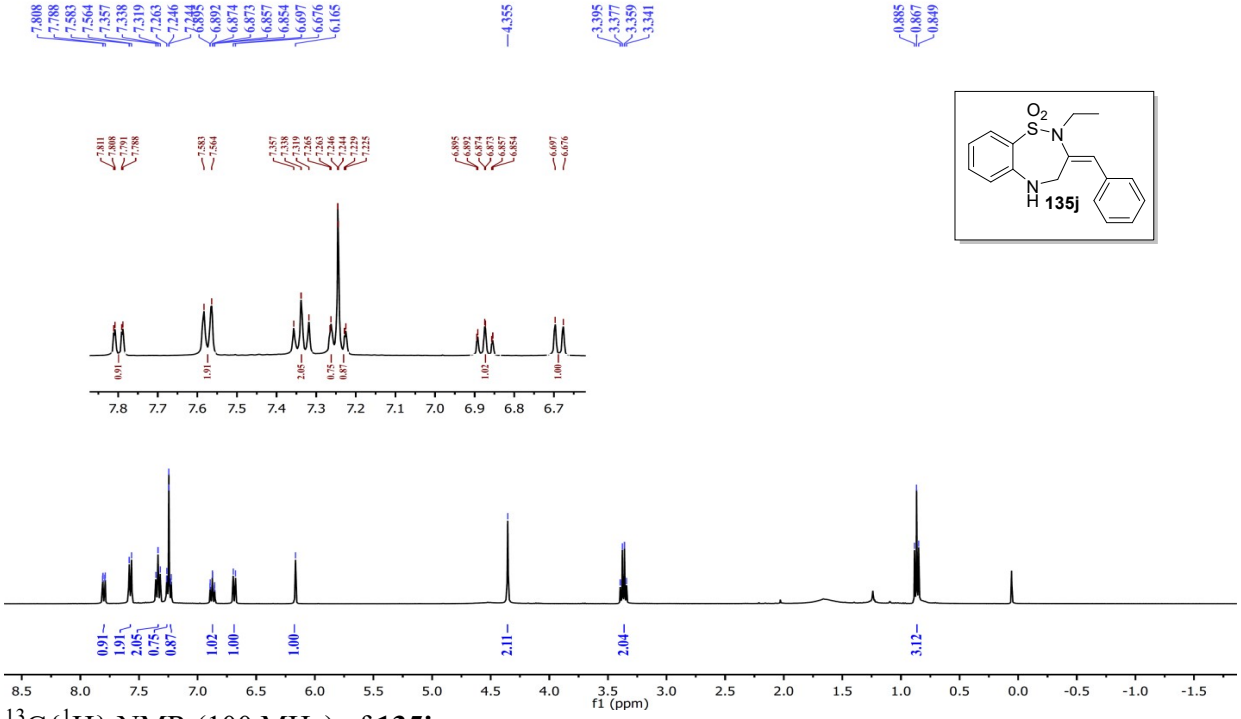

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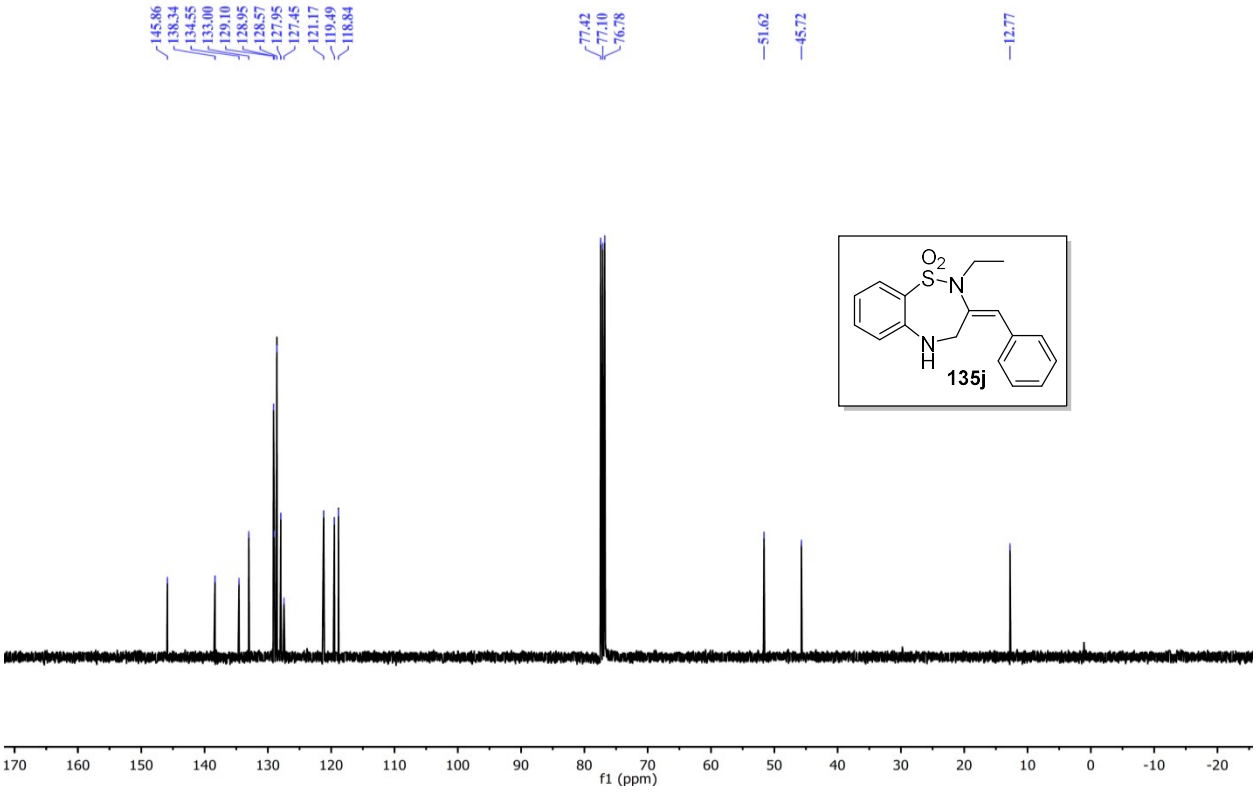

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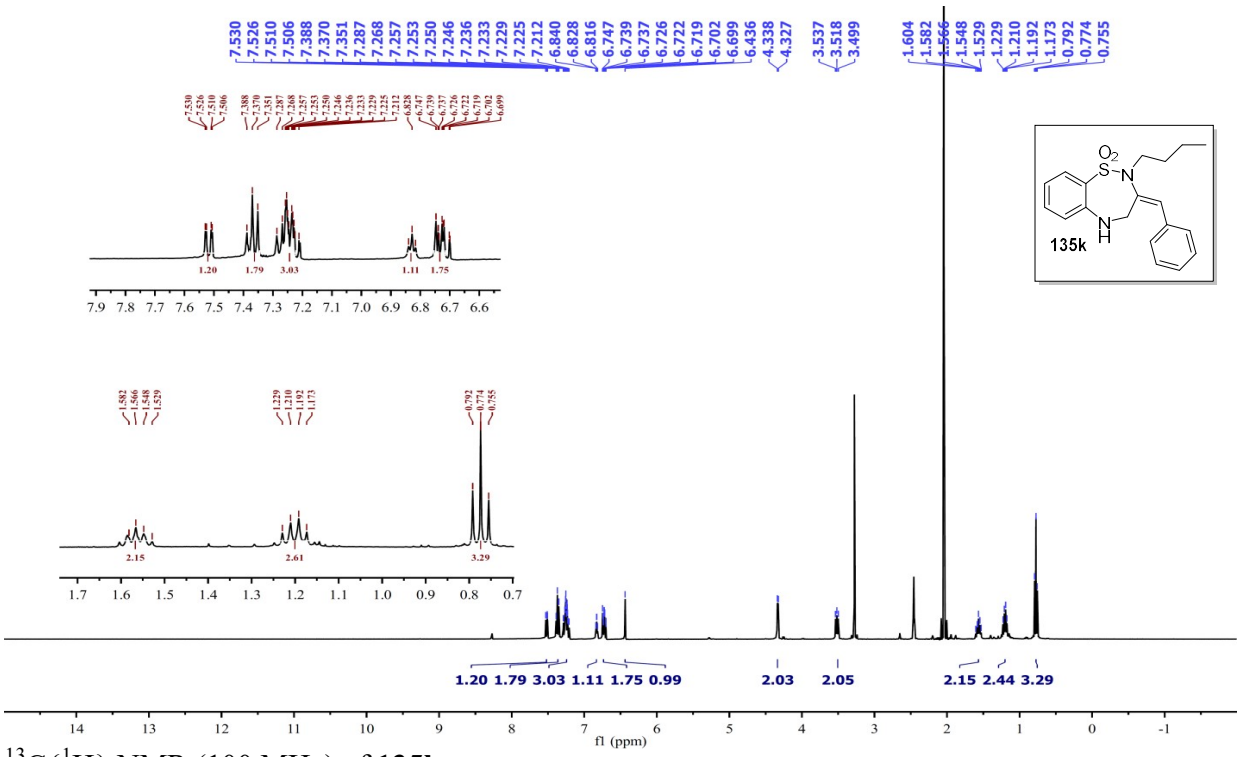
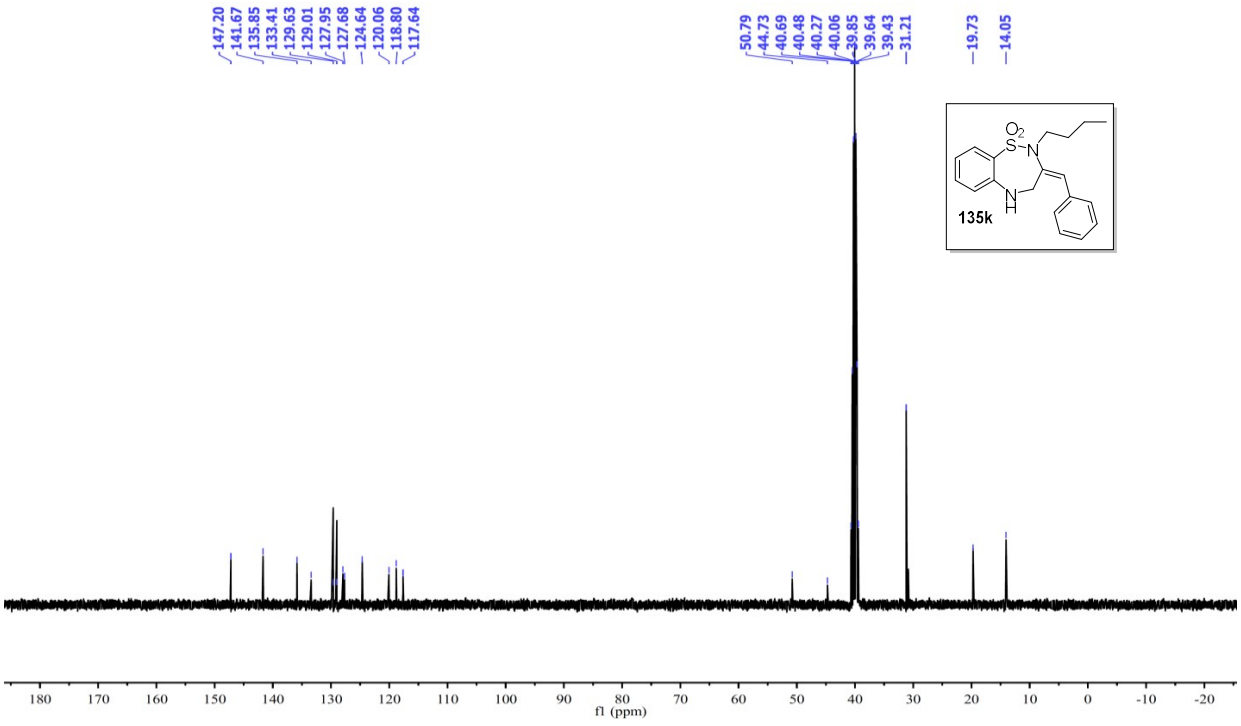
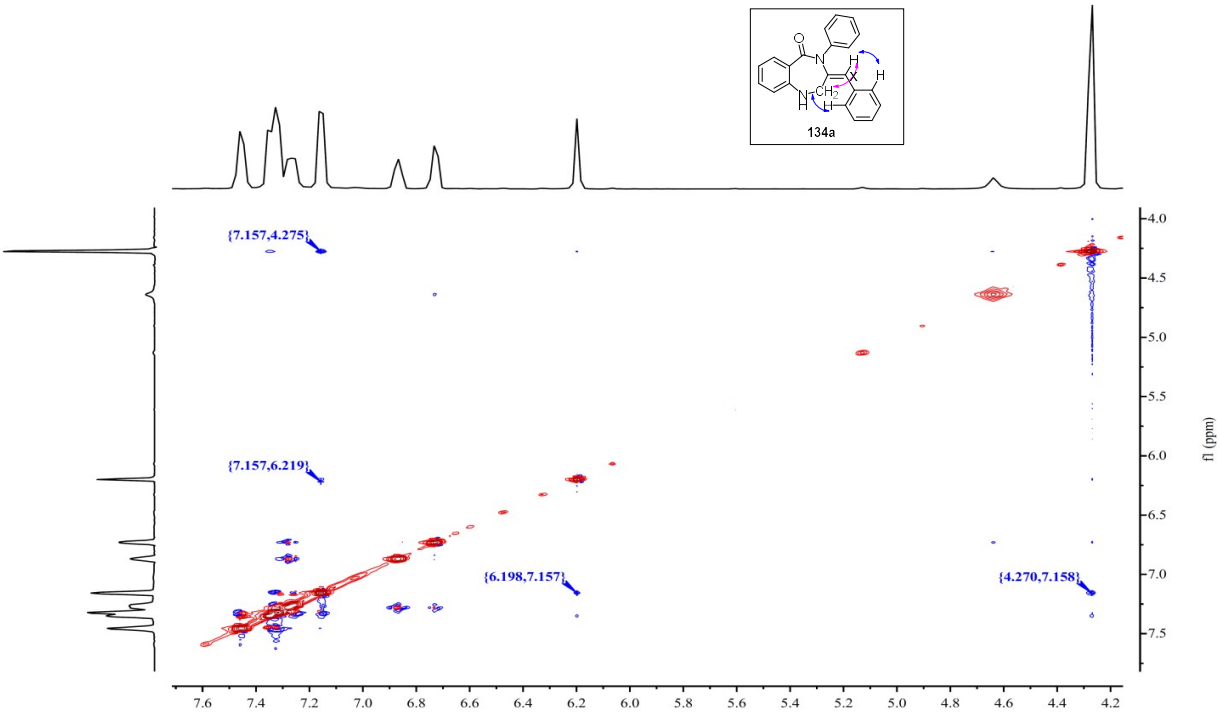


^{13}C{^{1}H} NMR (100 MHz) of **135k**:

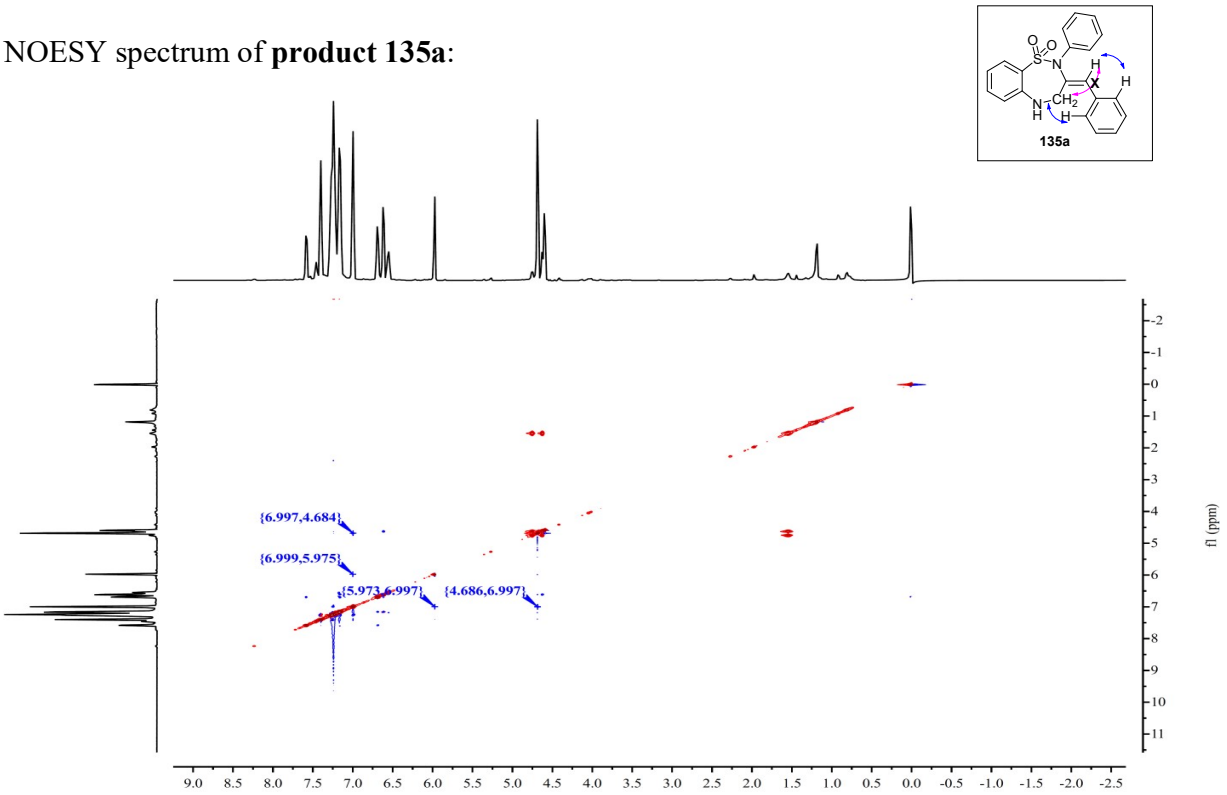


1.2.17.11 NOESY spectrum of products 134a, 135a, 135g:

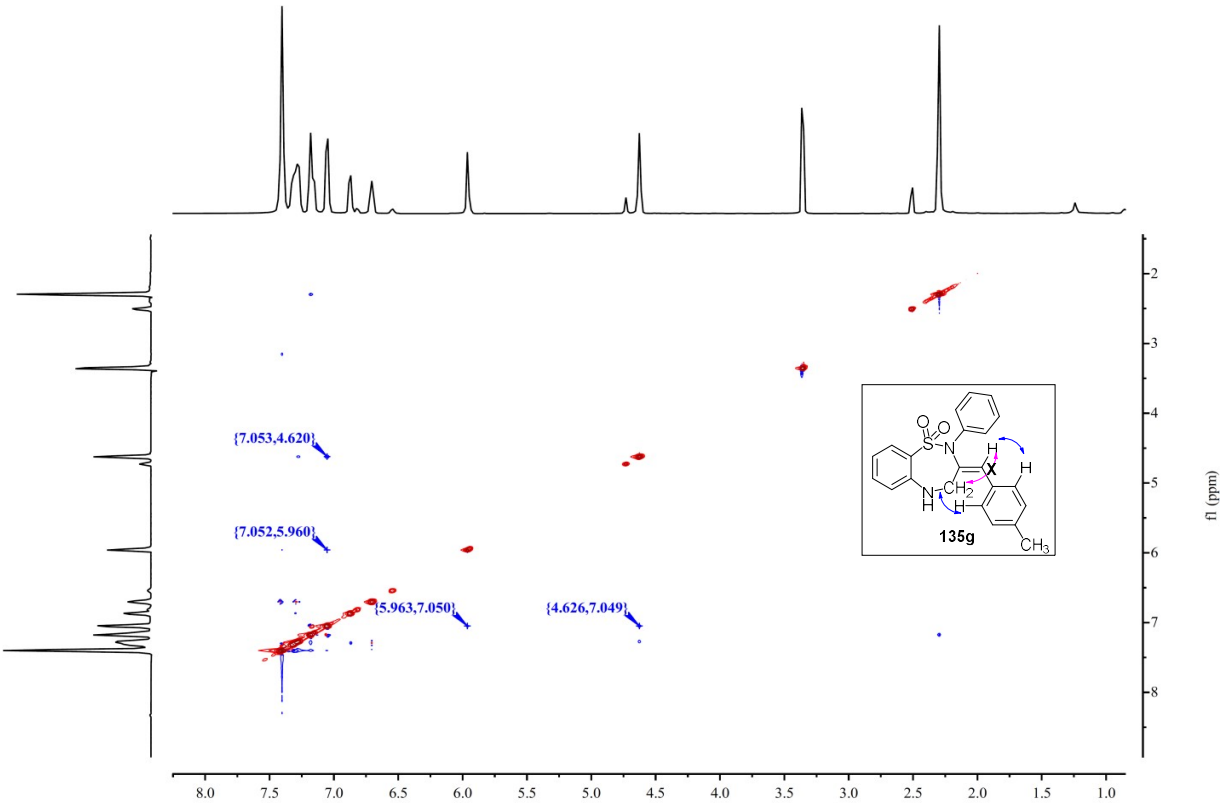
NOESY spectrum of **product 134a**:



NOESY spectrum of **product 135a**:



NOESY spectrum of **product 135g**:



1.2.17.12 NMR spectra of products 141a–141c:

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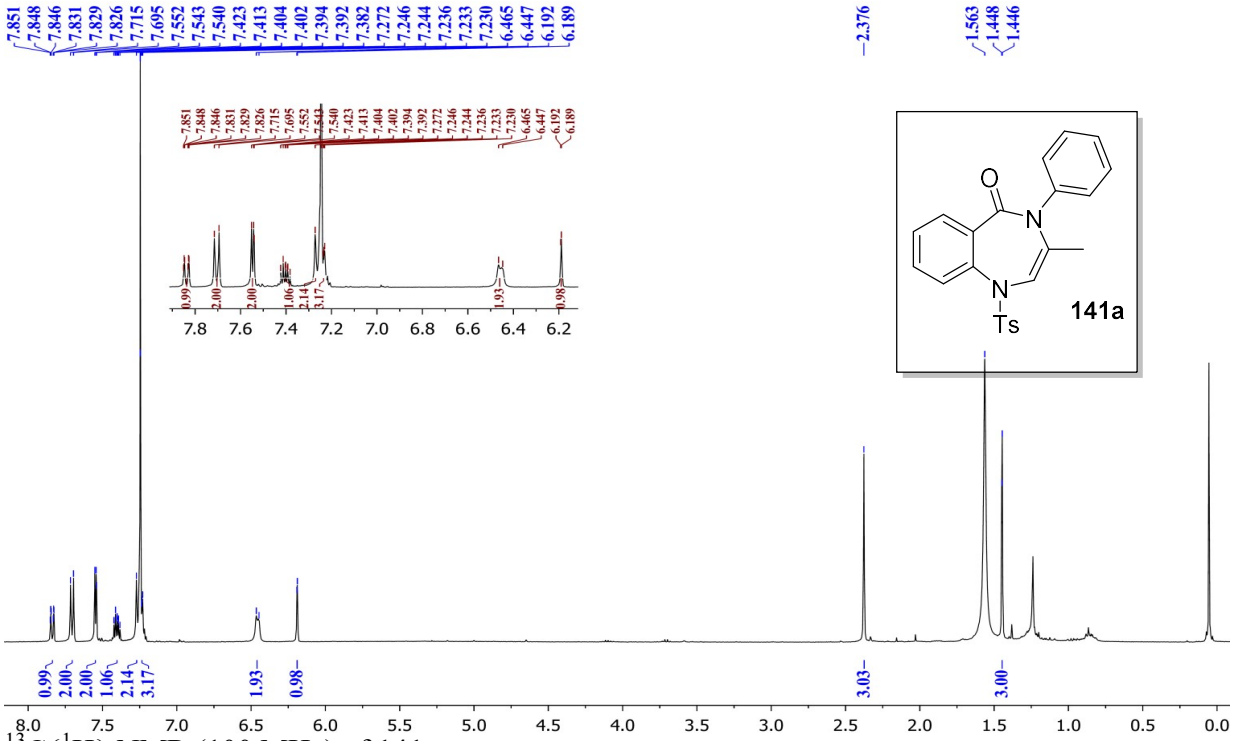
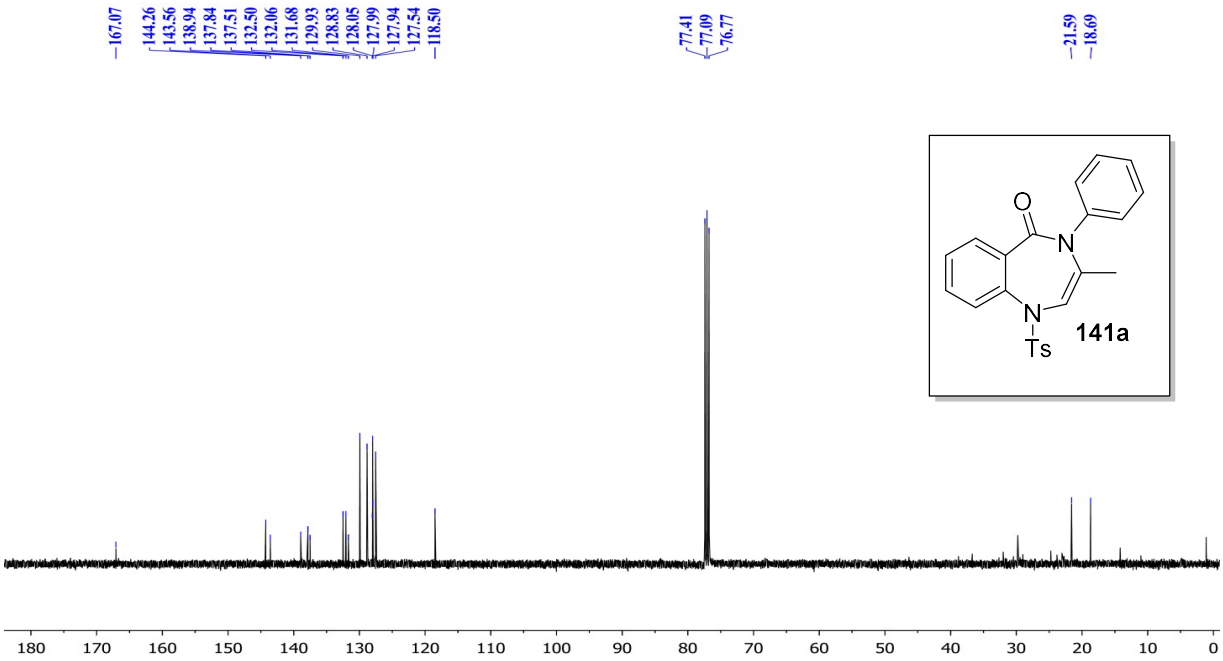
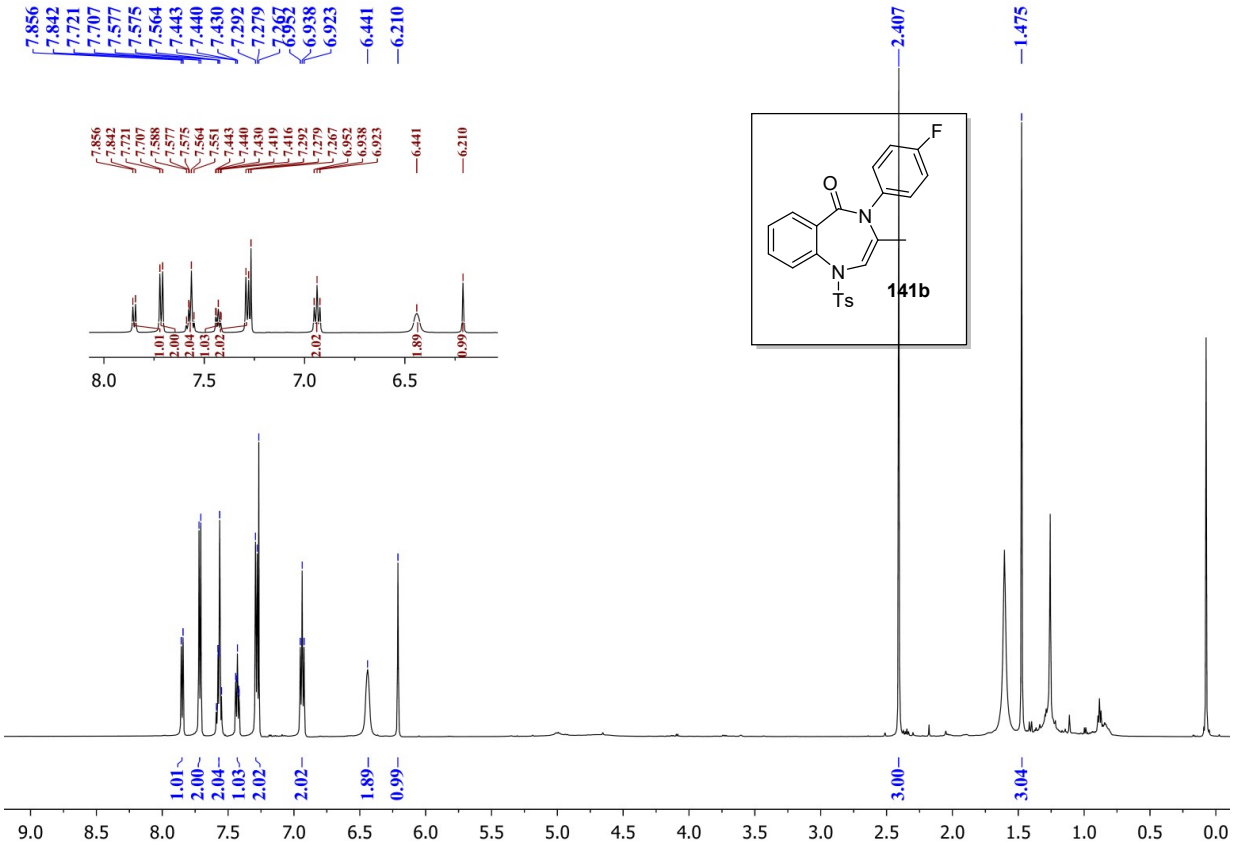


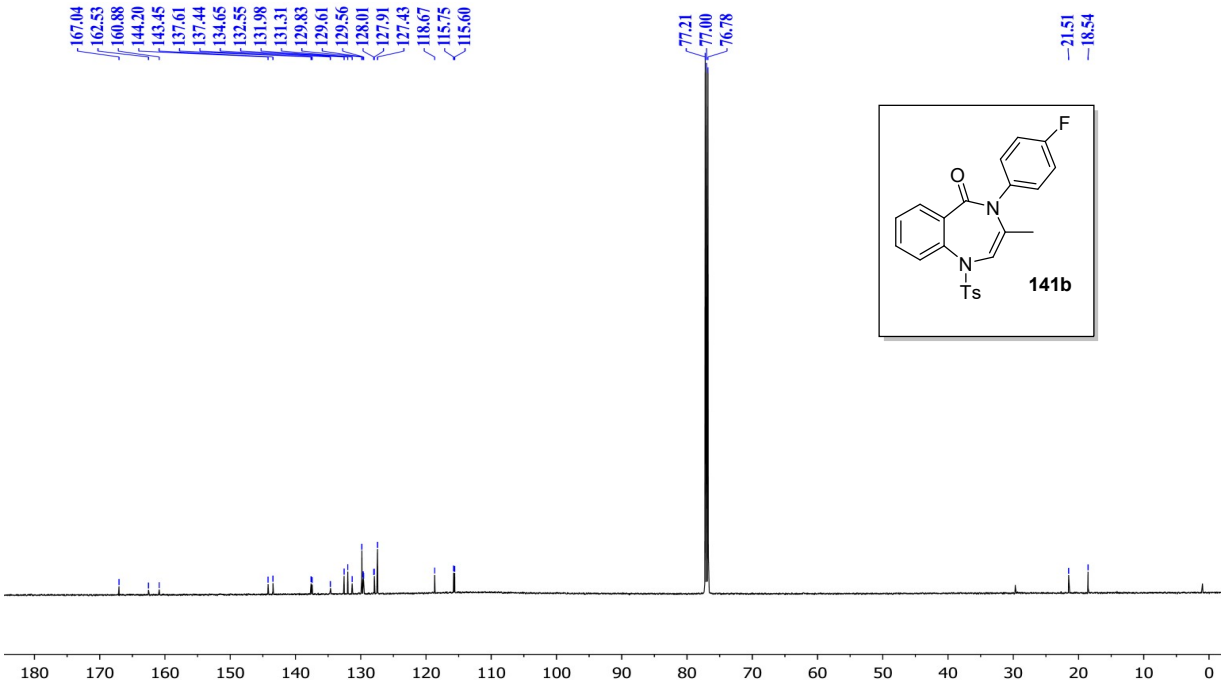
^{13}C{^{1}H} NMR (100 MHz) of **141a**:



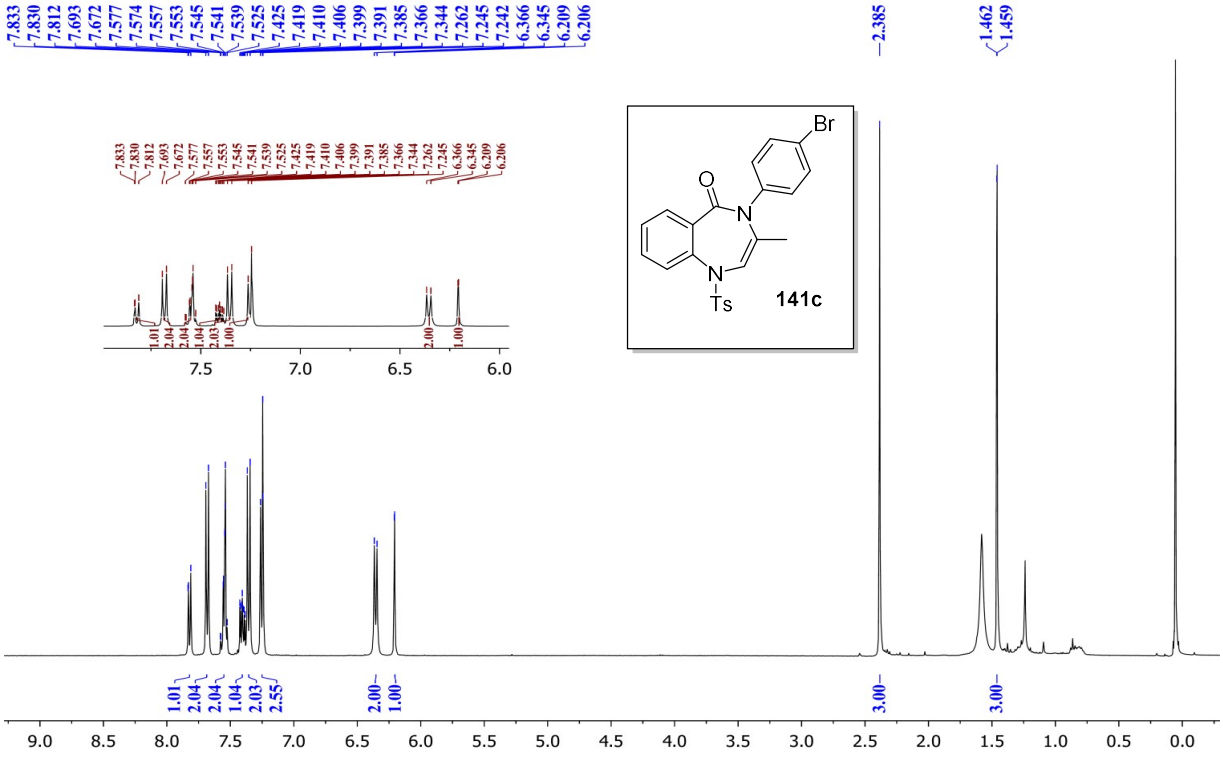
^{1}H NMR (600 MHz) of **141b:**



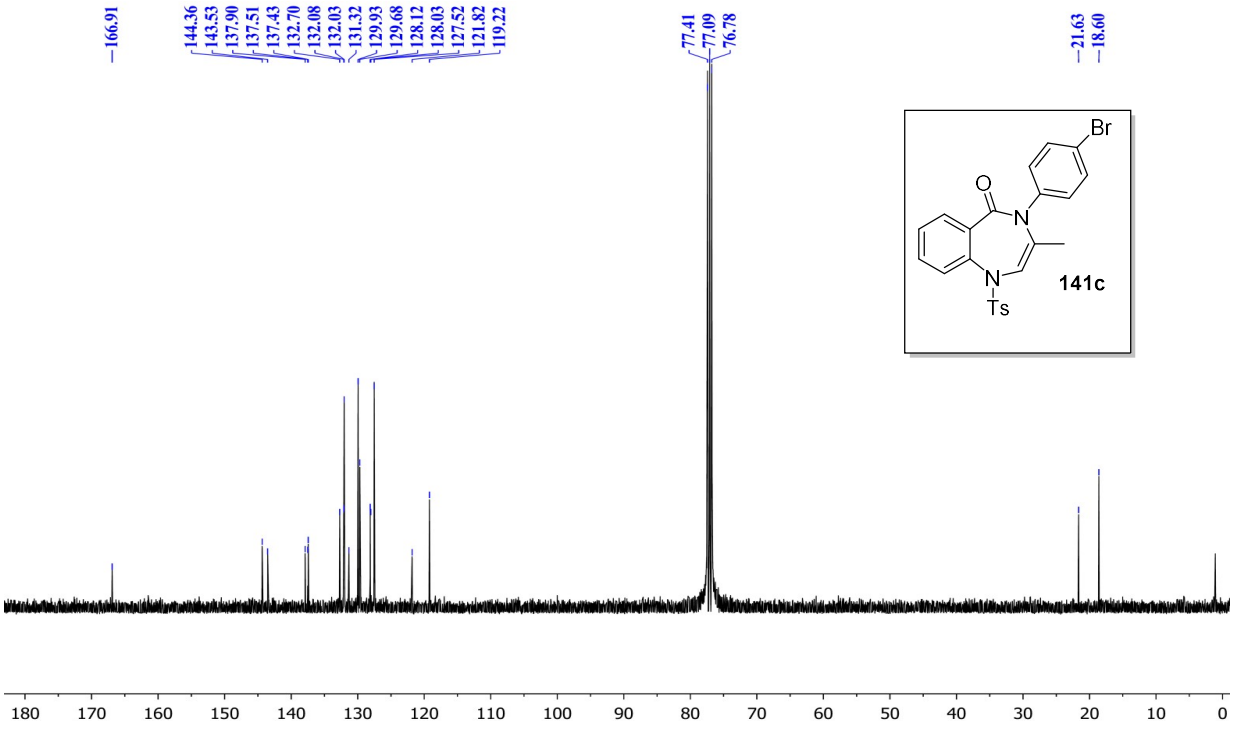
^{13}C{^{1}H} NMR (150 MHz) of **141b**:



^{1}H NMR (400 MHz) of **141c:**



^{13}C{^{1}H} NMR (100 MHz) of **141c**:



1.2.17.13 NMR spectra of products 142a and 142b:

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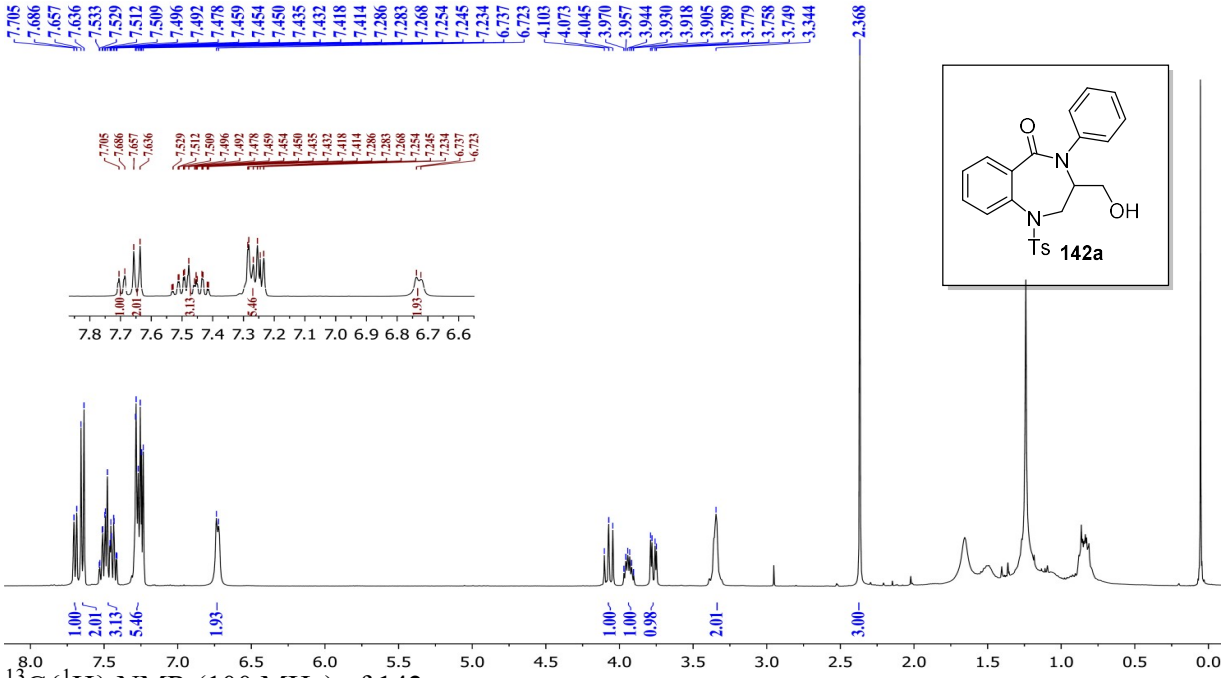
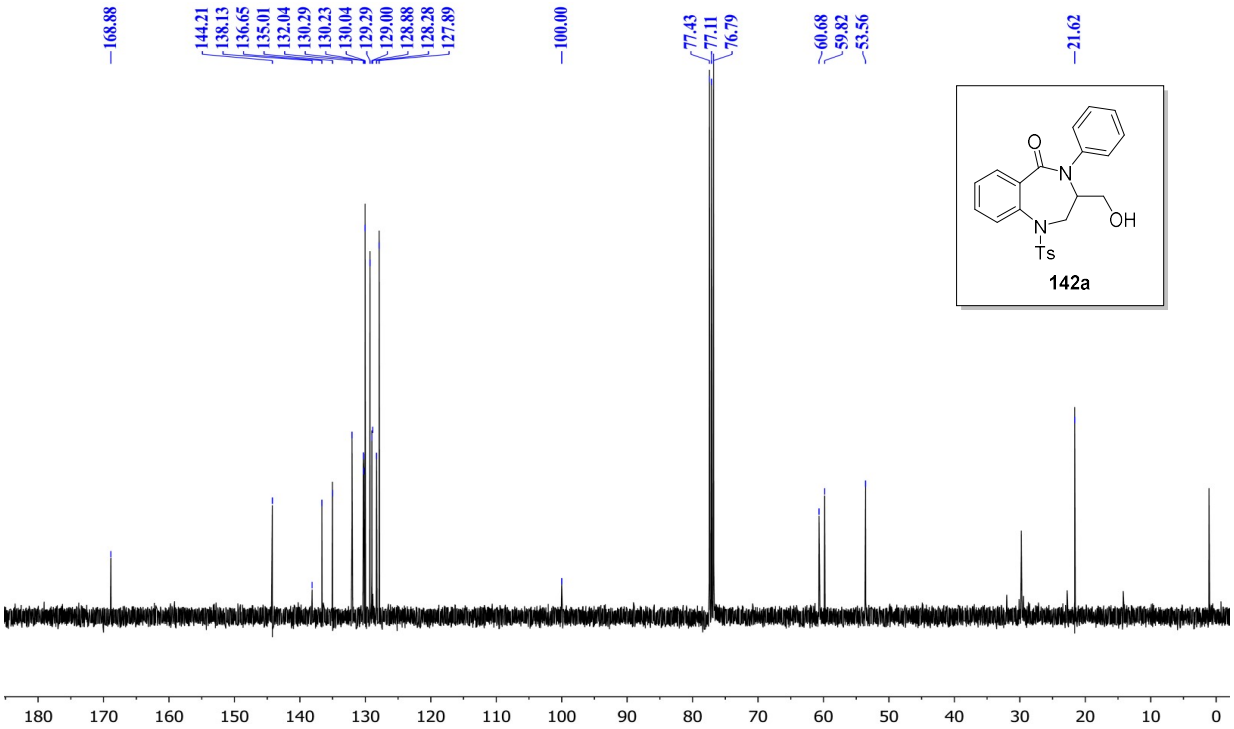
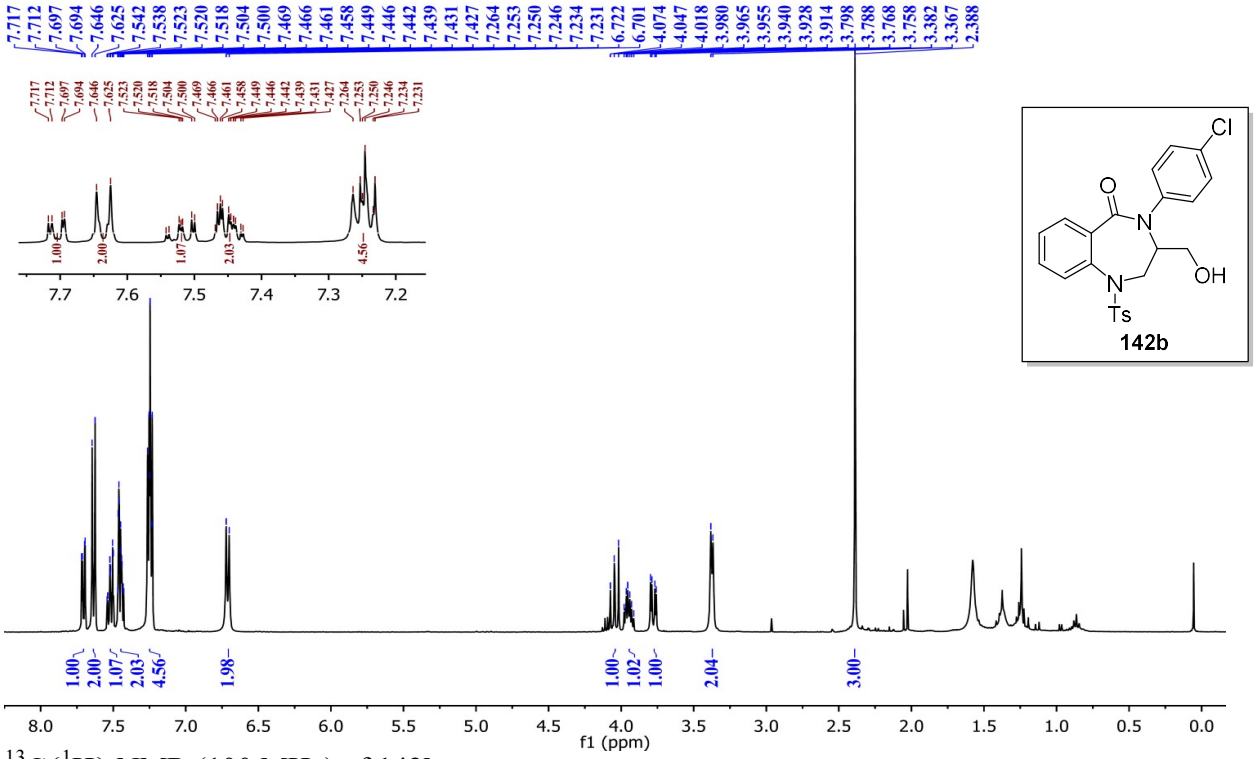


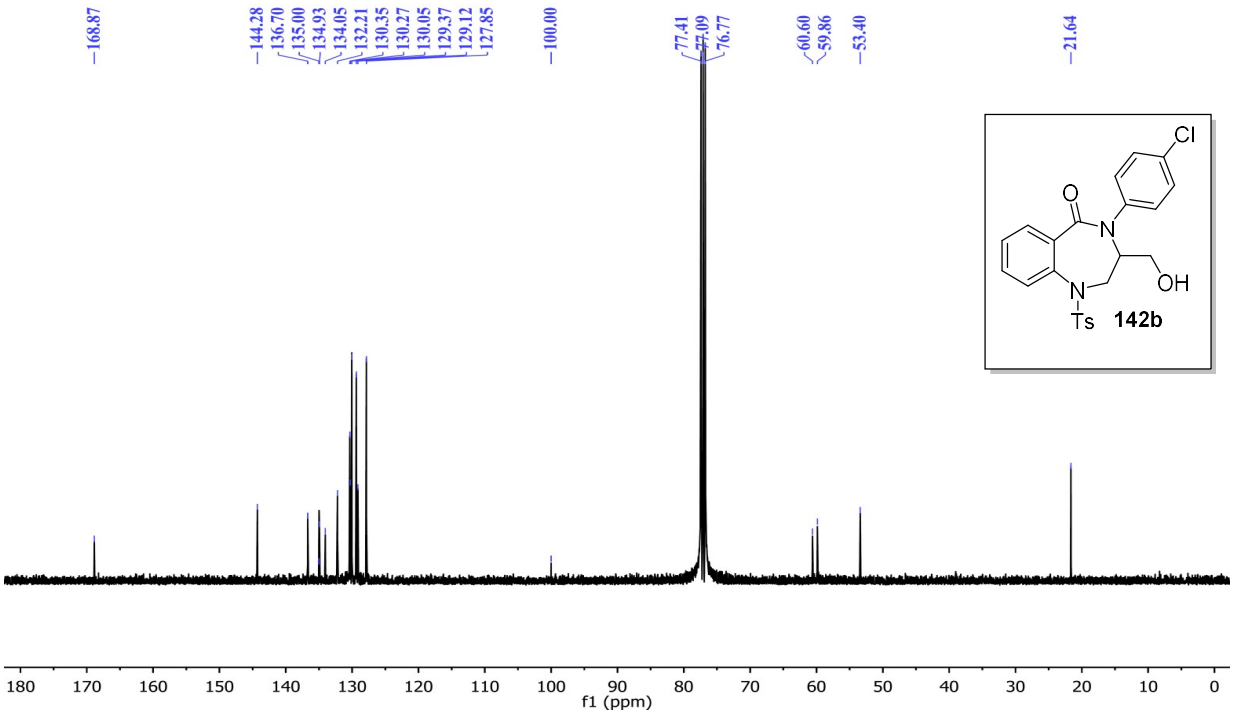
^{13}C{^{1}H} NMR (100 MHz) of **142a**:



^{1}H NMR (400 MHz) of **142b**:



^{13}C{^{1}H} NMR (100 MHz) of **142b**:



1.2.17.14 NMR spectra of products 143a and 143b:

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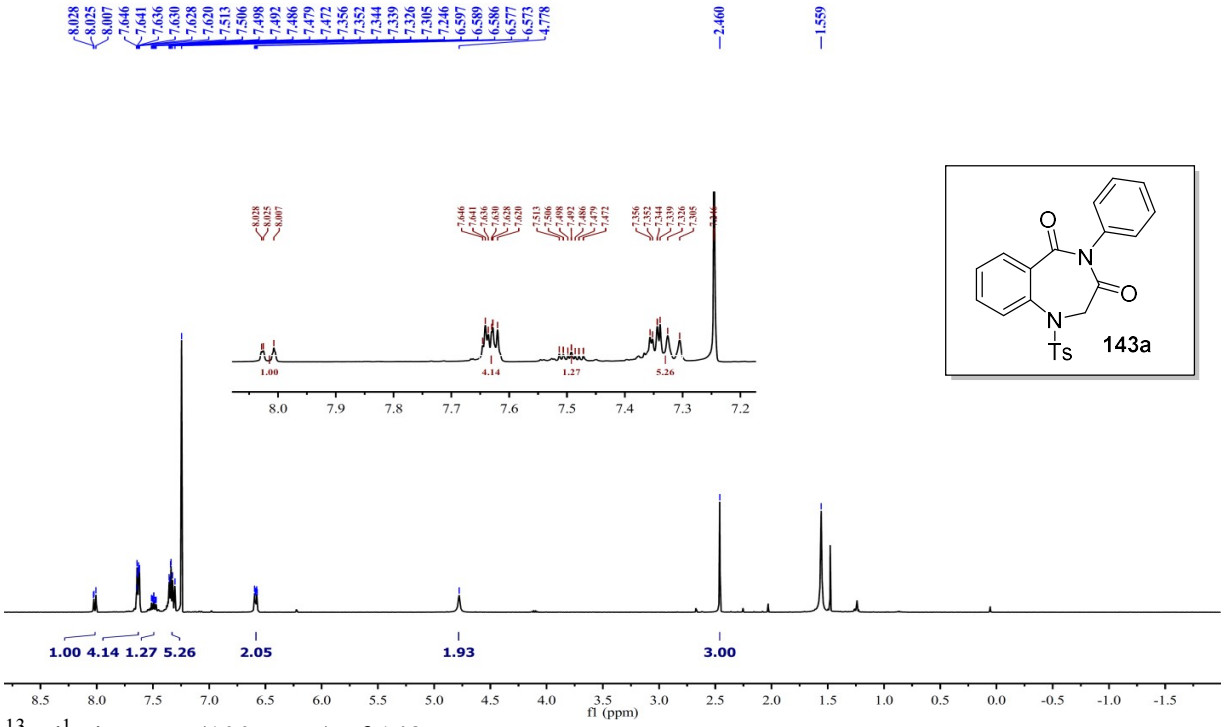
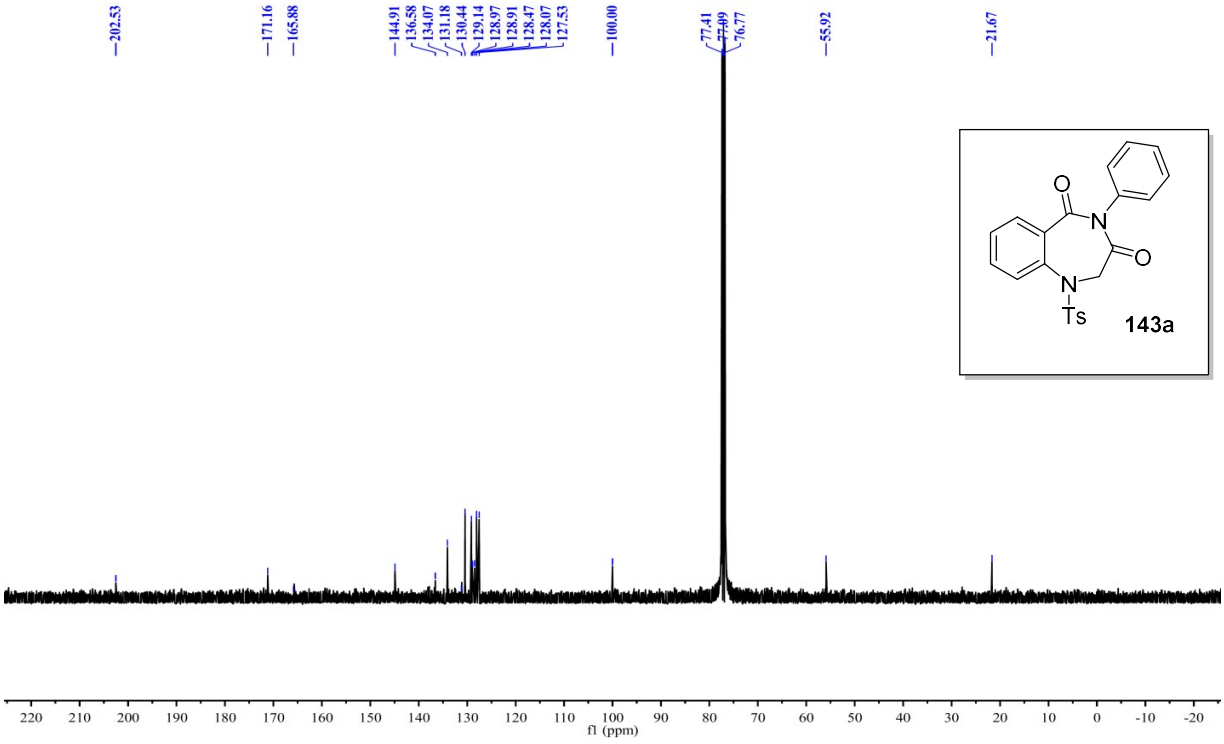
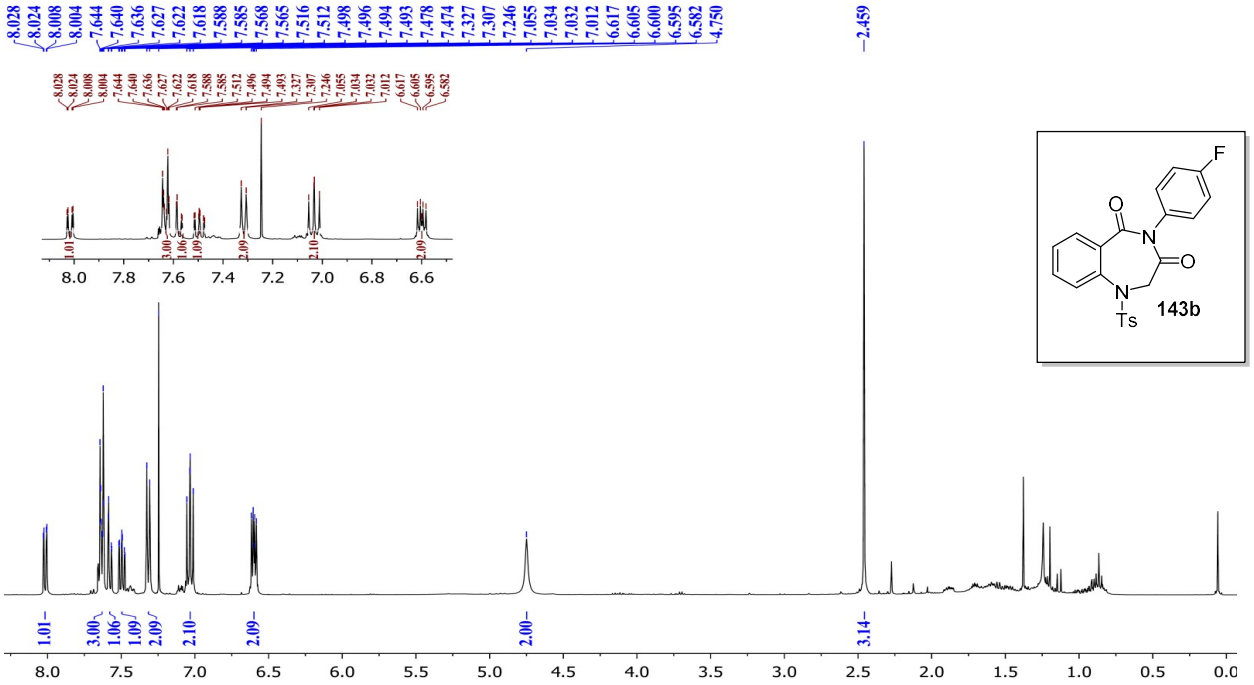


^{13}C{^{1}H} NMR (100 MHz) of **143a**:



^{1}H NMR (400 MHz) of**143b**:



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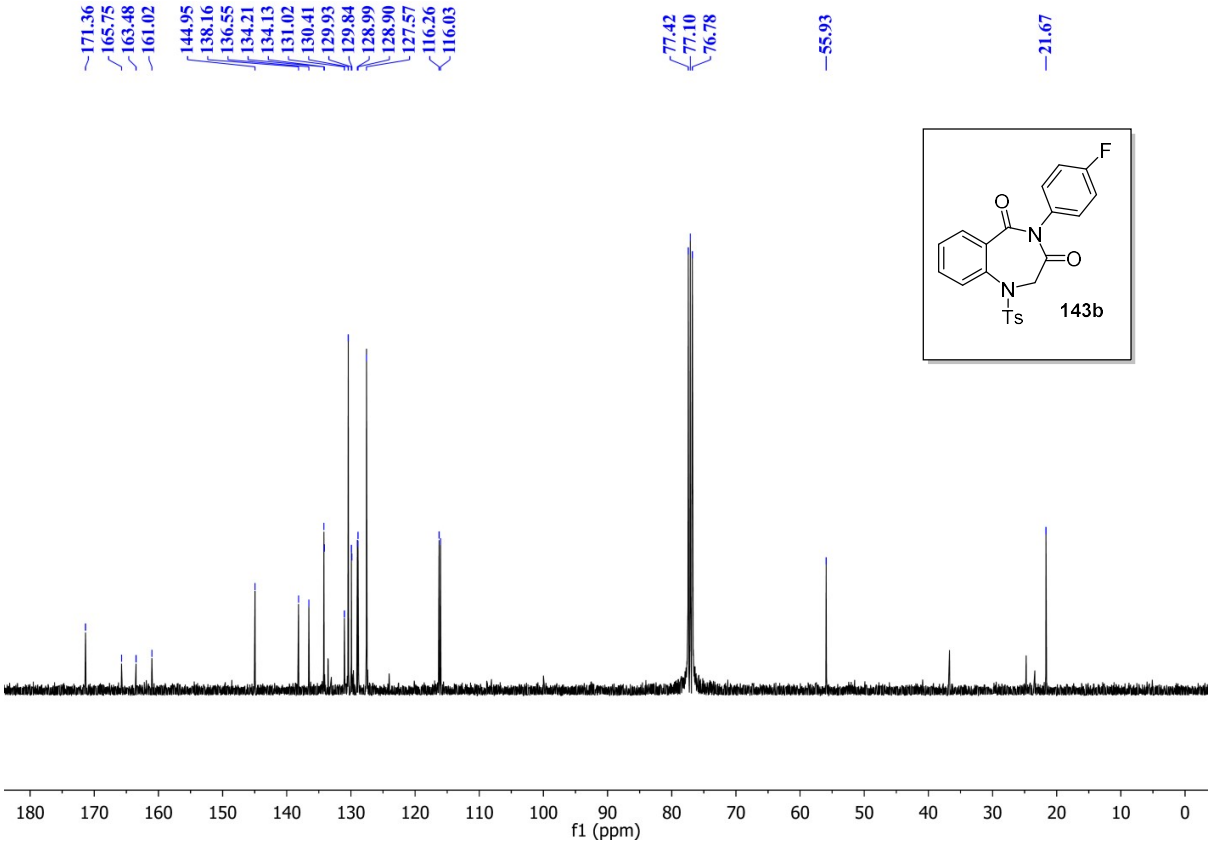

1.2.17.15 NMR spectra of products 144a and 144b:

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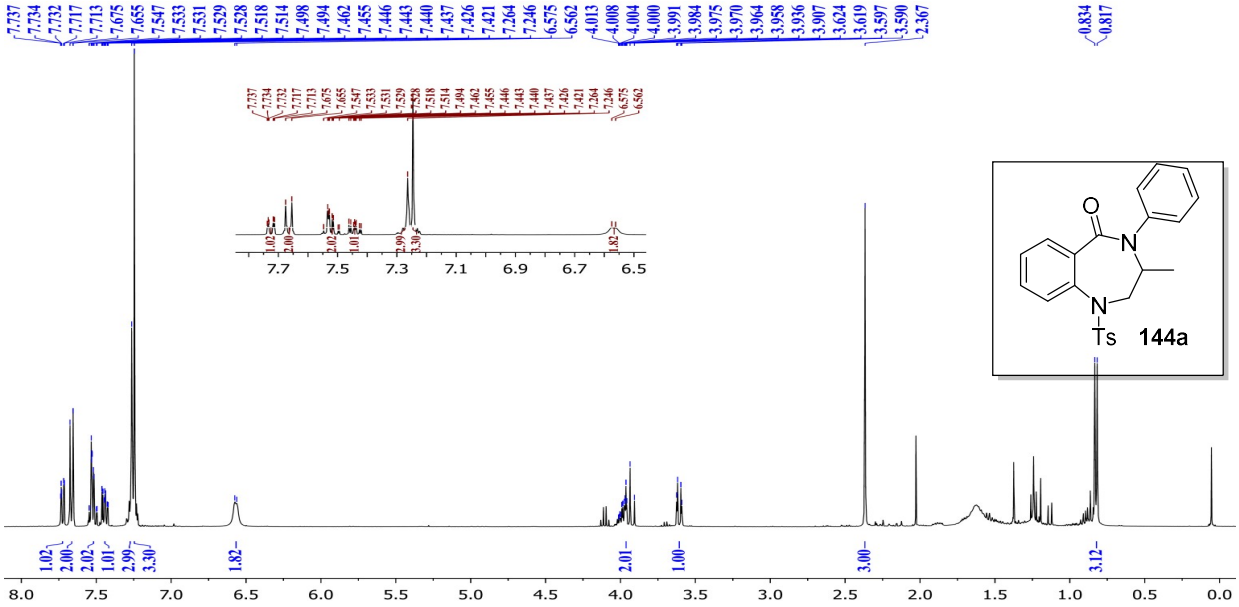
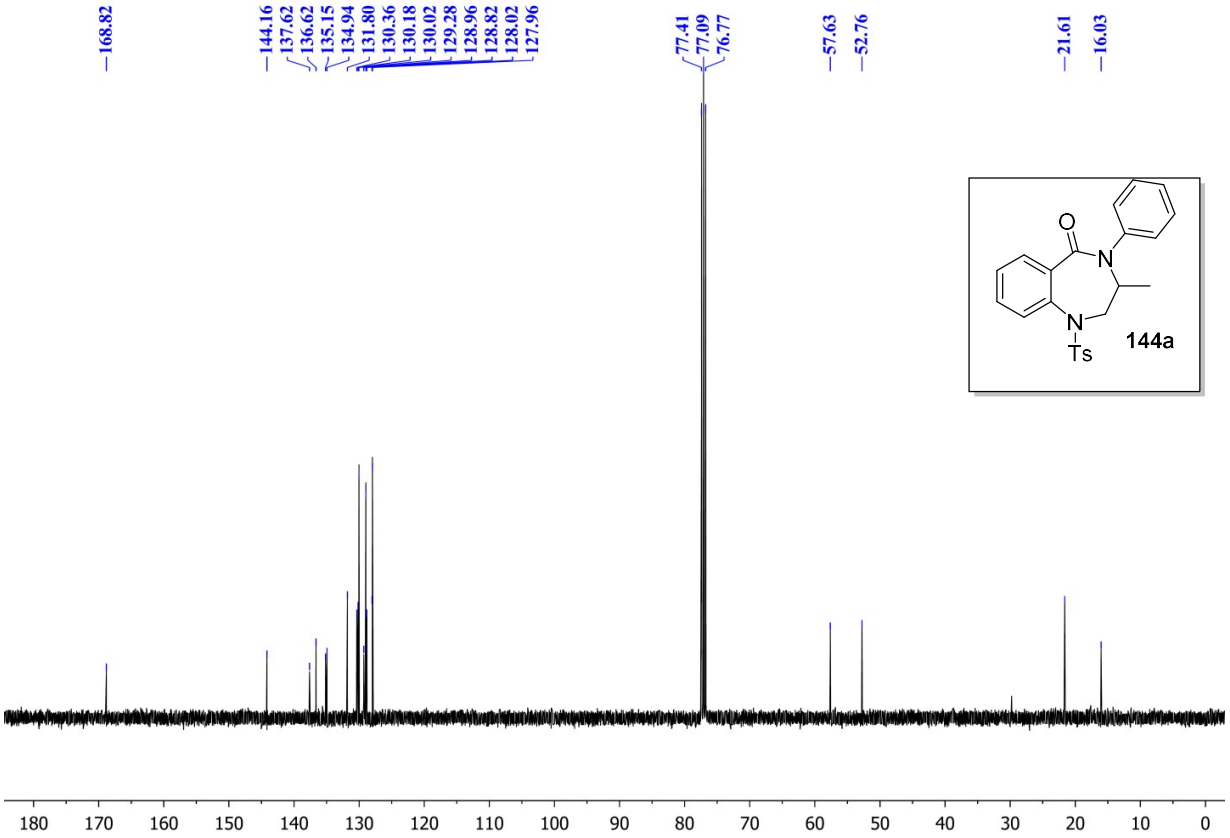
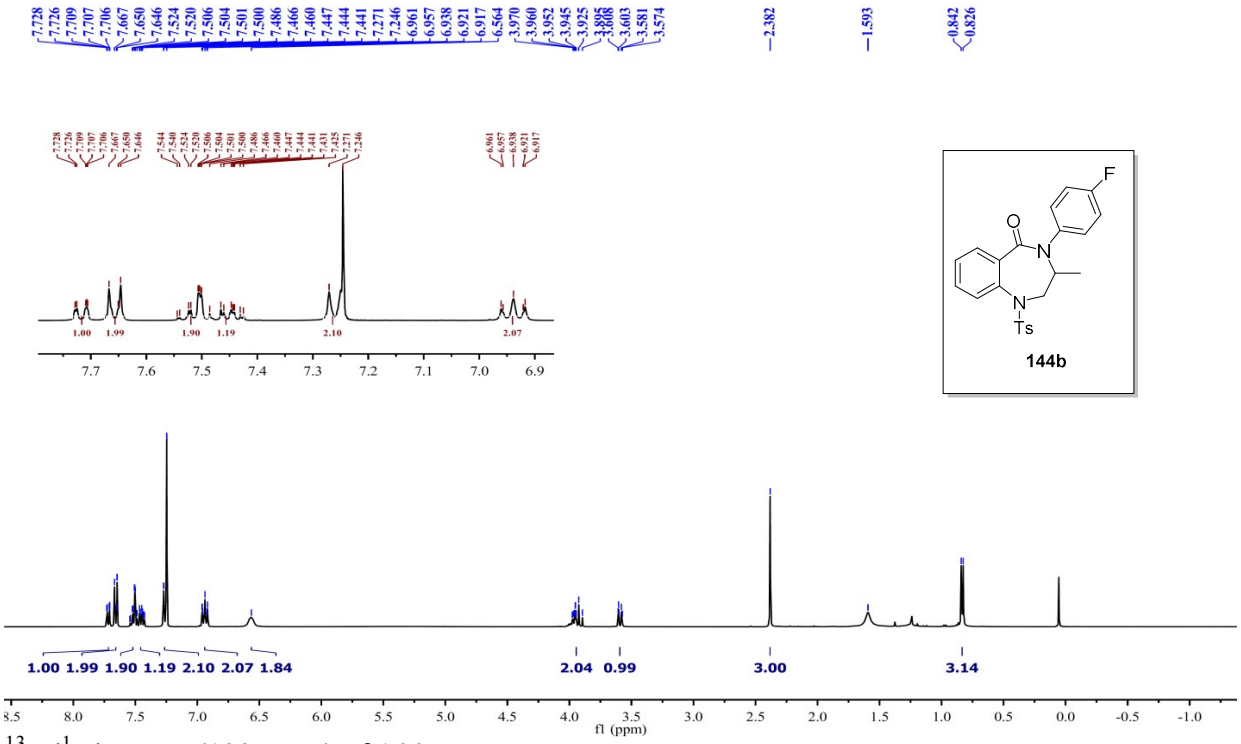


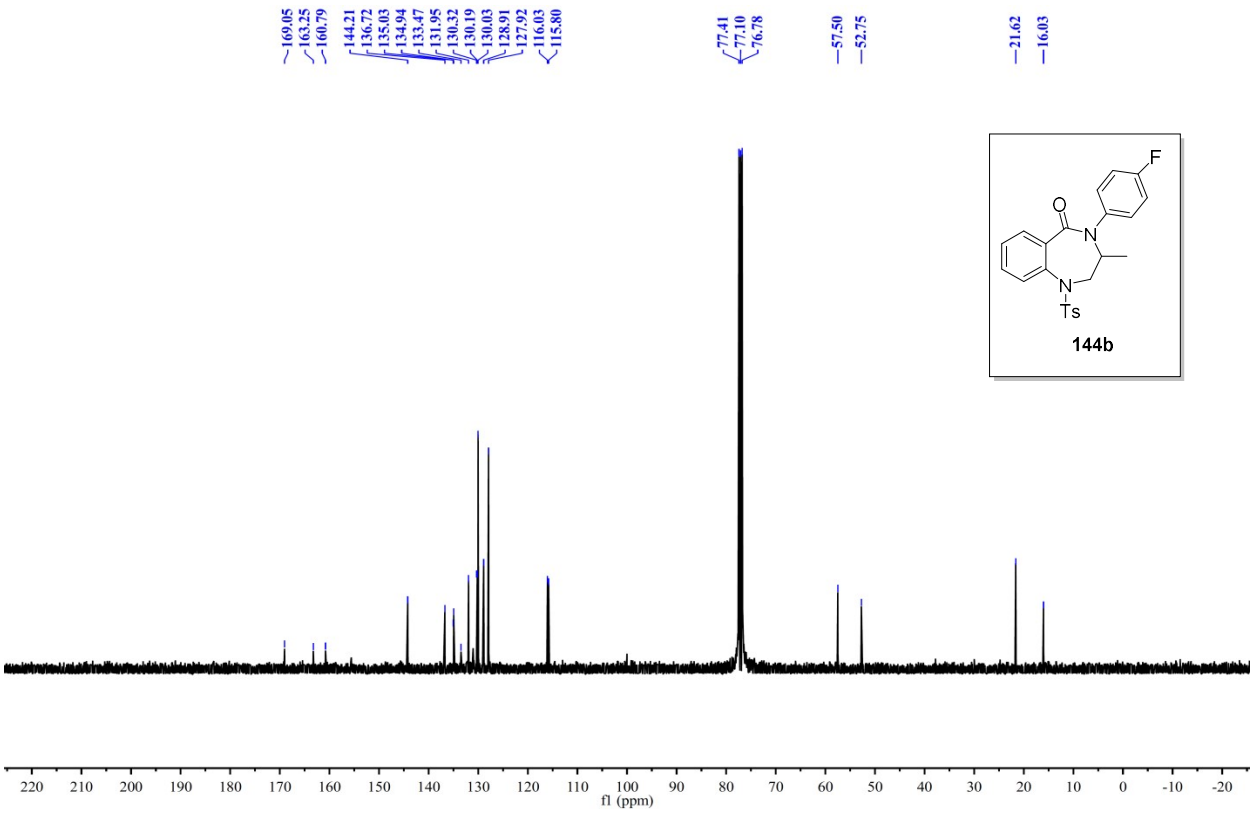
^{13}C{^{1}H} NMR (100 MHz) of **144a**:



^{1}H NMR (400 MHz) of **144b**:



^{13}C{^{1}H} NMR (100 MHz) of **144b**:



CHAPTER 2

Palladium(0)-Catalyzed Heteroannulations of Allenamides: General Synthesis of δ-Carbolines and Benzofuro[3,2-*b*]pyridines

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2.2.1 Introduction

2.1.1.1 Carboline - an important heterocycle

Carboline consisting of a pyridine ring fused with the five-membered ring of an indole with four isomeric skeleton are one of the most important and abundant heterocycles. Carboline is associated with a wide range of high-quality coatings, linings and fireproofing products that enhance durability and resilience of the assets exposed to harsh environments. The fireproofing character of carbolines help to delay the spread of fire and provide critical evacuation time. The isomeric α-, β-, γ-, δ-carbolines (**1**-**4**, respectively, in Figure 1) are important heterocyclic ring systems that are the key structural motifs in natural products. [1]

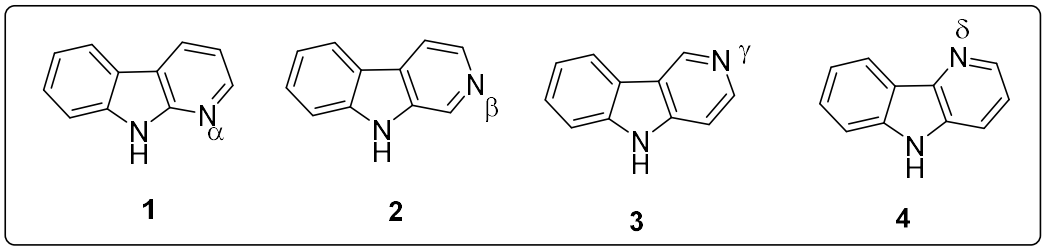


Figure 1: Isomeric α-, β-, γ-, δ-carbolines **(1- 4)**

Carbolines and tetrahydrocarbolines constitute the key structural motif in various natural products, pharmaceuticals, and other compounds of biological[2a,b] and optoeletronical interests.[2c] δ-carbolines (**4**, Fig. 1) are least studied compared to their α-, β-, γ- analogs, though they have received increasing interest in recent times as this scaffold has proven to be a privileged pharmacophore for applications in the design of compounds with wide ranging pharmacological properties[3] (e.g., anti-tumor,[3a] anti-fungal and anti-bacterial,[3b-c]antiplasmodial, antitrypanosomal,[3d] etc.) including drugs, in addition to its prevalence in various natural products[4] and significant applications in material sciences[5].

2.1.1.1.1 Importance of δ-carboline in medicinal chemistry

δ-Carbolines are the privileged structure that have gained significant attention in medicinal chemistry (**4**, fig. 1) due to their diverse biological activities and potential therapeutic applications. δ-carbolines **4** are used as a potential candidates for the treatment of cancer, infectious disease as they have shown various pharmacological properties as discussed earlier. Again, they can interact with receptors for neurotransmitters such as

serotonin, dopamine and gamma-aminobutyric acid (GABA). Medicinal chemist[6] can modify the molecular structure of δ-carbolines to improve their potency, pharmacokinetic properties and other desirable drug-like characteristics. For example, SYUIQ-5[7] (**5**, Fig. 2) is used as a potential cancer therapeutic because SYUIQ-5 could induce the formation of G-quadruplex in telomere structures and induce senescence and telomere shortening in cancer cells. Quindoline derivative, SYUIQ-5 could inhibit the c-myc promoter activity and decrease c-myc expression at both the mRNA and protein levels. SYUIQ-5 could inhibit E2F1 and hTERT expression and induce a delayed apoptosis of HL-60 cells.

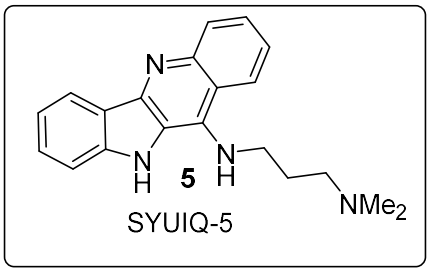


Figure 2: Bioactive natural product having δ-carboline moiety

2.1.1.1.2 Importance of δ-carboline in natural product chemistry

Many bioactive alkaloids containing the the core structure of δ–carboline have also been reported as shown in Figure 3. For example, Jusbetonin[8] (**6**, Fig. 3) the naturally occurring indolo[3,2-*b*]quinoline alkaloid glycoside isolated from Justicia betonica has a unique structure containing β-D-glucose exhibits anti-plasmodial, anti-inflammatory, and antitumor activity. While Cryptolepine **7** and its analogs **8-14** (Fig. 3) have also been reported for their cytotoxicity against B16 melanoma and M109 Madison lung cancer cells.[9]They are also known to interact with topoisomerase II that inhibit DNA synthesis. In addition, alkaloids (**8-14**) have shown remarkable pharmacological activities such as antiplasmodial[10a], antitrypanosomal[10b], antibacterial[10c], antitumor[10d], anticancer[10e] activities. In particular, aromatic ring-fused δ–carbolines such as cryptolepine **7**, cryptolepinone **10**, quindoline **13** have shown potential applications in fluorescent neuroanatomy techniques, organic electroluminescent device materials and flourorescent dyes.[10c]

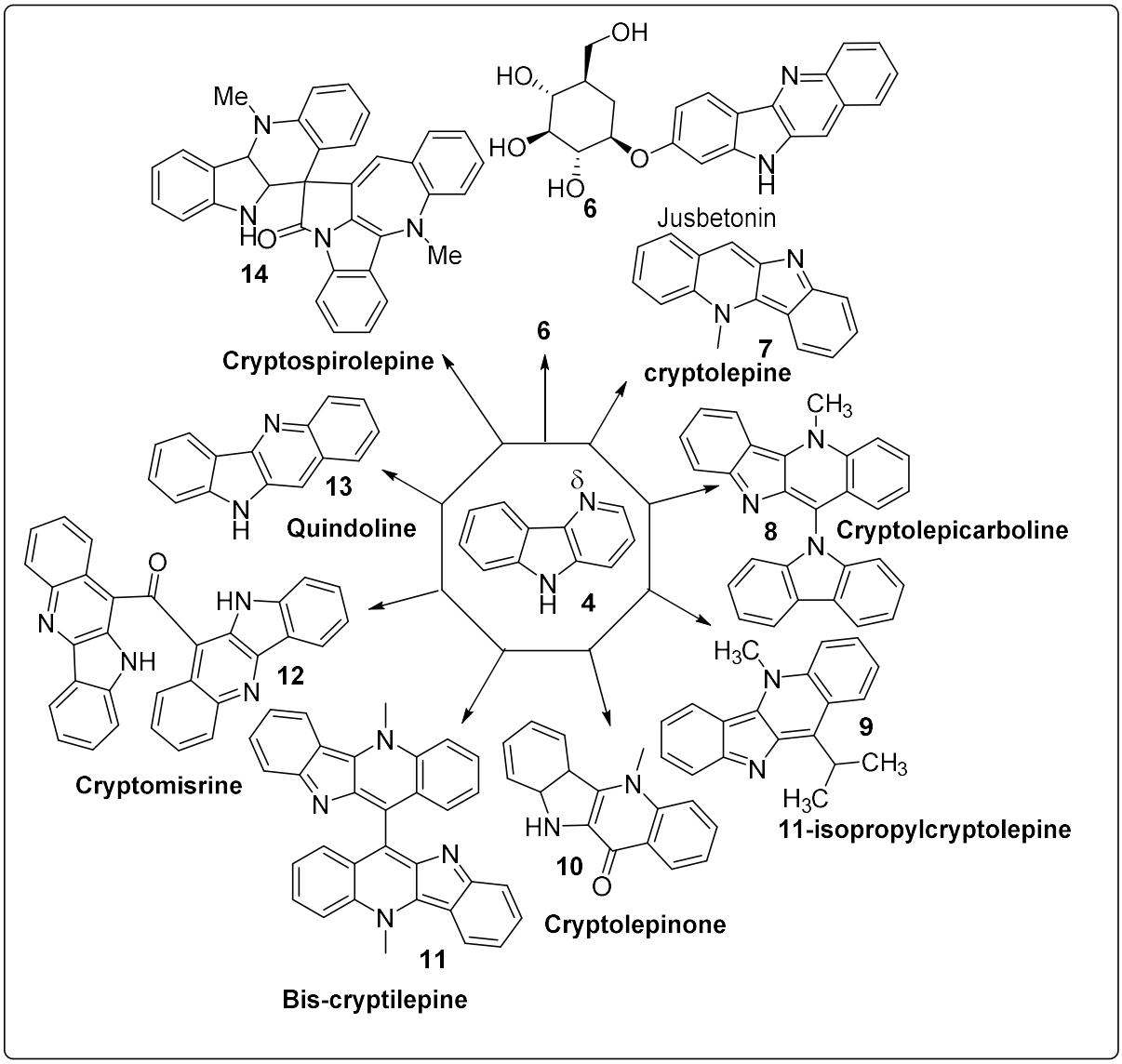


Figure 3: Few naturally occurring bioactive δ-carbolines

2.1.1.1.3 Importance of δ-carboline in material sciences:

δ-Carbolines are well known for their significant role in medicinal chemistry and pharmacology but their applications in material sciences have been limited in few numbers. Unfortunately, they don't possess any inherent properties or structural characteristics that make them well-suited for material application. However, a recent literature[5] reveals that two bipolar host materials namely, 8-(9H-carbazol-9-yl)-5-(pyridin-2-yl)-5H-pyrido[3,2-*b*]indole (CzCbPy) **15** (Fig. 4) and 5- (6-(9H-carbazol-9-yl)pyridin-2-yl)-8-(9H-carbazol-9-yl)-5H-pyrido[3,2-*b*]indole(2CzCbPy) **16** (Fig. 4) were synthesized for deep blue thermally activated delayed fluorescence organic light emitting diodes (TADF OLEDs). Both CzCbPy and 2CzCbPy hosts possess bipolar characteristic with high polarity, which results in high

delayed photoluminescence quantum yields by reducing the energy gap between singlet and triplet states of TADF materials. In addition, these hosts have high enough triplet energies of 3.05 eV to transfer exciton energy to a deep blue TADF emitter. As they act as electron donor or acceptors in organic semiconductors, their incorporation into device structures

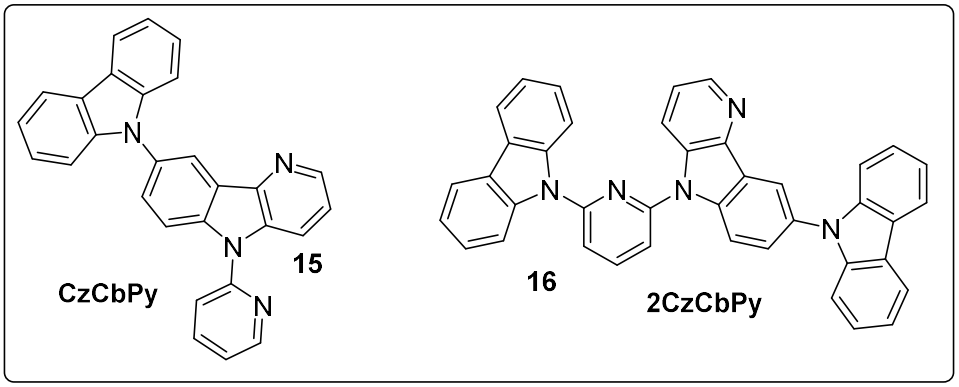


Figure 4: Few important δ-carbolines**15-16** having applications in material sciences

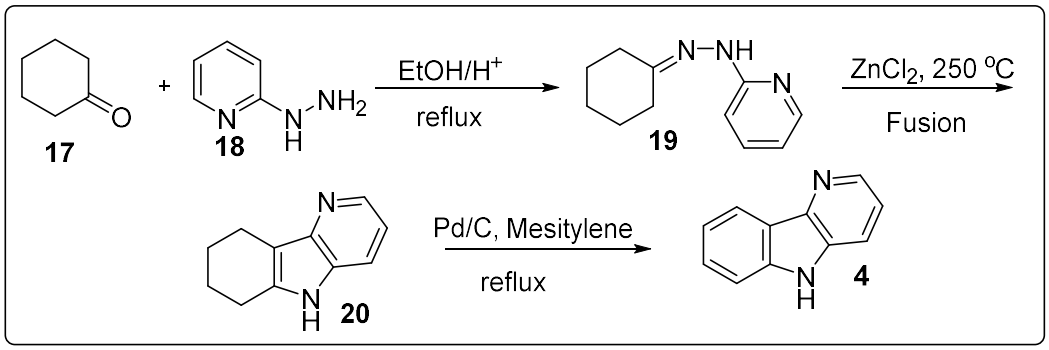
could play a crucial role for the development of efficient organic solar cells, organic light-emitting diodes (OLEDS), organic field effect transistors (OFETS) [5b] etc.

2.1.2. Synthesis of δ-carbolines

The synthesis of δ-carbolines has attracted considerable attention leading to the development of methods utilising classical [11]and metal catalysed reactions.[12] The classical reactions exploited include Fischer reaction,[11a] Graebe-Ullmann reaction,[11b] photochemical cyclization[11c]etc. In the domain of metal catalysed reactions, δ-carbolines are usually prepared through the fusion of either a newly formed pyrrole ring[12a-c] with diarylamine substrates or of a pyridine ring,[12d-g] preformed or generated in situ, with indole substrates. However, applications of the latter strategy have been restricted in numbers, though it appears to be more attractive as functionalization in the pyridine ring can be achieved easily instead of using a pre-functionalized substrate as in the former case. For instance, a Ni(II)-phosphine complex catalyzed [2+2+2] cycloaddition of ynamide-nitriles with alkynes has been reported[12d] by Liu et al. (**Scheme 21**); recently, the metal free version[13] of the same strategy has been adopted in the reactions using either TMSOTf[13a] as catalyst or TfOH[13b] (1.0 eqv.) in stoichiometric amount. In addition, a different approach[13c] using p-TSA is also reported for the synthesis of the same (i.e., **4**) in recent past. Thus, rapid construction of δ-carbolines from simple substrates using novel strategic approach is highly desirable.

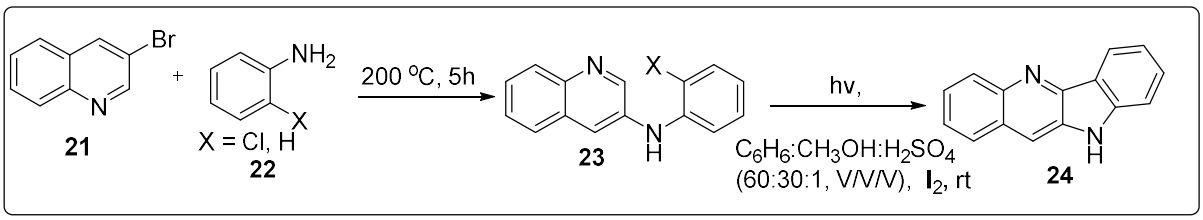
2.1.2.1 Synthetic pathways for the synthesis of δ-carbolines via formation of fused pyrrole ring:

Gupta *et al.*[3a] demonstrated the cyclization of cyclohexanone **17** with 2-pyridylhydrazine **18** to deliver iminium-intermediate **19** which underwent subsequent [3,3]-sigmatropic rearrangement (as adopted in Fisher indole reaction) triggering the formation of tetrahydrocarbolines **20** with the loss of ammonia. Thereafter the treatment of intermediate **20** with Pd/C delivered the product **4**. This is a modification of Fisher indole reaction for the synthesis of δ-carboline moiety as shown in **Scheme 1**.



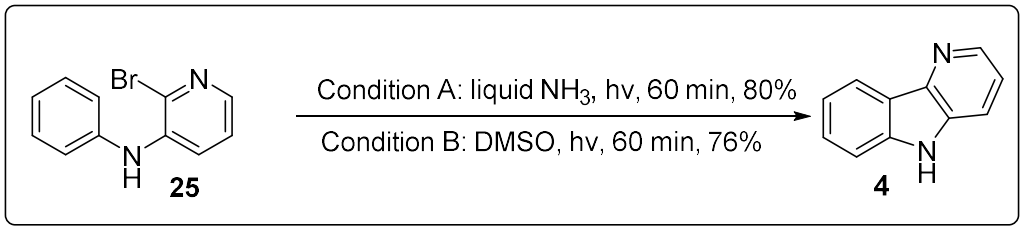
Scheme 1: Synthesis of δ-carboline

Dhanabal and coworkers[11c] demonstrated an efficient and novel approach for the preparation of benzofused δ-carboline **24** starting from commercially available 3-bromoquinoline **21** and aniline **22** (**Scheme 2**). Aniline **22** reacted with 3-bromoquinolines at elevated temperature (i.e., 100-200 °C) to generate intermediate **23** which undergoes regioselective intramolecular cyclization under photochemical conditions to generate product **24**.



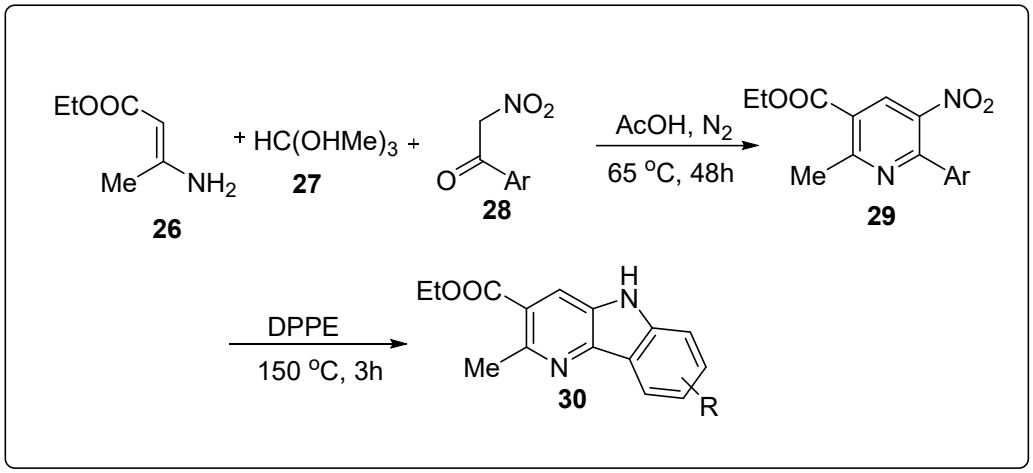
Scheme 2: Synthesis of benzofused δ-carbolines **24**

Laha and co-workers[14] adopted one-pot synthesis of δ-carbolines **4** via photo-stimulated unimolecular radical nucleophilic substitution ($S_{RN}1$). 3-anilino-2-bromopyridine **25** undergoes intramolecular nucleophilic substitution reaction under photochemical conditions (i.e., A or B) to generate the product **4** in 76-80% yields (**Scheme 3**).



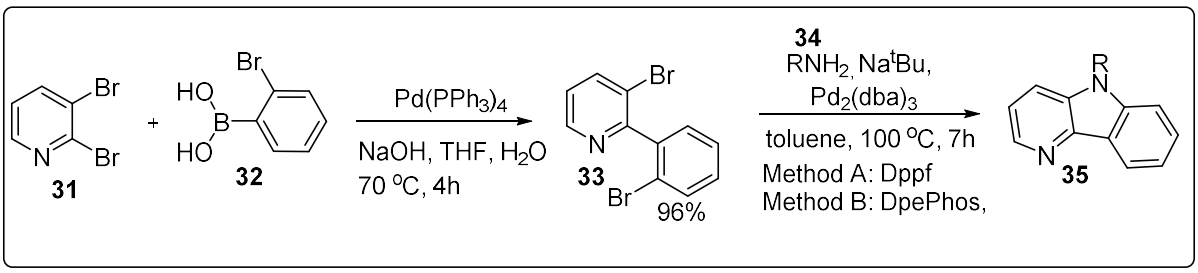
Scheme 3: Synthesis of δ-carbolines **4**

Shuvalov[15] *et al*. reported the synthesis of δ-carbolines **30** obtained through the "*Cadogan Reaction*" using DPPE under solvent-free conditions. In the first step of this reaction, the well-known "*Hantzsch Pyridine Synthesis*" was applied by allowing the reaction between amine **26**, ortho-ester **27** and ketone **28** to construct the nitro pyridine ring **29** which then underwent the aforesaid "*Cadogan Reaction"* under nitrogen atmosphere to afford the desired δ-carbolines (**Scheme 4**).



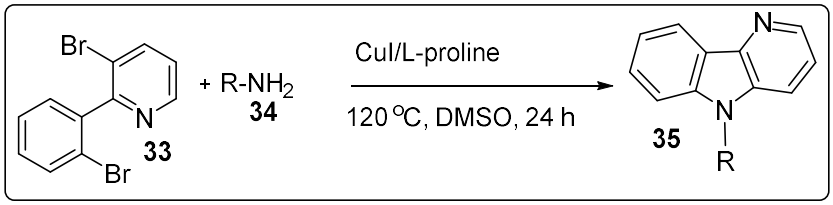
Scheme 4: Synthesis of substituted δ-carboline **30**

Hung and co-worker [2c] demonstrated the palladium catalysed site-selective two step synthesis of δ-carboline via *Suzuki-Miyara* reaction between commercially available 2,3-dibromopyridine **31** and 2-bromophenyl boronic acid **32** leading to the generation of bi-aryl intermediate **33** in excellent yield (96%). Intermediate **33** then undergoes palladium-catalyzed two-fold C-N coupling reactions to furnish δ-carboline **35** as depicted in **Scheme 5**.



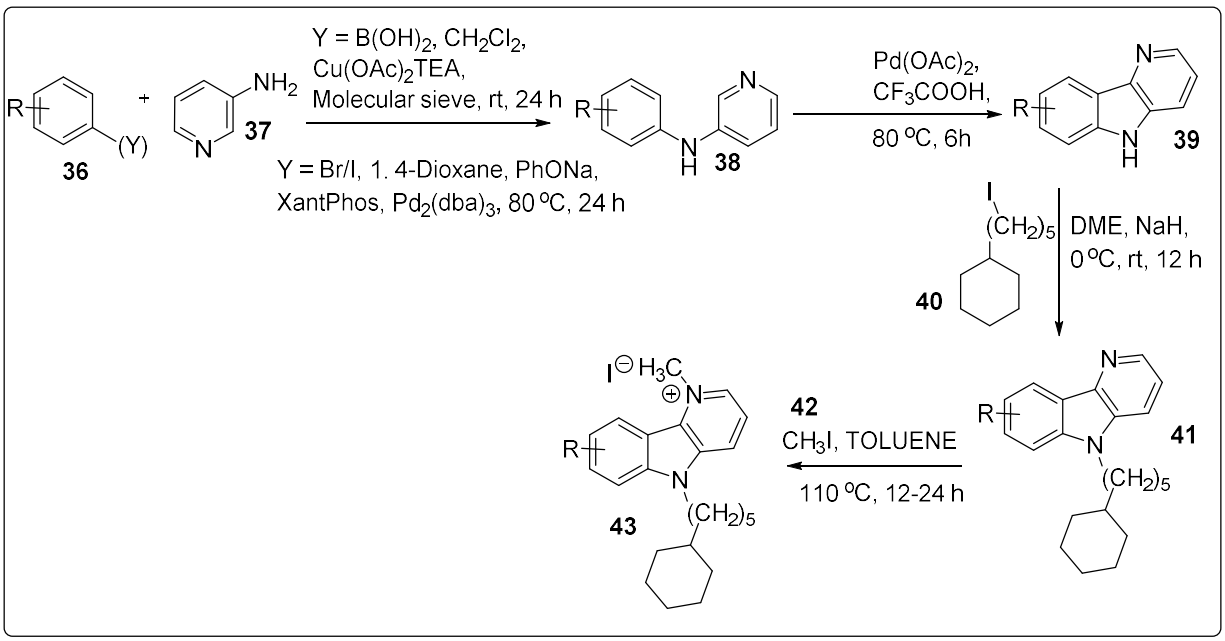
Scheme 5: Synthesis of N-substituted δ-carboline **35**

Phuc and coworkers[16] described an efficient and practical approaches for the synthesis of δ-carbolines from 2,3-dibromopyridine **35**. The reaction strategy was almost similar to previous one (**Scheme 5**) but copper (I) catalyst (instead of palladium catalyst) with proline ligand was used in DMSO at 120 °C for 24 h.



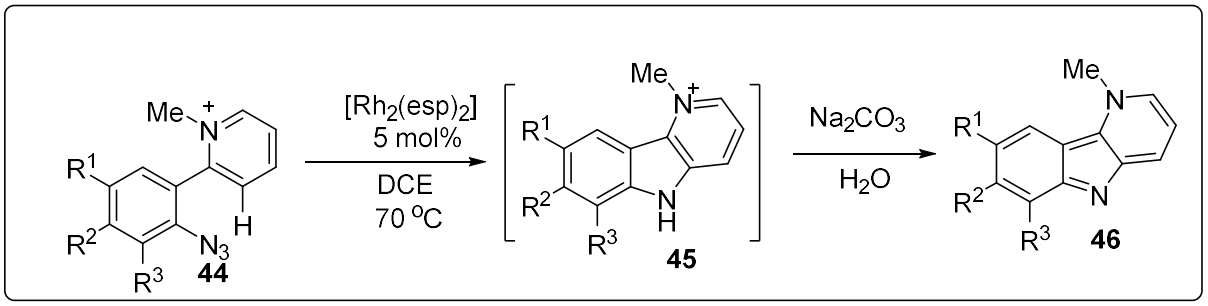
Scheme 6: Synthesis of N-substituted δ-carbolines **35**

Mazu[3c] *et al*. reported a convenient method for the preparation of δ-carbolines **43** starting from commercially available substituted aryl boronic acid **36** and 3-aminopyridine **37** (**Scheme 7**). In first step, intermediate product **38** is formed via copper (I) catalysed amination reaction between **36** and **37**. Thereafter, intermediate **38** undergoes self-cyclization under palladium-catalysed reaction conditions to generate product **39**. Next, -NH group of δ-carboline **39** reacts with alkyl iodide **40** in the presence of a base (NaH) to furnish the intermediate compound **41** which upon treatment with methyl iodide (**42**) generates a carbolinium salt **43**.



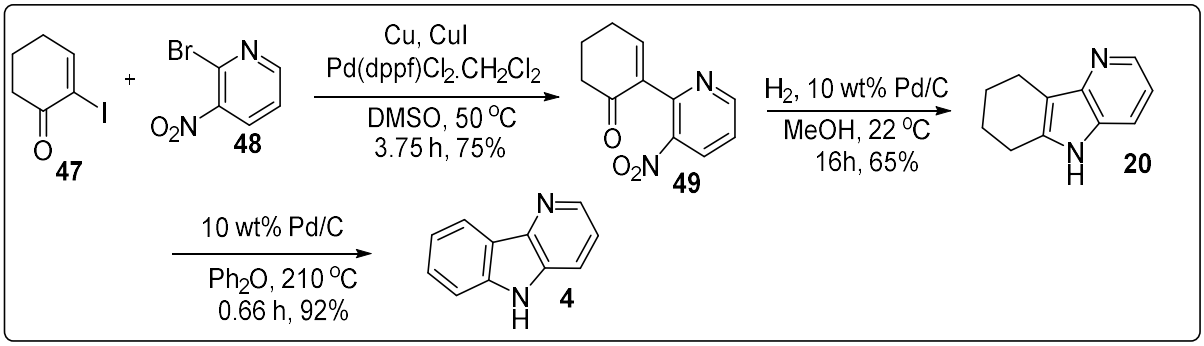
Scheme 7: Synthesis of N-alkylated δ-carboline **43**

Pumphrey *et al.*[12a] proposed a more convenient method where *ortho*-substituted aryl azide **44** undergoes C-H bond amination through Rh-catalysed condition to generate δ-carbolinium ion **45**. Next, dearomatization of the δ-carbolinium ion **45** by using aquous Na_2CO_3 easily generates product **46** (**Scheme 8**).



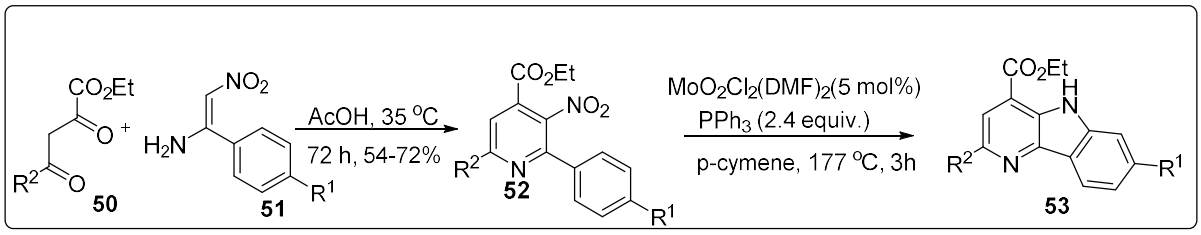
Scheme 8: Synthesis of substituted δ-carboline **46**

Yan and co-worker [12c] demonstrated an expedient and facile route for the general synthesis of δ-carbolines **4** where 2-iodocyclohex-2-en-1-one **47** undergoes palladium catalysed *Ullmann Cross-couping* reaction with 2-bromo-3-nitropyridine **48** to afford the intermediate product **49** (**Scheme 9**). Thereafter, the product **49** undergoes reductive cyclization to generate tetrahydrocarboline **20** which upon aromatization/oxidation under the treatment of Pd/C at elevated temperature delivered the desired product **4**.



Scheme 9: Synthesis of substituted δ-carbolines **4**

Shuvalov *et al.* [17] described "*Cadogan reductive cyclization*" for the construction of substituted 2-aryl-3-nitropyridines **52** which is then converted to δ-carbolines **53** with the aid of $MoO_2Cl_2(DMF)_2$ catalyst in the presence of triphenylphosphine as a reducing agent (**Scheme 10**).



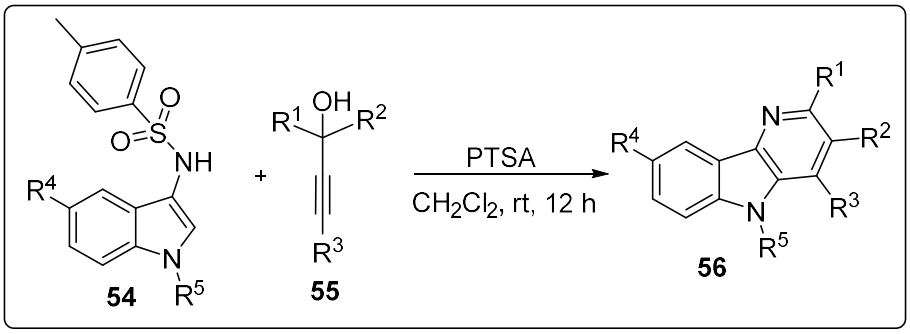
Scheme 10: Synthesis of substituted δ-carboline **53**

2.1.2.2. Synthesis of δ-carbolines from indole substrates:

In addition to the aforesaid strategy of pyrrole ring formation, synthesis of δ-carbolines from indole substrates has also been accomplished by adopting the strategy of pyridine ring formations involving either inter or intra-molecular reactions. Nevertheless, the later method of transformations of indole substrates to δ-carbolines primarily relies on *Friedel-Crafts* reaction carried out either one pot or multi-steps where C-N bonds are formed either through Lewis acid catalyst or by using conventional protocol. Few of them are illustrated below.

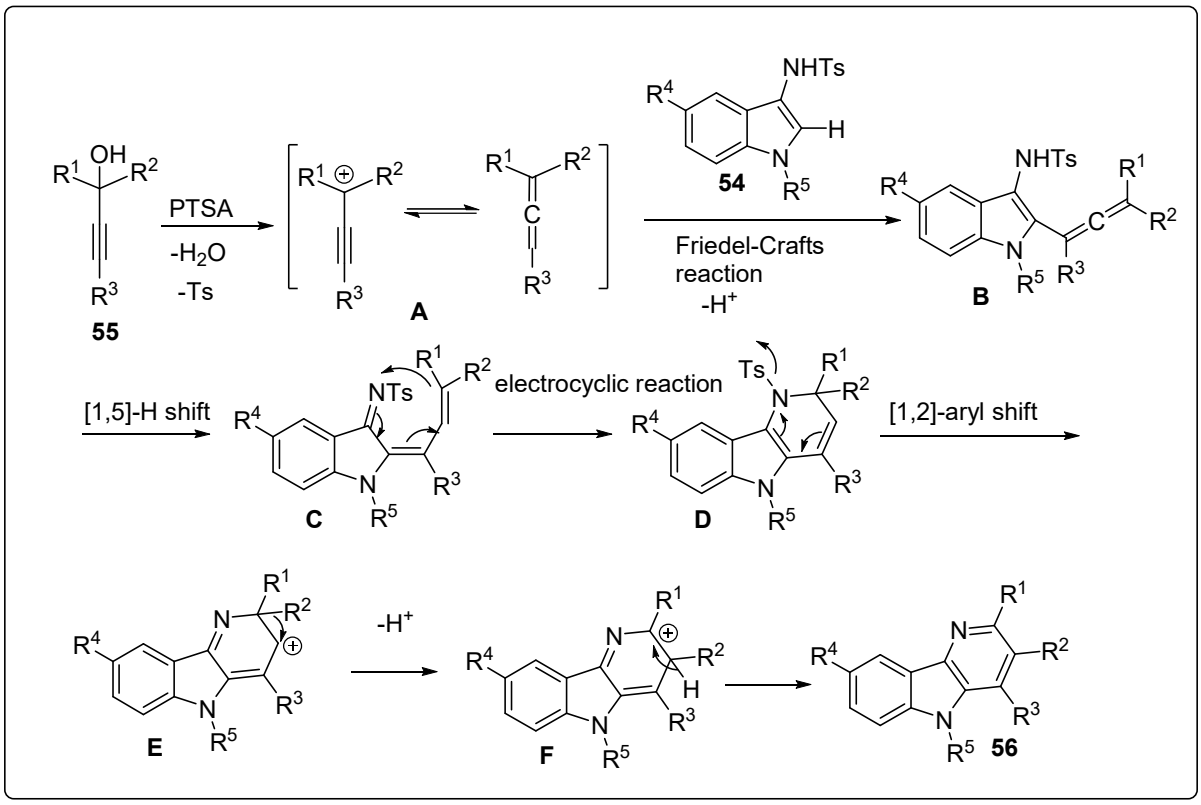
2.1.2.2.1 One pot reaction for the synthesis of δ-carbolines from indole substrates using Lewis acid catalyst:

Selvaraj *et al.*[13c] reported transition metal free, Brønsted acid mediated cascade sequential reaction between sulfomido-indoles **54** and propargyl alcohol **55** to synthesize highly substituted δ-carbolines **56**. The reaction protocol involves cascade reaction sequences of Friedel-Crafts alkylation/[1,5]-hydrogen shift/electrocyclization/elimination/[1,2]-aryl migration followed by aromatization.



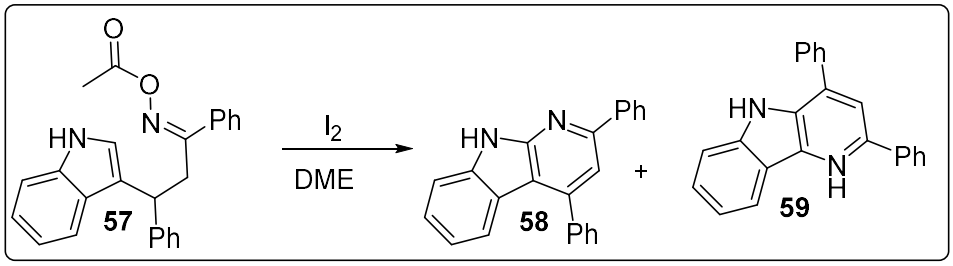
Scheme 11: Synthesis of δ-carboline derivatives **56**

A plausible reaction mechanism for the formation of **56** is illustrated under **Scheme 12**. Initially, propargylic alcohol **55** is converted into the allenic carbocation **A** in presence of Lewis acid (i.e., PTSA) via *Meyer Schuster rearrangement*, which would then undergo *Friedel-Crafts-type reaction* with **54** to generate the allene intermediate **B**. Then, intermediate **B** then undergoes [1,5]-hydride shift to form imine intermediate **C**. The intermediate **C** undergoes 6π-electrocyclization and in-situ elimination of *p*-toluenesulfonyl anion to produce intermediate **E**. After that intermediate **E** undergoes [1,2]-aryl group migration to afford intermediate **F** which upon subsequent aromatization delivers δ-carbolines **56**.



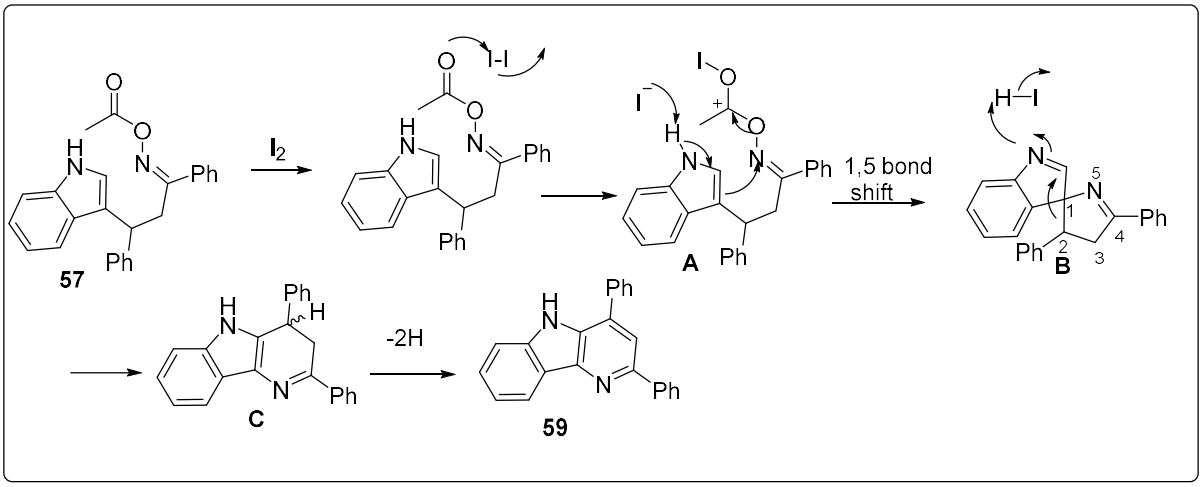
Scheme 12: Plausable mechanism for the formation of substituted δ-carbolines **56**

Yang *et al.*[12e] elaborated a elegant reaction of δ-carbolines **59** starting from common indolylchalcone oxime ester precursor **57.** In addition to the desired product **59**, another α-carboline derivative **58** was also generated in minor amount. The reaction involves mild reaction conditions and uses a region-divergent approach.



Scheme 13: Synthesis of substituted δ-carbolines **59**

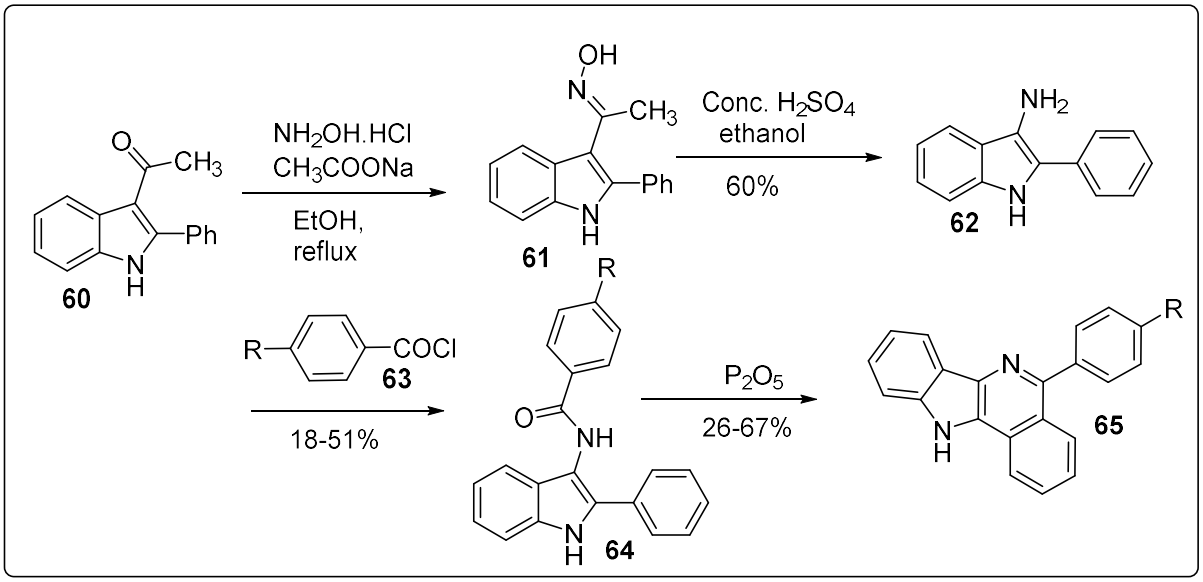
A plausible reaction mechanism is shortly elaborated in **scheme 14**. The treatment of indolylchalcone oxime esters **57** with a Lewis acid catalyst I_2would generate an iminium ion **A** which subsequently forms a common intermediate spiro-indole derivative **B** through the nucleophilic attack of the C3 carbon of the indole to the iminium ion . Further, this spiroindole derivative **B** would undergo 1,5-bond migration to generate intermediate **C** that undergoes aromatization to furnish δ-carboline **59**. The electron density of the C1-C5 bond is higher compared to the C1-C2 bond which would result in the formation of the δ-carboline **59** derivative as a major product.



Scheme 14: A Plausable reaction mechanism for the formation of δ-carboline **40**

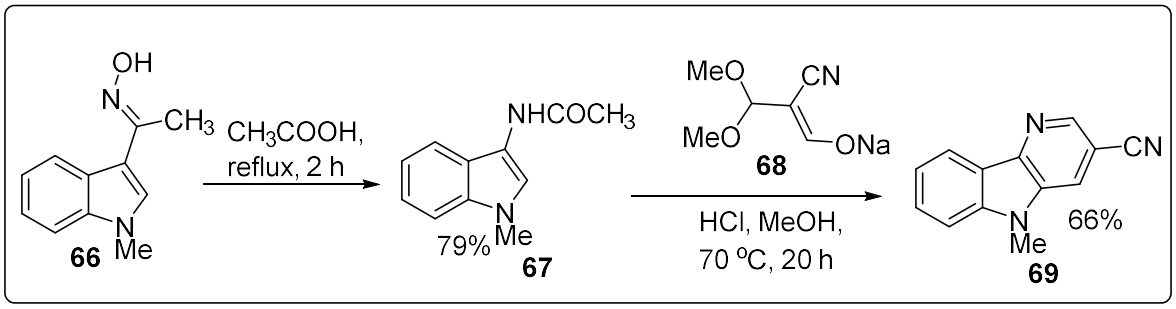
2.1.2.2.2 Multi-step reaction for the construction of δ-carbolines starting from indole substrates:

Qu and coworkers[18] developed a concise and synthetic strategy for the construction of δ-carboline **65** via Beckmann rearrangement of 2-phenylindole-3-oximes **61** through acid-catalyzed cyclization of 3-amino-2-phenylindoles **62**. Firstly, treatment of 3-acetyl-2-phenylindoles **60** with hydroxylamine hydrochloride in 95% ethanol containing sodium acetate gave the corresponding 2-phenylindole-3-acetoximes **61** in 85% yield. Next, compound **61** undergoes Beckmann rearrangement under the treatment of concentrated sulfuric acid in acetonitrile under reflux for 2–6 h to furnish 3-amino-2-phenylindole **62** in 54% yields. Then, treatment of 3-amino-2-phenylindole **62** with 4-substituted benzoylchlorides **63** in the presence of sodium bicarbonate gave the corresponding 3-benzamido-2-phenylindoles **64** (**Scheme 15**). The cyclization of 3-benzamido-2-phenylindoles **64** to give the 11*H*-indolo[3,2-*c*]isoquinolines **65** was achieved by heating with P_2O_5 in toluene in moderate yields.



Scheme 15: Synthesis of benzofuro δ-carbolines **65**

Papamicaël *et al.* [19] demonstrated an efficient and direct preparation of functionalized δ-carboline **69** via ring closure reaction between appropriate indole amine **67** and a masked 1,3-dicarbonyl compound **68** (**Scheme 16**). According to previous reported method,[3b] compound **66** was easily prepared from their corresponding ketone after the treatment of $NH_2OH.HCl$. Then, compound **66** undergoes *Backmann rearrangement* under refluxing acetic acid to generate 3-acyl-aminoindole **67**. Next, the amine derivative **67** reacted with masked 1,3-dicarbonyl compound **68** to generate δ-carboline **69** with 66% yield.

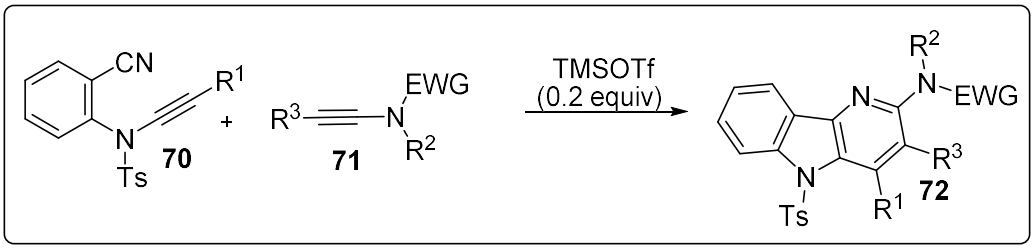


Scheme 16: Synthesis of benzofuro δ-carboline **69**

2.1.2.3. Synthesis of δ-carbolines via in situ formations of pyrrole and pyridine rings

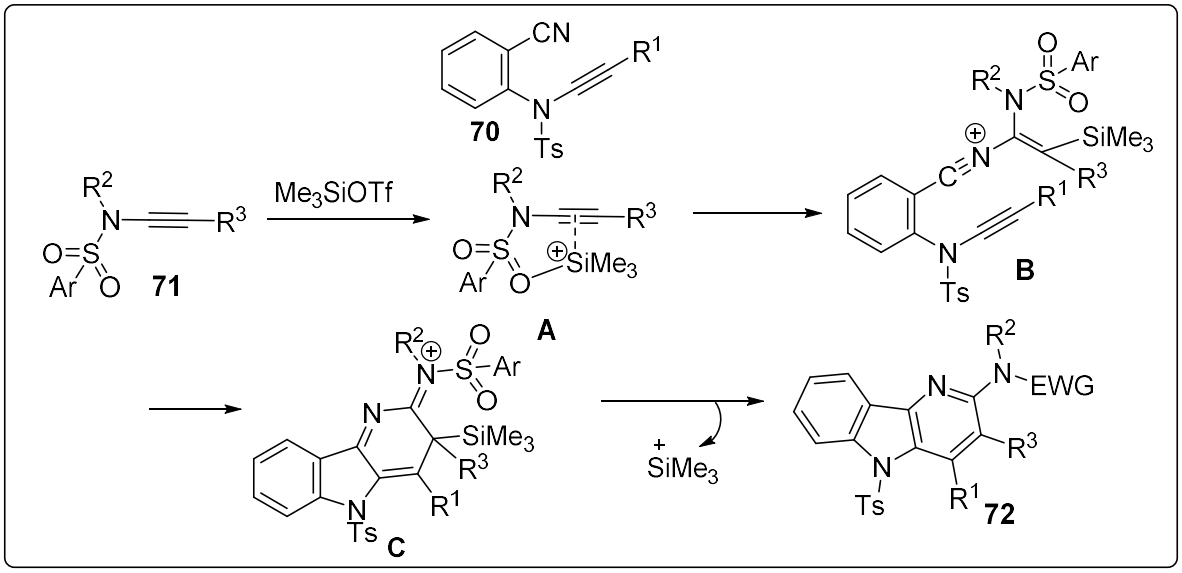
2.1.2.3.1 Metal free reaction:

Zhang and co-worker [13a] proposed a novel and highly efficient TMSOTf-catalyzed [2+2+2] cycloaddition reaction of alkyne-cyanamide **70** and ynamide**71** as shown in **Scheme 17**.



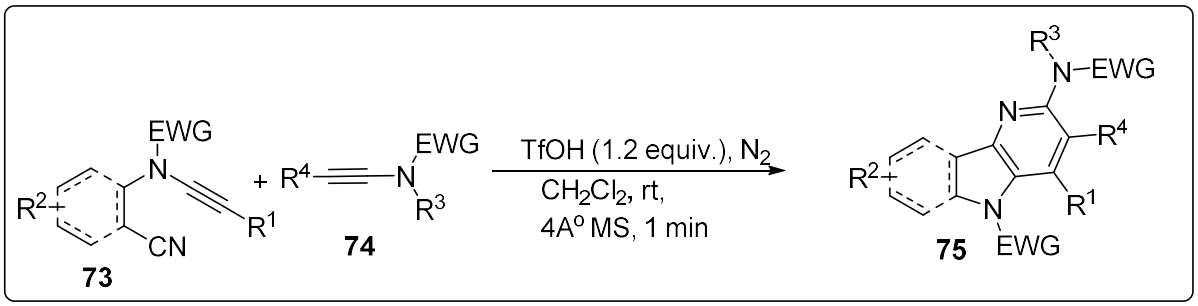
Scheme 17: Synthesis of substituted δ-carboline **72**

The proposed mechanism is described herein. Initially, ynamide **71** would coordinate with TMSOTf to generate π-alkyne species **A**. Next, species **A** would undergo nucleophilic addition onto the nitrile moiety of substrate **70** to provide a nitrilium species **B**. Subsequently, intermediate **B** undergoes intramolecular cyclization to generate intermediate **C** which immediately furnish the desire product 3-amino-δ-carboline **72** by removing $SiMe_3$.



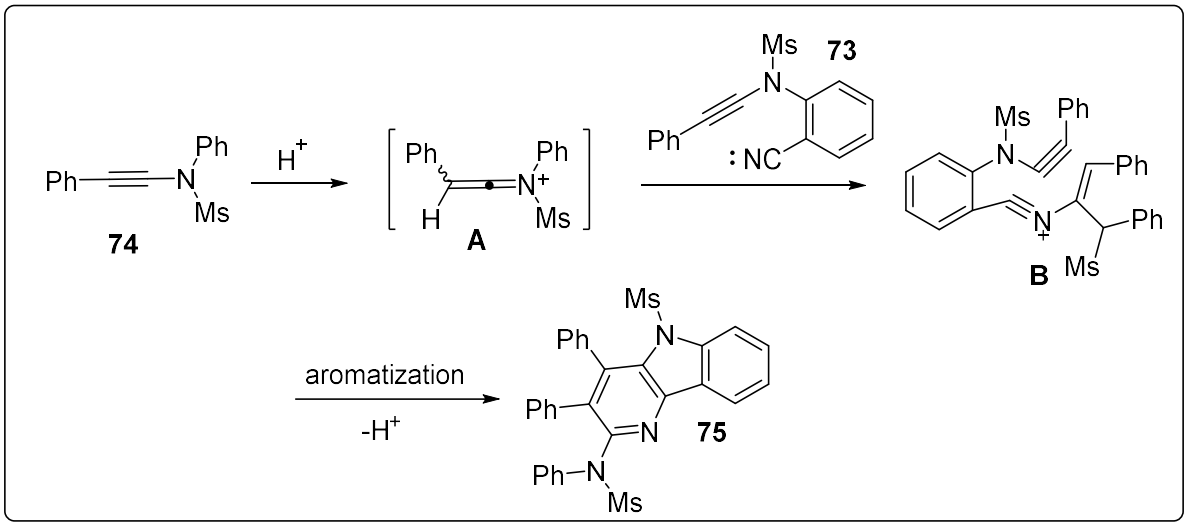
Scheme 18: A plausable mechanism for the formation of substituted δ-carbolines **72**

Wen and co-worker [13b] described rapid and highly efficient, transition metal free, highly regio- and chemoselective [2+2+2] cycloaddition reaction of ynamide-nitriles **73** with alkynes **74** to generate polysubstituted δ-carbolines **75** derivatives using stoichiometric amount of TfOH.



Scheme 19: Synthesis of δ-carboline derivatives **75**

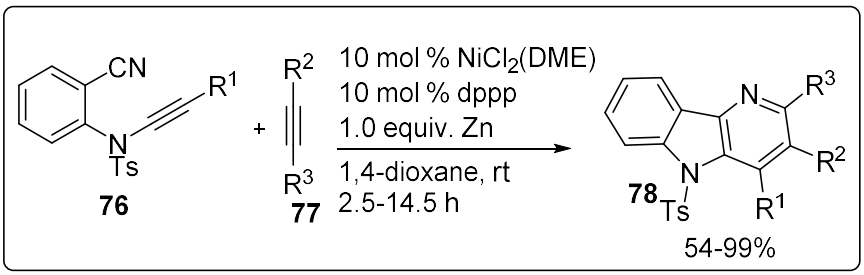
A plausible mechanism is depicted in **Scheme 20**. First, alkyne **74** would be protonated by TfOH to produce keteniminium intermediate **A** which is then attacked by ynamide-nitrile **73** to afford the intermediate **B**. On subsequent step, an intramolecular cyclization of **B** is promoted by the nucleophilicity of enamine, furnishing the final product **75**.



Scheme 20: Plausible mechanism for the formation of substituted δ-carboline **75**

2.1.2.3.2 Metal-catalyzed reaction:

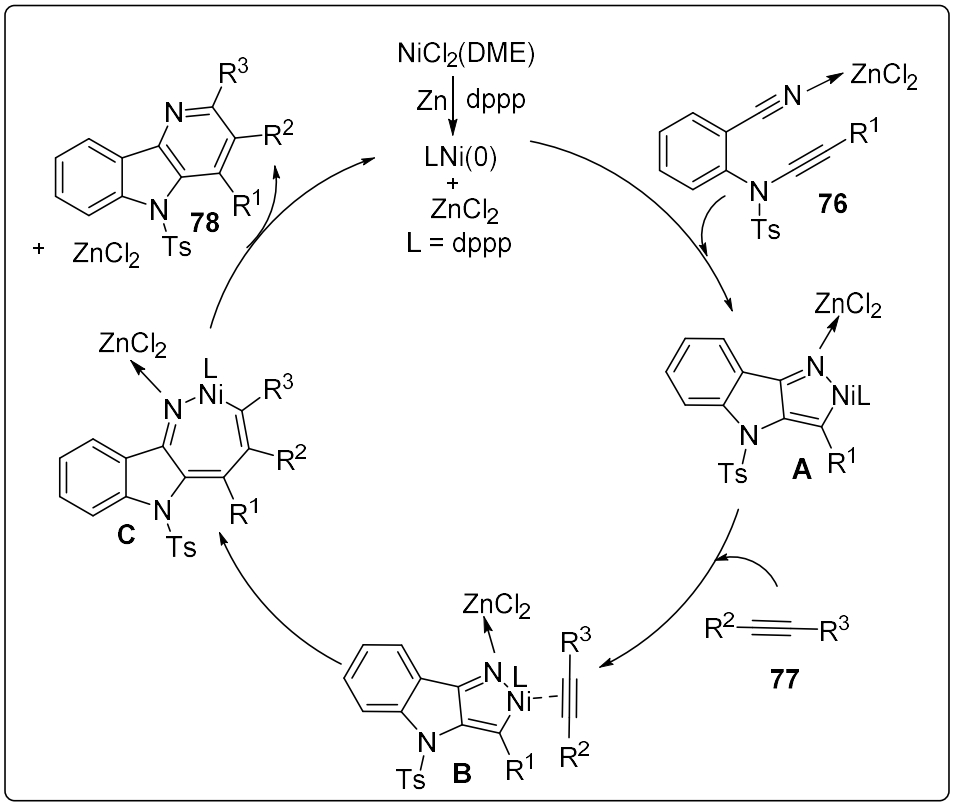
Wang et al.[12d] reported Nickel catalyzed [2+2+2] cycloaddition reaction between alkyne-cyanamides **76** with alkyne **77** to furnish δ-carboline **78** derivatives (**Scheme 21**) with wide



Scheme 21: Synthesis of substituted δ-carbolines **78**

diversity and functional group tolerance.

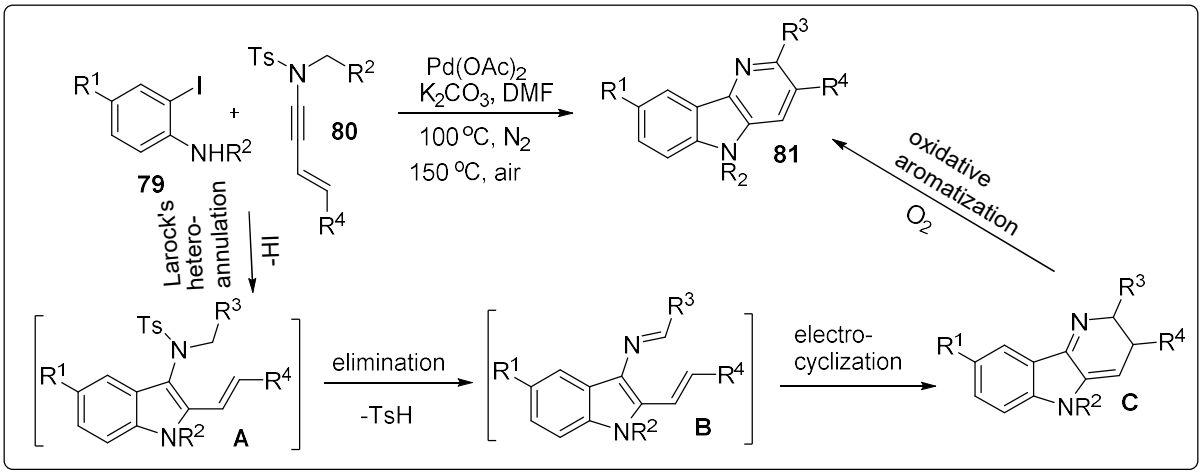
First, $ZnCl_2$ formed in situ acting as a Lewis acid, activates the nitrile moiety of compound **76** by coordinating with –CN group, thereby increasing the neucleophilicity of the nitrile moiety. Oxidative coupling of the alkyne **77** with the nitrile moiety at the Ni(0) center facilitated the formation of an aza-nickelacycle **A**. Insertion of the alkyne to the resulting intermediate **A** followed by reductive elimination to deliver the δ-carboline product **78**. The Ni-C bond is highly neucliophilic in azanickelacycle intermediate **B** due to the presence of enamine



Scheme 22: Plausable mechanism for the formation of substituted δ-carboline **78**

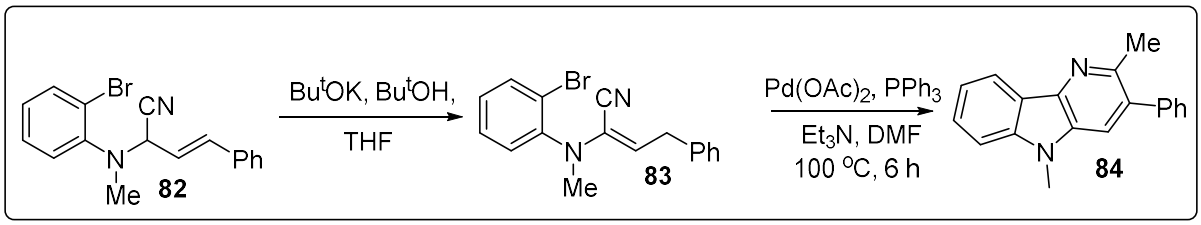
moiety, causing a clear and distinct preference for the insertion of terminal alkynes through electronic control.

Cao and co-worker[12f] reported a palladium catalysed synthesis of δ-carboline **81** starting from 2-iodoaniline **79** and N-tosyl-enynamine **80**. The reaction pathway follows Larock's hetero-annulation to generate intermediate sulphonamide **A** which upon elimination of 4-methylbenzenesulfinic acid (-TsH) affords intermediate **B .** Next, intermediate **B** undergoes subsequent electrocyclization reaction to form tricyclic intermediate **C**. Finally, oxidative aromatization by air gives the final product δ-carbolines **81**.



Scheme 23: A plausable mechanism for the formation of substituted δ-carboline **81**

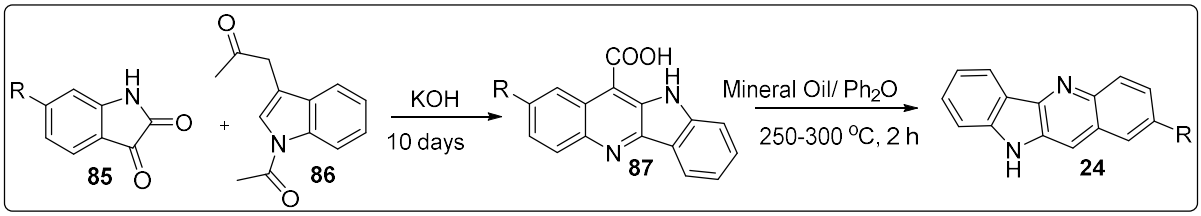
Yang *et al.*[12g] reported palladium catalysed regioselective cyclization of δ-carboline **83** which was synthesized from substrate **82** through base treatment. Two covalent bonds are formed in conversion of **83** to **84** by consecutive aryl-cyano addition and electrocyclisation.



Scheme 24: Synthesis of substituted δ-carbolines **84**

2.1.2.3.3 Some miscellaneous reaction:

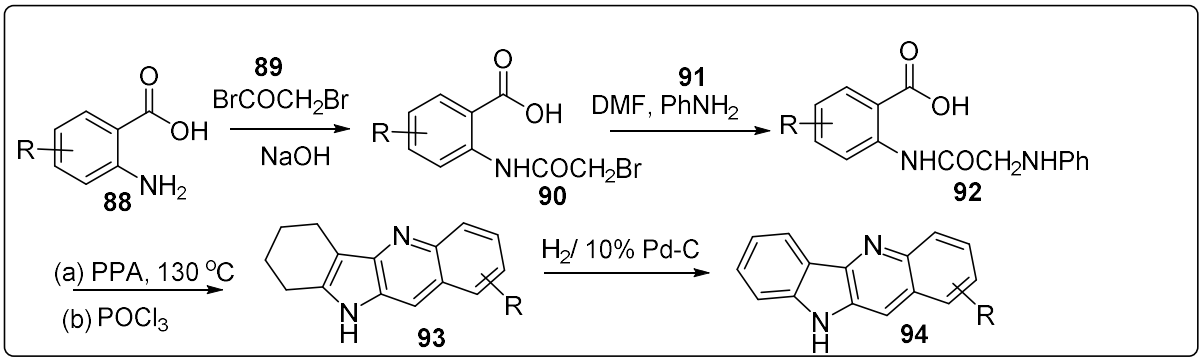
Mudududdla *et al.* [20] reported one of the most easiest and versatile method for the general synthesis of **24** in which isatin **85** was condensed with 1-acetyl-1*H*-indol-3-yl acetate **86** under basic condition leading to the formation of quindoline-11-carboxylic acid **87** that was easily decarboxylated by heating in diphenylether or mineral oil to generate δ-carboline **24** (**Scheme 25**).



Scheme 25: Synthesis of benzo-fused δ-carboline **24**

Mardenborough *et al.* [21] demonstrated an efficient and concise method for the general synthesis of substituted δ-carboline **94** derivatives. Firstly, substituted or unsubstituted

anthranilic acid **88** was acylated with 2-bromoacetyl bromide **89.** The resulting bromo intermediate **90** was then allowed to react with aniline **91**. The alkylated aniline **92** underwent a double cyclization reaction in the presence of polyohosphoric acid (PPA) and phosphorous oxychloride ($POCl_3$) to yield indolo-pyridine derivatives **93.** Aromatization of intermediate **93** with hydrogen and palladium/charcoal led to the desired compound **94**.



Scheme 26: Synthesis of δ-carboline **94**

2.1.3 Benzofuro[3,2-*b*]pyridines (BFPs)

Pyridine-fused polyheterocycle such as benzofuro[3,2-*b*]pyridines (BFPs) **95** have received considerable attention due to their immense importance in biological activities and applications in various fields. Nitrogen and oxygen atom attached to the fused cyclic system are pharmacologically active compounds as it activates the hydrogen bond acceptors to modulate the activity of target enzymes.[22] Besides, benzofuro[3,2-*b*]pyridines (BFPs) **95** can be used for biological imaging, target identification or understanding biological processes.

2.1.3.1 Importance of benzofuro[3,2-*b*]pyridine in medicinal chemistry

Benzofuro[3,2-*b*]pyridine **95** has gained an attention in medicinal chemistry due to their diverse pharmacological properties, making attractive targets for drug discovery and have shown potential therapeutic applications. Due to their anticancer properties, they inhibit tumor cell growth and interfere with specific significant pathways that involved in cancer progression. Their derivatives can be used for biological imaging, target identification and understanding of biological processes. Besides, benzofuro[3,2-*b*]pyridines (BFPs **95**, **Fig. 5**), serve as the core structure in a diverse array of natural products and bioactive compounds with wide-ranging pharmacological activities.[23] For example, *sinensine D*[24] (**96**) is found in fruiting bodies of *Ganoderma sinense*, a plant credited with beneficial effects in the treatment of chronic hepatitis, nephritis, etc. In addition, sinensine D **96** and its derivatives are acting as inhibitor of cyclin dependent kinase (CDK).[24] While compounds **97**[25] are reported as potent

topoisomerase inhibitors. Elbfluorene **98**[26a] have been utilized as a target enzymes in cancer progression due to their antiproliferative properties. While benzofuropyrimidine **99**[26b] (MP-470, SuperGenInc) is a novel multi target tyrosine kinase inhibitor and it is currently in Phase I clinical trials. Interestingly, compounds **100**[27] and **101**[28] are acting as a potential telomerase inhibitor and neuroblastoma RAS (NRAS) repressor.

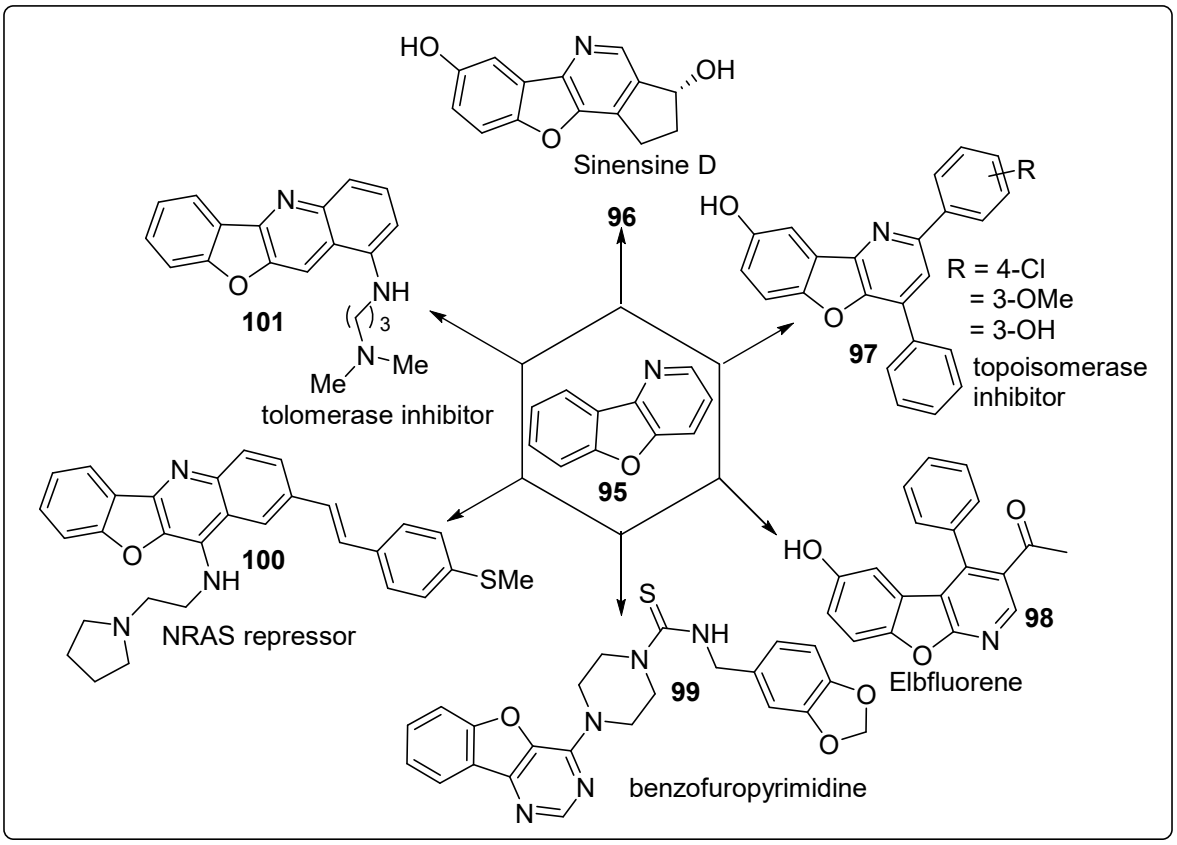


Figure 5: A few important benzofuro[3,2-*b*]pyridines (BFPs) **96-101**

2.1.3.2 Importance of benzofuro[3,2-*b*]pyridines 95 in material sciences:

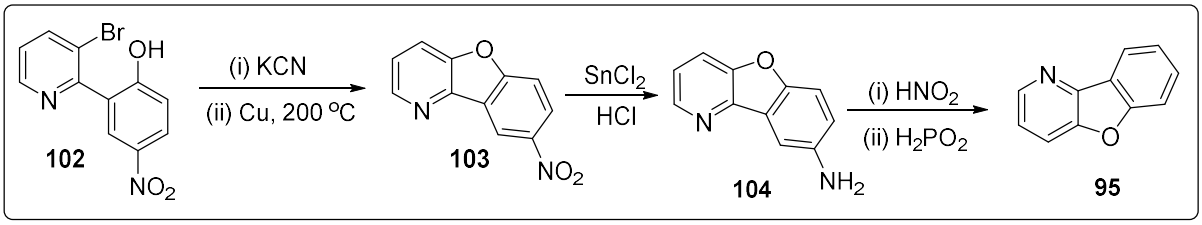
Scrutiny of literature reveals that applications of benzofuro[3,2-*b*]pyridine **95** in material science are only few. Benzofuro[3,2-*b*]pyridine **95** shows good light absorbtion properties and it is suitable for optoelectronic devices such as photodetector, molecular probe or sensor. One research article[29] reports a modified chemical structure of benzofuro[3,2-*b*]pyridine **95** and also shows to tune the emission properties that enable the production of materials with different colors and emission efficiencies.

2.1.4. Synthesis of benzofuro[3,2-*b*]pyridine (BFPs)

Synthesis of benzofuro[3,2-*b*]pyridines **95** usually follows two approaches comprising constructions of (a) a fused furan ring[30] or (b) a fused pyridine[31] ring employing appropriate benzofuran substrates. Among them, a general synthesis of **95** using former approach follows two steps reactions comprising (a) a Pd-catalyzed intramolecular dual C−H activation of 3-phenoxypyridine 1-oxides followed by (b) deoxygenation of the resulting products. Besides, few specific examples of **95** are also reported[30a,c-d] as part of the synthesis of other heterocycles. In contrast, the latter approach provides few general method[31] (**Scheme 35, 36**) employing the same substrate prepared in multiple steps. Therefore, development of more straightforward convenient and general methods using readily available different substrates would be worthwhile.

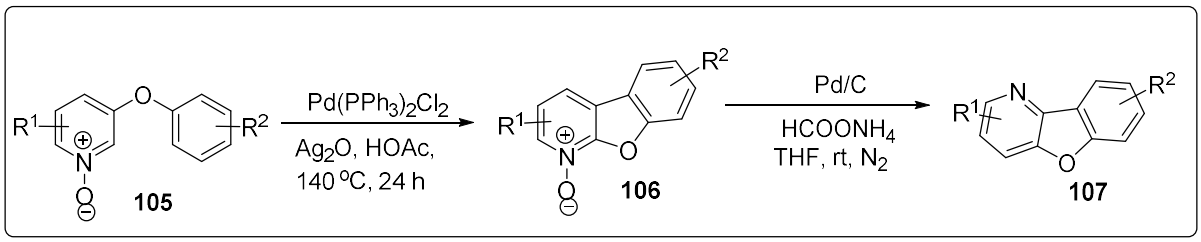
2.1.4.1 Synthetic pathways for the synthesis of benzofuro[3,2-*b*]pyridines via the formation of fused furan ring:

Abramovitch *et al.* [32] reported an easiest method for the general synthesis of benzofuro[3,2-*b*]pyridines **95** where 3-bromo-2-aryl pyridine **102** was used as a precursor (**Scheme 27**). New furan ring would be generated after the treatment of KCN in presence of Cu on substrate **102**. After reduction of NH_2 by using $SnCl_2$ /HCl, generated product **104** which upon treatment of HNO_2/H_2PO_2 furnishes desired benzofuro[3,2-*b*]pyridines **95**.



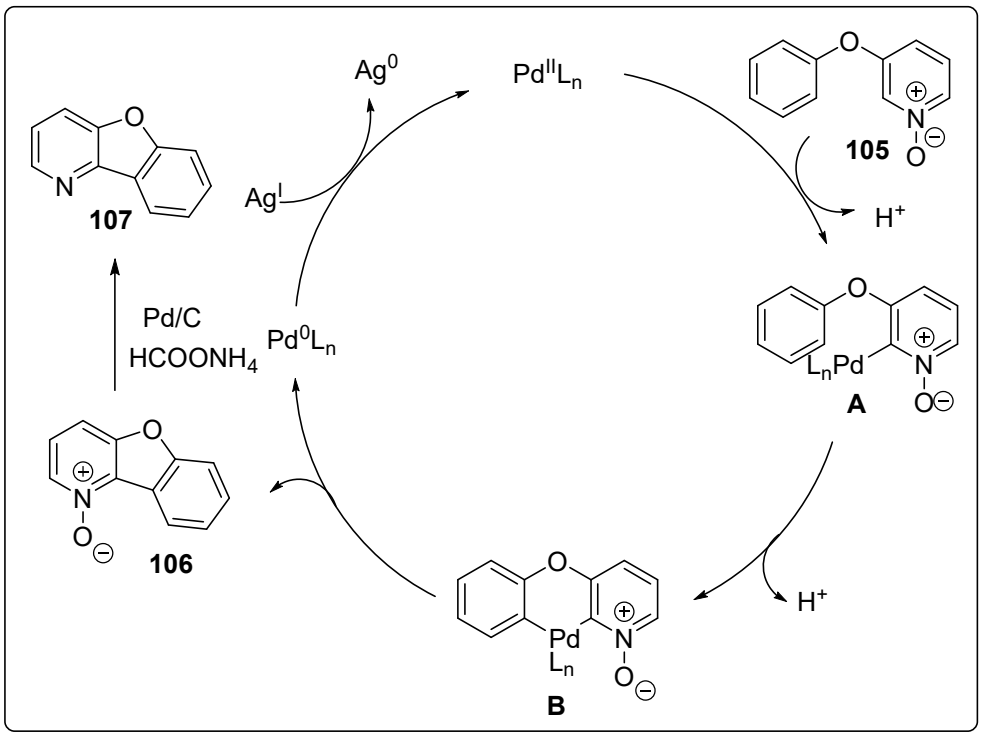
Scheme 27: Synthesis of benzofuro[3,2-*b*] pyridine **95**

Sun *et al.* [30b] described an efficient and straightforward method for the synthesis of benzofuro[3,2-*b*]pyridine-1-oxides **106** with high regioselectivity via Pd-catalysed intramolecular C-H activation. The resulting products could easily be oxidized into benzofuro[3,2-*b*]pyridines **107** derivatives through hydrogenolysis by using Pd/C (**Scheme 28**).



Scheme 28: Synthesis of 1,2-dihydrobenzofuro[3,2-*b*]pyridines **106** and benzofuro[3,2-*b*]pyridines **107**

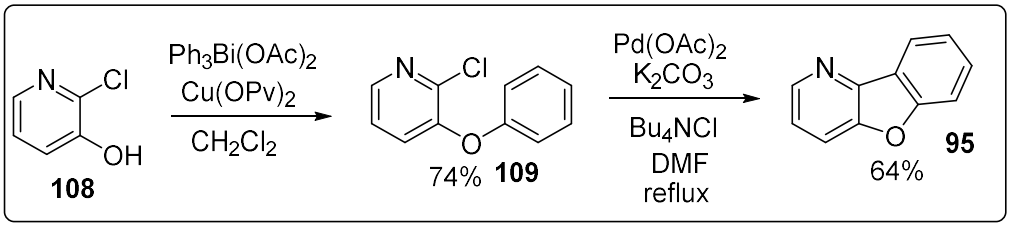
A probable mechanism is described in **Scheme 29**. Firstly, palladium (II) catalyst react with 3-phenoxypyridine-1-oxide **105** via C-H bond activation to afford a C2-palladated species **A**, which underwent an intramolecular cyclization to form bis-arylpalladium species **B** via another C-H bond activation. Next, species **B** underwent reductive elimination to afford the product **106** and Pd(0) species which was easily oxidized by Ag(I) to regenerate Pd(II) species to complete the catalytic cycle. Finally, **106** was deoxidized in the presence of Pd/C to give the deoxygenation product **107**.



Scheme 29: Plausible reaction mechanism for benzofuro[3,2-*b*]pyridines **107**

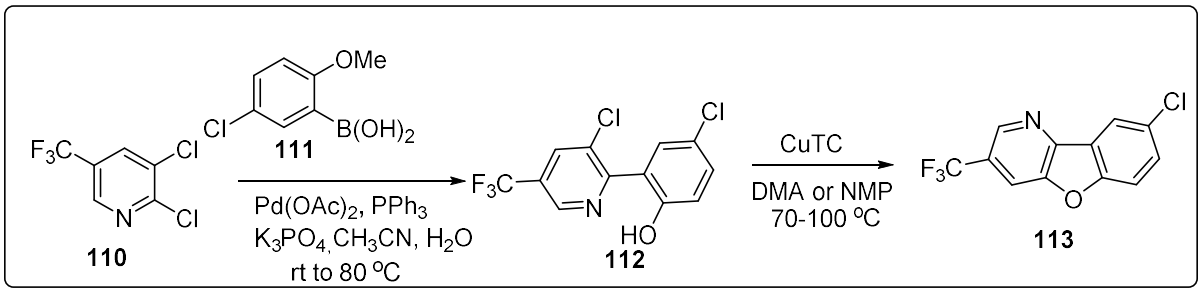
Yue *et al.*[30d] reported a palladium-catalyzed coupling approach for the synthesis of benzofuro[3,2-*b*]pyridine. Here, 3-hydroxypyridines **108** was phenylated using triphenylbismuth (V) diacetate in the presence of Cu(II) pivaloate to provide diarylether **109**

(**Scheme 30**). Next, an intramolecular cyclization via a C-C bond formation between aryl and heteroaryl moiety of intermediate **109** was achieved using Heck reaction under Jeffery's ligand free conditions to obtain the desired product benzofuro[3,2-*b*]pyridine **95** in 64% yield.



Scheme 30: Synthesis of benzofuro[3,2-*b*]pyridines **95**

Liu *et al*. [30a] reported chemo/regioselective Suzuki coupling between substituted pyridine **110** and substituted phenyl boronic acid **111** resulting in biaryl phenol **112** which then underwent a copper(I)thiophene-2-carboxylate (CuTC)-mediated intramolecular cyclization to generate benzofuro[3,2-*b*]pyridines **113** (**Scheme 31**).

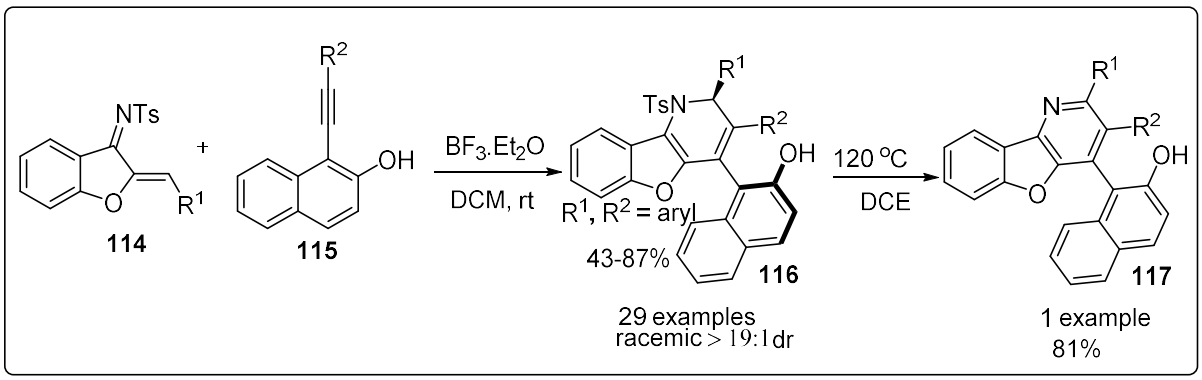


Scheme 31: Synthesis of benzofuro[3,2-*b*]pyridines **113**

2.1.4.2 Synthesis of benzofuro[3,2-*b*]pyridines through the construction of fused pyridine ring:

2.1.4.2.1 From aurone derivatives

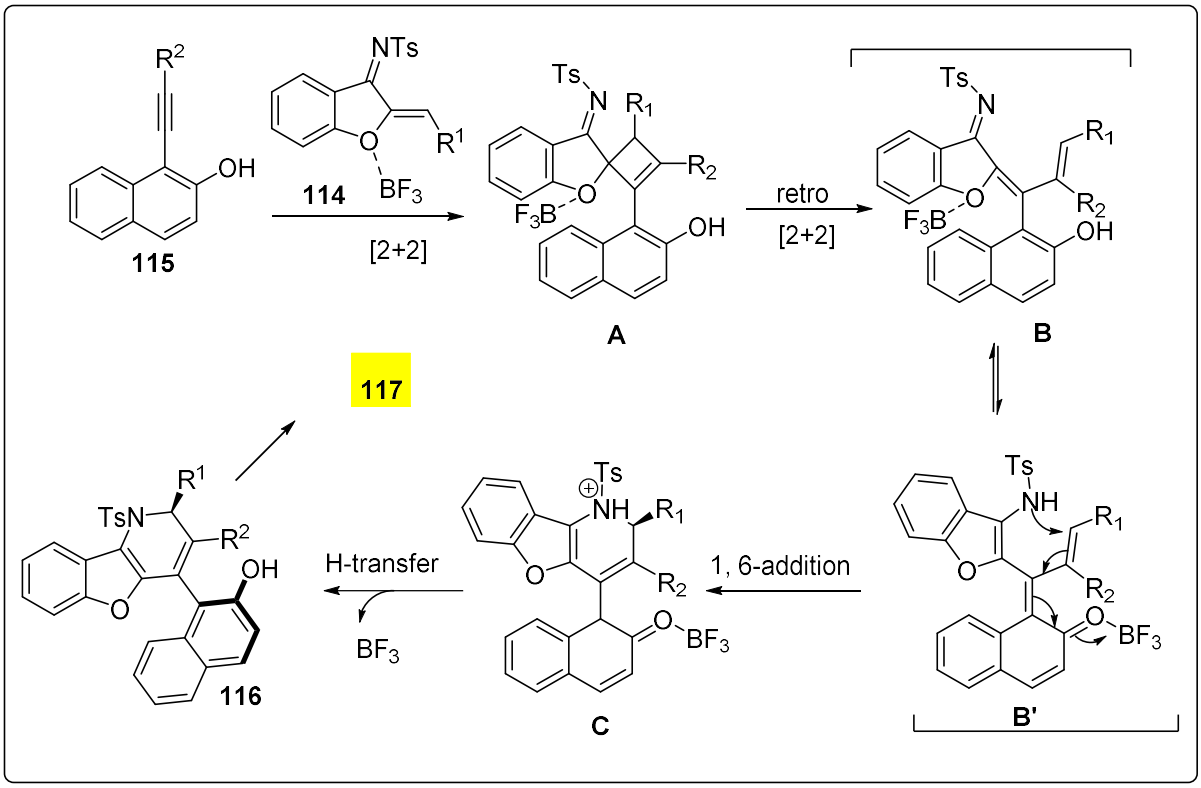
Zhu *et al.* [33] demonstrated an efficient and operationally simple method for a highly regio- and diastereoselective synthesis of 1,2-dihydrobenzofuro[3,2-*b*]pyridine **116** having chiral carbon center and an axial chirality with moderate to good yields using simple aurone-derived substrate like 1-azadienes **114** (**Scheme 32**).



Scheme 32: Synthesis of substituted benzofuro[3,2-*b*]pyridines **117**

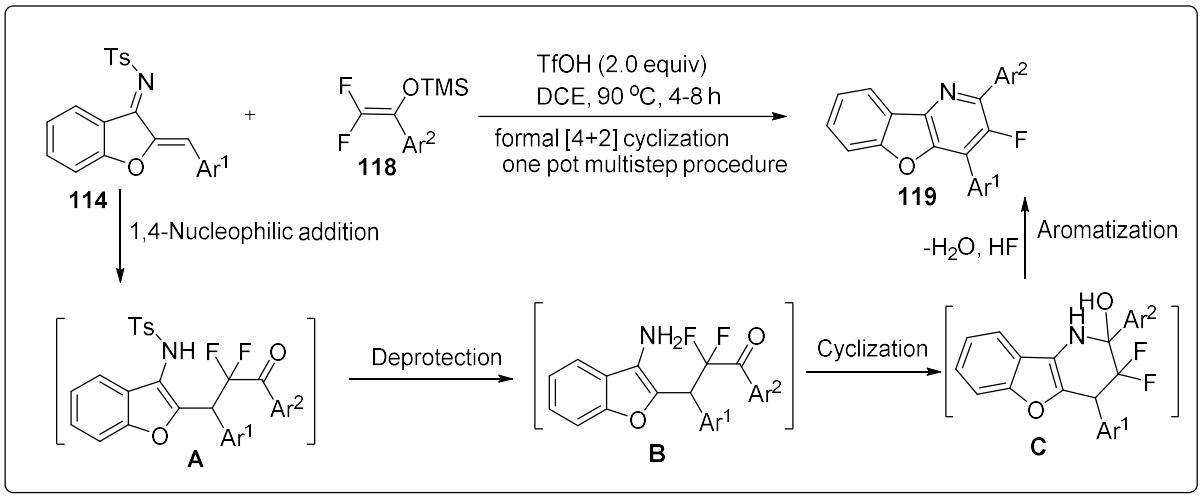
Next, Intermediate product **116** then undergoes elimination of tosyl group upon heating at 120 ^{o}C delivering the product **117**. A reasonable reaction mechanism was also illustrated as shown in **Scheme 33**.

From the mechanistic point of view, $BF_3 \cdot Et_2O$ initiates an intermolecular [2+2] cycloaddition reaction between 1-azadienes **114** and 1-alkynylnaphthalen-2-ol **115** (**Scheme 33**) resulting in the generation of spiro cyclobutene intermediate **A**. Next, species A undergoes retro-electrocyclization to form intermediate **B** which upon subsequent isomerization to give intermediate **B′**. The intermediate **B′** then undergoes intramolecular 1,6-conjugate addition (**B′** to **C**) and intramolecular proton transfer leading to the generation of dehydrobenzofuro[3,2-b]pyridines **116**. Steric hindrance may play an important role for the generation of high diastereoselective product **116** (>19:1 dr). The hall-marks of this reaction are (100%) atom-economic, a wide substrate scope and good compatibility with different functional groups and excellent diastereoselectivity.



Scheme **33**: Plausible mechanism for the formation of compound **117**

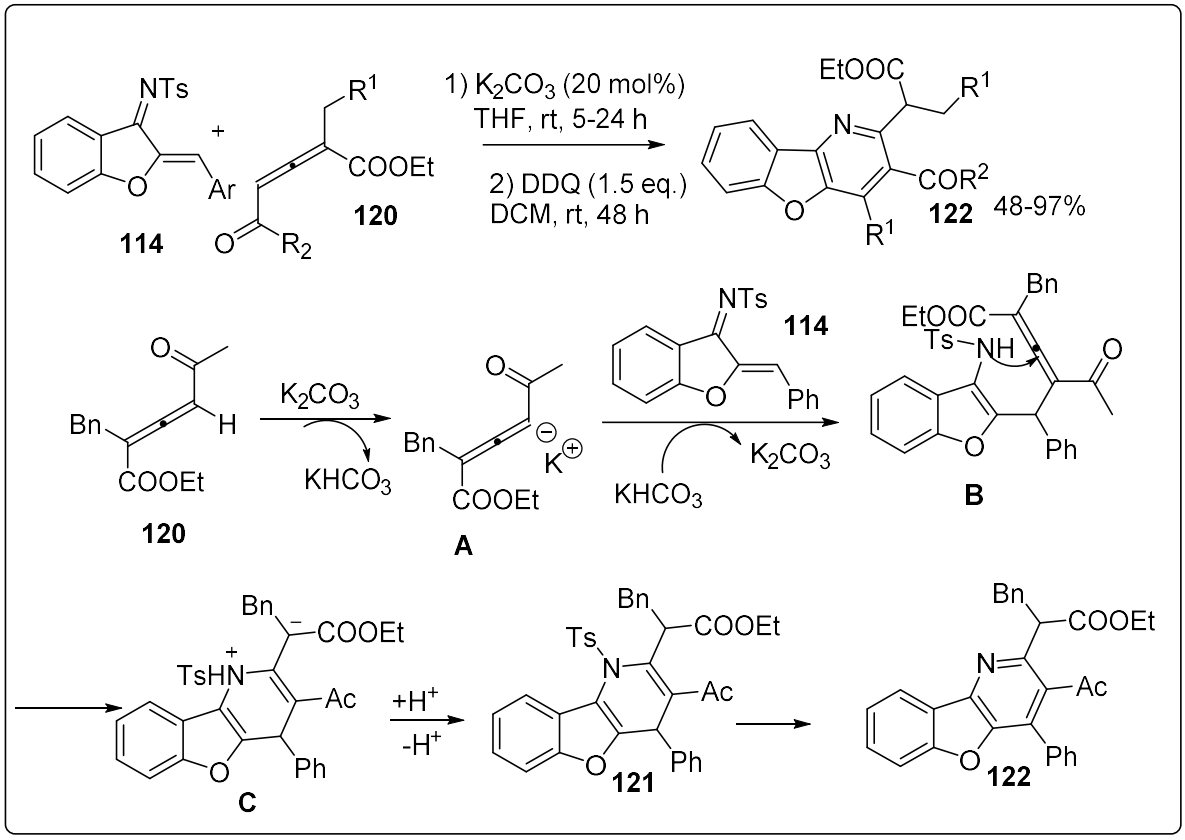
Li *et al.* [22] reported TfOH-promoted synthesis of fluorinated poly-fused heterocycles via the cascade cyclization of azadienes **114** and difluoroenoxysilanes **118** leading to the construction of fluorinated benzofuro[3,2-*b*]pyridines (**Scheme 34**). This [4+2]-cycloaddition reaction involves 1,4-difluoroalkylation, desulfonylation, cyclization, and aromatization. In presence of TfOH, azadienes **114** undergoes [4+2] cycloaddition reaction with difluoroenoxysilanes **118** to generate intermediate **A** which then undergo detosylation



Scheme 34: Synthesis of benzofuro[3,2-*b*]pyridine **119** with a plausible reaction mechanism

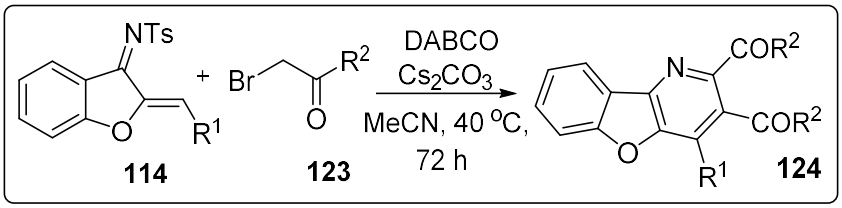
(intermediate **B**) followed by cyclization (intermediate **C**) and subsequent eliminations of water and hydrofluoric acid leading to the formation of desired products **119**.

Hu and coworkers[31a] illustrated a K_2CO_3-catalyzed 1,4-addition/intramolecular cyclization/aromatization reaction of aurone-derived 1-azadienes **114** with trisubstituted allenoates **120** to furnish a series of benzofuro[3,2-*b*]pyridines **122** with moderate to excellent 48-97% yields (**Scheme 35**). The proposed mechanism is discussed in **Scheme 34**. Initially, trisubstituted allenoate **120** is deprotonated in presence of K_2CO_3 to generate intermediate **A** which undergoes 1,4-addition with 1-azadienes **114** to generate the intermediate **B.** Then, intermediate **B** undergoes intramolecular cyclization to generate intermediate **C** which upon a proton transfer affords 1,4-dihydrobenzofuro[3,2-*b*]pyridine intermediate **121**. Then, detosylation followed by aromatization in presence of DDQ resulted in the final product benzofuro[3,2-*b*]pyridines **122**.



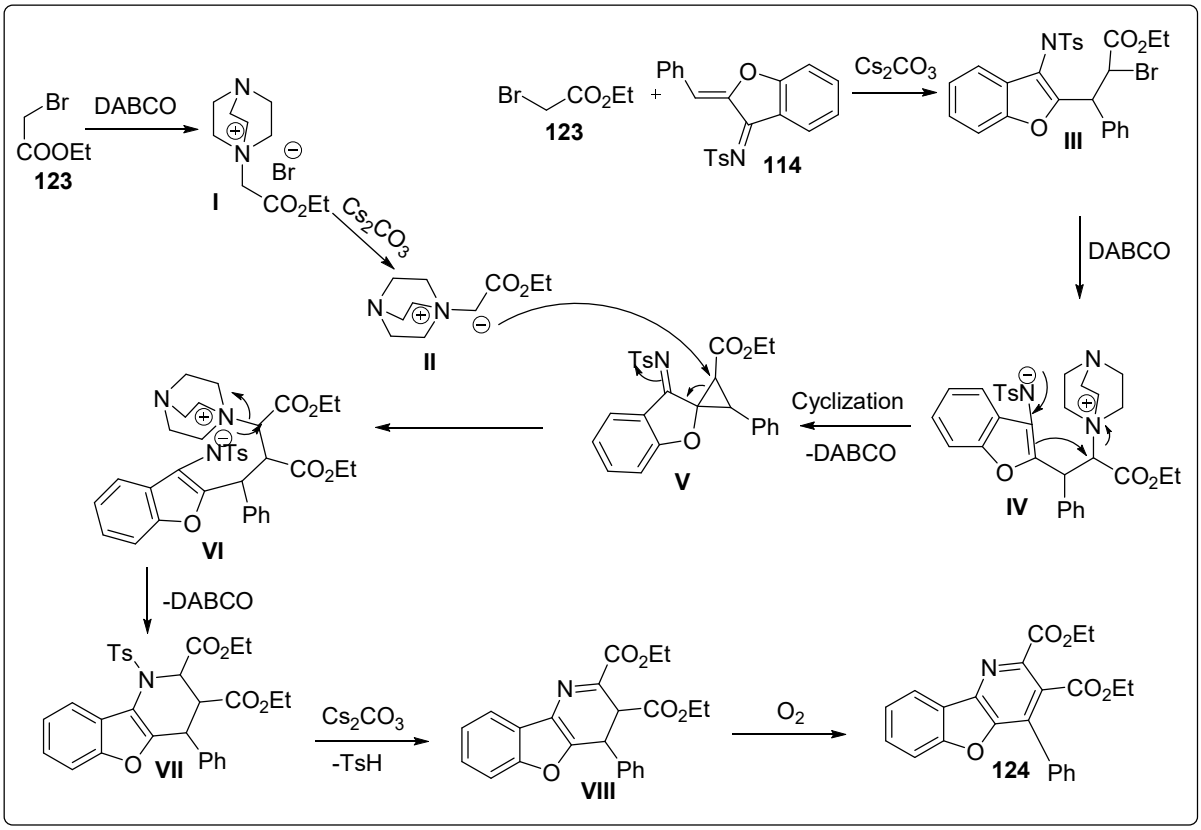
Scheme 35: Synthesis of substituted benzofuro[3,2-*b*]pyridines **122**

Zeng and co-workers [31c] developed metal and oxidant free efficient method for the synthesis of benzofuro[3,2-*b*]pyridine **124** via [4 + 1 + 1] annulation between α-bromo carbonyls **123** and 1-azadienes **114** in the presence of DABCO and Cs_2CO_3 (**Scheme 36**).



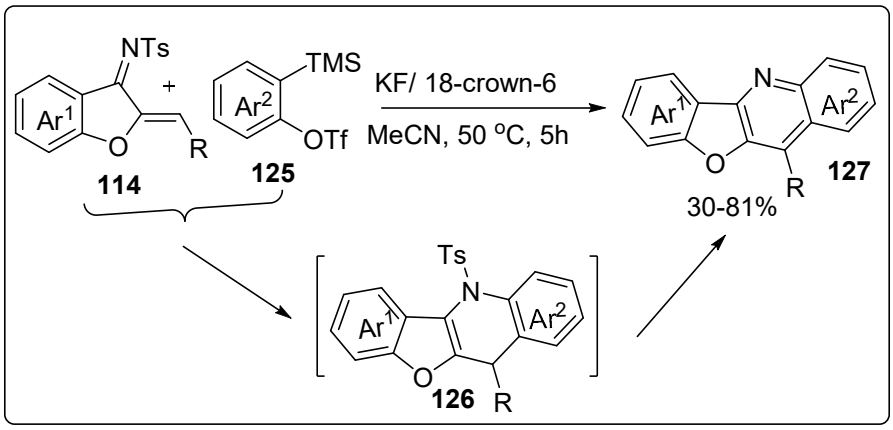
Scheme 36: Synthesis of substituted benzofuro[3,2-*b*]pyridines **124**

A plausible reaction mechanism is proposed in **Scheme 37**. α-Bromoacetate **123** reacts with DABCO to generate the ammonium salt **I**, which is subsequently deprotonated to form the nitrogen ylide **II** (**Scheme 37**). On the other hand, ester **123** undergoes 1,4-addition with substrate **124** to generate intermediate **III**, which would then afford ammonium salt **IV** with the aid of DABCO. Next, species **IV** is transformed into cyclopropane **V** via *3-exo-tet* cyclization. Thereafter, the ring-opening reaction occurs through the participation of nitrogen ylide **II** to furnish the intermediate **VI**, which easily undergoes ring closure to deliver the intermediate **VII**. Finally, elimination of *p*-toluenesulfinic acid (-TSH) assisted by Cs_2CO_3 yields the intermediate **VIII**, which produces the benzofuro[3,2-*b*]pyridine **124** upon oxidative aromatization.



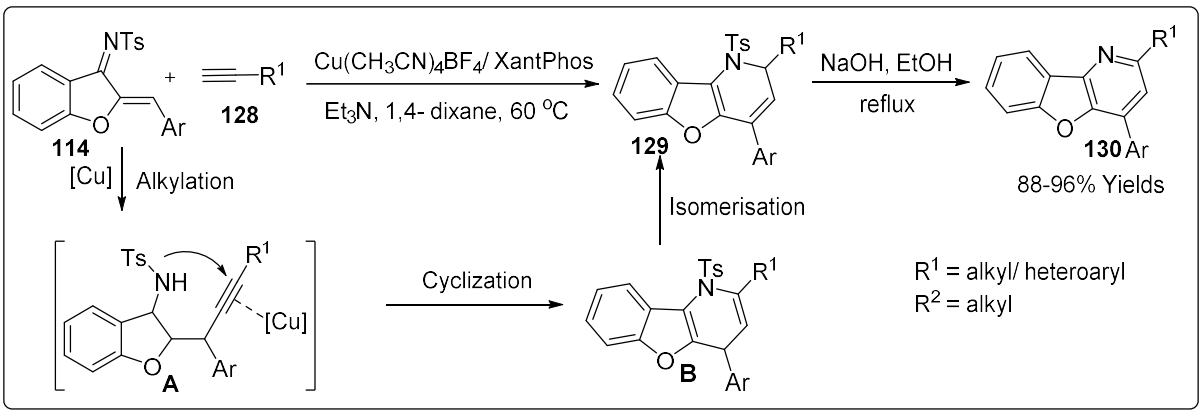
Scheme 37: Plausible mechanism for the formation of product **124**

Wang *et al.*[34] established an efficient method for the synthesis of benzofuro[3,2-*b*]pyridines **127** fused with benzene through tandem [4+2] cycloaddition reaction followed by aromatization under transition-metal-free conditions. A wide range of aurone-derived *N*-tosyl-1-azadienes **114** smoothly reacted with 2-(trimethylsilyl)aryl triflates **125** to generate benzofuro[3,2-*b*]quinolones **127**, (through the intermediate benzodihydropyridines **126**) in moderate to good (30-81%) yields. Benzodihydropyridines **126** undergoes elimination of TsH group (-TsH) with the aid of KF at room temperature to afford benzofuro[3,2-*b*]quinolone **127** with moderate to good yield.



Scheme 38: Synthesis of benzofuro[3,2-*b*]quinolones **127**

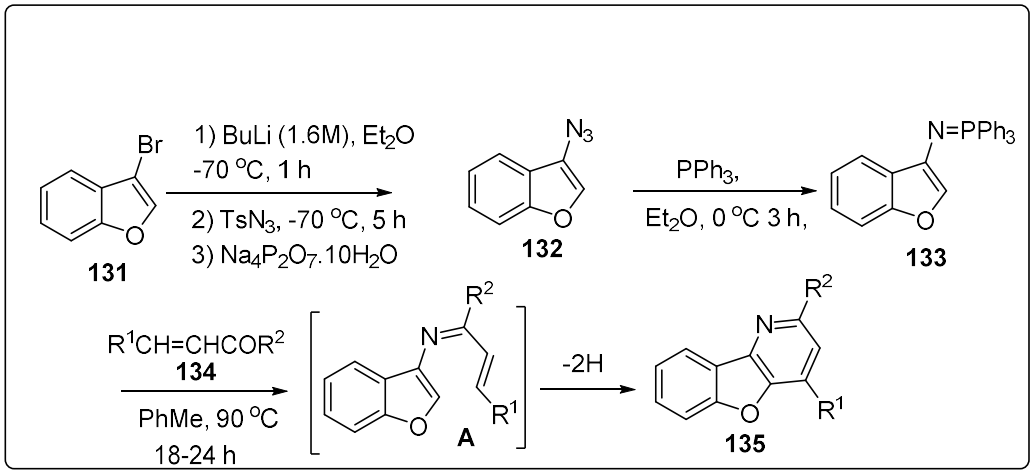
Xie *et al.*[31b] developed an efficient copper-catalyzed cascade alkynylation/cyclization/isomerization reaction for the general synthesis of benzofuro[3,2-*b*]pyridines by copper-catalyzed reaction between aurone-derived azadiene **114** and terminal alkyne **128** in a one-pot reaction (**Scheme 39**). Firstly, alkyne **128** undergoes alkylation reaction with azadiene **114** under copper catalysed reaction and generates an intermediate **A**. Subsequently, intermediate **A** underwent an intramolecular *6-endo-dig* cyclization through the activation of the triple bond, delivering 1,4-dihydropyridine **B**. Finally, the isomerization of intermediate **B** generates 1,2-dihydrobenzofuro[3,2-*b*]pyridines **129**. Next, 1,2-dihydrobenzofuro[3,2-*b*]pyridine **129** is transformed into corresponding benzofuro[3,2-*b*]pyridines `**130** under basic conditions through the E1cb mechanism. This method provides a facile approach to 1,2-dihydrobenzofuro[3,2-*b*]pyridines **129** and benzofuro[3,2-*b*]pyridines **130** with excellent yields (88-96%).



Scheme 39: Synthesis of 1,2-dihydrobenzofuro[3,2-*b*]pyridines **129** and benzofuro[3,2-*b*]pyridines **130**

2.1.4.2.2 Cyclization Reaction:

Funicello *et al.* [30c] described a simple method in which 3-bromobenzofuran **131** was treated with BuLi at -70 °C followed by subsequent reactions with tosyl azide followed by sodium pyrophosphate to produce intermediate azide compound **132** (**Scheme 40**). Next, Staudinger reaction of azide **132** with triphenyl phosphine generates iminotriphenylphosphorane **133** which is then react with α, β-unsaturated ketone **134** under refluxing toluene to generate intermediate **A** which upon cyclization furnishes the product **135**.



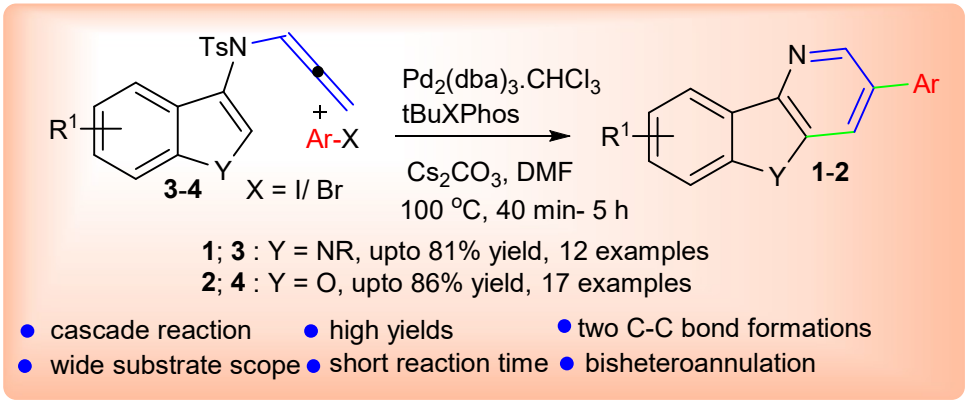
Scheme 40: Synthesis of benzofuro[3,2-*b*]pyridine **135**

2.1.5 Concluding remarks:

From the above literature survey, it is clear thar δ-carbolines **4** have received considerable attention due to its immense importance ranging from medicinal chemistry to material sciences. Also δ-carboline alkaloids are well-known for their antioxidant and neuprotective properties. On the other hand, benzofuro[3,2-*b*]pyridines **95** have been used as an important scaffolds in drug discovery program. Notably, the synthetic methods of benzofuro[3,2-*b*]pyridines **95** are less explored (via either conventional or metal catalysed methods) compared to δ-carbolines **4** underlining the importance of their convenient synthesis. Detailed findings towards this objective have been discussed in **part II** if this chapter.

Part II

Result and Discussion



Reference: **Debasmita Mondal**, Subhendu Pramanik and Chinmay Choudhury*; *Org. Lett.* **2022**, *24,* 8698−8702.

2.2.1 Introduction:

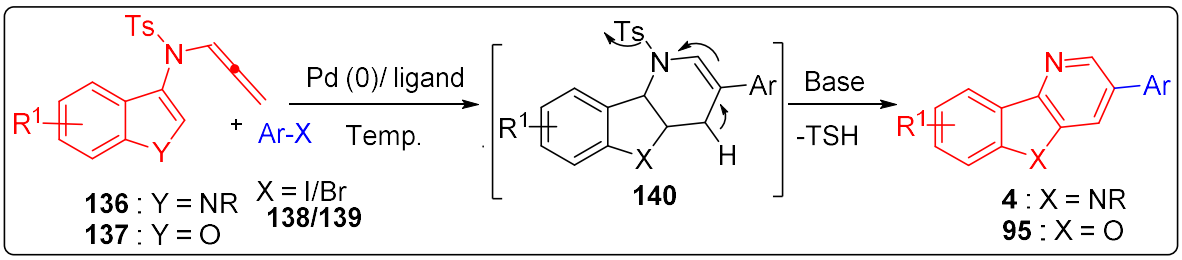
In the view of immense importance of δ-carbolines **4** and its derivatives being a core structure of many natural products and medicinally active compounds, the development of new methodology for these heterocyclic core structures appears to be more important. Scrutiny of the literature reveals that δ-carbolines are usually prepared through the fusion of either a newly formed pyrrole ring[12a-c] (**Scheme 8-10** of part 1) with diarylamine substrates or of a pyridine ring,[12d-g] (**Scheme 13, 15, 21, 23-24** of part 1) preformed or generated in situ, with indole substrates. However, applications of the latter strategy have been restricted in numbers, though it appears to be more interesting as functionalization in the pyridine ring can be achieved easily instead of using a pre-functionalized substrate as in the former case (as discussed previously in part-1). Besides, another method of transformations of indole substrates to δ-carbolines was reported primarily relying on *Friedel-Crafts* reaction carried out either one-pot or multi-steps where C-N bonds are formed either through Lewis acid catalyst or by using conventional protocol (**Scheme 11, 13** of part 1). Therefore, development of a straightforward and convenient method for the synthesis of **4** would be worthwhile.

On the other hand, benzofuro[3,2- *b*]pyridines **95** serve as the core structure in natural products and bioactive compounds. Importantly, the aforesaid scaffold has been explored as potential lead compound for the development of new drugs. Scrutiny of the literature reveals that there is only one method known for the general synthesis of **95** where 3-phenoxypyridine 1-oxides were used as a precursor[30b] (**Scheme 28** of part I) though there are also few specific examples (**Scheme 27, 30, 31** of part 1). Contrarily, most of the benzofuro[3,2- *b*]pyridines **95** were synthesized by using aurone derivatives synthesized in multi-steps are using as starting materials as discussed in part 1 of **Schemes 31-38**. Therefore, it underlines the urgency of convenient and practical method for their general synthesis.

In recent times allenamides[35] have emerged as potential building blocks in organic synthesis. In continuation of our works[36] on palladium-catalyzed reactions, we envisioned that a direct construction of pyridine ring fused to indole or benzofuran could be achieved via palladium-catalyzed reactions between allenamides **136** or **137** and aryl halides **138/139** resulting in the formation of transient dihydropyridine intermediates **140** which upon base induced elimination (-TsH) would trigger the formation of delta-carbolines **4** or

benzofuro[3,2-*b*]pyridines **95** (**Scheme 41**). We described here in details the results obtained so far.

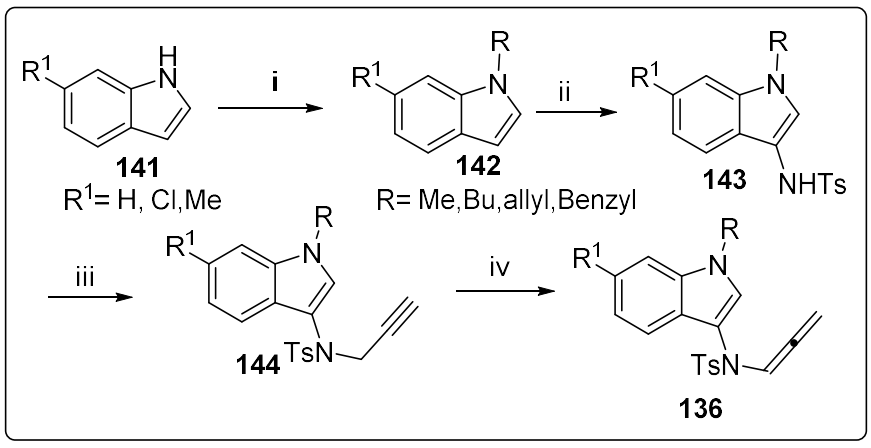
Present work:



Scheme 41: Pd(0)-catalysed Synthesis of δ-carbolines **4** and benzofuro[3,2-*b*]pyridines (BFPs) **95**

2.2.2. Synthesis of starting material 136

The requisite *N*-allenamide substrates **136** were synthesized in four steps starting from commercially available indoles as shown in **Scheme 42**. Thus intermediates **142** can be achieved by simple N-alkylation of indoles **141**. Next, 3-sulfonamidoindoline intermediate **143** could easily be achieved by treatment of **142** with TsN_3 in 1,4-dioxane. Finally, N-propargylation of **144** followed by a base treatment of the resulting compound (i.e., **136**) led to the formations of allenamide substrates **136**.



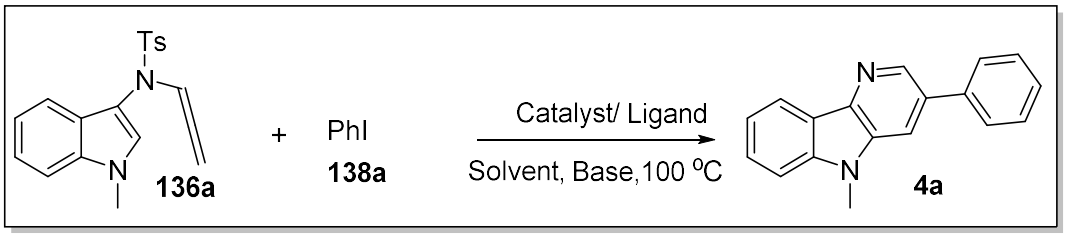
Scheme 42. Synthesis of allenamide substrates **136**. Reagent and Conditions: (i) NaH, alkyl iodide/benzyl (allyl) bromide (RX), DMF, 0 °C- rt, 6-8 h, 81-95%; (ii) TsN_3, 1,4 Dioxane, 80 °C, 18-24 h, 25-34%; (iii) Propargyl Bromide, NaH, DMF, 0 °C- rt, 3-5 h, 65-76%; (iv) ^{t}BuOK, THF, 5-15 min, rt, 49-70%.

2.2.3. Synthesis of δ-carbolines 4 from allenamide through palladium-catalyzed reactions

2.2.3.1 Optimisation of the reaction condition for the synthesis of δ-carbolines 4

To realize the synthesis of δ-carbolines **4** as depicted in **Scheme 41**, we carried out a model reaction between allenamide **136a** synthesized in few steps (**Scheme 42**) and phenyl iodide **138a** with variation of the reaction parameters; selected results are represented in Table 1**.** At the outset, we carried out the reaction in DMF employing 5 mol% of $Pd(OAc)_2$ and 10 mol% of PPh_3 in the presence of 2.0 equiv of potassium carbonate;[37] to our disappointment, there was no sign of formation (TLC) of δ-carboline **4a** even after heating the reaction at 100 ^oC for 10 h (Table 1, entry 1). Nevertheless, **4a** was found to be formed albeit in moderate yield (30%) by using[36c] $Pd_2(dba)_3$, ^{t}BuXantPhos and Ag_2CO_3 as catalyst, ligand, and base, respectively (Table 1, entry 2). Interestingly, replacing the bidented ligand by a monodented one (i.e., ^{t}BuXPhos) improved the yield and reduced the reaction time as well (Table 1, entry 3). Though $Pd(dba)_2$ employed along with Cs_2CO_3 (in place of Ag_2CO_3) failed to improve the outcome of this reaction (Table 1, entry 4), the use of another Pd(0) catalyst, i.e., $Pd_2(dba)_3$, furnished **4a** within 2.5 h with 72% yield (Table 1, entry 5). To our delight, $Pd_2(dba)_3.CHCl_3$ proved to be still more efficacious, delivering **4a** within 30 min with 81% yield (Table 1, entry 6). Notably, lowering of either the reaction temperature (80 °C) or catalyst loading diminished the yields of **4a** (Table 1, entries 7,8). Thereafter, we screened few more ligands having some structural similarity with ^{t}BuXPhos; to our disappointment, only moderate yields (35-54%) of **4a** were observed when one among XPhos, RuPhos, CyJohnPhos, or $P(Cy)_3$ was deployed (Table 1, entries 9-12, for structures of the said ligands, see Figure 6 as depicted below), while use of SPhos afforded only a trace amount of the product (Table 1, entry 13). We therefore pursued this reaction using ^{t}BuXPhos as ligand for further study (Table 1, entries 14-16) where different solvent systems comprising both low (THF) and high polar ones were utilized. Though THF and DCE proved to be inefficacious, DMSO furnished the product **4a** in moderate yield (32%). Thus, the reaction conditions of entry 6 of Table 1 proved to be optimal to explore the scope of this reaction as discussed under **Scheme-43**. (Structure of the all ligands used during this optimization study has been provided under Figure 6).

Table 1: **Optimization of the reaction conditions for the synthesis of 4a[a,b]**



Sl. No.	Catalyst	Ligand[b]	Solvent	Base	Time (hr)	Yields (%)[e]
1	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	10	-
2	$Pd_2(dba)_3$	t-Bu-XantPhos	DMF	Ag_2CO_3	8	30
3	$Pd_2(dba)_3$	^{t}BuXPhos	DMF	Ag_2CO_3	6	44
4	$Pd(dba)_2$	^{t}BuXPhos	DMF	Cs_2CO_3	3	45
5	$Pd_2(dba)_3$	^{t}BuXPhos	DMF	Cs_2CO_3	2.5	72
6	**$Pd_2(dba)_3.CHCl_3$**	**^{t}BuXPhos**	**DMF**	**Cs_2CO_3**	**0.5**	**81**
7[b]	$Pd_2(dba)_3.CHCl_3$	^{t}BuXPhos	DMF	Cs_2CO_3	7	67
8[c]	$Pd_2(dba)_3.CHCl_3$	^{t}BuXPhos	DMF	Cs_2CO_3	11	55
9	$Pd_2(dba)_3.CHCl_3$	XPhos	DMF	Cs_2CO_3	1	54
10	$Pd_2(dba)_3.CHCl_3$	RuPhos	DMF	Cs_2CO_3	2.5	35
11	$Pd_2(dba)_3.CHCl_3$	CyJohnPhos	DMF	Cs_2CO_3	1.5	45
12	$Pd_2(dba)_3.CHCl_3$	$P(Cy)_3$	DMF	Cs_2CO_3	8	42
13	$Pd_2(dba)_3.CHCl_3$	SPhos	DMF	Cs_2CO_3	2	Trace
14	$Pd_2(dba)_3.CHCl_3$	^{t}BuXPhos	DMSO	Cs_2CO_3	2.5	32
15	$Pd_2(dba)_3.CHCl_3$	^{t}BuXPhos	DCE	Cs_2CO_3	2.5	Trace
16	$Pd_2(dba)_3.CHCl_3$	^{t}BuXPhos	THF	Cs_2CO_3	2.5	n.r.

[a]Reaction conditions (Unless noted otherwise): A mixture of 1.0 equiv of **136a**, 1.2 equiv of **138a**, and 4.0 equiv. of Cs_2CO_3 in 2.0 mL solvent in the presence of 5 mol% of the Pd(0) catalyst and 10 mol% ligand was heated at 100 °C under argon.[b]The reaction mixture was heated to 80 °C. [c]The reaction was performed with 3 mol% of $Pd_2(dba)_3.CHCl_3$ along with 6 mol% of ^{t}BuXPhos .

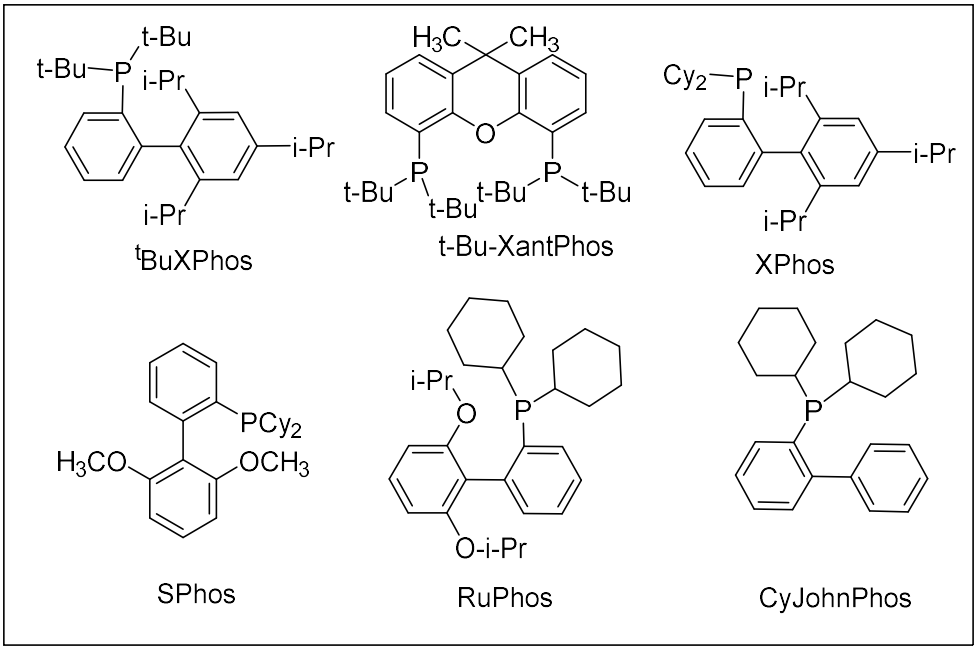


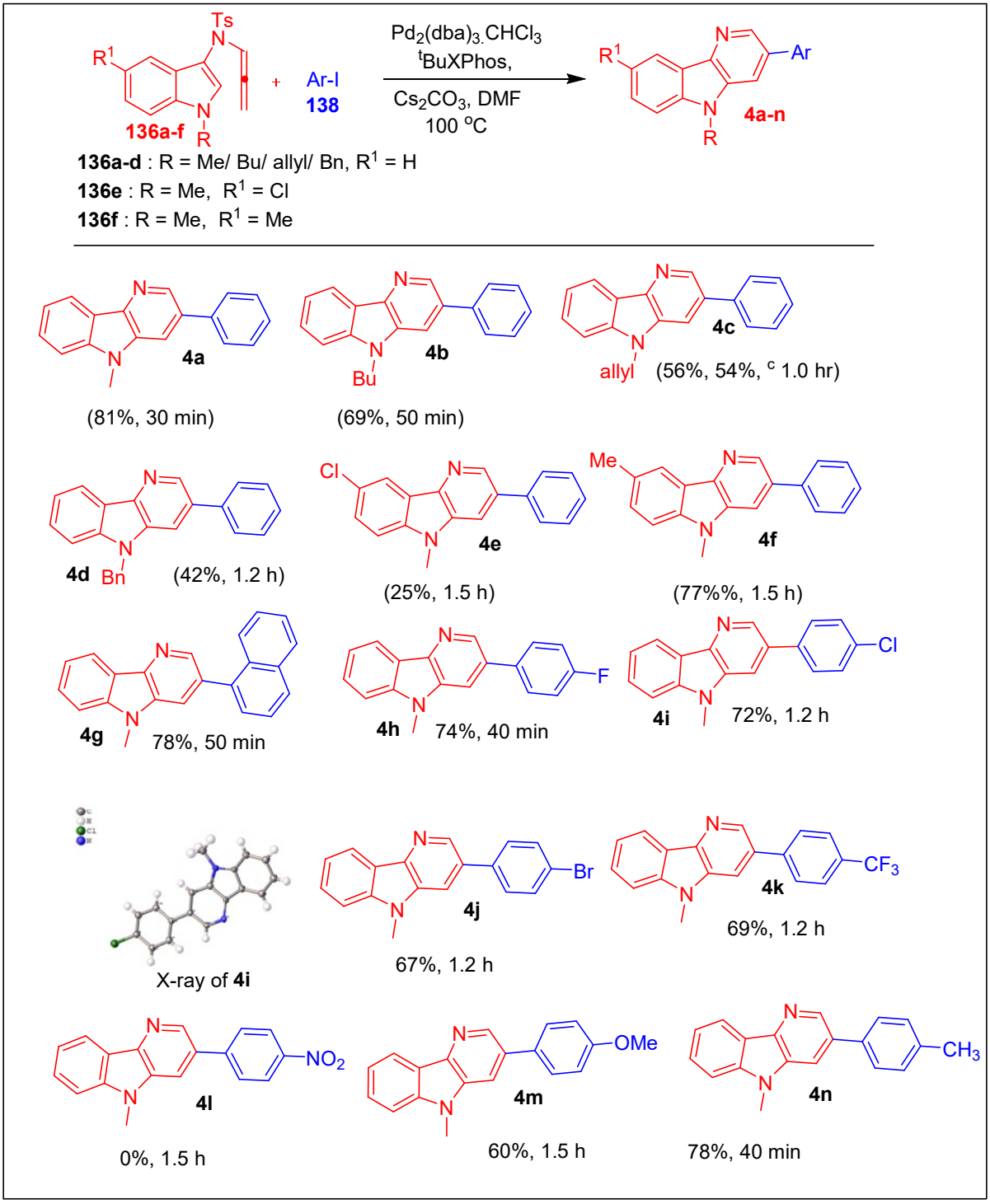
Figure 6. Structures of the ligands used during optimization study

2.2.3.2 Scope of the reaction for the synthesis of δ-carbolines 4:

With the optimized reaction conditions in hand, we investigated the scope of this reaction by carrying out reactions using a range of allenamides **136a-f** with a diverse array of aryl iodides **138a-i** (**Scheme 43**). Notably, when Bu/allyl/Bn groups are used as N-protecting group instead of Me in the indole ring of substrate **136** as in **136b-d**, the reaction required somewhat longer reaction time (50 min-1.2 h) and the yields (42-69%) of the products **4b**/**4c**/**4d** were found to be reduced to some extent. In subsequent reactions, when phenyl iodide (**138a**) was allowed to react with allenamides **136e** (R^1 = Cl) or **136f** (R^1 = Me) having an electron-withdrawing or electron-donating group (EWG or EDG) at C5 of the indole moiety, the desired carboline **4e** (25%) or **4f** (77%) was found to be formed within 1.5 h. The lower yield of **4e** is accounted for by the electron-withdrawing effect of the chloro group, which induces delocalization of electrons from the nitrogen atom (of the indole ring) of substrate **136e** toward the benzene ring, thereby reducing the nucleophilicity of C3 of the indole ring. Furthermore, the bulky naphthyl iodide (**138b**) participated in the reaction with equal ease affording the carboline **4g** within 50 min with 78% yield.

Next, we carried out the reaction of allenamide **136a** with a range of aryl iodides **138c-f**/**138h-i** bearing EDG or EWG as shown in **Scheme 43**. In this study, iodides **138c-f** possessing moderately EWG such as F/Cl/Br/CF_3 facilitated the reaction by delivering the

Scheme 43: Pd(0)-catalyzed synthesis of *δ*-carbolines **4**[a-c]



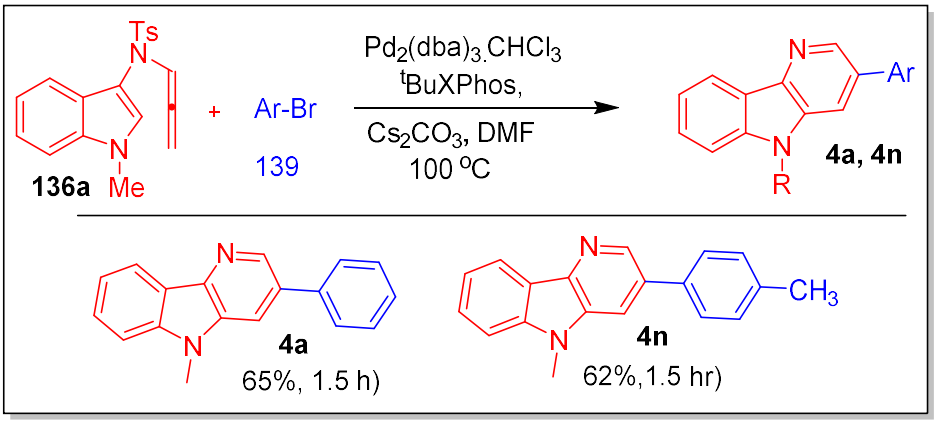
[a]Reaction conditions: A mixture of **136** (1 equiv.), **138** (1.2 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and $^tBuXphos$ (10 mol%) in DMF (2 mL) was refluxed under argon. [b]Isolated yield. [c] 1.0 mmol scale reaction.

carbolines **4h-k** within 40 min to 1.2 h with 67-74% yields. Surprisingly, incorporation of a strongly EWG like nitro at para position of **138a** made the resulting iodide (**138g**)

incompatible for the reaction as the desired product **4l** was not generated; instead few uncharacterised products were formed in minor amounts (TLC). In contrast, a strongly EDG (viz. OMe) placed at the same position as in **138h** promoted the reaction to furnish the carboline **4m** within 1.5 h with good yield (60%). Interestingly, iodide **138i** having a moderately EDG (viz. Me) was found to be more reactive, forming carboline **4n** within 40 min with 78% yield.

Of particular note, aryl bromides **139** were also found to be reactive towards this reaction though somewhat lower yields of the products were observed. For instance, when phenyl bromide (**139a**) is used in place of phenyl iodide (**138a**), *δ*-carboline **4a** was formed in 1.5 h with 65% yield, while *p*-bromo toluene (**139b**) afforded the product **1n** in 62% yield with the same reaction time (**Scheme 44**).

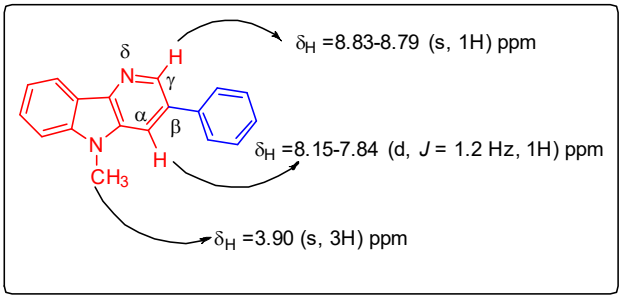
Scheme 44: Pd(0)-catalyzed synthesis of *δ*-carbolines **4**[a-b] by using aryl bromide



[a]Reaction conditions: A mixture of **136a** (1 equiv.), **139** (1.2 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and t-BuXPhos (10 mol%) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.

2.2.3.3 Nature and characterization of δ-carbolines 4

The structure of the intermediate **4** were unambiguously concluded by spectral (^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, proton (H_a) attached to the carbon atom adjacent to nitrogen atom of fused pyridine ring of product **4** appears as singlet at the range of



8.83-8.79 ppm, while the other proton (H_b) of δ-carbolines moiety appears as doublet at the range of 8.15-7.84 ppm. Whereas, the methyl protons of nitrogen atom of indole moiety displayed as singlet at 3.90 ppm. Further, the ^{13}C NMR gave additional support in the favour the structure.

Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **4i.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure are shown in Figure 7.

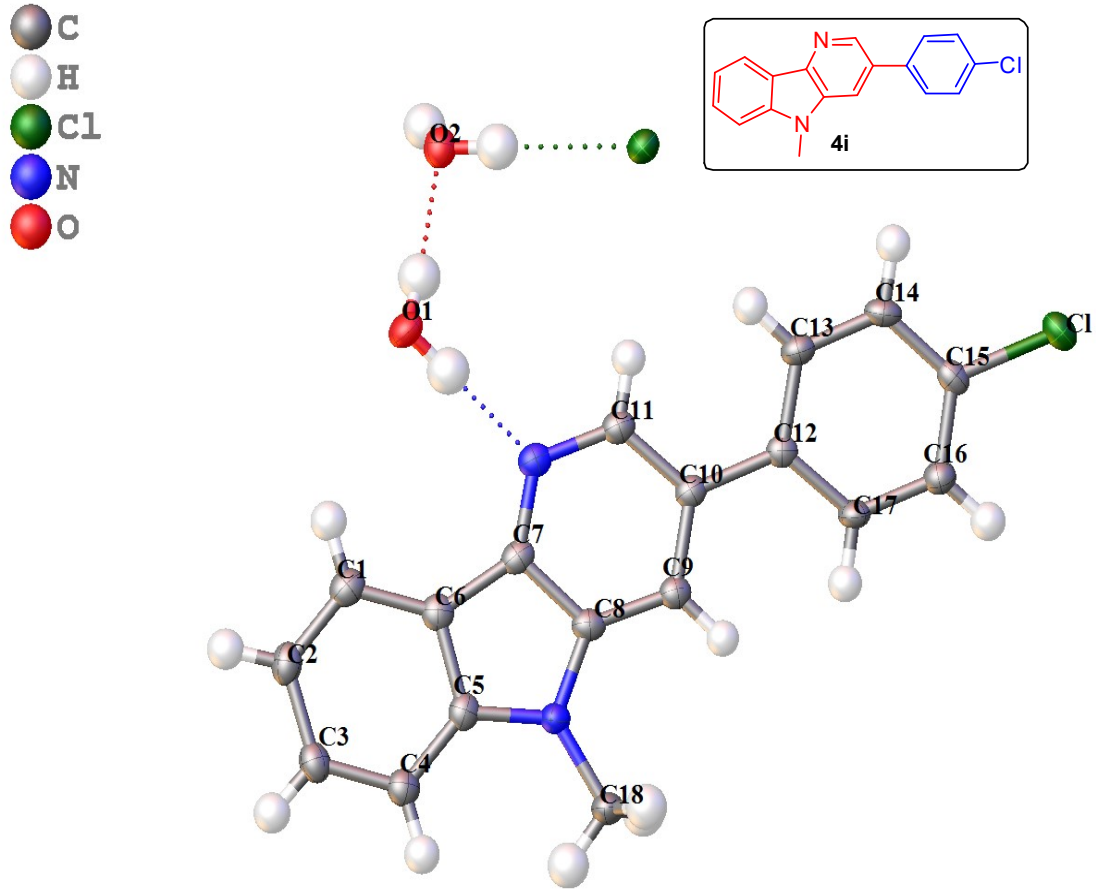


Figure 7. ORTEP Diagram (thermal ellipsoid plot) of product **4i** (drawn at 50% probability level).

Table 2: Important crystal data of product **4i**

Empirical formula	'C_{18} H_{13} Cl N_2' 2(H_2O) Cl
Formula weight	364.23
Temperature	100(2)
Wavelength	1.54178
Crystal system	'monoclinic'
Space group	'P 1 21/n 1'
Unit cell dimensions	a = 14.3318(4) Å α = 90
	b = 7.1230(2)Å β = 105.6930(10)
	c = 17.0200(5) Å γ = 90
Volume	1672.73(8) $Å^3$
Z	4
Density (calculated)	1.446g/cm^3
Absorption coefficient (Mu)	3.602 mm^{-1}
F(000)	756
Theta range for data collection	3.59to 65.02
Index ranges	-16<=h<=16, -8<=k<=8, -20<=l<=19
Reflection collected	23203
Independent reflections	2796 [R(int) = 0.0449]
Completeness to theta	98.2 %
Absorption correction	multi-scan
Max. and min. transmission	0.7526 and 0.5287
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2796/0/ 224
Goodness-of-fit on F^2	1.011
Final R indices [I>2sigma(I)]	R1 = 0.0390, wR2 = 0.1039
R indices (all data)	R1 = 0.0400, wR2 = 0.1048
Largest diff. peak and hole	0.541 & -0.522 e.A^{-3}

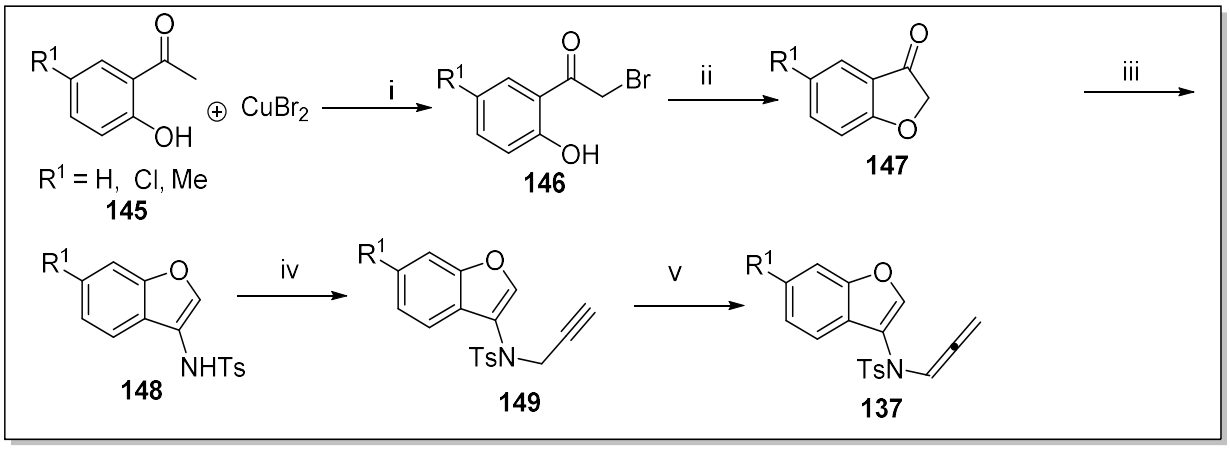
The single crystal of compound **4i** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **4i** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2195469**.

2.2.4. Extension of the methodology for the synthesis of benzofuro[3,2-*b*]pyridines 137

Encouraged by the above results, we decided to check the viability of the methodology for a domino synthesis of benzofuro[3,2-*b*]pyridines **137.**

2.2.4.1 Preparation of starting material 137

The requisite *N*-allenamide substrates **137** were synthesized in five steps starting from commercially available 2-hydroxy acetophenone **145**. Thus bromo intermediates **146** could easily be achieved through bromination of **145**. Next, a base induced cyclization of **146** resulted in the formation of intermediate **147** which upon treatment with *p*-toluenesulphonamide in the presence of *p*-toluenesulphonic acid at 120 ^{o}C afforded the sulfonamidobenzofuran intermediate **148**. Finally, N-propargylation of **149** followed by a base treatment of the resulting compound (i.e., **137**) led to the formations of allenamide substrates **137**.



Scheme 45. Synthesis of substrate **137**. Reagent and Conditions: (i) $CuBr_2$, EtOAc, $CHCl_3$, DMF, reflux, 10-12 h, 78-85%; (ii) Et_3N, CH_3CN, 30-45 min, 81-88%; (iii) *p*-$TsNH_2$, *p*-TsOH, toluene, 120 ^{o}C, 3-5.3 h, 81-85%; (iv) Propargyl Bromide, NaH, DMF, 0^{0}C- rt, 3-5 h, 78-85%; (v) ^{t}BuOK, THF, 5-15 min, rt, 68-74%.

2.2.4.2 Synthesis of benzofuro[3,2-*b*]pyridine derivatives 95

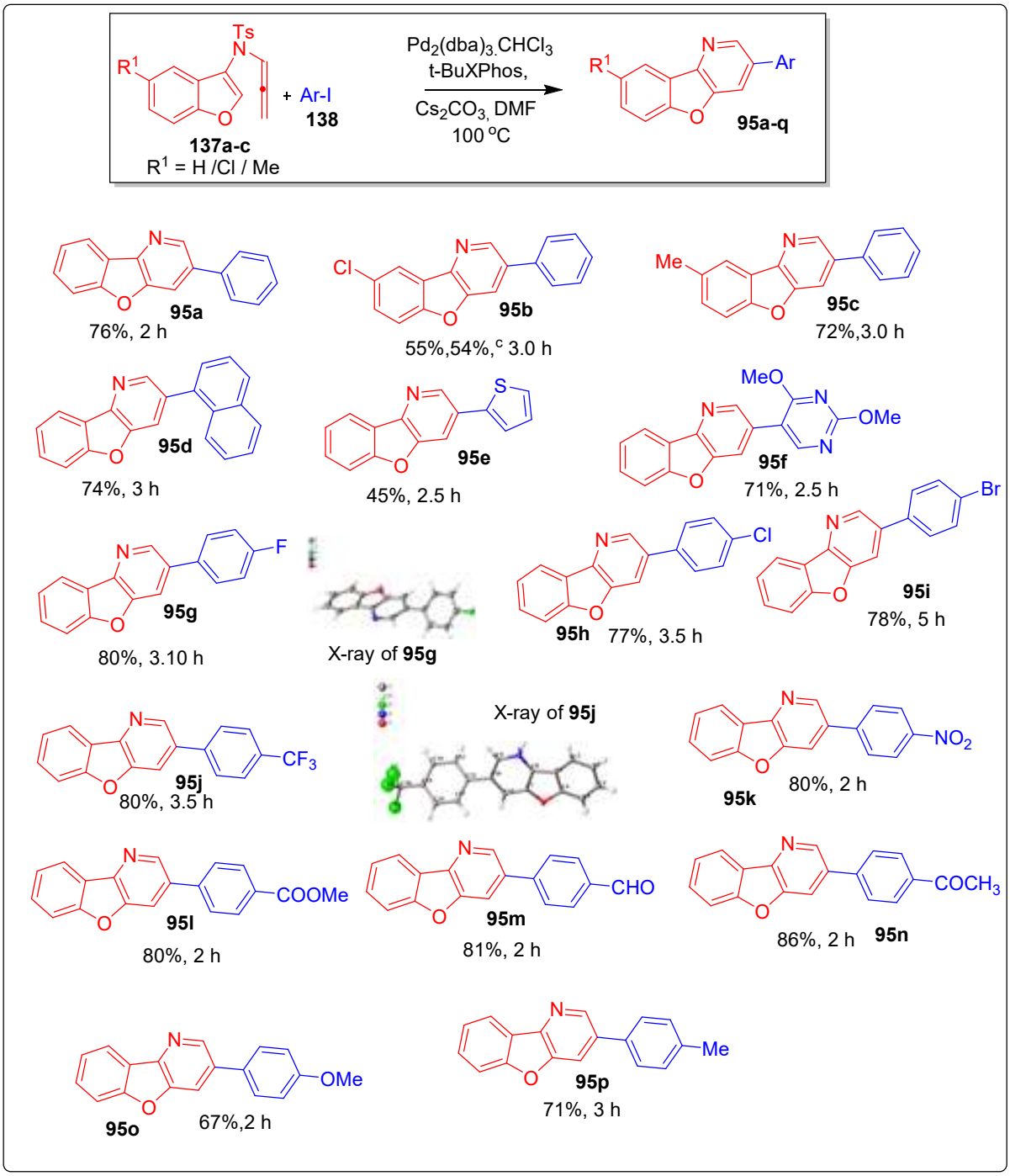
The starting material **137a** was allowed to react under the optimized reaction conditions of Table **1.** Surprisingly, use of the same reaction conditions, optimized previously, on **137a** delivered the desired product **95a** with excellent yields (45-82%) within 2-5 h. Therefore, we decided to explore the substrate scope by using same reaction conditions entry 6 of Table 1).

2.2.5.2 Scope of the reaction

Next, we became interested to extend the scope of this reaction for the general synthesis of benzofuro[3,2-*b*]pyridines **95** (**Scheme 46**). Toward this objective, requisite benzofuran substrates **137a-c** having an allenamide moiety at the C3 position were prepared in few steps

(**Scheme 45**) and utilized in subsequent reactions with various aryl iodides/bromides **138/139** (**Scheme 46** & **Scheme 47**) under the optimized reaction conditions (Table 1, entry 6). Similar to the results noted in the previous reactions of allenamides **3e-f** (**Scheme 43**),

Scheme 46. Pd(0)-catalyzed synthesis of benzofuro[3,2-b]pyridines **95**[a,c]



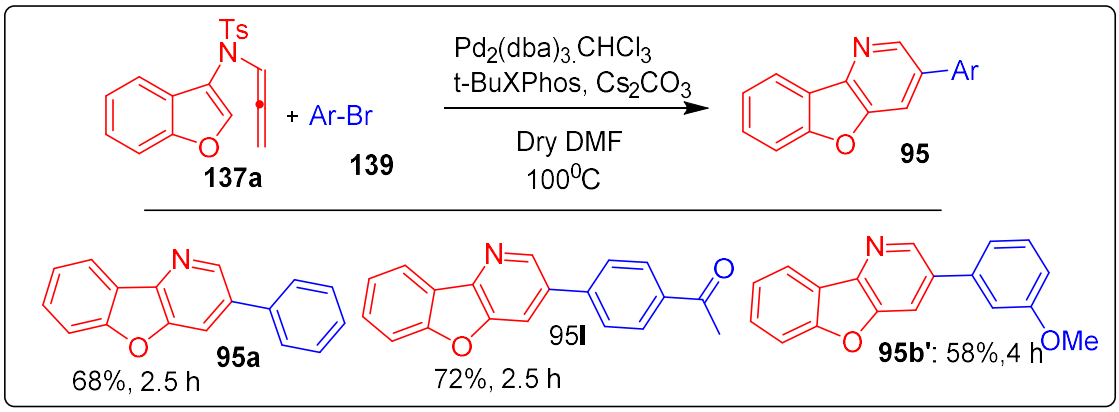
[a]Reaction conditions: A mixture of **137** (1 equiv), **138** (1.2 equiv), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and [t]BuXphos (10 mol %) in DMF (2 mL) was refluxed under argon. [b]Isolated yield. [c]1.0 mmol scale reaction

the reactions of phenyl iodide **138a** with substrates**137b** (R^1 = Cl) and **137c** (R^1 = Me) having a substitution at C5 of the benzofuran moiety resulted in the formation of benzofuro[3,2-*b*]pyridines **95b** and **95c**, respectively, within 3 h with 55-72% yields. Allenamide **137a** underwent reactions with naphthyl iodide **138b** and 2-iodo-thiophene **138j** too; the corresponding products **95d** (74%) and **95e** (45%) were formed within 2.5-3 h. But 5-iodo-2,4-dimethoxy pyrimidine (**138k**), a heteroaryl iodide, produced the product **95f** within 2.3 h with very good yield (71%) as compared to that of **95e.**

We then explored the reactivity of allenamide **137a** with different aryl iodides (**138c-g**, **138l-m**, **138h-i**) possessing either EWG or EDG. Substrates **138c-f** possessing a moderately EWG (viz., F, Cl, Br, CF_3) participated in the reaction with equal ease leading to the formations of benzofuro[3,2-*b*]pyridines **95g-j** with 3.1-5 h with 78-80% yield In contrast to the observation of product **4l** (of **Scheme 43**), iodides (**138g**, **138l-n**) having a strongly EWG (viz., NO_2, CHO, CO_2Me, COMe) proved to be more reactive leading to the formation of benzofuro[3,2-*b*]pyridines **95k-n** within 2 h with 80−86% yields. . Whereas iodides **138h** or **138i** containing either strong or moderate EDG also delivered the product **95o** or **95p** in 2-3 h, though the yields were somewhat lower (67-71%).

Besides, in tune with the observations of **Scheme 45**, aryl bromides also successfully participated in this reaction though slightly lower yields were observed in comparison to aryl iodides. For instance, phenyl bromide (**139a**), 4-bromoacetophenone (**139b**) and 3-bromoanisole (**139c**) reacted successfully with allenamide **137a** furnishing the products **95a** (68%), **95n** (72%) and **95q** (58%), respectively, within 2.5-4 h.

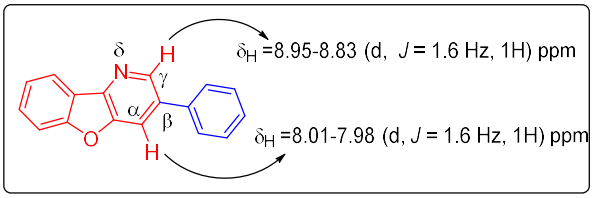
Scheme 47: Pd(0)-catalyzed synthesis of benzofuro[3,2-*b*]pyridines **95**[a-b] by using aryl bromide



[a]Reaction conditions: A mixture of **137a** (1 equiv), **139** (1.2 equiv), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and [t]BuXphos (10 mol %) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.

2.2.4.4 Nature and characterization of benzofuro[3,2-b]pyridines 95

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 ^{o}C) for several months. In ^{1}H NMR, proton (H_a) attached to the carbon atom adjacent to nitrogen atom of fused pyridine ring of the benzofuro[3,2-*b*]pyridines **95** appears as singlet at the range of 8.95-8.83 ppm while the other proton (H_b) of benzofuro[3,2-b]pyridines **95** moiety appears as doublet at the range of 8.01-7.98 ppm. Furthermore, ^{13}C-NMR and mass spectra gave additional support in the favour the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **95g.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure are shown in Figure 8 and Figure 9.

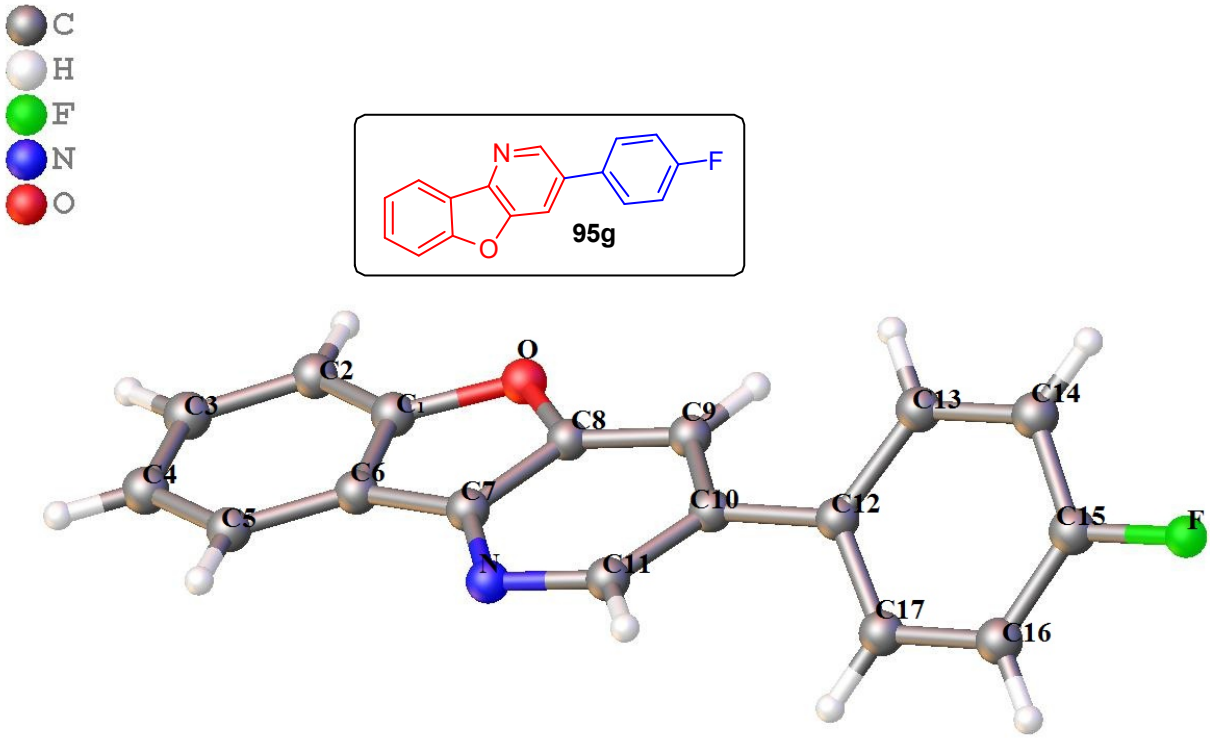


Figure 8. ORTEP Diagram (thermal ellipsoid plot) of Product **95g** (drawn at 50% probability level)

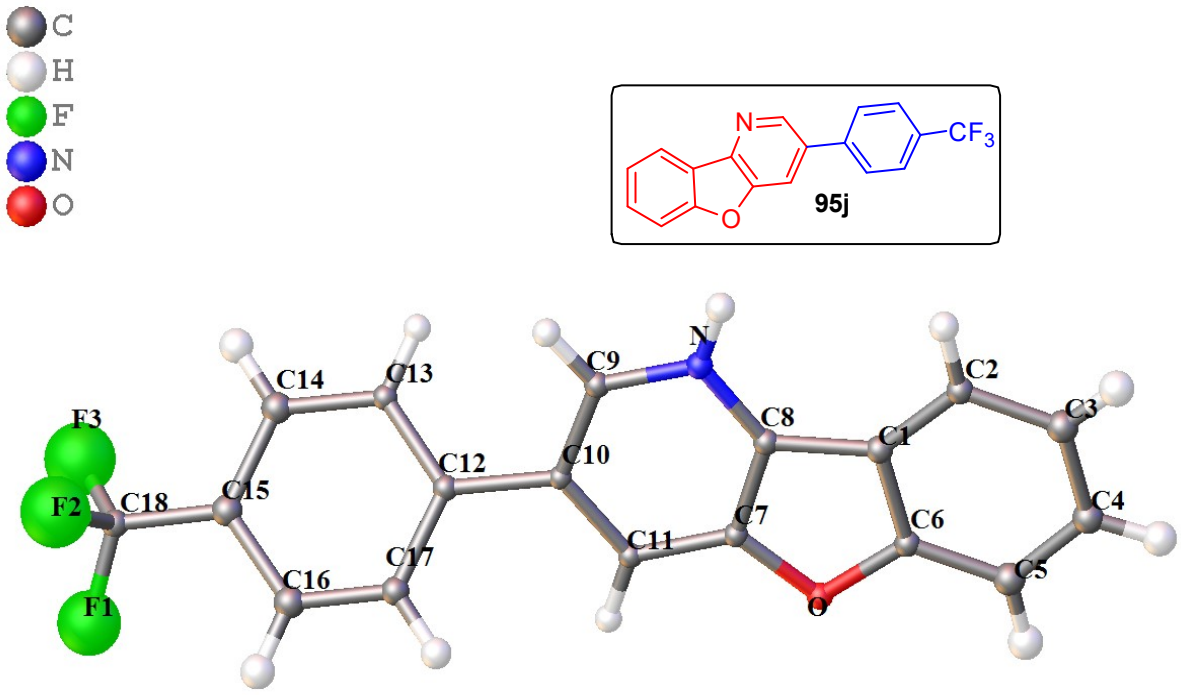


Figure 9. ORTEP Diagram (thermal ellipsoid plot) of Product **95j** (drawn at 50% probability level)

N.B., Few important crystal data of products **95g** and **95j** reported in **Scheme 46** are provided below.

Table 3: Important crystal data of product **95g**

Empirical formula	$C_{17}H_{10}FNO$
Formula weight	263.26
Temperature	100(2)
Wavelength	1.54178
Crystal system	'monoclinic'
Space group	' C 2/c '
Unit cell dimensions	a = 27.8646(7) Å α = 90
	b = 11.9738(3) Å β = 91.696(2)
	c = 7.1147(2) Å γ = 90
Volume	2372.75(11) $Å^3$
Z	8
Density (calculated)	1.474 g/cm^3
Absorption coefficient (Mu)	0.846 mm^{-1}
F(000)	1088
Theta range for data collection	4.019 ^{0} to 65.033 ^{o}
Index ranges	-32<=h<=32, -13<=k<=14, -8<=l<=8
Reflection collected	44746
Independent reflections	2011 [R(int) = 0.0928]
Completeness to theta	99.4 %
Absorption correction	multi-scan
Max. and min. transmission	0.7526 and 0.3755
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2011/0/ 182
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.1498
R indices (all data)	R1 = 0.0574, wR2 = 0.1502
Largest diff. peak and hole	0.299 & -0.420 $e.A^{-3}$

The single crystal of compound **95g** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **95g** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2195470.**

Table 4: Important crystal data of product **95j**

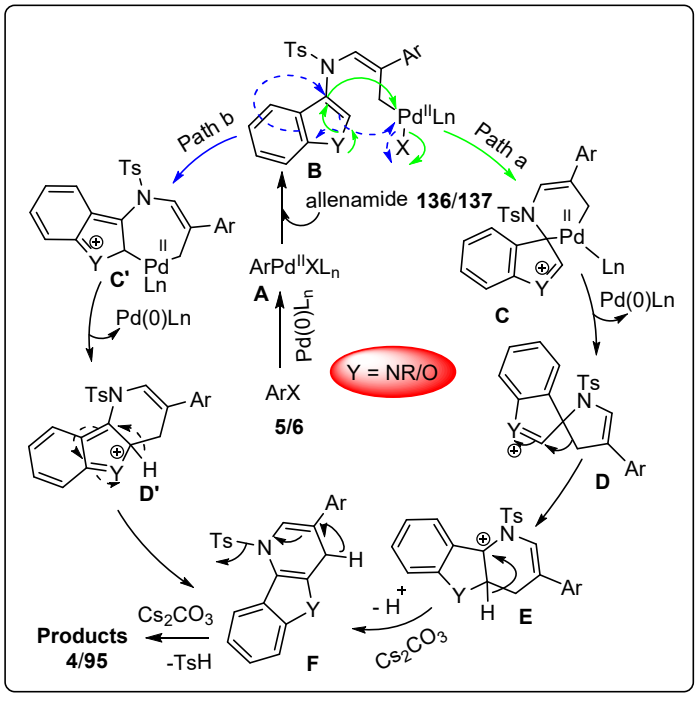
Empirical formula	$C_{18}H_{10}F_3NO$
Formula weight	313.27
Temperature	100.0
Wavelength	1.54184
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 16.3502(10) Å α = 90 ^{0} b = 11.8109(7) Å β = 98.058(2) ^{0} c = 7.1124(4) Å γ = 90 ^{0}
Volume	1359.92(14) $Å^3$
Z	4
Density (calculated)	1.530g/cm^3
Absorption coefficient (Mu)	1.058mm^{-1}
F(000)	640.0
Theta range for data collection	9.268 to 145.504
Index ranges	$-19 \leq h \leq 20, -14 \leq k \leq 14, -8 \leq l \leq 8$
Reflection collected	23016
Independent reflections	2679 [R_{int} = 0.0606]
Completeness to theta =	98.9 %
Absorption correction	multi-scan
Max. and min. transmission	0.5864 and 0.3912
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2679/36/237
Goodness-of-fit on F^2	1.196
Final R indices [I>2sigma(I)]	R_1 = 0.0699, wR_2 = 0.1928
R indices (all data)	R_1 = 0.0709, wR_2 = 0.1934
Largest diff. peak and hole	0.41/-0.33 e.A^{-3}

The single crystal of compound **95j** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **95j** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2195471.**

2.2.5. Plausible mechanism of the formation of product 4 and 95:

We propose a plausible reaction mechanism (**Scheme 48**) to explain the formation of products **4**/**95**. At the outset, aryl halides (ArX) undergoes oxidative addition with Pd(0) to form ArPd(II)X[38] (**A**), which then undergoes addition onto the allenic double bond of substrate **136/137** triggering the formation of palladium(II)-Π-allyl complex **B**.[39] Intermediate **B** undergoes (**path a**) intramolecular nucleophilic attack by C3 of the indole or furan moiety resulting in the formation of a six-membered palladium(II) species **C**. Next, a reductive elimination of palladium(II) from species **C** would lead to the formations of a transient spiro-intermediate **D** and Pd(0). Nevertheless, a preferential allylic group migration[36c] (from C3 position of indole or furan moiety) of intermediate **D** to its C2 position would produce a carbonium intermediate **E** which upon deprotonation would easily generate a dihydropyridine intermediate **F.** Finally, a base induced elimination of TsH from **F** leads to the formations of desired products **4** (or **95**).

Alternatively (path b), an intramolecular nucleophilic attack of C2 of the indole (or furan ring) of **B** onto the palladium would lead to the generation of a seven-membered palladium(II) intermediate **C´**, the reductive elimination of which would furnish intermediate **D´** with concurrent formation of Pd(0) which keeps the catalytic cycle active. Next, a base



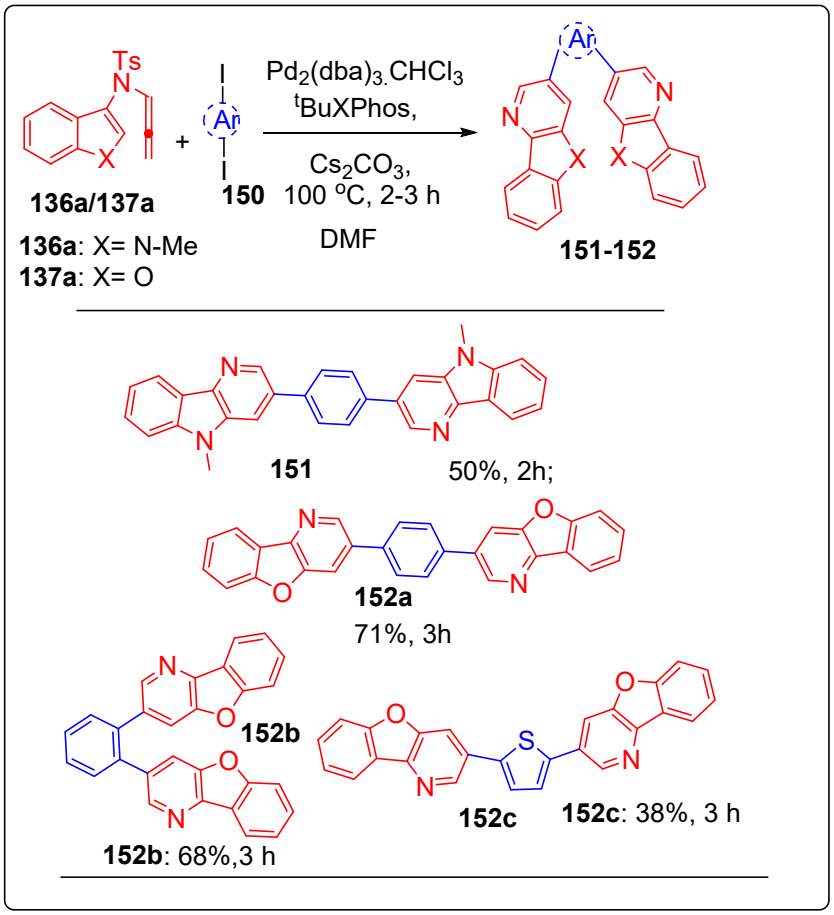
Scheme 48: A Plausible reaction mechanism

assisted deprotonation of **D´** would produce a fused dihydropyridine intermediate **F** which after base promoted elimination of TsH would trigger the formations of products **4** (or **95**).

2.2.6 Synthesis of bis-heteroannulated products 151-152[a,b]

In view of the importance of bis-δ-carbolines present in bioactive alkaloids[4] (e.g., *cryptomisrine*), we also checked the prospect of bisheteroannulations using few di-iodo substrates **150** (**Scheme 49**). Thus, bis-δ-carboline **151a** could easily be accessed by conducting the reaction between allenamide **136a** and 1,4-diiodobenzene **150a** under the optimized reaction conditions. On the other hand, when allenamide **137a** was allowed to react successively with 1,4-diiodobenzene (**150a**), 1,2-diiodobenzene (**150b**) and 1,2-diiodothiophene (**150c**), the expected bis-benzofuro[3,2-*b*]pyridine derivatives **152a-c** were generated within 3 h with 40-73% yields suggesting poly-heteroannulation in one-pot to be a viable process.

Scheme 49. Synthesis of bis-heteroannulated products 151-152[a,b]



[a]Reaction conditions: A mixture of **136a** or **137a** (1 equiv), **150** (0.6 equiv), $Pd_2(dba)_3.CHCl_3$ (5 mol%), and ^{t}BuXphos (10 mol%) in DMF (2 mL) was refluxed under argon. [b]Isolated yield.

2.2.7 Conclusion

In conclusion, we have successfully developed an efficient method for the general synthesis of δ-carbolines **4** in 25-81% yield with reaction time of 0.5-1.5 h via palladium(0)-catalyzed reactions between allenamides **136** and aryl iodides **138** or bromides **139** . Replacing the indole moiety of substrate **136** by benzofuran ring as in substrate **137** was also compatible to this reaction, triggering the formation of benzofuro[3,2-*b*]pyridines **95** within 2-4 h with 45-86% yield. A plausible reaction mechanism is proposed to explain the product formations. The method is amenable to the synthesis of bis-heteroannulated products **151**-**152** by using aryl/heteroaryl diiodides **150** instead of aryl iodides **138** thereby suggesting the viability of polyheteroannulation under one-pot. The hallmark of the method is operational simplicity, short reaction time, tolerance of various functional groups, and use of simple substrates.

2.2.8. Experimental section

2.2.8.1General information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 ^{o}C. CH_3CN (Acetonitrile) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane, THF (Tetrahydrofuran), were distilled over sodium and benzophenone. Commercial grade dry DMF (Dimethylformamide), DMSO (Dimethyl sulfoxide), $CHCl_3$ (Chloroform), Toluene, EtOAc were used as a solvent. 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 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 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), m (multiplet), and brs (broad singlet). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF. Some compounds were purified using preparative tlc. Reactions that require heating, oil bath containing of silicon oil is use as a heat source. The starting materials [i.e., Halides (**138**,**139**), **141** and **145**] are commercially available.

2.2.8.2 X-Ray crystallographic information of products 4i, 95g and 95j:

Single crystal of products **4i, 95g and 95j** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether or ethyl acetate- petroleum ether. A single crystal of **4i, 95g and 95j** 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 **4i, 95g and 95j** were measured with MoKα radiation (λ = 0.71073 Å) at 293 K. The structure was solved by direct methods using the SHELXS-97 program.[40] Refinements were carried out with a full matrix least squares method against F 2 using SHELXL-97.[41] 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. Important crystal data and ORTEP diagram (drawn at 50% probability level) of product **4i, 95g and 95j** are provided earlier.

2.2.8.3 General procedure for preparation of starting materials 137

*General Procedure for the synthesis[42] of 1-methyl-1H-indole (**142**) (of Scheme 41)*

NaH (12.8 mmol, 1.5 equiv) was added to a well-stirred solution of **141** (8.54 mmol, 1 equiv) in dry DMF (10 mL) at ice-cold condition under argon atmosphere and the stirriing was continued for 15 minutes. To this stirred solution, alkyl iodide (or allyl bromide or benzyl bromide) (11.1 mmol, 1.3 equiv) was added dropwise at 0 ^{o}C. Subsequently, the reaction mixture was allowed to stir at room temperature for another 6-8 h. After completion (TLC) of the reaction, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with water (3 x 40 mL) and brine (3 x10 mL), respectively. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash column chromatography over silica gel (100-200 mesh) using 2-8% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product N-protected indole **142** in 81-95% yield.

*General Procedure for the synthesis[13c] of 4-methyl-N-(1-methyl-1H-indol-3-yl)benzenesulfonamide (**143**) (Scheme 41):*

An oven-dried round-bottomed flask (25 mL) was charged with N-alkyl indole **142** (3.8 mmol, 1 equiv.) and *p*-toluenesulfonyl azide (5.3 mmol, 1.4 equiv) in dry 1,4-dioxane (5 mL)under nitrogen atmosphere. The mixture was stirred with heating (at 75−80 °C) for about 18−24 h. After the completion of the reaction (TLC), cold ethanol (25 mL) was added which led to the crystallization /precipitation of undesired side product, i.e., 2-sulfonamidoindoline. The filtrate was then removed under reduced pressure and the crude residue was purified by

column chromatography over silica gel (100-200 mesh) using hexane/ethyl acetate (70:30) as eluent to obtain 3-sulfonamidoindole **143** in 25-34% yields.

*General procedure for the preparation[43] of 4-methyl-N-(1-methyl-1H-indol-3-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide (**144**) (Scheme 41)*:

A well-stirred solution of **143** (0.33 mmol, 1equiv.) in DMF (4.0 mL) was cooled to 0 °C. Then NaH (60% oil suspension in mineral oil; 17.2 mg, 0.43 mmol, 1.3 equiv) was added to the ice-cold solution of **143**. After stirring for ten minutes, propargyl bromide (36 µl, 0.4 mmol, 1.2 equiv) was added dropwise under the same reaction medium. Next, the reaction mixture was allowed to reach at room temperature and stirred at rt until completion (TLC). After quenching with water (3.0 mL), the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed consecutively with brine water (10 mL) and dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography with petroleum ether: ethyl acetate (v/v, 8:1) as eluent to afford the products **144** in 65-76% yields.

General procedure for the preparation[44] of 4-methyl-N-(1-methyl-1H-indol-3-yl)-N-(propa-1,2-dien-1-yl)benzenesulfonamide 3(Scheme 41):

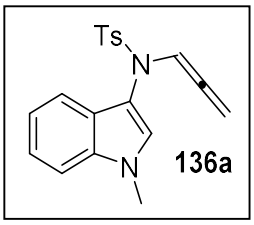
To a well-stirred solution of **144** (0.15 mmol, 1 equiv.) in dry THF (2.0 mL) at room temperature under argon atmosphere, KO^{t}Bu (0.10 mmol, 0.7 equiv) was added. The mixture was then stirred for another 5-15 min until the completion of reaction (TLC). The reaction mixture was then diluted with ethyl acetate (10 mL) and filtered through celite. After removal of the solvent, crude residue obtained was purified by silica gel column chromatography using 6-8% petroleum ether/ethyl acetate (v/v) as eluent to isolate the pure products **136** in 49-70% yields .

2.2.8.4 Method for the synthesis of the starting material 136a at 1 mmol scale

To a well-stirred solution of **144a** (1 mmol, 1 equiv.) in dry THF (12.0 mL) at room temperature under argon atmosphere, KO^{t}Bu (78.5 mg, 0.7 mmol, 0.7 equiv) was added pinched wise. The mixture was then stirred for another 12 min until the completion of reaction (TLC). The reaction mixture was then diluted with ethyl acetate (10 mL) and filtered through celite. After removal of the solvent, crude residue obtained was purified by silica gel column chromatography using 7% petroleum ether/ethyl acetate (v/v) as eluent to isolate the pure products **136a** in 66% yield (223.5 mg).

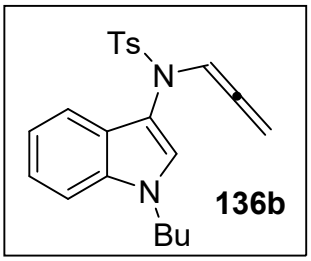
2.2.8.5 Spectral data of substrates 136a-136f:

4-Methyl-*N*-(1-methyl-1H-indol-3-yl)-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide(136a)



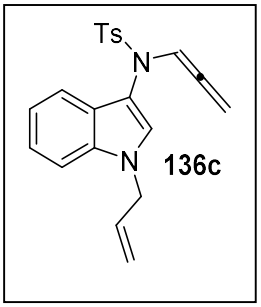
Brown solid (35 mg, 70% yield); mp. 122-124 ^{o}C; R_f = 0.51 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.56 (d, *J* = 8.4, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.19-7.10 (m, 3H), 6.97 (s, 1H), 6.88-6.79 (m, 2H), 4.93 (d, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.3, 143.8, 135.8, 135.4, 129.5, 128.7, 127.8, 124.8, 121.9, 119.6, 119.1, 112.0, 109.5, 102.8, 87.5, 33.2, 21.7; HRMS (ESI+) m/z calculated for $C_{19}H_{19}N_2O_2S$ $[M+H]^+$ 339.1167, found 339.1170.

***N*-(*1*-butyl-1H-indol-3-yl)-4-methy*l*-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (136b)**



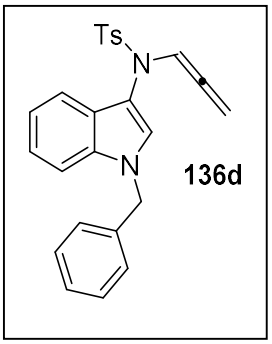
Brown solid (33.5 mg, 67% yield); mp. 116-118 ^{o}C; R_f = 0.47 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.57 (d, *J* = 8.4 Hz, 2H), 7.28-7.23 (m, 2H), 7.20-7.17 (m, 2H), 7.14-7.10 (m, 1H), 7.02-6.99 (m, 1H), 6.93-6.89 (m, 1H), 6.88 (s, 1H), 4.94 (d, *J* = 6.4 Hz, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.79-1.71 (m, 2H), 1.30-1.20 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.3, 143.8, 135.6, 134.7, 129.5, 127.9, 127.6, 125.2, 121.8, 119.7, 119.2, 111.9, 109.6, 103.0, 87.4, 46.3, 32.1, 21.7, 20.0, 13.7; HRMS (ESI+) m/z calculated for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$ 381.1637, found 381.1619.

***N*-(1-allyl-1H-indol-3-yl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide(136c)**



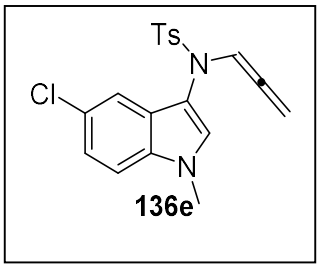
Brown solid (31 mg, 62% yield); mp. 80-82 ^{o}C; R_f = 0.49 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.58 (d, *J* = 8.4 Hz, 2H), 7.27-7.18 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.97-6.89 (m, 3H), 5.98-5.89 (m, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.97-4.94 (m, 3H), 4.65 (d, *J* = 4.8 Hz, 2H), 2.40 (s, 3H) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.3, 143.8, 135.6, 134.9, 133.0, 129.5, 127.9, 127.7, 125.1, 122.1, 119.9, 119.2, 117.5, 112.5, 109.8, 102.9, 87.6, 48.8, 21.7; HRMS (ESI+) m/z calculated for $C_{21}H_{21}N_2O_2S$ $[M+H]^+$ 365.1324, found 365.1314.

***N*-(1-benzyl-1*H*-indol-3-yl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide(136d)**



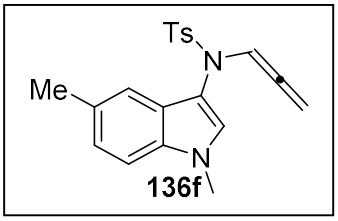
Brown solid (32.5 mg, 65% yield); mp. 115-117 °C; R_f = 0.46 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.56 (d, *J* = 8.0 Hz, 2H), 7.28-7.26 (m, 3H), 7.25-7.23 (m, 1H), 7.21-7.19 (m, 1H), 7.15(d, *J* = 8.4 Hz, 2H), 7.11-7.08 (m, 2H), 7.02-6.99 (m, 2H), 6.93-6.92 (m, 1H), 6.86 (s, 1H), 5.93 (s, 2H), 4.95 (d, *J* = 6.0 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.4, 143.8, 137.0, 135.4, 135.0, 129.5, 128.8, 127.93, 127.88, 127.85, 126.7, 125.4, 122.3, 120.1, 119.3, 112.8, 109.9, 103.0, 100.0, 87.5, 50.2, 21.7; HRMS (ESI+) m/z calculated for $C_{25}H_{23}N_2O_2S$ $[M+H]^+$ 415.1480, found 415.1476.

N-(5-chloro-1-methyl-1H-indol-3-yl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide (136e)



Brown solid (21 mg, 49% yield); mp. 106-108 °C; R_f = 0.55 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.53 (d, *J* = 8.40, 2H), 7.25-7.19 (m, 3H), 7.14-7.11 (m, 1H), 7.05 (s, 1H), 7.03(dd, *J* = 8.8, 2.0 Hz, 1H), 6.41 (dd, *J* = 2.0, 0.4 Hz, 1 H), 4.94 (d, *J* = 6.4 Hz, 2H), 3.72 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.1, 144.4, 135.3, 133.8, 130.3, 129.7, 127.8, 125.7, 125.6, 122.3, 118.4, 111.6, 110.7, 102.7, 87.8, 33.4, 21.7; HRMS (ESI+) m/z calculated for $C_{19}H_{18}ClN_2O_2S$ $[M+H]^+$ 373.0778, found 373.0765.

***N*-(1,5-dimethyl-1H-indol-3-yl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (136f)**



Brown solid (21 mg, 64% yield); mp. 118-120 °C; R_f = 0.37 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.58 (d, *J* = 8.4 Hz, 2H), 7.22-7.18 (m, 3H), 6.83 (s, 1H), 6.81-6.79 (m, 1H), 6.74-6.67 (m, 2H), 4.95 (d, *J* = 6.0 Hz, 2H), 3.98 (s, 3H), 2.70 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.3, 143.7, 135.9, 134.2, 130.0, 129.5, 127.8, 126.0, 124.7, 121.4, 119.8, 117.2, 111.7, 102.7, 87.5, 37.3, 21.7, 19.8; HRMS (ESI+) m/z calculated for $C_{20}H_{21}N_2O_2S$ $[M+H]^+$ 353.1324, found 353.1324.

2.2.8.6 General procedure for the synthesis of products 4:

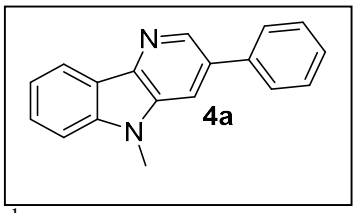
An oven dried two-neck round bottomed flask was charged with $Pd_2(dba)_3.CHCl_3$ (3.1 mg, 5 mol%) and $^tBuXphos$ (2.5 mg, 10 mol%) followed by addition of dry DMF (1 mL) *via* syringe; the whole reaction mixture was allowed to stir at rt for 30 min under argon atmosphere. Then aryl iodide (**138**) or aryl bromide (**139**)(0.07 mmol, 1.2 equiv) was then added and the stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (0.24 mmol, 4 equiv.) and allenamide **136** (0.06 mmol, 1equiv) were added successively under argon. The whole reaction mixture was then heated at 100 °C (using oil bath) for 0.30-1.5 h until completion (TLC). The resulting mixture was then extracted with dichloromethane (3 × 10 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel (100−200 mesh) column chromatography using 5−10% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **4** in 25-81% yields.

2.2.8.7 Method for the synthesis of the product 4c at 1 mmol scale:

An oven dried two-neck round bottomed flask was charged with $Pd_2(dba)_3.CHCl_3$ (21.8 mg, 5 mol%) and $^tBuXphos$ (17.9 mg, 10 mol%) followed by addition of dry DMF (6 mL) *via* syringe; the whole reaction mixture was allowed to stir at rt for 30 min under argon atmosphere. Then phenyl iodide (**138a**) (0.51 mmol, 1.2 equiv) was then added and the stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (549 mg 1.69 mmol, 4 equiv.) and N-(1-allyl-1H-indol-3-yl)-4-methyl-N-(propa-1,2-dien-1-yl)benzene sulfonamide **138c** (1 mmol, 1equiv) were added successively under argon. The whole reaction mixture was then heated at 100 °C (using oil bath) for 1 h until completion (TLC). The resulting mixture was then extracted with dichloromethane (3 × 30 mL) and washed with water (30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained was purified by silica gel (100−200 mesh) column chromatography using 7 % ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **138c** in 54% yield (153.7 mg).

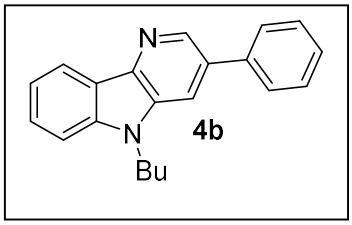
2.2.8.8 Spectral data of products 4a-n:

5-Methyl-3-phenyl-5H-pyrido[3,2-*b*]indole (4a)



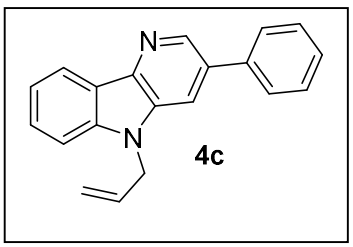
Brown solid (12.3 mg, 81% yield); mp. 174-176 ^{o}C; R_f = 0.16 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.79 (s, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.45-7.40 (m, 2H),), 7.33 (t, *J* = 7.4 Hz, 1H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 150.7, 142.4, 140.6, 139.2, 133.8, 129.2, 128.0, 127.8, 127.7, 120.2, 114.0, 108.9, 29.1; HRMS (ESI+) m/z calculated for $C_{18}H_{15}N_2$ $[M+H]^+$ 259.1235, found 259.1238.

5-Butyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole (4b)



Yellow gummy liquid(10.9 mg, 69% yield); R_f = 0.56 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.80 (d, *J* = 1.2 Hz, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.60-7.57 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.50-7.48 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 4.38 (t, *J* = 7.2 Hz, 2H), 1.91 (p, *J* = 7.5Hz, 2H), 1.46-1.40 (m, 2H), 0.98 (t, *J* = 7.5Hz, 3H); ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz) δ_C 141.9, 140.6, 140.4, 138.9, 134.3, 133.2, 129.6, 128.0, 121.6, 120.7, 120.2, 114.9, 110.5, 100.0, 31.3, 20.3, 14.3; HRMS (ESI+) m/z calculated for $C_{21}H_{21}N_2$ $[M+H]^+$ 301.1705, found 301.1702.

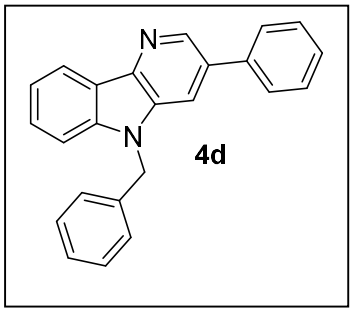
5-Allyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole (4c)



Yellow gummy liquid(8.7 mg, 56% yield); R_f = 0.47 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.77 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.83-7.81 (m, 2H), 7.65-7.63 (m, 1H), 7.56-7.49 (m, 3H), 7.42-7.38 (m, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 6.05-5.95 (m, 1H), 5.14-5.08 (m, 3H), 5.02-4.97 (m, 1H); ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz) δ_C 141.9, 140.8, 140.6, 138.8, 134.2, 133.6, 133.2, 129.6, 128.3, 128.2, 127.9, 121.7, 120.7, 120.4, 117.2, 115.0, 110.7, 45.1; HRMS (ESI+) m/z calculated for $C_{20}H_{17}N_2$ $[M+H]^+$ 285.1392, found 285.1402.

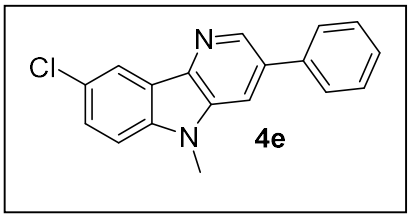
5-Benzyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole (4d)

Brownish gummy liquid (6.8 mg, 42% yield); R_f = 0.42 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.83 (s, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.80 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.45-7.36 (m, 3H), 7.31-7.28 (m, 3H), 7.17 (d, *J* = 7.2 Hz, 2H), 5.59 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 141.5, 140.8, 138.6, 136.0, 133.9, 133.4, 128.6, 128.5, 127.5, 127.3, 127.27, 127.2, 125.9, 120.5, 119.9, 113.7, 108.8, 46.1; HRMS (ESI+) m/z calculated for $C_{24}H_{19}N_2$ $[M+H]^+$ 335.1548, found 335.1538.



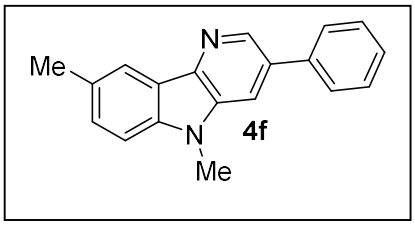
8-Chloro-5-methyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole (4e)

Brown solid (4 mg, 25% yield); mp. 152-154 ^{o}C; R_f = 0.52 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.82 (s, 1H), 8.38 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.56-7.53 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.40-7.39 (m, 1H),), 3.92 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 140.9, 140.0, 138.5, 134.7, 133.9, 128.7, 127.5, 127.3, 127.2, 125.3, 122.4, 120.1, 113.6, 109.4, 28.8; HRMS (ESI+) m/z calculated for $C_{18}H_{14}ClN_2$ $[M+H]^+$ 293.0846, found 293.0846.



5,8-Dimethyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole (4f)

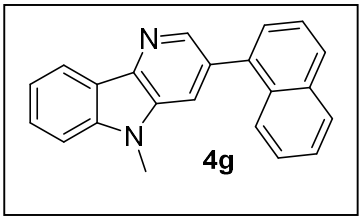
Brownish gummy liquid (21 mg, 77% yield); R_f = 0.62 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.77 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.71-7.69 (m, 2H), 7.53-7.49 (m, 2H), 7.43-7.39 (m, 1H), 7.28-7.26 (m, 1H), 7.22-7.18 (m, 1H), 4.16 (s, 3H), 2.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 141.2, 141.0, 139.4, 136.6, 135.3, 133.7, 130.9, 129.1, 127.7, 120.9, 120.4, 118.9, 114.0, 100.0, 32.4, 20.4; HRMS (ESI+) m/z calculated for $C_{19}H_{17}N_2$ $[M+H]^+$ 273.1392, found 273.1395.



J

5-Methyl-3-(naphthalen-1-yl)-5H-pyrido[3,2-*b*]indole (4g)

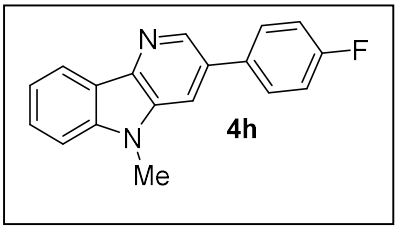
Brownish gummy liquid (11.9 mg, 78% yield); R_f = 0.85 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.52 (d, *J* = 1.6 Hz, 1H), 8.26-8.24 (m, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.04-8.00



(m, 2H), 7.84-7.82 (m, 1H), 7.71-7.69 (m, 1H), 7.65-7.47 (m, 5H), 7.33-7.29 (m, 1H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-D_6, 100 MHz) δ_C 142.6, 142.5, 140.4, 137.7, 134.4, 134.0, 132.9, 131.9, 129.0, 128.5, 128.3, 127.2, 126.6, 126.1, 125.8, 121.6, 120.6, 120.3, 118.0, 110.4, 100.0, 29.6; HRMS (ESI+) m/z calculated for $C_{22}H_{17}N_2$ $[M+H]^+$ 309.1392, found 309.1391.

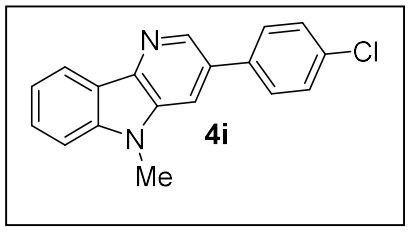
3-(4-Fluorophenyl)-5-methyl-5H-pyrido[3,2-*b*]indole (4h)

Brownish gummy liquid (12.0 mg, 74% yield); R_f = 0.73 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.73 (s, 1H), 8.27 (s, 1H), 8.19 (*J* = 7.6 Hz, 1H), 7.90-7.87 (m, 2H), 7.67-7.65 (m, 1H), 7.58-7.54 (m, 1H), 7.37-7.25 (m, 3H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-D_6, 100 MHz) δ_C 142.5, 140.4 (d, J_{C-F} = 3.3 Hz), 133.5 (d, J_{C-F} = 266.5 Hz), 129.9 (d, J_{C-F} = 8.3 Hz), 128.2, 121.5, 120.6, 120.2, 116.5 (d, J_{C-F} = 21.3 Hz), 114.9, 110.3, 29.6; HRMS (ESI+) m/z calculated for $C_{18}H_{14}FN_2$ $[M+H]^+$ 277.1141, found 277.1140.



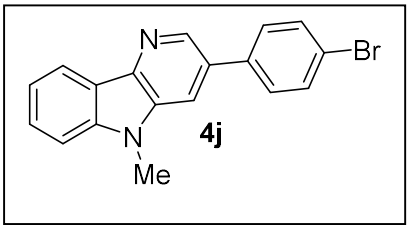
3-(4-Chlorophenyl)-5-methyl-5H-pyrido[3,2-*b*]indole (4i)

Brown solid (12.4 mg, 72% yield); mp. 90-92 °C; R_f = 0.63 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.77 (d, *J* = 1.8 Hz, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 1.2 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.52-7.48 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-D_6, 100 MHz) δ_C 142.6, 140.7, 140.4, 137.8, 134.8, 133.2, 131.8, 129.6, 128.3, 121.5, 120.6, 120.3, 114.9, 110.4, 29.6; HRMS (ESI+) m/z calculated for $C_{18}H_{14}ClN_2$ $[M+H]^+$ 293.0846, found 293.0848.

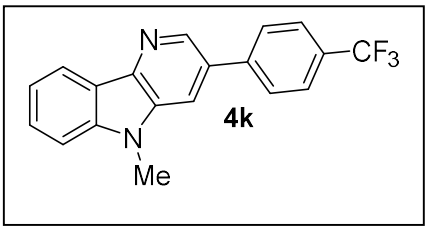


3-(4-Bromophenyl)-5-methyl-5*H*-pyrido[3,2-*b*]indole (4j)

Brown solid (13.3 mg, 67% yield); mp. 114-116 °C ; R_f = 0.60 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.77 (s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.67-7.65 (m, 2H), 7.63-7.59 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-D_6, 100 MHz) δ_C 142.6, 140.7, 140.3, 138.1, 134.8, 132.5, 131.8, 129.9, 128.3, 121.8, 121.5, 120.6, 120.3, 114.8, 110.4, 29.6; HRMS (ESI+) m/z calculated for $C_{18}H_{14}BrN_2$ $[M+H]^+$ 337.0340, found 337.0348.

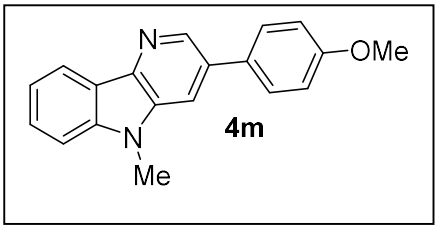


5-Methyl-3-(4-(trifluoromethyl)phenyl)-5*H*-pyrido[3,2-*b*]indole (4k)



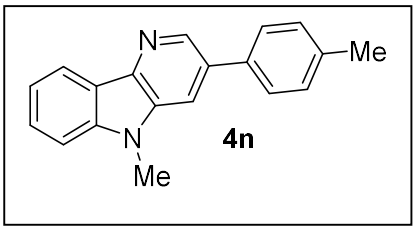
Brown solid (13.0 mg, 69% yield); mp. 120-122°C; R_f = 0.39 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.82 (d, *J* = 2 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 8.23-8.21 (m, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.69-7.67 (m, 1H), 7.61-7.56 (m, 1H), 7.31-7.27 (m, 1H) 3.95 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz) δ_C 143.0 (q, $J_{C\text{-}F}$ = 1.4 Hz), 142.7, 141.1, 140.6, 134.7, 128.6, 128.5, 128.4, 127.6 (q, *J* = 263.6 Hz), 126.4 (q, $J_{C\text{-}F}$= 4.0 Hz), 120.9 (q, $J_{C\text{-}F}$ = 32.6 Hz), 115.4, 110.4, 100.0, 29.6; HRMS (ESI+) m/z calculated for $C_{19}H_{14}F_3N_2$ $[M+H]^+$ 327.1109, found 327.1107.

3-(4-Methoxyphenyl)-5-methyl-5*H*-pyrido[3,2-*b*]indole (4m)



Brownish Gummy liquid (10.2 mg, 60% yield); R_f = 0.56 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.69 (s, 1H), 8.23-8.17 (m, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.65-7.49 (m, 1H), 7.35-7.24 (m, 1H), 7.12-7.02(m, 5H), 3.92 (s, 3H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 153.0, 141.9, 141.3, 137.8, 136.4, 129.4, 128.4, 127.6, 125.4, 122.7, 120.0, 114.7, 108.9, 107.6, 105.6, 55.7, 29.4; HRMS (ESI+) m/z calculated for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1341, found 289.1335.

5-methyl-3-(*p*-tolyl)-5*H*-pyrido[3,2-*b*]indole (4n)



Brown solid (12.8 mg, 78% yield); mp. 110-112 °C; R_f= 0.56 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 600 MHz) δ_H 8.77 (d, *J* = 1.8 Hz, 1H), 8.29 (d, *J* = 1.8 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.69 (m, *J* = 7.8 Hz, 1H), 7.60-7.58 (m, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 3.97 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 143.5, 136.9, 135.3, 129.5, 127.5, 126.4, 124.5, 122.2, 119.8, 117.6, 110.7, 109.5, 33.0, 21.6; HRMS (ESI+) m/z calculated for $C_{19}H_{17}N_2$ $[M+H]^+$ 273.1392, found 273.1382.

2.2.8.9 General procedure for the preparation of starting materials 137:

*General procedure for the synthesis[45] of 137 (**Scheme 44**).*

To a well-stirred solution of *o*-acetyl phenol (3.67 mmol, 1equiv) in $CHCl_3$ was added $CuBr_2$ (903 mg, 4.04 mmol, 1.1 eq) dissolved in ethyl acetate (3 mL). The whole reaction mixture was heated under reflux for 3-5 h until the starting material was consumed (TLC). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using 4-6% ethyl acetate-petroleum ether (v/v) as eluent to give the desired compound **146** in 78-85% yields.

The intermediate **146** (1.4 mmol, 1eq) was dissolved in MeCN (3.0 mL) under argon atmosphere and cooled to 0° C. Next, dry Et_3N (0.39 ml, 2.79 mmol, 2 eq) was added slowly to the reaction mixture. The solution was quenched with water (30 mL) and extracted with DCM (3 × 30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel by using 3-5% ethyl acetate-petroleum ether (v/v) as eluent to afford the intermediate **147** in 81-88% yields.

*General procedure for the synthesis[46] of N-(benzofuran-3-yl)-4-methylbenzenesulfonamide 148 (**Scheme 44**).*

Benzofuran-3(2*H*)-one **147** (1.49 mmol, 1 equiv), *p*-toluenesulfonamide (383 mg, 2.24 mmol, 1.5 equiv) and *p*-toluenesulfonic acid (0.07 mmol, 0.05 equiv) were dissolved in dry toluene (8 mL) and the mixture was then heated to reflux until the benzofuran-3(2*H*)-one was fully consumed (TLC). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (3x10 mL) and brine (3x10 mL), respectively. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After removing the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (with 8-10% ethyl acetate and petroleum ether as the eluent) to obtain the intermediate product **148** in 81-85% yield.

*General procedure for the preparation[43] of N-(benzofuran-3-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide 149 (of **Scheme 44**):*

The sulfonamidobenzofuran intermediate **148** (0.52 mmol, 1 equiv) was dissolved in dry DMF (5 .0 mL) and the reaction mixture was cooled to 0 °C under argon. Next, NaH (60% oil suspension in mineral oil; 27 mg, 0.67 mmol, 1.3 equiv) was added to the ice-cold solution of **148**. After stirring the reaction mixture for 10 min, propargyl bromide (60 µl, 0.67

mmol, 1.3 equiv) was added dropwise to the reaction mixture. Next, the temperature of the reaction was allowed to reach at room temperature and the whole reaction mixture was stirred at rt (3-5 h) until completion (TLC). After quenching with water (2.0 mL), the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed consecutively with brine water (10 mL) and dried over anhydrous sodium sulfate. After evaporation of solvent, the crude residue was purified by silica gel column chromatography with petroleum ether : ethyl acetate = 8:1 (v/v) as eluent to afford the products **149** in 78-85% yields.

*General procedure for the preparation[44] 4-methyl-N-(1-methyl-1H-indol-3-yl)-N-(propa-1,2-dien-1-yl)benzenesulfonamide 137 (**Scheme 44**):*

To a well-stirred solution of **149** (0.15 mmol, 1 equiv) in dry THF (3 mL), KO^tBu (20 mg, 0.10 mmol, 0.7 equiv) was added at room temperature. The mixture was then stirred at rt for about 5-15 min under argon. After completion of reaction (TLC), the reaction was diluted with ethyl acetate (10 mL) and it was filtered through celite. The crude product obtained after removal of solvent under reduced pressure was purified by column chromatography using 6-8% petroleum ether/ethyl acetate (v/v) used as eluting solvent) to get the pure products **95** in 85-96% yields**.**

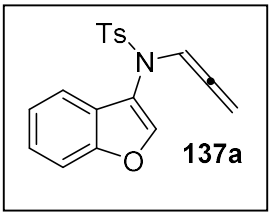
2.2.8.10 Method for the Synthesis of the starting material 137a at 1 mmol scale:

To a well-stirred solution of **149a** (1 mmol, 1 equiv) in dry THF (12 mL), KO^tBu (78.5 mg, 0.7 mmol, 0.7 equiv) was added pinch wise at room temperature. The mixture was then stirred at rt for about 15 min under argon. After completion of reaction (TLC), the reaction was diluted with ethyl acetate (10 mL) and it was filtered through celite. The crude product obtained after removal of solvent under reduced pressure was purified by column chromatography using 8% petroleum ether/ethyl acetate (v/v) used as eluting solvent) to get the pure products **137a** in 71% yield (231 mg)**.**

2.2.8.11 Spectral data of substrates 137a-137c:

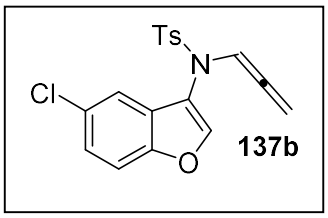
***N*-(benzofuran-3-yl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide (137a)**

Brown solid (37 mg, 74% yield); mp. 80-82 °C; R_f = 0.57 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.60 (d, *J* = 8.4, 2H), 7.49 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.25-7.16 (m, 4H), 7.06 (dt, *J* = 0.94 Hz, 1H), 7.01-6.98 (m, 1H), 5.02 (d, *J* = 6.0 Hz, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.1, 154.3, 144.4, 144.0, 135.0, 129.8, 127.8, 124.8, 124.6, 123.0, 120.0, 119.6, 111.9, 101.6, 88.3, 21.7; HRMS (ESI+) m/z calculated for $C_{18}H_{16}NO_3S$ $[M+H]^+$ 326.0851, found 326.0848.



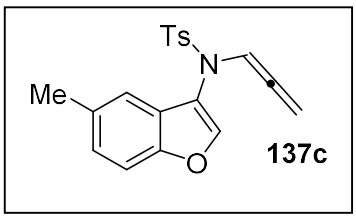
***N*-(5-chlorobenzofuran-3-yl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (137b)**

Brown solid (34 mg, 68% yield); mp. 98-100 °C; R_f = 0.27 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.59-7.56 (m, 3H), 7.32 (dd, *J* = 8.8, 0.4 Hz, 1H), 7.24 (dd, *J* = 8.6, 0.6 Hz, 2H), 7.18-7.14 (m, 2H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 2H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 200.9, 152.6, 145.8, 144.9, 134.7, 129.9, 128.8, 127.8, 125.8, 125.1, 119.6, 119.2, 113.0, 101.5, 88.5, 21.7; HRMS (ESI+) m/z calculated for $C_{18}H_{15}ClNO_3S$ $[M+H]^+$ 360.0461, found 360.0473.



4-Methyl-*N*-(5-methylbenzofuran-3-yl)-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide(137c)

Brown solid (35 mg, 70% yield); mp. 115-117 °C; R_f = 0.69 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.60 (d, *J* = 8.4 Hz, 2H), 7.42 (s, 1H), 7.29-7.22 (m, 3H), 7.17 (t, *J* = 6.2 Hz, 1H), 7.03 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.68-6.67 (m, 1H), 5.02 (d, *J* = 6.0 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 201.1, 152.8, 144.3, 144.2, 135.0, 132.5, 129.7, 127.9, 126.2, 124.6, 119.6, 119.3, 111.4, 101.8, 88.2, 21.6, 21.2; HRMS (ESI+) m/z calculated for $C_{19}H_{18}NO_3S$ $[M+H]^+$ 340.1007, found 340.1010.



2.2.8.12 General procedure for the Synthesis of Products 137a-q:

An oven dried two-neck round bottomed flask was charged with $Pd_2(dba)_3.CHCl_3$ (3.1 mg, 5 mol%) and ^{t}BuXphos (2.6 mg, 10 mol%) were stirred in dry DMF (2 mL) under argon atmosphere at rt for 30 min. Then aryl iodide (**138**) or aryl bromide (**139**) (0.12 mmol) was added and stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (80 mg, 4 equiv.)

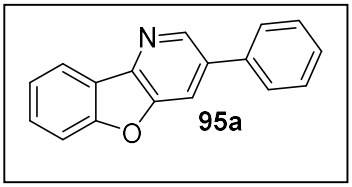
and allenamides **137** (0.1 mmol, 1 equiv.) were successively added to the reaction mixture under an argon atmosphere. The whole reaction mixture was allowed to stir at 100 °C for 2-5 h until completion (TLC). The resulting mixture was extracted with dichloromethane (3 × 20 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained after removal solvent was purified by silica gel (100−200 mesh) column chromatography using 5−15% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **95** in 45-86% yields.

2.2.8.13 Synthetic Method for the Synthesis of the Product 95b at 1 mmol scale:

An oven dried two-neck round bottomed flask was charged with $Pd_2(dba)_3.CHCl_3$ (21.6 mg, 5 mol%) and ^{t}BuXphos (17.7 mg, 10 mol%) were stirred in dry DMF (6 mL) under argon atmosphere at rt for 30 min. Then phenyl iodide **138a** (0.50 mmol) was added and stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (544 mg, 4 equiv.) and N-(5-chlorobenzofuran-3-yl)-4-methyl-N-(propa-1,2-dien-1-yl)benzenesulfonamide **137b** (1 mmol, 1 equiv.) were successively added to the reaction mixture under an argon atmosphere. The whole reaction mixture was allowed to stir at 100 °C for 3 h until completion (TLC). The resulting mixture was extracted with dichloromethane (3 × 30 mL) and washed with water (30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue obtained after removal solvent was purified by silica gel (100−200 mesh) column chromatography using 7% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **137b** in 54% yield (150.2 mg).

2.2.8.14 Spectral data of product 95a-95q:

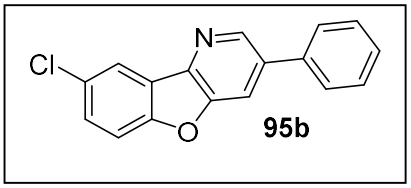
3-Phenylbenzofuro[3,2-*b*]pyridine (95a)



Brown solid (11.4 mg, 76% yield); mp. 90-92 °C; R_f = 0.56 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.87 (d, *J* = 1.6 Hz, 1H), 8.26-8.23 (m, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.69-7.66 (m, 2H), 7.64-7.57 (m, 2H), 7.56-7.50 (m, 2H), 7.47-7.41 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 150.2, 144.5, 143.3, 138.1, 135.4, 129.3, 129.2, 128.3, 127.7, 123.8, 123.3, 121.2, 117.0, 112.3, 100.0; HRMS (ESI+) m/z calculated for $C_{17}H_{12}NO$ $[M+H]^+$ 246.0919, found 246.0918.

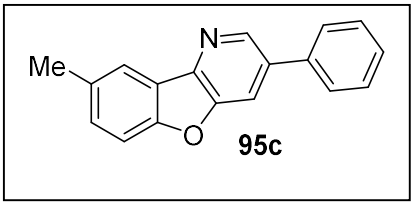
8-Chloro-3-phenylbenzofuro[3,2-*b*]pyridine (95b)

Yellow solid (8.5 mg, 55% yield); mp. 188-190 °C; R_f = 0.58 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.90 (d, *J* = 1.8 Hz, 1H), 8.22(d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.70-7.68 (m, 2H), 7.58-7.53 (m, 4H), 7.48-7.46 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 156.2, 150.9, 145.0, 142.2, 137.8, 136.1, 129.5, 129.3, 129.2, 128.5, 127.7, 124.7, 121.0, 117.2, 113.4, 100.0; HRMS (ESI+) m/z calculated for $C_{17}H_{11}ClNO$ $[M+H]^+$ 280.0529, found 280.0529.



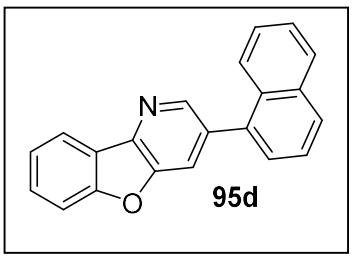
8-Methyl-3-phenylbenzofuro[3,2-*b*]pyridine (95c)

Yellow solid (11 mg, 72% yield); mp. 114-116 °C; R_f = 0.42 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.84 (d, *J* = 2.0 Hz, 1H), 8.04-8.03 (m, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.68-7.66 (m, 2H), 7.53-7.48 (m, 2H), 7.45-7.36 (m, 3H), 2.54 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 156.4, 144.2, 143.4, 138.1, 135.2, 133.5, 130.5, 129.3, 129.1, 128.5, 128.2, 127.6, 125.5, 121.1, 116.9, 111.8, 100.0, 21.4; HRMS (ESI+) m/z calculated for $C_{18}H_{14}NO$ $[M+H]^+$ 260.1075, found 260.1076.



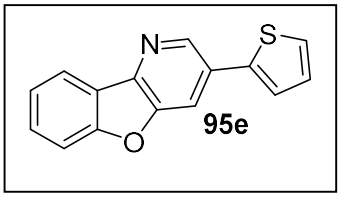
3-(Naphthalen-1-yl)benzofuro[3,2-*b*]pyridine (95d)

Brownish gummy liquid (13.4 mg, 74% yield); R_f = 0.37 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.78 (d, *J* = 1.6 Hz, 1H), 8.31-8.29 (m, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 8.0, 2.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.76-7.55 (m, 3H), 7.54-7.46 (m, 3H), 7.41-7.40 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 149.7, 146.6, 143.4, 136.3, 134.0, 131.8, 130.6, 129.4, 129.1, 128.8, 128.6, 128.5, 128.0, 126.8, 126.3, 125.5, 123.9, 121.3, 120.0, 112.3,; HRMS (ESI+) m/z calculated for $C_{21}H_{14}NO$ $[M+H]^+$ 296.1075, found 296.1064.



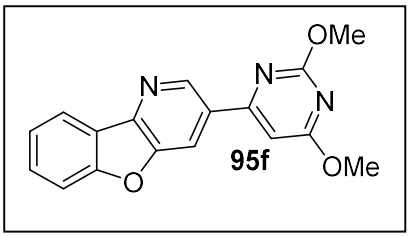
3-(Thiophen-2-yl)benzofuro[3,2-*b*]pyridine (95e)

Brown solid (7 mg, 45% yield); mp. 100-102 °C; R_f = 0.48 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.90 (d, *J* = 1.6 Hz, 1H), 8.22-8.19 (m, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.45-7.37 (m, 3H), 7.15-7.13 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 150.0, 143.3, 140.8, 129.3, 129.0, 128.5, 126.3,



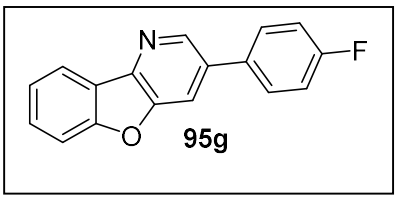
124.7, 123.9, 123.2, 121.2, 115.4, 112.3; HRMS (ESI+) m/z calculated for $C_{15}H_{10}NOS$ $[M+H]^+$ 252.0483, found 252.0472.

3-(2,6-Dimethoxypyrimidin-4-yl)benzofuro[3,2-*b*]pyridine (95f)



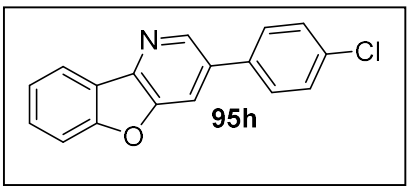
White solid (13.4 mg, 71% yield); mp. 192-194 °C; R_f = 0.21 (30% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.73 (d, *J* = 1.6 Hz, 1H), 8.39 (s, 1H), 8.25-8.22 (m, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.63-7.56 (m, 2H), 7.47-7.43 (m, 1H), 4.07 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 168.4, 165.2, 158.0, 149.6, 145.2, 143.5, 129.5, 127.5, 123.9, 123.2, 121.3, 118.8, 113.2, 112.3, 55.2, 54.5; HRMS (ESI+) m/z calculated for $C_{17}H_{14}N_3O_3$ $[M+H]^+$ 308.1035, found 308.1020.

3-(4-Fluorophenyl)benzofuro[3,2-*b*]pyridine (95g)



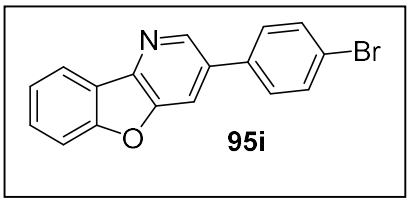
Brown solid (12.8 mg, 80% yield); mp. 168-170 °C; R_f = 0.41 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.81 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.64-7.55 (m, 4H), 7.47-7.43 (m, 1H), 7.22-7.18 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 163.1 (d, J_{C-F} = 247.0 Hz), 158.0, 150.1, 144.3, 143.3, 134.4, 134.2 (d, J_{C-F} = 3.0 Hz), 129.9, 129.33, 129.31 (d, J_{C-F} = 8.0 Hz), 123.2, 121.3, 116.8, 116.3 (d, J_{C-F} = 22.0 Hz), 112.3; HRMS (ESI+) m/z calculated for $C_{17}H_{11}FNO$ $[M+H]^+$ 264.0825, found 264.0815.

3-(4-Chlorophenyl)benzofuro[3,2-*b*]pyridine (95h)



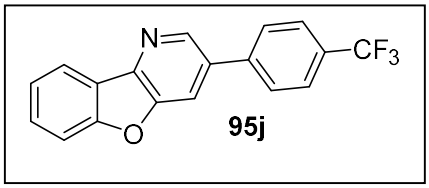
Brown solid (19.0 mg, 77% yield); mp. 130-132 °C; R_f = 0.45 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.85 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 1.8 Hz, 1H,) 7.65-7.59 (m, 4H,) 7.51-7.47 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 157.5, 149.5, 143.7, 143.1, 136.0, 134.0, 133.6, 129.0, 128.3, 123.4, 122.6, 120.8, 116.2, 111.8; HRMS (ESI+) m/z calculated for $C_{17}H_{11}ClNO$ $[M+H]^+$ 280.0529, found 280.0532.

3-(4-Bromophenyl)benzofuro[3,2-*b*]pyridine (95i)



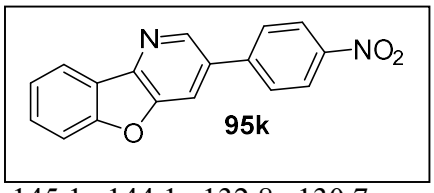
Brown solid (15.5 mg, 78% yield); mp. 114-116 °C; R_f= 0.45 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.82 (d, *J* = 2.0 Hz, 1H), 8.26-8.23 (m, 1H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.61-7.58 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.47-7.43 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.1, 150.1, 144.2, 143.7, 137.0, 134.2, 132.5, 129.5, 129.2, 123.9, 123.1, 122.7, 121.3, 116.7, 112.3, 100.0; HRMS (ESI+) m/z calculated for $C_{17}H_{11}BrNO$ $[M+H]^+$ 324.0024, found 324.0023.

3-(4-(Trifluoromethyl)phenyl)benzofuro[3,2-*b*]pyridine (95j)



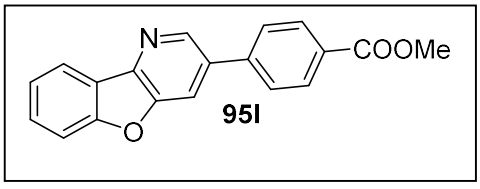
Brown solid (15.4 mg, 80% yield); mp. 125-127 °C; R_f= 0.54 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.87 (d, *J* = 2.0 Hz, 1H), 8.27-8.25 (m, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.78 (s, 4H), 7.65-7.58 (m, 2H), 7.49-7.45 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.2, 150.2, 144.4, 144.2, 133.8, 131.9, 130.7, 130.4 (q, J_{C-F}= 31.3), 130.1, 129.7, 126.2 (q, J_{C-F}= 4.1Hz), 124.0, 123.0, 121.5, (q, *J* = 265.5 Hz), 117.1, 112.4, 100.0; HRMS (ESI+) m/z calculated for $C_{18}H_{11}F_3NO$ $[M+H]^+$ 314.0793, found 314.0789.

3-(4-Nitrophenyl)benzofuro[3,2-*b*]pyridine (95k)



Brown solid (17.4 mg, 80% yield); mp. 225-227 °C; R_f= 0.36 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.95 (d, *J* = 1.6 Hz, 1H), 8.43 (d, *J* = 1.6 Hz, 1H), 8.18-8.16 (m, 1H), 7.85-7.78 (m, 3H), 7.67-7.62 (m, 1H), 7.54-7.41 (m, 3H); ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz) δ_C 158.1, 149.9, 148.1, 147.7, 145.1, 144.1, 132.8, 130.7, 129.2, 124.7, 122.8, 121.6, 118.2, 113.2, 100.0; HRMS (ESI+) m/z calculated for $C_{17}H_{11}N_2O_3$ $[M+H]^+$ 291.0770, found 291.0762.

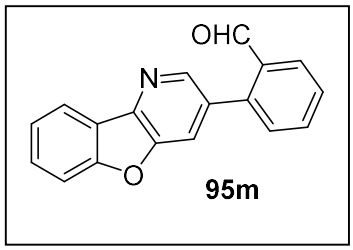
Methyl 4-(benzofuro[3,2-*b*]pyridin-3-yl)benzoate (95l)



Brown solid (14.9 mg, 80% yield); mp. 160-162 °C; R_f= 0.24 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.89 (d, *J* = 1.6 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.64-7.60 (m, 2H), 7.48-7.44 (m, 1H), 3.96 (s, 3H);

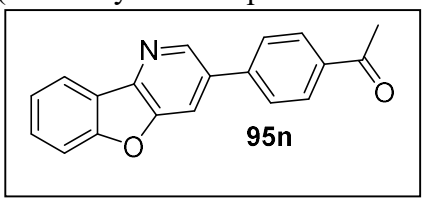
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 166.8, 158.2, 150.1, 144.4, 144.1, 142.5, 134.1, 130.6, 129.9, 129.6, 127.6, 124.0, 123.1, 121.4, 117.1, 112.4, 100.0, 52.4; HRMS (ESI+) m/z calculated for $C_{19}H_{14}NO_3$ $[M+H]^+$ 304.0974, found 304.0977.

2-(Benzofuro[3,2-*b*]pyridin-3-yl)benzaldehyde (95m)



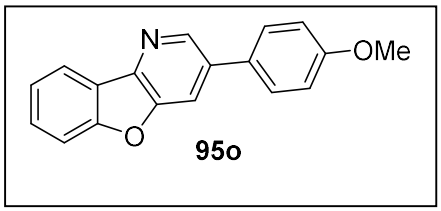
Yellow solid (13.5 mg, 81% yield); mp. 106-108 °C; R_f = 0.23 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.04 (d, *J* = 0.8 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 8.29-8.27 (m, 1H), 8.11-8.08 (m, 1H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.74-7.70 (m, 1H), 7.64-7.60 (m, 3H), 7.53-7.46 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 191.4, 158.2, 149.4, 146.1, 144.2, 141.8, 134.2, 134.0, 131.9, 131.5, 129.8, 128.9, 128.8, 124.1, 123.0, 121.5, 119.7, 112.4; HRMS (ESI+) m/z calculated for $C_{18}H_{12}NO_2$ $[M+H]^+$ 274.0868, found 274.0869.

1-(4-(Benzofuro[3,2-*b*]pyridin-3-yl)phenyl)ethan-1-one (95n)



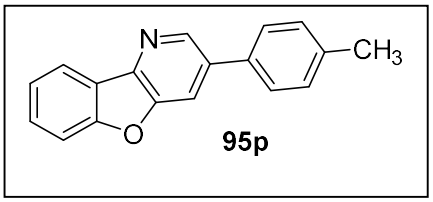
Yellow solid (15.2 mg, 86% yield); mp. 190-192 °C; R_f= 0.13 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.90 (d, *J* = 2.0 Hz, 1H), 8.27-8.25 (m, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.65-7.58 (m, 2H), 7.49-7.45 (m, 1H), 2.66 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 197.6, 158.2, 150.1, 144.3, 144.0, 142.5, 136.7, 134.0, 129.7, 129.3, 127.8, 124.0, 123.0, 121.5, 117.2, 112.4, 26.8; HRMS (ESI+) m/z calculated for $C_{19}H_{14}NO_2$ $[M+H]^+$ 288.1025, found 288.1024.

3-(4-Methoxyphenyl)benzofuro[3,2-*b*]pyridine (95o)



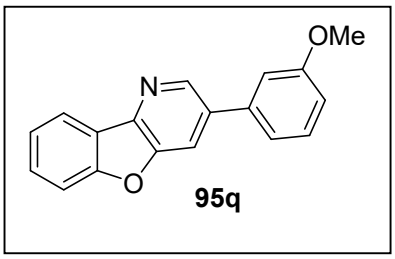
Brown solid (11.3 mg, 67% yield); mp. 112-114 °C; R_f= 0.45 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.83 (d, *J* = 1.6 Hz, 1H), 8.24-8.22 (m, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.62-7.60 (m, 3H), 7.58-7.54 (m, 1H), 7.46-7.42 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.0, 157.9, 150.3, 144.2, 142.7, 135.5, 135.2, 129.1, 128.7, 123.8, 123.3, 121.1, 116.5, 114.8, 112.2, 100.0,55.5; HRMS (ESI+) m/z calculated for $C_{18}H_{14}NO_2$ $[M+H]^+$ 276.1025, found 276.1024.

3-(*p*-Tolyl)benzofuro[3,2-*b*]pyridine (95p)



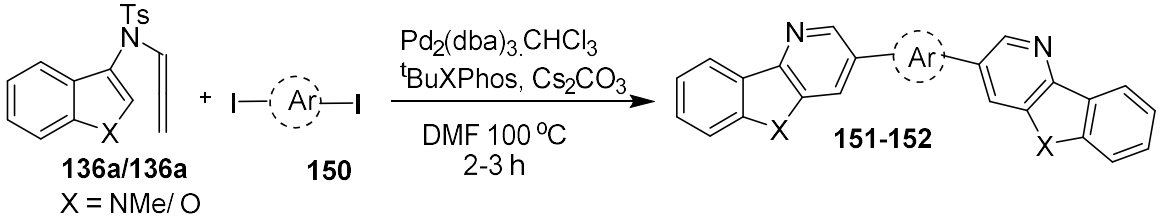
Brown solid (11.2 mg, 71% yield); mp. 110-112 °C; R_f = 0.58 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.88 (d, *J* = 1.2 Hz, 1H), 8.27(d, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 1.8 Hz, 1H), 7.65-7.63 (m, 1H), 7.60-7.58 (m, 3H), 7.47 (t, *J* = 7.2 Hz 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 157.4, 149.7, 143.8, 142.4, 137.8, 134.9, 134.6, 129.5, 128.6, 126.9, 123.3, 122.8, 120.7, 116.2, 111.7, 20.7; HRMS (ESI+) m/z calculated for $C_{18}H_{14}NO$ $[M+H]^+$ 260.1075, found 260.1079.

3-(3-Methoxyphenyl)benzofuro[3,2-*b*]pyridine (95q)



Brown solid (9.8 mg, 58% yield); mp. 112-114 °C; R_f = 0.45 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.86 (d, *J* = 2.0 Hz, 1H), 8.26-8.23 (m, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.63-7.55 (m, 2H), 7.47-7.41 (m, 2H), 7.27-7.24 (m, 1H), 7.20-7.19 (m, 1H), 7.00-6.96 (m, 1H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.3, 158.0, 150.1, 144.5, 143.4, 139.5, 135.3, 130.3, 129.3, 123.8, 123.3, 121.3, 120.1, 117.0, 113.53, 113.51, 112.3, 55.5; HRMS (ESI+) m/z calculated for $C_{18}H_{14}NO_2$ $[M+H]^+$ 276.1025, found 276.1024.

2.2.8.15 General procedure for the synthesis of bisheteroannulated products 151-152



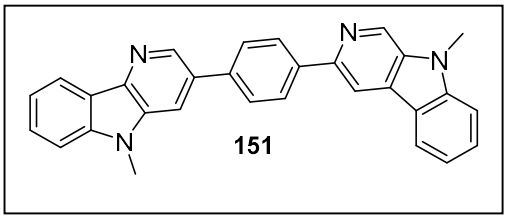
An oven dried round bottomed flask was charged with $Pd_2(dba)_3.CHCl_3$(3.05 mg, 5 mol%) and ^{t}BuXPhos (2.6 mg, 10 mol%) in dry DMF (2 mL) and the whole reaction mixture was stirred at rt under argon atmosphere for 30 min. Then diaryl iodide **150** (0.06 mmol) was added and stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (77 mg, 4 equiv.), and allenamide **136a** or **137a**(0.1 mmol) were added successively to the reaction mixture under argon atmosphere. The whole reaction mixture was allowed to stir at 100 °C (using oil bath) for 1-5 h until completion (TLC). The resulting mixture was extracted with dichloromethane (3 × 20 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue

obtained after removal of DMF was purified by silica gel (100−200 mesh) column chromatography using 5-9% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **151-152** in 40-73% yields.

2.2.8.16 Spectral data of substrates 151, 152a-c:

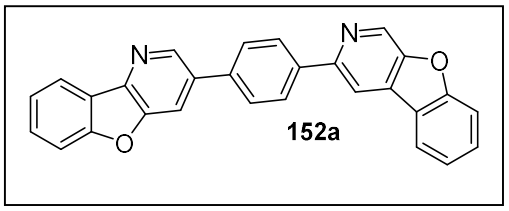
1,4-Bis(benzofuro[3,2-*b*]pyridin-3-yl)benzene (151)

Yellow gummy liquid (13.5 mg, 50% yield); R_f = 0.43 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-D_6, 400 MHz) δ_H 8.75 (t, *J* = 1.4 Hz, 2H), 8.30 (t, *J* = 1.6 Hz, 2H), 8.19 (d, *J* = 7.6 Hz, 2H), 7.88-7.85 (m, 2H), 7.68-7.66 (m, 4H), 7.59-7.55 (m, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 3.94 (s, 6H); ^{13}C{^{1}H} NMR (DMSO-D_6, 100 MHz) δ_C 142.6, 141.6, 140.7, 140.2, 138.4, 134.8, 132.0, 130.0, 128.3, 121.5, 120.6, 120.3, 114.7, 110.4, 100.0, 29.6 ; HRMS (ESI+) m/z calculated for $C_{30}H_{23}N_4$ $[M+H]^+$ 439.1923, found 439.1908.



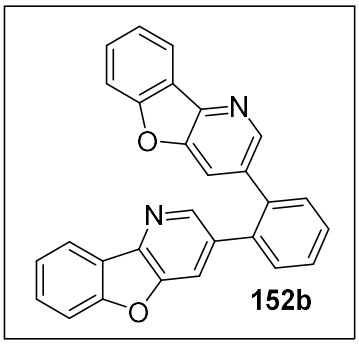
1,4-Bis(benzofuro[3,2-*b*]pyridin-3-yl)benzene (152a)

Yellow solid (14.6 mg, 71% yield); mp. 146-148 °C; R_f = 0.43 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.91 (d, *J* = 2.0 Hz, 1H), 8.23-8.21 (m, 1H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.75-7.71 (m, 1H), 7.63-7.54 (m, 4H), 7.46-7.38 (m, 6H), 7.17-7.14 (m, 1H), 7.10-7.06 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 157.5, 149.6, 143.6, 143.2, 137.9, 137.0, 133.7, 128.9, 128.8, 123.4, 122.6, 120.8, 116.2, 111.8, 93.7 ; HRMS (ESI+) m/z calculated for $C_{28}H_{17}N_2O_2$ $[M+H]^+$ 413.1290, found 413.1250.



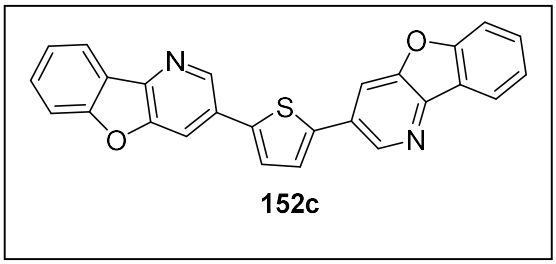
1,2-Bis(benzofuro[3,2-*b*]pyridin-3-yl)benzene (152b)

Brown solid (14 mg, 68% yield); mp. 95-97 °C; R_f = 0.49 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.91 (d, *J* = 1.6 Hz, 1H), 8.27-8.24 (m, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.76-7.69 (m, 5H), 7.64-7.56 (m, 3H), 7.48-7.44 (m, 1H), 7.39 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 150.2, 144.4, 143.5, 140.0, 138.1, 137.5, 137.4, 134.7, 129.4, 129.0, 128.1, 127.7, 123.9, 123.2, 121.3, 116.8, 112.3, 93.5; HRMS (ESI+) m/z calculated for $C_{28}H_{17}N_2O_2$ $[M+H]^+$ 413.1290, found 413.1285.



1,2-Bis(benzofuro[3,2-*b*]pyridin-3-yl)benzene (152c)

Brown solid (10.5 mg, 38% yield); mp. 114-116 ^{o}C; R_f = 0.45 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.85 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.65-7.60 (m, 3H), 7.49-7.42 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.0, 143.4, 143.3, 140.8, 134.9, 130.6, 129.3, 129.1, 128.5, 126.3, 125.5, 124.7, 123.9, 121.2, 115.5, 112.3 ; HRMS (ESI+) m/z calculated for $C_{26}H_{15}N_2O_2S$ $[M+H]^+$ 419.0854, found 419.0847.



152c

2.2.9. References:

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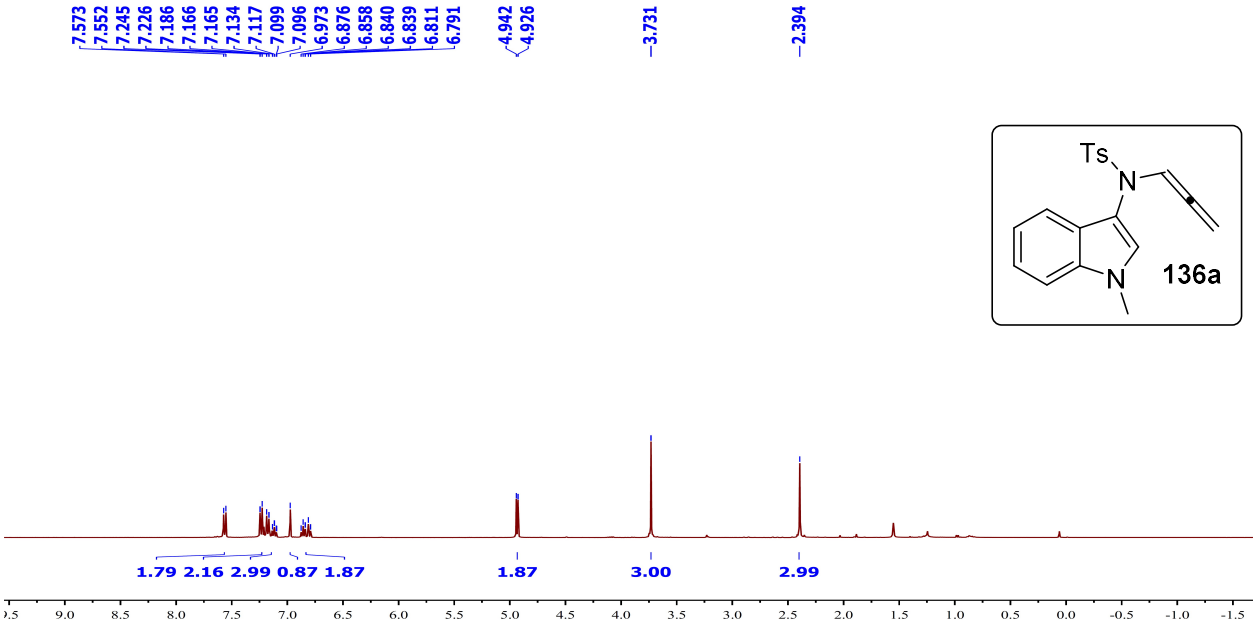
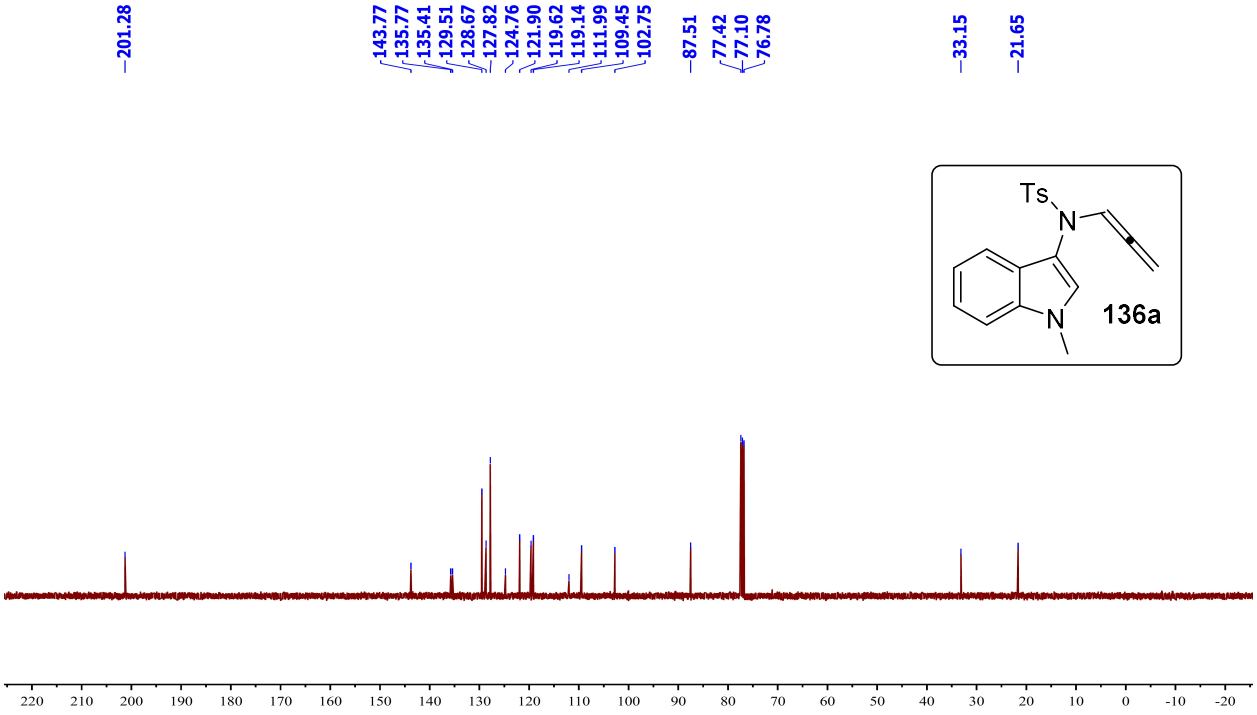
2.2.11 Copy of NMR spectra

2.2.11.1 NMR Spectra of Compounds 136a-136f:

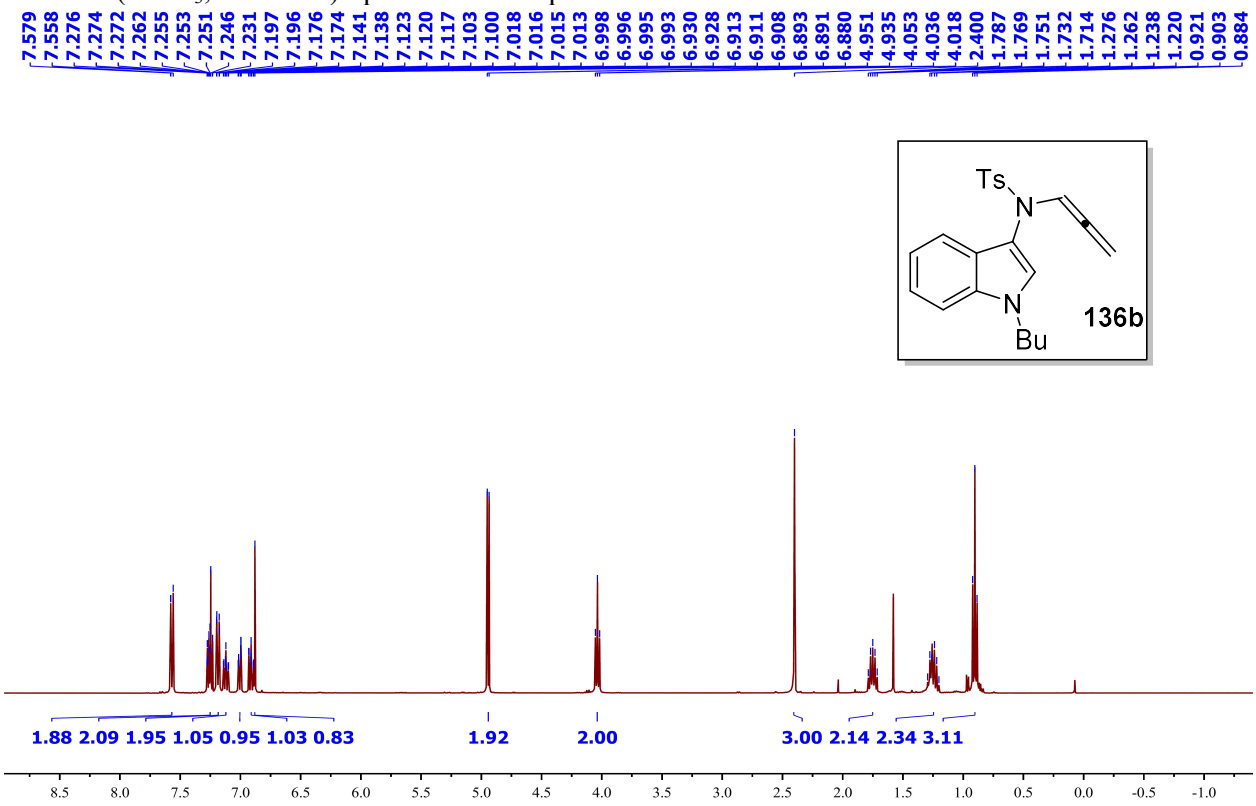
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **136a**:



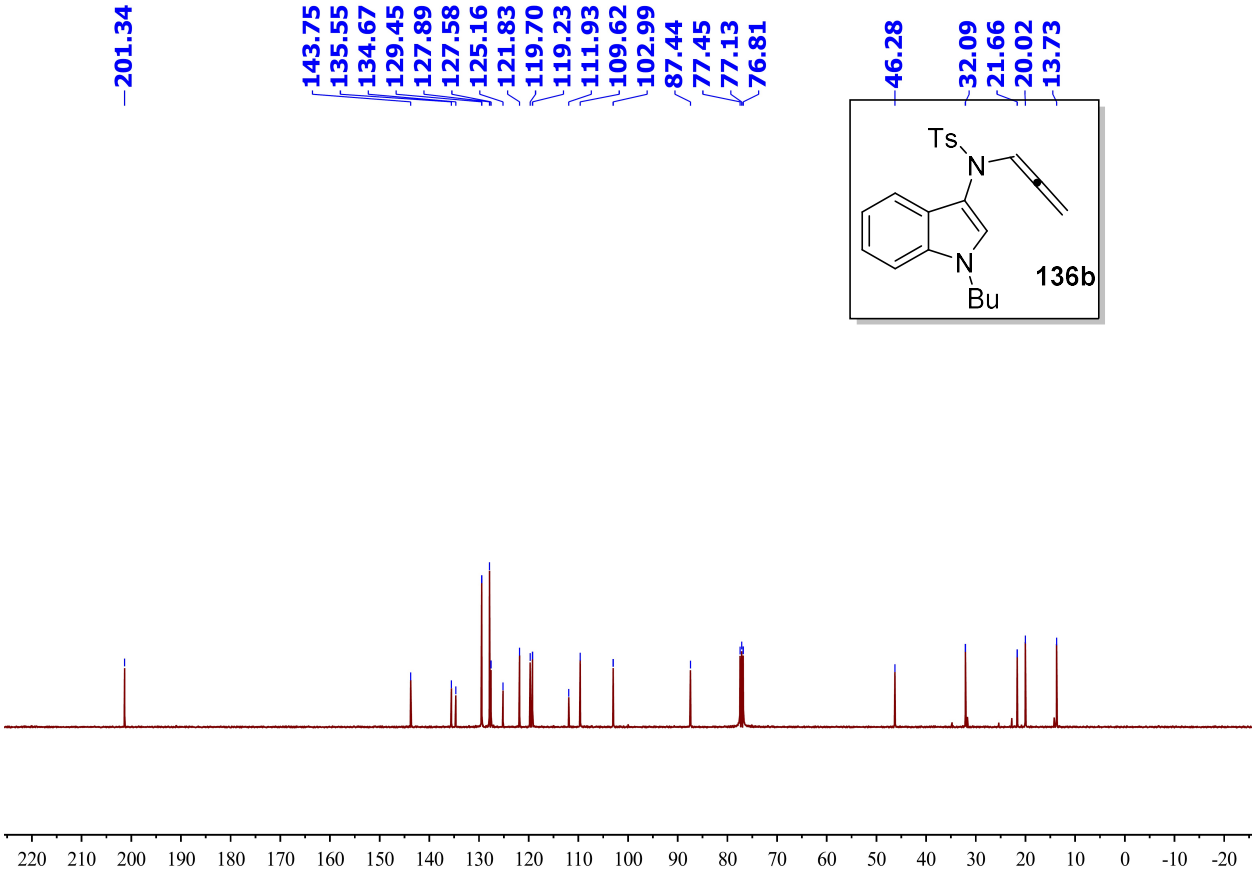
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136a**:



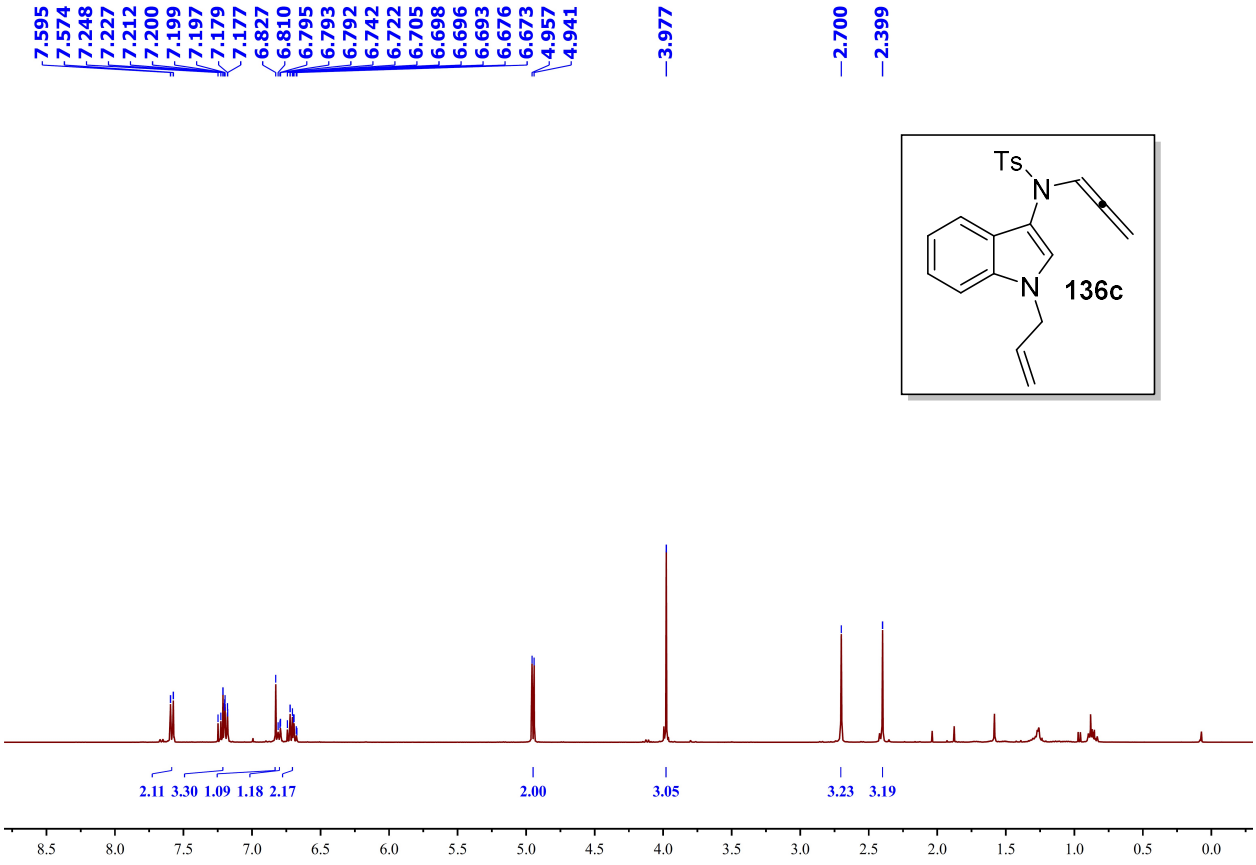
^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of compound **136b**:



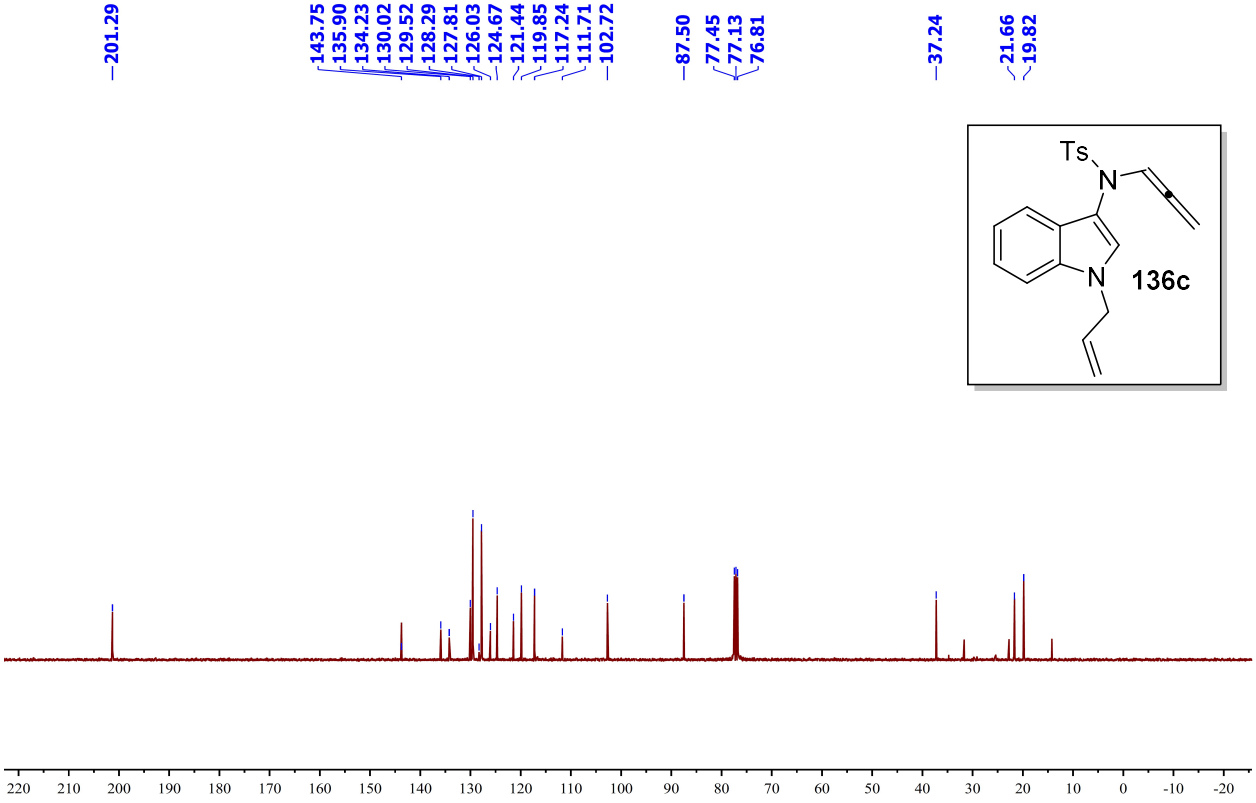
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136b**:



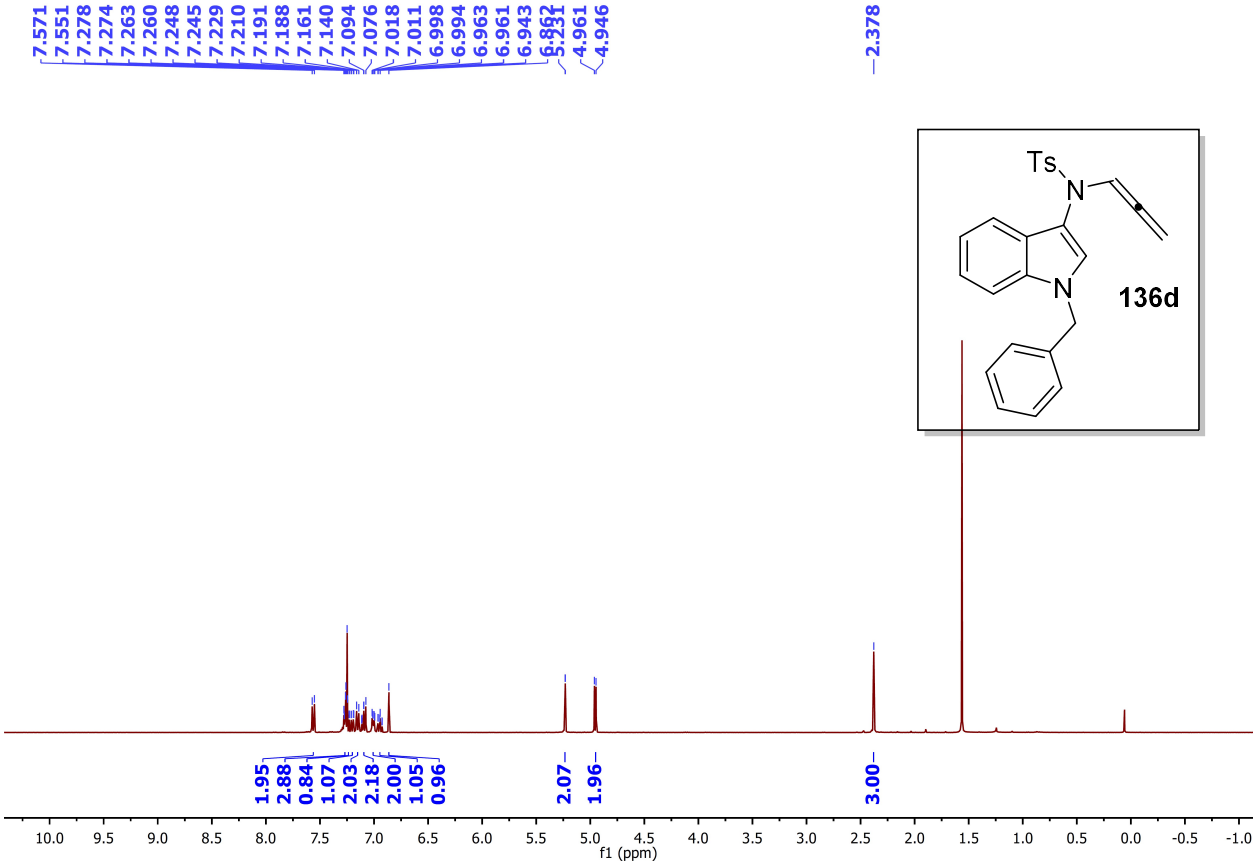
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **136c**:



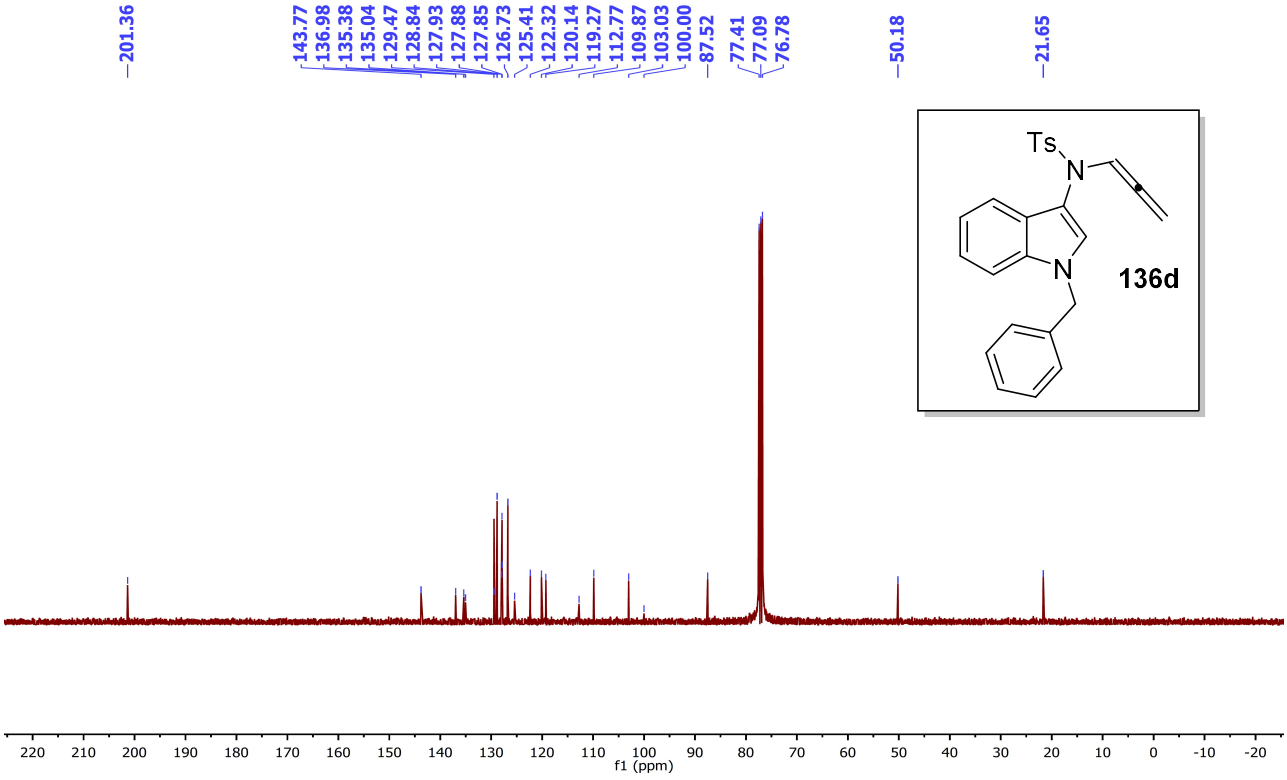
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136c**:



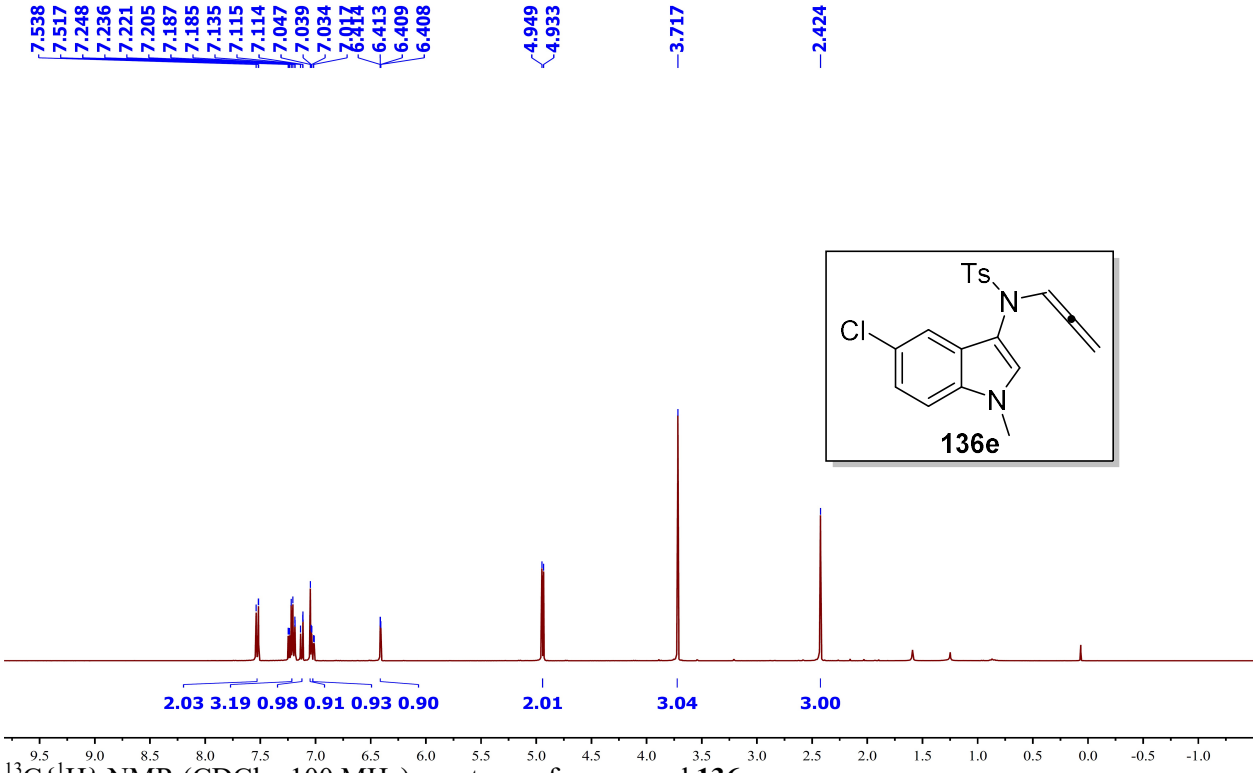
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **136d**:



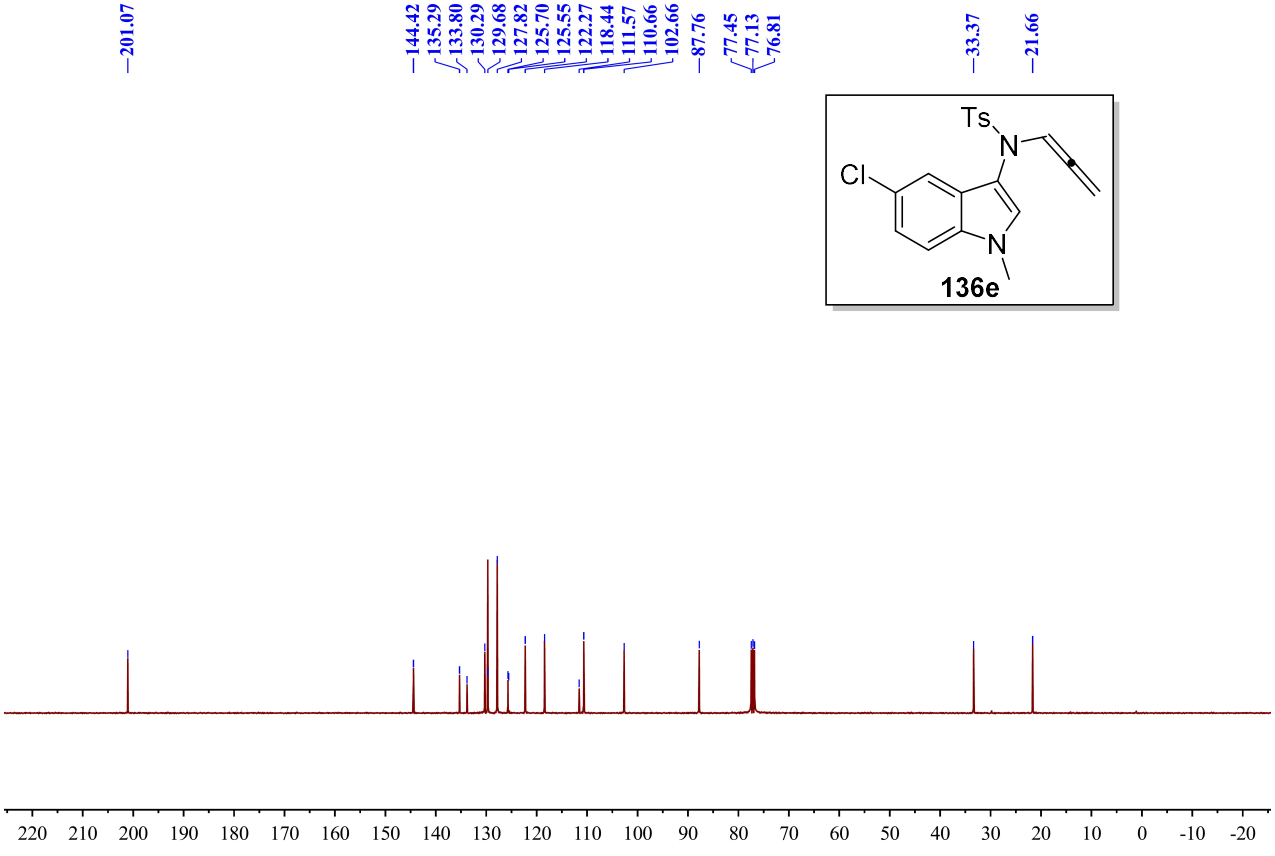
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136d**:



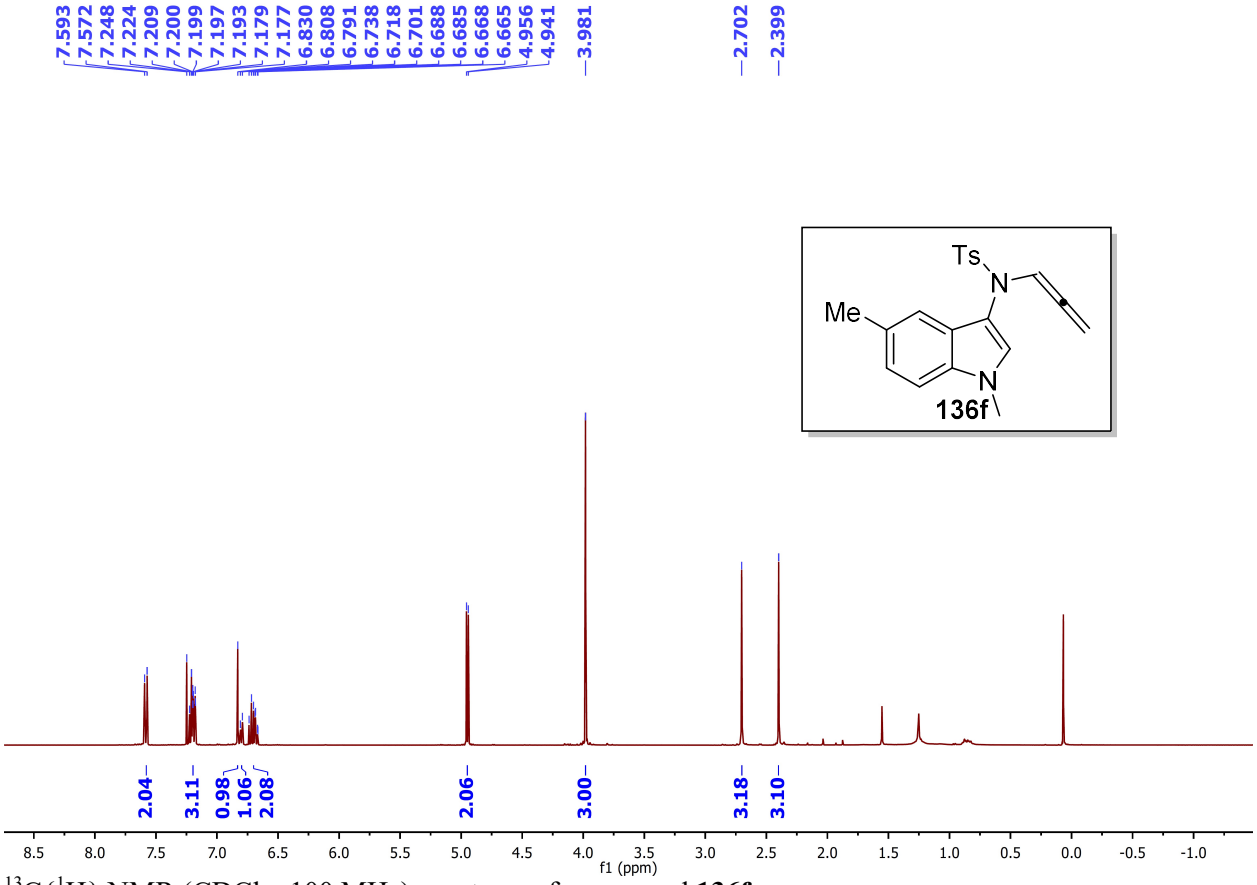
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **136e**:



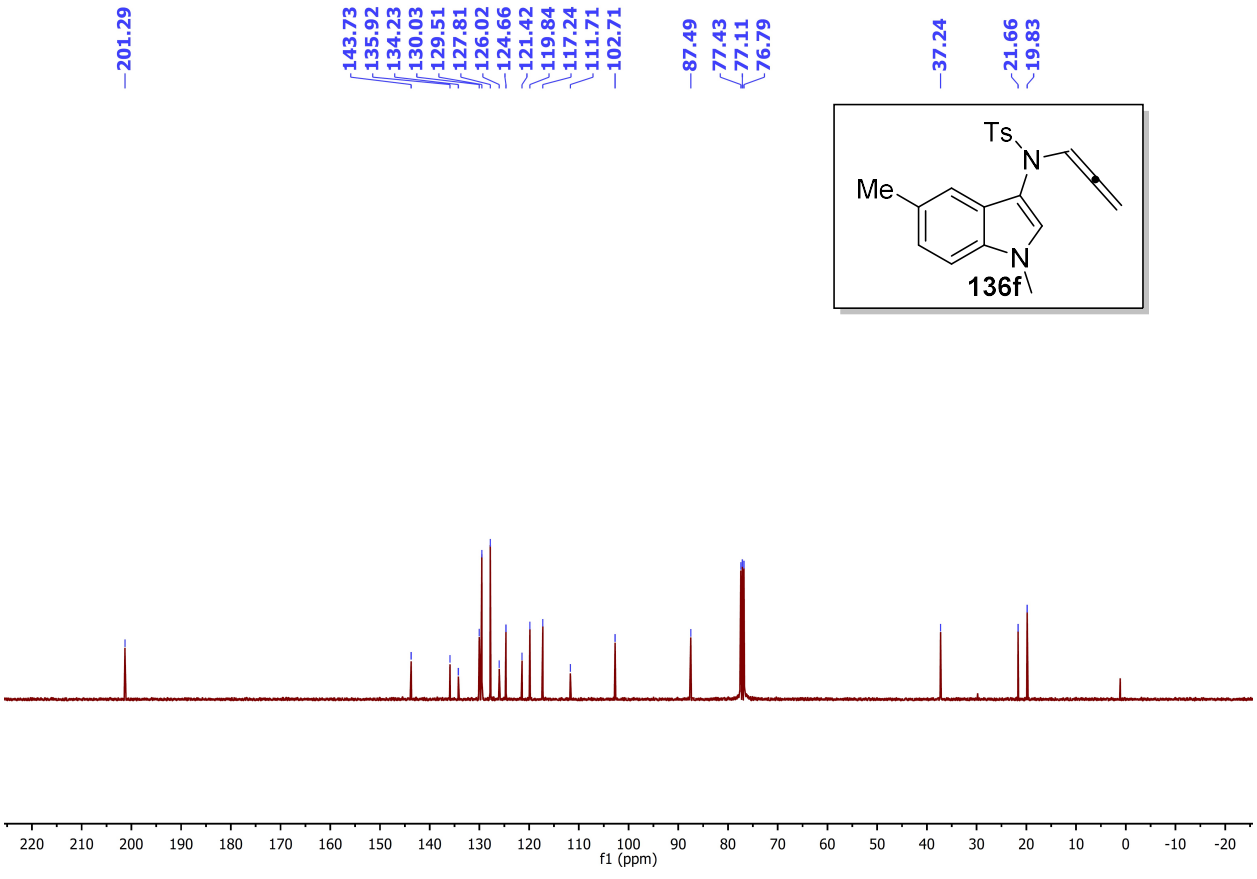
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136e**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **136f**:

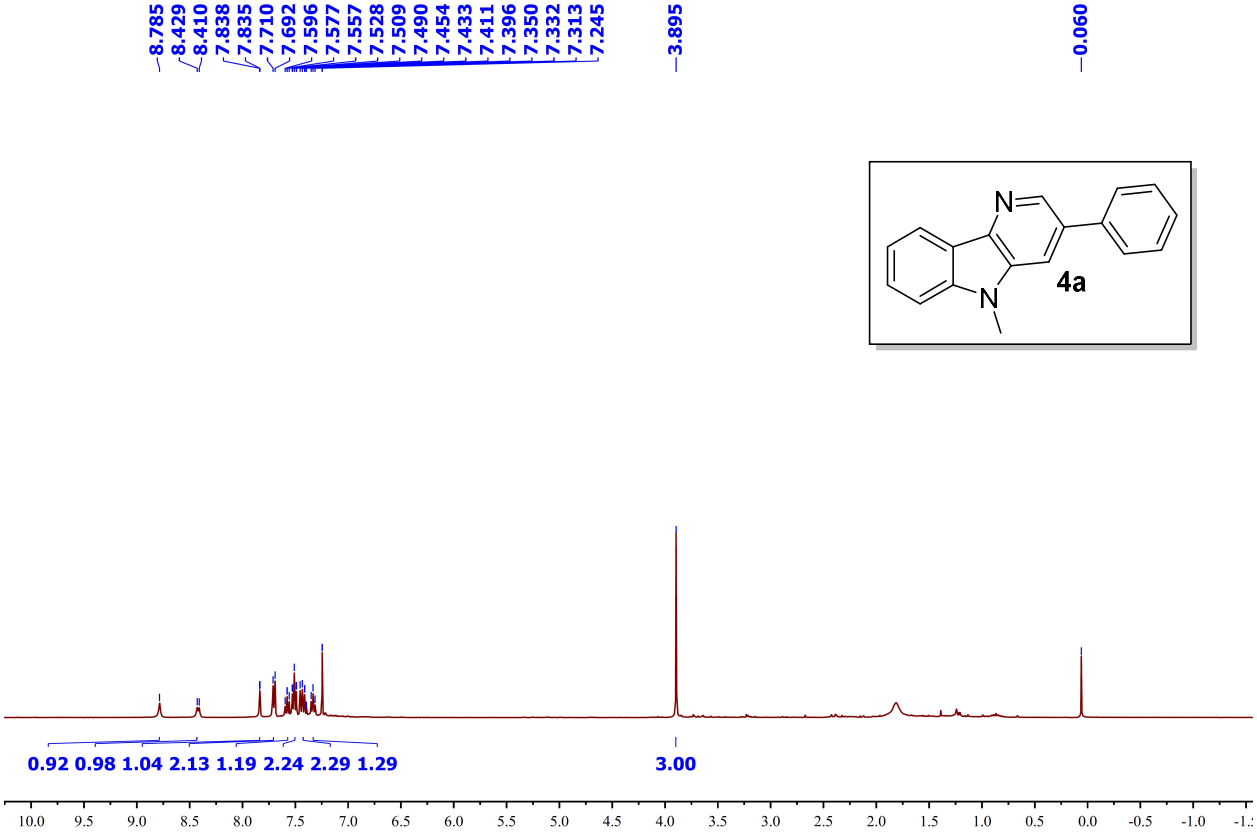


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **136f**:

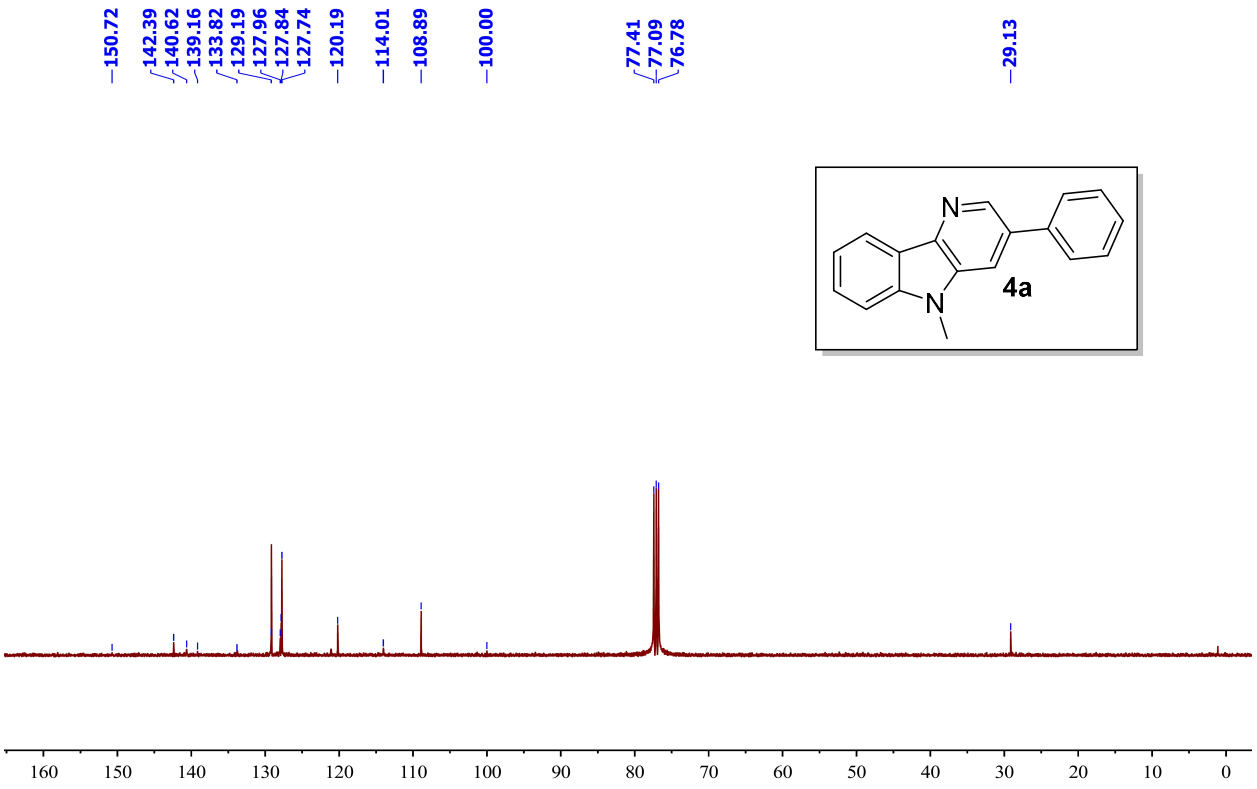


2.2.11.2 NMR spectra of compounds 4a-4n:

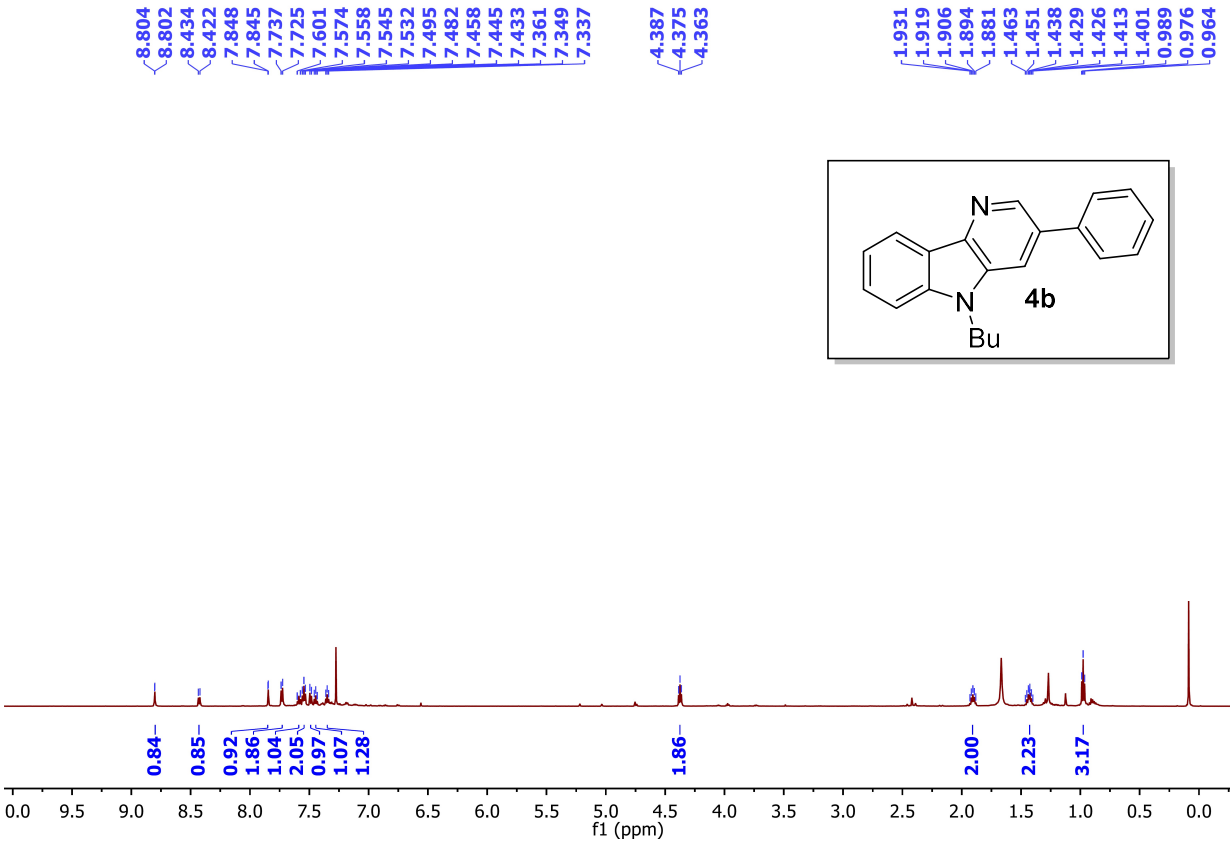
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **4a**:



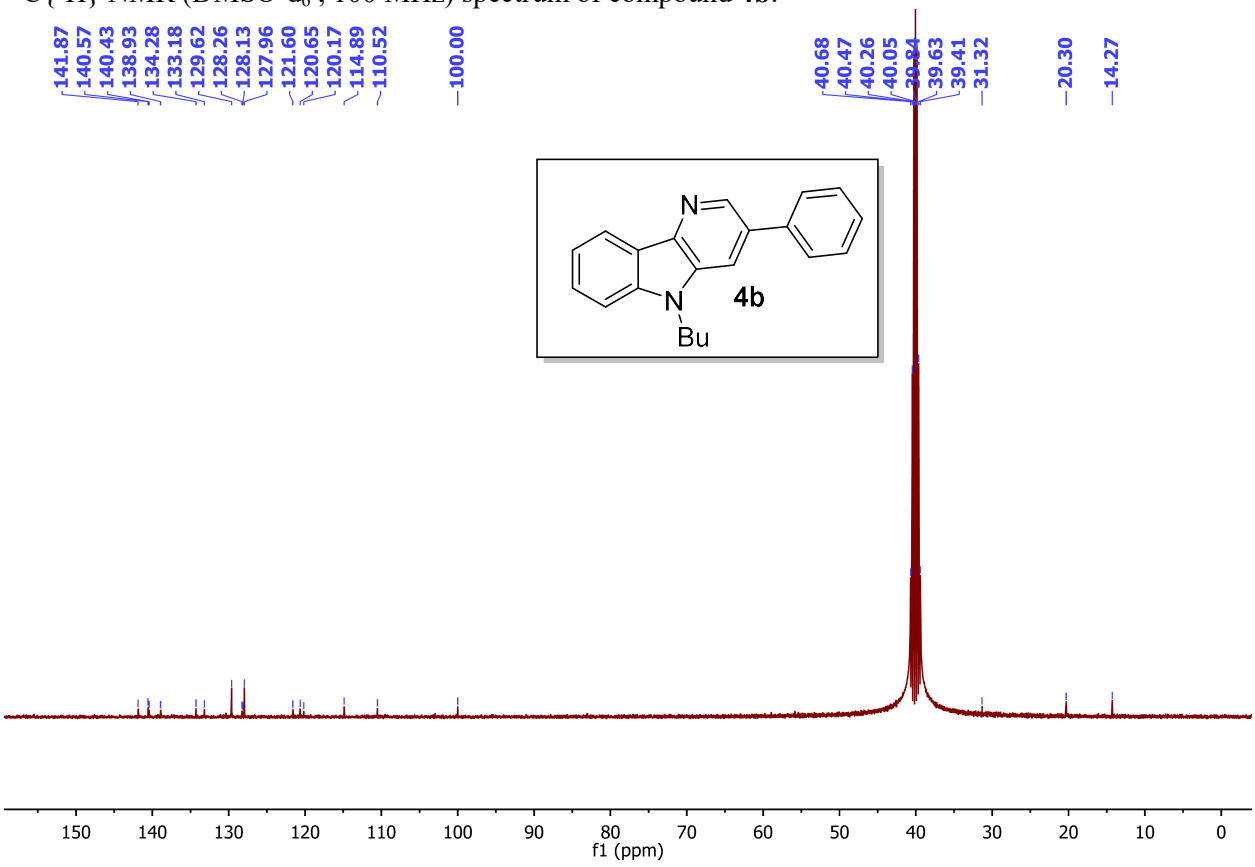
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **4a**:



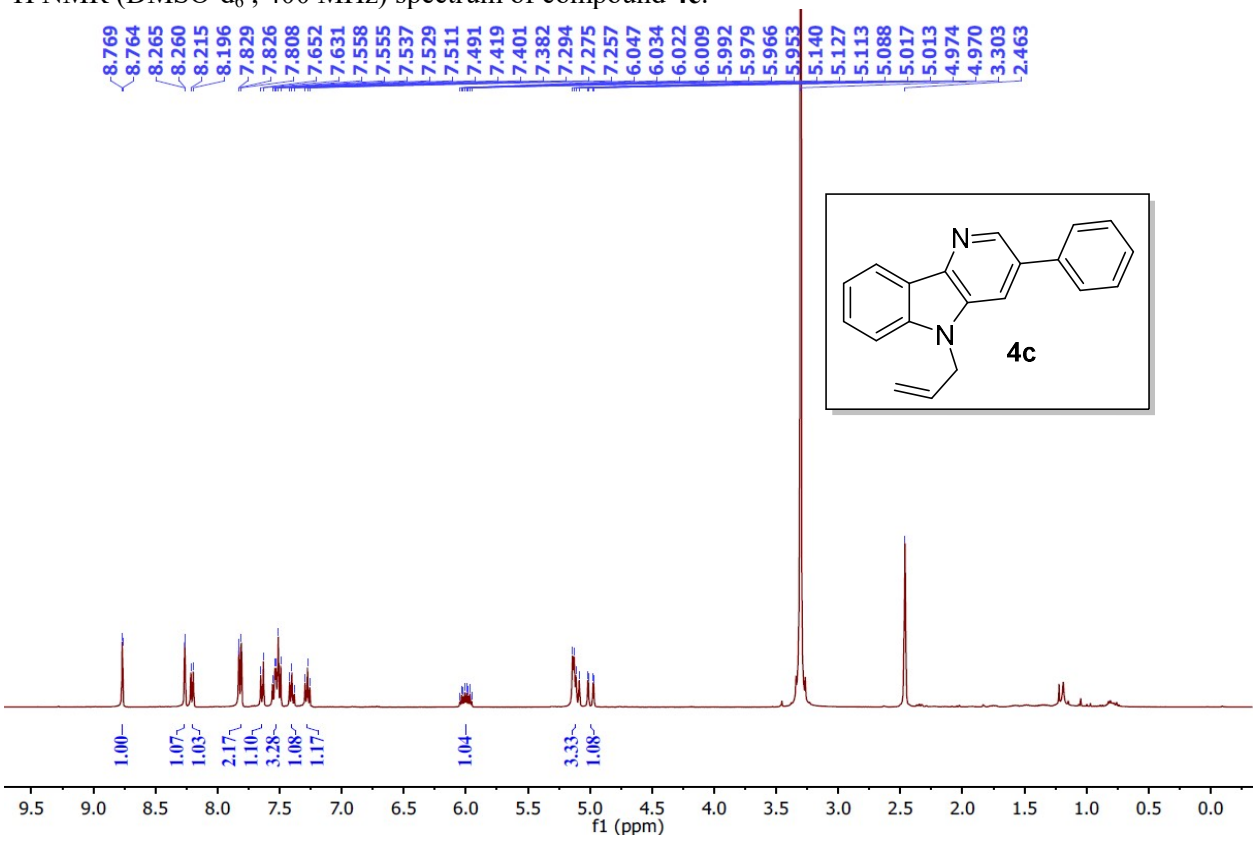
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4b**:



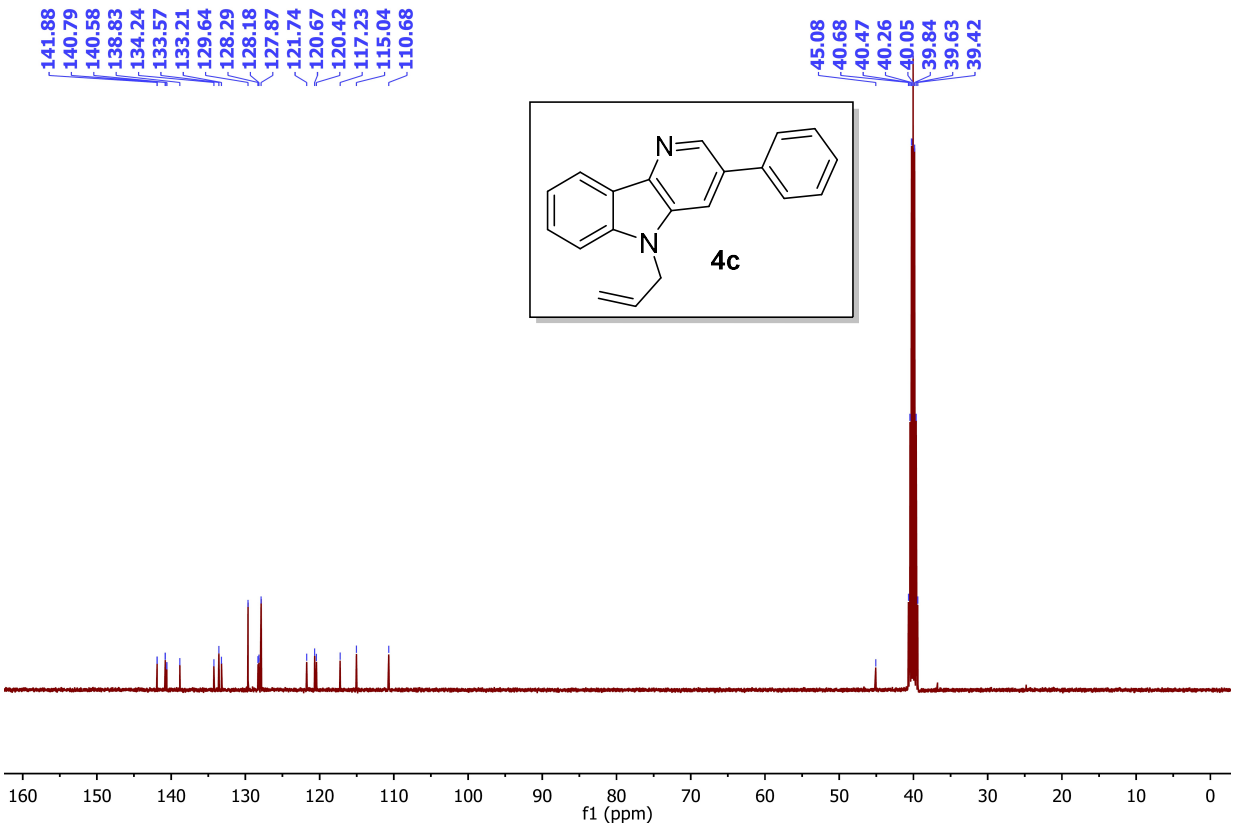
^{13}C{^{1}H} NMR (DMSO-d_6 , 100 MHz) spectrum of compound **4b**:



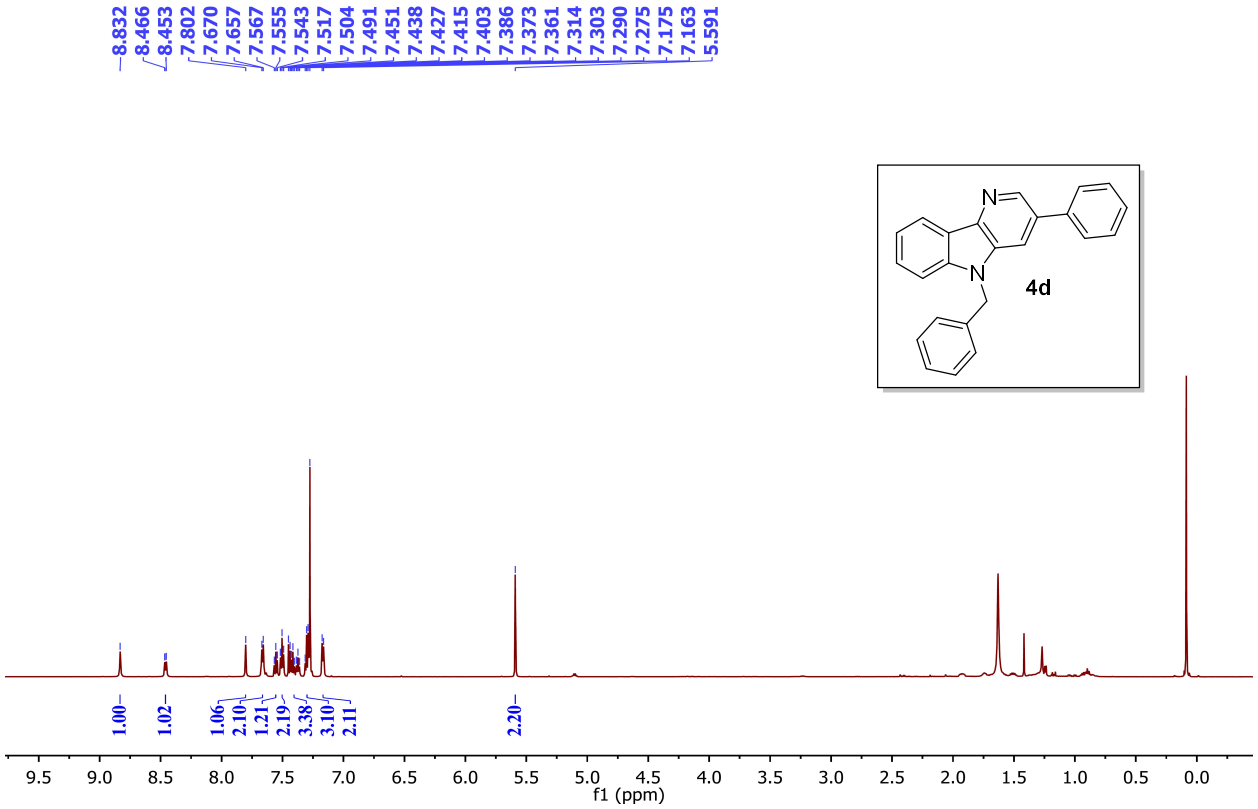
^{1}H NMR (DMSO-d_6 , 400 MHz) spectrum of compound **4c**:



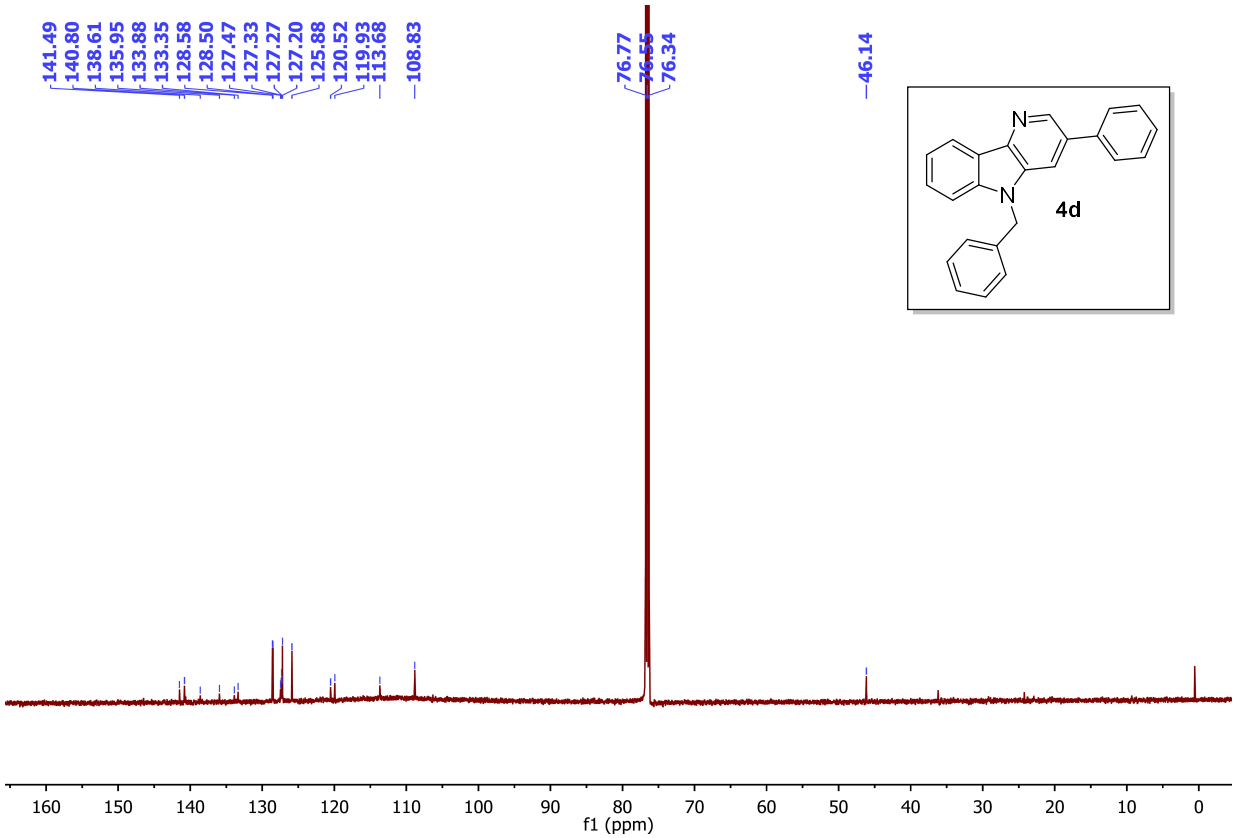
^{13}C{^{1}H} NMR (DMSO-d_6 , 100 MHz) spectrum of compound **4c**:



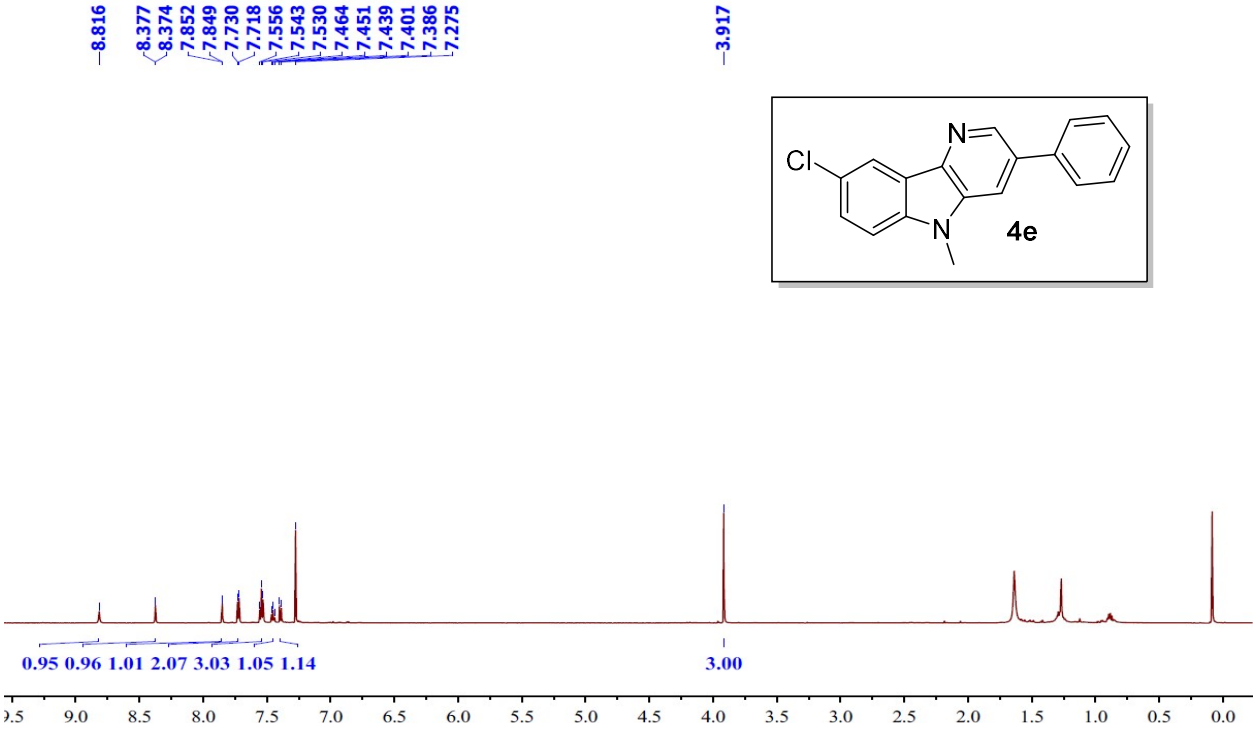
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4d**:



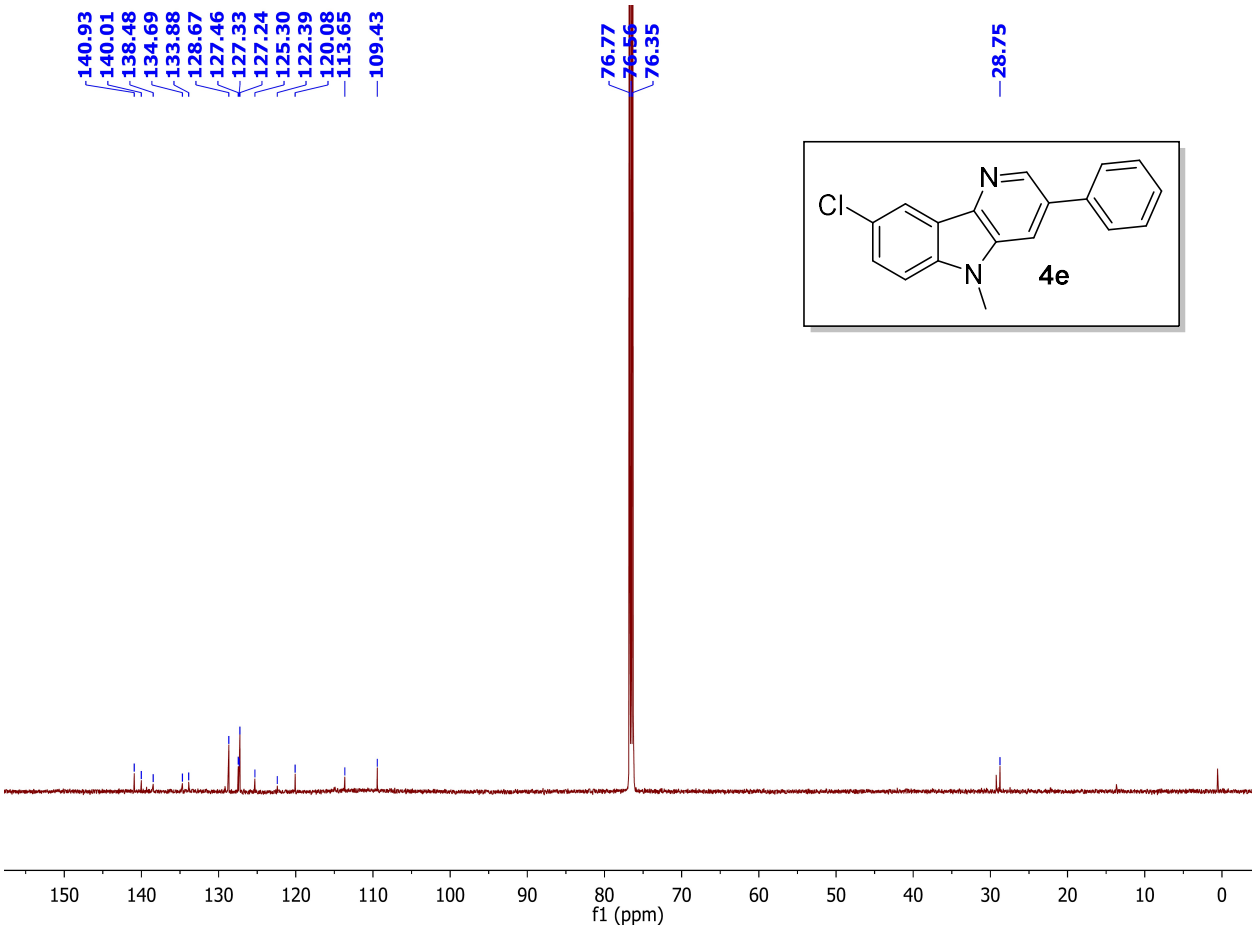
^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **4d**:



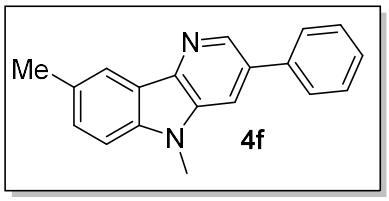
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4e:**

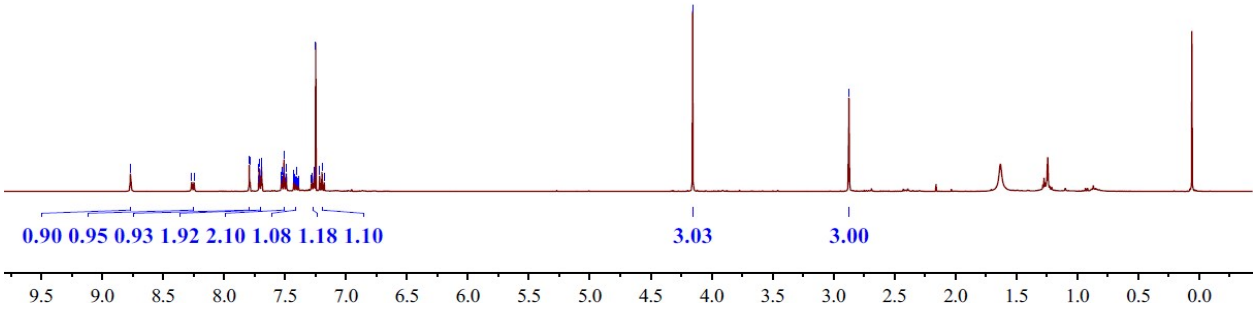


^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **4e:**

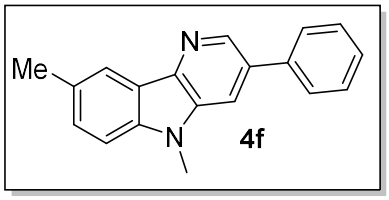


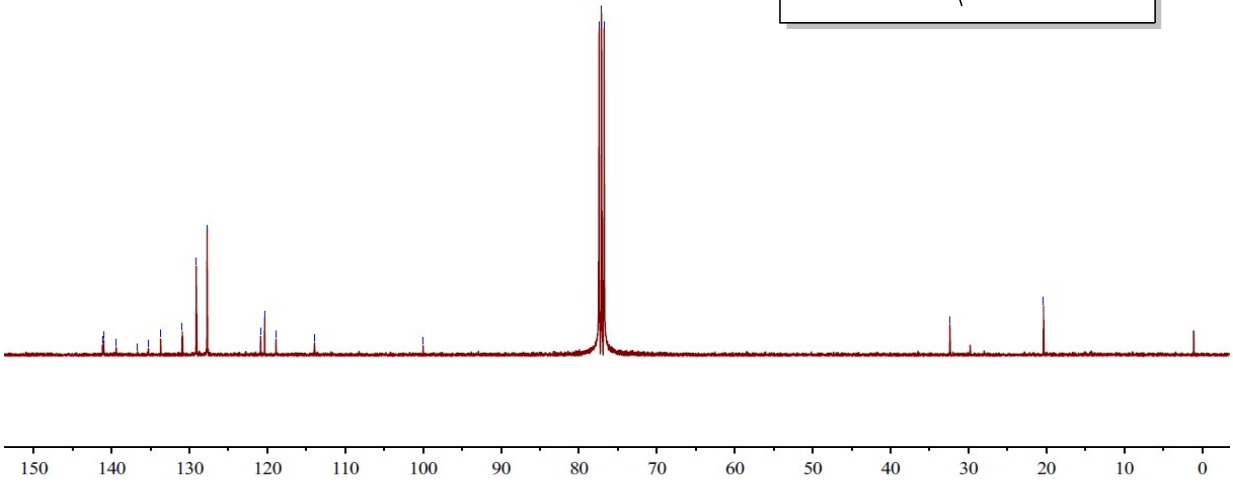
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **4f**:



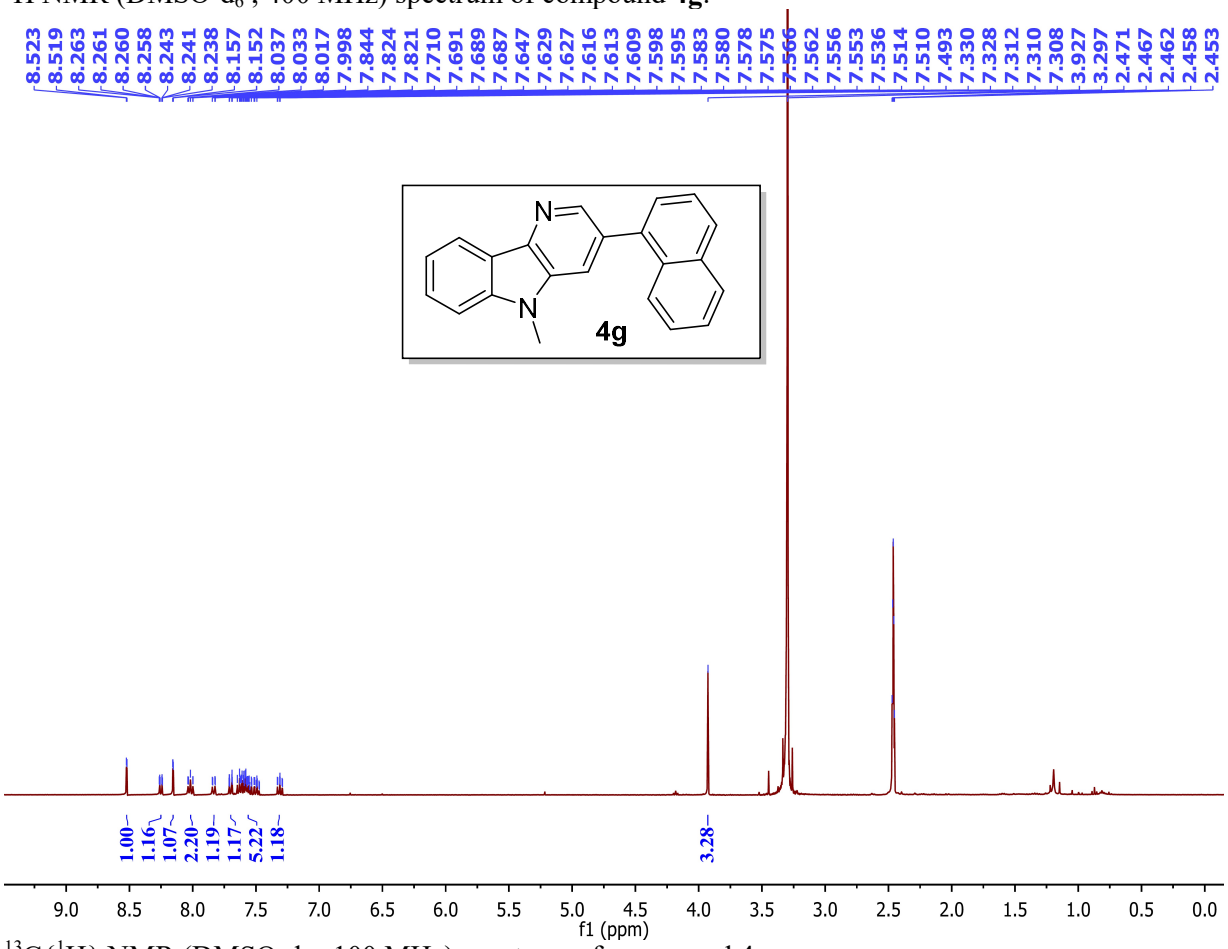


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **4f**:

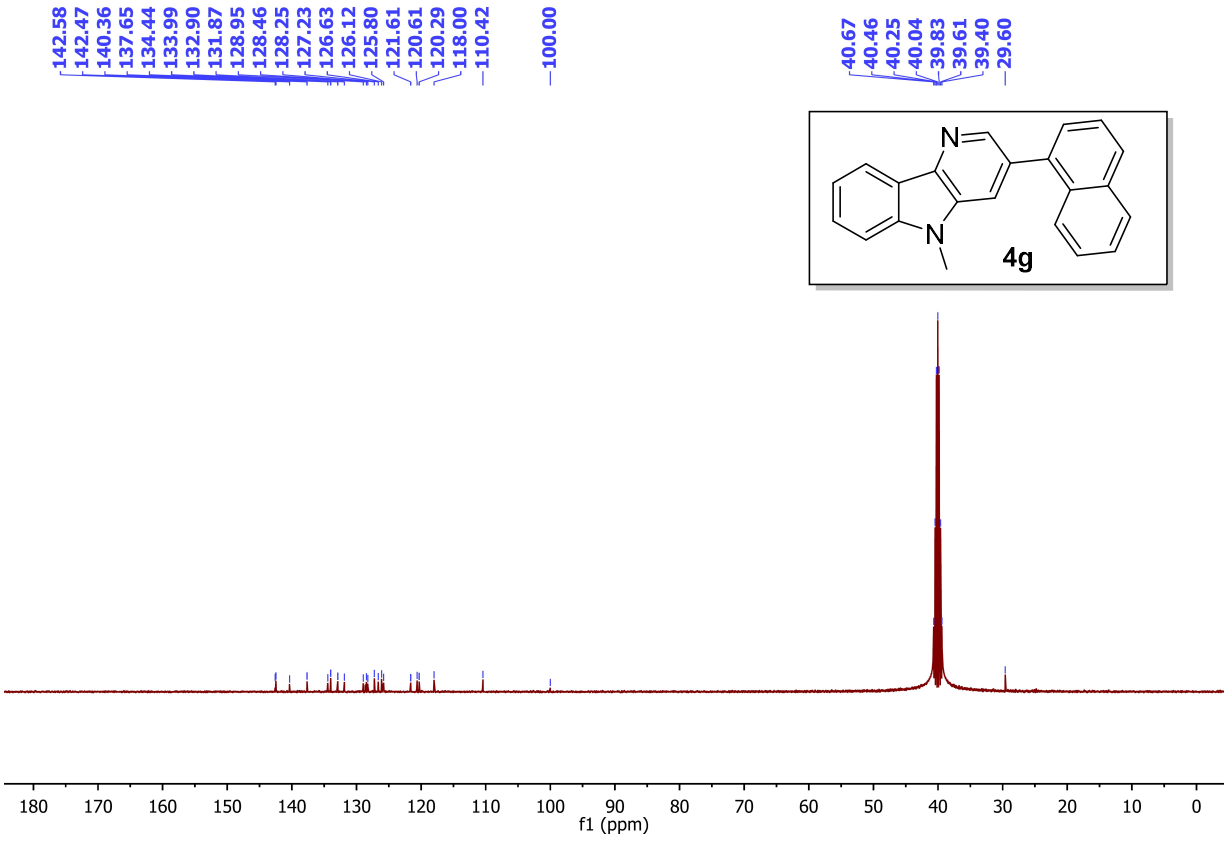




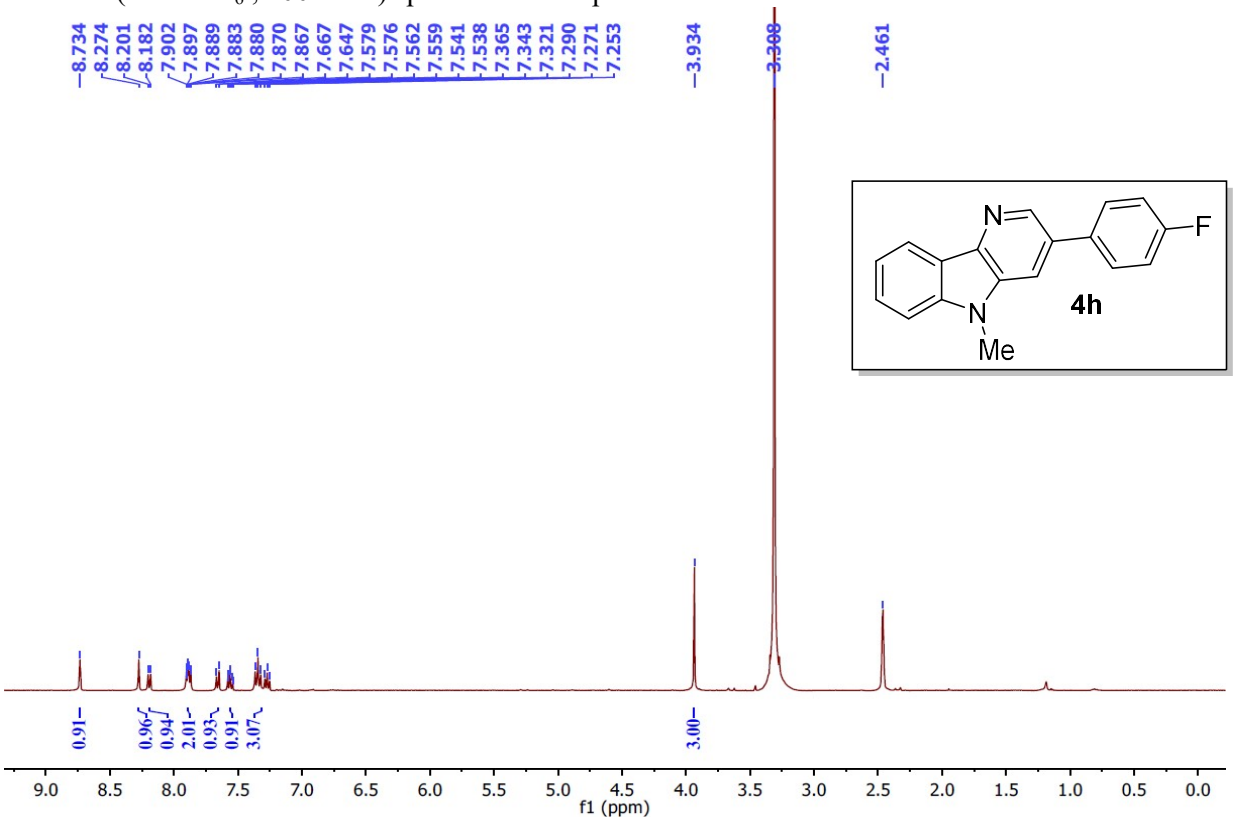
^{1}H NMR (DMSO-d$_6$, 400 MHz) spectrum of compound **4g**:



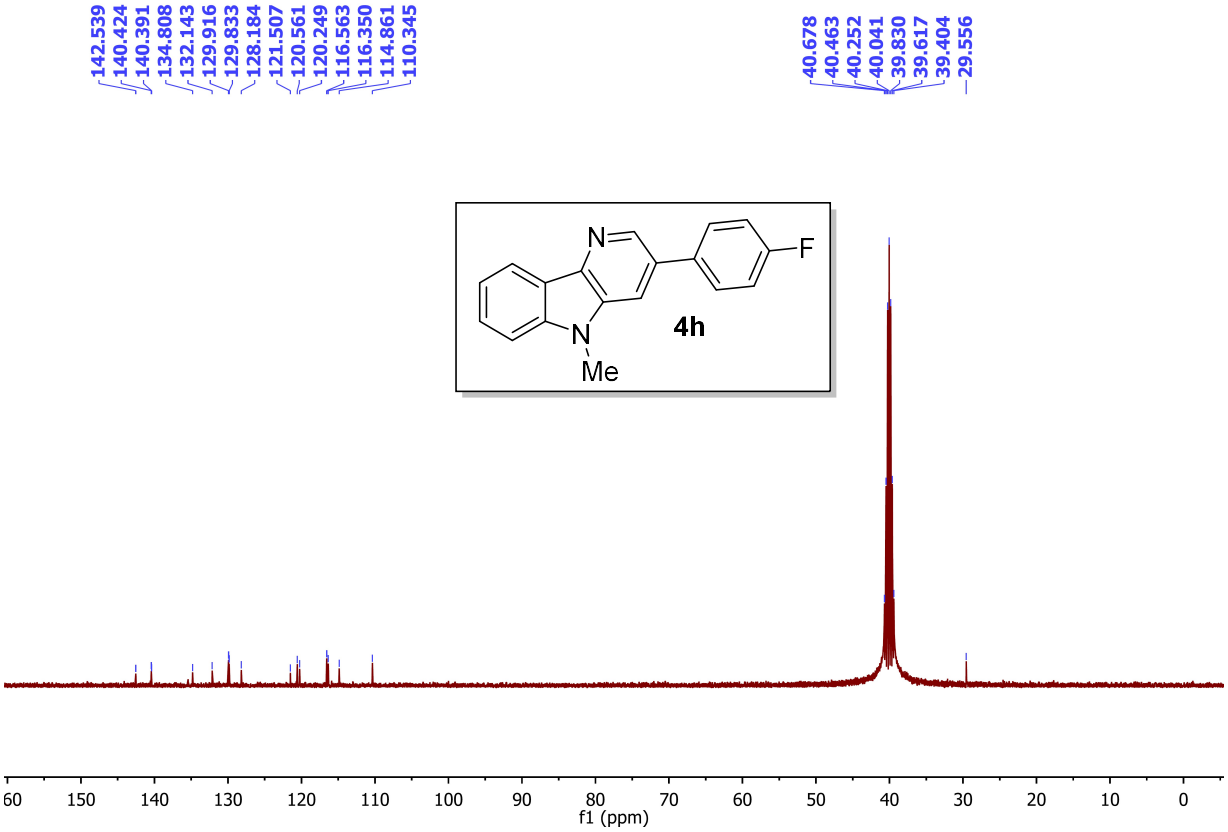
^{13}C{^{1}H} NMR (DMSO-d$_6$, 100 MHz) spectrum of compound **4g**:



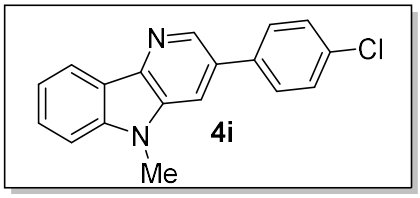
^{1}H NMR (DMSO-d_6 , 400 MHz) spectrum of compound **4h**:

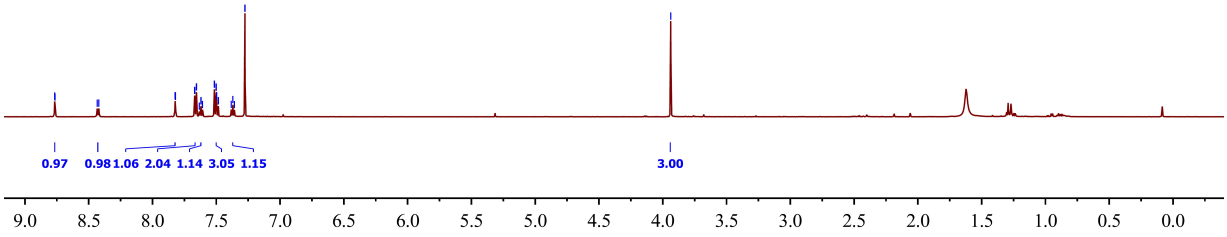


^{13}C{^{1}H} NMR (DMSO-d_6 , 100 MHz) spectrum of compound **4h**:

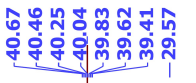


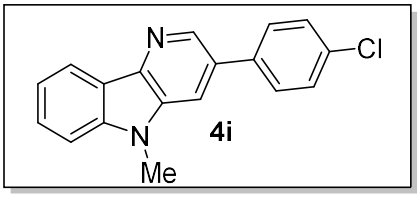
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4i**:

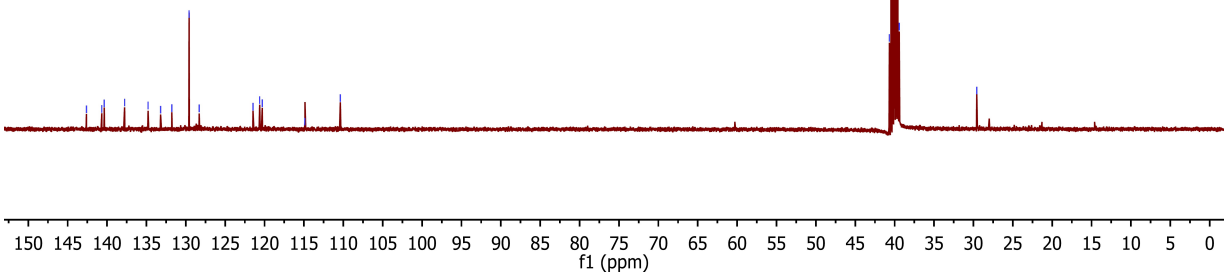




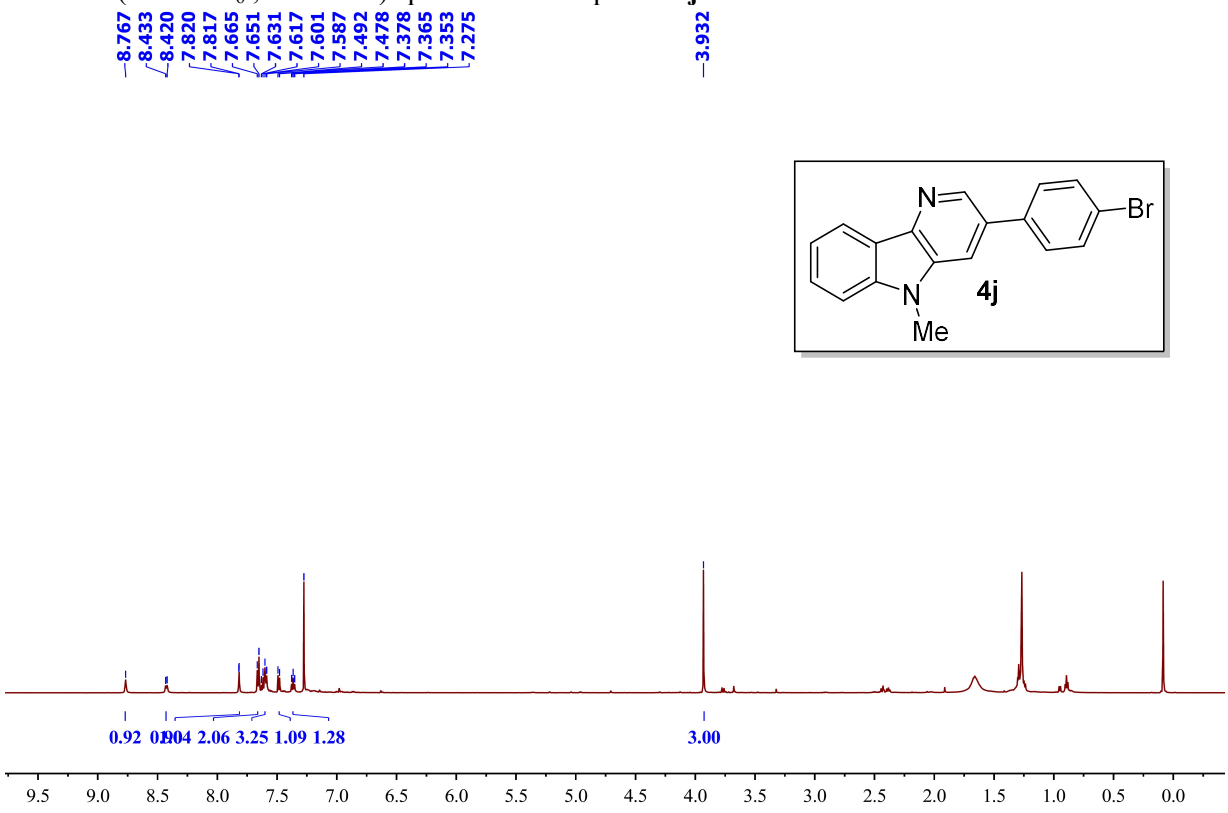
^{13}C{^{1}H} NMR (DMSO-d_6 , 100 MHz) spectrum of compound **4i**:



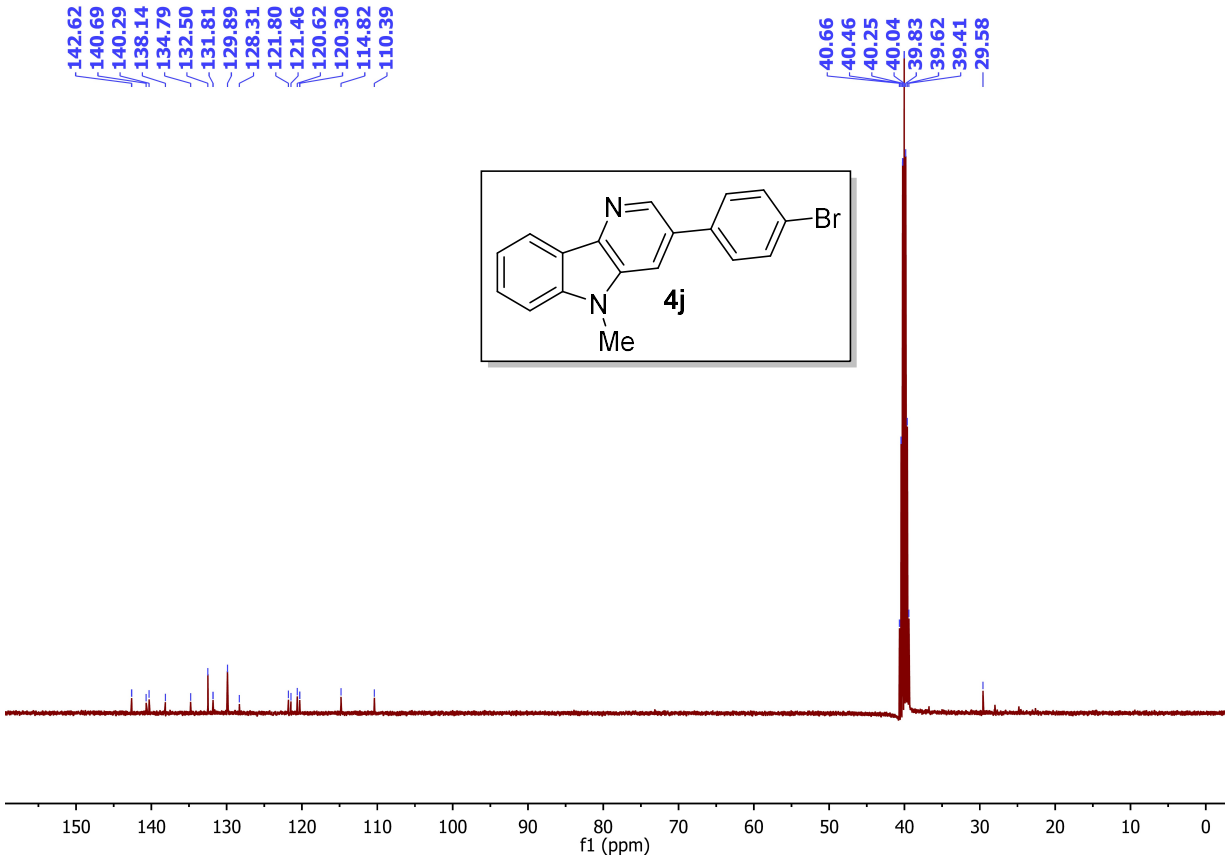




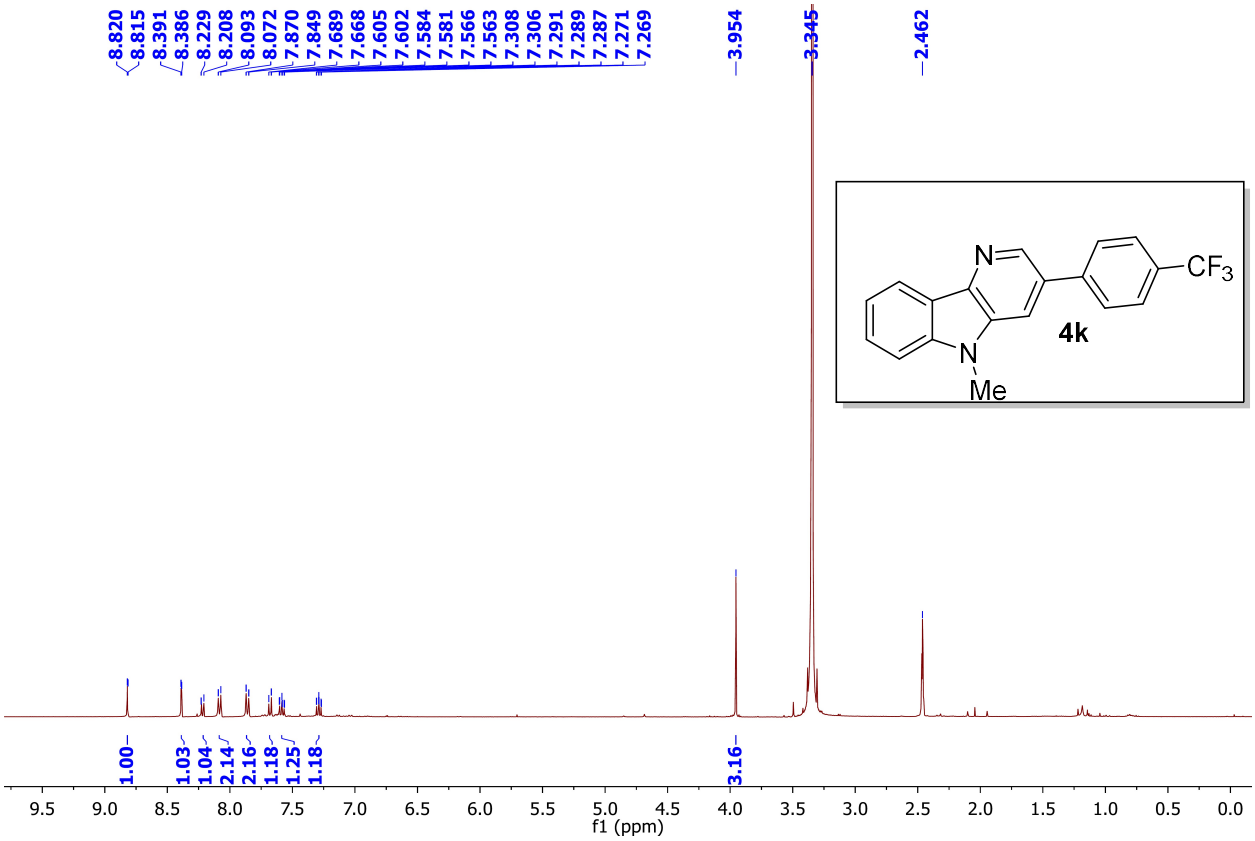
^{1}H NMR (DMSO-d$_6$, 400 MHz) spectrum of compound **4j**:



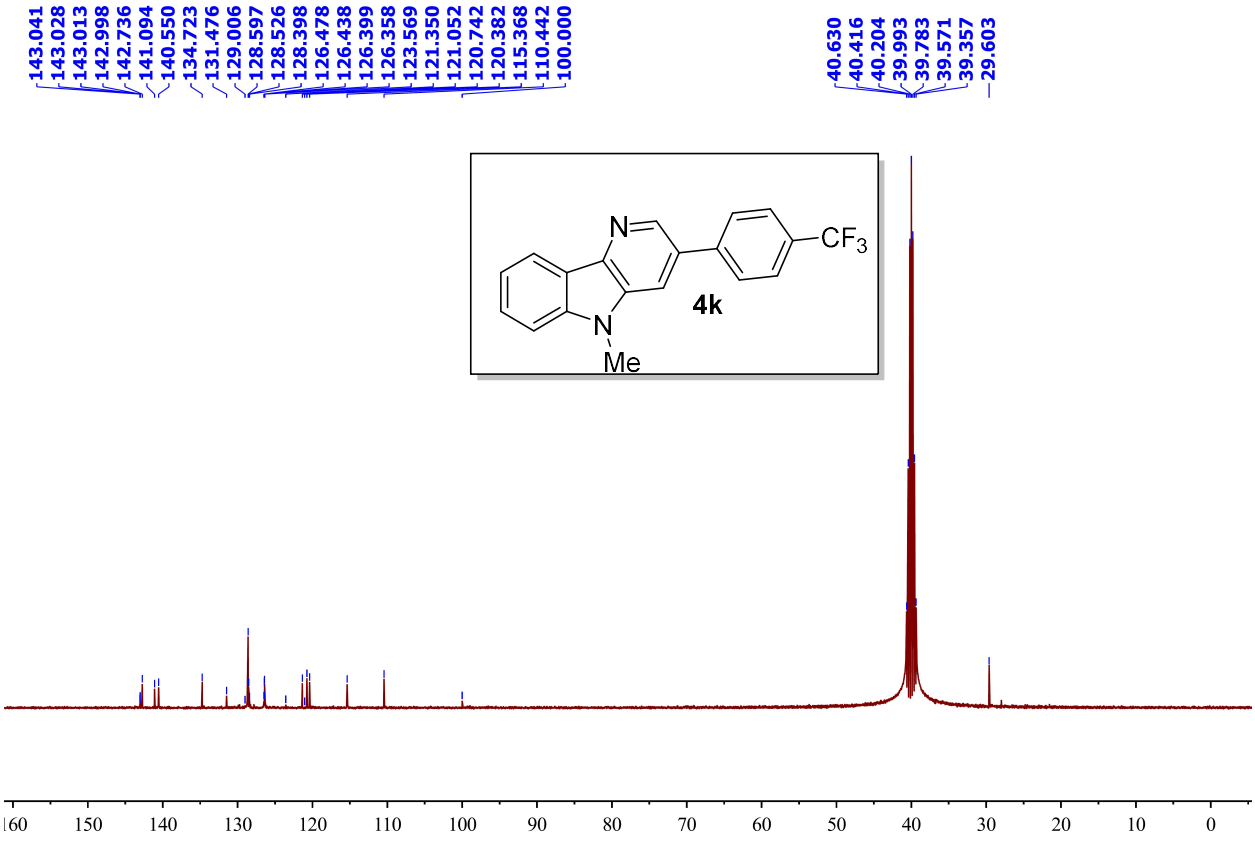
^{13}C{^{1}H} NMR (DMSO-d$_6$, 100 MHz) spectrum of compound **4j**:



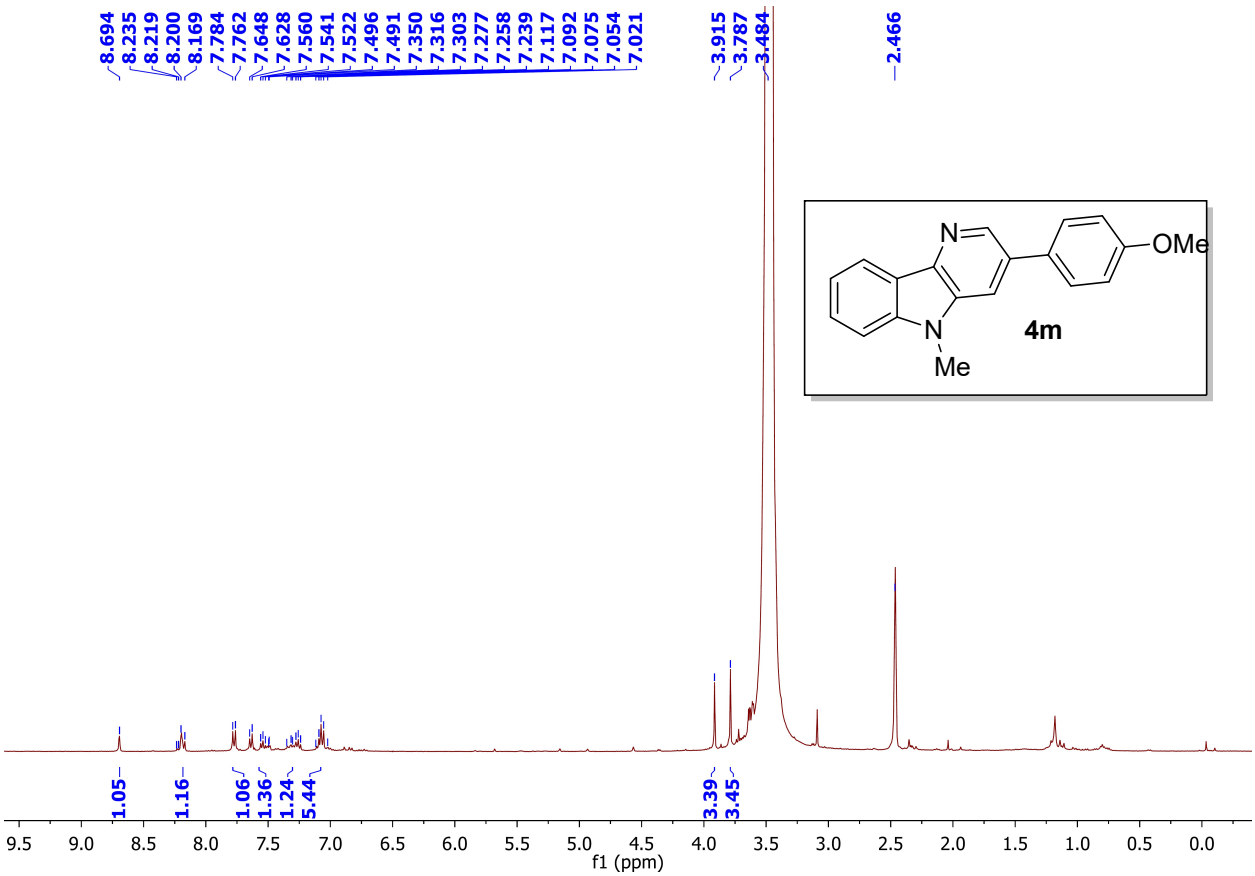
^{1}H NMR (DMSO-d$_6$, 400 MHz) spectrum of compound **4k**:



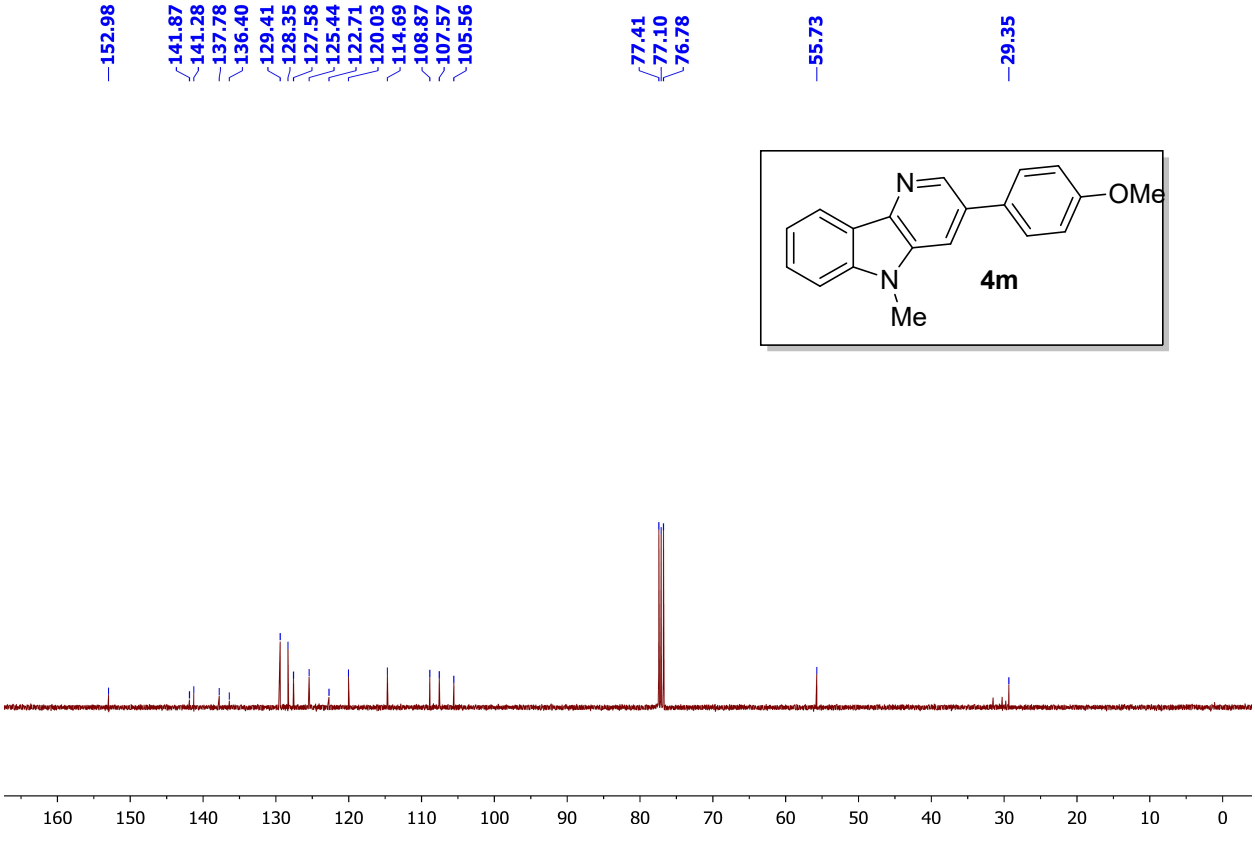
^{13}C{^{1}H} NMR (DMSO-d$_6$, 100 MHz) spectrum of compound **4k**:



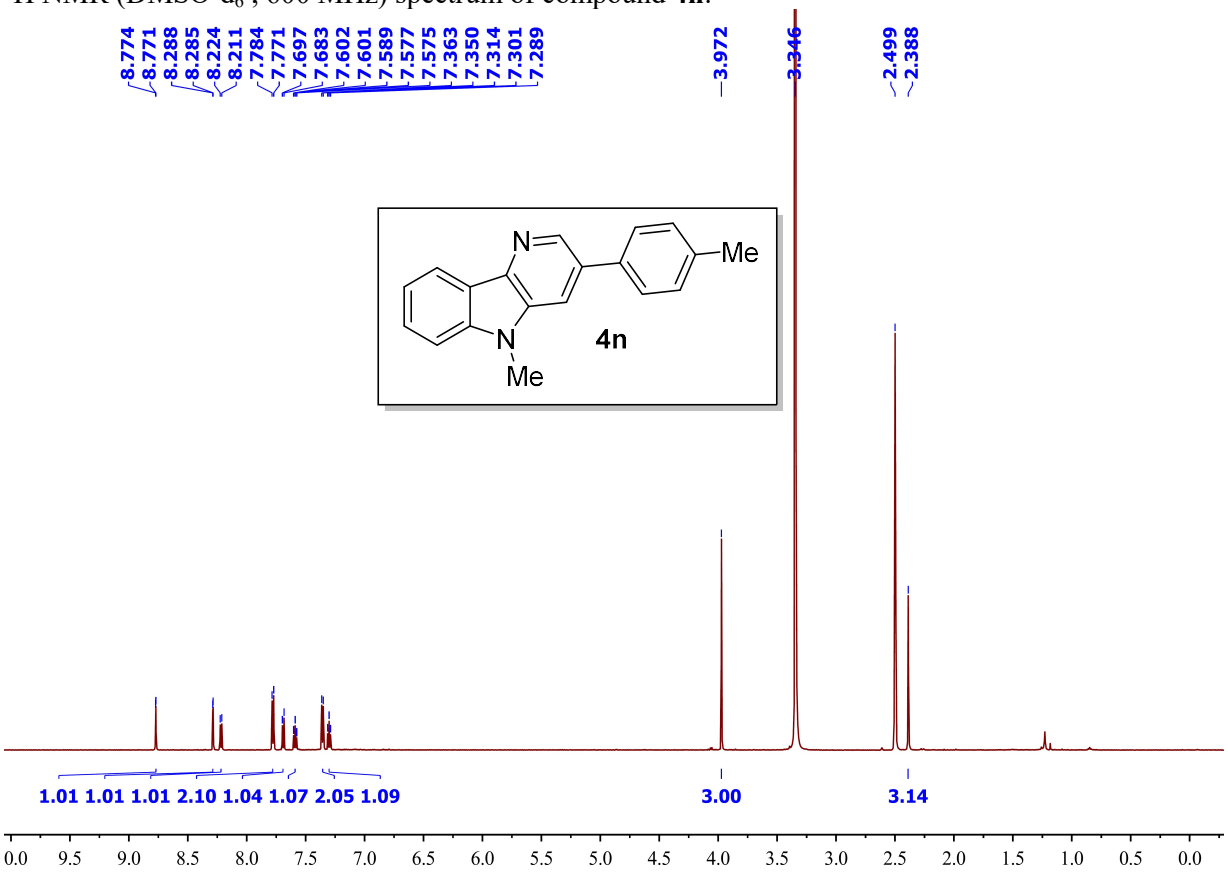
^{1}H NMR (DMSO-d_6 , 400 MHz) spectrum of compound **4m**:



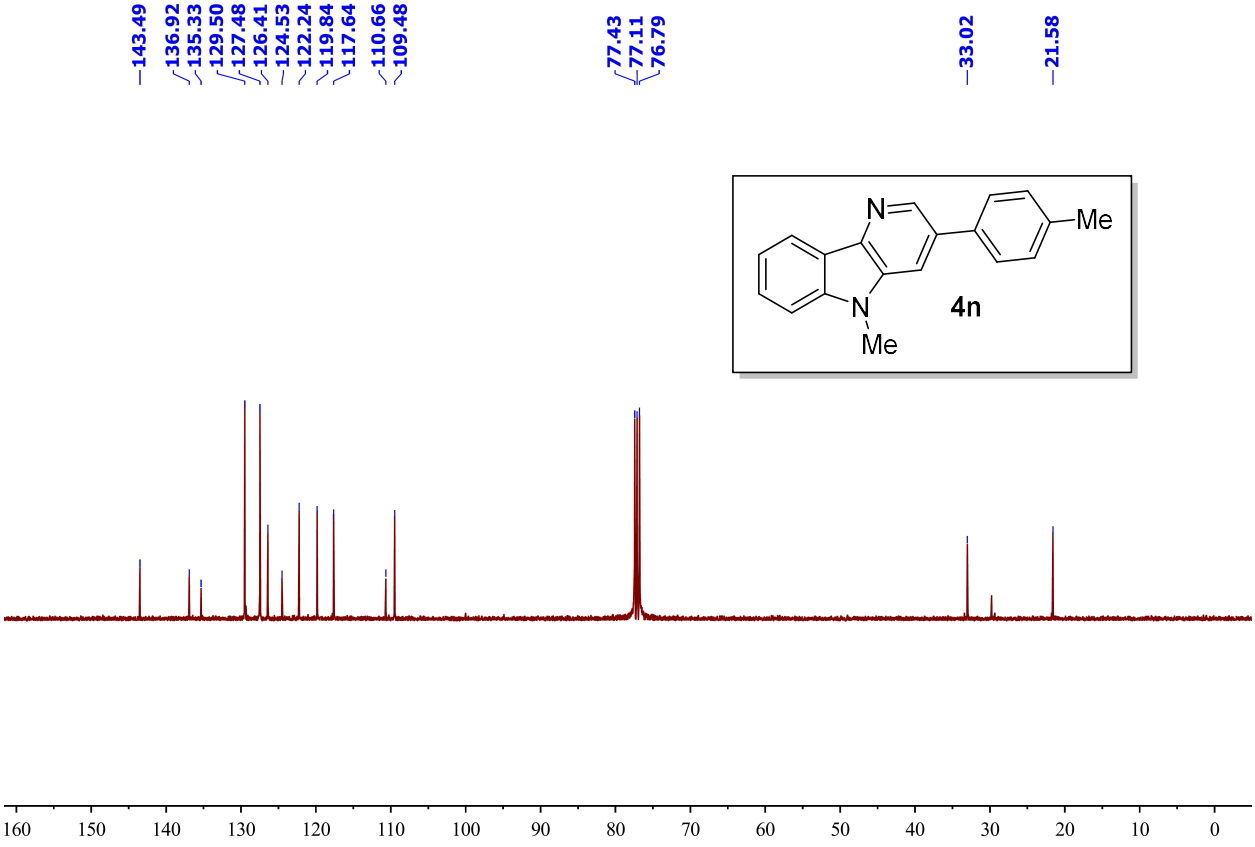
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **4m**:



^{1}H NMR (DMSO-d_6 , 600 MHz) spectrum of compound **4n**:

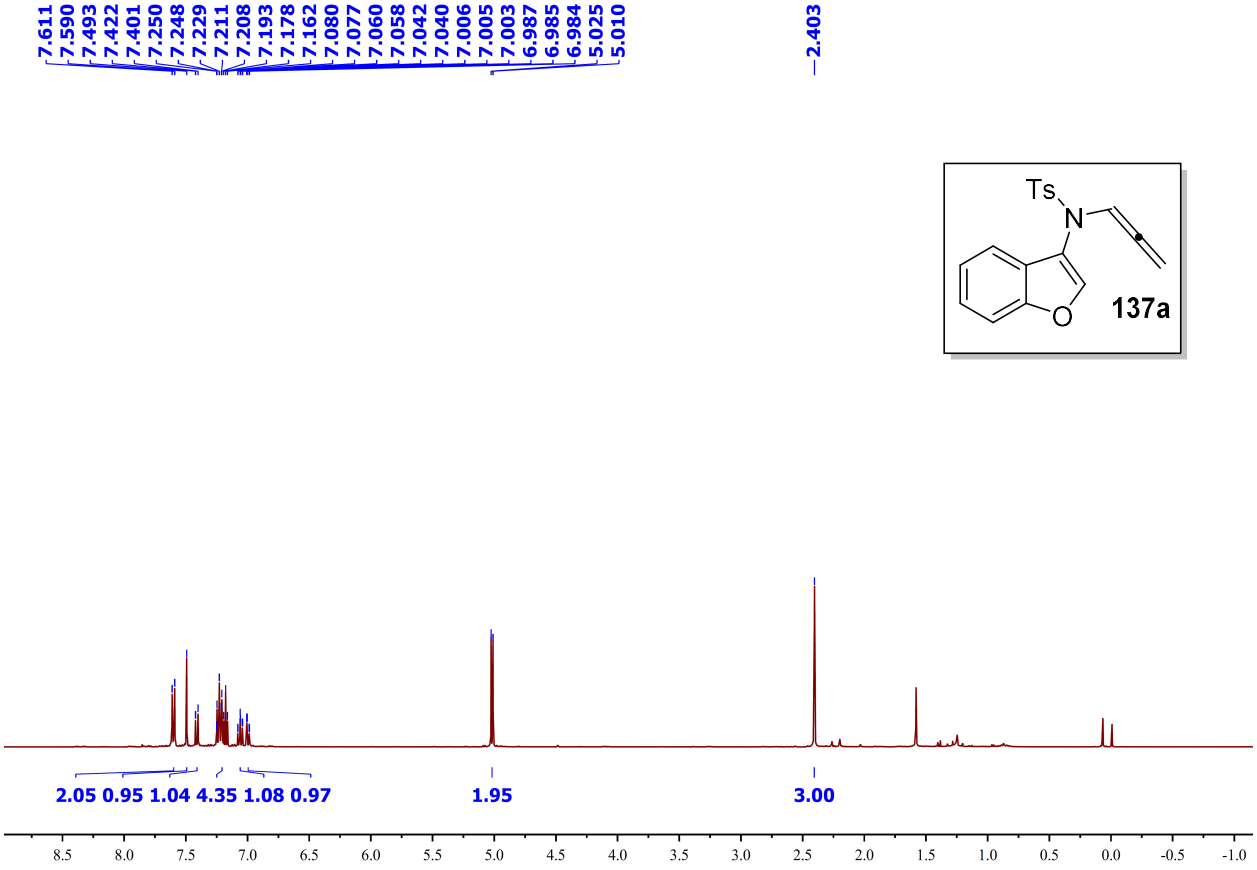


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **4n**:

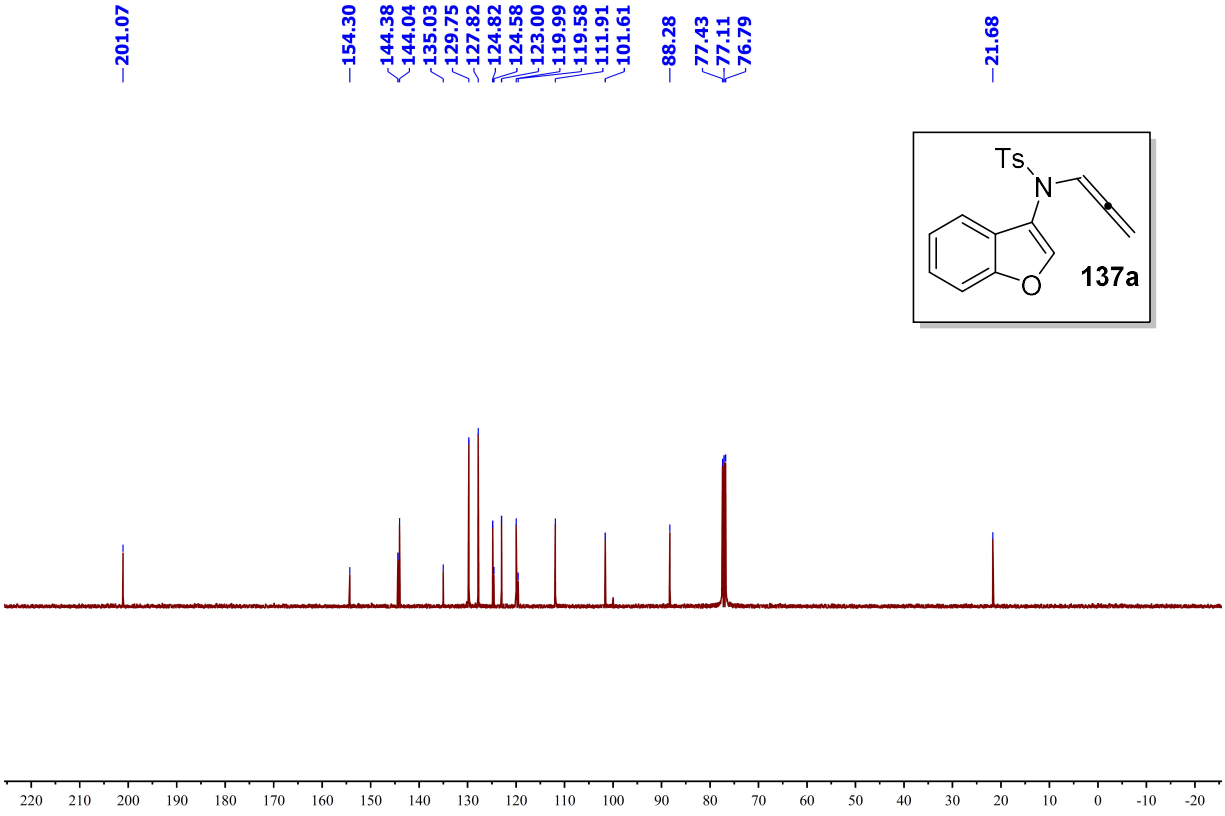


2.2.10.3 NMR spectra of compounds 137a-137c:

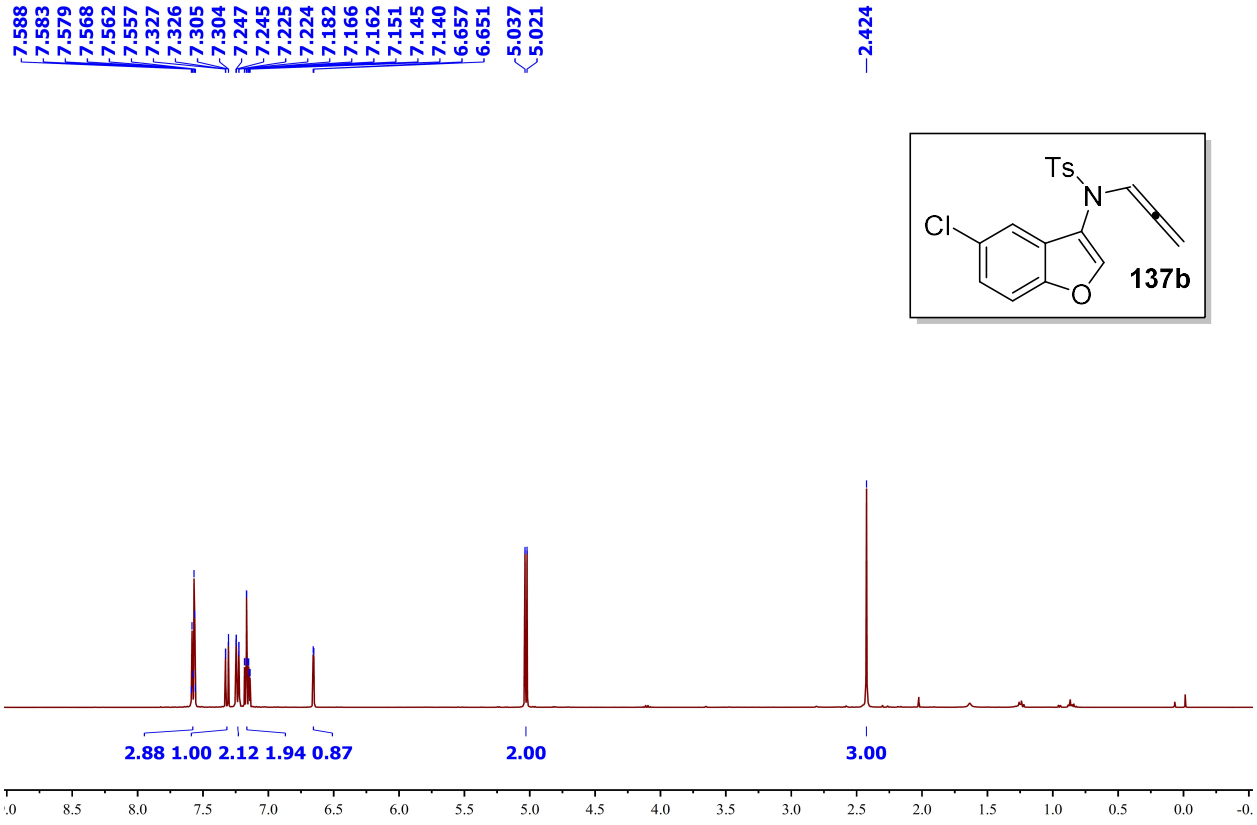
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **137a**



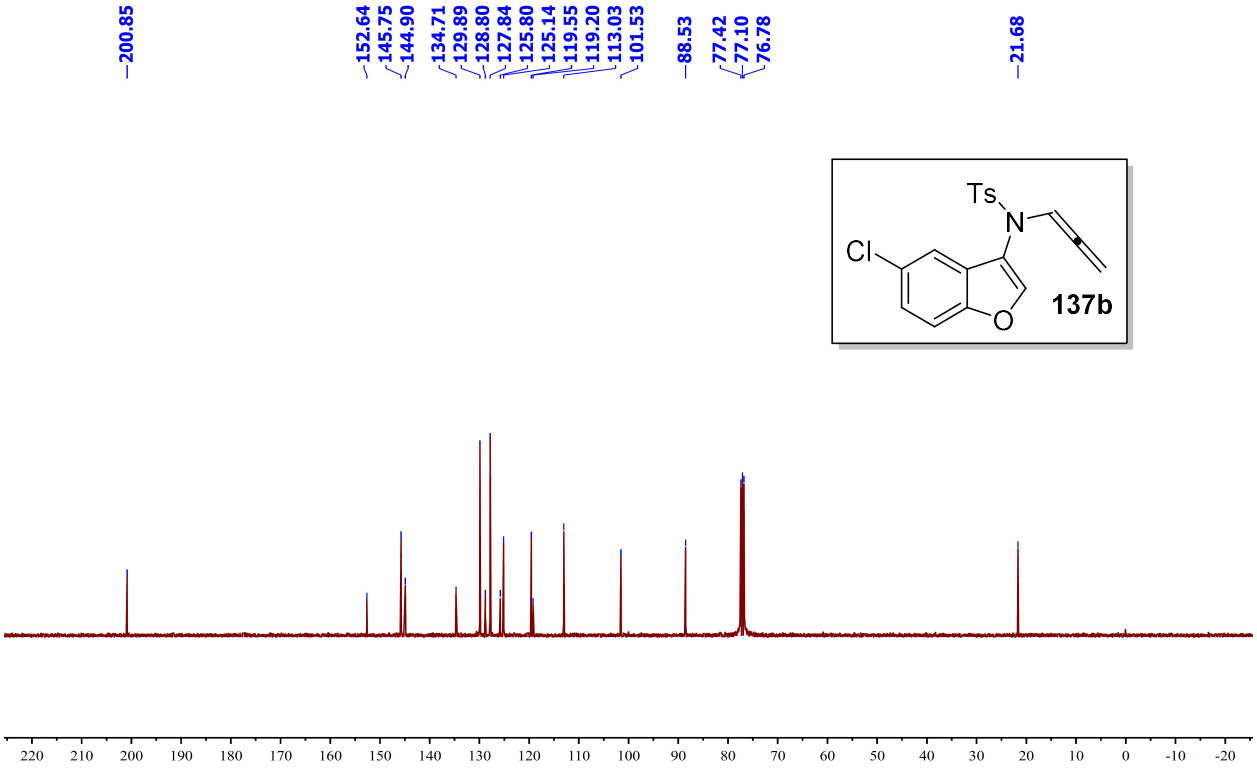
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **137a**:



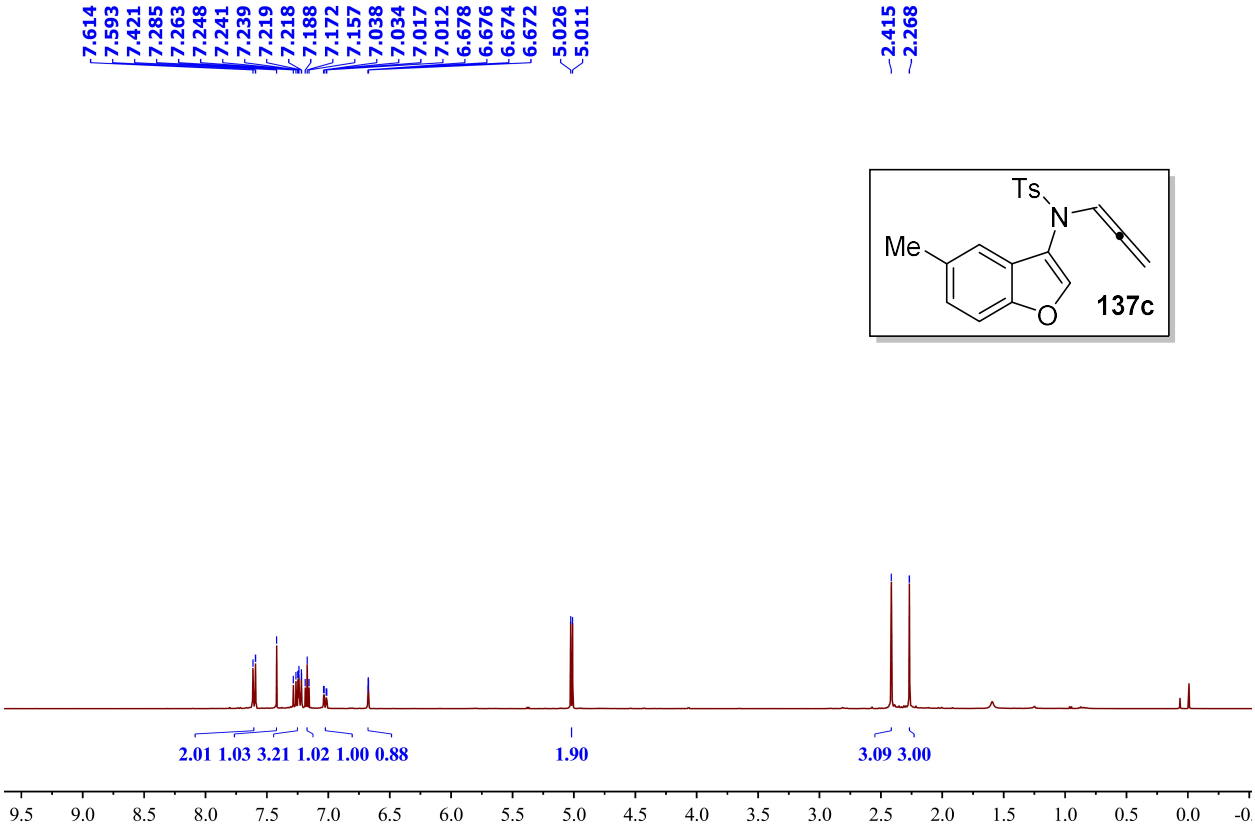
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **137b**:



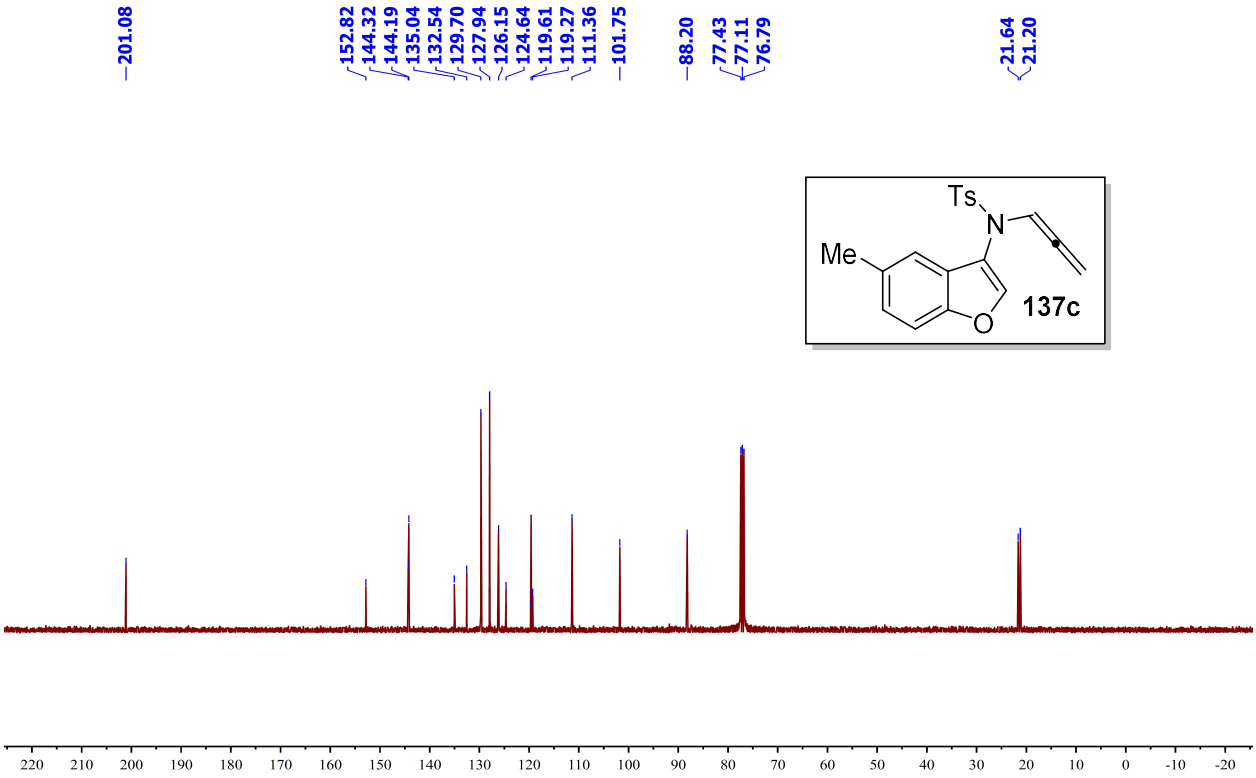
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **137b**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **137c**:

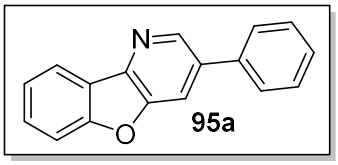


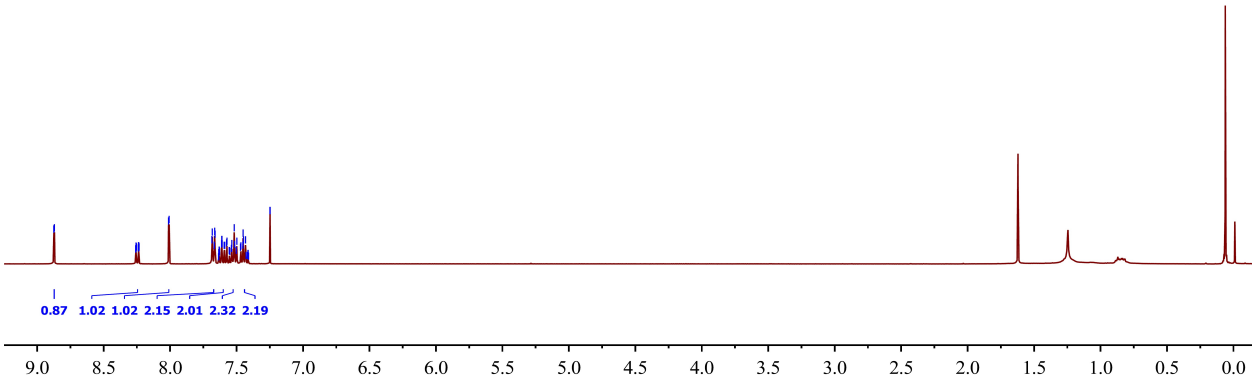
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **137c**:



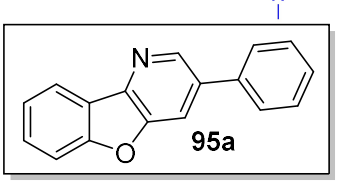
2.2.10.4 NMR spectra of compounds 95a-95q:

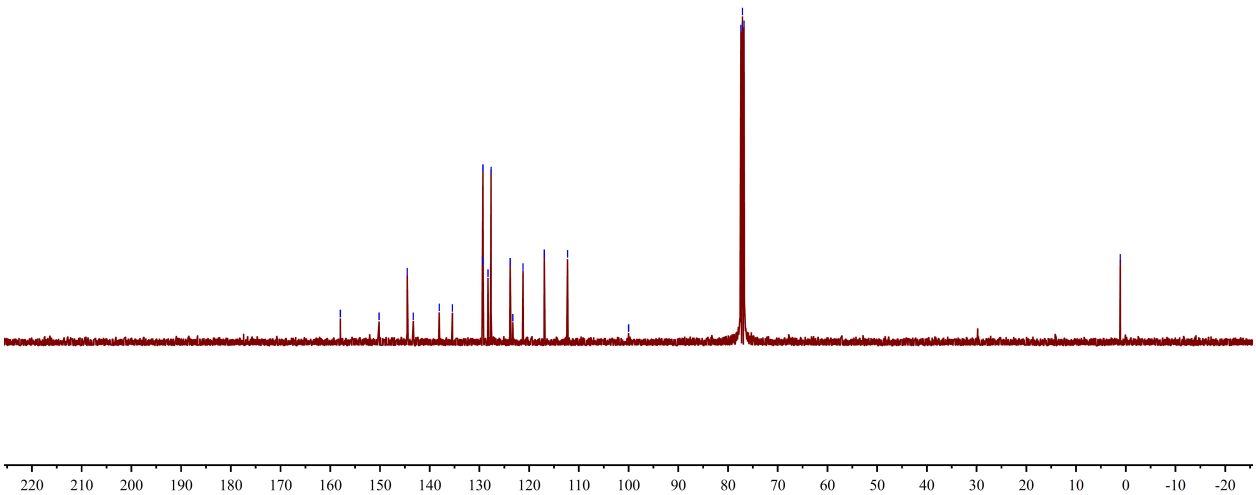
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95a**:



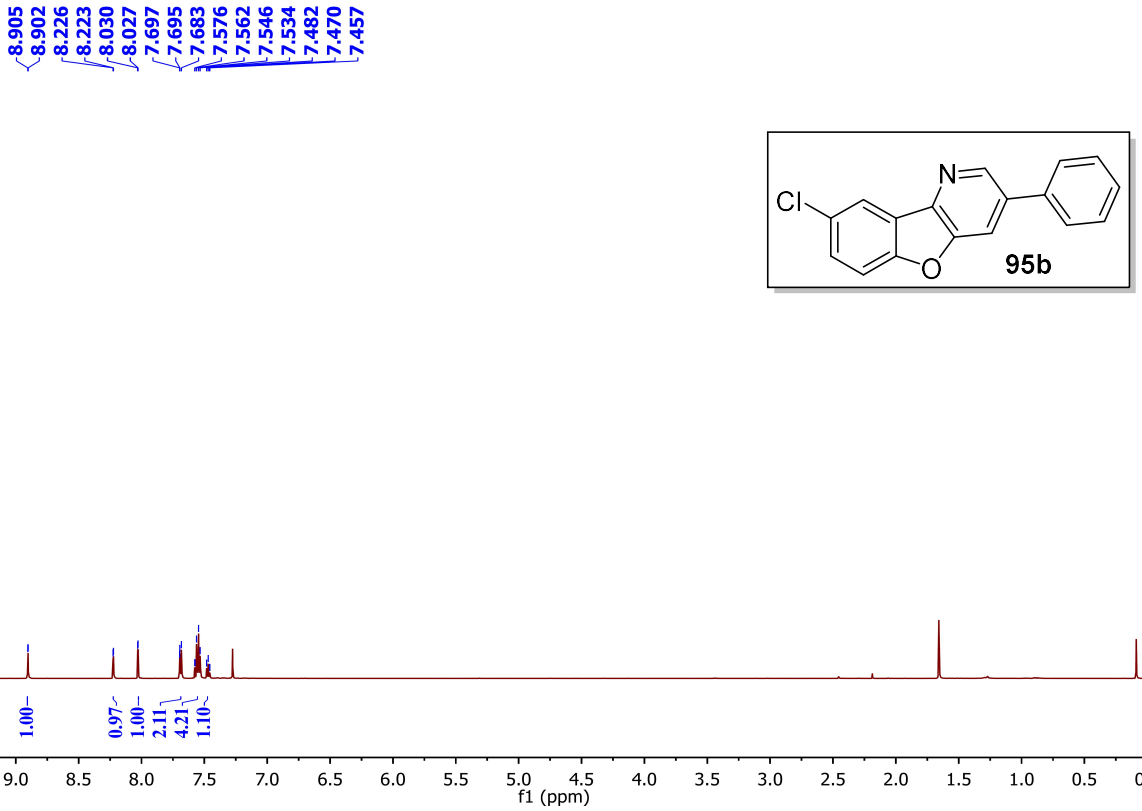


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95a**:

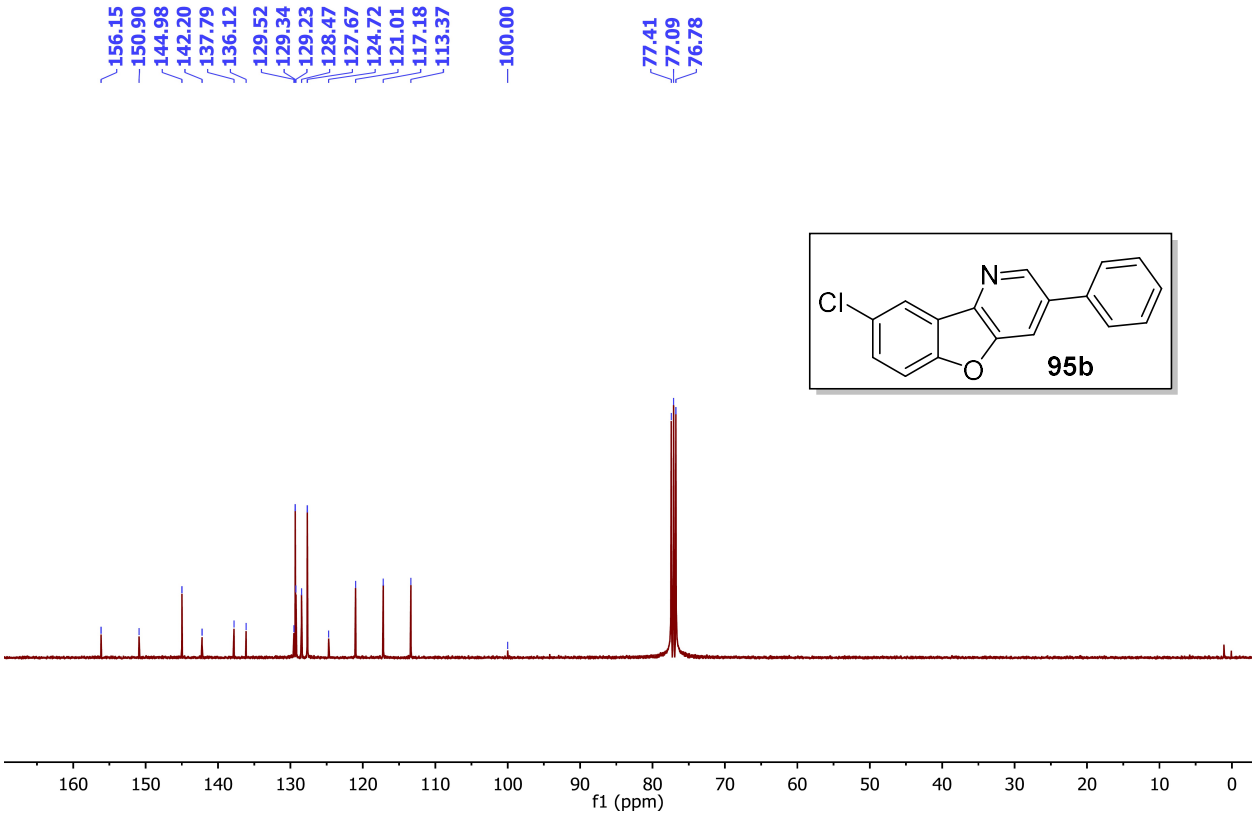




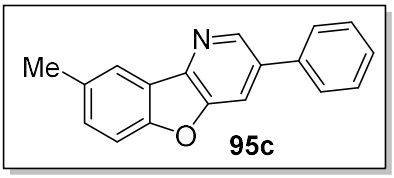
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **95b**:

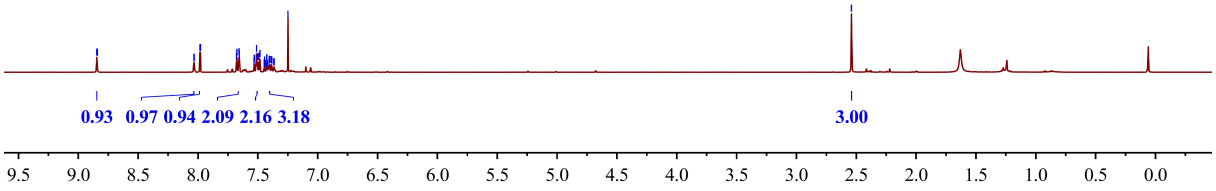


^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **95b**:

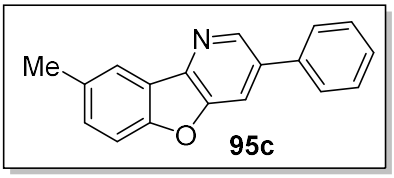


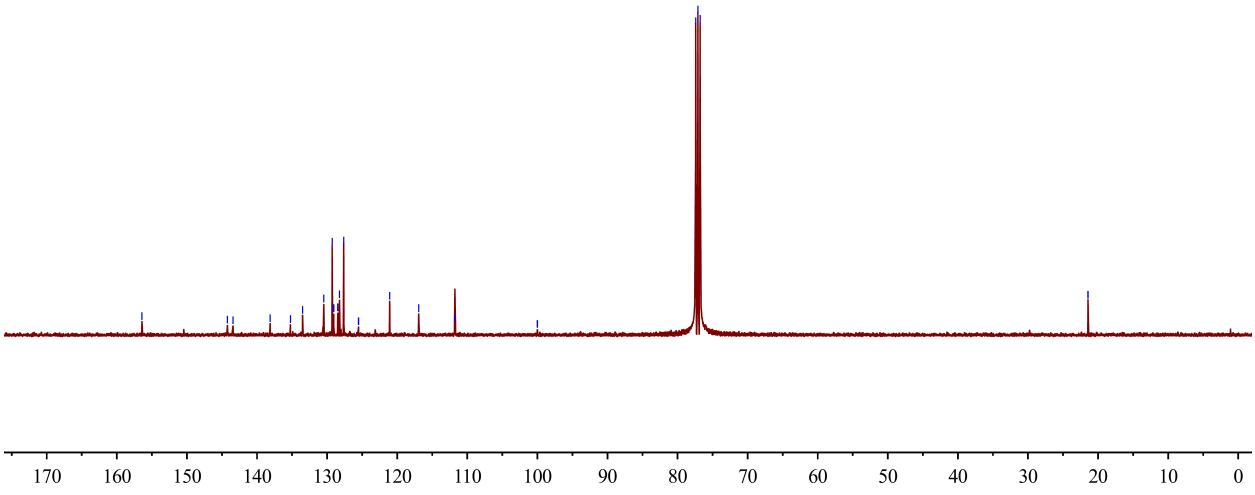
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95c**:



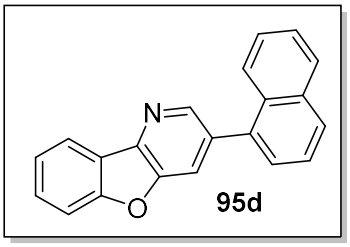


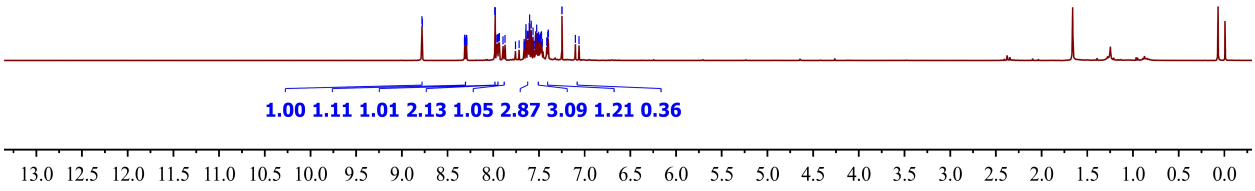
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95c**:



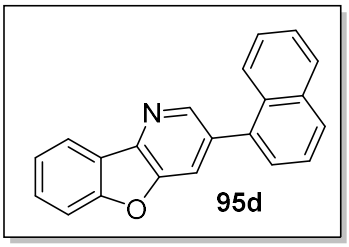


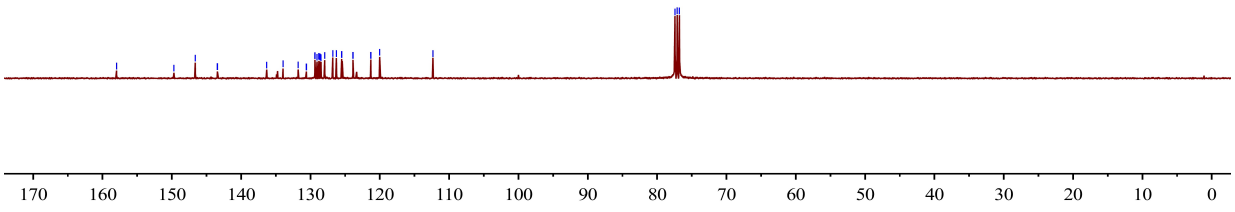
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95d**:



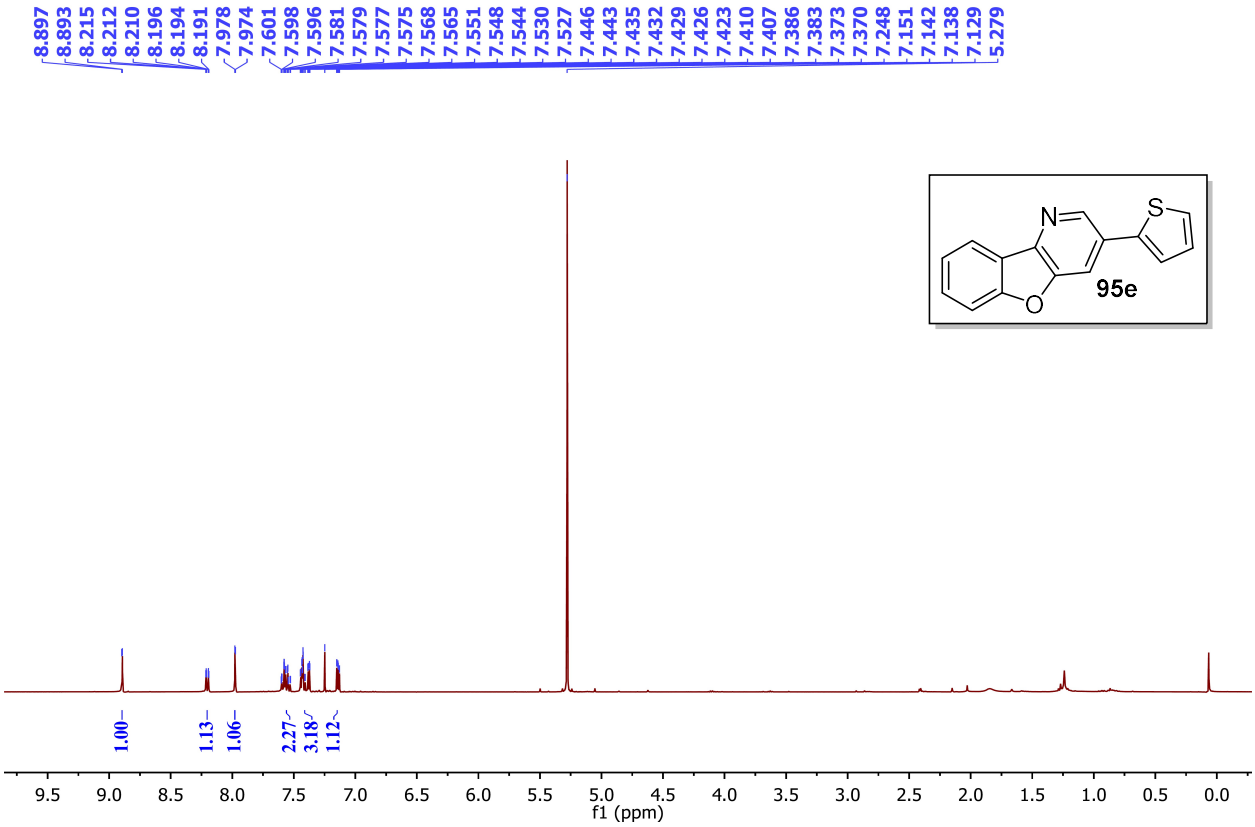


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95d**:

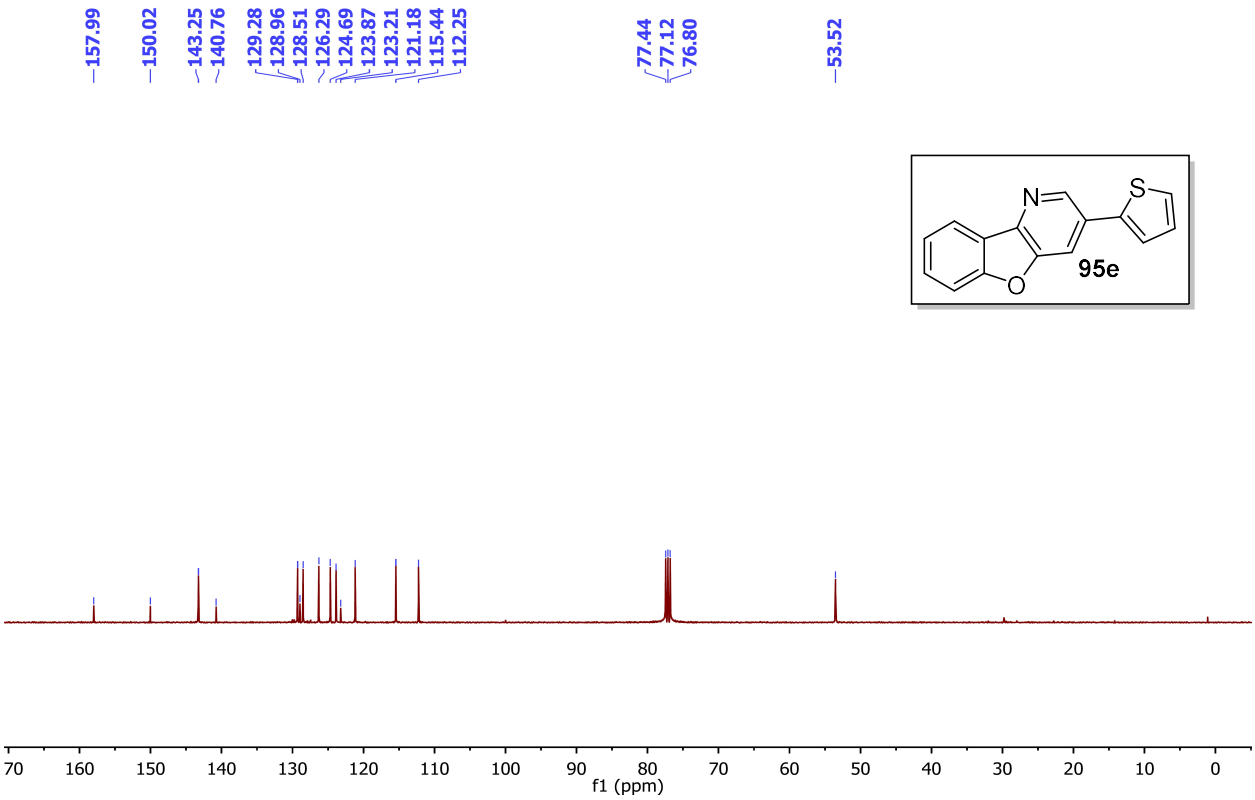




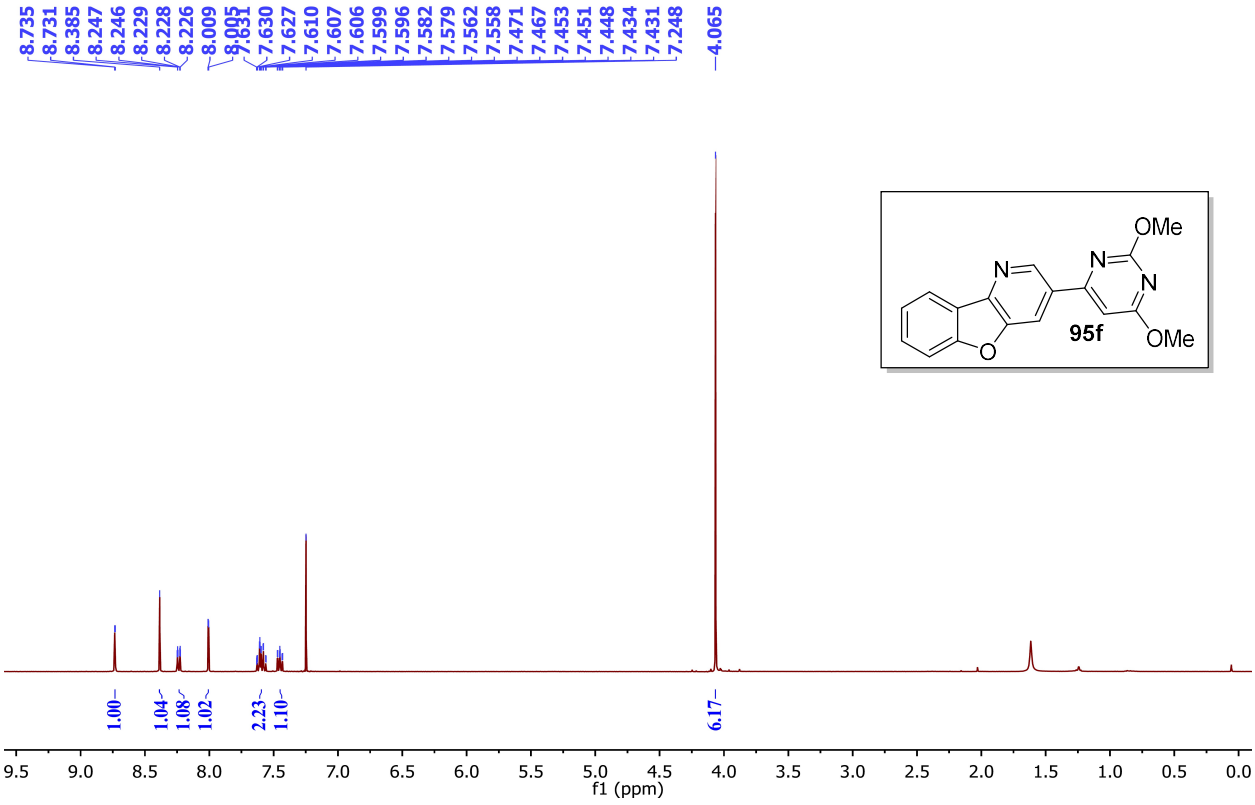
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95e**:



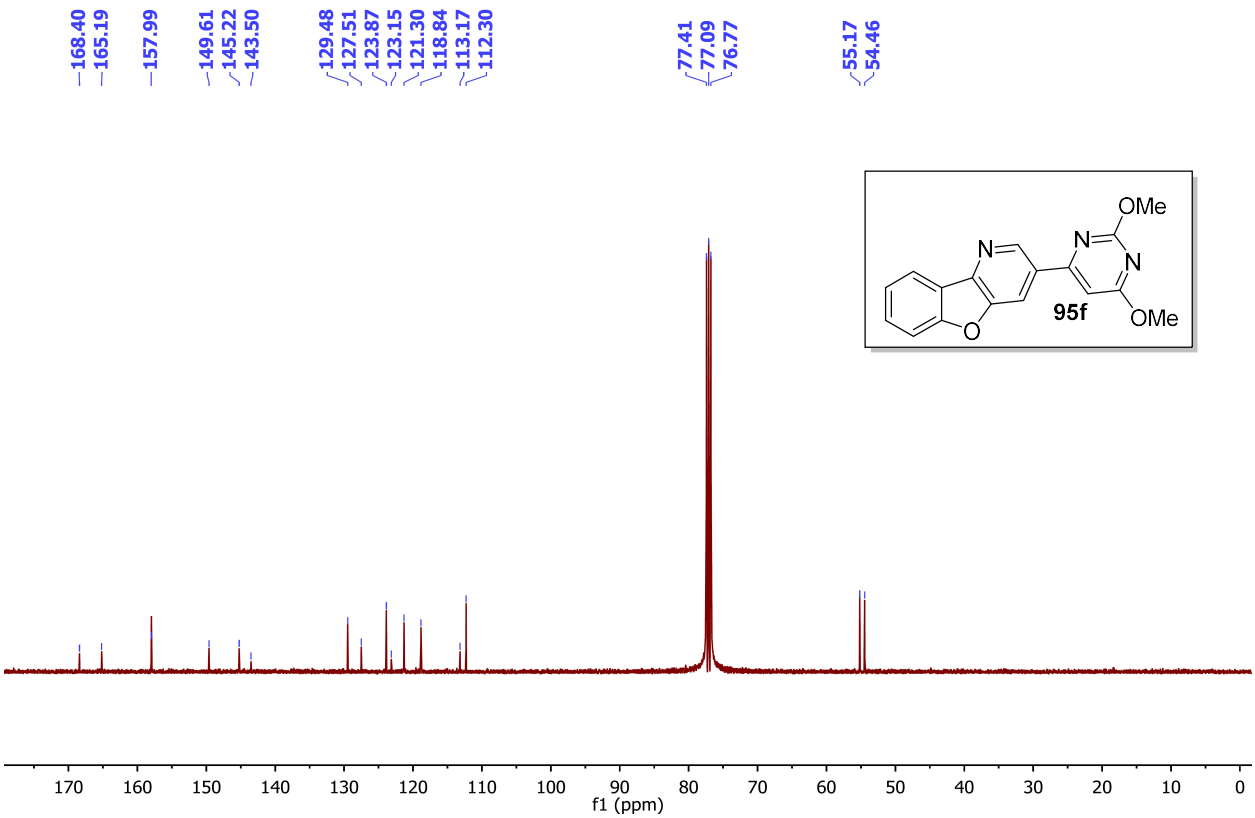
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95e**:



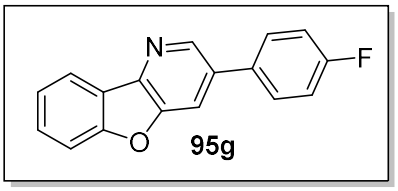
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95f**:

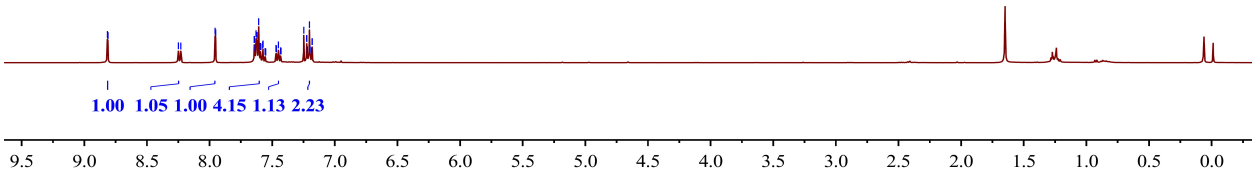


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95f**:

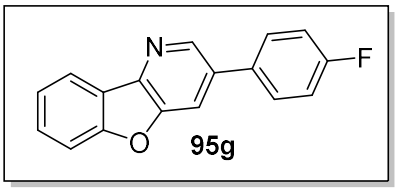


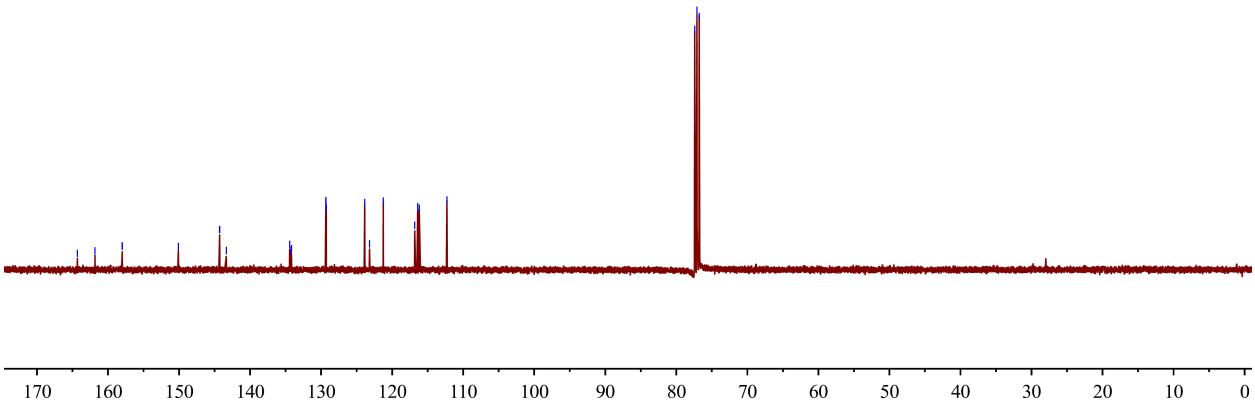
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95g**:



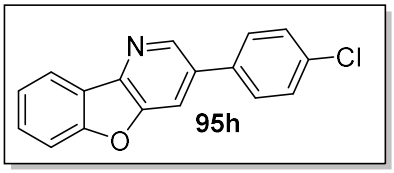


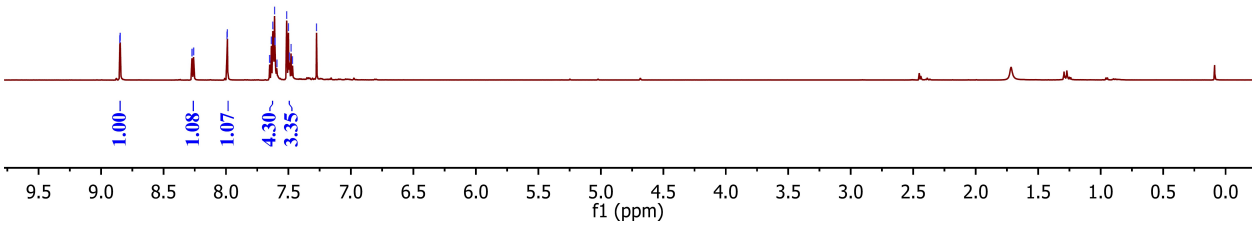
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95g**:



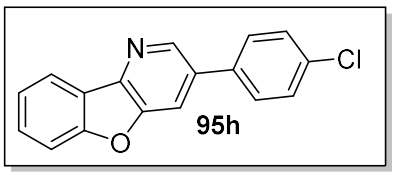


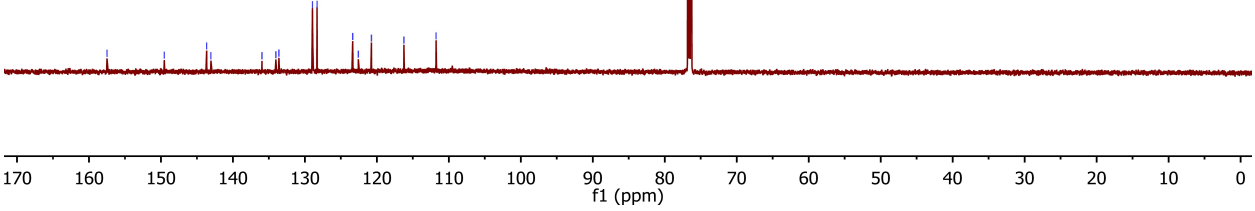
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95h**:



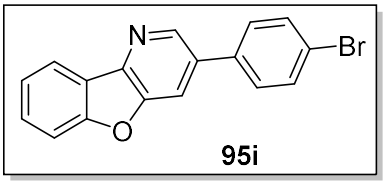


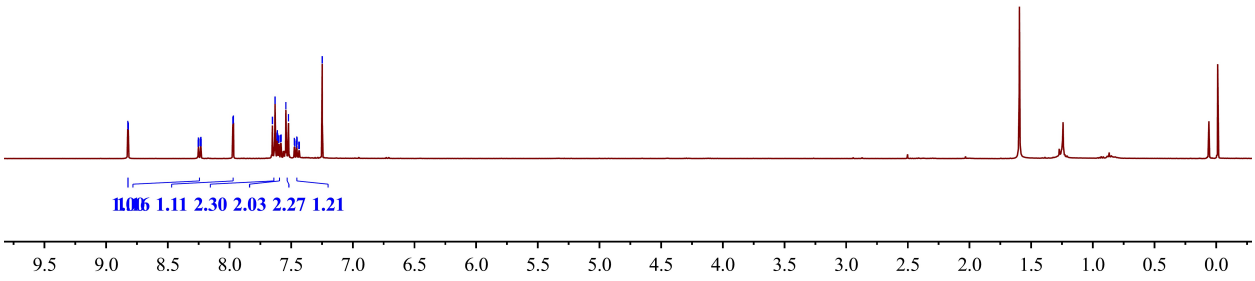
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95h**:



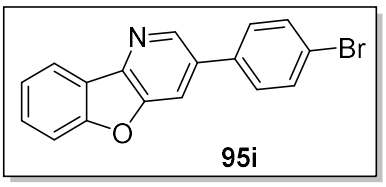


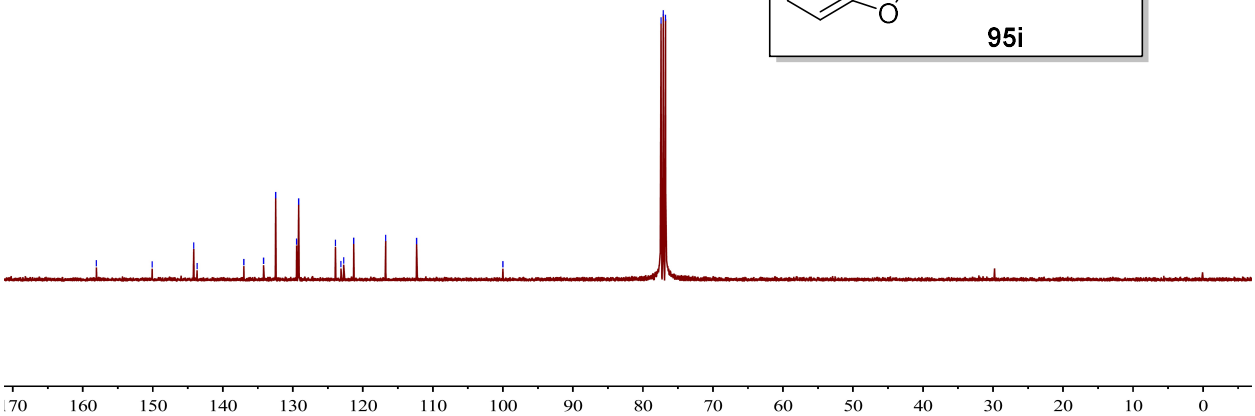
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95i**:



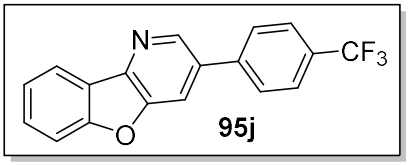


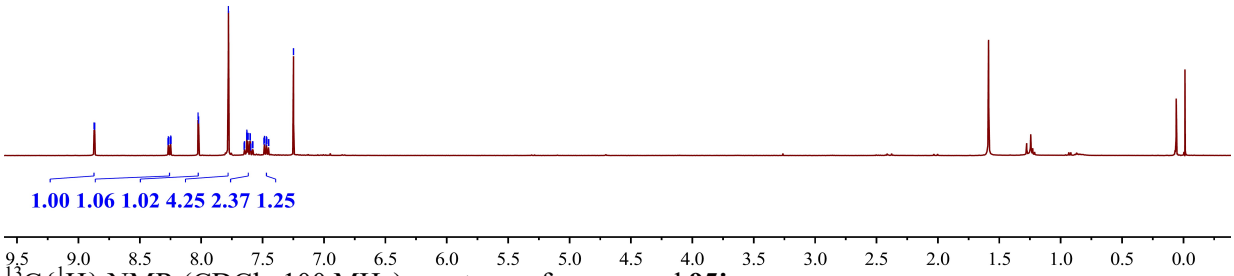
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95i**:



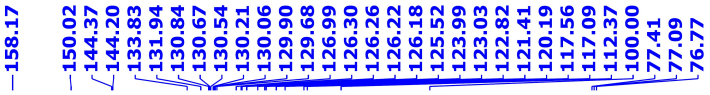


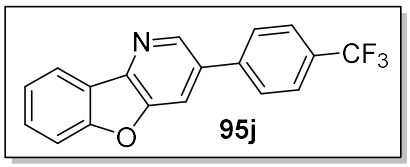
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95j**:

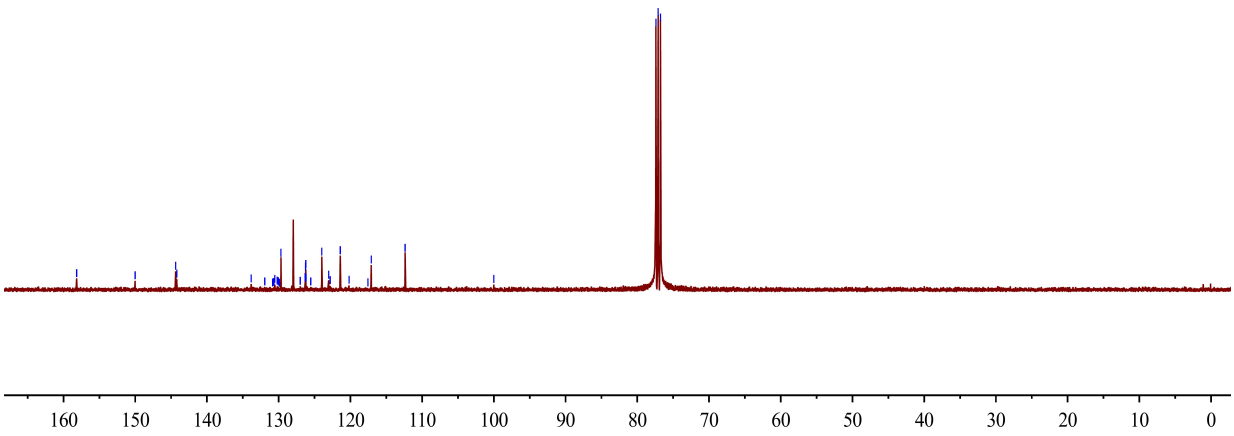




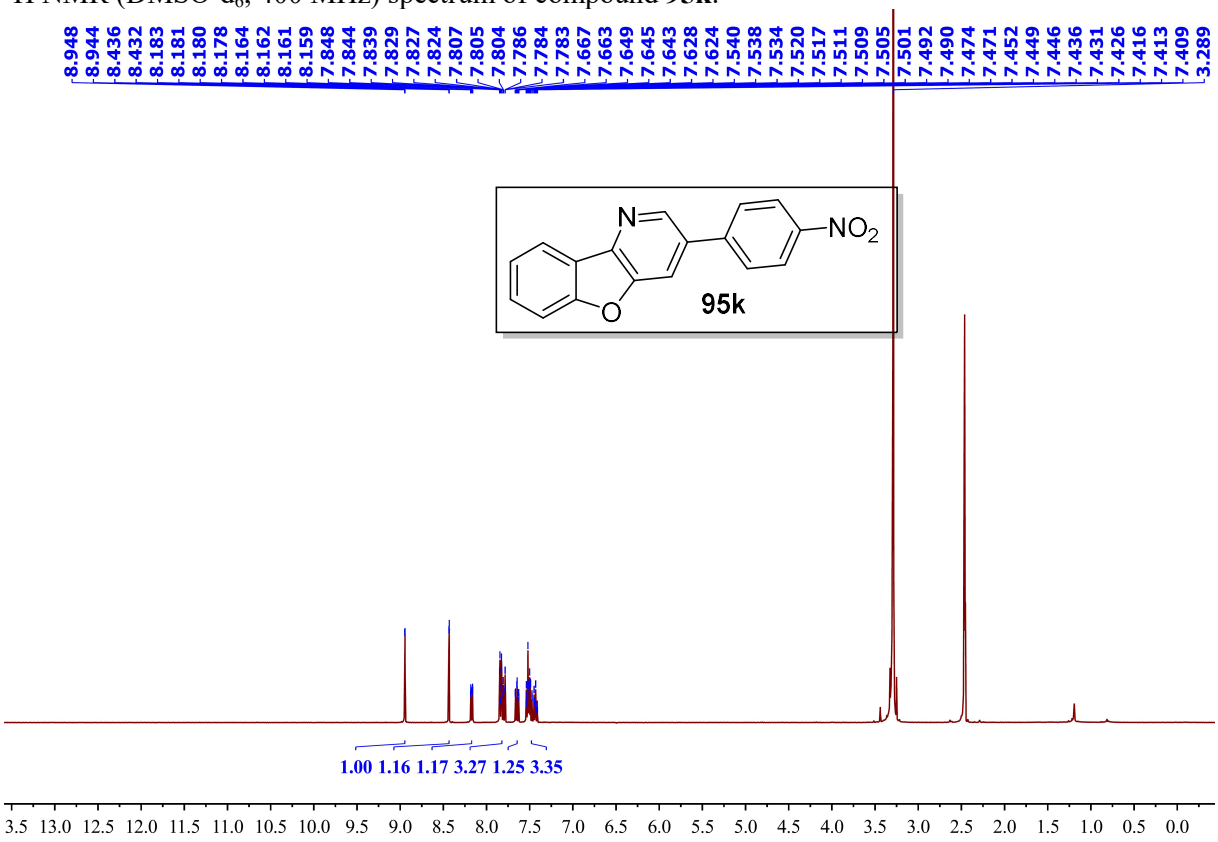
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95j**:



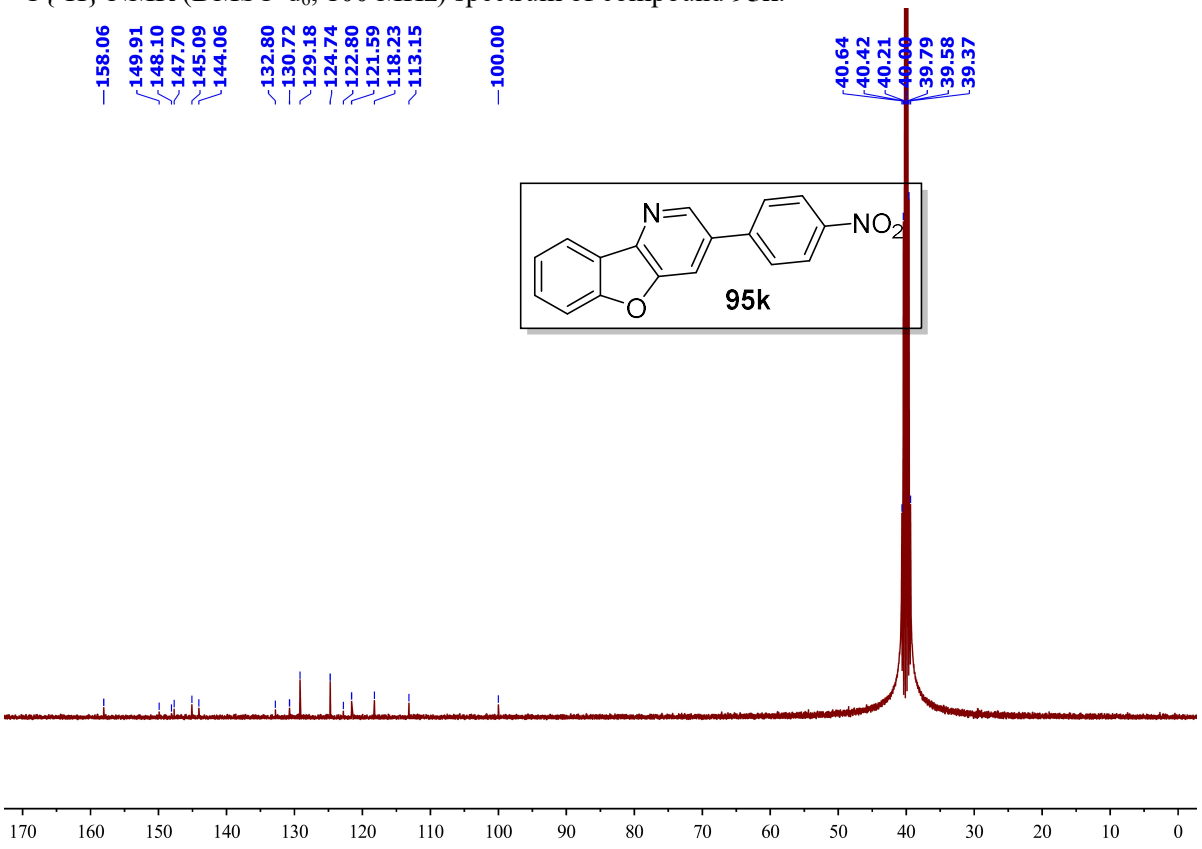




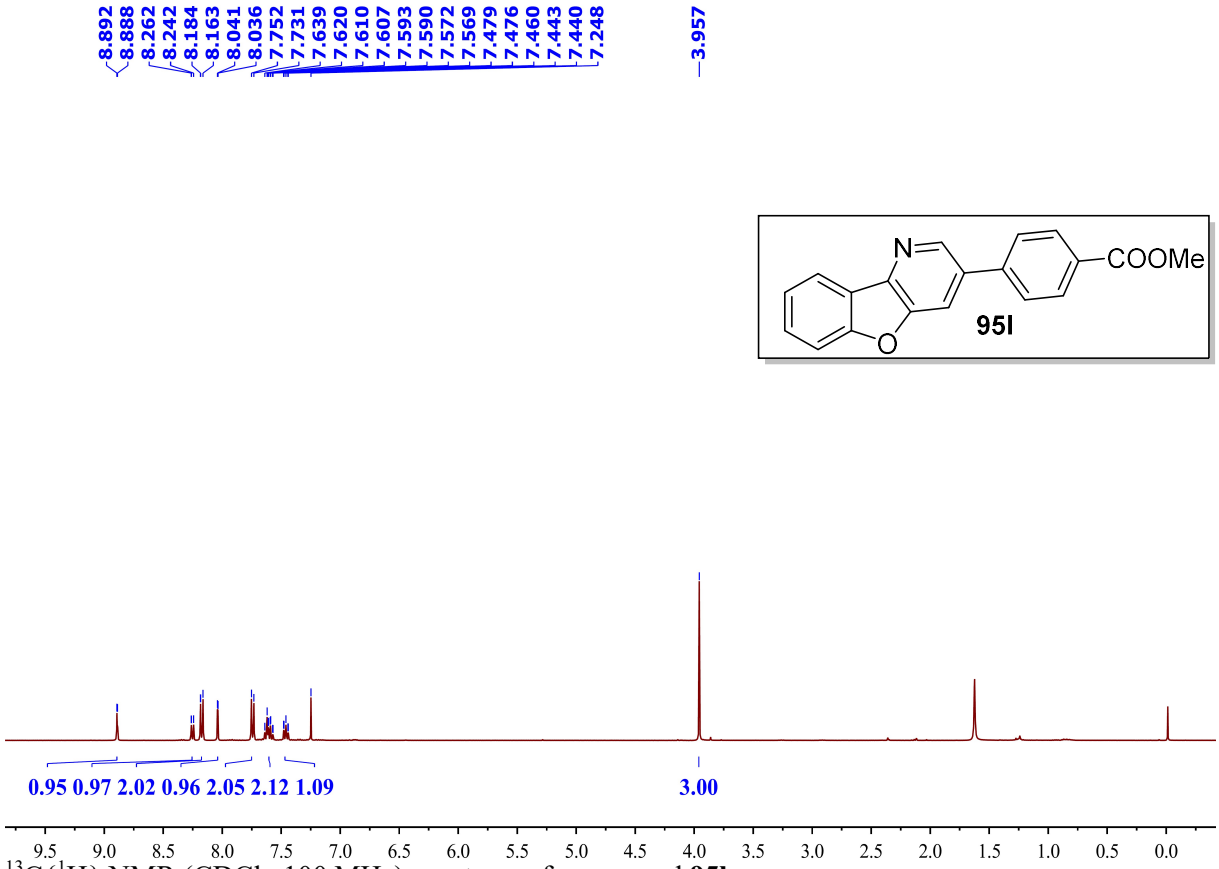
^{1}H NMR (DMSO-d$_6$, 400 MHz) spectrum of compound **95k**:



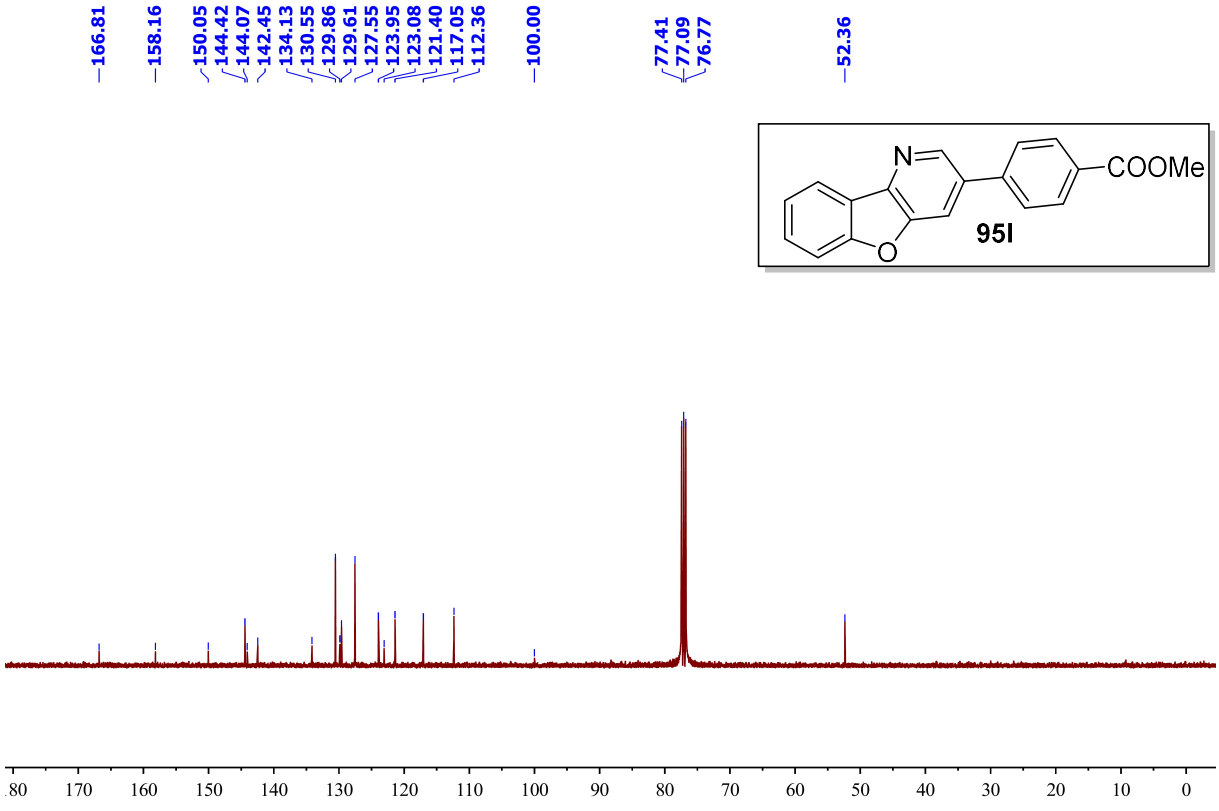
^{13}C{^{1}H} NMR (DMSO-d$_6$, 100 MHz) spectrum of compound **95k**:



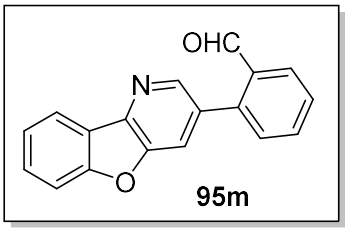
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95l**:

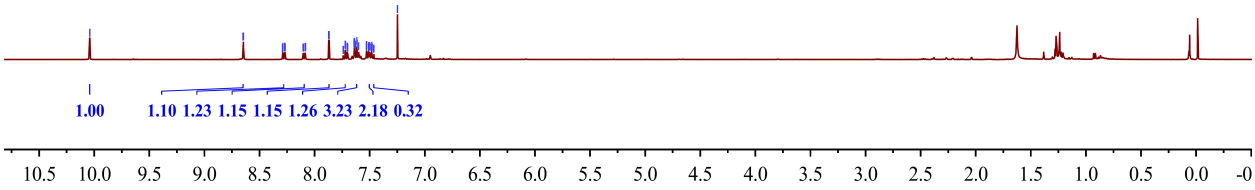


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95l**:

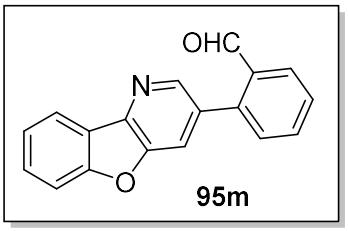


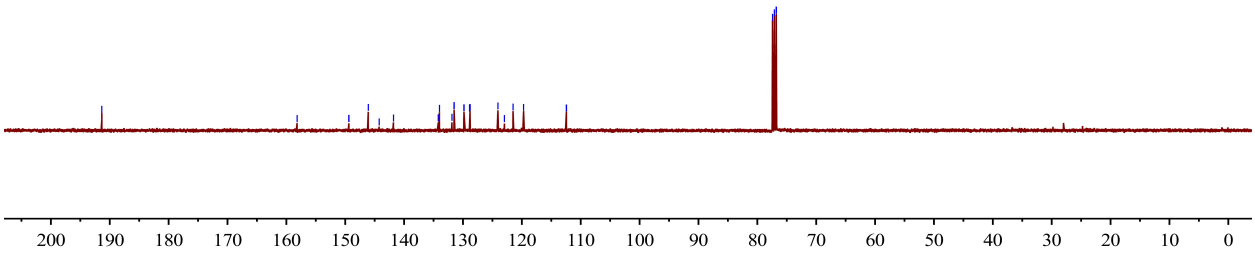
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95m**:





^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95m**:





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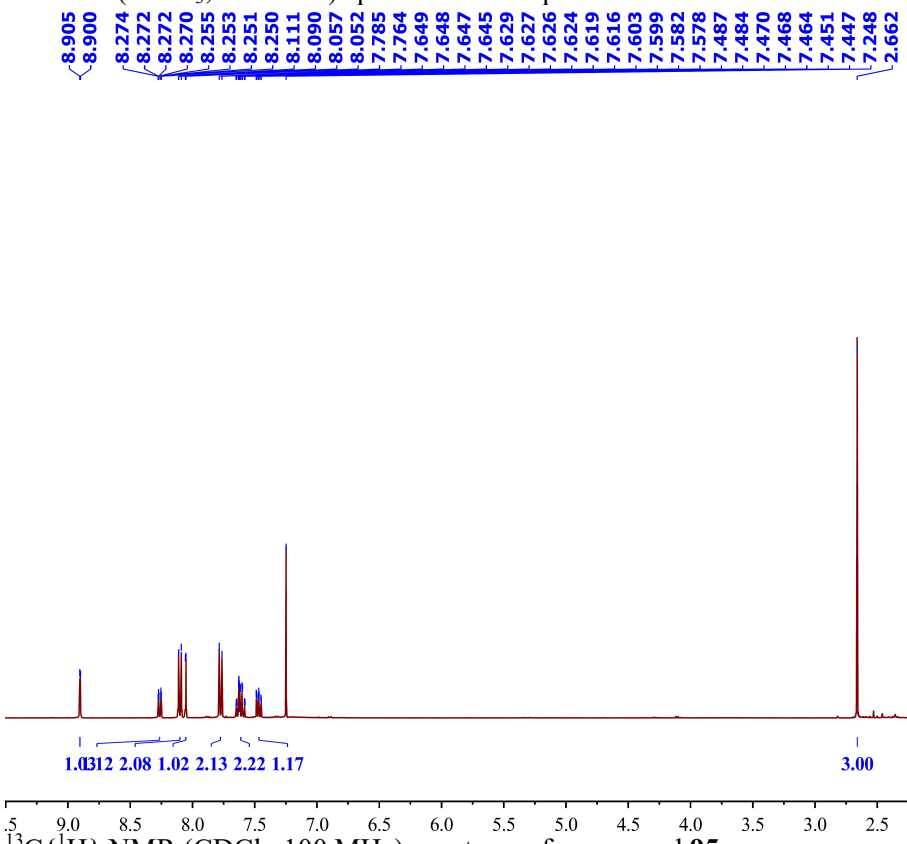
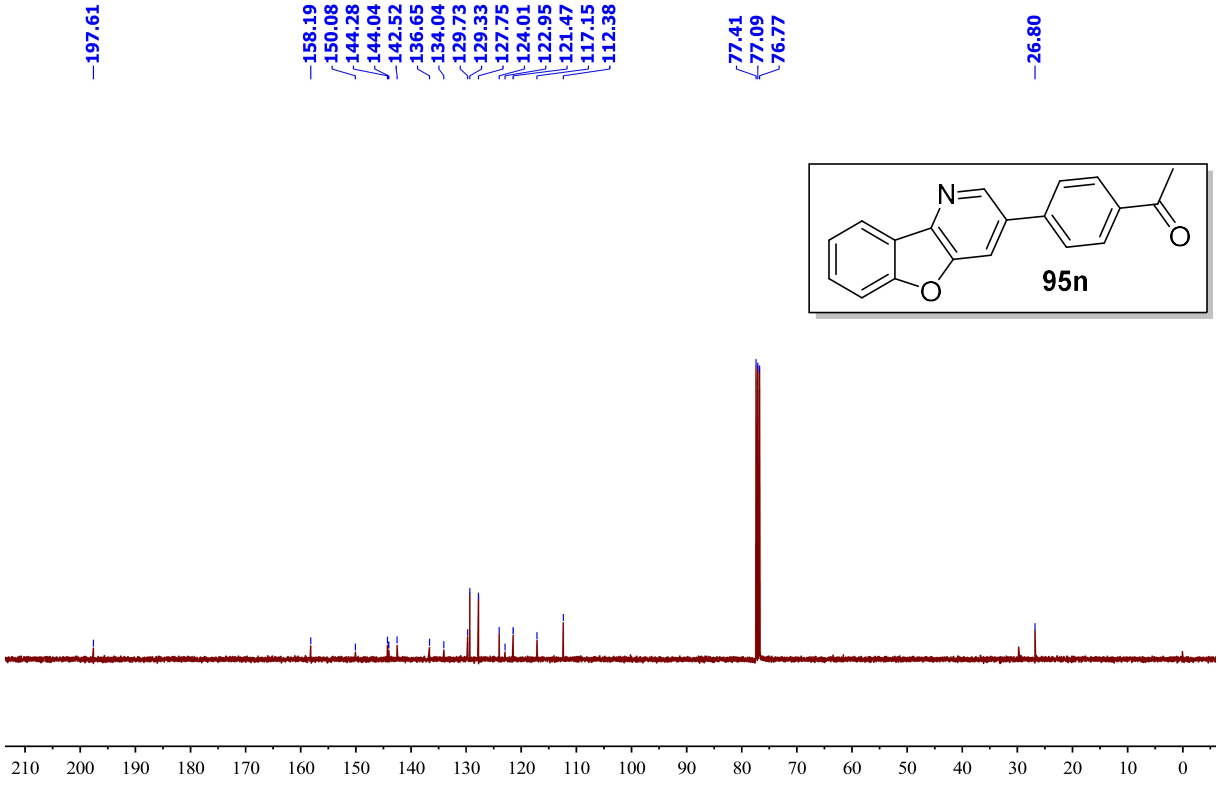
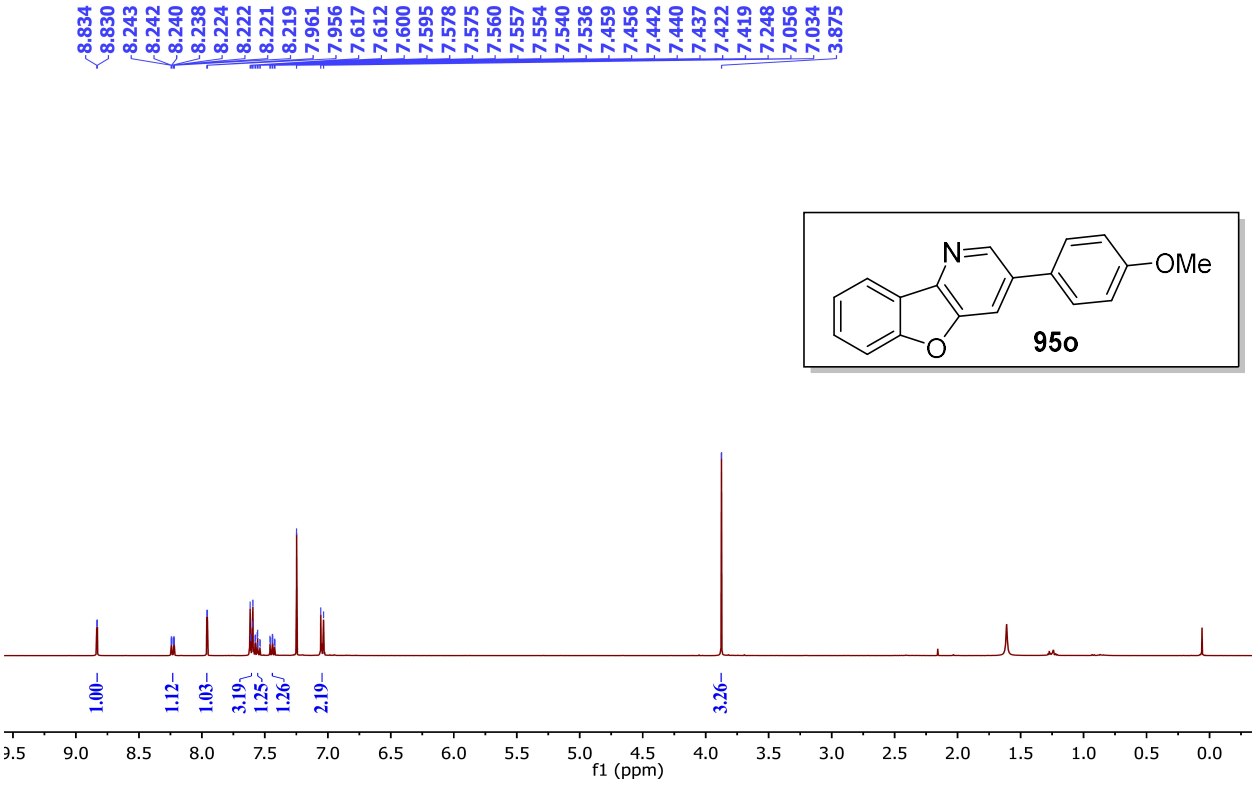


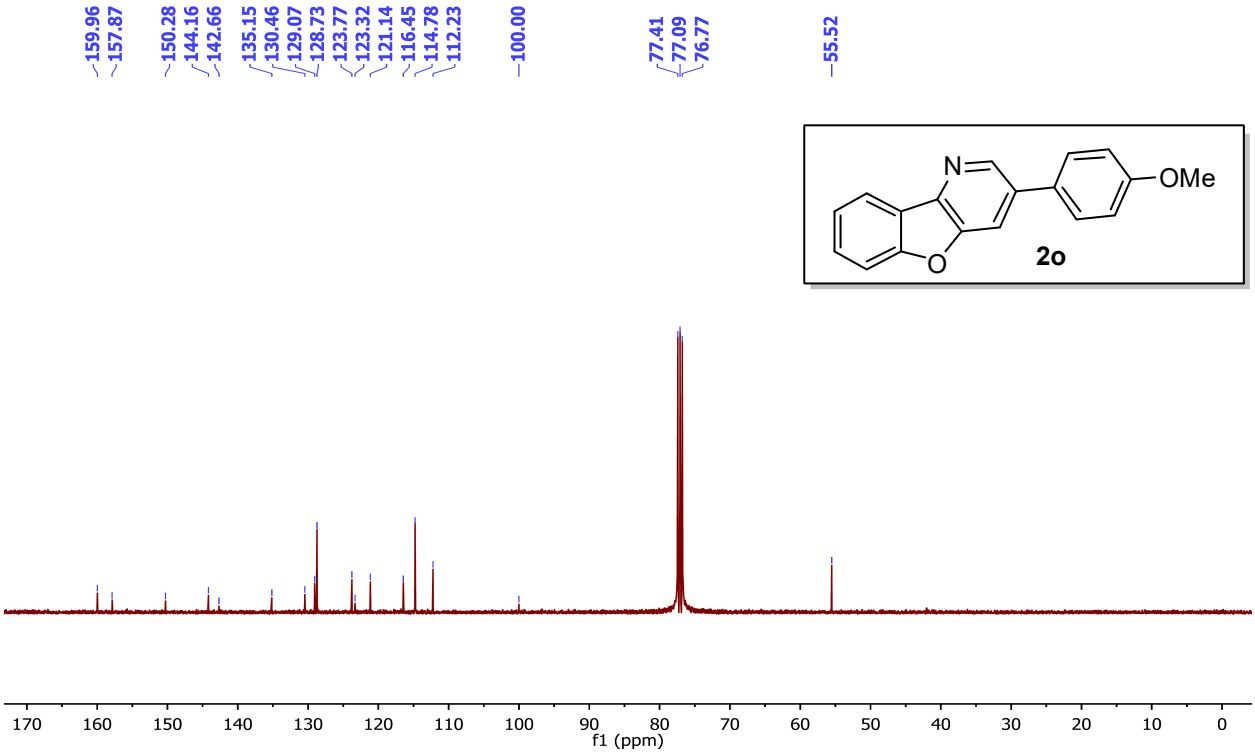
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95n**:



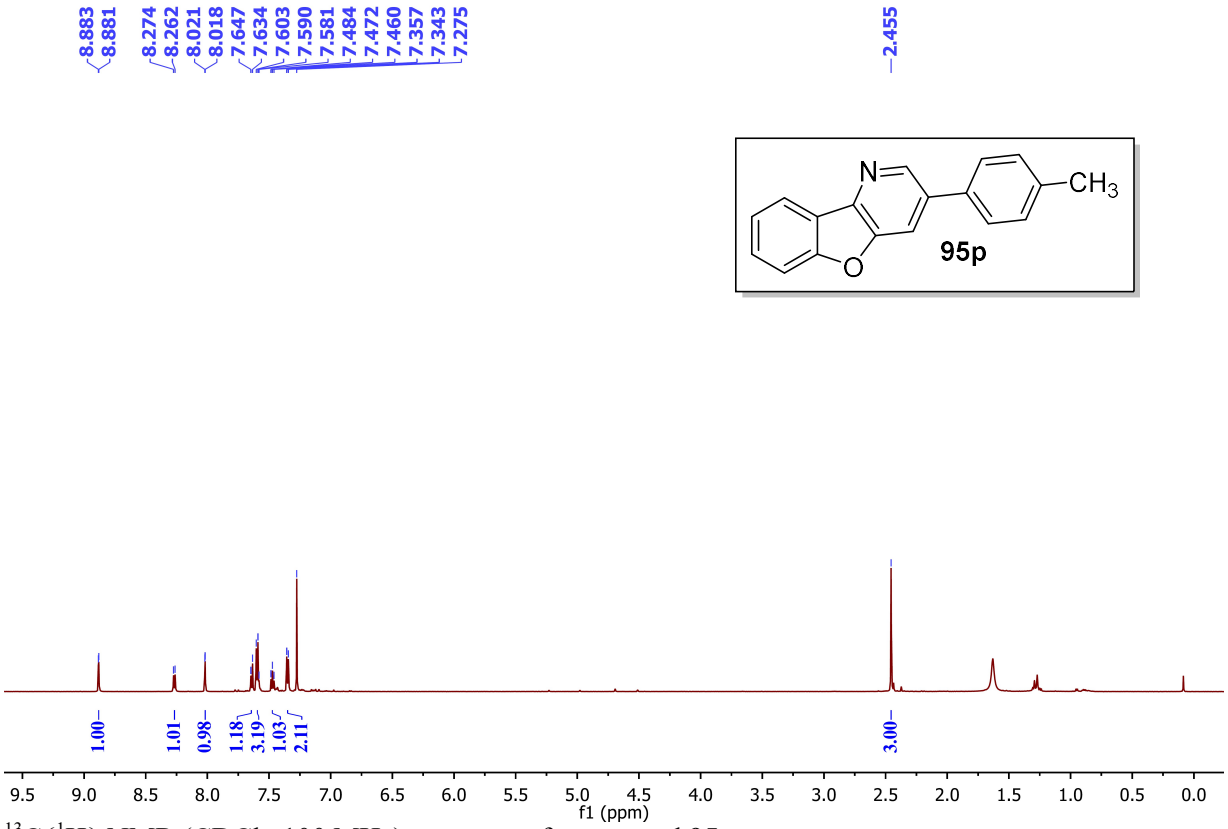
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95o**:



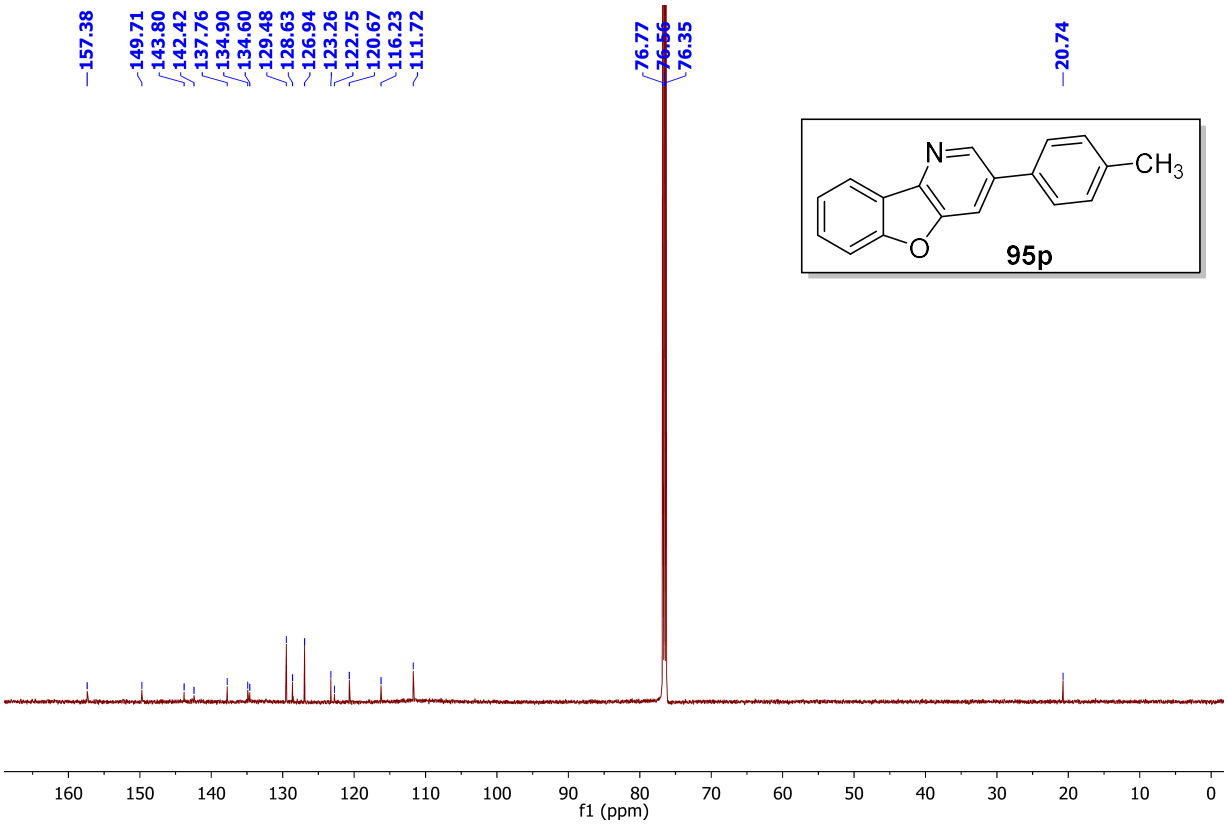
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95o**:



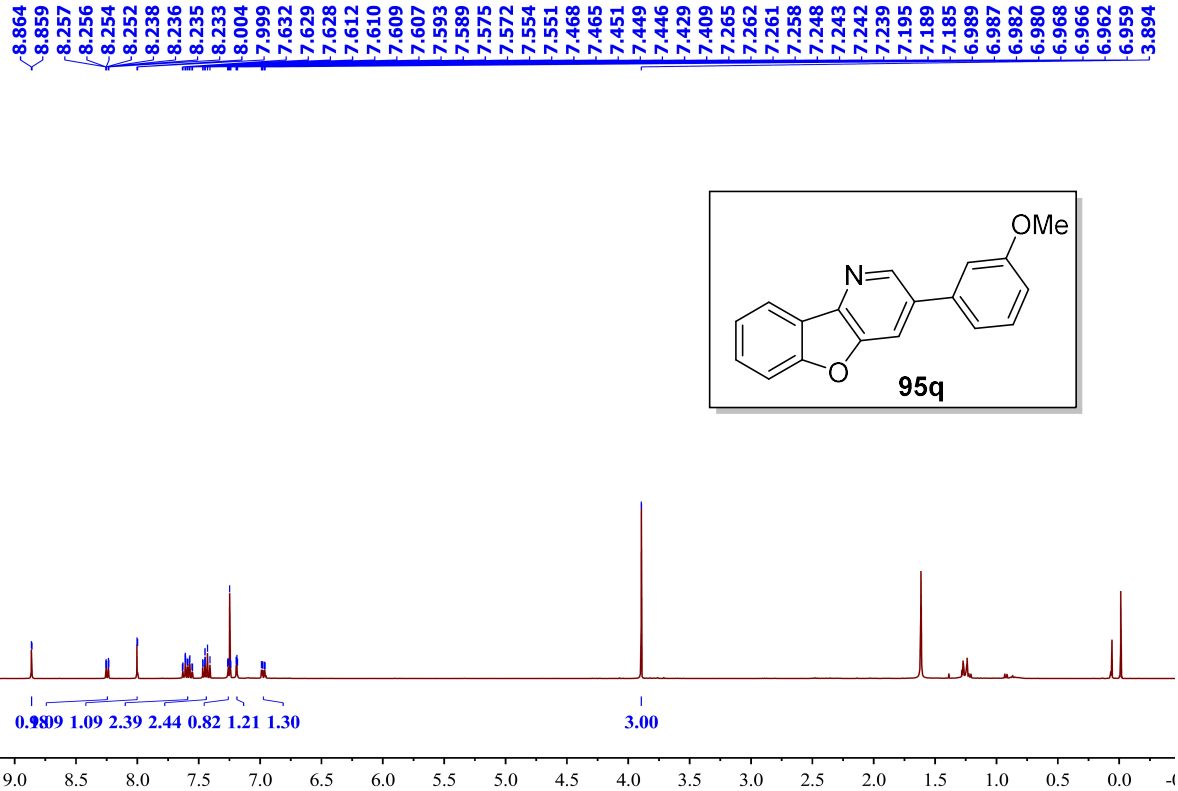
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95p**:



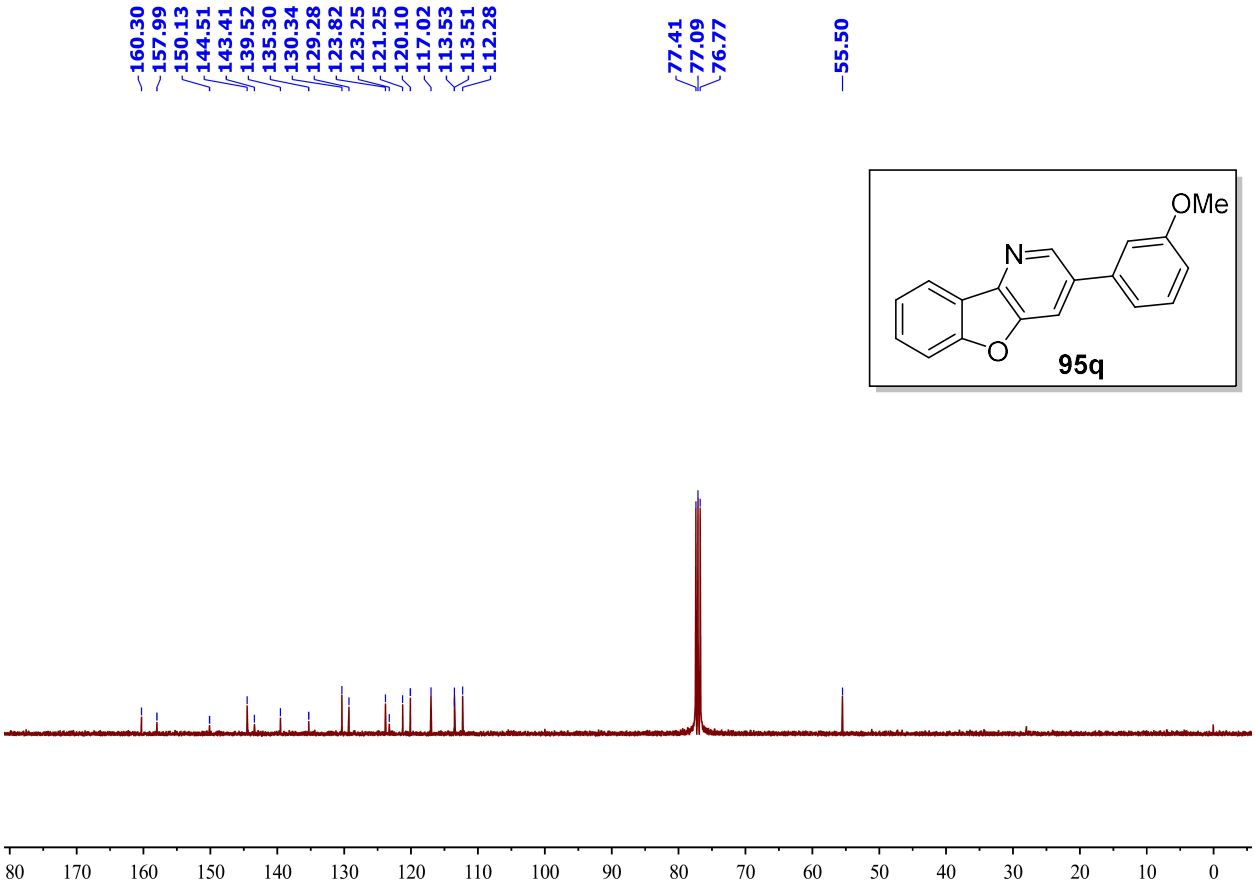
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95p**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **95q**:

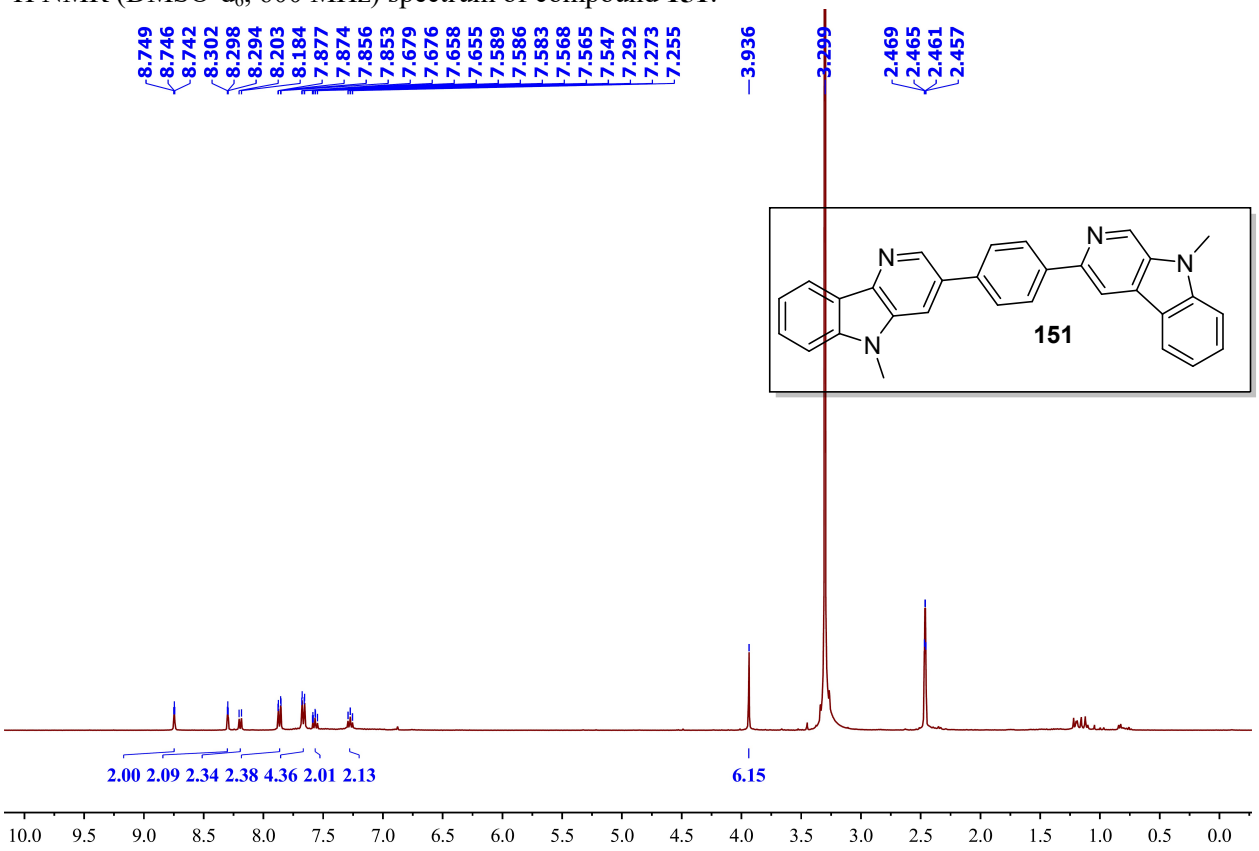


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **95q**:

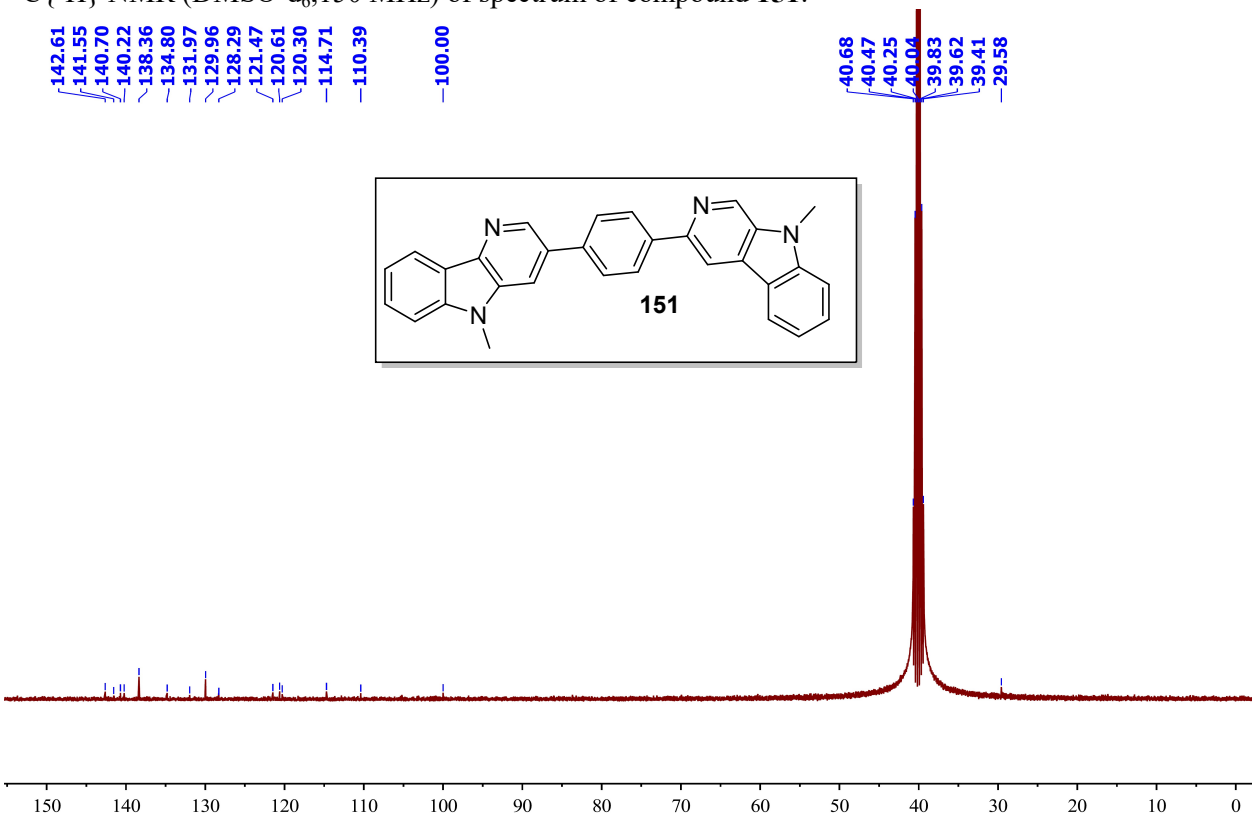


2.2.10.5. NMR spectra of compounds 151, 152a-152c:

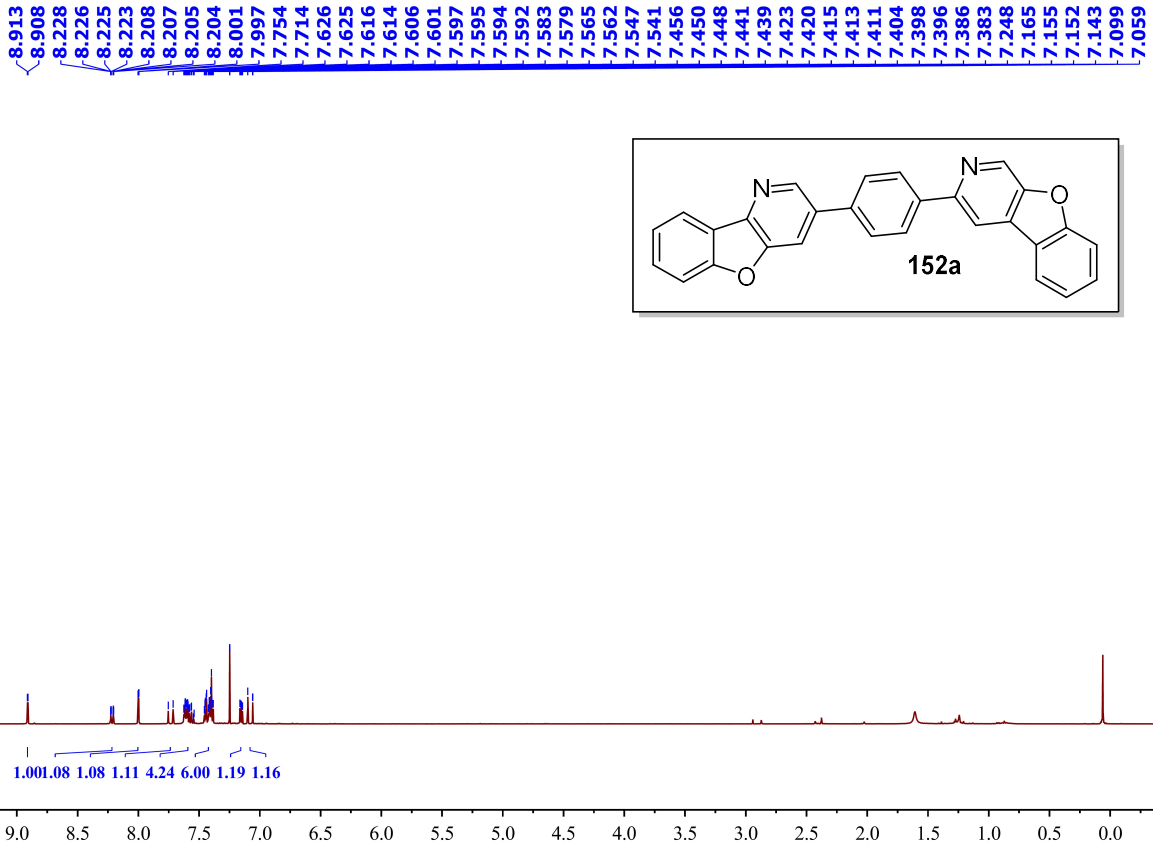
^{1}H NMR (DMSO-d_6, 600 MHz) spectrum of compound **151**:



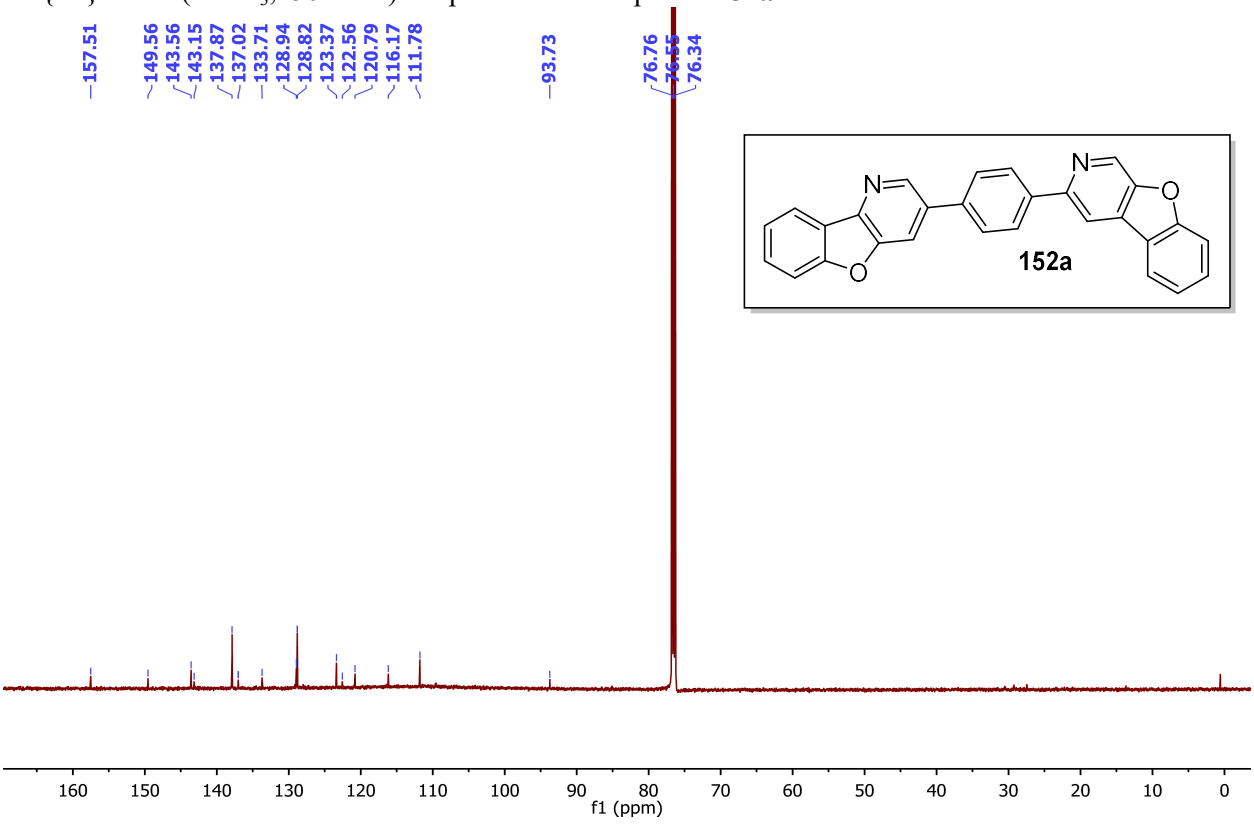
^{13}C{^{1}H} NMR (DMSO-d_6,150 MHz) of spectrum of compound **151**:



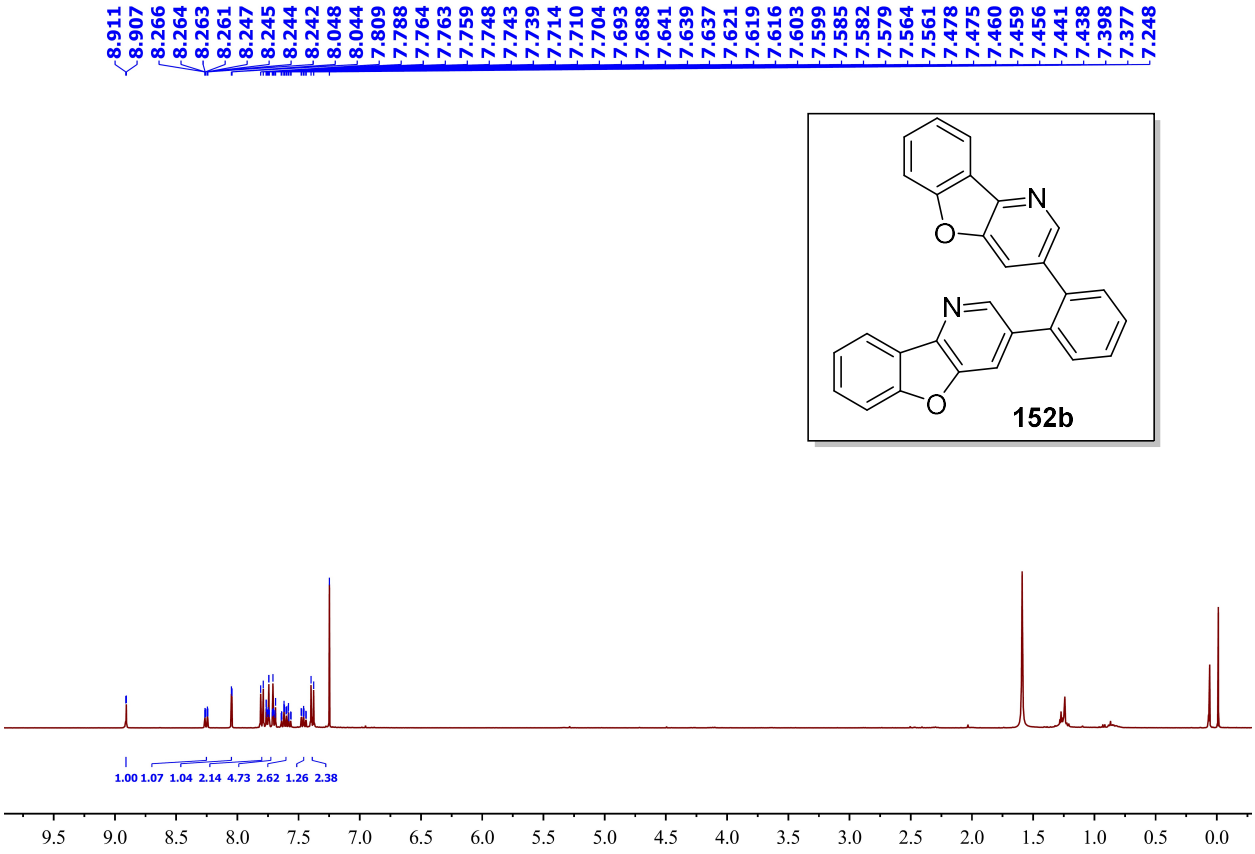
^{1}H NMR ($CDCl_3$, 400 MHz) of spectrum of compound **152a**:



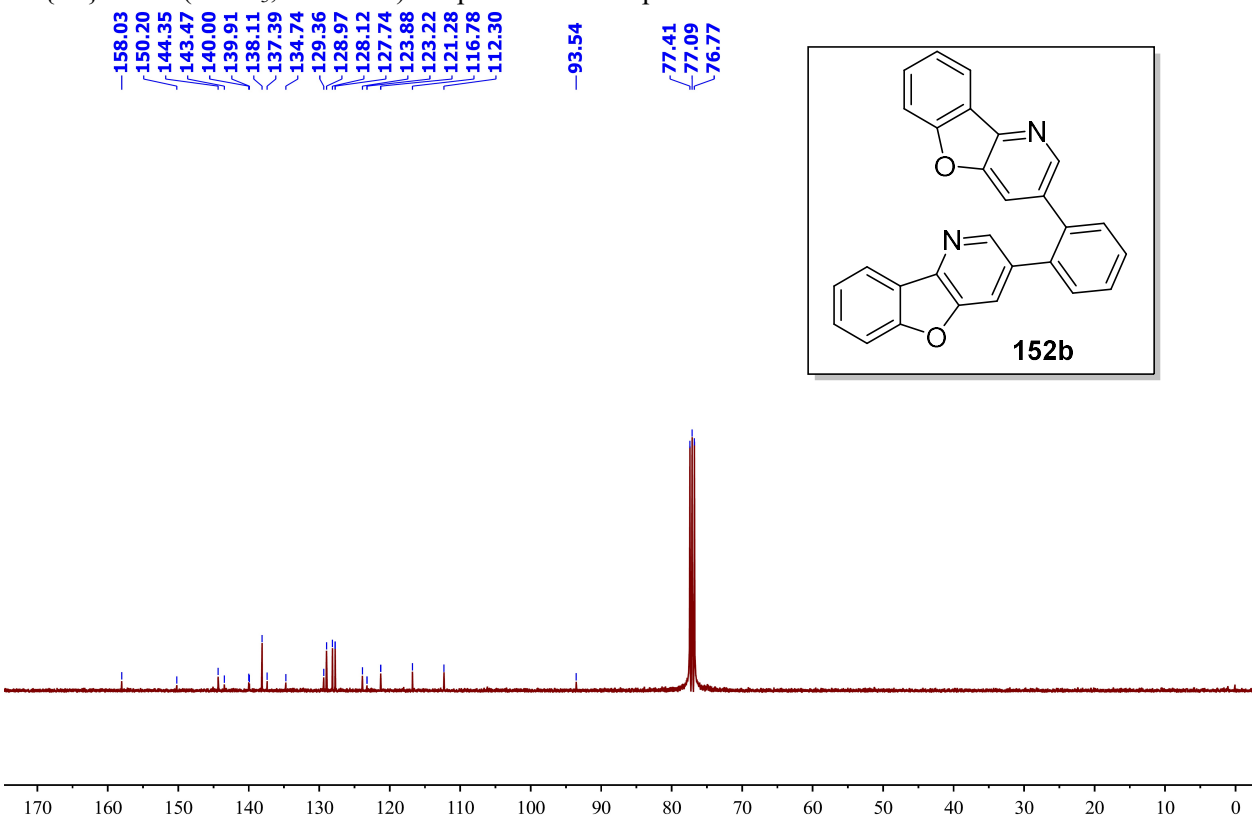
^{13}C{^{1}H} NMR ($CDCl_3$,150 MHz) of spectrum of compound **152a**:



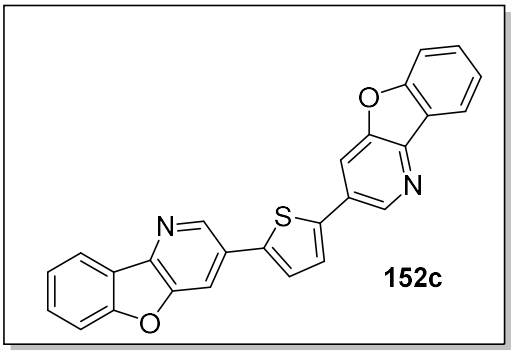
^{1}H NMR ($CDCl_3$, 400 MHz) of spectrum of compound **152b**:

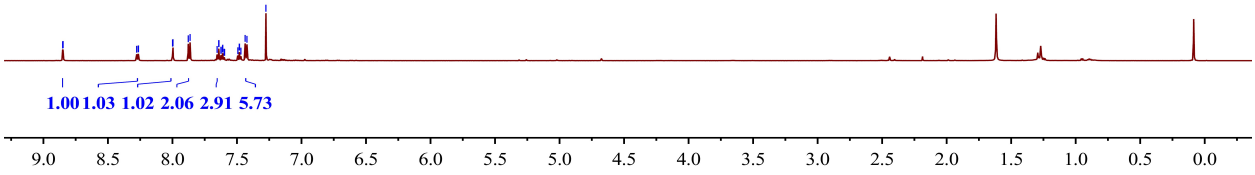


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) of spectrum of compound **152b**:

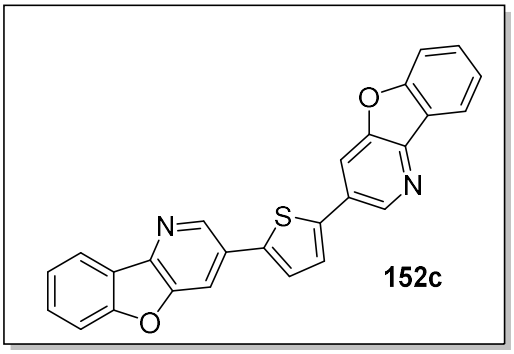


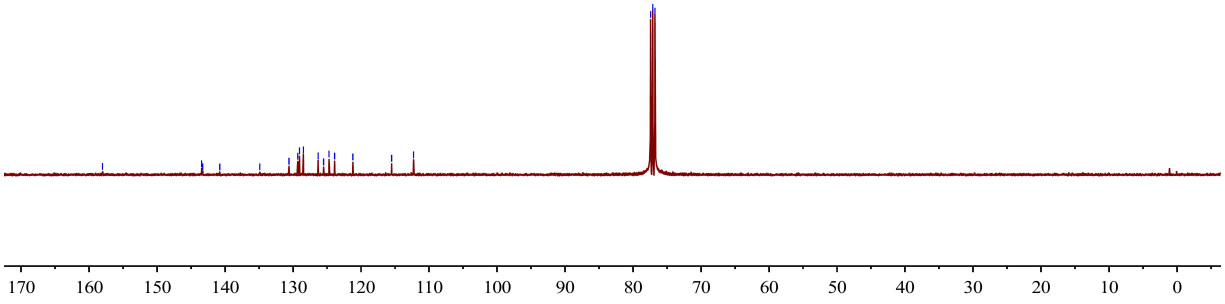
^{1}H NMR (600 MHz) of spectrum of compound **152c**:





^{13}C{^{1}H} NMR (100 MHz) of spectrum of compound **152c**:





CHAPTER 3

Palladium-catalyzed *5-exo-dig* cyclization/ DDQ-mediated dehydrogenative Diels–Alder reaction for the synthesis of functionalized benzofuro[3,2-*b*]pyrrole / benzofuro[3,2-*b*]indoles derivatives

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Part I- A Short Review

3.1.1 ntroduction:

3.1.1.1 Importance of benzofuro[3,2-*b*]pyrrole/ benzofuro[3,2-*b*]indole

Pyrroles are prevalent as fundamental building blocks in many biologically active molecules, natural products and drugs. They have shown various medicinal activity like antitumour,[1] anti-inflammatory,[2] antibacterial,[3]antimicrobial,[4] analgesic,[5] antiglaucoma,[6] psychiatric disorder,[7] antifungal[8] etc. For example, *Tensidol A*, and *Tensidol B* have shown miconazole activity as well as antimicrobial activity.[9] Besides, pyrrole cores are present in many bio-active naturally occurring compounds, such as porphyrins, chlorophylls, heme, and many alkaloids; notably, porphyrins and chlorophylls are essential pigments in photosynthesis, while heme is an important component of hemoglobin, myoglobin, and other hemeproteins that transport oxygen in the bloodstream[10]. On the other, indole and its derivatives have a wide range of applications in medicinal chemistry, and are promising candidates for the development of drugs to treat a variety of diseases. They have shown significant biological activities, such as anticancer, anti-inflammatory, anti-microbial, analgesic, anti-hypertensive, and anti-atherogenic effects[11]. Indole derivatives like Indomethacin, Vinblastine, and Tamoxifen have been shown to have potent anticancer activity against a variety of cancer types, including breast, lung, and colon cancer. They also have potential applications in the treatment of neurological disorders such as schizophrenia, depression, and anxiety. Examples of neurological agents that contain indole scaffolds include serotonin reuptake inhibitors like fluoxetine and sertraline.

In recent times, pyrrole or indole fused heterocycles have drawn considerable interests due to their immense importance ranging from medicinal chemistry to material science. In particular, benzofuran fused with pyrrole and indole ring resulted in the generation of benzofuro[3,2-*b*]pyrroles**1** (Fig. 1) and benzofuro[3,2-*b*]indoles (BFIs) **2** (Fig.1), respectively. Benzofuro[3,2-*b*]pyrroles play a key role by scavenging reactive oxygen species (ROS) and reducing oxidative stress.They have shown to possess antioxidant properties, which can protect cells from oxidative damage. Furthermore, they exhibit antimicrobial activity against bacteria and fungi by inhibiting bacterial growth and disrupting the cell wall of fungi. On the other hand, benzofuro[3,2-*b*]indoles (BFIs) **2** are considered as important scaffolds because of their uses in the treatment of sexual

hormone disorders[12], degenerative brain diseases[12] and different types of cancer due to their extensive anti-tumour activity.[13]

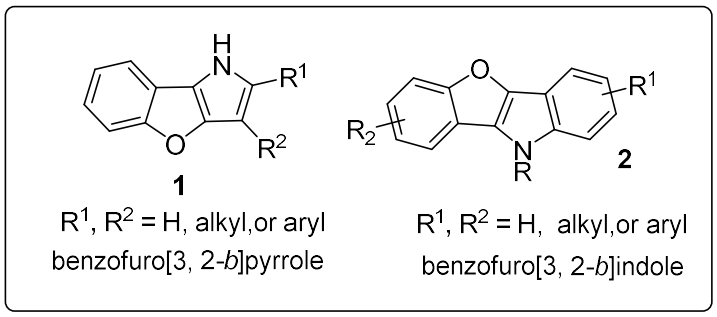


Figure 1: Structures of benzofuro[3,2-*b*]pyrrole**1** and benzofuro[3,2-*b*]indoles **2**

3.1.1.1.1 Importance of benzofuro[3,2-*b*]pyrroles in medicinal chemistry:

Benzofuro[3,2-*b*]pyrrole is a fused-ring heterocyclic compound that consists of a pyrrole ring fused with a benzofuran ring moiety. They have drawn considerable interests to the chemists and biologists because they exhibit a range of biological activities, including anti-cancer, anti-microbial, and anti-viral properties. These compounds have been shown to inhibit enzymes, such as topoisomerases, and to interact with DNA, making them potential candidates for the development of new drugs.[14] From mechanistic viewpoint, benzofuro[3,2-*b*]pyrrole[15] derivatives have the ability to inhibit DNA topoisomerases, which are enzymes involved in DNA replication and transcription. This inhibition can lead to DNA damage and cell death, making these compounds effective anticancer agents. In addition, due to extended conjugation and restricted bond rotation of 4,4-Difluoro-4-bora-diaza-*s*-indacene (BODIPY)[15]**3** (Fig. 2) showed DNA sequencing and other biotechnological applications. Benzofuro[3,2-*b*]pyrroles embodied with 1,2,4-triazine **4** (Fig. 2) has shown activity by acting as an anti-diabetic agent through induction of AMP-activated protein kinase (AMPK), which is involved in glucose and lipid metabolism due to their high extinction coefficient.

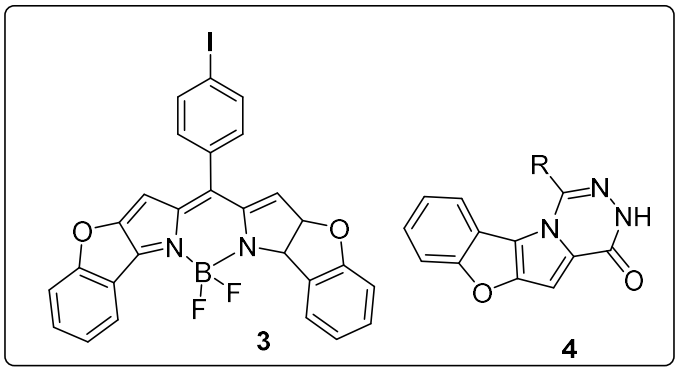


Figure 2: Some biologically active compounds **3-4** having benzofuro[3,2-*b*]pyrrole moiety

3.1.1.1.2 Importance of benzofuro[3,2-*b*]pyrroles in material science:

Benzofuro[3,2-*b*]pyrrole derivatives have potential applications in material science due to their interesting electronic and structural properties. These compounds have been investigated for use in a range of materials, including organic field-effect transistors (OFETs), organic light-emitting diodes (OLEDs), and dye-sensitized solar cells (DSSCs)[16]. In OFETs, benzofuro[3,2-*b*]pyrroles have shown promising results as active materials due to their high charge-carrier mobilities and good stability; benzofuro[3,2-*b*]pyrroles have shown promising results in organic field-effect transistors (OFETs). For example, a recent study[16] reported the synthesis of a benzofuro[3,2-*b*]pyrrole derivative and its use as an active material in a bottom-gate/top-contact OFET, which exhibited a high hole mobility of 0.23 $cm^2\ V^{-1}\ s^{-1}$. In OLEDs, benzofuro[3,2-*b*]pyrrole derivatives have been investigated as emitter materials due to their high fluorescent quantum yields and good thermal stability. In DSSCs,[17] benzofuro[3,2-*b*]pyrrole derivatives have been investigated as sensitizers due to their good light-harvesting properties and high molar extinction coefficients. Introduction of CF_3 moiety in the linearly annulated BF-BDP (**5**, Fig. 3) and NF-BDP (**6,** Fig. 3) is believed to facilitate the sublimation behavior which play crucial role in vacuum-deposited orgnic electronics.[17] Due to extended conjugations, compound **5** and compound **6** have shown excellent photo-stability and thermal-stability with negligible photo-bleaching and high decomposition temperature.

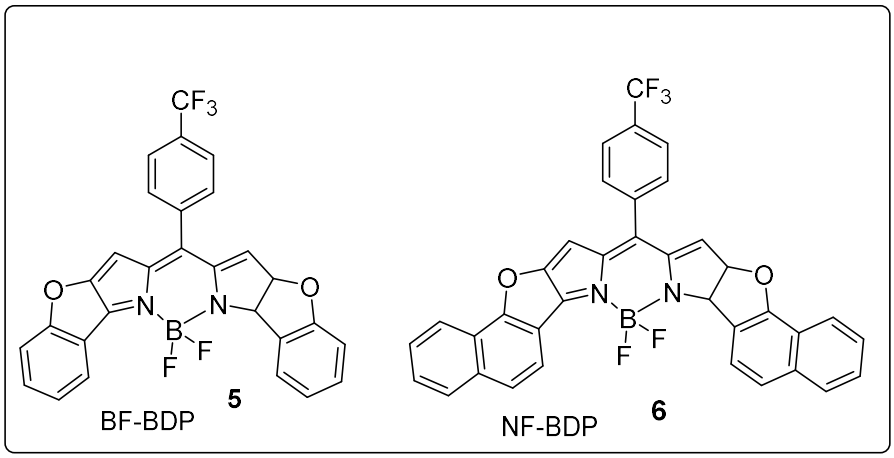


Figure 3: Structures of BF-BDP **5** and NF-BDP **6**

3.1.1.2 Importance of benzofuro[3,2-*b*]indoles (BFIs) in medicinal chemistry:

Benzofuro[3,2-*b*]indoles **1** are rarely found in natural products. However, benzofuro[3,2-*b*]indoles are the potential candidates for the treatment of urge urinary incontinence and are of considerable interest because of their bladder-selective smooth muscle relaxant properties. For example, compound **7** (Figure 4) has demonstrated its relaxant properties in both rat detrusor tissue and it was found to be a highly selective bladder relaxant[18] (IC_{50} = 15 mM) *in vitro* (IC_{50} ratio aorta/bladder = 8). Due to its novel structure and unique in vitro profile, a series of benzofuro-indoles **7** were evaluated for their smooth muscle relaxant properties. In isolated rat bladder cells, furanoindole**7**[18,19] was found to activate a hyperpolarizing current, due to their imbalance nature of calcium-dependent potassium channel. Besides, compound **7** causes an iberiotoxin-sensitive increase in hyperpolarizing current consistent with activation of the BK_{Ca}channel. Benzofuroindole derivatives also stabilize the open conformation of the BK_{Ca}channel by binding to the residues clustered across the extracellular part of the subunit interface.[20] While 8-Cl derivatives (compound **8,** Fig. 4) have shown bladder selective smooth muscle relaxant properties in *in vitr*o cell lines. They are also useful for the treatment of irritable bowel syndrome, asthma, congestive heart failure and cerebral vascular diseases, among others.[19,22]

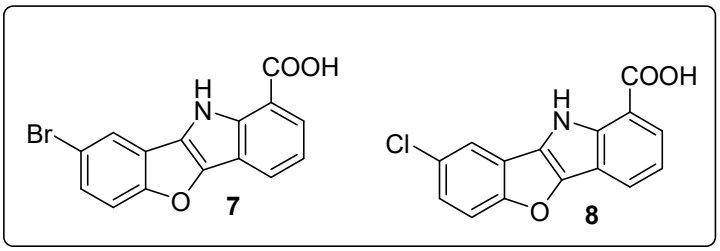


Figure 4: Biologically active benzofuro[3,2-*b*]indoles**7-8**

3.1.1.2.2Importance of Benzofuro[3,2-*b*]indoles (BFIs) in material science:

Apart from their biological activity, benzofuro[3,2-*b*]indoles (BFIs) are a class of organic compounds that have gained increasing attention in material chemistry due to their unique and tunable optoelectronic properties. Due to their rigid-fused coplanar structures (lack of conformational disorder), it endows a set of superior properties, like an intense luminescence and a high charge carrier mobility. It also has wide applications in other fields such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs) and organic photovoltaic cells.[21] Due to presence of heteroatoms and ladder type π conjugated system, they exhibit excellent electronic, photophysical, thermal, material and device properties, and also improving the stability of the materials. They are also used in next generation smart cards, solar cells, and flexible lightening devices and displays. They have shown physicochemical and electroluminescence properties due to presence of oxygen atom in the donor scaffold. The electronegativity of the heteroatom and the ionization potential of the donor unit played a crucial roles for the singlet–triplet energy splitting and thermally activated delayed fluorescence (TADF) mechanism of the compounds. For example, 2-(4b,9b-dihydro-10H-benzofuro[3,2-*b*]indol-10-yl)-5-(4,6-diphenyl-1,3,5-triazin-2-yl)benzonitrile, **BFICNTrz** (compound **9**[22], **Fig. 5**), shown singlet excited states that originated from the charge transfer (CT) states (^{1}CT), whereas the triplet excited states were tuned by the heteroatom in the donor unit. Besides, **BFICNTrz9** (**Fig. 5**) haveshown weaker ICT transition due to the poor electron donor strength of benzofuroindole. In addition, 10-(3-(4,6-di-phenyl-1,3,5-triazin-2-yl)phenyl)-10H-benzofuro[3,2-*b*] (**mBFITrz**) (compound **10**[23], **Fig. 5**) exhibits phosphorescent organic light-emitting diodes (PHOLEDS). The thermo-gravimetric analysis (TGA) and differential scanning calorimetry (DSC) measurements demonstrates that both the compounds **9** and **10** possessing higher decomposition temperature ≥400 ^{o}C, have exhibited maximum quantum efficiency and maximum current efficiency.

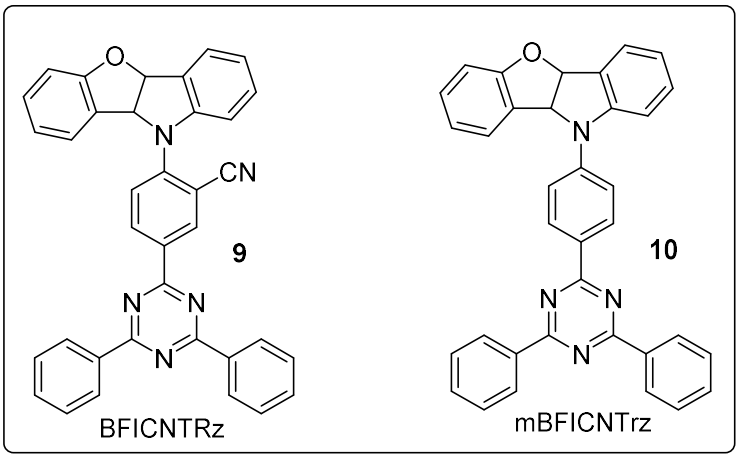


Figure 5: Few important bifunctionalbenzofuro[3,2-*b*]indoles**9**-**10**

3.1.2 Synthesis of benzofuro[3,2-b]pyrroles and benzofuro[3,2-*b*]indoles:

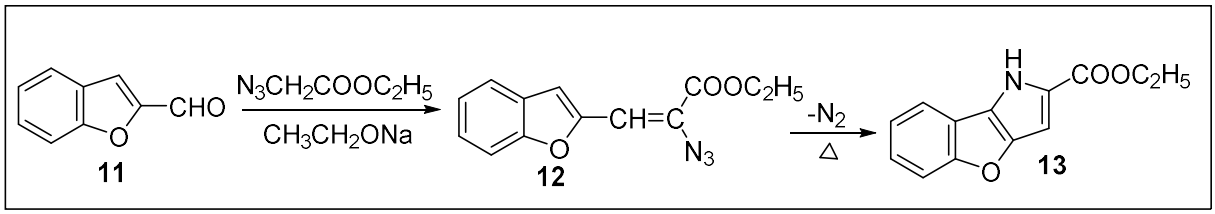
In view of the attractive biological properties of benzofuro[3,2-*b*]pyrrole**1** and benzofuro[3,2-*b*]indole **2,** and their wide applications in material sciences, considerable attention has been paid to their synthesis. Notably, benzofuro[3,2-*b*]pyrrole**1** are lessexplored as compared to benzofuro[3,2-*b*]indoles **2** despite their importance in drug discovery.

3.1.2.1 Synthesis of benzofuro[3,2-*b*]pyrroles 1:

Synthesis of benzofuro[3,2-*b*]pyrroles are usually carried out through conventional methods starting from benzofuran substrate. However, most of these methods report few specific examples of benzofuro[3,2-*b*]pyrroles (as shown below in **Schemes 1-3**) during the synthesis of other types of heterocycles. To the best of our knowledge, only one general method is reported using metal catalyst as described briefly below (under **Scheme 4**).

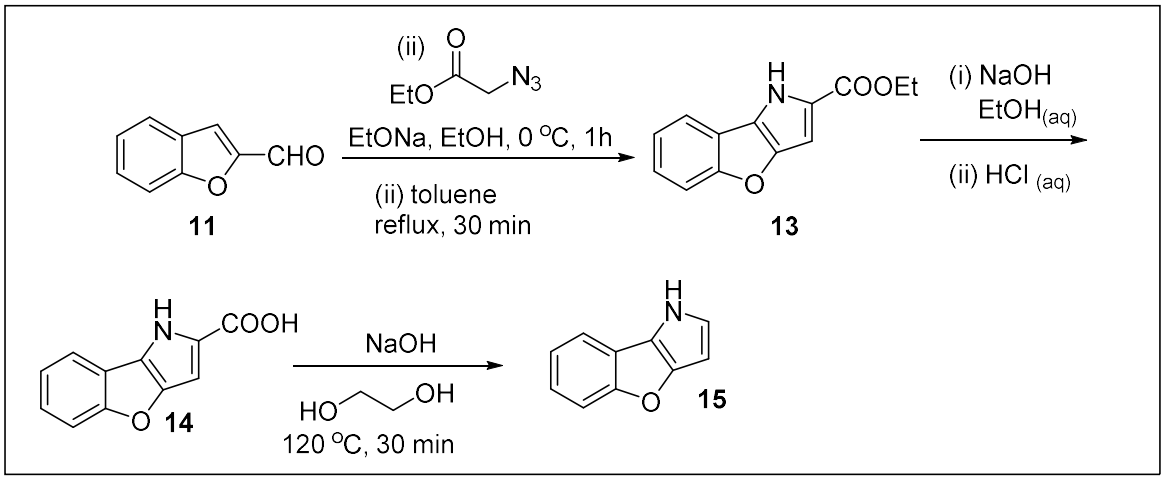
3.1.2.1.1: Conventional methods for the synthesis of benzofuro[3,2-*b*]pyrroles:

KRUTOŠÍKOVA *et al.* [24] synthesized a series of benzofuro[3,2-*b*]pyrroles **13** via photoinducednitrine-mediated N-H insertion reaction (**Scheme 1**). Benzofuran derivative **11** is converted into intermediate **12** which then undergoes thermally or photochemically induced nitrogen extrusion and subsequent addition onto double bond or C-H insertion to deliver the benzofuro[3,2-*b*]pyrrole **13**.



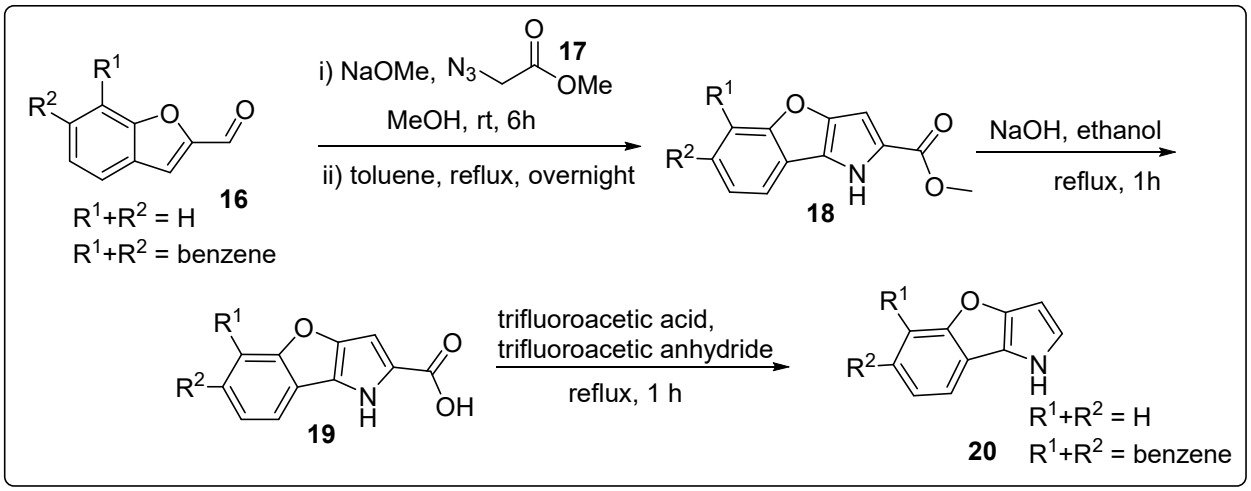
Scheme 1: Synthesis ofbenzofuro[3,2-*b*]pyrrole**13**

Chen and co-workers [15] investigated an efficient and general method for the synthesis of **15** through multi-step reactions (**Scheme 2**). Similar to the line of previous report (**Scheme 1**), carrying out the reaction under refluxing conditions (see, step 1) led to the formation of a new pyrrole ring fused with benzofuran moiety (i.e, intermediate **13**). Next, intermediate **13** undergoes hydrolysis (of the ester group) followed by decarboxylation through treatment of intermediate **14** with NaOH in ethelene glycol resulting in the formation of benzofuro[3,2-*b*]pyrrole**15** with 79% yield.



Scheme 2: Synthesis ofbenzofuro[3,2-*b*]pyrrole**15**

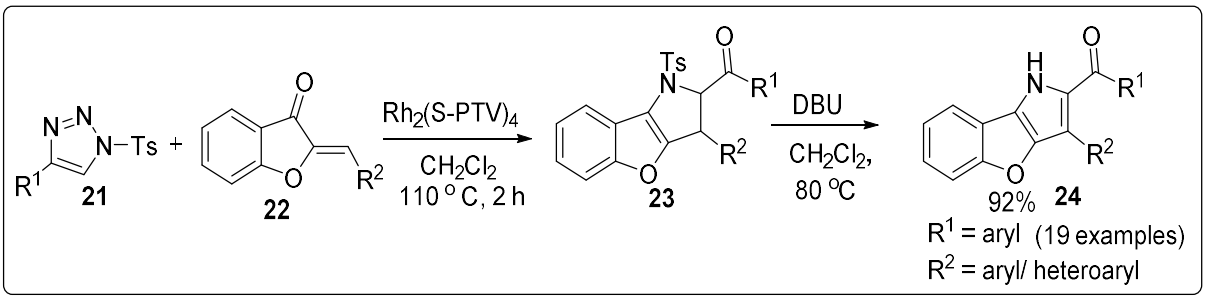
Li and co-workers [17] reported an efficient method for the synthesis of benzofuro[3,2-*b*]pyrrole in moderate to excellent yields (**Scheme 3**). The intermediate product **18** is generated by the reaction of **16** with excess amount of methyl azidoacetate **17** in presence of NaOMe via a *Knovenagel condensation* followed by *Hemetsbergerindolization*. The crude product **18** obtained was then directly used to deliver product **19.** Finally**,** the desired product **20** was obtained after treatment of a mixed solution of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) under reflux with moderate yield (>50%).



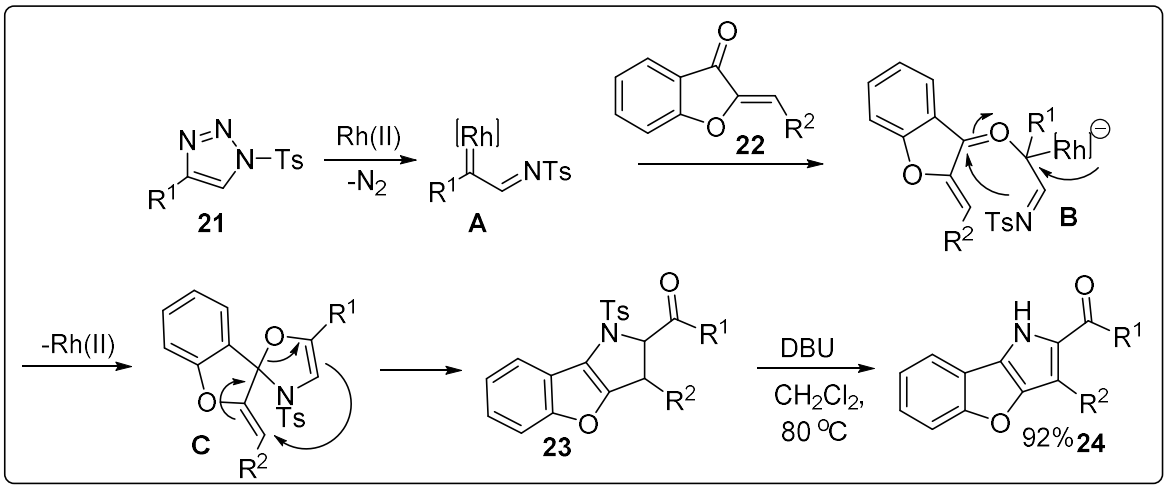
Scheme 3: Synthesis of substituted benzofuro[3,2-*b*]pyrrole**20**

3.1.2.1.2 Metal-catalyzed reactions for the general synthesis of benzofuro[3,2-*b*]pyrroles:

Ma *et al.*[25] reported a two-step synthesis of benzofuro[3,2-*b*]pyrroles**24** (**Scheme 4**). Toward this goal, intermediate **23** was generated by refluxing equimolecular amount of triazoles**21** and α, β unsaturated ketones or aurone**22** in DCM. Next, desired benzofuro[3,2-*b*]pyrroles**24** was obtained via a base-induced elimination/isomerization reaction.Mechanistically, α-imino rhodium carbine species **A** generated from triazole **21** undergoes nucleophilic attack by the oxygen atom of aurone moiety in presence of Rh catalyst resulting in the generation of oxoniumylide**B**. The intramolecular nucleophilic attack by the imino group of **B** on the carbonyl carbon of aurone system followed by 1,2-migration leading to oxazole compound **C.** The unstable compound **C** underwent C-O bond cleavage and followed by some structural rearrangement and generates substituted 2,3-dihydropyrrole intermediate **23**. After base treatment, intermediate **23** undergoes detosylation followed by aromatization with excellent yields (61-92%) of **24**.



Scheme 4: Rh-catalysed synthesis ofbenzofuro[3,2-*b*]pyrrole**24**



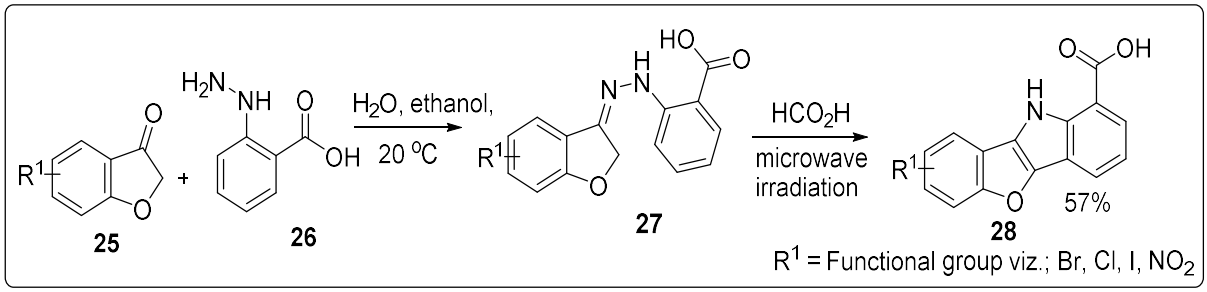
Scheme 5: Plausible mechanism for the formation of product **24**

3.1.2.2 Synthesis of benzofuro[3,2-*b*]indoles:

Synthesis of benzofuro[3,2-*b*]indoles are carried out via both conventional and metal-catalyzed reactions where formations of either pyrrole ring (**Schemes 6-13**) (employing benzofuran as starting substrates) or concurrent formations of both pyrrole and furan rings (**Schemes 14-15**) (using acetylenic or acyclic substrates) take place easily as depicted below.

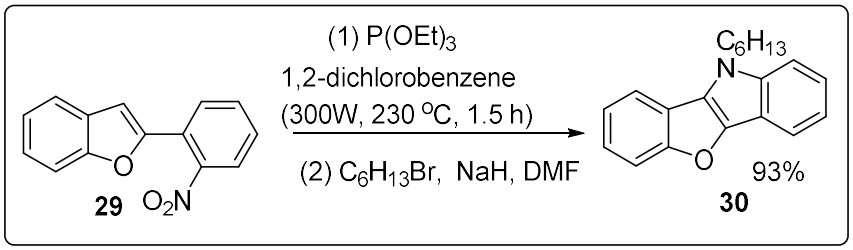
3.1.2.2.1: Conventional methods for the synthesis of benzofuro[3,2-*b*]indoles:

Butera *et al.*[18] synthesized a series of benzofuro[3,2-*b*]indole **28** (**Scheme 6**) using environmental benign solvent free microwave-induced technique involving condensation of benzofuranone**25** with 2-hydrazinobenzoic acid **26** in aqueous media affording phenyl hydrazines **27**. This phenyl hydrazine moiety undergoes *Fisher-indole* cyclization under microwave irradiation in the presence of 95% formic acid to construct the fused indole ring.



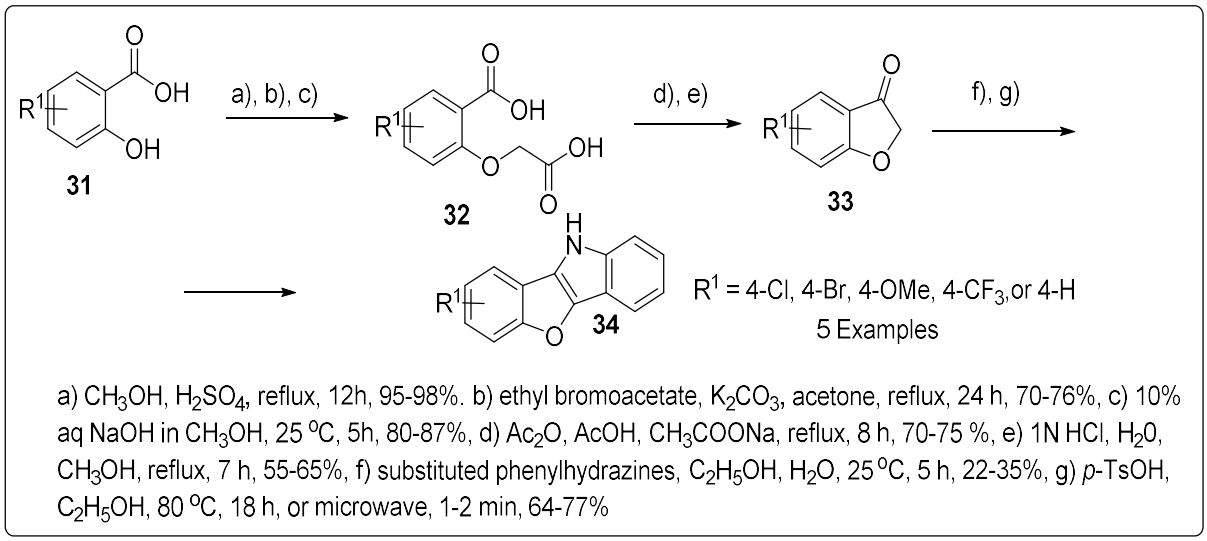
Scheme 6: Synthesis of substituted benzofuro[3,2-*b*]indole**28**

Srour and co workers[26] investigated an efficient and general method for the synthesis of*N*-alkylatedbenzofuro[3,2-*b*]indole **30** (**Scheme 7**) by using *Cadogan cyclization* protocol. *Cadogan cyclization* reaction is a robust method that helps in the generation of indole moiety by using trialkylphosphite or phosphane. This reaction involves the reaction of *ortho*-nitro biaryl **29** with triethyl phosphate in DCM under microwave heating (300 W, 230 ^{o} C) followed by N-alkylation of the resulting compound under one-pot leading to formations of benzofuro[3,2-*b*]indoles **30** with excellent yields.



Scheme 7: Synthesis ofsubstituted benzofuro[3,2-*b*]indole **30**

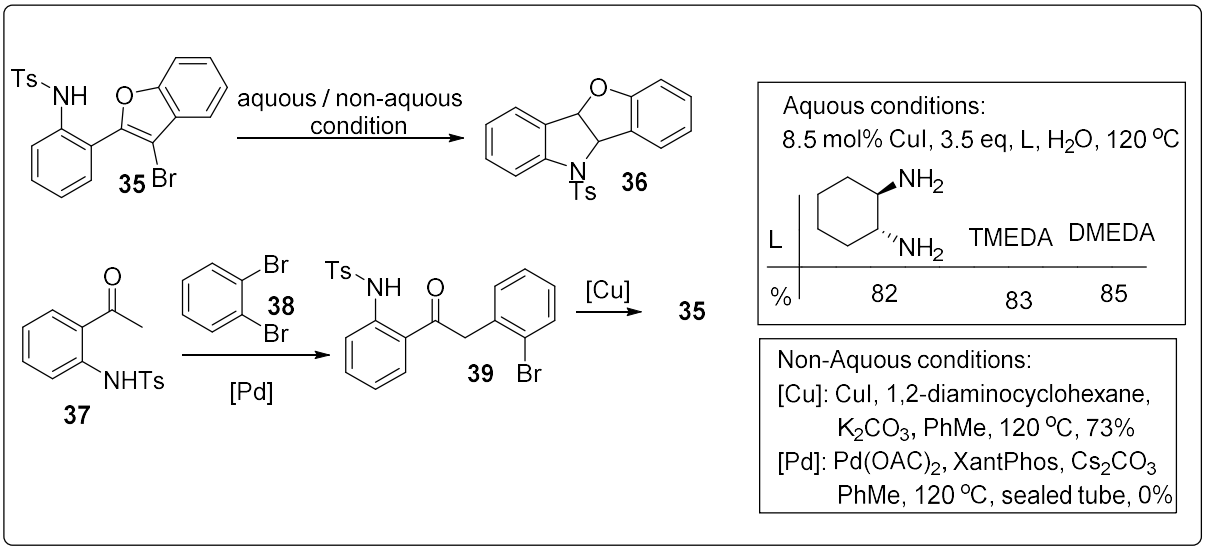
Gormemis and coworkers [19] reported a mild protocol for the synthesis of benzofuro[3,2-*b*]indoles **34** with different functional group with different position by using salicylic acid as simple starting material (**Scheme 8**). First, salicylic acid **31** undergoes esterification followed by alkylation (with ethyl bromoacetate) and ester hydrolysis leading to the formation of the intermediate compound **32**. Then, cyclization of **32** in the presence of acetic anhydride, sodium acetate and acetic acid followed by acidification resulted in the formation of intermediate benzofuranones**33**. Next, intermediate **33** was coupled with phenyl hydrazine to afford the corresponding hydrazone which undergoes *Fisher-Indole* reaction under refluxing conditions or microwave irradiation with the aid of acid catalyst (*p*-TSA) leading to the formation of substituted benzofuro[3,2-*b*]indoles derivatives **34**.



Scheme 8: Synthesis ofsubstituted benzofuro[3,2-*b*]indoles**34**

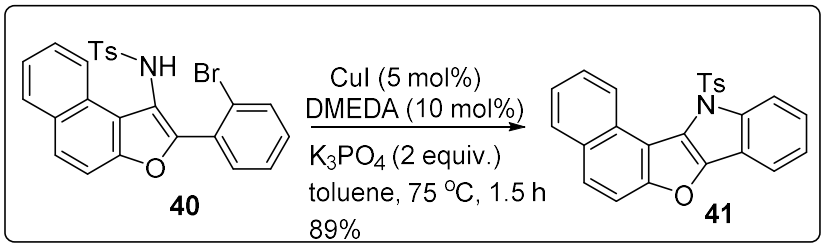
3.1.2.2.2: Metal-catalyzed methods for the synthesis of benzofuro[3,2-*b*]indoles:

Carril *et al.*[27] reported a facile and green approach for the preparation of benzofuroindole**36** by copper-catalysed intramolecular *O*-arylation in neat water medium (**Scheme 9**). The starting compound **35** could easily be achieved in two steps comprising palladium-catalyzed α-arylation of the acetophenone derivatives **37** with 1,2 dibromobenzene**38** and copper-catalyzed cyclization of the intermediate deoxybenzoin**39** in water medium. The method for the conversion of **35** to **36** involved an intramolecular *Goldberg-type reaction* (between sulfonamide and heteroaryl halides moiety).



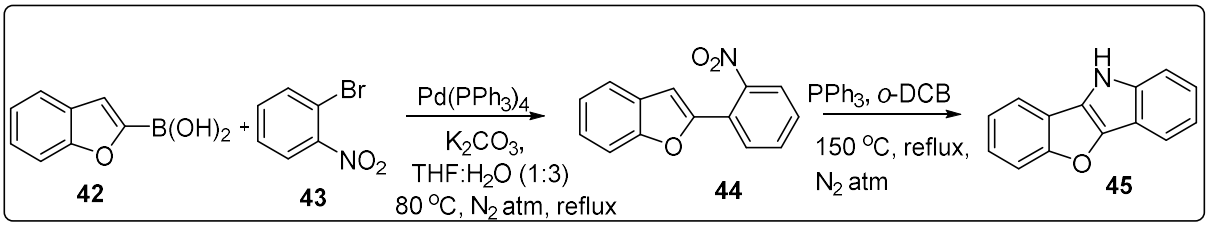
Scheme 9: Synthesis ofbenzofuro[3,2-*b*]indole **36**

Kaladevi*et al.*[28] described a new synthetic method for the synthesis of naphthofuroindole**41** (**Scheme 10**). The construction of this biologically important polycyclic heteroaromatic compound was achieved via copper-catalysed C-N bond cross coupling of *ortho*brominated naphthofuroindole**40** in presence of 5 mol% of CuI, 10 mol% of DMEDA, and K_3PO_4 at 70 °C in toluene.



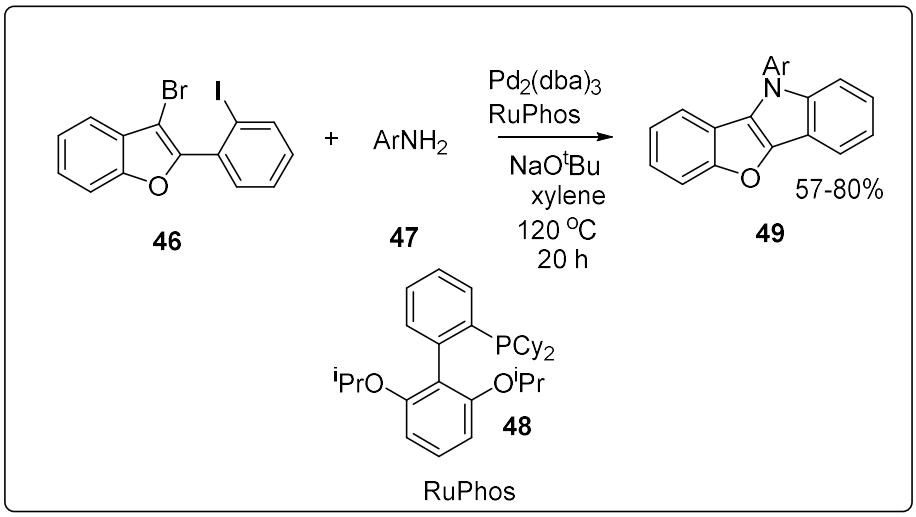
Scheme 10: Synthesis ofnapthofuro[3,2-*b*]indole **41**

Konidena and co workers[22] developed an efficient and general approach for the synthesis of **45** by treating benzofuro-boronic acid **42** with 2 bromo-nitrobenzene **43** through *Suzuki-Miyaura* coupling under palladium catalyzed conditions. Then resulting intermediate **44** undergoes efficient one pot amination followed by PPh_3 mediated cyclization to deliver highly regioselective benzofuro[3,2-*b*]indoles **45.**



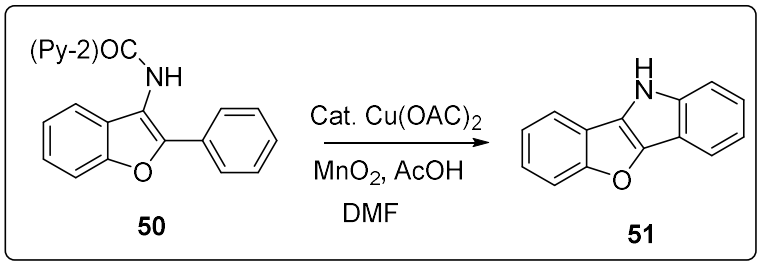
Scheme 11: Synthesis ofbenzofuro[3,2-*b*]indole **45**

Truong *et al.*[21] developed a simple and general palladium (0) catalyzed method for the synthesis of *N*-arylated benzofuro[3,2-*b*]indoles (BFIs) **49** (**Scheme 12**). This protocol uses readily available and simple starting materials such as dihalobiaryls **46** and arylamines **47.** The key feature of this reaction is the double N-arylation of anilines leading to the corresponding product benzofuro[3,2-*b*]indoles **49** with moderate to excellent yields (57-80%).



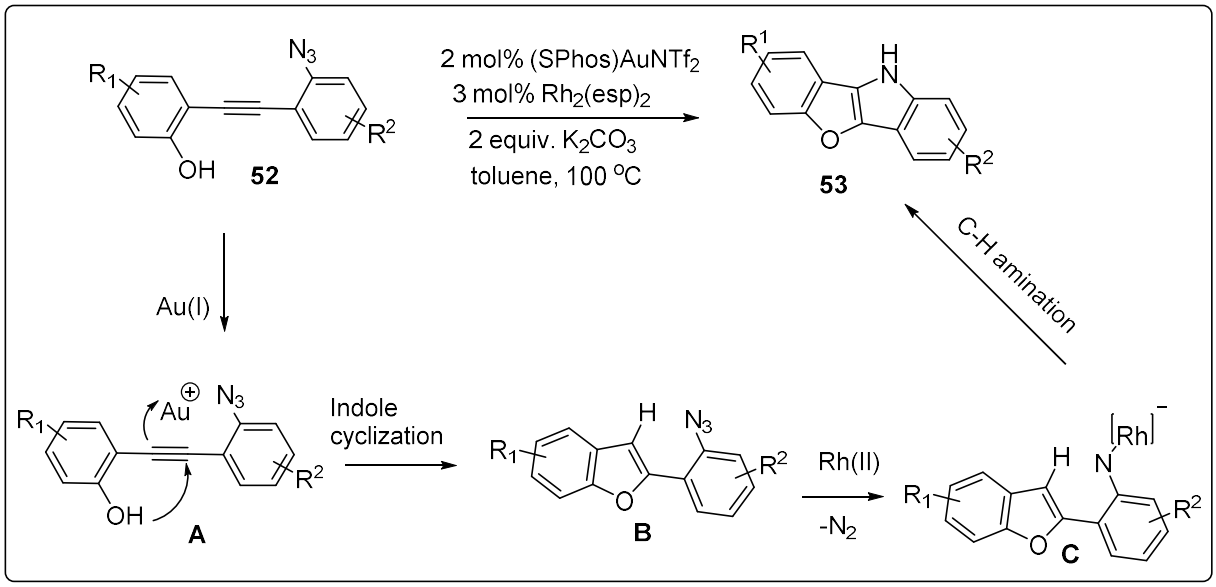
Scheme 12: Pd(0)-catalyzed synthesis ofbenzofuro[3,2-*b*]indole **49**

Takamatsu *et al.*[29] proposed a Cu-catalyzed intramolecular C-H amination reaction for the easy synthesis of benzofuro[3,2-*b*]indoles (BFIs) derivatives **51** (**Scheme 13**) . The key to the success for this reaction is the installation of the picolinamide-based directing group, which helps in the cyclization in the phenyl moiety followed by the spontaneous removal of picolinamide group leading to the formation of **51.**



Scheme 13: Cu(II) catalyzed synthesis ofbenzofuro[3,2-*b*]indole**51**

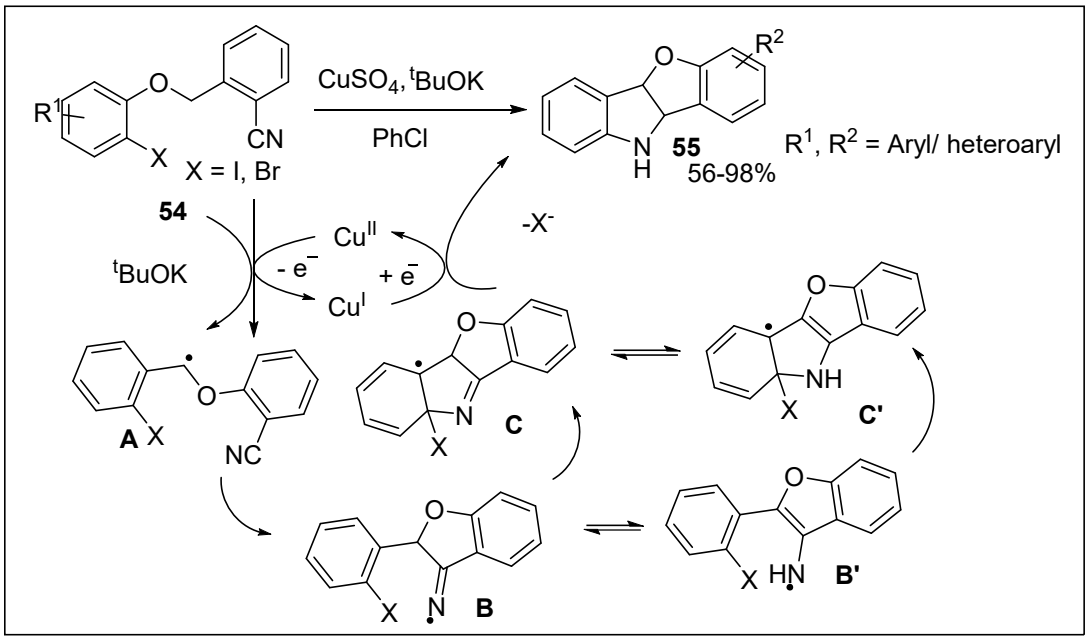
Matsuda *et al.*[30] developed a simple and efficient gold/rhodium catalyzed intramolecular cascade hydroamination/cycloisomerisation of 2-[(2-Azidophenyl)ethynyl]phenols **52** to produced10*H*-benzofuro[3,2-*b*]indoles **53** (**Scheme 14**). Reaction undergoes sequential C-O and C-N bond formations. Mechanistic studies reveal that Au(I) catalyst acting like a Lewis acid (intermediate **A**) first promotes the cascade cyclisation (5-*endo-dig*) of substrate **52** resulting in the synthesis of benzofuran intermediate **B** which then undergoes intramolecular C-H amination with azide moiety through the participation of Rh(II) catalyst as depicted in **Scheme 14**.



Scheme 14: Formation of products **53** using dual catalyst and a plausible reaction mechanism

Shan *et al.*[31] demonstrated an efficient and general method for the preparation of benzofuro[3,2-*b*]indoles **55** (**Scheme 15**) via base catalyzed benzylic C-H cleavage and copper catalytic carbanion-radical redox relay. Catalytic amount of naturally abundant and inexpensive

copper (II) sulfate plays a pivotal for anion-radical redox relay without any other external oxidant. While ^{t}BuOK promoted benzylic C-H cleavage of **54** to generate intermediate species **A**



Scheme 15: Formation of product **55** with a plausible reaction mechanism

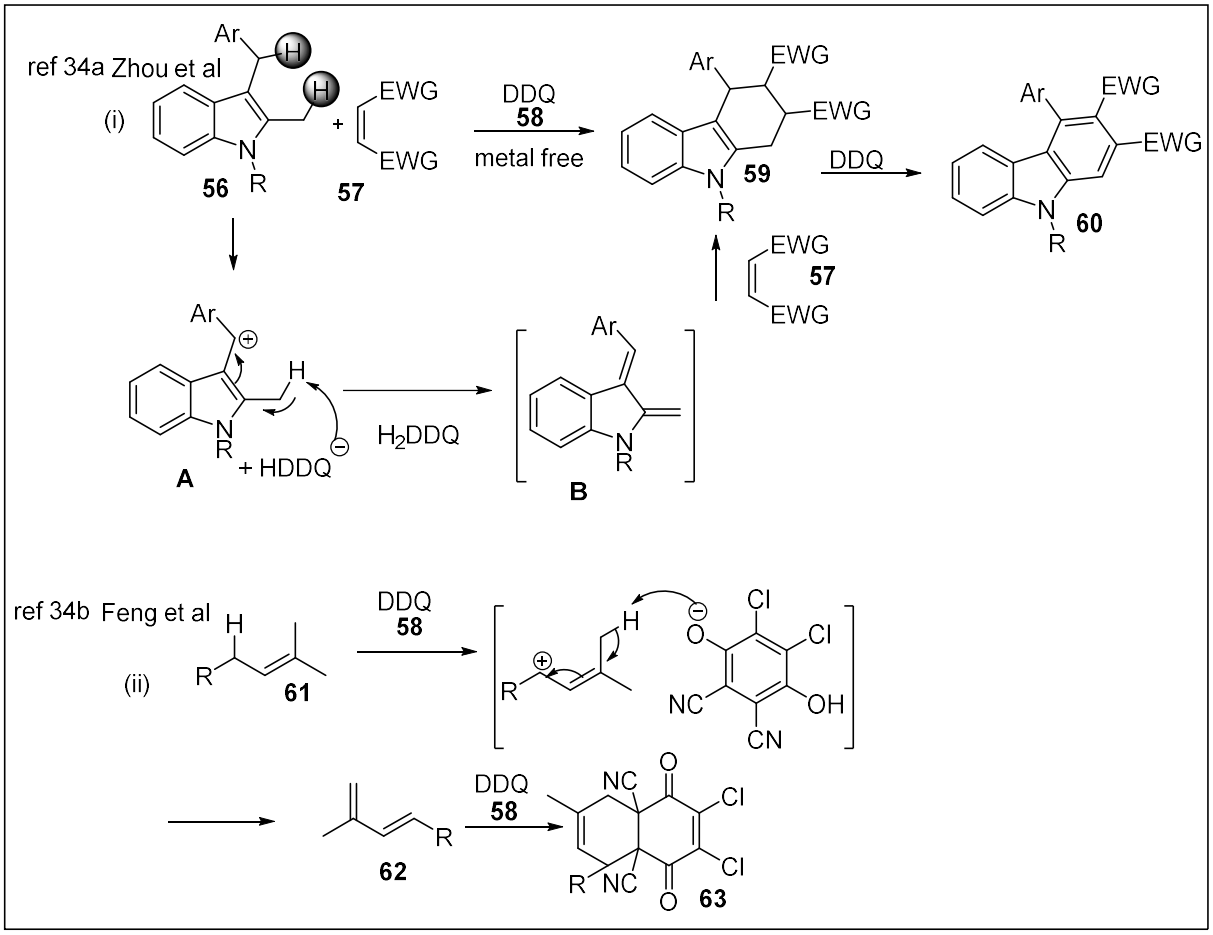
which then undergoes radical addition onto the –CN group resulting in the formation of **B**/**B'** using a metal oxidant such as Cu(II). Next, **B**/**B'** then transforms into **C**/**C'** which then triggers the formation of product **55**.

3.1.3 Few miscellaneous synthesis:

In addition, Zhou[32a] demonstrated novel DDQ-mediated direct dehydrogenative Diels Alder (DDA) reaction between 2-methyl-3-arylmethylindoles **56** and electron-deficient olefins **57** to provide an easy access to tetrahydrocarbazoles, carbazoles etc. The main objective of the reaction is to accomplish a metal-free dehydrogenative Diels–Alder (DDA) reaction with the formation of two C-C bonds in a single operation by a DDQ-mediated direct C(sp3)-H bond functionalization**.**

In addition, Feng and coworkers[32b] reported the oxidation of a prenyl motif **61** which upon exposer to DDQ would generate an allylic carbocation intermediate, then elimination of a proton

and rearrangement would form an isoprene motif **62** and finally Diels-Alder (DA) reaction of the isoprene derivative **62** with DDQ would yield a DHDA reaction product **63**.



Scheme 16: DDQ-mediated dehydrogenative Diels−Alder reactions

3.1.4 Concluding remarks:

The scrutiny of above literature survey reveals that benzofuro[3,2-*b*]pyrrole finds various applications ranging from medicinal chemistry to material science. Nevertheless, synthesis of heterocyclic moiety, i.e.,benzofuro[3,2-*b*]pyrroles **1** (Fig.1) are very less in numbers. Therefore, construction of new pyrrole ring attached to benzofuran moiety under one pot would be of interest.

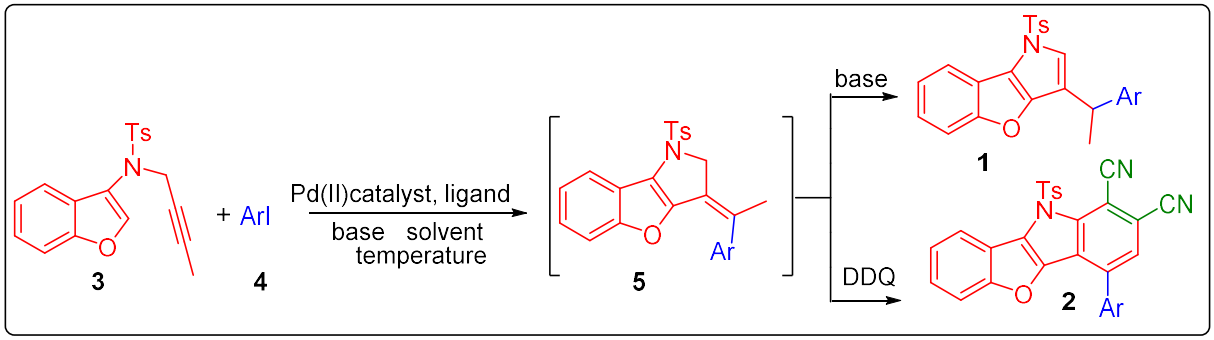
On the other hand, benzofuro[3,2-b]indole **2** (Fig.1) has shown promising pharmacological activities in medicinal chemistry and this scaffold has also been explored for its uses in organic electronics and as a building block for the construction of functional materials.

Surprisingly, synthesis of benzofuro[3,2-*b*]indole **2** via either conventional or metal catalyzed methods are comparatively are less explored. Thus, development of a domino reaction utilizing easily accessible starting material for the the construction of benzofuro[3,2-*b*]pyrroles under one-pot would be worthwhile.

Nevertheless, in**Part-II** of this chapter, the results on the general synthesis of benzofuro[3,2-*b*]pyrroles **1** and benzofuro[3,2-*b*]indoles **2** starting from 2-hydroxyacetophenones and the scope and limitations of the method have been discussed elaborately.

Part II

Result and Discussion



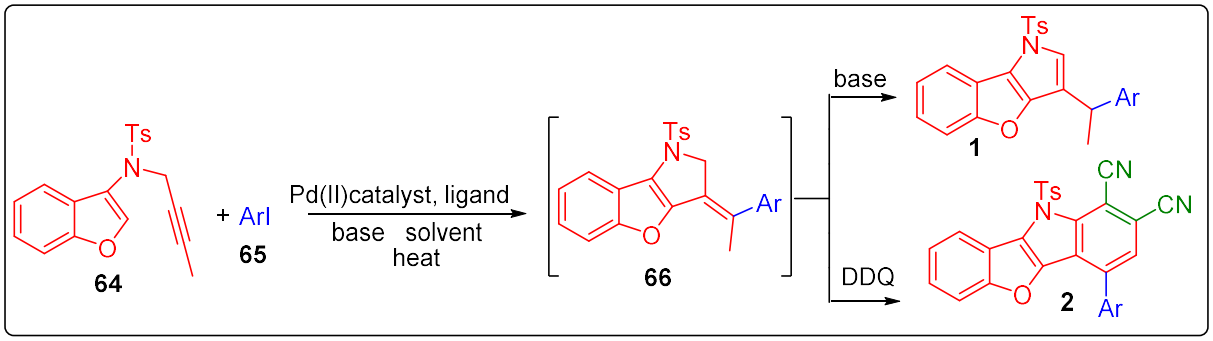
Reference: **Debasmita Mondal** and Chinmay Chowdhury* manuscript is under communication

3.2.1 Introduction:

In the view of immense importance in benzofuro[3,2-*b*]pyrrole **1** and its derivatives in medicinal chemistry and material sciences, the development of the facile method for these heterocycle appears to be an important topic to many researchers. Scruitinity of literature reveals that there are only few methods for the general synthesis of benzofuro[3,2-*b*]pyrroles. Thus, it underlines the urgency of need of a convenient and practical method for their general synthesis.

On the other hand, benzofuro[3,2-*b*]indole **2** and its derivatives have found to display various biological activities,[18-20] including anticancer, anti-inflammatory, and antimicrobial properties. It has been investigated as potential lead compound for the development of new drugs. These ladder type π-conjugated 6-5-5-6 systems have been exhibited various potential applications such as organic light emmiting diode (OLED), organic field-effect transistors (OFETs), photo-voltaic shell etc. Although many synthetic methods have been reported for the construction of this scaffold, most of these approaches however utilize pre-funtionalised substrates, multi-step synthetic procedures, hazardous reaction conditions, low yields. Therefore, a development of a straightforward and convenient method for the synthesis of **2** would be worthwhile.

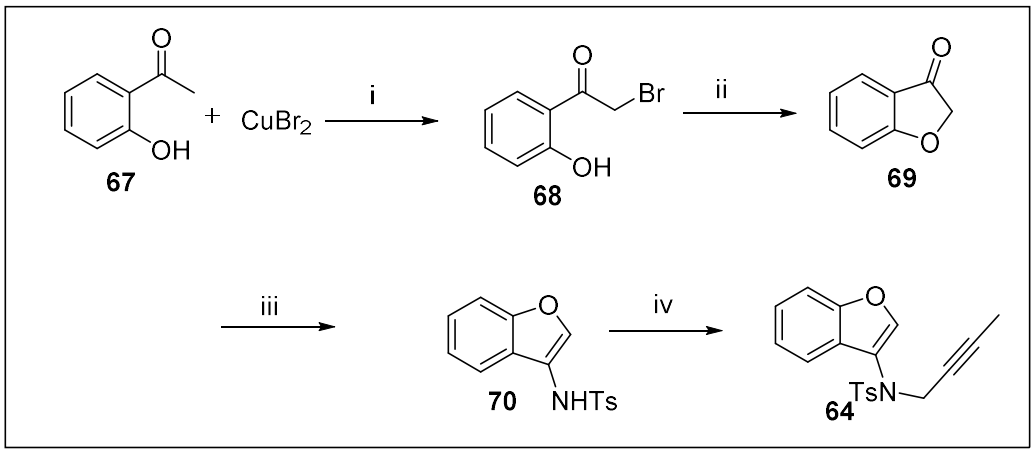
In continuation of our works,[33c] for the direct construction of pyridine ring fused to indole or benzofuran moiety using palladium-catalyzed cascade reactions, we anticipated that starting material **64** would undergo palladium-catalyzed reaction with aryl iodide **(**Ar-I) **65** *via 5-exo-dig* cyclisation resulting in the formation of 3-(1-arylethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole **66** which could be converted under base treatment into benzofuro[3,2-*b*]pyrrole **1**. In addition, we also anticipated that detosylation of intermediate product **66** could be achieved by the treatment of DDQ; to our surprise, a benzofuro[3,2-*b*]indole **2** was isolated instead. Herein, we describe in details the results obtained so far.



Scheme 17:Palladium(II)-catalysed synthesis of benzofuro[3,2-*b*]pyrrole **1** and benzofuro[3,2-*b*]indole **2**

3.2.2 Preparation of starting material 64:

The requisite *N*-(benzofuran-3-yl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide substrates **64** were synthesized in five steps starting from commercially available 2-hydroxy acetophenone**67** (**Scheme 18**). Thus, the resulting bromo-intermediate **68** could easily be achieved through bromination of **67**. Next, a base induced cyclization of **68** resulted in the formation of intermediate **69** which upon treatment with *p*-toluenesulphonamide in the presence of *p*-toluenesulphonic acid at 120 °C afforded the *N*-(benzofuran-3-yl)-4-methylbenzenesulfonamide **70**. Finally, benzofuran-intermediate **70** undergoes a base-induced propargylation reaction leading to the formations of *N*-(benzofuran-3-yl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide substrates **64**.



Scheme 18. Synthesis of substrate **64**. reagent and conditions: (i) $CuBr_2$, EtOAc, $CHCl_3$, DMF, reflux, 12 h, 85%; (ii) Et_3N, CH_3CN, 0 °C- rt, 30 min, 85%; (iii) *p*-$TsNH_2$, *p*-TsOH, toluene, 120 °C, 4 h, 82%; (iv) Propargyl bromide, NaH, DMF, 0 °C- rt, 3 h, 82%;

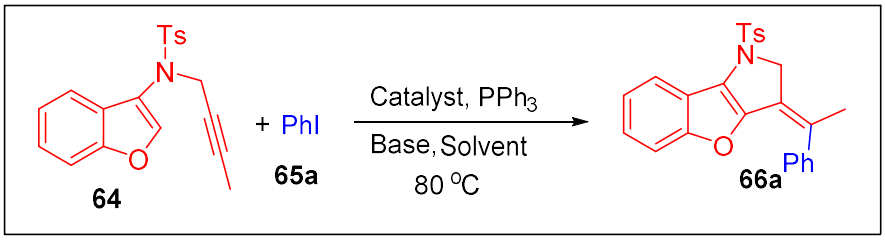
3.2.3 Synthesis of dehydrobenzofuro[3,2-*b*]pyrroles 66 from acetylenic substrate 64 through palladium-catalyzed reactions:

At the outset, an optimization study have been carried out by changing catalyst, base and solvent in the reaction between acetylene substrate **64** and iodobenzene **65a** for the synthesis of 3-(1-phenylethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole **66a**. After having the optimization conditions, we planned to explore the scopeof the reaction as depicted under **Scheme 19.**

3.2.3.1 Optimisation of the reaction condition for the synthesis of 3-(1-phenylethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole 66a through palladium-catalyzed reactions:

To establish the viability of forming the desired heterocycle **66a**, we initially decided to synthesize 3-(1-phenylethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole **66a** by reacting with *N*-(benzofuran-3-yl)-*N*-(but-2-yn-1-yl)-4-methylbenzenesulfonamide **64** and phenyl iodide **65a** under palladium catalysed reaction conditions as shown in Table 1. At the outset, the exposure of the reactants to 7 mol % $PdCl_2$ and 14 mol % PPh_3 along with stronger base K_2CO_3 in DMF afforded **66a** with 54% yield (Table 1, entry 1). Addition of tetrabutylammonium bromide (TBAB) to the said reaction conditions did not increase the yield of the products significantly (Table 1, entry 2). We therefore switched to other catalytic systems like $Pd(OAC)_2$/ PPh_3 with K_2CO_3 and executed the reaction at 80 ^oC, this reaction furnished the product **66a** in 65% yield (Table 1, entry 3). Gratifyingly, conducting this reaction by replacement of Cs_2CO_3 by K_2CO_3 led to the completion of the reaction within 45 min affording**66a** exclusively with 84% yield (Table 1, entry 4). In absence of PPh_3, acetylinic substrate **64** remains almost inert as very trace amount of desired product **66a** was obtained

Table 1: Optimization of the reaction conditions for the synthesis of **66a**[a]



Sl No.	Catalyst	Ligand	Solvent	Base	Time (h)	Yields (%)[d]
1	$PdCl_2$	PPh_3	DMF	K_2CO_3	1	54
2	$PdCl_2$	PPh_3(TBAB)	DMF	K_2CO_3,TBAB	1	56
3	Pd (OAC) $_2$	PPh_3	DMF	K_2CO_3	1	65
4	**Pd (OAC) $_2$**	**PPh_3**	**DMF**	**Cs_2CO_3**	**45 min**	**84**
5	Pd (OAC) $_2$	-	DMF	Cs_2CO_3	8	trace
6	Pd (OAC) $_2$	PPh_3	DMF	$NaHCO_3$	2.5	68
7	Pd (OAC) $_2$	PPh_3	DMF	^{t}BuOK	8	40
8	Pd (OAC) $_2$	PPh_3	DMF	K_3PO_4	8	34
9	Pd (OAC) $_2$	PPh_3	DMF	DBU	5	nr
10	Pd (PPh_3) $_4$	-	DMF	Cs_2CO_3	1	62
11	Pd_2(dba) $_3$	PPh_3	DMF	Cs_2CO_3	6	40
12	Pd_2(dba) $_3$.$CHCl_3$	PPh_3	DMF	Cs_2CO_3	8	35
13	Pd (OAC) $_2$	PPh_3	DMSO	Cs_2CO_3	5	22
14	Pd (OAC) $_2$	PPh_3	Toluene	Cs_2CO_3	5	nr
15[b]	Pd (OAC) $_2$	PPh_3	DMF	Cs_2CO_3	2.5	61
16[c]	Pd (OAC) $_2$	PPh_3	DMF	Cs_2CO_3	9	52

[a]Reaction conditions (Unless noted otherwise): A mixture of 1.0 equiv of **64** and 1.2 equiv of **65a,** 1 equiv. of Cs_2CO_3 in 2.0 mL solvent in the presence of 7 mol % of the $Pd(OAC)_2$ catalyst and 14 mol % PPh_3 was heated at 80^{o}C under argon. [b]The reaction was performed with 5 mol % of $Pd(OAC)_2$ along with 10 mol % PPh_3. [c]The reaction mixture was heated to 100^{o}C. [d]Isolated pure products after chromatography.

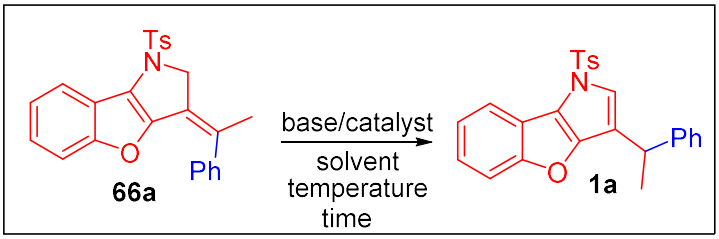
and the starting material was recovered (Table 1, entry 5). However, switching to other bases such as $NaHCO_3$, ^{t}BUOK, K_3PO_4 or DBU led to 34-68% yield (entries 6-8, Table 1) except the

entry 9 of Table 1 where the reaction did not take place at all. We therefore switched to Pd(0) catalyst; Accordingly, employing $Pd(PPh_3)_4$,or$Pd_2(dba)_3$, or $Pd_2(dba)_3.CHCl_3$ afforded **66a** only in moderate yields (35-62%) (Table, entries 10-12). Again, changing the solvent system (Table 1, entries 13-14) including both low (i.e., toluene) or high polar one (i.e., DMSO) did not proved to be effective though DMSO furnished **66a** in 22% yield. Next, decreasing the catalyst loading from 7 mol % to 5 mol % produced **66a** in 61% yieldwithin 2.5 h (Table 1, entry 15). Notably, increasing the reaction temperature 80 ^oC to 100 ^oC produced **66a** in 52% yield though entailing a slightly longer reaction time (Table 1, entry 16). We therefore considered the conditions used in the (Table 1, entry 4) is the optimal to explore the scope of this reaction.

3.2.3.2 Synthesis of benzofuro[3,2-*b*]pyrrole 1:

To explore the scope of the above reaction further, we decided to carry out a base induced isomerisation of products **66a** into **1a**. Toward this goal, we initially executed few reactions through the variation of excess amount of base, solvent and temperature to find out the optimized reaction conditions as shown in Table 2. Initially, performing the reaction with strong base like NaOH in ethanol under refluxing condition (Table 2, entry 1) or mild base like NaH in DMF (Table 2, entry 2) under room temperature failed to provide the desired product **1a**; generation of multi-spot (TLC) in minor amount was only observed from these reactions. Use of other base like Cs_2CO_3 or K_2CO_3 in DMF and heating at 80-120 ^oC (Table 2, entries 3-5) proved to be the substrate **66a** inert as no product was formed (TLC) and only starting material was recovered. Surprisingly, treatment of DBU (Table 2, entries 6-7) as a base in DMF at 80^o or 120 ^oC led to the complete isomerisation of the reaction within 3 h with 93% yield though the reaction at 80 ^oC proved to be somewhat sluggish. Interestingly, addition of catalytic amount of $FeCl_3$ (0.2 equiv) in dry DCM (Table 2, entry 6) promotes to the same isomerisation of **66a** to benzofuro[3,2-*b*]pyrrole**1a** though yield was found to be moderate (62%). Thus, DBU as a base (entry 7 of Table 2) proved to be most effective for this isomerization reaction and we therefore planned to adopt the strategy to carry out the transformation of **1** from **64** in one pot without isolation of intermediate product **66** as shown below in **Scheme19**.

Table 2. Optimization of the isomerization of the product 66a into benzofuro[3,2-*b*]pyrrole 1a[a]



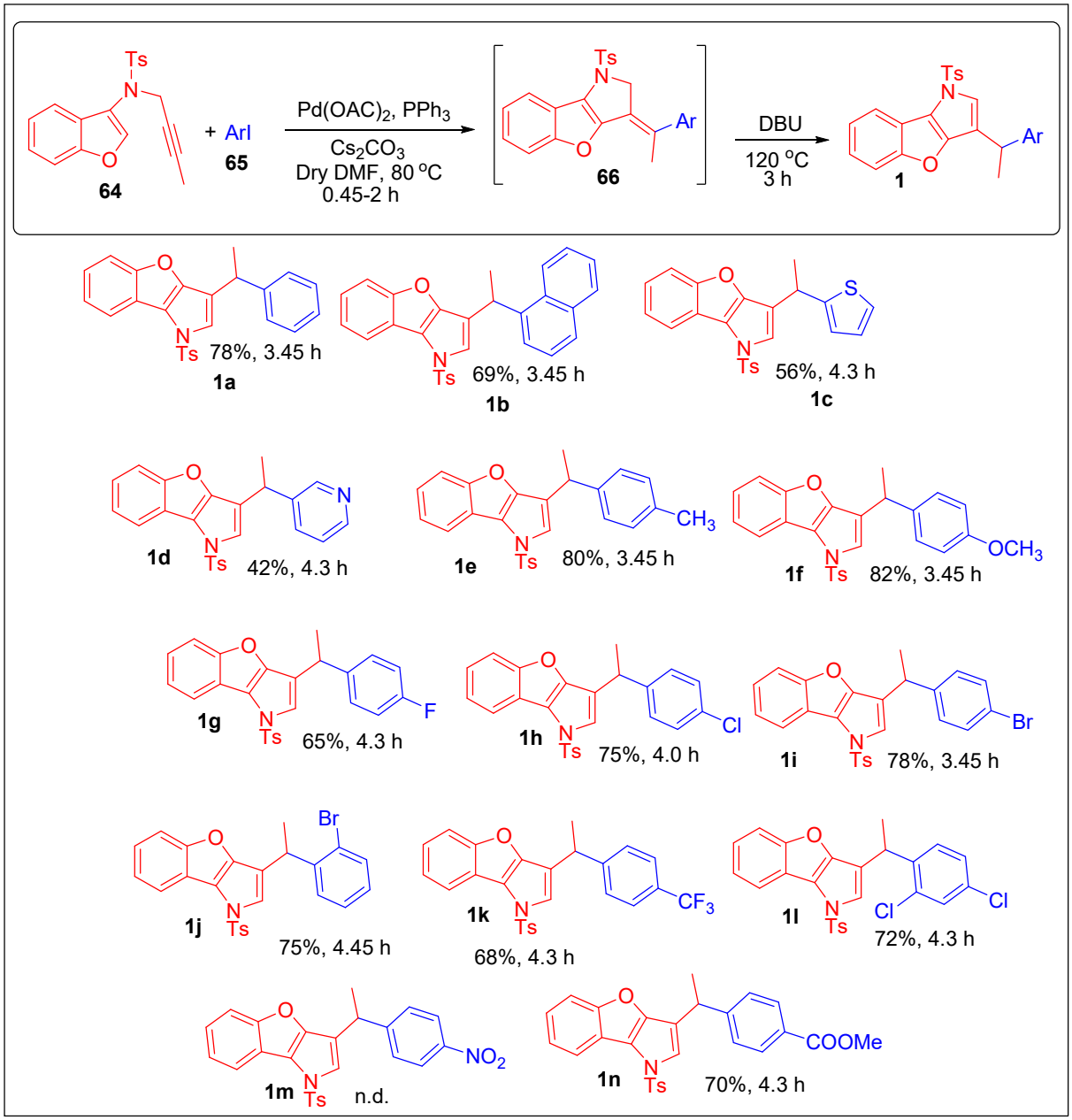
Sl no.	Base (equiv.)	Catalyst (equiv.)	Solvent	Temperature	Time	Yield (%)[b]
1	NaOH (3)	-	Ethanol	Reflux	3 h	n.d.
2	NaH(5)	-	DMF	rt	1 h	n.d.
3	Cs_2CO_3(4)	-	DMF	80 °C	8 h	n.r.
4	K_2CO_3(4)	-	DMF	80 °C	8 h	n.r.
5	Cs_2CO_3(4)	-	DMF	120 °C	8 h	n.r.
6	DBU (2)	-	DMF	80 °C	15h	60
7	**DBU (2)**	**-**	**DMF**	**120 °C**	**3 h**	**93**
8	-	$FeCl_3$ (0.2)	DCM	rt	3 h	62

Compound **66a** was treated with a base or catalyst (i.e., $FeCl_3$) in a solvent 2.0 mL and the whole reaction was stirred either at r.t or heated at 80-120 ° C under argon.[b]Yield of Isolated pure product after chromatography.

3.2.3.3. Scope of the reaction for the synthesis of benzofuro[3,2-*b*]pyrroles 1:

Having the optimized reaction conditions in hand, we then explored the scope and generality of the reaction of acetylenic substrate **64** with a variety of aryl/heteroaryl iodides **65** as shown in **Scheme 19**. A series of products **1a-n** have been synthesized within 3.45-4.3 h with moderate to very good yields (42-78%) and a range of functional groups (viz., Me, OMe, F, Cl, Br, CF_3, COOMe) attached to the phenyl ring of **65**were found to be well tolerated. Initially, we carried out subsequent reactions of acetylenic substrate **64** with 1-iodonaphthalene (**65b**), 2-iodothiophene (**65c**) and 3-iodopyridine (**65d**); these reactions furnished the expected products **1b**, **1c** and **1d,**respectively with good to moderate yields (42−69%). Gratifyingly, iodide having an electron-donating group (EDG) (viz., Me or OMe) such as **65e** or **65f** proved to be more

Scheme 19: Pd(II)-catalyzed synthesis of benzofuro[3,2-*b*]pyrroles 1 under one-pot[a,b]



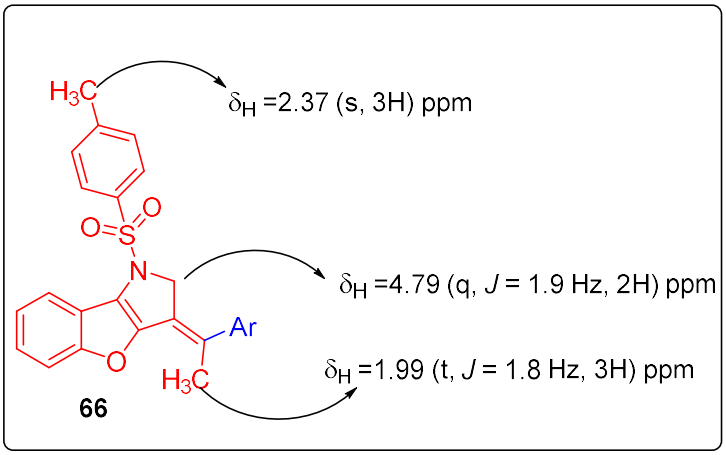
[a]Reaction conditions: A mixture of **64** (1 equiv.), **65** (1.2 equiv.), $Pd(OAc)_2$ (7 mol %), and PPh_3 (14 mol %), 1 equiv. Cs_2CO_3 in DMF (2 mL) was heated at 80 °C; after completion of the reaction (TLC), the DBU (2 equiv.) was added and the whole reaction mixture was heated to 120 °C . [b]Isolated yield.

reactive, thereby facilitating the reaction by delivering the products **1e** or **1f** within 3.45 h with excellent yields (80-82%). The trend of this reactivity was found to be continued even with substrates **65g-l** having moderately EWG (viz.; 4-F, 4-Cl, 2/4-Br, 4-CF_3, 2,4-Cl), delivering the products **1g-l** with 65-78% yields. In contrast, a strong EWG as in substrate 1-iodo-4-

nitrobenzene (**65m**) failed to provide the desired product **1m**, instead, only few undesired spots (TLC) were found to be formed in minor amount. To our surprise, methyl 4-iodobenzoate (**65n**) participated the reaction successfully leading to the generation of benzofuro[3,2-*b*]pyrrole**1n** within 4.3 h with 70% yield.

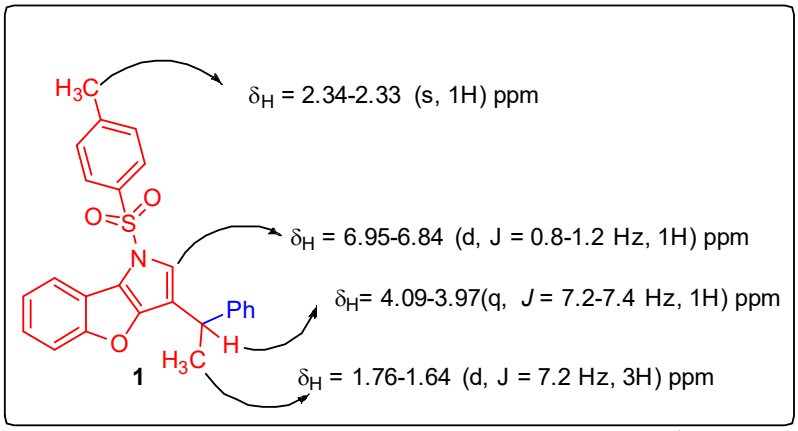
3.2.3.4.Nature and characterization of intermediate 66:

The structure of the intermediate **66** were unambiguously concluded by spectral (^{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 solidated $[M+Na]^{+}$ ion. In ^{1}H NMR, protonattached to the -CH_3 group of the vinylic position appears as triplet at the range of 1.99 ppm. The methelene protons vinyl group displayed as quartet at the range of 4.79 ppm. Whereas, the methyl protons of the tosyl group attached to the nitrogen atom appears as singlet at 2.37ppm. Further, the ^{13}C NMR gave additional support in the favour the structure.



3.2.3.5 Nature and characterization of products 1:

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 °C) for the several months. The structure of the product was unambiguously deduced by spectral (^{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, protonattached to the benzylic position appears as quartet at the range of 4.09-3.97 ppm as expected. While the protons of the methyl group attached to benzylic carbon appears as doublet at the range of 1.76-1.64 ppm as also expected. On the other hand, the proton of the pyrrole ring displayed as doublet at the range of 6.95-6.84 ppm. Whereas, the methyl protons of the tosyl moiety attached to the nitrogen atom appears as singlet at 2.34-2.33 ppm and the remaining aromatic protons appear in the range of 8.11-6.89 ppm. In ^{13}C NMR, benzylic carbon appears at 36.5-31.8 ppm and others carbons appear at appropriate position. Furthermore, mass Spectra gave additional support in the favour the structure.



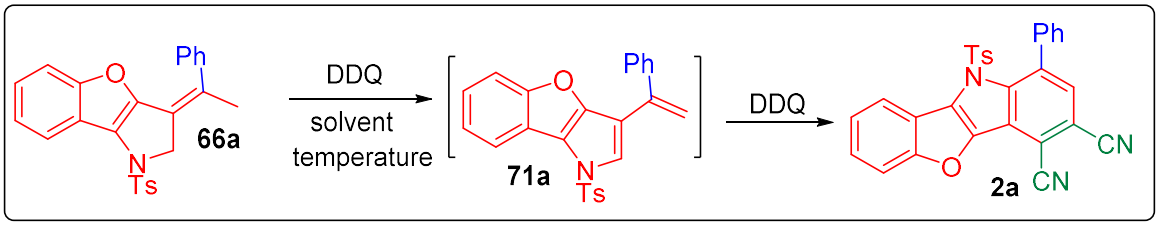
3.2.4. Synthesis of benzofuro[3,2-*b*]indole2:

3.2.4.1. Optimisation for the DDQ mediated synthesis of benzofuro[3,2-*b*]indole 2a:

Encouraged by the reported works by Zhou and Feng[32] for the synthesis of 1,3-dienes (see, **Schemes 16** in part I) as requisite substrates for Diels Alder reaction, we became interested to explore the potential of products **66** into 1,3-dienes **71** which could undergo Diels Alder reaction to generate important scaffolds of biological interests. To test this hypothesis, product **66a** was treated with DDQ (3 equiv.) in acetonitrile at room temperature (entry 1, Table 3); to our pleasure, 3-(1-phenylvinyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole**71a** was found to be formed at rt (12 h) with 60% yield (Table 3, entry 1). In contrast, instead of isolating the intermediate **71a,** heating the same reaction (in acetonitrile) at 120 °C after the formation of intermediate **71a** failed

to provide any product leading to the polymerization of the reaction (Table 1, entry 1). Next, replacing the acetonitrile with *o*-xylene and carrying out the reaction either at rt or heating at 120 ^{o}C did not provide the access of intermediate product **71a** (Table 3, entry 2). Nevertheless, changing the solvent to chlorobenzene and heating the reaction at 120 ^{o}C in same solvent provided the intermediate **71a** in moderate yield (42%) but failed to provide the targeted product **2a** (Table 3, entry 3). To our pleasure, exposer of **66a** with DDQ (3.0 equiv) and conductingthis reaction in toluene at 120 ^{o}C led to the formation of cycloadduct**2a** within 2 h with 89% yield (Table 3, entry 4).

Table 3: DDQ promoted synthesis of benzofuro[3,2-*b*]indole 2a[a]



Sl no	Solvent	Temperature	Time (h)	Yield(%)[b] of 71a	Yield(%)[b] of 2a
1[a]	CH_3CN	rt	12	60	-
2	*o*-Xylene	120 ^{o}C	12	n.r.	n.r.
3	Chlorobenzene	120 ^{o}C	8	42	-
4	**Toluene**	**120 ^{o}C**	2	**-**	**89**

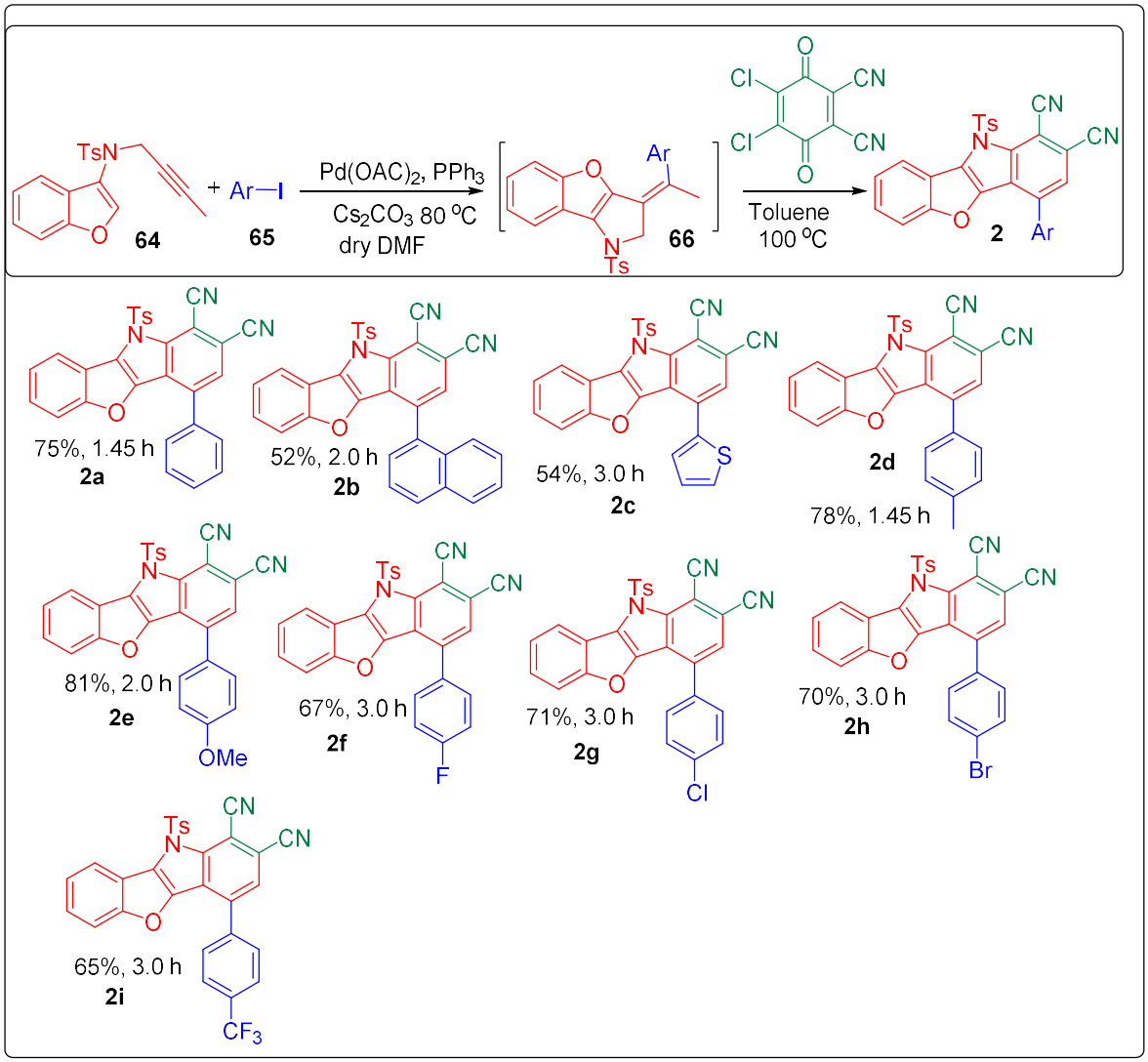
A mixture of 1.0 equiv of **66** and DDQ (3 equiv.) in 2.0 mL was stirred either r.t or heated at 120 ^{o} C under argon.[b]Isolated pure products after chromatography. The term "n.r." means no reaction.

3.2.4.2. Scope of the reaction for the synthesis of benzofuro[3,2-*b*]indole 2a:

With the aforesaid encouraging and novel results for the synthesis of product **2a** in hand, we attempted to explore the prospect of utilizing DDQ in the synthesis of different benzofuro[3,2-*b*]indole derivatives **2** as shown in **Scheme 20**. The desired product **2b** was found to be formed with moderate yield (52%) possibly steric hindrance faced by the bulky naphthalene moiety during cycloaddition reaction. Nevertheless, 2-iodo-thiophene (**65c**) participated this reaction successfully though the resulting product **2c** was found to be formed within 3 h with moderate yield 54% yield. Interestingly, attachment of moderate (Me) or strong (OMe) electron-donating group (EDG) as in intermediate **66e** or **66f** facilitated this reaction, generating the product **2d** or

2**e** with excellent yield (78-81%). Nevertheless, in contrast to the previous observations, intermediate **66g-j** possessing a moderately electron withdrawing group (EWG) (viz., F, Cl, Br, CF_3) participated in the reaction with less efficiency resulting in the products benzofuro[3,2-*b*]indoles**2f-i** with lower yields. The formation of product **2** is attributed to in situ generation of a di-ene intermediate **71** (*vide infra* under **Scheme 22**) which undergoes rapid [4+2] cycloaddition

Scheme 21: DDQ-mediated synthesis of benzofuro[3,2-*b*]indole 2[a,b]

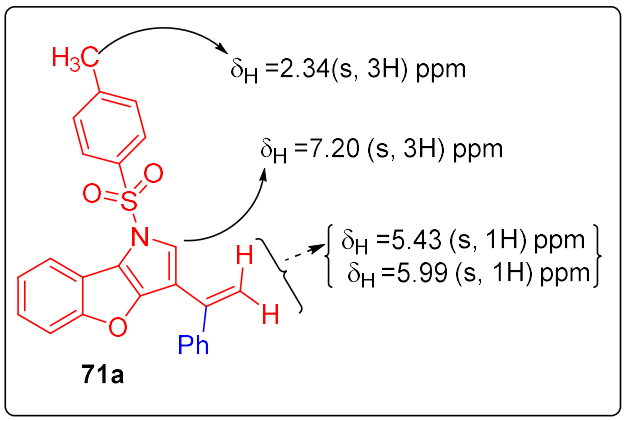


[a]Reaction conditions: A mixture of **64** (1 equiv.), **66** (1.2 equiv.), Pd $(OAc)_2$ (7 mol %), and PPh_3 (14 mol %), Cs_2CO_3 (1 equiv.) in DMF (2 mL) was heated at 80 °C. After completion of the reaction, solvent was evaporated to dryness and the resulting crude product dissolved in dry toluene (3 mL) was heated at 100 °C for few hours (1.45-3 h) in the presence of DDQ (3 equiv.). [b]Isolated yield.

with DDQ to generate the product **2**; a detailed mechanism is depicted under **Scheme 22** below.

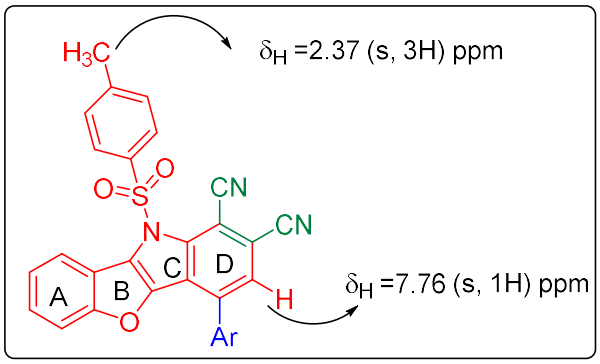
3.2.4.3 Nature and characterization of intermediate 71a:

The structure of the intermediate **71a** were unambiguously concluded by spectral (^{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 solidated $[M+Na]^{+}$ ion. In ^{1}H NMR, protons attached to to the vinylic position appears as singlet at the range of 5.43 ppm and 5.99 ppm, respectively. The proton of newly generated pyrrole moiety displayed as singlet at the range of 7.20 ppm. Whereas, the methyl protons of the tosyl group attached to the nitrogen atom appears as singlet at 2.34 ppm. Further, the ^{13}C NMR, mass spectra gave additional support in the favour the structure.



3.2.4.4. Nature and characterization of products 2:

All the synthesized products are moderately stable at room temperature but can be stored at room temperature (4 ^{o}C) for several months. The structures of the products were unambiguously deduced by spectral (^{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, protonattached to the phenyl moiety (D ring) appears as singlet at the range of 7.76 ppm as expected. Whereas, the methyl proton of the tosyl group attached to the nitrogen atom appears as singlet at 2.37 ppm. However, the remaining aromatic protons appear in the range of 8.10-7.24 ppm. Furthermore, ^{13}C-NMR and mass spectra gave additional support in the favour the structures.



Finally, the structural conclusion was supported by single crystal X-ray diffraction analysis of compound **2d.** The single crystal of the product was obtained by slow evaporation of solution of product dissolved in minimum volume of petroleum ether/dichloromethane mixture. The ORTEP diagram of the crystal structure is shown in Figure 6.

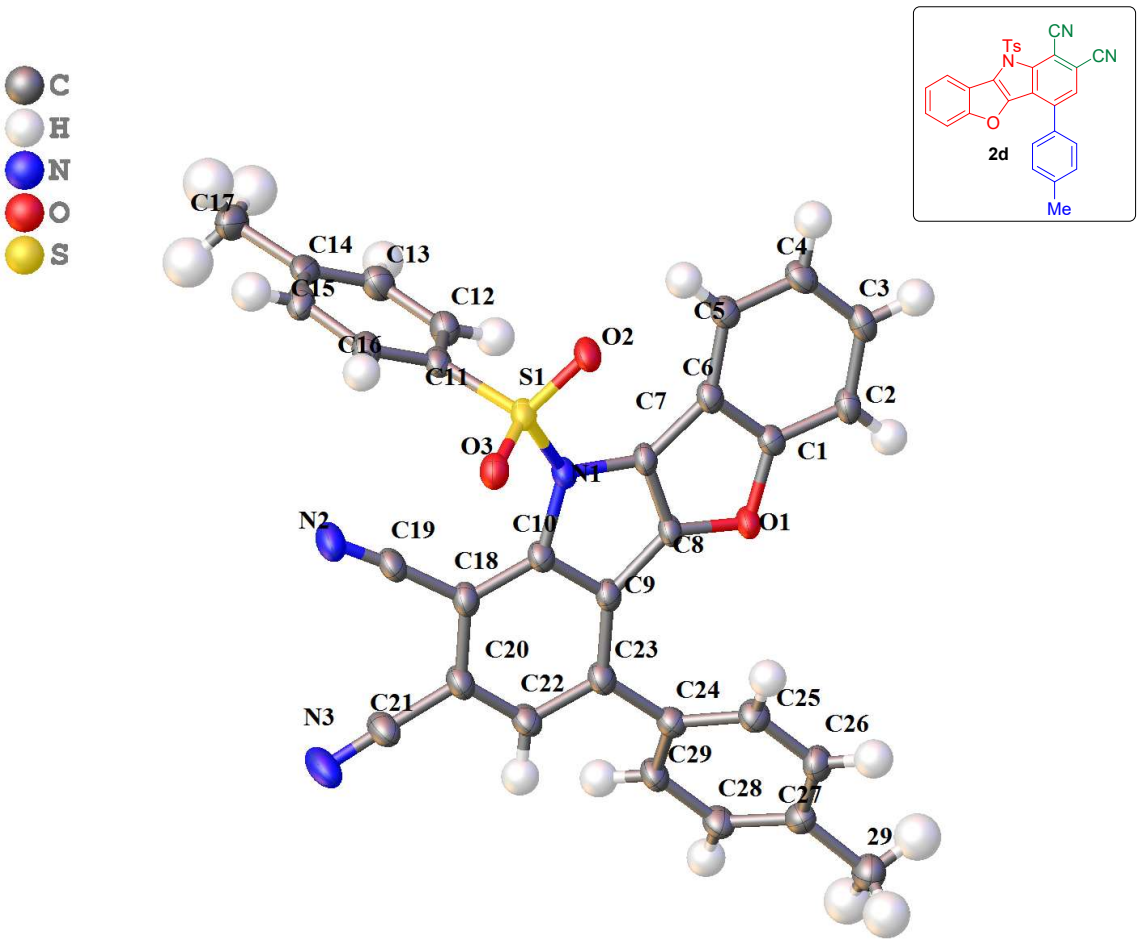


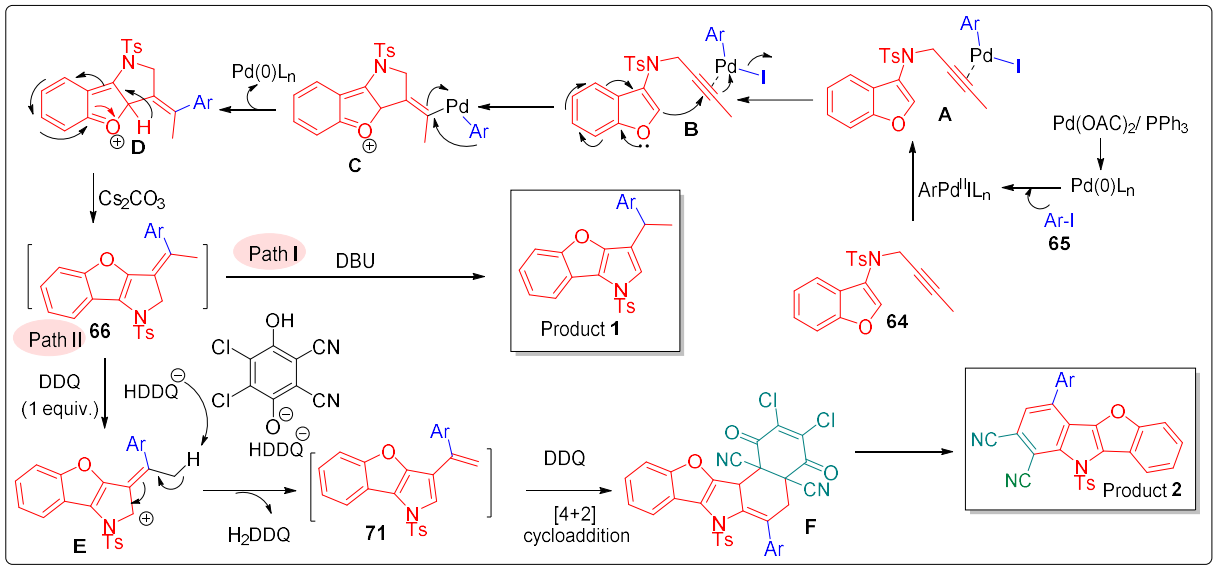
Figure 6: ORTEP Diagram (drawn at 50% propability level) of compound **2d**

Table 3: Important crystal data of product **2d**

Empirical formula	$C_{30}H_{19}N_3O_3S$
Formula weight	501.54
Temperature	273 K
Wavelength	1.54184
Crystal system	'triclinic'
Space group	'P -1'
Unit cell dimensions	a = 7.965(19) Å α = 117.24(13)
	b = 12.87(5) Å β = 91.14(13)
	c = 13.06(3) Å γ = 98.8(3)
Volume	1170(6) $Å^3$
Z	2
Density (calculated)	1.245 g/cm^3
Absorption coefficient (Mu)	1.557mm^{-1}
F(000)	520
Theta range for data collection	65.102-^{0} to 3.785°
Index ranges	-9<=h<=9, -15<=k<=15, -15<=l<=15
Reflection collected	20812
Independent reflections	3802 [R(int) = 0.0690]
Completeness to theta	99.9 %
Absorption correction	multi-scan
Max. and min. transmission	0.7456 and 0.6875
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3950/0/ 337
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0533, wR2 = 0.1398
R indices (all data)	R1 = 0.0545, wR2 = 0.1412
Largest diff. peak and hole	0.399& -0.461e.A^{-3}

The single crystal of compound **2d** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **2d** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **.**

3.2.5. Plausible mechanism of the formation of products 1 and 2:



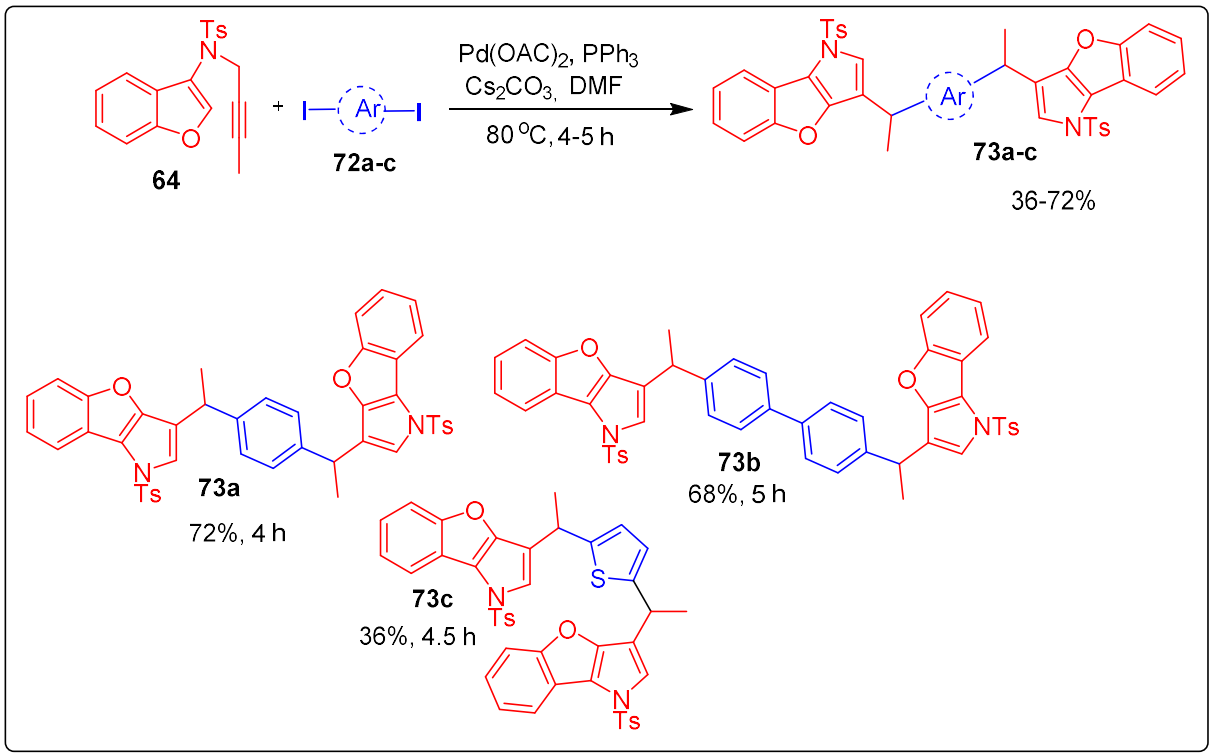
Scheme 22: Plausible reaction mechanism for the formation of products 1 and 2

Based on the experimental results and known Palladium chemistry,[34] a plausible reaction mechanism has been proposed in **Scheme 22**. First, Pd(0)[34] generated in situ from $Pd(OAc)_2$ and PPh_3 undergoes oxidative addition onto aryl iodide **65** resulting the formation of ArPd(II)I (**A**)[35] intermediate which subsequently coordinates with the triple bond of acetylenic substrate **64** to form an intermediate **B**. Then intermediate **B** undergoes intramolecular nucleophilic attack by C2 of the benzofuran moiety triggering the formation of vinyl palladium intermediate **C**. Next, reductive elimination of intermediate **C** led to the generation of intermediate **D** with the concomitant regeneration of Pd (0). Intermediate **D** undergoes deprotonation to yield the exocyclic intermediate **66**. Isomerisation of product **1** could easily be achieved after treatment of a base like DBU (**path-a**).

Next, in another reaction pathway (**path-b**), removal of a hydride ion from the exocyclic intermediate product **66** with the aid of DDQ generates intermediate **E** which upon deprotonation affords a di-ene intermediate **71** as shown in **Scheme 22**. Next, a [4+2]-cycloaddition of intermediate **71** with DDQ generates the cycloadduct **F** which finally furnishes the product **2**. The exact mechanism for the final step is still unknown to us and it is currently under our investigation.

3.2.6. Synthesis of bis-heteroannulated products73a-c:

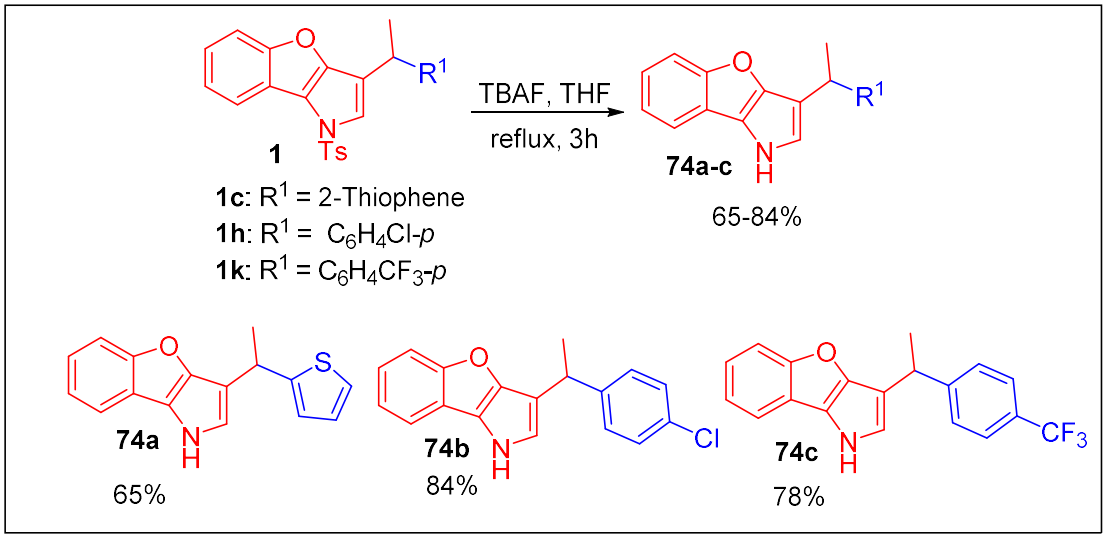
In view of the immense importance of bis-benzofuro[3,2-*b*]pyrroles which serve as core structure of bioactive alkaloids, attempts were made to check the feasibility of bis-heteroannulations by conducting the reaction of acetylene **64** with di-iodo compounds **72a-c** (**Scheme 33**). Accordingly, subsequent reactions of acetylenic substrate **64** with 1,4-diiodobenzene **72a,** 4,4'-diiodobiphenyl (**72b**), and 1,2-diiodothiophene (**72c**) were carried out under the optimized reaction conditions (of **Scheme 19**). Contrary to our previous observations (of **Scheme 19**), the bis-heteroannulated products **73a-c** (with isomerisation of the exocyclic double bond) were found to be formed under one-pot within 4-5 h with 36-72% yield (**Scheme 23**).



Scheme 23: Synthesis of bis-heteroannulated products **73a-c**

3.2.7. Synthesis of deprotected derivatives of 1:

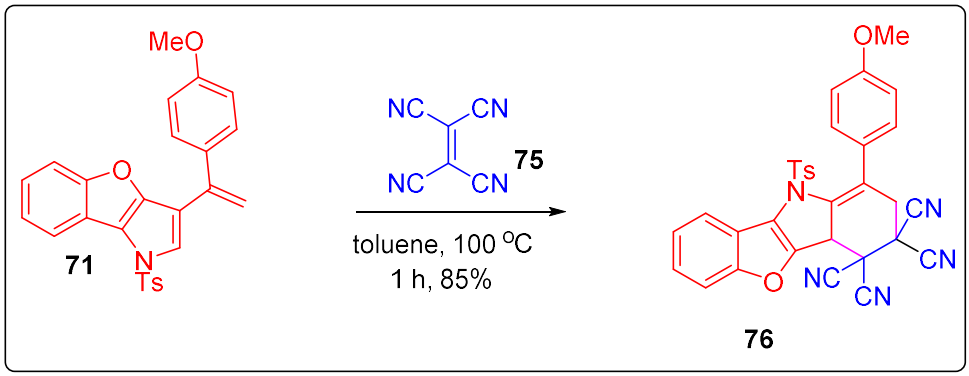
Thereafter, we became interested to make detosylation of the synthesized products **1** which could lead to the formations of benzofuro[3,2-*b*]pyrroles**74** having a free NH group which constitute the core structure of many bioactive compounds. To check the prospect of this reaction, compounds **1c/1h/1k** were exposed to tetrabutylammoniumfluride (TBAF) in refluxing THF (**Scheme 24**); gratifyingly, corresponding products **74a/74b/74c** were found to be formed easily within 3 h in 65-84% yield.



Scheme 24: N-Detosylation of products **1c/1h/1k**

3.2.8. Application of [4+2] cycloaddition reaction:

Besides, another diene intermediate **71** was isolated and it was allowed to react with tetracyanoethelene**75** in toluene at 100 ^{o}C. Pleasingly, the desired cycloadduct**76** was found to be formed within 1h with 85% yield.



Scheme 25: Synthesis of cycloadduct 76

3.2.9. Conclusions:

In conclusion, we have successfully developed a palladium(0)-catalyzed reactions followed by base induced isomerization for the general synthesis of benzofuro[3,2-*b*]pyrrole **1** using acetylenic substrate **64** and aryl iodides **65**. Addition of DDQ to the intermediate **66** was also compatible to this reaction, triggering the formation of benzofuro[3,2-*b*]indole**2** within 1.45-3 h with 52-81% yield. A plausible reaction mechanism is proposed to explain the product formations. The method is amenable to the synthesis of bis-heteroannulated products **73a-c** by using aryl/heteroaryldiiodides**72** instead of aryl iodides **65** thereby suggesting the viability of polyheteroannulation under one-pot. The hallmark of the method is operational simplicity, short reaction time, tolerance of various functional groups, and use of simple substrates.

3.2.10. Experimental section:

3.2.10.1. General information:

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 °C. CH_3CN (Acetonitrile) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. Tetrahydrofuran (THF) was distilled over sodium and benzophenone. Commercial grade dry DMF (Dimethylformamide), DMSO (Dimethyl sulfoxide), $CHCl_3$ (Chloroform), Toluene, EtOAcwere used as a solvent. 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 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 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), dt (doublet of triplet) m (multiplet), and brs (broad singlet). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF or EI mode. Reactions that require heating, oil bath containing of silicon oil is use as a heat source.

3.2.10.2. X-Ray crystallographic information of products 2d:

Single crystal of products **2d** were obtained through slow evaporation (at room temperature) of a solution in dichloromethane-petroleum ether or ethyl acetate- petroleum ether. A single crystal of **2d** 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 **2d** were measured with MoKα radiation (λ = 0.71073 Å) at 293 K. The structure was solved by direct methods using the SHELXS-97 program.[37] Refinements were carried out with a full matrix least squares method against F 2 using SHELXL-97.[38] 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. Important crystal data and ORTEP diagram (drawn at 50% probability level) of product **2d** are provided earlier.

3.2.10.3. General procedure for preparation of starting materials 64:

Synthesis of bromo derivatives ***68*** [39]

To a well-stirred solution of commertially available *o*-acetyl phenol derivatives (3.67 mmol, 1equiv) in $CHCl_3$ was added $CuBr_2$ (903 mg, 4.04 mmol, 1.1 eq) by dissolving in ethyl acetate (3 mL). The whole reaction mixture was heated under reflux for 5-7 h until the starting material was consumed. After completion of reaction (TLC), the reaction was diluted with ethyl acetate (10 mL) and it was filtered through celite. The crude product obtained after removal of the solvent under reduced pressure was then purified by silica gel (100-200) column chromatography

using 8% petroleum ether/ethyl acetate (v/v) as eluent to give the bromo intermediate **68** in 78-85% yields.

Synthesis of Coumaranone ***69*** [39]

The intermediate **68**(1.4 mmol, 1eq) was dissolved in MeCN (3.0 mL) under argon atmosphere and cooled to 0° C. Next, dry Et_3N (0.39 ml, 2.79 mmol, 2 eq) was added slowly to the reaction mixture. Afterthat the temperature of the mixture was raised to rt and the strring was continued for another 30-45 min. After completion of the reaction (TLC), the solution was quenched with water (30 mL) and extracted with DCM (3 × 30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (100-200) by using 3-5% ethyl acetate-petroleum ether (v/v) as eluent to afford the intermediate **69** in 81-88% yields.

Synthesis of N-(benzofuran-3-yl)-4-methylbenzenesulfonamide ***70*** [40]

Benzofuran-3(2*H*)-one **69** (1.49 mmol, 1 equiv), *p*-toluenesulfonamide (383 mg, 2.24 mmol, 1.5 equiv) and *p*-toluenesulfonic acid (0.07 mmol, 0.05 equiv) were dissolved in dry toluene (8 mL) and the mixture was then heated to reflux until the benzofuran-3(2*H*)-one was fully consumed (TLC). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (3x10 mL) and brine (3x10 mL), respectively. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After removing the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (with 8-10% ethyl acetate and petroleum ether as the eluent) to obtain the intermediate product **70** in 81-85% yield.

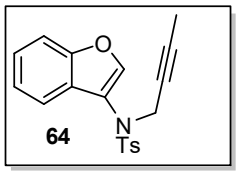
Synthesis of of N-(benzofuran-3-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide ***64*** [41]

The sulfonamidobenzofuran intermediate **70** (0.52 mmol, 1 equiv) was dissolved in dry DMF (5 .0 mL) and the reaction mixture was cooled to 0 °C under argon. Next, NaH (60% oil suspension in mineral oil; 27 mg, 0.67 mmol, 1.3 equiv) was added to the ice-cold solution of **70**. After stirring the reaction mixture for 10 min, propargyl bromide or 1-bromo-2-butyne (60 µl, 0.67 mmol, 1.3 equiv) was added dropwise to the reaction mixture. Next, the temperature of the reaction was allowed to reach at room temperature and the whole reaction mixture was stirred at rt (3-5 h) until completion (TLC). After quenching with water (2.0 mL), the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed

consecutively with brine water (10 mL) and dried over anhydrous sodium sulfate. After evaporation of solvent, the crude residue was purified by silica gel column chromatography with petroleum ether: ethyl acetate = 8:1 (v/v) as eluent to afford the products **64** in 78-85% yields.

3.2.10.4. Spectral data of substrate 64:

N-(benzofuran-3-yl)-N-(but-2-yn-1-yl)-4-methylbenzenesulfonamide (64):



64

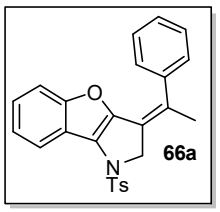
Brownish gummy liquid (19.1 mg, 78% yield); R_f= 0.48 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H7.65 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 1H), 7.47-7.43 (m, 2H), 7.31-7.21 (m, 1H), 7.23-7.18 (m, 3H), 4.42 (q, *J* = 2.4 Hz, 2H), 2.40 (s, 3H), 71.63 (t, *J* = 2.4 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 154.3, 143.9, 142.9, 135.6, 129.3, 128.3, 125.3, 125.1, 123.3, 122.3, 120.3, 111.9, 82.1, 73.7, 42.0, 21.7; HRMS (ESI+) m/z calculated for $C_{19}H_{18}NO_3S$ $[M+H]^+$ 340.1007, found 340.1007.

3.2.10.5. General procedure for the synthesis of intermediate 66:

An oven dried round bottomed flask was charged with $Pd(OAC)_2$ (1.32 mg, 7 mol%) and PPh_3 (3.1 mg, 14 mol%) followed by addition of dry DMF (1 mL) via syringe; the whole reaction mixture was allowed to stir at rt for 30 min under argon atmosphere. Then aryl iodide (**65**) (0.07 mmol, 1.2 equiv) was then added and the stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (0.06 mmol, 1 equiv.) and acetylenic substrate **64** (0.06 mmol, 1equiv) were added successively under argon. The whole reaction mixture was then heated at 80 °C (using oil bath) for 0.45-3.0 h until completion (TLC). The resulting mixture was then extracted with dichloromethane (3 × 10 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue obtained was purified by silica gel (100−200 mesh) column chromatography using 5−7% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **66** in upto 95% yields.

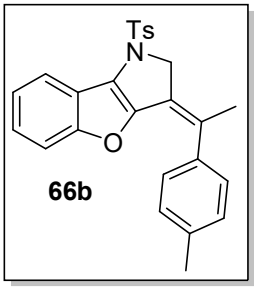
3.2.10.6. Spectral data of selective intermediate 66:

(*Z*)-3-(1-Phenylethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole (66a):



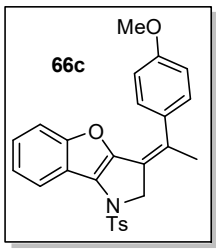
Brownish gummy liquid (19.1 mg, 78% yield); R_f= 0.48 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.15 (d, *J* = 4.8 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 2H), 7.37-7.31 (m, 4H), 7.29-7.22 (m, 6H), 4.81 (s, 2H), 2.38 (s, 3H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.4, 148.6, 143.9, 138.7, 132.7, 132.5, 131.4, 129.5, 128.6, 127.6, 127.5, 125.2, 123.5, 121.8, 120.4, 120.2, 118.9, 112.0, 60.1, 31.1, 22.2, 20.5; HRMS (ESI+) m/z calculated for $C_{25}H_{22}NO_3S$ $[M+H]^+$ 416.1320, found 416.1312.

(*Z*)-3-(1-(*p*-Tolyl)ethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole (66b):



Brown solid (20.2 mg, 80% yield); mp. 148-150 ^{o}C; R_f= 0.48 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.11 (dt, *J* = 1.2 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.32-7.26 (m, 3H), 7.22-7.16 (m, 6H), 4.79 (q, *J* = 1.9 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H), 1.99 (t, *J* = 1.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 158.9, 149.8, 144.3, 137.9, 137.2, 132.7, 132.0, 130.0, 128.7, 128.1, 127.6, 125.4, 124.0, 123.9, 120.6, 119.9, 119.6, 60.7, 21.6, 21.4, 21.2; HRMS (ESI+) m/z calculated for $C_{26}H_{24}NO_3S$ $[M+H]^+$ 430.1477, found 430.1471.

(*Z*)-3-(1-(4-Methoxyphenyl)ethylidene)-1-tosyl-2,3-dihydro-1*H*-benzofuro[3,2-*b*]pyrrole (66c)



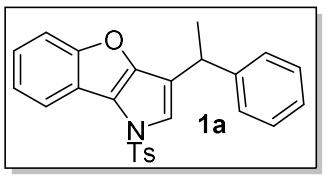
Brownish gummy liquid (21.5 mg, 94% yield); R_f= 0.54 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H8.13 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H),7.34-7.31 (m, 1H), 7.28-7.27 (m, 4H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.91-6.89 (m, 2H), 4.81 (s, 2H), 3.86 (s, 2H), 2.37 (s, 3H), 2.01 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 158.4, 158.3, 149.3, 143.8, 132.7, 131.9, 131.4, 129.4, 128.4, 127.6, 124.8, 123.4, 123.1, 120.0, 119.1, 118.9, 113.4, 112.8, 111.9, 60.1, 54.8, 21.1, 20.7; HRMS (ESI+) m/z calculated for $C_{26}H_{24}NO_4S$ $[M+H]^+$ 446.1426, found 416.1312.

3.2.10.7. General procedure for the synthesis of products 1a-n:

An oven dried round bottomed flask was charged with $Pd(OAC)_2$ (1.32 mg, 7 mol%) and PPh_3 (3.1 mg, 14 mol%) followed by addition of dry DMF (1 mL) via syringe; the whole reaction mixture was allowed to stir at rt for 30 min under argon atmosphere. Then aryl iodide (**65**) (0.07 mmol, 1.2 equiv) was then added and the stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (0.06 mmol, 1 equiv.) and acetylenic substrate **64** (0.06 mmol, 1equiv) were added successively under argon. The whole reaction mixture was then heated at 80 °C (using oil bath) for 0.45-3.0 h until completion (TLC). Afterthat, 2 equiv. of DBU was added to these reaction mixture and temperature increased to 120 ^oC for 3.0 h. The resulting mixture was then extracted with dichloromethane (3 × 10 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue obtained was purified by silica gel (100−200 mesh) column chromatography using 5−7% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **1** in 56-82% yields.

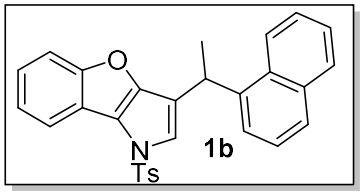
3.2.10.8. Spectral data of products 1a-n:

3-(1-Phenylethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1a):



Brownish gummy liquid (19.1 mg, 78% yield); R_f= 0.51 (10% ethyl acetate-petroleum ether,v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.07 (m, 1H), 7.71 (d, *J* = 8.8, 2H), 7.45-7.43 (m, 1H), 7.33-7.26 (m, 4H), 7.24-7.18 (m, 5H), 6.92 (d, *J* = 1.2Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 1.67 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 151.1, 140.2, 145.0, 144.5, 135.4, 130.0, 128.6, 127.3, 126.9, 126.7, 123.8, 123.4, 121.4, 118.97, 118.88, 112.5, 100.0, 36.4, 21.66, 21.55; HRMS (ESI+) m/z calculated for $C_{25}H_{22}NO_3S$ $[M+H]^+$ 416.1320, found 416.1312.

3-(1-(Naphthalen-1-yl)ethyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole (1b):

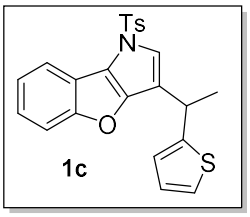


Brownish gummy liquid (18.9 mg,69% yield); R_f= 0.48 (10% ethyl acetate-petroleum ether,v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.11-8.09 (m, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.2Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.50-7.26 (m, 7H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 1.2 Hz, 1H), 4.97 (q, *J* = 7.07 Hz, 1H), 2.33 (s, 3H), 1.82 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 151.2, 144.9,

140.0, 135.3, 134.1, 131.2, 130.0, 129.1, 127.5, 126.8, 126.0, 125.7, 125.5, 124.1, 123.9, 123.5, 123.4, 122.3, 121.5, 120.9, 119.1, 118.9, 112.6, 31.8, 21.66, 21.0; HRMS (ESI+) m/z calculated for $C_{29}H_{24}NO_3S$ $[M+H]^+$ 466.1477, found 466.1455.

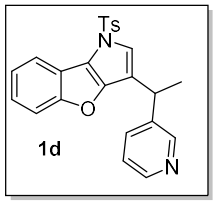
3-(1-(Thiophen-2-yl)ethyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole(1c)

Brownish gummy liquid (13.9 mg, 56% yield); R_f= 0.47 (10% ethyl acetate-petroleum ether,v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.48-7.45 (m, 1H), 7.34-7.27 (m, 2H), 7.21-7.18 (m, 2H), 7.14 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.00 (d, *J* = 0.8 Hz, 1H), 6.92-6.90 (m, 1H), 6.85-6.84 (m, 1H), 4.43 (d, *J* = 7.1 Hz, 1H), 2.33 (s, 3H), 1.76 (d, *J* = 7.2 Hz,, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.5, 148.4, 145.1, 135.4, 130.1, 129.3, 128.6, 127.3, 126.9, 126.8, 124.0, 123.9, 123.7, 123.5, 121.3, 121.0, 118.93, 118.90, 112.6, 31.8, 22.5, 21.7; HRMS (ESI+) m/z calculated for $C_{23}H_{20}NO_3S_2$ $[M+H]^+$ 422.0885, found 422.0884.



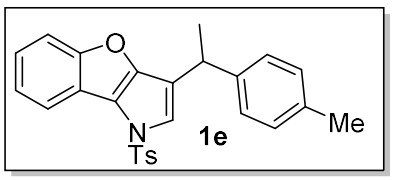
3-(1-(Pyridin-3-yl)ethyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole (1d)

Brownish gummy liquid (10.3 mg, 42% yield); R_f= 0.51 (10% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.46-7.43 (m, 2H), 7.33-7.26 (m, 4H), 7.24-7.22 (m, 2H), 7.20-7.18 (m, 2H), 6.92 (d, *J* = 1.2 Hz, 1H), 4.14 (q, *J* = 7.07 Hz, 1H), 2.33 (s, 3H), 1.67 (d, *J* = 7.2 Hz,, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 151.1, 145.0, 144.5, 134.4, 130.0, 128.6, 127.3, 126.9, 126.7, 123.8, 123.4, 121.4, 120.9, 119.0, 118.9, 112.5, 100.0, 36.4, 21.66, 21.55; HRMS (ESI+) m/z calculated for $C_{24}H_{21}N_2O_3S$ $[M+H]^+$ 417.1273, found 417.1269.



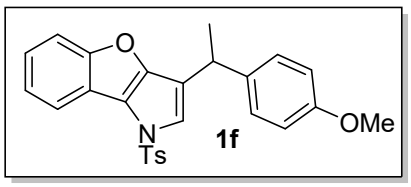
3-(1-(*p*-Tolyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1e)

Brownish gummy liquid (20.2 mg, 80% yield); R_f= 0.67 (10% ethyl acetate-petroleum ether,v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.46-7.44 (m, 1H), 7.33-7.29 (m, 1H), 7.27-7.22 (m, 1H), 7.20-7.18 (m, 2H), 7.15-7.08 (m, 4H), 6.92 (d, *J* = 0.8 Hz,



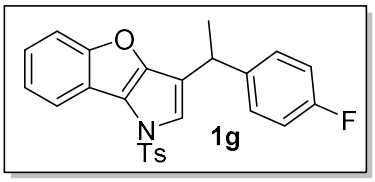
1H), 4.11 (q, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 151.1, 145.0, 141.5, 136.2, 135.5, 130.1, 129.3, 127.2, 126.9, 123.8, 123.4, 121.6, 121.4, 119.0, 118.9, 112.6, 36.0, 21.66, 21.60, 21.11; HRMS (ESI+) m/z calculated for $C_{26}H_{24}NO_3S$ $[M+H]^+$ 430.1477, found 430.1468.

3-(1-(4-Methoxyphenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1f)



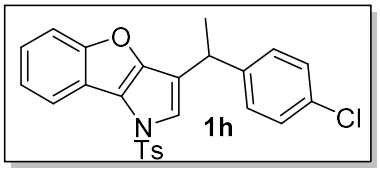
Yellowish gummy liquid (21.5 mg, 82% yield); R_f= 0.39 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.08 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.46-7.44 (m, 1H), 7.33-7.29 (m, 1H), 7.26-7.22 (m, 1H), 7.20-7.18 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 1.2 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.33 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 158.3, 151.1, 145.0, 136.6, 135.5, 130.07, 130.02, 128.2, 126.9, 123.8, 123.4, 121.8, 121.3, 120.9, 118.99, 118.86, 114.0, 112.5, 55.3, 35.6, 21.67, 21.26; HRMS (ESI+) m/z calculated for $C_{26}H_{24}NO_4S$ $[M+H]^+$ 446.1426, found 446.1410.

3-(1-(4-Fluorophenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1g):



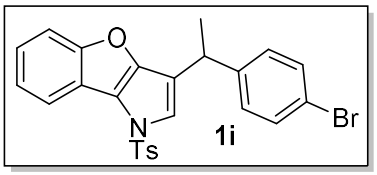
Brownish gummy liquid (16.6 mg, 65% yield); R_f= 0.54 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 1H), 7.72 (d, *J* = 8.4, 2H), 7.45-7.43 (m, 1H), 7.34-7.25 (m, 2H), 7.23-7.17 (m, 4H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 1.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.33 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 162.6 (d, *J* = 245.0 Hz), 159.3, 150.8, 145.1, 140.2 (d, *J* = 3.0 Hz), 135.4, 130.0, 128.7 (d, *J* = 8.0 Hz), 126.9, 123.9, 123.5, 121.2, 121.0, 118.9, 115.4, (d, *J* = 21.0 Hz), 112.5, 35.7, 21.66, 21.62 ; HRMS (ESI+) m/z calculated for $C_{25}H_{21}FNO_3S$ $[M+H]^+$ 434.1226, found 434.1223.

3-(1-(4-Chlorophenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1h):



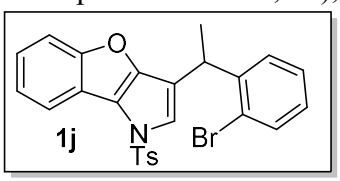
Brownish gummy liquid (19.8 mg, 75% yield); R_f= 0.52 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.45-7.43 (m, 1H), 7.32 (td, *J* = 1.2 Hz, 1H), 7.27-7.25 (m, 1H), 7.245-7.22 (m, 2H), 7.20-7.18 (m, 2H), 7.17-7.15 (m, 2H), 6.92 (d, *J* = 1.2 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 145.1, 143.0, 135.4, 132.4, 130.1, 128.8, 128.7, 126.9, 124.0, 123.5, 121.2, 120.99, 120.75, 118.93, 118.89, 112.6, 35.9, 21.67, 21.44; HRMS (ESI+) m/z calculated for $C_{25}H_{21}ClNO_3S$ $[M+H]^+$ 450.0931, found 450.0916.

3-(1-(4-Bromophenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1i)



Brownish gummy liquid (22.7 mg, 78% yield); R_f= 0.56 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.45-7.43 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34-7.25 (m, 2H), 7.20-7.18 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 0.8 Hz, 1H), 4.09 (q, *J* = 7.3 Hz, 1H), 2.34 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 145.1, 143.6, 135.4, 131.7, 130.1, 129.1, 126.9, 124.0, 123.5, 121.2, 121.0, 120.6, 120.4, 118.93, 118.88, 112.6, 35.9, 21.68, 21.38; HRMS (ESI+) m/z calculated for $C_{25}H_{21}BrNO_3S$ $[M+H]^+$ 494.0426, found 494.0411.

3-(1-(2-Bromophenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1j)

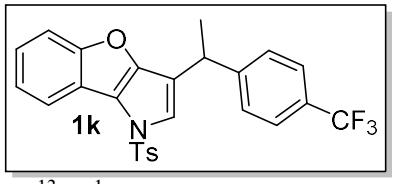


Brownish gummy liquid (21.8 mg, 75% yield); R_f= 0.65 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.07 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.45-7.43 (m, 5H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34-7.27 (m, 2H), 7.23-7.15 (m, 2H), 6.92 (d, *J* = 1.2 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 145.1, 143.0, 135.4, 132.4, 130.1, 128.75, 128.66, 126.9, 124.0, 123.5, 121.2, 121.0,

120.8, 120.4, 118.93, 118.89, 112.6, 35.9, 21.67, 21.44; HRMS (ESI+) m/z calculated for $C_{25}H_{21}BrNO_3S$ $[M+H]^+$ 494.0426, found 494.0411.

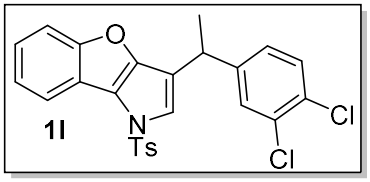
1-Tosyl-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-1*H*-benzofuro[3,2-*b*]pyrrole (1k)

Brownish gummy liquid (19.4 mg, 68% yield); R_f= 0.47 (10% ethyl acetate-petroleum ether,v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.72 (d, *J* = 8.4Hz, 2H), 7.52 (*J* = 8.0 Hz, 2H), 7.45-7.43 (m, 1H), 7.36-7.25 (m, 4H), 7.21-7.19 (m, 2H), 6.95 (d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 1H), 2.34 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.6, 148.6, 145.2, 135.4, 130.1, 127.6, 126.7, 126.9, 125.6 (q, *J* = 4.0 Hz), 124.0, 123.6, 121.2, 121.1, 120.2, 119.0, 118.9, 112.6, 36.3, 21.66, 21.34; HRMS (ESI+) m/z calculated for $C_{26}H_{21}F_3NO_3S$ $[M+H]^+$ 484.1194, found 484.1181.



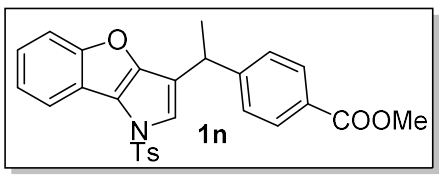
3-(1-(3,4-Dichlorophenyl)ethyl)-1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrole (1l)

Brownish gummy liquid (20.5 mg, 72% yield); R_f= 0.49 (10% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.46-7.43 (m, 1H), 7.34-7.31 (m, 2H), 7.28-7.24 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.09-7.07 (m, 1H), 6.95 (d, *J* = 1.2 Hz, 1H), 4.09 (q, *J* = 7.3 Hz, 1H), 2.34 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.5, 145.2, 144.9, 135.3, 132.5, 130.6, 130.1, 129.3, 126.9, 126.8, 124.1, 123.6, 121.2, 120.0, 118.98, 118.84, 112.6, 100.0, 35.7, 21.69, 21.29; HRMS (ESI+) m/z calculated for $C_{25}H_{20}Cl_2NO_3S$ $[M+H]^+$ 484.0541, found 484.0536.



Methyl 4-(1-(1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrol-3-yl)ethyl)benzoate (1n)

Brownish gummy liquid (19.5 mg, 70% yield); R_f= 0.59 (10% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.07 (m, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.44-7.42 (m, 1H), 7.33-7.27 (m, 4H), 7.20-7.18 (m, 2H), 6.93 (d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.07 Hz, 1H), 3.89 (s, 3H), 2.34 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 167.0, 159.3, 150.7, 149.8, 145.2, 135.4, 130.1, 130.0, 128.7, 127.4, 126.9, 124.0, 123.5, 121.2, 121.0, 120.4, 118.93,



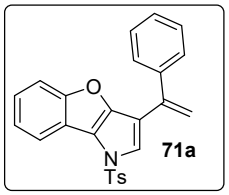
118.87, 112.6, 52.1, 36.5, 21.67, 21.26 ; HRMS (ESI+) m/z calculated for $C_{27}H_{24}NO_5S$ $[M+H]^+$ 474.1375, found 474.1370.

3.2.10.9. Synthesis of intermediate di-ene 71:

DDQ (11.4 mg, 0.05 mmol, 1 equiv.) was added to a well-stirred solution of **66** (20 mg, 0.05 mmol, 1 equiv.) in dry Toluene (2 ml) and the mixture was stirred for 1 h at 100 °C. The reaction mixture was quenched with 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 di-ene intermediated products **71** in 65−67% yield.

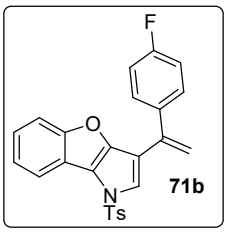
3.2.10.10. Spectral data of selective intermediated products 71:

3-(1-Phenylvinyl)-1-tosyl-1*H*-benzofuro[3,2-b]pyrrole (71a)



Brown solid (21.5 mg, 75% yield); mp. 154-156 °C; R_f= 0.29 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.16-8.14 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.55-7.53 (m, 1H), 7.39-7.30 (m, 7H), 7.22-7.20 (m, 2H), 6.97 (s, 1H), 5.99 (s, 1H), 5.43 (d, *J* = 0.8 Hz, 1H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.4, 149.9, 145.4, 138.6, 135.3, 134.1, 130.2, 129.4, 128.8, 127.0, 124.3, 123.7, 122.5, 121.2, 119.1, 118.6, 116.9, 116.8, 112.7, 100.0, 21.7; HRMS (ESI+) m/z calculated for $C_{25}H_{20}NO_3S$ $[M+H]^+$414.1164, found 414.1160.

3-(1-(4-fluorophenyl)vinyl)-1-tosyl-1H-benzofuro[3,2-*b*]pyrrole (71b)



Brown solid (21.5 mg, 75% yield); mp. 154-156 °C; R_f= 0.29 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.16-8.14 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.55-7.53 (m, 1H), 7.40-7.30 (m, 4H), 7.22-7.19 (m, 2H), 7.08 (t, J = 8.8 Hz, 2H), 6.98 (s, 1H), 5.98 (d, *J* = 0.8 Hz, 1H), 5.41 (d, *J* = 0.8 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 162.8 (d, *J* = 246 Hz), 159.4, 150.0, 145.4, 138.6, 136.1 (d, *J* = 3 Hz), 135.3, 130.2, 129.7 (d, *J* = 8.0 Hz), 127.0,

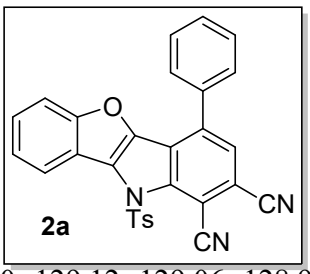
124.3, 123.7, 122.6, 121.2, 119.1, 118.7, 117.2, 116.5, 115.5 (d, J = 22 Hz), 112.7, 21.7; HRMS (ESI+) m/z calculated for $C_{25}H_{19}FNO_3S$ $[M+H]^+$432.1070, found 432.1066.

3.2.10.11. General procedure for the synthesis of products 2a-j:

An oven dried round bottomed flask was charged with $Pd(OAC)_2$ (0.92 mg, 7 mol %) and PPh_3 (2.2 mg, 14 mol %) followed by addition of dry DMF (1 mL) *via* syringe; the whole reaction mixture was allowed to stir at rt for 30 min under argon atmosphere. Then aryl iodide (**65**) (0.07 mmol, 1.2 equiv) was then added and the stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (0.06 mmol, 1equiv.) and acetylenic substrate **64** (0.06 mmol, 1equiv) were added successively under argon. The whole reaction mixture was then heated at 80 °C (using oil bath) for 0.45-3.0 h until completion (TLC). The resulting mixture was allowed to evaporated to dryness. Afterthat, to a well-stirred solution of **66** (0.05 mmol) in dry toluene (1.5 mL), DDQ (34.1 mg, 0.15 mmol) was added under argon atmosphere. Then reaction mixture was heated using an oil bath at 100 °C until completion (TLC). Then the solvent was evaporated in vacuo, and the reaction was quenched with a saturated solution of sodium bicarbonate. Then the resulting reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product obtained was purified through silica gel column chromatography using 10-20% ethyl acetate-petroleum ether (v/v) as eluting solvent to obtain products **2**.

3.2.10.12. Spectral data of products 2a-2j:

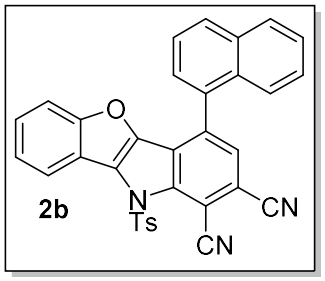
4-Phenyl-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2a):



2a

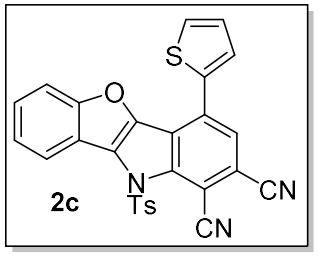
Brown solid (21.5 mg, 75% yield); mp. 154-156 ^oC; R_f= 0.29 (10% ethyl acetate-petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H8.44-8.40 (m, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.69-7.66 (m, 2H), 7.62-7.54 (m, 4H), 7.52-7.45 (m, 2H), 7.26-7.25 (m, 1H), 7.24-7.23 (m, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 160.0, 146.4, 143.7, 138.2, 136.9, 135.7, 134.3, 131.3, 130.3, 130.0, 129.12, 129.06, 128.9, 127.7, 127.6, 124.8, 122.3, 120.7, 118.1, 116.6, 114.5, 114.0, 113.2, 102.3, 21.8; HRMS (ESI+) m/z calculated for $C_{29}H_{18}N_3O_3S$ $[M+H]^+$488.1069, found 488.1066.

4-(Naphthalen-1-yl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2b):



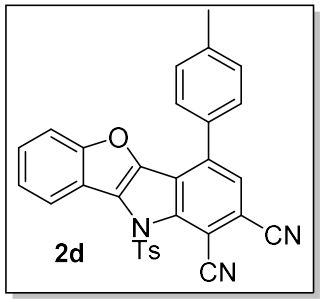
Brown solid (16.4 mg, 52% yield); mp. 130-132 ^{o}C; R_f= 0.20 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.40-8.37 (m, 1H), 8.07-7.99 (m, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.62-7.36 (m, 5H), 7.29-7.27 (m, 2H), 7.00-6.96 (m, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C145.2, 144.7, 143.7, 140.6, 137.3, 135.6, 133.4, 133.1, 131.0, 130.1, 129.1, 128.6, 127.6, 127.4, 126.6, 122.2, 119.8, 118.8, 115.2, 109.0, 108.5, 100.0, 20.8; HRMS (ESI+) m/z calculated for $C_{33}H_{19}N_3NaO_3S$ $[M+H]^+$ 560.1045, found 560.1034.

4-(Thiophen-2-yl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2c)



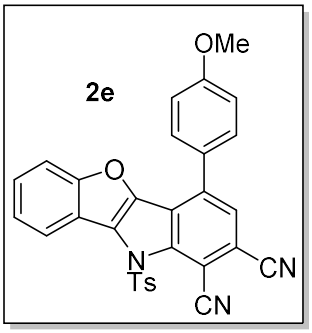
Brownish gummy liquid (15.7 mg, 54% yield); R_f= 0.48 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.44-8.42 (m, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.74-7.72 (m, 3H), 7.60-7.54 (m, 4H),7.52-7.46 (m, 2H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C160.0, 146.5, 134.6, 134.4, 132.4, 130.4, 130.3, 128.7, 127.8, 124.9, 122.4, 113.3, 21.8; HRMS (ESI+) m/z calculated for $C_{27}H_{16}N_3O_3S_2$ $[M+H]^+$ 494.0633, found 494.0625.

4-(*p*-Tolyl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2d):



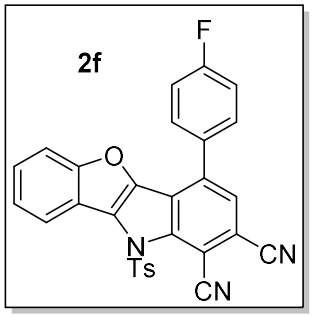
Yellowish solid (23.0 mg, 78% yield); mp. 150-152 ^{o}C; R_f= 0.29 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.43-8.40 (m, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.74 (s, 1H), 7.59-7.56 (m, 3H), 7.50-7.46 (m, 2H), 7.40-7.38 (m, 2H), 7.23-7.22 (m, 1H), 2.49 (s, 3H), 2.36 (s, 3H) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.9, 146.3, 140.3, 138.3, 137.0, 134.3, 132.8, 131.1, 130.3, 129.9, 129.0, 128.8, 127.7, 127.5, 124.7, 122.3, 120.6, 118.2, 116.6, 114.5, 114.1, 113.2, 102.0, 100.0, 21.8, 21.5; HRMS (ESI+) m/z calculated for $C_{30}H_{20}N_3O_3S$ $[M+H]^+$ 502.1225, found 502.1220

4-(4-Methoxyphenyl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2e):



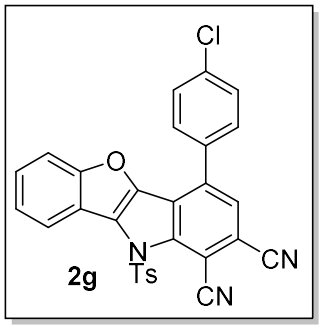
Brown solid (24.7 mg, 81% yield); mp. 160-162 °C; R_f= 0.18 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.41-8.39 (m, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H),7.58-7.56 (m, 1H), 7.51-7.44 (m, 2H), 7.24-7.22 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 1H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 161.2, 159.9, 146.3, 143.9, 138.1, 137.0, 134.3, 131.0, 130.33, 130.26, 128.7, 128.0, 127.7, 127.4, 122.2, 120.5, 118.2, 116.7, 114.6, 114.5, 114.2, 113.2, 101.6, 55.6, 21.8; HRMS (ESI+) m/z calculated for $C_{30}H_{19}N_3NaO_4S$ $[M+H]^+$ 540.0994, found 540.0983.

4-(4-Fluorophenyl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2f):



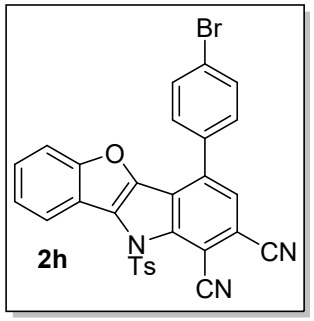
Brownish gummy liquid (20.0 mg, 67% yield); R_f= 0.49 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H8.23 (s, 1H), 8.16-8.12 (m, 2H), 8.07-8.05 (m, 1H), 7.69-7.56 (m,5H),7.46-7.31 (m, 5H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C146.3, 131.9 (*J* = 9 Hz), 130.5, 128.5, 127.3, 124.9, 124.0, 119.1, 115.9 (*J* = 22 Hz), 114.9, 113.8, 21.8 ; HRMS (ESI+) m/z calculated for $C_{29}H_{17}FN_3O_3S$ $[M+H]^+$ 506.0975, found 506.0972.

4-(4-Chlorophenyl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2g):



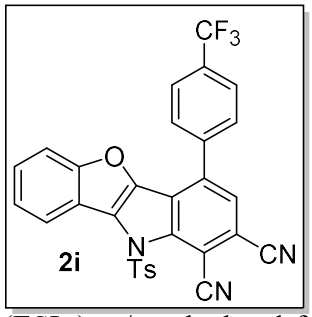
Brown solid (21.8 mg, 71% yield); mp. 120-122 °C; R_f= 0.18 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.43-8.41 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.63-7.56 (m, 6H),7.52-7.46 (m, 2H), 7.27 (s, 1H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 160.0, 146.5, 143.3, 136.77, 136.70, 136.4, 134.4, 134.1, 130.3, 130.2, 129.4, 128.7, 127.8, 124.9, 122.4, 120.4, 118.0, 116.5, 114.6, 113.9, 113.3, 100.0, 21.8; HRMS (ESI+) m/z calculated for $C_{29}H_{17}ClN_3O_3S$ $[M+H]^+$522.0679, found 522.0672.

4-(4-Bromophenyl)-10-tosyl-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2h):



Brown solid (23.3 mg, 70% yield); mp. 148-150 °C; R_f= 0.36 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H8.23 (s, 1H), 8.21-8.18 (m, 1H), 7.76-7.73 (m, 2H), 7.71-7.69 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.62-7.58 (m, 2H), 7.54-7.51 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ_C 159.6, 147.1, 144.9, 138.17, 138.13, 135.7, 133.3, 131.0, 130.9, 130.7, 130.4, 129.53, 129.46, 128.3, 127.4, 125.5, 121.8, 121.5, 118.2, 117.2, 114.5, 114.3, 113.9, 102.8, 100.0, 21.6; HRMS (ESI+) m/z calculated for $C_{29}H_{17}BrN_3O_3S$ $[M+H]^+$ 566.0174, found 566.0169.

10-Tosyl-4-(4-(trifluoromethyl)phenyl)-10*H*-benzofuro[3,2-*b*]indole-1,2-dicarbonitrile (2i):



Brown solid (21.3 mg, 65% yield); mp. 152-154 °C; R_f= 0.22 (10% ethyl acetate-petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.16-8.14 (m, 1H), 8.03-7.99 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.59-7.56 (s,1H),7.40-7.35 (m, 2H), 7.27-7.25 (m, 3H), 7.23-7.18 (m, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C156.4, 144.2, 143.4, 138.1, 135.2, 133.5, 130.5, 129.3, 129.1, 128.5, 128.2, 127.6, 125.5, 121.1, 116.9, 111.8, 100.0, 21.4; HRMS (ESI+) m/z calculated for $C_{30}H_{17}F_3N_3NaO_3S$ $[M+H]^+$578.0762, found 578.0784.

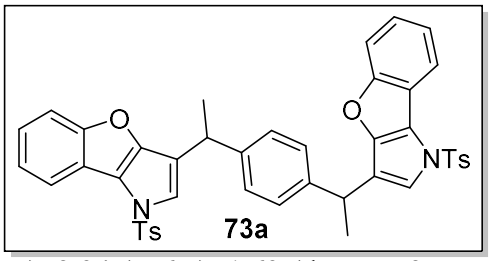
3.2.10.13. General procedure for the synthesis of bisheteroannulated products 73:

An oven dried round bottomed flask was charged with$Pd(OAC)_2$(0.93 mg, 7 mol%) and PPh_3 (2.16 mg, 14 mol%) in dry DMF (2 mL) and the whole reaction mixture was stirred at rt under argon atmosphere for 30 min. Then diaryl iodide **72** (0.06 mmol) was added and stirring was continued for another 30 min at rt. Next, Cs_2CO_3 (19.2 mg, 1 equiv.), and propargylic substrate **64** (0.1 mmol) were added successively to the reaction mixture under argon atmosphere. The whole reaction mixture was allowed to stir at 100 °C (using oil bath) for 2-3 h until completion (TLC). The resulting mixture was extracted with dichloromethane (3 × 20 mL) and washed with water (10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under

reduced pressure. The crude residue obtained after removal of DMF was purified by silica gel (100−200 mesh) column chromatography using 5-9% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired products **73** in 65-68% yields.

3.2.10.14. Spectral data of products 73a-c:

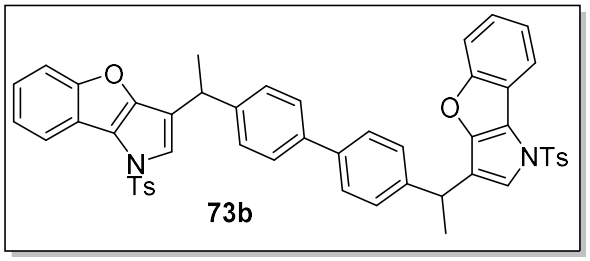
1,4-Bis(1-(1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrol-3-yl)ethyl)benzene (73a):



73a

Brownish gummy liquid (32 mg, 72% yield); R_f= 0.49 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.08 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.71 (d, *J* = 8.4, 4H), 7.58 (d, *J* = 8.4, 3H), 7.45-7.43 (m, 1H), 7.34-7.27 (m, 2H), 7.20-7.18 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 4H), 6.91 (d, *J* = 0.8 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 6H), 1.63 (d, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 145.1, 144.3, 137.7, 135.4, 130.1, 129.4, 128.6, 127.3, 126.9, 124.0, 123.5, 121.2, 121.0, 120.6, 118.92, 118.88, 112.6, 91.9, 36.0, 21.68, 21.34; HRMS (ESI+) m/z calculated for $C_{44}H_{37}N_2O_6S_2$ $[M+H]^+$ 753.2093, found 753.2088.

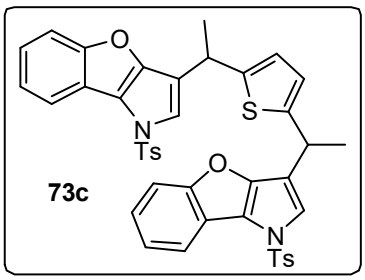
1,4-Bis(1-(1-tosyl-1*H*-benzofuro[3,2-*b*]pyrrol-3-yl)ethyl)benzene (73b):



73b

Brownish gummy liquid (33.2 mg, 68% yield); R_f= 0.49 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.08 (m, 2H), 7.74-7.72 (m, 5H), 7.46-7.44 (m, 4H), 7.32-7.28 (m, 10H), 7.21-7.18 (m, 3H), 6.96 (d, 1.2 Hz, 2H), 4.18(q, *J* = 7.2 Hz, 2H), 2.33 (s, 6H), 1.70(d, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.9, 145.1, 144.2, 140.5, 138.4, 137.9, 135.5, 130.1, 128.95, 127.9, 127.1, 126.9, 123.9, 123.5, 121.3, 121.0, 120.94, 118.94, 118.91, 112.6, 93.0, 36.1, 21.68, 21.51; HRMS (ESI+) m/z calculated for $C_{50}H_{41}N_2O_6S_2$ $[M+H]^+$ 829.2406, found 829.2401.

2,5-bis(1-(1-tosyl-1H-benzofuro[3,2-b]pyrrol-3-yl)ethyl)thiophene (73c)



73c

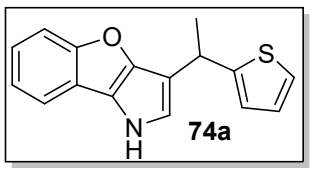
Brownish gummy liquid (16.1 mg,36% yield); R_f= 0.49 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.10-8.07 (m, 2H), 7.71 (d, *J* = 7.4 Hz, 4H), 7.45-7.43 (m, 2H), 7.31-7.25 (m, 5H), 7.22-7.18 (m, 5H), 6.92 (d, 0.8 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 6H), 1.67(d, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 151.1, 145.0, 144.5, 135.4, 133.1, 130.0, 129.3, 128.6, 128.4, 128.2, 127.9,127.3, 127.2, 126.9, 126.7, 123.8, 123.4, 121.9, 121.4, 120.9, 118.97, 118.88, 118.85, 112.54, 100.0, 36.4, 21.66, 21.55; HRMS (ESI+) m/z calculated for $C_{42}H_{35}N_2O_6S_3$ $[M+H]^+$ 759.1657, found 759.1650.

3.2.10.15. Procedure for the preparation of detosylated products 74:

To a well-stirred solution of **1c**, **1h** or **1k** (0.05mmol, 1 equiv) in dry THF (2 ml) was added tetrabutyl-ammonium fluoride (1 M solution in THF, 5 equiv), and the mixture was stirred for 3 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 **74a-c** in 65−84% yield.

3.2.10.16. Spectral data of products 74a-c:

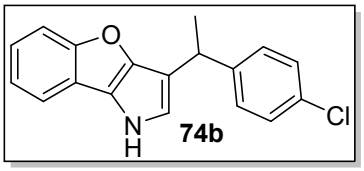
3-(1-(Thiophen-2-yl)ethyl)-1*H*-benzofuro[3,2-*b*]pyrrole (74a)



74a

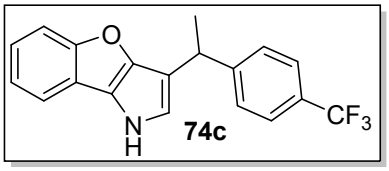
Brownish gummy liquid (8.2 mg, 65% yield); R_f= 0.53 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H7.99 (brs, 1H), 7.51-7.46 (m, 2H), 7.21-7.12 (m, 3H), 6.94-6.91 (m, 2H), 6.67 (d, *J* = 2.4 Hz, 1H), 4.52 (q, *J* = 7.07 Hz, 1H), 1.83 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.8, 148.7, 129.1, 128.5, 127.4, 127.2, 126.6, 123.5, 123.2, 122.27, 122.25, 120.3, 119.3, 118.8, 116.7, 113.2, 112.5, 31.9, 23.4; HRMS (ESI+) m/z calculated for $C_{16}H_{14}NOS$ $[M+H]^+$ 268.0796, found 268.0790.

3-(1-(4-Chlorophenyl)ethyl)-1*H*-benzofuro[3,2-*b*]pyrrole (74b)



Brownish gummy liquid (11.0 mg, 84% yield); R_f= 0.38 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H7.97 (brs, 1H), 7.50-7.45 (m, 2H), 7.31-7.28 (m, 2H), 7.27-7.26 (m, 1H), 7.25-7.24 (m, 1H), 7.21-7.16 (m, 2H), 6.57-6.56 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 1H), 1.72 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 149.0, 145.1, 131.8, 128.77, 128.55, 122.31, 122.28, 120.4, 119.3, 118.7, 116.7, 112.9, 112.5, 36.0, 22.3; HRMS (ESI+) m/z calculated for $C_{18}H_{15}ClNO$ $[M+H]^+$ 296.0842, found 296.0836.

3-(1-(4-(Trifluoromethyl)phenyl)ethyl)-1*H*-benzofuro[3,2-*b*]pyrrole (74c)



Brownish gummy liquid (10.9 mg, 78% yield); R_f= 0.28 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.01 (brs, 1H), 7.55-7.45 (m, 6H), 7.22-7.14 (m, 2H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 1H), 1.76 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 159.3, 150.7, 148.9, 128.6, 128.3, 127.7, 125.8, 125.4 (q, *J* = 3.67 Hz), 123.1, 122.4, 122.3, 120.5, 119.2, 118.7, 116.7, 112.5, 112.4, 36.5, 22.1; HRMS (ESI+) m/z calculated for $C_{19}H_{15}F_3NO$ $[M+H]^+$ 330.1106, found 330.1100.

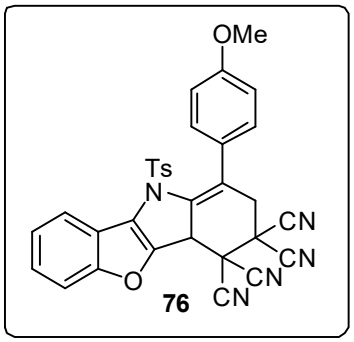
3.2.10.17. Procedure for the preparation of cycloadduct product 76:

To a solution of **72c** (0.048 mmol, 1 equiv) in dry Toluene (2 ml), tetracyanoethylene**75** was added and the mixture was stirred for 1 h at 100 ^{o}C under argon atmosphere. After completion of the reaction (TLC), reaction was quenched with 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 cycloadduct products **76** in 85% yield.

3.2.10.18. Spectral data of product 76:

1-(4-Methoxyphenyl)-10-tosyl-4a,10-dihydro-2*H*-benzofuro[3,2-*b*]indole-3,3,4,4-tetracarbonitrile

Brownish gummy liquid (21.8 mg, 85% yield); R_f= 0.27 (10% ethyl acetate-petroleum ether,v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H8.14-8.11 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.41-7.39 (m, 2H), 7.34-7.25 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.22 (t, *J* = 2.0 Hz, 1H), 3.86 (s, 3H), 3.76 (dd, J = 18.4, 2.0Hz, 1H), 3.38 (18.2, 1.6 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ_C 161.0, 159.7, 147.2, 146.5, 134.7, 130.6, 129.3, 129.0, 128.8, 127.7, 127.0, 125.0, 121.5, 120.7, 119.1, 117.8, 114.4, 113.0, 111.1, 110.5, 109.7, 107.8, 69.9, 55.6, 44.7, 40.2, 38.0, 21.8, 14.3; HRMS (ESI+) m/z calculated for $C_{32}H_{22}N_5O_4S$ $[M+H]^+$ 572.1392, found 572.1388.



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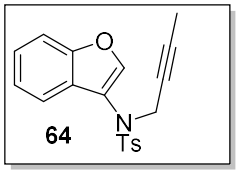
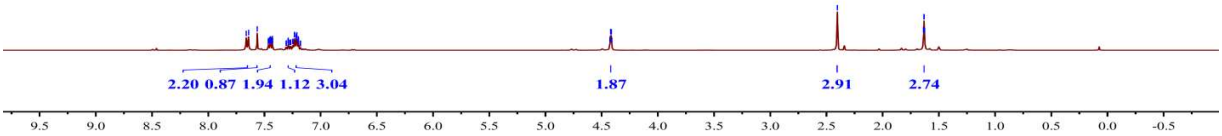
3.2.12 Copy of NMR spectra

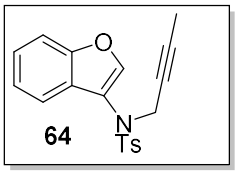
3.2.12.1 NMR spectra of compound 64:

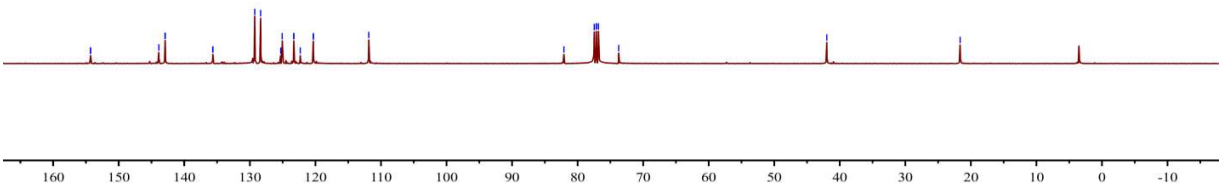
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **64:**





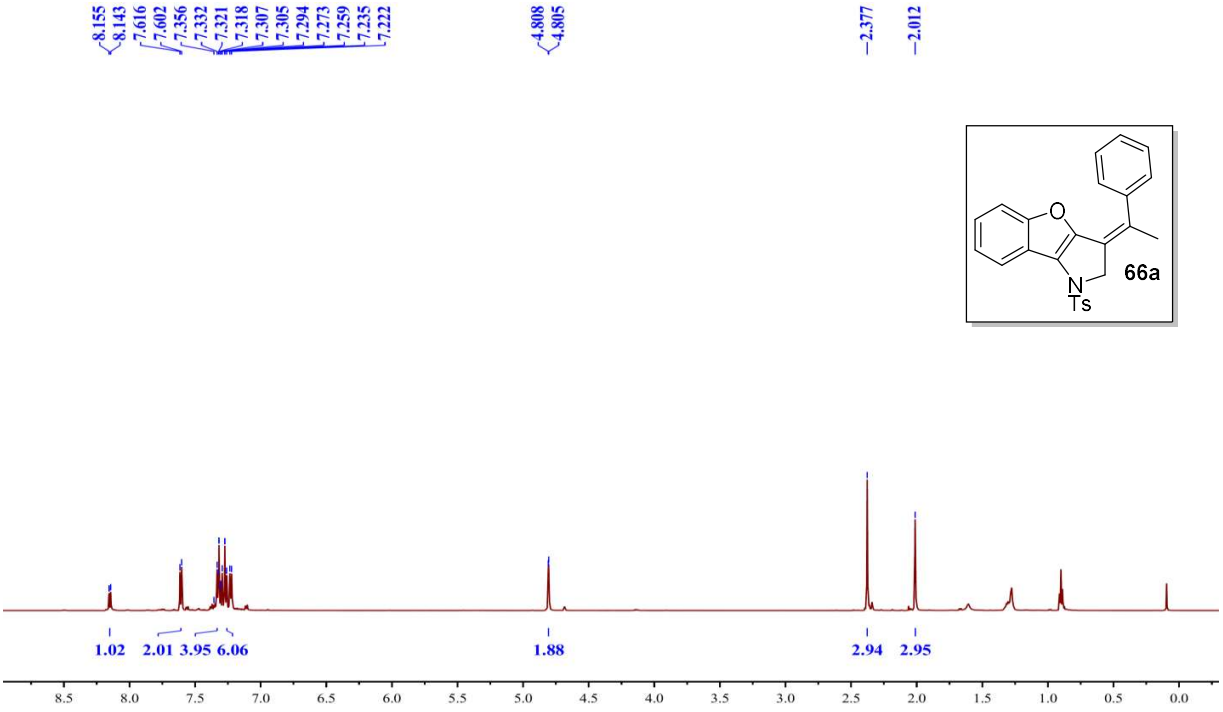
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **64**:



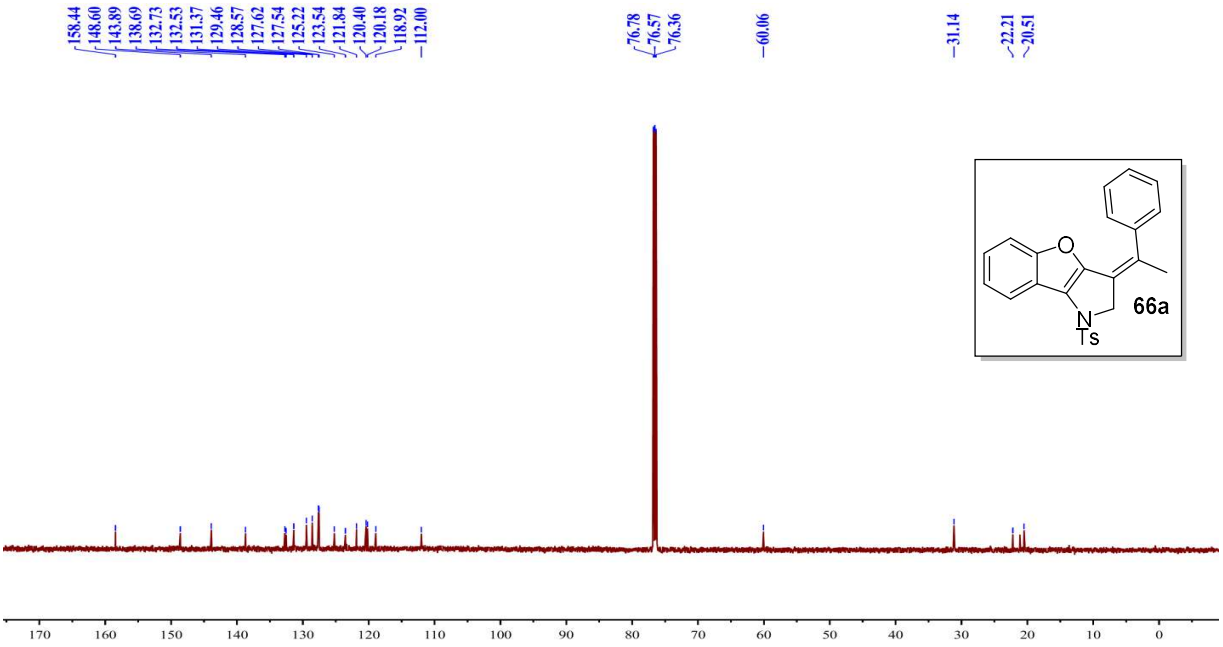


3.2.12.2 NMR spectra of compounds 66a-c:

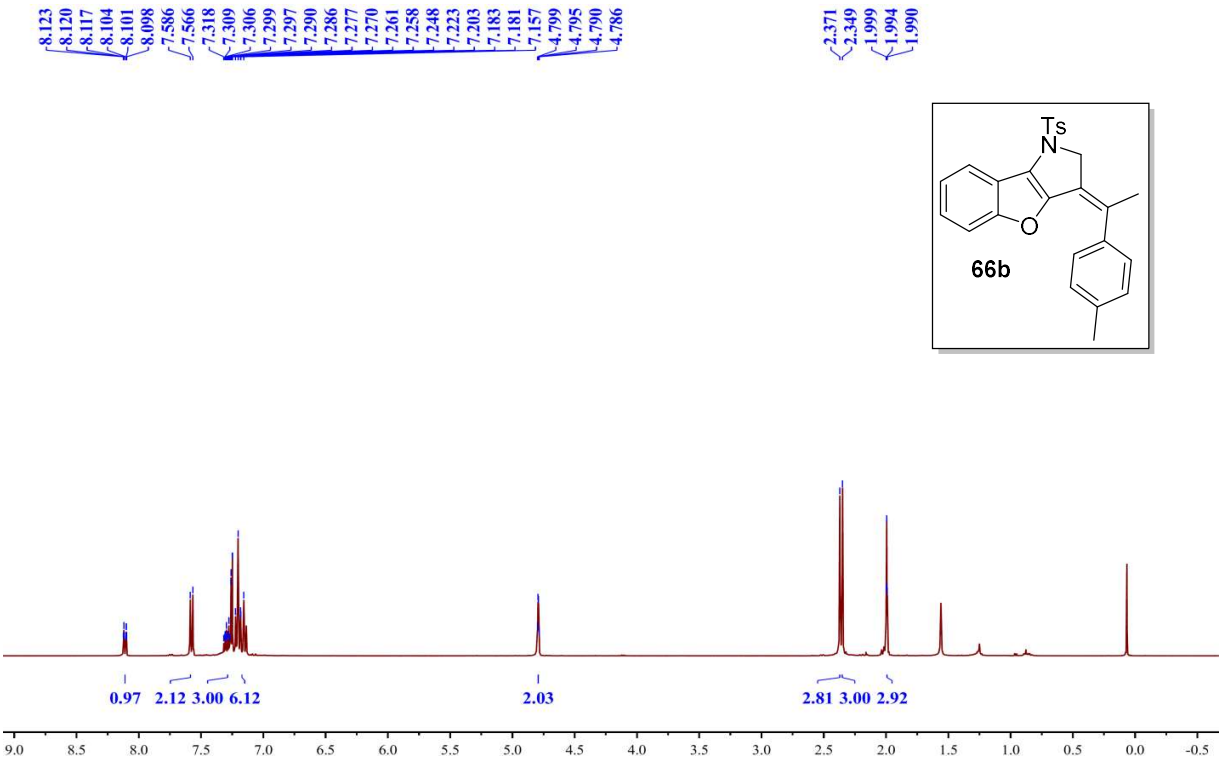
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **66a:**



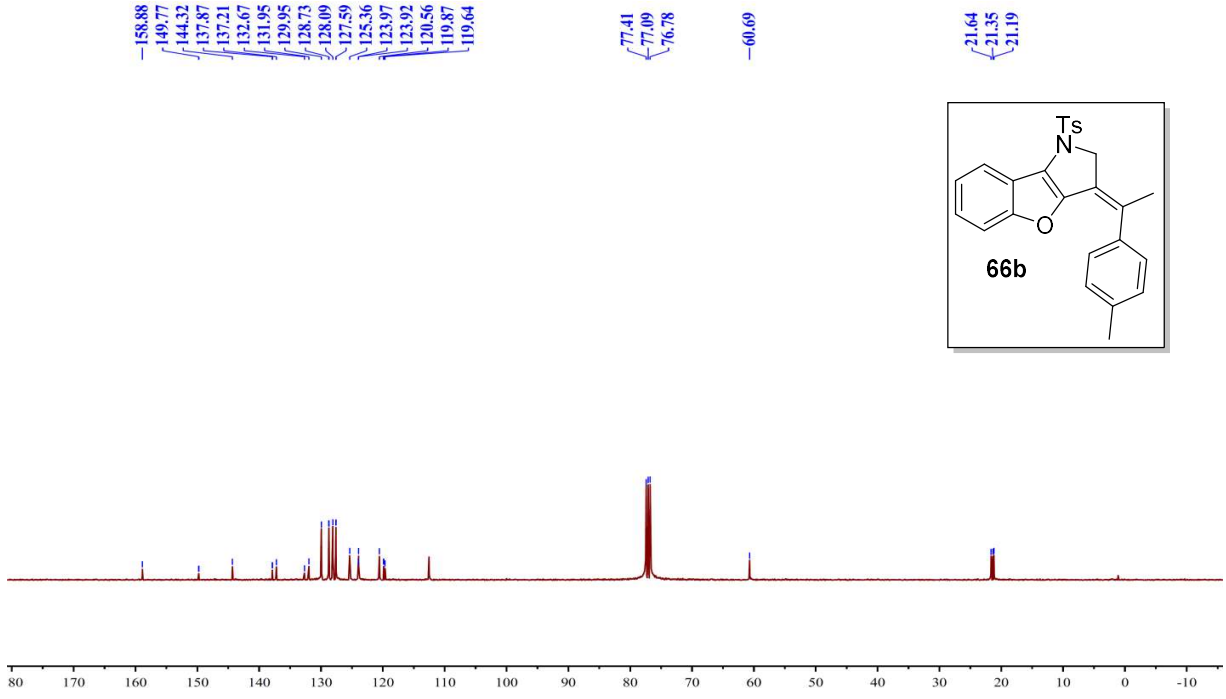
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **66a**:



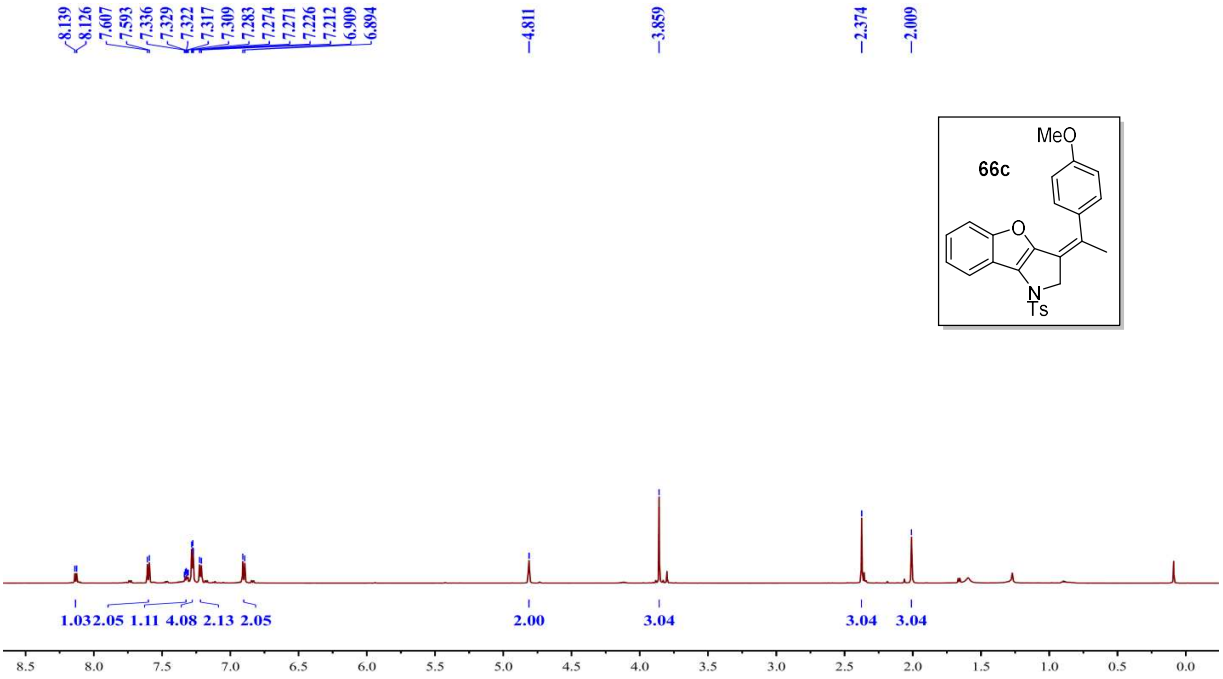
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **66b:**



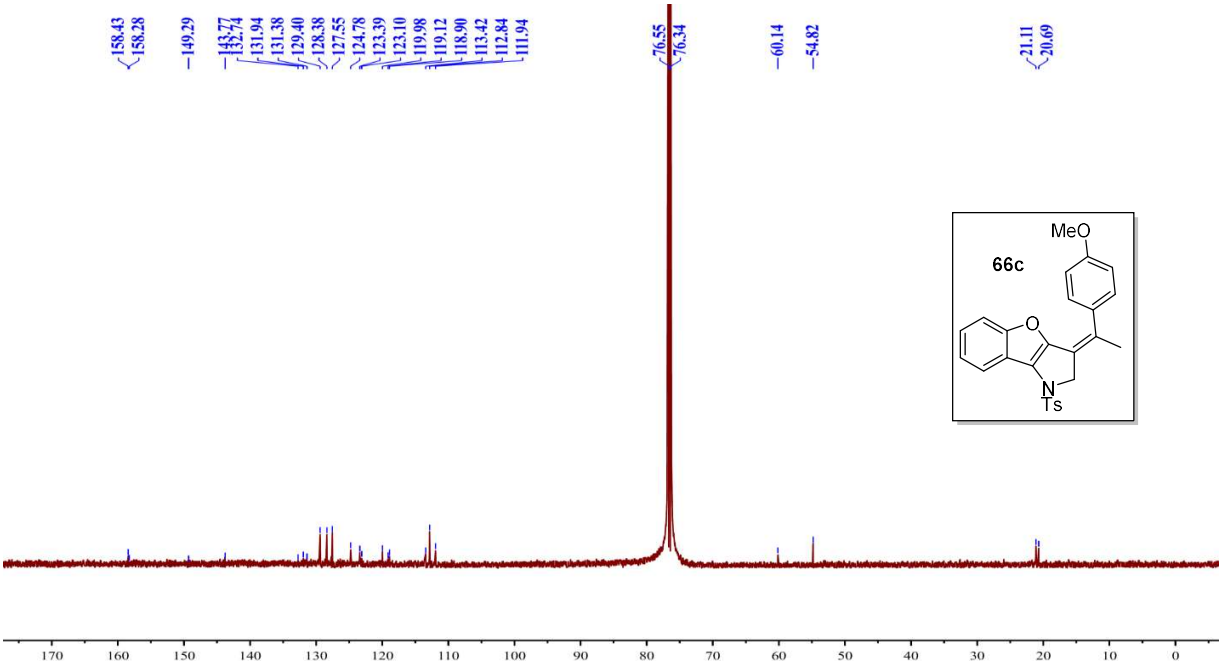
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **66b**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **66c:**

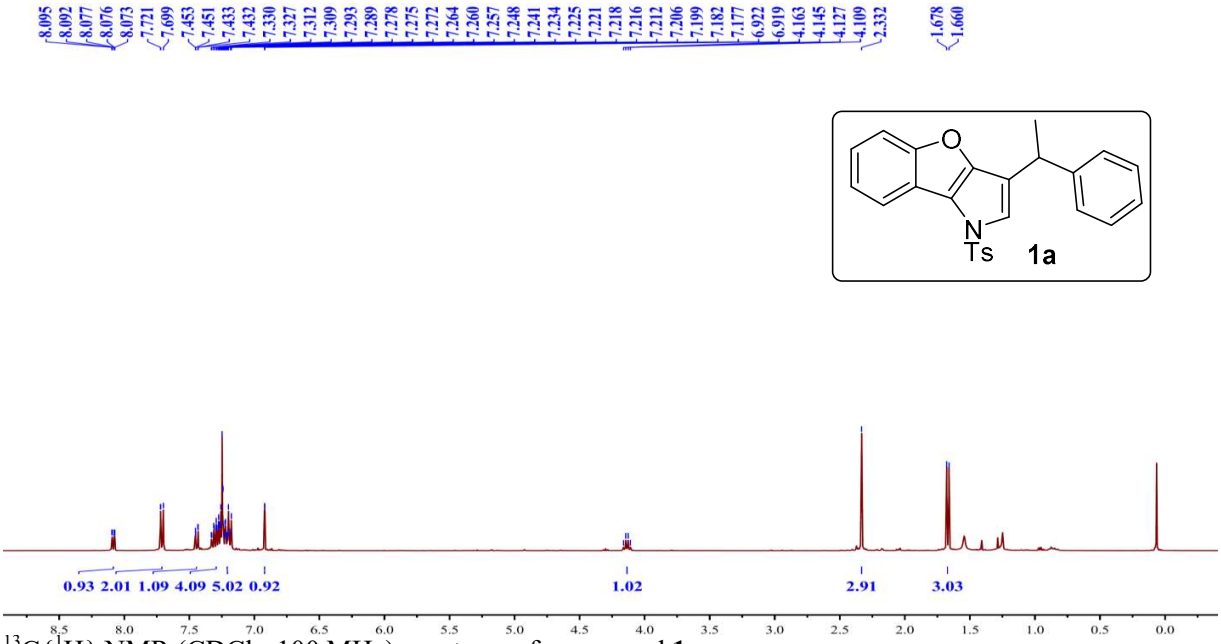


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **66c**:

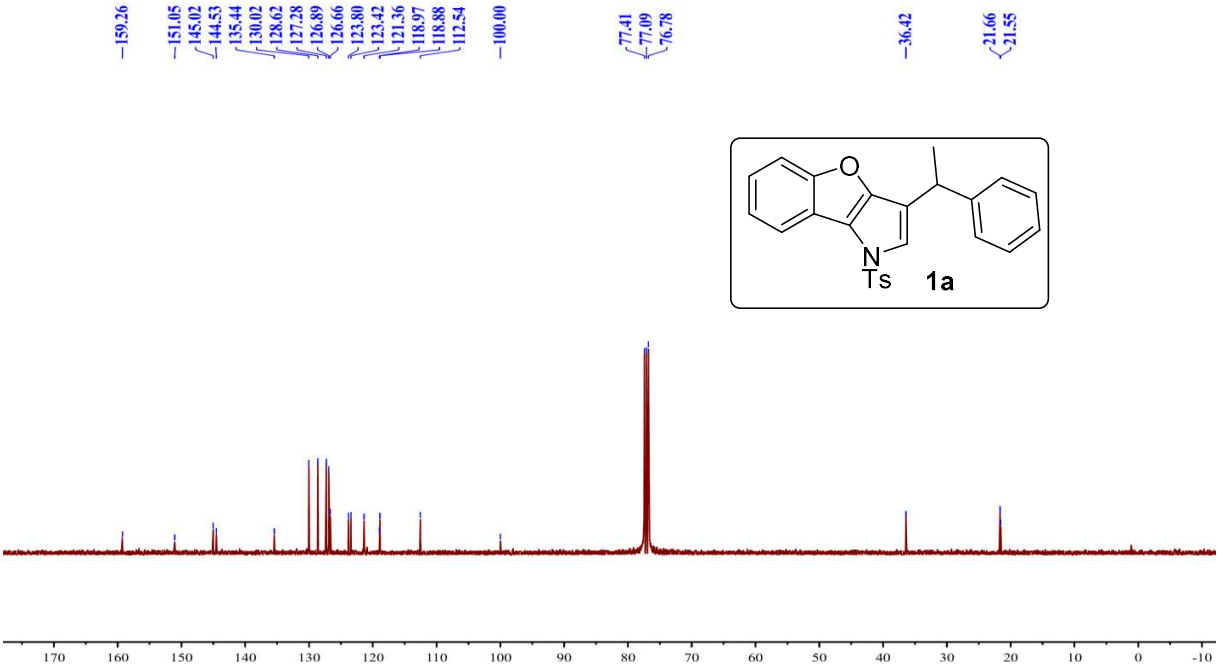


3.2.12.3 NMR Spectra of compounds 1a-n:

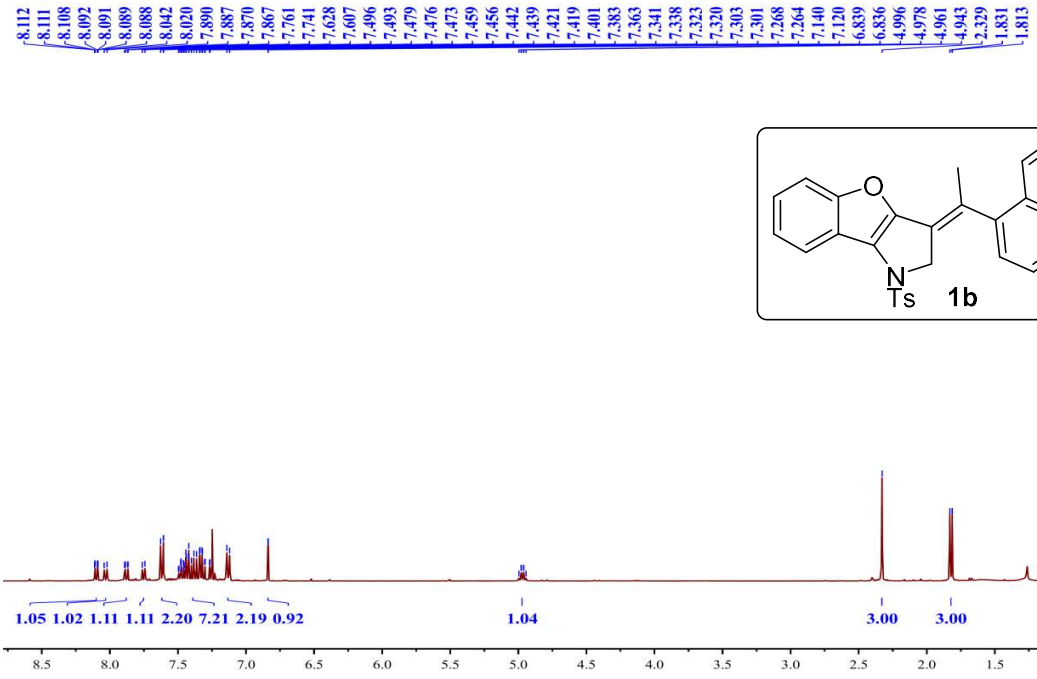
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1a:**



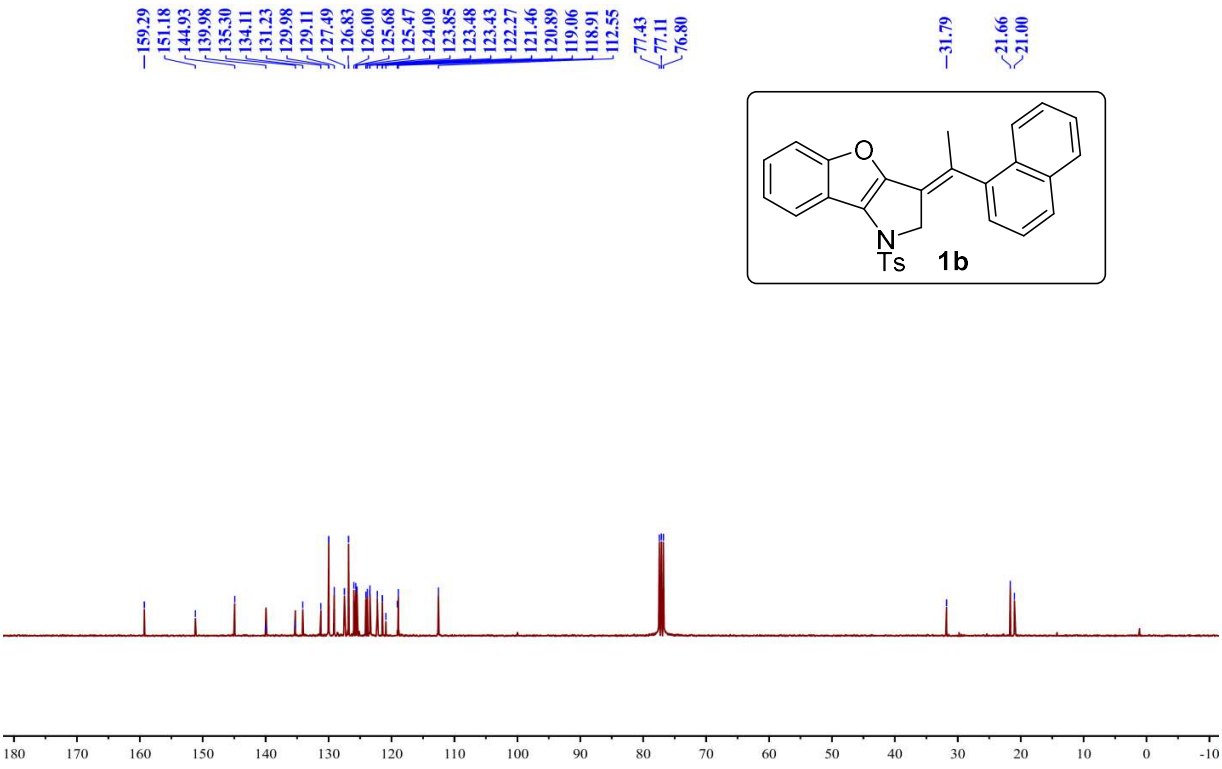
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1a**:



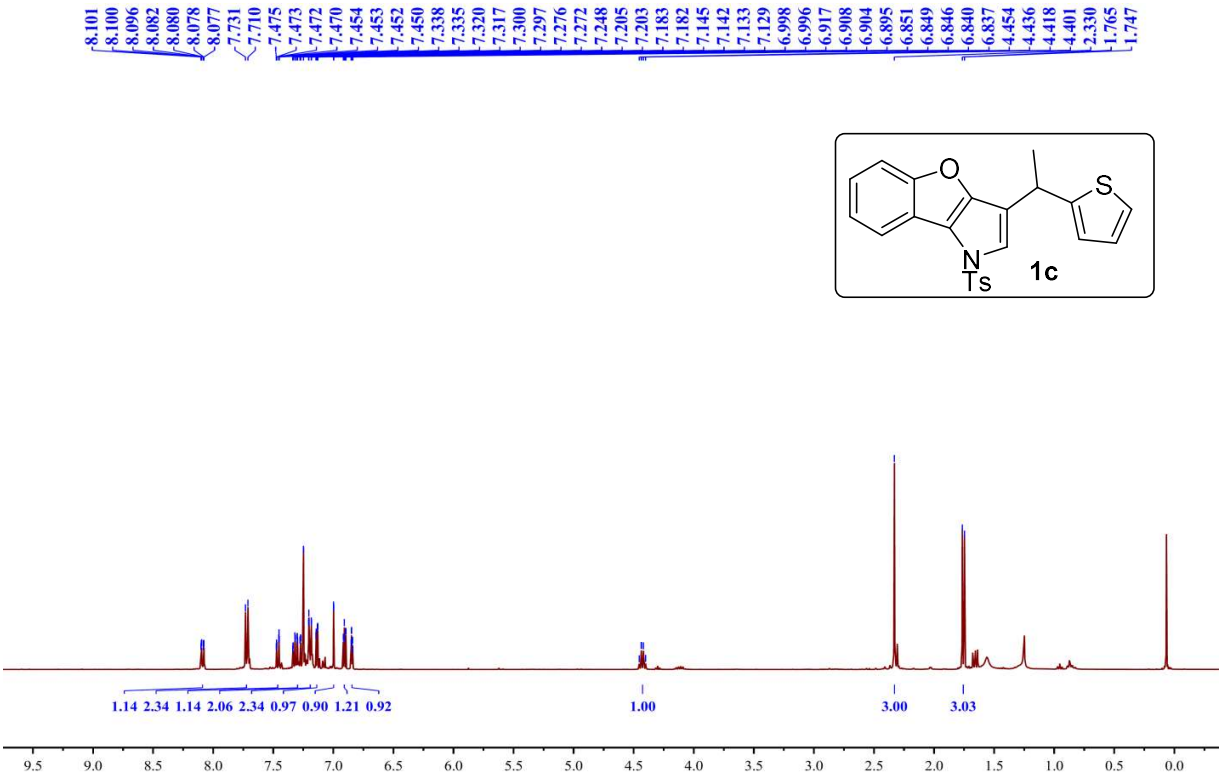
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1b:**



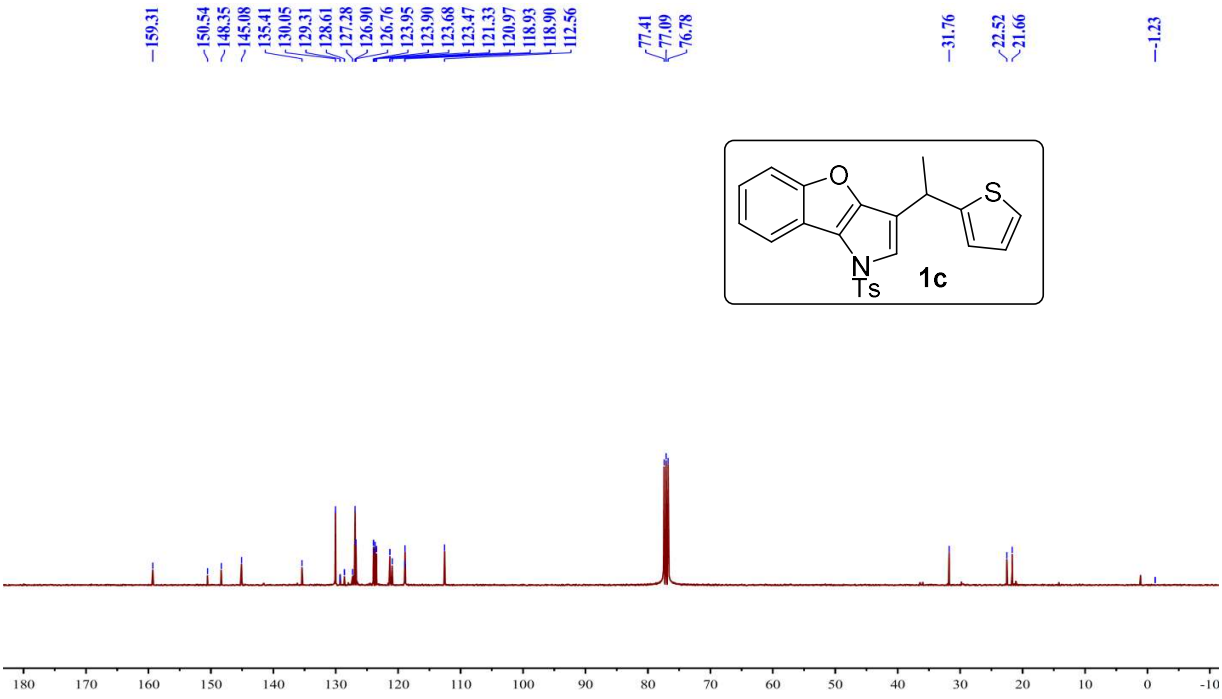
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1b**:



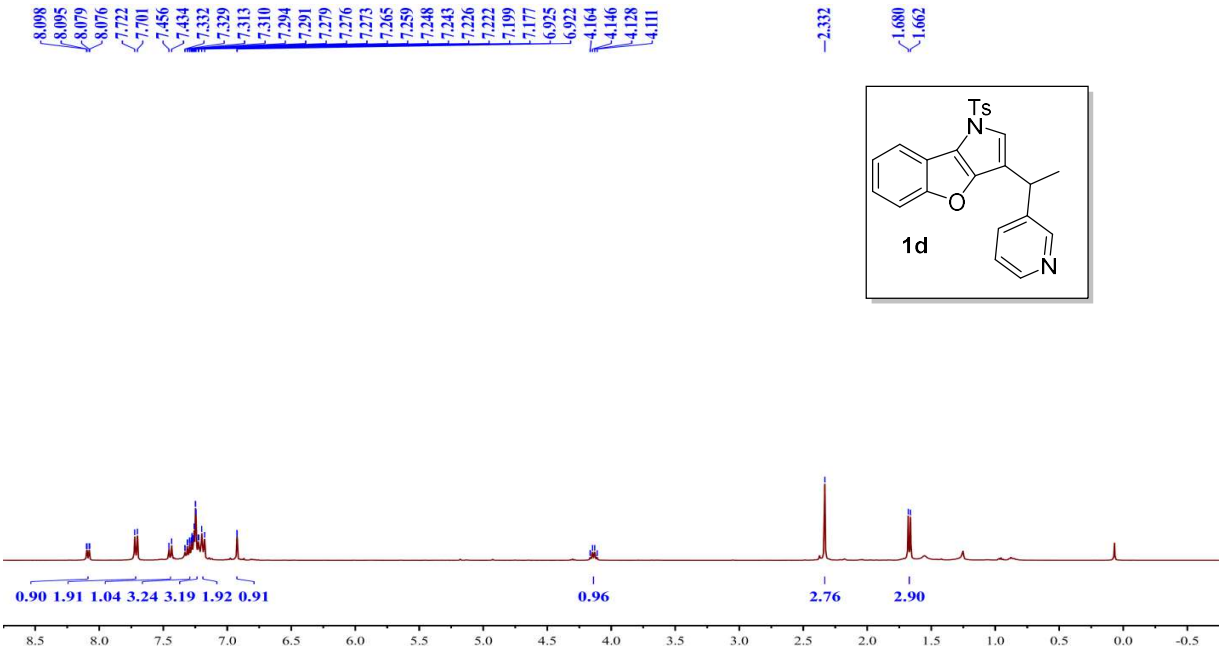
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1c:**



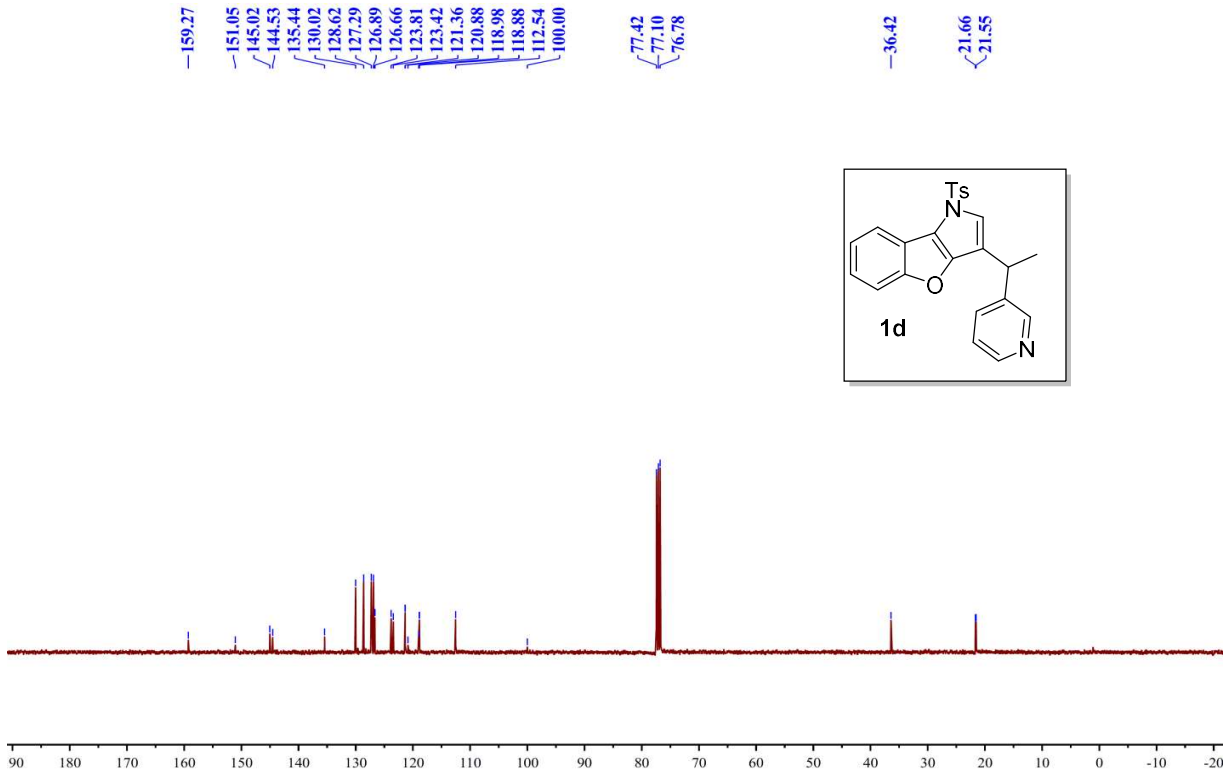
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1c**:



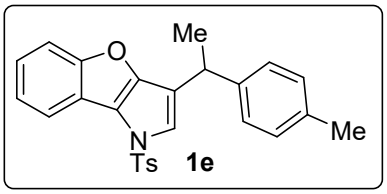
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1d:**

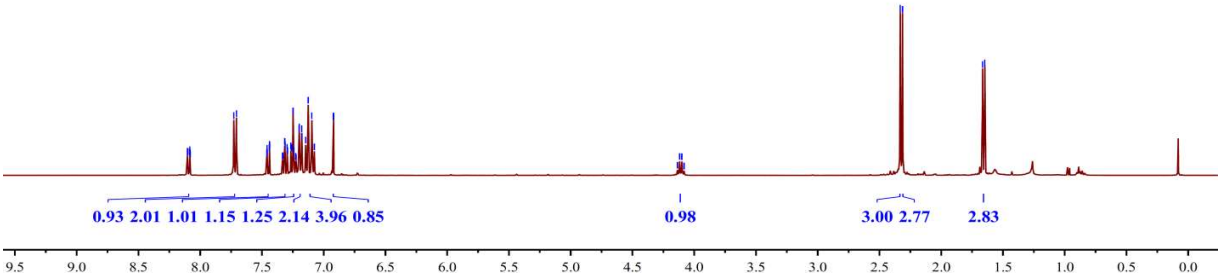


$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) spectrum of compound **1d**:

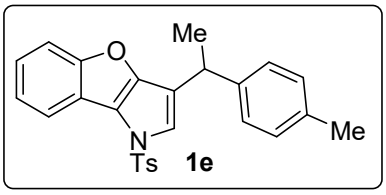


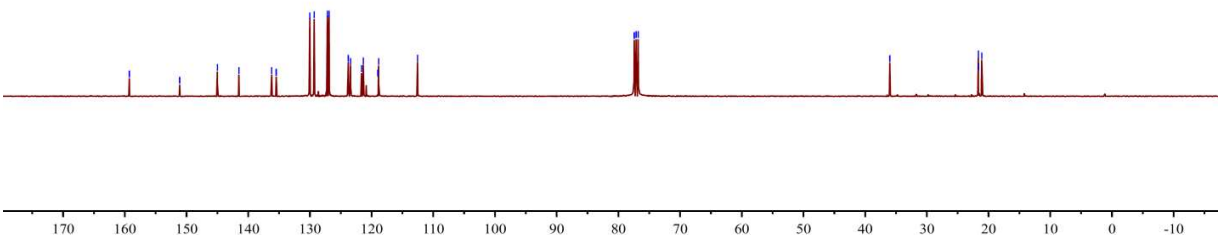
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1e:**



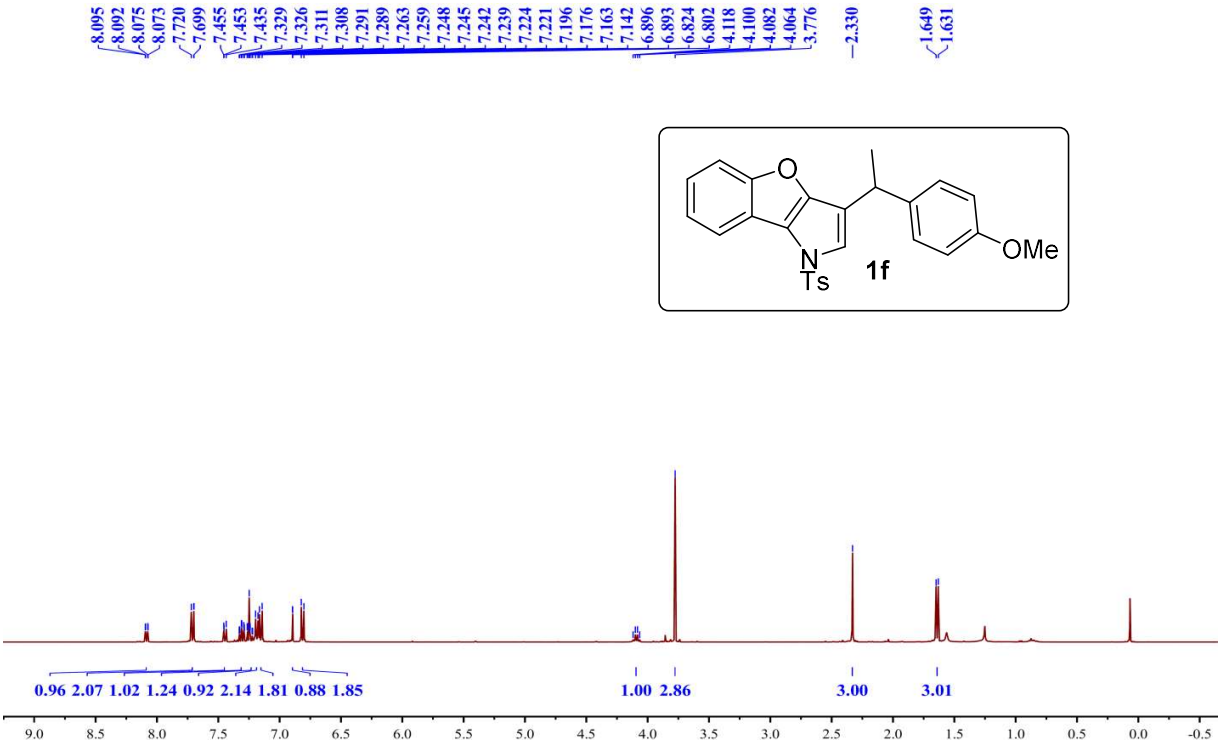


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1e**:

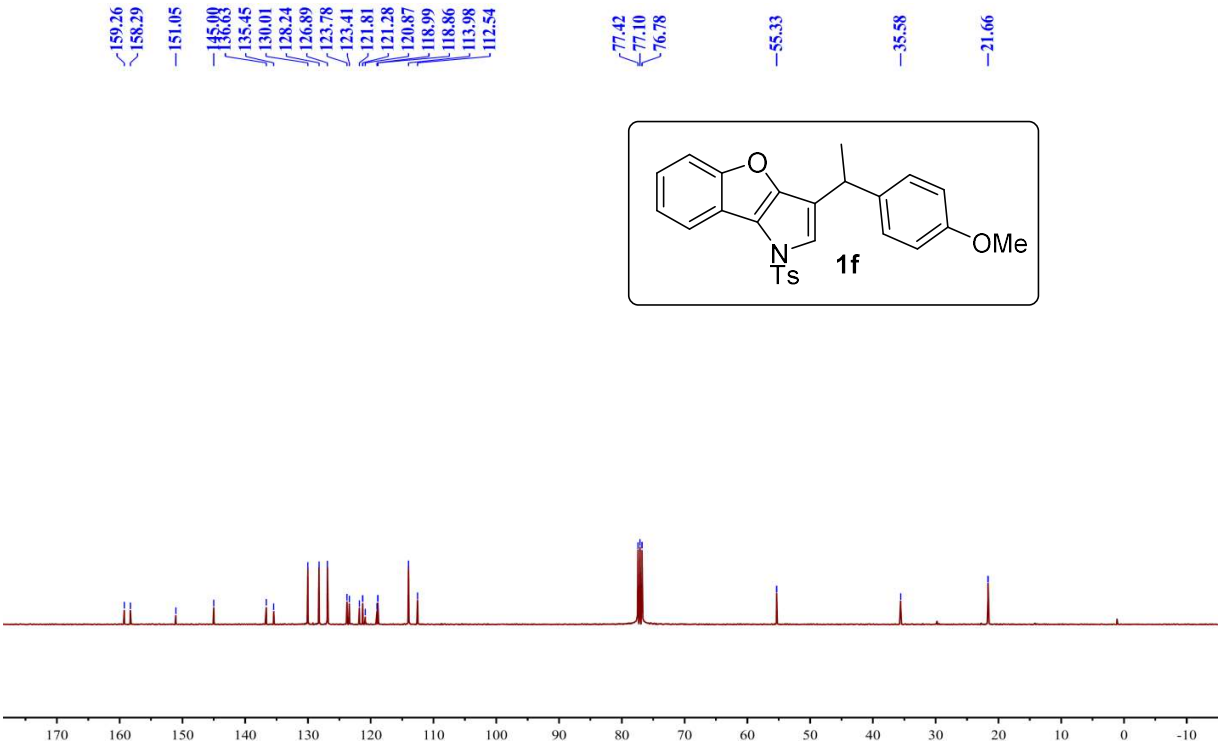




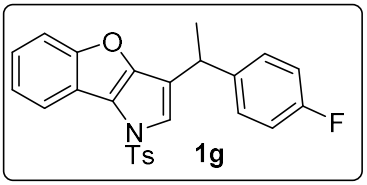
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1f:**

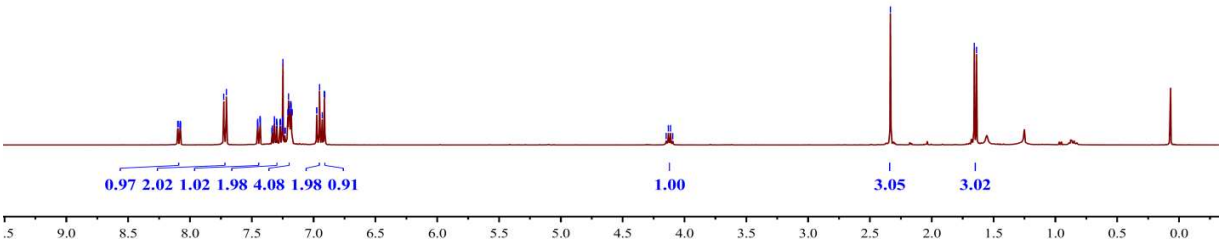


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1f**:

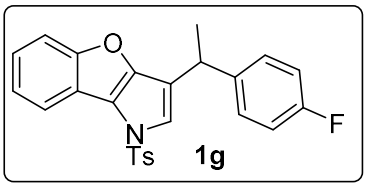


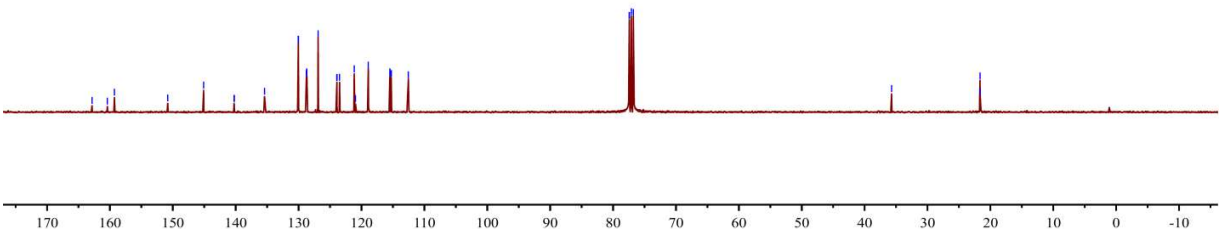
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1g:**



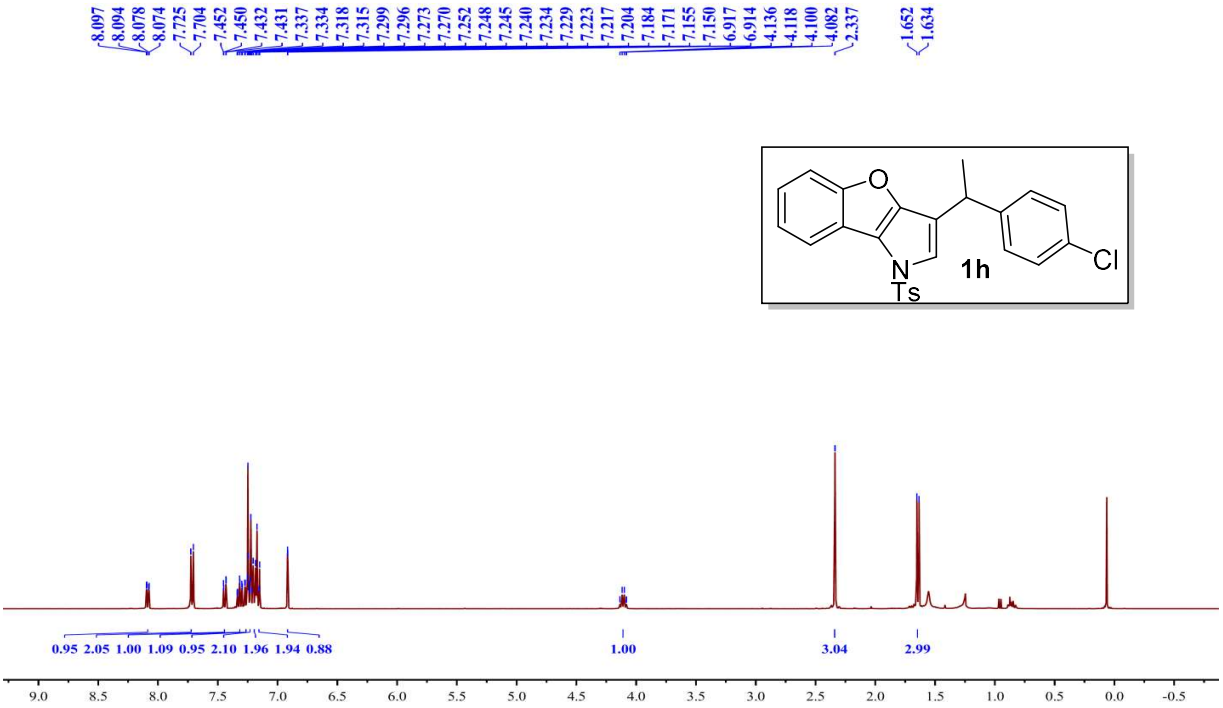


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1g**:

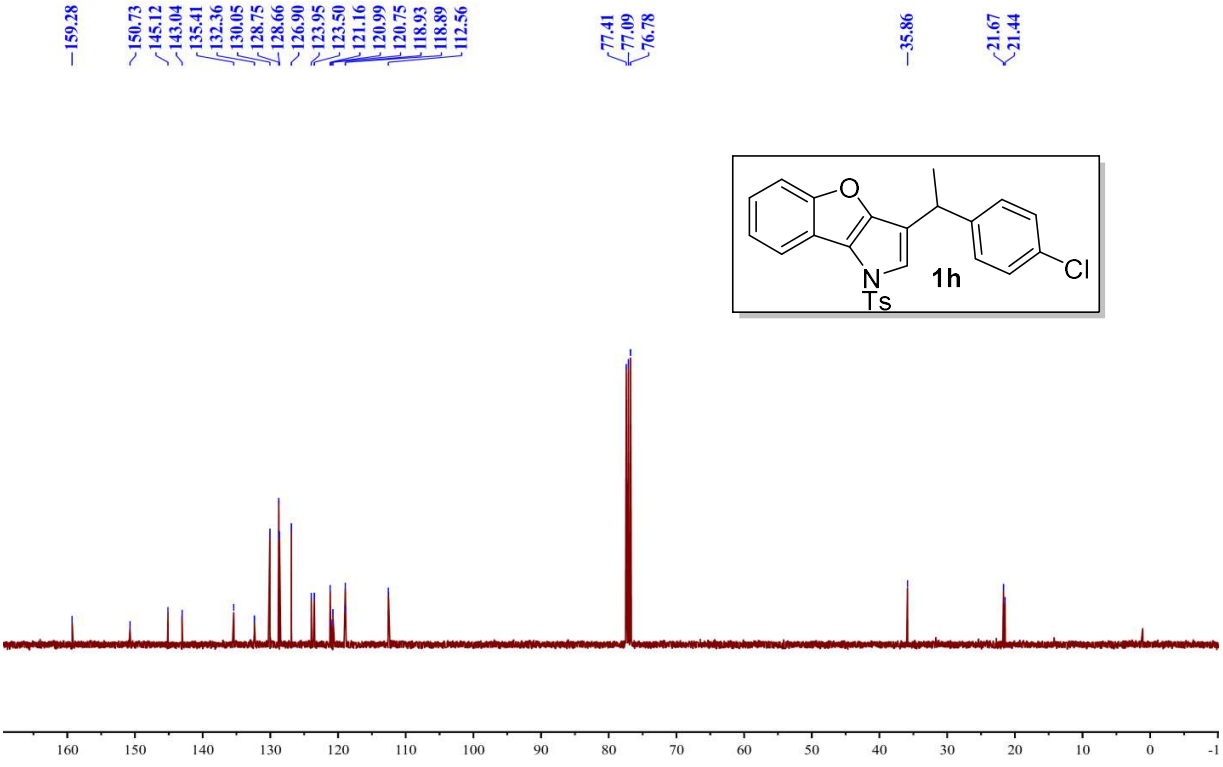




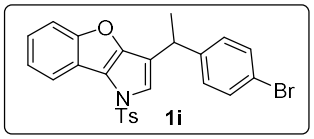
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1h:**

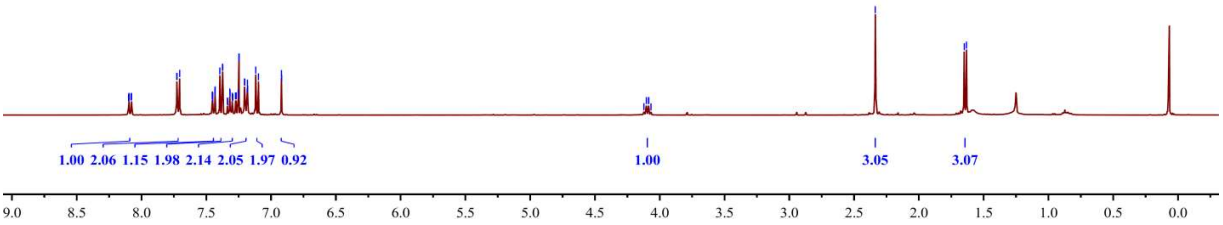


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1h**:

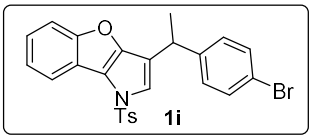


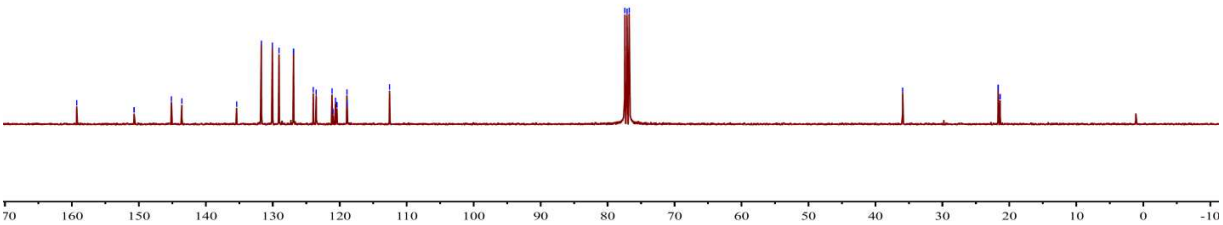
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1i:**



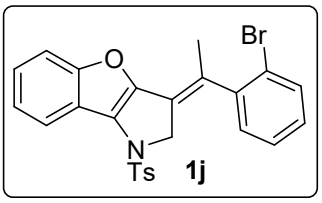


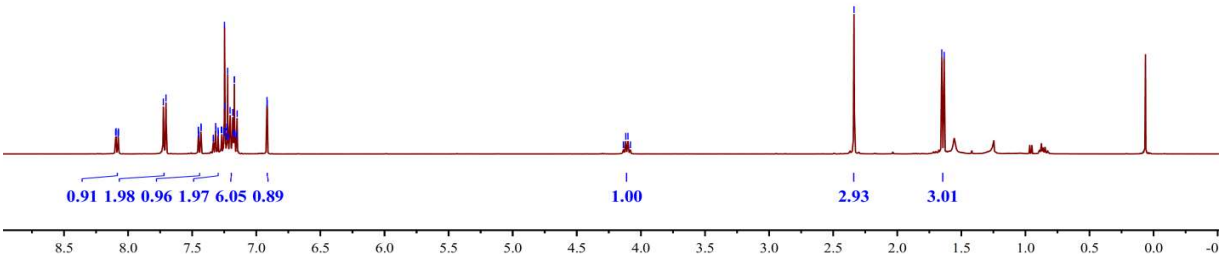
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1i**:



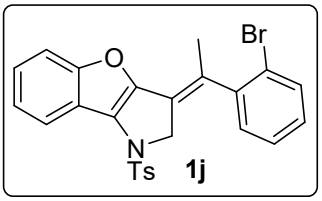


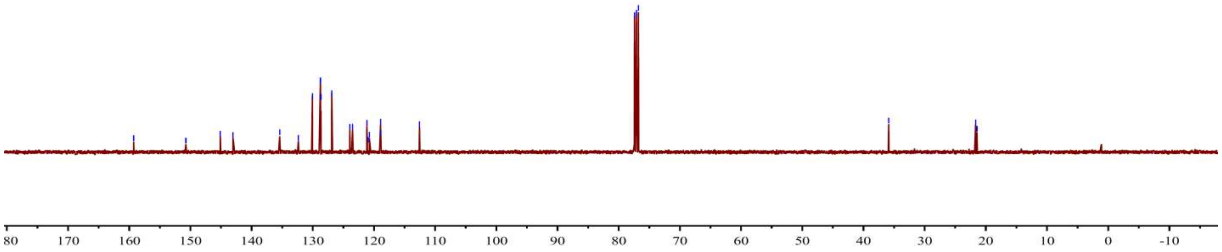
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1j**:



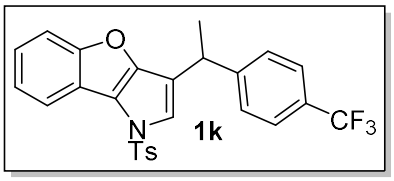


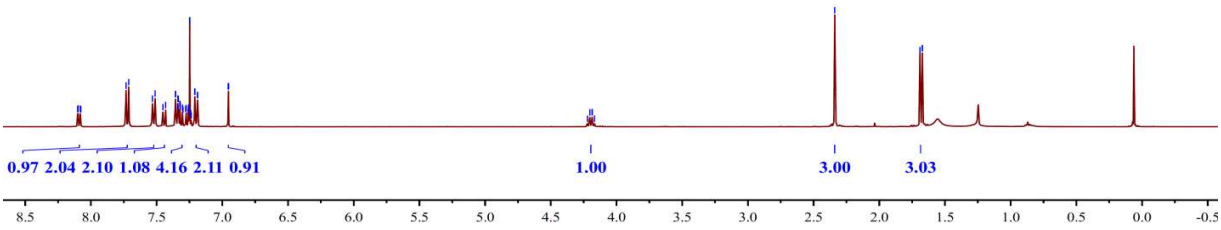
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1j**:



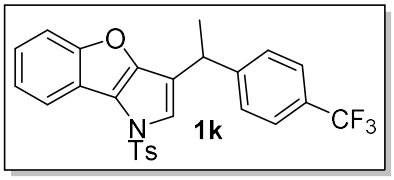


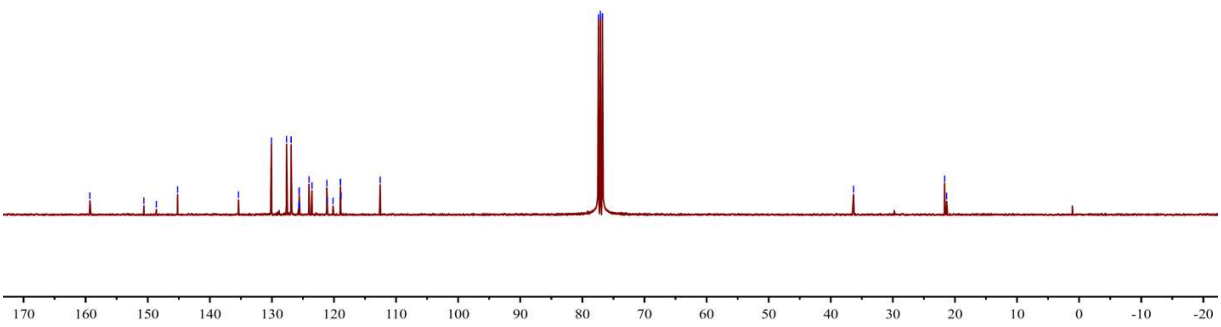
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1k:**



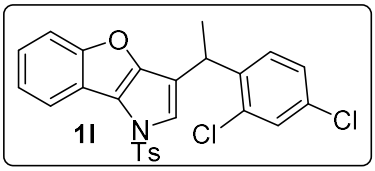


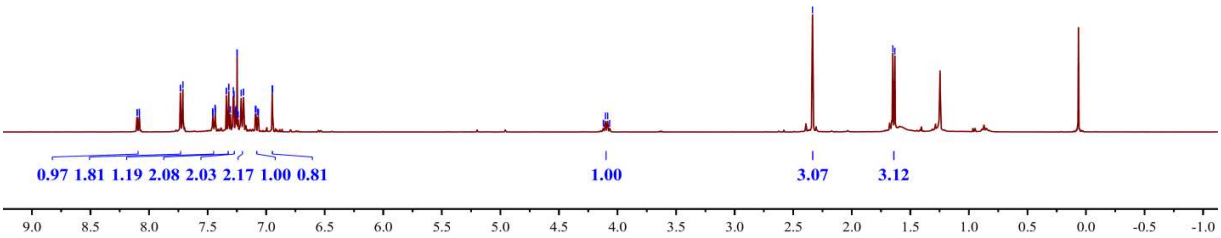
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1k**:



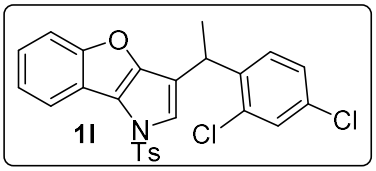


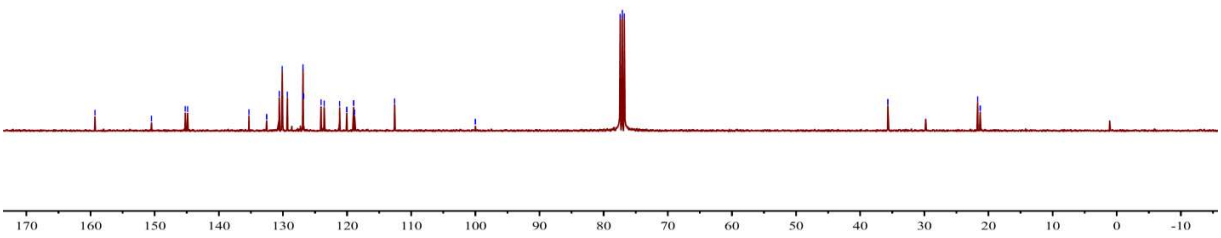
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1l:**



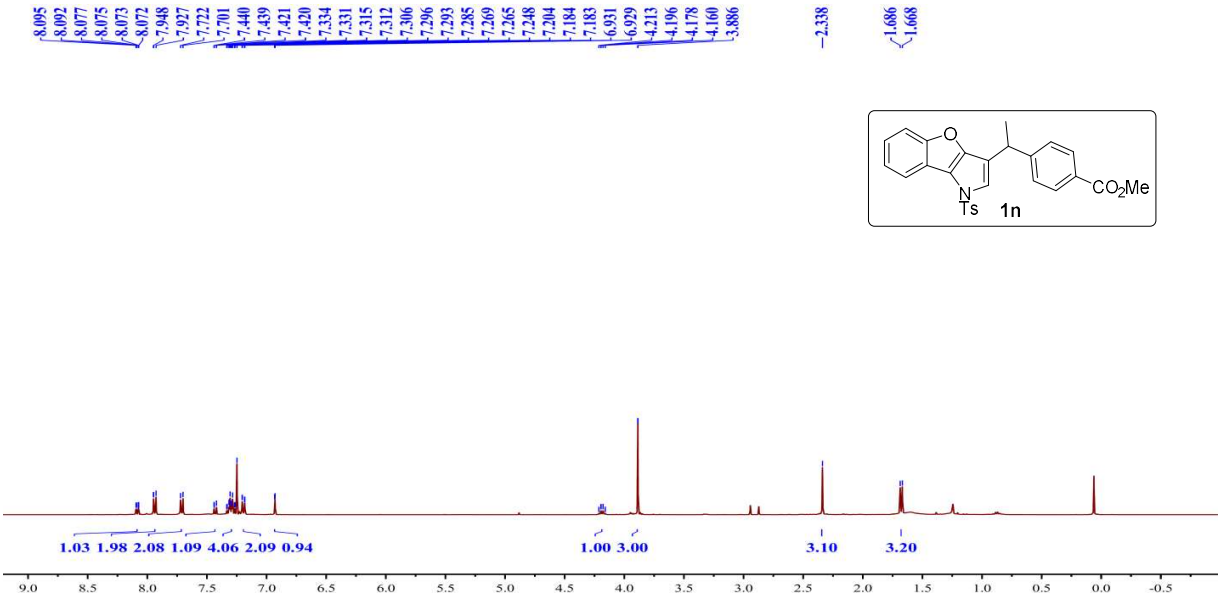


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1l**:

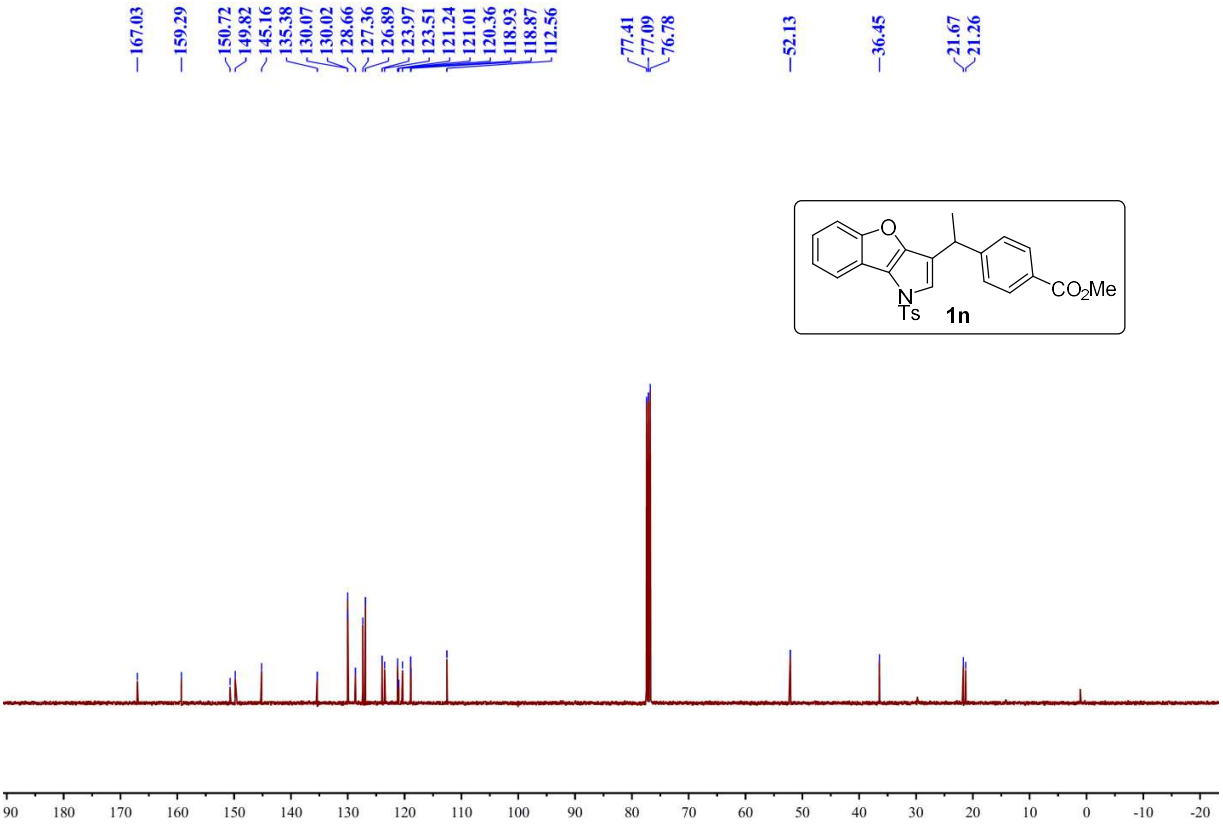




^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **1n:**

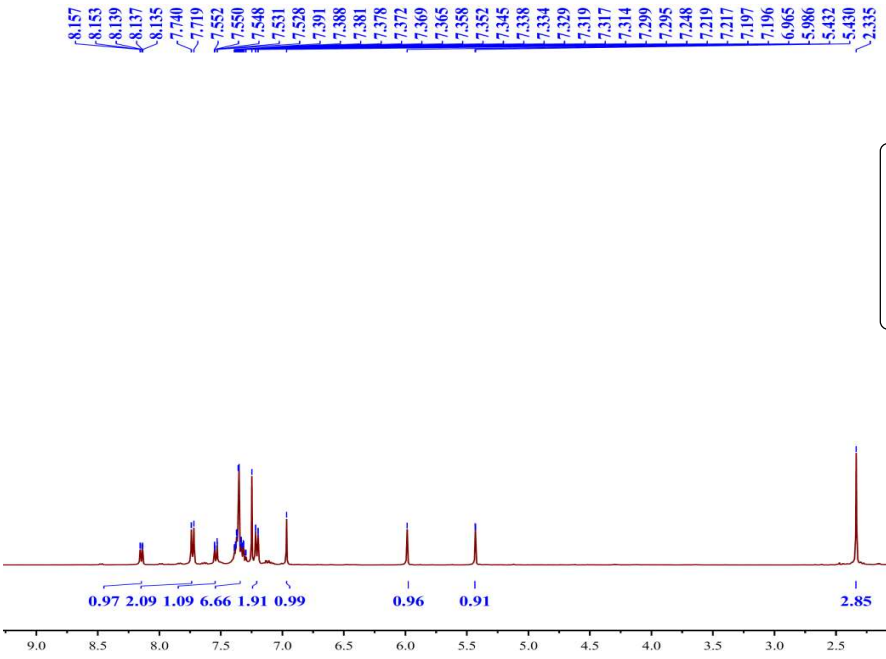


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **1n:**

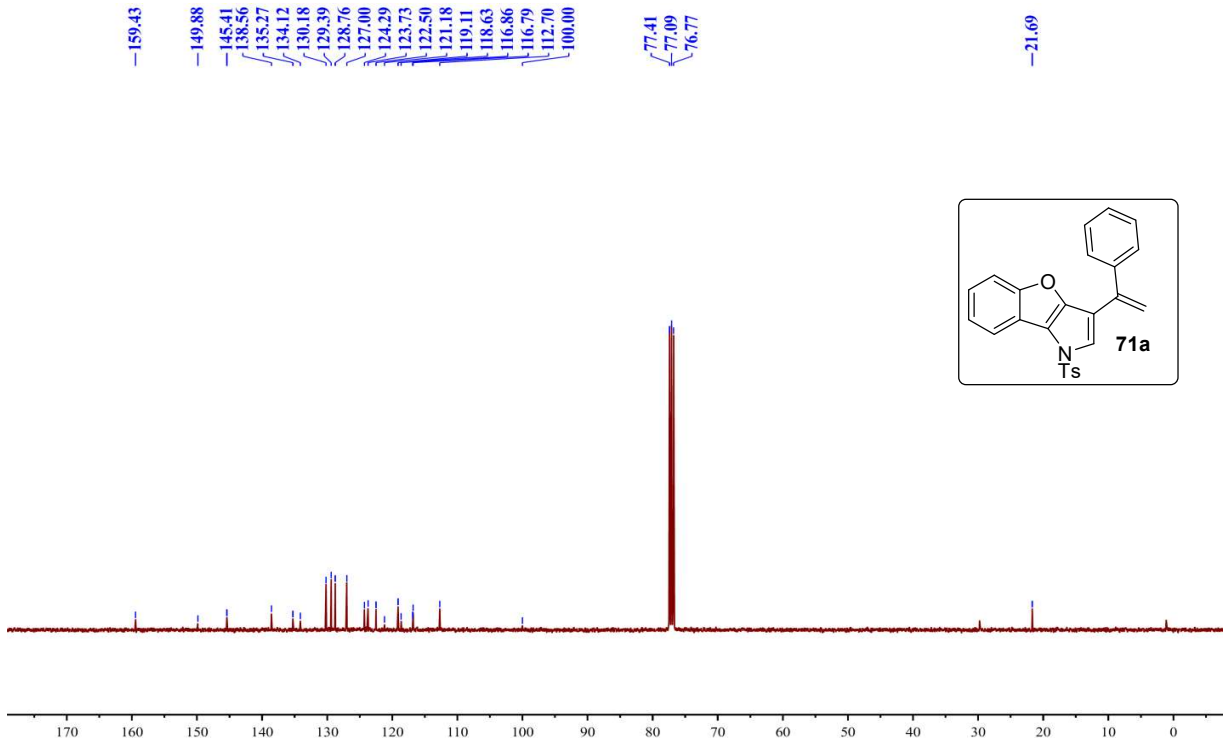


3.2.12.4 NMR spectra of compounds 71a-b:

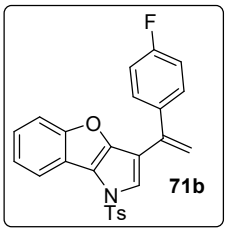
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound 7**1a:**

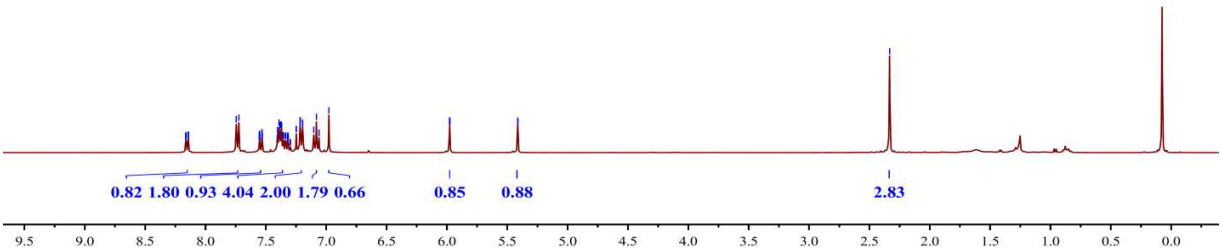


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound 7**1a**:

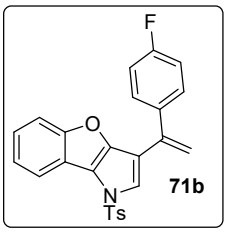


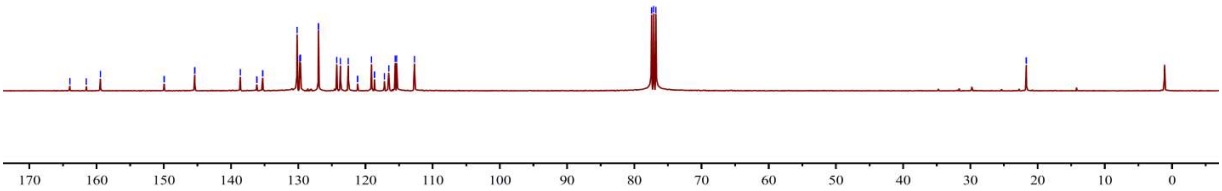
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound 7**1b:**





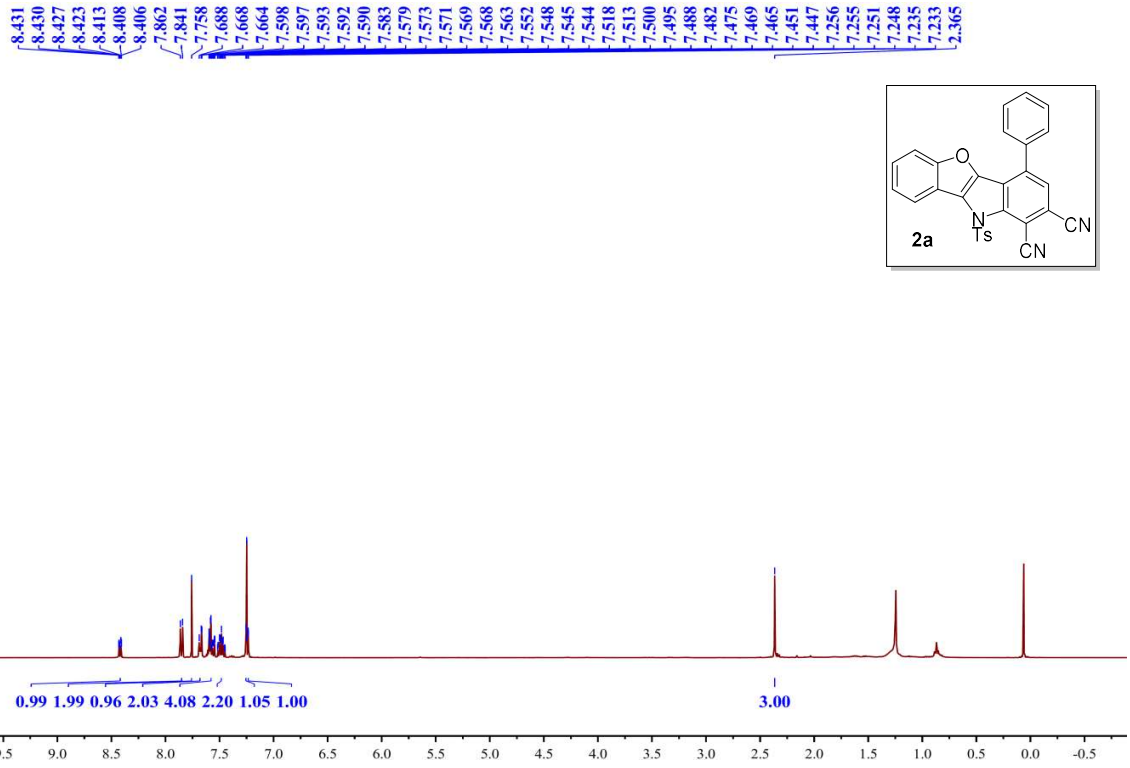
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound 7**1b**:



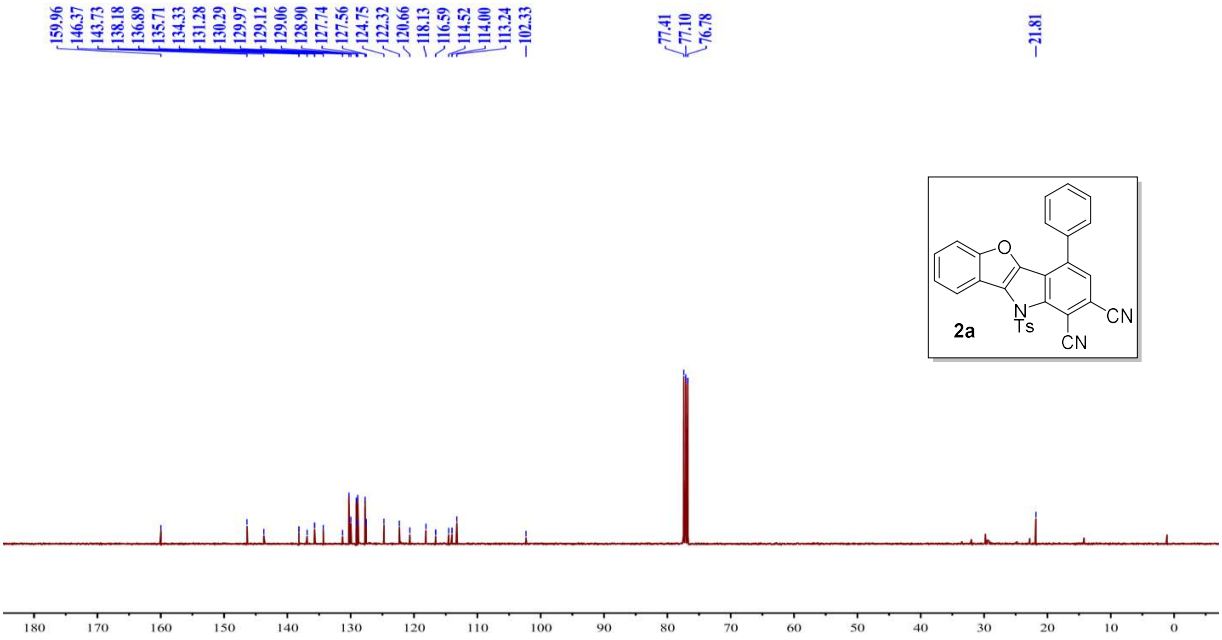


3.2.12.5 NMR spectra of compounds 2a-j:

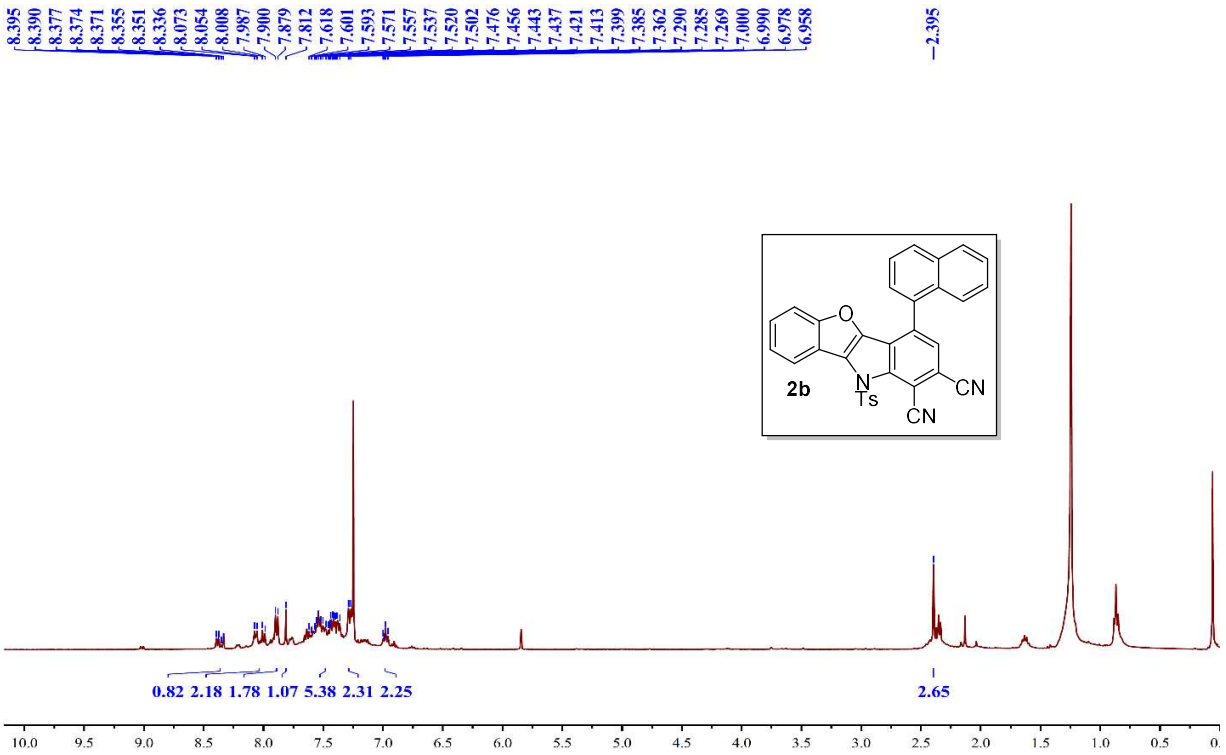
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2a:**



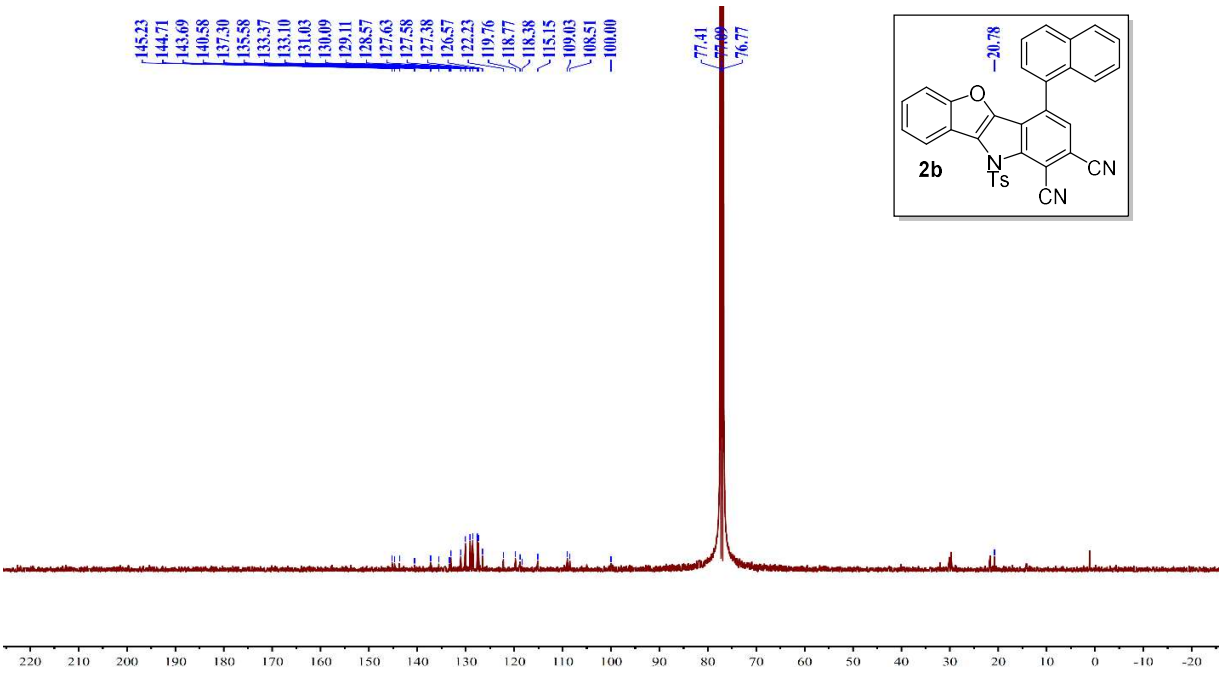
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2a**:



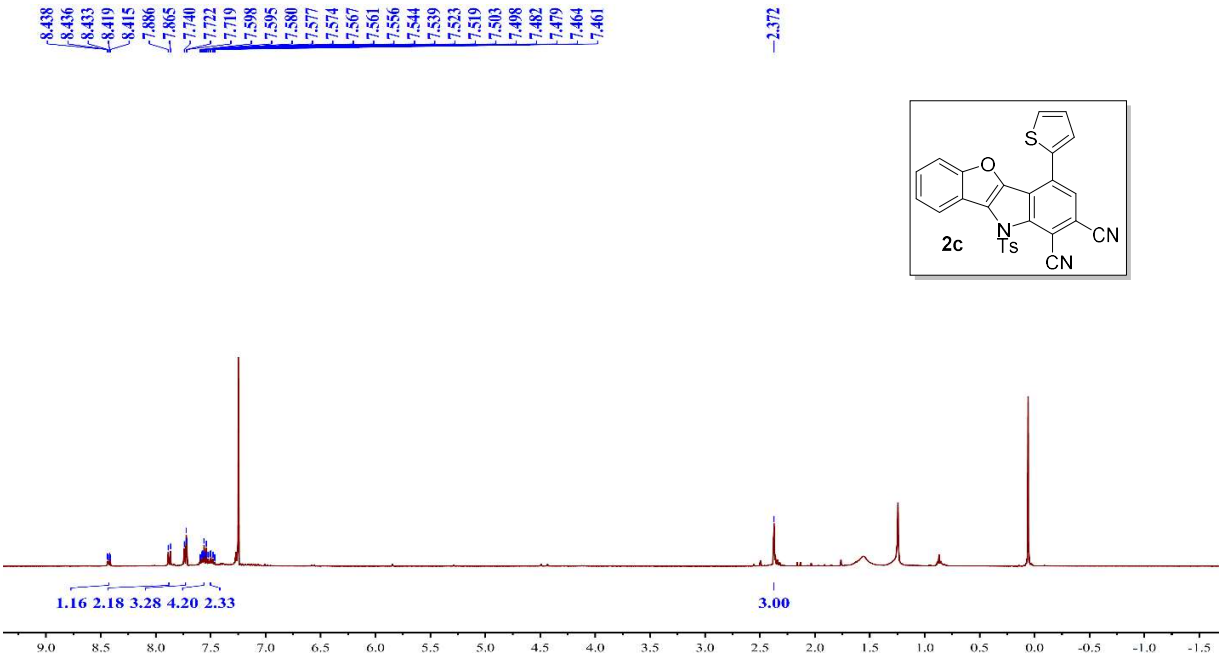
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2b:**



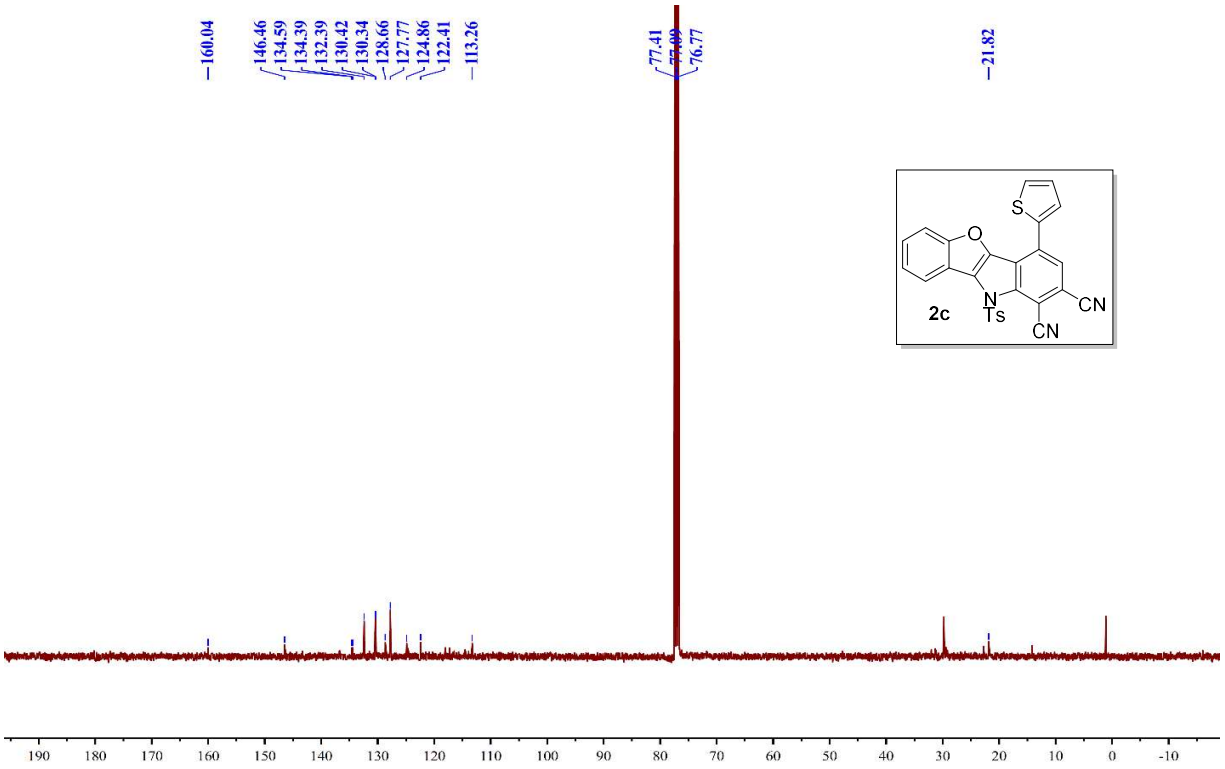
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2b**:



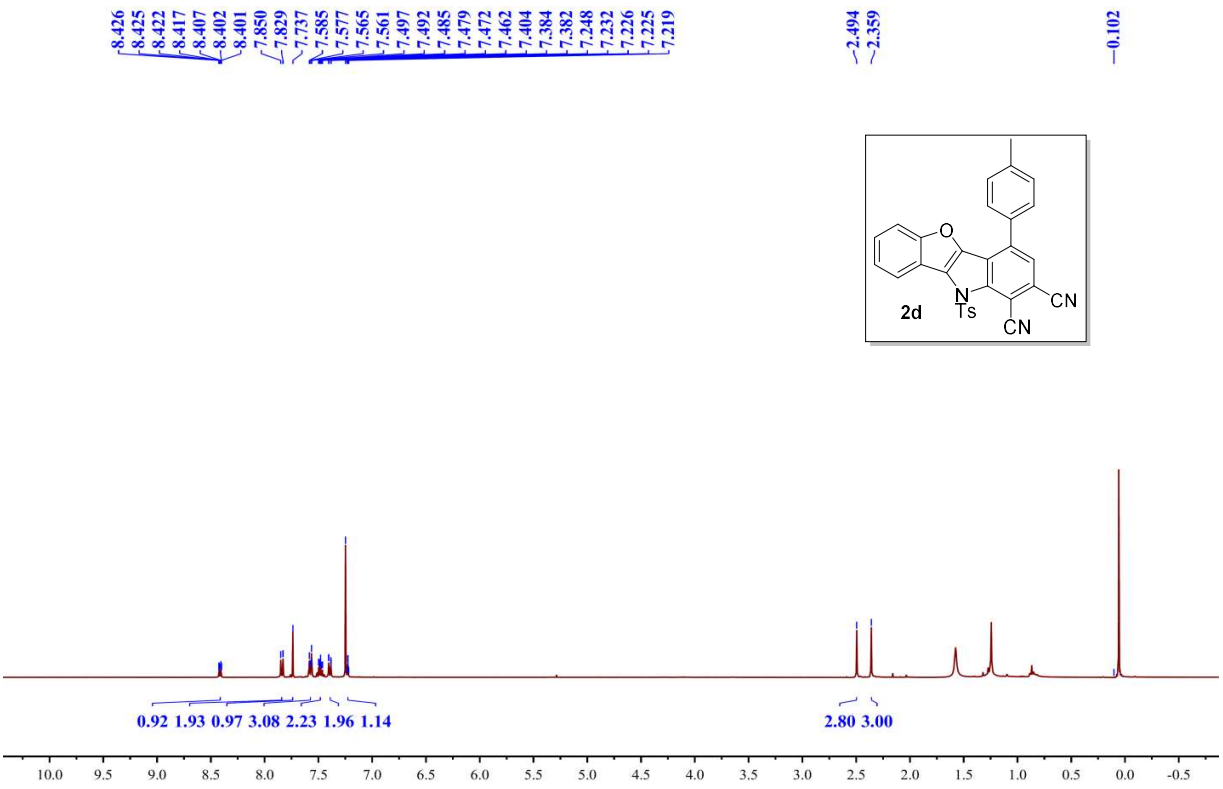
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2c:**



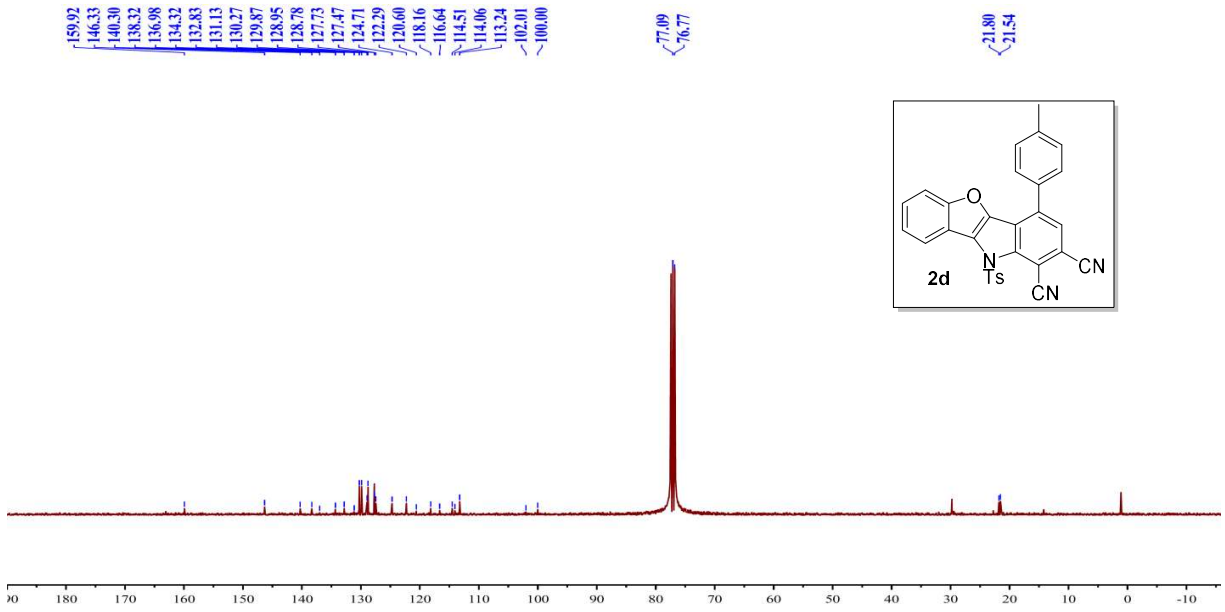
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) spectrum of compound **2c**:



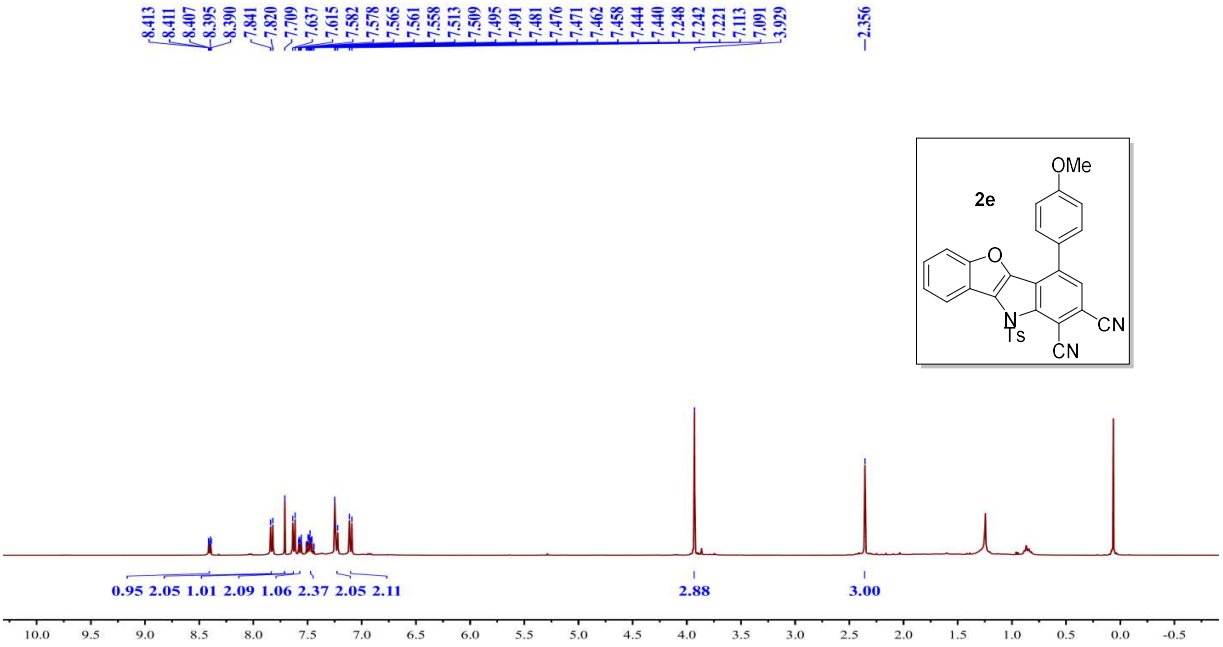
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2d:**



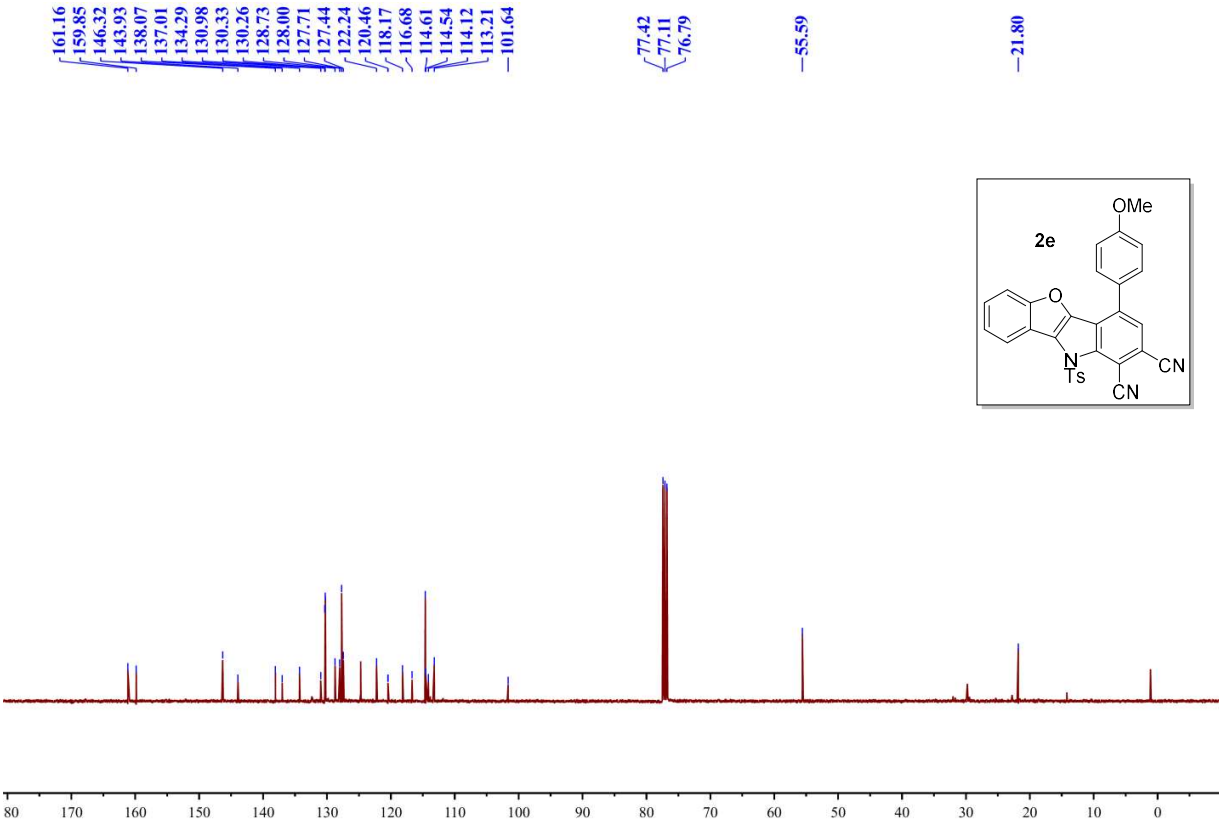
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2d**:



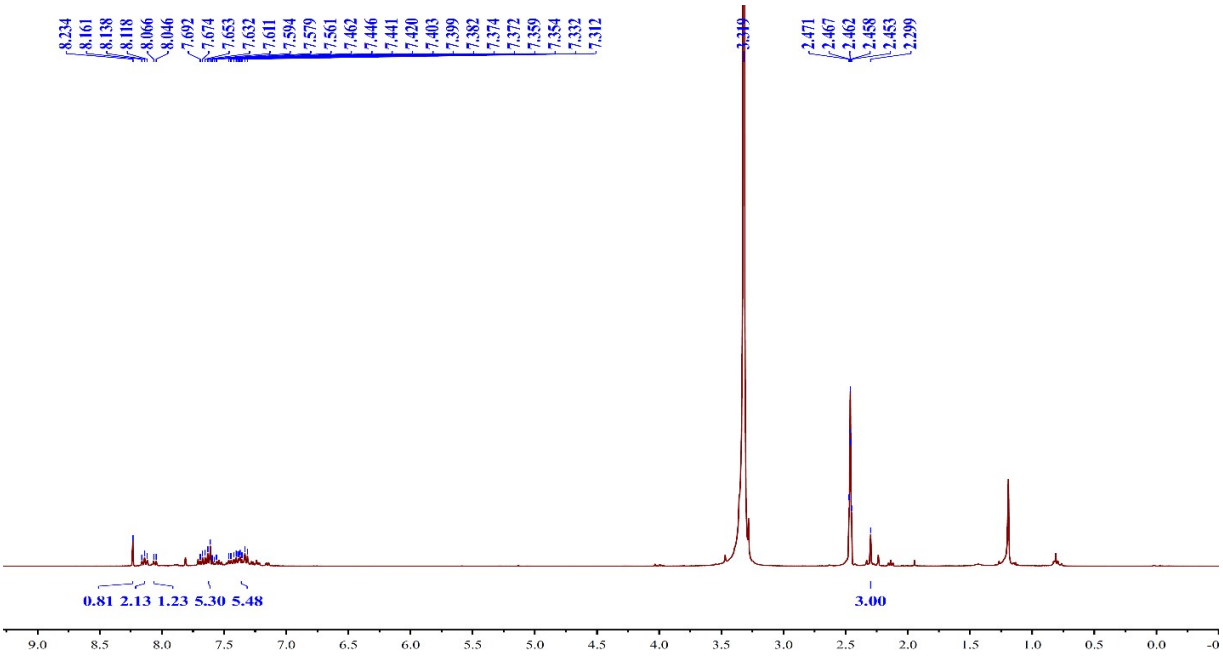
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2e:**



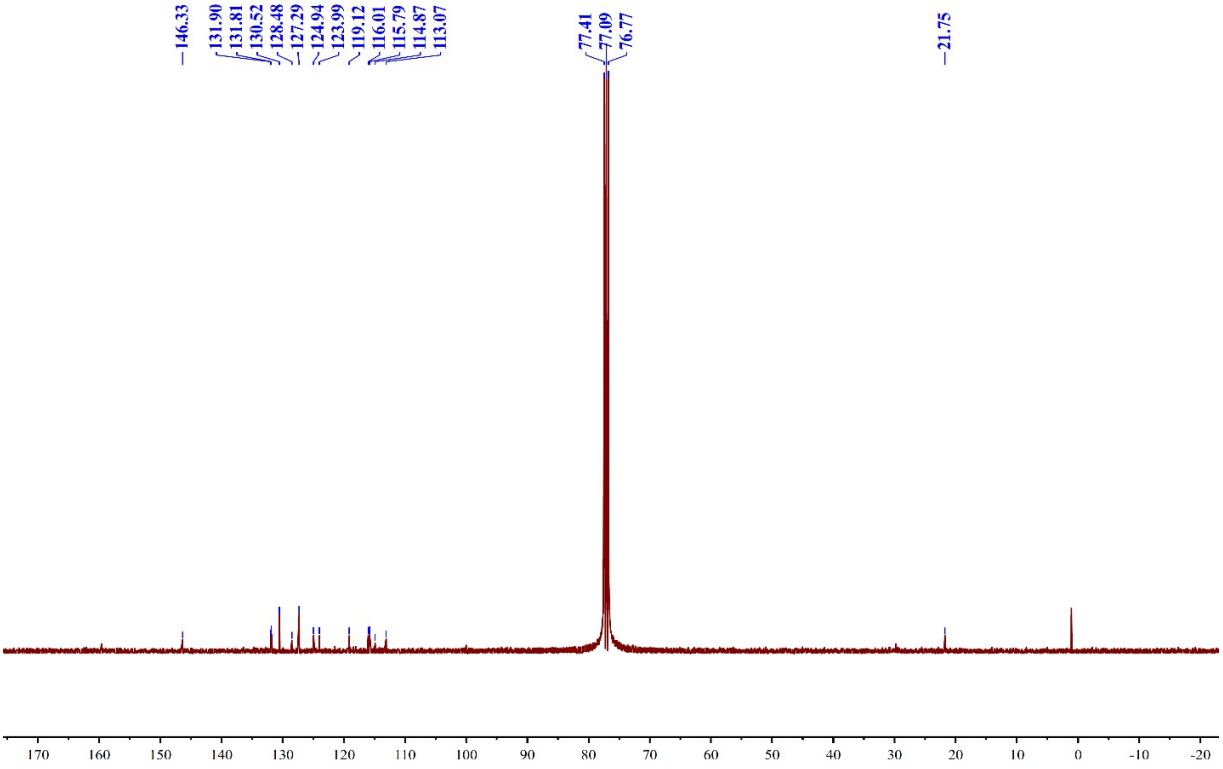
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2e**:



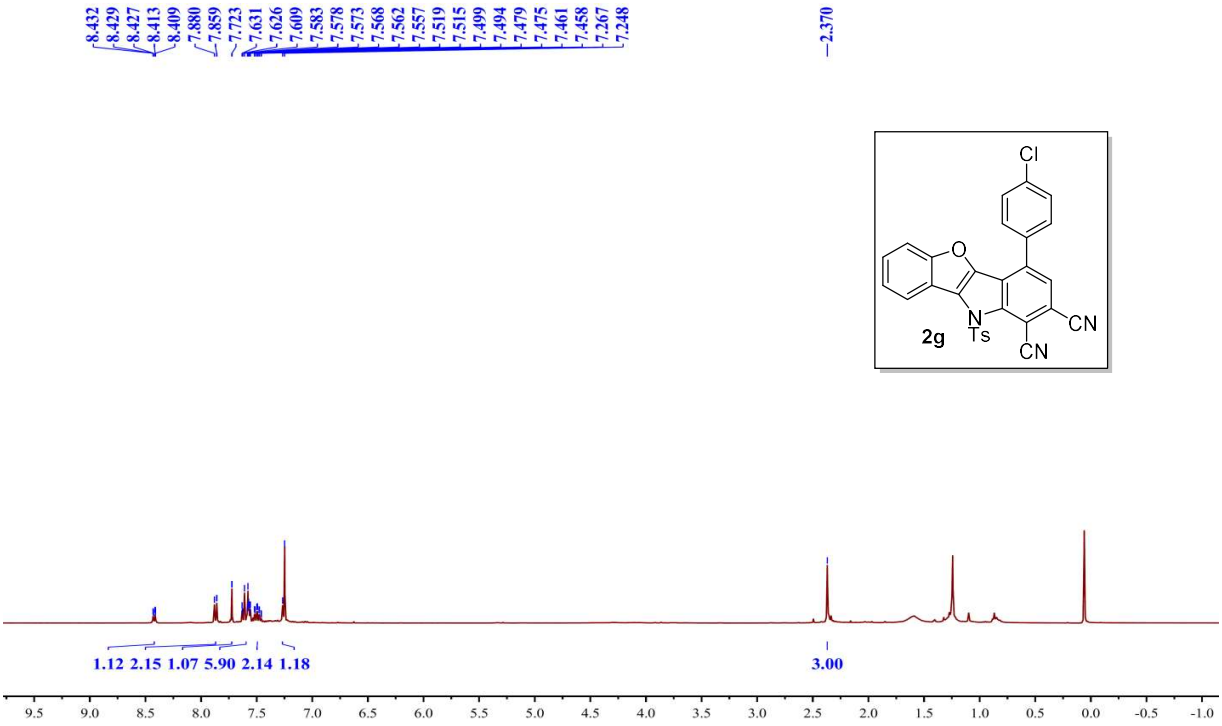
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2f:**



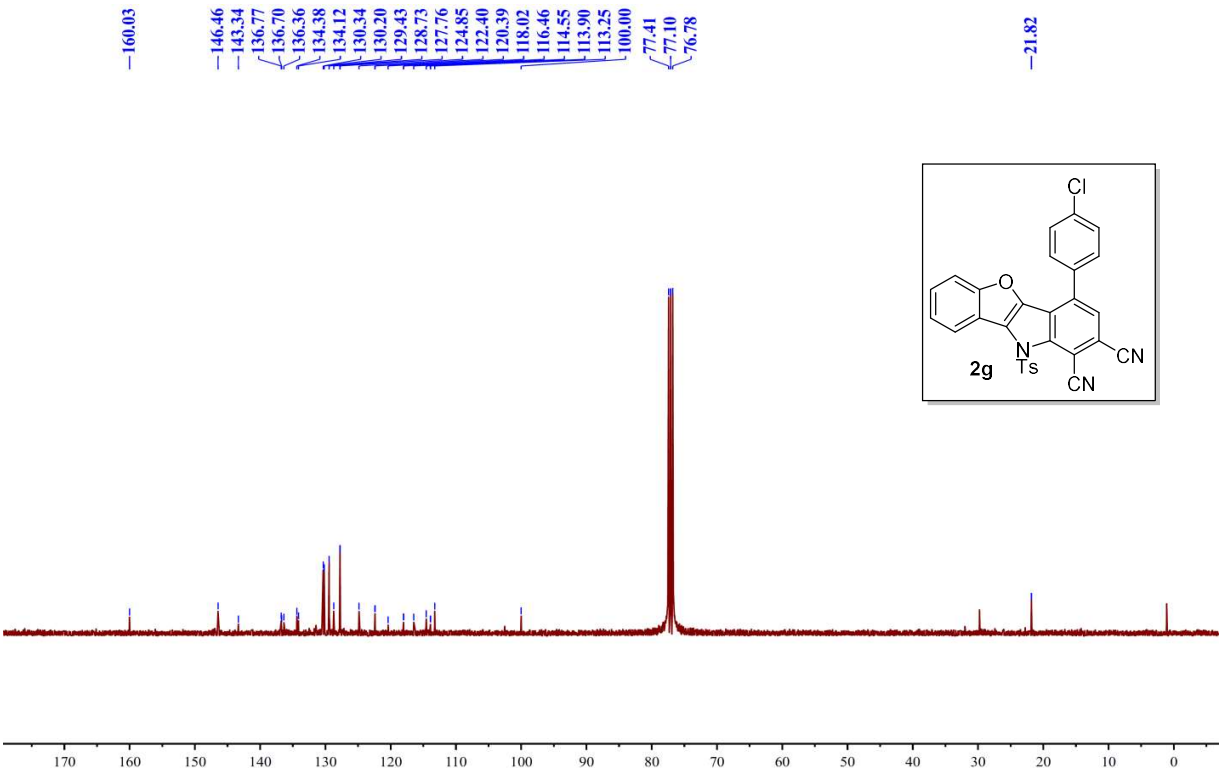
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2f**:



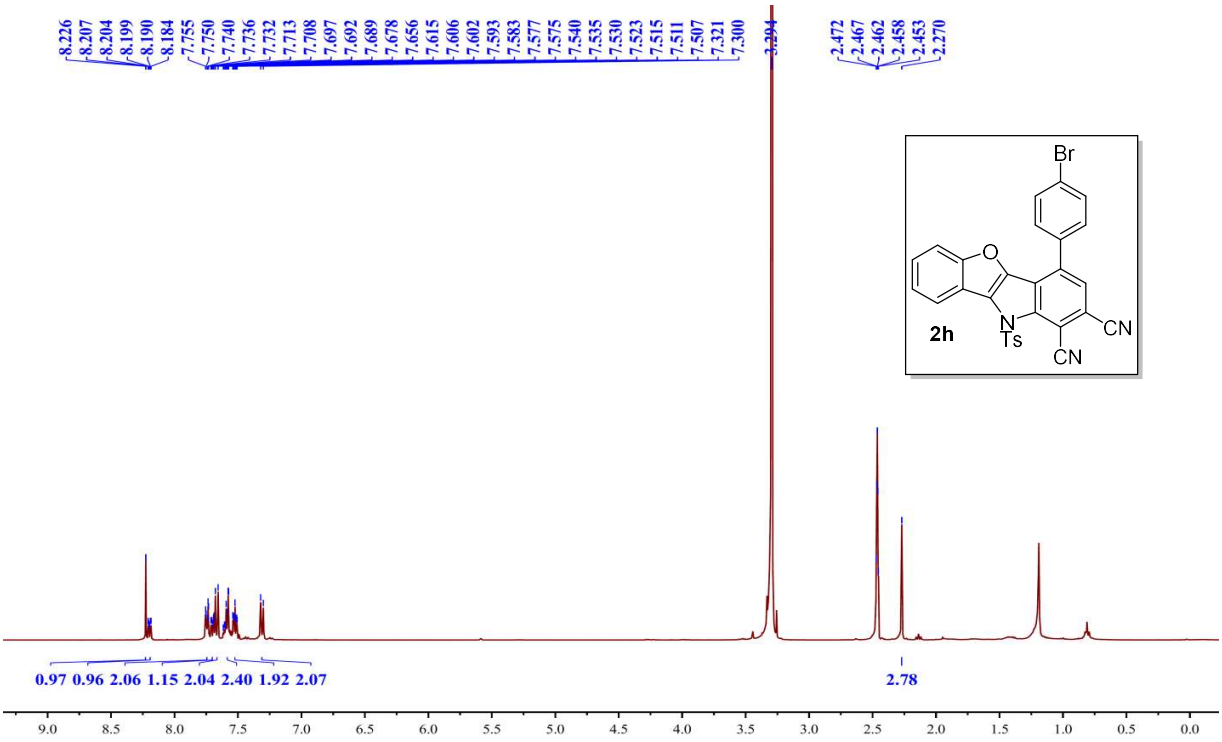
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2g:**



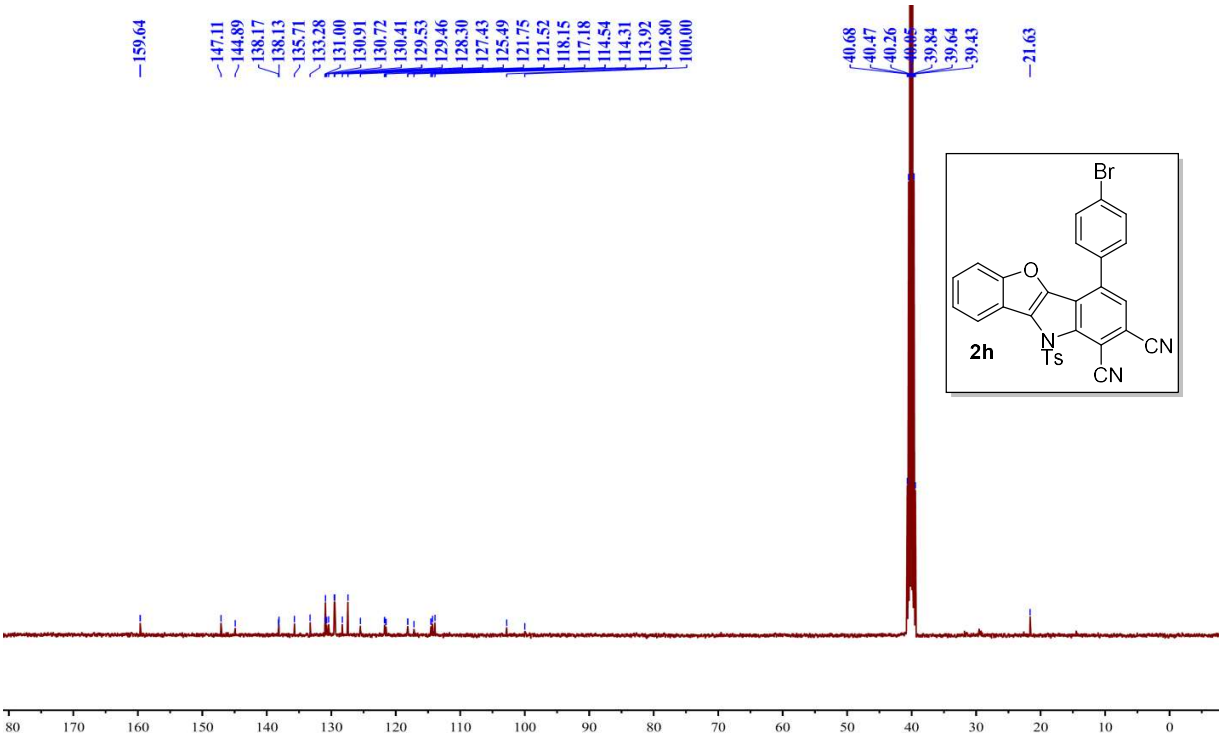
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2g**:



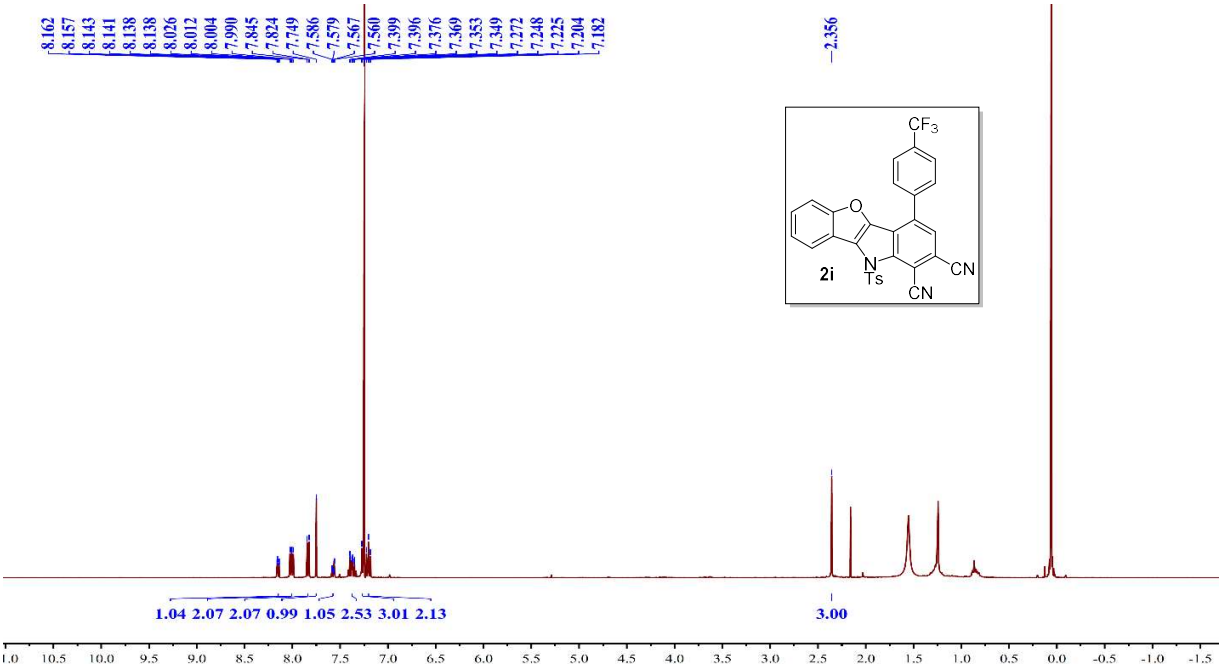
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2h:**



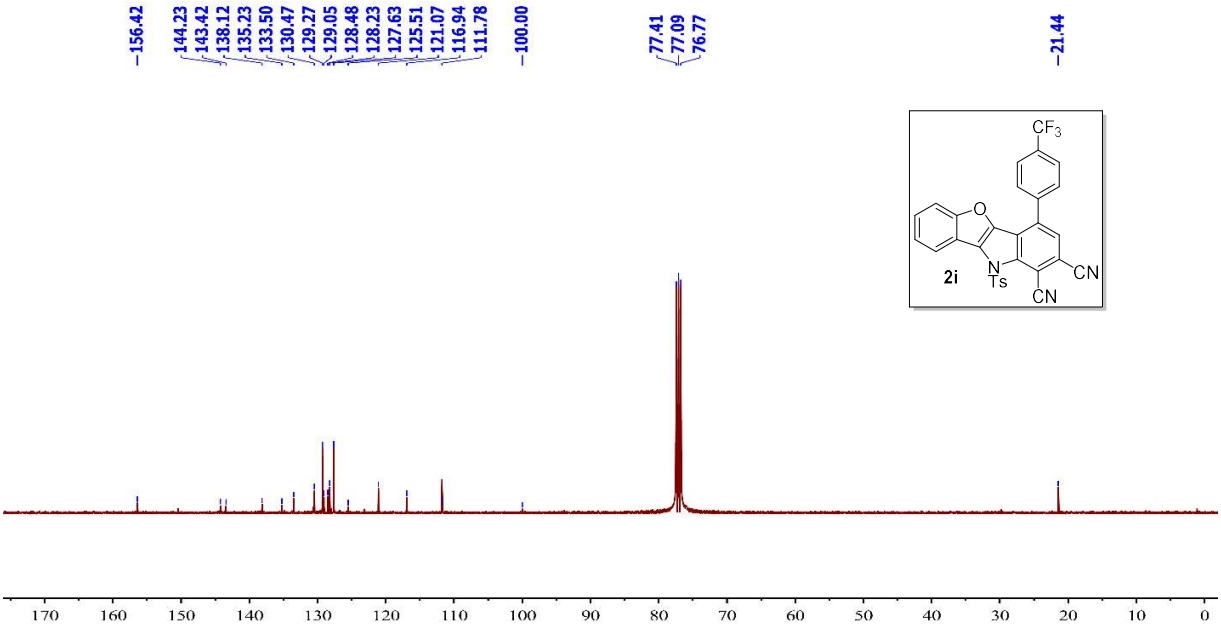
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2h**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **2i:**

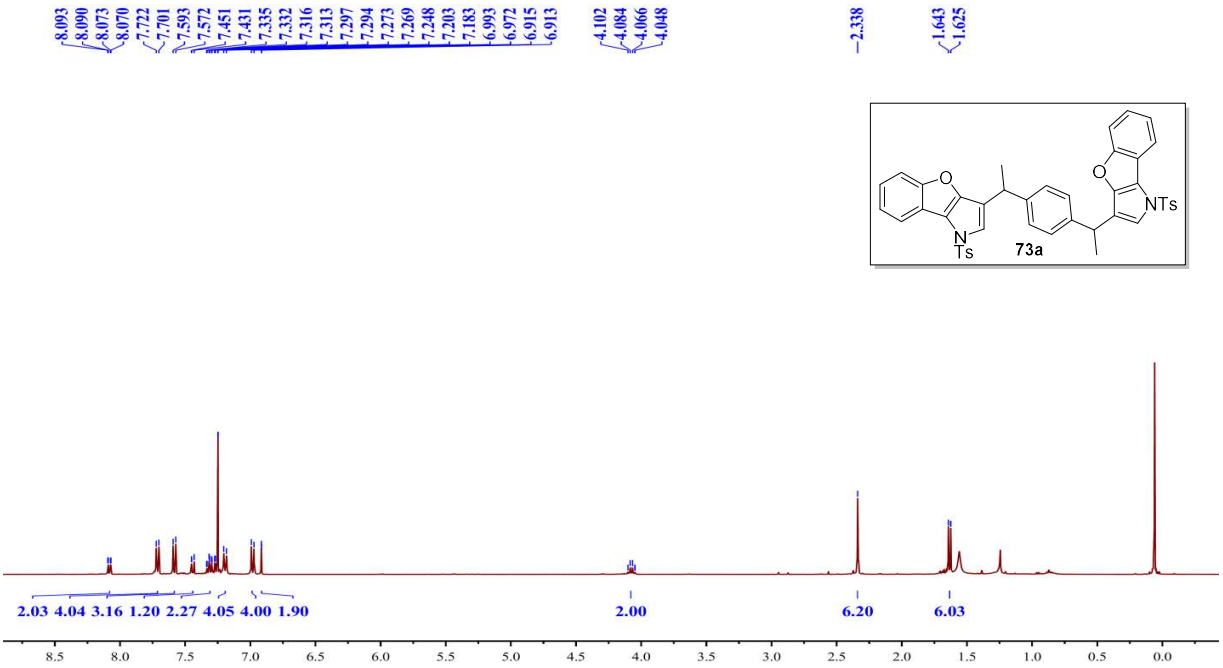


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **2i**:

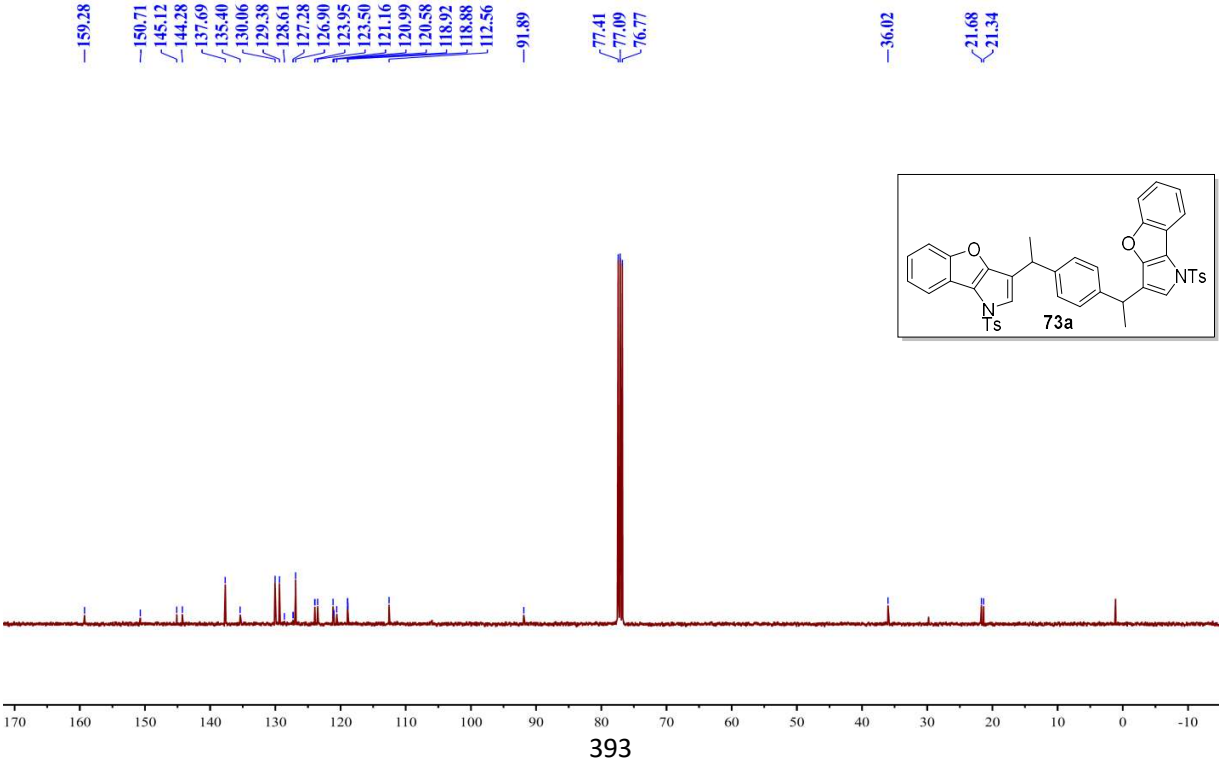


3.2.12.6 NMR spectra of 73a-c:

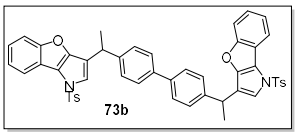
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **73a:**

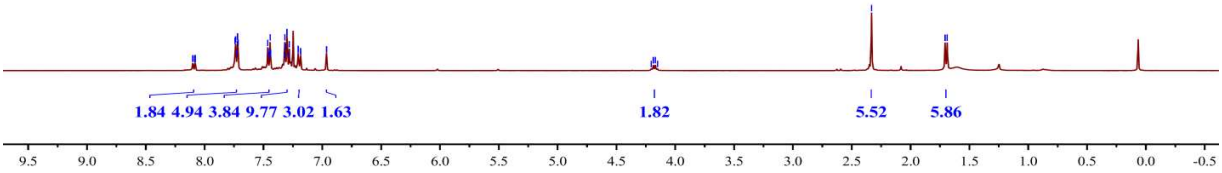


$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) spectrum of compound **73a**:

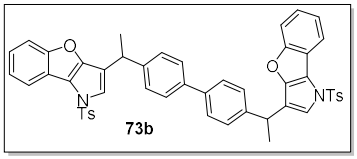


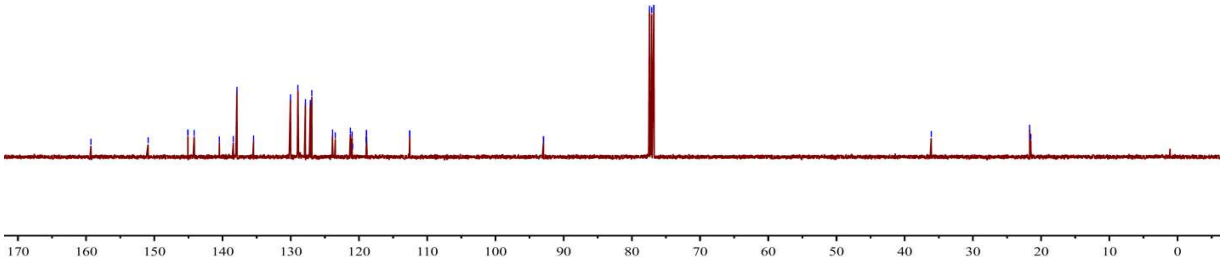
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **73b:**



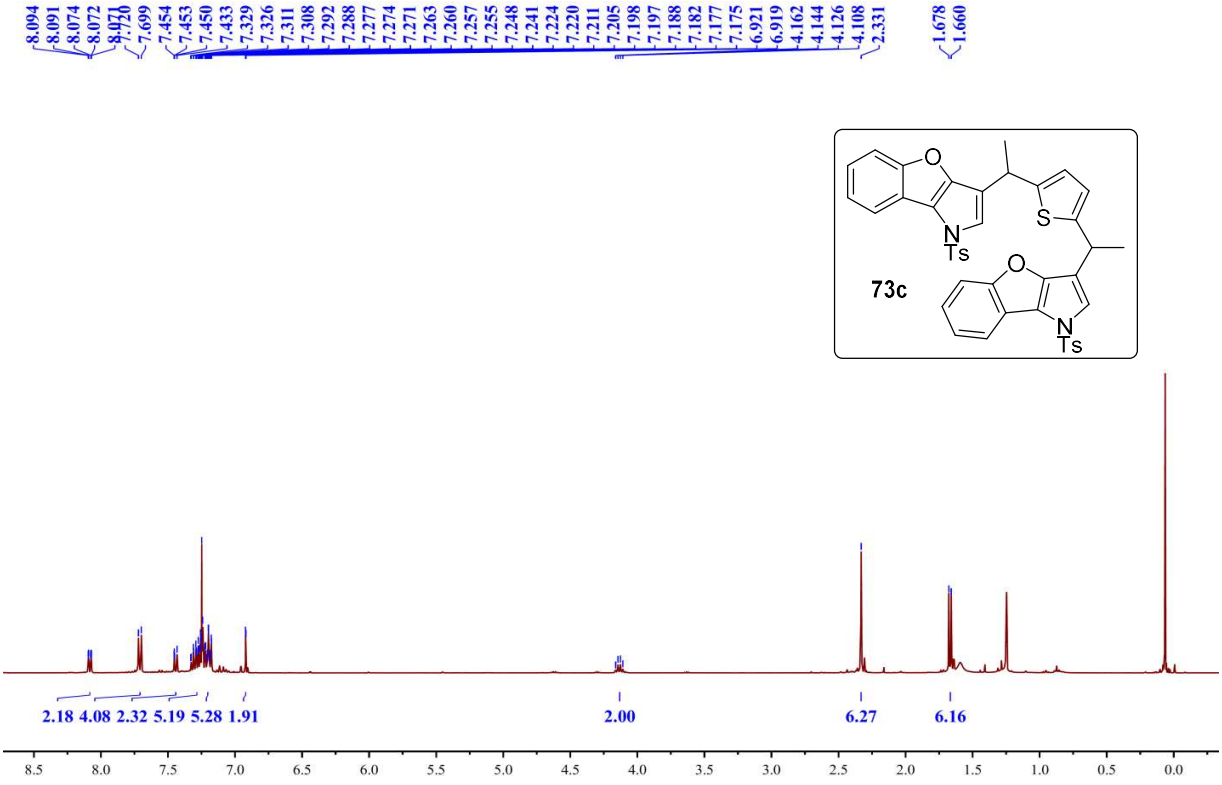


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **73b**:

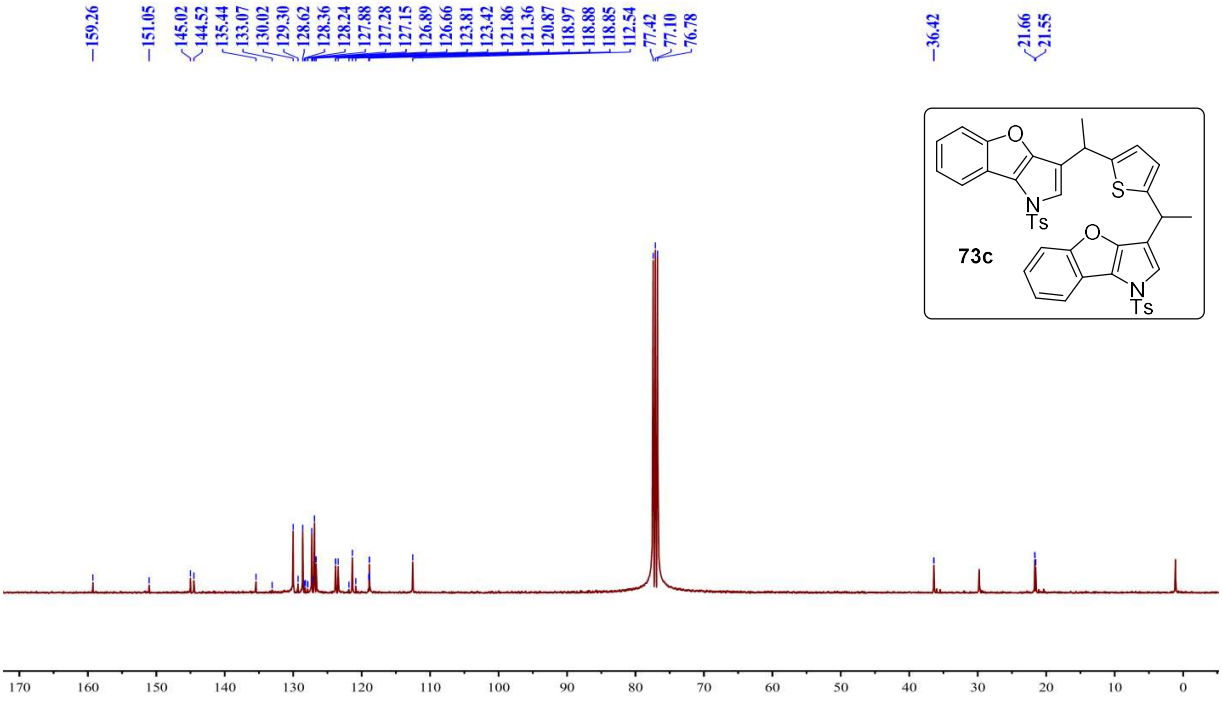




^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **73c:**

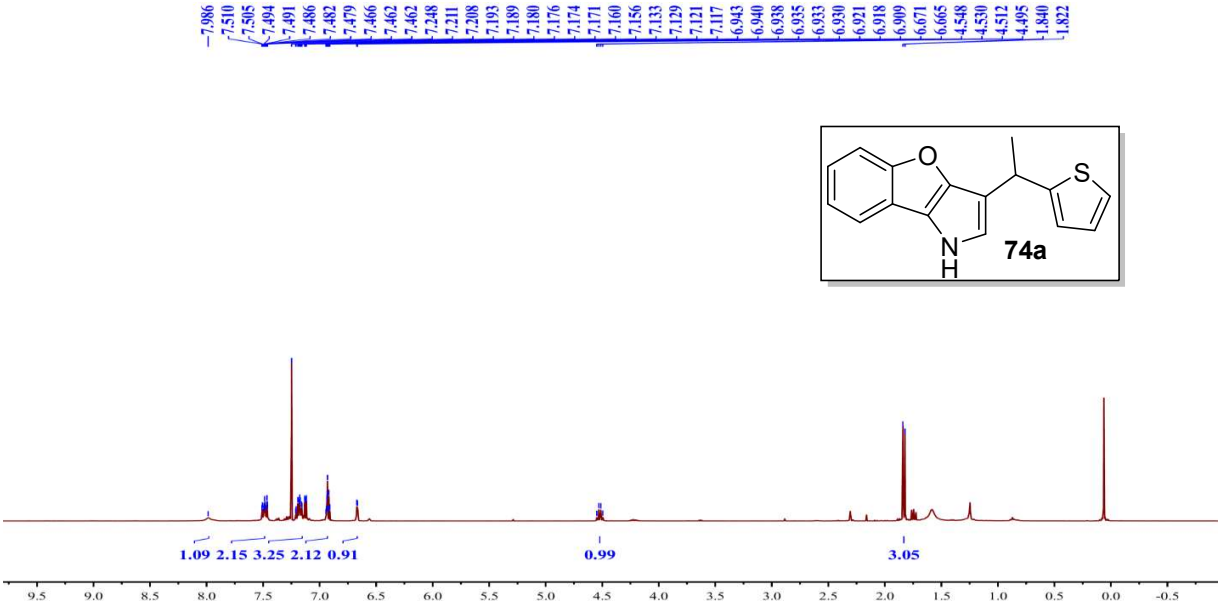


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **73c**:

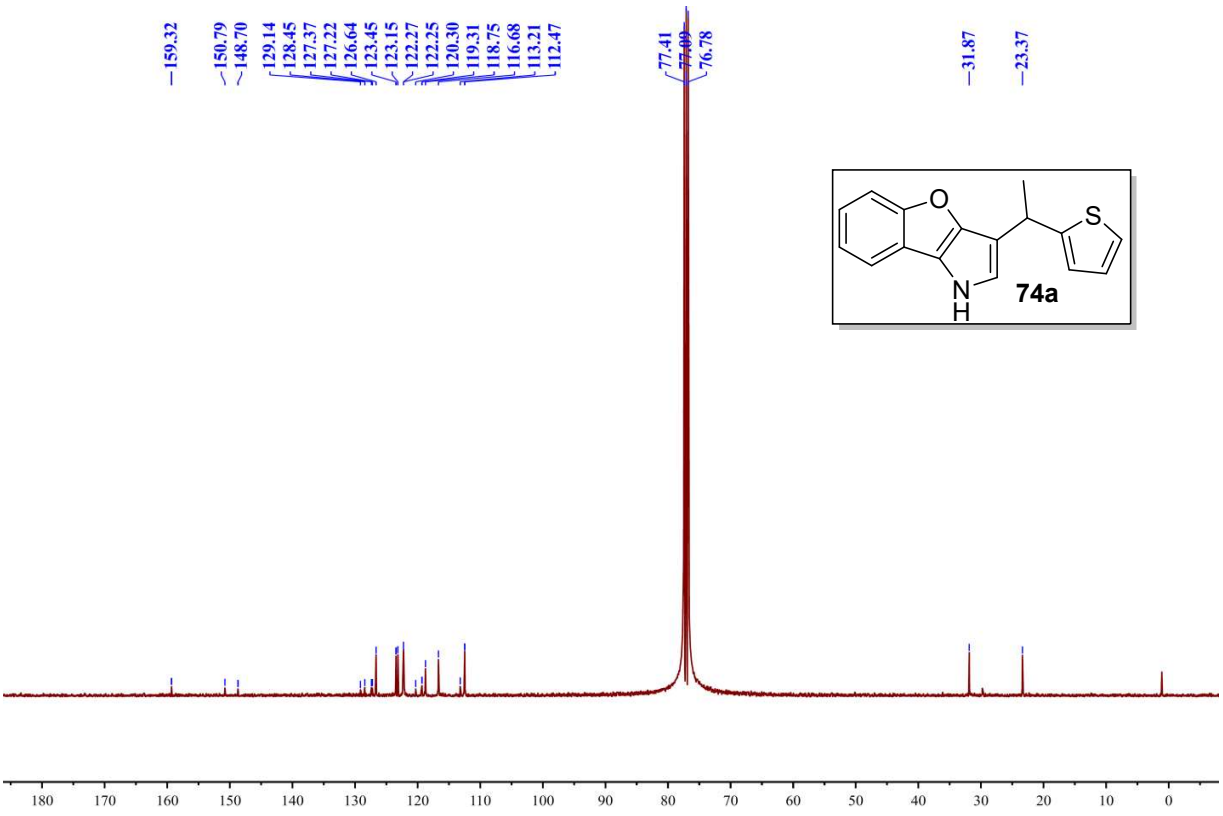


3.2.12.7 NMR spectra of 74a-c:

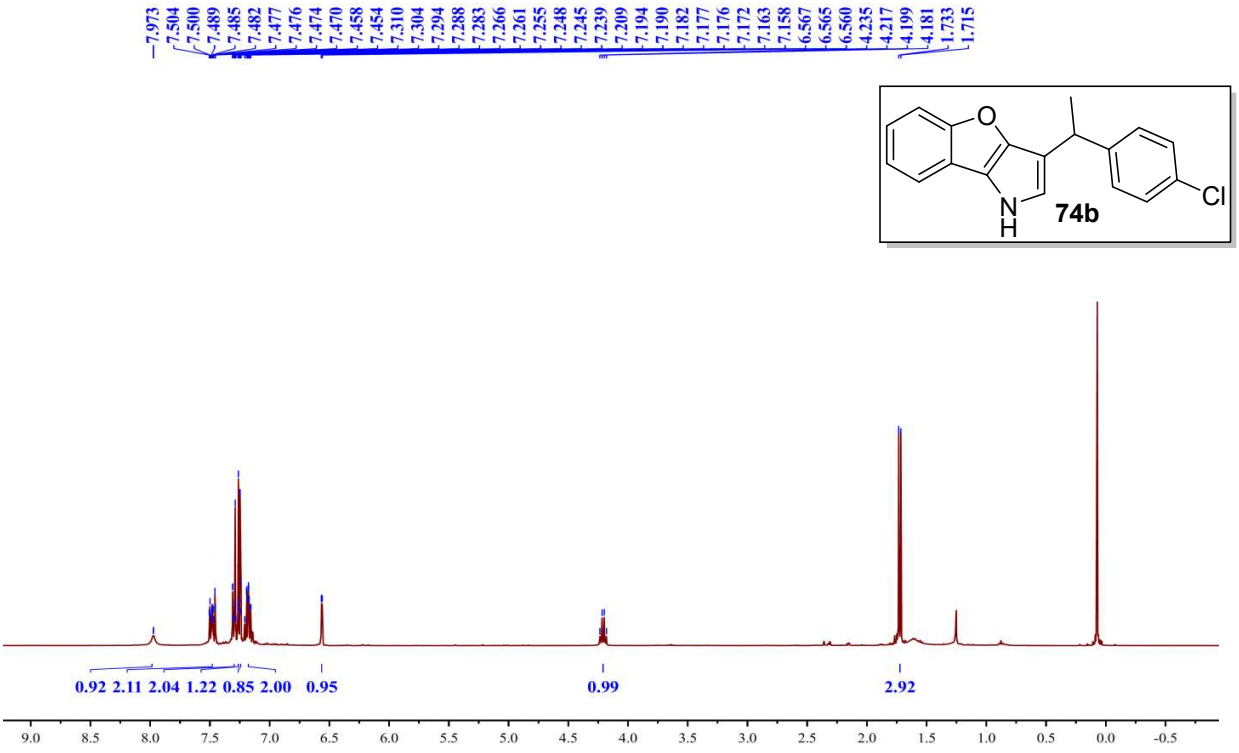
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74a:**



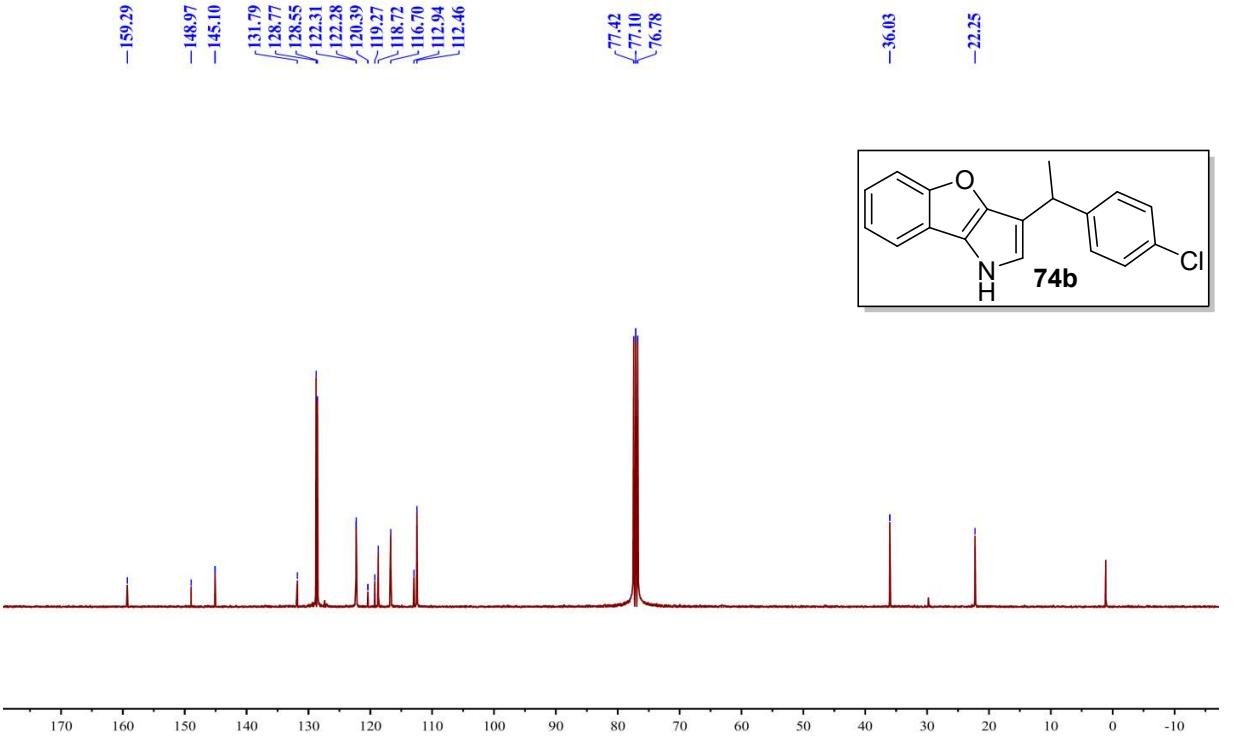
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74a**:



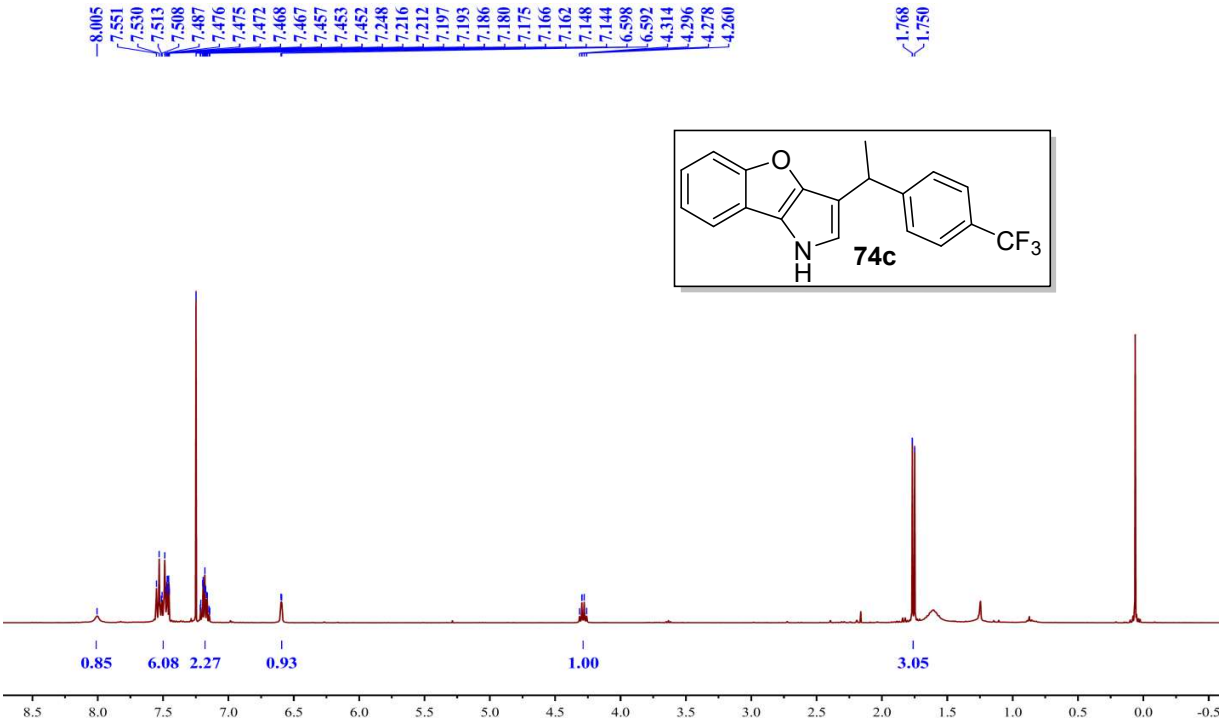
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74b:**



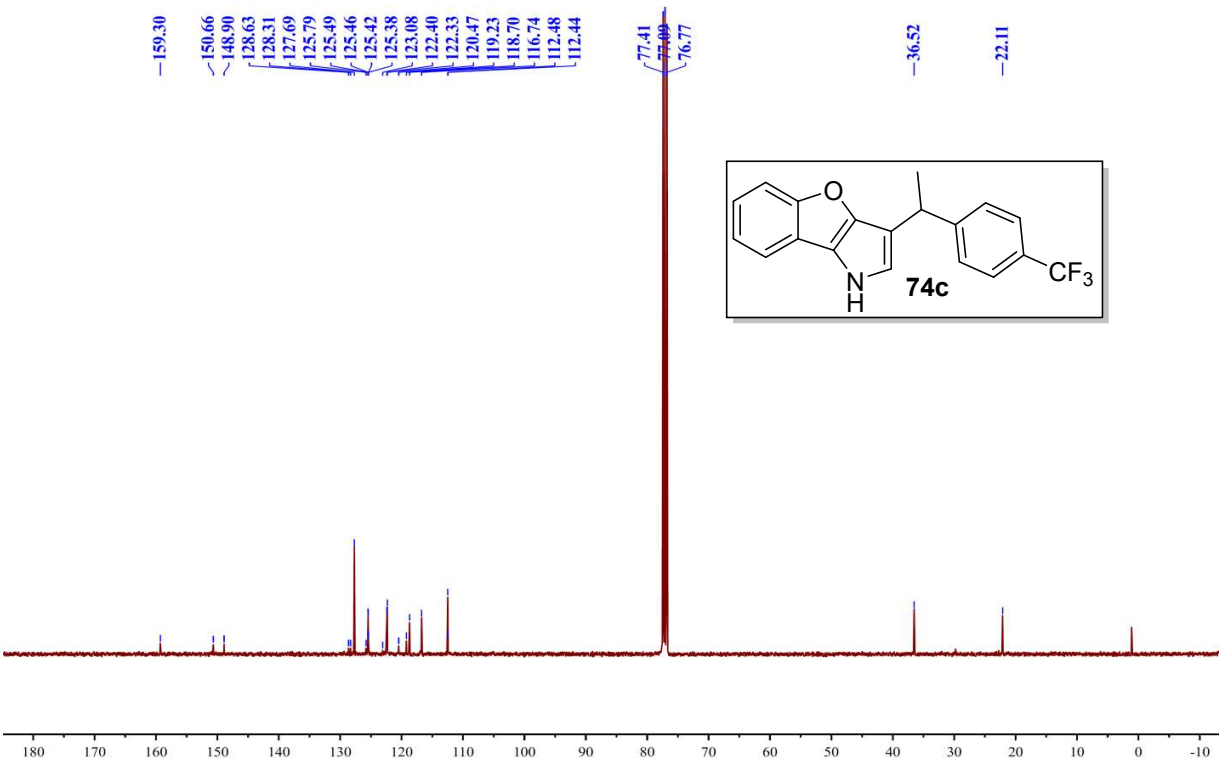
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74b**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74c:**

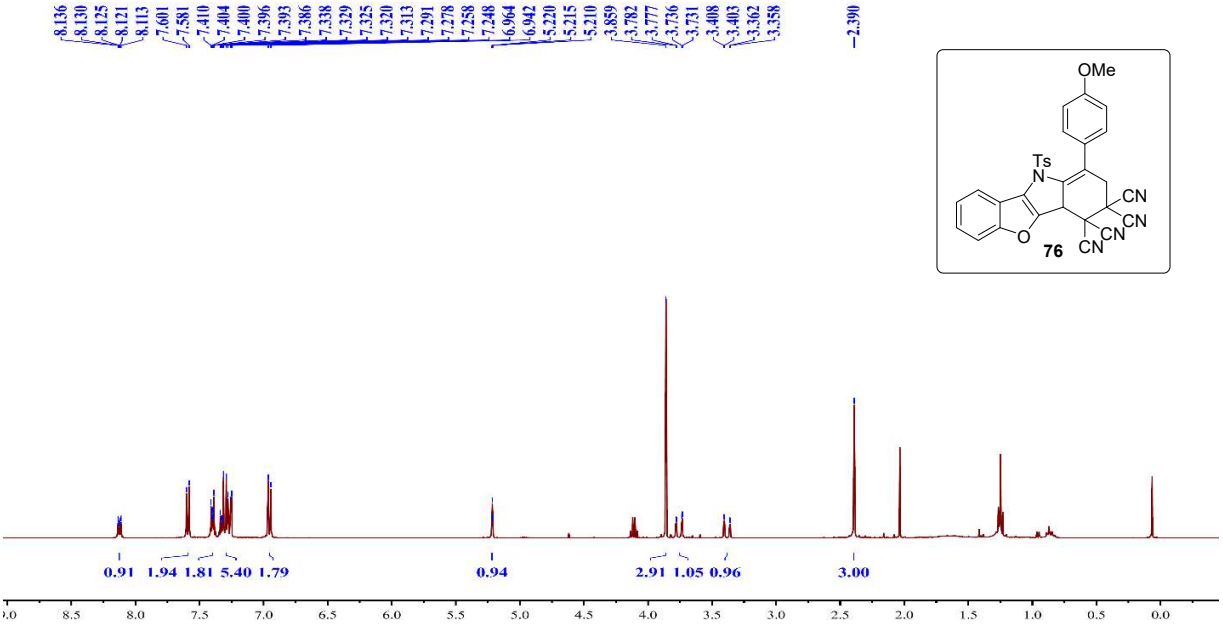


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74c**:

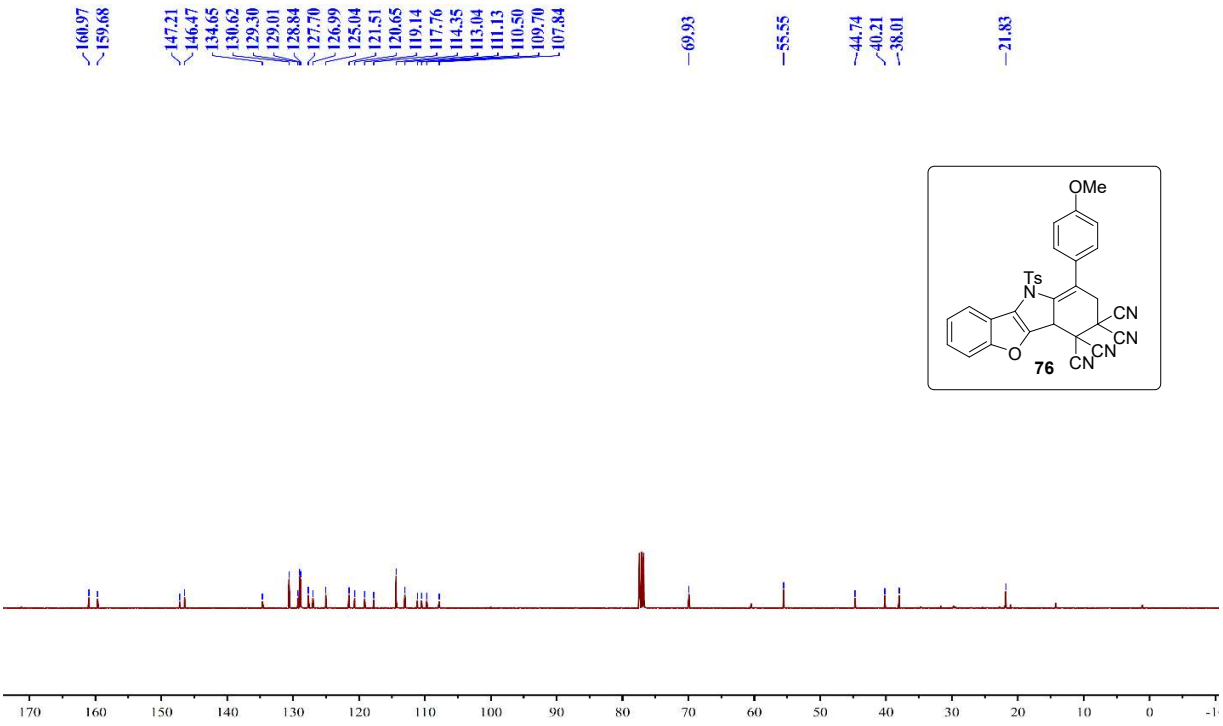


3.2.12.8 NMR spectra of 76:

^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **76:**



^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **76**:



National Institute of Technology Puducherry, Karaikal

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International Conference on Emerging Trends in Synthetic Organic Chemistry - 2021 (ICETSOC-2021)

Certificate of Appreciation

This is to certify that **Ms. Debasmita Mondal** of **CSIR-INDIAN INSTITUTE OF CHEMICAL BIOLOGY** has orally presented their research paper in the International Conference on Emerging Trends in Synthetic Organic Chemistry - 2021 (ICETSOC-2021), organized by the Department of Chemistry, National Institute of Technology Puducherry, Karaikal, on December 06-07, 2021 through virtual mode.

Dr. D. Ragupathy
Convenor

Prof. K. Sankaranarayanasamy
Director, NIT Puducherry, Karaikal

ONE DAY SYMPOSIUM IN CHEMICAL SCIENCES

CERTIFICATE FOR POSTER PRESENTATION

THIS CERTIFICATE IS AWARDED TO

Debasmita Mondal

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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